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Engaging isatins in solvent-free, sterically congested Passerini reaction†

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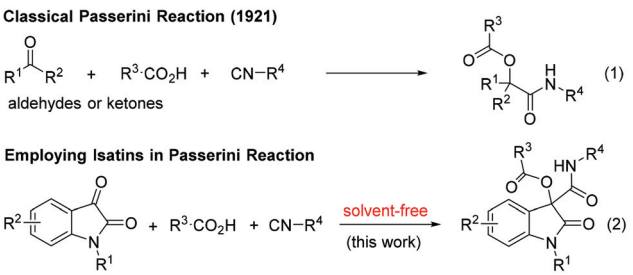
A facile, atom-economic and environmentally-benign protocol for the synthesis of biologically important oxindole derivatives in high yields has been demonstrated by employing isatins as carbonyl compound surrogates in a Passerini reaction carried out under solvent-free conditions. Moreover, electron-deficient phenols can also be used as the acid component in this reaction. In addition, the synthetic utility of the present methodology was examined by the one-pot synthesis of oxindoles with a free –OH group at the benzylic position.

Introduction

The Passerini reaction, the three-component reaction between a carboxylic acid, a carbonyl compound such as an aldehyde or a ketone, and an isocyanide, offers direct access to α-acyloxy carboxamide derivatives (Scheme 1, eqn (1)).[1] This is the first isocyanide based multicomponent reaction playing a central role in combinatorial chemistry,[2] and is widely utilized for the synthesis of various drug-like molecules, and in the total syntheses of biologically active natural products.[3,4] Intriguingly, the Passerini reaction employing ketones is generally slower and in some cases, the reactions carried out with bulky carbonyl substrate and the bulky isocyanide fail to afford the desired product.[5] However, the use of high pressure is one way to increase the efficiency of Passerini reactions involving bulky reactants.[6]

In the context of the Passerini reactions of sterically congested carbonyl compounds, it was envisaged that the multicomponent reaction involving isatin derivatives,[7] isocyanides and carboxylic acids could provide simple and straightforward access to oxindole derivatives (eqn (2)). This will be interesting because oxindoles having a quaternary benzylic centre represent a common structural motif in many natural products and biologically active compounds. Among them, the oxindoles with a heteroatom at the benzylic position are a useful class of compounds including the bioactive natural products (*R*)-convolutamydine A,[8] maremycin B[9] and the potent growth hormone secretion promoter SM-130686 (Fig. 1).[10] Herein, we report a practical and efficient solvent-free Passerini reaction[11] of isocyanides, isatins and carboxylic acids, leading to the formation of 3,3-disubstituted oxindole derivatives, and interestingly the reaction is carried out under air.[12]



Scheme 1 The Passerini reaction.

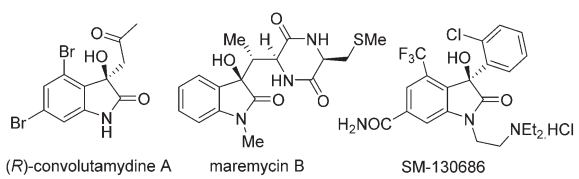


Fig. 1 Selected biologically active oxindoles having a quaternary benzylic centre having an OH group.

Results and discussion

Optimization of the reaction conditions

The present studies were initiated with the treatment of *N*-methyl isatin **1a** with benzoic acid **2a** and *tert*-butyl isocyanide **3a**. To our delight, when the reaction was carried out in CH_2Cl_2 at 25 °C, the expected product 3-benzoyloxy 3-carbamoyl indol-2-one derivative **4a** was formed in 49% yield (based on ^{1}H NMR spectroscopy, Table 1, entry 1). Increasing the

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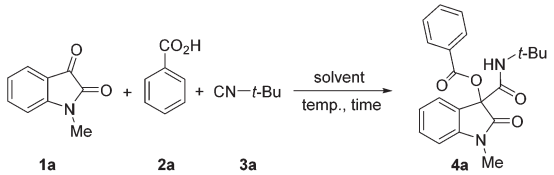
†Electronic supplementary information (ESI) available: ^{1}H-NMR and ^{13}C-NMR spectra of all compounds. See DOI: 10.1039/c3gc40454d

Table 1 Optimization of the reaction conditions[a]



Entry	2a (equiv.)	3a (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield of 4a[b] (%)
1	1.0	1.0	CH_2Cl_2	25	24	49
2	1.0	1.0	CH_2Cl_2	50	24	57
3	1.0	1.0	$CHCl_3$	70	24	61
4	1.5	1.5	$CHCl_3$	80	24	76
5	1.0	1.0	$(CH_2Cl)_2$	80	24	60
6	1.0	1.0	THF	70	24	33
7	1.0	1.0	CH_3CN	70	24	63
8	1.5	1.2	Solvent-free	80	24	82
9	1.5	1.2	Solvent-free	90	20	92
10	1.5	1.2	Solvent-free under air	100	12	96(91)[c]

