Friedel–Crafts 3-(2-Bromobenzoylation) of Indoles and Intramolecular Direct Arylation: An Efficient Route to Indenoindolones

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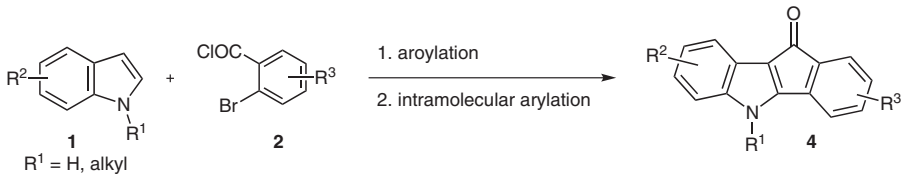
Abstract: An efficient two-step approach, comprising the Friedel–Crafts reaction of 2-bromobenzoyl chlorides with indoles to give 3-(2-bromobenzoyl)indoles and their palladium-catalyzed intramolecular direct arylation to give indenoindolones, has been developed. 3-(2-Bromobenzoyl)indoles were crucial intermediates; the method was successful with N-unprotected or N-protected indoles. This approach affords a convenient preparation of diverse substituted and functionalized indenoindolones in good to high yields from easily accessible starting materials. Several moieties, which are commonly integrated into bioactive compounds, can be incorporated with ease by this synthesis.

Key words: acylation, arylation, catalysis, coupling, heterocycles, indoles, Lewis acids, palladium

Indenoindole derivatives possess a wide range of pharmaceutical activity such as anticancer, anti-Alzheimer's disease, inhibitors of protein kinase CK2, ligands of the MT3 melatonin binding site, and antioxidant in lipid-peroxidation process.[1] Their structural resemblance to heterotetracycle-containing potent therapeutic agents and drugs is remarkable.[2] Indenoindolones are also used as intermediates in the synthesis of potential therapeutic agents.[1c,e,3] Current approaches to the synthesis of indeno[1,2-*b*]indol-10(5*H*)-ones include: (1) the preparation of benzylidene phthalide in four steps and its rearrangement to indane-1,3-dione mediated by strong base followed by reductive cyclization,[1a,b,e] (2) lithium diisopropylamide induced anionic N→C carbamoyl migration of 2-aryl-1-(carbamoyl)indoles, Boc derivatization, and lithium 2,2,6,6,-tetramethylpiperidide induced cyclization,[4] (3) cyclocarbonylation of NH-protected 3-iodo-2-phenylindoles,[5] (4) Fischer indolization reaction of arylhydrazone derivatives of indan-1-one to afford indenoindole and subsequent benzylic oxidation,[6] and (5) reaction of cyclic enaminone with ninhydrin, de-dihydroxylation, and oxidation.[1d] Recently, a method for the reductive cyclization of 3-hydroxy-2-(2-nitrophenyl)-1*H*-inden-1-ones was reported.[7] However, these methods suffer from either containing many reaction steps, or limitations in the generation of molecular diversity in the products, and/or they require harsh reaction conditions that are not amenable to drug discovery research. Accordingly, the development of an efficient rapid diversity-feasible synthesis of indenoindolone is significant. We envisioned an approach that involved Friedel–Crafts 3-acylation of indole[8] for the preparation of 3-(2-haloaroyl)indoles and their subsequent indole C2-arylation[9] as an efficient route to indenoindolones (Scheme 1). A method of palladium-catalyzed intramolecular arylation/cyclization of 3-(2-iodobenzoyl)indoles in the synthesis of indenoindolone is known.[10] However, our attempts to prepare 3-(2-iodobenzoyl)indoles via 3-acylation of indole following our recently developed zirconium(IV) chloride mediated method[8a,11] provided a poor (42%) yield of product. The process mediated by aluminum(III) chloride, a Lewis acid traditionally used in Friedel–Crafts reactions, resulted in a further decreased in the product yield.[12] These reactions caused considerable poly-aroylation and Mannich-type indole oligomerizations as side reactions. Since indole is a nucleophilic arene, these competing reactions are common in acylation reactions with less reactive acylating agents under Friedel–Crafts acidic conditions.[8] The iodobenzoylation of indole was relatively disfavored possibly due to the fact that the bulky and electron-donating iodo functionality at the 2-position in 2-iodobenzoyl chloride lowered the electrophilic reactivity of the carbonyl carbon in the donor–acceptor aroyl–Lewis acid complex or aroyl cation. On the other hand, the 2-iodoarene motif in 3-(2-iodobenzoyl)indoles is required for effecting intramolecular arylation by the reported method.



