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Palladium-mediated synthesis of poly-fused heterocycles from Baylis–Hillman adducts

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ABSTRACT

We synthesized various poly-fused heterocyclic compounds in good to moderate yields via the intramolecular Heck type reaction of Baylis–Hillman adducts modified with indole, imidazole, benzimidazole, and isatin.

1. Introduction

Due to the abundance of medium-sized (seven-, eight- and nine-membered) heterocyclic compounds in many natural products, drugs, and preclinical leads, syntheses of these compounds by intramolecular Heck type reaction have received much attention.[1] Palladium-mediated direct aryl–aryl bond-forming protocols have also been studied extensively in this respect.[2] Among the approaches of aryl–aryl bond-forming reactions, the use of heteroaromatic compound as one of the aryl group received special interest due to the biological importance of many heteroaryl moiety-containing compounds.[1c,2a,b,3,4]

Although palladium-mediated syntheses of medium-sized heterocyclic compounds have been investigated thoroughly,[1,3b,c] studies involving the Baylis–Hillman adducts[5] have not been reported much.[6,7] Very recently we reported the synthesis of indole moiety-containing tetracyclic compounds starting from the Baylis–Hillman acetate by applying S_N2' type reaction with indole and the following Pd-mediated cyclization protocol (Scheme 2, vide infra).[8]

Poly-fused heterocyclic compounds were known to possess many interesting biological activities[9–12] including hepatitis C virus (HCV) NS5B polymerase inhibitory activity.[9] The chemists at Bristol–Myers Squibb Company reported the synthesis of indole moiety-containing tetracyclic compounds as NS5B inhibitors.[9] They used four-step procedure comprising of (i) bromination of indole, (ii) Suzuki coupling with phenylboronic acid, (iii) alkylation with allyl bromide, and (iv) ring-closing metathesis (RCM) reaction protocol to form the target structure (Scheme 1).[9] Our synthesis is comprised of only two steps: alkylation of indole with the Baylis–Hillman acetate **1a** and the following Pd-mediated cyclization process (Scheme 1).[8] In view of the simplicity of the reaction sequence, the latter approach could be regarded as more efficient. Thus we examined the generality and efficiency of our protocol[8] with the modified Baylis–Hillman adducts with isatin, imidazole, and benzimidazoles.

2. Results and discussion

We started the synthesis of indole moiety-containing tetracyclic compounds **4a–g** and the preliminary results were reported very recently.[8] As summarized in Scheme 2, starting materials **3a–g** were synthesized by the reaction of Baylis–Hillman acetates **1**[6b] and indole derivatives **2a–f** (KOH, DMF, 0 °C) in 45–95% yields. In all cases, *E*-forms of **3a–g** were formed as the major isomers and we separated them easily from the minor *Z*-isomers (5–10%).[5–8] We have examined the optimum reaction conditions for the intramolecular palladium-catalyzed arylation with compound **3a** and found that the conditions comprising of $Pd(OAc)_2$/TBAB (tetrabutylammonium bromide)/K_2CO_3 in DMF is the best (65%).[8] Under the optimized conditions we synthesized **4a–g** and the results are

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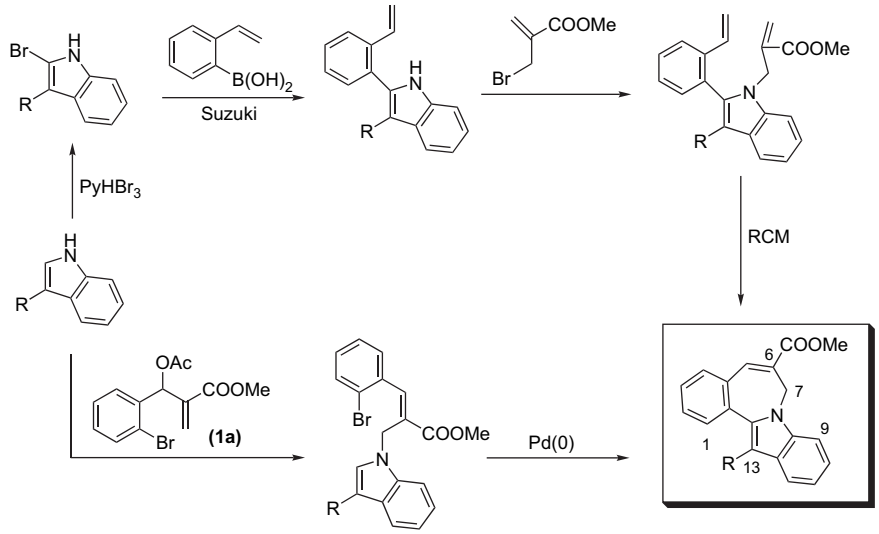


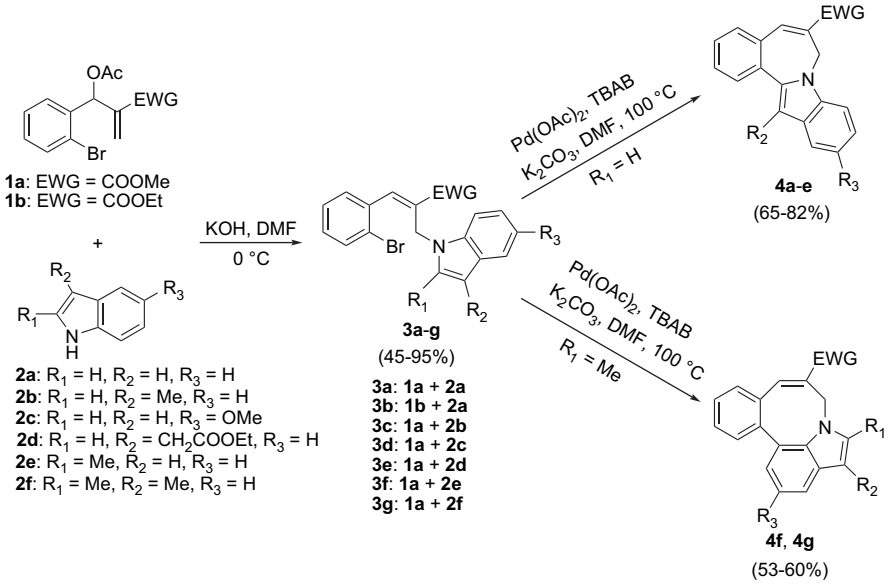
Scheme 1. Synthesis of 7*H*-benzo[3,4]azepino[1,2-*a*]indole derivatives.

summarized in Scheme 2. Seven-membered benzoazepino[1,2-*a*]-indole derivatives **4a**–**e** were synthesized in good yields (65–82%) from the indole derivatives **3a**–**e**, whereas eight-membered compounds **4f** and **4g** were obtained in moderate yields (53–60%) from **3f** and **3g**, which have 2-methyl substituent at the indole moiety (R_1=Me).

