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Cascade synthesis of spirooxindole δ-lactone derivatives through *N*-aryl hydroxymethylacrylamides with xanthates

Shucheng Wang, Xuhu Huang, Yanzhao Wen, Zemei Ge, Xin Wang, Runtao Li *

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, PR China

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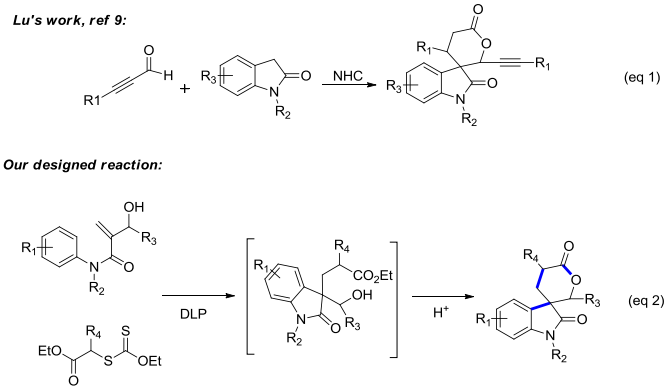
ABSTRACT

A novel and highly efficient cascade synthesis of spirooxindole δ-lactone derivatives from *N*-aryl hydroxymethylacrylamides and xanthates in good yields is described. The reaction proceeds through a radical addition/cyclization and ester exchange, in which two new C–C bonds and one C–O bond were formed.

1. Introduction

The spirooxindoles are among the most privileged scaffolds in medicinal chemistry.[1,2] Thus, numerous effective methods, including formal cycloaddition,[3] organocascade,[4] Prins cyclization,[5] and multicomponent reactions,[6] have been developed for the synthesis of diversely structured spirooxindoles. For example, Huang et al. disclosed that spirooxazolines could be synthesized from ynones and isatins using phosphine-catalyzed system.[4f] Zhu and co-workers reported a palladium-catalyzed oxidative carboheterofunctionalization of alkenes for the preparation of azaspirooxindoles.[12c] Very recently, Tu's group succeeded construction of spiro[indoline-3,2′-pyrrole] framework via catalytic asymmetric 1,3-dipolar cycloadditions of isatin-derived azomethine ylide with allenes.[3g] All of these methods result in a different class of spirocyclic oxindoles.[7,8] However, to the best of our knowledge, there is only one report on the synthesis of spirooxindole δ-lactones (Scheme 1, Eq. 1),[9] though δ-lactone is vital and useful subunit in many bioactive natural products.[10]

Nowadays, the cascade reaction has received much attention because the ability to undertake more than one synthetic step in a reaction vessel represents a useful method for saving time and energy, as well as for reducing the use of organic solvents in the purification the intermediates.[11] Thus, the cascade reaction has been used as a powerful tool for building up diversity bioactive compounds. Even so, a cascade synthesis of spirooxindole derivatives employing acrylamides with other reactants have scarcely been reported.[12]



Scheme 1. Design of new approach for spirooxindole δ-lactones.

Xanthate-based radical addition reactions developed by Zard and co-workers are powerful tools for the construction C–C bonds without utilizing potentially toxic metal agents.[13] It is well known that the intermediates generated by xanthate based radical reactions can be readily trapped by alkenes. Inspired by Lu's work and as part of our ongoing program to explore efficient methodologies for synthesize heterocyclic compounds,[14] we report herein a novel

* Corresponding author. Tel.: +86 10 82801504; e-mail address: lirt@bjmu.edu.cn (R. Li).

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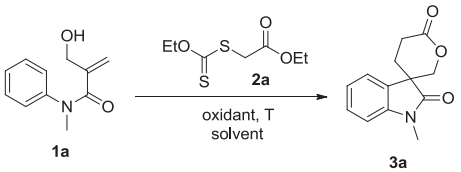
transition-metal-free tandem radical cyclization of olefinic amides with xanthates to the construction of highly functionalized spirooxindole δ-lactones under mild conditions, in which two new C–C bonds and one C–O bond were formed. (Scheme 1, Eq. 2).

