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Synthesis, Characterization and Evaluation of Antibacterial Activity of 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)one Derivatives

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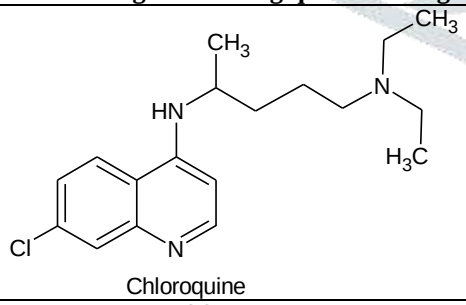
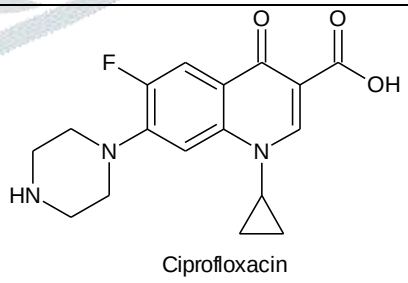
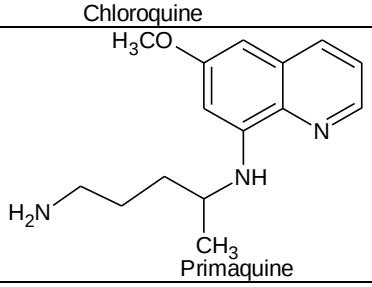
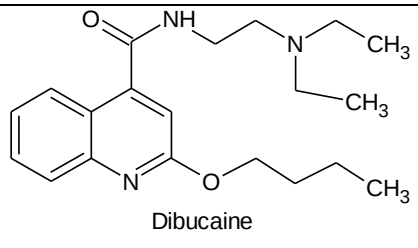
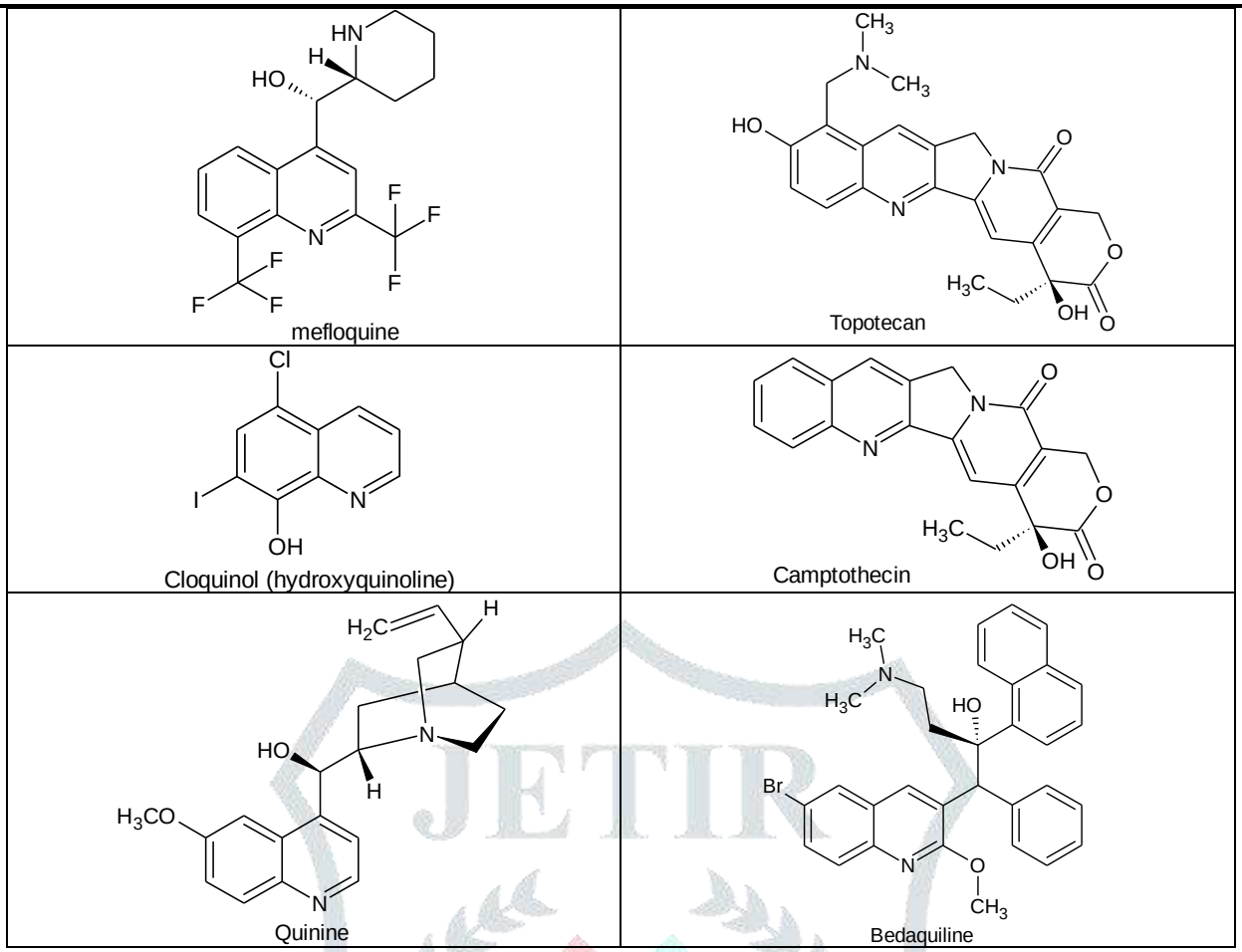
Abstract:
Heterocyclic compounds are present in most of the drugs, having therapeutic activities such as anticancer, antiamoebic, antibacterial, antimalarial, anticancer, antiviral and anti-inflammatory etc. In biological and therapeutic activities, heterocyclic compounds play a crucial role in the core structures of many drugs. A usual example of bicyclic heterocyclic compounds is quinoline which is present as pharmacophore in number of drugs responsible for their therapeutic activity. 2-pyridone is also nitrogen containing six member heterocyclic compound acts as pharmacophore in number of drugs. In present work quinoline and 2-pyridone is coupled and synthesized compound is characterized by FT-IR, ^{1}HNMR, spectral techniques and evaluated for its antibacterial activity against gram +ve *Bacillus anthraces* and gram -ve *Pseudomonas aeruginosa* bacteria. The coupled compounds showed moderate antibacterial activity against gram +ve bacteria (*Bacillus anthraces*) and gram –ve bacteria (*Pseudomonas aeruginosa*).
Keywords: Quinoline, 2-pyridone, *Bacillus anthraces* and *Pseudomonas aeruginosa*

