Metal-free tandem reaction in water: An efficient and regioselective synthesis of 3-hydroxyisoindolin-1-ones†

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A mild and effective method was developed for the construction of heterocyclic building blocks 3-hydroxyisoindolin-1-ones *via* a metal-free tandem transformation with excellent regioselectivity. Significantly, the strategy presents an atom-economical and environmentally friendly transformation, in which two new C–N bonds and one C–O bond are formed in water from two simple starting materials. Moreover, a broad spectrum of substrates can participate in the process effectively to produce the desired products in good yields.

Introduction

3-Hydroxyisoindolin-1-one is an important core structure of numerous natural products and artificially synthesized bioactive molecules,[1] such as chilenine (**1**), a natural isoindolobenzazepine alkaloid isolated from *Berberis empetrifolia*,[1a] fumadensine (**2**), an isoquinoline from *Fumaria densiflora*,[1b] as well as a molecule with antibacterial activity (**3**)[1c] (Fig. 1). Additionally, 3-hydroxyisoindolin-1-one moieties have been found in other bioactive molecules such as a Raf kinase inhibitor,[1d] an MEK protein kinase inhibitor[1e] as well as an HIV integrase inhibitor.[1f] 3-Hydroxyisoindolin-1-ones are also useful precursors for synthesis of arylmethyleneisoindolin-1-one compounds, which are important privileged structures of many biological active molecules, such as fumaridine (**4**)[1g] and compound **5**, which have local anesthetic activity superior to that of procaine.[1h] In addition, the products of dehydration of 3-hydroxyisoindolin-1-ones have been found to be useful intermediates in the total synthesis of isoindolobenzazepine alkaloids such as lennoxamine (**6**).[2]

Although 3-hydroxyisoindolin-1-ones play an important role in drug discovery, the available strategies for the synthesis of these compounds are limited. The common methods for the assembly of these compounds are based on the use of phthalimide derivatives as starting materials, which undergo a selective addition by organometallic reagents or other nucleophilic reagents to form the target hydroxylactams.[2e,3] However, these procedures normally require specific nucleophilic reagents or harsh reaction conditions (such as Grignard reagents and anhydrous environment), which may prevent the elaboration of some sensitive 3-hydroxyisoindolin-1-ones. Therefore, it is very important to develop novel and effective protocols involving mild reaction conditions and easily available materials for the synthesis of bioactive 3-hydroxyisoindolin-1-ones.

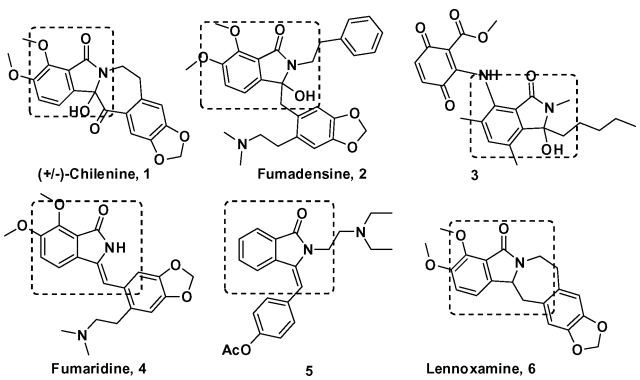

Fig. 1 The related structures of 3-hydroxyisoindolin-1-ones.

In recent years, we have witnessed some progress in the development of potentially useful heterocyclic compounds using transition-metal-catalysts.[4] During studies on the gold-catalyzed assembly of fused polycyclic heterocyclic structures, we discovered that pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones and pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones could be conveniently and effectively synthesized from some simple starting materials *via* one-pot domino transformations catalyzed by gold complexes and/or silver salts.[5] Here, we were interested in whether gold catalysts could promote the intramolecular cyclization of *o*-(substituted ethynyl)benzoic acids, and subsequent intermolecular coupling tandem transformation with amines to afford 3-hydroxyisoindolin-1-ones.

For this purpose, we carried out a reaction between 2-(phenylethynyl)benzoic acid and benzyl amine using $AuCl(PPh_3)/AgOTf/Bu_4N^+OAc^-$ as a catalytic system in an aqueous medium (Table 1). During the course of the study, we observed a metal-catalyst-free tandem transformation to expediently afford diversely substituted 3-hydroxyisoindolin-1-ones under microwave-assisted conditions. The reaction involves the formation of two new carbon–nitrogen bonds and one new carbon–oxygen bond in high regioselectivity in the absence of metal catalysts to prepare 3-hydroxyisoindolin-1-ones with good yields in aqueous media in a one-pot operation.

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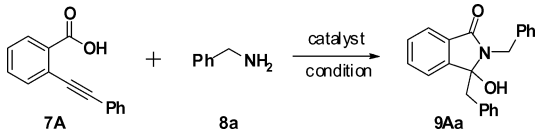
† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for target compounds. CCDC reference number 755262. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c004745g

Table 1 Optimization of the reaction conditions[a]



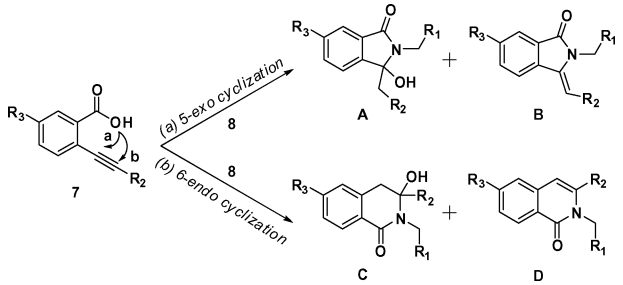
Entry	Catalyst system	Solvent	Yield (%)
1	$AuCl(PPh_3)/AgOTf/Bu_4N^+ OAc^-$	H_2O	75
2	$AuCl(PPh_3)/Bu_4N^+ OAc^-$	H_2O	74
3	$Bu_4N^+ OAc^-$	H_2O	80
4	—	H_2O	0
5	$Bu_4N^+ F^-$	H_2O	70
6	$Bu_4N^+ Cl^-$	H_2O	64
7	$Bu_4N^+ Br^-$	H_2O	65
8	$Bu_4N^+ OAc^-$	CH_3CN	75
9	$Bu_4N^+ OAc^-$	Toluene	73
10	$Bu_4N^+ OAc^-$	H_2O	94[b]
11	$Bu_4N^+ OAc^-$	H_2O	90[c]
12	$Bu_4N^+ OAc^-$	H_2O	93[d]
13	$Bu_4N^+ OAc^-$	H_2O	90[e]

[a] *Reagents and conditions*: **7A** (0.1 mmol), **8a** (0.2 mmol), catalyst (5 mol%), solvent (3 mL), M.W. irradiation (100 °C, 20 min). [b] Reaction performed by a two-step one-pot protocol. **7A** (0.1 mmol), **8a** (0.2 mmol), $Bu_4N^+ OAc^-$ (5 mol%), H_2O (3 mL), M.W. irradiation (100 °C, 10 min + 10 min). [c] **7A** (9 mmol), **8a** (18 mmol), $Bu_4N^+ OAc^-$ (5 mol%), H_2O (10 mL), M.W. irradiation (120 °C, 20 min + 30 min). [d] Reaction performed without Ar protection. [e] No microwave irradiation – the reaction time was prolonged to 5 h to complete substrate conversion.

