Iodine-Promoted Domino Reaction Leading to *N*-Substituted 2-Aminoquinoline-3-carbonitriles under Microwave Irradiation

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A new iodine-promoted domino reaction of 2-aminochromene-3-carbonitriles with various isocyanates is described, and a set of polyfunctionalized *N*-substituted 2-aminoquinoline-3-carbonitriles with high regioselectivity were successfully synthesized under microwave heating. In this reaction, the ring-opening/recyclization process occurs unexpectedly at the ring of 4*H*-pyran with different isocyanates.

Introduction

Creation of molecular complexity and diversity from simple substrates, with simultaneous consideration of the economic and environmental aspects, constitutes a great challenge in modern organic chemistry, both from academic and industrial points of view. In this context domino reactions have proven to be very effective and attractive.[1] The notable feature of a domino process is that bonds and new functionalities are constructed during the cascade, which, in turn, react further in subsequent steps under identical conditions to form new bonds and functionalities until termination leads to a stable final product. Clearly, the quality of a domino reaction is dependent on the number of bonds formed and the complexity of the product. These reactions can avoid time-consuming and costly processes, including the protection and deprotection of functional groups and the separation and purification of intermediates. They are also environmentally friendly and often proceed with excellent selectivity. As a result, they are very useful in the drug discovery process and serve as powerful tools in the total synthesis of complex natural products.[2]

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, and a readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields.[3] Iodine has a high tolerance to air as well as moisture and can be easily removed from reaction systems. Moreover, the mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to the advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful reagent in organic synthesis.[4]

It is well-known that six-membered nitrogen-containing heterocycles are abundant in numerous natural products that exhibit important biological properties. Quinoline derivatives are important heterocyclic compounds that constitute core structures of many naturally occurring substances that have interesting biological and pharmaceutical properties.[5] In this family, aminoquinoline derivatives are especially important because of these pharmaceutical activities including antimalarial,[6] anti-HIV,[7] anti-Alzheimer disease,[8] melanin-concentrating hormone 1 receptor (MCHR) antagonist,[9] and Src kinase inhibitor.[10] Consequently, the development of new and efficient methods for the synthesis of these molecules has continued to be an important goal. Srinivasan et al. reported the synthesis of 2-aminoquinoline-3-carbonitrile from the reaction of arylidenemalononitriles with enaminone, and also their antifungal properties were evaluated.[11] However, the *N*-substituted 2-aminoquinoline-3-carbonitriles can not be obtained through this method. Therefore, the design of new and simple routes for the preparation of new 2-aminoquinolines, particularly those that are highly functionalized, remains a significant challenge.

As a part of our continued interest in the development of domino reactions for the construction of important heterocyclic skeletons,[12] we now report a new domino reaction between 2-aminochromene-3-carbonitriles with isocyanates. This reaction is very unique because the ring-opening/recyclization process occurs unexpectedly at the 4*H*-pyran ring, and new *N*-substituted 2-aminoquinoline-3-carbonitrile derivatives, which are normally difficult to prepare, are obtained in a very convenient manner. In addition, the starting materials can be easily changed to obtain diverse polyfunctional *N*-substituted 2-aminoquinoline-3-carbonitrile, which can be used as versatile building blocks in organic synthesis.

Results and Discussion

We previously reported that,[13] during the reactions of arylidenemalononitrile and dimedone with aromatic amines under microwave heating in *N*,*N*-dimethylformamide (DMF), the desired *N*-aryl 2-aminoquinoline-3-carbonitrile can not be obtained. Instead, the chromene-3-carbonitrile was gener-

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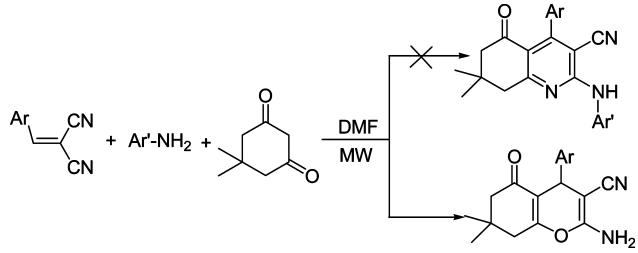
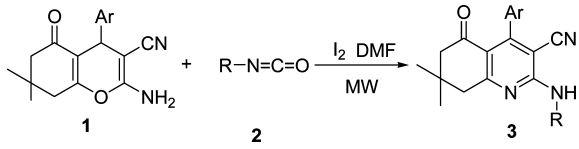
Scheme 1. Synthesis of Chromene-3-carbonitriles