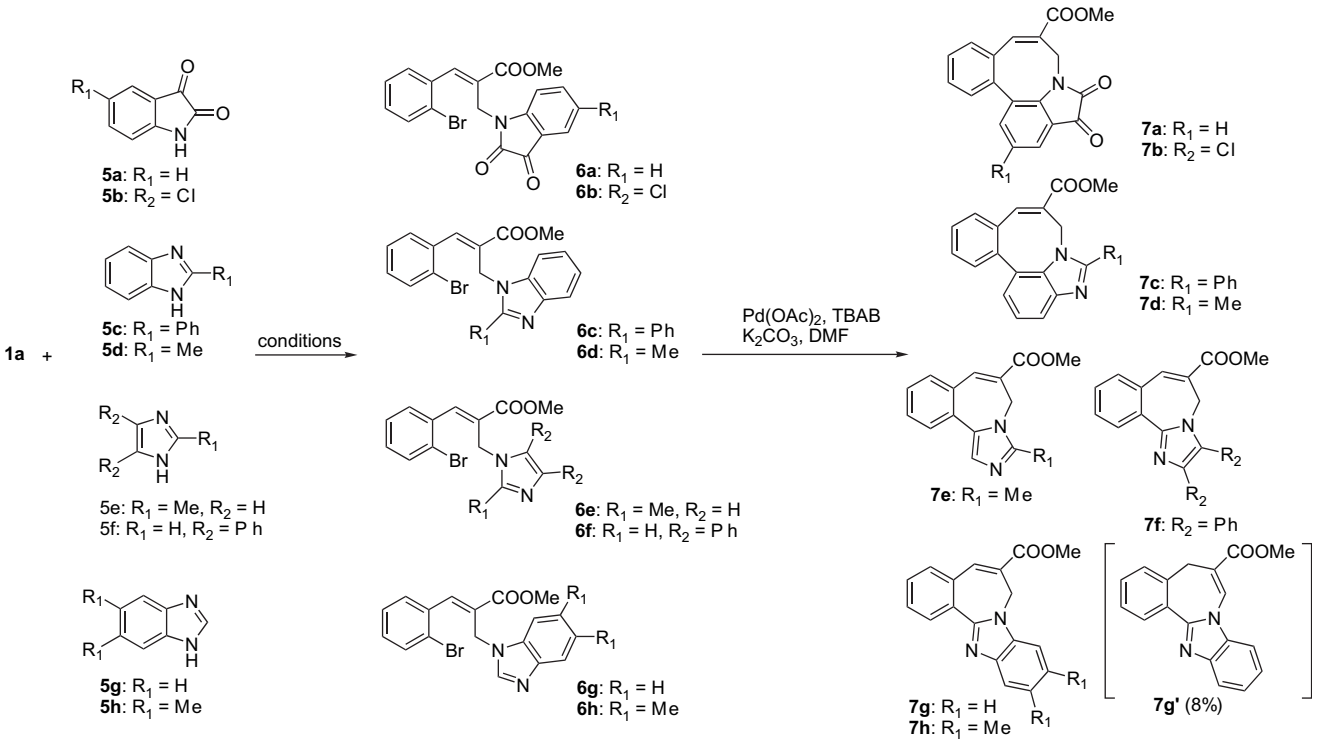
Encouraged by the preliminary results we examined the reactions of similar compounds derived from the reaction of Baylis–Hillman acetate **1a**, as the representative Baylis–Hillman adduct, isatins (**5a** and **5b**), benzimidazoles (**5c**, **5d**, **5g**, **5h**) and imidazoles (**5e** and **5f**) as summarized in Scheme 3. Compounds **6a**–**h** were prepared in 67–89% yields under the conditions of KOH/CH_3CN/0 °C or K_2CO_3/DMF/rt depending on the substrates (Table 1, vide infra). The reactions of **6a**–**h** showed the same reaction patterns as in the previous indole-attached Baylis–Hillman adducts **3a**–**g** in Scheme 2. Tetracyclic compounds containing eight-membered ring **7a**–**d** were formed from the reaction of **6a**–**d** in 36–55% yields. For the substrates **6a**–**d**, formation of seven-membered ring was impossible due to the presence of carbonyl group (for **6a** and **6b**) and substituent R_1 (for **6c** and **6d**).

The regioselective cyclization pathway was clearly demonstrated by the results obtained from **6e** and **6f**. When the 2-position of imidazole moiety was substituted with methyl group (**6e**), cyclization occurred at the 4-position of imidazole and produced compound **7e** as the sole product, whereas, cyclization occurred at the 2-position of imidazole moiety to afford **7f** when we used **6f** as the starting material, which has 4,5-diphenyl substituents. For the substrates **6g** and **6h** we obtained seven-membered ring compounds again. The results state that 2-position of benzimidazole is more reactive than that of 7-position. It is interesting to note that double bond-isomerized compound **7g′** was obtained in 8%. The structure of **7g′** could be easily deduced from its ^{1}H NMR spectrum by the upfield shift of methylene protons in seven-membered ring from δ=5.05 ppm (**7g**) to δ=3.76 ppm (**7g′**). However, the combined yield of **7g** and **7g′** was very low in this case, unfortunately.

The experimental conditions for the synthesis of **6a**–**h** and **7a**–**h** are summarized in Table 1 together with the yields. As compared with the results obtained from the indole-containing substrates **3a**–**g**, the reactions with **6a**–**h** occurred within shorter reaction time (15–40 min) and the yields of products were lower than those



Scheme 2.



Scheme 3.

of the indole cases. When we let the reaction mixture of **6a–h** for longer reaction time we observed some decomposition of products and the yields were reduced slightly.

