CHAPTER 6: EXPERIMENTAL SECTION

6.1. General

Chemical reagents, solvents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, Fluka, Acros, Novabiochem and Fisher Scientific. 2,4,5-trihydroxybenzaldehyde and 2,4-dihydroxy-5-methoxybenzaldehyde were prepared in our laboratory by Dr. Ana Simao. Staining agent CM-H$_2$DCFDA was obtained from Invitrogen, Paisley, Scotland). Analytical TLC was performed on Merck silica gel 60 aluminium plates F$_{254}$. Column chromatography was performed using Silica gel 60 Å (particle size 40-63 μm) purchased from Fisher Scientific or Sigma Aldrich.

$^1$H NMR and $^{13}$C NMR data were generated using JEOL Eclipse (270 MHz) or Varian Mercury VX (400 MHz) instruments. Chemical shifts stated are in parts per million (ppm). Coupling constant values (J) are given as Hertz (Hz). Mass spectrometry was performed using a micrOTOF instrument from Bruker Daltonics (Bremen, Germany) using electrospray ionisation and calibrated using sodium formate solution. Melting points were obtained using a heated stage microscope (Reichert-Jung). IR spectra were recorded on a Perkin-Elmer 782 infrared spectrometer, either as a KBr disk or solution in chloroform (CHCl$_3$ cell). Band values are given in cm$^{-1}$ and quoted as strong (s), medium (m) or weak (w) intensity. UV absorbance spectra were obtained on a Lambda 35 UV/Vis spectrometer (Perkin-Elmer, Norwalk, Connecticut, USA). $\lambda_{\text{max}}$ values are reported in nm and molar extinction coefficients ($\varepsilon$) in L mol$^{-1}$ cm$^{-1}$.

HPLC was performed on a Dionex Ultimate 3000 Instrument (Dionex, Sunnyvale, California, USA), equipped with a Phenomenex Gemini 5 μm C-18 (150 x 4.6 mm) column with a flow rate of 1 mL/min, detecting at UV 214 nm wavelength. Mobile phase A was 0.1% HCOOH in water, mobile phase B was 0.1% HCOOH in acetonitrile. Gradient was $t = 0$ min, B = 5%; $t = 10$ min, B = 95%; $t = 15$ min, B = 95%; $t = 15.1$ min, B = 5%; $t = 18.1$ min, B = 5%.
6.2. Synthesis of compounds

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\text{[Structural diagram]}
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\((E)-\text{N}-((3\text{-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl})\text{methylene)}\)  
isonicotinohydrazide (PIH, 8)[72]

A solution of INH (1.37 g, 9.82 mmol) in EtOH (100 mL) was treated with pyridoxal hydrochloride (2.0 g, 9.82 mmol), followed by an aqueous solution of NaOAc (805 mg, 9.82 mmol) in H\text{2}O (100 mL). The reaction mixture was stirred at reflux for 1 h, after which the cooled reaction mixture was stored at 2-8 °C overnight, and the resulting precipitate collected by suction filtration. The resulting yellow powder was washed with EtOH to give 8 as a bright yellow powder (2.17 g, 77%). R\text{f} = 0.62 (30% MeOH in DCM). Mp = 266-268 °C (lit. 268 °C).[183] 1H NMR (DMSO-d\text{6}, 400 MHz) δ 2.49 (3H, s, Pyr-Me), 4.68 (2H, d, J = 5.4, OCH\text{2}), 5.47 (1H, t, J = 5.4, OH), 7.94 (2H, d, J = 6.0, Pyr), 8.03 (1H, s, Ar), 8.89 (2H, d, J = 6.0, Pyr), 9.05 (1H, s, HC=N), 12.18 (1H, s, OH), 12.85 (1H, s, NH). 13C NMR (DMSO-d\text{6}, 100 MHz) δ 18.85 (Pyr-Me), 58.93 (OCH\text{2}), 120.07 (Ar), 121.50 (Pyr), 132.47 (Ar), 138.71 (Ar), 139.18 (Ar), 147.65 (Ar), 147.74 (C=N), 150.49 (Pyr), 150.71 (Ar), 161.58 (C=O).

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\text{[Structural diagram]}
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\((E)-\text{N}-(2\text{-hydroxybenzylidene)}\text{isonicotinohydrazide (SIH, 10)[72]}

A solution of salicylaldehyde (1.00 g 8.19 mmol) and INH (1.12 g, 8.19 mmol) in EtOH (24 mL) was heated at reflux for 3 h. The solid precipitate which formed was collected from the cooled reaction mixture by suction filtration and dried under vacuum at 40 °C. This gave 10 as a white powder (1.80 g, 90%). R\text{f} = 0.75 (10% MeOH in DCM). Mp = 250-253 °C (lit. 252-253 °C).[184] 1H NMR (DMSO-d\text{6}, 400 MHz) δ 6.89-6.93 (2H, m, Ar), 7.30 (1H, t, J = 6.9, Ar), 7.58 (1H, dd, J = 6.2, 1.5, Ar), 7.83 (2H, dd, J = 6.0, 1.6, Pyr), 8.69 (1H, s, HC=N), 8.78 (1H, dd, J = 6.0, 1.6, Pyr), 11.06 (1H, s, OH), 12.24 (1H, s, NH). 13C NMR (DMSO-d\text{6}, 100 MHz) δ 116.44 (Ar), 118.66 (Ar), 119.40 (Ar), 121.46 (Pyr), 129.29 (Ar), 131.69 (Ar), 139.98 (Ar), 149.11 (C=N), 150.36 (Pyr), 157.50 (Ar), 161.33 (C=O).
A solution of 2-hydroxy-1-naphthaldehyde (1.00 g, 5.81 mmol) and INH (798 mg, 5.81 mmol) in EtOH (25 mL) was heated at reflux for 1 h. The precipitate which formed was collected by suction filtration and washed with water and EtOH to give 11 as a bright yellow solid (1.44 g, 85%). R<sub>f</sub> = 0.88 (5% MeOH in DCM). Mp = 267-272 °C (lit. 268-269).<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 7.23 (1H, d, J = 8.9, Ar), 7.40 (1H, t, J = 7.1, Ar), 7.61 (1H, t, J = 7.1, Ar), 7.86-7.89 (3H, m, Ar), 7.94 (1H, d, J = 9.0, Ar), 8.29 (1H, d, J = 8.5, Ar), 8.82 (2H, d, J = 6.0, Pyr), 9.47 (1H, s, HC=N), 12.36 (1H, s, OH), 12.50 (1H, s, NH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 100 MHz) δ 108.53 (Ar), 118.83 (Ar), 120.92 (Ar), 121.41 (Pyr), 123.60 (Ar), 127.86 (Ar), 128.98 (Ar), 131.63 (Ar), 133.10 (Ar), 139.84 (Pyr), 148.02 (C=N), 150.47 (Pyr), 158.21 (Ar), 161.05 (C=O).

1-(1-bromoethyl)-2-nitrobenzene (49)<sup>120</sup>

A solution of N-bromosuccinimide (10.42 g, 58.2 mmol) and ABCN (134 mg, 0.55 mmol) in CCl<sub>4</sub> (160 mL) under an N<sub>2</sub> atmosphere was treated with 1-ethyl-2-nitrobenzene (8.02 g, 52.9 mmol) and refluxed for 22 h. After cooling, the precipitate was removed by suction filtration, and the solvent removed from the filtrate under reduced pressure to give a brown residue to which EtOAc (150 mL) was added. The solution was then extracted with water (2 x 100 mL). The organic phase was dried over MgSO<sub>4</sub> and solvent removed under reduced pressure to yield the crude product as an orange oil (13.05 g). The crude was purified by column chromatography eluting with 1% EtOAc in petroleum ether to give 49 as a yellow liquid (7.83 g, 64%) which was 90% pure. R<sub>f</sub> = 0.56 (4% EtOAc in petroleum ether). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.06 (3H, d, J = 6.8, Me), 5.78 (1H, q, J = 6.8, CHBr), 7.43 (1H, td, J = 7.5, 1.3, Ph), 7.63 (1H, td, J = 7.6, 1.0, Ar), 7.82 (1H, dd, J = 8.2, 1.2, Ar), 7.88 (1H, dd, J = 8.0, 1.0, Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 26.98 (Me), 41.84 (CHBr), 124.28 (Ar), 128.98 (Ar), 129.75 (Ar), 133.42 (Ar), 137.53 (Ar), 147.52 (Ar).
3-(1-(2-nitrophenyl)ethoxy)-2-naphthaldehyde (50)

A suspension of Cs$_2$CO$_3$ (9.28 g, 28.5 mmol) and 18-crown-6 (43 mg, 0.16 mmol) in DMF (110 mL) was treated with 2-hydroxy-1-naphthaldehyde (2.00 g, 11.6 mmol) and 49 (2.71 g, 11.6 mmol). The mixture was stirred at RT for 30 h, then the DMF was removed under reduced pressure and the resulting crude dissolved in DCM (100 mL) and extracted with 1 M NaOH (5 x 90 mL). Removal of solvent from the organic phase gave the crude product as a brown solid (4.86 g), which was purified by column chromatography, eluting with 10-30% EtOAc in petroleum ether to yield 50 as an orange solid (2.09 g, 56%). $R_f = 0.43$ (10% EtOAc in petroleum ether). Mp = 135-141 ºC. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.84 (3H, d, J = 6.2, Me), 6.36 (1H, q, J = 6.2, CH), 7.00 (1H, d, J = 9.2, Ar), 7.41 (1H, t, J = 7.0, Ar), 7.47 (1H, t, J = 8.4, Ar), 7.59-7.64 (2H, m, Ar), 7.72 (1H, d, J = 8.1, Ar), 7.81 (1H, dd, J = 7.9, 1.2, Ar), 7.90 (1H, d, J = 9.1, Ar), 8.07 (1H, dd, J = 8.2, 1.0, Ar), 9.26 (1H, d, J = 8.1, Ar), 11.10 (1H, s, CH=O). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 23.53 (Me), 72.93 (CH), 114.02 (Ar), 114.02 (Ar), 117.53 (Ar), 124.91 (Ar), 124.93 (Ar), 127.54 (Ar), 128.24 (Ar), 128.75 (Ar), 128.83 (Ar), 129.61 (Ar), 129.97 (Ar), 131.56 (Ar), 134.34 (Ar), 137.51 (Ar), 138.05 (Ar), 147.36 (Ar), 161.58 (Ar), 191.73 (HC=O). IR (KBr) 3019s (Ar), 1672s (C=O), 1351s (NO$_2$). [Found (ESI+) 344.0890 [M+Na]$^+$, C$_{19}$H$_{15}$NaNO$_4$ requires 344.0899].

2-(1-(2-nitrophenyl)ethoxy)benzaldehyde (51)[110]

A suspension of Cs$_2$CO$_3$ (8.00 g, 24.6 mmol) in anhydrous DMF (80 mL) was treated with 18-crown-6 (49 mg, 0.18 mmol), salicylaldehyde (1.00 g, 8.19 mmol) and 49 (2.00 g, 8.60 mmol). The mixture was stirred at RT under an N$_2$ atmosphere for 24 h. The DMF was removed under reduced pressure and the solid residue was dissolved in DCM (70 mL) and was extracted with 1 M NaOH (3 x 50 mL). The organic phase was dried over MgSO$_4$ and the solvent removed to yield the crude product as an oil
which was purified by column chromatography eluting from 6-12% EtOAc in petroleum ether. This gave 51 as a pale-yellow powder (1.78 g, 80%). Rf = 0.31 (5% EtOAc in petroleum ether). Mp = 79-81 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.78 (3H, d, J = 6.2, Me), 6.18 (1H, q, J = 6.2, CH), 6.72 (1H, d, J = 8.4, Ar), 6.98 (1H, t, J = 7.8, Ar), 7.38 (1H, td, J = 7.4, 1.9, Ar), 7.45 (1H, td, J = 7.8, 1.4, Ar), 7.62 (1H, t, J = 7.6, 1.0, Ar), 7.78 (1H, dd, J = 7.9, 1.4, Ar), 7.82 (1H, dd, J = 8.2, 1.2, Ar), 8.03 (1H, dd, J = 8.2, 1.2), 10.65 (1H, s, HC=O). \(^1\)^C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 23.41 (Me), 72.14 (CH), 113.70 (Ar), 121.29 (Ar), 124.85 (Ar), 125.42 (Ar), 127.38 (Ar), 128.71 (Ar), 128.82 (Ar), 134.27 (Ar), 135.88 (Ar), 138.17 (Ar), 147.41 (Ar), 159.49 (Ar), 189.43 (C=O).

\[6\text{-methyl-7-} (\text{1-(2-nitrophenyl)ethoxy})\text{-1,3-dihydrofuro-(3,4-c)pyridin-1-ol (52)} \]^{110}

