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Transition-Metal-Free Terminal Alkyne Addition to Isatins

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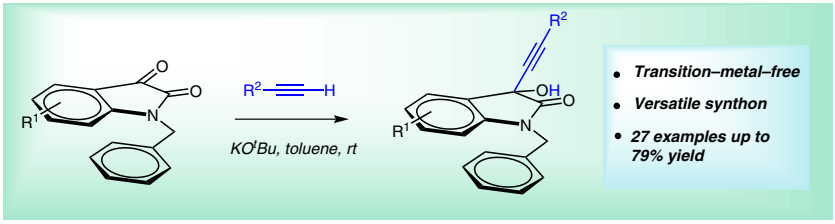

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Abstract A 'direct' alkynylation of isatins, which uses potassium *tert*-butoxide to provide the desired 3-hydroxy-3-ethynyl-2-oxindoles in good to high yields, is reported. This protocol proceeds smoothly for both electron-rich and electron-deficient alkynes in comparable reaction rates and does not require any specially design ligand or expensive transition-metal catalysts.

Key words alkynes, 3-hydroxy-3-ethynylindolin-2-ones, HIV, isatins, nucleophiles, addition, transition-metal-free

The addition of a carbon-centered nucleophile to the electrophilic carbonyl group is one of the important atom-economical methods[1] to construct complex molecules from simple starting materials. Recently, we have developed an 'on-water'-promoted aldol reaction of N-substituted thiazolidinediones with isatin derivatives to afford a new class of pharmacologically important thiazolidinedione-linked 3-hydroxy-2-oxindole derivatives.[2] The 3-hydroxy-2-oxindole motif is widely distributed in several biologically active natural products such as the celogentins,[3a] convolutamidine **A** to **E** (Figure 1)[3b] and donaxaridine.[3c–e] Furthermore, it has been reported that 3-(cyclopropylethynyl)-3-hydroxy-5-methylindolin-2-one **F** is more active than the anti-HIV drug efavirenz (Figure 1).[4] Ethynylindolin-2-ones can also serve as versatile synthons in a wide variety of synthetic applications to prepare biologically important compounds.

In this context, we were interested in developing a direct alkynylation of isatins **1** for the synthesis of 3-hydroxy-3-ethynylindolin-2-one derivatives under transition-metal-free conditions. Despite several methods having been reported for direct terminal alkyne addition to a carbonyl group,[5–8] only a few studies have used isatins as the electrophilic partners (Scheme 1, a–c).[9–11] We have previously reported that KO^{t}Bu can transform organonitriles to the corresponding amides via activation of the nitrile groups by potassium ions.[12] We hypothesised that if the carbonyl group of isatins could be activated by coordination with potassium ions, an alkoxide-promoted alkynylation would be possible (Scheme 1, d).

In order to test our proposed methodology, *N*-benzylisatin (**1a**) was used as a model substrate to optimize the direct alkynylation using phenylacetylene (**2a**) as the alkyne precursor (Table 1). Babler and co-workers reported that alkoxide can catalyze the addition of terminal alkynes to ketones in DMSO.[13] We first attempted the alkynylation of

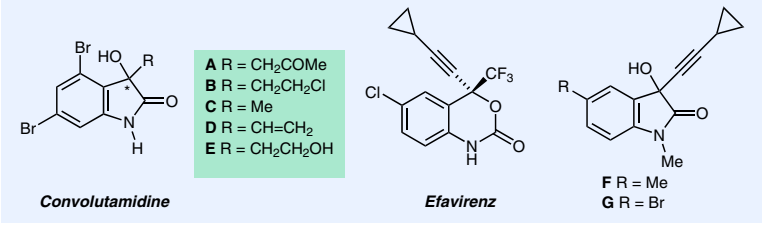
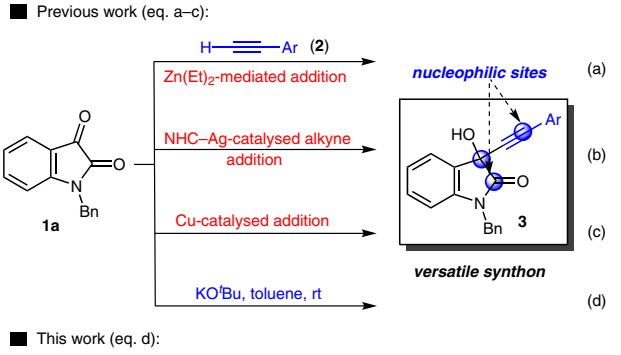
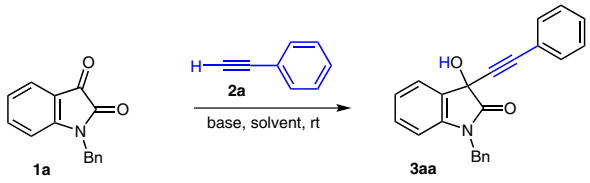


Figure 1 Naturally occurring and biologically active 3-hydroxy-2-oxindole derivatives



Scheme 1 Addition of alkynes to isatins

Table 1 Optimization of Phenylacetylene Addition to *N*-Benzylisatin[a]

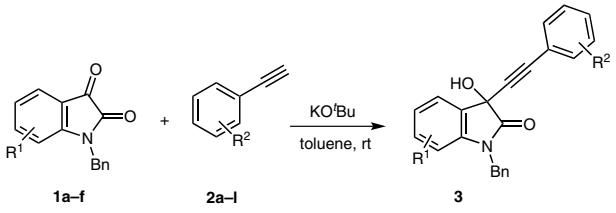


Entry	Base (mol%)	Solvent	Yield[b] (%)
1	KO^{t}Bu (10)	DMSO	–
2	KO^{t}Bu (100)	DMSO	30
3	KO^{t}Bu (100)	DMF	30
4	KO^{t}Bu (100)	MeCN	NR
5	KO^{t}Bu (50)	toluene	40
6	KO^{t}Bu (75)	toluene	52
7	**KO^{t}Bu (100)**	**toluene**	**79**
8	KO^{t}Bu (100)	xylene	56
9	KO^{t}Bu (100)	mesitylene	42
10	KO^{t}Bu (100)	nitrobenzene	trace
11	KO^{t}Bu (100)	DCE	NR
12	KO^{t}Bu (100)	CH_2Cl_2	NR
13	KO^{t}Bu (100)	^{t}BuOH	NR
14	KO^{t}Bu (100)	MeOH	trace
15	NaO^{t}Bu (100)	toluene	70
16	LiO^{t}Bu (100)	toluene	–
17	K_2CO_3 (100)	toluene	–
18	Cs_2CO_3 (100)	toluene	–
19	KOH (100)	toluene	–
20	NaOH (100)	toluene	–

