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Novel Quinolone Derivatives: Synthesis and Antioxidant Activity

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Abstract—Novel quinolone derivatives have been designed and readily synthesized according to a simple protocol including *O*-alkylation and Claisen rearrangement processes. Structures of the synthesized compounds have been confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectra. The new products have been tested for their antioxidant activity, and two of those demonstrate high antioxidant activity.

Keywords: quinolone, Claisen rearrangement, *O*-alkylation reaction, antioxidant activity

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INTRODUCTION

Among major applications of quinoline is synthesis of nicotinic acid (niacin) [1–3]. Some derivatives of quinolone, including alcaloids and quinine [4], are isolated from plants and used as synthetic antimalarial drugs including mefloquine, chloroquine and amodiaquine [5]. These derivatives are also active against various viruses like enterovirus, ebola, human immunodeficiency virus, and SARS virus [6, 7].

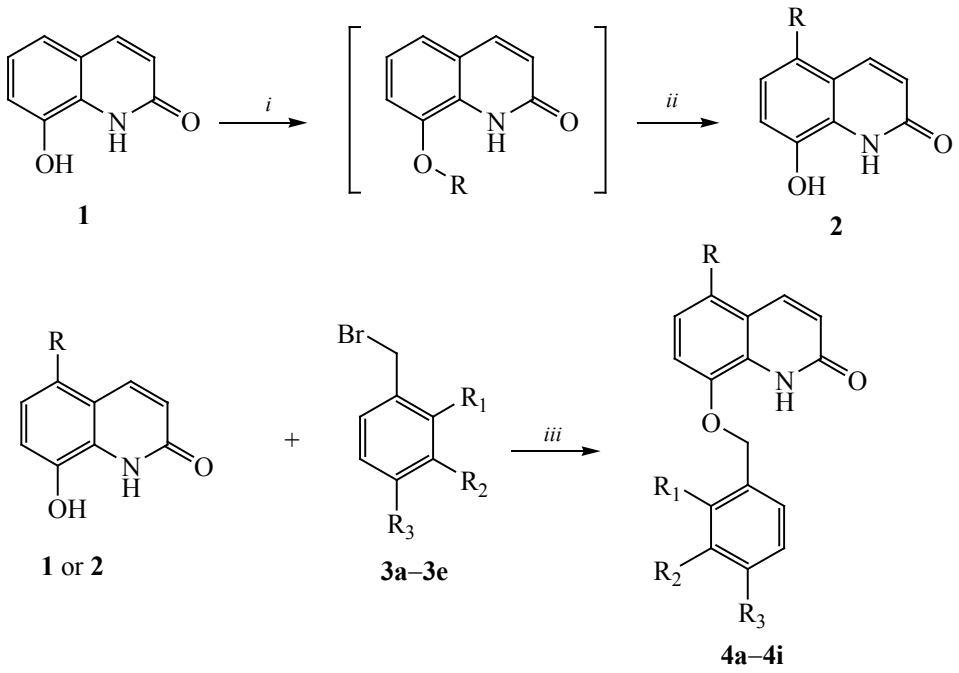
8-Hydroxyquinolin-2(1*H*)-one is an important derivative of quinoline which possesses the keto group in 2 position, and it can act as an excellent β2-adrenoceptor agonist [8], antiplatelet [9] and antiproliferative agent [10]. Various classes of phytochemicals including 8-hydroxyquinoline-2(1*H*)-one demonstrate antioxidant properties due to the presence of such substituents as carbonyl, phenolic, phenyl side chain, electron withdrawing and donating groups, and some more. The above data motivated us to develop simple and convenient synthesis of 8-hydroxyquinoline-2(1*H*)-one derivatives.

RESULTS AND DISCUSSION

The target compounds **4a**–**4i** were synthesized from 8-hydroxyquinoline-2(1*H*)-one (**1**) as presented in Scheme 1. Initially, compound **1** was converted into 5-acetyl-8-hydroxyquinoline-2(1*H*)-one (**2**) via Claisen rearrangement catalyzed by $AlCl_3$. The following 0-alkylation of **1** or **2** by various bromomethylphenyl derivatives **3a**–**3e** gave the target quinolone compounds **4a**–**4i**. Structures of the synthesized compounds **4a**–**4i** were confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectra. For instance, in IR spectrum of **4a** the bands at 3363–3341 (N–H), 1733–1712 (C=O) and 1264–1239 (C–O) indicated the structure, which was also supported by ^{1}H NMR spectrum containing singlets at 5.37 (CH_2-quinolone) and 7.99 ppm (NH of quinolone), and CH_2-quinolone signal at 69.0 ppm in its ^{13}C NMR spectrum. Structures of the synthesized compounds **4b-i** were supported by the similar data.

