HETEROCYCLES, Vol. 96, No. 11, 2018, pp. 1977 - 1990. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 26th September, 2018, Accepted, 1st November, 2018, Published online, 20th November, 2018
DOI: 10.3987/COM-18-13990

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

Wei Lin,[a,b] Mengye Zhang,[a] Ning Wang,[a] Wentao Xu,[a] and Daqing Shi[a]*

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, Jiangsu, P. R. China. E-mail: dqshi@suda.edu.cn [b]School of Chemical and Environmental Engineering, Jiangsu Technology of University, Changzhou 213001, P. R. China

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.

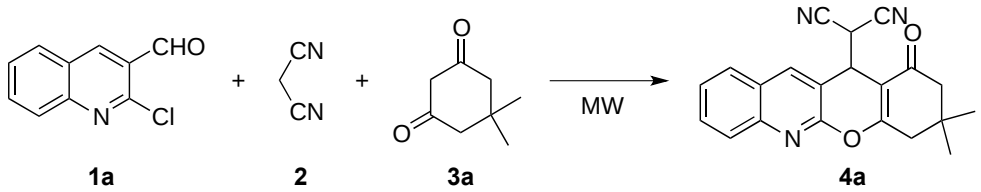
Quinoline scaffolds are interesting synthetic targets because these compounds possess a broad spectrum of biological activities, including anticancer,[1] antibacterial,[2] antimalarial,[3] anti-inflammatory,[4] antitumor,[5] anti-HIV,[6] antiallergic,[7] antidepressant,[8] and antiproliferative activities.[9] Additionally, some pyrano-quinoline 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, $HOCH_2CH_2OH$, DMF, and H_2O (entries 1-7, Table 1). To identify the optimum reaction temperature, the reaction was carried out at 80, 90, 100 and 110 ºC, 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 ºC. 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]



1a **2** **3a** **4a**

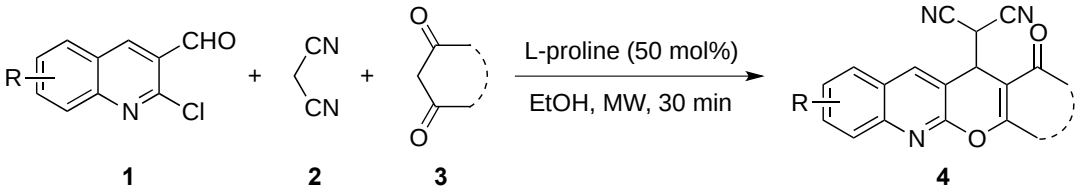
Entry	Solvent	Catalyst (mol%)	*T* (°C)	Time (min)	Yield[b] (%)
1	EtOH	no	100	20	43
2	MeCN	no	100	20	24
3	THF	no	100	20	24
4	toluene	no	100	20	15
5	$HOCH_2CH_2OH$	no	100	20	34
6	DMF	no	100	20	11
7	H_2O	no	100	20	18
8	EtOH	no	80	20	12
9	EtOH	no	90	20	28
10	EtOH	no	110	20	37
11	EtOH	no	100	10	36
12	EtOH	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_2CO_3 (50)	100	30	30
17	EtOH	Na_2CO_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

[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol), solvent (5 mL). [b]Yields was determined by HPLC-MS.

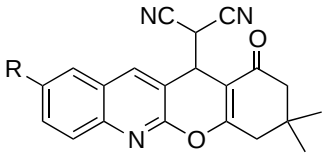
With the optimal reaction conditions in hand, the substrate scope of the transformation was then evaluated using four 6-substituted 2-chloroquinoline-3-carbaldehydes **1**, and seven 1,3-dicarbonyl compounds **3**. The corresponding functionalized pyrano[2,3-*b*]quinoline derivatives were obtained, and 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, ^{1}H NMR, and ^{13}C

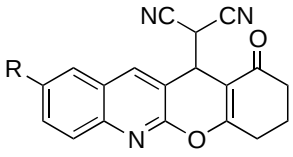
NMR spectroscopies, and HRMS analysis. The structure of compound **4b** was further confirmed by X-ray diffraction analysis (Figure 1).



