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Copper-catalysed synthesis of 3-hydroxyisoindolin-1-ones from benzylcyanide 2-iodobenzamides†

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An efficient one-pot two-step sequential reaction for the synthesis of biologically active 3-hydroxyisoindolin-1-one derivatives from 2-iodobenzamide derivatives and various substituted benzyl cyanides in the presence of CuCl and cesium carbonate in DMSO is reported. Furthermore, 3-hydroxyisoindolinone derivatives possessing bromo substituents were obtained from 2-iodobenzamide and 2-bromobenzyl cyanide substrates in two steps. Benzyl cyanide has been successfully used for the first time as a benzoyl synthon for the synthesis of 3-hydroxyisoindolin-1-ones. Interestingly, the mechanism of formation of 3-hydroxyisoindolin-1-ones is a novel pathway that involves carbon degradation followed by ring contraction.

Introduction

3-Hydroxyisoindolin-1-one derivatives are important constituents of natural products and are pharmaceutically active building blocks in medicinal chemistry, as shown in Fig. 1.[1] Molecules that contain the 3-hydroxyisoindolin-1-one core are known to exhibit a wide range of activities such as antimicrobial and antitumor activities and act as inhibitors of protein–tyrosine phosphatase and HIV-1 integrase.[2] Besides, anticonvulsant and antihypertensive drugs[3] contain the 3-hydroxyisoindolin-1-one core. Furthermore, 3-hydroxyisoindolinone derivatives are also important surrogates for the synthesis of various products.[4]

As a result, continuous efforts have been directed towards the development of efficient methods for the synthesis of 3-hydroxyisoindolin-1-one derivatives. A literature survey revealed that the most common method for the synthesis of 3-hydroxyisoindolinone derivatives is the selective addition of organometallic reagents such as RMgX, RLi, and R_2Zn to phthalimide derivatives.[5] The other methods for their synthesis from phthalimides include photodecarboxylative addition of carboxylates[6] and reductive coupling with aldehydes and ketones (Fig. 2).[7]

Liu *et al.*[8] introduced a green protocol for the synthesis of 3-hydroxyisoindolinone derivatives from 2-(ethynyl)benzoic acids and primary amines using a phase transfer catalyst in the presence of water under microwave conditions. Later, the Kim and Zhao research groups individually disclosed the synthesis of 3-hydroxyisoindolinone derivatives starting from benzamide derivatives *via* tandem metal-catalyzed oxidative acylation of secondary benzamides with aldehydes and an intramolecular cyclization strategy using Rh[9] and Pd[10] catalysts, respectively. Recently, Shen and coworkers reported base-promoted cascade C–C coupling/*N*-α-sp^3C–H hydroxylation for the synthesis of 3-hydroxyisoindolinone derivatives.[11] Subsequently other methods were also reported.[12] The need for expensive metal catalysts, additional oxidants, and harsh reaction conditions is the limitation of these protocols. Therefore, an efficient protocol that addresses these issues is highly desirable for the synthesis of 3-hydroxyisoindolinone derivatives.

Benzyl cyanide is a versatile reagent which plays multiple roles in reactions by functioning as a nucleophile, cyanating

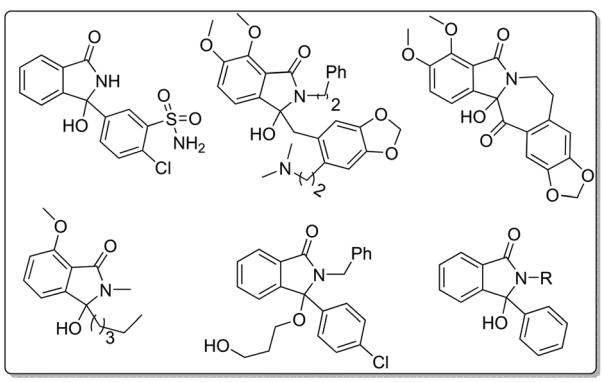

Fig. 1 Representative natural products and biologically active compounds that contain the 3-hydroxyisoindolin-1-one core.

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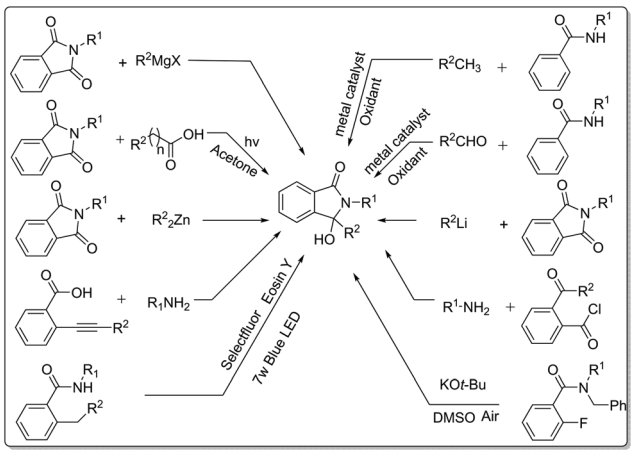


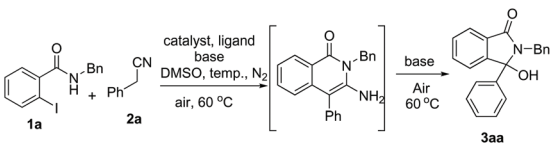
Fig. 2 Known synthetic route for accessing 3-hydroxyisoindolin-1-one derivatives.

agent and benzoyl protecting group. Moreover, the use of benzyl cyanide as a nucleophile[13] and cyanating agent[14] is well documented in the literature. Furthermore, several reports are available on the use of benzyl cyanide as a benzoyl synthon for the protection of amine and alcohol groups.[15] Previously, we reported that benzyl cyanide acts as a nucleophile as well as a cyanating agent in the same reaction by slight modification of the reaction conditions.[16]

As part of our interest in developing fascinating protocols for the synthesis of biologically active heterocycles using 2-iodobenzamides,[17] very recently, we reported the synthesis of benzopyridoindolone derivatives *via* a one-pot copper-catalyzed tandem reaction of 2-iodobenzamide and 2-iodobenzylcyanide derivatives.[18] When we replaced 2-iodobenzyl cyanide with 2-bromobenzylcyanide in the reaction, we obtained two products in which the first product corresponded to the benzofused pyridoindolone derivative. The other one was an unknown product, which was characterized by NMR and mass spectral data. From the spectral data, it was found that the unknown product was a 3-hydroxyisoindolinone derivative. This is an interesting result where the six-membered ring contracts to a five-membered ring through one carbon degradation. Hence, we envisioned that the investigation of this reaction would be very useful as 3-hydroxyisoindolinone derivatives exhibit a variety of biological activities. Moreover, the reaction of 2-bromobenzylcyanide and 2-iodobenzamide produced two products, and we speculate that the use of benzyl cyanide instead of 2-bromobenzyl cyanide would give single product as it can avoid the formation of benzofused pyridoindolone.

To test this hypothesis, we initiated the reaction of 2-iodo-*N*-benzylbenzamide (**1a**) and benzyl cyanide (**2a**) in the presence of CuI and Cs_2CO_3 (2 equiv.) at 60 °C in DMSO for 20 min under a nitrogen atmosphere. The reaction produced 3-amino-2-benzyl-4-phenylisoquinolin-1(2*H*)-one which remained unchanged even after 12 h. However, without isolating the aminoisoquinolinone compound, we continued the reaction by replacing the nitrogen atmosphere with an open atmosphere at the same temperature for 24 h. The reaction produced 35% of the expected product (**3aa**). Encouraged by this result, we screened various conditions to improve the yield of the desired product while maintaining the same sequence of conditions (initially the reaction was conducted under a nitrogen atmosphere until the formation of the intermediate, then the nitrogen balloon was removed and the reaction was conducted in an open atmosphere). In this regard, firstly, we increased the amount of the base in the reaction (Table 1, entries 2 and 3). We found that the reaction resulted in a better yield with 3 equiv. of Cs_2CO_3. Next, we optimized the amount of benzyl cyanide in the reaction (Table 1, entries 4–6). The use of 1.5 equiv. of benzyl cyanide in the reaction gave better yield compared with the use of a higher amount of benzyl cyanide. Furthermore, no marked improvement in the yield of the desired product was observed when the reactions were performed at 80 °C and 100 °C (Table 1, entries 7 and 8). Next, we screened different bases such as K_2CO_3, K_3PO_4, TEA, and DBU for use in this reaction. The reactions afforded a low yield of the product with these bases (Table 1, entries 9–12). After an extensive screening of parameters like the ratio of reagents, bases, solvents, and temperature, the product yield reached only 47%.

