Metal-free Deoxygenative Coupling of Alcohol-Derived Benzoates and Pyridines for Small Molecules and DNA-Encoded Libraries Synthesis

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1. General Information

Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded at ambient temperature on Varian Mercury 300 MHz or Bruker AVIII 500 MHz spectrometers. Chemical shifts (\(\delta\)) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in CDCl\(_3\) (7.26 ppm) and coupling constants (\(J\)) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported.

Carbon nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded at ambient temperature on Varian Mercury 300 MHz or Bruker AVIII 500 MHz spectrometers. Chemical shift (\(\delta\)) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in CDCl\(_3\) (77.16 ppm). DEPT135, nOe experiments and 2-dimensional experiments (COSY, HMBC and HSQC) were used to support assignments where appropriate.

High-resolution mass spectra (HRMS) were measured on Bruker micrOTOF spectrometer using direct injection APCI mode at the CACTUS facility of the University of Santiago de Compostela.

Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silica gel 60 F254). Flash column chromatography was undertaken on silica gel (40-60 μm) under a positive pressure of air unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with basic potassium permanganate solutions as appropriate.

Dichloromethane (DCM), Tetrahydrofuran (THF), dimethylformamide (DMF), Acetonitrile (MeCN) were dried and dispensed using solvent purification system. Dimethylsulfoxide (DMSO) was purchased from Sigma-Aldrich chemical company. All
reagents were purchased at the highest commercial quality and used without further purification. Diethylether (Et$_2$O) used as an eluent in flash column contained 200ppm of 2,6-Di-tert-butyl-4-methylphenol (BHT) as a stabilizer.

Reactions were carried out under an atmosphere of Argon unless otherwise stated. All reactions were monitored by TLC, $^1$H NMR spectra taken from reaction samples (NMR yields determined by $^1$H NMR with reference to 1,1,2,2-tetrachloroethane as an internal standard) or gas chromatography mass spectrometry (GC-MS) using Agilent 8890 (mass detector: Agilent 5977B GC/MSD).

Photochemical reactions were irradiated using Kessil A160WE LED Aquarium Light - Tuna Blue (40 W) as light source (settings: maximum blue and maximum intensity).

DNA headpiece $\text{Sx (5}'d \text{ Phos-GAGTCA-Spacer 9-Amino C7-Spacer 9-TGACTCCC 3')}$ was purchased from LGC Biosearch Technologies

2. Synthesis of starting materials

**General procedure A: synthesis of benzoate esters via the acyl chloride**

In a 100 mL round bottom flask equipped with stir bar, the appropriate alcohol (5.0 mmol, 1 equiv) was dissolved in dry DCM (50 mL) under argon atmosphere, followed by the addition of 4-(Dimethylamino)pyridine (4-DMAP) (18 mg, 0.15 mmol, 0.05 equiv) and triethylamine (Et$_3$N) (1.4 mL, 10 mmol, 2 equiv). The resulting suspension was cooled at 0 °C and the acyl chloride (5.5 mmol, 1.1 equiv) was slowly added. The reaction mixture was stirred at room temperature for 2 hours, solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel) under the stated conditions to provide the pure alcohol derivative.
General procedure B: synthesis of benzoate esters via the carboxylic acid

\[
\text{R}^2\text{OH} + \text{EWG} \text{CO}_2\text{H} \xrightarrow{\text{DCC} (1.1 \text{ equiv})} \text{R}^2\text{O}\text{EWG}
\]

1 equiv

1 equiv

4-DMAP (0.05 equiv)

In a 100 mL round bottom flask equipped with stir bar, the appropriate alcohol (3.0 mmol, 1 equiv) was dissolved in dry DCM (30 mL) under argon atmosphere, followed by the addition of the benzoic acid (3.0 mmol, 1 equiv) and 4-(Dimethylamino)pyridine (4-DMAP) (18 mg, 0.15 mmol, 0.05 equiv). The resulting suspension was cooled at 0 °C and N,N-Dicyclohexylcarbodimide (DCC) (681 mg, 3.3 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature for 17 hours, diluted with 20 mL of DCM and washed with: 5% HCl aqueous solution (20 mL), NaHCO₃ saturated aqueous solution (20 mL) and NaCl saturated aqueous solution (20 mL). The organic extract was dried (MgSO₄ or Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel) under the stated conditions to provide the pure alcohol derivative.

General procedure C: synthesis of benzoate esters from tertiary alcohols

\[
\text{NC} \text{CO}_2\text{Cl} \xrightarrow{\text{DMF, DCM}} \text{NC} \text{CO}_2\text{Cl} \xrightarrow{1 \text{ equiv}} \text{R}^1\text{O}\text{RC} \text{CN}
\]

1.2 equiv

1.44 equiv

1 equiv

4-DMAP, Et₃N, DCM

In a 100 mL round bottom flask equipped with stir bar, 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv) and dry DCM (15 mL) were charged under argon atmosphere, followed by the addition of oxalyl chloride (0.610 mL, 7.2 mmol, 1.44 equiv) and 7 drops of DMF at rt. The resulting suspension was stirred for 1 hour (until CO₂ evolution stopped and the solution became homogeneous), solvent was evaporated under reduced pressure and the acyl chloride redissolved in 2 mL of dry DCM. Meanwhile, in a 100 mL round bottom flask equipped with stir bar, the appropriate tertiary alcohol (5.0 mmol, 1 equiv) was dissolved in dry DCM (13 mL) under argon
atmosphere, followed by the addition of 4-(Dimethylamino)pyridine (4-DMAP) (306 mg, 2.5 mmol, 0.5 equiv) and triethylamine (Et₃N) (0.836 uL, 6.0 mmol, 1.2 equiv). The resulting solution was cooled at 0 °C and the freshly prepared acyl chloride solution was added dropwise. The reaction mixture was stirred at room temperature for 24 hours, diluted with 20 mL of DCM and washed with: water (15 mL) and NaCl saturated aqueous solution (15 mL). The organic extract was dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel) under the stated conditions to provide the pure alcohol derivative.

**General procedure D: synthesis of secondary alcohols from aldehydes**

\[
\begin{align*}
\text{R}^1\text{C} & \quad \text{OH} \\
1.0 \text{ equiv} & \quad 1.25 \text{ equiv} \\
\text{MgBr} & \quad \text{THF}
\end{align*}
\]

In a 25 mL round bottom flask equipped with stir bar, the appropriate aldehyde (2.0 mmol, 1 equiv) was dissolved in dry THF (4 mL) under argon atmosphere. The resulting solution was cooled at 0 °C and the (1,3-Dioxan-2-yethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour (until TLC shows the complete conversion of the aldehyde), quenched with NH₄Cl saturated aqueous solution at 0 °C (1 mL), diluted with water (10 mL) and Et₂O (10 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (10 mL). The combined organic phases were washed with NaCl saturated aqueous solution (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude alcohol was used in the next step without additional purification unless otherwise stated.

**General procedure E: synthesis of tertiary alcohols from ketones**

\[
\begin{align*}
\text{R}^1\text{C} & \quad \text{OH} \\
1.0 \text{ equiv} & \quad 1.2 \text{ equiv} \\
\text{MgBr} & \quad \text{THF}
\end{align*}
\]

In a 25 mL round bottom flask equipped with stir bar, the appropriate ketone (2.0 mmol, 1 equiv) was dissolved in dry THF (4 mL) under argon atmosphere. The resulting solution was cooled at 0 °C and the 1,3-Dioxane magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour (until TLC shows the complete conversion of the ketone), quenched with NH₄Cl saturated aqueous solution at 0 °C (1 mL), diluted with water (10 mL) and Et₂O (10 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (10 mL). The combined organic phases were washed with NaCl saturated aqueous solution (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude alcohol was used in the next step without additional purification unless otherwise stated.
In a 100 mL round bottom flask equipped with stir bar, the appropriate ketone (10.0 mmol, 1 equiv) was dissolved in dry THF (10 mL) under argon atmosphere. The resulting solution was cooled at 0 °C and the phenylmagnesium bromide solution (3M in Et₂O, 4 mL, 12.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour (until TLC shows the complete conversion of the ketone), quenched with NH₄Cl saturated aqueous solution at 0 °C (3 mL), diluted with water (20 mL) and Et₂O (20 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (20 mL). The combined organic phases were washed with NaCl saturated aqueous solution (15 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude alcohol was used in the next step without additional purification unless otherwise stated.

**General procedure F: synthesis of 3-Aryl-4-cyanopyridine via Suzuki-Miyaura cross-coupling reaction**

\[
\begin{align*}
\text{CN} & \quad \text{Cl} \\
\text{1.0 equiv} & \\
\text{1.5 equiv} & \\
+ & \\
\text{B(OH)}_2 & \\
\text{Pd(PPh}_3\text{)}_4 (0.05 \text{ equiv}) & \\
\text{K}_2\text{CO}_3 (2.5 \text{ equiv}) & \\
\text{PhMe/EtOH/H}_2\text{O} & \\
(4:1:1) & \\
\text{reflux} & \\
\rightarrow & \\
\text{CN} & \quad \text{R} \\
\text{3-chloroisonicotinonitrile} & \\
\text{1.0 equiv} & \\
\text{Arylboronic acid} & \\
\text{1.5 equiv} & \\
\text{K}_2\text{CO}_3 & \\
\text{2.5 equiv} & \\
\rightarrow & \\
\text{3-chloroisonicotinonitrile} & \\
\text{1.0 equiv} & \\
\text{K}_2\text{CO}_3 & \\
\text{2.5 equiv} & \\
\rightarrow & \\
\text{3-Aryl-4-cyanopyridine} & \\
\text{via Suzuki-Miyaura cross-coupling reaction} & \\
\end{align*}
\]

3-chloroisonicotinonitrile (1.0 equiv) was dissolved in toluene/ethanol/water (4:1:1, 10 mL). Arylboronic acid (1.5 equiv) and K₂CO₃ (2.50 equiv) were subsequently added. The mixture was purged with argon for 30 min, Pd(PPh₃)₄ (0.05equiv) was added and the reaction was refluxed overnight. The yellow solution was then allowed to cool down to rt and poured into water (40 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL), then the combined extracts were washed with 1.0 M NaOH (50 mL), brine (50 mL) and dried over MgSO₄ and then concentrated in vacuo. The residue was then purified by flash chromatography (silica gel) under the stated conditions to provide the desired compound.
1-phenylpropyl 3,5-dinitrobenzoate (1)

Prepared according to general procedure A using 1-phenyl-1-propanol (0.684 mL, 5.0 mmol) and 3,5-dinitrobenzoyl chloride (1.268 g, 5.5 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et₂O) to provide the title compound as a white solid (1.290 mg, 78% yield). ¹H NMR (300 MHz, CDCl₃) δ: 9.24 - 9.19 (s, 1H), 9.19 - 9.12 (s, 2H), 7.49 - 7.29 (m, 5H), 5.99 (t, J = 7.0 Hz, 1H), 2.27 - 1.96 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 162.05, 148.86, 139.23, 134.42, 129.54, 128.89, 128.77, 126.92, 122.46, 80.77, 29.22, 10.20; m/z HRMS (APCI) found [M⁺] 330.0838, C₁₆H₁₄N₂O₆ requires 330.0846.

1-phenylpropyl 4-nitrobenzoate (2)

Prepared according to general procedure A using 1-phenyl-1-propanol (0.684 mL, 5.0 mmol) and 4-nitrobenzoyl chloride (1.021 g, 5.5 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et₂O) to provide the title compound as a viscous oil (1.070 g, 75% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.29 (d, J = 9.1 Hz, 2H), 8.24 (d, J = 9.1 Hz, 2H), 7.46 - 7.28 (m, 5H), 5.95 (t, J = 6.9 Hz, 1H), 2.21 - 1.91 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 164.14, 150.68, 139.97, 136.06, 130.84, 128.71, 128.35, 126.69, 123.65, 79.33, 29.46, 10.07; m/z HRMS (APCI) found [M⁺] 285.0986, C₁₆H₁₄NO₄ requires 285.0996.

1-phenylpropyl 4-cyano-2-fluorobenzoate (3)
Prepared according to general procedure B using 1-phenyl-1-propanol (0.411 mL, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et2O) to provide the title compound as a white solid (654 mg, 77% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.04 (t, \(J = 7.3\) Hz, 1H), 7.50 (dd, \(J = 8.1, 1.2\) Hz, 1H), 7.45 (dd, \(J = 9.8, 1.2\) Hz, 1H), 7.43 – 7.27 (m, 5H), 5.94 (t, \(J = 6.8\) Hz, 1H), 2.16 – 2.02 (m, 1H), 2.02 – 1.88 (m, 1H), 0.96 (t, \(J = 7.4\) Hz, 4H) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 162.48 (d, \(J = 3.9\) Hz), 161.39 (d, \(J = 263.6\) Hz), 139.84, 133.34 (d, \(J = 1.4\) Hz), 128.69, 128.34, 127.83 (d, \(J = 4.5\) Hz), 126.75, 123.77 (d, \(J = 10.7\) Hz), 121.04 (d, \(J = 26.2\) Hz), 117.61 (d, \(J = 9.6\) Hz), 116.80 (d, \(J = 2.5\) Hz), 79.75, 29.58, 9.97; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\): -105.9; HRMS (APCI) found [M]\(^+\) 283.1005, C\(_{17}\)H\(_{14}\)FNO\(_2\) requires 283.1003.

1-phenylpropyl 5-cyanopicolinate (4)

Prepared according to general procedure B using 1-phenyl-1-propanol (0.411 mL, 3.0 mmol) and 5-Cyanopyridine-2-carboxylic acid (444 mg, 3.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et2O) to provide the title compound as a white solid (606 mg, 76% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 9.06 – 8.94 (m, 1H), 8.27 – 8.17 (m, 1H), 8.16 – 8.03 (m, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.26 (m, 3H), 5.98 (t, \(J = 7.0\) Hz, 1H), 2.25 – 1.93 (m, 2H), 0.97 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 163.21, 152.47, 151.14, 140.58, 139.66, 128.70, 128.43, 126.87, 124.83, 115.97, 112.82, 80.13, 29.28, 10.16; m/z HRMS (APCI) found [M]\(^+\) 266.1044, C\(_{16}\)H\(_{14}\)FNO\(_2\) requires 266.1050.

1,3-diethyl 5-(1-phenylpropyl) benzene-1,3,5-tricarboxylate (5)

Prepared according to general procedure B using 1-phenyl-1-propanol (0.411 mL, 3.0 mmol) and diethyl 1,3,5-benzenetricarboxylate (799 mg, 3.0 mmol). The crude product
was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a viscous oil (818 mg, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.90 – 8.86 (m, 2H), 8.86 – 8.83 (m, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.26 (m, 1H), 5.95 (t, J = 6.9 Hz, 1H), 4.44 (q, J = 7.1 Hz, 4H), 2.22 – 1.89 (m, 2H), 1.43 (t, J = 7.1 Hz, 6H), 0.98 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 165.19, 164.57, 140.23, 134.62, 134.58, 131.66, 128.65, 128.22, 126.75, 79.09, 61.82, 29.51, 14.42, 10.14; m/z HRMS (APCI) found [M⁺] 384.1563, C₂₂H₂₄O₆ requires 384.1567.

1-phenylpropyl 3,5-bis(trifluoromethyl)benzoate (6)

Prepared according to general procedure A using 1-phenyl-1-propanol (0.684 mL, 5.0 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (1.521 g, 5.5 mmol). The crude product was purified by flash column chromatography (95/5 to 90/10 Hexane/Et₂O) to provide the title compound as a viscous oil (1.466 g, 78% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.51 (s, 2H), 8.07 (s, 1H), 7.47 – 7.28 (m, 5H), 5.97 (t, J = 7.0 Hz, 1H), 2.26 – 1.93 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 163.45, 139.77, 132.92, 132.38 (q, J = 34.0 Hz), 130.03 – 129.59 (m), 128.79, 128.51, 126.82, 126.67 – 126.26 (m), 123.06 (q, J = 272.9 Hz), 79.81, 29.35, 10.16; ¹⁹F NMR (282 MHz, CDCl₃) δ: -63.00; m/z HRMS (APCI) found [M⁺] 376.0903, C₁₈H₁₆F₄O₂ requires 376.0893.

1-phenylpropyl 2,4-bis(trifluoromethyl)benzoate (7)

Prepared according to general procedure B using 1-phenyl-1-propanol (0.411 mL, 3.0 mmol) and 2,4-Bis(trifluoromethyl)benzoic acid (774 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 90/10 Hexane/Et₂O) to provide the title compound as a viscous oil (868 mg, 77% yield). ¹H NMR (300 MHz, CDCl₃) δ:
8.00 (s, 1H), 7.94 – 7.78 (m, 2H), 7.44 – 7.28 (m, 5H), 5.94 (t, J = 7.0 Hz, 1H), 2.22 – 1.88 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ: 165.12, 139.38, 135.25, 133.34 (q, J = 33.9 Hz), 131.04, 129.71 (q, J = 33.8 Hz), 129.05 – 128.75 (m), 128.69, 128.49, 127.03, 124.36 – 123.76 (m), 123.04 (q, J = 272.7 Hz), 122.75 (q, J = 274.0 Hz), 80.51, 29.04, 9.94; 19F NMR (282 MHz, CDCl3) δ: -59.5, -63.3; m/z HRMS (APCI) found [M]+ 376.0897, C18H14F6O2 requires 376.0893.

1-phenylpropyl 2,3,4,5,6-pentafluorobenzoate (8)

Prepared according to general procedure B using 1-phenyl-1-propanol (0.411 mL, 3.0 mmol) and pentafluorobenzoic acid (636 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 90/10 Hexane/Et2O) to provide the title compound as a colorless oil (723 mg, 73% yield). 1H NMR (300 MHz, CDCl3) δ: 7.43 – 7.28 (m, 5H), 5.94 (t, J = 6.8 Hz, 1H), 2.17 – 1.87 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ: 158.53, 139.35, 128.71, 128.48, 126.80, 80.73, 29.45, 9.92 (note: some carbon peaks are not reported due to the multiple coupling with fluorine atoms in the pentafluorobenzene system); 19F NMR (282 MHz, CDCl3) δ: -138.2, -149.0, -160.5; m/z HRMS (APCI) found [M]+ 330.0669, C16H11F5O2 requires 330.0674.

1-(4-cyanophenyl)ethyl 4-cyano-2-fluorobenzoate (S1)

Prepared according to the general procedure B using 4-(1-hydroxyethyl)benzonitrile (441 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (545 mg, 3.3 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 hexane/Et2O) to provide the title compound as a white solid (706 mg, 80% yield). 1H NMR (300 MHz, CDCl3) δ 8.16 – 7.97 (t, J = 7.2 Hz 1H), 7.79 – 7.62 (m, 2H), 7.60 – 7.45 (m, 4H), 6.17 (q, J = 6.7 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 162.18 (d, J
= 3.7 Hz), 161.35 (d, J = 263.9 Hz) 146.17, 133.33 (d, J = 1.6 Hz), 132.71, 127.93 (d, J = 4.5 Hz), 126.83, 123.05 (d, J = 10.4 Hz), 121.10 (d, J = 26.2 Hz), 118.54, 118.01 (d, J = 9.7 Hz), 116.62 (d, J = 2.6 Hz), 112.27. 19F NMR (282 MHz, CDCl3) δ -105.73 (dd, J = 9.8, 7.0 Hz).

