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Supporting Information

A Fluorescent Target-Guided Paal-Knorr Reaction

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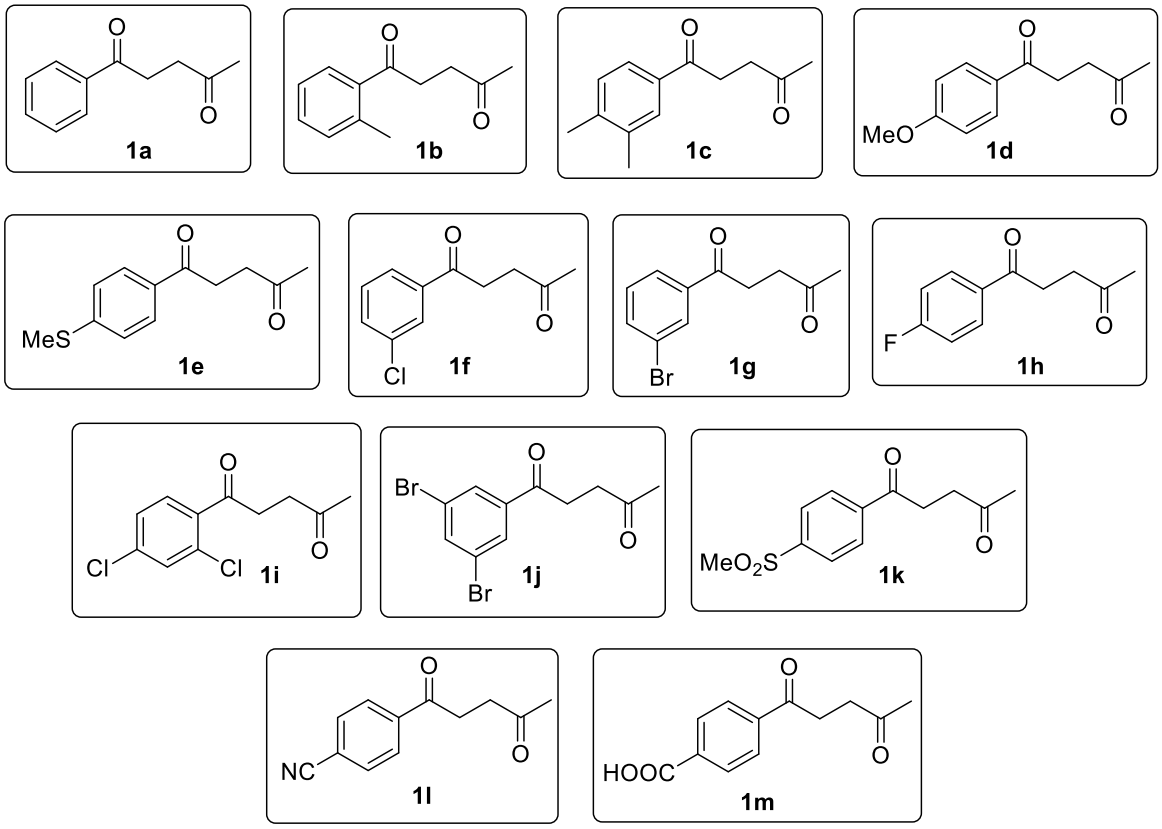
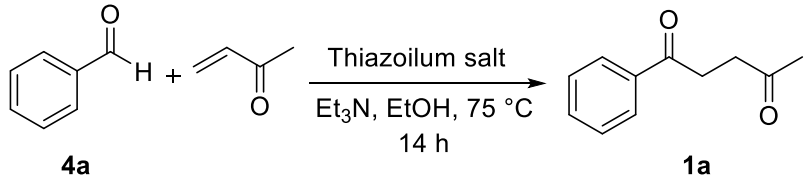
A. General Experimental Methods: Reagents were purchased from Fisher Scientific or Sigma-Aldrich unless stated otherwise. Unless otherwise noted proteins and media were obtained from Sigma-Aldrich. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories. Unless otherwise noted, all commercially available reagents were purchased and used without further purification. Dichloromethane (CH_2Cl_2) was refluxed in the presence of CaH_2 and distilled prior to use. EtOH was distilled under normal pressure and stored in the presence of molecular sieves. All chemical reactions were conducted in glass flask or vials under N_2 atmosphere with magnetic stirring. The reaction progress was monitored by TLC. Enzymatic reactions were conducted on black flat bottomed 200 µL 96 welled plates (675076, Greiner BioOne) or in 2 mL Eppendorf tubes.^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 400 or Bruker Advance 500 NMR spectrometers. Capillary NMR data were acquired on Bruker Advance III 600 equipped with a 1.7 mm cryoprobe. Chemical shifts (ppm) were referenced using the corresponding solvent signals (δ_H 7.26 and δ_C 77.2 for $CDCl_3$, δ_H 3.31 and δ_C 49.0 for CD_3OD). Coupling constants (*J*) are reported in Hertz (Hz) and coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet). The NMR spectra were processed using Mestrenova (Mnova 11.0 Mestrelab Research). Electrospray (ESI) mass spectrometric analyses were performed using a ThermoFinnigan LCQ Deca spectrometer, and high-resolution analyses were conducted using a ThermoFinnigan MAT900XL mass spectrometer with electron impact (EI) ionization. A Thermo Scientific LTQ Orbitrap XL mass spectrometer was used for high-resolution electrospray ionization mass spectrometry analysis (HR-ESI-TOF MS positive ion mode).

B. Synthesis of 1,4-diketones 1a-m: The following section provides the experimental methods for the synthesis of 1,4-diketones described within this manuscript.



Structures of diketones **1a**-**m** prepared and used within this study.

Common route: The following 1,4-diketones **1a-m** were synthesized using similar synthetic procedure from corresponding aromatic aldehydes. Characterization data of **1a-b**, **1d-i**, and **1k-l** were matching with those reported in the literature.[S1-S4]



To a solution of benzaldehyde **4a** (100 mg, 0.94 mmol) in EtOH (2.5 mL) at rt, methyl vinyl ketone (78 µL, 0.94 mmol), Et_3N (252 µL, 1.88 mmol) and thiazolium salt or 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (47 mg, 0.18 mmol) were added. The reaction mixture was then stirred at 75 °C. After complete consumption of **4a** by TLC analysis (14 h), reaction mixture was allowed to cool to rt and concentrated on a rotary evaporator. The resulting residue treated with 2 N HCl (4 mL), extracted with CH_2Cl_2 (15 mL). The organic layer washed with $NaHCO_3$ (15 mL) and water (15 mL), dried with $MgSO_4$ and evaporated under reduced pressure. Pure adduct **1a** (110 mg, 66%) was obtained by flash chromatography, eluting with a gradient of hexanes to 15:85 EtOAc/hexanes.

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1-phenylpentane-1,4-dione (1a): Colorless oil (110 mg, 0.62 mmol, 66% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09–7.80 (m, 2H), 7.59–7.52 (m, 1H), 7.49–7.41 (m, 2H), 3.27 (d, *J* = 6.3 Hz, 2H), 2.88 (d, *J* = 6.3 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.4, 198.6, 136.8, 133.3, 128.7, 128.7, 128.2, 128.2, 37.2, 32.5, 30.2; HR-ESI-MS *m/z* calcd. for $C_{11}H_{13}O_2^+$ $[M+H]^+$: 177.0910, found 177.0912. Characterization data of **1a** matched that reported in the literature.[S1]

1-(*o*-tolyl)pentane-1,4-dione (1b): Colorless oil (214 mg, 1.13 mmol, 79% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28–7.21 (m, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.47 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.3, 202.6, 138.2, 137.9, 132.0, 131.4, 128.6, 125.8, 37.5, 35.3, 30.1, 21.3; HR-ESI-MS *m/z* calcd. for $C_{12}H_{15}O_2^+$ $[M+H]^+$: 191.1067, found 191.1069. Characterization data of **1b** matched that reported in the literature.[S1]

1-(3,4-dimethylphenyl)pentane-1,4-dione (1c): Colorless solid (210 mg, 1.03 mmol, 72% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, *J* = 2.1 Hz, 1H), 7.69 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 3.22 (d, *J* = 6.3 Hz, 2H), 2.84 (t, *J* = 6.4 Hz, 2H), 2.28 (s, 6H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.4, 198.4, 142.6, 136.9, 134.7, 129.8, 129.2, 125.8, 37.2, 32.4, 30.1, 20.0, 19.8; HR-ESI-MS *m/z* calcd. for $C_{13}H_{17}O_2^+$ $[M+H]^+$: 205.1223, found 205.1225.

1-(4-methoxyphenyl)pentane-1,4-dione (1d): Colorless oil (125 mg, 0.60 mmol, 44% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 3.86 (s, 3H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.6, 197.2, 163.7, 130.5, 130.5, 129.9, 113.9, 113.9, 55.6, 37.3, 32.2, 30.3; HR-ESI-MS *m/z* calcd. for $C_{12}H_{15}O_3^+$ $[M+H]^+$: 207.1016, found 207.1017. Characterization data of **1d** matched that reported in the literature.[S1]

1-(4-(methylthio)phenyl)pentane-1,4-dione (1e): Yellow solid (147 mg, 0.66 mmol, 77% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 1H), 3.18 (t, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 6.2 Hz, 2H), 2.47 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.3, 197.4, 145.9, 133.0, 128.4, 128.4, 125.0, 125.0, 37.1, 32.2, 30.1, 14.8; HR-ESI-MS *m/z* calcd. for $C_{12}H_{15}O_2S^+$ $[M+H]^+$: 223.0787, found 223.0789. Characterization data of **1e** matched that reported in the literature.[S2]

1-(3-chlorophenyl)pentane-1,4-dione (1f): Yellow glass (220 mg, 1.04 mmol, 73% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95–7.92 (m, 1H), 7.84 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.52 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.42–7.37 (m, 1H), 3.22 (d, *J* = 6.3 Hz, 2H), 2.88 (d, *J* = 6.3 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.0, 197.4, 138.4, 135.1, 133.2, 130.1, 128.3, 126.3, 37.1, 32.6, 30.1; HR-ESI-MS *m/z* calcd. for $C_{11}H_{12}ClO_2^+$ $[M+H]^+$: 211.0520, found 211.0521. Characterization data of **1f** matched that reported in the literature.[S1]

1-(3-bromophenyl)pentane-1,4-dione (1g): Yellow glass (288 mg, 1.13 mmol, 79% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (t, *J* = 1.9 Hz, 1H), 7.89 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 7.68 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 3.22 (t, *J* = 6.3 Hz, 2H), 2.89 (d, *J* = 6.3 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.1, 197.3, 138.6, 136.1, 131.3, 130.3, 126.7, 123.1, 37.1, 32.6, 30.1; HR-ESI-MS *m/z* calcd. for $C_{11}H_{12}BrO_2^+$ $[M+H]^+$: 255.0015, found 255.0013. Characterization data of **1g** matched that reported in the literature.[S4]

1-(4-fluorophenyl)pentane-1,4-dione (1h): Off white solid (233 mg, 1.20 mmol, 42% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.88 (t, *J* = 6.3 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.3, 197.1, 165.9 (d, *J* = 254.7 Hz), 133.3 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.2 Hz), 130.8 (d, *J* = 9.2 Hz), 115.8 (d, *J* = 21.8 Hz), 115.8 (d, *J* = 21.8 Hz), 37.2, 32.4, 30.2; HR-ESI-MS *m/z* calcd. for $C_{11}H_{12}FO_2^+$

$[M+H]^+$: 195.0816, found 195.0820. Characterization data of **1h** matched that reported in the literature.[S1]

1-(2,4-dichlorophenyl)pentane-1,4-dione (1i): Colorless oil (252 mg, 1.03 mmol, 71% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.13 (d, *J* = 6.2 Hz, 2H), 2.87 (d, *J* = 6.2 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.7, 200.3, 137.4, 137.3, 132.1, 130.6, 130.5, 127.4, 37.6, 36.6, 29.9; HR-ESI-MS *m/z* calcd. for $C_{11}H_{11}Cl_2O_2^+$ $[M+H]^+$: 245.0131, found 245.0134. Characterization data of **1i** matched that reported in the literature.[S3]

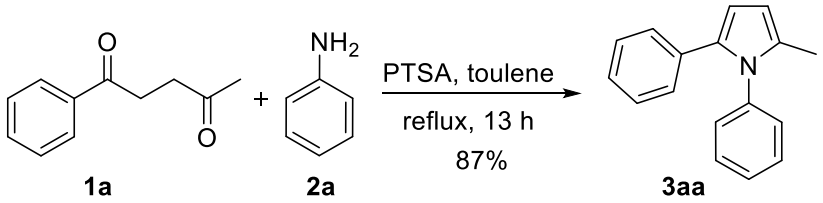
1-(3,5-dibromophenyl)pentane-1,4-dione (1j): Colorless solid (312 mg, 0.93 mmol, 65% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, *J* = 1.8 Hz, 2H), 7.83 (t, *J* = 1.8 Hz, 1H), 3.17 (t, *J* = 6.2 Hz, 2H), 2.88 (d, *J* = 6.2 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.7, 196.0, 139.6, 139.6, 138.4, 130.0, 130.0, 123.6, 37.1, 32.6, 30.0; HR-ESI-MS *m/z* calcd. for $C_{11}H_{12}Br_2O_2^+$ $[M+H]^+$: 334.9100, found 334.9095.

1-(4-(methylsulfonyl)phenyl)pentane-1,4-dione (1k): Colorless solid (132 mg, 0.52 mmol, 61% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17–8.13 (m, 2H), 8.07–8.03 (m, 2H), 3.27 (d, *J* = 6.3 Hz, 2H), 3.08 (s, 3H), 2.93 (d, *J* = 6.3 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.9, 197.6, 144.4, 140.8, 129.1, 129.1, 127.9, 127.9, 44.5, 37.2, 32.9, 30.1; HR-ESI-MS *m/z* calcd. for $C_{12}H_{15}O_4S^+$ $[M+H]^+$: 255.0686, found 255.0689. Characterization data of **1k** matched that reported in the literature.[S2]

4-(4-oxopentanoyl)benzonitrile (1l): Colorless solid (185 mg, 0.92 mmol, 64% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 3.32–3.13 (m, 2H), 2.94–2.75 (m, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.7, 197.3, 139.7, 132.5, 132.5 , 128.5, 128.5, 117.9, 116.4, 37.0, 32.6, 29.9; HR-ESI-MS *m/z* calcd. for $C_{12}H_{12}NO_2^+$ $[M+H]^+$: 202.0863, found 202.0862. Characterization data of **1l** matched that reported in the literature.[S1]

4-(4-oxopentanoyl)benzoic acid (1m): Colorless solid (148 mg, 0.67 mmol, 49% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 2H), 3.30 (t, *J* = 6.3 Hz, 2H), 2.93 (d, *J* = 6.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.2, 198.2, 170.0, 140.7, 133.1, 130.6, 130.6, 128.2, 128.2, 37.2, 32.9, 30.2; HR-ESI-MS *m/z* calcd. for $C_{12}H_{13}O_4^+$ $[M+H]^+$: 221.0808, found 221.0807.

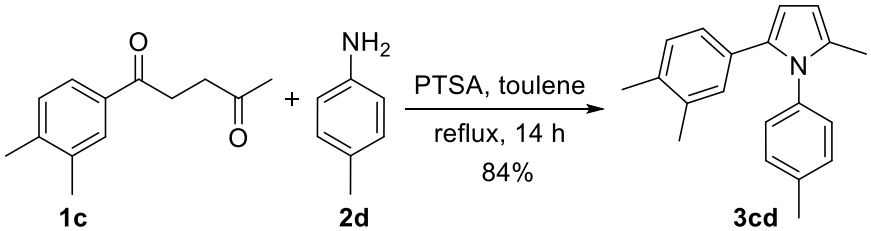
C. Chemical Paal-Knorr synthesis of pyrroles 3aa, 3cd, 3jd, 3je, and 3jf. The following methods were used to synthesize authentic samples of the pyrrole hits discovered in this program.



1a **2a** **3aa**

Aniline **2a** (8.7 mg, 0.094 mmol) and *p*-toulenesulfonic acid (3.2 mg, 0.017 mmol) were added to a solution of 1-phenylpentane-1,4-dione **1a** (15.0 mg, 0.085 mmol) in toluene (1.0 mL) at rt. After heating at reflux for 13 h, the mixture was cooled to rt and concentrated on a rotary evaporator. Pure adduct **3aa** (17.2 mg, 87%) was obtained by flash chromatography, eluting with a gradient of hexanes to 24:1 hexanes/EtOAc.

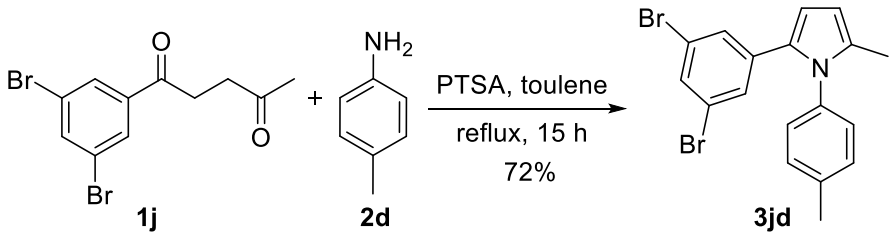
2-methyl-1,5-diphenyl-1*H*-pyrrole (3aa): Pale Yellow solid (17.2 mg, 0.074 mmol, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41–7.31 (m, 3H), 7.20–7.11 (m, 4H), 7.10–7.02 (m, 3H), 6.37 (d, *J* = 3.4 Hz, 1H), 6.10 (dd, *J* = 3.5, 0.9 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.6, 134.3, 133.7, 131.8, 129.1, 129.1, 128.6, 128.6, 128.1, 128.1, 127.9, 127.9, 127.5, 125.8, 108.8, 107.6, 13.5; HR-ESI-MS *m/z* calcd. for $C_{17}H_{16}N^+$ $[M+H]^+$: 234.1277, found 234.1276. Characterization data of **3aa** matched that reported in the literature.[S5]



1c **2d** **3cd**

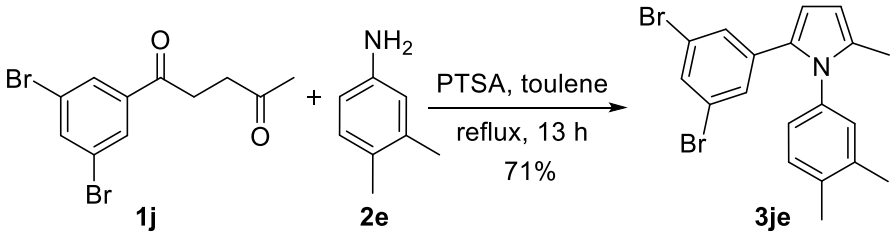
Aniline **2d** (14.4 mg, 0.134 mmol) and *p*-toulenesulfonic acid (4.6 mg, 0.024 mmol) were added to a solution of 1-phenylpentane-1,4-dione **1c** (25 mg, 0.122 mmol) in toluene (1.2 mL) at rt. After heating at reflux for 14 h, the mixture was cooled to rt and concentrated on a rotary evaporator. Pure adduct **3cd** (28 mg, 84%) was obtained by flash chromatography, eluting with a gradient of hexanes to 19:1 hexanes/EtOAc.

2-(3,4-dimethylphenyl)-5-methyl-1-(*p*-tolyl)-1*H*-pyrrole (3cd): Brown oil (28 mg, 0.101 mmol, 84%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21–7.14 (m, 2H), 7.12–7.03 (m, 2H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.74 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.33 (d, *J* = 3.3 Hz, 1H), 6.09 (dd, *J* = 3.3, 0.9 Hz, 1H), 2.40 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.16 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 1.9 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.68 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.18 (d, *J* = 3.4 Hz, 1H), 5.96 (dd, *J* = 3.4, 0.9 Hz, 1H), 2.34 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 2.05 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 137.2, 137.1, 136.1, 134.5, 134.0, 131.4, 131.4, 129.6, 129.6, 129.3, 129.3, 128.4, 128.4, 125.3, 108.0, 107.2, 21.2, 19.8, 19.4, 13.4; HR-ESI-MS m/z calcd. for $C_{20}H_{22}N^+$ $[M+H]^+$: 276.1747, found 276.1749.



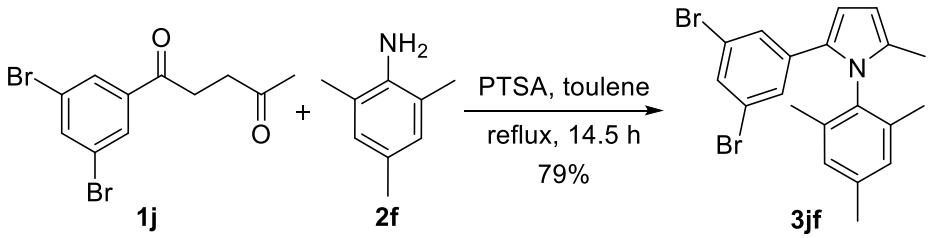
Aniline **2d** (5.3 mg, 0.049 mmol) and *p*-toulenesulfonic acid (1.7 mg, 0.009 mmol) were added to a solution of 1-phenylpentane-1,4-dione **1j** (15.0 mg, 0.045 mmol) in toluene (1.0 mL) at rt. After heating at reflux for 15 h, the mixture was cooled to rt and concentrated on a rotary evaporator. Pure adduct **3jd** (13.0 mg, 72%) was obtained by flash chromatography, eluting with a gradient of hexanes to 9:1 hexanes/EtOAc.

2-(3,5-dibromophenyl)-5-methyl-1-(*p*-tolyl)-1*H*-pyrrole (3jd): Yellow solid (13 mg, 0.032 mmol, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (t, *J* = 1.7 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.10 (dd, *J* = 1.8, 0.8 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 3.5 Hz, 1H), 6.08 (dd, *J* = 2.6, 0.9 Hz, 1H), 2.41 (s, 3H), 2.12 (s, 3H); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.34 (t, *J* = 1.8 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.12 (d, *J* = 1.8 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 3.6 Hz, 1H), 6.04 (dd, *J* = 3.6, 0.9 Hz, 1H), 2.41 (s, 3H), 2.07 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 138.1, 138.1, 137.1, 136.2, 133.5, 131.1, 130.7, 130.0, 130.0, 128.9, 128.9, 128.2, 128.2, 122.4, 110.3, 108.0, 21.3, 13.3; HR-ESI-MS *m/z* calcd. for $C_{18}H_{16}Br_2N^+$ $[M+H]^+$: 405.9624, found 405.9618.



Aniline **2e** (9.9 mg, 0.082 mmol) and *p*-toulenesulfonic acid (2.8 mg, 0.015 mmol) were added to a solution of 1-phenylpentane-1,4-dione **1a** (25.0 mg, 0.075 mmol) in toluene (1.2 mL) at rt. After heating at reflux for 13 h, the mixture was cooled to rt and concentrated on a rotary evaporator. Pure adduct **3je** (22.0 mg, 71%) was obtained by flash chromatography, eluting with a gradient of hexanes to 9:1 hexanes/EtOAc.

2-(3,5-dibromophenyl)-1-(3,4-dimethylphenyl)-5-methyl-1*H*-pyrrole (3je): Yellow glass (22 mg, 0.052 mmol, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, *J* = 1.7 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 1.7 Hz, 2H), 6.93–6.84 (m, 1H), 6.38 (d, *J* = 3.6 Hz, 1H), 6.06 (dd, *J* = 3.6, 0.9 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.33 (t, *J* = 1.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 1.8 Hz, 2H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.88 (dd, *J* = 7.8, 2.3 Hz, 1H), 6.39 (d, *J* = 3.6 Hz, 1H), 6.03 (dd, *J* = 3.6, 0.9 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.07 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 137.9, 137.9, 137.1, 136.8, 136.4, 133.6, 131.0, 130.6, 130.4, 129.3, 128.8, 128.8, 125.7, 122.4, 110.2, 107.8, 19.9, 19.6, 13.3; HR-ESI-MS *m/z* calcd. for $C_{19}H_{18}Br_2N^+$ $[M+H]^+$: 419.9781, found 419.9774.



