

Supporting Information

Synthesis of organic molecules via spray-drying

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Section S1: Materials and methods.

Acetic anhydride, 4-aminophenol, benzaldehyde, 4-methoxybenzaldehyde, 4-pyridinecarboxaldehyde, di-tert-butyl dicarbonate, formic acid (HCOOH), hydrochloric acid (HCl) 37%, potassium hydroxide (KOH), triethylamine and 1,3,5-trimethoxybenzene were purchased from Sigma Aldrich. 6-hydroxy-1-indanone was obtained from BLD Pharm. Methanol, tetrahydrofuran (THF) and ethyl acetate were purchased from Fischer. Ethanol was purchased from Scharlab S.L. Deionised water was obtained from a Milli-Q[®] system (18.2 M Ω ·cm). DMSO-d₆ was obtained from Euroisotop.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were measured using a Bruker 400 MHz Ascend[™] spectrophotometer equipped with a 5 mm iProbe ¹H/BB/D and a Sample Case exchanger using DMSO-d₆ as deuterated solvent. To determine sample purity using quantitative NMR (qNMR), 18 mg of collected powder were dissolved in 500 μ L DMSO-d₆ and 100 μ L of a 0.100 M solution of 1,3,5-trimethoxybenzene (TMB) in DMSO-d₆ were added to the previous solution, which was homogenized before transferring it inside the NMR tube. A ¹H pulse sequence was launched to record the spectra using a d1 delay of 25 s between pulses, taking 16 scans. ¹H non-quantitative spectra were measured using a standard pulse sequence registering 16 scans and ¹³C NMR were measured using a standard pulse sequence registering 2048 scans. Abbreviations for signal multiplicity are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet. Coupling constants were calculated directly from the obtained spectra.

High Performance liquid chromatography (HPLC) analysis of the experimental data from the obtention of paracetamol were obtained using an Agilent HPLC1200 equipped with an on-line Diode Array Detector with a set wavelength of 243 nm with a Luna Omega C18, 5 μ m internal diameter, 100 A (4.6x150 mm, 5 μ m) column from Phenomenex using two different mobile phases (mobile phase A: 0.1% HCOOH in H₂O, mobile phase B: 0.1% HCOOH in methanol). Samples were diluted in methanol before injection. Mobile phases were injected at 1.00 mL·min⁻¹ with an A:B proportion of 5:95 from 0 to 15 min which changed to A:B proportion of 95:5 from 15 to 30 min.

Electrospray ionization mass spectrometry (ESI-MS) was recorded using a UHPLC Elute+ / 436GC / timsTOF Pro 2 (Bruker Tech) at negative mode.

Field-Emission Scanning Electron Microscopy (FE-SEM) images were collected on a FEI Quanta 650L scanning electron microscope at an acceleration voltage of 5.0 KV, using carbon tape as support and platinum as coating.

Spray-Drying reactions were performed using a Büchi B-290 Mini Spray-Dryer (BUCHI Labortechnik) coupled with a B-295 Inert Loop (BUCHI Labortechnik) for safe-working with organic solvents. The dimensions of the drying chamber are of 15.1 cm internal diameter (ID), 55.2 cm total height and is equipped with a secondary collector of 11.7 cm height and 5.0 cm ID. Between the drying chamber and the cyclone there's a connection of 18.1 cm length and 3.1 cm ID. The cyclone has a total height of 20.1 cm and the collector has a height of 9.5 cm and 2.7 cm ID. The nozzle has a height of 19.4 cm and an external diameter of 2.4 cm with a spray cap hole of 0.5 mm). Work-up was performed unless purity of the designed product in the collected solid was equal or above 95%.

X-Ray Powder Diffraction (XRPD) diagrams were collected on a Panalytical X'pert mpd diffractometer with monochromatic Cu-K α radiation ($\lambda_{\text{Cu}} = 1.5406 \text{ \AA}$).

Section S2: Synthesis and characterization of Schiff bases.

Synthesis of (E)-4-((pyridin-4-ylmethylene)amino)phenol (3a)

4-aminophenol (5.00 mmol) and 4-pyridinecarboxaldehyde (5.00 mmol) were dissolved in 25 mL ethanol and fed at $3.0 \text{ mL}\cdot\text{min}^{-1}$ into a BUCHI B-290 Mini Spray-Dryer (BUCHI Labortechnik; spray cap: 0.5-mm-hole) with an inlet temperature of $130 \text{ }^{\circ}\text{C}$ and a sheath N_2 flow rate of $357 \text{ L}\cdot\text{h}^{-1}$. After 8.33 minutes, a yellow solid was collected and characterized by ^1H qNMR, ^1H NMR, ^{13}C NMR, ESI-MS and SEM. This characterization confirmed the formation of **3a** with purity of 98% and an yield of 90%.^[1] ^1H NMR (400 MHz, DMSO) δ 9.68 (s, 1H), 8.71 (d, $J = 5.9 \text{ Hz}$, 2H), 8.68 (s, 1H), 7.80 (dd, $J = 6.0 \text{ Hz}$, 2H), 7.29 (d, $J = 8.7 \text{ Hz}$, 2H), 6.83 (d, $J = 8.7 \text{ Hz}$, 2H). ^{13}C NMR (101 MHz, DMSO) δ 157.2, 155.1, 150.4, 143.0, 141.6, 123.1, 121.9, 115.8. ESI-MS m/z calculated for $[\text{C}_{12}\text{H}_9\text{N}_2\text{O}]$: 197.0720, found: 197.0722.

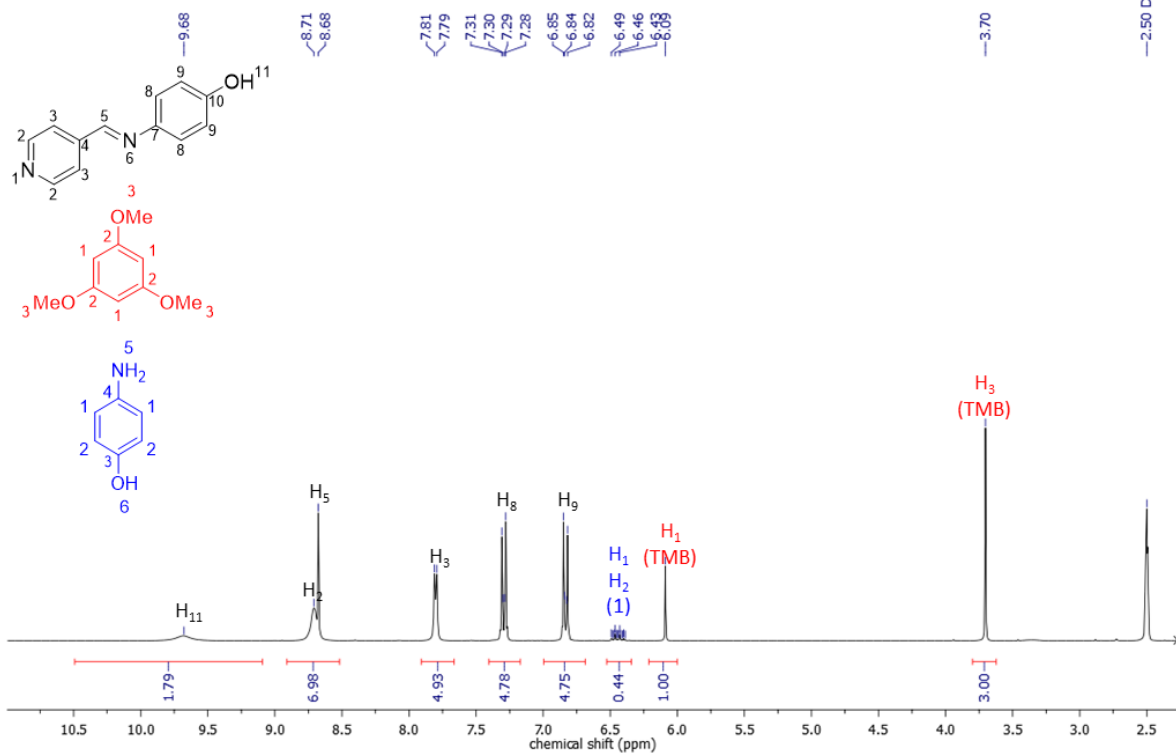


Figure S1. qNMR spectrum of **3a** crude.

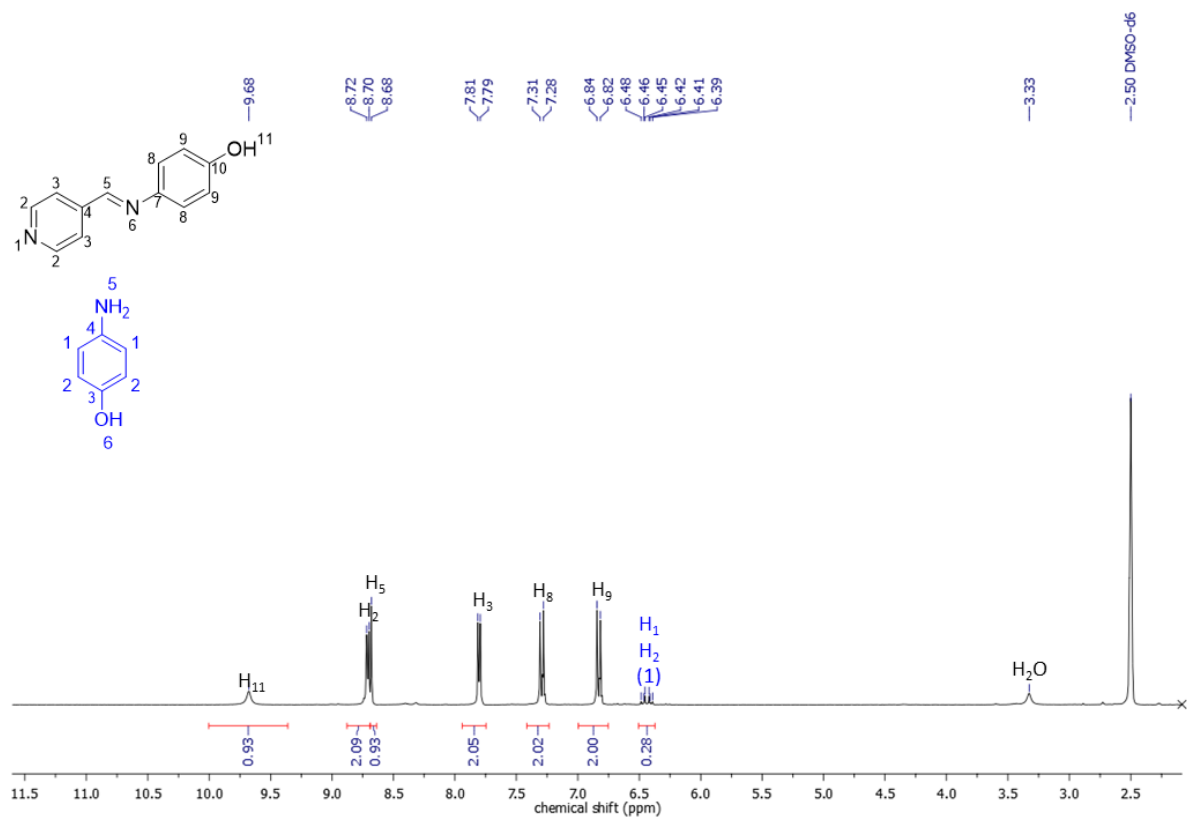


Figure S2. ¹H NMR spectrum of 3a.

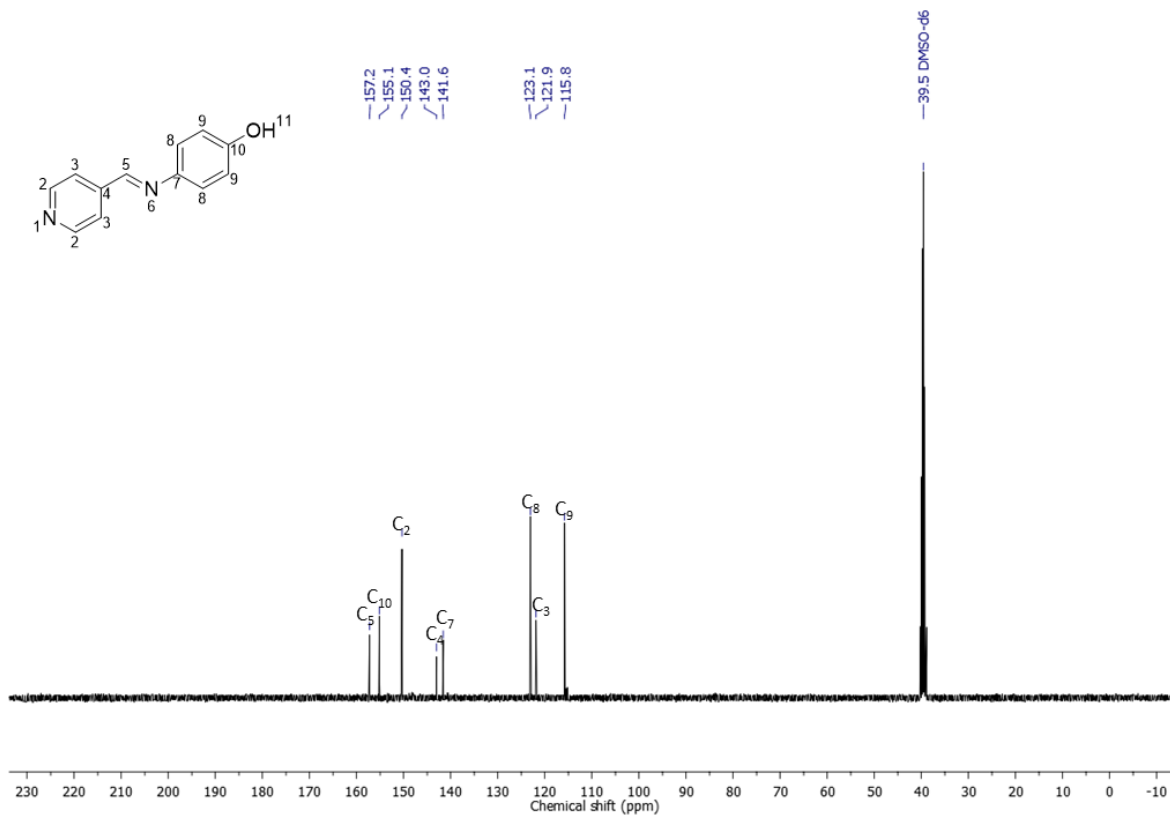


Figure S3. ¹³C NMR spectrum of 3a.

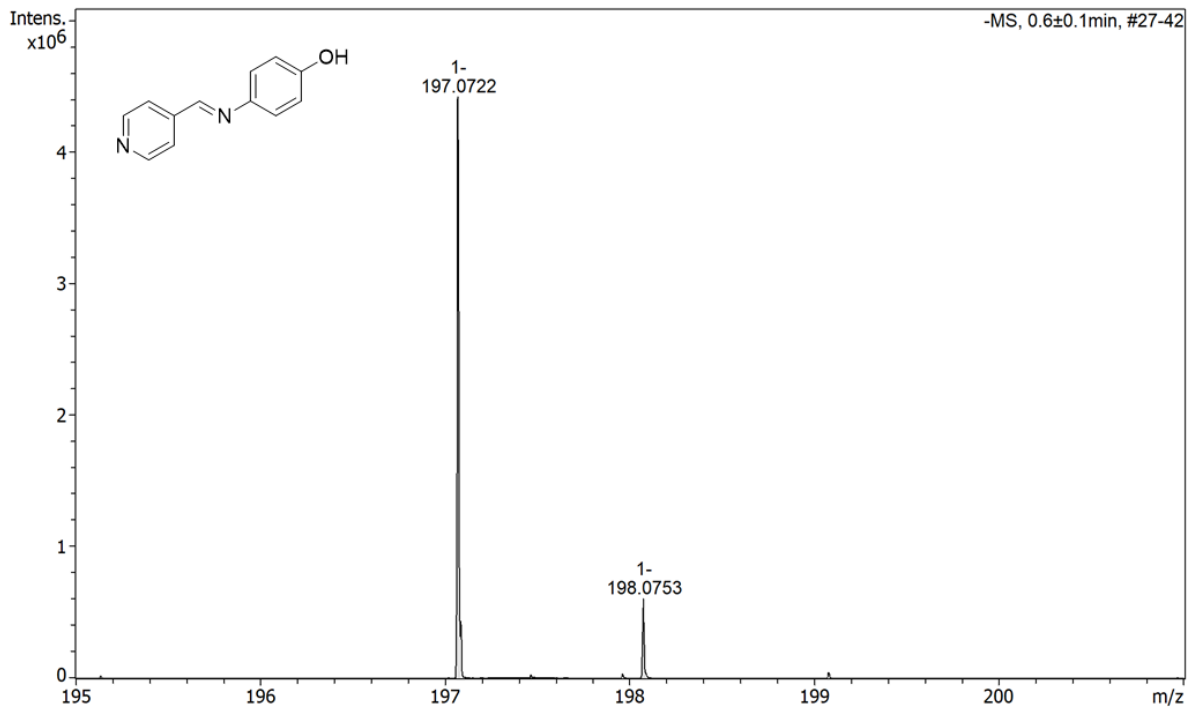


Figure S4. Registered ESI-MS of **3a**.

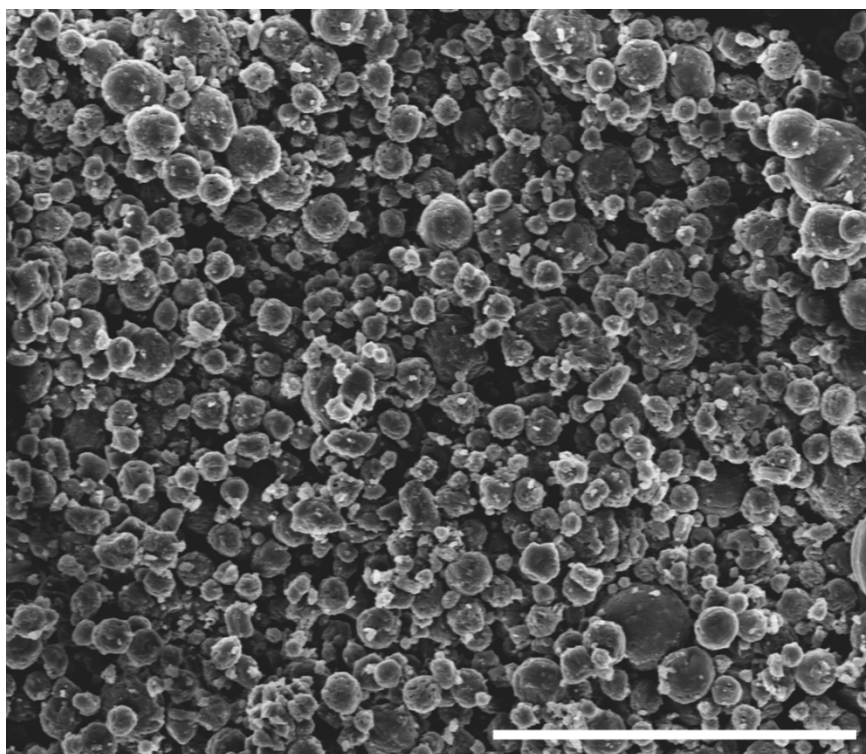


Figure S5. SEM image of **3a**. Scale bar = 20 μm .

Synthesis of (E)-4-benzylideneaminophenol (**3b**)

5.00 mmol of 4-aminophenol and 5.00 mmol of benzaldehyde (Table S1, Entry 1) were dissolved in 25 mL ethanol and fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer (BUCHI Labortechnik; spray cap: 0.5-mm-hole) with an inlet temperature of 130 °C and a sheath N₂ flow rate of 357 L·h⁻¹. After 8.33 minutes, a pale-yellow solid was obtained and characterized by ¹H qNMR, revealing that **3b** was directly produced from the spray-drier with a purity of 90%. To further purify it, the solid was dissolved in 30 mL of ethyl acetate and extracted with 3 × 30 mL of 0.01 M HCl. The organic phase was dried over 4 Å molecular sieves, and the solvent was removed under reduced pressure, yielding **3b** with a 62% yield.

In a second reaction, the spray-drying synthesis was repeated using 6.50 mmol of benzaldehyde (Table S2, Entry 2). Under these new conditions, **3b** was obtained with a purity of 97% and a yield of 85%.

¹H NMR (400 MHz, DMSO) δ 9.51 (s, 1H), 8.61 (s, 1H), 7.89 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.65 – 7.43 (m, 3H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 157.2, 156.3, 142.6, 136.5, 130.8, 128.7, 128.2, 122.5, 115.7.^[2] ESI-MS *m/z* calculated for [C₁₃H₁₀NO⁻]: 196.0768, found: 196.0770.

Table S1. Spray-drying synthesis of **3b**.

Entry	mmol 2b	1: 2b ratio	Purity (%)	Yield (%)
1	5.00	1:1	90	62 ^[a]
2	6.50	1:1.3	97	85 ^[b]

a]: After work-up. [b]: No work-up was done as purity of collected crude ≥ 95%.

