

SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY OF SOME NOVEL SCHIFF BASES DERIVED FROM 8-HYDROXY QUINOLINE

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ABSTRACT

A novel series of Schiff bases of 8-hydroxy quinoline (3a-j) have been synthesized and characterized by means of TLC, melting point and spectral data like IR, ¹HNMR. Synthesized compounds were screened for their antibacterial activity against four different strains like *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2708), *Pseudomonas aeruginosa* (NCIM 2242) and *Escherichia coli* (NCIM 2685) with standard drug ampicillin while antifungal activity was determined against strains like *Candida albicans* (NCIM 22491) with standard drug griseofulvin. Screening of antioxidative capacity was based on ability to scavenge free radicals by 1, 1-diphenyl-2-picryl hydrazyl (DPPH). The results were compared to standard substance ascorbic acid. All the synthesized compounds were screened for their antioxidant, antibacterial and antifungal activity. Some of the derivatives have promising antimicrobial and antioxidant activity.

KEYWORDS

Synthesis, 8-hydroxy quinoline, Schiff bases, DPPH, Antimicrobial activity, Antioxidant activity.

INTRODUCTION

Schiff bases, named after Hugo Schiff ¹, are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis and as polymer stabilizers ². Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties ²⁻⁵.

In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements for many naturally occurring

compounds ⁶. While 8-hydroxyquinolines have been explored as a viable drug discovery platform in many instances. It can exert their physiological properties through bidentate chelation of metal ions ⁷. The biological activities of the 8-hydroxyquinolines derived against EGLN-1 (a family of non-heme iron-containing prolyl hydroxylases) enzyme. Most of these 8-hydroxyquinoline analogs are potent inducers of VEGF (a downstream biomarker for hypoxia inducible factor (HIF-1) stabilization) ⁸.

In view of the facts mentioned above and as part of our initial efforts to discover potentially active new series of Schiff bases of 8-hydroxy quinolone incorporated with different aromatic aldehydes (3a-j) were synthesized and evaluated for their antimicrobial & antioxidant activity. Structures of the newly synthesized compounds were assigned on the basis of IR, ¹HNMR & Mass spectral data.

MATERIALS AND METHODS

Melting points of the newly synthesized compound was determined by open capillary method and are uncorrected. Purity of the compounds was checked by TLC on silica gel coated plates obtained from Merck as stationary phase and solvent mixture of toluene: ethyl acetate (3:1) was used as mobile phase at temperature 25^o C. ¹H-NMR spectrum was recorded on Bruker DRX 300 using deuteriated methanol as a solvent. The IR spectrum was recorded on Shimadzu-8201 PC.

General procedure for synthesis of Schiff bases (1-3)

8-hydroxy quinoline was treated with ethyl chloro acetate to give 8- hydroxy quinoline ethyl acetate, which on hydrazonolysis gave 8-hydroxy quinoline acetyl hydrazide. This compound was converted to corresponding Schiff bases of 8-hydroxy quinoline acetyl hydrazide by the reaction with different aromatic aldehydes **Scheme-1**.

8-hydroxy quinoline ethyl acetate (1)

A mixture of 8-hydroxy quinoline (0.1mol), ethylchloroacetate (0.1mol) and anhydrous potassium carbonate (19.5gm, 0.15mol) in dry acetone were refluxed on a water bath for 24 hours at 70°C. The resultant reaction mixture was cooled and filtered; the filtrate excess of acetone was removed by distillation. This reaction mixture of filtrate was then poured on to the ice cold water and stirred well. The

organic layer was extracted with ether and further the ether layer was washed with 5% HCl and dried over anhydrous sodium sulphate. Ether layer was evaporated by drying on water bath. Finally the resultant collected liquid was purified under reduced pressure to give pure 8-hydroxy quinoline ethyl acetate.

