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Fluorotetrahydroquinolines from Diethyl 2-Fluoromalonate Ester

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Abstract: A short series of fluorotetrahydroquinolines was synthesised in two steps from diethyl fluoromalonate and appropriate *ortho*-nitrobenzyl bromide precursors.

Keywords: Fluorinated heterocycle · Fluoromalonate · Fluorotetrahydroquinoline · Organofluorine chemistry · Selective fluorination

1. Introduction

The development of effective methods for the synthesis of selectively fluorinated heterocyclic systems continues to grow in importance due to the increasing number of commercially significant fluorinated heterocyclic structural units that are present in valuable pharmaceuticals and agrochemicals.[1] While fluoroheteroaromatic systems are sub-structures of many drugs, there are comparatively very few instances where saturated fluorinated heterocyclic rings form part of an active pharmaceutical ingredient (API) or marketed drug structure.[1]

As part of a long-term programme exploring the synthesis of fluorinated organic systems using elemental fluorine[2] for the crucial synthetic step of carbon–fluorine bond formation, we have established efficient methods for the large scale preparation of fluorinated 1,3-dicarbonyl derivatives including 1,3-ketoesters[3] and malonate systems.[4] Whereas the application of non-fluorinated malonate esters to the synthesis of a wide range of structurally sophisticated target molecules is, of course, well documented in general organic chemistry,[5] corresponding use of 2-fluoromalonate esters for the preparation of multi-functional selectively fluorinated products has not been developed to any great extent.[5] A small number of patents utilising 2-fluoromalonate esters for the synthesis of a variety of biologically active systems within pharmaceutical company pipelines have recently been disclosed[6] indicating the potential value of using 2-fluoromalonate esters as building blocks in multi-stage API synthesis. It is, however, not necessarily the case that reactions of fluoromalonate will mirror that of the corresponding hydrocarbon analogue and, indeed, reaction profiles of selectively fluorinated systems can be very different to analogous non-fluorinated substrates.[7]

In this paper, we describe the use of diethyl 2-fluoromalonate ester for the synthesis of rare fluorotetrahydroquinoline systems. Only very few related fluorodihydroquinoline systems, prepared by electrophilic fluorination of the corresponding dihydroquinoline, have been reported[8] and shown to act as potent nitric oxide synthase inhibitors.

2. Results and Discussion

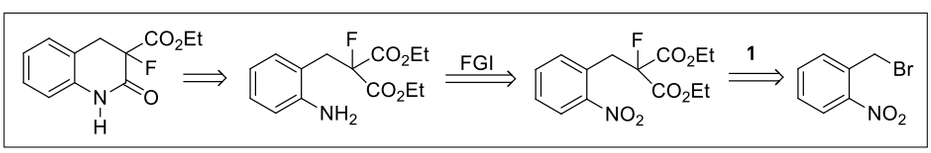
Our strategy for the synthesis of fluorotetrahydroquinolines from 2-diethyl 2-fluoromalonate ester **1** is outlined in Scheme 1 in which, in principle, reaction of fluoromalonate with *ortho*-nitrobenzyl bromide derivatives followed by reduction-cyclisation would lead to the fluorotetrahydroquinoline targets.

Reaction of *ortho*-nitrobenzyl bromide derivatives **2** with anions formed by deprotonation of diethyl 2-fluoromalonate ester **1** using sodium hydride in DMF gave good yields (unoptimised) of diester derivatives **3** which were purified by column chromatography on silica gel (Table 1). The molecular structure of diester **3c** was confirmed by X-ray crystallography (Fig.1).

By a similar process, reaction of the analogous mesylate system **4** with two equivalents of **1** gave the fluorinated diester **3e** and significant quantities of a tetraester derivative **5** by a mechanism shown in Scheme 2. Dehydrofluorination of **3e** to an intermediate alkene which then reacts with a further equivalent of **1** by a Michael addition process gives **5** in good yield. The structure of **5** was confirmed by X-ray crystallography (Fig. 2) and contains two virtually identical independent molecules linked together by a number of C–H…O interactions. The relatively short (2.934 Å) intermolecular F…Cl contacts may be regarded as halogen bonds.[9]

Reductions of the nitro groups in fluorodiester substrates **3** and subsequent cyclisation to fluorotetrahydroquinolines **6** were accomplished by using either sodium dithionite or hydrogenation over a palladium on carbon catalyst (Table 2). The molecular structure of fluorotetrahydroquinoline **6a** was confirmed by X-ray crystallography (Fig. 3).

The conformation of the stereogenic centre in **6a** is unusual in that the smaller fluorine atom occupies the equatorial position while the larger ester functionality is axial. α-Fluoroamides have a very strong preference (*syn-anti* 7.5 kcal mol^{-1}) for the carbon–fluorine bond to adopt an *anti-pla-*



Scheme 1. Synthetic strategy for the preparation of fluorotetrahydroquinoline derivatives.

