ORIGINAL RESEARCH PAPER

Chemistry

Synthesis, Characterization and Evaluation of Schiff's Bases of 2-Quinolones.

KEY WORDS: quinoline-2-one, Schiff base.

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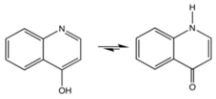
ABSTRACT

In the present study, we synthesized Schiff bases of quinoline-2-one and their antibacterial activity was evaluated by wells diffusion method. Schiff bases of quinoline-2-one (1 to 8 named as Q2ka-Q2kh) were prepared by refluxing with substituted aromatic ketones. The final test compounds has purified and characterized by IR, 1HNMR and Mass Spectral studies. M.P. of these compounds was confirmed by open capillary method instrument chemline cl 725. They have evaluated for antibacterial activity. Compounds were active against Klebsiella pneumonia and Enterococcus faecalis. While ciprofloxacin was used as standards.

INTRODUCTION

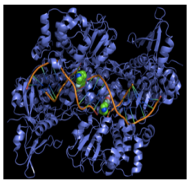
Thefoundingmemberofthequinolonedrugclass,nalidixicacid (1-ethyl-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxilyc acid) is a naphthyridine that was first isolated by George Lesher and colleagues in 1962 as a byproduct of chloroquine synthesis [1]. Nalidixic acid is considered the first quinolone drug. It was introduced in 1962 for treatment of urinary tract infections (UTIs) in humans[2] A quinolone antibiotic is a member of a large group of broad-spectrum bacteriocidals that share a bicyclic core structure[3] which contains a ring of type A 4-piridinona combined with aromatic or heteroaromatic ring B. The ring type A 4-piridinona is a ring with absolute necessity: an unsaturation in position 2-3, a free acid function in position 3 and a substituent at nitrogen in position 1.[4]

Fig.1:



A number of biological activities have been associated with quinoline-containing compounds such as antimalarial [5] antitubercular [6] antiallergic [7] anti-inflammatory [8]. Quinolones inhibit DNA topoisomerases II and IV which play an important role in bacterial duplication. The main target of quinolones in Gram negative bacteria is the A subunit of DNA topoisomerase II while quinolones exert their effect on Gram positive bacteria via inhibiting DNA topoisomerase IV [9,10] Specifically, they inhibit the ligase activity of the type II topoisomerases, gyrase, and topoisomerase IV, which cut DNA to introduce supercoiling and with their ligase activity disrupted, release DNA with single- and double-strand breaks that lead to cell death[11].

Fig.2



Structure of bacterial DNA gyrase complexed with DNA and two ciprofloxacin molecules (green)

In the present study, an attempt was made to synthesize other correlated structures nearing the existing quinolones present in the marketed drugs, to achieve improved biological activities of the parent compounds and a novel series of schiff's bases derived from 7-hydroxy-4-methyl-2-quinolone.

MATERIALS AND METHODS

The chemicals used were of AR grade and LR grade, purchased from Loba Chemicals, Qualigens, S.D Fine Chemicals Ltd. and Merck.

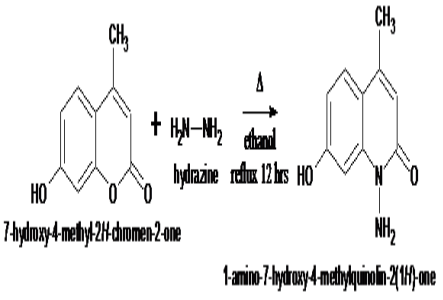
Synthesis of 7-hydroxy-4-methyl-2-quinolone[12] (Q2k).

2.92g of Coumarin dissolved in 30ml of ethanol and 6.4g of hydrazine hydrate was added to the mixture and reflux for 12 hours. Cool it and evaporate the solvent at reduced pressure. Then neutral the mixture, the brown color ppt obtained. Reaction confirms by TLC

Synthesis of Schiff Base of 7-hydroxy-4-methyl-2-quinolone[12] (Q2ka-Q2kh).

Quinolone (Q2a) (10mmol) was dissolved in 2M NaOH (5mL) and to it was added a solution of substituted benzaldehyde (10mmol) in methanol (20mL) drop wise. The mixture was heated under reflux for three hours. After cooling, the mixture was filtered and evaporated under reduced pressure. The product obtained was washed with acetone and dried. In the present study, N-amino quinoline-2-one was allowed to react with aryl ketones. (Fig.3)

Fig.3: Scheme of Synthesis



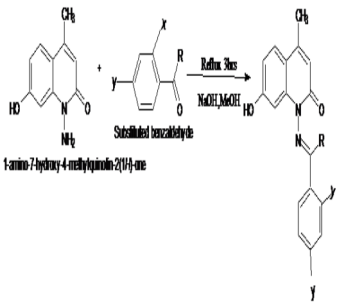


Table:1 list of substituted arylketones

S.NO.	COMPOUND	R	X	Y
1	Q_2ka	CH_3	H	OH
2	Q_2kb	CH_3	H	H
3	Q_2kc	$C6H_5$	H	H
4	Q_2kd	CH_3	H	NH_2
5	Q_2ke	CH_3	H	NO_2
6	Q_2kf	CH_3	H	F
7	Q_2kg	CH_3	H	Br
8	Q_2kh	CH_3	H	Cl

