The influence of molecular shape and electronic properties on the formation of the ferroelectric nematic phase. [Dataset]

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The influence of molecular shape and electronic properties on the formation of the ferroelectric nematic phase

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Materials and Methods

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).

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.

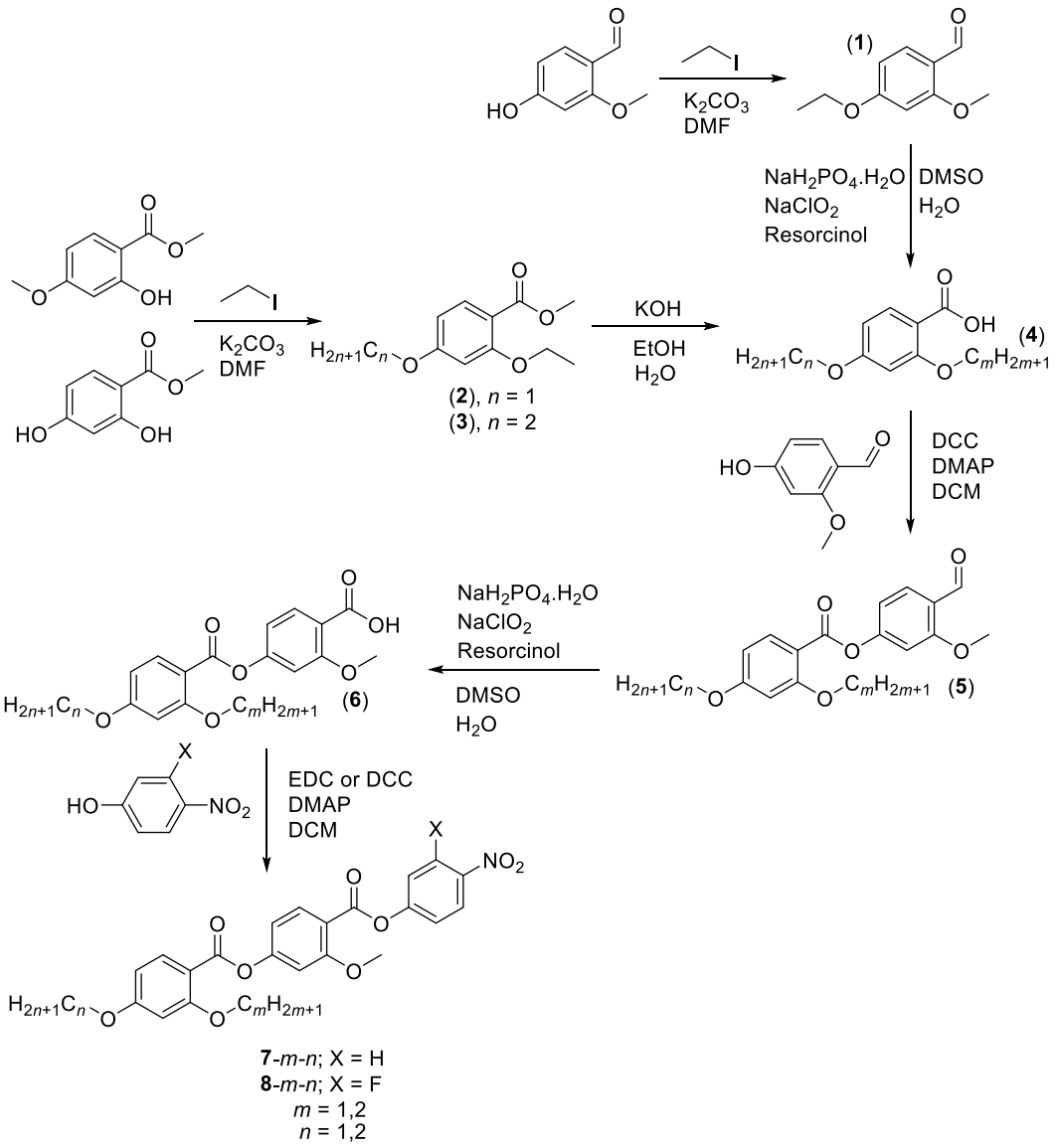
Structure Characterisation

All final products and intermediates that were synthesised were characterised using ^{1}H NMR, ^{19}F 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 with an ATR diamond cell.

High Resolution Mass Spectrometry

In order to determine if the molecular ions of the final products or their adducts were present, high-resolution mass spectrometry was carried out using a Waters XEVO G2 Q-Tof mass spectrometer by Dr. Morag Douglas at the University of Aberdeen.

Synthesis and Analytical Data



4-Methoxy-2-ethoxy-benzaldehyde (1)

To a pre-dried flask flushed with argon and fitted with a condenser, 4-hydroxy-2-methoxybenzaldehyde (1 eq, 5.00 g, 0.0329 mol), and potassium carbonate (2 eq, 9.09 g, 0.0658 mol) were combined in DMF (80 mL). To the mixture, iodoethane (1.05 eq, 2.77 mL, 5.38 g, 0.0345 mol) and stirred at 90°C overnight. The extent of the reaction was monitored by TLC using 100 % dichloromethane (RF value quoted in the product data). The reaction mixture was cooled to room temperature and poured into water (150 mL). The resulting suspension was extracted with ethyl acetate (2 x 250 mL). The organic fractions were combined, washed with water (3 x 100 mL), and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed using vacuum filtration and the solvent evaporated under vacuum to leave an orange solid. The product was carried forwards without any further purification.

Yield: 5.12 g, 86.4 %. RF: 0.189. M.P = 62 °C
ν_{max}/cm^{-1}: 2977, 2862, 2778, 1664, 1598, 1576, 1502, 1473, 1456, 1425, 1398, 1334, 1262, 1207, 1172, 1115, 1096, 1039, 1024, 970, 898, 837, 816, 800, 676, 640, 559, 493, 461.
δ_H/ppm (400 MHz, $CDCl_3$): 10.28 (1 H, s, (C=O)-H), 7.79 (1 H, d, J 8.7 Hz, Ar-H), 6.53 (1 H, dd, J 8.7 Hz, 2.1 Hz, Ar-H), 6.44 (1 H, d, J 2.1 Hz, Ar-H), 4.10 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.89 (3 H, s, O-$\underline{CH_3}$), 1.44 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, $CDCl_3$): 188.34, 165.60, 163.61, 130.76, 118.93, 106.11, 98.39, 63.99, 55.59, 14.66.

Methyl 2-ethoxy-4-methoxy-benzoate (2)

To a pre-dried flask flushed with argon and fitted with a condenser, methyl 4-methoxysilicylate (1 eq, 5.00 g, 0.0274 mol), and potassium carbonate (2 eq, 7.57 g, 0.0548 mol) were combined in DMF (80 mL). To the mixture, iodoethane (1 eq, 2.20 mL, 4.27 g, 0.0274 mol) and stirred at 90°C overnight. The extent of the reaction was monitored by TLC using 40 % ethyl acetate:60 % 40:60 petroleum ether (RF value quoted in the product data). The reaction mixture was cooled to room temperature and poured into water (150 mL). The resulting suspension was extracted with ethyl acetate (2 x 250 mL). The organic fractions were combined, washed with water (3 x 100 mL), and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed using vacuum filtration and the solvent evaporated under vacuum to leave a yellow solid. The product was carried forwards without any further purification.

Yield: 4.36 g, 75.6 %. RF: 0.559. M.P = 47 °C
ν_{max}/cm^{-1}: 2982, 2941, 2842, 1726, 1688, 1669, 1603, 1575, 1505, 1440, 1423, 1393, 1370, 1326, 1256, 1206, 1192, 1132, 1111, 1090, 1029, 982, 970, 893, 847, 822, 770, 728, 695, 652, 625, 585, 540, 469.
δ_H/ppm (400 MHz, $CDCl_3$): 7.83 (1 H, d, J 8.4 Hz, Ar-H), 6.47 (2 H, m, Ar-H), 4.08 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.84 (3 H, s, (C=O)-O-$\underline{CH_3}$), 3.82 (3 H, s, O-$\underline{CH_3}$), 1.46 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, $CDCl_3$): 166.21, 164.09, 160.71, 133.73, 112.65, 104.65, 100.04, 64.60, 55.43, 51.58, 14.66.

Methyl 2,4-diethoxy-benzoate (3)

To a pre-dried flask flushed with argon and fitted with a condenser, methyl 2,4-dihydroxybenzoate (1 eq, 3.00 g, 0.0178 mol), and potassium carbonate (4 eq, 9.84 g, 0.0712 mol) were combined in DMF (80 mL). To the mixture, iodoethane (2 eq, 2.86 mL, 5.55 g, 0.0356 mol) and stirred at 90°C overnight. The extent of the reaction was monitored by TLC using 40 % ethyl acetate:60 % 40:60 petroleum ether (RF value quoted in the product data). The reaction mixture was cooled to room temperature and poured into water (150 mL). The resulting suspension was extracted with ethyl acetate (2 x 250 mL). The organic fractions were combined, washed with water (3 x 100 mL), and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed using vacuum filtration and the solvent evaporated under vacuum to leave a yellow oil. The product was carried forwards without any further purification.

Yield: 3.06 g, 76.7 %. RF: 0.487.
ν_{max}/cm^{-1}: 2982, 2947, 2890, 1724, 1697, 1606, 1573, 1505, 1475, 1439, 1392, 1323, 1296, 1244, 1188, 1140, 1111, 1084, 1037, 1003, 965, 915, 844, 821, 812, 768, 699, 642, 606, 589, 565, 461.
δ_H/ppm (400 MHz, $CDCl_3$): 7.80 (1 H, d, J 9.3 Hz, Ar-H), 6.43 (2 H, m, Ar-H), 4.04 (4 H, m, O-$\underline{CH_2}$-CH_3), 3.82 (3 H, s, (C=O)-O-$\underline{CH_3}$), 3.82 (3 H, s, O-$\underline{CH_3}$), 1.44 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$), 1.44 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, $CDCl_3$): 166.22, 163.50, 160.71, 133.72, 112.43, 105.10, 100.46, 64.56, 63.69, 51.55, 14.68, 14.67.

2-Alkoxy-4-methoxybenzoic acids (4)

4.1 4-Ethoxy-2-methoxybenzoic acid

To a pre-dried flask flushed with argon, **Compound 1** (1 eq, 5.12 g, 0.0284 mol) and resorcinol (1.5 eq, 4.69 g, 0.0426 mol) were solubilised in DMSO (120 mL). Sodium chlorite (4 eq, 10.31 g, 0.114 mol) and sodium hydrogen phosphate monohydrate (3.5 eq, 13.72 g, 0.994 mol) were solubilised in water (90 mL) before being slowly poured into the reaction flask and the resultant mixture was stirred at room temperature overnight. 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 (50 mL). An orange solid precipitated after acidification and was collected by vacuum filtration. The product was carried forwards without any further purification.