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.5 mmol), N_2 atmosphere.
[b] Isolated yield; NR = no reaction.

isatin **1a** using catalytic KO^{t}Bu in DMSO (Table 1, entry 1); however, **1a** did not show any reactivity under these conditions. Next, a stoichiometric amount of KO^{t}Bu was used, and the desired product **3aa** was obtained in poor yield (Table 1, entry 2). No further improvement in yield was observed upon reaction in *N*,*N*-dimethylformamide and no product formation was detected in acetonitrile (Table 1, entries 3 and 4). Then, different polar aprotic solvents were tested, but only electron-rich aromatic solvents provided the desired product (Table 1, entries 5–12). Toluene was the best solvent among the tested electron-rich aromatic solvents (Table 1, entry 7). Furthermore, alkynylation in protic solvents, such as ^{t}BuOH and MeOH, proved to be inefficient (Table 1, entries 13 and 14).

Table 2 Addition of Alkynes to Isatins[a]



Entry	R^1	R^2	Product	Yield (%)
1	**1a**, H	**2a**, H	**3aa**	79
2	**1a**, H	**2b**, 3-OMe	**3ab**	62
3[b]	**1b**, H	**2b**, 3-OMe	**3bb**	47
4	**1a**, H	**2c**, 3-Me	**3ac**	48
5	**1a**, H	**2d**, 4-Me	**3ad**	76
6	**1a**, H	**2e**, 4-^{t}Bu	**3ae**	68
7	**1a**, H	**2f**, 2,4,6-Me_3	**3af**	50
8	**1a**, H	**2g**, 3,5-$(OMe)_2$	**3ag**	40
9	**1a**, H	**2h**, 4-C_5H_{11}	**3ah**	69
10	**1a**, H	**2i**, 4-COOMe	**3ai**	48
11	**1a**, H	**2j**, 3-F	**3aj**	46
12	**1a**, H	**2k**, 3,5-F_2	**3ak**	70
13	**1a**, H	**2l**, 4-CF_3	**3al**	55
14	**1c**, 5-Cl	**2a**, H	**3ca**	62
15	**1d**, 5-F	**2a**, H	**3da**	76
16	**1e**, 5-OCF_3	**2a**, H	**3ea**	42
17	**1f**, 5,7-Me_2	**2a**, H	**3fa**	56
18	**1c**, 5-Cl	**2d**, 4-Me	**3cd**	52
19	**1c**, 5-Cl	**2e**, 4-^{t}Bu	**3ce**	50
20	**1c**, 5-Cl	**2l**, 4-CF_3	**3cl**	46
21	**1c**, 5-Cl	**2b**, 3-OMe	**3cb**	42

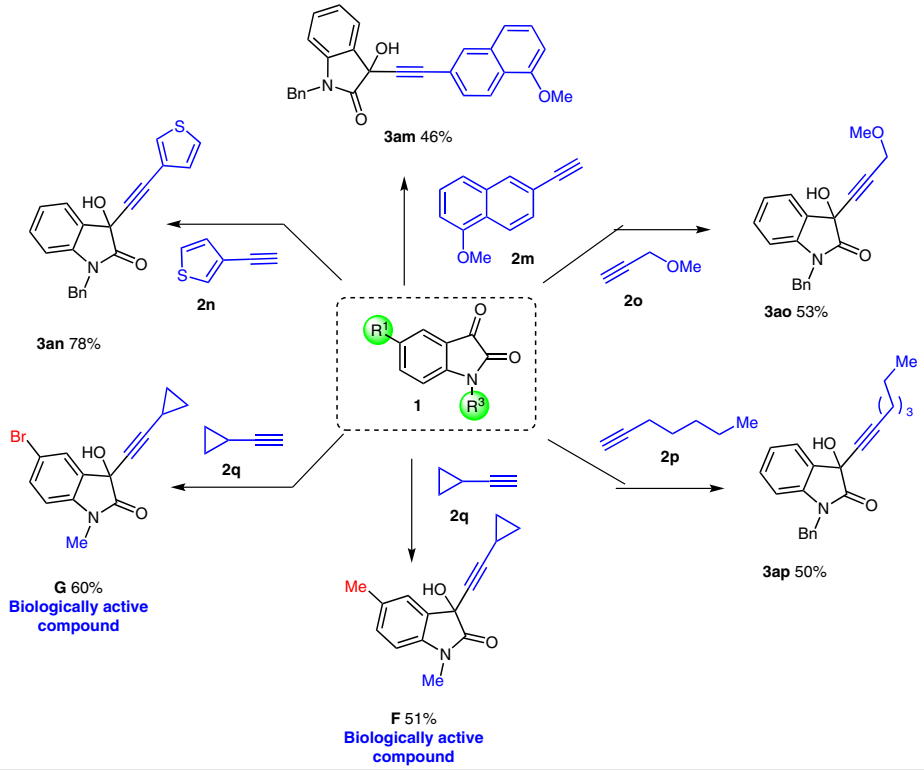
[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), KO^{t}Bu (1.0 equiv), toluene, rt, 0.5–3 h.
[b] *N*-Methylisatin was used.

To investigate counterion effects, NaO^{t}Bu and LiO^{t}Bu were also used (Table 1, entries 15 and 16). Surprisingly, only NaO^{t}Bu provided the desired product in a synthetically useful yield. This result indicates that the size of the positive counterion plays a significant role in activation of the electrophile. At this point we were curious as to whether any other base with a different counter anion could promote this transformation. We found that K_2CO_3 and Cs_2CO_3 could not provide the desired product **3aa** (Table 1, entries 17 and 18). In addition, the reaction was unsuccessful when KOH or NaOH was used (Table 1, entries 19 and 20). The optimized protocol is straightforward and uses commercially available reagents. No special experimental setup is necessary to perform this transformation.