Aniline **2f** (6.6 mg, 0.049 mmol) and *p*-toulenesulfonic acid (1.7 mg, 0.009 mmol) were added to a solution of 1-phenylpentane-1,4-dione **1a** (15.0 mg, 0.045 mmol) in toluene (1.0 mL) at rt. After heating at reflux for 17 h, the mixture was cooled to rt and concentrated on a rotary evaporator. Pure adduct **3jf** (15.5 mg, 79%) was obtained by flash chromatography, eluting with a gradient of hexanes to 9:1 hexanes/EtOAc.

2-(3,5-dibromophenyl)-1-mesityl-5-methyl-1*H*-pyrrole (3jf): Colorless solid (15.5 mg, 0.035 mmol, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, *J* = 1.8 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 2H), 6.96 (s, 2H), 6.50 (d, *J* = 3.7 Hz, 1H), 6.12 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.35 (s, 3H), 1.94 (s, 3H), 1.88 (s, 6H); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.33 (t, *J* = 1.8 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 2H), 7.03 (d, *J* = 1.2 Hz, 2H), 6.55 (d, *J* = 3.7 Hz, 1H), 6.13 (dd, *J* = 3.7, 0.9 Hz, 1H), 2.35 (s, 3H), 1.92 (s, 3H), 1.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 138.7, 138.7, 137.1, 137.1, 136.5, 134.6, 132.3, 130.5, 129.6, 129.3, 129.3, 127.2, 127.2, 122.7, 109.9, 108.1, 21.2, 17.6, 17.6, 12.4; HR-ESI-MS *m/z* calcd. for $C_{20}H_{20}Br_2N^+$ $[M+H]^+$: 433.9938, found 433.9930.

D. Fluorescent templated Paal-Knorr condensation screen: The following section provides the procedures used for the studies presented in Fig. 3 of the manuscript. Each screen repeated at least twice, and data from each reaction remained within 10% error. One run was selected and presented in Fig. 3.

Stock solutions: Stock solutions of each reagent and protein were prepared prior to running each screen. The following conditions were used to produce these solutions.

Substrates: Stock solutions of diketones and anilines were prepared by dissolving 2-6 mg of **1a**-**m** or **2a**-**m** in CH_3CN to deliver a 100 mM solution. These solutions were stored and diluted 1:10 in CH_3CN to generate 10 mM stock solutions used for each screen. All screening was conducted with the same solutions to minimize error associated with batch or lots differences.

COX-2: A 2.1 μM stock solution of human COX-2 was prepared by diluting 30 μL COX-2 solution (C0858, 1.5 mg/mL, 20.8 μM checked by SDS-PAGE provided by SIAL supplied in 80 mM Tris·•HCl, pH 8.0 with 0.1% TWEEN 20, 300 mM diethyldithiocarbamate and 10% glycerol) into 270 μL of PBS pH 7.2. The COX-2 stock was shipped on dry ice and warmed to 4 °C on an ice bath and used immediately once thawed. Efforts were made to complete this process within 5 min to maximize the activity of COX-2. This procedure delivered 300 μL of a 2.1 μM stock solution of COX-2. This solution was used as prepared, and any excess was discarded

COX-1: A 2.1 μM stock solution of human COX-1 was prepared by adding the 100 μg COX-2 (SRP0523-100UG) to PBS pH 7.2 buffer at 4 °C to afford a final volume of 680 μL. The COX-1 stock was shipped on dry ice and warmed to 4 °C on an ice bath and used immediately once it thawed. Efforts were made to complete this process in 5 min to maximize the activity of COX-1. This procedure delivered 680 μL of a 2.1 μM stock solution of COX-1. This solution was used as prepared, and any excess was discarded.

HSA: A 2.1 μM stock solution of Human Serum Albumin (HSA, SRP6182-1MG) was prepared by dilution a 100 μL sample 1 mg/mL stock of HSA in PBS pH 7.2 with 610 μL of PBS pH 7.2. Once prepared this solution was cooled to 4 °C prior to use. This procedure delivered 710 μL of a 2.1 μM stock solution of HSA. This solution was used as prepared, and any excess was discarded.

Procedure for reactions with COX-2: On ice, a 10 μL aliquot of a 2.1 μM stock of COX-2 was added to 180 μL PBS pH 7.2 pre-cooled to 4 °C in a black 200 μL 96-welled plate (675076, Greiner BioOne). Sequentially, 5 μL of the 10 mM diketone and 5 μL of the 10 mM aniline stock solutions in CH_3CN were added sequentially. Plates were shaken briefly and stored at 4 °C for 2 h, then allowed to warm to rt over 1 h and stored at rt for 12 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

Procedure for control reactions without COX-2: Control reactions were conducted at the same time as the reactions with COX-2 (prior paragraph). On ice, 190 μL PBS pH 7.2 was pre-cooled to 4 °C in a black 200 μL 96-welled plate (675076, Greiner BioOne). Sequentially, 5 μL of the 10 mM diketone stock solution in CH_3CN and 5 μL of the 10 mM aniline stock solutions in CH_3CN were added. Plates were shaken briefly and stored at 0 °C for 2 h, then allowed to warm to rt over 1 h and stored at rt for 12 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

Procedure for reactions with COX-1: On ice, a 10 μL aliquot of the 2.1 μM stock of COX-1 was added to 180 μL PBS pH 7.2 pre-cooled to 4 °C in a black 200 96-welled plate (675076, Greiner BioOne). Sequentially, 5 μL of the 10 mM diketone and 5 μL of the 10 mM aniline stock solutions in CH_3CN were added. Plates were shaken briefly and stored at 0 °C for 2 h, then

allowed to warm to rt over 1 h and stored at rt for 12 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

Procedure for reactions with HSA: On ice, a 10 µL aliquot of the 2.1 µM stock of HSA was added to 180 µL PBS pH 7.2 pre-cooled to 4 °C in a black 200 µL 96-welled plate (675076, Greiner BioOne). Sequentially, 5 µL of the 10 mM diketone and 5 µL of the 10 mM aniline stock solutions in CH_3CN were added. Plates were shaken briefly and stored at 0 °C for 2 h, then allowed to warm to rt over 1 h and stored at rt for 12 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

E. Fluorescent validation of Paal-Knorr condensations: Fluorescent spectra from the screens in Fig. 3 were compared against that from the Paal-Knorr products with and without COX-2 present. The following conditions were used for this study. This screen was conducted in triplicate with one of the runs presented in Fig. 4. Data from the repetition experiments was within 10% deviation for all reactions evaluated.

Stock solutions: The following stock solutions were prepared for these studies.

Products: Stock solutions of Paal-Knorr products were prepared by dissolving 2-6 mg of **3cd**, **3jd**, **3je**, or **3jf** in CH_3CN to deliver 5 mM parent stock solution. These solutions were stored and diluted 1:10 in CH_3CN to provide a 0.5 mM working stock. All screening was conducted with the same parent stock solutions to minimize error associated with batch or lots. This provided a 500 µL stock solution of **3cd**, **3jd**, **3je**, or **3jf** in CH_3CN.

COX-2: A 2.1 µM stock solution of human COX-2 was prepared by diluting 30 µL COX-2 solution (C0858, 1.5 mg/mL, 20.8 µM checked by SDS-PAGE supplied in 80 mM Tris•HCl, pH 8.0 with 0.1% TWEEN 20, 300 mM diethyldithiocarbamate and 10% glycerol) into 270 µL of PBS pH 7.2. The COX-2 stock was shipped on dry ice and warmed to 4 °C on an ice bath and used immediately once thawed. Efforts were made to complete this process within 5 min to maximize the activity of COX-2. This procedure delivered 300 µL of a 2.1 µM stock solution of COX-2. This solution was used as is prepared, and any excess was discarded.

Procedure for reactions with COX-2: Identical procedures were conducted as in Section D.

Procedure for control reactions without COX-2: Identical procedures were conducted as in Section D.

Fluorescence spectra from Paal-Knorr products with COX-2: A 20 µL aliquot of the 2.1 µM stock of COX-2 was added to a 170 µL PBS pH 7.2 at 23 °C in a black 200 96-welled plate (675076, Greiner BioOne). A 10 µL aliquot of the 500 µM Paal-Knorr product stock in CH_3CN was added. The plate was shaken briefly and stored at 23 °C for 4 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

Fluorescence spectra from Paal-Knorr products without COX-2: A 180 µL aliquot of PBS pH 7.2 was added to black 200 µL 96-welled plate (675076, Greiner BioOne). A 10 µL aliquot of the 500 µM Paal-Knorr product stock in CH_3CN was added. The plate was shaken briefly and stored at 23 °C for 4 h. Plates were read on a Varioskan LUX multimode microplate reader (Thermo Fischer Scientific) with λ_{ex} at 260 nM and collecting the emission spectrum with λ_{em} from 280-600 nm.

Data from these studies is presented in Fig. 4 of the manuscript.

F. NMR validation of COX-2 templated Paal-Knorr condensations: Reactivity was validated by use of capillary 1.7 mm NMR. The following section provides the procedures used for these studies. Each reaction was conducted twice and evaluated by NMR accordingly.

Stock solutions: The following stock solutions were prepared for these studies.

Substrates: Stock solutions of 10 mM diketone **1c**, 10 mM diketone **1j**, 50 mM 4-methylaniline (**2d**), 50 mM 3,4-dimethylaniline (**2e**) 50 mM 2,4,6-trimethylaniline (**2f**) were prepared in CH_3CN and stored at -20 °C until use (up to 3 months). Conversion calculations were based on the use of diketone **1c** or **1j**. To ensure complete reactivity, a 5-fold excess of aniline was added to each reaction. These stock solutions were prepared using the same methods in sections D-E (above).

COX-2: A 2.1 μM stock solution of human COX-2 was prepared by diluting 30 μL COX-2 solution (C0858, 1.5 mg/mL, 20.8 μM checked by SDS-PAGE supplied in 80 mM Tris • HCl, pH 8.0 with 0.1% TWEEN 20, 300 mM diethyldithiocarbamate and 10% glycerol) into 270 μL of PBS pH 7.2. The COX-2 stock was shipped on dry ice and warmed to 4 °C on an ice bath and used immediately once thawed. The solution was spin dialyzed on 3 kDa Amicon Ultra Centrifugal filters with 4 washes with 300 μL of ice-cold PBS pH 7.2 buffer. Centrifugation was conducted at 4 °C at 10000 g on a Biofuge 15 centrifuge (Heraeus). This buffer exchange was conducted to remove the TRIS, TWEEN, diethyldithiocarbamate and glycerol that would have complicated the NMR analyses. Efforts were made to complete this process in 1 h to maximize the activity of COX-2. This procedure delivered 300 μL of a 2.1 μM stock solution of COX-2.

Procedure for reactions with COX-2: On ice, a 100 μL aliquot of the 2.1 μM stock of COX-2 was added to 1800 μL PBS pH 7.2 pre-cooled to 4 °C. Sequentially, 50 μL of the 10 mM diketone and 50 μL of the 50 mM aniline stock solutions in CH_3CN were added. The tube was shaken briefly and stored at 0 °C for 2 h, then allowed to warm to rt over 1 h and stored at rt for 12 h. The contents of the tube were transferred to a glass vial (20 mL) equipped PTFE cap. The organic materials were extracted with EtOAc (2 × 5 mL), dried over Na_2SO_4, filtered and evaporated by airflow. The contents were transferred (to a ½ dram vial using three successive transfers with EtOAc (2 × 1 mL) and CH_2Cl_2 (1 mL) for capillary NMR analyses (solvent was dried by airflow after each transfer).

Procedure for control reactions without COX-2: Control reactions were conducted at the same time as the reactions with COX-2 (above paragraph). On ice, 1900 μL PBS pH 7.2 was pre-cooled to 4 °C. Sequentially, 50 μL of the 10 mM diketone stock solution in CH_3CN and 50 μL of the 50 mM aniline stock solutions in CH_3CN were added. A five-fold excess of the analine was added to further encourage the reaction. The tube was shaken briefly and stored at 4 °C for 2 h, it was then allowed to warm to rt over 1 h and stored at rt for 12 h. The contents of the tube were transferred to a glass vial (20 mL) equipped PTFE cap. The organic materials were extracted with EtOAc (2 × 5 mL), dried over Na_2SO_4, filtered and evaporated by airflow. The contents were transferred (to a ½ dram vial using three successive transfers with EtOAc (2 × 1 mL) and CH_2Cl_2 (1 mL) for capillary NMR analyses (solvent was dried by airflow after each transfer).

Procedure for celecoxib inhibition studies: As a means of control, we explored the inhibition of the COX-2-templated production of **3je**. Four concentrations of celecoxib (350 μM, 175 μM, 100 μM and 50 μM) were compared to reactions conducted without celecoxib (0 μM). On ice, a 100 μL aliquot of the 2.1 μM stock of COX-2 was added to 1750 μL PBS pH 7.2 pre-cooled to 4 °C. A 50 μL aliquot of celecoxib was added from a stock solution in CH_3CN (14 mM, 7 mM, 4 mM, 2.5 mM). An additional tube was run without celecoxib by the addition of 50 μL of CH_3CN. Next, 50 μL of the 10 mM diketone and 50 μL of the 50 mM aniline stock solutions in CH_3CN were added sequentially. The tube was shaken briefly and stored at 0 °C for 2 h, then allowed to

warm to rt over 1 h and stored at rt for 12 h. The contents of the tube were transferred to a glass vial (20 mL) equipped PTFE cap. The organic materials were extracted with EtOAc (2 × 5 mL), dried over Na_2SO_4, filtered and evaporated by airflow. The contents were transferred (to a ½ dram vial using three successive transfers with EtOAc (2 × 1 mL) and CH_2Cl_2 (1 mL) for capillary NMR analyses (solvent was dried by airflow after each transfer).

Capillary NMR analyses: Sample Jet NMR tubes (Bruker) were obtained in 96 format (1.7 mm OD, 103.5 mm length, 0.2 mm wall thickness, 60 µM camber). Prior to each spectrum the NMR tube was charged with 30 µL of CD_3OD and ^1H NMR spectrum was collected to ensure the tube and solvent were clean. Solvent controls and samples were loaded at 35 µL using a 100 µL removable needle syringe with a PTFE plunger (Hamilton 700 series). NMR tubes could be reused after washing 3 × 50 µL of CD_3OD and checking by NMR prior to use. Samples of reactions were dissolved in 100 µL of CD_3OD (minimum required for full solution of the sample) and 35 µL was added to the NMR tube. While one only needs 35 µL for spectral analyses accurate yields required 100 µL of solvent to properly dissolve the entire contents of each vial.

H. Additional references. Due to space limitations scope of referencing needed to be curtailed. We have included an expanded set of references within the manuscript as well as those used within this supporting information.

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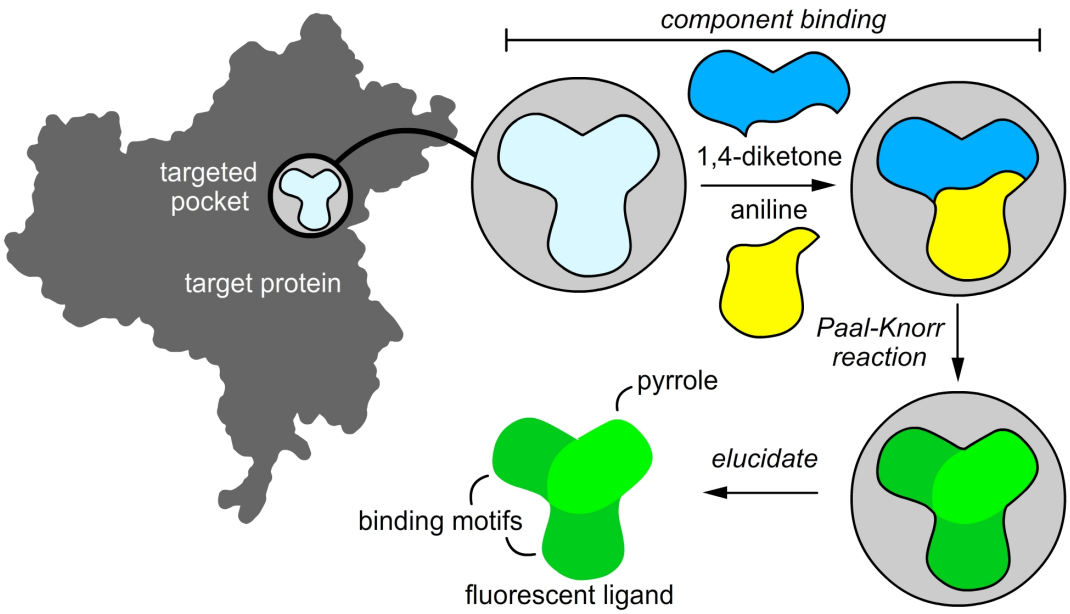
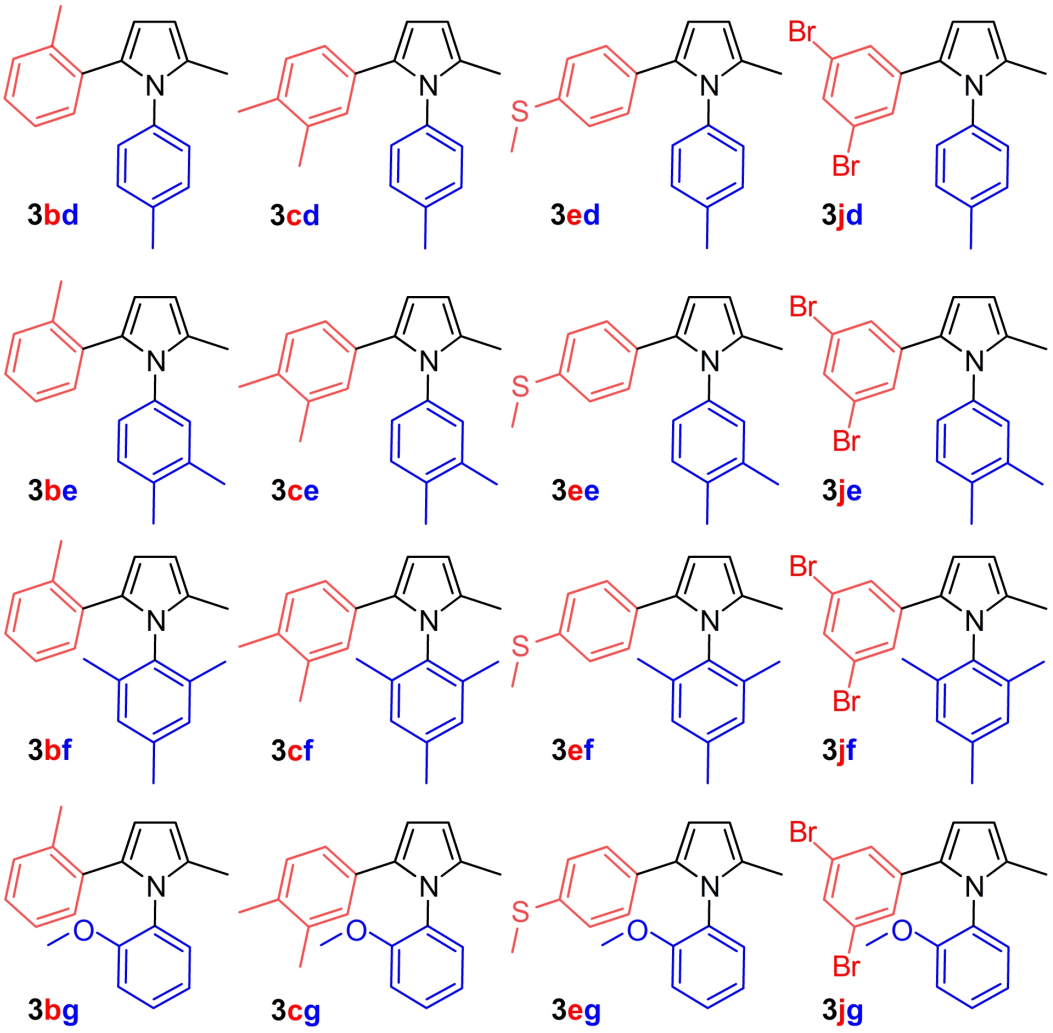
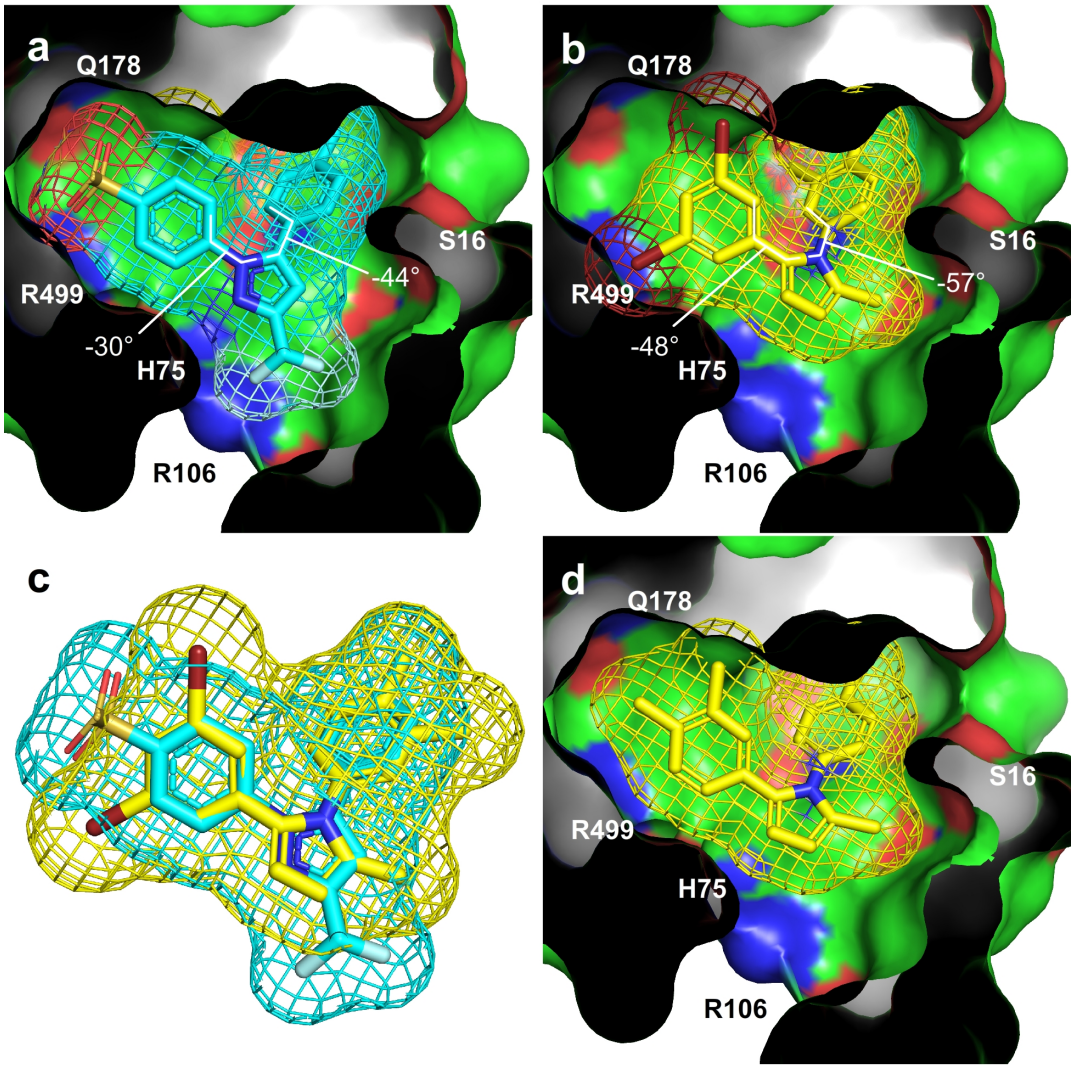


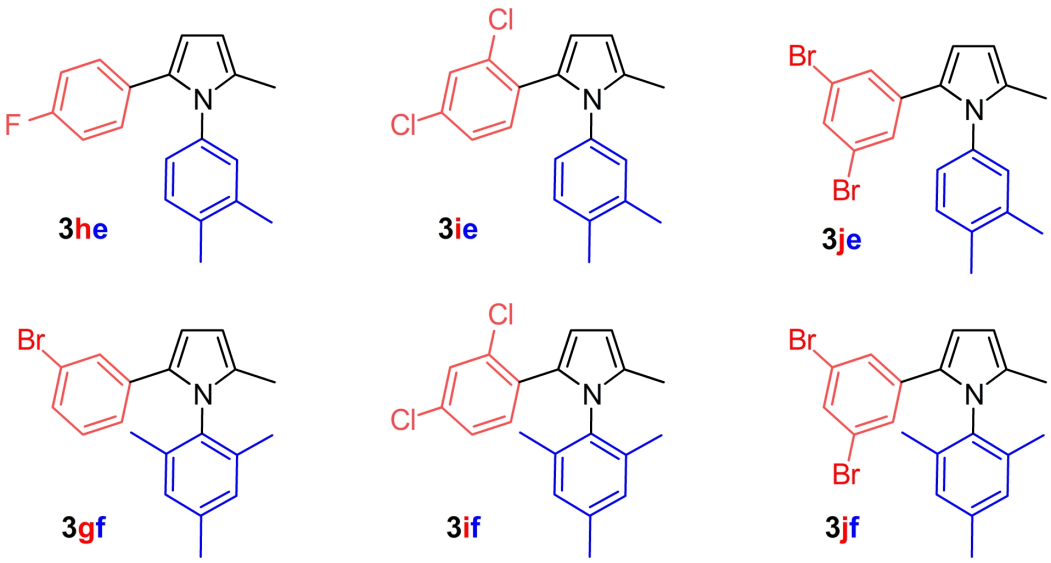
Supporting Fig. S1. Illustration of the Paal-Knorr target-guided synthesis strategy. The binding of an aniline (yellow) and 1,4-diketone (blue) within the active site of COX-2 enables an in situ Paal-Knorr reaction that delivers a pyrrole product whose structure can be tailored to be fluorescent by use of aryl-substituted diketones and aromatic amines, as illustrated by **1** and **2** in Fig. 1. A comparable scheme was rendered for the Table of Contents graphic.