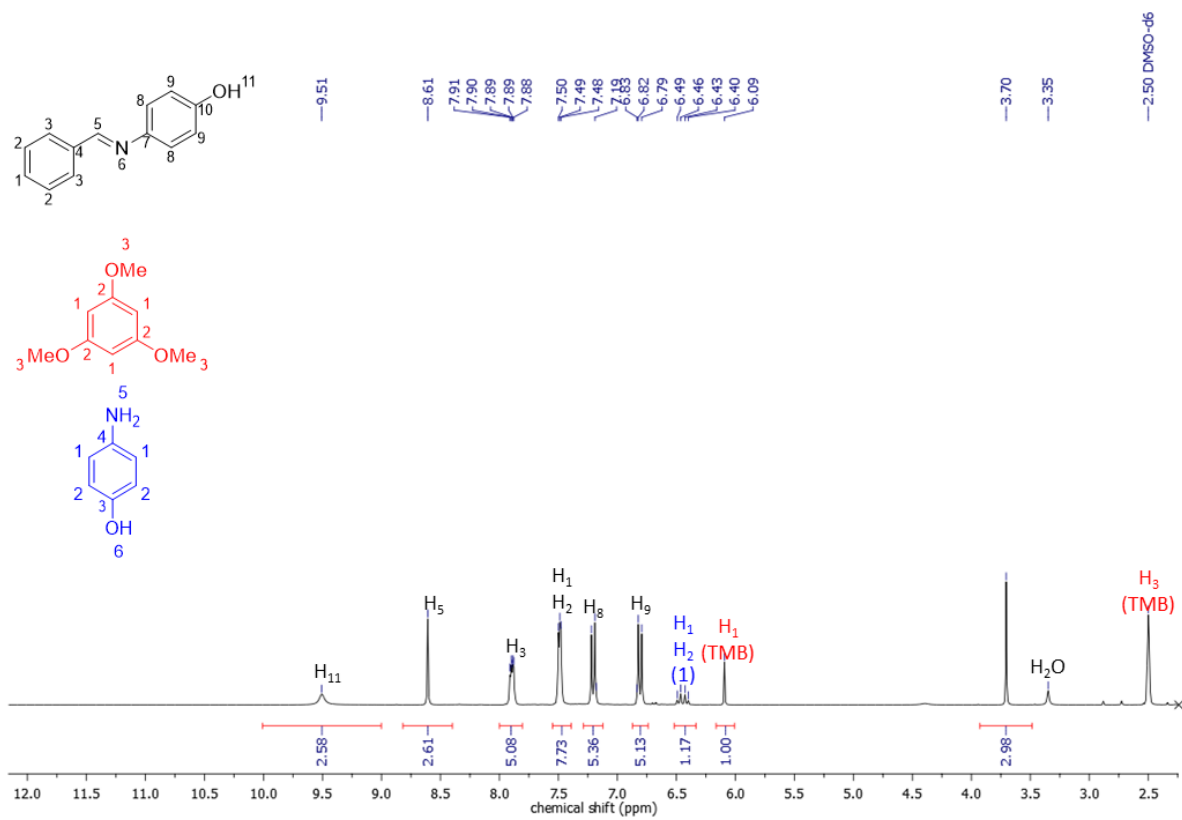


Figure S6. qNMR spectrum of **3b** crude (**1:2b** molar ratio = 1:1; Table S1, Entry 1).

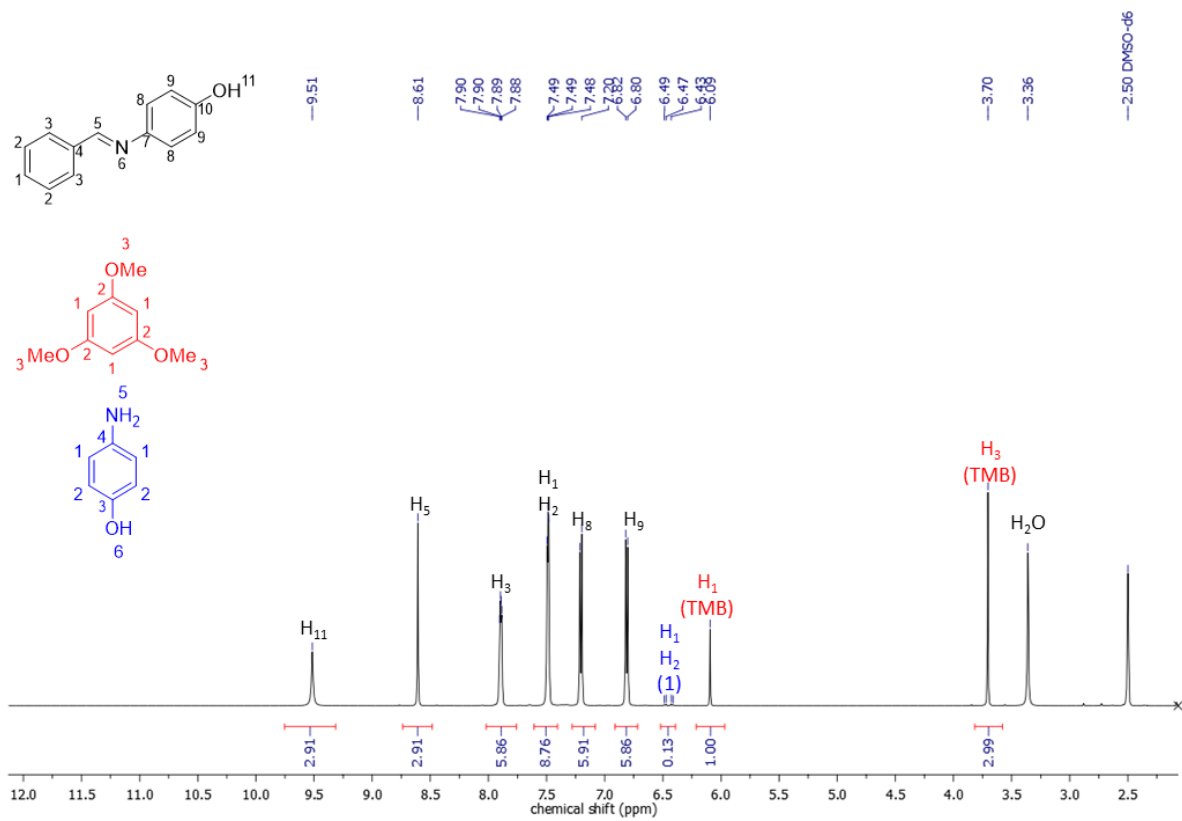


Figure S7. qNMR spectrum of **3b** crude (**1:2b** molar ratio = 1:1.3; Table S1, Entry 2)).

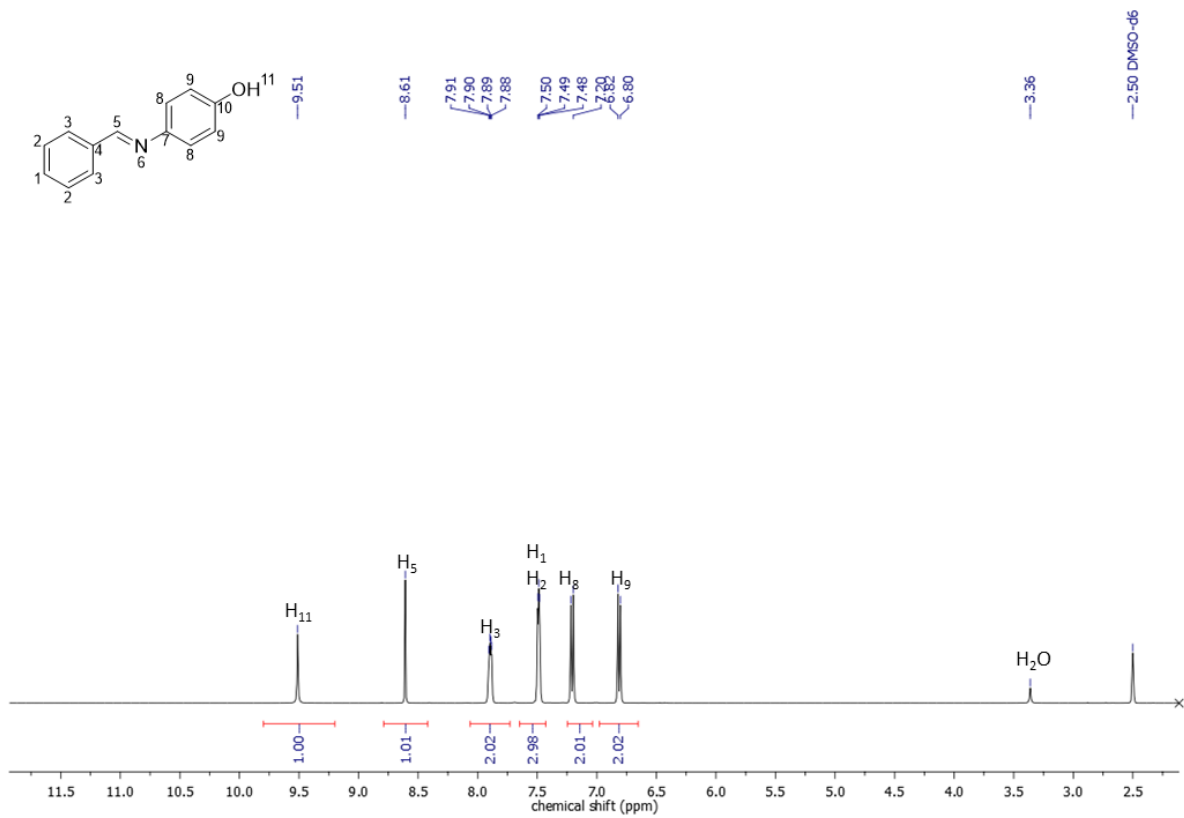


Figure S8. ¹H NMR spectrum of **3b**.

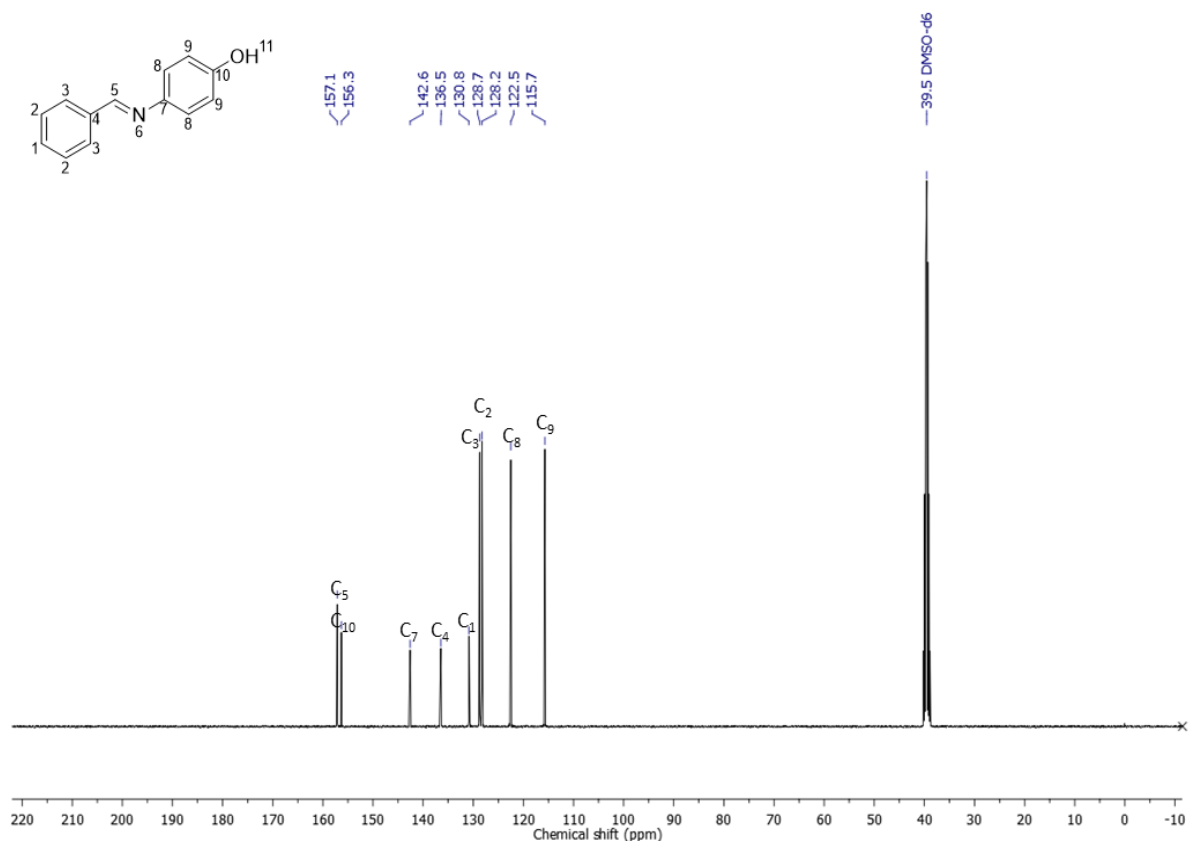


Figure S9. ¹³C NMR spectrum of **3b**.

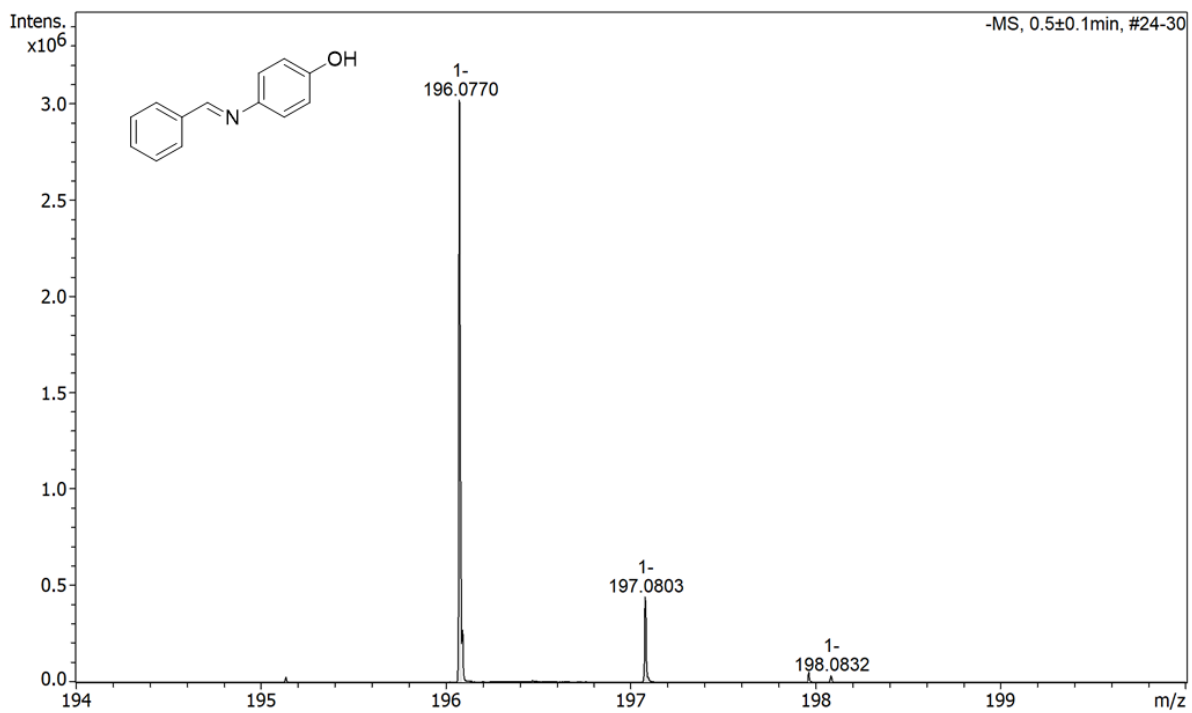


Figure S10. Registered ESI-MS of **3b**.

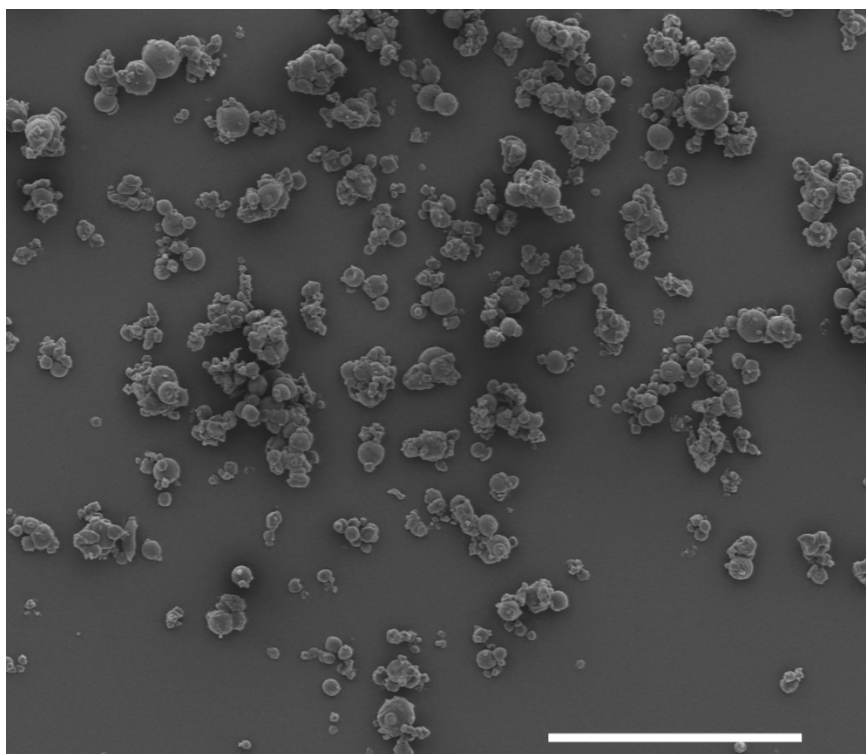


Figure S11. SEM images of collected **3b**. Scale bar = 50 μm .

Synthesis of (E)-4-(4-methoxybenzylidene)aminophenol (**3c**)

5.00 mmol of 4-aminophenol and 5.00 mmol (Table S2, Entry 1), 6.50 mmol (Table S2, Entry 2) or 10.0 mmol (Table S2, Entry 3) of benzaldehyde were dissolved in 25 mL ethanol and fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer (BUCHI Labortechnik; spray cap: 0.5-mm-hole) with an inlet temperature of 130 °C and a sheath gas flow rate of 357 L·h⁻¹. After 8.33 minutes, a pale-yellow solid was obtained and characterized by ¹H qNMR, revealing that **3c** was directly produced from the spray-drier with a purity of 44%, 59% and 73%, respectively. To further purify it, the solids were dissolved in 30 mL of ethyl acetate and extracted with 3 × 30 mL of 0.01 M HCl. The organic phases were dried over 4 Å molecular sieves, and the solvent was removed under reduced pressure, yielding **3c** with a 16%, 34% and 44% yield.

In a fourth reaction, the spray-drying synthesis was repeated using 15.0 mmol of benzaldehyde (Table S2, Entry 4). Under these new conditions, **3c** was obtained directly from the spray-drier with a purity of 97% and a yield of 80%.

¹H NMR (400 MHz, DMSO) δ 9.43 (s, 1H), 8.51 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 161.4, 156.6, 155.9, 148.2, 143.0, 140.7, 130.0, 129.4, 122.2, 115.7, 115.5, 115.2, 114.2, 55.3.^[3] ESI-MS m/z calculated for [C₁₄H₁₂NO₂]⁺: 226.0873, found: 226.0876.

Table S2. Spray-drying synthesis of **3c**

Entry	mmol 2b	1: 2b ratio	Purity (%)	Yield (%)
1	5.00	1:1.0	44	16 ^[a]
2	6.50	1:1.3	59	34 ^[a]
3	10.0	1:2.0	73	44 ^[a]
4	15.0	1:3.0	97	80 ^[b]

[a]: After work-up [b]: No work-up was done as purity of collected crude ≥ 95%.

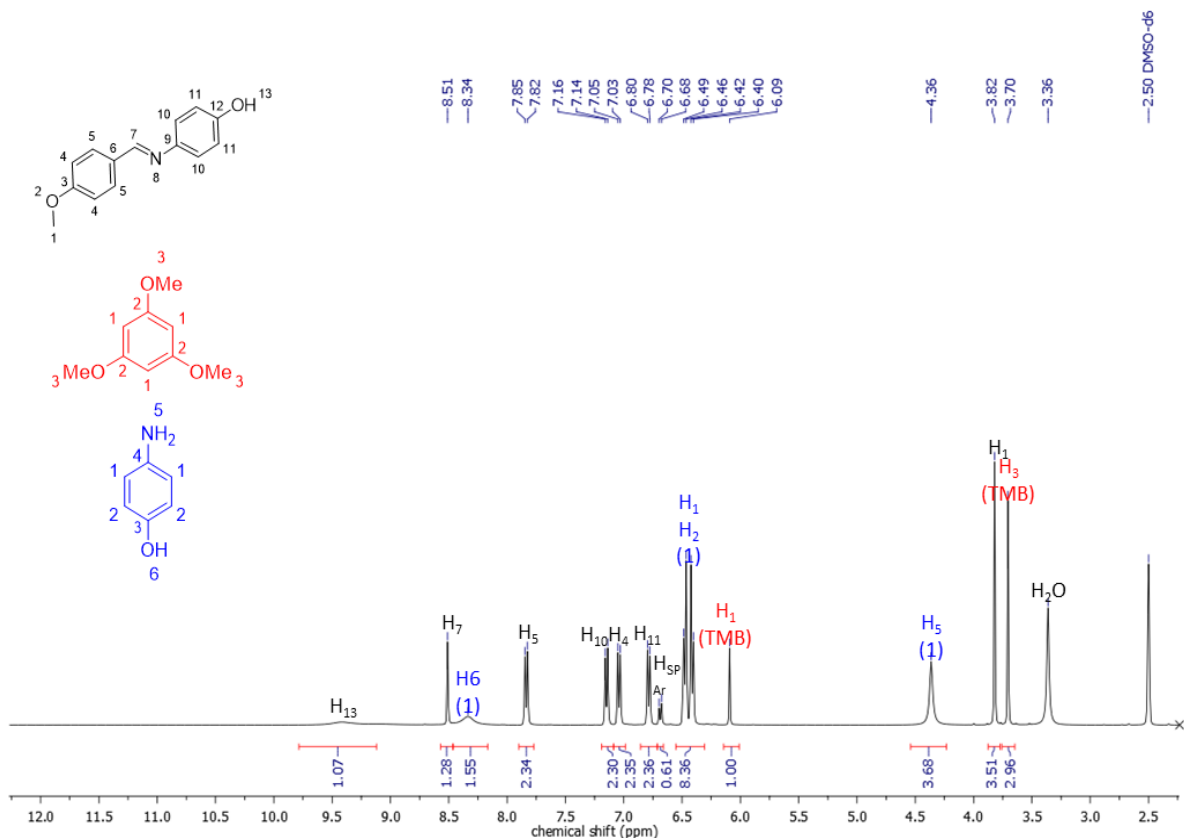


Figure S12. qNMR spectrum of **3b** crude (**1:2c** molar ratio = 1:1.0; Table S2, Entry 1). SP: Side-product; Ar: aromatic signal.