As in Scheme 4, when we used 5-methylbenzimidazole (**5i**) the reaction was somewhat complex. We obtained regioisomeric mixture of **6i** in 83% yield (2:1 mixture based on ^{1}H NMR) and the separation was almost impossible. Thus we subjected the mixture to the same Pd-mediated reaction conditions at 110 °C for 20 min, and we obtained desired compound **7i** in 30% yield and double bond-isomerized compound **7i′** in 9% yield, as inseparable mixtures again.

As the final trials we also examined the reactions of carbazole- and 6-benzylaminopurine-attached Baylis–Hillman adducts **6j** and **6k** (Scheme 5). The syntheses of these compounds were carried out similarly as for the compounds **6a–i** with KOH or K_2CO_3 in moderate yields. The reaction of **6j** under the same conditions produced the corresponding 8-membered ring compound **7j** in 68%. However, the purine compound **6k** was decomposed completely under the same conditions. Thus we tried different conditions, which were reported recently by Hocek and co-workers,[4e,f] and obtained desired compound **7k** albeit in low yield (23%) together with isomerized compound **7k′** (6%). The structure of **7k′** could also be assigned by the chemical shift value (δ=5.14 ppm for **7k** vs δ=3.76 ppm for **7k′**), as in the case of **7g**/**7g′**. This is the first example of intramolecular arylation of purine system.

Although the yields of products were somewhat low in some cases (especially for benzimidazole-attached Baylis–Hillman adducts) the protocol described herein could be used efficiently for the synthesis of a variety of poly-fused heterocyclic compounds. Examinations on the biological activities of prepared compounds are currently underway and will be reported in due course.

Table 1
Synthesis of compounds **6** and **7**

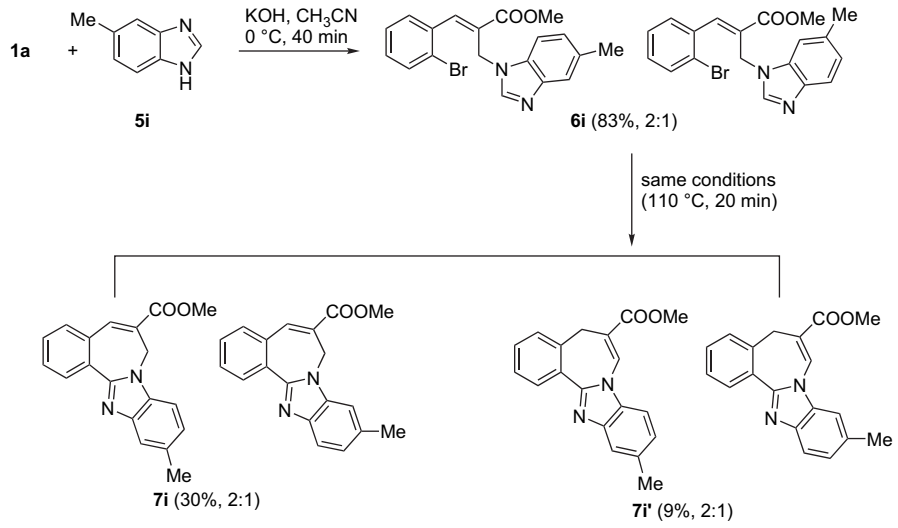
Entry	Conditions	**6** (%)	Conditions[a]	**7** (%)+others
1	K_2CO_3 (1.2 equiv), DMF, rt, 17 h	**6a** (87)	100 °C, 15 min	**7a** (55)
2	K_2CO_3 (1.2 equiv), DMF, rt, 8 h	**6b** (81)	100 °C, 15 min	**7b** (50)
3	KOH (1.2 equiv), CH_3CN, 0 °C, 5 h	**6c** (67)	110 °C, 25 min	**7c** (48)
4	KOH (1.2 equiv), CH_3CN, 0 °C, 40 min	**6d** (71)	110 °C, 20 min	**7d** (36)
5	KOH (1.2 equiv), CH_3CN, 0 °C, 2 h	**6e** (84)	110 °C, 15 min[b]	**7e** (46)
6	KOH (1.2 equiv), CH_3CN, 0 °C, 2 h	**6f** (89)	110 °C, 15 min[b]	**7f** (71)
7	KOH (1.2 equiv), CH_3CN, 0 °C, 1 h	**6g** (80)	110 °C, 40 min[b]	**7g** (32)+**7g′** (8)
8	KOH (1.2 equiv), CH_3CN, 0 °C, 1 h	**6h** (77)	110 °C, 20 min[b]	**7h** (46)

[a] Conditions: $Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), DMF.
[b] 20 mol % of $Pd(OAc)_2$ was used.

3. Experimental

3.1. General procedure

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in parts per million relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejeon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.



Scheme 4.

3.2. Synthesis of starting materials 3a–g[8]

To a stirred solution of indole (**2a**, 117 mg, 1.0 mmol) and KOH (79 mg, 1.2 mmol) in DMF (1.5 mL) was added a solution of Baylis–Hillman acetate **1a** (376 mg, 1.2 mmol) in DMF (0.5 mL) at 0 °C, and maintained at 0 °C for 4 h with stirring. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 10:1) we obtained **3a** (271 mg, 73%) as a white solid. Other compounds **3b–g** were synthesized similarly. The spectroscopic data of synthesized compounds **3b–g** are as follows.

*3.2.1. Compound **3b***

Yield 50%; white solid, mp 98–100 °C; IR (film) 1718, 1459, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J=7.2 Hz, 3H), 4.19 (q, J=7.2 Hz, 2H), 5.03 (s, 2H), 6.43 (d, J=3.3 Hz, 1H), 7.02–7.31 (m, 7H), 7.56 (d, J=7.2 Hz, 1H), 7.68 (d, J=7.5 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.03, 42.23, 61.36, 101.50, 109.57, 119.32, 120.70, 121.37, 123.89, 127.45, 127.46, 128.49, 129.90, 130.16, 130.45, 133.09, 135.03, 136.09, 142.22, 166.35. Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.25; H, 4.98; N, 3.47.