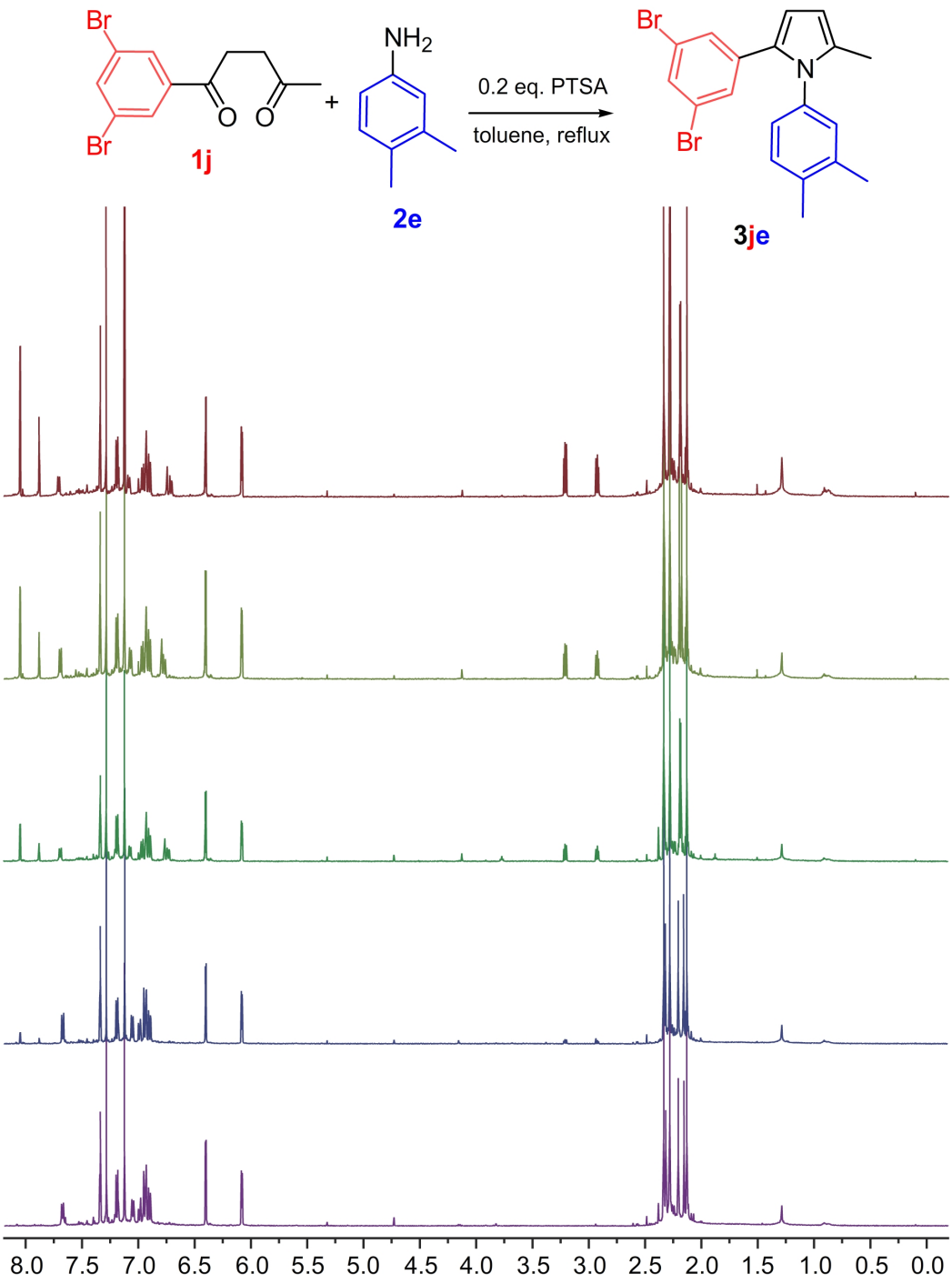
Supporting Fig. S2. Structures of the products from each well in Fig. 3.



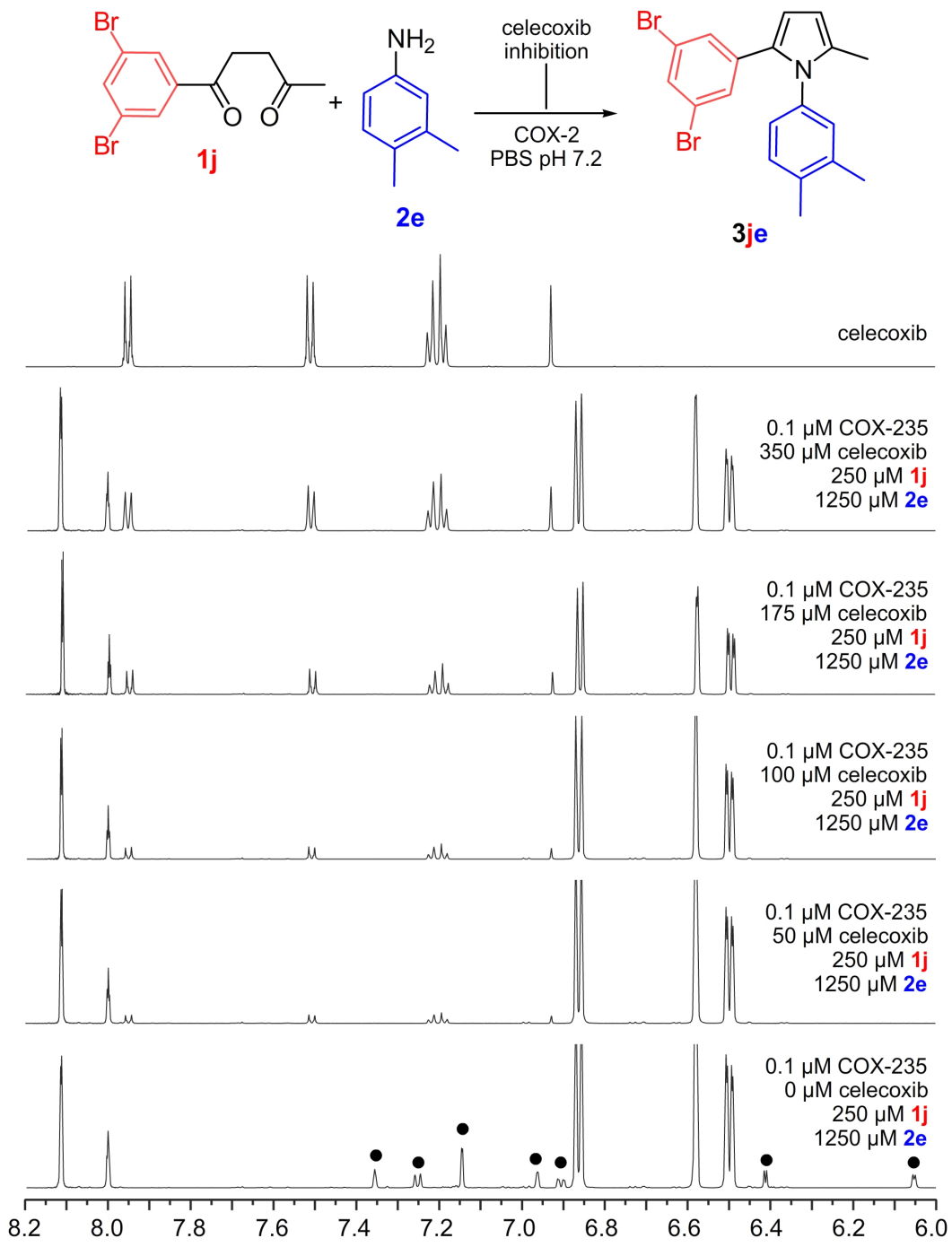
Supporting Fig. S3. An enlarged and expanded structural evaluation. **a)** X-ray crystal structure (PDB ID: 3LN1) depicting celecoxib (cyan) binding pocket in COX-2. **b)** Image depicting **3je** (yellow) docked within the celecoxib binding pocket of COX-2 shown in a). **c)** Overlay of **3je** (yellow) on the surface of celecoxib (cyan) demonstrates how the electron density of the sulfonamide group (orange) match that of the two bromines in **3je** (red). **d)** Image depicting **3cd** (yellow) docked within the celecoxib-binding pocket of COX-2. This figure supports that provided in Fig. 6.



Supporting Fig. S4. Structures of pyrroles **3** corresponding to the reactions that displayed the highest increase in fluorescence in presence of COX-2, as given by Δ > 20 in Fig. 3a.

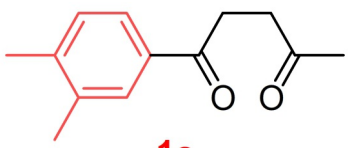


Supporting Fig. S5. NMR monitoring of the production of pyrrole **3je** from diketone **1j** and aniline **2e**. This reaction was conducted using the chemical methods shown in section C of the Supporting Information as given by 0.2 eq. of PTSA in refluxing toluene.

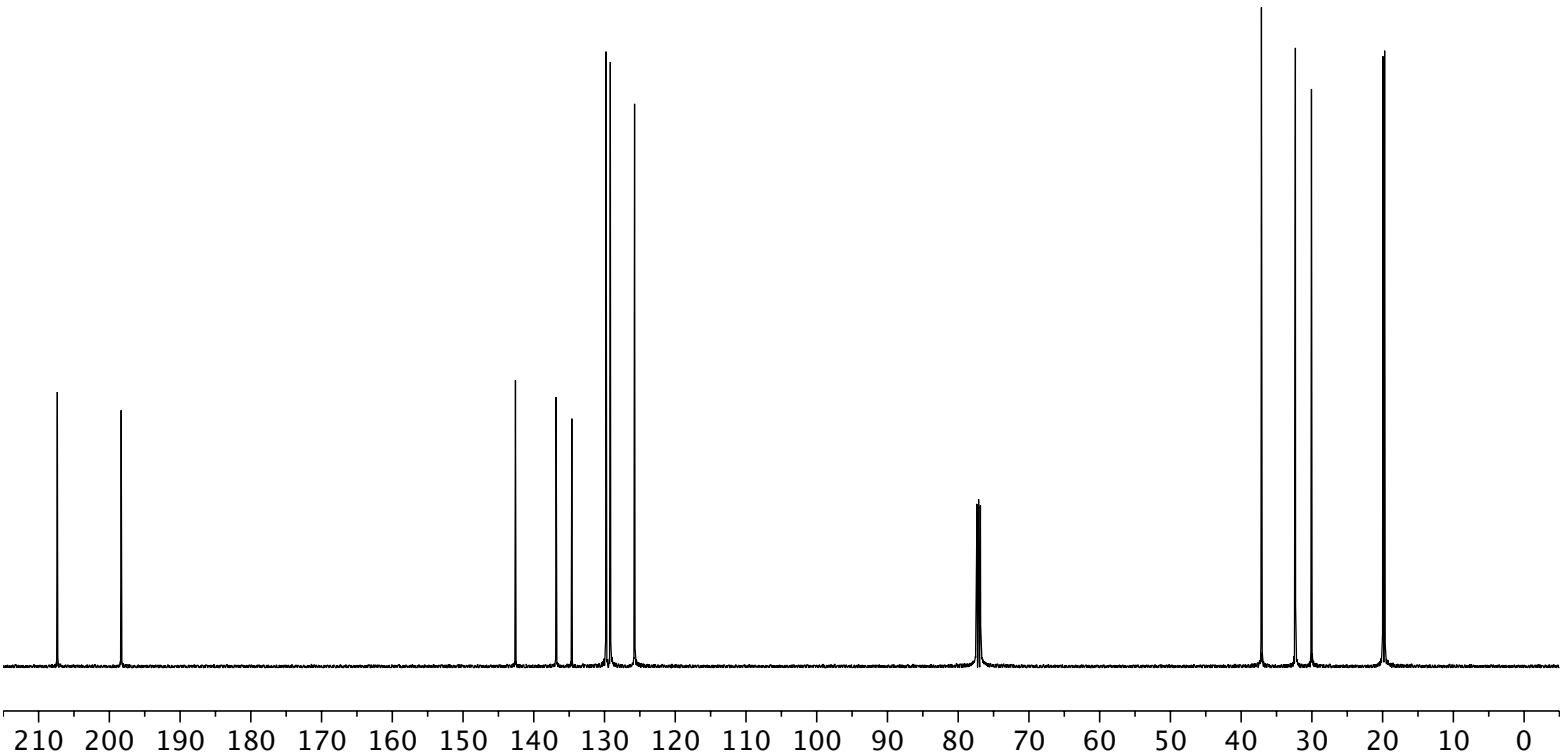


Supporting Fig. S6. NMR spectra collected from the inhibition of the COX-2 induced production of pyrrole **3je** by celecoxib. Four concentrations of celecoxib are shown and compared against the reaction without celecoxib. Peaks attributed to 3je are noted by a black dot.

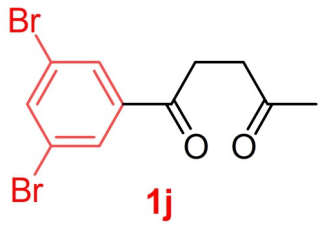
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of **1c** in $CDCl_3$

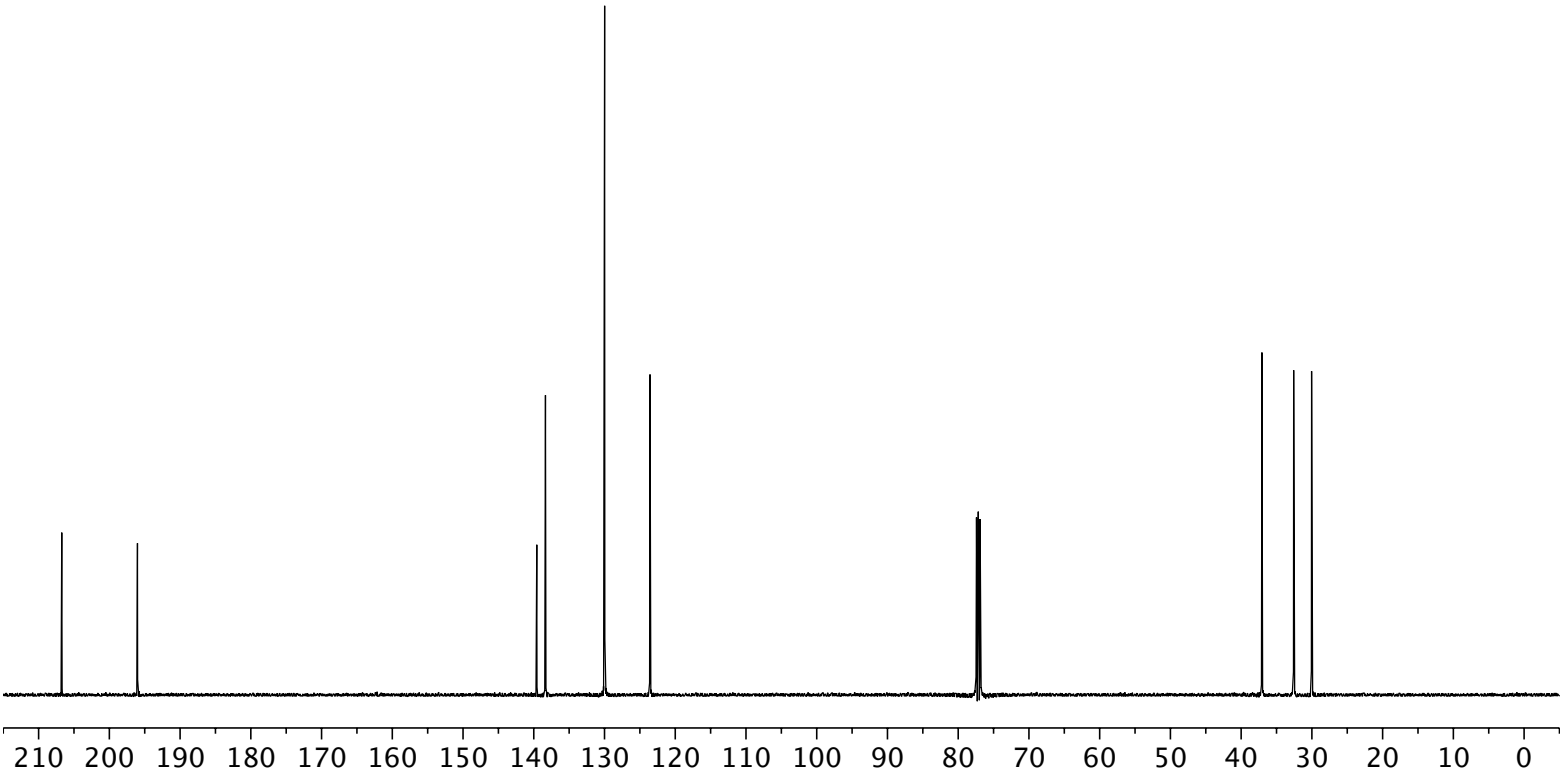


1c



^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of **1j** in $CDCl_3$





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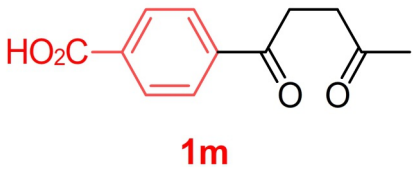
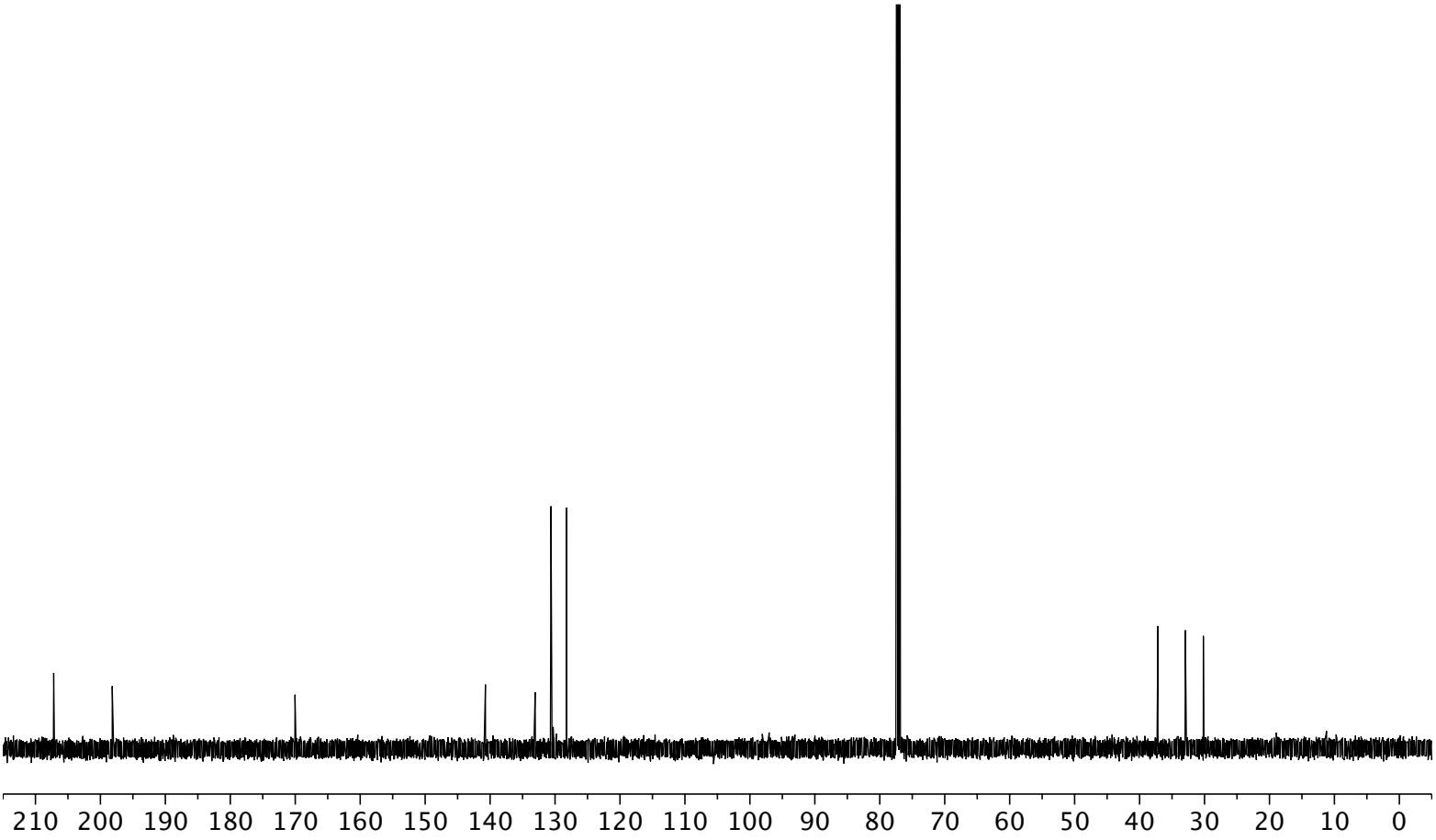
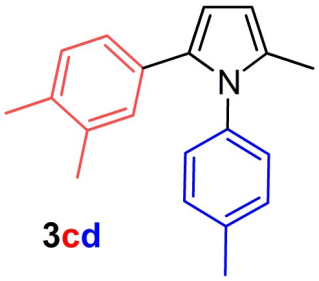


