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Quaternary Ammonium Salt-Promoted Multi-Component Reaction in Water: Access to 3-Alkyl-2, 3-Dihydro-1H-Isoindolin-1-One Derivatives

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Abstract: A concise synthesis of alkyl-2,3-dihydro-1H-isoindolin-1-one derivatives from 2-formyl benzoic acid, β-keto acid, and ammonia or primary amine was developed via a quaternary ammonium salt-promoted multi-component sequence of decarboxylative alkylation/lactamization reaction in water, in which the target products were obtained in good to excellent yields.

Keywords: quaternary ammonium salt; multi-component reaction; β-keto acid; isoindolinone; decarboxylation

Nitrogen-fused heterocycle skeletons are considered as one of the most abundant and integral motifs owing to their ubiquitous occurrence in numerous pharmaceuticals, nature products, agrochemicals, and other useful chemicals.[1] Among the various N-heterocylic compounds, functional isoindolinone frameworks are a privileged class of building blocks since they show a wide range of biological activities and therapeutic potential,[2] such as antihypertensive,[3] antipsychotic,[4] anesthetic,[5] antiulcer,[6] vasodilatory,[7] antiviral,[8] and antileukemic[9] properties. In particular, 3-alkyl-2,3-dihydro-1H-isoindolin-1-ones are omnipresent as key structural scaffolds in many medicinal molecules, in which pagoclone (**1a**),[10] pazinaclone (DN 2327, **1b**),[11] (*R*)-JM 1232 (**1c**),[12] (*S*)-PD 172938 (**1d**),[13] and (**1e**)[14] are in the most representative (Figure 1). Therefore, the design and synthesis of these core structures for the library generation of drug-like derivatives has attracted great attention from synthetic chemists and pharmacologists.

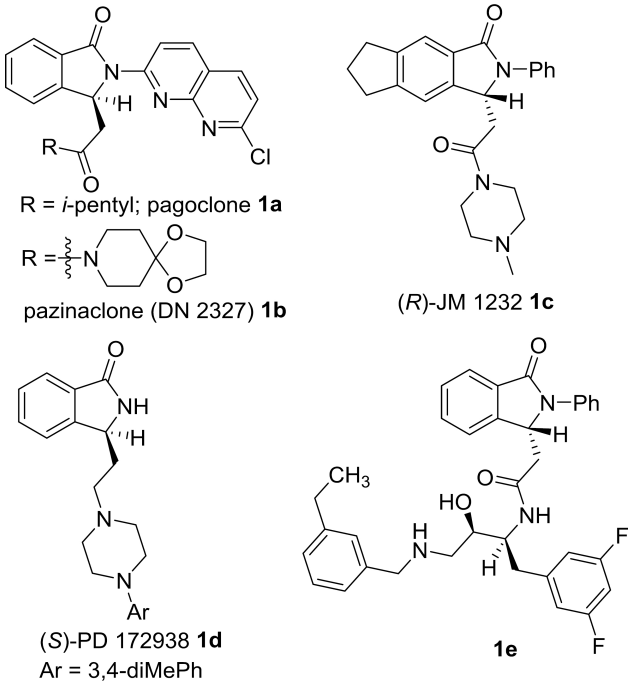


Figure 1. Bioactive molecules having isoindolinone core.

In the past decades, many synthetic methods toward the construction of substituted isoindolinones have been elegantly developed.[15] Among them, the exploration of practical and environmentally friendly multi-component cascade reactions for the construction of isoindolinone derivatives with different types of carbon nucleophiles has attracted much attention,[16] due to their intrinsic elegance, broad functional group compatibility, and especially the straightforward construction of molecular architectures in a

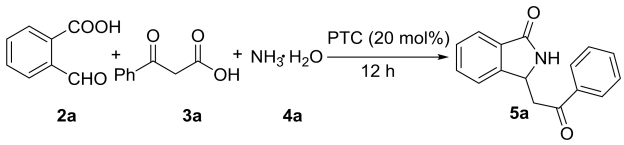
single step.[17] Among various carbon nucleophiles used in these reactions, silyl enol ethers represent one of the most successful ones in the synthesis of 3-alkyl-2,3-dihydro-1H-isoindolin-1-ones.[18] However, there are several limitations to this type of nucleophiles, such as pre-formation of silyl enol ethers from ketones or esters in which generated a large quantity of waste and used toxic and inflammable solvent. Therefore, it is desirable to develop processes by the use of the in situ formation of enolates and green solvents.

