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# Design, Synthesis, *In silico* Study and Biological Evaluation of 1,8-Naphthyridine Derivatives as Potential Antibacterial Agents

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**ABSTRACT**

The purpose of this article is to synthesize some novel 1,8-Naphthyridine-3-Carboxylic acid derivatives, analyze them, and assess their antibacterial potential. With the help of elemental analysis, IR, NMR, and mass spectrum data, the synthesized derivatives were identified. Derivatives' antibacterial activity was determined using the cup and plate diffusion method. At doses of 50 µg/mL and 100 µg/mL, the substance demonstrated substantial antibacterial potential against the tested strains. To predict the pharmacokinetic properties (ADME) of these derivatives, in silico investigations were also carried out. For the current study, the in silico Swiss ADME assisted results were shown to be suitable for the derivation and synthesis of efficient antibacterial drugs.

**Keywords:** ADMET, 1,8- Naphthyridine, Ciprofloxacin, Antimicrobial.

## INTRODUCTION

Microbes are the primary cause of many different diseases, including viral disease, coughing, amoebic dysentery, typhoid, malaria, and other diseases[1]. In the third world, communicable diseases are the main cause of illness. These illnesses are managed with a variety of medications, both synthetic and natural. Drugs or other chemicals that kill or inhibit the growth of microorganisms are known as antimicrobial agents. They consist of antibiotic, anti-quorum sensitive, antiviral, fungicidal, and anthelmintic substances[2-3]. In recent years, the harm caused by bacterial and fungal infections has greatly increased. Due to the widespread occurrence of antibiotic resistance, infectious diseases brought on by bacterial infections have emerged as a major public health concern. Health issues have developed as a result of antibiotic resistance, and treatment failures have led to mortality and morbidity[4]. Quinolones are effective antibacterial medications used to treat a variety of infectious diseases. The discovery of 1,8-naphthyridine derivative, nalidixic acid in 1962 marked the beginning of the quinolone era. Subsequently, first-generation quinolones were found, including enoxacin, lomefloxacin, and norfloxacin[5]. Because they contain a fluorine atom connected to the C5 on the core ring structure, the 2nd, 3rd and 4th generation

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quinolones are known as fluoroquinolones[6]. The most popular fluoroquinolones include ciprofloxacin, levofloxacin, and moxifloxacin, all of which were created with a wide range of *Gram-positive* and *Gram-negative* bacterial activities, against enterococci, *streptococci* and *staphylococci*[7]. The majority of Enterobacteriaceae bacteria as well as numerous species of bacteria that are multi-resistant to aminoglycoside and beta-lactam antibiotics are also significantly active against them[8-9]. Even though fluoroquinolones are very effective antibacterial agents, fluoroquinolone-resistant bacteria have unavoidably arisen as a result of their widespread use. Antibiotic resistance is a rapidly expanding public concern, and there is a high likelihood that people will get diseases that cannot be treated. The synthesis of new antibiotics has been the subject of extensive study to address this problem. The idea of adding structural alterations to current antibiotics is also being researched. These techniques have ran to the development of several new medications. The second tactic is more popular than the first because it is the most feasible one[10-11]. To stop this rapid rise in drug resistance, new drugs should preferably have chemical features that are distinct from those of currently available agents. The synthesis of compounds that are unique but resemble known physiologically active molecules due to the presence of important structural properties is a crucial part of the search for fresh leads in drug discovery programmes[12-13].

Fluoroquinolone-type medicines have some drawbacks despite their effectiveness against infectious illnesses. In rare circumstances, drug permeability changes in fluoroquinolones have been linked to multidrug resistance[14]. Additionally, quinolone effects like plasmid curability, the encouragement of deteriorations and frontward mutations, and successful outcomes in genotoxicity testing[15-16] imply that quinolones may be mutagenic for bacteria. Moreover, it has been observed that a key concern for fluoroquinolones is the generation of DNA mutations and DNA diminishing in both eukaryotic and prokaryotic cells[17]. Introducing new fluoroquinolones without mutagenesis potential may help resolve these troubling problems. To create effective and non-mutagenic derivatives, we developed a novel series of derivatives in this class based on the information provided above.

Therefore, the necessity to develop new chemotherapeutic drugs will always be critical to prevent the establishment of resistance and, preferably, cut the length of therapy. Due to the well-established pharmacokinetics and pharmacodynamics of these medications, a change to the established medication is an additional option for innovative drug discovery. According to reports, 1,8-naphthyridine analogs exhibit a variety of pharmacological actions, including those of A2A adenosine receptor ligands[18], antimycobacterial[19], A1 adenosine antagonists[20], anti-inflammatory[21], Cannabinoid receptor ligands[22], antibacterial activity[23-24]. Well-known antibiotics that fall within the category of antibacterial chemicals contain the 1,8-naphthyridine nucleus[25], called quinolones (Fig. 1). The quinolones are well-known antibacterial substances that also serve as DNA gyrase inhibitors[26]. The present work's objective was to develop potential naphthyridine derivative by modification at the C3 carboxylic acid end (Fig. 2, Scheme). The antibacterial efficacy of the produced compounds was evaluated *In vitro* against a group of reference bacterial strains, containing *Gram-positive* and *Gram-negative* bacteria. In the current study, we demonstrated the preparation, in-silico ADME study and antibacterial activity of several 1,8-naphthyridine derivatives that may be used to create "hybrid" molecules having antibacterial capabilities.

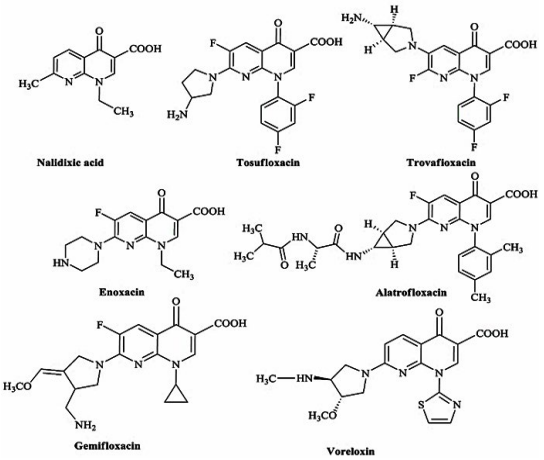



**Fig. 1. Marketed antibiotics having the 1,8-naphthyridine nucleus**

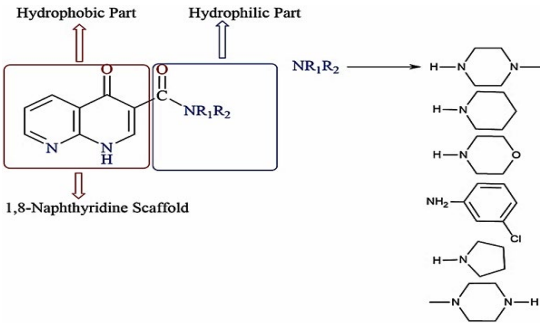
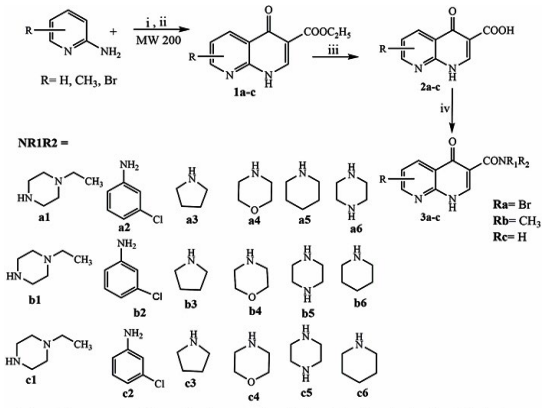



**Fig. 2. Design of Molecules**




**Scheme** Representative Scheme for the preparation of 1,8-naphthyridine-3-cabxylic acid derivatives. Reagents and conditions: (i) Diethyl ethoxy methylene malonate (ii) Diphenyl ether MW 5-20 Min (iii) NaOH, EtOH, 100 °C reflux; 2h (iv)DMF, R-$NH_2$, heat 25-100 °C .

**Scheme**

## MATERIAL AND METHODS

Reagents were often the highest-grade commercial items and were utilized without additional purification. Melting points of the derivatives were measured in open capillaries, using an X4 apparatus and were uncorrected. $^1$H NMR spectra of derivatives were recorded on a Bruker Avance II 400 MHz system. The coupling constants (*J*) for $^1$H were given in Hz and stated as (s) for a singlet, (d) for a doublet, (t) for a triplet, and (m) for a multiplate. All chemical shifts were expressed using the ppm scale. Mass spectra were recorded using Electrospray Ionization (ESI) technique on a Bruker's. All the reactions were supervised via TLC using silica gel GF254 purchased from Himedia and solvent systems methanol 4%, chloroform 96%, whereas spots were visualized using an iodine chamber.

