Ferroelectric nematogens containing a methylthio group

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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 μ m particle size, purchased from Fluorochem and using an appropriate solvent system.

Structure Characterisation

All final products and intermediates that were synthesised were characterised using ¹H NMR, ¹³C 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. Morag Douglas at the University of Aberdeen.



Scheme 1. Synthetic route used to obtain the S compounds.

2-Methoxy-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzaldehyde (1a)



To a pre-dried two-necked round bottom flask, 4-hydroxy-2-methoxy benzaldehyde (5.00 g, 3.30×10^{-2} mol) and pyridinium p-toluenesulfonate (0.828 g, 3.30×10^{-3} mol) were solubilised in dichloromethane, DCM, (100 mL) and the atmosphere was replaced by argon. Then 3,4-dihydro-2*H*-pyran (3.64 mL, 3.32 g, 3.95×10^{-2} mol) was added through a septum via a syringe and the reaction mixture was left stirring at room temperature for 4 h. The extent of the reaction was monitored by TLC. The mixture was diluted with saturated NaHCO₃ and extracted with DCM. The combined organic extracts were washed with brine, dried over MgSO₄, the solvent evaporated under vacuum and dry-loaded onto silica gel column for purification using 20% ethyl acetate and 80% petroleum ether (40-60) as the eluent to obtain a colourless oil.

Yield: 5.53 g, 73.6 %. RF: 0.45

IR (v_{max}/cm⁻¹): 2943 (C-H), 1731 (C=O).

¹H NMR (400 MHz, DMSO) δ: 10.19 (d, *J* = 0.7 Hz, 1H, -CHO), 7.66 (d, *J* = 8.6 Hz, 1H, Ar), 6.77 (d, *J* = 2.1 Hz, 1H, Ar), 6.73 (ddd, *J* = 8.7, 2.2, 0.8 Hz, 1H, Ar), 5.67 (t, *J* = 3.1 Hz, 1H, THP), 3.89 (s, 3H, -OCH₃), 3.78 – 3.55 (m, 2H, THP), 1.96 – 1.35 (m, 6H, THP).

¹³C NMR (101 MHz, DMSO) δ: 187.33, 163.33, 163.23, 129.68, 118.70, 108.41, 100.35, 95.59, 61.62, 55.94, 29.49, 24.54, 18.26.

2-Fluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzaldehyde (1b)



Quantities used: 2-fluoro-4-hydroxybenzaldehyde (4.50 g, 3.21×10^{-2} mol), 3,4-dihydro-2*H*-pyran (3.51 mL, 3.24 g, 3.86×10^{-2} mol), PPTS (0.807 g, 3.21×10^{-3} mol), DCM (100 mL). The experimental procedure was described in the preparation of compound **1a**. Column chromatography over silica with DCM as the eluent to obtain white solid.

Yield: 5.03 g, 69.4 %. RF: 0.45. Melting Point: 99 °C

IR (v_{max}/cm⁻¹): 3077 (C-H), 2772 ((C=O)-H), 1680 (C=O).

¹H NMR (400 MHz, DMSO) δ : 10.08 (s, 1H, -CHO), 7.79 (t, J = 8.7 Hz, 1H, Ar), 7.07 – 6.98 (m, 2H, Ar), 5.68 (t, J = 3.1 Hz, 1H, THP), 3.75 – 3.56 (m, 2H, THP), 1.94 – 1.48 (m, 6H, THP).

¹³C NMR (101 MHz, CDCl₃) δ: 186.26, 186.20, 167.53, 164.97, 163.88, 163.76, 130.06, 130.02, 118.51, 118.43, 113.29, 113.26, 104.01, 103.77, 96.66, 62.19, 30.00, 25.04, 18.36.

2,6-Difluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzaldehyde (1c)



Quantities used: 2,6-difluoro-4-hydroxybenzaldehyde (5.00 g, 0.032 mol), 3,4-dihydro-2*H*-pyran (3.46 mL, 3.19 g, 3.80×10^{-2} mol), PPTS (0.794 g, 3.20×10^{-3} mol), DCM (100 mL). The experimental procedure was described in the preparation of compound **1a**. Column chromatography over silica with 20% ethyl acetate and 80% petroleum ether (40-60) as eluent to obtain a colourless oil.

Yield: 4.93 g, 64.1 %. RF: 0.48

IR (v_{max}/cm⁻¹): 3075 (C-H), 1691 (C=O).

¹H NMR (400 MHz, DMSO) δ: 10.07 (s, 1H, -CHO), 6.95 – 6.88 (m, 2H, Ar), 5.72 (t, *J* = 2.9 Hz, 1H, THP), 3.73 – 3.56 (m, 2H, THP), 1.91 – 1.70 (m, 3H, THP), 1.67 – 1.48 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 183.12, 183.07, 183.03, 165.38, 165.28, 165.22, 165.06, 162.81, 162.72, 100.10, 100.08, 100.04, 99.89, 99.85, 99.84, 93.24, 61.65, 30.12, 25.01, 19.13.

4-((Tetrahydro-2*H*-pyran-2-yl)oxy)benzoic acid (2a)



Quantities used: 4-hydroxybenzoic acid (10.0 g, 7.20×10^{-2} mol), 3,4-dihydro-2H-pyran (7.95 mL, 7.31 g, 8.70×10^{-2} mol), PPTS (1.81 g, 7.20×10^{-3} mol), DCM (150 mL). The experimental procedure was described in the preparation of compound **1a**. Column chromatography over silica with 20:80 ethyl acetate and petroleum ether (40-60) as the eluent followed by recrystallisation from ethanol (100 mL) to obtain white solid.

Yield: 5.08 g, 31.1 %. RF: 0.30. Melting Point: 170 °C

IR (v_{max}/cm⁻¹): 3071-2946 (OH), 1668 (C=O).

¹H NMR (400 MHz, DMSO) δ : 12.64 (s, 1H, -COOH), 7.88 (d, J = 8.6 Hz, 2H, Ar), 7.09 (d, J = 9.0 Hz, 2H, Ar), 5.58 (t, J = 3.2 Hz, 1H, THP), 3.72 (ddd, J = 12.1, 8.9, 3.5 Hz, 1H, THP), 3.57 (dt, J = 10.8, 4.4 Hz, 1H, THP), 1.95 – 1.69 (m, 3H, THP), 1.69 – 1.46 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 166.96, 160.14, 131.20, 123.76, 115.94, 95.57, 61.66, 29.66, 24.59, 18.47.

2-Methoxy-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoic acid (2b)



To a round bottom flask, compound **1a** (2.78 g, 1.20×10^{-2} mol) and resorcinol (1.94 g, 1.80×10^{-2} mol) were dissolved in DMSO (50 mL). Sodium chlorite (4.32 g, 4.80×10^{-2} mol) and sodium dihydrogen phosphate monohydrate (5.80 g, 4.20×10^{-2} mol) were dissolved in water (40 mL) and slowly added to a stirred solution of aldehyde **1a** with cooling by ice-water. The mixture was allowed to warm to room temperature and stirred for 6 hours. The reaction was monitored by TLC using 80:20 mix of ethyl acetate and petroleum ether (40-60). The mixture was diluted with water and solid NaHCO₃ was added to adjust the solution pH to 8. The mixture was washed with ethyl acetate, then the pH was adjusted to 4 by the addition of 1M hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to give a brown oil.

Yield: 1.95 g, 65.7 %. RF: 0.55

IR (v_{max}/cm⁻¹): 3028 (OH), 2949 (C-H), 1695 (C=O).

