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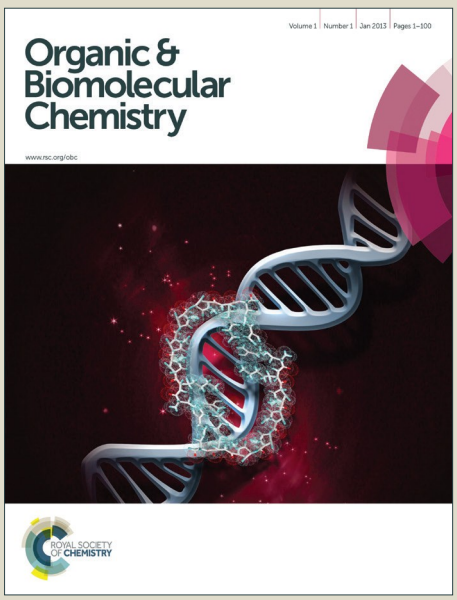





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# An unprecedented protocol for the synthesis of 3-hydroxy-3-phenacyloxindole derivatives with indolin-2-ones and α-substituted ketones

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**An unprecedented reaction between indolin-2-ones and α-substituted ketones has been developed. Using this protocol, a wide range of biologically important 3-hydroxy-3-phenacyloxindole derivatives could be obtained in good yield (up to 93%) under mild reaction conditions. A possible mechanism of this reaction was tentatively proposed based on some control experiments and MS spectrometry analysis.**

3,3'-Disubstituted oxindoles are ubiquitous heterocycles found in a wide range of natural products, pharmaceuticals, and agrochemicals.[1] Among them, 3-hydroxy-3-substituted oxindole constitutes a key structural feature of vast majority of important and complex compounds with a broad spectrum of biological activities.[1,2] In particular, various 3-hydroxy-3-phenacyloxindole analogs have served as a class of significant structural cores in medicinal chemistry (Fig. 1).[3] As a consequence, several efficient and facile methodologies for the preparation of diverse 3-hydroxy-3-phenacyloxindole derivatives have been developed in the last few years.[4] However, a survey of literature shows that these reported strategies overwhelmingly focused on the nucleophilic addition reaction by using isatins as electrophiles reacting with appropriate nucleophiles, such as methyl ketones and β-ketoacids (Scheme 1).[4] Despite these significant advances, given the profile between the potential bioactivities and molecular diversities, the development of new methods for the construction of the 3-hydroxy-3-phenacyloxindole derivatives with structural diversity is still one of the important and promising areas of chemical research.

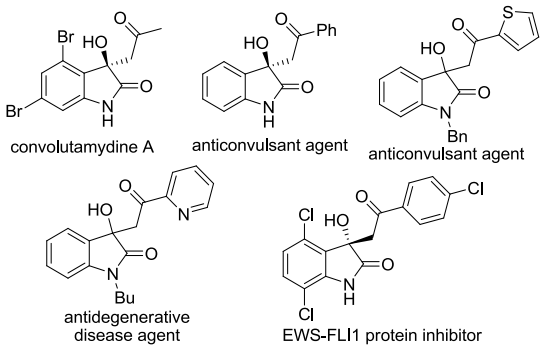


**Fig. 1**. Selected examples of bioactive 3-hydroxy-3-phenacyloxindole analogs.

As part of our research program aimed at establishing new methodologies for the synthesis of 2-oxindole compounds containing a tetrasubstituted carbon center at the C3-position,[5] we are interested in developing an innovative strategy by using simple and easily accessible starting materials, not isatins for the preparation of 3-hydroxy-3-phenacyloxindole analogs. In this context, we noticed that indolin-2-ones, which were used as efficient $C_1$ synthons for the construction of spirocyclic oxindoles,[6,7] had never been employed as nucleophiles for the synthesis of 3-hydroxy-3-substituted oxindoles. Herein, we present an unprecedented synthetic strategy to access 3-hydroxy-3-phenacyloxindole analogs in good to high yields under mild conditions. Notably, at the heart of the study is the use of indolin-2-ones and α-substituted ketones as starting materials for the first time, thus opening a new avenue to structurally diverse 3-hydroxy-3-phenacyloxindole derivatives (Scheme 1).

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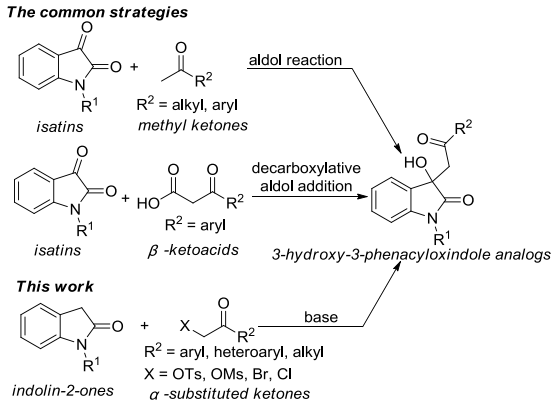
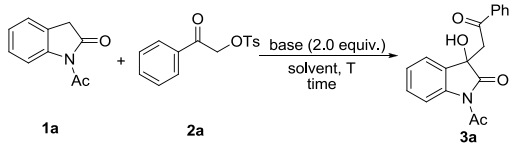



