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Electronic Supplementary Information

Utility of iron nanoparticles and a solution-phase iron species for the *N*-demethylation of alkaloids

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1. Synthesis of pivaloyl tropine (8a).

Tropine (1 g, 7.082 mmol, 1 eq.) was dissolved in DCM (20 mL) and the resulting solution cooled to 0°C. triethylamine (1.185 mL, 8.498 mmol, 1.2 eq.) and pivaloyl chloride (1.308 mL, 10.62 mmol, 1.5 eq.) were sequentially added and the reaction allowed to warm to room temperature and stir for 17 h. DCM (40 mL) was added and the organic phase washed sequentially with 1:1 (*v/v*) 2 M NaOH/brine (4 × 20 mL) and half-saturated brine (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The resulting residue was purified by silica column chromatography (89:10:1 EtOAc/MeOH/NH_4OH) to give the product as a yellow oil (915 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (t, *J* = 6.2 Hz 1H), 3.12–3.03 (m, 2H), 2.27 (s, 3H), 2.18-2.06 (m, 2H), 2.05–1.85 (m, 4H), 1.68–1.57 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 67.1, 59.9, 40.5, 38.7, 36.7, 27.2, 25.7.

2. Synthesis of benzoyl tropine (9a).

Tropine (2.12 g, 15.0 mmol, 1 eq.) and triethylamine (1.2 eq) were dissolved in toluene (20 mL) and heated to reflux. Benzoyl chloride (1.2 eq.) was added dropwise and the solution was stirred at reflux for 6 h, cooled to room temperature and left to stir overnight (approximately 20 h). The resulting yellow solution and white precipitate were gravity filtered and washed with toluene (75 mL). The filtrate was then washed with deionized water (2 x 10 mL) and 1 M NaOH (3 x 10 mL), and then extracted with 1 M HCl (5 x 10 mL). To the aqueous extract was added 1 M NaOH until the pH reached above 10. This caused a white/yellow precipitate to form, which was collected by gravity filtration and dried under vacuum to produce a yellow oil (1.33 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.96 (m, 2H), 7.58–7.49 (m, 3H), 5.24 (t, *J* = 5.2 Hz 1H), 3.14 (br s, 2H), 2.29 (s, 3H), 2.27-2.15 (m, 2H), 2.12–2.00 (m, 4H), 1.87–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 132.9, 130.9, 129.5, 128.5, 68.1, 59.9, 40.5, 36.8, 25.9.

3. Synthesis of alkaloid *N*-oxide hydrochloride salts (4b-9b).

Each alkaloid *N*-oxide hydrochloride salt was synthesised according to the general procedure for *N*-oxidation of alkaloids and then purified by one of the following procedures:

Procedure A: The volume of $CHCl_3$ was doubled and *i*-PrOH was added to make the solution a 3:1 (*v/v*) mixture of $CHCl_3$/*i*-PrOH. This was then washed successively with 1:4 (*v/v*) 2 M NaOH/brine (5 × 5 mL), followed by 1:4 (*v/v*) 2M HCl/brine (5 × 5 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the alkaloid *N*-oxide hydrochloride salt.

Procedure B: The reaction mixture was extracted with 1 M HCl (3 × 10 mL). The combined aqueous extracts were washed with $CHCl_3$ (2 × 10 mL) and the resulting aqueous phase reduced *in vacuo* to give the alkaloid *N*-oxide hydrochloride salt.

Dextromethorphan *N*-oxide hydrochloride (**4b**) was purified by procedure A. Product appears as a white foam in > 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.26 (br, 1H), 3.88 – 3.82 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.29 (dd, *J* = 19.8, 6.0 Hz, 1H), 3.04 (d, *J* = 19.9 Hz, 1H), 2.92 (td, *J* = 13.0, 3.6 Hz, 1H), 2.77 (dt, *J* = 4.8, 2.8 Hz, 1H), 2.42–2.29 (m, 2H), 1.69 (d, *J* = 12.2 Hz, 1H), 1.61–1.51 (m, 2H), 1.49–1.36 (m, 3H), 1.32–1.22 (m, 1H), 1.02 (qd, *J* = 12.6, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.9, 129.4, 112.6, 111.6, 72.7, 59.7, 55.5, 37.4, 36.7, 35.8, 35.2, 27.3, 25.9, 21.8; LC-MS *m/z* 288 (M^+).

Noscapine *N*-oxide hydrochloride (**5b**) was synthesised with 2.0 equivalents of *m*CPBA and purified by procedure A. Product appears as a yellow solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 6.55 (s, 1H), 6.33 (d, *J* = 11.8 Hz, 2H), 5.84 (dd, *J* = 12.8, 1.2 Hz, 2H), 4.26 (dd, *J* = 19.8, 11.2 Hz, 1H), 3.97 (s, 3H), 3.97 (s, 1H), 3.92 (s, 3H), 3.89–3.81 (m, 1H), 3.69 (s, 3H), 3.59 (s, 1H), 3.44 (dd, *J* = 18.1, 7.6 Hz, 1H), 3.26 (s, 3H), 3.19–3.06 (m, 1H), 1.20 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 153.0, 151.2, 147.7, 139.7, 138.7, 133.9, 125.5, 120.4, 120.0, 117.4, 108.5, 102.3, 101.6, 74.85, 73.1, 62.3, 59.1, 58.7, 57.1, 54.1, 25.4; LC-MS *m/z* 430 (M^+).