¹H NMR (400 MHz, DMSO) δ : 11.95 (s, 1H, -COOH), 7.61 (d, J = 8.5 Hz, 1H, Ar), 6.45 (d, J = 2.2 Hz, 1H, Ar), 6.38 (dd, J = 8.6, 2.2 Hz, 1H, Ar), 5.58 (t, J = 3.1 Hz, 1H, THP), 3.75 (s, 3H, -OCH₃), 3.62 – 3.40 (m, 2H, THP), 1.94 – 1.35 (m, 6H, THP).

¹³C NMR (101 MHz, DMSO) δ: 166.44, 162.53, 160.97, 133.57, 110.75, 107.17, 99.49, 97.83, 61.39, 55.49, 30.40, 25.07, 19.30.

2-Fluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoic acid (2c)



Quantities used: compound **1b** (4.93 g, 2.20×10^{-2} mol), resorcinol (3.63 g, 3.30×10^{-2} mol), sodium chlorite (7.92 g, 8.80×10^{-2} mol), sodium dihydrogen phosphate monohydrate (10.8 g, 7.70×10^{-2} mol), DMSO (80 mL), water (40 mL). The experimental procedure was described in the preparation of compound **2b**. The reaction mixture was stirred overnight at room temperature and the extent was monitored by TLC using 80:20 mix of petroleum ether (40-60) and ethyl acetate. The mixture was diluted with water and the pH was adjusted to 4 by the addition of 1M HCl solution. The precipitate was removed by vacuum filtration and followed by recrystallisation from ethanol (100 mL) to obtain a pale-yellow solid.

Yield: 3.43 g, 64.9 %. RF: 0.10. Melting Point: 149 °C

IR (v_{max}/cm⁻¹): 3082 (OH), 1677 (C=O).

¹H NMR (400 MHz, DMSO) δ: 12.89 (s, 1H, -COOH), 7.86 – 7.77 (m, 1H, Ar), 6.97 – 6.89

(m, 2H, Ar), 5.61 (t, *J* = 3.1 Hz, 1H, THP), 3.75 – 3.65 (m, 1H, THP), 3.63 – 3.55 (m, 1H, THP), 1.93 – 1.68 (m, 3H, THP), 1.68 – 1.47 (m, 3H, THP).

¹³C NMR (101 MHz, CDCl₃) δ: 169.53, 169.50, 165.50, 163.12, 163.00, 162.90, 134.06, 134.04, 112.42, 112.39, 110.58, 110.49, 105.03, 104.78, 96.57, 62.19, 30.03, 25.06, 18.41.

2,6-Difluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoic acid (2d)



Quantities used: compound **1c** (4.93 g, 2.00×10^{-2} mol), resorcinol (3.36 g, 3.10×10^{-2} mol), sodium chlorite (7.33 g, 8.10×10^{-2} mol), sodium dihydrogen phosphate monohydrate (9.98 g, 7.10×10^{-2} mol), DMSO (80 mL), water (60 mL). The experimental procedure was described in the preparation of compound **2b**. The reaction mixture was stirred overnight at room temperature and the extent was monitored by TLC using 80:20 mix of petroleum ether (40-60) and ethyl acetate. The mixture was diluted with water and the pH was adjusted to 4 by the addition of 1M HCl solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain a brown oil.

Yield: 3.59 g, 68.3 %. RF: 0.080

IR (v_{max}/cm⁻¹): 3060 (OH), 1687 (C=O).

¹H NMR (400 MHz, DMSO) δ: 13.07 (s, 1H, -COOH), 6.90 – 6.80 (m, 2H, Ar), 5.62 (t, *J* = 3.1 Hz, 1H, THP), 3.74 – 3.55 (m, 2H, THP), 1.91 – 1.68 (m, 3H, THP), 1.67 – 1.46 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 162.72, 162.62, 162.29, 161.78, 161.63, 161.48, 160.22, 160.12, 99.85, 99.82, 99.78, 99.59, 99.57, 93.27, 61.67, 30.14, 25.03, 19.14.

4-Nitrophenyl-2-methoxy-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (**3a**)



To a pre-dried flask, compound **2b** (2.77 g, 1.10×10^{-2} mol) was added and dissolved in DCM (50 mL). The addition of *N*,*N*'-dicyclohexylcarbodiimide, DCC, (2.68 g, 1.30×10^{-2} mol) was followed by 4-nitrophenol (1.39 g, 1.00×10^{-2} mol) and the mixture was allowed to stir for 2 min before adding 4-dimethylaminopyridine, DMAP (0.122 g, 1.00×10^{-3} mol). The reaction mixture was stirred overnight at room temperature and the extent was monitored by TLC. The white precipitate was removed by filtration and the solvent was evaporated under vacuum to

leave crude solid. This was purified using silica chromatography with DCM as the eluent to obtain pale yellow solid.

Yield: 1.20 g, 32.1 %. RF: 0.73. Melting Point: 149 °C

IR (v_{max}/cm⁻¹): 2965 (C-H), 1733 (C=O).

¹H NMR (400 MHz, DMSO) δ : 8.33 (d, J = 9.1 Hz, 2H, Ar), 7.98 (d, J = 8.7 Hz, 1H, Ar), 7.53 (d, J = 8.9 Hz, 2H, Ar), 6.81 (d, J = 2.2 Hz, 1H, Ar), 6.78 (dd, J = 8.7, 2.2 Hz, 1H, Ar), 5.69 (t, J = 3.1 Hz, 1H, THP), 3.86 (s, 3H, -OCH₃), 3.75 (ddd, J = 12.4, 9.3, 3.5 Hz, 1H, THP), 3.61 (dt, J = 11.0, 4.3 Hz, 1H, THP), 1.96 – 1.72 (m, 4H, THP), 1.70 – 1.52 (m, 2H, THP).

¹³C NMR (101 MHz, DMSO) δ: 162.42, 162.09, 161.71, 155.80, 144.89, 134.04, 125.25, 123.41, 110.17, 107.75, 101.11, 95.62, 61.61, 56.05, 29.52, 24.56, 18.28.

3-Fluoro-4-nitrophenyl 2-methoxy-4-((tetrahydro-2H-pyran-2-yl)oxy)benzoate (3b)



Quantities used: compound **2b** (5.15 g, 2.00×10^{-2} mol), 3-fluoro-4-nitrophenol (2.92 g, 1.90×10^{-2} mol), DCC (4.96 g, 2.40×10^{-2} mol), DMAP (0.227 g, 1.86×10^{-3} mol), DCM (100 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (100 mL) to obtain a pale yellow solid.

Yield: 3.36 g, 46.2 %. RF: 0.43. Melting Point: 115 °C

IR (v_{max}/cm⁻¹): 3112 (C-H), 1700 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.28 (t, *J* = 8.8 Hz, 1H, Ar), 7.99 (d, *J* = 8.8 Hz, 1H, Ar), 7.67 (dd, *J* = 12.2, 2.4 Hz, 1H, Ar), 7.41 – 7.33 (m, 1H, Ar), 6.84 – 6.74 (m, 2H, Ar), 5.70 (t, *J* = 3.1 Hz, 1H, THP), 3.86 (s, 3H, -OCH₃), 3.79 – 3.57 (m, 2H, THP), 1.99 – 1.47 (m, 6H, THP).

¹³C NMR (101 MHz, CDCl₃) δ: 163.49, 162.82, 162.04, 157.66, 156.48, 156.37, 155.01, 134.56, 127.14, 127.12, 118.39, 118.35, 112.67, 112.43, 110.01, 107.97, 100.83, 96.38, 62.18, 56.19, 30.15, 25.13, 18.47.

