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Microwave-assisted solid acid-catalyzed synthesis of quinolinyl quinolinones and evaluation of their antibacterial, antioxidant activities

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Abstract Microwave-assisted montmorillonite K-10-catalyzed Friedlander synthesis of quinolinylquinolinones has been developed. The efficient and eco-friendly catalyst along with the convenience of the product isolation make this process an attractive alternative for the synthesis of target heterocycles. The synthesized products were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic techniques. All the synthesized compounds showed good antibacterial property similar to standard Ampicillin and enhanced antioxidant activity.

Keywords Quinolinone · 2-Aminobenzophenone · Montmorillonite K-10 · Solvent-free conditions · Antibacterial · Antioxidant properties

Introduction

The quinoline structural motif occurs in several natural products (cinchona alkaloids) and are pharmacologically active substances displaying a broad range of biological activity [1–5]. Because of their importance as substructures in a broad range of natural and designed products, significant efforts have been directed in the development of new quinoline-based structures (Fig. 1) [6].

The quinolines has been found to possess antihelmintic [7], antibacterial [8], antifungal [9], antimalarial [10], anticonvulsant, cardiotonic, anti-inflammatory [11], and analgesic [12], antiprotozoal [13], antiviral [14], hypoglycemic [15], cardiovascular [16], and antineoplastic [17] activities. Similarly, the quinolinones

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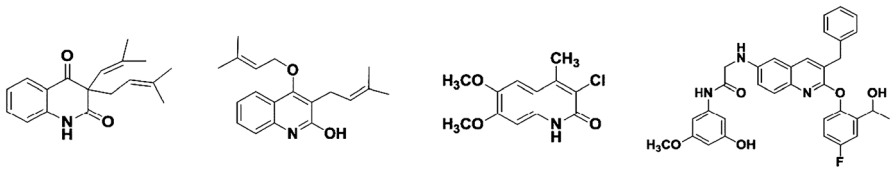


Fig. 1 New quinoline based structures

have been of considerable scientific and clinical interest since their discovery in the early 1960s [18–22]. The structural core of quinolinone is employed in medicinal chemistry and present in various medicinally valuable compounds [23, 24]. Quinolinones and quinolones are important constituents of pharmacologically active agents [25]. The first generation quinolinone, nalidixic acid, was introduced in 1962. Since then, structural modifications have resulted in second, third, and fourth generation fluoroquinolones, which have improved coverage of Gram-positive organisms [26]. Quinoline has frequently been recognized in the structure of numerous naturally occurring alkaloids [27, 28]. The functionalized quinolinones are attractive compounds for drug discovery since many of them have been shown to exhibit excellent biological activities. Therefore, the development of facile methodologies for the synthesis of highly functionalized quinolinone derivatives represents a challenge in medicinal chemistry [29, 30].

New developments in the chemistry of quinoline derivatives have been reviewed [31]. The structural core of quinoline and related poly heterocycles has been synthesized through Friedlander quinoline synthesis [32]. Amberlyst-15 is considered as a most effective catalyst in terms of the reaction times, yields, and reusability as reported by Das et al. [33]. Simple and environmentally benign operationally simple route for quinoline derivatives were efficiently prepared through acid-catalyzed Friedlander reaction in ionic liquid ([bmim][BF4]) by Zhang et al. [34]. A molecular iodine-mediated mild and efficient route for the synthesis of quinolines, via Friedlander annulations, has been reported by Wu et al. [35]. This method is not only a complement to quinoline synthesis via Friedlander annulations but also avoids the use of hazardous acids or bases and harsh reaction conditions.

Dabiri and Bashiribod [36] have reported an efficient and recyclable catalyst phosphotungstic acid ($H_3PW_{12}O_{40}$) in the synthesis of polysubstituted quinolines, through the Friedlander condensation, under solvent-free conditions. Zolfigol et al. [37] have reported a green chemical route involving Lewis acids catalyst in Friedlander annulation to quinolines where $Zr(NO_3)_4$ and $Zr(HSO_4)_4$ were found to be more efficient than other investigated Lewis acids in the catalyzed condensation of *o*-amino aryl ketones or *o*-amino benzonitrile with ketones or β-diketones in water under reflux conditions.

Habibi and Marvi [38] have reported microwave-irradiated montmorillonite KSF and montmorillonite K-10 clays catalysis under the solvent-free conditions for the synthesis of different bismaleimides and bisphthalimides, in a simple and environmentally benign method from the condensation reaction of maleic and phthalic anhydrides, with different diamines in good yields and short reaction times.

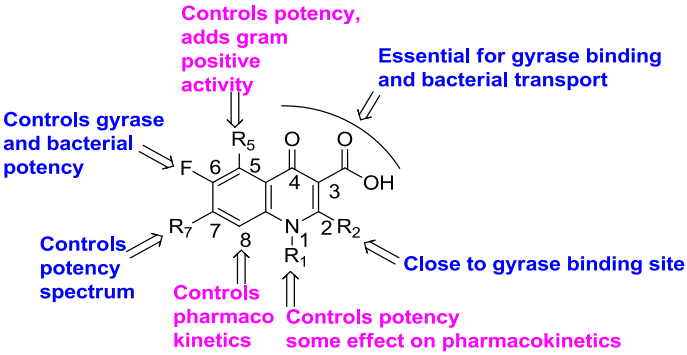


Fig. 2 Antibacterial efficacy of quinolones structure

The various structural features of the quinolinones that govern the antibacterial efficacy and influence the side-effect profile have been delineated and summarized at the molecular level (Fig. 2).

