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Efficient Synthesis and Evaluation of Antitumor Activities of Novel Functionalized 1,8-Naphthyridine Derivatives

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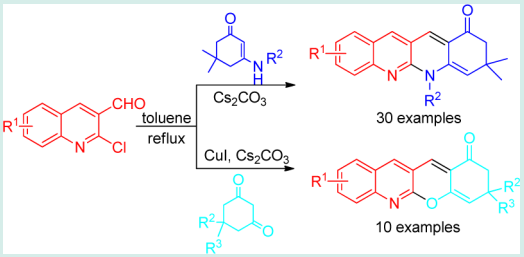
Supporting Information

ABSTRACT: An efficient synthesis of novel functionalized 1,8-naphthyridine and chromeno[2,3-*b*]quinoline derivatives via cascade reaction of 2-chloroquinoline-3-carbaldehyde and enaminones or cyclic 1,3-dicarbonyl compounds was developed. All of the 1,8-naphthyridine derivatives synthesized were evaluated for their antiproliferative properties in vitro against cancer cells and several compounds were found to have high activities.



KEYWORDS: *1,8-naphthyridine, chromeno[2,3-b]quinoline, cascade reaction, antitumor activity*

INTRODUCTION

Nitrogen-containing heterocyclic compounds have been widely used in pharmaceuticals, and designing novel heterocyclic motifs has become an increasingly urgent mission for chemists and biologists.[1] Among them, 1,8-naphthyridine scaffolds are interesting synthetic targets because these compounds possess a wide spectrum of biological activities (Figure 1), including antibacterial,[2] anti-inflammatory,[3] antitumor,[4] antimalarial,[5] antiproliferative,[6] antihypertensive,[7] and antioxidant activities.[8] Additionally, some 1,8-naphthyridine derivatives have been designed and developed as fluorescent dyes,[9] and sensors[10] because of their outstanding optical properties. Although several methods have been reported in the literature for the construction of 1,8-naphthyridine building blocks,[11] these methods invariably require long multistep process and provide low yields of the desired product. Therefore, there is an urgent need for the discovery of new and efficient methods for the construction of these complex molecules using readily available starting materials.[12]

The development of concise and effective protocols for the construction of structurally complex molecules with biological activities from readily available starting materials is a major challenge in both academia and the pharmaceutical industry. One of the most promising approaches to this type of efficient synthesis relies on the use of cascade (domino) reactions. Cascade reactions are one-pot transformations in which more than one synthetic step combine together in the same reaction vessel to give a final complex product. Obviation of the need for isolation and purification of the intermediates results in maximization of yields, saving time and energy, and reduction of waste, and thus renders the protocol ecofriendly.[13] For these reasons, the cascade reaction has been used as a powerful tool for the construction of compound libraries.[14]

2-Chloroquinoline-3-carbaldehydes, which can be prepared form the reaction of *N*-phenylacetamide with DMF and $POCl_3$,[15] are important synthons used for the synthesis of a variety of heterocyclic systems like pyrazolo[3,4-*b*]quinolones,[16] pyrano[4,3-*b*]quinolones,[17] quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*]-[1,2,4]triazepines,[18] isoxazolo[5,4-*b*]quinolones,[19] and benzo[*g*]naphtho[*b*][1,8]naphthyridines.[20] As part of our ongoing research into the development of heterocycle synthesis using domino reactions,[21] we report an efficient synthesis of functionalized 1,8-naphthyridine and chromeno[2,3-*b*]quinoline derivatives using substituted 2-chloroquinoline-3-carbaldehyde as starting material.

RESULTS AND DISCUSSION

Initially, we optimized the reaction conditions with 2-chloroquinoline-3-carbaldehyde **1**{*1*} and 5,5-dimethyl-3-(*p*-tolylamino)cyclohex-2-enone **2**{*1*}. The effects of solvents, bases, and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that the reaction could not proceed in ethanol under catalyst-free conditions (Table 1, entry 1). Pleasingly, when the reaction was conducted in the presence of Cs_2CO_3 (2 equiv) in ethanol, the target compound **3**{*1,1*} was obtained in 46% yield (Table 1, entry 2). To improve the yield, different solvents were evaluated. The results revealed that toluene provided much better results than ethanol, DMF, THF, $CHCl_3$, CH_3CN, and H_2O (Table 1, entries 2−8). Several other bases were then evaluated for their catalytic efficiency in this reaction. In all cases, two equiv of base was used and the reaction was carried out in toluene at reflux temperature.