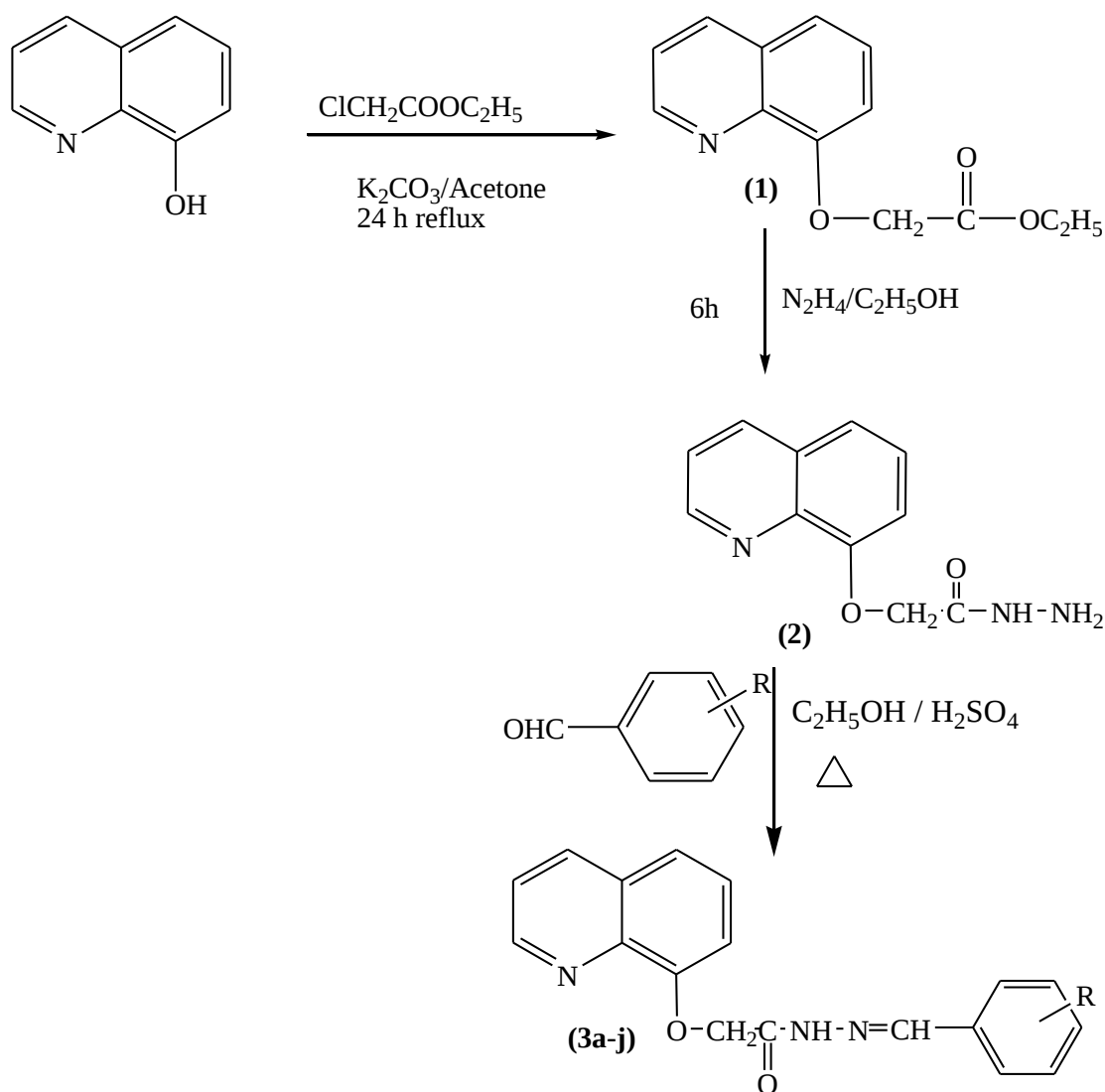
8-hydroxy quinoline acetyl hydrazide (2)

A mixture of 8-hydroxy quinoline ethyl acetate (0.05mol), hydrazine hydrate (99% 0.07 mol) in ethanol (100 ml) was refluxed for 6 hours. From the resultant mixture excess of ethanol was removed by distillation. On cooling, from the resultant mixture, white needle like crystals of 8-hydroxy quinoline acetyl hydrazide began to separate. It was collected and then recrystallized from ethanol.

Schiff bases (3a-j)

A mixture of 8-hydroxy quinoline acetyl hydrazide(0.01mol)(dissolved in minimum quantity of ethanol) and different aromatic or heterocyclic aldehydes (0.01 mol, dissolved in minimum quantity of ethanol) was refluxed together by employing sulphuric acid about 0.01 mol as catalyst in a round bottom flask on a water bath for 6 hours. The precipitate was filtered, washed with ice cold water and recrystallized from ethanol.

