

Original Article

DESIGN AND SYNTHESIS OF NOVEL QUINOLINE 3-CARBOHYDRAZONE DERIVATIVES FOR THEIR ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY

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ABSTRACT

Objective: To synthesize novel quinoline 3-carbohydrazone derivatives by conventional method and to characterize them by using IR, ¹H NMR and mass spectra and to screen the compounds for antimicrobial and antioxidant activities.

Methods: Series of ten new N'-substituted-2-methylquinoline-3-carbohydrazone scaffolds have been synthesized by the conventional method i.e., condensation of quinoline hydrazides with substituted aldehydes to form quinoline hydrazones. The synthesized compounds are evaluated for antimicrobial and antioxidant activities by using two fold serial dilution method and DPPH, H₂O₂ scavenging assay respectively.

Results: The synthesized compounds were characterized by IR, ¹H NMR and mass spectra and they were screened for their antimicrobial and antioxidant activities. Some of the compounds were exhibited moderate to good activities. Remaining matter deleted

Conclusions: Some matter deleted. This clearly reveals that the compounds substituted with electron withdrawing groups on aromatic ring exhibit significant activity than the unsubstituted compounds.

Keywords: Quinoline, Hydrazone, Antibacterial, Antifungal, Antioxidant.

INTRODUCTION

Among the wide variety of heterocyclic compounds that have been explored for developing pharmaceutically important molecules, quinolines have played an important role in medicinal chemistry in last few decades and it is endowed with various activities, such as antibiotic [1], anti-tuberculosis [2], antimalarial [3], anti-inflammatory [4], anticancer [5], anti-hypertensive [6], tyrosinase inhibiting agents [7] and anti-HIV[8]. Hydrazones are active pharmacophores which possesses an azomethine proton constituting an important class of compounds for new drug development. They form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, antifungal [9] and antioxidant activities [10]. Thus a program of synthesis of Quinolinyl hydrazones was envisaged to serve as a new scaffold for evaluation as antioxidant and antimicrobial agents. The search for new drugs is an area of active investigation with the goal of developing novel drugs in order to overcome the phenomenon of drug resistance. It is well-known that the quinoline nucleus and its derivatives play a vital role in the design of an important class of wide spectrum antibacterial agents. Structure-activity relationship (SAR) studies revealed that the antimicrobial activity in this class of compounds depends on the nature of the peripheral substituents and their spatial relationship within the quinoline nucleus.

MATERIALS AND METHODS

All the chemicals used were of Analytical grade obtained from Sd fine, Spectrochem and Aldrich chemicals. Completion of the reaction was monitored by thin layer chromatography (TLC) using E-Merk 0.25 mm silica gel plates. Visualization was accomplished with UV light (256nm). All the solvents were distilled and dried using appropriate drying agents before use. Melting points were determined on ANALAB melting point apparatus and were uncorrected. All the ¹H NMR spectra were recorded in DMSO-*d*₆ solvent. Chemical shifts are reported on AVANCE 300 MHz and INNOVA 500 MHz relative to TMS internal standard on the δ (ppm)-scale. The IR spectra were recorded on SCHIMADZU FT-IR SPECTROPHOTOMETER by using 1% Potassium bromide discs. The mass spectra were recorded on Agilent 1100 series.

Chemical synthesis

Procedure for the Synthesis of ethyl 2-methyl quinoline-3-carboxylate (3)

Iron powder (4mmol) and 0.1M HCl (0.05mmol) were sequentially added to a solution of an ortho-nitro benzaldehyde in methanol and the resulting mixture was stirred vigorously at 95 °C (oil bath temperature) while reaction mixture was monitored by TLC. On completion of the reduction, the β-ketoester was added and the reaction mixture was refluxed. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature; methanol was removed under reduced pressure, diluted with ethylacetate and filtered through the celite pad. The filtrate was neutralized with saturated sodium bicarbonate solution (NaHCO₃), washed with water two times, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried by using anhydrous Na₂SO₄, filtered and solvent was removed under reduced pressure. The crude material recrystallized from hexane and the colored impurities were removed by activated charcoal treatment.

Procedure for the synthesis of 2-methyl quinoline-3-carbohydrazone (4)

Quinoline ester (1eq) was dissolved in methanol (5ml) and excess amount of hydrazine hydrate (99%, 3eq) was added to the reaction mixture and refluxed for overnight. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature; white crystals were separated out from reaction mixture. Then crystals were filtered, and washed with methanol to get a pure compound. These crystals have enough purity to proceed for further step.