**Scheme 1** Strategies for the synthesis of 3-hydroxy-3-phenacyloxindole analogs.

## Results and Discussion

We began our study using the reaction between *N*-Ac-protected indolin-2-one **1a** and α-tosyloxyacetophenone (**2a**)[8] to screen for the optimal reaction conditions (Table 1). At first, with acetonitrile as the solvent at room temperature, we examined the different bases for the reaction (Table 1, entries 1-7). The results showed that some nitrogen-containing organic bases, such as triethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were invalid to the reaction of **1a** and 2**a** (Table 1, entries 1-3), while some inorganic bases could promoted the reaction to give 3-hydroxy-3-phenacyloxindole **3a** (Table 1, entries 4-6). Among them, two equivalents $Cs_2CO_3$ could provide **3a** with 63% yield in 10 h (Table 1, entry 5). Disappointingly, by switching $Cs_2CO_3$ to KOH under otherwise identical conditions, the reaction system became too messy to isolate **3a** (Table 1, entry 7). Afterwards, the screening of solvents (Table 1, entries 8-12) revealed that THF was the optimum choice for the reaction in terms of both rate of the reaction as well as the isolated yield of the product (Table 1, entry 12). When the reaction was carried out in 2.0 mL of THF, **3a** was achieved in only 61% yield in 24 h (Table 1, entry 13). This result suggested that low concentration was unfavorable to the reaction. Considering the generation of an equivalent of TsOH during the reaction, we thought that at least one equivalent of base was necessary to promote the reaction. And then, after investigating the different amount of the base (Table 1, entries 14-15), it was found that two equivalents $Cs_2CO_3$ was the most effective to the reaction. Ultimately, on the basis of probing into the reaction temperature (Table 1, entries 16-17), it was observed that **3a** could be obtained in up to 92% yield at 0 $^oC$ (Table 1, entry 17). It is worth mentioning that the structure of product **3a** was unequivocally confirmed by means of the single-crystal X-ray diffraction as shown in Fig. 2.[9]

**Table 1** Optimization of reaction conditions[a]




| Entry | Solvent | Base | T ($^oC$) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | $Et_3N$ | rt | 18 | nd |
| 2 | $CH_3CN$ | DABCO | rt | 18 | nd |
| 3 | $CH_3CN$ | DBU | rt | 18 | trace |
| 4 | $CH_3CN$ | $K_2CO_3$ | rt | 16 | 43 |
| 5 | $CH_3CN$ | $Cs_2CO_3$ | rt | 10 | 63 |
| 6 | $CH_3CN$ | $Na_3PO_4$ | rt | 18 | 34 |
| 7 | $CH_3CN$ | KOH | rt | 10 | messy |
| 8 | EtOAc | $Cs_2CO_3$ | rt | 24 | 77 |
| 9 | $CH_2Cl_2$ | $Cs_2CO_3$ | rt | 24 | trace |
| 10 | toluene | $Cs_2CO_3$ | rt | 24 | trace |
| 11 | DMF | $Cs_2CO_3$ | rt | 6 | 42 |
| 12 | THF | $Cs_2CO_3$ | rt | 8 | 79 |
| 13 | THF | $Cs_2CO_3$ | rt | 24 | 61[c] |
| 14 | THF | $Cs_2CO_3$ | rt | 18 | 36[d] |
| 15 | THF | $Cs_2CO_3$ | rt | 8 | 68[e] |
| 16 | THF | $Cs_2CO_3$ | 50 | 2 | 32 |
| 17 | THF | $Cs_2CO_3$ | 0 | 8 | 92 |

[a] Unless otherwise noted, the reactions were carried out with 0.15 mmol **1a**, 0.10 mmol **2a**, and 0.20 mmol base in 1.0 mL solvent at room temperature for the specified reaction time. [b] Isolated yields. [c] 2.0 mL THF and 0.2 mmol base were used. [d] 1.0 mL THF and 0.12 mmol base were used. [e] 1.0 mL THF and 0.25 mmol base were used. nd = not determined.