Scheme 2. Synthesis of *N*-substituted 2-Aminoquinoline-3-carbonitrile



ated in high yields (Scheme 1). The reason is that dimedone has high reactivity, in which the enolization of carbonyl group is converted to hydroxyl group, becoming a nucleophilic center. Therefore, there is a demand to develop a new method for the preparation of *N*-aryl 2-aminoquinoline-3-carbonitriles. In a further study, we are pleased to find that treatment of 2-aminochromene-3-carbonitriles **1** with isocyanates **2** can lead to *N*-substituted 2-aminoquinoline-3-carbonitrile **3** with good to excellent yield (Scheme 2). This interesting result is of value to us not only because the new domino reactions are developed to prepare new *N*-substituted 2-aminoquinoline-3-carbonitrile derivatives but also because we were unable to find such convenient synthesis in the literature.

2-Aminochromene-3-carbonitrile **1** possessing both electrophilic and nucleophilic centers are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of the amine group and the electrophilicity of the cyano-group.[14] They are frequently applied in the preparation of heterocycles.[15] Our strategy of synthesizing the *N*-substituted 2-aminoquinoline-3-carbonitrile derivatives was through the reaction of a preformed 2-aminochromene-3-carbonitrile **1** with isocyanates **2** in the presence of iodine under microwave heating using DMF as a solvent. Initially, the reaction of 2-aminochromene-3-carbonitrile **1a** with phenyl isocyanate **2a** in the presence of iodine was carried out under microwave heating. All of the analytical data showed that the synthesized product was a new *N*-aryl 2-aminoquinoline-3-carbonitrile derivative **3a** with high regioselectivity (Scheme 2).

Encouraged by the above interesting results, we devoted our efforts to the study of the reaction of **1a** with **2a** as a model reaction in the presence of iodine to optimize the reaction conditions. Experiments were carried out in various solvents such as toluene, CH_2Cl_2, EtOH, and water. Unfortunately, the reaction does not proceed in water or EtOH as isocyanate **2a** was converted to 1,3-diphenylurea (Table 1, entries 1−2); an incomplete reaction was observed in toluene, or CH_2Cl_2 (Table 1, entries 3−4). In another case, when DMF was used as the solvent, the reaction proceeded better, and product **3a** was obtained in 78% isolated yield by flash chromatography (Table 1, entry 5). Subsequently, further

Table 1. Optimization of Reaction Solvents and Temperature

entry	solvent	*T*/°C	I_2/equiv	time/min	yield/%
1	EtOH	100	1.0	25	0
2	water	100	1.0	25	0
3	toluene	100	1.0	25	41
4	CH_2Cl_2	100	1.0	25	34
5	DMF	100	1.0	25	78
6	DMF	100	0.5	25	42
7	DMF	100	1.5	25	79
8	DMF	120	1.0	25	80
9	DMF	150	1.0	20	85

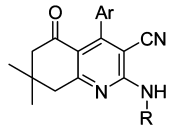
optimization of the reaction conditions, including reaction temperature and the influence of iodine concentration, was investigated. Impressively, after a series of experiments, the yield of product **3a** reached 85% without byproduct formation when the reaction was carried out in DMF at 150 °C for 20 min using 1.0 equiv of iodine as an additive (Table 1, entry 9). Without iodine, the reaction did not proceed to the desired product **3a**. Similarly, when the reaction was carried out in acidic media without iodine such as HOAc or formic acid, 1,3-diphenylurea was obtained as a byproduct instead of the desired compound **3a**.