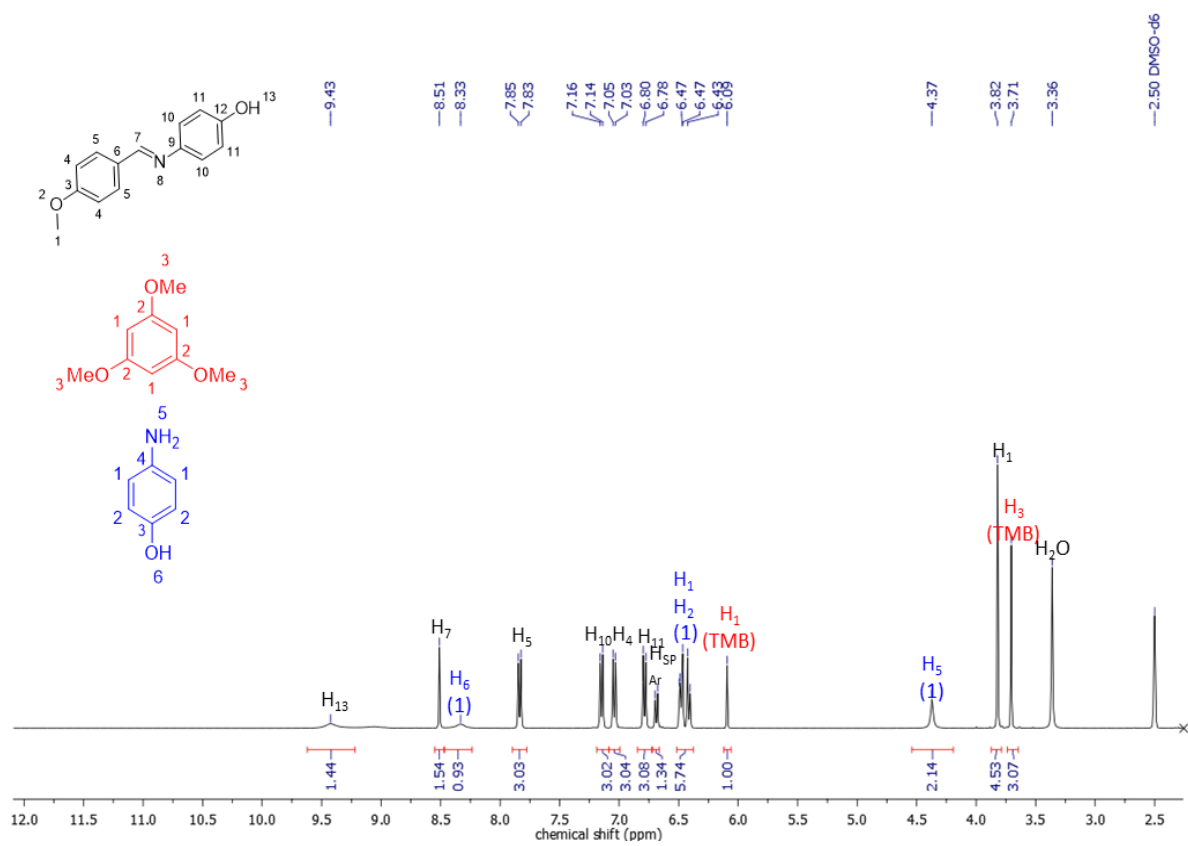


Figure S13. qNMR spectrum of **3b** crude (**1:2b** molar ratio = 1:1.3; Table S2, Entry 2). SP: Side-product; Ar: aromatic signal.

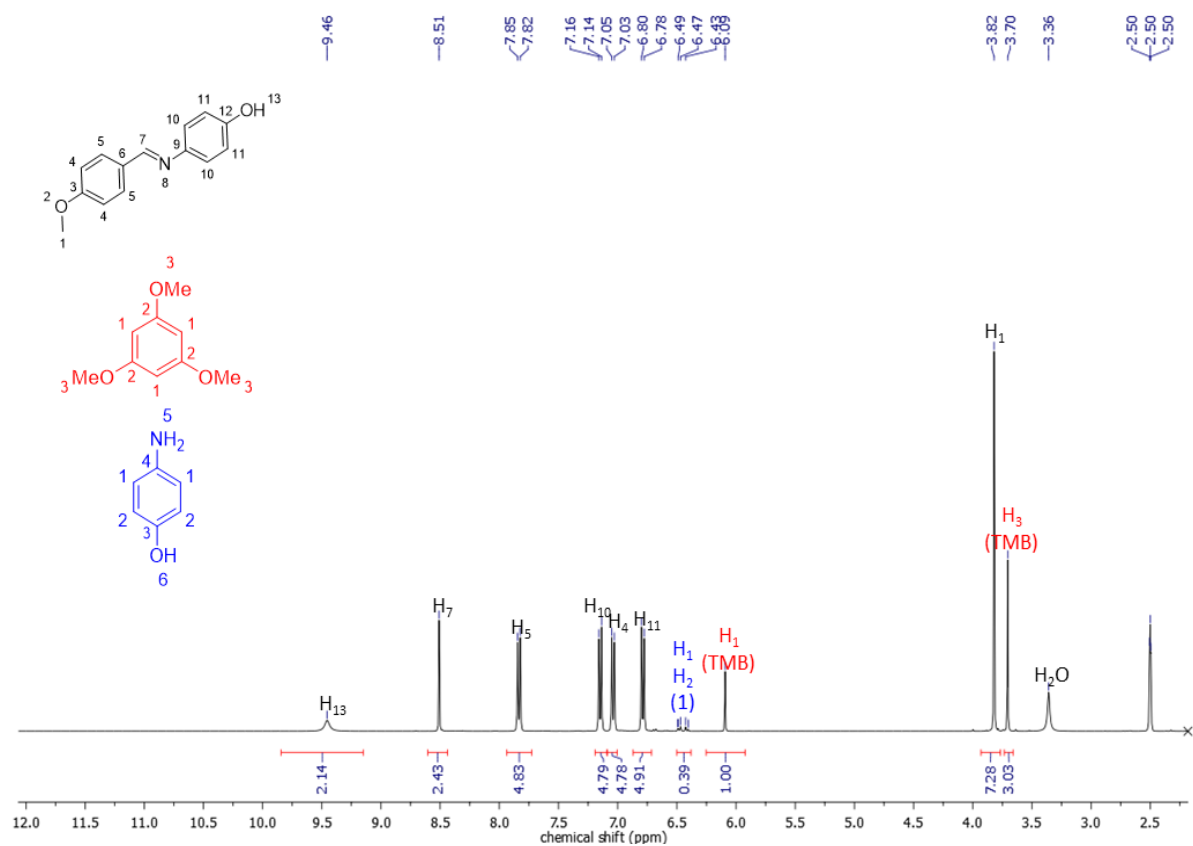


Figure S14. qNMR spectrum of **3b** crude (**1:2b** molar ratio = 1:2.0; Table S2, Entry 3).

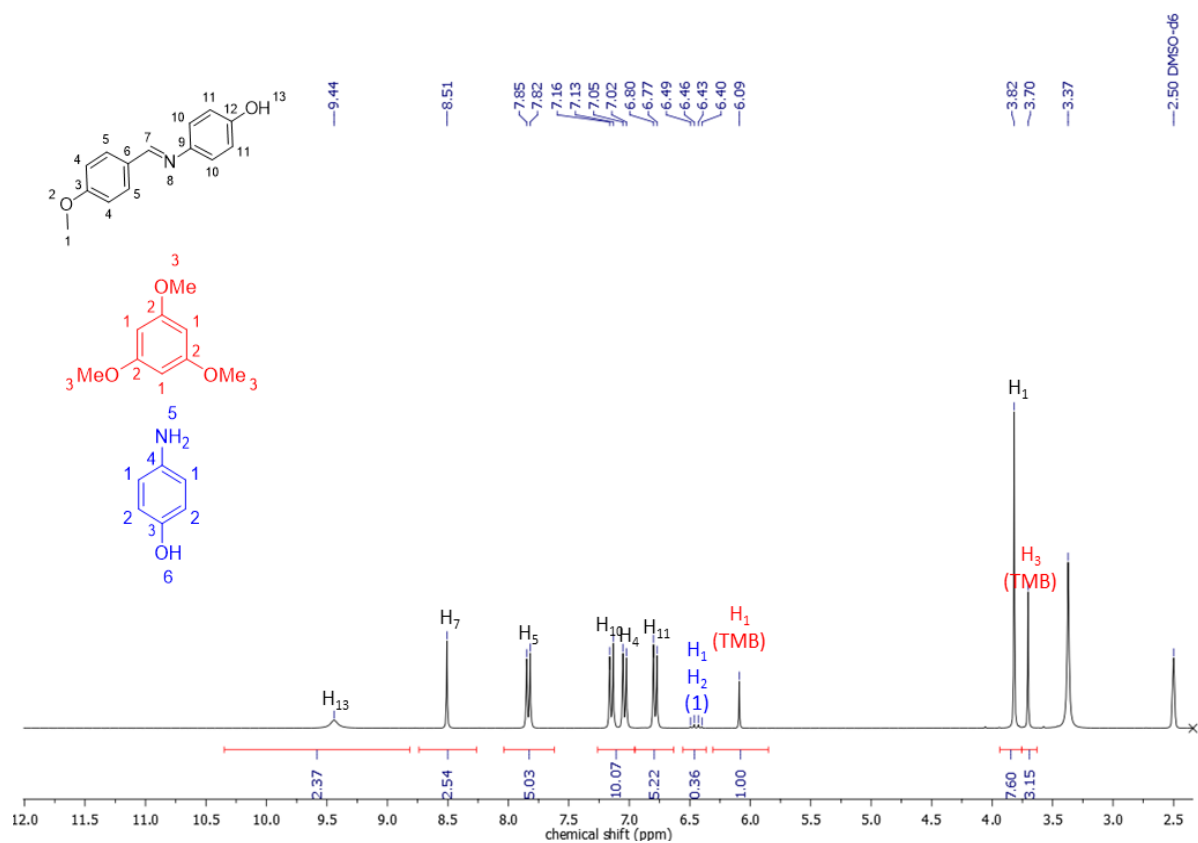


Figure S15. ¹H qNMR spectrum of **3b** crude (1:2**b** molar ratio = 1:3.0; Table S2, Entry 4).

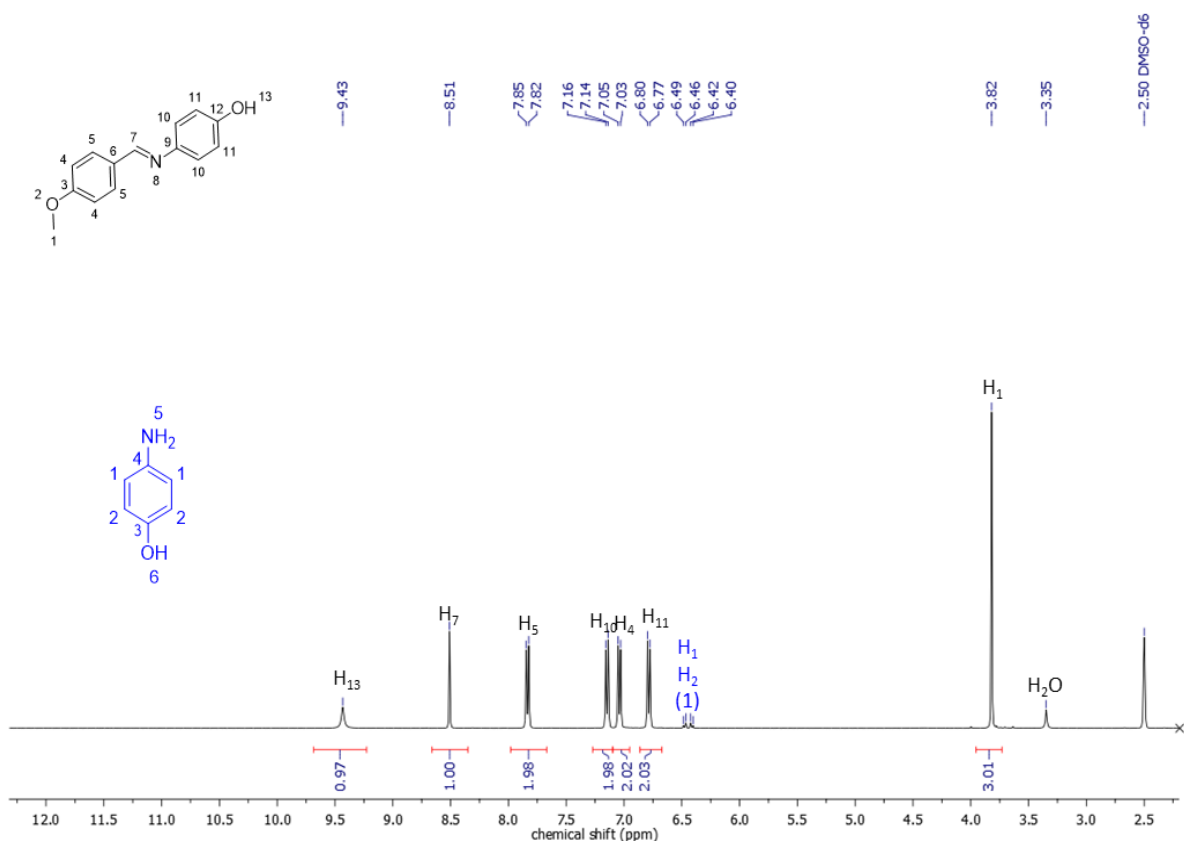


Figure S16. ¹H NMR spectrum of **3c**.

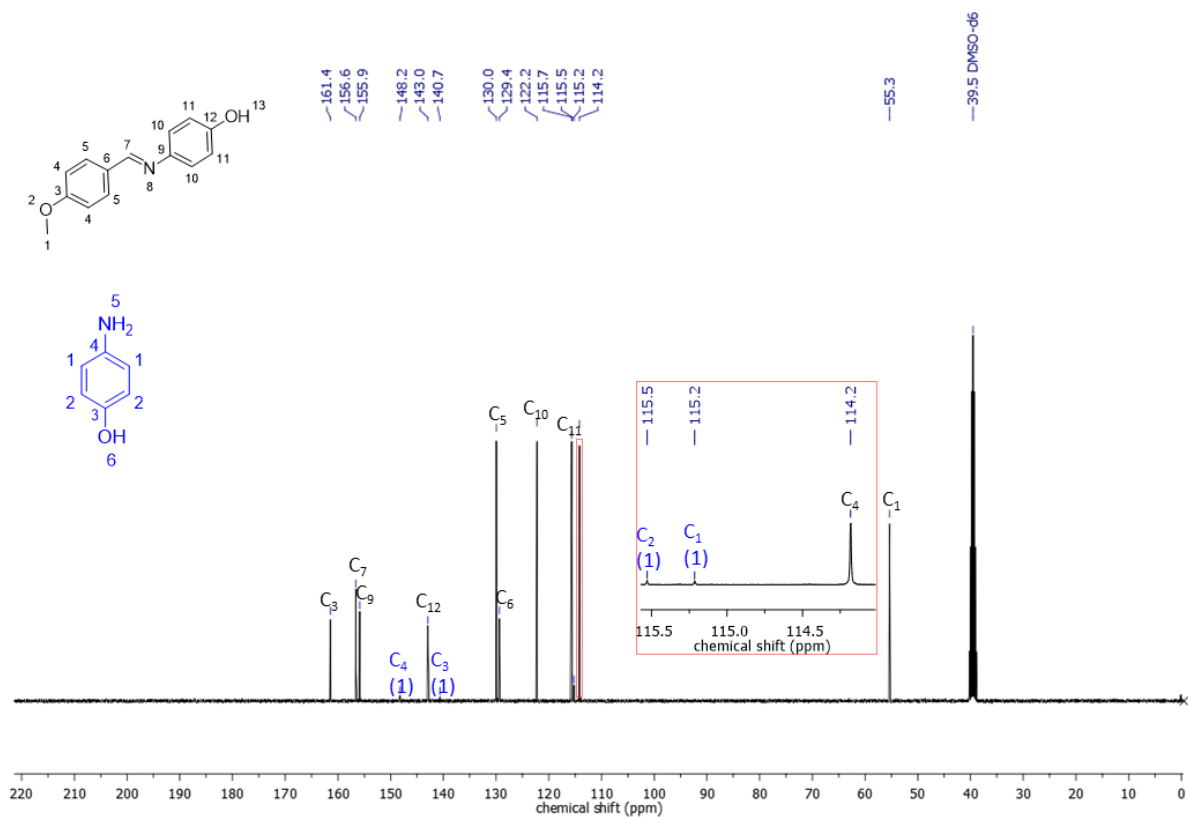


Figure S17. ^{13}C NMR spectrum of **3c**.

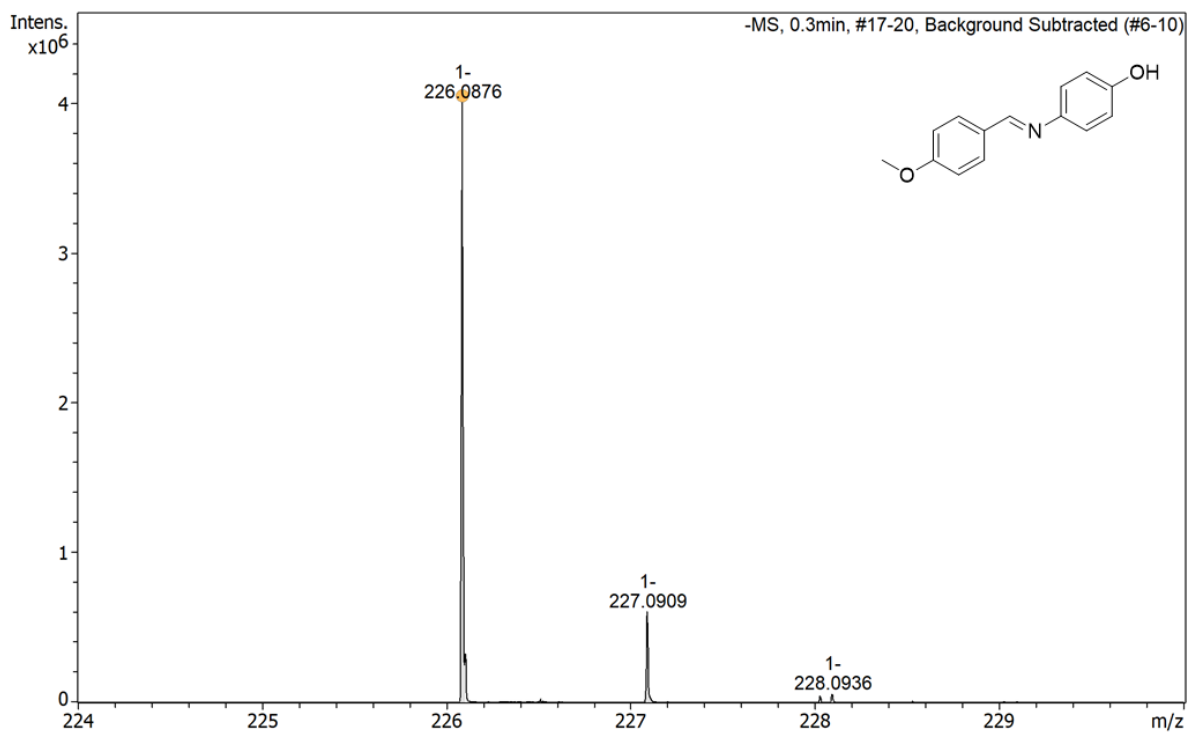


Figure S18. Registered ESI-MS of **3c**.

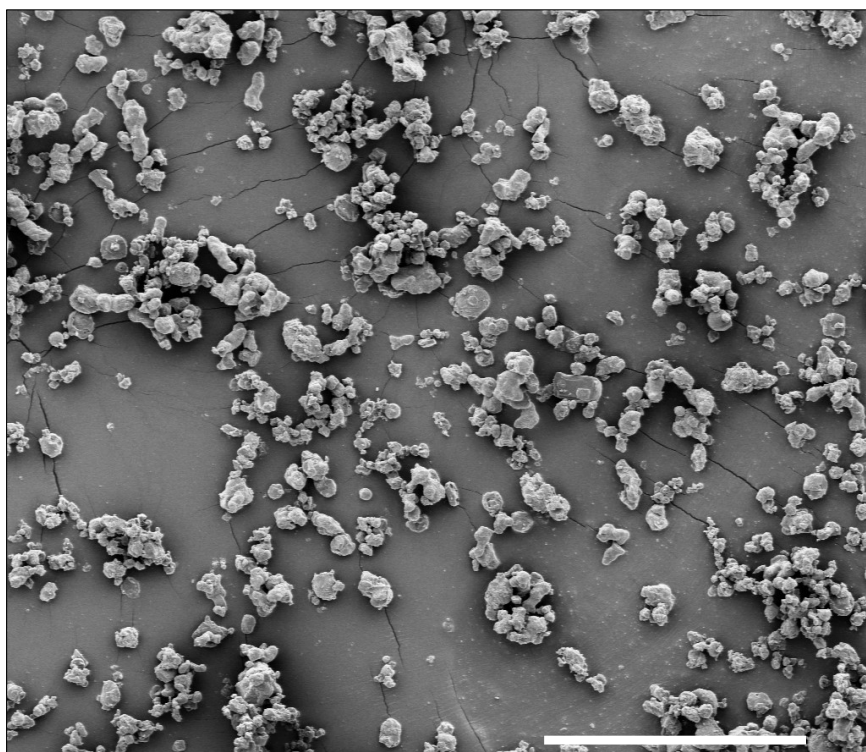


Figure S19. SEM images of collected **3c**. Scale bar = 100 μm .

Section S3: Synthesis and characterization of Claisen-Schmidt adducts.

Synthesis of (E)-6-hydroxy-2-(pyridine-4-ylmethylene)-2,3-dihydro-1H-inden-1-one (5a)

5.00 mmol of 6-hydroxy-1-indanone and 10.0 mmol of KOH were dissolved in 20 mL methanol and stirred at 0 °C for 15 min. Afterwards, 5.00 mmol (Table S3, Entry 1), 6.50 mmol (Table S3, Entry 2), or 7.50 mmol (Table S3, Entry 3) of 4-pyridincarboxaldehyde were added and the volume was adjusted to 25.0 mL with methanol. The resulting mixture was fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer (BUCHI Labortechnik; spray cap: 0.5-mm-hole) with an inlet temperature of 80 °C and a sheath N₂ flow rate of 357 L·h⁻¹. After 8.33 minutes, a red solid was obtained, which was dispersed in deionised water. The resulting mixture was acidified to pH 6-7 with HCl 1 M, and then left to rest at -20 °C for 1 hour. Finally, the solid was recovered by vacuum filtration, dried at 85 °C under vacuum overnight, and characterized by ¹H qNMR, revealing that **5a** was directly produced from the spray-drier with a purity of 76%, 90% and 93%, respectively. To further purify it, the solids were recrystallized from methanol, yielding **5a** with a 55%, 49% and 55% yield.