In the past decades, β-keto acids have been found to serve efficiently as ketone enolate equivalents via the decarboxylation and widely used in various decarboxylative transformations with many electrophilic partners.[19] On the other hand, water as a readily available, non-toxic, non-flammable and cheap solvent is still of significant concern in synthetic chemistry in recent years, however, its application in this type of transformations is still less explored.[20] We therefore surmised that β-keto acids may be used as ketone enolate equivalents, instead of silyl enol ethers, for the preparation of isoindolinones in the multi-component aqueous reaction systems. To the best of our knowledge, this strategy is relatively unexplored and remains a significant challenge. As a result, herein we wish to report our investigations about this process. The significant advantages of the present transformation included: 1) the use of quaternary ammonium salt was found to significantly facilitate the alkylation of β-keto acids with 2-formyl benzoic acids under mild conditions; 2) the reaction demonstrated here proceeded in water and generates nonhazardous wastes such as CO_2 and H_2O, thus providing an environmentally friendly strategy to construct the desired functional molecules.

Our investigations were initiated with the model reaction from substrate 2-formyl benzoic acid **2a** (1 mmol) and benzoylacetic acid **3a** (3 mmol) in commercially available ammonium hydroxide at 90 °C for 12 h. The results are listed in Table 1.

The desired product 3-(2-oxo-2-phenylethyl) isoindolin-1-one **5a** was obtained in disappointing yield without any additives (Table 1, entry 1). To improve the reaction efficiency, the identical reactions were further carried out via using quaternary ammonium salt. To our delight, a significantly improved reaction yield (78%) was afforded in the presence of 20 mol% TBAB (Table 1, entry 2). Encouraged by the above mentioned results, we then turned our attention to screen a variety of quaternary ammonium salts for the present transformation. Experimental results revealed that other different quaternary ammonium salts such as TBAC, TEBA, HTAC and MEAC showed different degrees of activities and furnished the products with 71–80% yields (Table 1, entries 3–5, 7). Gratifyingly, it is noteworthy that when DTAB was employed as the phase-transfer catalyst, the yield of desired product **5a** could be improved to 85% (Table 1, entry 6). In addition, raising the reaction temperature to 100 °C failed to improve the reaction yield (Table 1, entry 9).

Table 1. Optimization and screening of the reaction conditions.[a]



2a 3a 4a 5a

Entry	Temp. (°C)	PTC	Yield (%)[b]
1	90	none	7
2	90	TBAB	78
3	90	TBAC	73
4	90	TEBA	72
5	90	HTAC	71
6	90	DTAB	85
7	90	MEAC	80
8	90	PEG-400	62
9	100	DTAB	85

[a] Reaction conditions: **2a** (1.0 mmol), **3a** (3.0 mmol), PTC (0.2 mmol) and **4a** (25 wt%, 2 mL) at the indicated temperature for 12 h.

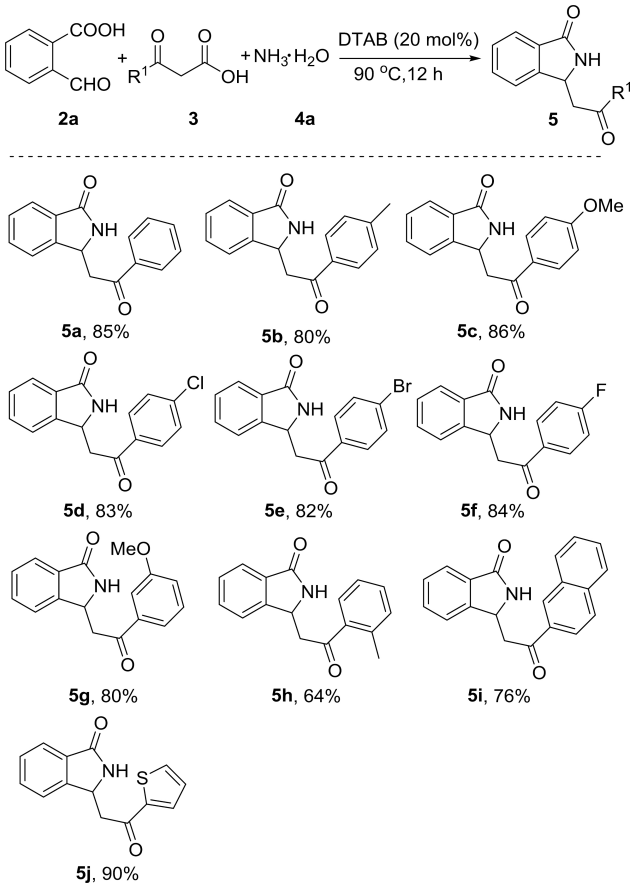
[b] Isolated yield. TBAB = tetrabutylammonium bromide, TBAC = tetrabutylammonium chloride, TEBA = benzyltriethylammonium chloride, HTAC = hexadecyltrimethylammonium chloride, DTAB = dodecyltrimethylammonium bromide, MEAC = methyltrioctyl ammonium chloride.

