Novel Synthesis of 1,2-Substituted 4-Quinolones

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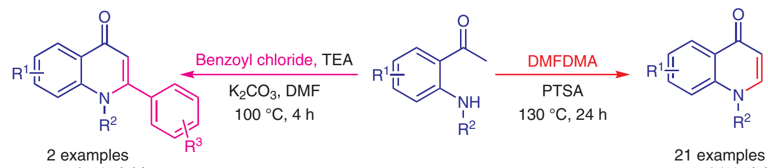


Received: 21.08.2018
Accepted after revision: 25.10.2018
Published online: 21.11.2018
DOI: 10.1055/s-0037-1610388; Art ID: so-2018-d0049-op

Abstract An efficient method for the straightforward synthesis of N-functionalized 4-quinolones and 1,2-substituted 4-quinolones from simple 2-aminoacetophenones has been developed.

Key words 2-aminoacetophenone, 4-quinolone, echinopsine

Nitrogen-containing heterocycles are frequently found in a variety of biologically active molecules that can be used in therapeutic areas.[1] Specifically, 4-quinolone derivatives have attracted considerable attention because of their diverse biological activities. Several quinolone compounds, such as oxolinic acid, Ciprofloxacin, Pefloxacin, and Ofloxacin, have emerged as potent antibiotics (Figure 1).[2]

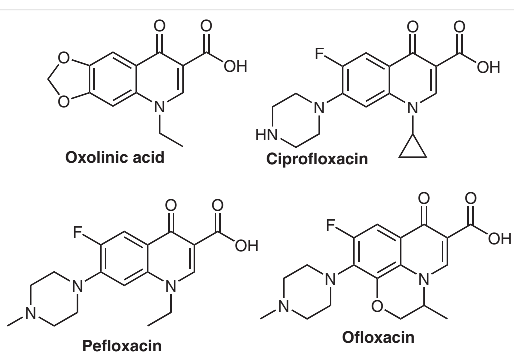
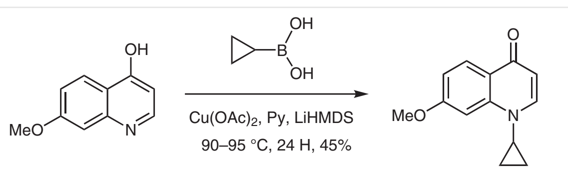


Figure 1 Representative potent antibiotics containing the 4-quinolone moiety

More recently, 4-quinolone derivatives have been explored for their antibacterial,[3] antitumor,[4] antimalarial,[5] antidiabetic,[6] antiviral[7] and HIV-1 integrase inhibition properties.[8] Given the importance of these heterocycles in medical chemistry, the development of synthetic methodology to access 4-quinolone derivatives remains an imperative. To date, numerous methods have been reported for the synthesis of quinolones.[9] The most frequently used approaches are based on various cyclocondensation strategies, such as the Camps,[10] Conrad–Limpach,[11] Gould–Jacobs,[12] and Niementowski cyclizations.[13] Often these synthetic methods are carried out under extremely harsh conditions, including temperatures up to 250 °C or the use of strong acids such as polyphosphoric acid or Eaton's reagent. As a result, the harsh conditions dramatically limit the substrate scope of these transformations. To develop milder processes for construction of the 4-quinolone framework, much effort has been focused on the development of transition-metal-catalyzed (Pd,[14] Cu,[15] and Au[16]) cyclization methodologies during the past decade. Despite significant progress, transition-metal-catalyzed synthetic methods often require specially designed ligands. Another disadvantage is the need to remove metal-related impurities from products, which is an important issue in the synthesis of pharmaceutical molecules.

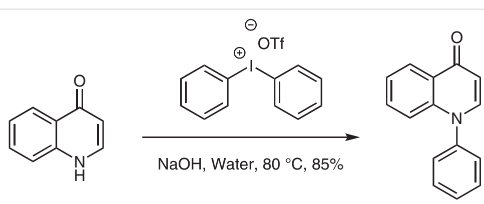
Some quinolones have been found to be active as mammalian topoisomerase-II inhibitors, including a series of 3-unsubstituted compounds.[17] 1-Methyl-1,4-dihydroquinolin-4-one, echinopsine,[18] is a nontoxic alkaloid from *Echinops* species that regulates the function of the parasympathetic autonomous nervous system.[19] Several 1-alkyl-3-unsubstituted derivatives have been prepared by decarboxylation of the corresponding 3-carboxylic acids.[20] This method usually requires high temperatures and the reported yields are generally low to medium. Some 1-aryl-3-unsubstituted 1,4-dihydroquinolin-4-ones have also been prepared by this method but the yields are also generally low.[17] Thermal rearrangement of 4-methoxy- and 4-ethoxyquinoline derivatives can be used for the synthesis of the corresponding 1-methyl- and 1-ethyl-1,4-dihydroquinolin-4-ones, respectively.[21] This method usually requires high temperatures (300–350 °C) and the yields are again usually low. Lower temperatures and higher yields were reported when the rearrangement was carried out in the presence of the appropriate iodoalkane,[22] alkyl tosylate,[23] or trialkyl phosphate.[23] 1-Alkyl-3-unsubstituted 1,4-dihydroquinolin-4-ones having a primary alkyl group at the 1-position can also be prepared by N-alkylation of the corresponding 1-unsubstituted 1,4-dihydroquinolin-4-ones.

