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A metal-free synthesis of oxindoles by a radical addition-cyclization onto *N*-arylacrylamides with xanthates

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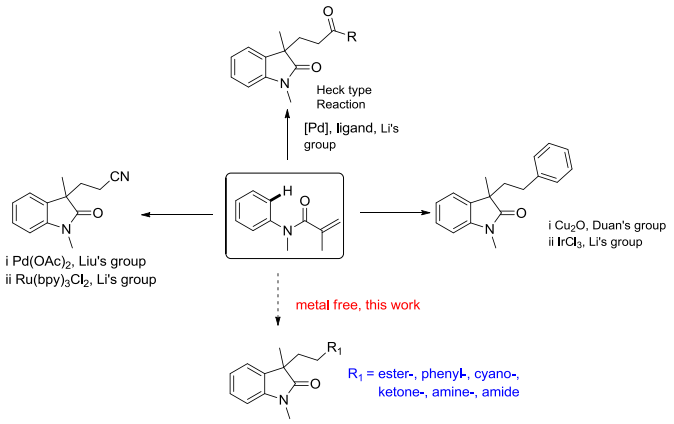
ABSTRACT

A convenient, high yielding synthesis of oxindoles by metal-free di-functionalization of alkenes with xanthates has been developed. This transformation involves a radical addition/cyclization process. Various arylalkylation products including alkyl ester-, benzyl-, cyano-, ketone-, amine-, and amide-substituted oxindoles were prepared in good to excellent yields.

1. Introduction

Oxindoles are important heterocycles found in a wide range of biologically active natural products and pharmaceutical molecules.[1] Consequently, oxindole analogs bearing versatile functional groups are considered as crucial building blocks for the synthesis of many natural products.[2] Thus novel synthetic methods to such scaffold are being actively pursued.[3] In recent years, several groups reported the synthesis of oxindoles via C(sp^3)–C(sp^2) bond formation reactions involving free-radical-initiated sp^3-hybridized C–H bond activation processes, as shown in Scheme 1.[4,5] For instance, Liu et al. disclosed the first oxidative arylalkylation of activated alkenes using the $Pd(OAc)_2$/$Ph(IOAc)_2$ catalytic system that can selectively activate the aryl C(sp^2)–H bond and α-C(sp^3)–H bond of alkyl nitriles.[5b] Later, Duan and Li's group independently reported the benzylarylation reaction of alkenes to prepare a diverse set of alkyl-substituted oxindole analogs.[5e,f] Very recently, Li's group demonstrated the first palladium-catalyzed oxidative di-functionalization of *N*-arylalkenes in the presence of α-carbonyl alkylbromides.[5i] So far, numerous functional groups have been incorporated into the oxindole ring by C–H bond activation chemistry, but examples involving the arylalkylation of activated alkenes via direct functionalization of sp^3 C–H bonds are scarce, particularly those going through metal-free oxidative reactions.



Scheme 1. Alkene di-functionalization processes involving C(sp^3)–H/C(sp^2)–H coupling/cyclization/oxidative reaction.

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.[6] It is well known that the intermediates generated by xanthate-based radical reactions can be readily trapped by alkenes. However, the tandem oxidative cyclization reaction of activated alkenes originated from xanthate initiated radical process has not been reported thus far, which theoretically should provide an elegant synthesis to oxindoles. Herein, we report a novel metal-free tandem oxidative cyclization reaction of activated alkenes mediated by xanthates.

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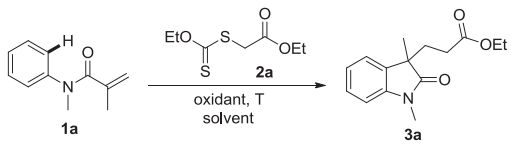
Notably, this chemistry possesses remarkable advantages as follows: (1) good to excellent yields of alkyl-substituted oxindoles can be obtained under mild, metal-free conditions, affording a convenient synthesis to such heterocycles; (2) a large variety of radical intermediates can be produced by the xanthate transfer technique employed in this chemistry, which could be readily manipulated to generate molecules with 'privileged' structures;[7] (3) these transformations are self-regulating, safe, and highly scalable.

2. Results and discussion

Initially, the oxidative cyclization of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with xanthate (**2a**) was chosen as the model reaction to optimize reaction conditions, and the results were summarized in Table 1. Specifically, when **1a** and **2a** were treated with 1.5 equiv of benzoyl peroxide (BPO) in DCE under Ar at 84 °C for 12 h, a 60% yield of the desired product **3a** was isolated (Table 1, entry 1). This result suggests that the selection of oxidant could be crucial for reaction efficiency. Therefore, the effect of oxidant was thoroughly examined and dilauroyl peroxide (DLP) was found to be the most suitable oxidizing reagent, affording an 85% yield of the desired product (Table 1, entries 1–6). Subsequently, we investigated the effect of solvent on this transformation, and it appears that DCE remained as the best solvent. As a matter of fact, polar solvents such as THF, dioxane, EA, and CH_3CN turned out to be detrimental to the reaction efficiency (Table 1, entries 7–10). Surprisingly, it was found that an 88% yield was obtained when this reaction was carried out under air (Table 1, entry 11), which is dramatically higher than what was reported by Li et al.[5i] However, when the reaction temperature was lowered to 55 °C, no conversion was observed. In addition, decreasing the amount of DLP and **2a** seems to dramatically reduce the reaction efficiency (Table 1, entries 14–16).