Scheme 1 Two-step approach to the synthesis of indenoindolones

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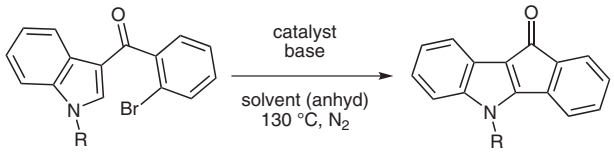
We reasoned that, in contrast to other halo analogues, 3-(2-bromobenzoyl)indoles could be prepared in good yields via Friedel–Crafts acylation and be potential precursors for intramolecular direct indole C2–H bond arylation with suitable catalysis. Herein, we describe an efficient two-step approach to the Friedel–Crafts acylation of indole and palladium-catalyzed intramolecular arylation reaction for the synthesis of indenoindolones. We first attempted the preparation of 3-(2-bromobenzoyl)indole via zirconium(IV) chloride mediated Friedel–Crafts acylation of indole with 2-bromobenzoyl chloride.[8] The reaction afforded the products in good yields for various indoles and aroyl chlorides. Realizing the feasibility of the method for the preparation of diverse 3-(2-bromobenzoyl)indoles, our investigation then focused on finding a catalyst and conditions effective for intramolecular direct indole C2-arylation of 3-(2-bromobenzoyl)indoles. 3-(2-Bromobenzoyl)-1*H*-indole (**3f**) and 3-(2-bromobenzoyl)-1-methyl-1*H*-indole (**3a**) were chosen as model substrates for the classes of NH-unprotected 3-aroylindoles and NH-protected 3-aroylindoles, respectively. The results of our evaluation of catalysts, ligands, bases, and solvents are summarized in Table 1. It was found that the base has a crucial influence on the direct arylation of unprotected and protected indoles. Potassium carbonate was found to be better than cesium acetate for protected indoles. In contrast, for unprotected indoles, potassium carbonate was detrimental and cesium acetate was found to be best. The highest yield of product for the intramolecular arylation of 3-(2-bromobenzoyl)-1-methyl-1*H*-indole (**3a**) was obtained utilizing Pd(dppf)$_2$Cl$_2$·CH$_2$Cl$_2$ as catalyst, potassium carbonate as base, and *N*,*N*-dimethylformamide as solvent (entry 5). Variation in equivalence of potassium carbonate revealed that two equivalents were sufficient (entries 4–6). For the intramolecular arylation of 3-(2-bromobenzoyl)-1*H*-indole (**3f**), the reaction with palladium(II) acetate, triphenylphosphine, cesium acetate, in *N*,*N*-dimethylacetamide solvent was found to be best (entry 9). The reduced yields of products while using cesium pivalate or potassium carbonate and pivalic acid (entries 11 and 12) indicated that the concerted metalation deprotonation process was not favorable for this arylation. The experimental procedures for both Friedel–Crafts aroylation and intramolecular arylation reactions using this approach are simple and straightforward.

With the optimized two-step protocol in hand for the synthesis of indenoindolones, we next set out to explore the scope. To our delight, various 2-bromoaroyl chlorides **2a–f**, and NH-unprotected **1e**,**f** and protected indoles **1a–d** produced diverse indenoindolones **4a–o** in good to high yields (Table 2). No intermolecular arylation product

Table 1 Evaluation of Catalysts, Reagents, and Conditions for Intramolecular Arylation[a]



3a R = Me
3f R = H

4a R = Me
4f R = H

Entry	Catalyst (5 mol%)	Base (equiv)	Solvent	Time (h)	Ligand (10 mol%)	Yield[a] (%)	
						4a	**4f**
1	$Pd(OAc)_2$	K_2CO_3 (3)	DMF	3	–	84	n.r.
2	$PdCl_2$	K_2CO_3 (3)	DMF	6	–	82	n.r.
3	$Pd(PPh_3)_4$	K_2CO_3 (2)	DMF	9	–	85	n.r.
4	$Pd(dppf)_2Cl_2·CH_2Cl_2$	K_2CO_3 (3)	DMF	2	–	98	n.r.
5	$Pd(dppf)_2Cl_2·CH_2Cl_2$	K_2CO_3 (2)	DMF	2	–	97	n.r.
6	$Pd(dppf)_2Cl_2·CH_2Cl_2$	K_2CO_3 (1)	DMF	4	–	80	n.r.
7	$NiCl_2(PPh_3)_2$	K_2CO_3 (2)	DMF	24	–	n.r.	n.r.
8	$Pd(dppf)_2Cl_2·CH_2Cl_2$	CsOAc (2)	DMA	3	Ph_3P	48	78
9	$Pd(OAc)_2$	CsOAc (2)	DMA	3	Ph_3P	55	83
10	$Pd(OAc)_2$	KOAc (2)	DMA	14	Ph_3P	–	34
11	$Pd(OAc)_2$	CsOPiv (2)	DMA	14	Ph_3P	–	42
12	$Pd(OAc)_2$	K_2CO_3 (2), PivOH (2)	DMA	24	Ph_3P	–	10
13	$Pd(OAc)_2$	CsOAc (2)	DMF	3	Ph_3P	–	65

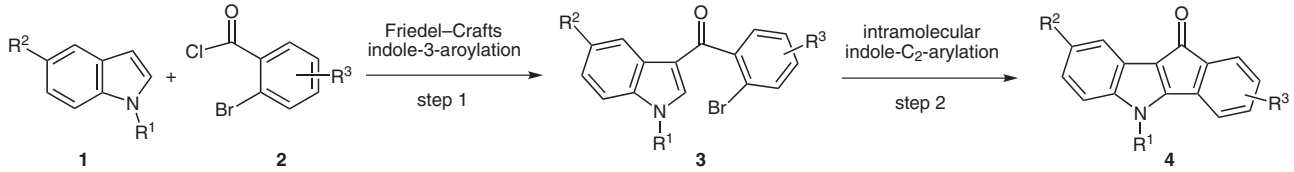
[a] Isolated yields; n.r. = almost no reaction even after 14 h.

formed in this protocol. Several moieties, which are commonly integrated into bioactive compounds, could be incorporated at ease using this two-step approach. The feasibility of NH-unprotected indoles as substrates in this protocol provides the opportunity for various further chemical manipulations such as N-glycosylation and side chain incorporation, which are of therapeutic importance.

The commercial availability or easy synthetic accessibility to the starting materials (various substituted indoles and 2-bromoaroyl chlorides), a simple two-step approach, and the generality of the protocol offers the opportunity to generate substitutional/functional-diversity in indenoindolones.

The electrophilic carbopalladation of nucleophilic arenes such as indole with palladium(II) catalysts or arylpalladium(II) complex is known in literature.[13] In this intramolecular indole C2-arylation, a similar mechanism may occur (Scheme 2). Palladium(0) undergoes oxidative addition to 3-(2-bromobenzoyl)indole and forms an arylpalladium complex **A**. Intramolecular electrophilic carbopalladation at the C3 position of the indole produces the palladacycle **B**, subsequent palladium-migration from positions C3 to C2 in the indole ring gives palladacycle **C**, and deprotonation of **C** constructs palladacycle **D**; this in turn results in direct indole C2-H functionalization. The reductive elimination of palladacycle **D** affords indenoindolone product and regenerates palladium(0).