It is known that amino-substituted acetophenones are valuable precursors for the synthesis of medicinally important substances such as 2-arylquinolin-4(1*H*)-ones and their analogues.[24,25] In recent years, interest in these compounds has prompted extensive studies into their properties, such as toxicity to human tumor cell lines and tubulin polymerization inhibition.[4a,26] The method most widely used to prepare 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones includes a two-step sequence consisting of base-catalyzed aldol condensation of 2-aminoacetophenones and aldehydes and then acid-catalyzed cyclization of the corresponding 2-aminochalcones thus formed via an intramolecular aza-Michael reaction.[25–27] Other groups have also investigated the synthesis of 4-quinolones from 2-aminoacetophenones,[28] 2-bromoacetophenones,[14d] 2-halophenones,[15a] and 2-iodoanilines,[29] as well as the reactions of isatoic anhydrides with aryl ketones[30a] or alkynes[30b] using transition-metal catalysts. Tambe and co-workers used copper-mediated N-cyclopropylation on substituted fused or unfused pyridinol systems to generate *N*-cyclopropyl quinolones in moderate yields (Equation 1).[31]



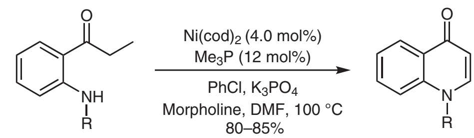
Equation 1

Kumar et al. synthesized *N*-aryl quinolones from quinolone and diaryliodonium salts in good yields (Equation 2).[32]



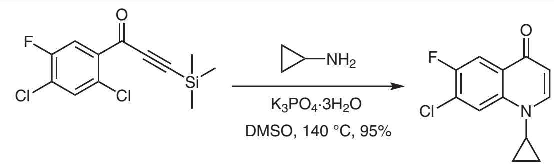
Equation 2

Ueno et al. prepared *N*-alkyl quinolones by the nickel-catalyzed intramolecular amination of 2-(*N*-alkylamino)propiophenones at the β-carbon in good yields (Equation 3).[18j]



Equation 3

Shao et al.[9h] prepared *N*-cyclopropyl quinolones from trimethylsilyl substituted substrates and cyclopropyl amine in good yields (Equation 4).



Equation 4

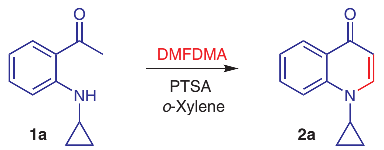
However, especially for structure–activity studies, the need for new methods for the preparation of the 3-unsubstituted compounds remains. This is particularly true for 1-*sec*-alkyl, 1-*tert*-alkyl, and 1-aryl-1,4-dihydroquinolin-4-ones.

At the outset, when we attempted the reaction of 1-(2-cyclopropylaminophenyl)ethanone[33] with dimethylformamide dimethylacetal (DMFDMA) as both reactant and solvent, the desired product **2a** was not observed (Table 1). However, product **2a** was formed in 90% yield when *para*-toluenesulfonic acid (PTSA, 0.1 mol) in *ortho*-xylene was employed (entry 10). The yields were not improved by using other acids such as methanesulfonic acid, benzenesulfonic acid, camphor sulfonic acid, conc. HCl or sulfuric acid (entries 11–15). A survey of reaction media showed that the use of polar solvents such as DMSO, DMF, and DMA provided better results than those obtained in either toluene or 1,4-dioxane (entries 16–21).

A series of experiments were then carried out to reveal the crucial role of the reaction temperature (Table 1, entries 4–9). The results showed that increasing reaction temperature led to higher yields (90% at 130 °C vs. 25% at 100 °C; entries 10 and 5). Investigation of the effect of time on the reaction showed that higher yields can be obtained by prolonging the reaction time from 8 to 24 hours (entries 8–10). Thus, optimal conditions used **1a** and DMFDMA in the presence of PTSA in *ortho*-xylene at 130 °C (entry 10).