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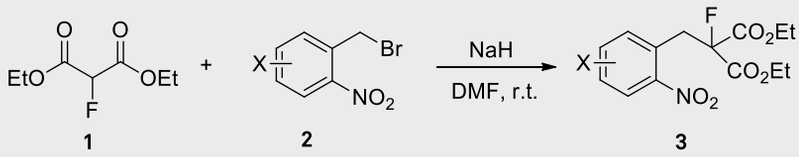
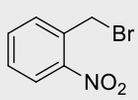
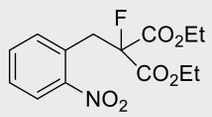
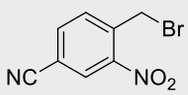
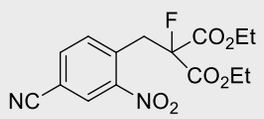
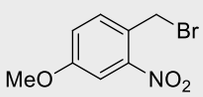
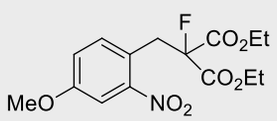
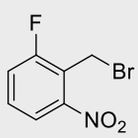
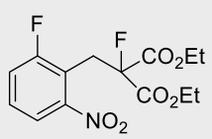
Table 1. Synthesis of diesters **3**.



Benzyl bromide **2**		Diester **3**	
	**2a**		**3a**, 87%
	**2b**		**3b**, 54%
	**2c**		**3c**, 56%
	**2d**		**3d**, 88%

4. Experimental

4.1 *General*

Proton, fluorine and carbon nuclear magnetic resonance (NMR) spectra (^{1}H, ^{19}F and ^{13}C NMR) were obtained from a Bruker 400 Ultrashield spectrometer (^{1}H NMR at 400 MHz, ^{19}F NMR at 376 MHz and ^{13}C NMR at 101 MHz) using residual solvent peaks as the internal standard (^{1}H NMR; $CHCl_3$ at 7.26 ppm, ^{19}F NMR; $CFCl_3$ at 0.00 ppm and ^{13}C NMR; $CDCl_3$ at 77.16 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and assignment.

GC-MS data were obtained from a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode. Accurate mass analysis was performed on a Xevo QtoF mass spectrometer (Waters Ltd, UK) with an atmospheric solids analysis probe (ASAP). Melting point data was obtained using a Gallenkamp apparatus at atmospheric pressure and are uncorrected. Infra-red (IR) spectroscopy was performed on a Perkin Elmer 1600 Series FTIR with an ATR probe.

Single crystal X-ray data were collected at 120.0 K on a Bruker SMART CCD 1K (compounds **3c** and **6a**) and an Agilent XCalibur (compound **5**) diffractometers (λ MoKα, graphite monochromators, λ = 0.71073 Å, ω-scan) equipped with Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats. All structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXTL software.[11] All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms in the structures **3c** and **6a** were located on the difference map and refined isotropically. The H atoms in twinned structure

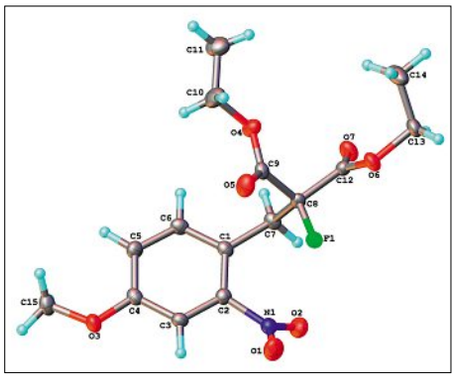
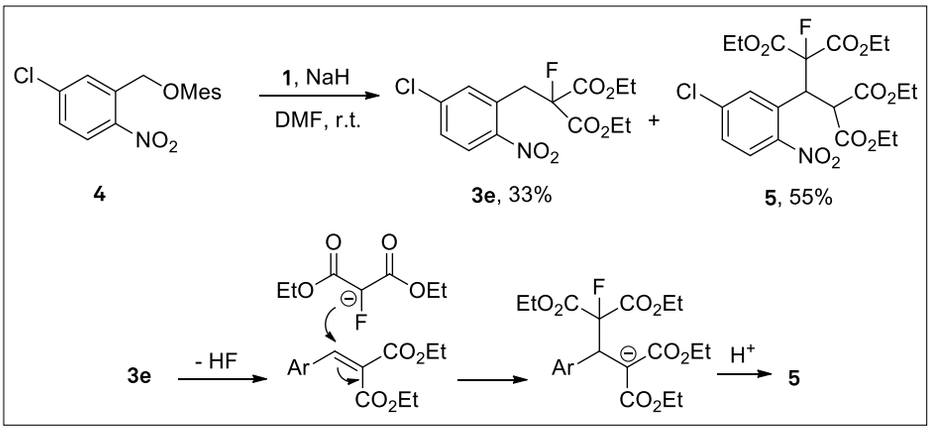


Fig. 1. Molecular structure of **3c**.



Scheme 2. Reaction of mesylate derivative **4** with **1**.

nar conformation relative to the amide carbonyl group so that the C–F and amide diploes maximally oppose one another.[10] Consequently, we may expect the fluorine atom to adopt an equatorial position in the structure of **6a** but, in the crystal analysed at least, this is not the case.