Atropine *N*-oxide hydrochloride (**6b**) was purified by procedure A. Product appears as a clear oil in > 90% yield. ^{1}H NMR (400 MHz, DMSO) δ 12.81 (d, *J* = 64.1 Hz, 1H), 7.37–7.25 (m, 5H), 4.93 (dt, *J* = 13.6, 5.0 Hz, 1H), 4.24–4.03 (m, 3H), 3.80 (ddd, *J* = 8.8, 5.5, 3.1 Hz, 1H), 3.67 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.48 (d, *J* = 50.5 Hz, 3H), 2.70–2.53 (m, 2H), 2.26–1.64 (m, 6H); ^{13}C NMR (101 MHz, DMSO) δ 171.2, 136.2, 136.1, 128.6, 128.1, 127.4, 127.4, 70.5, 70.4, 69.2, 69.1, 63.5, 63.0, 62.9, 54.19, 52.2, 46.2, 33.1, 33.1, 31.1, 31.1, 24.8, 24.5, 22.7, 22.4; LC-MS *m/z* 306 (M^+).

Tropine *N*-oxide hydrochloride (**7b**) was purified by procedure B. Product appears as a white solid in > 90% yield. ^{1}H NMR (400 MHz, D_2O) δ 4.15–4.10 (m, 2H), 4.07 (dd, *J* = 4.5, 2.6 Hz, 1H), 3.54–3.44 (m, 3H), 2.72 (dt, *J* = 16.1, 4.2 Hz, 1H), 2.59–2.50 (m, 2H), 2.47–2.39 (m, 2H), 2.31–2.22 (m, 1H), 2.14 (d, *J* = 16.7 Hz, 1H), 1.92 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 71.2, 69.8, 58.94, 58.6, 52.3, 46.1, 35.8, 33.8, 25.1, 23.1; LC-MS *m/z* 158 (M^+).

Pivaloyltropine *N*-oxide hydrochloride (**8b**) was purified by procedure A. Product appears as a yellow solid in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (q, *J* = 5.2 Hz, 1H), 4.50 (br s, 1H), 4.30 (br s, 1H), 3.75–3.62

(m, 3H), 3.05–2.95 (m, 1H), 2.67 – 2.52 (m, 2H), 2.44 (q, *J* = 5.0 Hz, 1H), 2.32–2.18 (m, 2H), 2.09 (d, *J* = 16.9 Hz, 1H), 1.86 (d, *J* = 16.2 Hz, 1H), 1.20 (s, *J* = 1.7 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 177.0, 71.1, 70.0, 63.0, 61.8, 52.8, 46.6, 38.7, 38.7, 34.2, 32.3, 27.1, 27.1, 25.6, 23.7; LC-MS *m/z* 242 (M^+) .

Benzoyltropine *N*-oxide hydrochloride (**9b**) was purified by procedure B. Product appears as a yellow solid in 80 % yield. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 13.12 (s, 1H), 7.97 (m, 2H), 7.69 (m, 1H), 7.57 (m, 2H), 5.28–5.14 (m, 1H), 4.34 (br s, 2H), 3.66 (s, 3H), 2.85–2.60 (m, 2H), 2.47-2.14 (m, 5H), 2.05 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$)) δ 164.8, 164.8, 133.5, 133.6, 129.8, 129.7, 129.1, 128.9, 70.6, 69.3, 64.0, 63.5, 52.3, 46.2, 33.2, 31.3, 25.1, 23.0; MS (ESI) *m/z* 262 (M^+).

4. Synthesis of *N*-nor alkaloids (4c–9c)

Each *N*-nor alkaloid was worked up according to the general procedure for *N*-demethylation of alkaloid *N*-oxides using nZVI or $Fe_3(CO)_{12}$ and subsequently purified by silica flash chromatography.

N-Nordextromethorphan (**4c**) was purified *via* flash chromatography (mobile phase 89:10:1 DCM/MeOH/NH_4OH). Product appears as a white foam/yellow oil. See Table 1 for yields. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.58 (s, 1H), 3.79 (s, 3H), 3.28–3.24 (m, 1H), 3.13 (dd, *J* = 18.2, 6.1 Hz, 1H), 2.88 (d, *J* = 18.3 Hz, 1H), 2.83 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.64 (td, *J* = 12.8, 3.0 Hz, 1H), 2.32 (d, *J* = 13.1 Hz, 1H), 1.88 (d, *J* = 12.5 Hz, 1H), 1.75–1.66 (m, 1H), 1.64 (d, *J* = 11.8 Hz, 1H), 1.52 (d, *J* = 10.5 Hz, 1H), 1.44–1.23 (m, 5H), 1.12–0.98 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.9, 129.4, 112.6, 111.6, 73.0, 59.7, 55.5, 37.4, 36.7, 35.8, 35.2, 27.3, 25.9, 21.8; LC-MS *m/z* 258 $(M+H)^+$.

