

Efficient and sustainable laccase-catalyzed iodination of *p*-substituted phenols using KI as iodine source and aerial O₂ as oxidant

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Electronic Supplementary Information

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1. General remarks

All chemicals were purchased from commercial suppliers and were used without further purification. Solvents used in extraction and purification were distilled prior to use. Laccase from *Trametes versicolor* (EC 1.10.3.2) was purchased from ASA Spezialenzyme (Wolfenbüttel, Germany). The pH of the buffer was adjusted using a pH 330/SET-1 pH-meter. The addition of reagents was achieved using a syringe pump (Harvard Apparatus, Model 22). Thin layer chromatography (TLC) was performed on precoated aluminium plates (silica gel Merck 60 F₂₅₄) and visualized by UV light (254 nm). Products were purified by flash chromatography on silica gel (MN 60, 0.04–0.063 mm; Machery & Nagel). Melting points were measured on a Büchi melting point apparatus B-545 and are uncorrected. IR spectra were measured on a Bruker Alpha FT-IR spectrometer. UV/VIS spectra were recorded with a Varian Cary 50 and Cary 4E spectrometer. ¹H- and ¹³C NMR spectra were recorded at 300 (75 MHz) and 500 (125 MHz) on Varian Unity Inova spectrometers and at 600 (150 MHz) on a Bruker Avance III HD spectrometer using CDCl₃ (referenced to $\delta = 7.26$ ppm in ¹H NMR and $\delta = 77.02$ ppm in ¹³C NMR) and DMSO-*d*₆ (referenced to $\delta = 2.50$ ppm in ¹H NMR and $\delta = 39.52$ ppm in ¹³C NMR). COSY-, HSQC- and HMBC spectra were recorded at 300 MHz, 500 MHz or 600 MHz. 1D and 2D homonuclear NMR spectra were measured with standard pulse sequences. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet) sex (sextet), m (multiplet) and br (broad signal). Overlapping signal structures are marked as *d-like*, *t-like* etc. All NMR spectra were processed with *Spinworks* 4.2.4 (copyright © 2018, Kirk Marat, University of Manitoba). Low resolution electron impact mass spectra (EI-LRMS) were measured on a Thermo Polaris Q or on a Finnigan MAT 95 instrument. Low resolution electrospray ionisation mass spectra (ESI-LRMS) were measured using an Agilent G1956B MSD single quadrupole mass spectrometer equipped with a G 1946 atmospheric pressure ionization electrospray (ESI) interface. Exact electron mass spectra (EI-HRMS) were obtained at 70 eV on a Finnigan MAT 95.

2. Determination of the activity of laccase from *Trametes versicolor*^{1,2}

A 0.1 M solution of 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) (0.3 mL) in acetate buffer was diluted with acetate buffer (2.6 mL) and treated with a solution of laccase in the same buffer (0.1 mL). The change in absorption was followed via UV

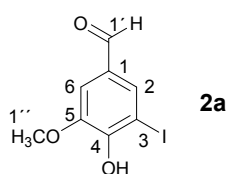
spectroscopy ($\lambda = 414 \text{ nm}$). One unit was defined as the amount of laccase (*Trametes versicolor*) that converts 1 mmol of ABTS per minute at the desired pH.

3. General procedure I for the laccase-catalyzed iodination

A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (996 mg, 3 equiv., 6 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). In case of two potential iodination sites, four equivalents potassium iodide (1328 mg, 8 mmol) were used. Additional laccase from *Trametes versicolor* (90 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 18 U/h) at room temperature. Simultaneously, the substrate (1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for the time given. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc ($5 \times 25 \text{ mL}$). The combined organic phases were washed with deionized water ($4 \times 15 \text{ mL}$) and brine ($1 \times 5 \text{ mL}$). The organic extracts were dried over anhydrous MgSO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 .

4. Synthesis and analytical data of iodination products 2 and 4

4.1 Synthesis and analytical data of 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**)³



Preparation of **2a** on a 2 mmol scale

According to general procedure I, 4-hydroxy-3-methoxybenzaldehyde (**1a**) (304 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/ CH_2Cl_2 /EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**) as a colourless powder (472 mg, 1.7 mmol, 85%).

Preparation of 2a on a 15 mmol scale

A 1000 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with 4-hydroxy-3-methoxybenzaldehyde (**1a**) (15 mmol, 1 equiv., 2.28 g), ABTS diammonium salt (82.2 mg, 1 mol%, 0.15 mmol), potassium iodide (7.47 g, 3 equiv., 45 mmol), laccase from *Trametes versicolor* (300 U) and acetate buffer (500 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (600 U), dissolved in acetate buffer (6 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 120 U/h) at room temperature. Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 15 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (10 × 20 mL). The combined organic phases were washed with deionized water (8 × 30 mL) and brine (1 × 30 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography on SiO₂ (petroleum ether/CH₂Cl₂/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**) as a colourless powder (3.211 g, 11.60 mmol, 77%).

Analytical data of 4-hydroxy-3-iodo-5-methoxybenzaldehyde (2a)

mp 181–182 °C (lit.,³ 179–180 °C); R_f = 0.53 (petroleum ether/CH₂Cl₂/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 228 (log ϵ , 5.31), 286 (4.99) and 362 (4.34); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3050 (OH), 2841 (CH₃), 1661 (C=O), 1569 (arom. C=C), 1139 (arom. C-O), 852 (arom. C-H) and 581 (arom. C-I); δ_H (300 MHz; DMSO-*d*₆) 3.89 (3H, s, 1'-H₃), 7.41 (1H, d, $^4J_{6-H, 2-H}$ = 1.4 Hz, 6-H), 7.88 (1H, d, $^4J_{2-H, 6-H}$ = 1.7 Hz, 2-H), 9.75 (1H, s, 1'-H) and 10.73 (1H, br, 4-OH); δ_C (75 MHz; DMSO-*d*₆) 56.2 (C-1'), 84.1 (C-3), 110.1 (C-6), 130.0 (C-1), 134.8 (C-2), 147.3 (C-5), 152.2 (C-4) and 190.2 (C-1''); MS (EI, 70 eV) m/z 278 (M⁺, 100%), 249 (5), 235 (15), 151 (12), 135 (15).

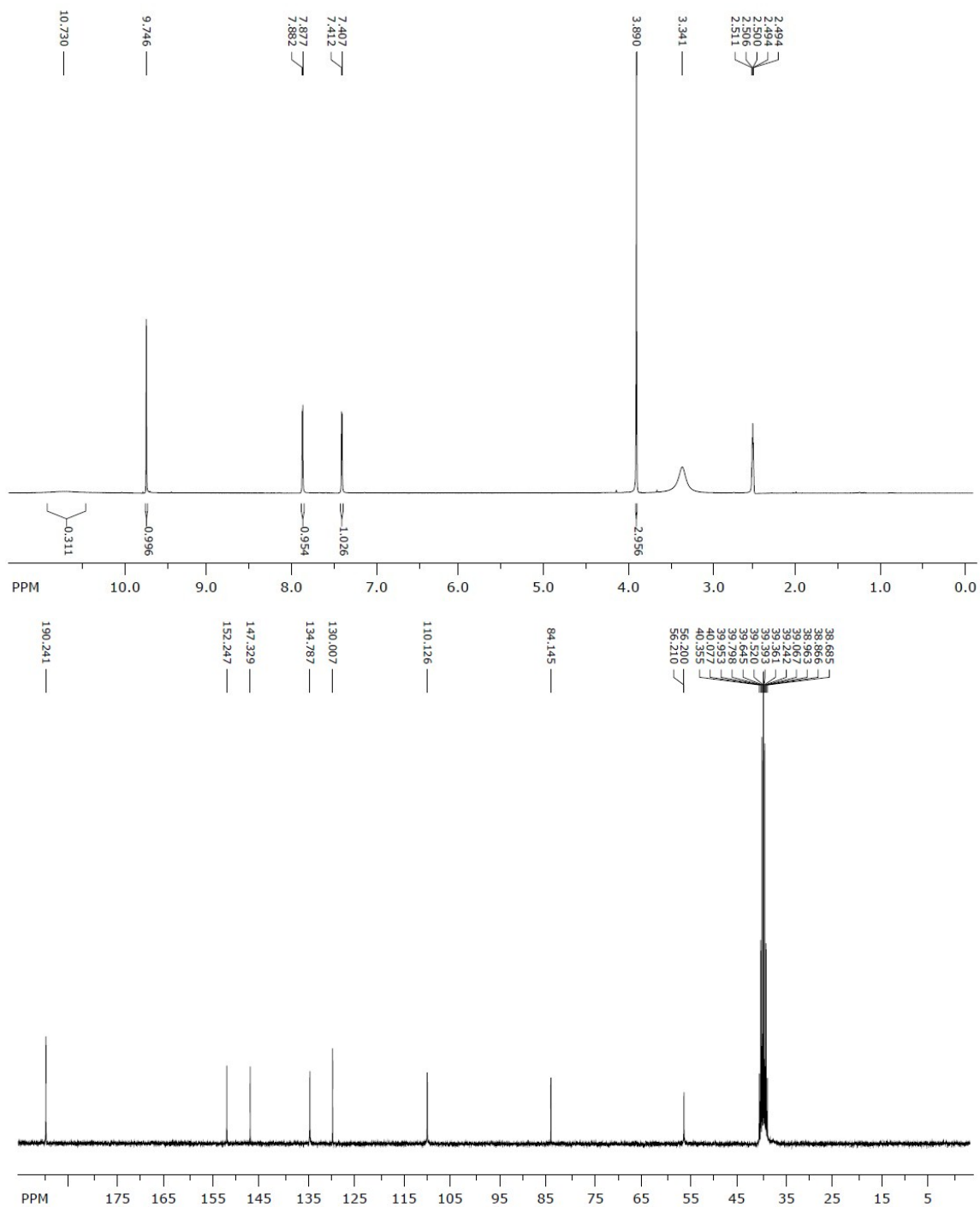
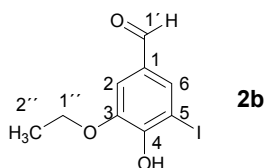
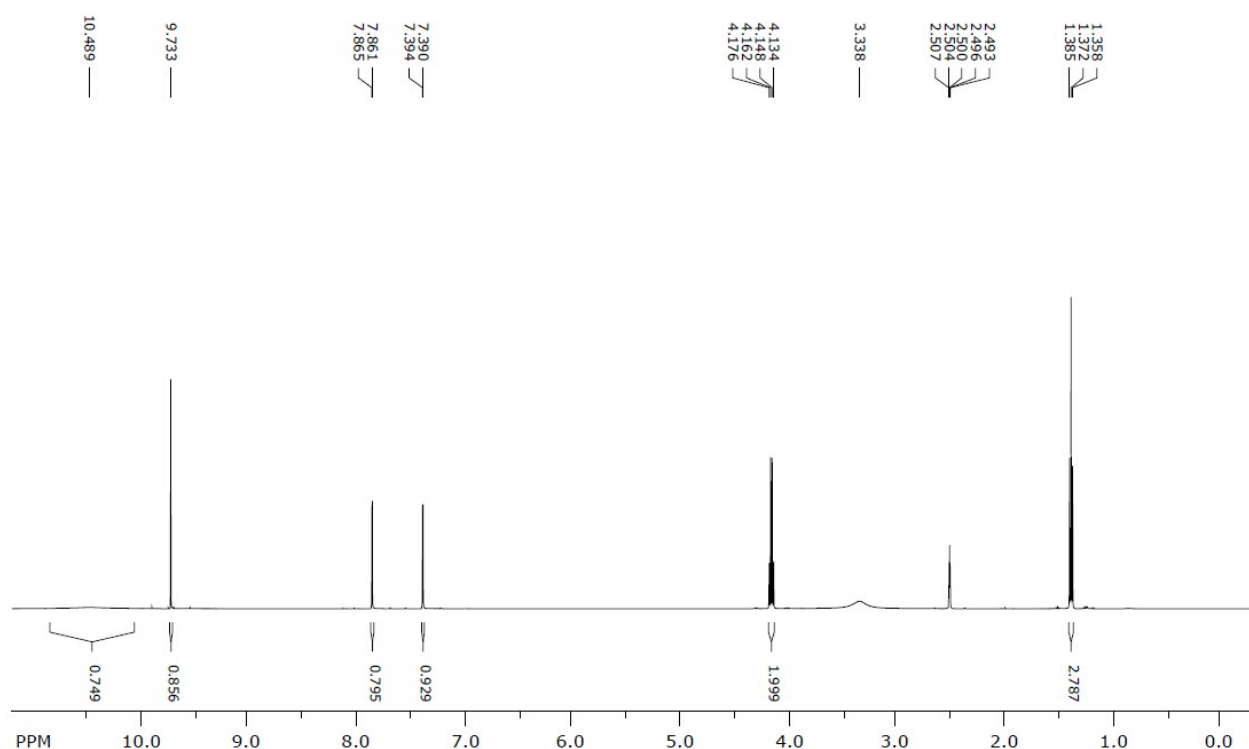


Fig.1 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2a** in DMSO-*d*₆

4.2 Synthesis and analytical data of 3-ethoxy-4-hydroxy-5-iodobenzaldehyde (**2b**)⁴



According to general procedure I, 3-ethoxy-4-hydroxybenzaldehyde (**1b**) (332 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/CH₂Cl₂/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give 3-ethoxy-4-hydroxy-5-iodobenzaldehyde (**2b**) as a colourless powder (473 mg, 1.62 mmol, 81%); mp 137–138 °C (lit.,⁴ 184 °C); *R*_f = 0.60 (petroleum ether/CH₂Cl₂/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 228 (log ε, 4.35), 286 (4.03) and 361 (3.21); IR (ATR) ν_{max}/cm⁻¹ 3204 (OH), 2979 (CH₂, CH₃), 1664 (C=O), 1568 (arom. C=C), 1174 (arom. C-O), 669 (arom. C-H) and 581 (arom. C-I); δ_H (500 MHz; DMSO-*d*₆) 1.37 (3H, t, ³*J*_{2''-H, 1''-H} = 7.3 Hz, 2''-H₃); 4.15 (2H, q, ³*J*_{1''-H, 2''-H} = 7.0 Hz, 1''-H₂); 7.39 (1H, d, ³*J*_{2-H, 6-H} = 1.7 Hz, 2-H); 7.86 (1H, d, ³*J*_{6-H, 2-H} = 1.8 Hz, 6-H); 9.73 (1H, s, 1'-H) and 10.49 (1H, br, 4-OH); δ_C (125 MHz; DMSO-*d*₆) 14.4 (C-2''), 64.6 (C-1□'), 84.2 (C-5), 111.2 (C-2), 130.0 (C-1), 134.5 (C-6), 146.4 (C-3), 152.4 (C-4) and 190.3 (C-1'); MS (ESI, neg.) *m/z* 292 [(M-H)⁻, 100%].



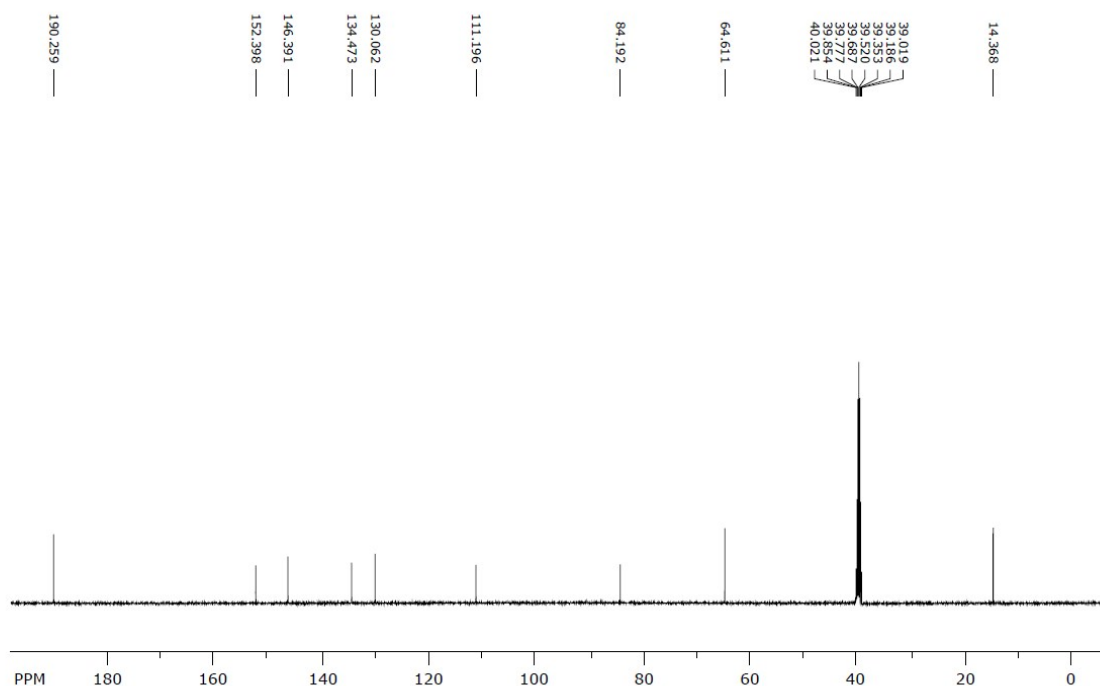
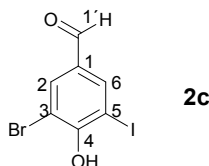


Fig. 2 ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **2b** in $\text{DMSO-}d_6$

4.3 Synthesis and analytical data of 3-bromo-4-hydroxy-5-iodobenzaldehyde (**2c**)



According to general procedure I, 3-bromo-4-hydroxybenzaldehyde (**1c**) (402 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give 3-bromo-4-hydroxy-5-iodobenzaldehyde (**2c**) as colourless powder (430 mg, 1.32 mmol, 66%); mp 186–187 °C; R_f = 0.52 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 237 (log ϵ , 4.33), 273 (3.99) and 353 (3.65); IR(ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3049 (OH), 1665 (C=O), 1568 (arom. C=C), 1224 (arom. C-O), 714 (arom. C-Br/I), 654 (arom. C-H) and 535 (arom. C-Br/I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 8.05 (1H, d, $^4J_{2\text{-H}, 6\text{-H}} = 2.0$ Hz, 2-H); 8.23 (1H, d, $^4J_{6\text{-H}, 2\text{-H}} = 1.9$ Hz, 6-H); 9.74 (1H, s, 1'-H) and 10.81 (1H, br, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 88.0 (C-5), 110.1 (C-3), 131.4 (C-1), 134.6 (C-2), 139.9 (C-6), 158.3 (C-4) and 189.4 (C-1'); MS (EI, 70 eV) m/z 326 (M^+ , 100%), 297 (5), 281 (5), 128 (65), 63 (50). HRMS (EI, M^+) calcd for $\text{C}_7\text{H}_4\text{BrIO}_2$: 327.8413; found: 327.8403.

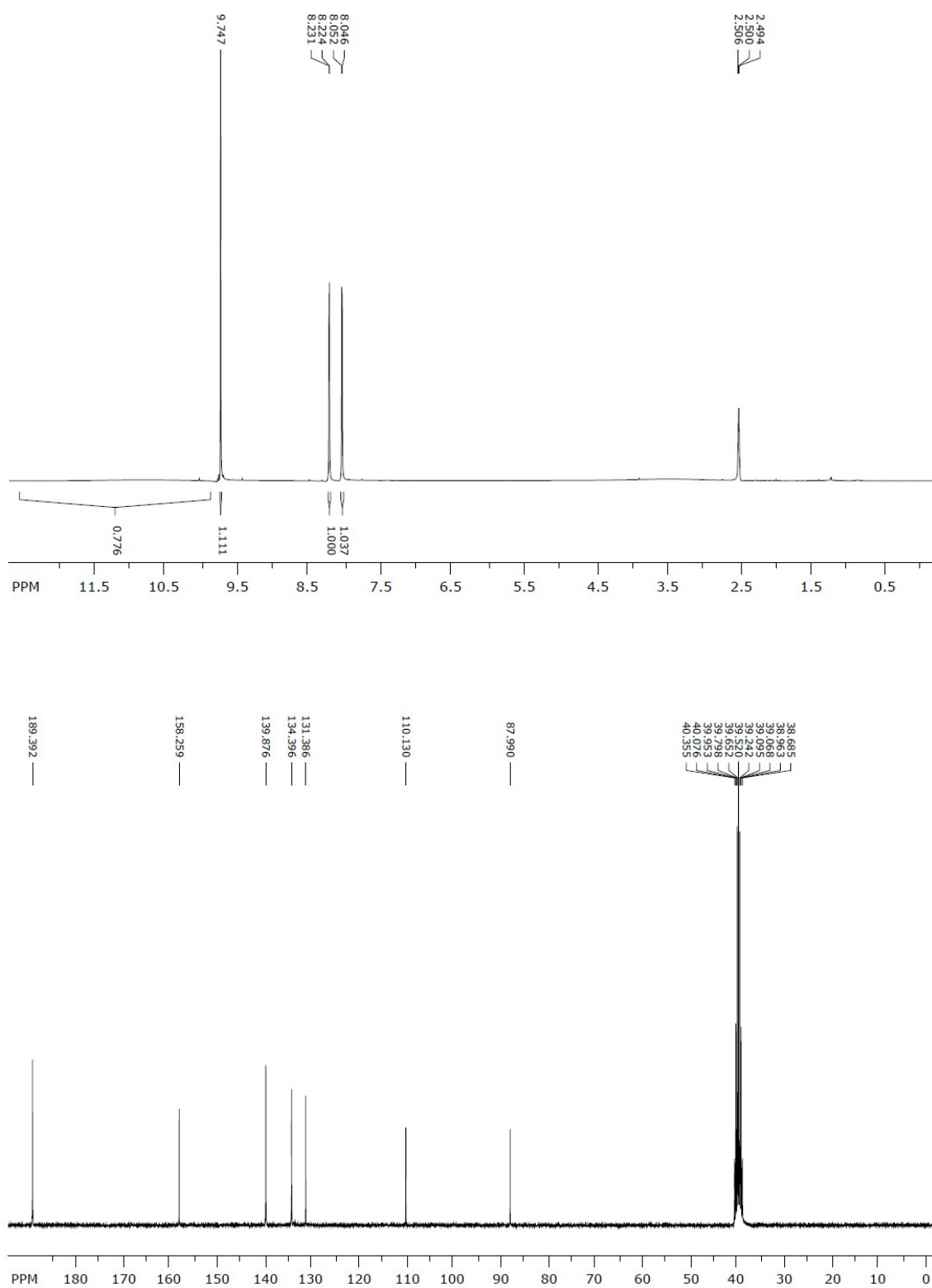
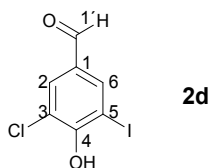
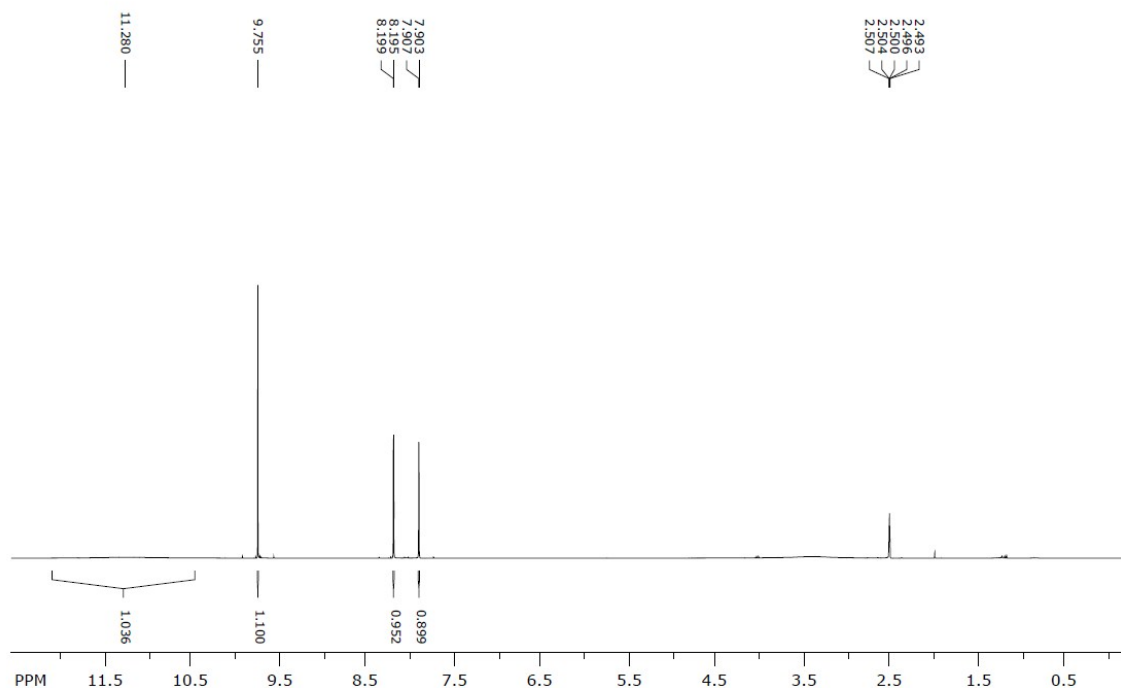


Fig. 3 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2c** in DMSO-*d*₆

4.4 Synthesis and analytical data of 3-chloro-4-hydroxy-5-iodobenzaldehyde (**2d**)



According to general procedure I, 3-chloro-4-hydroxybenzaldehyde (**1d**) (312 mg, 2 mmol) was reacted for 48 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 5.5 : 3 : 1.5) on SiO₂ to give 3-chloro-4-hydroxy-5-iodobenzaldehyde (**2d**) as colourless powder (282 mg, 1.00 mmol, 50%); mp 157–158 °C; *R_f* = 0.48; (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 206 (log ϵ , 4.10), 237 (4.33), 274 (4.02) and 353 (3.79); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm⁻¹ 3051 (OH), 1664 (C=O), 1572 (arom. C=C), 1195 (arom. C-O), 652 (arom. C-H) and 546 (arom. C-I); δ_{H} (500 MHz; DMSO-*d*₆) 7.90 (1H, d, ⁴*J*_{2-H, 6-H} = 1.8 Hz, 2-H); 8.21 (1H, d, ⁴*J*_{6-H, 2-H} = 1.8 Hz, 6-H); 9.75 (1H, s, 1'-H) and 11.27 (1H, br, 4-OH); δ_{C} (125 MHz; DMSO-*d*₆) 87.9 (C-5), 120.3 (C-1), 130.8 (C-2), 131.0 (C-3), 139.4 (C-6), 157.4 (C-4) and 189.5 (C-1'); MS (EI, 70 eV) *m/z* 282 (M⁺, 100%), 253 (5), 155 (10), 127 (10), 63 (20); HRMS (EI, M⁺) calcd for C₇H₄ClIO₂: 281.8939; found: 281.8941.