Yield: 4.69 g, 84.2 %. RF: 0.048. M.P = 128 °C
ν_{max}/cm^{-1}: 2943, 2891, 1666, 1615, 1569, 1507, 1454, 1428, 1396, 1274, 1253, 1203, 1164, 1113, 1095, 1035, 976, 918, 882, 819, 792, 762, 689, 639, 564, 429.
δ_H/ppm (400 MHz, DMSO-d_6): 12.08 (1 H, s, OH), 7.69 (1 H, d, J 8.6 Hz, Ar-H), 6.59 (1 H, d, J 2.2 Hz, Ar-H), 6.55 (1 H, dd, J 8.6 Hz, 2.2 Hz, Ar-H), 4.09 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.80 (3 H, s, O-$\underline{CH_3}$), 1.33 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 166.86, 163.41, 161.07, 133.74, 112.92, 105.89, 99.73, 63.95, 56.20, 14.97.

4.2 2-Ethoxy-4-methoxybenzoic acid and 4.3 2,4-Diethoxybenzoic acid

To a pre-dried flask flushed with argon and fitted with a condenser, potassium hydroxide (3 eq) was added to water. **Compound 2/3** (1 eq) was solubilised in EtOH, added to the flask and the resultant mixture stirred at reflux overnight. The quantities of the reagents used in each reaction are listed in **Table 1**. 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 cooled to room temperature and the pH of the mixture was adjusted to 1 using 32% hydrochloric acid (25 mL) and a white solid precipitated. The solid was collected by vacuum filtration and the product was carried forwards without any further purification.

Table 1. Quantities of reagents used in the syntheses of the 2-alkoxy-4-methoxybenzoic acids.

m	*n*	(**1**)	Ethanol	Potassium Hydroxide	Water

2	1	5.00 g, 0.0238 mol	50 mL	4.00 g, 0.0714 mol	30 mL
2	2	10.5 g, 0.0468 mol	80 mL	7.85 g, 0.140 mol	100 mL

4.2 2-Ethoxy-4-methoxybenzoic acid

Yield: 4.30 g, 92.0 %. RF: 0.306 (40 % ethyl acetate:60 % 40:60 petroleum ether). M.P = 121 °C

ν_{max}/cm^{-1}: 2985, 2874, 1666, 1613, 1569, 1506, 1451, 1413, 1386, 1311, 1275, 1254, 1202, 1174, 1150, 1114, 1094, 1034, 918, 890, 831, 815, 793, 765, 736, 690, 632, 616, 578, 490, 464, 410.

δ_H/ppm (400 MHz, DMSO-d_6): 12.07 (1 H, s, OH), 7.68 (1 H, d, J 8.6 Hz, Ar-H), 6.59 (1 H, d, J 2.2 Hz, Ar-H), 6.56 (1 H, dd, J 8.6 Hz, 2.2 Hz, Ar-H), 4.08 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.80 (3 H, s, O-$\underline{CH_3}$), 1.32 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 166.97, 163.96, 160.22, 133.60, 113.52, 105.72, 100.24, 64.58, 55.92, 14.97.

4.3 2,4-Diethoxybenzoic acid

Yield: 9.02 g, 91.7 %. RF: 0.030 (20 % ethyl acetate:80 % 40:60 petroleum ether). M.P = 106 °C

ν_{max}/cm^{-1}: 3258, 2985, 1725, 1608, 1577, 1506, 1477, 1444, 1398, 1326, 1288, 1260, 1234, 1190, 1153, 1125, 1108, 1086, 1041, 1026, 1001, 913, 850, 834, 814, 770, 734, 706, 684, 646, 595, 571, 532, 462, 436.

δ_H/ppm (400 MHz, DMSO-d_6): 12.05 (1 H, s, OH), 7.67 (1 H, d, J 8.5 Hz, Ar-H), 6.57 (1 H, d, J 2.2 Hz, Ar-H), 6.54 (1 H, dd, J 8.5 Hz, 2.2 Hz, Ar-H), 4.07 (4 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 1.32 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 166.96, 163.26, 160.21, 133.62, 113.35, 106.04, 100.63, 64.54, 63.91, 14.98, 14.96.

4-Formyl-3-methoxyphenyl 2-alkoxy-4-alkoxybenzoates (5)

To a pre-dried flask flushed with argon, **Compound 4** (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 (20 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 2**. 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 (volumes used are listed in **Table 2**).

Table 2. Quantities of reagents used in the syntheses of the 4-formyl-3-methoxyphenyl 2-alkoxy-4-alkoxybenzoates.

m	*n*	(**4**)	4-Hydroxy-2-methoxybenzaldehyde	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide	Ethanol

1	1	3.00 g, 0.0164 mol	2.75 g, 0.0275 mol	0.260 g, 2.13×10^{-3} mol	4.39 g, 0.0213 mol	400 mL
1	2	1.80 g, 9.17×10^{-3} mol	1.54 g, 0.0101 mol	0.145 g, 1.19×10^{-3} mol	2.46 g, 0.0119 mol	200 mL
2	1	2.00 g, 0.0102 mol	1.70 g, 0.0112 mol	0.162 g, 1.33×10^{-3} mol	2.74 g, 0.0133 mol	250 mL
2	2	3.00 g, 0.0143 mol	2.39 g, 0.0157 mol	0.227 g, 1.86×10^{-3} mol	3.84 g, 0.0186 mol	250 mL

5.1 4-Formyl-3-methoxyphenyl 2,4-dimethoxybenzoate

White solid. Yield: 4.30 g, 82.9 %. RF: 0.400 (40 % ethyl acetate:60 % 40:60 petroleum ether). M.P = 169 °C

ν_{max}/cm^{-1}: 2976, 2861, 1738, 1638, 1607, 1574, 1509, 1495, 1454, 1416, 1393, 1306, 1272, 1233, 1215, 1196, 1156, 1102, 1044, 1020, 870, 821, 795, 756, 740, 684, 670, 633, 612, 559, 527, 465, 412.

δ_H/ppm (400 MHz, $CDCl_3$): 10.41 (1 H, s, (C=O)-H), 8.07 (1 H, d, J 8.7 Hz, Ar-H), 7.88 (1 H, d, J 8.4 Hz, Ar-H), 6.91 (1 H, d, J 2.0 Hz, Ar-H), 6.87 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 6.57 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.54 (1 H, d, J 2.3 Hz, Ar-H), 3.93 (3 H, s, O-$\underline{CH_3}$), 3.92 (3 H, s, O-$\underline{CH_3}$), 3.90 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 188.77, 165.36, 162.81, 162.72, 162.52, 157.38, 134.65, 129.79, 122.40, 114.51, 110.42, 105.95, 104.97, 99.03, 56.07, 55.91, 55.64.

5.2 4-Formyl-3-methoxyphenyl 4-ethoxy-2-methoxybenzoate

Off-white solid. Yield: 2.14 g, 70.6 %. RF: 0.242 (20 % ethyl acetate:80 % 40:60 petroleum ether). M.P = 135 °C

ν_{max}/cm^{-1}: 2872, 1739, 1684, 1608, 1571, 1509, 1494, 1459, 1414, 1395, 1310, 1265, 1234, 1213, 1197, 1177, 1156, 1103, 1050, 1039, 1022, 977, 880, 864, 827, 819, 795, 757, 746, 686, 674, 646, 618, 563, 534, 486, 464, 416.

δ_H/ppm (400 MHz, $CDCl_3$): 10.41 (1 H, s, (C=O)-H), 8.07 (1 H, d, J 8.7 Hz, Ar-H), 7.88 (1 H, d, J 8.4 Hz, Ar-H), 6.91 (1 H, d, J 2.0 Hz, Ar-H), 6.87 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 6.57 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.54 (1 H, d, J 2.3 Hz, Ar-H), 4.13 (2 H, q, J 6.9 Hz, O-$\underline{CH_2}$-CH_3), 3.92 (6 H, s, O-$\underline{CH_3}$), 1.46 (3 H, t, J 6.9 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 188.77, 164.79, 162.80, 162.72, 162.53, 157.41, 134.64, 129.77, 122.37, 114.52, 110.18, 105.96, 105.38, 99.45, 63.98, 56.04, 55.90, 14.67.

5.3 4-Formyl-3-methoxyphenyl 2-ethoxy-4-methoxybenzoate

White solid. Yield: 2.78 g, 82.5 %. RF: 0.388 (40 % ethyl acetate:60 % 40:60 petroleum ether). M.P = 160 °C

ν_{max}/cm^{-1}: 2872, 1743, 1682, 1608, 1571, 1508, 1475, 1446, 1431, 1417, 1390, 1265, 1235, 1207, 1174, 1158, 1103, 1040, 1020, 963, 870, 817, 796, 755, 735, 684, 669, 635, 610, 575, 526, 495, 462.

δ_H/ppm (400 MHz, $CDCl_3$): 10.41 (1 H, s, (C=O)-H), 8.04 (1 H, d, J 8.7 Hz, Ar-H), 7.88 (1 H, d, J 8.2 Hz, Ar-H), 6.89 (2 H, m, Ar-H), 6.56 (1 H, dd, 8.8 Hz, 2.3 Hz, Ar-H), 6.51 (1 H, d, 8.8 Hz, Ar-

H), 4.13 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.92 (3 H, s, O-$\underline{CH_3}$), 3.88 (3 H, s, O-$\underline{CH_3}$), 1.48 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, $CDCl_3$): 188.76, 165.21, 162.98, 162.83, 161.84, 157.47, 134.54, 129.82, 122.38, 114.53, 110.70, 105.94, 105.04, 99.89, 64.67, 55.89, 55.60, 14.67.

5.4 4-Formyl-3-methoxyphenyl 2,4-diethoxybenzoate
White solid. Yield: 3.81 g, 77.4 %. RF: 0.212 (100 % dichloromethane). M.P = 109 °C
ν_{max}/cm^{-1}: 2986, 2876, 1740, 1682, 1606, 1569, 1508, 1476, 1454, 1444, 1436, 1391, 1308, 1272, 1263, 1232, 1197, 1156, 1102, 1042, 1020, 948, 915, 876, 863, 844, 818, 797, 757, 740, 686, 674, 645, 617, 606, 579, 531, 488, 463, 414.
δ_H/ppm (400 MHz, $CDCl_3$): 10.40 (1 H, s, (C=O)-H), 8.02 (1 H, d, J 8.7 Hz, Ar-H), 7.87 (1 H, d, J 8.3 Hz, Ar-H), 6.87 (2 H, m, Ar-H), 6.53 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.50 (1 H, d, J 2.3 Hz, Ar-H), 4.11 (4 H, m, O-$\underline{CH_2}$-CH_3), 3.92 (3 H, s, O-$\underline{CH_3}$), 1.46 (6 H, m, O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, $CDCl_3$): 188.76, 164.64, 162.98, 162.83, 161.85, 157.50, 134.52, 129.80, 122.35, 114.54, 110.46, 105.94, 105.47, 100.30, 64.62, 63.92, 55.88, 14.68, 14.67.