With the optimized reaction conditions established, we then studied the scope of the cyclization of DMFDMA with a series of other aminoacetophenones, as shown in Scheme 1. First, we examined the effect of substitution with electron-donating groups and electron-withdrawing groups (EWGS) on the phenyl ring. Both were well tolerated and gave the corresponding quinolones in good to excellent yields (60–90%). All *ortho*-, *meta*- and *para*-substituted

Table 1 Optimization of One-Pot Tandem Reaction Conditions of **2a**

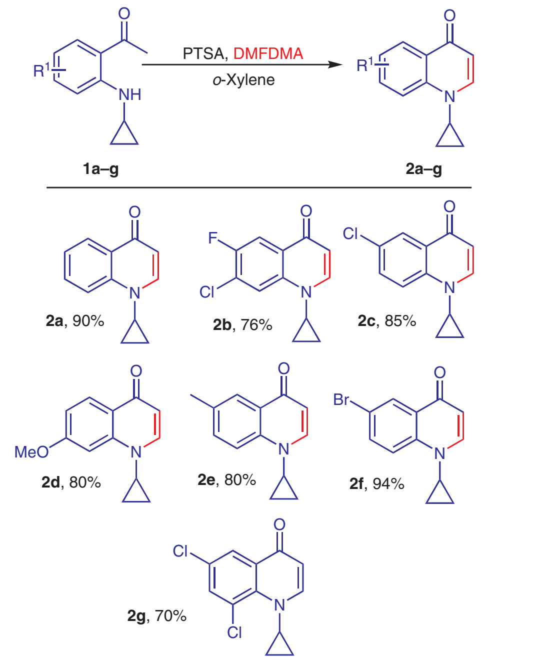


Entry	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)
1	DMFDMA	–	80	24	NR
2	DMFDMA	–	100	24	NR
3	DMFDMA	–	130	24	NR
4	*ortho*-xylene	PTSA	80	40	10
5	*ortho*-xylene	PTSA	100	38	25
6	*ortho*-xylene	PTSA	110	38	33
7	*ortho*-xylene	PTSA	120	38	42
8	*ortho*-xylene	PTSA	130	12	63
9	*ortho*-xylene	PTSA	130	20	82
10	*ortho*-xylene	PTSA	130	24	90
11	*ortho*-xylene	methanesulfonic acid	130	24	10
12	*ortho*-xylene	benzenesulfonic acid	130	24	15
13	*ortho*-xylene	camphorsulfonic acid	130	24	15
14	*ortho*-xylene	Conc. HCl	130	24	50
15	*ortho*-xylene	Conc. H_2SO_4	130	24	NR
16	DMF	PTSA	130	24	65
17	DMSO	PTSA	130	24	65
18	chlorobenzene	PTSA	130	24	55
19	toluene	PTSA	110	24	trace
20	dioxane	PTSA	100	24	NR
21	DMA	PTSA	130	24	trace

aminoacetophenones were smoothly transformed into the desired products, which indicates that steric bulk and electronic effects did not significantly alter the reactivity.

To explore substrate scope still further, we next examined variations in the nitrogen substituent R^2. When R^2 was cyclic (cyclopentyl, cyclohexyl), all substrates examined were smoothly converted into the corresponding quinolones **2h–k** (Scheme 2). The method was successfully utilized in the synthesis of echinopsine **2l**. Changing R^2 to an aryl group led to quinolones **2m–u** in good yields. Substrates possessing *N*-aryl substituents containing either electron-donating or electron-withdrawing groups also reacted efficiently.

We also evaluated the possibility of synthesizing 1,2-disubstituted 4-quinolones **4a** directly from 2-aminoacetophenone **1a** and benzoyl chloride, using TEA as the catalyst and THF as the solvent. Subsequently, the intermediate was cyclized with DMF and K_2CO_3 and the desired product **4a** was formed in 87% yield (Scheme 3).



