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Synthesis, Characterization and Antimicrobial Evaluation of Schiff's Bases of 1-Amino-7-hydroxy-2-methylquinoline-4(1H)-one

S.K. Vishwakarma[1*], A. Pradhan[2]

[1,2]Department of Chemistry, S .N. Govt. G.P.G. College, Bhopal (Madhya Pradesh), India

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***Abstract*:** We have synthesized eight Schiff bases of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one named as Q4AA-Q4AH by refluxing (Q4A) with substituted aromatic aldehydes in ethanol for 5-7 hrs. 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. Test compounds, such as Q4AD, Q4AE and Q4AF showed moderate activity against gram positive micro-organism while Q4AG and Q4AF showed activity against gram negatives organism lower than standard ciprofloxacin. Their antimicrobial activity was evaluated by wells diffusion method.

***Keywords*-** Resacetophenone, 4-quinolone, acylchloride, pyridine, Schiff's bases, well diffusion.

I. INTRODUCTION

Quinolone are synthetic antibacterial compounds based on a 4- quinolone skeleton (4-oxo-1,4dihydroquinoline) [1, 2]. They have been clinically successful and more used to treat bacterial infection and infectious diseases [3,4,5] .Schiff's bases derivatives possess wide range of pharmacological activities like antioxidant, antiinvasive, antiviral, antipyretic, anti-inflammatory, antidepressant, and blood pressure lowering etc. Azo compounds have been found to possess wide spectrum of biodynamic properties. Many of them have been reported as antibacterial [6], antimicrobial [7], diagnostic aid [8], antineoplastic [9] urinary antiseptic [10] and topical dermatologic activities. Nalidixic acid is the first member of quinolone [11].

In the present study, an attempt was made to synthesize other correlated structures nearing the existing quinolone present in the marketed drugs, to achieve improved biological activities of the parent compounds and a novel series of Schiff's bases. 1-amino-7-hydroxy-2-methylquinolin-4(1h)-one has been synthesized which was allowed to reflux with selected aryl aldehydes in ethanol. Our purpose of this study was evaluating antimicrobial activity against synthesized Schiff bases of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one by comparing with standard as ciprofloxacin.

II. MATERIAL AND METHODS

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

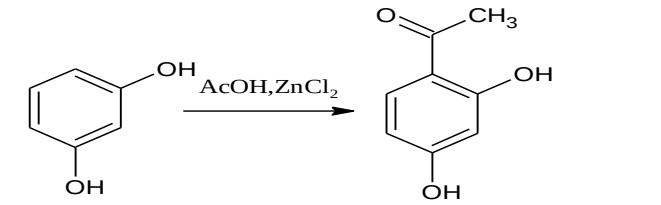
II.I Synthesis of 7-hydroxy-2methyl-4H-chromen-4-one (Q4) [12, 13, 14, 15]

4 g of acylchloride are added to a solution of 2, 4 –dihydroxyacetophenone in dry pyridine. Mixture is stirred for 18hrs at 40^0C, poured into water and extracted with ethylacetate.washed 3 times with 1N HCl and subsequently with aqueous sodium carbonate solution and added drop wise at 5^0C to a suspension of 330mg of sodium hydride (80% in mineral oil), cooling bath is removed and mixture is stirred for 4hrs at RT. Then 1.5ml of acetic acid and 250ml of water is added, followed by extraction of with ethyl acetate. The residue is chromatoghaphed on silica gel to remove starting material and major by product. Cyclization of the resultant 7-hydroxy-2methyl-4H-chromen-4-one is achieved by treatment with 20ml of 32% aqueous HCl in methanol.

