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SYNTHESIS & SCHIFF BASES OF QUINOLINE DERIVATIVES FOR ANTIMICROBIAL ACTIVITIES

Niggula Praveen Kumar[1]*, J. E. Rachel Nivedita[1], V. Arun Reddy[2], Togari Manoj Kumar[3] and Gatadi Srikanth[4]

[1]Department of Pharmacy, Bharat Institute of Technology-Pharmacy, Mangalpally, Ibrahimpatnam, R. R. Dist, TS, India.

[2,3,4]Department of Pharmacy, Bharat School of Pharmacy, Mangalpally, Ibrahimpatnam, R. R. Dist, TS, India.

***Corresponding Author: Niggula Praveen Kumar**

Department of Pharmacy, Bharat Institute of Technology-Pharmacy, Mangalpally, Ibrahimpatnam, R. R. Dist, TS, India.

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ABSTRACT

Quinoline derivatives are a class of compounds with a wide range of biological activities, including antimicrobial properties. The development of novel antimicrobial agents is essential to combat the growing threat of antibiotic resistance. In this study, we synthesized a series of quinoline derivatives and their Schiff bases, and evaluated their antimicrobial activities against a panel of Gram-positive and Gram-negative bacteria, as well as fungi. The quinoline derivatives were synthesized through the reaction of quinoline-2-carbaldehyde with various amines, including aniline, p-anisidine, and o-phenylenediamine. The resulting Schiff bases were characterized by FTIR, NMR, and mass spectroscopy. The antimicrobial activities of the synthesized compounds were evaluated using the disc diffusion method and minimum inhibitory concentration (MIC) assays. The results show that the quinoline derivatives and their Schiff bases exhibited significant antimicrobial activity against all tested microorganisms, with MIC values ranging from 0.5 to 64 µg/mL. The Schiff bases showed improved antimicrobial activity compared to their parent quinoline derivatives, with some exhibiting MIC values as low as 0.5 µg/mL. The most active compounds were found to be those containing the p-anisidine and o-phenylenediamine moieties. The results of this study demonstrate the potential of quinoline derivatives and their Schiff bases as novel antimicrobial agents. The synthesized compounds may be useful in the development of new antibiotics to combat the growing threat of antibiotic resistance. Further studies are needed to investigate the mechanism of action of these compounds and to evaluate their safety and efficacy in animal models.

KEYWORDS: Schff bases, Quinoline derivatives, QSAR, Antimicrobial drugs.

INTRODUCTION

Antimicrobial drugs have caused a dramatic change not only of the treatment of infectious diseases but of a fate of mankind. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in reality, emerging and re-emerging infectious diseases have left us facing a countercharge from infections. Infections with drug resistant organisms remain an important problem in clinical practice that is difficult to solve. If an improper antimicrobial agent happens to be chosen for the treatment of infection with drug- resistant microorganisms, the therapy may not achieve beneficial effect, and moreover, may lead to a worse prognosis. In addition, in a situation where multidrug-resistant organisms have spread widely, there may be quite a limited choice of agents for antimicrobial therapy. At present, fewer brand new antimicrobial agents are coming onto the market. Considering this situation together with the increasing awareness of drug safety, we are now facing a situation of severely limited options among antimicrobial agents.

The history of antimicrobial agents, and thereafter describes resistant organisms that have emerged in response to antimicrobial agents and discusses practical clues to prevent resistant microorganisms.

MATERIALS AND METHODS

Reagents and chemicals used

Aniline derivatives (aniline,4-chloroaniline,4-bromo aniline, 4- methoxyaniline, 3-methoxy aniline, 4-nitroaniline, 3-nitroaniline, 4-methylaniline, Phosphorous oxychloride, Dimethyl formamide, isoniazid, glacial acetic acid, Zn dust, methanol, 70% acetic acid.

All the reagents and chemicals were procured from Sigma Aldrich High media and Lobachem. All the

compounds procured were purified and dried, whenever necessary before use, following standard methods.

