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# Design, synthesis, and biological screening of some novel Quinoline-azetidinone derivative: an innovative approach towards the medicinal sciences.

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**ABSTRACT**

Heterocyclic compound with azetidinone has the unique identity in the medicinal field. A very little work had been done on the azetidinone, so more and more research should be expected on drug bearing such moiety. Here we prepared some distinctive derivative of 3-chloro-4-(7-methyl-2-(p-tolyloxyoquinoline-3-yl)-1-(4-nitrophenyl) azetidin-2-one which are prepared by interaction of 2-(p-tolyloxy) Quinoline-3-yl)methyleneN-))7-methyl)-4-nitroaniline and similar concentration of chloroacetyl chloride and triethyl amine in the presence of solvent DMF . Structure confirmation of titled compounds was done by physical and spectral techniques such as IR, $^1$H NMR. The synthesized compounds were evaluated at different concentration against Gram positive and Gram negative bacteria and fungi using reference standard. The result indicates that synthesized compound is a good antibacterial agent.

**Keywords:** Quinoline, azetidinone, antibacterial, antimalerial, anticancer**.**

## INTRODUCTION

Heterocyclic compound containing heteroatom nitrogen such as quinoline fascinated the considerable attention of researchers. Quinoline which was mostly originate from the bark of chinchona trees is the most promising antimalerial drugs with many more pharmacological applications like antifungal[1], anticancer[2], antibacterial[3-4], anti-inflammatory[5].

2-Chloroquinoline-3-carbaldehydes was the starting biologically active compound prepared by Vilsmeier-Haack reagent[6-7]. β-Lactam also known as Azetidinone, is a most used antibiotic can be found in common antibiotics such as Penicillin, Penam, Ampicillin, Cephalosporin, Carumonam, Aztreonam, Thienamicine etc. Antibiotic β-lactum was first antibiotics used for the management of superficial burn injury[8]. It is generally available in Clavulanic acid produced by Streptomycin which controls the production of β-lactamase usually occurs in both Gram-positive and Gram negative bacteria. β-lactam ring can be synthesized by different synthetic routes but commonly it was synthesized via the cycloaddition of mono acetyl chloride with imine.

Literature survey reveals that generally cyclocondensation of the Schiff's bases with chloroacetyl chloride in the presence of triethylamine resulted in the formation of the corresponding azetidinone analogues[9]. Azetidinone is a four membered heterocyclic ring in which nitrogen is attached to β carbon atom relative to carbonyl group commonly called as β-lactum is used as antibiotic. Azetidinone is the good example for β-lactam ring exhibiting the vast pharmacological applications including antihyperlipidemic [10], potent cholesterol absorbtion inhibitors[11], antitubercular agent[12-15], antibacterial[16], antifungal[17-18], anti-inflammatory[19], antioxidant, antimycobacterial and cytotoxic[20].

## METHODOLOGY

The melting points of newly synthesized compounds were determined in open capillary paraffin oil bath and found to be uncorrected. 1H NMR spectra was recorded on Bruker AM 400 instrument using tetramethylsilane as an internal reference and The DMSO-d6 as solvent. IR spectra were recorded on a Shimadzu IR 8400 Spectrophotometer with the frequency ranging from 4000-400 cm-1.

**General procedure for the synthesis of 6-methyl-2-chloroquinoline 3-carbaldehyde by vilsmeir-Haack reaction:**9.62 ml (0.125m) DMF was taken in round bottom flask. Round bottom flask containing DMF was placed in a salt ice bath and the temperature maintained up to $0^0$ c. Then 31.56 ml (0.35m) $POCl_3$ was added drop by drop by dropping funnel while stirring continuously. Then 4-methyl acetanilide (0.05m) was adeded in small portion. After addition was completed wait for 10-15 min. Refluxed for Round bottom flask 6 h at $75^0$c in oil bath. After complete reaction the mixture was poured in crushed ice and stirred for 30 min at $10^0$c. Separated product recrystallized from ethyl alcohol. Pale yellow colour was obtained[7].