*3.2.2. Compound **3c***

Yield 51%; yellow oil; IR (film) 1717, 1464, 1435, 1249, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 3.73 (s, 3H), 4.96 (s, 2H), 6.82 (s, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.04–7.26 (m, 5H), 7.49 (d, J=7.5 Hz, 1H), 7.66 (d, J=7.5 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.59, 41.97, 52.34, 109.34, 110.65, 118.61, 118.75, 121.33, 123.87, 124.92, 127.42, 128.75, 129.77, 130.16, 130.42, 133.00, 134.94, 136.36, 142.22, 166.94. Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.62; H, 4.58; N, 3.42.

*3.2.3. Compound **3d***

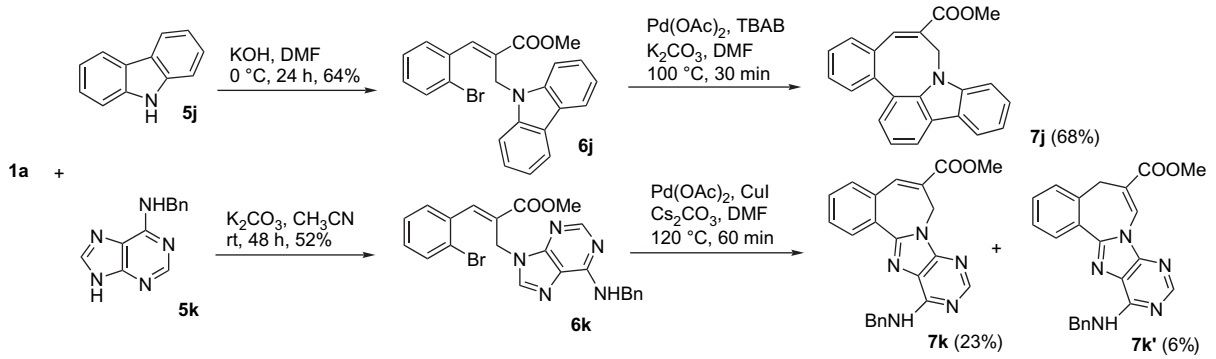
Yield 95%; colorless oil; IR (film) 1718, 1483, 1437, 1236, 1151, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 3.82 (s, 3H), 5.00 (s, 2H), 6.35 (d, J=3.0 Hz, 1H), 6.77 (dd, J=9.0 and 2.4 Hz, 1H), 6.90 (d, J=9.0 Hz, 1H), 7.03–7.35 (m, 5H), 7.69 (d, J=7.5 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.38, 52.38, 55.82, 101.13, 102.50, 110.24, 111.67, 123.88, 127.50, 128.01, 128.86, 129.59, 130.16, 130.54, 131.40, 133.12, 134.93, 142.43, 153.98, 166.85. Anal. Calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50. Found: C, 59.78; H, 4.77; N, 3.34.

*3.2.4. Compound **3e***

Yield 60%; yellow oil; IR (film) 1732, 1712, 1466, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J=7.2 Hz, 3H), 3.69 (d, J=0.6 Hz, 2H), 3.76 (s, 3H), 4.13 (q, J=7.2 Hz, 2H), 5.00 (s, 2H), 6.97–7.30 (m, 7H), 7.54 (d, J=7.5 Hz, 1H), 7.67 (d, J=6.9 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.18, 31.40, 42.17, 52.34, 60.62, 107.57, 109.59, 118.92, 119.20, 121.66, 123.78, 126.42, 127.45, 127.78, 129.60, 130.13, 130.47, 133.04, 134.89, 136.30, 142.43, 166.80, 171.92. Anal. Calcd for $C_{23}H_{22}BrNO_4$: C, 60.54; H, 4.86; N, 3.07. Found: C, 60.33; H, 4.91; N, 2.87.

*3.2.5. Compound **3f***

Yield 45%; white solid, mp 141–143 °C; IR (film) 1717, 1464, 1435, 1245, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.64 (s,



Scheme 5.

3H), 5.04 (s, 2H), 6.13 (s, 1H), 6.96–7.33 (m, 6H), 7.41 (d, J=6.6 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.86, 40.31, 52.12, 100.51, 109.85, 119.17, 119.32, 120.29, 123.68, 127.18, 128.13, 130.34, 130.43, 130.63, 133.12, 134.76, 137.00, 137.41, 140.75, 166.56. Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.68; H, 4.99; N, 3.54.

3.2.6. Compound ***3g***

Yield 62%; yellow solid, mp 111–113 °C; IR (film) 1720, 1468, 1435, 1331, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.22 (s, 3H), 3.63 (s, 3H), 5.02 (d, J=1.2 Hz, 2H), 6.97–7.24 (m, 6H), 7.36 (d, J=7.5 Hz, 1H), 7.64 (d, J=7.8 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.74, 10.14, 40.36, 52.07, 106.83, 109.50, 117.53, 118.49, 120.30, 123.56, 127.01, 128.66, 130.15, 130.55, 130.80, 132.91, 133.02, 134.75, 136.22, 140.40, 166.70. Anal. Calcd for $C_{21}H_{20}BrNO_2$: C, 63.33; H, 5.06; N, 3.52. Found: C, 63.12; H, 5.39; N, 3.57.

3.3. Synthesis of indole-containing tetracyclic compounds 4a–g[8]

A stirred mixture of **3a** (185 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), TBAB (161 mg, 0.5 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in DMF (2 mL) was heated to 100 °C for 1 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained **4a** (95 mg, 65%) as a pale yellow solid. Other compounds **4b**–**g** were synthesized analogously and the spectroscopic data of prepared compounds **4b**–**e** and **4g** are as follows.

3.3.1. Compound ***4b***

Yield 82%; yellow solid, mp 166–167 °C; IR (film) 1700, 1458, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, J=7.2 Hz, 3H), 4.29 (q, J=7.2 Hz, 2H), 4.97 (s, 2H), 6.74 (d, J=0.6 Hz, 1H), 7.08–7.13 (m, 1H), 7.22–7.28 (m, 1H), 7.34–7.47 (m, 3H), 7.56 (d, J=8.1 Hz, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.85 (d, J=8.7 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.28, 39.16, 61.37, 101.15, 109.26, 119.74, 120.69, 121.94, 127.54, 128.14, 129.64, 129.88, 130.57, 131.77, 131.88, 133.11, 136.30, 139.22, 142.38, 165.51. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.01; H, 5.93; N, 4.40.