Table 1 Optimization studies



Entry[a]	2a (eq.)	Catalyst	Ligand	Base (eq.)	Temp. (°C)	Yield[b] (%)
1	1.2	CuCl	No	Cs_2CO_3 (2)	60	35
2	1.2	CuCl	No	Cs_2CO_3 (3)	60	45
3	1.2	CuCl	No	Cs_2CO_3 (4)	60	36
4	1.5	CuCl	No	Cs_2CO_3 (3)	60	40
5	2	CuCl	No	Cs_2CO_3 (3)	60	47
6	2.5	CuCl	No	Cs_2CO_3 (3)	60	45
7	1.5	CuCl	No	Cs_2CO_3 (3)	80	41
8	1.5	CuCl	No	Cs_2CO_3 (3)	100	25
9	1.5	CuCl	No	K_2CO_3 (3)	60	24
10	1.5	CuCl	No	K_3PO_4 (3)	60	35
11	1.5	CuCl	No	DBU (3)	60	30
12	1.5	CuCl	No	TEA (3)	60	24
13	1.5	CuCl	L1	Cs_2CO_3 (3)	60	45
14	1.5	CuCl	L2	Cs_2CO_3 (3)	60	30
15	1.5	CuCl	L3	Cs_2CO_3 (3)	60	28
16	1.5	CuI	L1	Cs_2CO_3 (3)	60	44
17	1.5	CuBr	L1	Cs_2CO_3 (3)	60	33
18	1.5	$CuSO_4$	L1	Cs_2CO_3 (3)	60	20
19	1.5	$Cu(OAc)_2$	L1	Cs_2CO_3 (3)	60	26
20	1.5	$CuCl_2$	L1	Cs_2CO_3 (3)	60	20
21[c]	1.5	CuCl	No	Cs_2CO_3 (3)	60	50
22[c]	1.5	CuCl	L1	Cs_2CO_3 (3)	60	78
23[c,d]	1.5	CuCl	L1	Cs_2CO_3 (3)	60	52

[a] Reaction conditions: (1) **1a** (1 mmol), **2a**, catalyst (10 mol%), ligand (20 mol%), base, DMSO, temp., N_2; (2) air, 60 °C. [b] NMR yields. [c] Additional amount of Cs_2CO_3 was added after the formation of the intermediate. [d] The second step under O_2.

To improve the yield of the product, we performed the reaction using different ligands such as L-proline (L1), 1,10-phenanthroline (L2), and 8-hydroxyquinoline (L3). With proline, the reaction afforded the corresponding product in 45% yield (Table 1, entry 13) while a poor yield of the product was obtained with 1,10-phenanthroline and 8-hydroxyquinoline (Table 1, entries 14 and 15). Next, we screened other copper catalysts such as CuI, CuBr, $CuSO_4$, $Cu(OAc)_2$ and $CuCl_2$ along with CuCl (Table 1, entries 16–20). Among the copper catalysts used in this reaction, CuCl was found to be the best catalyst for this conversion. Next, we conducted the reaction by adding an additional amount of cesium carbonate (2 equiv.) after the formation of the intermediate. The reaction produced 50% of the desired product. When the reaction was carried out in the presence of L-proline with the addition of 2 more equivalents of cesium carbonate, 78% of the corresponding 3-hydroxyisolindolinone derivative was produced (Table 1, entry 22). Next, we conducted the reaction in the presence of oxygen. To our surprise, the reaction provided the desired product in 52% yield, which is less than that obtained in an open atmosphere. The optimized conditions for the reaction were 10 mol% of CuCl, 20 mol% of L-proline and 3 equiv. of cesium carbonate in DMSO at 60 °C under a nitrogen atmosphere until the formation of the intermediate (3-aminoisoquinolinone derivative) and the reaction was continued by the addition of 2 more equivalents of cesium carbonate in an open atmosphere in one pot. Later we examined the scope of the methodology by fixing 2-iodo-*N*-benzylbenzamide (**1a**) and changing the substituents on the benzyl cyanide substrate, as shown in Table 2.

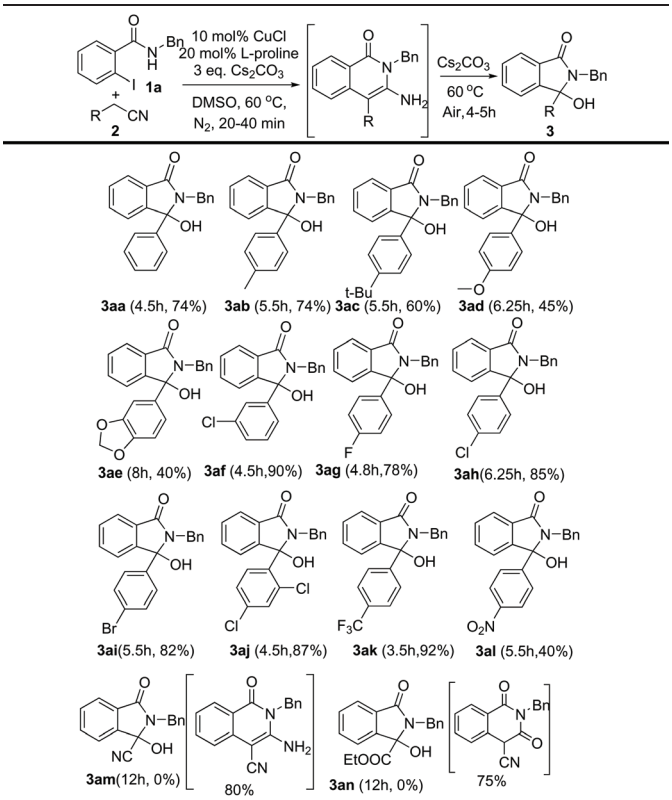
The reaction of **1a** and unsubstituted benzyl cyanide produced its corresponding 3-hydroxyisoindolin-1-one product (**3aa**) in 63% yield. Next, Benzyl cyanide bearing moderate electron-donating groups such as Me and *t*-Bu afforded the desired products (**3ab** and **3ac**) in moderate yields, whereas benzyl cyanide containing strong electron-donating groups such as OMe and OCH_2O furnished the corresponding products (**3ad** and **3ae**) in low yields. On the other hand, electron-withdrawing groups such as Cl, F, Br, dichloro, and CF_3 on the benzyl cyanide substrate work well in producing the desired products (**3af**, **3ag**, **3ah**, **3ai**, **3aj**, and **3ak**) in good to excellent yields. The reaction of benzyl cyanide containing strong electron-withdrawing groups with 2-iodo-*N*-benzylbenzamide gave a poor yield of the desired product (**3al**). When using ethylcyanoacetate and malanonitrile, we did not obtain the desired products. However, with ethylcyanoacetate, the reaction afforded 2-benzyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carbonitrile while with malanonitrile, 3-amino-2-benzyl-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile was obtained.

Next, we were interested in checking the scope of the protocol by fixing the benzyl cyanide substrate and varying the *N*-alkyl substituents of the starting material 2-iodobenzamide under the optimized reaction conditions (Table 3).

