The role of fluorine substituents on the formation of the ferroelectric nematic phase

Ewan Cruickshank[1,‡,*], Rebecca Walker[1], Grant Strachan[2], Ewa Gorecka[2], Damian Pociecha[2], John M.D. Storey[1] & Corrie T. Imrie[1]

[1]Department of Chemistry, University of Aberdeen, Old Aberdeen, AB24 3UE, U.K.

[2]Faculty of Chemistry, University of Warsaw, Zwirki i Wigury 101, 02-089 Warsaw, Poland

‡Present Address: School of Pharmacy and Life Sciences, Robert Gordon University, Aberdeen, AB10 7GJ, U.K.

*Author for correspondence: e.cruickshank2@rgu.ac.uk

Experimental Procedures

Synthesis

Reagents

All reagents and solvents that were available commercially were purchased from Sigma Aldrich, Fisher Scientific or Fluorochem and were used without further purification unless otherwise stated.

Thin Layer Chromatography

Reactions were monitored using thin layer chromatography, and the appropriate solvent system, using aluminium-backed plates with a coating of Merck Kieselgel 60 F254 silica which were purchased from Merck KGaA. The spots on the plate were visualised by UV light (254 nm) or by oxidation using either a potassium permanganate stain or iodine dip.

Column Chromatography

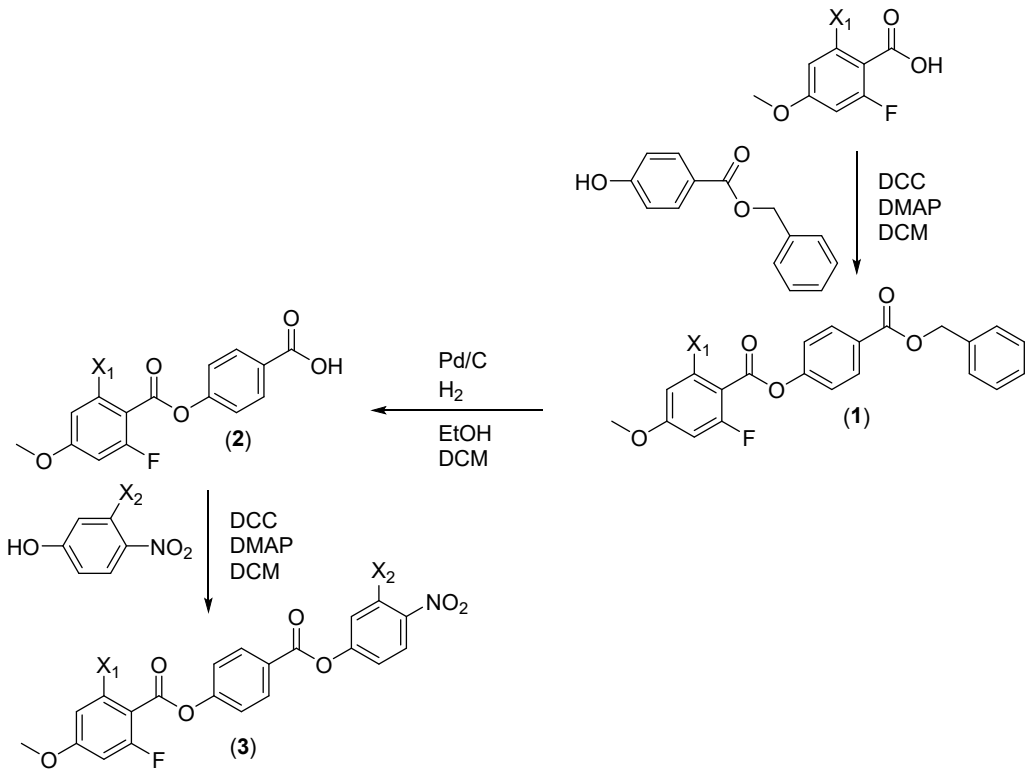
For normal phase column chromatography, the separations were carried out using silica gel grade 60 Å, 40-63 µm particle size, purchased from Fluorochem and using an appropriate solvent system.

Structure Characterisation

All final products and intermediates that were synthesised were characterised using ^{1}H NMR, ^{13}C NMR and infrared spectroscopies. The NMR spectra were recorded on a 400 MHz Bruker Avance III HD NMR spectrometer. The infrared spectra were recorded on a Perkin Elmer Spectrum Two FTIR spectrometer with an ATR diamond cell.

Purity Analysis

In order to determine the purity of the final products, high-resolution mass spectrometry was carried out using a Waters XEVO G2 QTof mass spectrometer by Dr. Jayne McCaskill at the University of Aberdeen.



Scheme 1. Synthesis of EC1F, EC2F, EC5F and EC6F.

Compound 1

To a pre-dried flask flushed with argon, 2-fluoro-4-methoxybenzoic acid (1 eq) or 2,6-difluoro-4-methoxybenzoic acid (1 eq), benzyl 4-hydroxybenzoate (1.1 eq) and 4-dimethylaminopyridine (0.13 eq) were added. The solids were solubilised with dichloromethane (80 mL) and stirred for 10 min before *N,N'*-dicyclohexylcarbodiimide (1.3 eq) was added to the flask and the reaction was allowed to proceed overnight. The quantities of the reagents used in each reaction are listed in **Table S1**. The extent of the reaction was monitored by TLC using an appropriate solvent system (RF values quoted in the product data). The precipitate which formed was removed by vacuum filtration and the filtrate collected. The collected solvent was evaporated under vacuum to leave a solid which was recrystallised from hot ethanol (100 mL).

