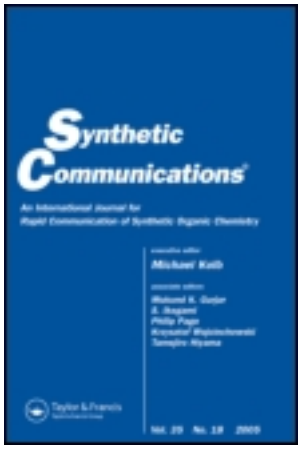

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ONE-POT SYNTHESIS OF ISOINDOLINONES VIA THREE-COMPONENT MANNICH/LACTAMIZATION CASCADE REACTION

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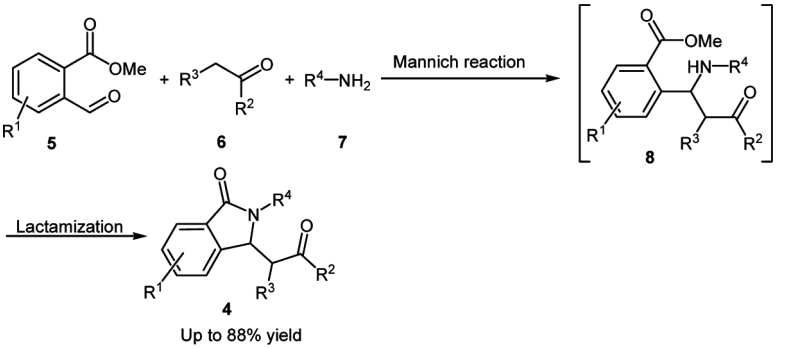
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of 3-substituted 2,3-dihydroisoindolin-1-ones was achieved with good yields (up to 88%). The process features broad substrate scope, high efficiency, and simplicity, using an one-pot, three-component Mannich/lactamization cascade reaction in the absence or presence of p-toluenesulfonic acid.*

Keywords Cascade reaction; isoindolinone; lactamization; Mannich reaction; three-component

INTRODUCTION

Molecules containing 3-substituted isoindolinone skeletons have drawn much attention in recent years because of their broad distribution and biological activities.[1] Typical examples include clinically used anxiolytic drugs pagoclone (**1**) and pazinaclone (**2**),[2] anticonvulsant agent zopiclone (**3**) (Fig. 1),[3] as well as other

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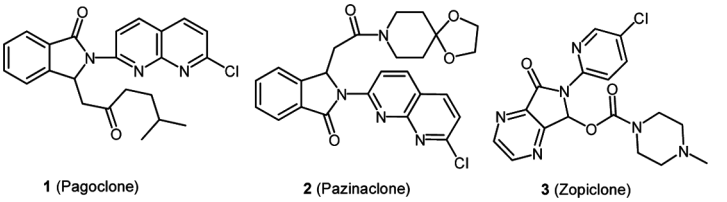
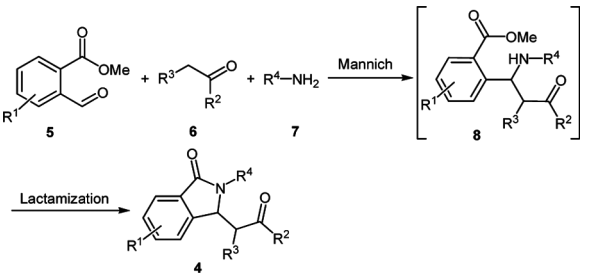


Figure 1. Examples of three isoindolinone therapeutic agents.



Scheme 1. The synthetic route to 2,3-disubstituted isoindolinones via a Mannich/lactamization cascade reaction.

therapeutic agents.[4] Despite their synthetic and medicinal importance, only a handful of synthetic methods relying on the use of a strong base[5] or metal-mediated catalysis[6] are available. More efficient synthetic protocols therefore are still needed. In this communication, we report an efficient three-component Mannich/lactamization cascade process for the facile synthesis of 3-substituted isoindolinones under mild reaction conditions.

The Mannich reaction is a cornerstone of synthetic organic chemistry that has afforded a multitude of nitrogenous compounds. As a result, the reaction has long-standing interest to organic chemists. An abundance of imaginative reagents, catalysts, and protocols have been devised for the synthesis of structurally diversified building blocks and pharmaceutical products.[7] We envision that through the de novo design of proper substrates and careful manipulation of functional group reactivity, a one-pot, three-component strategy with incorporation of an unprecedented Mannich-initiated lactamization reaction sequence can be applied for the efficient preparation of synthetically and biologically significant 3-substituted isoindolinones (Scheme 1).