2. Results and discussion

Initially, the starting material 2-hydroxymethyl-*N*-methyl-*N*-phenylacrylamide (**1a**) was firstly synthesized from *N*-methylaniline with two steps in a high yield.[15] **1a** was then allowed to react with xanthate (**2a**) in the presence of 1.5 equiv of dilauroyl peroxide (DLP) in DCE at 84 °C for 12 h[14] To our delight, the desired product **3a** was isolated in 87% yield (Table 1, entry 1). This result encouraged us to further optimize the reaction conditions. Several oxidants, including $PhI(OAc)_2$, TBHP, H_2O_2, $K_2S_2O_8$, were thoroughly examined, and the DLP remained as the best one (Table 1, entries 1–5). The solvent screening results revealed that DCE was the best choice (Table 1, entries 6–10). By altering the temperature to 120 °C, the yield of **3a** was slightly reduced due to the instability of DLP at high temperature (Table 1, entry 11). In addition, decreasing the amount of DLP and **2a** seems to dramatically reduce the reaction efficiency (Table 1, entry 12–14). Therefore, the best reaction conditions were concluded as follows: *N*-aryl hydroxymethylacrylamide **1a** (0.1 M), xanthate **2a** (1.5 equiv), DLP (oxidant, 1.5 equiv) in DCE at 84 °C in an open flask.

With the optimized reaction conditions in hand, we next examined the scope of this reaction (Table 2). The reactions of different *N*-aryl-*N*-methyl hydroxymethylacrylamides (**1**) with xanthate (**2a**) proceeded efficiently to deliver the spirooxindole lactones **3a-j** in good yields.[12d,15,16] The property and position of substituents R_1 in substrates **1** did not significantly effect to the reactions. Such as, **1b** (R_1=4-Me), **1d** (R_1=4-CF_3) and **1g** (R_1=6-Me) gave the products **3b**, **3d** and **3g** in 81%, 78% and 86% yields, respectively. The good tolerance of substrate bearing Cl and Br provides a convenient platform for further elaboration via conventional Pd-catalyzed cross-coupling (**3e**, **3f**, **3h**). Interestingly,

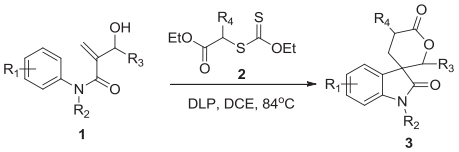
Table 1
Optimization of reaction conditions[a]

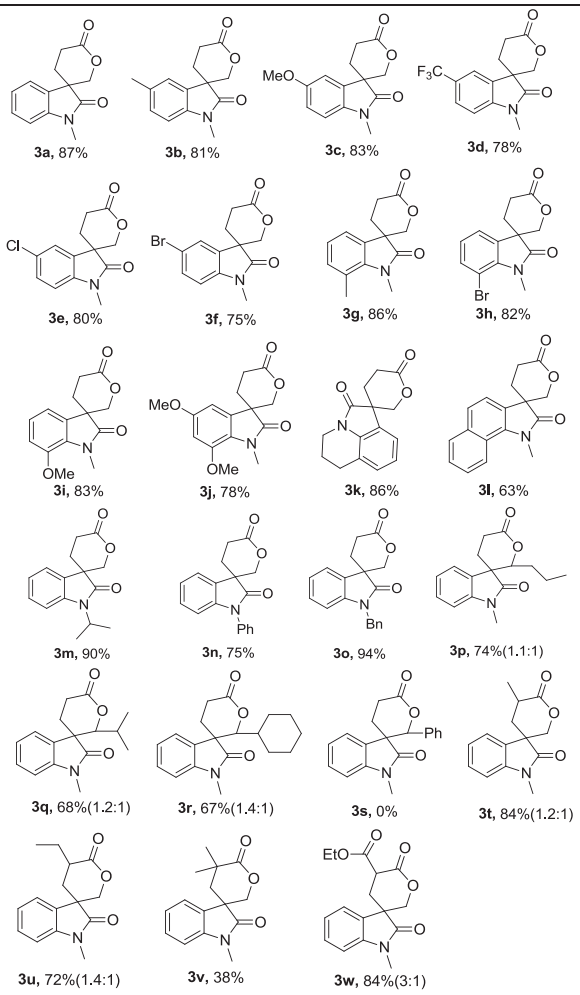


Entry	Oxidant	Temp (°C)	Solvent	Yield (%)[b]
1	DLP	84	DCE	87
2	$PhI(OAc)_2$	84	DCE	NR[c]
3	TBHP	84	DCE	62
4	H_2O_2	84	DCE	NR
5	$K_2S_2O_8$	84	DCE	NR
6	DLP	65	THF	65
7	DLP	60	EA	15
8	DLP	80	CH_3CN	21
9	DLP	100	Dioxane	53
10	DLP	130	C_6H_5Cl	22
11	DLP	120	DCE	80
12[d]	DLP	84	DCE	73
13[e]	DLP	84	DCE	71
14[d,e]	DLP	84	DCE	58

[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv), **2a** (0.45 mmol, 1.5 equiv), oxidant (1.5 equiv), solvent (3 mL), 12 h.
[b] Isolated yields.
[c] NR=no reaction.
[d] Oxidant (1.2 equiv).
[e] **2a** (1.2 equiv).