3. Conclusion

Inexpensive, readily available diethyl 2-fluoromalonate ester can be used to synthesise a new class of fluorotetrahydroquinoline systems in two steps from *ortho*-nitrobenzyl bromide precursors. Fluorine occupies the equatorial position in the solid-state structure of fluorotetrahydroquinoline **6a**.

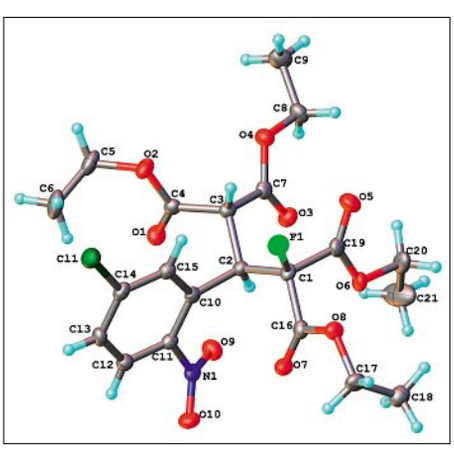
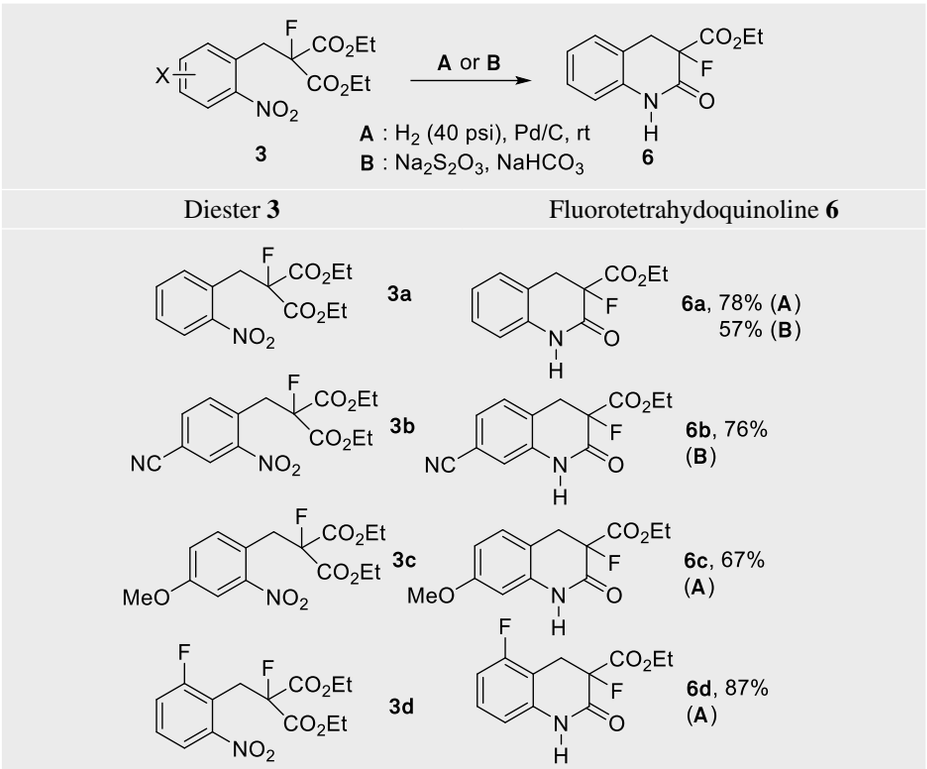


Fig. 2. Molecular structure of one of two independent molecules of **5**.

Table 2. Synthesis of fluorotetrahydroquinolines **6** by reduction-cyclisation processes.



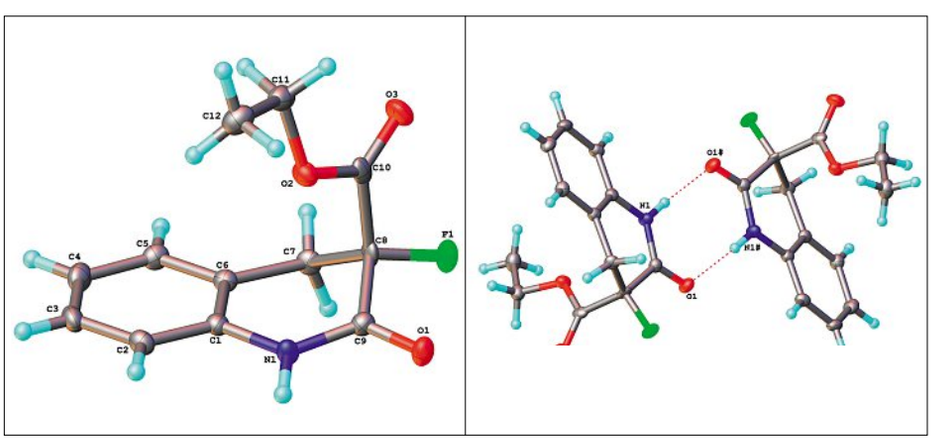


Fig. 3. Molecule **6a** (left) and the H-bonded dimer in the structure of **6a** (right).

5 were placed in calculated positions and refined in riding mode. Crystallographic data for the structures have been deposited with the Chembridge Crystallographic Data Centre as supplementary publications CCDC 991436-991438.