RESULTS AND DISCUSSION

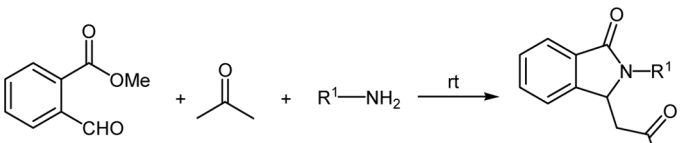
In the proposed process, 2-formylbenzoate **5** is the essential reactant, which serves as an acceptor for the Mannich reaction and also as a substrate for the subsequent lactamization. Although the Mannich reaction between aryl aldehydes and ketones has been intensively studied, to our knowledge, the version of 2-formyl-

benzoate **5** with ketones **6** and amines **7** has not been reported. A classic intermolecular three-component Mannich reaction, which consists of an amine and two different carbonyl species, is plagued by undesired side reactions, such as deamination and formation of methylene bisketones.[8] Moreover, because of the highly sensitive nature of both substrate structures and reaction conditions, the Mannich reaction with 2-formylbenzoate **5** requires optimal reaction conditions, which are also suitable for the subsequent lactamization process.

In an initial exploration, we found that the reaction occurred smoothly between methyl 2-formylbenzoate (**5a**), acetone (**6a**), and 4-methoxyaniline (**7a**, R^4=4-MeO-Ph) (Table 1, entry 1). This result led to our focus on the Mannich/lactamization cascade reaction in the absence of catalyst. To our knowledge, a catalyst-free Mannich/lactamization cascade reaction is unprecedented, although several catalyst-free Mannich reactions have been documented.[9]

We first examined the effect on reactivity of a range of substituted anilines and aliphatic amines in acetone at ambient temperature using Mannich acceptor methyl 2-formylbenzoate and Mannich donor acetone. With respect to anilines, the substituent pattern on phenyl played a very important role in the Mannich/lactamization process. The result revealed that anilines with electron-withdrawing and electron-donating substituents at the *para*-position were very reactive and gave good yields (78–84%) of the isoindolinones **4** (Table 1, entries 1–4). However, anilines with electron-donating substituents at the *ortho*- and *meta*-position gave only a trace amount of corresponding products (Table 1, entries 5 and 6). We speculated that the lactamization was delicately affected by the electronic effects (*meta*-position) and steric hindrance (*ortho*-position) of the ring substituents, indicating the structural sensitivity of the Mannich process. On the other hand, no reaction

Table 1. Scope of amines in the three-component catalyst-free Mannich/lactamization process[a]

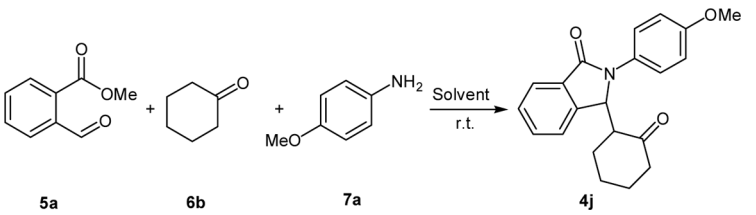


5a **6a** **7** **4**

Entry	R^1	Time (h)	Products	Yield[b] (%)
1	4-MeO-Ph	1	**4a**	82
2	Ph	4	**4b**	78
3	4-Cl-Ph	4	**4c**	84
4	4-Me-Ph	4	**4d**	80
5	2-MeO-Ph	12	**4e**	<5
6	3-MeO-Ph	8	**4f**	Complex
7	n-Bu	24	**4g**	No reaction
8	$PhCH_2$	24	**4h**	No reaction
9	Cyclohexyl	24	**4i**	No reaction

[a]**5a** (0.2 mmol), acetone (0.8 mL), and amine **7** (0.2 mmol) were used.
[b]Isolated yield.

Table 2. Effect of solvent on the three-component cascade reaction[a]



5a 6b 7a 4j

Entry	Solvent	Time (h)	Yield[b] (%)
1	CH_2Cl_2	1	88
2	$CHCl_3$	1	85
3	MeOH	1	68
4	i-PrOH	1	73
5	MeCN	1	52
6	DMF	1	50
7	H_2O	12	<5

[a]**5a** (0.2 mmol), cyclohexanone (0.2 mmol), 4-methoxybenzenamine (0.2 mmol), and solvent (0.5 mL) were used.
[b]Isolated yield.

occurred with aliphatic amines such as n-butylamine, benzylamine, and cyclohexylamine (Table 1, entries 7–9) under the catalyst-free condition.

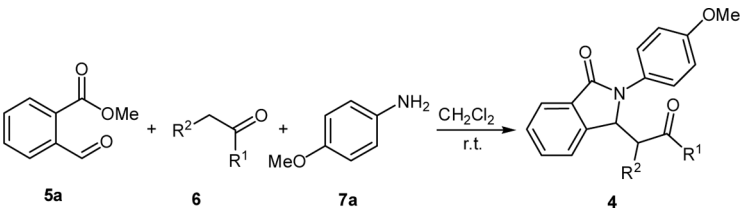
The reaction media had a signicicant impact on the cascade reaction (Table 2). In halogenated solvents (entries 1 and 2), the process proceeded smoothly to give 3-disubstituted isoindolinone **4j** in good yield; whereas in alcoholic media (entries 3 and 4) and polar aprotic solvents (entries 5 and 6), deamination was observed, resulting in slighly lower reaction yields. In addition, water is not suitable for the process (entry 7). Based on these experimental results, dichloromethane (DCM) was selected as solvent for exploration of the generality of the process.