Table 1
Optimization of reaction conditions[a]

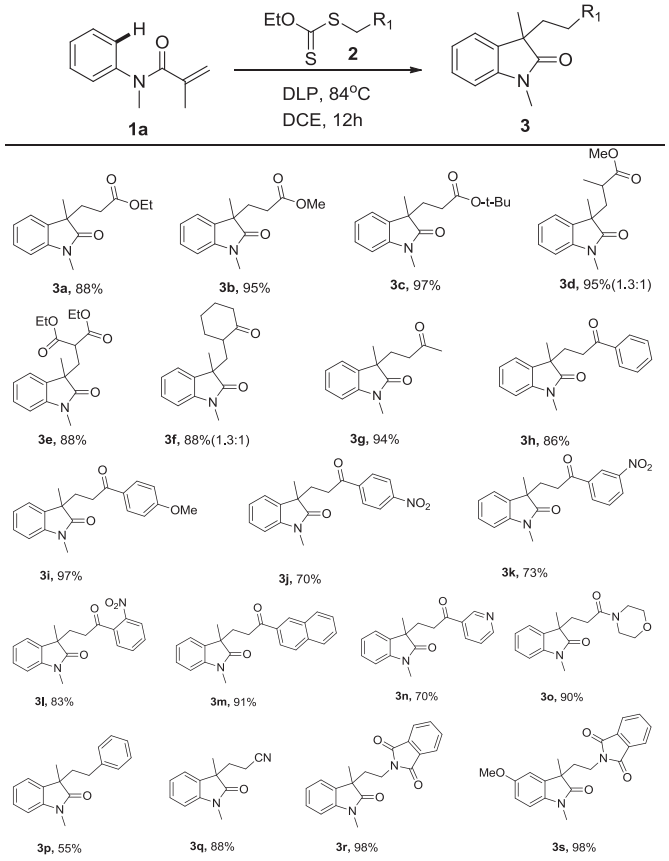


Entry	Oxidant	Temp (°C)	Solvent	Yield (%)
1	BPO	84	DCE	60
2	$PhI(OAc)_2$	84	DCE	Trace
3	DLP	84	DCE	85
4	TBHP	84	DCE	68
5	H_2O_2	84	DCE	NR[b]
6	$K_2S_2O_8$	84	DCE	NR
7	DLP	65	THF	72
8	DLP	100	Dioxane	62
9	DLP	60	EA	25
10	DLP	80	CH_3CN	36
11[c]	*DLP*	*84*	*DCE*	*88*
12[c]	DLP	rt	DCE	NR
13[c]	DLP	55	DCE	NR
14[c,d]	DLP	84	DCE	75
15[c,e]	DLP	84	DCE	73
16[c,d,e]	DLP	84	DCE	64

[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv), **2a** (1.5 equiv), oxidant (1.5 equiv), solvent (3 mL), 12 h, N_2.
[b] NR=no reaction.
[c] Under air.
[d] Oxidant (1.1 equiv).
[e] Compound **2a** (1.1 equiv).

With the optimal reaction conditions in hand, we next examined the scope and limitations of this di-functionalization process, in which various *N*-aryl acrylamides (**1**) and xanthates (**2**) have been employed. At first, a number of xanthates (**2a**–**2r**) bearing alkyl ester, benzyl, cyano, ketone, amine, and amide functional groups were subjected to the standard conditions, affording good to excellent yields of substituted oxindoles, as shown in Table 2. In particular, the functionalization reactions using xanthates containing different alkyl esters (**2a**–**2e**) gave 88–97% yield of the desired products (**3a**–**3e**). When xanthate **2p** was employed in this chemistry, a moderate yield of product **3p** was obtained (55%). Interestingly, the reaction using xanthate **2q** bearing a CN substituent resulted in an 88% yield of the product **3q**. We also examined the reaction efficiency of ketones **2f**–**o**, and good to excellent yields (70–94%) of the desired products (**3f**-**o**) were obtained, superior to literature results (21–61%).[5j] More interestingly, xanthates (**2r**, **2s**) bearing phthalimide protected amine resulted in the highest yield (98%) of products **3r** and **3s**. When xanthate **2d** with an α-substituted ester functional group and xanthate **2f** bearing a cyclohexanone group were allowed to react with **1a**, two regio-isomers were generally obtained in a ratio of 1.3:1 (determined by ^1H NMR analysis of the product mixture), and the isomers are compounds **3d** and **3f**, respectively.

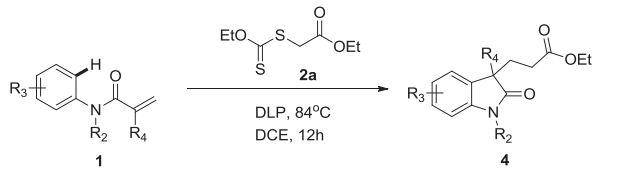
Table 2
Scope of substrate **2**[a]

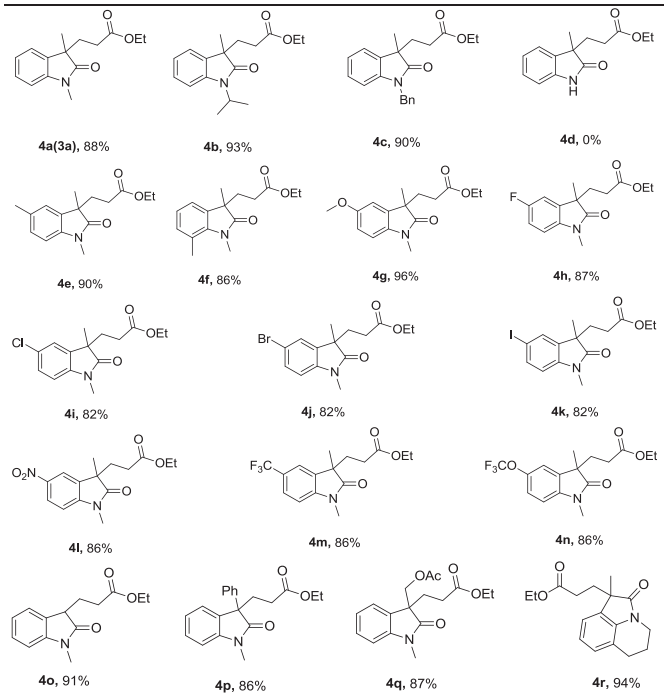


[a] Reaction conditions: **1a** (0.3 mmol, 1 eq.), **2** (1.5 eq.), oxidant (1.5 eq.), DCE (3 mL) at 84 °C for 12 hours under air. The d.r. value is given in parenthesis.