Table 2 Friedel–Crafts 2-Bromobenzoylation of Indoles and Intramolecular Arylation: Synthesis of Indenoindolones[a]



1 2 3 4

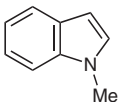
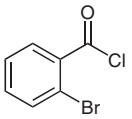
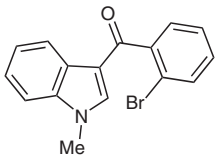
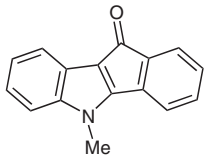
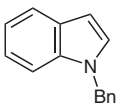
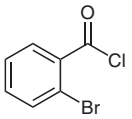
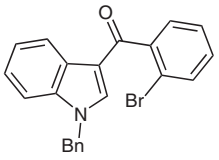
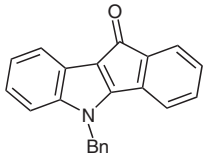
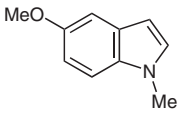
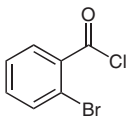
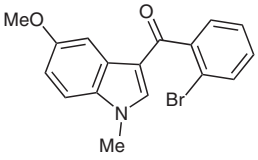
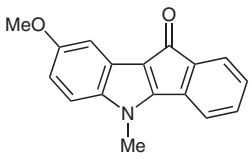
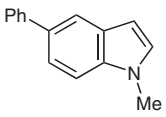
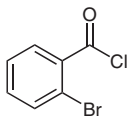
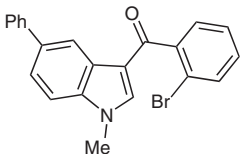
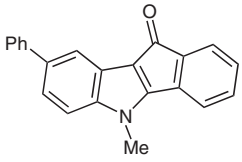
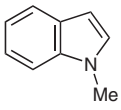
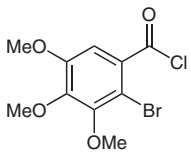
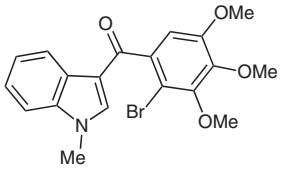
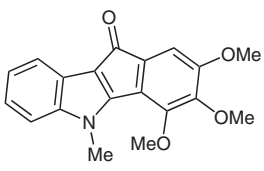
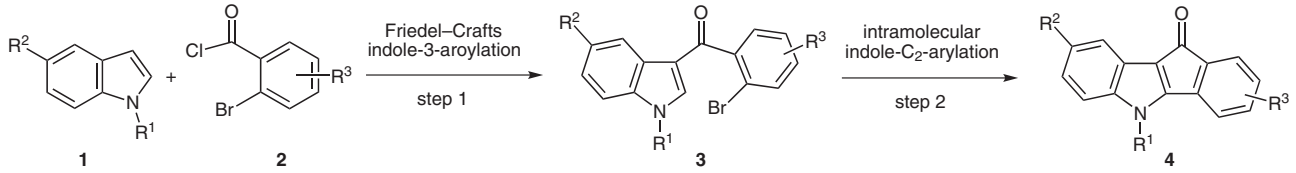
Entry	Indole	Aroyl chloride	Time[b] (h)	Friedel–Crafts product	Yield[c] (%)[c]	Time[d] (h)	Indenoindolone	Yield[e] (%)
1	 **1a**	 **2a**	6	 **3a**	72	2	 **4a**	97
2	 **1b**	 **2a**	6.5	 **3b**	68	3.5	 **4b**	78
3	 **1c**	 **2a**	6.5	 **3c**	62	3	 **4c**	87
4	 **1d**	 **2a**	7	 **3d**	45	3.5	 **4d**	81
5	 **1a**	 **2b**	6.5	 **3e**	60	4	 **4e**	74

Table 2 Friedel–Crafts 2-Bromobenzoylation of Indoles and Intramolecular Arylation: Synthesis of Indenoindolones[a] (continued)