HRMS (APCI) [M+H]+ found 295.0874, C17H11FN2O2 requires 295.0877.

Benzhydryl 4-cyano-2-fluorobenzoate (S2)

Prepared according to general procedure B using diphenylmethanol (553 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et2O) to provide the title compound as a white solid (716 mg, 72% yield). 1H NMR (300 MHz, CDCl3) δ: 8.11 (dd, J = 8.0, 7.0 Hz, 1H), 7.55-7.42 (m, 6H), 7.42-7.27 (m, 6H), 7.15 (s, 1H); 13C NMR (75 MHz, CDCl3) δ: 162.13 (d, J = 3.9 Hz), 161.47 (d, J = 263.9 Hz), 139.65, 133.50 (d, J = 1.7 Hz), 128.80, 128.37, 127.88 (d, J = 4.4 Hz), 127.22, 123.33 (d, J = 10.3 Hz), 121.10 (d, J = 26.2 Hz), 117.87 (d, J = 9.5 Hz), 116.73 (d, J = 2.6 Hz), 79.06; 19F NMR (282 MHz, CDCl3) δ: -105.3; HRMS (APCI) found [M]+ 331.1002, C21H14FN2O2 requires 331.1003.

1,2-dihydroacenaphthylene-1-yl 4-cyano-2-fluorobenzoate (S3)

Prepared according to general procedure B using 1-Aacenaphthenol (511 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 85/15 Hexane/Et2O) to provide the title compound as a white solid (638 mg, 67% yield). 1H NMR (500 MHz, CDCl3) δ: 8.04 (app t, J = 7.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.64 (d, J =
6.9 Hz, 1H), 7.57 (app t, J = 7.6 Hz, 1H), 7.53 (app t, J = 7.6 Hz, 1H), 7.48 (app d, J = 8.0 Hz, 1H), 7.43 (app d, J = 9.8, 1H), 7.37 (d, J = 6.8 Hz, 1H), 6.91 (dd, J = 7.4, 2.3 Hz, 1H), 3.98 (dd, J = 17.9, 7.4 Hz, 1H), 3.54 – 3.49 (d, J = 17.9 Hz,1H).; 

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 162.98 (d, J = 3.9 Hz), 161.46 (d, J = 264.5 Hz), 141.29, 140.85, 138.07, 133.25 (d, J = 1.7 Hz), 131.35, 128.45, 128.25, 127.80 (d, J = 4.5 Hz), 125.99, 123.44 (d, J = 9.9 Hz), 123.24, 122.28, 121.02 (d, J = 25.9 Hz), 120.14, 117.76 (d, J = 9.9 Hz), 116.74 (d, J = 2.7 Hz), 77.77, 38.84; $^{19}$F NMR (470 MHz, CDCl$_3$) δ: -106.1; HRMS (APCI) found [M+1]$^+$ 318.0925, C$_{20}$H$_{12}$FNO$_2$ requires 318.0925.

3-(1,3-dioxan-2-yl)-1-phenylpropyl 4-cyano-2-fluorobenzoate (S4)

![Chemical Structure](image)

1st step. 3-(1,3-dioxan-2-yl)-1-phenylpropan-1-ol: prepared according to general procedure D using benzaldehyde (0.203 mL, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure B using crude 3-(1,3-dioxan-2-yl)-1-phenylpropan-1-ol and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 Hexane/Et$_2$O) to provide the title compound as a white solid (465 mg, 63% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.04 (app t, J = 7.6 Hz, 1H), 7.56-7.24 (m, 7H), 6.03 (app t, J = 6.9 Hz, 1H), 4.55 (m, 1H), 4.08 (dd, J = 11.6, 4.8 Hz, 2H), 3.73 (td, J = 11.6, 2.1 Hz, 2H), 2.27-1.94 (m, 3H), 1.81-1.60 (m, 2H), 1.32 (d, J = 13.5 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 162.31 (d, J = 3.9 Hz), 161.37 (d, J = 263.7 Hz), 139.81, 133.35, 128.73, 128.37, 127.80 (d, J = 4.4 Hz), 126.66, 123.63 (d, J = 10.3 Hz), 121.02 (d, J = 26.2 Hz), 117.62 (d, J = 9.5 Hz), 116.78 (d, J = 2.6 Hz), 101.61, 78.13, 67.00, 31.18, 30.87, 25.86; $^{19}$F NMR (282 MHz, CDCl$_3$) δ: -105.8; HRMS (APCI) found [M-1]$^+$ 368.1302, C$_{21}$H$_{19}$FNO$_4$ requires 368.1293.
1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate (S5)

1st step. 1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol: prepared according to general procedure D using 4-chlorobenzaldehyde (281 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure B using crude 1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol and 4-cyano-2-fluorobenzoic acid (533 mg, 2.0 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 Hexane/Et₂O) to provide the title compound as a white solid (465 mg, 66% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: δ 8.02 (t, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.1, 0.9 Hz, 1H), 7.45 (dd, J = 9.8, 1.1 Hz, 1H), 7.38 – 7.28 (m, 4H), 5.99 (dd, J = 7.3, 6.2 Hz, 1H), 4.55 (t, J = 4.9 Hz, 1H), 4.07 (dd, J = 10.9, 4.9 Hz, 2H), 3.72 (td, J = 12.2, 2.1 Hz, 2H), 2.24 – 1.94 (m, 3H), 1.78 – 1.55 (m, 2H), 1.32 (d, J = 13.5 Hz, 1H);

¹³C NMR (75 MHz, CDCl₃) δ: 162.19 (d, J = 3.8 Hz), 161.26 (d, J = 263.8 Hz), 138.31, 134.08, 133.24, 128.85, 128.03, 127.78 (d, J = 4.4 Hz), 123.29 (d, J = 10.4 Hz), 120.97 (d, J = 26.2 Hz), 117.67 (d, J = 9.7 Hz), 116.66 (d, J = 2.5 Hz), 101.37, 77.29, 66.90, 30.97, 30.61, 25.76; ¹⁹F NMR (282 MHz, CDCl₃) δ: -105.8; HRMS (APCI) found [M-1]⁺ 402.0908, C₂₁H₁₈ClFNO₄ requires 402.0903.

1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate (S6)
1st step. 1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propan-1-ol: prepared according to general procedure D using piperonal (300 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure B using crude 1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propan-1-ol and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (70/30 to 50/50 Hexane/Et₂O) to provide the title compound as a white solid (604 mg, 73% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.01 (app t, J = 7.5 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 9.7 Hz, 1H), 6.89 (s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.93 (s, 2H), 4.54 (t, J = 4.9 Hz, 1H), 4.07 (dd, J = 11.3, 4.5 Hz, 2H), 3.72 (t, J = 11.3 Hz, 2H), 2.19-1.92 (m, 3H), 1.74-1.56 (m, 2H), 1.31 (d, J = 13.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.25 (d, J = 3.8 Hz), 161.34 (d, J = 263.8 Hz), 147.99, 147.65, 133.60, 133.29, 127.78 (d, J = 4.4 Hz), 123.61 (d, J = 10.5 Hz), 120.99 (d, J = 26.1 Hz), 120.65, 117.59 (d, J = 9.7 Hz), 116.77 (d, J = 2.6 Hz), 108.32, 107.10, 101.56, 101.26, 78.01, 66.98, 31.19, 30.75, 25.84; ¹⁹F NMR (282 MHz, CDCl₃) δ: -105.9; HRMS (APCI) found [M⁺] 413.1285, C₂₂H₂₆FNO₆ requires 413.1275.

3-(1,3-dioxan-2-yl)-1-(naphthalen-2-yl)propyl 4-cyano-2-fluorobenzoate (S7)

1st step. 3-(1,3-dioxan-2-yl)-1-(naphthalen-2-yl)propan-1-ol: prepared according to general procedure D using 2-Naphthaldehyde (312 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure B using crude 3-(1,3-dioxan-2-yl)-1-(naphthalen-2-yl)propan-1-ol and 4-cyano-2-fluorobenzoic acid
(330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 Hexane/Et2O) to provide the title compound as a resin-like solid (570 mg, 68% overall yield). 1H NMR (300 MHz, CDCl3) δ: 8.01 (app t, J = 7.6 Hz, 1H), 7.91 – 7.72 (m, 4H), 7.54 (dd, J = 8.5, 1.1 Hz, 1H), 7.50 – 7.35 (m, 4H), 6.21 (t, J = 6.8 Hz, 1H), 4.56 (t, J = 4.9 Hz, 1H), 4.06 (dd, J = 11.2, 4.5 Hz, 2H), 3.71 (td, J = 12.0, 2.1 Hz, 2H), 2.37 – 1.93 (m, 3H), 1.85 – 1.63 (m, 2H), 1.29 (d, J = 13.3 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ: 162.18, 161.11 (d, J = 260.8 Hz), 137.00, 133.12, 133.05, 128.50, 128.03, 127.66, 127.63, 126.29, 126.20, 125.86, 124.05, 123.33 (d, J = 10.4 Hz), 120.81 (d, J = 26.1 Hz), 117.37 (d, J = 9.7 Hz), 116.64 (d, J = 2.4 Hz), 101.39, 78.07, 66.78, 31.06, 30.60, 25.68; 19F NMR (470 MHz, CDCl3) δ: -105.8; HRMS (APCI) found [M]+ 419.1529, C23H22FNO3 requires 419.1527.

3-(1,3-dioxan-2-y1)-1-(furan-2-y1)propyl 4-cyano-2-fluorobenzoate (S8)

1st step. 3-(1,3-dioxan-2-y1)-1-(furan-2-y1)propan-1-ol: prepared according to general procedure D using furfural (0.166 mL, 2.0 mmol) and (1,3-Dioxan-2-y1)ethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure B using crude 3-(1,3-dioxan-2-y1)-1-(furan-2-y1)propan-1-ol and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 Hexane/Et2O) to provide the title compound as viscous oil (474 mg, 66% overall yield). 1H NMR (300 MHz, CDCl3) δ: 8.01 (app t, J = 7.4 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 9.7 Hz, 1H), 7.38 (app s, 1H), 6.42 (d, J = 3.1 Hz, 1H), 6.34 (dd, J = 3.1, 1.5 Hz, 1H), 6.12 (t, J = 7.1 Hz, 1H), 4.56 (t, J = 4.9 Hz, 1H), 4.08 (dd, J = 11.0, 4.9 Hz, 2H), 3.76 (app t, J = 11.0 Hz, 2H), 2.30 – 1.96 (m, 3H), 1.80 – 1.57 (m, 2H), 1.32 (d, J = 13.4 Hz, 1H); 13C NMR (75 MHz, CDCl3) δ: 162.14 (d, J = 3.7 Hz),
161.40 (d, \( J = 264.2 \) Hz), 151.75, 142.91, 133.28, 127.76 (d, \( J = 4.6 \) Hz), 123.49 (d, \( J = 9.9 \) Hz), 120.98 (d, \( J = 26.0 \) Hz), 117.64 (d, \( J = 9.7 \) Hz), 116.79 (d, \( J = 2.6 \) Hz), 110.44, 109.42, 101.48, 70.52, 67.01, 31.00, 27.06, 25.86; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta: -106.0; \) HRMS (APCI) found [M\(^{+}\)] 359.1168, C\(_{19}\)H\(_{18}\)FNO\(_3\)S requires 359.1164.

\( \text{3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propyl 4-cyano-2-fluorobenzoate (S9)} \)

\( \text{1st step. 3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propan-1-ol: prepared according to general procedure D using thiophene-2-carbaldehyde (0.187 mL, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.} \)

\( \text{2nd step. Prepared according to general procedure B using crude 3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propan-1-ol and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (80/20 to 60/40 Hexane/Et\(_2\)O) to provide the title compound as viscous oil (481 mg, 63% overall yield).} \)

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \( \delta: 8.02 \) (app t, \( J = 7.5 \) Hz, 1H), 7.49 (d, \( J = 8.1 \) Hz, 1H), 7.43 (d, \( J = 9.7 \) Hz, 1H), 7.28 (d, \( J = 5.0 \) Hz, 1H), 7.14 (d, \( J = 3.2 \) Hz, 1H), 6.97 (dd, \( J = 5.0, 3.2 \) Hz, 1H), 6.32 (app t, \( J = 7.0 \) Hz, 1H), 4.57 (t, \( J = 4.9 \) Hz, 1H), 4.09 (dd, \( J = 10.9, 4.8 \) Hz, 2H), 3.74 (app t, \( J = 11.2 \) Hz, 2H), 2.32 – 1.99 (m, 3H), 1.73 (m, 2H), 1.33 (d, \( J = 13.5 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta: 162.13 \) (d, \( J = 3.7 \) Hz), 161.40 (d, \( J = 264.3 \) Hz), 142.33, 133.31, 127.79 (d, \( J = 4.5 \) Hz), 126.80, 126.67, 125.86, 123.46 (d, \( J = 10.3 \) Hz), 121.01 (d, \( J = 26.0 \) Hz), 117.67 (d, \( J = 9.7 \) Hz), 116.79 (d, \( J = 2.6 \) Hz), 101.44, 73.22, 67.02, 31.27, 30.86, 25.85; \(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \( \delta: -105.9; \) HRMS (APCI) found [M\(^{+}\)] 375.0936, C\(_{19}\)H\(_{18}\)FNO\(_4\)S requires 375.0935.
1-(2-chloropyridin-3-yl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate (S10)

1\textsuperscript{st} step. 1-(2-chloropyridin-3-yl)-3-(1,3-dioxan-2-yl)propan-1-ol: prepared according to general procedure D using 2-Chloro-3-pyridinecarboxaldehyde (283 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.4 mL, 2.2 mmol, 1.1 equiv.). The crude alcohol was used in the next step without additional purification.

2\textsuperscript{nd} step. Prepared according to general procedure B using crude 1-(2-chloropyridin-3-yl)-3-(1,3-dioxan-2-yl)propan-1-ol and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (70/30 to 50/50 Hexane/Et\textsubscript{2}O) to provide the title compound as viscous oil (510 mg, 63% overall yield). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta: 8.34 (app d, J = 4.8 Hz, 1H), 8.06 (t, J = 7.5 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 9.7 Hz, 1H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 6.39 (app t, J = 6.0 Hz, 1H), 4.58 (t, J = 4.8 Hz, 1H), 4.07 (dd, J = 11.4, 4.0 Hz, 2H), 3.73 (app t, J = 11.0 Hz, 2H), 2.20 – 1.98 (m, 3H), 1.75 (app q, J = 8.2, 7.8 Hz, 2H), 1.32 (d, J = 13.5 Hz, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta: 162.09 (d, J = 3.9 Hz), 161.35 (d, J = 264.6 Hz), 149.25, 149.19, 136.21, 134.66, 133.50, 127.98 (d, J = 4.4 Hz), 122.97, 122.89 (d, J = 9.9 Hz), 121.11 (d, J = 26.2 Hz), 118.07 (d, J = 9.7 Hz), 116.63 (d, J = 2.5 Hz), 101.33, 74.01, 67.00, 30.72, 29.38, 25.82; \textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}) \delta: -105.9; HRMS (APCI) found [M+1]\textsuperscript{+} 405.1004, C\textsubscript{20}H\textsubscript{19}ClF\textsubscript{2}N\textsubscript{2}O\textsubscript{4} requires 405.1012.
**tert-butyl3-(1-((4-cyano-2-fluorobenzoyl)oxy)-3-(1,3-dioxan-2-yl)propyl)-1H-indole-1-carboxylate (S11)**

**1st step.** tert-butyl 3-(3-(1,3-dioxan-2-yl)-1-hydroxypropyl)-1H-indole-1-carboxylate: prepared according to general procedure D using N-Boc-indole-3-carboxaldehyde (491 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.0 mL, 2.0 mmol, 1.0 equiv.). The crude alcohol was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as viscous oil (535 mg, 74% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.14 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.30 (app t, J = 7.9 Hz, 1H), 7.22 (app t, J = 7.2 Hz, 1H), 5.00 (dt, J = 8.0, 3.8 Hz, 2H), 4.61 (t, J = 4.7 Hz, 1H), 4.12 (dd, J = 11.6, 4.4 Hz, 2H), 3.77 (t, J = 11.8 Hz, 2H), 2.76 (d, J = 3.8 Hz, 1H), 2.20 – 1.95 (m, 3H), 1.87 – 1.77 (m, 2H), 1.66 (s, 9H), 1.34 (d, J = 13.5 Hz, 1H).

**2nd step.** Prepared according to general procedure B using tert-butyl 3-(3-(1,3-dioxan-2-yl)-1-hydroxypropyl)-1H-indole-1-carboxylate (535mg, 1.48 mmol) and 4-cyano-2-fluorobenzoic acid (244 mg, 1.48 mmol). The crude product was purified by flash column chromatography (70/30 to 50/50 Hexane/Et₂O) to provide the title compound as resin-like solid (384 mg, 51% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.14 (d, J = 8.0 Hz, 1H), 8.02 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 9.8 Hz, 1H), 7.32 (app t, J = 7.5 Hz, 1H), 7.24 (app t, J = 7.3 Hz, 1H), 6.34 (t, J = 7.0 Hz, 1H), 4.57 (t, J = 5.0 Hz, 1H), 4.08 (dd, J = 11.4, 4.4 Hz, 2H), 3.72 (app td, J = 12.4, 1.9 Hz, 2H), 2.42 – 2.16 (m, 2H), 2.16 – 1.95 (m, 1H), 1.84 – 1.60 (m, 2H), 1.67 (s, 9H), 1.32 (d, J = 13.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.41 (d, J = 3.9 Hz), 161.35 (d, J = 264.0 Hz), 149.39, 136.57, 133.36, 129.38, 127.82 (d, J = 4.4 Hz), 124.88, 124.42, 123.57 (d, J = 10.0 Hz), 122.94, 121.04 (d, J = 26.1 Hz), 120.00, 119.02, 117.66 (d, J = 9.6 Hz), 116.79 (d, J = 2.5 Hz).
115.63, 101.57, 84.18, 72.11, 67.02, 31.41, 29.13, 28.33, 25.88; $^{19}$F NMR (282 MHz, CDCl$_3$) δ: -105.8; HRMS (APCI) found [M$^+$] 508.1998, C$_{28}$H$_{20}$FN$_2$O$_6$ requires 508.2004.

**tert-butyl 4-((4-cyano-2-fluorobenzoyl)oxy)-3-(1,3-dioxan-2-yl)propyl)-1H-imidazole-1-carboxylate (S12)**

**1st step.** tert-butyl 4-(3-(1,3-dioxan-2-yl)-1-hydroxypropyl)-1H-imidazole-1-carboxylate: prepared according to general procedure D using N-Boc-imidazole-4-carbaldehyde (392 mg, 2.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 4.0 mL, 2.0 mmol, 1.0 equiv.). The crude alcohol was used in the next step without additional purification.