Determination of antibacterial activity

All the eight synthesized test compounds were tested against two species of bacteria namely Klebsiella pneumonia and Enterococcus faecalis successfully procured from Microbial Culture collection, National Centre forcell science, Pune, Maharashtra, India The lyophilized cultures of bacterial strains upon culturing in nutrient broth for 24-48 hours at 37°C in an incubator resulted into turbid suspension of activated live bacterial cell ready to be used for microbiological study. From the broth of respective revived cultures of bacteria loop full of inoculum is taken and streaked on to the nutrient agar medium and incubated again at same culture conditions and duration that yielded the pure culture colonies on to the surface of the agar culture that are successfully stored in refrigerated conditions at 4°C as stock culture to be used for further experimentation. The lawn cultures were prepared with all the microbes used under present study and sensitivity of bacteria towards the various synthesized compound were studied at the concentration of 100 µl using well diffusion method[13-15].

The synthesized compound used to suitably dilute upto the concentrations of 100,50 and 25 g per ml and applied on to the test organism using well diffusion method. Results of the experiment are being concluded in the Table no. 1, which clearly shows the anti-microbial activity of synthesized compound of 2 bacteria used in present work.

RESULTS AND DISCUSSION

Synthesis And The Spectral Studies

The starting material for the synthesis of 7-hydroxy-3-methyl coumerin[16,17], 11mg Resorcinol was dissolve in 13mg of ethylacetoacetate and 160mg polyphosphoric acid was added to this mixture was Heated & stirred at 75-80oC for 20-30 min. Heated mixture was poured on ice-cold water ppt obtained. ppt collected by filtration and dry then re-crystelized with ehanol. gave white ppt.Purified test compound was checked by its melting point(185°C) and thin layer chromatography. The structure was established by IR, 1H-NMR and Mass studies (yield =65-70%).

Spectral Data

(E)-7-hydroxy-1-(1-(4-hydroxyphenyl)ethylideneamino) quinolin - 2(1H) - one(Q2ka) C17H14N2O3

Yield:67%, MP.100 °C, colour:light brown, IR (KBr, cm-1):3415(NH),2308(C=C),1961(Overtone of niotrogen heterocycle),1648(C=O),1554(C-C ar),1485(N-N). 1H NMR ppm 7.63(CH benzene),7.39(CH benzene),6.85(CH benzene),6.46(CH benzene adjacent to quinine),4.84(OH aromatic)0.87(CH3). Mass m/z (%):294.2 (Molecular ion)

(E)-7-hydroxy-1-(1-phenylethylideneamino)quinolin-2(1H)-one(Q2kb)

Yield:62%,MP.110°C, colour:cream , IR (KBr, cm-1):3345(OH stretching),2927(CH),1655(C=O),1608(C=N),1540(C-C ar),1489(N-N),1221(C-N),1065(C-O).1H NMR ppm 7.71(CH benzene),7.60(CH benzene),7.37(CH benzene),7.15(CH benzene),6.47(CH benzene adjacent to quinine),4.84(OH aromatic),0.89(CH3). Mass m/z (%): 278.18 (Molecular ion)

1-(diphenylmethyleneamino)-7-hydroxyquinolin-2(1H)-one(q2kc)C22H16N2O2

Yield: 52%, MP.73°C, colour:yellowish brown ,IR (KBr,cm-1):3312(OH stretching),1648(C=O),1621(C=N),1548(C-C ar),1498(N-N),1313(C-N). 1H NMR ppm 7.8(CH benzene),7.76(CH benzene),7.4(CH benzene),6.57(CH benzene adjacent to quinine),5.0(OH aromatic). Mass m/z (%):340.1 (Molecular ion)

(E)-1-(1-(4-aminophenyl)ethylideneamino)-7-hydroxyquinolin-2(1H)-one(Q2kd)C17H15N3O2

Yield: 61%, MP. 80°C, colour: brown,IR (KBr,cm-1):3325(OH),2897(C=C),1648(C=O),1648(C=N),1549(C-C ar).1487(N-N). 1H NMR ppm 7.50(CH benzene),7.28(CH benzene),7.12(CH benzene),6.77(CH benzene),6.50(CH benzene adjacent to quinine),4.99(OH aromatic),4.18(NH2),1.01(CH3).Mass m/z (%):293.1 (Molecular ion).

