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Catalyst-Free Synthesis of 3-(2-Quinolinemethylene)-Substituted Isoindolinones in Water

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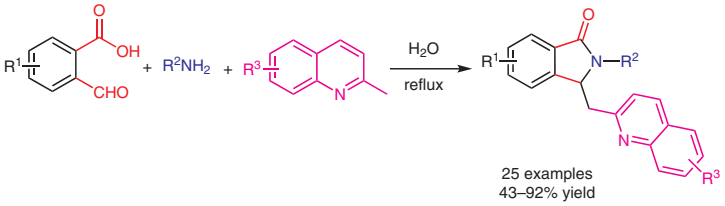

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Abstract A facile and environmentally benign approach toward the synthesis of novel 3-alkyl-substituted isoindolinones by three-component reactions of 2-formylbenzoic acids, primary amines and 2-methylazaarenes in water under catalyst- and additive-free conditions is described. This protocol features the direct construction of multiple C–N and C–C bonds via a tandem Mannich-type reaction and intramolecular cyclization in a one-pot fashion, affording the desired 3-(2-quinolinemethylene)-substituted isoindolinones in high to excellent yields.

Key words multicomponent reactions, isoindolines, catalyst-free, Mannich-type reaction, cyclization

3-Substituted isoindolinones and their derivatives are ubiquitous in a number of naturally occurring compounds and biologically active drug molecules such as glycine transporter 1 (GlyT1) inhibitors,[1] lennoxamine,[2] pagoclone[3] and (S)-PD 172938[4] (Figure 1). These compounds with an isoindolinone scaffold have been shown to possess a broad range of pharmacological properties such as antihypertensive,[5] antipsychotic,[6] anti-inflammatory,[7] anesthetic,[8] antiulcer,[4,9] vasodilatory,[10] antiviral,[11] and antileukemic[12] activities. Due to their wide spectrum of biological activity, several synthetic routes for the preparation of these compounds have been established over the past three decades. Traditional methods for the synthesis of isoindolinones include the Diels–Alder approach,[13] Heck cyclization,[14] Wittig reaction,[15] monoreduction of phthalimides,[15c,16] transition-metal-catalyzed[17] and Lewis acid catalyzed[18] approaches and radical cyclization.[19] However, these methods are generally associated with several drawbacks such as multistep procedures, operational complexity and the use of noble transition-metal catalysts, large amounts of reducing agents or toxic and inflammable solvents. Therefore, the development of simple, efficient and environmentally friendly protocols for the synthesis of isoindolinones is still a significant challenge and highly desirable.

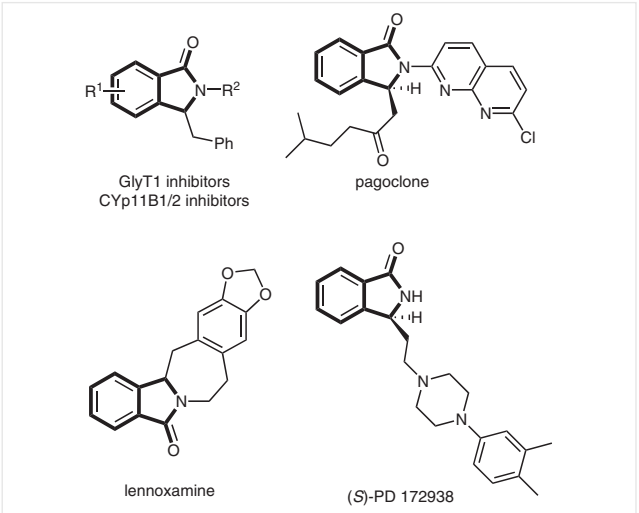
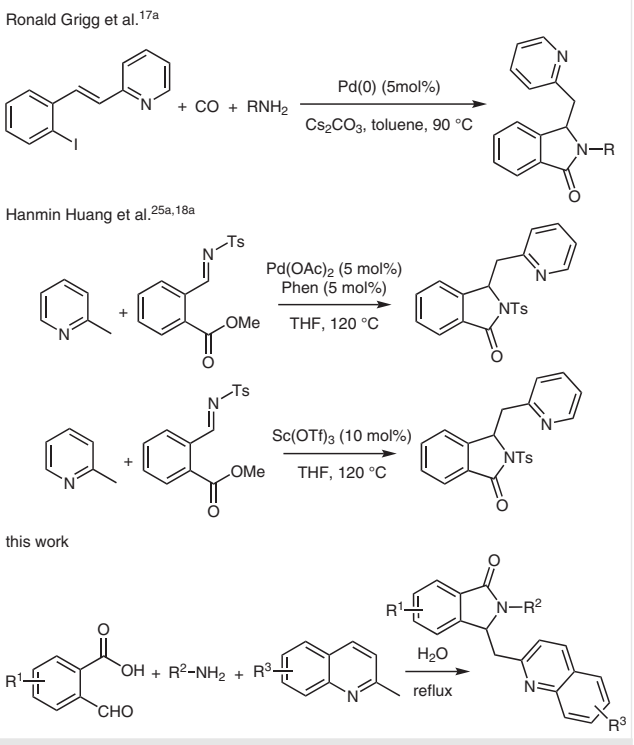


Figure 1 Biologically active N-substituted isoindolinones

Recently, catalyst-free methods for the synthesis of 3-substituted isoindolinones through the cyclization reaction of 2-formylbenzoic acid and primary amines with nucleophiles such as indoles,[20a] 4-hydroxycoumarin,[20b] trialkyl phosphates,[20c] pyrazolone[20d] and 1,3-diones[20e–g] have attracted much attention. In these developed approaches, the acidic proton of 2-formylbenzoic acid plays an important role in promoting the reaction process for it generally facilitates the protonation of the formed imine in the reaction. However, most of the above-mentioned catalyst-free protocols were confined to the synthesis of 3-heteroaryl-substituted isoindolinones, and methods for the efficient syntheses of 3-alkyl-substituted isoindolinones remain scarce.

Quinolines and their derivatives are valuable compounds in both medicinal and agricultural chemistry, and are widely found in biologically important natural products.[21] The direct benzylic C–H bond functionalization of azaarenes[22] such as 2-methylpyridine and 2-methylquinoline with various electrophiles possessing C=O,[23] C=C,[24] C=N,[25] and N=N[26] bonds has been realized by catalysis with Lewis/Brønsted acids or transition metals. Grigg[17a] reported that the palladium-catalyzed carbonylation–amination–Michael addition reaction of 1-iodo-2-alkenylbenzene with amines afforded various isoindolinones in good yields (Scheme 1, a). In 2010, Huang et al. developed a palladium-catalyzed benzylic addition of 2-methylazaarenes to *N*-sulfonyl aldimines in THF, which could be used to access 3-(2-pyridinemethylene)-substituted isoindolinones.[25a] In the same year, a Lewis acid approach involving the $Sc(OTf)_3$-catalyzed C–H functionalization of 2-methylazaarenes for the synthesis of 3-(2-pyridinemethylene)-substituted isoindolinones was also reported by Huang (Scheme 1, b).[18a] However, these two methods require pre-synthesized imines as substrates, which somewhat limit their application.