**2nd step.** Prepared according to general procedure B using crude tert-butyl 4-(3-(1,3-dioxan-2-yl)-1-hydroxypropyl)-1H-imidazole-1-carboxylate and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et$_2$O) to provide the title compound as a resin-like solid (551 mg, 60% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.03 (t, $J$ = 7.5 Hz, 1H), 8.00 (s, 1H), 7.48 (d, $J$ = 8.1 Hz, 1H), 7.42 (d, $J$ = 9.8 Hz, 1H), 7.38 (s, 1H), 6.06 (t, $J$ = 6.8 Hz, 1H), 4.56 (t, $J$ = 5.0 Hz, 1H), 4.07 (dd, $J$ = 11.5, 5.0 Hz, 2H), 3.73 (t, $J$ = 11.3 Hz, 2H), 2.30 – 2.12 (m, 2H), 2.12 – 1.97 (m, 1H), 1.74 – 1.63 (m, 2H), 1.60 (s, 9H), 1.31 (d, $J$ = 13.5 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 162.26 (d, $J$ = 4.1 Hz), 161.42 (d, $J$ = 264.0 Hz), 146.94, 141.27, 137.26, 133.35, 127.77 (d, $J$ = 4.5 Hz), 123.58 (d, $J$ = 10.0 Hz), 120.96 (d, $J$ = 26.0 Hz), 117.63 (d, $J$ = 9.8 Hz), 116.79 (d, $J$ = 2.6 Hz), 115.64, 101.69, 86.06, 71.85, 67.00, 30.89, 28.01, 27.95, 25.88; $^{19}$F NMR (282 MHz, CDCl$_3$) δ: -106.1; HRMS (APCI) found [M+1]$^+$ 460.1868, C$_{23}$H$_{27}$FN$_3$O$_6$ requires 460.1878.
**tert-butyl 4-(2-((4-cyano-2-fluorobenzoyl)oxy)-2-phenylethyl)piperidine-1-carboxylate (S13)**

**1st step.** tert-butyl 4-(2-hydroxy-2-phenylethyl)piperidine-1-carboxylate: prepared according to general procedure D using N-Boc-4-piperidineacetaldehyde (455 mg, 2.0 mmol) and Phenylmagnesium bromide solution (3.0 M in Et₂O, 0.66 mL, 2.0 mmol, 1.0 equiv.). The crude alcohol was used in the next step without additional purification.

**2nd step.** Prepared according to general procedure B using crude tert-butyl 4-(2-hydroxy-2-phenylethyl)piperidine-1-carboxylate and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a viscous oil (462 mg, 51% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.01 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.40 (m, 6H), 6.10 (dd, J = 8.1, 5.8 Hz, 1H), 4.06 (d, J = 12.6 Hz, 2H), 2.64 (app q, J = 10.5 Hz, 2H), 2.08 (m, 1H), 1.84 – 1.65 (m, 3H), 1.55 – 1.37 (m, 1H), 1.44 (s, 9H), 1.19 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.45 (d, J = 3.6 Hz), 161.39 (d, J = 264.3 Hz), 155.57, 140.04, 133.35, 128.89, 128.58, 127.89 (d, J = 4.4 Hz), 126.71, 123.57 (d, J = 10.6 Hz), 121.09 (d, J = 26.0 Hz), 117.77 (d, J = 9.8 Hz), 116.76 (d, J = 2.8 Hz), 80.48, 76.13, 43.92, 43.35, 32.80, 32.46, 31.99, 28.61; ¹⁹F NMR (282 MHz, CDCl₃) δ: -105.9; HRMS (APCI) found [M]⁺ 452.2099, C₂₆H₂₅FN₂O₄ requires 452.2106.
**tert-butyl 4-(2-(5-chlorothiophen-2-yl)-2-((4-cyano-2-fluorobenzoyl)oxy)ethyl) piperidine-1-carboxylate (S14)**

![Chemical Structure](image)

**1st step.** *tert*-butyl 4-(2-(5-chlorothiophen-2-yl)-2-hydroxyethyl)piperidine-1-carboxylate: prepared according to general procedure D using N-Boc-4-piperidineacetaldehyde (455 mg, 2.0 mmol) and 5-Chloro-2-thienylmagnesium bromide solution (0.5 M in THF, 4.0 mL, 2.0 mmol, 1.0 equiv.). The crude alcohol was used in the next step without additional purification.

**2nd step.** Prepared according to general procedure B using crude *tert*-butyl 4-(2-(5-chlorothiophen-2-yl)-2-hydroxyethyl)piperidine-1-carboxylate and 4-cyano-2-fluorobenzoic acid (330 mg, 2.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/\(\text{Et}_2\)O) to provide the title compound as a viscous oil (542 mg, 55% overall yield). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\): 8.00 (t, \(J = 7.5\) Hz, 1H), 7.51 (d, \(J = 8.1\) Hz, 1H), 7.45 (d, \(J = 9.7\) Hz, 1H), 6.93 (d, \(J = 3.7\) Hz, 1H), 6.79 (d, \(J = 3.7\) Hz, 1H), 6.25 (t, \(J = 7.2\) Hz, 1H), 4.07 (d, \(J = 11.6\) Hz, 2H), 2.65 (t, \(J = 12.6\) Hz, 2H), 2.16 – 2.02 (m, 1H), 1.94 – 1.81 (m, 1H), 1.71 (d, \(J = 12.7\) Hz, 2H), 1.58 – 1.49 (m, 1H), 1.44 (s, 9H), 1.31 – 1.09 (m, 2H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\): 162.19 (d, \(J = 3.8\) Hz), 161.40 (d, \(J = 264.3\) Hz), 154.90, 141.06, 133.27, 131.02, 127.90 (d, \(J = 4.5\) Hz), 126.38, 125.89, 123.11 (d, \(J = 10.2\) Hz), 121.09 (d, \(J = 26.0\) Hz), 117.98 (d, \(J = 9.7\) Hz), 116.65 (d, \(J = 2.5\) Hz), 80.07, 71.07, 44.45, 42.23, 33.23, 32.18, 31.51, 28.58; \(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)) \(\delta\): -105.8; HRMS (APCI) found [M]\(^+\) 492.1279, C\(_{23}\)H\(_{26}\)ClF\(_2\)O\(_4\)S requires 492.1280.
1-phenylhex-5-en-1-yl 4-cyano-2-fluorobenzoate (S15)

**1st step.** 1-phenylhex-5-en-1-ol: prepared according to general procedure D using benzaldehyde (0.406 mL, 4.0 mmol) and pent-4-en-1-ylmagnesium bromide solution (0.7 M in THF, 7.15 mL, 5.0 mmol, 1.25 equiv. Pre pared according to literature procedure: *J. Am. Chem. Soc.* **2016**, *138*, 15798–15800). The crude alcohol was purified by flash column chromatography (80/20 to 60/40 Hexane/Et₂O) to provide the title compound as a colorless oil (367 mg, 52% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.39 – 7.31 (m, 4H), 7.31 – 7.23 (m, 1H), 5.87 – 5.70 (m, 1H), 5.05 – 4.90 (m, 2H), 4.68 (dd, J = 7.4, 5.8 Hz, 1H), 2.08 (q, J = 7.3 Hz, 2H), 1.90 – 1.65 (m, 2H), 1.62 – 1.47 (m, 1H), 1.45 – 1.30 (m, 1H).

**2nd step.** Prepared according to general procedure B using 1-phenylhex-5-en-1-ol (144 mg, 0.82 mmol), 4-cyano-2-fluorobenzoic acid (165 mg, 1.0 mmol, 1.22 equiv), DCC (206 mg, 1.0 mmol, 1.22 equiv), DMAP (10 mg, 0.08 mmol, 10 mol%) and 5 mL of DCM. The crude product was purified by flash column chromatography (90/10 to 80/20 Hexane/Et₂O) to provide the title compound as a colorless oil (264 mg, quantitative). ¹H NMR (300 MHz, CDCl₃) δ: 8.03 (t, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.1, 1.1 Hz, 1H), 7.45 (dd, J = 9.7, 1.1 Hz, 1H), 7.43 – 7.30 (m, 5H), 6.01 (t, J = 6.8 Hz, 1H), 5.85 – 5.68 (m, 1H), 5.06 – 4.91 (m, 2H), 2.16 – 2.00 (m, 3H), 2.00 – 1.84 (m, 1H), 1.61 – 1.33 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.44 (d, J = 4.0 Hz), 161.38 (d, J = 263.7 Hz), 140.01, 138.19, 133.35 (d, J = 1.4 Hz), 128.75, 128.39, 127.83 (d, J = 4.5 Hz), 126.70, 123.72 (d, J = 10.7 Hz), 121.05 (d, J = 26.1 Hz), 117.64 (d, J = 9.7 Hz), 116.80 (d, J = 2.1 Hz), 115.21, 78.39, 35.91, 33.41, 24.81; ¹⁹F NMR (282 MHz, CDCl₃) δ: -105.9; HRMS (APCI) found [M]⁺ 323.1310, C₂₀H₁₈FNO₂ requires 323.1316.
1-phenylcyclohexyl 4-cyano-2-fluorobenzoate (S16)

![Chemical structure](image)

Prepared according to general procedure C using 1-phenylcyclohexan-1-ol (881 mg, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et₂O) to provide the title compound as a white solid (825 mg, 51% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.01 (t, J = 7.4 Hz, 1H), 7.56 – 7.42 (m, 4H), 7.38 (t, J = 7.4 Hz, 2H), 7.34 – 7.26 (m, 1H), 2.70 (d, J = 12.7 Hz, 2H), 2.00 – 1.70 (m, 7H), 1.49 – 1.27 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 161.47 (d, J = 3.7 Hz), 161.25 (d, J = 262.7 Hz), 144.77, 133.31 (d, J = 1.7 Hz), 128.58, 127.84 (d, J = 4.4 Hz), 127.55, 124.79, 124.67 (d, J = 10.3 Hz), 121.01 (d, J = 26.5 Hz), 117.28 (d, J = 9.6 Hz), 116.90 (d, J = 2.5 Hz), 85.77, 36.33, 25.34, 22.15; ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.0; HRMS (APCI) found [M]+ 323.1319, C₂₀H₁₈FNO₂ requires 323.1316.

1-phenylcyclopentyl 4-cyano-2-fluorobenzoate (S17)

![Chemical structure](image)

1st step. 1-phenylcyclopentan-1-ol: prepared according to general procedure E using cyclopentanone (0.880 mL, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 4.0 mL, 12.0 mmol, 1.2 equiv.). The crude alcohol was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a white solid (730 mg, 45% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.55 – 7.46 (m, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 3.6 Hz, 2H), 2.08 – 1.78 (m, 8H).

2nd step. Prepared according to general procedure C using 1-phenylcyclopentan-1-ol (487 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (594 mg, 3.6 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (95/5 to 80/20...
Hexane/Et₂O) to provide the title compound as a white solid (380 mg, 41% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.95 (t, J = 7.4 Hz, 1H), 7.55 – 7.41 (m, 4H), 7.41 – 7.24 (m, 3H), 2.77 – 2.57 (m, 2H), 2.36 – 2.14 (m, 2H), 2.09 – 1.80 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ: 161.90 (d, J = 3.6 Hz), 161.22 (d, J = 262.9 Hz), 142.46, 133.20, 128.42, 127.77 (d, J = 4.4 Hz), 127.67, 125.68, 124.67 (d, J = 10.9 Hz), 120.94 (d, J = 26.4 Hz), 117.24 (d, J = 9.6 Hz), 116.87 (d, J = 2.4 Hz), 94.56, 38.50, 23.30; ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.5; HRMS (APCI) found [M]+ 309.1150, C₁₉H₁₆FNO₂ requires 309.1160.

**1-phenylcyclobutyl 4-cyano-2-fluorobenzoate (S18)**

![Chemical Structure](image)

**1st step.** 1-phenylcyclobutan-1-ol: prepared according to general procedure E using cyclobutanone (0.747 mL, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 4.0 mL, 12.0 mmol, 1.2 equiv.). The crude alcohol was used in the next step without additional purification.

**2nd step.** Prepared according to general procedure C using 1-phenylcyclobutan-1-ol (741 mg, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et₂O) to provide the title compound as a white solid (1.122 g, 76% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.96 (t, J = 7.5 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.47 (dd, J = 7.9, 1.2 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.33 – 7.26 (m, 1H), 2.90 – 2.68 (m, 4H), 2.14 – 1.98 (m, 1H), 1.90 – 1.73 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 161.40 (d, J = 3.8 Hz), 161.35 (d, J = 263.3 Hz), 141.75, 133.25 (d, J = 1.4 Hz), 128.55, 127.93, 127.76 (d, J = 4.5 Hz), 125.99, 124.11 (d, J = 10.6 Hz), 120.97 (d, J = 26.2 Hz), 117.43 (d, J = 9.7 Hz), 116.82 (d, J = 2.5 Hz), 84.57, 34.95, 14.32; ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.2; HRMS (APCI) found [M]+ 295.1011, C₁₉H₁₆FNO₂ requires 295.1003.
1-phenylcycloheptyl 4-cyano-2-fluorobenzoate (S19)

1st step. 1-phenylcycloheptan-1-ol: prepared according to general procedure E using cycloheptanone (1.18 mL, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 4.0 mL, 12.0 mmol, 1.2 equiv.). The crude alcohol was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a white solid (818 mg, 43% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.51 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.28 – 7.19 (m, 1H), 2.07 (dd, J = 14.4, 10.3 Hz, 2H), 1.98 – 1.51 (m, 10H).

2nd step. Prepared according to general procedure C using 1-phenylcycloheptan-1-ol (571 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (594 mg, 3.6 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et₂O) to provide the title compound as a white solid (506 mg, 50% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: δ 7.98 (t, J = 7.5 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.41 – 7.29 (m, 4H), 7.28 – 7.21 (m, 1H), 2.54 – 2.29 (m, 4H), 1.91 – 1.78 (m, 2H), 1.78 – 1.58 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ: 161.64 (d, J = 3.9 Hz), 161.27 (d, J = 262.7 Hz), 146.09, 133.29 (d, J = 1.6 Hz), 128.56, 127.84 (d, J = 4.5 Hz), 127.26, 124.75 (d, J = 11.1 Hz), 124.38, 121.01 (d, J = 26.5 Hz), 117.26 (d, J = 9.6 Hz), 116.89 (d, J = 2.5 Hz), 90.00, 40.94, 29.54, 23.40. ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.1; HRMS (APCI) found [M]+ 337.1469, C₂₁H₂₀FNO₂ requires 337.1473.

2-phenylbicyclo[2.2.1]heptan-2-yl 4-cyano-2-fluorobenzoate (S20)

1st step. 2-phenylbicyclo[2.2.1]heptan-2-ol: prepared according to general procedure E using bicyclo[2.2.1]heptan-2-one (1.102 g, 10.0 mmol) and Phenylmagnesium bromide
solution (3 M in THF, 4.0 mL, 12.0 mmol, 1.2 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure C using 2-phenylbicyclo[2.2.1]heptan-2-ol (942 mg, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/Et$_2$O) to provide the title compound as a white solid (1.358 g, 81% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.93 (t, $J = 7.6$ Hz, 1H), 7.53 – 7.40 (m, 4H), 7.37 – 7.28 (m, 2H), 7.27 – 7.19 (m, 1H), 3.27 (app s, 1H), 2.48 (ddd, $J = 13.8$, 4.6, 2.3 Hz, 1H), 2.39 (app s, 1H), 1.95 (dd, $J = 13.8$, 3.6 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.65 (m, 3H), 1.50 – 1.37 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 162.10 (d, $J = 3.8$ Hz), 161.31 (d, $J = 262.9$ Hz), 144.87, 133.26 (d, $J = 1.5$ Hz), 128.45, 127.80 (d, $J = 4.4$ Hz), 127.31, 125.98, 124.33 (d, $J = 10.9$ Hz), 120.98 (d, $J = 26.4$ Hz), 117.33 (d, $J = 9.7$ Hz), 116.86 (d, $J = 2.5$ Hz), 91.53, 46.11, 45.51, 37.74, 36.75, 28.96, 23.26. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -106.4; HRMS (APCI) found [M]$^+$ 335.1303, C$_{21}$H$_{18}$FN$_2$O$_2$ requires 335.1316.

4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate (S21)

1st step. 4-phenyltetrahydro-2H-pyran-4-ol: prepared according to general procedure E using tetrahydro-4H-pyran-4-one (0.923 mL, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 4.0 mL, 12.0 mmol, 1.2 equiv.). The crude alcohol was used in the next step without additional purification.

2nd step. Prepared according to general procedure C using 4-phenyltetrahydro-2H-pyran-4-ol (891 mg, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (60/40 to 50/50 Hexane/Et$_2$O) to provide the title compound as a white solid (943 mg, 58% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.97 (t, $J = 7.6$ Hz, 1H), 7.56 – 7.26 (m, 7H), 4.04 – 3.84 (m, 4H), 2.62 (d, $J = 12.6$ Hz, 2H), 2.35 – 2.20 (m,
2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 161.49 (d, $J = 4.0$ Hz), 161.15 (d, $J = 262.6$ Hz), 143.10, 133.24 (d, $J = 1.5$ Hz), 128.74, 128.00, 127.89 (d, $J = 4.4$ Hz), 124.73, 124.08 (d, $J = 11.2$ Hz), 121.02 (d, $J = 26.6$ Hz), 117.56 (d, $J = 9.7$ Hz), 116.68 (d, $J = 2.5$ Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -105.8; HRMS (APCI) found [M$^+$] $325.1105$, C$_{19}$H$_{19}$FNO$_3$ requires 325.1109.

**tert-butyl 4-((4-cyano-2-fluorobenzoyl)oxy)-4-phenylpiperidine-1-carboxylate (S22)**

1$^{\text{st}}$ step. tert-butyl 4-hydroxy-4-phenylpiperidine-1-carboxylate: prepared according to general procedure E using tert-butyl 4-oxopiperidine-1-carboxylate (1.993 g, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 3.33 mL, 10.0 mmol, 1.0 equiv.). The crude alcohol was purified by flash column chromatography (70/30 to 50/50 Hexane/Et$_2$O) to provide the title compound as a white solid (693 mg, 25% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.48 (app d, $J = 7.2$ Hz, 2H), 7.36 (app t, $J = 7.4$ Hz, 2H), 7.27 (app t, $J = 7.1$ Hz, 1H), 4.01 (bs, 2H), 3.24 (t, $J = 11.7$ Hz, 2H), 1.98 (t, $J = 10.7$ Hz, 2H), 1.79 – 1.67 (m, 2H), 1.48 (d, $J = 3.3$ Hz, 9H).

2$^{\text{nd}}$ step. Prepared according to general procedure C using tert-butyl 4-hydroxy-4-phenylpiperidine-1-carboxylate (702 mg, 2.53 mmol) and 4-cyano-2-fluorobenzoic acid (502 mg, 3.04 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (70/30 to 60/40 Hexane/Et$_2$O) to provide the title compound as a white solid (698 mg, 65% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.94 (dd, $J = 8.2$, 7.0 Hz, 1H), 7.52 – 7.25 (m, 7H), 4.21 – 3.98 (m, 2H), 3.20 (t, $J = 12.5$ Hz, 2H), 2.65 (app d, $J = 12.5$ Hz, 2H), 2.06 (td, $J = 13.7$, 4.8 Hz, 2H), 1.48 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 161.50 (d, $J = 4.0$ Hz), 161.20 (d, $J = 262.7$ Hz), 154.89, 143.07, 133.32 (d, $J = 1.4$ Hz), 128.80, 128.07, 127.94 (d, $J = 4.3$ Hz), 124.71, 124.03 (d, $J = 11.3$ Hz), 121.07 (d, $J = 26.6$ Hz), 117.67 (d, $J = 9.7$ Hz), 116.69 (d, $J = 2.5$ Hz), 83.53, 79.93, 39.75, 35.50, 28.55. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -105.8; HRMS (APCI) found [M+1]$^+$ 425.1881, C$_{24}$H$_{26}$FN$_2$O$_3$ requires 425.1871.
**tert-butyl 3-((4-cyano-2-fluorobenzoyl)oxy)-3-phenylazetidine-1-carboxylate (S23)**

![Chemical Structure](image)

1**st step.** tert-butyl 3-hydroxy-3-phenylazetidine-1-carboxylate: prepared according to general procedure E using tert-butyl 3-oxoazetidine-1-carboxylate (1.712 g, 10.0 mmol) and Phenylmagnesium bromide solution (3 M in THF, 3.33 mL, 10.0 mmol, 1.0 equiv.). The crude alcohol was used in the next step without additional purification.

