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Expedient Synthesis and Antibacterial Activity of Tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile Derivatives Using Piperidine as Catalyst

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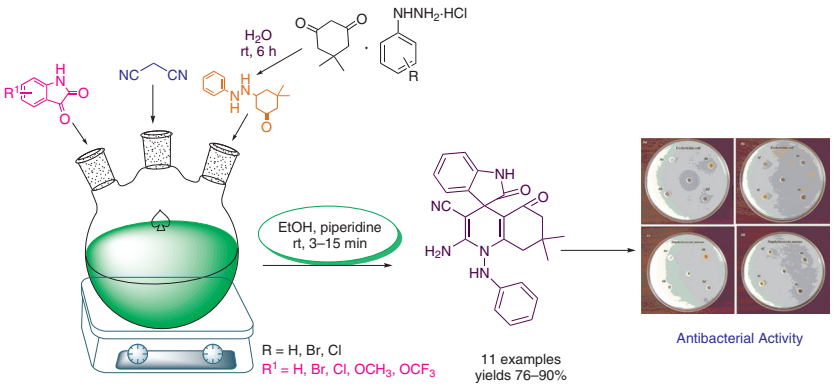

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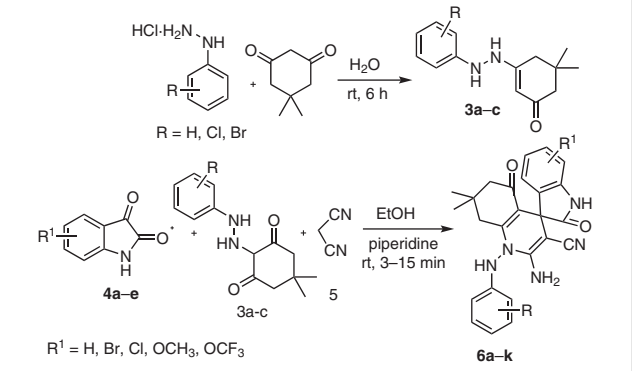
Abstract A convenient synthesis of 2′-amino-7′,7′-dimethyl-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile derivatives has been designed using different substituted isatins, various 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enones (arylhydrazones of dimedone) and malononitrile in ethanol with piperidine as catalyst at room temperature. The structures of the synthesized compounds have been elucidated by various spectroscopic techniques. The selected compounds have also been evaluated for their antibacterial activities against human pathogenic bacteria.

Key words antibacterial activity, base catalysts, quinolines, indoline, multistep synthesis

In recent years, quinolone based heterocyclic compounds have been found to have a broad range of applications in the fields of industry,[1–4] medicine,[5] natural products,[6] agrochemicals,[7] ligands in transition-metal complexes,[8] organic light-emitting diodes,[9] functional materials,[10] dyes,[11] electrochemical storage devices,[12] therapeutic agents,[13] chemosensors,[14] bioorganic, pH indicators and food colorants.[15] Moreover, their derivatives have been shown to have significant biological activities such as anthelmintic,[16] tuberculosis (TB),[17] anti-HIV,[18] antimicrobial,[19] anti-inflammatories,[20] antimalarial[21] and antitumor.[22] Significant spiroindole related heterocyclic compounds are present in several naturally occurring plant materials. Catalytic asymmetric synthesis of chiral spirooxindoles and spiropyrrolidines have been reported along with their biological properties.[23–26] The spiroindoles are attractive targets in organic and medicinal chemistry[27,28] due to their vast range of biological applications[29] as antitumor,[30] antitubercular,[31] antimicrobial,[32] antimycobacterial,[33] antifungal,[34] and antioxidant agents[35] etc. The combination of multiple step operations is a widely used method to access fine organic compounds and for the synthesis of new organic molecules.