When *N*-methyl and *N*-isopropyl substituents were used in the reactions, the desired products (**3ba** and **3ca**) were isolated in 65 and 52% yields, respectively. The reaction works well with *N*-phenyl, producing the corresponding product (**3da**) in good yield. Then, we examined the reactions of 2-iodobenzamide substrates containing *N*-phenethyl, *N*-phenylbutyl, *N*-ethylmethoxy, *N*-ethylindolyl and *N*-ethylmorphinyl substituents. Good yield of the products was obtained in the case of *N*-phenethyl (**3ea**), *N*-phenylbutyl (**3fa**), and *N*-ethylmethoxy (**3ga**) substrates. Moderate yields of the 3-hydroxyisoindolin-1-one derivatives were obtained with *N*-ethylindolyl (**3ha**) and *N*-ethylmorphinyl (**3ia**) substrates. Furthermore, we tested the reactions of various substituted 2-iodobenzamide substrates with benzyl cyanide. Halogens such as 5-bromo, 3-chloro, and 5-fluoro substituted 2-iodobenzamide derivatives readily participated in the reaction to furnish the corresponding 3-hydroxyisoindolinone derivatives **3ja**, **3ka** and **3la**, respectively, in good yields. On the other hand, the substrates containing electron-donating groups such as methoxy, dimethoxy, and methylenedioxy groups afforded the corresponding products (**3ma**, **3na**, and **3oa**) in moderate yields.

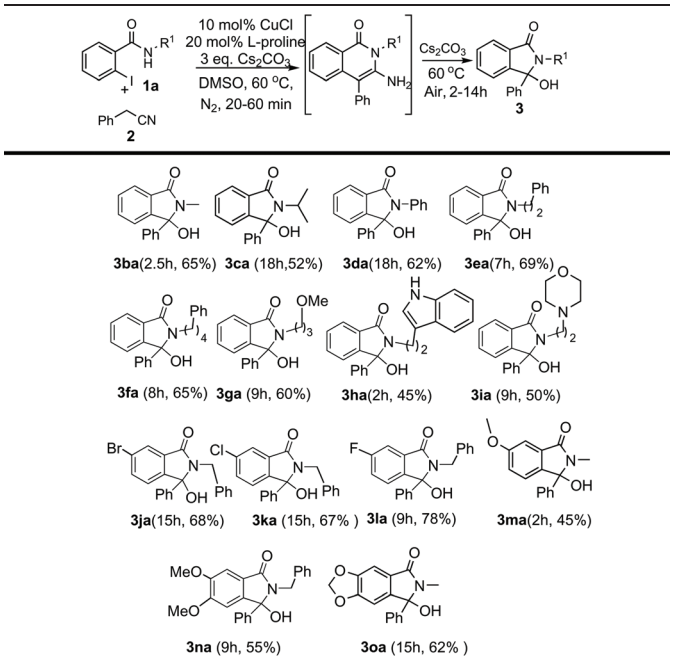
After the successful application of the one-pot reaction conditions to various benzyl cyanide substrates, we then turned our attention to utilize 2-bromobenzyl cyanide. To obtain the 3-hydroxyisoindolin-1-one derivative from this reaction, we performed the reaction in two steps, wherein we performed the reaction of 2-bromobenzylcyanide and 2-iodobenzamide

Table 2 Scope and limitation when using various cyanide derivatives[a,b]



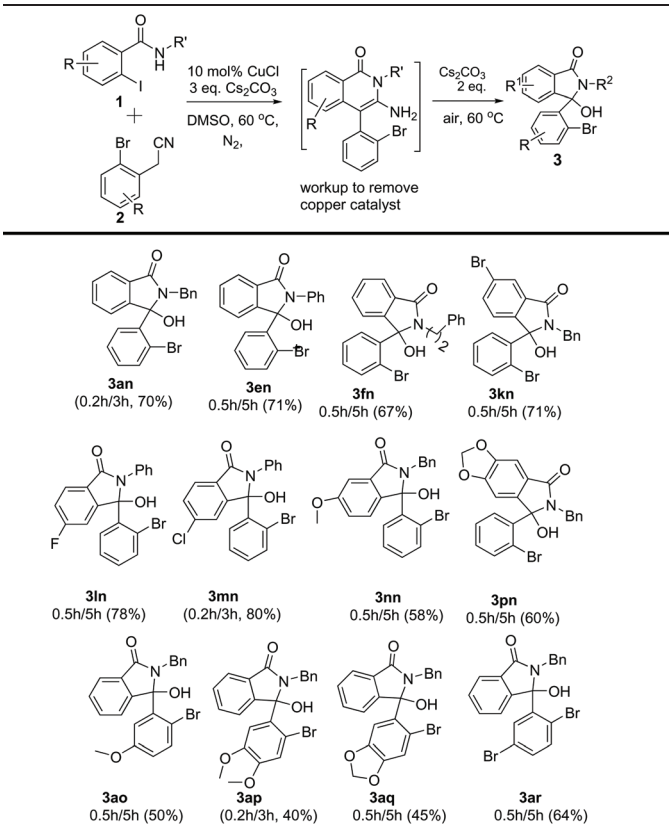
[a] Reaction conditions: **1** (1 mmol), **2** (1.1 eq.), CuCl (10 mol%), Cs_2CO_3 (3 eq.), DMSO (2 mL) heated at 60 °C under N_2 until the formation of the intermediate, which was confirmed by TLC; the reaction was continued by the addition of two more equiv. of Cs_2CO_3 at the same temperature in an open atmosphere in one pot. [b] Isolated yield.

Table 3 Scope and limitation when using substituted 2-iodobenzamide derivatives[a,b]



[a] Reaction conditions: **1** (1 mmol), **2** (1.1 eq.), CuCl (10 mol%), Cs_2CO_3 (3 eq.), DMSO (2 mL) heated at 60 °C under N_2 until the formation of the intermediate, which was confirmed by TLC; the reaction was continued by the addition of two more equivalents of Cs_2CO_3 at the same temperature in an open atmosphere in one pot. [b] Isolated yield.

Table 4 Scope and limitation when using substituted 2-iodobenzamide derivatives and 2-bromobenzylcyanide substrates[a,b,c]

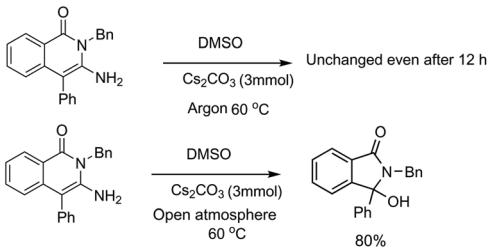


[a] Reaction conditions: **1** (1 mmol), **2** (1.1 eq.), CuCl (10 mol%), Cs_2CO_3 (3 eq.), DMSO (2 mL) heated at 60 °C under N_2 until the formation of the intermediate. Then the reaction was stopped with water and extracted with EA. The crude mixture was treated with two equiv. of Cs_2CO_3 at 60 °C in an open atmosphere (reaction conducted in two steps). [b] Isolated yield. [c] In all the cases, we observed the benzopyridoindole derivative as a side product in 10–15% yield.