4-Nitrophenyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (**3c**)



Quantities used: compound **2a** (2.00 g, 9.00×10^{-3} mol), 4-nitrophenol (1.38 g, 9.91×10^{-3} mol), DCC (3.71 g, 1.80×10^{-2} mol), DMAP (0.110 g, 9.00×10^{-4} mol), DCM (100 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (100 mL) to obtain a white solid.

Yield: 2.02 g, 65.1 %. RF: 0.73. Melting Point: 133 °C

IR (v_{max}/cm⁻¹): 2959 (C-H), 1735 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.35 (d, *J* = 9.2 Hz, 2H, Ar), 8.10 (d, *J* = 9.0 Hz, 2H, Ar), 7.59 (d, *J* = 9.3 Hz, 2H, Ar), 7.22 (d, *J* = 9.0 Hz, 2H, Ar), 5.67 (t, *J* = 3.1 Hz, 1H, THP), 3.78 – 3.67 (m, 1H, THP), 3.64 – 3.55 (m, 1H, THP), 1.97 – 1.72 (m, 3H, THP), 1.72 – 1.49 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 163.48, 161.31, 155.66, 145.05, 132.15, 125.27, 123.36, 121.01, 116.44, 95.56, 61.63, 29.52, 24.53, 18.32.

3-Fluoro-4-nitrophenyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (3d)



Quantities used: compound **2a** (2.00 g, 9.00×10^{-3} mol), 3-fluoro-4-nitrophenol (1.56 g, 9.91×10^{-3} mol), DCC (3.71 g, 1.80×10^{-2} mol), DMAP (0.110 g, 9.00×10^{-4} mol), DCM (100 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (100 mL) to obtain faint yellow solid.

Yield: 1.81 g, 55.6 %. RF: 0.73. Melting Point: 105 °C

IR (v_{max}/cm⁻¹): 2952 (C-H), 1733 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.30 (t, *J* = 8.9 Hz, 1H, Ar), 8.10 (d, *J* = 9.0 Hz, 2H, Ar), 7.73 (dd, *J* = 12.1, 2.4 Hz, 1H, Ar), 7.44 (ddd, *J* = 9.0, 2.4, 1.2 Hz, 1H, Ar), 7.22 (d, *J* = 8.9 Hz, 2H, Ar), 5.67 (t, *J* = 3.1 Hz, 1H, THP), 3.77 – 3.67 (m, 1H, THP), 3.64 – 3.55 (m, 1H, THP), 1.96 – 1.72 (m, 3H, THP), 1.72 – 1.51 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 163.15, 161.41, 156.55, 155.83, 155.72, 153.93, 134.62, 134.54, 132.23, 127.49, 127.47, 120.72, 119.23, 119.20, 116.47, 112.92, 112.68, 95.57, 61.64, 29.51, 24.52, 18.31.

3-Fluoro-4-nitrophenyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (3e)



Quantities used: compound 2c (1.63 g, 6.79×10^{-3} mol), 4-nitrophenol (0.858 g, 6.17×10^{-3} mol), DCC (1.65 g, 8.02×10^{-3} mol), DMAP (0.0750 g, 6.17×10^{-4} mol), DCM (50 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (50 mL) to obtain an off-white solid.

Yield: 1.53 g, 69.0 %. RF: 0.53. Melting Point: 125 °C

IR (v_{max}/cm⁻¹): 3112 (C-H), 1722 (C=O)

¹H NMR (400 MHz, CDCl₃) δ: 8.35 – 8.29 (m, 2H, Ar), 8.04 (t, *J* = 8.7 Hz, 1H, Ar), 7.45 – 7.39 (m, 2H, Ar), 6.97 – 6.88 (m, 2H, Ar), 5.53 (t, *J* = 3.0 Hz, 1H, THP), 3.86 – 3.79 (m, 1H, THP), 3.70 – 3.62 (m, 1H, THP), 2.07 – 1.87 (m, 3H, THP), 1.81 – 1.58 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 164.36, 162.66, 162.54, 161.78, 160.81, 160.77, 155.27, 145.16, 133.80, 133.78, 125.30, 123.39, 112.96, 112.93, 109.41, 109.32, 104.98, 104.73, 95.92, 61.67, 29.29, 24.44, 18.14.

3-Fluoro-4-nitrophenyl 2-fluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (3f)



Quantities used: compound **2c** (1.63 g, 6.79×10^{-3} mol), 3-fluoro-4-nitrophenol (0.969 g, 6.17×10^{-3} mol), DCC (1.65 g, 8.02×10^{-3} mol), DMAP (0.0750 g, 6.17×10^{-4} mol), DCM (50 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (50 mL) to obtain an off-white solid.

Yield: 1.35 g, 58.1 %. RF: 0.60. Melting Point: 146 °C

IR (v_{max}/cm⁻¹): 3104 (C-H), 1743 (C=O).

¹H NMR (400 MHz, CDCl₃) δ : 8.18 (t, J = 8.7 Hz, 1H, Ar), 8.02 (t, J = 8.7 Hz, 1H, Ar), 7.29 (dd, J = 11.3, 2.3 Hz, 1H, Ar), 7.24 – 7.19 (m, 1H, Ar), 6.97 – 6.88 (m, 2H, Ar), 5.53 (t, J = 3.0 Hz, 1H, THP), 3.87 – 3.79 (m, 1H, THP), 3.70 – 3.63 (m, 1H, THP), 2.07 – 1.87 (m, 3H, THP), 1.80 – 1.59 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 164.43, 162.79, 162.67, 161.85, 160.42, 160.37, 156.55, 155.41, 155.30, 153.93, 134.73, 134.66, 133.85, 133.83, 127.52, 127.50, 119.26, 119.22, 112.99, 112.73, 109.13, 109.04, 104.99, 104.74, 95.94, 61.68, 29.28, 24.44, 18.13.

4-Nitrophenyl 2,6-difluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (**3g**)



Quantities used: compound **2d** (1.68 g, 6.49×10^{-3} mol), 4-nitrophenol (0.820 g, 5.90×10^{-3} mol), DCC (1.58 g, 7.67×10^{-3} mol), DMAP (0.0720 g, 5.90×10^{-4} mol), DCM (100 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (20 mL) to obtain a white solid.

Yield: 0.275 g, 12.3 %. RF: 0.53. Melting Point: 106 °C

IR (v_{max}/cm⁻¹): 3116 (C-H), 1749 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.38 – 8.33 (m, 2H, Ar), 7.62 – 7.56 (m, 2H, Ar), 7.06 – 6.98 (m, 2H, Ar), 5.74 (t, *J* = 2.9 Hz, 1H, THP), 3.75 – 3.59 (m, 2H, THP), 1.88 – 1.73 (m, 3H, THP), 1.66 – 1.52 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 163.43, 163.35, 161.91, 161.75, 161.60, 160.88, 160.80, 154.73, 145.36, 125.47, 123.25, 101.56, 101.31, 101.28, 96.20, 61.71, 29.08, 24.35, 18.00.

3-Fluoro-4-nitrophenyl 2,6-difluoro-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzoate (3h)



Quantities used: compound **2d** (1.83 g, 7.09×10^{-3} mol), 3-fluoro-4-nitrophenol (1.01 g, 6.44×10^{-3} mol), DCC (1.73 g, 8.38×10^{-3} mol), DMAP (0.0790 g, 6.44×10^{-4} mol), DCM (100 mL). The experimental procedure was described in preparation of compound **3a**. Column chromatography over silica with DCM as the eluent followed by recrystallisation from ethanol (20 mL) to obtain a white solid.