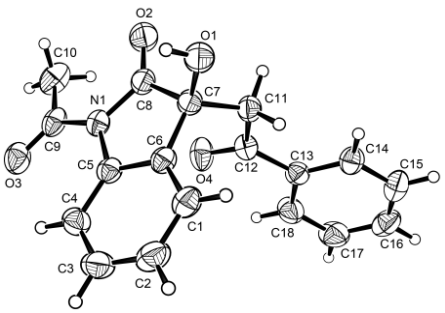
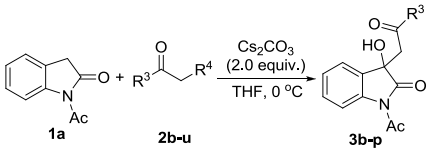



**Fig. 2.** Single-crystal structure of compound **3a**.

With optimized reaction conditions in hand, we then tested the scope of α-substituted ketone substrates by reacting with N-Ac-protected indolin-2-one **1a** (Table 2). For the α-tosyloxyacetophenones **2b-l** with different substituents on the phenyl ring, regardless of electron-donating or electron-withdrawing group, we found that the reactions could give the corresponding 3-hydroxy-3-phenacyloxindole derivatives **3b-l** in 42-93% yields (Table 2, entries 1-11). Although the electronic nature of the aryl group has no dramatic effect on the rate and yield, the substitution pattern on the aryl ring, regarding to para, meta, and ortho substituents, shows some influence on the reaction. The ortho substituted group led to lower yields compared to the para or meta group probably due to more steric hindrance (Table 2, entry 1 vs entries 2-3, entry 7 vs 8). Meanwhile, an α-tosyloxy heteroaromatic ketone **2m** was also successfully employed, giving the desired product **3m** in 82% yield (Table 2, entry 12). Additionally, the naphthyl moiety was tolerated in the reaction for the formation of the corresponding 3-hydroxy-3-substituted oxindole **3n** (Table 2, entry 13). On the other hand, it was observed that some other α-substituted ketone substrates, such as α-mesyloxyacetophenone (**2o**), α-bromoacetophenones (**2p-r**), and α-chloroacetophenone (**2s**), were also compatible with the developed reaction

conditions, leading to the generation of their respective 3-hydroxy-3-phenacyloxindole analogs in moderate to good yield (Table 2, entries 14-18). Ultimately, the possibility to employ α-tosyloxy aliphatic ketone as a substrate was also evaluated, under the standard conditions, α-tosyloxy acetone (**2t**) could smoothly react with indolin-2-one **1a** to give 3-hydroxy-3-substituted oxindole **3o** in 72% yield (Table 2, entry 19).

**Table 2** Scope of α-substituted ketones[a]

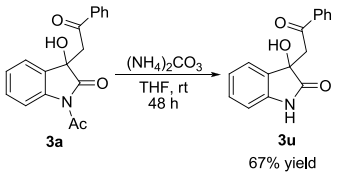



| Entry | $R^3$ | $R^4$ | 2 | Time (h) | 3 | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | *o*-$MeC_6H_4$ | OTs | **2b** | 16 | **3b** | 42 |
| 2 | *m*-$MeC_6H_4$ | OTs | **2c** | 10 | **3c** | 83 |
| 3 | *p*-$MeC_6H_4$ | OTs | **2d** | 8 | **3d** | 79 |
| 4 | *m*-$MeOC_6H_4$ | OTs | **2e** | 10 | **3e** | 86 |
| 5 | *p*-$MeOC_6H_4$ | OTs | **2f** | 8 | **3f** | 84 |
| 6 | *p*-$FC_6H_4$ | OTs | **2g** | 8 | **3g** | 93 |
| 7 | *o*-$ClC_6H_4$ | OTs | **2h** | 10 | **3h** | 56 |
| 8 | *p*-$ClC_6H_4$ | OTs | **2i** | 10 | **3i** | 90 |
| 9 | *m*-$BrC_6H_4$ | OTs | **2j** | 12 | **3j** | 71 |
| 10 | *p*-$BrC_6H_4$ | OTs | **2k** | 8 | **3k** | 78 |
| 11 | *p*-$NO_2C_6H_4$ | OTs | **2l** | 10 | **3l** | 74 |
| 12 | 2-thienyl | OTs | **2m** | 5 | **3m** | 82 |
| 13 | 1-naphthyl | OTs | **2n** | 8 | **3n** | 71 |
| 14 | Ph | OMs | **2o** | 8 | **3a** | 70 |
| 15 | Ph | Br | **2p** | 8 | **3a** | 49 |
| 16 | *p*-$BrC_6H_4$ | Br | **2q** | 4 | **3k** | 50 |
| 17 | *p*-$MeC_6H_4$ | Br | **2r** | 6 | **3d** | 58 |
| 18 | Ph | Cl | **2s** | 4 | **3a** | 77 |
| 19 | Me | OTs | **2t** | 8 | **3o** | 72 |

[a] Unless otherwise noted, the reactions were carried out with 0.15 mmol **1a**, 0.10 mmol **2**, and 0.20 mmol $Cs_2CO_3$ in 1.0 mL of THF at 0 °C for the specified reaction time. [b] Isolated yields.

