iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 8 **Issue:** V **Month of publication:** May 2020

DOI: http://doi.org/10.22214/ijraset.2020.5107

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 8 Issue V May 2020- Available at www.ijraset.com

Antimicrobial activity of Schiff Base of 1-Amino-7-Hydroxy-2-Methylquinolin-4(1H)-One

Dr. Alka Pradhan[1], Sanjay Kumar Vishwakarma[2]
[1]*Professor,* [2]*Research Scholar, Department of Chemistry, S .N. Govt. G.P.G. College Bhopal (Madhya Pradesh), India*

Abstract: ***The antimicrobial activity of Schiff base of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one (Q4ka-Q4kh) was investigated using the well diffusion method, against gram positive and gram negative pathogenic microorganisms such as Enterococcus faecalis and Klebsiella pneumonia. A series of these compounds were prepared and have been shown to inhibit pathogenic growth, judging from the area of the zone of inhibition. Test compounds, such as Q4ka showed activity against gram positive micro-organism less than gram negative organisms while Q4kd and Q4kf showed activity against gram negative organism better than gram positive bacteria. And other test compounds such as Q4kc, Q4ke and Q4kg and Q2ke lower activity while Q4kh did not show activity against both type gram +ve and gram –ve bacteria.***
Keyword: Quinolene-4(1H)-one, pyridine, hydrazine hydrate, well diffusion, resacetophenone.

I. INTRODUCTION

Nalidixic acid [1-ethyl-1, 4-dihydro-7-methyl-4-oxo-1, 8- naphthyridine-3-carboxylic acid] and related 4-quinolones are a group of synthetic anti-bacterial agents [1, 2] belong to a class of heterocyclic compounds widely used in modern medicine as broad-spectrum antibiotics. So far, a vast number of 4-quinolone derivatives has been synthesized in order to increase their antibacterial impact or to study their physicochemical properties.[3] Apart from being used as antibacterial agent it possesses various pharmacological activities like gastroprotective, anti-inflammatory, antitumour, hypoglycaemic, anti-HIV, antiallergy, bronchodilatory and antiasthmatic , PDE 4 inhibitor and platelet aggregation inhibition[4]. They have been developed for clinical use in human [5]. They
corrupt the activities of prokaryotic type II topoisomerases, DNA gyrase and topoisomerase IV, and induce them to kill cells by generating high levels of double-stranded DNA breaks. Type II topoisomerases modulate the topological state of the genetic material by passing an intact DNA helix through a transient double stranded break that they generate in a separate DNA segment [6].
In view of these reports and also due to continuation of our works on synthesis eight compound (Q4Ka-Q4Kh), we have developed synthesis of of Schiff base of quinolene-4(1H)-one with the hope to improve their biological activities against some gram-positive and gram-negative microorganisms.

II. MATERIAL AND METHODS

The chemicals and reagent used were of AR grade and LR grade, purchased from Loba Chemicals, Qualigens, S.D Fine Chemicals Ltd., Aldrich, Hi-Media, Merck, Sigma and Ranbaxy.

A. Synthesis of 7-hydroxy-2methyl-4H-chromen-4-one (Q4) [7, 8, 9, 10]

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.

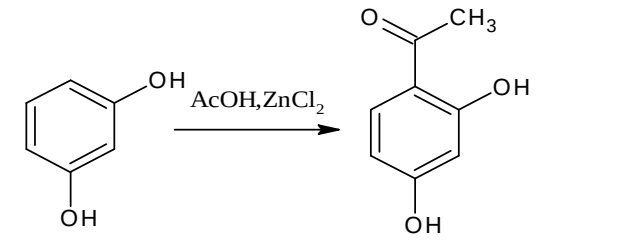
B. Synthesis of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one (Q4A) [11]:

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

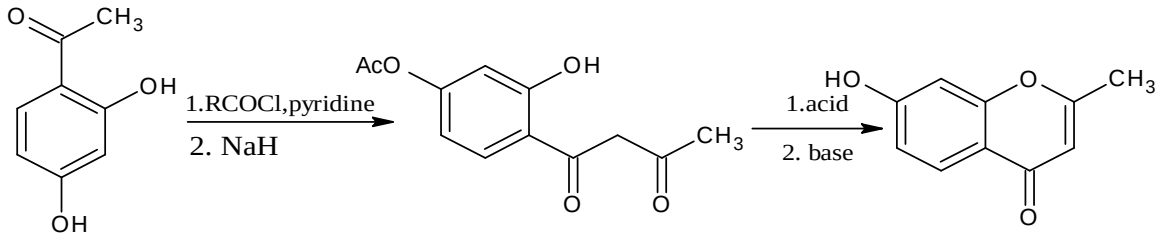
C. Synthesis of Schiff Base of 1-amino-7-hydroxy-2-methylquinolin-4(1H)-one (Q4AA-Q4AH) [12]

To a solution of 0.01 mol of quinolone in 30ml of ethanol, 0.01 mol of ketone 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.