### Synthesis protocol

### Synthesis of malonate (1a-c)

2-Aminopyridine and substituted 2-aminopyridine (6-picoline, for Compounds a, and 5-Bromo 2-aminopyridine for Compounds b) (1m mole) and diethyl ethoxy methylene malonate (1m mole) and phenoxy ether 5 mL was put under microwave oven for 5–20 min at 150–155°C, 250 Watt power, and pressor 35 PSI. After completion, the reaction mixture was cooled at 25°C temperature, and the solid crude producs were saperate out by filtration, washed with petroleum ether, and dried in the air. No further purification was done to get 1,8-naphthyridine-3-carboxylate (compounds 2a-c) Synthesis of (3a1-3a6, 3b1-3b6 and 3c1-3c6).

A mixture of the 1,8-naphthyridine derivative 2a-c (1 mmol) and cyclic amines (10 mmol) like N-ethyl piperazine, 3-Chloro aniline, pyrrolidine, pyrrolidine, morpholine, piperazine and piperidine heated in a tightly closed glass tube at 50-120°C for 24 h, then reaction mixture cooled at room temperature, after cooling ether was added to the mixture to get compounds 3a1-3a6, 3b1-3b6 and 3c1-3c6 as a pure solid.

### Assessment of antimicrobial activity

Biological activity or pharmacological activity in pharmacology refers to the favorable or unfavorable effects of medication on living things. This activity is exhibited by the substance's active ingredient or pharmacophore when medicine is a complex chemical combination, albeit it can be altered by the other ingredients. Pharmacological/biological activity is one of the many characteristics of chemical compounds that is important since it proposes uses for the compounds in medical applications. Chemical substances, however, may exhibit some unfavorable and harmful consequences, which may exclude their usage in medical procedures. In general, dose affects activity.

The test compounds (3a1-3a6, 3b1-3b6 and 3c1-3c6) were evaluated for their antibacterial activity by using cup plate method according to the method prescribed against reference bacterial strains. This traditional approach provides a measurable outcome for the number of antimicrobial drugs required to prevent the growth of particular microorganisms[27-28].

This study is carried out in Petri plates, *S. aureus* from the *Gram-positive* group of bacteria and *E. coli* from the *Gram-negative* group of bacteria for assessment of antibacterial activity were used. To find the drug effect on these bacteria we use the cup and plate method. In which the bacteria first are spread out on a nutrient agar media present in a plate and then in that plate a well-made borer adds drug solution which is made by dissolving drug compounds at different concentrations in DMSO solvent by a micropipette. The inoculation culture plates were cultured for the bacteria at 37° for 24 h and the fungus at 30° for 48 hours. By measure the diameter (mm) of the inhibitory zone that formed around the cylinder after incubation, the antibacterial activity was determined. Fluoroquinolone antibiotic ciprofloxacin was used as the standard drug for antimicrobial activity of the newly synthesized derivatives.

Sample test solutions of (3a1-3a6, 3b1-3b6, and 3c1-3c6) were prepared in dimethyl sulphoxide (DMSO) at 10 times concentrations and comprehensively covering a series of dilution from 50–100 µg $mL^{-1}$. This technique was practical and affordable for pipetting practice. Bacto agar in distilled water was used in preparing microbiological culture media for microbial experiments. The test analogs were mixed in to agar medium that was liquified at 45–50°C, combined, and then put into Petri plates to set. The reference methods for determining the susceptibility of antimicrobial drugs are dilution procedures, which are used to calculate the minimum inhibitory concentrations (MICs) of antibacterial agents. The MIC was determined to be the lowest concentration that prevented the organism's development. Before incubation, the growth rate from the control disc-which serves as the initial inoculum was compared. Spot inoculations of up to two different strains were made on each plate using the inoculating applicator. Putting the petri plate on a dark surface and determining which derivatives have the lowest concentration, preventing visible growth allowed us to calculate the minimum inhibitory concentration (MIC) endpoint after overnight incubation. All the antimicrobial activity experiments were repeated and representative data are presented[29-30].

Each synthetic derivative was diluted to a stock solution of 2000 mg/mL concentration. Concentrations of the synthesized derivatives 1000, 500, and 250 mg/mL were used in the initial screening. The initial screening's active ingredients were further diluted to provide secondary screening concentrations of 100, 50, 25, 12.5 and 6.25 µg/mL. The highest dilution in the investigation that demonstrated a least 99% inhibition zone was chosen as the MIC[31].

### In silico study

### ADMET analysis

Through the use of the Swiss online services Swiss ADMET the generated ligands were screened physiochemically in the lab. Molecular weight, broad nitrogen and oxygen range, hydrogen bond donor/ acceptor, solubility, % human absorbance, wide rotor range and background polar area are some examples of descriptive terms (PSA). To choose drug-like molecules, Lipinski's parameter was also taken into consideration.

The ADME investigation for this experiment was done using the SWISS ADME predictor. This is a free online tool for evaluating the properties of small molecules used in ADMET, including their solubility in water (log S), synthetic accessibility (SA), pharmacokinetics (PKs), permeability to the skin (log Kp), percentage absorption, and drug-likeness. The following parameters were selected for the current investigation: molecular weight, hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), and rotatable bonds (RBs)[32].

## RESULTS AND DISCUSSION

### Chemistry

The reaction procedure employed for synthesis of 1,8-naphthyridine derivatives are shown in Scheme. The initial steps of the synthesis of target compounds (3a1-3a6, 3b1-3b6 and 3c1-3c6) from commercially available 2-Aminopyridine, 5-Bromo-2-Aminopyridine and 6-methyl-2-Aminopyridine were carried out essentially as described in scheme[20,22,33]. The initial 2-aminopyridines are heated with diethylethoxymethylen malonate (EEMM) gives a malonates 1a-c. This crude ester gives naphthyridine-3-carboxylic acids 2a-c by alkaline hydrolysis. The carboxylic acids 2a-c was then treated with several primary and secondary cyclic amines like 3-Chloroaniline, morpholine, piperazine, etc. to get the target compounds (3a1-3a6, 3b1-3b6 and 3c1-3c6).

### Physical and spectral data of compounds

### Compound (1a)

Yield: 63%; m.p. 80-82°C; IR peaks: 3271.45 (N-H), 3076.03-2980.17 (C-H Aryl), 2896.03-2780.17 (C-H methyl) 1676.86 (C=O ester), 1645.44 (C=O ring), 1582.28(C=N), 1552.39 (C=C), 847.71 (C-Br), 795.03, 737.05 (C-H). $^1$H NMR: $\delta$ 1.30 (3H-methyl, t), 4.26 (2H-methylen, q), 7.99-8.19 (2H-Ar, 8.04 (d, *J*=1.7 Hz, Aromatic-H), 8.13 (d, *J*=1.7 Hz, H5), 8.53 (1H-Ar, s). m/z: 296.00, Chem. Formula: $C_{11}H_9BrN_2O_3$, mol. wt: 297.11, Elemnt. Anal:(Calc) C, 44.47; H, 3.05; N, 9.43; O, 16.15 Elemnt. Anal: (Found) C, 44.44; H, 3.00; N, 9.33; O, 16.25.

### Compound (1b)

Yield: 63%; m.p. 124-126°C; IR peaks: 3267.72 (N-H), 3082.39-2979.91 (C-H aryl), 2896.03-

2780.17 (C-H Alkyl), 1676.89 (C=O ring), 1645.12 (C=O ester), 1553.89, (C=N) 1467.92 (C=C), 795.13, 737.79 (C-H aryl). $^1$H NMR: δ 1.29 (3H-Methyl, t), 2.59 (3H-Methyl, s), 4.27 (2H-methylene, q), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.39-8.58 (2H-Ar, 8.44 (d, *J*=7.71 Hz, Aromatic-H), 8.50 (1H-Ar, s). m/z: 232.08, Chem. Formula: $C_{12}H_{12}N_2O_3$, mol. wt: 232.24, Elemnt. Anal: (Calc.) C, 62.07; H, 5.19; N, 12.06; O, 20.65. Elemnt. Anal: (Found) C, 62.16; H, 5.22; N, 12.05; O, 20.63.

**Compound (1c)**

Yield: 97%; m.p. 72-74°C; IR peaks: 3398.21 (N-H), 3071.8 (C-H, Ar) 1740.01 (C=O ester), 1673.9 (C=O keto ring) and 1572.9, 1491.6 (C=N and C=C), 791.0 and 776.61. $^1$H NMR: δ 1.33 (3H-methyl, t,), 4.27 (2H-methylene, q), 7.01 (1H-Ar, d, *J*=7.2, 4.7 Hz, Aromatic-H), 7.82 (1Ar, d, *J*=7.2, 1.9 Hz, Aromatic-H), 8.39 (1H-Ar, d, *J*=4.71, 1.9 Hz, Aromatic-H), 8.52 (1H-Ar, s). m/z: 218.07, Chem. Formula: $C_{11}H_{10}N_2O_3$, mol. wt: 218.21, Elemnt. Anal: (Calc.) C, 60.56; H, 4.61; N, 12.83; O, 22.01. Elemnt. Anal: (Found) C, 60.50; H, 4.52; N, 12.80; O, 22.09.