To examine the scope of the Mannich donor, three ketones and two dicarbonyl compounds were tested. As shown in Table 3, under the optimal reaction conditions, unsymmetric ketones smoothly participated in the process. As represented by butanone, the reaction afforded a mixture of regioisomeric products with a selectivity of 2.5/1 (less substituted product is major) (entry 2). Disappointingly, the process was completely inert to Mannich donors such as acetophenone (entry 3). With respect to the dicarbonyl compounds, acetylacetone and ethyl acetoacetate, the major deamination products were predominantly isolated and only a small portion of expected isoindolinones was observed (entries 4 and 5).

The effect of substitution on the phenyl of Mannich acceptor methyl 2-formylbenzoates **5** was probed next. However, the reaction of 5-substituted methyl 2-formylbenzoates with 4-methoxyaniline (**7a**) in acetone failed to give the desired products. We again speculated that the electronic effect of the substituents greatly affects the subsequent lactamization.

To generate a diverse set of 3-substituted isoindolinones, all of the unsuccessful examples under catalyst-free condition were reexamined in the presence of 20 mol%

Table 3. The scope of Mannich donors[a]



5a 6 7a 4

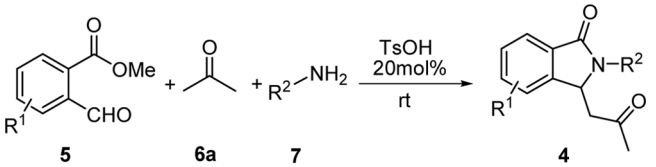
Entry	R^1, R^2	Time (h)	Products	Yield[b] (%)
1	$(CH_2)_4$	1	**4j**	88%
2[a]	Et, H	10	**4k**	70%
3	Ph, H	24	–	No reaction
4	CH_3COCH_2, H	10	–	<5%
5	$EtOOCCH_2$, H	10	–	<5%

[a]**5a** (0.2 mmol), **6** (0.2 mmol), 4-methoxybenzenamine (0.2 mmol), and dichloromethane (0.5 mL) were used.

[b]Regioselectivity ratio 2.5/1 (less substituted product dominantly).

p-toluenesulfonic acid. To our delight, this process proceeded smoothly to give 3-substituted isoindolinones (Table 4). The results showed that primary amines were more suitable substrates than secondary amines, which could be explained by the

Table 4. Scope of the three-component Mannich/lactamization cascade in the presence of p-TsOH[a]



5 6a 7 4

Entry	5	R^2	Time (h)	Products	Yield[b] (%)
1	**5a** (R^1, H)	*n*-Bu	1	**4g**	83
2[a]	**5a** (R^1, H)	Benzyl	10	**4h**	80
3	**5a** (R^1, H)	Cyclohexyl	10	**4i**	45
4	**5a** (R^1, H)	*i*-Bu	20	**4l**	76
5	**5a** (R^1, H)	2-Ethoxyethyl	10	**4m**	85
6	**5n** (R^1, 5-F)	4-MeO-Ph	10	**4n**	71
7	**5o** (R^1, 5-Cl)	4-MeO-Ph	6	**4o**	73
8	**5p** (R^1, 5-Br)	4-MeO-Ph	6	**4p**	86
9	**5q** (R^1, 5-OH)	4-MeO-Ph	6	**4q**	82
10	**5r** (R^1, 5-OMe)	4-MeO-Ph	6	**4r**	78
11	**5s** (R^1, 5-Ph)	4-MeO-Ph	6	**4s**	78
12	**5t** (R^1, 5-NO_2)	4-MeO-Ph	6	**4t**	74

[a]**5** (0.2 mmol), acetone (0.8 mL), amine **7** (0.2 mmol), and the catalyst *p*-toluenesulfonic acid (0.04 mmol) were used.

[b]Isolated yield.

formation of a substantial amount of deamination by-product in the secondary amine case (entry 4).

CONCLUSIONS

In brief, we have developed a one-pot, three-component Mannich/lactamization approach to the synthesis of 3-substituted isoindolinones under catalyst-free conditions or in the presence of *p*-toluenesulfonic acid. This method features a broad substrate scope, simple process (one pot), mild reaction conditions, and moderate to good yields. Therefore, this method should serve as a useful tool for the construction of biologically active molecules with the isoindolinone scaffold.

EXPERIMENTAL

Commercially available reagents were used as received, unless specified. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-400 spectrometers. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; and br, broad. Mass spectrometry was performed on a Micromass GCT CA055. Routine monitoring of reaction was performed by thin-layer chromatography (TLC) with silica gel GF254 precoated on glass plates, and spots were visualized with ultraviolet light. Flash column chromatography was performed on silica gel. Infrared (IR) spectra were recorded on an IR200 spectrometer. Melting points were measured with micro-melting-point apparatus.

General Procedure for Synthesis of 4

Method A (catalyst-free). Ketone (0.2 mmol, 1 eq) and amine (0.2 mmol, 1 eq) were added to a solution of **5a** (0.2 mmol, 1 eq) in solvent (0.8 mL), the resulting solution was stirred at room temperature. The reaction was monitored by TLC. When the reaction was completed, the reaction mixture was diluted with 20 mL DCM, washed with diluted HCl (0.1 M) (10 mL × 3) and brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the residue was purified with flash chromatography on silica gel to give compound **4**.