Crystal Data for ***3c***: $C_{15}H_{18}NO_7F$, M = 343.30, monoclinic, space group $P2_1/c$, a = 8.5269(7), b = 11.8392(10), c = 16.4098(14) Å, β = 98.129(2)°, V = 1640.0(2) Å^3, Z = 4, T = 120.0 K, μ(MoKα) = 0.118 mm^{-1}, D_{calc} = 1.390 g/mm^3, 22040 reflections measured (4.26 ≤ 2θ ≤ 58), 4365 unique (R_{int} = 0.0427) were used in all calculations. The final R_1 = 0.0444 (3279 > 2σ(I)) and wR_2 = 0.1133 (all data), GOOF = 1.010.

Crystal Data for ***5***: $C_{21}H_{25}ClFNO_{10}$, M = 505.87, monoclinic, space group $P2_1/c$, a = 25.4199(12), b = 9.5099(3), c = 21.6317(11) Å, β = 114.838(6)°, V = 4745.5(4) Å^3, Z = 8, T = 120.0 K, μ(MoKα)= 0.224 mm^{-1}, D_{calc} = 1.416 g/mm^3, 52581 reflections measured (5.14 ≤ 2θ ≤ 56), 11455 unique (R_{int} = 0.1057) were used in all calculations. The final R_1 = 0.0633 (7562>2σ(I)) and wR_2 = 0.1730 (all data), GOOF = 1.033.

Crystal Data for ***6a***: $C_{12}H_{12}NO_3F$ (M = 237.23): monoclinic, space group $P2_1/c$, a = 10.5275(12), b = 6.6687(8), c = 15.6871(18) Å, β = 102.677(2)°, V = 1074.5(2) Å^3, Z = 4, T = 120.0 K, μ(MoKα) = 0.117 mm^{-1}, D_{calc} = 1.466 g/mm^3, 9083 reflections measured (3.96 ≤ 2θ ≤ 58), 2841 unique (R_{int} = 0.0684) were used in all calculations. The final R_1 = 0.0643 (1827>2σ(I)) and wR_2 = 0.1601 (all data), GOOF = 1.020.

4.2 *Synthesis of Fluorodiesters 3*

4.2.1 *General Procedure*

Sodium hydride (60% NaH in mineral oil) was washed with hexane (2 × 50 mL) and added to DMF (15 mL). Diethyl 2-fluoromalonate **1** in DMF (10 mL) and the 2-nitrobenzyl bromide derivative **2** in DMF (15 mL) were added dropwise to the solution which was stirred at room temperature for 19 h. The reaction mixture was added to ice/water (150 mL), extracted with diethyl ether (3 × 50 mL), washed sequentially with water (3 × 50 mL) and brine (3 × 50 mL), dried ($MgSO_4$), concentrated and purified by column chromatography on silica gel or recrystallization to give the pure fluorodiester **3**.

4.2.2 *Diethyl 2-fluoro-2-(2-nitrobenzyl)malonate (**3a**)*

Sodium hydride (0.31 g, 13.11 mmol), **1** (2.00 g, 11.24 mmol) and 2-nitrobenzyl bromide **2a** (2.11 g, 9.79 mmol), after recrystallization, gave diethyl 2-fluoro-2-(2-nitrobenzyl)malonate **3a** (2.67 g, 87 %) as pale yellow crystals; mp 51–52 °C; ([MH]$^+$, 314.1053. $C_{14}H_{16}NO_6F$ requires [MH]$^+$, 314.1040); υ_{max} (neat, cm^{-1}) 2989, 1748, 1523, 1347, 1245, 1190, 1142, 1060; ^{1}H NMR δ 7.88 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.2, Ar-H), 7.57–7.39 (3H, m, Ar-H), 4.37–4.14 (4H, m, OCH_2), 3.95 (2H, d, $^3J_{HF}$ 23.5, CF-CH_2), 1.25 (6H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –164.06 (t, $^3J_{HF}$ 23.5); ^{13}C NMR δ 165.40 (d, $^2J_{CF}$ 25.5, C=O), 150.74 (s, C-NO_2), 133.34 (d, $^3J_{CF}$ 2.4, C-1), 132.72 (s, Ar), 128.82 (s, Ar), 127.76 (s, Ar), 125.02 (s, Ar), 93.90 (d, $^1J_{CF}$ 201.8, C-F), 63.10 (s, OCH_2), 35.36 (d, $^2J_{CF}$ 20.3, CF-CH_2), 13.97 (s, CH_3); *m/z* (ASAP) 314.1 ([MH]$^+$, 94%).