Table S1. Quantities of reagents used in the syntheses of **Compound 1**

Product	2-Fluoro-4-methoxybenzoic acid/*2,6-Difluoro-4-methoxybenzoic acid	Benzyl 4-hydroxybenzoate	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide
1.1	3.00 g, 0.0176 mol	5.23 g, 0.0194 mol	0.280 g, 2.29×10^{-3} mol	4.72 g, 0.0229 mol
1.2	*3.00 g, 0.0159 mol	3.99 g, 0.0175 mol	0.253 g, 2.07×10^{-3}	4.27 g, 0.0207 mol

			mol	

1.1 4-[(Benzyloxy)carbonyl]phenyl 2-fluoro-4-methoxybenzoate

White solid. Yield: 4.23 g, 63.2 %. RF: 0.60 (40 % ethyl acetate: 60 % 40:60 petroleum ether). M.P = 78 °C

ν_{max}/cm^{-1}: 2848, 1731, 1714, 1682, 1620, 1604, 1578, 1508, 1426, 1345, 1288, 1262, 1197, 1163, 1134, 1111, 1077, 1059, 1025, 956, 924, 882, 843, 779, 763, 754, 681, 653, 624, 541, 502, 460, 430, 415, 406

δ_H/ppm (400 MHz, $CDCl_3$): 8.15 (2 H, d, J 8.6 Hz, Ar-H), 8.05 (1 H, dd, J 8.7 Hz, 8.6 Hz, Ar-H), 7.41 (5 H, m, Ar-H), 7.30 (2 H, d, J 8.6 Hz, Ar-H), 6.80 (1 H, dd, J 8.7 Hz, 2.5 Hz, Ar-H), 6.71 (1 H, dd, J 12.7 Hz, 2.5 Hz, Ar-H), 5.38 (2 H, s, O-$\underline{CH_2}$-Ar), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -104.21 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 165.70, 165.46 (d, J 11.7 Hz), 164.06 (d, J 262.0 Hz), 161.89 (d, J 4.6 Hz), 154.50, 135.97, 133.92 (d, J 2.2 Hz), 131.31, 128.63, 128.30, 128.20, 127.69, 121.86, 110.55 (d, J 2.9 Hz), 109.72 (d, J 9.4 Hz), 102.56 (d, J 25.6 Hz), 66.83, 55.95

1.2 4-[(Benzyloxy)carbonyl]phenyl 2,6-difluoro-4-methoxybenzoate

Yellow solid. Yield: 4.91 g, 77.5 %. RF: 0.62 (40 % ethyl acetate: 60 % 40:60 petroleum ether). M.P = 68 °C

ν_{max}/cm^{-1}: 1727, 1715, 1625, 1601, 1575, 1507, 1496, 1466, 1455, 1438, 1415, 1379, 1355, 1311, 1277, 1249, 1198, 1164, 1146, 1116, 1099, 1071, 1047, 1034, 1017, 976, 890, 836, 797, 773, 760, 728, 693, 655, 619, 600, 555, 536, 516, 499, 458, 405

δ_H/ppm (400 MHz, $CDCl_3$): 8.15 (2 H, d, J 8.7 Hz, Ar-H), 7.41 (5 H, m, Ar-H), 7.32 (2 H, d, J 8.7 Hz, Ar-H), 6.55 (2 H, d, J 10.3 Hz, Ar-H), 5.38 (2 H, s, O-$\underline{CH_2}$-Ar), 3.87 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -106.08 (2 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 165.64, 164.26 (t, 14.4 Hz), 161.65 (dd, J 258.2 Hz, 8.3 Hz), 159.30 (t, J 2.9 Hz), 154.16, 135.94, 131.34, 128.63, 128.31, 128.20, 127.93, 121.76, 101.97 (t, J 15.9 Hz), 98.90 (dd, J 26.3 Hz, 3.1 Hz), 66.86, 56.18

Compound 2

To a pre-dried flask flushed with argon, **Compound 1** (1 eq) was dissolved in a mixture of dichloromethane and ethanol and stirred. The mixture was sparged with argon and 5 % Pd/C catalyst was added. The argon atmosphere was evacuated under vacuum and replaced by hydrogen gas. The quantities of the reagents used in each reaction are listed in **Table S2**. The reaction was allowed to proceed for 4 h at room temperature, with the extent of the reaction monitored by TLC using an appropriate solvent system (RF values quoted in the product data). After the reaction was completed, the hydrogen gas was evacuated under vacuum and the flask purged using argon. The mixture was filtered through Celite using copious amounts of dichloromethane, and the collected solvent was evaporated under vacuum to leave a white solid which was carried forwards without any further purification.

Table S2. Quantities of reagents used in the syntheses of **Compound 2**

Product	Compound 1.1/1.2*	5 % Palladium on Carbon	Dichloromethane	Ethanol
2.1	4.00 g, 0.0105 mol	0.223 g, 2.10×10^{-3} mol	70 mL	70 mL
2.2	*4.70 g, 0.0118 mol	0.251 g, 2.36×10^{-3} mol	80 mL	80 mL

2.1 4-(2-Fluoro-4-methoxybenzoyloxy)benzoic acid

Yield: 0.878 g, 28.8 %. RF: 0.057 (40 % ethyl acetate: 60 % 40:60 petroleum ether).

T_{CrN} 220 °C T_{NI} 225 °C

ν_{max}/cm^{-1}: 1732, 1713, 1615, 1602, 1579, 1508, 1454, 1440, 1431, 1414, 1377, 1311, 1296, 1277, 1252, 1199, 1164, 1131, 1114, 1050, 1017, 954, 936, 888, 849, 819, 795, 756, 729, 693, 680, 611, 632, 619, 600, 554, 541, 517, 500, 457, 440, 410

δ_H/ppm (400 MHz, DMSO-d_6): 13.05 (1 H, br, (C=O)-OH), 8.04 (3 H, m, Ar-H), 7.38 (2 H, d, J 8.7 Hz, Ar-H), 7.05 (1 H, dd, J 13.2 Hz, 2.4 Hz, Ar-H), 6.97 (1 H, dd, J 8.9 Hz, 2.4 Hz, Ar-H), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -105.54 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 167.22, 165.78 (d, J 12.0 Hz), 163.73 (d, J 259.4 Hz), 161.71 (d, J 4.5 Hz), 154.07, 134.19 (d, J 2.1 Hz), 131.32, 129.62, 122.57, 111.69 (d, J 2.8 Hz), 109.39 (d, J 9.3 Hz), 103.21 (d, J 25.6 Hz), 56.77

2.2 4-(2,6-Difluoro-4-methoxybenzoyloxy)benzoic acid

Yield: 1.23 g, 33.8 %. RF: 0.057 (40 % ethyl acetate: 60 % 40:60 petroleum ether).