Yield: 0.332 g, 13.1 %. RF: 0.58. Melting Point: 184 °C

IR (v_{max}/cm⁻¹): 3110 (C-H), 1738 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.31 (t, *J* = 8.8 Hz, 1H, Ar), 7.73 (dd, *J* = 11.9, 2.4 Hz, 1H, Ar), 7.42 (ddd, *J* = 9.1, 2.5, 1.2 Hz, 1H, Ar), 7.06 – 6.98 (m, 2H, Ar), 5.74 (t, *J* = 2.9 Hz, 1H, THP), 3.79 – 3.59 (m, 2H, THP), 1.93 – 1.73 (m, 3H, THP), 1.71 – 1.49 (m, 3H, THP).

¹³C NMR (101 MHz, DMSO) δ: 163.58, 163.50, 161.95, 161.03, 160.94, 158.03, 156.59, 154.80, 154.69, 153.97, 134.95, 134.88, 127.70, 127.68, 119.10, 119.06, 112.88, 112.64, 101.61, 101.57, 101.35, 101.31, 96.21, 61.72, 29.07, 24.34, 18.56.

4-Nitrophenyl-2-methoxy-4-hydroxybenzoate (4a)



A round bottom flask was charged with **3a** (0.620 g, 1.65×10^{-3} mol), pyridinium ptoluenesulfonate (0.0410 g, 1.65×10^{-4} mol), THF (20 mL) and ethanol (20 mL). The solution was heated to 60 °C and stirred for 6 h. The extent of the reaction was monitored by TLC using 95:5 DCM and ethyl acetate as the solvent. Once the reaction was completed, solvent was removed under vacuum and replaced with DCM. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain off-white solid which was carried forward without further purification.

Yield: 0.460 g, 97.2 %. RF: 0.40. Melting Point: 217 °C

IR (v_{max}/cm⁻¹): 3327 (OH), 2940 (C-H), 1699 (C=O).

¹H NMR (400 MHz, DMSO) δ : 10.07 (s, 1H, -OH), 7.82 (d, J = 9.2 Hz, 2H, Ar), 7.41 (d, J = 8.6 Hz, 1H, Ar), 7.01 (d, J = 9.2 Hz, 2H, Ar), 6.05 (d, J = 2.2 Hz, 1H, Ar), 6.00 (dd, J = 8.6, 2.2 Hz, 1H, Ar), 3.32 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, DMSO) δ: 164.70, 162.82, 162.52, 156.42, 145.21, 134.92, 125.65, 123.85, 108.20, 100.17, 93.72, 56.19.

3-Fluoro-4-nitrophenyl 4-hydroxy-2-methoxybenzoate (4b)



Quantities used: compound **3b** (0.464 g, 1.19×10^{-3} mol), PPTS (0.0300 g, 1.19×10^{-4} mol), ethanol (20 mL), THF (20 mL). The experimental procedure was described in preparation of compound **4a**. Once the reaction was completed, solvent was removed under vacuum and replaced with DCM. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain off-white solid which was carried forward without further

purification.

Yield: 0.226 g, 62.1 %. RF: 0.43. Melting Point: 217 °C

IR (v_{max}/cm⁻¹): 3333 (OH), 3062 (C-H), 1702 (C=O).

¹H NMR (400 MHz, DMSO) δ : 10.65 (s, 1H, -OH), 8.26 (t, J = 8.9 Hz, 1H, Ar), 7.90 (d, J = 8.7 Hz, 1H, Ar), 7.64 (dd, J = 12.2, 2.4 Hz, 1H, Ar), 7.38 – 7.31 (m, 1H, Ar), 6.57 – 6.47 (m, 2H, Ar), 3.81 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, DMSO) δ: 164.49, 162.59, 161.57, 156.66, 156.26, 156.15, 154.05, 134.64, 134.31, 134.24, 127.41, 127.39, 119.31, 119.27, 112.90, 112.67, 107.83, 107.20, 99.75, 55.79.

4-Nitrophenyl-4-hydroxybenzoate (4c)



Quantities used: compound 3c (1.92 g, 5.59×10^{-3} mol), PPTS (0.140 g, 5.59×10^{-4} mol), ethanol (40 mL), THF (40 mL). The experimental procedure was described in preparation of compound **4a**. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain off-white solid which was carried forward without further purification.

Yield: 1.31 g, 90.3 %. RF: 0.68. Melting Point: 218 °C

IR (v_{max}/cm⁻¹): 3445 (OH), 2989 (C-H), 1733 (C=O).

¹H NMR (400 MHz, DMSO) δ : 10.63 (s, 1H, -OH), 8.33 (d, J = 9.2 Hz, 2H, Ar), 8.01 (d, J = 8.7 Hz, 2H, Ar), 7.57 (d, J = 9.3 Hz, 2H, Ar), 6.95 (d, J = 8.8 Hz, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 163.64, 163.10, 155.79, 144.96, 132.54, 125.25, 123.37, 118.56, 115.73.

3-Fluoro-4-nitrophenyl-4-hydroxybenzoate (4d)



Quantities used: compound **3c** (1.71 g, 4.74×10^{-3} mol), PPTS (0.119 g, 4.74×10^{-4} mol), ethanol (40 mL), THF (40 mL). The experimental procedure was described in preparation of compound

4a. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain pale yellow solid which was carried forward without further purification.

Yield: 1.22 g, 92.5 %. RF: 0.68. Melting Point: 196 °C

IR (v_{max}/cm⁻¹): 3383 (OH), 2956 (C-H), 1708 (C=O).

¹H NMR (400 MHz, DMSO) δ : 10.66 (s, 1H, -OH), 8.28 (t, J = 8.9 Hz, 1H, Ar), 8.00 (d, J = 8.9 Hz, 2H, Ar), 7.71 (dd, J = 12.1, 2.4 Hz, 1H, Ar), 7.41 (ddd, J = 9.1, 2.4, 1.2 Hz, 1H, Ar), 6.95 (d, J = 8.8 Hz, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 163.30, 163.24, 156.57, 156.00, 155.89, 153.96, 134.51, 134.43, 132.64, 127.44, 127.42, 119.22, 119.18, 118.27, 115.77, 112.90, 112.66.

4-Nitrophenyl 2-fluoro-4-hydroxybenzoate (4e)



Quantities used: compound 3e (1.44 g, 3.99×10^{-3} mol), PPTS (0.100 g, 3.99×10^{-4} mol), ethanol (30 mL), THF (30 mL). The experimental procedure was described in preparation of compound 4a. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain pale yellow solid which was carried forward without further purification.

Yield: 1.06 g, 96.7 %. RF: 0.33. Melting Point: 224 °C

IR (v_{max}/cm⁻¹): 3399 (OH), 3114 (C-H), 1742 (C=O).

¹H NMR (400 MHz, DMSO) δ : 11.12 (s, 1H, -OH), 8.37 – 8.29 (m, 2H, Ar), 7.98 (t, *J* = 8.8 Hz, 1H, Ar), 7.61 – 7.53 (m, 2H, Ar), 6.82 – 6.70 (m, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 164.83, 164.70, 162.25, 160.96, 160.91, 155.38, 145.07, 134.17, 134.15, 125.27, 123.40, 112.37, 112.34, 107.00, 106.91, 103.93, 103.69.