4.2.3 *Diethyl 2-(4-cyano-2-nitrobenzyl)-2-fluoromalonate (**3b**)*

Sodium hydride (0.10 g, 4.32 mmol), **1** (0.62 g, 3.49 mmol) and 4-(bromomethyl)-3-nitrobenzonitrile **2b** (0.80 g, 3.32 mmol), after column chromatography and recrystallization, gave diethyl 2-(4-cyano-2-nitrobenzyl)-2-fluoromalonate **3b** (0.61 g, 54%) as a yellow solid; mp 52–53 °C; ([MH]$^+$, 339.1036. $C_{15}H_{15}N_2O_6F$ requires [MH]$^+$, 339.0992); υ_{max} (neat, cm^{-1}) 2982, 2234, 1763, 1541, 1279, 1239, 1196, 1131, 1060; ^{1}H NMR δ 8.19 (1H, s, H-3), 7.82 (1H, dd, $^3J_{HH}$ 8.1, $^4J_{HH}$ 1.5, H-5), 7.64 (1H, d, $^3J_{HH}$ 8.1, H-6), 4.31–4.18 (4H, m, OCH_2), 3.98 (2H, d, $^3J_{HF}$ 22.5, CF-CH_2), 1.27 (6H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –163.64 (t, $^3J_{HF}$ 22.5); ^{13}C NMR δ 163.86 (d, $^2J_{CF}$ 25.3, C=O), 149.59 (s, C-NO_2), 134.36 (s, Ar), 133.62 (d, $^3J_{CF}$ 2.7, C-1), 132.02 (s, Ar), 127.46 (s, Ar), 115.25 (s, C-4), 112.25 (s, CN), 92.22 (d, $^1J_{CF}$ 202.8, CF), 62.34 (OCH_2), 34.28 (d, $^2J_{CF}$ 20.1, CF-CH_2), 12.87 (s, CH_3); *m/z* (ASAP) 339.1 ([MH]$^+$, 100%), 311.1 (25), 265.1 (21), 173.0 (44).

4.2.4 *Diethyl 2-fluoro-2-(4-methoxy-2-nitrobenzyl)malonate (**3c**)*

Sodium hydride (0.10 g, 4.23 mmol), **1** (0.61 g, 3.42 mmol) and 1-(bromomethyl)-4-methoxy-2-nitrobenzene **2b** (0.80 g, 3.25 mmol), after recrystalisation, gave diethyl 2-fluoro-2-(4-methoxy-2-nitrobenzyl)malonate **3b** (0.63 g, 56%) as white crystals; mp 66–67 °C; ([MH]$^+$, 322.1160. $C_{15}H_{18}NO_7F$ requires [MH]$^+$, 344.1146); υ_{max} (neat, cm^{-1}) 2984, 1743, 1534, 1295.9, 1240, 1212, 1195, 1046; ^{1}H NMR δ 7.39 (1H, d, $^4J_{HH}$ 2.5, H-3), 7.34 (1H, d, $^3J_{HH}$ 8.6, H-6), 7.06 (1H, dd, $^3J_{HH}$ 8.6, $^4J_{HH}$ 2.6, H-5), 4.29–4.18 (4H, m, OCH_2), 3.87 (2H, d, $^3J_{HF}$ 22.9, CF-CH_2), 3.85 (3H, s, OCH_3), 1.26 (6H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –164.25 (t, $^3J_{HF}$ 23.6); ^{13}C NMR δ 165.51 (d, $^2J_{CF}$ 25.6, C=O), 159.45 (s, C-OMe), 151.21 (s, C-NO_2), 134.26 (d, $^3J_{CF}$ 2.3, C-1), 119.34 (s, Ar), 119.12 (s, Ar), 110.01 (s, Ar), 94.00 (d, $^1J_{CF}$ 200.8 , C-F), 63.05 (s, OCH_2), 55.94 (s, OCH_3), 34.83 (d, $^2J_{CF}$ 20.3, CF-CH_2), 14.00 (s, CH_3); *m/z* (ASAP) 344.1 ([MH]$^+$, 100%), 270.1 (33), 224.0 (67), 178.0 (63).

4.2.5 *Diethyl 2-fluoro-2-(2-fluoro-6-nitrobenzyl)malonate (**3d**)*

Sodium hydride (0.13 g, 5.56 mmol), **1** (0.80 g, 4.49 mmol) and 2-fluoro-6-nitrobenzyl bromide **2d** (1.00 g, 4.27 mmol), after recrystallization, gave diethyl 2-fluoro-2-(2-fluoro-6-nitrobenzyl) malonate **3d** (1.25 g, 88%) as a yellow solid; mp. 49–50 °C; ([MH]$^+$, 332.0953. $C_{14}H_{15}NO_6F_2$ requires [MH]$^+$, 332.0946); υ_{max} (neat, cm^{-1}) 2997, 1746, 1533, 1363, 1252, 1173, 1075, 1055; ^{1}H NMR δ 7.75 (1H, m, $^3J_{HH}$ 8.2, H-3), 7.44 (1H, td, $^3J_{HH}$ 8.3, $^4J_{HF}$ 5.5, H-4), 7.37–7.31 (1H, m, H-5), 4.34–4.22 (4H, m, OCH_2), 4.06 (2H, dd, $^3J_{HF}$ 20.6, $^4J_{HF}$ 1.8, CF-CH_2), 1.29 (6H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –110.14 (1F, m, Ar-F), –164.80 (1F, t, $^3J_{HF}$ 20.6, CH_2-CF); ^{13}C NMR δ 165.39 (d, $^2J_{CF}$ 25.6, C=O), 161.63 (d, $^1J_{CF}$ 250.9, Ar-F), 151.38 (d, $^3J_{CF}$ 3.9 Hz, C-NO_2), 129.68 (d, $^3J_{CF}$ 9.5, C-4), 121.02 (d, $^4J_{CF}$ 3.3, C-3), 120.20 (d, $^2J_{CF}$ 24.2, C-5), 116.37 (d, $^2J_{CF}$ 19.9, C-1), 92.69 (d, $^1J_{CF}$ 201.6, CF), 63.16 (s, OCH_2), 28.25 (dd, $^2J_{CF}$ 21.4, $^3J_{CF}$ 3.1, CF-CH_2), 13.95 (s, CH_3); *m/z* (ESI) 332.1 ([MH]$^+$, 100%).