derivatives at 60 °C until the complete consumption of the amide component. Later the reaction was quenched to remove the copper salt. After the workup, the crude reaction mixture was again reacted with cesium carbonate in DMSO at the same temperature to obtain the corresponding hydroxyisoindolin-1-one derivative. It is important to note that the reaction involving 2-bromobenzyl cyanide substrates did not require the L-proline ligand for the formation of intermediate 3-aminoisoquinolinone derivatives. Furthermore, in the presence of L-proline, a greater amount of the benzopyridoindole derivative was formed as a side product. Under modified conditions, we investigated the reactions of various substituted 2-iodobenzamides and 2-bromobenzylcyanides (Table 4). The results are shown in Table 4. The reaction of various *N*-substituted-2-iodbenzamide substrates such as *N*-phenyl, *N*-benzyl and *N*-ethylphenyl 2-iodobenzamide with 2-bromobenzyl cyanide furnished the corresponding hydroxyisoindolin-1-one derivatives (**3an**, **3en**, and **3fn**) in good yields. Under the present reaction conditions, halo substituted 2-iodobenzamide substrates reacted smoothly to afford the desired products (**3kn**, **3ln**, and **3mn**) in good yields. However, the electron-donating group substituted 2-iodobenzamide substrates produced the corresponding products (**3nn** and **3pn**) in slightly lower yields compared to the electron-withdrawing group substituted 2-iodobenzamides. Later the reaction scope was examined by fixing 2-iodo-*N*-benzylbenzamide and changing the substituents on the benzyl cyanide substrate as shown in Table 4. A moderate yield of the desired product is obtained using the OMe substituent on the 2-bromobenzyl cyanide substrate and 3,4-dimethoxy-2-bromobenzyl cyanide and 3,4-methylenedioxy-2-bromobenzyl cyanide substrates gave the desired products **3ap** and **3aq** in yields of 40% and 45%, respectively. Dibromobenzyl cyanide produced the desired product **3ar** in good yield.

We thought of two plausible pathways for the formation of 3-hydroxyisoindolin-1-one from 2-iodo-*N*-methylbenzamide and benzyl cyanide (Scheme 1).

Initially, the formation of the 3-amino isoquinolinone intermediate occurs in the presence of CuCl and a base (the isoquinilone intermediate was isolated and characterized). In the first pathway, intermediate [**A**] generates iminium salt [**B**] in the presence of a base, which undergoes ring opening to afford cyano intermediate 2-(cyano(phenyl)methyl)-*N*-methylbenzamide [**C**]. Next, intramolecular cyclization occurs by the loss of a cyanide ion to afford 2-methyl-3-phenylisoindolin-1-



Scheme 1 Plausible mechanistic pathways for the reaction.

one (**D**), which upon reaction with oxygen in the presence of a base furnishes peroxide intermediate [**E**].[11] Next, the peroxide intermediate decomposes to afford the 3-hydroxyisoindolin-1-one derivative (**3**). Another possibility is that after the formation of 2-(cyano(phenyl)methyl)-*N*-methylbenzamide intermediate [**C**], it reacts with oxygen in the presence of a base to produce peroxide intermediate [**F**], which subsequently decomposes to afford intermediate [**G**]. Further, intermediate [**G**] affords intermediate [**H**] by the elimination of a cyanide ion, which subsequently undergoes intramolecular cyclization to afford the desired product **3**.

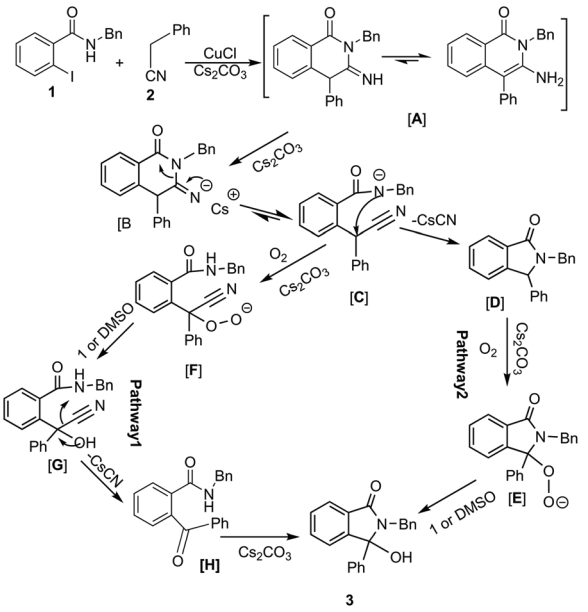
To check for the suitable pathway among the proposed pathways, we carried out a few controlled experiments. Initially, the intermediate (3-aminoisoquinolinone) was isolated and then it was subjected to the reaction in d6-DMSO in the presence of Cs_2CO_3 in an NMR tube. The reaction was monitored constantly. It was observed that the NH_2 peak disappeared in the ^{1}H NMR spectrum as soon as the base was added. This indicates the formation of intermediate [**B**]. Moreover, the proton NMR spectrum showed only two sets of protons, one corresponding to the final product and the other corresponding to intermediate **B**. We did not find any other products during the ^{1}H NMR experiment of the reaction of intermediate [**A**] (see NMR experiment results in the ESI, page S56†).

The reaction of intermediate **A** and cesium carbonate was conducted under an argon atmosphere. Intermediate **A** remained unchanged even after 12 h (Scheme 2), whereas in open air, the reaction afforded the 3-hydroxyisoindolinone derivative (**3a**) in 80% yield.

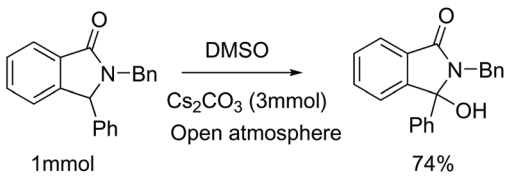
Next we synthesized 2-benzyl-3-phenylisoindolin-1-one using a known procedure and it was treated with cesium carbonate in DMSO at 60 °C in an open atmosphere. The reaction produced 3-hydroxy-*N*-benzyl-isoindolin-1-one (**3aa**) in 74% yield (Scheme 3).

Based on these observations, we cannot rule out either of two possibilities proposed in Scheme 1. However, under an argon atmosphere, the 3-aminoisoquinolinone derivative did not produce 2-benzyl-3-phenylisoindolin-1-one derivative. Hence, we speculate that pathway 1 is a more plausible mechanistic pathway for the formation of product **3**.

In conclusion, an efficient one-pot two-step sequential reaction for the synthesis of biologically active 3-hydroxyisoindolin-1-one derivatives from 2-iodobenzamide and



Scheme 2 Reaction of 3-aminoisoquinolinone with cesium carbonate under an argon atmosphere.



Scheme 3 Reaction of 2-benzyl-3-phenylisoindolin-1-one.

various substituted benzyl cyanides in the presence of CuCl and cesium carbonate in DMSO is reported. Furthermore, we also reported the synthesis of 3-hydroxyisoindolinone derivatives and benzofused pyridoindolone from 2-iodobenzamide and 2-bromobenzyl cyanide substrates by altering the reaction conditions. Benzyl cyanide has been successfully used for the first time as a benzoyl synthon for the synthesis of 3-hydroxyisoindolin-1-ones. Also, the proposed mechanism for the formation of 3-hydroxyisoindolin-1-ones is a novel pathway that involves carbon degradation followed by ring contraction.

Experimental section

General information

Reagents and solvents were purchased from various commercial sources and were used directly without any further purification, unless otherwise stated. Column chromatography was performed using 63–200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400/500/600 and 100/125/150 MHz, respectively. Chemical shifts are reported in parts per million (δ) using TMS and chloroform or DMSO-d_6 as internal stan-

dards and coupling constants are expressed in hertz. Melting points were recorded using an electro thermal capillary melting point apparatus and are uncorrected. HRMS spectra were recorded using ESI-TOF or ESI-Neg mode. The starting 2-iodobenzamide derivatives **1** and benzyl cyanide derivatives **2** were synthesized following previously reported methods.