Scheme 1 Background to the research and the method described in this work

In 2014, Xiao's group reported a benzylic C–H bond nucleophilic addition between azaarenes and coumarin-3-carboxylic acids.[24d,e] It was found that the introduction of a carboxylic group to the substrate activated 2-alkylazaarenes as a Brønsted acid and accelerated the reaction without an additional catalyst, a process which was called 'self-activation' and promoted the transformation in a more efficient way. To the best of our knowledge, the $C(sp^3)$–H bond functionalization of azaarenes with in situ generated iminium compounds for synthesis of 3-substituted isoindolinones with azaarene motifs in the absence of a catalyst in aqueous medium has not been realized. As part of our continuous endeavors on the development of environmentally friendly methods for the synthesis of value-added entities from multicomponent reactions, we report herein an unprecedented synthesis of 3-(2-quinolinemethylene)-substituted isoindolinones derivatives using water as the reaction medium under catalyst-free conditions (Scheme 1, c).

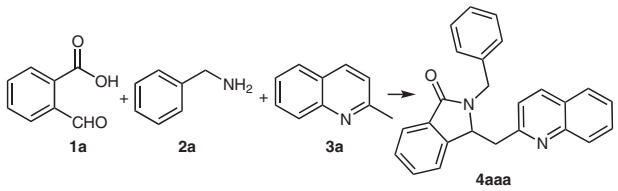
To test the possibility of the above hypothesis, phthalaldehydic acid (**1a**) (1.2 mmol), benzylamine (**2a**) (1 mmol), and 2-methylquinoline (**3a**) (1 mmol) were selected as substrates in a model reaction to prepare the desired 3-(2-quinolinemethylene)-substituted isoindolinone **4aaa**. To our delight, when the reaction was carried out without any catalyst under solvent-free conditions at 110 °C, the desired product **4aaa** was smoothly isolated in 50% yield (Table 1, entry 1). Encouraged by this result, we further evaluated the influence of different reaction parameters on the model reaction.

As shown in Table 1, common organic solvents, such as DMF, toluene, 1,4-dioxane, THF, EtOH, DMSO and MeCN were applied to promote the model reaction. Unfortunately, lower isolated yields of **4aaa** were obtained when the reaction was performed in these solvents (Table 1, entries 2–8). In recent decades, the use of water as a reaction medium instead of hazardous organic solvents to promote organic transformations has attracted much attention, because water is a readily available, cheap, safe and environmentally benign solvent. Therefore, the model reaction was next performed in water at reflux under catalyst-free conditions. Surprisingly, the reaction was complete in a shorter time of 12 hours and produced the desired compound **4aaa** in a greatly improved yield of 92% (Table 1, entry 9). Thus it was clear that water was the best reaction solvent for the current transformation.

The evaluation of the reaction temperature was next carried out. When the reaction temperature was slightly lowered to 80 °C, compound **4aaa** was isolated in a sharply decreased yield of 60%, even on lengthening the reaction time to 24 hours (Table 1, entry 10). Therefore, heating at reflux temperature was the best choice for the protocol in water.

When the amount of benzylamine (**2a**) was increased to 2 equivalents, the yield of product **4aaa** decreased sharply to 50% (Table 1, entry 11), which demonstrated that an excess of acid was essential to the formation of the isoindolinone. Furthermore, the effect of additional acids was examined. When 10 mol% of additional acids such as AcOH, PTSA and L-proline were added to the reaction system, the corre-

Table 1 Optimization of the Reaction Conditions[a]



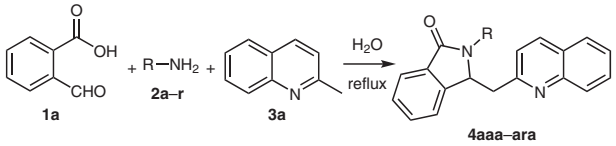
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	–	110	24	50
2	DMF	110	20	20
3	toluene	110	20	30
4	1,4-dioxane	reflux	20	20
5	THF	reflux	20	42
6	EtOH	reflux	20	40
7	DMSO	110	20	46
8	MeCN	reflux	20	40
9	H_2O	reflux	12	92
10	H_2O	80	24	60
11[c]	H_2O	reflux	18	50
12[d]	H_2O	reflux	18	62
13[e]	H_2O	reflux	18	51
14[f]	H_2O	reflux	18	48

[a] Reaction conditions: phthalaldehydic acid (**1a**) (1.2 mmol), benzylamine (**2a**) (1.0 mmol), 2-methylquinoline (**3a**) (1 mmol), solvent (3 mL).
[b] Yield of isolated product.
[c] Benzylamine (**2a**) (2 mmol) was used.
[d] L-proline (10 mol%) was used.
[e] PTSA (10 mol%) was used.
[f] AcOH (10 mol%) was used.

sponding isoindolinone **4aaa** was obtained in reduced yields of 62%, 51% and 48%, respectively (Table 1, entries 12–14). Therefore, the optimum reaction conditions are as follows: benzylamine (**2a**) (1 mmol), 2-methylquinoline (**3a**) (1 mmol) and 1.2 equivalents of phthalaldehydic acid (**1a**) in water at reflux for 12 hours (Table 1, entry 9).

With optimized reaction conditions in hand, we next investigated the scope of the amines **2a–r** in one-pot, three-component reactions with 2-methylquinoline (**3a**) and phthalaldehydic acid (**1a**). As shown in Table 2, various primary amines including aryl-alkylamines, heteroaryl-alkylamines, arylamines and alkylamines were selected to undergo the transformation under catalyst-free conditions in water. Aryl-alkylamines bearing both electron-withdrawing groups (Table 2, entries 2–5) and electron-donating groups (Table 2, entries 6–8) on the phenyl ring all smoothly provided the corresponding products **4aba–aja** in good to excellent yields (80–92%). It was noteworthy that aryl-alkylamines with halo substituents on the phenyl ring were well tolerated under the conditions of this protocol (Table 2, entries 2–5), which should permit further derivatization by means of simple coupling strategies and the like. Sterically demanding aryl-alkylamines also served as very good candidates in this transformation. The steric effects seemed to have no obvious influence on the formation of the desired isoindolinones, which were obtained in high yields (Table 2, entries 4 and 8). A heteroaryl-alkylamine, furfurylamine, also successfully afforded the corresponding isoindolinone **4aia** in 82% yield. Phenyl-ethylamine and phenyl-propylamine showed similar reactivities to that of benzylamine and produced the corresponding products in excellent yields (Table 2, entries 10 and 11). Alkylamines such as *n*-$BuNH_2$, 1-octylamine, 1-dodecylamine and *n*-$PrNH_2$ showed excellent reactivity in this one-pot, three-component reaction, producing the corresponding products **4ala–aoa** in good yields (Table 2, entries 12–15).

Table 2 Scope of the Amines[a]



Entry	R	Product	Yield (%)[b]
1	$C_6H_5CH_2$	**4aaa**	92
2	4-$ClC_6H_4CH_2$	**4aba**	83
3	4-$FC_6H_4CH_2$	**4aca**	86
4	2-$ClC_6H_4CH_2$	**4ada**	80
5	3,4-$Cl_2C_6H_3CH_2$	**4aea**	88
6	4-$MeC_6H_4CH_2$	**4afa**	89
7	4-$MeOC_6H_4CH_2$	**4aga**	88
8	2,4-$(MeO)_2C_6H_3CH_2$	**4aha**	83
9	furfuryl	**4aia**	82
10	2-phenylethyl	**4aja**	92
11	4-phenylbutyl	**4aka**	90
12	1-butyl	**4ala**	83
13	1-octyl	**4ama**	86
14	1-dodecyl	**4ana**	84
15	*n*-Pr	**4aoa**	60
16	*t*-Bu	–	0
17[c]	H	–	0
18	C_6H_5	**4apa**	40
19	4-ClC_6H_4	**4aqa**	30
20	4-MeC_6H_4	**4ara**	70

[a] Reaction conditions: **1a** (1.2 mmol, 1.2 equiv), **2a–r** (1.0 mmol), **3a** (1 mmol), H_2O (3 mL), reflux, 12 h.
[b] Yield of isolated product.
[c] Ammonium hydroxide (28%, 4 mL) was used as the ammonia gas precursor and the reaction was carried out at 80 °C.