Based on the literature survey and the importance of quinolinones, in this paper Friedlander synthesis of quinolinones, **4**, and quinolines, **3**, in the presence of amberlite Na sr1L and MK-10, respectively, has been explored and the results obtained are discussed in detail in continuation of our studies [39–48]. The catalyst amberlite Na sr1L was also efficiently used for the regioselective *N*-alkylation of the quinolinones. A variety of substituted quinolinones have also been prepared using the microwave technique in high yield and purity.

Experimental

Chemistry

Solvents and reagents were commercially sourced and used without further purification. Thin layered chromatography (TLC) was performed on preparative plates of silica gel. Visualization was made with an iodine chamber. Column chromatography was performed by using silica gel (100–200 mesh). Melting points were measured on Elchem Microprocessor-based DT apparatus using an open capillary tube and are corrected with standard benzoic acid. The NMR spectra were recorded on a Bruker Advance III-400 MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm). Mass was recorded on Finnigan Mat 8230 Mass Spectrometer.

General procedure

Ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylates, ***3a–e*** A mixture of *o*-amino ketones, **1** (1 mmol), ethyl -3-oxobutanoate, **2** (1.5 mmol), and MK-10 (100 mg) was taken in a vessel, mixed thoroughly and then irradiated in a microwave oven at power of 65 W and at a temperature of 115 °C for 10 min. The

completion of the reaction was monitored by TLC. Ethanol was added to the reaction mixture and the catalyst was filtered off. The excess solvent was removed under reduce pressure to gave the crystals of ethyl-2-methyl-4-phenylquinoline-3-carboxylates, **3a–e** in good yield.

Quinolin-2-yl-quinolin-2(1H)-ones, ***5a–h*** A mixture of o-amino ketone, **1** (1 mmol), quinoline-2-[1H]-ones, **4** (1 mmol), and MK-10 (100 mg) was taken in a reaction vessel, mixed thoroughly and then irradiated in a microwave oven at 500 W each time for 30 s up to 4–5 min. The completion of the reaction was monitored by TLC. The reaction mixture was treated with ethanol and filtered off to remove the catalyst. Then the ethanol was removed under reduced pressure and poured onto crushed ice. The solid obtained was collected and further purified by column chromatography (85:15- Pet.ether: EtOAc).

Analytical data

Ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate, ***3a*** Pale yellow solid, 95.1 % yield, mp 106–108 °C (Lit. 110 °C) (Dabiri and Bashiribod 2009). IR (KBr pellets, cm^{-1}) υ: 796, 1,558, 1,603, 1,720, 2,927, 3,077. ^{1}H NMR ($CDCl_3$, ppm, 300 MHz) δ: 0.95 (3H, t, $J = 6$ Hz, CH_2CH_3), 2.77 (3H, s, CH_3), 4.03 (2H, q, CH_2CH_3), 7.33 (2H, m, CH), 7.51 (4H, m, CH), 7.64 (1H, d, $J = 9$ Hz, CH), 8.01 (1H, d, $J = 9$ Hz, CH). ^{13}C NMR ($CDCl_3$, ppm, 75 MHz) δ: 13.3, 23.1, 59.9, 95.6, 2 × 124.9, 125.7, 125.9, 2 × 126.8, 128.1, 2 × 128.9, 129.3, 134.8, 145.1, 147.0, 153.1, 168.2. Mol. formula: $C_{19}H_{16}ClNO_2$ requires 325.0870; HRMS *m/z* 325.0816 (M+).

Ethyl-2-methyl-4-phenylquinoline-3-carboxylate, ***3b*** Pale yellow solid, 96 % yield, mp 96–98 °C (Lit. 99 °C) (Dabiri and Bashiribod 2009). IR (KBr pellets, cm^{-1}) υ: 1,561, 1,611, 1,712, 2,928, 2,972, 3,056. ^{1}H NMR ($CDCl_3$, ppm, 500 MHz) δ: 0.92 (3H, t, $J = 10$ Hz, CH_2CH_3), 2.69 (3H, s, CH_3), 3.91 (2H, q, CH_2CH_3), 7.35 (8H, m, CH), 8.03 (1H, d, $J = 10$ Hz, CH). ^{13}C NMR ($CDCl_3$, ppm, 125 MHz) δ: 14.1, 21.2, 62.3, 118.9, 2 × 123.4, 124.7, 2 × 126.1, 126.9, 2 × 128.2, 132.8, 133.7, 139.1, 140.3, 148.2, 155.5, 168.8. Mol. formula: $C_{19}H_{17}NO_2$ requires 291.1259; EI-MS *m/z* 292 (M+1).

Ethyl-2,4-dimethylquinoline-3-carboxylate, ***3c*** Pale yellow solid, 85 % yield, mp Liquid. IR (KBr pellets, cm^{-1}) υ: 1,543, 1,604, 1,718, 2,921, 3,033. ^{1}H NMR ($CDCl_3$, ppm, 500 MHz) δ: 1.66 (3H, t, $J = 10$ Hz, CH_2CH_3), 2.51 (3H, s, CH_3), 2.63 (3H, s, CH_3), 4.31 (2H, q, CH_2CH_3), 7.39 (1H, t, $J = 10$ Hz, CH), 7.61 (1H, t, $J = 10$ Hz, CH), 7.87 (1H, d, $J = 10$ Hz, CH), 7.93 (1H, d, $J = 10$ Hz, CH). ^{13}C NMR ($CDCl_3$, ppm, 125 MHz) δ: 14.5, 15.9, 23.8, 59.8, 2 × 122.9, 124.8, 125.8, 126.7, 129.1, 140.8, 146.5, 153.7, 167.3. Mol. formula: $C_{14}H_{15}NO_2$ requires 229.1103; LC–MS *m/z* 230 (M+1).