1) Scheme: 1

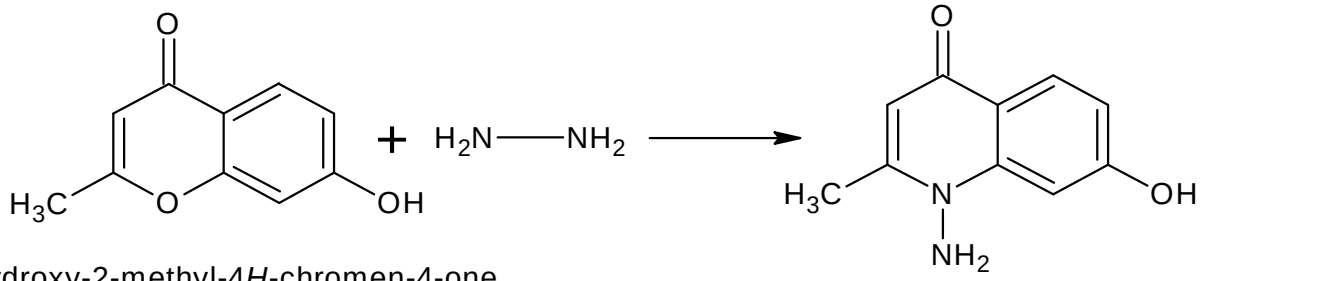


benzene-1,3-diol 1-(2,4-dihydroxyphenyl)ethanone



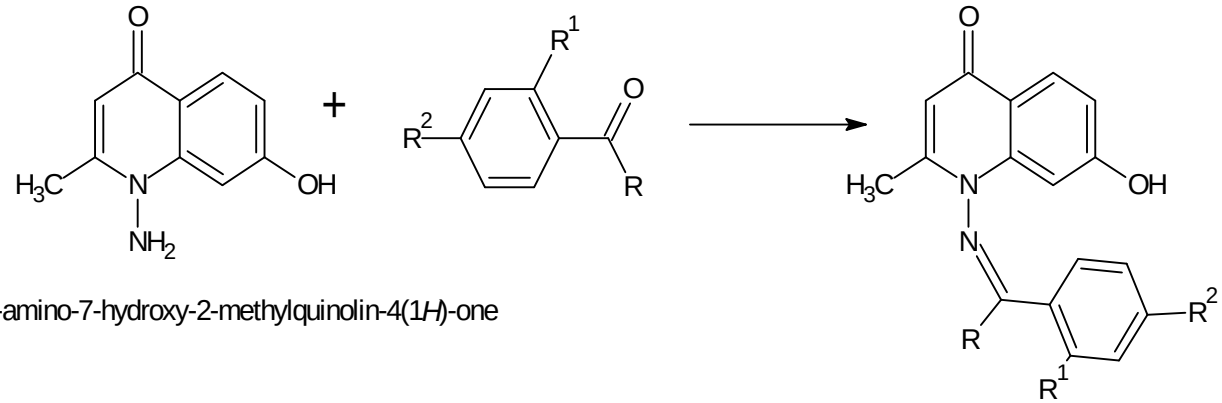
7-hydroxy-2-methyl-4*H*-chromen-4-one

2) Scheme: 2



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

3) Scheme: 3



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

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

S.NO.	COMPOUND	R	R^1	R^2
1	Q_4ka	CH_3	H	OH
2	Q_4kb	CH_3	H	H
3	Q_4kc	$C6H_5$	H	H
4	Q_4kd	CH_3	H	NH_2
5	Q_4ke	CH_3	H	NO_2
6	Q_4kf	CH_3	H	F
7	Q_4kg	CH_3	H	Br
8	Q_4kh	CH_3	H	Cl

D. 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 [13, 14, 15].

The synthesized compound used to suitably dilute up to 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