We therefore use 1.0 equiv of iodine as an additive for further investigation. At the beginning to explore the substrates **1** scope, phenyl isocyanate **2a** was used as a model substrate (Table 2, entries 1−6), and the results indicated that the substrate **1** bearing either electron donating or electron withdrawing functional group such as halogen, or methoxy were able to synthesize compounds **3**. To expand the scope of isocyanates, different 2-aminochromene-3-carbonitriles were employed as substrate and various isocyanates were examined including 4-chlorophenyl isocyanate (**2b**), 4-bromophenyl (**2c**), cyclohexyl (**2d**), and 4-methoxyphenyl (**2e**). In some cases (**2b**−**2d**), the reactions proceeded smoothly to give the corresponding *N*-aryl 2-aminoquinoline-3-carbonitriles in good yields (62−84%). Unfortunately, instead of the desired product **3**, isocyanate **2e** only gave 1,3-di(4-methoxyphenyl)urea with high yield. This result may be attributed to the electronic effect of substitution on aryl isocyanate. It is worth noting that to the best of our knowledge, there is no literature precedent for the synthesis of *N*-aryl 2-aminoquinoline-3-carbonitriles. Furthermore, the reaction is not only suitable for aryl isocyanates (Table 2, entries 1−16) but also can be used with alicyclic isocyanates such as cyclohexyl isocyanate (Table 2, entries 17−19). When acyclic and heteroaryl substituted 2-aminochromenes **1** were used as substrates, we have not achieved good results yet since very complex mixtures were generated.

In general, the reaction is very fast and can be finished within 20−36 min with CO_2 as the major byproduct, which makes workup convenient. Complete regioselectivity and good to excellent yields were obtained for all cases that were examined. The structures of all the synthesized compounds were established on the basis of their spectroscopic data.

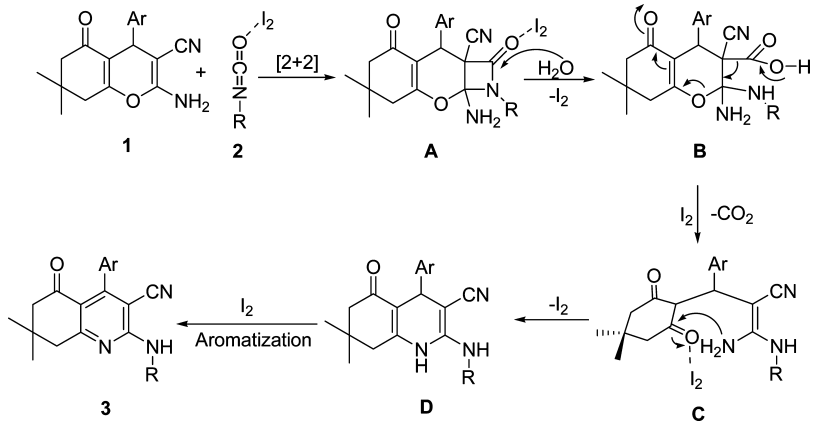
Although the exact mechanism of this transformation is not clear right now, a possible reaction mechanism is proposed (Scheme 3) based on the above results and the known literature. It was reported that the reaction of isocyanate with alkenes underwent [2 + 2] cyclization to

Table 2. Domino Autocatalytic Synthesis of Products **3**[a]

Entry	Product	Ar =		R =	Time / min	Yield[b]/%
1	 **3a-3s**	**3a**	4-Chlorophenyl (**1a**)	Phenyl (**2a**)	20	85
2		**3b**	4-Bromophenyl (**1b**)	Phenyl (**2a**)	20	81
3		**3c**	4-Fluorophenyl (**1c**)	Phenyl (**2a**)	20	74
4		**3d**	Phenyl (**1d**)	Phenyl (**2a**)	26	71
5		**3e**	4-Tolyl (**1e**)	Phenyl (**2a**)	28	72
6		**3f**	4-Methoxyphenyl (**1f**)	Phenyl (**2a**)	30	70
7		**3g**	4-Chlorophenyl (**1a**)	4-Chlorophenyl (**2b**)	22	84
8		**3h**	4-Bromophenyl (**1b**)	4-Chlorophenyl (**2b**)	20	83
9		**3i**	4-Fluorophenyl (**1c**)	4-Chlorophenyl (**2b**)	26	76
10		**3j**	4-Tolyl (**1e**)	4-Chlorophenyl (**2b**)	30	78
11		**3k**	4-Methoxyphenyl (**1f**)	4-Chlorophenyl (**2b**)	28	74
12		**3l**	3,4-Dimethoxyphenyl (**1g**)	4-Chlorophenyl (**2b**)	30	69
13		**3m**	4-Chlorophenyl (**1a**)	4-Bromophenyl (**2c**)	26	81
14		**3n**	4-Bromophenyl (**1b**)	4-Bromophenyl (**2c**)	26	79
15		**3o**	4-Fluorophenyl (**1c**)	4-Bromophenyl (**2c**)	28	72
16		**3p**	4-Tolyl (**1e**)	4-Bromophenyl (**2c**)	30	71
17		**3q**	4-Chlorophenyl (**1a**)	Cyclohexyl (**2d**)	35	78
18		**3r**	4-Bromophenyl (**1b**)	Cyclohexyl (**2d**)	32	71
19		**3s**	4-Methoxyphenyl (**1f**)	Cyclohexyl (**2d**)	36	62

[a] Reagents and conditions: I_2 (1.0 equiv), 150 °C, DMF, microwave heating. [b] Isolated yield.

