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Synthesis and Antibacterial Activity of Substituted 2-Quinolones

Noor Fathima Anjum[*1], Jagarlamudi Leela Rani[2], Abdul Aleem[3], Sukhen Som[4], Mohammed Saif ulla khan[4]

1. Krupanidhi College of Pharmacy[1]. Bangalore-560035, Karnataka. India
2. Bapatla College of pharmacy, Guntur Dist 522101, Andhra Pradesh. India
3. Al-Ameen College of Pharmacy, Bangalore- -560027, Karnataka. India
4. M.M.U College of Pharmacy. K.K.Doddi, Ramanagara- 562159, Karnataka. India

ABSTRACT

Quinolines are a class of heterocyclic compounds, widely present in nature as quinoline alkaloids. Compounds having 2-quinolone moiety are associated with interesting biological activities such as antimalarial, tuberculostatic, antibacterial, antiviral, antifungal, anticancer, antidiabetic, cardiotonic and bronchodilator activity etc. The present work deals with the synthesis, characterization of substituted 7-amino-4-methyl-2-quinolone. The synthesized compounds were characterized by the IR, ^{1}H-NMR & Mass spectral studies. Out of 10 test compounds evaluated for their antibacterial activities, four test compounds 3,6,8 & 9 were found to be active against *Bacillus subtilis* while amoxycillin and gentamycin were used as standard.

Keywords: 2-quinolone; Schiff bases, antibacterial activity.

*Corresponding Author Email: nfanjum@gmail.com
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INTRODUCTION

Quinoline is present in nature as alkaloids. Depending on the position of ketone or hydroxyl group present in the quinoline nucleus, it is available as 2-quinolones, 2-hydroxy quinolines, 4-quinolones, 4-hydroxy quinolines, 8-quinolones and 8-hydroxy quinoline etc. The 2-quinolones frame work is often found in quinoline alkaloids isolated from the rutaceace family[1] and numerous naturally occurring 2-quinolone have been synthesized. Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death[2]. As a general rule, gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive bacterial activity corresponds with inhibition of DNA type IV topoisomerase.

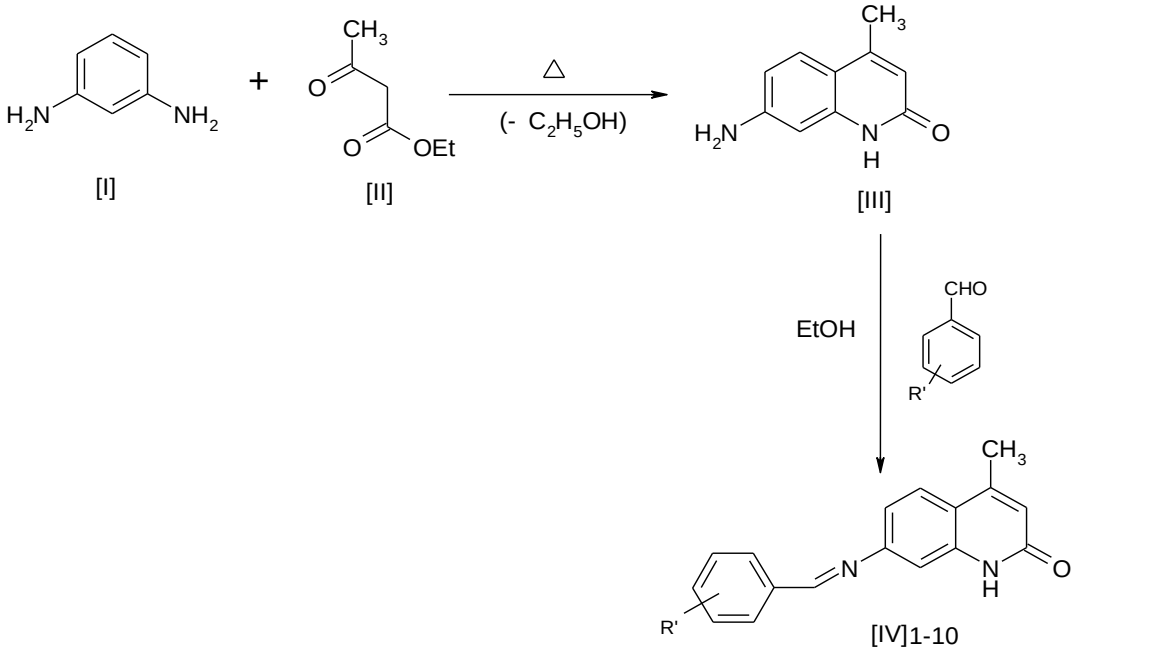
The inhibition of bacterial DNA gyrase has been the target of a worldwide research effort which began with the discovery of nalidixic acid in the early 1960s[3]. This first, nalidixic acid generation included other such "quinolone" drugs as oxolinic acid (a true 4-quinolone), pipemidic acid (a pyrodopyrimidine), and cinoxacin (a cinnoline), all introduced in the 1970s. Structure activity relationships (SAR) of quinolone antibacterial have led to a large group of synthetic antibacterial agents known collectively as the quinolones[4]. Introduction of a fluorine atom at the 6- position of the quinolone ring system led to norfloxacin, which had a broad spectrum antibacterial activity. Newer members of this family include ciprofloxacin, ofloxacin, enoxacin, lomefloxacin, fleroxacin and temafloxacin[5]. Fluoroquinolones are often used for genitourinary infections, and are widely used in the treatment of hospital-acquired infections associated with urinary catheters. In community-acquired infections, they are recommended only when risk factors for multidrug resistance are present or after other antibiotic regimens have failed. However, for serious acute cases of pyelonephritis or bacterial prostatitis where the patient may need to be hospitalized, fluoroquinolones are recommended as first-line therapy[6]. Due to sickel-cell disease patients being at increased risk for developing osteomyelitis from the *Salmonella* genus, fluoroquinolones are the "drugs of choice" due to their ability to enter bone tissue without chelating it as tetracycline's are known to do. Fluoroquinolones inhibit the topoisomerase II ligase domain, leaving the two nuclease domains intact. This modification, coupled with the constant action of the topoisomerase II in the bacterial cell, leads to DNA fragmentation via the nucleasic activity of the intact enzyme domains. Recent evidence has shown eukaryotic topoisomerase II is also a target for a variety of quinolone-based drugs. Thus far, most of the compounds that show high activity against the eukaryotic type II enzyme contain aromatic substituents at their C-7 positions[7,8]. Fluoroquinolones can enter cells easily via porins and, therefore, are often used to treat intracellular pathogens such as *Legionella pneumophila* and *Mycoplasma pneumoniae*. For many gram-negative bacteria, DNA gyrase is the target, whereas