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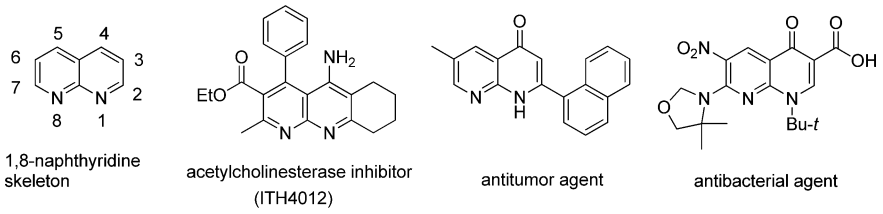
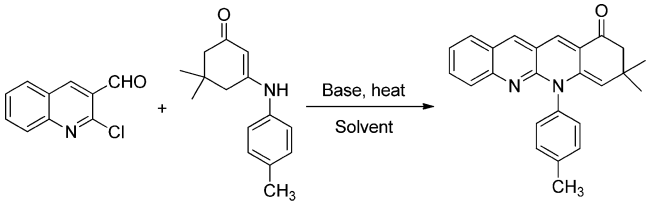


Figure 1. Some biologically important compounds containing the 1,8-naphthyridine skeletons.

Table 1. Optimization of Reaction Conditions for the Synthesis of Compound 3{*1,1*}[a]



1{*1*} 2{*1*} 3{*1,1*}

entry	solvent	base (equiv)	*T* (°C)	time (h)	yield (%)[b]
1	EtOH	no	reflux	2	trace
2	EtOH	Cs_2CO_3 (2)	reflux	0.5	46
3	DMF	Cs_2CO_3 (2)	120	3.5	52
4	THF	Cs_2CO_3 (2)	reflux	2.5	57
5	$CHCl_3$	Cs_2CO_3 (2)	reflux	1.4	55
6	CH_3CN	Cs_2CO_3 (2)	reflux	2.5	42
7	H_2O	Cs_2CO_3 (2)	90	2	trace
8	toluene	Cs_2CO_3 (2)	reflux	0.7	92
9	toluene	K_2CO_3 (2)	reflux	1.5	32
10	toluene	NaOH (2)	reflux	1.5	41
11	toluene	Et_3N (2)	reflux	1.5	trace
12	toluene	pyridine (2)	reflux	1.5	29
13	toluene	Cs_2CO_3 (2)	40	0.7	12
14	toluene	Cs_2CO_3 (2)	60	0.7	27
15	toluene	Cs_2CO_3 (2)	80	0.7	62
16	toluene	Cs_2CO_3 (2)	100	0.7	85

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

The results indicated that Cs_2CO_3 provided a superior catalytic effect to K_2CO_3, NaOH, Et_3N, and pyridine (Table 1, entries 8−12). To identify the optimum reaction temperature, the reaction was carried out at 40, 60, 80 and 100 °C and reflux temperature, providing the desired product in yields of 12%, 27%, 62%, 85%, and 92% (Table 1, entries 13−16 and 8), respectively. So, the best reaction temperature is at reflux temperature.

The optimized reaction conditions were then tested for library construction with nine 2-chloroquinoline-3-carbaldehydes **1**{*1*−*9*}, and 12 enaminones **2**{*1*−*12*} (Figure 2). The corresponding functionalized dibenzo[*b*,*g*][1,8]naphthyridin-1(5*H*)-one **3** were obtained in good yields at refluxing temperature in toluene in the presence of Cs_2CO_3 (2 equiv). The results are summarized in Table 2. It was also found that phenyl groups bearing either electron-withdrawing (such as fluoro, chloro, bromo, and nitro groups) or electron-donating groups (such as methyl, methoxy, ethoxy, *tert*-butyl, and *iso*-propyl groups) on the enaminone ring, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (75%−87%).