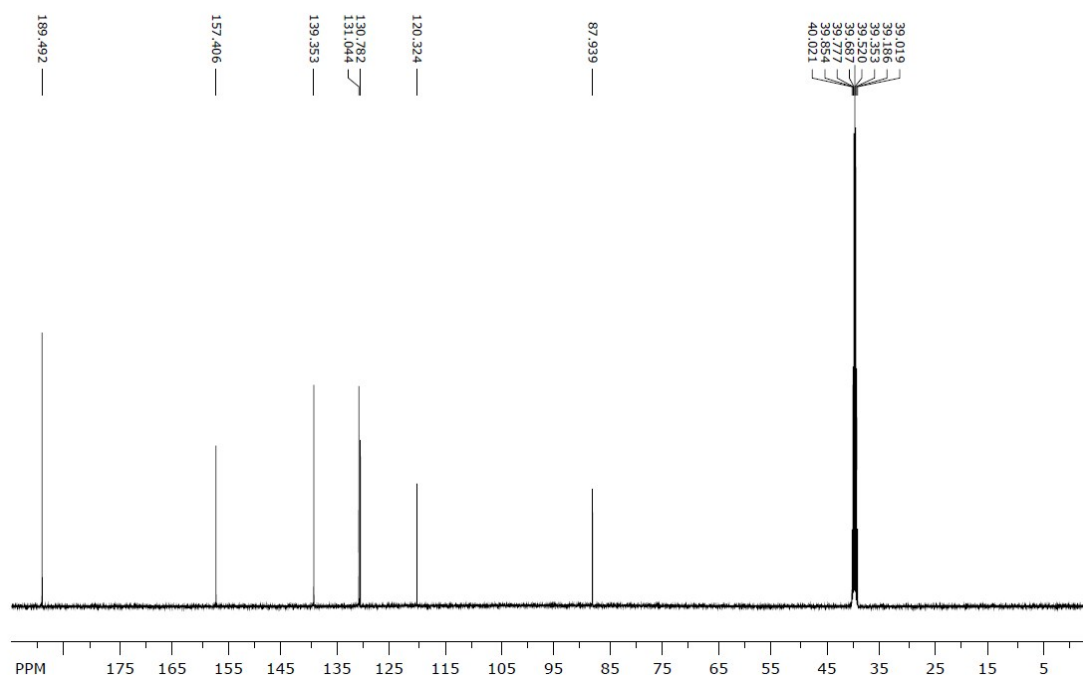
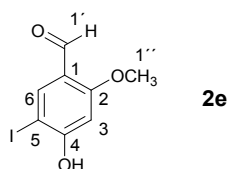


Fig. 4 ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **2d** in $\text{DMSO-}d_6$

4.5 Synthesis and analytical data of 4-hydroxy-5-iodo-2-methoxybenzaldehyde (**2e**)



According to the general procedure I, 4-hydroxy-2-methoxybenzaldehyde (**1e**) (304 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give 4-hydroxy-5-iodo-2-methoxybenzaldehyde (**2e**) as a colourless powder (462 mg, 1.66 mmol, 83%); mp 207–208 °C; R_f = 0.28 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 236 (log ϵ , 4.30), 269 (4.06) and 326 (3.82); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm $^{-1}$ 3019 (OH), 2712 (CH_3), 1634 (C=O), 1552 (arom. C=C), 1254 (arom. C-O), 825 (arom. C-H) and 516 (arom. C-I); δ_{H} (500 MHz; $\text{DMSO-}d_6$) 3.83 (3H, s, 1''-H $_3$), 6.61 (1H, s, 3-H), 7.92 (1H, s, 6-H), 10.01 (1H, s, 1'-H) and 11.60 (1H, br, 4-OH); δ_{C} (125 MHz; $\text{DMSO-}d_6$) 55.8 (C-1''), 75.0 (C-5), 98.8 (C-3), 119.0 (C-1), 138.5 (C-6), 163.4 (C-2), 163.6 (C-4) and 186.0 (C-1'); MS (EI, 70 eV) m/z 278 (M^+ , 100%), 260 (80), 232 (40), 167 (20), 85 (20); HRMS (EI, M^+) calcd for $\text{C}_8\text{H}_7\text{IO}_3$: 277.9434; found: 277.9436.

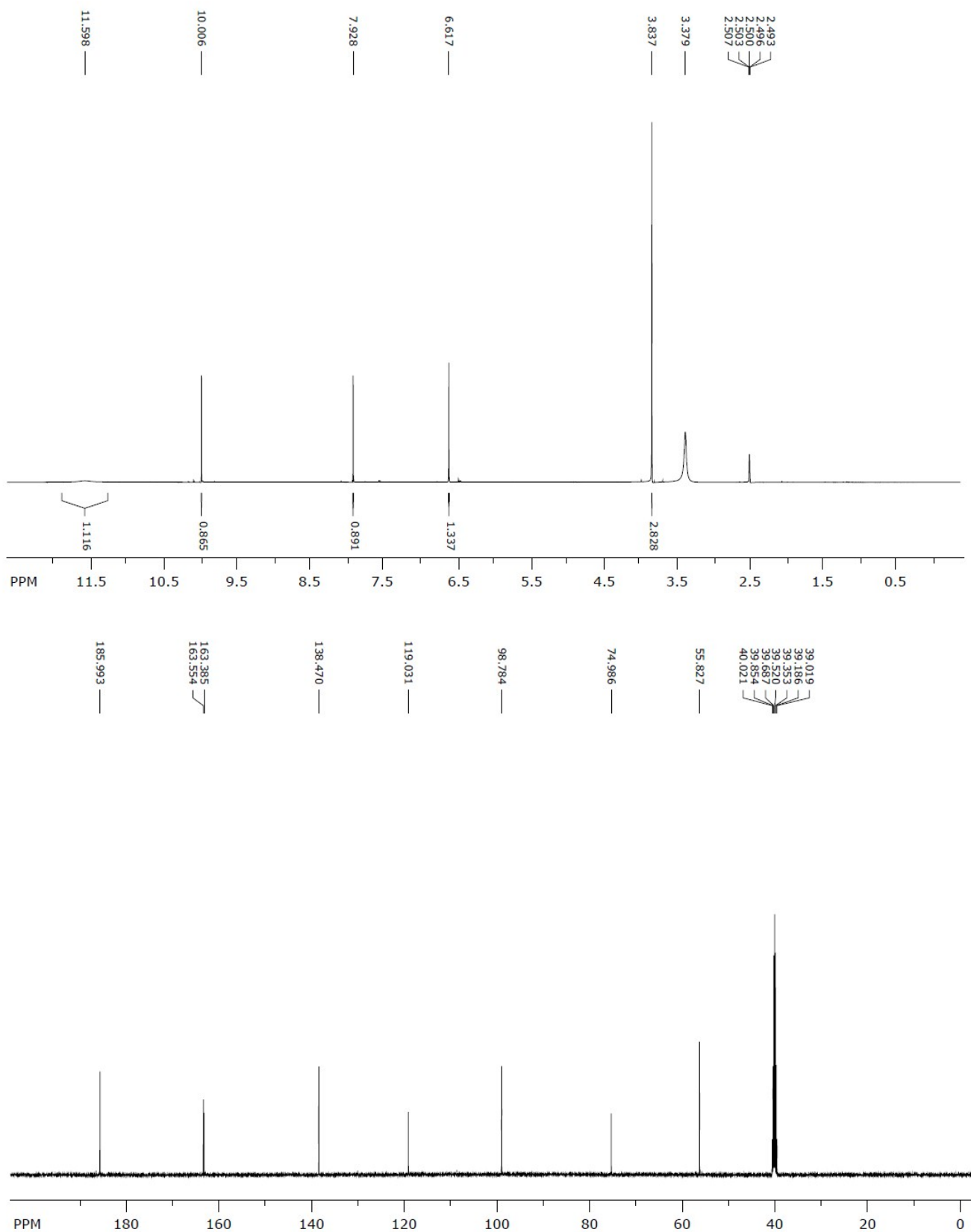
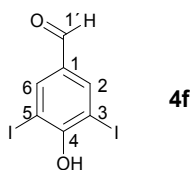


Fig. 5 ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **2e** in $\text{DMSO-}d_6$

4.6 Synthesis and analytical data of 4-hydroxy-3,5-diiodobenzaldehyde (**4f**)⁵



A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1.328 g, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (300 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (15 h, 20 U/h) at room temperature. Simultaneously, 4-hydroxy-benzaldehyde (**1f**) (304 mg, 2 mmol) in DMSO (3 mL) was added at a constant rate (0.2 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 144 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (8 × 25 mL). The combined organic phases were washed with deionized water (5 × 10 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give 4-hydroxy-3,5-diiodobenzaldehyde (**4f**) as colourless powder (522 mg, 1.40 mmol, 70%); mp 195–196 °C (lit.,⁵ 200–201 °C); R_f = 0.50 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 241 (log ϵ , 4.35), 270 (3.97) and 355 (3.72); IR(ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3162 (OH), 1663 (C=O), 1561 (arom. C=C), 1224 (arom. C-O), 701 (arom. C-I) and 638 (arom. C-H); δ_H (300 MHz; DMSO-*d*₆) 8.24 (2H, s, 2-H and 6-H); 9.72 (1H, s, 1'-H) and 10.58 (1H, br, 4-OH); δ_C (125 MHz; DMSO-*d*₆) 86.5 (C-3 and C-5), 132.2 (C-1), 140.7 (C-2 and C-6), 160.7 (C-4) and 189.3 (C-1'). MS (EI, 70 eV) m/z 374 (M⁺, 100%), 344 (5), 246 (5), 218 (5), 92 (10).

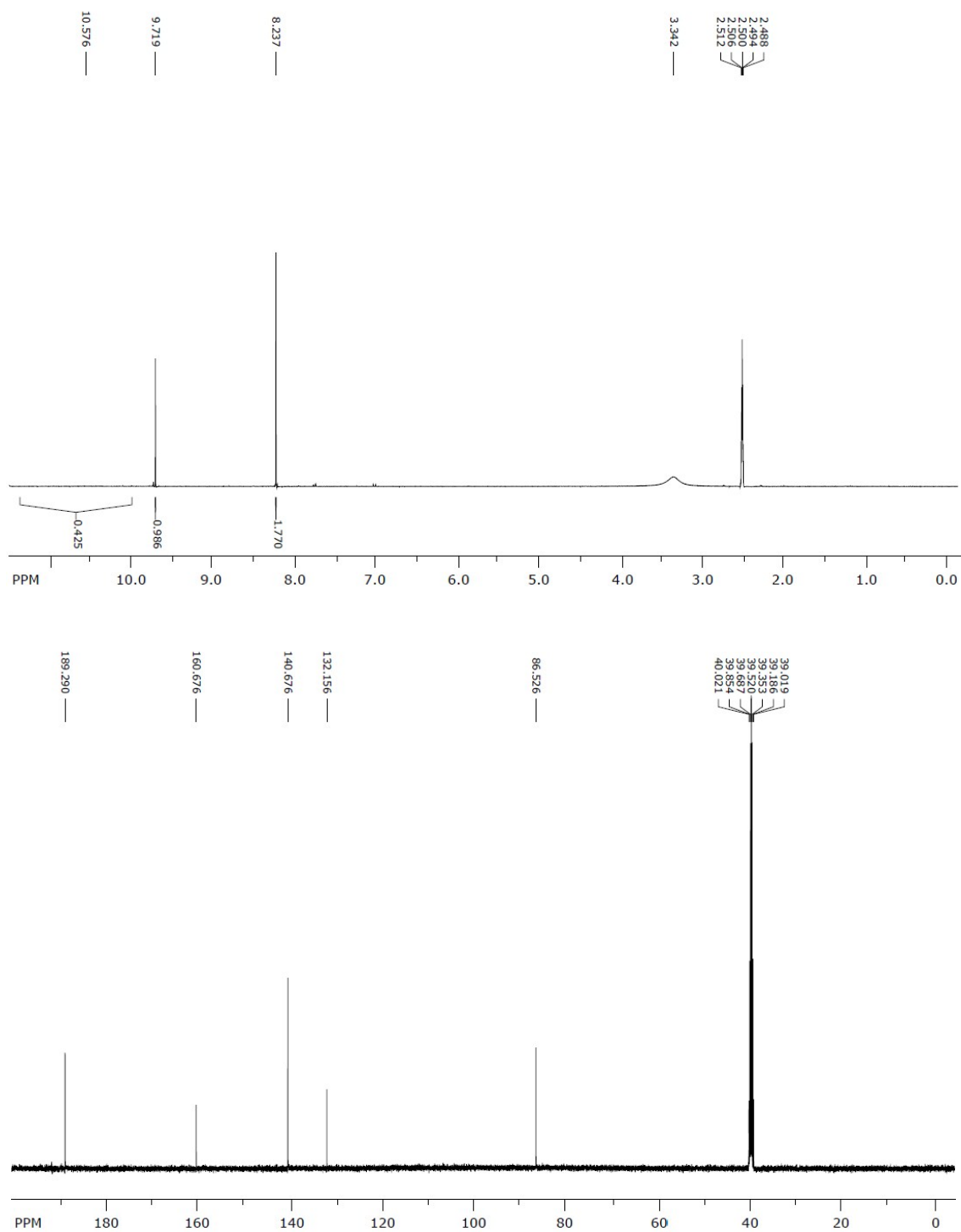
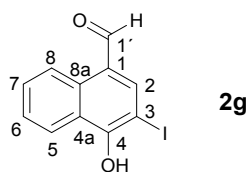


Fig. 6 ¹H (300 MHz) and ¹³C (125 MHz) NMR spectra of 4f in DMSO-*d*₆

4.7 Synthesis and analytical data of 4-hydroxy-3-iodo-1-naphthaldehyde (**2g**)



According to general procedure I, 4-hydroxy-1-naphthaldehyde (**1g**) (344 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM = 3 : 2) on SiO₂ to give 4-hydroxy-3-iodo-1-naphthaldehyde (**2g**) as slightly yellow powder (282 mg, 1.00 mmol, 50%); mp 140–141 °C; R_f = 0.57 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 202 (log ϵ , 4.42), 243 (4.47), 327 (3.96) and 397 (3.84); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3048 (OH), 1643 (C=O), 1564 (arom. C=C), 1159 (arom. C-O), 751 (arom. C-H) and 518 (arom. C-I); δ_H (600 MHz; DMSO-*d*₆) 7.65 (1H, dt-like, 6-H), 7.75 (1H, dt-like, 7-H); 8.36 (1H, d, ³ $J_{5-H, 6-H}$ = 8.4 Hz, 5-H); 8.43 (1H, s, 2-H), 9.18 (1H, d, ³ $J_{8-H, 7-H}$ = 8.2 Hz, 8-H), 10.11 (1H, s, 1'-H) and 11.29 (1H, br, 4-OH); δ_C (150 MHz; DMSO-*d*₆) 78.8 (C-3), 122.7 (C-5), 124.5 (C-4a), 124.6 (C-1), 125.3 (C-8), 126.8 (C-6), 129.5 (C-7), 131.2 (C-8a), 147.9 (C-2), 159.0 (C-4) and 191.9 (C-1'); MS (EI, 70 eV) m/z 298 (M⁺, 100%), 270 (5), 241 (10), 171 (10), 142 (30); HRMS (EI, M⁺) calcd for C₁₁H₇IO₂: 297.9486; found: 297.9476.

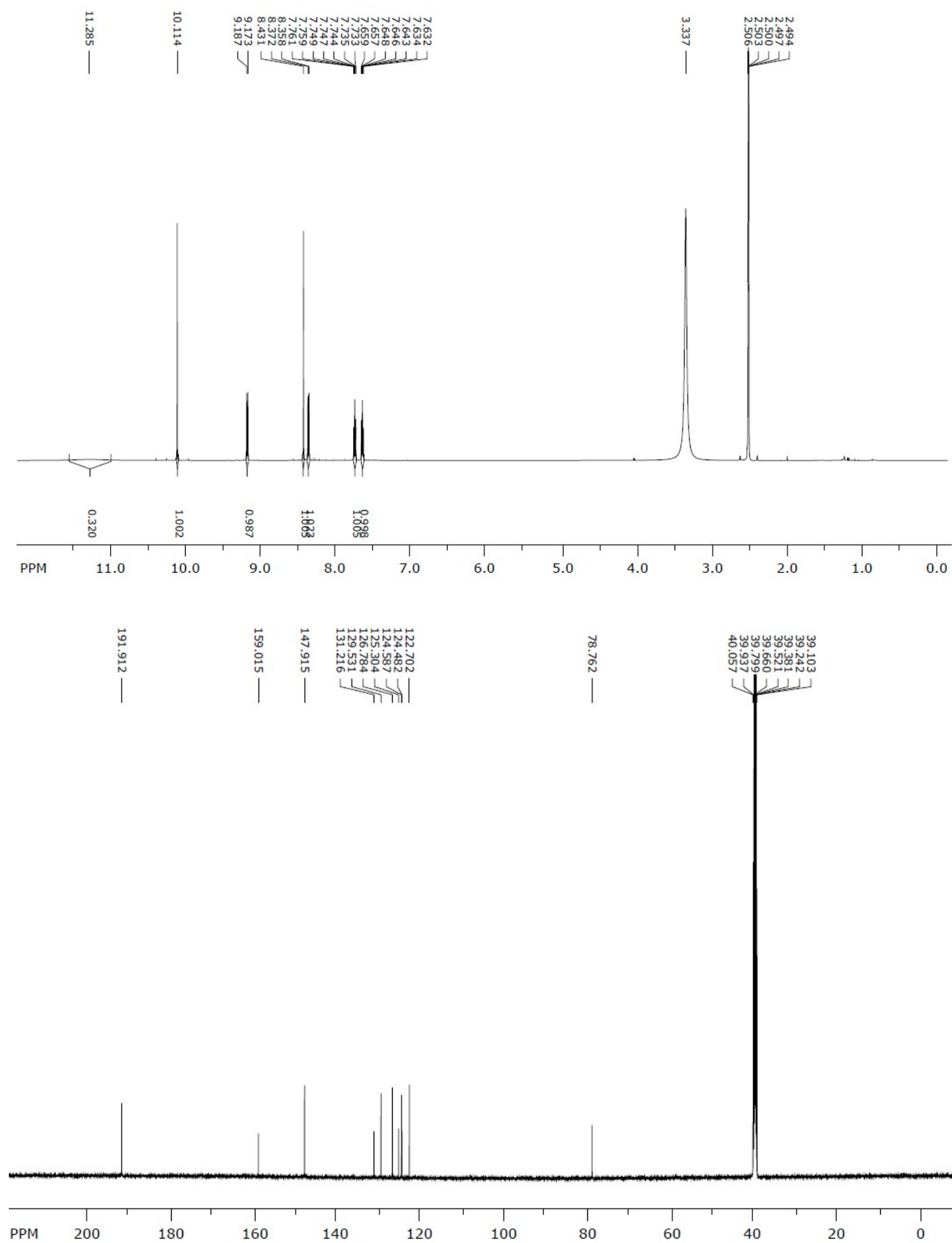
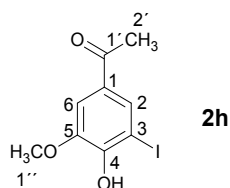
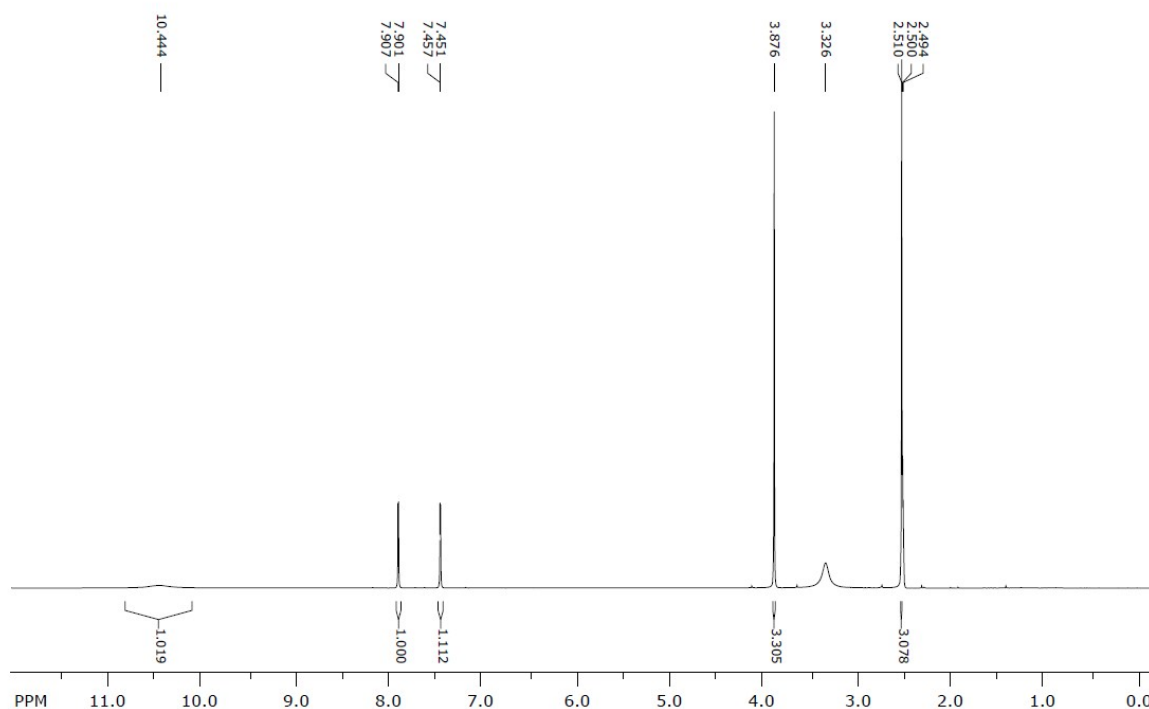


Fig. 7 ¹H (600 MHz) and ¹³C (150 MHz) NMR spectra of **2g** in DMSO-*d*₆

4.8 Synthesis and analytical data of 1-(4-hydroxy-3-iodo-5-methoxyphenyl)ethanone (**2h**)⁶



According to general procedure I, 1-(4-hydroxy-3-methoxyphenyl)ethanone (**1h**) (332 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give 1-(4-hydroxy-3-iodo-5-methoxyphenyl)ethanone (**2h**) as a colourless powder (426 mg, 1.46 mmol, 73%); mp 174–175 °C (lit.,⁶ 175–177 °C); *R*_f = 0.43 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 229 (log ϵ , 4.33) and 279 (3.97); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm⁻¹ 3236 (OH), 2933 (CH₃), 1655 (C=O), 1568 (arom. C=C), 1210 (arom. C-O), 874 (arom. C-H) and 583 (arom. C-I); δ_{H} (300 MHz; DMSO-*d*₆) 2.51 (3H, s, 2'-H₃), 3.87 (3H, s, 1''-H₃), 7.45 (1H, d, ⁴*J*_{6-H, 2-H} = 1.9 Hz, 6-H); 7.90 (1H, d, ⁴*J*_{2-H, 6-H} 1.9 Hz, 2-H) and 10.44 (1H, br, 4-OH); δ_{C} (75 MHz; DMSO-*d*₆) 26.3 (C-2'), 57.2 (C-1''), 84.0 (C-3), 110.8 (C-6), 130.2 (C-1), 131.9 (C-2), 146.7 (C-5), 150.1 (C-4) and 195.3 (C-1') MS (EI) *m/z* 292 (M⁺, 70%), 277 (100), 249 (5), 135 (5), 94 (10).



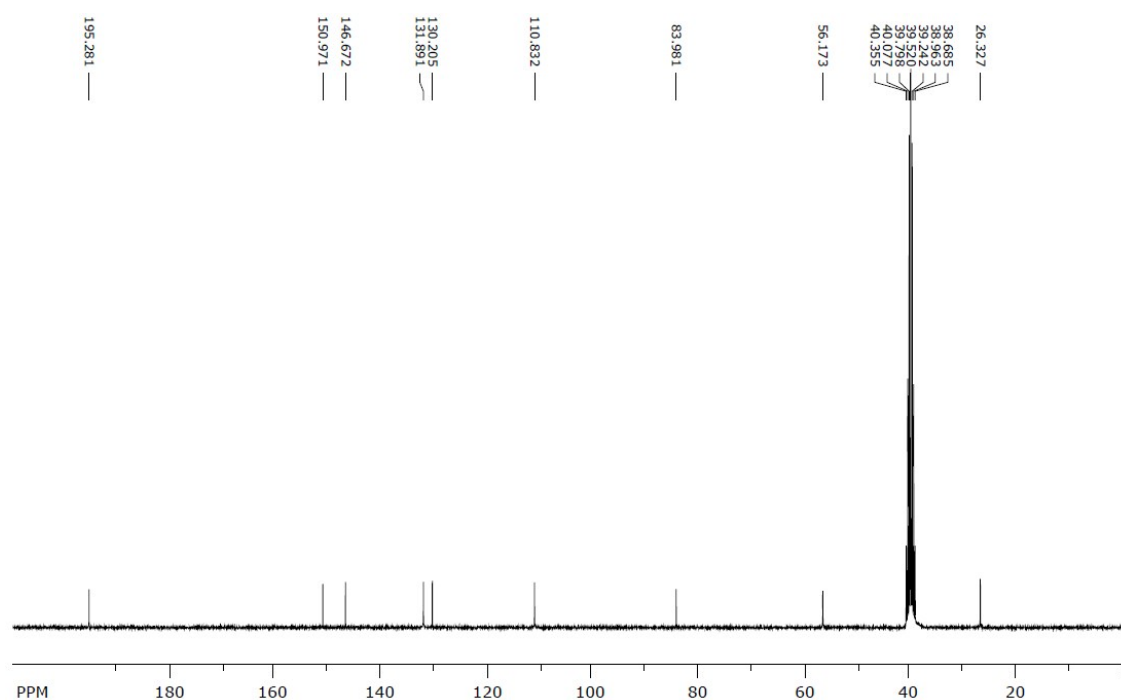
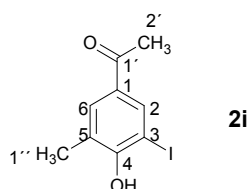


Fig. 8 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **2h** in CDCl_3

4.9 Synthesis and analytical data of 1-(4-hydroxy-3-iodo-5-methylphenyl)ethanone (**2i**)



According to general procedure I, 1-(4-hydroxy-3-methylphenyl)ethanone (**1i**) (300 mg, 2 mmol) was reacted for 15 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give 1-(4-hydroxy-3-iodo-5-methylphenyl)ethanone (**2i**) a colourless powder (480 mg, 1.74 mmol, 87%); mp 158–159 °C; R_f = 0.58 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 229 (log ϵ , 4.33), 269 (4.04) and 354 (3.35); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm $^{-1}$ 3140 (OH), 2908 (CH_3), 1651 (C=O), 1546 (arom. C=C), 1427 (CH_3), 1175 (arom. C-O), 723 (arom. C-I), 629 (arom. C-H) and 505 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 2.27 (3H, s, 1'- H_3), 2.47 (3H, s, 2'- H_3), 7.72 (1H, d, $^4J_{6\text{-H}, 2\text{-H}}$ = 1.6 Hz, 6-H); 8.10 (1H, d, $^4J_{2\text{-H}, 6\text{-H}}$ = 1.6 Hz, 2-H) and 9.96 (1H, br, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 17.5 (C-1'), 26.3 (C-2'), 86.7 (C-3), 124.9 (C-5), 130.7 (C-1), 131.7 (C-6), 137.2 (C-2), 158.8

(C-4) and 195.4 (C-1'); MS (EI, 70 eV) m/z 276 (M^+ , 30%), 261 (100), 134 (5), 105 (10), 77 (10);
HRMS (EI, M^+) calcd. for $C_9H_9IO_2$: 275.9642; found: 275.9641.