1. Introduction:

Heterocyclic compounds attract researchers for their similarity to biological compounds and have high biological activity. Quinoline is a class of compound used as pharmacophore in number of drugs. Quinoline analogs were used as antimalarial agent (chloroquine, primaquine, mefloquine, quinine), antiamoebic agents (hydroxyquinoline, aminoquinolines), local anaesthetic (dibucaine, cinchocaine), antibacterial (ciprofloxacin), anticancer (topotecan, camptothecin), antitubercular (bedaquiline) etc [1]. Kaur et al. in 2021 described the function of quinoline derivatives as antiviral agent. In his study he found that quinoline derivatives were effective against various strains of viruses like zika virus, entero virus, herpes virus, human immunodeficiency virus (HIV), ebola virus, hepatitis C virus, SARS virus and MERS virus etc [2].

Table 1: Structure of drugs containing quinoline ring.

 Chloroquine	 Ciprofloxacin
 Primaquine	 Dibucaine



2-pyridone is also nitrogen containing six member heterocyclic compound. Forrestall et al. in 2021, reported number of compounds containing 2-pyridone pharmacophore shows potent inhibitory activity against SARS-CoV-2 [3]. Lin et al. in 2022 reported that pyridinone derivatives possess various biological activities as antitumor, antimicrobial, antiinflammatory, anticoagulant, cardiotonic [4].

In the present work, an attempt is made to couple quinoline ring and 2-pyridone via methylene group. And evaluate its antibacterial activity against gram +ve *Bacillus anthraces* and gram -ve *Pseudomonas aeruginosa* bacteria.

2. Material and Methods

Starting materials were obtained from commercial sources or prepared using known procedures. Melting points were measured by open capillary technique and were corrected with reference to benzoic acid, the temperature was expressed in degree Celsius. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 °C. In case where chromatographic purification was done unless mentioned silica gel (60-120 mesh size) was used as stationary phase. The reaction progress was monitored by the thin layer plates coated with silica gel (Himedia) and visualized by fluorescence quenching or iodine. The IR spectra were recorded on AVATAR 330-FT-IR and IR absorbance is expressed in cm^{-1}. The ^1H NMR spectra were recorded on Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR. ^1H NMR spectra are reported in ppm. All the experiments were repeated two or more times.

