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Divergent synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones and indenoindolones: an investigation of Pd-catalyzed isocyanide insertion

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ABSTRACT

A novel Pd-catalyzed intramolecular cyclization via *tert*-butyl isocyanide insertion from 2-(2-bromophenyl)-1*H*-indoles has been developed, which demonstrates the utility of isocyanides in C–N or C–C bond construction. Treatment of 2-(2-bromophenyl)-1*H*-indoles with *tert*-butyl isocyanide affords 6*H*-isoindolo[2,1-*a*]indol-6-ones with high efficiency. However, *N*-methyl or *N*-Boc protected 2-(2-bromophenyl)-1*H*-indoles gives indenoindolones in excellent yields under the same condition, which reveals that under the described situation, isocyanides insertion for the formation of C–N bonds is prior to that of C–C bonds.

1. Introduction

Since the indole nucleus is ubiquitous in natural bioactive products, marketed drugs, functional materials and agrochemicals,[1] polycyclic derivatives of indole have drawn increasing attention. For example, 6*H*-isoindolo[2,1-*a*]indol-6-ones, possessing a tetracyclic structure, which incorporates fused five-membered rings, are of interest due to their inherent anticancer activity (**A1**)[2] and ability to bind to the nNK1 receptor (**A2**).[3] In addition, they have shown high subnanomolar affinity for the melatonin MT3 binding site (**A3**).[4] They can also be used as synthetic precursors for other bioactive molecules, such as bacterial NorA efflux pump inhibitors.[5] Indenoindolones, another kind of tetracyclic derivative of indole, also possess activity toward the inhibition of protein kinase CK2[6] and antioxidant activity due to their use as scavengers of reactive oxygen species.[7] Similar to 6*H*-isoindolo[2,1-*a*]indol-6-ones, they also act as new ligands of MT3 (**B1**).[4] Moreover, indenoindolones, acting as the potent topoisomerase II inhibitor, exhibit good anticancer activities against kidney cancer cells (HEK-293), compared to etoposide and 5-fluorouracil, and relatively low toxicity to normal cells (**B2**–**B3**).[8] In consideration of the tremendous activities of these two compounds (Fig. 1), a wide variety of synthetic approaches have been reported.[2,4,9,10] However, many of them are limited with respect to either lengthy or involving complex precursors. Herein, we develop a simple and convenient palladium-catalyzed intramolecular regioselective synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-one and indenoindolone framework starting from the same substrates 2-(2-bromophenyl)-1*H*-indoles via *tert*-butyl isocyanide insertion.

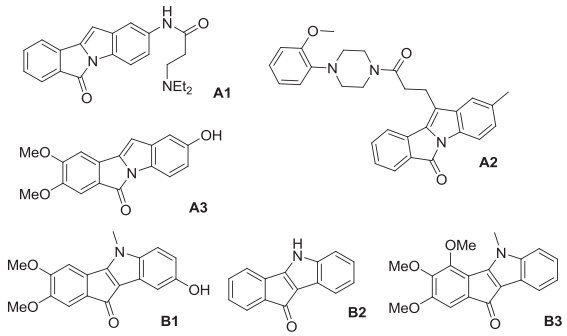

Fig. 1. Bioactive 6*H*-isoindolo[2,1-*a*]indol-6-ones and indenoindolones.

During the past few decades, isocyanides have emerged as powerful building blocks in modern synthetic organic chemistry since the pioneering work of Passerini[11] and Ugi[12] and subsequently related isocyanide-based two-component reactions[13] and evolutionary multicomponent reactions (MCRs).[14]

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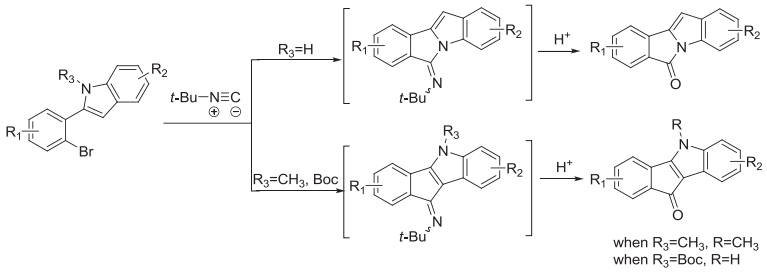
Isocyanides are isoelectronic with carbon monoxide and as such have found a new application as versatile C1 building blocks similar to carbon monoxide in palladium catalysis.[15] So far, a vast number of palladium-catalyzed coupling reactions for the formation of C–N,[16,17] C–O[18] and C–C[13b,13e,19] bonds utilizing isocyanide insertion have been investigated. However, the preferential orientation of isocyanides insertion to form C–N, C–O and C–C bonds is much less discussed. Herein, through the divergent synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones and indenoindolones from 2-(2-bromophenyl)-1*H*-indoles via *tert*-butyl isocyanide insertion (Scheme 1), we discuss that which is prior between isocyanide insertion for the formation of C–N bonds and that of C–C bonds under the described reaction conditions.

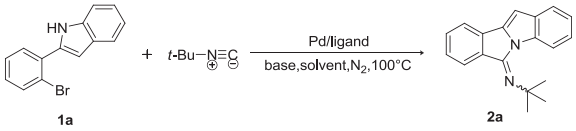


Scheme 1. Strategy to 6*H*-isoindolo[2,1-*a*]indol-6-ones and indenoindolones via *tert*-butyl isocyanide insertion.