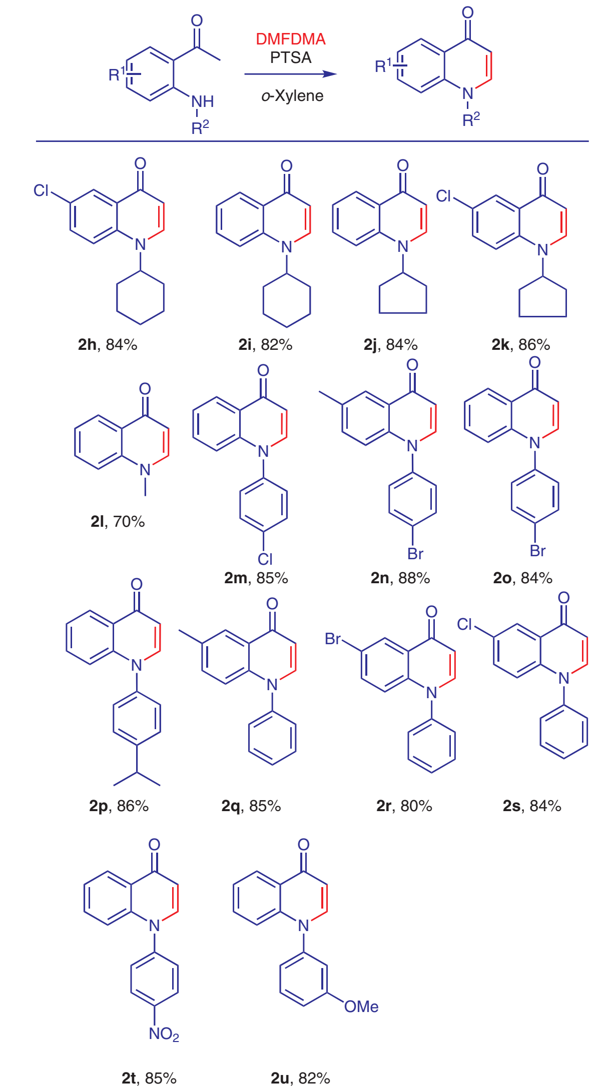
Scheme 1 One-pot synthesis of N-substituted-4-quinolone derivatives

Quinolones **4** were useful synthetic precursors; for example, the corresponding 3-functionalized quinolones can be readily generated by using well-documented amination,[34] cyanation,[35] Heck,[5a,36] Sonogashira,[37] and Suzuki–Miyaura[14e,38] reactions from 3-halogenated quinolones prepared by direct halogenation of products **4**.[14e,38b]

In summary, we have developed an efficient method for the straightforward synthesis of N-functionalized 4-quinolones and 1,2-substituted 4-quinolones from 2-aminoacetophenones. By using this method, N-alkyl and N-aryl aminoacetophenones can be successfully transformed into the corresponding 4-quinolones. This approach provides one of the simplest methods for the synthesis of this class of compounds, and a wide range of multisubstituted 4-quinolones can be generated accordingly.

Preparation of 1-Cyclopropyl-1*H*-quinolin-4-one (2a); Typical Procedure

A mixture of 1-(2-cyclopropylamino-phenyl)ethanone **1** (1.0 gm, 5.71 mmol), dimethylformamide dimethylacetal (2.0 mL), and PTSA (100 mg, 0.571 mmol) in *o*-xylene (30 mL) was heated to reflux for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool and then diluted with *o*-xylene (10 mL). Water (20 mL) was added and the organic phase was separated. The aqueous layer was then extracted further with *o*-xylene (10 mL) and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give **2a**.



Scheme 2 Synthesis of N-substituted-4-quinolone derivatives

Yield: 950 mg (90%); yellow solid; mp 79.8–81.4 °C.

IR (KBr): 3488, 1610, 1620, 1565, 1485, 1299, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.12 (q, 2 H), 1.23–1.30 (q, 2 H), 3.36–3.42 (m, 1 H), 6.23 (d, *J* = 7.92 Hz, 1 H), 7.37–7.41 (m, 1 H), 7.66–7.70 (m, 2 H), 7.91 (d, *J* = 8.6 Hz, 1 H), 8.42 (dd, J_1 = 0.84, J_2 = 0.88 Hz, 1 H).

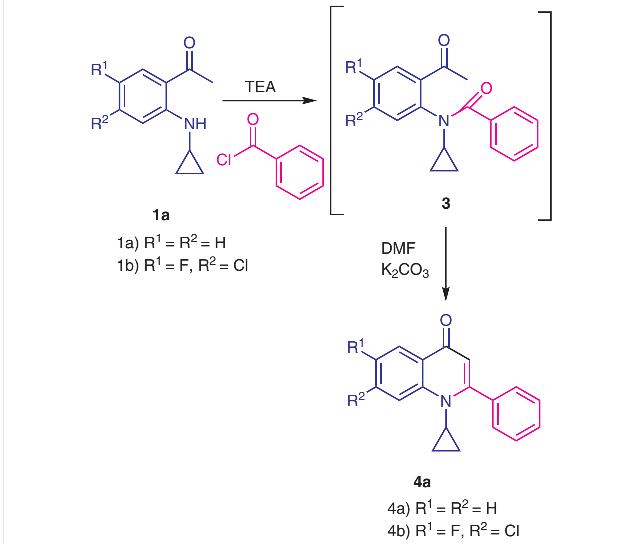
^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.19, 33.61, 109.89, 116.91, 123.75, 126.67, 131.96, 141.51, 142.51, 178.33.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56; Found: C, 77.80; H, 5.97; N, 7.53.