A. 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 [16]

B. Spectral data

1) *7-hydroxy-1-{[(1E)-1-(4-hydroxyphenyl)ethylidene]amino}quinolin-4(1H)-one(Q4ka):* Yield: 63%, MP. 98^{0}C, colour: Cream, IR (KBr, cm-1):3293(OH stretching), 1648(C=O), 1598(C=N), 1548(C-C ar), 1484(N-N), 1235(C-N), 1058(C-O). 1H NMR δ ppm 7.40(CH benzene), 7.38(CH benzene), 7.27(CH benzene), 4.84(OH ar), 3.28(CH aliphatic), 1.26(CH aliphatic). Mass:295.0(M+1 peak).
2) *7-hydroxy-1-{[(1E)-1-phenylethylidene]amino}quinolin-4(1H)-one(Q4kb):* Yield: 65%, MP. 110^{0}C, colour: Dull red, IR (KBr,cm-1): 3396(OH stretching),3021(CH),1656(C=0),1609(C=N),1539(C-C ar),1489(N-N),1221(C-N),1065(C-O). 1H NMR δ ppm 7.71(CH benzene), 7.69(CH benzene), 7.37(CH benzene), 7.36(CH benzene), 7.15(CH benzene), 6.47(CH benzene), 4.84(OH ar, CH aliphatic), 1.21(CH aliphatic). Mass:279.0(M+2 peak).
3) *1-[(diphenylmethylidene)amino]-7-hydroxyquinolin-4(1H)-one(Q4kc):* Yield: 46%, MP.104^{0}C, colour: Cream, IR (KBr, cm-1) 3280(OH sretching), 1643(C=O), 1602(C=N), 1547(C-C ar), 1493(N-N), 1230(C-N). 1H NMR δ ppm 7.4(CH benzene), 7.27(CH benzene), 6.99(CH benzene), 4.84(OH ar), 3.29(CH aliphatic), 1.26(CH aliphatic). Mass: 341.3(Molecular ion peak).
4) *1-{[(1E)-1-(4-aminophenyl) ethylidene] amino}-7-hydroxyquinolin-4(1H)-one (Q4kd):* Yield: 61%, MP. 180^{0}C, colour: Cream, IR (KBr,cm-1) 3284(OH stretching),1642(C=O),1602(C=N),1547(C-C ar),1439(N-N),1234(C-N),1062(C-O). 1H NMR δ ppm 7.4(CH benzene),7.27(CH benzene),6.99(CH benzene),4.84(OH ar),3.18(CH aliphatic),1.23(CH aliphatic), Mass:294.2(M+1 peak).
5) *7-hydroxy-1-{[(1E)-1-(4-nitrophenyl) ethylidene] amino} quinolin-4(1H)-one (Q4ke):* Yield: 60%, MP.190^{0}C, colour: Cream,IR (KBr,cm-1) 3396(OH stretching),1650(C=O),1606(C=N),1567(C-C ar),1487(N-N),1387(N-O), 1H NMR δ ppm

7.4(CH benzene),7.38(CH benzene),7.25(CH benzene),4.84(OH ar), 3.28(CH aliphatic),1.26(CH aliphatic), Mass:323.9(M+1 peak).

6) *1-{[(1E)-1-(4-fluorophenyl)ethylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4kf):* Yield: 55%, MP. 200^{0}C, colour:light brown,IR (KBr,cm-1)3391(OH stretching),1657(C=O),1612(C=N),1551(C-C ar),1441(N-N), 1H NMR δ ppm 7.4(CH benzene),7.26(CH benzene),6.99(CH benzene),4.84(OH ar), 2.31(CH aliphatic),1.26(CH aliphatic).Mass: 298.1(M+2 peak).
7) *1-{[(1E)-1-(4-bromophenyl)ethylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4kg):* Yield: 61%, MP. 193^{0}C, colour: Cream, IR (KBr, cm-1) 3351(OH),1646(C=O),1612(C=N),1551(C-C ar),1432(N-N), 1H NMR δ ppm 7.3(CH benzene),7.37(CH benzene),7.36(CH benzene),7.24(CH benzene),4.84(OH ar),3.29(CH aliphatic),1.26(CH aliphatic). Mass: 357.6(Molecular ion peak).
8) *1-{[(1E)-1-(4-chlorophenyl)ethylidene]amino}-7-hydroxyquinolin-4(1H)-one(Q4kh):* Yield: 58%, MP. 210^{0}C, colour: Cream ,IR (KBr,cm-1) 3372(OH), 1652(C=O),1622(C=N),1557(C-C ar),1435(N-N), 1H NMR δ ppm 7.4(CH benzene),7.25(CH benzene),7.00(CH benzene),6.60(CH benzene),6.43(CH benzene),4.84(OH ar),3,29(CH aliphatic),1.26(CH aliphatic). Mass: 314.1(M+1 peak).