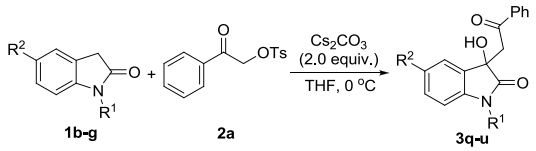
Next, we turned our attention to the scope of indolin-2-one substrates by reacting with α-tosyloxyacetophenone (**2a**) (Table 3). Incorporating a bromine substituent on the aromatic ring of **1a**, the reaction also proceeded smoothly and could give product **3p** in 89% yield (Table 3, entry 1). Furthermore, replacing the *N*-Ac-protecting group in **1a** with other *N*-protecting groups, such as Boc, Cbz, and $CO_2Et$, the reactions worked well under the standard conditions and delivered the corresponding 3-hydroxy-3-phenacyloxindoles **3q-s** in high yields (Table 3, entries 2-4). However, changing the *N*-Ac-protecting group in **1a** with a methyl group had significantly detrimental effects on the reaction (Table 3, entry 5). Nevertheless, employing the *N*-unprotected indolin-2-one **1g** as a substrate reacting with **2a**, the reaction system became very messy under the developed conditions and none of the expected product **3u** was observed (Table 3, entry 6).

Although the *N*-H indolin-2-one **1g** failed to react with **2a** to give the *N*-free 3-hydroxy-3-phenacyloxindole **3u** under the developed conditions, to our delight, this product could be obtained from **3a**. As shown in Scheme 2, the *N*-Ac group of product **3a** was smoothly removed with 1.1 equivalent of ammonium carbonate in THF at room temperature.[9] The desired *N*-free 3-hydroxy-3-phenacyloxindole **3u** could be obtained in 67% yield after 48 h.




**Scheme 2** Transformation of product **3a** to compound **3u**.

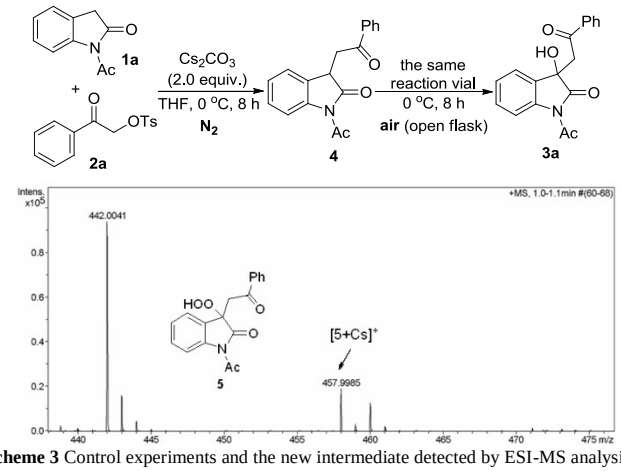
**Table 3** Scope of indolin-2-ones[a]




| Entry | $R^1$ | $R^2$ | 1 | Time (h) | 3 | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | Ac | Br | **1b** | 8 | **3p** | 89 |
| 2 | Boc | H | **1c** | 5 | **3q** | 84 |
| 3 | Cbz | H | **1d** | 5 | **3r** | 90 |
| 4 | $CO_2Et$ | H | **1e** | 6 | **3s** | 88 |
| 5 | Me | H | **1f** | 36 | **3t** | nd |
| 6 | H | H | **1g** | 36 | **3u** | messy |

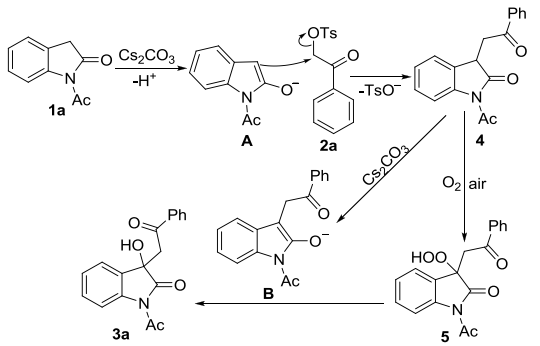
[a] Unless otherwise noted, the reactions were carried out with 0.15 mmol **1**, 0.10 mmol **2a**, and 0.20 mmol $Cs_2CO_3$ in 1.0 mL of THF at 0 °C for the specified reaction time. [b] Isolated yields. nd = not determined.

To gain some insight into the reaction mechanism, some control experiments were performed (Scheme 3). Firstly, performing the reaction of **1a** and **2a** under the standard conditions but especially at nitrogen atmosphere for 8 h, we could successfully obtain the 3-monosubstituted oxindole **4**. On the basis of these results, we can infer that a $S_N2$ process takes place at the alkaline condition. And then, we opened the flask and continued to run the reaction in the air for 8 h, leading to the formation of 3-hydroxy-3-phenacyloxindole **3a**. In light of this experimental result and relevant literatures,[10] we think that the 3-substituted oxindole **4** reacts with molecular oxygen in the presence of a base, resulting in the 3-hydroxy derivatives through a possible hydroxylation reaction. Nevertheless, we also carried out the further study with the help of mass spectrometry. When the reaction mixture was analyzed by ESI-MS, a base peak at *m/z* 457.9985 was detected and assigned as the intermediate hydroperoxide oxindole (Scheme 3).[9]