1 **2** **3** **4**

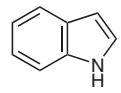
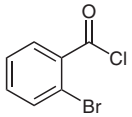
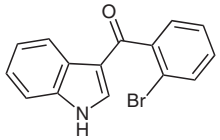
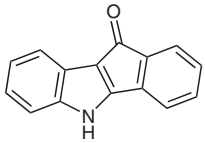
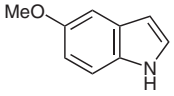
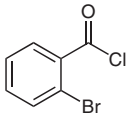
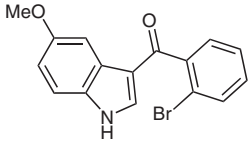
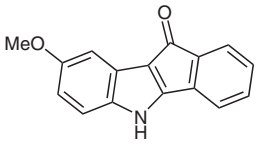
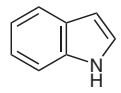
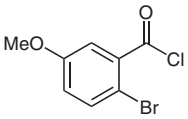
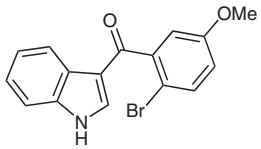
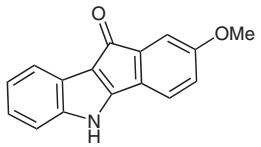
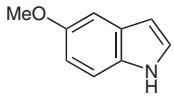
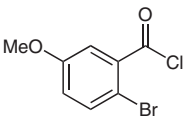
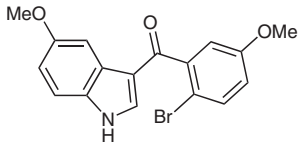
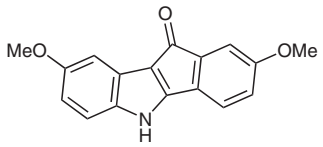
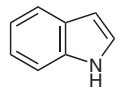
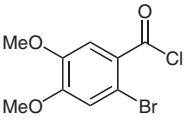
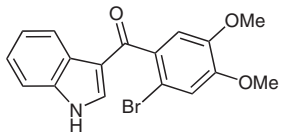
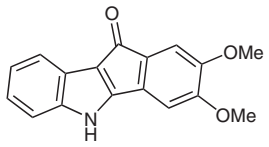
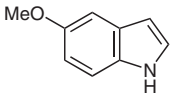
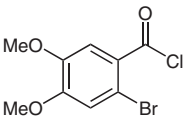
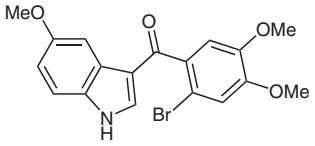
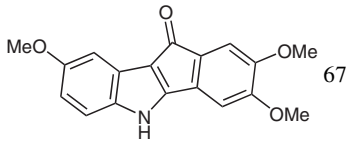
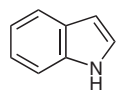
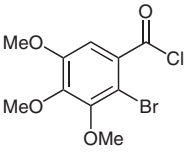
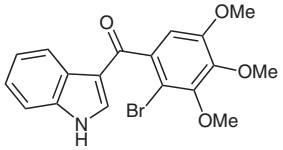
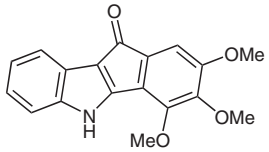
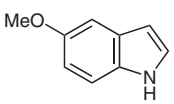
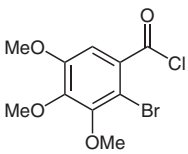
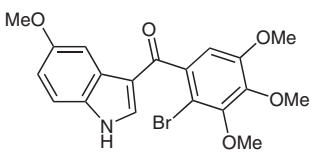
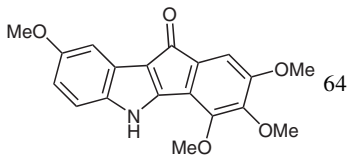
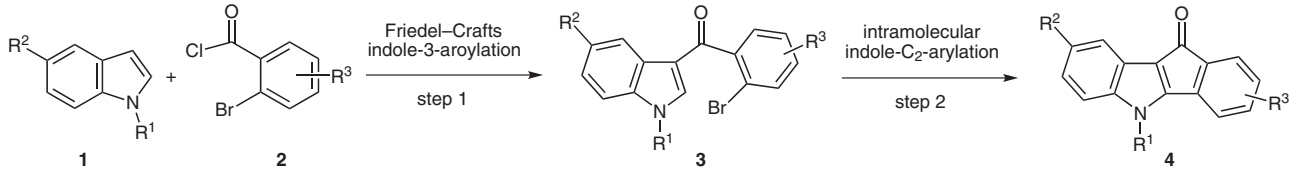
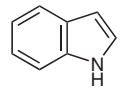
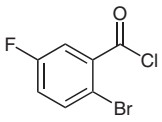
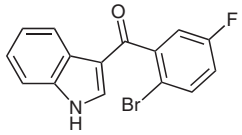
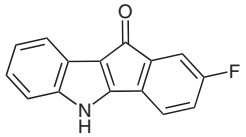
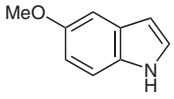
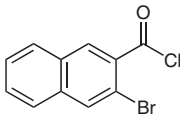
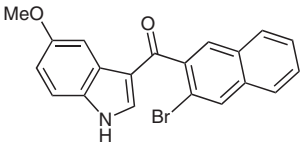
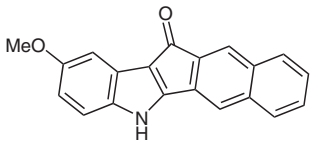
Entry	Indole	Aroyl chloride	Time[b] (h)	Friedel–Crafts product	Yield[c] (%)[c]	Time[d] (h)	Indenoindolone	Yield[e] (%)
6	 **1e**	 **2a**	6	 **3f**	64	3	 **4f**	83
7	 **1f**	 **2a**	7	 **3g**	54	3.5	 **4g**	84
8	 **1e**	 **2c**	6.5	 **3h**	58	4	 **4h**	72
9	 **1f**	 **2c**	7	 **3i**	52	4	 **4i**	68
10	 **1e**	 **2d**	7	 **3j**	57	4	 **4j**	71
11	 **1f**	 **2d**	7.5	 **3k**	54	4.5	 **4k**	67
12	 **1e**	 **2b**	6.5	 **3l**	55	4.5	 **4l**	67
13	 **1f**	 **2b**	7.5	 **3m**	51	4.5	 **4m**	64

Table 2 Friedel–Crafts 2-Bromobenzoylation of Indoles and Intramolecular Arylation: Synthesis of Indenoindolones[a] (continued)



1 2 3 4

Entry	Indole	Aroyl chloride	Time[b] (h)	Friedel–Crafts product	Yield[c] (%)[c]	Time[d] (h)	Indenoindolone	Yield[e] (%)
14	 **1e**	 **2e**	7	 **3n**	47	3.5	 **4n**	77
15	 **1f**	 **2f**	6	 **3o**	61	3	 **4o**	81

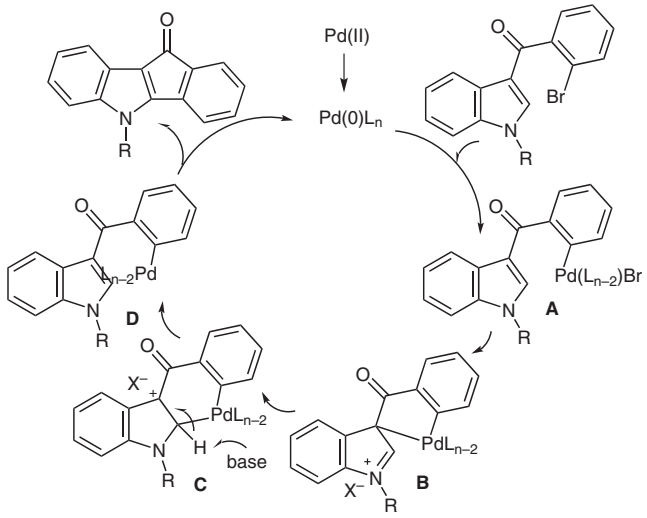
[a] Reaction conditions: step 1: indole **1** (1.3 mmol), 2-bromobenzoyl chloride **2** (1 mmol), $ZrCl_4$ (1.5 mmol), DCE, addition at 0 °C, 0 to 30 °C, then continuation at 30 °C; step 2 (entries 1–5): 3-(2-bromobenzoyl)indole **3a–e** (1 mmol), $Pd(dppf)_2Cl_2·CH_2Cl_2$ (5 mol%), K_2CO_3 (2 equiv), DMF, 130 °C; step 2, entries 6–15: 3-(2-bromobenzoyl)indole **3f–o** (1 mmol), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), CsOAc (2 equiv), DMA, 130 °C.

[b] Reaction time for step 1.

[c] Yield(%) of isolated product in step 1.

[d] Reaction time for step 2.

[e] Yield (%) of isolated product in step 2.



Scheme 2 Proposed mechanism for intramolecular direct arylation

In conclusion, we have developed a two-step approach, zirconium(IV) chloride mediated Friedel–Crafts 3-acylation of indoles with 2-bromobenzoyl chlorides and intramolecular direct arylation, for the synthesis of indenoindolones. This protocol offers several significant advantages including the employment of commercially/synthetically accessible starting materials, the use of only two reaction steps, substitutional and/or functional diversity in the products, and a simple experimental procedure that provides high yields of products.

The starting materials and solvents were used as received from commercial sources without further purification. ^1H and ^{13}C spectra were recorded in $CDCl_3$, DMSO-d_6, or CD_3OD on a 400 MHz spectrometer using TMS as internal standard. Melting points determined are uncorrected. All new compounds were characterized by physical and spectroscopic data; compounds **3a**,[8a] **4a**,[14a] **4f**,[14b] **4h–k**[6] had physical and spectroscopic data corresponding to those given in the literature.

3-(2-Bromobenzoyl)-1-methyl-1*H*-indole (3a); Typical Procedure[8a]

To a soln of 1-methyl-1*H*-indole (**1a**, 170.5 mg, 1.3 mmol) in anhyd DCE (1.5 mL) at 0 °C under N_2 were added 2-bromobenzoyl chloride (**2a**, 218 mg, 1 mmol) in anhyd DCE (1.5 mL) by a syringe and $ZrCl_4$ (349.5 mg, 1.5 mmol). The reaction temperature was gradually increased to 30 °C and the reaction was then continued at 30 °C. On completion (TLC monitoring) after 6 h, the resultant mixture was quenched with H_2O (5 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water (2 × 10 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. Column chromatographic purification of the crude mass (silica gel, EtOAc–petroleum ether) provided **3a** (225.3 mg, 72%) as a white solid; mp 150–152 °C. Spectroscopic data was identical to that in the literature.[8a]

1-Benzyl-3-(2-bromobenzoyl)-1*H*-indole (3b)

Brownish-black solid; yield: 265 mg (68%); mp 107–109 °C.

IR (KBr): 3097, 1633, 1520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 7.3 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.45–7.29 (m, 10 H), 7.12 (d, *J* = 6.0 Hz, 2 H), 5.32 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 142.5, 138.4, 137.3, 135.5, 133.2, 130.5, 129.0, 128.7 (2 CH), 128.2, 127.1, 126.7 (2 CH), 123.9, 123.2, 122.7, 119.5, 116.5, 110.4, 50.9.

MS (APCI): *m*/*z* = 390 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{22}H_{16}BrNNaO$: 412.0313; found: 412.0318.

3-(2-Bromobenzoyl)-5-methoxy-1-methyl-1*H*-indole (3c)
White solid; yield: 213 mg (62%); mp 175–177 °C.

IR (KBr): 3119, 2953, 1729, 1614, 1215, 1031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.41–7.37 (m, 2 H), 7.32–7.30 (m, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.19 (s, 1 H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.90 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 156.8, 142.5, 138.9, 133.2, 132.7, 130.4, 128.6, 127.3, 127.0, 119.5, 115.7, 114.3, 110.7, 103.8, 55.8, 33.8.

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{17}H_{14}BrNNaO_2$: 366.0106; found: 366.0106.

3-(2-Bromobenzoyl)-1-methyl-5-phenyl-1*H*-indole (3d)
Yellow oil; yield: 175 mg (45%).

IR (neat): 3191, 1603, 1423 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.36 (s, 1 H), 7.74–7.66 (m, 6 H), 7.52–7.46 (m, 5 H), 7.35–7.34 (m, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.1, 142.6, 141.5, 141.3, 137.7, 135.7, 133.3, 131.4, 129.4 (2 CH), 129.0, 128.0, 127.4, 127.3 (2 CH), 126.9, 123.1, 119.7, 119.0, 115.3, 112.0, 33.7.

MS (APCI): *m*/*z* = 390 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{22}H_{16}BrNNaO$: 412.0313; found: 412.0311.