A suspension of pyridoxal hydrochloride (1.00 g, 4.91 mmol) in anhydrous DMF (30 mL) was treated with Cs\(_2\)CO\(_3\) (4.83 g, 14.73 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 49 (1.14 g, 5.16 mmol). The mixture was stirred at RT under an N\(_2\) atmosphere for 24 h. The DMF was removed under reduced pressure and the solid residue was dissolved in DCM and extracted with 1M NaOH (3 x 60 mL) and brine (3 x 60 mL). The organic phase was dried over MgSO\(_4\) and the solvent removed to yield the crude product as a brown solid which was purified by column chromatography over eluting with 75% EtOAc in petroleum ether. This gave 52 as an off-white powder (1.06 g, 68%) as two diastereoisomers A:B 2:1. Rf = 0.30 (70% EtOAc in petroleum ether). Mp = 159-162 °C (lit. 163-165 °C).^{110} \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (diastereoisomer A) 1.73 (3H, d, J = 6.2, Me), 2.61 (3H, s, Pyr-Me), 3.02 (1H, d, J = 6.0, OH), 4.92 (1H, d, J = 12.8, CH), 5.21 (1H, d, J = 12.7, CH), 6.13 (1H, d, J = 4.0, CHO\(_\text{OH}\)), 6.31 (1H, q, J = 6.2, CH), 7.49 (1H, t, J = 7.8, Ar), 7.66 (1H, td, J = 7.8, 1.2, Ar), 7.85 (1H, dd, J = 7.9, 1.2, Ar), 8.01 (1H, dd, 7.8, 1.4, Ar), 8.11 (1H, s, Pyr); (diastereoisomer B) 1.72 (3H, d, J = 6.2, Me), 2.58 (3H, s, Pyr-Me), 2.88 (1H, d, J = 6.0, OH), 4.99 (1H, d, J = 12.8, CH), 5.21 (1H, d, J = 12.7, CH), 6.19 (1H, q, J = 6.2, Ph), 6.51 (1H, d, J = 4.0, CHO\(_\text{OH}\)), 7.49 (1H, t, J = 7.8, Ar), 7.72 (1H, td, J = 7.8, 1.2, Ar), 7.97 (1H, dd, J = 7.9, 1.2, Ar), 8.04 (1H, dd, 7.8, 1.4, Ar), 8.14 (1H, s, Pyr). \(^1\)^C NMR (DMSO-d\(_6\), 100 MHz)
\( \delta 19.68 \) (Me), 23.05 (Pyr-Me), 68.40 (CH\(_2\)), 74.48 (CH), 98.93 (C–OH), 124.11 (Ar), 124.59 (Ar), 127.47 (Ar), 128.10 (Ar), 129.03 (Pyr), 133.92 (Pyr), 134.22 (Pyr), 135.76 (Pyr), 137.50 (Ar), 146.14 (Pyr), 147.24 (Ar).

(E)-N-\(((5\text{-hydroxymethyl})\text{-2\text{-methyl}}\text{-3\text{-}(1\text{-}(2\text{-nitrophenyl})\text{ethoxy})\text{pyridin}}\text{-4\text{yl}) methylene})\text{isonicotinohydrazide} (34)\)\(^{[110]}\)

A solution of 52 (234 mg, 0.74 mmol) and INH (102 mg, 0.64 mmol) in 90% EtOH (7 mL) was treated with DOWEX 50WX8-100 ion-exchange resin (201 mg) and heated at reflux for 21 h. The resin was removed by suction filtration and the solvent was removed from the filtrate under reduced pressure to yield an orange-yellow oil. The crude product was purified by column chromatography eluting with 0-5% MeOH in DCM + 0.1% pyridine. Removal of solvent gave a yellow oil, which was co-evaporated with toluene (3 x 10 mL) to give 34 as a pale yellow solid (52 mg, 38%). R\(_f\) = 0.63 (10% MeOH in DCM). Mp = 194-196 °C (lit. 191-193 °C).\(^{[110]}\) UV (EtOH): \( \lambda_{\text{max}} \) 296 (19733).

\(^1\text{H NMR} \) (acetone-\(d_6\), 270 MHz) \( \delta \) 1.67 (3H, d, J = 6.1, Me), 2.42 (3H, s, Pyr-Me), 4.59 (2H, s, CH\(_2\)), 4.97 (1H, t, J = 5.5, OH), 5.62 (1H, q, J = 6.1, CH), 7.63 (1H, t, J = 5.7, Ar), 7.85 (2H, d, J = 3.4, Ar), 7.87 (1H, t, J = 3.4, Ar), 7.94 (1H, t, J = 6.8, Ar), 8.17 (1H, d, J = 5.7, Ar), 8.36 (1H, s, CH=N), 8.81 (3H, s, Ar), 11.8 (1H, s, NH). \(^{13}\text{C NMR} \) (\(d_6\)-DMSO, 67.5 MHz) \( \delta \) 19.5 (Me), 21.9 (Pyr-Me), 61.0 (CH\(_2\)), 77.9 (CH), 124.3 (Ar), 128.6 (Ar), 129.4 (Ar), 133.8 (Ar), 143.8 (CH=N), 146.0 (Ar), 150.8 (Pyr), 162.8 (C=O).
(E)-N-(2-(1-(2-nitrophenyl)ethoxy)benzylidene)isonicotinohydrazide (37)\textsuperscript{[110]}

A solution of 51 (300 mg, 1.11 mmol) and INH (151 mg, 1.10 mmol) in 90% EtOH (10 mL) was heated at reflux for 22 h. The precipitate was collected from the cooled reaction mixture by suction filtration and dried under vacuum to give 37 as a white powder (287 mg, 66%). R\textsubscript{f} = 0.83 (10% MeOH in DCM). Mp = 228-231 °C (lit. 227-229 °C).\textsuperscript{[110]} UV (EtOH): \(\lambda_{\text{max}}\) 326 (16110).

\(\text{H NMR (DMSO-d}_6, 400 MHz) \delta\) 1.70 (3H, t, J = 6.2, Me), 6.06 (1H, q, J = 6.2, CH), 6.81 (1H, q, J = 8.3, Ar), 6.98 (1H, t, J = 7.4, Ar), 7.26 (1H, d, J = 7.2, Ar), 7.57-7.59 (1H, m, Ar), 7.74 (2H, d, J = 4.1, Ar), 7.83-7.88 (2H, m, Ar), 8.03 (1H, d, J = 8.1, Ar), 8.78 (2H, d, J = 5.0, Pyr), 8.94 (1H, s, CH=N), 12.10 (1H, s, NH). \(\text{C NMR (DMSO-d}_6, 100MHz) \delta\) 22.79 (Me), 71.32 (CH), 113.79 (Ar), 121.55 (Pyr), 123.03 (Ar), 124.62 (Ar), 126.11 (Ar), 127.25 (Ar), 129.18 (Ar), 131.69 (Ar), 134.24 (Ar), 136.94 (Ar), 140.58 (Pyr), 144.35 (C=N), 147.57 (Ar), 150.29 (Pyr), 155.40 (Ar), 161.59 (C=O).

(E)-N-(3-(1-(2-nitrophenyl)ethoxy)-naphthalen-2-yl)methyleneisonicotinohydrazide (53)

A solution of 50 (302 mg, 0.94 mmol) and INH (130 mg, 0.95 mmol) in 90% EtOH (10 mL) was heated at reflux for 24 h. The precipitate that formed upon cooling was collected by suction filtration and washed with EtOH to give 53 as a yellow powder (132 mg, 32%) as two stereoisomers A:B 10:2. R\textsubscript{f} = 0.5 (5% MeOH in DCM). Mp = 203-205 °C. UV (EtOH): \(\lambda_{\text{max}}\) 231 (40493), 361 (14287). \(\text{H NMR (DMSO-d}_6, 400 MHz) \delta\) (stereoisomer A) 1.84 (3H, d, J = 6.2, Me), 6.33 (1H, q, J = 6.2, CH), 7.35
(1H, d, J = 7.6, Ar), 7.48 (1H, t, J = 7.4, Ar), 7.60-7.68 (2H, m, Ar), 7.82 (2H, t, J = 7.4, Ar), 7.89-7.92 (2H, m, Ar), 7.95-7.98 (3H, m, Pyr + Ar), 8.12 (1H, d, J = 7.6, Ar), 8.90 (2H, d, J = 5.5, Pyr), 9.41 (1H, s, CH=N), 9.47 (1H, d, J = 7.7, Ar), 12.30 (1H, s, NH₂); (stereoisomer B) 1.79 (3H, d, J = 6.2, Me), 6.26 (1H, q, J = 6.2, CH), 7.30 (1H, d, J = 7.1, Ar), 7.39 (1H, t, J = 7.1, Ar), 7.60-7.68 (1H, m, Ar), 7.75 (2H, d, J = 5.7, Pyr), 7.80-7.84 (2H, m, Ar), 7.89-7.92 (2H, m, Ar), 7.95-7.97 (1H, m, Ar), 8.10 (1H, d, J = 7.6, Ar), 8.67 (1H, d, J = 8.6, Ar), 8.83 (2H, d, J = 5.7, Pyr), 9.10 (1H, s, HC=N), 12.26 (1H, s, NH)²⁸. C NMR (DMSO-d₆, 100 MHz) δ (stereoisomer A) 22.95 (Me), 72.27 (CH), 114.88 (Ar), 115.41 (Ar), 121.69 (Pyr), 124.50 (Ar), 124.66 (Ar), 125.87 (Ar), 127.57 (Ar), 127.96 (Ar), 128.23 (Ar), 128.47 (Ar), 128.97 (Ar), 129.24 (Ar), 130.77 (Ar), 132.92 (Ar), 134.29 (Ar), 136.97 (Ar), 140.70 (Pyr), 146.42 (C=N), 147.56 (Ar), 150.35 (Pyr), 155.48 (Ar), 161.74 (C=O); (stereoisomer B) 22.80 (Me), 72.18 (CH), 115.15 (Ar), 122.51 (Ar), 124.36 (Ar), 125.20 (Ar), 127.75 (Ar), 128.90 (Ar), 130.28 (Ar), 132.55 (Ar), 142.57 (Pyr), 142.65 (C=N), 149.56 (Pyr), 155.31 (Ar), 168.49 (C=O). IR (KBr) 3019s (Ar), 1676s (C=N), 1527s (NO₂). [Found (ESI+) 441.1565 [M+H]⁺, C₂₅H₂₁N₄O₄ requires 441.1563].

(E)-2-((3-hydroxynaphthalen-2-yl)methylene)-N,N-dimethylhydrazinecarbothioamide (54a)²⁸

A solution of 2-hydroxy-1-naphthaldehyde (400 mg, 2.32 mmol) and 4,4-dimethyl-3-thiosemicarbazide (277 mg, 2.32 mmol) in EtOH (13 mL) was heated at reflux for 3 h. The precipitate which formed was collected by suction filtration and washed with water and EtOH to give 54a as a yellow solid (473 mg, 75%). Rᵣ = 0.70 (70% EtOAc in petroleum ether). Mp = 218-221 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 3.32 (6H, s, NMe₂), 7.17 (1H, d, J = 9.0, Ar), 7.37 (1H, t, J = 7.5, Ar), 7.57 (1H, t, J = 7.7, Ar), 7.87 (1H, d, J = 9.3, Ar), 8.06 (1H, d, J = 8.6, Ar), 9.44 (1H, s, HC=N), 11.21 (1H, s, OH), 12.89 (1H, s, NH). ₁³C NMR (DMSO-d₆, 100 MHz) δ 39.58 (NMe₂), 108.57 (Ar), 119.20 (Ar), 120.13 (Ar), 123.30 (Ar), 127.44 (Ar), 127.69 (Ar), 128.92 (Ar), 131.59 (Ar), 131.88 (Ar), 143.94 (C=N), 157.04 (Ar), 178.84 (C=S).
(E)-2-((3-hydroxynaphthalen-2-yl)methylene)hydrazinecarbothioamide (54b)$^{[88]}$

A solution of 2-hydroxy-1-naphthaldehyde (1.00 g, 5.81 mmol) and thiosemicarbazide (530 mg, 5.81 mmol) in EtOH (35 mL) was heated at reflux for 2 h. The precipitate which formed was collected by suction filtration and washed with water and EtOH to give 54b as a light yellow solid (1.24 g, 87%). $R_f = 0.87$ (10% MeOH in DCM). $Mp = 267-270 \degree C$ (lit. 271 $\degree C$).$^{[185]}$ $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.18 (1H, d, $J = 8.9$, Ar), 7.34 (1H, t, $J = 7.9$, Ar), 7.54 (1H, t, $J = 8.4$, Ar), 7.78-7.87 (3H, m, Ar), 9.03 (1H, s, HC=N), 10.50 (1H, s, OH), 11.34 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 109.74 (Ar), 118.37 (Ar), 122.73 (Ar), 123.43 (Ar), 127.83 (Ar), 128.08 (Ar), 128.67 (Ar), 131.54 (Ar), 132.44 (Ar), 143.06 (C=N), 156.60 (Ar), 177.42 (C=S).

(E)-N,N-dimethyl-2-((3-(1-(2-nitrophenyl)ethoxy)naphthalen-2-yl)methylene) hydrazinecarbothioamide (55a)

A solution of 50 (300 mg, 0.93 mmol) and 4,4-dimethyl-3-thiosemicarbazide (112 mg, 0.93 mmol) in EtOH (12 mL) was heated at reflux for 3 h. The reaction mixture was allowed to cool and the precipitate which formed was collected by suction filtration and washed with ice-cold EtOH to give 55a as a bright orange solid (257 mg, 65%). $R_f = 0.28$ (20% EtOAc in petroleum ether). $Mp = 186-187 \degree C$. UV (EtOH): $\lambda_{max}$ 237 (39786), 360 (15017). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.75 (3H, d, $J = 6.2$, Me), 3.35 (6H, s, NMe$_2$), 6.20 (1H, q, $J = 6.2$, CH), 7.19 (1H, d, $J = 9.9$, Ar), 7.37 (1H, t, $J = 7.2$, Ar), 7.52 (2H, q, $J = 7.6$, Ar), 7.72-7.88 (3H, m, Ar), 8.01 (1H, d, $J = 8.1$, Ar), 9.12 (1H, s, CH=N), 9.43 (1H, d, $J = 8.7$, Ar), 11.19 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 22.95 (Me), 41.88 (NMe$_2$), 72.14 (>C–O), 114.95 (Ar), 116.31 (Ar), 124.34 (Ar), 124.49 (Ar), 126.44 (Ar), 127.76 (Ar), 128.25 (Ar), 129.05 (Ar), 129.18
(Ar), 130.63 (Ar), 131.94 (Ar), 134.16 (Ar), 137.04 (Ar), 141.98 (C=N), 147.65 (Ar), 154.80 (Ar), 180.58 (C=S).