The 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging activity (RSA) is considered as a standard assay involved in antioxidant studies. Interaction of quinolone derivatives **4a**–**4i** with the stable DPPH free radical (Table 1) envisioned their free radical scavenging ability. Majority of the tested compounds demonstrated good to moderate interaction with the DPPH radical. Among the tested compounds, the product **4e** exhibited the highest activity due to presence of both CF_3 and Br in it along with the acetyl group in the quinoline moiety.

Scheme 1. Synthesis of the target compounds **4a**–**4i**.



4a, R = H, R_1 = H, R_2 = CF_3, R_3 = H, **4b**, R = H, R_1 = C_2H_5, R_2 = H, R_3 = $COCH_3$, **4c**, R = H, R_1 = H, R_2 = CF_3, R_3 = Br, **4d**, R = H, R_1 = H, R_2 = CF_3, R_3 = cyclohexyl, **4e**, R = $COCH_3$, R_1 = H, R_2 = CF_3, R_3 = Br, **4f**, R = $COCH_3$, R_1 = H, R_2 = CF_3, R_3 = cyclohexyl, **4g**, R = $COCH_3$, R_1 = H, R_2 = CF_3, R_3 = H, **4h**, R = $COCH_3$, R_1 = C_2H_5, R_2 = H, R_3 = $COCH_3$, **4i**, R = $COCH_3$, R_1 = F, R_2 = H, R_3 = H.
Reagents and conditions: (*i*) Acetyl chloride, $AlCl_3$ (*ii*) Reflux, 40–45°C, (*iii*) Water, K_2CO_3.

Compound **4c** containing CF_3 and Br substituents at phenyl ring also demonstrated pronounced activity. The above results indicated that the electron-withdrawing groups such as CF_3 and Br/F attached to benzene ring strongly affected the antioxidant activity. The compounds **4a**, **4d**, and **4h** exhibited moderate activity, while antioxidant activity of the other products was low (Table 1).

EXPERIMENTAL

All chemicals were purchased from Sigma Aldrich (India) and used without additional purification. Melting points were determined on a Buchi oil melting point apparatus in open capillary tubes and are uncorrected. Elemental analysis was carried out on an Elementor vairo-EL instrument. IR spectra were recorded for KBr discs on an Avtar 370 FT-IR (Thermo Nicolet) spectrophotometer.

Table 1. The DPPH assay of the synthesized compounds **4a**–**4i**

Parameter	IC_{50}								
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**
Bottom	107.9	119.5	104.2	106.5	102.2	110.8	108.5	107.4	112.8
Top	–17.23	–4.84	–26.42	–6.442	–28.53	–9.670	–5.502	–17.23	–8. 75
Log IC_{50}	1.075	1.4727	0.958	1.059	0.8304	1.218	1.136	1.075	1.318
IC_{50}	12.76	26.71	8.59	12.86	6.767	16.52	13.67	11.89	18.52

NMR spectra were measured on a Bruker Avance 400 spectrometer usining DMSO-d_6 as a solvent. Mass spectra were measured on a Bruker-Franzen Esquire LC mass spectrometer. Silica gel 60 (Merck, 15–40 mm) was used for flash column chromatography. TLC was carried out on aluminum sheets precoated with silica gel (60 F254, 0.2 mm, Merck). Chromatographs were developed by UV light and/or in an iodine chamber.

Synthesis of 5-acetyl-8-hydroxyquinolin-2(1*H*)-one (2). The mixture of 8-hydroxyquinoline-2(1*H*)-one (5 g, 31.02 mmol, 1 eq) with acetyl chloride (2.92 g, 37.24 mmol, 1.2 eq), $AlCl_3$ (9.10 g, 68.25 mmol, 2.2 eq) and dichloromethane (50 mL) was refluxed for 10–12 h. The reaction progress was monitored by TLC. After completion of the process, the reaction mixture was poured into ice-cold water upon stirring. The precipitated solid was separated, filtered off and washed with ice water followed by acetone. The crude product was dried for 3–4 h under vacuum, then mixed with *N*,*N*-dimethyl formamide (25 mL) and refluxed at 40–45°C for 2 h (TLC). Then the reaction mixture was cooled down to room temperature, the solid residue filtered off, washed with ice water and acetone to give compound **2**, yield 85%.