**Scheme 3** Control experiments and the new intermediate detected by ESI-MS analysis.

Based on the above experimental findings and the observations we have gathered so far, we tentatively propose a plausible pathway for the reaction as depicted in Scheme 4. Initially, treatment of **1a** with $Cs_2CO_3$ can form an enolate ion **A**. The enolate ion will react with α-tosyloxyacetophenone (**2a**) via a $S_N2$ process to generate the 3-substituted oxindole **4**. Under the basic reaction condition, intermediate **4** can be transformed to an enolate ion **B**, in the meantime, **4** also can be converted to intermediate hydroperoxide oxindole **5** by reacting with the $O_2$ in the air. Finally, compound **5** is able to be reduced by the enolate ion **B**,[10d] resulting in the generation of 3-hydroxy-3-phenacyloxindole **3a**.




**Scheme 4.** Proposed pathway for the reaction of indolin-2-ones and α-substituted ketones.

## Conclusions

In conclusion, we have successfully developed an unprecedented reaction of indolin-2-ones and α-substituted ketones. The developed protocol leads to an efficient preparation of a wide range of 3-hydroxy-3-phenacyloxindole derivatives under mild reaction conditions. This method will open a new opportunity to access biologically significant 3-hydroxy-3-substituted oxindoles from readily available indolin-2-ones. Meanwhile, a possible mechanism of this reaction was tentatively proposed based on some control experiments and mass spectrometry analysis. Further studies in the development of creative strategies for the construction of structurally diverse 3,3-disubstituted oxindoles are ongoing in our laboratory.

## Acknowledgements

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## Experimental section

## General Methods

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. $^1$H NMR and $^{13}$C NMR (300 and 75 MHz, respectively) spectra were recorded in $CDCl_3$ and DMSO-$d_6$. 1H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-$d_6$ at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. $^{13}$C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-$d_6$ at 39.51 ppm). Melting points were recorded on a Buchi Melting Point B-545.

## General procedure for the synthesis of 3a-t

In an ordinary vial equipped with a magnetic stirring bar, the compounds **2** (0.1 mmol, 1.0 equiv.), oxindoles **1** (0.15 mmol) and $Cs_2CO_3$ (2.0 equiv.) was dissolved in 1.0 mL of freshly distilled THF at 0 °C in open air. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1～5/1) to yield products **3a-t**.

## General procedure for the synthesis of 3u

A mixture of 1-acetyl-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one **3a** (0.3 mmol) and $(NH_4)_2CO_3$ (130.32 mg, 1.1 equiv.) in THF (3.0 mL) was stirred at room temperature for 48 h. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to yield products **3u**.

1-acetyl-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (**3a).** yellow solid, 92% yield; mp 139.0-139.8 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.58 (s, 3H), 3.74 (d, $J$ = 17.4 Hz, 1H), 3.97 (d, $J$ = 17.4 Hz, 1H), 4.36 (s, 1H), 7.14-7.19 (m, 1H), 7.32-7.45 (m, 4H), 7.54-7.57 (m, 1H), 7.82-7.85 (m, 2H), 8.23 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.3, 46.1, 74.1, 116.9, 123.2, 125.5, 128.1, 128.7, 128.9, 130.5, 134.0, 135.7, 140.5, 171.1, 177.4, 197.0; HRMS (ESI): Calculated for $C_{18}H_{15}NNaO_4$ $[M+Na]^+$: 332.0106, found: 332.0105.

1-acetyl-3-hydroxy-3-(2-oxo-2-(o-tolyl)ethyl)indolin-2-one (**3b).** white solid, 42% yield; mp 148.3-148.9 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.33 (s, 3H), 2.65 (s, 3H), 3.63 (d, $J$ = 17.1 Hz, 1H), 3.80 (d, $J$ = 17.1 Hz, 1H), 4.26 (s, 1H), 7.18-7.26 (m, 3H), 7.36-7.43 (m, 3H), 7.57 (d, $J$ = 7.8 Hz, 1H), 8.26 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.2, 26.5, 48.1, 74.5, 117.0, 123.3, 125.6, 125.8, 128.8, 128.9, 130.5, 132.2, 132.3, 136.4, 138.9, 140.3, 170.9, 177.4, 201.0; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_4$ $[M+Na]^+$: 346.1050, found: 346.1055.

1-acetyl-3-hydroxy-3-(2-oxo-2-(m-tolyl)ethyl)indolin-2-one (**3c**). yellow solid, 83% yield; mp 156.3-157.1 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.37 (s, 3H), 2.62 (s, 3H), 3.71 (d, $J$ = 17.4 Hz, 1H), 3.95 (d, $J$ = 17.4 Hz, 1H), 4.27 (s, 1H), 7.15-7.20 (m, 1H), 7.29-7.40 (m, 4H), 7.65 (m, 2H), 8.25 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.2, 26.4, 46.0, 74.1, 116.9, 123.2, 125.4, 125.5, 128.6, 128.9, 130.5, 134.8, 135.7, 138.6, 140.4, 171.1, 177.4, 197.3; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_5$ $[M+Na]^+$: 346.1050, found: 346.1052.