IR (KBr) 2916m (C-H), 1526s (C=N), 1316s (NO₂), 1142m (C=S), 1059s (C-O). [Found (ESI+) 423.1482 [M+H]⁺, C₂₂H₂₃N₄O₃S requires 423.1491].

(E)-2-((3-(1-(2-nitrophenyl)ethoxy)naphthalen-2-yl)methylene)hydrazinecarbothioamide (44)

A solution of 50 (300 mg, 0.93 mmol) and thiosemicarbazide (86 mg, 0.93 mmol) in EtOH (12 mL) was heated at reflux for 5 h. The EtOH was removed under reduced pressure and the crude product purified by column chromatography eluting with DCM + 0.1% pyridine to give 55b as a pale yellow powder (144 mg, 39%). Rᵣ = 0.72 (4% MeOH in DCM). Mp = 82-85 °C. UV (EtOH): λₑₘₐₓ 233 (35347), 357 (16383). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.72 (3H, d, J = 6.2, Me), 6.18 (1H, q, J = 6.2, CH), 7.15 (1H, d, J = 7.2, Ar), 7.22 (2H, d, J = 9.2, Ar), 7.39 (1H, t, J = 7.4, Ar), 7.52-7.58 (3H, m, J = 7.4, Ar), 7.75 (1H, t, J = 7.1, Ar), 7.80 (1H, d, J = 8.0, Ar), 7.85 (1H, d, J = 6.4, Ar), 7.90 (1H, dd, Ar), 8.01 (1H, dd, J = 8.2, Ar), 8.21 (1H, s, NH), 8.97 (1H, d, J = 8.8, Ar), 9.04 (1H, s, HC=N), 11.57 (1H, s, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 22.86 (Me), 72.25 (CH), 115.05 (Ar), 115.80 (Ar), 124.41 (Ar), 125.68 (Ar), 127.83 (Ar), 128.17 (Ar), 128.35 (Ar), 128.87 (Ar), 128.95 (Ar), 129.19 (Ar), 130.60 (Ar), 132.37 (Ar), 134.17 (Ar), 136.97 (Ar), 141.54 (C=N), 147.60 (Ar), 155.32 (Ar), 177.74 (C=S). IR (KBr) 3519m (NH₂), 1523s (NO₂), 1236 (C-O), 1059 (C=S). [Found (ESI+) 395.1178 [M+ H]⁺, C₂₀H₁₈N₄O₃S requires 395.1178].
(E)-N-((3-hydroxymethyl)-2-methylpyridin-4-yl)methylenebenzothiohydrazide (56)\textsuperscript{[87]}

A solution of pyridoxal hydrochloride (267 mg, 1.31 mmol) and thiobenzhydrazide 59 (200 mg, 1.31 mmol) was heated at reflux for 10 min. The precipitate which formed upon cooling was collected by suction filtration and washed with chilled EtOH to give 56 as a bright orange powder (345 mg, 87%). R\textsubscript{r} = 0.10 (10% MeOH in DCM). Mp = 225-229 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) δ 2.70 (3H, s, Me), 4.84 (2H, s, CH\textsubscript{2}), 7.58 (2H, t, J = 7.5, Ph), 7.67-7.70 (1H, m, Ph), 8.02 (2H, d, J = 7.0, Ph), 8.28 (1H, s, Pyr), 9.45 (1H, s, HC=N), 13.00 (1H, s, ArOH), 14.40 (1H, s, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) δ 14.78 (Me), 58.04 (CH\textsubscript{2}), 126.12 (Ar), 128.11 (Ph), 128.33 (Ph), 129.51 (Ar), 132.13 (Ph), 137.34 (Ar), 138.31 (Ar), 144.04 (Ar), 148.80 (C=N), 152.63 (Ar), 195.21 (C=S).

(E)-N-((5-(5-hydroxymethyl)-2-methyl-3-(1-(2-nitrophenyl)ethoxy)pyridin-4-yl) methylene)benzothiohydrazide (57)

A solution of 52 (400 mg, 1.26 mmol) and thiobenzhydrazide 59 (197 mg, 1.30 mmol) in EtOH (3 mL) was treated with DOWEX 50WX8-100 ion-exchange resin (300 mg) and heated at reflux for 17 h. The resin was removed by suction filtration and the EtOH evaporated off under reduced pressure to give the crude product as an orange oil. This was purified by column chromatography eluting with 1% MeOH in DCM + 0.1% pyridine to give 57 as a bright orange powder (206mg, 37%). R\textsubscript{r} = 0.48 (5% MeOH in DCM). Mp = 92-95 °C. UV (EtOH): \textlambda_{\text{max}} 279 (16280), 352 (9039). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) δ 1.63 (3H, d, J = 6.1, Me), 2.34 (3H, s, PyrMe), 4.67 (2H, d, J = 6.2, CH\textsubscript{2}), 5.19 (1H, t, J = 6.9, OH), 5.53 (1H, q, J = 6.1, CH), 7.51 (1H, d, J = 7.7,
Ar), 7.56-7.63 (3H, m, Ar), 7.81 (3H, t, J = 8.0, Ar), 7.96 (1H, d, J = 8.1, Ar), 8.06-8.10 (1H, m, Ar), 8.43 (1H, s, CH=N), 8.95 (1H, s, Pyr), 13.50 (1H, s, NH).  13C NMR (DMSO-d₆, 100 MHz) δ 19.65 (Me), 21.79 (Pyr Me), 60.29 (CH₂), 77.06 (CH), 124.12 (Ar), 127.36 (Ar), 127.77 (Ar), 128.05 (Ar), 128.28 (Ar), 128.68 (Ar), 128.88 (Ar), 129.43 (Ar), 131.34 (Ar), 133.74 (Ar), 139.85 (Ar), 144.74 (C=N), 147.46 (Ar), 148.19 (Ar), 150.12 (Ar), 151.69 (Ar), 195.06 (C=S).  IR (KBr) 3321m (OH), 3015s (Ar), 1523s (NO₂), 1400s (OH), 1236s (C=O), 1057m (C=S).


**Thiobenzhydrazide (59)**[87]

A solution of S-(thiobenzoyl)-thioglycolic acid (4.00 g, 18.9 mmol) in 1 M aqueous NaOH (19 mL) and water (20 mL) was chilled to 0 °C and hydrazine monohydrate (2.8 mL, 56.5 mmol) was added. This was followed by slow addition of 5 M HCl (8 mL) to achieve the desired pH of 4-5. After stirring at 0 °C for 1 h, the pH of the resulting suspension was adjusted to pH 9 using 1 M NaOH, and it was extracted with DCM (4 x 40 mL). The organic layers were combined and solvent removed under reduced pressure to yield 59 as a brown solid (2.79 g, 98%). Rf = 0.67 (10% MeOH in DCM).Mp = 68-70 °C (lit. 67-70 °C).[186] 1H NMR (CDCl₃, 400 MHz) δ 5.0 (2H, s, NH₂), 7.38-7.43 (2H, d, J = 6.2, Ph), 7.46-7.51 (1H, m, Ph), 7.69-7.72 (2H, m, Ph), 8.8 (1H, s, NH). 13C NMR (CDCl₃, 100 MHz) δ 126.8 (Ph), 128.7 (Ph), 131.3 (Ph), 139.0 (Ph), 195.2 (C=S). IR (KBr) 3300s (NH₂), 1567s (NH₂), 1119m (C=S).

**1-(bromomethyl)-4,5-dimethoxy-2-nitrobenzene (63)**[187]

A suspension of 4,5-dimethoxy-2-nitrobenzyl alcohol (500 mg, 2.35 mmol) in anhydrous DCM (4 mL) under argon atmosphere was treated with PBr₃ (0.2 mL, 2.35 mmol) and stirred at RT for 1 h, then at reflux for a further 2 h. The reaction mixture
was poured into water (4 mL), neutralised with 1 M NaOH solution and extracted with DCM (3 × 15 mL). Removal of solvent gave pure 63 as an orange-brown solid (501 mg, 77%). Rf = 0.67 (40% EtOAc in petroleum ether). Mp = 132-134 °C (lit. 131-132 °C).\[187\] $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.95 (3H, s, OMe), 3.98 (3H, s, OMe), 4.86 (2H, s, CH$_2$Br), 6.93 (1H, s, Ar), 7.66 (1H, s, Ar). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 29.96 (CH$_2$Br), 56.41 (OMe), 56.48 (OMe), 108.54 (Ar), 113.66 (Ar), 127.35 (Ar), 127.35 (Ar), 140.25 (Ar), 148.91 (Ar), 153.19 (Ar).

2-(4,5-dimethoxy-2-nitrobenzyloxy)benzaldehyde (64)

**Method A:**
A suspension of Cs$_2$CO$_3$ (1.30g, 3.96 mmol) and 18-crown-6 (10 mg, 0.02 mmol) in DMF (16 mL) was treated with salicylaldehyde (160 mg, 1.32 mmol) and 63 (400 mg, 1.45 mmol). The mixture was stirred at RT overnight, after which the DMF was removed under reduced pressure and the resulting residue dissolved in DCM (100 mL), washed with 1 M NaOH (4 × 20 mL) and water (20 mL), and then the combined organic layers dried over MgSO$_4$. Removal of solvent from the organic phase gave a brown solid (4.86 g), which was purified by column chromatography eluting with 10-30% EtOAc in petroleum ether. $^1$H NMR spectrum of the isolated compound suggested an intramolecular-aldol product instead of the expected benzyl-aryl ether.

**Method B:**
A suspension of K$_2$CO$_3$ (136 mg, 0.98 mmol) in acetone (30 mL) was treated with salicylaldehyde (100 mg, 0.82 mmol), followed by 63 (453 mg, 1.64 mmol) and heated at reflux for 5 h. The acetone was removed under reduced pressure and the residue was suspended in DCM (40 mL) and washed with 0.5 M NaOH solution (2 × 40 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure to give the crude product as a yellow solid (540 mg) which was purified by column chromatography eluting with 10% petroleum ether in DCM to give 64 as an orange solid (260 mg, 99%). Rf = 0.53 (10% petroleum ether in DCM). Mp = 169-172 °C. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.98 (3H, s, OMe), 4.06 (3H, s, OMe),
5.59 (2H, s, CH₂), 7.12-7.15 (2H, m, Ar), 7.60 (1H, td, J = 7.6, 1.9, Ar), 7.69 (1H, s, Ar), 7.79 (1H, s, Ar), 7.85 (1H, dd, J = 7.6, 1.9, Ar), 10.45 (1H, s, HC=O). ¹³C NMR (CDCl₃, 100 MHz) δ 56.35 (OMe), 56.66 (OMe), 67.49 (CH₂), 108.00 (Ar), 109.65 (Ar), 113.03 (Ar), 121.43 (Ar), 125.17 (Ar), 128.45 (Ar), 131.62 (Ar), 136.05 (Ar), 138.74 (Ar), 148.00 (Ar), 154.29 (Ar), 159.33 (Ar), 189.45 (C=O). IR (KBr) 2986m (Ar), 1682s (C=O), 1526s (Ar), 1342s (NO₂).

IR (KBr) 2986m (C-H), 2861m (C-H), 1682s (C=O), 1342s (NO₂). [Found (ESI+) 340.0802 [M+Na]⁺, C₁₆H₁₅NNaO₆ requires 340.0797].