4-((2-Alkoxy-4-alkoxybenzoyl)oxy)-2-methoxybenzoic acid (6)

To a pre-dried flask flushed with argon, **Compound 5** (1 eq) and resorcinol (1.5 eq) were solubilised in DMSO (80 mL). Sodium chlorite (4 eq) and sodium hydrogen phosphate monohydrate (3.5 eq) were solubilised in water (60 mL) before being slowly poured 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 3**. 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 3. Quantities of reagents used in the syntheses of the 4-((2-alkoxy-4-alkoxybenzoyl)oxy)-2-methoxybenzoic acids.

m	*n*	(**5**)	Sodium Chlorite	Sodium Hydrogen Phosphate Monohydrate	Resorcinol
1	1	2.30 g, 7.27×10^{-3} mol	2.63 g, 0.0291 mol	3.05 g, 0.0254 mol	1.20 g, 0.0109 mol
1	2	2.00 g, 6.05×10^{-3} mol	2.19 g, 0.0242 mol	2.93 g, 0.0212 mol	1.00 g, 9.08×10^{-3} mol
2	1	1.40 g, 4.24×10^{-3} mol	1.54 g, 0.0170 mol	2.04 g, 0.0148 mol	0.700 g, 6.36×10^{-3} mol
2	2	1.90 g, 5.52×10^{-3} mol	2.00 g, 0.0221 mol	2.66 g, 0.0193 mol	0.912 g, 8.28×10^{-3} mol

6.1 4-((2,4-Dimethoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 2.30 g, 95.2 %. RF: 0.024 (100 % ethyl acetate). M.P = 171 °C

ν_{max}/cm^{-1}: 2990, 1732, 1716, 1609, 1587, 1568, 1508, 1453, 1417, 1404, 1304, 1282, 1210, 1185, 1154, 1118, 1078, 1043, 1017, 869, 826, 803, 769, 754, 741, 678, 649, 612, 578, 549, 524, 463, 427.

δ_H/ppm (400 MHz, DMSO-d_6): 12.59 (1 H, s, OH), 7.97 (1 H, d, J 8.7 Hz, Ar-H), 7.73 (1 H, d, J 8.4 Hz, Ar-H), 7.01 (1 H, d, J 2.0 Hz, Ar-H), 6.85 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 6.72 (1 H, d, J 2.2 Hz, Ar-H), 6.68 (1 H, dd, J 8.7 Hz, 2.2 Hz, Ar-H), 3.88 (3 H, s, O-$\underline{CH_3}$), 3.87 (3 H, s, O-$\underline{CH_3}$), 3.82 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.05, 165.36, 162.89, 162.20, 159.91, 154.99, 134.51, 132.29, 118.74, 114.20, 110.38, 107.32, 106.14, 99.46, 56.55, 56.47, 56.19.

6.2 4-((4-Ethoxy-2-methoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 1.57 g, 74.9 %. RF: 0.020 (100 % dichloromethane). M.P = 159 °C

ν_{max}/cm^{-1}: 2979, 2906, 1735, 1701, 1673, 1607, 1582, 1569, 1504, 1469, 1406, 1306, 1235, 1205, 1189, 1149, 1119, 1079, 1050, 1034, 1016, 871, 826, 804, 775, 759, 688, 666, 649, 611, 579, 555, 525, 463, 427.

δ_H/ppm (400 MHz, DMSO-d_6): 12.60 (1 H, s, OH), 7.96 (1 H, d, J 8.7 Hz, Ar-H), 7.72 (1 H, d, J 8.4 Hz, Ar-H), 7.01 (1 H, d, J 2.0 Hz, Ar-H), 6.84 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 6.69 (1 H, d, J 2.2 Hz, Ar-H), 6.66 (1 H, dd, J 8.7 Hz, 2.2 Hz, Ar-H), 4.16 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.86 (3 H, s, O-$\underline{CH_3}$), 3.81 (3 H, s, O-$\underline{CH_3}$), 1.36 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.07, 164.65, 162.88, 162.20, 159.90, 154.98, 134.54, 132.28, 118.79, 114.20, 110.23, 107.31, 106.38, 99.87, 64.23, 56.55, 56.44, 14.93.

6.3 4-((2-Ethoxy-4-methoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 1.31 g, 89.2 %. RF: 0.028 (40 % ethyl acetate:60 % 40:60 petroleum ether). M.P = 197 °C

ν_{max}/cm^{-1}: 3446, 2989, 1745, 1723, 1694, 1668, 1611, 1569, 1508, 1464, 1433, 1406, 1391, 1331, 1307, 1240, 1205, 1189, 1158, 1136, 1114, 1092, 1041, 1028, 1015 ,964, 871, 854, 816, 800, 772, 757, 745, 736, 686, 663, 608, 594, 562, 525, 463, 444.

δ_H/ppm (400 MHz, DMSO-d_6): 12.62 (1 H, s, OH), 7.94 (1 H, d, J 8.7 Hz, Ar-H), 7.73 (1 H, d, J 8.4 Hz, Ar-H), 7.00 (1 H, d, J 2.0 Hz, Ar-H), 6.85 (1 H, dd, J 8.4 Hz, 2.0 Hz, Ar-H), 6.67 (2 H, m, Ar-H), 4.14 (2 H, q, J 6.9 Hz, O-$\underline{CH_2}$-CH_3), 3.86 (3 H, s, O-$\underline{CH_3}$), 3.82 (3 H, s, O-$\underline{CH_3}$), 1.35 (3 H, t, J 6.9 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.06, 165.20, 163.07, 161.44, 159.91, 155.04, 134.36, 132.32, 118.74, 114.14, 110.72, 107.20, 106.64, 100.26, 64.71, 56.53, 56.15, 14.92.

6.4 4-((2,4-Ethoxybenzoyl)oxy)-2-methoxybenzoic acid

Yield: 1.29 g, 64.9 %. RF: 0.028 (40 % ethyl acetate:60 % 40:60 petroleum ether). M.P = 138 °C

ν_{max}/cm^{-1}: 2983, 2886, 1730, 1701, 1658, 1596, 1568, 1499, 1473, 1434, 1404, 1389, 1329, 1294, 1237, 1203, 1162, 1127, 1071, 1040, 1024, 953, 918, 848, 831, 807, 781, 760, 687, 674, 643, 589, 567, 528, 472, 436.

δ_H/ppm (400 MHz, DMSO-d_6): 12.62 (1 H, s, OH), 7.93 (1 H, d, J 8.6 Hz, Ar-H), 7.73 (1 H, d, J 8.5 Hz, Ar-H), 7.00 (1 H, d, J 2.0 Hz, Ar-H), 6.85 (1 H, dd, J 8.5 Hz, 2.0 Hz, Ar-H), 6.65 (2 H, m, Ar-H), 4.13 (4 H, m, O-$\underline{CH_2}$-CH_3), 3.82 (3 H, s, O-$\underline{CH_3}$), 1.35 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.06, 164.50, 163.05, 161.44, 159.92, 155.06, 134.39, 132.32, 118.71, 114.14, 110.56, 107.20, 106.45, 100.64, 64.66, 64.18, 56.53, 14.92, 14.91.

3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2-alkoxy-4-alkoxybenzoates (7-m-n)

To a pre-dried flask flushed with argon and kept in an ice bath in order to maintain the temperature at 0°C, **Compound 6** (1 eq), 4-nitrophenol (1.5 eq) and 4-dimethylaminopyridine (0.15 eq) were added. The solids were solubilised with dichloromethane (30 mL) and stirred for 10 min before *N,N'*-dicyclohexylcarbodiimide (1.5 eq) or *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq for *m* = 1, *n* = 1 and *m* = 2, *n* = 1) was added to the flask. The quantities of the reagents used in each reaction are listed in **Table 4**. The temperature of the reaction mixture was increased to room temperature and the reaction was allowed to proceed overnight. For the reactions with *N,N'*-dicyclohexylcarbodiimide, 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 (50 mL, 100 mL for *m* = 2, *n* = 1).

Table 4. Quantities of reagents used in the syntheses of the 3-methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2-alkoxy-4-alkoxybenzoates.

m	*n*	(**6**)	4-Nitrophenol	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide/ N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
1	1	0.300 g, 9.03×10^{-4} mol	0.188 g, 1.35×10^{-3} mol	0.016 g, 1.35×10^{-4} mol	0.259 g, 1.35×10^{-3} mol
1	2	0.300 g, 8.66×10^{-4} mol	0.181 g, 1.30×10^{-3} mol	0.016 g, 1.30×10^{-4} mol	0.268 g, 1.30×10^{-3} mol
2	1	0.600 g, 1.73×10^{-3} mol	0.361 g, 2.60×10^{-3} mol	0.032 g, 2.60×10^{-4} mol	0.498 g, 2.60×10^{-3} mol
2	2	0.300 g, 8.33×10^{-4} mol	0.174 g, 1.25×10^{-3} mol	0.015 g, 1.25×10^{-4} mol	0.258 g, 1.25×10^{-3} mol

7.1 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2,4-dimethoxybenzoate (7-1-1)

Yield: 0.163 g, 39.8 %. RF: 0.553 (2 % ethyl acetate: 98 % dichloromethane).

T_{CrI} 169 °C T_{N_FI} (104 °C)

ν_{max}/cm^{-1}: 2947, 1757, 1741, 1607, 1580, 1516, 1491, 1463, 1440, 1408, 1353, 1336, 1271, 1216, 1202, 1167, 1136, 1124, 1090, 1028, 1007, 942, 865, 827, 759, 743, 719, 687, 650, 611, 601, 541, 497, 462.

δ_H/ppm (400 MHz, $CDCl_3$): 8.31 (2 H, d, J 9.1 Hz, Ar-H), 8.11 (2 H, m, Ar-H), 7.41 (2 H, d, J 9.1 Hz, Ar-H), 6.97 (1 H, d, J 2.1 Hz, Ar-H), 6.94 (1 H, dd, J 8.5 Hz, 2.1 Hz, Ar-H), 6.58 (1 H, dd, J 8.8 Hz, 2.3 Hz, Ar-H), 6.55 (1 H, d, 2.3 Hz, Ar-H), 3.95 (3 H, s, O-$\underline{CH_3}$), 3.94 (3 H, s, O-$\underline{CH_3}$), 3.91 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 165.43, 162.67, 162.57, 162.46, 161.67, 156.76, 155.85, 145.25, 134.67, 133.62, 125.17, 122.77, 114.63, 114.02, 110.31, 106.64, 105.02, 99.02, 56.33, 56.09, 55.65.

MS = $[M+Na]^+$: Calculated for $C_{23}H_{19}NO_9Na$: 476.0958. Found: 476.0954. Difference: 0.8 ppm

7.2 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 4-ethoxy-2-methoxybenzoate (7-1-2)

Yield: 0.060 g, 14.8 %. RF: 0.275 (40 % ethyl acetate:60 % 40:60 petroleum ether).