Table 2
Reaction scope for the synthesis of substrate **3**[a]





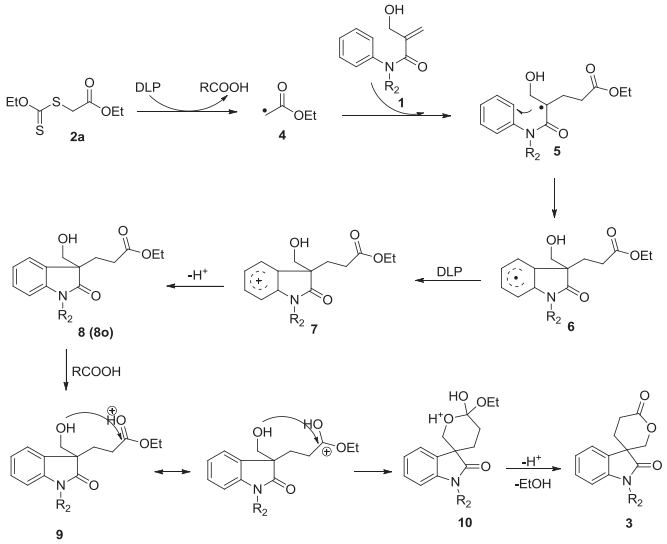
[a] Reaction conditions: **1** (0.3 mmol, 1 eq.), **2** (0.45 mmol, 1.5 eq.), oxidant (0.45 mmol, 1.5 eq.), DCE (3 mL) at 84 °C for 12 hours under air. The d.r. value is given in parenthesis.

the reaction of 2-hydroxymethyl-*N*-acryloyltetrahydroquinoline **1k** and **2a** produced a tetracyclic oxindole product **3k** in 86% yield. For 2-hydroxymethyl-*N*-methyl-*N*-naphthylacrylamide **1l**, the desired product **3l** was also formed in moderate yield (63%). Next, changing the N-substituent group R_2 of **1a** from the methyl group to isopropyl, phenyl and benzyl also gave the desired products **3m**, **3n** and **3o** in 90%, 75% and 94% yields, respectively. Much to our delight, replacing R_3=H in **1a** with bulkier alkyl groups (R_3=*n*-Pr, *i*-Pr, cyclohexyl) also react smoothly with xanthate **2a** affording the products **3p**–**r** in 67–74% yields. However, **1s** (R_3=Ph) as substrate did not result any desired product **3s** under the same reaction conditions. The probable reason is the formation of stable benzylic carbocation, which easy leave away to form monosubstituted oxindole. Finally, the reactions of a variety of xanthates **2** with **1a** were investigated under the optimized reaction conditions. It was found that steric bulk of R_4 of xanthates **2** significantly influenced the yields of the reactions.

For examples, the reactions of **2b** (R_4=Me), **2c** (R_4=Et) and **2d** (R_4=di-Me) afforded the corresponding products (**3t**, **3u**,**3v**) in 84%,

72% and 38% yields, respectively. However, we are happy to find that **2e** (R_4=CO_2Et) could be smoothly transformed into product **3w** in 84% yield with 3:1 dr value.

Based on these experiments and the previous reports,[13,14c] a plausible mechanism is presented in Scheme 2. Initially, xanthate **2a** reacts with DLP to give radical **4**, which would promptly add to acrylamide **1** to generate radical species **5**. Subsequently, this intermediate **5** undergoes intramolecular carbocyclization to afford **6**, followed by DLP oxidation to produce oxindole cation **7**. Deprotonation of **7** generates the intermediate **8**. Finally, the desired product **3** was formed via the intramolecular ester exchange reaction of **8** with the presence of carboxylic acid. To confirm this possible mechanism, we carefully separated the key intermediate **8o** (R_2=Bn, see Supplementary data), which could be converted to the **3o** under our reaction conditions.



Scheme 2. Plausible reaction pathway.

3. Conclusion

In summary, we have developed a novel cascade synthesis of spirooxindole δ-lactone derivatives from *N*-aryl hydroxymethylacrylamides with xanthates via a radical addition/cyclization and ester exchange process. The advantages of this method include available starting materials, broad substrate scope, high yields and mild reaction conditions. Further application to other heterocyclic systems is underway.