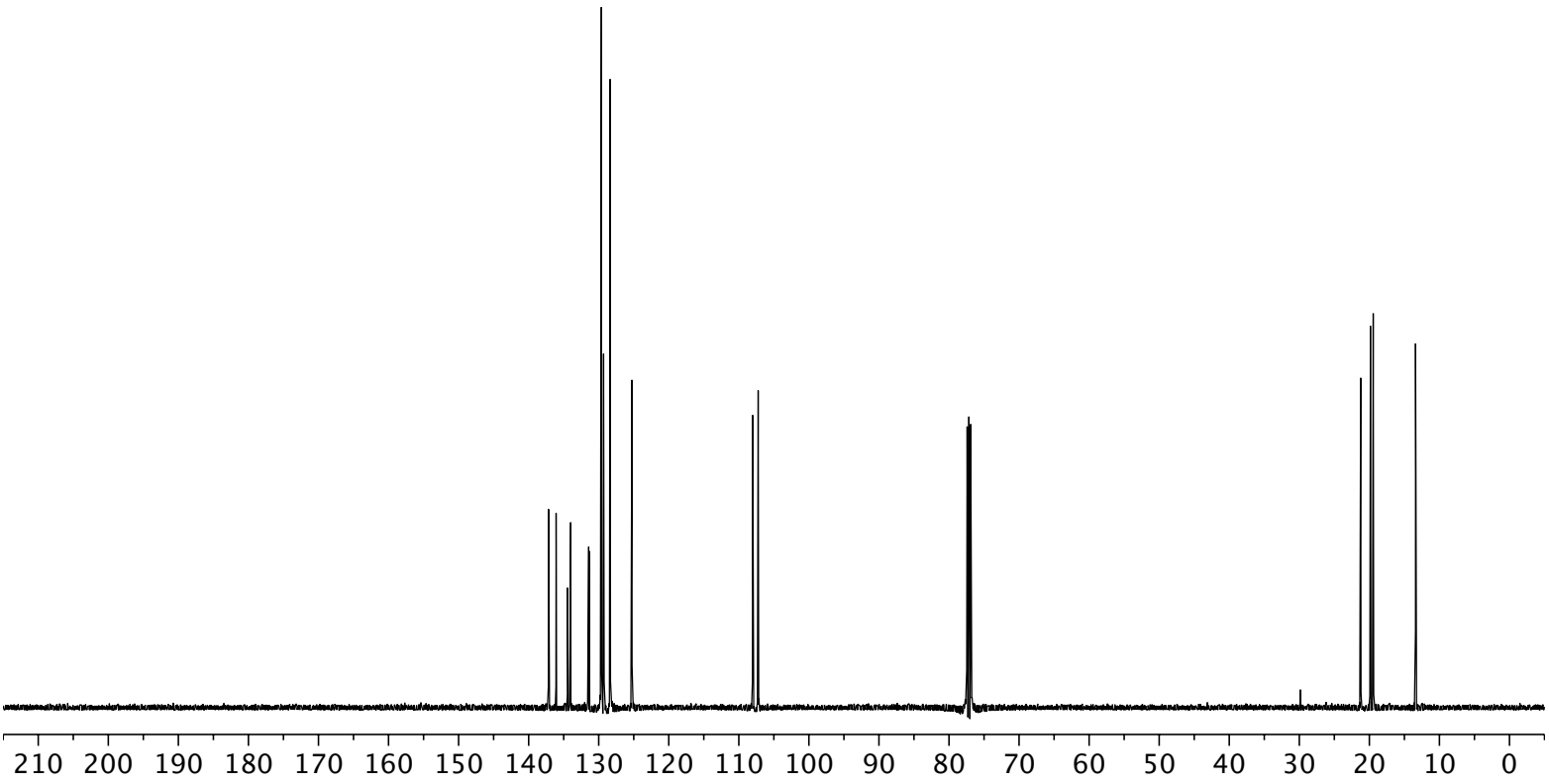
1m



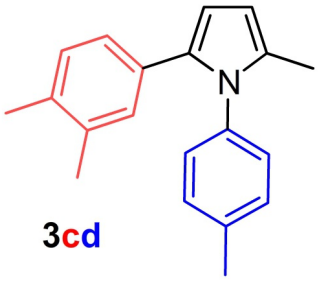
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of **3cd** in $CDCl_3$



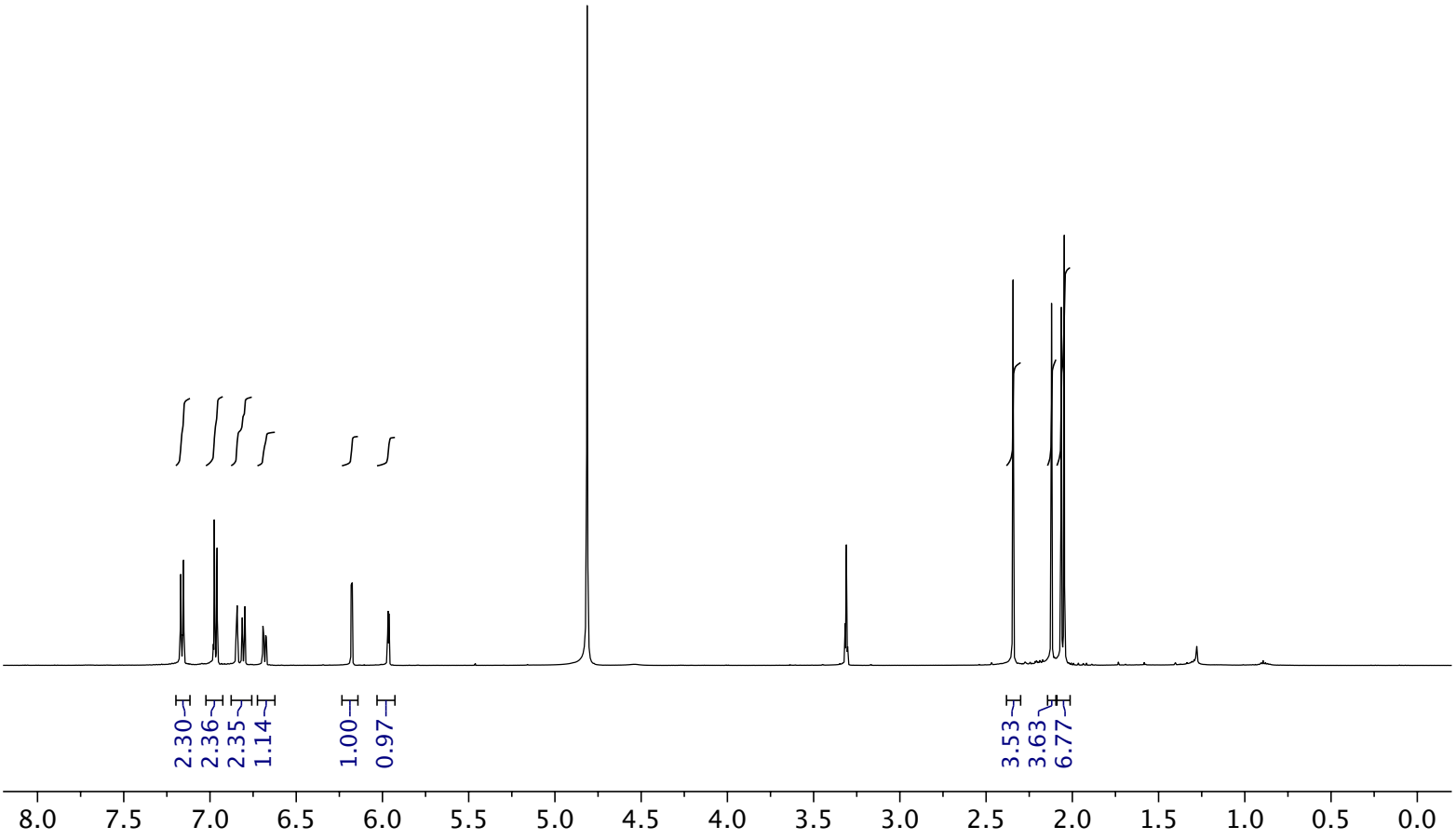
3cd



^{1}H NMR (500 MHz) spectra of **3cd** in $CDCl_3$ *versus* CD_3OD

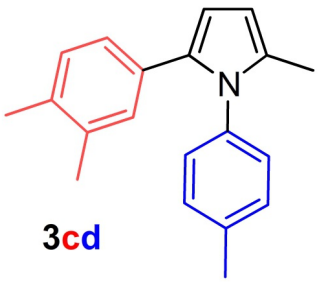


3cd



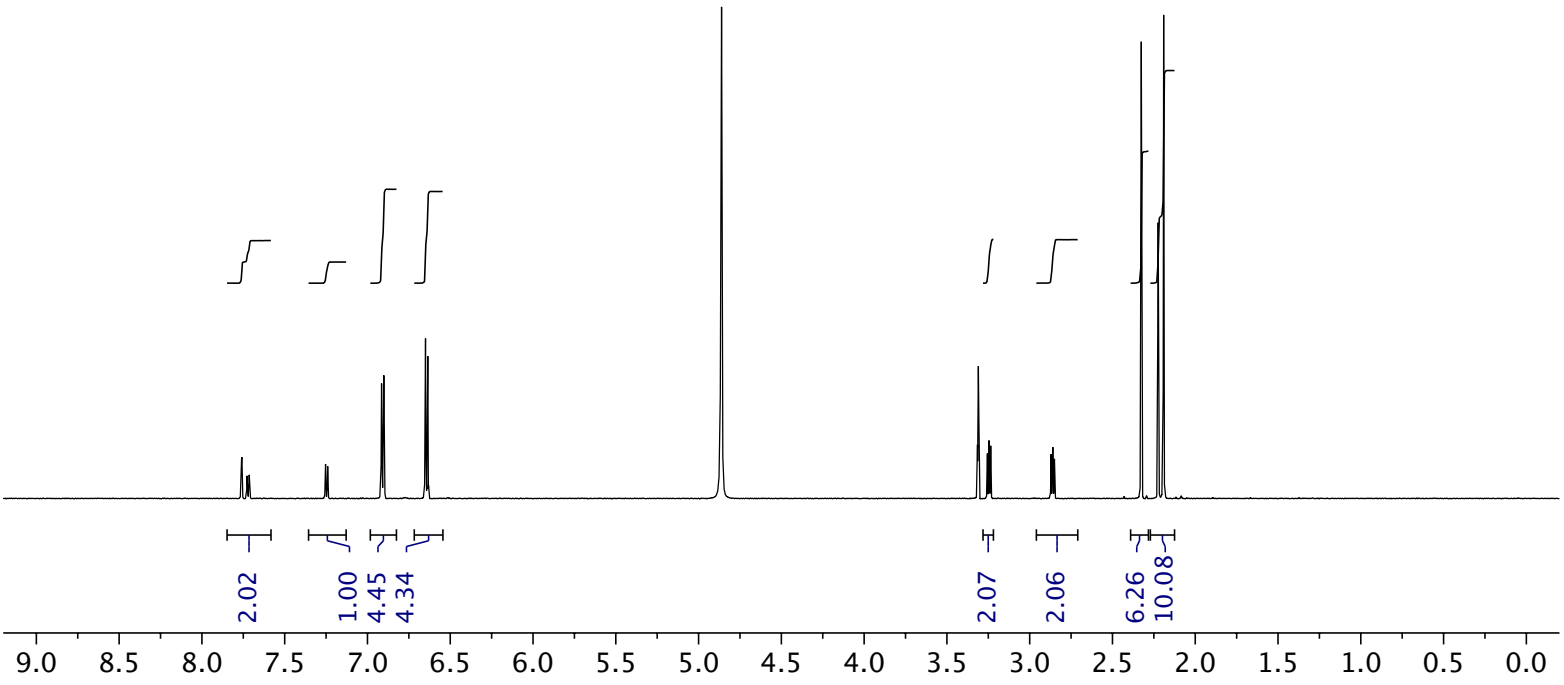
^{1}H NMR (500 MHz) of the production of **3cd** in CD_3OD

without COX-2



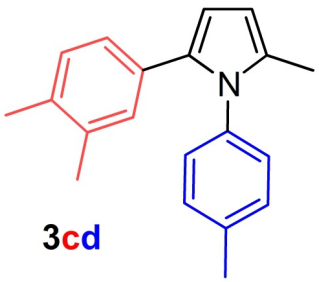
3cd

with COX-2



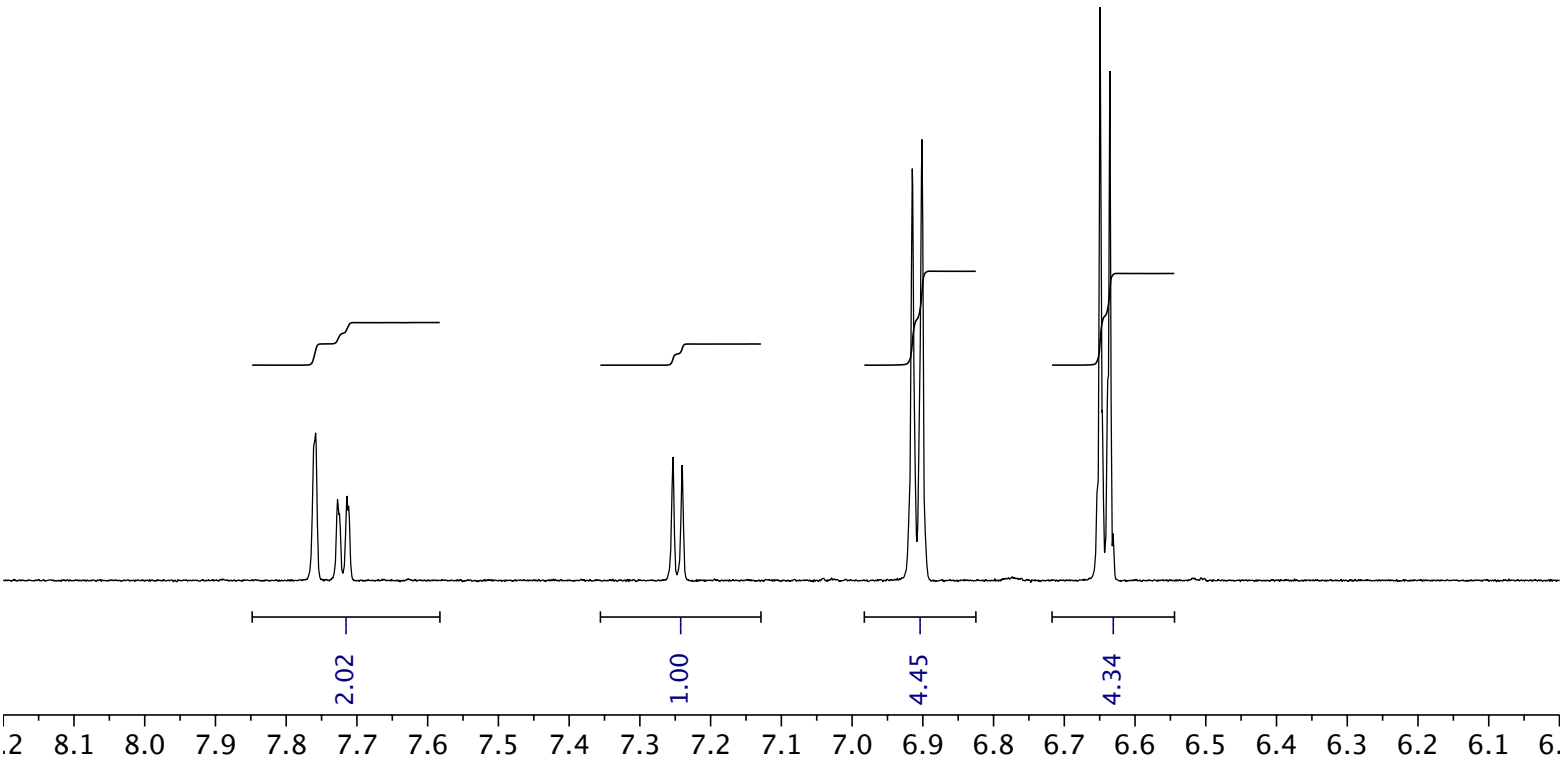
^{1}H NMR (500 MHz) of the production of **3cd** in CD_3OD

without COX-2



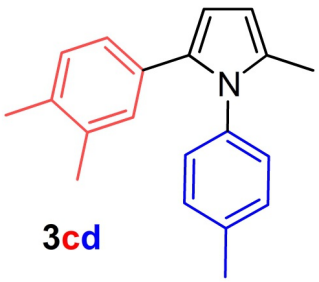
3cd

with COX-2



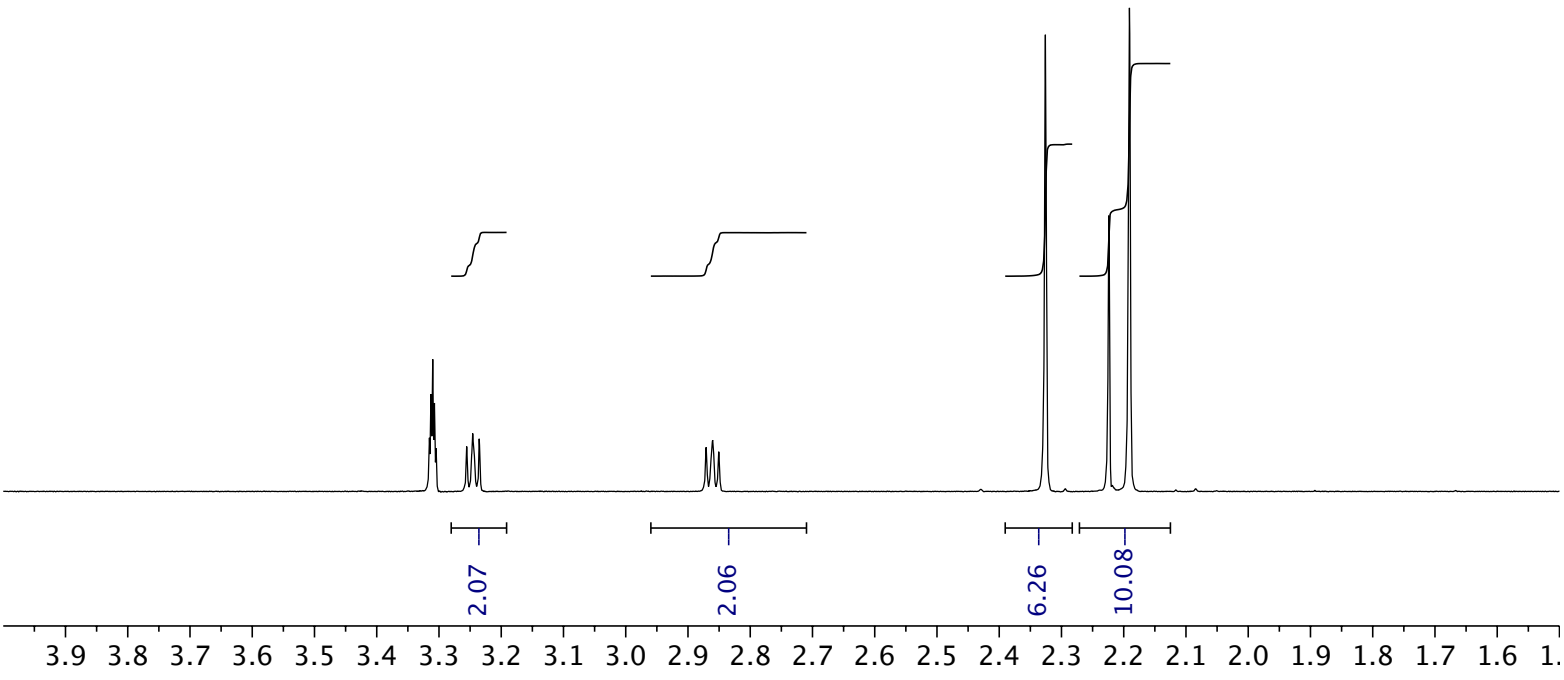
^{1}H NMR (500 MHz) of the production of **3cd** in CD_3OD