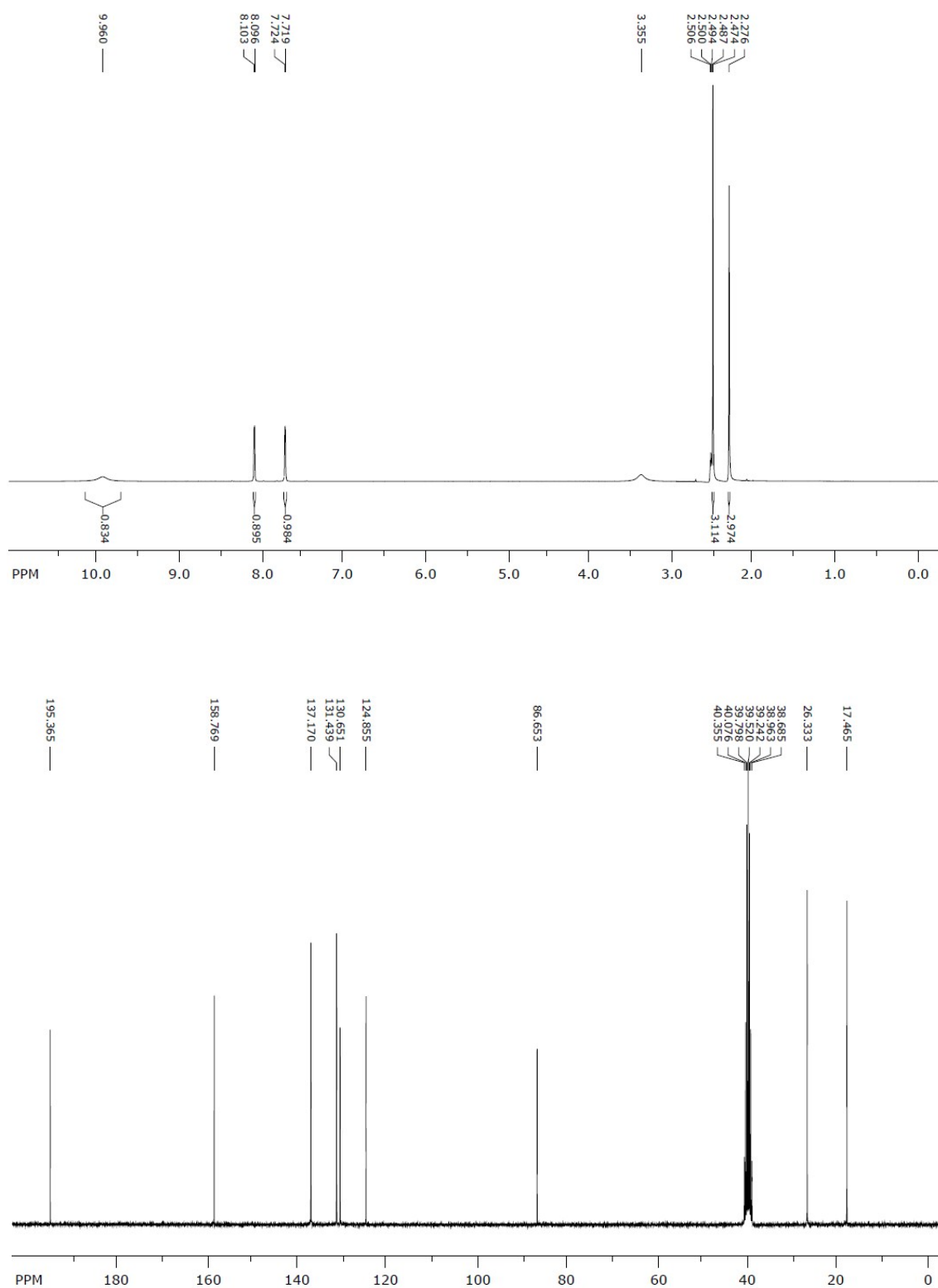
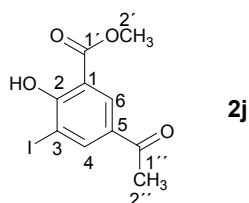


Fig. 9 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of 2i in CDCl₃

4.10 Synthesis and analytical data of methyl 5-acetyl-2-hydroxy-3-iodobenzoate (**2j**)



A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (996 mg, 3 equiv., 6 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (180 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 36 U/h) at room temperature. Simultaneously, methyl 5-acetyl-2-hydroxybenzoate (**1j**) (388 mg, 1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 168 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM = 1 : 1) on SiO₂ to give methyl-5-acetyl-2-hydroxy-3-iodobenzoate (**2j**) (71 mg, 0.22 mmol, 11%) as colourless powder; mp 135–136 °C; *R_f* = 0.65 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 241 (log ε, 4.35) and 321 (3.65); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3082 (OH), 2960 (CH₃), 1677 (C=O), 1590 (arom. C=C), 1247 (arom. C-O), 792 (arom. C-H) and 572 (arom. C-I); δ_{H} (300 MHz; DMSO-*d*₆) 2.55 (3H, s, 2''-H₃), 3.96 (3H, s, 2'-H₃), 8.33 (1H, d, ⁴*J*_{6-H, 4-H} = 2.1 Hz, 6-H); 8.50 (1H, d, ⁴*J*_{2-H, 6-H} = 2.1 Hz, 2-H) and 11.75 (1H, s, 2-OH); δ_{C} (75 MHz; DMSO-*d*₆) 26.4 (C-2''), 53.3 (C-2'), 86.9 (C-3), 112.6 (C-1), 130.1 (C-5), 130.5 (C-6), 144.2 (C-4), 162.3 (C-2), 168.5 (C-1') and 194.8 (C-1''); MS (EI, 70 eV) *m/z* 320 (M⁺, 70%), 291 (100), 273 (80), 245 (15), 206 (5), 127 (20); HRMS (EI, M⁺) calcd for C₁₀H₉IO₄: 319.9540; found: 319.9533.

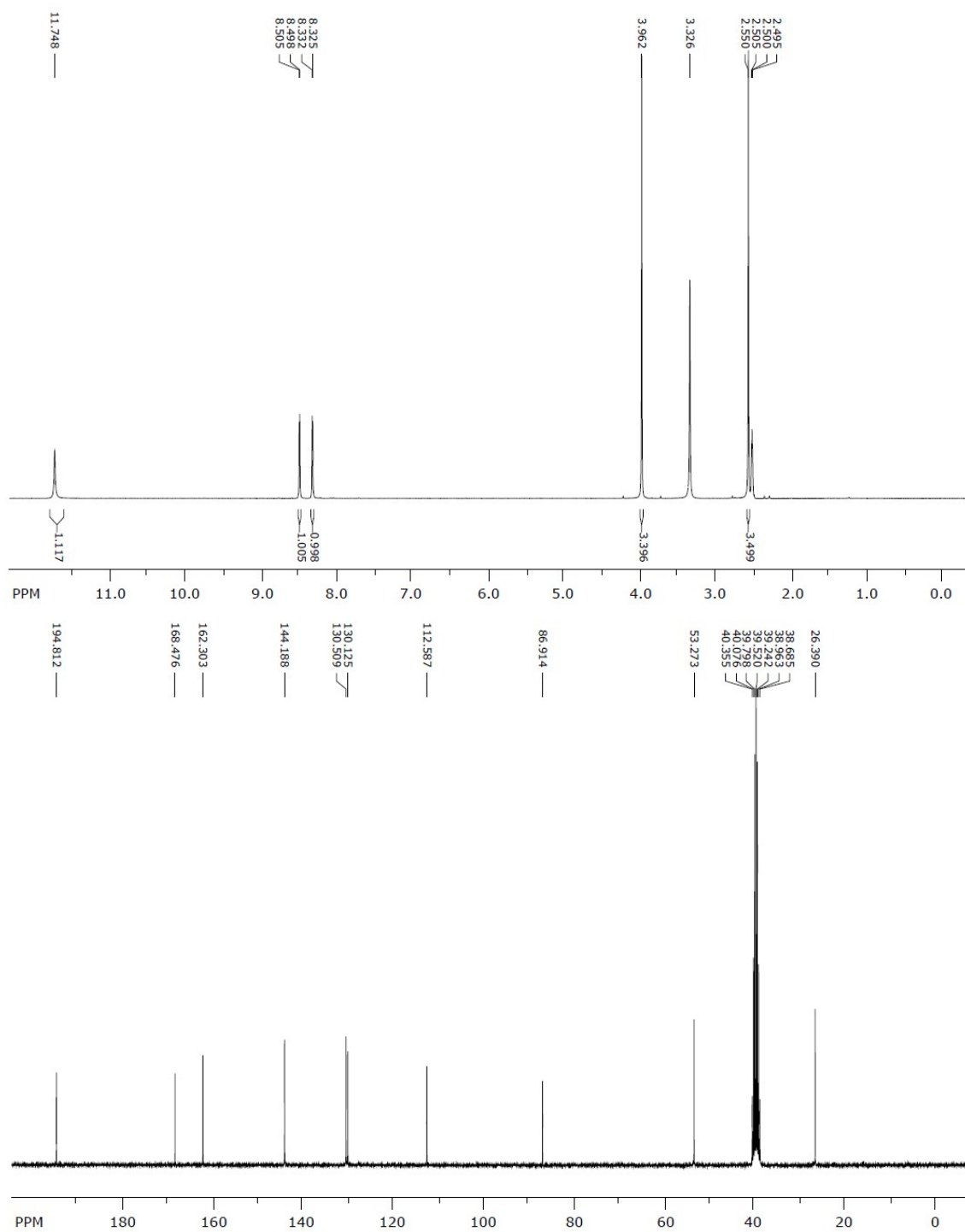


Fig. 10 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2j** in DMSO-*d*₆

4.11 Synthesis and analytical data of 1-(4-hydroxy-5-iodo-2-methylphenyl)ethanone (**2k**) and 1-(4-hydroxy-3,5-diiodo-2-methylphenyl)ethanone (**4k**)



Iodination of **1k** with four equivalents KI

A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1328 mg, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (180 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 36 U/h) at room temperature. Simultaneously, 1-(4-hydroxy-2-methylphenyl)ethanone (**1k**) (300 mg, 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 15 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give (4-hydroxy-5-iodo-2-methylphenyl)ethanone (**2k**) (402 mg, 1.46 mmol, 73%) and (4-hydroxy-3,5-diiodo-2-methylphenyl)ethanone (**4k**) (104 mg, 0.26 mmol, 13%) as colourless powders.

Iodination of **1k** with 1.1 equivalents KI under optimized conditions

A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (365 mg, 1.1 equiv., 2.2 mmol), laccase from *Trametes versicolor* (45 U), 1-(4-hydroxy-2-methylphenyl)ethanone (**1k**) (300 mg, 2 mmol) and acetate buffer (90 mL, 0.1 M, pH 5.0). Additional laccase from *Trametes*

versicolor (180 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (12 h, 15 U/h) at room temperature. Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 15 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give (4-hydroxy-5-iodo-2-methylphenyl)ethanone (**2k**) (430 mg, 1.56 mmol, 78%) and (4-hydroxy-3,5-diiodo-2-methyl-phenyl)ethanone (**4k**) (30 mg, 0.07 mmol, 4%) as colourless powders.

Analytical data for 1-(4-hydroxy-5-iodo-2-methylphenyl)ethanone (2k)

mp 208–209 °C; R_f = 0.44 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 229 (log ϵ , 4.32) and 264 (3.92); IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ 3197 (OH), 2961 (CH₃), 1640 (C=O), 1589 (arom. C=C), 1255 (arom. C-O), 864 (arom. C-H) and 538 (arom. C-I); δ_{H} (300 MHz; DMSO-*d*₆) 2.36 (3H, s, 1''-H₃), 2.47 (3H, s, 2'-H₃), 6.73 (1H, s, 3-H), 8.13 (1H, s, 6-H) and 11.01 (1H, br, 4-OH); δ_{C} (75 MHz; DMSO-*d*₆) 21.7 (C-1''), 29.1 (C-2'), 80.5 (C-5), 117.8 (C-3), 130.3 (C-1), 140.8 (C-2), 141.5 (C-6), 159.6 (C-4) and 198.0 (C-1'); MS (EI, 70 eV) m/z 276 (M⁺, 35%), 261 (100), 233 (20), 149 (10), 134 (5). HRMS (EI, M⁺) calcd for C₉H₉IO₂: 275.9642; found: 275.9637.

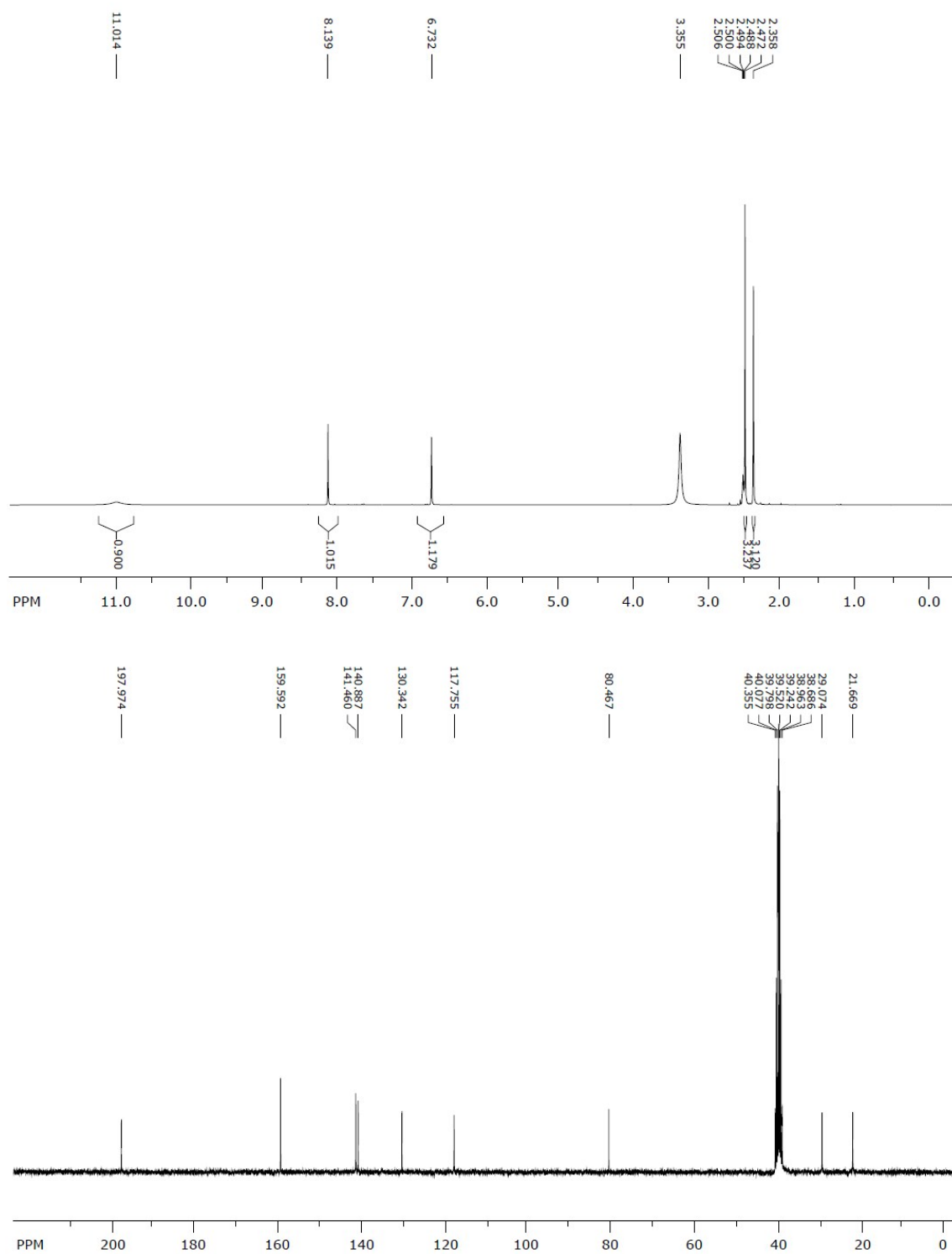
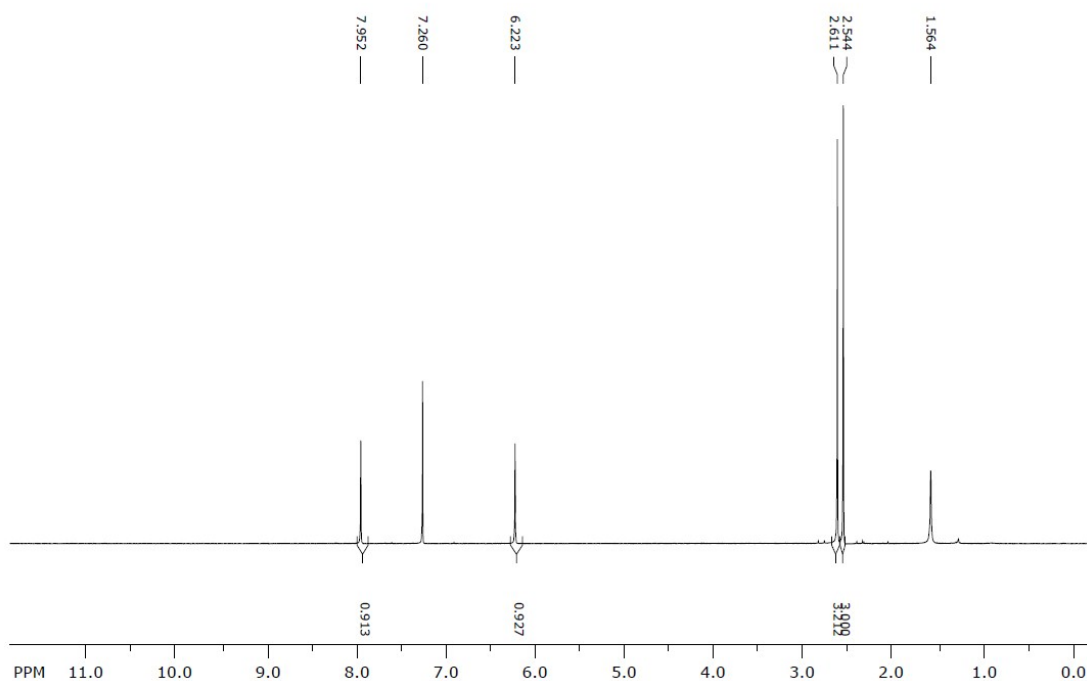


Fig. 11 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2k** in DMSO-*d*₆

Analytical data for 1-(4-hydroxy-3,5-diiodo-2-methyl-phenyl)ethanone (4k)

mp 106–107 °C; R_f = 0.65 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 237 (log ϵ , 4.41) and 336 (3.58); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3147 (OH), 2921 (CH₃), 1655 (C=O), 1566 (arom. C=C), 1110 (arom. C-O), 874 (arom. C-H) and 547 (arom. C-I); δ_H (300 MHz; CDCl₃) 2.54 (3H, s, 2'-H₃), 2.61 (3H, s, 1''-H₃) and 7.95 (1H, s, 6-H); δ_C (75 MHz; CDCl₃) 27.1 (C-1''), 29.7 (C-2'), 77.1 (C-5), 95.0 (C-3), 134.40 (C-1), 139.4 (C-6), 143.4 (C-2), 155.6 (C-4) and 199.0 (C-1'); MS (EI, 70 eV) m/z 402 (M⁺, 85%), 387 (100), 359 (5), 261 (5), 43 (10); HRMS (EI, M⁺) calcd for C₉H₉I₂O₂: 401.8609; found: 401.8604.



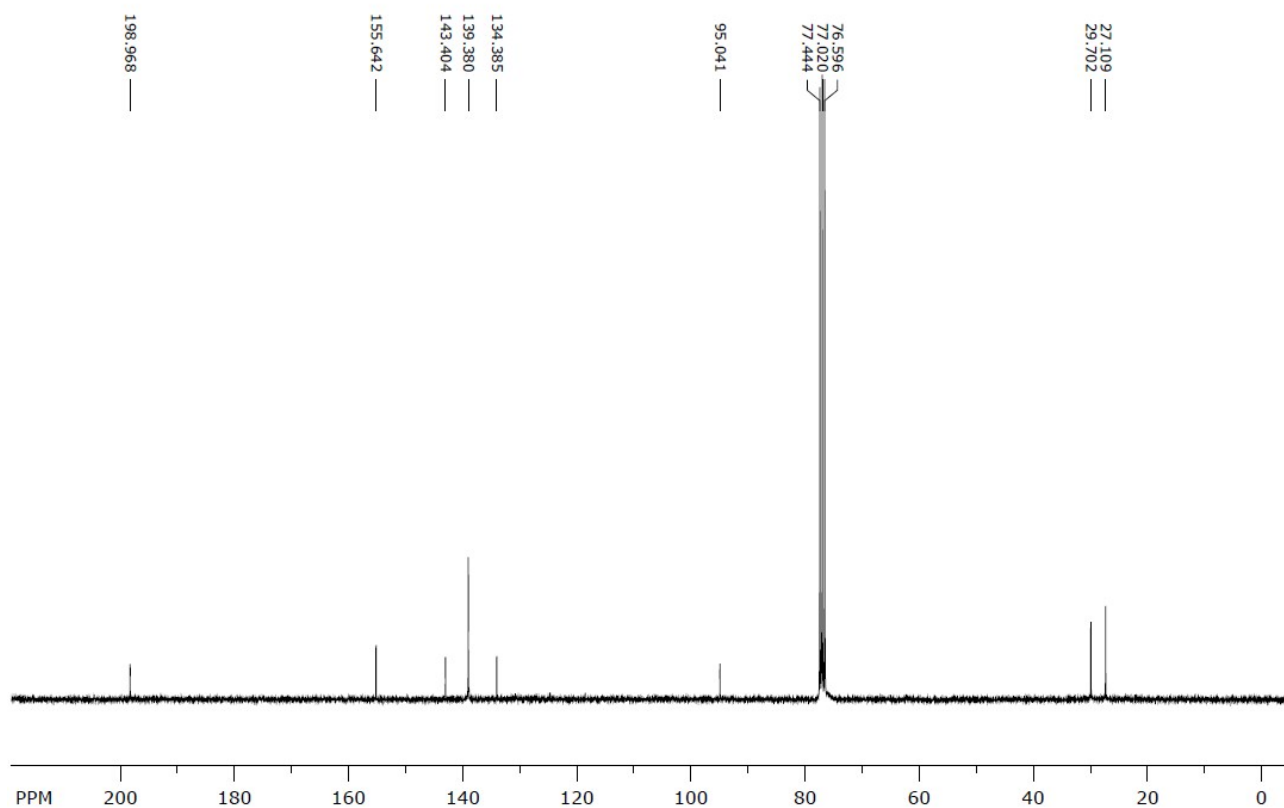
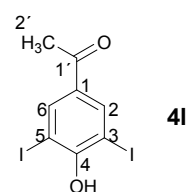
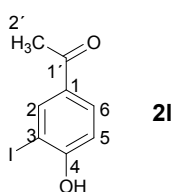


Fig. 12 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **4k** in $\text{DMSO-}d_6$

4.12 Synthesis and analytical data of 1-(4-hydroxy-3-iodophenyl)ethanone (**2l**)⁷ and 1-(4-hydroxy-3,5-diiodophenyl)ethanone (**4l**)⁸



Iodination of **1l** with four equivalents KI

A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1328 mg, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (225 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 45 U/h)

at room temperature. Simultaneously, 1-(4-hydroxyphenyl)ethanone (**11**) (272 mg, 1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 24 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give to give 1-(4-hydroxy-3,5-diiodophenyl)ethanone (**41**) (496 mg, 1.28 mmol, 64%) and 1-(4-hydroxy-3-iodophenyl)ethanone (**21**) (120 mg, 0.46 mmol, 23%) as colourless powders.

Iodination of 11 with six equivalents KI under optimized conditions

A 300 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1.992 g, 6 equiv., 12 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (180 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (300 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was slowly added to the reaction mixture by means of a syringe pump (5 h, 60 U/h) at room temperature with stirring. Simultaneously, 1-(4-hydroxyphenyl)ethanone **11** (272 mg, 1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the reaction mixture at a rate of 20 mL/min at rt for the reaction time of 24 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15:7.5:2.5) on SiO₂ to give 1-(4-hydroxy-3,5-diiodophenyl)ethanone (**41**) (650 mg, 1.68 mmol, 84%) as a colourless powder.

Analytical data for 1-(4-hydroxy-3-iodophenyl)ethanone (21)

mp 152–153 °C (lit.,⁷ 152–154 °C); R_f = 0.36 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 231 (log ϵ , 4.31), 266 (4.06) and 344 (3.15); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3116 (OH), 2774

(CH₃), 1745 (C=O), 1648 (arom. C=C), 1284 (arom. C-O), 822 (arom. C-H) and 589 (arom. C-I); δ_{H} (300 MHz; DMSO-*d*₆) 2.48 (3H, s, 2'-H₃), 6.94 (1H, d, ³J_{5-H, 6-H} = 8.5 Hz, 5-H), 7.83 (1H, dd, ³J_{6-H, 5-H} = 8.4 Hz, ⁴J_{6-H, 2-H} = 2.0 Hz 6-H), 8.24 (1H, d, ⁴J_{2-H, 6-H} = 2.0 Hz, 2-H) and 11.26 (1H, br, 4-OH); δ_{C} (75 MHz; DMSO-*d*₆) 26.3 (C-2'), 84.7 (C-3), 114.5 (C-5), 130.3 (C-1), 130.4 (C-6), 139.5 (C-2), 161.0 (C-4) and 195.2 (C-1'); MS (EI, 70 eV) *m/z* 262 (M⁺, 25%), 247 (100), 120 (5), 92 (20), 63 (5).