Method B (catalyzed by *p*-toluenesulfonic acid). The amine (0.2 mmol, 1 eq), ketone (0.2 mmol, 1 eq), and the catalyst *p*-toluenesulfonic acid (8.0 mg, 0.04 mmol, 0.2 eq) were added to a stirred solution of **5a** (0.2 mmol, 1 eq) in solvent (0.8 mL). The resulting mixture was stirred at room temperature. The reaction was monitored by TLC. When the reaction finished, the reaction mixture was diluted with 20 mL DCM, washed with diluted HCl (0.1 M) (10 mL × 3) and brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the residue was purified with flash chromatography on silica gel to give compound **4**.

2-(4-Methoxyphenyl)-3-(2-oxopropyl)isoindolin-1-one (4a). The compound **4a** was prepared following general method A to give a white solid, 48 mg,

yield: 82%. Mp: 127–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.92 (d, 1H, $J = 7.6$ Hz, ArH), 7.42–7.59 (m, 5H, ArH), 6.98 (d, 2H, $J = 7.6$ Hz, ArH), 5.63 (dd, 1H, $J = 9.0$, 3.6 Hz, NCH), 3.84 (s, 3H, OMe), 3.00 (dd, 1H, $J = 17.8$, 3.6 Hz, $COCH_2$), 2.63 (dd, 1H, $J = 17.8$, 9.0 Hz, $COCH_2$), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 166.8, 157.7, 145.0, 132.1, 132.9, 129.3, 128.6, 125.6, 124.0, 122.8, 114.6, 57.1, 55.5, 46.5, 30.7; MS (EI) m/z (%) 295.1 (M^+, 18), 264.0 (17), 238.1 (100), 108.1 (12), 77.0 (9). IR (KBr): 2962, 2917, 1708, 1687, 1518, 1403, 1250 cm^{-1}; HRMS (EI) m/z calcd. for $C_{18}H_{17}NO_3$ 295.1208 (M^+); found 295.1209.

2-Phenyl-3-(2-oxopropyl)isoindolin-1-one (4b). The compound **4b** was prepared following general method A to give a white solid, 41 mg, yield: 78%. Mp: 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.92 (d, 1H, $J = 7.2$ Hz, ArH), 7.56–7.58 (m, 5H, ArH), 7.43–7.53 (m, 4H, ArH), 7.23–7.28 (m, 1H, ArH), 5.72 (dd, 1H, $J = 9.2$, 3.2 Hz, NCH), 3.05 (dd, 1H, $J = 18$, 3.2 Hz, $COCH_2$), 2.64 (dd, 1H, $J = 18.0$, 9.2 Hz, $COCH_2$), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 166.8, 145.0, 136.5, 132.4, 131.8, 129.3, 128.7, 125.7, 124.1, 123.4, 122.8, 56.5, 46.5, 30.7; MS (EI) m/z (%) 265.1 (M^+) (12), 236.1 (12), 222.1 (84), 208.1 (100), 77.0(18); HRMS (EI) m/z calcd. for $C_{17}H_{15}NO_2$ 265.1103 (M^+); found 265.1105.

2-(4-Chlorophenyl)-3-(2-oxopropyl)isoindolin-1-one (4c). The compound **4c** was prepared following general method A to give a white solid, 50 mg, yield: 84%. Mp: 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 (d, 1H, $J = 7.2$ Hz, ArH), 7.46–7.61 (m, 5H, ArH), 7.40–7.43 (m, 2H, ArH), 5.69 (dd, $J = 9.2$, 3.2 Hz, NCH), 3.04 (dd, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.65 (dd, 1H, $J = 18.0$, 9.2 Hz), 2.13 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.8, 166.8, 144.9, 135.2, 132.6, 131.4, 131.0, 129.4, 128.8, 124.3, 124.2, 122.8, 56.3, 46.3, 30.7; MS (EI) m/z (%) 299.1 (M^+) (22), 270.1 (11), 256.1 (43), 242.0 (100), 111.0 (10), 77.0 (4); HRMS (EI) m/z calcd. for $C_{17}H_{14}ClNO_2$: 299.0713 (M^+); found 299.0717.

2-(4-Methylphenyl)-3-(2-oxopropyl)isoindolin-1-one (4d). The compound **4d** was prepared following general method A to give a white solid, 44 mg, yield: 80%. Mp: 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.90 (d, 1H, $J = 3.2$ Hz, ArH), 7.42–7.58 (m, 5H, ArH), 7.24–7.28 (m, 2H, ArH), 5.67 (dd, 1H, $J = 9.2$, 3.2 Hz, ArH), 3.03 (dd, 1H, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.62 (dd, 1H, $J = 18.0$, 9.2 Hz, $COCH_2$), 2.37 (s, 3H, $ArCH_3$), 2.09 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 166.7, 145.0, 135.6, 133.9, 132.2, 131.9, 129.9, 128.6, 124.1, 123.6, 122.8, 56.7, 46.5, 30.7, 20.9; MS (EI) m/z (%) 279.1 (M^+) (24), 236.1 (58), 222.1 (100), 91.1 (13); HRMS (EI) m/z calcd. for $C_{18}H_{17}NO_2$ 279.1259 (M^+); found 279.1260.