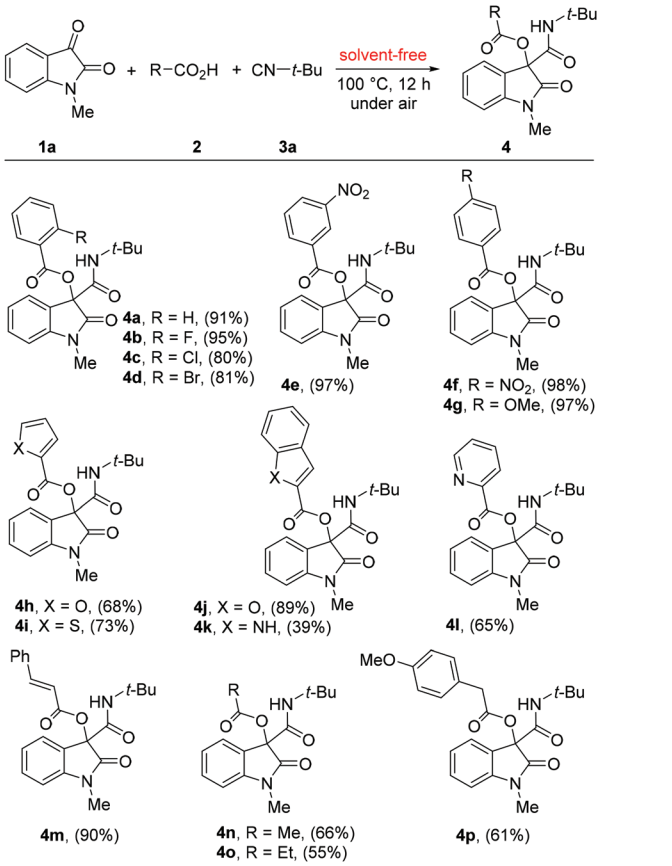
[a] All reactions were carried out at the 0.25 mmol scale of **1a** in 1.0 mL of solvent under an Ar atmosphere unless otherwise specified. [b] The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c] Isolated yield at the 0.50 mmol scale in parentheses.

reaction temperature resulted in an improved yield of the product (entry 2). Moreover, the reactions carried out in $CHCl_3$ at a higher temperature furnished better yields of the product (entries 3, 4). However, other chlorinated solvent including $(CH_2Cl)_2$ and solvents like THF and CH_3CN afforded the product in diminished yields (entries 5–7). At this stage, we thought of carrying out reactions under solvent-free conditions. Interestingly, when the reaction was carried out under solvent-free conditions at 80 °C, the product **4a** was formed in 82% yield (entry 8). Increasing the reaction temperature under solvent-free conditions improved the yield of **4a**, and finally when the reaction was carried out at 100 °C under solvent-free conditions in air for 12 h, **4a** was isolated in 91% yield (entry 10).

Investigation of the substrate scope of the reaction

With the optimized reaction conditions in hand, we then examined the substrate scope of this sterically congested, solvent-free Passerini reaction. First we evaluated the variation of the carboxylic acid moiety (Table 2). The unsubstituted benzoic acid worked well and a variety of electron releasing and -withdrawing groups at various positions of the aromatic ring of benzoic acid are well tolerated, leading to the formation of the oxindole derivatives in ≥80% in all cases (**4a–g**). Gratifyingly, a range of heterocyclic carboxylic acids also resulted in a smooth conversion to the desired product, further expanding the scope of this three-component reaction (**4h–l**). It is important to note in this context that *N*-unprotected indole 2-carboxylic acid also afforded the expected product **4k** in moderate yield.[13] Moreover, the reaction of α,β-unsaturated acid furnished an excellent yield of the oxindole derivative **4m**.

Table 2 Employing istains in a solvent-free Passerini reaction: scope of carboxylic acids[a]

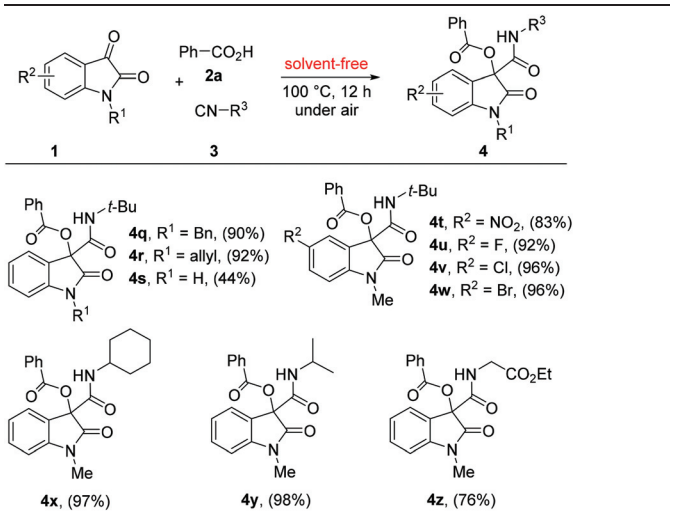


[a] General conditions: **1a** (0.50 mmol), **2** (0.75 mmol), **3a** (0.60 mmol) solvent-free conditions under air, 100 °C and 12 h.