2**nd step.** Prepared according to general procedure C using tert-butyl 3-hydroxy-3-phenylazetidine-1-carboxylate (1.247 g, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (70/30 to 60/40 Hexane/Et₂O) to provide the title compound as a white solid (1.546 g, 78% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.04 (app t, J = 7.5 Hz, 1H), 7.55 – 7.29 (m, 7H), 4.50 (s, 4H), 1.46 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ: 161.52 (d, J = 264.7 Hz), 161.43 (d, J = 4.1 Hz), 156.32, 139.06, 133.45, 128.92, 128.65, 127.93 (d, J = 4.5 Hz), 125.37, 122.78 (d, J = 10.3 Hz), 121.18 (d, J = 26.1 Hz), 118.25 (d, J = 9.7 Hz), 116.61 (d, J = 2.4 Hz), 80.43, 78.17, 61.32, 28.46. ¹⁹F NMR (282 MHz, CDCl₃) δ: -105.3; HRMS (APCI) found [M+1]⁺ 397.1543, C₂₂H₂₂FN₂O₄ requires 397.1558.

**1-(2-(1,3-dioxan-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-yl-4-cyano-2-fluorobenzoate (S24)**

![Chemical Structure](image)

1**st step.** 1-(2-(1,3-dioxan-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol: prepared according to general procedure E using α-tetralone (0.665 mL, 5.0 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution (0.5 M in THF, 10 mL, 5.0 mmol, 1.0 equiv.). The crude alcohol was purified by flash column chromatography (50/50 to
30/70 Hexane/Et₂O) to provide the title compound as a viscous oil (328 mg, 25% overall yield). ¹H NMR (300 MHz, CDCl₃) δ: 7.54 (d, J = 6.4 Hz, 1H), 7.23 – 7.10 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 4.53 (t, J = 5.0 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.82 – 3.68 (m, 2H), 2.87 – 2.64 (m, 2H), 2.15 – 1.63 (m, 8H), 1.39 – 1.18 (m, 2H).

2nd step. Prepared according to general procedure C using 1-(2-(1,3-dioxan-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (328 mg, 1.25 mmol) and 4-cyano-2-fluorobenzoic acid (248 mg, 1.5 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (80/20/3 to 70/30/3 Hexane/Et₂O/Et₃N) to provide the title compound as a yellow viscous oil (159 mg, 31% overall yield). *Note:* Product unstable over time and/or acidic media; used immediately for the photochemical coupling. ¹H NMR (300 MHz, CDCl₃) δ: 7.94 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.18 – 7.06 (m, 3H), 4.54 (t, J = 5.0 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.81 – 3.65 (m, 2H), 3.02 – 2.86 (m, 1H), 2.83 – 2.60 (m, 2H), 2.33 – 1.97 (m, 5H), 1.97 – 1.65 (m, 3H), 1.33 (d, J = 13.5 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 161.45 (d, J = 3.6 Hz), 161.20 (d, J = 262.9 Hz), 138.68, 137.12, 133.19, 129.04, 127.76 (d, J = 4.4 Hz), 127.51, 125.65, 124.84 (d, J = 10.6 Hz), 122.82, 120.94 (d, J = 26.4 Hz), 117.17 (d, J = 9.7 Hz), 116.85 (d, J = 2.5 Hz), 102.21, 85.83, 67.02, 31.33, 29.93, 29.50, 26.93, 25.86, 20.70; ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.2.

2-(5-chlorothiophen-2-yl)-4-phenylbutan-2-yl 4-cyano-2-fluorobenzoate (S25)

![](image)

1st step. 2-(5-chlorothiophen-2-yl)-4-phenylbutan-2-ol: prepared according to general procedure E using 4-phenyl-2-butanone (0.750 mL, 10.0 mmol) and 5-Chloro-2-thienylmagnesium bromide solution (0.5 M in THF, 10 mL, 10.0 mmol, 1.0 equiv.). The crude alcohol was used in the next step without additional purification.
2nd step. Prepared according to general procedure C using 2-(5-chlorothiophen-2-yl)-4-phenylbutan-2-ol (1.33 g, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (80/20/3 Hexane/Et₂O/Et₃N) to provide the title compound as a yellow viscous oil (1.035 g, 50% overall yield). Note: Product unstable over time and/or acidic media; used immediately for the photochemical coupling.

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \delta: 7.95 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 9.7 Hz, 1H), 7.34 – 7.11 (m, 5H), 6.88 (d, J = 3.8 Hz, 1H), 6.81 (d, J = 3.8 Hz, 1H), 2.73 – 2.60 (m, 2H), 2.60 – 2.47 (m, 2H), 2.07 (s, 3H). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)} \delta: \]

\[ \text{19F NMR (282 MHz, CDCl}_3\text{)} \delta: -105.9. \]

Benzyl 4-cyano-2-fluorobenzoate (S26)

Prepared according to general procedure B using benzyl alcohol (0.312 mL, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 85/15 Hexane/Et₂O) to provide the title compound as a white solid (536 mg, 70% yield). \[ \text{1H NMR (500 MHz, CDCl}_3\text{)} \delta: 8.06 (dd, J = 8.1, 7.1 Hz, 1H), 7.51 (dd, J = 8.1, 1.3 Hz, 1H), 7.48 – 7.43 (m, 3H), 7.43 – 7.34 (m, 3H), 5.41 (s, 2H); \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{)} \delta: 162.78 (d, J = 3.8 Hz), 161.38 (d, J = 264.1 Hz), 135.17, 133.30 (d, J = 1.4 Hz), 128.82, 128.71, 128.40, 127.83 (d, J = 4.5 Hz), 123.27 (d, J = 10.3 Hz), 121.03 (d, J = 26.0 Hz), 117.75 (d, J = 9.8 Hz), 116.73 (d, J = 2.6 Hz), 67.87; \]

\[ \text{19F NMR (470 MHz, CDCl}_3\text{)} \delta: -106.0; \text{HRMS (APCI)} \text{ found [M+1]^{+} 256.0762, C}_{13}\text{H}_{11}\text{FNO}_2 \text{ requires 256.0768.} \]
**4-methoxybenzyl 4-cyano-2-fluorobenzoate (S27)**

Prepared according to general procedure B using 4-methoxybenzyl alcohol (0.372 mL, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (95/5 to 85/15 Hexane/Et₂O) to provide the title compound as a white solid (565 mg, 66% yield). ¹H NMR (500 MHz, CDCl₃) δ: 8.03 (dd, J = 8.0, 7.1 Hz, 1H), 7.49 (dd, J = 8.0, 1.1 Hz, 1H), 7.43 (dd, J = 9.7, 1.1 Hz, 1H), 7.41 – 7.35 (m, 2H), 6.94 – 6.89 (m, 2H), 5.33 (s, 2H), 3.82 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 162.85 (d, J = 3.8 Hz), 161.37 (d, J = 264.1 Hz), 160.05, 133.27 (d, J = 1.4 Hz), 130.39, 127.80 (d, J = 4.5 Hz), 127.29, 123.46 (d, J = 10.3 Hz), 121.00 (d, J = 26.1 Hz), 117.65 (d, J = 9.7 Hz), 116.76 (d, J = 2.5 Hz), 114.21, 67.78, 55.43; ¹⁹F NMR (470 MHz, CDCl₃) δ: -106.2; HRMS (APCI) found [M]+ 285.0795, C₁₆H₁₂FNO₃ requires 285.0796.

**3-(((tert-butoxycarbonyl)amino)benzyl 4-cyano-2-fluorobenzoate (S28)**

Prepared according to general procedure B using N-Boc-3-aminobenzyl alcohol (670 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a white solid (711 mg, 64% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.05 (t, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.49 (d, J = 8.0, Hz, 1H), 7.44 (d, J = 9.7, Hz, 1H), 7.29 (app d, J = 4.3 Hz, 2H), 7.15 – 7.05 (m, 1H), 6.61 (s, 1H), 5.35 (s, 2H), 1.51 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.69 (d, J = 3.7 Hz), 161.38 (d, J = 264.2 Hz), 152.79, 138.93, 136.09, 133.32, 129.44, 127.81 (d, J = 4.5 Hz), 123.26 (d, J = 10.1 Hz), 122.84, 120.99 (d, J = 26.0 Hz), 118.71, 118.33, 117.72 (d, J = 9.7 Hz), 116.72 (d, J = 2.4 Hz) 80.83, 67.70, 28.43; ¹⁹F NMR (282 MHz, CDCl₃) δ: -106.0; HRMS (APCI) found [M]+ 370.1336, C₂₀H₁₉FN₂O₄ requires 370.1323.
tert-butyl 3-(((4-cyano-2-fluorobenzoyl)oxy)methyl)-1H-indole-1-carboxylate (S29)

Prepared according to general procedure B using N-Boc-indole-3-carbinol (742 mg, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et₂O) to provide the title compound as a white solid (805 mg, 68% yield). 

\(^1H\) NMR (300 MHz, CDCl₃) δ: 8.16 (d, J = 8.2 Hz, 1H), 8.02 (app t, J = 7.5 Hz, 1H), 7.75 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.47 (app d, J = 8.1 Hz, 1H), 7.42 (dd, J = 9.8, 1.2 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.25 (m, 1H), 5.56 (s, 2H), 1.68 (s, 9H); 

\(^13C\) NMR (75 MHz, CDCl₃) δ: 162.86 (d, J = 3.7 Hz), 161.38 (d, J = 264.3 Hz), 149.57, 135.76, 133.28, 129.28, 127.80 (d, J = 4.4 Hz), 126.33, 125.03, 123.28 (d, J = 10.3 Hz), 123.13, 121.01 (d, J = 26.0 Hz), 119.26, 117.75 (d, J = 9.7 Hz), 116.71 (d, J = 2.5 Hz), 115.57, 114.83, 84.30, 59.78, 28.30; 

\(^19F\) NMR (282 MHz, CDCl₃) δ: -106.1; HRMS (APCI) found [M⁺] 394.1327, C₂₂H₁₉FN₂O₄ requires 394.1323.

4-(4-chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)piperidin-4-yl-4-cyano-2-fluorobenzoate (Haloperidol ester) (S30)

Prepared according to general procedure C using Haloperidol (1.88 g, 5.0 mmol) and 4-cyano-2-fluorobenzoic acid (990 mg, 6.0 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (40/60 to 30/70 Hexane/Et₂O) to provide the title compound as a white solid (1.674 g, 64% overall yield). 

\(^1H\) NMR (300 MHz, CDCl₃) δ: 8.03 – 7.96 (m, 2H), 7.93 (app t, J = 7.4 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.31 (app s, 4H), 7.12 (t, J = 8.6 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.92 – 2.82 (m, 2H), 2.58
(d, J = 12.7 Hz, 2H), 2.53 – 2.38 (m, 4H), 2.14 – 1.93 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 165.78 (d, J = 254.5 Hz), 161.46 (d, J = 3.9 Hz), 161.23 (d, J = 262.9 Hz), 142.03, 133.77, 133.31, 130.75 (d, J = 9.2 Hz), 128.91, 127.96 (d, J = 4.4 Hz), 126.31, 124.09 (d, J = 11.1 Hz), 121.09 (d, J = 26.4 Hz), 117.67 (d, J = 9.6 Hz), 116.76 (d, J = 2.5 Hz), 115.76 (d, J = 21.8 Hz), 82.94, 57.66, 49.12, 36.22, 35.43, 21.85. $^{19}$F NMR (282 MHz, CDCl$_3$) δ: -105.6, -112.8, -117.7; HRMS (APCI) found [M+1]$^+$ 523.1583, C$_{29}$H$_{26}$ClF$_2$N$_2$O$_3$ requires 523.1595.

3-(2-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-4-oxoazetidin-3-yl)-1-(4-fluorophenyl)propyl 4-cyano-2-fluorobenzoate (OBn-Ezetimibe ester) (S31)

![Chemical structure](image)

Prepared according to general procedure B using OBn-Ezetimibe (340 mg, 0.68 mmol) and 4-cyano-2-fluorobenzoic acid (116 mg, 0.7 mmol, 1.03 equiv.). The crude product was purified by flash column chromatography (60/40 to 50/50 Hexane/Et$_2$O) to provide the title compound as a white solid (361 mg, 82% overall yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.04 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.50 – 7.33 (m, 8H), 7.31 – 7.21 (m, 4H), 7.07 (t, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.02 (t, J = 6.6 Hz, 1H), 5.09 (s, 2H), 4.59 (d, J = 2.0 Hz, 1H), 3.13 (td, J = 7.6, 2.0 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.05 – 1.91 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 166.98, 162.74 (d, J = 247.4 Hz), 162.30 (d, J = 3.9 Hz), 161.88 (d, J = 175.6 Hz), 159.26, 158.52 (d, J = 155.6 Hz), 136.73, 135.08 (d, J = 3.2 Hz), 133.96 (d, J = 2.6 Hz), 133.36 (d, J = 0.9 Hz), 129.57, 128.75, 128.47 (d, J = 8.2 Hz), 128.23, 127.88 (d, J = 4.4 Hz), 127.55, 127.28, 123.18 (d, J = 10.5 Hz), 121.05 (d, J = 26.2 Hz), 118.49 (d, J = 7.8 Hz), 117.84 (d, J = 9.7 Hz), 116.65 (d, J = 2.6 Hz), 116.02 (d, J = 6.8 Hz), 115.73 (d, J = 5.7 Hz), 115.73, 77.10, 70.24, 61.06, 60.06, 33.80, 24.93. $^{19}$F NMR (282 MHz, CDCl$_3$) δ: -105.4, -112.8, -117.7; HRMS (APCI) found [M]$^+$ 646.2079, C$_{30}$H$_{29}$F$_3$N$_2$O$_4$ requires
Pent-3-en-2-yl 4-cyano-2-fluorobenzoate (predominantly trans) (S32)

Prepared according to general procedure B using 3-penten-2-ol (predominantly trans, 0.306 mL, 3.0 mmol) and 4-cyano-2-fluorobenzoic acid (495 mg, 3.0 mmol). The crude product was purified by flash column chromatography (90/10 to 70/30 Hexane/Et2O) to provide the title compound as a white solid (532 mg, 76% yield). 1H NMR (300 MHz, CDCl3) δ: 8.01 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 8.1, 1.3 Hz, 1H), 7.43 (dd, J = 9.7, 1.3 Hz, 1H), 5.91 – 5.76 (m, 1H), 5.64 – 5.50 (m, 2H), 1.72 (d, J = 6.6 Hz, 3H), 1.43 (d, J = 6.0 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ: 162.30 (d, J = 3.7 Hz), 161.32 (d, J = 263.6 Hz), 133.17 (d, J = 1.6 Hz), 130.16, 129.49, 127.76 (d, J = 4.4 Hz), 124.14 (d, J = 10.4 Hz), 120.96 (d, J = 26.2 Hz), 117.40 (d, J = 9.6 Hz), 116.85 (d, J = 2.6 Hz), 73.63, 20.51, 17.82; 19F NMR (282 MHz, CDCl3) δ: -106.5; HRMS (APCI) found [M+H]+ 233.0845, C13H12FNO2 requires 233.0847.

2-methyl-3-oxobutan-2-yl 4-cyano-2-fluorobenzoate (S33)

Prepared according to general procedure C using 3-hydroxy-3-methylbutan-2-one (1.46 mL, 8.0 mmol) and 4-cyano-2-fluorobenzoic acid (1.58 g, 9.6 mmol). The crude product was purified by flash column chromatography (90/10 to 85/15 hexane/EtOAc) to provide the title compound as a white solid (1.69 g, 85% yield). 1H NMR (300 MHz, CDCl3) δ 8.03 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 9.8 Hz, 1H), 2.21 (s, 3H), 1.63 (s, 6H). 13C NMR (75 MHz, CDCl3) δ 205.76, 162.26, 161.39 (d, J = 263.8 Hz), 133.34, 127.92 (d, J = 4.3 Hz), 123.24 (d, J = 10.7 Hz), 121.09 (d, J = 26.0 Hz), 118.02 (d, J = 9.5 Hz), 116.69, 86.10, 24.06, 23.64. HRMS (APCI) [M+H]+ found 250.0865, C13H13FNO3 requires 250.0874.
methyl 3-((4-cyanopyridin-2-yl)methoxy)propanoate (S34)

To a stirred solution of 2-(hydroxymethyl)pyridine-4-carbonitrile (402 mg, 3.0 mmol) in THF (6.0 mL) was added NaH (60% in mineral oil, 144 mg, 3.6 mmol) in small portions under argon atmosphere and at 0 °C followed by methyl 3-bromopropionate (0.327 mL, 3.0 mmol). The reaction temperature was slowly raised to room temperature and stirred for 3 h. The reaction mixture was cooled to 10 °C, treated with ice water (20 mL) and extracted with EtOAc (2 x 25 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude was purified by flash column chromatography (80/20 to 50/50 Hexane/AcOEt) to provide the title compound as a white solid (370 mg, 56% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.75 – 8.65 (m, 1H), 7.74 – 7.65 (m, 1H), 7.45 – 7.36 (m, 1H), 4.70 (s, 2H), 3.88 (t, $J = 6.2$ Hz, 2H), 3.73 (s, 3H), 2.69 (t, $J = 6.2$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 171.87, 160.68, 149.95, 123.89, 122.95, 121.31, 116.75, 73.15, 66.84, 51.98, 34.98; HRMS (APCI) found [M+H]$^+$ 221.0919, C$_{11}$H$_{13}$N$_2$O$_3$ requires 221.0921.

3-phenylisonicotinonitrile (S35)

Prepared according to the general procedure F using 3-chloroisonicotino nitrile (693 mg, 5.00 mmol), phenylboronic acid (915 mg, 7.50 mmol), Pd(PPh$_3$)$_4$ (289 mg, 0.25 mmol) and K$_2$CO$_3$ (1.73 g, 12.50 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (802 mg, 89% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.87 (s, 1H), 8.76 (d, $J = 5.1$ Hz, 1H), 7.68 – 7.46 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 151.14, 148.86, 138.86, 134.59, 129.70, 129.29, 128.94, 126.16, 118.99, 116.44. HRMS (APCI) found [M+H]$^+$ 181.0758, C$_{12}$H$_{9}$N$_2$ requires 181.0760.
3-(p-tolyl)isonicotinonitrile (S36)

![Chemical Structure](image)

Prepared according to the general procedure F using 3-chloroisocotino nitrile (339 mg, 2.45 mmol), p-tolyboronic acid (500 mg, 3.7 mmol), Pd(PPh\(_3\))\(_4\) (142 mg, 0.12 mmol) and K\(_2\)CO\(_3\) (848 mg, 6.12 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (300 mg, 63% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.87 (s, 1H), 8.74 (d, \(J = 5.0\) Hz, 1H), 7.62 (d, \(J = 5.0\) Hz, 1H), 7.50 (d, \(J = 8.1\) Hz, 2H), 7.37 (d, \(J = 8.1\) Hz, 2H), 7.26 (d, 3H). \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 151.12, 148.55, 139.89, 138.91, 131.71, 130.01, 128.81, 126.14, 118.82, 116.61, 21.43. HRMS (APCI) [M+H\(^+\)] found 195.0919, C\(_{13}\)H\(_{11}\)N\(_2\) requires 195.0917.