Next, we explored the reaction of different *N*-arylacrylamides **1** with xanthate **2a**, and the results were summarized in Table 3. First, *N*-arylacrylamides **1a** substituted with methyl, isopropyl, and benzyl groups were allowed to react with xanthate **2a**, and the desired products **4a**–**c** were obtained in excellent yields. Arylacrylamide **1d** bearing a free NH group did not produce any desired product due to the dominance of the rotamer with unfavorable geometry for cyclization.[8] Subsequently, it was found that the

Table 3
Scope of *N*-arylacrylamides **1**[a]





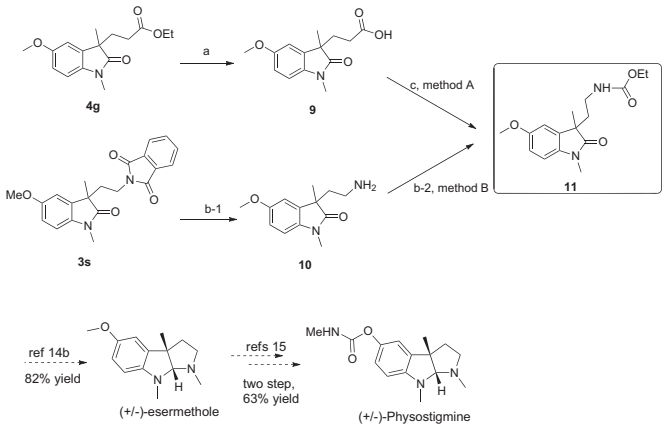
[a] Reaction conditions: **1** (0.3 mmol, 1 eq.), **2a** (1.5 eq.), oxidant (1.5 eq.), DCE (3 mL) at 84 °C for 12 hours under air.

reactions of *N*-arylacrylamides bearing electron-donating or electron-withdrawing groups at the aromatic ring can give excellent yields of the desired products (**4e**–**n**). When the 2-substituted *N*-aryl acrylamides (**1p** and **1q**) were employed, 86% and 87% yields of the desired product were obtained, respectively. Interestingly, the α-unsubstituted *N*-aryl acrylamide **1o** also gave the corresponding oxindole **4o** in a 91% yield. In addition, the reaction of *N*-acryloyl tetrahydroquinoline **1r** and **2a** produced a tricyclic oxindole product **4r** in a 94% yield.

(−)-Physostigmine is a clinical useful anticholinesterase agent that has been used in the treatment of glaucoma and myasthenia gravis.[9] To demonstrate the utility of this method, we applied it in the synthesis of **11**, a key intermediate for the synthesis of (+/−)-physostigmine (Scheme 2).[10,11]

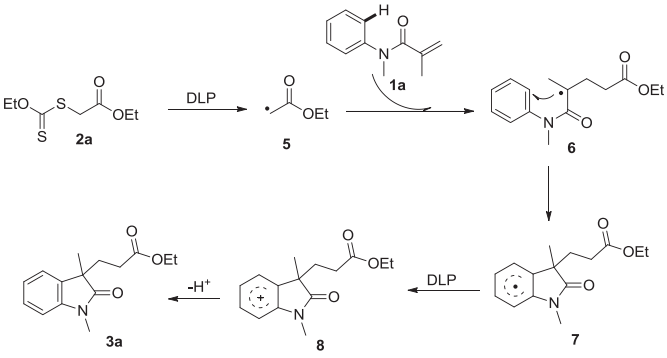
Hydrolysis of oxindole carboxylic acid ester **4g** gave the corresponding oxindole carboxylic acid **9**, which was treated with diphenylphosphoryl azide (DPPA) in the presence of ethanol through the Curtius rearrangement affording the urethane **11** in 75% yield (method A).[12] On the other hand, treating the phthalimide **3s** with hydrazine hydrate provided deprotected product oxindole amine **10**, which reacted with ethyl chloroformate also giving the urethane **11** in 81% yield (method B).[13]

To confirm that this chemistry proceeds through radical-based mechanism, the reaction of **1a** and **2a** was repeated in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under the standard reaction conditions. As expected, no desired product was obtained after 1 equiv of TEMPO was added and the starting material **1a** was fully recovered.



Scheme 2. Synthesis of intermediate **11**. Reaction conditions: (a) 4 N NaOH, MeOH, 2 h, 99%; (b) (b-1): $NH_2NH_2H_2O$, MeOH, 36 h; (b-2): $ClCO_2Et$, Et_3N, DCM, 1 h, 81%; (c) DPPA, Et_3N, EtOH, reflux, 48 h, 75%.[14b,15]

Based on these results and previous observations,[6] we proposed a plausible mechanism for the oxidative arylalkylation reaction of alkenes presented in this work, as depicted in Scheme 3. Initially, xanthate **2a** reacts with DLP to give radical **5**, which would promptly add to acrylamide **1a** to generate radical species **6**. Subsequently, this intermediate undergoes intramolecular carbocyclization to afford **7**, followed by DLP oxidation to produce oxindole cation **8**. De-protonation of **8** would generate the final product **3a**.



Scheme 3. Proposed mechanism for the oxidative arylalkylation of alkenes.

3. Conclusion

In summary, we have developed a facile synthesis of oxindoles by metal-free di-functionalization of alkenes with xanthates. Particularly, various arylalkylation products including alkyl ester-, benzyl-, cyano-, ketone-, amine-, and amide-substituted oxindoles have been prepared in good to excellent yields. This transformation involves a radical addition/cyclization process. It is noteworthy that a wide variety of functional groups including electron-donating, electron-withdrawing, and heteroatom-containing groups can be tolerated. Further studies to extend this chemistry to the synthesis of other heterocyclic systems are currently 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 (ppm) 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, qn=quintet, m=multiplet or unresolved, coupling constant(s) in hertz (Hz)). ^{13}C NMR spectra were obtained by using the same NMR spectrometers. High-resolution mass spectra (HRMS) were 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 3a–s and 4a–r

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 under air. 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 eluant to afford the desired product **3** or **4**.

*4.2.1. Ethyl 3-(1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**3a**).*[5i] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29 (t, J=8.0 Hz, 1H), 7.20 (d, J=7.2 Hz, 1H), 7.08 (t, J=7.2 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 4.08–3.94 (m, 2H), 3.23 (s, 3H), 2.30–2.20 (m, 1H), 2.19–2.01 (m, 2H), 1.92–1.82 (m, 1H), 1.40 (s, 3H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 172.7, 143.2, 132.9, 128.0, 122.7, 122.7, 108.1, 60.3, 47.5, 32.0, 29.7, 26.2, 23.6, 14.0.

*4.2.2. Methyl 3-(1,3-dimethyl-2-oxoindolin-3yl)propanoate (**3b**).* Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28 (t, J=7.7 Hz, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.86 (d, J=7.8 Hz, 1H), 3.54 (s, 3H), 3.22 (s, 3H), 2.30–2.19 (m, 1H), 2.18–2.02 (m, 2H), 1.97–1.82 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 173.2, 143.3, 132.9, 128.1, 122.7, 122.7, 108.1, 51.5, 47.6, 33.0, 29.4, 26.2, 23.6. HRMS (ESI): exact mass calculated for $C_{14}H_{17}NNaO_3$ ($[M+Na]^+$) 270.1101, found 270.1106.