3-(2-Bromo-3,4,5-trimethoxybenzoyl)-1-methyl-1*H*-indole (3e)
Yellowish-white solid; yield: 242 mg (60%); mp 78–80 °C.

IR (KBr): 1737, 1628, 1217, 1025 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 (d, *J* = 6.8 Hz, 1 H), 7.78 (s, 1 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.35–7.27 (m, 2 H), 6.95 (s, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.4, 153.0, 150.7, 143.4, 141.0, 138.3, 138.1, 128.7, 126.3, 123.8, 121.7, 114.8, 111.3, 108.4, 105.3, 61.3, 61.2, 56.6, 33.6.

MS (APCI): *m*/*z* = 404 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{19}H_{18}BrNNaO_4$: 426.0317; found: 426.0319.

3-(2-Bromobenzoyl)-1*H*-indole (3f)
White solid; yield: 191 mg (64%); mp 195–198 °C.

IR (KBr): 3359, 2970, 1738, 1614 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (br s, 1 H), 7.63 (dd, *J* = 8, 0.9 Hz, 1 H), 7.43–7.28 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.4, 142.3, 136.6, 135.3, 133.2, 130.5, 128.6, 127.0, 125.6, 124.1, 123.1, 122.4, 119.5, 117.6, 111.6.

MS (APCI): *m*/*z* = 300 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{15}H_{10}BrNNaO$: 321.9843; found: 321.9842.

3-(2-Bromobenzoyl)-5-methoxy-1*H*-indole (3g)
White solid; yield: 178 mg (54%); mp 203–205 °C.

IR (KBr): 3352, 2925, 1737, 1606, 1216, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (br s, 1 H), 7.90 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.43–7.30 (m, 5 H), 6.96 (m, 1 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 156.7, 142.3, 135.1, 133.2, 131.2, 130.5, 128.7, 127.0, 126.5, 119.5, 117.5, 114.8, 112.3, 103.5, 55.8.

MS (APCI): *m*/*z* = 330 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{16}H_{12}BrNNaO_2$: 351.9949; found: 351.9953.

3-(2-Bromo-5-methoxybenzoyl)-1*H*-indole (3h)
White solid; yield: 191 mg (58%); mp 140–143 °C.

IR (KBr): 3362, 2970, 1738, 1609, 1235, 1017 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.09 (d, *J* = 7 Hz, 1 H), 7.46 (s, 1 H), 7.44 (d, *J* = 2.6 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 7.18–7.15 (m, 2 H), 6.89–6.86 (m, 2 H), 3.70 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 192.4, 160.3, 144.5, 138.8, 138.5, 135.0, 127.0, 124.8, 123.7, 122.7, 117.7, 117.6, 115.3, 113.2, 110.4, 56.2.

MS (APCI): *m*/*z* = 330 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{16}H_{12}BrNNaO_2$: 351.9949; found: 351.9949.

3-(2-Bromo-5-methoxybenzoyl)-5-methoxy-1*H*-indole (3i)
White solid; yield: 187 mg (52%); mp 137–139 °C.

IR (KBr): 3271, 2936, 1737, 1604, 1215, 1017 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.72 (br s, 1 H), 7.57–7.53 (m, 1 H), 7.47 (s, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.31 (s, 1 H), 6.99–6.96 (m, 1 H), 6.92–6.90 (m, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 192.3, 160.3, 158.0, 144.5, 138.5, 136.0, 135.0, 119.4, 117.7, 117.2, 115.3, 114.8, 113.9, 110.4, 104.4, 56.2, 56.0.

MS (APCI): *m*/*z* = 360 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{17}H_{14}BrNNaO_3$: 382.0055; found: 382.0055.

3-(2-Bromo-4,5-dimethoxybenzoyl)-1*H*-indole (3j)
White solid; yield: 205 mg (57%); mp 230–233 °C.

IR (KBr): 3418, 2970, 1737, 1605, 1216, 1028 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (d, *J* = 6.4 Hz, 1 H), 7.68 (s, 1 H), 7.50 (d, *J* = 6.4 Hz, 1 H), 7.24–7.22 (m, 3 H), 7.06 (s, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.3, 150.2, 148.2, 137.4, 137.3, 134.8, 126.0, 123.6, 122.6, 121.6, 116.3, 116.1, 112.8, 112.5, 109.5, 56.4, 56.2.

MS (APCI): *m*/*z* = 360 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{17}H_{14}BrNNaO_3$: 382.0055; found: 382.0046.

3-(2-Bromo-4,5-dimethoxybenzoyl)-5-methoxy-1*H*-indole (3k)
Off-white solid; yield: 210 mg (54%); mp 207–209 °C.

IR (KBr): 3152, 2955, 1733, 1625, 1602, 1463, 1259, 1026 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.74 (s, 1 H), 7.69 (s, 1 H), 7.48 (d, *J* = 8.6 Hz, 1 H), 7.30 (s, 1 H), 7.13 (s, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.2, 156.1, 150.2, 148.2, 137.4, 134.8, 132.2, 126.8, 116.2 (2 CH), 113.6, 113.5, 112.4, 109.5, 103.3, 56.4, 56.2, 55.7.

MS (APCI): *m*/*z* = 390 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{18}H_{16}BrNNaO_4$: 412.0160; found: 412.0162.

3-(2-Bromo-3,4,5-trimethoxybenzoyl)-1*H*-indole (3l)
Yellowish-white solid; yield: 214 mg (55%); mp 98–100 °C.

IR (KBr): 3322, 2933, 1610, 1238, 1105, 1007 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.0 (br s, 1 H), 8.15 (d, *J* = 5.8 Hz, 1 H), 7.70 (s, 1 H), 7.50 (d, *J* = 6.6 Hz, 1 H), 7.25–7.24 (m, 2 H), 6.95 (s, 1 H), 3.83 (s, 6 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 153.0, 150.7, 143.4, 138.4, 137.7, 137.4, 125.9, 123.7, 122.7, 121.6, 116.0, 112.9, 108.4, 105.3, 61.3, 61.2, 56.7.