2.1. General procedure for Synthesis of 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one derivatives 2a-2d:

t-BuOK (2.5mM) and n-Bu_4NBr (0.1mM) were added to a cooled solution (0 °C) of 2-pyridone (2.0 mM) in DMF (5 mL) and the resulting reaction mixture was stirred at 0 °C for 15 min. After that a solution of compounds 1a-1d (2.0mM) in THF was added and resulting reaction mixture was left stirring for 6-10 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent. The mixture was concentrated in vacuo, and ice water was added in concentrated mixture and extracted with ethylacetate. The compounds were purified by column chromatography.

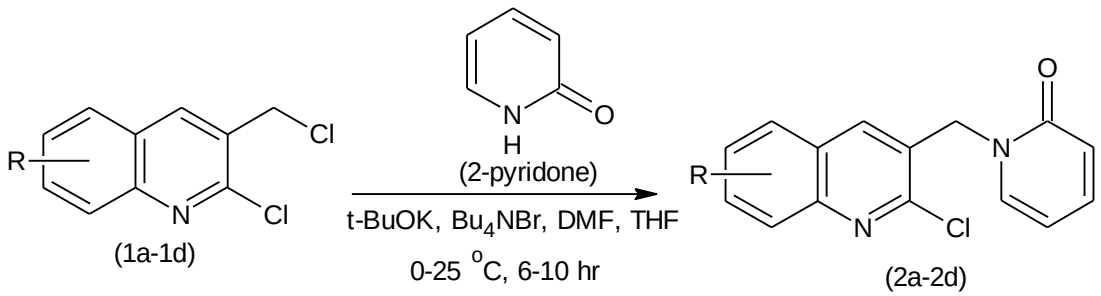
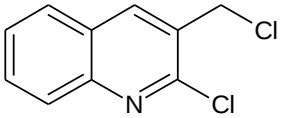
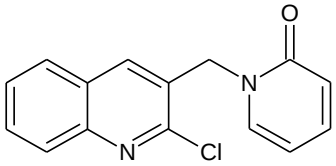
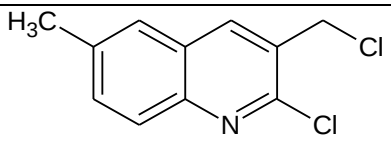
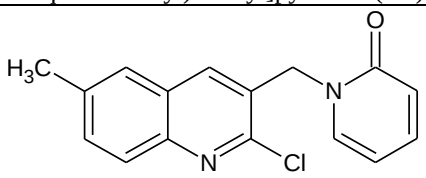
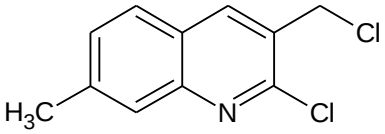
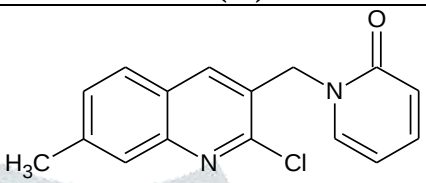
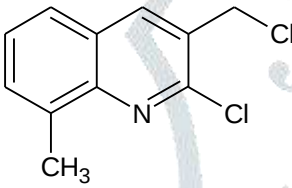
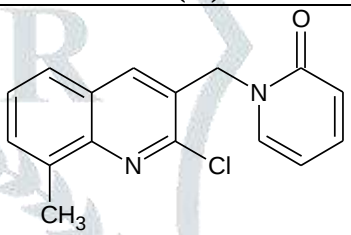


Figure 1: Synthetic scheme

Table 2: Structure and name of compounds 1a-1d and 2a-2d.

1a-1d	2a-2d
 2-chloro-3-(chloromethyl)quinoline **(1a)**	 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one **(2a)**
 2-chloro-3-(chloromethyl)-6-methylquinoline **(1b)**	 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one **(2b)**
 2-chloro-3-(chloromethyl)-7-methylquinoline **(1c)**	 1-[(2-chloro-7-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one **(2c)**
 2-chloro-3-(chloromethyl)-8-methylquinoline **(1d)**	 1-[(2-chloro-8-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one **(2d)**

2.2. Biological activity:

The anti bacterial activity was evaluated by measuring the diameter inhibition zone. The diameter of the inhibition zone was calculated. The diameter of inhibition zones are shown in table 4.