Results and discussion

In the light of this encouraging result, we sought to identify the optimal reaction conditions. Initially, we investigated the effectiveness of various combinations of catalysts and reaction conditions using 2-(phenylethynyl)benzoic acid (**7A**) and benzyl amine (**8a**) as the model substrates. The results of these experiments are shown in Table 1, while using $AuCl(PPh_3)/AgOTf/Bu_4N^+ OAc^-$ as a catalyst in aqueous media under microwave irradiation, 75% yield of the product was obtained (Table 1, entry 1). However, a similarly good yield was also obtained in the absence of Ag salt (Table 1, entry 2). Further exploration showed that a higher yield (80% yield) could be achieved only in the presence of phase-transfer catalyst $Bu_4N^+ OAc^-$ (Table 1, entry 3). However, without any of the catalysts, the reaction could not proceed and only the starting materials **7A** and **8a** were recovered (Table 1, entry 4). Therefore, $Bu_4N^+ OAc^-$ seems to be an important factor for this transformation.

In principle, there are two possible mechanisms for this tandem transformation to give four possible products: (a) 5-*exo* cyclization, leading to the formation of **A** and a subsequent dehydrated product **B**; (b) 6-*endo* cyclization, leading to the formation of **C** and a subsequent dehydrated product **D** (Scheme 1). However, ^1H NMR, ^{13}C NMR, and X-ray crystallography (as shown in Fig. 2) indicated that the above product was the expected product **A**,[6] and no other products were detected. Subsequently, the usefulness of other phase-transfer catalysts, such as $Bu_4N^+ F^-$, $Bu_4N^+ Cl^-$, and $Bu_4N^+ Br^-$, was also investigated under the same conditions. Among these tested catalysts, $Bu_4N^+ OAc^-$ was found to be the most effective phase-transfer catalyst (Table 1, entries 3–7). Moreover, we also investigated the effectiveness of the reaction using different



Scheme 1 The 5-*exo* and 6-*endo* cyclization pathways.

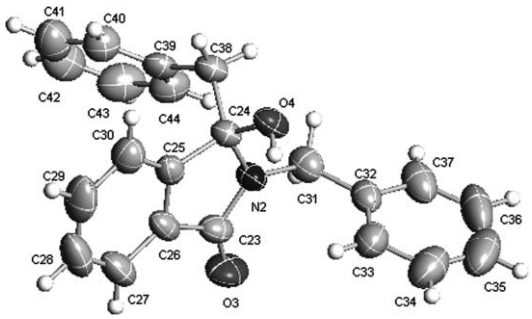
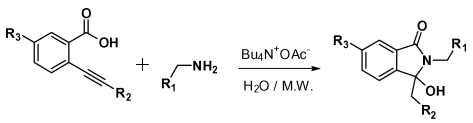


Fig. 2 X-ray crystallographic structure of **9Aa**.

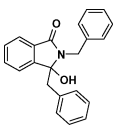
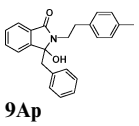
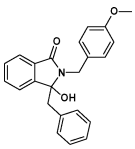
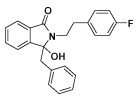
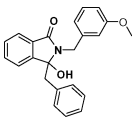
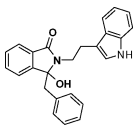
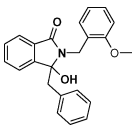
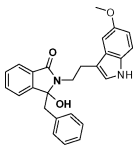
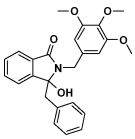
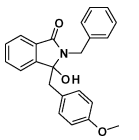
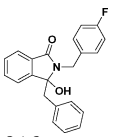
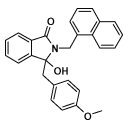
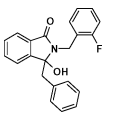
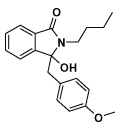
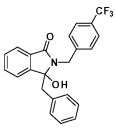
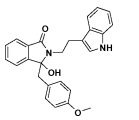
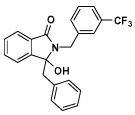
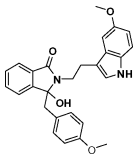
organic solvents, but no improvement in the yield of products was observed (Table 1, entries 8 and 9). To further improve the yield of products, we attempted to change the operation procedures. After treatment of 2-(phenylethynyl)benzoic acid (**7A**) with $Bu_4N^+ OAc^-$ in H_2O at 100 °C for 10 min in the presence of microwave irradiation under Ar protection, benzyl amine (**8a**) was added, and subsequently heated to 100 °C for an additional 10 min under the same microwave conditions. Surprisingly, an excellent yield (94%) was obtained (Table 1, entry 10). This protocol can be scaled up to the gram-scale synthesis of 3-hydroxyisoindolin-1-ones. A one-pot, two-step reaction of **7A** (2 g, 9 mmol) with **8a** (18 mmol) in the presence of 5 mol% of $Bu_4N^+ OAc^-$ afforded the desired product **9Aa** with a yield of 90%, and the product could be purified by simple flash chromatography (Table 1, entry 11).[7] Without Ar protection, the yield of **9Aa** was not drastically decreased (Table 1, entry 12). Although this transformation could be also performed under normal heating conditions (no microwave irradiation) with a good yield (90%), a longer reaction time (5 h overall) was needed to complete the substrate conversion (Table 1, entry 13).