To expand the scope of the current method, dimedone (5,5-dimethylcyclohexane-1,3-dione) (**4**{*1*}) was examined as a replacement for the enaminones (**2**) (Scheme 1). Surprisingly, this reaction could not proceed under the optimized conditions. Pleasingly, when 20 mol % CuI was added, the reaction could proceed and the target compound **5**{*1,1*} was obtained in 62% yield. When the ratio of **1**{*1*} and **4**{*1*} was improved to 1:1.5, the yield of product **5**{*1,1*} was reached 87%. These optimized reaction conditions were then tested for library construction with eight 2-chloroquinoline-3-carbaldehydes **1** and substituted cyclohexane-1,3-dione **4**. The corresponding chromeno[2,3-*b*]quinoline derivatives **5** were obtained in excellent yields (85%−94%). The results are summarized in Table 3.

Interestingly, when the reaction of 2-chloroquinoline-3-carbaldehyde (**3**{*1*}) with dimedone (**4**{*1*}) in ethanol in the presence of Et_3N, the desired product **5**{*1,1*} was not obtained. HPLC analysis of the product mixture; however, indicated that most of the starting materials had been consumed by the reaction with the formation of a new product, which was subsequently identified as 9-(quinolin-3-yl)hexahydroxanthene-1,8-dione **6**{*1,1*}. This shows that the reaction proceeded in a different direction when the reaction conditions were changed. Based on this result, a series of 9-(quinolin-3-yl)hexahydroxanthene-1,8-dione derivatives **6** has been synthesized (Table 4).

The structures of all products **3**, **5** and **6** were characterized using IR, ^1H NMR, ^{13}C NMR spectroscopies and HRMS analysis. The structures of compound **5**{*1,1*} and **6**{*8,1*} were further confirmed by X-ray diffraction analysis[22] (Figures 3 and 4).

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compound **3** could be explained by the reaction sequence in Scheme 2. Initially, the aza-ene addition of enaminones **2** to 2-chloroquinoline-3-carbaldehyde **1** catalyzed by base lead to the formation intermediate **B**, based on the imine-enamine tautomerization of intermediate **A**. Intermediate **B** would then undergo an intramolecular cyclization to give intermediate **C**. The product **3** was obtained by the elimination of water from intermediate **C**.

All of the 1,8-naphthyridine derivatives synthesized were tested for their antitumor activities against hepatic carcinoma (HepG2) cells in vitro. Initially, the inhibitory rates were obtained for all tested compounds. Some compounds with inhibitory rates greater than 50% were tested further to determined the IC_{50} value. The results are shown in Table 5. The most active compounds were **3**{*7,12*}, **3**{*7,3*}, **3**{*7,1*}, and **3**{*7,2*}, with IC_{50} values of 1.9 ± 0.1, 6.4 ± 2.2, 4.8 ± 0.6, and 5.7 ± 0.7 μM, respectively.

CONCLUSION

In summary, we have develpoed an efficient method for the synthesis of pharmacologically important, functionalized 1,8-naphthyridine derivatives by cascade reaction of 2-chloroquinoline-3-carbaldehyde and enaminones in the presence of Cs_2CO_3. This method has the advantages of excellent yields, mild reaction conditions, short reaction times and high selectivity. Overall, our study suggests that the 1,8-naphthyridine derivatives presented