However, sterically hindered *tert*-butylamine was completely ineffective in this transformation and no desired product was obtained (Table 2, entry 16). Furthermore, when ammonium hydroxide was used as the ammonia gas precursor to undergo the transformation, unfortunately, no desired product was formed (Table 2, entry 17).

For the aromatic amines, decreased yields of isoindolinones were observed (Table 2, entries 18–20), which was mainly caused by the weak nucleophilicity of the arylamine. The structure of compound **4ara** was confirmed unambiguously by single-crystal X-ray analysis (Figure 2).

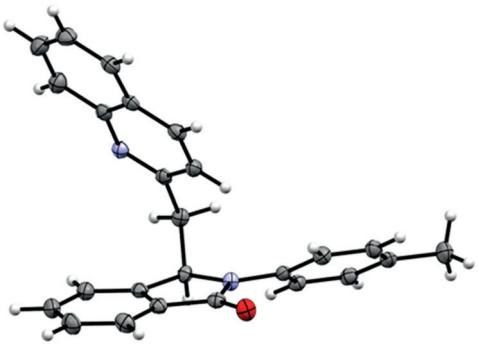
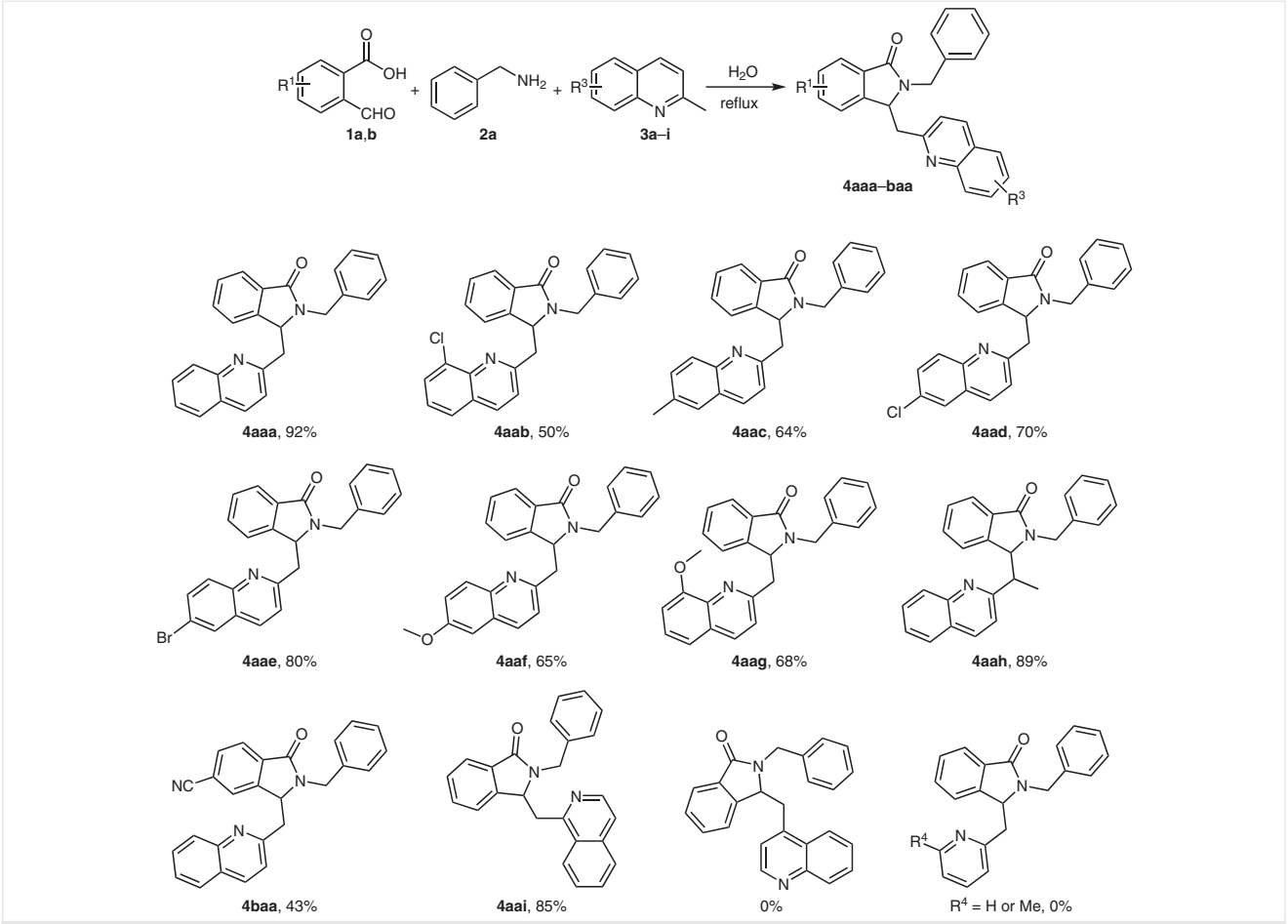


Figure 2 X-ray crystal structure of compound **4ara** (CCDC 1546209)

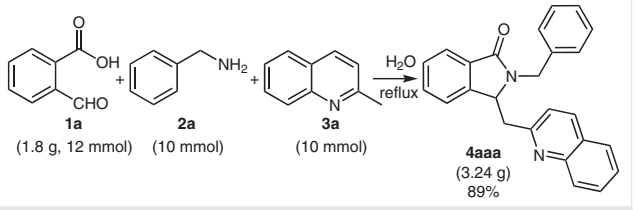
To further investigate the generality of this one-pot, three-component reaction, various substituted 2-methylquinolines were selected and the results are shown in Scheme 2. 2-Methylquinolines with different substituents such as 8-chloro, 8-methoxy, 6-methyl, 6-chloro, 6-bromo and 6-methoxy all smoothly afforded the corresponding products in moderate to good yields. Additionally, 2-ethylquinoline and 1-methylisoquinoline were examined and successfully gave the corresponding products **4aah** and **4aai** in 89% and 85% yields, respectively. When 4-cyanophthalaldehydic acid (**1b**) was utilized to evaluate the potential of this protocol, the desired isoindolinone **4baa** was successfully obtained in 43% yield. However, when 4-methylquinoline, 2-methylpyridine and 2,6-lutidine were used in-



Scheme 2 Scope of the phthalaldehydic acids and azaarenes. *Reagents and conditions*: **1a,b** (1.2 mmol), **2a** (1 mmol), **3a–i** (1 mmol), H_2O (3 mL), reflux, 12 h. Yields are those of isolated products.