without COX-2

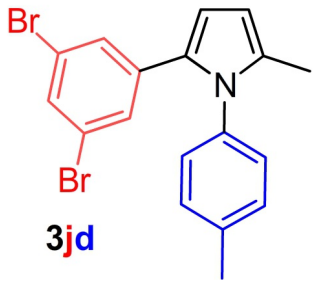


3cd

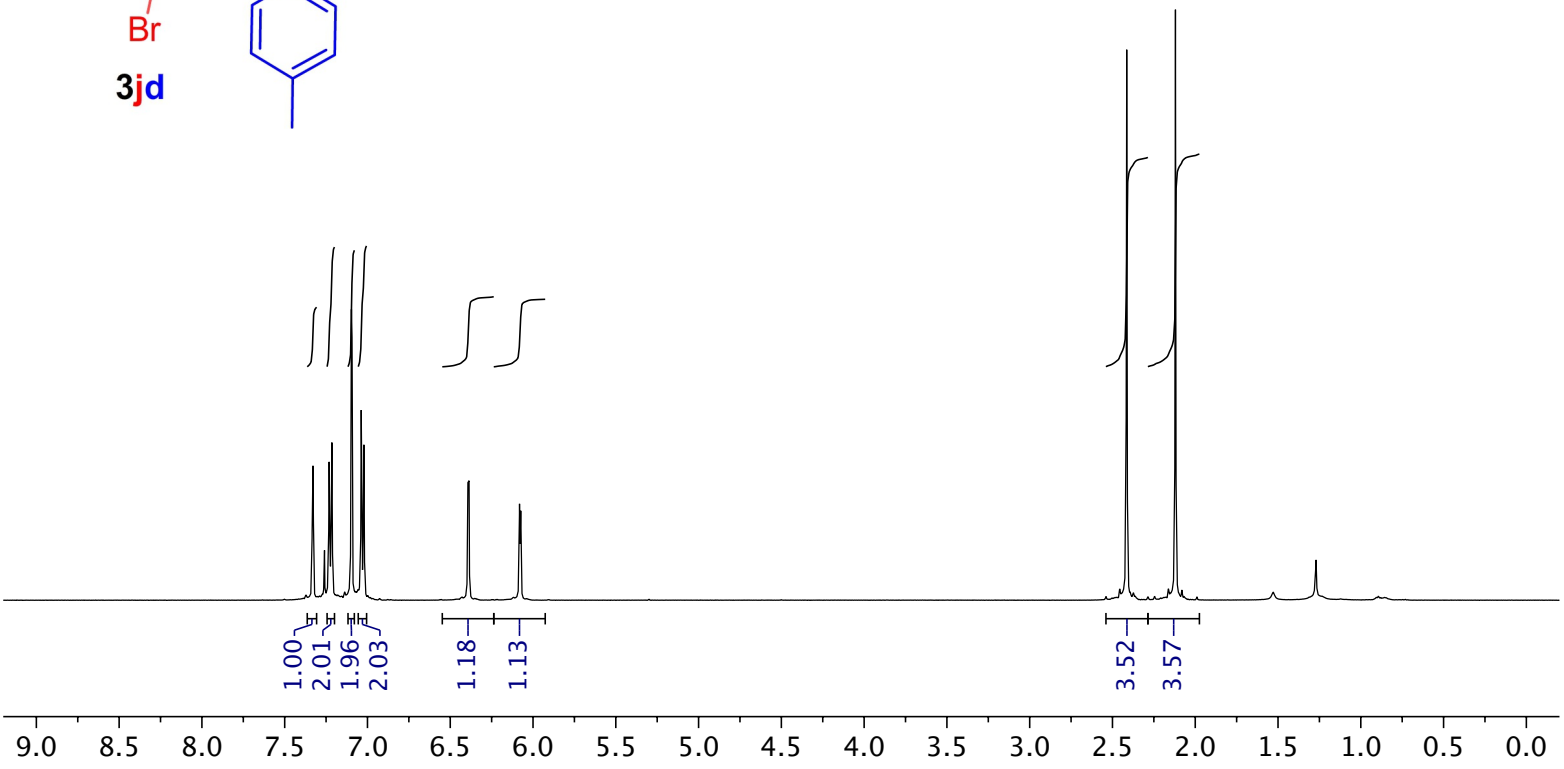
with COX-2

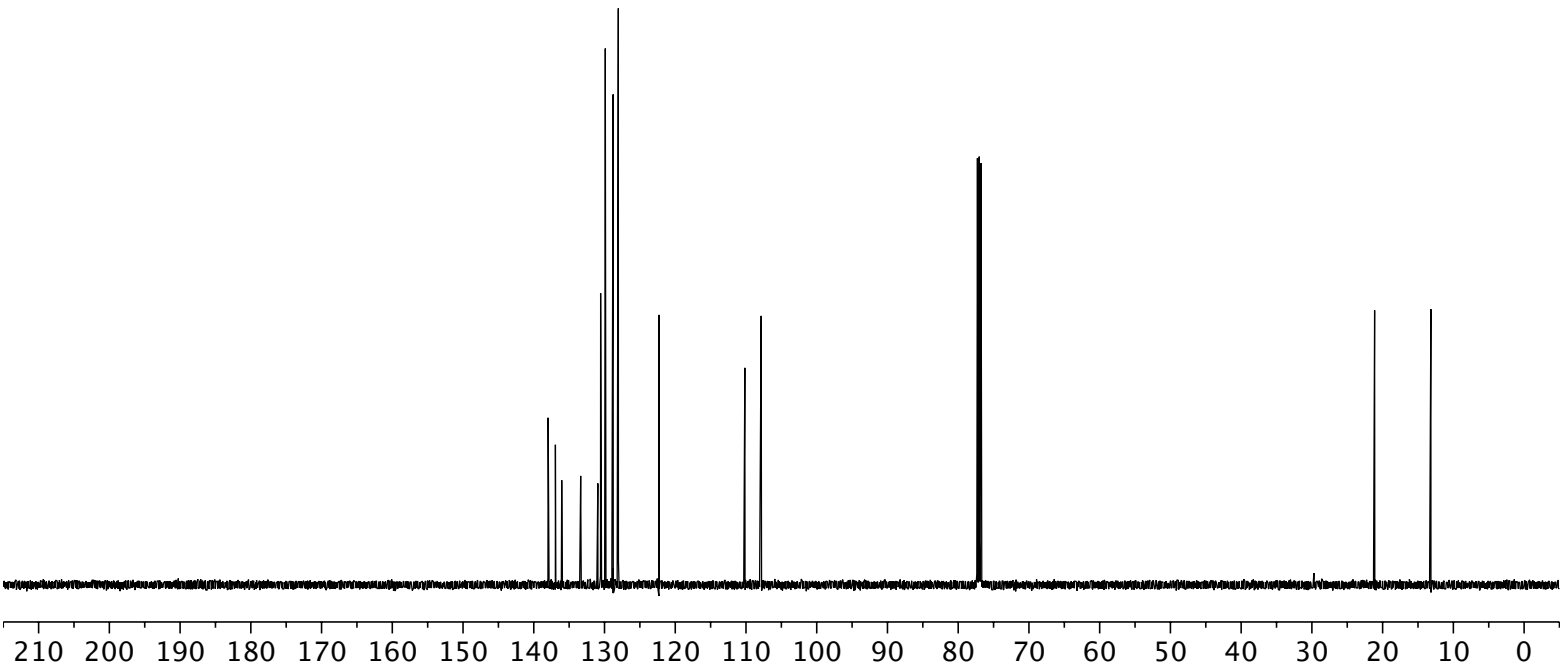


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of **3jd** in $CDCl_3$

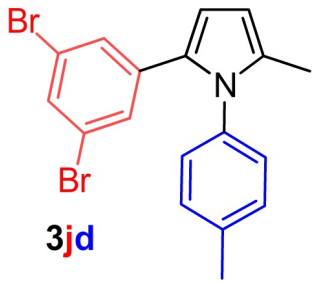


3jd

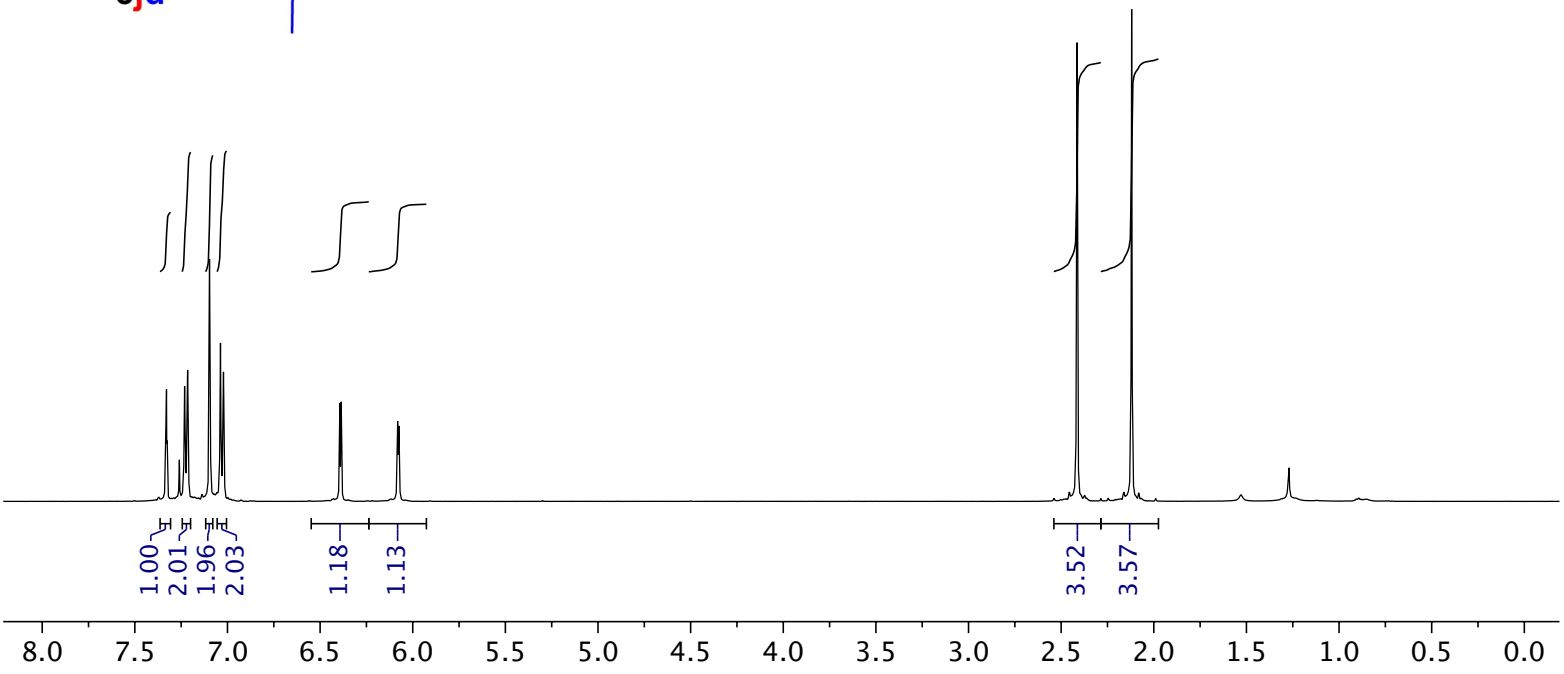


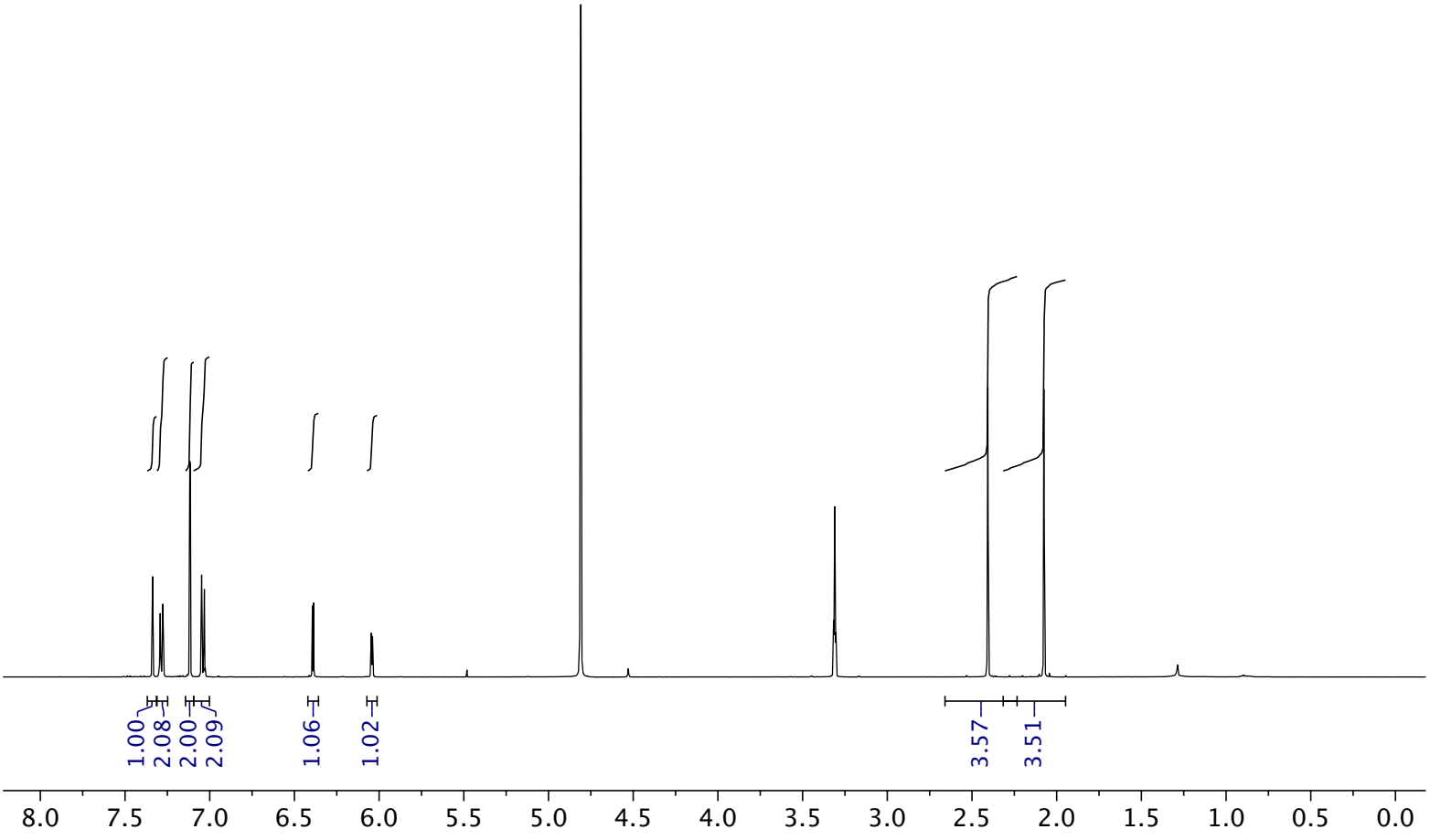


^{1}H NMR (500 MHz) spectra of **3jd** in $CDCl_3$ *versus* CD_3OD



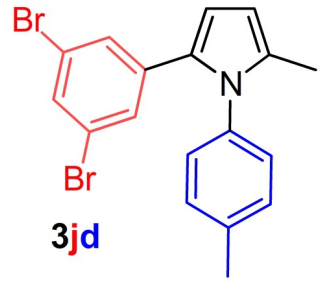
3jd





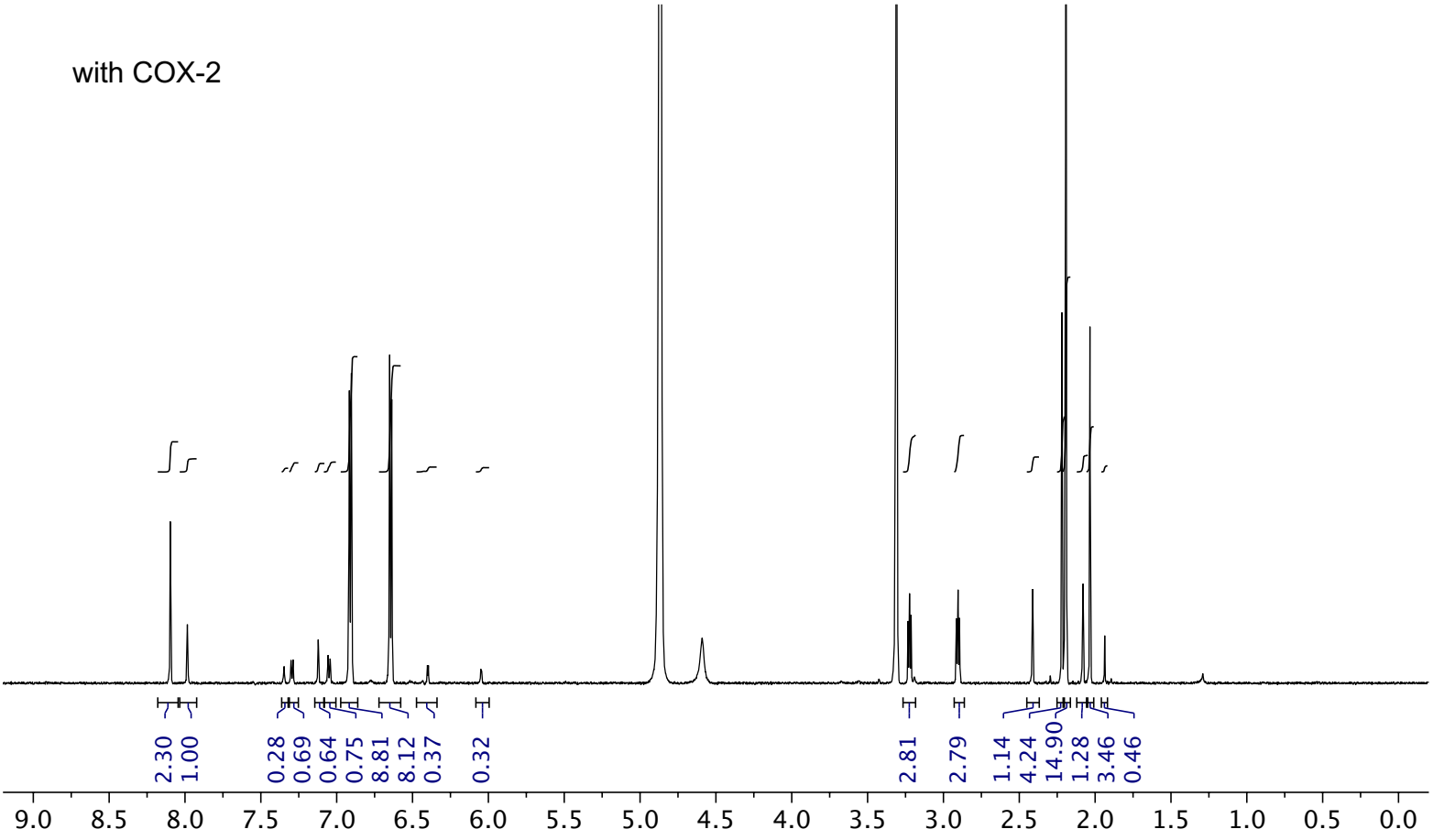
^{1}H NMR (500 MHz) of the production of **3jd** in CD_3OD

without COX-2



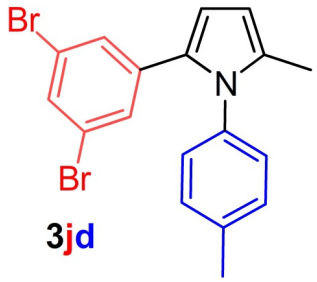
3jd

with COX-2



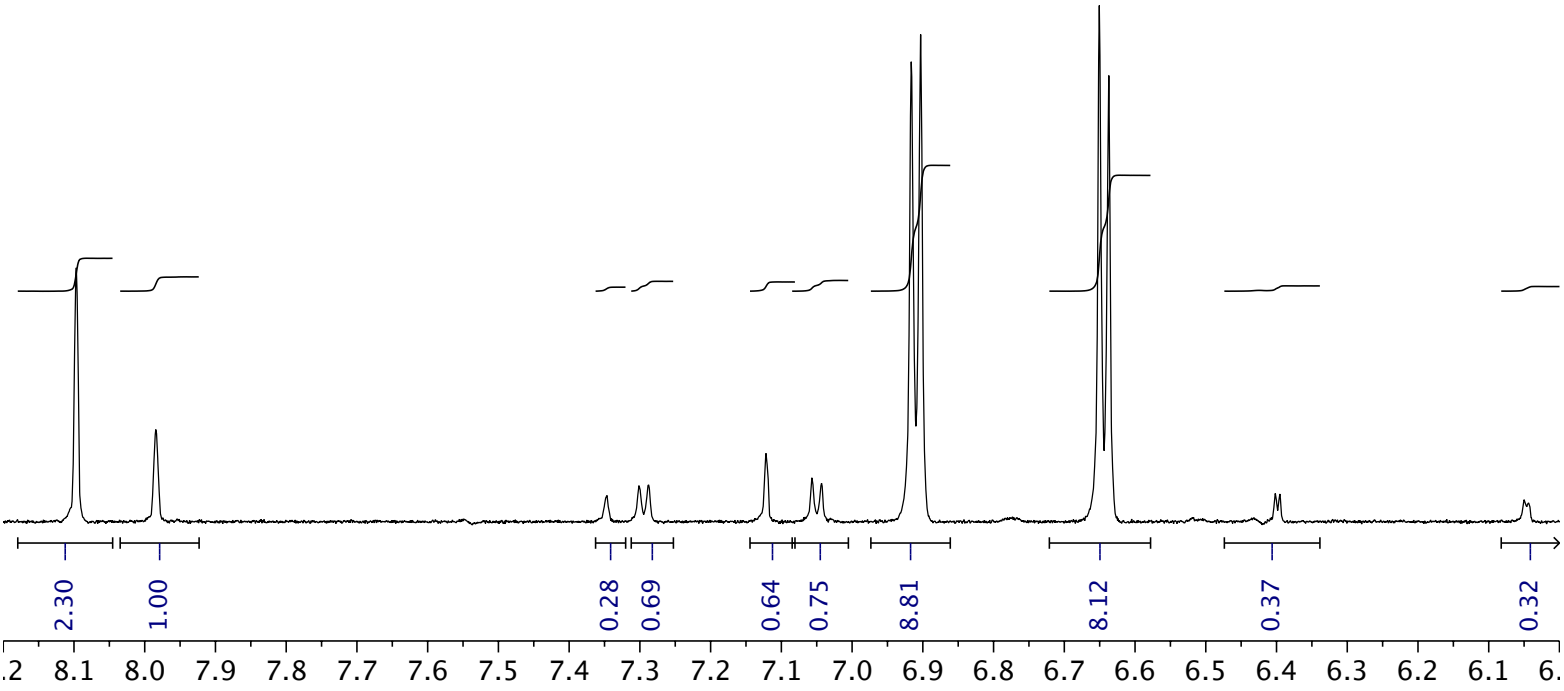
^{1}H NMR (500 MHz) of the production of **3jd** in CD_3OD

without COX-2



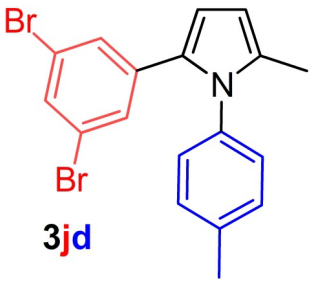
3jd

with COX-2



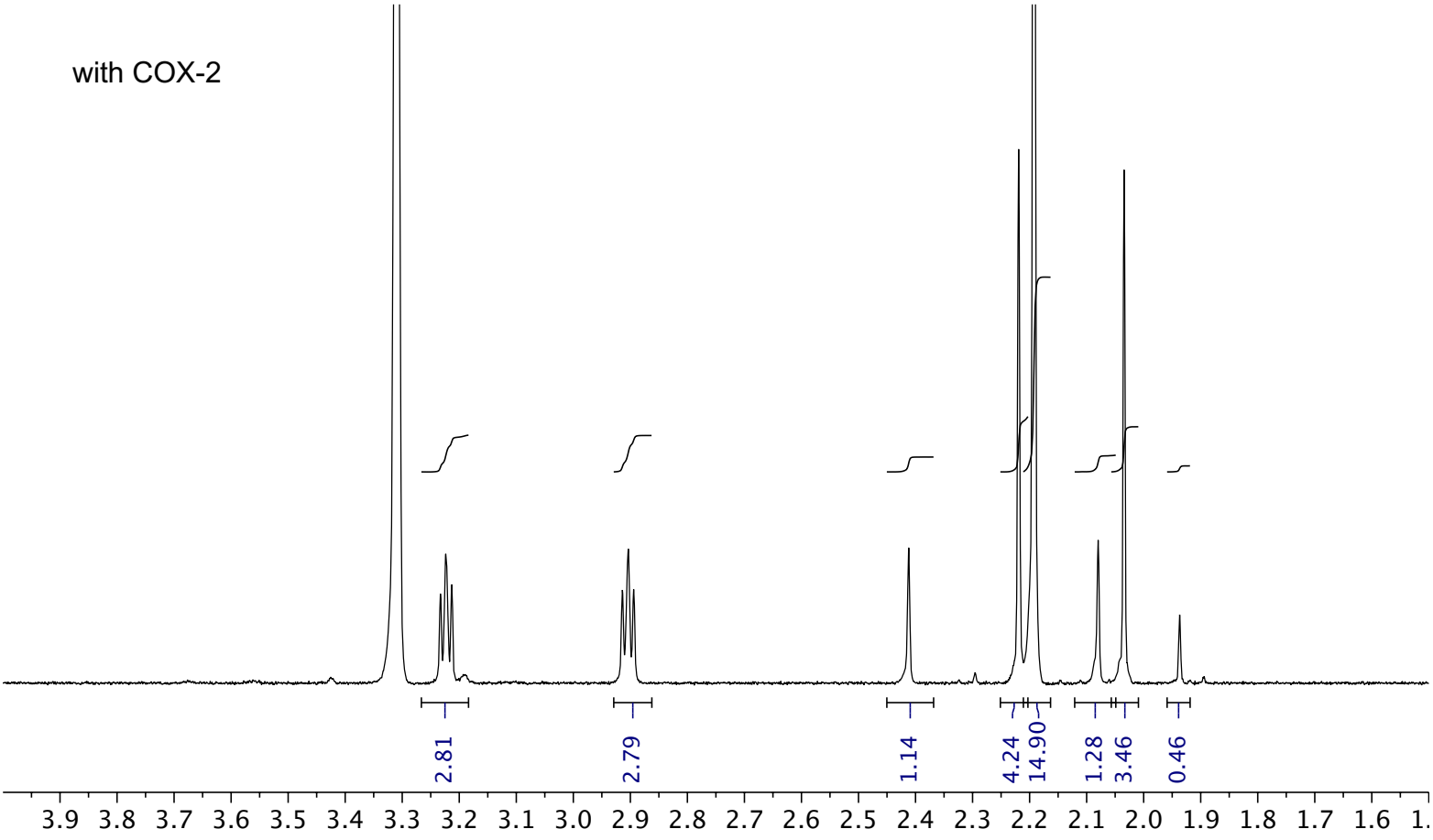
^{1}H NMR (500 MHz) of the production of **3jd** in CD_3OD

