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AN EFFICIENT SYNTHESIS AND EVALUATION OF ANTITUMOR ACTIVITIES OF FUNCTIONALIZED PYRANO[2,3-*b*]QUINOLINES

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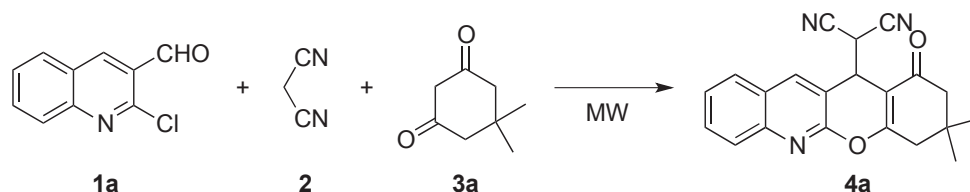
Abstract – An efficient synthesis of novel functionalized pyrano[2,3-*b*]quinoline derivatives via a three-component reaction of 2-chloroquinoline-3-carbaldehydes, malononitrile and 1,3-dicarbonyl compounds under microwave irradiation is described. This protocol has the advantages of high efficiency, mild reaction conditions, a one-pot procedure, and convenient operation. All of these compounds were evaluated for their antiproliferative properties *in vitro* against hepatic carcinoma cells and several compounds were found to have good activities.

Quinoline scaffolds are interesting synthetic targets because these compounds possess a broad spectrum of biological activities, including anticancer,¹ antibacterial,² antimalarial,³ anti-inflammatory,⁴ antitumor,⁵ anti-HIV,⁶ antiallergic,⁷ antidepressant,⁸ and antiproliferative activities.⁹ Additionally, some pyranoquinoline moiety have been attracted great attention from synthetic as well as medicinal chemists because of their wide applications as drugs, pharmaceuticals and agrochemicals. Pyranoquinoline derivatives possess a wide range of interesting biological activities, such as anti-inflammatory, psychotropic, anti-allergic and estrogenic activities.¹⁰ Although several methods have been reported in the literatures for construction of pyranoquinoline derivatives,¹¹ these methods invariably require long multistep process and provide low yields of the desired products. Thus, the development of an efficient method for their synthesis still attracts much interest using readily available starting materials.

Multi-component reactions (MCRs) in which multiple reactions are combined into one synthetic operation has been used extensively to form carbon–carbon bonds in the synthetic chemistry. MCRs offer a wide range of possibilities for the efficient construction of highly complex molecules in a single

procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there have been major developments in three- and four-component reactions and much effort continuous to be devoted to developing new MCRs.¹² 2-Chloroquinoline-3-carbaldehydes, which can be easily accessible from simple acetanilides via Vilsmeier-Haack reaction,¹³ are important synthons and have been used for the construction of some heteroaryl-fused quinoline scaffolds like pyrazolo[3,4-*b*]quinolones,¹⁴ pyrano[4,3-*b*]quinolones,¹⁵ pyrano[2,3-*b*]quinolines,¹⁶ quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines,¹⁷ isoxazolo[5,4-*b*]quinolones,¹⁸ and tetrahydrofuro[2',4':4,6]pyrano[2,3-*b*]quinolines.¹⁹ We recently reported the use of this synthon in the construction of some novel quinoline derivatives.²⁰ Here we extend this methodology to the facile synthesis of novel functionalized pyrano[2,3-*b*]quinoline derivatives via a three-component reaction of 2-chloroquinoline-3-carbaldehydes, malononitrile and 1,3-dicarbonyl compounds under microwave irradiation conditions.

Initially, we optimized the reaction conditions using a three-component reaction of 2-chloroquinoline-3-carbaldehyde (**1a**), malononitrile (**2**), and 5,5-dimethyl-1,3-cyclohexanedione (**3a**) as the model reaction. The effects of solvents, catalysts, and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in EtOH for 20 min without any catalyst under microwave irradiation conditions the desired product **4a** was obtained in 43% yield (entry 1, Table 1). To improve the yield, different solvents were evaluated. The results revealed that ethanol provided much better results than MeCN, THF, toluene, HOCH₂CH₂OH, DMF, and H₂O (entries 1-7, Table 1). To identify the optimum reaction temperature, the reaction was carried out at 80, 90, 100 and 110 °C, providing the desired product in yields of 12%, 28%, 43%, and 37% (entries 1 and 8-10, Table 1), respectively. So, the best reaction temperature is 100 °C. Then, the reaction was performed at different reaction times to determine the optimum reaction time. The results showed that the best reaction time was 30 min (entries 1 and 11-13, Table 1). To improve the yield, several catalysts were evaluated: acetic acid, *p*-toluenesulfonic acid (*p*-TSA), cesium carbonate, sodium carbonate, sodium hydroxide, piperidine and L-proline (entries 14-20, Table 1). The results revealed that the catalytic efficiency of L-proline was the highest. Finally, we evaluated the amount of L-proline required for this reaction. The results from Table 1 (entries 20-25) show that 50 mol% L-proline is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. On the basis of all of these experiments, the optimum reaction conditions were identified as ethanol at 100 °C for 30 min under microwave irradiation catalyzed by 50 mol% L-proline.