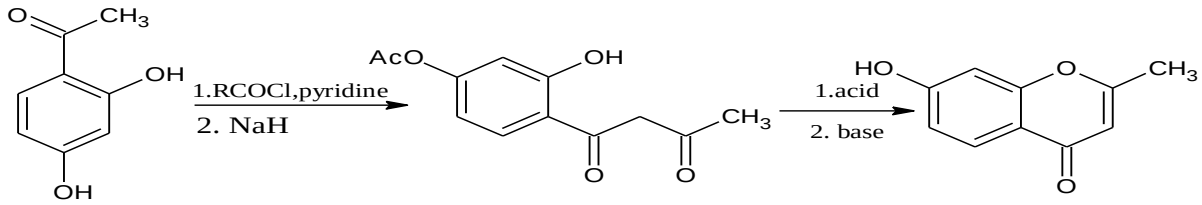
II.II Synthesis of 1-amino-7-hydroxy-2-methylquinolin-4(1*H*)-one (Q4A) [16]:
2.92g of 7-hydroxy-2methyl-4H-chromen-4-one dissolved in 30ml of ethanol and 6.4g of hydrazine hydrate was added to the mixture and reflux for 12hours. Cool it and evaporate the solvent at reduced pressure. Then neutral the mixture, the brown color ppt obtained.Reaction confirms by **TLC.**

II.III Synthesis of Schiff Base of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one (Q4AA-Q4AH) [17]
To a solution of 0.01 mol of quinolone in 30ml of ethanol, 0.01 mol of aromatic aldehydes was added. The mixture was refluxed for 5-7hrs.Cool to room temperature and pour into 100ml of ice cold water. Filter the solid wash out with 30ml of cold water, dry and crystallized from ethanol, water.

Scheme: 1

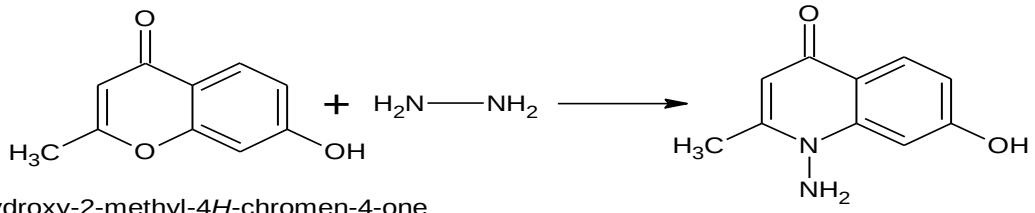


benzene-1,3-diol 1-(2,4-dihydroxyphenyl)ethanone



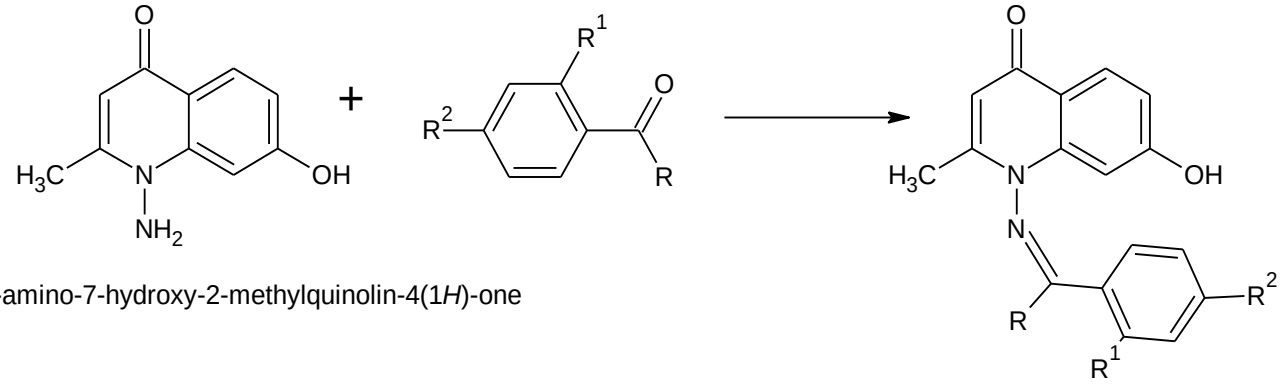
7-hydroxy-2-methyl-4*H*-chromen-4-one

Scheme:2



7-hydroxy-2-methyl-4*H*-chromen-4-one 1-amino-7-hydroxy-2-methylquinolin-4(1*H*)-one

Scheme :3



1-amino-7-hydroxy-2-methylquinolin-4(1*H*)-one

R=CH_3

Table 1: List of aryl aldehydes used for synthesis of Schiff's bases

S.NO.	COMPOUND	R^1	R^2
1	Q_4AA	H	Cl
2	Q_4 AB	H	NO2
3	Q_4AC	H	-n(CH)3
4	Q_4AD	Cl	Cl
5	Q_4AE	H	Br
6	Q_4AF	H	OCH3
7	Q_4AG	OH	OCH3
8	Q_4AH	H	H

II.IV 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^{o}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^{o}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[18-20].