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone, ***3d*** Pale yellow solid, 91 % yield, mp 150–152 °C (Lit.150 °C). IR (KBr pellets, cm^{-1}) υ: 711, 1,561, 1,720, 2,976, 3,071. ^{1}H NMR ($CDCl_3$, ppm, 500 MHz) δ: 2.00 (3H, s, CH_3), 2.68 (3H, s, CH_3), 7.35 (4H, m, CH), 7.95 (4H, m, CH). ^{13}C NMR ($CDCl_3$, ppm,

125 MHz) δ: 16.9, 25.7, 122.1, 2 × 123.7,2 × 124.0, 125.4, 2 × 126.3, 127.8, 3 × 129.0, 134.1, 138.2, 156.3, 199.6 (–$COCH_3$). Mol. formula: $C_{18}H_{14}ClNO$ requires 295.0764; LC–MS *m/z* 296 (M+1).

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone, ***3e*** Pale yellow solid, 89 % yield, mp 112–114 °C (Lit. 115 °C). IR (KBr pellets, cm^{-1}) υ: 1,548, 1,609, 1,713, 2,934, 3,013. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.05 (3H, s, CH_3), 2.69 (3H, s, CH_3), 7.36–8.09 (9H, m, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 26.1, 121.7, 122.4, 2 × 124.9, 125.7, 125.9, 126.8, 2 × 128.1, 128.9, 129.3, 134.8, 136.1, 137.0, 157.4, 198.2 (–$COCH_3$). Mol. formula: $C_{18}H_{15}NO$ requires 261.1154; GC–MS *m/z* 262 (M+1).

6-Chloro-3-(6-chloro-4-phenylquinolin-2-yl)-4-phenylquinolin-2(1H)-one, ***5a*** Colorless solid, 91 % yield, mp 160–162 °C. IR (KBr, cm^{-1}) υ: 3,421, 2,917, 1,647. ^1H NMR (DMSO-d_6, ppm, 500 MHz): δ 7.25–7.27 (2H, m, CH), 7.29–7.30 (2H, m, CH), 7.34–7.36 (2H, dd, CH), 7.39 (1H, s, CH), 7.00 (1H, d, $J = 5$ Hz, CH), 7.48–7.49 (1H, d, $J = 8.5$ Hz, CH), 7.53–7.58 (4H, m, CH), 7.63–7.65 (1H, dd, CH), 7.68 (1H, d, $J = 5$ Hz, CH), 7.72–7.74 (1H, dd, CH), 7.91–7.93 (1H, d, $J = 10$ Hz, CH), 12.40 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 125 MHz): δ 117.9, 121.3, 2 × 124.0, 125.1, 125.6, 2 × 126.1, 126.3, 128.5, 3 × 129.3, 2 × 129.6, 2 × 129.7, 130.3, 131.2, 132.0, 2 × 132.6, 135.1, 136.9, 137.9, 146.2, 146.4, 148.9, 156.0, 161.1 (NH–C=O). Mol. formula: $C_{30}H_{18}Cl_2N_2O$ requires 492.0796; HRMS: *m/z* 492.0366 (M+).

3-(6-Chloro-4-phenylquinolin-2-yl)-4-methylquinolin-2(1H)-one, ***5b*** Color less solid, 87 % yield, m.p. 143–145 °C. IR (KBr, cm^{-1}) υ: 3,407, 2,886, 1,639. ^1H NMR (DMSO-d6, ppm, 400 MHz): δ 2.41 (3H, s, CH_3), 7.24 (2H, m, CH), 7.29 (2H, m, CH), 7.34–7.39 (2H, m, CH), 7.56 (1H, s, CH), 7.62–7.66 (1H, d, $J = 8$ Hz, CH), 7.72–7.76 (1H, d, $J = 8$ Hz, CH), 7.88–8.05 (3H, m, CH), 8.10–8.21 (1H, dd, CH), 12.1 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz): δ 13.4, 116.7, 121.3, 123.1, 124.6, 125.5, 126.2, 2 × 127.6, 2 × 128.2, 3 × 129.3, 130.1, 131.4, 2 × 132.5, 135.8, 137.6, 144.6, 145.1, 148.3, 159.2, 160.1 (NH–C=O). Mol. formula: $C_{25}H_{17}ClN_2O$ requires 396.1029; HRMS: *m/z* 396.1000 (M+).