topoisomerase IV is the target for many gram-positive bacteria. Some compounds in this class have been shown to inhibit the synthesis of mitochondrial DNA[9,10,11,12,13,14,15]. Quinoline have been found to exhibit antimalarial[23], tuberculostatic[16,17], anti-bacterial[18], antiviral[18], anticancer[17,18], anti-inflammatory[16,17], antifungal[20], antidiabetic[24], cardiotonic[22], diuretic[21] and bronchodilator activity[19].

MATERIALS AND METHOD:

All the chemicals required for the synthesis of the compounds were obtained from Merck and SD Fine chemicals and were of analytical grade. Melting points of the test compounds synthesized were determined using Thiele's melting point apparatus and were uncorrected. Purity of the compounds was checked by Thin Layer Chromatography using silica gel G as stationary phase and combination of Ethyl acetate:Chloroform(1:4); as mobile phase. The spots resolved were visualized using iodine chamber. The IR spectra of the synthesized compounds were recorded using KBr pellets in the range of 4000-500 cm^{-1} on a Fourier Transform IR Spectrometer (Model Shimadzu 8700). ^{1}H-NMR (400 MHz) Spectra were recorded in chloroform-d, acetone-d, in AMX-400 liquid state NMR spectrometer (Indian Institute of Science, Bangalore). Mass Spectra were recorded on Sciex3000 (Applied BioSystems, Canada) LC-MS-MS, "Triple Quadruple MS" using Autospecto Ionization -Positive ion mode. (Indian Institute of Chemical Technology. Hyderabad).

Scheme of Synthesis:



R' = p- Cl, $(OMe)_3$, m- NO_2,CH_3, $(OMe)_2$,o-NO_2,p-NO_2,OMe, 0- Cl•

Synthesis of 7-amino-4-methyl-2-Quinolones [III]

10.8 g (0.1mole) of m-phenylene diamine [I] and 12.64 mL (0.1mole) of the ethylacetoacetate [II] were mixed and heated together in a flask. The reaction was heated at 150 ^{0}C for 18 h on an oil bath. The end of reaction period, 100 to 200 mL of water was added to the flask. The contents were heated on a hot plate to the boiling temperature of the water. The mixture was then chilled, filtered and the precipitate dried in air. The compound was recrystallised from methanol.