C. 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 Base of 1-amino-2-methyl-7-hydroxy-4-quinolone.

Table: 2

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_4KA	18±0.28	12±0.28	10±0.57	-	-	-
Q_4KB	-	-	-	13±0.86	12±0.28	6±0.57
Q_4KC	16±0.57	13±0.86	9±0.5	-	-	-
Q_4KD	-	-	-	22±0.57	19±0.86	15±0.76
Q_4KE	16±0.57	10±0.57	6±0.57	13±0.86	10±0.57	9±0.28
Q_4KF	-	-	-	20±0.28	15±0.76	10±0.57
Q_4KG	14±0.28	13±0.86	10±0.57	14±0.28	10±0.57	8±0.5
Q_4KH	-	-	-	-	-	-
Ciproploxacin	26±4.04	14±1.15	12±0.57	33±1.5	30±2.88	25±0.57

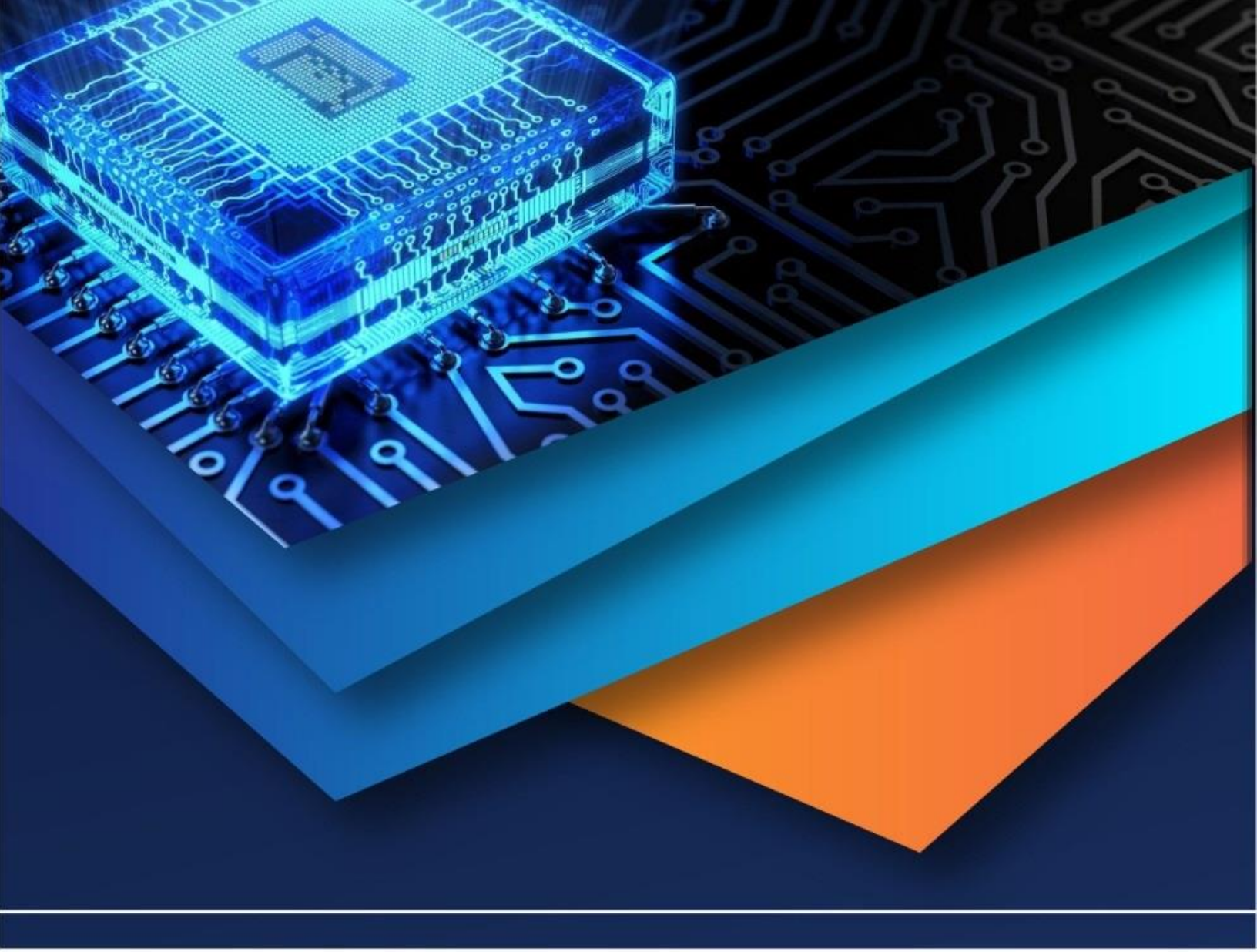
Test compounds, such as Q4ka showed activity against gram positive micro-organism less than gram negative organisms while Q4kd and Q4kf showed activity against gram negative organism better than gram positive bacteria. And other test compounds such as Q4kc, Q4ke and Q4kg and Q2ke lower activity while Q4kh did not show activity against both type gram +ve and gram –ve bacteria.

