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SYNTHESIS OF 3-AROYLINDOLES AS INTERMEDIATES OF CANNABIMIMETICS AND ELUCIDATION OF THEIR PHYSICOCHEMICAL PROPERTIES

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Abstract – In order to synthesize the intermediates of cannabimimetics, the benzoylation of indoles with 2'/3'/4'-substituted benzoyl chloride in the presence of Et_2AlCl was examined. Among the products, we found that the ^1H NMR spectra of 3-(2'-substituted)-benzoyl-2-methylindoles had interesting features. We investigated their physicochemical properties based on VT-NMR, and it was revealed that conformer **A** (s-*trans*) is present in preference to conformer **B** in these compounds.

Since the biological functions of the endocannabinoid system consisting of two cannabinoid receptors (CB_1 and CB_2 receptors) was elucidated,[1] drugs binding to cannabinoid receptors have been expected to find a huge market for the treatment of a variety of conditions such as diabetes, metabolic disorders, and neuroinflammatory diseases.[2] Among numerous synthetic ligands for the CB receptors, indole-containing compounds have been recognized as popular scaffolds.[3] In particular, *N*-alkyl-3-aroylindoles show exceptionally strong affinity for CB receptors.[4] We are interested in these derivatives including their variously substituted isomers from the viewpoint of pharmacological activity. Therefore, we attempted to synthesize their useful intermediates, the 3-benzoylindole derivatives. Here we describe the syntheses of 3-(2'/3'/4'-substituted)-benzoylindoles and the corresponding 2-methylindoles (Figure 1). Additionally, we discuss the physicochemical properties of 3-(2'-substituted)-benzoyl-2-methylindoles.

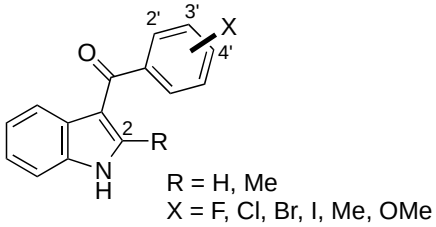
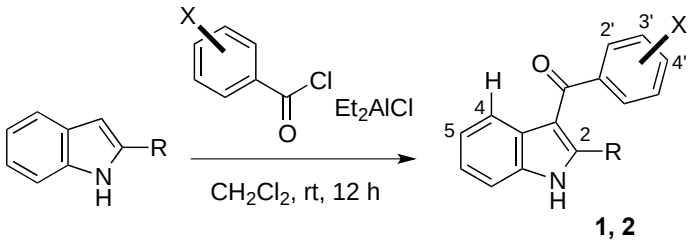


Figure 1. 3-(2'/3'/4'-Substituted)-benzoylindoles

Table 1. Benzoylation of indoles with 2'/3'/4'-substituted benzoyl chloride



1: R = H, **2**: R = Me
X = F, Cl, Br, I, Me, OMe

Entry		R	X	Yield (%)	Entry		R	X	Yield (%)
1	**1a**	H	2'-F	81	14	**2a**	Me	2'-F	78
2	**1b**[10]	H	2'-Cl	68	15	**2b**	Me	2'-Cl	76
3	**1c**[11]	H	2'-Br	80	16	**2c**	Me	2'-Br	76
4	**1d**[12]	H	2'-I	73	17	**2d**	Me	2'-I	79
5	**1e**	H	2'-Me	63	18	**2e**	Me	2'-Me	82
6	**1f**[13]	H	3'-F	83	19	**2f**	Me	3'-F	95
7	**1g**[12]	H	3'-Cl	71	20	**2g**	Me	3'-Cl	93
8	**1h**[14]	H	3'-Br	91	21	**2h**	Me	3'-Br	94
9	**1i**	H	3'-I	85	22	**2i**	Me	3'-I	36
10	**1j**[14]	H	3'-Me	78	23	**2j**	Me	3'-Me	85
11	**1k**[14]	H	4'-F	65	24	**2k**	Me	4'-F	68
12	**1l**[10]	H	4'-I	68	25	**2l**	Me	4'-I	34
13	**1m**[10]	H	4'-Me	60	26	**2m**	Me	4'-Me	91

Because the 3-position of indole is suitable for electrophilic substitution, there are many methods for direct 3-acylation. The acylations of indole salts prepared using the alkylzinc[5] or Grignard reagent,[6] Vilsmeier-Haack acylations,[7] and Friedel-Crafts acylations[8] are commonly used. After examining those procedures, we found that benzoylation in the presence of Et_2AlCl, as reported by Okauchi *et al.*,[9] was the most applicable to benzoyl chloride bearing various substitutions. Following the reported procedure, the benzoylation of indoles proceeded efficiently when 1.5 equivalents of 2'/3'/4'-substituted benzoyl chlorides are used in the presence of a 1.5 equivalent of Et_2AlCl. Thus, the variously substituted 3-benzoylindoles (**1**[10-14], **2**) were synthesized in moderate to high yields (Table 1).