T_{CrI} 134 °C T_{N_FI} (97 °C)

ν_{max}/cm^{-1}: 3088, 2978, 1758, 1746, 1610, 1567, 1519, 1487, 1456, 1439, 1416, 1390, 1343, 1299, 1270, 1238, 1206, 1189, 1164, 1145, 1130, 1110, 1055, 1039, 1010, 944, 863, 843, 832, 821, 802, 758, 748, 693, 672, 654, 631, 618, 584, 522, 496, 471, 406.

δ_H/ppm (400 MHz, $CDCl_3$): 8.31 (2 H, d, J 9.1 Hz, Ar-H), 8.11 (1 H, d, J 8.5 Hz, Ar-H), 8.08 (1 H, d, J 8.5 Hz, Ar-H), 7.41 (2 H, d, J 9.1 Hz, Ar-H), 6.97 (1 H, d, J 2.1 Hz, Ar-H), 6.93 (1 H, dd, J 8.5 Hz, 2.2 Hz, Ar-H), 6.56 (2 H, m, Ar-H), 4.14 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.95 (3 H, s, O-$\underline{CH_3}$), 3.94 (3 H, s, O-$\underline{CH_3}$), 1.47 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 164.85, 162.68, 162.58, 162.46, 161.67, 156.79, 155.86, 145.25, 134.66, 133.61, 125.17, 122.77, 114.60, 114.02, 110.08, 106.64, 105.41, 99.45, 64.01, 56.32, 56.07, 14.67.

MS = $[M+Na]^+$: Calculated for $C_{24}H_{21}NO_9Na$: 490.1114. Found: 490.1097. Difference: 3.5 ppm

7.3 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2-ethoxy-4-methoxybenzoate (7-2-1)

Yield: 0.271 g, 33.5 %. RF: 0.108 (10 % ethyl acetate:90 % 40:60 petroleum ether).

T_{CrI} 145 °C T_{N_FI} (81 °C)

ν_{max}/cm^{-1}: 2981, 1749, 1707, 1610, 1574, 1514, 1452, 1440, 1398, 1343, 1328, 1307, 1289, 1266, 1239, 1201, 1188, 1177, 1163, 1122, 1039, 1014, 949, 881, 865, 845, 814, 760, 753, 743, 687, 675, 641, 622, 593, 579, 541, 526, 498, 467.

δ_H/ppm (400 MHz, DMSO-d_6): 8.35 (2 H, d, J 9.1 Hz, Ar-H), 8.08 (1 H, d, J 8.5 Hz, Ar-H), 7.97 (1 H, d, J 8.7 Hz, Ar-H), 7.59 (2 H, d, J 9.1 Hz, Ar-H), 7.16 (1 H, d, J 2.0 Hz, Ar-H), 7.00 (1 H, dd, J 8.5 Hz, 2.0 Hz, Ar-H), 6.69 (2 H, m, Ar-H), 4.16 (2 H, q, J 6.9 Hz, O-$\underline{CH_2}$-CH_3), 3.90 (3 H, s, O-$\underline{CH_3}$), 3.87 (3 H, s, O-$\underline{CH_3}$), 1.36 (3 H, t, J 6.9 Hz, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 165.34, 162.82, 162.70, 161.58, 161.28, 156.70, 156.01, 145.52, 134.48, 133.62, 125.77, 123.87, 115.16, 114.61, 110.48, 107.64, 106.26, 100.26, 64.74, 56.91, 56.18, 14.92.

MS = $[M+H]^+$: Calculated for $C_{24}H_{22}NO_9$: 468.1295. Found: 468.1310. Difference: 3.2 ppm

7.4 3-Methoxy-4-((4-nitrophenoxy)carbonyl)phenyl 2,4-ethoxybenzoate (7-2-2)

Yield: 0.090 g, 22.4 %. RF: 0.231 (5 % tetrahydrofuran: 10 % ethyl acetate: 85 % 40:60 petroleum ether).

T_{CrI} 130 °C T_{N_FI} (79 °C)

ν_{max}/cm^{-1}: 2986, 1759, 1741, 1608, 1586, 1567, 1517, 1489, 1463, 1449, 1437, 1409, 1391, 1343, 1305, 1284, 1267, 1230, 1195, 1186, 1162, 1147, 1124, 1112, 1051, 1029, 1004, 948, 882, 864 ,841, 826, 758, 747, 687, 675, 653, 630, 613, 594, 527, 505, 462, 409.

δ_H/ppm (400 MHz, DMSO-d_6): 8.35 (2 H, d, J 9.1 Hz, Ar-H), 8.08 (1 H, d, J 8.6 Hz, Ar-H), 7.96 (1 H, d, J 8.6 Hz, Ar-H), 7.59 (2 H, d, J 9.1 Hz, Ar-H), 7.16 (1 H, d, J 2.1 Hz, Ar-H), 7.00 (1 H, dd, J 8.6 Hz, 2.1 Hz, Ar-H), 6.67 (2 H, m, Ar-H), 4.15 (4 H, m, O-$\underline{CH_2}$-CH_3), 3.89 (3 H, s, O-$\underline{CH_3}$), 1.36 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 164.64, 162.80, 162.70, 161.57, 161.28, 156.72, 156.01, 145.52, 134.51, 133.62, 125.77, 123.86, 115.13, 114.61, 110.31, 107.63, 106.52, 100.64, 64.69, 64.22, 56.91, 14.93, 14.92.

MS = $[M+Na]^+$: Calculated for $C_{25}H_{23}NO_9Na$: 504.1271. Found: 504.1291. Difference: 4.0 ppm

3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2-alkoxy-4-alkoxybenzoates (8-m-n)

To a pre-dried flask flushed with argon and kept in an ice bath in order to maintain the temperature at 0 °C, **Compound 6** (1 eq), 3-fluoro-4-nitrophenol (1.2 eq, 1.5 eq for *m* = 1, *n* = 1 and *m* = 2, *n* = 2) and *N,N'*-dicyclohexylcarbodiimide (1.5 eq) or *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq for *m* = 2, *n* = 2) 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 5**. The temperature of the reaction mixture was increased to room temperature and the reaction was allowed to proceed overnight. For the reactions with *N,N'*-dicyclohexylcarbodiimide, 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 (50 mL).

Table 5. Quantities of reagents used in the syntheses of the 3-methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2-alkoxy-4-alkoxybenzoates.

m	*n*	(**6**)	3-Fluoro-4-nitrophenol	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide/ N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
1	1	0.300 g, 9.03×10^{-4} mol	0.212 g, 1.35×10^{-3} mol	0.016 g, 1.35×10^{-4} mol	0.279 g, 1.35×10^{-3} mol

1	2	0.300 g, 8.66×10^{-4} mol	0.163 g, 1.04×10^{-3} mol	0.016 g, 1.30×10^{-4} mol	0.268 g, 1.30×10^{-3} mol
2	1	0.300 g, 8.66×10^{-4} mol	0.163 g, 1.04×10^{-3} mol	0.016 g, 1.30×10^{-4} mol	0.268 g, 1.30×10^{-3} mol
2	2	0.300 g, 8.33×10^{-4} mol	0.196 g, 1.25×10^{-3} mol	0.015 g, 1.25×10^{-4} mol	0.240 g, 1.25×10^{-3} mol

8.1 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2,4-dimethoxybenzoate (8-1-1)

Yield: 0.103 g, 24.2 %. RF: 0.500 (2 % ethyl acetate: 98 % dichloromethane).

T_{Crl} 204 °C T_{N_Fl} (99 °C)

ν_{max}/cm^{-1}: 2947, 1757, 1741, 1607, 1580, 1516, 1491, 1463, 1440, 1408, 1353, 1336, 1271, 1216, 1202, 1167, 1136, 1124, 1090, 1028, 1007, 942, 865, 827, 759, 743, 719, 687, 650, 611, 601, 541, 497, 462.

δ_H/ppm (400 MHz, DMSO-d_6): 8.18 (1 H, t, J 8.7 Hz, Ar-H), 8.09 (2 H, d, J 8.6 Hz, Ar-H), 7.28 (1 H, dd, J 11.4 Hz, 2.4 Hz, Ar-H), 7.21 (1 H, m, Ar-H), 6.97 (1 H, d, J 2.1 Hz, Ar-H), 6.94 (1 H, dd, J 8.6 Hz, 2.1 Hz, Ar-H), 6.58 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.55 (1 H, d, J 2.3 Hz, Ar-H), 3.96 (3 H, s, O-$\underline{CH_3}$), 3.95 (3 H, s, O-$\underline{CH_3}$), 3.91 (3 H, s, O-$\underline{CH_3}$).

δ_F/ppm (376 MHz, DMSO-d_6): -115.42 (s, Ar-F).

δ_C/ppm (100 MHz, DMSO-d_6): 165.06, 162.17, 161.90, 161.72, 161.03, 156.40, 155.73 (d, J 11.4 Hz), 153.99 (d, J 262.4 Hz), 134.59 (d, J 7.1 Hz) 134.19, 133.33, 127.51 (d, J 1.1 Hz), 119.27 (d, J 4.0 Hz), 114.28, 114.27, 112.84 (d, J 23.3 Hz), 109.66, 107.34, 105.77, 99.01, 56.49, 56.04, 55.77.

MS = $[M+Na]^+$: Calculated for $C_{23}H_{18}FNO_8Na$: 494.0863. Found: 494.0875. Difference: 2.4 ppm

8.2 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 4-ethoxy-2-methoxybenzoate (8-1-2)

Yield: 0.040 g, 9.5 %. RF: 0.105 (100 % dichloromethane).

T_{Crl} 131 °C T_{N_Fl} (86 °C)

ν_{max}/cm^{-1}: 2981, 1740, 1710, 1604, 1574, 1521, 1469, 1450, 1412, 1354, 1337, 1287, 1272, 1209, 1193, 1146, 1124, 1114, 1093, 1003, 971 ,947, 886, 870, 843, 814, 755, 744, 687, 673, 651, 619, 544, 461.

δ_H/ppm (400 MHz, DMSO-d_6): 8.30 (1 H, t, J 9.0 Hz, Ar-H), 8.08 (1 H, d, J 8.6 Hz, Ar-H), 7.97 (1 H, d, J 8.7 Hz, Ar-H), 7.72 (1 H, dd, J 12.0 Hz, 2.4 Hz, Ar-H), 7.43 (1 H, d, J 9.0 Hz, Ar-H), 7.16 (1 H, d, J 2.0 Hz, Ar-H), 7.00 (1 H, dd, J 8.6 Hz, 2.0 Hz, Ar-H), 6.69 (2 H, m, Ar-H), 4.16 (2 H, q, J 6.9 Hz, O-$\underline{CH_2}$-CH_3),4.14 (2 H, q, J 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.95 (3 H, s, O-$\underline{CH_3}$), 3.94 (3 H, s, O-$\underline{CH_3}$), 1.47 (3 H, t, J 7.0 Hz, O-CH_2-$\underline{CH_3}$).