(E)-1-(1-(4-aminophenyl)ethylideneamino)-7-hydroxyquinolin-2(1H)-one(Q2ke)C17H13N3O4

Yield:45 %, MP.180°C, colour: orange ,IR (KBr,cm-1):3389(OH),1648(C=O),1604(C=N),1565(C-C ar),1489(N-N),1385(N-O). 1H NMR ppm 8.21(CH benzene),7.40(CH benzene),7.38(CH benzene),7.27(CH benzene),6.99(CH benzene),6.51(CH benzene adjacent to quinine),4.48(OH aromatic),0.90(CH3).Mass m/z (%): 323.0 (Molecular ion)

(E)-1-(1-(4-fluorophenyl)ethylideneamino)-7-hydroxyquinolin-2(1H)-one(Q2kf)C17H13FN2O2

Yield:58 %, MP. 98°C, colour:cream, IR (KBr,cm-1):3387(OH),1655(C=O),1610(C=N),1550(C-C ar),1441(N-N).1H NMR ppm 7.39(CH benzene),7.24(CH benzene),6.53(CH benzene),6.44(CH benzene adjacent to quinine),4.84(OH aromatic),0.87(CH3).Mass m/z (%):296.1 (Molecular ion)

(E)-1-(1-(4-bromophenyl)ethylideneamino)-7-hydroxyquinolin-2(1H)-one(Q2kg)C17H13BrN2O2

Yield: 63%, MP.78°C, colour:greenish,IR (KBr,cm-1):3345(OH),1640(C=O),1607(C=N),1545(C-C ar),1432(N-N). 1H NMR ppm 7.40(CH benzene),7.38(CH benzene),7.20(CH benzene),6.57(CH benzene),6.39(CH benzene adjacent to quinine),4.99(OH aromatic),0.83(CH3). Mass m/z (%):356.5 (Molecular ion).

(E)-1-(1-(4-chlorophenyl) ethylideneamino)-7-hydroxyquinolin-2(1H)-one (Q2kf) C17H13ClN2O2.

TABLE 2: Antibacterial Activity of Schiff Bases of Schiff Base of 7-hydroxy-4-methyl-2-quinolone.

Micro-organism Sample	Enterococcus faecalis			Klebsiella pneumoniae		
	Inmm Mean			Inmm Mean		
	100(g/ml)	50(g/ml)	25(g/ml)	100(g/ml)	50(g/ml)	25(g/ml)
Q_2KA	17±0.28	13±0.57	12±0.28	13±0.57	12±0.28	8±0.5
Q_2KB	15±0.76	14±0.28	13±0.86	14±0.28	12±0.28	10±0.57
Q_2KC	15±0.76	13±0.86	12±0.28	25±0.86	20±0.28	18±0.28
Q_2KD	15±0.76	10±0.57	6±0.57	12±0.28	10±0.57	8±0.5
Q_2KE	12±0.28	8±0.5	6±0.57	15±0.76	11±0.57	8±0.86
Q_2KF	20±0.28	15±0.76	6±0.57	15±0.76	13±0.86	10±0.57
Q_2KG	16±0.57	13±0.86	8±0.5	17±0.28	13±0.57	12±0.28
Q_2KH	17±0.28	15±0.76	11±0.57	12±0.28	10±0.57	8±0.5
Ciproploxacin	26±4.04	14±1.15	12±0.57	33±1.5	30±2.88	25±0.57

Yield: 63%, MP.67 °C, colour: yellow, IR (KBr, cm-1):3358(OH), 1647(C=O), 1618(C=N), 1552(C-C ar), 1435(N-N). 1H NMR ppm 7.4(CH benzene),7.36(CH benzene),7.11(CH benzene),7.06(CH benzene),6.57(CH benzene adjacent to quinine),6.6(CH benzene adjacent to N-CH3),5.0(OH aromatic),0.9(CH3),2.85(N-CH3).Mass m/z (%):308.1 (Molecular ion).

Antibacterial Activity

All the eight compounds synthesized, purified and characterized were screened for their qualitative antibacterial activity. They were tested against two species of bacteria namely, Klebsiella pneumonia(gram- negative) and Enterococcus faecalis(gram-positive). The technique used was well diffusion method using Ciprofloxacin as standard Stock solutions of the synthesized compounds were prepared in DMSO. Table 2 shows the antibacterial activity of Schiff bases of Schiff Base of 7-hydroxy-4-methyl-2-quinolone.

Test compounds, such as Q2ka, Q2kf, Q2kg and Q2kh showed activity against gram positive micro-organism greater than gram negative organisms and other test compounds such as Q2kb, Q2kc, Q2kd and Q2ke showed lower activity while Q2kc and Q2kg showed activity against gram negateitve organism betterthangrampositivebacteria.

CONCLUSION:

In the present study, eight new derivatives of 7-hydroxy-4-methyl-2-quinolonewere synthesized. Theschemeofsynthesis is efficient and provides satisfactory yield of the desired compounds. These compounds were confirmed by physical data and spectral studies. The compounds were screened for antimicrobial activity against Klebsiella pneumonia and Enterococcus faecalis. One (Q2kf) out of eight compounds has good activity against Eneterococcus faecalis as good as has activity of standard drug while Q2kc and Q2kg showed good antimicrobial activity against Klebsiella pneumoniae. Present study shows that there is lots of effort needed to improve their potency by reacting synthesized compounds with several molecules to improve their antimicrobial activity compare to drugsalreadyinmarkethavingquinolonemoiety.

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