3.3.2. Compound ***4c***

Yield 66%; yellow solid, mp 158–160 °C; IR (film) 1705, 1460, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.81 (s, 3H), 4.94 (s, 2H), 7.07–7.19 (m, 1H), 7.24–7.32 (m, 1H), 7.36–7.56 (m, 4H), 7.61 (d, J=7.8 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.17, 39.10, 52.33, 108.86, 109.06, 119.00, 119.07, 122.17, 127.13, 128.66, 129.07, 131.08, 131.19, 131.22, 132.55, 133.43, 134.40, 134.86, 142.53, 166.03; ESIMS m/z 304.18 (M^++1). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.38; H, 5.93; N, 4.44.

3.3.3. Compound ***4d***

Yield 69%; yellow solid, mp 130–132 °C; IR (film) 1716, 1458, 1243, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3H), 3.86 (s, 3H), 4.94 (s, 2H), 6.68 (s, 1H), 6.93 (dd, J=9.0 and 2.7 Hz, 1H), 7.08 (d, J=2.7 Hz, 1H), 7.36–7.50 (m, 4H), 7.85 (d, J=8.1 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.39, 52.44, 55.88, 100.76, 101.93, 110.11, 112.70, 127.50, 128.42, 129.60, 129.97, 130.24, 131.76, 131.87, 131.88, 133.22, 139.66, 142.67, 154.20, 166.06; ESIMS m/z 320.24 (M^++1). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.05; H, 5.61; N, 4.65.

3.3.4. Compound ***4e***

Yield 78%; yellow solid, mp 134–136 °C; IR (film) 1730, 1714, 1460, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J=7.2 Hz, 3H), 3.77 (s, 2H), 3.83 (s, 3H), 4.19 (q, J=7.2 Hz, 2H), 5.04 (s, 2H), 7.12–7.17 (m, 1H), 7.24–7.31 (m, 1H), 7.45–7.59 (m, 4H), 7.68 (d, J=7.5 Hz, 1H), 7.85 (s, 1H), 8.01 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.22, 31.62, 39.18, 52.39, 60.87, 106.17, 109.12, 119.33, 119.61, 122.44, 127.78, 128.07, 129.48, 130.96, 131.15, 131.43, 131.63, 133.56, 134.92, 136.01, 142.31, 165.89, 172.34; ESIMS m/z 376.26 (M^++1). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.52; H, 5.88; N, 3.42.

3.3.5. Compound ***4g***

Yield 60%; white solid, mp 151–153 °C; IR (film) 1714, 1435, 1290, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 2.48 (s, 3H), 3.71 (s, 3H), 4.80 (d, J=14.1 Hz, 1H), 4.99 (d, J=14.1 Hz, 1H), 6.77 (dd, J=7.2 and 0.9 Hz, 1H), 7.06–7.11 (m, 1H), 7.15 (d, J=7.2 Hz, 1H), 7.32–7.49 (m, 4H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.91, 9.93, 40.93, 51.96, 106.67, 117.66, 119.38, 125.53, 125.76, 126.66, 127.37, 130.01, 130.14, 131.85, 133.38, 133.52, 134.00, 135.33, 140.48, 145.24, 166.68; ESIMS m/z 318.23 (M^++1). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.30; H, 6.26; N, 4.19.

3.4. Synthesis of starting materials 6a and 6b

A mixture of isatin (**5a**, 147 mg, 1.0 mmol), Baylis–Hillman acetate **1a** (376 mg, 1.2 mmol), and K_2CO_3 (166 mg, 1.2 mmol) in DMF (2.0 mL) was stirred at room temperature for 17 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/ether, 8:2:3) we obtained **6a** (349 mg, 87%) as a white solid. Compound **6b** was synthesized similarly and the spectroscopic data of **6a** and **6b** are as follows.

3.4.1. Compound ***6a***

Yield 87%; white solid, mp 151–153 °C; IR (film) 1739, 1712, 1614, 1469, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 4.76 (s, 2H), 6.68 (d, J=8.1 Hz, 1H), 7.02–7.53 (m, 7H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.45, 52.59, 111.24, 117.33, 122.93, 123.57, 124.94, 126.75, 127.46, 130.22, 130.52, 132.64, 134.37, 138.13, 143.09, 150.13, 157.71, 166.27, 182.66; ESIMS m/z 400.19 (M^++1), 402.33 (M^++3). Anal. Calcd for $C_{19}H_{14}BrNO_4$: C, 57.02; H, 3.53; N, 3.50. Found: C, 56.87; H, 3.51; N, 3.34.

3.4.2. Compound ***6b***

Yield 81%; white solid, mp 120–122 °C; IR (film) 1745, 1712, 1610, 1473, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 4.75 (d, J=0.9 Hz, 2H), 6.67 (d, J=8.4 Hz, 1H), 7.17–7.56 (m, 6H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.49, 52.62, 112.58, 118.16, 122.88, 124.74, 126.45, 127.54, 129.36, 130.18, 130.63, 132.72, 134.27, 137.44, 143.38, 148.43, 157.13, 166.14, 181.65. Anal. Calcd for $C_{19}H_{13}BrClNO_4$: C, 52.50; H, 3.01; N, 3.22. Found: C, 52.32; H, 3.13; N, 2.94.

3.5. Synthesis of starting materials 6c–h

To a stirred solution of benzimidazole (**5c**, 194 mg, 1.0 mmol) and KOH (79 mg, 1.2 mmol) in CH_3CN (1.5 mL) was added a solution of Baylis–Hillman acetate **1a** (376 mg, 1.2 mmol) in CH_3CN (0.5 mL) at 0 °C, and maintained at 0 °C for 5 h with stirring. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/ether, 7:3:3) we obtained **6c** (300 mg, 67%) as a white solid. Other compounds **6d**–**h** were synthesized similarly and the spectroscopic data of **6c**–**h** are as follows.

3.5.1. Compound ***6c***

Yield 67%; white solid, mp 56–58 °C; IR (film) 1718, 1458, 1442, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58 (s, 3H), 5.32 (s, 2H), 7.08 (dd, J=7.8 and 1.2 Hz, 1H), 7.19–7.31 (m, 5H), 7.49–7.51 (m, 3H), 7.63 (dd, J=7.8 and 1.2 Hz, 1H), 7.71–7.76 (m, 3H), 7.89 (s, 1H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 42.08, 52.24, 111.00, 119.71, 122.24, 122.65, 123.59, 127.30, 128.55, 128.68, 129.53, 129.59, 130.03, 130.52, 130.59, 133.15, 134.25, 135.11, 142.12, 142.87, 154.32, 165.90; ESIMS *m*/*z* 447.25 (M^++1), 449.27 (M^++3). Anal. Calcd for $C_{24}H_{19}BrN_2O_2$: C, 64.44; H, 4.28; N, 6.26. Found: C, 64.76; H, 4.19; N, 6.35.