2. Results and discussion

The initial screening studies were carried out using 2-(2-bromophenyl)-1*H*-indole **1a** and *tert*-butyl isocyanide as model substrates in the presence of $Pd(OAc)_2$, DPEPhos and K_2CO_3 under nitrogen. When the reaction was performed in DMF at 100 °C for 8 h, the expected product, *N*-(6*H*-isoindolo[2,1-*a*]indol-6-ylidene)-2-methylpropan-2-amine **2a**, was obtained successfully in 42% yield (Table 1, entry 1). When the solvent was switched to DMSO, the yield was improved to 66% (Table 1, entries 2–4). We next examined the effect of bases on the outcome of the reaction. To our delight, the yield was significantly improved by Cs_2CO_3, affording **2a** in 87% yield (Table 1, entries 5 and 6). DPEPhos afforded the best results in ligand screening studies (Table 1, entries 7–12). A control experiment in the absence of any ligand resulted in no product formation at all (Table 1, entry 13). In comparison with $Pd(OAc)_2$, other palladium sources, such as $PdCl_2$ or $Pd_2(dba)_3$ gave rise to diminished yields (Table 1, entries 14 and 15). The optimized reaction conditions were eventually identified as: 5 mol % of $Pd(OAc)_2$, 10 mol % of DPEPhos and 2 equiv Cs_2CO_3 in DMSO under nitrogen atmosphere at 100 °C. Subsequently, acid hydrolysis of **2a** afforded the generation of 6*H*-isoindolo[2,1-*a*]indol-6-one **3a** in almost theoretical yield.

Table 1
Conditions optimization of **1a** with *tert*-butyl isocyanide[a]



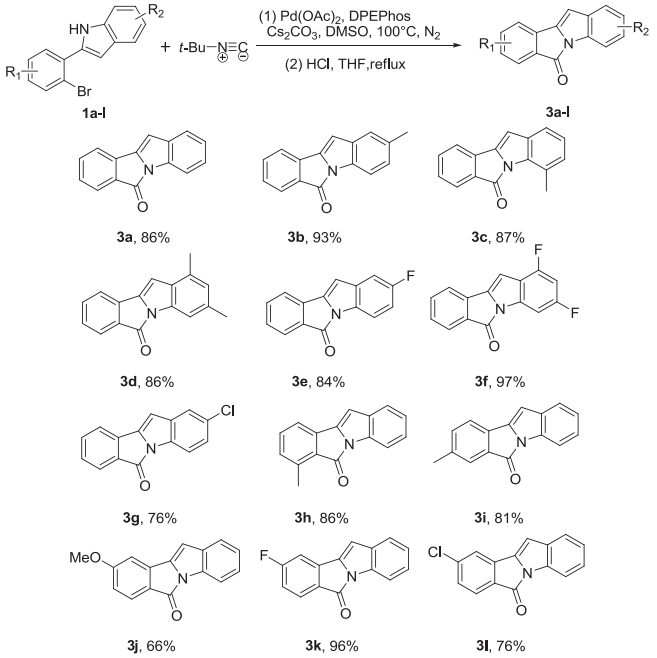
Entry	Catalyst	Ligand	Base	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	DPEPhos	K_2CO_3	DMF	42
2	$Pd(OAc)_2$	DPEPhos	K_2CO_3	DMSO	66
3	$Pd(OAc)_2$	DPEPhos	K_2CO_3	Dioxane	51
4	$Pd(OAc)_2$	DPEPhos	K_2CO_3	Toluene	26
5	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	DMSO	87
6	$Pd(OAc)_2$	DPEPhos	*t*-BuONa	DMSO	Trace
7	$Pd(OAc)_2$	(*R*)-BINAP	Cs_2CO_3	DMSO	35
8	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	DMSO	Trace
9	$Pd(OAc)_2$	DPPF	Cs_2CO_3	DMSO	15
10	$Pd(OAc)_2$	DPPE	Cs_2CO_3	DMSO	56
11	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMSO	17
12	$Pd(OAc)_2$	*S*-Phos	Cs_2CO_3	DMSO	Trace
13	$Pd(OAc)_2$	—	Cs_2CO_3	DMSO	0
14	$PdCl_2$	DPEPhos	Cs_2CO_3	DMSO	37
15	$Pd_2(dba)_3$	DPEPhos	Cs_2CO_3	DMSO	Trace

[a] Reactions conditions: all reactions were performed with **1a** (0.3 mmol), *tert*-butyl isocyanide (0.45 mmol), catalyst (0.015 mmol), ligand (0.03 mmol) and base (0.6 mmol) in 2.0 mL of solvent at 100 °C for 8 h. Abbreviations: DPEPhos=bis[(2-diphenylphosphino)phenyl]ether, (*R*)-BINAP=(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Xantphos=4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DPPF=1,1′-bis(diphenylphosphino)ferrocene, DPPE=1,2-bis(diphenylphosphino) ethane, *S*-Phos=2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl.

[b] Isolated by neutral alumina chromatography.