In a fourth reaction, the spray-drying synthesis was repeated using 8.50 mmol of 4-pyridincarboxaldehyde (Table S3, Entry 4). Under these new conditions, **5a** was obtained directly from the spray-drier with a purity of 96% and a yield of 79%.

¹H NMR (400 MHz, DMSO) δ 9.91 (s, 1H), 9.91 (s, 1H), 8.68 (d, J = 5.3 Hz, 2H), 8.68 (d, J = 5.3 Hz, 2H), 7.69 (d, J = 5.3 Hz, 2H), 7.69 (d, J = 5.3 Hz, 2H), 7.48 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.43 (s, 1H), 7.43 (s, 1H), 7.17 (dd, J = 8.2, 1.8 Hz, 1H), 7.17 (dd, J = 8.2, 1.8 Hz, 1H), 7.09 (s, 1H), 7.09 (s, 1H), 4.04 (s, 2H), 4.04 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 193.1, 157.3, 150.3, 142.0, 141.0, 140.5, 138.1, 129.5, 127.6, 124.2, 124.1, 108.3, 31.0.

ESI-MS m/z calculated for [C₁₅H₁₀NO₂]: 236.07170, found: 236.0718.^[4]

Table S3. Spray-drying synthesis of **5a**.

Entry	mmol 2b	4:2b ratio	Purity (%)	Yield (%)
1	5.00	1:1.0	76	55 ^[a]
2	6.50	1:1.3	90	49 ^[a]
3	7.50	1:1.5	93	55 ^[a]
4	8.50	1:1.7	96	79 ^[b]

[a]: After recrystallization [b] No recrystallization was done as purity was ≥95%

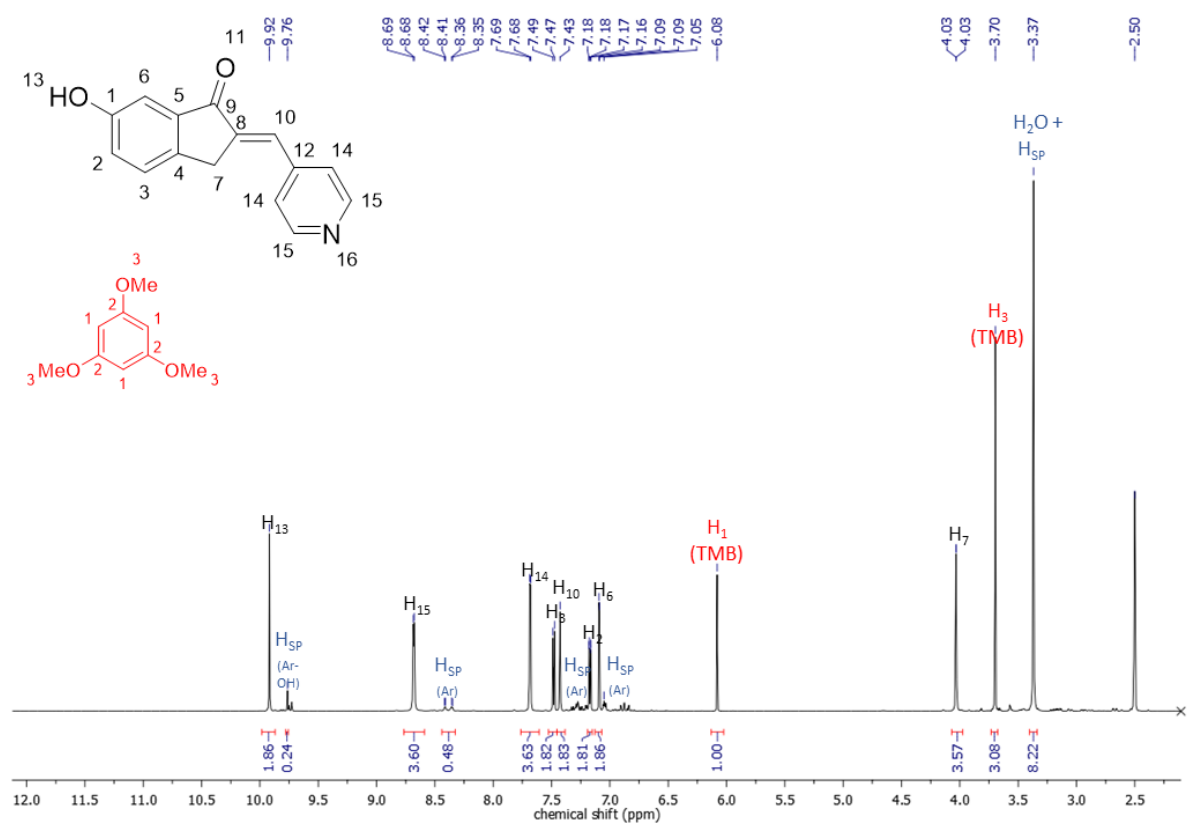


Figure S20. qNMR spectrum of **5a** crude (**1:2a** molar ratio = 1:1.0; Table S3, Entry 1). SP: side-product; Ar-OH: hydroxylic ^1H attached to an aromatic ring; and Ar: Aromatic signal.

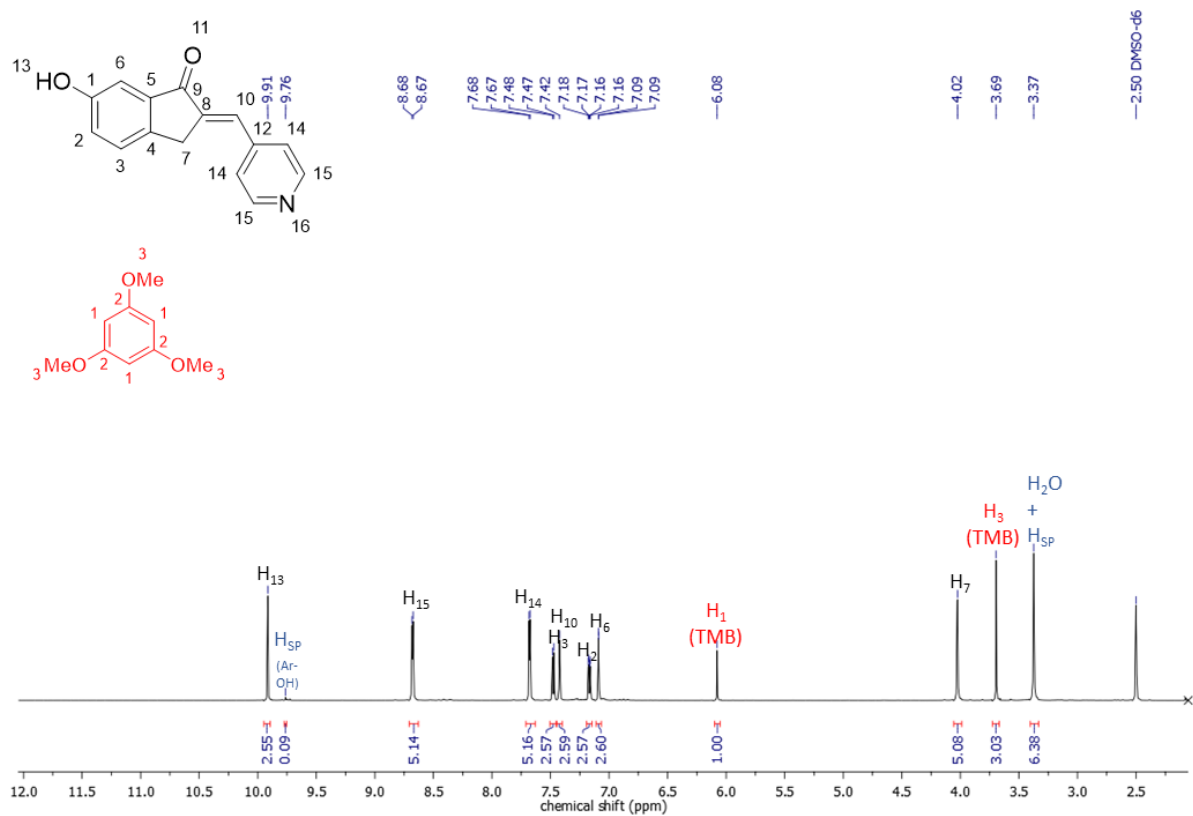


Figure S21. qNMR spectrum of **5a** crude (**1:2a** molar ratio = 1:1.3; Table S3, Entry 2). SP: side-product; Ar-OH: hydroxylic ¹H attached to an aromatic ring; Ar: Aromatic signal.

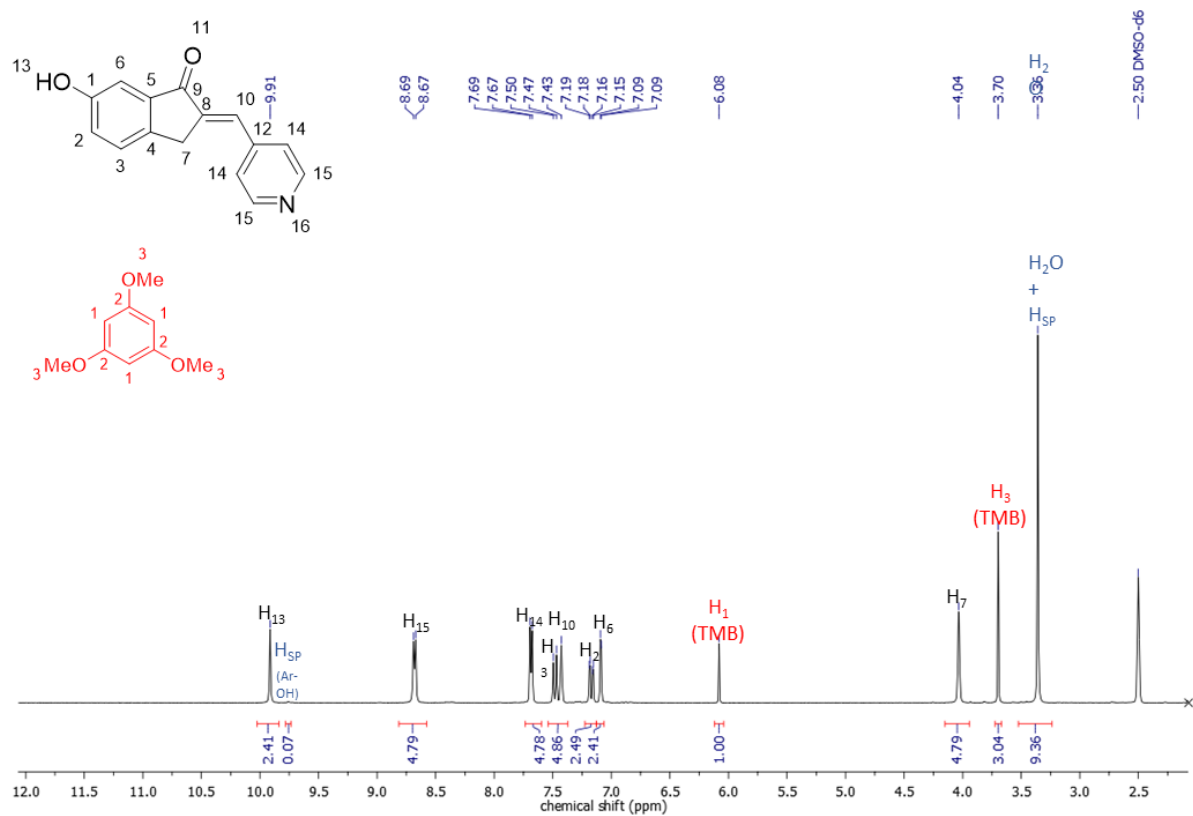


Figure S22. qNMR spectrum of **5a** crude (1:2a molar ratio = 1:1.5; Table S3, Entry 3). SP: side-product; Ar-OH: hydroxylic ¹H attached to an aromatic ring.

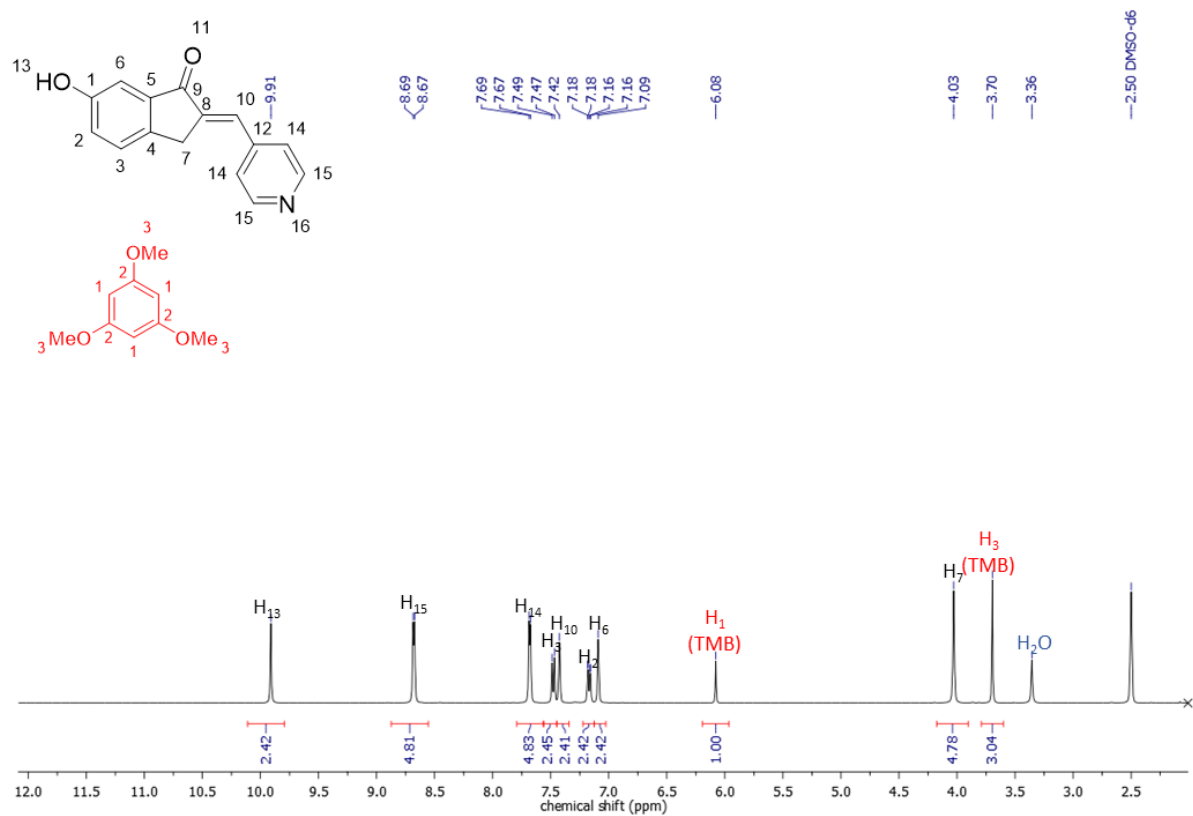


Figure S23. qNMR spectrum of **5a** crude (1:2a molar ratio = 1:1.7; Table S3, Entry 4).

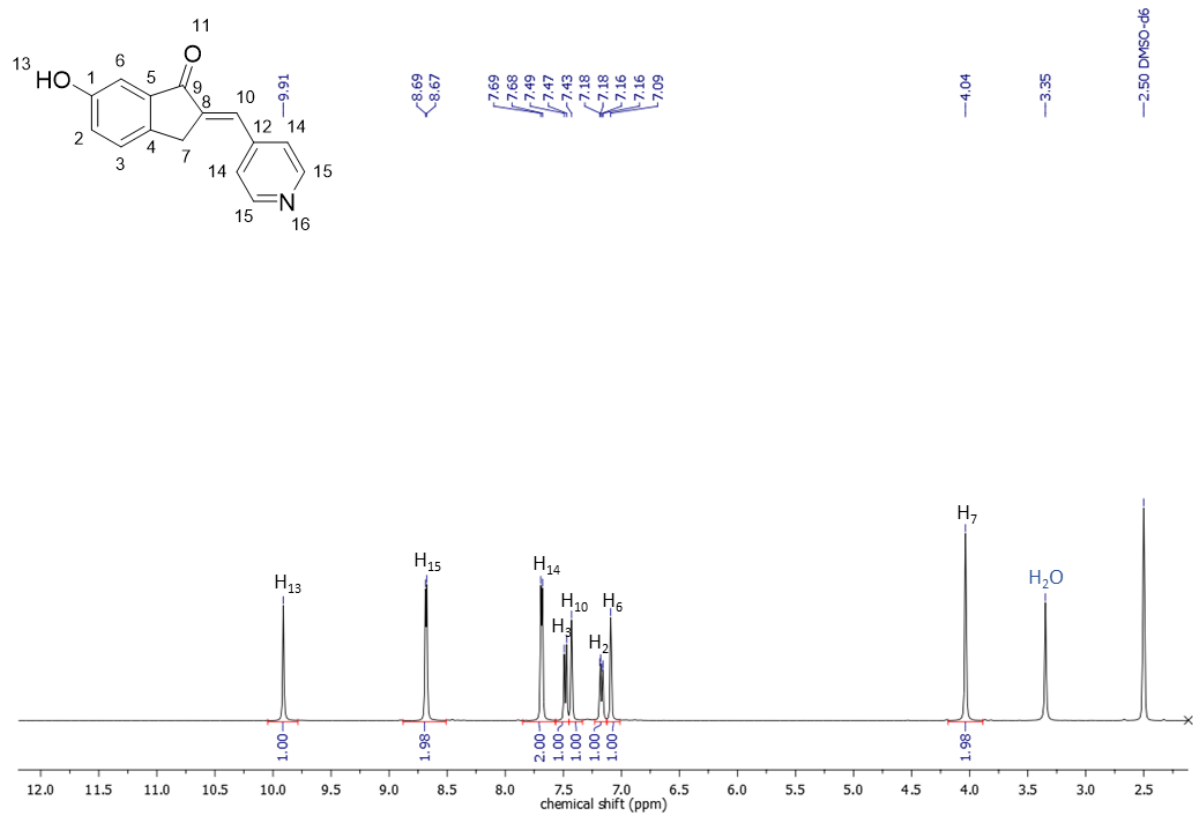


Figure S24. ¹H NMR spectrum of **5a**.

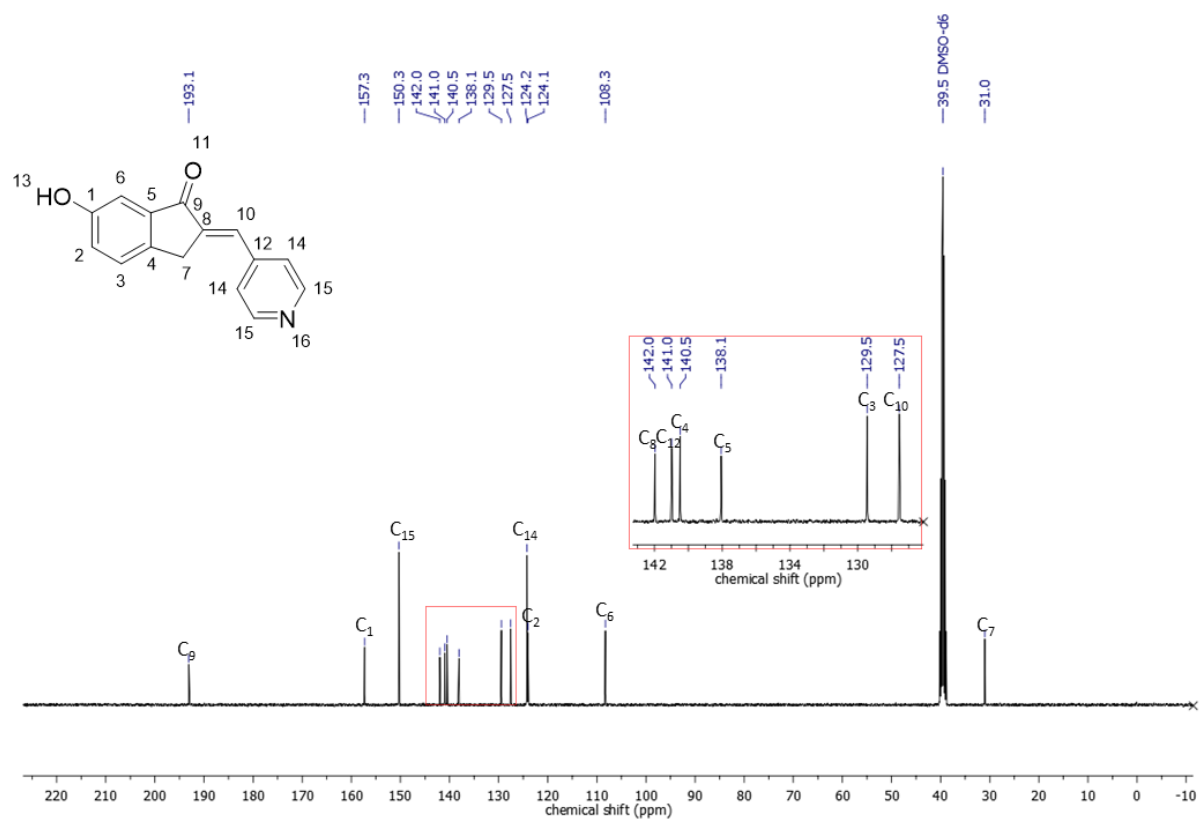


Figure S25. ¹³C NMR spectrum of 5a.