Furthermore, the reaction is not limited to aromatic and α,β-unsaturated acids, but instead aliphatic acids including acetic acid also worked well, leading to the desired products in moderate yields (**4n–p**).[14]

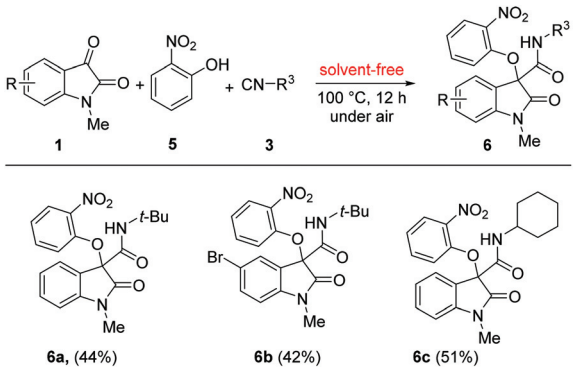
Next, we investigated the scope of this reaction with various substituted isatin derivatives and isocyanides (Table 3). Substituents on nitrogen of isatin including the benzyl group and allyl moiety are well tolerated (**4q**, **4r**). It is interesting to note that even unprotected isatin also afforded moderate yield of the Passerini adduct (**4s**), demonstrating the versatility of the present method. Moreover, various substituents at the carbocyclic ring of isatin also underwent a smooth three-component reaction leading to the desired product in excellent yield (**4t–w**). Furthermore, various isocyanides also furnished good to excellent yields of the desired products, further expanding the scope of this isocyanide initiated three-component reaction (**4x–z**). It is noteworthy, however, that in preliminary experiments commercially available isocyanide such as *p*-tolylsulfonyl methyl isocyanide and 4-methoxyphenyl isocyanide failed to undergo this reaction under optimized reaction conditions.

Table 3 Variation of the isatin moiety and isocyanide moiety[a]



[a] General conditions: **1** (0.50 mmol), **2a** (0.75 mmol), **3** (0.60 mmol) solvent-free conditions under air, 100 °C and 12 h.

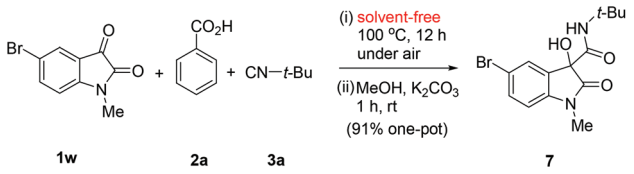
Table 4 Utility of 2-nitrophenol in the reaction as an acid surrogate[a]



[a] General conditions: **1** (0.50 mmol), **5** (0.75 mmol), **3** (0.60 mmol) solvent-free conditions under air, 100 °C and 12 h.

Utility of 2-nitrophenol as an acid surrogate

The synthetic potential of this solvent-free Passerini reaction has been demonstrated by utilizing electron-deficient phenols as the acid component in the reaction. Thus treatment of *N*-substituted isatins **1** with 2-nitrophenol **5** and isocyanides **3** under optimized reaction conditions resulted in the synthesis of *O*-arylated oxindole derivative **6** in moderate yields (Table 4). This reaction is an example of the use of the Smiles rearrangement in a Passerini reaction and the key step is the irreversible Smiles rearrangement of the intermediate phenoxyimidate adducts leading to the formation of the *O*-arylated product **6**.[15] The substituted isatin derivative as well as cyclohexyl isocyanide worked in the *O*-arylative Passerini reaction under solvent-free conditions leading to moderate yield of the product (**6a–c**). It is anticipated that the presence of the nitro group in the final adduct allows interesting applications to heterocyclic synthesis.



Scheme 2 One-pot synthesis of oxindoles with a free –OH group at the benzylic position.

One-pot synthesis of oxindoles with a free –OH group

The synthetic utility of the present methodology was further examined by the one-pot synthesis[16] of oxindoles with a free –OH group at the benzylic position by combining the Passerini reaction employing isatins with a base-mediated hydrolysis under mild conditions. The one-pot reaction worked well furnishing the oxindole derivative **7** in 91% yield (Scheme 2). It is important to note that oxindole derivatives are ubiquitously present in many natural products and biologically active compounds.[7]

Conclusions

In conclusion, we have demonstrated an efficient, atom-economic and environmentally-benign sterically congested Passerini reaction by employing isatins as the carbonyl compound component under solvent-free conditions. The reaction resulted in the synthesis of biologically important 3-acyloxy 3-carbamoyl indol-2-ones in high yields. Moreover, electrophilic phenols are used as the acid component in these reactions and the utility of the reaction was established by a one-pot synthesis of oxindoles with a free –OH group at the benzylic position. Further studies on the application of isatins in various multicomponent reactions are ongoing in our laboratory.

Experimental section

The reaction temperature is reported as the temperature of the bath surrounding the reaction vessel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400, in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of the recorded IR-signals are expressed in cm^{-1}. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}.

