Synthesis W. Han et al. Paper

Synthesis of *N*-Aryl-4-arylhexahydroquinoline Derivatives by Reaction of Cyclic Enaminones with Arylidenemalononitriles in DMSO

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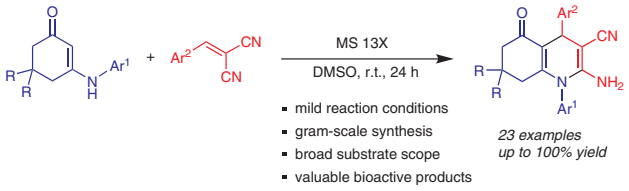

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Abstract The reaction of cyclic enaminones with arylidenemalononitriles was carried out in the presence of 13X molecular sieves in dimethyl sulfoxide. Under these mild reaction conditions, various bioactive *N*-aryl-4-arylhexahydroquinoline derivatives were obtained in high yields without the necessity of using transition-metal catalyst, organobase, or reflux conditions.

Key words dimethyl sulfoxide, molecular sieves, cyclic enaminones, arylidenemalononitriles, *N*-aryl-4-arylhexahydroquinolines

N-Aryl-4-aryl-hexahydroquinoline derivatives exhibit a range of significant antitumor,[1] anticancer, cytotoxic,[2] antioxidant,[3] antiproliferative,[4] and antibacterial bioactivities[5] (Figure 1). Because of their great pharmaceutical value, the synthesis of *N*-aryl-4-arylhexahydroquinoline derivatives has attracted much attention.

The reaction of cyclic enaminones with arylidenemalononitriles is an effective and straightforward process for the preparation of *N*-aryl-4-arylhexahydroquinoline derivatives. Although some examples of this type of reaction have been reported,[1–6] catalysts such as oxidovanadium(V) metal complexes,[6a] ZnO nanoparticles,[6b] chitosan,[6c] tetrabutylammonium fluoride (TBAF),[6d] or triethylbenzylammonium chloride (TEBAC)[6e] are usually needed in these reports. In some of the other previous studies for the reaction of cyclic enaminones with arylidenemalononitriles, ultrasonic irradiation was used.[5,6b] Moreover, in most of the above examples, either a base or reflux conditions are necessary for this transformation. However, from a green chemical point of view, a simple and convenient procedure for constructing *N*-aryl-4-arylhexahydroquinoline derivatives under transition-metal-catalyst-, organobase-, and refluxing-free conditions is more desirable.

Molecular sieves (MS) are not merely known as a dehydrating agent, but are also used as the promoter for many organic reactions due to their weak basicity.[7] Moreover, molecular sieves are all inexpensive, commercially available, and recyclable.[7c,f]

We have reported various reactions using the combination of dimethyl sulfoxide (DMSO) and molecular sieves.[8] For example, the double Michael addition of dithiols to acetylenic carbonyl compounds,[8g] the aza-Henry reaction of *N*-tosylimines with nitroalkanes,[8i] and the ring-opening reaction of aziridines with amines[8j] proceed smoothly in DMSO with MS 4A at room temperature, without the necessity of a transition-metal catalyst or an organobase.

Encouraged by these results, we here report the cascade Michael–cyclization reaction of cyclic enaminones with arylidenemalononitriles, which yields useful *N*-aryl-4-arylhexahydroquinoline derivatives under mild reaction conditions when using DMSO with MS 13X.

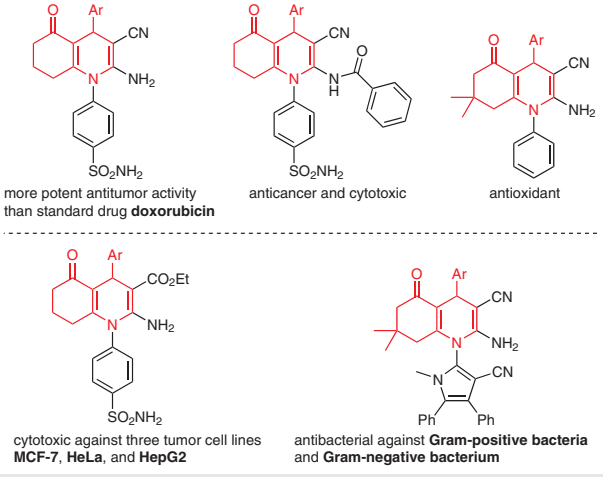

Figure 1 Selected bioactive *N*-aryl-4-arylhexahydroquinoline derivatives

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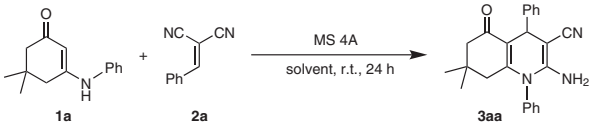
Initially, we attempted the reaction of cyclic enaminone **1a** (0.1 mmol) with benzylidenemalononitrile **2a** (1.2 equiv) using MS 4A (100 mg) in various solvents (Table 1, entries 1–7). Although the desired product **3aa** was obtained in only 35% yield, we found that DMSO was the most suitable solvent (entry 1). Other aprotic and protic polar solvents such as MeCN, DMF, dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP), THF, and MeOH were less effective for this reaction (entries 2–7). Therefore, we decided to screen other reaction conditions in DMSO to improve the yield of **3aa**.

Table 1 Screening of Solvents[a]



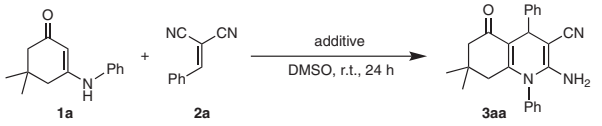
Entry	Solvent	Yield[b] (%)
1	DMSO	35
2	MeCN	7
3	DMF	16
4	DMA	15
5	NMP	18
6	THF	trace
7	MeOH	5

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), MS 4A (100 mg), solvent (1 mL), r.t., 24 h.
[b] Isolated yield by TLC.

Subsequently, we investigated various additives for the cascade reaction in DMSO as summarized in Table 2. Without an additive, the desired product **3aa** was obtained in trace amounts (entry 1). The use of H_2O as an additive was also unsuccessful (entry 2). In contrast, MS 3A promoted the reaction to afford **3aa** in similar yield to MS 4A (entries 3 and 4). However, MS 5A was less effective for the reaction (entry 5). MS 13X was more suitable than other molecular sieves, given that the corresponding yield of **3aa** was 69% (entry 5). Other dehydrating agents ($MgSO_4$, Na_2SO_4, and Drierite) and activated alumina were also tested as additives in DMSO, but the yields decreased (entries 7–10). Overall, MS 13X was determined to be the most suitable additive for this reaction.