Synthesis of compounds 4a–4i. The mixture of 8-hydroxyquinoline-2(1*H*)-one (1, 0.16 g, 1.00 mmol, 1 eq) with potassium carbonate (0.24 g, 1.80 mmol, 1.8 eq) and DMF (10 mL) was stirred at room temperature for 10 min. Then 1-(bromomethyl)-3-(trifluoromethyl)-benzene (**3a**, 0.26 g, 1.10 mmol, 1.1 eq) was added to it drop-wise. The mixture was stirred at room temperature for 16 h (TLC). Upon completion of the process, water (20 mL) was added to the reaction mixture, and it was stirred thoroughly. The precipitated solid was filtered off, washed with water (10 mL) and dried on an evaporator for 1 h at 60–65°C to give the product **4a** as white solid.

The same synthetic method was used for the other aryl-quinolone derivatives **4b-i** using the appropriate substituted brommethylbenzenes.

8-{[3-(Trifluoromethyl)benzyl]oxy}quinolin-2(1*H*)-one (4a). Yield 87%, mp 207°C. IR spectrum, ν, cm^{-1}: 3350 (N–H), 1720 (C=O), 1250 (C–O). ^{1}H NMR spectrum, δ, ppm: 5.37 s (2H, CH_2), 6.51–6.54 d (1H, ArH), 7.07–7.11 t (1H, ArH), 7.24–7.26 d (2H, ArH), 7.60–7.64 t (1H, ArH), 7.67–7.69 d (1H, ArH), 7.87–7.89 d (1H, ArH), 7.92–7.94 d (1H, ArH), 7.99 s (1H, NH), 10.99 s (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 69.0, 112.6, 119.7, 120.1, 121.6, 122.5, 124.4, 124.5, 125.5, 129.0, 129.1, 129.2, 131.9, 138.0, 140.1, 144.1, 161.5. MS: *m/z*: 320.50 $[M + 1]^+$. Found, %: C 63.90, H 3.82, F 17.80, N 4.41, O 10.07. $C_{17}H_{12}F_3NO_2$. Calculated, %: C 63.95, H 3.79, F 17.85, N 4.39, O 10.02.

8-{(4-Acetyl-2-ethylbenzyl)oxy}quinolin-2(1*H*)-one (4b). Yield 77%, mp 174°C. IR spectrum, ν, cm^{-1}: 3348 (N–H), 1725 (C=O), 1244 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.19–1.23 t (3H, CH_3), 2.57 s (3H, CH_3), 2.76–2.82 q (2H, CH_2), 5.35 s (2H, CH_2), 6.50–6.53 d (1H, ArH), 7.07–7.11 t (1H, ArH), 7.20–7.25 m (2H, ArH), 7.73–7.89 m (4H, ArH), 8.01 s (1H, NH), 10.81 s (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 14.6, 24.4, 26.7, 67.7, 112.4, 119.7, 119.9, 121.6, 122.4, 125.7, 127.6, 128.5, 128.9, 136.4, 139.2, 140.2, 142.3, 144.3, 161.5, 197.7. MS: *m/z*: 322.52 $[M + 1]^+$. Found, %: C 74.65, H 5.99, N 4.46, O 14.91. $C_{20}H_{19}NO_3$. Calculated, %: C 74.75, H 5.96, N 4.36, O 14.94.

8-{[4-Bromo-3-(trifluoromethyl)benzyl]oxy}-quinolin-2(1*H*)-one (4c). Yield 80%, mp 195°C. IR spectrum, ν, cm^{-1}: 3344 (N–H), 1730 (C=O), 1260 (C–O). ^{1}H NMR spectrum, δ, ppm: 5.32 s (2H, CH_2), 6.51–6.53 d (1H, ArH), 7.07–7.11 t (1H, ArH), 7.23–7.26 m (2H, ArH), 7.84–7.91 m (3H, ArH), 8.07 s (1H, NH), 11.06 s (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 71.3, 112.2, 119.3, 121.1, 121.4, 123.7, 125.5, 125.9, 127.4, 130.3, 131.4, 132.1, 132.7, 139.8, 140.6, 152.7, 162.4. MS: *m/z*: 399.90 $[M + 1]^+$. Found: C 51.24, H 2.80, Br 20.10, F 14.30, N 3.54, O 8.06. $C_{17}H_{11}BrF_3NO_2$. Calculated, %: C 51.28, H 2.78, Br 20.07, F 14.31, N 3.52, O 8.04.

