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Isoindolinone Synthesis

Metal-Free Selective and Diverse Synthesis of Three Distinct Sets of Isoindolinones from 2-Alkynylbenzoic Acids and Amines

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Abstract: The metal-free selective and diverse synthesis of three distinct sets of isoindolinones from 2-alkynylbenzoic acids and amines has been achieved in a reaction-condition-controlled manner. This method exhibits valuable advantageous features such as available starting materials, broad substrate scope, excellent selectivity, good to high yields, good functional group tolerance, simple operation, high bond-forming efficiency, and step economy, thus providing a convenient and efficient access to a variety of heterocyclic compounds incorporating the bioactive isoindolinone motif.

Introduction

Diversity-oriented synthesis (DOS) provides a powerful platform for the generation of molecular complexity and diversity.[1] The high efficiency of DOS in generating structurally complex and diverse compounds represents an incentive for chemists to develop new DOS methodologies to synthesize valuable molecules for drug discovery.[2] Particularly, the intermolecular cyclizations of DOS substrates represent an efficient tool to construct a variety of functionalized heterocycles, which are the core structure of numerous natural products and marketed drugs. However, most of the reported cyclization transformations from the same set of substrates are limited as a single annulation process, which leads to the formation of a single heterocycle. This is partly because of the challenge in achieving high levels of chemoselectivity. Obviously, it is quite appealing but also challenging to realize the diverse assembly of distinct sets of heterocycles from the same set of substrates in a highly selective manner, thus allowing access to both skeletal diversity and molecular complexity.

On the other hand, *N*-heterocycles are considered as one of the most prominent privileged structures in drug development because of their large presence in bioactive molecules.[3] Among them, the isoindolinone motif represents an important nucleus because of its diverse range of pharmacological properties.[4] In particular, the 3-hydroxyisoindolinones, 3-methyleneisoindolinones, and isoindolinone-fused tetracyclic ring system of 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones form three important classes of compounds since they are widely found in natural products and pharmaceutical agents (Figure 1).[5–10] Therefore, methods for the assembly of these three architectures have captured considerable attention and tremendous efforts have been made to synthesize these heterocyclic compounds. First of all, the synthesis of 3-hydroxyisoindolinones has been well studied and established. Despite the remarkable achievements made, however, it should be noted that most of the reported methods realized the synthesis of 3-hydroxyisoindolinones from various starting materials in the presence of metals,[11] acids,[10,12] bases,[4b,13] small organic molecules,[14] reductants,[15] initiators,[16] or phase transfer reagents[17] (Scheme 1). The development of a catalyst- and additive-free protocol for 3-hydroxyisoindolinone synthesis is still highly desirable. Secondly, representative methods for 3-meth-

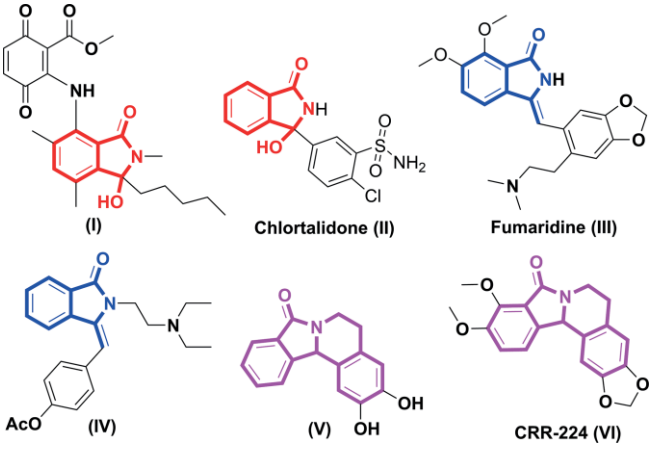

Figure 1. Representative bioactive molecules with the isoindolinone nucleus.

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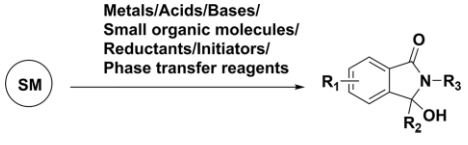
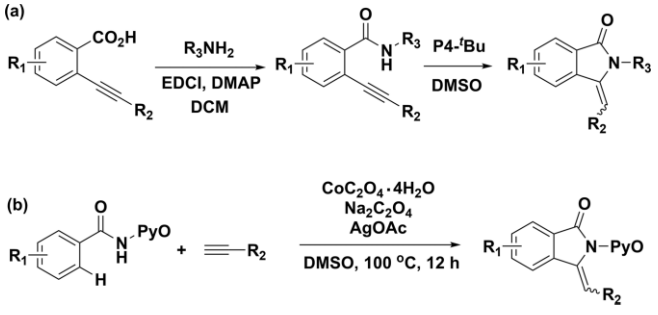
yleneisoindolinone synthesis include Terada's two-step procedure from 2-alkynylbenzoic acids in which a complex organic superbase (P4-^{t}Bu) catalyzed nucleophilic addition was involved (Scheme 2a),[18] and Song's protocol that achieved the assembly of 3-methyleneisoindolinones via a cobalt-catalyzed alkynylation/annulation of benzamides with terminal alkynes assisted by an *N*,*O*-bidentate directing group, which could be removed in three steps (Scheme 2b).[19] Thirdly, the processes from phenylethanamines via the key *N*-phenethyl phthalimide intermediates form a traditional and typical route to the 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one skeleton, but multi-step syntheses as well as purifications were involved and lithium bases or Lewis/Brønsted acids were normally needed for the final cyclizations (Scheme 3a).[20] By contrast, the tandem reactions between alkynoic acids and amine nucleophiles constitute a simpler method to assemble 5,6-dihydroisoindolo-[1,2-*a*]isoquinolin-8(12b*H*)-ones and related structures, despite the fact that expensive gold catalysts must be required in all cases (Scheme 3b).[21] Apparently, compared with the above-mentioned multistep processes and metal-catalyzed procedures, one-pot metal-free cascade reactions, which feature operational simplicity, high bond-forming efficiency, low cost and environmental benignity, represent a more efficient and convenient access to these three scaffolds. This promotes us to investigate metal-free cascade processes to construct these three frameworks.

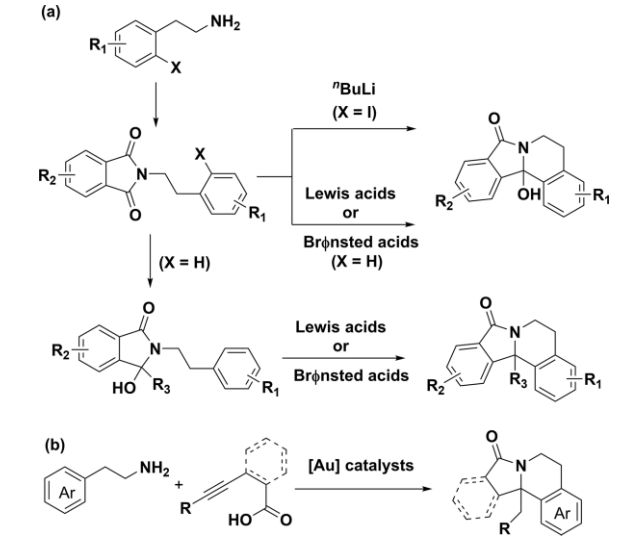


Scheme 1. Reported methods for 3-hydroxyisoindolinone synthesis.

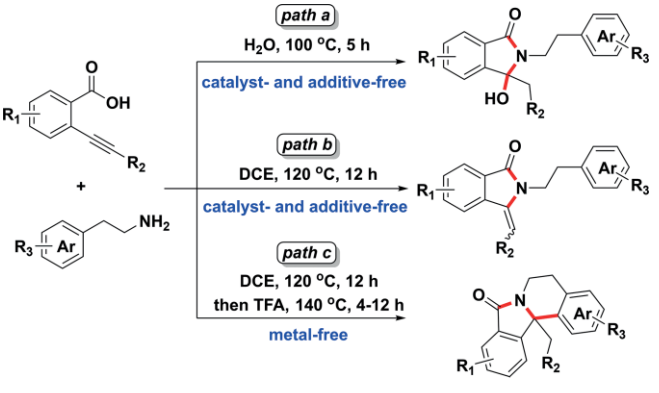


Scheme 2. Representative methods for 3-methyleneisoindolinone synthesis.

Combining the ideas of DOS and cascade reactions for the generation of *N*-heterocycles, and with our interest in *N*-heterocycle synthesis,[22] we aim to develop a DOS protocol in which the same set of substrates could be diverged to different *N*-heterocycles through divergent cascade reaction pathways. Herein, we present the metal-free selective and diverse synthesis of 3-hydroxyisoindolinones, 3-methyleneisoindolinones and 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones through three divergent cascade reaction pathways between 2-alkynylbenzoic acids and amines. Firstly, we achieved the synthesis of 3-hydroxyisoindolinones on water from readily available 2-alkynylbenzoic acids and amines via a catalyst- and additive-free cascade reaction (Scheme 4, *path a*). This process is an improvement of the reported procedure,[17] in which a phase-transfer catalyst $Bu_4N^+OAc^-$ is still required. Compared with most of the reported methods for 3-hydroxyisoindolinone synthesis,[4b,10–17] which requires catalysts or additives, our protocol represents a catalyst- and additive-free, more economical, convenient and greener method for the synthesis of 3-hydroxyisoindolinones. Secondly, 3-methyleneisoindolinones were also assembled efficiently through a catalyst- and additive-free cascade reaction in DCE from the same set of substrates (Scheme 4, *path b*). This process provides a simpler, more facile and direct access to 3-methyleneisoindolinones, which contrasts sharply with Terada's two-step synthesis[18] and Song's cobalt-catalyzed protocol.[19] To the best of our knowledge, this is also the first example of 3-methyleneisoindolinone synthesis through the cascade reactions between 2-alkynylbenzoic acids and amines. Thirdly, 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones were successfully obtained from 2-alkynylbenzoic acids and amines through TFA-promoted two-step one-pot cascade reactions (Scheme 4, *path c*). This metal-free protocol of-



Scheme 3. Typical methods for 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one synthesis.



Scheme 4. Metal-free cascade reactions for the selective and diverse synthesis of 3-hydroxyisoindolinones, 3-methyleneisoindolinones and 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones.

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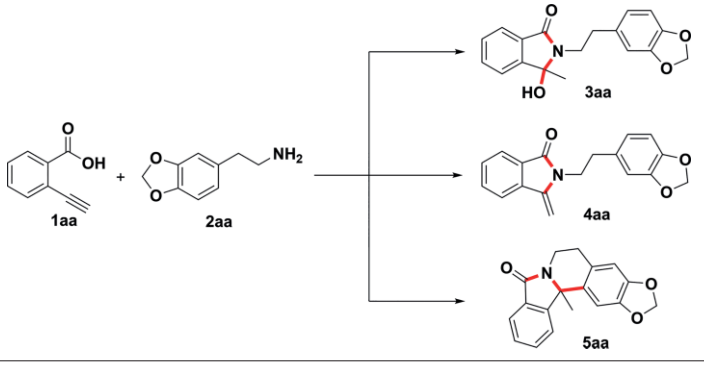
fers a more straightforward, convenient and efficient route to tetracyclic 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones as compared with the conventional multi-step processes[20] and gold-catalyzed procedures.[21] Thus, the metal-free synthesis of three distinct sets of isoindolinones from 2-alkynylbenzoic acids and amines is achieved in a selective and diverse manner.