Apparatus used

Beakers, test tubes, glass rods, magnetic stirrer, thermometer, round bottom flask, reflux condenser, iodine flasks, watch glass, conical flasks, burette and pipettes.

Analytical work

- Melting point was determined by using melting point apparatus MR-VIS, visual melting range apparatus, LABINDIA and uncorrected.
- Reactions were monitored by thin layer chromatography (TLC) on a pre- coated silica gel G plated using Iodine vapor as visualizing agent.
- UV spectra were recorded on JASCO V-530 UV-VIS spectrometer
- IR spectra were recorded on JASCO FTIR-420.
- NMR spectra were recorded on Bruker AVANCE III 500MHz NMR spectrometer at spectra labs
- Mass spectra were recorded on JEOL GCMATE II GC-MS spectrometer

METHODOLOGY

Step 1: Synthesis of acetanilides

(Aniline, 4-bromoaniline, 4-chloroaniline, 3-methoxyaniline, 4- methoxyaniline,3-nitroaniline, 4-nitroaniline, 4-methylaniline were converted into their corresponding acetanilides)

A mixture of aniline and substituted anilines 0.11mol and Zn dust were added to acetic acid(30ml) in a 100ml round bottom flask, and heated over a gentle flame using water condenser. Heating was continued for about 2hrs. The reaction mixture was then carefully poured in cold water(100ml) in 250ml beaker with cooling and vigorous stirring. The shining crystals of their corresponding acetanilides were separated slowly. After 15mins the corresponding acetanilide crystals were collected by filtration. The solid crystals were washed over Buchner funnel with water and product was dried (yield 10g). It was crystallized in boiling water (if necessary charcoal may be used).

Acetanilide-90%yield,3-Methoxy acetanilide-95yield, 4-Methoxy acetanilide 90%yield, 4-chloroacetanilide-90%yield,4-bromoacetanilide-90% yield, 4-methyl acetanilide-80% yield,3-nitroacetanilide 50% yield, 4-nitroacetanilide 60% yield.

Step 2: Synthesis of 2-chloro-3-formyl quinolones[1]

The compounds were prepared from acetanilide and corresponding substituted acetanilides under Vilsmeier - Haack reagent ($POCl_3$/DMF).

To a solution of acetanilide and corresponding substituted acetanilides (5 mmol) in dry DMF (15mmol) at 0-5^{o} C with stirring $POCl_3$ (60mmol) was added dropwise. The reaction mixture was stirred at 80-90^{o} C for time ranging between 4-16hr. This mixture was poured in crushed ice, stirred for 5 mins where corresponding 2-chloro-3-formyl quinolines formed was filtered, washed well with water and dried. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile.

2-chloro-3-formyl quinoline-70% yield,6-bromo- 2-chloro-3-formyl quinoline -80% yield,6-chloro 2-chloro-3-formyl quinolone-80% yield,7- methoxy-2-chloro-3-formyl quinolone-90% yield, 6-methoxy-2-chloro-3-formyl quinolone-90% yield,7-nitro-2-chloro-3-formyl quinolone-40% yield, 6-nitro-2- chloro-3-formyl quinolone-60% yield, 4-methyl-2-chloro-3-formyl quinolone- 60% yield.

Step 3: Synthesis of 3-formyl 2(H)quinolones[1]

A suspension of 2-chloro-3-formyl quinoline and substituted 2- chloro-3-formyl quinolines (1mmol) was dissolved in 70% CH_3COOH(10ml) and heated under reflux for 4-6hrs. The completion of reaction was checked by TLC. Upon cooling the reaction mixture, corresponding 3-formyl-2- quinolones formed were precipitated, filtered, washed well with water, dried and purified by recrystallization from DMF.