With the optimized reaction conditions established above, we next evaluated the substrates cope of substituted β-keto acids **3**, and the results are summarized in Scheme 1.

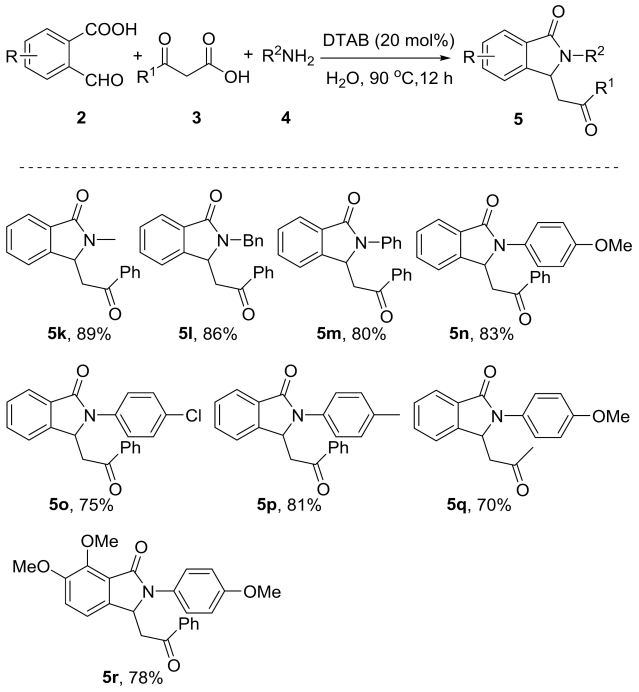
A broad range of β-keto acids bearing meta- and para-electron-withdrawing, as well as electron-donating substituents were well tolerated to give the desired products (**5a–g**) in 80–86% yields. However, for sterically hindered 3-oxo-3-(*o*-tolyl)propanoic acid, the product **5h** was obtained in a lower yield of 64%. In addition, 3-(naphthalen-2-yl)-3-oxopro panoic acid gave the desired compound **5i** in 76% yield, whereas 3-(thiophen-2-yl)-3-oxopropanoic acid furnished the desired product **5j** with 90% yield.

Further exploration of the scope and generality of the present method was focused on a variety of primary amines including alkylamines, aryl-alkylamines, and arylamines under optimal conditions. It was found that the substituents on the amines had slight influence on the yields of products **5** (Scheme 2).

Firstly, in the presence of methylamine and benzylamine, the reaction rate was accelerated considerably, affording the corresponding isoindolinones **5k–l** in 89% and 86% yields, respectively. Furthermore, various aromatic amines which are weak nucleophilicities were



Scheme 1. Scope of β-keto acids **3.** Reaction conditions: **2a** (1.0 mmol), **3a–j** (3.0 mmol), DTAB (0.2 mmol) and **4a** (25 wt%, 2.0 mL) at 90 °C for 12 h. The yields indicated are the isolated yields by column purification.