8-{[4-Cyclohexyl-3-(trifluoromethyl)benzyl]oxy}-quinolin-2(1*H*)-one (4d). Yield 84%, mp 179°C. IR spectrum, ν, cm^{-1}: 3354 (N–H), 1722 (C=O), 1241 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.34–1.44 m (6H, cyclohexane), 1.61–1.67 m (4H, cyclohexane), 2.78–2.81 m (1H, cyclohexane), 5.31 s (2H, CH_2), 6.50–6.53 d (1H, ArH), 7.07–7.11 t (1H, ArH), 7.23–7.26 m (2H, ArH), 7.60–7.62 m (2H, ArH), 7.83 s (1H, ArH), 8.01 s (1H, NH), 10.96 s (1H, ArH). 13C NMR spectrum, δ, ppm: 25.3, 26.1, 29.9, 34.8, 71.3, 112.2, 121.4, 121.9, 124.3, 124.7, 125.2, 125.9, 127.0, 130.2, 131.2, 139.2, 139.5, 139.9, 152.4, 155.3, 162.6. MS: *m/z*: 402.26 $[M + 1]^+$. Found, %: C 68.78, H 5.60, F 14.16, N 3.55, O 7.91. $C_{23}H_{22}F_3NO_2$. Calculated, %: C 68.82, H 5.52, F 14.20, N 3.49, O 7.97.

5-Acetyl-8-{[4-bromo-3-(trifluoromethyl)benzyl]-oxy}quinolin-2(1*H*)-one (4e). Yield 82%, mp 236°C. IR spectrum, ν, cm^{-1}: 3360 (N–H), 1712 (C=O), 1249

(C–O). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 5.44 s (2H, CH_2), 6.62–6.64 d (1H, ArH), 7.27–7.29 d (1H, ArH), 7.79–7.81 s (1H, ArH), 7.84–7.86 d (1H, ArH), 7.90–7.92 d (1H, ArH), 8.10 s (1H, NH), 8.65–8.67 d (1H, ArH), 11.15 d (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 29.3, 70.3, 108.3, 113.2, 119.2, 121.6, 123.4, 125.7, 127.1, 127.4, 127.8, 130.5, 132.2, 132.6, 139.6, 140.7, 156.9, 162.6, 205.8. MS: *m/z*: 440.30 $[M + 1]^+$. Found, %: C 51.79, H 2.90, Br 18.20, F 12.99, N 3.20, O 10.92. $C_{19}H_{13}BrF_3NO_3$. Calculated, %: C 51.84, H 2.98, Br 18.15, F 12.95, N 3.18, O 10.90.

5-Acetyl-8-((4-cyclohexyl-3-(trifluoromethyl)-benzyl)oxy)quinolin-2(1*H*)-one (4f). Yield 77%, mp 216°C. IR spectrum, ν, cm^{-1}: 3344 (N–H), 1719 (C=O), 1239 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.26–1.38 m (3H, cyclohexane), 1.48–1.57 m (2H, cyclohexane), 1.66–1.69 d (3H, cyclohexane), 1.79–1.81 d (2H, cyclohexane), 2.60 s (3H, CH_3), 2.78–2.84 m (1H, cyclohexane), 5.42 s (2H, CH_2), 6.63–6.65 d (1H, ArH), 7.30–7.32 d (1H, ArH), 7.63–7.65 d (1H, ArH), 7.81–7.89 m (3H, ArH), 8.66 68 d (1H, ArH), 11.14 s (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 25.3, 26.4, 29.0, 33.8, 69.1, 110.5, 113.6, 116.4, 117.3, 124.1, 125.2-125.3, 126.0, 126.3, 126.9, 128.5, 129.9, 132.4, 134.2, 137.8, 146.0, 147.3, 158.1, 158.5, 160.7, 199.6. MS: *m/z*: 444.28 $[M + 1]^+$. Found, %: C 67.62, H 5.50, F 12.91, N 3.19, O 10.78. $C_{25}H_{24}F_3NO_3$. Calculated, %: C 67.71, H 5.45, F 12.85, N 3.16, O 10.82.