General procedure for the solvent-free Passerini reaction

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the isatin derivative **1** (0.5 mmol, 1.0 equiv.), the isocyanide **3** (0.6 mmol, 1.2 equiv.) and carboxylic acid **2** or 2-nitrophenol **5** (0.75 mmol, 1.5 equiv.) under

air. Then the reaction mixture was placed in a preheated oil bath at 100 °C for 12 h under solvent-free conditions. Then the crude reaction mixture was purified by silica gel column chromatography (eluting with a CH_2Cl_2–EtOAc solvent system, typically 1% EtOAc in CH_2Cl_2).

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl benzoate (4a). R_f (EtOAc–DCM = 5/95): 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.39–7.34 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.81 (bs, 1H), 3.32 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.70, 163.73, 163.25, 145.25, 134.03, 130.82, 130.19, 129.97, 128.79, 128.58, 125.13, 124.16, 123.29, 108.92, 81.22, 52.23, 28.69, 27.04. HRMS calculated $[M + H]^+$ for $C_{21}H_{23}O_4N_2$: 367.1652, found: 367.1650. FTIR (cm^{-1}): 3440, 3020, 2931, 17 331, 1690, 1617, 1518, 1472, 1269, 1216, 1109, 1068, 1024, 754, 710.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 2-fluoro benzoate (4b). R_f (EtOAc–DCM = 5/95): 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (t, J = 7.6 Hz, 1H), 7.63–7.59 (m, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.42–7.21 (m, 4H), 7.07 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 3.34 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.03, 163.75, 162.20 (d, J = 257.2 Hz), 161.04 (d, J = 3.2 Hz), 145.71, 136.09, 136.0, 133.36, 130.92, 125.61, 124.76 (d, J = 3.3 Hz), 122.50 (d, J = 9.67), 117.29 (d, J = 23.3 Hz), 116.78 (d, J = 9.7 Hz), 108.99, 81.74, 52.11, 28.64, 27.01. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2F$: 385.1558, found: 385.1556. FTIR (cm^{-1}): 3428, 3019, 1735, 1686, 1614, 1524, 1369, 1300, 1216, 1119, 755, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 2-chloro benzoate (4c). R_f (EtOAc–DCM = 5/95): 0.43; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.8 Hz, 1H), 7.51–7.47 (m, 2H), 7.41–7.28 (m, 3H), 7.12–7.07 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 3.31 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.12, 163.55, 162.63, 145.66, 133.92, 133.42, 133.24, 131.41, 130.89, 128.33, 127.28, 125.40, 123.26, 109.02, 82.17, 52.30, 28.69, 27.01. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2Cl$: 401.1263, found: 401.1259. FTIR (cm^{-1}) 3671, 3440, 3352, 2970, 2936, 2253, 1719, 1691, 1607, 1581, 1494, 1471, 1352, 1260, 1169, 1106, 1030, 911, 846, 732, 648.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 2-bromo benzoate (4d). R_f (EtOAc–DCM = 5/95): 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.78 (m, 1H), 7.69–7.67 (m, 1H), 7.40–7.33 (m, 4H), 7.09–7.06 (m, 2H), 6.90 (d, J = 7.9 Hz, 1H,), 3.32 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.11, 163.47, 145.66, 145.66, 134.59, 133.79, 133.11, 130.88, 130.73, 127.79, 125.35, 123.55, 123.22, 121.30, 109.03, 82.21, 52.37, 28.75, 27.02. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2Br$: 445.0757, found: 445.0756. FTIR (cm^{-1}): 3407, 2969, 1734, 1686, 1614, 1590, 1433, 1115, 1025, 874, 748.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 3-nitro benzoate (4e). R_f (EtOAc–DCM = 5/95): 0.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.46–8.44 (m, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.78 (bs, 1H), 3.33 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.30, 162.49, 161.90, 148.40, 145.19, 135.59, 131.19, 130.38, 130.17, 128.34, 124.95, 124.80, 124.38, 123.58, 109.10, 81.61, 52.47, 28.67, 27.12. HRMS calculated $[M + Na]^+$ for $C_{21}H_{21}O_6N_3Na$: 434.1323, found: 434.1323. FTIR (cm^{-1}): 3446, 3020, 2928, 2856, 1735, 1692, 1617, 1537, 1352, 1216, 1123, 757, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 4-nitro benzoate (4f). R_f (EtOAc–DCM = 5/95): 0.63; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.43–7.39 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.73 (bs, 1H), 3.32 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.32, 162.34, 162.22, 151.06, 145.10, 133.96, 131.18, 131.16, 124.96, 124.12, 123.91, 123.58, 109.08, 81.54, 52.42, 28.65, 27.11. HRMS calculated $[M + Na]^+$ for $C_{21}H_{21}O_6N_3Na$: 434.1323, found: 434.1322. FTIR (cm^{-1}): 3020, 2400, 1732, 1693, 1616, 1532, 1472, 1350, 1272, 1216, 758, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 4-methoxy benzoate (4g). R_f (EtOAc–DCM = 5/95): 0.59; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.6 Hz, 2H), 7.38–7.32 (m, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.94–6.89 (m, 3H), 6.79 (s, 1H), 3.86 (s, 3H), 3.31 (s, 3h), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.91, 164.21, 163.44, 145.24, 132.34, 132.13, 130.70, 124.09, 120.85, 114.07, 113.76, 108.85, 81.07, 55.64, 52.17, 28.70, 27.01. HRMS calculated $[M + H]^+$ for $C_{21}H_{25}O_5N_2$: 397.1758, found: 397.1757. FTIR (cm^{-1}); 3439, 3060, 2968, 1727, 1689, 1606, 1512, 1471, 1260, 1090, 732.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl furan-2-carboxylate (4h). R_f (EtOAc–DCM = 5/95): 0.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.42–7.38 (m, 3H), 7.09 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 7.98 Hz, 1H), 6.88 (bs, 1H), 6.57–6.56 (m, 1H), 3.32 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.23, 163.31, 155.51, 147.25, 145.47, 143.18, 130.93, 125.18, 123.69, 123.27, 120.13, 112.49, 108.98, 81.10, 52.20, 28.65, 27.01. HRMS calculated $[M + H]^+$ for $C_{19}H_{21}O_5N_2$: 357.1445, found: 357.1444. FTIR (cm^{-1}): 33 429, 3020, 2928, 1731, 1690, 1615, 1519, 1471, 1302, 1216, 112, 927, 757, 668.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl thiophene-2-carboxylate (4i). R_f (EtOAc–DCM = 5/95): 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 3.8 Hz, 1H), 7.63 (d, J = 4.9 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 3.8 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.78 (bs, 1H), 3.3 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.34, 163.21, 158.88, 145.38, 135.05, 133.77, 131.49, 130.92, 128.36, 125.15, 123.87, 123.28, 108.95, 81.34, 52.23, 28.68, 27.02. HRMS calculated $[M + H]^+$ for $C_{19}H_{21}O_4N_2S$: 373.1217, found: 373.1216. FTIR (cm^{-1}): 3438, 3020, 2400, 1729, 1690, 1617, 1494, 1472, 1361, 1215, 1072, 929, 759, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl benzofuran-2-carboxylate (4j). R_f (EtOAc–DCM = 5/95): 0.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.60–7.58 (m, 2H), 7.53–7.49 (m, 1H), 7.43–7.33 (m, 3H), 7.07 (t, J = 7.6 Hz, 1H), 6.94 (bs, 1H), 6.91 (d, J = 8.1 Hz, 1H), 3.32 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.12, 163.18, 156.24, 156.02, 145.53, 143.88, 131.07, 128.54, 126.79, 124.94, 124.26, 123.96, 123.40, 123.22, 115.99, 112.44, 109.06, 81.40, 52.34, 28.69, 27.08. HRMS calculated $[M + H]^+$ for $C_{23}H_{23}O_5N_2$: 407.1601,