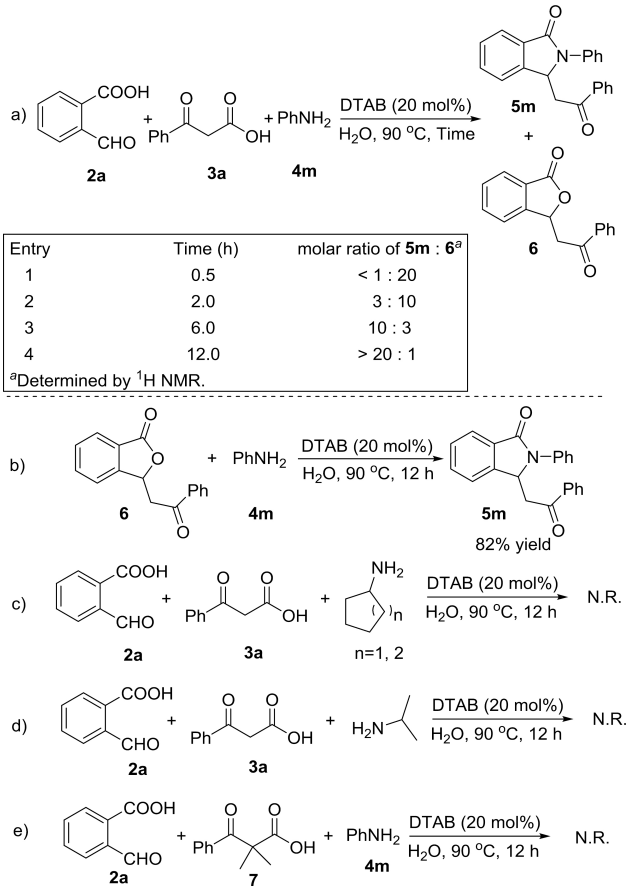


Scheme 2. Scope of amines **4.** Reaction conditions: **2** (1.0 mmol), **3** (3.0 mmol), DTAB (0.2 mmol) and **4** (6.0 mmol) in H_2O (2.0 mL) at 90 °C for 12 h. The yields indicated are the isolated yields by column purification.

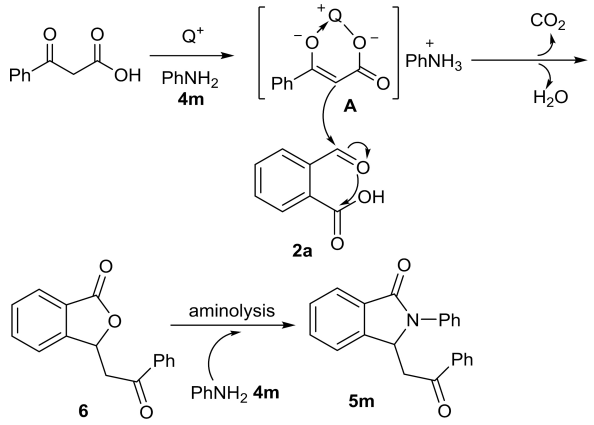
submitted to this process. It was found that aromatic amines with an para-electron-withdrawing or donating substituent on the aromatic ring proceed smoothly to give isoindolinones **5m–p** in good to excellent yields (75–83%). In addition, in the presence of *p*-methoxyphenylamine, the aliphatic β-keto acid could also react well in this reaction and form the desired product **5q** in 70% yield. Finally, the substituted 2-formyl benzoic acid **2b** (5, 6-$(OCH_3)_2$) was also tested for this decarboxylative cascade transformation upon the addition of *p*-methoxyphenylamine, and the target product **5r** was successfully obtained with satisfactory yield.

To gain insight on the mechanism of this multi-component reaction, several control experiments traced by ^{1}HNMR were subsequently carried out (Scheme 3). When the reaction of 2-formyl benzoic acid **2a**, benzoylacetic acid **3a** and aniline were performed under the optimum conditions, only the 3-(2-oxo-2phenylethyl)-isobenzofuran-1(3H)-one **6** was obtained in 0.5 h. Both **5m** and **6** were observed after 2 h, and the molar ratio of **5m**: **6** was approximately 3:10. Then, the molar ratio of **5m: 6** was changed to 10:3 at 6 h. By prolonging the reaction time to 12 h, **6** was almost completely disappeared and **5m** was clearly observed. Further studies were conducted to support the possible involvement of intermediate **6**. Reaction of **6** with aniline under our standard reaction conditions afforded **5m** in 82% yield. Furthermore, more basic aliphatic amines, such as cyclopentylamine, cyclopropylamine and *iso*-propylamine were used in this multi-component reaction. The reactions were carried out under the standard conditions, but no desired product was detected (Scheme 3c and 3d). These studies indicate that the compound **6** probably served as the intermediate of this transformation.