N-Nornoscapine (**6c**) was purified *via* flash chromatography (mobile phase 2:1 EtOAc/petroleum spirits (40–60^{o}C) with 1% TEA). Product appears as a yellow oil. See Table 2 for yields.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.3 Hz, 1H), 6.33 (s, 1H), 5.96 (dd, *J* = 5.5, 1.5 Hz, 3H), 5.91 (d, *J* = 3.8 Hz, 1H), 4.85 (d, *J* = 3.9 Hz, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 3.84 (s, 3H), 2.67–2.61 (m, 1H), 2.52–2.44 (m, 1H), 2.35–2.28 (m, 1H), 2.19–2.12 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 152.4, 148.6, 141.3, 140.67, 134.7, 132.2, 119.9, 118.7, 117.7, 103.4, 101.0, 80.9, 62.5, 59.7, 56.9, 53.0, 39.8, 29.9; LC-MS *m/z* 400 $(M+H)^+$.

N-Noratropine (**7c**) was purified *via* flash chromatography (mobile phase 89:10:1 $CHCl_3$/MeOH/NH_4OH). Product appears as a yellow oil. See Table 2 for yields.

^{1}H NMR (400 MHz, DMSO) δ 7.37–7.22 (m, 5H), 4.90 (t, *J* = 5.0 Hz, 1H), 4.00–3.93 (m, 1H), 3.71 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.63 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.37–3.33 (m, 2H), 3.29–3.24 (m, 1H), 1.97–1.82 (m, 3H), 1.63–1.40 (m, 5H); ^{13}C NMR (101 MHz, DMSO) δ 171.3, 136.4, 128.5, 127.9, 127.2, 68.0, 63.0, 54.9, 54.5, 52.4, 52.3, 36.4, 36.3, 28.5, 28.3; LC-MS *m/z* 276 $(M+H)^+$.

N-Norpivaloyltropine (**8c**) was purified *via* flash chromatography (mobile phase 89:10:1 EtOAc/MeOH/NH_4OH). Product appears as yellow oil. See Table 2 for yields.

^{1}H NMR (400 MHz, CDCl3) δ 5.03 (t, *J* = 5.2 Hz, 1H), 3.55 (s, 2H), 2.13–2.03 (m, 4H), 1.87–1.81 (m, 2H), 1.74 (s, 1H), 1.71 (s, 1H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 67.6, 53.4, 38.7, 37.3, 29.0, 27.2; LC-MS *m/z* 212 $(M+H)^+$.

N-Norbenzoyltropine (**9c**) was purified *via* flash chromatography (mobile phase 89:10:1 EtOAc/MeOH/NH_4OH). Product appears as yellow oil. See Table 2 for yields.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–7.98 (m, 2H), 7.62-7.50 (m, 1H), 7.50–7.38 (m, 2H), 5.32 (t, *J* = 5.1 Hz, 1H), 3.61-3.50 (m, 2H), 2.27–2.01 (m, 4H), 2.01-1.68 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 133.0, 131.0, 129.6, 128.6, 68.9, 53.5, 37.8, 29.6; MS (ESI) *m/z* 232 $(M+H)^+$.

5. General procedure for monitoring *N*-demethylation reaction by HPLC-DAD.

For each of the four iron reagents tested (nZVI, triiron dodecacarbonyl, iron(0) dust, ferric sulphate heptahydrate), dextromethorphan *N*-oxide hydrochloride was used as the substrate (161.2 g, 0.500 mmol), *i*-PrOH (15 mL) as the reaction solvent and the reaction was performed at room temperature (22–23 °C). 1 molar equivalent of iron was used, except in the case if triiron dodecacarbonyl, where 5 mol % was used. The reaction was stirred at 900 RPM with a 12 mm magnetic bead. 250 µL aliquots were taken from the reaction flask at appropriate time intervals (see Figure 3) and loaded into 1.5 mL LC vials and diluted with 1 mL *i*-PrOH. In the case of nZVI and triiron dodecacarbonyl, which form suspensions in the reaction solvent, the aliquots were diluted with 1 mL *i*-PrOH and then centrifuged to separate the iron. The supernatant fluid was then loaded into LC vials. Because the HPLC-DAD method took approximately 10 min to complete a single run, not all aliquots were run immediately after being prepared. The LC system was an Agilent 1100 series and separations were carried out at 30 °C in a Zorbax Bonus-RP column (4.6 x 150 mm, 5 µm). The mobile phase consisted of a combination of 0.1% aqueous formic acid (phase A) and a 50/50 (*v/*v) mixture of acetonitrile and methanol (phase B), with a ratio of 82 parts phase A to 18 parts phase B. Each sample was run isocratically with a flow rate of 1.5 ml/min and a run time of 8 min. The volume injected into the chromatographic system was 1 µL. The disappearance of DXM *N*-oxide

hydrochloride was monitored using a diode array detector (DAD) at 284 nm. The retention time of DXM *N*-oxide hydrochloride was 4.82 min.