Having established optimized reaction conditions, we explored the substrate scope of this methodology with respect to the nucleophile using commercially available anhydrous toluene (Table 2). Electron-rich alkynes **2a–h** provided the corresponding products **3aa–ah** in moderate to good yields in comparable reaction rates (Table 2, entries 1–9).

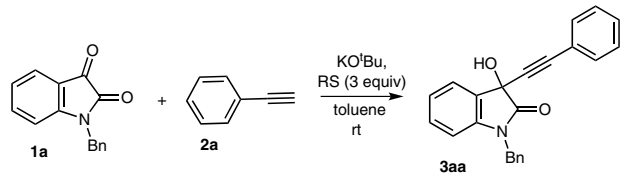
Next, electron-deficient alkynes **2i–2l** were used as the nucleophile, and the corresponding alkynylation products **3ai–3al** were obtained in 46–70% yield (Table 2, entries 10–13). Then, both electron-rich and electron-deficient isatins were examined as the electrophilic partner. Thus, addition of phenylacetylene (**2a**) to both electron-deficient and electron-rich isatins was investigated (Table 2, entries 14–17). Since the 5-chloro- and 5-fluoroisatins **1c** and **1d** are highly electrophilic in nature, the corresponding alkyne addition products **3ca** and **3da** were isolated in 62% and 76% yield, respectively. As expected, the electron-rich isatin **1f**, due to its poor electrophilicity, afforded the corresponding addition product **3fa** in 56% yield. Since isatin **1c** was a good electrophilic partner in the direct alkyne addition, the nucleophilic addition of different alkynes (**2d**, **2e**, **2l** and **2b**) was also performed (Table 2, entries 18–21). The corresponding products **3cd**, **3ce**, **3cl** and **3cb** were isolated in synthetically useful yields.

The reaction of aliphatic alkynes **2o** and **2p** with isatin **1a** afforded the corresponding addition products **3ao** and **3ap** in 53% and 50% yield, respectively (Scheme 2). Encouraged by these results, we attempted the direct addition of ethynylcyclopropane (**2q**) to *N*,5-dimethylisatin and 5-bromo-*N*-methylisatin. To our delight, the anti-HIV drug analogues **F** and **G** were synthesised in a single step starting from commercially available materials in synthetically useful yields. Efficient synthesis of **3an** (78% yield) using alkyne **2n** containing the heterocyclic thiophene ring system and successful addition of the more complex alkyne **2m** demonstrate the synthetic utility of this protocol for the diversity oriented synthesis[14] of biologically active molecules (Scheme 2).



Scheme 2 Addition of aromatic, heteroaromatic and aliphatic alkynes to isatins

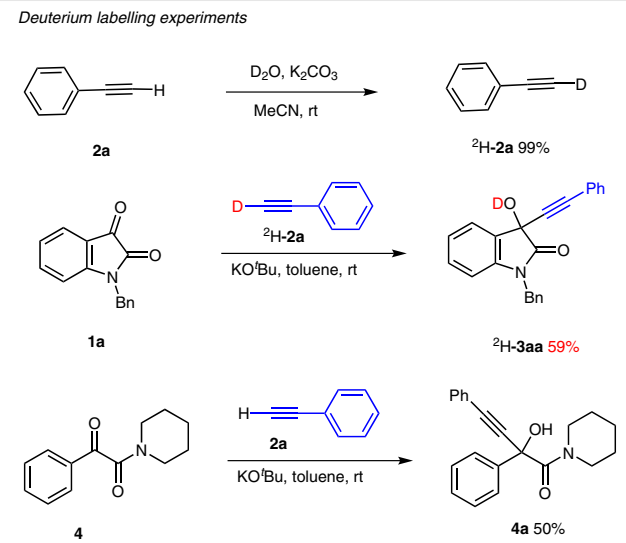
To examine whether this alkynylation process involves the formation of any radicals, the reaction of isatin **1a** with phenylacetylene (**2a**) was performed in the presence of TEMPO or galvinoxyl as a radical scavenger (Scheme 3). No significant change in the yield of **3aa** was observed, indicating that radical intermediates are not involved in this process.



Radical Scavenger (RS)	Yield
none	79%
TEMPO	75%
galvinoxyl	73%

Scheme 3 Addition of phenylacetylene to isatin **1a** in the presence of a radical scavenger

A deuterium labelling experiment was then carried out to evaluate the proton source for protonation of the resultant alkoxide formed during the direct alkyne addition to isatins. A deuterium atom was incorporated into phenylacetylene upon treatment with K_2CO_3 and D_2O.[15] When the alkyne ^{2}H-**2a** was employed under our alkynylation conditions with isatin **1a**, an excellent level of deuterium incorporation was observed to afford ^{2}H-**3aa** in 59% yield (Scheme 4). This experimental data indicates that the alkyne serves as the proton source during protonation of the resultant alkoxide in this alkynylation method.



Scheme 4 Deuterium labelling and control experiments

To investigate the role of potassium ion, the alkynylation of isatin **1a** with phenylacetylene (**2a**) was carried out using 18-crown-6 as a potassium ion scavenger: only 20% inhibition of product formation was observed.[16] To study the role of isatin conformation, alkynylations of aromatic and aliphatic ketones were tested, but none of these ketones afforded the desired product. The same result was also observed for cyclic and acyclic diketone substrates.[17] These data suggest that the lactam functionality plays an important role in enhancing the electrophilicity of the keto group of isatin. To clarify this point, the direct alkynylation of acyclic keto amide **4** was undertaken and, gratifyingly, the addition product **4a** was isolated in 50% yield. This result provides direct evidence that the presence of an amide group or lactam is essential for this transformation.

Combining these results, the following mechanism is proposed for the direct alkynylation reaction of isatins (Scheme 5). Upon treatment of isatin **1d** with KO^{t}Bu, potassium cation would coordinate with the two carbonyl groups to form a stable five-membered complex **A**. In the proposed complex **A**, the electrophilicity of the carbonyl group is increased due to the presence of the electrophilic iminium ion (resonance form of lactam). This facilitates a direct nucleophilic attack of in situ formed phenylacetylide to the most electrophilic carbonyl group to form the corresponding potassium alkoxide, which upon protonation generates the desired alcohol **3da**. Our deuterium labelling experiment showed that alkyne acts as the proton source in this reaction. X-ray crystal structure[18] analysis unambiguously proved the structure of the product **3da**. The crystal packing shows that the two structural units are stacked in three-dimensional orientations via H-bonding and π–π* interactions (Figure 2).