2-Butyl-3-(2-oxopropyl)isoindolin-1-one (4g). The compound **4g** was prepared following general method B to give a light yellow oil, 41 mg, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.82 (d, 1H, $J = 7.2$ Hz, ArH), 7.43–7.52 (m, 2H, ArH), 7.38 (d, 1H, $J = 7.2$ Hz, ArH), 5.08 (dd, 1H, $J = 13.6$, 5.2 Hz, CHN), 3.95–4.03 (m, 1H), 2.99–3.06 (m, 2H), 2.70 (dd, 1H, $J = 17.6$, 7.6 Hz), 2.23 (s 3H), 1.49–1.69 (m, 2H), 1.29–1.38 (m, 2H), 0.94 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.8, 168.0, 145.4, 132.0, 131.5, 128.4, 123.6, 122.5,

54.8, 46.4, 39.8, 30.8, 30.2, 20.0, 13.7; IR (neat): 2958, 2931, 2871, 1716, 1679, 1469, 1413, 1365, 1160, 1091, 755, 694, 538 cm^{-1}; MS (EI) m/z (%) 245.1 (M^+) (10), 202.1 (100), 188.1 (23), 146.1 (34), 131.1 (32), 77.0 (4), 43.0 (4); HRMS (EI) m/z calcd. for $C_{15}H_{19}NO_2$ 245.1416 (M^+); found 245.1416.

2-Benzyl-3-(2-oxopropyl)isoindolin-1-one (4h). The compound **4h** was prepared following general method B to give a light yellow solid, 45 mg, yield: 81%. Mp: 89–90 °C. ^1H and ^{13}C NMR spectroscopic data are in agreement with those reported. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.89 (d, 1H, $J = 7.2$ Hz, ArH), 7.46–7.54 (m, 2H, ArH), 7.35 (d, 1H, $J = 7.2$ Hz, ArH), 7.25–7.32 (m, 5H, ArH), 5.02 (t, 1H, $J = 6.0$ Hz), 4.90 (d, 1H, $J = 15.6$ Hz), 4.60 (d, 1H, $J = 15.6$ Hz), 2.89 (dd, $J = 17.8$, 5.6 Hz), 2.69 (dd, $J = 17.8$, 5.6 Hz), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.5, 168.5, 145.5, 137.2, 131.8, 131.7, 128.7, 128.4, 127.9, 127.5, 123.8, 122.4, 55.6, 46.7, 44.7, 30.3; IR (KBr): 3056, 2898, 2845, 1717, 1679, 1433, 1411, 1367, 1303, 1149, 989, 730 cm^{-1}; MS (EI) m/z (%) 279.1 (M^+) (4), 221.1 (28), 188.1 (100), 146.1 (86), 131.0 (23), 91.1 (81), 77.0 (4), 43.0 (4); HRMS (EI) m/z calcd. for $C_{18}H_{17}NO_2$ 279.1259 (M^+); found 279.1260.

2-Cyclohexyl-3-(2-oxopropyl)isoindolin-1-one (4i). The compound **4i** was prepared following the general method B to give a light yellow oil, 24 mg, yield: 45%. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.76 (d, 1H, $J = 7.2$ Hz), 7.39–7.47 (m, 2H), 7.31 (d, 1H, $J = 7.2$ Hz), 5.08 (dd, 1H, $J = 9.2$, 2.8 Hz), 3.19 (dd, 1H, $J = 17.6$, 2.8 Hz), 2.68 (dd, 1H, $J = 17.6$, 8.8, Hz), 2.19 (s, 3H), 1.99–2.03 (m, 1H), 1.76–1.87 (m, 5H), 1.66–1.69 (m, 1H), 1.29–1.41 (m, 2H), 1.15–1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 168.3, 145.9, 134.3, 132.5, 131.5, 129.4, 128.3, 125.7, 123.4, 122.4, 55.6, 53.8, 47.9, 31.2, 31.0, 30.7, 26.1, 26.0, 25.4; HRMS (EI) m/z calcd. for $C_{17}H_{21}NO_2$ 271.1572 (M^+); found 271.1575.