**General procedure for the synthesis of 6-methyl-2(p-tolyloxy)quinoline 3-carbaldehyde(1a):**(0.031m) p-cresol, KOH 12.85g (0.031m) 6-methyl-2-chloroquinoline 3-carbaldehyde were refluxed at 80-900c for 4-5h in oil bath. After completion of reaction the mixture was poured in ce cold water. The product was filtered and recrystalised from ethyl alcohol.

**General procedure for the synthesis of 2-(p-tolyloxy)quinoline-3-yi)methylene N-((7-methyl)-4-nitroaniline(2a):**Similar concentration of p-nitroaniline and 1awere refluxed in ethanol along with few drops of acetic acid for 3-5h and content pour into crushed ice. The product was purified from ethanol.

**General procedure for the synthesis of 3-chloro-4-(7-methyl-2-(p-tolyloxyoquinoline-3-yl)-1-(4-nitrophenyl)azetidin-2-one(3a)**: A solution of 1a (0.01mol) and triethyl amine (0.01 mol) was prepared by adding them collectively in DMF (10mL) as a solvent. Chloro acetyl chloride (0.01 mol) in DMF(10mL) was added drop by drop to the reaction content at $0^oC$ and stirred for 8h. To maintain the reaction condition the reaction flask was placed in ice bath. The follow-on product was separated, filtered, washed, dried and purified by DMF to get **2a**.

**Spectral, Elemental and physical data of synthesized compounds**:

**3-chloro-4-(7-methyl-2-(p-tolyloxyoquinoline-3-yl)-1-(4-nitrophenyl) azetidin-2-one(2a)** Yellow crystalline solid; Recrystallizing solvent, DMF; mp, 201-203; Yield, 64%;, $C_{26}H_{20}ClN_3O_4$. **IR (KBr $\nu_{max}$ in $cm^{-1}$):** 3030 (Ar C-H str -sym), 1687 (C=O str., azetidinone), 1611(-C=N str), 1163(C-N-C str.,), 832(C-Cl str., azetidinone).

**$^1$H NMR (DMSO-$d_6$) : δ(ppm)** 2.50(s, 3H, $CH_3$ group

Phenyl ring), 2.7(s, 3H, $CH_3$ group quinoline ring), 4.3(s,1H,CH-Cl azetidinone ring ), 4.2(s, 1H, CH, azetidinone ring), 7-8 (m, 12 H, Ar-H+quinoline ring).

**ANTIMICROBIAL ACTIVITY**

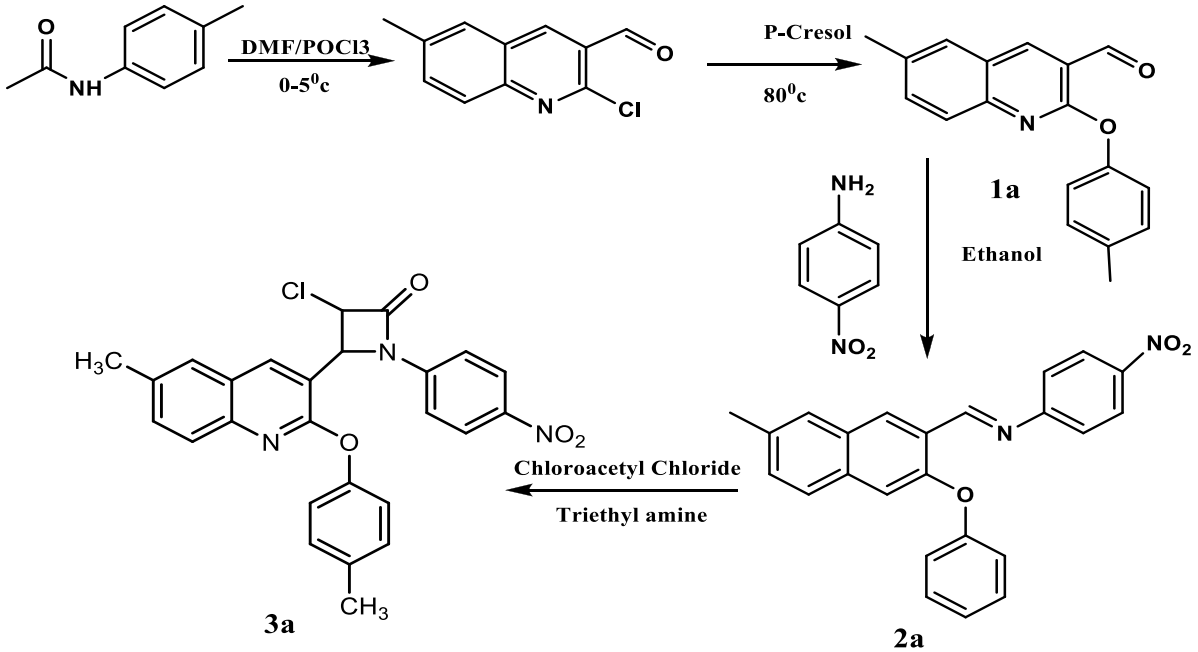
Compound was screened in vitro for their antibacterial activities at concentration of 05mg/mL 10mg/mL. and 15 mg/mL. against the strain of E.coli and S.aureus