4. Experimental section

4.1. General information

All melting points (mp) were measured on a melting point apparatus with a microscope and a hot stage and were uncorrected. ^{1}H NMR spectra were determined in $CDCl_3$ on a Bruke 400 MHz spectrometer and chemical shifts were reported in parts per million from internal TMS (δ). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (integration, s=singlet, d=doublet, dd=doublets, t=triplet, q=quartet, m=multiplet or unresolved, coupling constant(s) in Hertz). ^{13}C NMR spectra were obtained by using the same NMR spectrometers. High-resolution mass spectra (HRMS) was recorded using a Bruker Apex IV FTMS instrument. Column chromatography was performed with 200–300 mesh silica gel using flash column techniques. All of the reagents obtained commercially were used directly unless otherwise noted.

4.2. General procedure for the synthesis of compounds 3

DLP (0.45 mmol, 1.5 equiv) was added to a solution of **1** (0.3 mmol, 1 equiv) and **2** (0.45 mmol, 1.5 equiv) in DCE (3 mL) in one portion. The solution was stirred at 84 °C for 12 h. Water (10 mL) was added to the solution and the mixture was extracted with DCM (2×10 mL). The combined organic phase was dried over Na_2SO_4. After removal of solvents with a rotary evaporator, the residue was purified on a silica gel column with petroleum ether and ethyl acetate as eluents to afford the desired product **3**.

*4.2.1. 1-Methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3a**).* 87% yield, white solid, mp=121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J*=7.6 Hz, 1H), 7.30 (d, *J*=6.8 Hz, 1H), 7.12 (t, *J*=7.6 Hz, 1H), 6.93 (d, *J*=7.6 Hz, 1H), 4.55 (d, *J*=11.2 Hz, 1H), 4.26 (d, *J*=11.2 Hz, 1H), 3.25 (s, 3H), 3.13–2.99 (m, 1H), 2.88–2.75 (m, 1H), 2.52–2.45 (m, 1H), 2.16–2.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 170.9, 143.0, 131.1, 129.1, 123.5, 123.3, 108.7, 72.8, 46.0, 28.6, 27.3, 26.5. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}NNaO_3$ $[M+Na]^+$: 254.0788; found: 254.0792.

*4.2.2. 1,5-Dimethyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3b**).* 81% yield, white solid, mp=153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J*=7.9 Hz, 1H), 7.12 (s, 1H), 6.81 (d, *J*=7.9 Hz, 1H), 4.55 (d, *J*=11.2 Hz, 1H), 4.24 (d, *J*=11.2 Hz, 1H), 3.23 (s, 3H), 3.13–2.99 (m, 1H), 2.85–2.78 (m, 1H), 2.56–2.43 (m, 1H), 2.36 (s, 3H), 2.14–2.01 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 171.0, 140.5, 133.0, 131.3, 129.3 (s), 124.4, 108.4, 72.9, 46.1, 28.6, 27.3, 26.5, 21.1. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0944; found: 268.0945.

*4.2.3. 5-Methoxy-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3c**).* 83% yield, white solid, mp=113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.87 (m, 2H), 6.82 (d, *J*=8.4 Hz, 1H), 4.55 (d, *J*=11.4 Hz, 1H), 4.25 (d, *J*=11.4 Hz, 1H), 3.81 (s, 3H), 3.23 (s, 3H), 3.15–2.96 (m, 1H), 2.85–2.78 (m, 1H), 2.52–2.45 (m, 1H), 2.11–2.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 171.0, 156.5, 136.3, 132.5, 113.3, 111.1, 109.0, 72.7, 55.9, 46.4, 28.7, 27.3, 26.6. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NNaO_4$ $[M+Na]^+$: 284.0893; found: 284.0896.

*4.2.4. 1-Methyl-5-(trifluoromethyl)-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3d**).* 78% yield, white solid, mp=154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.2 Hz, 1H), 7.53 (s, 1H), 7.01 (d, *J*=8.2 Hz, 1H), 4.55 (d, *J*=11.6 Hz, 1H), 4.30 (d, *J*=11.6 Hz, 1H), 3.30 (s, 3H), 3.14–3.05 (m, 1H), 2.87–2.76 (m, 1H), 2.57–2.43 (m, 1H), 2.23–2.09 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 170.5, 145.9, 131.8, 128.0, 126.9 (q, *J*=4.0 Hz, 1C), 125.5 (q, *J*=16.8 Hz, 1C), 120.4 (q, *J*=3.7 Hz, 1C), 108.5, 72.2, 46.0, 28.6, 27.2, 26.7. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}F_3NNaO_3$ $[M+Na]^+$: 322.0661; found: 322.0667.