**Compound (2a)**

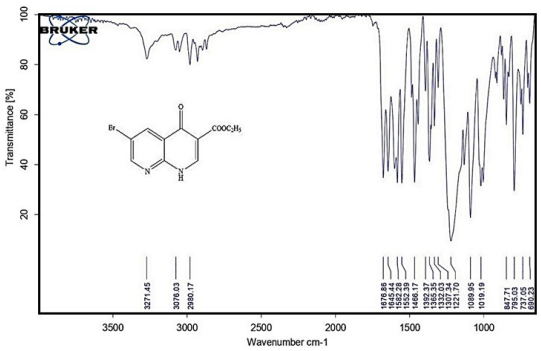
Yield: 63%; m.p. 86-88°C; IR peaks: 3275.40 (N-H), 3069.13-2982.27 (C-H Aryl), 2890.03-2782.17 (C-H methyl), 1672.86 (C=O acid), 1646.44 (C=O ring), 1581.21(C=N), 1550.31 (C=C), 847.71 (C-Br), 797.03, 73778.05 (C-H). $^1$H NMR: δ 7.97-8.19 (2H-Ar, 8.01 (d, *J*=1.70 Hz, Aromatic-H), 8.14 (d, *J*=1.72 Hz, Aromatic-H), 8.50 (1H-Ar, s). 8.53 (1H-Ar, s). m/z: 267.95, Chem. Formula: $C_9H_5BrN_2O_3$, mol. wt: 269.95, Elemnt. Anal: (Calc.) C, 40.18; H, 1.87; N, 10.41; O, 17.84. Elemnt. Anal: (Found) C, 40.16; H, 1.80; 29.71; N, 10.42; O, 17.80.

**Compound (2b)**

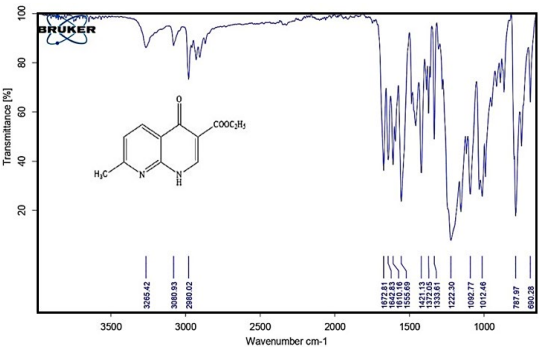
Yield: 92%; m.p. 132-134°C; IR peaks: 3269.72 (N-H), 3080.39-2972.91 (C-H aryl), 1671.89 (C=O ring), 1641.12 (C=O acid), 1551.89, (C=N) 1461.92 (C=C), 791.13, 731.79 (C-H aryl). $^1$H NMR: δ 2.59 (3H-Methyl, s), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.39-8.57 (2H-Ar, 8.45 (d, *J*=7.7 Hz, Aromatic-H), 8.52 (s)). 8.50 (1H-Ar, s). m/z: 204.01, Chem. Formula: $C_{10}H_8N_2O_3$, mol. wt: 204.18, Elemnt. Anal: (Calc.) C, 58.80; H, 3.94; N, 13.70; O, 23.50. Elemnt. Anal: (Found) C, 58.81; H, 3.91; N, 13.71; O, 23.48.

**Compound (2c)**

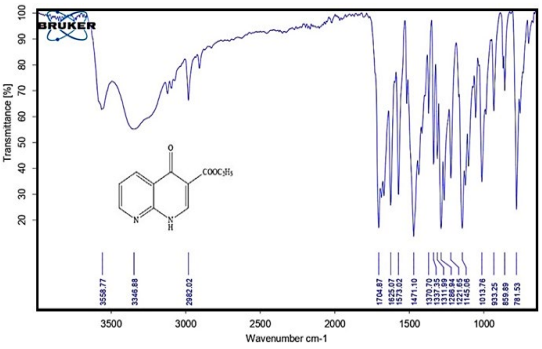
Yield: 73%; mp 120-122°C; IR peaks: 3268.88 (N-H), 3080-3000 (C-H Aryl), 2980.16, 2898.76 (C-H alkyl), 1675.28 (C=O acid) 1645.32 (C=O ring), 1486.32 (C=N) 1470.07 (C=C), 792.01 (C-H Aryl). $^1$H NMR: δ 7.12 (1H-Ar, d, *J*=7.21, 4.69 Hz, Aromatic-H), 7.82 (1H-Ar, d, *J*=7.21, 1.9 Hz, Aromatic-H), 8.38 (1H-Ar, d, *J*=4.71, 1.9 Hz, Aromatic-H), 8.51 (1H-Ar, s), 10.52 (1H, s). m/z: 190.01, Chem. Formula: $C_9H_6N_2O_3$, mol. wt: 190.15, Elemnt. Anal: (Calc.) C, 56.84; H, 3.20; N, 14.70; O, 25.20, Elemnt. Anal: (Found) C, 56.80; H, 3.19; N, 14.70; O, 25.18.



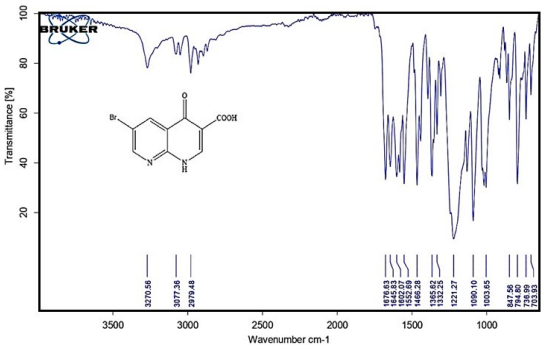

**IR spectra of compound 1A**



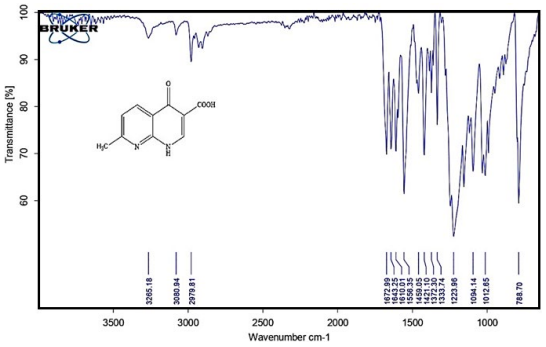

**IR spectra of compound 1B**



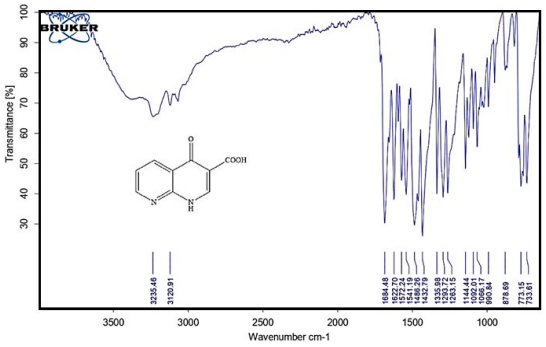

**IR spectra of compound 1C**




**IR spectra of compound 2C**




**IR spectra of compound 2B**




**IR spectra of compound 2C**

**Physical and spectral data of compounds 3a1-a6, 3b1-b6, 3c1-c6.**

**Compound (3a1)**

Yield: 82%; m.p. 197-199°C; IR peaks: 3270.56 (N-H), 3071.36-2979.48 (C-H Aryl), 2890.03-2782.17 (C-H Alkyl), 1676.63 (C=O ring), 1645.83 (C=O), 1552.69 (C=N), 1466.28 (C=C), 847.56 (C-Br), 794.80, 736.99 (C-H Aryl). $^1$H NMR: δ 1.31 (3H-Methyl, t), 2.36 (2H-Methylene, q), 2.61 (4H, m, *J*=13.2, 6.7, 2.8 Hz, Piperazine), 3.56 (4H, m, *J*=14.1, 6.7, 2.8 Hz, Piperazine), 8.07-8.19 (2H-Ar, 8.10 (d, *J*=1.7 Hz, Aromatic-H), 8.13 (d, *J*=1.73 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 364.05, Chem. Formula: $C_{15}H_{17}BrN_4O_2$, mol. wt: 365.23, Elemnt. Anal: (Calc.) C, 49.33; H, 4.69; Br, 21.88; N, 15.34; O, 8.77, Elemnt. Anal: (Found) C, 49.24; H, 4.61; N, 15.34; O, 8.70.

**Compound (3a2)**

Yield: 79%; m.p. 138-140°C; IR peaks: 3271.21 (N-H), 3071.18-3050.54 (C-H Aryl), 1671.07 (C=O ring), 1645.39 (C=O), 1582.26 (C=N), 1552.75 (C=C), 847.56 (C-Br), 795.03 (C-Cl), 736.87, 703.99 (C-H Aryl). $^1$H NMR: δ 7.15 (1H-Ar, d, *J*=8.11, 1.7 Hz, Aromatic-H), 7.34 (1H-Ar, d, *J*=8.0, 0.5 Hz, Aromatic-H), 7.58 (1H-Ar, d, *J*=8.2, 1.6 Hz, Aromatic-H), 7.77 (1H-Ar, d, *J*=1.7, 0.5 Hz, Aromatic-H), 8.07-8.20 (2H-Ar, 8.11 (d, *J*=1.7 Hz, Aromatic-H), 8.13 (d, *J*=1.7 Hz, Aromatic-H), 8.49 (1H-Ar, s). m/z: 376.96, Chem. Formula: $C_{15}H_9BrClN_3O_2$, mol. wt: 378.61, Elemnt. Anal: (Calc.) C, 47.59; H, 2.41; Br, 21.12; Cl, 9.36; N, 11.11; O, 8.46. Elemnt. Anal: (Found) C, 47.52; H, 2.39; N, 11.11; O, 8.30.