**General procedure for antimicrobial screening of the synthesized compound:**

Initially the stock culture of S.aureus and E.coli were revived by inoculating in broth media and grown at $37^0$c for 18 h .The agar plate of Nutrient Agar media were prepared well and sterilised. After the inoculation of bacterial cultural, the discs were dipped in the different concentration of the compound which was prepared in DMSO and placed on the surface of agar plate. All the plates were incubated for $37^0$c for 24 Hrs and diameter of the zone of inhibitation were noted

## RESULTS AND DISCUSSION

Out of several methods possible for the formation of quinoline derivatives, 2-chloro substitutedquinoline-3-carbaldehyde as starting compound was synthesized by Vilsmeier-Haack reaction[7] which upon treatment with p-cresol in potassium carbonate as base afforded 2-(*p*-tolyloxy) substituted quinoline-3-carbaldehyde **(1a). 1a** were reacted with p-nitro aniline gives **2a** which on further reaction with acetyl chloride and trimethyl amine gives azetidinone **(Scheme-1).** The synthesized compounds were recrystallized by a suitable solvent adopting an appropriate method and melting points were reported. The newly synthesized compound was subjected for spectral analysis such as IR, $^1$H NMR. The IR Spectrum shows a characteristics band at 1611 $cm^{-1}$ due to -C=N str.peak at 823 $cm^{-1}$ is due to C-Cl. Formation of azetidinone ring also confirmed by the peak at 1687 $cm^{-1}$ due to carbonyl group. $^1$H NMR spectrum of 3a having molecular formula $\mathbf{C_{26}H_{20}ClN_3O_4}$ shows peaks at **δ**7-8 multiplet for12 hydrogen indicates that proton belongs to aromatic and Quinoline ring proton. Signal at **δ**2.5 and 2.7 shows two $CH_3$ group on phenyl ring and Quinoline ring respectively. Peak at **δ**4.3 showing singlet is due to –C<u>H</u>Cl. Similarly singlet at **δ**4.2 is due to -C<u>H</u> present on azetidinone ring. The spectral data supports and confirmed the structure of synthesized compound. Antimicrobial study confirmed that the compound is pharmacologically active.




**Scheme-1**

**1) For S. aureus**

| Content | Bacterial Culture | Zone of Inhibition |
|---|---|---|
| 05 mg/ml | S. aureus | 15 mm |
| 10 mg/ml | S. aureus | 12 mm |
| 15 mg/ml | S. aureus | 10 mm |

**2) For E. Coli**

| Content | Bacterial Culture | Zone of Inhibition |
|---|---|---|
| 05 mg/ml | E. coli | 25 mm |
| 10 mg/ml | E. coli | 20 mm |
| 15 mg/ml | E. coli | 18 mm |

## CONCLUSION

The final results indicated that Quinoline associated azetidinone ring **(3a)** is more effective antimicrobial agents. Hence there is enough scope for further study in developing such compounds as an innovative approach towards the medicinal sciences.

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**Conflicts of interest:** The authors stated that no conflicts of interest.

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