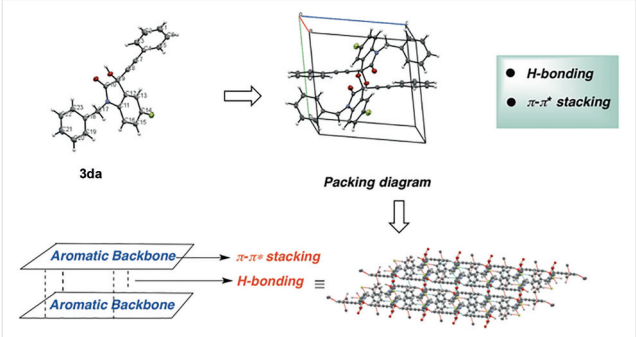
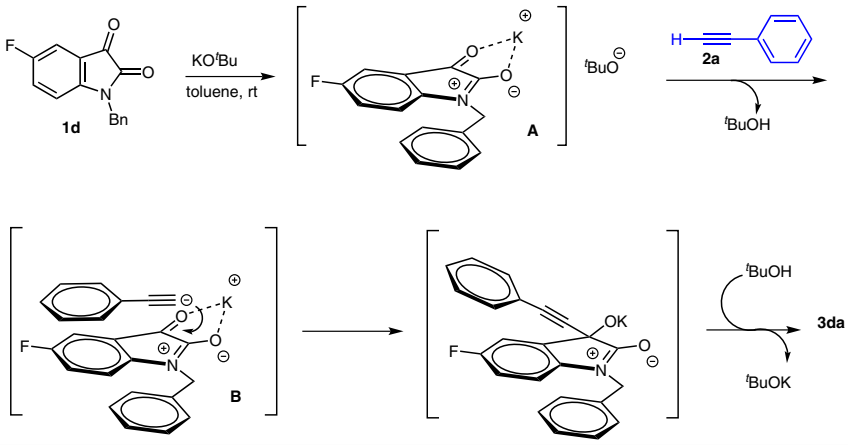


Figure 2 Crystal packing of the direct alkynylation product **3da**

In conclusion, a direct alkynylation of isatins mediated by potassium *tert*-butoxide has been developed. A wide range of substrates are compatible under these reaction conditions, providing the corresponding alkynylation products in good to high yields. The transition-metal-free process, inexpensive base reagent and the direct alkynylation



Scheme 5 Proposed mechanism

of isatins are highlights of this method. This work is promising for the large-scale synthesis of 3-hydroxy-3-ethynyl-2-oxindoles from various isatins and alkynes. Studies directed towards the synthetic applications of the ethynyloxindole products are currently underway in our laboratory, and the results will be reported in due course.

All solvents and reagents were obtained from commercial sources. Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of argon using anhydrous solvents. N-Protected isatin derivatives **1a–f** were prepared following a literature procedure.[2] Reactions were monitored by analytical TLC which was visualized by exposure to UV light (254 nm). Silica gel (100–200 mesh) was used for flash column chromatography. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 or 500 MHz and the data are reported relative to the residual solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, coupling constant(s), integration. Chemical shifts (δ) and coupling constants (*J*) are reported in ppm and Hz, respectively. The following abbreviations are used to indicate the multiplicity in the NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 or 125 MHz and the data are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer and the data are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry was recorded with a Q-TOF YA263 (Waters Corporation) high-resolution instrument by positive-mode electrospray ionization. Single crystal X-ray analysis of **3da** was recorded on a Bruker Kappa Apex II high-resolution X-ray diffractometer. Compounds **3aa**, **3ca**, **3da**, **3ea** and **3cd** are known compounds and their characterization data match those previously reported[10,11] (see Supporting Information).

3-Ethynyl-3-hydroxyindolin-2-ones 3; General Procedure

To a solution of an alkyne **2** (1.2 equiv) in anhydrous toluene (3 mL) under an argon atmosphere, KO^{t}Bu (1.0 equiv) was added, and the mixture was stirred for 10–15 min. Then, an N-protected isatin **1** (1.0 equiv) was added to the reaction mixture, which was stirred for 30 min to 3 h until all the isatin was consumed (confirmed by TLC). The reaction was finally quenched with a few drops of 1 N HCl and the resulting mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel (EtOAc–hexane, 10:90 to 30:70) to give compounds **3**.

1-Benzyl-3-hydroxy-3-[(3-methoxyphenyl)ethynyl]indolin-2-one (3ab)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-ethynylanisole (**2b**) (0.06 mL, 0.5 mmol) provided compound **3ab** (92 mg, 62%) as a grey solid; mp 177–179 °C.

IR (KBr): 3270, 2831, 2721, 1410, 1340, 1210, 1108 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.63 (d, *J* = 9.0 Hz, 1 H), 7.32–7.29 (m, 4 H), 7.28–7.24 (m, 2 H), 7.20 (t, *J* = 10.0 Hz, 1 H), 7.13 (t, *J* = 9.4 Hz, 1 H), 7.06 (d, *J* = 9.5 Hz, 1 H), 7.00–6.98 (m, 1 H), 6.90 (dd, *J* = 10.4, 2.7 Hz, 1 H), 6.74 (d, *J* = 9.8 Hz, 1 H), 4.94 (s, 2 H), 3.94 (br s, 1 H), 3.77 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.1, 159.2, 142.1, 135.0, 130.4, 129.3, 128.9, 128.8, 127.8, 127.2, 124.8, 124.6, 123.8, 122.5, 116.6, 116.0, 110.0, 86.5, 85.2, 69.6, 55.3, 44.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{19}NNaO_3$: 392.1263; found: 392.1201.