1-acetyl-3-hydroxy-3-(2-oxo-2-(p-tolyl)ethyl)indolin-2-one (**3d**). yellow solid, 79% yield; mp 147.2-148.5 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.39 (s, 3H), 2.63 (s, 3H), 3.66 (d, $J$ = 17.4 Hz, 1H), 3.91 (d, $J$ = 17.4 Hz, 1H), 4.28 (s, 1H), 7.17-7.26 (m, 3H), 7.33-7.40 (m, 2H), 7.75 (d, $J$ = 8.1 Hz, 2H), 8.26 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75

MHz, $CDCl_3$) $\delta$ 21.7, 26.4, 45.7, 74.2, 116.9, 123.2, 125.5, 128.3, 129.0, 129.4, 130.4, 133.4, 140.4, 145.1, 171.0, 177.4, 196.9; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_4$ $[M+Na]^+$: 346.1050, found: 346.1050.

1-acetyl-3-hydroxy-3-(2-(3-methoxyphenyl)-2-oxoethyl)indolin-2-one (**3e**). white solid, 86% yield; mp 137.2-137.5 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.63 (s, 3H), 3.72 (d, $J$ = 17.4 Hz, 1H), 3.80 (s, 3H), 3.95 (d, $J$ = 17.4 Hz, 1H), 4.11 (s, 1H), 7.10-7.21 (m, 2H), 7.31-7.46 (m, 5H), 8.26 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 46.1, 55.4, 74.1, 112.0, 117.0, 120.7, 120.9, 123.2, 125.6, 128.8, 129.7, 130.5, 137.0, 140.5, 159.8, 171.0, 177.4, 196.9; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_5$ $[M+Na]^+$: 362.0999, found: 362.0998.

1-acetyl-3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one (**3f**). white solid, 84% yield; mp 144.2-145.1 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.63 (s, 3H), 3.72 (d, $J$ = 17.4 Hz, 1H), 3.80 (s, 3H), 3.95 (d, $J$ = 17.4 Hz, 1H), 4.16 (s, 1H), 7.09-7.20 (m, 2H), 7.31-7.46 (m, 5H), 8.26 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 46.2, 55.4, 74.1, 112.0, 117.0, 120.7, 120.9, 123.2, 125.5, 128.9, 129.7, 130.5, 137.0, 140.5, 159.8, 171.1, 177.4, 196.8; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_5$ $[M+Na]^+$: 362.0999, found: 362.0998.

1-acetyl-3-(2-(4-fluorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (**3g**). yellow solid, 93% yield; mp 160.5-161.1 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.61 (s, 3H), 3.70 (d, $J$ = 17.4 Hz, 1H), 3.92 (d, $J$ = 17.4 Hz, 1H), 4.14 (s, 1H), 7.08-7.21 (m, 3H), 7.35-7.40 (m, 2H), 7.86-7.91 (m, 2H), 8.25 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 46.0, 74.0, 115.9 (d, $J$ = 21.9 Hz, 1C), 117.0, 123.2, 125.6, 128.8, 130.6, 130.9 (d, $J$ = 9.5 Hz, 1C), 132.2 (d, $J$ = 3.0 Hz, 1C), 140.4, 166.2 (d, $J$ = 255.1 Hz, 1C), 171.1, 177.3, 195.4; HRMS (ESI): Calculated for $C_{18}H_{14}FNNaO_4$ $[M+Na]^+$: 350.0799, found: 350.0797.

1-acetyl-3-(2-(2-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (**3h**). yellow solid, 56% yield; mp 176.7-177.3 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.65 (s, 3H), 3.71 (d, $J$ = 17.1 Hz, 1H), 3.92 (d, $J$ = 17.1 Hz, 1H), 4.12 (s, 1H), 7.18-7.23 (m, 1H), 7.26-7.31 (m, 1H), 7.35-7.43 (m, 5H), 8.25 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 49.9, 74.4, 117.0, 123.4, 125.6, 127.1, 128.3, 129.7, 130.6, 130.7, 131.4, 132.8, 137.7, 140.4, 170.9, 177.2, 200.1; HRMS (ESI): Calculated for $C_{18}H_{14}ClNNaO_4$ $[M+Na]^+$: 366.0504, found: 366.0511.

1-acetyl-3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (**3i**). yellow solid, 90% yield; mp 122.1-122.7 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.65 (s, 3H), 3.68 (d, $J$ = 17.4 Hz, 1H), 3.91 (d, $J$ = 17.4 Hz, 1H), 3.95 (s, 1H), 7.17-7.26 (m, 1H), 7.36-7.43 (m, 4H), 7.80 (d, $J$ = 8.7 Hz, 2H), 8.27 (d, $J$ = 8.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.5, 45.8, 74.1, 117.0, 123.2, 125.6, 128.6, 129.1, 129.5, 130.7, 134.1, 140.5, 140.7, 170.9, 177.2, 195.9; HRMS (ESI): Calculated for $C_{18}H_{14}ClNNaO_4$ $[M+Na]^+$: 366.0505, found: 366.0513.