**Compound (3a3)**

Yield: 60%; m.p. 130-132°C; IR peaks: 3271.65 (N-H), 3078.28-3050.65 (C-H Aryl), 1677.09 (C=O ring), 1645.44 (C=O), 1582.51 (C=N), 1553.09 (C=C), 847.65 (C-Br), 795.39, 736.90 (C-H Aryl). $^1$H NMR: δ 2.00 (4H-pyrrolidine, m, *J*=13.1, 7.4, 3.9, 3.5 Hz, pyrrolidine), 3.43 (4H-pyrrolidine, m, *J*=15.0, 7.3, 4.01 Hz, pyrrolidine), 8.06-8.19 (2H-Ar, 8.11 (d, *J*=1.70 Hz, Aromatic-H), 8.13 (d, *J*=1.71 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 321.01, Chem. Formula: $C_{13}H_{12}BrN_3O_2$, mol. wt: 322.16, Elemnt. Anal: (Calc.) C, 48.47; H, 3.76; Br, 24.81; N, 13.05; O, 9.92. Elemnt. Anal: (Found) C, 48.36; H, 3.75; N, 13.14; O, 9.91.

**Compound (3a4)**

Yield: 75%; m.p. 145-147°C; IR peaks: 3271.40 (N-H), 3077.03-3050.48 (C-H Aryl), 1676.98 (C=O ring), 1645.26 (C=O), 1582.48 (C=N), 1552.75 (C=C), 847.52 (C-Br), 794.90, 736.79 (C-H Aryl). $^1$H NMR: δ 3.53-3.69 (8H-Morpholine, 3.61 (m, *J*=15.2, 6.7, 2.8 Hz, Morpholine), 3.62 (m, *J*=12.0, 6.7, 2.8 Hz, Morpholine)), 8.05-8.19 (2H-Ar, d, *J*=1.7 Hz, Aromatic-H), 8.13 (d, *J*=1.71 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 337.01, Chem. Formula: $C_{13}H_{12}BrN_3O_3$, mol. wt: 338.16, Elemnt. Anal: (Calc.) C, 46.17; H, 3.58; Br, 23.63; N, 12.42; O, 14.19. Elemnt. Anal: (Found) C, 46.14; H, 3.54; N, 12.47; O, 14.15.

**Compound (3a5)**

Yield: 84%; m.p. 156-158°C; IR peaks: 3271.04 (N-H), 3077.20-3050.51 (C-H Aryl), 1677.08 (C=O ring), 1645.35 (C=O), 1582.33 (C=N), 1553.14 (C=C), 847.68 (C-Br), 794.76, 736.91 (C-H Aryl). $^1$H NMR: δ 1.38-1.67 (6H-piperazine, m,), 3.34 (4H, m), 8.06-8.18 (2H-Ar, d, *J*=1.71 Hz, Aromatic-H), 8.13 (d, *J*=1.73 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 335.03, Chem. Formula: $C_{14}H_{14}BrN_3O_2$. mol. wt: 336.19. Elemnt. Anal: (Calc.) C, 50.03; H, 4.21; Br, 23.76; N, 12.51; O, 9.53. Elemnt. Anal: (Found) C, 49.97; H, 4.21; N, 12.55; O, 9.51.

**Compound (3a6)**

Yield: 70%; m.p. 150-152°C; IR peaks: 3268.57 (N-H), 3049.88-2980.38 (C-H Aryl), 1676.79 (C=O ring), 1643.92 (C=O), 1604.36 (C=N), 1554.49 (C=C), 847.80 (C-Br), 794.62, 737.20 (C-H Aryl). $^1$H NMR: δ 2.80 (4H- piperidine, m), 3.61 (4H-piperidine, m), 8.07-8.19 (2H-Ar, 8.12 (d, *J*=1.71 Hz, Aromatic-H), 8.13 (d, *J*=1.72 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 336.02, Chem. Formula: $C_{13}H_{13}BrN_4O_2$. mol. wt: 337.18. Elemnt. Anal: (Calc.) C, 46.30; H, 3.87; Br, 23.69; N, 16.59; O, 9.49. Elemnt. Anal: (Found) C, 46.29; H, 3.84; N, 16.58; O, 9.44.

**Compound (3b1)**

Yield: 63%; m.p. 146-148°C; IR peaks: 3265.18 (N-H), 3080.94-2979.81 (C-H Aryl), 2890.03-2782.17 (C-H Alkyl), 1672.99 (C=O ring), 1643.50 (C=O), 1610.01 (C=N), 1556.35 (C=C), 788.70 (C-H Aryl). $^1$H NMR: δ 0.96 (3H-methyl, t), 2.45 (2H-methylene, q), 2.6 (4H-Piperazine, m), 3.55 (4H-Piperazine, m), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.38-8.51 (2H-Ar, 8.43 (1H-Ar, s), 8.44 (d, *J*=7.73 Hz, Aromatic-H). m/z: 300.16, Chem. Formula: $C_{16}H_{20}N_4O_2$, mol. wt: 300.36, Elemnt. Anal: (Calc.) C, 63.97; H, 6.72; N, 18.61; O, 10.66. Elemnt. Anal: (Calc.) (Found) C, 63.90; H, 6.68; N, 18.62; O, 10.60.

**Compound (3b2)**

Yield: 74%; m.p. 156-158°C; IR peaks: 3264.92 (N-H), 3081.26-2980.13 (C-H Ar), 2929.69-2904.61(C-H methyl), 1673.10 (C=O ring), 1642.88 (C=O), 1609.89 (C=N), 1555.95 (C=C), 788.87 (C-Cl). $^1$H NMR: δ 2.59 (3H-methyl, s), 7.06-7.21 (2H-Ar, 7.10 (d, *J*=7.71 Hz, Aromatic-H), 7.15 (d, *J*=8.1 Hz, Aromatic-H), 7.34 (1H-Ar, d, *J*=8.1 Hz, Aromatic-H), 7.58 (1H-Ar, d, *J*=8.2 Hz, Aromatic-H), 7.77 (1H-Ar, d, *J*=1.7, 0.5 Hz, Aromatic-H), 8.39-8.53 (2H-Ar, 8.44 (d, *J*=7.7 Hz, Aromatic-H), 8.48 (1H-Ar, s). m/z: 313.06, Chem. Formula: $C_{16}H_{12}ClN_3O_2$, mol. wt: 313.74, Elemnt. Anal: (Calc.) C, 61.26; H, 3.88; Cl, 11.29; N, 13.40; O, 10.19. Elemnt. Anal: (Found) C, 61.21; H, 3.82; N, 13.31; O, 10.19.

**Compound (3b3)**

Yield: 63%; m.p. 141-143°C; IR peaks: 3266.12 (N-H), 3081.30-2979.78 (C-H Ar), 2929.69-2894.61(C-H methyl), 1672.95 (C=O ring), 1642.95 (C=O), 1610.15 (C=N), 1558.00 (C=C), $^1$H NMR: δ 2.04 (4H-pyrrolidine, m), 2.58 (3H-methyl, s), 3.45 (4H-mrthylene, m), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.37-8.51 (2H-Ar, d), 8.42 (1H-Ar, s), 8.45 (1H-Ar, d, *J*=7.71 Hz, Aromatic-H). m/z: 257.12, Chem. Formula: $C_{14}H_{15}N_3O_2$, mol. wt: 257.29, Elemnt. Anal: (Calc.) C, 65.33; H, 5.87; N, 16.32; O, 12.45. Elemnt. Anal: (Found) C, 65.27; H, 5.81; N, 16.26; O, 12.37.

**Compound (3b4)**

Yield: 72%; m.p. 130-132°C; IR peaks: 3258.67 (N-H), 3081.06-2979.49 (C-H Aryl), 2904.07-2894.61(C-H Alkyl), 1673.23 (C=O ring), 1642.61 (C=O), 1609.95 (C=N), 1555.91 (C=C). $^1$H NMR: δ 2.59 (3H-mrthyl, s), 3.52-3.69 (4H-Morpholine, m), 2.62 (4H-Morpholine, m), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.38-8.51 (2H-Ar, 8.43 (s), 8.45 (1H-Ar, s). m/z: 273.11, Chem. Formula: $C_{14}H_{15}N_3O_3$, MWt: 273.29, Elemnt. Anal: (Calc.) C, 61.53; H, 5.54; N, 15.39; O, 17.56. Elemnt. Anal: (Found) C, 61.47; H, 5.49; N, 15.31; O, 17.51.