Results and Discussion

As shown in Table 1, compounds **1aa** and **2aa** were employed as the model substrates to optimize the reaction conditions. Initially, equimolar **1aa** and **2aa** were heated directly without any catalysts or additives in various solvents at 100 °C in an oil bath for 5 h. Interestingly, the reaction results were largely influenced by the solvent used. The reactions in 1,2-dimethoxyethane, THF, 1,4-dioxane, CH_3CN, DMSO, DMF, EtOH and H_2O (entries 2–3, 5–6, 8–11) selectively gave the 3-hydroxyisoindolinone **3aa** as the single product in good to high yields, while reactions in toluene, DCE and CH_3NO_2 (entries 1, 4, 7) provided a mixture of 3-hydroxyisoindolinone **3aa** and 3-methyleneisoindolinone **4aa**. Notably, an excellent yield (94 %) and selectivity for product **3aa** were observed in the environmentally friendly, abundant, and cheap solvent–water (entry 11), thus affording a green access to 3-hydroxyisoindolinones. Although a mixture of products **3aa** and **4aa** were obtained in toluene, DCE and CH_3NO_2, we envisaged that elevating the reaction temperature or prolonging the reaction time could promote the dehydration of **3aa**, thus leading to the conversion of **3aa** into **4aa**. Pleasingly, 3-methyleneisoindolinone **4aa** was obtained exclusively when the reactions were carried out at 120 °C for 12 h (entries 12–14), and DCE was proved to be the best choice of solvent (entry 13). With the optimal reaction conditions for the generation of **4aa**, we then adopted a two-step one-pot procedure to explore the possibility of assembling the isoindolinone-fused heterocyclic compound **5aa** through the addition of an appropriate Brønsted acid into the precursor **4aa** formed in situ in DCE. As a result, HOAc was found to be ineffective, but with the recovery of **4aa** (entry 15). Surprisingly, the strong acid HOTf caused the decomposition of **4aa**, producing a complex black reaction mixture (entry 16). TFA and H_3PO_4 turned

Table 1. Survey of the reaction conditions of the divergent cascade reactions between **1aa** and **2aa**.[a]



Entry	Condition	**3aa**:**4aa**/**5aa**[b]	Yield [%][c]		
			3aa	**4aa**	**5aa**
1	Toluene, 100 °C, 5 h	6.5:1:0	76	12	–
2	1,2-dimethoxyethane, 100 °C, 5 h	1:0:0	86	–	–
3	THF, 100 °C, 5 h	1:0:0	89	–	–
4	DCE, 100 °C, 5 h	2:1:0	62	31	–
5	1,4-dioxane, 100 °C, 5 h	1:0:0	90	–	–
6	CH_3CN, 100 °C, 5 h	1:0:0	92	–	–
7	CH_3NO_2, 100 °C, 5 h	1.2:1:0	50	42	–
8	DMSO, 100 °C, 5 h	1:0:0	80	–	–
9	DMF, 100 °C, 5 h	1:0:0	77	–	–
10	EtOH, 100 °C, 5 h	1:0:0	68	–	–
11	**H_2O, 100 °C, 5 h**	**1:0:0**	**94**	–	–
12	Toluene, 120 °C, 12 h	0:1:0	–	83	–
13	**DCE, 120 °C, 12 h**	**0:1:0**	–	**91**	–
14	CH_3NO_2, 120 °C, 12 h	0:1:0	–	90	–
15	DCE, 120 °C, 12 h, then HOAc, 140 °C, 4 h	0:1:0	–	88	–
16	DCE, 120 °C, 12 h, then HOTf, 140 °C, 4 h	–	–	–	–
17	**DCE, 120 °C, 12 h, then TFA, 140 °C, 4 h**	**0:0:1**	–	–	**86**
18	DCE, 120 °C, 12 h, then H_3PO_4, 140 °C, 4 h	0:0:1	–	–	84
19[d]	H_2O, 100 °C, 50 min	1:0:0	92	–	–
20[d]	DCE, 120 °C, 2 h	0:1:0	–	90	–
21[d]	DCE, 120 °C, 2 h, then TFA, 140 °C, 1 h	0:0:1	–	–	87

[a] Reaction conditions: for entries 1–11: **1aa** (0.2 mmol), **2aa** (0.2 mmol), solvent (2.0 mL), 100 °C, 5 h; for entries 12–14: **1aa** (0.2 mmol), **2aa** (0.2 mmol), solvent (2.0 mL), 120 °C, 12 h; for entries 15–18: **1aa** (0.2 mmol), **2aa** (0.2 mmol), DCE (2.0 mL), 120 °C, 12 h, then acid (0.4 mmol), 140 °C, 4 h. [b] The ratio was determined by ^{1}H-NMR integration of the crude products. [c] Isolated yield. "–" means that product was not detected. [d] The reaction was performed under microwave irradiation (sealed vessel at fixed power, 30 W).

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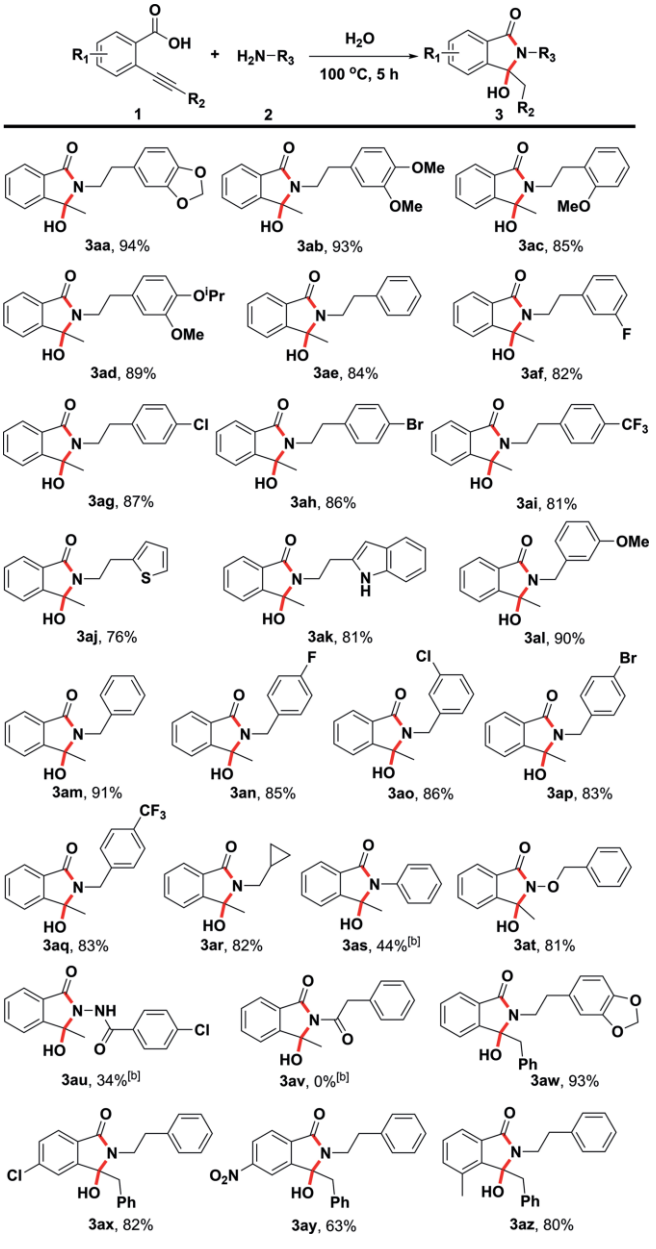
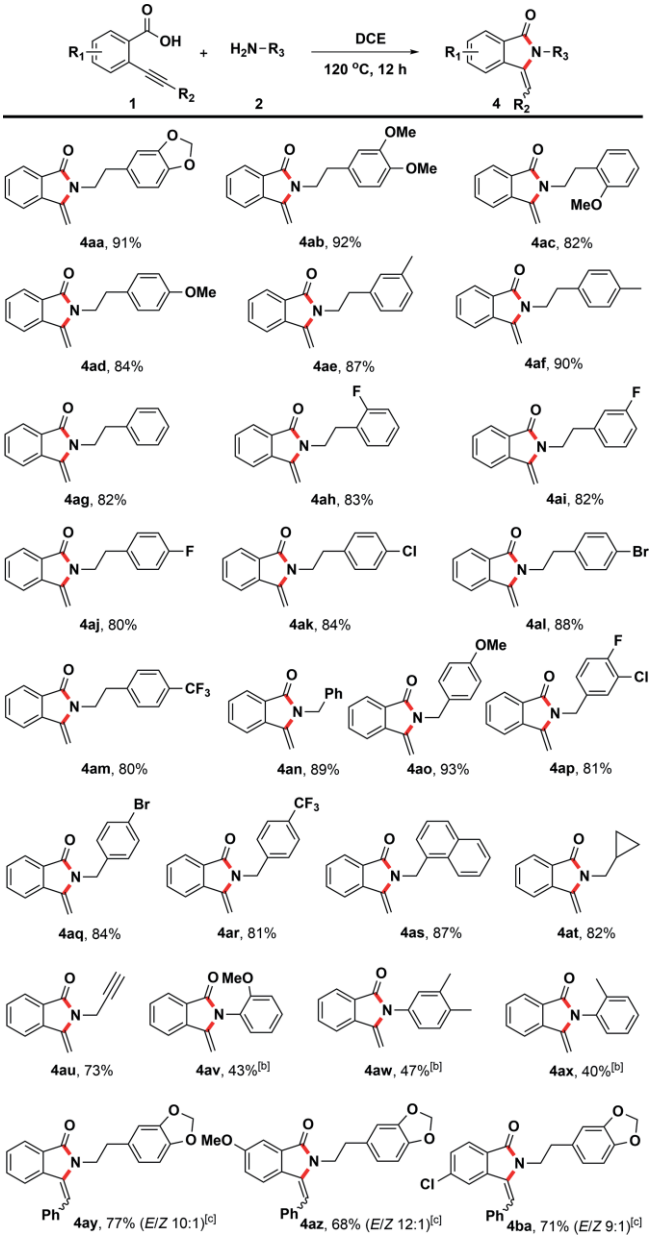
out to be effective for the assembly of **5aa** in 86 % and 84 % yield, respectively (entries 17–18). Additionally, the abovementioned three reactions for the generation of **3aa**, **4aa** and **5aa** could complete in a shorter time under microwave irradiation with comparable yields (entries 19–21). In this way, the optimal reaction conditions for the metal-free selective and diverse synthesis of 3-hydroxyisoindolinones, 3-methyleneisoindolinones, and 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones were identified.

The selective conditions identified were then applied to synthesize a range of 3-hydroxyisoindolinones **3**, 3-methyleneisoindolinones **4**, and 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones **5** from two diverse inputs of the cascade reaction (Scheme 5, Scheme 6, and Scheme 7). Firstly, the substrate scope of the catalyst- and additive-free synthesis of 3-hydroxyisoindolinones was explored (Scheme 5). For example, 2-ethynylbenzoic acid **1aa** could undergo the cascade reaction smoothly with various 2-phenylethanamines bearing electron-donating substituents, halogens or electron-withdrawing groups to give the desired products **3aa**–**3ai** in high yields. Expectedly, 2-arylethanamines such as 2-(thiophen-2-yl)ethanamine and 2-(1*H*-indol-2-yl)ethanamine were also proved to be suitable amine substrates, providing the corresponding products **3aj**–**3ak** in 76–81 % yields. Similarly, benzylamines encompassing electron-donating groups, halogens or electron-withdrawing substituents reacted well with **1aa** to deliver products **3al**–**3aq** in high yields. As an example, the representative linear



Scheme 5. Catalyst- and additive-free synthesis of 3-hydroxyisoindolinones. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), H_2O (2.0 mL), 100 °C, 5 h. [b] 0.4 mmol of **2** were used.



Scheme 6. Catalyst- and additive-free synthesis of 3-methyleneisoindolinones. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), DCE (2.0 mL), 120 °C, 12 h. [b] 0.4 mmol of **2** were used. [c] The ratio was determined by ^{1}H-NMR integration of the crude products.

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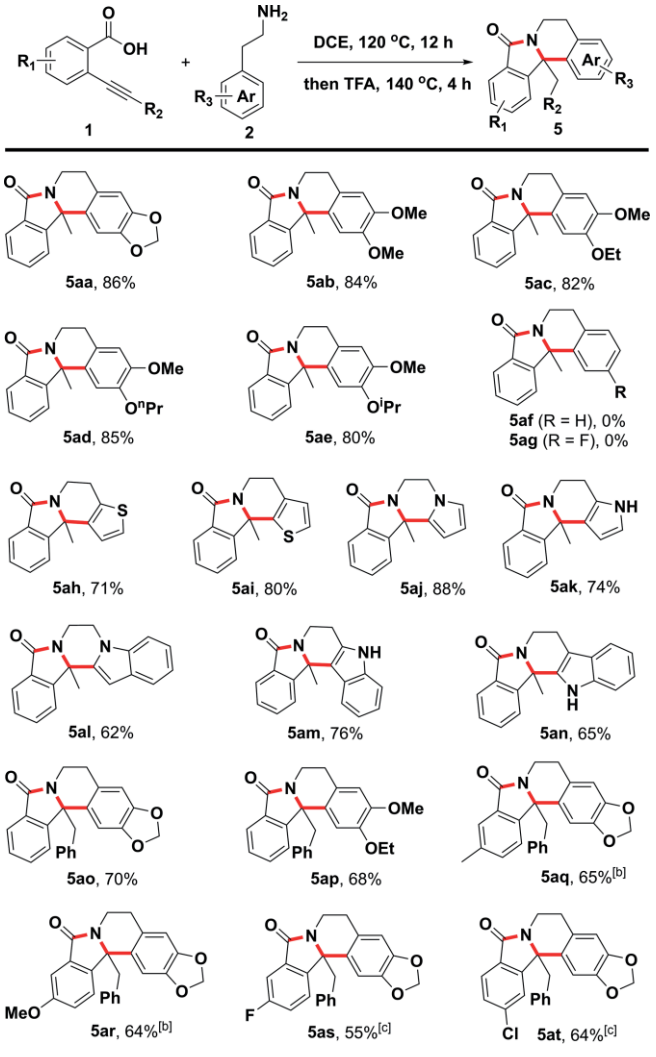
aliphatic amine–cyclopropylmethanamine could take part in this reaction well to produce the corresponding product **3ar** in a high yield (82 %). In addition, aniline was well tolerated despite a moderate yield (44 %) was observed with the corresponding product **3as**. Interestingly, *O*-benzylhydroxylamine could also undergo this transformation to furnish the desired product **3at** in a high yield. Gratifyingly, this cascade reaction was also compatible with benzohydrazide, although a lower yield was observed with the corresponding product **3au**. We also made our efforts to synthesize compound **3av** from 2-phenylacetamide, but an unsuccessful result was obtained. The low reactivities of the nitrogen-containing nucleophiles observed in the examples of **3as**, **3au** and **3av** were justified by their weaker nucleophilicities as compared with alkylamines. Pleasingly, this cascade process could also be applicable to 2-alkynylbenzoic acids **1** carrying different substituents at the alkyne moiety or on the benzene ring, affording the desired products **3aw**–**3az** in 63–93 % yields.