1-acetyl-3-(2-(3-bromophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (**3j**). yellow solid, 71% yield; mp 182.5-183.1 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.62 (s, 3H), 3.71 (d, $J$ = 17.7 Hz, 1H), 3.92 (d, $J$ = 17.7 Hz, 1H), 4.06 (brs, 1H), 7.16-7.21 (m, 1H), 7.29-7.40 (m, 3H), 7.70 (d, $J$ = 7.8 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.98 (s, 1H), 8.26 (d, $J$ = 8.7 Hz, 1H),; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 46.2, 74.0, 117.0, 123.1, 125.6, 126.6, 128.6, 130.3, 130.6, 131.2, 136.8, 137.3, 140.5, 171.0, 177.3, 195.6; HRMS (ESI): Calculated for $C_{18}H_{14}BrNNaO_4$ $[M+Na]^+$: 409.9998, found: 409.9990.

1-acetyl-3-(2-(4-bromophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (**3k**). yellow solid, 78% yield; mp 179.2-180.5 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.65 (s, 3H), 3.67 (d, $J$ = 17.4 Hz, 1H), 3.90 (d, $J$ = 17.4 Hz, 1H), 3.97 (s, 1H), 7.19-7.22 (m, 1H), 7.36-7.40 (m, 2H), 7.57-7.60 (m, 2H), 7.70-7.73 (m, 2H), 8.25-8.28 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 45.9, 74.1, 117.0, 123.2, 125.6, 128.7, 129.4, 129.6, 130.6, 132.1, 134.5, 140.5, 170.9, 177.2, 196.1; HRMS (ESI): Calculated for $C_{18}H_{14}BrNNaO_4$ $[M+Na]^+$: 409.9998, found: 409.9989.

1-acetyl-3-hydroxy-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one (**3l**). yellow solid, 74% yield; mp 193.0.2-193.7 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.71 (s, 3H), 3.69 (dd, $J$ = 6.9, 18.6 Hz 1H), 3.91 (dd, $J$ = 3.3, 18.6 Hz 1H), 4.16-4.20 (m, 1H), 7.12-7.21 (m, 2H), 7.31-7.36 (m, 1H), 8.11 (d, $J$ = 8.7 Hz, 2H), 8.26-8.34 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.7, 40.5, 41.8, 116.7, 123.0, 124.0, 125.1, 127.2, 128.7, 129.2, 140.1, 140.7, 150.6, 170.8, 178.0, 194.7; HRMS (ESI): Calculated for $C_{18}H_{14}N_2NaO_6$ $[M+Na]^+$: 377.1057, found: 377.1053.

1-acetyl-3-hydroxy-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one (**3m**). yellow solid, 82% yield; mp 110.2-110.8 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.63 (s, 3H), 3.61 (d, $J$ = 16.8 Hz, 1H), 3.80 (d, $J$ = 16.8 Hz, 1H), 4.31 (s, 1H), 7.11-7.14 (m, 1H), 7.17-7.22 (m, 1H), 7.35-7.43 (m, 2H), 7.67-7.70 (m, 2H), 8.24 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.5, 46.0, 74.2, 117.0, 123.3, 125.6, 128.4, 128.6, 130.6, 133.1, 135.3, 140.3, 142.9, 170.9, 177.1, 189.8; HRMS (ESI): Calculated for $C_{16}H_{13}NNaO_4S$ $[M+Na]^+$: 338.0457, found: 338.0467.

1-acetyl-3-hydroxy-3-(2-(naphthalen-1-yl)-2-oxoethyl)indolin-2-one (**3n**). yellow solid, 71% yield; mp 123.6-124.1 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.66 (s, 3H), 3.84 (d, $J$ = 17.4 Hz, 1H), 4.10 (d, $J$ = 17.4 Hz, 1H), 4.27 (s, 1H), 7.19 (t, $J$ = 7.5 Hz, 1H), 7.35-7.45 (m, 2H), 7.53-7.64 (m, 2H), 7.84-7.94 (m, 4H), 8.29 (d, $J$ = 8.1 Hz, 1H), 8.40 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.5, 45.9, 74.3, 117.0, 123.3, 125.6, 127.1, 127.8, 128.7, 128.9, 129.0, 129.6, 130.4, 130.5, 132.3, 133.1, 135.9, 140.5, 171.0, 177.4, 197.1; HRMS (ESI): Calculated for $C_{22}H_{17}NNaO_4$ $[M+Na]^+$: 382.1050, found: 382.1052.