found: 407.1599. FTIR (cm^{-1}) 3428, 2930, 1732, 1688, 1614, 1569, 1519, 1494, 1471, 1369, 1350, 1298, 1215, 1173, 1092, 1006, 748.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 1*H*-indole-2-carboxylate (4k). R_f (EtOAc–DCM = 10/90): 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (bs, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.34–7.19 (m, 5H), 7.13 (t, J = 6.4 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.79 (bs, 1H), 3.24 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.55, 163.21, 159.14, 145.24, 137.63, 130.88, 127.18, 126.23, 125.27, 125.12, 124.18, 123.35, 122.76, 121.30, 112.34, 109.98, 108.95, 81.28, 52.31, 28.69, 27.02. HRMS calculated $[M + H]^+$ for $C_{23}H_{24}O_4N_3$: 406.1761, found: 406.1762. FTIR (cm^{-1}): 3347, 3019, 2974, 2400, 1725, 1690, 1617, 1369, 1311, 1215, 758, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl picolinate (4l). R_f (EtOAc–DCM = 20/80): 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.53–7.50 (m, 1H), 7.35 (t, J = 7.67 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.25 (bs, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 3.29 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.05, 163.74, 162.04, 150.00, 146.67, 145.66, 137.11, 130.86, 127.70, 125.60, 125.30, 123.34, 123.17, 108.87, 81.36, 52.06, 28.60, 26.94. HRMS calculated $[M + H]^+$ for $C_{20}H_{22}O_4N_3$: 368.1605, found: 368.1602. FTIR (cm^{-1}): 3407, 2969, 1734, 1686, 1614, 1590, 1433, 1115, 1025, 874, 748.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl cinnamate (4m). R_f (EtOAc–DCM = 5/95): 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 16.1 Hz, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.41–7.35 (m, 4H), 7.33 (d, J = 7.4 Hz, 1H), 7.09–7.06 (m, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.74 (bs, 1H), 6.52 (d, J = 16.26 Hz, 1H), 3.30 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.78, 164.08, 163.40, 147.82, 145.35, 133.91, 131.10, 130.72, 129.12, 129.05, 128.47, 128.40, 125.50, 123.83, 123.25, 115.83, 108.87, 81.13, 52.22, 28.69, 27.0. HRMS calculated $[M + H]^+$ for $C_{23}H_{25}O_4N_2$: 393.1809, found: 393.1807. FTIR (cm^{-1}): 3020, 2400, 1731, 1688, 1635, 1616, 1418, 1216, 1154, 1042, 929, 767, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl acetate (4n). R_f (EtOAc–DCM = 5/95): 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 8.2 Hz, 1H), 7.28–7.26 (m, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.01 Hz, 1H), 6.63 (bs, 1H), 3.26 (s, 3H), 2.17 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.67, 167.75, 163.30, 145.33, 130.70, 125.47, 123.50, 123.18, 108.90, 81.06, 52.15, 28.64, 26.93, 20.91. HRMS calculated $[M + H]^+$ for $C_{16}H_{21}O_4N_2$: 305.1496, found: 305.1494. FTIR (cm^{-1}): 3341, 3019, 1720, 1612, 1374, 1216, 1111, 771, 669, 507, 474, 487, 479.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl propionate (4o). R_f (EtOAc–DCM = 5/95): 0.39; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, J = 7.2 Hz, 1H), 7.26–7.23 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.62 (bs, 1H), 3.25 (s, 3H), 2.52–2.38 (m, 2H), 1.38 (s, 9H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.71, 171.29, 163.40, 145.32, 130.68, 125.54, 123.35, 123.16, 108.88, 80.89, 52.10, 28.63, 27.33, 26.92, 8.72. HRMS calculated $[M + H]^+$ for $C_{17}H_{23}O_4N_2$: 319.1652, found: 319.1651. FTIR (cm^{-1}): 3347, 2938, 1759, 1724, 1671, 1611, 1532, 1216, 1156, 1110, 890, 755.

