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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL QUINOLINE DERIVATIVES

Shiwangini Solanki[1]; Tiwari Archana[2]; Dr. Dubey P.K.[3]
Swami Vivekanand College of Pharmacy, Indore

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Abstract:- This study presents the synthesis and antimicrobial evaluation of a series of novel quinoline derivatives. The structures of the synthesized derivatives were confirmed through spectroscopic techniques, including IR spectrometry. The antimicrobial activities of these quinoline derivatives were assessed against a panel of Gram-positive and Gram-negative bacterial strains disc diffusion method. Several compounds exhibited significant antimicrobial activity, with minimum inhibitory concentrations (MICs) comparable to standard antibiotics. The structure-activity relationship (SAR) analysis revealed that substitutions at specific positions on the quinoline ring significantly influenced the antimicrobial efficacy. These findings suggest that the synthesized quinoline derivatives hold potential as promising candidates for the development of new antimicrobial agents.

Keywords: Quinoline derivatives, antimicrobial activity, structure-activity relationship, novel compounds, spectroscopy.

1. Introduction:- Quinolones are a class of synthetic antibiotics that have revolutionized the treatment of various bacterial infections since their discovery in the 1960s. Over the decades, extensive research and development have led to the synthesis of numerous derivatives with improved efficacy, spectrum of activity, and pharmacokinetic properties. These derivatives have played a crucial role in combating bacterial resistance and expanding the therapeutic options for

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infectious diseases. Quinolone derivatives share a common core structure, typically consisting of a bicyclic ring system with various substituents. These structural modifications have resulted in a wide range of compounds with diverse mechanisms of action and enhanced potency against both Gram-positive and Gram-negative bacteria. Moreover, their favorable pharmacokinetic profile has made them valuable agents for treating a multitude of infections, including urinary tract infections, respiratory tract infections, and skin and soft tissue infections**.** The antimicrobial evaluation of quinolone derivatives is essential for assessing their efficacy against a wide range of bacterial pathogens. These evaluations involve several key steps, including in vitro susceptibility testing, determination of minimum inhibitory concentration (MIC), and in vivo efficacy studies. In vitro susceptibility testing is typically performed using standardized methods such as the broth microdilution or agar diffusion techniques. These tests evaluate the ability of quinolone derivatives to inhibit the growth of bacterial strains collected from clinical isolates or reference strains. The MIC, defined as the lowest concentration of the compound that inhibits visible bacterial growth, is the primary outcome measure in these assays.

2. Synthesis of 2-phenylquinoline-4-carboxylicacid(I)

Isatin (1 mmol) was dissolved in a mixture of ethanol and water, followed by the addition of KOH (5 mmol), and the resulting solution was stirred at room temperature for 20-30 minutes. Afterward, concentrated HCl was added to acidify the mixture, and acetophenone (1 mmol) was introduced. The resulting mixture underwent reflux at 80°C for 12-13 hours, leading to the formation of a precipitate. Post-reaction, the precipitate was isolated via filtration, washed with water, and subjected to recrystallization from ethanol, affording the desired product as a white solid with a yield of 77% and a melting point of 212-214°C.

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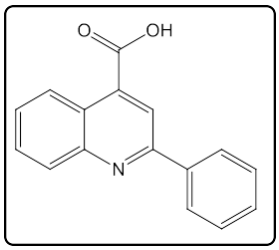

General procedure for the synthesis of target compounds(II-VI)

At 0°C, SOCl2 (20 mmol) was introduced to 2-phenylquinoline-4-carboxylic acid (I) (2.0 mmol), followed by refluxing the resulting mixture at 80°C for 4 hours, yielding the corresponding acid chloride upon evaporation. Subsequently, the solid product, 2-phenylquinoline-4-carboxylic acid chloride (1.1 mmol), was dissolved in THF, and respective amines (1.6 mmol) and NaH (1.3 mmol) were added at 0°C. The resulting mixture was stirred at room temperature for 1 hour. Upon completion of the reaction, the mixture was quenched by addition into ice-water, followed by extraction with ethyl acetate. The combined organic layers were then dried over Na2SO4, evaporated, and the crude product was purified via column chromatography, resulting in the isolation of the target compounds (II-VI).