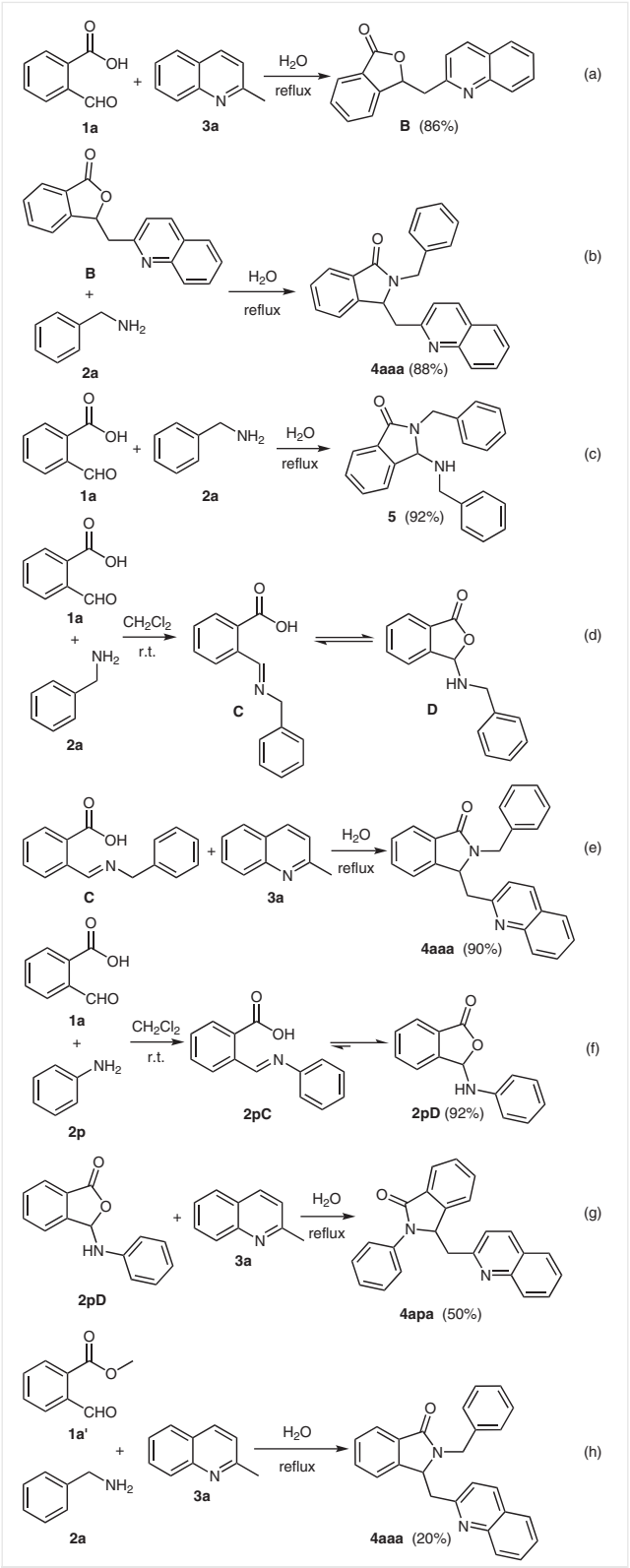
stead of 2-methylquinoline, no desired product was detected, with the reason possibly being due to the electronic effect of the methyl group on the pyridyl ring.[25e]

To further demonstrate the potential utility of this protocol, a gram-scale synthesis of 2-benzyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (**4aaa**) was next carried out (Scheme 3). When a mixture of phthalaldehydic acid (**1a**) (1.8 g, 12 mmol), benzylamine (**2a**) (10 mmol) and 2-methylquinoline (**3a**) (10 mmol) was selected to perform the isoindolinone synthesis in water without any catalyst, an 89% yield of 2-benzyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (**4aaa**) was obtained. No obvious decrease of the reaction efficiency was observed. This is very meaningful for potential large-scale applications of this methodology.



Scheme 3 Gram-scale synthesis of **4aaa**

To provide insight into the reaction mechanism, several control experiments were conducted (Scheme 4). When phthalaldehydic acid (**1a**) and 2-methylquinoline (**3a**) were subjected to the optimized reaction conditions for 6 hours, product **B** was isolated in 86% yield (Scheme 4, eq. a). When a mixture of compound **B** and benzylamine (**2a**) was subjected to the optimized reaction conditions for 5 hours, product **4aaa** was generated in 88% yield (Scheme 4, eq. b). The intermediate **5** was isolated in 92% yield from the reaction mixture of **1a** and **2a** under the optimized conditions after 8 hours (Scheme 4, eq. c). These results validated that the imine **C** might be formed as the key intermediate of this conversion. To prove this hypothesis, phthalaldehydic acid (**1a**) and benzylamine (**2a**) were mixed in CH_2Cl_2 at room temperature for 12 hours until the imine **C**[27] was completely formed (Scheme 4, eq. d), which was monitored by TLC analysis. Next, the reaction mixture was concentrated under reduced pressure, after which 2-methylquinoline (**3a**) was added to the residue to perform the transformation under the optimized conditions and smoothly afford product **4aaa** in 90% yield (Scheme 4, eq. e). Unfortunately, we failed to isolate the imine **C**, which might be caused by an equilibrium between the imine **C** and 3-(benzylamino)isobenzofuran-1(3*H*)-one (**D**).[27a,b] However, when benzylamine (**2a**) was changed to phenylamine (**2p**) to perform the same procedure, we successfully isolated 3-(phenylamino)isobenzofuran-1(3*H*)-one (**2pD**) in 92% yield, the special stability of which can be explained by the *p*-π conjugation effect (Scheme 4, eq. f).[27c] Compound **2pD** was next utilized to react with 2-methylquinoline (**3a**) under the standard reaction conditions, with the product **4apa** being smoothly ob-



Scheme 4 Control experiments

tained in 50% yield (Scheme 4, eq. g). However, product **4aaa** was obtained in only 20% yield when methyl 2-formylbenzoate (**1a′**) was tested with benzylamine (**2a**) and 2-methylquinoline (**3a**) under the optimized conditions (Scheme 4, eq. h). This suggested that phthalaldehydic acid, as a Brønsted acid, played a key role in the functionalization of the methyl group of 2-methylquinoline (**3a**).

On the basis of the experiments described above and previous reports,[20a,g,23k,24d,28a] a plausible reaction mechanism concerning two possible reaction pathways for the formation of 2-benzyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (**4aaa**) is depicted in Scheme 5. In path a, 2-methylquinoline (**3a**) firstly isomerized into the enamine intermediate **3a′** with the aid of acid.[28b] The intermediate **3a′** then nucleophilically attacks phthalaldehydic acid (**1a**), producing compound **A**, which was further dehydrated to give intermediate **B**. The intermediate **B** next reacts with benzylamine (**2a**) to provide the final product **4aaa**. In path b, the nucleophilic addition of benzylamine (**2a**) on phthalaldehydic acid (**1a**) first generates imine **C**, which may partly isomerize into intermediate **D**. The reaction of the imine **C** and intermediate **3a′** affords the Mannich product **E**, which is subsequently dehydrated to produce the desired product **4aaa**.

In conclusion, we have developed a highly efficient and environmentally friendly method for the preparation of 3-alkyl-substituted isoindolinones in water under catalyst-free conditions. The developed protocol provides a straightforward synthetic method for the construction of 3-subsituted isoindolinones in good to excellent yields without using precious transition-metal catalysts. Importantly, this reaction could be readily scaled up to gram scale and no obviously decreased yield was observed, which is very meaningful for future applications. Further studies to extend this method to the synthesis of other isoindolinone derivatives are in progress in our laboratory.