Table 1. Optimization of the reaction conditions for the synthesis of compound **4a**^a

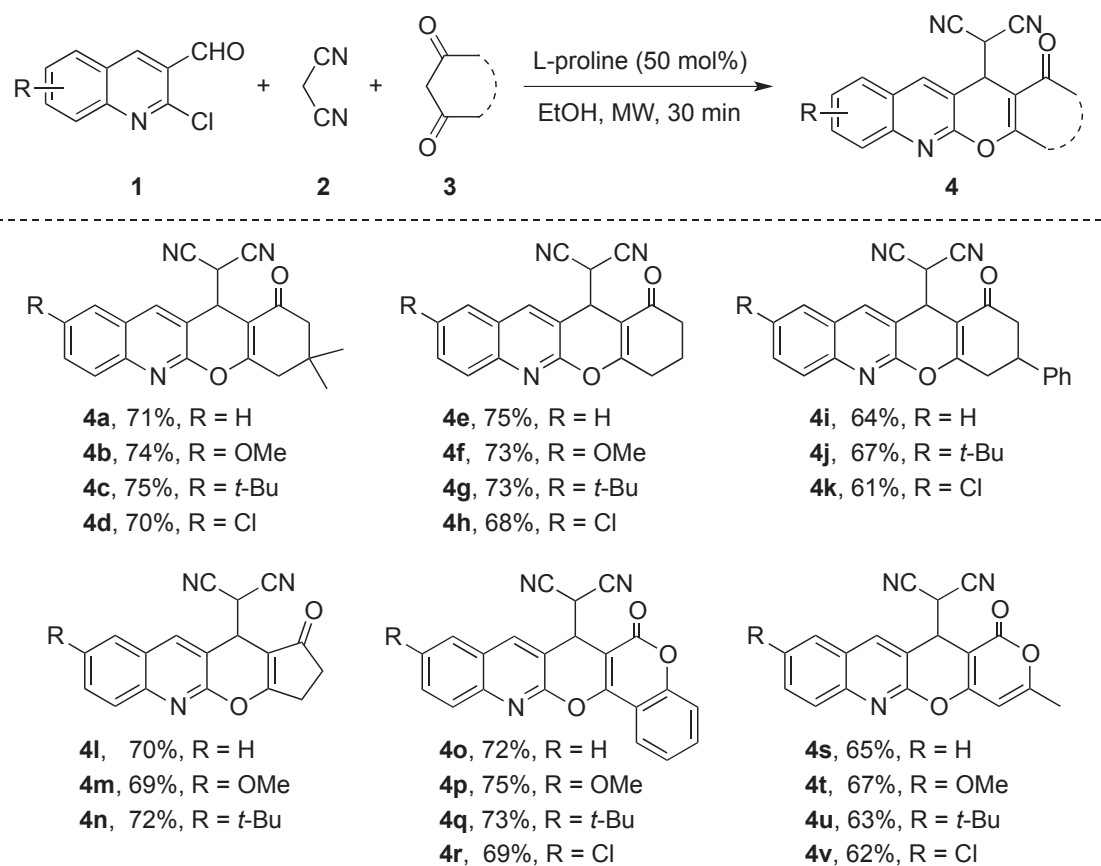
Entry	Solvent	Catalyst (mol%)	<i>T</i> (°C)	Time (min)	Yield ^b (%)
1	EtOH	no	100	20	43
2	MeCN	no	100	20	24
3	THF	no	100	20	24
4	toluene	no	100	20	15
5	HOCH ₂ CH ₂ OH	no	100	20	34
6	DMF	no	100	20	11
7	H ₂ O	no	100	20	18
8	EtOH	no	80	20	12
9	EtOH	no	90	20	28
10	EtOH	no	110	20	37
11	EtOH	no	100	10	36
12	EtOH	no	100	30	49
13	EtOH	no	100	40	40
14	EtOH	HOAc (50)	100	30	60
15	EtOH	TsOH (50)	100	30	56
16	EtOH	Cs ₂ CO ₃ (50)	100	30	30
17	EtOH	Na ₂ CO ₃ (50)	100	30	24
18	EtOH	NaOH (50)	100	30	29
19	EtOH	piperidine (50)	100	30	36
20	EtOH	L-proline (50)	100	30	77
21	EtOH	L-proline (10)	100	30	51
22	EtOH	L-proline (20)	100	30	55
23	EtOH	L-proline (30)	100	30	61
24	EtOH	L-proline (40)	100	30	68
25	EtOH	L-proline (60)	100	30	72

^aReaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol), solvent (5 mL). ^bYields was determined by HPLC-MS.

With the optimal reaction conditions in hand, the substrate scope of the transformation was then evaluated using four 6-substituted 2-chloroquinoline-3-carbaldehydes **1**, and seven 1,3-dicarbonyl compounds **3**. The corresponding functionalized pyrano[2,3-*b*]quinoline derivatives were obtained, and the results are summarized in Scheme 1. As displayed in Scheme 1, the 2-chloroquinoline-3-carbaldehydes bearing either electron-withdrawing or electron-donating groups were tolerated under this reaction conditions, leading to the final products in satisfactory yields. However, when the other substituted acetonitrile such as ethyl 2-cyanoacetate or 2-cyanoacetamide were used, the desired products were not obtained.

The structures of the products synthesized in the current study were identified using IR, ¹H NMR, and ¹³C

NMR spectroscopies, and HRMS analysis. The structure of compound **4b** was further confirmed by X-ray diffraction analysis (Figure 1).