2.2.1. Antibacterial screening:

Organisms	:	*Bacillus anthraces* and *Pseudomonas aeruginosa*
Method	:	Well diffusion technique.
Medium used	:	Muller Hinton agar
Preparation of medium	:	Agar and Muller Hinton agar were dissolved in water by boiling then it was autoclaved for 15 min at 15psi.
Standard	:	Amikacin, Vancomycin
Control	:	DMSO
Incubation time	:	17 hours at 37 °C.

2.2.2. Antimicrobial assay:

Compounds were evaluated for their in vitro antibacterial activity against *Bacillus anthraces and pseudomonas aeruginosa* by the well diffusion method. Muller Hinton agar for bacteria and beef extract broth sterilized in a flask and cooled to 40-45 °C was distributed to sterilized Petri dishes and allowed solidity. Well was made by using sterilized probe. Inoculation was done by using sterilized swaps. Compounds dissolved in DMSO (2mg/mL) and added in wells. The Petri plates were incubated at 37 °C for 17 hour.

Stock solution preparation: 2 mg of compounds was dissolved in 1ml of the DMSO solvent. Standard antibiotic: Vancomycin and Amikacin; Control: DMSO; A: 10µL of the stock solution; B: 20µL of the stock solution. Biological activity carried out on following compounds 2a-2d.

3. Results and Discussion:

3.1.1. Synthesis of 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one (2a):

Following the general procedure compound 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one was obtained by using 2-pyridone and 2-chloro-3-(chloromethyl)quinoline (1a) in 1:1 ratio kept on stirring for 6 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent. FT-IR (KBr) ν 1665 (C=O), 1595 (N=C), 1534 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.1 (s, 1H), 8.01 (d, 1H), 7.75 (m, 2H), 7.55 (t, 1H), 7.49 (d, 1H) 7.4 (t, 1H), 6.66 (d, 1H), 6.24 (t, 1H), 5.38 (s, 2H, CH_2).

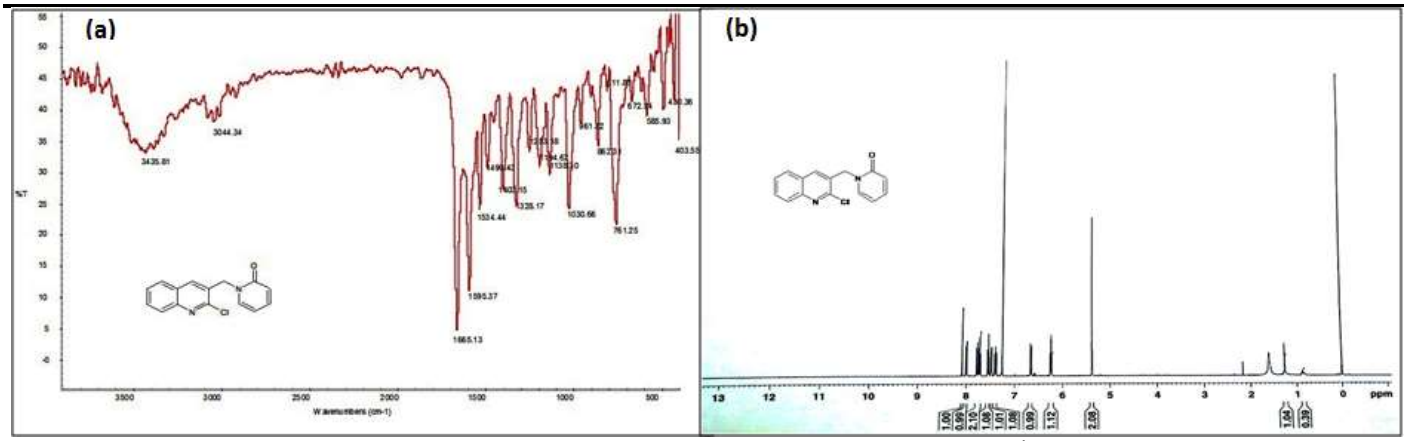


Figure 2: (a) FT-IR spectra of 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one (b) ^{1}H NMR, 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one, ($CDCl_3$, 500 MHz)