IV. CONCLUSION

In the present study, eight new derivatives of 1-amino-2-methyl-7-hydroxy-4-quinolone were synthesized. The scheme of synthesis 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 Enterococcus faecalis as good as has activity of standard drug while Q2kc and Q2kg showed good antimicrobial activity against Klebsiella pneumonia. 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 drugs already in market having quinolone moiety.

REFERENCES

[1] Chu D.T.W. and Fernandes P.B., Recent developments of the field of quinolone antibacterial agents, In Advances in Drug Research. Test, 21, 42–144 (1991)
[2] Crumplin G.C. and Smith J.T., Nalidix Acid: An antibacterial paradox, Antimicrob Agents Chemother., 8(3), 251-261 (1975).
[3] Maroš Bella, Marcel Schultz, and Viktor Milata, Synthesis of [1,2,5]selenadiazolo[3,4-f]quinolone derivatives by the Gould-Jacobs reaction of 5-amino-2,1,3-benzoselenadiazole, ARKIVOC 2012 (iv) 242-251.
[4] Asmita Gajbhiye and Lavlesh Chaturvedi , synthesis of 4-quinolones derivatives for their antihistaminic activity, int j pharm pharm sci, vol 5, suppl 1, 223-227.
[5] 12. Alipour E, Mohammadhosseini N, Panah F, Ardestani SK, Safavi M, Shafiee A, et al. Synthesis and In Vitro Cytotoxic Activity of N-2-(2- Furyl)-2-(chlorobenzyloxyimino)ethyl Ciprofloxacin Derivatives. Eur J Med Chem. 2011; 8: 1226-1231.
[6] Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev. 1997; 61: 377-392
[7] W. Baker, “Molecular rearrangement of some o-acycloxycetophenone and the mechanism of the production of 3-acylchromone,” J. Chem. Soc., 1381-1389, 1933.
[8] R.H., Erickson, Jr. Natalie., k.J. Bock, “(aminolkoxy)chromones. Selective sigma receptor ligand,” J. Med. Chem. 35, 1526-1535, 1992.
[9] Nuss baumer, P.,Lehr , A.J. Billich, “2-Substituted 4-(thio)Chromenone 6-o-sulfamates: potent inhibitors of human steroids sulfatase,” Med. Chem. 45, 4310-4320, 2002.
[10] Billich,A.,Nussbaumer ,P., Schreiner,E., Schuster,I.,1999.preparation of Chromanone and Thiochromanone Derivatives as Steroid Sulfatase Inhibitors. Patent WO 9952890.
[11] R. I. H. Al-Bayati and M. F. Radi, “Synthesis of novel 2-quinolone derivatives,”African Journal of Pure and Applied Chemistry, vol. 4, Issue 10, 228-232, 2010.
[12] Saied M E Khalil, “Metal complex of Schiff base ligands derived from 4-hydroxy -2(1H) quinolone and ethylnediamine or 1, 2-propylenediamine,” Indian journal of chemistry 33A (9), 830-836, 1994.
[13] S. Magaldi. Well diffusion for antifungal susceptibility testing. International journal of infectious diseases., 2004,8:39-45.
[14] Antara sen and Amla Batra, evaluation of antimicrobial activity of different solvent extracts of medicinal plant:Melia Azedarach L. International journal of current pharmaceutical research, 2012,4(2), 67-73.
[15] Hossein jahagirian,Md jelas haron,leiri afsah-hejari,well diffusion method for evaluation of antibacterial activity of copper phenyl fatty hydroxamate synthesided from canola and palm kernel oil. Digest Journal of Nanomaterial and Biostructure,2013:8(3); 1263-1270
[16] Systematic organic chemistry, by W.M. Cumming, 91, 1937.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY