Supporting Information File 1

for

Syntheses of fluorooxindole and 2-fluoro-2-arylacetic acid derivatives from diethyl 2-fluoromalonate ester

Antal Harsanyi¹, Graham Sandford¹*, Dmitri S. Yufit² and Judith A.K. Howard²

Address: ¹Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, U.K, ²Chemical Crystallography, Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, U.K.

Email: Graham Sandford - graham.sandford@durham.ac.uk

*Corresponding author

Experimental procedures

General S3

Synthesis of diethyl 2-fluoro-2-(2-nitrophenyl)malonate ‘3’ S3

Synthesis of 2-aryl-2-fluoroacetic acids 4a–f: general procedure. S4

2-Fluoro-2-(2-nitrophenyl)acetic acid (4a) S5

2-Fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetic acid (4b) S5

2-Fluoro-2-(2-nitro-4-bromophenyl)acetic acid (4c) S6

2-Fluoro-2-(2,4-dinitrophenyl)acetic acid (4d) S6
2-Fluoro-2-(2-nitro-5-methoxyphenyl)acetic acid (4e)  S7

Potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate (4f)  S7

Synthesis of methyl esters 6a–e: general procedure  S8

Methyl 2-fluoro-2-(2-nitrophenyl)acetate (6a)  S8

Methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate (6b)  S9

Methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate (6c)  S9

Methyl 2-fluoro-2-(2,4-dinitrophenyl)acetate (6d)  S10

Methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate (6e)  S10

Reductive cyclisation for the synthesis of fluorooxindole derivatives 8:

general procedure  S11

3-Fluorooxindole (8a)  S11

3-Fluoro-6-trifluoromethyloxindole (8b)  S11

3-Fluoro-6-bromooxindole (8c)  S12

3-Fluoro-5-methoxyoxindole (8e)  S12

Synthesis of fluoromethyl nitroarenes  S13

2,4-Dinitrobenzyl fluoride (5)  S13

2-Fluoromethyl-3-nitropyridine (7)  S13
General

Analysis: Proton, carbon and fluorine nuclear magnetic resonance spectra (1H NMR, 13C NMR and 19F NMR) were recorded (1H NMR, 400 MHz; 13C NMR, 100 MHz; 19F NMR, 376 MHz) using solvent resonance as the internal standard (1H NMR, CHCl3 at 7.26 ppm; 13C NMR, CDCl3 at 77.36 ppm; 19F NMR, CFCl3 at 0.00 ppm). 1H, 13C and 19F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. Crystallographic data was recorded with a Rigaku R-Axis SPIDER IP diffractometer equipped with Cryostream (Oxford Cryosystems) low-temperature device at 120 K with graphite-monochromated Mo Kα-radiation (λ = 0.71073 Å). Melting points were measured at atmospheric pressure and are uncorrected.

Chemicals and solvents: Unless otherwise stated, commercially available reagents were used without purification. DMF was dried by colorimetric titration. Hexane, ethyl acetate, diethyl ether and DCM were purchased from Fischer and used without further purification. Flash column chromatography was carried out using Fluorochem Silicagel LC60A (40–63 micron).

Synthesis of diethyl 2-fluoro-2-(2-nitrophenyl)malonate (3)

NaH (0.88 g, 22 mmol 60% in mineral oil) was washed free from the oil with hexanes (3 × 10 mL) and was suspended in dry DMF (30 mL). Diethyl fluoromalonate (2.85 g, 16 mmol) dissolved in dry DMF (10 mL) was added dropwise while cooled in ice. After stirring for 10 minutes, 1-fluoro-2-nitrobenzene (2.10 g, 15 mmol) in dry DMF (10 mL) was added and the mixture was heated to 90 °C for 18 hours. After cooling to room temperature, the mixture
was poured into water (300 mL), acidified with concentrated HCl (2 mL) and extracted with ether (3 × 70 mL). The combined extracts were washed with saturated NaHCO₃ solution (2 × 50 mL) and brine (1 × 50 mL) and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure an orange oil was obtained that was purified by Kugelrohr distillation (8 mbar, 200 °C) to afford diethyl 2-fluoro-2-(2-nitrophenyl)malonate (3, 3.21 g, 71%) as an orange solid. M.p. 48-49 °C; IR (neat, cm⁻¹) 2996, 1755, 1530, 1276, 1103; δH (CDCl₃, 400 MHz) 1.33 (6H, t, J 7.1, CH₃), 4.31 – 4.43 (4H, m, CH₂), 7.57 – 7.63 (2H, m, Ar-H), 7.66 – 7.71 (1H, m, Ar-H), 8.04 (1H, d, J 8.0, Ar-H); δF (CDCl₃, 376 MHz) -152.98 (s, C-F); δC (CDCl₃, 100 MHz) 14.01 (s, CH₃), 63.55 (s, CH₂), 94.05 (d, 1JCF 198.7, C-F), 125.87 (s, Ar), 128.54 (s, Ar), 128.66 (s, Ar), 128.89 (s, Ar), 130.97 (s, Ar), 133.30 (s, Ar), 164.68 (d, 2JCF 25.1, COO); m/z (ASAP): 226.0 (85%, [M-CO₂Et]+), 134.0 (100%).