General procedure for the one-pot synthesis of 3-hydroxyisoindolinone derivatives from benzylcyanide and 2-iodobenzamide derivatives

A 25 mL round-bottom flask was charged with 3 mL of DMSO, followed by 2-iodobenzamide derivative **1** (1 mmol), copper(I) chloride (0.15 mmol), proline (0.3 mmol), benzyl cyanide derivative **2** (2 mmol), and cesium carbonate (3 mmol). The reaction mixture was stirred at 60 °C until the complete consumption of 2-iodobenzamide to form an intermediate, as evidenced by TLC. Then, 2 mmol of additional cesium carbonate was added and the reaction was continued in an open atmosphere at the same temperature until the completion of the reaction, as evidenced by TLC. Then, the mixture was cooled down to room temperature and ice/water was added to it. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered and the dried organic layer was then concentrated to give the crude product. The resulting residue was further purified by flash column chromatography using 1 : 5 ethyl acetate/hexane on silica gel.

General procedure for the synthesis of 3-hydroxyisoindolinone derivatives from 2-bromobenzylcyanide and 2-iodobenzamide derivatives

A 25 mL round-bottom flask was charged with 3 mL of DMSO, followed by 2-iodobenzamide derivative **1** (1 mmol), copper(I) chloride (0.15 mmol), 2-bromobenzyl cyanide derivative **2** (2 mmol), and cesium carbonate (3 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C until the complete consumption of 2-iodobenzamide to form the intermediate, as evidenced by TLC. Then, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered and the dried organic layer was then concentrated to give the crude intermediate. The crude intermediate product was dissolved in DMSO and 2 mmol of cesium carbonate was added. The reaction mixture was stirred at 60 °C in an open atmosphere until the completion of the reaction, as evidenced by TLC. Then the reaction mixture was cooled down to room temperature and ice/water was added to it. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered and the dried organic layer was then concentrated to give the crude product. The resulting residue was further purified by flash column chromatography using 1 : 5 ethyl acetate/hexane on silica gel.

Spectral data

Known compounds **3aa**,[11] **3ak**,[9] **3al**, **3ba**, **3ca**, **3da**.[11]

2-Benzyl-3-hydroxy-3-(*p*-tolyl)isoindolin-1-one (3ab)

Yield 74% (244 mg); pale yellow solid. Mp: 166.0–168.0 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76–7.74 (m, 1H), 7.47–7.40 (m, 2H), 7.25–7.24 (m, 1H), 7.21–7.13 (m, 7H), 7.08–7.06 (m, 2H), 4.70 (d, J = 14.98 Hz, 1H), 4.02 (d, J = 14.98 Hz, 1H), 3.43 (s, 1H), 2.32 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.0, 149.4, 138.4, 138.3, 135.5, 132.9, 130.4, 129.6, 129.3, 128.9, 128.3, 127.2, 126.4, 123.6, 122.9, 91.9, 43.2, 21.3; HRMS (ESI-neg) m/z calcd for $C_{22}H_{18}NO_2$ (M^- − H) 328.1338, found 328.1334.

2-Benzyl-3-(4-(*tert*-butyl)phenyl)-3-hydroxyisoindolin-1-one (3ac)

Yield: 60% (223 mg); pale yellow solid. Mp: 194.4–196.3 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.92 Hz, 1H), 7.49–7.41 (m, 2H), 7.29–7.27 (m, 1H), 7.25–7.19 (m, 4H), 7.17–7.10 (m, 5H), 4.66 (d, J = 16.0 Hz, 1H), 4.10 (d, J = 16.0 Hz, 1H), 1.28 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.1, 151.5, 149.4, 138.2, 135.3, 132.9, 130.5, 129.6, 129.0, 128.2, 127.0, 126.2, 125.4, 123.5, 123.0, 91.8, 43.1, 34.7, 31.5; HRMS (ESI-neg) m/z calcd for $C_{25}H_{24}NO_2$ (M^- − H) 370.1807, found 370.1806.

2-Benzyl-3-hydroxy-3-(4-methoxyphenyl)isoindolin-1-one (3ad)

Yield: 45% (155 mg); white solid. Mp: 176.3–177.3 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79–7.77 (m, 1H), 7.49–7.42 (m, 2H), 7.26–7.20 (m, 5H), 7.19–7.14 (m, 3H), 6.79–6.77 (m, 2H), 4.73 (d, J = 14.98 Hz, 1H), 4.05 (d, J = 14.98 Hz, 1H), 3.78 (s, 3H), 3.13 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.0, 159.8, 149.4, 138.4, 132.9, 130.4, 130.4, 129.6, 128.9, 128.3, 127.9, 127.2, 123.6, 122.9, 113.9, 91.8, 55.5, 43.1; HRMS (ESI-neg) m/z calcd for $C_{22}H_{18}NO_3$ (M^- − H) 344.1287, found 344.1295.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-benzyl-3-hydroxyiso indolin-1-one (3ae)

Yield: 40% (143 mg); pale yellow solid. Mp: 203.2–205.0 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82–7.80 (m, 1H), 7.51–7.43 (m, 2H), 7.28–7.24 (m, 3H), 7.22–7.16 (m, 3H), 6.92–6.89 (dd, J = 8.12, 1.76 Hz, 1H), 6.72–6.69 (m, 2H), 5.92–5.91 (m, 2H), 4.77 (d, J = 15.00 Hz, 1H), 4.10 (d, J = 15.00 Hz, 1H), 2.90 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9, 149.2, 148.0, 147.9, 138.4, 133.0, 132.3, 130.4, 129.8, 128.9, 128.4, 127.3, 123.7, 122.8, 120.3, 108.2, 107.3, 101.4, 91.7, 43.1. HRMS (ESI-neg) m/z calcd for $C_{22}H_{16}NO_4$ (M^- − H) 358.1079, found 358.1072.

2-Benzyl-3-(3-chlorophenyl)-3-hydroxyisoindolin-1-one (3af)

Yield: 87% (315 mg); white solid. Mp: 197.8–199.7 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77–7.75 (m, 1H), 7.51–7.43 (m, 2H), 7.33 (s, 1H), 7.26 (d, J = 7.60 Hz, 1H), 7.21–7.18 (m, 1H), 7.15–7.10 (m, 7H), 4.59 (d, J = 14.96 Hz, 1H), 4.13 (d, J = 14.96 Hz, 1H), 3.62 (s, 1H); ^{13}C-NMR

(100 MHz, $CDCl_3$) δ 168.2, 148.8, 140.6, 137.7, 134.5, 133.2, 130.2, 129.9, 129.7, 128.9, 128.6, 128.3, 127.3, 127.1, 124.8, 123.7, 123.0, 91.1, 43.0; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{15}NO_2Cl$ (M^- − H) 348.0791, found 348.0797.

2-Benzyl-3-(4-fluorophenyl)-3-hydroxyisoindolin-1-one (3ag)

Yield: 78% (260 mg); pale yellow solid. Mp: 179.5–180.3 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.40 Hz, 1H), 7.49 (t, J = 7.42 Hz, 1H), 7.43 (t, J = 7.40 Hz, 1H), 7.24–7.20 (m, 3H), 7.10–7.05 (m, 5H), 6.86 (t, J = 8.54 Hz, 2H), 4.44 (d, J = 15.0 Hz, 1H), 4.13 (d, J = 15.0 Hz, 1H), 4.25 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 162.8 (d, J_{C-F} = 247.29 Hz), 149.2, 138.0, 134.2 (d, J_{C-F} = 2.84 Hz), 133.1, 130.2, 129.8, 128.9, 128.6 (d, J_{C-F} = 8.33 Hz), 128.3, 127.2, 123.6, 122.9, 115.2 (d, J_{C-F} = 21.64 Hz), 91.3, 42.9; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{15}NO_2F$ (M^- − H) 332.1087, found 332.1078.

2-Benzyl-3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (3ah)

Yield: 85% (297 mg); yellow solid. Mp: 195.5–197.2 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 1H), 7.50–7.42 (m, 2H), 7.24–7.09 (m, 10H), 4.54 (d, J = 14.9 Hz, 1H), 4.09 (d, J = 14.9 Hz, 1H), 3.76 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 148.9, 137.9, 137.0, 134.5, 133.1, 130.2, 129.8, 128.9, 128.5, 128.3, 128.1, 127.2, 123.6, 122.9, 91.3, 42.9; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{15}NO_2Cl$ (M^- − H) 348.0791, found 348.0798.