3-Fluoro-4-nitrophenyl 2-fluoro-4-hydroxybenzoate (4f)



Quantities used: compound **3f** (1.26 g, 3.30×10⁻³ mol), PPTS (0.0830 g, 3.30×10⁻⁴ mol),

ethanol (30 mL), THF (30 mL). The experimental procedure was described in preparation of compound **4a**. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain pale yellow solid which was carried forward without further purification.

Yield: 0.973 g, 99.5 %. RF: 0.45. Melting Point: 180 °C

IR (v_{max}/cm⁻¹): 3334 (OH), 3101 (C-H), 1706 (C=O).

¹H NMR (400 MHz, DMSO) δ : 11.15 (s, 1H, -OH), 8.29 (t, J = 8.9 Hz, 1H, Ar), 7.99 (t, J = 8.8 Hz, 1H, Ar), 7.72 (dd, J = 12.1, 2.4 Hz, 1H, Ar), 7.46 – 7.38 (m, 1H, Ar), 6.85 – 6.71 (m, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 164.98, 164.91, 164.85, 162.33, 160.57, 160.52, 156.56, 155.55, 155.44, 153.95, 134.65, 134.57, 134.23, 134.21, 127.49, 127.47, 119.28, 119.24, 112.98, 112.74, 106.73, 106.64, 103.95, 103.72.

4-Nitrophenyl 2,6-difluoro-4-hydroxybenzoate (4g)



Quantities used: compound **3g** (0.140 g, 3.69×10^{-4} mol), PPTS (0.00900 g, 3.69×10^{-5} mol), ethanol (20 mL), THF (20 mL). The experimental procedure was described in preparation of compound **4a**. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain a white solid which was carried forward without further purification.

Yield: 0.111 g, 99.5 %. RF: 0.35. Melting Point: 222 °C

IR (v_{max}/cm⁻¹): 3382 (OH), 3116 (C-H), 1748 (C=O).

¹H NMR (400 MHz, DMSO) δ: 11.49 (s, 1H, -OH), 8.36 – 8.32 (m, 2H, Ar), 7.61 – 7.52 (m, 2H, Ar), 6.68 – 6.61 (m, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 164.02, 163.86, 161.39, 161.31, 154.85, 145.27, 125.43, 123.27, 100.55, 100.28.

3-Fluoro-4-nitrophenyl 2,6-difluoro-4-hydroxybenzoate (4h)



Quantities used: compound **3h** (0.260 g, 6.55×10^{-4} mol), PPTS (0.0160 g, 6.55×10^{-5} mol), ethanol (20 mL), THF (20 mL). The experimental procedure was described in preparation of compound **4a**. Once the reaction was completed, solvent was removed under vacuum and replaced with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO₄. The solvent was removed to obtain pale yellow solid which was carried forward without further purification.

Yield: 0.208 g, 99.2 %. RF: 0.45. Melting Point: 196 °C

IR (v_{max}/cm⁻¹): 3369 (OH), 3110 (C-H), 1739 (C=O).

¹H NMR (400 MHz, DMSO) δ: 11.54 (s, 1H, -OH), 8.29 (t, *J* = 8.8 Hz, 1H, Ar), 7.71 (dd, *J* = 12.0, 2.4 Hz, 1H, Ar), 7.44 – 7.36 (m, 1H, Ar), 6.69 – 6.60 (m, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 164.99, 164.86, 164.20, 164.12, 164.03, 161.56, 161.48, 158.29, 158.27, 158.24, 156.64, 154.99, 154.88, 154.02, 134.84, 134.77, 127.65, 127.63, 119.10, 119.06, 119.02, 112.87, 112.63, 100.60, 100.57, 100.35, 100.32.

4-Nitrophenyl-2-methoxy-4-((4-methylthio)benzoyl)oxy)benzoate (5a)



To a pre-dried flask, 4-(methylthio)benzoic acid (0.323 g, 1.90×10^{-3} mol) was added and dissolved in DCM (50 mL). The addition of DCC (0.430 g, 2.10×10^{-3} mol) was followed by a compound **4a** (0.463 g, 1.60×10^{-3} mol) and the mixture was allowed to stir for 2 min before adding DMAP (0.0200 g, 1.60×10^{-4} mol). The reaction mixture was stirred at room temperature overnight and the extent was monitored by TLC. The white precipitate was removed by filtration and the solvent was evaporated under vacuum to leave crude solid. This was purified using silica chromatography with DCM as the eluent followed by recrystallisation from acetonitrile (20 mL) to obtain a white solid.

Yield: 0.110 g, 15.8 %. RF: 0.55. Melting Point: 164 °C

 $T_{NI} 172 \degree C T_{N_X N} (97 \degree C)$

IR (v_{max}/cm⁻¹): 2923 (C-H), 1734 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.36 (d, *J* = 8.9 Hz, 2H, Ar), 8.10 (d, *J* = 8.6 Hz, 1H, Ar), 8.07 (d, *J* = 8.3 Hz, 2H, Ar), 7.60 (d, *J* = 8.9 Hz, 2H, Ar), 7.47 (d, *J* = 8.3 Hz, 2H, Ar), 7.28 (d, *J* =

2.1 Hz, 1H, Ar), 7.08 (dd, *J* = 8.6, 2.1 Hz, 1H, Ar), 3.90 (s, 3H, -OCH₃), 2.58 (s, 3H, -SCH₃).

¹³C NMR (101 MHz, DMSO) δ: 164.27, 162.70, 161.27, 156.41, 156.00, 147.47, 145.56, 133.67, 130.76, 125.79, 125.56, 124.72, 123.88, 115.59, 114.57, 107.78, 56.99, 14.38.

M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{18}NO_7S$: 440.0801. Found: 440.0804. Difference: -0.7 ppm.



Figure S1. DSC trace for S7.

3-Fluoro-4-nitrophenyl 2-methoxy-4-((4-(methylthio)benzoyl)oxy)benzoate (5b)



To a pre-dried flask, 4-(methylthio)benzoic acid (0.300 g, 1.79×10^{-3} mol) was added and dissolved in DCM (50 mL). The reaction mixture was cooled to 0 °C before adding DCC (0.276 g, 1.34×10^{-3} mol) and stirred for 30 min. Compound **4b** (0.411 g, 1.34×10^{-3} mol) was added and stirred overnight at room temperature and the extent was monitored by TLC. The white precipitate was removed by filtration and the solvent was evaporated under vacuum to leave crude solid. This was purified using silica chromatography with DCM as the eluent followed by recrystallisation from acetonitrile (10 mL) to obtain a white solid.

Yield: 0.0300 g, 4.80 %. RF: 0.48. Melting Point: 164 °C

 $T_{NI} (143 \text{ °C}) T_{N_FN} (124 \text{ °C})$

IR (v_{max}/cm⁻¹): 3079 (C-H), 1751 (C=O).

¹H NMR (400 MHz, DMSO) δ : 8.30 (t, J = 8.9 Hz, 1H, Ar), 8.10 (d, J = 8.6 Hz, 1H, Ar), 8.08 – 8.03 (m, 2H, Ar), 7.73 (dd, J = 12.0, 2.4 Hz, 1H, Ar), 7.50 – 7.41 (m, 3H, Ar), 7.28 (d, J = 2.1 Hz, 1H, Ar), 7.08 (dd, J = 8.6, 2.1 Hz, 1H, Ar), 3.90 (s, 3H, -OCH₃), 2.58 (s, 3H, -SCH₃).