*4.2.3. tert-Butyl 3-(1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**3c**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28 (t, J=7.6 Hz, 1H), 7.20 (d, J=7.2 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.85 (d, J=7.7 Hz, 1H), 3.22 (s, 3H), 2.22–2.16 (m, 1H), 2.10–2.04 (m, 2H), 1.82–1.74 (m, 1H), 1.39 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.1, 172.0, 143.2, 133.2, 128.0, 122.7, 108.0, 80.3, 47.5, 33.0, 30.7, 28.0, 26.2, 23.6. HRMS (ESI): exact mass calculated for $C_{17}H_{23}NNaO_3$ ($[M+Na]^+$) 312.1570, found 312.1572.

*4.2.4. Methyl 3-(1,3-dimethyl-2-oxoindolin-3-yl)-2-methylpropanoate (**3d**).*[5i] dr=1.3:1. The mixture of isomers cannot be separated by column chromatography on silica gel. Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.22 (m, 1H), 7.16–7.12 (m, 1H), 7.09–7.03 (m, 1H), 6.87–6.84 (m, 1H), 3.59 (s, 1.3H), 3.23 (s, 1.7H), 3.19 (s, 1.3H), 3.18 (1.6H), 2.50–2.44 (m, 0.44H), 2.39–2.34 (m, 0.56H), 2.21–2.17 (m, 0.45H), 2.06–1.98 (m, 1H), 1.81–1.75 (m, 0.73H), 1.35 (s, 3H), 1.04 (d, J=6.8Hz, 1.7H), 0.94 (d, J=7.2Hz, 1.3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 179.7, 176.5, 176.3, 143.4, 143.2, 133.4, 132.1, 128.0, 127.9, 123.7, 122.5, 122.4, 122.3, 108.1, 108.0, 51.5, 51.1, 48.0, 47.4, 41.7, 41.3, 36.6, 36.2, 26.2, 26.0, 25.0, 24.6, 19.1, 18.9.

*4.2.5. Diethyl 2-((1,3-dimethyl-2-oxoindolin-3-yl)methyl)malonate (**3e**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.24 (m, 1H), 7.16 (d, J=7.3 Hz, 1H), 7.04 (t, J=7.5Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 4.12 (q, J=7.1 Hz, 2H), 3.86–3.80 (m, 1H), 3.72–3.64 (m, 1H), 3.21 (s, 3H), 3.02 (q, J=5.6 Hz, 1H), 1.39 (s, 3H), 1.21 (t, J=7.2 Hz, 3H), 1.07 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.5, 168.9, 168.7, 143.4, 132.1, 128.2, 123.4, 122.4, 108.0, 61.6, 61.3, 48.7, 47.0, 35.8, 26.2, 24.4, 13.9, 13.7. HRMS (ESI): exact mass calculated for $C_{18}H_{24}NO_5$ ($[M+H]^+$) 334.1649, found 334.1643.

*4.2.6. 1,3-Dimethyl-3-(((R)-2-oxocyclohexyl)methyl)indolin-2-one (**3f**).*[3b] dr=1.3:1. The mixture of isomers cannot be separated by column chromatography on silica gel. Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.24 (m, 1H), 7.20–7.15 (m, 1H), 7.08–7.02 (m, 1H), 6.85 (d, J=8.0 Hz, 1H), 3.23 (s, 1.7H), 3.21 (s, 1.3H), 2.75–2.65 (m, 1H), 2.44–2.40 (m, 1H), 2.31–2.20 (m, 1H), 2.08–2.00 (m, 1H), 1.90–1.85 (m, 2H), 1.77–1.43 (m, 5H), 1.36 (s, 1.7H), 1.33 (s, 1.3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.4, 211.5, 180.6, 180.2, 143.0, 143.0, 134.5, 133.3, 127.8, 127.8, 123.2, 122.6, 122.5, 108.1, 108.0, 47.3, 47.1, 46.9, 41.7, 41.5, 37.1, 36.1, 35.6, 35.0, 28.2, 27.9, 26.2, 26.1, 25.1, 25.0, 24.5, 24.3.

*4.2.7. 1,3-Dimethyl-3-(3-oxobutyl)indolin-2-one (**3g**).*[3b] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30–7.26 (m, 1H), 7.16 (d, J=7.3 Hz, 1H), 7.09–7.05 (m, 1H), 6.86 (d, J=7.8 Hz, 1H), 3.23 (s, 3H), 2.24–2.06 (m, 3H), 1.99–1.91 (m, 1H), 1.97 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.6, 180.1, 143.0, 133.3, 128.0, 122.7, 122.7, 108.1, 47.3, 38.6, 31.8, 29.8, 26.2, 23.6.

*4.2.8. 1,3-Dimethyl-3-(3-oxo-3-phenylpropyl)indolin-2-one (**3h**).*[3b] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, J=8.1 Hz, 2H), 7.53–7.49 (m, 1H), 7.41–7.38 (m, 2H), 7.31–7.27 (m, 1H), 7.22 (d, J=7.3 Hz, 1H), 7.11–7.07 (m, 1H), 6.87 (d, J=7.7 Hz, 1H), 3.27 (s, 3H), 2.84–2.77 (m, 1H), 2.54–2.51 (m, 1H), 2.39–2.33 (m, 1H), 2.27–2.21 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.3, 180.2, 143.2, 136.7, 133.4, 133.0, 128.5, 128.1, 128.0, 122.8, 122.7, 108.1, 47.6, 33.6, 32.4, 26.1, 23.7.

*4.2.9. 3-(3-(4-Methoxyphenyl)-3-oxopropyl)-1,3-dimethylindolin-2-one (**3i**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J=8.7 Hz, 2H), 7.28 (t, J=7.6 Hz, 1H), 7.22 (d, J=7.2 Hz, 1H), 7.08 (t, J=7.2 Hz, 1H), 6.87 (d, J=8.0 Hz, 3H), 3.84 (s, 3H), 3.26 (s, 3H), 2.80–2.72 (m, 1H), 2.48–2.19 (m, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.9, 180.2, 163.4, 143.2, 133.5, 130.3, 129.7, 128.0, 122.8, 122.7, 55.4, 47.7, 33.2, 32.7, 26.2, 23.8. HRMS (ESI): exact mass calculated for $C_{20}H_{22}NO_3$ ($[M+H]^+$) 324.1594, found 324.1592.