2-Benzyl-3-(4-bromophenyl)-3-hydroxyisoindolin-1-one (3ai)

Yield: 82% (323 mg); white solid. Mp: 183.5–185.5 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.48–7.39 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.12–6.96 (m, 7H), 4.45 (d, J = 16.0 Hz, 1H), 4.17 (s, 1H), 4.13 (d, J = 16.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9, 148.6, 137.7, 137.3, 132.9, 130.0, 129.6, 128.7, 128.2, 128.1, 127.0, 123.4, 122.7, 91.1, 42.7; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{16}BrNO_2$ (M^- − H) 382.1055, found 382.1047.

2-Benzyl-3-(2,4-dichlorophenyl)-3-hydroxyisoindolin-1-one (3aj)

Yield: 87% (335 mg); yellow solid. Mp: 194.0–195.4 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0, 1H), 7.66–7.61 (m, 1H), 7.49–7.34 (m, 3H), 7.17 (d, J = 8.0, 1H), 7.11–6.99 (m, 5H), 6.87 (s, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.26 (d, J = 12.0 Hz, 1H), 4.25 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 147.1, 136.5, 135.3, 133.3, 133.2, 132.7, 131.7, 131.0, 130.6, 129.7, 128.9, 127.8, 127.0, 126.8, 123.4, 122.1, 89.2, 42.7; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{14}Cl_2NO_2$ (M^- − H) 382.0402, found 382.0405.

2-Benzyl-3-hydroxy-3-(4-nitrophenyl) isoindolin-1-one (3al)

Yield: 40% (143 mg); yellow solid. Mp: 206.6–208.4 °C (EA/hexane). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.05–8.03 (m, 2H), 7.82–7.80 (m, 1H), 7.60–7.57 (m, 2H), 7.54 (s, 1H), 7.49–7.47 (m, 2H), 7.29–7.27 (m, 1H), 7.13–7.10 (m, 5H), 4.45 (d, J = 15.5 Hz, 1H), 4.36 (d, J = 15.5 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 166.8, 148.6, 147.4, 147.0, 137.8, 132.9, 130.3, 129.8, 128.0, 127.8, 127.7, 126.6, 123.3, 122.9, 122.9, 89.9, 42.3; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{15}N_2O_4$ (M^- − H) 359.1032, found 359.1029.

3-Hydroxy-2-phenethyl-3-phenylisoindolin-1-one (3ea)

Yield: 69% (228 mg); yellow solid. Mp: 194.0–196.0 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71–7.69 (d, J = 7.24 Hz, 1H), 7.47–7.38 (m, 4H), 7.35–7.32 (m, 3H), 7.27–7.25 (m, 1H), 7.24–7.20 (m, 2H), 7.18–7.14 (m, 1H), 7.07–7.06 (m, 2H), 3.67–3.60 (m, 1H), 3.45 (s, 1H), 3.19–3.11 (m, 1H), 2.99–2.92 (m, 1H), 2.59–2.52 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.0, 149.2, 139.5, 138.9, 132.9, 130.7, 129.7, 129.0, 128.8, 128.6, 126.5, 126.4, 123.4, 122.9, 91.5, 41.6, 34.8; HRMS (ESI-neg) *m*/*z* calcd for $C_{22}H_{18}NO_2$ (M^- − H) 328.1338, found 328.1341.

3-Hydroxy-3-phenyl-2-(4-phenylbutyl)isoindolin-1-one (3fa)

Yield: 65% (232 mg); white solid. Mp: 133.8–135.2 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.24 Hz, 1H), 7.50–7.38 (m, 4H), 7.33–7.32 (m, 3H), 7.28–7.22 (m, 3H), 7.18–7.08 (m, 3H), 3.87 (s, 1H), 3.45–3.38 (m, 1H), 3.00–2.93 (m, 1H), 2.49 (t, J = 7.22 Hz, 2H), 1.54–1.44 (m, 3H), 1.38–1.34 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.1, 149.2, 142.5, 138.9, 132.8, 130.8, 129.6, 128.6, 128.6, 128.4, 126.4, 125.8, 123.4, 122.9, 91.5, 39.5, 35.6, 29.2, 28.5; HRMS (ESI-neg) *m*/*z* calcd for $C_{24}H_{22}NO_2$ (M^- − H) 356.1651, found 356.1653.

3-Hydroxy-2-(3-methoxypropyl)-3-phenylisoindolin-1-one (3ga)

Yield: 60% (192 mg); white solid. Mp: 130–132 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79–7.77 (m, 1H), 7.47–7.25 (m, 8H), 5.10 (s, 1H), 3.83–3.79 (m, 1H), 3.57–3.44 (m, 2H), 3.18 (s, 3H), 2.97–2.91 (m, 1H), 2.01–1.88 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.1, 149.6, 139.2, 132.5, 130.3, 129.1, 128.5, 128.3, 126.1, 123.1, 122.5, 91.5, 71.3, 58.3, 37.2, 28.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{19}NO_3Na$ $(M + Na)^+$ 320.163, found 320.1264.

3-Hydroxy-2-(2-morpholinoethyl)-3-phenylisoindolin-1-one (3ha)

Yield: 45% (153 mg); pale yellow solid. Mp: 166.0–168.0 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.48 (brs, 1H), 7.83–7.81 (m, 1H), 7.51–7.39 (m, 4H), 7.38–7.30 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 4.17–4.13 (m, 1H), 3.76 (m, 4H), 2.91 (t, J = 13.6 Hz, 1H), 2.76 (t, J = 12.4 Hz, 1H), 2.53–2.34 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 149.6, 140.4, 132.7, 129.5, 128.9, 128.7, 128.4, 126.2, 123.4, 122.3, 90.0, 66.1, 58.3, 53.0, 35.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{23}N_2O_3$ (M^+H) 339.1709, found 339.1709.

2-(2-(1*H*-Indol-3-yl)ethyl)-3-hydroxy-3-phenylisoindolin-1-one (3ia)

Yield: 50% (183 mg); yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.72–7.70 (d, J = 7.28 Hz, 1H), 7.45–7.36 (m, 5H), 7.36–7.28 (m, 4H), 7.26–7.24 (d, J = 7.36 Hz, 1H), 7.16–7.12 (m, 1H), 7.06–7.02 (m, 1H), 6.89–6.88 (m, 1H), 3.80–3.73 (m, 1H), 3.60 (s, 1H), 3.31–3.23 (m, 1H), 3.11–3.03 (m, 1H), 2.82–2.75 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.3, 149.3, 138.9,

136.3, 132.8, 130.7, 129.6, 128.7, 128.7, 127.5, 126.5, 123.3, 122.9, 122.2, 122.0, 119.3, 119.1, 113.4, 111.2, 91.6, 40.6, 24.5; HRMS (ESI-neg) *m*/*z* calcd for $C_{24}H_{19}N_2O_2$ (M^- − H) 367.1447, found 367.1454.

2-Benzyl-6-bromo-3-hydroxy-3-phenylisoindolin-1-one (3ja)

Yield: 68% (266 mg); white solid. Mp: 209.8–210.7 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.60–7.57 (m, 1H), 7.29–7.23 (m, 5H), 7.13–7.11 (m, 6H), 4.64 (d, J = 16.0 Hz, 1H), 4.15 (d, J = 16.0 Hz, 1H), 3.65 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 147.7, 137.5, 137.4, 135.8, 132.1, 128.7, 128.6, 128.5, 128.2, 127.1, 126.5, 126.2, 124.4, 123.7, 91.5, 43.1 HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{15}NO_2Br$ (M^- − H) 392.0286, found 392.0293.