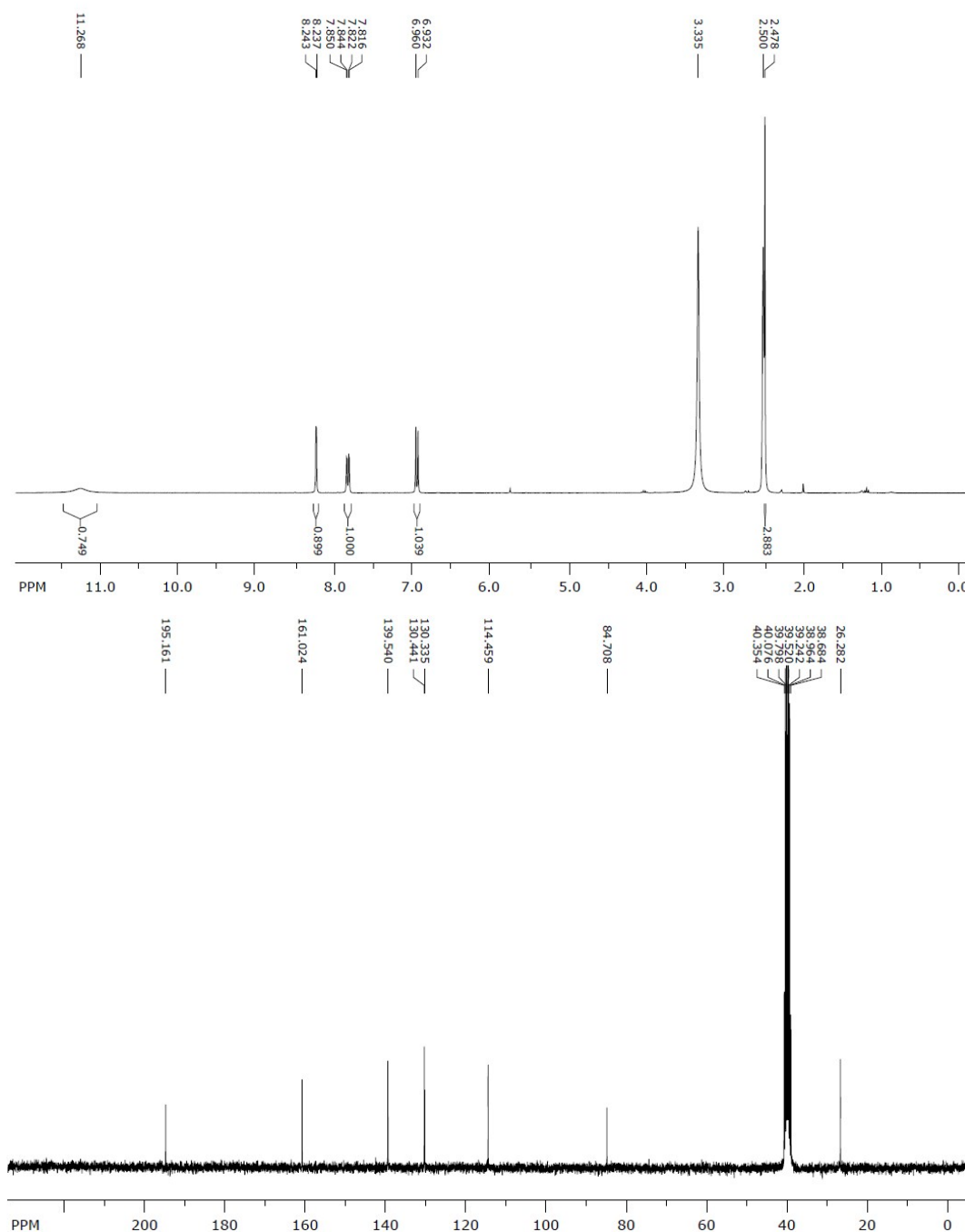
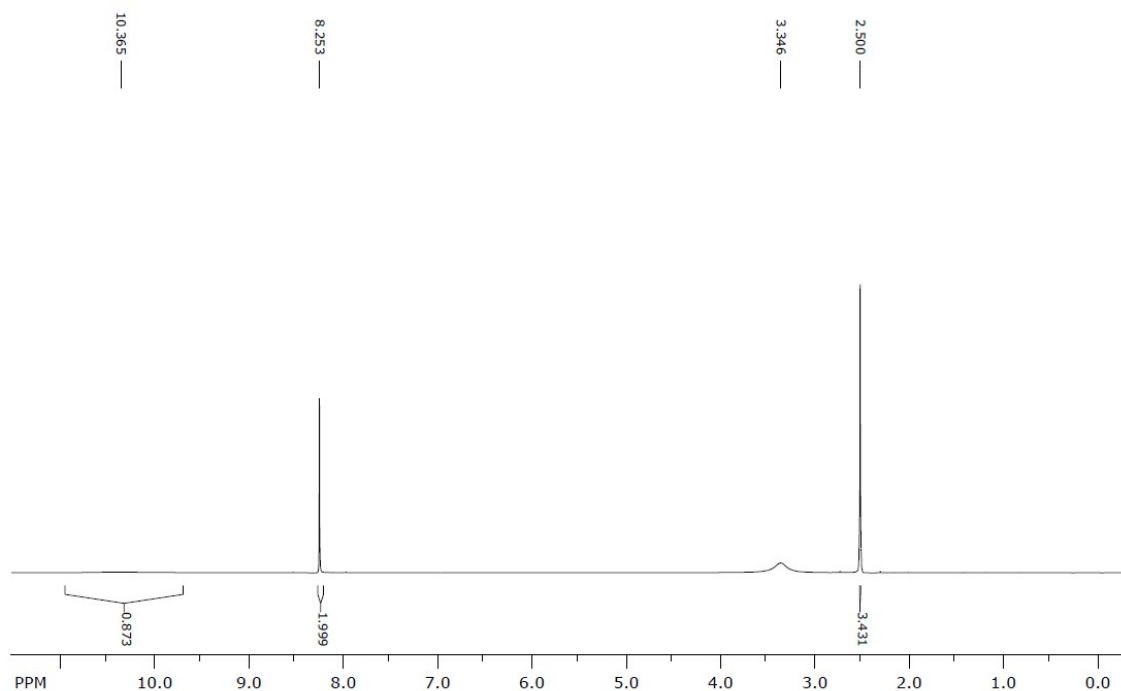


Fig. 13 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of 21 in DMSO-*d*₆

Analytical data for 1-(4-hydroxy-3,5-diiodophenyl)ethanone (4l)

mp 172–173 °C (lit.,⁸ 175–177 °C); R_f = 0.60 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 240 (log ϵ , 4.36) and 344 (3.77); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3064 (OH), 1664 (C=O), 1575 (arom. C=C), 1231 (arom. C-O), 700 (arom. C-H) and 549 (arom. C-I); δ_H (300 MHz; DMSO- d_6) 2.50 (3H, s, 2'-H₃), 8.25 (2H, s, 2-H and 6-H) and 10.37 (1H, br, 4-OH); δ_C (75 MHz; DMSO- d_6) 26.4 (C-2'), 86.2 (C-3 and C-5), 139.5 (C-2 and C-6), 159.6 (C-4) and 194.5 (C-1'); MS (EI, 70 eV) m/z 388 (M⁺, 40%), 373 (100), 127 (15), 91 (5); 63 (5).



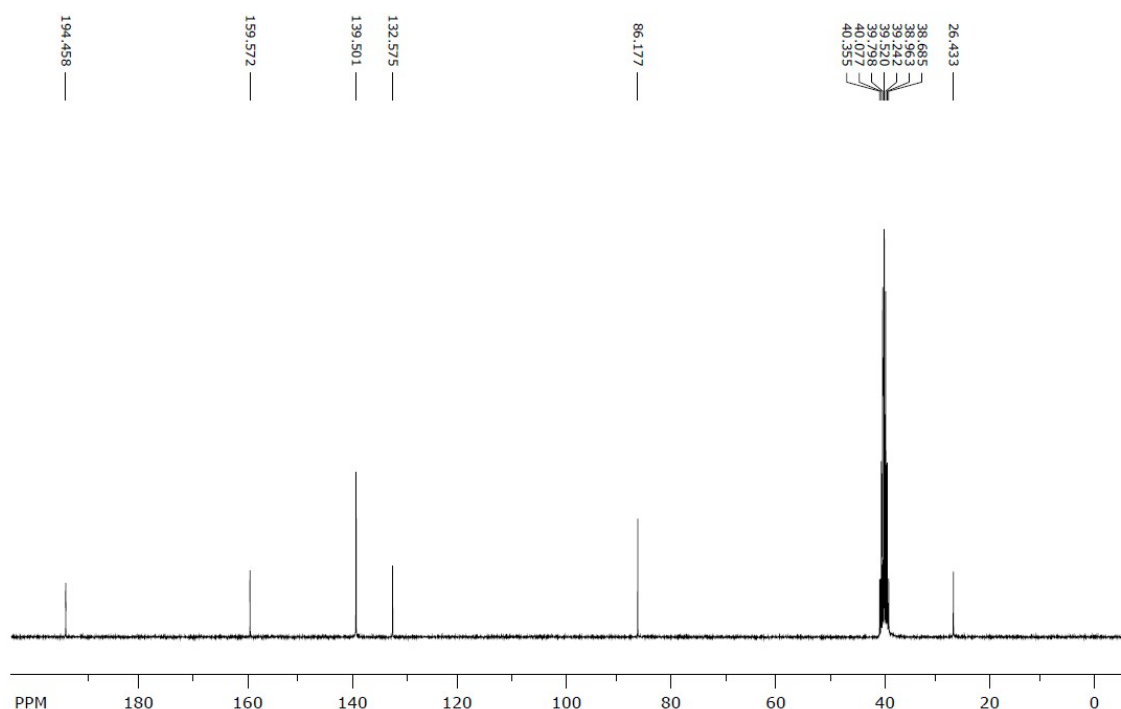
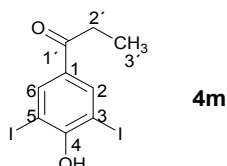


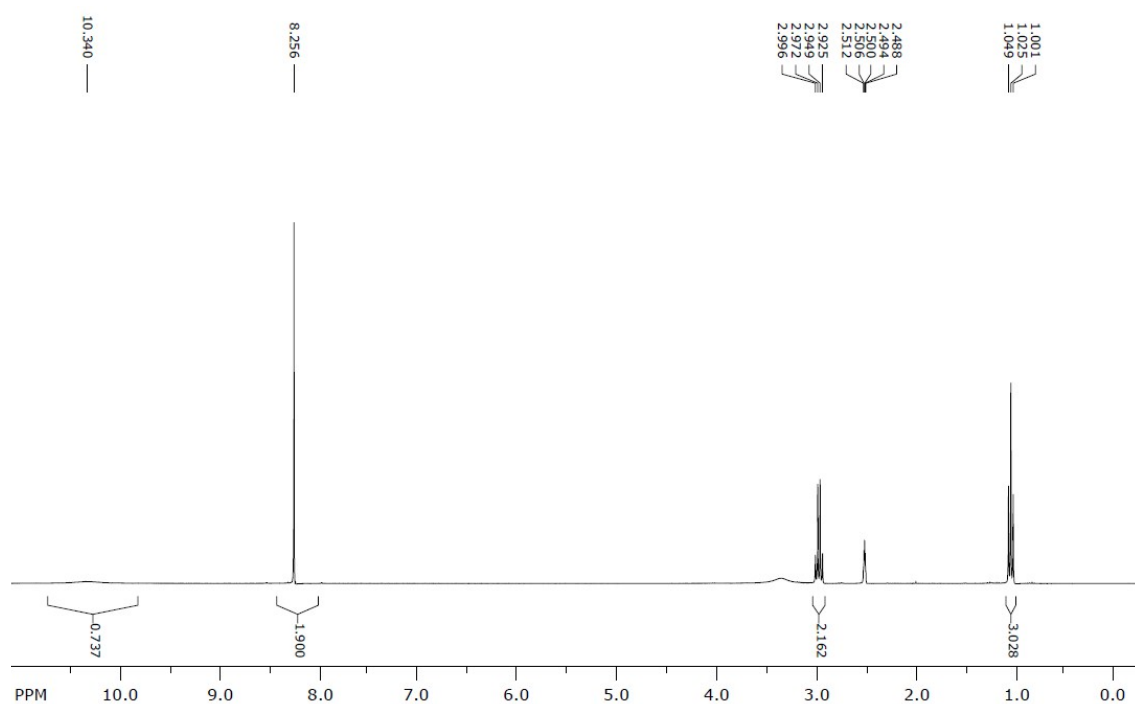
Fig. 14 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **4l** in $\text{DMSO-}d_6$

4.13 Synthesis and analytical data of 1-(4-hydroxy-3,5-diiodophenyl)propan-1-one (**4m**)⁹



A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1328 mg, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (360 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (30 h, 12 U/h) at room temperature. Simultaneously, 1-(4-hydroxyphenyl)propan-1-one (**1m**) (300 mg, 1 equiv. 2 mmol) in DMSO (3 mL) was added at a constant rate (0.1 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 168 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL).

The combined organic phases were washed with deionized water (4×15 mL) and brine (1×5 mL). The organic extracts were dried over anhydrous MgSO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give 1-(4-hydroxy-3,5-diiodophenyl)propan-1-one (602 mg, 1.50 mmol, 75 %) (**4m**) as colourless powder; mp 122–123 °C (lit.,⁹ 124 °C); R_f = 0.64 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 204 (log ϵ , 4.14), 239 (4.41), 264 (3.97) and 344 (3.67); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3274 (OH), 2939 (CH_2 , CH_3), 1674 (C=O), 1575 (arom. C=C), 1196 (arom. C-O), 717 (arom. C-H) and 558 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 1.00 (3H, t, $^3J_{3'-\text{H}, 2'-\text{H}} = 7.2$ Hz, 3'- H_3), 2.96 (2H, q, $^3J_{2'-\text{H}, 3'-\text{H}} = 7.2$ Hz, 2'- H_2), 8.26 (2H, s, 2-H and 6-H) and 10.34 (1H, br, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 8.0 (C-3'), 30.8 (C-2'), 86.2 (C-3 and C-5), 132.4 (C-1), 139.1 (C-2 and C-6), 159.4 (C-4) and 197.0 (C-1'); MS (ESI, neg.) m/z 402 [(M-H)⁻, 100%].



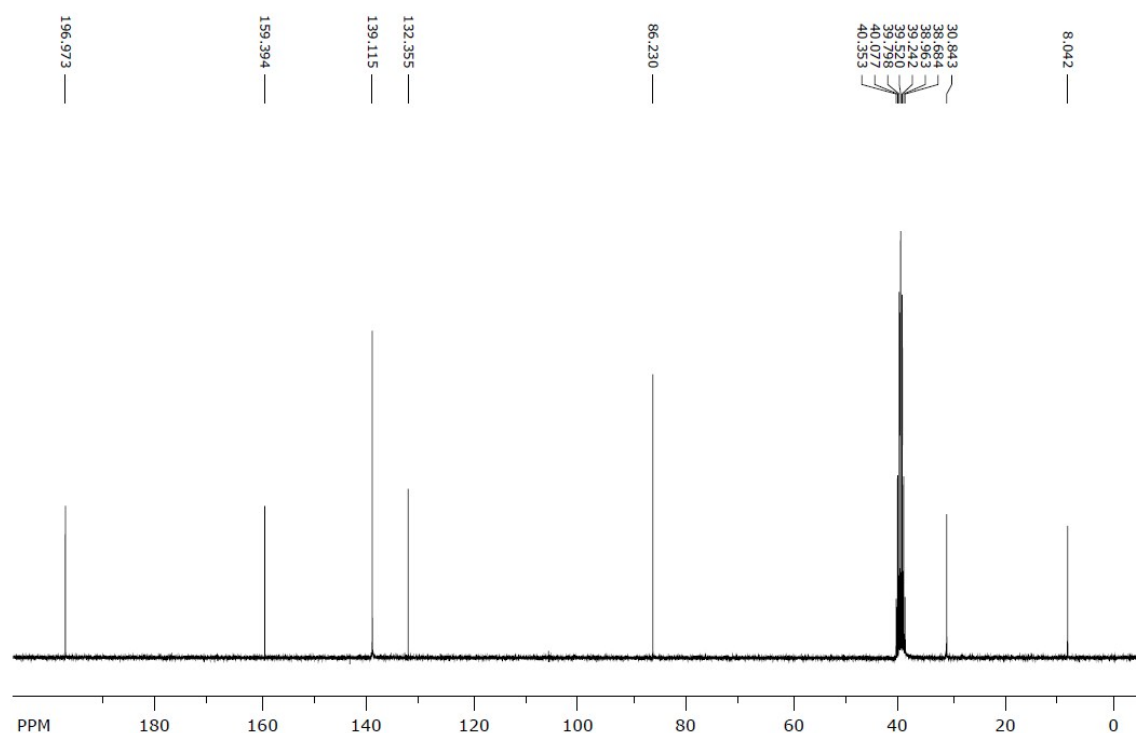


Fig. 15 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **4m** in $\text{DMSO-}d_6$

4.14 Synthesis and analytical data of (4-hydroxy-3-iodophenyl)(phenyl)methanone (**2n**)¹⁰ and (4-hydroxy-3,5-diiodophenyl)(phenyl)methanone (**4n**)¹⁰

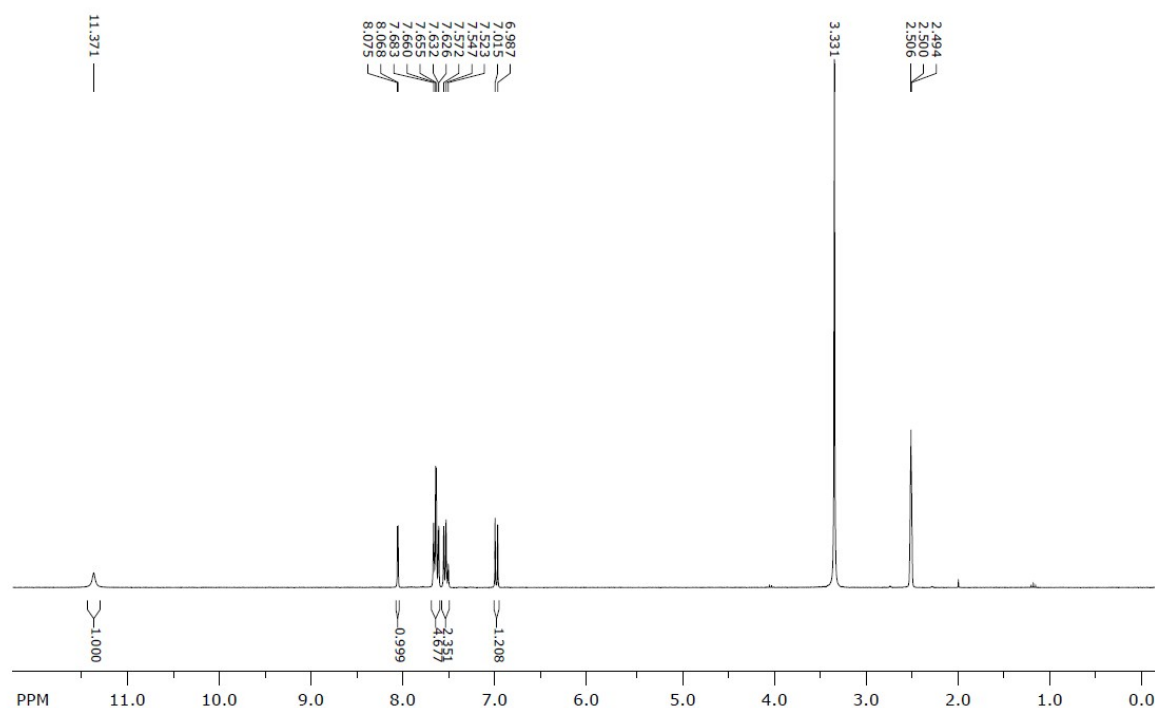


A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1328 mg, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (180 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 36 U/h) at room temperature. Simultaneously, (4-hydroxyphenyl)(phenyl)methanone (**1n**) (396 mg, 1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for 60 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction

mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5×25 mL). The combined organic phases were washed with deionized water (4×15 mL) and brine (1×5 mL). The organic extracts were dried over anhydrous MgSO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give (4-hydroxy-3-iodophenyl)(phenyl)methanone (**2n**) (455 mg, 1.40 mmol, 70%) and (4-hydroxy-3,5-diiodophenyl)(phenyl)methanone (**4n**) (55 mg, 0.12 mmol, 6%) as colourless powders.

Analytical data of (4-hydroxy-3-iodophenyl)(phenyl)methanone (**2n**)

mp 185–186 °C (lit.,¹⁰ 184 °C); R_f = 0.49 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 240 (log ϵ , 4.28) and 278 (4.10); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3199 (OH), 1630 (C=O), 1548 (arom. C=C), 1153 (arom. C-O), 618 (arom. C-H) and 528 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 7.00 (1H, d, $^3J_{5\text{-H}, 6\text{-H}} = 8.5$ Hz, 5-H), 7.54 (2H, t-like, 3'-H and 5'-H), 7.64 (1H, dd-like, 6-H), 7.65 (1H, t, $^3J_{4\text{-H}, 3\text{-H}} = 7.8$ Hz, $^3J_{4\text{-H}, 5\text{-H}} = 7.8$ Hz, 4'-H), 7.66 (2H, dd-like, 2'-H and 6'-H), 8.07 (1H, d, $^4J_{2\text{-H}, 6\text{-H}} = 2.2$ Hz, 2-H) and 11.37 (1H, s, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 84.7 (C-3), 114.4 (C-5), 128.5 (C-3' and C-5'), 129.2 (C-2' and C-6'), 129.8 (C-1), 132.1 (C-4'), 132.3 (C-6), 137.5 (C-1'), 141.0 (C-2), 161.0, (C-4) and 193.1 (C-1''); MS (EI, 70 eV) m/z 324 (M^+ , 40%), 247 (100), 219 (15), 197 (85), 105 (10).



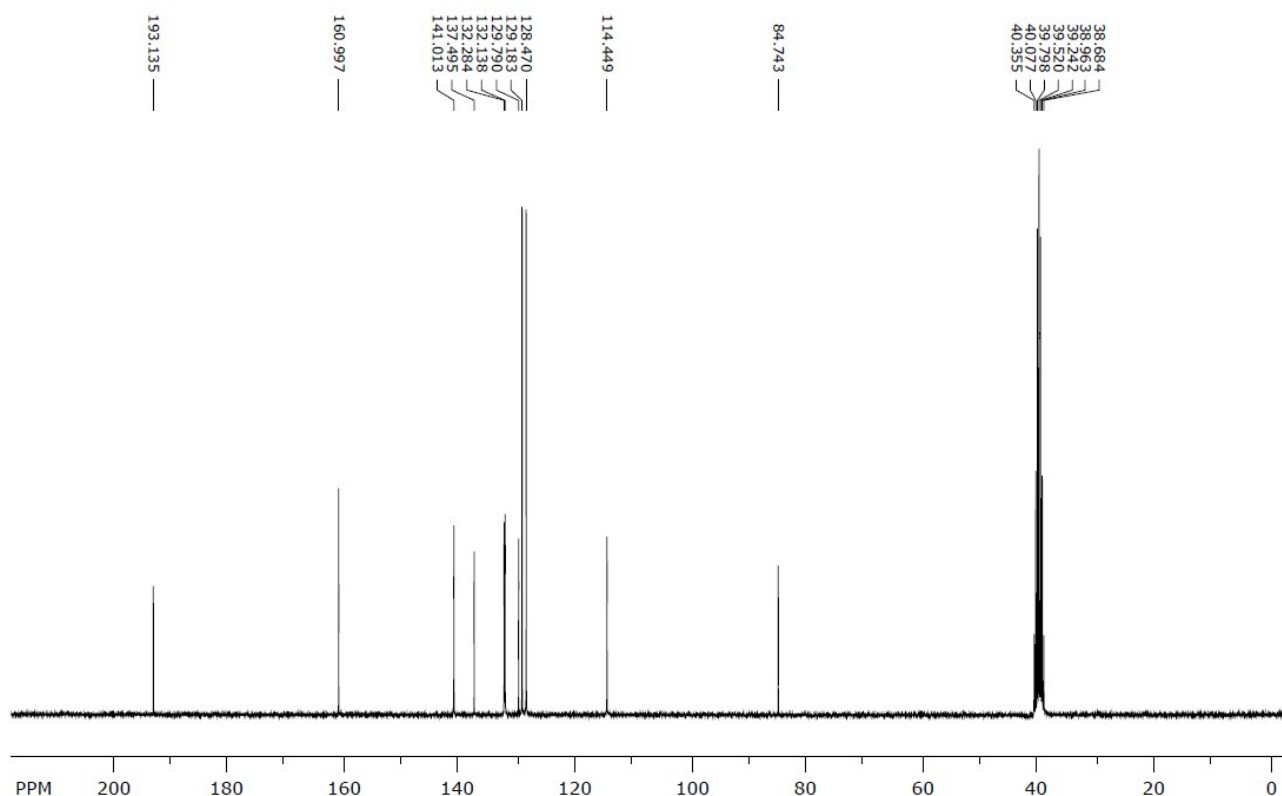


Fig. 16 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **2n** in $\text{DMSO-}d_6$

Analytical data of (4-hydroxy-3,5-diiodophenyl)(phenyl)methanone (**4n**)

mp 142–143 °C (lit.,¹⁰ 145 °C); R_f = 0.64 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 244 (log ϵ , 4.37) and 367 (3.92); IR(ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3325 (OH), 1638 (C=O), 1560 (arom. C=C), 1232 (arom. C-O), 731 (arom. C-H) and 585 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 7.56 (2H, *t-like*, 3'-H and 5'-H), 7.67 (1H, *t-like*, 4'-H), 7.68 (2H, *dd-like*, 2'-H and 6'-H), 8.04 (2H, s, 2-H and 6-H) and 10.51 (1H, br, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 86.1 (C-3 and C-5), 128.6 (C-3' and C-5'), 129.3 (C-2' and C-6'), 132.3 (C-1), 132.6 (C-4'), 136.8 (C-1'), 140.9 (C-2 and C-6), 159.6 (C-4) and 192.0 (C-1'); MS (EI, 70 eV) m/z 449 (M^+ , 100%), 372 (50), 344 (5), 217 (5), 105 (45).