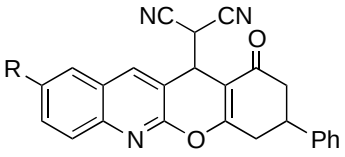
1 **2** **3** **4**



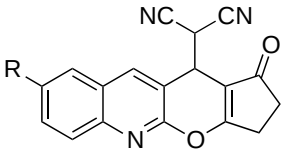
4a, 71%, R = H
4b, 74%, R = OMe
4c, 75%, R = *t*-Bu
4d, 70%, R = Cl



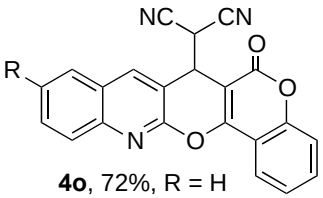
4e, 75%, R = H
4f, 73%, R = OMe
4g, 73%, R = *t*-Bu
4h, 68%, R = Cl



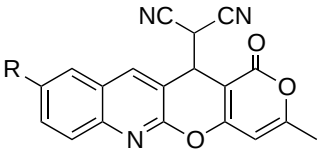
4i, 64%, R = H
4j, 67%, R = *t*-Bu
4k, 61%, R = Cl



4l, 70%, R = H
4m, 69%, R = OMe
4n, 72%, R = *t*-Bu



4o, 72%, R = H
4p, 75%, R = OMe
4q, 73%, R = *t*-Bu
4r, 69%, R = Cl



4s, 65%, R = H
4t, 67%, R = OMe
4u, 63%, R = *t*-Bu
4v, 62%, R = Cl

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

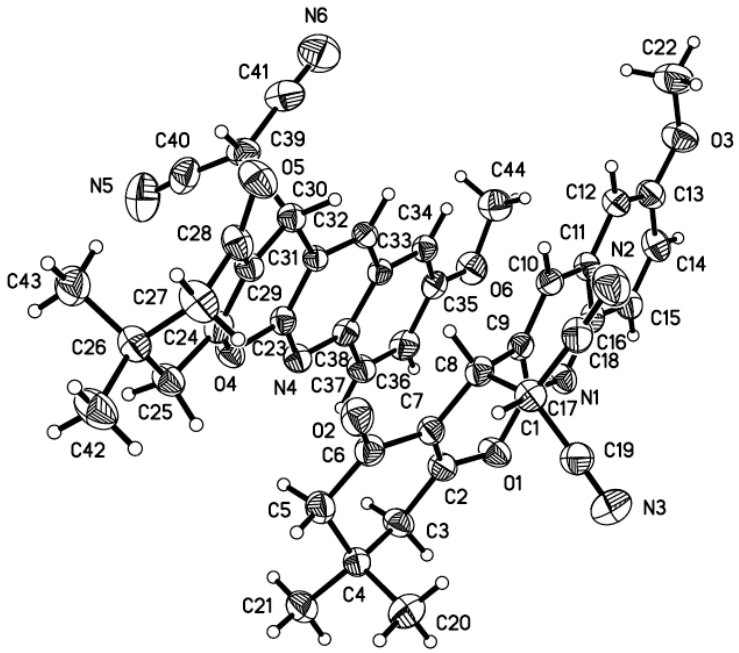
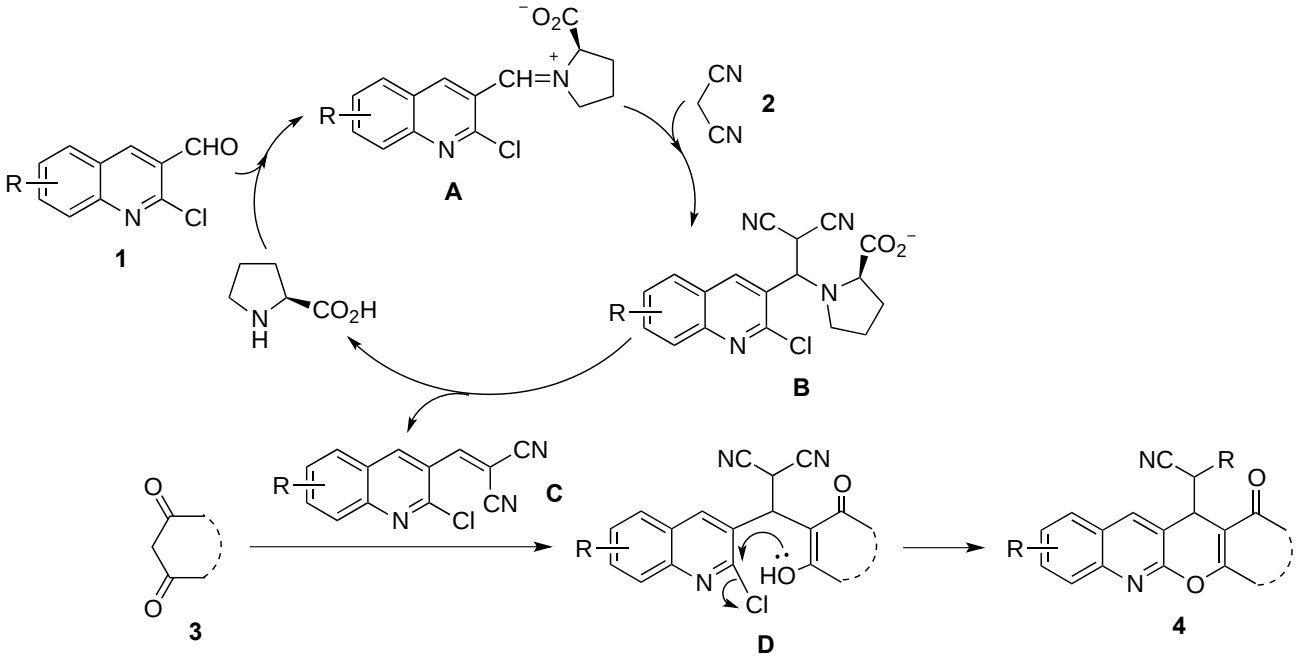


Figure 1. The crystal structure of compound **4b**

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 ± 0.01 μM, 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 ± 0.1 μM, and 3.4 ± 0.1 μM, 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}. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz or Invoa-300 MHz spectrometer in 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 ºC 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 ºC; IR (KBr) 3047, 2920, 2254, 1622, 1598, 1448, 1399, 1215, 