Procedure for the synthesis of 2-methyl-N'-[(E)-phenyl methylidene] quinoline-3-carbohydrazone (5a-j)

To a solution of quinolinehydrazone (1 mol) in methanol (5ml) and then corresponding arylaldehydes (1 mol) were added and refluxed for requisite time. Completion of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, solid thus obtained was filtered and washed with methanol to obtain pure product.

Ethyl 2-methylquinoline-3-carboxylate (3)

¹H NMR (DMSO-d₆) δ_H: 8.7 (1H,s), 8.0 (1H, d), 7.8 (1H,d), 7.7 (1H, t), 7.5 (1H, t), 4.4 (2H, q, CH₂), 3.0 (3H, s), 1.5 (3H, t, CH₃); IR (KBr Disc) cm⁻¹: 3050 (ArH), 1714 (ester -C=O); LC-MS (ESI, m/z): 216 (M+H).

2-methylquinoline-3-carbohydrazide (4)

¹H NMR (DMSO-d₆) δ_H: 9.6 (1H,s), 8.18 (1H, s), 7.93 (1H,t), 7.7 (1H, t), 7.83 (1H, d), 7.68 (1H, s), 7.51 (1H, s), 1.8 (3H, s, CH₃); IR (KBr Disc) cm⁻¹: 3259-3141 (-NH-NH₂), 2928 (Ar-H), 1620 (-C=O); LC-MS (ESI, m/z): 202 (M+H). **2-methyl-N'-[(E)-phenylmethylidene]quinoline-3-carbohydrazide (5a)**

¹H NMR (DMSO-d₆) δ_H: 11.69 (1H, s), 8.29 & 8.15 (1H, s, Cis-trans conformer), 8.17-7.47 (1H, m), 7.88-7.61 (3H, m), 7.57-7.47 (1H, q), 7.42-7.32 (2H, m), 7.24 (2H,d), 2.85 & 2.73 (3H,s, Cis-trans conformer); IR (KBr Disc) cm⁻¹: 3360 (NH), 1648 (C=O); LC-MS (ESI, m/z): 290 (M+H)

2-methyl-N'-[(E)-(4-methylphenyl) methylidene] quinoline-3-carbohydrazide (5b)

¹H NMR (DMSO-d₆) δ_H: 11.76 & 11.68 (1H, s, Cis-trans conformers), 8.30 & 8.25 (1H, s, Cis-trans conformer), 7.98 (1H, d), 7.91-7.60 (4H, m), 7.53 (1H,t), 7.22 (2H, t), 7.03 (1H, d), 2.83 (3H, s, Cis-trans conformer), 2.40-2.29 (3H,s, Cis-trans conformer); IR (KBr Disc) cm⁻¹: 3215 (NH), 1651 (C=O); LC-MS (ESI, m/z): 304 (M+H), 330 (M+Na).

N'-[(E)-(4-methoxyphenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5c)

¹H NMR (DMSO-d₆) δ_H: 8.30 & 8.24 (1H, s, Cis-trans Conformer), 7.99 (1H, d), 7.93-7.64 (4H, m), 7.55 (1H, t), 7.29 (1H, d), 6.91 (1H, d), 6.74 (1H, d), 3.85 & 3.75 (3H, s, Cis-trans Conformer), 2.83 & 2.70 (3H, s, Cis-trans Conformer); IR (KBr Disc) cm⁻¹: 3464 (NH), 1666 (C=O); LC-MS (ESI, m/z): 320 (M+H), 342 (M+Na).

2-methyl-N'-[(E)-(2-nitrophenyl) methylidene] quinoline-3-carbohydrazide (5d)

¹H NMR (DMSO-d₆) δ_H: 11.85 & 11.87 (1H, s, Cis-trans Conformer), 8.33 & 8.28 (1H, s, Cis-trans Conformer), 8.07-7.82 (3H, m), 7.80-7.63 (2H, m), 7.61-7.47 (2H, m), 7.36 (1H, d), 7.25 (1H, d), 2.82 & 2.69 (3H, s, Cis-trans Conformer); IR (KBr Disc) cm⁻¹: 3184 (NH), 1654 (C=O); LC-MS (ESI, m/z): 335 (M+H).