Synthesis of Schiff bases of 7-amino-4-methyl-2-Quinolones [IV]$_{1-10}$

To a solution of 0.01 mole of 7-amino-4-methyl-2-quinolone [III] in 30mL of alcohol and 0.01 mol of aldehyde was added and refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and then poured into 100 mL of ice cold water. The solid formed was filtered and washed twice with 30 mL of cold water, dried and recrystallised from aqueous ethanol.

Antimicrobial activity:

All the ten test compounds synthesized, purified and characterized were screened for their qualitative antimicrobial activity. They were tested against four species of bacteria namely, *Bacillus subtilis* (Gram-positive), *Escherichia coli* (Gram-negative), *Pseudomonas aeruginosa* (gram-negative), *Staphylococcus aureus* (Gram-positive). The technique used was Agar Diffusion Method using 100 µg/0.1 mL of Amoxicillin and Gentamycin as standard. Specified quantity of beef extract, peptone & agar were accurately weighed, dissolved in distilled water and sterilized by autoclaving at 121^{o}C for 15 minutes. The plates were prepared with the assay media was cooled to 50 ^{o}C. It was then inoculated with the test organisms. Four bores per plate were made using sterile cork borer. The above operation was carried out under aseptic condition in sterile area.

Spectral data:

IR spectra of 7- amino 4- methyl-2-quinolone KBr (cm^{-1}): 3421.5, 3311.5 (primary amino N-H stretch as doublet), 3201.6 (secondary amino N-H stretch as singlet), 2922.0 (Ar C-H stretch), 1629.7 (C=O stretch), 1552.6,1469.7,1415.7 (Ar C=C stretch), 1060.8 (C-N stretch). ^{1}H-NMR (400MHz in d-Chloroform): 2.2 (methyl 3H), 2.5 (Amine 2 H), 5.9 (Pyridine H), 5.7 (Aryl 2 H), 6.4(1 H), 6.3(1 H). MS m/e = 174.

IR spectra of 7-(benzylidene)amino-4-methyl-2-quinolone (1). KBr (cm^{-1}): 3394.5 (N-H stretch), 2825.5 (Ar C-H stretch), 1654.8 (C=O stretch), 1606.6 (C=N stretch), 1546.8, 1512.1, 1465.8 (Ar C=C stretch), 1068.5 (C-C stretch).

IR spectra of 7-(4- chloro benzylidene)amino-4-methyl-2-quinolone (2). KBr (cm^{-1}): 3340.1 (N-H stretch), 2918.1 (Ar C-H stretch), 1676.0 (C=Ostretch), 1600.8 (C=N stretch), 1554.5, 1554.5, 1461.9 (Ar C=C stretch), 1089.7(C-C stretch), 941.2 (C-Cl stretch). ^{1}H-NMR(400MHz in d-Chloroform): 2.4 (methyl 3H), 5.2 (1 H), 6.3 (1 H), 7.1 (2 H), 8.0 (2 H), 7.8 (1 H), 8.7 (1 H).

IR spectra of 7- (3, 4, 5- trimethoxy benzylidene)amino-4-methyl-2-quinolone (3). KBr (cm^{-1}): 3342.2 (N-H stretch), 2945.1 (Ar C-H stretch), 1654.8 (C=O stretch), 1610.5 (C=N stretch), 1546.7, 1502.4, 1461.9 (Ar C=C stretch), 1128.3 (C-O stretch) 1070.4 (C-C stretch). ^{1} H-NMR(400MHz in d-Acetone): 2.3 (3 H), 3.9 (9 H), 6.1 (1H), 7.2 (1H), 7.3 (2 H), 7.8 (1 H), 7.1 (1 H).

IR spectra of 7- (3- nitro benzylidene)amino-4-methyl-2-quinolone (4). KBr (cm^{-1}): 3456.2 (N-H stretch), 2821.7 (C-H stretch), 1658.7 (C=O stretch), 1604.5 (C=N stretch), 1546.7, 1519.3, 1471.6 (Ar C=C stretch), 1166.3 (N-O stretch) 1070.4(C-C stretch).