7-Chloro-1-cyclopropyl-6-fluoro-1*H*-quinolin-4-one (2b)

Yield: 396 mg (76%); yellow solid; mp 195.6–197.2 °C.

IR (KBr): 3100, 3027, 1633, 1610, 1589, 1477, 1259, 971, 893, 824 cm^{-1}.



Scheme 3 Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-one **4**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.09 (q, 2 H), 1.29–1.34 (q, 2 H), 3.34–3.39 (m, 1 H), 6.20 (d, *J* = 7.92 Hz, 1 H), 7.66 (d, *J* = 7.92 Hz, 1 H), 7.97 (d, *J* = 5.92 Hz, 1 H), 8.14 (d, *J* = 9.12 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.27, 33.83, 109.72, 112.69, 118.52, 126.42, 138.23, 142.73, 153.55, 156.05, 176.76.

Anal. Calcd for $C_{12}H_9ClFNO$: C, 60.65; H, 3.82; N, 5.89; Found: C, 60.66; H, 3.80; N, 5.90.

6-Chloro-1-cyclopropyl-1*H*-quinolin-4-one (2c)

Yield: 445 mg (85%); white solid; mp 168.4–174.1 °C.

IR (KBr): 3075, 3012, 1630, 1582, 1473, 1287, 1144, 823 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03–1.09 (q, 2 H), 1.26–1.33 (q, 2 H), 3.35–3.42 (m, 1 H), 6.24 (d, *J* = 7.8 Hz, 1 H), 7.60 (dd, J_1 = 2.4, J_2 =2.4 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 8.39 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.31, 33.80, 110.25, 118.10, 126.09, 127.77, 130.08, 132.27, 140.02, 142.68, 177.6.

Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59; N, 6.38; Found: C, 65.59; H, 4.57; N, 6.40.

1-Cyclopropyl-7-methoxy-1*H*-quinolin-4-one (2d)

Yield: 419 mg (80%); yellow solid; mp 78.1–82.4 °C.

IR (KBr): 3010, 1614, 1569, 1460, 1264, 1016, 827 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.08 (q, 2 H), 1.23–1.28 (q, 2 H), 3.30–3.36 (m, 1 H), 3.94 (s, 3 H), 6.17 (d, *J* = 7.8 Hz, 1 H), 6.97 (dd, J_1 = 2.4, J_2 = 2.1 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 8.34 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.21, 33.60, 55.62, 99.03, 109.88, 112.36, 121.03, 128.69, 142.39, 143.35, 162.65, 177.92.

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51; Found: C, 72.55; H, 6.07; N, 6.53.

1-Cyclopropyl-6-methyl-1*H*-quinolin-4-one (2e)

Yield: 421 mg (80%); yellow solid; mp 96.4–100.7 °C.

IR (KBr): 3032, 3008, 1633, 1604, 1582, 1488, 1341, 1296, 1154, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.07 (q, 2 H), 1.23–1.27 (q, 2 H), 2.47 (s, 3 H), 3.35–3.40 (m, 1 H), 6.21 (d, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 8.7 Hz, 1 H), 8.23 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.16, 20.95, 33.63, 109.65, 116.17, 126.11, 126.65, 133.42, 133.70, 139.65, 142.13, 178.29.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03; Found: C, 78.34; H, 6.59; N, 7.04.

6-Bromo-1-cyclopropyl-1*H*-quinolin-4-one (2f)

Yield: 488 mg (94%); yellow solid; mp 166.3–169.8 °C.

IR (KBr):3075, 3010, 1630, 1580, 1469, 822 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03–1.08 (q, 2 H), 1.25–1.32 (q, 2 H), 3.34–3.41 (m, 1 H), 6.22 (d, *J* = 8.0 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.75–7.81 (2 H, m), 8.55 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.29, 33.75, 110.32, 117.69, 118.31, 128.02, 129.22, 134.93, 140.35, 142.72, 176.89.

Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30; Found: C, 54.56; H, 3.79; N, 5.32.

6,8-Dichloro-1-cyclopropyl-1*H*-quinolin-4-one (2g)

Yield: 364 mg (70%); pale-yellow solid; mp 127.4–132.8 °C.