3.1.2. Synthesis of 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (2b):

Following the general procedure compound 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one was obtained by using 2-pyridone and 2-chloro-3-(chloromethyl)-6-methylquinoline (1b) in 1:1 ratio kept on stirring for 6 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent. FT-IR (KBr) ν 3029 (C-H), 2924 (C-H), 1662 (C=O), 1597 (N=C), 1537 (C=C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.88 (d, 1H), 7.55 (d, 2H), 7.46 (d, 1H), 7.38 (t, 1H), 6.65 (d, 1H), 6.22 (t, 1H), 5.36 (s, 2H, CH_2), 2.50 (s, 3H, CH_3).

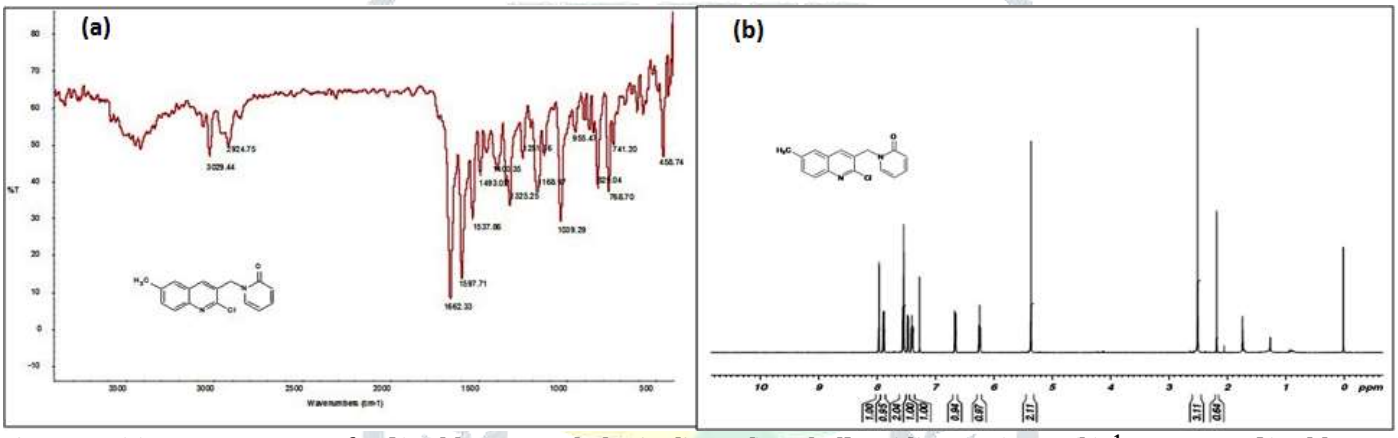


Figure 3: (a) FT-IR spectra of 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (b) ^{1}H NMR, 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one, ($CDCl_3$,500MHz)

3.1.3. Synthesis of 1-[(2-chloro-7-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (2c):

Following the general procedure compound 1-[(2-chloro-7-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one was obtained by using 2-pyridone and 2-chloro-3-(chloromethyl)-7-methylquinoline (1c) in 1:1 ratio kept on stirring for 8 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent. FT-IR (KBr) ν 3025 (C-H), 2925 (C-H), 1659 (C=O), 1584 (N=C), 1532 (C=C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.77 (s, 1H), 7.66 (d, 1H), 7.48 (d, 1H), 7.37 (m, 2H), 6.65 (d, 1H), 6.23 (t, 1H), 5.36 (s, 2H, CH_2), 2.55 (s, 3H, CH_3).