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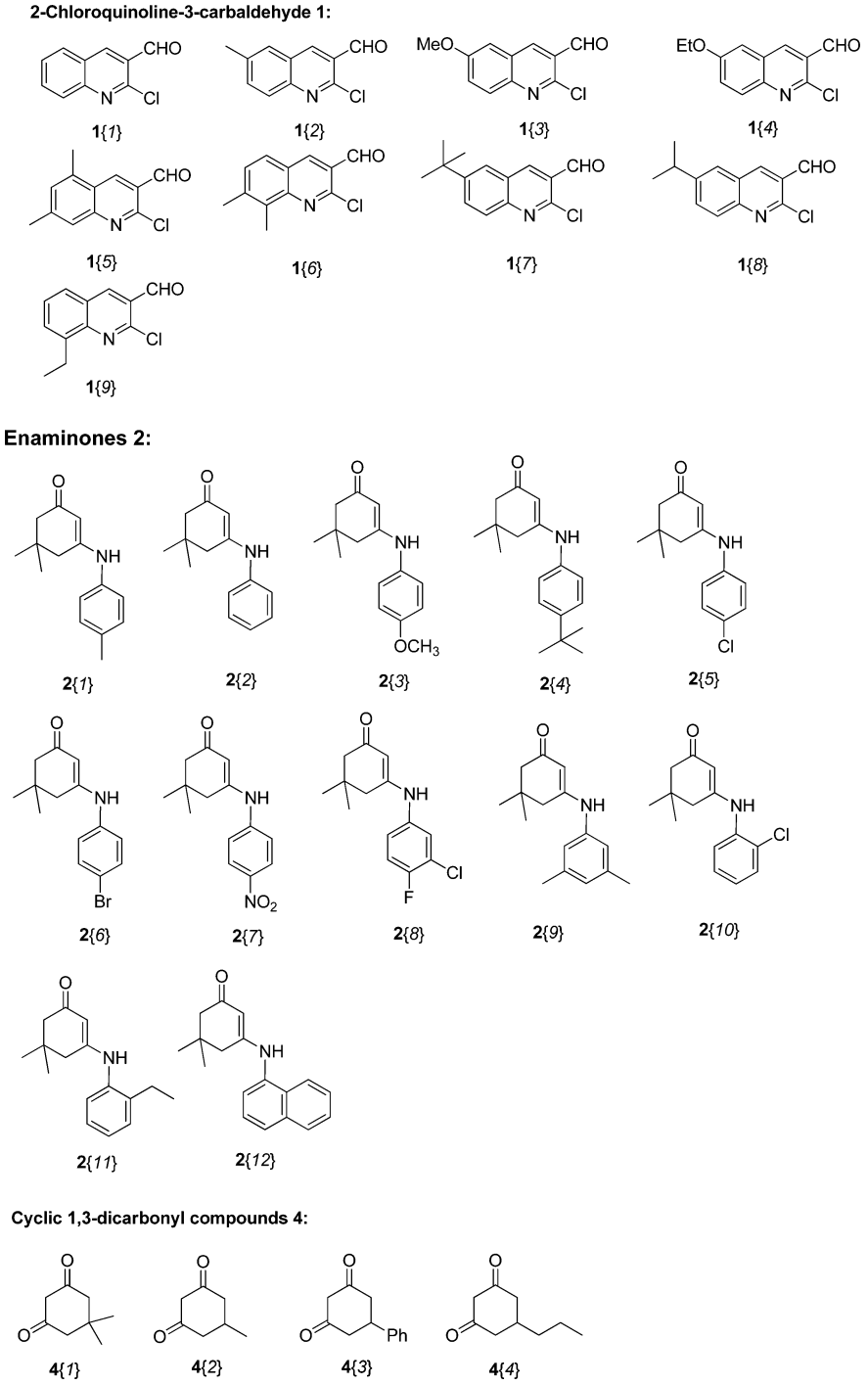

Figure 2. Substrates used in the synthesis of compounds **3**, **5**, and **6**.

here have medicinal values and the basic framework of this class of heterocyclic compounds is an attractive template for the identification of novel potential antitumor agents.

EXPERIMENTAL PROCEDURES

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 Invoa-400 MHz or Invoa-300 MHz spectrometer in $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. HRMS analyses were carried out using Bruker micrOTOF-Q instrument. 2-Chloroquinoline-3-carbaldehydes were synthesized according to the procedure reported in the literature.[15]

General Procedure for the Synthesis of Functionalized 1,8-Naphthyridine Derivatives 3. A dry 50 mL flask was charged with 2-chloroquinoline-3-carbaldehyde **1** (1 mmol), enaminones **2** (1 mmol), Cs_2CO_3 (2 mmol, 2 equiv) and toluene (5 mL). The mixture was stirred at refluxing temperature for 0.7 h. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The mixture was then quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4, After evaporation of the solvent

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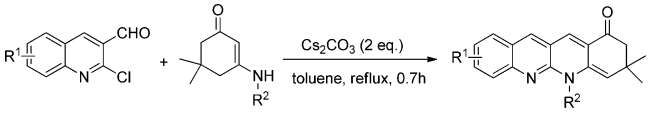
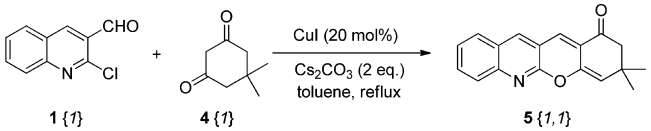
Table 2. Synthesis of Functionalized 1,8-Naphthyridine Derivatives 3