Based on experiment results described above, a possible reaction pathway has been tentatively proposed (Scheme 4). First of all, benzoylacetic acid **3a** was deprotonated by aniline in the presence of quaternary ammonium salt Q^+(DTAB) to form the dianion intermediate **A** via an electrostatic interaction between the lone pair of the substrate and the ammonium cation.[21] Subsequently, the condensation between intermediate **A** and 2-formyl benzoic acid **2a** furnishes the intermediate **6**, which undergoes decarboxylative addition and subsequent ring-closing reactions. The α,α-disubstituted acid **7** did not undergo the reaction (Scheme 3e) and may suggest that decarboxylation occurs after alkylation. Afterward, the addition of aniline to the intermediate **6** leads to the formation of **5m**.[22]



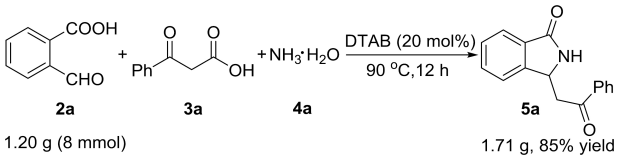
Scheme 3. Control experiments.



Scheme 4. A proposed reaction pathway.

This multi-component reaction can be scaled up to gram scale. For example, when the model reaction was run on 8 mmol (1.20 g) scale under the standard conditions, the desired product **5a** could also be obtained in 85% yield (Scheme 5).

In conclusion, we have developed a novel and practical multi-component cascade decarboxylative alkylation/lactamization in water. This process tolerates a series of aryl- and alkyl-substituted β-keto acids and primary amines, affording a wide variety of 3-alkyl-2,3-dihydro-1H-isoindolin-1-one products in good to excellent yields (up to 90%). With our protocol, a key intermediate 3-(2-oxo-2-phenylethyl) isobenzofuran-1(3H)-one can be readily obtained. Notablely, quaternary ammonium salt (DTAB) plays an important role in this environmentally friendly transformation. The extension to the development of other analogous of this strategy is currently underway in our laboratory.



Scheme 5. Gram-scale synthesis.

Experimental Section

General Remarks

All reactions were carried out under air. Commercial reagents (2-formyl benzoic acid, ammonium hydroxide and primary amine) were used without further purification. Flash chromatography was performed on silica gel 60 (40–63 μm, 60 Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on a Bruker 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.28, DMSO = δ 2.50). Carbon nuclear magnetic resonance (^{13}CNMR) spectra were recorded on a Bruker 150 MHz spectrometer. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.07, DMSO = 39.6). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration. β-keto acids[19i] were synthesized according to reported procedures. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a Bruke P-SIMS-Gly FT-ICR mass spectrometer.

Typical procedure for quaternary ammonium salt-promoted multi-component reaction.

A 25 mL Schlenk flask, fitted with a reflux condenser, DTAB (0.2 mmol, 20 mol%), **2** (1.0 mmol), **3** (3.0 mmol), and **4** (6.0 mmol) and 2.0 mL H_2O. The mixture was heated at 90 °C for 12 h, cooled down, and extracted three times with ethyl acetate. The combined organic extracts were dried with anhydrous Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 10:1–1:1) to give product **5**.

3-(2-oxo-2-phenylethyl)isoindolin-1-one (5a).[18] White solid, 85% yield, m.p. = 160–162 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.56 (s, 1H), 8.01 (d, *J* = 7.4 Hz, 2H), 7.67–7.63 (m, 3H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 5.12 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.70 (dd, *J* = 17.9, 4.7 Hz, 1H), 3.37 (dd, *J* = 17.9, 8.0 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 198.2, 169.6, 148.0, 136.8, 134.0, 132.8, 132.0, 129.2, 128.6, 128.6, 123.8, 123.3, 52.6, 44.0.

3-(2-oxo-2-(p–tolyl)ethyl)isoindolin-1-one (5b). White solid, 80% yield, m.p. = 115–116 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.54 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63-7.58 (m, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.10 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.65 (dd, *J* = 17.8, 4.8 Hz, 1H), 3.32 (dd, *J* = 18.0, 7.9 Hz, 1H), 2.38 (s, 3H). ^{13}CNMR (151 MHz, DMSO) δ 197.7, 169.6, 148.0, 144.4, 134.4, 132.8, 132.0, 129.8, 128.7, 128.5, 123.8, 123.3, 52.7, 43.9, 21.7. HRMS calc. for $[M+Na]^+$ $C_{17}H_{15}NNaO_2$: 288.1000, found: 288.0993.

3-(2-(4-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (5c).[18] White solid, 86% yield, m.p. = 166–167 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.54 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63-7.58 (m, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 5.10 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.85 (s, 3H), 3.62 (dd, *J* = 17.6, 4.9 Hz, 1H), 3.30 (dd, *J* = 17.7, 7.9 Hz, 1H).^{13}CNMR (151 MHz, DMSO) δ 196.3, 169.4, 163.7, 147.9, 132.7, 131.8, 130.8, 129.7, 128.4, 123.6, 123.1, 114.2, 55.9, 52.6, 43.5.