Next, the effects of reaction concentration and additive loading on the cascade reaction were screened (Table 3). We found that increasing the concentration of the reaction improved the yield of **3aa**. By scaling the amount of MS 13X used with **1a** from 0.1–0.5 mmol in 1 mL DMSO, the yield of the desired product was improved from 69% to 95% (entries 1–6). However, considering both purification[9] and yield, we next conducted all reactions on a 0.4 mmol scale of enaminone **1a** to optimize the amount of MS 13X (entries 7–10). Fortunately, despite decreasing the amount of MS 13X to 300 or 200 mg, almost no loss of yield occurred (entries 5, 7, and 8). Further reducing the amount of MS 13X resulted in lower yields of **3aa** (entries 8, 9, and 10). Thus, the optimal reaction conditions were determined to be enaminone **1** (0.4 mmol), arylidenemalononitrile **2** (0.48 mmol), and MS 13X (200 mg) in DMSO (1 mL) at room temperature.

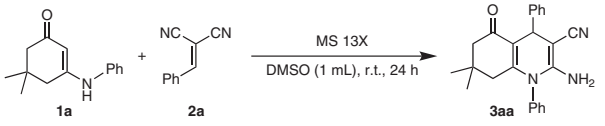
Table 2 Screening of Additives[a]



Entry	Additive	Yield[b] (%)
1	none	trace
2	H_2O (100 µL)	4
3	MS 3A	37
4	MS 4A	35
5	MS 5A	9
6	MS 13X	69
7	$MgSO_4$	48
8	Na_2SO_4	8
9	Drierite®	11
10	activated alumina	19

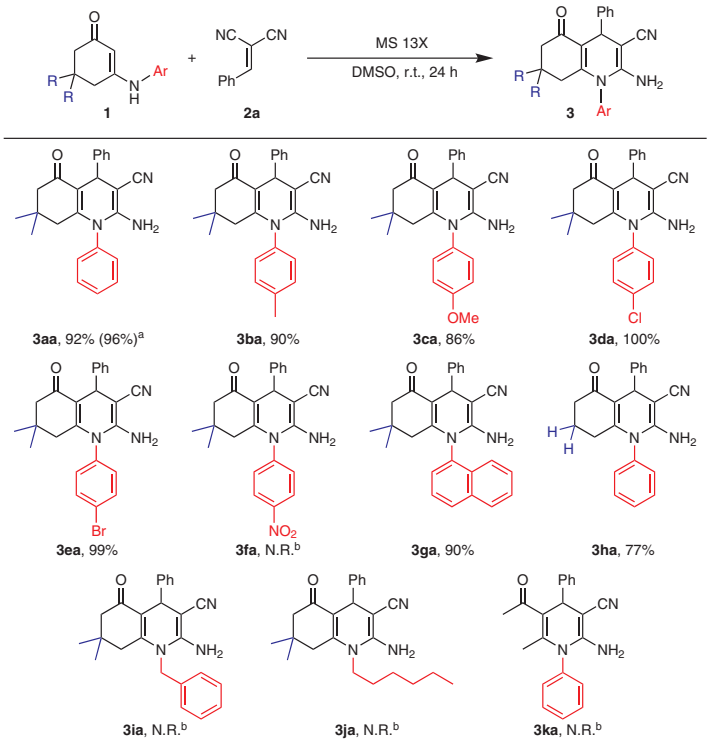
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), additive (100 mg), DMSO (1 mL), r.t., 24 h.
[b] Isolated yield by TLC.

Table 3 Optimization of the Reaction Conditions[a]



Entry	**1a** (mmol)	MS 13X (mg)	Yield (%)
1[b]	0.1	100	69
2[b]	0.2	200	84
3[b]	0.3	300	89
4[c]	0.3	300	86
5[c]	0.4	400	94
6[c]	0.5	500	95
7[c]	0.4	300	93
8[c]	0.4	200	92
9[c]	0.4	150	88
10[c]	0.4	100	78

[a] Reaction conditions: **1a**, **2a** (1.2 equiv), MS 13X, DMSO (1 mL), r.t., 24 h.
[b] Isolated yield by TLC.
[c] Product **3aa** was purified by recrystallization and TLC due to its high crystallinity.