Scheme 1. Substrate scope for synthesis of products **4**

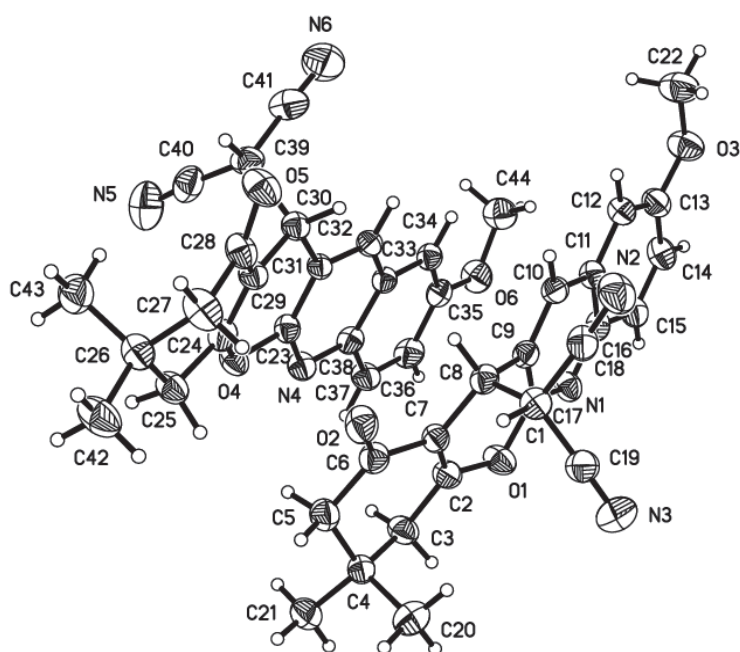
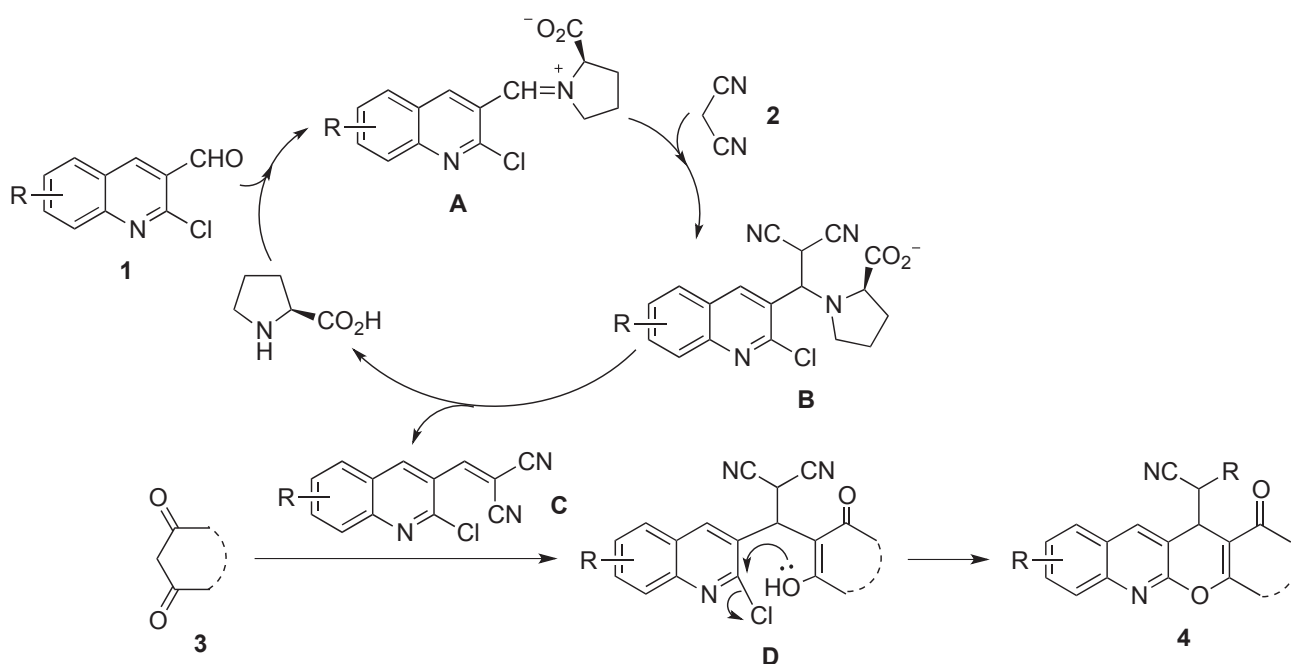


Figure 1. The crystal structure of compound **4b**

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compound **4** could be explained by the reaction sequence in Scheme 2. We suggest that L-proline catalyze the formation of iminium **A** in a reversible reaction with the 2-chloroquinoline-3-carbaldehyde **1**. The higher reactivity of the iminium ion compared with the carbonyl species could facilitate Knoevenagel condensation with malononitrile **2** to afford the intermediate **B**, which upon elimination of L-proline would produce the intermediate **C**. The product **4** was obtained by the Michael addition of intermediate **C** with 1,3-dicarbonyl compound **3**, and followed by intramolecular nucleophilic cyclization.



Scheme 2. Proposed mechanism for the synthesis of compound **4**

All of the functionalized pyrano[2,3-*b*]quinoline derivatives synthesized were tested for their antiproliferative properties against hepatic carcinoma (HepG2) cells *in vitro*. The IC_{50} values are shown in Table 2. The most active compounds were **4q**, **4u**, **4n** and **4c**, with IC_{50} values of $1.0 \pm 0.01 \mu\text{M}$, 1.4 ± 0.1

Table 2. IC_{50} Values of synthesized compounds

Compound	IC_{50} (μm)	Compound	IC_{50} (μm)	Compound	IC_{50} (μm)
4a	13.8 ± 2.8	4i	7.1 ± 0.4	4q	1.0 ± 0.01
4b	12.2 ± 1.0	4j	18.8 ± 2.5	4r	6.9 ± 0.1
4c	3.4 ± 0.1	4k	11.7 ± 1.2	4s	5.0 ± 0.7
4d	9.4 ± 0.3	4l	42.6 ± 5.0	4t	9.6 ± 1.1
4e	11.8 ± 0.8	4m	44.3 ± 4.9	4u	1.4 ± 0.1
4f	> 100	4n	2.1 ± 0.1	4v	> 100
4g	6.9 ± 0.5	4o	6.7 ± 0.4		
4h	> 100	4p	5.9 ± 0.6		

μM , $2.1 \pm 0.1 \mu\text{M}$, and $3.4 \pm 0.1 \mu\text{M}$, respectively. All of these molecules possess a 6-*t*-butyl group at the quinoline ring, so this is suggested as being important for cytotoxic activity. The activity of compound **4q** is higher than the corresponding 1,8-naphthyridine derivatives.^{20b}

In summary, we have developed an efficient method for the synthesis of pharmacologically important, functionalized pyrano[2,3-*b*]quinoline derivatives by a three-component reaction of 2-chloroquinoline-3-carbaldehydes, malononitrile and 1,3-dicarbonyl compounds catalyzed by L-proline under microwave irradiation conditions. This method has the advantages of high efficiency, mild reaction conditions, a one-pot procedure, and convenient operation. The cytotoxicity studies against hepatic carcinoma (HepG2) cells showed that the pyrano-fused quinoline **4** is a potent scaffold for anticancer drug discovery.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1} . ^1H NMR and ^{13}C NMR were determined on Varian Inova-400 MHz or Inova-300 MHz spectrometer in $\text{DMSO-}d_6$ or CDCl_3 solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using a Bruker micrOTOF-Q II mass spectrometer with an ESI resource. X-Ray diffraction analysis was carried out on a Smart-1000 diffractometer. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured using an infrared detector during microwave heating.