Table No.1: Physical data of the compounds(II-VI)

Compound No.	Colour	Yield(%)	M.P.(°C)
II	Pale yellow	72	194-196
III	Yellow	71	164-166
IV	White	70	216-218
V	White	78	222-224
VI	Brown	78	160-162

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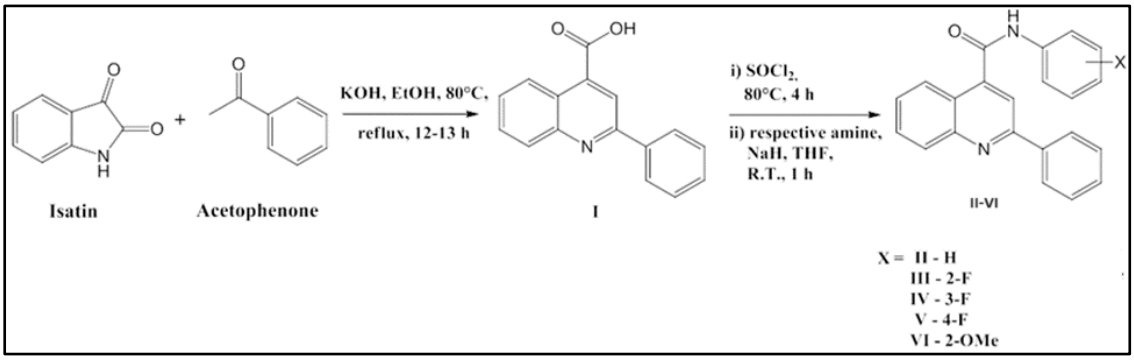
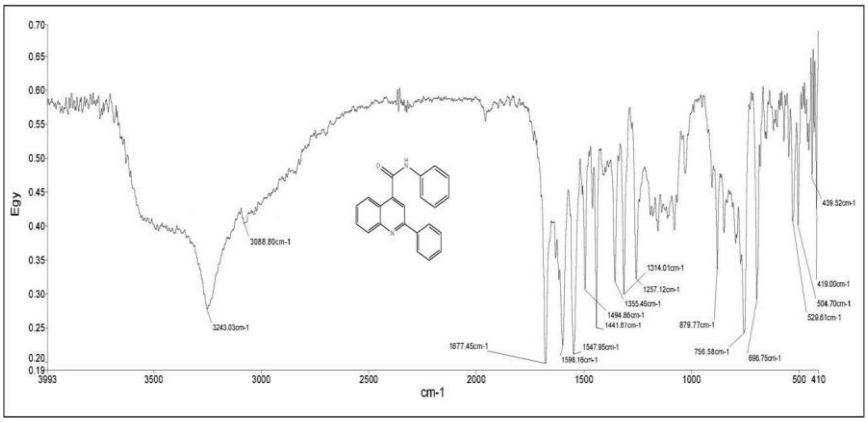
3. SYNTHETIC SCHEME:-



4. SPECTRAL ANALYSIS

IR spectrum of the compound(II)



IR(KBr,ν_{max}/cm^{-1}):3243(-NHofCONH),3089(Ar-H),1677(C=O),1598(C=N), 1548(C=C),1495(C-N).