*4.2.5. 5-Chloro-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3e**).* 80% yield, white solid, mp=184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J*=8.3, 2.0 Hz, 1H), 7.32–7.25 (m, 1H), 6.85 (d, *J*=8.3 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.25 (d, *J*=11.5 Hz, 1H), 3.25 (s, 3H), 3.14–2.95 (m, 1H), 2.92–2.74 (m, 1H), 2.53–2.47 (m, 1H), 2.16–2.00 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 170.6, 141.5, 132.8, 129.1, 128.7, 124.1, 109.6 (s), 72.3, 46.3, 28.5, 27.2, 26.6. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}ClNNaO_3$ $[M+Na]^+$: 288.0398; found: 288.0401.

*4.2.6. 5-Bromo-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3f**).* 75% yield, white solid, mp=125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J*=8.3, 1.6 Hz, 1H), 7.42 (d, *J*=1.6 Hz, 1H), 6.81 (d, *J*=8.3 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.25 (d,

J=11.5 Hz, 1H), 3.24 (s, 3H), 3.10–3.01 (m, 1H), 2.85–2.79 (m, 1H), 2.52–2.45 (m, 1H), 2.13–2.05 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 170.6, 142.0, 133.1, 132.0, 126.8, 115.9, 110.1, 72.3, 46.2, 28.5, 27.2, 26.6. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}BrNNaO_3$ $[M+Na]^+$: 331.9893; found: 331.9898.

*4.2.7. 1,7-Dimethyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3g**).* 86% yield, white solid, mp=125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.09 (m, 2H), 7.01 (t, *J*=7.6 Hz, 1H), 4.52 (d, *J*=11.6 Hz, 1H), 4.25 (d, *J*=11.6 Hz, 1H), 3.54 (s, 3H), 3.16–3.00 (m, 1H), 2.86–2.73 (m, 1H), 2.62 (s, 3H), 2.52–2.37 (m, 1H), 2.16–2.01 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 171.1, 140.1, 132.8, 131.9, 123.2, 121.3, 120.3, 73.0, 45.2, 29.8, 29.0, 27.3, 19.0. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0944; found: 268.0946.

*4.2.8. 7-Bromo-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3h**).* 82% yield, white solid, mp=69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=8.2 Hz, 1H), 7.22 (d, *J*=7.0 Hz, 1H), 6.97 (t, *J*=7.8 Hz, 1H), 4.53 (d, *J*=11.5 Hz, 1H), 4.24 (d, *J*=11.5 Hz, 1H), 3.64 (s, 3H), 3.13–2.98 (m, 1H), 2.88–2.72 (m, 1H), 2.58–2.39 (m, 1H), 2.16–2.01 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 170.8, 140.3, 134.7, 134.4, 124.4, 122.5, 103.0, 72.5, 45.7, 30.2, 29.0, 27.3. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}BrNNaO_3$ $[M+Na]^+$: 331.9893; found: 331.9898.

*4.2.9. 7-Methoxy-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3i**).* 83% yield, white solid, mp=111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.02 (t, *J*=8.2 Hz, 1H), 6.95–6.90 (m, 2H), 4.53 (d, *J*=11.4 Hz, 1H), 4.24 (d, *J*=11.4 Hz, 1H), 3.89 (s, 3H), 3.52 (s, 3H), 3.13–2.98 (m, 1H), 2.83–2.75 (m, 1H), 2.56–2.38 (m, 1H), 2.17–1.99 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 171.1, 145.6, 132.8, 130.8, 123.9, 116.0, 112.8, 72.9, 56.0, 46.0, 29.8, 28.8, 27.3. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NNaO_4$ $[M+Na]^+$: 284.0893; found: 284.0896.

*4.2.10. 5,7-Dimethoxy-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3j**).* 78% yield, white solid, mp=45–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J*=2.2 Hz, 1H), 6.47 (d, *J*=2.2 Hz, 1H), 4.53 (d, *J*=11.5 Hz, 1H), 4.24 (d, *J*=11.5 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.47 (s, 3H), 3.11–3.01 (m, 1H), 2.83–2.74 (m, 1H), 2.52–2.40 (m, 1H), 2.12–2.02 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 171.4, 157.2, 146.3, 133.5, 124.2, 100.9, 100.1, 72.8, 55.9, 55.9, 46.5, 29.7, 28.9, 27.4. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}NO_5$ $[M+H]^+$: 292.1180; found: 292.1182.