Scheme 7. Metal-free synthesis of 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones and their analogues. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), DCE (2.0 mL), 120 °C, 12 h, then TFA (0.4 mmol), 140 °C, 4 h. [b] TFA (0.4 mmol), 140 °C, 12 h. [c] TFA (0.8 mmol), 140 °C, 12 h.

Secondly, the general applicability of the catalyst- and additive-free synthesis of 3-methyleneisoindolinones was examined. As shown in Scheme 6, a variety of 2-phenylethanamines bearing electron-donating groups, halogens or electron-withdrawing groups reacted well with 2-ethynylbenzoic acid **1aa** to deliver the desired products **4aa**–**4am** in high yields. Likewise, the reactions of a diversity of arylmethanamines or linear aliphatic amines with **1aa** happened smoothly to give the products **4an**–**4au** in high yields. Besides, anilines could also react with **1aa** to produce the desired products **4av**–**4ax**, albeit with lower yields. This may be attributed to the poor nucleophilicities of the anilines. Various 2-alkynylbenzoic acids **1** carrying a phenyl group at the alkyne moiety underwent this transformation successfully to provide the corresponding products **4ay**–**4ba** in good yields and excellent stereoselectivities (*E*/*Z* > 9:1). The assignment of *E*- or *Z*-isomers was determined by X-ray crystallography of the major isomer of compound **4az** (Figure 2).

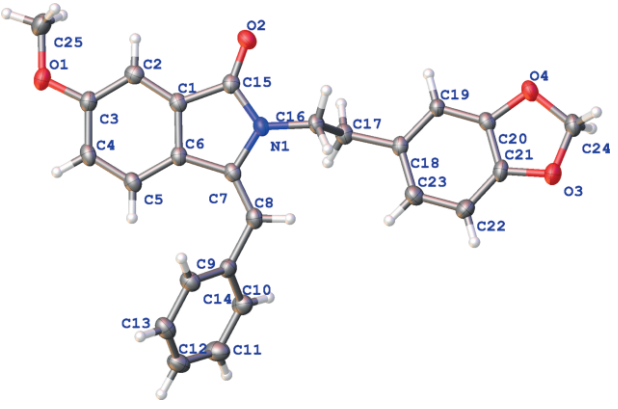


Figure 2. X-ray crystallographic structure of the major isomer of compound **4az** (CCDC 1984364).

Thirdly, the substrate scope of the metal-free two-step one-pot synthesis of 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones and their analogues was investigated. As illustrated in Scheme 7, this cascade process tolerated a broad range of 2-phenylethanamines bearing electron-donating substituents, which reacted smoothly with 2-ethynylbenzoic acid **1aa** to offer the desired 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-ones **5aa**–**5ae** carrying a crowded quaternary carbon center in high yields. In contrast, unsubstituted and 4-F-substituted 2-phenylethanamines could not undergo this transformation to give the products **5af**–**5ag**. This indicates that an electron-rich benzene ring in the phenylethanamine components is essential for this cascade reaction. Therefore, a variety of 2-arylethanamines bearing an electron-rich aromatic ring such as thiophene, pyrrole and indole were tested as the substrates. To our delight, they all reacted well with **1aa** to afford the isoindolinone-fused polycyclic products **5ah**–**5an** in good to high yields. Next, the substituents on the 2-alkynylbenzoic acid component were explored. The reactions of 2-alkynylbenzoic acids **1** carrying a phenyl group at the alkyne moiety with diverse 2-phenylethanamines bearing electron-donating groups took place successfully to provide the corresponding products **5ao**–**5ap** in good yields. In addition, the reactions of 2-alkynylbenzoic acids **1** having diverse substituents on benzene ring also worked well

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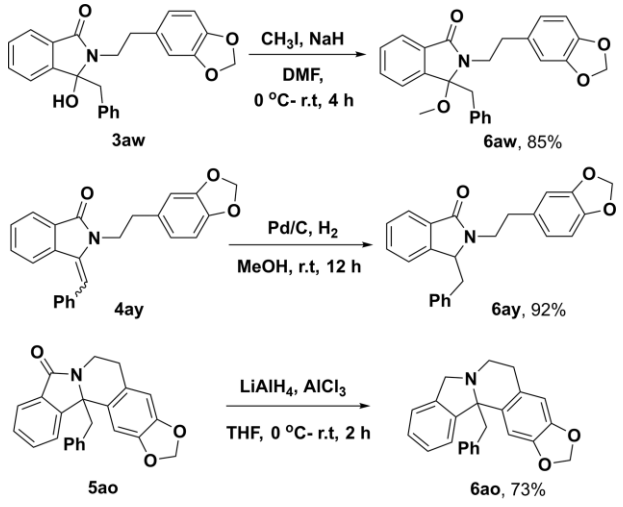
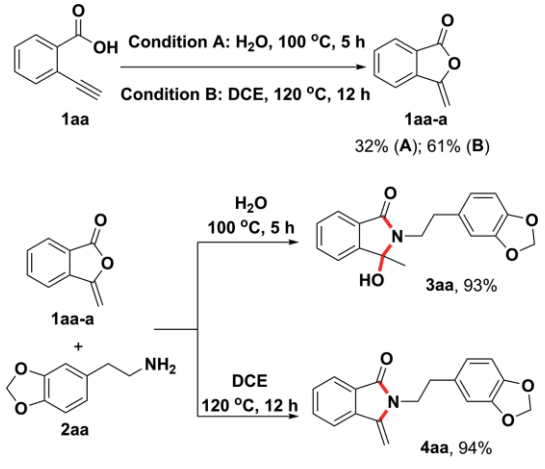
to produce the desired products **5aq**–**5at** in good yields, although harsher reaction conditions were required.

To further illustrate the synthetic application of this methodology, the downstream transformations of the products obtained were studied (Scheme 8). Taking products **3aw**, **4ay** and **5ao** as examples, the hydroxyl group in **3aw** could undergo nucleophilic substitutions like methylation with MeI to provide **6aw** in 85 % yield. The C=C bond in **4ay** could be hydrogenated by H_2 to give **6ay** in 92 % yield. The carbonyl group in **5ao** could be reduced by $LiAlH_4$ to afford **6ao** in 73 % yield. These aspects further highlight the advantages and potential application of this approach.



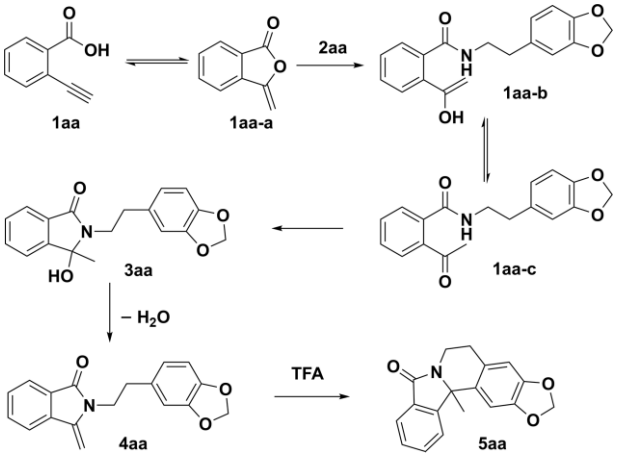
Scheme 8. Synthetic applications.

To explore the reaction mechanism, mechanistic experiments were carried out (Scheme 9). Treatment of **1aa** in H_2O or DCE under standard conditions without amine nucleophiles both gave the enol lactone product **1aa-a**, which could react with **2aa** in H_2O or DCE under standard conditions to deliver products **3aa** or **4aa**, respectively. These results suggest the enol lactone species was likely involved as the key intermediate.



Scheme 9. Mechanism studies.

Based on the preliminary mechanistic studies, a plausible mechanism was proposed in Scheme 10. The intramolecular cyclization of **1aa** driven by the high temperature takes place first to give the key enol lactone **1aa-a**, which is attacked by the amine **2aa** to produce the aminolysis intermediate **1aa-b**. Then enol-ketone tautomerization occurs to yield intermediate **1aa-c**, which undergoes an intramolecular annulation to afford the 3-hydroxyisoindolinone product **3aa**. The further heating of **3aa** at a higher temperature for a longer reaction time leads to the formation of the dehydration product, namely 3-methyleneisoindolinone **4aa**. At last, compound **4aa** could be converted into the 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one product **5aa** by a TFA-promoted intramolecular alkylation reaction.



Scheme 10. Proposed reaction mechanism.

Conclusion

In conclusion, we have developed an efficient metal-free methodology for the selective and diverse synthesis of three distinct sets of isoindolinones through the divergent cascade reactions between 2-alkynylbenzoic acids and amines. This protocol achieved both scaffold diversity of three different skeletons and molecular complexity with two modular inputs. In addition, this reaction-condition-controlled synthetic strategy features readily available materials, broad substrate scope, excellent selectivity, good to high yields, good functional group tolerance, operational simplicity, high bond-forming efficiency, and step economy. We anticipate that these heterocyclic compounds incorporating the bioactive isoindolinone motif may find their pharmaceutical applications after further investigations.

Experimental Section

General Information

The reagents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on HSGF 254 (0.15–0.2 mm thickness), visualized by irradiation with UV light (254 nm). Column chromatography was performed using silica gel FCP 200–300. Melting points were measured with a micro melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Bruker instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from

tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass were measured on a spectrometer with an electrospray ionization (ESI) source.

Preparation and Characterization Data of Compounds 3

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with **1aa** (0.2 mmol), **2aa** (0.2 mmol), H_2O (2.0 mL) and then capped with a septa. After that, the vial was kept in the preheated oil bath at 100 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (18.0 mL) and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give the desired product **3aa**. Compounds **3ab**–**3az** were prepared with the detailed conditions indicated in Scheme 5 following the similar procedure carried out for compound **3aa**.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-hydroxy-3-methylisoindolin-1-one (3aa): White solid (58.6 mg, yield 94 %), m.p. 131–132 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.63–7.54 (m, 3H), 7.50–7.43 (m, 1H), 6.81 (s, 1H), 6.77–6.70 (m, 2H), 5.91 (s, 2H), 4.31 (s, 1H), 3.66–3.55 (m, 1H), 3.55–3.44 (m, 1H), 2.96–2.82 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.41, 149.64, 148.57, 146.94, 134.52, 133.13, 131.70, 130.19, 123.28, 122.69, 110.08, 108.99, 102.03, 89.36, 41.27, 35.65, 24.67; LRMS (ESI) *m/z*: 312 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NO_4$ + H^+ 312.1230, found 312.1230.

2-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-methylisoindolin-1-one (3ab): White solid (60.8 mg, yield 93 %), m.p. 131–132 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.64 (d, *J* = 7.4 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.46 (m, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.16 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.68–3.59 (m, 1H), 3.58–3.46 (m, 1H), 2.99–2.88 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 167.40, 150.03, 149.66, 148.66, 133.25, 133.12, 131.82, 130.22, 123.26, 122.71, 121.70, 113.55, 112.68, 89.37, 56.26, 56.22, 41.24, 35.51, 24.66; LRMS (ESI) *m/z*: 350 [M + Na]$^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{21}NO_4$ + Na^+ 350.1363, found 350.1365.

3-Hydroxy-2-(2-methoxyphenethyl)-3-methylisoindolin-1-one (3ac): White solid (50.8 mg, yield 85 %), m.p. 162–164 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.62–7.55 (m, 2H), 7.52–7.45 (m, 1H), 7.23–7.19 (m, 1H), 7.18 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.89–6.85 (m, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.67–3.58 (m, 1H), 3.57–3.47 (m, 1H), 3.08–2.91 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.35, 158.81, 149.69, 133.07, 131.91, 131.42, 130.20, 128.78, 128.67, 123.24, 122.69, 121.38, 111.58, 89.28, 56.01, 39.37, 30.96, 24.47; LRMS (ESI) *m/z*: 298 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{19}NO_3$ + H^+ 298.1438, found 298.1444.