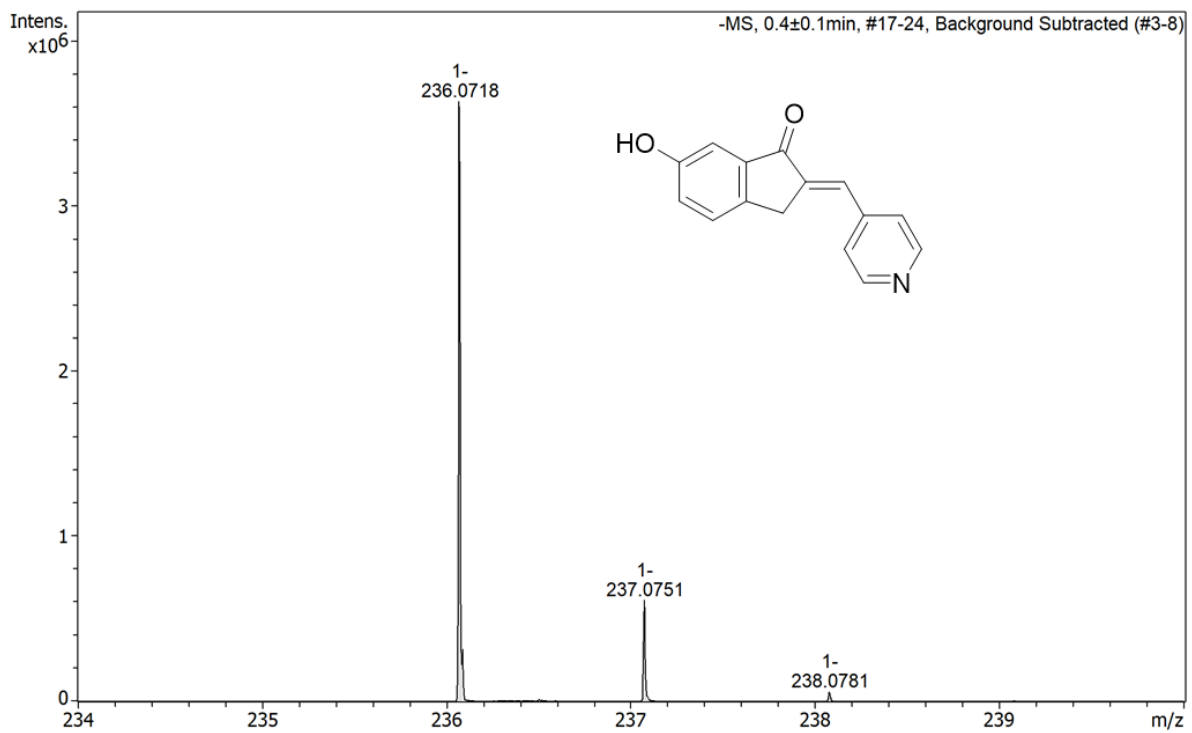


Figure S26. Registered ESI-MS of **5a**.

Synthesis of (E)-6-hydroxy-2 benzylidene-2,3-dihydro-1H-inden-1-one (**5b**)

5.00 mmol of 6-hydroxy-1-indanone and 10.0 mmol of KOH were dissolved in 20 mL methanol and stirred at 0 °C for 15 min. Afterwards, 5.00 mmol (Table S4, Entry 1), 6.50 mmol (Table S4, Entry 2), 7.50 mmol (Table S4, Entry 3) or 8.50 mmol (Table S4, Entry 4) of benzaldehyde were added and the volume was adjusted to 25.0 mL with methanol. The resulting mixture was fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer (BUCHI Labortechnik; spray cap: 0.5-mm-hole) with an inlet temperature of 80 °C and a sheath N₂ flow rate of 357 L·h⁻¹. After 8.33 minutes, a red solid was obtained, which was dispersed in deionised water. The resulting mixture was acidified to pH 6-7 with HCl 1 M, and then left to rest at -20 °C for 1 hour. Finally, the solid was recovered by vacuum filtration, dried at 85 °C under vacuum overnight, and characterized by ¹H qNMR, revealing that **5b** was directly produced from the spray-drier with a purity of 92%, 86%, 94% and 92%, respectively. To further purify it, the solids were recrystallized from methanol, yielding **5b** with a 41%, 46%, 51% and 65% yield.

In a fifth reaction, the spray-drying synthesis was repeated using 10 mmol of benzaldehyde (Table S4, Entry 5). Under these new conditions, **5b** was obtained directly from the spray-drier with a purity of 95% and a yield of 67%.

¹H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 7.76 (d, J = 7.3 Hz, 2H), 7.54 – 7.41 (m, 5H), 7.15 (dd, J = 8.2, 2.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 3.98 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 193.3, 157.2, 140.8, 138.5, 136.1, 135.0, 132.4, 130.7, 129.7, 129.0, 127.5, 123.5, 108.2, 31.2. ESI-MS m/z calculated for [C₁₆H₁₁O₂]: 235.07645, found: 235.0764.^[5]

Table S4: Optimization of yield and purity for the synthesis of **5b**

Entry	Mmol 2b	4:2b ratio	Purity (%)	Yield (%)
1	5.00	1:1.0	92	41 ^[a]
2	6.50	1:1.3	86	46 ^[a]
3	7.50	1:1.5	94	51 ^[a]
4	8.50	1:1.7	92	65 ^[a]
5	10.0	1:2.0	95	67 ^[b]

[a]: After recrystallization [b] No recrystallization was done as purity was ≥95%

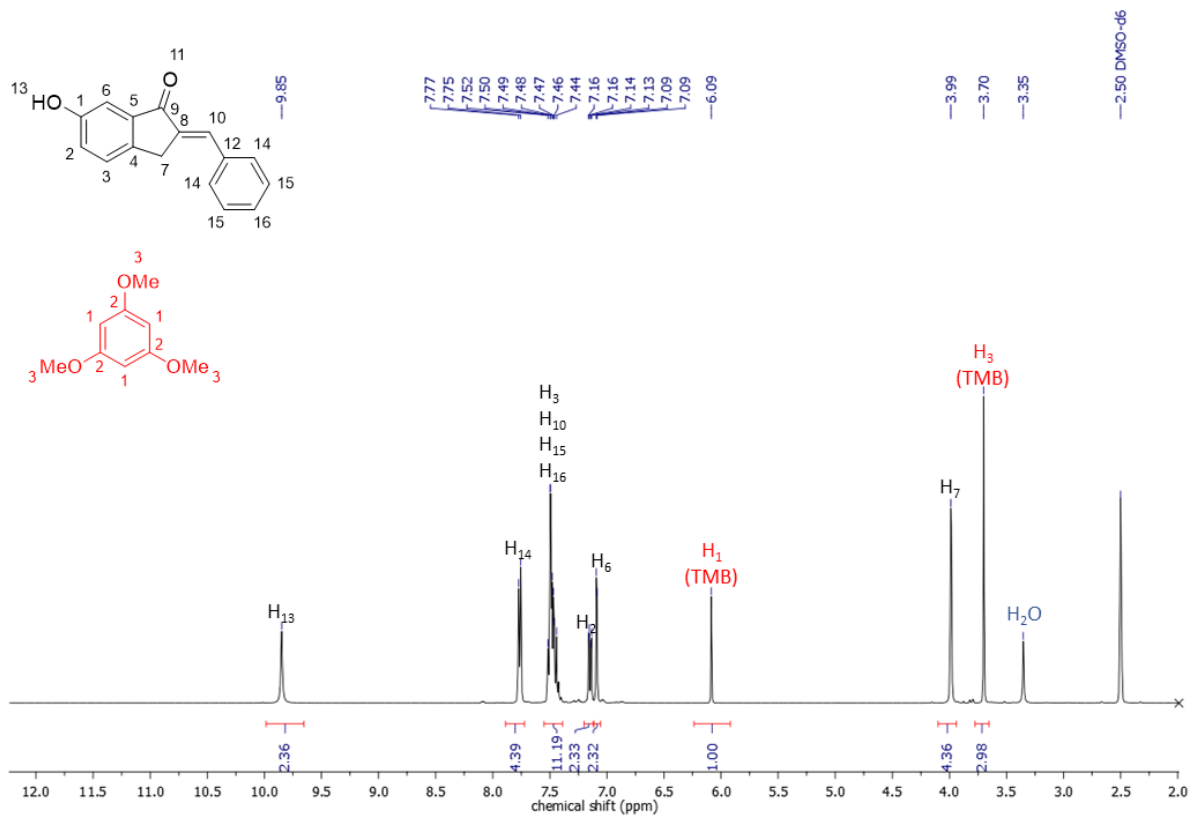


Figure S27. qNMR spectrum of **5b** crude (1:**2b** molar ratio = 1:1.0; Table S4, Entry 1).

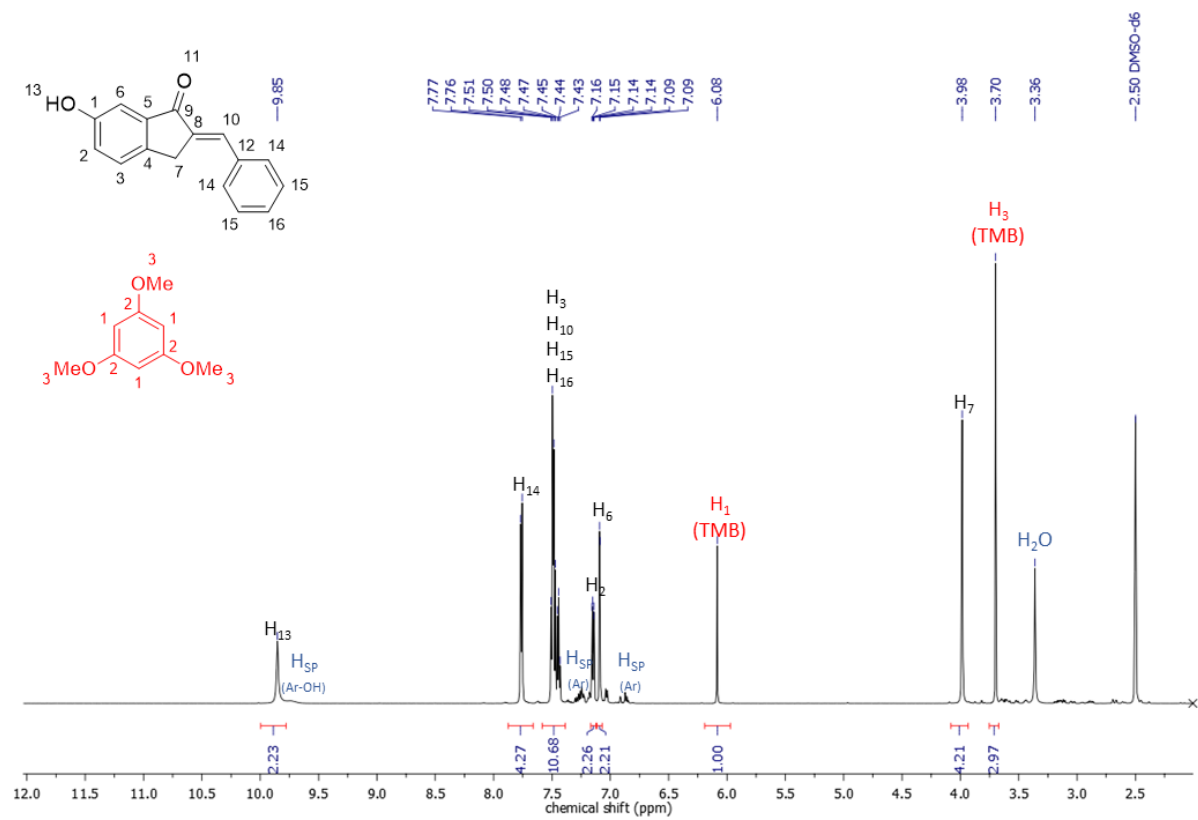


Figure S28. qNMR spectrum of **5a** crude (**1:2b** molar ratio = 1:1.3; Table S4, Entry 2).

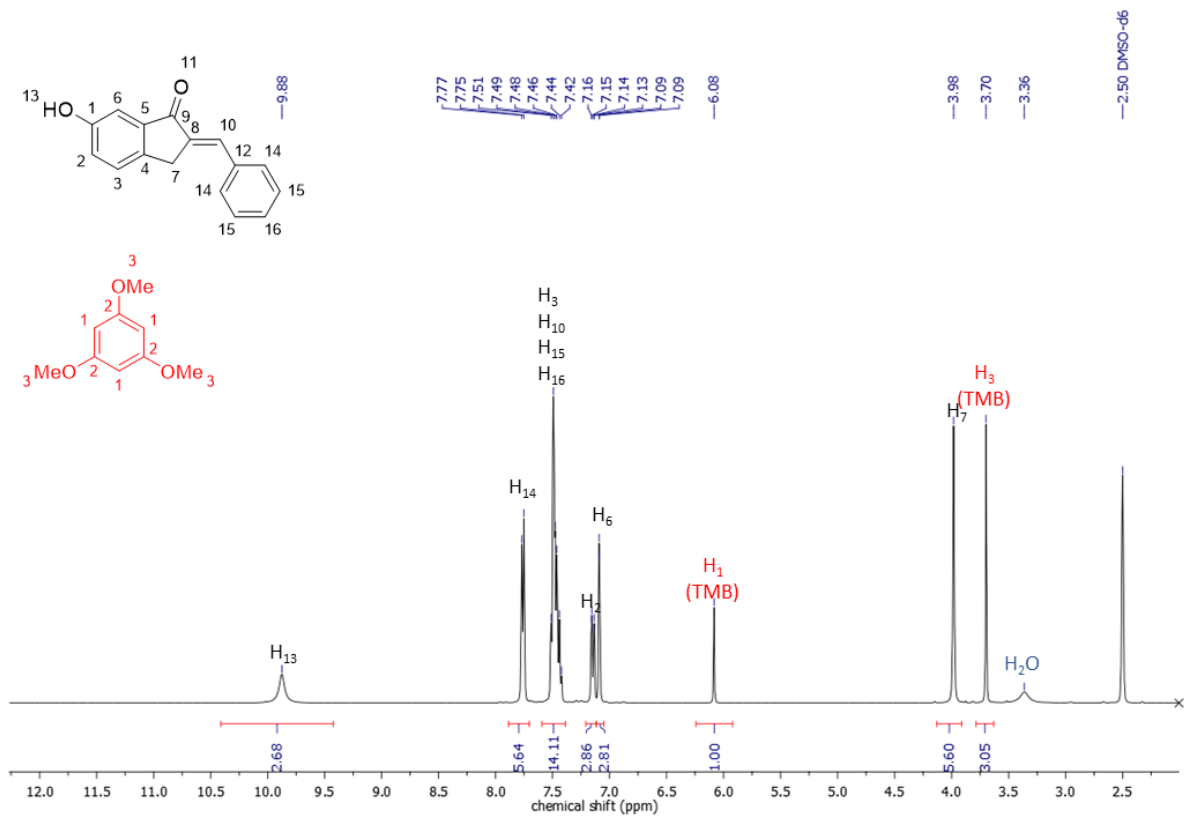


Figure S29. qNMR spectrum of **5b** crude (1:2a molar ratio = 1:1.5; Table S4, Entry 3).

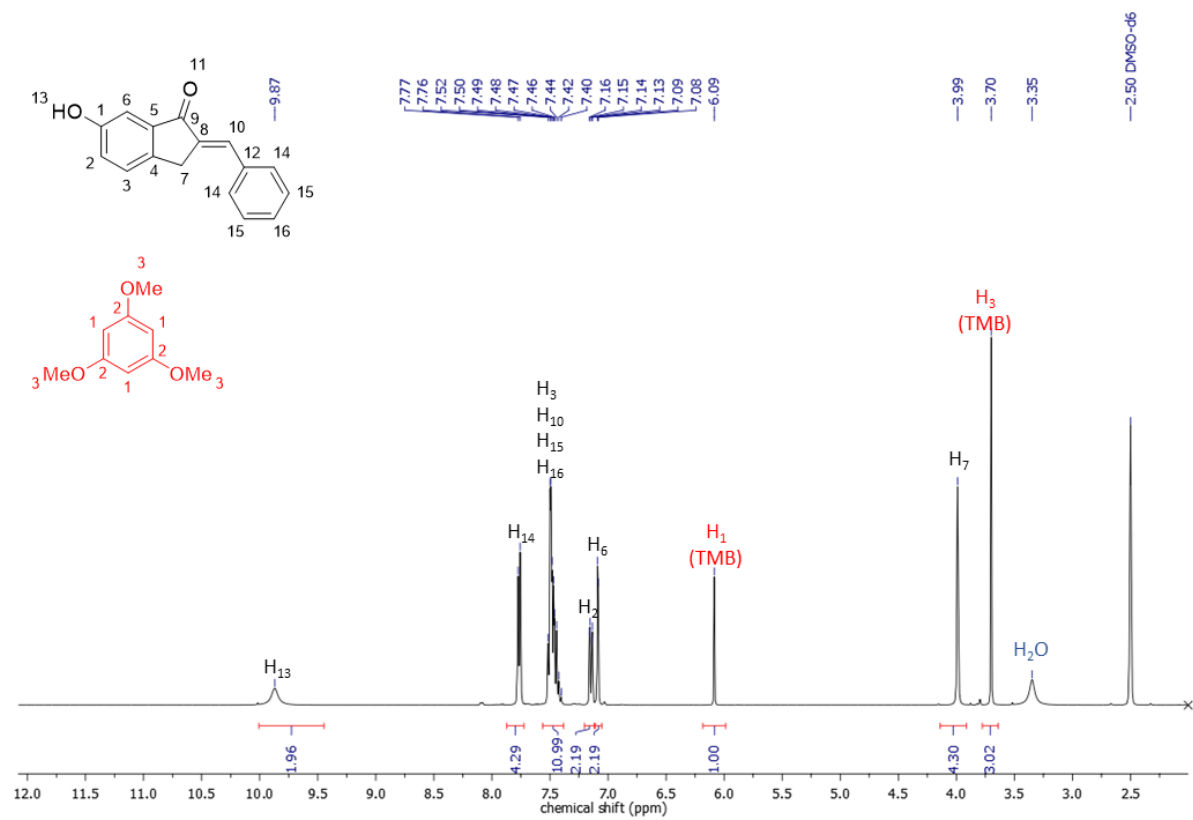


Figure S30. qNMR spectrum of **5b** crude (1:2**b** molar ratio = 1:1.7; Table S4, Entry 4).

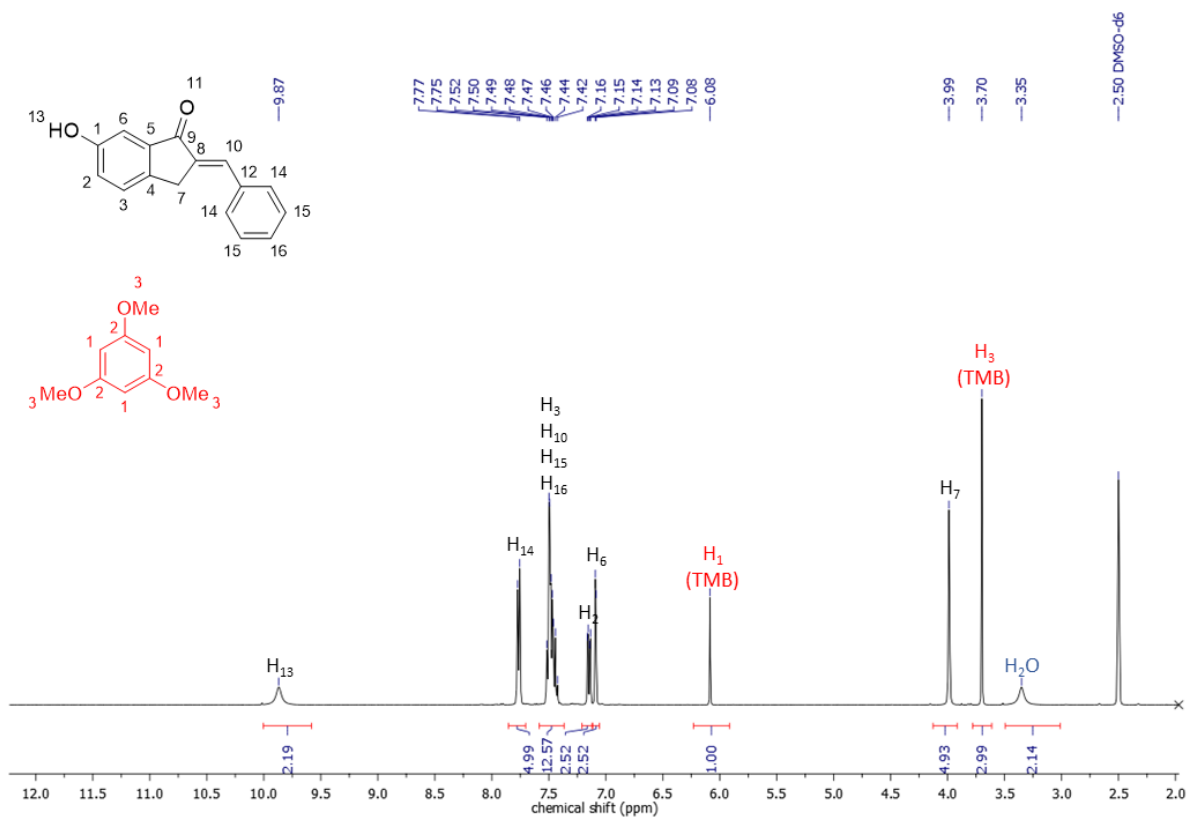


Figure S31. qNMR spectrum of **5b** crude (**1:2a** molar ratio = 1:2.0; Table S4, Entry 5).