3-(4-methoxyphenyl)isonicotinonitrile (S37)

![Chemical Structure](image)

Prepared according to the general procedure F using 3-chloroisocotino nitrile (303 mg, 2.19 mmol), p-tolyboronic acid (500 mg, 3.29 mmol), Pd(PPh\(_3\))\(_4\) (126 mg, 0.11 mmol) and K\(_2\)CO\(_3\) (756 mg, 5.47 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (290 mg, 63% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.85 (s, 1H), 8.70 (d, \(J = 5.0\) Hz, 1H), 7.60 (d, \(J = 5.0\) Hz, 1H), 7.55 (d, \(J = 8.8\) Hz, 2H), 7.07 (d, \(J = 8.8\) Hz, 2H), 3.89 (s, 3H). \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 160.92, 150.94, 148.11, 138.65, 130.26, 126.79, 126.19, 118.65, 116.69, 114.83, 55.56. HRMS (APCI) [M+H\(^+\)] found 211.0866, C\(_{13}\)H\(_{11}\)N\(_2\)O requires 211.0866.
3-(4-fluorophenyl)isonicotinonitrile (S38)

Prepared according to the general procedure F using 3-chloroisonicotino nitrile (330 mg, 2.38 mmol), (4-fluorophenyl)boronic acid (500 mg, 3.57 mmol), Pd(PPh₃)₄ (137 mg, 0.12 mmol) and K₂CO₃ (822 mg, 5.95 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (431 mg, 91% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.86 (s, 1H), 8.77 (d, J = 5.0 Hz, 1H), 7.69 – 7.52 (m, 3H), 7.34 – 7.18 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 163.77 (d, J = 250.5 Hz), 151.00, 149.03, 137.86, 130.90 (d, J = 8.6 Hz), 130.65 (d, J = 3.4 Hz), 126.13, 119.00, 116.52 (d, J = 22.0 Hz), 116.31. HRMS (APCI) [M+H]⁺ found 199.0667, C₁₂H₈FN₂ requires 199.0666.

3-(4-(morpholinomethyl)phenyl)isonicotinonitrile (S39)

Prepared according to the general procedure F using 3-chloroisonicotino nitrile (208 mg, 1.50 mmol), (4-(morpholinomethyl)phenyl)boronic acid (500 mg, 2.26 mmol), Pd(PPh₃)₄ (87 mg, 0.08 mmol) and K₂CO₃ (520 mg, 3.76 mmol). The crude product was purified by flash column chromatography (20/80 to 10/90 Hexane/EtOAc) to provide the title compound as a yellow oil (226 mg, 54% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.86 (s, 1H), 8.74 (d, J = 5.1 Hz, 1H), 7.62 (d, J = 5.1 Hz, 1H), 7.59 – 7.47 (m, 4H), 3.81 – 3.67 (m, 4H), 3.58 (s, 2H), 2.53 – 2.44 (m, 4H). ¹³C NMR (75 MHz, cdc₃) δ 151.04, 148.70, 139.84, 138.58, 133.34, 129.85, 128.81, 126.13, 118.78, 116.46, 67.09, 63.01, 53.78. HRMS (APCI) [M+H]⁺ found 280.1449, C₁₇H₁₆N₃O requires 280.1444.

3-(m-tolyl)isonicotinonitrile (S40)

Prepared according to the general procedure F using 3-chloroisonicotino nitrile (340 mg,
2.45 mmol), m-tolylboronic acid (500 mg, 3.67 mmol), Pd(PPh₃)₄ (141 mg, 0.12 mmol) and K₂CO₃ (846 mg, 6.12 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (434 mg, 91% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.87 (s, 1H), 8.75 (d, J = 5.0 Hz, 1H), 7.63 (d, J = 5.0 Hz, 1H), 7.51 – 7.31 (m, 4H), 2.47 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 151.00, 148.57, 139.11, 134.50, 130.47, 129.55, 129.18, 126.19, 126.05, 119.07, 116.44, 21.56. HRMS (APCI) [M+H]⁺ found 195.0916, C₁₃H₁₁N₂ requires 195.0917.

3-(3-methoxyphenyl)isonicotinonitrile (S41)

Prepared according to the general procedure F using 3-chloroisonicotino nitrile (303 mg, 2.19 mmol), (3-methoxyphenyl)boronic acid (500 mg, 3.29 mmol), Pd(PPh₃)₄ (126 mg, 0.11 mmol) and K₂CO₃ (756 mg, 5.47 mmol). The crude product was purified by flash column chromatography (95/5 to 80/20 Hexane/EtOAc) to provide the title compound as a white solid (403 mg, 88% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.86 (s, 1H), 8.74 (d, J = 5.0 Hz, 1H), 7.61 (d, J = 5.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.21 – 7.00 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 151.00, 148.57, 139.11, 134.50, 130.47, 129.55, 129.18, 126.19, 126.05, 119.00, 116.41, 115.41, 114.48, 55.58. HRMS (APCI) [M+H]⁺ found 211.0865, C₁₃H₁₁N₂O requires 211.0866.

3-((4-cyanopyridin-2-yl)methoxy)propanoic acid (S42)

3-((4-cyanopyridin-2-yl)methoxy)propanoic acid was synthesized according to literature procedure (Tetrahedron Letters 2007, 48, 2497–2499). Methyl 3-((4-cyanopyridin-2-yl)methoxy)propanoate (100 mg, 0.45 mmol) was dissolved in 2 mL of acetonitrile containing water (2 vol%). Triethylamine (0.188 mL, 1.35 mmol, 3 equiv.) and lithium bromide (390 mg, 4.5 mmol, 10 equiv.) were added and the reaction
was stirred vigorously at room temperature for 3 hours. The liquids were removed under reduced pressure and the residue redissolved in water (10 mL) and AcOEt (10 mL). The organic phase was discarded and the aqueous phase was washed with AcOEt (2 x 10 mL), acidified with aqueous HCl (1 M) until pH=2-3 and extracted with AcOEt (3 x 10 mL). The organic phases recovered after the acidification were combined, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to provide the title compound as a white solid (80 mg, 86% yield, 95% purity). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.72 (d, $J$ = 4.8 Hz, 1H), 7.73 (s, 1H), 7.44 (d, $J$ = 4.8 Hz, 1H), 6.09 (bs, 1H), 4.72 (s, 2H), 3.89 (t, $J$ = 6.1 Hz, 2H), 2.74 (t, $J$ = 6.1 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 176.13, 160.43, 149.80, 124.09, 123.18, 121.52, 116.63, 72.91, 66.60, 34.92; HRMS (APCI) found [M-1]$^+$ 207.0764, C$_{10}$H$_{11}$N$_2$O$_3$ requires 207.0764.
3. Metal-free deoxygenative coupling of alcohol-derived benzoates and pyridines for small molecules synthesis

General procedure G

In a 10 mL Schlenk tube equipped with stir bar, the appropriate alcohol derivative (0.1 mmol, 1 equiv.), 4-cyanopyridine (15.6 mg, 0.15 mmol, 1.5 equiv.), Hantzsch ester (50.6 mg, 0.2 mmol, 2 equiv.) and sodium acetate (0.2 mmol, 2 equiv.) were dissolved in anhydrous DMSO (2 mL) under air. The use of anhydrous DMSO serves to maximize the reproducibility of the reaction, although a small amount of water is tolerated. The solution was degassed via freeze pump thaw method (3 cycles), backfilled with Argon and irradiated with visible light. The Schlenk tube was placed at 3 cm distance from the Kessil LED lamp and the reaction temperature was kept constant using a fan placed on top of the reaction at 20 cm distance. After 17 hours, two equal reactions (0.1 mmol scale) were joined and placed in a separation funnel; DCM (20 mL) and 5% Na₂CO₃ aqueous solution (4 mL) were added. The organic phase was separated and the aqueous phase was extracted once with DCM (15 mL). The combined organic phases were washed twice with saturated Brine solution (40 mL), dried over sodium sulfate and concentrated under reduced pressure. The reaction crude was purified by flash column chromatography (silica gel) under the stated conditions to provide the pure coupling product. All isolated yields are given on 0.2 mmol scale.

Important note: The Schlenk tube and the freeze pump thaw method were chosen for maximize the reproducibility of the reaction, given its sensitivity to oxygen. However, traces of oxygen can be tolerated, and similar yields were obtained for selected substrates when the reactions were conducted in microwave vials and degassed via
Argon purging for 10 minutes.

4-(1-phenylpropyl)pyridine (10)

![Chemical Structure](image)

Prepared according to general procedure G using 1-phenylpropyl 4-cyano-2-fluorobenzoate 3 (28.3 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et2O) to provide the title compound as a colorless viscous oil (33 mg, 84% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.49 (d, J = 4.6 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 7.15 (d, J = 5.9 Hz, 2H), 3.77 (t, J = 7.7 Hz, 1H), 2.08 (p, J = 7.4 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 154.12, 149.96, 143.32, 128.77, 128.06, 126.79, 123.43, 52.78, 28.06, 12.67. HRMS (APCI) found [M+H]⁺ 198.1075, C₁₄H₁₆N requires 198.1073.

4-(1-(pyridin-4-yl)ethyl)benzonitrile (11)

![Chemical Structure](image)

Prepared according to general procedure G using 1-(4-cyanophenyl)ethyl 4-cyano-2-fluorobenzoate S1 (29.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol), Hantzsch ester (50.6 mg, 0.2 mmol) and NaOAc (16.4 mg, 0.2 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (25/75 to 20/80 hexane/Et₂O) to provide the title compound as a colorless oil (23 mg, 53% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.62 – 8.48 (d, J = 5.8 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.39 – 7.27 (m, 2H), 7.11 (d, J = 6.1 Hz, 2H), 4.19 (q, J = 7.2 Hz, 1H), 1.67 (d, J = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 153.45, 150.29, 149.95, 132.65, 128.60, 122.95, 118.80, 110.89, 44.45, 20.86. HRMS (APCI) [M+H]⁺ found 209.1075, C₁₄H₁₂N₂ requires 209.1073.
4-benzhydrylpyridine (12)

\[
\begin{align*}
\text{Prepared according to general procedure G using benzhydryl 4-cyano-2-fluorobenzoate S2 (33 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et}_2\text{O) to provide the title compound as a white solid (35 mg, 72\% yield).} \\
{^1}\text{H NMR (300 MHz, CDCl}_3\text{) }\delta: 8.52 (d, J = 5.2 Hz, 2H), 7.39 – 7.19 (m, 6H), 7.10 (d, J = 7.1 Hz, 4H), 7.05 (d, J = 5.6 Hz, 2H), 5.51 (s, 1H).} \\
{^{13}}\text{C NMR (75 MHz, CDCl}_3\text{) }\delta: 152.93, 149.94, 142.24, 129.48, 128.73, 127.01, 124.78, 56.42.} \\
{HRMS (APCI) found [M+1]^{+} 246.1274, C_{18}H_{16}N requires 246.1277.}
\end{align*}
\]

4-(1,2-dihydroacenaphthylene-1-yl)pyridine (13)

\[
\begin{align*}
\text{Prepared according to general procedure G using 1,2-dihydroacenaphthylene-1-yl 4-cyano-2-fluorobenzoate S3 (31.7 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et}_2\text{O) to provide the title compound as a colorless viscous oil (37 mg, 80\% yield).} \\
{^1}\text{H NMR (300 MHz, CDCl}_3\text{) }\delta: 8.51 (d, J = 5.6 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (app t, J = 7.3 Hz, 1H), 7.47 (app t, J = 7.5 Hz, 1H), 7.33 (d, J = 6.9 Hz, 1H), 7.10 (d, J = 6.0 Hz, 3H), 4.85 (dd, J = 8.7, 3.7 Hz, 1H), 3.98 (dd, J = 17.5, 8.8 Hz, 1H), 3.37 (dd, J = 17.5, 3.8 Hz, 1H).} \\
{^{13}}\text{C NMR (125 MHz, CDCl}_3\text{) }\delta: 154.60, 150.25, 146.96, 143.33, 138.86, 131.72, 128.43, 128.23, 123.67, 123.13, 123.00, 120.35, 119.73, 48.89, 41.14.} \\
{HRMS (APCI) found [M+1]^{+} 232.1120, C_{17}H_{14}N requires 232.1121.}
\end{align*}
\]
4-(3-(1,3-dioxan-2-yl)-1-phenylpropyl)pyridine (14)

![Chemical Structure Image]

Prepared according to general procedure G using 3-(1,3-dioxan-2-yl)-1-phenylpropyl 4-cyano-2-fluorobenzoate S4 (37 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 20/80 Hexane/Et2O) to provide the title compound as a colorless viscous oil (41 mg, 72% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.50 (bs, 2H), 7.36 – 7.25 (m, 2H), 7.26 – 7.09 (m, 5H), 4.52 (t, $J$ = 4.8 Hz, 1H), 4.09 (dd, $J$ = 11.2, 4.6 Hz, 2H), 3.87 (t, $J$ = 7.8 Hz, 1H), 3.73 (t, $J$ = 11.8 Hz, 2H), 2.17 (q, $J$ = 7.9 Hz, 2H), 2.11 – 1.97 (m, 1H), 1.64 – 1.51 (m, 2H), 1.33 (d, $J$ = 13.4 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.91, 149.89, 143.02, 128.81, 128.05, 126.85, 123.49, 101.96, 67.00, 50.73, 33.65, 29.13, 25.89. HRMS (APCI) found [M+1]$^+$ 284.1643, C$_{18}$H$_{22}$NO$_2$ requires 284.1645.

4-(1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propyl)pyridine (15)

![Chemical Structure Image]

Prepared according to general procedure G using 1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate S5 (40 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et2O) to provide the title compound as a yellowish viscous oil (44 mg, 69% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.49 (d, $J$ = 5.6 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.23 – 7.09 (m, 4H), 4.52 (t, $J$ = 4.9 Hz, 1H), 4.08 (dd, $J$ = 11.3, 4.9 Hz, 2H), 3.85 (t, $J$ = 7.8 Hz, 1H), 3.73 (td, $J$ = 12.4, 2.4 Hz, 2H), 2.21 – 1.97 (m, 4H), 1.60 – 1.49 (m, 2H),
1.33 (app d, J = 13.3 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.42, 150.00, 141.54, 132.70, 129.41, 128.96, 123.27, 101.80, 67.01, 50.04, 33.52, 29.02, 25.87. HRMS (APCI) found [M+1]$^+$ 318.1259, C$_{18}$H$_{21}$ClNO$_2$ requires 318.1255.

4-(1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propyl)pyridine (16)

Prepared according to general procedure G using 1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate S6 (41.3 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et$_2$O) to provide the title compound as a yellowish viscous oil (44 mg, 67% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.47 (d, J = 4.5 Hz, 2H), 7.13 (d, J = 5.2 Hz, 2H), 6.76 – 6.61 (m, 3H), 5.90 (s, 2H), 4.51 (t, J = 4.9 Hz, 1H), 4.07 (dd, J = 11.2, 4.7 Hz, 2H), 3.82 – 3.65 (m, 3H), 2.16 – 1.95 (m, 3H), 1.63 – 1.46 (m, 2H), 1.31 (d, J = 13.5 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.97, 150.00, 148.07, 146.44, 136.96, 123.20, 121.20, 108.43, 108.32, 101.96, 101.12, 67.02, 50.34, 33.62, 29.20, 25.90. HRMS (APCI) found [M+1]$^+$ 328.1545, C$_{19}$H$_{22}$NO$_4$ requires 328.1543.

4-(3-(1,3-dioxan-2-yl)-1-(naphthalen-2-yl)propyl)pyridine (17)

Prepared according to general procedure G using 3-(1,3-dioxan-2-yl)-1-(naphthalen-2-yl)propyl 4-cyano-2-fluorobenzoate S7 (42 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 20/80 Hexane/Et$_2$O) to provide the title compound as a colorless viscous oil (47 mg, 71%
yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.50 (bs, 2H), 7.85 – 7.65 (m, 4H), 7.53 – 7.38 (m, 2H), 7.33 – 7.14 (m, 3H), 4.54 (t, $J$ = 4.9 Hz, 1H), 4.16 – 3.96 (m, 3H), 3.74 (td, $J$ = 12.3, 2.0 Hz, 2H), 2.32 – 2.19 (m, 2H), 2.14 – 1.96 (m, 1H), 1.68 – 1.54 (m, 2H), 1.32 (d, $J$ = 13.4 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 154.03, 149.71, 140.35, 133.61, 132.50, 128.60, 127.86, 127.73, 126.52, 126.40, 126.33, 125.89, 101.93, 67.02, 50.76, 33.67, 28.90, 25.88. HRMS (APCI) found [M+1]$^+$ 334.1803, C$_{22}$H$_{24}$NO$_2$ requires 334.1802.

4-(3-(1,3-dioxan-2-yl)-1-(furan-2-yl)propyl)pyridine (18)

Prepared according to general procedure G using 3-(1,3-dioxan-2-yl)-1-(furan-2-yl)propyl 4-cyano-2-fluorobenzoate S8 (36 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et$_2$O) to provide the title compound as a yellowish viscous oil (34 mg, 63% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.53 (bs, 2H), 7.31 (s, 1H), 7.16 (bs, 2H), 6.35 – 6.23 (m, 1H), 6.12 (d, $J$ = 3.1 Hz, 1H), 4.50 (t, $J$ = 5.0 Hz, 1H), 4.08 (dd, $J$ = 11.2, 4.6 Hz, 2H), 3.92 (t, $J$ = 7.7 Hz, 1H), 3.72 (t, $J$ = 11.1 Hz, 2H), 2.28 – 2.11 (m, 1H), 2.11 – 1.91 (m, 2H), 1.67 – 1.45 (m, 2H), 1.32 (d, $J$ = 13.5 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 155.79, 151.67, 149.94, 141.95, 123.35, 110.28, 106.38, 101.86, 67.03, 44.67, 33.25, 28.48, 25.90. HRMS (APCI) found [M+1]$^+$ 274.1439, C$_{16}$H$_{20}$NO$_3$ requires 274.1438.

4-(3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propyl)pyridine (19)
Prepared according to general procedure G using 3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propyl 4-cyano-2-fluorobenzoate S9 (37.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et₂O) to provide the title compound as a yellowish viscous oil (42 mg, 73% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.50 (d, J = 4.3 Hz, 2H), 7.18 (dd, J = 4.6, 1.4 Hz, 2H), 7.16 (dd, J = 5.1, 1.2 Hz, 1H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 6.85 (dt, J = 3.5, 1.0 Hz, 1H), 4.51 (t, J = 5.0 Hz, 1H), 4.13 – 4.04 (m, 3H), 3.76 – 3.68 (m, 2H), 2.26 – 1.98 (m, 3H), 1.66 – 1.49 (m, 2H), 1.34 – 1.28 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ: 153.24, 150.12, 146.84, 126.86, 124.61, 124.21, 123.10, 101.79, 67.00, 46.17, 33.49, 30.97, 25.86. HRMS (APCI) found [M+1]⁺ 290.1215, C₁₆H₂₀NO₂S requires 290.1209.