3-Hydroxy-2-(4-isopropoxy-3-methoxyphenethyl)-3-methylisoindolin-1-one (3ad): White solid (63.1 mg, yield 89 %), m.p. 131–132 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.63–7.55 (m, 2H), 7.52–7.46 (m, 1H), 6.89 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.54–4.39 (m, 1H), 4.14 (s, 1H), 3.77 (s, 3H), 3.65–3.59 (m, 1H), 3.58–3.51 (m, 1H), 2.94 (t, *J* = 8.0 Hz, 2H), 1.58 (s, 3H), 1.25 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.20, 150.42, 148.25, 145.75, 132.41, 130.48, 129.55, 123.19, 121.70, 120.91, 116.29, 112.84, 88.77, 71.62, 56.00, 40.70, 34.51, 24.23, 22.19; LRMS (ESI) *m/z*: 378 [M + Na]$^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{25}NO_4$ + Na^+ 378.1676, found 378.1676.

3-Hydroxy-3-methyl-2-phenethylisoindolin-1-one (3ae): Colorless oil (44.8 mg, yield 84 %). ^{1}H NMR (600 MHz, CD_3CN) δ 7.10–7.07 (m, 1H), 7.07–7.04 (m, 2H), 6.97–6.92 (m, 1H), 6.78–6.71 (m, 4H), 6.69–6.63 (m, 1H), 5.79 (s, 1H), 3.04–2.90 (m, 2H), 2.48–2.29 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 165.86, 149.09, 139.53, 132.14, 130.59, 129.11, 128.74, 128.51, 126.29, 122.25, 122.03, 87.94, 39.97, 34.90, 24.79; LRMS (ESI) *m/z*: 268 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{17}NO_2$ + H^+ 268.1332, found 268.1335.

2-(3-Fluorophenethyl)-3-hydroxy-3-methylisoindolin-1-one (3af): White solid (46.9 mg, yield 82 %), m.p. 81–82 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.46 (m, 1H), 7.34–7.27 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.09–7.05 (m, 1H), 6.99–6.93 (m, 1H), 4.19 (s, 1H), 3.71–3.63 (m, 1H), 3.60–3.53 (m, 1H), 3.03 (t, *J* = 7.9 Hz, 2H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.37, 162.92 (d, $J_{C\text{-}F}$ = 245.7 Hz), 148.38, 141.72 (d, $J_{C\text{-}F}$ = 7.2 Hz), 132.43, 130.16, 129.96 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129.39, 124.55 (d, $J_{C\text{-}F}$ = 2.7 Hz), 123.14, 121.72, 115.72 (d, $J_{C\text{-}F}$ = 20.9 Hz), 113.35 (d, $J_{C\text{-}F}$ = 21.0 Hz), 88.82, 40.13, 34.80, 24.31; LRMS (ESI) *m/z*: 286 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{16}FNO_2$ + H^+ 286.1238, found 286.1238.

2-(4-Chlorophenethyl)-3-hydroxy-3-methylisoindolin-1-one (3ag): White solid (52.6 mg, yield 87 %), m.p. 90–91 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.66–7.53 (m, 3H), 7.50–7.43 (m, 1H), 7.35–7.22 (m, 4H), 4.29 (s, 1H), 3.68–3.57 (m, 1H), 3.57–3.47 (m, 1H), 3.04–2.93 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.48, 149.62, 139.64, 133.18, 132.41, 131.65, 131.56, 130.22, 129.30, 123.31, 122.72, 89.37, 40.84, 35.25, 24.68; LRMS (ESI) *m/z*: 304 ([M + H]$^+$, ^{37}Cl), 302 ([M + H]$^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{17}H_{16}ClNO_2$ + H^+ 302.0942, found 302.0946.

2-(4-Bromophenethyl)-3-hydroxy-3-methylisoindolin-1-one (3ah): White solid (59.3 mg, yield 86 %), m.p. 90–91 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.64 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.47 (m, 1H), 7.47–7.43 (m, 2H), 7.23 (dd, *J* = 8.2, 1.5 Hz, 2H), 4.16 (s, 1H), 3.69–3.61 (m, 1H), 3.59–3.51 (m, 1H), 3.02–2.94 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.44, 149.62, 140.16, 133.18, 132.29, 131.97, 131.70, 130.25, 123.30, 122.73, 120.44, 89.34, 40.76, 35.32, 24.66; LRMS (ESI) *m/z*: 348 ([M + H]$^+$, ^{81}Br), 346 ([M + H]$^+$, ^{79}Br); HRMS (ESI) *m/z* calculated for $C_{17}H_{16}BrNO_2$ + H^+ 346.0437, found 346.0434.

3-Hydroxy-3-methyl-2-(4-(trifluoromethyl)phenethyl)isoindolin-1-one (3ai): White solid (54.4 mg, yield 81 %), m.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.59–7.50 (m, 4H), 7.46–7.40 (m, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 3.71 (ddd, *J* = 14.1, 9.9, 6.2 Hz, 1H), 3.50–3.38 (m, 1H), 3.14 (ddd, *J* = 15.4, 9.9, 5.7 Hz, 1H), 3.02 (ddd, *J* = 13.3, 9.9, 6.3 Hz, 1H), 2.85 (s, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.34, 148.28, 143.35, 132.56, 130.27, 129.60, 129.29, 128.96 (q, $J_{C\text{-}F}$ = 32.4 Hz), 125.53 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.36 (q, $J_{C\text{-}F}$ = 271.8 Hz), 123.30, 121.76, 88.86, 40.12, 35.01, 24.27; LRMS (ESI) *m/z*: 336 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{16}F_3NO_2$ + H^+ 336.1206, found 336.1196.

3-Hydroxy-3-methyl-2-(2-(thiophen-2-yl)ethyl)isoindolin-1-one (3aj): White solid (41.7 mg, yield 76 %), m.p. 92–94 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.66 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.64–7.56 (m, 2H), 7.53–7.47 (m, 1H), 7.25–7.19 (m, 1H), 6.98–6.91 (m, 2H), 4.15 (s, 1H), 3.76–3.66 (m, 1H), 3.65–3.56 (m, 1H), 3.27–3.19 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.44, 149.62, 142.71, 133.23, 131.70, 130.28, 128.02, 126.34, 124.79, 123.33, 122.76, 89.37, 41.23, 29.93, 24.56; LRMS (ESI) *m/z*: 274 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{15}NO_2S$ + H^+ 274.0896, found 274.0898.

2-(2-(1*H*-Indol-2-yl)ethyl)-3-hydroxy-3-methylisoindolin-1-one (3ak): Pale yellow oil (49.5 mg, yield 81 %). ^{1}H NMR (600 MHz, CD_3CN) δ 9.42 (s, 1H), 7.70–7.65 (m, 1H), 7.63–7.57 (m, 2H), 7.52–

7.47 (m, 1H), 7.47–7.42 (m, 1H), 7.34–7.29 (m, 1H), 7.09–7.02 (m, 1H), 7.01–6.95 (m, 1H), 6.27 (d, *J* = 2.6 Hz, 1H), 4.14 (s, 1H), 3.91–3.79 (m, 1H), 3.77–3.64 (m, 1H), 3.21–3.14 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.57, 149.66, 138.50, 137.27, 133.25, 131.71, 130.29, 129.72, 123.35, 122.75, 121.68, 120.42, 120.10, 111.57, 100.52, 89.49, 39.21, 28.68, 24.49; LRMS (ESI) *m/z*: 329 $[M + Na]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{18}N_2O_2 + Na^+$ 329.1260, found 329.1261.

3-Hydroxy-2-(3-methoxybenzyl)-3-methylisoindolin-1-one (3al): White solid (51.1 mg, yield 90 %), m.p. 106–107 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.70 (dd, *J* = 7.2, 3.9 Hz, 1H), 7.66–7.58 (m, 2H), 7.55–7.48 (m, 1H), 7.25–7.18 (m, 1H), 6.93 (d, *J* = 7.7 Hz, 2H), 6.82–6.75 (m, 1H), 4.72 (dd, *J* = 15.9, 4.5 Hz, 1H), 4.51 (dd, *J* = 15.9, 2.6 Hz, 1H), 4.20 (s, 1H), 3.74 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.79, 160.70, 149.74, 141.82, 133.33, 131.50, 130.33, 123.56, 122.78, 120.64, 114.03, 113.08, 89.42, 55.73, 42.25, 25.22; LRMS (ESI) *m/z*: 284 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{17}NO_3 + H^+$ 284.1281, found 284.1284.

2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (3am): White solid (46.3 mg, yield 91 %), m.p. 159–160 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.66–7.57 (m, 2H), 7.55–7.49 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.33–7.28 (m, 2H), 7.26–7.20 (m, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.19 (s, 1H), 1.51 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.77, 149.75, 140.13, 133.33, 131.53, 130.34, 129.26, 128.45, 127.78, 123.54, 122.78, 89.42, 42.29, 25.27; LRMS (ESI) *m/z*: 254 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{15}NO_2 + H^+$ 254.1176, found 254.1178.

2-(4-Fluorobenzyl)-3-hydroxy-3-methylisoindolin-1-one (3an): White solid (46.0 mg, yield 85 %), m.p. 162–163 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.70 (d, *J* = 7.3 Hz, 1H), 7.66–7.56 (m, 2H), 7.55–7.49 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.69 (d, *J* = 15.9 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.12 (s, 1H), 1.52 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.76, 162.71 (d, $J_{C\text{-}F}$ = 242.0 Hz), 149.71, 136.21 (d, $J_{C\text{-}F}$ = 2.6 Hz), 133.37, 131.44, 130.49 (d, $J_{C\text{-}F}$ = 8.4 Hz), 130.35, 123.54, 122.79, 115.81 (d, $J_{C\text{-}F}$ = 21.6 Hz), 89.44, 41.65, 25.22; LRMS (ESI) *m/z*: 272 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{14}FNO_2 + H^+$ 272.1081, found 272.1084.

2-(3-Chlorobenzyl)-3-hydroxy-3-methylisoindolin-1-one (3ao): White solid (49.6 mg, yield 86 %), m.p. 152–153 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.67–7.58 (m, 2H), 7.56–7.50 (m, 1H), 7.40 (s, 1H), 7.34–7.28 (m, 2H), 7.26 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.15 (s, 1H), 1.55 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.79, 149.69, 142.65, 134.54, 133.43, 131.39, 130.91, 130.38, 128.44, 127.81, 127.07, 123.58, 122.82, 89.42, 41.89, 25.10; LRMS (ESI) *m/z*: 290 ($[M + H]^+$, ^{37}Cl), 288 ($[M + H]^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{16}H_{14}ClNO_2 + H^+$ 288.0786, found 288.0788.

2-(4-Bromobenzyl)-3-hydroxy-3-methylisoindolin-1-one (3ap): White solid (55.2 mg, yield 83 %), m.p. 176–177 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.65–7.58 (m, 2H), 7.54–7.49 (m, 1H), 7.41–7.37 (m, 2H), 7.07–7.01 (m, 2H), 4.70 (d, *J* = 15.8 Hz, 1H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.21 (s, 1H), 1.52 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.74, 149.70, 139.62, 133.41, 132.19, 131.42, 130.67, 130.37, 123.56, 122.81, 121.04, 89.41, 41.76, 25.18; LRMS (ESI) *m/z*: 334 ($[M + H]^+$, ^{81}Br), 332 ($[M + H]^+$, ^{79}Br); HRMS (ESI) *m/z* calculated for $C_{16}H_{14}BrNO_2 + H^+$ 332.0281, found 332.0279.

3-Hydroxy-3-methyl-2-(4-(trifluoromethyl)benzyl)isoindolin-1-one (3aq): White solid (53.4 mg, yield 83 %), m.p. 180–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.62–7.54 (m, 2H), 7.54–7.49 (m, 2H), 7.49–7.44 (m, 1H), 7.43–7.37 (m, 2H), 4.59–4.42 (m, 2H), 3.71 (s, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.66, 148.38, 142.60, 132.95, 129.89, 129.78, 129.69 (q, $J_{C\text{-}F}$ = 32.4 Hz), 128.15, 125.60 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.63, 122.87, 121.93, 89.17, 41.44, 24.94; LRMS (ESI) *m/z*: 322 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}F_3NO_2 + H^+$ 322.1049, found 322.1042.

2-(Cyclopropylmethyl)-3-hydroxy-3-methylisoindolin-1-one (3ar): White solid (35.7 mg, yield 82 %), m.p. 124–125 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.63 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.61–7.57 (m, 2H), 7.50–7.47 (m, 1H), 4.14 (s, 1H), 3.31 (dd, *J* = 14.7, 7.2 Hz, 1H), 3.24 (dd, *J* = 14.6, 6.9 Hz, 1H), 1.68 (s, 3H), 1.24–1.12 (m, 1H), 0.51–0.45 (m, 2H), 0.37–0.31 (m, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ = 167.40, 149.70, 133.07, 131.85, 130.16, 123.30, 122.69, 89.05, 43.59, 25.11, 11.94, 5.24, 4.64; LRMS (ESI) *m/z*: 218 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{15}NO_2 + H^+$ 218.1176, found 218.1177.