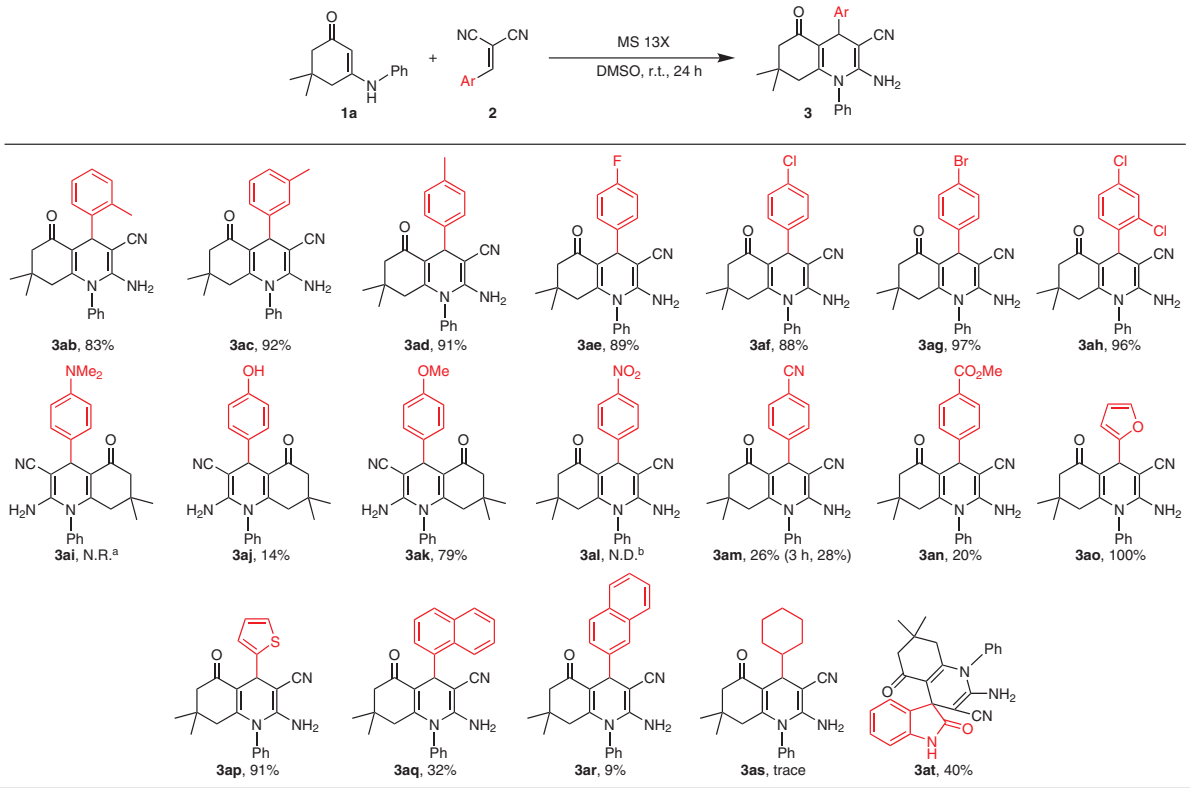


Scheme 1 Scope of enaminones. *Reagents and conditions*: **1** (0.4 mmol), **2a** (0.48 mmol), DMSO (1 mL), MS 13X (200 mg), r.t., 24 h; products **3** purified by recrystallization and TLC. [a] Gram-scale reaction: **1a** (4.64 mmol, 1.0 g), **2a** (5.57 mmol), DMSO (20 mL), MS 13X (2.0 g), 2 d. [b] N.R. = no reaction.

With the optimized reaction conditions in hand, we next examined the cascade Michael–cyclization reaction of various enaminones **1** with benzylidenemalononitrile (**2a**) (Scheme 1). Enaminones **1** bearing electron-donating and halogen-atom substituents at the *para*-position of the phenyl ring yielded the corresponding products **3ba**–**3ea** in good to excellent yields (86–100%). However, when the strongly electron-withdrawing group NO_2 was present at the *para*-position of the aromatic ring, the reactivity of the enaminone decreased significantly, so that no reaction occurred (**3fa**). Enaminone **1g** prepared from 1-naphthylamine and dimedone provided the corresponding product in 90% yield (**3ga**).

Furthermore, 1,3-cyclohexanedione-derived enaminone **1h** was also tolerated under the optimal reaction conditions, resulting in a 77% yield of product **3ha**. However, enaminones derived from benzylamine and hexylamine (aliphatic amines) and an acyclic enaminone gave poor results (**3ia**, **3ja**, and **3ka**, respectively). Moreover, the gram-scale synthesis of **3aa** was also achieved in 96% yield.

We further evaluated the cascade Michael–cyclization reaction of various arylidenemalononitriles **2** with enaminone **1a** (Scheme 2). Arylidenemalononitriles **2** containing a methyl group at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring were tolerated, giving high yields of the corresponding products **3ab**–**3ad**. Moreover, arylidenemalononitriles **2** bearing various halo substituents (F, Cl and Br) at the *para*-position and 2,4-dichloro substituents on the phenyl ring reacted smoothly with **1a** to produce the desired products **3ae**–**3ah** in good to excellent yields (88–97%). Electron-donating groups such as 4-dimethylamino (**3ai**) and 4-hydroxy (**3aj**) drastically reduced the reactivity of the arylidenemalononitriles. Fortunately, when the 4-methoxy group was present on the phenyl ring instead of a free hydroxy group (**3aj**), the reaction proceeded smoothly, resulting in 79% yield of product **3ak**. In contrast, the reactivity of the arylidenemalononitriles bearing electron-withdrawing groups (4-NO_2, 4-CN, and 4-CO_2Me) was too high, causing side reactions in these cases. An unidentified complex mixture was obtained instead of **3al**. Reacting 4-cyanobenzylidenemalononitrile for either 24 or 3 h gave **3am** in nearly the same yield (26% or 28%, respectively). A low yield of **3an** was also obtained (20%). Gratifyingly, arylidenemalononitriles bearing heteroaryl rings (2-furyl and 2-thienyl) gave products **3ao** and **3ap** in quantitative and 91% yield, respectively. Despite the low yields, the naphthyl-group-containing products **3aq** and **3ar** were also isolated. Although cyclohexylmethylenemalononitrile was explored, product **3as** was obtained only in trace amounts. In addition, isatylidenemalononitrile was examined producing a 40% yield of the corresponding product **3at**.



Scheme 2 Scope of arylidenemalononitriles. *Reagents and conditions*: **1** (0.4 mmol), **2a** (0.48 mmol), DMSO (1 mL), MS 13X (200 mg), r.t., 24 h; products **3** purified by recrystallization and TLC. [a] N.R. = no reaction. [b] N.D. = not determined.

In conclusion, we have developed an efficient and environmentally friendly cascade Michael–cyclization reaction of cyclic enaminones with arylidenemalononitriles by using a combination of MS 13X and DMSO. In contrast to the conventional methods, this reaction was carried out successfully for the first time without using a transition-metal catalyst, an organobase, or heating conditions. Moreover, this protocol resulted in high yields (up to 100%) of various bioactive *N*-aryl-4-arylhexahydroquinoline derivatives. Further studies on the development of other useful and novel reactions in DMSO are currently being assessed in our laboratory.

^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, on a Bruker spectrometer. Chemical shifts δ in ppm were determined relative to TMS as an internal standard. IR spectra were recorded on an IR spectrometer by using KBr disc plates. Melting points were measured by using a Mel-Temp® apparatus. DMSO and other solvents were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. Molecular sieves (MS) were powdered in a mortar and dried by using a heat gun prior to use. TLC was performed on Wakogel® B-5F. Commercially available materials and solvents were used without further purification. If not noted otherwise, all reactions were carried out under open air condition. Enaminones **1** and arylidenemalononitriles **2** were synthesized according to literature procedures.[10,11]

2-Amino-7,7-dimethyl-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3aa);[6d] Typical Procedure

Enaminone **1a** (86.1 mg, 0.4 mmol), benzylidenemalononitrile **2a** (74.0 mg, 0.48 mmol), DMSO (1 mL), and MS 13X (200 mg) were loaded into a 30 mL two-necked flask at r.t. The reaction mixture was stirred for 24 h at r.t., and then quenched with phosphate buffer. After extraction with EtOAc and washing with brine, the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallized from hexane/EtOAc and filtered to give most of product **3aa**. The filtrate was concentrated and purified by TLC (silica gel, hexane–EtOAc, 3:1); this afforded the remaining **3aa**.

Yield: 136 mg (92%); white solid; mp 238–239 °C.