Scheme:-1



R=H,2,4-Dihydroxy,2-Nitro,4-Chloro,4-Chloro-3-methoxy,4-Hydroxy, 2-Hydroxy,4-Methoxy, 4-Dimethylamino,2,6-Dihydroxy.

Biological activity:

Minimum inhibitory concentration (MIC) for bacteria of **3a-j** of all the synthesized compounds was determined against four different strains, viz two gram positive bacteria (*S.aureus* and *B.subtilis*) and two gram negative bacteria (*E. coli* and *P. aeruginosa*) as compared to the standard drug ampicillin by broth dilution method ^{9,10}. Minimum inhibitory concentration (MIC) for antifungal activity was carried out against *C.albicans* and the results were compared with the standard drug griseofulvin by the same method.

Antimicrobial activity:

The newly synthesized compounds were screened for their *in-vitro* antibacterial activity against *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2708), *Pseudomonas aeruginosa* (NCIM 2242) and *Escherichia coli* (NCIM 2685) bacterial stains by serial plate dilution method ^{11, 12}. Serial dilutions of the drug in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium

was inoculated and incubated for 16 to 18 h at 37°C.

The minimum inhibitory concentration (MIC) was noted by observing the lowest concentration of the drug at which there was no visible growth. Numbers of antibacterial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using a punch, wells were made on these seeds agar plates and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The petri dishes were prepared in triplicate and maintained a 37 °C for 3 to 4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ampicillin as standard. All the synthesized compounds were taken at different concentration of 500 and 600 µg/ml. The result was compared with the ampicillin (500 µg/ml) in the **Table-2**.

Antifungal activity:

Newly prepared compounds were also screened for their antifungal activity against *Candida albicans* (NCIM 22491), in DMSO by serial plate dilution method ¹². Sabourauds agar media was prepared by dissolving peptone (1g), D glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. DMSO was used to make a suspension of sore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates. Minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37°C for 3 to 4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. All the synthesized compounds were taken at different concentration of 500 and 600 µg/ml. The result was compare with the griseofulvin (500 µg/ml) in the **Table -2**.

Table 1: Physicochemical parameter of the synthesized compounds (3a-j)

Compound	(-R)	Mol.formula ^a	Mol.wt.	R _f ^b	Elemental analysis % calculated ^c		
					C	H	N
3a	2,4-Dihydroxy	C ₁₈ N ₃ O ₄ H ₁₅	337.33	0.78	64.09	4.48	12.46
3b	2-Nitro	C ₁₈ N ₄ O ₄ H ₁₄	350.33	0.77	61.71	4.03	15.99
3c	4-Chloro	C ₁₈ N ₃ O ₂ H ₁₄ Cl	339.78	0.65	63.63	4.15	12.37
3d	4-Chloro-3-methoxy	C ₁₉ N ₃ O ₃ H ₁₆ Cl	369.80	0.68	61.71	4.36	11.36
3e	4-Hydroxy	C ₁₈ N ₃ O ₃ H ₁₅	321.33	0.77	67.28	4.71	13.08
3f	H	C ₁₈ N ₃ O ₂ H ₁₅	305.33	0.82	70.81	4.95	13.76
3g	2-Hydroxy	C ₁₈ N ₃ O ₃ H ₁₅	321.33	0.87	67.28	4.71	13.08
3h	4-Methoxy	C ₁₉ N ₃ O ₃ H ₁₇	335.36	0.73	68.05	5.11	12.53
3i	4-Dimethylamino	C ₂₀ N ₄ O ₂ H ₂₀	348.40	0.83	68.95	5.79	16.08
3j	2,6-Dihydroxy	C ₁₈ N ₃ O ₄ H ₁₅	337.33	0.72	64.09	4.48	12.46

^a Solvent crysllization-Ethanol

^b Solvent system- Toluene: Ethyl acetate (3:1)

^c Elemental analysis calculated by using software Chemdraw ultra 8.0

Table 2: Antimicrobial activity of synthesized Schiff bases (3a - j)