3-Hydroxy-3-methyl-2-phenylisoindolin-1-one (3as): White solid (21.1 mg, yield 44 %), m.p. 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.55 (m, 3H), 7.51–7.45 (m, 2H), 7.45–7.34 (m, 3H), 7.33–7.27 (m, 1H), 3.68 (s, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.71, 148.01, 135.54, 132.96, 130.19, 129.82, 129.07, 127.27, 127.16, 123.85, 121.79, 90.58, 24.47; LRMS (ESI) *m/z*: 240 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{13}NO_2 + H^+$ 240.1019, found 240.1013.

2-(Benzyloxy)-3-hydroxy-3-methylisoindolin-1-one (3at): White solid (43.5 mg, yield 81 %), m.p. 116–117 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 7.70–7.64 (m, 2H), 7.60–7.51 (m, 4H), 7.44–7.37 (m, 3H), 5.21 (d, *J* = 2.2 Hz, 2H), 4.61 (s, 1H), 1.69 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ = 164.19, 147.07, 136.73, 134.00, 130.55, 130.39, 129.65, 129.41, 129.13, 123.69, 122.97, 89.38, 80.43, 23.99; LRMS (ESI) *m/z*: 270 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{15}NO_3 + H^+$ 270.1125, found 270.1127.

4-Chloro-*N*-(1-hydroxy-1-methyl-3-oxoisoindolin-2-yl)benzamide (3au): White solid (21.7 mg, yield 34 %), m.p. 170–171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.64–7.58 (m, 1H), 7.54 (dd, *J* = 15.0, 7.5 Hz, 2H), 7.44–7.39 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.52 (s, 1H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.07, 166.38, 147.40, 139.11, 133.78, 129.73, 129.23, 129.13, 128.92, 127.41, 123.80, 122.26, 89.80, 23.38; LRMS (ESI) *m/z*: 341 ($[M + Na]^+$, ^{37}Cl), 339 ($[M + Na]^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{16}H_{13}ClN_2O_3 + Na^+$ 339.05069, found 339.04980.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzyl-3-hydroxyisoindolin-1-one (3aw): White solid (72.1 mg, yield 93 %), m.p. 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.48–7.42 (m, 1H), 7.41–7.34 (m, 1H), 7.17–7.05 (m, 4H), 6.86 (d, *J* = 6.6 Hz, 2H), 6.76 (d, *J* = 1.3 Hz, 1H), 6.73–6.63 (m, 2H), 5.92 (s, 2H), 3.88 (ddd, *J* = 14.0, 9.5, 5.0 Hz, 1H), 3.52–3.40 (m, 2H), 3.06 (ddd, *J* = 13.3, 11.7, 6.0 Hz, 2H), 2.98–2.91 (m, 1H), 2.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.06, 147.85, 146.24, 146.19, 134.52, 133.31, 131.84, 131.46, 130.27, 129.73, 128.10, 127.16, 123.17, 122.80, 121.90, 109.59, 108.45, 101.02, 91.27, 43.21, 41.82, 34.83; LRMS (ESI) *m/z*: 410 $[M + Na]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{21}NO_4 + Na^+$ 410.1363, found 410.1367.

3-Benzyl-5-chloro-3-hydroxy-2-phenethylisoindolin-1-one (3ax): White solid (62.1 mg, yield 82 %), m.p. 186–187 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.49 (m, 1H), 7.35 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.31–7.27 (m, 2H), 7.25–7.20 (m, 3H), 7.18–7.11 (m, 3H), 7.09 (d, *J* = 1.6 Hz, 1H), 6.88–6.83 (m, 2H), 3.95 (ddd, *J* = 13.6, 8.9, 4.6 Hz, 1H), 3.57–3.45 (m, 1H), 3.37 (d, *J* = 13.9 Hz, 1H), 3.23–3.13 (m, 1H), 3.08–2.97 (m, 2H), 2.19 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.06, 147.88, 139.48, 138.16, 134.04, 130.22, 130.13, 129.85, 129.16, 128.81, 128.25, 127.39, 126.79, 124.36, 123.37, 90.80, 43.20, 41.88, 34.77; LRMS (ESI) *m/z*: 380 ($[M + H]^+$, ^{37}Cl), 378 ($[M + H]^+$, ^{35}Cl);

HRMS (ESI) *m/z* calculated for $C_{23}H_{20}ClNO_2 + H^+$ 378.1255, found 378.1263.

3-Benzyl-3-hydroxy-5-nitro-2-phenethylisoindolin-1-one (3ay): Yellow solid (49.2 mg, yield 63 %), m.p. 231–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.95 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.32–7.28 (m, 2H), 7.26–7.21 (m, 3H), 7.19–7.08 (m, 3H), 6.82 (d, *J* = 7.0 Hz, 2H), 4.12–4.03 (m, 1H), 3.65–3.57 (m, 1H), 3.42 (d, *J* = 14.0 Hz, 1H), 3.30–3.22 (m, 1H), 3.13–3.04 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 163.80, 149.69, 148.24, 139.19, 136.68, 134.80, 130.04, 128.69, 128.54, 127.74, 126.64, 126.35, 124.89, 123.40, 118.41, 91.09, 41.91, 40.97, 34.81; LRMS (ESI) *m/z*: 389 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{23}H_{20}N_2O_4 + H^+$ 389.1496, found 389.1505.

3-Benzyl-3-hydroxy-4-methyl-2-phenethylisoindolin-1-one (3az): White solid (57.1 mg, yield 80 %), m.p. 163–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.1 Hz, 1H), 7.33–7.27 (m, 4H), 7.26–7.19 (m, 3H), 7.06–6.96 (m, 3H), 6.64 (d, *J* = 7.0 Hz, 2H), 4.07–3.98 (m, 1H), 3.57–3.49 (m, 1H), 3.47 (d, *J* = 14.2 Hz, 1H), 3.29 (d, *J* = 14.2 Hz, 1H), 3.23–3.14 (m, 1H), 3.10–3.01 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.10, 143.10, 139.86, 134.32, 134.18, 133.37, 132.10, 129.67, 129.33, 129.25, 128.79, 128.15, 127.12, 126.73, 120.61, 92.36, 41.83, 40.63, 34.83, 17.86; LRMS (ESI) *m/z*: 358 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{23}NO_2 + H^+$ 358.1802, found 358.1807.

Preparation and Characterization Data of Compounds 4

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with **1aa** (0.2 mmol), **2aa** (0.2 mmol), DCE (2.0 mL) and then capped with a septa. After that, the vial was kept in the pre-heated oil bath at 120 °C for 12 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to give the desired product **4aa**. Compounds **4ab**–**4ba** were prepared with the detailed conditions indicated in Scheme 6 following the similar procedure carried out for compound **4aa**.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-methyleneisoindolin-1-one (4aa): White solid (53.4 mg, yield 91 %), m.p. 101–102 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.69–7.64 (m, 1H), 7.57–7.53 (m, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.95 (s, 2H), 5.45 (d, *J* = 2.3 Hz, 1H), 5.12 (d, *J* = 2.3 Hz, 1H), 3.95–3.84 (m, 2H), 2.84–2.72 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.82, 147.21, 145.69, 140.67, 136.02, 132.32, 132.29, 129.71, 128.51, 122.45, 121.74, 120.64, 109.24, 108.13, 100.71, 90.62, 40.41, 33.50; LRMS (ESI) *m/z*: 294 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{15}NO_3 + H^+$ 294.1125, found 294.1124.

2-(3,4-Dimethoxyphenethyl)-3-methyleneisoindolin-1-one (4ab): White solid (56.8 mg, yield 92 %), m.p. 99–100 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.61–7.55 (m, 1H), 7.52–7.46 (m, 1H), 6.79 (s, 2H), 6.72 (s, 1H), 5.18 (d, *J* = 2.2 Hz, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 4.00–3.94 (m, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.96–2.88 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.07, 149.01, 147.80, 141.79, 136.41, 132.00, 131.20, 129.60, 129.44, 123.21, 120.84, 119.95, 112.10, 111.36, 88.83, 55.99, 55.90, 41.26, 34.17; LRMS (ESI) *m/z*: 310 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{19}NO_3 + H^+$ 310.1438, found 310.1441.

2-(2-Methoxyphenethyl)-3-methyleneisoindolin-1-one (4ac): White solid (45.9 mg, yield 82 %), m.p. 90–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.73–7.64 (m, 2H), 7.58–7.53 (m, 1H), 7.23–7.16 (m, 1H), 7.13–7.07 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.85–6.79 (m, 1H), 5.44 (d, *J* = 1.8 Hz, 1H), 5.04 (d, *J* = 1.9 Hz, 1H), 3.93–3.84 (m, 2H), 3.77 (s, 3H), 2.91–2.81 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.75, 157.42, 140.87, 136.02, 132.22, 130.27, 129.67, 128.59, 128.03, 126.29, 122.40, 120.59, 120.34, 110.64, 90.00, 55.29, 38.74, 29.01; LRMS (ESI) *m/z*: 280 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NO_2 + H^+$ 280.1332, found 280.1331.

2-(4-Methoxyphenethyl)-3-methyleneisoindolin-1-one (4ad): Colorless oil (46.8 mg, yield 84 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.60–7.54 (m, 1H), 7.52–7.46 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.86–6.80 (m, 2H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.83 (d, *J* = 2.3 Hz, 1H), 4.00–3.90 (m, 2H), 3.78 (s, 3H), 2.96–2.86 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.04, 158.39, 141.78, 136.42, 131.96, 130.68, 129.89, 129.56, 129.45, 123.19, 119.95, 114.08, 88.78, 55.35, 41.34, 33.77; LRMS (ESI) *m/z*: 280 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NO_2 + H^+$ 280.1332, found 280.1336.

3-Methylene-2-(3-methylphenethyl)isoindolin-1-one (4ae): Colorless oil (45.9 mg, yield 87 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.81 (m, 1H), 7.70–7.67 (m, 1H), 7.60–7.55 (m, 1H), 7.52–7.47 (m, 1H), 7.23–7.17 (m, 1H), 7.10–7.04 (m, 3H), 5.21 (d, *J* = 2.4 Hz, 1H), 4.87 (d, *J* = 2.5 Hz, 1H), 4.02–3.94 (m, 2H), 2.96–2.89 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.02, 141.73, 138.53, 138.30, 136.41, 131.96, 129.72, 129.56, 129.44, 128.59, 127.41, 125.88, 123.17, 119.95, 88.76, 41.17, 34.58, 21.46; LRMS (ESI) *m/z*: 264 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NO + H^+$ 264.1383, found 264.1384.

3-Methylene-2-(4-methylphenethyl)isoindolin-1-one (4af): White solid (47.6 mg, yield 90 %), m.p. 83–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.60–7.55 (m, 1H), 7.52–7.47 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 5.20 (d, *J* = 2.2 Hz, 1H), 4.85 (d, *J* = 2.3 Hz, 1H), 4.00–3.95 (m, 2H), 2.95–2.91 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.03, 141.78, 136.43, 136.20, 135.53, 131.95, 129.56, 129.48, 129.39, 128.79, 123.19, 119.96, 88.75, 41.24, 34.23, 21.19; LRMS (ESI) *m/z*: 264 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NO + H^+$ 264.1383, found 264.1382.

3-Methylene-2-phenethylisoindolin-1-one (4ag): White solid (40.9 mg, yield 82 %), m.p. 87–88 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.80 (m, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.59–7.54 (m, 1H), 7.51–7.47 (m, 1H), 7.31–7.27 (m, 2H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.25–7.20 (m, 2H), 5.18 (d, *J* = 2.6 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 4.01–3.96 (m, 2H), 2.98–2.94 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.06, 141.79, 138.67, 136.44, 134.05, 132.00, 129.60, 128.95, 128.73, 126.71, 123.22, 119.98, 88.75, 41.17, 34.70; LRMS (ESI) *m/z*: 250 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{15}NO + H^+$ 250.1226, found 250.1226.

2-(2-Fluorophenethyl)-3-methyleneisoindolin-1-one (4ah): White solid (44.2 mg, yield 83 %), m.p. 71–72 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.60–7.55 (m, 1H), 7.52–7.47 (m, 1H), 7.24–7.19 (m, 2H), 7.07–7.01 (m, 2H), 5.19 (d, *J* = 2.6 Hz, 1H), 4.92 (d, *J* = 2.6 Hz, 1H), 4.03–3.97 (m, 2H), 3.04–2.99 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.04, 161.54 (d, $J_{C\text{-}F}$ = 244.6 Hz), 141.65, 136.45, 132.00, 131.43 (d, $J_{C\text{-}F}$ = 4.9 Hz), 129.56, 129.39, 128.62 (d, $J_{C\text{-}F}$ = 8.4 Hz), 125.47 (d, *J* = 15.9 Hz), 124.36 (d, $J_{C\text{-}F}$ = 2.8 Hz), 123.20, 119.99, 115.40 (d, $J_{C\text{-}F}$ = 21.9 Hz), 88.88, 39.59, 28.39; LRMS (ESI) *m/z*: 268 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}FNO + H^+$ 268.1132, found 268.1132.