2-methyl-N'-[(E)-(4-nitrophenyl) methylidene] quinoline-3-carbohydrazide (5e)

¹H NMR (DMSO-d₆) δ_H: 10.72 & 10.76 (1H, s, Cis-trans Conformer), 8.43 & 8.38 (1H, s, Cis-trans Conformer), 7.87-7.72 (3H, m), 7.60-7.53 (2H, m), 7.51-7.39 (2H, m), 7.26 (1H, d), 7.18 (1H, d), 2.12 & 2.29 (3H, s, Cis-trans Conformer); IR (KBr Disc) cm⁻¹: 3172 (NH), 1537 (C=O); LC-MS (ESI, m/z): 335 (M+H)

N'-[(E)-(4-chlorophenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5f)

¹H NMR (DMSO-d₆) δ_H: 10.71 & 11.51 (1H, s, Cis-trans Conformer), 7.67 & 7.94 (1H, s, Cis-trans Conformer), 7.19 (1H, t), 7.85 (1H, t), 7.42 (1H, q), 6.21 (1H, s), 5.91 (1H, s); IR (KBr Disc) cm⁻¹: 3290 (NH), 1514 (C=O); LC-MS (ESI, m/z): 324 (M+H).

N'-[(E)-(3-chlorophenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5g)

¹H NMR (DMSO-d₆) δ_H: 11.71 & 11.63 (1H, s, Cis-trans Conformer), 8.27 & 8.24 (1H, s, Cis-trans Conformer), 7.99 (1H, t), 7.84 (1H, t), 7.73 (1H, q), 6.86 (1H, s), 6.51 (1H, s); IR (KBr Disc) cm⁻¹: 3340 (NH), 1664 (C=O); LC-MS (ESI, m/z): 324 (M+H).

N'-[(E)-(2-chlorophenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5h)

¹H NMR (DMSO-d₆) δ_H: 11.53 & 11.21 (1H, s, Cis-trans Conformer), 8.17 & 8.14 (1H, s, Cis-trans Conformer), 7.19 (1H, t), 7.34 (1H, t), 7.13 (1H, q), 6.36 (1H, s), 6.31 (1H, s); IR (KBr Disc) cm⁻¹: 3280 (NH), 1594 (C=O); LC-MS (ESI, m/z): 324 (M+H).

N'-[(E)-(4-fluorophenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5i)

¹H NMR (DMSO-d₆) δ_H: 8.35 & 8.29 (1H, s, Cis-trans Conformer), 8.16 & 8.05 (1H, s, Cis-trans Conformer), 8.01-7.94 (2H, m), 7.80-7.69 (2H, t), 7.60-7.49 (1H, t), 7.44-7.21 (3H, m), 2.81 & 2.68 (3H, s, Cis-trans Conformer); IR (KBr Disc) cm⁻¹: 3256 (NH), 1681 (C=O); LC-MS (ESI, m/z): 308 (M+H).

N'-[(E)-(4-hydroxy-3-methoxyphenyl) methylidene]-2-methylquinoline-3-carbohydrazide (5j)

¹H NMR (DMSO-d₆) δ_H: 11.84 & 11.74 (1H, s, Cis-trans Conformer), 8.53 & 8.30 (1H, s, Cis-trans conformer), 8.18 (1H, d), 8.02-7.67 (3H, m), 7.58-6.91 (4H, m), 2.81 & 2.70 (3H, s, Cis-trans Conformer); IR (KBr Disc) cm⁻¹: 3240 (NH), 1674 (C=O); LC-MS (ESI, m/z): 336 (M+H), 378 (M+Na)

Antimicrobial activity

All the synthesized compounds (5 a-j) were evaluated for their *in vitro* antibacterial & antifungal activities using the two-fold serial dilution technique [11]. The analogs & standard drugs were further diluted in test medium to provide concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/ml. Minimal inhibitory concentration (MIC) for each test compound was investigated against standard bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus pyogenes* (Gram-positive), *Klebsiella pneumoniae*, *Enterococcus aerogenes* and *Escherichia coli* (Gram negative); *Candida albicans*, *Fusarium oxysporium* (fungal strain). Itraconazole & Streptomycin were used as standard drugs. The MIC values for all the synthesized agents & reference drug were shown in Table 2.

In vitro antioxidant assays

In vitro Antioxidant activity was performed by two methods.