*4.2.10. 1,3-Dimethyl-3-(3-(4-nitrophenyl)-3-oxopropyl)indolin-2-one (**3j**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J=8.8 Hz, 2H), 7.93 (d, J=8.8 Hz, 2H), 7.31–7.27 (m, 1H), 7.21 (d, J=7.1 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 6.88 (d, J=7.8 Hz, 1H), 3.27 (s, 3H), 2.87–2.79 (m, 1H), 2.65–2.57 (m, 1H), 2.40–2.33 (m, 1H), 2.29–2.21 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 180.1, 150.2, 143.1, 141.0, 133.2, 128.9, 128.2, 123.6, 122.9, 122.7, 108.2, 47.5, 34.2, 26.3, 23.8. HRMS (ESI): exact mass calculated for $C_{19}H_{19}N_2O_4$ ($[M+H]^+$) 339.1339, found 339.1343.

*4.2.11. 1,3-Dimethyl-3-(3-(3-nitrophenyl)-3-oxopropyl)indolin-2-one (**3k**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 8.34 (d, J=8.2 Hz, 1H), 8.11 (d, J=7.8 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.25 (t, J=7.7 Hz, 1H), 7.20 (d, J=7.3 Hz, 1H), 7.06 (t, J=7.4 Hz, 1H), 6.86 (d, J=7.8 Hz, 1H), 3.26 (s, 3H), 2.87–2.74 (m, 1H), 2.67–2.56 (m, 1H), 2.43–2.21 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 180.1, 148.3, 143.1, 137.8, 133.6, 133.1, 129.8, 128.2, 127.2, 122.9, 122.8, 108.3, 47.5, 33.8, 32.2, 26.3, 23.9. HRMS (ESI): exact mass calculated for $C_{19}H_{19}N_2O_4$ ($[M+H]^+$) 339.1339, found 339.1342.

*4.2.12. 1,3-Dimethyl-3-(3-(2-nitrophenyl)-3-oxopropyl)indolin-2-one (**3l**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (d, J=1.6 Hz, 1H), 8.68 (dd, J=1.6, 4.8 Hz, 1H), 8.04 (dt, J=8.0, 12.0 Hz, 1H), 7.33 (dd, J=8.0, 4.8 Hz, 1H), 7.28–7.23 (m, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.05

(t, *J*=7.5 Hz, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 3.23 (s, 3H), 2.81–2.69 (m, 1H), 2.59–2.47 (m, 1H), 2.35–2.22 (m, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.0, 180.0, 153.3, 149.4, 143.1, 135.3, 133.1, 131.8, 128.2, 123.5, 122.8, 122.7, 108.2, 47.5, 33.9, 32.1, 26.2, 23.7. HRMS (ESI): exact mass calculated for $C_{19}H_{19}N_2O_4$ ($[M+H]^+$) 339.1339, found 339.1341.

*4.2.13. 1,3-Dimethyl-3-(3-(naphthalen-2-yl)-3-oxopropyl)indolin-2-one (**3m**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.94–7.80 (m, 4H), 7.60–7.51 (m, 2H), 7.34–7.21 (m, 2H), 7.11 (t, *J*=7.5 Hz, 1H), 6.87 (d, *J*=7.7 Hz, 1H), 3.28 (s, 3H), 3.00–2.92 (m, 1H), 2.73–2.61 (m, 1H), 2.48–2.37 (m, 1H), 2.37–2.25 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.3, 180.3, 143.2, 135.5, 134.0, 133.5, 132.4, 129.6, 129.6, 128.4, 128.3, 128.1, 127.7, 126.7, 123.8, 122.8, 122.7, 108.2, 47.7, 33.6, 32.7, 26.3, 23.8. HRMS (ESI): exact mass calculated for $C_{23}H_{22}NO_2$ ($[M+H]^+$) 344.1645, found 344.1648.

*4.2.14. 1,3-Dimethyl-3-(3-oxo-3-(pyridin-3-yl)propyl)indolin-2-one (**3n**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (dd, *J*=0.8, 8.4 Hz, 1H), 7.67 (dt, *J*=0.8, 8.4 Hz, 1H), 7.56 (dt, *J*=1.2, 7.8 Hz, 1H), 7.32–7.23 (m, 3H), 7.12 (t, *J*=7.5 Hz, 1H), 6.86 (d, *J*=7.5 Hz, 1H), 3.22 (s, 3H), 2.62–2.53 (m, 1H), 2.45–2.41 (m, 2H), 2.35–2.25 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.5, 180.0, 143.1, 138.0, 134.2, 133.3, 130.3, 128.1, 127.2, 124.4, 122.9, 122.7, 108.1, 47.3, 38.1, 31.9, 26.2, 23.7. HRMS (ESI): exact mass calculated for $C_{18}H_{19}N_2O_2$ ($[M+H]^+$) 295.1441, found 295.1441.

*4.2.15. 1,3-Dimethyl-3-(3-morpholino-3-oxopropyl)indolin-2-one (**3o**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (t, *J*=7.2 Hz, 1H), 7.20 (d, *J*=7.3 Hz, 1H), 7.07 (t, *J*=7.5 Hz, 1H), 6.85 (d, *J*=7.7 Hz, 1H), 3.63–3.52 (m, 5H), 3.50–3.42 (m, 1H), 3.32–3.26 (m, 2H), 3.22 (s, 3H), 2.21–2.03 (m, 3H), 1.87–1.81 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.7, 170.5, 142.6, 133.3, 128.0, 122.8, 122.7, 108.0, 66.8, 66.5, 47.6, 45.8, 41.8, 33.2, 28.0, 26.2, 23.9. HRMS (ESI): exact mass calculated for $C_{17}H_{23}N_2O_3$ ($[M+H]^+$) 303.1703, found 303.1697.

*4.2.16. 1,3-Dimethyl-3-phenethylindolin-2-one (**3p**).*[5e] White solid, mp=81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (t, *J*=7.6 Hz, 1H), 7.26–7.21 (m, 3H), 7.14 (q, *J*=7.2 Hz, 2H), 7.05 (d, *J*=7.2 Hz, 2H), 6.89 (d, *J*=7.7 Hz, 1H), 3.23 (s, 3H), 2.37–2.27 (m, 2H), 2.20–2.16 (m, 1H), 2.09–2.01 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.5, 143.4, 141.3, 133.7, 128.3, 128.2, 127.9, 125.9, 122.6, 122.5, 108.0, 48.4, 40.2, 30.9, 26.1, 23.9.