Starting Materials. All chemicals used in this study were commercially available.

Typical experimental procedure for the synthesis of functionalized pyrano[2,3-*b*]quinoline derivatives **4.** 2-Chloroquinoline-3-carbaldehydes (**1**) (0.2 mmol), malononitrile (**2**) (0.2 mmol), and 1,3-dicarbonyl compounds (**3**) (0.2 mmol) were introduced into a 5 mL initiator microwave reaction vial, and 50 mol% L-proline as well as EtOH (2 mL) were then successively added. Subsequently, the reaction vial was closed and then stirred for 10 sec. The reaction mixture was irradiation at 100 °C for 30 min with Initiator 2.5 Microwave Synthesizer. The reaction was monitored by TLC. After the completion, the reaction mixture was then cooled to room temperature. The precipitate was collected and purified by recrystallization from DMF and water to give the pure products **4**.

2-(3,3-Dimethyl-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4a**):** Yellow solid; mp 248-250 °C; IR (KBr) 3047, 2920, 2254, 1622, 1598, 1448, 1399, 1215, 1091, 1055, 1027, 999, 752, 689 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.71 (s, 1H, ArH), 8.07 (d, *J* = 7.6 Hz, 1H, ArH), 7.94 (d, *J* = 8.4 Hz, 1H, ArH), 7.88-7.84 (m, 1H, ArH), 7.67-7.63 (m, 1H, ArH), 5.23 (d, *J* = 4.0 Hz,

1H, CH), 5.00 (d, $J = 4.0$ Hz, 1H, CH), 2.81 (d, $J = 18.0$ Hz, 1H, CH), 2.68 (d, $J = 18.0$ Hz, 1H, CH), 2.48 (d, $J = 16.0$ Hz, CH), 2.35 (d, $J = 16.0$ Hz, 1H, CH), 1.16 (s, 3H, CH₃), 1.14 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.1, 169.6, 155.0, 146.0, 141.1, 132.1, 128.6, 128.0, 127.1, 114.4, 113.3, 113.1, 107.7, 50.1, 33.7, 32.3, 31.0, 29.5, 26.5. HRMS calcd for C₂₁H₁₈N₃O₂ [M+H]⁺ 344.1399, found 344.1401.

2-(9-Methoxy-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1H-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4b): Yellow solid; mp 268-270 °C; IR (KBr) 3045, 2896, 2254, 1635, 1613, 1466, 1356, 1238, 1216, 1142, 1112, 1029, 834 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (s, 1H, ArH), 7.84 (d, $J = 9.2$ Hz, 1H, ArH), 7.51-7.48 (m, 1H, ArH), 7.45 (d, $J = 2.4$ Hz, 1H, ArH), 5.20 (d, $J = 4.0$ Hz, 1H, CH), 4.97 (d, $J = 3.6$ Hz, 1H, CH), 3.92 (s, 3H, CH₃O), 2.79 (d, $J = 17.6$ Hz, 1H, CH), 2.65 (d, $J = 17.2$ Hz, 1H, CH), 2.45 (d, $J = 16.4$ Hz, 1H, CH), 2.33 (d, $J = 16.4$ Hz, 1H, CH), 1.15 (s, 3H, CH₃), 1.13 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.2, 169.7, 157.8, 153.4, 141.6, 139.5, 129.4, 128.2, 124.6, 114.4, 113.4, 113.1, 107.5, 106.3, 56.2, 50.1, 33.8, 32.3, 30.9, 29.5, 26.5. HRMS calcd for C₂₂H₂₀N₃O₃ [M+H]⁺ 374.1510, found 374.1498.

2-(9-(*tert*-Butyl)-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1H-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4c): Yellow solid; mp 228-230 °C; IR (KBr) 2960, 2937, 2254, 1642, 1611, 1439, 1394, 1346, 1265, 1236, 1212, 1174, 1145, 1118, 1024, 997, 831 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 (s, 1H, ArH), 8.01-7.89 (m, 3H, ArH), 5.25 (d, $J = 3.6$ Hz, 1H, CH), 4.99 (d, $J = 2.4$ Hz, 1H, CH), 2.81 (d, $J = 18.0$ Hz, 1H, CH), 2.68 (d, $J = 18.0$ Hz, 1H, CH), 2.51 (d, $J = 18.8$ Hz, 1H, CH₂), 2.36 (d, $J = 16.0$ Hz, 1H, CH), 1.41 (s, 9H, (CH₃)₃C), 1.17 (s, 3H, CH₃), 1.16 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 196.0, 169.3, 154.2, 149.2, 143.9, 140.6, 130.6, 127.1, 126.4, 122.7, 113.5, 112.8, 112.6, 107.1, 49.5, 40.5, 34.7, 33.5, 31.8, 30.8, 29.0, 26.0. HRMS calcd for C₂₅H₂₆N₃O₂ [M+H]⁺ 400.2025, found 400.2021.