IR (KBr): 3461, 3333, 3220, 2957, 2179, 1655, 1620, 1571, 1490, 1415, 1373, 1258, 1176, 1145, 1041, 738, 697, 575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.96 (s, 3 H), 1.79–1.82 (d, *J* = 17.45 Hz, 1 H), 2.03–2.06 (d, *J* = 17.45 Hz, 1 H), 2.13–2.22 (dd, *J* = 16.35, 14.22 Hz, 2 H), 4.01 (s, 2 H, NH_2), 4.76 (s, 1 H), 7.18–7.59 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.02, 29.46, 32.40, 36.00, 41.71, 49.99, 63.68, 113.26, 120.84, 126.67, 127.13, 128.57, 129.78, 130.33, 130.62, 136.32, 145.56, 149.13, 150.09, 195.57.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ba)

Yield: 138 mg (90%); yellow solid; mp 192–194 °C.

IR (KBr): 3564, 3462, 3336, 2956, 2925, 2179, 1653, 1570, 1509, 1452, 1414, 1373, 1257, 1177, 1144, 1043, 1017, 755, 699, 591, 560, 533 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.96 (s, 3 H), 1.81–1.84 (d, *J* = 17.55 Hz, 1 H), 2.04–2.14 (d, *J* = 17.55 Hz, 1 H), 2.12–2.21 (dd, *J* = 16.3, 14.5 Hz, 2 H), 2.47 (s, 3 H), 4.01 (s, 2 H, NH_2), 4.75 (s, 1 H), 7.16–7.20 (m, 3 H), 7.29–7.37 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.30, 27.02, 29.46, 32.37, 35.98, 41.66, 49.98, 63.48, 113.14, 120.93, 126.63, 127.12, 128.54, 129.40, 133.49, 140.65, 145.64, 149.39, 150.24, 195.57.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{25}N_3NaO$: 406.1890; found: 406.1881.

2-Amino-1-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ca)

Yield: 137 mg (86%); orange solid; mp 196–198 °C.

IR (KBr): 3455, 3418, 3322, 3214, 2957, 2934, 2181, 1732, 1648, 1564, 1509, 1454, 1441, 1417, 1374, 1297, 1252, 1170, 1144, 1040, 1026, 762, 701, 565, 548 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.96 (s, 3 H), 1.82–1.85 (d, *J* = 17.45 Hz, 1 H), 2.03–2.06 (d, *J* = 17.45 Hz, 1 H), 2.11–2.21 (dd, *J* = 16.3, 15.2 Hz, 2 H), 3.89 (s, 3 H), 4.07 (s, 2 H, NH_2), 4.74 (s, 1 H), 7.04–7.05 (m, 2 H), 7.16–7.20 (m, 3 H), 7.28–7.35 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.21, 21.07, 27.03, 29.51, 32.34, 35.98, 41.69, 49.97, 55.70, 60.41, 113.15, 126.62, 127.12, 128.39, 128.54, 130.78, 145.68, 149.73, 150.52, 160.56, 195.61.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{25}N_3NaO_2$: 422.1839; found: 422.1860.

2-Amino-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3da)[12]

Yield: 162 mg (100%); white solid; mp 249–250 °C.

IR (KBr): 3463, 3335, 2956, 2180, 1655, 1620, 1591, 1572, 1488, 1413, 1373, 1257, 1145, 1090, 1042, 1013, 757, 700, 581 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 0.98 (s, 3 H), 1.79–1.82 (d, *J* = 17.40 Hz, 1 H), 2.03–2.06 (d, *J* = 17.40 Hz, 1 H), 2.13–2.22 (dd, *J* = 16.3, 11.9 Hz, 2 H), 3.97 (s, 2 H, NH_2), 4.75 (s, 1 H), 7.18–7.57 (m, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.03, 29.47, 32.44, 35.96, 41.76, 49.92, 64.28, 113.56, 120.54, 126.76, 127.08, 128.61, 130.88, 131.12, 134.79, 136.56, 145.29, 148.64, 149.74, 195.47.

2-Amino-1-(4-bromophenyl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ea)

Yield: 178 mg (99%); white solid; mp 240–242 °C.

IR (KBr): 3463, 3333, 3221, 2955, 2180, 1655, 1644, 1621, 1571, 1486, 1413, 1373, 1255, 1145, 1069, 1041, 1011, 755, 700, 576 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 0.97 (s, 3 H), 1.79–1.82 (d, *J* = 17.50 Hz, 1 H), 2.02–2.05 (d, *J* = 17.50 Hz, 1 H), 2.13–2.22 (dd, *J* = 16.5, 10.5 Hz, 2 H), 3.97 (s, 2 H, NH_2), 4.74 (s, 1 H), 7.17–7.21 (m, 3 H), 7.29–7.34 (m, 4 H), 7.71–7.73 (d, *J* = 8.50 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.03, 29.47, 32.45, 35.96, 41.76, 49.92, 64.31, 113.55, 120.52, 124.62, 126.76, 127.08, 128.61, 131.41, 133.89, 135.33, 145.27, 148.57, 149.66, 195.46.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}BrN_3NaO$: 470.0838; found: 470.0837.

2-Amino-7,7-dimethyl-1-(1-naphthyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ga)[13]

Yield: 151 mg (90%); white solid; mp 264–266 °C.

IR (KBr): 3463, 3370, 2951, 2927, 2881, 2184, 1650, 1640, 1604, 1572, 1454, 1402, 1394, 1372, 1345, 1335, 1311, 1259, 1239, 1147, 1040, 809, 778, 756, 707, 699, 573 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (mixture of rotamers) = 0.74 (0.87) (s, 2.5 H), 0.79 (0.83) (s, 3.5 H), 1.74–1.78 (1.91–1.95) (d, *J* = 17.30 Hz, 1 H), 2.11–2.16 (2.17–2.24) (m, 2 H), 3.93 (4.06) (s, 2 H, NH_2), 4.85 (4.93) (s, 1 H), 7.19–8.07 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (mixture of rotamers) = 27.57 (26.37), 28.46 (29.71), 32.51 (32.04), 36.21 (35.91), 40.25 (41.31), 50.14 (50.01), 63.73 (63.09), 113.26 (113.07), 120.97 (120.88), 121.78 (121.65), 125.35, 126.71 (126.00), 127.25 (127.35), 127.73 (127.76), 128.04 (128.37), 128.58 (128.61), 128.61 (128.65), 129.13, 130.09 (130.97), 131.34 (131.44), 132.65 (132.15), 134.50 (134.67), 145.69 (145.42), 149.87 (149.92), 150.47 (150.27), 195.64 (195.79).