Stereoselective synthesis of new kinds of spirooxindole, indoline and quinolone derivatives have been achieved with different catalysts.[36–39] Isatin is one of the most favorable classes of heterocyclic molecules, having many interesting activities and being well-tolerated in chemical transformations.[40,41] In this paper, we report the synthesis of 2′-amino-7′,7′-dimethyl-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile derivatives (Scheme 1). The reaction with isatin and phenyl hydrazine hydrochloride resulting in the formation of tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile is of great interest as it produces compounds that incorporate both indoline and quinolone moieties. Hence,



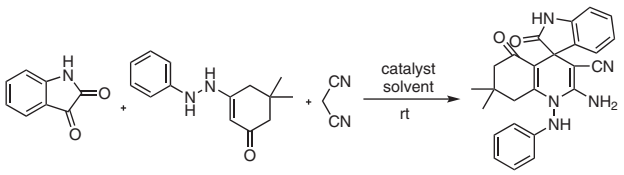
Scheme 1 Synthesis of tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile derivatives

these compounds are expected to have effective biological activities.

Initially, synthesis of tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitriles was performed with isatin, 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enoneand malononitrile as a model reaction for the optimization studies.

The reaction of isatin, 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enone and malononitrile in either water or ethanol as reaction media in the absence of catalyst did not yield any product even after 24 h (Table 1, entries 1 and 2). So the reaction was tried in ethanol using various base catalysts and the results are presented in Table 1. In the case of ethanol with piperidine as a catalyst, the yield was 87% after 7 minutes at room temperature (entry 3) and in methanol as the solvent with piperidine, the product yield was found to be 84% (entry 4). It is evident that, with triethylamine, dimethylamine and pyridine as catalysts, no reaction was observed at room temperature (entries 5, 6 and 7). The reaction was also carried out in water with piperidine as a catalyst; however, no reaction was observed at room temperature (entry 8). From the above optimization studies, it was evident that suitable conditions for the formation of good yield of product were the use of piperidine as catalyst at room temperature in absolute ethanol. Further derivatives were prepared under these optimized conditions.

Table 1 Optimization of the Reaction Conditions[a]

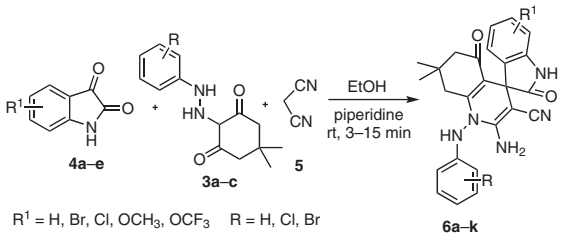


Entry	Solvent	Catalyst	Temp (°C)	Time (min)	Yield (%)[b]
1	water	–	RT	1440	–
2	ethanol	–	RT	1440	–
3	ethanol	piperidine	RT	7	87
4	methanol	piperidine	RT	15	84
5	ethanol	triethylamine	RT	80	–
6	ethanol	dimethylamine	RT	80	–
7	ethanol	pyridine	RT	80	–
8	water	piperidine	RT	600	–

[a] Reaction conditions: Isatin (1 mmol), 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enone (1 mmol), malononitrile (1 mmol) and solvent (10 mL) with catalyst (0.1ml) at room temperature.
[b] Isolated yield.

With the optimized reaction conditions in hand, we have investigated the scope of the reaction with respect to various isatins (**4a–e**), different substituted 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enones (**3a–c**) and malononitrile (**5**) to give the corresponding products **6a–k**, as shown in Table 2. The electron-withdrawing groups in the isatin moiety slightly enhance the product yield and decreases the reaction time, which may be due to the facile formation of Knoevenagel adduct. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. The yield and physical constant data of all the synthesized compounds are presented in Table 2.