3-(6-Chloro-4-phenylquinolin-2-yl)-4-phenylquinolin-2(1H)-one, ***5c*** Color less solid, 89.3 % yield, mp 195–197 °C. IR (KBr, cm^{-1}) υ: 3,414, 2,916, 1,641. ^1H NMR (500 MHz, DMSO-d_6, ppm): δ 7.10–7.14 (2H, m,CH), 7.23–7.30 (5H, m, CH), 7.35–7.38 (3H, m, CH), 7.45–7.47 (1H, d, J = 10 Hz, CH), 7.53–7.57 (4H, m, CH), 7.68 (1H, s, CH), 7.71–7.74 (1H, dd, CH), 7.91–7.93 (1H, d, J = 10 Hz, CH), 12.20 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d6): δ 115.9, 120.0, 2 × 122.5, 124.0, 125.3, 2 × 127.5, 2 × 128.2, 128.3, 2 × 129.2, 129.4, 129.6, 129.8, 2 × 130.2, 131.3, 131.5, 2 x 131.8, 132.0, 135.7, 136.9, 146.1, 146.4, 150.0, 156.4, 161.3 (NH–C=O). Mol. formula: $C_{30}H_{19}ClN_2O$ requires 458.1186; HRMS: *m/z* 458.1201 (M+).

6-Chloro-3-(4-methylquinolin-2-yl)-4-phenylquinolin-2(1H)-one, ***5d*** Color less solid, 87.2 % yield, mp 174–176 °C. IR (KBr, cm^{-1}) υ: 3,371, 2,827, 1,641. ^1H NMR (DMSO-d_6, ppm, 400 MHz): δ 2.23 (3H, s, CH_3), 6.91 (2H, m, CH), 7.06–7.08 (1H, d, $J = 8$ Hz, CH), 7.21 (3H, m, CH), 7.42 (3H, m, CH), 7.59–7.61 (1H, d, $J = 8$ Hz, CH), 7.79 (2H, m, CH), 8.02 (1H, d, $J = 8$ Hz, CH), 12.31 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz): δ 22.3, 117.1, 121.9, 2 × 122.3,

124.6, 3 × 126.3, 2 × 128.1, 128.4, 2 × 129.2, 3 × 129.7, 2 × 133.6, 139.2, 143.3, 145.8, 151.8, 157.9, 161.1 (NH–C=O). Mol. formula: $C_{25}H_{17}ClN_2O$ requires 396.1029; HRMS: *m/z* 396.5001 (M+).

4-Methyl-3-(4-methylquinolin-2-yl)quinolin-2(1H)-one, ***5e*** Colorless solid, 83.7 % yield, mp 118–120 °C. IR (KBr, cm^{-1}) υ: 3,372, 2,917, 1,642. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz): δ 2.32 (3H, s, CH_3), 2.41 (3H, s, CH_3), 6.89 (1H, t, CH), 7.09 (2H, m, CH), 7.16–7.18 (1H, d, J = 8 Hz, CH), 7.59 (3H, m, CH), 7.71 (2H, m, CH), 12.19 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz): δ 14.8, 26.0, 117.8, 121.7, 2 × 122.3, 124.6, 2 × 126.2, 126.8, 128.2, 2 × 128.6, 129.3, 134.4, 136.7, 144.3, 150.3, 156.8, 160.7 (NH–C=O). Mol. formula: $C_{20}H_{16}N_2O$ requires 300.1263; LC–MS: *m/z* 301 (M+1).

3-(4-Methylquinolin-2-yl)-4-phenylquinolin-2(1H)-one, ***5f*** Colorless solid, 88.6 % yield, mp 196–198 °C. IR (KBr, cm^{-1}) υ: 3,341, 2,891, 1,646. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.23 (3H, s, CH_3), 6.89 (1H, t, *J* = 8 Hz, CH), 7.12–7.16 (3H, m, CH), 7.26 (4H, m, CH), 7.61–7.63 (1H, d, *J* = 8 Hz, CH), 7.79 (4H, m, CH), 8.00 (1H, d, *J* = 8 Hz, CH), 12.21 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz): δ 22.9, 118.3, 121.6, 2 × 122.7, 2 × 124.1, 124.8, 3 × 126.3, 127.1, 2 × 128.1, 2 × 129.2, 132.8, 134.1, 136.2, 141.1, 143.4, 146.2, 151.8, 156.2, 161.1 (NH–C=O). Mol. formula: $C_{25}H_{18}N_2O$ requires 362.1419; HRMS: *m/z* 362.6311 (M+).

6-Chloro-4-phenyl-3-(4-phenylquinolin-2-yl)quinolin-2(1H)-one, ***5g*** Color less solid, 87 % yield, mp 265–267 °C. IR (KBr, cm^{-1}) υ: 3,427, 2,923, 1,644. ^{1}H NMR (DMSO-d_6, ppm, 500 MHz): δ 6.99 (1H, d, *J* = 5 Hz, CH), 7.34–7.36 (2H, m, CH), 7.48–7.57 (5H, m, CH), 7.65 (3H, m, CH), 7.63 (4H, m, CH), 7.69 (1H, t, *J* = 10 Hz, CH), 7.76–7.78 (1H, d, *J* = 10 Hz, CH), 7.90–7.92 (1H, d, *J* = 10 Hz, CH), 12.30 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 125 MHz): δ 117.9, 121.3, 2 × 124.2, 124.8, 125.4, 2 × 126.1, 126.3, 127.4, 128.5, 3 × 129.0, 2 × 129.2, 2 × 129.7, 129.8, 131.0, 133.2, 2 × 135.1, 137.6, 137.9, 146.2, 148.1, 148.6, 155.1, 161.4 (NH–C=O). Mol. formula: $C_{30}H_{19}ClN_2O$ requires 458.1186; HRMS: *m/z* 458.1199 (M+).