3-(2-(4-chlorophenyl)-2-oxoethyl)isoindolin-1-one (5d). White solid, 83% yield, m.p. = 158–159 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.59 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.64- 7.59 (m, 4H), 7.50 (t, *J* = 7.3 Hz, 1H), 5.11 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.72 (dd, *J* = 17.9, 4.5 Hz, 1H), 3.36 (dd, *J* = 17.9, 8.1 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 197.2, 169.6, 147.8, 138.9, 135.5, 132.8, 132.0, 130.6, 129.3, 128.6, 123.8, 123.3, 52.6, 44.0. HRMS calc. for $[M+Na]^+$ $C_{16}H_{12}ClNNaO_2$: 308.0454, found: 308.0446.

3-(2-(4-bromophenyl)-2-oxoethyl)isoindolin-1-one (5e). White solid, 82% yield, m.p. = 176–177 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.58 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.75 (t, *J* = 6.6 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.0 Hz, 1H), 5.10 (dd, *J* = 7.7, 4.6 Hz, 1H), 3.71 (dd, *J* = 17.9, 4.5 Hz, 1H), 3.34 (dd, *J* = 17.9, 8.1 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 197.4, 169.6, 147.8, 135.8, 132.8, 132.3, 132.0, 130.6, 128.6, 128.1, 123.8, 123.3, 52.5, 44.0. HRMS calc. for $[M+Na]^+$ $C_{16}H_{12}BrNNaO_2$: 351.9949, found: 351.9950.

3-(2-(4-fluorophenyl)-2-oxoethyl)isoindolin-1-one (5f). White solid, 84% yield, m.p. = 141–142 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.56 (s, 1H), 8.10 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 8.8 Hz, 2H), 5.11 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.70 (dd, *J* = 17.9, 4.6 Hz, 1H), 3.36 (dd, *J* = 18.0, 8.1 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 198.2, 171.1, 167.1 (d, *J* = 252.1 Hz), 149.3, 135.0 (d, *J* = 2.7 Hz), 134.3, 133.4, 133.1 (d, *J* = 9.5 Hz), 130.0, 125.2, 124.7, 117.7(d, *J* = 21.9 Hz), 54.0, 45.4. HRMS calc. for $[M+Na]^+$ $C_{16}H_{12}FNNaO_2$: 292.0750, found: 292.0750.

3-(2-(3-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (5g). White solid, 80% yield, m.p. = 171–172 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.58 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.50-7.48 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 5.11 (dd, *J* = 7.4, 5.0 Hz, 1H), 3.82 (s, 3H), 3.70 (dd, *J* = 18.0, 4.6 Hz, 1H), 3.37 (dd, *J* = 18.1, 8.0 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 198.0, 169.6, 159.9, 147.9, 138.2, 132.6, 132.0, 130.4, 128.5, 123.8, 123.3, 121.1, 120.1, 113.0, 55.8, 52.6, 44.1. HRMS calc. for $[M+Na]^+$ $C_{17}H_{15}NNaO_3$: 304.0950, found: 304.0947.

3-(2-oxo-2-(o–tolyl)ethyl)isoindolin-1-one (5h). Yellow solid, 64% yield, m.p. = 125–127 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.62 (s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.66 (dd, *J* = 14.6, 7.6 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 2H), 5.10 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.64 (dd, *J* = 17.8, 4.6 Hz, 1H), 3.27 (dd, *J* = 17.8, 8.0 Hz, 1H), 2.47 (s, 3H).

^{13}CNMR (151 MHz, DMSO) δ 201.67 (s), 169.6, 147.9 138.0, 137.5, 132.9 132.2 132.2 132.0, 129.7, 128.5, 126.4 123.8, 123.3, 52.8, 46.5, 21.4. HRMS calc. for $[M+Na]^+$ $C_{17}H_{15}NNaO_2$: 288.1000, found: 288.0996.