1091, 1055, 1027, 999, 752, 689 cm^{-1}; ^{1}H NMR (400 MHz, 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, CH_3), 1.14 (s, 3H, CH_3); ^{13}C 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 $C_{21}H_{18}N_3O_2$ $[M+H]^+$ 344.1399, found 344.1401.

2-(9-Methoxy-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4b): Yellow solid; mp 268-270 ºC; IR (KBr) 3045, 2896, 2254, 1635, 1613, 1466, 1356, 1238, 1216, 1142, 1112, 1029, 834 cm^{-1}; ^{1}H 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, CH_3O), 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, CH_3), 1.13 (s, 3H, CH_3); ^{13}C 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 $C_{22}H_{20}N_3O_3$ $[M+H]^+$ 374.1510, found 374.1498.

2-(9-(*tert*-Butyl)-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4c): Yellow solid; mp 228-230 ºC; IR (KBr) 2960, 2937, 2254, 1642, 1611, 1439, 1394, 1346, 1265, 1236, 1212, 1174, 1145, 1118, 1024, 997, 831 cm^{-1}; ^{1}H 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, CH_2), 2.36 (d, *J* = 16.0 Hz, 1H, CH), 1.41 (s, 9H, $(CH_3)_3C$), 1.17 (s, 3H, CH_3), 1.16 (s, 3H, CH_3); ^{13}C 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 $C_{25}H_{26}N_3O_2$ $[M+H]^+$ 400.2025, found 400.2021.