3-Hydroxy-3-[(3-methoxyphenyl)ethynyl]-1-methylindolin-2-one (3bb)

Following the general procedure, isatin **1b** (65 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-ethynylanisole (**2b**) (0.06 mL, 0.5 mmol) provided compound **3bb** (55 mg, 47%) as a grey solid; mp 171–173 °C.

IR (KBr): 3285, 2981, 2861, 2740, 2430, 1670, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 9.4 Hz, 1 H), 7.36 (dd, *J* = 14.4, 5.4 Hz, 1 H), 7.15 (dt, *J* = 9.7, 4.1 Hz, 2 H), 7.00 (d, *J* = 9.5 Hz, 1 H), 6.94 (d, *J* = 1.9 Hz, 1 H), 6.86–6.83 (m, 2 H), 3.72 (s, 3 H), 3.22 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.1, 159.1, 143.0, 130.4, 129.2, 129.0, 125.0, 125.0, 124.0, 123.0, 116.5, 116.0, 109.0, 86.1, 85.3, 70.0, 55.2, 27.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{15}NNaO_3$: 316.0950; found: 316.1023.

1-Benzyl-3-hydroxy-3-(*m*-tolylethynyl)indolin-2-one (3ac)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-ethynyltoluene (**2c**) (0.06 mL, 0.5 mmol) provided compound **3ac** (68 mg, 48%) as a white solid; mp 195–197 °C.

IR (KBr): 3210, 2831, 2831, 2710, 1680, 1370, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.62 (d, *J* = 10.0 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.34–7.24 (m, 6 H), 7.12 (dd, *J* = 9.6, 2.8 Hz, 3 H), 6.72 (d, *J* = 9.8 Hz, 1 H), 4.93 (s, 2 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.5, 142.0, 138.0, 135.0, 133.0, 130.2, 130.0, 129.1, 129.0, 129.0, 128.1, 128.0, 127.1, 125.0, 124.0, 121.4, 110.0, 87.0, 85.1, 70.0, 44.0, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{19}NNaO_2$: 376.1313; found: 376.1287.

1-Benzyl-3-hydroxy-3-(*p*-tolylethynyl)indolin-2-one (3ad)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 4-ethynyltoluene (**2d**) (0.06 mL, 0.5 mmol) provided compound **3ad** (107 mg, 76%) as a white solid; mp 199–201 °C.

IR (KBr): 3303, 2223, 1705, 1612, 1395, 1256, 1220, 1156 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 7.3 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.32–7.21 (m, 6 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 4.93 (s, 2 H), 3.52 (br s, 1 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.1, 142.1, 139.3, 135.0, 132.0, 130.3, 129.0, 128.9, 127.8, 127.1, 124.8, 123.7, 118.5, 109.9, 86.8, 84.7, 69.6, 44.1, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{19}NNaO_2$: 376.1313; found: 376.1308.

1-Benzyl-3-[(4-*tert*-butylphenyl)ethynyl]-3-hydroxyindolin-2-one (3ae)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 4-*tert*-butylphenylacetylene (**2e**) (0.09 mL, 0.5 mmol) provided compound **3ae** (107 mg, 68%) as a white solid; mp 188–190 °C.

IR (KBr): 3110, 2931, 2821, 2710, 1680, 1470, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 7.2 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 2 H), 7.35–7.28 (m, 6 H), 7.27–7.22 (m, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 4.93 (s, 2 H), 1.29 (s, 9 H).

^{13}C NMR (125 Hz): δ = 174.2, 152.4, 142.2, 135.0, 132.0, 130.3, 129.0, 129.0, 128.0, 127.1, 125.2, 125.0, 124.0, 119.0, 110.0, 87.0, 85.0, 70.0, 44.1, 35.0, 31.1, 30.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{25}NNaO_2$: 418.1783; found: 418.1701.

1-Benzyl-3-hydroxy-3-(mesitylethynyl)indolin-2-one (3af)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 2-ethynyl-1,3,5-trimethylbenzene (**2f**) (0.08 mL, 0.5 mmol) provided compound **3af** (76 mg, 50%) as a white solid; mp 219–221 °C.

IR (KBr): 3240, 3060, 2820, 1810, 1680, 1470, 1230 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 7.4 Hz, 1 H), 7.31 (d, *J* = 4.2 Hz, 4 H), 7.27–7.19 (m, 3 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 6.94 (s, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 4.99–4.87 (m, 2 H), 2.32 (s, 3 H), 2.21 (s, 3 H), 2.16 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.4, 142.3, 138.4, 138.2, 135.3, 134.0, 133.4, 131.0, 130.4, 129.4, 129.0, 128.0, 127.3, 125.0, 124.0, 119.0, 110.0, 89.0, 86.2, 70.0, 44.2, 20.1, 20.0, 19.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{23}NNaO_2$: 404.1626; found: 404.1598.

1-Benzyl-3-[(3,5-dimethoxyphenyl)ethynyl]-3-hydroxyindolin-2-one (3ag)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 1-ethynyl-3,5-dimethoxybenzene (**2g**) (81 mg, 0.5 mmol) provided compound **3ag** (64 mg, 40%) as a white solid; mp 193–195 °C.

IR (KBr): 3080, 2820, 2621, 1820, 1680, 1470, 1280 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 7.3 Hz, 1 H), 7.34–7.30 (m, 4 H), 7.29–7.27 (m, 2 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 7.9 Hz, 1 H), 6.61 (d, *J* = 2.3 Hz, 2 H), 6.45 (t, *J* = 2.3 Hz, 1 H), 4.94 (s, 2 H), 3.75 (s, 6 H).

^{13}C NMR (125 MHz): δ = 160.5, 142.2, 135.0, 130.5, 129.0, 128.8, 128.7, 128.7, 128.0, 127.2, 125.0, 124.0, 123.0, 119.4, 110.0, 109.8, 103.0, 87.0, 85.0, 70.0, 55.5, 44.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{21}NNaO_4$: 422.1368; found: 422.1320.

1-Benzyl-3-hydroxy-3-[(4-pentylphenyl)ethynyl]indolin-2-one (3ah)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 1-ethynyl-4-pentylbenzene (**2h**) (0.09 mL, 0.5 mmol) provided compound **3ah** (113 mg, 69%) as a white solid; mp 141–143 °C.