Crystals suitable for X-ray crystallography were obtained by crystallisation from EtOH/H₂O (1:1 mixture).

**Synthesis of 2-aryl-2-fluoroacetic acids 4a–f: general procedure.**

Diethyl 2-fluoromalonate (1, 1.07 g, 6.0 mmol) in DMF (5 mL) was added dropwise to a suspension of sodium hydride (0.32 g, 8.0 mmol, 60% in mineral oil) in DMF (10 mL) and the mixture was stirred at room temperature for 20 min. Fluoroarene 2 (5.0 mmol) in DMF (10 mL) was added and the mixture was heated to 80 °C. The mixture was poured into crushed ice (150 mL), acidified with conc. HCl (5 mL) and extracted with diethyl ether (3 × 30 mL). The organic phase was washed with saturated aq. NaHCO₃ solution (25 mL) and saturated brine (2 × 25 mL), dried (Na₂SO₄) and concentrated to give the crude diester. ¹H and ¹⁹F NMR analysis confirmed the formation of the intermediate aryl-fluoromalonate 3 (δF ~ −150 ppm) which was used in the next step without any further purification.
The aryl-fluoromalonate 3 was dissolved in anhydrous ethanol (40 mL) and KOH (0.68 g, 12.0 mmol) in ethanol (10 mL) was added dropwise with cooling (0 °C). The mixture was stirred for 1 h, hexane (50 mL) was added, and stirring continued for a further 30 min. The solid formed was filtered and washed with hexane:ethanol (20 mL, 1:1 mixture). The resulting solid was dissolved in water (40 mL), the solution acidified with conc. HCl (5 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with saturated brine (2 × 20 mL) and dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated under reduced pressure to give pure 2-aryl-2-fluoroacetic acid derivative 4 which was purified by recrystallisation if required.

2-Fluoro-2-(2-nitrophenyl)acetic acid (4a)

2-Fluoronitrobenzene (2a, 0.71 g, 5.0 mmol) gave 2-fluoro-2-(2-nitrophenyl)acetic acid (4a, 0.62 g, 62%) as a yellow powder; mp 119-121 °C (Found: C, 48.2, H, 3.0, N, 6.9. C$_8$H$_6$FNO$_4$ requires: C, 48.25, H, 3.0, N, 7.0%); IR (neat, cm$^{-1}$) 3014 (br), 1732, 1530, 1340, 1204, 1063; $\delta$H (d$_6$-DMSO, 400 MHz) 6.52 (1H, d, $^2$J$_{HF}$ 45.5, C$_F$H), 7.70 - 7.75 (2H, m, ArH), 7.86 (1H, t, $^3$J$_{HH}$ 7.6, ArH), 8.14 (1H, d, $^3$J$_{HH}$ 7.6, ArH), 13.40 (1H, bs, COOH); $\delta$F (d$_6$-DMSO, 376 MHz) - 185.10 (d, $^2$J$_{HF}$ 45.5); $\delta$C (d$_6$-DMSO, 100 MHz) 86.62 (d, $^1$J$_{CF}$ 181.7, CHF), 124.96 (s, C$_{-3}$), 128.85 (d, $^3$J$_{CF}$ 11.0, C$_6$), 129.79 (d, $^2$J$_{CF}$ 20.3, C-1), 132.52 (d, $^4$J$_{CF}$ 1.6, C-5), 134.20 (d, $^5$J$_{CF}$ 1.1, C-4), 146.91 (s, C-2), 169.94 (d, $^2$J$_{CF}$ 24.2, COOH); m/z (ESI) 154 (100%, [M-COOH]$^+$), 104 (23). [1]

2-Fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetic acid (4b)