δ_F/ppm (376 MHz, DMSO-d_6): -115.43 (s, Ar-F).

δ_C/ppm (100 MHz, DMSO-d_6): 164.35, 162.14, 161.89, 161.70, 161.02, 156.40, 155.67 (d, J 11.4 Hz), 153.98 (d, J 264.0 Hz), 134.58 (d, J 7.2 Hz), 134.21, 133.32, 127.49 (d, J 1.6 Hz), 119.27 (d, J 3.7 Hz), 114.26, 114.24, 112.83 (d, J 23.7 Hz), 109.50, 107.33, 105.99, 99.42, 63.81, 56.48, 56.01, 14.46.

MS = $[M+Na]^+$: Calculated for $C_{24}H_{20}FNO_9Na$: 508.1020. Found: 508.1035. Difference: 3.0 ppm

8.3 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2-ethoxy-4-methoxybenzoate (8-2-1)

Yield: 0.145 g, 34.5 %. RF: 0.182 (100 % dichloromethane).

T_{CrI} 174 °C T_{N_FI} (82 °C)

ν_{max}/cm^{-1}: 2949, 1759, 1745, 1608, 1576, 1522, 1482, 1455, 1409, 1394, 1351, 1332, 1267, 1212, 1195, 1169, 1152, 1134, 1122, 1090, 1025, 1001, 984, 947, 892, 866, 841, 812, 757, 744, 684, 611, 577, 545, 527, 467.

δ_H/ppm (400 MHz, DMSO-d_6): 8.30 (1 H, t, J 9.0 Hz, Ar-H), 8.08 (1 H, d, J 8.6 Hz, Ar-H), 7.97 (1 H, d, J 8.7 Hz, Ar-H), 7.72 (1 H, dd, J 12.0 Hz, 2.4 Hz, Ar-H), 7.43 (1 H, m, Ar-H), 7.16 (1 H, d, J 2.0 Hz, Ar-H), 7.00 (1 H, dd, J 8.6 Hz, 2.0 Hz, Ar-H), 6.69 (2 H, m, Ar-H), 4.16 (2 H, q, J 6.9 Hz, O-$\underline{CH_2}$-CH_3), 3.89 (3 H, s, O-$\underline{CH_3}$), 3.87 (3 H, s, O-$\underline{CH_3}$), 1.37 (3 H, t, J 6.9 Hz, O-CH_2-$\underline{CH_3}$).

δ_F/ppm (376 MHz, DMSO-d_6): -115.42 (s, Ar-F).

δ_C/ppm (100 MHz, DMSO-d_6): 164.90, 162.33, 161.71, 161.14, 161.02, 156.44, 155.67 (d, J 11.2 Hz), 153.99 (d, J 263.3 Hz), 134.58 (d, J 6.9 Hz), 134.03, 133.35, 127.50 (d, J 2.0 Hz), 119.27 (d, J 3.7 Hz), 114.23, 114.17, 112.83 (d, J 23.8 Hz), 109.98, 107.20, 105.80, 99.80, 64.28, 56.46, 55.72, 14.45.

MS = $[M+H]^+$: Calculated for $C_{24}H_{20}FNO_9Na$: 508.1020. Found: 508.1036. Difference: 3.1 ppm

8.4 3-Methoxy-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl 2,4-ethoxybenzoate (8-2-2)

Yield: 0.080 g, 19.2 %. RF: 0.314 (5 % tetrahydrofuran: 10 % ethyl acetate: 85 % 40:60 petroleum ether).

T_{CrI} 133 °C T_{N_FI} (76 °C)

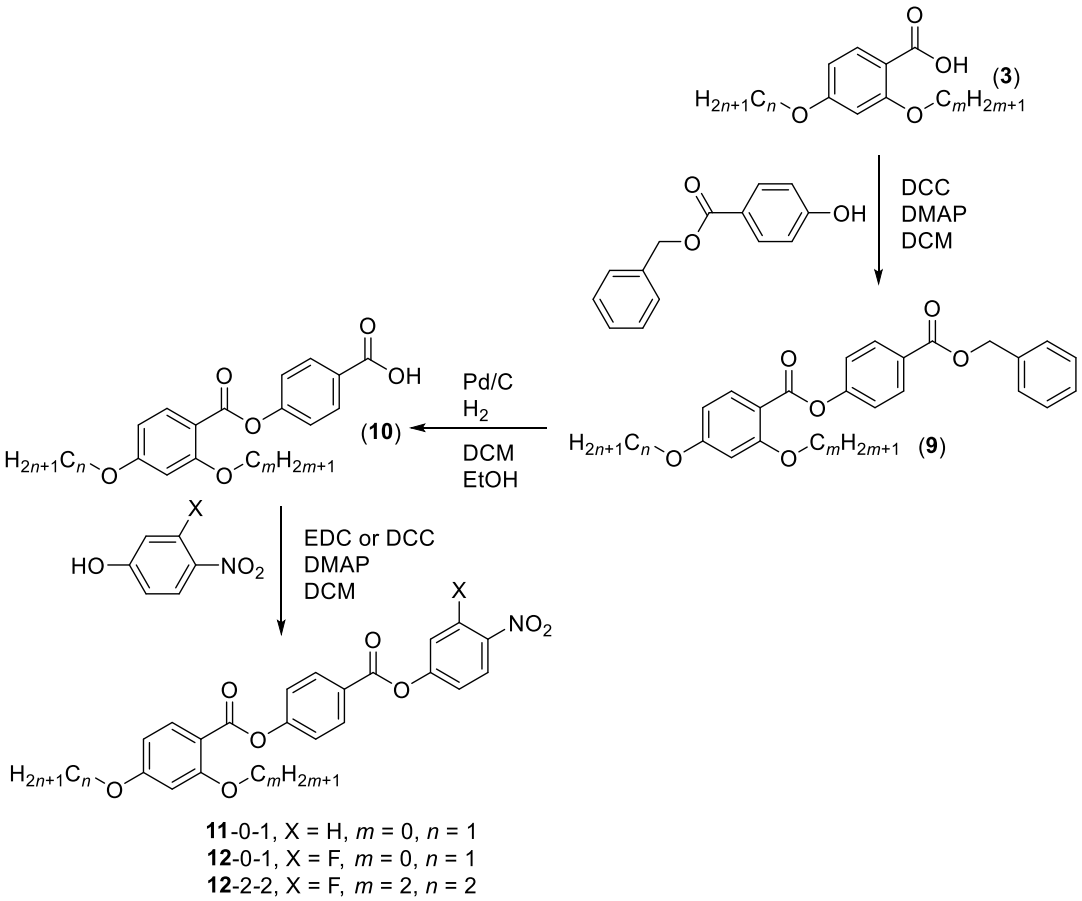
ν_{max}/cm^{-1}: 2990, 1716, 1708, 1603, 1584, 1571, 1533, 1470, 1455, 1440, 1431, 1417, 1391, 1348, 1290, 1250, 1234, 1195, 1168, 1143, 1132, 1118, 1094, 1081, 1048, 1032, 966, 952, 917, 883, 845, 816, 755, 746, 684, 619, 585, 550, 520, 461, 436.

δ_H/ppm (400 MHz, DMSO-d_6): 8.30 (1 H, t, J 8.9 Hz, Ar-H), 8.08 (1 H, d, J 8.6 Hz, Ar-H), 7.96 (1 H, d, J 8.6 Hz, Ar-H), 7.72 (1 H, dd, J 12.0 Hz, 2.4 Hz, Ar-H), 7.43 (1 H, m, Ar-H), 7.16 (1 H, d, J 2.0 Hz, Ar-H), 7.00 (1 H, dd, J 8.6 Hz, 2.0 Hz, Ar-H), 6.67 (2 H, m, Ar-H), 4.15 (4 H, m, O-$\underline{CH_2}$-CH_3), 3.90 (3 H, s, O-$\underline{CH_3}$), 1.36 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_F/ppm (376 MHz, DMSO-d_6): -115.42 (s, Ar-F).

δ_C/ppm (100 MHz, DMSO-d_6): 164.19, 162.30, 161.70, 161.13, 161.01, 156.45, 155.61 (d, J 10.6 Hz), 153.98 (d, J 262.8 Hz), 134.57 (d, J 7.2 Hz), 134.06, 133.34, 127.49 (d, J 2.0 Hz), 119.26 (d, J 3.8 Hz), 114.20, 114.16, 112.82 (d, J 23.7 Hz), 109.81, 107.19, 106.06, 100.17, 64.22, 63.76, 56.45, 14.46.

MS = $[M+Na]^+$: Calculated for $C_{25}H_{22}FNO_9Na$: 522.1176. Found: 522.1162. Difference: 2.7 ppm



4-[(Benzyloxy)carbonyl]phenyl 2-alkoxy-4-alkoxybenzoates (9)

To a pre-dried flask flushed with argon, **Compound 3** (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 6**. The extent of the reaction was monitored by TLC using an appropriate solvent system (RF values quoted in the product data). The white precipitate which formed was removed by vacuum filtration and the filtrate collected. The collected solvent was evaporated under vacuum to leave a white solid which was recrystallised from hot ethanol (250 mL).

Table 6. Quantities of reagents used in the syntheses of the 4-[(benzyloxy)carbonyl]phenyl 2-alkoxy-4-alkoxybenzoates.

m	*n*	(**3**)	Benzyl 4-Hydroxybenzoate	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide
0	1	3.00 g, 0.0197 mol	4.95 g, 0.0217 mol	0.313 g, 2.56×10^{-3} mol	5.28 g, 0.0256 mol

2	2	10.00 g, 0.0476 mol	11.96 g, 0.0524 mol	0.756 g, 6.19×10^{-3} mol	12.77 g, 0.0619 mol

9.1 4-[(Benzyloxy)carbonyl]phenyl 4-methoxybenzoate

Yield: 4.47 g, 62.6 %. RF: 0.378 (100 % dichloromethane). M.P = 126 °C

ν_{max}/cm^{-1}: 3063, 2970, 1727, 1712, 1602, 1581, 1509, 1494, 1471, 1454, 1422, 1413, 1379, 1307, 1267, 1253, 1213, 1172, 1157, 1106, 1094, 1062, 1023, 987, 950, 911, 893, 845, 823, 802, 784, 761, 748, 695, 653, 636, 609, 598, 520, 501, 458, 417.

δ_H/ppm (400 MHz, $CDCl_3$): 8.15 (4 H, m, Ar-H), 7.43 (5 H, m, Ar-H), 7.29 (2 H, d, J 8.7 Hz, Ar-H), 6.99 (2 H, d, J 8.9 Hz, Ar-H), 5.38 (2 H, s, (C=O)-O-$\underline{CH_2}$-Ar), 3.90 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 165.73, 164.32, 164.13, 154.89, 135.99, 132.41, 131.32, 128.63, 128.29, 128.19, 127.56, 121.87, 121.35, 113.95, 66.81, 55.56.