T_{CrN} 228 °C T_{NI} 241 °C

ν_{max}/cm^{-1}: 2849, 1721, 1684, 1630, 1603, 1578, 1507, 1449, 1424, 1363, 1313, 1288, 1263, 1200, 1152, 1127, 1108, 1084, 1049, 1033, 1015, 961, 920, 884, 838, 779, 760, 683, 650, 629, 581, 559, 554, 526, 502, 449, 413

δ_H/ppm (400 MHz, DMSO-d_6): 13.12 (1 H, br, (C=O)-OH), 8.04 (2 H, d, J 8.7 Hz, Ar-H), 7.39 (2 H, d, J 8.7 Hz, Ar-H), 6.97 (2 H, d, J 11.1 Hz, Ar-H), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -106.98 (2 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 167.05, 164.92 (t, J 15.1 Hz), 162.60 (dd, J 255.5 Hz, 8.7 Hz), 159.30 (t, J 2.8 Hz), 153.77, 131.52, 129.42, 122.46, 101.27 (t, J 16.0 Hz), 99.98 (dd, J 26.2 Hz, 2.9 Hz), 57.21

Compound 3

To a pre-dried flask flushed with argon, **Compound 2** (1 eq), 4-nitrophenol (1.2 eq) or 3-fluoro-4-nitrophenol (1.2 eq), and *N,N'*-dicyclohexylcarbodiimide (1.5 eq) were added to the flask. The solids were solubilised with a mixture of dichloromethane (30 mL) and tetrahydrofuran (15 mL) and stirred for 30 min before 4-dimethylaminopyridine (0.15 eq) was added. The quantities of the reagents used in each reaction are listed in **Table S3**. The temperature of the reaction mixture was increased to room temperature and the reaction was allowed to proceed overnight. The white precipitate which formed was removed by vacuum filtration and the filtrate collected. The solvent was removed under vacuum and the crude product was purified using a silica gel column with an appropriate solvent system (RF

values quoted in product data). The eluent fractions of interest were evaporated under vacuum to leave a white solid which was recrystallised from hot ethanol (80 mL).

Table S3. Quantities of reagents used in the syntheses of **Compound 3**

Product	Compound 2.1/2.2*	4-Nitrophenol/*3-Fluoro-4-nitrophenol	*N*,*N*′-Dicyclohexylcarbodiimide	4-Dimethylaminopyridine
3.1	0.300 g, 1.03×10^{-3} mol	0.172 g, 1.24×10^{-3} mol	0.297 g, 1.55×10^{-3} mol	0.019 g, 1.55×10^{-4} mol
3.2	0.300 g, 1.03×10^{-3} mol	*0.195 g, 1.24×10^{-3} mol	0.297 g, 1.55×10^{-3} mol	0.019 g, 1.55×10^{-4} mol
3.3	*0.300 g, 9.73×10^{-4}	0.163 g, 1.17×10^{-3} mol	0.280 g, 1.46×10^{-3} mol	0.018 g, 1.46×10^{-4} mol
3.4	*0.300 g, 9.73×10^{-4}	*0.184 g, 1.17×10^{-3} mol	0.280 g, 1.46×10^{-3} mol	0.018 g, 1.46×10^{-4} mol

3.1 4-[(4-Nitrophenoxy)carbonyl]phenyl 2-fluoro-4-methoxybenzoate

Yield: 0.107 g, 25.3 %. RF: 0.272 (100 % dichloromethane).

T_{CrN} 207 °C $T_{N_FN_X}$ (144 °C) T_{N_XN} (157 °C) T_{NI} 278 °C

ν_{max}/cm^{-1}: 1737, 1720, 1625, 1605, 1588, 1578, 1517, 1506, 1484, 1474, 1442, 1432, 1414, 1339, 1268, 1235, 1194, 1165, 1110, 1061, 1017, 964, 954, 892, 862, 836, 819, 754, 726, 693, 681, 663, 641, 628, 543, 505, 486, 479, 457, 422, 414

δ_H/ppm (400 MHz, DMSO-d_6): 8.37 (2 H, d, 9.2 Hz, Ar-H), 8.26 (2 H, d, 8.8 Hz, Ar-H), 8.09 (1 H, dd, J 8.8 Hz, 8.7 Hz, Ar-H), 7.66 (2 H, d, 9.2 Hz, Ar-H), 7.55 (2 H, d, 8.8 Hz, Ar-H), 7.07 (1 H, dd, J 13.2 Hz, 2.4 Hz, Ar-H), 6.99 (1 H, dd, J 8.8 Hz, 2.4 Hz, Ar-H), 3.90 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -105.44 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 165.90 (d, J 12.1 Hz), 163.81 (d, J 259.4 Hz), 163.72, 161.56 (d, J 4.2 Hz), 155.95, 155.40, 145.69, 134.27 (d, J 1.7 Hz), 132.27, 126.51, 125.80, 123.86, 123.27, 111.74 (d, J 2.7 Hz), 109.24 (d, J 9.1 Hz), 103.24 (d, J 25.5 Hz), 56.81

MS = $[M+H]^+$: Calculated for $C_{21}H_{15}NO_7F$: 412.0833. Found: 412.0848. Difference: 3.6 ppm

3.2 4-[(3-Fluoro-4-nitrophenoxy)carbonyl]phenyl 2-fluoro-4-methoxybenzoate

Yield: 0.120 g, 27.1 %. RF: 0.324 (100 % dichloromethane).