*4.2.17. 3-(1,3-Dimethyl-2-oxoindolin-3-yl)propanenitrile (**3q**).*[5d] Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (t, *J*=7.5 Hz, 1H), 7.20 (d, *J*=7.2 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 3.23 (s, 3H), 2.37–2.29 (m, 1H), 2.12–1.96 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.9, 143.2, 131.7, 128.7, 123.1, 122.6, 118.8, 108.5, 47.3, 33.4, 26.3, 23.5, 12.8.

*4.2.18. 2-(2-(1,3-Dimethyl-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (**3r**).* White solid; mp=143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.59 (m, 4H), 7.08 (d, *J*=7.2 Hz, 1H), 6.95 (t, *J*=7.6 Hz, 1H), 6.73 (dd, *J*=7.2, 7.6 Hz, 2H), 3.71–3.52 (m, 1H), 3.48–3.41 (m, 1H), 3.20 (s, 3H), 2.56–2.38 (m, 1H), 2.37–2.20 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 167.8, 143.1, 133.6, 132.9, 131.9, 127.5, 122.8, 122.3, 122.0, 108.3, 47.0, 34.6, 34.5, 26.3, 25.1. HRMS (ESI): exact mass calculated for $C_{20}H_{19}N_2O_3$ ($[M+H]^+$) 335.1390, found 335.1397.

*4.2.19. 2-(2-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (**3s**).* Yellow solid, 98% yield; mp=100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.57 (m, 4H), 6.65 (d, *J*=2.4 Hz, 1H), 6.56 (d, *J*=8.4 Hz, 1H), 6.37 (dd, *J*=8.4, 2.4 Hz, 1H), 3.73–3.59 (m, 1H), 3.56 (s, 3H), 3.50–3.37 (m, 1H), 3.18 (s, 3H), 2.60–2.41 (m, 1H), 2.39–2.19 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 167.7, 155.7, 136.57, 134.2, 133.5, 131.8, 122.7, 111.6, 109.3, 108.8, 55.3, 47.5, 34.7, 34.4, 26.4, 25.3. HRMS (ESI): exact mass calculated for $C_{21}H_{21}N_2O_4$ ($[M+H]^+$) 365.1496, found 365.1507.

*4.2.20. Ethyl 3-(1-isopropyl-3-methyl-2-oxoindolin-3-yl)propanoate (**4b**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27–7.15 (m, 2H), 7.06–7.01 (m, 2H), 4.65 (dt, *J*=10.5, 7.0 Hz, 1H), 4.01–3.96 (m, 2H), 2.28–2.17 (m, 1H), 2.17–1.97 (m, 2H), 1.88–1.74 (m, 1H), 1.49 (dd, *J*=7.0, 1.7 Hz, 6H), 1.36 (s, 3H), 1.16 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 172.8, 141.8, 133.4, 127.7, 123.0, 122.1, 109.8, 60.3, 47.2, 43.6, 33.2, 29.4, 23.8, 19.5, 19.4, 14.1. HRMS (ESI): exact mass calculated for $C_{17}H_{24}NO_3$ ($[M+H]^+$) 290.1751, found 290.1742.

*4.2.21. Ethyl 3-(1-benzyl-3-methyl-2-oxoindolin-3-yl)propanoate (**4c**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.24 (m, 5H), 7.22–7.15 (m, 2H), 7.05 (t, *J*=7.5 Hz, 1H), 6.76 (d, *J*=7.8 Hz, 1H), 4.94 (s, 2H), 4.07–3.95 (m, 2H), 2.35–2.29 (m, 1H), 2.24–2.10 (m, 2H), 1.94–1.90 (m, 1H), 1.46 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.1, 172.8, 142.4, 136.0, 133.0, 128.8, 128.0, 127.6, 127.3, 122.9, 122.7, 109.2, 60.4, 47.6, 43.7, 33.0, 29.8, 24.0, 14.1. HRMS (ESI): exact mass calculated for $C_{21}H_{24}NO_3$ ($[M+H]^+$) 338.1751, found 338.1752.

*4.2.22. Ethyl 3-(1,3,5-trimethyl-2-oxoindolin-3-yl)propanoate (**4e**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (d, *J*=7.9 Hz, 1H), 7.00 (s, 1H), 6.74 (d, *J*=7.9 Hz, 1H), 4.03–3.99 (m, 2H), 3.20 (s, 3H), 2.35 (s, 3H), 2.26–2.17 (m, 1H), 2.15–2.00 (m, 2H), 1.94–1.81 (m, 1H), 1.38 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 172.9, 140.9, 132.9, 132.2, 128.2, 123.6, 107.8, 60.3, 47.7, 33.0, 29.7, 26.2, 23.5, 21.0, 14.0. HRMS (ESI): exact mass calculated for $C_{16}H_{22}NO_3$ ($[M+H]^+$) 276.1594, found 276.1598.

*4.2.23. Ethyl 3-(1,3,7-trimethyl-2-oxoindolin-3-yl)propanoate (**4f**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02–6.93 (m, 3H), 4.02–3.96 (m, 2H), 3.50 (s, 3H), 2.58 (s, 3H), 2.29–2.15 (m, 1H), 2.15–1.96 (m, 2H), 1.93–1.77 (m, 1H), 1.36 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.7, 172.8, 141.0, 133.6, 131.7, 122.6, 120.6, 119.7, 60.3, 46.9, 33.4, 29.6, 29.5, 24.0, 19.0, 14.1. HRMS (ESI): exact mass calculated for $C_{16}H_{22}NO_3$ ($[M+H]^+$) 276.1594, found 276.1593.

*4.2.24. Ethyl 3-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**4g**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 (dd, *J*=5.9, 2.4 Hz, 2H), 6.76–6.71 (m, 1H), 4.02–3.96 (m, 2H), 3.78 (s, 3H), 3.18 (s, 3H), 2.27–2.15 (m, 1H), 2.13–1.97 (m, 2H), 1.90–1.81 (m, 1H), 1.36 (s, 3H), 1.15 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 172.7, 156.2, 136.7, 134.3, 112.1, 110.3, 108.3, 60.3, 55.8, 48.0, 33.0, 29.6, 26.2, 23.6, 14.1. HRMS (ESI): exact mass calculated for $C_{16}H_{22}NO_4$ ($[M+H]^+$) 292.1543, found 292.1542.