With the optimized reaction conditions in hand, we then explored the substrate scope of this protocol with a range of substituted 2-(2-bromophenyl)-1*H*-indoles and the results were summarized in Table 2. In most cases, the insertion reactions of 2-(2-bromophenyl)-1*H*-indoles **1** with *tert*-butyl isocyanide delivered the desired products in good to excellent yields. Both electron-donating and electron-withdrawing substituents were well tolerated (**3a**–**l**). To our delight, the substrates containing sensitive

Table 2
Synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones via *tert*-butyl isocyanide insertion[a,b]



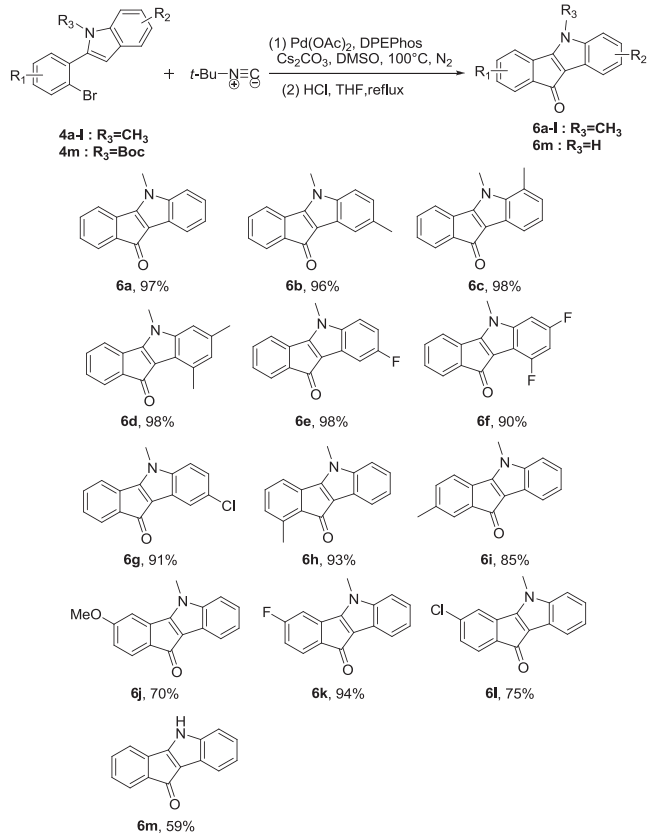
[a] All reactions were performed under N_2 on a 0.3 mmol scale, using *tert*-butyl isocyanide (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), DPEPhos (0.03 mmol), and Cs_2CO_3 (0.6 mmol) in DMSO (2 mL) at 100 °C for 8 h. Followed by refluxing in THF/hydrochloric acid for 4 h.

[b] Isolated yield.

functional group, such as *p*-Cl were coupled smoothly (**3g** and **3l**). Besides, dimethyl and difluoro substituted substrates were also efficiently transformed to the desired products (**3d** and **3f**).

We further studied the reaction when the substrates were switched to *N*-methyl derivatives of 2-(2-bromophenyl)-1*H*-indoles. By screening of conditions, we surprisingly found that the above highly optimized conditions were well suited, affording the desired 2-methyl-*N*-(5-methylindeno[1,2-*b*]indol-10(5*H*)-ylidene) propan-2-amine **5a** in excellent yields, following acid hydrolysis of **5a** generated indenoindolone. Then, the feasibility of the current protocol was investigated. As illustrated in Table 3, 2-(2-bromophenyl)-1-methyl-1*H*-indoles containing the same functional groups as **1** were all high efficiently coupled with *tert*-butyl isocyanide and furnished the corresponding products in higher yields (**6a**–**l**). Nevertheless, *N*-Boc protected 2-(2-bromophenyl)-1*H*-indole afforded **6m** in lower yield, suggesting that the electron density on indole was crucial.

Table 3
Synthesis of indenoindolones via *tert*-butyl isocyanide insertion[a,b]



[a] All reactions were performed under N_2 on a 0.3 mmol scale, using *tert*-butyl isocyanide (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), DPEPhos (0.03 mmol), and Cs_2CO_3 (0.6 mmol) in DMSO (2 mL) at 100 °C for 5 h. Followed by refluxing in THF/hydrochloric acid for 4 h.
[b] Isolated yield

A plausible mechanism for this reaction is depicted in Scheme 2. Oxidative addition of **1a** to Pd(0) leads to a palladium complex **7**, followed by *tert*-butyl isocyanide insertion to form **8**. Then, hydrogen bromide is extruded out of **8** to generate **9** with the aid of base. Finally, reductive elimination of **9** gives the intermediate **2a**, following acid hydrolysis yields **3a**. When the substrate is *N*-methyl derivative **4a**, the mechanism is the same as **1a**, affording the intermediate **5a** and subsequent acid hydrolysis product **6a**.

3. Conclusion

In summary, we have developed a tunable intramolecular synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones and indenoindolones, which possess potent and varied biological activities via *tert*-butyl isocyanide insertion starting from the readily obtainable 2-(2-bromophenyl)-1*H*-indoles. This methodology provides an example of isocyanides as carbonyl source in the catalytic C–N or C–C bond construction. More importantly, it reveals that under the described reaction conditions, isocyanides insertion for the formation of C–N bonds is prior to that of C–C bonds. Characterized by wide substrate scope, simplified operational procedure, easily available material, and good to excellent yields, this protocol may aid the further development of the reactions incorporating isocyanides. Related studies on the activities of the stable imine intermediates are underway in our laboratory.