To evaluate the scope of this metal-free cascade cyclization/coupling reaction in water, we decided to investigate the changes in both the substituted *o*-(substituted ethynyl)benzoic acids and the amines under the aforementioned optimum reaction conditions (Table 2). We found that several *o*-(substituted ethynyl)benzoic acids and benzyl amines, aryl ethylamines and alkylamines can all participate in the reaction to afford the desired products **9Aa–9Es** with good to excellent yields (70–98%). Although the position and type of substituents on the benzyl amines did not have a dramatic influence on the yields of the target compounds (Table 2, entries 1–10), the introduction of some substituents into the *o*- and/or *m*-position of benzyl amines resulted in a slight reduction in the yields, presumably

Table 2 One-pot tandem synthesis of **9Aa–9Es** in H_2O[a]

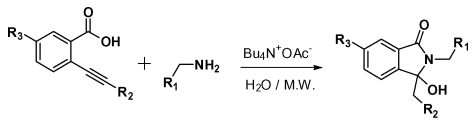


7A-E 8a-t 9Aa-Et

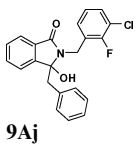
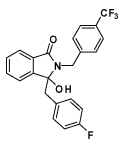
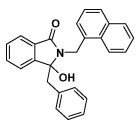
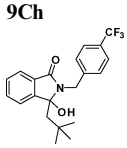
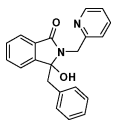
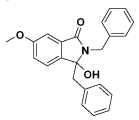
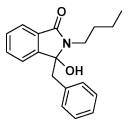
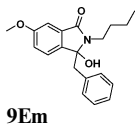
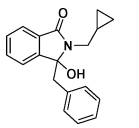
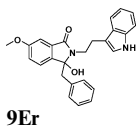
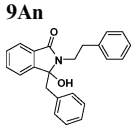
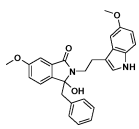
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **9Aa**	94	16	 **9Ap**	97
2	 **9Ab**	93	17	 **9Aq**	90
3	 **9Ac**	89[b]	18	 **9Ar**	97
4	 **9Ad**	89[b]	19	 **9As**	98
5	 **9Ae**	95[b]	20	 **9Ba**	95
6	 **9Af**	98	21	 **9Bk**	98[b]
7	 **9Ag**	92	22	 **9Bm**	85
8	 **9Ah**	96	23	 **9Br**	96
9	 **9Ai**	80	24	 **9Bs**	97

due to steric effects of the substituents (Table 2, entries 3, 4, 9 and 10). A high yield was obtained in the case of both naphthalen-1-ylmethanamine and *n*-butylamine as substrates (Table 2, entries

Table 2 Continued[a]



7A-E 8a-t 9Aa-Et

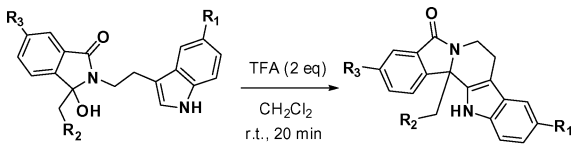
Entry	Product	Yield (%)	Entry	Product	Yield (%)
10	 **9Aj**	85	25	 **9Ch**	70
11	 **9Ak**	98[b]	26	 **9Dh**	75
12	 **9Al**	87[b]	27	 **9Ea**	95
13	 **9Am**	91	28	 **9Em**	82
14	 **9An**	76	29	 **9Er**	95
15	 **9Ao**	93	30	 **9Es**	86

[a] *Reagents and conditions*: **7A** (0.1 mmol), **8a** (0.2 mmol), Bu_4N^+ OAc^- (5 mol%), H_2O (3–4 mL), M.W. irradiation (100 °C, 10 min + 10 min). [b] A longer reaction time was needed for the full conversion of the substrates. **7A** (0.1 mmol), **8a** (0.2 mmol), Bu_4N^+ OAc^- (5 mol%), H_2O (3–4 mL), M.W. irradiation (100 °C, 10 min + 20 min).

11 and 13). However, the use of pyridin-2-ylmethanamine and cyclopropylmethan-amine led to a decrease in the yield of the products, maybe owing to the charge effects (Table 2, entries 12 and 14). Further, a longer reaction time was needed for the full conversion of the substrates when arylmethanamines with steric hindrance or strong charge effects were used (Table 2, entries 3–5, 11, 12 and 21). We also treated 2-(phenylethynyl)benzoic acid with some representative aryl ethylamines under optimal reaction conditions, and all the selected aryl ethylamines afforded excellent yields (Table 2, entries 15–19). In addition, a variety of substituted *o*-(substituted ethynyl)benzoic acids have also been investigated to explore the scope of the applicability of this transformation. Our results revealed that all tested substrates are tolerant of the cascade transformation (Table 2, entries 20–30). High yields of the products were observed for most of the selected substrates. However, when the R_2 group was a

p-fluorophenyl or *tert*-butyl group, a lower yield of products was obtained, presumably because of the charge effects and the steric effects, respectively (Table 2, entries 25 and 26).

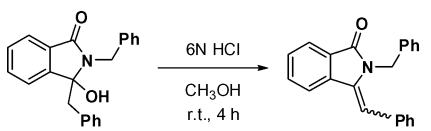
Further investigations demonstrated that some of 3-hydroxyisoindolin-1-ones (**9Ar**–**9Es**, Table 2) could be effectively converted to more intriguing fused polycyclic heterocyclic compounds (**10Ar**–**10Es**, Scheme 2) by treatment with trifluoroacetic acid (TFA) in dry CH_2Cl_2 at room temperature for 20 min. The resulting fused heterocyclic scaffolds could be employed as an alternative intermediate for the synthesis of dopamine/serotonin receptor antagonist derivatives.[8]



9Ar, R_1=H, R_2=Ph, R_3=H — **10Ar**, 97%
9As, R_1=OCH_3, R_2=Ph, R_3=H — **10As**, 94%
9Br, R_1=H, R_2=4-OCH_3-Ph, R_3=H — **10Br**, 95%
9Bs, R_1=OCH_3, R_2=4-OCH_3-Ph, R_3=H, — **10Bs**, 99%
9Er, R_1=H, R_2=Ph, R_3=OCH_3, — **10Er**, 96%
9Es, R_1=OCH_3, R_2=Ph, R_3=OCH_3, — **10Es**, 93%

Scheme 2 Some intriguing derivatives from 3-hydroxyisoindolin-1-ones.

In addition, dehydration of 3-hydroxyisoindolin-1-ones (**9Aa**) was also performed using 6 N HCl in methanol,[9] to give 3-methyleneisoindolin-1-ones (**11**), which are important intermediates for the total synthesis of some isoindolobenzazepine alkaloids (for example, lennoxamine derivatives).[2] Assignment as the *E*- or *Z*-isomers could be determined by comparing the ^{1}H NMR data with the reported data (Scheme 3).[2a,10]



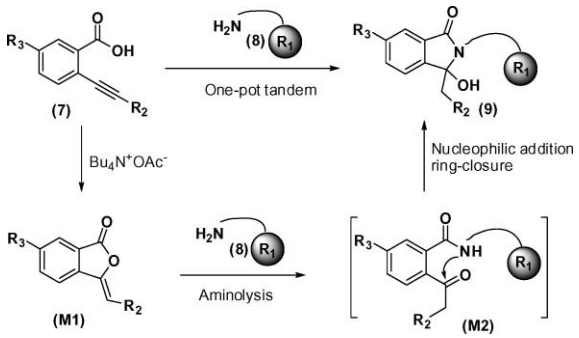
9Aa — **11 (E/Z = 10/1)** (98% yield)

Scheme 3 The dehydration of **9Aa**.