2-(4-Methoxyphenyl)-3-(2-oxocyclohexyl)isoindolin-1-one (4j). The compound **4j** was prepared following general method A to give a white solid, 59 mg, yield: 88%. Mp: 145–147 °C. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 (d, 1H, $J = 7.2$ Hz, ArH), 7.54–7.58 (m, 3H, Ar), 7. 45–7.52 (m, 4H, ArH), 7.25–7.28 (m, 1H, ArH), 6.02 (d, 1H, $J = 2.4$ Hz, NCH), 3.85 (s, 3H, OMe), 2.83–2.88 (m, 1H, COCH), 2.49–2.53 (m, 1H, $COCH_2$), 2.24–2.32 (m, 1H, $COCH_2$), 1.96–2.01 (m, 1H, CH_2), 1.69–1.71 (m, 1H, CH_2), 1.56–1.63 (m, 1H, CH_2), 1.35–1.50 (m, 2H, CH_2), 0.72–0.82 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 211.1, 157.7, 142.9, 133.0, 131.9, 129.2, 128.4, 125.5, 124.4, 123.9, 114.7, 60.2, 55.5, 50.6, 42.0, 26.3, 25.2, 24.1; MS (EI) m/z (%) 335.2 (M^+) (17), 238.1 (100), 167.1 (6). IR (KBr): 2941, 2927, 2848, 1685, 1606, 1510, 1467, 1382, 1251, 1128, 1031, 827, 755, 701, 528; HRMS (EI) m/z calcd. for $C_{21}H_{21}NO_3$ 335.1521 (M^+); found 335.1524.

2-(4-Methoxyphenyl)-3-(2-oxobutyl)isoindolin-1-one (4k). The compound **4k** was prepared following general procedure A to give an inseparable mixture with a ratio of regioisomers 2/1, 30 mg, yield: 46%. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.92 (d, 1H, $J = 7.6$ Hz, ArH), 7.51–7.56 (m, 2H, ArH), 7.41–7.46 (m, 3H, ArH), 6.97–7.01 (m, 2H, ArH), 5.66 (dd, 1H, $J = 8.8$, 3.6 Hz, NCH), 3.83 (s, 3H, OMe), 2.98 (dd, 1H, $J = 17.8$, 3.6 Hz, $COCH_2$), 2.60 (dd, 1H, $J = 17.8$, 9.0 Hz, $COCH_2$), 2.33 (q, 2H, $J = 7.2$ Hz, $COCH_2Me$), 1.01 (t, 3H, $J = 7.2$ Hz,

$COCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 209.7, 208.9, 167.3, 166.8, 157.8, 157.7, 145.0, 141.9, 133.1, 132.1, 131.9, 131.8, 129.3, 129.2, 128.6, 125.6, 124.0, 123.8, 122.7, 114.7, 114.5, 61.2, 57.2, 55.5, 47.3, 45.3, 36.9, 28.7, 8.8, 7.5; MS (EI) m/z (%) 279.1 (M^+) (24), 236.1 (58), 222.1 (100), 91.1 (13); HRMS (EI) m/z calcd. for $C_{19}H_{19}NO_3$ 309.1365 (M^+); found 309.1364.

2-Isobutyl-3-(2-oxopropyl)isoindolin-1-one (4l). The compound **4l** was prepared following general method B to give a pale yellow oil, 38 mg, yield: 78%. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.84 (d, 1H, $J = 7.6$ Hz), 7.44–7.53 (m, 2H), 7.39 (d, 1H, $J = 7.6$ Hz), 5.08 (dd, $J = 7.2$, 5.2 Hz), 3.80 (dd, 1H, $J = 14.0$, 10.0 Hz), 3.04 (dd, 1H, $J = 17.6$, 4.8 Hz), 8.87 (dd, 1H, $J = 14.0$, 5.2 Hz), 2.69 (dd, 1H, $J = 17.8$, 8.0 Hz), 2.25 (s, 3H), 1.98–2.08 (m, 1H), 0.98 (d, 3H, $J = 6.8$ Hz), 0.85 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.8, 168.3, 145.4, 131.9, 131.6, 128.4, 123.8, 122.5, 55.0, 47.3, 46.3, 30.9, 27.4, 20.4, 19.7; MS (EI) m/z (%) 245.1 (M^+) (9), 202.1 (100), 131.0 (35), 103.1 (5), 77.0 (4), 43.0 (4); HRMS (EI) m/z calcd. for $C_{15}H_{19}NO_2$ 245.1416 (M^+); found 245.1420.

2-(2-Ethoxylethyl)-3-(2-oxopropyl)isoindolin-1-one (4m). The compound **4m** was prepared following general method B to give a pale yellow oil, 44 mg, yield: 85%. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.81 (d, 1H, $J = 7.2$ Hz, ArH), 7.50 (t, 1H, $J = 7.2$ Hz, ArH), 7.43 (dd, 2H, $J = 7.6$, 7.4 Hz, ArH), 5.18 (dd, 1H, $J = 7.6$, 4.4 Hz, CHN), 4.01–4.07 (m, 1H), 3.68–3.73 (m, 1H), 3.53–3.58 (m, 1H), 3.37–3.48 (m, 3H), 3.30 (dd, 1H, $J = 17.8$, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 168.3, 145.9, 131.7, 131.6, 128.2, 123.5, 122.6, 69.1, 66.4, 56.6, 46.2, 40.8, 30.6, 15.1; HRMS (EI) m/z calcd. for $C_{15}H_{19}NO_3$ 261.1365 (M^+); found 261.1378.