2-(9-Chloro-3,3-dimethyl-1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4d): Yellow solid; mp 264-266 ºC; IR (KBr) 2901, 2257, 1637, 1345, 1232, 1212, 1024, 993, 827, 763 cm^{-1}; ^{1}H 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, CH_3), 1.13 (s, 3H, CH_3); ^{13}C 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 $C_{21}H_{17}ClN_3O_2$ $[M+H]^+$ 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 ºC; 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, CH_2), 2.49-2.43 (m, 2H, CH_2), 2.15-1.97 (m, 2H, CH_2); ^{13}C 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 $C_{19}H_{14}N_3O_2$ $[M+H]^+$ 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 ºC; 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, OCH_3), 2.82 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.0, 2H, CH_2), 2.15-2.08 (m, 1H, CH), 2.05-1.96 (m, 1H, CH); ^{13}C 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 $C_{20}H_{16}N_3O_3$ $[M+H]^+$ 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 ºC; 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, CH_2), 2.48-2.47 (m, 2H, CH_2), 2.14-1.99 (m, 2H, CH_2), 1.40 (s, 9H, 3 × CH_3); ^{13}C 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 $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 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 ºC; 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 × CH_2), 2.15-2.08 (m, 1H, CH), 2.03-1.96 (m, 1H, CH); ^{13}C 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 $C_{19}H_{14}N_3O_3$ $[M+H]^+$ 350.0695, found 337.1162.

2-(1-Oxo-3-phenyl-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4i): Yellow solid; mp 226-228 ºC; *dr* = 74:36; IR (KBr) 2936, 2257, 2130, 1636, 1497, 1397, 1240, 1203, 1024, 993, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C 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 $C_{25}H_{18}N_3O_2$ $[M+H]^+$ 392.1399, found 392.1400.

2-(9-(*tert*-Butyl)-1-oxo-3-phenyl-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4j): Yellow solid; mp 248-250 ºC; *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, $C(CH_3)_3$); ^{13}C 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 $C_{29}H_{26}N_3O_2$ $[M+H]^+$ 448.2025, found 448.2034.

2-(9-Chloro-1-oxo-3-phenyl-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitrile (4k): Yellow solid; mp 270-272 ºC; *dr* = 70:30; IR (KBr) 2902, 2256, 1639, 1492, 1454, 1444, 1234, 1200, 1024, 997, 839, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C 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 $C_{25}H_{17}ClN_3O_2$ $[M+H]^+$ 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 ºC; 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 $C_{19}H_{14}N_3O_3$ $[M+H]^+$ 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 ºC; IR (KBr) 2935, 2255, 1694, 1648, 1615, 1503, 1356, 1328, 1210, 1194, 1178, 1140, 1105, 1048, 993, 822 cm^{-1}; ^{1}H 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 $C_{19}H_{14}N_3O_3$ $[M+H]^+$ 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 ºC; IR (KBr) 2968, 2912, 2255, 1704, 1653, 1608, 1501, 1435, 1415, 1346, 1217, 1205, 1112, 1092, 1049, 838 cm^{-1}; ^{1}H 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 × 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 $C_{22}H_{20}N_3O_2$ $[M+H]^+$ 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 ºC; IR (KBr) 2917, 2250, 1701, 1638, 1607, 1493, 1404, 1332, 1244, 1204, 1169, 1151, 1050, 1025, 987, 769, 754 cm^{-1}; ^{1}H 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 $C_{22}H_{12}N_3O_3$ $[M+H]^+$ 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 ºC; IR (KBr) 2903, 2254, 1686, 1637, 1609, 1497, 1455, 1353, 1236, 1172,