Scheme 3. Proposed Reaction Mechanism of Formation Product **3**



generate β-lactam derivatives.[16] Similarly, a [2 + 2] cyclization reaction between 2-aminochromene-3-carbonitrile **1** and phenyl isocyanate **2** occurs, resulting in β-lactam **A** as the key intermediate, which was hydrolyzed to ring-opening **B**.[17] Subsequently, the intermediate **B** releases carbon dioxide to give intermediate **C**, which undergoes intramolecular cyclization to afford the 1,4-dihydropyridine **D**, followed dehydrogenation to the aromatized compound **3**. We have not been able to separate the β-lactam **A** to subject them to the reaction conditions with the goal of probing this hypothesis.

Conclusion

In conclusion, a new iodine-promoted domino reaction of 2-aminochromene-3-carbonitrile with isocyanate under microwave irradiation, providing *N*-substituted 2-aminoquinoline-3-carbonitrile with high regioselectivity, has been developed. The reactions showed broad scopes of substrates which can employ a wide range of common commercial 2-aminochromene-3-carbonitrile and isocyanate. The syntheses were finished within short periods (20−36 min) with good to excellent chemical yields and regioselectivity that avoided tedious workup isolations. New mechanism involving ring-opening/recyclization process has been proposed for this reaction.

Experimental Section

General Procedures. Microwave irradiation was carried out with microwave oven Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were deter-

mined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ (100 MHz, ^{13}C NMR) with chemical shift (δ) given in parts per million (ppm) relative to tetramethysilane (TMS) as internal standard. ESI-MS was determined by using the LCQ Advantage HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (Bruker).

General procedure for the synthesis of 4-(4-Chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (**3a**) with microwave irradiation (Table 2, Entry 1). 2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (**1a**, 1 mmol, 0.33 g, 1 equiv.) was introduced into a 10-mL Emrys reaction vial, phenyl isocyanate (**2a**, 1.1 mmol, 0.13 g, 1.1 equiv) was then successively added, followed by I_2 (1 mmol, 0.25 g, 1 equiv.) and DMF (1.5 mL). Subsequently, the reaction vial was capped and then pre-stirred for 20 s. The mixture was irradiated (initial power 100 W and maximum power 200 W) at 150 °C until TLC (petroleum ether/acetone 4:1) revealed that conversion of the starting material **1a** was completed (20 min). The reaction mixture was then cooled to room temperature and then diluted with cold water (40 mL). The solid product was collected by Büchner filtration and was purified by recrystallization from 95% EtOH to afford the desired pure products **3a** as a pale yellow solid, Mp: 249−250 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 8.0 Hz, 2H, ArH), 7.48−7.43 (m, 5H, NH, 1H and ArH 4H), 7.24−7.18 (m, 3H, ArH), 3.04 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.14 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 168.0, 156.1, 156.0, 137.7, 135.5, 134.9, 129.1, 128.7, 128.7, 124.9, 121.3, 117.9, 115.2, 94.7, 53.3, 48.1, 32.2, 28.2. IR (KBr, ν, cm^{-1}): 3317, 2956, 2226, 1683, 1610, 1544, 1447, 1256, 889. HRMS (ESI): *m*/*z* calcd for: $C_{24}H_{20}ClN_3ONa$, 424.1188; found: 424.1202.

4-(4-Bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (3b). A pale yellow solid; Mp: 263−265 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 8.4 Hz, 2H, ArH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 7.45 (s, 1H, NH), 7.46−7.41 (m, 2H, ArH), 7.22 (t, J = 7.4 Hz, 1H, ArH), 7.13 (d, J = 8.4 Hz, 2H, ArH), 3.03 (s, 2H, CH_2), 2.45 (s, 2H, CH_2), 1.13 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 168.0, 156.1, 156.0, 137.6, 136.0, 131.73, 129.1, 128.9, 124.9, 123.2, 121.3, 117.9, 115.2, 94.6, 53.3, 48.1, 32.2, 28.2. IR (KBr, ν, cm^{-1}): 3317, 2933, 2225, 1678, 1611, 1568, 1546, 1496, 1446, 1255, 1011, 749. HRMS (ESI): *m*/*z* calcd for: 446.0683 $[M+H]^+$; found: 446.0687.