7-(4,5-dimethoxy-2-nitrobenzyloxy)-6-methyl-1,3-dihydrofuro[3,4-c]pyridin-1-ol (65)

A suspension of K₂CO₃ (160 mg, 1.12 mmol) in acetone (30 mL) was treated with pyridoxal hydrochloride (200 mg, 0.98 mmol), followed by 63 (540 mg, 1.96 mmol) and heated at reflux for 5 h. The acetone was removed under reduced pressure and the residue was suspended in DCM (40 mL) and washed with water (2 × 80 mL). Volatiles were removed from the organic layer under reduced pressure and the resulting crude product was purified by column chromatography eluting with 4-5% MeOH in DCM to give 65 as a beige solid (131 mg, 37%). Rᵣ = 0.34 (5% MeOH in DCM). Mp = 220-222 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 2.50 (3H, s, Me), 3.96 (3H, s, OMe), 4.00 (3H, s, OMe), 4.99 (1H, d, J = 13.0, CH), 5.15 (1H, d, J = 13.0, CH), 5.63 (1H, d, J = 13.6, CH), 5.73 (1H, d, J = 13.6, CH), 6.68 (1H, dd, J = 7.6, 1.6, CH), 7.13 (1H, d, J = 7.6, OH), 7.51 (1H, s, Ar), 7.80 (1H, s, Ar), 8.21 (1H, s, Pyr). ¹³C NMR (DMSO-d₆, 100 MHz) δ 19.26 (Me), 56.12 (OMe), 56.19 (OMe), 68.53 (CH₂), 69.92 (CH₂), 99.05 (CHOH), 108.23 (Ar), 110.65 (Ar), 127.71 (Ar), 135.49 (Pyr), 135.71 (Pyr), 135.94 (Pyr), 139.18 (Ar), 147.49 (Pyr), 147.84 (Ar), 148.48 (Pyr), 153.38 (Ar). IR (KBr) 3381s (OH), 1579m (Ar), 1523s (NO₂), 1342s (NO₂). [Found (ESI+) 363.1196 [M+H]⁺, C₁₇H₁₈N₂O₇ requires 363.1192].
A solution of 64 (300 mg, 0.95 mmol) and INH (130 mg, 0.95 mmol) in 90% EtOH (10 mL) was heated at reflux for 1 h. The insoluble precipitate was collected from the cooled reaction mixture by suction filtration, washed with EtOAc and allowed to air dry to give pure 66 as a white solid (280 mg, 68%). Rf = 0.55 (10% MeOH in DCM). Mp = 242-244 ºC. UV (EtOH): \( \lambda_{\text{max}} \) 329 (21570). \(^1\)H NMR (DMSO-d6, 400 MHz) \( \delta \) 3.95 (3H, s, OMe), 3.96 (3H, s, OMe), 5.56 (2H, s, CH\(_2\)), 7.15 (1H, t, J = 7.2, Ar), 7.29 (1H, d, J = 8.5, Ar), 7.42 (1H, s, Ar), 7.52 (1H, t, J = 7.2, Ar), 7.81 (1H, s, Ar), 7.86 (2H, d, J = 4.4, Pyr), 7.98 (1H, d, J = 7.4, Ar), 8.83 (2H, d, J = 4.4, Pyr), 8.87 (1H, s, HC=N), 12.09 (1H, s, NH). \(^{13}\)C NMR (DMSO-d6, 100 MHz) \( \delta \) 56.18 (OMe), 56.29 (OMe), 67.29 (CH\(_2\)), 108.43 (Ar), 112.14 (Ar), 113.32 (Ar), 121.42 (Pyr), 121.48 (Ar), 122.53 (Ar), 125.95 (Ar), 126.55 (Ar), 131.89 (Ar), 140.04 (Ar), 140.49 (Pyr), 144.32 (C=N), 148.14 (Ar), 150.27 (Pyr), 153.18 (Ar), 156.81 (Ar), 161.53 (C=O). IR (KBr) 3217s (N-H), 3064s (Ar), 2840s (C-O), 1650s (C=N), 1545s (NO\(_2\)), 1266 (C-O). [Found (ESI+) 437.1453 [M+H]+, C\(_{22}\)H\(_{21}\)N\(_4\)O\(_6\) requires 437.1461].

A solution of 65 (100 mg, 0.28 mmol) and INH (38 mg, 0.28 mmol) in 90% EtOH (6 mL) was treated with DOWEX 50WX8-100 ion-exchange resin (104 mg) and heated at reflux overnight. The resin was removed by suction filtration and the solvent was removed from the filtrate under reduced pressure to yield a brown residue which was
purified by column chromatography eluting with 1-5% MeOH in DCM + 0.1% pyridine to give 67 as a light brown solid (35 mg, 26%). \( R_f = 0.67 \) (10% MeOH in DCM). Mp = 122-127 °C. UV (EtOH): \( \lambda_{\text{max}} \) 300 (21880). \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \( \delta \) 2.52 (3H, s, Pyr-Me), 3.91 (3H, s, OMe), 3.97 (3H, s, OMe), 4.76 (2H, d, J = 6.4, CH\(2\)), 5.36 (1H, t, J = 6.4, OH), 5.37 (2H, s, CH\(2\)), 7.50 (1H, s, Ar), 7.79 (1H, s, Ar), 7.85 (2H, d, J = 5.5, Pyr), 8.53 (1H, s, Pyr), 8.71 (1H, s, HC=N), 8.86 (2H, d, J = 5.5, Pyr), 12.38 (1H, s, NH). \(^{13}\)C NMR (DMSO-\(d_6\), 100 MHz) \( \delta \) 19.20 (Me), 56.09 (OMe), 56.28 (OMe), 60.17 (CH\(2\)), 72.40 (CH\(2\)), 108.15 (Ar), 111.19 (Ar), 121.47 (Pyr), 127.10 (Ar), 132.24 (Pyr), 133.83 (Pyr), 139.25 (Ar), 139.74 (Pyr), 143.68 (C=N), 144.57 (Pyr), 148.03 (Ar), 150.40 (Pyr), 150.95 (Pyr), 151.99 (Pyr), 153.44 (Ar), 162.03 (C=O). IR (KBr) 3444w (OH), 3023s (Ar), 2862w (C=O), 1691s (C=N), 1527s (NO\(2\)). [Found (ESI+) 482.1681 [M+H]⁺, C\(_{23}\)H\(_{24}\)N\(_5\)O\(_7\) requires 482.1676].

7-diethylamino-4-formylcoumarin (72)\(^{[188]}\)

A solution of 7-diethylamino-4-methylcoumarin (5.0 g, 21.6 mmol) and SeO\(_2\) (3.6 g, 32.4 mmol) in anhydrous \(p\)-xylene (90 mL) and under \(N_2\) atmosphere was stirred at 155 °C overnight. The reaction mixture was allowed to cool and the solvent removed under reduced pressure to give a black residue which was dissolved in acetone and then filtered through celite. The dark brown filtrate was evaporated to dryness under reduced pressure and purified by column chromatography eluting with 2.5-20% acetone in petroleum ether to give 72 as a red oil (1.73 g, 35%). \( R_f = 0.34 \) (20% acetone in petroleum ether). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.21 (6H, t, J = 7.1, 2 \( \times \) Me), 3.41 (4H, q, J = 7.1, 2 \( \times \) NCH\(_2\)), 6.44 (1H, s, C=CH), 6.52 (1H, d, J = 2.6, Ar), 6.60 (1H, dd, J = 9.2, 2.6, Ar), 8.30 (1H, d, J = 9.2, Ar), 10.02 (1H, s, HC=O). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 12.37 (2 \( \times \) Me), 44.70 (2 \( \times \) NCH\(_2\)), 97.53 (Ar), 103.64 (Ar), 109.43 (Ar), 117.11 (C=CH), 126.90 (Ar), 143.81 (Ar), 150.96 (Ar), 157.29 (C=O), 161.70 (Ar), 192.37 (HC=O).
7-diethylamino-4-hydroxymethylcoumarin (70)\textsuperscript{189}

A solution of 72 (1.70 g, 6.93 mmol) in isopropyl alcohol (170 mL) was treated with NaBH\textsubscript{4} (400 mg, 10.6 mmol) and stirred at RT for 1 h, after which the reaction mixture was concentrated under reduced pressure and adjusted to pH 5 with 1 M HCl. The resulting suspension was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. Removal of volatiles under reduced pressure gave the crude product which was purified by column chromatography eluting with 30-50% EtOAc in petroleum ether to give 70 as a green solid (900 mg, 53%). \( R_f = 0.45 \) (70% EtOAc in petroleum ether). \( M_p = 143-146 \degree C \) (lit. 146-148 \degree C).\textsuperscript{189} \textsuperscript{1H} NMR (DMSO-d\textsubscript{6}, 400 MHz) \( \delta \) 1.18 (6H, t, \( J = 7.0, 2 \times \text{Me} \)), 3.48 (4H, q, \( J = 7.0, 2 \times \text{NCH}_2 \)) 4.72 (2H, d, \( J = 5.6, \text{CH}_2 \)), 5.53 (1H, t, \( J = 5.6, \text{OH} \)), 6.12 (1H, s, C=CH), 6.57 (1H, d, \( J = 2.1, \text{Ar} \)), 6.72 (1H, dd, \( J = 9.0, 2.1, \text{Ar} \)), 7.49 (1H, d, \( J = 9.0, \text{Ar} \)). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) \( \delta \) 12.30 (2 \( \times \text{Me} \)), 43.92 (2 \( \times \text{NCH}_2 \)), 59.04 (OCH\textsubscript{2}), 96.79 (Ar), 103.95 (C=C), 105.71 (Ar), 108.53 (Ar), 125.05 (Ar), 150.19 (Ar), 155.62 (Ar), 156.79 (Ar), 161.11 (C=O).

4-bromomethyl-7-diethylaminocoumarin (73)\textsuperscript{190}

A solution of 70 (600 mg, 2.42 mmol) and Et\textsubscript{3}N (0.65 mL, 4.84 mmol) in anhydrous DCM under argon atmosphere was chilled to 0 \degree C and treated with methanesulfonyl chloride (0.3 mL, 3.64 mmol). The reaction mixture was stirred for 15 min, after which the solution was washed with 5% NaHCO\textsubscript{3} solution (2 \( \times \) 15 mL), and the organic layer dried over MgSO\textsubscript{4}. Removal of volatiles under reduced pressure gave a dark green residue which was dissolved in anhydrous THF (30 mL), treated with LiBr (860 mg, 9.68 mmol) and stirred at RT for 3 h. After removal of the solvent in vacuo, water (100 mL) was added to the resulting residue and the mixture was
extracted with DCM (2 × 100 mL). The organic layers were combined, dried over MgSO₄ and the solvent removed to give the crude product which was purified by column chromatography eluting with 15-25% EtOAc in petroleum ether to give 73 as an orange solid (670 mg, 89%). Rᵣ = 0.59 (30% EtOAc in petroleum ether). Mp = 124-126 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 1.19 (6H, t, J = 7.1, 2 × Me), 3.40 (4H, q, J = 7.1, 2 × NCH₂), 4.38 (2H, s, CH₂Br), 6.10 (1H, s, C=CH), 6.48 (1H, d, J = 2.6, Ar), 6.60 (1H, dd, J = 9.0, 2.6, Ar), 7.46 (1H, d, J = 9.0, Ar). ¹³C NMR (DMSO-d₆, 100 MHz) δ 11.43 (2 × Me), 26.11 (CH₂Br), 43.76 (2 × NCH₂), 96.84 (Ar), 105.15 (Ar), 107.67 (Ar), 108.22 (C=C), 124.35 (Ar), 149.31 (Ar), 149.88 (Ar), 155.67 (C=C), 160.66 (C=O).

7-(diethylamino)-4-((1-hydroxy-6-methyl-1,3-dihydrofuro[3,4-c]pyridin-7-yloxy) methyl)-2H-chromen-2-one (74)

A suspension of K₂CO₃ (200 mg, 1.4 mmol) in acetone (35 mL) was treated with pyridoxal hydrochloride (200 mg, 0.98 mmol), followed by 73 (372 mg, 1.2 mmol) and stirred at reflux for 5 h. The acetone was removed under reduced pressure and the residue was suspended in water (100 mL) and washed with DCM (4 × 50 mL). The combined organic layers were washed with brine (90 mL), dried over Na₂SO₃ and concentrated under reduced pressure to yield the crude product which was purified by column chromatography eluting with 1-4% MeOH in DCM to give 74 as an orange solid (182 mg, 46 %). Rᵣ = 0.40 (6% MeOH in DCM). Mp = 187-189 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 1.19 (6H, t, J = 7.0, Me), 2.52 (3H, s, Pyr-Me), 3.50 (4H, q, J = 7.0, NCH₂), 5.01 (1H, d, J = 12.9, CH), 5.17 (1H, d, J = 12.9, CH), 5.53 (1H, d, J = 14.7, CH), 5.59 (1H, d, J = 14.7, CH), 5.62 (1H, s, C=CH), 6.63 (1H, d, J = 2.3, Ar), 6.77 (2H, d, J = 7.2, CH), 7.23 (1H, d, J = 7.2, OH), 7.55 (1H, d, J = 9.0, Ar), 8.23 (1H, s, Pyr). ¹³C NMR (DMSO-d₆, 100 MHz) δ 12.18 (Me), 19.00 (Pyr-Me), 44.02 (NCH₂), 68.51 (CH₂), 86.61 (CH₂), 96.72 (Ar), 98.74 (CHOH), 104.77 (C=C), 105.07 (Ar), 108.91 (Ar), 125.41 (Ar), 135.73 (Pyr), 135.82 (Pyr), 136.05 (Pyr), 147.24 (Pyr), 148.65 (Pyr), 150.57 (Ar), 151.54 (Ar), 155.76 (Ar), 161.19 (C=O). IR (KBr) 3288m
(OH), 1343s (C=O), 1202s (C-O). [Found (ESI+) 419.1579 [M+Na]+, C22H24N2O5Na requires 419.1583].