On the basis of our previous knowledge and the results of our present study, we propose a plausible mechanism for construction of the intriguing 3-hydroxyisoindolin-1-one frameworks. As shown in Scheme 4, the *o*-(substituted ethynyl)benzoic acid (**7**) is first activated by Bu_4N^+ OAc^- to generate the cyclic activated enol lactone intermediate **M1**,[11] which is then attacked by an amino group of compound **8** to form aminolysis product **M2**. The resulting keto amide **M2** undergoes further intramolecular nucleophilic addition to afford the ring-closed target product **9**.

Conclusion

In summary, we have developed a mild and effective method for the construction of 3-hydroxyisoindolin-1-ones *via* a metal-free tandem transformation using a phase transfer catalyst in good yields with excellent regioselectivity. Significantly, the strategy presents an atom-economical and environmentally friendly transformation, and has a high functional group tolerance. We



Scheme 4 A plausible mechanism.

expect that these potential privileged structures will have wide applicability in medicinal chemistry. Further studies are under investigation, and the corresponding results will be reported in due course.

Experimental section

General experimental procedures

The reagents were purchased from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed using HSGF 254 (0.15–0.2 mm thickness). All of the microwave-assisted reactions were performed in an Initiator™ EXP microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation. Column chromatography was performed with Combi*Flash*® Companion system (Teledyne Isco, Inc.). All melting points are uncorrected. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were either recorded in $CDCl_3$ (with the following internal standards – ^{1}H NMR: tetramethylsilane at 0.00 ppm; $CHCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or in DMSO-d_6 (with the following internal standards – ^{1}H NMR: tetramethylsilane at 0.00 ppm; DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm). Low- and high-resolution mass spectra (LR-MS and HR-MS) were measured on Finnigan MAT 95 spectrometer.

Typical procedure for synthesis of the 3-hydroxyisoindolin-1-ones in water

To a suspension solution of 2-(phenylethynyl)benzoic acid (**7A**, 0.1 mmol) in H_2O (3 mL) was added Bu_4N^+ OAc^- (5 mol%). After the mixture was heated to 100 °C under Ar for 10 min with microwave irradiation, benzyl amine (**8a**, 0.2 mmol) was added. Subsequently, the resulting mixture was underwent additional microwave irradiation at 100 °C under Ar for 10 min. The cold mixture was then concentrated in vacuum, and the resulting residue was purified by flash chromatography (petroleum ether–ethyl acetate = 4 : 1, v/v) to afford the expected product **9Aa**.

Mp 134–136 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.56 (m, 1H), 7.43 (m, 5H), 7.28 (m, 3H), 7.05 (m, 3H), 6.77 (m, 3H), 4.78 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 15.6 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 3.23 (d, J = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 146.1, 138.5, 134.6, 131.7, 131.0, 130.4, 129.6, 128.5, 128.3, 127.9, 127.3, 127.0, 123.3, 123.0, 91.4, 43.7, 42.5; LRMS (ESI) m/z 352 [M + Na]$^+$; HRMS (ESI) m/z calcd $C_{22}H_{19}NO_2Na$ [M + Na]$^+$ 352.1313, found 352.1306.

Characterization data for other target compounds

3-Benzyl-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (9Ab). Mp 137–139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.53 (m, 1H), 7.40 (m, 5H), 7.04 (m, 3H), 6.85 (d, J = 6.8 Hz, 2H), 6.74 (d, J = 7.2 Hz, 2H), 6.71 (s, 1H), 4.69 (d, J = 15.2 Hz, 1H), 4.55 (d, J = 15.2 Hz, 1H), 3.72 (s, 3H), 3.38 (d, J = 13.6 Hz, 1H), 3.18 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1, 158.1, 146.9, 135.2, 131.4, 131.3, 130.9, 130.0, 129.5, 129.0, 127.5, 126.4, 123.1, 122.0, 113.4, 91.0, 55.0, 43.2, 41.6; LRMS (EI) m/z 359 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{21}NO_3$ (M$^+$) 359.1521, found 359.1521.

3-Benzyl-3-hydroxy-2-(3-methoxybenzyl)isoindolin-1-one (9Ac). Mp 111–113 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (m, 1H), 7.44 (m, 3H), 7.21 (t, 1H), 7.02 (m, 5H), 6.75 (m, 4H), 4.73 (d, J = 15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 3.71 (s, 3H), 3.39 (d, J = 14.0 Hz, 1H), 3.22 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1, 159.1, 146.9, 140.5, 135.1, 131.5, 131.2, 129.9, 129.0, 127.5, 126.4, 123.2, 122.0, 120.2, 113.7, 111.9, 91.0, 54.9, 43.1, 42.2; LRMS (EI) m/z 359 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{21}NO_3$ (M$^+$) 359.1521, found 359.1539.

3-Benzyl-3-hydroxy-2-(2-methoxybenzyl)isoindolin-1-one (9Ad). Mp 149–151 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (m, 1H), 7.46 (m, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.18 (m, 2H), 7.03 (m, 4H), 6.80 (m, 3H), 6.68 (s, 1H), 4.75 (d, J = 16.8 Hz, 1H), 4.57 (d, J = 16.8 Hz, 1H), 3.88 (s, 3H), 3.36 (d, J = 13.6 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3, 156.3, 147.1, 135.2, 131.5, 131.2, 130.0, 129.1, 127.8, 127.6, 127.5, 126.4, 126.0, 123.2, 122.0, 120.0, 110.2, 91.0, 55.4, 43.1, 36.8; LRMS (EI) m/z 359 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{21}NO_3$ (M$^+$) 359.1521, found 359.1529.

3-Benzyl-3-hydroxy-2-(3,4,5-trimethoxybenzyl)isoindolin-1-one (9Ae). Mp 124–125 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.56 (m, 1H), 7.45 (m, 3H), 7.01 (m, 3H), 6.77 (m, 3H), 6.70 (d, J = 6.0 Hz, 2H), 4.67 (d, J = 15.3 Hz, 1H), 4.69 (d, J = 15.3 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.41 (d, J = 14.1 Hz, 1H), 3.26 (d, J = 14.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 152.5, 147.0, 136.3, 135.1, 134.5, 131.6, 131.2, 129.9, 129.1, 127.4, 126.4, 123.1, 122.1, 105.7, 91.0, 59.9, 55.8, 42.9, 42.6; LRMS (EI) m/z 419 (M$^+$); HRMS (EI) m/z calcd $C_{25}H_{25}NO_5$ (M$^+$) 419.1733, found 419.1738.