2-(3-Fluorophenethyl)-3-methyleneisoindolin-1-one (4ai): Colorless oil. (43.7 mg, yield 82 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.69–7.64 (m, 1H), 7.57–7.52 (m, 1H), 7.30–7.25 (m, 1H), 7.11 (dd, *J* = 10.3, 1.5 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.02–6.97 (m, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 5.14 (d, *J* = 2.3 Hz, 1H), 4.00–3.95 (m, 2H), 2.94–2.89 (m, 2H); ^{13}C

NMR (150 MHz, DMSO-d_6) δ = 165.78, 162.13 (d, $J_{C\text{-}F}$ = 242.9 Hz), 141.45 (d, $J_{C\text{-}F}$ = 7.4 Hz), 140.60, 135.96, 132.24, 130.09 (d, $J_{C\text{-}F}$ = 8.4 Hz), 129.64, 128.41, 124.92, 122.39, 120.55, 115.53 (d, $J_{C\text{-}F}$ = 21.0 Hz), 113.10 (d, $J_{C\text{-}F}$ = 20.9 Hz), 90.52, 39.80, 33.36; LRMS (ESI) *m/z*: 268 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}FNO + H^+$ 268.1132, found 268.1132.

2-(4-Fluorophenethyl)-3-methyleneisoindolin-1-one (4aj): Colorless oil (42.7 mg, yield 80 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.60–7.55 (m, 1H), 7.52–7.47 (m, 1H), 7.20–7.17 (m, 2H), 6.99–6.92 (m, 2H), 5.18 (d, *J* = 2.2 Hz, 1H), 4.79 (d, *J* = 2.4 Hz, 1H), 3.99–3.93 (m, 2H), 2.97–2.91 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.06, 161.81 (d, $J_{C\text{-}F}$ = 244.5 Hz), 141.75, 136.36, 134.28 (d, $J_{C\text{-}F}$ = 2.6 Hz), 132.05, 130.38 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.64, 129.34, 123.23, 119.99, 115.51 (d, $J_{C\text{-}F}$ = 21.3 Hz), 88.73, 41.11, 33.82; LRMS (ESI) *m/z*: 268 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}FNO + H^+$ 268.1132, found 268.1128.

2-(4-Chlorophenethyl)-3-methyleneisoindolin-1-one (4ak): Colorless oil (47.7 mg, yield 84 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.59–7.54 (m, 1H), 7.51–7.46 (m, 1H), 7.25–7.23 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.17 (d, *J* = 2.3 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 1H), 3.98–3.93 (m, 2H), 2.96–2.91 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.07, 141.72, 137.05, 136.35, 132.51, 132.08, 130.30, 129.66, 129.29, 128.82, 123.25, 120.01, 88.78, 40.88, 33.99; LRMS (ESI) *m/z*: 286 ([M + H]$^+$, ^{37}Cl), 284 ([M + H]$^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{17}H_{14}ClNO + H^+$ 284.0837, found 284.0840.

2-(4-Bromophenethyl)-3-methyleneisoindolin-1-one (4al): White solid (57.8 mg, yield 88 %), m.p. 124–125 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.67–7.64 (m, 1H), 7.56–7.52 (m, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.19–7.16 (m, 2H), 5.45 (d, *J* = 2.3 Hz, 1H), 5.11 (d, *J* = 2.3 Hz, 1H), 3.97–3.91 (m, 2H), 2.90–2.84 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 165.79, 140.61, 138.01, 135.95, 132.25, 131.11, 131.09, 129.66, 128.39, 122.41, 120.58, 119.43, 90.53, 39.87, 33.08; LRMS (ESI) *m/z*: 330 ([M + H]$^+$, ^{81}Br), 328 ([M + H]$^+$, ^{79}Br); HRMS (ESI) *m/z* calculated for $C_{17}H_{14}BrNO + H^+$ 328.0332, found 328.0333.

3-Methylene-2-(4-(trifluoromethyl)phenethyl)isoindolin-1-one (4am): White solid (50.5 mg, yield 80 %), m.p. 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.62–7.47 (m, 4H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.19 (d, *J* = 2.5 Hz, 1H), 4.80 (d, *J* = 2.5 Hz, 1H), 4.09–3.97 (m, 2H), 3.11–2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.07, 142.72, 141.77, 136.41, 132.15, 129.73, 129.31, 129.13 (q, $J_{C\text{-}F}$ = 32.5 Hz), 125.66 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.30, 123.01, 120.04, 88.62, 40.66, 34.48; LRMS (ESI) *m/z*: 318 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{14}F_3NO + H^+$ 318.1100, found 318.1092.

2-Benzyl-3-methyleneisoindolin-1-one (4an): White solid (41.9 mg, yield 89 %), m.p. 112–113 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.97–7.94 (m, 1H), 7.82–7.79 (m, 1H), 7.72–7.67 (m, 1H), 7.62–7.57 (m, 1H), 7.34–7.29 (m, 2H), 7.28–7.22 (m, 3H), 5.43 (d, *J* = 2.3 Hz, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 4.97 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 166.17, 140.68, 137.23, 136.02, 132.48, 129.79, 128.54, 128.39, 127.16, 126.97, 122.66, 120.68, 91.20, 42.11; LRMS (ESI) *m/z*: 236 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{13}NO + H^+$ 236.1070, found 236.1070.

2-(4-Methoxybenzyl)-3-methyleneisoindolin-1-one (4ao): White solid (49.5 mg, yield 93 %) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60–7.55 (m, 1H), 7.53–7.48 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.85–6.80 (m, 2H), 5.15 (d, *J* = 2.6 Hz, 1H), 4.94 (s, 2H), 4.82 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.37, 158.98, 141.65, 136.52, 132.14, 129.61, 129.34, 129.10, 128.64, 123.42, 120.01, 114.13, 90.10, 55.38, 42.71; LRMS (ESI) *m/z*: 288 [M + Na]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{15}NO_2 + Na^+$ 288.0995, found 288.0998.

2-(3-Chloro-4-fluorobenzyl)-3-methyleneisoindolin-1-one (4ap): Colorless oil (46.7 mg, yield 81 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.64–7.58 (m, 1H), 7.56–7.51 (m, 1H), 7.30 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.17–7.12 (m, 1H), 7.10–7.04 (m, 1H), 5.18 (d, *J* = 2.6 Hz, 1H), 4.94 (s, 2H), 4.75 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.30, 157.52 (d, $J_{C\text{-}F}$ = 248.5 Hz), 141.44, 136.41, 134.00 (d, $J_{C\text{-}F}$ = 3.4 Hz), 132.46, 129.84, 129.41, 129.02, 127.03 (d, $J_{C\text{-}F}$ = 7.2 Hz), 123.57, 121.40 (d, $J_{C\text{-}F}$ = 18.2 Hz), 120.16, 116.90 (d, $J_{C\text{-}F}$ = 21.0 Hz), 90.06, 42.17; LRMS (ESI) *m/z*: 290 ([M + H]$^+$, ^{37}Cl), 288 ([M + H]$^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{16}H_{11}ClFNO + H^+$ 288.0586, found 288.0582.

2-(4-Bromobenzyl)-3-methyleneisoindolin-1-one (4aq): White solid (52.7 mg, yield 84 %), m.p. 91–92 °C· ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90–7.87 (m, 1H), 7.69–7.66 (m, 1H), 7.62–7.58 (m, 1H), 7.55–7.51 (m, 1H), 7.44–7.41 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.16 (d, *J* = 2.5 Hz, 1H), 4.95 (s, 2H), 4.74 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.35, 141.53, 136.46, 135.98, 132.37, 131.92, 129.78, 129.14, 129.00, 123.54, 121.43, 120.11, 90.10, 42.70; LRMS (ESI) *m/z*: 316 ([M + H]$^+$, ^{81}Br), 314 ([M + H]$^+$, ^{79}Br); HRMS (ESI) *m/z* calculated for $C_{16}H_{12}BrNO + H^+$ 314.0175, found 314.0178.

3-Methylene-2-(4-(trifluoromethyl)benzyl)isoindolin-1-one (4ar): White solid (48.9 mg, yield 81 %), m.p. 111–112 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.64–7.60 (m, 1H), 7.58–7.52 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.17 (d, *J* = 2.5 Hz, 1H), 5.06 (s, 2H), 4.73 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.38, 141.51, 140.96, 136.42, 132.47, 129.87 (q, $J_{C\text{-}F}$ = 32.3 Hz), 129.86, 129.06, 127.46, 125.81 (q, $J_{C\text{-}F}$ = 3.3 Hz), 124.16 (q, $J_{C\text{-}F}$ = 272.3 Hz), 123.60, 120.17, 90.12, 42.84; LRMS (ESI) *m/z*: 304 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{12}F_3NO + H^+$ 304.0944, found 304.0940.

3-Methylene-2-(naphthalen-1-ylmethyl)isoindolin-1-one (4as): Pale yellow solid (49.4 mg, yield 87 %), m.p. 193–194 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.64–7.51 (m, 4H), 7.38–7.34 (m, 1H), 7.18–7.14 (m, 1H), 5.50 (s, 2H), 5.16 (d, *J* = 2.5 Hz, 1H), 4.75 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.46, 141.95, 136.57, 133.84, 132.29, 131.62, 130.94, 129.69, 129.28, 129.01, 128.08, 126.57, 125.99, 125.46, 124.06, 123.56, 122.88, 120.07, 90.71, 41.31; LRMS (ESI) *m/z*: 286 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{15}NO + H^+$ 286.1226, found 286.1223.

2-(Cyclopropylmethyl)-3-methyleneisoindolin-1-one (4at): White solid (32.5 mg, yield 82 %), m.p. 78–79 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.70–7.63 (m, 1H), 7.59–7.53 (m, 1H), 5.47 (d, *J* = 2.2 Hz, 1H), 5.15 (d, *J* = 2.2 Hz, 1H), 3.61 (d, *J* = 7.0 Hz, 2H), 1.20–1.05 (m, 1H), 0.49–0.37 (m, 2H), 0.36–0.30 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 166.09, 141.14, 136.01, 132.24, 129.69, 128.64, 122.45, 120.60, 90.46, 42.87, 10.32, 3.57; LRMS (ESI) *m/z*: 200 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{13}NO + H^+$ 200.1070, found 200.1071.

3-Methylene-2-(prop-2-yn-1-yl)isoindolin-1-one (4au): White solid (26.7 mg, yield 73 %), m.p. 129–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.81 (m, 1H), 7.69 (dd, *J* = 4.5, 3.9 Hz, 1H), 7.60–7.56 (m, 1H), 7.51–7.46 (m, 1H), 5.29 (d, *J* = 2.6 Hz, 1H), 5.07 (d, *J* = 2.6 Hz, 1H), 4.58 (d, *J* = 2.5 Hz, 2H), 2.24 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.21, 140.79, 136.39, 132.38, 129.67, 128.90, 123.49, 120.07, 90.13, 77.81, 72.09, 28.74; LRMS (ESI) *m/z*: 184 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_9NO + H^+$ 184.0757, found 184.0757.

2-(2-Methoxyphenyl)-3-methyleneisoindolin-1-one (4av): Yellow oil (21.6 mg, yield 43 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.65–7.60 (m, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.45–7.40 (m, 1H), 7.28 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.10–7.05 (m, 2H), 5.16 (d, *J* = 2.0 Hz, 1H), 4.54 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.83, 156.07, 143.07, 136.66, 132.16, 130.67, 130.35, 129.58, 129.50, 123.64, 123.10, 121.05, 120.23, 112.53, 89.96, 55.94; LRMS (ESI) *m/z*: 252 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{13}NO_2 + H^+$ 252.1019, found 252.1021.

2-(3,4-Dimethylphenyl)-3-methyleneisoindolin-1-one (4aw): White solid (23.6 mg, yield 47 %), m.p. 111–112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.66–7.61 (m, 1H), 7.58–7.53 (m, 1H), 7.26–7.18 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.17 (d, *J* = 1.9 Hz, 1H), 4.47 (d, *J* = 1.9 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.74, 143.18, 138.48, 136.37, 135.82, 133.29, 132.26, 130.59, 129.73, 129.30, 126.83, 126.38, 123.64, 120.22, 90.66, 20.51, 14.34; LRMS (ESI) *m/z*: 250 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{15}NO + H^+$ 250.1226, found 250.1226.