Sl. No.	Compounds	Concentration (µg/ml)	Zone of inhibition (mm) (Mean±SEM)				
			Gram negative bacteria		Gram positive bacteria		Fungus
			<i>E. coli</i>	<i>P. aureginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>C. albicans</i>
1	3a	500	16.2±0.19*	18.2±0.37**	16.3±0.07*	15.2±0.71*	15.3±0.21*
		600	17.6±0.31*	19.5±0.63***	17.3±0.29*	16.5±0.32**	15.4±0.26*
2	3b	500	18.3±0.26**	15.7±0.21*	16.6±0.29*	16.6±0.36**	15.7±0.31**
		600	20.1±0.19***	16.7±0.38*	17.8±0.27**	16.9±0.23**	16.8±0.27***
3	3c	500	15.4±0.23*	17.3±0.32**	21.3±0.21***	17.4±0.26***	14.1±0.14*
		600	16.8±0.28*	18.9±0.41***	22.3±0.37***	18.3±0.19***	15.5±0.31*
4	3d	500	17.1±0.36*	15.2±0.39*	15.3±0.24*	-	-
		600	18.9±0.23**	16.3±0.25*	16.6±0.27*	-	-
5	3e	500	19.1±0.27**	18.1±0.31**	19.3±0.32**	16.7±0.42**	16.3±0.13**
		600	20.9±0.26***	18.9±0.52***	19.9±0.21***	17.2±0.71***	17.7±0.21***
6	3f	500	19.3±0.24**	-	16.5±0.29*	15.4±0.32*	-
		600	21.0±0.19***	-	17.7±0.27**	16.2±0.13**	-
7	3g	500	19.7±0.21**	16.6±0.21*	16.5±0.32*	16.5±0.37**	16.1±0.12**
		600	21.3±0.29***	17.3±0.17**	17.7±0.19**	17.1±0.28***	17.3±0.11***
8	3h	500	17.1±0.23*	15.8±0.31*	16.3±0.26*	15.3±0.31*	-
		600	17.9±0.26*	16.3±0.76*	16.9±0.19*	16.2±0.21*	-
9	3i	500	16.7±0.18*	18.3±0.23**	17.9±0.53**	16.1±0.21*	16.5±0.21**
		600	16.8±0.23*	18.9±0.98***	18.8±0.42**	16.9±0.01**	16.9±0.32**
10	3j	500	-	-	15.1±0.71*	15.2±0.21*	-
		600	-	-	16.5±0.31*	16.6±0.27**	-
11	Ampicillin	500	22.0±0.24	20.3±0.16	23.0±0.22	19.1±0.17	-
12	Griseofulvin	500	-	-	-	-	18.5±0.21

Each value represents Mean ± SEM, value of three determinants. One-way ANOVA followed by Dunnet test through Instant software, compare all vs. standard applied. Statistically extremely significant and significant at ***P < 0.001 & **P < 0.01 respectively.

Antioxidant activity:

Reduction of 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical (DPPH method):

The nitrogen centered stable free radical 1, 1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color^{13, 14}. This property makes it suitable for spectrophotometer studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts it into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The

change in the absorbance produced in this reaction has been used to measure antioxidant properties. The solutions of test compounds (100 µM) were added to DPPH (100 µM) in dioxane/ethanol. The tubes were kept at an ambient temperature for 30 min and the absorbance was measured at λ 517 nm. The inhibition percentage was calculated by using the formula % inhibition = [(A_{Control} - A_{Sample})/ A_{Control}] x 100 where A_{Control} is the absorbance of the L-ascorbic acid and A_{Sample} is the absorbance of different compounds. The result was compare with the standard ascorbic acid (100 µM) in the **Table -3**.

Table 3: Antioxidant property of synthesized Schiff bases (3a - j)

Compounds	DPPH Scavenging (%)
3a	89.61±0.59***
3b	39.62±0.82*
3c	76.27±0.73***
3d	37.73±0.91*
3e	29.47±0.42*
3f	57.96±0.37**
3g	47.98±0.38*
3h	67.24±0.21**
3i	49.25±0.45*
3j	79.22±0.41***
Ascorbic acid	96.36±0.32

Each value represents Mean $\pm$ SEM, value of three determinants. One-way ANOVA followed by Dunnet test through Instant software, compare all vs. standard applied. Statistically extremely significant and significant at *** $P < 0.001$ & ** $P < 0.01$ respectively.