**Compound (3b5)**

Yield: 56%; m.p. 151-153°C; IR peaks: 3258.67 (N-H), 3081.06-2979.49 (C-H Aryl), 2904.07-2894.61(C-H Alkyl), 1673.23 (C=O ring), 1642.61 (C=O), 1609.95 (C=N), 1555.91 (C=C). $^1$H NMR: δ 2.59 (3H-methyl, s), 2.79 (4H-piperazine, m), 3.61 (4H, m), 7.12 (1H-Ar, d, *J*=7.7 Hz, Aromatic-H), 8.37-8.51 (2H-Ar, d, *J*=7.73 Hz, Aromatic-H), 8.45 (1H-Ar, s). m/z: 271.12, Chem. Formula: $C_{14}H_{16}N_4O_2$, mol. wt: 271.30, Elemnt. Anal: (Calc.) C, 61.98; H, 5.57; N, 20.65; O, 11.79. Elemnt. Anal: (Found) C, 62.02; H, 5.60; N, 20.60; O, 11.82.

**Compound (3b6)**

Yield: 65%; m.p. 153-155°C; IR peaks: 3258.19 (N-H), 3080.87-2979.46 (C-H Aryl), 2904.23-2894.61(C-H Alkyl), 1673.19 (C=O ring),

1642.94 (C=O), 1610.06 (C=N), 1555.85 (C=C). $^1$H NMR: δ 1.35-1.67 (6H-Piperidine, m, *J*=12.1, 6.6, 2.7 Hz, Piperidine), 1.58 (3H-Methyl, s), 3.34 (4H- Piperidine, d, *J*=14.9, 6.81, 2.8 Hz, Piperidine), 8.01-8.19 (2H-Ar, d, *J*=1.70 Hz, Aromatic-H), 8.12 (d, *J*=1.7 Hz, Aromatic-H), 8.43 (1H-Ar, s). m/z: 271.13, Chem. Formula: $C_{15}H_{17}N_3O_2$, mol. wt: 271.32, Elemnt. Anal: (Calc.) C, 66.41; H, 6.33; N, 15.50; O, 11.78. Elemnt. Anal: (Calc) C, 66.38; H, 6.30; N, 15.50; O, 11.81.

**Compound (3c1)**

Yield: 65%; m.p. 145-147°C; IR peaks: 3235.46(N-H), 3120-3000 (C-H Aryl), 1664.48, 1622.70 (C=O), 1486.26 (C=N) 1486.32 (C=C), 773.15, 733.61 (C-H Aryl). $^1$H NMR: δ 0.96 (3H-methyl, t), 2.45 (2H-piperazine, q, *J*=6.01 Hz, piperazine), 2.61 (4H-Piperazine, d), 3.56 (4H-Piperazine, d), 7.11 (1H-Ar, d, *J*=7.82, 4.7 Hz, Aromatic-H), 7.81 (1H-Ar, d, *J*=7.81 Hz, Aromatic-H), 8.34-8.47 (2H-Ar, d, *J*=4.71, 1.9 Hz, Aromatic-H), 8.42 (1H-Ar, s). m/z: 286.14, Chem. Formula: $C_{15}H_{18}N_4O_2$, mol. wt: 286.34, Elemnt. Anal: (Calc.) C, 62.91; H, 6.34; N, 19.58; O, 11.19. Elemnt. Anal: (Found) C, 62.87; H, 6.31; N, 19.54; O, 11.15.

**Compound (3c2)**

Yield: 70%; m.p. 146-148°C; IR peaks: 3236.11 (N-H), 3118.19-3067.31 (C-H Aryl), 1664.55, 1622.46 (C=O), 1480.00 (C=N) 1431.19 (C=C), 866.59 (C-Cl), 772.80, 733.18 (C-H Aryl). $^1$H NMR: δ 7.03 (1H-Ar, d, *J*=7.81 Hz, Aromatic-H), 7.15 (1H-Ar, d, *J*=8.1Hz, Aromatic-H), 7.34 (1H-Ar, d, *J*=8.11 Hz, Aromatic-H), 7.58 (1H-Ar, d, *J*=8.2 Hz, Aromatic-H), 7.72-7.88 (2H-Ar, d, *J*=1.7 Hz, Aromatic-H), 7.81 (1H-Ar, d, *J*=7.8 Hz, Aromatic-H), 8.34-8.53 (2H-Ar, d, *J*=4.7 Hz, Aromatic-H), 8.48 (1H-Ar, s). m/z: 299.05, Chem. Formula: $C_{15}H_{10}ClN_3O_2$, mol. wt: 299.71, Elemnt. Anal: (Calc.) C, 60.11; H, 3.36; N, 14.02; O, 10.68. Elemnt. Anal: (Found) C, 59.99; H, 3.31; N, 13.98; O, 10.62.

**Compound (3c3)**

Yield: 69%; m.p. 149-151°C; IR peaks: 3236.71 (N-H), 3124.96-3088.74 (C-H Aryl), 1685.84, 1624.35 (C=O), 1496.17 (C=N) 1431.19 (C=C), 788.73, 735.15 (C-H Aryl). $^1$H NMR: δ 2.00 (4H-Pyrrolidine, t), 3.43 (4H- Pyrrolidine, t), 7.01 (1H-Ar, d, *J*=7.81, 4.7 Hz, Aromatic-H), 7.81 (1H-Ar, d, *J*=7.82, 1.9 Hz, Aromatic-H), 8.34-8.47 (2H-Ar, d, *J*=4.71, 1.81 Hz, Aromatic-H), 8.40 (1H-Ar, s). m/z: 243.10 (100.0%), Chem. Formula: $C_{13}H_{13}N_3O_2$, mol. wt: 243.27, Elemnt. Anal: (Calc.) C, 64.20; H, 5.38; N, 17.27; O, 13.15. Elemnt. Anal: (Found) C, 64.15; H, 5.35; N, 17.21; O, 13.10.

**Compound (3c4)**

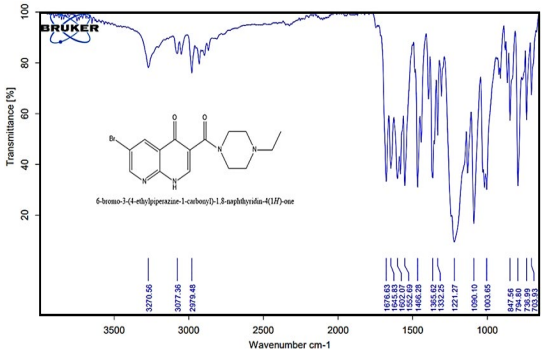
Yield: 73%; m.p. 140-142°C; IR peaks: 3236.20 (N-H), 3123.96-3069.11 (C-H Aryl), 1686.68, 1623.67 (C=O), 1487.77 (C=N) 1434.01 (C=C), 774.42, 734.93 (C-H Aryl). $^1$H NMR: δ 3.52-3.68 (4H-Morpholine, m), 2.42-2.46 (4H-Morpholine, m), 7.00 (1H-Ar, d, *J*=7.83, 4.7 Hz, Aromatic-H), 7.81 (1H-Ar, d, *J*=7.80 Hz, Aromatic-H), 8.34-8.45 (2H-Ar, d, *J*=4.71 Hz, Aromatic-H), 8.45 (1H-Ar, s). m/z: 259.10, Chem. Formula: $C_{13}H_{13}N_3O_3$, mol. wt: 259.27, Elemnt. Anal: (Calc.) C, 59.98; H, 5.05; N, 16.21; O, 18.51. Elemnt. Anal: (Found) C, 59.89; H, 4.99; N, 16.17; O, 18.50.

**Compound (3c5)**

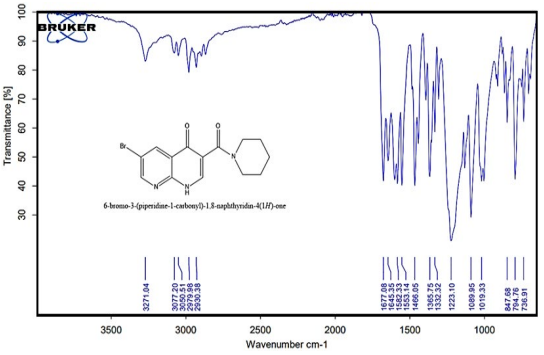
Yield: 70%; m.p. 145-147°C; IR peaks: 3256.67 (N-H), 3080.06-2977.49 (C-H Aryl), 2906.07-2895.61(C-H Alkyl), 1671.23 (C=O ring), 1640.61 (C=O), 1608.95 (C=N), 1554.91 (C=C). $^1$H NMR: δ 2.79 (4H-Piperazine, m), 3.62 (4H-Piperazine, m), 7.00 (1H-Ar, d, *J*=7.83 Hz, Aromatic-H), 7.82 (1H-Ar, d, *J*=7.87 Hz, Aromatic-H), 8.34-8.47 (2H-Ar, d, *J* = 4.7 Hz, Aromatic-H), 8.40 (1H-Ar, s). m/z: 258.11, Chem. Formula: $C_{13}H_{14}N_4O_2$, mol. wt: 258.28, Elemnt. Anal: (Calc.) C, 59.96; H, 5.45; N, 21.70; O, 12.39. Elemnt Analysis (Found) C, 59.91; H, 5.44; N, 20.90; O, 12.40.