4-Phenyl-3-(4-phenylquinolin-2-yl)quinolin-2(1H)-one, ***5h*** Colorless solid, 89 % yield, mp 232–234 °C. IR (KBr, cm^{-1}) υ: 3,414, 2,923, 1,641. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz): δ 7.09 (4H, m, CH), 7.17–7.19 (1H, d, *J* = 8 Hz, CH), 7.32 (5H, m, CH), 7.48 (2H, m, CH), 7.59 (3H, m, CH), 7.68 (1H, d, *J* = 8 Hz, CH), 7.79 (2H, m, CH), 8.01 (1H, d, *J* = 8 Hz, CH), 12.20 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz): δ 119.2, 2 × 121.4, 122.6, 123.4, 2 × 124.6, 3 × 126.2, 126.8, 2 × 128.1, 128.9, 2 × 129.4, 131.1, 132.4, 2 × 136.3, 2 × 138.1, 140.1, 2 × 142.4, 146.5, 149.7, 151.2, 156.0, 161.6 (NH–C=O). Mol. formula: $C_{30}H_{20}N_2O$ requires 424.1576; HRMS: *m/z* 424.1602 (M+).

Anti-oxidant property

Radical scavenging activity of compounds against stable DPPH (2,2-diphenyl-2-picrylhydrayl hydrate) was determined spetrophotometrically. When DPPH reacts with an antioxidant compound, which can donate hydrogen, it is reduced. The changes in color (from deep violet to light yellow) were measured at 517 nm on a

UV–Vis light spectrophotometer. A solution of DPPH is mixed with that of a substance that can donate a hydrogen atom and then give rise to the reduced form with the loss of violet color. The reaction is:

$$\mathrm{DPPH}\cdot + \mathrm{RH} = \mathrm{DPPH} + \mathrm{R}\cdot$$

Stock solutions were prepared by dissolving 1 mg of compound in 1 ml of ethanol. Then, different concentrations of the sample, 10, 50, and 100 μg, were dissolved in 3 ml ethanol. The solution of DPPH in ethanol was prepared just before UV measurements. Next, 3 ml of the sample and 1 ml of the DPPH solution were mixed and kept in the dark for 30 min at room temperature, when the decrease in absorption was measured. For the control absorption, a blank sample containing the same amount of ethanol and DPPH solution was measured. Ascorbic acid was used as standard. The experiment was carried out in triplicate. The IC_{50} value were calculated for each compound as well as ascorbic acid as standard is represented in Table 3 (below) and graphically represented in Fig. 1. The scavenging activity increased with increasing concentrations of the test samples. The IC_{50} values for compounds **5a**, **5b**, **5c**, and **5d** were 43.22, 48.62, 55.85, and 72.18, respectively, which were comparatively higher than the IC_{50} value (39.81) of standard ascorbic acid. From the results of the DPPH, it demonstrated that all four compounds are equally effective as antioxidants compared to ascorbic acid. The radical scavenging activity was calculated by the following formula:

$$\mathrm{I}\%(\text{percentage inhibition}) = [\mathrm{AB} - \mathrm{AA/AB}] \times 100,$$

where AB is the absorption of the blank sample and AA is the absorption of the sample

In vitro antibacterial studies

In vitro antibacterial activity was studied by thr agar disc diffusion method. In this method, a Petri plate containing an agar growth medium was inoculated uniformly over its entire surface. Paper discs impregnated with various chemotherapeutic agents are placed on the surface of the agar. During incubation, the chemotherapeutic agent diffuses from the disc, i.e. from the area of high concentration to the area of lower concentration. An effective chemotherapeutic agent can inhibit the bacterial growth, and measurements can be made of the size of the zone of inhibition around the disc.

The concentration of the chemotherapeutic agent at the edge of the zone of inhibition represents its minimum inhibitory concentration (MIC). In the agar disc diffusion method, Mueller–Hinton agar was used since it allows chemotherapeutic agents to diffuse freely.

Pure cultures of the organisms were inoculated onto nutrient broth (Himedia, India), incubated for 24 h at 37 °C and maintained on respective agar slants at 4 °C. The cultures used for screening the antibacterial activities were Gram-positive *S. aureus* ATCC 700699 and *B. subtilis* MTCC 430, and Gram-negative *E. coli* ATCC 11105, *Klebsiella* ATCC 10273, and *P. aeruginosa* ATCC 27853 by the agar well technique. All the compounds were dissolved in 100 % DMSO to obtain concentrations of 15.6, 31.2, 62.5, 125, 250, 500, 1,000, 5,000, and 10,000 μg/ml.

Standard antibacterial ampicillin was also tested under similar conditions for comparison. The MIC of all the compounds was determined by the modified agar well diffusion method. The concentration of test cultures was adjusted to 0.5 McFarland standards by using a spectrophotometer. Test organisms were lawn cultured on the MHA plates. The agar surface was bored by using a sterilize cork borer. Then, 100 µl of each dilution was poured into the wells. All test plates were incubated at 37 °C for 24 h. MIC was noted as the minimum concentration of each compound which showed a clear zone of inhibition. Experiments were repeated thrice (Table 4, below).