3.5.2. Compound ***6d***

Yield 71%; white solid, mp 124–126 °C; IR (film) 1720, 1462, 1398, 1284, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H), 3.66 (s, 3H), 5.07 (d, *J*=1.2 Hz, 2H), 7.05–7.38 (m, 6H), 7.56–7.61 (m, 1H), 7.70 (dd, *J*=7.8 and 1.2 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.96, 40.56, 52.25, 109.92, 118.70, 121.56, 121.77, 123.57, 127.39, 128.64, 130.40, 130.70, 133.28, 134.35, 134.99, 142.18, 142.34, 152.23, 165.94. Anal. Calcd for $C_{19}H_{17}BrN_2O_2$: C, 59.23; H, 4.45; N, 7.27. Found: C, 59.04; H, 4.81; N, 7.12.

3.5.3. Compound ***6e***

Yield 84%; colorless oil; IR (film) 1716, 1435, 1263, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 3.81 (s, 3H), 4.74 (s, 2H), 6.76 (d, *J*=1.5 Hz, 1H), 6.84 (d, *J*=1.5 Hz, 1H), 7.13 (dd, *J*=7.5 and 1.2 Hz, 1H), 7.24–7.38 (m, 2H), 7.68 (dd, *J*=7.5 and 1.2 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.88, 41.92, 52.49, 118.50, 123.62, 127.13, 127.53, 128.96, 129.73, 130.67, 133.14, 134.60, 143.04, 144.82, 166.20. Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.54; H, 4.43; N, 8.21.

3.5.4. Compound ***6f***

Yield 89%; white solid, mp 152–153 °C; IR (film) 1716, 1506, 1437, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 3H), 4.66 (s, 2H), 7.03–7.46 (m, 13H), 7.56 (s, 1H), 7.60 (dd, *J*=7.5 and 1.8 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.55, 52.54, 123.83, 126.20, 126.44, 127.47, 128.00, 128.30, 128.57, 128.60, 128.90, 129.31, 130.37, 130.64, 130.87, 133.09, 134.28, 134.48, 135.77, 138.07, 143.65, 166.17; ESIMS *m*/*z* 473.27 (M^++1), 475.29 (M^++3). Anal. Calcd for $C_{26}H_{21}BrN_2O_2$: C, 65.97; H, 4.47; N, 5.92. Found: C, 66.09; H, 4.74; N, 5.89.

3.5.5. Compound ***6g***

Yield 80%; white solid, mp 93–95 °C; IR (film) 1718, 1493, 1435, 1284, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H), 5.10 (s, 2H), 6.93–6.97 (m, 1H), 7.15–7.39 (m, 5H), 7.70–7.76 (m, 2H), 7.88 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.00, 52.55, 109.67, 120.18, 122.00, 122.79, 123.64, 127.63, 128.38, 129.95, 130.84, 133.33, 133.51, 134.62, 143.27, 143.47, 143.48, 166.23. Anal. Calcd for $C_{18}H_{15}BrN_2O_2$: C, 58.24; H, 4.07; N, 7.55. Found: C, 58.45; H, 4.08; N, 7.44.

3.5.6. Compound ***6h***

Yield 77%; white solid, mp 98–100 °C; IR (film) 1716, 1493, 1435, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.32 (s, 3H), 3.78 (s, 3H), 5.06 (s, 2H), 6.57 (s, 1H), 7.24 (dd, *J*=7.8 and 1.5 Hz, 1H), 7.30–7.42 (m, 2H), 7.48 (s, 1H), 7.75 (dd, *J*=7.8 and 1.5 Hz, 1H), 7.82 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.14, 20.32, 40.86, 52.49, 109.83, 120.13, 123.80, 127.63, 128.51, 130.24, 130.82, 130.83, 131.87, 132.00, 133.32, 134.82, 142.08, 142.73, 143.10, 166.25; ESIMS *m*/*z* 399.25 (M^++1), 401.20 (M^++3). Anal. Calcd for $C_{20}H_{19}BrN_2O_2$: C, 60.16; H, 4.80; N, 7.02. Found: C, 60.38; H, 4.99; N, 6.78.

3.6. Synthesis of tetracyclic compounds 7a–h

A stirred mixture of **6a** (200 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), TBAB (161 mg, 0.5 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in DMF (2 mL) was heated to 100 °C for 15 min. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 1:1) we obtained **7a** (88 mg, 55%) as a white solid. Other compounds **7b**–**h** and **7g′** were synthesized similarly and the representative spectroscopic data of **7a**–**h** and **7g′** are as follows.

3.6.1. Compound ***7a***

Yield 55%; white solid, mp 210–212 °C (decomposed); IR (film) 1741, 1712, 1599, 1290, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 3.93 (dd, *J*=13.8 and 0.9 Hz, 1H), 5.35 (d, *J*=13.8 Hz, 1H), 7.16 (dd, *J*=7.8 and 7.2 Hz, 1H), 7.25–7.32 (m, 3H), 7.45–7.56 (m, 2H), 7.63 (dd, *J*=7.2 and 1.2 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.80, 52.49, 118.82, 124.18, 124.98, 126.89, 128.18, 128.42, 129.11, 130.11, 132.55, 134.43, 136.46, 143.14, 146.21, 146.38, 157.60, 165.75, 183.80; ESIMS *m*/*z* 320.25 (M^++1). Anal. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.54; H, 4.36; N, 4.32.

3.6.2. Compound ***7b***

Yield 50%; white solid, mp 166–168 °C (decomposed); IR (film) 1743, 1716, 1597, 1458, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 3H), 3.92 (d, *J*=13.8 Hz, 1H), 5.33 (d, *J*=13.8 Hz, 1H), 7.26–7.34 (m, 3H), 7.48–7.58 (m, 3H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.92, 52.57, 119.71, 124.69, 128.37, 128.51, 128.94, 129.05, 129.85, 130.32, 132.44, 134.45, 135.20, 141.83, 144.91, 146.02, 157.12, 165.57, 182.88. Anal. Calcd for $C_{19}H_{12}ClNO_4$: C, 64.51; H, 3.42; N, 3.96. Found: C, 64.33; H, 3.67; N, 3.65.