3-(*tert*-Butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl 2-(4-methoxyphenyl)acetate (4p). R_f (EtOAc–DCM = 5/95): 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 7.9 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 7.8 Hz, 1H), 6.32 (bs, 1H), 3.79 (s, 3H), 3.66 (s, 2H), 3.23 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.33, 168.39, 163.42, 159.03, 145.40, 130.74, 130.43, 125.34, 125.12, 123.12, 123.09, 114.36, 108.92, 81.08, 55.38, 52.0, 40.19, 28.55, 26.91. HRMS calculated $[M + H]^+$ for $C_{23}H_{27}O_5N_2$: 411.1914, found: 411.1913. FTIR (cm^{-1}): 3413, 3019, 1736, 1687, 1614, 1514, 1370, 1217, 1133, 1037, 770, 669.

1-Benzyl-3-(*tert*-butylcarbamoyl)-2-oxoindolin-3-yl benzoate (4q). R_f (EtOAc–DCM = 5/95): 0.61; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.41–7.36 (m, 3H), 7.28 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.83 (bs, 1H), 6.72 (d, J = 7.9 Hz, 1H), 5.08 (d, J = 16.5 Hz, 2H), 5.07 (d, J = 19.5 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.80, 163.62, 163.34, 144.28, 135.29, 134.05, 130.63, 130.04, 128.95, 128.81, 128.66, 127.68, 127.20, 125.32, 123.87, 123.27, 110.09, 81.44, 52.25, 44.99, 28.75. HRMS calculated $[M + H]^+$ for $C_{27}H_{27}O_4N_2$: 443.1965, found: 443.1961. FTIR (cm^{-1}) 3020, 2926, 2855, 1731, 1688, 1615, 1516, 1468, 1367, 1268, 1216, 1178, 1088, 770, 669.

1-Allyl-3-(*tert*-butylcarbamoyl)-2-oxoindolin-3-yl benzoate (4r). R_f (EtOAc–DCM = 5/95): 0.56; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.35–7.31 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.1 Hz, 1H), 6.78 (bs, 1H), 5.93–5.88 (m, 1H), 5.45 (d, J = 19.2 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.45–4.42 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.42, 163.56, 163.31, 144.40, 134.60, 130.78, 130.61, 129.97, 128.77, 128.61, 125.29, 123.88, 123.17, 117.97, 109.86, 81.29, 52.19, 42.95, 28.70. HRMS calculated $[M + H]^+$ for $C_{23}H_{25}O_4N_2$: 393.1809, found: 393.1805. FTIR (cm^{-1}) 3439, 3020, 2400, 1734, 1689, 1615, 1517, 1424, 1267, 1215, 1115, 929, 850, 780, 669.

3-(*tert*-Butylcarbamoyl)-2-oxoindolin-3-yl benzoate (4s). R_f (EtOAc–DCM = 10/90): 0.30; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02–7.90 (m, 3H), 7.66–7.59 (m, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.74 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.03, 163.83, 163.26, 142.48, 134.08, 130.78, 130.03, 128.82, 128.57, 125.54, 124.33, 123.14, 110.92, 81.50, 52.29, 30.93, 28.69. HRMS calculated $[M + H]^+$ for $C_{20}H_{21}O_4N_2$: 353.1496, found: 353.1495. FTIR (cm^{-1}): 3683, 3436, 3019, 2977, 2400, 1736, 1689, 1623, 1519, 1268, 1215, 1110, 929, 758, 669.