Results and discussion

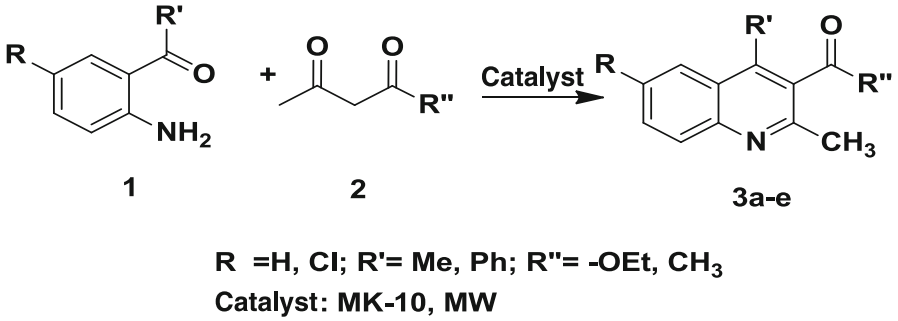
The product formation **3a–e** (Scheme 1) was confirmed by comparing the literature melting points. Single crystal for compound ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate, **3a** was grown and published [49] (Fig. 3). When the same reaction was carried out with other catalysts, such as amberlite and acidic alumina, the reaction did not proceed to the expected product. Optimization of the catalyst, MK-10, offered maximum yield of 95 % at 100 mg. Reusability of the catalyst was found to be effective with comparable yield.

Quinolin-2[1*H*]-ones, **4** [50], readily underwent Friedlander condensation with *o*-amino ketones, **1**, in the presence of MK-10 under solvent-free condition in microwave (MW) at a power level of 500 W for the appropriate time (Table 1) to yield 4-phenyl-3-(4-phenyl quinolin-2-yl)quinolin-2(1*H*)- ones, **5** (Scheme 2). Earlier, the reaction was effected with glacial acetic acid and a few drops of conc. H_2SO_4 for 8 h on a water bath, but the conversion of the desired product was less. When 100 mg of the catalyst, MK-10, was used, it led to complete conversion of the compound, **5**, with high yield and purity. After an initial amino-ketone condensation, the intermediate undergoes MK-10 catalyzed cyclocondensation to produce a quinoline derivative, **5**. Selection of the catalyst was carried out using various catalysts, such as amberlite Na sr1L, bentonite, montmorillonite KSF, amberlite, acidic alumina, montmorillonite K-10, among which MK-10 gave a very high yield (Table 2; Fig. 4). The amount of catalyst used was optimized starting from 20, 40, 60, 80, 100, and 140 mg and found to be effective at 100 mg.

All the synthesized compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies. Compound **5a** showed FTIR absorption bands at 3,427, 1,644, and 1,484 cm^{-1} corresponding to –NH, NH–C = O, and –C = N groups, respectively, the disappearance of –C = O at 1,707 cm^{-1} of **4a** at C-3, indicates that the Friedlander annulations have occurred at the acetyl moiety of the quinolinones, **4**.

^{1}H NMR spectrum of **5a** revealed a signal at δ 12.4 (–NH) as singlet for one proton.

The aromatic proton appears at δ 7.39, 7.91, 7.68, 7.48, and 7.00 gave various doublets for four aromatic protons, doublet of doublet appears at δ 7.72, 7.63, and 7.34 accounts for four aromatic protons, at δ 7.53, 7.29, and 7.25 gave multiplet which accounts for eight aromatic protons of the quinolinylquinolinones compound,



Scheme 1 Synthesis of ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylates and 1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone analogues, **3a–e**

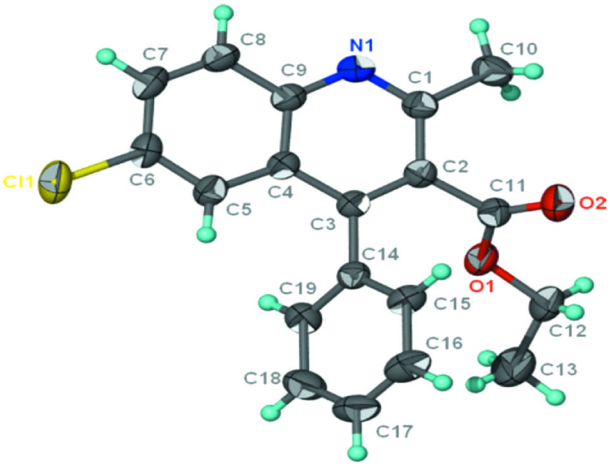


Fig. 3 Single crystal structure of ethyl-6-chloro-2-methyl-4-phenylquinoline-3 carboxylate, **3a**

5a. ^{13}C NMR spectrum showed the signals at δ 117.0–156 for 29 aromatic carbons and at δ 161 for the NHC = O. HRMS of the compound, **5a**, gave a peak at 492.3667 which matches with the molecular formula $C_{30}H_{18}Cl_2N_2O$.