(E)-N’-((3-((7-(diethylamino)-2-oxo-2H-chromen-4-yl)methoxy)-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)isonicotinohydrazide (75)

A solution of 74 (80 mg, 0.20 mmol) and INH (30 mg, 0.21 mmol) in 90% EtOH (6 mL) was treated with DOWEX 50WX8-100 ion-exchange resin (110 mg) and heated at reflux overnight. The resin was removed by suction filtration and the solvent was removed from the filtrate under reduced pressure to yield a yellow residue which was purified by column chromatography eluting with 1-5% MeOH in DCM + 0.1% pyridine to give 75 as a yellow solid (17 mg, 16%). Rf = 0.32 (8% MeOH in DCM). Mp = 149-152 °C. UV (EtOH): λmax 381 (13037). 1H NMR (DMSO-d6, 400 MHz) δ 1.16 (6H, t, J = 6.9, Me), 3.47 (4H, q, J = 6.9, NCH2), 4.79 (2H, d, J = 6.3, CH2), 5.24 (2H, s, OCH2), 5.40 (1H, t, J = 6.5, OH), 6.38 (1H, s, C=CH), 6.61 (1H, d, J = 2.2, Ar), 6.70 (1H, dd, J = 9.0, 2.2, Ar), 7.51 (1H, d, J = 9.0, Ar), 7.86 (2H, d, J = 5.6, Pyr), 8.55 (1H, s, Ar), 8.80 (1H, s, HC=N), 8.84 (2H, br s, Pyr), 12.44 (1H, br s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 12.27 (Me), 19.15 (Pyr-Me), 43.95 (NCH2), 60.21 (CwaterH), 71.20 (OCH2), 96.86 (Ar), 105.00 (C=CH), 105.17 (Ar), 108.67 (Ar), 121.51 (Pyr), 125.55 (Ar), 132.15 (Ar), 133.92 (Ar), 139.74 (Pyr), 143.51 (C=N), 144.64 (Ar), 150.40 (Pyr), 150.44 (Ar), 151.02 (Ar), 151.21 (Ar), 151.93 (Ar), 155.82 (Ar), 160.81 (C=O), 162.11 (C=O). IR (KBr) 3437w (OH), 1687s (C=O), 1687s (C=O), 1150m (C=O). [Found (ESI+) 538.2100 [M+Na]+, C28H29N5O5Na requires 538.2066].
2-((7-(diethylamino)-coumarin-4-yl)methoxy)benzaldehyde (76)

Method A:
A suspension of K$_2$CO$_3$ (18.2 mg, 0.13 mmol) in acetone (3 mL) was treated with salicylaldehyde (13 mg, 0.11 mmol), followed by 73 (50 mg, 0.16 mmol) and stirred at reflux for 5 hours. The acetone was removed under reduced pressure and the residue was suspended in DCM (15 mL) and washed with 0.5 M NaOH solution (3 × 15 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure to give a yellow solid which was purified by column chromatography eluting with 20-30% EtOAc in petroleum ether. This gave a mixture of compounds by $^1$H NMR spectra however the expected benzyl-aryl ether product was not detected.

Method B:
A suspension of K$_2$CO$_3$ (20 mg, 0.14 mmol) in anhydrous DMF (3 mL) was treated with salicylaldehyde (17 mg, 0.14 mmol), followed by 73 (50 mg, 0.16 mmol) and stirred at reflux for 2 hours. Multiple side-product formation observed by TLC. Reaction terminated.

Method C:
A solution of salicylaldehyde (25 mg, 0.2 mmol) in anhydrous THF (2 mL) and under argon atmosphere was treated with PPh$_3$ (94 mg, 0.36 mmol) and 70 (50 mg, 0.2 mmol), followed addition of DEAD (40% solution in anhydrous toluene, 0.2 mL, 0.36 mmol) dropwise and stirred at RT overnight. Volatiles were removed under reduced pressure and the resulting residue was dissolved in DCM (15 mL), washed with water (2 × 15 mL) and brine (15 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the resulting residue purified by column chromatography eluting with 20-30% EtOAc in petroleum ether; however $^1$H NMR spectra of the isolated compound did not show the expected benzyl-aryl ether product.
**Method D:**

A solution of salicylaldehyde (15 μL, 0.15 mmol) in anhydrous THF (2 mL) was treated with tBuOK solution in THF (0.13 mL, 0.13 mmol) and stirred for 2 min, after which the mixture was added dropwise to a solution of 73 (50 mg, 0.16 mmol) in anhydrous THF (2 mL) and stirred at 50 ºC under N₂ atmosphere for 3 h. The THF was removed under reduced pressure, DCM was added to the residue and the mixture was washed with water (2 × 20 mL). The organic layer was dried over MgSO₄ and concentrated down under reduced pressure to give the crude product which was purified by column chromatography eluting with 20-30% EtOAc in petroleum ether to give 76 as a light yellow solid (22 mg, 48%). Rp = 0.27 (30% EtOAc in petroleum ether). Mp = 126-129 ºC. ¹H NMR (CDCl₃, 400 MHz) δ 1.22 (6H, t, J = 7.1, 2 × Me), 3.42 (4H, q, J = 7.1, 2 × NCH₂), 5.27 (2H, s, OCH₂), 6.23 (1H, s, C=CH), 6.54 (1H, d, J = 2.6, Ar), 6.59 (1H, dd, J = 9.0, 2.6, Ar), 7.02 (1H, d J = 8.4, Ar), 7.10 (1H, t, 7.6, Ar), 7.38 (1H, d, J = 9.0, Ar), 7.55 (1H, td, J = 7.0, 1.8, Ar), 7.88 (1H, dd, J = 7.6, 1.8, Ar), 10.53 (1H, s, HC=O). ¹³C NMR (CDCl₃, 100 MHz) δ 11.43 (2 × Me), 43.76 (2 × NCH₂), 65.64 (OCH₂), 96.99 (Ar), 104.96 (Ar), 106.42 (C=C), 107.78 (Ar), 111.76 (Ar), 120.86 (Ar), 123.50 (Ar), 124.42 (Ar), 128.02 (Ar), 134.89 (Ar), 148.19 (Ar), 149.84 (Ar), 155.50 (Ar), 159.03 (Ar), 160.61 (C=O) 188.01 (HC=O). IR (KBr) 2981 s (Ar), 1717 s (C=O), 1609 s (C=O), 1269 m (C=O). [Found (ESI⁺) 352.1528 [M+H]⁺, C₂₁H₂₂NO₄ requires 352.1549].

![Image of compound 77](image-url)

(7-(diethylamino)-2-oxo-2H-chromen-4-yl)methyl-2-formylphenylcarbonate (77)

A solution of 70 (50 mg, 0.2 mmol) in anhydrous DMF (1 mL) and under argon atmosphere was treated with p-nitrophenylchloroformate (58 mg, 0.3 mmol) and DMAP (30 mg, 0.25 mmol) and stirred at RT for 4.5 h, after which DMAP (30 mg, 0.25 mmol) and salicylaldehyde (24 mg, 0.18 mmol) was added and stirred at RT overnight. Removal of DMF under reduced pressure gave a residue which was purified by column chromatography eluting with 2-15% MeOH in DCM + 0.1%
pyridine; however, $^1$H NMR spectra of the isolated compound did not show the expected product.

(E)-N’-(2-((7-(diethylamino)coumarin-4-yl)methoxy)benzylidene)isonicotinohydrazide (78)

A solution of 76 (80 mg, 0.24 mmol) and INH (36 mg, 0.24 mmol) in 90% EtOH (8 mL) was heated at reflux for 2 h. The precipitate was collected from the cooled reaction mixture by suction filtration, washed with EtOH and allowed to air-dry to give 78 as a pale yellow solid (61 mg, 54%). $R_f = 0.44$ (8% MeOH in DCM). Mp = 237-239 °C UV (EtOH): $\lambda_{max}$ 251 (22187), 380 (23046). $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 1.18 (6H, t, $J$ = 6.9, 2 × Me), 3.50 (4H, q, $J$ = 6.9, 2 × NCH$_2$), 5.49 (1H, s, OCH$_2$), 6.31 (1H, s, C=CH), 6.62 (1H, d, $J$ = 2.5, Ar), 6.78 (1H, dd, $J$ = 9.1, 2.5, Ar), 7.17 (1H, t, $J$ = 7.9, Ar), 7.42 (1H, d, $J$ = 7.9, Ar), 7.53 (1H, t, $J$ = 6.6, Ar), 7.68 (1H, d, $J$ = 9.1, Ar), 7.88 (2H, d, $J$ = 5.9, Pyr), 8.01 (1H, d, $J$ = 6.6, Ar), 8.85 (2H, d, $J$ = 5.9, Pyr), 8.96 (1H, s, N=CH), 12.20 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$, 400 MHz) $\delta$ 12.29 (Me), 43.98 (NCH$_2$), 65.79 (OCH$_2$), 96.86 (Ar), 105.24 (C=C), 105.40 (Ar), 108.76 (Ar), 113.38 (Ar), 121.54 (Pyr), 122.50 (Ar), 125.72 (Ar), 125.92 (Ar), 131.80 (Ar), 140.65 (Pyr), 143.89 (C=N), 149.51 (Ar), 150.29 (Pyr), 150.52 (Ar), 151.12 (Ar), 155.85 (Ar), 156.32 (Ar), 160.75 (C=O), 161.64 (C=O). IR (KBr) 3023m (C=C), 1698s (C=O), 1232m (C-O). [Found (ESI+) 471.2059 [M+H]$^+$, C$_{27}$H$_{26}$N$_4$O$_4$ requires 471.2032].
1-nitro-2-vinylbenzene (80)$^{[138]}$

A solution of 2-nitrophenethyl alcohol (1.00 g, 5.98 mmol) and DBU (4.5 mL, 30.0 mmol) in anhydrous THF (12 mL) was chilled to 0 °C and treated with methanesulfonyl chloride (0.9 mL, 12.0 mmol) which was added slowly over 5 minutes. The mixture was stirred at RT under an Ar atmosphere for 16 h. The solid precipitate was removed by suction filtration and washed with Et₂O (100 mL). The filtrate was extracted with 5% HCl (2 x 30 mL) water (1 x 30 mL) and brine (1 x 30 mL). The organic layers were combined and the solvent removed under reduced pressure to yield 80 as a yellow liquid (858 mg, 96%). $R_f = 0.70$ (2% EtOAc in petroleum ether). $^1$H NMR (CDCl₃, 400 MHz) δ 5.40 (1H, dd, J = 11.0, 0.9, CH₂), 5.66 (1H, dd, J = 17.3, 0.9, CH₂), 7.10 (1H, dd, J = 17.3, 11.0, CH), 7.32 (1H, td, J = 8.5, 5.8, 1.6, Ar), 7.47-7.55 (2H, m, Ar), 7.84 (1H, dd, J = 8.2, 1.6, Ar). $^{13}$C NMR (CDCl₃, 400 MHz) δ 118.86 (C=C), 124.31 (Ar), 128.26 (Ar), 128.42 (Ar), 128.41 (C=C), 132.98 (Ar), 133.29 (Ar), 147.87 (Ar).

1-(2-nitrosophenyl)ethanone (NPK, 35)$^{[139]}$

Concentrated H₂SO₄ (1 mL, 20.1 mmol) was chilled to -15 °C and treated with 80 (300 mg, 2.01 mmol) which was added dropwise while stirring. The mixture was stirred for 50 mins at -15 °C to -10 °C, and carefully poured onto ice and water (10 mL). The precipitate was collected by suction filtration, washed with water and allowed to air dry to yield 35 as an off-white solid (183 mg, 61%). $R_f = 0.27$ (10% EtOAc in petroleum ether). Mp = 126-127 °C (lit. 128 °C)$^{[139]}$. IR 3029.7 (C–H), 1694.4 (C=O), 1601.4 (Ar), 1503.5 (N=O). $^1$H NMR (CDCl₃, 400 MHz) δ 2.66 (3H, s, Me), 6.89 (1H, dd, J = 8.0, 0.8, Ar), 7.48-7.52 (1H, m, Ar), 7.62 (1H, dd, J = 7.5, 1.3, Ar), 7.68 (1H, td, J = 7.5, 1.2, Ar). $^{13}$C NMR (CDCl₃, 100 MHz) δ 32.58 (Me), 112.92 (Ar), 128.11 (Ar), 130.92 (Ar), 135.67 (Ar), 138.65 (Ar), 162.08 (Ar), 202.32 (C=O). [Found (ESI+) 150.0539 [M+H⁺]: C₈H₇NO₂ requires 150.0555].
3,5-dibromo-2,4-dihydroxybenzaldehyde (95)[151]
A solution of 2,4-dihydroxybenzaldehyde (5.00 g, 36.2 mmol) in AcOH (50 mL) was treated with bromine (3.6 mL, 70.3 mmol) added dropwise over 40 min. After stirring at RT for a further 2.5 h, distilled water (100 mL) was added to the reaction mixture and the resulting precipitate collected by suction filtration as a beige solid. The crude product was washed with distilled water and recrystallised from hot EtOH to give 95 as a peach solid (5.31 g, 50%). R<sub>f</sub> = 0.40 (8% MeOH in DCM). Mp = 204-206 °C (lit. 200 °C).[151] <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 400 MHz) δ 7.97 (1H, s, Ar), 9.77 (1H, s, CHO).<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 100 MHz), δ 99.53 (Ar), 101.58 (Ar), 116.90 (Ar), 137.70 (Ar), 158.89 (Ar), 160.54 (Ar), 195.55 (C=O).