¹³C NMR (101 MHz, DMSO) δ: 163.80, 161.70, 161.02, 156.62, 156.15, 155.72, 155.61, 154.01, 147.05, 134.65, 134.58, 133.43, 130.31, 127.56, 127.54, 125.09, 124.23, 119.33, 119.29, 114.64, 114.14, 112.99, 112.75, 107.35, 56.55, 13.91.

M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{17}NO_7FS$: 458.0712. Found: 458.0710. Difference: 0.4 ppm.



Figure S2. DSC trace for S8.

4-((4-Nitrophenoxy)carbonyl)phenyl 2-methoxy-4-(methylthio)benzoate (5c)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.300 g, 1.52×10^{-3} mol), compound 4c (0.360 g, 1.38×10^{-3} mol), DCC (0.370 g, 1.79×10^{-3} mol), DMAP (0.0200 g, 1.52×10^{-4} mol) and DCM (50 mL). The experimental procedure was described in the preparation of compound 5a. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a white solid.

Yield: 0.290 g, 48.4 %. RF: 0.50. Melting Point: 147 °C

 T_{NI} 169 °C T_{N_XN} (111 °C) $T_{N_FN_X}$ (106 °C)

IR (v_{max}/cm⁻¹): 2972 (C-H), 1731 (C=O).

¹H NMR (400 MHz, DMSO) δ : 8.41 – 8.33 (m, 2H, Ar), 8.29 – 8.21 (m, 2H, Ar), 7.93 (d, J = 8.3 Hz, 1H, Ar), 7.70 – 7.61 (m, 2H, Ar), 7.54 – 7.46 (m, 2H, Ar), 7.03 (d, J = 1.7 Hz, 1H, Ar), 6.98 (dd, J = 8.3, 1.7 Hz, 1H, Ar), 3.91 (s, 3H, -OCH₃), 2.58 (s, 3H, -SCH₃).

¹³C NMR (101 MHz, CDCl₃) δ: 163.72, 163.04, 160.62, 155.98, 155.81, 148.53, 145.58, 133.03, 132.05, 125.85, 125.44, 122.79, 122.59, 116.71, 114.08, 109.10, 56.26, 14.97.

M/Z: $[M+Na]^+$ Calculated mass for $C_{22}H_{17}NO_7SNa$: 462.0644 Found: 462.0623. Difference: 4.5 ppm.



Figure S3. DSC trace for S1.

4-((3-Fluoro-4-nitrophenoxy)carbonyl)phenyl 2-methoxy-4-(methylthio)benzoate (5d)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.300 g, 1.52×10^{-3} mol), compound 4d (0.380 g, 1.38×10^{-3} mol), DCC (0.370 g, 1.79×10^{-3} mol), DMAP (0.0200 g, 1.52×10^{-4} mol) and DCM (50 mL). The experimental procedure was described in the preparation of compound 5a. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a yellow solid.

Yield: 0.228 g, 36.2 %. RF: 0.50. Melting Point: 147 °C

 $T_{NI} (135 \text{ °C}) T_{N_EN} (122 \text{ °C})$

IR (v_{max}/cm⁻¹): 2988 (C-H), 1739 (C=O).

¹H NMR (400 MHz, DMSO) δ : 8.32 (t, J = 8.9 Hz, 1H, Ar), 8.28 – 8.20 (m, 2H, Ar), 7.93 (d, J = 8.3 Hz, 1H, Ar), 7.79 (dd, J = 12.0, 2.4 Hz, 1H, Ar), 7.55 – 7.46 (m, 3H, Ar), 7.03 (d, J = 1.7 Hz, 1H, Ar), 6.98 (dd, J = 8.4, 1.7 Hz, 1H, Ar), 3.91 (s, 3H, -OCH₃), 2.58 (s, 3H, -SCH₃).

 $^{13}\mathrm{C}$ NMR (101 MHz, CDCl₃) &: 163.13, 162.86, 160.51, 157.56, 156.04, 155.82, 155.71, 154.91, 148.48, 134.91, 134.84, 132.91, 131.99, 127.27, 127.25, 125.28, 122.55, 118.14, 118.10, 116.58, 113.88, 112.54, 112.30, 108.96, 56.14, 14.84.

M/Z: $[M+Na]^+$ Calculated mass for $C_{22}H_{16}NO_7FSNa$: 480.0537. Found: 480.0529. Difference: 1.7 ppm.



Figure S4. DSC trace for S2.

3-Fluoro-4-((4-nitrophenoxy)carbonyl)phenyl 2-methoxy-4-(methylthio)benzoate (5e)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.300 g, 1.52×10^{-3} mol), compound **4e** (0.315 g, 1.14×10^{-3} mol), DCC (0.234 g, 1.14×10^{-3} mol) and DCM (50 mL). The experimental procedure was described in the preparation of compound **5b**. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a white solid.

Yield: 0.197 g, 38.3 %. RF: 0.54. Melting Point: 162 °C

 $T_{NI} (152 \text{ °C}) T_{N_{F}N} (126 \text{ °C})$

IR (v_{max}/cm⁻¹): 3073 (C-H), 1728 (C=O).

¹H NMR (400 MHz, DMSO) δ : 8.40 – 8.34 (m, 2H, Ar), 8.23 (t, *J* = 8.5 Hz, 1H, Ar), 7.94 (d, *J* = 8.3, 1H, Ar), 7.69 – 7.63 (m, 2H, Ar), 7.53 (dd, *J* = 11.7, 2.2 Hz, 1H, Ar), 7.39 – 7.34 (m, 1H, Ar), 7.05 – 6.96 (m, 2H, Ar), 3.91 (s, 3H, -OCH₃), 2.59 (s, 3H, -SCH₃).

¹³C NMR (101 MHz, DMSO) δ: 163.34, 162.01, 160.75, 160.67, 159.93, 156.22, 156.10, 155.12, 148.34, 145.32, 133.49, 132.51, 125.37, 123.43, 118.99, 118.95, 116.55, 114.36, 114.27, 112.90, 111.94, 111.69, 108.97, 56.13, 13.96.

M/Z: $[M+H]^+$ Calculated mass for C₂₂H₁₇NO₇FS: 458.0708. Found: 458.0710. Difference: -0.4 ppm.



Figure S5. DSC trace for S3.

2-methoxy-4-(methylthio)benzoate

3-Fluoro-4-((3-fluoro-4-nitrophenoxy)carbonyl)phenyl (**5f**)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.300 g, 1.52×10⁻³ mol), compound 4f (0.335 g, 1.14×10⁻³ mol), DCC (0.234 g, 1.14×10⁻³ mol) DCM (30 mL). The experimental procedure was described in the preparation of compound 5b. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a white solid.

Yield: 0.104 g, 19.3 %. RF: 0.38. Melting Point: 150 °C

 $T_{N_{F}I}(129 \ ^{\circ}C)$

IR (v_{max}/cm⁻¹): 3056 (C-H), 1727 (C=O).

¹H NMR (400 MHz, DMSO) δ: 8.33 (t, *J* = 8.8 Hz, 1H, Ar), 8.22 (t, *J* = 8.5 Hz, 1H, Ar), 7.94 (d, J = 8.3 Hz, 1H, Ar), 7.79 (dd, J = 11.9, 2.3 Hz, 1H, Ar), 7.56 – 7.47 (m, 2H, Ar), 7.37 (dd, J = 8.6, 2.1 Hz, 1H, Ar), 7.05 - 6.96 (m, 2H, Ar), 3.91 (s, 3H, -OCH₃), 2.59 (s, 3H, -SCH₃).