9.2 4-[(Benzyloxy)carbonyl]phenyl 2,4-diethoxybenzoate

Yield: 17.07 g, 85.3 %. RF: 0.469 (20 % ethyl acetate:80 % 40:60 petroleum ether). M.P = 105 °C

ν_{max}/cm^{-1}: 2985, 1743, 1716, 1604, 1568, 1500, 1471, 1453, 1433, 1413, 1392, 1304, 1275, 1239, 1195, 1165, 1147, 1122, 1107, 1034, 1011, 909, 875, 826, 808, 783, 764, 756, 740, 690, 667, 627, 598, 582, 545,526, 508, 460.

δ_H/ppm (400 MHz, $CDCl_3$): 8.13 (2 H, d, J 8.8 Hz, Ar-H), 8.03 (1 H, d, J 8.7 Hz, Ar-H), 7.40 (5 H, m, Ar-H), 7.29 (2 H, d, J 8.8 Hz, Ar-H), 6.53 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.54 (1 H, d, J 2.3 Hz, Ar-H), 5.37 (2 H, s, (C=O)-O-$\underline{CH_2}$-Ar), 4.11 (4 H, m, O-$\underline{CH_2}$-CH_3), 1.46 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 165.83, 164.48, 163.23, 161.74, 155.10, 136.05, 134.48, 131.22, 128.61, 128.25, 128.14, 127.23, 122.02, 110.77, 105.39, 100.34, 66.73, 64.62, 63.89, 14.68.

4-(2-Alkoxy-4-alkoxybenzoyloxy)benzoic acids (10)

To a pre-dried flask flushed with argon, **Compound 9** (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 7**. 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). The hydrogen gas, after the reaction was completed, was evacuated under vacuum and the flask was purged using argon. The mixture was filtered through Celite, and the collected solvent was evaporated under vacuum to leave a white solid which was recrystallised from hot ethanol (200 mL)

Table 7. Quantities of reagents used in the syntheses of the 4-(2-alkoxy-4-alkoxybenzoyloxy)benzoic acids.

m	*n*	(**9**)	5 % Palladium on Carbon	Dichloromethane	Ethanol
0	1	4.30 g, 0.0119 mol	0.252 g, 2.37×10^{-3} mol	70 mL	70 mL
2	2	8.30 g, 0.0197 mol	1.47 g, 0.0138 mol	100 mL	100 mL

10.1 4-(2-Ethoxy-4-methoxybenzoyloxy)benzoic acid

Yield: 0.580 g, 17.9 %. RF: 0.026 (100 % dichloromethane).

T_{CrN} 219 °C T_{NI} 266 °C

ν_{max}/cm^{-1}: 2843, 1724, 1686, 1603, 1580, 1512, 1421, 1317, 1297, 1261 ,1208, 1162, 1129, 1113, 1065, 1025, 923, 881, 847, 838, 797, 761, 688, 651, 630, 605, 549, 506, 467, 410.

δ_H/ppm (400 MHz, DMSO-d_6): 13.04 (1 H, br, OH), 8.10 (2 H, d, J 8.9 Hz, Ar-H), 8.04 (2 H, d, J 8.7 Hz, Ar-H), 7.39 (2 H, d, J 8.7 Hz, Ar-H), 7.13 (2 H, d, J 8.9 Hz, Ar-H), 3.88 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.14, 164.36, 164.30, 154.60, 132.60, 131.34, 128.97, 122.66, 121.09, 114.81, 56.15.

10.2 4-(2,4-Methoxybenzoyloxy)benzoic acid

Yield: 5.32 g, 81.7 %. RF: 0.242 (100 % ethyl acetate). M.P = 193 °C

ν_{max}/cm^{-1}: 2979, 2870, 1712, 1680, 1602, 175, 1506, 1477, 1440, 1423, 1388, 1368, 1294, 1264, 1247, 1208, 1189, 1153, 1140, 1110, 1074, 1037, 1013, 917, 887, 845, 812, 781, 763, 753, 684, 661, 638, 606, 568, 546, 502, 461, 441, 415.

δ_H/ppm (400 MHz, DMSO-d_6): 13.00 (1 H, br, OH), 8.01 (2 H, d, J 8.6 Hz, Ar-H), 7.92 (1 H, d, J 8.6 Hz, Ar-H), 7.33 (2 H, d, J 8.6 Hz, Ar-H), 6.66 (2 H, m, Ar-H), 4.14 (4 H, m, O-$\underline{CH_2}$-CH_3), 1.35 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_C/ppm (100 MHz, DMSO-d_6): 167.13, 164.53, 163.17, 161.43, 154.81, 134.35, 131.31, 128.52, 122.66, 110.53, 106.52, 100.68, 64.68, 64.20, 14.93, 14.92.

4-[(4-Nitrophenoxy)carbonyl]phenyl 4-methoxybenzoate (11-0-1)

To a pre-dried flask flushed with argon and kept in an ice bath in order to maintain the temperature at 0°C, **Compound 10.1** (1 eq, 0.250 g, 9.18×10^{-4} mol), 4-nitrophenol (1.2 eq, 0.153 g, 1.10×10^{-3} mol) and 4-dimethylaminopyridine (0.15 eq, 0.017 g, 1.38×10^{-4} mol) were added. The solids were solubilised with dichloromethane (30 mL) and stirred for 10 min before *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq, 0.265 g, 1.38×10^{-3} mol) was added to the flask. The temperature of the reaction mixture was increased to room temperature and the reaction was allowed to proceed overnight. The solvent was removed under vacuum and the crude product was purified using a silica gel column with 100 % dichloromethane (RF value quoted in product data). The eluent fractions of interest were evaporated under vacuum to leave a white solid which was recrystallised from hot ethanol (100 mL).

Yield: 0.125 g, 34.6 %. RF: 0.306.

T_{CrN} 159 °C T_{NI} 284 °C

ν_{max}/cm^{-1}: 2850, 1733, 1605, 1513, 1492, 1466, 1413, 1354, 1322, 1306, 1263, 1204, 1159, 1111, 1058, 1009, 877, 863, 844, 812, 788, 760, 750, 744, 691, 681, 671, 631, 596, 508, 496, 485, 410.

δ_H/ppm (400 MHz, $CDCl_3$): 8.37 (2 H, d, J 9.0 Hz, Ar-H), 8.24 (2 H, d, J 8.6 Hz, Ar-H), 7.97 (1 H, d, J 8.6 Hz, Ar-H), 8.34 (2 H, d, J 9.0 Hz, Ar-H), 8.28 (2 H, d, J 8.7 Hz, Ar-H), 8.17 (2 H, d, J 8.9 Hz, Ar-H), 7.42 (4 H, m, Ar-H), 7.01 (2 H, d, J 8.9 Hz, Ar-H), 3.92 (3 H, s, O-$\underline{CH_3}$).

δ_C/ppm (100 MHz, $CDCl_3$): 164.27, 164.21, 163.54, 155.86, 155.65, 145.47, 132.48, 132.01, 125.86, 125.32, 122.65, 122.36, 121.11, 114.03, 55.60.

MS = $[M+H]^+$: Calculated for $C_{21}H_{16}NO_7$: 394.0927. Found: 394.0942. Difference: 3.8 ppm

4-[(3-Fluoro-4-nitrophenoxy)carbonyl]phenyl 2-alkoxy-4-methoxybenzoates (12)

To a pre-dried flask flushed with argon and kept in an ice bath in order to maintain the temperature at 0 °C, **Compound 10** (1 eq), 3-fluoro-4-nitrophenol and 4-dimethylaminopyridine were added. The solids were solubilised with dichloromethane (30 mL) and stirred for 10 min before *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (*m* = 0, *n* = 1) or *N,N'*-dicyclohexylcarbodiimide (*m* = 2, *n* = 2) was added to the flask. The temperature of the reaction mixture was increased to room temperature and the reaction was allowed to proceed overnight. The quantities of the reagents used in each reaction are listed in **Table 8**. For the reaction with *N,N'*-dicyclohexylcarbodiimide, 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 solid which was recrystallised from hot ethanol (100 mL).

Table 8. Quantities of reagents used in the syntheses of the 4-[(3-fluoro-4-nitrophenoxy)carbonyl]phenyl 2-alkoxy-4-methoxybenzoates.

m	*n*	(**10**)	3-Fluoro-4-nitrophenol	4-Dimethylaminopyridine	*N,N'*-Dicyclohexylcarbodiimide/ N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
0	1	0.250 g, 9.18×10^{-4} mol	0.173 g, 1.10×10^{-3} mol	0.017 g, 1.38×10^{-4} mol	0.265 g, 1.38×10^{-3} mol
2	2	0.300 g, 9.08×10^{-4} mol	0.157 g, 9.99×10^{-4} mol	0.014 g, 1.18×10^{-4} mol	0.243 g, 1.18×10^{-3} mol

12.1 4-[(3-Fluoro-4-nitrophenoxy)carbonyl]phenyl 4-methoxybenzoate (12-0-1)

Off-white solid. Yield: 0.090 g, 23.8 %. RF: 0.389 (100 % dichloromethane).

T_{CrN} 160 °C T_{NI} 252 °C

ν_{max}/cm^{-1}: 1755, 1733, 1604, 1527, 1513, 1489, 1415, 1356, 1322, 1266, 1213, 1168, 1148, 1096, 1049, 1015, 968, 878, 844, 810, 759, 749, 688, 669, 630, 598, 536, 506.

δ_H/ppm (400 MHz, $CDCl_3$): 8.21 (5 H, m, Ar-H), 7.42 (2 H, d, J 8.8 Hz, Ar-H), 7.30 (1 H, dd, J 11.2 Hz, 2.4 Hz, Ar-H), 7.23 (1 H, m, Ar-H), 7.01 (2 H, d, J 8.9 Hz, Ar-H), 3.92 (3 H, s, O-$\underline{CH_3}$).

δ_F/ppm (376 MHz, $CDCl_3$): -113.04 (s, Ar-F).

δ_C/ppm (100 MHz, $CDCl_3$): 164.32, 164.19, 163.09, 156.06, 155.73 (d, J 10.4 Hz), 154.92 (d, J 267.0 Hz), 134.94 (d, J 6.9 Hz), 132.50, 132.09, 127.27 (d, J 2.1 Hz), 125.42, 122.46, 121.06, 118.10 (d, J 4.0 Hz), 114.05, 112.42 (d, J 23.8 Hz), 55.61.