T_{CrN} 192 °C $T_{N_FN_X}$ (166 °C) T_{N_XN} (175 °C) T_{NI} 245 °C

ν_{max}/cm^{-1}: 1746, 1716, 1615, 1601, 1574, 1548, 1507, 1482, 1443, 1426, 1413, 1341, 1324, 1284, 1267, 1240, 1196, 1164, 1137, 1110, 1093, 1056, 1013, 964, 953, 891, 846, 808, 751, 687, 664, 640, 616, 605, 594, 543, 504, 473, 457, 406

δ_H/ppm (400 MHz, $CDCl_3$): 8.26 (2 H, d, 8.7 Hz, Ar-H), 8.20 (1 H, dd, J 8.9 Hz, 8.6 Hz, Ar-H), 8.06 (1 H, dd, 8.7 Hz, 8.6 Hz, Ar-H), 7.42 (2 H, d, 8.7 Hz, Ar-H), 7.30 (1 H, dd, 11.2 Hz, 2.4 Hz, Ar-H), 7.23 (1 H, ddd, J 8.9 Hz, 2.4 Hz, 1.33 Hz, Ar-H), 6.82 (1 H, dd, J 8.9 Hz, 2.4 Hz, Ar-H), 6.73 (1 H, dd, 12.7 Hz, 2.4 H, Ar-H), 3.91 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -104.01 (1 F, s, Ar-F), -113.05 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 165.66 (d, J 11.7 Hz), 164.13 (d, J 262.2 Hz), 163.03, 161.72 (d, J 4.6 Hz), 156.22 (d, J 267.0 Hz), 155.75, 155.64, 134.89 (d, J 7.1 Hz), 133.96 (d, J 2.1 Hz), 132.06, 127.25 (d, J 2.1 Hz), 125.55, 122.43, 118.09 (d, J 4.0 Hz), 112.41 (d, J 23.9 Hz), 110.66 (d, J 2.9 Hz), 109.44 (d, J 9.3 Hz), 102.61 (d, J 25.7 Hz), 55.99

MS = $[M+Na]^+$: Calculated for $C_{21}H_{13}NO_7F_2Na$: 452.0558. Found: 452.0543. Difference: 3.3 ppm

3.3 4-[(4-Nitrophenoxy)carbonyl]phenyl 2,6-difluoro-4-methoxybenzoate

Yield: 0.079 g, 18.9 %. RF: 0.270 (100 % dichloromethane).

T_{CrN} 186 °C $T_{N_FN_X}$ (172 °C) T_{N_XN} (177 °C) T_{NI} 265 °C

ν_{max}/cm^{-1}: 1734, 1637, 1615, 1604, 1592, 1577, 1523, 1506, 1491, 1447, 1414, 1350, 1318, 1259, 1207, 1157, 1108, 1084, 1062, 1045, 1029, 1013, 956, 880, 864, 843, 771, 751, 743, 702, 685, 665, 652, 625, 592, 557, 523, 504, 480, 448, 430, 407

δ_H/ppm (400 MHz, $CDCl_3$): 8.34 (2 H, d, 9.2 Hz, Ar-H), 8.28 (2 H, d, 8.8 Hz, Ar-H), 7.43 (4 H, m, Ar-H), 6.58 (2 H, d, J 10.3 Hz, Ar-H), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -105.64 (2 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 164.45 (t, J 14.6 Hz), 163.45, 163.02 (dd, J 258.4 Hz, 8.4 Hz), 159.18 (t, J 2.8 Hz), 155.61, 155.08, 145.49, 132.03, 126.24, 125.32, 122.64, 122.26, 101.73 (t, J 15.7 Hz), 98.97 (dd, J 26.3 Hz, 3.0 Hz), 56.22

MS = $[M+H]^+$: Calculated for $C_{21}H_{14}NO_7F_2$: 430.0738. Found: 430.0732. Difference: 1.4 ppm

3.4 4-[(3-Fluoro-4-nitrophenoxy)carbonyl]phenyl 2,6-difluoro-4-methoxybenzoate

Yield: 0.092 g, 21.1 %. RF: 0.297 (100 % dichloromethane).