DPPH Radical Scavenging Method

Blois [12] showed that 2,2'-diphenyl-1-picryl hydrazyl radical (DPPH) can be used for determining antioxidant activity. DPPH in ethanol shows a strong absorption band at 517 nm (independent of pH from 5.0 to 6.5), and the solution appears to be deep violet in color. As the DPPH radical is scavenged by the donated hydrogen from the antioxidant, the absorbance is diminished according to the stoichiometry. Briefly, 0.5 mL of DPPH solution (0.2 mM) was mixed with 0.1 mL of various concentrations of test compounds and 1.5 mL ethanol was added. The mixture was kept at room temperature for 30 min, and then the absorbance (OD) was read at 517 nm against blank. The % reduction of free radical concentration (OD) with different concentration of test compounds was calculated and was compared with standard, ascorbic acid. The results were expressed as IC₅₀ values (the concentration of test required to scavenge 50% free radicals) (Table 3).

Hydrogen peroxide scavenging assay

The solution of hydrogen peroxide (100 mM) was prepared by the addition of various concentrations of compound (50-300 µg/ml) to hydrogen peroxide solution (2 ml) in phosphate buffer saline of pH 7.4. Absorbance of hydrogen peroxide at 230 nm was determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. For each concentration, a separate blank sample was used for background subtraction. For control sample, absorbance of hydrogen peroxide solution was taken at 230 nm [13]. The percentage inhibition activity (Table 3) was calculated from the formula $[(A_0 - A_1)/A_0] \times 100$, where A₀ is the absorbance of the control, and A₁ is the absorbance of test/ standard taken as ascorbic acid (50-300 µg/ml).

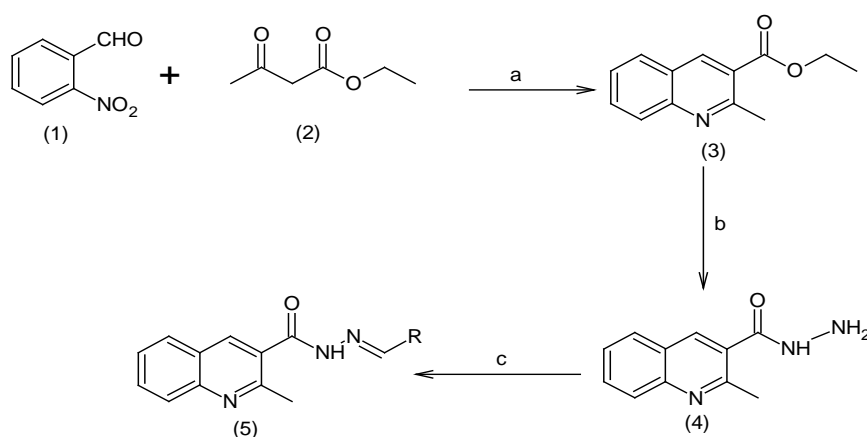
RESULTS AND DISCUSSION**Chemistry**

The compounds having arylidene-hydrazide structure may exist as E/Z geometrical isomers about -C=N double bond and *cis-trans* amide conformers. According to the literature [14], the compounds containing imine bond are present in higher percentage in dimethyl-

D₆ Sulfoxide solution in the form of geometrical E-isomer about —C=N double bond. The Z-isomer can be stabilized in less polar solvents by an intramolecular hydrogen bond. In the present study, the spectral data were obtained in dimethyl-D₆ Sulfoxide solution and no signal belonging to 'Z' isomer was observed. On the other hand, the cis-trans conformers of 'E' isomer were present in the dimethyl-D₆ Sulfoxide solution.

The structures of all the newly synthesized compounds were confirmed by IR, ¹H NMR, and LC MS studies. The IR spectrum of compound 3 revealed the presence of —ArH group due to the appearance of strong band at 3050 cm⁻¹, while that of —C=O of ester was observed at 1714 cm⁻¹. Further, in the ¹H NMR spectra the signal derived from ester group (-OCH₂CH₃) was observed at 4.4 (Quartet) and 1.5 (triplet) ppm integrating for two and three protons respectively. The LCMS showed its molecular ion peak at 216 (M+H), which is in accordance with its molecular formula C₁₃H₁₃NO₂. The