3-Nitro-4-fluorobenzotrifluoride (2b, 1.05 g, 5.0 mmol) gave 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetic acid (4b, 1.03 g, 77%) as a white powder; mp 110-112 °C (Found: C, 40.2; H, 1.9; N, 5.1. C$_9$H$_5$F$_4$NO$_4$ requires: C, 40.5; H, 1.9; N, 5.2%); IR (neat, cm$^{-1}$) 3018 (br), 1736, 1549, 1319, 1196, 1131, 1096, 1059; $\delta$H (CD$_3$OD, 400 MHz) 6.63 (1H, d,
δF (CD3OD, 376 MHz) - 67.11 (3F, s, CF3), -192.48 (1F, d, 2JHF 46.3, CHF); δC (CD3OD, 100 MHz) 87.88 (d, 1JCF 186.3, CHF), 123.32 (q, 3JCF 4.0, C-3), 124.27 (q, 1JCF 271.5, CF3), 130.24 (d, 3JCF 14.4, C-6), 131.52 – 131.54 (m, C-5), 133.19 (q, 2JCF 33.6, C-4), 136.00 (d, 3JCF 21.3, C-1), 148.77 (s, C-2), 169.06 (d, 2JCF 24.3, COOH); m/z (ASAP) 222 (100%).

2-Fluoro-2-(2-nitro-4-bromophenyl)acetic acid (4c)

2-Fluoro-5-bromonitrobenzene (2c, 1.10 g, 5.0 mmol) gave 2-fluoro-2-(2-nitro-4-bromophenyl)acetic acid (4c, 1.15 g, 83%) as a tan powder; mp 155-158 °C (Found: C, 34.5, H, 1.8, N, 4.9. C8H5BrFNO4 requires: C, 34.6, H, 1.8, N, 5.0%); IR (neat, cm⁻¹) 3084 (br), 2360, 1537, 1339, 1205, 1060; δH (CD3OD, 400 MHz) 6.51 (1H, d, 2JHF 46.4, CFH), 7.65 (1H, d, 3JHH 8.4, ArH), 7.94 (1H, dd, 3JHH 8.4, 4JHF 2.0, ArH), 8.27 - 8.29 (1H, m, ArH); δF (CD3OD, 376 MHz) - 189.70 (d, 2JHF 46.4); δC (CD3OD, 100 MHz) 87.66 (d, 1JCF 182.9, CHF), 124.19 (d, 4JCF 1.9, C-5), 129.02 (s, C-3), 130.80 (d, 3JCF 13.3, C-6), 130.98 (d, 2JCF 21.4, C-1), 137.99 (d, 5JCF 1.5, C-4), 149.10 (s, C-2), 169.47 (d, 2JCF 24.3, COOH); m/z (ASAP) 234 (96%), 232 (100%).

2-Fluoro-2-(2,4-dinitrophenyl)acetic acid (4d)

1-Fluoro-2,4-dinitrobenzene (2d, 1.50 g, 8 mmol) was used to synthesise the crude fluoromalonate as above which was dissolved in glacial acetic acid (25 mL) and water (15 mL). Conc. sulfuric acid (4 mL) was added and the mixture was heated at 100 °C for 25 h. The mixture was poured into crushed ice (350 mL), extracted with DCM (3 × 100 mL) and the organic phase was evaporated. The residue was dissolved in saturated NaHCO3 solution (60 mL) and extracted with DCM (2 × 30 mL). The aqueous solution was acidified to pH 1 with concentrated aq. HCl and extracted with DCM (3 × 50 mL). The organic phase was dried (Na2SO4), filtered and evaporated to give 2-fluoro-2-(2,4-dinitrophenyl)acetic acid (4d, 1.10
g, 56%) as an orange solid; mp 74-77 °C; IR (neat, cm⁻¹) 3585, 3109, 2481, 1715, 1521, 1354, 1093; δ_H (CDCl₃, 400 MHz) 6.80 (1H, d, 2_J_HF 46.5, CFH), 8.05 (1H, d, 3_J_HH 8.5, ArH), 8.59 (1H, dd, 3_J_HH 8.5, 4_J_HF 2.4, ArH), 8.72 (1H, bs, COOH), 9.00 – 9.01 (1H, m, ArH); δ_F (CDCl₃, 376 MHz) - 190.37 (d, 2_J_HF 46.5); δ_C (CDCl₃, 100 MHz) 86.16 (d, 1_J_CF 189.4, CHF), 120.88 (s, C-3), 128.38 (d, 4_J_CF 2.3, C-5), 129.29 (d, 3_J_CF 15.9, C-6), 136.06 (d, 2_J_CF 21.5, C-1), 147.14 (s, C-4), 148.51 (s, C-2), 169.21 (d, 2_J_CF 23.6, COOH); m/z (ASAP) 199 (55 %), 179 (44).