T_{CrN_F} 181 °C $T_{N_FN_X}$ 188 °C T_{N_XN} 191 °C T_{NI} 231 °C

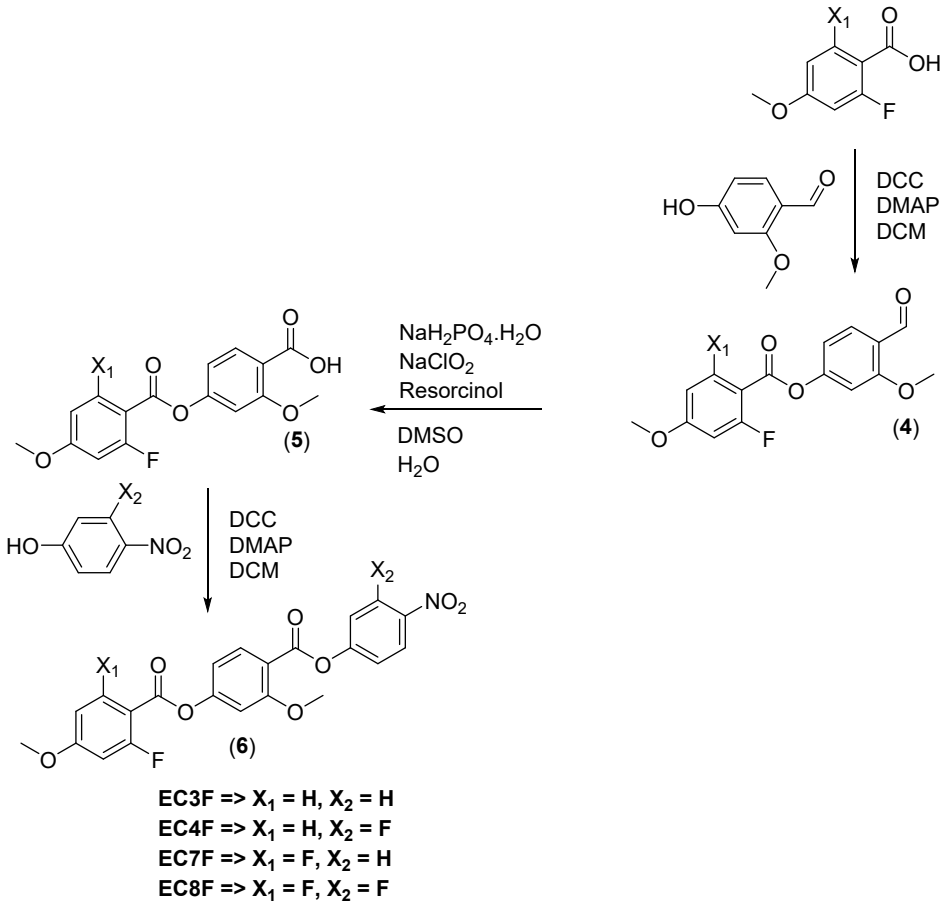
ν_{max}/cm^{-1}: 1741, 1637, 1601, 1578, 1531, 1504, 1484, 1446, 1415, 1347, 1317, 1250, 1207, 1158, 1145, 1093, 1078, 1044, 1027, 1015, 967, 954, 878, 836, 808, 770, 750, 702, 683, 655, 649, 622, 605, 587, 555, 522, 502,476, 458, 413, 402

δ_H/ppm (400 MHz, $CDCl_3$): 8.26 (2 H, d, 8.8 Hz, Ar-H), 8.20 (1 H, dd, J 8.8 Hz, 8.6 Hz, Ar-H), 7.44 (2 H, d, 8.8 Hz, Ar-H), 7.30 (1 H, dd, 11.2 Hz, 2.4 Hz, Ar-H), 7.23 (1 H, ddd, J 8.8 Hz, 2.4 Hz, 1.33 Hz, Ar-H), 6.57 (2 H, d, 10.37 Hz, Ar-H), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -105.86 (2 F, s, Ar-F), -113.03 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 164.55 (t, J 14.6 Hz), 163.03 (dd, J 258.3 Hz, 8.2 Hz), 162.98, 159.13 (t, J 3.0 Hz), 156.22 (d, J 267.0 Hz), 155.67 (d, J 10.5 Hz), 155.26, 134.91 (d, J 7.2 Hz), 132.10, 127.26 (d, J 2.0 Hz), 125.80, 122.35, 118.09 (d, J 4.0 Hz), 112.41 (d, J 23.8 Hz), 101.67 (t, J 16.0 Hz), 98.98 (dd, J 26.2 Hz, 3.0 Hz), 56.23

MS = $[M+H]^+$: Calculated for $C_{21}H_{13}NO_7F_3$: 448.0644. Found: 448.0626. Difference: 1.8 ppm



Scheme 2. Synthesis of EC3F, EC4F, EC7F and EC8F.

Compound 4

To a pre-dried flask flushed with argon, 2-fluoro-4-methoxybenzoic acid (1 eq) or 2,6-difluoro-4-methoxybenzoic acid, (1 eq), 4-hydroxy-2-methoxybenzaldehyde (1.1 eq) and 4-dimethylaminopyridine (0.13 eq) were added. The solids were solubilised with dichloromethane (100 mL) and tetrahydrofuran (50 mL) while being stirred for 10 min before *N,N'*-dicyclohexylcarbodiimide (1.3 eq) was added to the flask and the reaction was allowed to proceed overnight. The quantities of the reagents used in each reaction are listed in **Table S4**. The extent of the reaction was monitored by TLC using an appropriate solvent system (RF values quoted in the product data). The precipitate which formed was removed by vacuum filtration and the filtrate collected. The collected solvent was evaporated under vacuum to leave a solid which was recrystallised from hot ethanol (200 mL).

Table S4. Quantities of reagents used in the syntheses of **Compound 4**

Product	2-Fluoro-4-methoxybenzoic acid/*2,6-Difluoro-4-methoxybenzoic acid	4-Hydroxy-2-methoxybenzaldehyde	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide

4.1	3.00 g, 0.0176 mol	2.95 g, 0.0194 mol	0.280 g, 2.29×10^{-3} mol	4.72 g, 0.0229 mol
4.2	*3.00 g, 0.0159 mol	2.66 g, 0.0175 mol	0.253 g, 2.07×10^{-3} mol	4.27 g, 0.0207 mol

4.1 4-Formyl-3-methoxyphenyl 2-fluoro-4-methoxybenzoate

Yield: 2.88 g, 53.8 %. RF: 0.400 (40 % ethyl acetate: 60 % 40:60 petroleum ether). M.P = 185 °C

ν_{max}/cm^{-1}: 1737, 1675, 1620, 1605, 1589, 1574, 1503, 1470, 1457, 1445, 1436, 1416, 1396, 1309, 1245, 1239, 1194, 1171, 1154, 1141, 1100, 1051, 1024, 950, 883, 867, 829, 816, 795, 758, 738, 685, 664, 612, 584, 555, 524, 484, 463, 442, 431, 419, 410