2-Amino-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ha)[6a]

Yield: 105 mg (77%); pale yellow solid; mp 149–151 °C.

IR (KBr): 3564, 3472, 3425, 3318, 3216, 2948, 2179, 1735, 1650, 1621, 1589, 1566, 1489, 1453, 1409, 1372, 1337, 1264, 1192, 1074, 1045, 1002, 746, 702, 637, 547 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.73–2.04 (m, 3 H), 2.14–2.40 (m, 3 H), 4.00 (s, 2 H, NH_2), 4.82 (s, 1 H), 7.15–7.22 (m, 1 H), 7.30–7.37 (m, 6 H), 7.54–7.59 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 20.98, 28.28, 35.66, 36.51, 60.41, 63.48, 114.22, 126.68, 127.10, 128.60, 129.77, 130.32, 136.30, 145.63, 150.10, 151.01, 195.73.

2-Amino-7,7-dimethyl-5-oxo-1-phenyl-4-(2-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ab)[14]

Yield: 112 mg (83%); white solid; mp 266–267 °C.

IR (KBr): 3472, 3342, 2957, 2177, 1652, 1620, 1592, 1570, 1488, 1412, 1372, 1258, 1144, 1047, 744, 706, 575 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (s, 3 H), 0.96 (s, 3 H), 1.83–1.87 (dd, *J* = 17.40 Hz, 0.8 Hz, 1 H), 2.04–2.19 (m, 3 H), 2.66 (s, 3 H), 3.92 (s, 2 H, NH_2), 4.99 (s, 1 H), 7.04–7.22 (m, 4 H), 7.34–7.35 (m, 2 H), 7.58–7.61 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.70, 27.12, 29.46, 31.87, 32.47, 41.72, 49.87, 64.36, 113.87, 120.91, 126.27, 126.45, 127.29, 129.86, 130.32, 130.50, 135.38, 136.34, 144.81, 149.31, 149.50, 195.62.

2-Amino-7,7-dimethyl-5-oxo-1-phenyl-4-(3-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ac)[14]

Yield: 141 mg (92%); pale yellow solid; mp 233–235 °C.

IR (KBr): 3461, 3328, 3218, 2970, 2957, 2903, 2868, 2177, 1647, 1620, 1594, 1568, 1490, 1449, 1416, 1372, 1315, 1296, 1260, 1235, 1178, 1167, 1144, 1124, 1070, 1024, 805, 765, 752, 697, 583, 572 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 0.96 (s, 3 H), 1.79–1.83 (d, *J* = 17.40 Hz, 1 H), 2.03–2.06 (d, *J* = 17.40 Hz, 1 H), 2.13–2.22 (dd, *J* = 16.30, 4.9 Hz, 2 H), 2.34 (s, 3 H), 4.02 (s, 2 H, NH_2), 4.70 (s, 1 H), 6.99–7.00 (d, *J* = 7.40 Hz, 1 H), 7.11–7.21 (m, 3 H), 7.29–7.30 (m, 2 H), 7.57–7.59 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.64, 27.04, 29.44, 32.41, 35.90, 41.69, 49.97, 63.83, 113.25, 120.90, 123.94, 127.47, 128.02, 128.46, 129.76, 130.29, 130.59, 136.35, 137.94, 145.50, 149.16, 150.00, 195.59.

2-Amino-7,7-dimethyl-5-oxo-1-phenyl-4-(4-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ad)[6a]

Yield: 140 mg (91%); white solid; mp 241–242 °C.

IR (KBr): 3458, 3333, 2952, 2178, 1653, 1619, 1593, 1571, 1491, 1412, 1384, 1371, 1257, 1179, 1169, 1144, 1124, 1039, 1017, 699, 575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 0.95 (s, 3 H), 1.78–1.82 (d, *J* = 17.40 Hz, 1 H), 2.02–2.05 (d, *J* = 17.40 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.30, 7.95 Hz, 2 H), 2.30 (s, 3 H), 3.98 (s, 2 H, NH_2), 4.72 (s, 1 H), 7.11–7.12 (d, *J* = 7.75 Hz, 2 H), 7.23–7.31 (m, 4 H), 7.57–7.61 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.11, 27.11, 29.43, 32.42, 35.61, 41.70, 50.01, 63.97, 113.35, 120.86, 126.98, 129.30, 129.79, 130.29, 130.60, 136.12, 136.39, 142.69, 149.00, 149.91, 195.59.

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ae)[6d]

Yield: 138 mg (89%); yellow solid; mp 254–255 °C.

IR (KBr): 3453, 3336, 2957, 2178, 1652, 1640, 1593, 1557, 1504, 1490, 1416, 1372, 1257, 1216, 1203, 1173, 1153, 1042, 850, 702, 574, 528 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.95 (s, 3 H), 1.78–1.81 (d, *J* = 17.30 Hz, 1 H), 2.02–2.05 (d, *J* = 17.30 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.35, 8.90 Hz, 2 H), 4.02 (s, 2 H, NH_2), 4.75 (s, 1 H), 6.98–7.01 (m, 2 H), 7.28–7.34 (m, 4 H), 7.59–7.60 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.92, 29.43, 32.38, 35.44, 41.69, 49.94, 63.45, 113.19, 115.22, 115.39, 120.70, 128.66, 128.72, 129.72, 130.41, 136.16, 141.45, 149.07, 150.09, 195.58.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3af)[6d]

Yield: 142 mg (88%); white solid; mp 261–262 °C.

IR (KBr): 3731, 3708, 3646, 3605, 3593, 3584, 3542, 3465, 3330, 2952, 2352, 2178, 1694, 1681, 1651, 1620, 1594, 1567, 1557, 1488, 1454, 1415, 1385, 1258, 1171, 1144, 1125, 1087, 1041, 1011, 858, 842, 698, 574, 517 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.95 (s, 3 H), 1.77–1.81 (d, *J* = 17.50 Hz, 1 H), 2.02–2.05 (d, *J* = 17.50 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.35, 8.90 Hz, 2 H), 4.06 (s, 2 H, NH_2), 4.74 (s, 1 H), 7.27–7.31 (m, 6 H), 7.58–7.62 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.95, 29.44, 32.40, 35.64, 41.70, 49.93, 63.08, 112.93, 120.64, 128.60, 128.70, 129.72, 130.45, 130.71, 132.33, 136.11, 144.13, 149.26, 150.21, 195.55.

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ag)[6a]

Yield: 174 mg (97%); yellow solid; mp 263–264 °C.