Table 2 Synthesis of Tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile Derivatives[a]



4a–e 3a–c 5 6a–k

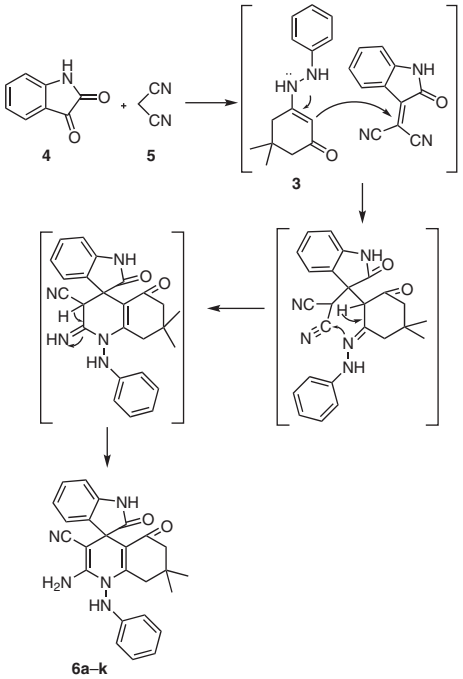
R^1 = H, Br, Cl, OCH_3, OCF_3 R = H, Cl, Br

Entry	R^1	R	Time (min)	Product **6**	Yield (%)[b]	Mp (°C)
1	H	H	7	**6a**	87	230–232
2	5-OCH_3	H	8	**6b**	77	226–228
3	5-Cl	H	9	**6c**	83	230–232
4	5-Br	Br	10	**6d**	79	232–234
5	5-OCF_3	H	7	**6e**	90	230–232
6	5-OCH_3	Cl	11	**6f**	80	224–226
7	H	Cl	9	**6g**	78	218–220
8	H	Br	8	**6h**	82	218–220
9	5-OCH_3	Br	9	**6i**	77	222–224
10	5-Cl	Cl	12	**6j**	79	232–234
11	5-Cl	Br	11	**6k**	76	228–230

[a] Reaction conditions: Isatin (1 mmol), 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enone (1 mmol), malononitrile (1 mmol) and solvent (10 mL) with piperidine (0.1ml) at room temperature.
[b] Isolated yield.

A plausible mechanism for the reaction is described in Scheme 2. The reaction occurs via initial formation of the Knoevenagel adduct from the isatin (**4**) and malononitrile (**5**) by the loss of a water molecule. Michael addition of 5,5-dimethyl-3-(2-phenylhydrazinyl)cyclohex-2-enone (**3**) to the Knoevenagel adduct leads to the formation of an acyclic intermediate, which undergoes cyclization by intramolecular nucleophilic attack of the -NH group on the electron-deficient cyano carbon, followed by tautomerization, providing the final products **6a–k**.

The synthesized tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile compounds were tested for their antibacterial activity against clinical pathogens such as *Escherichia coli* and multi-drug-resistant *Staphylococcus*



Scheme 2 Proposed mechanism for the formation of tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile

aureus. The antibacterial activity results are presented in Table 3. Compounds **6a**, **6k**, **6h**, and **6d** exhibited inhibition against *Escherichia coli*, and **6f** showed inhibition against *Staphylococcus aureus*. Compound **6c** acted as a good inhibition agent against both *Escherichia coli* (10 mm) and *Staphylococcus aureus* (12 mm) (Figure 1).

Table 3 Antibacterial Activity of Synthesized Compounds

Entry	Sample (40 µg)	Zone of inhibition (mm)	
		Staphylococcus aureus	*Escherichia coli*
1	**6a**	–	13
2	**6c**	12	10
3	**6d**	–	9
4	**6e**	–	–
5	**6f**	10	–
6	**6h**	–	9
7	**6i**	–	–
8	**6k**	–	10
9	control (tetracyclines)	–	18

In conclusion, we have designed a very simple, efficient, and convenient method that allows easy access to a wide range of pharmaceutically interesting functionalized tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile related compounds in the presence of green solvents with base catalyst at room temperature.[42] Mild reaction conditions, short reaction time, excellent yields, as well as the use of inexpensive and environmentally benign solvent system are key advantages of this method.