2-Benzyl-6-chloro-3-hydroxy-3-phenylisoindolin-1-one (3ka)

Yield: 67% (235 mg); pale yellow solid. Mp: 202.0–204.4 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.45–7.42 (m, 1H), 7.31–7.28 (m, 5H), 7.26–7.15 (m, 6H), 4.72 (d, J = 16.0 Hz, 1H), 4.12 (d, J = 16.0 Hz, 1H), 3.26 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 147.1, 137.7, 137.6, 135.8, 132.9, 132.0, 128.7, 128.6, 128.5, 128.3, 127.2, 126.2, 124.1, 123.5, 91.4, 43.2; HRMS (ESI+) *m*/*z* calcd for $C_{21}H_{17}NO_2Cl$ (M + H) 350.0948, found 350.0942.

2-Benzyl-6-fluoro-3-hydroxy-3-phenylisoindolin-1-one (3la)

Yield: 78% (260 mg); pale yellow solid. Mp: 165.7–167.8 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.33–7.28 (m, 5H), 7.24–7.14 (m, 7H), 4.77 (d, J = 16.0 Hz, 1H), 4.09 (d, J = 16.0 Hz, 1H), 2.97 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 163.6 (d, J_{C-F} = 248.3 Hz), 144.5, 137.8 (d, J_{C-F} = 4.4 Hz), 132.6 (d, J_{C-F} = 8.6 Hz), 128.7, 128.6, 128.5, 128.3, 127.2, 126.2, 124.5 (d, J_{C-F} = 8.6 Hz), 120.1 (d, J_{C-F} = 23.6 Hz), 110.3 (d, J_{C-F} = 23.6 Hz), 91.4, 43.2; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{17}NO_2F$ (M + H) 334.1243, found 334.1240.

3-Hydroxy-6-methoxy-2-methyl-3-phenylisoindolin-1-one (3ma)

Yield: 45% (131 mg); pale yellow solid. Mp: 192.2–194.2 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 7.20–7.18 (m, 1H), 6.99–6.96 (m, 2H), 3.94 (s, 1H), 3.79 (s, 3H), 2.76 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.6, 160.8, 141.1, 138.2, 131.8, 128.6, 128.4, 125.9, 123.6, 120.0, 106.2, 90.8, 55.6, 55.5, 24.1; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}NO_3Na$ (M + Na) 292.0.0950, found 292.0.0952.

2-Benzyl-3-hydroxy-5,6-dimethoxy-3-phenylisoindolin-1-one (3na)

Yield: 55% (206 mg); white solid. Mp: 205.3–207.2 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31–7.29 (m, 2H), 7.26–7.24 (m, 3H), 7.20–7.12 (m, 6H), 6.67 (s, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.13 (d, J = 16.0 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.38 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.0, 153.2, 150.5, 142.6, 138.4, 138.2, 128.5, 128.4, 128.3, 128.1, 126.9, 126.3, 122.6, 105.0, 104.8, 91.2, 56.3, 56.2, 43.0; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{20}NO_4$ (M^- − H) 374.1392, found 374.1390.

7-Hydroxy-6-methyl-7-phenyl-6,7-dihydro-5*H*-[1,3]dioxolo[4,5-*f*]isoindol-5-one (3oa)

Yield: 62% (176 mg); pale yellow solid. Mp: 226.4–227.9 °C (EA/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 5H), 6.88 (s, 1H), 6.71 (s, 1H), 6.03 (s, 1H), 5.98 (s, 1H), 4.09 (brs, 1H), 2.73 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.6, 151.8, 148.9, 144.8, 138.1, 128.6, 128.4, 125.9, 124.1, 103.3, 10.6, 102.1, 90.4, 24.1.

2-Benzyl-3-(2-bromophenyl)-3-hydroxyisoindolin-1-one (3an)

Yield: 70% (276 mg); white solid. Mp: 185.0–187.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 7.98, 1.46 Hz, 1H), 7.77–7.75 (m, 1H), 7.50–7.44 (m, 3H), 7.29–7.27 (d, J = 7.36 Hz, 1H), 7.17–7.12 (m, 7H), 4.54 (d, J = 14.9 Hz, 1H), 4.14 (d, J = 14.9 Hz, 1H), 3.44 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.9, 147.3, 136.9, 135.7, 134.8, 132.6, 132.4, 130.4, 130.3, 129.6, 129.1, 127.9, 127.3, 127.0, 123.4, 122.3, 121.6, 90.5, 43.0; HRMS (ESI-neg) *m*/*z* calcd for $C_{21}H_{15}NO_2Br$ (M − H) 392.0286, found 392.0278.

2-Phenyl-3-(2-bromophenyl)-3-hydroxyisoindolin-1-one (3en)

Yield: 71% (270 mg); white solid. Mp: 247.3–249.5 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.98, 1.46 Hz, 1H), 7.84–7.82 (m, 1H), 7.79 (brs, 1H), 7.62–7.59 (m, 2H), 7.56–7.54 (m, 2H), 7.45–7.40 (m, 2H), 7.27–7.23 (m, 2H), 7.22–7.17 (m, 1H), 7.15–7.09 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.2, 147.3, 136.9, 136.4, 134.5, 133.0, 132.4, 130.7, 130.5, 129.6, 128.2, 127.6, 125.7, 124.6, 122.9, 120.0, 91.2; HRMS (TOF-MS-ES-TOF) *m*/*z* calcd for $C_{20}H_{15}NO_2Br$ (M^- + H) 380.0286, found 380.0287.

3-(2-Bromophenyl)-3-hydroxy-2-phenethylisoindolin-1-one (3fn)

Yield: 67% (273 mg); white solid. Mp: 186–188 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.49–7.40 (m, 3H), 7.39 (t, J = 5.0 Hz, 1H), 7.25–7.21 (m, 3H), 7.03–7.02 (m, 2H), 3.63 (s, 1H), 3.62–3.53 (m, 1H), 3.13–3.00 (m, 2H), 2.58–2.30 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.9, 147.2, 139.3, 135.8, 134.9, 132.6, 132.5, 130.6, 130.4, 129.6, 128.7, 128.4, 127.5, 126.2, 123.1, 122.3, 121.2, 90.3, 41.4, 34.2; HRMS (TOF-MS-ES+) *m*/*z* calcd for $C_{22}H_{19}NO_2Br$ (M + H) 408.0599, found 408.0599.

2-Benzyl-6-bromo-3-(2-bromophenyl)-3-hydroxyisoindolin-1-one (3kn)

Yield: 71% (335 mg); white solid. Mp: 214.0–216 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 8.0, 1.4 Hz, 1H), 7.68 (d, J = 1.4 Hz, 1H), 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.50–7.42 (m, 1H), 7.21–7.19 (m, 1H), 7.14–7.00 (m, 7H), 4.54 (d, J = 16.0 Hz, 1H), 4.14 (d, J = 16.0 Hz, 1H), 4.28 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.8, 146.1, 136.3, 135.7, 134.9, 134.7, 134.2, 130.5, 130.4, 129.1, 127.9, 127.4, 127.1, 126.3, 123.9, 123.7, 121.5, 90.2, 43.1; HRMS (TOF-MS-ES+) *m*/*z* calcd for $C_{21}H_{16}NO_2Br_2$ (M + H) 471.9548, found 471.9548.