formation of hydrazide 4 from ester 3 was evidenced by its IR, ¹H NMR, and LCMS spectra. Its IR spectrum showed absorbance bands at 3259-3141 and 1620 cm⁻¹ indicating the presence of —NH₂ and —C=O groups, respectively, while its ¹H NMR spectrum showed disappearance of corresponding -OCH₂CH₃ peaks and appearance of 3.32 ppm (-NH-NH₂) and 9.62 ppm (-NH-NH₂) integrating for two protons and one proton respectively (D₂O exchangeable) clearly confirming the conversion of ester into hydrazide. The LCMS spectrum of compound 4 showed a molecular ion peak at 202 (M+H), which matches with its molecular formula C₁₁H₁₁N₃O. The structures of compounds 5(a-j) were interpreted by its IR, ¹H NMR and LC-MS spectra. Its IR Spectrum clearly reveals that the disappearance of peak due to —NH₂, ¹H NMR spectrum showed sharp singlet at 8.25 ppm confirming that the formation of the (—N=C—) group. The LCMS spectrum of compound 5 showed a Molecular ion peak at 290(M+H), which Matches with its molecular formula C₁₈H₁₅N₃O.



R = C₆H₅(a), 4-CH₃-C₆H₄(b), 4-OCH₃-C₆H₄(c), 2-NO₂-C₆H₄(d), 4-NO₂-C₆H₄(e), 4-Cl-C₆H₄(f), 3-Cl-C₆H₄(g), 2-Cl-C₆H₄(h), 4-F-C₆H₄(i), 4-OH-3-OCH₃-C₆H₃(j)

Scheme 1: Synthesis of compounds 5(a-j): Reagents and conditions: a. Fe-HCl, Methanol, Reflux b. NH₂-NH₂/H₂O, Methanol, Reflux c. R-CHO, Methanol, Reflux, 2hrs

Table 1: The physicochemical characteristics of the Quinoline-3-carbohydrazides 5(a-j)

Compound	R	Mol. formula	Mol. weight	Yield (%)	M.p (°C)
5a	C ₆ H ₅ -	C ₁₈ H ₁₅ N ₃ O	289	92	182-184
5b	4-CH ₃ -C ₆ H ₄ -	C ₁₉ H ₁₇ N ₃ O	303	89	204-206
5c	4-OCH ₃ -C ₆ H ₄ -	C ₁₉ H ₁₇ N ₃ O ₂	319	90	170-172
5d	2-NO ₂ -C ₆ H ₄	C ₁₈ H ₁₄ N ₄ O ₃	334	93	202-204
5e	4-NO ₂ -C ₆ H ₄	C ₁₈ H ₁₄ N ₄ O ₃	334	92	200-202
5f	4-Cl-C ₆ H ₄	C ₁₈ H ₁₄ N ₃ OCl	323	89	210-212
5g	3-Cl-C ₆ H ₄	C ₁₈ H ₁₄ N ₃ OCl	323	91	210-212
5h	2-Cl-C ₆ H ₄	C ₁₈ H ₁₄ N ₃ OCl	323	88	211-213
5i	4-F-C ₆ H ₄ -	C ₁₈ H ₁₄ N ₃ OF	307	91	180-183
5j.	4-OH 3-OCH ₃ C ₆ H ₃	C ₁₉ H ₁₇ N ₃ O ₃	335	90	223-225

Biological activity

Antimicrobial evaluation

All the newly synthesized compounds (5a-j) were evaluated for their in vitro antibacterial and antifungal activities against bacterial and fungal species by means of two-fold serial dilution. The in vitro antibacterial activity was performed against three Gram-positive bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus pyogenes* and three Gram-negative strains including *Klebsiella pneumonia*, *Enterococcus aerogens* and *Escherichia coli*. Streptomycin used as a reference drug. Further, the invitro antifungal activity was performed against two fungal strains including *Candida albicans*, *Fusarium oxysporium*. The data generated from this study (Table 2) showed

that some of the target compounds exhibit good potency in inhibiting the growth of Gram-positive bacteria such as *Staphylococcus aureus*. The in vitro activity of compounds 5f and 5j against Gram-negative bacteria such as *Klebsiella pneumonia*, *Escherichia coli* are equipotent to the standard drug. The antifungal activity of compounds 5d and 5j against fungal strains such as *Candida albicans*, *F.oxysporium* are equivalent or less potent than the standard drug Itraconazole