IR (KBr): 3646, 3626, 3606, 3593, 3584, 3564, 3542, 3463, 3330, 3217, 2953, 2352, 2177, 1681, 1651, 1621, 1593, 1567, 1557, 1487, 1415, 1385, 1371, 1258, 1144, 1068, 1039, 1007, 839, 696, 574, 515 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.95 (s, 3 H), 1.77–1.81 (d, *J* = 17.35 Hz, 1 H), 2.02–2.05 (d, *J* = 17.35 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.35, 8.90 Hz, 2 H), 4.05 (s, 2 H, NH_2), 4.73 (s, 1 H), 7.23–7.29 (m, 4 H), 7.43–7.44 (m, 2 H), 7.59–7.60 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.94, 29.42, 32.38, 35.70, 41.69, 49.90, 62.86, 112.81, 120.48, 120.66, 128.97, 129.69, 130.45, 130.70, 131.62, 136.05, 144.64, 149.33, 150.26, 195.57.

2-Amino-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ah)[15]

Yield: 168 mg (96%); light orange solid; mp 254–256 °C.

IR (KBr): 3585, 3564, 3459, 3345, 2959, 2182, 1644, 1591, 1562, 1490, 1468, 1417, 1370, 1256, 1153, 1098, 1071, 1047, 1023, 1001, 858, 732, 703, 574 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 0.95 (s, 3 H), 1.77–1.81 (d, *J* = 17.65 Hz, 1 H), 2.02–2.05 (d, *J* = 17.65 Hz, 1 H), 2.08–2.19 (dd, *J* = 16.35, 18.25 Hz, 2 H), 4.01 (s, 2 H, NH_2), 5.13 (s, 1 H), 7.20–7.22 (dd, *J* = 8.30, 2.15 Hz, 1 H), 7.30–7.36 (m, 4 H), 7.59–7.60 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.16, 29.36, 32.32, 35.49, 41.76, 49.75, 61.71, 110.97, 120.41, 127.24, 130.03, 130.49, 130.63, 131.69, 132.92, 133.79, 135.93, 140.73, 150.41, 195.48.

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3aj)[6d]

Yield: 22.0 mg (14%); yellow solid; mp 262–263 °C.

IR (KBr): 3626, 3585, 3564, 3543, 3470, 3332, 2961, 2178, 1651, 1633, 1613, 1591, 1565, 1557, 1510, 1489, 1454, 1415, 1376, 1257, 1228, 1168, 1147, 1041, 852, 703, 576 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.74 (s, 3 H), 0.88 (s, 3 H), 1.67–1.70 (d, *J* = 17.45 Hz, 1 H), 1.99–2.02 (d, *J* = 17.45 Hz, 1 H), 2.17–2.21 (dd, *J* = 19.50, 3.70 Hz, 2 H), 4.37 (s, 1 H), 5.24 (s, 2 H, NH_2), 6.70–6.72 (d, *J* = 8.40 Hz, 2 H), 7.07–7.08 (d, *J* = 6.85 Hz, 2 H), 7.38–7.39 (d, *J* = 6.85 Hz, 2 H), 7.57–7.61 (m, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.71, 29.57, 32.32, 35.84, 41.42, 49.86, 61.44, 112.74, 115.52, 122.12, 128.23, 130.16, 130.41, 130.65, 136.84, 137.54, 150.13, 151.42, 156.25, 195.33.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ak)[6d]

Yield: 126 mg (79%); pale yellow solid; mp 243–244 °C.

IR (KBr): 3457, 3331, 2955, 2937, 2176, 1646, 1592, 1564, 1508, 1490, 1452, 1412, 1373, 1301, 1256, 1239, 1177, 1143, 1030, 850, 841, 705, 573 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H), 0.95 (s, 3 H), 1.78–1.81 (d, *J* = 17.45 Hz, 1 H), 2.01–2.05 (d, *J* = 17.45 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.35, 13.70 Hz, 2 H), 3.78 (s, 3 H), 3.98 (s, 2 H, NH_2), 4.71 (s, 1 H), 6.84–6.86 (d, *J* = 8.55 Hz, 2 H), 7.27–7.31 (m, 4 H), 7.58–7.59 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.01, 29.45, 32.40, 35.23, 41.69, 50.01, 63.91, 113.48, 113.94, 120.93, 128.17, 129.78, 130.30, 130.60, 136.36, 138.06, 148.85, 149.94, 158.28, 195.68.

2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3am)

Yield: 41.0 mg (26%); brown solid; mp 263–264 °C.

IR (KBr): 3626, 3606, 3593, 3584, 3564, 3469, 3340, 2958, 2224, 2196, 2177, 1650, 1615, 1594, 1565, 1492, 1463, 1416, 1373, 1258, 1143, 1042, 866, 845, 704, 576 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.96 (s, 3 H), 1.80–1.83 (d, *J* = 17.45 Hz, 1 H), 2.04–2.07 (d, *J* = 17.45 Hz, 1 H), 2.12–2.23 (dd, *J* = 16.35, 8.90 Hz, 2 H), 4.09 (s, 2 H, NH_2), 4.82 (s, 1 H), 7.29–7.31 (m, 2 H), 7.46–7.48 (d, *J* = 8.25 Hz, 2 H), 7.61–7.63 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.96, 29.38, 32.42, 36.60, 41.74, 49.84, 62.26, 110.50, 112.20, 119.06, 120.32, 128.08, 129.66, 130.64, 132.55, 135.83, 149.78, 150.42, 150.75, 195.45.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{22}N_4NaO$: 417.1686; found: 417.1696.

2-Amino-4-[4-(methoxycarbonyl)phenyl]-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3an)

Yield: 34.2 mg (20%); white solid; mp 254–255 °C.

IR (KBr): 3469, 3329, 2956, 2182, 1721, 1656, 1621, 1609, 1592, 1570, 1488, 1434, 1415, 1373, 1307, 1284, 1258, 1147, 1109, 1044, 1019, 753, 702, 575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (s, 3 H), 0.96 (s, 3 H), 1.79–1.82 (d, *J* = 17.60 Hz, 1 H), 2.04–2.07 (d, *J* = 17.60 Hz, 1 H), 2.12–2.22 (dd, *J* = 16.30, 18.45 Hz, 2 H), 3.89 (s, 3 H), 4.06 (s, 2 H, NH_2), 4.82 (s, 1 H), 7.30–7.31 (m, 2 H), 7.43–7.44 (d, *J* = 8.20 Hz, 2 H), 7.60–7.61 (m, 3 H), 7.99–8.01 (d, *J* = 8.15 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.85, 29.47, 32.38, 36.18, 41.71, 49.89, 52.00, 112.70, 120.53, 127.20, 128.53, 129.71, 130.06, 130.48, 130.70, 136.05, 149.51, 150.33, 150.58, 167.07, 195.48.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}N_3NaO_3$: 450.1788; found: 450.1802.