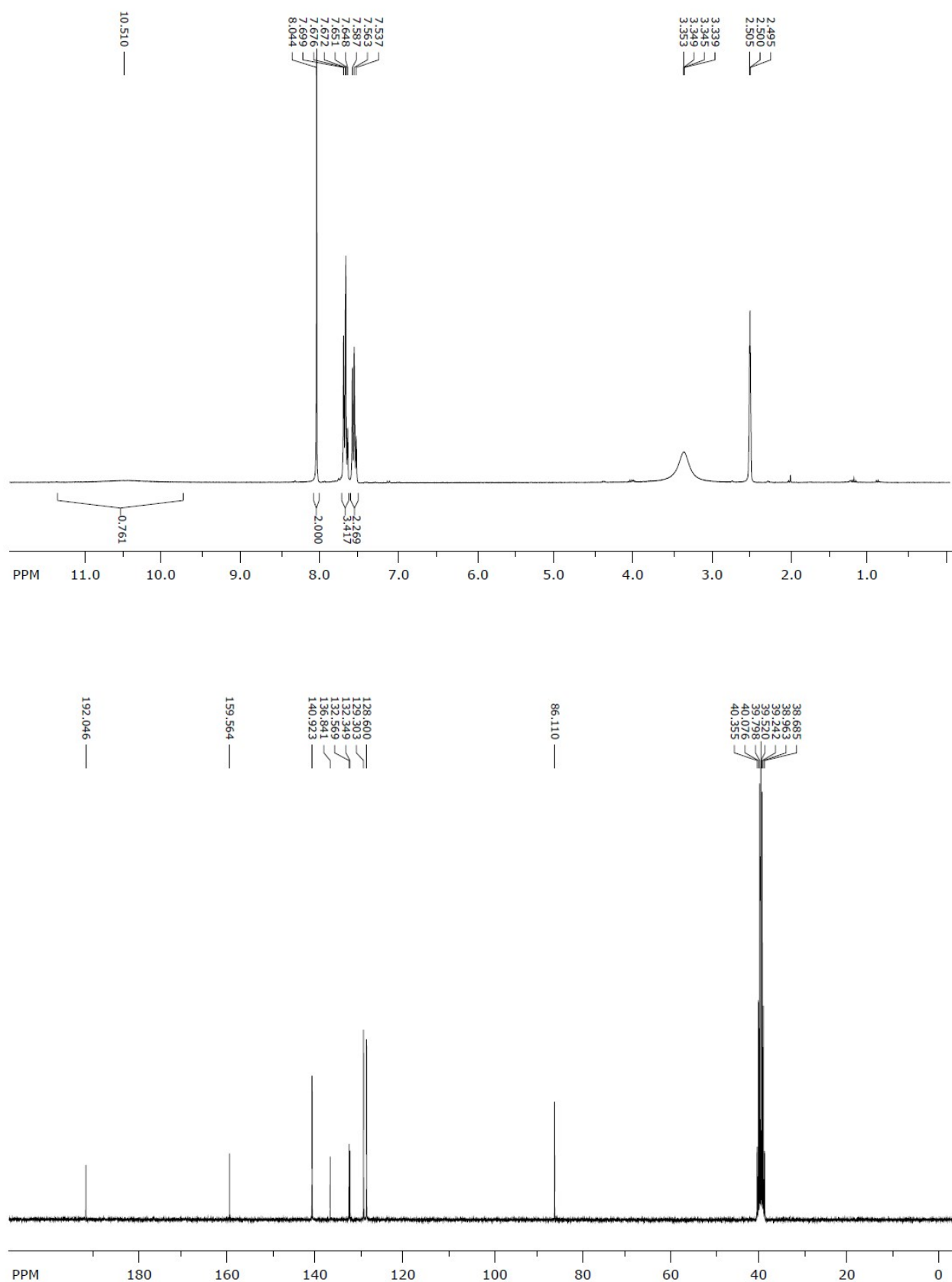
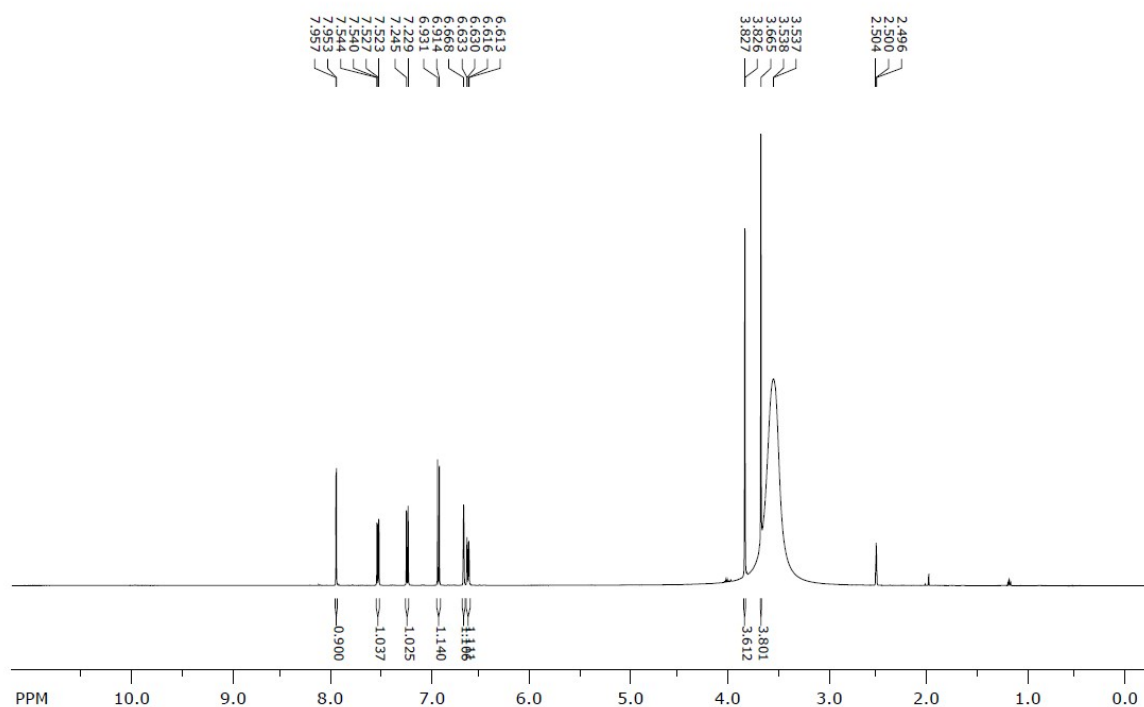


Fig. 17 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **4n** in DMSO-*d*₆

$^3J_{6'-H, 5'-H} = 8.5$ Hz, 6'-H), 7.53 (1H, dd, $^3J_{6-H, 5-H} = 8.5$ Hz, $^4J_{6-H, 2-H} = 2.2$ Hz, 6-H) and 7.96 (1H, d, $^4J_{2-H, 6-H} = 2.2$ Hz, 2-H); δ_C (125 MHz; DMSO- d_6) 55.7 (2'-OCH₃) 55.8 (4'-OCH₃), 84.5 (C-3), 98.9 (C-3'), 105.7 (C-5'), 114.5 (C-5), 120.9 (C-1'), 130.9 (C-6'), 131.2 (C-1), 131.8 (C-6), 140.8 (C-2), 158.6 (C-2'), 161.1 (C-4), 162.8 (C-4') and 192.2 (C-1''); MS (EI, 70 eV) m/z 384 (M^+ , 10%), 367 (100), 339 (50), 165 (40), 77 (10). HRMS (EI, M^+) calcd for C₁₅H₁₃IO₄: 383.9854; found: 383.9851.



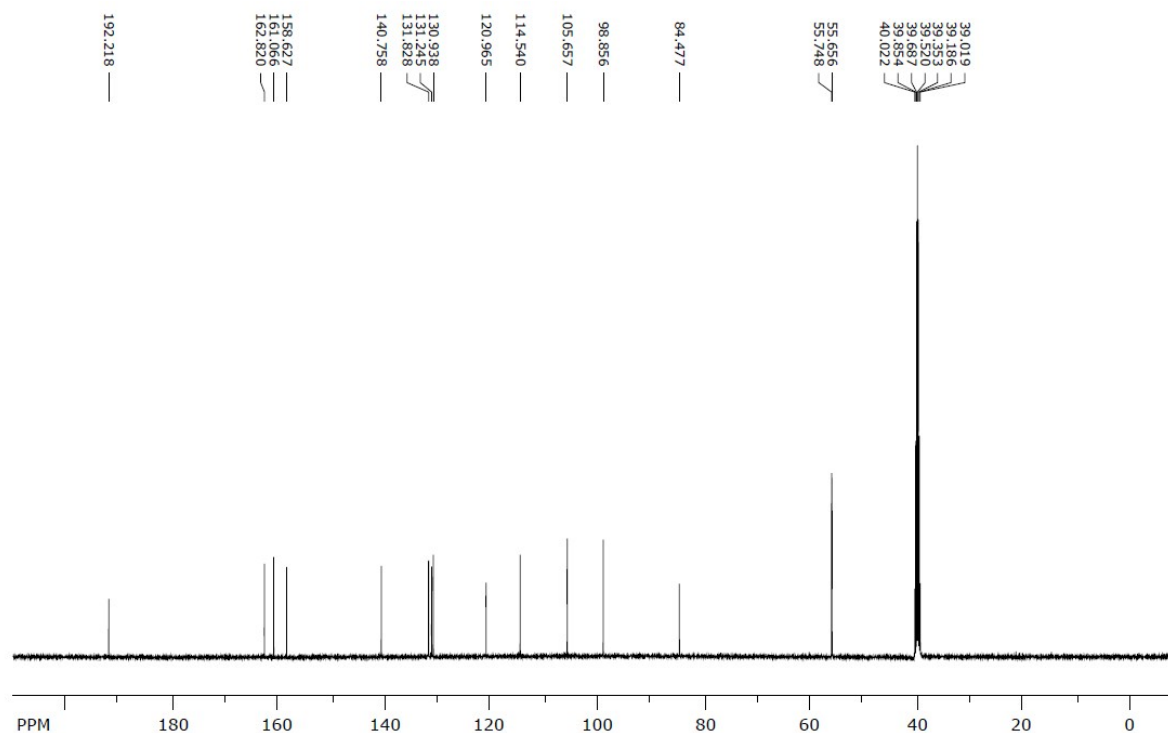


Fig. 18 ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **2o** in $\text{DMSO-}d_6$

Analytical data of (2,4-dimethoxyphenyl)(4-hydroxy-3,5-diiodophenyl)methanone (4o)

mp 138–139 °C; R_f = 0.51 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 241 (log ϵ , 4.40), 278 (4.05) and 362 (3.84); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm $^{-1}$ 3416 (OH), 2837 (CH $_3$), 1641 (C=O), 1603 (arom. C=C), 1122 (arom. C-O), 618 (arom. C-H) and 550 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 3.69 (3H, s, 2'-OCH $_3$), 3.85 (3H, s, 4'-OCH $_3$), 6.65 (1H, dd, $^3J_{5\text{'-H}, 6\text{'-H}}$ = 8.5 Hz, $^4J_{5\text{'-H}, 3\text{'-H}}$ = 2.2 Hz, 5'-H), 6.71 (1H, d, $^4J_{3\text{'-H}, 5\text{'-H}}$ = 2.2 Hz, 3'-H), 7.94 (2H, s, 2-H and 6-H) and 10.40 (1H, br, 4-OH); δ_{C} (75 MHz; $\text{DMSO-}d_6$) 55.6 (4'-OCH $_3$), 55.7 (2'-OCH $_3$), 85.8 (C-3 and C-5), 98.8 (C-3'), 105.8 (C-5'), 120.0 (C-1'), 131.2 (C-6'), 133.5 (C-1), 140.5 (C-2 and C-6), 158.7 (C-4), 159.4 (C-2'), 163.1 (C-4') and 190.7 (C-1'); MS (EI, 70 eV) m/z 510 (M^+ , 95%), 493 (85), 241 (15), 165 (100), 151 (15). HRMS (EI, M^+) calcd for $\text{C}_{15}\text{H}_{12}\text{I}_2\text{O}_4$: 509.8820; found: 509.8823.

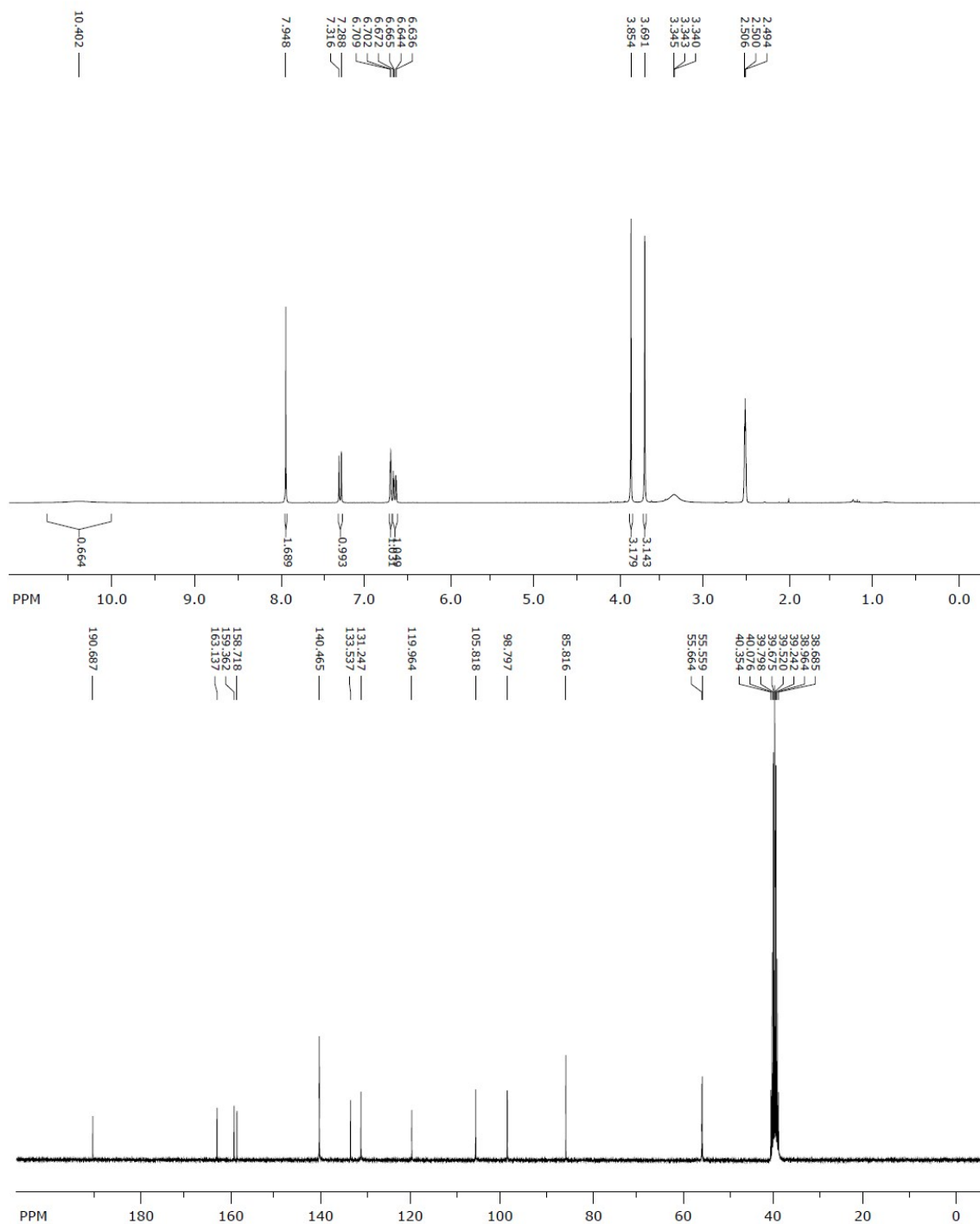


Fig. 19 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **4o** in $\text{DMSO-}d_6$

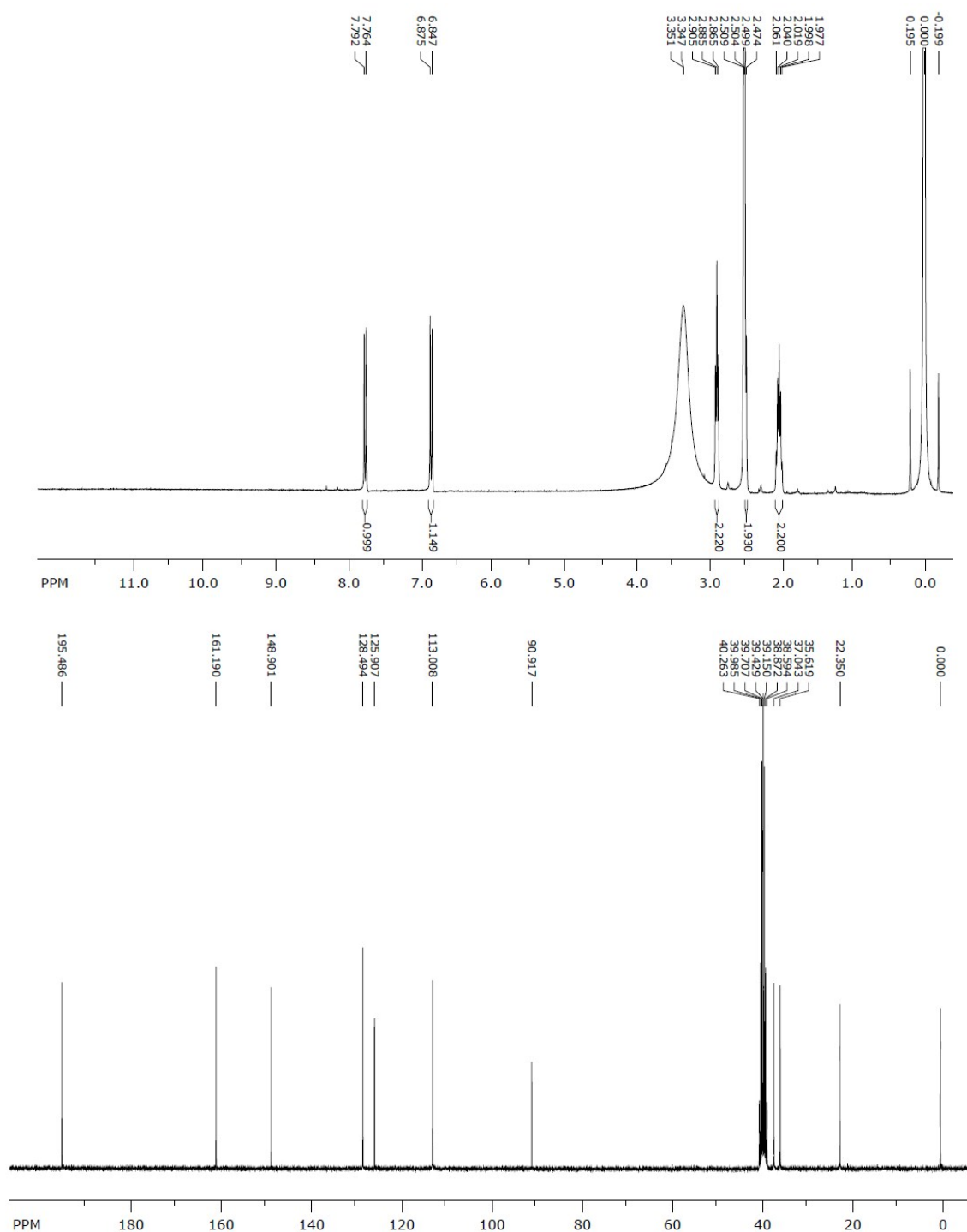
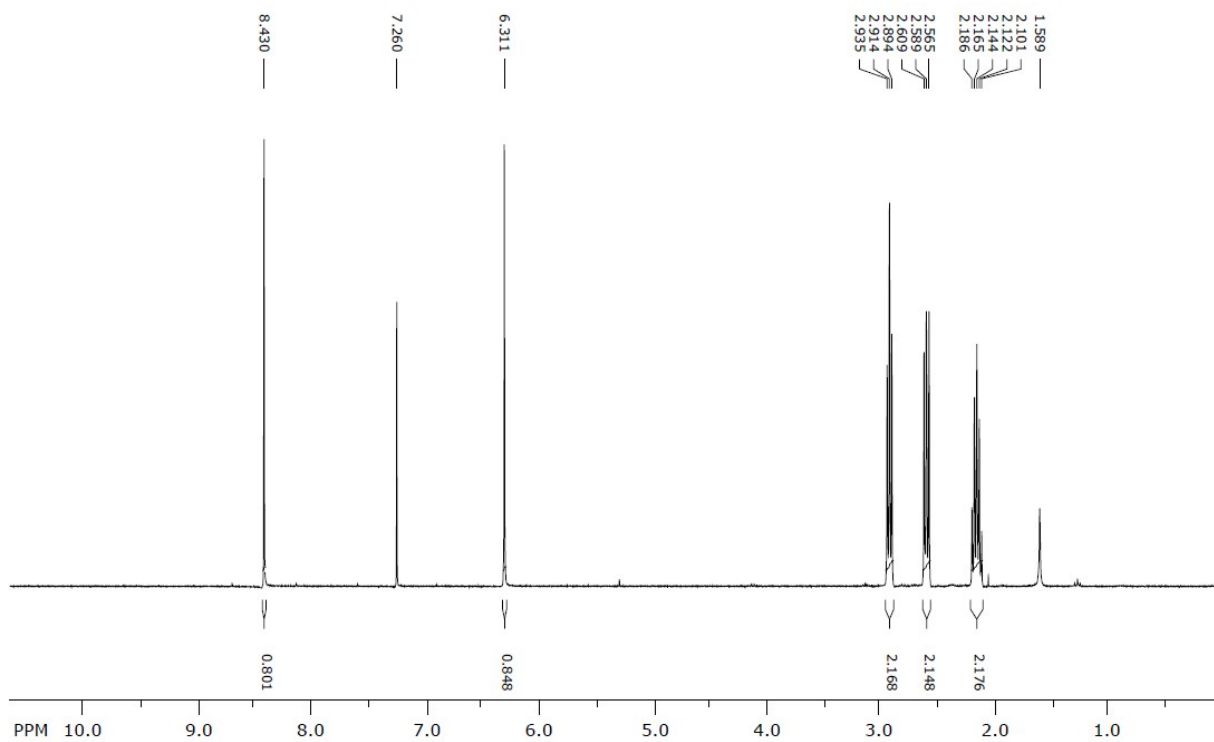


Fig. 20 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2p** in DMSO-*d*₆

Analytical data of 6-hydroxy-5,7-diiodo-3,4-dihydronaphthalen-1(2*H*)-one (4p**)**

mp 178–179 °C (lit.,¹¹ 153–155 °C); *R*_f = 0.59 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 239 (log ϵ , 4.36), 268 (3.92) and 351 (3.65); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm⁻¹ 3048 (OH), 2867

(CH₂), 1655 (C=O), 1548 (arom. C=C), 1132 (arom. C-O), 757 (arom. C-H) and 541 (arom. C-I); δ_{H} (300 MHz; CDCl₃) 2.14 (2H, *quint-like* 3-H₂), 2.58 (2H, *t-like*, 2-H₂), 2.91 (2H, *t-like*, 4-H₂), 6.31 (1H, s, 6-OH) and 8.44 (1H, s, 8-H); δ_{C} (75 MHz; CDCl₃) 22.6 (C-3), 36.2 (C-4), 37.3 (C-2), 80.4 (C-7), 89.3 (C-5), 129.0 (C-8a), 138.7 (C-8), 149.0 (C-4a), 157.2 (C-6) and 195.1 (C-1); MS (EI, 70 eV) m/z 414 (M⁺, 100%), 385 (45), 358 (10), 270 (5), 160 (25).



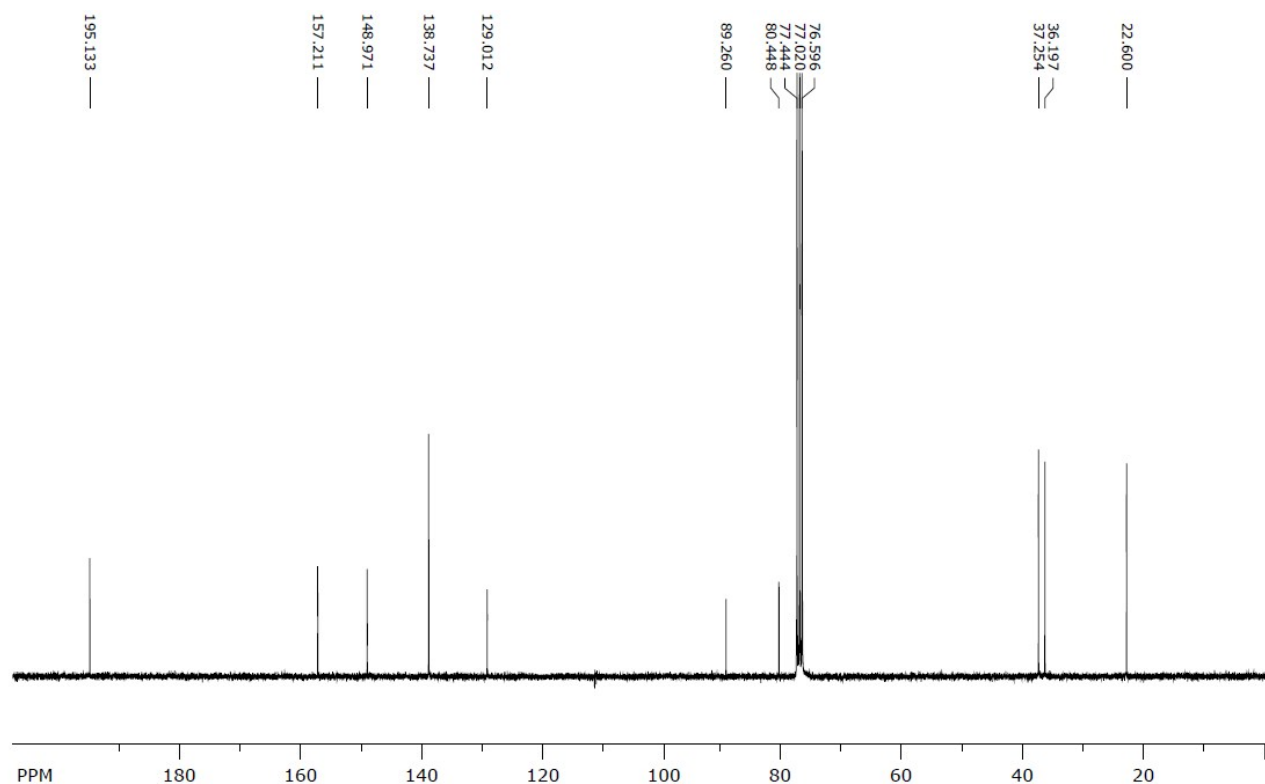
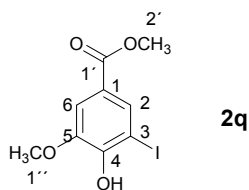


Fig. 21 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **4p** in $\text{DMSO-}d_6$

4.17 Synthesis and analytical data of methyl 4-hydroxy-3-iodo-5-methoxybenzoate (**2q**)



According to general procedure I, methyl 4-hydroxy-3-methoxybenzoate (**1q**) (364 mg, 2 mmol) was reacted for 36 h. After evaporation of the volatiles *in vacuo*, the crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO_2 to give methyl 4-hydroxy-3-iodo-5-methoxybenzoate (**2q**) as colourless powder (504 mg, 1.64 mmol, 82%); mp 154–155 °C; R_f = 0.53 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 226 (log ϵ , 4.49) and 263 (4.00); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm $^{-1}$ 3285 (OH), 2935 (CH_3), 1704 (C=O), 1599 (arom. C=C), 1285 (arom. C-O), 819 (arom. C-H) and 659 (arom. C-I); δ_{H} (300 MHz; $\text{DMSO-}d_6$) 3.80 (1H, s, 2'- H_3); 3.87 (1H, s, 1''- H_3); 7.45 (1H, d, $^4J_{6-\text{H}, 2-\text{H}} = 1.9$ Hz, 6-H); 7.87 (1H, d, $^4J_{2-\text{H}, 6-\text{H}} =$

1.9 Hz, 2-H) and 10.50 (1H, br, 4-OH); δ_C (75 MHz; DMSO- d_6) 52.1 (C-2'), 56.2 (C-1'), 83.9 (C-3), 112.0 (C-6), 122.1 (C-1), 132.0 (C-2), 146.6 (C-5), 150.9 (C-4) and 164.9 (C-1'); MS (EI, 70 eV) m/z 308 (M^+ , 75%), 277 (50), 182 (60), 151(100), 123 (15); HRMS (EI, M^+) calcd for $C_9H_9IO_4$: 307.9540; found: 307.9553.