δ_H/ppm (400 MHz, $CDCl_3$): 10.42 (1 H, s, (C=O)-H), 8.05 (1 H, dd, J 8.7 Hz, 8.6 Hz, Ar-H), 7.90 (1 H, d, J 9.0 Hz, Ar-H), 6.91 (2 H, m, Ar-H), 6.80 (1 H, dd, J 9.0 Hz, 2.5 Hz, Ar-H), 6.71 (1 H, dd, J 12.7 Hz, 2.5 Hz, Ar-H), 3.94 (3 H, s, O-CH_3), 3.90 (3 H, s, O-CH_3)

δ_F/ppm (376 MHz, $CDCl_3$): -104.14 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 188.67, 165.59 (d, J 11.6 Hz), 164.10 (d, J 262.1 Hz), 162.82, 161.69 (d, J 4.6 Hz), 156.80, 133.93 (d, J 2.2 Hz), 129.89, 122.68, 114.33, 110.62 (d, J 3.0 Hz), 109.53 (d, J 9.3 Hz), 105.79, 102.59 (d, J 25.8 Hz), 55.97, 55.94

4.2 4-Formyl-3-methoxyphenyl 2,6-difluoro-4-methoxybenzoate

Yield: 3.31 g, 64.6 %. RF: 0.514 (40 % ethyl acetate: 60 % 40:60 petroleum ether). M.P = 176 °C

ν_{max}/cm^{-1}: 1747, 1732, 1672, 1633, 1604, 1575, 1491, 1469, 1446, 1416, 1399, 1358, 1252, 1213, 1194, 1152, 1103, 1084, 1046, 1025, 958, 941, 873, 828, 817, 799, 775, 737, 665, 650, 620, 590, 527, 487, 457, 414

δ_H/ppm (400 MHz, $CDCl_3$): 10.42 (1 H, s, (C=O)-H), 7.90 (1 H, d, J 9.0 Hz, Ar-H), 6.92 (2 H, m, Ar-H), 6.56 (1 H, d, J 10.4 Hz, Ar-H), 3.94 (3 H, s, O-CH_3), 3.87 (3 H, s, O-CH_3)

δ_F/ppm (376 MHz, $CDCl_3$): -105.93 (2 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 188.65, 164.41 (t, J 14.6 Hz), 162.99 (dd, J 258.3 Hz, 8.3 Hz), 162.82, 159.09 (t, J 3.0 Hz), 156.40, 129.92, 122.84, 114.22, 105.68, 101.75 (t, J 15.7 Hz), 98.95 (dd, J 26.4 Hz, 3.1 Hz), 56.21, 55.98

Compound 5

To a pre-dried flask flushed with argon, **Compound 4** (1 eq) and resorcinol (1.5 eq) were solubilised in tetrahydrofuran (80 mL) and *N,N'*-dimethylformamide (60 mL). Sodium chlorite (4 eq) and sodium hydrogen phosphate monohydrate (3.5 eq) were solubilised in water (60 mL) before being slowly added to into the reaction flask and the resultant mixture was stirred at room temperature overnight. The quantities of the reagents used in each reaction are listed in **Table S5**. The extent of the reaction was monitored by TLC using an appropriate solvent system (RF values quoted in the product data). The reaction mixture was diluted with water (300 mL) and the pH of the mixture was adjusted to 1 using 32% hydrochloric acid (25 mL). A white solid precipitated after acidification which was collected by vacuum filtration and recrystallised from hot ethanol (200 mL).

Table S5. Quantities of reagents used in the syntheses of the **Compound 5**

Product	Compound 4.1/4.2*	Sodium Chlorite	Sodium Hydrogen Phosphate Monohydrate	Resorcinol
5.1	2.60 g, 8.55×10^{-3} mol	3.09 g, 0.0342 mol	4.13 g, 0.0299 mol	1.41 g, 0.0128 mol
5.2	*3.00 g, 9.31×10^{-3} mol	3.36 g, 0.0372 mol	4.50 g, 0.0326 mol	1.54 g, 0.0140 mol

5.1 4-((2-Fluoro-4-methoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 1.75 g, 63.9 %. RF: 0.086 (40 % ethyl acetate: 60 % 40:60 petroleum ether). M.P = 205 °C

ν_{max}/cm^{-1}: 2980, 1741, 1719, 1698, 1624, 1607, 1576, 1515, 1463, 1435, 1402, 1308, 1253, 1188, 1163, 1148, 1131, 1102, 1050, 1021, 953, 869, 838, 812, 795, 771, 758, 739, 684, 658, 632, 615, 596, 555, 524, 464, 440, 410

δ_H/ppm (400 MHz, DMSO-d_6): 12.66 (1 H, br, (C=O)-OH), 8.05 (1 H, dd, J 8.9 Hz, 8.7 Hz, Ar-H), 7.74 (1 H, d, J 8.4 Hz, Ar-H), 6.99 (4 H, m, Ar-H), 3.89 (3 H, s, O-CH_3), 3.82 (3 H, s, O-CH_3)

δ_F/ppm (376 MHz, DMSO-d_6): -105.51 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 167.04, 165.76 (d, J 12.0 Hz), 163.73 (d, J 259.5 Hz), 161.65 (d, J 4.5 Hz), 159.89, 154.47, 134.21 (d, J 2.1 Hz), 132.32, 119.19, 114.08, 111.66 (d, J 2.6 Hz), 109.41 (d, J 9.3 Hz), 107.30, 103.18 (d, J 25.5 Hz), 56.77, 56.59

5.2 4-((2,6-Difluoro-4-methoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 2.11 g, 67.0 %. RF: 0.023 (30 % ethyl acetate: 70 % 40:60 petroleum ether). M.P = 198 °C

ν_{max}/cm^{-1}: 2978, 1750, 1698, 1671, 1637, 1607, 1580, 1496, 1476, 1460, 1436, 1402, 1359, 1306, 1254, 1202, 1185, 1149, 1135, 1103, 1079, 1048, 1033, 1022, 949, 915, 877, 841, 817, 794, 774, 740, 688, 658, 620, 597, 587, 565, 525, 422, 413