4. Experimental section

4.1. General

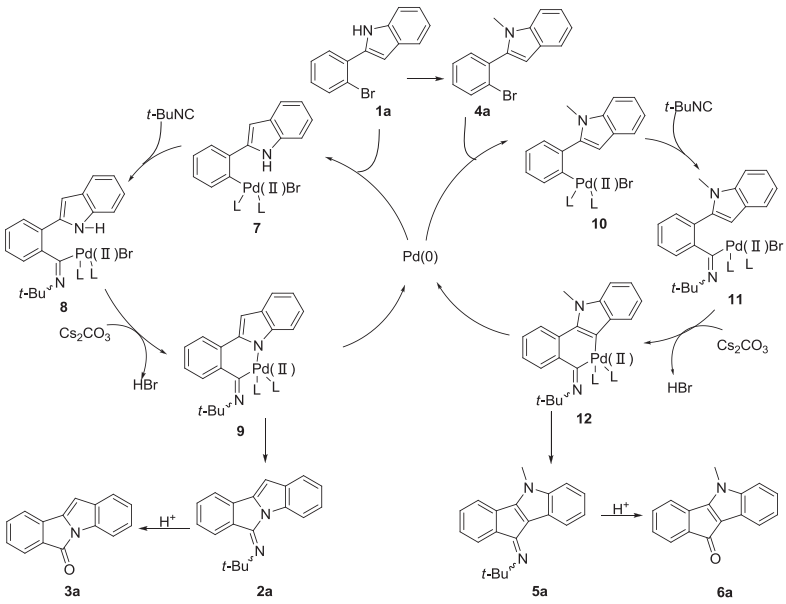
Chemicals and reagents were purchased from commercial suppliers and used without further purification. TLC was performed on silica HSGF254 plates. Melting points were determined with a digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Bruker V70 spectrometer and wavelengths are given in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ or DMSO-d_6 with TMS as internal standard using a 400/101 MHz ($^1H/^{13}C$) or 300/75 MHz ($^1H/^{13}C$) spectrometer. LRMS and HRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

4.2. General procedure for the synthesis of compounds 3a–l and 6a–m

To a 15 mL of sealed tube equipped with a magnetic stirring bar were added **1** or **4**(0.3 mmol), *tert*-butyl isocyanide (0.45 mmol, 51 μL), $Pd(OAc)_2$ (0.015 mmol, 3 mg), DPEPhos (0.03 mmol, 16 mg), Cs_2CO_3 (0.6 mmol, 196 mg) and DMSO (2.0 mL). The mixture was stirred under nitrogen atmosphere at 100 °C for 8 h for substrates **1** and 5 h for substrates **4**, respectively. After completion of the reaction as indicated by TLC, the reaction liquid was filtered through neutral aluminium oxide and the solvent was removed under vacuum. The mixture was refluxed in THF (9 mL) and hydrochloric acid (0.1 M, 3 mL) for 4 h, respectively. Then, the mixture was extracted with EtOAc, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to provide the pure target product.

*4.2.1. N-(6H-Isoindolo[2,1-a]indol-6-ylidene)-2-methylpropan-2-amine (**2a**).* Yellow solid (71 mg, 86%); mp 101–103 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J=8.0 Hz, 1H), 7.96 (d, J=7.9 Hz, 1H), 7.59 (d, J=7.5 Hz, 1H), 7.50 (d, J=7.8 Hz, 1H), 7.42 (t, J=7.4 Hz, 1H), 7.30 (t, J=7.6 Hz, 1H), 7.23 (t, J=7.9 Hz, 1H), 7.09 (t, J=7.4 Hz, 1H), 6.51 (s, 1H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 138.3, 135.9, 133.7, 133.6, 130.9, 130.8, 128.7, 127.2, 124.4, 121.7, 121.5, 121.3, 113.5, 96.3, 53.6, 30.8. IR (ATR): ν=2960, 2924, 1649, 1604, 1438, 1357, 1205, 1142, 945, 799, 767, 746, 665, 640 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2$ $[M+H]^+$, 275.1548; found, 275.1543.

*4.2.2. 6H-Isoindolo[2,1-a]indol-6-one (**3a**).*[9j] Yellow solid (71 mg, 86%); mp 155–157 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.44 (d, J=4.0 Hz, 2H), 7.39 (d, J=7.8 Hz, 1H), 7.30–7.21 (m, 2H), 7.11 (t, J=7.3 Hz, 1H), 6.52 (s, 1H). ^{13}C NMR



Scheme 2. Plausible mechanism for the synthesis of **4a** and **6a** from **1a**.

(101 MHz, $CDCl_3$) δ 162.5, 138.7, 134.5, 134.4, 133.7, 133.6, 133.4, 128.6, 126.2, 125.1, 123.8, 122.2, 121.1, 113.2, 103.4. IR (ATR): ν=2962, 2925, 1719, 1608, 1465, 1442, 1376, 1261, 1140, 1072, 1014, 801, 738, 690 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{15}H_9NO$ $[M+H]^+$, 220.1; found, 220.1.