¹³C NMR (101 MHz, DMSO) δ: 163.40, 161.97, 160.80, 160.24, 159.94, 156.53, 156.35, 156.24, 155.22, 155.11, 153.91, 148.37, 134.91, 134.84, 133.54, 132.51, 127.61, 127.59, 119.30, 119.26, 119.03, 118.99, 116.54, 114.07, 113.99, 113.01, 112.86, 112.77, 111.98, 111.73, 108.96, 56.13, 13.95.

M/Z: $[M+Na]^+$ Calculated mass for $C_{22}H_{15}NO_7F_2NaS$: 498.0415. Found: 498.0435. Difference: -4.0 ppm.



Figure S6. DSC trace for S4.

4-Nitrophenyl 2,6-difluoro-4-((2-methoxy-4-(methylthio)benzoyl)oxy)benzoate (5g)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.134 g, 6.78×10^{-4} mol), compound **4g** (0.100 g, 3.99×10^{-4} mol), DCC (0.0700 g, 3.39×10^{-4} mol) and DCM/THF (45/5 mL). The experimental procedure was described in the preparation of compound **5b**. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a white solid.

Yield: 0.0370 g, 23.0 %. RF: 0.38. Melting Point: 174 °C

 $T_{NI} (127 \ ^{\circ}C) T_{N_{F}N} (121 \ ^{\circ}C)$

IR (v_{max}/cm⁻¹): 3070 (C-H), 1731 (C=O).

¹H NMR (400 MHz, CDCl₃) δ: 8.36 – 8.31 (m, 2H, Ar), 7.96 (d, *J* = 8.1 Hz, 1H, Ar), 7.49 – 7.44 (m, 2H, Ar), 7.06 – 7.00 (m, 2H, Ar), 6.90 – 6.85 (m, 2H, Ar), 3.96 (s, 3H, -OCH₃), 2.56 (s, 3H, -SCH₃).

 13 C NMR (101 MHz, CDCl₃) δ : 163.20, 163.13, 162.07, 160.78, 160.62, 160.55, 158.64, 155.70, 155.56, 155.41, 155.04, 149.35, 145.82, 133.04, 125.47, 122.69, 116.68, 113.08, 108.97, 107.43, 107.40, 107.18, 107.14, 106.69, 106.53, 106.37, 56.24, 14.90.



M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{16}NO_7F_2S$: 476.0611. Found: 476.0616. Difference: - 1.1 ppm.

Figure S7. DSC trace for S5.

3-Fluoro-4-nitrophenyl 2,6-difluoro-4-((2-methoxy-4-(methylthio)benzoyl)oxy)benzoate (5h)



Quantities used: 2-methoxy-4-(methylthio)benzoic acid (0.182 g, 9.20×10^{-3} mol), compound **4h** (0.144 g, 4.60×10^{-3} mol), DCC (0.0950 g, 4.60×10^{-3} mol) and DCM/THF (45/5 mL). The experimental procedure was described in the preparation of compound **5b**. Purified using column chromatography over silica with DCM as the eluent followed by hot ethanol wash to obtain a white solid.

Yield: 0.0690 g, 30.4 %. RF: 0.53. Melting Point: 171 °C

 $T_{N_FI}(122 \ ^{\circ}C)$

IR (v_{max}/cm⁻¹): 3056 (C-H), 1730 (C=O).

¹H NMR (400 MHz, CDCl₃) δ: 8.20 (t, *J* = 8.6 Hz, 1H, Ar), 7.96 (d, *J* = 8.1 Hz, 1H, Ar), 7.33 (dd, *J* = 11.1, 2.4 Hz, 1H, Ar), 7.29 – 7.27 (m, 1H, Ar), 7.07 – 7.00 (m, 2H, Ar), 6.90 – 6.85 (m, 2H, Ar), 3.96 (s, 3H, -OCH₃), 2.56 (s, 3H, -SCH₃).

 13 C NMR (101 MHz, CDCl₃) δ : 163.17, 163.09, 161.90, 160.68, 160.58, 160.51, 158.03, 157.51, 155.86, 155.71, 155.56, 154.94, 154.85, 154.84, 149.31, 135.18, 135.11, 132.92, 127.32, 127.30, 118.02, 117.98, 116.56, 112.89, 112.47, 112.23, 108.84, 107.38, 107.34, 107.12, 107.09, 105.95, 56.12, 14.78.

M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{15}NO_7F_3S$: 494.0512. Found: 494.0521. Difference: - 1.8 ppm.



Figure S8. DSC trace for S6.





2,6-Difluoro-4-hydroxybenzoic acid (6)



2,6-Difluoro-4-hydroxybenzonitrile (19.0 g, 1.23×10^{-1} mol) was dissolved in water (150 mL) while stirring. Sodium hydroxide (15.0 g, 3.80×10^{-1} mol) was carefully dissolved in water (150 ml) and added to the solution. The solution was then left stirring at reflux overnight. Reaction progress was monitored using thin layer chromatography using petroleum ether (40-60) (70%) and ethyl acetate (30%) as eluent. After cooling to room temperature, the solution was acidified using 1M HCl solution, it was then extracted using ethyl acetate. The ethyl acetate was removed under vacuum to afford the crude product, which was then recrystalised using water. Solid was redissolved in ethyl acetate, dried with MgSO₄, and concentrated under vacuum to afford a white solid.

Yield: 9.26 g, 47.0 %. RF: 0.030. Melting Point: 198 °C

IR (v_{max}/cm⁻¹): 3535 (OH), 3081 (OH), 1687 (C=O).

¹H NMR (400 MHz, DMSO) δ: 13.17 (s, 1H, -COOH), 11.00 (s, 1H, -OH), 6.55 – 6.45 (m, 2H, Ar).

¹³C NMR (101 MHz, DMSO) δ: 162.78, 162.68, 162.35, 162.33, 162.32, 161.83, 161.68, 161.53, 160.28, 160.18, 102.44, 102.26, 102.08, 99.89, 99.87, 99.82, 99.68, 99.64, 99.61.

Phenyl 2,6-difluoro-4-hydroxybenzoate (7)



Compound **6** (5.00 g, 2.87×10^{-2} mol) and Na₂CO₃ (3.04 g, 2.87×10^{-2} mol) were first azeotroped in dry toluene three times. Following this, dry DMF (50 ml) was added. Benzyl bromide (3.40 mL, 4.91 g, 2.87×10^{-2} mol) was added and the mixture was left stirring at room temperature overnight. The mixture was added to distilled water (200 mL) and acidified to approximately pH 4 using dilute HCl. It was extracted using diethyl ether (5 x 25 mL). The combined organic extracts were washed using water and brine before finally being dried over magnesium sulfate. The crude product was purified by flash chromatography using petroleum ether (40-60) (70%) and ethyl acetate (30%) as eluent. The residue was recrystalised from toluene (30 mL) to obtain a white solid.

Yield: 2.86 g, 38.0 %. RF: 0.40. Melting Point: 163 °C

IR (v_{max}/cm⁻¹): 3182 (OH), 1672 (C=O).

¹H NMR (400 MHz, DMSO) δ: 11.17 (s, 1H, -OH), 7.46 – 7.29 (m, 5H, Ar), 6.60 – 6.50 (m, 2H, Ar), 5.31 (s, 2H, (C=O)-O-<u>CH</u>₂-).

¹³C NMR (101 MHz, DMSO) δ: 163.05, 162.96, 162.70, 162.55, 162.40, 160.75, 160.73, 160.71, 160.53, 160.44, 135.78, 128.49, 128.13, 127.91, 100.73, 100.56, 100.39, 100.14, 100.11, 100.07, 99.89, 99.86, 66.49.