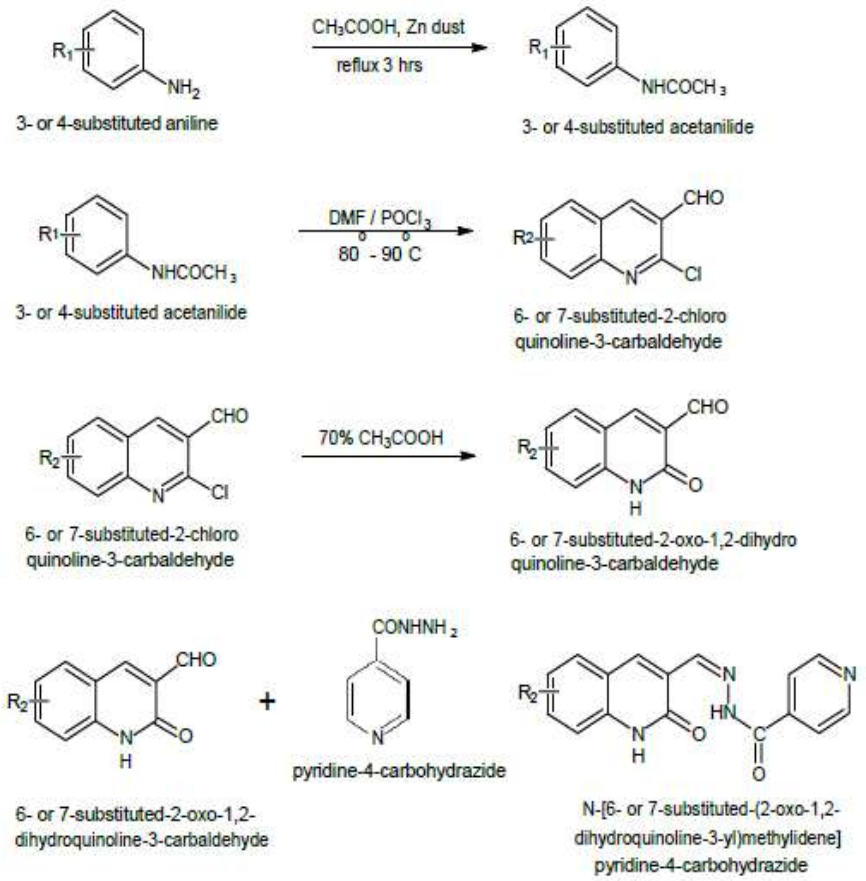
3-formyl-2-quinolones-70%,6-bromo-3formyl-2-quinolones -80% yield, 6-bromo-3formyl-2-quinolones -80% yield, 6-chloro-3formyl-2-quinolones -80% yield, 7-methoxy-3formyl-2-quinolones -80% yield, 6-methoxy-3formyl-2-quinolones -80% yield,7-nitro-3formyl-2-quinolones -60% yield, 6-nitro-3formyl-2-quinolones -60% yield, 6-methyl-3formyl-2-quinolones -80% yield.

Step 4: Synthesis of Schiff base from 3-formyl-2-quinolones[33]

Equimolar quantities of 3-formyl-2-quinolone and substituted 3-formyl-2- quinolones (0.01mol) and isoniazid(0.01mol) was dissolved in ethanol and 2-4 drops conc. sulphuric acid was added and refluxed for 2-4hrs. It was then cooled and poured into crushed ice. Schiff bases of corresponding 3-formyl-2- quinolones thus obtained were filtered, washed with water and recrystallised fromethanol.

3-formyl-2-quinolone Schiff base -77% yield,6-bromo-3-formyl-2- quinolone Schiff base -80% yield, 6-chloro-3-formyl-2-quinolone Schiff base - 90% yield,7-methoxy- 3-formyl-2-quinolone Schiff base -90% yield, 6-methyl- 3- formyl-2-quinolone Schiff base -85% yield, 7-nitro- 3-formyl-2-quinolone Schiff base -50% yield, 6-nitro- 3-formyl-2-quinolone Schiff base -60% yield, 6-methyl- 3-formyl-2-quinolone Schiff base -85% yield.