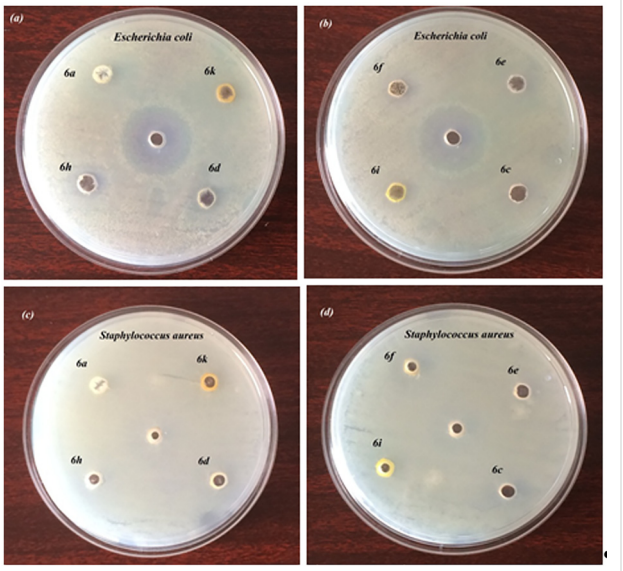


Figure 1 Antibacterial activity: (a), (b) *Escherichia coli* (c), (d) *Staphylococcus aureus*

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706682.

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(42) **Synthesis of Tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile Derivatives; General Procedure:** All the chemicals used for this study were commercially available and were freshly used after being purified by standard procedures. All the conventional reactions were performed with 50 mL RB flasks. TLC was performed on Merck pre-coated aluminum sheets of 60 F-254 silica gel plates with visualization by UV-light using a 1:1 mixture of ethyl acetate and *n*-hexane as solvent system. Melting points were determined in capillary tubes with a Büchi melting point BB-545 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 400 MHz high-resolution NMR spectrometers. DMSO-d_6 was used as a solvent for the NMR spectral measurements and the spectra were recorded in parts per million with TMS as internal standard.

Spectral Data for Tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile Derivatives

2′-Amino-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6a): Yield: 87%; white solid; mp 230–232 °C. IR (KBr): 3413.80, 3261.14, 3030.31, 2952.89, 2184.18, 1717.19, 16630.76 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.22 (s, 1 H, -NH), 8.79 (s, 1 H, -NH), 7.38–6.42 (m, 11 H, Ar-H and –NH$_2$), 2.19–1.91 (m, 4 H, 2 × CH$_2$), 0.93–0.81 (m, 6 H, 2 × CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.17, 28.67 (C(CH$_3$)$_2$), 31.17 (-CH), 38.36 (-CH$_2$), 49.60 (CH$_2$-CO), 58.74 (C-CN), 109.39, 110.73, 111.03, 120.79, 121.89, 122.02, 128.16, 130.10, 137.09, 142.15, 153.09, 179.82, 190.10 (Ar-C).

2′-Amino-6-methoxy-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6b): Yield: 80%; white solid; mp 226–228 °C; IR (KBr): 3429.77, 3248.56, 3030.35, 2957.27, 2186.55, 1723.40, 1650.66 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (s, 1 H, -NH), 8.80 (s, 1 H, -NH), 7.35–6.43 (m, 10 H, Ar-H and –NH$_2$), 3.66 (s, 3 H, OCH$_3$), 2.19–1.93 (m, 4 H, 2 × CH$_2$), 0.93–0.74 (m, 6 H, 2 × CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.13, 28.56 (C(CH$_3$)$_2$), 32.18 (-CH), 38.34 (-CH$_2$), 49.41 (CH$_2$-CO), 55.63 (-OCH$_3$), 58.80 (C-CN), 109.55, 111.02, 120.66, 129.89, 135.53, 147.25, 155.24, 179.67 (Ar-C).