MS = $[M+H]^+$: Calculated for $C_{21}H_{15}FNO_7$: 412.0833. Found: 412.0824. Difference: 2.2 ppm

12.2 4-[(3-Fluoro-4-nitrophenoxy)carbonyl]phenyl 2,4-diethoxybenzoate (12-2-2)

White solid. Yield: 0.167 g, 39.2 %. RF: 0.500 (98 % dichloromethane: 2 % ethyl acetate).
$T_{Cr|}$ 139 °C $T_{N_F|}$ (105 °C) $T_{N|}$ (110 °C)

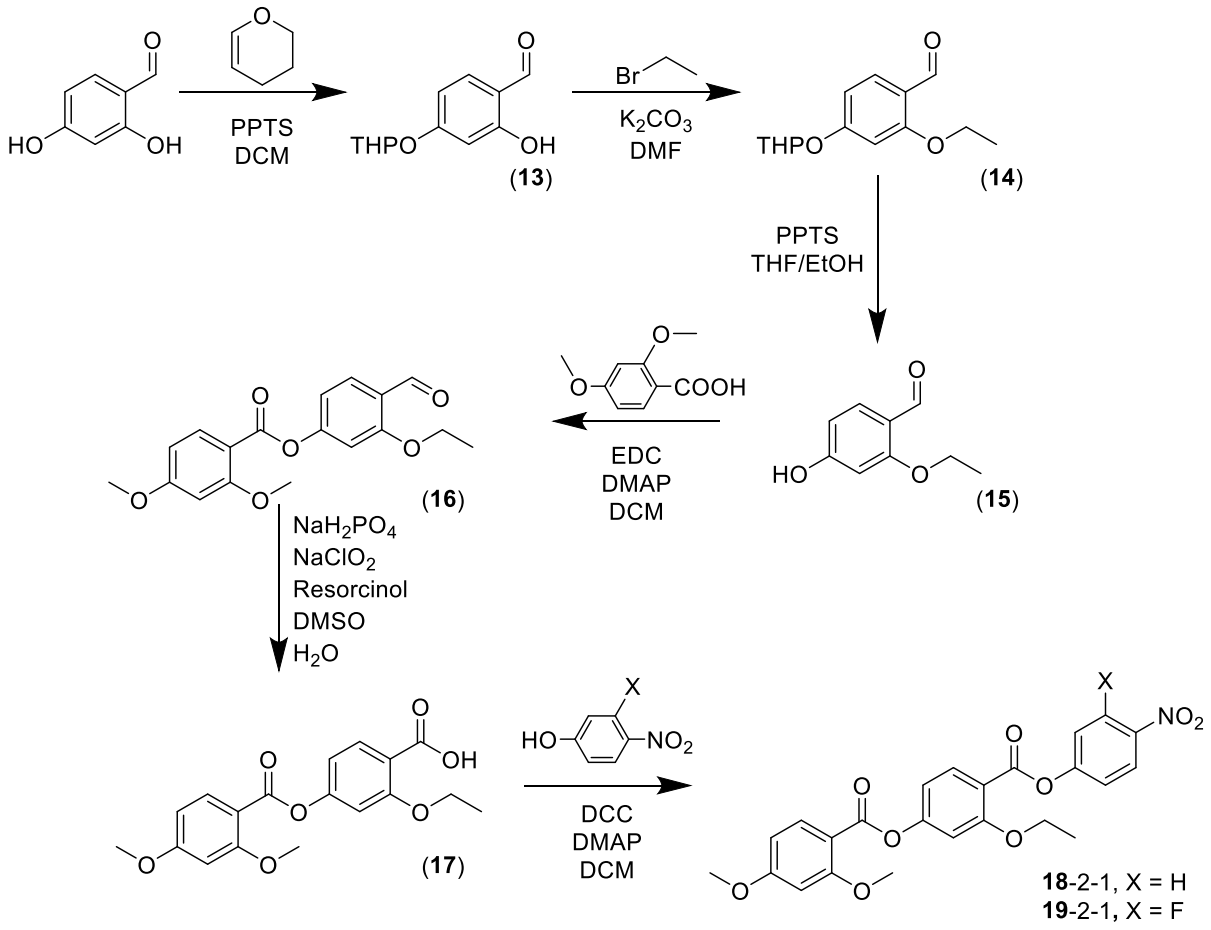
ν_{max}/cm^{-1}: 2991, 1738, 1711, 1702, 1602, 1571, 1534, 1507, 1487, 1444, 1414, 1390, 1347, 1308, 1250, 1215, 1195, 1158, 1140, 1109, 1093, 1050, 1036, 1015, 966, 888, 839, 815, 747, 756, 685, 671, 643, 628, 611, 569, 539, 505, 477, 461.

δ_H/ppm (400 MHz, $CDCl_3$): 8.21 (3 H, m, Ar-H), 8.05 (1 H, d, J 8.7 Hz, Ar-H), 7.40 (2 H, d, J 8.8 Hz, Ar-H), 7.30 (1 H, dd, J 11.3 Hz, 2.4 Hz, Ar-H), 7.23 (1 H, m, Ar-H), 6.55 (1 H, dd, J 8.7 Hz, 2.3 Hz, Ar-H), 6.52 (1 H, d, J 2.3 Hz, Ar-H), 4.13 (4 H, m, O-$\underline{CH_2}$-CH_3), 1.47 (6 H, m, O-CH_2-$\underline{CH_3}$).

δ_F/ppm (376 MHz, $CDCl_3$): -113.11 (s, Ar-F).

δ_C/ppm (100 MHz, $CDCl_3$): 164.84, 163.29, 163.12, 162.03, 156.43, 155.92 (d, J 10.6 Hz), 155.03 (d, J 266.5 Hz), 134.98 (d, J 7.1 Hz), 134.69, 132.11, 127.37 (d, J 2.0 Hz), 125.18, 122.72, 118.24 (d, J 4.0 Hz), 112.54 (d, J 23.8 Hz), 110.51, 105.62, 100.44, 64.75, 64.08, 14.81.

MS = $[M+Na]^+$: Calculated for $C_{24}H_{20}FNO_8Na$: 492.1071. Found: 492.1089. Difference: 3.7 ppm



2-Hydroxy-4-(oxan-2-yloxy)benzaldehyde (13)

Under inert conditions, to a solution of 2,4-dihydroxybenzaldehyde (1 eq, 10.0 g, 7.24×10^{-2} mol) and 3,4-dihydropyran (1.2 eq, 7.30 g, 7.92 mL, 8.68×10^{-2} mol) in 30 mL dichloromethane (DCM), pyridinium *p*-toluenesulfonate (0.1 eq, 1.80 g, 7.16×10^{-2} mol) was added dissolved in 5 mL of DCM. The reaction mixture was allowed to react for 2 h and then quenched by the

addition of aqueous $NaHCO_3$. The mixture was extracted with dichloromethane (3 × 50 mL) and then dried with $MgSO_4$. The drying agent was filtered, and the solvent removed on the rotary evaporator. The product was then purified by flash column using a mixture of 5 % ethyl acetate:95 % hexane (RF value quoted in the product data) to obtain the pure compound as a colourless oil.

Yield: 10.45 g, 65.0 %. RF: 0.38 (10 % ethyl acetate: 90 % hexane)
ν_{max}/cm^{-1}: 3228, 2945, 2854, 1627, 1506, 1426, 1340, 1283, 1218, 1103, 1086, 952, 906, 867, 830, 772, 712, 626, 591, 544, 479, 458, 420.
δ_H/ppm (400 MHz, DMSO-d_6): 11.35 (1 H, s, (C=O)-H), 9.71 (1 H, s, OH), 7.42 (1 H, d, J 8.6 Hz, Ar-H), 6.64 (1 H, dd, J 8.6, 2.2 Hz, Ar-H), 6.61 (1 H, d, J 2.3 Hz, Ar-H), 5.49 (1 H, t, J 3.2 Hz, THP), 3.81 (1 H, ddd, J 11.2 Hz, 9.9 Hz, 3.1 Hz, THP), 3.62 (1 H, dtd, J 11.4 Hz, 4.1 Hz, 1.4 Hz, THP), 1.98 – 1.41 (6 H, m, THP).
δ_C/ppm (100 MHz, DMSO-d_6): 194.69, 164.46, 164.29, 135.41, 115.87, 109.52, 103.79, 96.35, 62.31, 30.07, 25.08, 18.55.

2-Ethoxy-4-(oxan-2-yloxy)benzaldehyde (14)

A two-neck round bottom flash is charged with **Compound 13** (1 eq, 4.00 g, 1.79×10^{-2} mol) and potassium carbonate (1.2 eq, 2.97 g, 2.16×10^{-2} mol) under inert conditions. The solids were dissolved in dimethylformamide (DMF) (40 mL) and then 1-bromoethane (1.2 eq, 2.28 g 2.16×10^{-2} mol) was injected. The reaction was allowed to proceed overnight at 60 °C. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 50 mL) and then dried with $MgSO_4$ (RF value quoted in the product data). The drying agent was filtered, and the solvent removed on the rotary evaporator to obtain the pure compound as a colourless oil without further purification.

Yield: 4.27 g, 95.7 %. RF: 0.45 (20 % ethyl acetate:80 % hexane)
ν_{max}/cm^{-1}: 2941, 2852, 1674, 1596, 1575, 1498, 1436, 1389, 1356, 1253, 1173, 1097, 1034, 996, 948, 912, 872, 817, 675, 605, 574, 462.
δ_H/ppm (400 MHz, DMSO-d_6): 10.21 (1 H, s, (C=O)-H), 7.65 (1 H, d, J 8.6 Hz, Ar-H), 6.75 (1 H, d, J 2.1 Hz, Ar-H), 6.72 (1 H, dd, J 8.6 Hz, 2.2 Hz, Ar-H), 5.65 (1 H, t, J 3.1 Hz, THP), 4.16 (2 H, qd, J 6.9 Hz, 2.9 Hz, -O-$\underline{CH_2}$-CH_3), 3.72 (1 H, m, THP), 3.59 (1 H, m, THP), 1.94 – 1.47 (6 H, m, THP), 1.38 (3 H, t, J 7.0 Hz, -O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 187.89, 163.72, 163.09, 129.89, 119.19, 108.95, 101.48, 96.05, 64.62, 62.10, 29.95, 25.00, 18.75, 14.82.

2-Ethoxy-4-hydroxybenzaldehyde (15)

To a solution of **Compound 14** (1 eq, 4.00 g, 1.60×10^{-2} mol) in tetrahydrofuran/ethanol (1:1, 50 mL), solid pyridinium *p*-toluenesulfonate (1.5 eq, 6.05 g, 2.40×10^{-2} mol) was added. The reaction mixture was allowed to react at reflux overnight and then quenched by evaporation of the solvent to dryness. The reaction crude was dissolved in dichloromethane and washed with water and brine. The organic layer was dried with $MgSO_4$, the drying agent was filtered, and the solvent removed on the rotary evaporator. The product was then purified by flash column using a mixture of 50 % ethyl acetate: 50 % hexane (RF value quoted in the product data) to obtain the pure product as a yellow crystal.