4-(4-Fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (3c). A pale yellow solid; Mp: 238−240 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.45 (s, 1H, NH), 7.43−7.41 (m, 2H, ArH), 7.26−7.17(m, 5H, ArH), 3.04 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.14 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 167.9, 156.3, 156.0, 137.7, 129.3, 129.2, 129.1, 124.9, 121.3, 118.1, 115.7, 115.5, 115.3, 95.0, 53.4, 48.1, 32.2, 28.2; IR (KBr, ν, cm^{-1}): 3316, 2957, 2226, 1676, 1609, 1572, 1548, 1497, 1256, 1311, 987, 837. HRMS (ESI): *m*/*z* calcd for: 386.1664 $[M+H]^+$; found: 386.1671.

5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-2-(phenylamino)quinoline-3-carbonitrile (3d). A pale yellow solid; Mp: 225−227 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 7.6 Hz, 2H, ArH), 7.50−7.49 (m, 3H, ArH), 7.45 (s, 1H, NH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.26−7.19 (m, 3H, ArH), 3.04 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.14 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 167.8, 157.4, 156.0, 137.8, 137.1, 129.1, 128.8, 128.4, 127.1, 124.8, 121.2, 118.1, 115.4, 94.9, 53.3, 48.1, 32.2, 28.2. IR (KBr, ν, cm^{-1}): 3313, 2929, 2228, 1675, 1611, 1547, 1497, 1446, 1297, 1257, 752. HRMS (ESI): *m*/*z* calcd for: 368.1758 $[M+H]^+$; found: 368.1757.

5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2-(phenylamino)-4-*p*-tolylquinoline-3-carbonitrile (3e). A pale yellow solid. Mp: 244−245 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 8.8 Hz, 2H, ArH), 7.45 (s, 1H, NH), 7.44−7.41 (m, 2H, ArH), 7.30 (d, J = 8.8 Hz, 2H, ArH), 7.21 (t, J = 7.4 Hz, 1H, ArH), 7.15 (d, J = 8.0 Hz, 2H, ArH), 3.03 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.13 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 167.7, 156.0, 138.7, 137.8, 134.1, 129.1, 128.8, 128.4, 127.1, 124.7, 121.2, 118.3, 115.4, 94.9, 53.3, 48.1, 32.2, 28.2, 21.5. IR (KBr, ν, cm^{-1}): 3317, 2933, 2224, 1675, 1611, 1570, 1546, 1497, 1373, 1256, 746. HRMS (ESI): *m*/*z* calcd for: 382.1913 $[M+H]^+$; found: 382.1917.

4-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (3f). A pale yellow solid; Mp: 249−252 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 7.6 Hz, 2H, ArH), 7.45 (s, 1H, NH), 7.42 (d, J = 7.6 Hz, 2H, ArH), 7.22−7.20 (m, 3H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 3.89 (s, 3H, OCH_3), 3.03 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.13 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3332, 2957, 2215, 1671, 1608, 1570, 1542, 1498, 1447, 1282, 1246, 1174, 1033, 748. HRMS (ESI): *m*/*z* calcd for: 398.1864 $[M+H]^+$; found: 398.1869.

2-(4-Chlorophenylamino)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3g). A pale yellow solid; Mp: 247−249 °C.

^1H NMR (400 MHz, DMSO) δ: 9.72 (s, 1H, NH), 7.69 (d, J = 8.8 Hz, 2H, ArH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 7.41 (d, J = 8.8 Hz, 2H, ArH), 7.27 (d, J = 8.4 Hz, 2H, ArH), 2.90 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 1.02 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO) δ: 194.0, 167.1, 156.2, 155.8, 138.1, 136.7, 132.8, 129.3, 128.2, 124.3, 117.3, 115.0, 94.3, 52.5, 47.1, 31.7, 27.6. IR (KBr, ν, cm^{-1}): 3301, 2954, 2235, 1681, 1612, 1546, 1488, 1371, 1256, 1090, 822. HRMS (ESI): *m*/*z* calcd for: 436.0978 $[M+H]^+$; found: 436.0976.