4.2.6 *Diethyl 2-(5-chloro-2-nitrobenzyl)-2-fluoromalonate (**3e**) and Tetraethyl 2-(5-chloro-2-nitrophenyl)-1-fluoropropane-1,1,3,3-tetracarboxylate (**5**)*

Sodium hydride (0.12 g, 4.91 mmol) was washed with hexane (2 × 50 mL) and added to dry DMF (15 mL). **1** (0.69 g, 3.89 mmol) in dry DMF (10 mL) was added drop wise, followed by 5-chloro-2-nitrobenzyl methanesulfonate **4** (1.00 g, 3.78 mmol) in DMF (15 mL). After 5 h, more **1** (0.17 g, 0.95 mmol) was added with NaH (0.09 g, 3.75 mmol), then after 20 h the solution was added to ice/water (150 mL), extracted with diethyl ether (3 × 50 mL), washed with water and brine, dried ($MgSO_4$), concentrated and purified by column chromatography using hexane, ethyl acetate as elutant to give diethyl 2-(5-chloro-2-nitrobenzyl)-2-fluoromalonate **3e** (0.44 g, 33%) as yellow crystals; mp 52–53 °C; ([MH]$^+$, 348.0648. $C_{14}H_{15}NO_6F^{35}Cl$ requires [MH]$^+$, 348.0650); υ_{max} (neat, cm^{-1}) 2992, 1746, 1524, 1352, 1276, 1192, 1044; ^{1}H NMR δ 7.87 (1H, d, $^3J_{HH}$ 8.6, H-3), 7.44 (1H, s, H-6), 7.41 (dd, $^3J_{HH}$ 8.6, $^4J_{HH}$ 2.3, H-4), 4.34–4.19 (4H, m, OCH_2), 3.94 (2H, d, $^3J_{HF}$ 22.8, CH_2-CF), 1.27 (6H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –164.12 (t, $^3J_{HF}$ 22.8); ^{13}C NMR δ 165.19 (d, $^2J_{CF}$ 25.4, C=O), 148.88 (s, C-NO_2), 139.04 (s, C-Cl), 133.36 (s, Ar), 129.84 (s, Ar), 128.99 (s, Ar), 126.54 (s, Ar), 93.55 (d, $^1J_{CF}$ 202.3, C-F), 63.27 (s, OCH_2), 35.29 (d, $^2J_{CF}$ 20.4, CF-CH_2), 13.98 (s, CH_3); *m/z* (ASAP) 348.1 ([MH]$^+$), 100%), 274.0 (14), 228.0 (20); and, tetraethyl 2-(5-chloro-2-nitrophenyl)-1-fluoropropane-1,1,3,3-tetracarboxylate **5** (0.73 g, 55%) as an orange oily solid; mp 40–41 °C; ([MH]$^+$, 506.1210. $C_{21}H_{25}NO_{10}F^{35}Cl$ requires [MH]$^+$, 506.1229); υ_{max} (neat, cm^{-1}) 2982, 1752, 1532, 1231, 1147, 1095, 1047: ^{1}H NMR δ 7.83 (1H, d, $^3J_{HH}$ 8.7, H-3), 7.64–7.58 (1H, m, H-8), 7.39 (1H, dd, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.2, H-4), 5.63 (1H, dd, $^3J_{HF}$ 27.4, $^3J_{HH}$ 9.8, CH-CF), 4.37–3.76 (9H, m, OCH_2, CH-C=O), 1.33 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.27 (3H, t, $^3J_{HH}$ 7.1, CH_3), 1.06 (3H, t, $^3J_{HH}$ 7.1, CH_3), 1.00 (3H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –168.93 (d, $^3J_{HF}$ 27.4); ^{13}C NMR δ 166.89 (s, C=O), 166.35 (s, C=O), 164.48 (d, $^2J_{CF}$ 24.5, FC-C=O), 164.22 (d, $^2J_{CF}$ 23.9, FC-C=O), 148.96 (s, C-NO_2), 139.00 (s, C-Cl), 132.56 (d, $^4J_{CF}$ 1.3, C-6), 130.95 (d, $^3J_{CF}$ 6.3, C-1), 129.19 (s, C-4), 126.37 (s, C-3), 94.91 (d, $^1J_{CF}$ 207.2, C-F), 63.65 (s, OCH_2), 63.23 (s, OCH_2), 62.49 (s, OCH_2), 62.12 (s, OCH_2), 52.85 (d, $^3J_{CF}$ 5.7, CH-C=O), 40.75 (d, $^2J_{CF}$ 18.6, CF-CH), 14.02 (s, CH_3), 13.88 (s, CH_3), 13.72 (s, CH_3), 13.67 (s, CH_3); *m/z* (ASAP) 506.1 ([MH]$^+$, 100%), 460.1 (85), 414.0 (72).