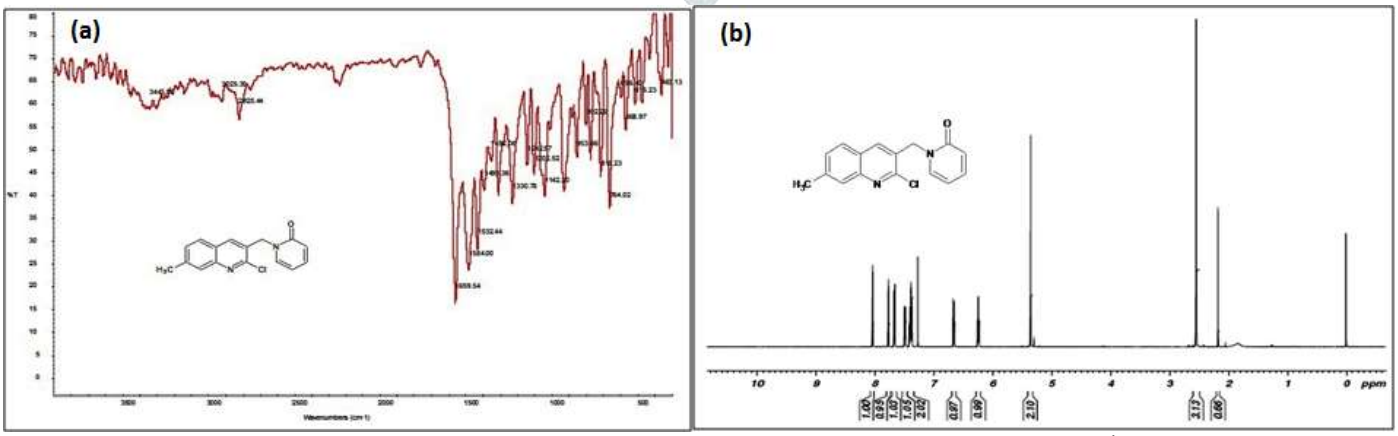


Figure 4: (a) FT-IR spectra of 1-[(2-chloro-7-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (b) ^{1}H NMR, 1-[(2-chloro-7-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one, (CDCl3, 500MHz)

3.1.4. Synthesis of 1-[(2-chloro-8-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (2d):

Following the general procedure compound 1-[(2-chloro-8-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one was obtained by using 2-pyridone and 2-chloro-3-(chloromethyl)-8-methylquinoline (1d) in 1:1 ratio kept on stirring for 8 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent.

FT-IR (KBr) ν 3074 (C-H), 2913 (C-H), 1663 (C=O), 1591 (N=C), 1533 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.6 (d, 1H), 7.57 (d, 1H), 7.47 (d, 1H), 7.38 (m, 2H), 6.65 (d, 1H), 6.22 (t, 1H), 5.38 (s, 2H, CH_2), 2.75 (s, 3H, CH_3).

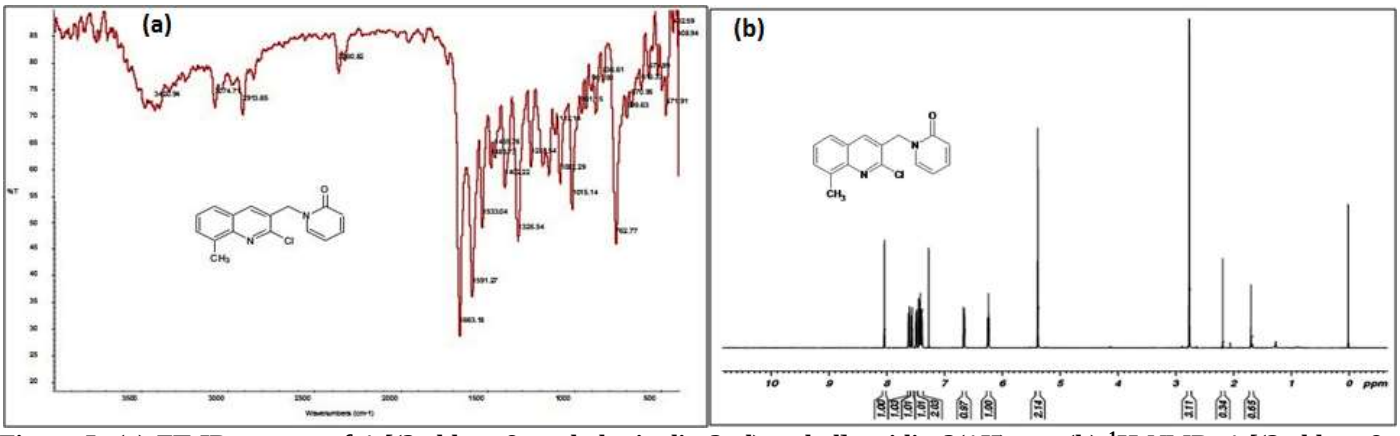


Figure 5: (a) FT-IR spectra of 1-[(2-chloro-8-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (b) ^1H NMR, 1-[(2-chloro-8-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one, (CDCl3, 500MHz)