In-Vitro Antioxidant Activity

The antioxidant activities of all the synthesized compounds are evaluated by using DPPH and H₂O₂ method and the results given in Table 3. The values are expressed in IC₅₀ that is, ability of the test compound required to decrease the concentration of test free radical

by 50%. All the synthetic compounds produced a concentration dependent scavenging of free radical. Among all the test compounds, compounds **5d**, **5j** had more potent antioxidant activity against DPPH and H₂O₂ free radicals. It is proposed that DPPH may be

scavenged by an antioxidant through donation of hydrogen (H) to form a stable DPPH-H molecule which does not absorb at 517 nm. It was observed that the test compounds with electron withdrawing groups on the aromatic ring favors anti-oxidant activity.

Table 2: Anti microbial activity of compounds Quinoline-3-carbohydrazides 5(a-j)

Compound code	Antibacterial activity MIC (µg/ml)						Antifungal activity MIC (µg/ml)	
	Gram positive			Gram negative			C.albicans	F.oxysporium
	S.pyogens	S.aureus	B.subtilis	E.coli	K.pneumoniae	E.aerogens		
5a	166.66 ± 57.73	66.66 ± 28.86	83.33 ± 28.86	33.33 ± 14.43	66.66 ± 28.86	33.33 ± 14.43	66.66± 28.86	25±0
5b	-	66.66 ±28.86	166.66 ±57.73	66.66 ±28.86	-	50±0	-	66.66 ±28.86
5c	66.66 ±28.86	-	66.66 ±28.86	33.33 ±14.43	166.66 ± 57.73	-	66.66 ±28.86	-
5d	33.33 ±28.86	166.66 ±57.73	25±0	8.33 ±3.6	10.41 ±3.6	66.66 ±28.86	16.66 ±7.21	41.66 ±14.43
5f	41.66 ±14.43	66.66 ± 28.86	166.66 ±57.73	16.66 ±7.21	6.25±0	8.33 ±3.6	16.66 ±7.21	66.66 ±28.86
5i	-	10.41 ±3.6	41.66 ±14.43	-	66.66 ±28.86	66.66 ±28.86	-	33.33 ±14.43
5j	33.33 ±14.43	66.66 ±28.86	10.41 ±3.6	33.33 ±14.43	66.66 ±28.86	33.33 ±14.43	33.33 ±14.43	10.41 ±3.6
Streptomycin	4.16 ±1.80	5.20 ±1.80	2.6 ±0.9	2.6 ±0.9	2.6 ±0.9	4.16 ±1.80	--	--
Itraconazole							4.16 ±1.80	4.16 ±1.80

Table 3: Antioxidant activity of compounds Quinoline-3-carbohydrazides 5(a-j)

Compound code	DPPH -IC ₅₀ (µg/ml) Mean ± S.D	H ₂ O ₂ Scavenging ability-IC ₅₀ (µg/ml) Mean ± S.D
5a	71.37 ± 1.55	205.23 ± 0.32
5b	88.66 ± 0.78	166.47 ± 0.67
5c	93.08 ± 1.42	142.44 ± 1.47
5d	54.51 ± 1.14	129.75 ± 1.07
5f	68.22 ± 0.32	142.73 ± 0.97
5i	72.43 ± 0.43	155.50 ± 1.15
5j	53.79 ± 0.97	127.83 ± 1.57
Ascorbic acid	28.06 ± 0.54	123.67 ± 1.01

CONCLUSION

The ten new quinoline hydrazone compounds (5a–j) were synthesized through multistep synthesis. The synthesized compounds were characterized by IR, ¹H NMR and ESI-MS. In-vitro antibacterial, antifungal and antioxidant activities were examined using representative Gram-positive, Gram-negative, fungal strains and standard assays respectively. Out of the ten derivatives, 5f and 5j exhibited very good potency in inhibiting the growth of *Staphylococcus aureus*, *Klebsiella pneumonia*, *Escherichia coli*, *Candida albicans* and *Fusarium oxysporium*. These compounds suggested that introduction of ring deactivating groups significantly improved the antimicrobial activity. Among the results obtained from the two methods for the evaluation of antioxidant activity of compounds 5d and 5j has shown the most promising antioxidant activity in DPPH and Hydrogen peroxide scavenging assay. The activity is facilitated with the presence of electron withdrawing groups and di-substitution on the aryl ring.

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