4.3 *Synthesis of Fluorotetrahydroquinolines 6 by Reduction-Cyclisation*

4.3.1 *Method A: Hydrogenation over Pd/C*

Diester **3** and Pd/C in acetic acid were placed in a Parr hydrogenator and pressurised (40 psi) with hydrogen. After stirring for 1 h the solution was filtered through celite, concentrated, DCM (50 mL) added, washed with sodium bicarbonate (3 × 50 mL), dried ($MgSO_4$) and concentrated to give the desired fluorotetrahydroquinoline **6** which was purified by recrystallization if required.

4.3.2 *Method B: Sodium Dithionite*

Sodium bicarbonate was added slowly to a solution of diester **3** in THF and water. Sodium dithionite was added portion wise over 10 minutes with vigorous stirring. After 30 minutes, brine (8 mL) and ethyl acetate (8 mL) were added, the organic layer separated and washed with sodium bicarbonate (3 × 50 mL) and brine (3 × 50 mL), concentrated and the residue purified by column chromatography using hexane:ethyl acetate (9:1) as elutant to give the desired fluorotetrahydroquinoline product **6**.

4.3.3 *Ethyl 3-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**6a**)*

Method A: Diethyl 2-fluoro-2-(2-nitrobenzyl)malonate **3a** (1.25 g, 4 mmol) and Pd/C (0.43 g, 5 mol% Pd) in acetic acid (40 mL) gave ethyl 3-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **6a** (0.73 g, 78%) as a white powder; mp 84–85 °C; ([MH]$^+$, 238.0862. $C_{12}H_{12}FNO_3$ requires [MH]$^+$, 238.0879); υ_{max} (neat, cm^{-1}) 3215, 3096, 2992, 1752, 1688, 1493, 1200, 1131; ^{1}H NMR δ 9.03 (1H, s, NH), 7.24 (1H, t, $^3J_{HH}$ 8, Ar-H), 7.18 (1H, d, $^3J_{HH}$ 7.4, Ar-H), 7.06 (1H, t, $^3J_{HH}$ 7.0, Ar-H), 6.90 (1H, d, $^3J_{HH}$ 7.9, Ar-H), 4.35–4.21 (2H, m, OCH_2), 3.68–3.40 (2H, m, CF-CH_2), 1.23 (3H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –165.17 (dd, $^3J_{HH}$ 23.4, $^3J_{HF}$ 15.4); ^{13}C NMR δ 166.57 (d, $^2J_{CF}$ 25.8, C=O), 164.05 (d, $^2J_{CF}$ 22.8, C=O), 135.52 (s, C-NH), 128.77 (s, Ar), 128.58 (s, Ar), 124.22 (s, Ar), 118.98 (d, $^3J_{CF}$ 6.5, C-4a), 116.00 (s, Ar), 90.32 (d, $^1J_{CF}$ 195.1, C-F), 62.93 (s, OCH_2) 35.65 (d, $^2J_{CF}$ 23.8, CF-CH_2), 14.03 (s, CH_3); *m/z* (ASAP) 238.1 ([MH]$^+$, 23%), 210.1 (40), 164.0 (100).

Method B: Sodium bicarbonate (1.51 g, 17.98 mmol), diethyl 2-fluoro-2-(2-nitrobenzyl)malonate **3a** (1.00 g, 3.19 mmol) in THF (8 mL) and water (8 mL) and sodium dithionite (2.85 g, 16.38 mmol) gave ethyl 3-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **6a** (0.43 g, 57%) as a white powder; physical and spectral data as above.

4.3.4 *Ethyl 7-cyano-3-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**6b**)*

Method B: Sodium bicarbonate (1.51 g, 17.98 mmol), diethyl 2-(4-cyano-2-nitrobenzyl)-2-fluoromalonate **3b** (0.5 g, 1.48 mmol) in THF (8 mL) and water (8 mL) and sodium dithionite (2.85 g, 16.38 mmol), gave ethyl 7-cyano-3-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **6b** (0.30 g, 76%) as an orange solid; mp 137–138 °C; ([MH]$^+$, 263.0848. $C_{13}H_{11}N_2O_3F$ requires [MH]$^+$, 263.0832); υ_{max} (neat, cm^{-1}) 2981, 2922, 2226, 1758, 1695, 1257, 1205, 1103; ^{1}H

NMR δ 9.23 (1H, s, NH), 7.38 (1H, d, $^3J_{HH}$ 8.3, H-6), 7.32 (1H, d, $^3J_{HH}$ 7.8, H-5), 7.20 (1H, s, H-8), 4.38–4.28 (2H, m, OCH_2), 3.79–3.42 (2H, m, CF-CH_2), 1.28 (3H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –165.38 (dd, $^3J_{HF}$ 24.9, $^3J_{HF}$ 15.3); ^{13}C NMR δ 165.94 (d, $^2J_{CF}$ 25.4, C=O), 163.87 (d, $^2J_{CF}$ 22.3, C=O), 136.47 (s, C-NHR), 129.70 (s, Ar), 127.86 (s, Ar), 124.48 (d, $^3J_{CF}$ 6.2, C-4a), 119.07 (s, Ar), 117.96 (s, C-7), 112.53 (s, CN), 89.51 (d, $^1J_{CF}$ 196.3, CF), 63.41 (OCH_2), 35.68 (d, $^2J_{CF}$ 24.1, CF-CH_2), 14.06 (s, CH_3); *m/z* (ASAP) 263.1 ([MH]$^+$, 100%), 243.1 (43), 189.0 (27).