In the course of these synthetic studies, we found that the ^{1}H NMR spectra (in DMSO-d_6, +23 °C) of 3-(2'-substituted)-benzoyl-2-methylindoles (**2b**, **2c**, **2d**) had common features. In these spectra, only the 4-H proton peak was strangely broad, which prompted us to conduct a conformational study using VT-NMR (–80 °C to +23 °C in acetone-d_6). As a clear example, the spectrum of 3-(2'-iodo)-benzoyl-2-methylindole **2d** is shown in Figure 2.

As the temperature decreased, the 4-H proton peak in **2d** broadened and was observed as two divided broad peaks (2 : 1) at –80 °C.[15] The major downfield-shifted peak observed at around 8.5 ppm and the minor upfield-shifted peak at around 6.1 ppm were consistent with the two conformers **A** (s-*trans*) and **B** (s-*cis*), which are caused by the rotations of the C–(C=O) axis of the ketone moiety (Figure 3). Based on our previous investigations of the conformation of the *o*-substituted benzoyl moiety,[16] the benzene ring should be nearly orthogonal to the carbonyl group due to the bulky *o*-substitution. In conformer **B**, that benzene ring caused a shielding effect of the 4-H proton in indole, shifting it upfield to 6.1 ppm. On the contrary, the downfield shift of 4-H (8.5 ppm) suggested the deshielding effect of the carbonyl group in conformer **A**.

In connection with this, we found that the 2-methyl peak in **2d** became broader gradually and divided into two broad peaks (2 : 1) at –80 °C. The major upfield-shifted peak observed at around 1.9 ppm and the minor downfield-shifted peak at around 2.8 ppm corresponded to the shielded 2-methyl peak in conformer **A** and the deshielded one in conformer **B**, respectively. We assumed that the carbonyl group rotated to a co-planar relationship with the indole ring as a result of the stereoelectronic interaction with either the 4-H proton or 2-methyl group (anisotropy effect). These features were observed in the spectra of compounds **2b** and **2c** (see Supporting Information). Considering these results, we assumed that compounds **2b**, **2c**, and **2d** should exist preferentially in conformer **A**, and the averaged conformations of **A** and **B** were observed at +23 °C. The existence of conformers **A** and **B** in 3-aroylindoles caused by the rotation of the carbonyl group was proposed by Bell and co-workers in 1991.[17] Our results using VT-NMR therefore provide validation for their proposal.