2-Fluoro-2-(2-nitro-5-methoxyphenyl)acetic acid (4e)

3-Fluoro-4-nitroanisole (2e, 1.0 g, 5.8 mmol) gave 2-fluoro-2-(2-nitro-5-methoxyphenyl)-acetic acid (4e, 0.80 g, 60%) as a tan powder; mp 129–131 °C (Found: C, 46.9; H, 3.5; N, 6.1. C₁₀H₈FNO₅ requires: C, 47.2; H, 3.5; N, 6.1%); IR (neat, cm⁻¹) 2848 (br), 1724, 1582, 1324, 1283, 1235, 1087; δ_H (d₆-DMSO, 400 MHz) 3.92 (3H, s, CH₃), 6.52 (1H, d, 2_J_HF 46.0, CFH), 7.18 - 7.24 (2H, m, ArH), 8.22 (1H, d, 3_J_HH 8.9, ArH), 13.73 (1H, s, COOH); δ_F (d₆-DMSO, 376 MHz) - 185.36 (d, 2_J_HF 46.0); δ_C (d₆-DMSO, 100 MHz) 56.37 (s, CH₃), 87.39 (d, 1_J_CF 183.2, CHF), 114.18 (d, 3_J_CF 13.5, C-6), 114.45 (s, C-4), 128.10 (s, C-3), 133.21 (d, 2_J_CF 19.8, C-1), 139.45 (d, 3_J_CF 1.9, C-2), 163.58 (d, 4_J_CF 1.4, C-5), 167.73 (d, 2_J_CF 23.5, COOH); m/z (ASAP) 184 (100%), 164 (24).

Potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate (4f)

2-Fluoro-3-nitropyridine (2f, 0.72 g, 5.0 mmol) gave potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate (4f, 1.03 g, 86%) as a deep red powder; mp >140 °C (decomposes); IR (neat, cm⁻¹) 1654, 1523, 1359; δ_H (D₂O, 400 MHz) 6.32 (1H, d, 2_J_HF 47.7, CFH), 7.69 – 7.73 (1H, m, ArH), 8.52 (1H, d, 3_J_HH 8.4, ArH), 8.80 (1H, dd, 3_J_HH 4.9, 4_J_HF 1.4, ArH); δ_F (D₂O, 376 MHz) - 180.27 (d, 2_J_HF 47.7); δ_C (D₂O, 100 MHz) 87.91 (d, 1_J_CF 185.2, CHF), 124.29 (d,
Synthesis of methyl esters 6a–e: general procedure

2-Fluoro-2-arylacetic acid ‘4’ (20–30 mmol) was dissolved in methanol (50 mL) and HCl in methanol (1.4 M, 10 mL, 14 mmol) was added. The mixture heated to reflux for 16 h then the solvent was evaporated. The resulting oil was partitioned between DCM (50 mL) and saturated aqueous NaHCO₃ solution (20 mL). The aqueous phase was extracted with DCM (2 × 20 mL), the combined organic phase was washed with saturated brine (20 mL) and dried (Na₂SO₄). Filtration and evaporation gave the methyl 2-fluoro-2-arylacetate derivative 6 which was purified by distillation or column chromatography if required.

Methyl 2-fluoro-2-(2-nitrophenyl)acetate (6a)

2-Fluoro-2-(2-nitrophenyl)acetic acid (4a, 5.98 g, 30 mmol) after vacuum distillation gave methyl 2-fluoro-2-(2-nitrophenyl)acetate (6a, 5.67 g, 88%) as a yellow crystalline solid; mp 41-43 °C; bp 110-112 °C (5 mbar) ([MH]⁺: 214.0500. C₉H₈FNO₄ requires: [MH]⁺, 214.0516); IR (neat, cm⁻¹) 1749, 1526, 1348, 1216, 1022; δH (CDCl₃, 400 MHz) 3.76 (3H, s, CH₃), 6.57 (1H, d, JHF 46.7, CFH), 7.55 - 7.59 (1H, m, ArH), 7.70 - 7.75 (2H, m, ArH), 8.12 (1H, d, JHH 8.4, ArH); δF (CDCl₃, 376 MHz) - 188.04 (d, JHF 46.7); δC (CDCl₃, 100 MHz) 53.07 (s, CH₃), 86.60 (d, JCF 185.4, CHF), 125.07 (s, C-4), 127.80 (d, JCF 15.1, C-6), 130.12 (d, JCF 1.3, C-5), 130.17 (d, JCF 21.1, C-1), 134.21 (d, JCF 1.9, C-3), 146.82 (d, JCF 3.2, C-2), 167.13 (d, JCF 25.0, COO); m/z (ASAP) 214 (4 %, [MH]⁺), 194 (8), 154 (100).
Methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate (6b)