**Compound (3c6)**

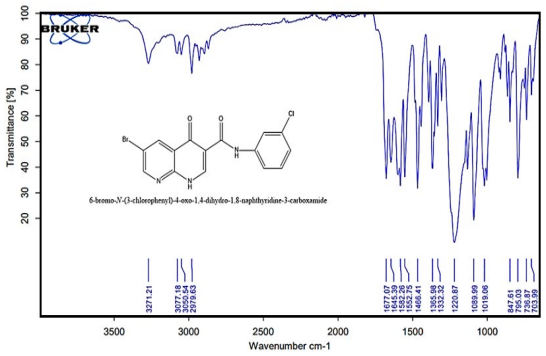
Yield: 67%; m.p. 145°C; IR peaks: 3237.42(N-H), 3125.55-3069.15 (C-H Aryl), 1684.84, 1623.68(C=O), 1470.07 (C=C). 1486.47 (C=N) 1433.87 (C=C), 773.16, 733.82 (C-H Aryl). $^1$H NMR: δ 1.44 (2H-piperidine, m), 1.66 (4H- piperidine, m), 3.34 (4H- piperidine, d), 7.10 (1H-Ar, d, *J*=7.82 Hz, Aromatic-H), 7.81 (1H-Ar, d, *J*=7.81 Hz, Aromatic-H), 8.34-8.47 (2H-Ar, d, *J*=4.7, Aromatic-H), 8.42 (1H-Ar, s). m/z: 257.12, Chem. Formula: $C_{14}H_{15}N_3O_2$, mol. wt: 258.20, Elemnt. Anal: (Calc.) C, 65.30; H, 5.86; N, 16.31; O, 12.41. Elemnt. Anal: (Found) C, 65.29; H, 5.81; N, 16.30; O, 12.42.



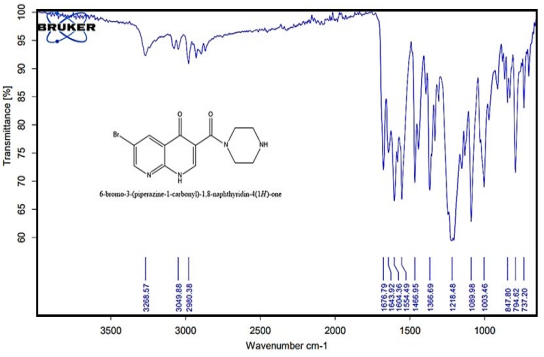

**IR Spectra of compound 3A1**



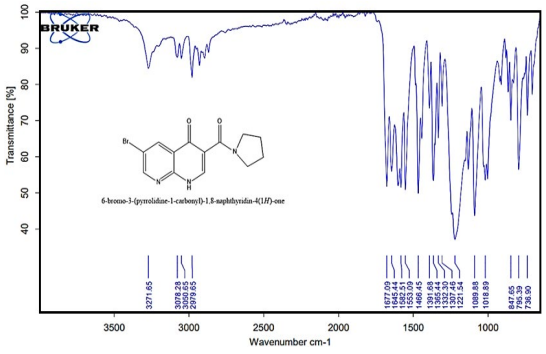

**IR Spectra of compound 3A5**




**IR Spectra of compound 3A2**




**IR Spectra of compound 3A6**

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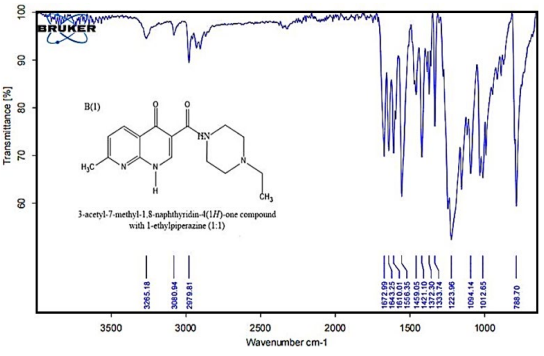
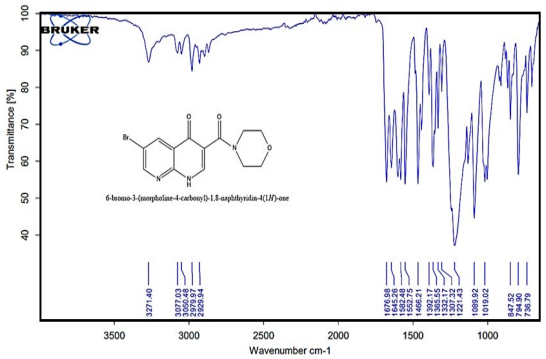
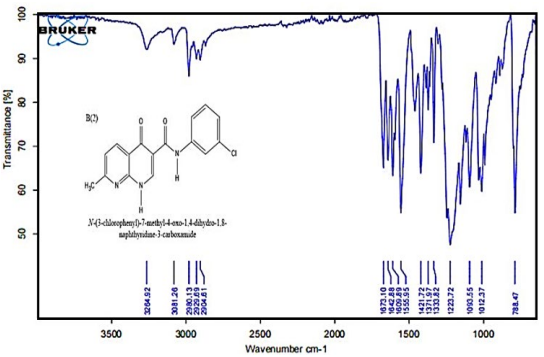



**IR Spectra of compound 3B1**




**IR Spectra of compound 3A4**

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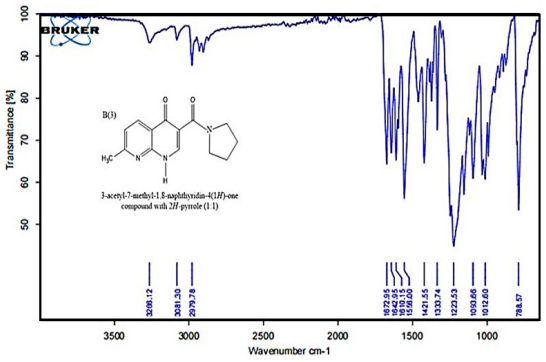


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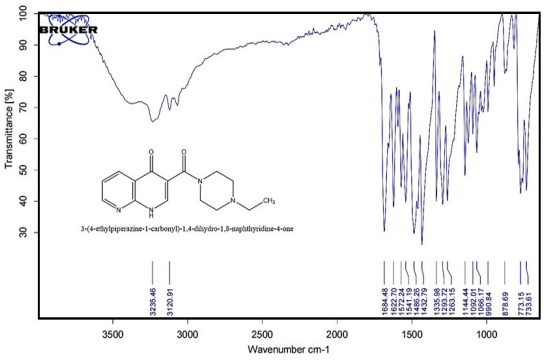


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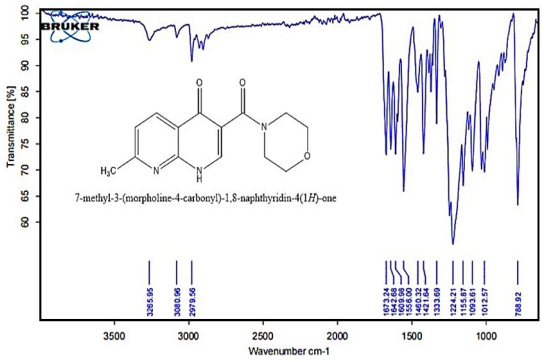


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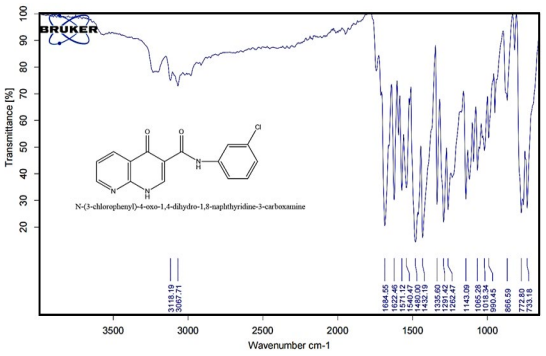
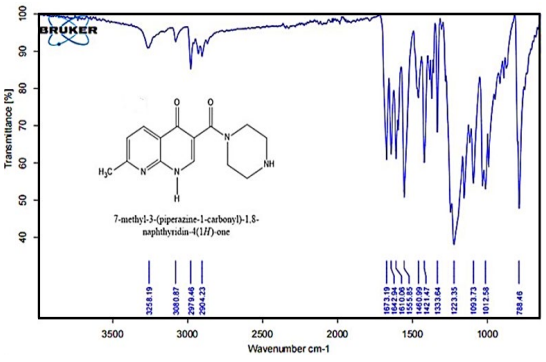