2-Amino-4-(2-furyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ao)

Yield: 144 mg (100%); gray solid; mp 222–223 °C.

IR (KBr): 3408, 3327, 3211, 2956, 2176, 1650, 1617, 1593, 1571, 1492, 1409, 1382, 1370, 1276, 1259, 1145, 1036, 1013, 782, 725, 712, 693, 571 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.96 (s, 3 H), 1.76–1.80 (d, *J* = 17.55 Hz, 1 H), 2.03–2.07 (d, *J* = 17.55 Hz, 1 H), 2.18–2.25 (dd, *J* = 16.35, 2.40 Hz, 2 H), 4.08 (s, 2 H, NH_2), 4.89 (s, 1 H), 6.16 (d, *J* = 3.10 Hz, 1 H), 6.28–6.29 (dd, *J* = 3.10, 1.90 Hz, 1 H), 7.30–7.31 (m, 3 H), 7.56–7.58 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.63, 29.52, 29.60, 32.39, 41.62, 49.95, 60.56, 104.96, 110.44, 110.69, 120.68, 129.80, 130.30, 130.59, 136.40, 141.41, 150.15, 151.18, 156.66, 195.41.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{21}N_3NaO_2$: 382.1526; found: 382.1548.

2-Amino-7,7-dimethyl-5-oxo-1-phenyl-4-(2-thienyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ap)

Yield: 137 mg (91%); brown solid; mp 213–214 °C.

IR (KBr): 3457, 3361, 2947, 2867, 2182, 1648, 1628, 1607, 1593, 1564, 1492, 1402, 1378, 1359, 1315, 1287, 1258, 1240, 1142, 1038, 1023, 698, 666, 575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.96 (s, 3 H), 1.74–1.78 (d, *J* = 17.40 Hz, 1 H), 2.04–2.07 (d, *J* = 17.40 Hz, 1 H), 2.18–2.26 (dd, *J* = 16.50, 4.40 Hz, 2 H), 4.07 (s, 2 H, NH_2), 5.11 (s, 1 H), 6.91–6.93 (dd, *J* = 3.50, 1.50 Hz, 1 H), 7.01–7.02 (d, *J* = 3.25 Hz, 1 H), 7.11–7.12 (dd, *J* = 3.50, 1.50 Hz, 1 H), 7.30–7.32 (m, 2 H), 7.57–7.58 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.80, 29.61, 30.93, 32.36, 41.53, 49.93, 63.25, 113.37, 120.64, 123.52, 123.61, 127.15, 129.82, 130.37, 136.18, 149.12, 150.51, 150.61, 195.45.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{21}N_3NaOS$: 398.1298; found: 398.1321.

2-Amino-7,7-dimethyl-4-(1-naphthyl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3aq)

Yield: 53.7 mg (32%); yellow solid; mp 247–249 °C.

IR (KBr): 3626, 3606, 3593, 3573, 3564, 3460, 3342, 2959, 2922, 2175, 1651, 1594, 1565, 1492, 1415, 1374, 1259, 1240, 1140, 1040, 794, 781, 708, 575, 550 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 0.98 (s, 3 H), 1.90–1.94 (d, *J* = 17.45 Hz, 1 H), 2.09–2.14 (dd, *J* = 12.05, 5.75 Hz, 2 H), 2.18–2.21 (d, *J* = 17.45 Hz, 1 H), 3.95 (s, 2 H, NH_2), 5.61 (s, 1 H), 7.38–7.49 (m, 5 H), 7.58–7.64 (m, 4 H), 7.71–7.73 (m, 1 H), 7.81–7.83 (d, *J* = 8.40 Hz, 1 H), 8.60–8.62 (d, *J* = 8.95 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.25, 28.43, 31.38, 40.75, 48.82, 63.59, 112.57, 119.79, 122.87, 123.99, 124.30, 124.62, 125.10, 126.47, 127.47, 128.86, 129.34, 129.61, 130.06, 132.99, 135.30, 141.78, 148.45, 148.81, 194.51.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{25}N_3NaO$: 442.1890; found: 442.1879.

2-Amino-7,7-dimethyl-4-(2-naphthyl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (3ar)

Yield: 15.1 mg (9%); orange solid; mp 172–173 °C.

IR (KBr): 3458, 3331, 3220, 2955, 2925, 2176, 1653, 1593, 1569, 1491, 1416, 1376, 1367, 1257, 1152, 1142, 1122, 1041, 704, 574 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H), 0.96 (s, 3 H), 1.81–1.85 (d, *J* = 17.95 Hz, 1 H), 2.06–2.09 (d, *J* = 17.95 Hz, 1 H), 2.13–2.23 (dd, *J* = 16.35, 21.70 Hz, 2 H), 4.05 (s, 2 H, NH_2), 4.95 (s, 1 H), 7.33–7.62 (m, 8 H), 7.78–7.84 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.93, 29.51, 32.38, 36.13, 41.75, 49.97, 63.43, 113.18, 120.83, 125.41, 125.65, 125.83, 127.53, 128.14, 128.44, 129.77, 130.37, 130.65, 132.56, 133.55, 136.30, 142.73, 149.25, 150.27, 195.62.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{25}N_3NaO$: 442.1890; found: 442.1881.

2′-Amino-1,2,5′,6′,7′,8′-hexahydro-7′,7′-dimethyl-2,5′-dioxo-1′-phenylspiro[3*H*-indole-3,4′(1′*H*)-quinoline]-3′-carbonitrile (3at)[16]

Yield: 65.7 mg (40%); yellow solid; mp 314–315 °C.