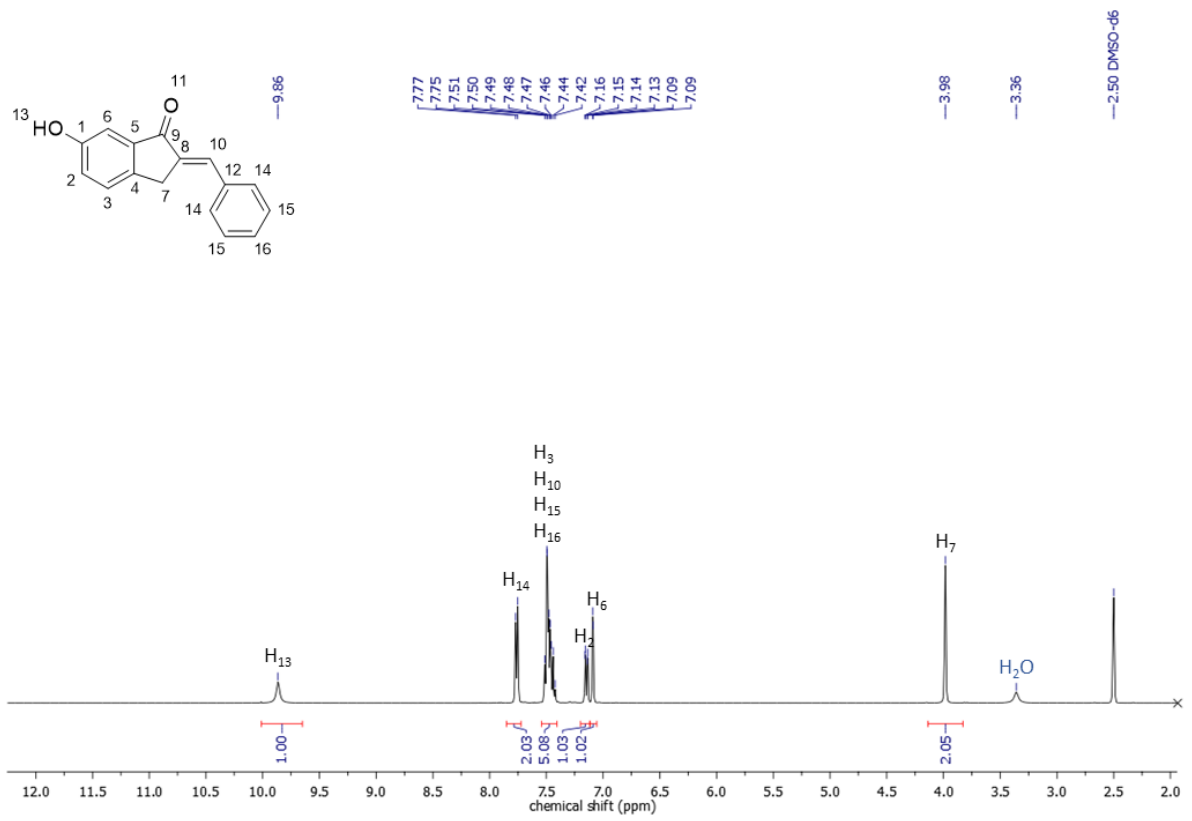


Figure S32. ¹H NMR spectrum of **5b**.

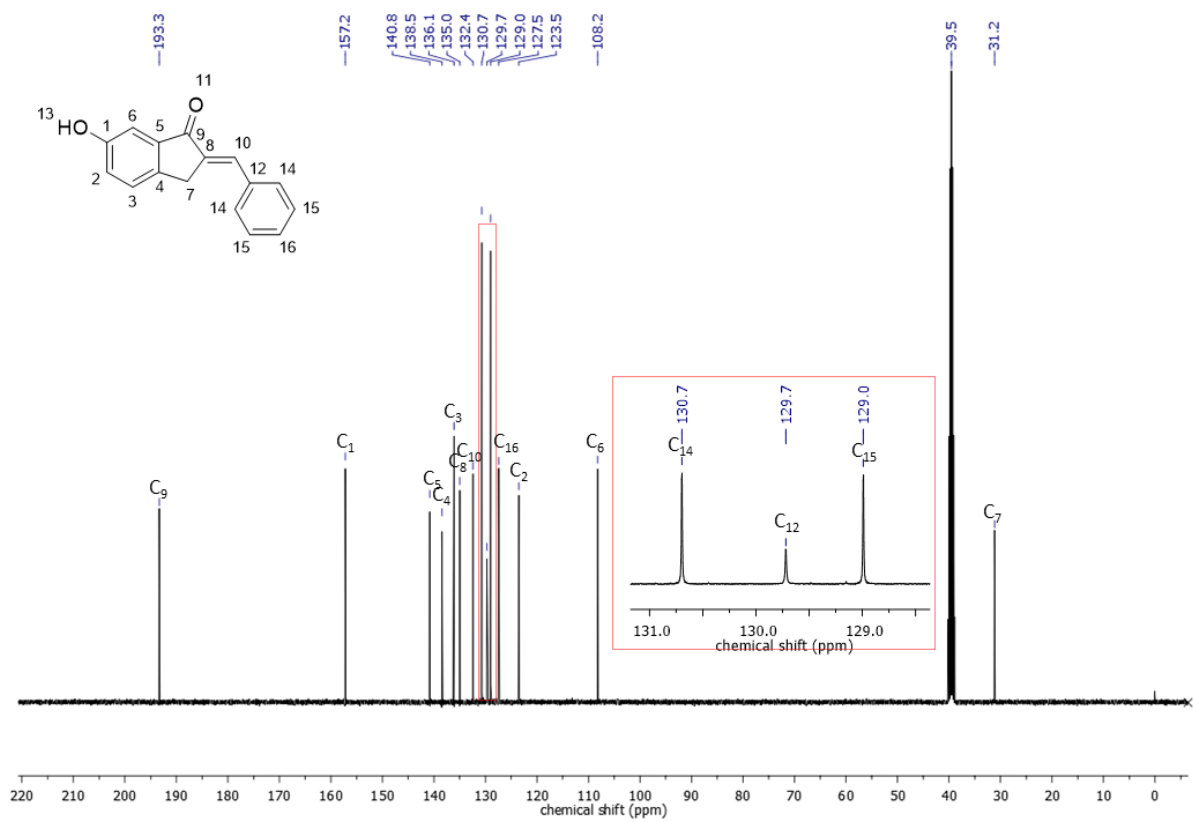


Figure S33. ^{13}C NMR spectrum of **5b**.

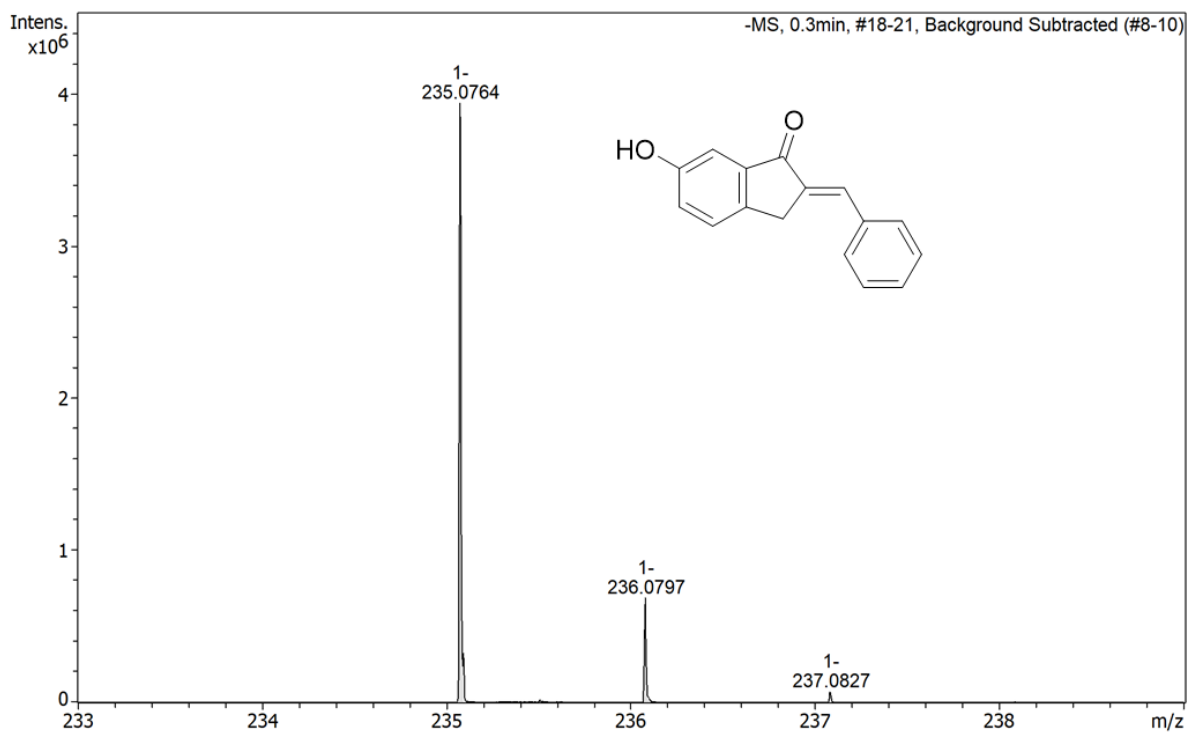


Figure S34. Registered ESI-MS of **5b**.

Synthesis of (E)-6-hydroxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one (5c)

5.00 mmol of 6-hydroxy-1-indanone and 10.0 mmol of KOH were dissolved in 20 mL methanol and stirred at 0 °C for 15 minutes. Afterwards, 5.00 mmol of 4-methoxybenzaldehyde (Table S5, Entry 1) were added and the volume was adjusted to 25.0 mL with methanol. The resulting mixture was fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer with an inlet temperature of 80 °C and a sheath N₂ flow rate of 357 L·h⁻¹. After 8.33 minutes, a red solid was obtained, which was dispersed in deionised water. The resulting mixture was acidified to pH 6-7 with HCl 1 M, and then left to rest at -20 °C for 1 hour. Finally, the solid was recovered by vacuum filtration, dried at 85 °C under vacuum overnight, and characterized by ¹H qNMR, revealing that **5c** was directly produced from the spray-drier with a purity of 94 %. To further purify it, the solids were recrystallized from methanol yielding **5c** with a yield of 78 %

In a second reaction, the spray-drying synthesis was repeated using 6.50 mmol of 4-methoxybenzaldehyde (Table S5, Entry 2). Under these new conditions, **5c** was obtained directly from the spray-drier with a purity of 97% and a yield of 93%.

¹H NMR (400 MHz, DMSO) δ 9.83 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.12 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 9.1 Hz, 3H), 3.93 (s, 2H), 3.82 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 193.2, 160.6, 157.2, 140.6, 138.7, 133.6, 132.6, 132.4, 127.6, 127.4, 123.1, 114.6, 108.1, 55.4, 31.2 ESI-MS m/z calculated for [C₁₇H₁₃O₃]⁻: 265.0870, found: 265.0870.^[6]

Table S5: Optimization of yield and purity for the synthesis of **5c**.

Entry	Mmol 2b	4:2b ratio	Purity (%)	Yield (%)
1	5.00	1:1.0	94	78
2	6.50	1:1.3	97	93

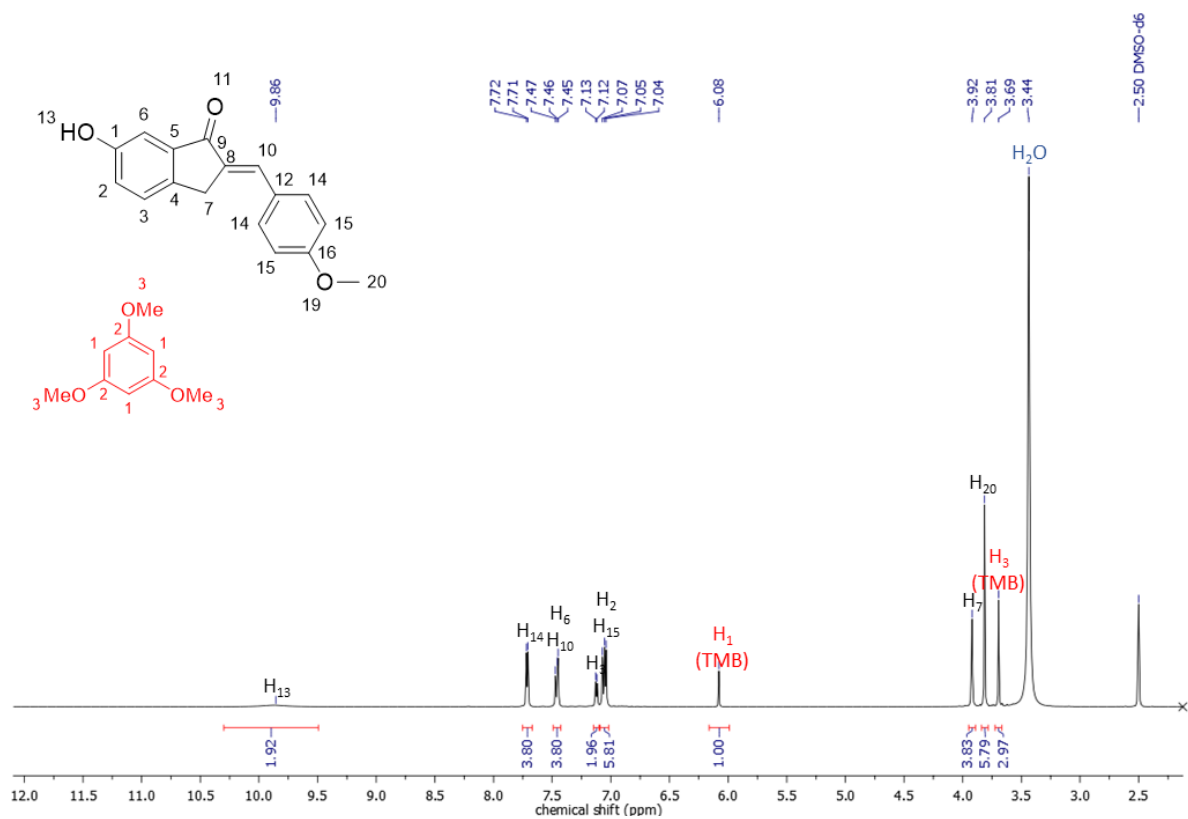


Figure S35. qNMR spectrum of **5c** crude (1:2c molar ratio = 1:1.0; Table S5, Entry 1).

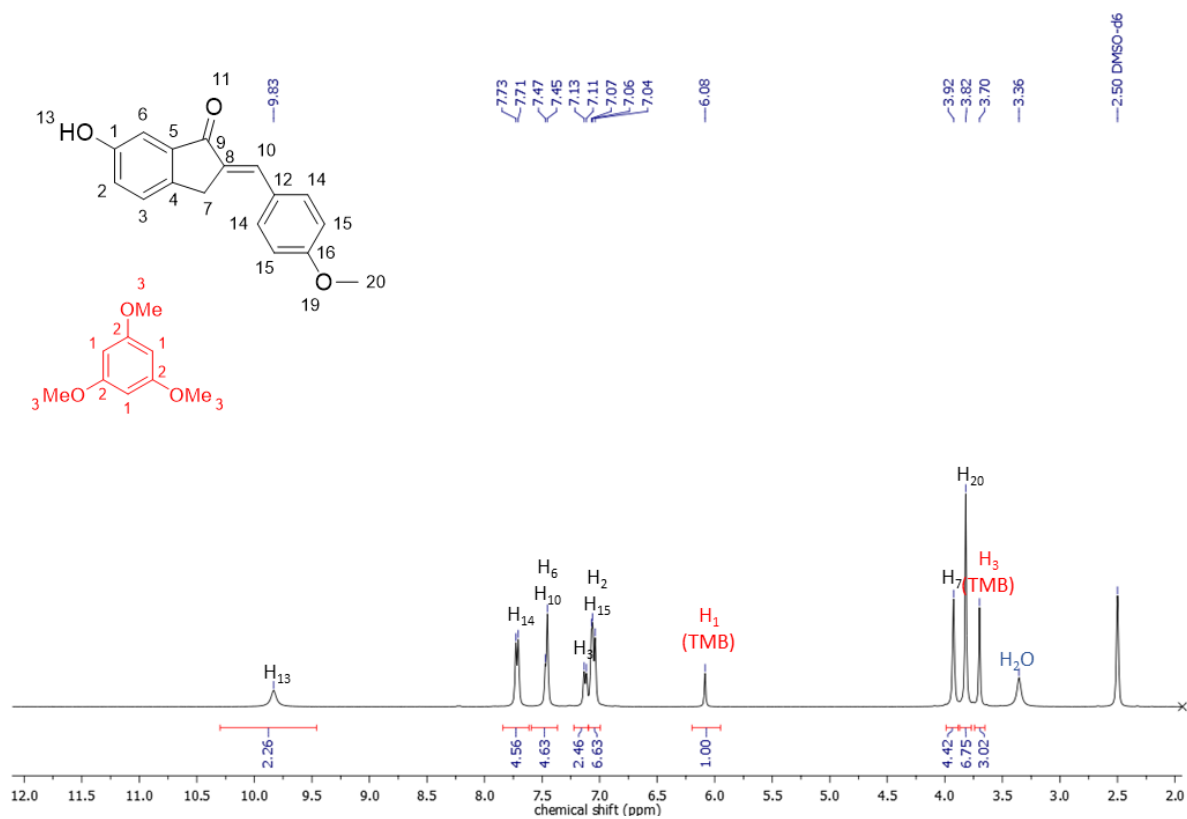


Figure S36. qNMR spectrum of **5c** crude (1:2c molar ratio = 1:1.3; Table S5, Entry 2).

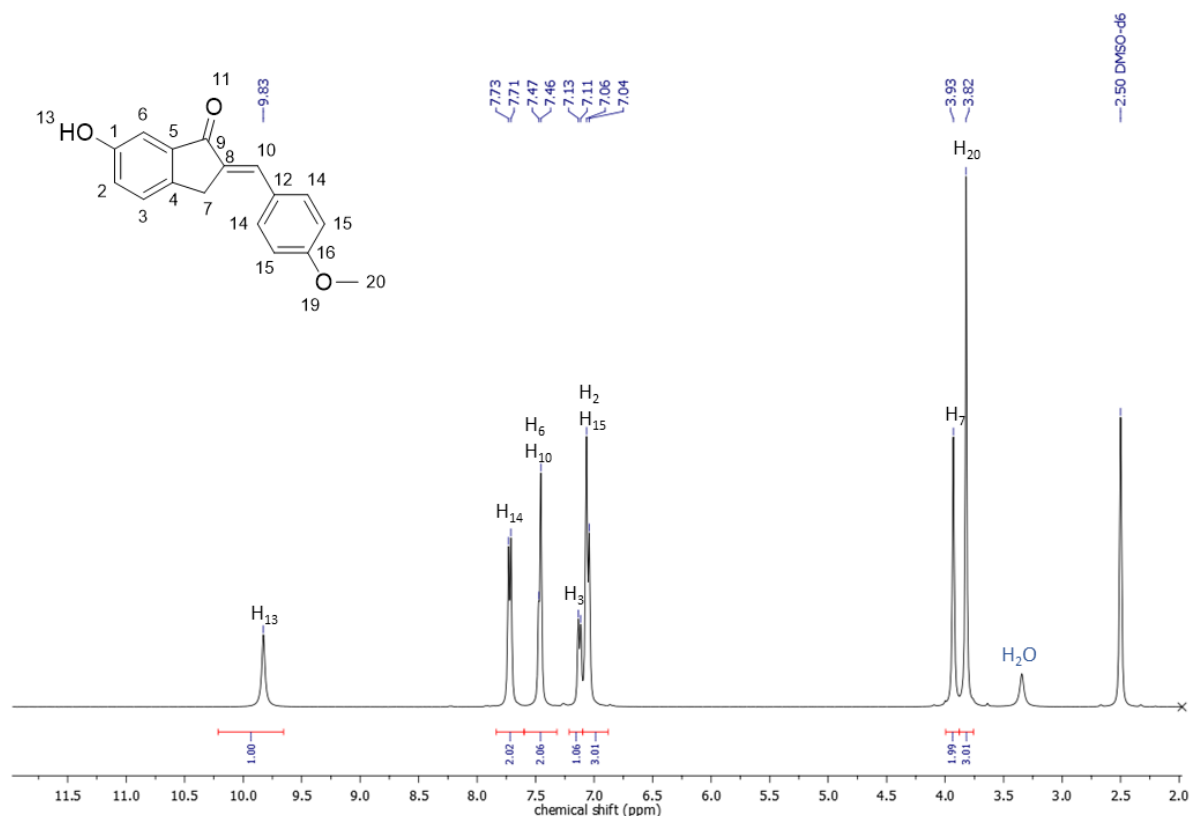


Figure S37. ¹H NMR spectrum of **5c**.

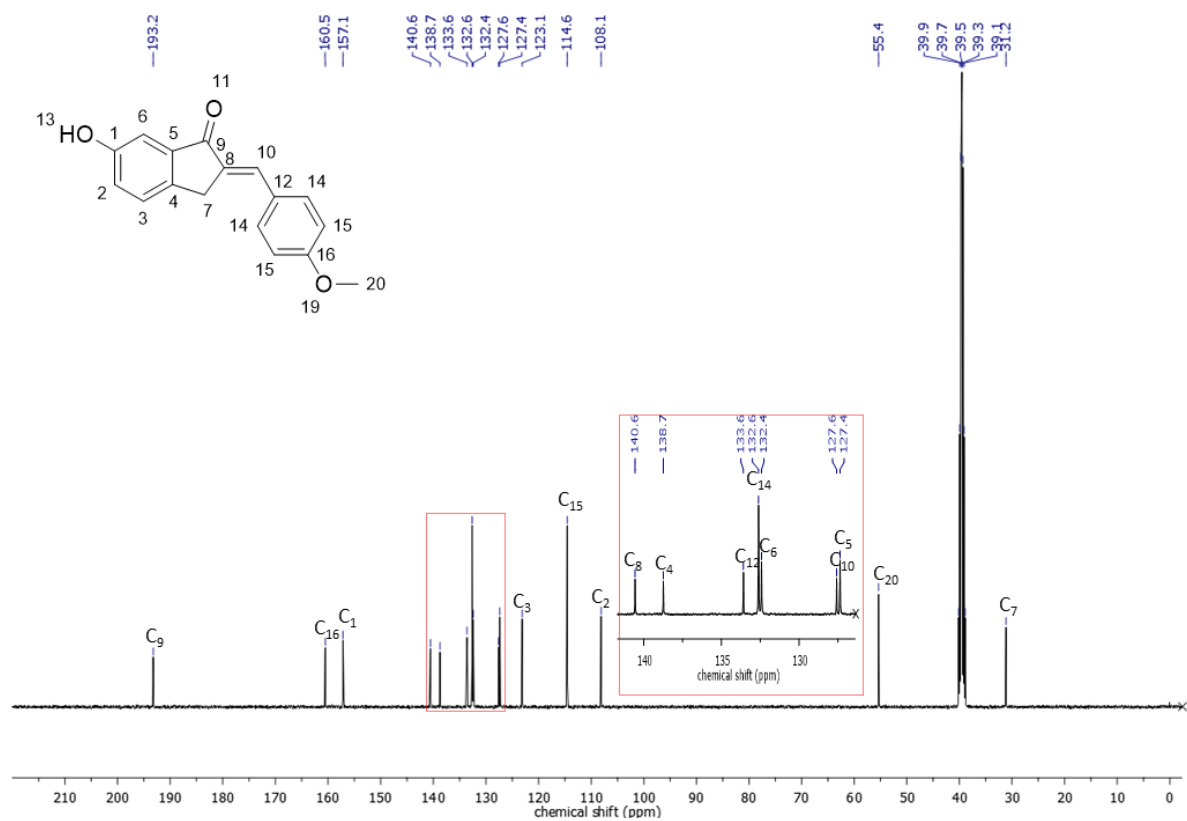


Figure S38. ^{13}C NMR spectrum of **5c**.