IR (KBr): 3250, 3040, 2621, 2410, 1820, 1670, 1180 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.60 (d, *J* = 7.4 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.33–7.29 (m, 4 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 7.11 (t, *J* = 7.8 Hz, 3 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 4.94 (s, 2 H), 3.60 (d, *J* = 3.5 Hz, 1 H), 2.58 (t, *J* = 7.7 Hz, 2 H), 1.60–1.57 (m, 2 H), 1.33–1.26 (m, 4 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz): δ = 174.1, 144.4, 142.2, 135.1, 132.0, 130.4, 129.0, 129.0, 128.4, 128.0, 127.2, 125.0, 124.0, 119.0, 110.0, 87.0, 85.0, 70.0, 44.1, 36.0, 31.4, 31.0, 22.5, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{27}NNaO_2$: 432.1939; found: 432.1910.

Methyl 4-[(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)ethynyl]benzoate (3ai)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and methyl 4-ethynylbenzoate (**2i**) (80 mg, 0.5 mmol) provided compound **3ai** (76 mg, 48%) as a white solid; mp 146–148 °C.

IR (KBr): 3260, 2824, 2220, 1810, 1680, 1470, 1220 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 7.4 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.33–7.28 (m, 6 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 4.94 (s, 2 H), 3.91 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.2, 166.4, 142.1, 135.0, 132.0, 131.0, 130.3, 129.4, 129.0, 129.0, 128.0, 127.2, 127.0, 126.2, 125.0, 124.0, 115.0, 110.0, 88.2, 86.0, 70.0, 52.3, 44.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{19}NNaO_4$: 420.1212; found: 420.1188.

1-Benzyl-3-[(3-fluorophenyl)ethynyl]-3-hydroxyindolin-2-one (3aj)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 1-ethynyl-3-fluorobenzene (**2j**) (0.06 mL, 0.5 mmol) provided compound **3aj** (66 mg, 46%) as a brown solid; mp 164–166 °C.

IR (KBr): 3210, 2831, 2621, 1710, 1480, 1370, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.54 (d, *J* = 7.6 Hz, 1 H), 7.27–7.22 (m, 4 H), 7.21–7.14 (m, 4 H), 7.05 (t, *J* = 7.7 Hz, 2 H), 6.94–6.79 (m, 1 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 4.86 (s, 2 H).

^{13}C NMR (125 MHz): δ = 174.1, 163.4, 161.0, 142.1, 135.0, 130.5, 130.0, 129.8, 129.0, 128.0, 127.8, 127.2, 125.0, 124.0, 119.0, 118.7, 116.5, 116.3, 110.0, 86.4, 85.2, 70.0, 44.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{16}FNNaO_2$: 380.1063; found: 380.1002.

1-Benzyl-3-[(3,5-difluorophenyl)ethynyl]-3-hydroxyindolin-2-one (3ak)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 1-ethynyl-3,5-difluorobenzene (**2k**) (0.06 mL, 0.5 mmol) provided compound **3ak** (105 mg, 70%) as a white solid; mp 173–175 °C.

IR (KBr): 3210, 2931, 2881, 2790, 1680, 1370, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.62 (d, *J* = 6.8 Hz, 1 H), 7.33–7.27 (m, 6 H), 7.24–7.13 (m, 1 H), 6.91 (d, *J* = 6.9 Hz, 2 H), 6.75 (d, *J* = 9.2 Hz, 2 H), 4.93 (s, 2 H).

^{13}C NMR (125 MHz): δ = 174.3, 164.0 (d), 161.1 (d), 142.0 (d), 135.0, 131.0, 128.8, 128.6, 128.5, 128.0, 127.1, 127.0, 125.0, 124.0, 115.1, 115.0, 110.0, 105.2, 87.5, 70.0, 44.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{15}F_2NNaO_2$: 398.0969; found: 398.1067.

1-Benzyl-3-hydroxy-3-{[4-(trifluoromethyl)phenyl]ethynyl}indolin-2-one (3al)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (**2l**) (0.08 mL, 0.5 mmol) provided compound **3al** (90 mg, 55%) as a white solid; mp 155–157 °C.

IR (KBr): 3303, 2223, 1705, 1612, 1493, 1419, 1388, 1272, 1248 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.63 (d, *J* = 9.1 Hz, 1 H), 7.53 (d, *J* = 1.7 Hz, 4 H), 7.34–7.27 (m, 6 H), 7.14 (t, *J* = 8.8 Hz, 1 H), 6.74 (d, *J* = 9.8 Hz, 1 H), 4.94 (s, 2 H), 4.43 (br s, 1 H).

^{13}C NMR (125 MHz): δ = 174.1, 142.1, 134.8, 132.3, 130.6, 128.9, 128.5, 127.9, 127.1, 125.2, 125.1, 124.8, 124.0, 110.0, 87.8, 85.0, 69.5, 44.1, 22.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{16}F_3NNaO_2$: 430.1031; found: 430.1035.

1-Benzyl-3-hydroxy-5,7-dimethyl-3-(phenylethynyl)indolin-2-one (3fa)

Following the general procedure, isatin **1f** (106 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and phenylacetylene (**2a**) (0.05 mL, 0.5 mmol) provided compound **3fa** (82 mg, 56%) as a white solid; mp 155–157 °C.

IR (KBr): 3280, 2631, 1821, 1710, 1480, 1270, 1208 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.38 (dd, *J* = 8.0, 1.3 Hz, 2 H), 7.25–7.15 (m, 7 H), 7.09 (d, *J* = 7.3 Hz, 2 H), 6.74 (s, 1 H), 5.08 (d, *J* = 7.6 Hz, 2 H), 2.22 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (125 MHz): δ = 175.2, 138.0, 137.0, 135.0, 134.0, 133.0, 130.0, 129.0, 128.2, 127.3, 126.0, 123.5, 122.0, 120.4, 86.4, 86.0, 69.2, 45.3, 21.1, 18.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{21}NNaO_2$: 390.1470; found: 390.1397.

1-Benzyl-3-[(4-*tert*-butylphenyl)ethynyl]-5-chloro-3-hydroxyindolin-2-one (3ce)

Following the general procedure, isatin **1c** (108 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 4-*tert*-butylphenylacetylene (**2e**) (0.09 mL, 0.5 mmol) provided compound **3ce** (86 mg, 50%) as a white solid; mp 191–193 °C.