IR (KBr): 3467, 3333, 2957, 2196, 2187, 1712, 1689, 1641, 1620, 1592, 1555, 1489, 1470, 1416, 1362, 1336, 1315, 1260, 1222, 1195, 1176, 1152, 1052, 1017, 740, 723, 688, 647, 573 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.82 (s, 3 H), 0.89 (s, 3 H), 1.81–1.84 (d, *J* = 17.30 Hz, 1 H), 1.92–1.96 (d, *J* = 17.30 Hz, 1 H), 2.09–2.15 (dd, *J* = 14.40, 2.65 Hz, 2 H), 5.36 (s, 2 H, NH_2), 6.77–6.78 (d, *J* = 7.60 Hz, 1 H), 6.91–6.94 (t, *J* = 7.40 Hz, 1 H), 7.12–7.15 (t, *J* = 7.40 Hz, 1 H), 7.17–7.19 (d, *J* = 7.60 Hz, 1 H), 7.49–7.64 (m, 5 H), 10.23 (s, NH, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.09, 28.69, 32.58, 41.84, 48.98, 49.78, 61.40, 109.31, 110.86, 119.39, 121.87, 123.63, 128.15, 130.42, 130.78, 136.45, 137.13, 141.92, 151.57, 152.35, 179.94, 194.36.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705984.

References

(1) (a) Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Noaman, E.; Ghorab, M. M. *Eur. J. Med. Chem.* **2010**, *45*, 738. (b) Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Ghorab, M. M.; Noaman, E. *Eur. J. Med. Chem.* **2010**, *45*, 1849.

(2) (a) Ghorab, M. M.; Ragab, F. A.; Heiba, H. I.; Arafa, R. K.; El-Hossary, E. M. *Eur. J. Med. Chem.* **2010**, *45*, 3677. (b) Al-Said, M. S.; Ghorab, M. M.; Al-Dosari, M. S.; Hamed, M. M. *Eur. J. Med. Chem.* **2011**, *46*, 201. (c) Ghorab, M. M.; Ragab, F. A.; Heiba, H. I.; Ghorab, W. M. *J. Heterocycl. Chem.* **2011**, *48*, 1269.

(3) Chandak, N.; Bhardwaj, J. K.; Zheleva-Dimitrova, D.; Kitanov, G.; Sharma, R. K.; Sharma, P. K.; Saso, L. *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 722.

(4) Alafeefy, A. M. *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 189.

(5) Vazirimehr, S.; Davoodnia, A.; Nakhaei-Moghaddam, M.; Tavakoli-Hoseini, N. *Heterocycl. Commun.* **2017**, *23*, 65.

(6) For selected examples, see: (a) Ebrahimipour, S. Y.; Abaszadeh, M.; Castro, J.; Seifi, M. *Polyhedron* **2014**, *79*, 138. (b) Abaszadeh, M.; Seifi, M.; Asadipour, A. *Res. Chem. Intermed.* **2015**, *41*, 5229. (c) Ghozlan, S. A. S.; Ahmed, A. G.; Abdelhamid, I. A. *J. Heterocycl. Chem.* **2016**, *53*, 817. (d) Gao, S.; Tsai, C. H.; Tseng, C.; Yao, C.-F. *Tetrahedron* **2008**, *64*, 9143. (e) Wang, X.-S.; Zhang, M.-M.; Jiang, H.; Shi, D.-Q.; Tu, S.-J. *J. Chin. Chem. Soc.* **2007**, *54*, 1033. (f) Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Hamed, M. M.; Noaman, E.; Ghorab, M. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6939. (g) Abdelmoniem, A. M.; Abdelrahman, M. G. M.; Ghozlan, S. A. S.; Abdelhamid, I. A. *J. Heterocycl. Chem.* **2019**, *56*, 3387.

(7) For selected examples, see: (a) Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667. (b) Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861. (c) Chen, F.; Jiang, X.-J.; Er, J.-C.; Yeung, Y.-Y. *Tetrahedron Lett.* **2010**, *51*, 3433. (d) Zhong, F.-R.; Jiang, C.-H.; Yao, W.-J.; Xu, L.-W.; Lu, Y.-X. *Tetrahedron Lett.* **2013**, *54*, 4333. (e) Guo, Y.-L.; Li, Y.-H.; Chang, H.-H.; Kuo, T.-S.; Han, J.-L. *RSC Adv.* **2016**, *6*, 74683. (f) Liu, Y.-T.; Cheng, C.-W.; Lu, H.-C.; Chang, T.-Y.; Chen, C.-Y.; Yang, H.-C.; Yu, S.-H.; Zehra, S.; Liu, S.-H.; Leung, M.-K.; Lee, K.-M.; Chen, H.-H. *J. Org. Chem.* **2020**, *85*, 13655.

(8) For catalyst-free reactions in DMSO reported by our group, see: (a) Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679. (b) Iwanami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett.* **2005**, *46*, 5881. (c) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112. (d) Oriyama, T.; Aoyagi, M.; Iwanami, K. *Chem. Lett.* **2007**, *36*, 612. (e) Kakinuma, T.; Chiba, R.; Oriyama, T. *Chem. Lett.* **2008**, *37*, 1204. (f) Chiba, R.; Oriyama, T. *Chem. Lett.* **2008**, *37*, 1218. (g) Kakinuma, T.; Oriyama, T. *Tetrahedron Lett.* **2010**, *51*, 290. (h) Buniuchi, K.; Oriyama, T. *J. Synth. Org. Chem., Jpn.* **2012**, *70*, 1041. (i) Isobe, T.; Kato, A.; Oriyama, T. *Chem. Lett.* **2015**, *44*, 483. (j) Isobe, T.; Oriyama, T. *Tetrahedron Lett.* **2016**, *57*, 2849.

(9) When reactions were carried out on ≥0.3 mmol scale, products **3** were purified by recrystallization and TLC, due to their high crystallinity.

(10) Bhattacherjee, D.; Thakur, V.; Sharma, S.; Kumar, S.; Bharti, R.; Reddy, C. B.; Das, P. *Adv. Synth. Catal.* **2017**, *359*, 2209.

(11) Bertuzzi, G.; Thøgersen, M. K.; Giardinetti, M.; Vidal-Albalat, A.; Simon, A.; Houk, K. N.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2019**, *141*, 3288.

(12) El-Helby, A. A.; Amin, M. A.; El-Sawah, M. M.; Bayoni, A. H.; El-Azab, A. S.; Sherbiny, F. F. *J. Saudi Chem. Soc.* **2006**, *10*, 77.

(13) Assy, M. G.; Fikry, R. M.; Aouf, N. H. *J. Indian Chem. Soc.* **1997**, *74*, 152.

(14) Adeleh, M. Z.; Mina, R. O. *J. Chin. Chem. Soc.* **2013**, *60*, 275.

(15) Tu, S.-J.; Jiang, B.; Jia, R.-H.; Zhang, J.-Y.; Zhang, Y.; Yao, C.-S.; Shi, F. *Org. Biomol. Chem.* **2006**, *4*, 3664.

(16) So, R. K.; Yong, R. L. *Synthesis* **2013**, *45*, 2593.