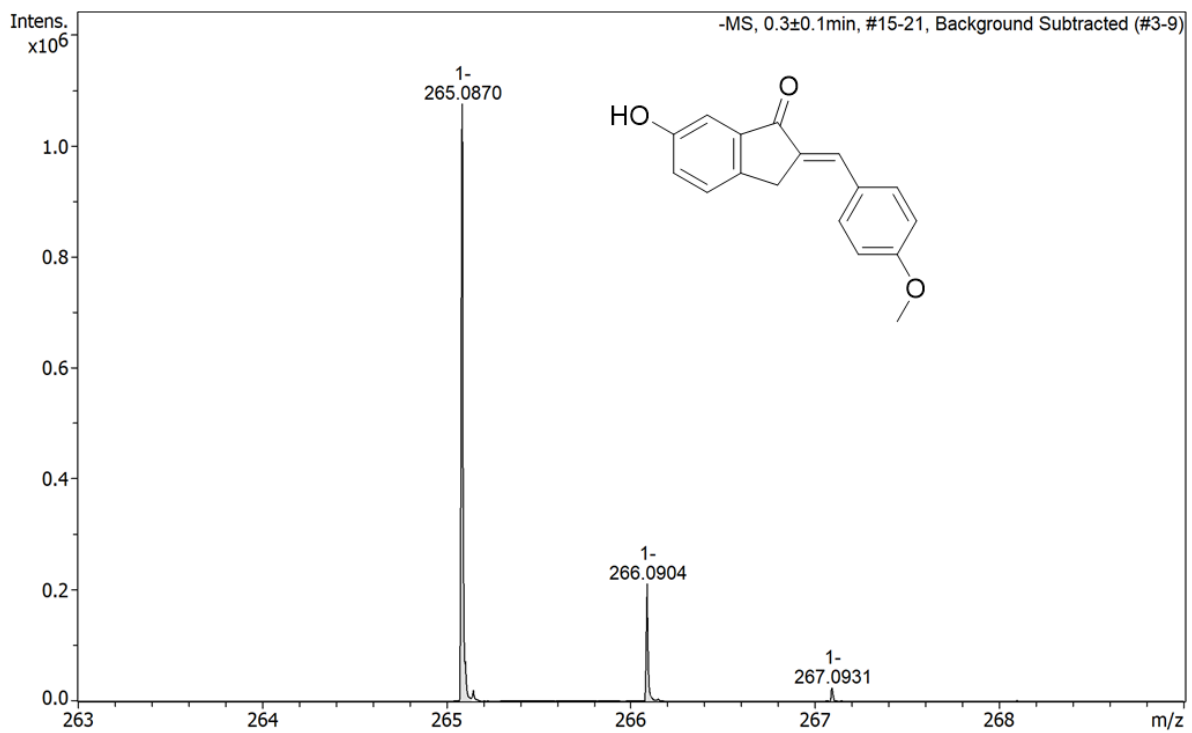


Figure S39: Registered ESI-MS for **5c**.

Section S4: Synthesis and characterization of amides.

Synthesis of 4-(N-tertbutoxycarbonylamino)phenol (**7a**)

5.00 mmol of 4-aminophenol and 7.50 mmol of triethylamine were dissolved in 15 mL methanol under stirring. Afterwards, 5.00 mmol (Table S6, Entry 1) or 6.50 mmol (Table S6, Entry 2) of di-tert-butyl dicarbonate were added and the volume adjusted to 25.0 mL with methanol. The resulting mixture was fed at 3.0 mL·min⁻¹ into a Büchi B-290 Mini Spray-Dryer with an inlet temperature of 100 °C and a sheath N₂ flow rate of 357 L·h⁻¹. After 8.33 minutes, a white solid was obtained, and characterized by ¹H qNMR, revealing that **7a** was directly produced from the spray-drier with a purity of 88% and 91 %, respectively. Afterwards, the solid was purified by dissolving it in 30 mL ethyl acetate and extracting it with 3 x 30 mL saturated NH₄Cl. The organic fraction was dried over 4A molecular sieves and the solvent removed *in vacuo*, obtaining **7a** in yields of 66% and 81%, respectively.

¹H NMR (400 MHz, DMSO) δ 9.01 (s, 1H), 9.01 (s, 1H), 8.96 (s, 1H), 8.96 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 1.45 (s, 9H), 1.45 (s, 9H). ¹³C NMR (101 MHz, DMSO) δ 153.0, 152.5, 131.0, 120.0, 115.0, 78.4, 28.2 ESI-MS m/z calculated for [C₁₁H₁₄O₃]: 208.0979, found: 208.0980.^[7]

Table S6: Optimization of yield and purity for the synthesis of **6a**.

Entry	mmol 6a	1:2c ratio	Purity (%)	Yield (%)
1	5.00	1:1.0	88	66 ^[a]
2	6.50	1:1.3	91	81 ^[a]

[a]: After work-up

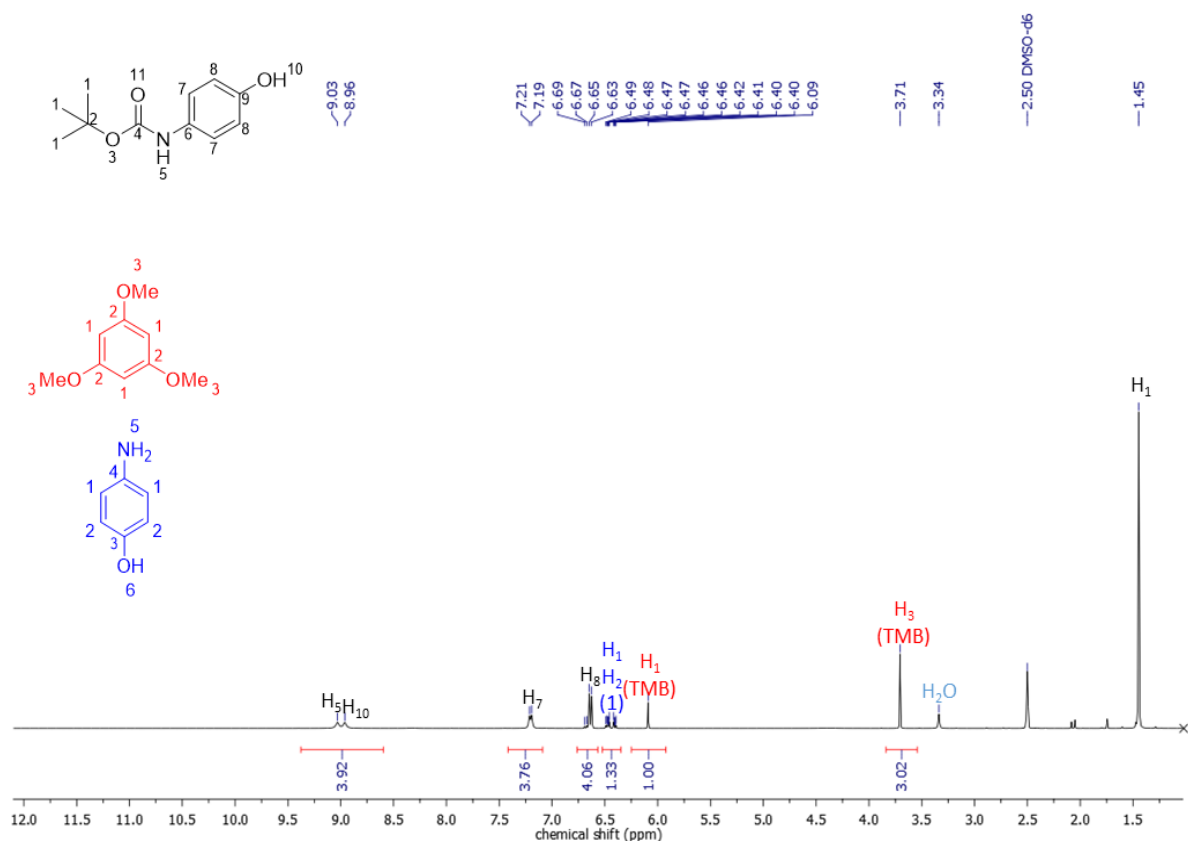


Figure S40. qNMR spectrum of **7a** crude (1:**6a** molar ratio = 1:1.0; Table S6, Entry 1).

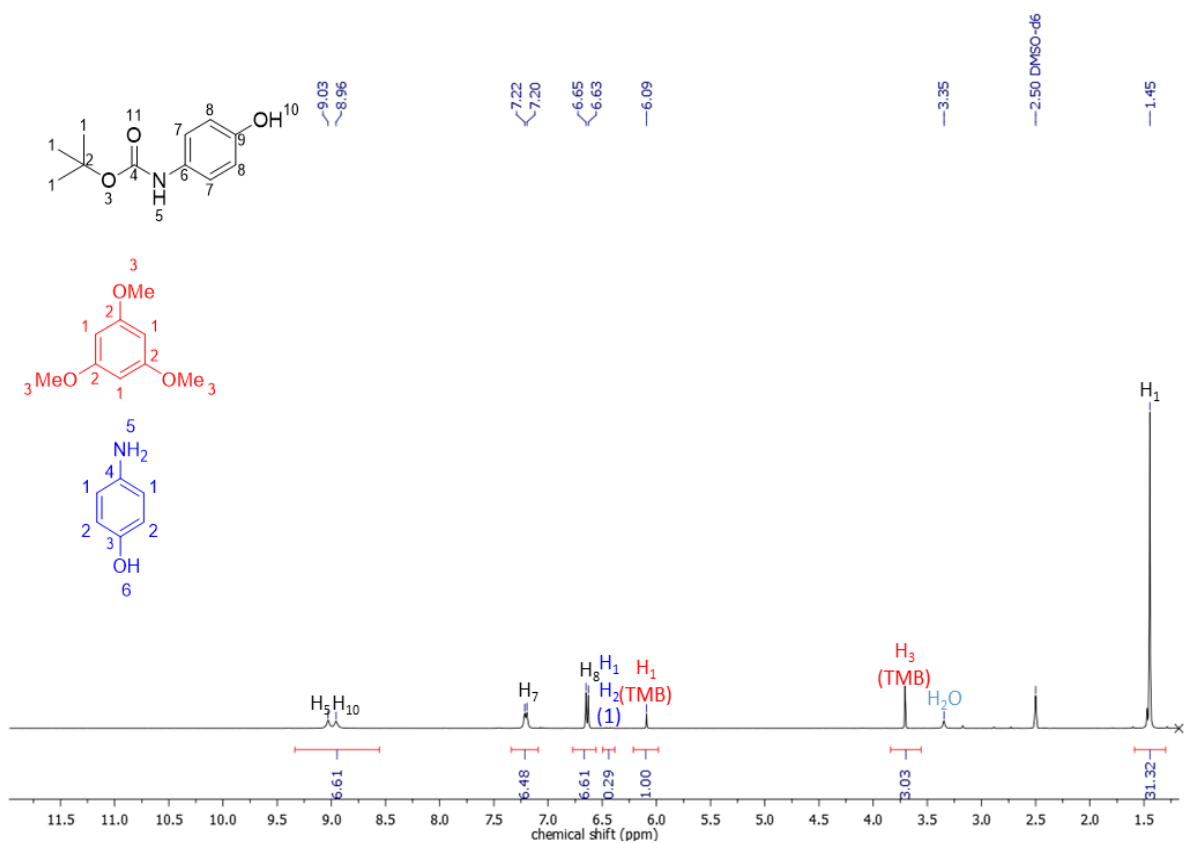


Figure S41. ¹H qNMR spectrum of **7a** crude (**1**:**6a** molar ratio = 1:1.3; Table S6, Entry 2).

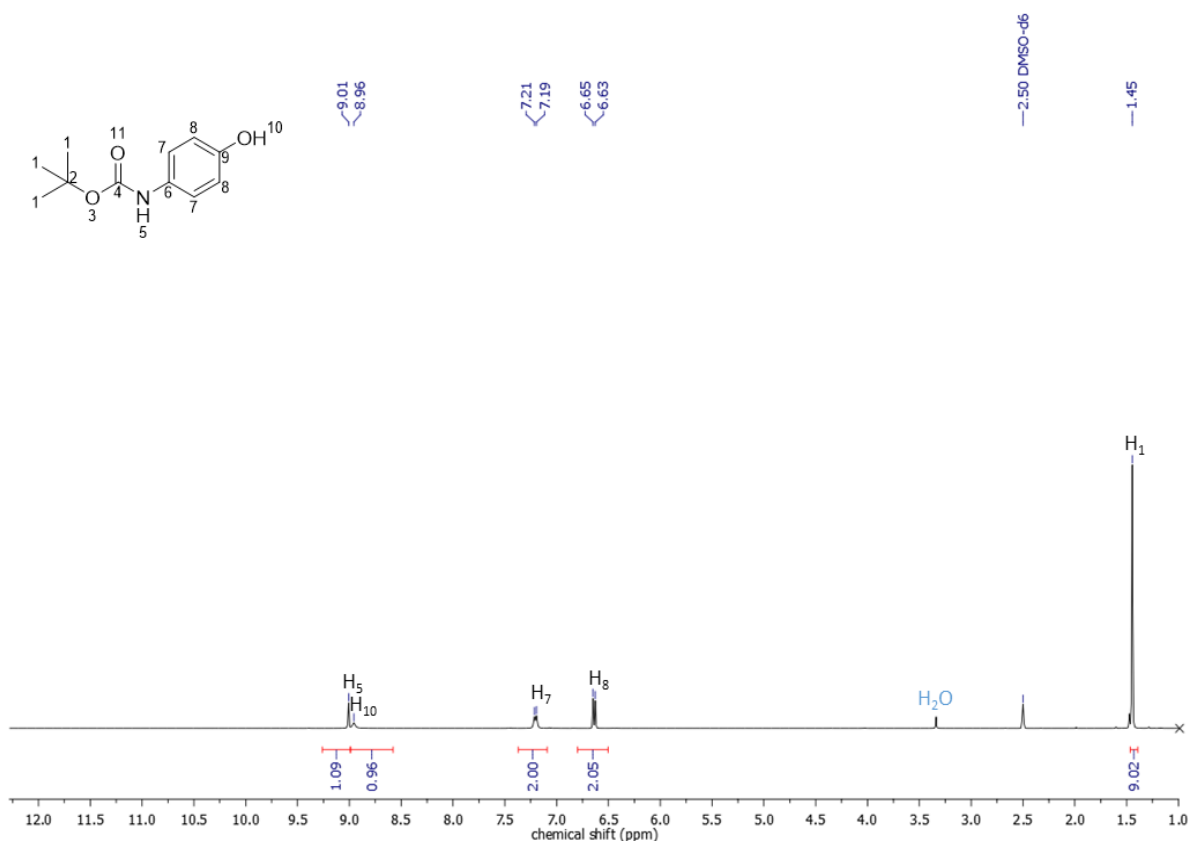


Figure S42. ¹H NMR spectrum of **7a**.

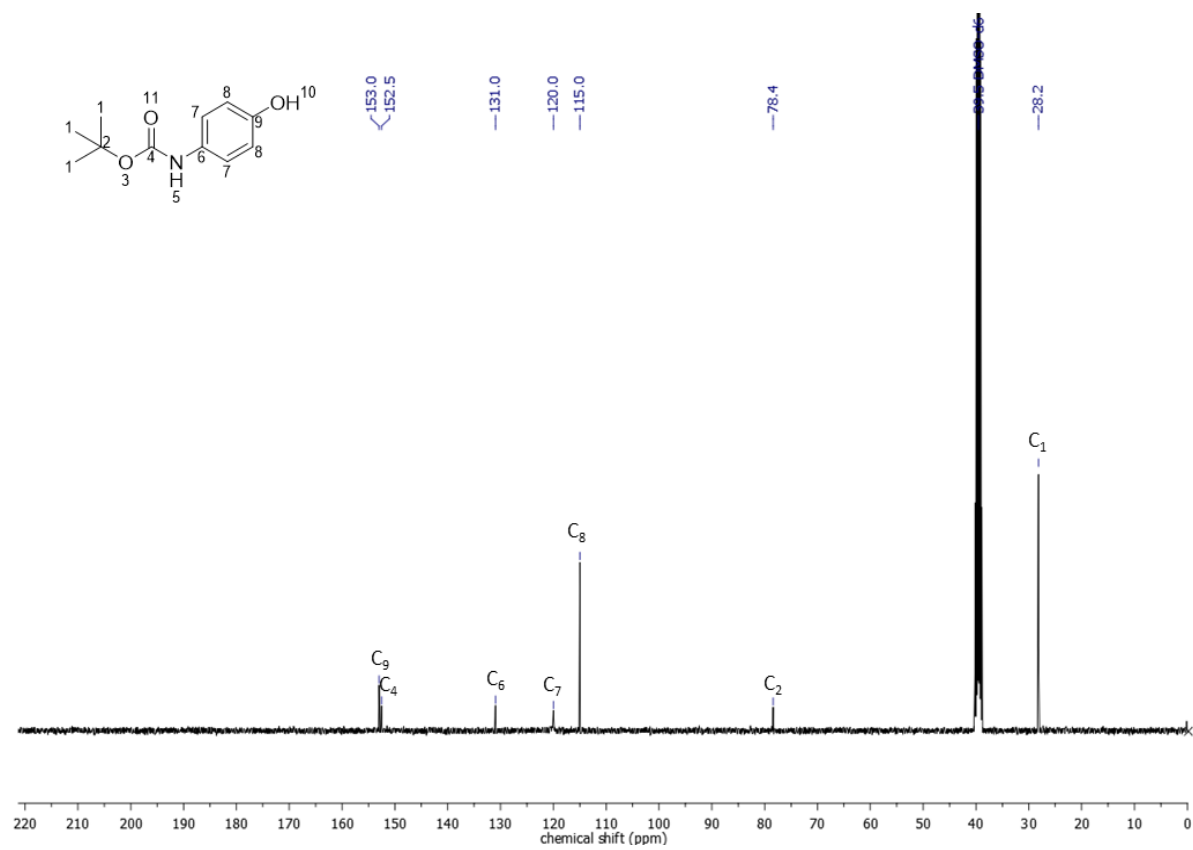


Figure S43. ^{13}C NMR spectrum of 7a.

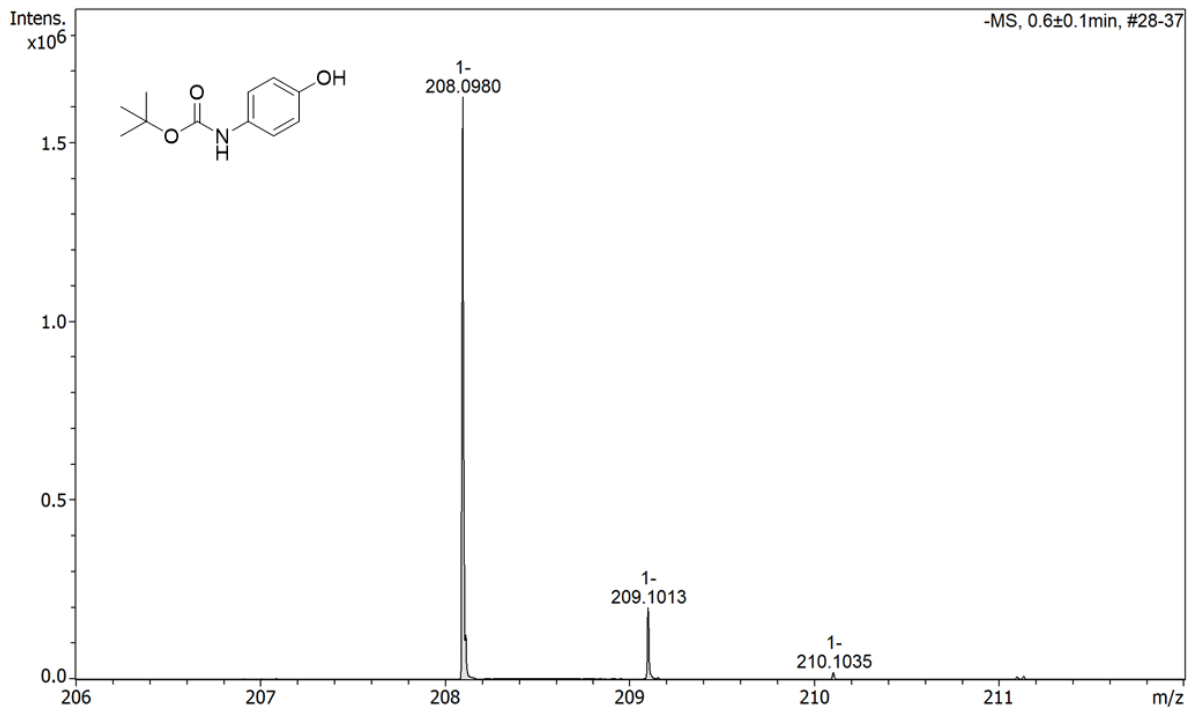


Figure S44. Registered ESI-MS of **7a**.

Synthesis of 4-N-acetylaminophenol (7b)

5.00 mmol of 4-aminophenol and 6.50 mmol of acetic anhydride were dissolved in 25 mL tetrahydrofuran. The resulting mixture was fed at $3.0 \text{ mL} \cdot \text{min}^{-1}$ into a Büchi B-290 Mini Spray-Dryer with an inlet temperature of $80 \text{ }^\circ\text{C}$ and a sheath N_2 flow rate of $357 \text{ L} \cdot \text{h}^{-1}$. After 8.33 minutes, a white solid was obtained that was characterized by ^1H qNMR, revealing that **7b** was directly produced from the spray-drier with a purity of 97 % and a yield of 83 %.

Scaled-up synthesis of 4-N-acetylaminophenol (7b)

50.0 mmol of 4-aminophenol and 65.0 mmol of acetic anhydride were dissolved in 250 mL tetrahydrofuran. The resulting mixture was fed at $3.0 \text{ mL} \cdot \text{min}^{-1}$ into a Büchi B-290 Mini Spray-Dryer with an inlet temperature of $80 \text{ }^\circ\text{C}$ and a sheath N_2 flow rate of $357 \text{ L} \cdot \text{h}^{-1}$. After 83.3 minutes, a white solid was obtained that was characterized by ^1H qNMR, revealing that **7b** was directly produced from the spray-drier with a purity of 98 % and a yield of 85 %.