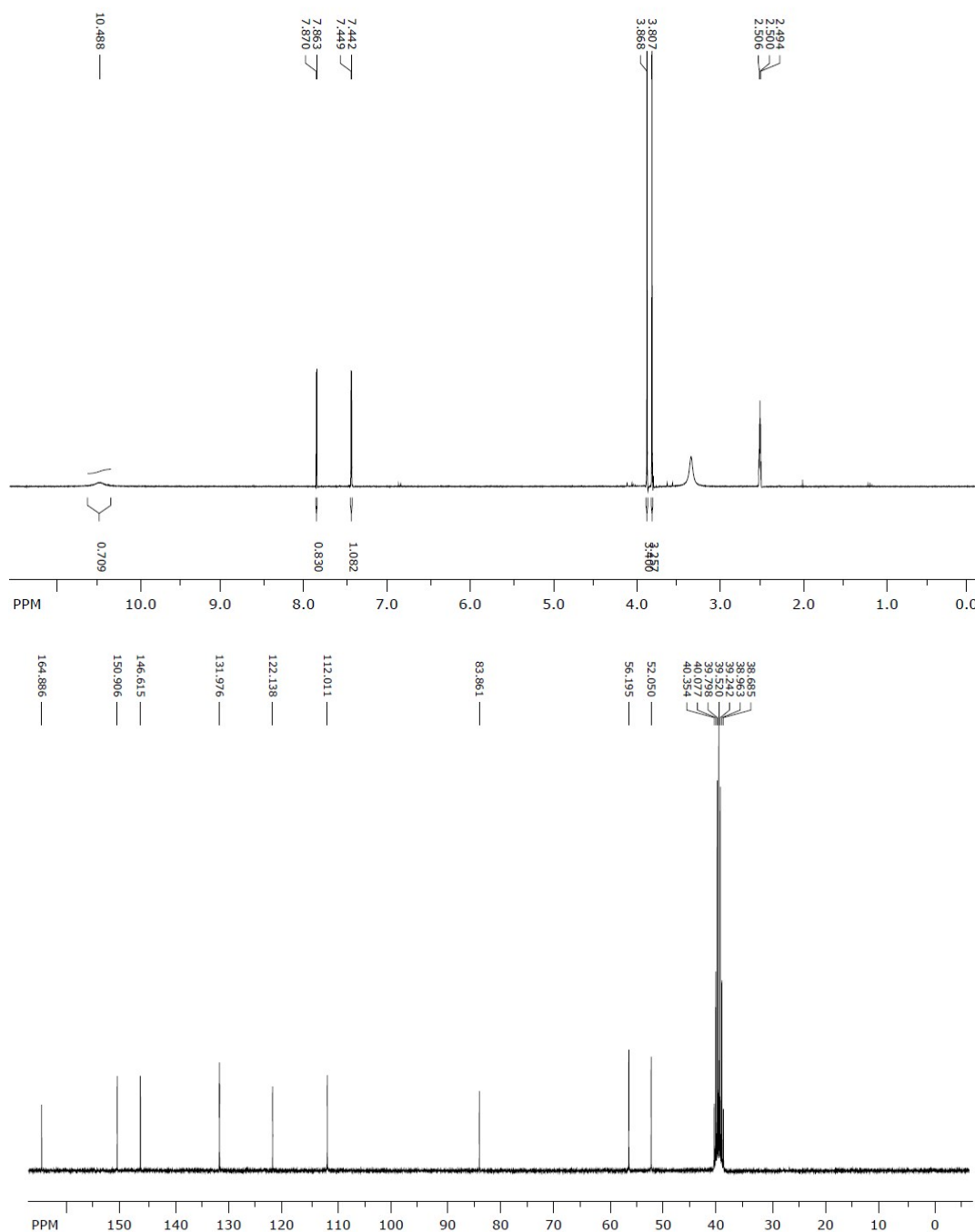


Fig. 22 1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of 2q in DMSO- d_6

4.18 Synthesis and analytical data of methyl 4-hydroxy-3-iodobenzoate (**2r**)¹² and methyl 4-hydroxy-3,5-diiodo-benzoate (**4r**)¹³

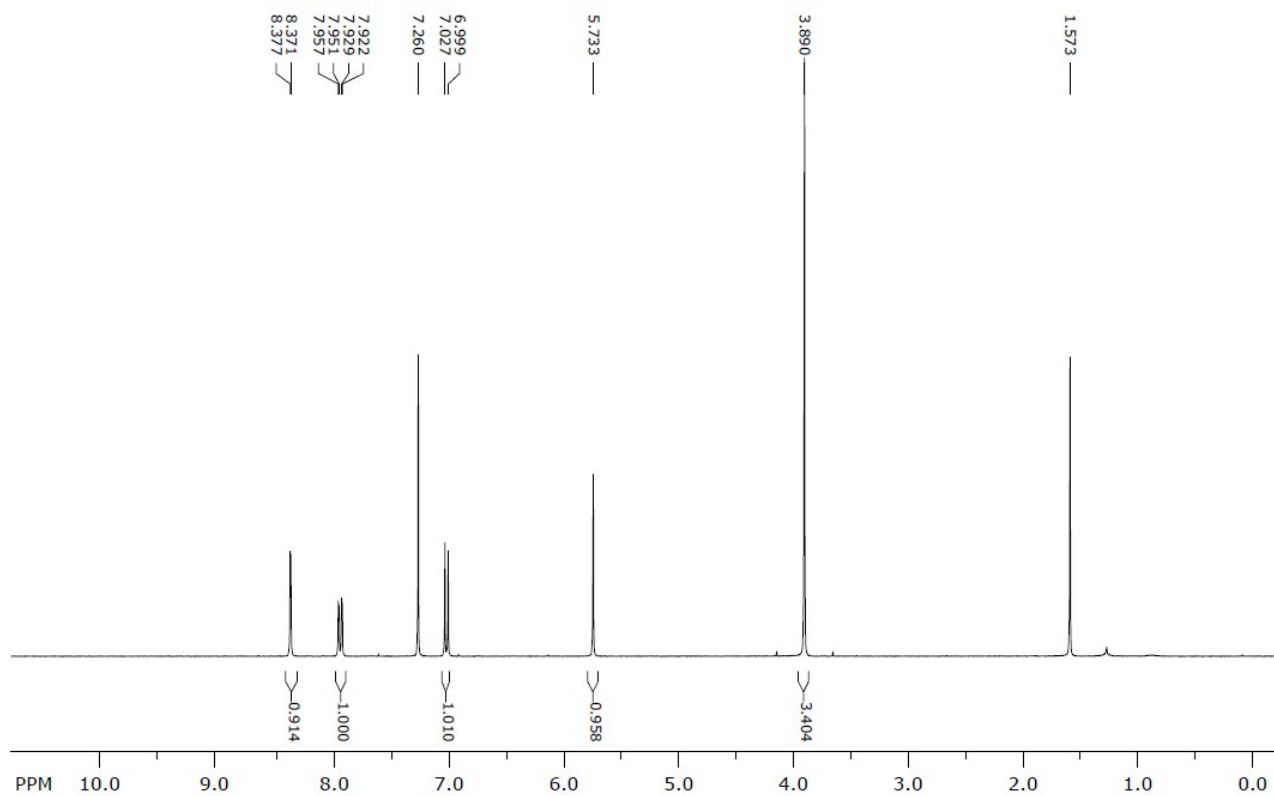


A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1.328 g, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (180 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (10 h, 18 U/h) at room temperature. Simultaneously, 4-hydroxybenzoate (**1r**) (304 mg, 1 equiv. 2 mmol) in DMSO (3 mL) was added at a constant rate (0.3 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for the reaction time of 120 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/EtOAc = 15 : 7.5 : 2.5) on SiO₂ to give methyl 4-hydroxy-3-iodobenzoate (**2r**) (194 mg, 0.70 mmol, 35%) and methyl 4-hydroxy-3,5-diiodobenzoate (**4r**) (436 mg, 1.08 mmol, 54%) as colourless powders.

Analytical data for methyl 4-hydroxy-3-iodobenzoate (**2r**)

mp 155–156 °C (lit.,¹² 156–158 °C); R_f = 0.46 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{\max} (MeCN)/nm 225 (log ϵ , 4.41), 254 (4.07) and 293 (3.38); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3306 (OH), 2946 (CH₃), 1686 (C=O), 1598 (arom. C=C), 1286 (arom. C-O), 761 (arom. C-H) and 631 (arom. C-I); δ_H (300 MHz; CDCl₃) 3.89 (3H, s, 2'-H₃), 5.73 (1H, s, 4-OH) 7.03 (1H, d, $^3J_{5-H, 6-H}$ = 8.6 Hz, 5-H),

7.93 (1H, dd, $^3J_{6-H, 5-H} = 8.6$ Hz, $^4J_{6-H, 2-H} = 2.0$ Hz, 6-H) and 8.38 (1H, d, $^4J_{2-H, 6-H} = 2.0$ Hz, 2-H); δ_C (75 MHz; CDCl₃) 52.2 (C-2'), 85.2 (C-3), 114.7 (C-5), 124.5 (C-1) 132.2 (C-6), 140.2 (C-2), 158.7 (C-4) and 165.4 (C-1'); MS (EI, 70 eV) m/z 278 (M⁺, 50%), 247 (100), 136 (5), 120 (10), 92 (15).



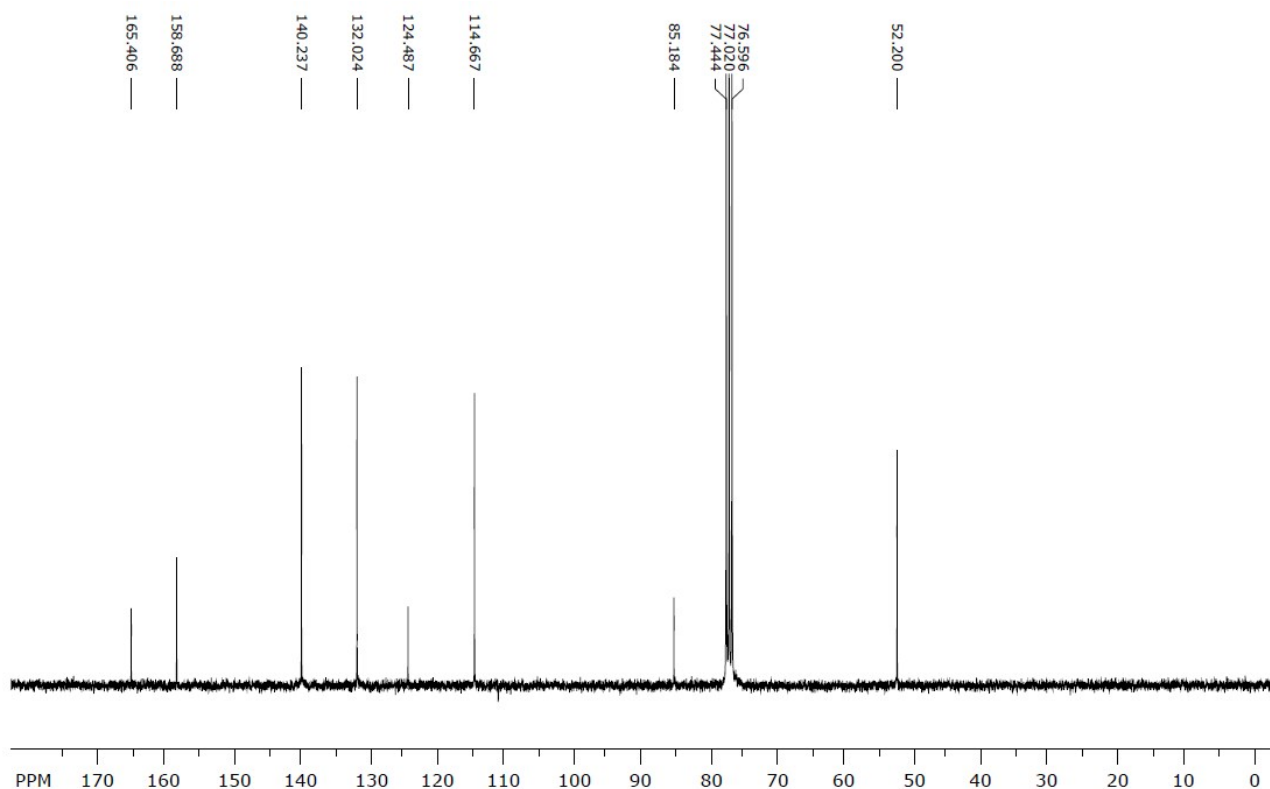


Fig. 23 ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **2r** in CDCl_3

Analytical data for methyl 4-hydroxy-3,5-diiodo-benzoate (**4r**)

mp 168–169 °C (lit.,¹³ 169–172 °C); R_f = 0.71 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 235 (log ϵ , 4.49) and 317 (3.68); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm⁻¹ 3350 (OH), 2951 (CH₃), 1706 (C=O), 1578 (arom. C=C), 1087 (arom. C-O), 759 (arom. C-H) and 564 (arom. C-I); δ_{H} (300 MHz; CDCl_3) 3.89 (3H, s, 2'-H₃), 6.13 (1H, s, 4-OH) and 8.36 (2H, s, 2-H and 6-H); δ_{C} (75 MHz; CDCl_3) 52.4 (C-2'), 81.6 (C-3 and C-5), 126.0 (C-1), 140.9 (C-2 and C-6), 157.2 (C-4) and 164.0 (C-1'); MS (EI, 70 eV) m/z 404 (M⁺, 95%), 373 (100), 277 (8), 127 (15), 119 (8).

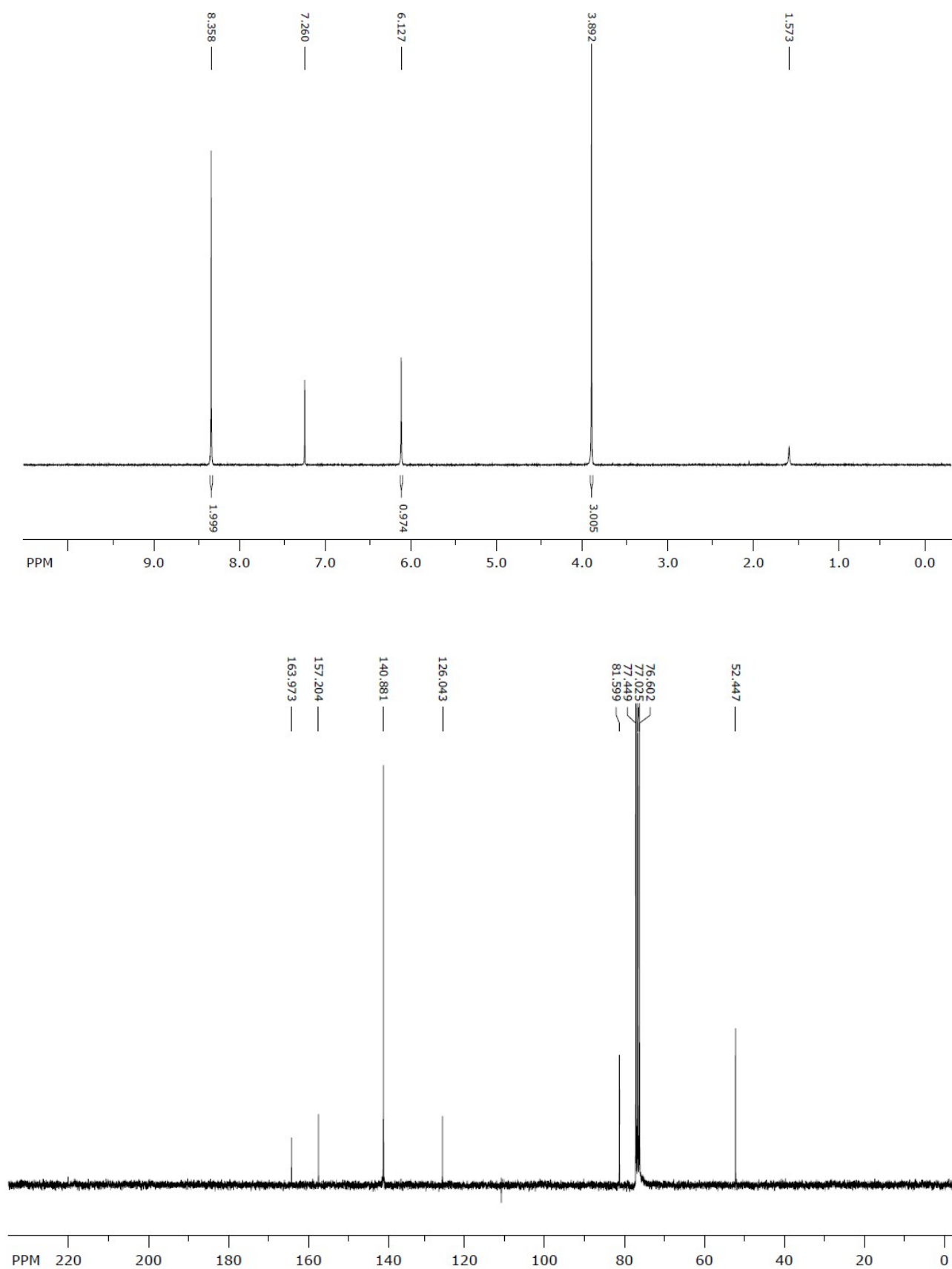
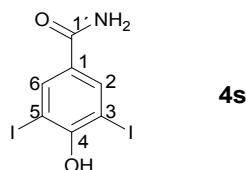


Fig. 24 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **4r** in CDCl₃

4.19 Synthesis and analytical data of 4-hydroxy-3,5-diiodobenzamide (4s)



A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (1.328 g, 4 equiv., 8 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (500 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (30 h, 16.7 U/h) at room temperature. Simultaneously, 4-hydroxybenzamide (**1s**) (274 mg, 1 equiv. 2 mmol) in DMSO (3 mL) was added at a constant rate (0.1 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for the reaction time of 48 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (DCM/MeOH = 9 : 1) on SiO₂ to give 4-hydroxy-3,5-diiodobenzamide (**4s**) (482 mg, 1.24 mmol, 62%) as a colourless powder; mp 247–248 °C; R_f 0.45 = (EtOH/DCM = 1 : 9); UV λ_{max} (MeCN)/nm 232 (log ϵ , 4.31) and 300 (3.52); IR(ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3466 (OH), 3172 (NH₂), 1687 (C=O), 1600 (arom. C=C), 1235 (arom. C-O), 874 (arom. C-H) and 550 (arom. C-I); δ_H (300 MHz; DMSO-*d*₆) 7.31 (1H, s, 1'-NH₂) 7.93 (1H, s, 1'-NH₂), 8.24 (2H, s, 2-H and 6-H) and 10.04 (1H, br, 4-OH); δ_C (75 MHz; DMSO-*d*₆) 86.0 (C-3 and C-5), 129.4 (C-1), 138.7 (C-2 and C-6), 158.0 (C-4) and 164.8 (C-1'); MS (EI, 70 eV) m/z 389 (M⁺, 100%), 373 (70), 345 (5), 245 (10), 127 (20); HRMS (EI, M⁺) calc. for C₇H₇NI₂O₂: 388.8405; found: 388.8398.

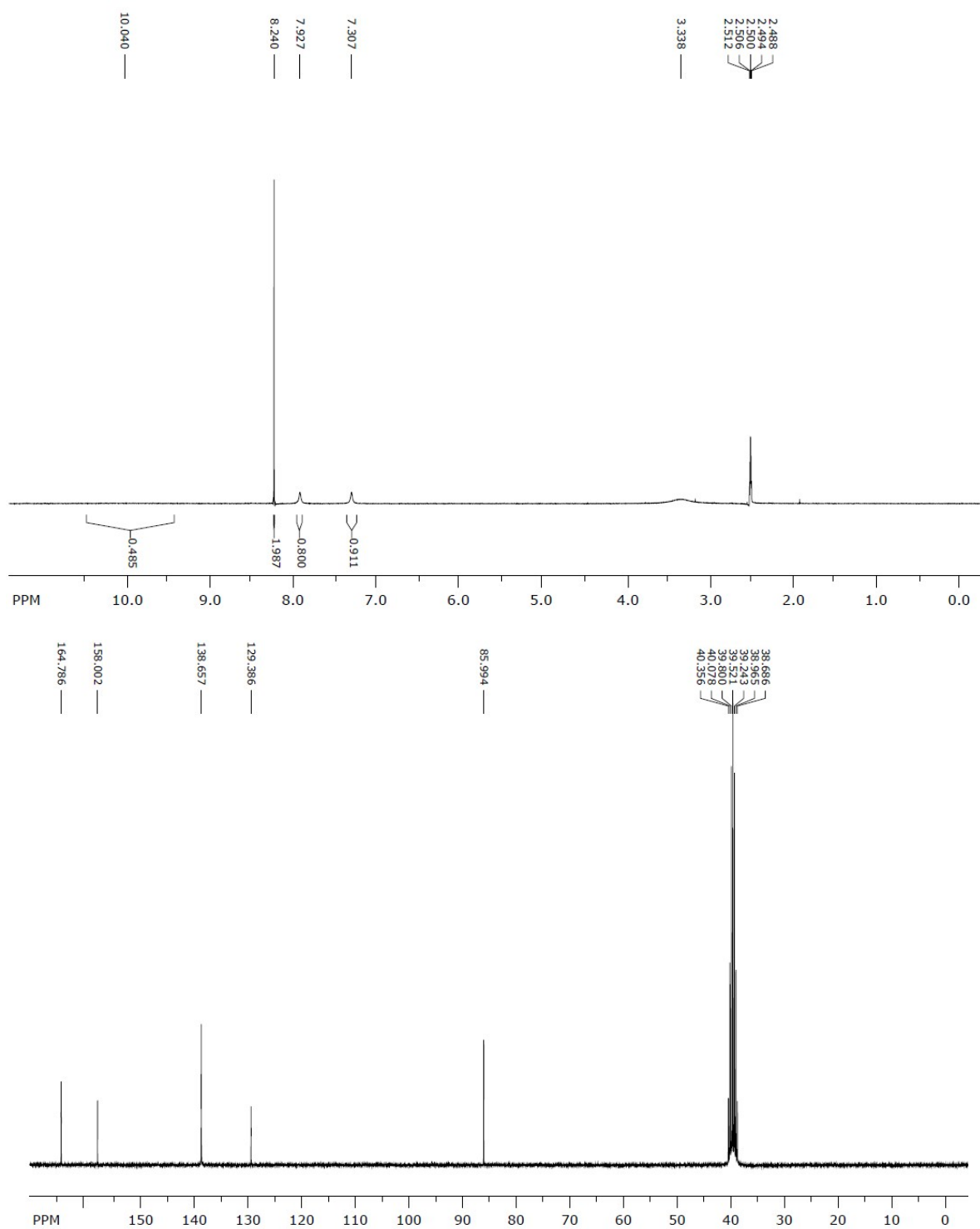
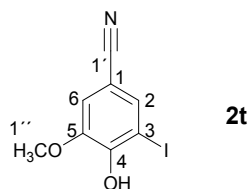


Fig. 25 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **4s** in DMSO-*d*₆

4.20 Synthesis and analytical data of 4-hydroxy-3-iodo-5-methoxybenzonitrile (**2t**)¹⁴



A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (996 mg, 3 equiv., 6 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (90 mL, 0.1 M, pH 5.0, 10% (v/v) DMSO). Additional laccase from *Trametes versicolor* (270 U), dissolved in acetate buffer (3 mL, 0.1 M, pH 5.0), was added to the stirred reaction mixture by means of a syringe pump (5 h, 54 U/h) at room temperature. Simultaneously, 4-hydroxy-3-methoxybenzonitrile (**1t**) (298 mg, 1 equiv., 2 mmol) in DMSO (3 mL) was added at a constant rate (0.6 mL/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/min at rt for the reaction time of 24 h. After completion of the reaction, solid sodium thiosulfate was added until the brown colour disappeared. The reaction mixture was acidified (pH 5) with concentrated HCl (37%) and extracted with EtOAc (5 × 25 mL). The combined organic phases were washed with deionized water (4 × 15 mL) and brine (1 × 5 mL). The organic extracts were dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/DCM/MeOH = 15 : 7.5 : 2.5) on SiO₂ to give 4-hydroxy-3-iodo-5-methoxybenzonitrile (**2t**) (429 mg, 1.56 mmol, 78%) as a colourless powder. mp 128–129 °C (lit.,¹⁴ 131–133 °C); *R*_f = 0.50 (petroleum ether/DCM/EtOAc = 5 : 17.5 : 2.5); UV λ_{max} (MeCN)/nm 226 (log ε, 4.52), 258 (3.93) and 298 (3.52); IR (ATR) ν̄_{max}/cm⁻¹ 3215 (OH), 2940 (CH₃), 2228 (CN), 1666 (arom. C=C), 1259 (arom. C-O), 852 (arom. C-H) and 611 (arom. C-I); δ_H (300 MHz; DMSO-*d*₆) 3.86 (3H, s, 1''-H₃), 7.43 (1H, d, ⁴*J*_{6-H, 2-H} = 1.8 Hz, 6-H) 7.75 (1H, d, ⁴*J*_{2-H, 6-H} = 1.8 Hz, 2-H) and 10.74 (1H, br, 4-OH); δ_C (75 MHz; DMSO-*d*₆) 56.6 (C-1''), 84.5 (C-3), 103.1 (C-1), 115.0 (C-6), 118.1 (C-1'), 134.6 (C-2), 146.9 (C-3) and 151.0 (C-4); MS (EI, 70 eV) *m/z* 275 (M⁺, 100%), 260 (30), 232 (10), 149 (10), 128 (5).