without COX-2

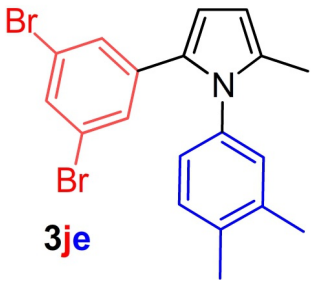


3jd

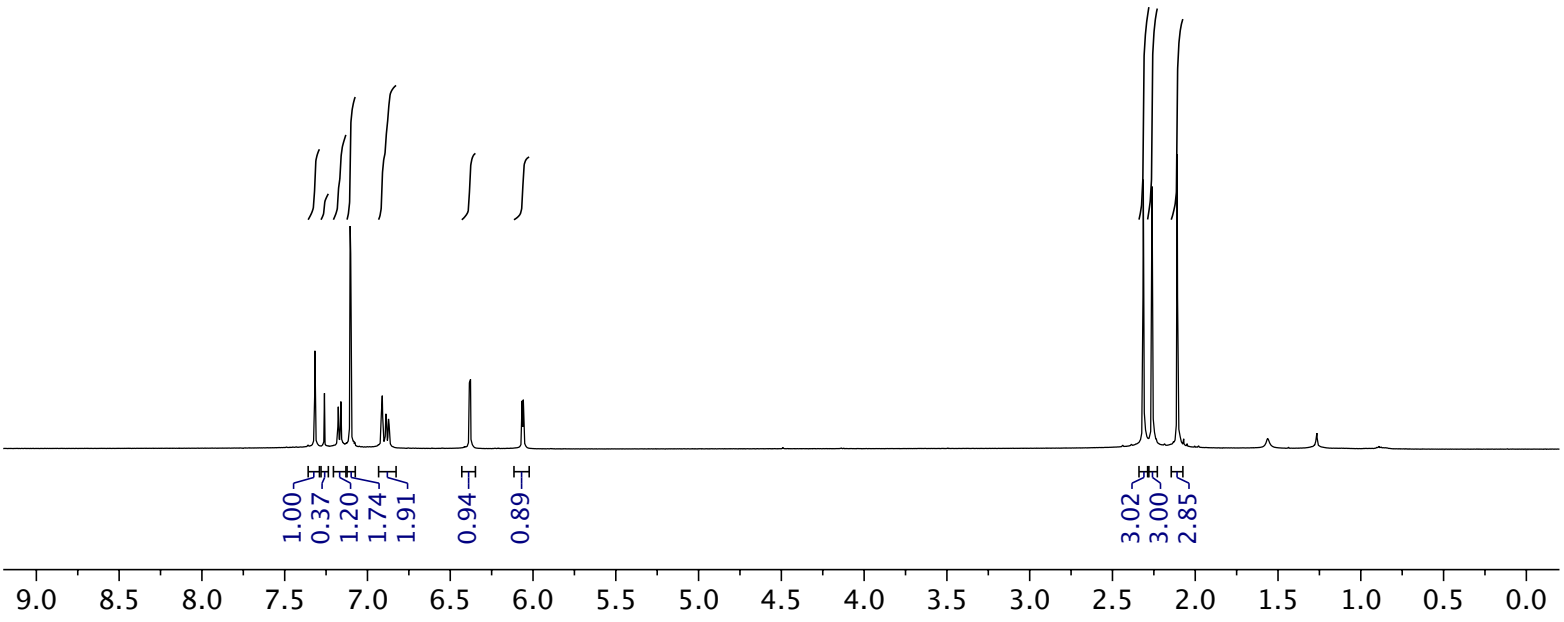
with COX-2

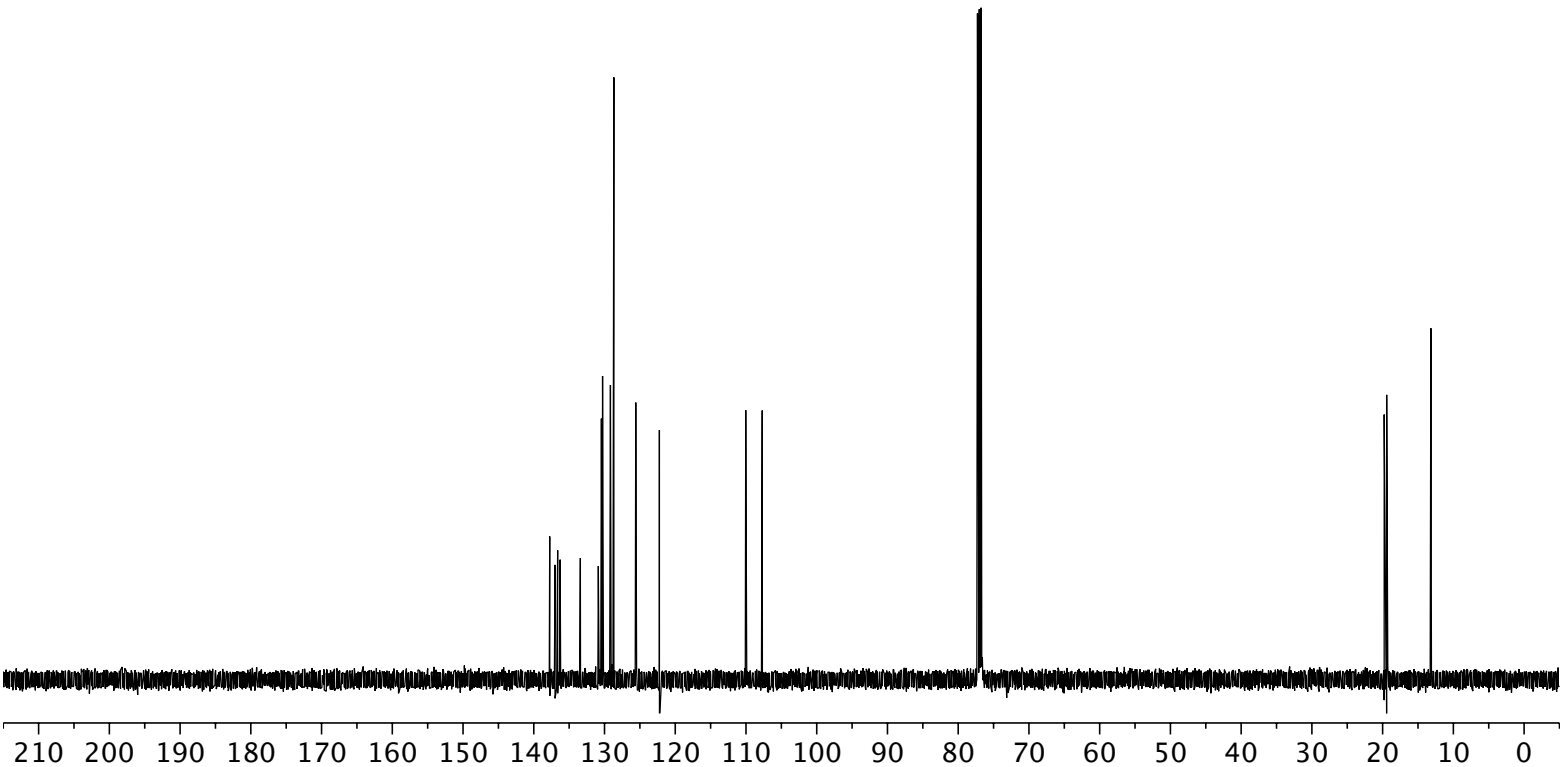


^{1}H NMR (500 MHz) spectra of **3je** in $CDCl_3$

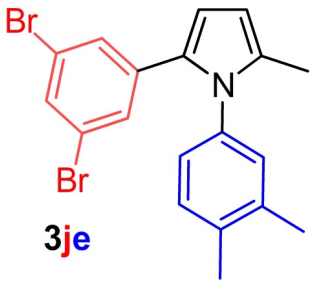


3je

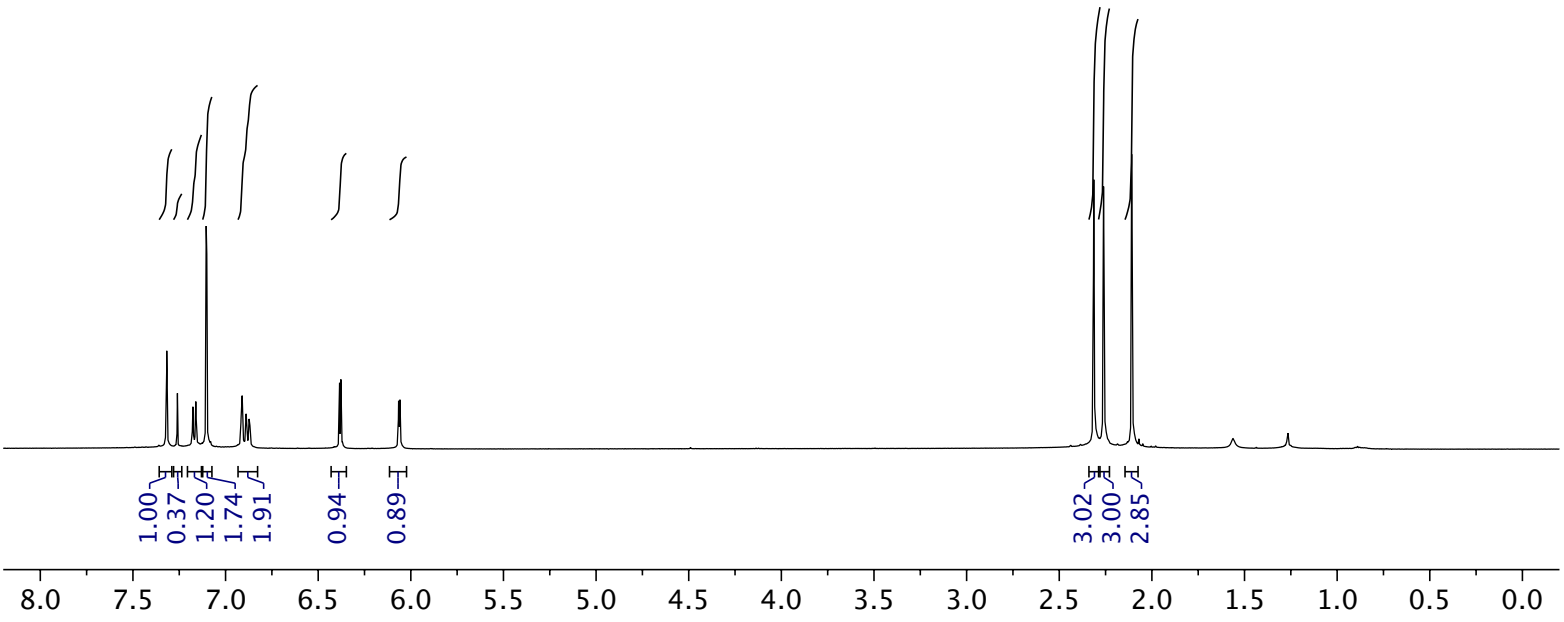


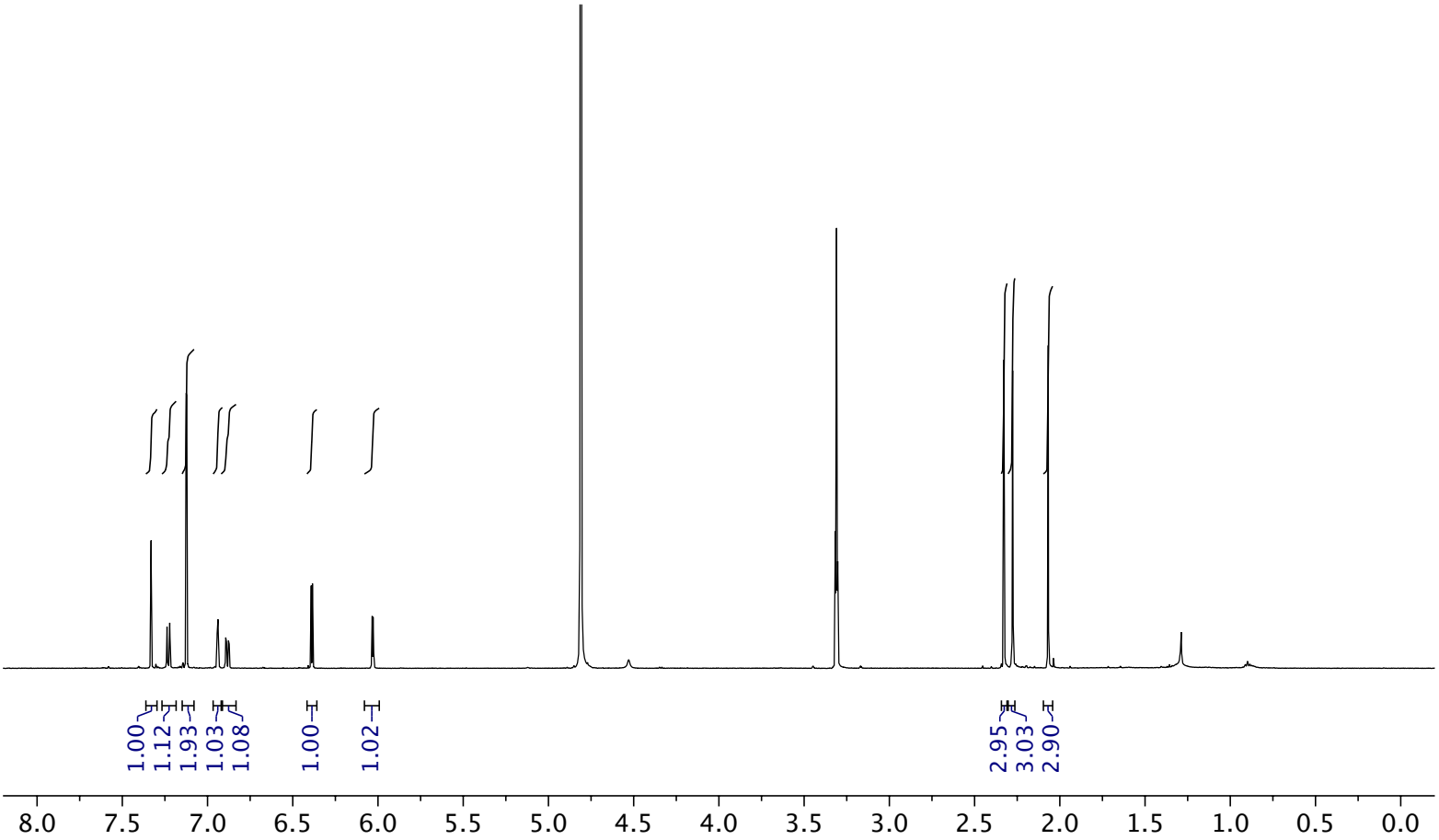


^{1}H NMR (500 MHz) spectra of **3je** in $CDCl_3$ *versus* CD_3OD



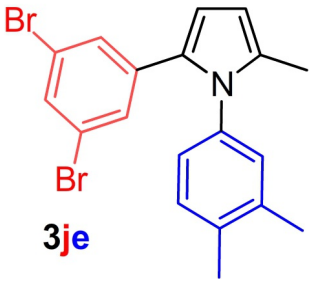
3je





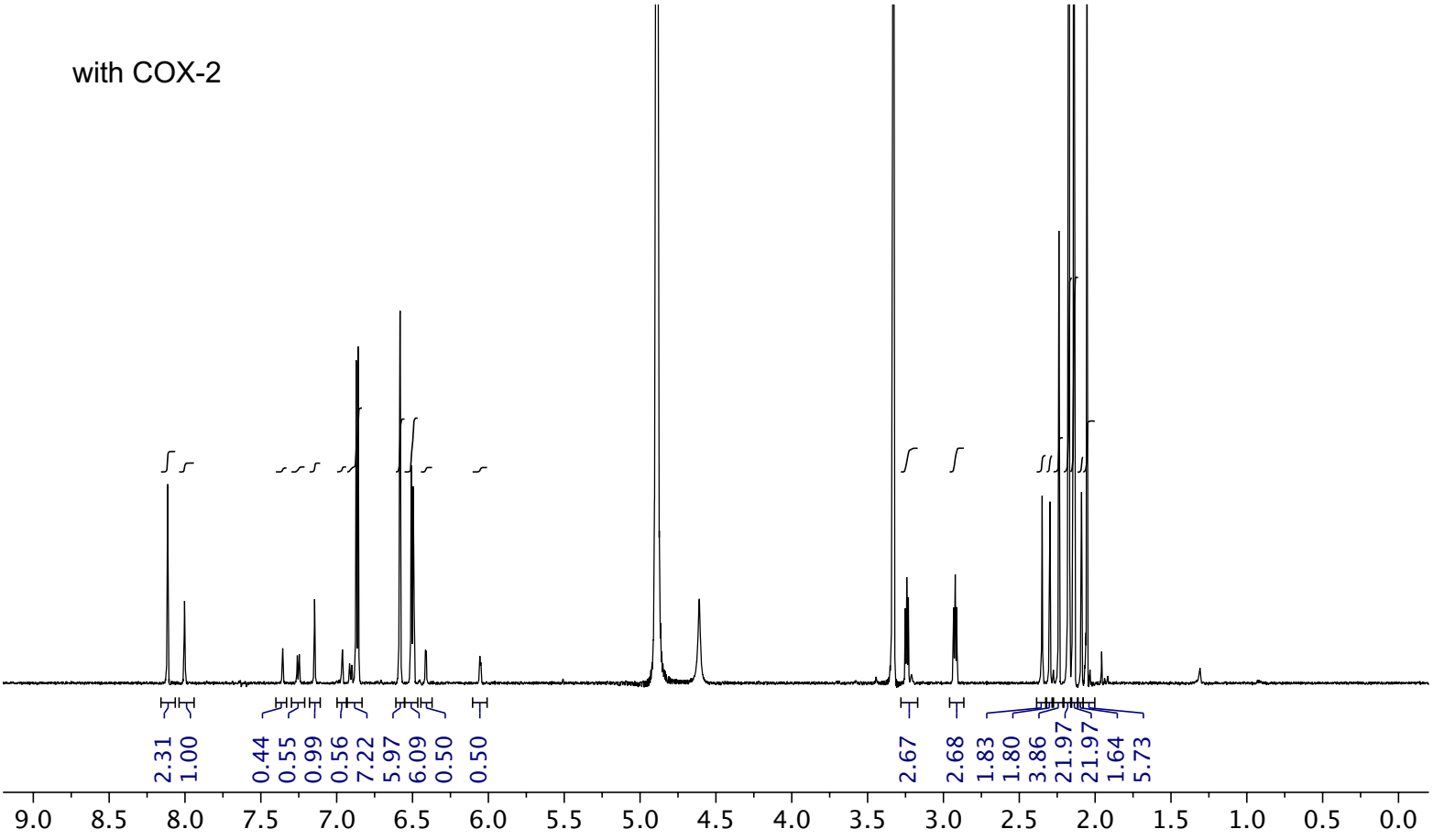
^{1}H NMR (500 MHz) of the production of **3je** in CD_3OD