IR spectra of 7-(4-methyl benzylidene)amino-4-methyl-2-quinolone (5). KBr (cm^{-1}): 3352.1 (N-H stretch), 2928.4 (Ar C-H stretch), 1654.0 (C=O stretch), 1602.6 (C=N stretch), 1546.8, 1524.1, 1465.8 (Ar C=C stretch), 1069.2 (C-C stretch).

IR spectra of 7- (3,5- dimethoxy benzylidene) amino-4-methyl-2-quinolone (6). KBr (cm^{-1}): 3441.2 (N-H stretch), 2837.1 (C-H stretch), 1658.7 (C=O stretch), 1602.7 (C=N stretch), 1550.7, 1535.8, 1461.9 (Ar C=C stretch), 10222 (C-O stretch)1070.4 (C-C stretch).

IR spectra of 7- (2- nitrobenzylidene) amino -4- methyl-2-quinolone (7). KBr (cm^{-1}): 3448.5 (N-H stretch), 2821.7 (C-H stretch), 1658.7 (C=O stretch), 1604.5(C=N stretch), 1579.8 (N=O stretch), 1546.7, 1519.8, 1471.9 (Ar C=C stretch), 1128.3(N-O stretch) 1070.4 (C-C stretch).

IR spectra of 7- (4 - nitro benzylidene amino-4-methyl-2-quinolone (8). KBr (cm^{-1}): 3456.2 (N-H stretch), 2821.7 (C-H stretch), 1658.7 (C=O stretch), 1602.7 (C=N stretch), 1546.7, 1519.3, 1471.6 (Ar C=C stretch), 1166.9(N-O stretch) 1070.4 (C-C stretch).

IR spectra of 7- (3- methoxy benzylidene) amino-4-methyl-2-quinolone (9). KBr (cm^{-1}): 3441.2 (N-H stretch), 2837.1 (C-H stretch), 1656.7 (C=O stretch), 1587.5 (C=N stretch), 1548.7, 1512.1, 1463.9 (Ar C=C stretch), 1022.2 (C-O stretch) 1070.4 (C-C stretch).

IR spectra of 7- (2- chlorobenzylidene) amino-4-methyl-2-quinolone (10). KBr (cm^{-1}): 3344.2 (N-H stretch), 2918.1 (C-H stretch), 1678.0 (C=O stretch), 1629.1 (C=N stretch), 1546.8, 1519.8, 1481.0 (Ar C=C stretch), 1163.0 (N-O stretch), 951.9 (C-Cl stretch).

RESULTS AND DISCUSSION:

The starting materials for the synthesis of 7-amino-4-methyl-2-quinolone were m-phenylene diamine and ethylacetoacetate. The quinolone derivatives were synthesized successfully in moderate to good yields.

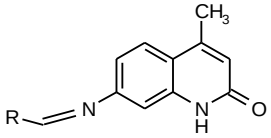
IR spectra of the 7-amino-4-methyl-2-quinolone showed characteristic band at 3421.5 and 3311.5 cm^{-1} due to NH_2 (primary amine), C=O stretching was observed at low frequency between 1670-1640 cm^{-1} and this presumably may be due to carbonyl group tendency to conjugate with the double bond and inductive effect of nitrogen. Thus indicating the formation of the 7-amino-4-methyl-2-quinolone. The absence of doublet of primary amine N-H stretching and

presence of C=N stretching indicated completion of reaction and formation of Schiff bases of 7-amino 4-methyl-2-quinolones. The absence of doublet of primary amine N-H stretching and presence of C=N stretching indicated completion of reaction and formation of Schiff bases of 7-amino-4-methyl-2-quinolone.