Spectral data

N-(2,4-dihydroxybenzylidene)-2-(quinolin-8-yloxy)acetohydrazide(3a):

IR(KBr) $\nu_{\max}$ cm⁻¹:3324(NHstr.),3152(OHstr.),2990(CHstr.),1810(C=Nstr.),1603(C=Ostr.),1217(N-Nstr.),1120(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.71(s,2H,CH₂-acetamide),6.85-8.37(m,6H,CH-quinoline),6.12(s,2H,Ar-OH),6.20-7.38(m,3H,Ar-H),8.90 (s,1H,NH-acetamide).

N-(2-nitrobenzylidene)-2-(quinolin-8-yloxy)acetohydrazide(3b):

IR(KBr) $\nu_{\max}$ cm⁻¹:3300(NHstr.),2950(CHstr.),1822(C=Nstr),1612(C=Ostr),1201(N-Nstr.),1327(NO₂str),1127(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.38(s,2H,CH₂-acetamide),6.90-8.89(m,6H,CH-quinoline),7.91-8.23(m,4H,Ar-H),8.31(s,1H,NH-acetamide).

N-(4-chlorobenzylidene)-2-(quinolin-8-yloxy) acetohdrazide (3c):

IR(KBr) $\nu_{\max}$ cm⁻¹:3359(NHstr.),2962(CHstr),1810(C=Nstr),1610(C=Ostr),1223(N-Nstr.),1110(C-O-C),835(C-Clstr).

¹HNMR(DMSO-d₆, δ ppm):4.53(s,2H,CH₂-acetamide),6.91-8.78(m,6H,CH-quinoline),7.31-7.62(m,4H,Ar-H),9.21(s,1H,NH-acetamide).

N-(4-chloro-3-methoxybenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (3d):

IR(KBr) $\nu_{\max}$ cm⁻¹:3374(NHstr.),3102(CHstr),1789(C=Nstr),1645(C=Ostr),1239(N-Nstr.),1130(OCH₃str.),1120(C-O-C),833(C-Clstr).

¹HNMR(DMSO-d₆, δ ppm):3.72(s,3H,OCH₃),4.85(s,2H,CH₂-acetamide),6.93-8.13(m,6H,CH-quinoline),7.10-7.23(m,3H,Ar-H),9.24(s,1H,NH-acetamide).

N-(4-hydroxybenzylidene)-2-(quinolin-8-yloxy)acetohydrazide(3e):

IR(KBr) $\nu_{\max}$ cm⁻¹:3392(NHstr.),3250(OHstr.),3122(CHstr.),1736(C=Nstr.),1617(C=Ostr),
1210(N-Nstr.),1120(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.79(s,2H,CH₂-acetamide),6.82-8.64(m,6H,CH-quinoline),6.82-7.64(m,4H,Ar-H),6.21(s,1H,Ar-OH),8.26(s,1H,NH-acetamide).

N-benzylidene-2-(quinolin-8-yloxy)acetohydrazide (3f):

IR(KBr) $\nu_{\max}$ cm⁻¹:3390(NHstr.),2885(CHstr.),1736(C=Nstr.),1610(C=Ostr),1267(N-Nstr.),1125(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.29(s,2H,CH₂-acetamide),6.72-8.27(m,6H,CH-quinoline),7.31-7.62(m,5H,Ar-H),9.29(s,1H,NH-acetamide).

N-(2-hydroxybenzylidene)-2-(quinolin-8-yloxy) acetohydrazide(3g):

IR(KBr) $\nu_{\max}$ cm⁻¹:3392(NHstr.),3240(OHstr.),2875(CHstr.),1727(C=Nstr.),1650(C=Ostr),1286(N-str.),1121(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.83(s,2H,CH₂-acetamide),6.91-8.34(m,6H,CH-quinoline),6.27(s,1H,Ar-OH),6.83-7.45(m,4H,Ar-H),9.17(s,1H,NH-acetamide).

N-(4-methoxybenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (3h):

IR(KBr) $\nu_{\max}$ cm⁻¹:3375(NHstr.),2895(CHstr.),1757(C=Nstr.),1670(C=Ostr),1226(N-Nstr.),1135(OCH₃str),1117(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):3.83(s,3H,OCH₃),4.81(s,2H,CH₂-acetamide),6.73-8.81(m,6H,CH-quinoline),6.90-7.56(m,4H,Ar-H),8.47(s,1H,NH-acetamide).