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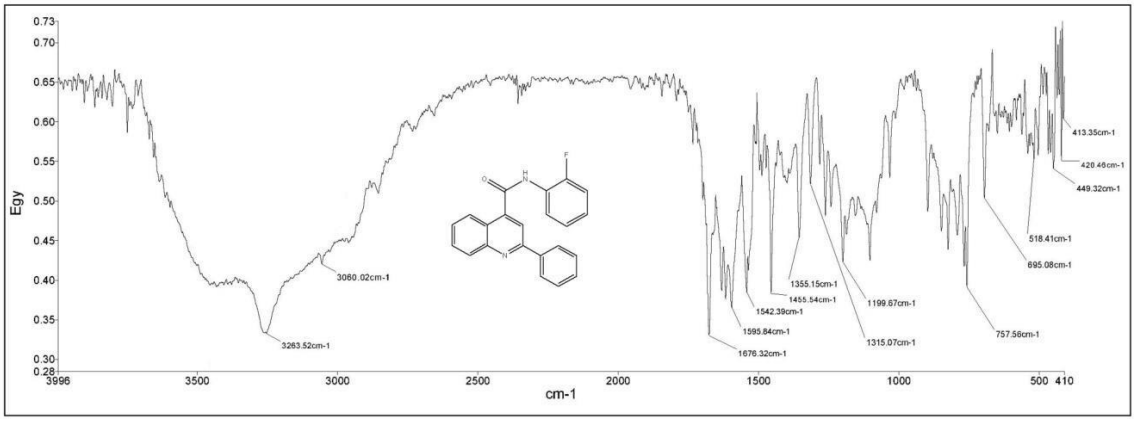
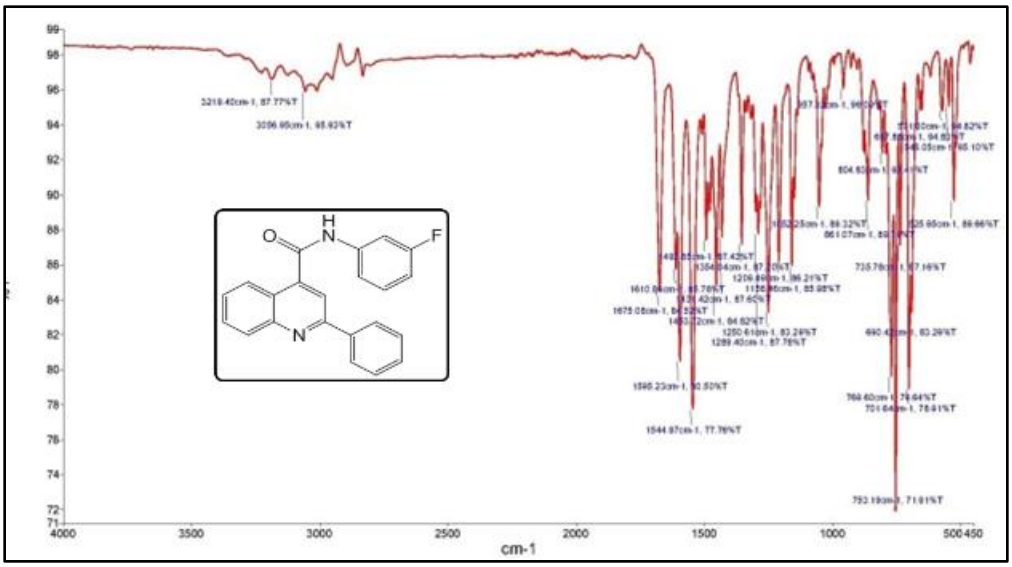
IR spectrum of the compound (III)



IR(KBr,ν_{max}/cm^{-1}):3263(-NHofCONH),3060(Ar-H),1676(C=O),1596(C=N), 1542(C=C),1456(C-N),1199(C-F).

IR spectrum of the compound (IV)



IR(KBr,ν_{max}/cm^{-1}):3184(-NHofCONH),3055(Ar-H),1685(C=O),1614(C=N),1549(C=C),1493(C-N),1128(C-F).

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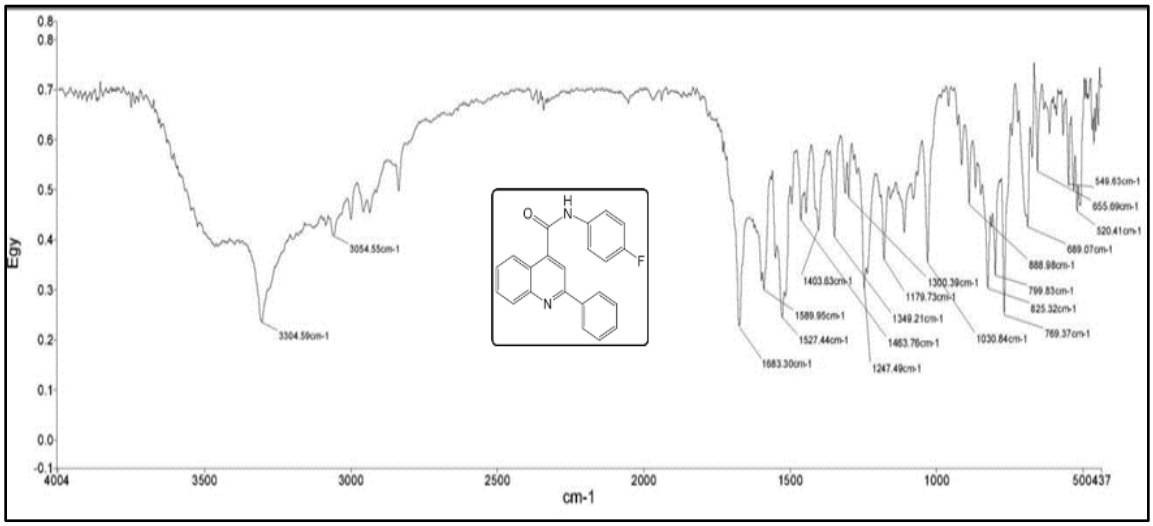
IR spectrum of the compound (V)



IR(KBr,ν_{max}/cm^{-1}):3242(-NHofCONH),3093(Ar-H),1679(C=O),1616(C=N), 1553 (C=C),1508(C-N),1152(C-F).