Reagents and solvents were obtained commercially and were used without further purification. All the reactions were carried out under air. Products were purified by flash chromatography with Qingdao Make Silica Gel Dryer Co., Ltd. silica gel (300–400 mesh). Melting points were obtained using a BeijingTech X-5 instrument apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 M and Bruker 400 M spectrometers at ambient temperature with $CDCl_3$ as the solvent and TMS as the internal standard. High-resolution mass analyses were performed on a Bruker Esquire 6000 (ESI-ION Trap) mass spectrometer.

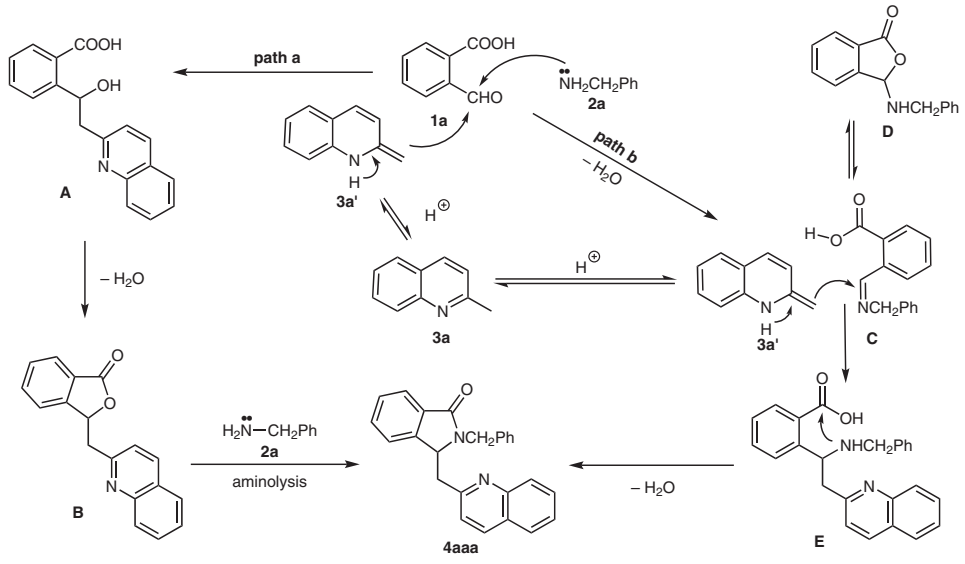
Substituted Isoindolinones; General Procedure

A mixture of phthalaldehydic acid (**1a**) or 4-cyanophthalaldehydic acid (**1b**) (1.2 mmol), amine **2** (1 mmol), and 2-methylquinoline **3a** (1 mmol) was stirred in H_2O (3 mL) at reflux temperature until the reaction was complete (TLC analysis). The mixture was allowed to cool to room temperature and a solution of saturated $NaHCO_3$ (5 mL) was added. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a residue that was purified by column chromatography (EtOAc/petroleum ether, 1:5 to 1:2).

2-Benzyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aaa)

Yellow oil; yield: 334.9 mg (92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.86–7.83 (m, 1 H), 7.76–7.65 (m, 2 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.25–7.12 (m, 5 H), 7.07–7.04 (m, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 5.26 (d, *J* = 15.3 Hz, 1 H), 5.20 (t, *J* = 6.2 Hz, 1 H), 4.40 (d, *J* = 15.3 Hz, 1 H), 3.54 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.31 (dd, *J* = 14.4, 6.9 Hz, 1 H).



Scheme 5 Proposed reaction mechanism

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.2, 147.8, 145.6, 137.3, 136.3, 132.0, 131.4, 129.7, 129.0, 128.6, 128.3, 127.9, 127.6, 127.4, 127.0, 126.4, 123.8, 122.8, 121.9, 58.8, 44.5, 41.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2O$: 365.1648; found: 365.1649.

2-(4-Chlorobenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aba)

Yellow oil; yield: 330.2 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (t, *J* = 9.0 Hz, 2 H), 7.86–7.83 (m, 1 H), 7.77–7.75 (m, 1 H), 7.71–7.68 (m, 1 H), 7.53–7.49 (m, 1 H), 7.42–7.40 (m, 2 H), 7.14–7.09 (m, 3 H), 7.00 (d, *J* = 8.2 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 5.25 (t, *J* = 6.2 Hz, 1 H), 5.14 (d, *J* = 15.4 Hz, 1 H), 4.35 (d, *J* = 15.4 Hz, 1 H), 3.46 (dd, *J* = 14.6, 5.8 Hz, 1 H), 3.33 (dd, *J* = 14.6, 6.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.0, 147.8, 145.5, 136.4, 135.8, 133.1, 131.7, 131.5, 129.8, 129.2, 128.9, 128.6, 128.3, 127.6, 126.9, 126.4, 123.8, 122.7, 121.9, 58.8, 44.0, 41.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}{}^{35}ClN_2O$: 399.1259; found: 399.1254.

2-(4-Fluorobenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aca)

Yellow oil; yield: 328.5 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (t, *J* = 8.8 Hz, 2 H), 7.86–7.84 (m, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.73–7.69 (m, 1 H), 7.54–7.50 (m, 1 H), 7.44–7.41 (m, 2 H), 7.12–7.05 (m, 3 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.90–6.85 (m, 2 H), 5.25 (t, *J* = 6.2 Hz, 1 H), 5.18 (d, *J* = 15.3 Hz, 1 H), 4.35 (d, *J* = 15.3 Hz, 1 H), 3.50 (dd, *J* = 14.5, 5.9 Hz, 1 H), 3.35 (dd, *J* = 14.5, 6.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5, 162.1 (d, *J* = 246.6 Hz), 157.1, 147.8, 145.5, 136.4, 133.1 (d, *J* = 3.2 Hz), 131.5, 129.7, 129.5 (d, *J* = 8.5 Hz), 128.9, 128.3, 127.6, 126.9, 126.4, 123.8, 122.7, 121.9, 115.3 (d, *J* = 21.6 Hz), 58.7, 43.8, 41.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}FN_2O$: 383.1554; found: 383.1548.

2-(2-Chlorobenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4ada)

Yellow oil; yield: 318.4 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (t, *J* = 8.6 Hz, 2 H), 7.86–7.84 (m, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.65 (t, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.41–7.39 (m, 2 H), 7.27–7.24 (m, 2 H), 7.16–7.14 (m, 2 H), 7.07–7.05 (m, 1 H), 6.91 (d, *J* = 8.7 Hz, 1 H), 5.31 (t, *J* = 6.2 Hz, 1 H), 5.20 (d, *J* = 16.2 Hz, 1 H), 4.74 (d, *J* = 16.2 Hz, 1 H), 3.59 (dd, *J* = 14.5, 5.3 Hz, 1 H), 3.33 (dd, *J* = 14.5, 7.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 156.8, 147.8, 145.5, 136.2, 134.7, 131.7, 131.5, 129.5, 129.4, 129.3, 129.0, 128.6, 128.2, 127.5, 127.0, 126.9, 126.3, 123.7, 122.9, 121.7, 59.1, 42.1, 41.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}{}^{35}ClN_2O$: 399.1259; found: 399.1262.