2′-Amino-6-chloro-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6c): Yield: 76%; white solid; mp 230–232 °C; IR (KBr): 3327.35, 3096.69, 2958.88, 2876.92, 1722.43, 1691.16, 1644.67 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.99 (s, 1 H, -NH), 8.86 (s, 1 H, -NH), 7.44–6.65 (m, 10 H, Ar-H and –NH$_2$), 1.94–1.84 (m, 4 H, 2 × CH$_2$), 0.94–0.80 (m, 6 H, 2 × CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 26. 44, 27.04, 28.73 (C(CH$_3$)$_2$), 33.68 (-CH$_2$), 50.63 (CH$_2$-CO), 59.10 (C-CN), 100.59, 108.51, 111.70, 112.99, 121.99, 126.89, 133.56, 144.76, 167.54, 180.32, 194.66, 203.54 (Ar-C).

2′-Amino-6-bromo-2,5′-dioxo-1′-(phenylamino)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6d): Yield: 79%; white solid; mp 232–234 °C; IR (KBr): 3422.48, 3246.68, 3029.36, 2954.58, 2186.34, 1724.50 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, -NH), 8.94 (s, 1 H, -NH), 7.50–6.58 (m, 9 H, Ar-H and –NH$_2$), 2.16–2.03 (m, 4 H, 2 × CH$_2$), 0.94–0.82 (m, 6 H, 2 × CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.65, 28.01 (C(CH$_3$)$_2$), 38.18 (-CH$_2$), 110.26, 111.55, 113.53, 119.10, 125.91, 130.78, 139.35, 146.42, 155.81, 179.41, 194.33 (Ar-C).

2′-Amino-2,5′-dioxo-1′-(phenylamino)-6-(trifluoromethoxy)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6e): Yield: 83%; white solid; mp 230–232 °C; IR (KBr): 3477.11, 3361.15, 3210.53, 3111.86, 3026.47, 2959.66, 2185.02, 1707.70 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (s, 1 H, -NH), 8.82 (s, 1 H, -NH), 7.33–6.56 (m, 10 H, Ar-H and –NH$_2$), 2.12–1.94 (m, 4 H, 2 × CH$_2$), 0.93–0.71 (m, 6 H, 2 × CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): 26.84, 27.19, 28.51 (C(CH$_3$)$_2$), 38.34 (-CH$_2$), 49.44 (CH$_2$-CO), 57.80 (C-CN), 110.04, 111.97, 116.14, 119.15, 120.71, 121.29, 129.90, 138.52, 141.26, 146.82, 147.13, 155.88, 179.92, 194.26 (Ar-C).

2′-Amino-1′-((4-chlorophenyl)amino)-6-methoxy-2,5′-dioxo-

5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6f): Yield: 85%; white solid; mp 224–226 °C; IR (KBr): 3414.56, 3273.42, 3032.56, 2953.14, 2185.96, 1717.59, 1632.96 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.66 (s, 1 H, -NH), 8.93 (s, 1 H, -NH), 7.39–6.47 (m, 9 H, Ar-H and $-NH_2$), 3.66 (s, 3 H, OCH_3), 2.10–1.95 (m, 4 H, 2 × CH_2), 0.94–0.77 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.30, 28.57 ($C(CH_3)_2$), 39.35 (-CH_2), 49.39 (CH_2-CO), 55.66 (-OCH_3), 58.89 (C-CN), 109.58, 110.30, 111.16, 119.30, 124.08, 129.68, 135.57, 138.28, 145.93, 152.71, 155.04, 179.63, 194.10 (Ar-C).

2′-Amino-1′-((4-chlorophenyl)amino)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6g): Yield: 88%; white solid; mp 218–220 °C; IR (KBr): 3835.27, 3740.79, 3647.38, 3588.71, 3415.87, 3274.02, 3022.86, 2955.53, 2365.09, 2187.03, 1717.43, 1633.23 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.23 (s, 1 H, -NH), 8.92 (s, 1 H, -NH), 7.43–6.48 (m, 10 H, Ar-H and $-NH_2$), 2.14–1.92 (m, 4 H, 2 × CH_2), 0.94–0.76 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 27.27, 28.61 ($C(CH_3)_2$), 32.21, 38.31 (-CH_2), 48.98 (CH_2-CO), 58.88 (C-CN), 109.41, 110.86, 113.48, 122.04, 128.15, 129.69, 142.15, 145.93, 146.15, 152.68, 179.88 (Ar-C).