3-Benzyl-2-(4-fluorobenzyl)-3-hydroxyisoindolin-1-one (9Af). Mp 222–224 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (m, 1H), 7.42 (m, 4H), 7.15 (m, 3H), 7.03 (m, 1H), 6.97 (m, 2H), 6.88 (m, 2H), 4.79 (d, J = 14.7 Hz, 1H), 4.56 (d, J = 15.3 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 2.98 (d, J = 13.2 Hz, 1H), 2.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 162.0 (d, J = 244.1 Hz), 146.0, 134.4, 134.3, 131.9, 130.9, 130.3, 130.1 (d, J = 8.2 Hz), 129.7, 128.0, 127.1, 123.3, 123.0, 115.3 (d, J = 21.4 Hz), 91.4, 43.6, 41.9; LRMS (ESI) m/z 348 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{22}H_{18}NO_2NaF$ [M + Na]$^+$ 370.1219, found 370.1240.

3-Benzyl-2-(2-fluorobenzyl)-3-hydroxyisoindolin-1-one (9Ag). Mp 148–150 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.59 (m, 1H), 7.44 (m, 4H), 7.29 (m, 1H), 7.18 (m, 1H), 7.07 (m, 4H), 6.79 (m, 3H), 4.78 (d, J = 15.9 Hz, 1H), 4.69 (d, J = 16.5 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.24 (d, J = 13.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 159.9 (d, J = 242.4 Hz), 147.0, 135.0, 131.7, 130.9, 129.9, 129.1, 128.6 (d, J = 8.3 Hz), 127.5, 126.5, 125.4 (d, J = 13.9 Hz), 124.1, 123.2, 122.1, 114.8 (d, J = 21.1 Hz), 90.9, 42.9, 35.3; LRMS (EI) m/z 347 (M$^+$); HRMS (EI) m/z calcd $C_{22}H_{18}FNO_2$ (M$^+$) 347.1322, found 347.1287.

3-Benzyl-3-hydroxy-2-(4-(trifluoromethyl)benzyl)isoindo-lin-1-one (9Ah). Mp 219–221 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.60 (m, 5H), 7.46 (m, 3H), 7.02 (m, 3H), 6.77 (m, 3H), 4.83 (d, J = 16.2 Hz, 1H), 4.75 (d, J = 15.9 Hz, 1H), 3.42 (d, J = 12.5 Hz, 1H), 3.32 (d, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 147.0, 143.7, 135.0, 131.7, 131.0, 129.9, 129.1, 128.5, 127.5, 126.5, 124.9, 124.8, 123.2, 122.1, 91.1, 42.9, 41.9; LRMS (ESI) m/z 398 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{22}H_{18}NO_2F_3Na$ [M + Na]$^+$ 420.1187, found 420.1191

3-Benzyl-3-hydroxy-2-(3-(trifluoromethyl)benzyl)isoindo-lin-1-one (9Ai). Mp 179–181 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.79 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.60 (m, 2H), 7.53 (m, 2H), 7.45 (m, 2H), 7.02 (m, 3H), 6.82 (s, 1H), 6.76 (d, J = 8.0 Hz, 2H), 4.83 (d, J = 16.0 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 3.42 (d, J = 14.0 Hz, 1H), 3.30 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 147.0, 140.3, 135.0, 132.1, 131.8, 131.0, 129.8, 129.1, 129.0, 128.8, 127.5, 126.4, 124.6, 123.4, 123.1, 122.1, 91.1, 42.8, 41.9; LRMS (EI) m/z 397 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{18}F_3NO_2$ (M$^+$) 397.1290, found 359.1261.

3-Benzyl-2-(3-chloro-2-fluorobenzyl)-3-hydroxyisoindolin-1-one (9Aj). Mp 180–182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.60 (m, 1H), 7.46 (m, 4H), 7.35 (m, 1H), 7.12 (m, 1H), 7.05 (m, 3H), 6.78 (m, 3H), 4.79 (d, J = 16.0 Hz, 1H), 4.71 (d, J = 16.0 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 14.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 155.0 (d, J = 245.6 Hz), 147.0, 135.0, 131.8, 130.8, 129.8, 129.2, 128.9, 128.9, 127.6, 127.5, 126.5, 124.9, 123.2, 122.1, 119.2 (d, J = 17.9 Hz), 91.0, 42.8, 35.6; LRMS (ESI) m/z 382 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{22}H_{17}ClFNO_2Na$ [M + Na]$^+$ 404.0830, found 404.0832.

3-Benzyl-3-hydroxy-2-(naphthalen-1-ylmethyl)isoindolin-1-one (9AK). Mp 170–172 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.54 (m, 8H), 7.02 (m, 3H), 6.75 (m, 3H), 5.20 (m, 2H), 3.39 (d, J = 13.8 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3, 147.2, 135.1, 133.5, 133.2, 131.6, 131.1, 130.8, 130.0, 129.1, 128.5, 127.4, 127.1, 126.4, 126.1, 125.6, 125.3, 125.2, 123.6, 123.2, 122.2, 91.4, 43.1, 40.1; LRMS (ESI) m/z 380 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{26}H_{21}NO_2Na$ [M + Na]$^+$ 402.1470, found 402.1469.

3-Benzyl-3-hydroxy-2-(pyridin-2-ylmethyl)isoindolin-1-one (9Al). Mp 126–128 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.49 (d, J = 4.2 Hz, 1H), 7.71 (m, 1H), 7.60 (m, 1H), 7.45 (m, 4H), 7.26 (m, 1H), 7.05 (m, 3H), 6.94 (s, 1H), 6.81 (m, 2H), 4.85 (d, J = 16.5 Hz, 1H), 4.77 (d, J = 16.5 Hz, 1H), 3.42 (d, J = 13.5 Hz, 1H), 3.28 (d, J = 13.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3, 158.0, 148.5, 147.3, 136.7, 135.2, 131.7, 130.9, 129.9, 129.1, 127.5, 126.4, 123.2, 122.1, 121.6, 90.8, 44.3, 42.9; LRMS (ESI) m/z 353 [M + Na]$^+$; HRMS (ESI) m/z calcd $C_{21}H_{18}N_2O_2Na$ [M + Na]$^+$ 353.1266, found 353.1260.

3-Benzyl-2-butyl-3-hydroxyisoindolin-1-one (9Am). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (m, 1H), 7.37

(m, 2H), 7.14 (m, 3H), 7.04 (m, 1H), 6.94 (m, 2H), 3.57 (m, 2H), 3.10 (m, 2H), 1.72 (m, 2H), 1.37 (m, 2H), 0.95 (t, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.7, 146.9, 135.3, 131.6, 131.3, 129.8, 128.9, 127.5, 126.3, 122.8, 121.7, 90.9, 42.4, 38.7, 31.0, 20.1, 13.8; LRMS (ESI) m/z 296 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{19}H_{21}NO_2Na$ [M + Na]$^+$ 318.1470, found 318.1463.