The synthesized compound used to suitably dilute upto the concentrations of 100, 50 and 25 µg 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.

III. RESULTS AND DISCUSSION

Synthesis and the spectral studies

The starting material for the synthesis of 7-hydroxy-2methyl-4H-chromen-4-one, resacetophenone is prepared by taking equal amount of fused $ZnCl_2$ and resorcinol according to literature [21]

Spectral data

1-{[(E)-(4-chlorophenyl)methylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4Aa)

Yield:51%, MP.140 ^{0}C, colour:Black, IR (KBr, cm-1):3479(N-H stretching),2813(C=CH,C=O overtone),1597(C-C,C-N ar),1434(N-N). 1H NMR δ ppm 8.1(C=CH),7.4(CH benzene),7.0(CH benzene),4.84(OH aromatic),1.3(CH aliphatic). **Mass m/z (%):** 312.7 (M +1 peak)

7-hydroxy-1-{[(E)-(4-nitrophenyl)methylidene]amino}quinolin-4(1H)-one(Q4Ab)

Yield 52 %, MP.147 ^{0}C, colour:Cream, IR (KBr, cm-1):3280(NH stretching),1652(C=O),1606(Heterocyclic ring skelrton),1552(C-C ar),1439(N-N). 1H NMR δ ppm 1.3(CH aliphatic). **Mass m/z (%):** 323.3 (M +1 peak)

1-{[(E)-(2-amino-3,4-dimethylphenyl)methylidene]amino}-7-hydroxyquinolin-4(1H) one(Q4Ac):

Yield:52%, MP.148 ^{0}C, Cream, IR (KBr, cm-1):3289(NH stretching),1643(C=O),1557(C-C ar),1489(N-N). 1H NMR δ ppm 7.70(C=NH),7.25(CH benzene),6.75(CH benzene),4.84(OH ar),1.25 (CH aliphatic)
3.2(NH2). **Mass m/z (%):**321.3 (M +1 peak)

1-{[(E)-(2,4-dichlorophenyl)methylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4Ad)

Yield:43%, MP.97^{0}C, colour:Cream, IR (KBr, cm-1):3307(NH stretching),1629(C=O),1556(C-C ar),1448(N-N).
1H NMR δ ppm 7.76(C=NH),7.41(CH benzene),7.41(CH benzene),6.75(CH benzene),5.97(CH benzene),5.0(OH ar), 1.21(CH aliphatic). **Mass m/z (%):** 347.2 (M +1 peak)

1-{[(E)-(4-bromophenyl)methylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4Ae)

Yield:47%, MP.159 ^{0}C, colour:Cream, IR (KBr, cm-1):3297(NH),1630(C=O),1566(C-C ar), 1448(N-N),1312(Nitrogen heterocyclic ring skeleton bands). 1H NMR δ ppm 8.18(C=-NH),7.53(CH benzene),7.36(CH benzene),7.23(CH benzene),4.87(OH ar),1.26(CH aliphatic). **Mass m/z (%):** 357.2 (M +1 peak)

7-hydroxy-1-{[(E)-(4-methoxyphenyl)methylidene]amino}quinolin-4(1H)-one - ethane (1:1)(Q4Af)

Yield:50%, MP.166 ^{0}C, colour: Cream, IR (KBr, cm-1):3303(NH),1634(C=O),1547(C-C ar),1443(N-N),1303(Heterocyclic nitrogen ring skeleton band). 1H NMR δ ppm 8.08(C=NH),7.85(CH benzene),7.40(CH benzene),7.26(CH benzene),4.84(OH ar),1.26(CH aliphatic),3.87(OCH3). **Mass m/z (%):** 308.3 (M +1 peak)