3-(3-(1,3-dioxan-2-yl)-1-(pyridin-4-yl)propyl)-2-chloropyridine (20)

Prepared according to general procedure G using 1-(2-chloropyridin-3-yl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate S10 (40.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 20/80 Hexane/AcOEt) to provide the title compound as a yellowish viscous oil (26 mg, 57% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.51 (d, J = 5.5 Hz, 2H), 8.27 (dd, J = 4.6, 1.2 Hz, 1H), 7.63 (dd, J = 7.8, 1.2 Hz, 1H), 7.24 (dd, J = 7.8, 4.6 Hz, 1H), 7.14 (d, J = 5.5 Hz, 2H), 4.54 (t, J = 4.8 Hz, 1H), 4.40 (t, J = 7.8 Hz, 1H), 4.08 (dd, J = 11.4, 4.4 Hz, 2H), 3.73 (t, J = 12.0 Hz, 2H), 2.22 – 1.96 (m, 3H), 1.64 – 1.52 (m, 2H), 1.33 (d, J = 13.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 151.75, 151.34, 150.21, 148.02, 137.27, 123.49, 122.98, 101.52, 67.04, 46.11, 33.15, 28.53, 25.86. HRMS (APCI) found [M+1]⁺ 319.1203, C₁₇H₂₀ClN₂O₂ requires 319.1208.
**tert-butyl 3-(3-(1,3-dioxan-2-yl)-1-(pyridin-4-yl)propyl)-1H-indole-1-carboxylate (21)**

Prepared according to general procedure G using tert-butyl 3-(1-((4-cyano-2-fluorobenzoyl)oxy)-3-(1,3-dioxan-2-yl)propyl)-1H-indole-1-carboxylate S11 (51 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et₂O) to provide the title compound as a yellowish viscous oil (55 mg, 65% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.50 (s, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.32 – 7.19 (m, 4H), 7.12 (t, J = 7.5 Hz, 1H), 4.55 (t, J = 4.9 Hz, 1H), 4.17 – 4.02 (m, 3H), 3.75 (t, J = 11.5 Hz, 2H), 2.39 – 2.23 (m, 1H), 2.21 – 1.97 (m, 2H), 1.78 – 1.55 (m, 2H), 1.70 (s, 9H), 1.34 (d, J = 13.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 153.24, 149.92, 149.80, 135.78, 129.81, 124.63, 123.54, 122.98, 122.57, 122.42, 119.47, 115.45, 101.91, 83.94, 67.00, 42.06, 33.43, 29.03, 28.36, 25.88. HRMS (APCI) found [M+1]⁺ 423.2279, C₂₅H₃₁N₂O₄ requires 423.2278.

**tert-butyl 4-(3-(1,3-dioxan-2-yl)-1-(pyridin-4-yl)propyl)-1H-imidazole-1-carboxylate (22)**

Prepared according to general procedure G using tert-butyl 4-(1-((4-cyano-2-fluorobenzoyl)oxy)-3-(1,3-dioxan-2-yl)propyl)-1H-imidazole-1-carboxylate S12 (46 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (10/90 to 5/95 Hexane/AcOEt) to provide the title compound as a yellowish viscous oil.
(23 mg, 31% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.49 (bs, 2H), 7.99 (s, 1H), 7.22 (d, $J = 4.7$ Hz, 2H), 7.15 (s, 1H), 4.51 (t, $J = 5.0$ Hz, 1H), 4.07 (dd, $J = 10.9, 4.8$ Hz, 2H), 3.83 (t, $J = 7.7$ Hz, 1H), 3.72 (t, $J = 11.1$ Hz, 2H), 2.30 – 2.15 (m, 1H), 2.15 – 1.92 (m, 2H), 1.66 – 1.45 (m, 2H), 1.60 (s, 9H), 1.32 (d, $J = 13.5$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 152.57, 149.93, 147.00, 137.18, 123.91, 113.38, 101.99, 85.73, 67.02, 44.51, 33.38, 28.94, 28.05, 25.91. HRMS (APCI) found [M+1]$^+$ 374.2078, C$_{20}$H$_{28}$N$_3$O$_4$ requires 374.2074.

**tert-butyl 4-(2-phenyl-2-(pyridin-4-yl)ethyl)piperidine-1-carboxylate (23)**

Prepared according to general procedure G using tert-butyl 4-((4-cyano-2-fluorobenzoyl)oxy)-2-phenylethyl)piperidine-1-carboxylate S13 (45 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et$_2$O) to provide the title compound as a yellowish viscous oil (51 mg, 70% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.50 (d, $J = 3.7$ Hz, 2H), 7.31 (t, $J = 6.9$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 3H), 7.16 (d, $J = 5.5$ Hz, 2H), 4.11 – 3.96 (m, 3H), 2.57 (t, $J = 12.2$ Hz, 2H), 2.08 – 1.88 (m, 2H), 1.77 – 1.60 (m, 2H), 1.45 (s, 9H), 1.36 – 1.06 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 154.89, 154.06, 149.91, 142.87, 128.90, 127.91, 126.96, 123.26, 79.39, 47.54, 43.86, 41.93, 33.53, 32.38, 32.10, 30.44, 28.56. HRMS (APCI) found [M+1]$^+$ 367.2395, C$_{23}$H$_{31}$N$_2$O$_2$ requires 367.2380.

**tert-butyl 4-(2-(5-chlorothiophen-2-yl)-2-(pyridin-4-yl)ethyl)piperidine-1-carboxylate (24)**
Prepared according to general procedure G using tert-butyl 4-(2-(5-chlorothiophen-2-yl)-2-((4-cyano-2-fluorobenzoxy)ethyl)piperidine-1-carboxylate S14 (49 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 10/90 Hexane/Et₂O) to provide the title compound as a yellowish viscous oil (51 mg, 63% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.53 (s, 2H), 7.14 (d, J = 4.4 Hz, 2H), 6.73 (d, J = 3.5 Hz, 1H), 6.60 (d, J = 3.3 Hz, 1H), 4.19 – 3.94 (m, 3H), 2.57 (t, J = 12.5 Hz, 2H), 2.02 – 1.79 (m, 2H), 1.65 (d, J = 11.8 Hz, 2H), 1.43 (s, 9H), 1.37 – 1.04 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 154.88, 152.55, 150.35, 145.60, 128.71, 125.93, 123.96, 122.83, 79.52, 43.83, 43.48, 43.25, 33.60, 32.09, 30.46, 28.57. HRMS (APCI) found [M+1]+ 407.1562, C₂₁H₂₈ClN₂O₂S requires 407.1555.

4-(1-phenylhex-5-en-1-yl)pyridine (25)

Prepared according to general procedure G using 1-phenylhex-5-en-1-yl 4-cyano-2-fluorobenzoate S15 (32.3 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as a colorless oil (15 mg, 74% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.51 (d, J = 5.9 Hz, 2H), 7.36 – 7.27 (m, 2H), 7.27 – 7.19 (m, 3H), 7.19 – 7.13 (m, 2H), 5.88 – 5.69 (m, 1H), 5.09 – 4.89 (m, 2H), 3.89 (t, J = 7.8 Hz, 1H), 2.16 – 2.02 (m, 4H), 1.45 – 1.32 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ: 154.13, 150.00, 143.31, 138.42, 128.81, 128.01, 126.83, 123.35, 115.02, 50.84, 34.49, 33.69, 27.20. HRMS (APCI) found [M+1]+ 238.1590, C₁₇H₂₀N requires 238.1590.
4-(1-phenylcyclohexyl)pyridine (26)

Prepared according to general procedure G using 1-phenylcyclohexyl 4-cyano-2-fluorobenzoate S16 (32.4 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as a yellowish viscous oil (34 mg, 72% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.46 (d, J = 5.4 Hz, 2H), 7.33 – 7.21 (m, 4H), 7.16 (d, J = 5.3 Hz, 3H), 2.35 – 2.18 (m, 4H), 1.65 – 1.44 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ: 157.87, 149.97, 146.75, 128.63, 127.21, 126.15, 122.60, 46.27, 36.51, 26.27, 22.83. HRMS (APCI) found [M+1]+ 238.1585, C₁₇H₂₀N requires 238.1590.

4-(1-phenylcyclopentyl)pyridine (27)

Prepared according to general procedure G using 1-phenylcyclopentyl 4-cyano-2-fluorobenzoate S17 (31 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as a yellowish viscous oil (31 mg, 70% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.59 (bs, 2H), 7.34 – 7.13 (m, 7H), 2.32 (bs, 4H), 1.75 (bs, 4H). ¹³C NMR (75 MHz, CDCl₃) δ: 157.86, 149.72, 147.23, 128.44, 127.12, 126.26, 122.63, 55.76, 38.22, 23.03. HRMS (APCI) found [M+1]+ 224.1433, C₁₆H₁₈N requires 224.1434.
4-(1-phenylcyclobutyl)pyridine (28)

Prepared according to general procedure G using 1-phenylcyclobutyl 4-cyano-2-fluorobenzoate S18 (29.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et$_2$O) to provide the title compound as a yellowish viscous oil (26 mg, 62% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.49 (bs, 2H), 7.35 – 7.25 (m, 4H), 7.24 – 7.15 (m, 3H), 2.86 – 2.64 (m, 4H), 2.00 (p, $J = 7.4$ Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 158.51, 149.90, 148.03, 128.63, 126.29, 126.22, 121.60, 50.90, 34.73, 16.74. HRMS (APCI) found [M+1]$^+$ 210.1271, C$_{15}$H$_{16}$N requires 210.1277.

4-(1-phenylcycloheptyl)pyridine (29)

Prepared according to general procedure G using 1-phenylcycloheptyl 4-cyano-2-fluorobenzoate S19 (34 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et$_2$O) to provide the title compound as a white solid (32 mg, 64% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.48 (bs, 2H), 7.33 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 7.09 (d, $J = 5.8$ Hz, 2H), 2.42 – 2.21 (m, 4H), 1.83 – 1.67 (m, 4H), 1.67 – 1.54 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 160.09, 149.74, 149.16, 128.39, 127.33, 126.01, 122.69, 50.15, 39.71, 30.11, 24.30. HRMS (APCI) found [M+1]$^+$ 252.1744, C$_{18}$H$_{22}$N requires 252.1747.
4-(2-phenylbicyclo[2.2.1]heptan-2-yl)pyridine (30)

Prepared according to general procedure G using 2-phenylbicyclo[2.2.1]heptan-2-yl 4-cyano-2-fluorobenzoate S20 (33.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as a white solid (38 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.45 (bs, 2H), 7.34 – 7.19 (m, 6H), 7.19 – 7.09 (m, 1H), 3.21 (s, 1H), 2.47 – 2.32 (m, 2H), 2.26 (ddd, J = 12.9, 4.5, 1.6 Hz, 1H), 1.61 (d, J = 9.8 Hz, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.38 (m, 1H), 1.30 – 1.15 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ: 161.26, 149.75, 146.70, 128.37, 128.02, 125.92, 122.48, 56.33, 44.22, 43.01, 38.32, 38.12, 29.53, 24.60. HRMS (APCI) found [M+1]⁺ 250.1592, C₁₈H₂₀N requires 250.1590.

4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (31)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (32.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (20/80 to 5/95 Hexane/Et₂O) to provide the title compound as a white solid (40 mg, 84% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.53 (bs, 2H), 7.40 – 7.10 (m, 7H), 3.89 – 3.65 (m, 4H), 2.56 – 2.36 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ: 156.60, 150.16, 145.19, 128.94, 127.06, 126.67, 122.29, 64.58, 44.20, 36.21. HRMS (APCI) found [M+1]⁺ 240.1383, C₁₈H₁₈NO requires 240.1383.
**tert-butyl 4-phenyl-4-(pyridin-4-yl)piperidine-1-carboxylate (32)**

Prepared according to general procedure G using tert-butyl 4-((4-cyano-2-fluorobenzoyl)oxy)-4-phenylpiperidine-1-carboxylate S22 (42.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (30/70 to 10/90 Hexane/Et2O) to provide the title compound as a viscous oil (47 mg, 70% yield). 

**1H NMR** (300 MHz, CDCl3) δ: 8.50 (bs, 2H), 7.37 – 7.28 (m, 2H), 7.28 – 7.17 (m, 3H), 7.14 (d, J = 6.1 Hz, 2H), 3.62 – 3.35 (m, 4H), 2.47 – 2.25 (m, 4H), 1.45 (s, 9H). 

**13C NMR** (75 MHz, CDCl3) δ: 156.27, 154.94, 150.17, 144.55, 128.95, 127.13, 126.73, 122.24, 79.71, 44.86, 40.68, 35.37, 28.54. HRMS (APCI) found [M+1]^+ 339.2054, C21H27N2O2 requires 339.2067.

**tert-butyl 3-phenyl-3-(pyridin-4-yl)azetidine-1-carboxylate (33)**

Prepared according to general procedure G using tert-butyl 3-((4-cyano-2-fluorobenzoyl)oxy)-3-phenylazetidine-1-carboxylate S23 (40 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (30/70 to 10/90 Hexane/Et2O) to provide the title compound as a viscous oil (34 mg, 55% yield). 

**1H NMR** (300 MHz, CDCl3) δ: 8.55 (d, J = 6.1 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.33 – 7.25 (m, 1H), 7.21 – 7.11 (m, 4H), 4.57 (d, J = 8.4 Hz, 2H), 4.45 (d, J = 8.4 Hz, 2H), 1.46 (s, 9H). 

**13C NMR** (75 MHz, CDCl3) δ: 156.35, 155.24, 150.25, 144.05, 129.04, 127.39, 126.72, 121.67, 80.28, 62.41, 45.24, 28.49. HRMS (APCI) found [M+1]^+ 311.1758,
C₁₉H₂₃N₂O₂ requires 311.1754.

4-(1-(2-(1,3-dioxan-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pyridine (34)

Prepared according to general procedure G using 1-(2-(1,3-dioxan-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-yl 4-cyano-2-fluorobenzoate S24 (41 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (40/60 to 10/90 Hexane/Et₂O) to provide the title compound as a viscous oil (46 mg, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.42 (d, J = 5.3 Hz, 2H), 7.20 – 7.05 (m, 3H), 7.03 – 6.92 (m, 3H), 4.49 (t, J = 5.0 Hz, 1H), 4.15 – 4.00 (m, 2H), 3.80 – 3.64 (m, 2H), 2.82 – 2.71 (m, 2H), 2.26 – 2.15 (m, 2H), 2.15 – 1.98 (m, 2H), 1.93 (ddd, J = 13.5, 5.7, 3.2 Hz, 1H), 1.80 – 1.66 (m, 1H), 1.64 – 1.36 (m, 3H), 1.36 – 1.26 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 160.17, 149.49, 139.36, 138.43, 129.56, 129.10, 126.45, 126.12, 123.04, 102.51, 67.04, 67.02, 46.03, 36.55, 34.59, 30.99, 30.10, 25.91, 19.11. HRMS (APCI) found [M+1]^+ 324.1956, C₂₁H₂₆N₂O requires 324.1958.

4-(2-(5-chlorothiophen-2-yl)-4-phenylbutan-2-yl)pyridine (35)

Prepared according to general procedure G using 2-(5-chlorothiophen-2-yl)-4-phenylbutan-2-yl 4-cyano-2-fluorobenzoate S25 (41.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (60/40 to 40/60 Hexane/Et₂O) to provide the title compound as a viscous oil (43 mg, 66% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.57 (d, J = 5.5 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 7.18 – 7.11 (m, 2H), 6.79 (d, J = 3.8 Hz, 1H), 6.66 (d, J = 3.8 Hz, 1H), 2.63 –
2.26 (m, 4H), 1.79 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 156.71, 151.50, 150.09, 141.69, 128.87, 128.69, 128.39, 126.25, 125.64, 123.89, 121.85, 45.46, 44.57, 31.16, 27.36. HRMS (APCI) found [M+1]$^+$ 328.0921, C$_{19}$H$_{15}$ClINS requires 328.0921.

**4-benzylpyridine (36)**

![4-benzylpyridine](image)

Prepared according to general procedure G using benzyl 4-cyano-2-fluorobenzoate S26 (25.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et$_2$O) to provide the title compound as a colorless viscous oil (21 mg, 62% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.50 (d, $J$ = 5.8 Hz, 2H), 7.32 (t, $J$ = 7.1 Hz, 2H), 7.28 – 7.21 (m, 1H), 7.18 (d, $J$ = 7.0 Hz, 2H), 7.10 (d, $J$ = 5.5 Hz, 2H), 3.97 (s, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 150.14, 149.95, 138.99, 129.17, 128.86, 126.81, 124.35, 41.38. HRMS (APCI) found [M+1]$^+$ 170.0966, C$_{12}$H$_{12}$N requires 170.0964.

**4-(4-methoxybenzyl)pyridine (37)**

![4-(4-methoxybenzyl)pyridine](image)

Prepared according to general procedure G using 4-methoxybenzyl 4-cyano-2-fluorobenzoate S27 (28.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et$_2$O) to provide the title compound as a yellowish viscous oil (24 mg, 60% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.48 (d, $J$ = 5.8 Hz, 2H), 7.11 – 7.05 (m, 4H), 6.88 – 6.83 (m, 2H), 3.90 (s, 3H), 3.79 (s, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 158.52, 150.60, 149.96, 131.07, 130.15, 124.20, 114.26, 55.40, 40.48. HRMS (APCI) found [M+1]$^+$ 200.1068, C$_{13}$H$_{14}$NO requires 200.1070.

**tert-butyl (3-(pyridin-4-ylmethyl)phenyl)carbamate (38)**

![tert-butyl (3-(pyridin-4-ylmethyl)phenyl)carbamate](image)

Prepared according to general procedure G using 3-((tert-butoxycarbonyl)amino)benzyl
4-cyano-2-fluorobenzoate S28 (37 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et2O) to provide the title compound as a yellowish viscous oil (35 mg, 62% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.53 (bs, 2H), 7.35 – 7.08 (m, 4H), 6.87 (d, $J = 6.5$ Hz, 1H), 6.61 (s, 1H), 3.97 (s, 2H), 1.54 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 152.84, 150.12, 149.83, 139.94, 138.98, 129.44, 124.40, 123.81, 119.23, 116.97, 80.73, 41.39, 28.48. HRMS (APCI) found [M+1]$^+$ 285.1601, C$_{17}$H$_{21}$N$_2$O$_2$ requires 285.1598.

**tert-butyl 3-(pyridin-4-ylmethyl)-1H-indole-1-carboxylate (39)**

![structure](image1)

Prepared according to general procedure G using tert-butyl 3-(((4-cyano-2-fluorobenzoyl)oxy)methyl)-1H-indole-1-carboxylate S29 (39.5 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 30/70 Hexane/Et2O) to provide the title compound as a yellowish viscous oil (39 mg, 63% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.50 (bs, 2H), 8.13 (d, $J = 8.1$ Hz, 1H), 7.40 (s, 1H), 7.37 – 7.28 (m, 2H), 7.23 – 7.15 (m, 3H), 4.04 (s, 2H), 1.67 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 149.95, 149.07, 130.21, 124.78, 124.16, 123.62, 122.74, 119.22, 117.93, 115.54, 108.55, 83.93, 30.96, 28.37. HRMS (APCI) found [M+1]$^+$ 309.1609, C$_{19}$H$_{21}$N$_2$O$_2$ requires 309.1598.