SCHEME



R_1	R_2
H	H
4-Br	6-Br
4-Cl	6-Cl
3-OCH_3	7-OCH_3
4-OCH_3	6-OCH_3
3-NO_2	7-NO_2
4-NO_2	6-NO_2
4-CH_3	6-CH_3

Physical data characterization

C.C.	R1	R2	Molecular formula	Molecular Weight	MP	RF value	%Yield
5a	H	H	$C_{16}H_{12}N_4O_2$	292.2902	140.6	0.48	77
5b	4-Br	6-Br	$C_{16}H_{11}N_4O_2Br$	371.188	148.9	0.7	80
5c	4-Cl	6-Cl	$C_{16}H_{11}N_4O_2Cl$	326.7371	154.2	0.76	90
5d	3-OCH_3	7-OCH_3	$C_{17}H_{14}N_4O_3$	322.3181	85.8	0.40	90
5e	4 -OCH_3	6-OCH_3	$C_{17}H_{14}N_4O_3$	322.3181	89.4	0.42	85
5f	3-NO_2	7-NO_2	$C_{16}H_{11}N_5O_4$	337.2902	119	0.74	50
5g	4-NO_2	6-NO_2	$C_{16}H_{11}N_5O_4$	337.2902	123	0.75	60
5h	4-CH_3	6-CH_3	$C_{17}H_{14}N_4O_2$	306.3187	145.2	0.52	85

Recrystallization solvent: Ethanol
Solvent system used: Dioxan: Ethylacetate: Water (9:1:1)
Visualizing agent: Iodine vapour

Antimicrobial studies

Apparatus and chemicals required

Sterile swab: Hi Media
Non-absorbent cotton: Rama Raju Surgical cotton Ltd.
Conical flask: Borosil
Test tubes: Borosil
Petri dishes: SD Fine-Chem Ltd.
Micropipettes: VARI pipettes (Hi-Tab Lab)
Autoclave: Universal Autoclave
Laminar Air Flow unit: CLEAN AIR Instruments Inc.
Microtips: Tarsons

The antibacterial screening was carried out in the Pharmaceutical Biotechnology laboratory,

Media used

Nutrient media which is gelled with 2% agar (Bacteriological grade) is used as the medium for the antibacterial screening.

The nutrient media contains the following ingredients
Nutrient broth: 13g/l
Agar: 15.00 g/l
Final pH at 25°C: 7.4(±0.2)

Media Preparation and Sterilization

The ingredients were dissolved in distilled water with the aid of heat and the pH was adjusted to 7.4(±0.2) by using dilute acid or alkali.

30-35 ml of nutrient media was transferred to Petri plates and sealed. The media is autoclaved at a pressure of 15 psi (121°C) for not less than 15 minutes.

Microorganisms used

Staphylococcus aureus NCIM 2079, *Bacillus subtilis* NCIM 2063, *Escherichia coli* NCIM 2918 and *Pseudomonas aeruginosa* NCIM 2036 were procured from National Chemical Laboratory, Pune and stored in the Pharmaceutical Biotechnology laboratory.

- The strains were confirmed for their purity and identified by Gram's staining method and their characteristic biochemical reactions.
- The selected strains were preserved by sub culturing them periodically on nutrient agar slants and storing them under frozen conditions.
- For antimicrobial study, fresh 24 hours broth cultures were used after the standardization of the culture.

Drugs used: 5a-h(500µg/ml)
Standard drug: Ofloxacin (200µg/ml)
Solvent: Dimethyl sulfoxide

Working conditions in laboratory

The entire work was done by using horizontal laminar flow hood so as to provide aseptic conditions. Before the commencement of the work, air sampling was carried out using a sterile nutrient agar plate and exposing it to the environment inside the hood.

After incubation, it was checked for the growth of microorganism and absence of growth confirmed aseptic working condition.