2-(3,4-Dichlorobenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aea)

Yellow oil; yield: 380.1 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 2 H), 7.86–7.83 (m, 1 H), 7.78–7.68 (m, 2 H), 7.53–7.49 (m, 1 H), 7.45 -7.42 (m, 2 H), 7.19–7.17 (m, 2 H), 7.03 (d, *J* = 2.0 Hz, 1 H), 6.94–6.89 (m, 2 H), 5.33 (t, *J* = 6.2 Hz,1 H), 5.03 (d, *J* = 15.6 Hz, 1 H), 4.33 (d, *J* = 15.6 Hz, 1 H), 3.38 (dd, *J* = 6.2, 3.0 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 156.9, 147.7, 145.6, 137.7, 136.5, 132.4, 131.7, 131.5, 131.2, 130.4, 129.9, 129.5, 128.8, 128.4, 127.7, 127.1, 126.9, 126.4, 123.8, 122.7, 121.8, 58.8, 43.7, 42.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{19}{}^{35}Cl_2N_2O$: 433.0869; found: 433.0869.

2-(4-Methylbenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4afa)

Yellow oil; yield: 336.4 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.85–7.83 (m, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.68–7.64 (m, 1 H), 7.48–7.45 (m, 1 H), 7.39–7.32 (m, 2 H), 7.07–7.00 (m, 5 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 5.26 (d, *J* = 15.2 Hz, 1 H), 5.18 (t, *J* = 6.0 Hz, 1 H), 4.36 (d, *J* = 15.2 Hz, 1 H), 3.54 (dd, *J* = 14.4, 5.3 Hz, 1 H), 3.28 (dd, *J* = 14.3, 7.1 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.4, 157.1, 147.8, 145.5, 137.0, 136.3, 134.2, 132.0, 131.3, 129.6, 129.2, 129.0, 128.2, 127.9, 127.6, 126.9, 126.3, 123.7, 122.8, 121.9, 58.6, 44.1, 41.5, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O$: 379.1805; found: 379.1806.

2-(4-Methoxybenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aga)

Yellow oil; yield: 346.7 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.84–7.82 (m, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.40–7.34 (m, 2 H), 7.09–7.03 (m, 3 H), 6.92 (d, *J* = 8.7 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 5.24–5.16 (m, 2 H), 4.32 (d, *J* = 15.0 Hz, 1 H), 3.72 (d, *J* = 2.1 Hz, 3 H), 3.55 (dd, *J* = 14.3, 5.4 Hz, 1 H), 3.31 (dd, *J* = 14.3, 7.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.4, 158.9, 157.2, 147.8, 145.5, 136.3, 131.3, 129.6, 129.4, 129.2, 129.0, 128.2, 127.6, 126.9, 126.3, 123.6, 122.8, 121.9, 113.9, 58.6, 55.2, 43.8, 41.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{22}N_2NaO_2$: 417.1573; found: 417.1571.

2-(2,4-Dimethoxybenzyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aha)

Yellow oil; yield: 351.9 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.80–7.77 (m, 1 H), 7.70 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.45–7.41 (m, 1 H), 7.33–7.24 (m, 2 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 6.94–6.92 (m, 2 H), 6.37–6.34 (m, 2 H), 5.23 (dd, *J* = 7.7, 4.8 Hz, 1 H), 5.10 (d, *J* = 15.2 Hz, 1 H), 4.53 (d, *J* = 15.2 Hz, 1 H), 3.72–3.68 (m, 4 H), 3.58 (s, 3 H), 3.21 (dd, *J* = 14.3, 7.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.4, 160.3, 158.1, 157.4, 147.7, 145.7, 136.0, 132.1, 131.0, 130.5, 129.4, 129.0, 127.9, 127.5, 126.8, 126.1, 123.4, 122.8, 121.9, 117.8, 104.3, 98.2, 58.9, 55.2, 55.1, 41.1, 38.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}N_2O_3$: 425.1860; found: 425.1850.

2-(Furan-2-ylmethyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aia)

Yellow oil; yield: 290.3 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.80–7.74 (m, 2 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.39–7.37 (m, 2 H), 7.30 (s, 1 H), 7.09–7.07 (m, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.28–6.27 (m, 1 H), 6.20 (d, *J* = 3.3 Hz, 1 H), 5.30–5.15 (m, 2 H), 4.51 (d, *J* = 16.0 Hz, 1 H), 3.67 (dd, *J* = 14.3, 4.9 Hz, 1 H), 3.38 (dd, *J* = 14.3, 7.3 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 157.0, 150.6, 147.8, 145.3, 142.3, 136.2, 131.9, 131.4, 129.6, 129.0, 128.2, 127.6, 126.9, 126.3, 123.7, 122.7, 121.8, 110.4, 108.3, 59.0, 41.2, 37.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_2$: 355.1441; found: 355.1429.

2-Phenethyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aja)

Yellow oil; yield: 347.8 mg (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.3 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.85–7.81 (m, 2 H), 7.77–7.73 (m, 1 H), 7.58–7.54 (m, 1 H), 7.43–7.38 (m, 2 H), 7.21–7.15 (m, 3 H), 7.08–7.03 (m, 4 H), 5.33 (t, *J* = 6.3 Hz, 1 H), 4.26–4.19 (m, 1 H), 3.49 (dd, *J* = 14.5, 5.8 Hz, 1 H), 3.45–3.22 (m, 2 H), 3.00–2.96 (m, 1 H), 2.92–2.85 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3, 157.4, 147.9, 145.5, 138.8, 136.5, 132.2, 131.2, 129.8, 129.0, 128.7, 128.4, 128.1, 127.7, 127.0, 126.4, 126.3, 123.5, 122.6, 122.0, 59.2, 42.5, 41.9, 34.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{22}N_2O$: 379.1805; found: 379.1805.

2-(4-Phenylbutyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aka)

Yellow oil; yield: 365.4 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.6 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 1 H), 7.85–7.81 (m, 2 H), 7.77–7.73 (m, 1 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.44–7.37 (m, 2 H), 7.28–7.24 (m, 2 H), 7.19–7.03 (m, 5 H), 5.40 (t, *J* = 6.4 Hz, 1 H), 4.08–4.00 (m, 1 H), 3.59–3.51 (m, 1 H), 3.27 (dd, *J* = 14.5, 7.3 Hz, 1 H), 3.21–3.14 (m, 1 H), 2.59–2.54 (m, 2 H), 1.74–1.50 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 157.4, 147.8, 145.4, 142.1, 136.4, 132.3, 131.1, 129.8, 129.0, 128.4, 128.3, 128.1, 127.7, 127.0, 126.4, 125.7, 123.5, 122.7, 122.1, 58.6, 41.8, 40.2, 35.4, 28.6, 27.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O$: 407.2118; found: 407.2121.

2-Butyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4ala)

White solid; yield: 273.9 mg (83%); mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.3 Hz, 1 H), 7.78–7.74 (m, 2 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.36–7.31 (m, 2 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.97–6.95 (m, 1 H), 5.39 (dd, *J* = 7.4, 5.6 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.58 (dd, *J* = 14.4, 5.5 Hz, 1 H), 3.22–3.08 (m, 2 H), 1.64–1.52 (m, 2 H), 1.27–1.15 (m, 2 H), 0.81 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 157.4, 147.8, 145.4, 136.4, 132.3, 131.0, 129.7, 128.9, 128.1, 127.6, 126.3, 123.4, 122.7, 122.1, 58.6, 41.7, 40.2, 30.3, 20.0, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O$: 331.1805; found: 331.1796.