*4.2.11. 4,5,5′,6′-Tetrahydrospiro[pyran-3,1′-pyrrolo[3,2,1-ij]quinoline]-2′,6(2H,4′H)-dione (**3k**).* 86% yield, white solid, mp=147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.08 (m, 2H), 7.01 (t, *J*=7.6 Hz, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.27 (d, *J*=11.3 Hz, 1H), 3.76 (t, *J*=5.8 Hz, 2H), 3.13–2.95 (m, 1H), 2.87–2.79 (m, 3H), 2.56–2.49 (m, 1H), 2.15–1.98 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 170.8, 138.7, 129.7, 127.9, 122.7, 121.4, 120.8, 72.9, 47.4, 39.1, 28.3, 27.3, 24.5, 21.0. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1125; found: 258.1126.

*4.2.12. 1-Methyl-4′,5′-dihydrospiro[benzo[g]indole-3,3′-pyran]-2,6′(1H,2′H)-dione (**3l**).* 63% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J*=8.0, 1.2 Hz 1H), 7.68–7.44 (m, 4H), 7.07 (d, *J*=7.8 Hz, 1H), 4.88 (d, *J*=11.6 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 3.59 (s, 3H), 3.15–2.99 (m, 1H), 2.98–2.83 (m, 1H), 2.75–2.70 (m, 1H), 2.37–2.20 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.4, 136.2, 135.3, 133.4, 127.4, 127.3, 126.7, 123.6, 123.1, 118.8, 109.4, 75.4, 45.6, 34.0, 30.2, 28.8. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}NO_3$ $[M+H]^+$: 282.1125; found: 282.1128.

*4.2.13. 1,3-Dimethyl-3-(3-(naphthalen-2-yl)-3-oxopropyl)indolin-2-one (**3m**).* 90% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H), 7.09 (t, *J*=7.5 Hz, 2H), 4.63 (h, 7.0 Hz, 1H), 4.53 (d, *J*=11.4 Hz, 1H), 4.25 (d, *J*=11.4 Hz, 1H), 3.09–3.01 (m, 1H), 2.82–2.77 (m, 1H), 2.52–2.42 (m, 1H), 2.12–2.02 (m, 1H), 1.50 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 171.1, 141.6, 131.7, 128.8, 123.8, 122.7, 110.3, 73.0, 45.7, 44.2, 28.7, 27.3, 19.4, 19.4. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1281; found: 260.1281.

*4.2.14. 1-Phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3n**).* 75% yield, white solid, mp=151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J*=7.6 Hz, 2H), 7.51–7.35 (m, 4H), 7.31 (t, *J*=7.8 Hz, 1H), 7.17 (t, *J*=7.5 Hz, 1H), 6.92 (d, *J*=7.9 Hz, 1H), 4.68 (d, *J*=11.4 Hz, 1H), 4.42 (d, *J*=11.4 Hz, 1H), 3.16–3.05 (m, 1H), 2.95–2.79 (m, 1H), 2.71–2.57 (m, 1H), 2.32–2.17 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 170.9, 142.9, 133.8, 131.0, 129.8, 129.0, 128.5, 126.4, 123.8, 123.7, 110.0, 72.9, 46.2, 29.1, 27.3. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NNaO_3$ $[M+Na]^+$: 316.0944; found: 316.0944.

*4.2.15. 1-Benzyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3o**).* 94% yield, light yellow solid, mp=42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.21 (m, 7H), 7.09 (t, *J*=7.5 Hz, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 4.94 (s, 2H), 4.61 (d, *J*=11.4 Hz, 1H), 4.33 (d, *J*=11.4 Hz, 1H), 3.16–2.99 (m, 1H), 2.89–2.80 (m, 1H), 2.59–2.50 (m, 1H), 2.26–2.08 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 170.9, 142.0, 135.4, 131.0, 129.0, 129.0, 127.9, 127.3, 123.6, 123.3, 109.7, 72.8, 46.0, 43.9, 28.8, 27.3. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{17}NNaO_3$ $[M+Na]^+$: 330.1101; found: 330.1104.

*4.2.16. Ethyl 3-(1-benzyl-3-(hydroxymethyl)-2-oxoindolin-3-yl) propanoate (**8o**).* Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.15 (m, 7H), 7.07 (t, *J*=7.5 Hz, 1H), 6.76 (d, *J*=7.8 Hz, 1H), 5.03–4.87 (m, 2H), 4.06–3.85 (m, 4H), 2.45–2.37 (m, 1H), 2.27–2.12 (m, 2H), 2.01–1.92 (m, 1H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 172.7, 143.4, 135.6, 129.1, 128.8, 128.6, 127.7, 127.2, 123.4, 122.9, 109.4, 67.2, 60.5, 54.0, 43.8, 29.2, 27.9, 14.1.

