Novel Quinolone Derivatives: Synthesis and Antioxidant Activity

Mutyala Veera Venkata Vara Prasad\textsuperscript{a,*}, Radha Hunasenahalli Raghavendra Rao\textsuperscript{b}, Vadde Veeranna\textsuperscript{a}, Venkata Suryanarayana Chennupalli\textsuperscript{d}, and Byrappa Sathish\textsuperscript{e}

\textsuperscript{a} Department of Chemistry, T John Institute of Technology, Bangalore, Karnataka, 560076 India
\textsuperscript{b} Department of Chemistry, K. S. School of Engineering and Management, Bangalore, Karnataka, 560109 India
\textsuperscript{c} Department of Chemistry, AMC Engineering College, Bangalore, Karnataka, 560083 India
\textsuperscript{d} Department of Chemistry, Amrita Sai Institute of Science & Technology, Paritala, Krishna District, Andhra Pradesh, 521180 India
\textsuperscript{e} Department of Chemistry, Apotex pharma India Pvt. Ltd. Bangalore, Karnataka, 560099 India
*e-mail: mutyalavvprasad@gmail.com

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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, \(^1\text{H}\) and \(^{13}\text{C}\) 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 alkaloids 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 \(\beta2\)-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 4\textsubscript{a}–4\textsubscript{i} 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 \(O\)-alkylation of 1 or 2 by various bromomethylphenyl derivatives 3\textsubscript{a}–3\textsubscript{e} gave the target quinolone compounds 4\textsubscript{a}–4\textsubscript{i}. Structures of the synthesized compounds 4\textsubscript{a}–4\textsubscript{i} were confirmed by IR, \(^1\text{H}\) and \(^{13}\text{C}\) NMR, and mass spectra. For instance, in IR spectrum of 4\textsubscript{a} the bands at 3363–3341 (N–H), 1733–1712 (C=O) and 1264–1239 (C–O) indicated the structure, which was also supported by \(^1\text{H}\) 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 \(^{13}\text{C}\) NMR spectrum. Structures of the synthesized compounds 4\textsubscript{b}–4\textsubscript{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 4\textsubscript{a}–4\textsubscript{i} 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 4\textsubscript{e} exhibited the highest activity due to presence of both CF\(_3\) and Br in it along with the acetyl group in the quinoline moiety.
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 | 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 using 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(1H)-one (2).** The mixture of 8-hydroxyquinoline-2(1H)-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(1H)-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 bromomethylbenzenes.

**8-{[3-(Trifluoromethyl)benzyl]oxy}quinolin-2(1H)-one (4a).** Yield 87%, mp 207°C. IR spectrum, v, 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$_7$F$_3$NO$_2$. Calculated: %: C 63.95, H 3.79, F 17.85, N 4.39, O 10.02.

**8-{[4-Acetyl-2-ethylbenzyl]oxy}quinolin-2(1H)-one (4b).** Yield 77%, mp 174°C. IR spectrum, v, 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 5.46, N 4.32, O 14.94.

**8-{[4-Bromo-3-(trifluoromethyl)benzyl]oxy}quinolin-2(1H)-one (4c).** Yield 80%, mp 195°C. IR spectrum, v, 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$_3$NO$_2$. 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(1H)-one (4d).** Yield 84%, mp 179°C. IR spectrum, v, 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). $^{13}$C 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 69.88, H 5.60, F 14.16, N 3.55, O 7.91. C$_{23}$H$_{22}$F$_3$NO$_2$. 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(1H)-one (4e).** Yield 82%, mp 236°C. IR spectrum, v, cm$^{-1}$: 3360 (N–H), 1712 (C=O), 1249...
(C–O). 1H NMR spectrum, δ, ppm: 2.60 s (3H, CH3), 5.44 s (2H, CH3), 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). 13C 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, N 3.20, O 13.99.

5-Acetyl-8-((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)quinolin-2(1H)-one (4f). Yield 77%, mp 216°C. IR spectrum, v, cm−1: 3344 (N–H), 1719 (C=O), 1239 (C–O). 1H 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, CH3), 2.78–2.84 m (1H, cyclohexane), 5.42 s (2H, CH2), 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). 13C 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 5.45, N 3.97, O 15.37. C19H14F3NO3. Calculated, %: C 67.71, H 5.45, N 3.95, O 15.37.

5-Acetyl [(2-fluorobenzyl)oxy]quinolin-2(1H)-one (4i). Yield 83%, mp 170°C. IR spectrum, v, cm−1: 3357 (N–H), 1722 (C=O), 1243 (C–O). 1H NMR spectrum, δ, ppm: 2.60 s (3H, CH3), 5.45 s (2H, CH2), 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). 13C 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 = 364.31. [M + 1] +. Found, %: C 69.40, H 4.58, F 6.20, N 15.37. C19H14F3NO3. 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 IC50 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

The online version contains supplementary material available at https://doi.org/10.1134/S1070363221120239.

REFERENCES

1. Susai, N., Kuroita, T., Ishikawa, T., Kuronuma, K., and Yoshioka, T., Br. J. Nutr., 2021, vol. 3, p. 1. https://doi.org/10.1017/S0007114521001835

2. Prabhu, D., Dawe, R.S., and Mponda, K., Photodermatol. Photoimmunol. Photomed., 2021, vol. 37(2), p. 99. https://doi.org/10.1111/phpp.12659

3. Viljoen, M., Bipath, P., and Tosh, C., Public Health Nutr., 2021, vol. 26, p. 1. https://doi.org/10.1017/S1368980021001336

4. Christensen, S.B., Biomedicines., 2021, vol. 9(5), p. 472. https://doi.org/10.3390/biomedicines9050472

5. Olateju, O.A., Babalola, C.P., Olubiyi, O.O., Kotila, O.A., Kwasi, D.A., Oaikhena, A.O., and Okeke, I.N., Front. Microbiol., 2021, vol. 12, p. 1245. https://doi.org/10.3389/fmicb.2021.556550

6. Kaur, R. and Kumar, K., Eur. J. Med. Chem., 2021, vol. 24, p. 113220. https://doi.org/10.1016/j.ejmech.2021.113220

7. Xing, G., Zhi, Z., Yi, C., Zou, J., Jing, X., Woo, A.Y., Lin, B., Pan, L., Zhang, Y., and Cheng, M., Eur. J. Med. Chem., 2021, vol. 224, p. 113697. https://doi.org/10.1016/j.ejmech.2021.113697

8. Xing, G., Pan, L., Yi, C., Li, X., Ge, X., Zhao, Y., Liu, Y., Li, J., Woo, A., Lin, B., and Zhang, Y., Bioorg. Med. Chem., 2019, vol. 27(12), p. 2306. https://doi.org/10.1016/j.bmc.2018.10.043

9. Tzeng, C.C., Chen, I.L., Chen, Y.L., Wang, T.C., Chang, Y.L., and Teng, C.M., Helv. Chim. Acta., 2000, vol. 83(2), p. 349. https://doi.org/10.1002/(SICI)1522-2675(20000216)83:2%3C349::AID-HLCA349%3E3.0.CO;2-B

10. Chen, I.L., Chen, J.J., Lin, Y.C., Peng, C.T., Juang, S.H., and Wang, T.C., Eur. J. Med.Chem., 2013, vol. 59, p. 227. https://doi.org/10.1016/j.ejmech.2012.11.016