3-Methylene-2-(*o*-tolyl)isoindolin-1-one (4ax): White solid (18.6 mg, yield 40 %), m.p. 124–125 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.55 (m, 1H), 7.39–7.36 (m, 2H), 7.35–7.30 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 5.18 (d, *J* = 2.1 Hz, 1H), 4.49 (d, *J* = 2.1 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.62, 142.98, 137.34, 136.43, 133.43, 132.33, 131.28, 129.80, 129.36, 129.32, 129.19, 127.08, 123.70, 120.26, 90.51, 17.85; LRMS (ESI) *m/z*: 236 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{13}NO + H^+$ 236.1070, found 236.1065.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzylideneisoindolin-1-one (4ay): White solid (56.7 mg, yield 77 %), m.p. 161–162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.45–7.41 (m, 3H), 7.40–7.36 (m, 3H), 7.32–7.27 (m, 1H), 7.26–7.24 (m, 1H), 6.78–6.70 (m, 3H), 6.42 (s, 1H), 5.92 (s, 2H), 4.09–4.03 (m, 2H), 2.99–2.92 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.56, 147.87, 146.38, 136.23, 135.27, 135.11, 132.53, 131.58, 130.38, 129.66, 129.33, 128.80, 127.94, 123.28, 123.23, 121.95, 110.41, 109.47, 108.55, 101.02, 41.47, 34.63; LRMS (ESI) *m/z*: 392 $[M + Na]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{19}NO_3 + Na^+$ 392.1257, found 392.1256.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzylidene-6-methoxyisoindolin-1-one (4az): White solid (54.5 mg, yield 68 %), m.p. 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.32 (m, 5H), 7.31 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.81–6.63 (m, 3H), 6.33 (s, 1H), 5.91 (s, 2H), 4.09–4.00 (m, 2H), 3.85 (s, 3H), 3.01–2.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.49, 160.91, 147.87, 146.37, 136.05, 135.46, 132.55, 132.22, 129.71, 128.75, 127.81, 127.77, 124.54, 121.95, 119.59, 109.48, 108.98, 108.53, 105.99, 101.01, 55.82, 41.51, 34.72; LRMS (ESI) *m/z*: 400 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{25}H_{21}NO_4 + H^+$ 400.1543, found 400.1532.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzylidene-5-chloroisoindolin-1-one (4ba): White solid (57.2 mg, yield 71 %), m.p. 167–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.53–7.31 (m, 6H), 7.19 (d, *J* = 1.6 Hz, 1H), 6.82–6.61 (m, 3H), 6.45 (s, 1H), 5.91 (s, 2H), 4.10–3.99 (m, 2H), 3.01–2.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.60, 147.92, 146.46, 137.84, 136.51, 135.27, 134.63, 132.36, 129.68, 129.52, 128.96, 128.72, 128.39, 124.37, 123.52, 121.95, 111.66, 109.45, 108.58, 101.06, 41.64, 34.57; LRMS (ESI) *m/z*: 406 ($[M + H]^+$, ^{37}Cl), 404 ($[M + H]^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{24}H_{18}ClNO_3 + H^+$ 404.1048, found 404.1041.

Preparation and Characterization Data of Compounds 5

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with **1aa** (0.2 mmol), **2aa** (0.2 mmol), DCE (2.0 mL) and then capped with a septa. After that, the vial was kept in the preheated oil bath at 120 °C for 12 h. After cooling to room temperature, TFA (0.4 mmol) was added and the resulting mixture was stirred at 140 °C for another 4 h. After cooling, a saturated $NaHCO_3$ solution (18 mL) was added. The mixture obtained was then extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give the desired product **5aa**. Compounds **5ab**–**5at** were prepared with the detailed conditions indicated in Scheme 7 following the similar procedure carried out for compound **5aa**.

12b-Methyl-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (5aa): White solid (50.4 mg, yield 86 %), m.p. 159–160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.72–7.62 (m, 2H), 7.56 (s, 1H), 7.52–7.45 (m, 1H), 6.66 (s, 1H), 5.99 (d, *J* = 0.9 Hz, 1H), 5.91 (d, *J* = 0.8 Hz, 1H), 4.39–4.25 (m, 1H), 3.34–3.24 (m, 1H), 2.80–2.62 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.53, 150.95, 146.17, 146.09, 132.20, 132.09, 130.28, 128.39, 126.51, 123.42, 122.80, 108.71, 106.75, 100.97, 63.62, 34.55, 29.26, 28.23; LRMS (ESI) *m/z*: 294 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{15}NO_3 + H^+$ 294.1125, found 294.1121.

2,3-Dimethoxy-12b-methyl-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (5ab): White solid (52.2 mg, yield 84 %), m.p. 188–189 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.63–7.56 (m, 1H), 7.46 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.16 (s, 1H), 6.57 (s, 1H), 4.62 (ddd, *J* = 13.3, 6.5, 1.3 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.42–3.28 (m, 1H), 3.09–2.97 (m, 1H), 2.71 (dd, *J* = 16.1, 3.4 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.54, 150.82, 148.27, 147.75, 131.97, 131.35, 131.06, 128.40, 125.96, 124.05, 122.17, 111.98, 109.37, 63.67, 56.37, 55.97, 35.13, 29.39, 29.01; LRMS (ESI) *m/z*: 310 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{19}NO_3 + H^+$ 310.1438, found 310.1432.

2-Ethoxy-3-methoxy-12b-methyl-5,6-dihydroisoindolo[1,2-*a*]-isoquinolin-8(12b*H*)-one (5ac): Pale yellow oil (52.8 mg, yield 82 %), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33–8.20 (m, 1H), 7.72–7.63 (m, 2H), 7.53–7.44 (m, 1H), 7.38 (s, 1H), 6.68 (s, 1H), 4.40–4.29 (m, 1H), 4.21–4.11 (m, 1H), 4.08–3.98 (m, 1H), 3.69 (s, 3H), 3.41–3.33 (m, 1H), 2.84–2.63 (m, 2H), 1.80 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.52, 151.14, 147.95, 146.59, 132.16, 130.82, 130.35, 128.28, 125.27, 123.37, 122.81, 112.29, 111.39, 64.16, 63.37, 55.41, 34.65, 28.77, 28.17, 14.72; LRMS (ESI) *m/z*: 324 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{21}NO_3 + H^+$ 324.1594, found 324.1597.

3-Methoxy-12b-methyl-2-propoxy-5,6-dihydroisoindolo[1,2-*a*]-isoquinolin-8(12b*H*)-one (5ad): White solid (57.5 mg, yield 85 %), m.p. 114–115 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.76–7.63 (m, 2H), 7.56–7.44 (m, 1H), 7.38 (s, 1H), 6.67 (s, 1H), 4.42–4.24 (m, 1H), 4.12–4.01 (m, 1H), 3.99–3.86 (m, 1H), 3.69 (s, 3H), 3.36–3.32 (m, 1H), 2.80–2.66 (m, 2H), 1.80 (s, 3H), 1.76- 1.67 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.54, 150.85, 148.75, 147.16, 131.93, 131.28, 130.99, 128.33, 125.99, 123.96, 122.15, 112.33, 111.44, 71.13, 63.62, 56.01, 35.12, 29.37, 28.98, 22.59, 10.59; LRMS (ESI) *m/z*: 338 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{23}NO_3 + H^+$ 338.1751, found 338.1751.

2-Isopropoxy-3-methoxy-12b-methyl-5,6-dihydroisoindolo-[1,2-*a*]isoquinolin-8(12b*H*)-one (5ae): White solid (54.0 mg, yield 80 %), m.p. 70–71 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.26 (d, *J* =

8.0 Hz, 1H), 7.70–7.63 (m, 2H), 7.52–7.46 (m, 1H), 7.40 (s, 1H), 6.68 (s, 1H), 4.72–4.60 (m, 1H), 4.34 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.67 (s, 3H), 3.39–3.36 (m, 1H), 2.81–2.64 (m, 2H), 1.79 (s, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ = 166.55, 151.22, 149.01, 145.13, 132.11, 130.86, 130.35, 128.30, 125.73, 123.28, 122.82, 114.34, 112.62, 70.51, 63.31, 55.45, 34.66, 28.79, 28.11, 22.09, 21.53; LRMS (ESI) *m/z*: 338 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{23}NO_3$ + H$^+$ 338.1751, found 338.1751.

11b-Methyl-4,5-dihydrothieno[3′,2′:3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (5ah): Yellow solid (36.2 mg, yield 71 %), m.p. 199–200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.76–7.73 (m, 1H), 7.62–7.56 (m, 1H), 7.48–7.42 (m, 1H), 7.20 (d, *J* = 5.3 Hz, 1H), 7.15 (dd, *J* = 5.3, 0.8 Hz, 1H), 4.74 (ddd, *J* = 13.4, 6.4, 0.9 Hz, 1H), 3.36 (ddd, *J* = 13.4, 11.7, 4.6 Hz, 1H), 3.06–2.93 (m, 1H), 2.87 (dd, *J* = 16.1, 4.4 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.96, 150.16, 137.65, 133.51, 132.17, 131.00, 128.45, 124.25, 124.11, 123.81, 122.02, 63.86, 35.22, 27.78, 25.49; LRMS (ESI) *m/z*: 256 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{13}NOS$ + H$^+$ 256.0791, found 256.0785.

11b-Methyl-4,5-dihydrothieno[2′,3′:3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (5ai): Pale yellow solid (40.9 mg, yield 80 %), m.p. 155–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.64–7.57 (m, 1H), 7.50 –7.41 (m, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 6.73 (d, *J* = 5.0 Hz, 1H), 4.68 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.39–3.28 (m, 1H), 2.90–2.79 (m, 1H), 2.77–2.65 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.81, 150.33, 138.44, 133.50, 132.22, 130.88, 128.58, 127.08, 124.01, 123.69, 122.01, 63.71, 34.95, 29.56, 26.24; LRMS (ESI) *m/z*: 256 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{13}NOS$ + H$^+$ 256.0791, found 256.0796.

12b-Methyl-5,6-dihydropyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoindol-8(12b*H*)-one (5aj): Pale yellow solid (41.8 mg, yield 88 %), m.p. 156–157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.65–7.55 (m, 1H), 7.51–7.38 (m, 1H), 6.53 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.25 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.20–6.11 (m, 1H), 4.72–4.68 (m, 1H), 4.03–3.91 (m, 2H), 3.61–3.55 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.12, 150.96, 132.61, 130.66, 130.39, 128.44, 123.99, 122.08, 119.61, 108.61, 104.22, 61.87, 44.46, 35.33, 28.99; LRMS (ESI) *m/z*: 239 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N_2O$ + H$^+$ 239.1179, found 239.1177.

11b-Methyl-4,5-dihydro-3*H*-pyrrolo[3′,2′:3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (5ak): Pale yellow solid (35.4 mg, yield 74 %), m.p. 236–237 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.60–7.52 (m, 1H), 7.45–7.37 (m, 1H), 6.70–6.61 (m, 1H), 6.34–6.26 (m, 1H), 4.70 (dd, *J* = 13.4, 6.3 Hz, 1H), 3.36 (ddd, *J* = 13.3, 11.7, 4.8 Hz, 1H), 2.87 (ddd, *J* = 15.4, 11.6, 6.4 Hz, 1H), 2.62 (dd, *J* = 15.3, 4.7 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.29, 151.84, 132.06, 130.68, 128.03, 123.89, 123.63, 121.68, 120.84, 117.42, 104.56, 62.83, 34.85, 28.03, 23.20; LRMS (ESI) *m/z*: 239 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N_2O$ + H$^+$ 239.1179, found 239.1177.

13b-Methyl-6,7-dihydroisoindolo[1′,2′:3,4]pyrazino[1,2-*a*]indol-9(13b*H*)-one (5al): Pale yellow solid (35.9 mg, yield 62 %), m.p. 235–236 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 13.5, 7.6 Hz, 2H), 7.70–7.64 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52–7.46 (m, 1H), 7.28–7.25 (m, 1H), 7.22–7.16 (m, 1H), 7.15–7.08 (m, 1H), 6.64 (s, 1H), 4.87 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.27 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.03–3.93 (m, 1H), 3.70 (ddd, *J* = 13.6, 12.1, 4.8 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.79, 150.22, 137.85, 135.83, 132.73, 130.54, 128.77, 127.85, 124.13, 122.23, 121.95, 120.64, 120.55, 109.36, 98.06, 61.82, 41.47, 34.76, 28.85; LRMS (ESI) *m/z*: 289 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O$ + H$^+$ 289.1335, found 289.1332.

13b-Methyl-6,7-dihydro-5*H*-benzo[1,2]indolizino[7,8-*b*]indol-9(13b*H*)-one (5am): Pale yellow solid (43.6 mg, yield 76 %), m.p. 223–224 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.61–7.55 (m, 1H), 7.45–7.37 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.24–7.19 (m, 1H), 7.19–7.13 (m, 1H), 4.76 (dd, *J* = 13.2, 6.1 Hz, 1H), 3.43–3.25 (m, 1H), 3.15–2.94 (m, 1H), 2.71 (dd, *J* = 15.8, 4.1 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.75, 151.40, 136.16, 132.11, 131.93, 130.84, 128.20, 124.84, 123.99, 122.83, 121.77, 120.03, 119.24, 113.15, 111.46, 64.24, 35.13, 26.29, 24.14; LRMS (ESI) *m/z*: 289 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O$ + H$^+$ 289.1335, found 289.1330.