MS (APCI): *m*/*z* = 390 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{18}H_{16}BrNNaO_4$: 412.0160; found: 412.0153.

3-(2-Bromo-3,4,5-trimethoxybenzoyl)-5-methoxy-1*H*-indole (3m)
Yellowish-white solid; yield: 214 mg (51%); mp 159–162 °C.

IR (KBr): 3312, 2931, 1602, 1269, 1111, 1010 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.99 (br s, 1 H), 7.63 (s, 2 H), 7.40 (d, *J* = 8.6 Hz, 1 H), 6.93 (s, 1 H), 6.88 (d, *J* = 8.6 Hz, 1 H), 3.82 (s, 6 H), 3.79 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.9, 156.1, 153.0, 150.7, 143.4, 138.5, 137.7, 132.2, 126.7, 115.8, 113.7, 113.6, 108.3, 105.3, 103.1, 61.3, 61.2, 56.7, 55.7.

MS (APCI): *m*/*z* = 420 [M (^{79}Br) + H$^+$].

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{19}H_{18}BrNNaO_5$: 442.0266; found: 442.0259.

3-(2-Bromo-5-fluorobenzoyl)-1*H*-indole (3n)
White solid; yield: 149 mg (47%); mp 173–177 °C.

IR (KBr): 3449, 2953, 1722, 1610 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (d, *J* = 6.6 Hz, 1 H), 7.77–7.74 (m, 1 H), 7.71 (s, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.34–7.23 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.0, 161.5 (d, *J* = 245 Hz, 1C), 144.5, 137.7 (d, *J* = 38 Hz, 1C), 135.1 (d, *J* = 8 Hz, 1C), 125.8, 123.9, 122.8, 121.6, 118.5, 118.3, 116.4, 116.2, 115.7, 113.0.

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{15}H_9BrFNNaO$: 339.9749; found: 339.9747.

3-(2-Bromo-2-naphthoyl)-5-methoxy-1*H*-indole (3o)
White-orange solid; yield: 231 mg (61%); mp 203–205 °C.

IR (KBr): 3470, 3166, 1620, 1595, 1456, 1275, 1132 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.36 (s, 1 H), 8.08 (s, 1 H), 8.00 (t, *J* = 8.6 Hz, 2 H), 7.71 (s, 1 H), 7.63–7.62 (m, 3 H), 7.41 (d, *J* = 8.6 Hz, 1 H), 6.91 (d, *J* = 8.6 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.3, 156.2, 139.8, 137.8, 134.4, 132.3, 131.9, 131.5, 128.7, 128.2, 127.6, 127.3, 126.8, 116.7, 116.4, 113.7, 113.6, 103.3, 55.7.

HRMS (ESI): *m*/*z* [M (^{79}Br) + Na]$^+$ calcd for $C_{20}H_{14}BrNNaO_2$: 402.0106; found: 402.0100.

5-Methylindeno[1,2-*b*]indol-10(5*H*)-one (4a); Typical Procedure for 4a–e
3-(2-Bromobenzoyl)-1*H*-methyl-1*H*-indole (**3a**, 313 mg, 1.00 mmol) was added to an oven-dried round-bottom flask under N_2. K_2CO_3 (2 equiv), $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$ (5 mol%), and anhyd DMF (2 mL) were subsequently added. The resulting mixture was then stirred at 130 °C. On completion of the reaction (TLC monitoring) after 2 h, H_2O (5 mL) was added to the mixture and it was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with H_2O (10 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. Column chromatographic purification of the crude mass (silica gel, EtOAc–petroleum ether), provided **4a** (226 mg, 97% yield) as a reddish solid; mp 215–217 °C. Spectroscopic data are in accord with literature values.[14a]

5-Benzylindeno[1,2-*b*]indol-10(5*H*)-one (4b)
Orange solid; yield: 241 mg (78%); mp 192–193 °C.

IR (KBr): 2927, 1714, 1684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.82 (m, 1 H), 7.47–7.45 (m, 1 H), 7.37–7.30 (m, 3 H), 7.23–7.16 (m, 7 H), 7.02–7.00 (m, 1 H), 5.51 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 158.7, 142.6, 141.1, 135.5, 134.7, 132.0, 129.6, 129.1, 128.1, 126.2, 123.6, 123.3, 123.2, 123.0, 120.8, 118.5, 115.5, 111.0, 48.7.

MS (APCI): *m*/*z* = 310 (M + H$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{15}NNaO$: 332.1051; found: 332.1051.

8-Methoxy-5-methylindeno[1,2-*b*]indol-10(5*H*)-one (4c)
Orange solid; yield: 229 mg (87%); mp 178–179 °C.

IR (KBr): 2929, 1735, 1367, 1216, 1152, 1072 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 1 H), 7.23–7.21 (m, 2 H), 7.19–7.15 (m, 2 H), 7.10 (d, *J* = 8.9 Hz, 1 H), 6.78 (dd, *J* = 8.9, 3.8 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 158.4, 157.0, 141.4, 137.8, 134.8, 131.8, 129.5, 123.6, 123.1, 118.1, 114.6, 113.0, 111.3, 102.3, 55.7, 31.8.

MS (APCI): *m*/*z* = 264 (M + H$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}NNaO_2$: 286.0844; found: 286.0841.

5-Methyl-8-phenylindeno[1,2-*b*]indol-10(5*H*)-one (4d)
Yellowish-brown solid; yield: 250 mg (81%); mp 168–170 °C.