Table 3: Synthesis of 1-[(2-chloroquinolin-3-yl)methyl]pyridin-2(1*H*)-one derivatives (2a-2d)

S.N.	R	Mol. formula (mol.wt.)	Melting point (°C)	Yield
2a	H	$C_{15}H_{11}N_2OCl$ (270.7)	156-168	67%
2b	6-Me	$C_{16}H_{13}N_2OCl$ (284.7)	163-165	65%
2c	7-Me	$C_{16}H_{13}N_2OCl$ (284.7)	167-169	68%
2d	8-Me	$C_{16}H_{13}N_2OCl$ (284.7)	169-171	62%

All the compounds were confirmed and characterized by FT-IR, and ^{1}HNMR. The coupled products, 6a-f showed the presence of C=O (1662-1665 cm^{-1}) in IR spectra also in NMR aromatic protons in range of 6.2-8.1 ppm, 2 protons of CH_2 group at 5.3. Compounds 2a-2d was evaluated for their antibacterial activity. Compounds 2a-2d showed moderate antibacterial activity against gram +ve bacteria (*Bacillus anthraces*) and gram –ve bacteria (*Pseudomonas aeruginosa*) (Table 4). Methyl substituent at 6, 7 and 8 position does not cause effective change in antibacterial activity.

3.2. Biological activity:

Table 4: Antibacterial activity of the compounds 2a-2d Against Gram +ve bacteria *Bacillus anthraces* and against gram –ve bacteria *Pseudomonas aeruginosa*

Compounds	Against Gram +ve bacteria *Bacillus anthraces*		against gram –ve bacteria *Pseudomonas aeruginosa*	
	Zone of inhibition (mm)		Zone of inhibition (mm)	
	A	B	A	B
C	-	-	-	-
2a	09	14	12	15
2b	10	17	10	16
2c	11	17	-	14
2d	11	14	-	-
	Standard – Vancomycine (30 µg) : zone of inhibition 28 mm		Standard – Amikacin (30 µg) : zone of inhibition 30 mm	
A – 10 µL (20 µg), B – 20 µL (40 µg), C – control (DMSO)				

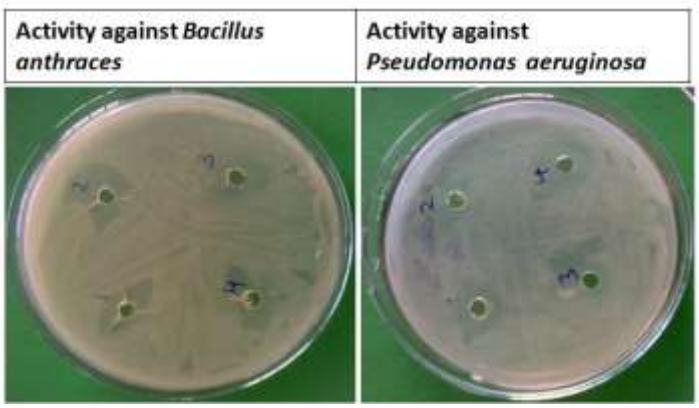


Figure 6: Activity against *Bacillus anthraces* & Activity against *Pseudomonas aeruginosa*

4. Conclusion:

All the reactions were carried out on ordinary laboratory condition by employing cheaper, easily available chemicals and reagents in moderate to good yield. The synthesized compounds 2a-2d showed moderate antibacterial activity against gram +ve bacteria (*Bacillus anthraces*) and gram –ve bacteria (*Pseudomonas aeruginosa*).

References:

[1] Ajani O.O., Iyaye K.T. and Ademosun O.T., 2022. Recent advances in chemistry and therapeutic potential of functionalized quinoline motifs – a review. *Royal Society of Chemistry Advances*, 12: 18594–18614.

[2] Kaur R., Kumar K., 2021. Synthetic and medicinal perspective of quinolines as antiviral agents. *European Journal of Medicinal Chemistry*, 215: 113220.

[3] Forrestall K.L., Burley D.E., Cash M.K., Pottie I.R., Darvesh S., 2021. 2-Pyridone natural products as inhibitors of SARS-CoV-2 main protease. *Chemico-Biological Interactions*, 335: 109348.

[4] Lin S., Liu C., Zhao X., Han X., Li X., Ye Y. and Zheyu L, 2022. Recent Advances of Pyridinone in Medicinal Chemistry. *Frontiers in Chemistry*, 10: 869860.