2-(9-Chloro-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1H-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4d): Yellow solid; mp 264-266 °C; IR (KBr) 2901, 2257, 1637, 1345, 1232, 1212, 1024, 993, 827, 763 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (s, 1H, ArH), 8.25 (d, $J = 2.4$ Hz, 1H, ArH), 7.96 (d, $J = 9.2$ Hz, 1H, ArH), 7.89-7.86 (m, 1H, ArH), 5.23 (d, $J = 4.4$ Hz, 1H, CH), 5.00 (d, $J = 4.0$ Hz, 1H, CH), 2.80 (d, $J = 18.0$ Hz, 1H, CH), 2.67 (d, $J = 18.0$ Hz, 1H, CH), 2.47 (d, $J = 16.4$ Hz, 1H, CH), 2.34 (d, $J = 16.4$ Hz, 1H, CH), 1.15 (s, 3H, CH₃), 1.13 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.0, 169.4, 155.3, 144.5, 140.5, 132.5, 131.4, 130.1, 127.8, 127.2, 115.7, 113.2, 113.0, 107.8, 50.1, 33.7, 32.3, 30.9, 29.5, 26.5. HRMS calcd for C₂₁H₁₇ClN₃O₂ [M+H]⁺ 378.1009, found 378.1010.

2-(1-Oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4e): Yellow solid; mp 272-274 °C; IR (KBr) 2930, 2253, 1656, 1634, 1498, 1240, 1214, 1184, 1048, 1024, 789, 764 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H, ArH), 8.07 (d, *J* = 8.0 Hz, 1H, ArH), 7.94 (d, *J* = 8.4 Hz, 1H, ArH), 7.88-7.84 (m, 1H, ArH), 7.67-7.63 (m, 1H, ArH), 5.14 (d, *J* = 4.0 Hz, 1H, CH), 5.00 (d, *J* = 3.6 Hz, 1H, CH), 2.85-2.82 (m, 2H, CH₂), 2.49-2.43 (m, 2H, CH₂), 2.15-1.97 (m, 2H, CH₂); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.2, 171.1, 155.3, 144.5, 140.4, 132.5, 131.4, 130.1, 127.8, 127.2, 115.7, 113.2, 112.9, 108.8, 36.5, 33.7, 31.0, 27.7, 20.3. HRMS calcd for C₁₉H₁₄N₃O₂ [M+H]⁺ 316.1086, found 316.1096.

2-(9-Methoxy-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4f): Yellow solid; mp 278-280 °C; IR (KBr) 2912, 2254, 1629, 1614, 1504, 1457, 1398, 1358, 1218, 1142, 1025, 1002, 829, 785 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (s, 1H, ArH), 7.84 (d, *J* = 9.2 Hz, 1H, ArH), 7.51-7.48 (m, 1H, ArH), 7.45 (d, *J* = 2.8 Hz, 1H, ArH), 5.11 (d, *J* = 4.0 Hz, 1H, CH), 4.97 (d, *J* = 3.6 Hz, 1H, CH), 3.92 (s, 3H, OCH₃), 2.82 (t, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 6.0, 2H, CH₂), 2.15-2.08 (m, 1H, CH), 2.05-1.96 (m, 1H, CH); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.3, 171.3, 157.8, 153.4, 141.6, 139.4, 129.4, 128.2, 124.6, 114.4, 113.4, 113.0, 108.6, 106.3, 56.2, 36.5, 33.8, 31.0, 27.8, 20.4. HRMS calcd for C₂₀H₁₆N₃O₃ [M+H]⁺ 346.1192, found 346.1198.

2-(9-(*tert*-Butyl)-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4g): Yellow solid; mp 246-248 °C; IR (KBr) 2956, 2931, 2257, 1639, 1504, 1393, 1236, 1211, 1185, 1047, 1023, 995, 831, 763 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (s, 1H, ArH), 8.00-7.97 (m, 1H, ArH), 7.93 (d, *J* = 2.0 Hz, 1H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 5.12 (d, *J* = 3.6 Hz, 1H, CH), 4.97 (d, *J* = 3.6 Hz, 1H, CH), 2.84-2.81 (m, 2H, CH₂), 2.48-2.47 (m, 2H, CH₂), 2.14-1.99 (m, 2H, CH₂), 1.40 (s, 9H, 3 × CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.3, 171.2, 154.7, 149.5, 144.4, 140.9, 131.0, 127.7, 126.9, 123.2, 114.1, 113.4, 113.0, 108.7, 36.5, 35.2, 33.8, 31.3, 31.1, 27.8, 20.4. HRMS calcd for C₂₃H₂₂N₃O₂ [M+H]⁺ 372.1712, found 372.1702.

2-(9-Chloro-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4h): Yellow solid; mp 292-294 °C; IR (KBr) 2895, 2256, 1630, 1486, 1391, 1341, 1234, 1185, 1024, 995, 921, 827 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 (s, 1H, ArH), 8.24 (s, 1H, ArH), 7.96-7.93 (m, 1H, ArH), 7.88-7.84 (m, 1H, ArH), 5.14-5.12 (m, 1H), 5.01-4.96 (m, 1H, CH), 2.89-2.72 (m, 4H, 2 × CH₂), 2.15-2.08 (m, 1H, CH), 2.03-1.96 (m, 1H, CH); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 196.2, 171.1, 155.3, 144.5, 140.4, 132.5, 131.4, 130.1, 127.8, 127.2, 115.7, 113.2, 112.9, 108.8, 36.5, 33.7, 31.0, 27.7, 20.3. HRMS calcd for C₁₉H₁₄N₃O₃ [M+H]⁺ 350.0695, found 337.1162.