1 {1-9} 2 {1-12} 3 {1(1-9),2(1-12)}

entry	products	isolated yield (%)	mp (°C)
1	3{1,1}	79	171−173
2	3{1,2}	80	170−172
3	3{1,6}	83	182−183
4	3{1,7}	84	246−248
5	3{1,10}	85	196−198
6	3{1,12}	83	192−194
7	3{2,1}	87	178−180
8	3{2,8}	82	287−288
9	3{3,1}	84	244−246
10	3{3,2}	85	182−184
11	3{4,2}	82	185−186
12	3{4,3}	76	180−182
13	3{5,1}	83	197−198
14	3{6,1}	84	181−182
15	3{6,5}	84	198−199
16	3{7,1}	87	198−200
17	3{7,2}	82	203−204
18	3{7,3}	85	221−222
19	3{7,4}	86	236−237
20	3{7,5}	78	215−216
21	3{7,6}	75	232−233
22	3{7,7}	82	192−194
23	3{7,8}	85	212−214
24	3{7,9}	84	233−234
25	3{7,11}	83	185−186
26	3{7,12}	82	222−223
27	3{8,1}	84	191−193
28	3{8,2}	82	243−245
29	3{8,7}	86	203−205
30	3{9,9}	82	188−189

Scheme 1. Cascade Reaction of 2-Chloroquinoline-3-carbaldehyde with Dimedone



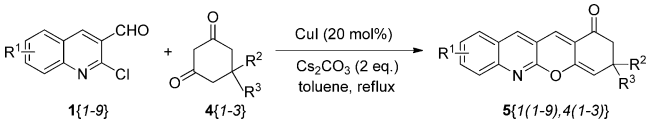
1 {1} 4 {1} 5 {1,1}

under reduced pressure, the crude products were purified by recrystallization from 95% ethanol to give pure products **3**.

3,3-Dimethyl-5-(p-tolyl)-2,3-dihydrodibenzo[b,g][1,8]-naphthyridin-1(5H)-one ***3****{1,1}:* . Red solid; IR (KBr, ν, cm^{-1}) 2957, 1658, 1607, 1560, 1512, 1462, 1383, 1350, 1284, 1175, 1106, 923, 819, 793; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (s, 1H, ArH), 7.48 (d, J = 8.0 Hz, 1H, ArH), 7.39−7.30 (m, 5H, ArH), 7.15 (d, J = 8.0 Hz, 3H, ArH, CH), 4.23 (s, 1H, CH), 2.48 (s, 3H, CH_3), 2.46 (s, 2H, CH_2), 1.00 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 197.7, 153.1, 148.4, 138.8, 137.5, 136.8, 136.4, 131.0, 130.6, 129.5, 128.1, 127.5, 127.4, 126.1, 125.1, 123.6, 118.6, 112.2, 52.3, 33.6, 30.2, 21.4; HRMS calcd for $C_{25}H_{22}N_2NaO$ $[M + Na]^+$ 389.1630, found 389.1647.

General Procedure for the Synthesis of Chromeno[2,3-*b*]quinoline Derivatives 5. A dry 50 mL flask was charged with

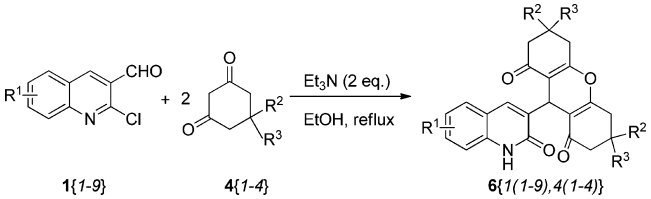
Table 3. Synthesis of Chromeno[2,3-*b*]quinoline Derivatives 5



1{1-9} 4{1-3} 5{1(1-9),4(1-3)}

entry	products	isolated yields (%)	mp (°C)
1	5{1,1}	87	168−169
2	5{2,1}	89	189−190
3	5{3,1}	89	182−183
4	5{4,1}	92	170−172
5	5{5,1}	89	158−159
6	5{7,1}	85	186−187
7	5{8,1}	94	196−198
8	5{9,1}	87	165−166
9	5{7,2}	81	162−163
10	5{7,3}	84	168−169