3-(2-(naphthalen-2-yl)-2-oxoethyl)isoindolin-1-one (5i). White solid, 76% yield, m.p. = 202–204 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.75 (s, 1H), 8.67 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.07-8.04 (m, 2H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.69 (q, *J* = 7.2 Hz, 3H), 7.64–7.61 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 5.20 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.86 (dd, *J* = 17.7, 4.5 Hz, 1H), 3.52 (dd, *J* = 17.7, 8.2 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 198.0, 169.7, 148.0, 135.6, 134.1, 132.9, 132.7, 132.0, 131.0, 130.1, 129.3, 128.8, 128.6, 128.2, 127.5, 123.9, 123.8, 123.3, 52.7, 44.1. HRMS calc. for $[M+Na]^+$ $C_{20}H_{15}NNaO_2$: 324.1000, found: 324.0995.

3-(2-oxo-2-(thiophen-2-yl)ethyl)isoindolin-1-one (5j). White solid, 90% yield, m.p. = 152–154 °C. ^{1}HNMR (600 MHz, DMSO) δ 8.65 (s, 1H), 8.05 (d, *J* = 4.9 Hz, 1H), 8.00 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.63-7.58 (m, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 4.3 Hz, 1H), 5.10 (dd, *J* = 7.7, 5.1 Hz, 1H), 3.62 (dd, *J* = 17.2, 4.8 Hz, 1H), 3.32 (dd, *J* = 17.2, 8.1 Hz, 1H). ^{13}CNMR (151 MHz, DMSO) δ 191.0, 169.6, 147.7, 144.0, 135.9, 134.6, 132.8, 132.0, 129.3, 128.6, 123.8, 123.3, 52.7, 44.2. HRMS calc. for $[M+Na]^+$ $C_{14}H_{11}NNaO_2S$: 280.0408, found: 280.0408.

2-methyl-3-(2-oxo-2-phenylethyl)isoindolin-1-one (5k). [17h] White solid, 89% yield, m.p. = 114–115 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.63-7.60 (m, 1H), 7.51-7.48 (m, 3H), 7.47-7.43 (m, 2H), 5.24 (t, *J* = 6.3 Hz, 1H), 3.54 (dd, *J* = 17.6, 5.5 Hz, 1H), 3.28 (dd, *J* = 17.6, 7.1 Hz, 1H), 3.11 (s, 3H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.4, 168.3, 145.6, 136.4, 133.9, 132.1, 131.6, 128.9, 128.4, 128.2, 123.6, 122.7, 57.7, 41.9, 27.9.

2-benzyl-3-(2-oxo-2-phenylethyl)isoindolin-1-one (5l).[18] White solid, 86% yield, m.p. = 111–112 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.92-7.91 (m, 1H), 7.79 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.58-7.55 (m, 1H), 7.50-7.46 (m, 2H), 7.43–7.41 (m, 2H), 7.39–7.38 (m, 1H), 7.27–7.26 (m, 1H), 7.25 (s, 1H), 7.24–7.21 (m, 2H), 7.18–7.16 (m, 1H), 5.25 (dd, *J* = 7.1, 5.4 Hz, 1H), 5.07 (d, *J* = 15.4 Hz, 1H), 4.53 (d, *J* = 15.4 Hz, 1H), 3.49 (dd, *J* = 17.5, 5.3 Hz, 1H), 3.15 (dd, *J* = 17.5, 7.3 Hz,

1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.1, 168.6, 145.9, 137.1, 136.3, 133.7, 131.9, 131.8, 128.7, 128.7, 128.5, 128.1, 128.0, 127.5, 123.9, 122.9, 55.9, 44.7, 42.1.

3-(2-oxo-2-phenylethyl)-2-phenylisoindolin-1-one (5m).[18] White solid, 80% yield, m.p. = 165–167 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.95-7.94 (m, 1H), 7.86 (dd, J = 8.4, 1.1 Hz, 2H), 7.65 (dd, J = 8.6, 1.0 Hz, 2H), 7.57–7.55 (m, 1H), 7.53-7.49 (m, 3H), 7.45–7.42 (m, 4H), 7.22 (t, J = 7.4 Hz, 1H), 6.00 (dd, J = 9.7, 2.7 Hz, 1H), 3.54 (dd, J = 17.8, 2.9 Hz, 1H), 3.22 (dd, J = 17.8, 9.7 Hz, 1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.7, 166.9, 145.2, 136.7, 136.4, 133.8, 132.4, 131.9, 129.4, 128.8, 128.1, 125.6, 124.2, 123.2, 123.2, 56.9, 42.0.