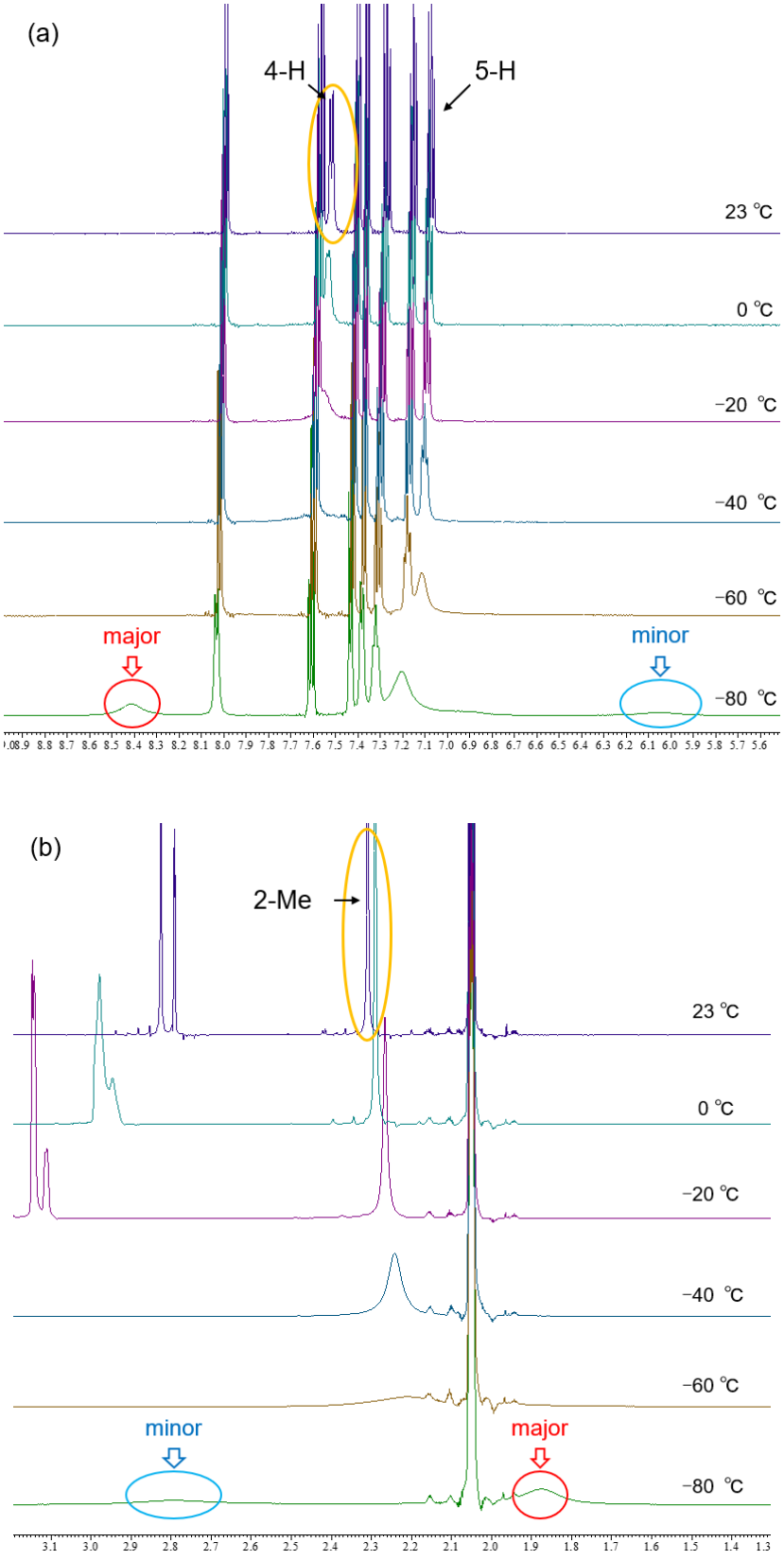


Figure 2. VT-NMR spectrum of **2d** (–80 °C to +23 °C in acetone-d_6). (a) Change in 4-H; (b) Change in 2-Me.

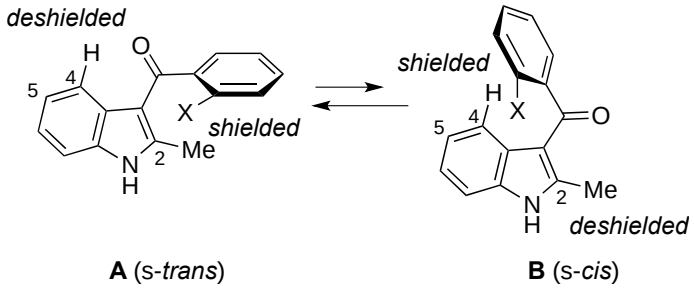


Figure 3. Anisotropy effect caused by the carbonyl group

In summary, a variety of 3-aroylindoles as the intermediates of the cannabimimetics were synthesized efficiently. Using Et_2AlCl, benzoylation of indoles with 2'/3'/4'-substituted benzoyl chloride proved feasible. We also investigated the physicochemical properties of 3-(2'-substituted)-benzoyl-2-methylindoles (**2b**, **2c**, **2d**) based on VT-NMR, and it was apparent that conformer **A** (s-*trans*) is present in preference to conformer **B** (s-*cis*).

EXPERIMENTAL

General remarks

Materials were obtained from commercial suppliers. NMR spectra were recorded on a spectrometer at 400 MHz or 600 MHz for ^{1}H-NMR, and 100 MHz or 150 MHz for ^{13}C-NMR. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard, and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). IR spectra were recorded on a FT-IR spectrometer equipped with ATR (Diamond). The high-resolution mass spectra (HRMS) were obtained with an ionization mode of ESI. Melting points were recorded on a melting point apparatus and are uncorrected. Optical rotations were determined with a digital polarimeter. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel plates. Column chromatography was performed using silica gel (45–60 μm). Extracted solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4. Solvents were evaporated under reduced pressure.