**IR Spectra of compound 3C2**

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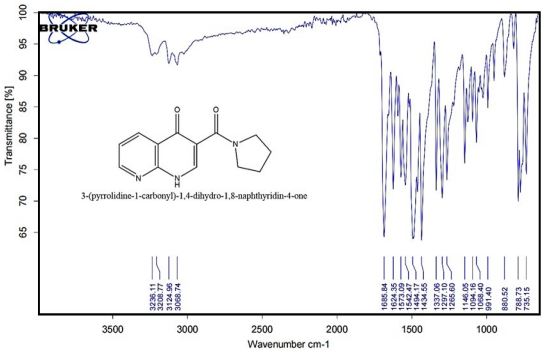
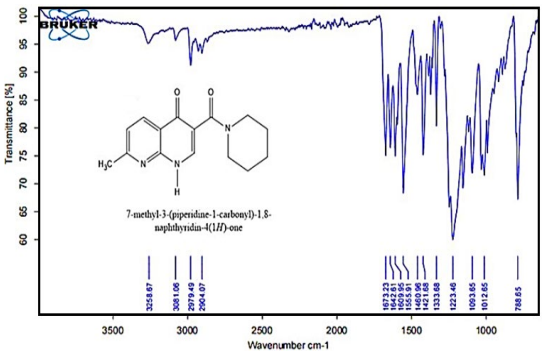
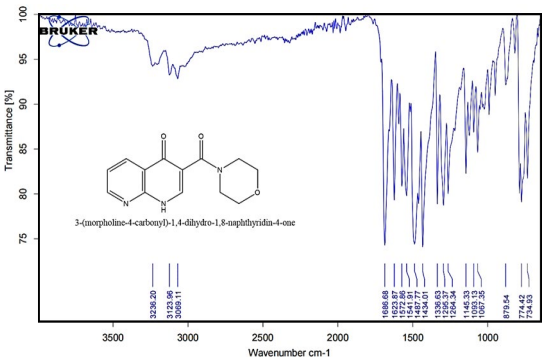


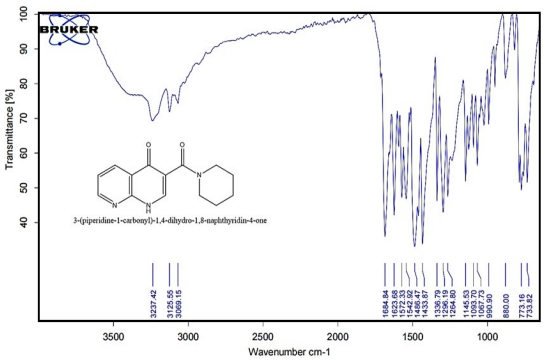

**IR Spectra of compound 3C3**



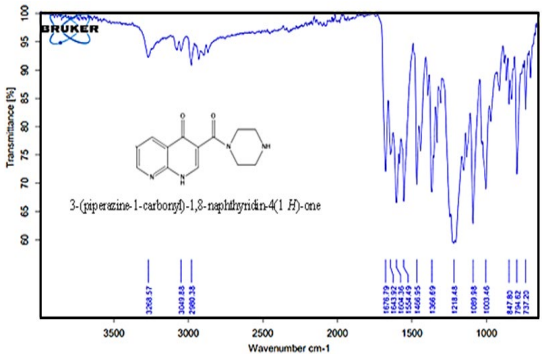

**IR Spectra of compound 3B6**




**IR Spectra of compound 3C4**




**IR Spectra of compound 3C5**




**IR Spectra of compound 3C6**

## Biological evaluation

### Antimicrobial assay

An agar diffusion well technique was used to test the antibacterial activity of each of the recently synthesized derivatives (3a1-3a6, 3b1-3b6, and 3c1-3c6)[34-35]. The zone of inhibition was determined by a serial dilution method[36-37]. The newly synthesized compounds 3a1-3a6, 3b1-3b6, and 3c1-3c6 were found to have the greatest impact and the broadest spectrum of antibacterial activity against all tested reference bacterial strains. The observed inhibition zone (IZ) is shown in Fig. 3, 4, and Table 2. Derivatives were less effective against *Gram-positive* bacteria, while good to very strong bactericidal action toward *Gram-negative* bacteria. Minimum doses that prevented these microbes from growing ranged from 50 to 100 µg/mL Table 1.

### ADMET analysis and Target prediction

The In silico research findings unmistakably demonstrated that the compounds have drug-like candidate homes without straying from the aforementioned drug-likeness standards. Intriguingly, leading drug similarity recommendations and the data get from the Swiss ADME prediction value for Log P, molar potency, and overall pole position within Molecule One were in great agreement. The halogen spin-off with high lipophilicity is anxiously expecting the opening of reasonable GI absorption, despite the compounds' good hydrophilic-lipophilic stability and equivalent anticipated bioavailability. We also computed the Topological polar surface area (TPSA), which is another crucial element associated with medication bioavailability. Environment (TPSA), is one of the other important factors affecting a drug's bioavailability. Therefore, it is believed that compounds that are passively absorbed and have a TPSA>100 and 40 have limited oral bioavailability. Table 3 lists the outcomes from the Swiss search engine ADME. The radar charts and the chart for hard-boiled eggs (Fig. 5, 6) provided evidence in the evaluation that derivatives were in the permitted range of the classical capsules.

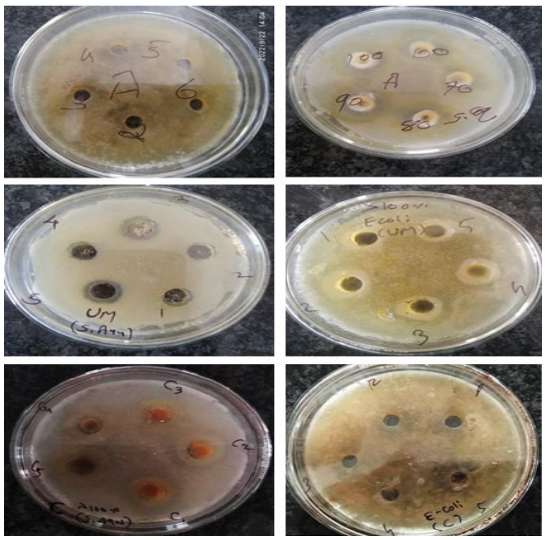


**Fig. 3. ZOI for 3a1-3a6, 3b1-3b6 and 3c1-3c6 against bacterial strain *S. aureus* & *E. coli* NCTC 5933**

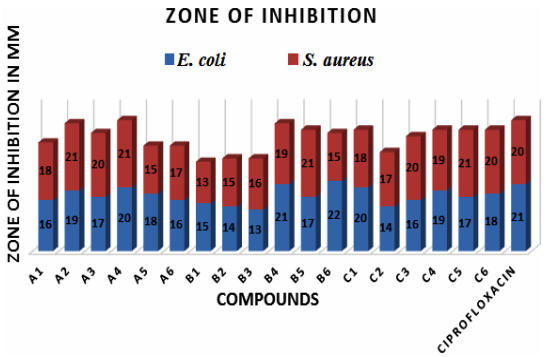



**Fig. 4. Bar Graph for ZOI of Antibacterial activity**
**In silico study**

**Table 1: MIC In *µg*/mL against bacterial strain *E. coli* and *S. aureus***

| Compounds | MIC in µg/mL *E. coli* | *S. aureus* |
|---|---|---|
| A1 | >50 | >70 |
| A2 | >70 | >60 |
| A3 | >60 | >80 |
| A4 | >100 | >70 |
| A5 | >80 | >50 |
| A6 | >50 | 100 |
| B1 | >30 | >40 |
| B2 | >60 | >50 |
| B3 | >40 | >20 |
| B4 | >20 | >30 |
| B5 | >40 | >40 |
| B6 | >30 | >50 |
| C1 | >70 | >80 |
| C2 | >60 | >70 |
| C3 | >80 | >70 |
| C4 | >70 | >80 |
| C5 | >80 | >60 |
| C6 | >80 | >60 |
| Ciprofloxacin | >20 | >30 |

**Table 2: ZOI In mm against bacterial strain *E. coli* and *S. aureus***

| Compound | ZOI in mm *E. coli* | *S. sureus* |
|---|---|---|
| A1 | 16 | 18 |
| A2 | 19 | 21 |
| A3 | 17 | 20 |
| A4 | 20 | 21 |
| A5 | 18 | 15 |
| A6 | 16 | 17 |
| B1 | 15 | 13 |
| B2 | 14 | 15 |
| B3 | 13 | 16 |
| B4 | 21 | 19 |
| B5 | 17 | 21 |
| B6 | 22 | 15 |
| C1 | 20 | 18 |
| C2 | 14 | 17 |
| C3 | 16 | 20 |
| C4 | 19 | 19 |
| C5 | 17 | 21 |
| C6 | 18 | 20 |
| Ciprofloxacin | 21 | 20 |