2-Octyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4ama)

Yellow oil; yield: 332.1 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (t, *J* = 9.3 Hz, 2 H), 7.78–7.76 (m, 2 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.37–7.30 (m, 2 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 6.98 (d, *J* = 7.3 Hz, 1 H), 5.38 (t, *J* = 6.5 Hz, 1 H), 3.99–3.92 (m, 1 H), 3.56 (dd, *J* = 14.4, 5.7 Hz, 1 H), 3.21 (dd, *J* = 14.4, 7.3 Hz, 1 H), 3.12–3.05 (m, 1 H), 1.62–1.54 (m, 2 H), 1.24–1.15 (m, 10 H), 0.82 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 157.6, 147.8, 145.4, 136.6, 132.4, 131.1, 129.9, 129.0, 128.2, 127.8, 127.0, 126.5, 123.6, 122.8, 122.3, 58.8, 41.9, 40.6, 31.8, 29.3, 29.3, 28.4, 27.0, 22.7, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{31}N_2O$: 387.2431; found: 387.2413.

2-Dodecyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4ana)

Yellow oil; yield: 371.4 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.3, 4.3 Hz, 2 H), 7.82–7.79 (m, 2 H), 7.75–7.71 (m, 1 H), 7.56–7.52 (m, 1 H), 7.45–7.33 (m, 2 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 5.48–5.35 (m, 1 H), 4.06–3.87 (m, 1 H), 3.60 (dd, *J* = 14.4, 5.7 Hz, 1 H), 3.26 (q, *J* = 7.7 Hz, 1 H), 3.15–3.09 (m, 1 H), 1.29–1.14 (m, 20 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 147.8, 145.4, 136.4, 132.3, 131.0, 129.7, 128.9, 128.0, 127.6, 126.3, 123.4, 122.6, 122.1, 58.7, 41.7, 40.5, 31.8, 29.59, 29.55, 29.48, 29.44, 29.3, 29.2, 28.2, 26.8, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{39}N_2O$: 443.3057; found: 443.3059.

2-Propyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aoa)

Yellow oil; yield: 189.7 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (t, *J* = 8.8 Hz, 2 H), 7.81 (d, *J* = 7.2 Hz, 2 H), 7.75–7.70 (m, 1 H), 7.56–7.51 (m, 1 H), 7.41–7.33 (m, 2 H), 7.10–7.07 (m, 1 H), 6.96 (d, *J* = 7.4 Hz, 1 H), 5.42–5.38 (m, 1 H), 4.00–3.95 (m, 1 H), 3.67–3.56 (m, 1 H), 3.25–3.12 (m, 2 H), 1.79–1.56 (m, 2 H), 0.85 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3, 157.5, 148.0, 145.4, 136.6, 132.4, 131.1, 129.9, 129.0, 128.2, 127.8, 127.0, 126.5, 123.6, 122.8, 122.3, 58.7, 42.1, 41.8, 21.7, 11.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O$: 317.1648; found: 317.1635.

2-Phenyl-3-(quinolin-2-ylmethyl)isoindolin-1-one (4apa)

White solid; yield: 140.0 mg (40%); mp 157–159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.5 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H), 7.86–7.70 (m, 4 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.47–7.37 (m, 4 H), 7.19 (t, *J* = 7.4 Hz, 1 H), 7.03 (t, *J* = 8.6 Hz, 2 H), 6.13 (dd, *J* = 8.7, 4.3 Hz, 1 H), 3.68 (dd, *J* = 14.6, 4.3 Hz, 1 H), 3.11 (dd, *J* = 14.6, 8.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 157.6, 147.9, 145.1, 137.2, 136.3, 131.1, 131.9, 129.7, 129.2, 129.1, 128.5, 127.7, 127.0, 126.4, 125.4, 124.1, 123.6, 123.1, 122.4, 60.2, 41.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{19}N_2O$: 351.1492; found: 351.1488.

2-(4-Chlorophenyl)-3-(quinolin-2-ylmethyl)isoindolin-1-one (4aqa)

White solid; yield: 115.2 mg (30%), mp 160–162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.77–7.73 (m, 1 H), 7.67–7.63 (m, 2 H), 7.57–7.53 (m, 1 H), 7.47–7.40 (m, 2 H), 7.34–7.32 (m, 2 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 6.08 (dd, *J* = 8.5, 4.4 Hz, 1 H), 3.63 (d, *J* = 14.0 Hz, 1 H), 3.16–3.10 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 157.3, 147.9, 145.0, 136.4, 135.9, 132.1, 130.6, 129.9, 129.2, 129.1, 128.7, 127.7, 127.0, 126.5, 124.53, 124.52, 124.2, 123.1, 122.4, 60.2, 41.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{18}{}^{35}ClN_2O$: 385.1102; found: 385.1104.

3-(Quinolin-2-ylmethyl)-2-(*p*-tolyl)isoindolin-1-one (4ara)

White solid; yield: 254.8 mg (70%); mp 168–170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 9.6 Hz, 1 H), 7.98 (d, *J* = 8.3 Hz, 1 H), 7.89 (d, *J* = 9.0 Hz, 1 H), 7.79 (d, *J* = 8.9 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.58–7.51 (m, 3 H), 7.45–7.36 (m, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.02 (d, *J* = 9.3 Hz, 2 H), 6.05 (dd, *J* = 8.8, 4.3 Hz, 1 H), 3.67 (dd, *J* = 14.6, 4.3 Hz, 1 H), 3.08 (dd, *J* = 14.4, 8.8 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 157.6, 147.9, 145.1, 136.3, 135.3, 134.5, 132.2, 131.7, 129.8, 129.7, 129.1, 128.4, 127.7, 127.0, 126.4, 124.1, 123.7, 123.1, 122.4, 60.4, 41.8, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2O$: 365.1648; found: 365.1649.

2-Benzyl-3-[(8-chloroquinolin-2-yl)methyl]isoindolin-1-one (4aab)

Yellow oil; yield: 199.1 mg (50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.6 Hz, 1 H), 7.77 (t, *J* = 6.8 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.46–7.34 (m, 4 H), 7.28–7.25 (m, 1 H), 7.21–7.26 (m, 4 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 5.27–5.23 (m, 2 H), 4.59 (d, *J* = 15.2 Hz, 1 H), 3.56–3.44 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.7, 145.4, 143.9, 137.4, 136.7, 132.1, 131.6, 129.8, 128.7, 128.6, 128.4, 128.2, 128.1, 127.5, 126.8, 126.3, 123.8, 122.9, 122.7, 58.8, 44.7, 41.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}{}^{35}ClN_2O$: 399.1259; found: 399.1258.

2-Benzyl-3-[(6-methylquinolin-2-yl)methyl]isoindolin-1-one (4aac)

Yellow oil; yield: 241.9 mg (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.9 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 2 H), 7.51–7.48 (m, 2 H), 7.37–7.31 (m, 2 H), 7.21–7.11 (m, 5 H), 7.01 (d, *J* = 6.7 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 5.24 (d, *J* = 15.3 Hz, 1 H), 5.17 (t, *J* = 6.4 Hz, 1 H), 4.38 (d, *J* = 15.4 Hz, 1 H), 3.49 (dd, *J* = 14.4, 5.7 Hz, 1 H), 3.25 (dd, *J* = 14.3, 6.9 Hz, 1 H), 2.48 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 156.2, 146.4, 145.6, 137.4, 136.3, 135.9, 132.1, 131.4, 128.7, 128.6, 128.3, 128.0, 127.5, 127.1, 126.5, 123.9, 123.4, 122.9, 122.0, 58.9, 44.6, 41.6, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{22}N_2NaO$: 401.1624; found: 401.1631.