General experimental procedure for the syntheses of compounds 1 and 2

To a CH_2Cl_2 solution (85.0 mL) of indole (1.00 g, 8.53 mmol) was added 14.7 mL (12.8 mmol) of Et_2AlCl (0.87 mol/L in hexane) at 0 °C. The mixture was stirred at 0 °C for 30 min. To this solution, 3-iodobenzoyl chloride (3.41 g, 12.8 mmol) was added dropwise at 0 °C. The resulting solution was stirred at room temperature for 12 h, and the reaction was quenched with sat. aq. NH_4Cl. After the usual work-up, the crude product was purified by silica gel column chromatography to give **1i** in 85% yield

(2.53 g, 7.28 mmol) as crystals.

3-(2-Fluorobenzoyl)-1*H*-indole (1a)

Pink solid (yield 81%) mp 194–199 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.20 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.79 (s, 1H), 7.60–7.56 (m, 2H), 7.52 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.37–7.33 (m, 2H), 7.29–7.24 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.2, 158.7 (d, *J* = 245.6 Hz), 136.9, 131.9 (d, *J* = 8.6 Hz), 129.7, 129.2, 129.1, 125.5, 124.5, 123.4, 122.3, 121.2, 116.3 (d, *J* = 17.3 Hz), 116.1, 112.5; IR (ATR) 1609 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{11}NOF$ 240.0819; Found 240.0802.

3-(2-Methylbenzoyl)-1*H*-indole (1e)

Orange solid (yield 63%) mp 195–197 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.40–7.37 (m, 2H), 7.33–7.23 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.1, 141.0, 136.9, 136.3, 134.8, 130.6, 129.1, 127.2, 125.7, 125.3, 123.2, 122.0, 121.3, 116.6, 112.4, 19.2; IR (ATR) 1601 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1043.

3-(3-Iodobenzoyl)-1*H*-indole (1i)

White solid (yield 85%) mp 225–226 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.23 (dd, *J* = 1.2, 7.2 Hz, 1H), 8.04 (dd, *J* = 1.2, 1.2 Hz, 1H), 7.96 (ddd, *J* = 1.2, 1.2, 7.8 Hz, 1H), 7.95 (s, 1H), 7.79 (ddd, *J* = 1.2, 1.2, 7.8 Hz, 1H), 7.53 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.35 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.29–7.23 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 188.3, 142.5, 139.5, 136.8, 136.5, 136.2, 130.6, 127.8, 126.1, 123.3, 122.1, 121.4, 114.7, 112.3, 94.9; IR (ART) 1593 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{11}NOI$ 347.9880; Found 347.9882.

3-(2-Fluorobenzoyl)-2-methyl-1*H*-indole (2a)

White solid (yield 78%) mp 214–220 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.61–7.57 (m, 1H), 7.45 (ddd, *J* = 1.2, 7.2, 7.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.36–7.35 (m, 2H), 7.34 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.14 (ddd, *J* = 1.2, 7.8, 8.4 Hz, 1H), 7.04 (ddd, *J* = 1.2, 7.8, 8.4 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.8, 158.3 (d, *J* = 244.1 Hz), 146.0, 135.0, 131.8 (d, *J* = 8.6 Hz) 130.9 (d, *J* = 17.3 Hz), 128.8 (d, *J* = 2.9 Hz), 126.9, 124.9 (d, *J* = 2.9 Hz), 122.3, 121.6, 119.7, 116.1 (d, *J* = 21.6 Hz), 113.1, 111.4, 13.9; IR (ATR) 1609 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOF$ 254.0976; Found 254.0973.

3-(2-Chlorobenzoyl)-2-methyl-1*H*-indole (2b)

White solid (yield 76%) mp 203–206 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.59 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.53 (ddd, *J* = 1.8, 7.8, 7.8 Hz, 1H), 7.48 (ddd, *J* = 1.2, 7.8, 7.8 Hz, 1H), 7.40 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.38 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.34 (br d, *J* = 7.8 Hz, 1H), 7.14 (ddd, *J* =1.2, 7.8, 7.8 Hz, 1H), 7.04 (ddd, *J* = 1.2, 7.8, 7.8 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 188.6, 146.3, 142.0, 135.0, 130.6, 129.7, 129.0, 127.8, 127.8, 126.9, 122.3, 121.7, 119.9, 112.5, 111.4, 13.9; IR (ATR) 1568 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOCl$ 270.0680; Found 270.0679.