Table 4. Synthesis of 9-(Quinolin-3-yl)hexahydroxanthene-1,8-dione derivatives 6



1{1-9} 4{1-4} 6{1(1-9),4(1-4)}

entry	products	isolated yields (%)	mp (°C)
1	6{1,1}	89	>300
2	6{3,1}	89	>300
3	6{4,1}	88	>300
4	6{5,1}	93	>300
5	6{7,1}	86	>300
6	6{8,1}	90	>300
7	6{9,1}	90	>300
8	6{1,2}	89	>300
9	6{1,4}	86	>300
10	6{7,4}	88	>300

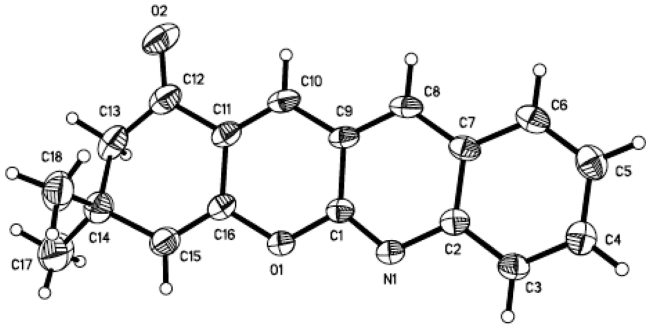


Figure 3. X-ray structure of compound 5{1,1}.

2-chloroquinoline-3-carbaldehyde **1** (1 mmol), cyclic 1,3-dicarbonyl compounds **4** (1.5 mmol, 1.5 equiv), Cs_2CO_3 (2 mmol, 2 equiv), CuI (0.2 mmol, 20 mol %), and toluene (5 mL). The mixture was stirred at refluxing temperature for 0.8 h under N_2 atmosphere. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The mixture was then quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous

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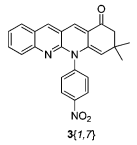
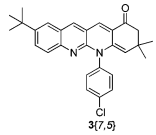
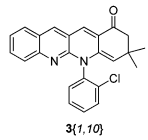
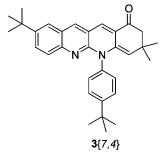
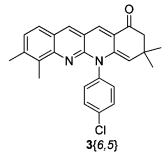
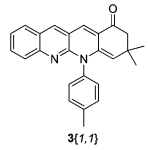
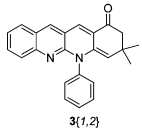
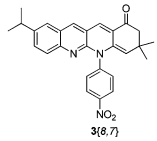
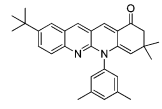
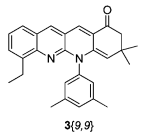
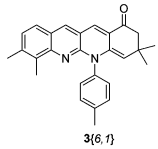
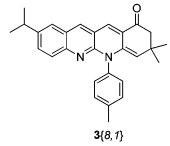
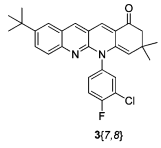
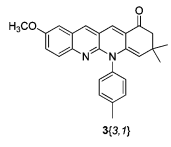
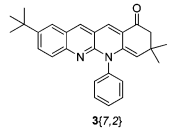
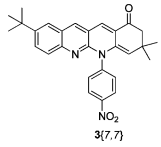
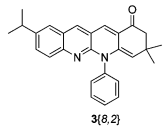
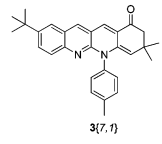
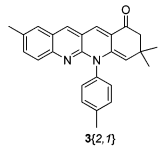
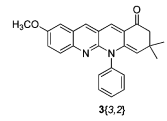
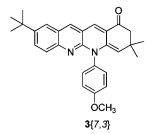
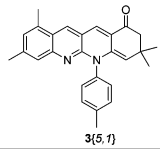
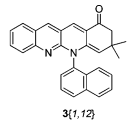
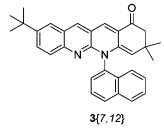
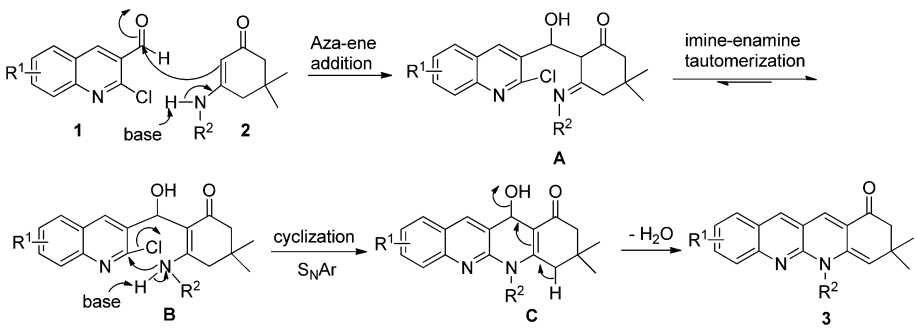
Table 5. IC_{50} Values of Selected Compounds 3