*4.2.3. 2-Methyl-6H-isoindolo[2,1-a]indol-6-one (**3b**).* Yellow solid (65 mg, 93%); mp 132–134 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, *J*=7.8 Hz, 2H), 7.44 (d, *J*=4.8 Hz, 2H), 7.30–7.24 (m, 1H), 7.18 (s, 1H), 7.05 (d, *J*=8.1 Hz, 1H), 6.47 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 138.9, 134.7, 134.6, 133.9, 133.5, 133.4, 131.6, 128.6, 127.4, 125.1, 122.3, 121.0, 112.8, 103.3, 21.4. IR (ATR): ν=2915, 1723, 1619, 1462, 1443, 1374, 1350, 1308, 1265, 1133, 1070, 907, 809, 759, 741, 693 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO$ $[M+H]^+$, 234.0919; found, 234.0913.

*4.2.4. 4-Methyl-6H-isoindolo[2,1-a]indol-6-one (**3c**).* Yellow solid (61 mg, 87%); mp 154–156 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.5 Hz, 1H), 7.49 (d, *J*=5.9 Hz, 2H), 7.36–7.30 (m, 1H), 7.25–7.21 (m, 1H), 7.07–7.02 (m, 2H), 6.61 (s, 1H), 2.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 139.8, 135.2, 134.2, 134.1, 133.5, 133.4, 128.7, 128.5, 125.0, 124.7, 124.0, 120.5, 119.4, 103.7, 21.2. IR (ATR): ν=2926, 1731, 1618, 1466, 1448, 1330, 1304, 1246, 1120, 1084, 1031, 908, 820, 772, 735, 692, 671 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO$ $[M+H]^+$, 234.0919; found, 234.0914.

*4.2.5. 1,3-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**3d**).* Yellow solid (64 mg, 86%); mp 150–152 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=7.5 Hz, 1H), 7.46 (s, 1H), 7.43–7.34 (m, 2H), 7.25–7.20 (m, 1H), 6.69 (s, 1H), 6.47 (s, 1H), 2.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 137.4, 136.7, 134.7, 133.6, 133.3, 131.6, 131.3, 128.1, 125.8, 124.9, 120.7, 111.1, 109.7, 102.0, 21.6, 18.2. IR (ATR): ν=2916, 1719, 1616, 1467, 1445, 1414, 1364, 1282, 1260, 1235, 1214, 1079, 1028, 903, 841, 757, 740, 690 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}NO$ $[M+H]^+$, 248.1075; found, 248.1070.

*4.2.6. 2-Fluoro-6H-isoindolo[2,1-a]indol-6-one (**3e**).* Yellow solid (60 mg, 84%); mp 155–157 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J*=8.6, 4.5 Hz, 1H), 7.69 (d, *J*=7.5 Hz, 1H), 7.50–7.42 (m, 2H), 7.31 (t, *J*=7.1 Hz, 1H), 7.06 (dd, *J*=8.8, 1.7 Hz, 1H), 6.98–6.91 (m, 1H), 6.48 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 161.0, 158.6, 140.4, 135.5, 135.4, 134.4, 133.8, 133.6, 129.9, 129.1, 125.3, 121.3, 113.9, 113.8, 113.7, 113.5, 108.4, 108.1, 102.9, 102.9. IR (ATR): ν=3114, 2963, 1721, 1620, 1464, 1444, 1357, 1258, 1138, 1118, 1071, 909, 850, 796, 754, 692 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{15}H_8FNO$ $[M+H]^+$, 238.0668; found, 238.0673.

*4.2.7. 1,3-Difluoro-6H-isoindolo[2,1-a]indol-6-one (**3f**).* Yellow solid (74 mg, 97%); mp 200–201 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.5 Hz, 1H), 7.53 (q, *J*=7.1 Hz, 2H), 7.42 (d, *J*=8.4 Hz, 1H), 7.36 (t, *J*=7.0 Hz, 1H), 6.63 (d, *J*=12.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 163.6, 162.5, 160.5, 160.32, 157.6, 157.4, 154.2, 154.0, 138.7, 138.7, 134.3, 134.2, 133.2, 129.1, 125.6, 121.3, 119.3, 119.2, 119.0, 99.7, 99.4, 99.3, 99.0, 98.7, 97.5, 97.5, 97.2, 97.1. IR (ATR): ν=3124, 2963, 1728, 1628, 1440, 1287, 1227, 1171, 1123, 976, 904, 819, 758, 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{15}H_7F_2NO$ $[M+H]^+$, 256.0574; found, 256.0563.

*4.2.8. 2-Chloro-6H-isoindolo[2,1-a]indol-6-one (**3g**).* Yellow solid (58 mg, 76%); mp 174–176 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, *J*=8.5 Hz, 2H), 7.52–7.41 (m, 2H), 7.36–7.28 (m, 2H), 7.17 (d, *J*=8.5 Hz, 1H), 6.45 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 139.9, 135.6, 134.2, 133.8, 133.5, 131.7, 129.2, 129.1, 126.2, 125.3, 121.8, 121.4, 113.9, 102.4. IR (ATR): ν=3115, 2962, 1714, 1438, 1353, 1139, 1014, 862, 796, 756, 694 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{15}H_8ClNO$ $[M+H]^+$, 254.0372; found, 254.0357.