2-Benzyl-3-[(6-chloroquinolin-2-yl)methyl]isoindolin-1-one (4aad)

Yellow oil; yield: 278.7 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 9.0 Hz, 1 H), 7.88–7.83 (m, 2 H), 7.75 (d, *J* = 2.3 Hz, 1 H), 7.64 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.45–7.40 (m, 2 H), 7.25–7.22 (m, 3 H), 7.14 (dd, *J* = 6.8, 2.8 Hz, 2 H), 7.09–7.07 (m, 1 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 5.27 (d, *J* = 15.3 Hz, 1 H), 5.19 (t, *J* = 6.0 Hz, 1 H), 4.41 (d, *J* = 15.4 Hz, 1 H), 3.54 (dd, *J* = 14.5, 5.4 Hz, 1 H), 3.34 (dd, *J* = 14.5, 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.5, 146.2, 145.4, 137.3, 135.4, 132.1, 131.5, 130.8, 130.7, 128.7, 128.4, 128.0, 127.6, 127.5, 126.3, 124.0, 122.8, 122.7, 58.7, 44.6, 41.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}{}^{35}ClN_2O$: 399.1259; found: 399.1262.

2-Benzyl-3-[(6-bromoquinolin-2-yl)methyl]isoindolin-1-one (4aae)

Yellow oil; yield: 353.6 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.72 (m, 5 H), 7.40 (s, 2 H), 7.26–7.06 (m, 6 H), 6.92–6.89 (m, 1 H), 5.27–5.17 (m, 2 H), 4.40 (d, *J* = 15.5 Hz, 1 H), 3.50 (d, *J* = 14.5 Hz, 1 H), 3.31 (d, *J* = 14.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.7, 146.4, 145.3, 137.3, 135.3, 133.2, 132.1, 131.5, 130.9, 129.7, 128.7, 128.4, 128.1, 127.9, 127.5, 123.9, 122.8, 122.7, 58.7, 44.6, 41.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{19}{}^{79}BrN_2NaO$: 465.0573; found: 465.0579.

2-Benzyl-3-[(6-methoxyquinolin-2-yl)methyl]isoindolin-1-one (4aaf)

White solid; yield: 256.2 mg (65%); mp 148–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.83 (m, 3 H), 7.42–7.35 (m, 3 H), 7.24–7.21 (m, 3 H), 7.13 (dd, *J* = 6.8, 2.7 Hz, 2 H), 7.05–7.03 (m, 2 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 5.27 (d, *J* = 15.3 Hz, 1 H), 5.17 (t, *J* = 6.4 Hz, 1 H), 4.37 (d, *J* = 15.6 Hz, 1 H), 3.92 (s, 3 H), 3.52 (dd, *J* = 14.3, 5.5 Hz, 1 H), 3.28 (dd, *J* = 14.3, 7.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 157.7, 145.6, 137.4, 135.1, 132.1, 131.4, 131.3, 130.5, 128.7, 128.3, 128.0, 127.4, 123.9, 122.9, 122.4, 122.2, 105.1, 58.9, 55.6, 44.6, 41.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_2$: 395.1754; found: 395.1759.

2-Benzyl-3-[(8-methoxyquinolin-2-yl)methyl]isoindolin-1-one (4aag)

White solid; yield: 268.0 mg (68%); mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.4 Hz, 1 H), 7.85–7.83 (m, 1 H), 7.47–7.42 (m, 3 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 7.23–7.20 (m, 3 H), 7.17–7.15 (m, 2 H), 7.12–7.10 (m, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 5.24–5.19 (m, 2 H), 4.39 (d, *J* = 15.4 Hz, 1 H), 4.06 (s, 3 H), 3.59 (dd, *J* = 14.3, 5.8 Hz, 1 H), 3.47 (dd, *J* = 14.3, 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 156.1, 155.2, 145.5, 139.8, 137.4, 136.4, 132.1, 131.5, 128.6, 128.3, 128.2, 128.0, 127.4, 126.6, 123.9, 122.9, 122.5, 119.5, 108.2, 59.1, 56.3, 44.6, 42.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{22}N_2NaO_2$: 417.1573; found: 417.1575.

2-Benzyl-3-[1-(quinolin-2-yl)ethyl]isoindolin-1-one (4aah)

White solid; yield: 344.4 mg (89%); mp 214–216 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.6 Hz, 1 H), 8.04 (d, *J* = 9.5 Hz, 1 H), 7.87 (s, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.74–7.70 (m, 1 H), 7.57–7.52 (m, 1 H), 7.42–7.28 (m, 6 H), 7.23–7.19 (m, 2 H), 6.48–6.42 (m, 1 H), 5.45 (d, *J* = 15.2 Hz, 1 H), 5.32 (d, *J* = 8.0 Hz, 1 H), 4.40 (d, *J* = 15.2 Hz, 1 H), 3.92 (d, *J* = 9.8 Hz, 1 H), 0.97 (d, *J* = 9.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.0, 161.4, 147.8, 143.2, 137.3, 136.5, 133.0, 131.0, 129.7, 129.5, 128.9, 128.5, 128.2, 127.7, 127.6, 127.0, 126.5, 123.8, 123.7, 120.4, 63.2, 44.3, 41.2, 10.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{22}N_2NaO$: 401.1624; found: 401.1631.

2-Benzyl-3-(isoquinolin-1-ylmethyl)isoindolin-1-one (4aai)

White solid; yield: 309.4 mg (85%); mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5.7 Hz, 1 H), 7.90 (d, *J* = 7.3 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.71 (d, *J* = 8.6 Hz, 1 H), 7.66–7.60 (m, 2 H), 7.42 (q, *J* = 8.2 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.21–7.15 (m, 3 H), 7.08–7.06 (m, 2 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 5.40 (t, *J* = 6.4 Hz, 1 H), 5.24 (d, *J* = 15.4 Hz, 1 H), 4.30 (d, *J* = 15.4 Hz, 1 H), 3.88 (dd, *J* = 14.9, 6.1 Hz, 1 H), 3.41 (dd, *J* = 14.9, 7.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.8, 157.1, 146.0, 141.7, 137.3, 136.3, 131.9, 131.4, 130.2, 128.7, 128.3, 127.9, 127.6, 127.5, 124.6, 123.9, 123.1, 120.3, 58.6, 44.8, 38.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2O$: 365.1648; found: 365.1659.

2-Benzyl-1-oxo-3-(quinolin-2-ylmethyl)isoindoline-5-carbonitrile (4baa)

White solid; yield: 167.3 mg (43%); mp 140–142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.2 Hz, 1 H), 7.99–7.93 (m, 2 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.75–7.71 (m, 2 H), 7.57–7.53 (m, 1 H), 7.43 (s, 1 H), 7.27–7.25 (m, 3 H), 7.18–7.16 (m, 2 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 5.35–5.27 (m, 2 H), 4.45 (d, *J* = 15.1 Hz, 1 H), 3.60 (dd, *J* = 14.8, 5.0 Hz, 1 H), 3.24 (dd, *J* = 14.8, 7.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 156.1, 147.8, 146.2, 136.8, 136.6, 136.0, 132.4, 130.1, 129.1, 128.9, 128.1, 127.9, 127.8, 127.2, 127.0, 126.8, 124.7, 121.7, 118.4, 114.8, 58.7, 44.9, 40.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{19}N_3NaO$: 412.1420; found: 412.1419.

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Supporting Information

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