2-(1-Oxo-3-phenyl-2,3,4,12-tetrahydro-1H-chromeno[2,3-b]quinolin-12-yl)malononitrile (4i):

Yellow solid; mp 226-228 °C; *dr* = 74:36; IR (KBr) 2936, 2257, 2130, 1636, 1497, 1397, 1240, 1203, 1024, 993, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.75-8.73 (m, 1H, ArH), 8.09 (d, *J* = 8.4 Hz, 1H, ArH), 7.95 (d, *J* = 8.0 Hz, 1H, ArH), 7.89-7.85 (m, 1H, ArH), 7.68-7.64 (m, 1H, ArH), 7.47-7.34 (m, 4H, ArH), 7.31-7.25 (m, 1H, ArH), 5.18-5.13 (m, 1H, CH), 5.08-5.05 (m, 1H, CH), 3.67-3.50 (m, 1H, CH), 3.26-3.13 (m, 1H, CH), 3.06-2.99 (m, 1H, CH), 2.88-2.74 (m, 1H, CH), 2.68-2.63 (m, 1H, CH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 195.6, 195.3, 170.4, 170.0, 162.7, 155.0, 146.0, 142.8, 141.2, 141.0, 132.1, 129.1, 128.6, 128.1, 127.5, 127.1, 114.4, 114.2, 113.3, 113.0, 108.8, 108.6, 43.6, 38.1, 36.2, 34.7, 33.6, 31.2. HRMS calcd for C₂₅H₁₈N₃O₂ [M+H]⁺ 392.1399, found 392.1400.

2-(9-(tert-Butyl)-1-oxo-3-phenyl-2,3,4,12-tetrahydro-1H-chromeno[2,3-b]quinolin-12-yl)malono-

nitrile (4j): Yellow solid; mp 248-250 °C; *dr* = 70:30; IR (KBr) 2963, 2933, 2255, 1638, 1502, 1418, 1366, 1239, 1205, 1123, 1098, 1025, 999, 947, 833, 757 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73-8.72 (m, 1H, ArH), 8.04-7.91 (m, 3H, ArH), 7.50-7.30 (m, 5H, ArH), 5.20-5.15 (m, 1H, CH), 5.09-5.05 (m, 1H, CH), 3.70-3.53 (m, 1H, CH), 3.26-3.16 (m, 1H, CH), 3.08-3.02 (m, 1H, CH), 2.95-2.88 (m, 1H, CH), 2.71-2.66 (m, 1H, CH), 1.44 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 195.6, 195.4, 170.4, 170.0, 154.7, 149.6, 144.5, 142.8, 141.0, 140.8, 131.0, 129.1, 129.0, 127.7, 127.5, 126.9, 123.2, 114.2, 113.9, 113.4, 113.0, 108.5, 43.6, 38.2, 35.2, 35.0, 33.7, 31.3. HRMS calcd for C₂₉H₂₆N₃O₂ [M+H]⁺ 448.2025, found 448.2034.

2-(9-Chloro-1-oxo-3-phenyl-2,3,4,12-tetrahydro-1H-chromeno[2,3-b]quinolin-12-yl)malononitrile

(4k): Yellow solid; mp 270-272 °C; *dr* = 70:30; IR (KBr) 2902, 2256, 1639, 1492, 1454, 1444, 1234, 1200, 1024, 997, 839, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.73-8.71 (m, 1H, ArH), 8.27-7.86 (m, 1H, ArH), 7.98-7.96 (m, 1H, ArH), 7.89-7.86 (m, 1H, ArH), 7.47-7.34 (m, 4H, ArH), 7.31-7.25 (m, 1H, ArH), 5.19-5.14 (m, 1H, CH), 5.08-5.05 (m, 1H, CH), 3.67-3.50 (m, 1H, CH), 3.26-3.11 (m, 1H, CH), 3.06-2.98 (m, 1H, CH), 2.87-2.77 (m, 1H, CH), 2.68-2.63 (m, 1H, CH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 195.5, 195.2, 170.2, 169.9, 162.7, 155.3, 144.5, 142.7, 140.5, 140.3, 132.6, 131.5, 130.1, 129.1, 129.0, 127.8, 127.5, 127.3, 115.7, 115.5, 113.2, 113.0, 108.9, 108.6, 43.6, 38.1, 35.0, 33.6, 31.2. HRMS calcd for C₂₅H₁₇ClN₃O₂ [M+H]⁺ 426.1009, found 426.1019.

2-(1-Oxo-1,2,3,11-tetrahydrocyclopenta[5,6]pyrano[2,3-b]quinolin-11-yl)malononitrile (4l):

Yellow solid; mp >300 °C; IR (KBr) 2927, 2254, 1700, 1647, 1494, 1377, 1217, 1199, 1176, 1115, 1022, 993, 825, 763 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.74 (s, 1H, ArH), 8.07 (d, *J* = 8.0 Hz, 1H, ArH), 7.96 (d, *J* = 8.4 Hz, 1H, ArH), 7.90-7.86 (m, 1H, ArH), 7.69-7.65 (m, 1H, ArH), 5.27 (d, *J* = 3.6 Hz, 1H, CH),

5.06 (d, $J = 3.6$ Hz, 1H, CH), 3.09-3.02 (m, 1H, CH), 2.95-2.89 (m, 1H, CH), 2.71-2.64 (m, 1H, CH), 2.60-2.53 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO- d_6) δ 201.4, 182.7, 155.2, 145.8, 141.9, 132.3, 128.6, 128.1, 127.4, 127.0, 114.0, 113.3, 112.9, 112.1, 33.8, 33.4, 30.9, 26.0. HRMS calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 302.0930, found 302.0955.

2-(8-Methoxy-1-oxo-1,2,3,11-tetrahydrocyclopenta[5,6]pyrano[2,3-*b*]quinolin-11-yl)malononitrile

(4m): Yellow solid; mp 294-296 °C; IR (KBr) 2935, 2255, 1694, 1648, 1615, 1503, 1356, 1328, 1210, 1194, 1178, 1140, 1105, 1048, 993, 822 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (s, 1H, ArH), 7.86 (d, $J = 9.2$ Hz, 1H, ArH), 7.53-7.50 (m, 1H, ArH), 7.45 (d, $J = 2.8$ Hz, 1H, ArH), 5.24 (d, $J = 3.6$ Hz, 1H, CH), 5.05 (s, 1H, CH), 3.93 (s, 3H, CH_3O), 3.07-3.00 (m, 1H, CH), 2.94-2.88 (m, 1H, CH), 2.69-2.62 (m, 1H, CH), 2.59-2.54 (m, 1H, CH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 201.5, 182.7, 158.0, 153.7, 141.5, 140.2, 129.5, 128.2, 124.8, 113.9, 113.4, 112.9, 111.8, 106.2, 56.2, 33.8, 33.4, 30.8, 26.0. HRMS calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 332.1035, found 332.1034.