2-(4-Chlorophenylamino)-4-(4-bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3h). A pale yellow solid; Mp: 253−255 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J = 8.8 Hz, 2H, ArH), 7.62 (d, J = 8.4 Hz, 2H, ArH), 7.43 (s, 1H, NH), 7.39 (d, J = 8.8 Hz, 2H, ArH), 7.12 (d, J = 8.4 Hz, 2H, ArH), 3.03 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.13 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 167.9, 155.8, 155.2, 136.2, 135.8, 131.7, 129.1, 128.9, 123.3, 122.6, 115.1, 113.2, 94.8, 53.3, 48.0, 32.2, 28.2. IR (KBr, ν, cm^{-1}): 3301, 2955, 2233, 1681, 1633, 1546, 1514, 1491, 1370, 1281, 1012, 824. HRMS (ESI): *m/z* calcd for: 480.0473 $[M+Na]^+$; found: 480.0466.

2-(4-Chlorophenylamino)-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3i). A pale yellow solid; Mp: 241−243 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J = 8.8 Hz, 2H, ArH), 7.43 (s, 1H, NH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.23−7.16 (m, 5H, ArH), 3.03 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.14 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 167.9, 161.8, 156.4, 155.8, 136.3, 129.9, 129.3, 129.2, 129.1, 122.6, 118.4, 115.7, 115.5, 115.2, 95.1, 53.3, 48.1, 32.2, 28.2. IR (KBr, ν, cm^{-1}): 3301, 2956, 2233. 1681, 1613, 1548, 1491, 1409, 1280, 1255, 1220, 1094, 824. HRMS (ESI): *m/z* calcd for: 420.1274 $[M+H]^+$; found: 420.1279.

2-(4-Chlorophenylamino)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-p-tolylquinoline-3-carbonitrile (3j). A pale yellow solid; Mp: 259−261 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J = 8.8 Hz, 2H, ArH), 7.40 (s, 1H, NH), 7.38 (d, J = 8.8 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.14 (d, J = 8.0 Hz, 2H, ArH), 3.03 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.14 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 167.6, 157.7, 155.8, 138.8, 136.5, 134.0, 129.7, 129.1, 129.1, 127.1, 122.4, 118.5, 115.5, 95.1, 53.4, 48.1, 32.2, 28.2, 21.5. IR (KBr, ν, cm^{-1}): 3321, 2955, 2229, 1689, 1612, 1545, 1491, 1406, 1300, 1092, 824. HRMS (ESI): *m/z* calcd for: 416.1525 $[M+H]^+$; found:.416.1539.

2-(4-Chlorophenylamino)-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3k). A pale yellow solid; Mp: 241−242 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J = 8.8 Hz, 2H, ArH), 7.41 (s, 1H, NH), 7.38 (d, J = 8.8 Hz, 2H, ArH), 7.20 (d, J = 8.8 Hz, 2H, ArH), 7.01 (d, J = 8.4 Hz, 2H, ArH), 3.89 (s, 3H, OCH_3), 3.02 (s, 2H, CH_2), 2.47 (s, 2H, CH_2), 1.35 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3321, 2955, 2228, 1685, 1617, 1545, 1493, 1411, 1262, 1226, 1026, 824. HRMS (ESI): *m/z* calcd for: 432.1474 $[M+H]^+$; found: .432.1474

2-(4-Chlorophenylamino)-5,6,7,8-tetrahydro-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3l). A pale yellow solid; Mp: 235−237 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.62 (s, 1H, NH), 7.69 (d, J = 8.8 Hz, 2H, ArH), 7.41 (d, J = 8.8 Hz, 2H, ArH), 7.00 (d, J = 8.4 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 6.78−6.76 (m, 1H, ArH), 3.82 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.90 (s, 2H, CH_2), 2.41 (s, 2H, CH_2), 1.02 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3319, 2991, 2267, 1685, 1608, 1543, 1523, 1445, 1225, 1141, 1026. HRMS (ESI): *m/z* calcd for: 462.1579 $[M+H]^+$; found: 462.1580.