IR (KBr): 3068, 1633, 1623, 1457, 1336, 1270, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–0.96 (q, 2 H), 1.17–1.24 (q, 2 H), 4.04–4.11 (m, 1 H), 6.21 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 2.4 Hz, 1 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 8.31 (d, *J* =2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.52, 38.96, 110.57, 123.63, 125.60, 129.81, 130.60, 135.16, 138.28, 146.10, 176.37.

Anal. Calcd for $C_{12}H_9Cl_2NO$: C, 56.72; H, 3.57; N, 5.51; Found: C, 56.69; H, 3.58; N, 5.48.

6-Chloro-1-cyclohexyl-1*H*-quinolin-4-one (2h)

Yield: 436 mg (84%); white solid; mp 126.8–131.2 °C.

IR (KBr):3061, 2929, 2861, 1621, 1587, 1479, 1353, 1326, 1210, 1170, 827, 805 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.36 (m, 1 H), 1.48–1.52 (m, 2 H), 1.68–1.76 (m, 2 H), 1.83–1.87 (m, 1 H), 2.00–2.05 (m, 1 H), 2.11–2.15 (m, 2 H), 4.29–4.36 (m, 1 H), 6.30 (d, *J* = 8.1 Hz, 1 H), 7.47 (d, *J* = 9.0 Hz, 1 H), 7.57 (dd, J_1 =2.1, J_2 =2.4 Hz, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 8.46 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.41, 26.00, 32.76, 58.93, 110.35, 116.56, 126.65, 128.64, 129.59, 132.25, 138.25, 138.53, 176.53.

Anal. Calcd for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35; Found: C, 68.85; H, 6.17; N, 5.32.

1-Cyclohexyl-1*H*-quinolin-4-one (2i)

Yield: 428 mg (82%); white solid; mp 145.3–148.4 °C.

IR (KBr): 3080, 2934, 2860, 1623, 1605, 1581, 1485, 1359, 1209, 1175, 833 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.32 (m, 1 H), 1.49–1.57 (m, 2 H), 1.69–1.77 (m, 2 H), 1.83–1.87 (m, 1 H), 2.00–2.04 (m, 2 H), 2.12–2.16 (m, 2 H), 4.35–4.43 (m, 1 H), 6.31 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 8.49 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.53, 26.10, 32.86, 58.54, 110.20, 114.63, 123.44, 127.51, 127.70, 132.09, 138.10, 140.18, 177.85.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; Found: C, 79.24; H, 7.55; N, 6.14.

1-Cyclopentyl-1*H*-quinolin-4-one (2j)

Yield: 440 mg (84%); yellow solid; mp 104.6–107.8 °C.

IR (KBr): 3067, 2963, 1625, 1606, 1579, 1488, 1354, 1210, 1179, 838 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–1.93 (m, 6 H), 2.25–2.29 (m, 2 H), 4.94 (m, 1 H), 6.31 (d, *J* = 7.8 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.60–7.70 (m, 3 H), 8.48 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.05, 32.29, 60.61, 110.10, 115.43, 123.49, 127.27, 127.57, 132.01, 138.22, 140.73, 177.94.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; Found: C, 78.85; H, 7.10; N, 6.54.

6-Chloro-1-cyclopentyl-1*H*-quinolin-4-one (2k)

Yield: 448 mg (86%); white solid; mp 141.7–143.2 °C.

IR (KBr): 3079, 2954, 2877, 1626, 1585, 1483, 1206, 1008, 845, 823 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–1.93 (m, 6 H), 2.25–2.27 (m, 2 H), 4.87–4.88 (m, 1 H), 6.29 (d, *J* = 8.1 Hz, 1 H), 7.54–7.61 (m, 2 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 8.45 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.03, 32.28, 60.98, 110.36, 117.31, 126.56, 128.63, 129.78, 132.25, 138.36, 139.15.

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65; Found: C, 67.86; H, 5.67; N, 5.67.

1-Methyl-1*H*-quinolin-4-one (2l)

Yield: 373 mg (70%); white solid; mp 144.6–148.1 °C.

IR (KBr): 3061, 3017, 1625, 1576, 1493, 1237, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.28 (d, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 3.4 Hz, 2 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 8.48 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.61, 110.15, 115.23, 123.77, 127.06, 127.13, 132.20, 140.67, 143.62, 178.32.

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80; Found: C, 75.43; H, 5.68; N, 8.81.

1-(4-Chloro-phenyl)-1*H*-quinolin-4-one (2m)

Yield: 884 mg (85%); yellow solid; mp 177.2–181.5 °C.