2-Fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetic acid (4b, 5.91 g, 22 mmol) gave methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate (6b, 6.10 g, 98%) as a brown oil; ([MH]+, 282.0394. C_{10}H_{7}F_{4}NO_{4} requires: [MH]+, 282.0389); IR (neat, cm⁻¹) 1752, 1543, 1324, 1179, 1133, 1095; δH (CDCl₃, 400 MHz) 3.81 (3H, s, CH₃), 6.70 (1H, d, 2JHF 46.4, CFH), 7.96 - 8.05 (2H, m, ArH), 8.44 (1H, s, ArH); δF (CDCl₃, 376 MHz) - 64.09 (3F, s, CF₃), - 189.74 (1F, d, 2JHF 46.4, CHF); δC (CDCl₃, 100 MHz) 53.55 (s, CH₃), 86.54 (d, 1JCF 186.2, CHF), 122.65 (q, 1JCF 272.6, CF₃), 122.66 (q, 3JCF 3.7, C-3), 128.70 (d, 3JCF 16.0, C-6), 130.77 - 130.85 (m, C-5), 132.80 (q, 2JCF 34.8, C-4), 134.25 (d, 2JCF 21.8, C-1), 146.97 (s, C-2), 166.41 (d, 2JCF 24.0, COO); m/z (ASAP) 282 (13%, [MH]+), 222 (100).

Methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate (6c)

2-Fluoro-2-(2-nitro-4-bromophenyl)acetic acid (4c, 5.83 g, 21 mmol) gave methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate (6c, 5.93 g, 97%) as a tan powder; mp 78-79 °C; ([MH]+, 291.9641. C₉H₇[⁷⁹Br]FNO₄ requires: [MH]+, 291.9621); IR (neat, cm⁻¹) 1744, 1525, 1345, 1214, 1021, 986; δH (CDCl₃, 400 MHz) 3.79 (3H, s, CH₃), 6.56 (1H, d, 2JHF 46.5, CFH), 7.65 (1H, d, 3JHH 8.6, ArH), 7.86 (1H, dd, 3JHH 8.5, 4JHH 2.0, ArH), 8.29 (1H, s, ArH). δF (CDCl₃, 376 MHz) - 188.89 (d, 2JHF 46.5); δC (CDCl₃, 100 MHz) 53.38 (s, CH₃), 86.39 (d, 1JCF 185.4, CHF), 123.70 (d, 5JCF 2.0, C-4), 128.31 (s, C-3), 129.23 (d, 3JCF 14.8, C-6), 129.39 (d, 2JCF 21.7, C-1), 137.27 (d, 4JCF 1.7, C-5), 147.28 (s, C-2), 166.41 (d, 2JCF 24.7, COO); m/z (ASAP) 292 (6%, [M(⁷⁹Br)H]+), 294 (6%, [M(⁸¹Br)H]+), 272 (15), 274 (15), 232 (100), 234 (96).
Methyl 2-fluoro-2-(2,4-dinitrophenyl)acetate (6d)

2-Fluoro-2-(2,4-dinitrophenyl)acetic acid (4d, 4.69 g, 19 mmol) after purification by column chromatography on silica gel using hexane:ethyl acetate (3:1) as eluant, Rf: 0.36) gave methyl 2-fluoro-2-(2,4-dinitrophenyl)acetate (6d, 3.21 g, 65%) as a yellow oil; ([MH]+, 259.0372. C9H7FN2O6 requires: [MH]+, 259.0366); IR (neat, cm⁻¹) 3101, 1760, 1530, 1349, 1228, 1087; δH (CDCl3, 400 MHz) 3.82 (3H, s, CH3), 6.74 (1H, d, 2JHF 46.8, CFH), 8.06 (1H, d, 3JHH 8.6, ArH), 8.59 (1H, dd, 3JHH 8.6, 4JHH 2.3, ArH), 9.00 - 9.02 (1H, m, ArH); δF (CDCl3, 376 MHz) -189.83 (d, 2JHF 46.8); δC (CDCl3, 100 MHz) 53.73 (s, CH3), 86.56 (d, 1JCF 187.8, CHF), 120.77 (s, C-3), 128.31 (d, 4JCF 2.3, C-5), 129.17 (d, 3JCF 16.7, C-6), 136.66 (d, 2JCF 21.4, C-1), 147.17 (s, C-4), 148.39 (s, C-2), 165.95 (d, 2JCF 23.7, COO); m/z (ASAP) 259 (10 %, [MH]+), 212 (54), 199 (100).

Methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate (6e)

2-Fluoro-2-(2-nitro-5-methoxyphenyl)acetic acid (4e) gave methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate (6e, 4.35 g, 98%) as a brown oil; ([MH]+, 244.0598. C10H10FNO5 requires: [MH]+, 244.0621); IR (neat, cm⁻¹) 2956, 1751, 1582, 1514, 1340, 1288, 1238; δH (CDCl3, 400 MHz) 3.76 (3H, s, CH3), 3.90 (3H, s, CH3), 6.57 (1H, d, 2JHF 46.9, CFH), 6.97 (1H, dd, 3JHH 9.3, 4JHH 2.8, ArH), 7.18 (1H, d, 4JHH 3.0, ArH), 8.17 (1H, dd, 3JHH 9.3, 5JHH 1.0, ArH); δF (CDCl3, 376 MHz) - 187.68 (d, 2JHF 46.9); δC (CDCl3, 100 MHz) 53.06 (s, CH3), 56.16 (s, CH3), 87.18 (d, 1JCF 183.5, CHF), 112.66 (d, 3JCF 16.8, C-6), 114.41 (s, C-4), 128.03 (s, C-3), 133.42 (d, 2JCF 20.6, C-1), 139.53 (d, 3JCF 3.0, C-2), 164.06 (d, 4JCF 2.4, C-5) 166.92 (d, 2JCF 24.5, COO); m/z (ASAP) 244 (7 %, [MH]+), 212 (24), 198 (17), 184 (100%).
Reductive cyclisation for the synthesis of fluorooxindole derivatives 8: general procedure

The methyl 2-fluoro-2-(2-nitroaryl)acetate derivative 6 (5 mmol) was dissolved in THF (20 mL) and water (20 mL). NaHCO$_3$ (1.68 g, 20 mmol) was added and the mixture was stirred vigorously. Na$_2$S$_2$O$_4$ (2.61 g, 15 mmol) was added over 40 min and the mixture was stirred for 20 min. Ethyl acetate (40 mL) was added, the aqueous layer was removed, HCl in methanol (3 mL, 1.4 M, 4.2 mmol) was added and the mixture was heated to reflux for 3 h. The solution was cooled, dried (Na$_2$SO$_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel using hexane:ethyl acetate (5:1) as eluent to give fluorooxindole derivative 8.

3-Fluorooxindole (8a)

Methyl 2-fluoro-2-(2-nitrophenyl)acetate (6a, 1.06 g, 5 mmol) gave 3-fluorooxindole (8a, 0.24 g, 32%) as a yellow powder; $R_t$: 0.21; mp 92-94 °C; ([MH]$^+$, 152.0496. C$_8$H$_6$FNO requires: [MH]$^+$, 152.0512); IR (neat, cm$^{-1}$) 3188, 1772, 1642, 1050; $\delta_H$ (CDCl$_3$, 400 MHz) 5.70 (1H, d, $^2$$J_{HF}$ 51.0, CFH), 6.91 (1H, dm, $^3$$J_{HH}$ 7.8, ArH), 7.11 (1H, tt, $^3$$J_{HH}$ 7.6, $^5$$J_{HH}$ 0.8, ArH), 7.35 (1H, tm, $^3$$J_{HH}$ 7.8, ArH), 7.46 (1H, dm, $^3$$J_{HH}$ 7.4, ArH), 8.42 (1H, bs, N-H); $\delta_F$ (CDCl$_3$, 376 MHz) -194.56 (d, $^2$$J_{HF}$ 51.0); $\delta_C$ (CDCl$_3$, 100 MHz) 85.87 (d, $^1$$J_{CF}$ 189.4, CHF), 110.84 (d, $^3$$J_{CF}$ 1.5, C-7), 123.36 (d, $^2$$J_{CF}$ 16.4, C-4), 123.52 (d, $^4$$J_{CF}$ 3.0, C-8), 126.57 (d, $^4$$J_{CF}$ 1.7, C-6), 131.68 (d, $^3$$J_{CF}$ 3.3, C-5), 141.92 (d, $^3$$J_{CF}$ 5.5, C-9), 173.39 (d, $^2$$J_{CF}$ 17.9, C=O); m/z (ASAP) 152 (100 %, [MH]$^+$), 132 (53).