2-(4-Methoxyphenyl)-6-flouro-3-(2-oxopropyl)isoindolin-1-one (4n). The compound **4n** was prepared following the general method B to give a white solid, 44 mg, yield: 71%. Mp: 161–162 °C. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.58 (dd, 1H, $J = 7.6$, 2.4 Hz, ArH), 7.47 (dd, 1H, $J = 8.4$, 4.4 Hz, ArH), 7.40–7.43 (m, 2H, ArH), 7.27 (ddd, 1H, $J = 8.4$, 2.4 Hz, ArH), 6.98–7.01 (m, 2H, ArH), 5.59 (dd, 1H, $J = 9.6$, 3.2 Hz, NCH), 3.85 (s, 3H, OCH_3), 3.03 (dd, 1H, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.59 (dd, 1H, $J = 18.0$, 9.6 Hz, $COCH_2$), 2.12 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.0, 165.8, 165.7, 164.4, 161.9, 157.9, 140.5, 134.1, 134.0, 128.9, 125.5, 124.7, 124.6, 119.6, 119.4, 114.7, 110.8, 110.6, 56.8, 55.5, 46.5, 30.7; IR (KBr): 2919, 1708, 1686, 1518, 1490, 1401, 1255, 1174, 1137, 1027, 887, 833,782 cm^{-1}; MS (EI) m/z (%) 313.2 (M^+) (49), 284.2 (8), 270.1 (22), 256.1 (100), 185.1 (8), 108.1 (10), 77.1 (2); HRMS (EI) m/z calcd. for $C_{18}H_{16}FNO_3$ 313.1114 (M^+); found 313.1115.

2-(4-Methoxyphenyl)-6-chloro-3-(2-oxopropyl)isoindolin-1-one (4o). The compound **4o** was prepared following the general method B to give a white solid, 48 mg, yield: 73%. Mp: 180–182 °C. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.89 (d, 1H, $J = 2.0$ Hz, ArH), 7.53 (dd, 1H, $J = 8.0$, 2.0 Hz, ArH), 7.40–7.45 (m, 3H, ArH), 6.99 (dd, 2H, $J = 8.0$, 2.0 Hz, ArH), 5.60 (dd, 1H, $J = 9.2$, 3.2 Hz, NCH), 3.85 (s, 3H, OCH_3), 3.04 (dd, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.59 (dd, $J = 18.0$, 9.6 Hz, $COCH_3$), 2.12 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.9, 165.4, 157.9, 143.1, 135.0, 133.7, 132.2, 128.9, 125.5, 124.3, 124.1, 114.7, 56.9, 55.5, 46.4, 30.6; MS (EI) m/z (%) 329.1 (M^+) (48), 286.1 (26), 272.1 (100), 108.1

(17), 77.1 (3); HRMS (EI) m/z calcd. for $C_{18}H_{16}ClNO_3$ 328.0819 (M^+); found 328.0819.

2-(4-Methoxyphenyl)-6-bromo-3-(2-oxopropyl)isoindolin-1-one (4p). The compound **4p** was prepared following general method B to give a white solid, 64 mg, yield: 86%. Mp: 198–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.04 (s, 1H, ArH), 7.68 (dd, 1H, $J = 8.0$, 1.6 Hz, ArH), 7.41 (d, 2H, $J = 8.8$ Hz, ArH), 7.38 (d, 1H, $J = 8.0$ Hz, ArH), 6.99 (d, 2H, $J = 8.8$ Hz, ArH), 5.56 (dd, 1H, $J = 9.2$, 3.2 Hz, CHN), 3.84 (s, 3H, CH_3), 3.03 (dd, 1H, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.59 (dd, 1H, $J = 18.0$, 9.2 Hz, $COCH_2$), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.9, 165.3, 157.9, 143.6, 135.0, 133.9, 128.8, 127.1, 125.6, 124.6, 122.8, 114.6, 56.9, 55.5, 46.3, 30.6; IR (KBr): 2964, 2911, 1706, 1686, 1517, 1399, 1175, 1022, 829, 781, 551 cm^{-1}; MS (EI) m/z (%) 373.2 (M^+) (2), 328.2 (23), 314.2 (100), 243.2 (8), 108.1 (6), 77.1 (1); HRMS (EI) m/z calcd. for $C_{18}H_{16}BrNO_3$ 373.0314 (M^+); found 373.0314.

2-(4-Methoxyphenyl)-6-hydroxy-3-(2-oxopropyl)isoindolin-1-one (4q). The compound **4q** was prepared following the general method B to give a white solid, 51 mg, yield: 82%. Mp: 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.51 (d, 1H, $J = 2.4$ Hz, ArH), 7.41 (d, 2H, $J = 9.2$ Hz, ArH), 7.32 (d, 1H, $J = 8.4$ Hz, ArH), 7.13 (s, 1H, ArOH), 7.07 (dd, 1H, $J = 8.4$, 2.4 Hz, ArH), 6.98 (d, 2H, $J = 9.2$ Hz, ArH), 5.55 (dd, 1H, $J = 9.2$, 3.6 Hz, NCH), 3.84 (s, 3H, OCH_3), 2.98 (dd, 1H, $J = 17.6$, 3.6 Hz, $COCH_2$), 2.60 (dd, 1H, $J = 17.6$, 9.2 Hz, $COCH_2$), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.4, 167.4, 157.9, 157.3, 136.6, 132.8, 128.9, 125.9, 123.9, 120.5, 114.6, 110.2, 57.3, 55.5, 46.6, 30.8; MS (EI) m/z (%) 311.2 (M^+) (43), 282.2 (8), 268.2 (22), 254.1 (100), 183.1 (6), 108.1 (7), 77.1 (2); HRMS (EI) m/z calcd. for $C_{18}H_{17}NO_4$ 311.1158 (M^+); found 311.1159.