without COX-2



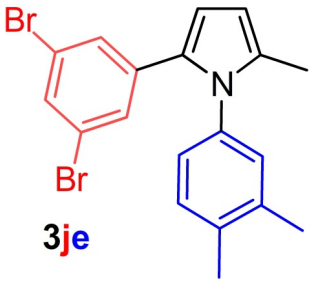
3je

with COX-2

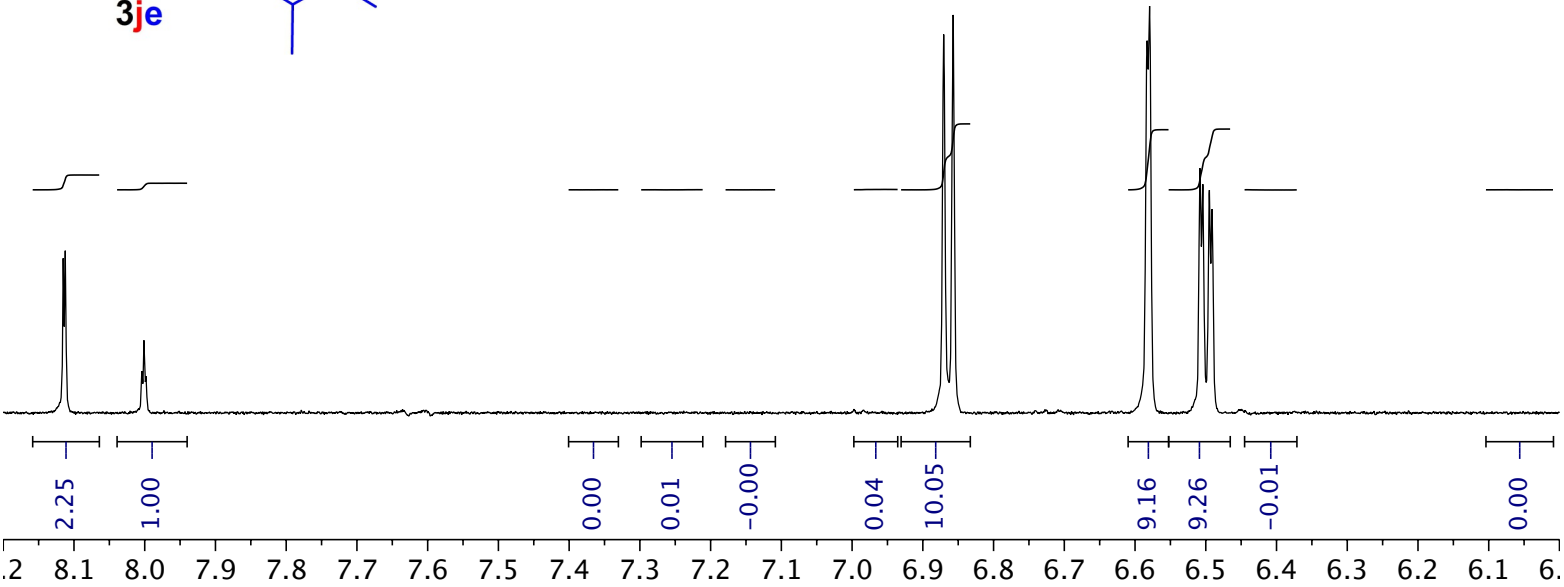


^{1}H NMR (500 MHz) of the production of **3je** in CD_3OD

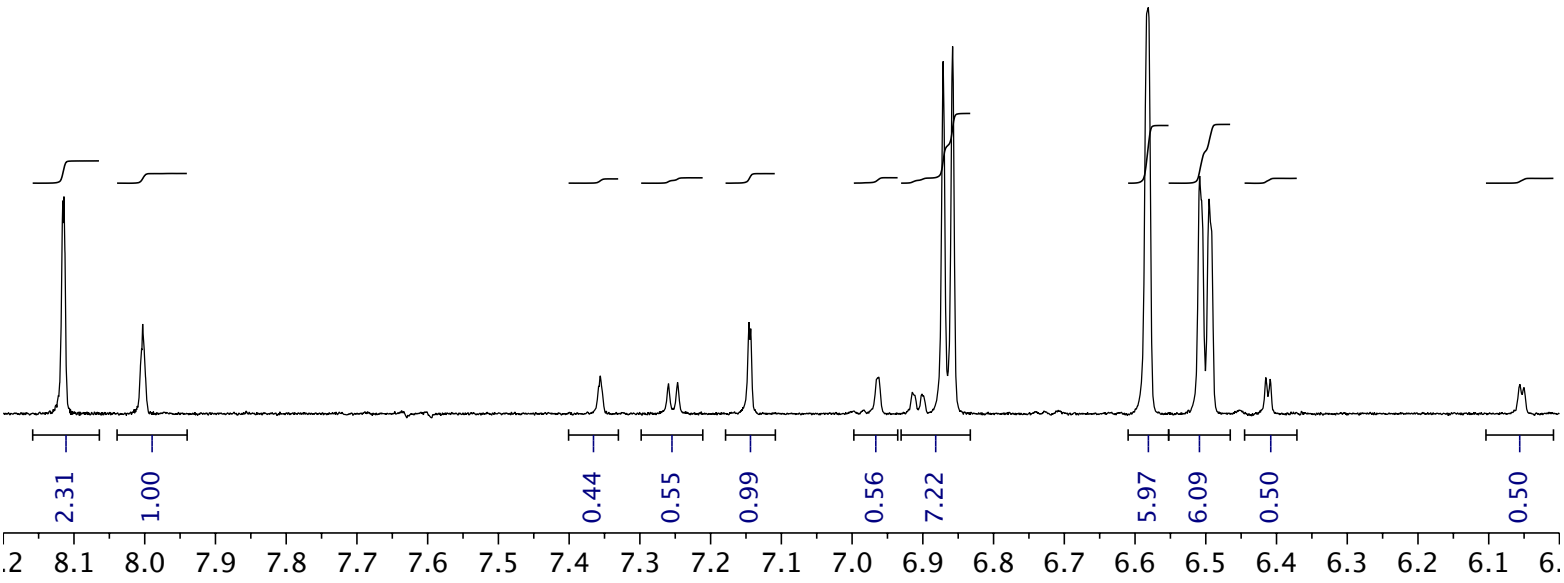
without COX-2



3je

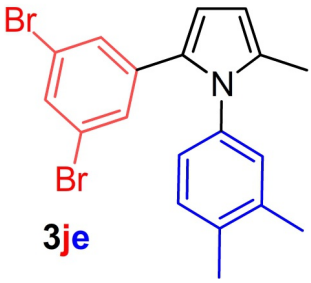


with COX-2



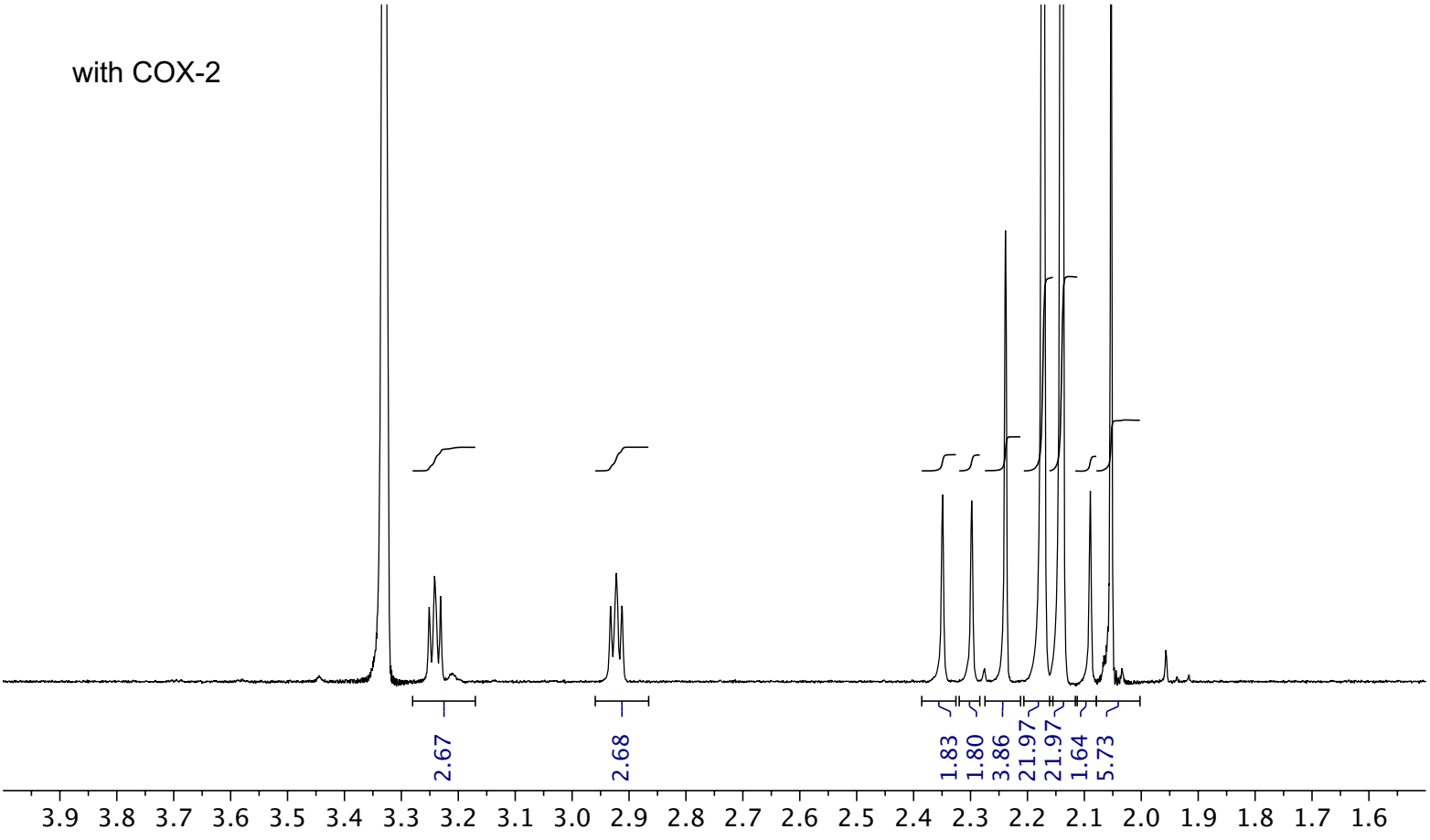
^{1}H NMR (500 MHz) of the production of **3je** in CD_3OD

without COX-2

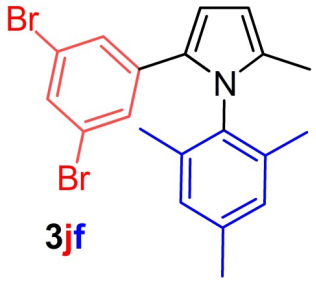


3je

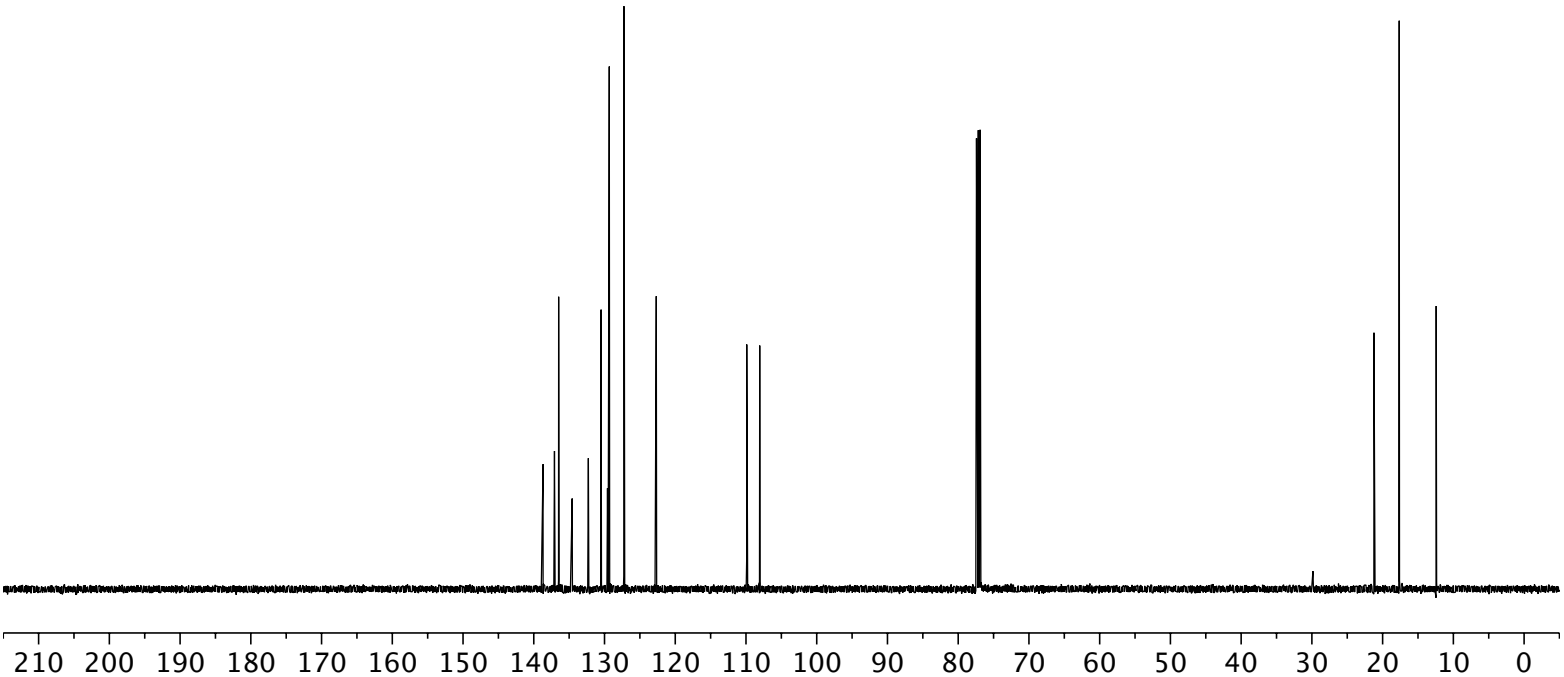
with COX-2



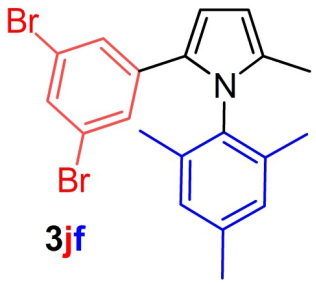
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of **3jf** in $CDCl_3$



3jf

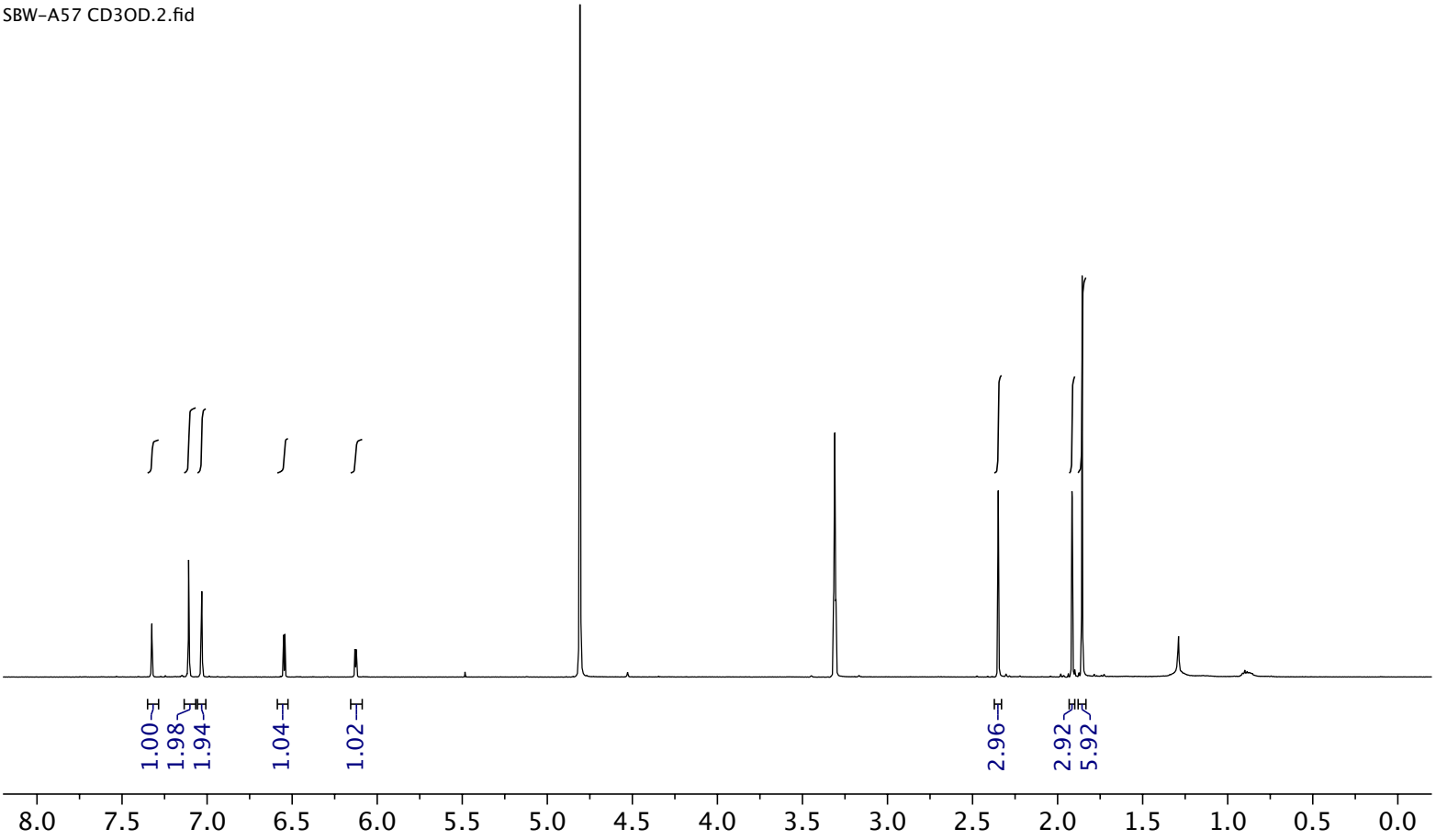


^{1}H NMR (500 MHz) spectra of **3jf** in $CDCl_3$ *versus* CD_3OD



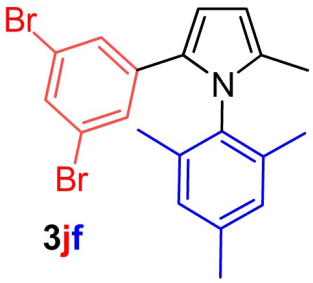
3jf

SBW-A57 CD3OD.2.fid



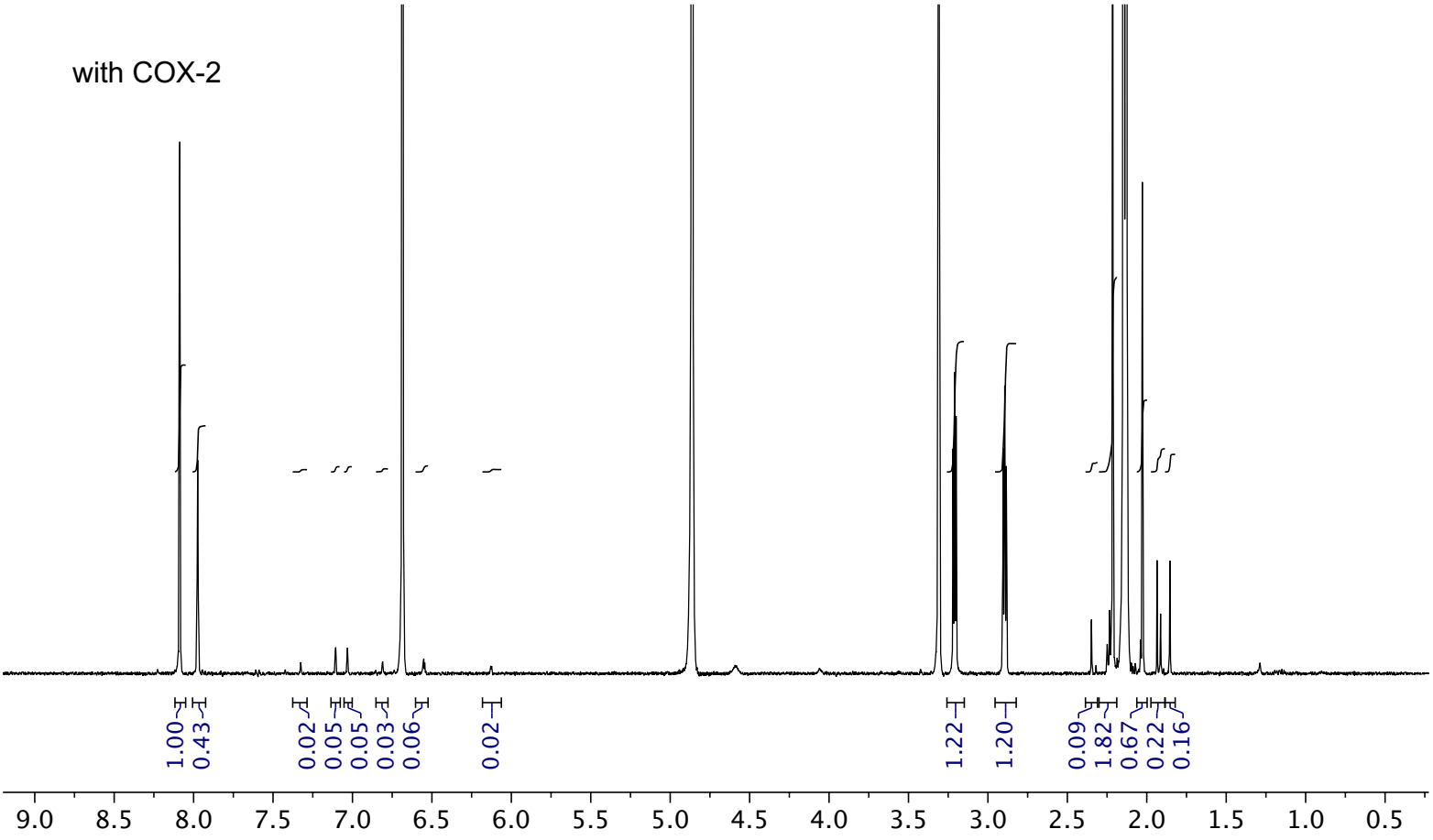
^{1}H NMR (500 MHz) of the production of **3jf** in CD_3OD

without COX-2



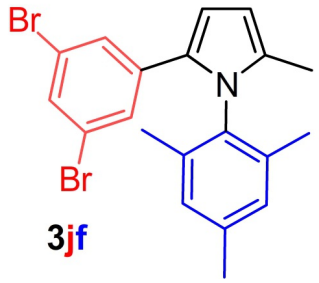
3jf

with COX-2



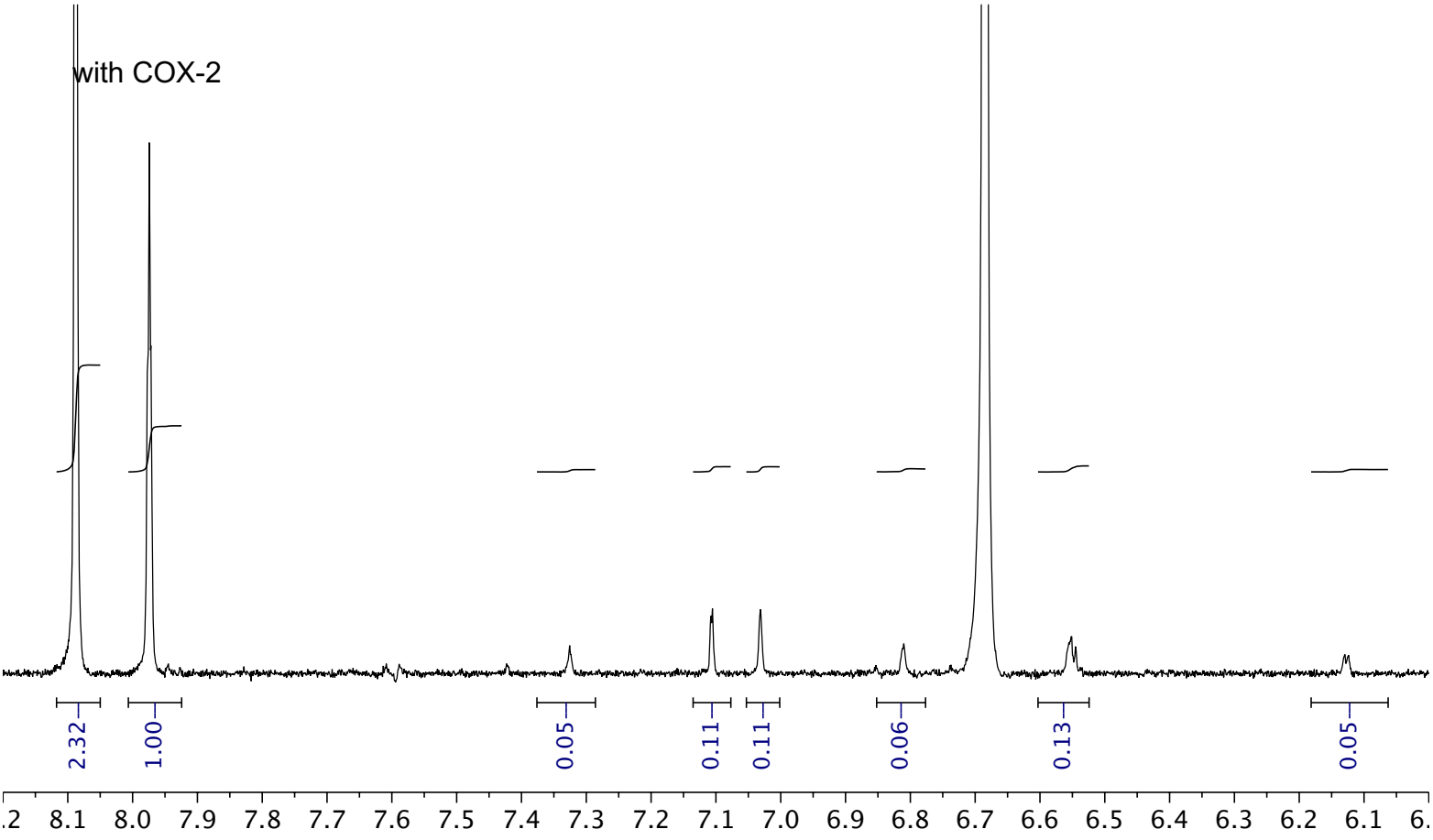
^{1}H NMR (500 MHz) of the production of **3jf** in CD_3OD

without COX-2



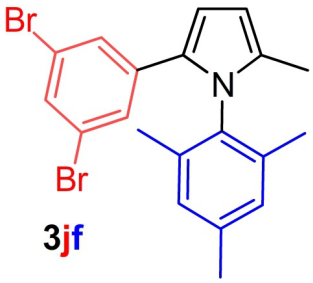
3jf

with COX-2



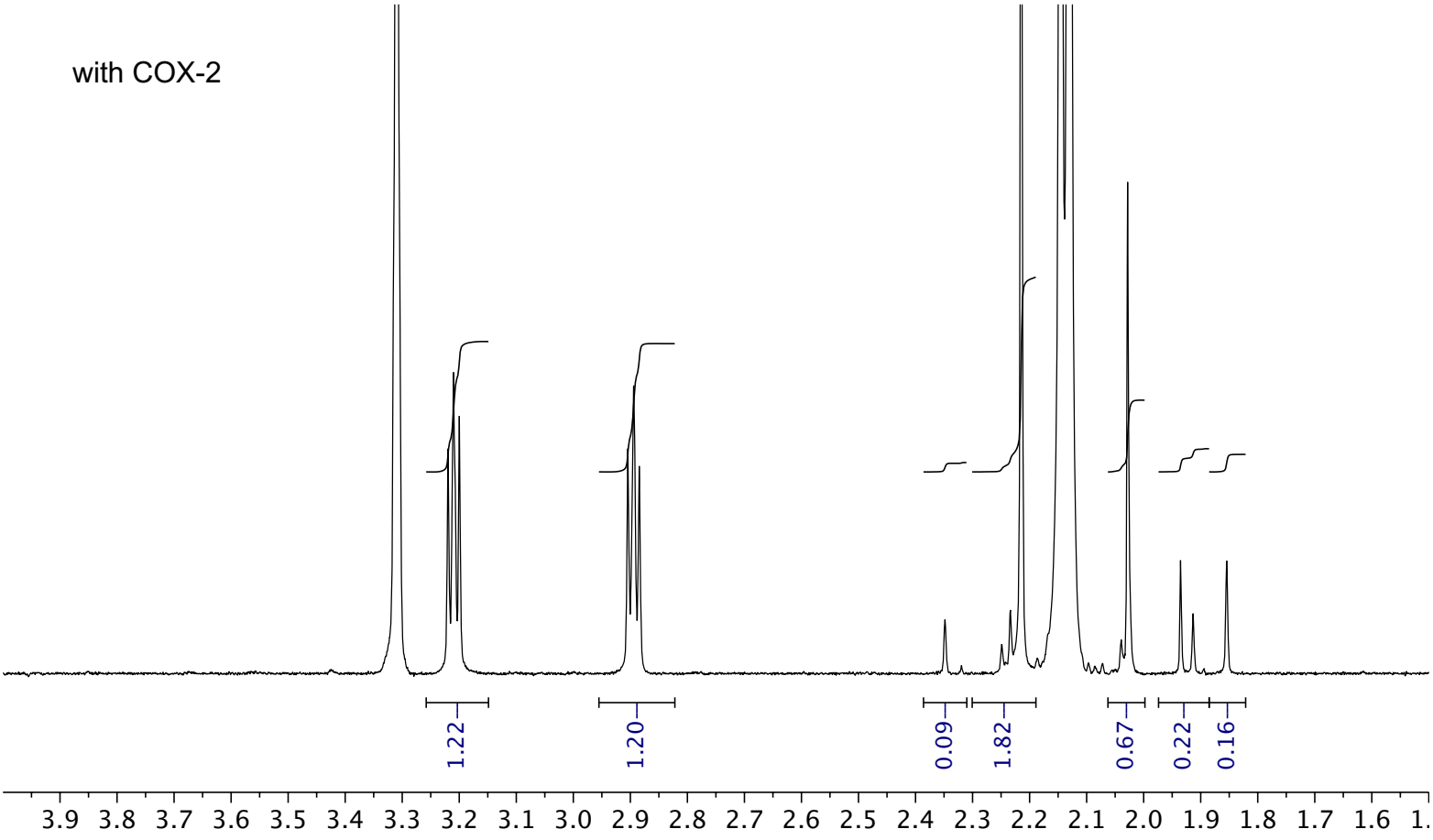
^{1}H NMR (500 MHz) of the production of **3jf** in CD_3OD