3-Benzyl-2-(cyclopropylmethyl)-3-hydroxyisoindolin-1-one (9An). Mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, J = 6.9 Hz, 1H), 7.35 (m, 2H), 7.10 (m, 4H), 6.92 (m, 2H), 3.55 (m, 2H), 3.34 (br, 1H), 3.11 (m, 2H), 1.26 (m, 1H), 0.49 (m, 2H), 0.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 146.0, 134.7, 131.5, 131.3, 130.2, 129.4, 127.9, 126.9, 123.0, 122.8, 91.0, 43.8, 43.2, 11.2, 4.7, 4.6; LRMS (ESI) m/z 294 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{19}H_{19}NO_2Na$ [M + Na]$^+$ 316.1313, found 316.1317.

3-Benzyl-3-hydroxy-2-phenethylisoindolin-1-one (9Ao). Mp 144–146 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (m, 2H), 7.44 (m, 2H), 7.34 (m, 4H), 7.26 (m, 1H), 7.04 (m, 3H), 6.81 (m, 2H), 6.71 (s, 1H), 3.69 (m, 2H), 3.38 (m, 2H), 2.99 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.8, 147.0, 139.5, 135.2, 131.5, 131.4, 129.8, 129.0, 128.6, 128.5, 127.5, 126.4, 126.2, 122.9, 121.8, 91.0, 42.4, 40.7, 35.0; LRMS (EI) m/z 343 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{21}NO_2$ (M$^+$) 343.1572, found 343.1578.

3-Benzyl-3-hydroxy-2-(4-methylphenethyl)isoindolin-1-one (9Ap). Mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 7.8 Hz, 1H), 7.41 (m, 2H), 7.12 (m, 8H), 6.84 (m, 2H), 3.93 (m, 1H), 3.48 (m, 2H), 3.06 (m, 3H), 2.33 (s, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 146.1, 136.4, 136.0, 134.4, 131.6, 131.4, 130.1, 129.5, 129.3, 128.9, 127.9, 127.0, 123.0, 122.6, 91.1, 43.0, 41.7, 34.3, 21.0; LRMS (EI) m/z 357 (M$^+$); HRMS (EI) m/z calcd $C_{24}H_{23}NO_2$ (M$^+$) 357.1729, found 357.1728.

3-Benzyl-2-(4-fluorophenethyl)-3-hydroxyisoindolin-1-one (9Aq). Mp 133–135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, J = 6.9 Hz, 1H), 7.41 (m, 2H), 7.22 (m, 2H), 7.12 (m, 4H), 6.97 (m, 2H), 6.87 (m, 2H), 3.88 (m, 1H), 3.47 (m, 2H), 3.06 (m, 3H), 2.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.9, 160.9 (d, J = 240.2 Hz), 147.0, 135.7, 135.2, 131.5, 131.4, 130.4 (d, J = 7.9 Hz), 129.9, 129.0, 127.5, 126.4, 122.9, 121.9, 115.1 (d, J = 20.8 Hz), 91.0, 42.4, 40.6, 34.2; LRMS (EI) m/z 361 (M$^+$); HRMS (EI) m/z calcd $C_{23}H_{20}FNO_2$ (M$^+$) 361.1478, found 361.1502.

2-(2-(1*H*-Indol-3-yl)ethyl)-3-benzyl-3-hydroxyisoindolin-1-one (9Ar). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.41 (m, 3H), 7.11 (m, 7H), 6.85 (m, 2H), 4.06 (m, 1H), 3.69 (m, 1H), 3.47 (d, J = 14.0 Hz, 1H), 3.27 (m, 2H), 3.14 (d, J = 14.0 Hz, 1H), 2.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.0, 146.1, 136.2, 134.4, 131.6, 131.5, 130.1, 129.6, 127.9, 127.3, 127.0, 123.0, 122.6, 122.2, 119.6, 119.0, 113.5, 111.2, 91.2, 43.0, 40.5, 24.8; LRMS (ESI) m/z 383 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{25}H_{22}N_2O_2Na$ [M + Na]$^+$ 405.1579, found 405.1592.

3-Benzyl-3-hydroxy-2-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-isoindolin-1-one (9As). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.70 (s, 1H), 7.57 (m, 2H), 7.43 (m, 2H), 7.25 (m, 3H), 7.02 (m, 3H), 6.77 (m, 4H), 3.78 (m, 4H), 3.65 (m, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.30 (d, J = 13.6 Hz, 1H), 3.09 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.9, 153.0, 147.1, 135.3, 131.7, 131.5, 129.9, 129.9, 129.0, 127.6, 126.4, 123.4, 122.9, 121.9, 112.1, 111.7, 111.0, 100.4, 91.0, 55.3, 42.5, 40.1, 25.1; LRMS (ESI) m/z 435 [M + Na]$^+$; HRMS (ESI) m/z calcd $C_{26}H_{24}N_2O_3Na$ [M + Na]$^+$ 435.1685, found 435.1702.

2-Benzyl-3-hydroxy-3-(4-methoxybenzyl)isoindolin-1-one (9Ba). Mp 150–151 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (m, 1H), 7.45 (m, 5H), 7.29 (m, 3H), 6.69 (s, 1H), 6.65 (d, J = 6.9 Hz, 2H), 6.57 (d, J = 6.9 Hz, 2H), 4.73 (d, J =15.3 Hz, 1H), 4.62 (d, J =15.6 Hz, 1H), 3.62 (s, 3H), 3.31 (d, J =13.8 Hz, 1H), 3.14 (d, J =13.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1, 157.7, 147.0, 138.9, 131.5, 131.2, 130.9, 129.0, 128.0, 127.9, 126.9, 126.6, 123.1, 122.0, 112.9, 91.1, 54.8, 42.3, 42.2; LRMS (ESI) m/z 360 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{23}H_{21}NO_3Na$ [M + Na]$^+$ 382.1419, found 382.1426.

3-Hydroxy-3-(4-methoxybenzyl)-2-(naphthalen-1-ylmethyl)isoindolin-1-one (9Bk). Mp 160–162 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.36 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.57 (m, 8H), 6.70 (s, 1H), 6.63 (d, J = 9.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 2H), 5.15 (m, 2H), 3.59 (s, 3H), 3.28 (d, J =13.6 Hz, 1H), 3.19 (d, J =14.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.6, 157.3, 143.5, 143.2, 141.6, 141.1, 141.0, 140.8, 139.1, 138.5, 137.1, 136.9, 136.1, 135.6, 135.3, 135.1, 133.6, 133.1, 132.1, 122.8, 101.4, 64.7, 52.2, 49.7; LRMS (EI) m/z 409 (M$^+$); HRMS (EI) m/z calcd $C_{27}H_{23}NO_3$ (M$^+$) 409.1678, found 409.1681.