^{1}H NMR (600 MHz, acetone-d_6 at 23 °C) δ 11.28 (s, 1H), 7.55–7.48 (m, 4H), 7.40 (dd, *J* = 1.8, 7.2 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.14 (ddd, *J* =1.2, 7.8, 7.8 Hz, 1H), 7.06 (ddd, *J* = 1.2, 7.8, 7.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6 at 23 °C) δ 189.7, 146.5, 146.3, 143.6, 136.2, 131.2, 130.6, 128.9, 128.4, 123.3, 122.6, 121.4, 114.2, 111.9, 111.9, 14.3.

3-(2-Bromobenzoyl)-2-methyl-1*H*-indole (2c)

White solid (yield 76%) mp 219–221 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.45 (ddd, *J* = 1.8, 8.4, 8.4 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.35 (br, 1H), 7.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.5, 146.3, 144.0, 135.0, 132.8, 130.7, 128.2, 127.8, 127.0, 122.3, 121.7, 120.0, 118.0, 112.1, 111.4, 14.0; IR (ATR) 1567 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOBr$ 314.0175; Found 314.0176.

^{1}H NMR (600 MHz, acetone-d_6 at 23 °C) δ 10.99 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.54 (m, 2H), 7.45 (ddd, *J* = 1.2, 8.4, 8.4 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H) 7.40 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.07 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6 at 23 °C) δ 189.6, 145.7, 144.8, 135.4, 133.0, 130.5, 128.1, 128.0, 127.6, 122.4, 121.8, 120.7, 118.4, 113.1, 111.1, 13.5.

3-(2-Iodobenzoyl)-2-methyl-1*H*-indole (2d)

Pale pink solid (yield 79%) mp 210–212 °C: ^{1}H NMR (600 MHz, DMSO-d_6 at 23 °C) δ 12.08 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.34 (br d, *J* = 7.2 Hz, 1H), 7.31 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.25 (ddd, *J* = 1.8, 7.2, 7.8 Hz, 1H), 7.14 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.04 (dd, *J* = 7.2, 7.8 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6 at 23 °C); δ 191.5, 147.8, 146.2, 139.0, 135.0, 130.5, 128.7, 127.1, 127.0, 122.3, 121.7, 120.1, 111.7, 111.4, 92.5, 14.1; IR (ATR) 1567 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOI$ 362.0036; Found 362.0038.

^{1}H NMR (600 MHz, acetone-d_6 at 23 °C) δ 10.99 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.8, 7.8

Hz, 1H), 7.52 (br d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.27 (ddd, *J* = 1.8, 7.8, 7.8 Hz, 1H), 7.15 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.07 (dd, *J* = 7.2, 8.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6 at 23 °C); δ 192.4, 149.4, 146.4, 140.3, 136.2, 131.2, 129.5, 128.5, 128.2, 123.2, 122.6, 121.6, 113.3, 111.9, 92.4, 14.4.

^{1}H NMR (600 MHz, acetone-d_6 at –80 °C) δ 11.69 (br, 0.33H), 11.51 (br, 0.66H), 8.42 (br, 0.66H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.33 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.21 (br, 2H), 5.98 (br, 0.33H), 2.81 (br, 1H), 1.88 (br, 2H); ^{13}C NMR (150 MHz, acetone-d_6 at –80 °C); δ 192.3, 148.8, 139.7, 135.5, 131.1, 129.5, 127.3, 123.4, 122.7, 122.0 (m), 111.8, 92.5, 14.8 (m).

3-(2-Methylbenzoyl)-2-methyl-1*H*-indole (2e)

Pale pink solid (yield 82%) mp 222–225 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.39 (ddd, *J* = 1.2, 7.8, 7,8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.11 (dd, *J* = 6.6, 8.4 Hz, 1H), 7.00 (dd, *J* = 6.6, 8.4 Hz, 1H), 2.25 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.9, 145.6, 143.0, 135.0, 133.6, 130.4, 129.0, 127.1, 126.1, 125.9, 122.1, 121.4, 120.0, 113.0, 111.3, 18.7, 14.0; IR (ATR) 1568 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1226; Found 250.1225.