2-(8-(*tert*-Butyl)-1-oxo-1,2,3,11-tetrahydrocyclopenta[5,6]pyrano[2,3-*b*]quinolin-11-yl)malononitrile

(4n): Yellow solid; mp 282-284 °C; IR (KBr) 2968, 2912, 2255, 1704, 1653, 1608, 1501, 1435, 1415, 1346, 1217, 1205, 1112, 1092, 1049, 838 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 8.70 (s, 1H, ArH), 8.02-7.99 (m, 1H, ArH), 7.92 (d, $J = 2.0$ Hz, 1H, ArH), 7.90 (d, $J = 9.2$ Hz, 1H, ArH), 5.26 (d, $J = 3.6$ Hz, 1H, CH), 5.04 (s, 1H, CH), 3.08-3.02 (m, 1H, CH), 2.95-2.89 (m, 1H, CH), 2.70-2.64 (m, 1H, CH), 2.60-2.55 (m, 1H, CH), 1.40 (s, 9H, $3 \times \text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ 201.0, 182.2, 154.5, 149.5, 143.8, 141.3, 130.8, 127.3, 126.3, 122.8, 122.7, 113.2, 112.9, 112.4, 111.5, 34.8, 33.3, 33.0, 30.8, 30.4, 25.5. HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 358.1556, found 358.1547.

2-(6-Oxo-6,7-dihydrochromeno[3',4':5,6]pyrano[2,3-*b*]quinolin-7-yl)malononitrile (4o):

Yellow solid; mp 274-276 °C; IR (KBr) 2917, 2250, 1701, 1638, 1607, 1493, 1404, 1332, 1244, 1204, 1169, 1151, 1050, 1025, 987, 769, 754 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 8.84 (s, 1H, ArH), 8.15 (d, $J = 8.0$ Hz, 2H, ArH), 8.04 (d, $J = 8.4$ Hz, 1H, ArH), 7.94-7.90 (m, 1H, ArH), 7.86-7.82 (m, 1H, ArH), 7.70 (t, $J = 7.6$ Hz, 1H, ArH), 7.61 (d, $J = 8.4$ Hz, 1H, ArH), 7.57 (t, $J = 8.0$ Hz, 1H, ArH), 5.38 (d, $J = 4.0$ Hz, 1H, CH), 5.34 (d, $J = 3.6$ Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.0, 158.5, 153.7, 152.6, 145.6, 140.8, 134.0, 131.9, 128.3, 127.6, 127.0, 126.9, 125.2, 123.0, 117.0, 113.2, 113.1, 112.7, 112.4, 98.4, 35.2, 30.7. HRMS calcd for $\text{C}_{22}\text{H}_{12}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 366.0879, found 366.0870.

2-(10-Methoxy-6-oxo-6,7-dihydrochromeno[3',4':5,6]pyrano[2,3-*b*]quinolin-7-yl)malononitrile (4p):

Yellow solid; mp 256-260 °C; IR (KBr) 2903, 2254, 1686, 1637, 1609, 1497, 1455, 1353, 1236, 1172,

1113, 1025, 1005, 993, 794, 747 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.69 (s, 1H, ArH), 8.14-8.11 (m, 1H, ArH), 7.94 (d, $J = 9.2$ Hz, 1H, ArH), 7.85-7.81 (m, 1H, ArH), 7.61-7.53 (m, 4H, ArH), 5.35 (d, $J = 3.6$ Hz, 1H, CH), 5.31 (d, $J = 3.6$ Hz, 1H, CH), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 160.5, 159.0, 158.1, 153.1, 152.6, 141.7, 139.6, 134.4, 129.5, 128.6, 125.7, 124.9, 123.4, 117.4, 113.7, 113.6, 113.2, 112.9, 106.4, 98.7, 56.2, 35.7, 30.8. HRMS calcd for $\text{C}_{23}\text{H}_{14}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 396.0984, found 396.098.

2-(10-(*tert*-Butyl)-6-oxo-6,7-dihydrochromeno[3',4':5,6]pyrano[2,3-*b*]quinolin-7-yl)malononitrile

(4q): Yellow solid; mp 282-284 $^\circ\text{C}$; IR (KBr) 2963, 2255, 1702, 1640, 1610, 1497, 1460, 1438, 1396, 1380, 1366, 1271, 1183, 1169, 1150, 1126, 1095, 988, 969, 915, 831 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.82 (s, 1H, ArH), 8.17 (d, $J = 7.6$ Hz, 1H, ArH), 8.09-8.00 (m, 3H, ArH), 7.86 (t, $J = 8.0$ Hz, 1H, ArH), 7.64-7.58 (m, 2H, ArH), 5.36 (d, $J = 18.8$ Hz, 2H, $2 \times \text{CH}$), 1.45 (s, 9H, $3 \times \text{CH}_3$); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 160.5, 158.9, 153.9, 153.1, 150.0, 144.5, 141.1, 134.5, 131.4, 127.7, 127.1, 125.7, 123.4, 117.4, 113.7, 113.2, 112.9, 98.8, 35.8, 35.3, 31.3, 31.9. HRMS calcd for $\text{C}_{26}\text{H}_{20}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 422.1510, found 422.1505.