Pharmacology

Anti-oxidant activity

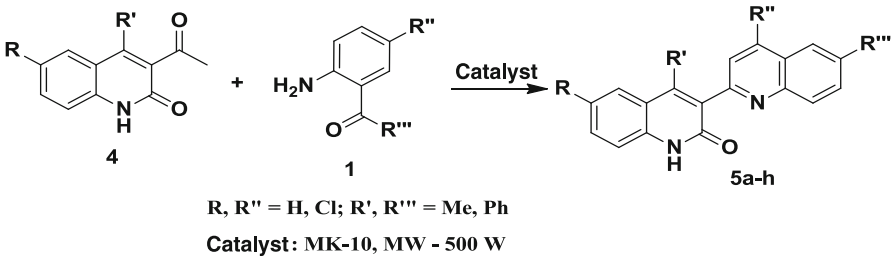
Oxidative stress occurs when the production of free radicals in the body goes beyond the protective defences, which initiates early stages of cancer and heart disease. The free radicals are also suspected in the development of arthritis, Alzheimer's disease, arthritis, cataracts, diabetes, kidney disease, and age-related

Table 1 Synthesis of quinolin-2-yl-quinolin-2(1*H*)-ones, **5a–h**

Entry	R	R′	R″	R‴	Product	Time/yield[b]	
						Conventional heating h/(%)	MW Irradiation min/(%)
1	−Cl	$-C_6H_5$	−Cl	$-C_6H_5$	**5a**	8/66	4/91
2	−H	$-CH_3$	−Cl	$-C_6H_5$	**5b**	8.5/65	5/87
3	−H	$-C_6H_5$	−Cl	$-C_6H_5$	**5c**	9/62	5/89.3
4	−Cl	$-C_6H_5$	−H	$-CH_3$	**5d**	7/61	6/87.2
5	−H	$-CH_3$	−H	$-CH_3$	**5e**	8/59	6/83.7
6	−H	$-C_6H_5$	−H	$-CH_3$	**5f**	8.5/60	4/88.6
7	−Cl	$-C_6H_5$	−H	$-C_6H_5$	**5g**	7.5/61	5/87
8	−H	$-C_6H_5$	−H	$-C_6H_5$	**5h**	8/58	5.5/89

[a] **4** (1 mmol); **1** (1 mmol); MK-10 (100 mg); MW irradiation 500 W, Conventional heating: Gl. AcOH, Conc. H_2SO_4

[b] Isolated yield

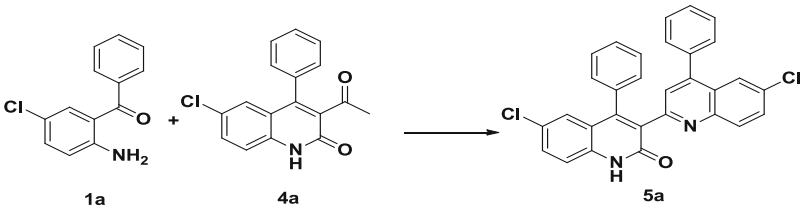


Scheme 2 Synthesis of 4-phenyl-3-(4-phenyl quinolin-2-yl)quinolin-2(1*H*)-ones, **5**

blindness. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit cell death and other oxidation reactions.

In the present study, quinazolinone derivatives were evaluated for their free radical scavenging activity using the DPPH radical assay. Reduction of DPPH radicals can be observed by a decrease in absorbance at 517 nm. Different derivatives of quinazolinone significantly reduced DPPH radicals. Activity of quinazolinone derivatives was compared with commercial antioxidant ascorbic acid. 2-Thioxo-2, 3-dihydro-1*H*-quinazolin-4-one had relatively high DPPH radical scavenging activity. The IC_{50} value were calculated for each compound as well as ascorbic acid as standard represented in Table 3 and graphically represented in Fig. 5. The scavenging activity increased with increasing concentrations of the test samples. The IC_{50} values for compounds **5a–h** were 48.62, 43.22, 89.25, 93.49, 91.60, 95.52, 55.85, and 72.18, respectively, which were comparatively higher than the IC_{50} value (39.81) of standard Ascorbic acid. From the results of DPPH, it showed that out of eight compounds four compounds namely **5a**, **5b**, **5g**, and **5h** are equally effective as antioxidant compared to standard ascorbic acid.

Table 2 Catalyst effect and its amount for the synthesis of quinolin-2-yl-quinolin-2(1*H*)-ones[a], **5**



1a 4a 5a

S. no	Catalyzed used	Amount (mg)	Time/min Yield[b]/ %		S. no.	MK-10 (mg)	Time/min	Yield[b]/ %
1	No catalyst	–	10 h	Nil	1	20	8	59
2	AcOH/Conc. H_2SO_4	Few drops	8 h	66	2	40	8	64
3	Amberlite Na sr1L	100	30	Nil	3	60	8	72
4	Bentonite	100	30	Nil	4	80	8	81
5	Montmorillonite KSF	100	30	Nil	5	100	8	93
6	Amberlite	100	20	40	6	100	4	91
7	Acidic alumina	100	20	48	7	120	4	92
8	Montmorillonite K-10	100	4	91				