13b-Methyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino-[8,7-*b*]indol-5-one (5an): White solid (37.7 mg, yield 65 %), m.p. 283–284 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.63–7.55 (m, 1H), 7.49–7.42 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.20–7.13 (m, 1H), 7.11–7.06 (m, 1H), 4.83 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.45 (ddd, *J* = 13.4, 11.6, 4.9 Hz, 1H), 2.99 (ddd, *J* = 15.5, 11.5, 6.3 Hz, 1H), 2.87 (dd, *J* = 15.5, 4.4 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.41, 148.97, 136.53, 134.89, 132.28, 131.24, 128.88, 126.78, 124.51, 122.63, 121.54, 120.07, 118.87, 111.25, 108.30, 7 62.40, 35.85, 26.42, 21.95; LRMS (ESI) *m/z*: 289 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O$ + H$^+$ 289.1335, found 289.1330.

12b-Benzyl-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (5ao): Colorless oil (51.6 mg, yield 70 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.44 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.69–7.58 (m, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 7.37–7.33 (m, 1H), 7.05–6.92 (m, 3H), 6.81 (dd, *J* = 6.3, 3.0 Hz, 2H), 6.72 (s, 1H), 6.04 (s, 1H), 5.95 (s, 1H), 4.39–4.25 (m, 1H), 3.70 (d, *J* = 13.9 Hz, 1H), 3.54–3.43 (m, 2H), 2.82–2.66 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.10, 148.31, 146.86, 146.63, 134.85, 131.92, 131.60, 131.26, 129.93, 128.41, 127.87, 127.58, 126.91, 123.75, 122.85, 109.31, 106.34, 101.32, 67.35, 46.91, 35.56, 29.92; LRMS (ESI) *m/z*: 370 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{19}NO_3$ + H$^+$ 370.1438, found 370.1436.

12b-Benzyl-2-ethoxy-3-methoxy-5,6-dihydroisoindolo[1,2-*a*]-isoquinolin-8(12b*H*)-one (5ap): White solid (54.2 mg, yield 68 %), m.p. 170–171 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.44 (d, *J* = 7.7 Hz, 1H), 7.68–7.62 (m, 1H), 7.61 (s, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 7.37–7.32 (m, 1H), 7.02–6.97 (m, 3H), 6.83 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.72 (s, 1H), 4.42–4.32 (m, 1H), 4.28–4.19 (m, 1H), 4.13–4.06 (m, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.71 (s, 3H), 3.47–3.41 (m, 2H), 2.81–2.69 (m, 2H), 1.37 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.10, 148.82, 148.59, 146.92, 134.99, 132.02, 131.53, 130.03, 129.94, 128.34, 127.87, 126.90, 126.72, 123.84, 122.73, 112.27, 111.66, 67.04, 65.11, 55.99, 47.00, 35.65, 29.44, 15.00; LRMS (ESI) *m/z*: 400 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{26}H_{25}NO_3$ + H$^+$ 400.1907, found 400.1908.

12b-Benzyl-10-methyl-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (5aq): White solid (50.1 mg, yield 65 %), m.p. 220–221 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.44 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.30 (s,1H), 7.10–6.99 (m, 3H), 6.79–6.73 (m, 2H), 6.57 (s, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 4.55 (ddd, *J* = 13.0, 6.4, 1.3 Hz, 1H), 3.47 (d, *J* = 14.1 Hz, 1H), 3.38 (d, *J* = 14.1 Hz, 1H), 3.29–3.21 (m, 1H), 3.00–2.89 (m, 1H), 2.68 (dd, *J* = 16.1, 3.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.34, 146.82, 146.61, 145.69, 138.51, 135.06, 132.60, 132.06, 131.61, 129.98, 127.90, 127.50, 126.89, 124.03, 122.58, 109.28, 106.40, 101.29, 67.20, 46.93, 35.63, 29.89, 21.29. LRMS (ESI) *m/z*: 384 [M + H]$^+$; HRMS (ESI) *m/z* calculated for $C_{25}H_{21}NO_3$ + H$^+$ 384.1594, found 384.1586.

12b-Benzyl-10-methoxy-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (5ar): White solid (50.9 mg, yield 64 %), m.p. 233–234 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H), 7.13 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.09–7.03 (m, 3H), 6.78–6.72 (m, 2H), 6.58 (s, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 4.55 (ddd, *J* = 13.1, 6.5, 1.5 Hz, 1H), 3.78 (s, 3H), 3.46 (d, *J* = 14.1 Hz, 1H), 3.38 (d, *J* = 14.1 Hz, 1H), 3.32–3.24 (m, 1H), 3.01–2.92 (m, 1H), 2.70 (dd, *J* = 16.3, 3.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.07, 160.13, 146.84, 146.64, 140.62, 135.02, 133.43, 131.74, 129.97, 127.93, 127.33, 126.91, 123.75, 119.97, 109.30, 106.39, 106.30, 101.32, 67.02, 55.76, 46.91, 35.72, 29.96; LRMS (ESI) *m/z*: 400 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{25}H_{21}NO_4 + H^+$ 400.1543, found 400.1537.

12b-Benzyl-10-fluoro-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo-[1,2-*a*]isoquinolin-8(12b*H*)-one (5as): White solid (42.5 mg, yield 55 %), m.p. 205–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.78 (m, 1H), 7.33–7.20 (m, 3H), 7.13–6.99 (m, 3H), 6.75 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.59 (s, 1H), 5.99 (d, *J* = 1.3 Hz, 1H), 5.92 (d, *J* = 1.3 Hz, 1H), 4.57 (ddd, *J* = 13.2, 6.4, 1.6 Hz, 1H), 3.48 (d, *J* = 14.0 Hz, 1H), 3.39 (d, *J* = 14.0 Hz, 1H), 3.30 (ddd, *J* = 13.1, 11.9, 4.5 Hz, 1H), 3.04–2.91 (m, 1H), 2.77–2.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.87 (d, J_{C-F} = 3.4 Hz), 162.90 (d, J_{C-F} = 248.3 Hz), 147.04, 146.77, 143.84 (d, J_{C-F} = 2.6 Hz), 134.65, 134.23 (d, J_{C-F} = 8.6 Hz), 131.07, 129.94, 128.02, 127.50, 127.09, 124.42 (d, J_{C-F} = 8.3 Hz), 118.98 (d, J_{C-F} = 23.6 Hz), 110.44 (d, J_{C-F} = 23.2 Hz), 109.43, 106.25, 101.42, 67.22, 46.90, 35.73, 29.93; LRMS (ESI) *m/z*: 388 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{18}FNO_3 + H^+$ 388.1343, found 388.1333.

12b-Benzyl-11-chloro-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo-[1,2-*a*]isoquinolin-8(12b*H*)-one (5at): White solid (51.8 mg, yield 64 %), m.p. 233–234 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.33 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.29–7.22 (m, 1H), 7.15–7.00 (m, 3H), 6.84–6.71 (m, 2H), 6.59 (s, 1H), 6.01 (s, 1H), 5.93 (s, 1H), 4.55 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.49 (d, *J* = 14.0 Hz, 1H), 3.36 (d, *J* = 14.0 Hz, 1H), 3.31–3.17 (m, 1H), 3.03–2.87 (m, 1H), 2.68 (dd, *J* = 16.1, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.08, 150.05, 147.14, 146.84, 137.94, 134.54, 130.48, 129.98, 128.97, 128.07, 127.77, 127.13, 124.95, 123.30, 109.47, 106.20, 101.47, 67.29, 46.98, 35.76, 29.91; LRMS (ESI) *m/z*: LRMS (ESI) *m/z*: 406 ($[M + H]^+$, ^{37}Cl), 404 ($[M + H]^+$, ^{35}Cl); HRMS (ESI) *m/z* calculated for $C_{24}H_{18}ClNO_3 + H^+$ 404.1048, found 404.1041.

Preparation and Characterization Data of Compound 6aw

To a solution of compound **3aw** (0.2 mmol) in dry DMF (8.0 mL) was added NaH (0.3 mmol) portionwise at 0 °C, then the mixture was stirred at 0 °C for 0.5 h. After that, CH_3I (0.24 mmol) was added, and the resulting mixture was stirred at room temperature for 3.5 h. Then the reaction mixture was diluted with H_2O (20.0 mL) and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give compound **6aw**.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzyl-3-methoxyisoindolin-1-one (6aw): Colorless oil (68.1 mg, yield 85 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63–7.58 (m, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.51–7.46 (m, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.10–7.04 (m, 3H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.88–6.82 (m, 3H), 6.78 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.99 (s, 2H), 3.63–3.56 (m, 2H), 3.51 (d, *J* = 13.9 Hz, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 2.95–2.88 (m, 2H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 166.66, 147.33, 145.68, 142.30, 134.71, 132.94, 132.30, 131.78, 129.99, 129.78, 127.65, 126.61, 123.39, 122.41, 121.59, 109.09, 108.25, 100.71, 95.62, 50.18, 41.73, 40.90, 33.68; LRMS (ESI) *m/z*: 402 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{25}H_{23}NO_4 + H^+$ 402.1700, found 402.1701.

Preparation and Characterization Data of Compound 6ay

To a solution of **4ay** (0.2 mmol) in MeOH (12 mL) was added 10 % Pd/C catalyst (15.0 mg), and the resulting mixture was stirred under H_2 atmosphere at room temperature for 12 h. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give compound **6ay**.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-benzylisoindolin-1-one (6ay): Colorless oil (68.2 mg, yield 92 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82–7.78 (m, 1H), 7.43–7.38 (m, 2H), 7.31–7.22 (m, 3H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.97–6.89 (m, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.68 (s, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 5.92 (s, 2H), 4.60 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.29–4.14 (m, 1H), 3.42–3.32 (m, 1H), 3.26 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.94–2.78 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 168.3, 147.8, 146.2, 145.0, 136.2, 132.7, 132.2, 131.0, 129.4, 128.6, 128.2, 127.1, 123.5, 122.8, 121.7, 109.2, 108.4, 100.9, 60.7, 42.4, 38.6, 34.6. LRMS (ESI) *m/z*: 394 $[M + Na]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{21}NO_3 + Na^+$ 394.1414, found 394.1416.

Preparation and Characterization Data of Compound 6ao

To a suspension of $LiAlH_4$ (0.4 mmol) and $AlCl_3$ (0.4 mmol) in anhydrous THF was added a THF solution of **5ao** (0.2 mmol) dropwise at 0 °C. After addition, the mixture was stirred at room temperature for 2 h. Then dichloromethane (20.0 mL) was added to dilute the reaction mixture, and water was added dropwise at 0 °C to quench the reaction. The solid which precipitated out was removed by filtration, and the organic phase obtained was dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give compound **6ao**.

12b-Benzyl-5,6,8,12b-tetrahydro-[1,3]dioxolo[4,5-*g*]isoindolo-[1,2-*a*]isoquinoline (6ao): Colorless oil (51.6 mg, yield 73 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.40–7.35 (m, 1H), 7.31–7.27 (m, 1H), 7.26–7.22 (m, 5H), 7.21–7.17 (m, 2H), 6.62 (s, 1H), 6.06 (d, *J* = 1.5 Hz, 1H), 5.96 (d, *J* = 1.5 Hz, 1H), 4.29 (d, *J* = 12.9 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 3.65 (d, *J* = 13.9 Hz, 1H), 3.44 (d, *J* = 13.9 Hz, 1H), 3.22–3.13 (m, 3H), 2.45–2.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.2, 146.1, 145.8, 139.4, 138.5, 133.9, 130.7, 128.3, 127.5, 127.0, 126.7, 126.0, 123.4, 122.7, 108.8, 107.1, 100.8, 71.1, 54.7, 47.6, 42.5, 23.2. LRMS (ESI) *m/z*: 356 $[M + H]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{21}NO_2 + H^+$ 356.1645, found 356.1649.

Preparation and Characterization Data of Compound 1aa-a

Condition A: A suspension of 2-ethynylbenzoic acid **1aa** (0.2 mmol) in H_2O (2.0 mL) in a 25 mL Schlenk tube was stirred at 100 °C for 5 h. After cooling, the reaction mixture was diluted with H_2O (15.0 mL) and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give compound **1aa-a**.

Condition B: A suspension of 2-ethynylbenzoic acid 1aa (0.2 mmol) in DCE (2.0 mL) in a 25 mL Schlenk tube was stirred at 120 °C for 12 h. After cooling, the reaction mixture was diluted with H_2O (15.0 mL) and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was purified by flash chromatography on silica gel to give compound **1aa-a**.

3-Methyleneisobenzofuran-1(3*H*)-one (1aa-a): Colorless oil (Condition A: 9.4 mg, yield 32 %; Condition B: 17.8 mg, yield 61 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.90–7.83 (m, 1H), 7.74–7.66 (m, 1H), 5.62 (d, *J* = 3.0 Hz,

1H), 5.32 (d, J = 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.02, 151.94, 139.12, 134.61, 130.60, 125.42, 125.22, 120.73, 91.44; LRMS (ESI) m/z: 147 $[M + H]^+$; HRMS (ESI) m/z calculated for $C_9H_6O_2 + H^+$ 147.0441, found 147.0438.

Deposition Number 1984364 (for **4az**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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