7-hydroxy-1-{[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]amino}quinolin-4(1H)-one(Q4Ag)

Yield:52%, MP.106 ^{0}C, colour:Cream, **IR (KBr, cm-1)**:3316(NH stretching),2650(C=C),1868(overtone of nitrogen heterocyclic),1798(N-C=O),1464(N-N). **1H NMR δ ppm** 7.85(C=NH),7.40(CH benzene),7.38(CH benzene),7.26(CH benzene),4.48(OH ar),1.26(CH aliphatic),3.29(0CH3). **Mass m/z (%):**324.3 (M +1 peak)

7-hydroxy-1-{[(1E,2E)-3-phenylprop-2-en-1-ylidene]amino}quinolin-4(1H)-one(Q4Ah)

Yield:51%, MP.80 ^{0}C, colour:Cream, IR (KBr, cm-1):3392(NH),3057(CH),2319(C=C), 1954(overtone of nitrogen heterocycle),1672(C=O),1597 (C-C ar), 1H NMR δ ppm 7.63(C=NH),7.39(CH benzene),7.29(CH benzene),4.84(OH ar),1.26(CH aliphatic), **Mass m/z (%):**304.3 (M +1 peak).

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-quinolone.

TABLE 2: Antibacterial Activity of Schiff Bases of Schiff Base of 1-amino-7-hydroxy-2-methylquinolin-4(1h)-one.

Micro- organism→	**Enterococcus faecalis**			**Klebsiella pneumoniae**		
	In mm Mean			In mm Mean		
Sample↓	100(µg/ml)	50(µg/ml)	25(µg/ml)	100(µg/ml)	50(µg/ml)	25(µg/ml)
Q_4AA	-	-	-	13±0.86	11±0.57	10±0.57
Q_4AB	13±0.86	12±0.28	8±0.5	16±0.57	11±0.57	10±0.57
Q_4AC	11±0.57	10±0.57	8±0.5	-	-	-
Q_4AD	18±0.28	13±0.86	11±0.57	-	-	-
Q_4AE	20±0.28	14±0.28	11±0.57	17±0.28	15±0.76	14±0.28
Q_4AF	19±0.86	13±0.86	11±0.57	16±0.57	15±0.76	9±0.5
Q_4AG	16±0.57	12±0.28	11±0.57	-	-	-
Q_4AH	13±0.86	12±0.28	10±0.57	16±0.57	15±0.76	11±0.57
Ciproploxacin	26±4.04	14±1.15	12±0.57	33±1.5	30±2.88	25±0.57

Test compounds, such as Q4AD, Q4AE and Q4AF showed moderate activity against gram positive micro-organism while Q4AG and Q4AF showed activity against gram negatives organism lower than standard and other test compounds such as Q4AA, Q4AC, Q4AD and Q4AG did not show any activity against microorganism.

IV. CONCLUSION

In the present study, a series of eight new Schiff base derivatives from 1-amino-7-hydroxy-2-methylquinolin-4(1h)-one has been synthesized with good yields. These compounds were screened for their antibacterial activity against Klebsiella

pneumonia and Enterococcus faecalis. Based on the reported results, it may be concluded that Effort is needed to improve the antibacterial activity of synthesized compound by adding various substituent or metals to the synthesized compounds.

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Author's Profile

Mr. S. K. Vishwakarma pursed Master of Science from Govt. Motilal Vigyan Mahavidyalaya, Barkatullah university of Bhopal in 2009. He is currently pursuing Ph.D. in Department of Chemistry. He worked as Assistant professor in department of Engineering chemistry, IITM Ratibad, RGPV University Bhopal since 2009-2015. He has published more than 5 Research paper also available online. His main research work focused on synthesis of Schiff's bases of 2 and 4-quinolones derivatives and metal complexes to perform Antileptic potentials. He has 6 year teaching experience and 6 month industry experience.