(E)-Ethyl-(3,5-dibromo-2,4-dihydroxy)-2-methylacrylate (96)[151]
A light-protected solution of 95 (100 mg, 0.34 mmol) and ECETP (187 mg, 0.52 mmol) in THF (3 mL) was stirred at RT under argon atmosphere for 25 h. Removal of the solvent gave the crude product as a yellow oil, which was purified by column chromatography eluting with 40% EtOAc in petroleum ether to give 96 as a pale yellow solid (56 mg, 44%). Rf = 0.83 (70% EtOAc in petroleum ether). Mp = 111-113 °C (lit. 112-114 °C).[151] <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.32 (3H, t, J = 7.4, Me), 2.03 (3H, s, Me), 4.24 (2H, q, J = 7.4, CO<sub>2</sub>CH<sub>2</sub>), 7.37 (1H, s, Ar), 7.65 (1H, s, HC=O).
3,5-dibromo-2,4-bis-(4-methoxybenzyl oxy)benzaldehyde (97)

A stirred solution of 95 (1.00 g, 3.39 mmol) in anhydrous DMF (27 mL) under an Ar atmosphere was treated with 4-methoxybenzyl chloride (1 mL, 7.46 mmol), followed by portionwise addition of potassium tert-butoxide (837 mg, 7.46 mmol). The mixture was heated at 60 ºC for 21 h, after which time glacial AcOH (2.5 mL) was added to quench the reaction. The DMF was removed under reduced pressure and the resulting residue was dissolved in toluene (50 mL) which was then extracted with water (3 x 50 mL). The organics were dried over MgSO4, and the solvent removed under reduced pressure to give the crude product. The crude was purified by column chromatography eluting with 10-15% EtOAc in petroleum ether to give 97 as a yellow solid (552 mg, 30%). Rf = 0.60 (20% EtOAc in petroleum ether). Mp = 112-118 ºC. 1H NMR (CDCl3, 400 MHz) δ 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 5.12 (4H, s, OCH2), 6.93 (2H, d, J = 8.7, Ar), 6.98 (2H, d, J = 8.7, Ar), 7.32 (2H, d, J = 8.7, Ar), 7.56 (2H, d, J = 8.7, Ar), 8.03 (1H, s, Ar), 9.93 (1H, s, HC=O). 13C NMR (CDCl3, 100MHz) δ 55.34 (OMe), 74.99 (CH2), 77.96 (CH2), 113.79 (Ar), 113.99 (Ar), 114.79 (Ar), 116.00 (Ar), 126.72 (Ar), 126.93 (Ar), 128.56 (Ar), 129.35 (Ar), 129.74 (Ar), 130.56 (Ar), 158.96 (Ar), 159.12 (Ar), 160.12 (Ar), 160.39 (Ar), 187.14 (C=O). IR (KBr) 2836s (C=O), 1685s (C=O), 1578m (Ar), 674m (C-Br). [Found (ESI+) 556.9604 [M+H]+, C23H21Br2O5 requires 556.9575].

(E)-Ethyl-(3,5-dibromo-2,4-bis-(4-methoxybenzyl oxy)phenyl)-2-methylacrylate (98)

A solution of 97 (474 mg, 0.88 mmol) and ECETP (384 mg, 1.06 mmol) in anhydrous toluene (25 mL) was stirred under argon at 65 ºC overnight. The solvent was removed under reduced pressure and the crude product purified by column chromatography eluting with 1% MeOH in DCM + 0.1% pyridine to yield 98 as a
yellow solid (217 mg, 40%). $R_t = 0.63$ (2% MeOH in DCM). $\text{Mp} = 77-79 \degree C$. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.40 (3H, t, $J = 7.1$, Me), 2.05 (3H, d, $J = 1.5$, Me), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 4.31 (2H, q, $J = 7.1$, CO$_2$CH$_2$), 4.88 (2H, s, OCH$_2$), 5.06 (2H, s, OCH$_2$), 6.91 (2H, d, $J = 6.8$, Ar), 6.98 (2H, d, $J = 6.8$, Ar), 7.38 (2H, d, $J = 6.8$, Ar), 7.54 (1H, s, Ar), 7.57 (2H, d, $J = 6.8$, Ar), 7.69 (1H, d, $J = 1.5$, C=CH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 13.07 (Me), 14.18 (Me), 55.07 (OMe), 55.11 (OMe), 60.81 (CO$_2$CH$_2$), 74.44 (OCH$_2$), 75.65 (OCH$_2$), 112.93 (Ar), 113.59 (Ar), 113.69 (Ar), 115.42 (Ar), 127.84 (C=C), 128.04 (Ar), 129.21 (Ar), 130.26 (Ar), 130.42 (Ar), 130.60 (Ar), 132.28 (Ar), 132.35 (C=C), 153.56 (Ar), 154.65 (Ar), 158.99 (Ar), 159.72 (Ar), 159.76 (Ar), 167.61 (C=O). IR (KBr) 2943w (C-H), 2836w (C-O). [Found (ESI+) 641.0128 [M+Na$^+$], C$_{28}$H$_{26}$Br$_2$NaO$_5$ requires 641.0150].

(\textit{E})-\textit{Ethyl-(3,5-dibromo-2,4-bis-(4-methoxybenzyl)oxy)phenyl)-2-methylacrylic acid (99)

A solution of 98 (200 mg, 0.32 mmol) in THF (6 mL) was treated with 1 M NaOH (1 mL) and EtOH (1.2 mL), and stirred at 35 \degree C for 14 h. The organic solvents were removed under reduced pressure and the remaining residue dissolved in water (20 mL) and the pH adjusted to 5 with 5 M HCl. The resulting suspension was extracted with DCM (2 x 20 mL) and the organics were dried over MgSO$_4$. Removal of the solvent under reduced pressure gave 99 as a white solid (99 mg, 52%). $R_t = 0.68$ (5% MeOH in DCM). $\text{Mp} = 158-162 \degree C$. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.05 (3H, s, Me), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 4.90 (2H, s, CH$_2$), 5.07 (2H, s, CH$_2$), 6.91 (2H, d, $J = 8.4$, Ph), 6.98 (2H, d, $J = 8.4$, Ph), 7.37 (2H, d, $J = 8.5$, Ph), 7.55 (1H, s, Ph), 7.58 (2H, d, $J = 8.5$, Ph), 7.77 (1H, br s, C=CH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 13.87 (Me), 55.21 (OMe), 55.29 (OMe), 74.63 (OCH$_2$), 76.03 (OCH$_2$), 113.16 (Ar), 113.76 (Ar), 113.87 (Ar), 113.93 (Ar), 115.73 (Ar), 127.82 (Ar), 128.15 (Ar), 128.66 (Ar), 129.41 (Ar), 130.37 (Ar), 130.43 (Ar), 130.86 (Ar), 132.42 (C=C), 135.11 (C=C), 154.08 (Ar), 154.93 (Ar), 159.14 (Ar), 159.88 (Ar), 159.95 (Ar), 173.45 (C=O). IR (KBr) 2948m (O-H), 2832m (C-O). [Found (ESI-) 588.9893, [M–H]$^-$, C$_{26}$H$_{23}$Br$_2$O$_6$, 588.9861].
(E)-2-[(E)-(2-isonicotinoylhydrazono)methyl]phenyl-3-(3,5-dibromo-2,4-bis-(4-methoxybenzyloxy)phenyl)-2-methylacrylate (100)

A solution of 99 (200 mg, 0.34 mmol) in anhydrous DMF (7 mL) and under N₂ atmosphere was chilled to 0 °C and treated with EDC hydrochloride (65 mg, 0.34 mmol) and DMAP (41 mg, 0.34 mmol). After stirring for 5 min, a solution of SIH (65 mg, 0.26 mmol) and DIPEA (45 µL) in anhydrous DMF (3 mL) was added, and the mixture stirred at RT for 2 days. The solvent was removed under reduced pressure and the resulting residue was dissolved in DCM and washed with saturated NH₄Cl solution (2 × 15 mL), H₂O (20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄ and purified by column chromatography eluting with 1-2% MeOH in DCM + 0.1% pyridine to give 100 as a white solid (102 mg, 50%). Rᵣ = 0.74 (6% MeOH in DCM). Mp = 88-91 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 2.19 (3H, s, Me), 3.71 (3H, s, OMe), 3.84 (3H, s, OMe), 4.96 (2H, s, OCH₂), 5.06 (2H, s, OCH₂), 6.86 (2H, d, J = 8.6, Ar), 7.06 (2H, d, J = 8.6, Ar), 7.35-7.40 (3H, m, Ar), 7.50 (1H, t, J = 7.7, Ar), 7.58 (2H, d, J = 8.6, Ar), 7.65 (1H, t, J = 7.7, Ar), 7.77 (2H, d, J = 6.0, Pyr), 7.85 (1H, s, Ar), 7.87 (1H, s, C=CH), 8.04 (1H, d, J = 7.7, Ar), 8.56 (1H, s, HC=N), 8.80 (2H, d, J = 6.0, Pyr), (1H, s, NH). ¹³C NMR (DMSO-d₆, 125 MHz) 14.28 (Me), 54.98 (OMe), 55.18 (OMe), 74.34 (OCH₂), 75.57 (OCH₂), 112.80, 113.68 (Ar), 113.82 (Ar), 115.27 (Ar), 121.47 (Pyr), 123.37 (Ar), 126.47 (Ar), 126.60 (Ar), 127.38 (Ar), 127.77 (Ar), 127.85 (Ar), 128.34 (C=C), 130.42 (Ar), 130.72 (Ar), 131.47 (Ar), 132.43 (C=C), 134.17 (Ar), 140.29 (Pyr), 143.65 (C=N), 149.41 (Ar), 150.30 (Pyr), 153.61 (Ar), 154.76 (Ar), 159.46 (Ar), 159.53 (Ar), 161.63 (C=O), 165.85 (C=O). IR (KBr) 3434m (N-H), 2840w (C-O), 1726s (C=O), 1663s (C=N), 1173m (C=O). [Found (ESI⁺) 814.0779 [M+H]⁺, C₃₉H₃₄Br₂N₃O₇ requires 814.0764].
(E)-2-((E)-2-isonicotinoylhydrazino)methyl)phenyl-3-(3,5-dibromo-2,4-dihydroxyphenyl)-2-methylacrylate (101)

A solution of 100 (70 mg, 0.08 mmol) in anhydrous DCM (3 mL) and anisole (185 μL) chilled to 0 °C and under N₂ atmosphere was treated with TFA (4 mL) and stirred for 15 min. Volatiles were removed under reduced pressure and TFA removed by co-evaporation with toluene (2 × 15 mL). The crude product was purified by column chromatography eluting with 2-3% MeOH in DCM + 0.1% pyridine to give 101 as a white solid (28 mg, 58%). Rᵣ = 0.48 (10% MeOH in DCM). Mp = 206-208 °C. UV (EtOH): λ_max 297 (27700). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.23 (3H, s, Me), 7.34 (1H, d, J = 8.1, Ar), 7.47 (1H, t, J = 7.4, Ar), 7.59 (1H, td, J = 8.3, 1.6, Ar), 7.62 (1H, s, Ar), 7.86 (2H, d, J = 5.9, Pyr), 8.00 (1H, s, C=CH), 8.07 (1H, dd, J = 8.3, 1.6), 8.58 (1H, s, HC=N), 8.83 (2H, s, Pyr), 9.95 (1H, br s, OH), 10.28 (1H, br s, OH), 12.19 (1H, s, NH). ¹³C NMR (DMSO-d₆, 125 MHz) δ 14.38 (Me), 101.22 (Ar), 102.89 (Ar), 117.49 (Ar), 121.58 (Pyr), 123.41 (Ar), 125.86 (C=C), 126.47 (Ar), 126.59 (Ar), 126.62 (Ar), 131.44 (Ar), 131.60 (Ar), 135.49 (C=C), 140.40 (Pyr), 143.31 (C=N), 149.59 (Ar), 149.74 (Ar), 150.35 (Pyr), 152.56 (Ar), 153.37 (Ar), 161.72 (C=O), 166.40 (C=O). IR (KBr) 3465s (N-H), 3052s (O-H), 1712s (C=O), 1649s (C=N), 696m (C-Br). [Found (ESI+) 573.9570 [M+H]+, C₂₃H₁₈Br₂N₃O₅ requires 573.9613].

(E)-tert-butyldimethylsilyl-3-(2-(tert-butyldimethylsilyloxy)phenyl)acrylate (103)[¹⁶⁴]

A solution of trans-2-hydroxycinnamic acid (1.04 g, 6.34 mmol), imidazole (938 mg, 13.78 mmol) and TBDMSI (2.04 g, 13.54 mmol) in anhydrous DMF (20 mL) was
stirred under argon at RT overnight, and then 60 °C for 2h. Removal of DMF under reduced pressure gave an oil which was dissolved in DCM (40 mL) and washed with water (3 × 40mL). The organic layer was dried over MgSO₄, concentrated down and purified by column chromatography eluting with 0-2% MeOH in DCM to give 103 as a pale yellow oil (1.82 g, 73%). Rf = 0.82 (10% EtOAc in petroleum ether). ¹H NMR (CDCl₃, 400 MHz) δ 0.24 (6H, s, SiMe₂), 0.32 (6H, s, SiMe₂), 0.98 (9H, s, CMe₃), 1.01 (9H, s, CMe₃), 6.37 (1H, d, J = 16.1, C=CH), 6.83 (1H, dd, J = 8.2, 1.0, Ar), 6.95 (1H, t, J = 7.6, Ar), 7.26 (1H, td, J = 7.8, 1.7, Ar), 7.53 (1H, dd, J = 7.8, 1.7, Ar), 7.96 (1H, d, J = 16.1, C=CH₂OOSi). ¹³C NMR (CDCl₃, 100 MHz) δ -4.67 (SiMe₂), -4.21 (SiMe₂), 17.81 (C-tBu), 18.31 (C-tBu), 25.72 (Me₃), 25.79 (Me₃), 119.70 (ArCH=CH), 120.00 (Ar), 121.43 (Ar), 125.92 (Ar), 127.68 (Ar), 131.11 (Ar), 140.16 (CH=CHCOO), 154.47 (Ar), 167.16 (C=O).