*4.2.17. 1-Methyl-2′-propyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3p**).* 74% yield, d.r.=1.1:1. Major; Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dt, *J*=7.6, 1.2 Hz, 1H), 7.21–7.04 (m, 2H), 6.90 (d, *J*=7.8 Hz, 1H), 4.56 (dd, *J*=10.4, 1.8 Hz, 1H), 3.30–3.11 (m, 4H), 2.79–2.70 (m, 1H), 2.39–2.29 (m, 1H), 2.15–2.03 (m, 1H), 1.59–1.44 (m, 2H), 0.96–0.84 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 170.3, 143.6, 129.9, 129.1, 123.0, 122.0, 108.6, 83.1, 48.2, 32.4, 29.1, 26.4, 26.1, 18.8, 13.4. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438; found: 274.1440. Minor; Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dt, *J*=7.6, 1.2 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 7.10 (t, *J*=7.6 Hz, 1H), 6.93 (d, *J*=7.6 Hz, 1H), 4.65 (dd, *J*=10.0, 2.4 Hz, 1H), 3.25 (s, 3H),3.02–2.92 (m, 1H), 2.82–2.74 (m, 1H), 2.64–2.49 (m, 1H), 1.94–1.87 (m, 1H), 1.35–1.28 (m, 1H), 1.22–1.07 (m, 1H), 1.00–0.84 (m, 2H), 0.78 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 171.8, 143.3, 129.5, 128.8, 124.5, 123.2, 108.6, 82.4, 50.4, 32.7, 29.7, 27.2, 26.4, 18.6, 13.6.

*4.2.18. 2′-Isopropyl-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3q**).* 68% yield, d.r.=1.2:1. Major, white solid, mp=103–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, *J*=7.7, 1.6 Hz, 1H), 7.20–7.07 (m, 2H), 6.90 (d, *J*=7.7 Hz, 1H), 4.54 (d, *J*=3.7 Hz, 1H), 3.33–3.13 (m, 4H), 2.89–2.67 (m, 1H), 2.41–2.21 (m, 1H), 2.14–1.91 (m, 1H), 1.76–1.52 (m, 1H), 0.85 (d, *J*=6.7 Hz, 3H), 0.77 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 170.6, 143.3, 130.2, 129.0, 123.0, 122.0, 108.6, 87.8, 47.5, 30.8, 29.8, 26.3, 26.2, 21.1, 16.6. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438; found: 274.1440. Minor, white solid, mp=108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J*=8.2 Hz, 1H), 7.27 (d, *J*=7.5 Hz, 1H), 7.11 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=7.8 Hz, 1H), 4.45 (d, *J*=8.1 Hz, 1H), 3.25 (s, 3H), 3.01–2.93 (m, 1H), 2.80–2.68 (m, 1H), 2.51–2.44 (m, 1H), 1.90–1.77 (m, 1H),

1.68–1.61 (m, 1H), 0.89 (d, *J*=6.6 Hz, 3H), 0.56 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 171.8, 143.0, 129.6, 128.9, 124.7, 123.1, 108.7, 87.2, 49.7, 31.9, 30.9, 27.2, 26.5, 19.3, 18.3.

*4.2.19. 2′-Cyclohexyl-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3r**).* 67% yield, d.r.=1.4:1. Major, white solid, mp=129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (td, *J*=7.8, 1.9 Hz, 1H), 7.18–7.07 (m, 2H), 6.90 (d, *J*=7.8 Hz, 1H), 4.51 (d, *J*=3.9 Hz, 1H), 3.23 (s, 3H), 3.22–3.11 (m, 1H), 2.82–2.67 (m, 1H), 2.39–2.27 (m, 1H), 2.08–2.00 (m, 1H), 1.63 (d, *J*=10.4 Hz, 2H), 1.49–1.47 (m, 1H), 1.42–1.29 (m, 2H), 1.20–1.13 (m, 3H),1.01–0.94 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 170.6, 143.2, 130.3, 128.9, 122.9, 122.0, 108.6, 87.6, 47.3, 39.7, 31.1, 30.6, 27.1, 26.3, 26.2, 25.8, 25.7. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751; found: 314.1775. Minor, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (m, 1H), 7.29–7.24 (m, 1H), 7.11 (t, *J*=7.7 Hz, 1H), 6.93 (d, *J*=7.7 Hz, 1H), 4.51 (d, *J*=8.0 Hz, 1H), 3.25 (s, 3H), 2.99–2.91 (m, 1H), 2.81–2.64 (m, 1H), 2.48–2.40 (m, 2H), 1.84–1.75 (m, 1H), 1.52–1.49 (m, 2H), 1.02–1.00 (m, 4H), 0.91–0.88 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 171.8, 142.8, 129.7, 128.8, 124.6, 123.1, 108.8, 86.5, 49.5, 40.2, 32.1, 29.0, 27.9, 27.2, 26.5, 25.9, 25.8, 25.4.