3-(3-Fluorobenzoyl)-2-methyl-1*H*-indole (2f)

Pale orange solid (yield 95%) mp 187–191 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.58–7.54 (m, 1H), 7.45–7.42 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.13 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.04 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.0, 162.0 (d, *J* = 244.1 Hz), 145.1, 144.0 (d, *J* = 57.0 Hz), 135.0, 130.6 (d, *J* = 7.2 Hz), 127.1, 124.1, 122.0, 121.2, 119.9, 117.7 (d, *J* = 21.6 Hz), 114.5 (d, *J* = 21.6 Hz), 112.1, 111.4, 14.3; IR (ATR) 1568 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{11}NOF$ 252.0830; Found 252.0821.

3-(3-Chlorobenzoyl)-2-methyl-1*H*-indole (2g)

Pale yellow solid (yield 93%) mp 230–231 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.66 (ddd, *J* = 1.8, 1.8, 6.6 Hz, 1H), 7.60 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.56–7.52 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 6.6, 7.8 Hz, 1H), 7.04 (dd, *J* = 6.6, 7.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.9, 145.1, 143.6, 135.0, 133.2, 130.7, 130.5, 127.6, 127.1, 126.7, 122.0, 121.2, 119.9, 112.1, 111.4, 14.3; IR (ATR) 1593 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{11}NOCl$ 268.0535; Found 268.0535.

3-(3-Bromobenzoyl)-2-methyl-1*H*-indole (2h)

Pink solid (yield 94%) mp 243–244 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.79 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.73 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.59 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 6.6, 8.4 Hz, 1H), 7.04 (dd, *J* = 6.6, 8.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.8, 145.1, 143.8, 135.0, 133.6, 130.7, 130.5, 127.1, 127.0, 122.0, 121.7, 121.2, 119.9, 112.0, 111.4, 14.3; IR (ATR) 1564 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOBr$ 314.0175; Found 314.0165.

3-(3-Iodobenzoyl)-2-methyl-1*H*-indole (2i)

Pale pink solid (yield 36%) mp 259–260 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.90 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.04 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.8, 145.0, 143.6, 139.5, 136.3, 135.0, 130.6, 127.3, 127.1, 122.0, 121.2, 119.9, 112.0, 111.4, 94.7, 14.3; IR (ATR) 1563 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{11}NOI$ 359.9891; Found 359.9880.

3-(3-Methylbenzoyl)-2-methyl-1*H*-indole (2j)

Pink solid (yield 85%) mp 190–194 °C: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 11.92 (s, 1H), 7.42 (br s, 1H), 7.40–7.37 (m, 4H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.37 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.8, 144.3, 141.7, 137.6, 134.9, 131.6, 128.4, 128.2, 127.3, 125.2, 121.8, 120.9, 120.0, 112.5, 111.2, 20.9, 14.2; IR (ATR) 1582 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1226; Found 250.1224.

3-(4-Fluorobenzoyl)-2-methyl-1*H*-indole (2k)

Pale yellow solid (yield 68%) mp 204–205 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.97 (s, 1H), 7.71–7.64 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.34–7.32 (m, 3H), 7.12 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.03 (dd, *J* = 8.4, 8.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.2, 163.8 (d, *J* = 247.1 Hz), 144.4, 138.0, 135.0, 130.9 (d, *J* = 8.7 Hz), 130.9 (d, *J* = 8.7 Hz), 127.2, 121.9, 121.0, 119.9, 115.3 (d, *J* = 21.5 Hz), 115.3 (d, *J* = 21.5 Hz), 112.3, 111.3, 14.2; IR (ATR) 1597 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOF$ 254.0976; Found 254.0969.

3-(4-Iodobenzoyl)-2-methyl-1*H*-indole (2l)

Yellow solid (yield 34%) mp 164–167 °C: ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.89 (d, *J* =

8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.03 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.7, 144.7, 140.9, 137.3, 137.3, 135.0, 130.1, 130.1, 127.1, 121.9, 121.1, 119.9, 112.2, 111.3, 98.6, 14.3; IR (ATR) 1598 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}NOI$ 362.0036; Found 362.0024.

3-(4-Methylbenzoyl)-2-methyl-1*H*-indole (2m)

Pale pink solid (yield 91%) mp 215–216 °C: ^{1}H NMR (600 MHz, DMSO-d_6) 11.91 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.00 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.40 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.4, 144.0, 141.1, 138.8, 134.9, 128.9, 128.9, 128.4, 128.4, 127.3, 121.7, 120.8, 120.0, 112.6, 111.2, 21.1, 14.2; IR (ATR) 1593 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}NO$ 250.1226; Found 250.1212.

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