*4.2.9. 7-Methyl-6H-isoindolo[2,1-a]indol-6-one (**3h**).*[9j] Yellow solid (60 mg, 86%); mp 147–149 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.0 Hz, 1H), 7.42 (d, *J*=7.7 Hz, 1H), 7.32 (q, *J*=7.4 Hz, 2H), 7.25 (t, *J*=7.6 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 7.05 (d, *J*=6.7 Hz, 1H), 6.53 (s, 1H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 139.8, 138.5, 134.9, 134.4, 133.5, 133.3, 131.3, 130.6, 126.0, 123.6, 122.1, 118.9, 113.1, 102.6, 17.3. IR (ATR): ν=2923, 1718, 1610, 1447, 1380, 1259, 1093, 1012, 876, 791, 744, 700 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO$ $[M+H]^+$, 234.1; found, 234.0.

*4.2.10. 8-Methyl-6H-isoindolo[2,1-a]indol-6-one (**3i**).*[9j] Yellow solid (57 mg, 81%); mp142–144 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79

(d, *J*=7.9 Hz, 1H), 7.44 (s, 1H), 7.34 (d, *J*=7.7 Hz, 1H), 7.26 (d, *J*=7.6 Hz, 1H), 7.19 (dd, *J*=16.0, 7.8 Hz, 2H), 7.08 (t, *J*=7.5 Hz, 1H), 6.41 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 139.0, 138.8, 134.5, 134.1, 133.9, 133.3, 131.8, 125.9, 125.5, 123.6, 122.0, 120.8, 113.0, 102.6, 21.3. IR (ATR): ν=2919, 1722, 1467, 1446, 1374, 1353, 1261, 1156, 1089, 813, 781, 742, 646 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO$ $[M+H]^+$, 234.1; found, 234.1.

4.2.11. 9-Methoxy-6H-isoindolo[2,1-a]indol-6-one (***3j***).[9j] Yellow solid (42 mg, 56%); mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J*=8.0 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 7.29 (d, *J*=7.4 Hz, 1H), 7.13 (t, *J*=7.6 Hz, 1H), 7.01 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=8.4, 2.1 Hz, 1H), 6.60 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 162.5, 138.4, 136.9, 134.2, 133.6, 126.9, 126.3, 126.1, 123.5, 122.2, 114.1, 113.1, 107.0, 103.2, 55.8. IR (ATR): ν=2922, 1728, 1625, 1478, 1438, 1376, 1338, 1304, 1280, 1222, 1140, 1091, 811, 733, 665 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO_2$ $[M+H]^+$, 250.1; found, 250.1.

4.2.12. 9-Fluoro-6H-isoindolo[2,1-a]indol-6-one (***3k***). Yellow solid (68 mg, 96%); mp 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.9 Hz, 1H), 7.78 (dd, *J*=7.5, 5.2 Hz, 1H), 7.51 (d, *J*=7.7 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.22 (t, *J*=8.0 Hz, 2H), 7.05 (t, *J*=8.5 Hz, 1H), 6.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 164.8, 161.5, 137.4, 137.4, 137.1, 137.0, 134.1, 133.6, 129.7, 127.4, 127.3, 126.8, 124.0, 122.5, 115.9, 115.6, 113.3, 109.1, 108.8, 104.5. IR (ATR): ν=3115, 2962, 1721, 1624, 1474, 1445, 1333, 1258, 1134, 1082, 1013, 962, 791, 735, 654 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{15}H_8FNO$ $[M+H]^+$, 238.0668; found, 238.0667.

4.2.13. 9-Chloro-6H-isoindolo[2,1-a]indol-6-one (***3l***).[9j] Yellow solid (50 mg, 76%); mp 242–244 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.8 Hz, 1H), 7.68 (d, *J*=7.9 Hz, 1H), 7.50 (s, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.31 (dd, *J*=4.9, 2.5 Hz, 2H), 7.17 (t, *J*=7.4 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 140.2, 137.4, 136.1, 134.2, 133.7, 132.1, 128.9, 126.8, 126.4, 124.1, 122.5, 121.6, 113.4, 104.6. IR (ATR): ν=3115, 2963, 1718, 1613, 1421, 1323, 1260, 1144, 1081, 797, 736, 646 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{15}H_8ClNO$ $[M+H]^+$, 254.0; found, 253.9.

4.2.14. 2-Methyl-N-(5-methylindeno[1,2-b]indol-10(5H)-ylidene) propan-2-amine (***5a***). Yellow solid (85 mg, 98%); mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=7.8 Hz, 1H), 7.80 (s, 1H), 7.31–7.12 (m, 6H), 3.85 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 153.8, 145.6, 142.5, 131.5, 129.1, 127.8, 123.5, 122.5, 122.2, 121.7, 121.6, 117.3, 110.2, 55.1, 31.1, 30.8. IR (ATR): ν=2955, 2901, 1621, 1596, 1535, 1416, 1389, 1236, 1055, 894, 727, 708 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}N_2$ $[M+H]^+$, 289.1704; found, 289.1694.

4.2.15. 5-Methylindeno[1,2-b]indol-10(5H)-one (***6a***).[10j] Red solid (68 mg, 97%); mp 218–220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.6 Hz, 1H), 7.40 (d, *J*=7.4 Hz, 1H), 7.25–7.14 (m, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 158.6, 142.8, 141.0, 134.5, 131.7, 129.4, 123.3, 122.8, 122.8, 122.6, 120.3, 118.3, 114.6, 110.4, 31.4. IR (ATR): ν=2961, 2923, 1671, 1599, 1530, 1437, 1414, 1260, 1023, 868, 794, 743, 714, 758, 698, 649 cm^{-1}. LRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}NO$ $[M+H]^+$, 234.1; found, 234.1.