compound	$IC_{50}/\mu M$	compound	$IC_{50}/\mu M$	compound	$IC_{50}/\mu M$
 3{1,7}	> 30	 3{7,5}	20.2 ±8.1	 3{1,10}	9.8±0.9
 3{7,4}	> 30	 3{6,5}	18.3 ±1.0	 3{1,1}	9.4±0.8
 3{1,2}	> 30	 3{8,7}	17.0 ±5.7	 3{7,9}	8.9±1.6
 3{9,9}	> 30	 3{6,1}	16.5 ±4.2	 3{8,1}	7.8±0.3
 3{7,8}	> 30	 3{3,1}	11.4 ±1.6	 3{7,2}	5.7±0.7
 3{7,7}	> 30	 3{8,2}	11.3 ±1.3	 3{7,1}	4.8±0.6
 3{2,1}	27.1 ±0.7	 3{3,2}	12.6 ±3.7	 3{7,3}	6.4±2.2
 3{5,1}	19.7 ±6.3	 3{1,12}	11.9 ±3.4	 3{7,12}	1.9±0.1

Scheme 2. Proposed Mechanism for the Formation of Compound 3



Na_2SO_4, After evaporation of the solvent under reduced pressure, the crude products were purified by column chromatography (petroleum ether/acetone = 8:1) to afford the pure products **5**.

3,3-Dimethyl-2,3,5a,12a-tetrahydro-1H-chromeno[2,3-b]-quinolin-1-one ***5****{1,1}:* Yellow solid; IR (KBr, ν, cm^{-1}) 2950, 1678, 1610, 1388, 1268, 1172, 953; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.86 (s, 1H, ArH), 7.79 (d, J = 8.1 Hz, 1H, ArH),

dx.doi.org/10.1021/co500120b | *ACS Comb. Sci.* 2015, 17, 24−31

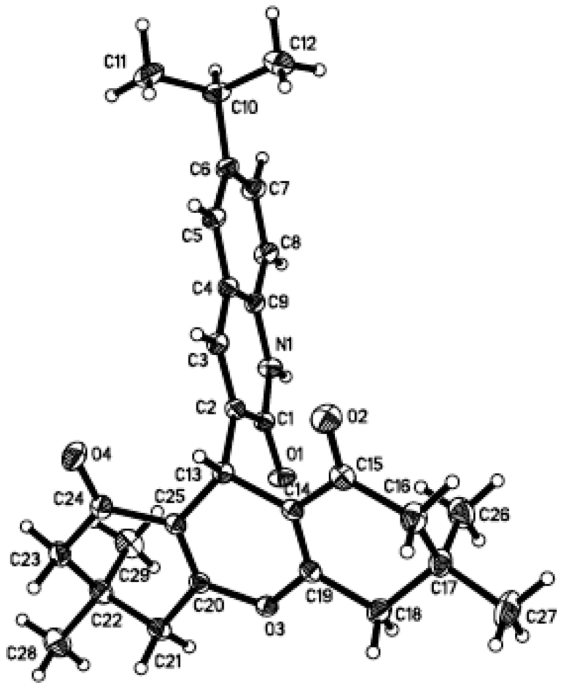


Figure 4. X-ray structure of compound **6**{*8,1*}.

7.69−7.61 (m, 2H, ArH), 7.40 (t, J = 7.5 Hz, 1H, ArH), 7.19 (s, 1H, CH), 5.51 (s, 1H, CH), 2.53 (s, 2H, CH_2), 1.19 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.2, 157.6, 147.1, 147.0, 137.5, 131.4, 127.8, 127.7, 126.7, 126.6, 125.7, 123.4, 116.8, 115.8, 52.7, 33.0, 30.1; HRMS calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$ 278.1181, found 278.1175.