Yield: 2.12 g, 80.0 %. RF: 0.11 (20 % ethyl acetate: 80 % hexane). M.P. = 167 °C

ν_{max}/cm^{-1}: 3015, 2980, 2876, 2805, 2707, 2585, 1639, 1615, 1568, 1466, 1407, 1283, 1246, 1185, 1105, 1033, 804, 737, 654, 584, 502, 461, 410.
δ_H/ppm (400 MHz, DMSO-d_6): 10.62 (1 H, s, Ar-OH), 10.14 (1 H, s, (C=O)-H), 7.56 (1 H, d, J 8.4 Hz, Ar-H), 6.50 – 6.41 (2 H, m, Ar-H), 4.10 (2 H, q, J 6.9 Hz, -O-$\underline{CH_2}$-CH_3), 1.37 (3 H, t, J 6.9 Hz, -O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 186.89, 165.13, 163.15, 129.77, 116.99, 108.47, 99.52, 63.82, 14.39.

(3-Ethoxy-4-formylphenyl) 2,4-methoxybenzoate (16)

Under inert conditions, the required **Compound 15** (1 eq, 0.85 g, 5.11×10^{-3} mol) and 2,4-methoxybenzoic acid (1.5 eq, 1.11 g, 6.13×10^{-3} mol) were dissolved in dichloromethane (60 mL). To this, dissolved 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 1.5 eq, 1.47 g, 7.65×10^{-3} mol) in 10 mL DCM was added and allowed to react on ice for 30-40 min. A catalytic amount of solid 4-dimethylaminopyridine (DMAP) was added to the solution and left to react overnight slowly warming up to room temperature. The reaction mixture is then quenched by the addition of distilled water (40 mL) and washed with water and brine. The organic layer was dried with $MgSO_4$, the drying agent was filtered, and the solvent removed on the rotary evaporator. The product was then purified by hot recrystallization in ethanol (RF value quoted in the product data).

Yield: 0.737 g, 43.9 %. RF: 0.09 (20 % ethyl acetate:80 % hexane) M.P. = 130 °C
ν_{max}/cm^{-1}: 2991, 2852, 1739, 1684, 1604, 1571, 1501, 1468, 1390, 1235, 1207, 1160, 1044, 1016, 872, 825, 759, 670, 613, 548, 467, 413.
δ_H/ppm (400 MHz, DMSO-d_6): 10.33 (1 H, s, (C=O)-H), 7.98 (1 H, d, 8.8 Hz, Ar), 7.75 (1 H, d, J 8.5 Hz, Ar), 7.13 (1 H, d, J 2.0 Hz, Ar), 6.92 (1 H, dd, J 8.5 Hz, 2.0 Hz, Ar), 6.72 (1 H, d, J 2.3 Hz, Ar), 6.68 (1 H, dd, J 8.8 Hz, 2.3 Hz, Ar), 4.20 (2 H, q, J 7.0 Hz, -O-$\underline{CH_2}$-CH_3), 3.89 – 3.88 (6 H, 2×s, 2×-O-$\underline{CH_3}$), 1.39 (3 H, t, J 7.0 Hz, -O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 188.24, 165.03, 162.16, 161.98, 161.85, 157.14, 134.14, 128.89, 121.87, 114.71, 109.70, 107.75, 105.74, 99.00, 64.62, 56.02, 55.76, 14.34.

2-Ethoxy-4-(2,4-methoxybenzoyl)oxybenzoic acid (17)

To a mixture of **Compound 16** (1 eq, 0.258 g, 7.81×10^{-4} mol) in DMSO (30 mL), a solution of $H_2NaO_4P.H_2O$ (4 eq, 0.431 g, 3.12×10^{-3} mol) and $ClNaO_2$ (3.5 eq, 0.247 g, 2.73×10^{-3} mol) in water was slowly added dropwise. The reaction mixture is allowed to react overnight and then diluted with water (150 mL). The pH is adjusted to 8 with $NaHCO_3$ saturated and left for 1 h, then acidified with 1 M HCl solution to pH 4 until precipitation is observed. The precipitated solid is filtered and recrystallized in hot ethanol to obtain the pure product as white crystals (RF value quoted in the product data).

Yield: 0.081 g, 29.8 %. RF: 0 (20 % ethyl acetate:80 % hexane) M.P. = 160 °C
ν_{max}/cm^{-1}: 2974, 2850, 1738, 1668, 1607, 1570, 1505 1470, 1391, 1305, 1233, 1207, 1158, 1045, 1016, 870, 825, 758, 687, 663, 607, 531, 467.
δ_H/ppm (400 MHz, DMSO-d_6): 7.97 (1 H, d, J 9.0 Hz, Ar), 7.69 (1 H, d, J 8.4 Hz, Ar), 6.99 (1 H, d, J 2.1 Hz, Ar), 6.83 (1 H, dd, J 8.4 Hz, 2.1 Hz, Ar), 6.71 (1 H, d, J 2.5 Hz, Ar), 6.68 (1 H, dd, J 8.8 Hz, 2.8 Hz, Ar), 4.09 (2 H, q, J 7.0 Hz, -O-$\underline{CH_2}$-CH_3), 1.32 (3 H, t, J 7.0 Hz, -O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 166.79, 164.90, 162.47, 161.74, 158.53, 157.15, 154.31, 134.06, 131.66, 113.72, 109.98, 107.76, 105.69, 99.00, 64.37, 56.01, 55.74, 14.49.

(4-Nitrophenyl) 2-ethoxy-4-(2,4-methoxybenzoyl)oxybenzoate (18-2-1)

Under inert conditions, a mixture of **Compound 17** (2 eq, 0.200 g, 4.59×10^{-4} mol) and *N,N'*-dicyclohexylcarbodiimide (DCC, 1.5 eq, 0.0945 g, 4.58×10^{-4} mol) were dissolved in DCM (10 mL) on ice and allowed to react for 30 min. 4-Nitrophenol (1.1 eq, 0.051 g, 3.67×10^{-4} mol) was dissolved in dry dichloromethane (2 mL), added to the solution and allowed to react overnight slowly warming up to room temperature. The reaction mixture is then quenched by filtration of the precipitated 1,3-dicyclohexyl urea and then purified by flash column chromatography with DCM (RF value quoted in the product data). The product was then purified by hot recrystallization in ethanol.

Yield: 0.036 g, 19.0 %. RF: 0.10 (DCM)
T_{CrI} 154 °C T_{N_FI} (72 °C).

ν_{max}/cm^{-1}: 3086, 2971, 2930, 2840, 1743, 1698, 1593, 1516, 1427, 1342, 1287, 1233, 1199, 1163, 1117, 1022, 822, 764, 746, 674, 619, 519, 423.
δ_H/ppm (400 MHz, DMSO-d_6): 8.36 (2 H, d, J 9.0 Hz, Ar-H), 8.04 (1 H, d, J 8.5 Hz, Ar-H), 8.00 (1 H, d, J 8.7 Hz, Ar-H), 7.58 (2 H, d, J 9.1 Hz, Ar-H), 7.15 (1 H, d, J 2.2 Hz, Ar-H), 6.98 (1 H, dd, J 8.5 Hz, 2.1 Hz, Ar-H), 6.73 (1 H, d, J 2.3 Hz, Ar-H), 6.69 (1 H, dd, J 8.8 Hz, 2.3 Hz, Ar-H), 4.17 (2 H, q, J 6.9 Hz, -O-$\underline{CH_2}$-CH_3), 3.89 – 3.87 (6 H, 2×s, 2×-O-CH_3), 1.35 (3 H, t, J 6.9 Hz, -O-CH_2-$\underline{CH_3}$).
δ_C/ppm (100 MHz, DMSO-d_6): 165.05, 162.52, 162.25, 161.89, 160.02, 156.07, 155.63, 145.08, 134.19, 133.03, 125.38, 123.35, 115.08, 114.22, 109.75, 108.14, 105.78, 99.02, 64.75, 56.06, 55.79, 14.46.
MS = $[M+H]^+$ Calculated mass for $C_{24}H_{22}NO_9$:468.130. Found: 468.131. Difference: 2.3 ppm.

(3-Fluoro-4-nitrophenyl) 2-ethoxy-4-(2,4-methoxybenzoyl)oxybenzoate (19-2-1)

Under inert conditions, a mixture of **Compound 17** (2 eq, 0.200 g, 4.59×10^{-4} mol) and *N,N'*-dicyclohexylcarbodiimide (DCC, 1.5 eq, 0.0945 g, 4.58×10^{-4} mol) were dissolved in DCM (10 mL) on ice and allowed to react for 30 min. 3-Fluoro-4-nitrophenol (1.25 eq, 0.066 g, 4.17×10^{-4} mol) was dissolved in dry dichloromethane (2 mL), added to the solution and allowed to react overnight slowly warming up to room temperature. The reaction mixture is then quenched by filtration of the precipitated 1,3-dicyclohexyl urea and then purified by flash column chromatography with DCM (RF value quoted in the product data). The product was then purified by hot recrystallization in ethanol.

Yield: 0.055 g, 24.7 %. RF: 0.09 (DCM)
T_{CrI} 153 °C T_{N_FI} (77 °C).

ν_{max}/cm^{-1}: 3060, 2973, 2932, 2843, 1762, 1743, 1607, 1524, 1356, 1269, 1215, 1126, 1010, 826, 761, 682, 556, 528, 465.
δ_H/ppm (400 MHz, DMSO-d_6): 8.30 (1 H, t, J 8.9 Hz, Ar-H), 8.05 (1 H, d, J 8.6 Hz, Ar-H), 8.00 (1 H, d, J 8.7 Hz, Ar-H), 7.71 (1 H, dd, J 12.0 Hz, 2.4 Hz, Ar-H), 7.45 – 7.38 (1 H, m, Ar-H), 7.15 (1 H, d, J 2.4 Hz, Ar-H), 6.98 (1 H, dd, J 8.4 Hz, 2.4 Hz, Ar-H), 6.73 (1 H, d, J 2.4 Hz, Ar-H), 6.69 (1 H, d, J 2.4 Hz, Ar-H), 4.17 (2 H, q, J 6.9 Hz, -O-$\underline{CH_2}$-CH_3), 3.91 – 3.86 (6 H, 2xs, 2×-O-$\underline{CH_3}$), 1.35 (3 H, t, J 6.9 Hz, -O-CH_2-$\underline{CH_3}$).
δ_F/ppm (376 MHz, DMSO): -115.36 (s, Ar-F).
δ_C/ppm (100 MHz, DMSO-d_6): 165.02, 162.15, 161.86, 160.22, 156.24, 155.65 (d, J 10.6 Hz), 153.98 (d, J 262.6 Hz), 134.59 (d, J 7.3 Hz), 134.16, 133.20, 127.53 (d, J 2.3 Hz), 119.19 (d, J

3.5 Hz), 114.51, 114.18, 112.73 (d, J 23.7 Hz), 109.68, 108.12, 105.73, 98.99, 64.72, 56.02, 55.76, 14.39.