Standardization of inoculums

- All organisms were grown overnight (24 hours) at 37°C on nutrient agar and harvested during the stationary growth phase.
- Active cultures for experiments were prepared by transferring a loopful of cells from the stock culture to the test tubes containing nutrient media, incubated for 24 hours at 37°C.
- Inoculum was standardized by matching the turbidity of the culture to 0.5 McFarland standard. The standard was produced by mixing 0.05 ml of 0.048 $BaCl_2$ (1.175%w/v bariumchloridedehydrates) with 99.5 ml of 0.36N H_2SO_4.
- If the turbidity of the culture matches that of the McFarland standard, the culture inoculating suspension has approximately 2.0×10.6CFU/ml of bacteria.

Anti- bacterial screening by kirby-bauer method

- Nutrient media plates were prepared aseptically to get a thickness of 5-6mm. The plates were allowed to solidify and inverted to prevent condensate falling on the agar surface. The plates were dried at 37°C before inoculation. The organisms were inoculated as per the following method in the plates prepared earlier.
- The sterile swab was dipped in the previously standardized inoculum and excess of inoculums was removed by pressing and rotating the swab firmly against the sides of the culture tube above level of liquid. The swab was streaked all over the surface of the medium three times, rotating the plates through an angle of 60°C after each application.
- Finally the swab was pressed round the edges of the agar surface.
- The inoculation medium was allowed to dry at room temperature, with the lid closed.
- The drug was poured in the wells, which are made with the help of a borer. And the measured quantity of the drug is poured with the help of the micro-pipette. Nearly 50µl of the solution is poured into the wells. The plates were kept in the refrigerator for 1 hour to facilitate the diffusion of the drugs.
- Plates were prepared in triplicate and they were then incubated for 18-24 hours at 37°C.
- After the incubation, the diameter of the zone of inhibition around the drugs were measured and compared with that of the standard.
- All the synthesized compounds were tested for antibacterial activity against Gram positive and Gram negative bacteria.
- Saturated solutions of the compounds were first studied and thecompounds with zones of inhibition greater than 15mm were taken for quantitative

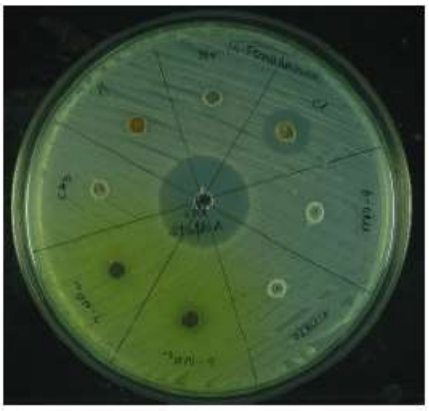
studies.

Screening of newly synthesized compound for antibacterial activity againstgram-positive bacteria
Test drug: Synthesized compounds 5a-h (500 µg/ml)
Standard drug: Ofloxacin 200µg/ml
Solvent used: Dimethyl sulfoxide
Blank solution: Dimethyl sulfoxide

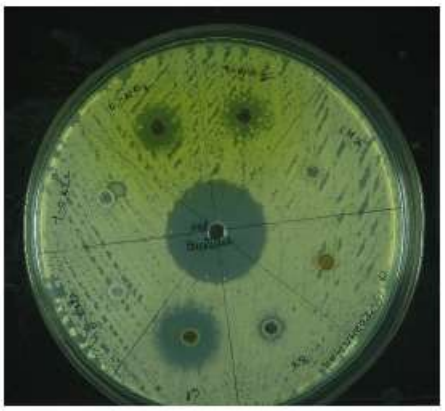
Antibacterial activity against gram-positive bacteria

Compound code	Diameter of zone inhibition(mm)	
	***Staphylococcus aureus* NCIM 2079**	**Bacillus subtilus NCIM 2063,**
5a	-	-
5b	-	11
5c	17	22
5d	-	-
5e	-	-
5f	-	18
5g	-	16
5h	-	-
Control	-	-
std ofloxacin	32	39