*4.2.20. 1,5′-Dimethyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3t**).* 84% yield, d.r.=1.2:1. Major, yellow solid, mp=95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.29 (m, 2H), 7.12 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=7.8 Hz, 1H), 4.61 (d, *J*=11.3 Hz, 1H), 4.14 (d, *J*=11.3 Hz, 1H), 3.25 (s, 3H), 3.23–3.12 (m, 1H), 2.56 (dd, *J*=14.1, 6.7 Hz, 1H), 1.88–1.75 (m, 1H), 1.31 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 175.4, 142.6, 133.1, 128.8, 123.5, 123.4, 108.5, 71.8, 47.5, 37.2, 32.7, 26.5, 15.3. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0944; found: 268.0946. Minor, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.31 (m, 2H), 7.13 (t, *J*=7.5 Hz, 1H), 6.94 (d, *J*=7.8 Hz, 1H), 4.52 (d, *J*=11.5 Hz, 1H), 4.32 (d, *J*=11.5 Hz, 1H), 3.26 (s, 3H), 3.10–2.92 (m, 1H), 2.33–2.27 (m, 1H), 2.17–2.03 (m, 1H), 1.49–1.36 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 173.2, 143.1, 130.1, 129.2, 123.6, 122.9, 108.6, 72.5, 46.8, 36.7, 32.6, 26.6, 16.8.

*4.2.21. 5′-Ethyl-1-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3u**).* 72% yield, d.r.=1.4:1; The mixture of isomers cannot be separated by column chromatography on silica gel. Yellow oil; Major diastereoisomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (m, 2H), 7.13–7.06 (m, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 4.54 (d, *J*=11.3 Hz, 1H), 4.09 (d, *J*=11.3 Hz, 1H), 3.23 (s, 3H), 3.02–2.76 (m, 1H), 2.58–2.52 (m, 1H), 2.09–1.93 (m, 1H), 1.81–1.68 (m, 1H), 1.59–1.48 (m, 1H), 1.01 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 174.7, 142.6, 133.0, 128.8, 123.7, 123.4, 108.5, 71.5, 47.4, 38.8, 34.7, 26.5, 23.2, 11.3. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NNaO_3$ $[M+Na]^+$: 282.1101; found: 282.1103.

*4.2.22. 1,5′,5′-Trimethyl-4′,5′-dihydrospiro[indoline-3,3′-pyran]-2,6′(2′H)-dione (**3v**).* 38% yield, light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (td, *J*=7.8, 1.1 Hz, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 7.11 (td, *J*=7.6, 1.1 Hz, 1H), 6.91 (d, *J*=7.8 Hz, 1H), 4.64 (d, *J*=11.2 Hz, 1H), 4.24 (d, *J*=11.2 Hz, 1H), 3.25 (s, 3H), 2.44 (d, *J*=14.4 Hz, 1H), 2.02 (d, *J*=14.4 Hz, 1H), 1.58 (s, 3H), 1.44 (s, 3H). HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NNaO_3$ $[M+Na]^+$: 282.1101; found: 282.1103.

*4.2.23. Ethyl 1-methyl-2,6′-dioxo-2′,4′,5′,6′-tetrahydrospiro[indoline-3,3′-pyran]-5′-car-Boxylate (**3w**).* 84% yield, d.r.=3:1; The mixture of isomers cannot be separated by column chromatography on silica gel. Yellow oil; Major diastereoisomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (m, 2H), 7.16–7.11 (m, 1H), 6.96–6.89 (m, 1H), 4.46 (d, *J*=11.6 Hz, 1H), 4.35–4.24 (m, 3H), 3.25 (s, 3H), 2.68–2.50 (m, 2H), 1.34 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 168.2, 167.9, 142.9, 130.7, 129.3, 123.7, 123.5, 108.7, 72.4, 62.1, 45.7, 44.8, 31.4, 26.5, 14.1. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}NNaO_5$ $[M+Na]^+$: 326.0999; found: 326.1004.

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Supplementary data

Supplementary data (The original data of ^{1}H NMR and ^{13}C NMR of all products are supplied. The supplementary data files are to be used as an aid for the refereeing of the paper only.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.039.

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