(E)-2-tert-butyldimethylsiloxycinnamic acid (104)[158]

A solution of 103 (2.00 g, 5.10 mmol) in a 2:1 mixture of THF/MeOH (5mL) was treated with K₂CO₃ (1.80 g, 12.73 mmol) in water (2mL), and stirred at RT for 2 h. The reaction mixture was diluted with Et₂O (20 mL) and the organic layer collected which was then washed with 10% HCl solution (3 × 80 mL) and water (80 mL). The organic layer was dried over MgSO₄ and purified by column chromatography, eluting with 1-2% acetone in DCM to give a clear liquid which was dried under reduced pressure to give 104 as a white solid (876 mg, 62%). Rf = 0.45 (10% Acetone in DCM). Mp = 65-69 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 0.28 (6H, s, SiMe₂), 1.05 (9H, s, Me₃), 6.50 (1H, d, J = 16.2, C=CH), 6.98 (1H, d, J = 8.2, Ar), 7.06 (1H, t, J = 7.6, Ar), 7.38 (1H, td, J = 7.3, 1.8, Ar), 7.77 (1H, dd, J = 7.8, 1.8, Ar), 7.95 (1H, d, J = 16.2, C=CH), 12.28 (1H, s, COOH). ¹³C NMR (DMSO-d₆, 100 MHz) δ -4.67 (SiMe₂), 17.99 (SiC), 25.57 (Me₃), 118.97 (C=C), 119.80 (Ar), 121.80 (Ar), 124.86 (Ar), 127.68 (Ar), 131.54 (Ar), 138.57 (C=C), 153.84 (Ar), 167.59 (C=O).
(E)-2-((E)-(2-isonicotinoylhydrazono)methyl)phenyl-3-(2-(tert-butyldimethylsilyl-oxy)phenyl)acrylate (105)

**Method A:**
A solution of 104 (52 mg, 0.32 mmol) in anhydrous DMF (3 mL), under argon atmosphere was chilled to 0 °C and treated with EDC hydrochloride (61 mg, 0.32 mmol) and DMAP (39 mg, 0.32 mmol). The mixture was stirred for 5 min, followed by addition of SIH (50 mg, 0.21 mmol) in a solution of anhydrous DMF (4 mL) and DIPEA (36 µL, 0.21 mmol). The resulting mixture was heated to 30ºC and stirred for 2 days. The DMF was removed under reduced pressure, and the resulting residue dissolved in DCM (15 mL) and washed with saturated aqueous NH₄Cl solution (3 × 15 mL). Removal of volatiles under reduced pressure gave a yellow residue; however the expected product was not detected by ¹H NMR analysis.

**Method B:**
A mixture of bisilylated compound 103 (500 mg, 1.27 mmol) and a catalytic amount of anhydrous DMF (2 drops), was treated with 2M oxalyl chloride solution in DCM (0.8 mL, 1.59 mmol) at 0°C. The reaction mixture was stirred at this temperature under argon atmosphere for 2.5 h, after which time the volatiles were removed under reduced pressure. To the resulting white residue was slowly added a solution of SIH (256 mg, 1.06 mmol) and anhydrous pyridine (0.1 mL, 1.1 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred at RT under argon for a further 2.5 h and the volatiles were then removed under reduced pressure to give an orange oil which was dissolved in DCM (10 mL) and washed with water (3 × 20 mL). The organic layers were dried over MgSO₄ and the crude product purified by column chromatography eluting with 0-4% MeOH in DCM + 0.1% pyridine to give 105 as a pale peach coloured solid (193 mg, 36%). Rf = 0.44 (6% MeOH in DCM). Mp = 89-92 ºC. ¹H NMR (DMSO-d₆, 400 MHz) δ 0.29 (6H, s, Me₂), 1.02 (9H, s, Me₃), 6.97 (1H, d, J = 16.2, C=CH), 7.04 (1H, d, J = 8.2, Ar), 7.14 (1H, t, J = 7.6, Ar), 7.34 (1H, d, J = 7.6, Ar), 7.47 (2H, t, J = 7.1, Ar), 7.60 (1H, t, J = 8.2, Ar), 7.84 (2H, d, J = 6.0,
Pyr), 7.99 (1H, d, J = 7.8, Ar), 8.09 (1H, d, J = 7.8, Ar), 8.32 (1H, d, J = 16.2, HC=C), 8.61 (1H, s, NH).  

\[13\] C NMR (DMSO-d_6, 100 MHz) \(\delta\) -4.66 (SiMe_2), 17.95 (Si-C), 25.57 (Me_3), 116.31 (C=C), 119.87 (Ar), 121.47 (Ar), 121.95 (Pyr), 123.26 (Ar), 124.60 (Ar), 126.13 (Ar), 126.47 (Ar), 126.57 (Ar), 127.86 (Ar), 131.43 (Ar), 132.71 (Ar), 140.36 (Pyr), 141.53 (Ar), 143.13 (C=N), 149.50 (C=C), 150.30 (Pyr), 154.38 (Ar), 157.28 (Ar), 161.64 (C=O), 165.04 (C=O).  

IR (KBr) 3442m (N-H), 2946m (C-H), 2933m (C-H), 1731s (C=O), 1664s (C=N), 838m (Si-C).  
[Found (ESI+) 502.2153 [M+H]^+], C_{28}H_{32}N_{3}O_{4}Si requires 502.2162].

Method C

A solution of 104 (200 mg, 0.72 mmol) in anhydrous DCM (2.5 mL) and under N_2 atmosphere was treated with SOCl_2 (0.6 mL, 8.64 mmol) and stirred under reflux for 5 h, after which volatiles were removed under reduced pressure. To the resulting white solid was slowly added a solution of SIH (156 mg, 0.65 mmol), and anhydrous pyridine (0.75 mL, 0.65 mmol), in anhydrous DCM (20 mL). The reaction mixture was stirred at 30 °C under N_2 atmosphere for 2 days after which the resulting orange solution was washed with water (2 \times 10 mL) and sat. NH_4Cl solution (2 \times 10 mL). The organic layers were dried over MgSO_4 and the crude product purified by column chromatography eluting with 1-3% MeOH in DCM + 0.1% pyridine to give 93 as a white solid (187 mg, 57%).

\(\text{(E)}-2-(\text{(E)}-\text{(2-isonicotinoylhydrazono)methyl})\text{phenyl-3)-(2-hydroxyphenyl})\text{acrylate (106)}\)

A solution of TBAF trihydrate (133 mg, 0.51 mmol) and glacial acetic acid (26 \(\mu\)L) in anhydrous DMF (2 mL) was stirred at 0 °C under argon atmosphere for 30 min. The solution was then treated with a solution of 105 (70 mg, 0.14 mmol) in anhydrous DMF (2 mL), added dropwise, and the reaction mixture stirred for a further 10 min at 0 °C, after which time water (40 mL) was added and the mixture extracted with Et_2O (3 \times 40 mL) and EtOAc (1 \times 40 mL). The organic layers were dried over MgSO_4 and
the volatiles removed under reduced pressure to give the crude product as a yellow oil which was purified by column chromatography eluting with 4% MeOH in DCM + 0.1% pyridine to give **106** as an off-white solid (46 mg, 85%). $R_f = 0.41$ (8% MeOH in DCM). $Mp = 169-172 \, ^\circ C$. UV (EtOH): $\lambda_{max}$ 284 (23459). $^1H$ NMR (DMSO-d$_6$, 500 MHz) $\delta$ 6.90 (1H, t, J = 7.5, Ar), 6.96-6.99 (2H, m, Ar, C=CH), 7.30-7.33 (2H, m, Ar), 7.42 (1H, t, J = 7.6, Ar), 7.55 (1H, t, J = 7.7, Ar), 7.74 (1H, d, J = 7.8, Ar), 7.80 (2H, d, J = 6.0, Pyr), 8.05 (1H, d, J = 7.9, Ar), 8.12 (1H, d, J = 16.1, HC=C), 8.55 (1H, s, HC=N), 8.77 (2H, br s, Pyr), 10.46 (1H, s, OH), 12.14 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz) $\delta$ 115.60 (C=C), 116.30 (Ar), 119.52 (Ar), 120.38 (Ar), 121.58 (Pyr), 123.40 (Ar), 125.97 (Ar), 126.46 (Ar), 126.63 (Ar), 129.56 (Ar), 131.44 (Ar), 132.47 (Ar), 140.36 (Pyr), 142.94 (Ar), 143.00 (C=N), 149.60 (C=C), 150.30 (Pyr), 157.29 (Ar), 161.68 (C=O), 165.51 (C=O). IR (KBr) 3173s (O-H), 1717s (C=O), 1663s (C=O). [Found (ESI+) 388.1306 [M+H]$^+$, C$_{22}$H$_{18}$N$_3$O$_4$ requires 388.1297].

![Image of 107](image_url)

(E)-**tert**-butyl 3-(2,4-dihydroxyphenyl)acrylate (107)

A light-protected solution of 2,4-dihydroxybenzaldehyde (500 mg, 3.62 mmol) and BCMTP (1.64 g, 4.34 mmol) in anhydrous toluene (40 mL) was stirred at 60 °C for 2 h. Removal of toluene under reduced pressure gave a yellow oil which was purified by column chromatography eluting with 40-50% EtOAc in petroleum ether to give **107** as a white solid (719 mg, 84%). $R_f = 0.33$ (40% EtOAc in petroleum ether). $Mp = 65$-69 °C. $^1H$ NMR (DMSO-d$_6$, 400 MHz) $\delta$ 1.51 (9H, s, Me$_3$), 6.31 (1H, dd, J = 8.5, 2.2, Ar), 6.31 (1H, d, J = 16.1, C=CH), 6.40 (1H, d, J = 2.2, Ar), 7.42 (1H, d, J = 8.5, Ar), 7.72 (1H, d, J = 16.1, C=CH), 9.83 (1H, s, OH), 10.07 (1H, s, OH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 28.21 (Me$_3$), 80.46 (C-O), 103.30 (Ar), 108.71 (Ar), 115.10 (Ar), 117.94 (C=C), 130.33 (Ar), 138.63 (C=C), 156.22 (Ar), 158.33 (Ar), 167.73 (C=O). [Found (ESI-) 235.0970 [M-H]$^-$, C$_{13}$H$_{15}$O$_4$ requires 235.0970].
**Method A:**
A mixture of 107 (50 mg, 0.21 mmol) and water (80 μL) was treated with HCl (4 M solution in dioxane, 1.6 mL, 6.36 mmol) and stirred at RT for 15 min. Addition of DCM gave an orange precipitate which was collected by suction filtration and washed with DCM; however analysis by $^1$H NMR suggested polymer generation instead of the expected product formation.

**Method B:**
A solution of 107 (20 mg, 0.08 mmol) in DCM (0.2 mL) was treated with TFA (0.2 mL) and stirred for 10 minutes at RT. Removal of volatiles under reduced pressure gave a white precipitate; however analysis by $^1$H NMR did not show expected product formation.

**(E)-tert-butyldimethylsilyl-3-(2,4-bis(tert-butyldimethylsilyloxy)phenyl)acrylate (109)**
A solution of trans-2,4-dihydroxycinnamic acid (3.00 g, 16.7 mmol), imidazole (3.6 g, 52.5 mmol) and TBDMSI (8.30 g, 55.0 mmol) in anhydrous DMF (60 mL) was stirred under argon at RT overnight. Removal of DMF under reduced pressure gave an oil which was dissolved in DCM (150 mL) and washed with water (3 × 100 mL). The organic layer was dried over MgSO$_4$, concentrated down and purified by column chromatography eluting with 1-2% EtOAc in petroleum ether to give 109 as a clear oil which solidified upon storing at 2-8 ºC into a white solid (5.05 g, 58%). $R_f$ = 0.79 (5% EtOAc in petroleum ether). $Mp$ = 39-42 ºC. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.21 (6H, s, SiMe$_2$), 0.25 (6H, s, SiMe$_2$), 0.32 (6H, s, SiMe$_2$), 0.98 (9H, s, Me$_3$), 0.98 (9H, s, Me$_3$), 1.02 (9H, s, Me$_3$), 6.27 (1H, d, J = 16.0, CH), 6.32 (1H, d, J = 2.3, Ar), 6.47 (1H, dd, J = 8.6, 2.3, Ar), 7.42 (1H, d, J = 8.6, Ar), 7.90 (1H, d, J = 16.0, CH). $^{13}$C
NMR (CDCl$_3$, 100 MHz) $\delta$ –4.65 (SiMe$_2$), –4.42 (SiMe$_2$), –4.20 (SiMe$_2$), 17.80 (Si-C), 18.18 (Si-C), 18.31 (Si-C), 25.56 (Me$_3$), 25.75 (Me$_3$), 25.79 (Me$_3$), 111.24 (Ar), 114.05 (Ar), 117.65 (C=C), 119.55 (Ar), 128.50 (Ar), 139.96 (C=C), 155.68 (Ar), 158.51 (Ar), 167.35 (C=O). IR (KBr) 2944s (C-H), 2857s (C-H), 1284s (Si-C), 1190s (C=O), 838s (Si-C). [Found (ESI+) 545.2951 [M+H]$^+$, C$_{27}$H$_{50}$NaO$_4$Si$_3$ requires 545.2915].