[a] **1a** (1.2 mol), **4a** (1 mol), MK-10 (100 mg), MW irradiation 500 W

[b] Isolated yield

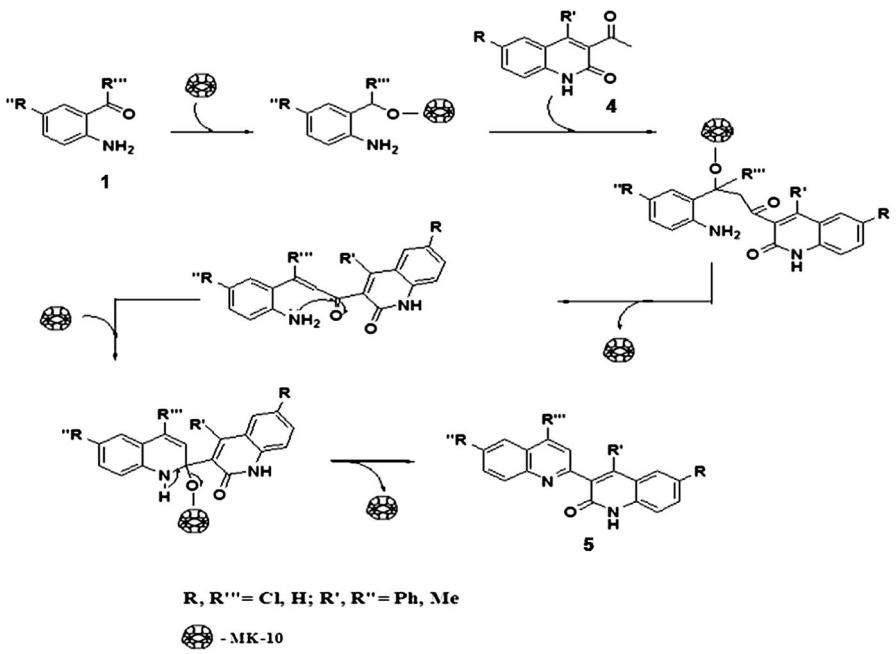


Fig. 4 Mechanistic pathways for the synthesis of quinolin-2-yl-quinolin-2(1*H*)-ones, **5**

Table 3 Percentage inhibition, IC_{50} values of standard and **5a–h**

S. no	Conc µg/ml	I % (Std) IC_{50} 39.81	I % (**5a**) IC_{50} 48.62	I % (**5b**) IC_{50} 43.22	I % (**5c**) IC_{50} 89.25	I % (**5d**) IC_{50} 93.49	I % (**5e**) IC_{50} 91.60	I % (**5f**) IC_{50} 95.52	I % (**5g**) IC_{50} 55.85	I % (**5h**) IC_{50} 72.18
1.	10	26.20	15.77	18.01	10.25	9.23	10.12	8.33	13.44	10.74
2.	50	62.78	52.40	57.84	28.01	26.74	27.29	26.17	44.76	33.05
3.	100	93.30	86.23	86.41	63.12	61.08	60.85	59.24	85.27	72.93

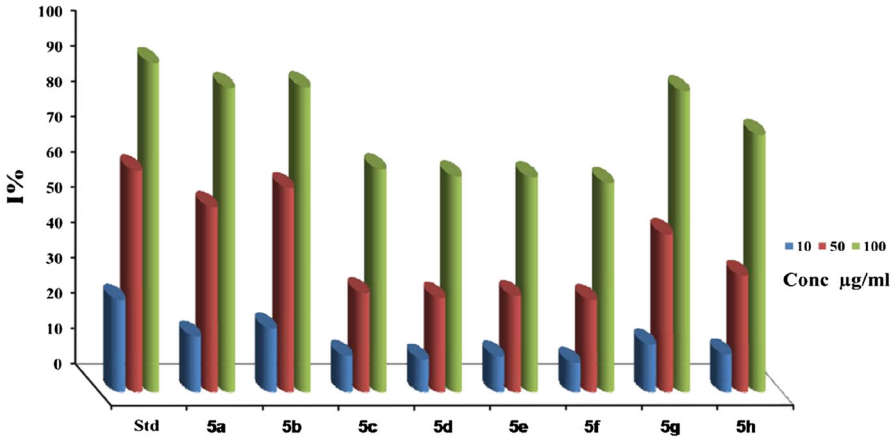


Fig. 5 Antioxidant activity of Ccompounds **5a–h** and standard (ascorbic acid)

Table 4 Determination of minimum inhibition concentration of **5a–h** and standard

Test organisms	MIC (µg/mL)								
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**S***
S. aureus	15.62	31.25	15.62	31.62	125	125	>200	31.25	15.62
B. subtilis	125	15.62	31.25	62.5	125	125	31.25	>200	15.62
E. coli	125	31.25	62.5	125	15.62	>200	125	15.62	31.25
K.pneumonia	62.5	31.25	125	15.62	31.25	>200	62.5	31.25	31.25
P.aeruginosa	125	>200	125	62.5	15.62	15.62	>200	31.25	15.62

*S** ampicillin

The quinalinone derivatives were also screened successfully for their in vitro antibacterial studies using agar well diffusion method. All the derivatives were screened for MIC and data reveals that all the compounds showed antibacterial activity in good to moderate range in comparison to the standard drug. Compound **5a** possess good antibacterial activity and comparable that of standard ampicillin against *S.aureus.* Compound **5e** shows better MIC than the standard against *E.Coli*

and compound **5b** possess comparable activity with that of standard against *B. subtilis*. Compound **5h** possess good antibacterial activity when compared to all other derivatives in comparison with that of ampicilin represented in Table 4.

Conclusion

In conclusion, we have reported a facile synthesis of quinolin-2-yl-quinolin-2(1*H*)-one derivatives under solvent-free conditions under microwave irradiation, demonstrating the use of montmorillonite K10 as an efficient, rapid, mild, and inexpensive catalyst. The present procedure has advantages of a simple experimental and product isolation procedure coupled with high purity and yields. The synthesized compounds were evaluated for in vitro antibacterial and antioxidant studies. The results showed that all compounds possess antibacterial activity in good to moderate range when compared to that of standard ampicillin. The quinolinone derivatives were also screened for antioxidant studies and, from the IC_{50} values, it can be concluded that all the four compounds are equally potent as antioxidant and comparable to that of standard ascorbic acid.

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