Phenyl 4-((2,4-dimethoxybenzoyl)oxy)-2,6-difluorobenzoate (8)



2,4-Dimethoxybenzoic acid (0.860 g, 4.70×10^{-3} mmol) and DCC (1.14 g, 5.5×10^{-3} mol) were dissolved in DCM (50 mL) and left stirring for 10 min. Compound 7 (1.13 g, 4.27×10^{-3} mol) and DMAP (0.520 g, 0.430×10^{-3} mol) were added together, and the mixture was left stirring at room temperature overnight. The mixture was filtered to remove the dicyclohexylurea. The crude product was purified by flash chromatography using DCM (98%) and ethyl acetate (2%) as eluent to obtain a white solid.

Yield: 1.19 g. 65.0 %. RF: 0.71. Melting Point: 101 °C

IR (v_{max}/cm⁻¹): 3016 (C-H), 1727 (C=O).

¹H NMR (400 MHz, DMSO) δ : 7.97 (d, J = 8.8 Hz, 1H, Ar), 7.50 – 7.28 (m, 7H, Ar), 6.71 (d, J = 2.3 Hz, 1H, Ar), 6.68 (dd, J = 8.8, 2.4 Hz, 1H, Ar), 5.41 (s, 2H, (C=O)-O-<u>CH₂</u>-), 3.88 (s, 3H, -OCH₃), 3.87 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, DMSO) δ: 165.32, 162.13, 161.49, 161.46, 161.37, 160.23, 158.93, 158.85, 154.51, 154.36, 154.21, 135.35, 134.34, 128.55, 128.33, 128.08, 108.93, 107.88, 107.84, 107.70, 107.63, 107.59, 107.52, 107.34, 105.84, 98.98, 67.29, 56.03, 55.78.

4-((2,4-Dimethoxybenzoyl)oxy)-2,6-difluorobenzoic acid (9)



Compound 8 (1.14 g, 2.66×10^{-3} mol) was dissolved in a 50:50 mixture of DCM and ethanol (100 mL). This solution was first evacuated under vacuum and purged with argon. Pd/C 5% (0.0140g, 0.130×10^{-3} mol) was added, the argon atmosphere was replaced with hydrogen gas and the mixture was left stirring at room temperature overnight. Hydrogen was pumped out of

the system and the flask was purged thoroughly with argon. Reaction progress was monitored using thin layer chromatography using DCM (98%) and ethyl acetate (2%) as eluent. The mixture was filtered through Celite and the solvents were removed under vacuum to obtain a white solid which was used without further purification.

Yield: 0.730 g, 81.0 %. RF: 0.010. Melting Point: 204 °C

IR (v_{max}/cm⁻¹): 2847 (OH), 1757 (C=O).

¹H NMR (400 MHz, DMSO) δ: 13.84 (s, 1H, -COOH), 7.97 (d, J = 8.7 Hz, 1H, Ar), 7.29 – 7.20 (m, 2H, Ar), 6.71 (d, J = 2.2 Hz, 1H, Ar), 6.67 (dd, J = 8.6, 2.4 Hz, 1H, Ar), 3.88 (s, 3H, -OCH₃), 3.87 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, DMSO) δ: 165.26, 162.07, 161.83, 161.71, 160.92, 160.82, 158.42, 158.32, 153.38, 153.23, 153.09, 134.30, 110.11, 109.91, 109.10, 107.54, 107.51, 107.47, 107.28, 107.25, 105.82, 98.99, 56.04, 55.78.

4-Nitrophenyl 4-((2,4-dimethoxybenzoyl)oxy)-2,6-difluorobenzoate (10a)



Compound 9 (0.540 g, 1.60×10^{-3} mol) and DCC (0.170 g, 0.800×10^{-3} mol) were dissolved in DCM (50 mL) at 0° and were left stirring for 20 min. 4-nitrophenol (0.110 g, 0.800×10^{-3} mmol) was added and the mixture was left stirring at room temperature overnight. The solvent was removed under vacuum and the crude product was purified by flash chromatography using DCM as the eluent. The residue was washed with hot ethanol to obtain a white solid.

Yield: 0.0550 g, 15.0 %. RF: 0.34. Melting Point: 192 °C

 $T_{NI} (139 \text{ °C}) T_{N_{E}N} (132 \text{ °C})$

IR (v_{max}/cm⁻¹): 3123 (C-H), 1754 (C=O).

¹H NMR (400 MHz, CDCl₃) δ : 8.38 – 8.29 (m, 2H, Ar), 8.04 (d, J = 8.8 Hz, 1H, Ar), 7.51 – 7.43 (m, 2H, Ar), 7.06 – 7.00 (m, 2H, Ar), 6.58 (dd, J = 8.8, 2.3 Hz, 1H, Ar), 6.54 (d, J = 2.3 Hz, 1H, Ar), 3.95 (s, 3H, -OCH₃), 3.91 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, CDCl₃) δ: 165.94, 163.23, 163.15, 162.93, 161.96, 160.65, 160.58, 158.71, 155.75, 155.08, 145.83, 134.88, 125.49, 122.71, 109.61, 107.48, 107.44, 107.23, 107.19, 106.40, 105.31, 99.16, 56.21, 55.84.

M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{16}NO_8F_2$: 460.0825. Found: 460.0844. Difference: -4.1 ppm.



Figure S9. DSC trace for O5.

3-Fluoro-4-nitrophenyl 4-((2,4-dimethoxybenzoyl)oxy)-2,6-difluorobenzoate (10b)



Compound **9** (0.600 g, 1.78×10^{-3} mol) and DCC (0.180 g, 0.890×10^{-3} mol) were dissolved in DCM (50 mL) at 0 °C and were left stirring for 20 min. 3-Fluoro-4-nitrophenol (0.140 g, 0.890×10^{-3} mol) was added and the mixture was left stirring at room temperature overnight. The solvent was removed under vacuum and the crude product was purified by flash chromatography using DCM as the eluent. The residue was washed with hot ethanol to produce a white solid.

Yield: 0.0440 g, 10.0 %. RF: 0.43. Melting Point: 160 °C

 $T_{N_{r}I}(131 \text{ °C})$

IR (v_{max}/cm⁻¹): 3112 (C-H), 1745 (C=O).

¹H NMR (400 MHz, CDCl₃) δ : 8.19 (t, J = 8.7 Hz, 1H, Ar), 8.03 (d, J = 8.6 Hz, 1H, Ar), 7.32 (dd, J = 11.2, 2.4 Hz, 1H, Ar), 7.29 – 7.22 (m, 1H, Ar), 7.06 – 6.98 (m, 2H, Ar), 6.56 (dd, J = 8.9, 2.3 Hz, 1H, Ar), 6.54 (d, J = 2.2 Hz, 1H, Ar), 3.94 (s, 3H, -OCH₃), 3.90 (s, 3H, -OCH₃).

¹³C NMR (101 MHz, CDCl₃) δ: 165.96, 163.29, 163.22, 162.93, 161.88, 160.71, 160.64, 158.20, 157.63, 156.16, 156.02, 155.87, 155.09, 154.99, 154.97, 135.28, 135.21, 134.87,

127.43, 127.41, 118.16, 118.11, 112.59, 112.35, 109.50, 107.52, 107.49, 107.27, 107.23, 105.89, 105.33, 99.13, 56.19, 55.82.

M/Z: $[M+H]^+$ Calculated mass for $C_{22}H_{15}NO_8F_3$: 478.0727. Found: 478.0750. Difference: -4.8 ppm.



Figure S10. DSC trace for O6.