4.2.16. 5,8-Dimethylindeno[1,2-b]indol-10(5H)-one (***6b***). Red solid (71 mg, 96%); mp 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.29 (d, *J*=6.6 Hz, 1H), 7.10 (dt, *J*=21.1, 7.0 Hz, 2H), 6.97 (dd, *J*=16.9, 7.5 Hz, 2H), 6.88 (d, *J*=8.1 Hz, 1H), 3.68 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 158.5, 141.2, 134.6, 133.0, 131.6, 129.3, 124.3, 122.8, 122.7, 120.3, 118.1, 114.2, 110.1, 31.4, 21.3. IR (ATR): ν=2959, 2922, 1662, 1533, 1436, 1415, 1275, 1181, 1054, 866, 806, 760, 749, 716, 692 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}NO$ $[M+H]^+$, 248.1075; found, 248.1073.

4.2.17. 5,6-Dimethylindeno[1,2-b]indol-10(5H)-one (***6c***).[10j] Red solid (73 mg, 98%); mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.8 Hz, 1H), 7.22 (d, *J*=6.9 Hz, 1H), 7.09–7.00 (m, 2H), 6.92 (t, *J*=7.4 Hz, 2H), 6.68 (d, *J*=7.2 Hz, 1H), 3.82 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 158.9, 141.4, 141.1, 134.6, 131.7, 129.2, 126.1, 123.5, 123.3, 122.7, 122.6, 118.3, 118.3, 114.4, 35.0, 19.4. IR (ATR): ν=2963, 2929, 1683, 1595, 1528, 1454, 1441, 1411, 1342, 1261, 1083, 864, 761, 745, 719, 639 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}NO$ $[M+H]^+$, 248.1075; found, 248.1079.

4.2.18. 5,7,9-Trimethylindeno[1,2-b]indol-10(5H)-one (***6d***). Red solid (77 mg, 98%); mp 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.8 Hz, 1H), 7.22 (d, *J*=6.9 Hz, 1H), 7.09–7.00 (m, 2H), 6.92 (t, *J*=7.4 Hz, 2H), 6.68 (d, *J*=7.2 Hz, 1H), 3.82 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 158.9, 141.4, 141.1, 134.6, 131.7, 129.2, 126.1, 123.5, 123.3, 122.7, 122.6, 118.3, 118.3, 114.4, 35.0, 19.4. IR (ATR): ν=2962, 2923, 1679, 1601, 1529, 1485, 1439, 1413, 1375, 1341, 1260, 1081, 1011, 929, 796, 747, 710 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO$ $[M+H]^+$, 262.1232; found, 262.1229.

4.2.19. 8-Fluoro-5-methylindeno[1,2-b]indol-10(5H)-one (***6e***). Red solid (74 mg, 98%); mp 215–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J*=7.7 Hz, 2H), 7.11 (dt, *J*=24.2, 7.5 Hz, 2H), 7.00 (d, *J*=7.0 Hz, 1H), 6.96 (dd, *J*=8.9, 4.1 Hz, 1H), 6.75 (td, *J*=9.0, 1.5 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 161.7, 159.5, 158.5, 140.9, 139.3, 134.2, 131.9, 129.7, 123.2, 123.0, 118.5, 114.5, 114.4, 111.3, 111.2, 111.1, 110.7, 106.1, 105.8, 31.7. IR (ATR): ν=2961, 2923, 1668, 1538, 1436, 1254, 1084, 1017, 926, 859, 795, 758, 762, 740, 713, 686 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{10}FNO$ $[M+H]^+$, 252.0824; found, 252.0812.

4.2.20. 7,9-Difluoro-5-methylindeno[1,2-b]indol-10(5H)-one (***6f***). Red solid (73 mg, 90%); mp 280–281 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.54 (d, *J*=7.1 Hz, 1H), 7.44–7.32 (m, 3H), 7.32–7.26 (m, 1H), 7.02 (t, *J*=9.6 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 182.5, 160.1, 159.6, 157.7, 157.6, 144.5, 144.4, 144.3, 139.4, 133.8, 132.7, 130.2, 122.9, 120.0, 111.0, 98.9, 98.7, 98.4, 96.0, 95.7, 32.4. IR (ATR): ν=2988, 2901, 1707, 1587, 1490, 1345, 1228, 1091, 951, 826, 740, 711, 651 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_9F_2NO$ $[M+H]^+$, 270.0730; found, 270.0712.

4.2.21. 8-Chloro-5-methylindeno[1,2-b]indol-10(5H)-one (***6g***).[10j] Red solid (73 mg, 91%); mp 235–237 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.54 (d, *J*=4.0 Hz, 1H), 7.52 (d, *J*=2.3 Hz, 1H), 7.46 (d, *J*=1.6 Hz, 1H), 7.37 (t, *J*=7.4 Hz, 1H), 7.32 (d, *J*=6.5 Hz, 1H), 7.28 (d, *J*=7.3 Hz, 1H), 7.17 (dd, *J*=8.8, 2.0 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 159.4, 141.3, 140.9, 134.4, 132.0, 129.9, 129.5, 123.5, 123.3, 123.2, 120.1, 118.6, 114.2, 111.4, 31.8. IR (ATR): ν=2961, 2922, 1686, 1608, 1521, 1464, 1435, 1415, 1259, 1073, 1016, 871, 862, 790, 712, 658 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{10}ClNO$ $[M+H]^+$, 268.0529; found, 268.0524.