*4.2.25. Ethyl 3-(5-fluoro-1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**4h**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (ddd, *J*=2.4, 8.0, 8.8 Hz, 1H), 6.93 (dd, *J*=2.4, 8.8 Hz, 1H), 6.76 (dd, *J*=4.1, 8.0 Hz, 1H), 4.02–3.99 (m, 2H), 3.20 (s, 3H), 2.28–2.16 (m, 1H), 2.15–1.98 (m, 2H), 1.93–1.77 (m, 1H), 1.37 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 172.4, 160.6, 158.1, 139.1 (d, *J*=1.6 Hz), 134.7 (d, *J*=7.8 Hz), 114.2 (d, *J*=23.4 Hz), 110.9 (d, *J*=24.4 Hz), 108.5 (d, *J*=8.1 Hz), 60.5, 48.1, 32.9, 29.6, 26.2, 23.4, 14.1. HRMS (ESI): exact mass calculated for $C_{15}H_{19}FNO_3$ ($[M+H]^+$) 280.1344, found 280.1345.

*4.2.26. Ethyl 3-(5-chloro-1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**4i**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (dd, *J*=8.3, 2.1 Hz,

1H), 7.16 (d, *J*=2.1 Hz, 1H), 6.77 (d, *J*=8.3 Hz, 1H), 4.04–3.97 (m, 2H), 3.20 (s, 3H), 2.29–2.15 (m, 1H), 2.15–2.00 (m, 2H), 1.92–1.83 (m, 1H), 1.38 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.4, 172.5, 141.8, 134.7, 128.1, 128.0, 123.3, 109.0, 60.5, 47.9, 32.9, 29.6, 26.3, 23.5, 14.1. HRMS (ESI): exact mass calculated for $C_{15}H_{18}ClNNaO_3$ ($[M+Na]^+$) 318.0867, found 318.0871.

*4.2.27. Ethyl 3-(5-bromo-1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**4j**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, *J*=8.3 Hz, 1H), 7.28 (s, 1H), 6.72 (d, *J*=8.3 Hz, 1H), 4.00 (q, *J*=7.1 Hz, 2H), 3.19 (s, 3H), 2.28–2.15 (m, 1H), 2.10–2.01 (m, 2H), 1.88–1.82 (m, 1H), 1.37 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.3, 172.5, 142.3, 135.1, 131.0, 126.0, 115.3, 110.0, 60.5, 47.7, 32.9, 29.7, 26.3, 23.4, 14.1. HRMS (ESI): exact mass calculated for $C_{15}H_{19}BrNO_3$ ($[M+H]^+$) 340.0543, found 340.0545.

*4.2.28. Ethyl 3-(5-iodo-1,3-dimethyl-2-oxoindolin-3-yl)propanoate (**4k**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (dd, *J*=8.2, 1.6 Hz, 1H), 7.46 (d, *J*=1.6 Hz, 1H), 6.64 (d, *J*=8.2 Hz, 1H), 4.02 (q, *J*=7.1 Hz, 2H), 3.19 (s, 3H), 2.26–2.17 (m, 1H), 2.15–2.00 (m, 2H), 1.97–1.80 (m, 1H), 1.37 (s, 3H), 1.19 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 172.5, 142.9, 136.8, 135.5, 131.5, 110.1, 85.2, 60.6, 47.6, 32.9, 29.5, 26.3, 23.4, 14.01. HRMS (ESI): exact mass calculated for $C_{15}H_{19}INO_3$ ($[M+H]^+$) 388.0404, found 388.0406.

*4.2.29. Ethyl 3-(1,3-dimethyl-5-nitro-2-oxoindolin-3-yl)propanoate (**4l**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (dd, *J*=8.6, 2.3 Hz, 1H), 8.09 (d, *J*=2.3 Hz, 1H), 6.95 (d, *J*=8.6 Hz, 1H), 4.01 (q, *J*=7.1 Hz, 2H), 3.29 (s, 3H), 2.36–2.31 (m, 1H), 2.23–2.06 (m, 2H), 1.96–1.88 (m, 1H), 1.45 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 172.1, 148.9, 143.6, 133.9, 125.5, 118.7, 107.7, 60.7, 47.6, 32.8, 29.5, 26.6, 23.3, 14.1. HRMS (ESI): exact mass calculated for $C_{15}H_{18}N_2NaO_5$ ($[M+Na]^+$) 329.1108, found 329.1109.

*4.2.30. Ethyl 3-(1,3-dimethyl-2-oxo-5(trifluoromethyl)indolin-3-yl) propanoate (**4m**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J*=8.2 Hz, 1H), 7.42 (s, 1H), 6.93 (d, *J*=8.2 Hz, 1H), 4.00 (q, *J*=7.1, 2H), 3.26 (s, 3H), 2.35–2.22 (m, 1H), 2.21–2.03 (m, 2H), 1.92–1.82 (m, 1H), 1.42 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.8, 172.4, 146.2, 133.6, 125.96 (m, 1C), 125.0 (d, *J*=32.2 Hz, 1C), 123.0, 119.79 (d, *J*=3.7 Hz, 1C), 107.9, 60.5, 47.6, 32.8, 29.6, 26.4, 23.4, 14.0. HRMS (ESI): exact mass calculated for $C_{16}H_{18}F_3NNaO_3$ ($[M+H]^+$) 352.1131, found 352.1135.

*4.2.31. Ethyl 3-(1,3-dimethyl-2-oxo-5-(trifluoromethoxy)indolin-3-yl)propanoate (**4n**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (t, *J*=8.4 Hz, 1H), 7.08 (s, 1H), 6.84 (d, *J*=8.4 Hz, 1H), 4.12–3.94 (m, 2H), 3.23 (s, 3H), 2.28–2.21 (m, 1H), 2.18–2.02 (m, 2H), 1.95–1.86 (m, 1H), 1.40 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 172.4, 144.9, 141.9, 134.6, 127.8, 121.1, 116.8, 108.4, 60.5, 48.0, 32.8, 29.5, 26.3, 23.4, 14.1. HRMS (ESI): exact mass calculated for $C_{16}H_{18}F_3NNaO_4$ ($[M+Na]^+$) 368.1080, found 368.1081.