**4-(4-(4-chlorophenyl)-4-(pyridin-4-yl)piperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (from Haloperidol) (40)**

![structure](image2)
Prepared according to general procedure G using 4-(4-chlorophenyl)-1-(4-(fluorophenyl)-4-oxobutyl)piperidin-4-yl 4-cyano-2-fluorobenzoate S30 (Haloperidol ester, 52.3 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (98/1/1 to 95/4/1 AcOEt/MeOH/Et3N) to provide the title compound as a yellowish solid (64 mg, 73% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.49 (d, J = 6.0 Hz, 2H), 8.05 – 7.93 (m, 2H), 7.31 – 7.23 (m, 2H), 7.18 – 7.07 (m, 6H), 2.95 (t, J = 7.0 Hz, 2H), 2.57 – 2.42 (m, 4H), 2.42 – 2.27 (m, 6H), 1.92 (p, J = 7.0 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ: 198.40, 165.76 (d, J = 254.5 Hz), 156.40, 150.17, 150.04, 133.83 (d, J = 3.1 Hz), 132.34, 130.77 (d, J = 9.2 Hz), 128.89, 128.72, 122.42, 115.73 (d, J = 21.8 Hz), 57.84, 50.21, 44.47, 36.24, 35.62, 21.95. HRMS (APCI) found [M+1]+ 437.1775, C₂₆H₂₇ClFN₂O requires 437.1790.

4-(4-(benzylxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-(pyridin-4-yl)propyl)azetidin-2-one (from OBn-Ezetimibe) (41)

Prepared according to general procedure G using 3-(2-(4-(benzylxy)phenyl)-1-(4-fluorophenyl)-4-oxoazetidin-3-yl)-1-(4-fluorophenyl)propyl 4-cyano-2-fluorobenzoate S31 (OBn-Ezetimibe ester, 64.7 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (30/70 to 10/90 Hex/Et₂O) to provide the title compound as a yellowish solid (81 mg, 72% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.61 (bs, 2H), 7.46 – 7.29 (m, 5H), 7.28 – 7.11 (m, 8H), 7.06 – 6.86 (m, 6H), 5.06 (s, 2H), 4.51 (t, J = 2.6 Hz, 1H), 3.94 (td, J = 7.9, 3.0 Hz, 1H), 3.16 – 3.02 (m, 1H), 2.43 – 2.24 (m, 1H), 2.24 – 2.09 (m, 1H), 1.96 – 1.71 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ: 167.14, 162.17 (d, J = 213.8 Hz), 159.29, 158.92 (d, J = 211.0 Hz), 154.96, 148.64, 137.63 (d, J = 3.4 Hz), 136.74, 133.96 (d, J = 2.5 Hz), 129.62, 129.44 (d, J =
7.8 Hz), 128.77, 128.25, 127.58, 127.30, 123.66, 118.51 (d, J = 7.8 Hz), 115.99 (d, J = 19.4 Hz), 115.97 (d, J = 19.4 Hz), 115.78, 70.27, 61.06, 60.38, 50.09, 32.45, 30.46, 27.29. HRMS (APCI) found [M+1]+ 561.2344, C₃₆H₃₁F₂N₂O₂ requires 561.2348.

4-(pent-3-en-2-yl)pyridine (42)

Prepared according to general procedure G using pent-3-en-2-yl 4-cyano-2-fluorobenzoate S32 (predominantly trans, 23.3 mg, 0.1 mmol) and 4-cyanopyridine (15.6 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product (trans: cis ratio 4:1) was purified by flash column chromatography (50/50 to 30/70 Hexane/Et₂O) to provide the title compound as a colorless oil (trans: cis ratio 5.4:1, 15 mg, 51% yield). ¹H NMR (300 MHz, CDCl₃) δ: 8.50 (d, J = 5.5 Hz, 2H), 7.16 (d, J = 5.5 Hz, 2H), 5.62 – 5.40 (m, 2H), 5.34 – 5.37 (m, 1H), 1.68 (d, J = 6.0 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 155.97, 149.40, 134.31, 125.61, 122.91, 41.96, 20.84, 18.01.

3-methyl-3-(pyridin-4-yl)butan-2-one (43)

Prepared according to general procedure G using 2-methyl-3-oxobutan-2-yl 4-cyano-2-fluorobenzoate S33 (75 mg, 0.3 mmol) and 4-pyridinecarbonitrile (10.4 mg, 0.1 mmol), Hantzsch ester (101.2 mg, 0.4 mmol) and NaOAc (32.8 mg, 0.4 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (30/70 to 20/80 hexane/Et₂O) to provide the title compound as a pale yellow liquid (22 mg, 67% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.66 – 8.49 (m, 2H), 7.24 – 7.11 (m, 2H), 1.95 (s, 3H), 1.49 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 209.38, 153.17, 150.44, 121.38, 52.49, 25.80, 24.72. HRMS (APCI) [M+H]+ found 164.1071, C₁₀H₁₄NO requires 164.1070.
2-methyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (44)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 4-cyano-2-methylpyridine (17.7 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (10/90 to 5/95 Hexane/Et₂O) to provide the title compound as a white solid (40 mg, 79% yield). 1H NMR (300 MHz, CDCl₃) δ 8.40 (d, J = 5.4 Hz, 1H), 7.40 – 7.18 (m, 5H), 7.04 (s, 1H), 6.99 (d, J = 5.4 Hz, 1H), 3.85 – 3.67 (m, 4H), 2.53 (s, 3H), 2.50 – 2.36 (m, 4H). 13C NMR (75 MHz, CDCl₃) δ 158.76, 156.74, 149.50, 145.44, 128.89, 126.99, 126.57, 121.62, 119.39, 64.62, 44.03, 36.19, 24.82. HRMS (APCI) [M+H]+ found 254.1539, C₁₇H₂₀NO requires 254.1539.

4-(4-phenyltetrahydro-2H-pyran-4-yl)-2-propylpyridine (45)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 2-propylisonicotinonitrile (22 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (50/50 to 45/55 Hexane/Et₂O) to provide the title compound as a colorless oil (42 mg, 75% yield). 1H NMR (300 MHz, CDCl₃) δ 8.43 (d, J = 5.3 Hz, 1H), 7.39 – 7.17 (m, 5H), 7.03 (s, 1H), 6.97 (d, J = 5.3 Hz, 1H), 3.87 – 3.57 (m, 4H), 2.73 (t, J = 7.4 Hz, 2H), 2.54 – 2.30 (m, 4H), 1.86 – 1.63 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). 13C NMR (75 MHz, CDCl₃) δ 162.68, 156.67, 149.58, 145.55, 128.88, 127.03, 126.57, 121.16, 119.65, 64.66, 44.17, 40.70, 36.32, 23.25, 13.93. HRMS (APCI) [M+H]+ found 282.1851, C₁₉H₂₄NO requires 282.1852.
(4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridin-2-yl)methanol (46)

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\begin{align*}
\text{Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl} \\
\text{4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and} \\
\text{2-(hydroxymethyl)isonicotinonitrile (20.1 mg, 0.15 mmol); 2 x reaction of 0.1 mmol} \\
\text{scale. The crude product was purified by flash column chromatography (01/99 to 0/100} \\
\text{Hexane/Et}_2\text{O) to provide the title compound as a pale yellow solid (40 mg, 74% yield).} \\
\text{\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \delta 8.46 (d, J = 5.3 Hz, 1H), 7.38 – 7.19 (m, 5H), 7.14 (s,} \\
\text{1H), 7.09 (d, J = 5.3 Hz, 1H), 4.72 (s, 2H), 3.83 – 3.69 (m, 4H), 2.55 – 2.34 (m, 4H).} \\
\text{\(^1\)C NMR (75 MHz, CDCl\textsubscript{3}) \delta 159.63, 157.65, 148.95, 145.06, 129.02, 127.07, 126.75,} \\
\text{121.08, 118.78, 64.61, 64.53, 44.29, 36.27. HRMS (APCI) [M+H]^+ found 270.1487,} \\
\text{C\textsubscript{17}H\textsubscript{20}NO\textsubscript{2} requires 270.1489.} \\
\text{methyl 3-((4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridin-2-yl)methoxy)propanoate (47) \\
\end{align*}
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\begin{align*}
\text{Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl} \\
\text{4-cyano-2-fluorobenzoate S21 (32.5 mg, 0.1 mmol) and methyl} \\
\text{3-((4-cyanopyridin-2-yl)methoxy)propanoate S34 (33 mg, 0.15 mmol); 2 x reaction of} \\
\text{0.1 mmol scale. The crude product was purified by flash column chromatography} \\
\text{(20/80 to 5/95 Hexane/Et}_2\text{O) to provide the title compound as a colorless viscous oil (40} \\
\text{mg, 56% yield). \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \delta: 8.43 (d, J = 5.3 Hz, 1H), 7.39 (d, J =} \\
\text{1.3 Hz, 1H), 7.36 – 7.24 (m, 4H), 7.24 – 7.16 (m, 1H), 7.04 (dd, J = 5.3, 1.8 Hz, 1H),} \\
\text{4.63 (s, 2H), 3.81 (t, J = 6.3 Hz, 2H), 3.78 – 3.72 (m, 4H), 3.71 (s, 3H), 2.65 (t, J = 6.3} \\
\end{align*}
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Hz, 2H), 2.53 – 2.40 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 172.02, 158.62, 157.72, 149.23, 145.29, 128.92, 127.04, 126.62, 121.13, 119.59, 73.88, 66.39, 64.63, 51.81, 44.32, 36.18, 34.99.

HRMS (APCI) found [M+1]$^+$ 356.1860, C$_{21}$H$_{26}$NO$_4$ requires 356.1856.

2-phenyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (48)

![Chemical Structure](image)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 2-phenylisonicotinonitrile (27 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (70/30 to 60/40 of hexane/Et$_2$O) to provide the title compound albeit with some unknown impurities, therefore it is reported considering the NMR yield (31% yield). 1,1,2,2-tetrachloroethane was used as the internal standard. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.59 (d, $J = 5.3$ Hz, 1H), 7.90 (d, $J = 7.4$ Hz, 2H), 7.58 (s, 1H), 7.53 – 7.17 (m, 8H), 7.10 (d, $J = 5.3$ Hz, 1H), 3.79 (t, $J = 5.2$ Hz, 4H), 2.50 (m, 4H).

2,6-dimethyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (49)

![Chemical Structure](image)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 2,6-dimethylisonicotinonitrile (19.8 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (25/75 to 20/80 Hexane/Et$_2$O) to provide the title compound as a pale yellow solid (40 mg, 78% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.39 – 7.17 (m, 5H), 6.85 (s, 2H), 3.83 – 3.69 (m, 4H), 2.49 (s, 6H), 2.46 – 2.39 (m, 4H).
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.08, 156.97, 145.77, 128.86, 126.99, 126.51, 118.78, 64.70, 43.99, 36.32, 24.83. HRMS (APCI) [M+H]$^+$ found 268.1696, C$_{18}$H$_{22}$NO requires 268.1696.

3-methyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (50)

![Chemical structure of 3-methyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine](attachment:structure.png)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 4-cyano-3-methylpyridine (17.7 mg, 0.15 mmol); 2 x reaction of 0.1 mmol scale. The crude product was purified by flash column chromatography (10/90 to 5/95 Hexane/Et$_2$O) to provide the title compound as a colorless oil (42 mg, 83% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.50 (d, $J = 5.3$ Hz, 1H), 8.25 (s, 1H), 7.48 (d, $J = 5.3$ Hz, 1H), 7.35 – 7.13 (m, 5H), 3.94 – 3.65 (m, 4H), 2.44 (t, $J = 5.3$ Hz, 4H), 1.90 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 153.81, 153.34, 147.59, 145.89, 132.61, 128.50, 127.43, 126.37, 122.40, 64.67, 45.05, 36.31, 18.85. HRMS (APCI) [M+H]$^+$ found 254.1540, C$_{17}$H$_{20}$NO requires 254.1539.

3-phenyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (51)

![Chemical structure of 3-phenyl-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine](attachment:structure.png)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol), 3-phenylisonicotinonitrile S35 (27 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (50/50 to 40/60 Hexane/Et$_2$O) to provide the title compound as a white solid (32 mg, 51% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.67 (d, $J = 5.4$ Hz, 1H), 8.22 (s, 1H), 7.60 (d, $J = 5.4$ Hz, 1H), 7.31 – 7.08 (m, 6H), 7.01 – 6.88 (m, 2H), 6.51 (d, $J = 7.2$ Hz, 2H), 3.78 – 3.58 (m, 4H), 2.36 – 2.10 (m, 4H). $^{13}$C
NMR (75 MHz, CDCl₃) δ 153.46, 152.44, 148.93, 146.55, 139.56, 138.37, 129.82, 128.42, 127.70, 127.58, 127.41, 126.40, 122.63, 64.51, 45.33, 37.13. HRMS (APCI) [M+H]⁺ found 316.1700, C₂₂H₂₂NO requires 316.1696.

4-(4-phenyltetrahydro-2H-pyran-4-yl)-3-(p-tolyl)pyridine (52)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S₂₁ (33 mg, 0.1 mmol), 3-(p-tolyl)isonicotinonitrile S₃₆ (29.1 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (40/60 to 30/70 Hexane/Et₂O) to provide the title compound as a white solid (35.5 mg, 54% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.64 (d, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.58 (d, J = 5.5 Hz, 1H), 7.26 – 7.15 (m, 3H), 7.04 – 6.90 (m, 4H), 6.39 (d, J = 8.1 Hz, 2H), 3.77 – 3.50 (m, 4H), 2.35 (s, 3H), 2.32 – 2.12 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 153.69, 152.38, 148.75, 146.77, 138.39, 137.15, 136.65, 129.63, 128.40, 128.30, 127.66, 126.36, 122.73, 64.54, 45.38, 37.11, 21.30. HRMS (APCI) [M+H]⁺ found 330.1857, C₂₃H₂₄NO requires 330.1852.

3-(4-methoxyphenyl)-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (53)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S₂₁ (33 mg, 0.1 mmol) and 3-(4-methoxyphenyl)isonicotinonitrile S₃₇ (31.5 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (30/70 to 20/80 Hexane/Et₂O) to provide the title compound as a white
solid (37 mg, 54% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.64 (d, $J = 5.4$ Hz, 1H), 8.21 (s, 1H), 7.58 (d, $J = 5.4$ Hz, 1H), 7.31 – 7.13 (m, 3H), 7.02 – 6.91 (m, 2H), 6.72 – 6.61 (m, 2H), 6.45 – 6.34 (m, 2H), 3.82 (s, 3H), 3.76 – 3.56 (m, 4H), 2.35 – 2.11 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.98, 153.89, 152.72, 148.78, 146.76, 138.11, 131.84, 130.89, 128.41, 127.69, 126.37, 122.68, 113.05, 64.53, 55.36, 45.33, 37.10. HRMS (APCI) [M+H]$^+$ found 346.1802, C$_{23}$H$_{24}$NO$_2$ requires 346.1802.

3-(4-fluorophenyl)-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (54)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 3-(4-fluorophenyl)isonicotinonitrile S38 (29.7 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol), NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (30/70 to 20/80 Hexane/Et$_2$O) to provide the title compound as a white solid (27 mg, 40.5% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.67 (d, $J = 5.4$ Hz, 1H), 8.18 (s, 1H), 7.60 (d, $J = 5.4$ Hz, 1H), 7.26 – 7.15 (m, 3H), 6.97 – 6.88 (m, 2H), 6.87 – 6.77 (m, 2H), 6.49 – 6.35 (m, 2H), 3.78 – 3.60 (m, 4H), 2.34 – 2.13 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.07 (d, $J = 247.2$ Hz), 153.39, 152.87, 149.07, 146.19, 137.26, 135.20 (d, $J = 3.7$ Hz), 131.35 (d, $J = 8.1$ Hz), 128.35, 127.61, 126.38, 122.36, 114.40 (d, $J = 21.4$ Hz), 64.30, 45.10, 36.97. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -114.72. HRMS (APCI) [M+H]$^+$ found 334.1600, C$_{23}$H$_{21}$FNO requires 334.1602.

4-(4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridin-3-yl)benzyl)morpholine (55)
Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 3-(4-(morpholinomethyl)phenyl)isonicotinonitrile S39 (42 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (2% NEt3 in Et2O) to provide the title compound albeit with some unknown impurities, therefore it is reported as an NMR yield (43% NMR yield).

1,1,2,2-tetrachloroethane was used as the internal standard. \( ^1\)H NMR (300 MHz, CDCl3) \( \delta \) 8.63 (d, \( J = 5.4 \) Hz, 1H), 8.18 (s, 1H), 7.57 (d, \( J = 5.4 \) Hz, 1H), 7.19 – 7.12 (m, 3H), 7.06 (d, \( J = 7.7 \) Hz, 2H), 6.95 – 6.86 (m, 2H), 6.43 (d, \( J = 7.6 \) Hz, 2H), 3.83 – 3.67 (m, 4H), 3.67 – 3.65 (m, 4H), 3.48 (s, 2H), 2.55 – 2.36 (m, 4H), 2.27 – 2.13 (m, 4H). \( ^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 153.53, 152.54, 148.91, 146.64, 138.42, 138.25, 137.02, 129.75, 128.40, 128.29, 127.70, 126.42, 122.65, 67.17, 64.52, 63.20, 53.78, 45.36, 37.16. HRMS (APCI) [M+H]\(^+\) found 415.2379, C\(_{27}\)H\(_{31}\)N\(_2\)O\(_2\) requires 415.2380.

4-(4-phenyltetrahydro-2H-pyran-4-yl)-3-(m-tolyl)pyridine (56)

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 3-(m-tolyl)isonicotinonitrile S40 (29.1 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (30/70 to 20/80 Hexane/Et\(_2\)O) to provide the title compound as a white solid (29 mg, 44% yield). \( ^1\)H NMR (300 MHz, CDCl3) \( \delta \) 8.66 (d, \( J = 5.4 \) Hz, 1H), 8.22 (s, 1H), 7.59 (d, \( J = 5.4 \) Hz, 1H), 7.27 – 7.15 (m, 3H), 7.11 – 7.03 (m, 2H), 7.01 – 6.92 (m, 2H), 6.57 – 6.47 (m, 1H), 6.03 (s, 1H), 3.76 – 3.53 (m, 4H), 2.39 – 2.15 (m, 4H), 2.13 (s, 3H). \( ^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 153.45, 152.30, 148.81, 146.88, 139.37, 138.48, 137.01, 130.80, 128.34, 128.19, 127.67, 127.52, 126.66, 126.29, 122.63, 64.53, 45.27, 36.03, 21.44. HRMS (APCI) [M+H]\(^+\) found 330.1852,
C_{23}H_{24}NO requires 330.1852.