2-(4-Bromophenylamino)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3m). A pale yellow solid; Mp: 264−265 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.72 (s, 1H, NH), 7.64 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 7.27 (d, J = 8.0 Hz, 2H, ArH), 2.91 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 1.02 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3300, 2954, 2869, 2234, 1681, 1611, 1544, 1488, 1371, 1256, 1090, 822. HRMS (ESI): *m/z* calcd for: 480.0473 $[M+Na]^+$; found: 480.0471.

2-(4-Bromophenylamino)-4-(4-bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3n). A pale yellow solid; Mp: 268−270 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.72 (s, 1H, NH), 7.64 (d, J = 8.4 Hz, 4H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 2.91 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 1.01 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3303, 2954, 2229, 1681, 1610, 1545, 1515, 1488, 1372, 1255, 1011, 822. HRMS (ESI): *m/z* calcd for: 523.9968 $[M+Na]^+$; found: 523.9984.

2-(4-Bromophenylamino)-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3o). A pale yellow solid; Mp: 237−238 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.70 (s, 1H, NH), 7.64 (d, J = 8.8 Hz, 2H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 7.29−7.27 (m, 4H, ArH), 2.91 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 1.02 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3301, 2955, 2870, 2233, 1680, 1611, 1546, 1488, 1371, 1255, 1077, 822. HRMS (ESI): *m/z* calcd for: 464.0769 $[M+H]^+$; found: 464.0784.

2-(4-Bromophenylamino)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-*p*-tolylquinoline-3-carbonitrile (3p). A pale yellow solid; Mp: 292−293 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 1H, NH), 7.64 (d, J = 8.8 Hz, 2H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 7.24 (d, J = 8.0 Hz, 2H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 2.90 (s, 2H, CH_2), 2.38 (s, 5H, CH_2 and CH_3), 1.01 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3320, 2954, 2867, 2230, 1689, 1612, 1543, 1488, 1368, 1256, 1114, 821, 752. HRMS (ESI): *m/z* calcd for: 460.1019 $[M+H]^+$; found: 460.1026.

4-(4-Chlorophenyl)-2-(cyclohexylamino)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3q). A pale yellow solid; Mp: 247−248 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, J = 8.4 Hz, 2H, ArH), 7.14 (d, J = 8.4 Hz, 2H, ArH), 5.52 (d, J = 7.2 Hz, 1H, NH), 4.20−4.17 (m, 1H, CH), 2.94 (s, 2H,CH_2), 2.40 (s, 2H,CH_2), 2.09−2.06 (m, 1H, CH_2), 1.97−1.53 (m, 9H, CH_2), 1.11 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3330, 2931, 2852, 2216, 1673, 1627, 1558, 1457, 1284, 1089, 1016. HRMS (ESI): *m/z* calcd for: 408.1838 $[M+H]^+$; found: 408.1847.

4-(4-Bromophenyl)-2-(cyclohexylamino)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3r). A pale yellow solid; Mp: 260−262 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.08 (d, J = 8.4 Hz, 2H, ArH), 5.52 (d, J = 7.6 Hz, 1H, NH), 4.21−4.16 (m, 1H, CH), 2.94 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 2.10−2.06 (m, 2H, CH_2), 1.84−1.80 (m, 2H, CH_2), 1.80−1.31 (m, 6H, CH_2), 1.28 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 168.5, 157.6, 155.8, 136.5, 131.5, 128.8, 122.8, 116.0, 115.6, 92.9, 53.2, 50.2, 48.3, 32.9,

32.1, 28.2, 25.5, 24.9. IR (KBr, ν, cm^{-1}): 3328, 2934, 2222, 1672, 1636, 1577, 1557, 1508, 1457, 1285. HRMS (ESI): *m/z* calcd for: 452.1333 $[M+H]^+$; found: 452.1334.

2-(Cyclohexylamino)-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (3s). A pale yellow solid; Mp: 191−192 °C.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, $J = 8.4$ Hz, 2H, ArH), 7.96 (d, $J = 8.4$ Hz, 2H, ArH), 5.47 (d, $J = 7.6$ Hz, 2H, NH), 4.19−4.13 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 2.91 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 2.08−2.04 (m, 2H, CH_2), 1.81−1.23 (m, 8H, CH_2), 1.09 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3362, 2956, 2213, 1679, 1574, 1520, 1498, 1280, 1249, 1028, 813.

HRMS (ESI): *m/z* calcd for: 404.2333 $[M+H]^+$; found: 404.2348.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **3a**−**3s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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