5-Acetyl {[3-(trifluoromethyl)benzyl]oxy}-quinolin-2(1*H*)-one (4g). Yield 85%, mp 207°C. IR spectrum, ν, cm^{-1}: 3341 (N–H), 1717 (C=O), 1264 (C–O). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 5.49 s (2H, CH_2), 6.63–6.66 d (1H, ArH), 7.30–7.32 d (1H, ArH), 7.61–7.65 t (1H, ArH), 7.69–7.71 d (1H, ArH), 7.80–7.83 d (1H, ArH), 7.92–7.94 d (1H, ArH), 8.02 s (1H, NH), 8.65–8.68 d (1H, ArH), 11.17 d (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 29.0, 69.1, 35.8, 110.5, 117.3, 124.1, 124.6, 124.6, 124.7, 126.1, 126.9, 129.3, 129.9, 132.0, 137.4, 137.7, 147.1, 160.7, 199.6. MS: *m/z*: 362.3 $[M + 1]^+$. Found, %: C 63.30, H 3.81, F 15.81, N 3.90, O 13.26. $C_{19}H_{14}F_3NO_2$. Calculated, %: C 63.16, H 3.91, F 15.77, N 3.88, O 13.28.

5-Acetyl [(4-acetyl-2-ethylbenzyl)oxy]quinolin-2(1*H*)-one (4h). Yield 80%, mp 201°C. IR spectrum, ν, cm^{-1}: 3363 (N–H), 1733 (C=O), 1248 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.20–1.24 t (3H, CH_3), 2.60 s (6H, CH_3), 2.79–2.85 q (2H, CH_2), 5.48 s (2H, CH_2), 6.63–6.66 d (1H, ArH), 7.26–7.28 d (1H, ArH), 7.69–7.71 d (1H, ArH), 7.80–7.84 m (3H, ArH), 8.67 69 d (1H, ArH), 10.98 d (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 14.8, 24.8 , 26.8, 29.1, 68.3,110.8, 124.1, 126.0, 126.6, 127.2, 128.0, 129.0, 130.0, 137.0, 138.3, 138.7, 143.0, 147.6, 158.3, 160.9, 198.0, 199.8. MS: *m/z*: 364.31 $[M + 1]^+$. Calculated, %: C 72.71, H 5.82, N 3.85, O 17.61. $C_{22}H_{21}NO_4$. Found, %: C 72.80, H 5.80, N 3.80, O 17.59.

5-Acetyl [(2-fluorobenzyl)oxy]quinolin-2(1*H*)-one (4i). Yield 83%, mp 170°C. IR spectrum, ν, cm^{-1}: 3357 (N–H), 1722 (C=O), 1243 (C–O). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 5.45 s (2H, CH_2), 6.60–6.63 d (1H, ArH), 7.21–7.31 m (3H, ArH), 7.40–7.44 m (1H, ArH), 7.69–7.81 m (1H, ArH), 7.83 s (1H, NH), 8.66 68 d (1H, ArH), 10.93 d (1H, ArH). ^{13}C NMR spectrum, δ, ppm: 29.0, 64.4, 110.3, 115.1, 115.3, 122.6, 122.8, 126.2, 126.93, 129.9, 130.4, 130.5, 130.8, 137.7, 159.1, 160.5, 161.5, 199.6. MS: *m/z*: 312.17 $[M + 1]^+$. Found, %: C 69.40, H 4.58, F 6.20, N 4.45, O 15.37. $C_{18}H_{14}FNO_3$. Calculated, %: C 69.45, H 4.53, F 6.10, N 4.50, O 15.42.

Antioxidant activity. The DPPH assay was carried out as per the method described by Rajakumar et al. In brief, 90 μL of DPPH solution was treated with 180 μL of the test solutions of different concentrations (0.5, 1.0, 1.5, 2.0, 2.5 mg/mL) and the standard. The reaction mixture was mixed and incubated at 25°C for 15 min. Absorbance was measured at 510 nm using a Plate reader. The control reaction was carried out without the test sample. The % inhibition was calculated. The IC_{50} values for DPPH radical scavenging activity of the test compounds were derived from a nonlinear regression analysis (curvefit) based on sigmoidal dose-response curve (variable) and computed using GraphPad Prism 5 (Graphpad, SanDiego, CA, USA).

CONCLUSIONS

We have carried out synthesis of new quinolone derivatives via the *O*-alkylation reaction and Claisen rearrangement. Structure of the target compounds has been confirmed by spectral methods. Antioxidant activity of the target compounds indicates that the product **4e** is a potent lead for DPPH scavenging activity and the efficient lead for discovery of new antioxidant candidates.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY INFORMATION

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