1113, 1025, 1005, 993, 794, 747 cm^{-1}; ^1H NMR (400 MHz, 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, 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 $C_{23}H_{14}N_3O_4$ $[M+H]^+$ 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 ºC; 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, 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 × CH), 1.45 (s, 9H, 3 × CH_3); ^{13}C NMR (75 MHz, 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 $C_{26}H_{20}N_3O_3$ $[M+H]^+$ 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 ºC; 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, 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, 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 $C_{22}H_9ClN_3O_3$ $[M-H]^+$ 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 ºC; IR (KBr) 2895, 2255, 1707, 1647, 1589, 1488, 1439, 1399, 1346, 1256, 1234, 1195, 1166, 996, 841, 793 cm^{-1}; ^1H NMR (400 MHz, 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, 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 $C_{19}H_{12}N_3O_3$ $[M+H]^+$ 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 ºC; 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, OCH_3), 2.35 (s, 3H, CH_3); ^{13}C 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 $C_{20}H_{14}N_3O_4$ $[M+H]^+$ 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 ºC; 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, CH_3), 1.43 (s, 9H, 3 × CH_3); ^{13}C 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 $C_{23}H_{20}N_3O_3$ $[M+H]^+$ 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 ºC; 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, CH_3); ^{13}C 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 $C_{19}H_{11}ClN_3O_3$ $[M+H]^+$ 364.0489, found 364.0484.

ACKNOWLEDGEMENTS

This work was supported by the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 15KJA150006) and a project fund from the Priority Academic Project Development of Jiangsu Higher Education Institutions.

REFERENCES

1. T. Nakamura, M. Oka, K. Aizawa, H. Soda, M. Fukuda, K. Terashi, K. Ikeda, Y. Mizuta, Y. Noguchi, Y. Kimura, T. Tsuruo, and S. Kohno, *Biochem. Biophys. Res. Commun.*, 1999, **255**, 618.
2. (a) N. Fokialakis, P. Magiatis, I. Chinou, S. Mitaku, and F. Tillequin, *Chem. Pharm. Bull.*, 2002, **50**,

413; (b) A. A. Bekhit, O. A. El-Sayed, E. Aboulmaged, and J. Y. Park, *Eur. J. Med. Chem.*, 2004, **39**, 249.