3-(2-Bromophenyl)-5-fluoro-3-hydroxy-2-phenylisoindolin-1-one (3ln)

Yield: 78% (335 mg); white solid. Mp: 254.0–256.0 °C. ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 7.94 (brs, 1H), 7.89–7.87 (m, 1H), 7.52–7.50 (m, 2H), 7.45–7.40 (m, 3H), 7.28–7.23 (m, 3H), 7.12 (t, J = 8.0 Hz, 1H), 7.00 ((dd, J = 8.0, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 166.1, 164.0 (d, J_{C-F} = 249.0 Hz), 150.1 (d, J_{C-F} = 9.0 Hz), 136.3, 136.1, 134.5, 130.7 (d, J_{C-F} = 9.0 Hz), 128.7, 128.3, 127.6, 125.9, 125.5 (d, J_{C-F} = 9.0 Hz), 124.7, 120.0, 117.2 (d, J_{C-F} = 24 Hz), 109.7 (d, J_{C-F} = 24 Hz), 90.5 (d, J_{C-F} = 2 Hz); HRMS (TOF-MS-ES+) m/z calcd for $C_{20}H_{14}NO_2BrF$ (M^- − H) 398.0192, found 398.0194.

3-(2-Bromophenyl)-5-chloro-3-hydroxy-2-phenylisoindolin-1-one (3mn)

Yield: 80% (332 mg); white solid. Mp: 262–264 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.23 (dd, J = 8.0, 2.0 Hz, 1H), 7.96 (brs, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.0, 2.0 Hz, 1H), 7.52–7.50 (m, 2H), 7.45–7.42 (m, 2H), 7.27–7.19 (m, 4H), 7.15–7.09 (m, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 166.1, 149.2, 137.7, 136.2, 134.6, 131.2, 130.8, 130.7, 130.0, 128.3, 127.7, 126.0, 124.8, 124.7, 122.4, 120.0, 90.7; HRMS (TOF-MS-ES+) m/z calcd for $C_{20}H_{14}NO_2ClBr$ (M^- + H) 413.9896, found 413.9897.

2-Benzyl-3-(2-bromophenyl)-3-hydroxy-6-methoxyisoindolin-1-one (3nn)

Yield: 58% (246 mg); white solid. Mp: 192.0–194.0 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.36 (dd, J = 8.0, 1.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.29–7.27 (m, 1H), 7.18–7.16 (m, 7H), 7.02–7.01 (m, 1H), 7.00–6.98 (m, 1H), 4.58 (d, J = 14.9 Hz, 1H), 4.26 (d, J = 14.9 Hz, 1H), 3.84 (s, 3H), 3.44 (s, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 168.7, 161.1, 139.4, 137.0, 135.7, 134.8, 134.2, 130.4, 130.2, 129.1, 127.9, 127.3, 127.0, 123.2, 121.5, 119.8, 106.8, 90.5, 55.6, 43.2; HRMS (TOF-MS-ES+) m/z calcd for $C_{22}H_{19}NO_3Br$ (M + H) 424.0548, found 424.05449.

6-Benzyl-7-(2-bromophenyl)-7-hydroxy-6,7-dihydro-5*H*-[1,3]dioxolo[4,5-*f*]isoindol-5-one (3pn)

Yield: 60% (263 mg); white solid. Mp: 209–211 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.32 (dd, J = 8.0, 4.0 Hz, 1H), 7.44–7.40 (m, 1H), 7.29 (dd, J = 8.0, 1.6 Hz, 1H), 7.13–7.05 (m, 6H), 6.99 (s, 1H), 6.55 (s, 1H), 5.99 (t, J = 1.4 Hz, 2H), 4.44 (d, J = 16 Hz, 1H), 4.14 (d, J = 16 Hz, 1H), 4.06 (s, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 168.6, 151.8, 149.1, 143.0, 139.9, 135.6, 134.8, 134, 136.9, 135.7, 134.8, 130.4, 130.2, 129.1, 127.9, 127.3, 126.9, 126.6, 121.5, 103.2, 103.0, 102.1, 89.7, 43.1; HRMS (TOF-MS-ES+) m/z calcd for $C_{22}H_{17}NO_4Br$ (M + H) 438.0341, found 438.0339.

2-Benzyl-3-(2-bromo-5-methoxyphenyl)-3-hydroxyisoindolin-1-one (3ao)

Yield: 50% (212 mg); white solid. Mp: 194.0–196.0 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.96 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.47–7.39 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.13–7.10 (m, 6H), 6.69 (dd, J = 8.0, 4.0 Hz, 1H), 4.49 (d, J = 16.0 Hz, 1H), 4.14 (d, J = 16.0 Hz, 1H), 4.01 (brs, 1H) 3.90 (s, 3H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 168.9, 158.9, 147.2, 136.9, 136.7, 135.4, 132.6, 132.4, 129.6, 129.1, 127.9, 127.0, 123.3, 122.3, 116.4, 115.8, 111.7, 90.3, 55.6, 43.0; HRMS (TOF-MS-ES+) m/z calcd for $C_{22}H_{19}NO_3Br$ (M + H) 424.0548, found 424.0550.

2-Benzyl-3-(2-bromo-4,5-dimethoxyphenyl)-3-hydroxyisoindolin-1-one (3ap)

Yield: 40% (181 mg); white solid. Mp: 202.3–203.7 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.61–7.59 (d, J = 7.40 Hz, 1H), 7.48–7.45 (t, J = 7.44 Hz, 1H), 7.40–7.37 (t, J = 7.34 Hz, 1H), 7.20–7.18 (d, J = 7.44 Hz, 1H), 7.10–7.06 (m, 5H), 6.65 (s, 1H), 4.43 (d, J = 14.8 Hz, 1H), 4.17 (d, J = 14.8 Hz, 1H), 4.30 (s, 1H), 4.02 (s, 3H), 3.78 (s, 3H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 169.1, 149.7, 148.2, 147.8, 137.1, 132.8, 132.5, 129.7, 129.3, 128.0, 127.8, 127.1, 123.5, 122.5, 117.6, 113.4, 112.2, 90.5, 56.5, 56.3, 43.1; HRMS (ESI-neg) m/z calcd for $C_{23}H_{19}NO_4Br$ (M^- − H) 452.0497, found 452.0491.

2-Benzyl-3-(6-bromobenzo[*d*][1,3] dioxol-5-yl)-3-hydroxyisoindolin-1-one (3aq)

Yield: 45% (197 mg); white solid. Mp: 214–216.0 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.70 (d, J = 4.0 Hz, 1H), 7.50–7.44 (m, 2H), 7.18–7.13 (m, 6H), 6.70 (s, 1H), 6.04 (dd, J = 8.0, 1.6 Hz, 1H), 4.54 (d, J = 16.0 Hz, 1H), 4.14 (d, J = 16 Hz, 1H), 3.61 (s, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 168.7, 148.5, 147.5, 147.3, 137.1, 132.6, 132.3, 129.6, 129.0, 128.0, 127.1, 123.3, 122.1, 114.5, 112.6, 110.4, 102.0, 90.4, 43.0; HRMS (TOF-MS-ES+) m/z calcd for $C_{22}H_{17}NO_4Br$ (M + H) 438.0341, found 438.0346.

2-Benzyl-3-(2,5-dibromophenyl)-3-hydroxyisoindolin-1-one (3ar)

Yield: 64% (301 mg); white solid. Mp: 213–215 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.52 (d, J = 4.0 Hz, 1H), 7.66 (dd, J = 8.0, 1.2 Hz, 1H), 7.48–7.43 (m, 2H), 7.22 (dd, J = 8.0, 1.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.10–7.05 (m, 5H), 7.00 (d, J = 4.0 Hz, 1H), 4.35 (d, J = 16.0 Hz, 1H), 4.26 (brs, 1H); 4.25 (d, J = 16.0 Hz, 1H), ^{13}C-NMR (100 MHz, CDCl$_3$) δ 168.9, 146.7, 137.7, 136.4, 136.0, 133.4, 133.1, 132.8, 132.3, 129.9, 129.1, 127.9, 127.1, 123.4, 122.3, 121.4, 120.2, 89.8, 42.9; HRMS (TOF-MS-ES+) m/z calcd for $C_{21}H_{16}NO_2Br_2$ (M + H) 471.9548, found 471.9550.

Conflicts of interest

There are no conflicts to declare.

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