2-Butyl-3-hydroxy-3-(4-methoxybenzyl)isoindolin-1-one (9Bm). Mp 135–137 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.52 (m, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.38 (m, 2H), 6.67 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 3.59 (s, 3H), 3.48 (m, 1H), 3.32 (m, 2H), 3.17 (d, J = 14.4 Hz, 1H), 1.64 (m, 2H), 1.33 (m, 2H), 0.91 (t, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.8, 157.6, 147.0, 131.9, 131.6, 130.8, 128.1, 127.1, 122.5, 121.8, 112.9, 91.0, 54.8, 41.5, 38.7, 31.0, 20.1, 13.8; LRMS (ESI) m/z 326 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{20}H_{23}NO_3Na$ [M + Na]$^+$ 348.1576, found 348.1588.

2-(2-(1*H*-Indol-3-yl)ethyl)-3-hydroxy-3-(4-methoxybenzyl)-isoindolin-1-one (9Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.87 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58 (m, 2H), 7.47 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 7.07 (m, 2H), 6.69 (m, 3H), 6.57 (d, J = 8.8 Hz, 2H), 3.78 (m, 1H), 3.60 (m, 4H), 3.37 (d, J = 14.4 Hz, 1H), 3.25 (d, J = 13.2 Hz, 1H), 3.11 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.9, 157.6, 147.2, 136.3, 131.9, 131.5, 130.8, 129.0, 127.2, 127.1, 122.9, 122.7, 121.8, 121.0, 118.4, 118.3, 112.9, 111.9, 111.4, 91.1, 54.7, 41.6, 25.0; LRMS (ESI) m/z 413 [M + H]$^+$; HRMS (ESI) m/z calcd $C_{26}H_{24}N_2O_3Na$ [M + Na]$^+$ 413.1685, found 413.1698.

3-Hydroxy-2-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-3-(4-methoxybenzyl)isoindolin-1-one (9Bs). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.70 (s, 1H), 7.59 (m, 2H), 7.44 (m, 2H), 7.25 (m, 3H), 6.75 (m, 1H), 6.68 (m, 3H), 6.58 (d, J = 9.2 Hz, 2H), 4.02 (m, 4H), 3.77 (m, 4H), 3.38 (d, J = 13.6 Hz, 1H), 3.23 (d, J = 13.2 Hz, 1H), 3.07 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.0, 157.7, 153.0, 147.2, 131.7, 131.5, 131.5, 130.8, 129.0, 127.6, 127.1, 123.5, 122.9, 121.9, 112.9, 112.1, 111.7, 111.0, 100.4, 91.1, 55.3, 54.7, 41.6, 40.1, 25.1; LRMS (ESI) m/z 465

[M + Na]$^+$; HRMS (ESI) *m/z* calcd $C_{27}H_{26}N_2O_4Na$ [M + Na]$^+$ 465.1790, found 465.1803.

3-(4-Fluorobenzyl)-3-hydroxy-2-(4-(trifluoromethyl)benzyl)-isoindolin-1-one (9Ch). Mp 213–215 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.60 (m, 5H), 7.44 (m, 3H), 6.82 (m, 5H), 4.80 (d, J = 16.0 Hz, 1H), 4.73 (d, J = 16.0 Hz, 1H), 3.38 (d, J = 14.6 Hz, 1H), 3.28 (d, J = 14.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.1, 171.1 (d, J = 241 Hz), 156.8, 153.7, 141.8, 141.7 (d, J = 8.1 Hz), 141.3, 141.2, 141.0, 139.2, 138.5, 134.9, 134.8, 133.1, 132.1, 124.2 (d, J = 20.9 Hz), 101.0, 51.9, 51.8; LRMS (ESI) *m/z* 416 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{23}H_{17}F_4NO_2Na$ [M + Na]$^+$ 438.1093, found 438.1095.

3-Hydroxy-3-neopentyl-2-(4-(trifluoromethyl)benzyl)isoindolin-1-one (9Dh). Mp 132–134 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.57 (m, 8H), 6.40 (s, 1H), 4.70 (d, J = 15.9 Hz, 1H), 4.53 (d, J = 15.6 Hz, 1H), 2.33 (d, J = 15.0 Hz, 1H), 2.15 (d, J = 15.0 Hz, 1H), 0.54 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2, 148.3, 143.6, 131.8, 130.8, 129.2, 128.7, 124.7, 123.7, 122.3, 89.8, 47.7, 42.4, 30.3, 29.7; LRMS (EI) *m/z* 377 (M)$^+$; HRMS (EI) *m/z* calcd $C_{21}H_{22}F_3NO_2$ (M)$^+$ 377.1603, found 377.1610.

2,3-Dibenzyl-3-hydroxy-6-methoxyisoindolin-1-one (9Ea). Mp 165–167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.41 (d, J = 8.4 Hz, 2H), 7.25 (m, 4H), 7.06 (m, 4H), 6.94 (s, 1H), 6.77 (d, J = 6.8 Hz, 2H), 6.60 (s, 1H), 4.73 (d, J = 16.0 Hz, 1H), 4.60 (d, J = 16.0 Hz, 1H), 3.75 (s, 3H), 3.34 (d, J = 13.6 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.0, 160.1, 139.0, 138.9, 135.3, 132.8, 130.0, 128.0, 127.9, 127.5, 126.6, 126.4, 124.2, 118.4, 105.7, 90.7, 55.5, 43.3, 42.3; LRMS (ESI) *m/z* 360 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{23}H_{21}NO_3Na$ [M + Na]$^+$ 382.1419, found 382.1428.

3-Benzyl-2-butyl-3-hydroxy-6-methoxyisoindolin-1-one (9Em). Mp 119–120 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.29 (d, J = 8.0 Hz, 1H), 7.05 (m, 4H), 6.88 (s, 1H), 6.80 (m, 2H), 6.42 (s, 1H), 3.74 (s, 3H), 3.48 (m, 1H), 3.35 (m, 2H), 3.19 (d, J = 14.0 Hz, 1H), 1.64 (m, 2H), 1.33 (m, 2H), 0.90 (t, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.6, 160.1, 139.0, 135.5, 133.2, 129.8, 127.5, 126.3, 123.9, 118.1, 105.8, 90.6, 55.5, 42.6, 38.9, 31.0, 20.1, 13.8; LRMS (ESI) *m/z* 326 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{20}H_{23}NO_3Na$ [M + Na]$^+$ 348.1576, found 348.1578.

2-(2-(1*H*-Indol-3-yl)ethyl)-3-benzyl-3-hydroxy-6-methoxy-isoindolin-1-one (9Er). Mp 166–169 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.87 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.38 (m, 2H), 7.28 (s, 1H), 7.12 (m, 2H), 7.05 (m, 4H), 6.97 (s, 1H), 6.81 (m, 2H), 6.63 (m, 1H), 3.78 (m, 4H), 3.61 (m, 1H), 3.42 (d, J = 13.6 Hz, 1H), 3.26 (d, J = 14.0 Hz, 1H), 3.10 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.7, 160.1, 139.2, 136.3, 135.4, 133.3, 129.9, 127.5, 127.2, 126.4, 124.0, 122.7, 121.0, 118.4, 118.3, 118.2, 111.9, 111.4, 105.7, 90.8, 55.5, 42.6, 39.9, 25.0; LRMS (ESI) *m/z* 413 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{26}H_{24}N_2O_3Na$ [M + Na]$^+$ 413.1685, found 413.1688.