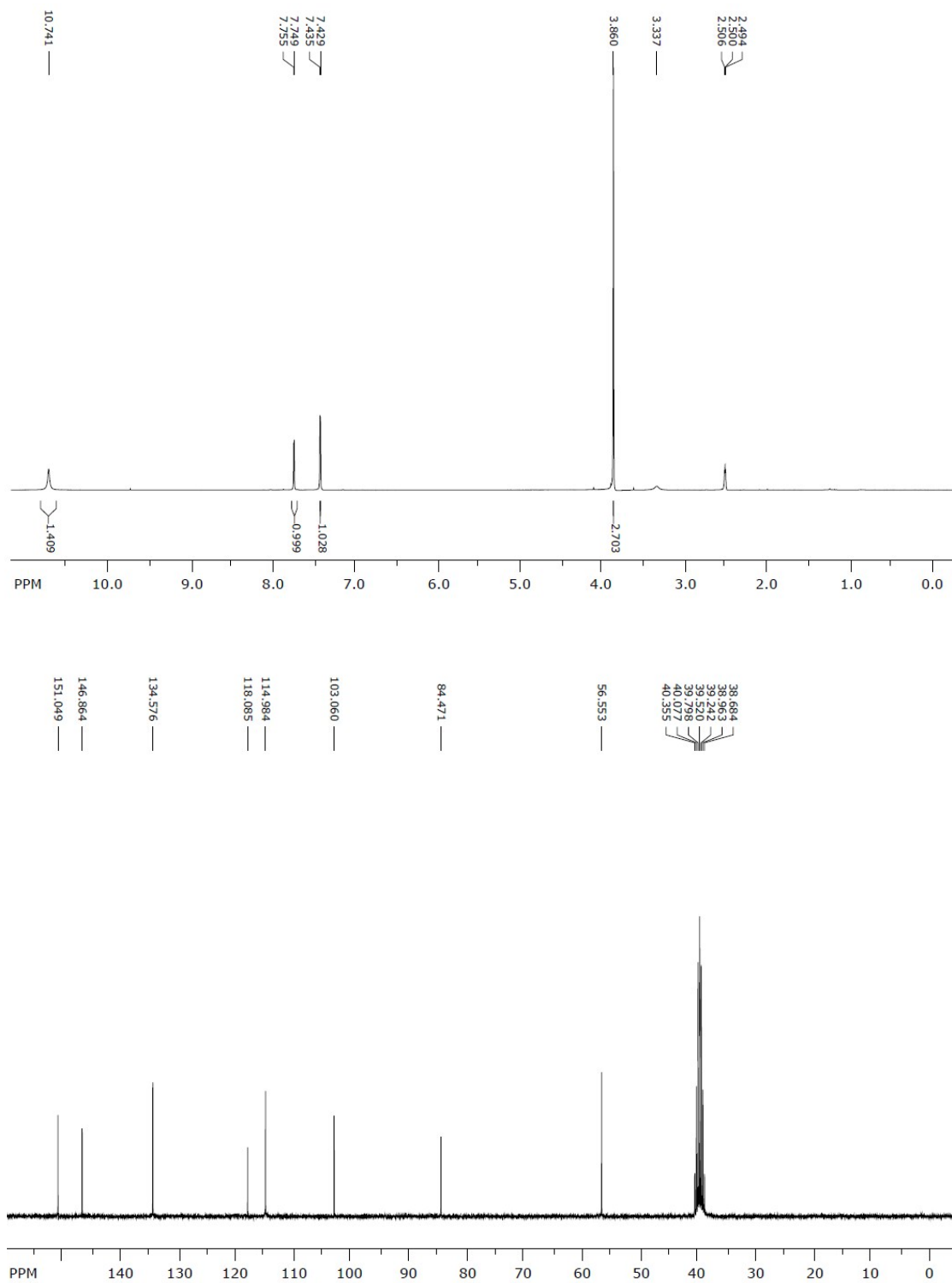
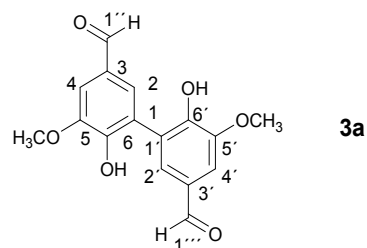


Fig. 26 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **2t** in DMSO-*d*₆

5. Synthesis and analytical data of divanillin (**3a**)¹⁵



An air-saturated solution of 4-hydroxy-3-methoxybenzaldehyde (**1a**) (2 mmol, 304 mg) in acetate buffer (25 mL, 0.1 M, pH 5) containing 10 vol% DMSO was treated with ABTS (0.02 mmol, 10.26 mg) and laccase from *Trametes versicolor* (45 U). The reaction mixture was vigorously stirred under air at room temperature for 7 h. The grey precipitate was filtered through a Buchner funnel and dissolved in sodium hydroxide solution (15–20 mL, 2 M). After acidification (pH 2–3) with HCl (2 M) the precipitated dimer was filtered off, washed with small amounts of deionized water (3 × 5 mL) and dried in a desiccator over CaCl₂ (12 h). Finally, divanillin (**3a**) was obtained as a greyish solid (275 mg, 0.91 mmol, 91%); mp 303–304°C (lit.,¹⁵ 303–304 °C); R_f = 0.41 (MeOH/DCM) = 2.5 : 22.5); IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ 3253 (OH), 1670 (C=O), 1584 (arom. C=C) 1455 (arom. C=C) and 1138 (arom. C-O-C); ¹H NMR δ_{H} (300 MHz; DMSO-*d*₆) 3.92 (6H, s, 5-OCH₃ and 5'-OCH₃), 7.43 (4H, dd-like, 2-H, 4-H, 2'-H and 4'-H) and 9.81 (2H, s, 1''-H and 1'''-H); δ_{C} (75 MHz; DMSO-*d*₆) 56.1 (5-OCH₃ and 5'-OCH₃), 109.2 (C-4 and C-4'), 124.6 (C-1 and C-1'), 127.8 (C-3 and C-3'), 128.2 (C-2 and C-2'), 148.2 (C-5 and C-5'), 150.5 (C-6 and C-6') and 192.3 (C-1'' and C-1''').

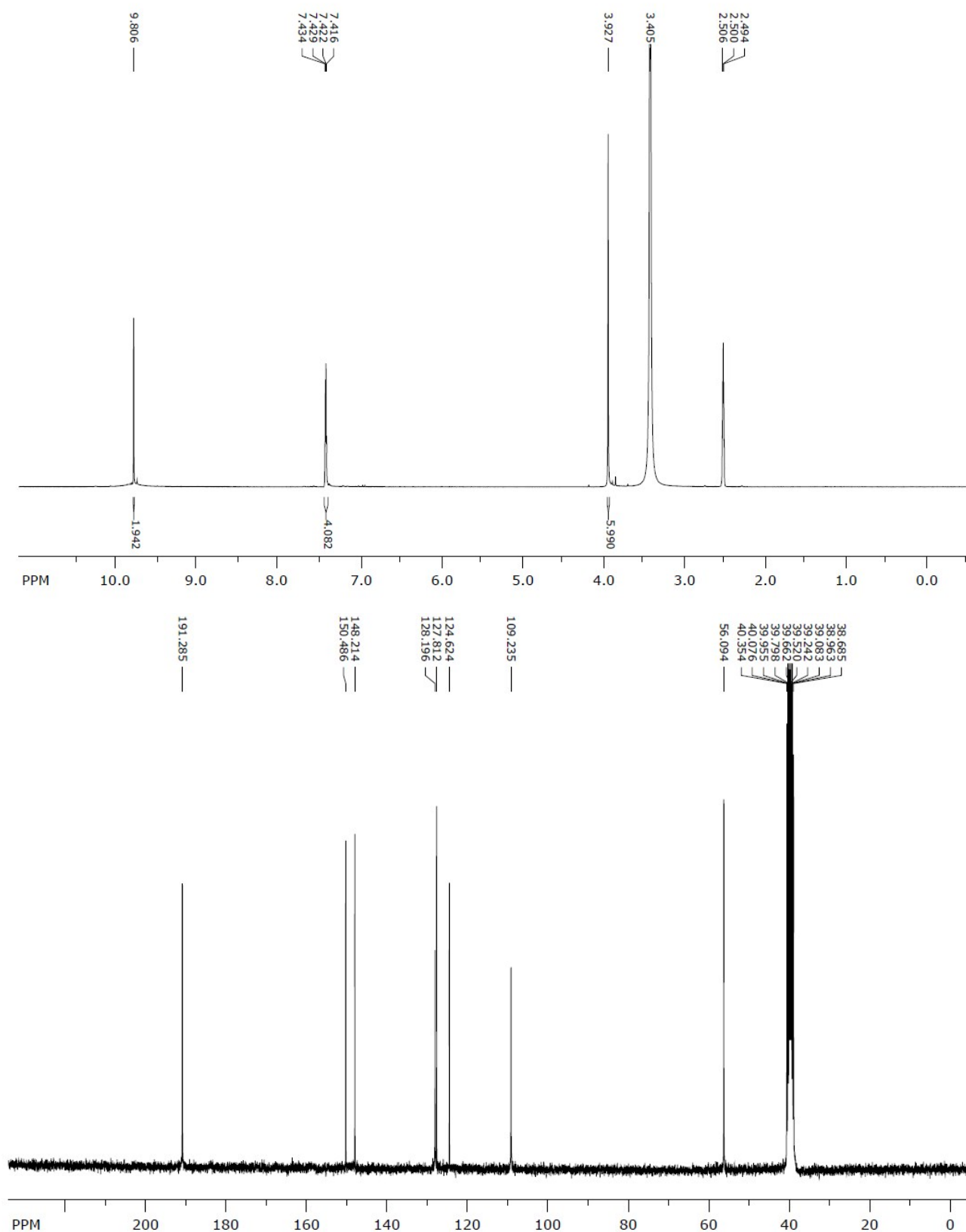


Fig. 27 ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **3a** in DMSO-*d*₆

6. Quantification of the ratio between iodination products **2**, **4** and dimers **3**

The ratio between iodination products **2** and/or **4** and dimers **3** was determined by comparing the integrals of suitable signals by ^1H NMR. As an example (Table 1, entry 1), for calculation of the ratio between 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**) and divanillin (**3a**), the integrals of the aldehyde proton (1-H) of **2a**, resonating at $\delta = 9.75$ ppm, and the aldehyde protons in divanillin (**3a**), resonating at $\delta = 9.81$ ppm, were used (Figure 28). The molar ratio of **2a** and **3a** in the crude product obtained from the reaction given in Table 1, entry 1, amounted to 1 : 2.

Alternatively, the ratio between **2a** and **3a** could also be calculated from comparison of the integrals of the protons of the methoxy group of **2a**, resonating at $\delta = 3.89$ ppm, and the protons of the methoxy groups in divanillin (**3a**), resonating at $\delta = 3.92$ ppm (Figure 29). The molar ratio of **2a** and **3a** in the crude product obtained from the reaction given in Table 1, entry 1, amounted to 1 : 2.

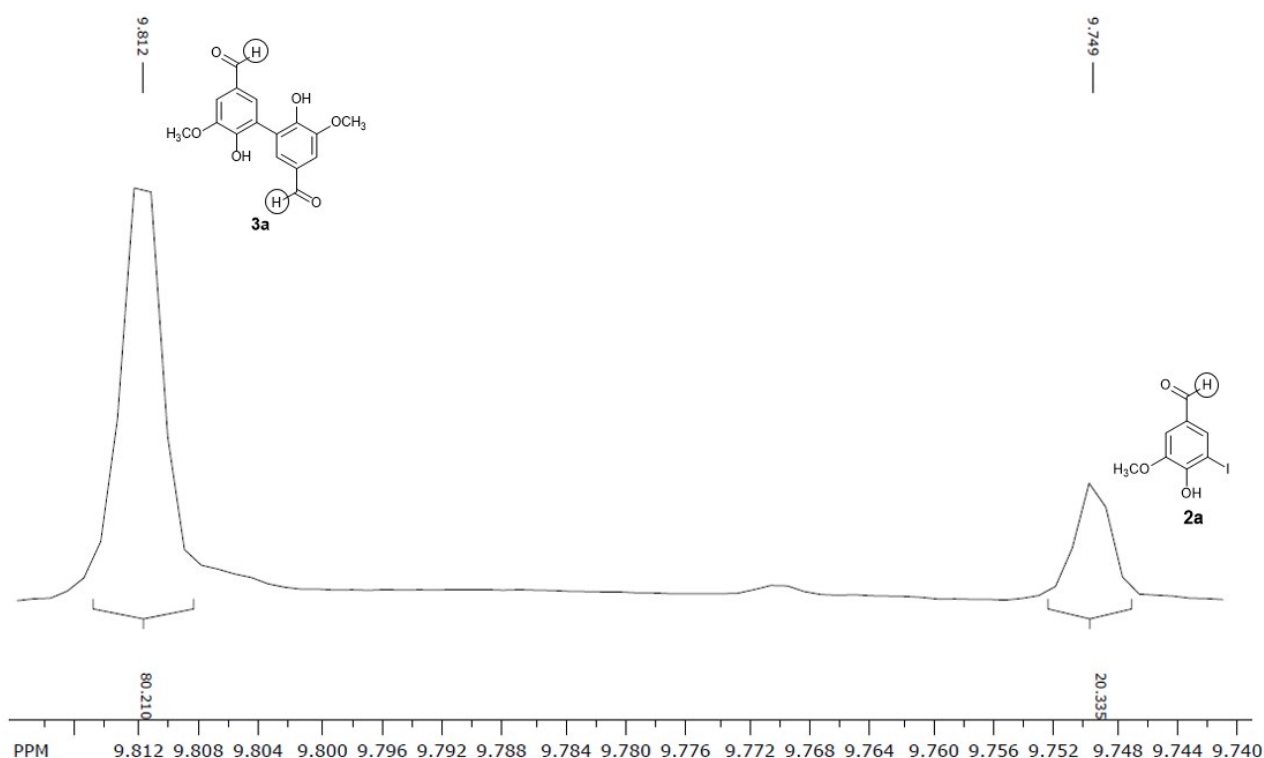


Fig. 28 Determination of the ratio of **2a** and **3a** of the reaction presented in Table 1, entry 1, by ^1H NMR: integration of the signal intensities of the aldehyde proton of **2a**, resonating at $\delta = 9.75$ ppm, and the aldehyde protons of **3a**, resonating at $\delta = 9.81$ ppm.

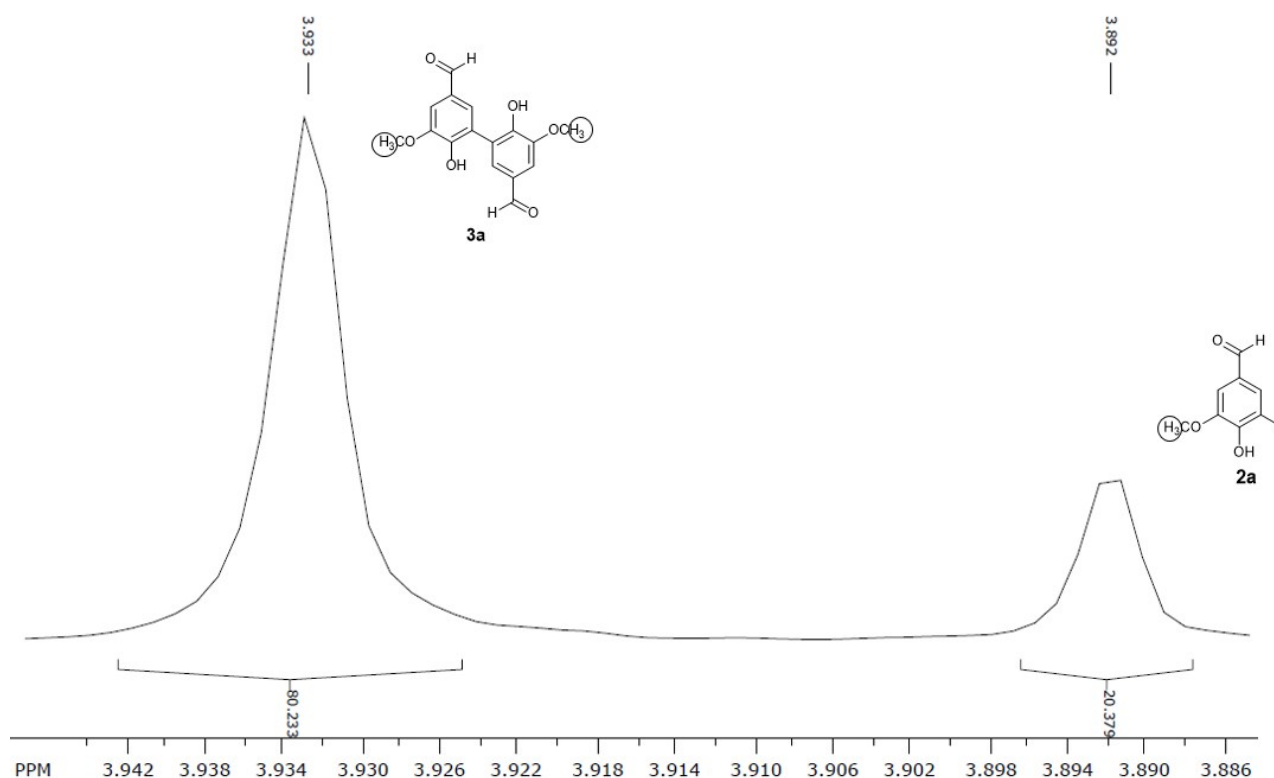


Fig. 29 Determination of the ratio of **2a** and **3a** of the reaction presented in Table 1, entry 1, by ¹H NMR: integration of the signal intensities of the methoxy group of **2a**, resonating at $\delta = 3.89$ ppm, and the methoxy groups of **3a**, resonating at $\delta = 3.93$ ppm.

7. Development of sustainable methods for the laccase-catalyzed iodination

General procedure II, method A:

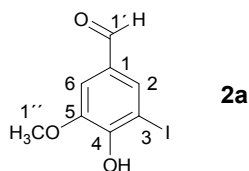
A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (498 mg, 1.5 equiv., 3 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (43.88 mL, 0.2 M, pH 5.0). Additional laccase from *Trametes versicolor* (225 U), dissolved in acetate buffer (563 μ L, 0.2 M, pH 5.0), was slowly added during 15 h (15 U/h) at rt. Simultaneously, the substrate (2 mmol) in DMSO (563 μ L) was added at a constant rate (38 μ L/h). Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/h at rt for the time given. After completion of the reaction, solid ascorbic acid was added until the brown colour disappeared. Subsequently, the solvents were evaporated *in vacuo*, the residue was suspended in ice-cold water (20 mL) and filtered on a Buchner funnel. Finally, the product was washed with ice-cold water (5 x 5 mL) and dried *in vacuo*. In the crude products, traces of impurities (substrate and/or dimer) could be detected by ¹H NMR. If required, the products were further purified by flash chromatography on SiO₂.

Method B:

A 100 mL Erlenmeyer flask equipped with a magnetic stirrer bar was charged with ABTS diammonium salt (10.96 mg, 1 mol%, 0.02 mmol), potassium iodide (498 mg, 1.5 equiv., 3 mmol), laccase from *Trametes versicolor* (45 U) and acetate buffer (44.44 mL, 0.2 M, pH 5.0). Additional laccase from *Trametes versicolor* (225 U), dissolved in acetate buffer (563 μ L, 0.2 M, pH 5.0), was slowly added during 15 h (15 U/h) at rt and the substrate (2 mmol) was added portionwise as a solid to the reaction mixture during 10 h. Air was bubbled through the well-stirred reaction mixture at a rate of 20 mL/h at rt for the time given. After completion of the reaction, solid ascorbic acid was added until the brown colour disappeared. Subsequently, the solvents were evaporated *in vacuo*, the residue was suspended in ice-cold water (20 mL) and filtered on a Buchner funnel. Finally, the product was washed with ice-cold water (5 x 5 mL) and dried *in vacuo*. In the crude products, traces of impurities (substrate and/or dimer) could be detected by ^1H NMR. If required, the products were further purified by flash chromatography on SiO_2 .

8. Sustainable iodination of selected *p*-hydroxyarylcarbonyl- and *p*-hydroxyaryl-carboxylic acid derivatives

8.1 Synthesis and analytical data of 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**)³



According to general procedure II, method A, 4-hydroxy-3-methoxybenzaldehyde (**1a**) (304 mg, 2 mmol) was reacted for 24 h to yield **2a** (428 mg, 1.54 mmol, 77%) as a slightly grey powder. δ_{H} (300 MHz; $\text{DMSO-}d_6$) 3.89 (3H, s, 1''-H₃), 7.41 (1H, d, $^4J_{6\text{-H}, 2\text{-H}} = 1.4$ Hz, 6-H), 7.88 (1H, d, $^4J_{2\text{-H}, 6\text{-H}} = 1.7$ Hz, 2-H), 9.75 (1H, s, 1'-H) and 10.74 (1H, br, 4-OH).

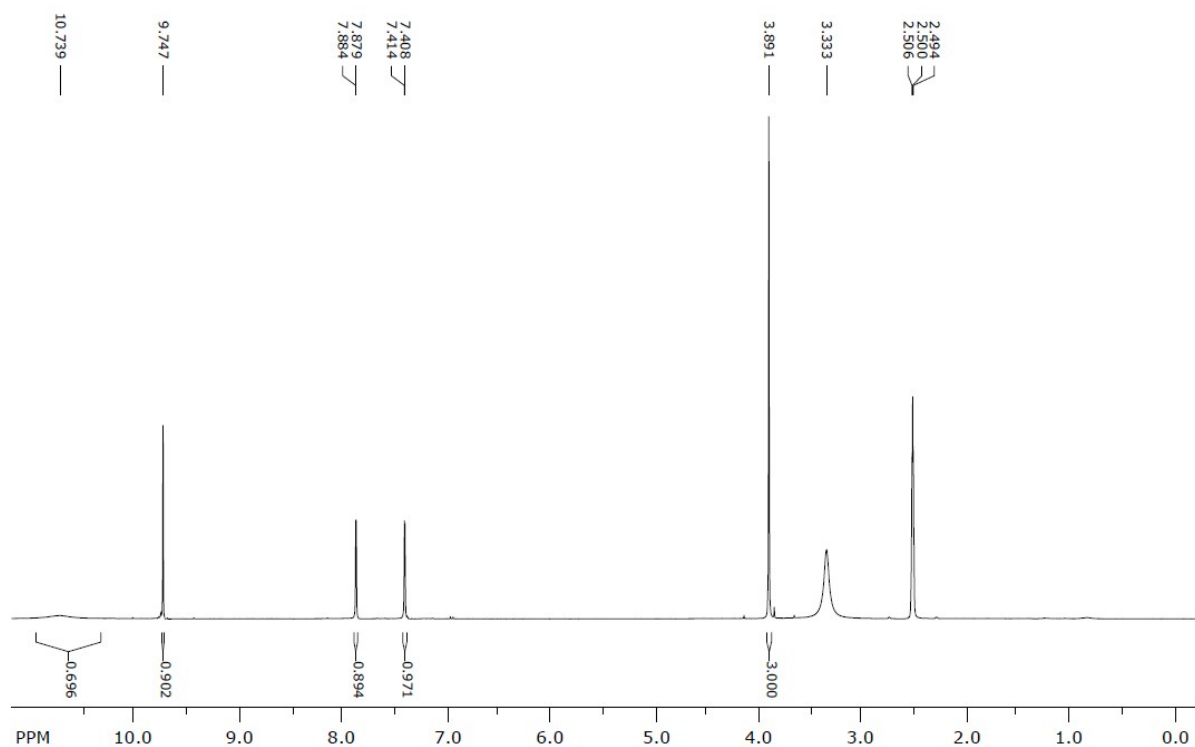
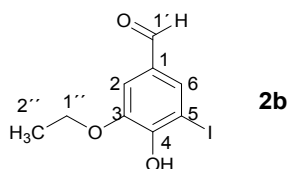


Fig. 30 ^1H (300 MHz) NMR spectrum of the crude product **2a** in $\text{DMSO-}d_6$

8.2 Synthesis and analytical data of 3-ethoxy-4-hydroxy-5-iodobenzaldehyde (**2b**)⁴



According to general procedure II, method A, 3-ethoxy-4-hydroxybenzaldehyde (**1b**) (332 mg, 2 mmol) was reacted for 24 h to yield **2b** (473 mg, 1.60 mmol, 80%) as a colourless solid. δ_{H} (300 MHz; $\text{DMSO-}d_6$) 1.37 (3H, t, $^3J_{2''\text{-H}, 1''\text{-H}} = 7.3$ Hz, $2''\text{-H}_3$); 4.15 (2H, q, $^3J_{1''\text{-H}, 2''\text{-H}} = 7.0$ Hz,

1''-H₂); 7.39 (1H, d, $^3J_{2-H, 6-H} = 1.7$ Hz, 2-H); 7.86 (1H, d, $^3J_{6-H, 2-H} = 1.8$ Hz, 6-H); 9.74 (1H, s, 1'-H) and 10.49 (1H, br, 4-OH).

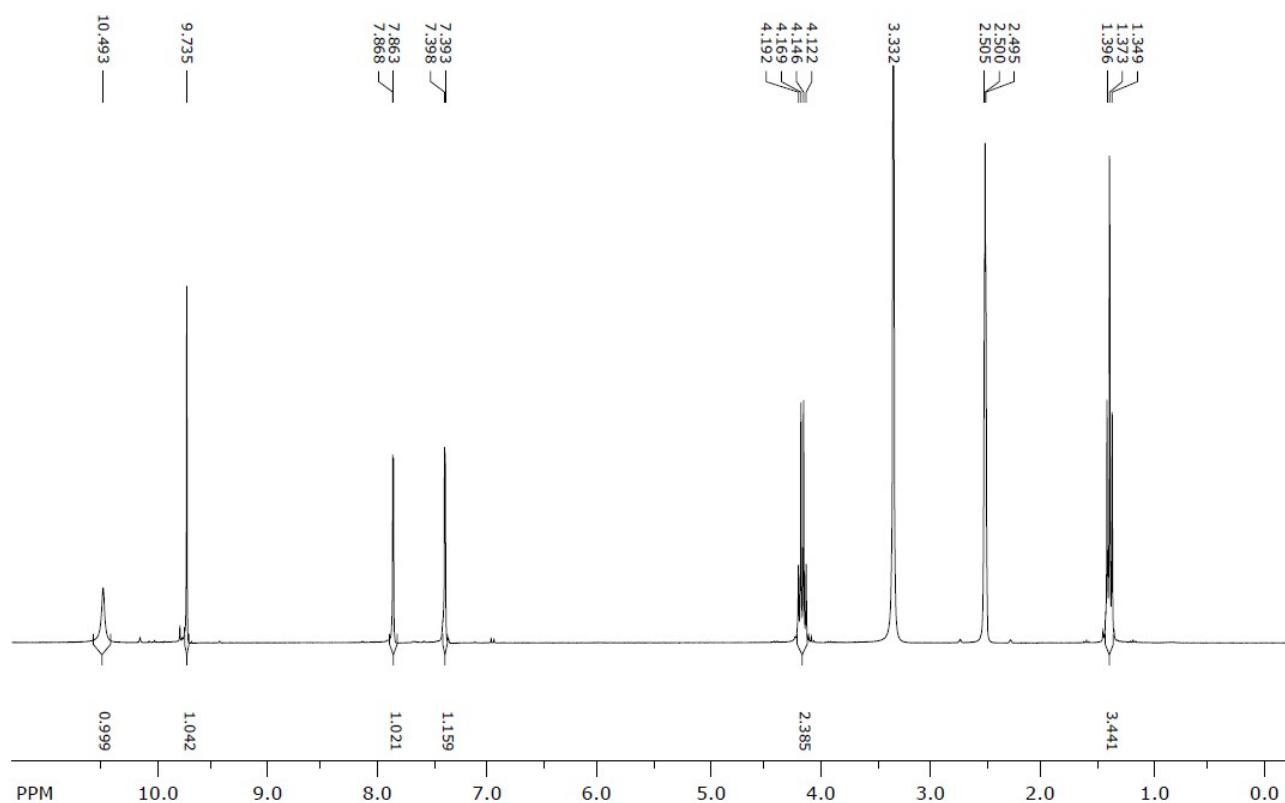
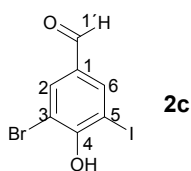


Fig. 31 ^1H (300 MHz) NMR spectrum of the crude product **2b** in $\text{DMSO-}d_6$

8.3 Synthesis and analytical data of 3-bromo-4-hydroxy-5-iodobenzaldehyde (**2c**)



According to general procedure II, method B, 3-bromo-4-hydroxybenzaldehyde (**1c**) (402 mg, 2 mmol) was reacted for 72 h. Laccase from *Trametes versicolor* (255 U) dissolved in acetate buffer (563 μL , 0.2 M, pH 5.0) was slowly (36h, 7 U/h) added to the flask. The product **2c** (590 mg,

1.80 mmol, 90%) was obtained as a slightly greyish solid. δ_{H} (300 MHz; DMSO- d_6) 8.05 (1H, d, $^4J_{2\text{-H}, 6\text{-H}} = 2.0$ Hz, 2-H); 8.23 (1H, d, $^4J_{6\text{-H}, 2\text{-H}} = 1.9$ Hz, 6-H) and 9.75 (1H, s, 1'-H).