3-(*tert*-Butylcarbamoyl)-1-methyl-5-nitro-2-oxoindolin-3-yl benzoate (4t). R_f (EtOAc–DCM = 5/95): 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 8.5 Hz, 1H), 8.19 (m, 1H), 7.96 (d, J = 6.8 Hz, 2H), 7.65 (t, J = 8.5 Hz, 1H), 7.50 (t, J = 6.8 Hz, 2H), 7.01 (d, J = 8.5 Hz, 1H), 6.77 (bs, 1H), 3.38 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.82, 163.79, 162.22, 150.93, 143.84, 134.62, 130.06, 129.04, 127.76, 126.36, 119.79, 108.59, 80.19, 52.71, 28.69, 27.50. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_6N_3$: 412.1503, found: 412.1502. FTIR (cm^{-1}) 3684,

3437, 3020, 2400, 1736, 1691, 1617, 1524, 1496, 1337, 1215, 1267, 1108, 1067, 929, 768, 669, 625.

3-(*tert*-Butylcarbamoyl)-5-fluoro-1-methyl-2-oxoindolin-3-yl benzoate (4u). R_f (EtOAc–DCM = 5/95): 0.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.96 (m, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.9 Hz, 2H), 7.13–7.06 (m, 2H), 6.85–6.83 (dd, J_1 = 4.0 Hz, J_2 = 8.8 Hz, 1H), 6.80 (bs, 1H), 3.31 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.51, 163.78, 162.67, 159.44 (d, J = 244.2 Hz), 141.20, 134.22, 130.0, 128.66, 128.31, 126.52, 126.43, 117.02 (d, J = 24.4 Hz), 112.72 (d, J = 25.6 Hz), 109.49 (d, J = 7.8 Hz), 80.97, 52.37, 28.66, 27.19. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2F$: 385.1558, found: 385.1556. FTIR (cm^{-1}) 3384, 2973, 2934, 1731, 1671, 1623, 1523, 1497, 1473, 1454, 1369, 1351, 1268, 1233, 1162, 1112, 1008, 820, 711, 559.

3-(*tert*-Butylcarbamoyl)-5-chloro-1-methyl-2-oxoindolin-3-yl benzoate (4v). R_f (EtOAc–DCM = 5/95): 0.69; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.9 Hz, 2H), 7.64–7.61 (m, 1H), 7.48 (t, J = 2.9 Hz, 2H), 7.36–7.33 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.80 (bs, 1H), 3.30 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.36, 163.74, 162.66, 143.85, 134.26, 130.69, 130.21, 130.01, 128.89, 128.69, 128.52, 128.26, 126.68, 124.75, 109.86, 80.80, 52.41, 28.68, 27.18. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2Cl$: 401.1263, found: 401.1263. FTIR (cm^{-1}): 3439, 3020, 1732, 1692, 1615, 1492, 1366, 1268, 1216, 1108, 759, 709, 669.

5-Bromo-3-(*tert*-butylcarbamoyl)-1-methyl-2-oxoindolin-3-yl benzoate (4w). R_f (EtOAc–DCM = 5/95): 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 6.8 Hz, 2H), 7.63 (t, J = 6.6 Hz, 1H), 7.51–7.46 (m, 4H), 6.79 (d, J = 8.3 Hz, 2H), 3.29 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.27, 163.73, 162.66, 144.36, 130.02, 128.89, 128.54, 128.26, 127.42, 127.02, 115.92, 110.34, 80.73, 52.42, 28.69, 27.16. HRMS calculated $[M + H]^+$ for $C_{21}H_{22}O_4N_2Br$: 447.0737, found: 447.0727. FTIR (cm^{-1}) 3439, 3020, 2972, 2400, 1732, 1691, 1611, 1453, 1107, 757.

3-(Cyclohexylcarbamoyl)-1-methyl-2-oxoindolin-3-yl benzoate (4x). R_f (EtOAc–DCM = 5/95): 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39–7.34 (m, 2H), 7.06 (t, J = 7.7 Hz, 1H), 6.90 (d, J = 8.04 Hz, 1H), 6.80 (bs, 1H), 3.88–3.80 (m, 1H), 3.32 (s, 3H), 2.04–1.95 (m, 2H), 1.74–1.71 (m, 2H), 1.64–1.60 (m, 1H), 1.43–1.21 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.55, 163.79, 163.32, 145.19, 134.02, 130.85, 129.99, 128.77, 128.57, 125.04, 124.26, 123.27, 108.92, 81.01, 49.0, 32.88, 32.64, 27.03, 25.55, 24.77, 24.72. HRMS calculated $[M + H]^+$ for $C_{23}H_{25}O_4N_2$: 393.1809, found: 393.1799. FTIR (cm^{-1}): 3020, 2936, 2858, 1732, 1683, 1617, 1518, 1375, 1270, 1215, 929, 759, 669.