3. (a) A. Ryckebusch, R. Deprez-Poulain, L. Maes, M.-A. Debreu-Fontaine, E. Mouray, P. Grellier, and C. Sergheraert, *J. Med. Chem.*, 2003, **46**, 542; (b) Z. Xiao, N. C. Waters, C. L. Woodard, Z. Li, and P.-K. Li, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2875.
4. E. W. Chia, A. N. Pearce, M. V. Berridge, L. Larsen, N. B. Perry, C. E. Sansom, C. A. Godfrey, L. R. Hanton, G.-L. Lu, M. Walton, W. A. Denny, V. L. Webb, B. R. Copp, and J. L. Harper, *Bioorg. Med. Chem.*, 2008, **16**, 9432.
5. S. C. Kuo, H. Z. Lee, J. P. Juang, Y. T. Lin, T. S. Wu, J. J. Chang, D. Lednicer, K. D. Paull, C. M. Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem.*, 1993, **36**, 1146.
6. L. Strekowski, J. L. Mokrosz, V. A. Honkan, A. Czarny, M. T. Cegla, R. L. Wydra, S. E. Patterson, and R. F. Schinazi, *J. Med. Chem.*, 1991, **34**, 1739.
7. H. Cairns, D. Cox, K. J. Gould, A. H. Ingall, and J. L. Suschitzky, *J. Med. Chem.*, 1985, **28**, 1832.
8. Y. Oshiro, Y. Sakurai, S. Sato, N. Kurahashi, T. Tanaka, T. Kikuchi, K. Tottori, Y. Uwahodo, T. Miwa, and T. Nishi, *J. Med. Chem.*, 2000, **43**, 177.
9. P. Fossa, L. Mosti, G. Menozzi, C. Marzano, F. Baccichetti, and F. Bordin, *Bioorg. Med. Chem.*, 2002, **10**, 743.
10. (a) K. Faber, H. StÚckler, and T. Kappe, *J. Heterocycl. Chem.*, 1984, **21**, 1177; (b) N. Yamada, S. Kadowaki, K. Takahashi, and K. Umezu, *Biochem. Pharmacol.*, 1992, **44**, 1211; (c) M. Sekar and K. J. R. Prasad, *J. Nat. Prod.*, 1998, **61**, 294.
11. (a) P. Kalita, B. Baruah, and P. J. Bhuyan, *Tetrahedron Lett.*, 2006, **47**, 7779; (b) J. Marco-Contelles, R. León, M. G. López, A. G. García, and M. Villarroya, *Eur. J. Med. Chem.*, 2006, **41**, 1464; (c) D. Xiang, X. Xin, X. Liu, S. Kumar, and D. Dong, *Synlett*, 2011, 2187; (d) M. Eghtedari, Y. Sarrafi, H. Nadri, M. Mahdavi, A. Moradi, F. H. Moghadam, S. Emami, L. Firoozpour, A. Asadipour, O. Sabzevari, and A. Foroumadi, *Eur. J. Med. Chem.*, 2017, **128**, 237; (e) P. Mosset, M. Laabassi, R. Boulcina, and F. Guenfoud, *Lett. Org. Chem.*, 2014, **11**, 736; (f) R. Velmurugan, *Indian J. Heterocycl. Chem.*, 2010, **20**, 73.
12. (a) J. Sun, Y. Sun, H. Gong, Y.-J. Xie, and C.-G. Yan, *Org. Lett.*, 2012, **14**, 5172; (b) M. Li, H. Cao, Y. Wang, X.-L. Lv, and L.-R. Wen, *Org. Lett.*, 2012, **14**, 3470; (c) Z. Xun, X. Feng, J. Wang, D. Shi, and Z. Huang, *Chin. J. Chem.*, 2016, **34**, 696; (d) X. Feng, J.-J. Wang, Z. Xun, J.-J. Zhang, Z.-B. Huang, and D.-Q. Shi, *Chem. Commun.*, 2015, **51**, 1528; (e) W. Lin, Y.-X. Zheng, Z. Xun, Z.-B. Huang, and D.-Q. Shi, *ACS Comb. Sci.*, 2017, **19**, 708; (f) G. Yang, G. Li, J. Huang, Z. Tang, and J. Zhao, *Org. Biomol. Chem.*, 2017, **15**, 10167; (g) Y. Li, X. Gao, Y. Liu, and J.-P. Wan, *Org. Biomol. Chem.*, 2017, **15**, 9585; (h) Y. Zhang, J. Sun, G.-L. Shen, and C.-G. Yan, *Org. Biomol. Chem.*, 2017,

15, 8072.

13. R. M. Singh and A. Srivastava, *Indian J. Chem.*, 2005, **44B**, 1868.
14. S. Paul, M. Gupta, R. Gupta, and A. Loupy, *Tetrahedron Lett.*, 2001, **42**, 3827.
15. A. Chandra, B. Singh, R. S. Khanna, and R. M. Singh, *J. Org. Chem.*, 2009, **74**, 5664.
16. M. K. Singh, A. Chandra, B. Singh, and R. M. Singh, *Tetrahedron Lett.*, 2007, **48**, 5987.
17. M. Gupta, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4919.
18. V. Nadaraj and S. T. Selvi, *J. Chem. Pharm. Res.*, 2012, **4**, 2850.
19. B. Singh, A. Chandra, S. Upadhyay, R. M. Singh, M. C. Puerta, and P. Valerga, *Tetrahedron Lett.*, 2008, **49**, 6423.
20. (a) L. Fu, W. Lin, M.-H. Hu, X.-C. Liu, Z.-B. Huang, and D.-Q. Shi, *ACS Comb. Sci.*, 2014, **16**, 238; (b) L. Fu, X. Feng, J.-J. Wang, Z. Xun, J.-D. Hu, J.-J. Zhang, Y.-W. Zhao, Z.-B. Huang, and D.-Q. Shi, *ACS Comb. Sci.*, 2015, **17**, 24.