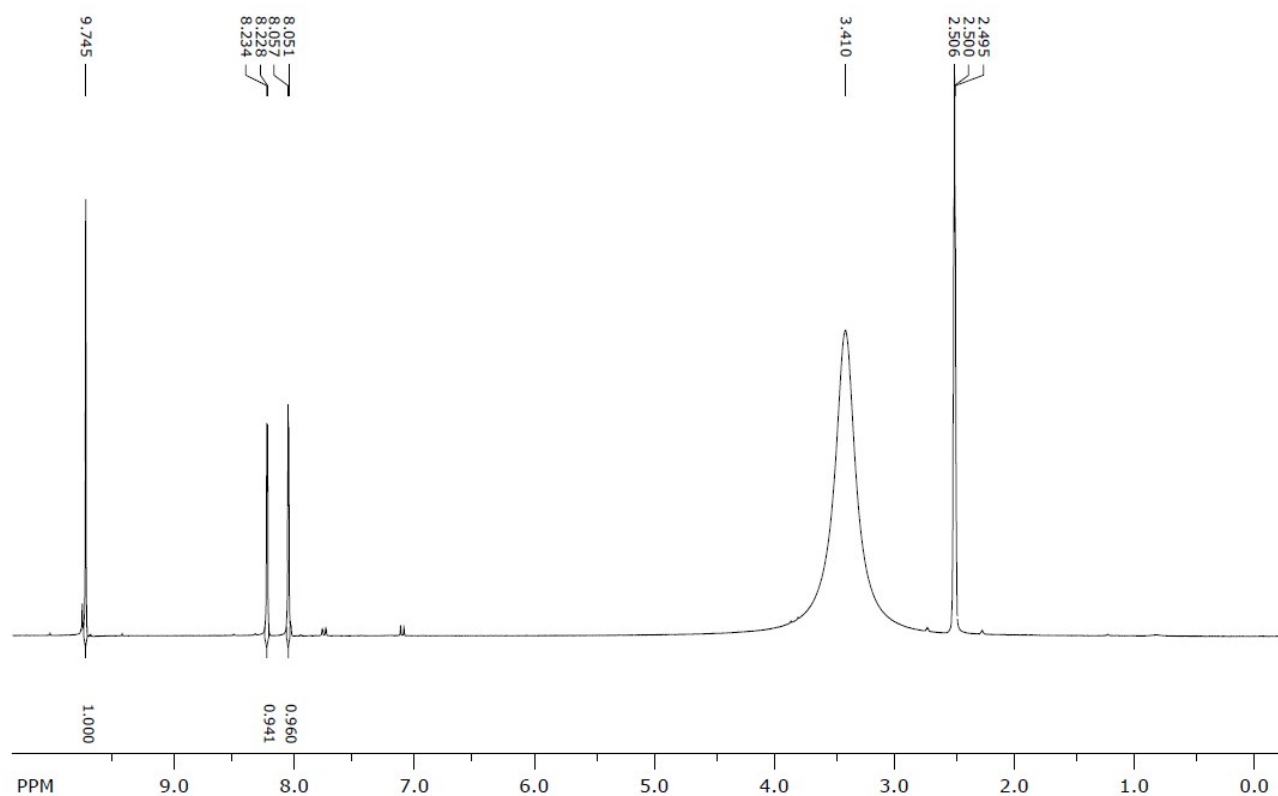
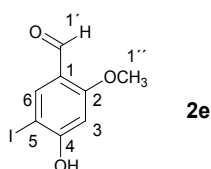


Fig. 32 ^1H (300 MHz) NMR spectrum of the crude product **2c** in DMSO- d_6

8.4 Synthesis and analytical data of 4-hydroxy-5-iodo-2-methoxybenzaldehyde (**2e**)



According to general procedure II, method B, 4-hydroxy-2-methoxybenzaldehyde (**1e**) (304 mg, 2 mmol) was reacted for 24 h to yield **2e** (501 mg, 1.80 mmol, 90%) as a slightly greyish solid. δ_{H} (300 MHz; DMSO- d_6) 3.84 (3H, s, 1''-H₃), 6.62 (1H, s, 3-H), 7.94 (1H, s, 6-H), 10.01 (1H, s, 1'-H) and 11.63 (1H, br, 4-OH).

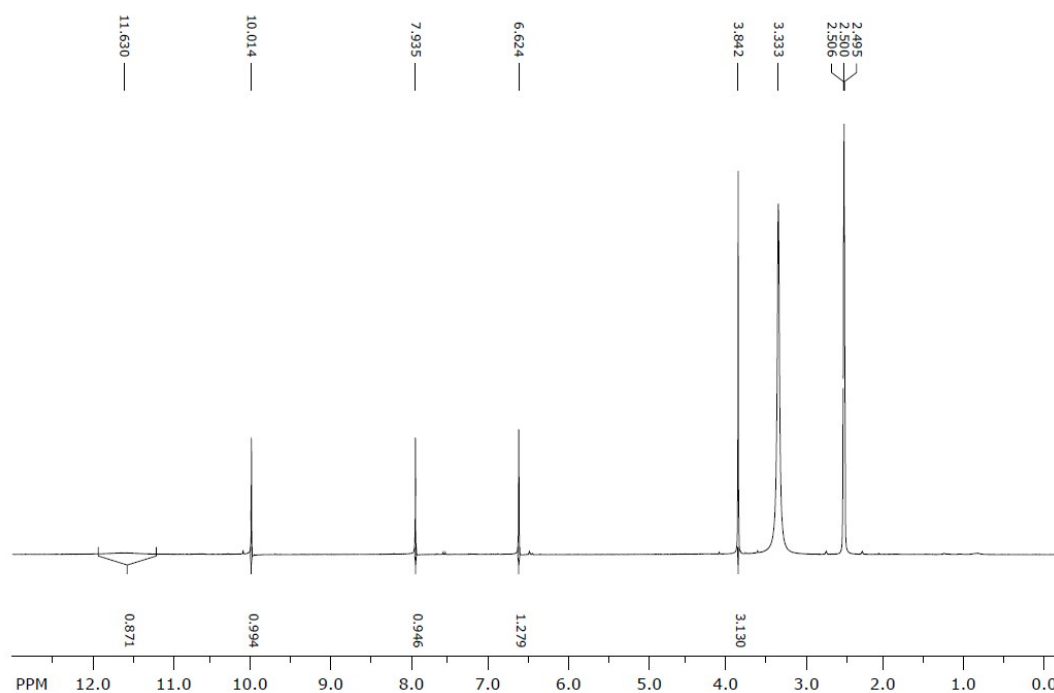
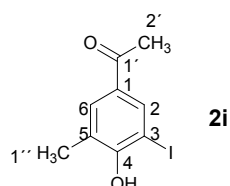


Fig. 33 ^1H (300 MHz) NMR spectrum of the crude product **2e** in $\text{DMSO-}d_6$

8.5 Synthesis and analytical data of 1-(4-hydroxy-3-iodo-5-methylphenyl)ethanone (**2i**)



According to general procedure II, method B, 1-(4-hydroxy-3-methylphenyl)ethanone (**1i**) (300 mg, 2 mmol) was reacted for 48 h to yield **2i** (507 mg, 1.84 mmol, 92%) as a slightly greyish solid. δ_{H} (300 MHz; $\text{DMSO-}d_6$) 2.28 (3H, s, 1''-H₃), 2.48 (3H, s, 2'-H₃), 7.73 (1H, d, $^4J_{6\text{-H}, 2\text{-H}} = 1.6$ Hz, 6-H); 8.10 (1H, d, $^4J_{2\text{-H}, 6\text{-H}} = 1.6$ Hz, 2-H) and 9.97 (1H, br, 4-OH).

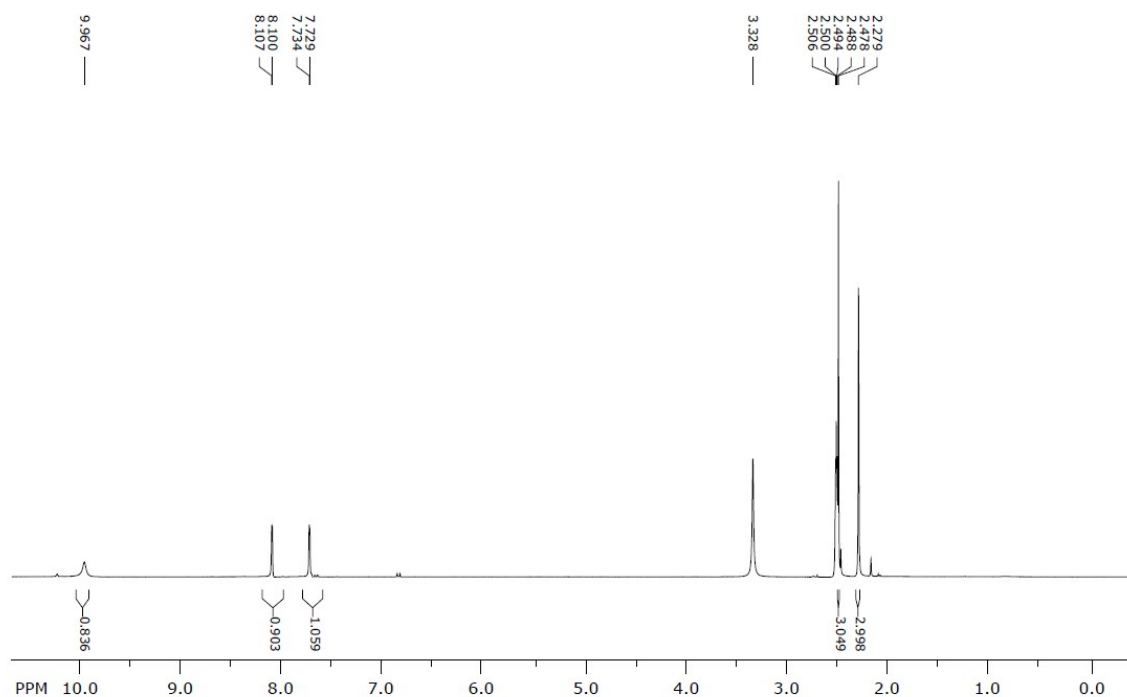
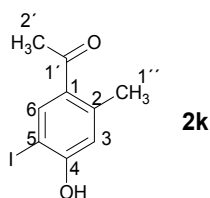


Fig. 34 ^1H (300 MHz) NMR spectrum of the crude product **2i** in $\text{DMSO-}d_6$

8.6 Synthesis and analytical data of 1-(4-hydroxy-5-iodo-2-methylphenyl)ethanone (**2k**)



According to general procedure II, method B, 1-(4-hydroxy-2-methylphenyl)ethanone (**1k**) (300 mg, 2 mmol) was reacted for 24 h. The product **2k** (513 mg, 1.86 mmol, 93%) was obtained as a slightly greyish solid. δ_{H} (300 MHz; $\text{DMSO-}d_6$) 2.36 (3H, s, 1''-H₃), 2.47 (3H, s, 2'-H₃), 6.73 (1H, s, 3-H) 8.14 (1H, s, 6-H) and 11.00 (1H, s, 4-OH).

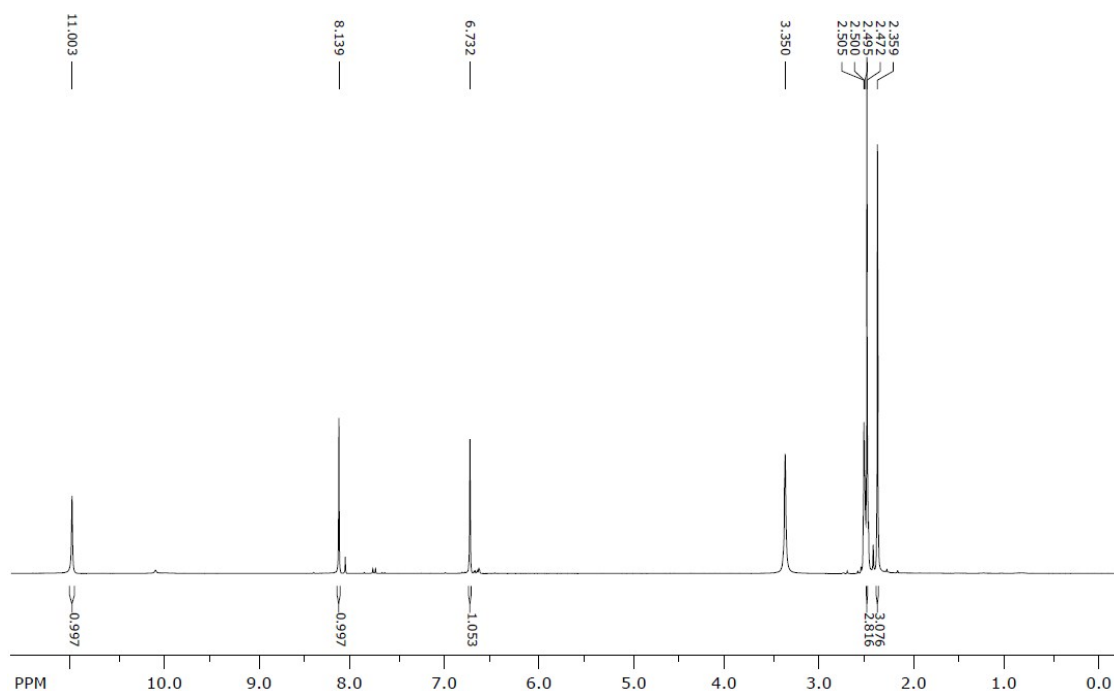


Fig. 35 ^1H (300 MHz) NMR spectrum of the crude product **2k** in $\text{DMSO-}d_6$

9. The greenness of the laccase-catalyzed iodination according to the twelve principles of green chemistry¹⁶

Principle 1 - Prevention

Typical monoiodinations of aromatic compounds with elemental iodine require at least 1 equiv. molecular I_2 for full conversion of the substrate. This implies that only one of the two iodine atoms is used for the iodination; the other iodine atom is wasted and remains in the form of I^- in the reaction mixture. The laccase-catalyzed iodination described in this work employs KI as iodine-source, which undergoes laccase-catalyzed oxidation to I_2 during the reaction. The methods presented here (general procedures II) require only 1.5 equiv. of KI, which corresponds to 0.75 equiv. I_2 . This means that iodide anions formed as byproduct during the iodination of the phenolic substrate are transformed into molecular iodine by laccase-catalyzed reaction.

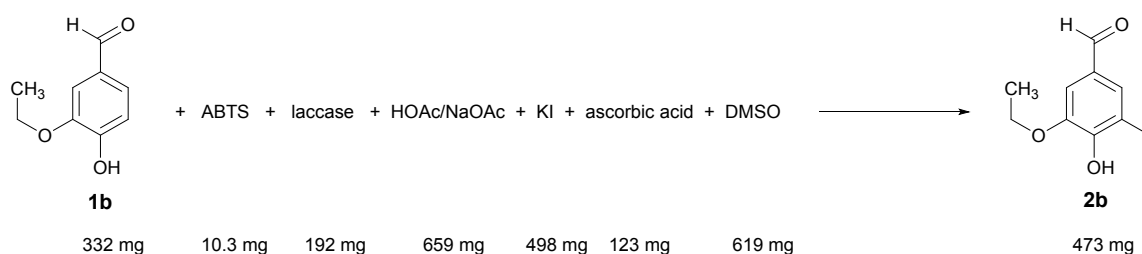
The laccase-catalyzed iodination which makes use of KI as iodine source, ABTS as mediator and aerial oxygen as oxidant is a highly selective process that allows an environmentally friendly synthesis of iodinated *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives with yields up to 93%. No toxic byproducts are formed. Molecular oxygen as the oxidant is converted into nontoxic water.

For the sustainable laccase-catalyzed iodination two methods (general procedure II, methods A and B) which allow for a substantial reduction of waste have been developed. For both methods, no organic solvent for workup and no purification by column chromatography is required.

Method A which requires 1.25 vol% DMSO as a cosolvent and which is particularly suitable for dimerization-sensitive substrates delivers the products with yields up to 80%. Using the iodination of **1b** to **2b** as an example, the E-factor¹⁷(kg waste per kg product) of the overall process amounts to **4.14 kg kg⁻¹**. This value compares well with the E-factors of other synthetic methods for the iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives.

Method B which is performed in the absence of any organic cosolvent delivers the products with yields up to 93%. Using the iodination of **1c** to **2c** as an example, the E-factor (kg waste per kg product) of the overall process amounts to **2.22 kg kg⁻¹**. This value compares well with the E-factors of other synthetic methods for the iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives.

Calculation of the E-factor for the iodination of 3-ethoxy-4-hydroxybenzaldehyde (**1b**) to 3-ethoxy-4-hydroxy-5-iodobenzaldehyde (**2b**) according to general procedure II, method A. The isolated yield of **2b** was 80% (473 mg, 1.60 mmol). For details of the reaction, see page 57.



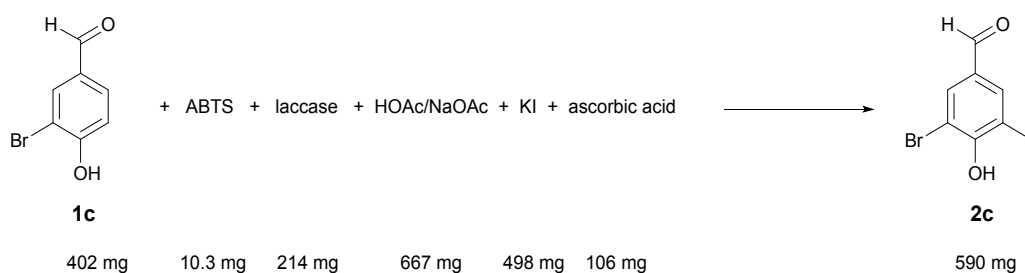
Total amount of reactants: 332 mg + 10.3 mg + 192 mg + 659 mg + 498 mg + 123 mg + 619 mg = 2433.3 mg

Amount of product = 473 mg

Amount of waste = 2433.3 – 473 = 1960.3 mg

E-factor = Amount of waste [kg]/ Amount of product [kg] = 1960.3/473 = **4.14 kg kg⁻¹**

Calculation of the E-factor for the iodination of 3-bromo-4-hydroxy-5-iodobenzaldehyde (**1c**) to 3-bromo-4-hydroxy-5-iodobenzaldehyde (**2c**) according to general procedure II, method B. The isolated yield of **2c** was 90% (590 mg, 1.80 mmol). For details of the reaction, see page 58.



Total amount of reactants: 402 mg + 10.3 mg + 214 mg + 667 mg + 498 mg + 106 mg = 1897.3 mg

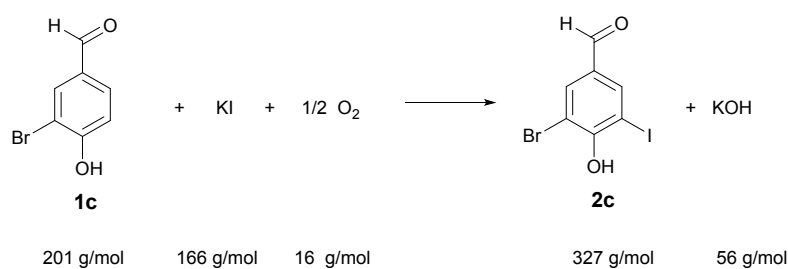
Amount of product = 590 mg

Amount of waste = 1897.3 – 590 = 1307.3 mg

E-factor = Amount of waste [kg]/ Amount of product [kg] = 1307.3/590 = **2.22 kg kg⁻¹**

Principle 2 – Atom Economy¹⁸

The reaction of **1c** to **2c** was taken as an example for the calculation of the atom economy of the laccase-catalyzed iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives. The value of the atom economy compared to other iodinations is very high; it amounts to **85%**.



The atom economy was calculated using the following equation:

$$\% \text{ Atom economy} = 100 \times \frac{\text{Molecular weight of the desired product}}{\text{Molecular weight of all reactants}}$$

$$\text{Atom economy} = 100 \times 327 / 383 = \mathbf{85\%}$$

Principle 3 – Less Hazardous Chemical Synthesis

In comparison to established methods, the procedure described here avoids the use of any toxic reagents, such as hazardous heavy metals, toxic oxidants and/or toxic solvents. Instead, the iodination presented here makes use of safe aerial oxygen as oxidant and safe laccase as catalyst. Elemental iodine (I₂), which forms toxic fumes and is irritant to the eyes and the skin, was replaced with easy to handle alkali iodides, such as KI.^{19,20}

Principle 4 – Designing Safer Chemicals

Does not apply to the developed method.

Principle 5 – Safer Solvents and Auxiliaries

In all reactions, acetate buffer was used as solvent. If required, small amounts of DMSO were used as cosolvent. Both are regarded as green solvents.²¹

For the removal of excess iodine, ascorbic acid was employed. Ascorbic acid is considered a green reduction agent.

Whenever necessary, ethyl acetate, which is an environmentally preferred solvent, was used for extraction.

Principle 6 – Design for Energy Efficiency

The laccase-catalyzed iodination is highly energy efficient. All reactions could be performed at room temperature under air at atmospheric pressure and at pH 5.0.

Principle 7 – Use of Renewable Feedstocks

The laccase, ascorbic acid and the acetic acid of the acetate buffer can be obtained from renewable raw materials and are completely biodegradable. It is assumed that the buffer waste from the reaction is suitable for biotreatment.

Principle 8 – Reduce Derivatives

Does not apply to the developed reaction

Principle 9 - Catalysis

The laccase-catalyzed iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives using aerial oxygen as an oxidant is an efficient biotransformation.

General procedure I, is characterized by high turnover numbers and high turnover frequencies. Using the iodination of **1i** to **2i** as an example, the TON of the process amounts to **1269**. This value confirms the high catalytic efficiency of the process. The turnover frequencies of the process are also high; in the above mentioned example the TOF is **85 h⁻¹**. The space time yield (STY) of the reaction amounts to **0.00120 Mol × L⁻¹ × h⁻¹**.

Calculation of TON, TOF and STY for the laccase-catalyzed iodination of 1-(4-hydroxy-3-methylphenyl)ethanone (1i) to 1-(4-hydroxy-3-iodo-5-methylphenyl)ethanone (2i) according to general procedure I

Yield of 1-(4-hydroxy-3-iodo-5-methylphenyl)ethanone (**2i**): 480 mg, 1.74 mmol, 87%; reaction time = 15 h; for more details of the reaction, see page 17.

Calculation of TON

Specific activity of the laccase = 1.4 U/mg

Molecular weight of laccase from *Trametes versicolor*²² = 70 kDa

135 U laccase correspond to 96 mg (1.371 × 10⁻³ mmol)

TON = Amount of the substrate consumed [mmol]/Amount of catalyst [mmol]

TON = 1.74 mmol/1.371 × 10⁻³ mmol = **1269**

Calculation of TOF

$$\text{TOF} = \frac{\text{TON}}{\text{Time [h]}}$$

$$\text{TOF} = 1269 / 15\text{h} = \mathbf{85\ h^{-1}}$$

Calculation of the space time yield (STY)

$$\text{STY} = \text{Desired product quantity [Mol]} / \text{Volume [L]} \times \text{Time [h]}$$

$$\text{STY} = \frac{0.00174\ \text{mol}}{0.096\ \text{L} \times 15\ \text{h}} = \mathbf{0.00120\ \text{Mol} \times \text{L}^{-1} \times \text{h}^{-1}}$$

General procedures II are characterized by reduction of the amounts of the iodination reagent, reduction of the volume of the cosolvent and very high yields of the iodination products. All these factors contribute to low E-values. However, higher amounts of the enzyme are required which results in less favourable high turnover numbers and high turnover frequencies. Using the iodination of **1k** to **2k** as an example, the TON of the process amounts to **678**. The turnover frequency of this process is **28 h⁻¹**. The space time yield (STY) of the reaction amounts to **0.00172 Mol × L⁻¹ × h⁻¹**.

Calculation of TON, TOF and STY for the laccase-catalyzed iodination of 1-(4-hydroxy-2-methylphenyl)ethanone (1k) to 1-(4-hydroxy-5-iodo-2-methylphenyl)ethanone (2k) according to general procedure II, method B

Yield of (4-hydroxy-5-iodo-2-methylphenyl)ethanone me (**2k**): 513 mg, 1.86 mmol, 93%; reaction time = 24 h; for more details of the reaction, see 61.

Calculation of TON

Specific activity of the laccase = 1.4 U/mg

Molecular weight²⁶ of laccase from *Trametes versicolor* = 70 kDa

270 U laccase correspond to 192 mg (2.742×10^{-3} mmol)

TON = Amount of the substrate consumed [mmol]/Amount of catalyst [mmol]

$$\text{TON} = 1.86\ \text{mmol} / 2.742 \times 10^{-3}\ \text{mmol} = \mathbf{678}$$

Calculation of TOF

$$\text{TOF} = \frac{\text{TON}}{\text{Time [h]}} =$$

$$\text{TOF} = 678 / 24\text{h} = \mathbf{28 \text{ h}^{-1}}$$

Calculation of the space time yield (STY)

$$\text{STY} = \text{Desired product quantity [Mol]} / \text{Volume [L]} \times \text{Time [h]}$$

$$\text{STY} = \frac{0.00186 \text{ mol}}{0.045 \text{ L} \times 24 \text{ h}} = \mathbf{0.00172 \text{ Mol} \times \text{L}^{-1} \times \text{h}^{-1}}$$

Principle 10 – Design for Degradation

Does not apply to the developed reaction.

Principle 11 – Real-time Analysis for Pollution Prevention

Does not apply to the developed method since no hazardous substances are formed.

Principle 12 – Inherently Safer Chemistry for Accident Prevention

The reactions are performed under mild conditions, i.e., in an aqueous system at pH 5.0, at room temperature and under aerial oxygen at atmospheric pressure. Potassium hydroxide, which is generated during the process, is neutralized by the acetate buffer.

10. References

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