General Procedure for the Synthesis of 9-(Quinolin-3-yl)hexahydroxanthene-1,8-dione Derivatives 6. A dry 50 mL flask was charged with 2-chloroquinoline-3-carbaldehyde **1** (1 mmol), cyclic 1,3-dicarbonyl compounds **4** (2 mmol), Et_3N (2 mmol, 2 equiv), and ethanol (5 mL). The mixture was stirred at refluxing temperature for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The crude products were collected and purified by recrystallization from 95% ethanol to give pure products **6**.

3,3,6,6-Tetramethyl-9-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione ***6****{1,1}:* White solid; IR (KBr, ν, cm^{-1}) 3036, 2957, 1663, 1434, 1361, 1199, 1124, 1002, 923, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.19 (s, 1H, NH), 8.11 (s, 1H, CH), 7.65 (d, J = 7.6 Hz, 1H, ArH), 7.46 (t, J = 7.2 Hz, 1H, ArH), 7.33 (d, J = 8.4 Hz, 1H, ArH), 7.19 (t, J = 7.6 Hz, 1H, ArH), 4.82 (s, 1H, CH), 2.47 (s, 4H, 2 × CH_2), 2.25−2.12 (m, 4H, 2 × CH_2), 1.05 (s, 6H, 2 × CH_3), 0.87 (s, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.4, 165.0, 163.5, 141.3, 138.4, 130.5, 129.6, 128.8, 122.3, 120.5, 115.2, 111.7, 51.1, 41.2, 32.4, 31.4, 29.5, 27.2; HRMS calcd for $C_{26}H_{27}NNaO_4$ $[M + Na]^+$ 440.1838, found 440.1841.

Inhibition of Cell Proliferation. Hepatic carcinoma HepG2 cells were grown in the minimum essential medium Eagles with Earle's balanced salts (MEM-EBSS) medium (Hyclone, Logan, Utah). The medium was supplemented with 100 U/mL penicillin and 100 mg/mL streptomycin and 10% fetal bovine serum (FBS) at 37 °C in a humidified atmosphere containing 5% CO_2.

For cell proliferation assay, cells were seeded into 96-well plates (4000 cells/well) and incubated at 37 °C in a humidified 5% CO_2 atmosphere. After 24 h, cells were treated with different concentration compounds for 48 h in triplicate to generate dose−response curves. Cell proliferation was determined by the SRB assay as previoud described.[23] The IC_{50} value was calculated using SigmaPlot 10.0 software, which defined as the inhibitor concentration of 50% cell growth inhibition

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic characterization for compounds **3**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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(22) Crystallographic data for the structures of compounds **5**{*1,1*} and **6**{*8,1*} have been deposited at the Cambridge Crystallographic Data Center, and the deposit numbers are CCDC-1030078 and CCDC-1030079, respectively. Copy of available material can be obtained free of change on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336 033; e-mail deposit@ccdc.aom.ac.uk). Crystal data of compound **5**{*1,1*}: molecular formula = $C_{18}H_{15}NO_2$, formula weight = 277.31, (crystal system) monoclinic, (space group) $P2_1/c$, a = 15.5160(16) Å, b = 7.5160(8) Å, c = 12.3310(12) Å, β = 92.5230(10)°, V = 1436.6(3) Å^3, T = 298(2) K, Z = 4, Dc = 1.282 Mg m^{-3}, μ(MoKα) = 0.084 mm^{-1}, 6985 reflection measured, 2522 independent reflections, R_1 = 0.0488, R_2 = 0.0900. Crystal data of compound **6**{*8,1*}: molecular formula = $C_{29}H_{33}NO_4$, formula weight = 459.56, (crystal system) monoclinic, (space group) $P2_1/n$, a = 12.9044(9) Å, b = 12.0994(5) Å, c = 17.6179(10) Å, β = 110.508(7)°, V = 2576.4(3) Å^3, T = 293(2) K, Z = 4, Dc = 1.185 Mg m^{-3}, μ(MoKα) = 0.078 mm^{-1}, 12276 reflection measured, 4588 independent reflections, R_1 = 0.0456, R_2 = 0.1073.

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