2′-Amino-1′-((4-bromophenyl)amino)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6h): Yield: 85%; white solid; mp 218–220 °C; IR (KBr): 3834.72, 3740.38, 3670.97, 3647.88, 3418.33, 3252.46, 2952.41, 2867.11, 2353.77, 2187.88, 1720.88 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.23 (s, 1 H, -NH), 8.93 (s, 1 H, -NH), 7.55–6.48 (m, 10 H, Ar-H and $-NH_2$), 2.14–1.92 (m, 4 H, 2 × CH_2), 0.94–0.77 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.24, 28.59 ($C(CH_3)_2$), 32.21, 38.31 (-CH_2), 48.98 (CH_2-CO), 58.88 (C-CN), 109.41, 110.83, 111.15, 111.68, 113.96, 119.30, 121.90, 122.05, 123.14, 128.16, 132.52, 136.98, 137.24, 142.14, 146.34, 152.65, 155.03, 179.77, 194.10 (Ar-C).

2′-Amino-1′-((4-bromophenyl)amino)-6-methoxy-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6i): Yield: 77%; white solid; mp 222–224 °C; IR (KBr): 3414.69, 3275.63, 3034.04, 2953.82, 2185.81, 1717.55, 1678.20, 1633.28 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.06 (s, 1 H, -NH), 8.93 (s, 1 H, -NH), 7.51–6.47 (m, 9 H, Ar-H and $-NH_2$), 3.63 (s, 3 H, OCH_3), 2.15–1.95 (m, 4 H, 2 × CH_2), 1.08–0.84 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.28, 28.55 ($C(CH_3)_2$), 32.23, 49.39 (CH_2-CO), 55.67 (-OCH_3), 58.85 (C-CN), 109.58, 109.74, 110.33, 115.15, 112.39, 113.97, 132.50, 135.57, 138.28, 146.34, 152.68, 155.02, 179.63, 194.10 (Ar-C).

2′-Amino-6-chloro-1′-((4-chlorophenyl)amino)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6j): Yield: 79%; white solid; mp 232–234 °C; IR (KBr): 3914.60, 3790.02, 3702.05, 3423.01, 3249.96, 3030.35, 2956.62, 2355.64, 2186.71, 1723.46, 1654.28, 1630.26 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.39 (s, 1 H, -NH), 8.98 (s, 1 H, -NH), 7.39–6.58 (m, 9 H, Ar-H and $-NH_2$), 2.15–2.03 (m, 4 H, 2 × CH_2), 0.94–0.80 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.69, 28.07 ($C(CH_3)_2$), 32.31, 38.20 (-CH_2), 49.29 (CH_2-CO), 58.05 (C-CN), 110.22, 113.66, 123.20, 124.15, 125.79, 127.91, 128.08, 129.68, 138.96, 139.23, 141.30, 141.37, 145.89, 152.93, 153.13, 155.60, 179.52, 194.30 (Ar-C).

2′-Amino-1′-((4-bromophenyl)amino)-6-chloro-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (6k): Yield: 76%; white solid; mp 228–230 °C; IR (KBr): 3423.43, 3242.89, 2956.16, 2871.31, 2186.75, 1725.02, 1654.56, 1630.70 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.39 (s, 1 H, -NH), 8.94 (s, 1 H, -NH), 7.51–6.58 (m, 9 H, Ar-H and $-NH_2$), 2.15–2.03 (m, 4 H, 2 × CH_2), 0.94 (m, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.65, 28.27 ($C(CH_3)_2$), 32.30, 38.19 (-CH_2), 49.29 (CH_2-CO), 58.02 (C-CN), 110.21, 111.73, 114.12, 123.20, 125.79, 127.92, 128.08, 132.50, 132.65, 138.94, 139.22, 141.29, 146.29, 152.90, 153.09, 155.57, 179.52, 194.31 (Ar-C).