**Table 3: Drug likeness and ADME parameters**

| Compound | HBA | HBD | MR | TPSA | Log P | GI absorption | BBB permeant | Lipinski violations | Bioavailability score | PAINS alerts | Synthetic accessibility |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A1 | 4 | 1 | 95.8 | 69.3 | 2.69 | High | No | 0 | 0.55 | 0 | 2.38 |
| A2 | 3 | 2 | 89.29 | 74.85 | 2.1 | High | Yes | 0 | 0.55 | 0 | 2.14 |
| A3 | 3 | 1 | 79.38 | 66.06 | 2.1 | High | Yes | 0 | 0.55 | 0 | 1.98 |
| A4 | 4 | 1 | 80.46 | 75.29 | 2.22 | High | No | 0 | 0.55 | 0 | 2.15 |
| A5 | 3 | 1 | 84.18 | 66.06 | 2.44 | High | Yes | 0 | 0.55 | 0 | 2.08 |
| A6 | 4 | 2 | 86.09 | 78.09 | 1.98 | High | No | 0 | 0.55 | 0 | 2.17 |
| B1 | 5 | 2 | 93.81 | 72.46 | 2.93 | High | No | 0 | 0.55 | 0 | 3.02 |
| B2 | 3 | 3 | 87.29 | 78.01 | -0.01 | High | Yes | 0 | 0.55 | 0 | 2.81 |
| B3 | 4 | 2 | 77.38 | 69.22 | 2.48 | High | No | 0 | 0.55 | 0 | 2.6 |
| B4 | 5 | 2 | 78.47 | 78.45 | 2.42 | High | No | 0 | 0.55 | 0 | 2.82 |
| B5 | 5 | 3 | 84.1 | 81.25 | 2.03 | High | No | 0 | 0.55 | 0 | 2.81 |
| B6 | 4 | 2 | 82.19 | 69.22 | 2.64 | High | No | 0 | 0.55 | 0 | 2.69 |
| C1 | 5 | 2 | 88.84 | 72.46 | 2.69 | High | No | 0 | 0.55 | 0 | 2.87 |
| C2 | 3 | 3 | 82.33 | 78.01 | 2.35 | High | No | 0 | 0.55 | 0 | 2.67 |
| C3 | 4 | 2 | 72.42 | 69.22 | 1.81 | High | No | 0 | 0.55 | 0 | 2.43 |
| C4 | 5 | 2 | 73.5 | 78.45 | 1.71 | High | No | 0 | 0.55 | 0 | 2.68 |
| C5 | 5 | 3 | 79.13 | 81.25 | 1.52 | High | No | 0 | 0.55 | 0 | 2.65 |
| C6 | 4 | 2 | 77.22 | 69.22 | 2.07 | High | No | 0 | 0.55 | 0 | 2.53 |
| CFL | 5 | 2 | 95.25 | 74.57 | 2.24 | High | No | 0 | 0.55 | 0 | 2.51 |

CFL-Ciprofloxacin, HBA-Hydrogen bond acceptors, HBA-Hydrogen bond donors, TPSA-Topological polar surface area

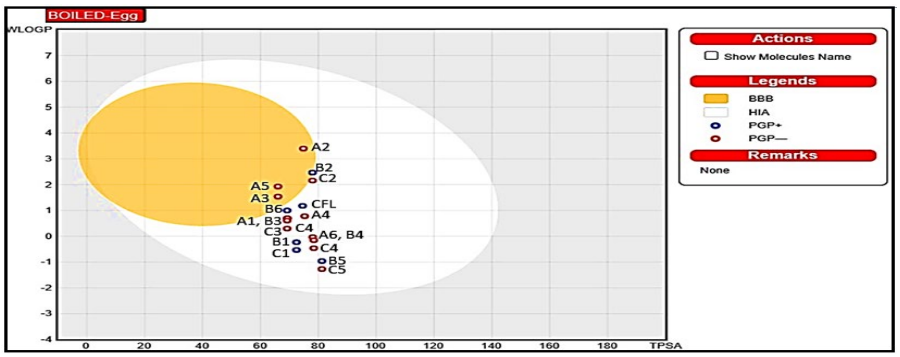



**Fig. 5. ADME properties of derivatives and ciprofloxacin by Graphical picture (BOILED-Egg) (Predict GI Absorption and BBB Penetration of small molecules)**

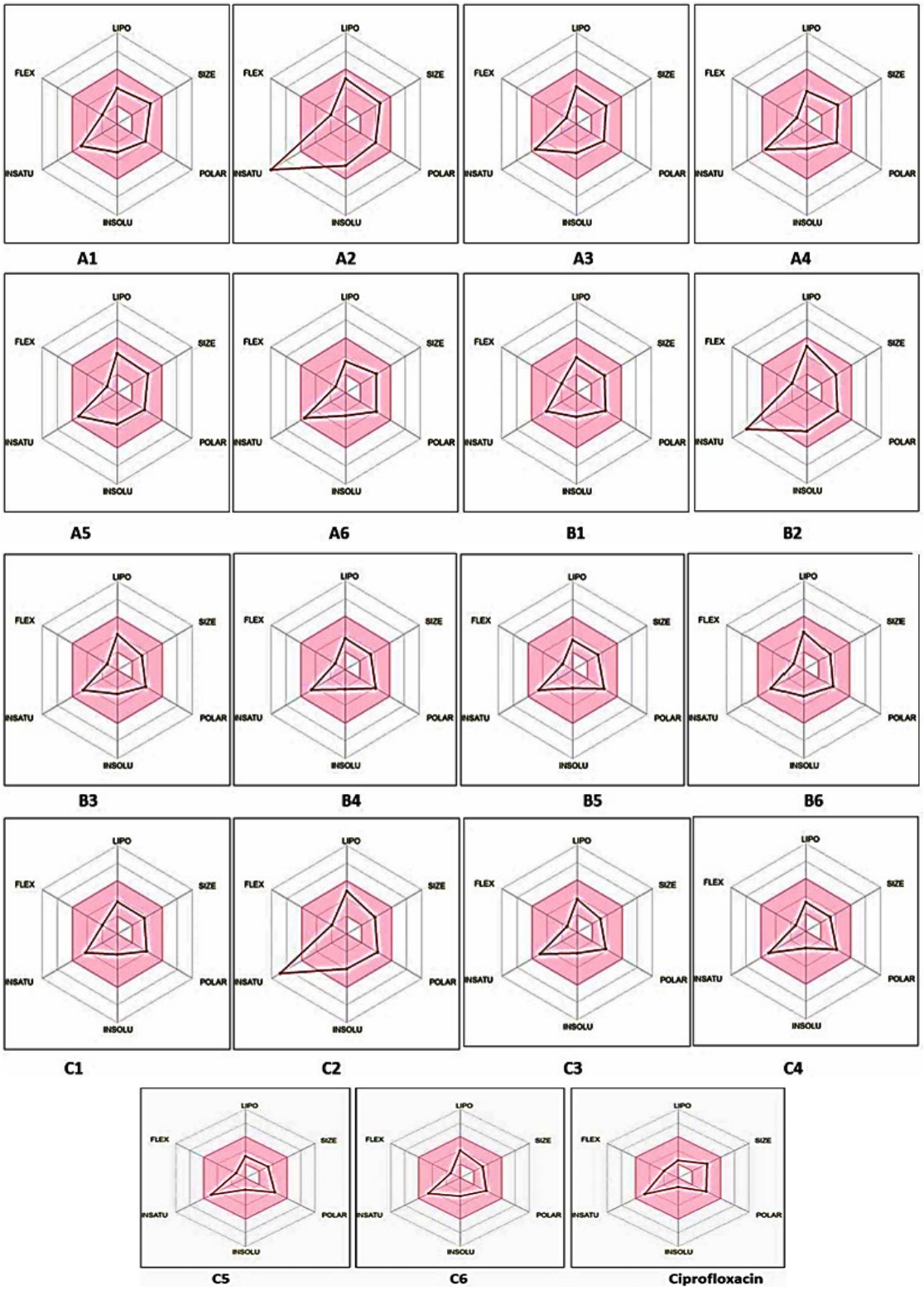



**Fig. 6. Bioavailability Radar graph of derivatives and reference drug (pink area reflects the allowed values of drug-likeness properties of a small molecule)**

**Structure Activity Relationship (SAR)**

According to this research, 1,8 naphthyridine is a potential scaffold for antibacterial activity. The pyridine ring must be fused with an aromatic ring. The isotactic replacement of nitrogen atom for carbon atoms at positions 2, 5, 6, and 8 leads to the relation of antibacterial activity. The substituted position of 5, 6, 7 & 8 of the annulated ring produces good effects. Ex. The amino group at 5 positions increases the activity. Aryl substitution at the 1-position is also consistent with antibacterial activity. 1,8-positions also lead to produce active compounds. Increase the joining of a molecule the drug molecule antibacterial biological activity is an increase.

## CONCLUSION

With differently substituted amines, several 1,8-Naphthyridine derivatives were synthesized. The yield of the synthetic chemicals was discovered to be between 50 and 85%. Based on their physical and spectral data, all the newly synthesized substances were described. Analysis was done on the representative compounds' FT-IR, $^1$H NMR, and mass spectral data. Antimicrobial tests were conducted on synthetic substances. All of the compounds that were synthesized had an antibacterial activity that was between average and good. The 1,8-Naphthyridine ring has been substituted in the current investigation with a variety of amines at C3, and produced compounds have been tested for antibacterial activity. Synthesized substances showed inhibition of *E. coli* growth. In a similar vein, the derivative inhibited *S. aureus*.

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**Conflict of Interest:** None declared.

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