without COX-2

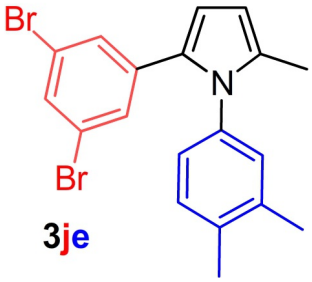


3jf

with COX-2

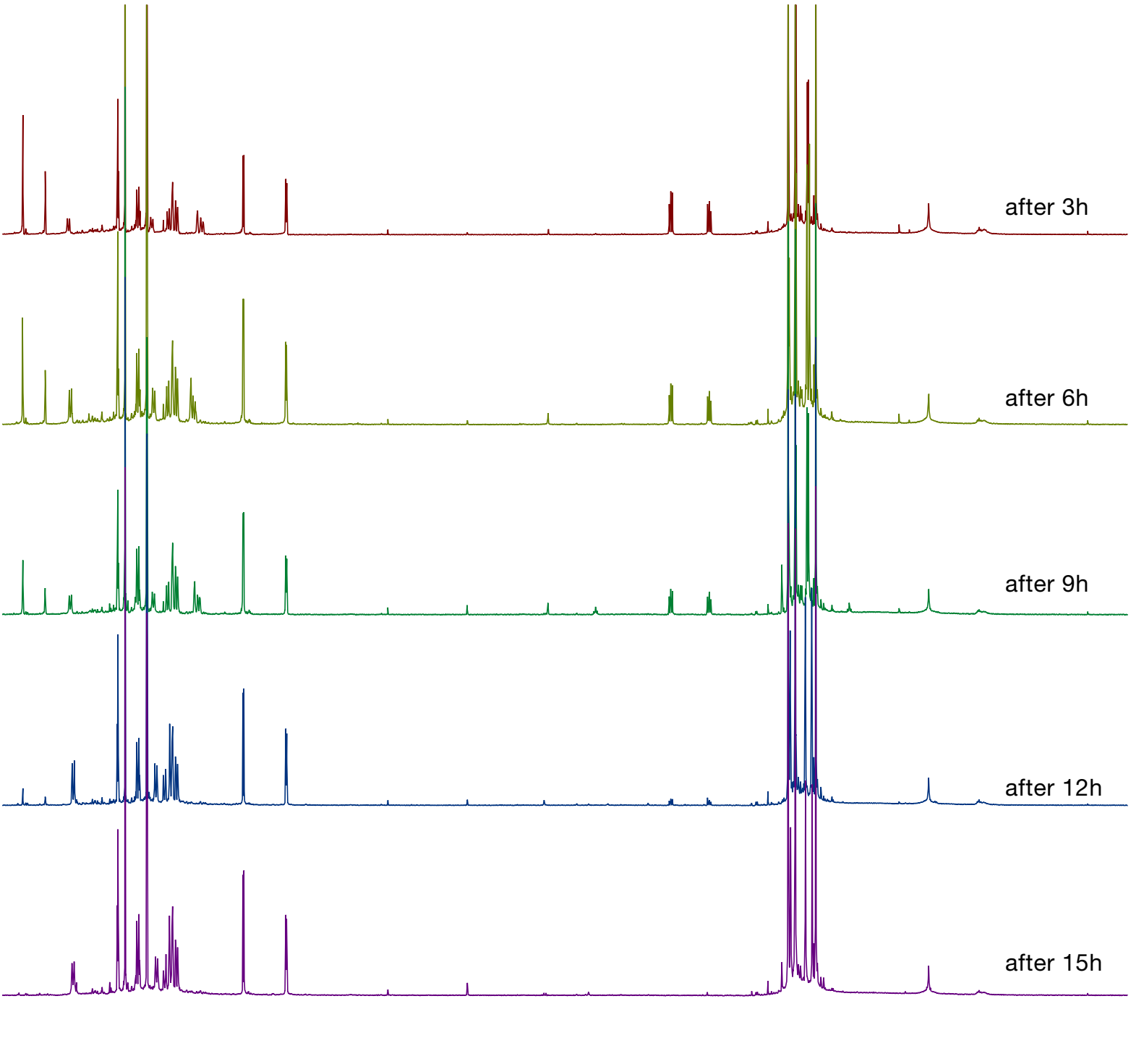


^{1}H NMR (500 MHz) time course monitor depicting the production of **3je** in $CDCl_3$

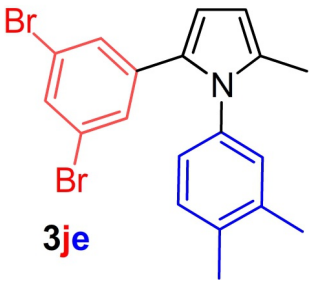


3je

reaction conditions: 0.2 equivalents of pTSA in refluxing toluene

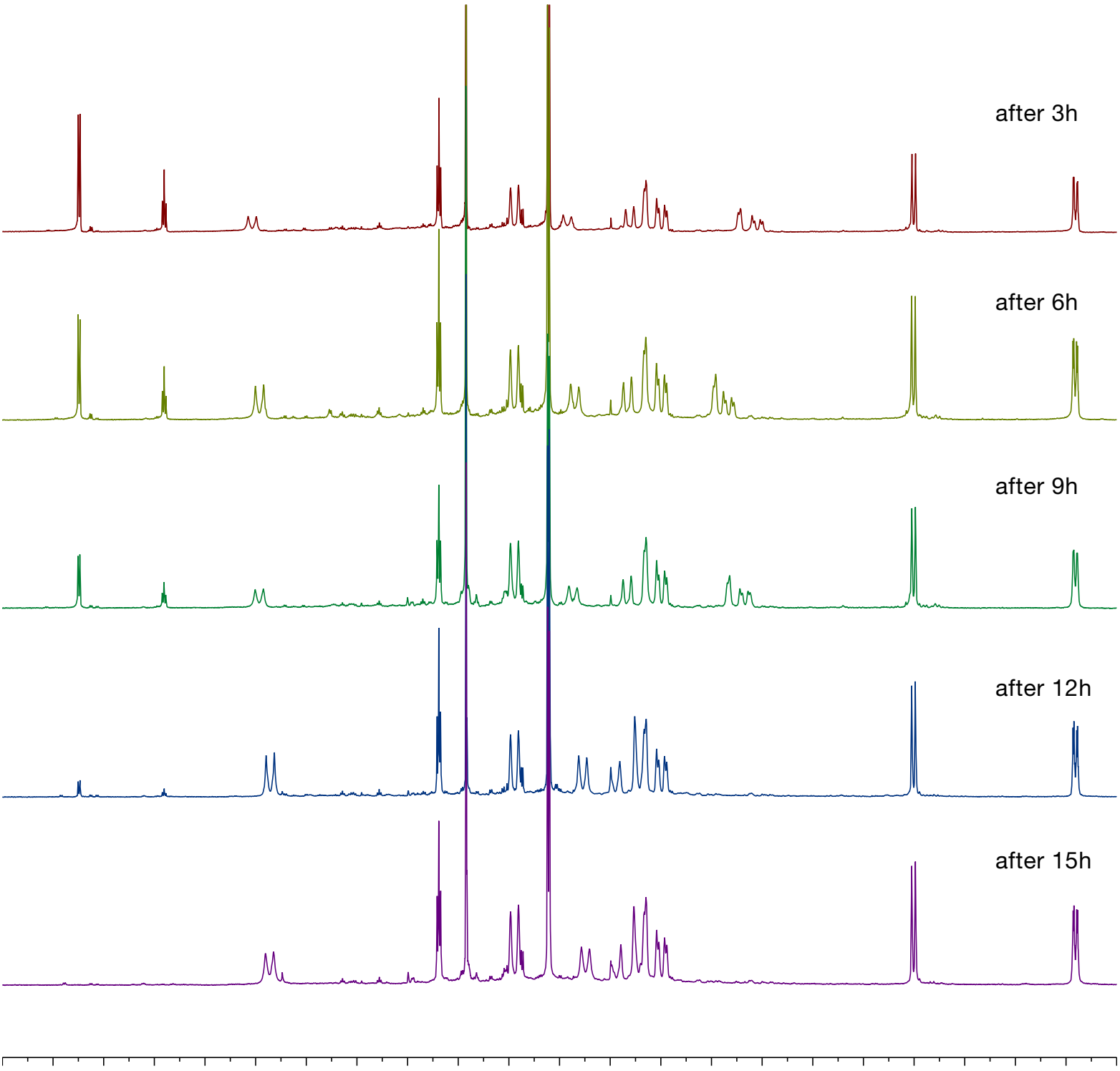


^{1}H NMR (500 MHz) time course monitor depicting the production of **3je** in $CDCl_3$

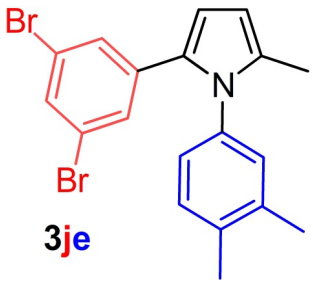


3je

reaction conditions: 0.2 equivalents of pTSA in refluxing toluene

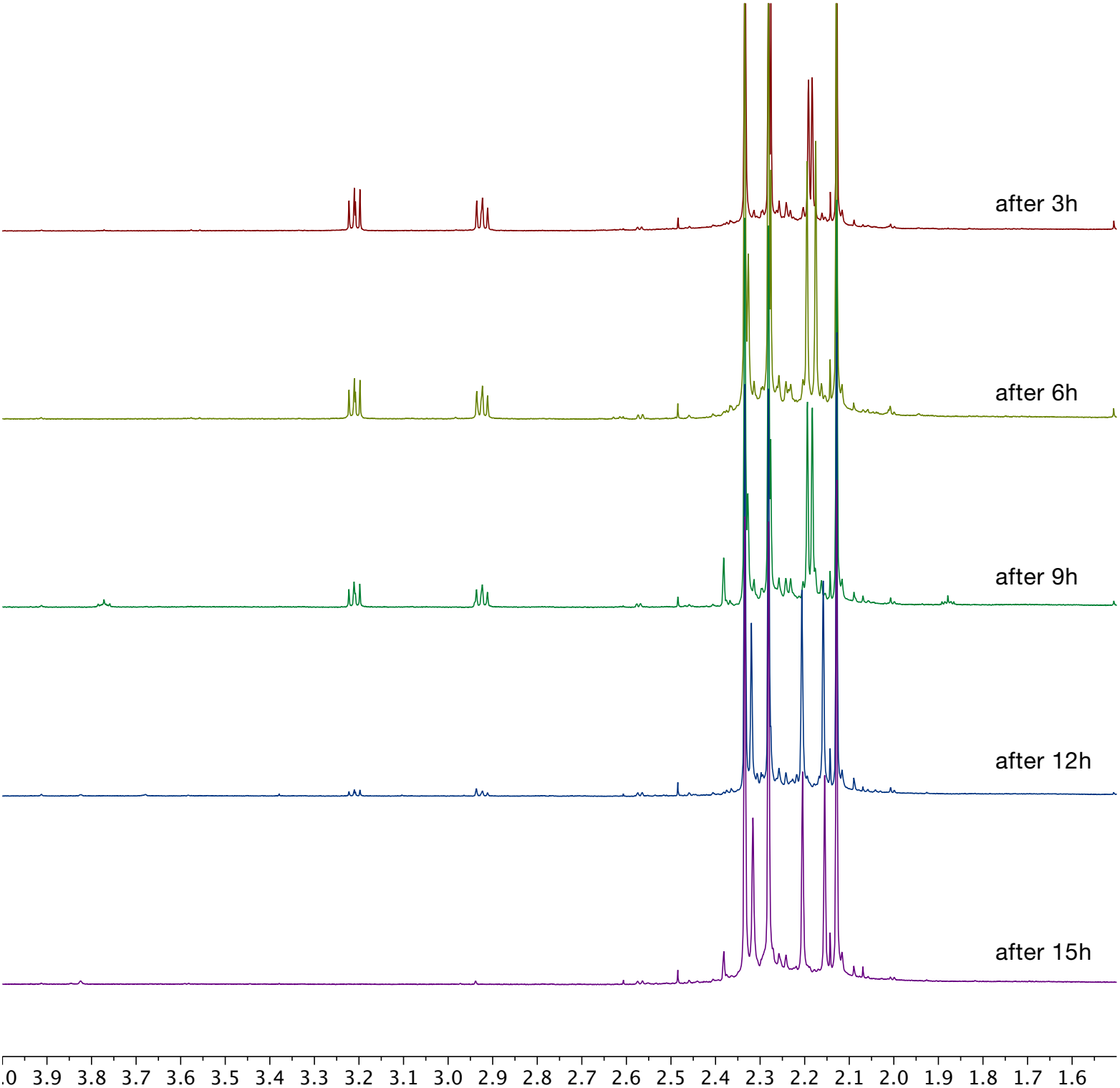


^{1}H NMR (500 MHz) time course monitor depicting the production of **3je** in $CDCl_3$

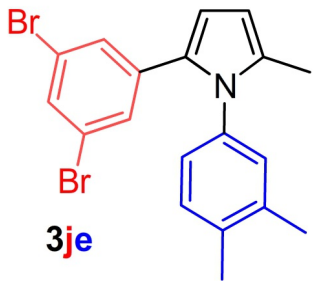


3je

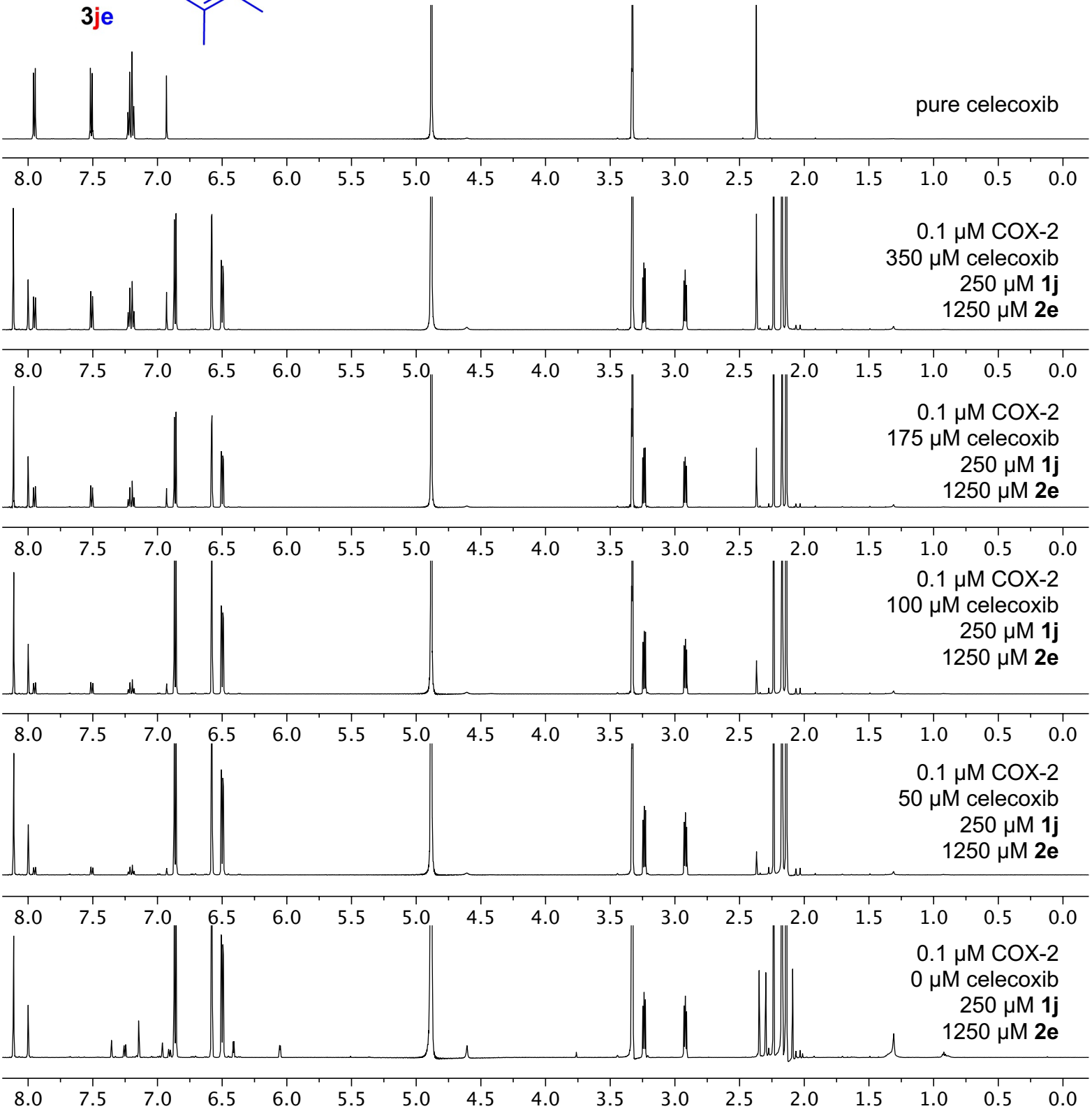
reaction conditions: 0.2 equivalents of pTSA in refluxing toluene



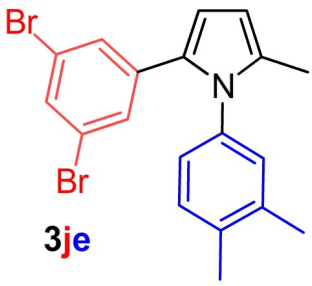
^{1}H NMR (500 MHz) spectra depicting the inhibiton of the production **3je i**n the presence of COX-2 by the addition of celcoxib. NMR spectra are collected in CD_3OD



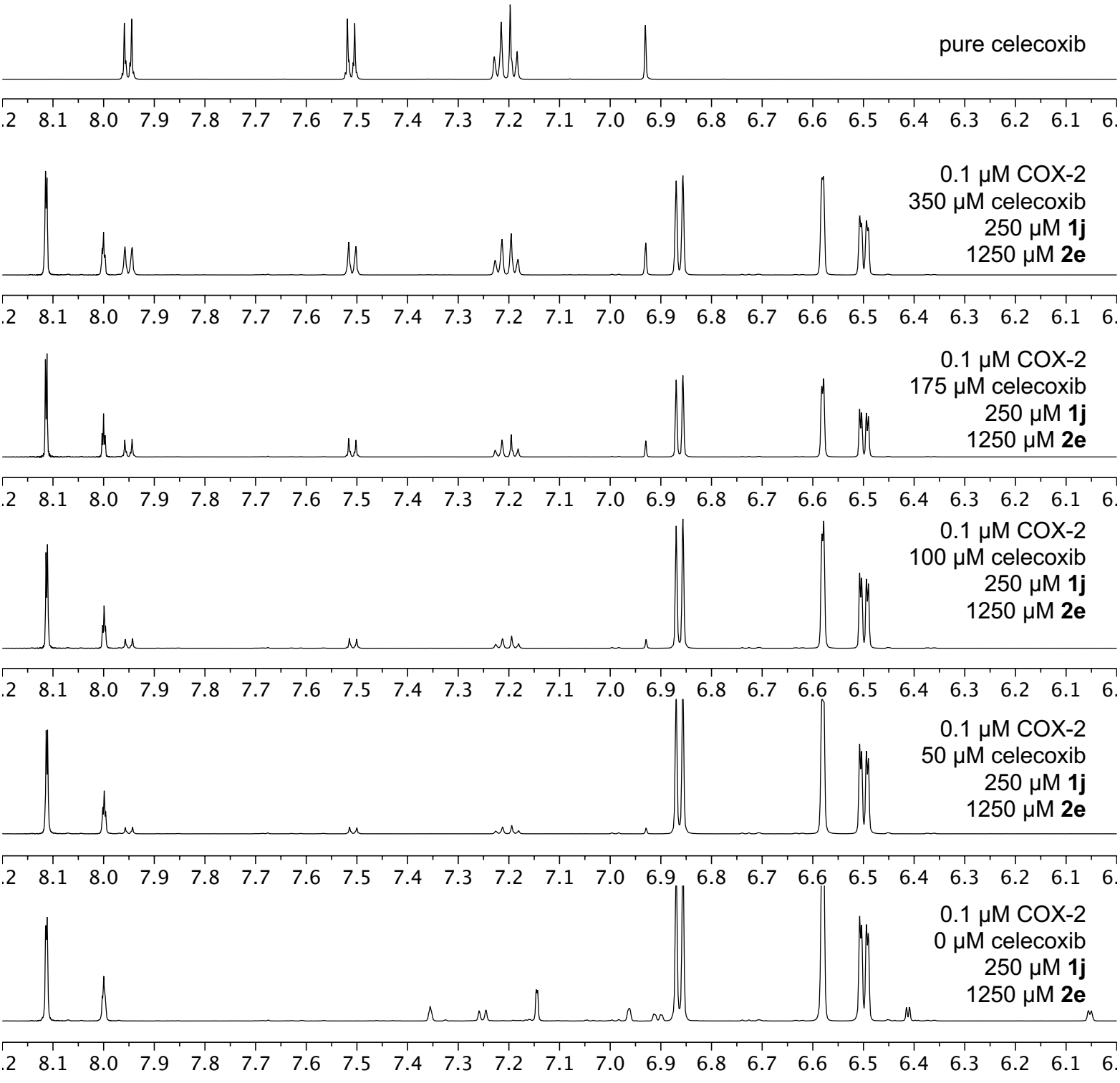
3je



^{1}H NMR (500 MHz) spectra depicting the inhibiton of the production **3je i**n the presence of COX-2 by the addition of celcoxib. NMR spectra are collected in CD_3OD



3je



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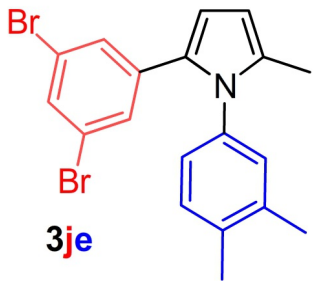

3je