3-Fluoro-6-trifluoromethyloxindole (8b)

Methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate (6b, 1.41 g, 5 mmol) gave 3-fluoro-6-trifluoromethyloxindole (8b, 0.90 g, 82%) as a pale yellow powder; $R_t$: 0.17; mp
175-177 °C; ([M]+, 219.0305). C₈H₅F₄NO requires: [M]+, 219.0307); IR (neat, cm⁻¹) 3143, 1753,1698, 1317, 1292, 1257, 1114, 1054; δ_H (d₆-DMSO, 400 MHz) 5.99 (1H, d, 2_J_HF 49.5, CFH), 7.08 (1H, s, ArH), 7.41 (1H, d, 3_J_HH 7.6, ArH), 7.68 (1H, d, 3_J_HH 7.6, ArH), 10.91 (1H, bs, N-H); δ_F (d₆-DMSO, 376 MHz) - 62.55 (3F, s, CF₃), - 195.89 (1F, d, 2_J_HF 49.5, CHF); δ_C (d₆-DMSO, 100 MHz) 85.44 (d, 1_J_CF 184.9, CHF), 106.50 (m, C-8), 119.11 (m, C-6), 123.70 (q, 1_J_CF 271.5, CF₃), 126.99 (s, C-5), 127.67 (d, 2_J_CF 15.6, C-4), 131.48 (qd, 2_J_CF 32.1, 4_J_CF 3.1, C-7), 144.24 (d, 3_J_CF, C-9), 172.06 (d, 2_J_CF 17.4, COO); m/z (ASAP) 220 (100 %, [MH]+), 219 (21), 200 (95), 191 (24).  

3-Fluoro-6-bromooxindole (8c)  

Methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate (6c, 1.45 g, 5 mmol) gave 3-fluoro-6-bromooxindole (8c, 0.65 g, 57%) as a white solid; R_f: 0.18; mp 207-208 °C (decomposes) ([M]+, 228.9534. C₈H₅⁷⁹BrFNO requires: [M]+, 229.9539); IR (neat, cm⁻¹) 3136, 1728, 1617, 1451, 1048; δ_H (d₆-DMSO, 400 MHz) 5.85 (1H, d, 2_J_HF 50.3, CHF), 7.01 – 7.02 (1H, m, ArH), 7.23 (1H, dm, 3_J_HH 8.0, ArH), 7.40 (1H, dd, 3_J_HH 8.0, 4_J_HH 2.0, ArH), 10.78 (1H, bs, N-H); δ_F (d₆-DMSO, 376 MHz) - 193.44 (d, 2_J_HF 50.2); δ_C (d₆-DMSO, 100 MHz) 85.49 (d, 1_J_CF 183.9, CHF), 113.23 (s, C-8), 122.63 (d, 2_J_CF 16.1, C-4), 124.02 (d, 5_J_CF 4.0, C-7), 124.85 (d, 3_J_CF 2.9, C-5), 127.99 (s, C-6), 144.99 (d, 3_J_CF 5.8, C-9), 172.16 (d, 2_J_CF 17.4, C=O); m/z (ASAP) 232 (92%, [M(⁸¹Br)H]+), 230 (100 %, [M(⁷⁹Br)H]+), 229 (26), 212 (86), 210 (91).  

3-Fluoro-5-methoxyoxindole (8e)  

Methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate (6e, 1.15 g, 5 mmol) gave 3-fluoro-5-methoxyoxindole (8e, 0.25 g, 30%) as a tan powder; R_f: 0.20; mp 130-132 °C; ([MH]+, 182.0612. C₉H₅FNO₂ requires: [MH]+, 182.0617); IR (neat, cm⁻¹) 3192, 1716, 1486, 1309, 1206, 1050; δ_H (d₆-DMSO, 400 MHz) 3.72 (3H, s, CH₃), 5.84 (1H, d, 2_J_HF 50.5, CHF), 6.78 (1H, dd, 3_J_HH 8.5, 4_J_HH 1.4, ArH), 6.91 (1H, dt, 3_J_HH 8.5, 4_J_HH 2.3, ArH), 7.10 (1H, t, 4_J_HH 2.3,
ArH), 10.45 (1H, bs, N-H); δF (d6-DMSO, 376 MHz) - 193.13 (d, 2JHF 50.5); δC (d6-DMSO, 100 MHz) 55.60 (s, CH3), 86.40 (d, 1JCF 183.6 Hz, CHF), 110.92 (s, C-7), 112.69 (s, C-5), 116.25 (d, 4JCF 3.8, C-8), 124.37 (d, 2JCF 15.9, C-4), 136.36 (d, 3JCF 5.9, C-9), 155.11 (d, 4JCF 3.3, C-6), 172.21 (d, 2JCF 17.5, C=O); m/z (ASAP) 182 (37 %, [MH]+), 162 (100).