(-)indicates no zone of inhibition



Staphylococcus aureus NCIM 2079



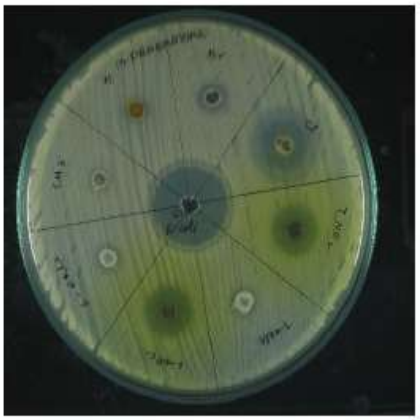
Bacillus subtilus NCIM 2063

Screening of newly synthesized compound for antibacterial activity againstgram-negative bacteria
Test drug: Synthesized compounds 5a-h (500µg/ml)
Standard drug: Ofloxacin 200µg/ml
Solvent used: Dimethyl sulfoxide
Blank solution: Dimethyl sulfoxide

Antibacterial activity against gram-negativebacteria

Compound code	Diameter of zone inhibition(mm)	
	***Escherichia coli* NCIM2918**	***Pseudomonas aeruginosa* NCIM 2036**
5a	-	-
5b	13	-
5c	19	24
5d	-	-
5e	-	-
5f	19	18
5g	18	18
5h	12	-
Control	-	-
Std ofloxacin	32	32

(-) indicates no zone of inhibition



SUMMARY AND CONCLUSION

With the view of synthesizing new compounds with minimum side effects, less toxicity, non-resistant and more selective against disease-producing microorganisms, the present work was undertaken to synthesize 8 different Schiff bases of 3-formyl-2-quinolone and substitutes of 3-formyl-2-quinolones with isoniazid.

Scheme

All the intermediate and final compounds are synthesized by traditionalmethod.

Step 1

Initially Acetanilde and substituted acetanilides were prepared byrefluxing aniline and substituted anilies with acetic acid and zinc dust**.**

Step 2

2-chloro-3-formyl quinoline and substituted 2-chloro-3-formyl quinolines were synthesized from acetanilide and substituted acetanilides correspondingly using Vilsmeier Haack reaction**.**

Step3

The synthesized compounds were refluxed with a 70% acetic acid to give 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones

Step4

Finally, 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones were refluxed with isoniazid in presence of ethanol and concentrated sulphuric acid to get different Schiff bases.

Spectral studies

Structures of all the newly synthesized compounds were confired by UV,IR, MASS and NMR.

A) Antibacterial screening

The synthesized compounds were screened for antibacterial activity against both gram positive (*Staphylococcus aureus* NCIM 2079 and *Bacillussubtilis* NCIM 2063) and gram negative (*Escherichia coli* NCIM 2911 and *Pseudomonas aeruginosa* NCIM 2036) organisms by Kirby-Bauer method. Three of eight compounds were found to be sensitive active against bacteria. **5c,5f,5g** were found to be sensitive activity against Gram positive bacteria and Gram negative bacteria.

CONCLUSION

Based on the results of synthetic works, characterization data, antimicrobial screening and antimycobacterial screening the following conclusions were made.

- Using the schemes evolved, eight different Schiff bases of 3-formyl-2- quinolone and substituted 3-formyl-2-quinolones were synthesized in good yields.
- Four synthesized derivatives (5a,5b,5f,5g) showed equipotent antitubercular activity compared to the standard streptomycin at concentration of 6.12µg/ml. Compound 5c showed equipotent antitubercular activity compared to the standards Pyrazinamide and Ciprofloxacin at concentration of 3.125µg/ml
- The synthesized compounds showed poor to moderate antibacterial activity.

The *in vitro* antimicrobial studies showed that three of eight compounds exhibited good antibacterial activity in which compound 5c showed the highest activity against *Bacillus subtillis* NCIM 2063 and *Pseudomonas aeruginosa* NCIM 2036. The compounds 5b,5c,5f,5g exhibited the highest antifungal activities.

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