IR (KBr): 3220, 2840, 2721, 2610, 2370, 1870, 1308 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.59 (d, *J* = 1.5 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.32–7.29 (m, 7 H), 7.20 (dd, *J* = 2.2, 10.3 Hz, 1 H), 6.62 (d, *J* = 10.5 Hz, 1 H), 4.91 (s, 2 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz): δ = 174.0, 153.0, 141.0, 135.0, 132.0, 131.0, 130.2, 129.2, 129.0, 128.0, 127.1, 125.4, 125.3, 118.2, 111.0, 87.4, 84.1, 69.5, 44.2, 35.0, 31.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{24}ClNNaO_2$: 452.1393; found: 452.1372.

1-Benzyl-5-chloro-3-hydroxy-3-{[4-(trifluoromethyl)phenyl]ethynyl}indolin-2-one (3cl)

Following the general procedure, isatin **1c** (108 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (**2l**) (0.08 mL, 0.5 mmol) provided compound **3cl** (81 mg, 46%) as a brown solid; mp 175–177 °C.

IR (KBr): 3280, 2950, 2820, 2740, 2470, 1670, 1408 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.52 (d, *J* = 2.3 Hz, 1 H), 7.48 (br s, 4 H), 7.25–7.19 (m, 5 H), 7.16 (dd, *J* = 2.2, 8.4 Hz, 1 H), 6.58 (d, *J* = 8.4 Hz, 1 H), 4.85 (d, *J* = 3.1 Hz, 2 H).

^{13}C NMR (125 MHz): δ = 173.7, 140.5, 134.4, 132.3, 130.5, 130.0, 129.4, 129.0, 128.7, 128.1, 127.1, 125.4, 125.2, 111.1, 87.1, 85.5, 69.4, 53.4, 44.3, 30.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{15}ClF_3NNaO_2$: 464.0641; found: 464.0602.

1-Benzyl-5-chloro-3-hydroxy-3-[(3-methoxyphenyl)ethynyl]indolin-2-one (3cb)

Following the general procedure, isatin **1c** (108 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-ethynylanisole (**2b**) (0.06 mL, 0.5 mmol) provided compound **3cb** (68 mg, 42%) as a white solid; mp 186–188 °C.

IR (KBr): 3250, 2822, 2711, 2650, 2270, 1670, 1408 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.52 (d, *J* = 2.2 Hz, 1 H), 7.24–7.18 (m, 5 H), 7.12 (t, *J* = 9.7 Hz, 2 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 6.90 (br s, 1 H), 6.82 (dd, *J* = 2.6, 10.4 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 4.84 (s, 2 H), 3.69 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.0, 159.2, 141.0, 134.5, 130.3, 130.2, 129.4, 129.2, 129.0, 128.0, 127.1, 125.4, 124.7, 122.2, 116.6, 116.1, 111.0, 87.0, 84.4, 69.4, 55.3, 44.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{18}ClNNaO_3$: 426.0873; found: 426.0798.

1-Benzyl-3-hydroxy-3-[(5-methoxynaphthalen-2-yl)ethynyl]indolin-2-one (3am)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 6-ethynyl-1-methoxynaphthalene (**2m**) (91 mg, 0.5 mmol) provided compound **3am** (77 mg, 46%) as a white solid; mp 205–207 °C.

IR (KBr): 3220, 3031, 2821, 2610, 1880, 1670, 1420 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.92 (s, 1 H), 7.67–7.63 (m, 3 H), 7.45 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.33 (d, *J* = 4.4 Hz, 4 H), 7.28–7.25 (m, 2 H), 7.15–7.13 (m, 2 H), 7.08 (d, *J* = 2.0 Hz, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 4.95 (s, 2 H), 3.92 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.2, 159.0, 142.2, 135.1, 135.0, 132.3, 130.4, 129.4, 129.0, 129.0, 129.0, 128.3, 128.0, 127.2, 127.0, 125.0, 124.0, 120.0, 116.4, 110.0, 106.0, 87.2, 85.0, 70.0, 55.4, 44.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{21}NNaO_3$: 442.1419; found: 442.1387.

1-Benzyl-3-hydroxy-3-(thien-3-ylethynyl)indolin-2-one (3an)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-ethynylthiophene (**2n**) (0.05 mL, 0.5 mmol) provided compound **3an** (108 mg, 78%) as a white solid; mp 161–163 °C.

IR (KBr): 2840, 2620, 2421, 2010, 1680, 1470, 1206 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.60 (d, *J* = 7.3 Hz, 1 H), 7.50 (d, *J* = 2.9 Hz, 1 H), 7.33–7.28 (m, 4 H), 7.25–7.23 (m, 3 H), 7.12 (dd, *J* = 9.8, 5.1 Hz, 2 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 4.92 (s, 2 H), 3.72 (s, 1 H).

^{13}C NMR (125 MHz): δ = 174.0, 142.2, 135.0, 130.4, 130.0, 129.0, 129.0, 128.0, 127.2, 125.4, 125.0, 124.0, 121.0, 110.0, 85.1, 82.0, 70.0, 44.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}NNaO_2S$: 368.0721; found: 368.1011.

1-Benzyl-3-hydroxy-3-(3-methoxyprop-1-yn-1-yl)indolin-2-one (3ao)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 3-methoxyprop-1-yne (**2o**) (0.04 mL, 0.5 mmol) provided compound **3ao** (65 mg, 53%) as a white solid; mp 131–133 °C.

IR (KBr): 2880, 2640, 2420, 1810, 1680, 1470, 1240 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.55 (d, *J* = 7.4 Hz, 1 H), 7.33–7.23 (m, 6 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.71 (d, *J* = 7.9 Hz, 1 H), 4.90 (d, *J* = 3.8 Hz, 2 H), 4.15 (s, 2 H), 3.35 (s, 3 H).

^{13}C NMR (125 MHz): δ = 174.0, 142.2, 135.0, 130.4, 129.0, 129.0, 128.0, 127.2, 125.0, 124.0, 110.0, 83.1, 83.0, 69.2, 60.0, 58.0, 44.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{17}NNaO_3$: 330.1106; found: 330.1086.