4.2.22. 1,5-Dimethylindeno[1,2-b]indol-10(5H)-one (***6h***). Red solid (69 mg, 93%); mp 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=7.5 Hz, 1H), 7.08 (dt, *J*=15.2, 7.0 Hz, 2H), 7.02–6.94 (m, 2H), 6.81 (t, *J*=7.4 Hz, 2H), 3.58 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.8, 157.7, 142.6, 137.6, 136.4, 134.9, 132.9, 131.0, 122.9, 122.5, 120.1, 116.3, 114.8, 110.2, 31.2, 17.0. IR (ATR): ν=2919, 1730, 1686, 1573, 1524, 1478, 1412, 1155, 1127, 881, 755, 649, 621 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}NO$ $[M+H]^+$, 248.1075; found, 248.1069.

4.2.23. 2,5-Dimethylindeno[1,2-b]indol-10(5H)-one (***6i***). Red solid (63 mg, 85%); mp 186–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70

(d, J=6.9 Hz, 1H), 7.14 (d, J=17.1 Hz, 4H), 6.95 (s, 2H), 3.76 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0, 159.2, 142.6, 141.3, 139.7, 131.4, 123.9, 123.1, 122.7, 122.5, 120.1, 118.1, 114.2, 110.3, 31.3, 21.4. IR (ATR): ν=2965, 2918, 1675, 1610, 1531, 1440, 1321, 1281, 1126, 1091, 1064, 920, 827, 782, 741, 723, 621 cm^{-1}. HRMS (ESI): m/z calcd for $C_{17}H_{13}NO$ $[M+H]^+$, 248.1075; found, 248.1059.

*4.2.24. 3-Methoxy-5-methylindeno[1,2-b]indol-10(5H)-one (**6j**).*[10j] Red solid (47 mg, 59%); mp 196–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79–7.73 (m, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.23–7.15 (m, 3H), 6.76 (d, J=1.8 Hz, 1H), 6.54 (dd, J=8.0, 1.7 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 162.9, 156.9, 142.8, 136.8, 133.5, 124.6, 123.3, 123.0, 120.6, 116.2, 110.4, 109.6, 108.5, 55.7, 31.6. IR (ATR): ν=2958, 2923, 1670, 1609, 1533, 1453, 1352, 1261, 1219, 1095, 1016, 845, 777, 746, 658 cm^{-1}. HRMS (ESI): m/z calcd for $C_{17}H_{13}NO_2$ $[M+H]^+$, 264.1024; found, 264.1009.

*4.2.25. 3-Fluoro-5-methylindeno[1,2-b]indol-10(5H)-one (**6k**).* Red solid (71 mg, 94%); mp 237–239 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J=5.5 Hz, 1H), 7.29 (dd, J=7.3, 5.6 Hz, 1H), 7.15 (s, 3H), 6.76 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7, 166.9, 163.6, 156.6, 142.9, 137.3, 137.2, 136.7, 136.6, 124.6, 124.5, 123.6, 123.4, 122.6, 120.7, 116.0, 114.6, 114.3, 110.6, 107.6, 107.3, 31.5. IR (ATR): ν=2961, 2923, 1672, 1607, 1538, 1482, 1444, 1413, 1348, 1260, 1052, 1019, 922, 845, 779, 745, 649 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{10}FNO$ $[M+H]^+$, 252.0824; found, 252.0822.

*4.2.26. 3-Chloro-5-methylindeno[1,2-b]indol-10(5H)-one (**6l**).*[10j] Red solid (60 mg, 75%); mp 226–227 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.17 (s, 3H), 7.10 (d, J=7.7 Hz, 1H), 7.06 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.6, 156.8, 143.0, 139.2, 137.8, 136.4, 128.8, 123.8, 123.6, 123.5, 122.5, 120.7, 118.9, 115.7, 110.6, 31.6. IR (ATR): ν=2988, 2901, 1673, 1602, 1537, 1462, 1441, 1407, 1344, 1057, 1022, 890, 648 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{10}ClNO$ $[M+H]^+$, 268.0529; found, 268.0521.

*4.2.27. Indeno[1,2-b]indol-10(5H)-one (**6m**).*[10e] Red solid (60 mg, 75%); mp 271–272 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.57 (br s, 1H), 7.56 (m, 1H), 7.49–7.43 (m, 1H), 7.39 (t, J=7.3 Hz, 1H), 7.36–7.23 (m, 3H), 7.19–7.12 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 184.5, 158.6, 141.7, 140.4, 134.6, 132.6, 129.8, 123.1, 123.0, 122.4, 119.3, 119.1, 114.1, 113.7. IR (ATR): ν=3401, 2962, 2923, 1657, 1536, 1441, 1311, 1258, 1229, 1024, 1009, 922, 865, 793, 732, 709, 687, 658 cm^{-1}. LRMS (ESI): m/z calcd for $C_{15}H_9NO$ $[M+H]^+$, 220.1; found, 220.1.

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Supplementary data

Copies of ^{1}H, ^{13}C NMR spectra for all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.018.

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