2-(4-Methoxyphenyl)-6-methoxy-3-(2-oxopropyl)isoindolin-1-one (4r). The compound **4r** was prepared following the general method B to give a white solid, 50 mg, yield: 77%. Mp: 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.43 (d, 2H, $J = 8.8$ Hz, ArH), 7.40 (d, 1H, $J = 2.4$ Hz, ArH), 7.37 (d, 1H, $J = 8.4$ Hz, ArH), 7.12 (dd, $J = 8.4$, 2.4 Hz, ArH), 6.99 (d, 2H, $J = 8.8$ Hz, ArH), 5.56 (dd, 1H, $J = 9.2$, 3.2 Hz, NCH), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.00 (dd, 1H, $J = 17.6$, 3.2 Hz, $COCH_2$), 2.58 (dd, 1H, $J = 17.6$, $J = 9.2$ Hz, $COCH_2$), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.2, 166.8, 160.4, 157.7, 137.3, 133.3, 129.4, 125.6, 123.8, 120.4, 114.6, 106.6, 56.8, 55.7, 55.5, 46.7, 30.8; MS (EI) m/z (%) 325.2 (M^+) (42), 296.2 (8), 282.2 (20), 268.1 (100), 253.1 (10), 108.1 (5), 77.1 (2); HRMS (EI) m/z calcd. for $C_{19}H_{19}NO_4$ 325.1314 (M^+); found 325.1314.

2-(4-Methoxyphenyl)-6-phenyl-3-(2-oxopropyl)isoindolin-1-one (4s). The compound **4s** was prepared following general method B to give a white solid, 58 mg, yield: 78%. Mp: 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.15 (d, 1H, $J = 1.2$ Hz, ArH), 7.80 (dd, 1H, $J = 8.0$, 1.6 Hz, ArH), 7.67 (s, 1H, ArH), 7.65 (s, 1H, ArH), 7.55 (d, 1H, $J = 8.0$ Hz, ArH), 7.45–7.51 (m, 4H, ArH), 7.39–7.42 (m, 1H, Ar), 7.00 (s, 1H, Ar), 7.02 (s, 1H, Ar), 5.68 (dd, 1H, $J = 9.2$, 3.2 Hz, NCH), 3.86 (s, 3H, OCH_3), 3.06 (dd, 1H, $J = 18.0$, 3.2 Hz, $COCH_2$), 2.67 (dd, 1H,

$J = 18.0$, 9.2 Hz, $COCH_2$), 2.13 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 206.1, 166.7, 157.7, 143.8, 142.1, 140.0, 132.6, 131.1, 129.3, 128.9, 127.8, 127.2, 125.6, 123.3, 122.4, 114,6, 57.0, 55.5, 46.6, 30.7; MS (EI) m/z (%) 373.0 (M^+) (54), 330.0 (30), 316.0 (100), 303.0 (7), 288.0 (6), 166.1 (12), 108.1 (21), 77.0 (6); HRMS (EI) m/z calcd. for $C_{24}H_{21}NO_3$ 371.1521 (M^+); found 371.1522.

2-(4-Methoxyphenyl)-6-nitro-3-(2-oxopropyl)isoindolin-1-one (4t). The compound **4t** was prepared following the general method B to give a white solid, 50 mg, yield: 74%. Mp: 190–192 °C. ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.75 (d, 1H, $J = 2.0$ Hz, ArH), 8.44 (dd, 1H, $J = 8.4$, 2.0 Hz, ArH), 7.71 (d, 1H, $J = 8.4$ Hz, ArH), 7.41 (d, 2H, $J = 6.8$ Hz, ArH), 7.02 (d, 2H, $J = 6.8$ Hz, ArH), 5.70 (dd, 1H, $J = 9.6$, 3.2 Hz, NCH), 3.86 (s, 3H, OCH_3), 3.12 (dd, 1H, $J = 18.2$, 3.2 Hz, $COCH_2$), 2.66 (dd, 1H, $J = 18.2$, 9.6 Hz, $COCH_2$), 2.15 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 205.5, 164.5, 158.2, 150.6, 148.7, 133.7, 128.3, 126.9, 125.6, 124.4, 119.5, 114.8, 57.3, 55.5, 45.8, 30.5; MS (EI) m/z (%) 340.1 (M^+) (100), 297.1 (47), 283.1 (90), 237.1 (50), 166.1 (11), 108.1 (21), 77.0 (3); HRMS (EI) m/z calcd. for $C_{18}H_{16}N_2O_5$ 340.1059 (M^+); found 340.1050.

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