1-Benzyl-3-(hept-1-yn-1-yl)-3-hydroxyindolin-2-one (3ap)

Following the general procedure, isatin **1a** (100 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and 1-heptyne (**2p**) (0.07 mL, 0.5 mmol) provided compound **3ap** (64 mg, 50%) as a white solid; mp 137–139 °C.

IR (KBr): 3420, 3230, 2821, 2710, 2480, 2270, 1820 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.52 (d, *J* = 6.6 Hz, 1 H), 7.33–7.25 (m, 5 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.69 (d, *J* = 7.8 Hz, 1 H), 4.90 (d, *J* = 4.0 Hz, 2 H), 3.32 (br s, 1 H), 2.25–2.22 (m, 2 H), 1.52–1.50 (m, 2 H), 1.36–1.27 (m, 4 H), 0.89–0.86 (m, 3 H).

^{13}C NMR (125 MHz): δ = 174.4, 142.1, 135.1, 130.2, 129.3, 129.0, 128.0, 127.1, 125.0, 124.0, 110.0, 88.4, 86.2, 69.3, 44.0, 31.0, 28.0, 22.1, 19.0, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO_2$: 356.1626; found: 356.1620.

3-(Cyclopropylethynyl)-3-hydroxy-1,5-dimethylindolin-2-one (F)

Following the general procedure, 1,5-dimethylindoline-2,3-dione (70 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and ethynylcyclopropane (**2q**) (0.04 mL, 0.5 mmol) provided compound **F** (49 mg, 51%) as a white solid; mp 184–186 °C.

IR (KBr): 2880, 2640, 2421, 1810, 1680, 1250, 1160 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.32 (s, 1 H), 7.13 (d, *J* = 7.9 Hz, 1 H), 6.71 (d, *J* = 7.9 Hz, 1 H), 3.52 (br s, 1 H), 3.18 (s, 3 H), 2.35 (s, 3 H), 1.26 (t, *J* = 6.6 Hz, 1 H), 0.78–0.69 (m, 4 H).

^{13}C NMR (125 MHz): δ = 174.1, 141.0, 133.3, 130.4, 129.2, 125.2, 108.4, 91.0, 72.2, 69.3, 29.7, 26.5, 21.0, 8.4 (d).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NNaO_2$: 264.1000; found: 264.0421.

5-Bromo-3-(cyclopropylethynyl)-3-hydroxy-1-methylindolin-2-one (G)

Following the general procedure, 5-bromo-*N*-methylisatin (96 mg, 0.4 mmol), KO^{t}Bu (45 mg, 0.4 mmol) and ethynylcyclopropane (**2q**) (0.04 mL, 0.5 mmol) provided compound **G** (73 mg, 60%) as a white solid; mp 197–199 °C.

IR (KBr): 3080, 2730, 2440, 1710, 1680, 1220, 1180 cm^{-1}.

^{1}H NMR (400 MHz): δ = 7.61 (d, *J* = 1.7 Hz, 1 H), 7.47 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 3.19 (s, 3 H), 1.28–1.26 (m, 1 H), 0.81–0.73 (m, 4 H).

^{13}C NMR (125 MHz): δ = 173.6, 142.0, 133.0, 131.0, 128.0, 125.0, 116.2, 110.2, 92.0, 71.4, 69.0, 27.0, 8.5 (d).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{12}BrNNaO_2$: 327.9949; found: 327.9887.

Deuterium Labelling Experiment

To a mixture of phenylacetylene (**2a**) (1.0 equiv) and K_2CO_3 (1.5 equiv) in MeCN (2 mL) under an argon atmosphere was added D_2O (500 µL, ~50 equiv). After the mixture was stirred for 1 h, it was diluted with CH_2Cl_2 (5 mL) and transferred to a separating funnel. The organic layer was separated and dried with $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent NMR analysis showed that phenylacetylene (**2a**) was deuterated. Then, isatin **1a** (100 mg, 0.4 mmol) was added to a mixture of KO^{t}Bu (45 mg, 0.4 mmol) and phenylacetylene-*d* (^{2}H-**2a**) (0.05 mL, 0.5 mmol) in toluene (3 mL), and this mixture was stirred for 3 h. The crude mixture was dried and purified by column chromatography (silica gel; EtOAC–hexane, 10:90 to 30:70) to provide compound ^{2}H-**3aa** in 59% yield.

2-Hydroxy-2,4-diphenyl-1-(piperidin-1-yl)but-3-yn-1-one (4a)

Following the general procedure, keto amide **4** (100 mg, 0.46 mmol), KO^{t}Bu (52 mg, 0.46 mmol) and phenylacetylene (**2a**) (0.06 mL, 0.55 mmol) provided compound **4a** (74 mg, 50%) as a white solid; mp 171–173 °C.

IR (KBr): 3300, 2223, 1700, 1610, 1390, 1253, 1210, 1150 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.4 Hz, 2 H), 7.55–7.53 (m, 2 H), 7.41–7.32 (m, 6 H), 6.15 (s, 1 H), 3.69 (s, 2 H), 3.47–3.43 (m, 1 H), 3.25–3.24 (m, 1 H), 1.60 (s, 4 H), 1.37 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 141.0, 132.0, 129.0, 128.9, 128.7, 128.6, 126.4, 122.3, 87.7, 86.8, 72.1, 47.9, 45.6, 25.7, 24.9, 24.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}NO_2$: 320.1651; found: 320.1654.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562611.

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(16) A stoichiometric amount of 18-crown-6 was added to the alkynylation reaction of isatin **1a** with phenylacetylene (**2a**) under the standard reaction conditions. The reaction afforded **3aa** in 60% yield, a 20% inhibition of product formation compared to the reaction in the absence of 18-crown-6 (Table 1, entry 7). Only partial inhibition of the product yield was observed; possibly toluene is not the best solvent for efficient 1:1 complex formation; see: (a) Izzat, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *91*, 1721. (b) Li, Y.; Huszthy, P.; Móczár, I.; Szemenyei, B.; Kunsági-Máté, S. *Chem. Phys. Lett.* **2013**, *556*, 94.
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(18) CCDC 1433098 contains the supplementary crystallographic data for **3da** in this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.