3-(Isopropylcarbamoyl)-1-methyl-2-oxoindolin-3-yl benzoate (4y). R_f (EtOAc–DCM = 5/95): 0.36; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 7.19 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39–7.35 (m, 2H), 7.07 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.74 (d, J = 7.06 Hz, 1H), 4.17–4.10 (m, 1H), 3.32 (s, 3H), 1.29 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.55, 163.81, 163.38, 145.21, 134.03, 130.85, 130, 128.77, 128.59, 125.02, 124.29, 123.29, 108.92, 80.99, 42.41, 27.03, 22.69, 22.48. HRMS calculated $[M + H]^+$ for $C_{20}H_{21}O_4N_2$: 353.1496, found: 353.1495. FTIR (cm^{-1}): 3020, 2406, 1732, 1679, 1616, 1416, 1270, 1215, 1021, 758, 669.

3-((2-Ethoxy-2-oxoethyl)carbamoyl)-1-methyl-2-oxoindolin-3-yl benzoate (4z). R_f (EtOAc–DCM = 5/95): 0.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.04 (m, 2H), 7.60–7.33 (m, 6H), 7.07 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 4.30–4.20 (m, 3H), 4.08–4.02 (dd, J_1 = 4.5 Hz, J_2 = 18.6 Hz, 1H), 3.32 (s, 3H), 1.31 (t, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.02, 169.34, 164.84, 163.59, 145.37, 134.11, 133.67, 131.08, 130.22, 130.11, 128.81, 128.53, 128.35, 124.39, 123.87, 123.33, 109.07, 81.22, 61.96, 41.81, 27.07, 14.25. HRMS calculated $[M + H]^+$ for $C_{21}H_{21}O_6N_2$: 397.1394, found: 397.1393. FTIR (cm^{-1}) 3430, 3020, 2400, 1732, 1693, 1616, 1524, 1473, 1422, 1273, 1215, 1108, 759, 669, 497.

***N*-(*tert*-Butyl)-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide (6a).** R_f (EtOAc–DCM = 5/95): 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.37 (t, J = 7.6, 1H), 7.28–7.19 (m, 2H), 7.07–7.01 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 6.8 Hz, 1H), 3.32 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.19, 164.54, 148.59, 145.00, 140.76, 135.00, 131.57, 126.81, 123.92, 123.90, 123.25, 118.43, 109.47, 85.19, 52.21, 28.65, 27.02. HRMS calculated $[M + H]^+$ for $C_{20}H_{22}O_5N_3$: 384.1554, found: 384.1554. FTIR (cm^{-1}) 3389, 3063, 2971, 2252, 1735, 1685, 1609, 1348, 911, 733.

5-Bromo-*N*-(*tert*-butyl)-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide (6b). R_f (EtOAc–DCM = 5/95): 0.45; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05–8.01 (m, 1H), 7.77 (s, 1H), 7.55–7.50 (m, 1H), 7.35–7.26 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 8.3 Hz, 1H), 3.29 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.41, 163.88, 148.35, 143.98, 140.61, 135.14, 134.45, 127.10, 126.63, 123.50, 117.87, 116.60, 110.92, 84.69, 52.43, 50.35, 28.64, 27.16. HRMS calculated $[M + H]^+$ for $C_{20}H_{21}O_5N_3$: 462.0659, found: 462.0662. FTIR (cm^{-1}) 3390, 3020, 2400, 1740, 1688, 1607, 1526, 1347, 1215, 1104, 1037, 858, 757, 669.

***N*-Cyclohexyl-1-methyl-3-(2-nitrophenoxy)-2-oxoindoline-3-carboxamide (6c).** R_f (EtOAc–DCM 5/99): 0.30; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.12 Hz, 1H), 7.78 (s, 1H), 7.37–7.19 (m, 3H), 7.05–6.91 (m, 3H), 6.87 (d, J = 7.42 Hz, 1H), 3.78 (s, 1H), 3.31 (s, 3H), 1.99 (s, 2H), 1.78 (s, 2H), 1.60 (s, 1H), 1.39–1.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.03, 164.52, 148.62, 144.97, 140.84, 134.99, 131.59, 126.81, 124.41, 124.08, 123.86, 123.29, 118.57, 109.46, 85.11, 48.94, 32.79, 32.64, 27.04, 25.59, 24.75. HRMS calculated $[M + H]^+$ for $C_{22}H_{24}O_5N_3$: 410.1710, found: 410.1711. FTIR (cm^{-1}) 3944, 3054, 2987, 2685, 2410, 2305, 1731, 1604, 1421, 1265, 1021, 896, 739, 706.

5-Bromo-*N*-(*tert*-butyl)-3-hydroxy-1-methyl-2-oxoindoline-3-carboxamide (7). R_f (EtOAc–DCM = 20/80): 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 6.4 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 6.72 (d, J = 8.9 Hz, 1H), 6.64 (bs, 1H), 4.99 (s, 1H,), 3.14 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.70, 166.99, 143.76, 133.34, 130.69, 126.84, 116.21, 110.53, 78.37, 52.05, 28.67, 26.85. HRMS calculated $[M + H]^+$ for $C_{14}H_{18}O_3N_2Br$:

341.0495, found: 341.0497. FTIR (cm^{-1}): 3373, 2969, 2923, 1734, 1607, 1488, 1366, 1218, 1099, 878, 824, 760.

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