3.6.3. Compound ***7c***

Yield 48%; white solid, mp 148–150 °C; IR (film) 1718, 1473, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3H), 4.94 (d, *J*=13.8 Hz, 1H), 5.31 (d, *J*=13.8 Hz, 1H), 7.01 (d, *J*=7.5 Hz, 1H), 7.21–7.26 (m, 1H), 7.30–7.35 (m, 1H), 7.42–7.58 (m, 6H), 7.70–7.74 (m, 2H), 7.78 (d, *J*=7.5 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.83, 51.81, 119.55, 123.01, 126.67, 126.86, 127.42, 127.74, 128.50, 129.43, 129.61, 130.19, 130.42, 131.06, 132.90, 134.19, 134.79, 138.63, 143.55, 145.81, 155.20, 165.62; ESIMS *m*/*z* 367.31 (M^++1). Anal. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.62; H, 5.07; N, 7.50.

3.6.4. Compound ***7d***

Yield 36%; white solid, mp 156–158 °C; IR (film) 1714, 1437, 1398, 1292, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (s, 3H), 3.77 (s, 3H), 4.82 (d, *J*=13.8 Hz, 1H), 5.10 (d, *J*=13.8 Hz, 1H), 6.95 (dd, *J*=7.8 and 0.9 Hz, 1H), 7.20–7.27 (m, 2H), 7.39–7.55 (m, 3H), 7.63 (dd, *J*=7.8 and 0.9 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.69, 41.26, 52.32, 118.75, 122.43, 125.70, 126.33, 127.26, 127.97, 130.30, 130.98, 132.88, 133.29, 134.51, 138.43, 143.19, 145.94, 152.49, 166.20. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.22; H, 5.56; N, 9.04.

3.6.5. Compound ***7e***

Yield 46%; white solid, mp 135–137 °C; IR (film) 1703, 1437, 1294, 1255, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H), 3.87 (s, 3H), 4.74 (s, 2H), 7.16 (s, 1H), 7.32–7.46 (m, 3H), 7.65 (d, *J*=7.8 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.93, 40.09, 52.47, 125.75, 127.10, 128.12, 128.16, 130.20, 130.23, 130.76, 131.91, 132.40, 143.35, 144.40, 165.93. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.66; H, 5.31; N, 10.76.

3.6.6. Compound ***7f***

Yield 71%; white solid, mp 181–183 °C; IR (film) 1709, 1471, 1442, 1292, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 4.60 (s, 2H), 7.12–7.26 (m, 3H), 7.39–7.60 (m, 10H), 7.99 (s, 1H), 8.40 (d, *J*=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.55, 52.38, 126.48, 127.04, 128.08, 128.20 (2C), 128.46, 128.78, 128.79, 129.83, 130.01, 130.28, 130.83, 131.16, 131.32, 131.59, 134.52, 139.34, 143.56, 146.39, 165.46; ESIMS *m*/*z* 393.26 (M^++1). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.45; H, 5.27; N, 7.02.

3.6.7. Compound ***7g***

Yield 32%; white solid, mp 110–113 °C; IR (film) 1705, 1448, 1304, 1259, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3H),

5.05 (s, 2H), 7.30–7.42 (m, 2H), 7.53–7.67 (m, 4H), 7.88 (d, J=6.9 Hz, 1H), 7.99 (s, 1H), 8.46 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.88, 52.68, 109.40, 119.94, 122.52, 122.98, 129.41, 129.84, 130.32, 130.34, 130.92, 131.68, 132.52, 134.86, 142.55, 143.68, 151.80, 165.67. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.64; H, 4.99; N, 9.62.

3.6.8. Compound ***7g′***

Yield 8%; white solid, mp 144–146 °C; IR (film) 1714, 1456, 1273, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 2H), 3.89 (s, 3H), 7.38–7.52 (m, 5H), 7.57 (d, J=7.5 Hz, 1H), 7.90 (d, J=6.6 Hz, 1H), 8.13 (s, 1H), 8.24 (d, J=6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.02, 52.44, 110.06, 120.27, 121.20, 123.85, 124.44, 127.50, 128.40, 128.89, 130.97 (2C), 131.43, 134.62, 139.02, 142.52, 152.27, 165.86. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.19; H, 4.54; N, 9.36.

3.6.9. Compound ***7h***

Yield 46%; white solid, mp 168–170 °C; IR (film) 1709, 1446, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 2.43 (s, 3H), 3.89 (s, 3H), 4.95 (s, 2H), 7.33 (s, 1H), 7.46–7.60 (m, 4H), 7.92 (s, 1H), 8.39 (dd, J=7.5 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.33, 20.62, 38.83, 52.62, 109.43, 119.82, 129.29, 129.46, 130.21, 130.61, 130.74, 131.46, 131.64, 132.29, 132.33, 133.46, 142.38, 142.55, 151.01, 165.77; ESIMS m/z 319.31 (M^++1). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.66; H, 5.92; N, 8.71.

3.7. Synthesis of compounds 6i, 7i, and 7i′

Compound **6i** was prepared according to the procedure of **6c** with KOH and the next Pd-mediated cyclization of **6i** was carried out at 110 °C for 20 min.

3.7.1. Compound ***6i***

Yield 83% (*major*:*minor*=2:1); IR (film) 1718, 1498, 1437, 1286, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, major 3H), 2.44 (s, minor 3H), 3.78 (s, major 3H, minor 3H), 5.07 (s, major 2H, minor 2H), 6.58 (s, major 1H), 6.84 (d, J=8.1 Hz, minor 1H), 7.00 (dd, J=8.1 and 1.5 Hz, minor 1H), 7.02 (dd, J=8.1 and 1.2 Hz, major 1H), 7.18–7.42 (m, major 3H, minor 3H), 7.52 (s, minor 1H), 7.59 (d, J=8.1 Hz, major 1H), 7.70–7.76 (m, major 1H, minor 1H), 7.82 (s, minor 1H), 7.86 (s, major 1H), 8.00 (s, major 1H, minor 1H).