3-(3-methoxyphenyl)-4-(4-phenyltetrahydro-2H-pyran-4-yl)pyridine (57)

![Chemical Structure]

Prepared according to general procedure G using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (33 mg, 0.1 mmol) and 3-(3-methoxyphenyl)isonicotinonitrile S41 (31.5 mg, 0.15 mmol), Hantzsch ester (63.3 mg, 0.25 mmol) and NaOAc (20.5 mg, 0.25 mmol); 2 x reaction of 0.1 mmol scale. Reaction time: 20 hours. The crude product was purified by flash column chromatography (30/70 to 20/80 Hexane/Et2O) to provide the title compound as a white solid (32 mg, 46% yield). 1H NMR (300 MHz, CDCl3) δ 8.66 (d, J = 5.4 Hz, 1H), 8.24 (s, 1H), 7.59 (d, J = 5.4 Hz, 1H), 7.27 – 7.14 (m, 3H), 7.09 (t, J = 7.9 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.85 – 6.76 (m, 1H), 6.31 – 6.25 (m, 1H), 5.99 – 5.90 (m, 1H), 3.75 – 3.58 (m, 4H), 3.54 (s, 3H), 2.40 – 2.09 (m, 4H). 13C NMR (75 MHz, CDCl3) δ 158.62, 153.24, 151.93, 148.80, 146.65, 140.77, 138.07, 128.54, 128.33, 127.47, 126.25, 122.66, 122.04, 114.79, 113.69, 64.40, 54.89, 45.37, 36.52. HRMS (APCI) [M+H]^+ found 346.1802, C_{23}H_{24}NO_2 requires 346.1802.
4. Mechanistic experiments

UV-Vis absorption studies

The UV-Vis absorption spectra were recorded using a Jasco V-770 spectrophotometer equipped with photomultiplier detector, monochromator and deuterium/halogen light source. The samples were prepared in a 1mL quartz cuvette with a path length of 1 cm. Final concentration of the single components: HE (0.02 M), ester 1 (0.01 M), PyCN (0.015 M).

![Absorption spectra](image)

The combination of HE and dinitro ester 1 showed a new absorption band in the visible region (yellow line), indicating the formation of a charge transfer complex. On the other hand, the mixture of HE and PyCN did not shown any difference from the absorption spectra of the single components, excluding a ground-state association between these two species.

We performed the same studies with benzoate 3; final concentration of the single components: HE (0.02 M), ester 3 (0.01 M).
In this case, no appreciable difference in the absorption spectra was observed when HE and ester 3 were mixed, excluding a ground-state association between these two species. We then carefully studied the changing in the absorption spectra of HE \((1.0 \times 10^{-4} \text{ M})\) in the presence of NaOAc. The sample was prepared in a vial and 2.5 mg of NaOAc were added (0.03 mmol). After sonicating for 60 seconds, the solution was transferred to the cuvette for the experiment. *Note: only a small portion of NaOAc is soluble in DMSO; this method ensures the preparation of a saturated solution of NaOAc.*

The HE absorption spectra clearly changed in the presence of NaOAc, suggesting an ground-state interaction between these two species.
Next, we repeated the experiment with increasing concentrations of benzoate 3: 0.01, 0.02, 0.03 and 0.04 M.

As evident from the graph, the increase in benzoate 3 concentrations did not significantly alter the absorption spectra of the HE/NaOAc mixture with a clear trend, indicating the absence of a ternary association in the ground state (small fluctuations are probably due to slight difference in concentration of NaOAc in each sample).

**Emission studies**

The emission spectra were recorded using a FS5 Spectrofluorometer equipped with photomultiplier detector, double monochromator and 150 W xenon light source. 3 mL of a \(1 \times 10^{-3}\) M solution of Hantzsch ester (HE) in DMSO were placed in a quartz fluorescence cuvette (10x10 mm light path) equipped with septum. The sample was degassed with a stream of Argon for 15 min. The excitation wavelength was fixed at 400 nm (bandwidth = 3 nm), while the emission spectra was acquired from 410 nm to 700 nm. The same experiment was repeated in the presence of NaOAc. In this case, the sample was prepared in a vial and 2.5 mg of NaOAc were added (0.03 mmol). After sonicating for 60 seconds, the solution was transferred to the cuvette for degassing. *Note: only a small portion of NaOAc is soluble in DMSO; this method ensures the preparation of a saturated solution of NaOAc.*
In the presence of NaOAc, we observed a small but appreciable change in the emission spectra of HE, possibly due to a ground state interaction between the two species and consistent with the UV-Vis studies above.

We repeated the same experiment using 373 nm as excitation wavelength (bandwidth = 1 nm) and [HE] = 1⋅10^{-4} M. In this case, a small static quenching was visible in the presence of NaOAc.

For Stern-Volmer quenching studies, the excitation wavelength was fixed at 373 nm and the emission spectra was acquired from 410 nm to 700 nm. The samples were prepared mixing a HE stock solution (final [HE] = 1.0⋅10^{-4} M) with 0.1 M stock solution of benzoate 3 (final [3] = 0.01, 0.02, 0.03 and 0.04 M) in a total volume of 3 mL of DMSO in a quartz fluorescence cuvette (10x10 mm light path) equipped with septum. After
degassing the sample with a stream of argon for 15 minutes, the emission spectra of the samples were collected. In case of the quenching studies with NaOAc, the samples were prepared in a vial and 2.5 mg of NaOAc was added (0.03 mmol). After sonicating for 60 seconds, the solutions were transferred to the cuvette for degassing. Note: only a small portion of NaOAc is soluble in DMSO; this method ensures the preparation of a saturated solution of NaOAc favoring the suggested interaction with HE.

HE emission quenching with increasing concentrations of Benzoate 3

HE/NaOAc emission quenching with increasing concentrations of Benzoate 3
The Stern-Volmer plots show linear correlations between the amounts of 3 and the ratio \( \frac{I_0}{I} \) for the quenching of both HE and HE/NaOAc. On the basis of the following equation, it is possible to calculate the Stern-Volmer constants \( K_{SV} \) (J. R. Lakowicz Principles of Fluorescence Spectroscopy, chap. 3, pp. 52-93, Plenum Press, New York 1983):

\[
\frac{I_0}{I} = 1 + K_{SV}[Q]
\]

\( K_{SV} \) for HE = 5.15; \( K_{SV} \) for HE/NaOAc = 11.22

**SET quencher experiment**

According to the general procedure G, 1-phenylpropyl 4-cyano-2-fluorobenzoate 3 (28.3 mg, 0.1 mmol), 4-cyanopyridine 9 (15.6 mg, 0.15 mmol), Hantzsch ester (50.6 mg, 0.2 mmol), NaOAc (16.4 mg, 0.2 mmol) and 1,4-dinitrobenzene (33.6 mg, 0.2 mmol) were dissolved in DMSO (2 mL) under air. The reaction was degassed via freeze pump thaw method (3 cycles), backfilled with Argon and irradiated with visible light. The reaction crude was analyzed by NMR and no conversion of 1-phenylpropyl 4-cyano-2-fluorobenzoate 3 and 4-pyridinecarbonitrile 9 was observed.
This experiment confirmed that single electron transfer processes are key to the photochemical reaction, since 1,4-dinitrobenzene is a known competitor for SET due to its strong tendency to accept an electron ($E_{\text{red}} = -0.64$ V vs SCE, refs: *Nat. Chem.* 2013, 5, 750-756 and *Int. J. Electrochem.* 2011, Article ID 346043).

**Studies of the reaction without 4-cyanopyridine**

According to the general procedure G, 1-phenylpropyl 4-cyano-2-fluorobenzoate 3 (28.3 mg, 0.1 mmol), Hantzsch ester (50.6 mg, 0.2 mmol) and NaOAc (16.4 mg, 0.2 mmol) were dissolved in DMSO (2 mL) under air. The reaction was degassed via freeze pump thaw method (3 cycles), backfilled with Argon and irradiated with visible light. Reaction was done in 2 x 0.1 mmol scale. The crude product was purified using flash column chromatography (98/2 to 95/5 hexane/Et$_2$O) to provide the byproduct 58 as a 4:1 mixture of diastereoisomers and colorless oil (13 mg, 35% yield). Major diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (t, $J = 7.7$ Hz, 1H), 7.51 – 7.14 (m, 10H), 7.13 – 6.91 (m, 2H), 5.91 (t, $J = 6.6$ Hz, 1H), 3.82 (t, $J = 7.7$ Hz, 1H), 2.00 (m, 4H), 0.93 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 163.87 (d, $J = 3.5$ Hz), 162.30 (d, $J = 260.1$ Hz), 153.23 (d, $J = 7.9$ Hz), 143.63, 140.65, 132.30, 129.93, 128.77, 128.52, 127.94 (d, $J = 3.4$ Hz), 126.71 (d, $J = 5.5$ Hz), 123.71 (d, $J = 3.3$ Hz), 116.54, 116.24, 78.31, 53.13, 29.75, 28.31, 12.70, 9.97. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -108.93. HRMS (APCI) [M+H]$^+$ found 376.1844, C$_{25}$H$_{25}$FO$_2$ requires 376.1833.

We propose that product 58 is obtained via radical-radical coupling of 1-phenylpropyl radical and the radical anion of benzoate 3, before the desired $\beta$-scission fragmentation can occur.
TEMPO trapping experiment

To probe the intermediacy of radical species, a trapping experiment was performed using TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxy] as a radical scavenger. According to the general procedure G, 1-phenylpropyl 4-cyano-2-fluorobenzoate (28.3 mg, 0.1 mmol), Hantzsch ester (50.6 mg, 0.2 mmol), NaOAc (16.4 mg, 0.2 mmol) and TEMPO (31.2 mg, 0.2 mmol) were dissolved in DMSO (2 mL) under air. The reaction was degassed via freeze pump thaw method (3 cycles), backfilled with Argon and irradiated with visible light. Reaction was done in 2 x 0.1 mmol scale. The crude product was purified using flash column chromatography (98/2 to 95/5 hexane/Et₂O) to provide the TEMPO adduct 59 in 10% yield. The NMR spectral data match with the previously published data (Nat. Chem. 2019, 11, 1158-1166): ¹H NMR (300 MHz, CDCl₃) δ 7.27 (m, 5H), 4.53 (dd, J = 9.5, 4.0 Hz, 1H), 2.18 – 2.00 (m, 1H), 1.88 – 1.70 (m, 1H), 1.48 (brs, 3H), 1.21 – 1.39 (m, 6H), 1.17 (brs, 3H), 1.01 (brs, 3H), 0.89 – 0.81 (m, 1H), 0.66 (t, J = 7.5 Hz, 3H), 0.60 (brs, 2H).

The detection of the TEMPO product 59 confirms the formation of the proposed radical specie, which is obtained after the reduction of benzoate 3 and β-scission of the corresponding radical anion.
5. Metal-free deoxygenative coupling of alcohol-derived benzoates and DNA headpieces for DEL synthesis

LCMS Analysis

Liquid chromatography-mass spectrometry (HPLC-MS) analyses were performed on Thermo Scientific Dionex Ultimate 3000 UHPLC coupled with Bruker Amazon SL using an Electrospray ionization (ESI) ion source.

**Column:** Reverse phase (Waters XBridge Premier Oligo BEH C18 column 130Å, 2.5 μm, 2.1x50mm); column oven temperature: 30 °C; flow rate: 0.2 mL/min.

**Mobile phase:** (A). H₂O containing 10mM Et₃N and 100 mM HFIP; (B). MeOH.

**UHPLC method:** 5% phase B isocratic for 5 min, 5% to 50% phase B gradient 10 min, 50% phase B isocratic for 5 min, 50% to 5% phase B gradient 2 min.

**UV detection:** 260 nm.

**MS method:** capillary voltage 4500 V, range: 700-2200 m/z; ionization polarity: negative, triply charged mass was observed (M–3)/3.

**Injection amount:** 20 μL of purified sample (ca. 50 μM).

**Important note:** normally, the MS signal is delayed by 0.2 min respect to the UV signal.

Synthesis of DNA derivative 60

![Chemical Structure]

The DNA derivative 60 was synthesized according to the literature procedure (J. Am. Chem. Soc. 2020, 142, 20143–20151). 3-((4-cyanopyridin-2-yl)methoxy)propanoic acid S42 (10 μL of 1.0 M stock solution in DMA, 10 μmol, 100 equiv.) and
*N,N*-diisopropylethylamine (10 μL of 1.0 M stock solution in DMA, 10 μmol, 100 equiv.) were added in an Eppendorf tube containing 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU; 3.8 mg, 10 μmol, 100 equiv.). The reaction mixture was vortexed and allowed to stand at room temperature for 1 h, followed by the addition to a solution of the DNA headpiece (10 μL of 10 mM stock solution in H2O, 0.1 μmol, 1.0 equiv.) in borate buffer (70 μL, 100 mM, pH 9.5). The mixture was vortexed and allowed to stand at room temperature for 3 h. Sodium chloride (10 μL of 5.0 M stock solution in H2O) and cold ethanol (0.3 mL) were added. The resulting mixture was vortexed and allowed to stand at −20 °C for 30 min. The suspension was centrifuged at 12000 RPM for 3 min. After discarding the supernatant, the pellet was dried under reduced pressure and redissolved in H2O (100 μL) to afford a stock solution of DNA-conjugate 60 (1.0 mM). *Note: small impurities (< 5% by mass) are coeluting with DNA derivative 60. m/z = 1611 is due to the loss of one C and a phosphate from 60, while m/z = 1769 is due an additional inclusion of acid S42.*

![Graph](image1.png)

![Graph](image2.png)
Conjugate 60 is stable for 5-10 days in the freezer at -20 °C as stock solution. After this time, a new unknown impurity (coeluting with 60) is found by LC-MS analysis:

**General procedure H**

A 0.5-2 mL Microwave vial was charged with the appropriate alcohol derivative (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative
60 (2.5 μL of 1 mM stock solution in H₂O, 2.5 nmol, 1 equiv.). The vial was flushed 15 seconds with Argon and sealed. The reaction was irradiated with visible light for 75 minutes. *Note: the vial was placed at 3 cm distance from the Kessil LED lamp and the reaction temperature was kept constant using a fan placed on top of the reaction at 20 cm distance.* After irradiation, the functionalized DNA was purified using Mini Quick Spin Oligo Column by Roche and analyzed by HPLC-MS.

**Yield determination for the DNA functionalization**

The yield of the DNA functionalization was determined by LC-MS as reported in the literature for DEL synthesis (*J. Am. Chem. Soc.* 2020, 142, 20143–20151 and ref therein) by integration of the UV absorbance at 260 nm, assuming total DNA recovery and that all DNA compounds have similar UV absorbance. To calculate the yield, the area of the product was divided by the summed-up area of all DNA containing compounds. Non-DNA impurities (molecular weight < 1000 g/mol) were not included in the yield calculation.

*Note: During our studies we noticed that most of the UV peaks of the desired coupling products have a small shoulder. We investigated this issue during the optimization phase with alcohol derivative 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21.*

Integration of UV peak 3 revealed a yield of 88% of the expected DNA-conjugate coupling product with alcohol-derived benzoate S21. The mass spectra of the entire peak 3 (including the shoulder) showed that the desired coupling product mass (m-3/3 = 1752, m-4/4 = 1314, m-5/5 = 1050, m-6/6 = 876, m-7/7 = 750) is the major signal (>
90%, considering only m-3/3 adducts). We identified the major impurity (m-3/3 = 1656) as the coupling product of the initial impurity found in the starting conjugate 60 (m-3/3 = 1611, which is due to the loss of one C and a phosphate from 60) and alcohol-derived benzoate S21. Therefore, we assumed that integration of UV peak 3 is a good estimation of the reaction yield despite the small shoulder, which is arguably due to the coupling product of impurity m-3/3 = 1611 found in the starting conjugate 60.
Synthesis of DNA functionalized product 61

DNA functionalized product 61 was synthesized and purified according to general procedure H using 1-phenylpropyl 4-cyano-2-fluorobenzoate 3 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 84%
DNA functionalized product 62 was synthesized and purified according to general procedure H using 3-(1,3-dioxan-2-yl)-1-phenylpropyl 4-cyano-2-fluorobenzoate S4 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 85%
Synthesis of DNA functionalized product 63

DNA functionalized product 63 was synthesized and purified according to general procedure H using 1-(4-chlorophenyl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-
2-fluorobenzoate S5 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 80%
Synthesis of DNA functionalized product 64

DNA functionalized product 64 was synthesized and purified according to general procedure H using 1-(benzo[d][1,3]dioxol-5-yl)-3-(1,3-dioxan-2-yl)propyl 4-cyano-2-fluorobenzoate S6 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 87%
Synthesis of DNA functionalized product 65

DNA functionalized product 65 was synthesized and purified according to general procedure H using 3-(1,3-dioxan-2-yl)-1-(furan-2-yl)propyl 4-cyano-2-fluorobenzoate S8 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 85%.
Synthesis of DNA functionalized product 66

DNA functionalized product 66 was synthesized and purified according to general procedure using 3-(1,3-dioxan-2-yl)-1-(thiophen-2-yl)propyl
4-cyano-2-fluorobenzoate $S_9$ (5 µL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 µL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 µL), H2O (6.5 µL), sodium acetate (1 µL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative $60$ (2.5 µL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 87%
Synthesis of DNA functionalized product 67

DNA functionalized product 67 was synthesized and purified according to general procedure H using tert-butyl 3-((4-cyano-2-fluorobenzoyl)oxy)-3-(1,3-dioxan-2-yl)propyl)-1H-indole-1-carboxylate S11 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 57%
DNA functionalized product 68 was synthesized and purified according to general procedure H using tert-butyl 4-(2-((4-cyano-2-fluorobenzoyl)oxy)-2-phenylethyl) piperidine-1-carboxylate S13 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 59%
Synthesis of DNA functionalized product 69
DNA functionalized product 69 was synthesized and purified according to general procedure H using 1-phenylcyclobutyl 4-cyano-2-fluorobenzoate S18 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 87%
Synthesis of DNA functionalized product 70

DNA functionalized product 70 was synthesized and purified according to general procedure H using 4-phenyltetrahydro-2H-pyran-4-yl 4-cyano-2-fluorobenzoate S21 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 90%
DNA functionalized product 71 was synthesized and purified according to general procedure H using 2-phenylbicyclo[2.2.1]heptan-2-yl 4-cyano-2-fluorobenzoate S20 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 83%
DNA functionalized product 72 was synthesized and purified according to general procedure H using 4-methoxybenzyl 4-cyano-2-fluorobenzoate S27 (5 μL of 50 mM
stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 90%
Synthesis of DNA functionalized product 73

DNA functionalized product 73 was synthesized and purified according to general procedure H using 3-((tert-butoxycarbonyl)amino)benzyl 4-cyano-2-fluorobenzoate S28 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 73%
Synthesis of DNA functionalized product 74 (from Haloperidol)

DNA functionalized product 74 was synthesized and purified according to general procedure H using 4-(4-chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobuty) piperidin-4-yl-4-cyano-2-fluorobenzoate (Haloperidol ester) S30 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 68%
Synthesis of DNA functionalized product 75 (from OBN-Ezetimibe)
DNA functionalized product 75 was synthesized and purified according to general procedure H using 3-(2-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-4-oxazetidin-3-yl)-1-(4-fluorophenyl)propyl 4-cyano-2-fluorobenzoate (OBn-Ezetimibe ester) S31 (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), Hantzsch ester (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 equiv.), DMSO (30 μL), H2O (6.5 μL), sodium acetate (1 μL of 250 mM stock solution in H2O, 250 nmol, 100 equiv.) and DNA derivative 60 (2.5 μL of 1 mM stock solution in H2O, 2.5 nmol, 1 equiv.). Yield = 87%
6. NMR traces

![NMR spectrum image](image-url)
contains unknown impurity (*)