1-acetyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one (**3o**). yellow solid, 72% yield; mp 121.2-121.5 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.14 (s, 3H), 2.63 (s, 3H), 3.20 (d, $J$ = 15.0 Hz, 1H), 3.31 (d, $J$ = 15.0 Hz, 1H), 4.22 (s, 1H), 7.21-7.28 (m, 1H), 7.37-7.42 (m, 2H), 8.22-8.24 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 30.8, 50.2, 73.8, 117.0, 123.2, 125.6, 128.7, 130.6, 140.3, 170.9, 177.3, 206.3; HRMS (ESI): Calculated for $C_{13}H_{13}NNaO_4$ $[M+Na]^+$: 270.2469, found: 270.2478.

1-acetyl-5-bromo-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (**3p**). yellow solid, 89% yield; mp 142.7-143.3 ℃; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.62 (s, 3H), 3.86 (d, $J$ = 18.3 Hz, 1H), 4.49 (d, $J$ = 18.3 Hz, 1H), 6.68 (brs, 1H), 7.48-7.57 (m, 3H), 7.62-7.67 (m, 1H), 7.80 (d, $J$ = 1.5 Hz, 1H), 7.91 (d, $J$ = 7.8 Hz, 2H), 8.10 (d, $J$ = 8.7 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (major) 26.1, 47.0, 72.6,

117.2, 117.8, 126.7, 128.2, 128.8, 132.1, 133.4, 133.9, 135.2, 139.7, 170.4, 177.3, 197.2; HRMS (ESI): Calculated for $C_{18}H_{14}BrNNaO_4$ $[M+Na]^+$: 410.1312, found: 410.1306.

tert-butyl 3-hydroxy-2-oxo-3-(2-oxo-2-phenylethyl)indoline-1-carboxylate (**3q**). white solid, 84% yield; syrup; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.64 (s, 9H), 3.66 (d, $J$ = 17.4 Hz, 1H), 3.88 (d, $J$ = 17.4 Hz, 1H), 4.23 (s, 1H), 7.13-7.16 (m, 1H), 7.32-7.45 (m, 4H), 7.54-7.56 (m, 1H), 7.85-7.93 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.1, 45.5, 74.1, 84.5, 115.5, 123.5, 124.8, 128.1, 128.7, 128.8, 130.2, 133.8, 136.0, 140.0, 149.1, 175.0, 197.4; HRMS (ESI): Calculated for $C_{21}H_{21}NNaO_5$ $[M+Na]^+$: 390.1312, found: 390.1306.

benzyl 3-hydroxy-2-oxo-3-(2-oxo-2-phenylethyl)indoline-1-carboxylate (**3r**). white solid, 90% yield; mp 128.8-129.7 ℃; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.69 (d, $J$ = 17.4 Hz, 1H), 3.92 (d, $J$ = 17.4 Hz, 1H), 4.13 (s, 1H), 5.42 (d, $J$ = 12.3 Hz, 1H), 5.48 (d, $J$ = 12.3 Hz, 1H), 7.15 (t, $J$ = 7.5 Hz, 1H), 7.33-7.45 (m, 7H), 7.50-7.59 (m, 3H), 7.83-7.86 (m, 2H), 7.97 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 45.8, 68.7, 74.1, 115.6, 123.5, 125.1, 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 130.4, 133.9, 134.9, 135.9, 139.7, 150.7, 174.9, 197.2; HRMS (ESI): Calculated for $C_{24}H_{19}NNaO_5$ $[M+Na]^+$: 424.1155, found: 424.1151.

ethyl 3-hydroxy-2-oxo-3-(2-oxo-2-phenylethyl)indoline-1-carboxylate (**3s**). 88% yield; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.43 (t, $J$ = 7.2 Hz, 3H), 3.72 (d, $J$ = 17.7 Hz, 1H), 3.94 (d, $J$ = 17.7 Hz, 1H), 4.22 (s, 1H), 4.41-4.48 (m, 2H), 7.14-7.16 (m, 1H), 7.35-7.44 (m, 4H), 7.53-7.56 (m, 1H), 7.83-7.86 (m, 2H), 7.95 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 46.0, 63.5, 74.0, 115.5, 123.4, 125.0, 128.1, 128.6, 128.7, 130.3, 133.8, 135.8, 139.8, 150.8, 175.1, 197.0; HRMS (ESI): Calculated for $C_{19}H_{17}NNaO_5$ $[M+Na]^+$: 362.0999, found: 362.1006.

3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (**3u**).[11] white solid, 67% yield; mp 140.2-141.0 ℃; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 3.59 (d, $J$ = 17.7 Hz, 1H), 4.07 (d, $J$ = 17.7 Hz, 1H), 6.07 (s, 1H), 6.80-6.88 (m, 2H), 7.13-7.19 (m, 1H), 7.26-7.29 (m, 1H), 7.46-7.51 (m, 2H), 7.59-7.61 (m, 1H), 7.87-7.90 (m, 2H), 10.27 (s, 1H); HRMS (ESI): Calculated for $C_{16}H_{13}NNaO_3$ $[M+Na]^+$: 290.2779, found: 290.2788.

## Notes and references

‡ Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data of new compounds, and crystallographic data See DOI: 10.1039/b000000x/

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