2-(4-methoxyphenyl)-3-(2-oxo-2-phenylethyl) isoindolin-1-one (5n).[18] White solid, 83% yield, m.p. = 166–168 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.93 (dt, J = 6.4, 1.4 Hz, 1H), 7.86–7.84 (m, 2H), 7.57–7.54 (m, 1H), 7.52–7.49 (m, 5H), 7.44–7.41 (m, 2H), 6.96-6.95 (m, 2H), 5.89 (dd, J = 9.5, 3.2 Hz, 1H), 3.81 (s, 3H), 3.50 (dd, J = 17.7, 3.2 Hz, 1H), 3.18 (dd, J = 17.7, 9.5 Hz, 1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.7 166.9, 157.6, 145.2, 136.4, 133.7, 132.2, 132.0, 129.4, 128.7, 128.7, 128.1, 125.4, 124.1, 123.2, 114.6, 57.5, 55.5, 42.0.

2-(4-chlorophenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (5o). White solid, 75% yield, m.p. = 171–172 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.94-7.93 (m, 1H), 7.86 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.59-7.50 (m, 4H), 7.44 (t, J = 7.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 5.96 (dd, J = 9.5, 2.7 Hz, 1H), 3.51 (dd, J = 17.8, 2.9 Hz, 1H), 3.22 (dd, J = 17.8, 9.5 Hz, 1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.5, 145.1, 136.2, 135.3, 133.9, 132.6, 131.5, 130.9, 129.5, 128.9, 128.8, 128.1, 124.3, 124.2, 123.2, 56.8, 41.9. HRMS calc. for $[M+Na]^+$ $C_{22}H_{16}ClNNaO_2$: 384.0767, found: 387.0760.

3-(2-oxo-2-phenylethyl)-2-(p–tolyl)isoindolin-1-one (5p).[17i] White solid, 81% yield, m.p. = 179–180 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 6.7 Hz, 1H), 7.85 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.52–7.49 (m, 5H), 7.42 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 5.94 (dd, J = 9.7, 2.9 Hz, 1H), 3.52 (dd, J = 17.8, 2.9 Hz, 1H), 3.19 (dd, J = 17.8, 9.7 Hz, 1H), 2.35 (s, 3H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.8, 166.9, 145.3, 136.4, 135.6, 134.0, 133.7, 132.2, 132.0, 130.0, 128.7, 128.7, 128.1, 124.1, 123.4, 123.2, 57.1, 42.0, 21.0.

2-(4-methoxyphenyl)-3-(2-oxopropyl)isoindolin-1-one (5q).[18] Brown solid, 70% yield, m.p. = 129–130 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 1H), 7.56 (td, J = 7.5, 1.2 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.48-7.46 (m, 1H), 7.45-7.42 (m, 2H), 5.63 (dd, J = 9.1, 3.5 Hz, 1H), 3.83 (s, 3H), 3.01 (dd, J = 17.9, 3.5 Hz, 1H), 2.62 (dd, J = 17.9, 9.1 Hz, 1H), 2.09 (s, 3H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 206.2, 166.9, 157.7, 145.0, 132.2, 131.9, 129.3, 128.7, 125.6, 124.1, 122.8, 114.6, 57.1, 55.5, 46.6, 30.8.

6,7-dimethoxy-2-(4-methoxyphenyl)-3-(2-oxo-2-phenylethyl) isoindolin-1-one (5r).[18] Brown solid, 78% yield, m.p. = 103–105 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 5.78 (dd, J = 9.1, 2.2 Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H), 3.44 (dd, J = 17.5, 2.7 Hz, 1H), 3.16 (dd, J = 17.5, 9.4 Hz, 1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 197.9, 165.0, 157.5, 152.9, 147.4, 138.6, 136.5, 133.7, 129.5, 128.7, 128.1, 125.4, 124.3, 118.3, 116.9, 114.5, 62.6, 56.7, 56.4, 55.5, 42.5.

3-(2-oxo-2-phenylethyl)isobenzofuran-1(3H)-one (6).[22b] White solid, m.p. = 143–144 °C. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.97 (d, J = 7.9 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.59-7.54 (m, 2H), 7.50 (t, J = 7.7 Hz, 2H), 6.19 (t, J = 6.5 Hz, 1H), 3.79 (dd, J = 17.6, 5.7 Hz, 1H), 3.40 (dd, J = 17.6, 7.4 Hz, 1H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 196.1, 170.2, 149.8, 136.2, 134.3, 133.9, 129.5, 128.9, 128.2, 125.9, 125.8, 122.9, 77.2, 43.7.

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