5. PHARMACOLOGICAL SCREENING

In-vitro antibacterial activity of title compound (II-VI)

The antimicrobial activity of all compounds was meticulously assessed against a panel of bacterial pathogens, including two Gram-positive strains—Staphylococcus aureus (NCIM 2079) and Bacillus subtilis (NCIM 2250) as well as two Gram-negative strains Escherichia coli (NCIM 2109) and Pseudomonas aeruginosa (NCIM 2036). To establish a comparative reference, well-known antibacterial drugs such as ciprofloxacin, gatifloxacin, and streptomycin were employed as standards. This evaluation, conducted in collaboration with the microbiology department of Maharaja Ranjeet Singh College in Indore, Madhya Pradesh, India, utilized nutrient agar (Hi-media) as the microbial growth medium. By leveraging this standardized approach, the in-vitro antibacterial activity of the synthesized compounds was rigorously assessed, providing valuable insights into their potential as novel antibacterial agents.

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Antibacterial Activity

In assessing the antibacterial activity against S. aureus, B. subtilis (gram-positive), E. coli, and P. aeruginosa (gram-negative), the compounds underwent evaluation in a nutrient broth environment. The disk diffusion method was employed to gauge their efficacy in inhibiting bacterial growth, a widely recognized technique for antibacterial assessment. To prepare the bacterial inoculums, the culture medium utilized was nutrient broth, while nutrient agar served as the screening medium. Solutions of the test compounds were meticulously formulated by dissolving 10 mg of each in Dimethylsulfoxide (10 ml; analytical grade). Additionally, reference standards for both gram-positive and gram-negative bacteria Ciprofloxacin, Gatifloxacin, and Streptomycin (10 microgram/disk) were prepared and moistened with DMSO. By adhering to this standardized protocol, the antibacterial potential of the test compounds was systematically evaluated, providing crucial insights into their effectiveness against a spectrum of bacterial pathogens.

Table No.-2 Composition of Nutrient agar medium

S. No.	Ingredients	Quantity
1.	Peptone	10.0 gm
2.	Beef extract	10.5 gm
3.	NaCl	5.0 gm
4.	Distilled water	1000ml
5.	pH	7.4±0.2

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Table No.-3 Zone of Inhibition

ZONE OF INHIBITION (mm)					
S. No.	**Compound**	***B. subtilis***	***S.aureus***	***E. coli***	***P. aeroginosa***
1	**II**	19.17	18.63	18.51	18.45
2	**III**	21.68	19.65	24.97	13.66
3	**IV**	25.46	28.17	32.56	26.63
4	**V**	23.42	20.21	29.16	19.19
5	**VI**	25.80	20.38	27.56	17.52
6	**IV(f)**	25.97	23.87	26.34	14.76
7	**Ciprofloxacin**	24.06	19.56	27.19	14.40
8	**Amoxicillin**	34.72	27.22	35.12	30.64
9	**Moxifloxacin**	26.88	18.65	26.77	16.35

Result & Discussion

After successfully synthesizing a range of novel N-substituted-2-phenylquinoline-4-carboxamide derivatives (II-VI) with promising yields, their structural integrity was further corroborated through spectral characterization using infrared (IR) spectroscopy. Armed with this diverse set of N-substituted-2-phenylquinoline-4-carboxamide derivatives, the focus shifted towards identifying potent agents against both breast cancer and bacterial infections. To this end, the final compounds (II-VI) underwent rigorous evaluation for their in-vitro anti-breast cancer efficacy against breast adenocarcinoma cells using the MTT assay, a widely employed colorimetric method. Additionally, their potential as antibacterial agents was assessed through in-vitro antibacterial assays, targeting both Gram-positive and Gram-negative bacteria, employing the agar well diffusion technique. This comprehensive approach not only underscores the versatility of the synthesized compounds but also highlights their potential in combating both cancerous and bacterial threats, paving the way for further investigations into their therapeutic applications.

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