NMR spectra of **7-** amino-4-methyl-2-quinolone showed singlet peak at 2.2 δ due to the presence of methyl proton (H). A singlet peak was observed at 5.6 δ due to the presence of amine proton. A singlet peak appeared at 5.9 δ was indicated the presence of pyridine NH. Doublet peak appeared at 6.4 δ was due to the electro negative of the nitrogen. A singlet peak observed at 6.3 δ was due to the space effect of the double bond and inductive effect of the nitrogen. NMR spectra of 7-(4-chloro benzylidene amino)-4-methyl-2-quinolone showed singlet peaks at 2.4 δ due to the presence of methyl proton. A singlet peak was observed at 5.3 δ due to the presence of the NH proton in pyrilidine ring. A singlet peak was observed at 6.3 δ due to the space effect of the double bond and inductive effect of the nitrogen. A singlet peak observed at 7.1 δ was due to the Aryl protons. Doublet peak was observed at 8.0 δ due to the presence two electro negative make strain on the ring proton. Chemical shift was due to the space effect of the ring proton showed single peak observed at 7.8 δ. One more chemical shift was observed at 8.7 δ at pyridine proton due to the space effect and inductive of the oxygen so it was appeared at the higher value. NMR spectra of 7-(3,4,5-trimethoxy benzylidene amino)4-methyl-2-quinolone showed singlet peak at 2.3 δ due to the presence of the methyl proton. A single peak was observed at 3.9 δ due to the methoxy protons (9 protons). The intensity indicate the methoxy protons due to the inductive effect of the oxygen. A singlet peak was observed at 6.1 it indicated NH proton of the pyridine, it might be due to the inductive effect of nitrogen which caused chemical shift. A singlet peak was appeared at 7.2 it indicated proton of the H in the pyridine ring it appear at higher value due to the space effect of the double bond and inductive effect of the oxygen. At 7.3 doublet peak was shown. it indicated the Aryl proton split due to the two electro negative groups make strain on the ring proton this contributed in the chemical shift. At 7.8 a singlet peak was due to the proton which is affected by the anisotropic effect of the double bond and inductive effect of the nitrogen.

Mass spectra of 7- amino-4-methyl-2-quinolone the molecular ion peak was observed at m/e= 174 it indicated molecular weight of the test compound. All the newly synthesized derivatives were screened for antibacterial activity using agar diffusion method.

Table 1 Physical properties of various substituted 7-amino-4-methyl-2-quinolones



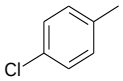
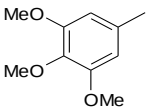
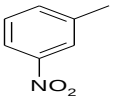
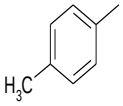
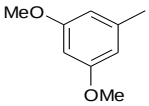
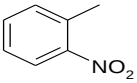
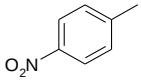
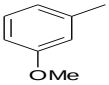
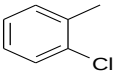
Compound Code	R	Mol. Formula	Mol. Wt	Melting Point (^{o}C)	Yield (%)
N-1		$C_{17}H_{14}O_2N_2$	278	> 320	81
N-2		$C_{17}H_{14}N_2O_2Cl$	313	272	73
N-3		$C_{20}H_{20}N_2O_4$	352	250	78
N-4		$C_{17}H_{13}N_3O_3$	307	>300	79
N-5		$C_{18}H_{16}N_2O$	276	266	79
N-6		$C_{19}H_{18}O_5N_2$	322	266	79
N-7		$C_{17}H_{18}N_3O_3$	307	> 300	85
N-8		$C_{17}H_{13}N_3O_3$	307	>300	85
N-9		$C_{17}H_{13}N_3O_3$	292	270	69
N-10		$C_{17}H_{13}N_2OCl$	296	274	79

Table 2: Antimicrobial activity of synthesized molecules

Compound Code	Zone of inhibition (in mm)			
	B.S	***P.a***	***E.c***	***S.a***
Amoxicillin	28	29	35	32
Gentamycin	26	31	29	33
N-1	10	08	09	14
N-2	12	07	10	15
N-3	24	12	15	25
N-4	11	07	09	11
N-5	09	09	06	10
N-6	23	12	10	26

N-7	08	05	06	06
N-8	20	10	03	22
N-9	21	12	09	24
N-10	09	06	07	09

CONCLUSION:

From the antibacterial screening data it was concluded that the compounds 3, 6, 9 and 8 showed activity against gram positive microorganisms greater than that of against gram negative organisms and other test compounds 1,2, 4, 5, 7 and 10 showed activity lower than that of 3, 6, 9 and 8. The zones of inhibition were found to at 28 mm, 26 mm, 23 mm, and 24 mm of respectively against *Staphylococcus aureus*. The same derivatives showed zones of inhibition at 17 mm, 14 mm, 12 mm, 10 mm against *Escherichia coli* and 20mm, 18mm, 18mm and 15mm against *Bacillus subtilis* respectively. All the ten test compounds showed less activity lower than that of against *Pseudomonas aeruginosa*. Thus, the following optimal structural requirements for optimal antibacterial activity of schiff bases of 7- amino-4-methyl-2-quinolone are:

- The presence of trimethoxy benzyl group at meta and para positions or 3, 4, 5 positions.
- The presence of 3, 5 – Dimethoxy benzyl group.
- The presence of methoxy benzyl group.
- The presence of 4-nitro benzyl group.

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