N-(4-(dimethylamino)benzylidene)-2-(quinolin-8-yloxy)acetohydrazide(3i):

IR(KBr) $\nu_{\max}$ cm⁻¹:3350(NHstr.),2945(CHstr.),1810(C=Nstr.),1590(C=Ostr),1210(N-Nstr.),1120(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):2.30,2.52(s,3H,CH₃),4.90(s,2H,CH₂-acetamide),6.87-8.79(m,6H,CH-quinoline),6.67-7.43(m,4H,Ar-H),8.41(s,1H,NH-acetamide).

N-(2,6-dihydroxybenzylidene)-2-(quinolin-8-yloxy)acetohydrazide(3j):

IR(KBr) $\nu_{\max}$ cm⁻¹:3320(NHstr.),3150(OHstr.),2920(CHstr.),1710(C=Nstr.),1603(C=Ostr),1195(N-Nstr.),1123(C-O-C).

¹HNMR(DMSO-d₆, δ ppm):4.10(s,2H,CH₂-acetamide),6.75-7.14(m,6H,CH-quinoline),7.20(s,1H,Ar-OH),7.16-7.87(m,3H,Ar-H),9.12(s,1H,NH-acetamide).

RESULTS & DISCUSSION

Formation of 8-hydroxy quinoline nucleus containing Schiff bases was confirmed by recording their IR, ¹HNMR and mass spectrum. The IR spectra of all the derivatives **3a-j** showed absorption band at 3320-3392 cm⁻¹ due to NH stretching,3152-3250 cm⁻¹ due to OH stretching,2875-3122 cm⁻¹ due to CH stretching,1710-1822 cm⁻¹ due to C=N stretching,1590-1670 cm⁻¹ due to C=O stretching,1327 cm⁻¹ due to NO₂ stretching,1195-1286 cm⁻¹ due to N-N stretching,1130-

1135 cm⁻¹ for OCH₃ stretching,1110-1127 cm⁻¹ due to C-O-C stretching, 833-835 cm⁻¹ for C-Cl stretching.

The ¹HNMR spectrum of **3a-j** appeared as singlet in the region of δ , 8.26-9.29 due to NH-acetamide. δ , 6.20-8.23 appeared as multiplet due to Ar-H. δ , 6.75-8.89 appeared as multiplet due to CH-quinoline. δ , 4.10-4.90 appeared as singlet due to CH₂ acetamide. **3a**, **3e**, **3g**, **3j** δ , 6.21-7.20 region appeared as singlet due to Ar-OH. **3d** & **3h** δ , 3.72-3.83 region appeared

as singlet due to OCH_3 and **3i** δ ,2.30-2.52 appeared as singlet due to CH_3 .

From screening results, it was observed that final compounds **3b**, **3d**, **3e**, **3f** & **3g** possessed significant activity against *E. coli*, compounds **3b**, **3e** and **3g** possessed extremely significant activity against *E. coli*. Final compounds **3a**, **3c**, **3e**, **3g**, & **3i** possessed significant activity against *P. aeruginosa* and compounds **3a**, **3c**, **3e** & **3i** possessed extremely significant activity against *P. aeruginosa*. Final compounds **3b**, **3e**, **3g** & **3i** possessed significant activity against *S. aureus*, while compounds **3c** & **3e** only possessed extremely significant activity against *S. aureus*. Compounds **3a**, **3b**, **3e**, **3f**, **3g**, **3i** and **3j** and were shown to significant activity against *B. subtilis*, while compound **3c**, **3e** & **3g** possessed extremely significant activity. The remaining compounds of the entire series possessed moderate to poor antibacterial activity. The discussion and comparison of antibacterial activity were given with respect to ampicillin antibiotic. The antibacterial activity is described in **Table 2**.

Antifungal screening data showed that final compounds **3b**, **3e**, **3g** and **3i** possess significant activity, while compounds **3b**, **3e**, **3g** possessed extremely significant activity against *C. albicans*. The remaining compounds of the entire series possess moderate antifungal activity. The discussion and comparison of antifungal activity were compared with griseofulvin. The antifungal activity is described in **Table 2**.

The compounds **3a-j** were tested for antioxidant property by DPPH method. The results revealed that the compounds **3f**, **3h** showed significant activity while compound **3a**, **3c**, **3j** showed extremely significant activity with standard substance ascorbic acid.

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