4.3.5 *Ethyl 3-fluoro-7-methoxy -2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**6c**)*

Method A: Diethyl 2-fluoro-2-(4-methoxy-2-nitrobenzyl)malonate **3c** (0.50 g, 1.46 mmol) and Pd/C (0.16 g, 5 mol% Pd) in acetic acid (20 mL) after column chromatography and recrystallization, gave ethyl 3-fluoro-7-methoxy-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **6c** (0.26 g, 67%) as white needles; mp 111–112 °C; ([MH]$^+$, 268.0984. $C_{13}H_{15}FNO_4$ requires [MH]$^+$, 268.0985); υ_{max} (neat, cm^{-1}) 2984, 1761, 1693, 1288, 1255, 1068; ^{1}H NMR δ 7.84 (1H, s, NH), 7.08 (1H, d, $^3J_{HH}$ 8.4, Ar-H), 6.59 (1H, d, $^3J_{HH}$ 8.4, Ar-H), 6.36 (1H, s, Ar-H), 4.33–4.22 (2H, m, OCH_2), 3.79 (3H, s, OCH_3), 3.63–3.29 (2H, m, CF-CH_2), 1.24 (3H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR δ –165.75 (dd, $^3J_{HF}$ 22.3, $^3J_{HF}$ 15.0); ^{13}C NMR δ 166.59 (d, $^2J_{CF}$ 25.8, C=O), 163.95 (d, $^2J_{CF}$ 22.8, C=O), 159.97 (s, C-OMe), 136.44 (s, C-NHR), 129.70 (s, Ar), 110.92 (d, $^3J_{CF}$ 7.0, Ar), 109.41 (s, Ar), 102.03 (s, Ar), 90.42 (d, $^1J_{CF}$ 195.5, C-F), 62.90 (s, OCH_2), 55.63 (s, OCH_3), 34.97 (d, $^2J_{CF}$ 23.8, CF-CH_2), 14.06 (s, CH_3); *m/z* (ASAP) 268.1 ([MH]$^+$, 100%), 248.1 (28), 194.1 (39).

4.3.6 *Ethyl 3,5-difluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**6d**)*

Method A: Diethyl 2-fluoro-2-(2-fluoro-6-nitrobenzyl)malonate **3d** (1.00 g, 3.02 mmol) and Pd/C (0.32 g, 5 mol% Pd) in acetic acid (30 mL) after 3.5 h gave ethyl 3,5-difluoro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **6d** (0.67 g, 87%) as a dark red viscous oil; ([MH]$^+$, 256.0785. $C_{12}H_{11}F_2NO_3$ requires [MH]$^+$, 256.0785); υ_{max} (neat, cm^{-1}) 3232, 2984, 1691, 1600, 1486, 1273, 1073; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.18 (1H, s, NH), 7.28 (1H, q, $^3J_{HH}$ 8.0, H-6), 6.91 (1H, t, $^3J_{HH}$ 8.8, H-7), 6.81 (1H, d, $^3J_{HH}$ 8.0, H-8), 4.29–4.16 (2H, m, OCH_2), 3.68–3.46 (2H, m, CF-CH_2), 1.16 (3H, t, $^3J_{HH}$ 7.1, CH_3); ^{19}F NMR (564 MHz, DMSO-d_6) δ –119.34 – –119.44 (1F, m, Ar-F), –163.80 (1F, dd, $^3J_{HF}$ 24.4, $^3J_{HF}$ 20.6, C-F); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.05 (d, $^2J_{CF}$ 25.7, C=O), 161.92 (d, $^2J_{CF}$ 22.7, C=O), 159.73 (d, $^1J_{CF}$ 243.4, Ar-F), 138.08 (d, $^3J_{CF}$ 6.8, C-8a), 129.35 (d, $^3J_{CF}$ 9.5, C-7), 111.49 (d, $^4J_{CF}$ 2.8, C-8), 109.80 (d, $^2J_{CF}$ 21.3, C-6), 106.46 (dd, $^2J_{CF}$ 21.2, $^3J_{CF}$ 5.7, C-4a), 89.56 (d, $^1J_{CF}$ 192.0, CF-CH_2), 62.27 (s, OCH_2), 28.01 (dd, $^2J_{CF}$ 24.4, $^3J_{CF}$ 3.0, CF-CH_2), 13.73 (s, CH_3); *m/z* (ASAP) 256.1 ([MH]$^+$, 34%), 236.1 (100).

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