^1H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.16 (s, 1H), 7.37 (d, $J = 8.8 \text{ Hz}$, 2H), 6.71 (d, $J = 8.8 \text{ Hz}$, 2H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.8, 153.3, 131.1, 121.1, 115.2, 23.8 ESI-MS m/z calculated for $[\text{C}_6\text{H}_8\text{NO}_2]$: 150.0560, found: 150.0558.^[8]

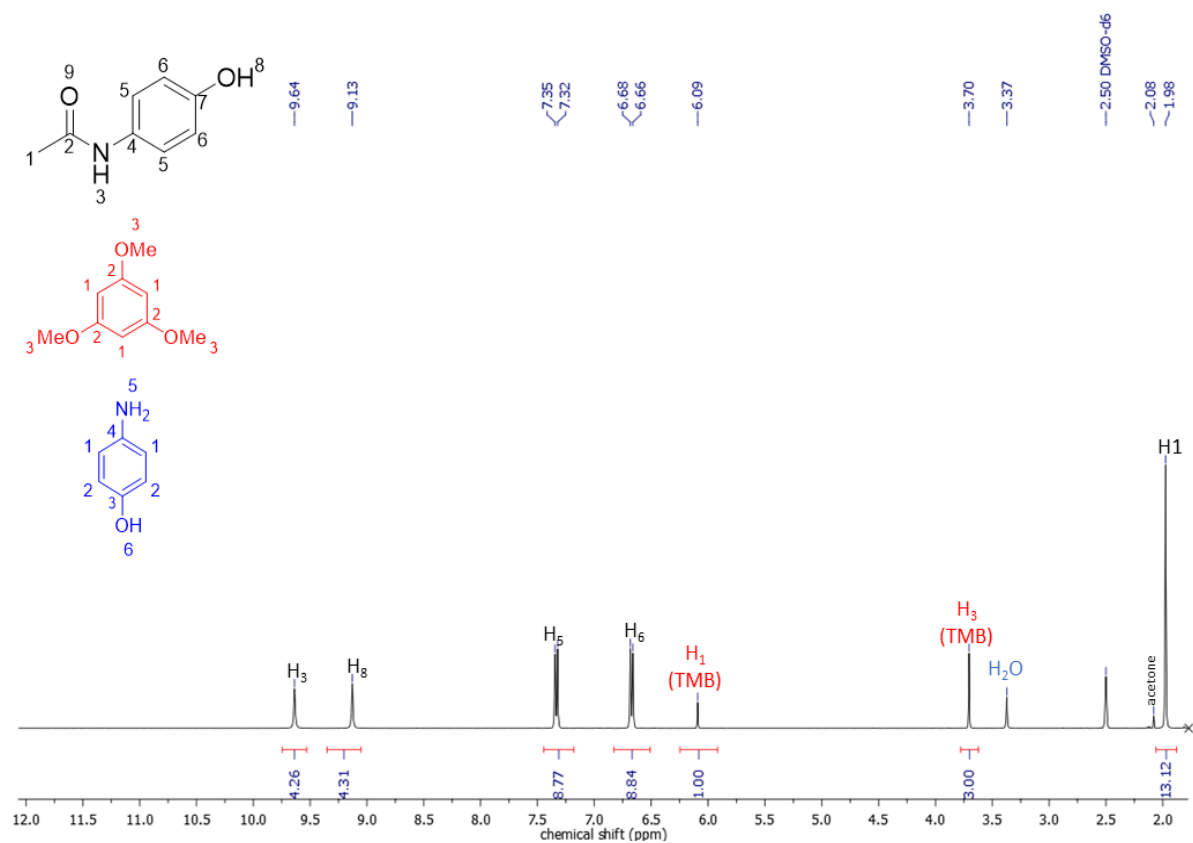


Figure S45. qNMR spectrum of **7b** crude.

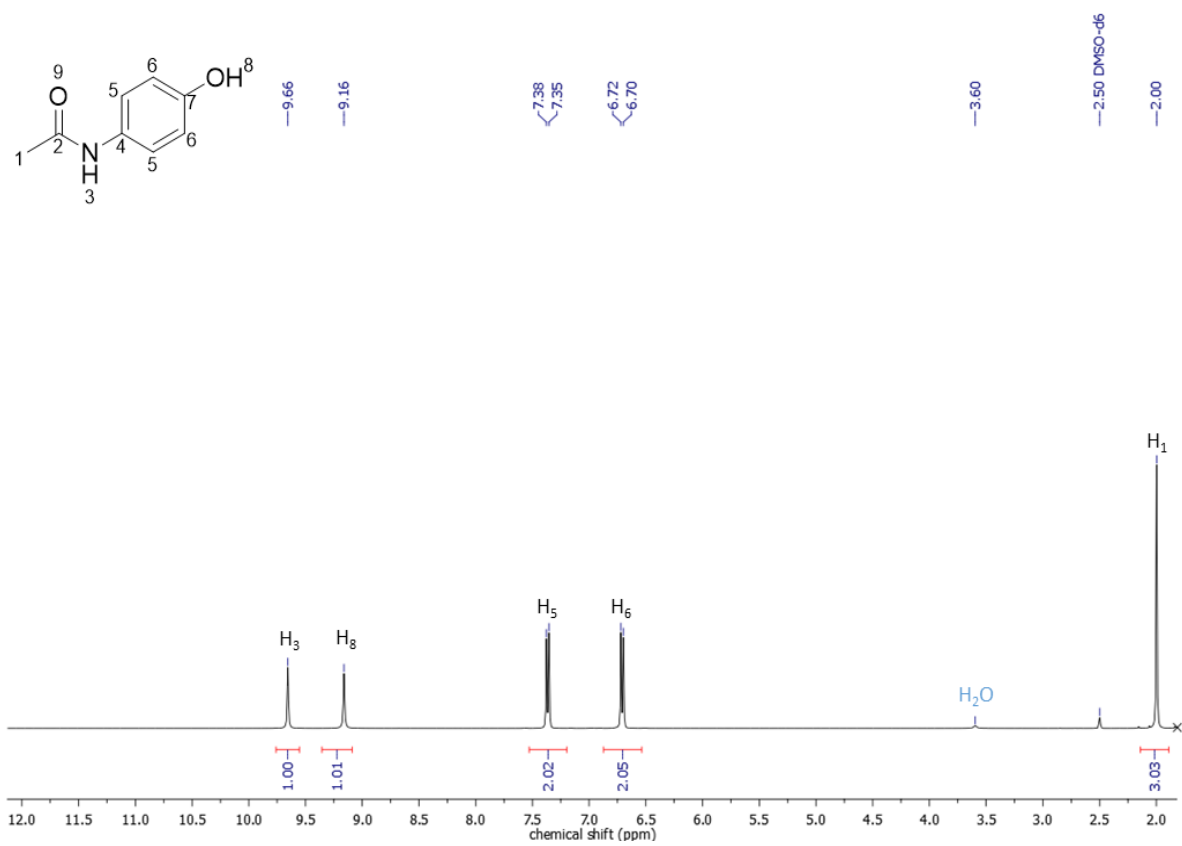


Figure S46. ¹H NMR spectrum of **7b**.

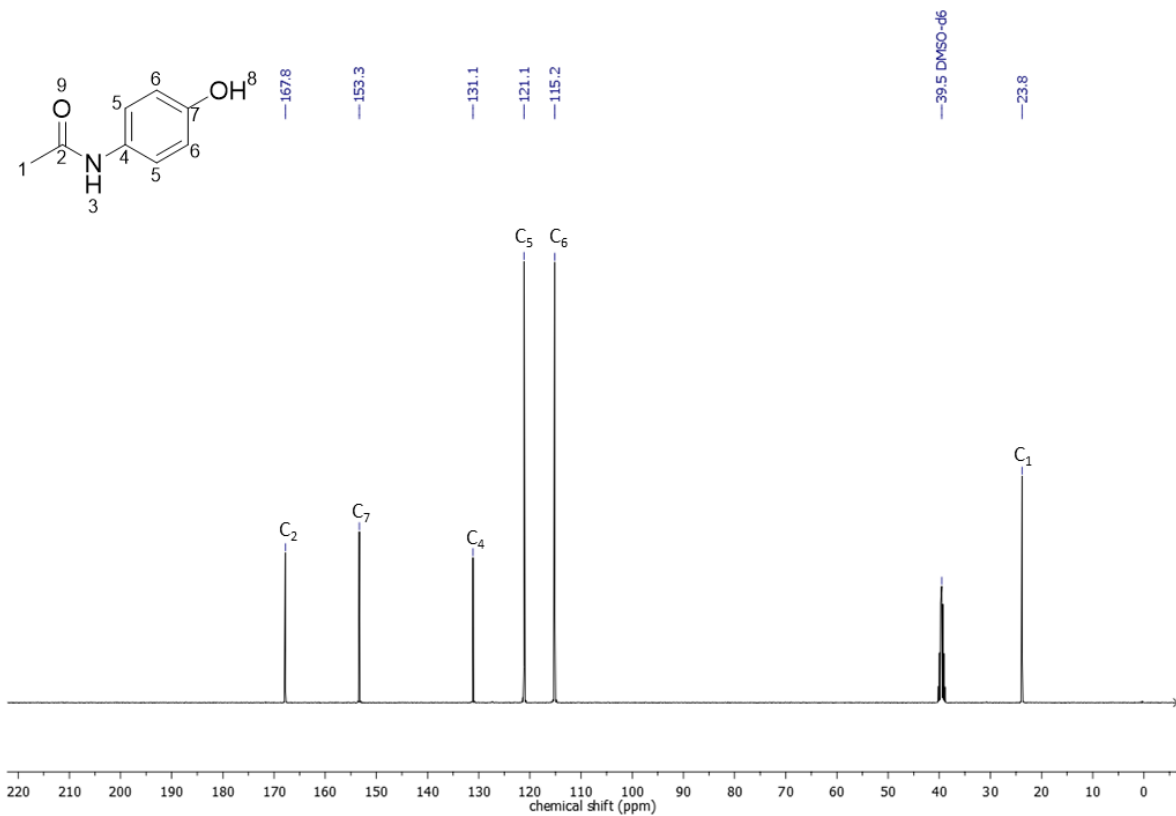


Figure S47. ¹³C NMR spectrum of 7b.

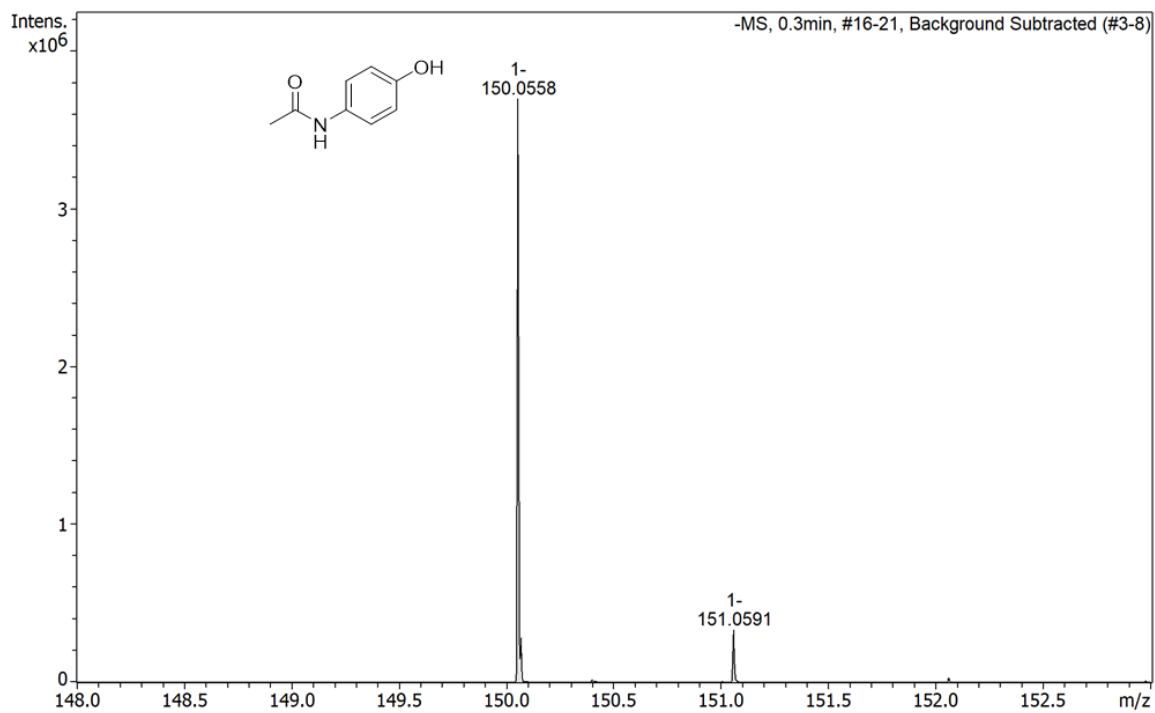


Figure S48. Registered ESI-MS of **7b**.

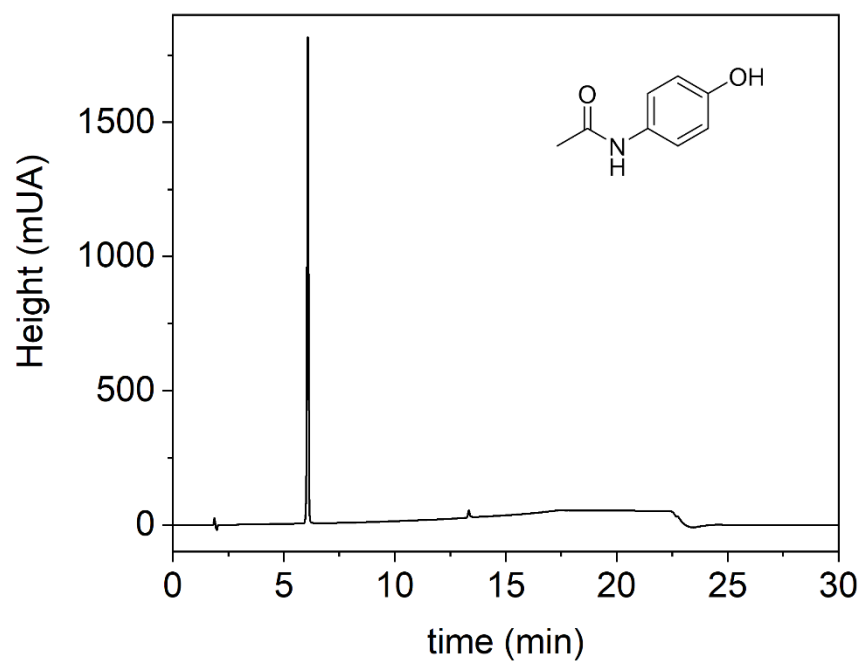


Figure S49. HPLC chromatogram of **7b** after collection from the spray-dryer.

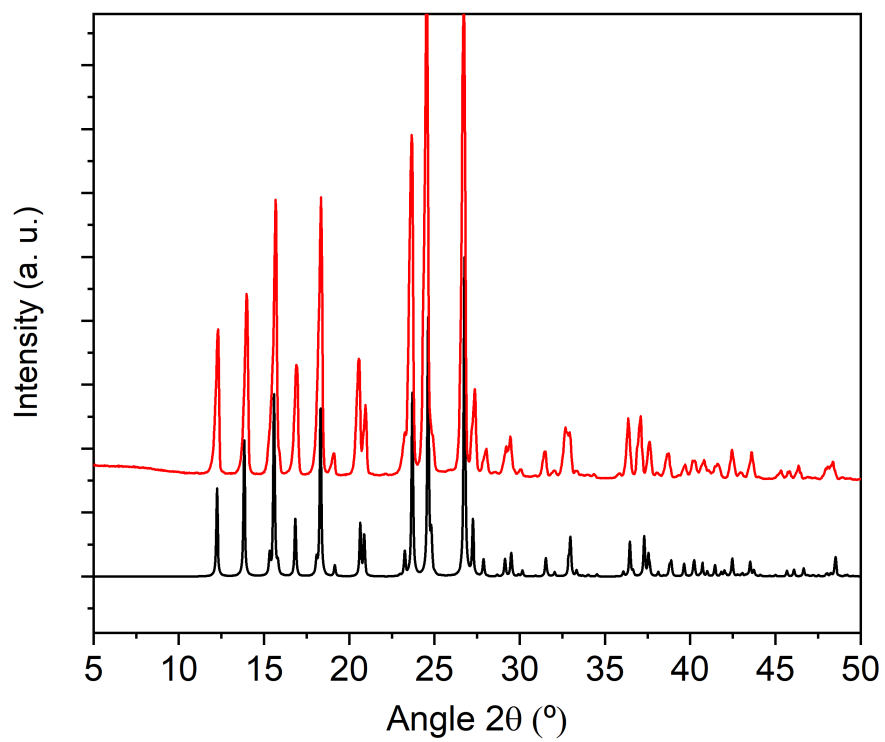


Figure S50. PXRD patterns of **7b** (red) and simulated from the crystal structure of paracetamol/acetaminophen reported in the literature.^[9]

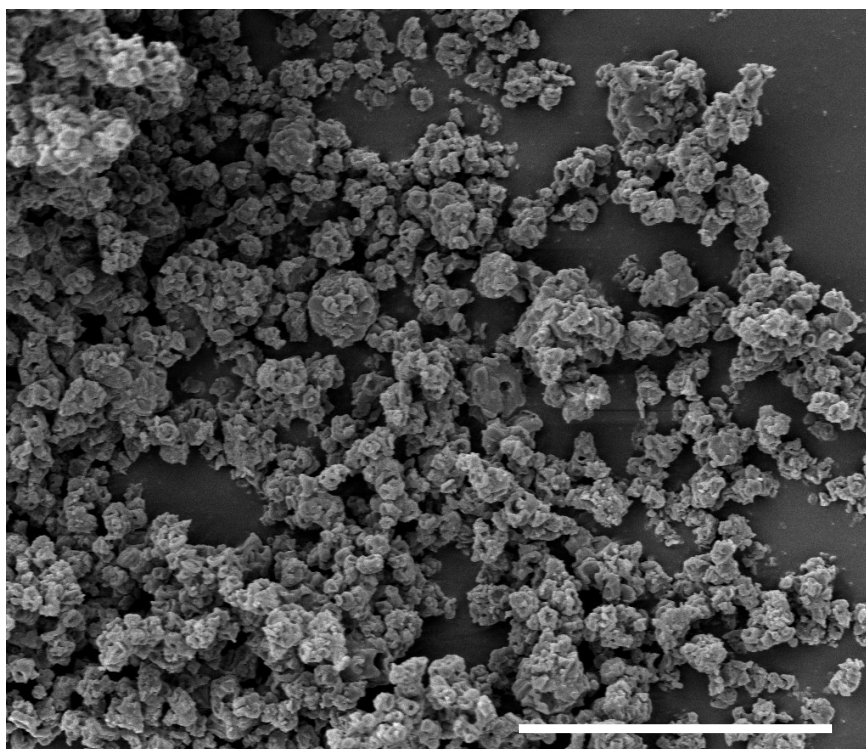


Figure S51. SEM image of collected **7b**. Scale bar = 30 μm .

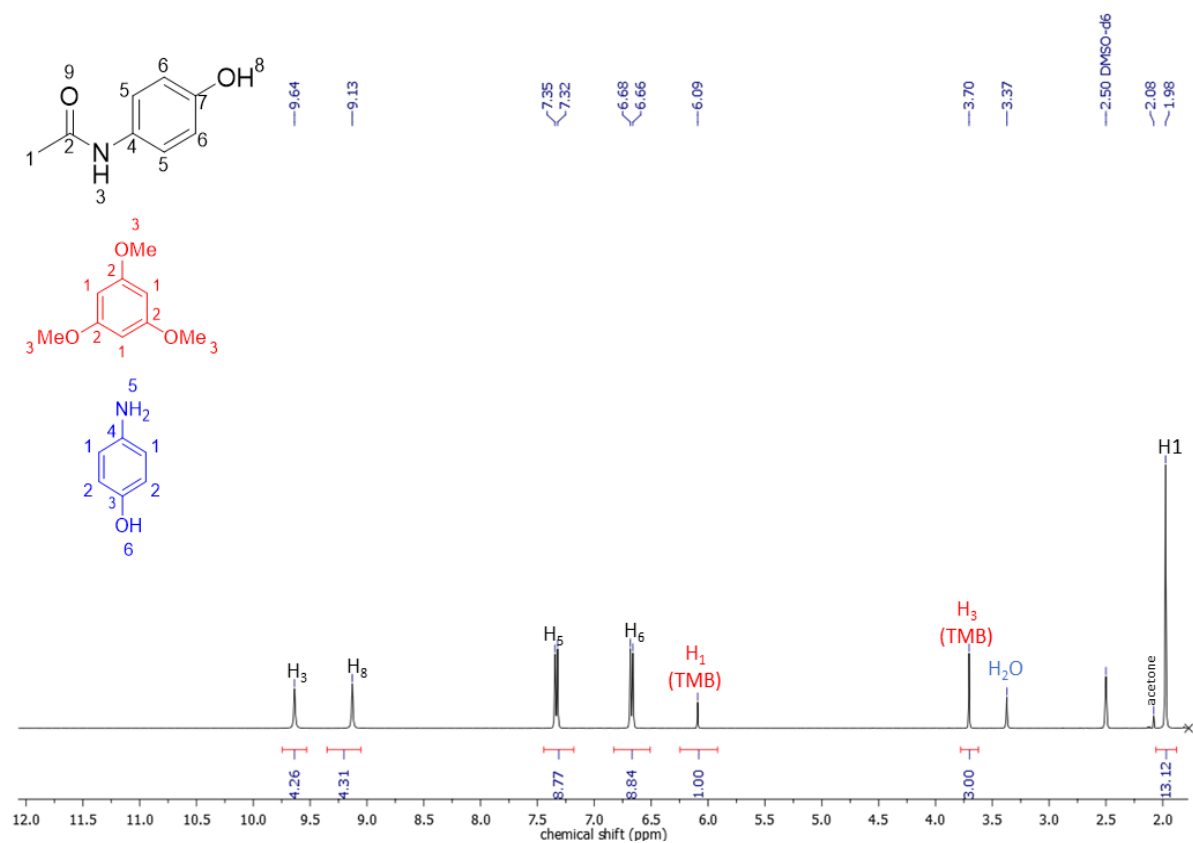


Figure S52. qNMR spectrum of **7b** crude (scaled-up spray-drying synthesis).

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