2-(10-Chloro-6-oxo-6,7-dihydrochromeno[3',4':5,6]pyrano[2,3-*b*]quinolin-7-yl)malononitrile (4r):

Yellow solid; mp 284-286 $^\circ\text{C}$; IR (KBr) 2903, 2256, 1689, 1642, 1604, 1577, 1417, 1392, 1344, 1272, 1206, 1119, 1050, 1024, 991, 930, 823, 767 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.82 (s, 1H, ArH), 8.32 (d, $J = 2.4$ Hz, 1H, ArH), 8.14-8.11 (m, 1H, ArH), 8.05 (d, $J = 9.2$ Hz, 1H, ArH), 7.92-7.90 (m, 1H, ArH), 7.86-7.82 (m, 1H, ArH), 7.61 (d, $J = 8.4$ Hz, 1H, ArH), 7.59-7.55 (m, 1H, ArH), 5.38 (d, $J = 3.6$ Hz, 1H, CH), 5.34 (d, $J = 3.2$ Hz, 1H, CH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 159.9, 158.3, 154.0, 152.6, 144.1, 140.1, 134.0, 132.4, 131.4, 129.7, 127.6, 126.9, 125.2, 122.9, 116.9, 114.4, 113.1, 112.6, 112.4, 98.4, 35.2, 30.3. HRMS calcd for $\text{C}_{22}\text{H}_9\text{ClN}_3\text{O}_3$ $[\text{M}-\text{H}]^+$ 398.0332, found 398.0330.

2-(3-Methyl-1-oxo-1,12-dihydropyrano[3',4':5,6]pyrano[2,3-*b*]quinolin-12-yl)malononitrile (4s):

Yellow solid; mp 228-230 $^\circ\text{C}$; IR (KBr) 2895, 2255, 1707, 1647, 1589, 1488, 1439, 1399, 1346, 1256, 1234, 1195, 1166, 996, 841, 793 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.76 (s, 1H, ArH), 8.11 (d, $J = 8.0$ Hz, 1H, ArH), 7.96 (d, $J = 8.4$ Hz, 1H, ArH), 7.91-7.87 (m, 1H, ArH), 7.69-7.65 (m, 1H, ArH), 6.64 (s, 1H, ArH), 5.31 (d, $J = 4.0$ Hz, 1H, CH), 5.18 (d, $J = 3.6$ Hz, 1H, CH), 2.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 165.4, 163.8, 162.1, 154.3, 146.0, 141.2, 132.3, 128.6, 128.0, 127.3, 127.2, 113.7, 113.2, 112.8, 99.5, 95.3, 35.1, 30.7, 20.1. HRMS calcd for $\text{C}_{19}\text{H}_{12}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 330.0879, found 330.0875.

2-(9-Methoxy-3-methyl-1-oxo-1,12-dihydropyrano[3',4':5,6]pyrano[2,3-*b*]quinolin-12-yl)malononitrile (4t): Yellow solid; mp 270-272 °C; IR (KBr) 2896, 2257, 1706, 1646, 1590, 1505, 1364, 1243, 1024, 993, 827, 764 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (s, 1H, ArH), 7.86 (d, *J* = 9.2 Hz, 1H, ArH), 7.53-7.48 (m, 2H, ArH), 6.62 (s, 1H, ArH), 5.29 (d, *J* = 3.2 Hz, 1H, CH), 5.15 (d, *J* = 2.4 Hz, 1H, CH), 3.93 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 165.2, 163.8, 162.2, 158.0, 152.6, 141.7, 139.5, 129.4, 128.3, 124.8, 113.6, 113.2, 112.9, 106.3, 99.5, 95.1, 56.2, 35.1, 30.6, 20.0. HRMS calcd for C₂₀H₁₄N₃O₄ [M+H]⁺ 360.0984, found 360.0974.

2-(9-(*tert*-Butyl)-3-methyl-1-oxo-1,12-dihydropyrano[3',4':5,6]pyrano[2,3-*b*]quinolin-12-yl)malononitrile (4u): Yellow solid; mp 280-282 °C; IR (KBr) 2926, 2256, 1699, 1656, 1498, 1435, 1359, 1269, 1256, 1236, 1194, 1024, 991, 829 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 (s, 1H, ArH), 8.05-8.03 (m, 1H, ArH), 7.99 (d, *J* = 2.0 Hz, 1H, ArH), 7.92 (d, *J* = 8.8 Hz, 1H, ArH), 6.66 (s, 1H, ArH), 5.32 (d, *J* = 3.6 Hz, 1H, CH), 5.17 (d, *J* = 3.6 Hz, 1H, CH), 2.38 (s, 3H, CH₃), 1.43 (s, 9H, 3 × CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 165.3, 163.8, 162.1, 154.0, 149.8, 144.5, 141.0, 131.2, 127.7, 126.9, 123.3, 113.4, 113.2, 112.8, 99.4, 95.2, 35.2, 35.2, 31.3, 30.7, 20.0. HRMS calcd for C₂₃H₂₀N₃O₃ [M+H]⁺ 386.1505, found 386.1505.

2-(9-Chloro-3-methyl-1-oxo-1,12-dihydropyrano[3',4':5,6]pyrano[2,3-*b*]quinolin-12-yl)malononitrile (4v): Yellow solid; mp >300 °C; IR (KBr) 2895, 2254, 1709, 1644, 1592, 1369, 1263, 1039, 894 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 (s, 1H, ArH), 8.29 (s, 1H, ArH), 7.97 (d, *J* = 9.2 Hz, 1H, ArH), 7.89 (d, *J* = 9.2 Hz, 1H, ArH), 6.65 (s, 1H, ArH), 5.31 (d, *J* = 3.6 Hz, 1H, CH), 5.18 (d, *J* = 2.4 Hz, 1H, CH), 2.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 165.5, 163.7, 162.0, 154.6, 144.6, 140.5, 132.8, 131.7, 130.1, 127.9, 127.3, 115.0, 113.1, 112.8, 99.4, 95.3, 35.1, 31.2, 20.1. HRMS calcd for C₁₉H₁₁ClN₃O₃ [M+H]⁺ 364.0489, found 364.0484.

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