IR (KBr): 3045, 3022, 1622, 1606, 1590, 1476, 1367, 1285, 1236, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (d, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.59–7.49 (m, 4 H), 8.46 (dd, J_1 =0.8, J_2 =0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.54, 116.99, 124.10, 126.60, 126.74, 129.01, 130.61, 132.04, 135.59, 139.81, 141.20, 142.41, 178.23.

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48; Found: C, 70.47; H, 3.92; N, 5.46.

1-(4-Bromo-phenyl)-6-methyl-1*H*-quinolin-4-one (2n)

Yield: 454 mg (88%); white solid; mp 145.3–148.4 °C.

IR (KBr): 3021, 1630, 1610, 1583, 1483, 1289, 1201, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 6.36 (d, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.34 (dd, J_1 = 2.0, J_2 =2.0 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 8.26 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.89, 110.25, 116.91, 123.45, 126.05, 126.45, 129.24, 133.46, 133.55, 134.17, 139.20, 140.44, 141.99, 178.18.

Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46; Found: C, 61.15; H, 3.87; N, 4.43.

1-(4-Bromo-phenyl)-1*H*-quinolin-4-one (2o)

Yield: 806 mg (78%); yellow solid; mp 198.1–200.1 °C.

IR (KBr): 3043, 3020, 1619, 1591, 1475, 1366, 1283, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.53 (dd, J_1 = 1.2, J_2 = 1.6 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 2 H), 8.48 (dd, J_1 = 0.8, J_2 = 0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.57, 116.98, 123.56, 124.10, 126.61, 126.75, 129.31, 132.04, 133.62, 140.34, 141.13, 142.31, 178.21.

Anal. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67; Found: C, 60.03; H, 3.34; N, 4.64.

1-(4-Isopropyl-phenyl)-1*H*-quinolin-4-one (2p)

Yield: 893 mg (86%); yellow solid; mp 44.7–46.5 °C.

IR (KBr): 2964, 1620, 1585, 1291, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.8 Hz, 6 H), 3.00–307 (m, 1 H), 6.38 (d, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 8.48 (dd, J_1 = 1.2, J_2 = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.94, 33.95, 110.11, 117.45, 123.81, 126.52, 126.60, 127.35, 128.25, 131.77, 138.99, 141.52, 142.93, 150.49, 178.29.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32; Found: C, 82.08; H, 6.52; N, 5.30.

6-Methyl-1-phenyl-1*H*-quinolin-4-one (2q)

Yield: 887 mg (85%); white solid; mp 113.2–115.7 °C.

IR (KBr): 3030, 1584, 1486, 1286, 830, 808, 765, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 6.36 (d, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 8.7 Hz, 1 H), 7.301 (d, *J* = 8.4 Hz, 1 H), 7.39 (d, *J* = 6.3 Hz, 2 H), 7.56–7.60 (m, 4 H), 8.27 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.00, 110.03, 117.34, 125.98, 126.57, 127.65, 129.53, 130.37, 133.39, 133.99, 139.57, 141.60, 142.50, 178.35.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95; Found: C, 81.66; H, 5.58; N, 5.97.

6-Bromo-1-phenyl-1*H*-quinolin-4-one (2r)

Yield: 827 mg (80%); yellow solid; mp 158–162.8 °C.

IR (KBr): 3054, 3043, 1630, 1584, 1471, 1292, 818, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 7.5 Hz, 1 H), 6.88 (d, *J* = 9.0 Hz, 1 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 7.54–7.61 (m, 5 H), 8.61 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.68, 117.85, 119.39, 127.53, 127.94, 129.25, 129.91, 130.61, 134.96, 140.26, 141.09, 143.03, 177.04.

Anal. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67; Found: C, 60.00; H, 3.32; N, 4.65.

6-Chloro-1-phenyl-1*H*-quinolin-4-one (2s)

Yield: 832 mg (80%); white solid; mp 161.5–164.7 °C.

IR (KBr): 3042, 1630, 1590, 1473, 1294, 817, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 7.8 Hz, 1 H), 6.95 (d, *J* = 9.0 Hz, 1 H), 7.38–7.44 (m, 3 H), 7.58–7.62 (m, 4 H), 8.44 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.58, 119.20, 126.05, 127.56, 127.65, 129.90, 130.23, 130.60, 132.28, 139.90, 141.16, 142.97, 177.16.

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48; Found: C, 70.47; H, 3.92; N, 5.46.

1-(4-Nitro-phenyl)-1*H*-quinolin-4-one (2t)

Yield: 441 mg (85%); yellow solid; mp 164.1–167.8 °C.