δ_H/ppm (400 MHz, DMSO-d_6): 12.70 (1 H, br, (C=O)-H), 7.75 (1 H, d, J 8.4 Hz, Ar-H), 7.06 (1 H, d, J 2.0 Hz, Ar-H), 6.97 (2 H, d, J 11.5 Hz, Ar-H), 6.90 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 3.89 (3 H, s, O-CH_3), 3.83 (3 H, s, O-CH_3)

δ_F/ppm (376 MHz, DMSO-d_6): -106.69 (2 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 166.98, 164.91 (t, J 15.1 Hz), 162.65 (dd, J 255.7 Hz, 8.6 Hz), 159.93, 159.24 (t, J 3.0 Hz), 153.98, 132.44, 119.51, 113.83, 107.03, 101.27 (t, J 15.8 Hz), 99.97 (dd, J 26.3, 2.9 Hz), 57.21, 56.62

Compound 6

To a pre-dried flask flushed with argon, **Compound 5** (1 eq), 4-nitrophenol (1.2 eq) or 3-fluoro-4-nitrophenol (1.2 eq), and *N,N'*-dicyclohexylcarbodiimide (1.5 eq) were added to the flask. The solids were solubilised with dichloromethane (30 mL) and stirred for 30 min before 4-dimethylaminopyridine (0.15 eq) was added. The quantities of the reagents used in each reaction are listed in **Table S6**. The temperature of the reaction mixture was increased to room temperature and the reaction was

allowed to proceed overnight. The white precipitate which formed was removed by vacuum filtration and the filtrate collected. The solvent was removed under vacuum and the crude product was purified using a silica gel column with an appropriate solvent system (RF values quoted in product data). The eluent fractions of interest were evaporated under vacuum to leave a white solid which was recrystallised from hot ethanol (80 mL).

Table S6. Quantities of reagents used in the syntheses of the **Compound 6**

Product	Compound 5.1/5.2*	4-Nitrophenol/*3-Fluoro-4-nitrophenol	*N*,*N'*-Dicyclohexylcarbodiimide	4-Dimethylaminopyridine
6.1	0.300 g, 9.37×10^{-4} mol	0.156 g, 1.12×10^{-3} mol	0.270 g, 1.41×10^{-3} mol	0.017 g, 1.41×10^{-4} mol
6.2	0.300 g, 9.37×10^{-4} mol	*0.176 g, 1.12×10^{-3} mol	0.270 g, 1.41×10^{-3} mol	0.017 g, 1.41×10^{-4} mol
6.3	*0.300 g, 8.87×10^{-4}	0.147 g, 1.33×10^{-3} mol	0.255 g, 1.33×10^{-3} mol	0.016 g, 1.33×10^{-4} mol
6.4	*0.300 g, 8.87×10^{-4}	*0.167 g, 1.33×10^{-3} mol	0.255 g, 1.33×10^{-3} mol	0.016 g, 1.33×10^{-4} mol

6.1 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2-fluoro-4-methoxybenzoate

Yield: 0.062 g, 15.0 %. RF: 0.485 (1 % ethyl acetate: 99 % dichloromethane).

T_{CrN} 169 °C T_{N_FN} (156 °C) T_{NI} 177 °C

ν_{max}/cm^{-1}: 1720, 1710, 1628, 1607, 1584, 1577, 1519, 1491, 1478, 1454, 1445, 1433, 1414, 1344, 1316, 1286, 1272, 1237, 1208, 1184, 1162, 1112, 1058, 1023, 951, 879, 862, 837, 810, 762, 744, 683, 670, 651, 635, 622, 612, 587, 530, 500, 461, 418, 411

δ_H/ppm (400 MHz, DMSO-d_6): 8.35 (2 H, d, J 9.2 Hz, Ar-H), 8.08 (2 H, m, Ar-H), 7.59 (2 H, d, J 9.2 Hz, Ar-H), 7.26 (1 H, d, J 2.1 Hz, Ar-H), 7.06 (2 H, m, Ar-H), 6.99 (1 H, dd, J 8.9 Hz, 2.5 Hz, Ar-H), 3.90 (3 H, s, O-$\underline{CH_3}$), 3.89 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -105.40 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 165.87 (d, J 11.8 Hz), 163.80 (d, J 259.4 Hz), 162.67, 161.47 (d, J 4.5 Hz), 161.25, 156.11, 155.98, 145.54, 134.28 (d, J 1.8 Hz), 133.66, 125.77, 123.87, 115.62, 114.59, 111.71 (d, J 2.3 Hz), 109.28 (d, J 9.2 Hz), 107.80, 103.22 (d, J 25.6 Hz), 56.98, 56.80

MS = $[M+Na]^+$: Calculated for $C_{22}H_{16}NO_8FNa$: 464.0758. Found: 464.0781. Difference: 5.0 ppm

6.2 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2-fluoro-4-methoxybenzoate

Yield: 0.083 g, 19.3 %. RF: 0.455 (1 % ethyl acetate: 99 % dichloromethane).