*4.2.32. Ethyl 3-(1-methyl-2-oxoindolin-3-yl)propanoate (**4o**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.26 (m, 2H), 7.08 (t, *J*=7.2 Hz, 1H), 6.84 (d, *J*=7.6 Hz, 1H), 4.17–4.01 (m, 2H), 3.52 (t, *J*=5.9 Hz, 1H), 3.22 (s, 3H), 2.53–2.20 (m, 4H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 172.9, 144.4, 128.2, 123.9, 122.5, 108.0, 60.4, 44.4, 30.4, 26.1, 25.6, 14.2. HRMS (ESI): exact mass calculated for $C_{14}H_{18}NNaO_3$ ($[M+Na]^+$) 270.1101, found 270.1104.

*4.2.33. Ethyl 3-(1-methyl-2-oxo-3-phenylindolin-3-yl)propanoate (**4p**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.22 (m, 7H), 7.14 (t, *J*=7.9 Hz, 1H), 6.93 (d, *J*=7.8 Hz, 1H), 4.07–4.01 (m, 2H), 3.25 (s, 3H), 2.81–2.69 (m, 1H), 2.64–2.52 (m, 1H), 2.23–2.15 (m, 1H), 2.03–1.95 (m, 1H), 1.20 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 172.6, 143.8, 139.5, 131.3, 128.6, 128.5, 127.5, 126.9, 124.9, 122.8, 108.5, 60.5, 55.8, 32.5, 29.8, 26.4, 14.1. HRMS (ESI): exact mass calculated for $C_{20}H_{21}NNaO_3$ ($[M+Na]^+$) 346.1414, found 346.1415.

*4.2.34. Ethyl 3-(3-(acetoxymethyl)-1-methyl-2-oxoindolin-3-yl) propanoate (**4q**).* Ligh yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (t, *J*=7.8 Hz, 1H), 7.22 (d, *J*=7.2 Hz, 1H), 7.07 (t, *J*=7.6 Hz, 1H), 6.86 (d, *J*=7.8 Hz, 1H), 4.50 (d, *J*=10.8 Hz, 1H), 4.16 (d, *J*=10.8 Hz, 1H), 4.01–3.95 (m, 2H), 3.23 (s, 3H), 2.28–2.18 (m, 2H), 2.11–2.02 (m, 1H), 1.94–1.80 (m, 4H), 1.16 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 172.3, 170.3, 144.0, 128.8, 128.5, 123.7, 122.8, 108.2, 67.1, 60.5, 51.7, 28.9, 28.4, 26.3, 20.5, 14.1. HRMS (ESI): exact mass calculated for $C_{17}H_{21}NNaO_5$ ($[M+Na]^+$) 342.1312, found 342.1309.

*4.2.35. Ethyl 3-(1-methyl-2-oxo-2,4,5,6-tetrahydro-1H-pyrrolo [3,2,1-ij]quinolin-1-yl)propanoate (**4r**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09–6.83 (m, 3H), 4.02–3.95 (m, 2H), 3.72–3.69 (m, 2H), 2.78 (t, *J*=6.0 Hz, 2H), 2.26–1.86 (m, 6H), 1.38 (s, 3H), 1.16 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.8, 172.8, 139.0, 131.5, 126.8, 122.1, 120.6, 120.2, 60.4, 48.9, 38.8, 32.8, 29.6, 24.6, 23.3, 21.3, 14.1. HRMS (ESI): exact mass calculated for $C_{17}H_{21}NNaO_3$($[M+Na]^+$) 310.1414, found 310.1409.

4.3. Synthesis of compound 9

A 4 N NaOH solution (15.0 mL) was added to a solution of **4g** (582 mg, 3 mmol) in MeOH (15.0 mL). The mixture was stirred at room temperature for 2 h. Then, the aqueous solution was acidified by 3 N HCl to pH 1, and evaporated to remove MeOH. The mixture was extracted with DCM (3×10 mL). The combined organic phase was dried over Na_2SO_4. After removal of solvents with a rotary evaporator, product **9** was obtained as a white solid (525 mg, 99%). Mp=140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84–6.72 (m, 3H), 3.79 (s, 3H), 3.19 (s, 3H), 2.23 (dd, *J*=17.2, 5.5 Hz, 1H), 2.16–2.00 (m, 2H), 1.95–1.86 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.7, 178.1, 156.3, 136.6, 134.2, 112.3, 110.2, 108.6, 55.8, 48.0, 32.7, 29.3, 26.3, 23.6. HRMS (ESI): exact mass calculated for $C_{14}H_{18}NO_4$ ($[M+H]^+$) 264.1230, found 264.1234.

4.4. Synthesis of compound 11[13b]

Method A: A mixture of acid **9** (105.2 mg, 0.4 mmol), diphenylphosphoryl azide (220 mg, 0.8 mmol), and TEA (80.8 mg, 0.8 mmol) in EtOH (5 mL) was refluxed for 48 h. After the solvent was evaporated under reduced pressure, the residue was purified by column to give product **11** as a colorless oil (91.8 mg, 75%).

Method B: A solution of hydrazine hydrate (51.2 mg, 0.83 mmol) and phthalimide protected amine **3s** (200 mg, 0.55 mmol) in MeOH (9 mL) was stirred at room temperature for 36 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 and concentrated to give product **10** without purification for next step. The residue **10** was dissolved in CH_2Cl_2 (5 mL) and were added Et_3N (83.8 mg, 0.83 mmol) and $ClCO_2Et$ (89.6 mg, 0.83 mmol). The reaction mixture was stirred at room temperature for another 1 h. Standard workup gave product **11** (136 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82–6.73 (m, 3H), 4.74 (br s, 1H), 4.02 (q, *J*=7.0 Hz, 2H), 3.80 (s, 3H), 3.19 (s, 3H), 3.08–2.77 (m, 2H), 2.15–2.08 (m, 1H), 2.00 (s, 1H), 1.36 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ: 180.0, 156.3, 156.3, 136.5, 134.7, 112.1, 110.3, 108.5, 60.6, 55.8, 47.4, 37.4, 37.2, 26.3, 24.1, 14.6.

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Supplementary data

The original data of ^{1}H NMR and ^{13}C NMR of all products are supplied. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.049. These data include MOL files and InChiKeys of the most important compounds described in this article.

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