3.7.2. Compound ***7i***

Yield 30% (*major*:*minor*=2:1); IR (film) 1709, 1637, 1446, 1304, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, major 3H), 2.54 (s, minor 3H), 3.88 (s, major 3H), 3.89 (s, minor 3H), 4.96 (s, major 2H, minor 2H), 7.12 (d, J=8.1 Hz, minor 1H), 7.16 (d, J=8.4 Hz, major 1H), 7.36 (s, minor 1H), 7.44–7.61 (m, major 5H, minor 3H), 7.71 (d, J=8.1 Hz, minor 1H), 7.93 (s, major 1H, minor 1H), 8.40 (d, J=7.5 Hz, major 1H, minor 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.60, 21.88, 38.75, 38.88, 52.62, 52.64, 108.87, 109.15, 119.41, 119.56, 124.18, 124.51, 129.29, 129.36, 129.61, 129.65, 130.23, 130.25, 130.44, 130.47, 130.76, 130.81, 131.63, 131.65, 132.17, 132.35, 132.40, 133.02, 133.07, 135.04, 141.85, 142.50, 142.55, 143.99, 151.38, 151.66, 165.66, 165.73; ESIMS m/z 305.22 (M^++1).

3.7.3. Compound ***7i′***

Yield 9% (*major*:*minor*=2:1); IR (film) 1712, 1651, 1458, 1435, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (s, major 3H), 2.55 (s, minor 3H), 3.75 (s, major 2H, minor 2H), 3.88 (s, major 3H, minor 3H), 7.20–7.51 (m, major 5H, minor 5H), 7.67 (s, major 1H), 7.76 (d, J=8.1 Hz, minor 1H), 8.09 (s, major 1H, minor 1H), 8.22 (dd, J=7.5 and 1.5 Hz, major 1H, minor 1H); ESIMS m/z 305.22 (M^++1).

3.8. Synthesis of compounds 6j and 7j

Compound **6j** was prepared according to the procedure of **6c** with KOH and the next Pd-mediated cyclization of **6j** was carried out at 100 °C for 30 min.

3.8.1. Compound ***6j***

Yield 64%; IR (film) 1720, 1597, 1485, 1458, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59 (s, 3H), 5.27 (d, J=1.2 Hz, 2H), 7.13–7.66 (m, 10H), 7.92 (s, 1H), 7.98 (ddd, J=7.8, 1.2, and 0.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.36, 52.12, 109.62, 118.95, 119.89, 122.99, 123.56, 125.45, 127.15, 129.96, 130.31, 130.54, 133.05, 134.81, 140.54, 141.31, 166.70. Anal. Calcd for $C_{23}H_{18}BrNO_2$: C, 65.73; H, 4.32; N, 3.33. Found: C, 65.66; H, 4.45; N, 3.17. Trace amount of *Z*-isomer (<10%) was observed in ^{1}H and ^{13}C NMR spectra.

3.8.2. Compound ***7j***

Yield 68%; white solid, mp 118–120 °C; IR (film) 1714, 1458, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 3H), 5.00 (d, J=14.1 Hz, 1H), 5.43 (d, J=14.1 Hz, 1H), 7.10 (dd, J=7.5 and 1.2 Hz, 1H), 7.19–7.28 (m, 3H), 7.39–7.55 (m, 4H), 7.66 (d, J=8.4 Hz, 1H), 8.05 (dd, J=7.5 and 1.2 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.52, 52.04, 109.82, 119.15, 119.74, 119.88 (2C), 122.62, 124.44, 125.71, 125.87, 27.04, 127.73, 130.17, 130.73, 131.40, 133.57, 135.58, 137.71, 139.97, 140.42, 145.17, 166.63. Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.21; H, 5.32; N, 4.04.

3.9. Synthesis of compounds 6k, 7k, and 7k′

Compound **6k** was prepared according to the procedure of **6a** with K_2CO_3 and the next Pd-mediated cyclization of **6k** was carried out at 120 °C for 60 min under the influence of $Pd(OAc)_2$/CuI/Cs_2CO_3.

3.9.1. Compound ***6k***

Yield 52%; white solid, mp 180–182 °C; IR (film) 3275, 1712, 1620, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 4.86 (s, 2H), 5.10 (s, 2H), 6.15 (br s, NH), 7.20–7.39 (m, 7H), 7.49 (dd, J=7.8 and 1.2 Hz, 1H), 7.63 (dd, J=7.8 and 1.2 Hz, 1H), 7.72 (s, 1H), 8.03 (s, 1H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.12, 44.70, 52.61, 119.38, 123.63, 127.42, 127.52, 127.69, 127.86, 128.61, 130.12, 130.62, 132.87, 134.46, 138.50, 139.81, 144.25, 149.31, 153.01, 154.56, 166.42. Anal. Calcd for $C_{23}H_{20}BrN_5O_2$: C, 57.75; H, 4.21; N, 14.64. Found: C, 57.49; H, 4.34; N, 14.92.

3.9.2. Compound ***7k***

Yield 23%; white solid, mp 214–216 °C; IR (film) 3259, 1714, 1616, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 3H), 4.91 (s, 2H), 5.14 (s, 2H), 6.10 (br s, NH), 7.28–7.41 (m, 5H), 7.50–7.58 (m, 3H), 7.96 (s, 1H), 8.25–8.28 (m, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.60, 44.78, 52.77, 120.73, 127.44, 127.77, 128.61, 129.28, 129.59, 130.08, 130.13, 130.28, 132.01, 132.38, 138.44, 142.55, 149.02, 153.13, 154.58, 165.42 (one carbon is overlapped). Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.36; H, 4.99; N, 17.27.

3.9.3. Compound ***7k′***

Yield 6%; white solid, mp 78–80 °C; IR (film) 3257, 1716, 1618, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 2H), 3.86 (s, 3H), 4.93 (s, 2H), 6.21 (br s, NH), 7.28–7.61 (m, 8H), 8.08 (d, J=7.5 Hz, 1H), 8.32 (s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.96, 44.79, 52.43, 119.03, 122.04, 127.60, 127.65, 127.88, 128.65, 128.76, 128.82, 130.03, 130.31, 131.63, 138.21, 138.73, 149.08, 153.58, 154.55, 165.72 (one carbon is overlapped). Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.88; H, 4.75; N, 17.46.

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