3-Benzyl-3-hydroxy-6-methoxy-2-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)isoindolin-1-one (9Es). Mp 181–183 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.69 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.24 (m, 3H), 7.11 (m, 1H), 7.05 (m, 3H), 6.97 (m, 1H), 6.77 (s, 3H), 6.63 (s, 1H), 3.78 (m, 7H), 3.62 (m, 1H), 3.43 (d, J = 14.0 Hz, 1H), 3.25 (d, J = 13.6 Hz, 1H), 3.07 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.7, 160.1, 153.0, 139.2, 135.4, 133.3, 131.5, 129.9, 127.6, 126.3, 124.0, 123.4, 118.2, 112.1, 111.7, 111.0, 105.6, 100.4, 90.8, 55.5, 55.3, 42.6, 39.9, 25.1; LRMS (ESI) *m/z* 465 [M + Na]$^+$; HRMS (ESI) *m/z* calcd $C_{27}H_{26}N_2O_4Na$ [M + Na]$^+$ 465.1790, found 465.1790.

Compound 10Ar. Mp 267–270 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.54 (t, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.36 (m, 2H), 7.18 (t, 1H), 7.09 (m, 4H), 6.82 (d, J = 6.8 Hz, 2H), 4.82 (m, 1H), 3.56 (s, 2H), 3.34 (m, 1H), 2.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 146.9, 136.4, 134.4, 133.6, 131.7, 131.6, 130.0, 128.6, 127.9, 127.0, 126.6, 124.1, 122.5, 122.2, 119.9, 118.8, 111.2, 109.0, 65.7, 44.9, 36.2, 21.8; LRMS (ESI) *m/z* 365 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{25}H_{20}N_2ONa$ [M + Na]$^+$ 387.1473, found 387.1490.

Compound 10As. Mp 288–289 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (br, 1H), 7.73 (m, 2H), 7.57 (t, 1H), 7.41 (m, 1H), 7.24 (m, 1H), 7.10 (m, 3H), 6.91 (m, 1H), 6.85 (m, 3H), 4.78 (m, 1H), 3.84 (s, 3H), 3.51 (s, 2H), 3.32 (m, 1H), 2.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 153.4, 146.9, 135.1, 135.0, 131.8, 131.3, 131.0, 129.8, 128.4, 127.5, 126.4, 126.3, 123.3, 122.8, 112.0, 111.7, 106.8, 100.2, 65.6, 55.3, 43.0, 35.7, 21.6; LRMS (ESI) *m/z* 395 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{26}H_{26}N_2O_2Na$ [M + Na]$^+$ 417.1579, found 417.1578.

Compound 10Br. Mp 307–308 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.50 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.69 (t, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.42 (m, 3H), 7.12 (t, 1H), 6.99 (t, 1H), 6.71 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 4.51 (m, 1H), 3.60 (s, 3H), 3.55 (s, 2H), 3.41 (m, 1H), 2.70 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.6, 157.8, 147.0, 136.2, 134.6, 131.7, 131.1, 130.8, 128.5, 126.8, 126.0, 123.3, 122.8, 121.7, 119.0, 118.4, 113.0, 111.3, 106.9, 65.7, 54.8, 42.2, 35.6, 21.5; LRMS (ESI) *m/z* 395 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{26}H_{22}N_2O_2Na$ [M + Na]$^+$ 417.1579, found 417.1584.

Compound 10Bs. Mp 257–259 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.32 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.69 (t, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.41 (t, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 6.75 (m, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 4.49 (m, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.53 (s, 2H), 3.38 (m, 1H), 2.73 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.6, 157.8, 153.4, 147.1, 135.2, 131.7, 131.2, 131.1, 130.8, 128.4, 126.8, 126.3, 123.3, 122.8, 112.9, 112.0, 111.6, 106.8, 100.2, 65.7, 55.4, 54.8, 42.3, 35.7, 21.6; LRMS (ESI) *m/z* 425 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{27}H_{24}N_2O_3Na$ [M + Na]$^+$ 447.1685, found 447.1693.

Compound 10Er. Mp 286–287 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.42 (t, 2H), 7.27 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 6.88 (m, 6H), 6.82 (m, 2H), 4.51 (m, 1H), 3.74 (s, 3H), 3.62 (d, J = 13.2 Hz, 1H), 3.56 (d, J = 13.6 Hz, 1H), 3.42 (m, 1H), 2.68 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.5, 159.6, 139.1, 136.2, 135.1, 135.0, 132.6, 129.8, 127.6, 126.5, 126.0, 124.3, 121.6, 119.3, 118.9, 118.4, 111.3, 106.6, 106.0, 65.1, 55.5, 42.9, 35.8, 21.5; LRMS (ESI) *m/z* 395 [M + H]$^+$; HRMS (ESI) *m/z* calcd $C_{26}H_{22}N_2O_2Na$ [M + Na]$^+$ 417.1579, found 417.1592.

Compound 10Es. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (br, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.24 (m, 1H), 7.18 (m, 1H), 7.09 (m, 4H), 6.90 (m, 1H), 6.82 (m, 3H), 4.77 (m, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.48 (s, 2H), 3.32 (m, 1H), 2.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 159.6, 153.4, 139.2, 135.6, 135.1, 132.6, 131.2, 129.8, 127.6, 126.4, 124.4, 124.4, 119.4, 112.0, 111.6, 106.5, 106.1, 100.4, 65.1, 55.5, 55.4, 43.0, 35.8, 21.6; LRMS (ESI) m/z 425 $[M + H]^+$; HRMS (ESI) m/z calcd $C_{27}H_{24}N_2O_3Na$ $[M + Na]^+$ 447.1685, found 447.1689.

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6 ^{1}H NMR, ^{13}C NMR and mass spectroscopy of **9Aa** are in the Experimental Section; see ESI for crystal structure data†.

7 The gram-scale target product could be also purified by using recrystallisation with ethyl acetate and petroleum ether.

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9 A solution of **9Aa** (0.5 mmol) in 6 N hydrochloric acid solution (2 mL) and methanol (20 mL) was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluent: petroleum ether–ethyl acetate = 25 : 1, v/v) to product (*E*)-**11** and (*Z*)-**11**, respectively (see the ESI for details†).

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11 To further explore the proposed mechanism, we attempted to synthesize one of the intermediates (**M1**) from Scheme 4 as the starting material for this catalytic cycle, and found that the same good yield (95%) of the target product (**9Aa**) was obtained under the optimum reaction conditions (see the ESI for details of intermediate **M1**†).