IR (KBr): 3354, 1682, 1594, 1504, 1330, 1304, 1111, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, *J* = 7.6 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 1 H), 7.54–7.58 (m, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 8.49 (d, *J* = 8.8 Hz, 3 H).

^{13}C NMR (100 Hz, $CDCl_3$): δ = 111.21, 116.52, 124.59, 125.82, 126.62, 127.05, 128.73, 132.37, 140.57, 141.65, 146.58, 147.94, 178.10.

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52; Found: C, 67.62; H, 3.74; N, 10.49.

1-(3-Methoxy-phenyl)-1*H*-quinolin-4-one (2u)

Yield: 426 mg (82%); yellow solid; mp 163.5–167.1 °C.

IR (KBr): 3056, 2840, 1631, 1585, 1225, 1032, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.36 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 6.98 (t, *J* = 7.6 Hz, 1 H), 7.04–7.10 (m, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.47–7.52 (m, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 8.46 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 Hz, $CDCl_3$): δ = 55.65, 110.17, 113.25, 115.21, 117.35, 119.59, 123.87, 126.56, 131.02, 131.85, 141.29, 142.39, 142.59, 161.00, 178.29.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; Found: C, 76.49; H, 5.23; N, 5.56.

Preparation of 1-Cyclopropyl-2-phenyl-1*H*-quinolin-4-one (4a)

To a mixture of 1-(2-cyclopropylaminophenyl)ethanone **1** (1.0 g, 5.71 mmol) and triethylamine (2.88 g, 28.5 mmol) in THF (10 mL) at 25 °C, benzoyl chloride (0.802 g, 5.71 mmol) was added and the mixture was heated to reflux for 4 h. After completion of reaction (as monitored by TLC), the THF was removed under reduced pressure and potassium carbonate (2.36 g, 17.10 mmol) and DMF (10 mL) were added at 25 °C. The reaction mixture was then heated to 100 °C until completion of the reaction (monitored by TLC). The reaction mixture was then poured into water and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc/*n*-hexane to obtain **4a**.

1-Cyclopropyl-2-phenyl-1*H*-quinolin-4-one (4a)

Yield: 650 mg (87%); white solid; mp 170.1–172.4 °C.

IR (KBr): 3049, 3009, 1617, 1597, 1478, 1462, 1408, 1311, 1271, 1138, 1043, 775, 758, 709 cm^{-1}.

[1]H NMR (400 MHz, $CDCl_3$): δ = 0.57–0.58 (q, 2 H), 0.91–0.95 (q, 2 H), 3.32–3.35 (m, 1 H), 6.32 (s, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.47–7.54 (m, 5 H), 7.68–7.72 (m, 1 H), 7.96 (d, J = 8.8 Hz, 1 H), 8.44 (dd, J_1 = 1.2, J_2 = 1.2 Hz, 1 H).

[13]C NMR (100 MHz, $CDCl_3$): δ = 12.92, 32.37, 113.32, 117.82, 123.53, 126.41, 126.77, 128.36, 128.52, 129.20, 131.67, 136.96, 143.12, 155.45, 178.19.

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36; Found: C, 82.74; H, 5.76; N, 5.34.

7-Chloro-1-cyclopropyl-6-fluoro-2-phenyl-1*H*-quinolin-4-one (4b)

Yield: 575 mg (84%); white solid; mp 209.2–211.5 °C.

IR (KBr): 3073, 1631, 1609, 1468, 1271, 986, 840 cm^{-1}.

[1]H NMR (400 MHz, $CDCl_3$): δ = 0.58–0.59 (q, 2 H), 0.95–1.00 (q, 2 H), 3.29–3.32 (m, 1 H), 6.26 (s, 1 H), 7.49 (m, 5 H), 8.03 (d, J = 6.0 Hz, 1 H), 8.13 (d, J = 8.8 Hz, 1 H).

[13]C NMR (100 MHz, $CDCl_3$): δ = 12.96, 32.66, 112.25, 112.47, 113.00, 120.18, 125.99, 126.19, 126.66, 126.72, 128.29, 128.67, 129.53, 136.38, 139.74, 153.42, 155.85, 155.89, 176.58, 176.60.

Anal. Calcd for $C_{18}H_{13}ClFNO$: C, 68.91; H, 4.18; N, 4.46; Found: C, 68.90; H, 4.17; N, 4.45.

Acknowledgment

We would like to thank Suven Life Sciences for providing analytical facilities and acknowledge CEO Mr Jasti for permission to publish this work.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610388.

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