IR (KBr): 2927, 1672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 1 H), 7.67–7.65 (m, 2 H), 7.46–7.43 (m, 4 H), 7.36–7.22 (m, 5 H), 3.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 159.2, 141.3, 137.0, 131.9, 129.7, 128.7 (2 CH), 127.3 (2 CH), 127.0, 125.7, 123.4, 123.3, 122.6, 119.2, 118.3, 110.7, 31.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{15}NNaO$: 332.1051; found: 332.1045.

2,3,4-Trimethoxy-5-methylindeno[1,2-*b*]indol-10(5*H*)-one (4e)
Orange solid; yield: 239 mg (74%); mp 143–145 °C.

IR (KBr): 2929, 1727, 1217, 1152, 1072 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 1 H), 7.23–7.12 (m, 3 H), 6.96 (s, 1 H), 4.05 (s, 3 H), 4.01 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 159.3, 154.9, 146.2, 144.9, 143.0, 137.4, 123.4, 123.1, 122.4, 120.0, 119.3, 114.4, 110.8, 105.2, 61.2, 60.9, 56.5, 31.6.

MS (APCI): m/z = 324 (M + H^+).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NNaO_4$: 346.1055; found: 346.1053.

Indeno[1,2-*b*]indol-10(5*H*)-one (4f); Typical Procedure 4f–o

3-(2-Bromobenzoyl)-1*H*-indole (**3f**, 299 mg, 1.00 mmol) was added to an oven-dried round-bottom flask under N_2. CsOAc (2 equiv), Ph_3P (10 mol%), $Pd(OAc)_2$ (5 mol%), and anhyd DMA (2 mL) were subsequently added. The resulting mixture was then stirred at 130 °C. On completion of the reaction (TLC monitoring) after 3 h, H_2O (5 mL) was added to the mixture and it was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with H_2O (10 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. The column chromatographic purification of the crude mass (silica gel, EtOAc–petroleum ether) provided **4f** (182 mg, 83% yield) as a reddish solid; mp 333–336 °C. Spectroscopic data are in accord with literature values.[14b]

8-Methoxyindeno[1,2-*b*]indol-10(5*H*)-one (4g)

Orange solid; yield: 184 mg (74%); mp 256–260 °C.

IR (KBr): 3225, 2928, 1736, 1217, 1153, 1072 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.72–7.70 (m, 1 H), 7.51–7.33 (m, 5 H), 6.93 (d, J = 8.7 Hz, 1 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 193.9, 157.8, 142.1, 137.5, 133.7, 133.4, 133.0, 132.3, 130.7, 129.9, 129.6, 129.4, 114.9, 113.7, 104.6, 56.0.

MS (APCI): m/z = 250 (M + H^+).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{11}NNaO_2$: 272.0687; found: 272.0687.

2,3,4-Trimethoxyindeno[1,2-*b*]indol-10(5*H*)-one (4l)

Reddish solid; yield: 207 mg (67%); mp 202–205 °C.

IR (KBr): 3172, 1661, 1521, 1442, 1230, 1065 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47 (d, J = 6.8 Hz, 1 H), 7.40 (d, J = 7.4 Hz, 1 H), 7.12–7.06 (m, 2 H), 6.90 (s, 1 H), 3.95 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.8, 157.4, 155.3, 146.5, 144.9, 142.4, 136.4, 123.5, 122.9, 122.7, 119.2, 119.1, 114.0, 113.3, 105.7, 61.9, 61.0, 56.9.

MS (APCI): m/z = 310 (M + H^+).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{15}NNaO_4$: 332.0899; found: 332.0894.

2,3,4,8-Tetramethoxyindeno[1,2-*b*]indol-10(5*H*)-one (4m)

Reddish solid; yield: 217 mg (64%); mp 222–225 °C.

IR (KBr): 2929, 1736, 1455, 1217, 1152, 1072 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.27 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 2.3 Hz, 1 H), 6.90 (s, 1 H), 6.68 (dd, J = 8.8, 2.3 Hz 1 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.2, 156.7, 155.2, 146.4, 144.9, 137.1, 136.6, 123.8, 119.2, 114.7, 113.3, 112.0, 105.6, 101.4, 61.8, 61.0, 56.9, 55.7.

MS (APCI): m/z = 340 (M + H^+).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NNaO_5$: 362.1004; found: 362.1006.

2-Fluoroindeno[1,2-*b*]indol-10(5*H*)-one (4n)

Reddish solid; yield: 183 mg (77%); mp 220–222 °C.

IR (KBr): 2957, 1736, 1365, 1216 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58–7.53 (m, 1 H), 7.45–7.43 (m, 1 H), 7.30–7.27 (m, 1 H), 7.19–7.12 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.8, 163.9 (d, J = 247 Hz, 1 C), 158.8, 142.1, 131.0, 123.7, 123.5, 123.0, 120.9, 119.8, 118.2, 118.0, 114.2, 112.0, 111.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_8FNNaO$: 260.0488; found: 260.0488.

10-Methoxybenzo[5,6]indeno[1,2-*b*]indol-12(7*H*)-one (4o)

Yellowish-brown solid; yield: 242 mg (81%); mp >300 °C.

IR (KBr): 3446, 3212, 1666, 1209, 1056 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (d, J = 7.8 Hz, 1 H), 7.90–7.88 (m, 2 H), 7.64 (s, 1 H), 7.56–7.46 (m, 2 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.12 (d, J = 2.4 Hz, 1 H), 6.83 (dd, J = 7.8, 2.4 Hz, 1 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.5, 158.0, 156.6, 139.7, 137.5, 135.4, 133.9, 130.6, 130.2, 129.4, 129.0, 127.7, 123.3, 118.7, 118.1, 114.9, 113.8, 102.3, 55.8.

MS (APCI): m/z = 300 (M + H^+).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{13}NNaO_2$: 322.0844; found: 322.0839.

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