Synthesis of fluoromethyl nitroarenes

2,4-Dinitrobenzyl fluoride 5

2-Fluoro-2-(2,4-dinitrophenyl)acetic acid was synthesised according to the general procedure from 2,4-dinitrofluorobenzene (0.93 g, 5 mmol). The crude acid (dark oil) was dissolved in toluene (40 mL) that evaporated (10 mbar) in a 40 °C water bath to leave a dark solid that was purified by column chromatography on silica gel using hexane:ethyl acetate (4:1), Rf: 0.19 as elutant to give 2,4-dinitrobenzyl fluoride 5 (0.61 g, 61%) as an off white solid; mp 68-70 °C (Found: C, 42.1; H, 2.5; N, 13.8. C7H5FN2O4 requires: C, 42.0; H, 2.5; N, 14.0%); ([MH]+, 201.0312); IR (neat, cm−1) 2360, 1522, 1341, 1027; δH (CDCl3, 400 MHz) 5.97 (2H, d, 2JHF 47.8, CFH), 8.08 (1H, d, 3JHH 8.7, ArH), 8.60 (1H, dd, 3JHH 8.7, 4JHH 2.4, ArH), 9.08 (1H, s, ArH); δF (CDCl3, 376 MHz) - 219.93 (t, 2JHF 47.8); δC (CDCl3, 100 MHz) 81.93 (d, 1JCF 176.4, CH2F), 120.58 (s, C-3), 128.51 (d, 3JCF 12.7, C-6), 128.56 (d, 4JCF 3.5, C-5), 140.97 (d, 2JCF 19.2, C-1), 145.66 (s, C-4), 147.64 (s, C-2); m/z (ASAP) 201 (100 %, [MH]+), 181 (43), 123 (55).

2-Fluoromethyl-3-nitopyridine (7)

Potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate (4f, 6.00 g, 25 mmol) was suspended in methanol (100 mL), HCl in methanol (1.4 M, 50 mL, 70 mmol) was added and the mixture
was heated at reflux for 17 hours. After cooling, the solvent was evaporated and the solid residue was partitioned between DCM (100 mL) and saturated aq. NaHCO₃ (25 mL). The organic layer was washed with saturated brine (25 mL) and dried (Na₂SO₄). After filtration, the solvent was evaporated to leave a brown solid (3.50 g) that was purified by column chromatography on silica gel using hexane:ethyl acetate (2:1, Rf 0.27) as elutant to give 2-fluoromethyl-3-nitropyridine (7, 2.66 g, 68%) as an orange crystalline solid; mp 74-76 °C; ([MH]⁺, 157.0406. C₆H₅FN₂O₂ requires: [MH]⁺, 157.0413); IR (neat, cm⁻¹) 2358, 1598, 1522, 1349, 1022; δH (CDCl₃, 400 MHz) 5.83 (2H, d, ²JHF 47.3, CFH), 7.53 (1H, dd, ³JHH 8.3, ³JHH 4.8, ArH), 8.41 (1H, dt, ¹JHH 8.3, ⁴JHH 1.2, ArH), 8.88 (1H, dd, ³JHH 4.8, ⁴JHH 1.5, ArH); δF (CDCl₃, 376 MHz) - 221.85 (t, ²JHF 47.0); δC (CDCl₃, 100 MHz) 82.16 (d, ¹JCF 175.7, CH₂F), 124.06 (d, ⁴JCF 1.8, C-6), 132.97 (s, C-5), 144.04 (s, C-4), 151.02 (d, ²JCF 17.1, C-2), 153.47 (s, C-3); m/z (ASAP) 157 (100%, [MH]⁺), 137 (46). Crystals suitable for X-ray crystallography were grown by slow evaporation of chloroform.

References