T_{CrI} 172 °C T_{N_FI} (153 °C)

ν_{max}/cm^{-1}: 1748, 1718, 1627, 1604, 1585, 1523, 1497, 1474, 1449, 1430, 1406, 1343, 1264, 1221, 1197, 1187, 1159, 1125, 1113, 1088, 1072, 1013, 970, 954, 877, 845, 833, 810, 763, 755, 743, 678, 659, 628, 610, 573, 558, 535, 458, 403

δ_H/ppm (400 MHz, $CDCl_3$): 8.18 (1 H, dd, J 8.9 Hz, 8.7 Hz, Ar-H), 8.09 (2 H, m, Ar-H), 7.28 (1 H, dd, J 11.4 Hz, 2.4 Hz, Ar-H), 7.21 (1 H, ddd, J 8.9 Hz, 2.5 Hz, 1.3 Hz, Ar-H), 6.97 (2 H, m, Ar-H), 6.82 (1 H, dd, J 8.9 Hz, 2.5 Hz, Ar-H), 6.73 (1 H, dd, J 12.7 Hz, 2.4 Hz, Ar-H), 3.97 (3 H, s, O-$\underline{CH_3}$), 3.91 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, $CDCl_3$): -104.03 (1 F, s, Ar-F), -113.37 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, $CDCl_3$): 165.68 (d, J 11.8 Hz), 164.14 (d, J 262.1 Hz), 161.85, 161.79, 161.66 (d, J 4.6 Hz), 156.40, 156.22 (d, J 266.5 Hz), 155.92 (d, J 10.5 Hz), 134.67 (d, J 7.0 Hz), 133.96 (d, J 2.2 Hz), 133.77, 127.11 (d, J 2.1 Hz), 118.20 (d, J 3.9 Hz), 114.60, 113.89, 112.45 (d, J 23.7 Hz), 110.68 (d, J 2.8 Hz), 109.43 (d, J 9.3 Hz), 106.48, 102.61 (d, J 25.6 Hz), 56.38, 56.00

MS = $[M+Na]^+$: Calculated for $C_{22}H_{15}NO_8F_2Na$: 482.0663. Found: 482.0670. Difference: 1.5 ppm

6.3 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2,6-difluoro-4-methoxybenzoate

Yield: 0.073 g, 17.9 %. RF: 0.368 (1 % ethyl acetate: 99 % dichloromethane).

T_{CrI} 167 °C T_{N_FI} (159 °C)

ν_{max}/cm^{-1}: 1737, 1637, 1611, 1580, 1517, 1490, 1447, 1408, 1346, 1321, 1256, 1204, 1186, 1152, 1134, 1086, 1048, 1023, 958, 878, 864, 844, 758, 744, 685, 671, 653, 642, 610, 594, 544, 533, 520, 499, 418, 402

δ_H/ppm (400 MHz, DMSO-d_6): 8.35 (2 H, d, J 9.0 Hz, Ar-H), 8.10 (1 H, d, J 8.6 Hz, Ar-H), 7.60 (1 H, d, J 9.0 Hz, Ar-H), 7.22 (1 H, d, J 2.1 Hz, Ar-H), 7.05 (1 H, dd, J 8.6 Hz, 2.1 Hz, Ar-H), 7.00 (2 H, m, Ar-H), 3.91 (3 H, s, O-$\underline{CH_3}$), 3.90 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -106.40 (2 F, s, Ar-F),

δ_C/ppm (100 MHz, DMSO-d_6): 165.05 (t, J 15.0 Hz), 162.76 (dd, J 256.0 Hz, 8.5 Hz), 162.63, 161.28, 159.07 (t, J 3.2 Hz), 155.95, 155.59, 145.56, 133.79, 125.78, 123.87, 115.92, 114.34, 107.54, 101.17 (t, J 15.8 Hz), 100.03 (dd, J 26.4 Hz, 2.7 Hz), 57.25, 57.01

MS = $[M+H]^+$: Calculated for $C_{22}H_{16}NO_8F_2$: 460.0844. Found: 460.0858. Difference: 3.0 ppm

6.4 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2,6-difluoro-4-methoxybenzoate

Yield: 0.130 g, 30.7 %. RF: 0.417 (1 % ethyl acetate: 99 % dichloromethane).

T_{CrI} 162 °C T_{N_FI} (149 °C)

ν_{max}/cm^{-1}: 1744, 1717, 1638, 1609, 1578, 1532, 1493, 1474, 1456, 1448, 1413, 1348, 1314, 1286, 1251, 1230, 1202, 1146, 1112, 1098, 1083, 1058, 1043, 1025, 968, 954, 877, 839, 811, 772, 760, 745, 679, 644, 625, 605, 586, 577, 515, 456, 421, 411

δ_H/ppm (400 MHz, DMSO-d_6): 8.30 (1 H, dd, J 8.9 Hz, 8.8 Hz, Ar-H), 8.11 (1 H, d, J 8.6 Hz, Ar-H), 7.73 (1 H, dd, J 12.0 Hz, 2.4 Hz, Ar-H), 7.43 (1 H, ddd, J 8.9 Hz, 2.4 Hz, 1.2 Hz, Ar-H), 7.22 (1 H, d, J 2.1 Hz, Ar-H), 7.05 (1 H, dd, J 8.6 Hz, 2.1 Hz, Ar-H), 7.00 (1 H, d, 11.2 Hz, Ar-H), 3.91 (3 H, s, O-$\underline{CH_3}$), 3.90 (3 H, s, O-$\underline{CH_3}$)

δ_F/ppm (376 MHz, DMSO-d_6): -106.37 (2 F, s, Ar-F), -115.41 (1 F, s, Ar-F)

δ_C/ppm (100 MHz, DMSO-d_6): 165.06 (t, J 15.3 Hz), 163.21 (dd, J 255.9 Hz, 8.4 Hz), 162.10, 161.48, 159.05 (t, J 3.1 Hz), 156.06 (d, J 11.1 Hz), 155.77, 155.73 (d, J 262.8 Hz), 135.08 (d, J 7.3 Hz), 133.98, 127.97 (d, J 1.8 Hz), 119.73 (d, J 3.8 Hz), 115.45, 114.36, 113.29 (d, J 23.7 Hz), 107.57, 101.07 (t, J 15.7 Hz), 100.03 (dd, J 26.1 Hz, 2.7 Hz), 57.25, 57.02

MS = $[M+Na]^+$: Calculated for $C_{22}H_{14}NO_8F_3Na$: 500.0569. Found: 500.0571. Difference: 0.4 ppm