(E)-2-((E)-(2-isonicotinoylhydrazono)methyl)phenyl-3-(2,4-bis(tert-butyldimethyl silyloxy)phenyl)acrylate (110)

A mixture of trisilylated compound 109 (142 mg, 0.27 mmol) and a catalytic amount of anhydrous DMF (2 drops), was treated with 2 M oxalyl chloride solution in DCM (0.2 mL, 0.41 mmol) at 0°C. The reaction mixture was stirred at this temperature under argon atmosphere for 2.5 h, after which time the volatiles were removed under reduced pressure. To the resulting residue was slowly added a solution of SIH (52 mg, 0.22 mmol), DMAP (2 mg) and pyridine (0.1 mL, 1.1 mmol) in anhydrous DMF (0.5 mL). The reaction mixture was stirred at RT under argon overnight and the volatiles were then removed under reduced pressure to give an orange oil which was dissolved in DCM (10 mL) and washed with water (3 x 15 mL). The organic layers were dried over MgSO$_4$ and the crude product purified by column chromatography eluting with 0-30% Acetone in DCM + 0.1% pyridine to give 110 as a white solid (42 mg, 30%). R$_f$ = 0.75 (40% Acetone in DCM). Mp = 88-91 °C. $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 0.29 (6H, s, SiMe$_2$), 0.29 (6H, s, SiMe$_2$), 1.01 (9H, s, Me$_3$), 1.01 (9H, s, Me$_3$), 6.41 (1H, d, J = 2.4, Ar), 6.66 (1H, dd, J = 8.6, 2.0, Ar), 6.82 (1H, d, J = 6.1, C=CH), 7.32 (1H, d, J = 8.2, Ar), 7.46 (1H, t, J = 7.8, Ar), 7.59 (1H, t, J = 7.1, Ar), 7.84 (2H, d, J = 6.0, Pyr), 7.90 (1H, d, J = 9.0, Ar), 8.08 (1H, d, J = 8.0, Ar), 8.22 (1H, d, J = 16.0, HC=C), 8.60 (1H, s, HC=N), 8.82 (2H, d, J = 6.0, Pyr), 12.14 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ -4.50 (2 x SiMe$_2$), 17.96 (SiC), 18.03 (SiC), 25.45 (2 x Me$_3$), 110.87 (Ar), 113.48 (C=C), 114.53 (Ar), 118.57 (Ar), 121.46 (Pyr), 123.29
(Ar), 126.03 (Ar), 126.38 (Ar), 126.60 (Ar), 129.24 (Ar), 131.40 (Ar), 140.37 (Pyr), 141.30 (C=C), 143.14 (C=N), 149.60 (Ar), 150.30 (Pyr), 155.76 (Ar), 159.01 (Ar), 161.64 (C=O), 165.23 (C=O). IR (KBr) 3433m (N-H), 2959m (C-H), 2933m (C-H), 1669s (C=N), 833m (Si-C). [Found (ESI+) 632.2966 (M+H)+, C34H46N3O5Si2 requires 632.2976].

(E)-2-((E)-(2-isonicotinoylhydrazono)methyl)phenyl-3-(2,4-dihydroxyphenyl) acrylate (111) A solution of TBAF trihydrate (114 mg, 0.36 mmol) and AcOH (0.6 mL) in DMF (2 mL) was stirred at 0 °C for 1 h. The reaction mixture was then treated with a solution of 110 (50 mg, 0.08 mmol) in DMF (1 mL), allowed to warm to RT and stirred for 15 min. DMF was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (15 mL) and washed with water (2 × 10 mL). The organic layers were combined and volatiles removed under reduced pressure to give the crude product which was purified by column chromatography eluting with 4-8% MeOH in DCM + 0.1% pyridine to give 111 as a yellow solid (11mg, 38%). Rf = 0.31 (10% MeOH in DCM). Mp = 183-185 °C. UV (EtOH): λmax 302 (20471). 1H NMR (DMSO-d6, 400 MHz) δ 6.38 (1H, dd, J = 8.5, 2.2, Ar), 6.46 (1H, d, J = 2.2, Ar), 6.77 (1H, d, J = 16.0, C=CH), 7.31 (1H, d, J = 8.1, Ar), 7.45 (1H, t, J = 7.8, Ar), 7.59 (2H, t, J = 8.6, Ar), 7.85 (2H, d, J = 6.0, Pyr), 8.05-8.08 (2H, m, Ar), 8.59 (1H, s, HC=N), 8.81 (2H, d, J = 4.6, Pyr), 10.06 (1H, s, OH), 10.38 (1H, s, OH), 12.17 (1H, s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 102.51 (Ar), 108.09 (Ar), 111.02 (C=C), 112.45 (Ar), 121.55 (Ar), 123.44 (Ar), 125.85 (Ar), 126.24 (Ar), 126.73 (Ar), 131.22 (Ar), 131.36 (Ar), 140.40(Ar), 143.11 (C=N), 143.42 (C=C), 149.82 (Ar), 150.28 (Ar), 159.19 (Ar), 161.70 (C=O), 165.92 (C=O). IR (KBr) 3434m (N-H), 3272m (O-H), 2932m (C-H), 1676s (C-N). [Found (ESI+) 404.1228 [M+H]+, C22H18N3O5 requires 404.1246].
3,4'-O-isopropylideneypyridoxine (113)[160]

A suspension of pyridoxine (500 mg, 2.96 mmol) and 2,2-dimethoxypropane (6 mL, 48.8 mmol) in acetone (9 mL) was treated with p-toluenesulfonic acid (300 mg, 2.25 g, 11.84 mmol) which had been dried under reduced pressure at 130 °C for 3 h prior to use. The reaction mixture was stirred at RT under argon atmosphere for 5 h, after which the resulting brown solution was adjusted to pH 8 with 5% aqueous NaHCO₃ solution, concentrated down under reduced pressure and extracted with DCM (2 x 15 mL). The organic layer was washed with water (1 x 15 mL), dried over MgSO₄ and purified by column chromatography eluting with 0-5% MeOH in DCM to give 113 as an off-white solid (410 mg, 66%). Rₜ = 0.43 (5% MeOH in DCM). Mp = 108-111 °C (lit = 110-111 °C).[160] ¹H NMR (DMSO-d₆, 400 MHz) δ 1.54 (6H, s, Me₂), 2.33 (3H, s, Pyr-Me), 4.46 (2H, d, J = 5.4, CH₂), 4.93 (2H, s, CH₂), 5.17 (1H, t, J = 5.4, OH), 7.97 (1H, s, Ar). ¹³C NMR (DMSO-d₆, 100 MHz) δ 18.23 (Me), 24.50 (Me₂), 57.84 (CH₂), 58.20 (CH₂), 99.33 (ketalic C), 125.13 (Ar), 130.52 (Ar), 138.41 (Ar), 145.02 (Ar), 145.37 (Ar).

5-((tert-butyldiphenylsilyloxy)methyl)-2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridine (114)[161]

A solution of 113 (300 mg, 1.43 mmol) in anhydrous DMF (3 mL) was treated with imidazole (244 mg, 3.58 mmol) and TBDPSCl (0.4 mL, 1.57 mL). The reaction mixture was stirred at RT overnight, and the DMF was then removed under reduced pressure. The residue was dissolved in DCM, washed with water and brine and dried over MgSO₄ to give the crude product as a yellow oil which was purified by column chromatography eluting with 10% EtOAc in petroleum ether to give 114 as a
clear oil (506 mg, 79%). Rf = 0.72 (30% EtOAc in petroleum ether). 1H NMR (CDCl3, 400 MHz) δ 1.04 (9H, s, Me3), 1.55 (6H, s, Me2), 2.41 (3H, s, Pyr–Me), 4.58 (2H, s, CH2), 4.87 (2H, s, CH2), 7.36-7.46 (6H, m, Ph), 7.64-7.67 (4H, m, Ph), 8.78 (1H, s, Pyr). 13C NMR (CDCl3, 100 MHz) δ 18.47 (Pyr–Me), 19.15 (CMe3), 24.66 (Me2), 26.71 (Me3), 58.69 (CH2), 61.57 (CH2), 99.53 (ketalsic C), 125.25 (Ph), 127.77 (Ph), 128.72 (Pyr), 129.86 (Pyr), 132.88 (Pyr), 135.48 (Ph), 138.66 (Pyr), 145.77 (Pyr), 147.40 (Pyr).

5-((tert-butyldiphenylsilyloxy)methyl)-4-(hydroxymethyl)-2-methylpyridin-3-ol (115)[161]

A solution of 114 (500 mg, 1.12 mmol) was refluxed in AcOH / water (3:2) for 3 h, after which the reaction mixture was concentrated under reduced pressure, and the resulting residue was dried by co-evaporation with toluene. The resulting crude product was recrystallised from MeOH to yield 115 as a white solid (214 mg, 47%). Rf = 0.24 (50:50 EtOAc / petroleum ether). Mp = 204-207 °C (lit = 206-208°C).[161] 1H NMR (DMSO-d6, 400 MHz) δ 1.07 (9H, s, Me3), 2.41 (3H, s, Pyr–Me), 4.75 (2H, s, CH2), 4.84 (2H, s, CH2), 5.72 (1H, br s, benzylic OH), 7.47-7.56 (6H, m, Ph), 7.68-7.71 (4H, m, Ph), 7.97 (1H, s, Pyr), 9.23 (1H, br s, phenolic OH). 13C NMR (DMSO-d6, 100 MHz) δ 18.83 (SiC), 19.36 (Pyr–Me), 26.61 (Me3), 56.25 (CH2), 61.41 (CH2), 127.94 (Ph), 129.95 (Ph), 130.96 (Pyr), 131.65 (Pyr), 132.78 (Ph), 134.99 (Ph), 138.24 (Pyr), 146.27 (Pyr), 149.33 (Pyr).

5-((tert-butyldiphenylsilyloxy)methyl)-3-hydroxy-2-methylpyridine-4-carbaldehyde (116)[161]
A solution of 115 (150 mg, 0.37 mmol) and activated MnO$_2$ (96.5 mg, 1.11 mmol) in anhydrous pyridine (3 mL) was stirred at RT for 3 days. The MnO$_2$ was removed from the reaction mixture by filtering through celite, and the celite pad was washed with pyridine. The filtrate was concentrated down under reduced pressure, and remaining pyridine removed by co-evaporation with toluene. The crude residue was purified by column chromatography eluting with 25% EtOAc in petroleum ether to give 116 as a yellow oil (112 mg, 75%). $R_f = 0.80$ (1:1 EtOAc / petroleum ether). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.04 (9H, s, Me$_3$), 2.53 (3H, s, Pyr–Me), 4.94 (2H, s, CH$_2$), 7.37-7.45 (6H, m, Ph), 7.65 (4H, d, J = 8.0, Ph), 7.83 (1H, s, Pyr), 10.54 (1H, s, HC=O), 11.44 (1H, s, OH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 18.74 (SiC), 19.08 (Pyr–Me), 26.69 (Me$_3$), 61.17 (CH$_2$), 120.20 (Ar), 127.88 (Ph), 130.06 (Ph), 132.17 (Ar), 132.53 (Ar), 135.47 (Ph), 138.62 (Pyr), 151.83 (Pyr), 153.75 (Pyr), 197.27 (HC=O).

(E)-N’-((5-((tert-butyldiphenylsilyloxy)methyl)-3-hydroxy-2-methylpyridin-4-yl)methylene)isonicotinohydrazide (117)

A solution of 116 (110 mg, 0.27 mmol) and INH (37 mg, 0.27 mmol) in EtOH (8 mL) was refluxed for 90 min and concentrated under reduced pressure. The resulting yellow oil was co-evaporated with Et$_2$O to remove remaining EtOH, and the crude product was recrystallised from toluene to yield 117 as pale yellow crystals (123 mg, 87%). Mp = 99-101 °C. $R_f = 0.33$ (6% MeOH in DCM). $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 1.06 (9H, s, Me$_3$), 2.49 (3H, s, Pyr–Me), 5.03 (2H, s, CH$_2$), 7.47-7.54 (6H, m, Ph), 7.68 (4H, d, J = 7.1, Ph), 7.89 (2H, d, J = 5.9, Pyr), 7.91 (1H, s, Pyr), 8.89 (2H, br d, J = 5.9, Pyr), 8.91 (1H, s, HC=N), 12.15 (1H, s, OH), 12.78 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 18.78 (Me), 18.89 (SiC), 26.62 (Me$_3$), 61.28 (OCH$_2$), 119.36 (Ar), 121.48 (Ar), 127.95 (Ar), 130.04 (Ar), 130.78 (Ar), 132.63 (Ar), 135.03 (Ar), 137.56 (Ar), 139.29 (Ar), 146.72 (C=N), 147.72 (Ar), 150.48 (Ar), 150.53 (Ar), 161.74 (C=O). IR (KBr) 3358w (N–H), 2959s (O–H), 1695s (C=N), 1261s (Si–C) [Found (ESI−) 523.2189 [M–H]−. C$_{30}$H$_{31}$N$_4$O$_3$Si requires 523.2165].
(E)-5-((tert-butyldiphenylsilyloxy)methyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2-(tert-butyldimethylsilyloxy)phenyl)acrylate (118)

A mixture of 103 (235 mg, 0.60 mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2 M oxalyl chloride solution in DCM (0.4 mL, 0.79 mmol). The reaction mixture was allowed to warm to RT and stirred for 3 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with a solution of 117 (200 mg, 0.38 mmol) and DMAP (2 mg) in anhydrous pyridine (0.1 mL) and anhydrous DMF (2 mL) and stirred at RT for 2 days. DMF was removed under reduced pressure and the resulting residue was dissolved in DCM (10 mL) and washed with water (3 × 10 mL). The organic layer was concentrated down and purified by column chromatography eluting with 4% acetone in DCM + 0.1% pyridine to give 118 as a white solid (200 mg, 67%). Rf = 0.74 (15% acetone in DCM). Mp = 87-89 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 0.29 (6H, s, SiMe₂), 1.02 (9H, s, Me₃), 1.16 (9H, s, Me₃), 2.43 (3H, s, Me), 5.33 (2H, s, CH₂), 6.98-7.05 (2H, m, Ar and C=CH), 7.14 (1H, t, J = 7.8, Ar), 7.46-7.52 (9H, m, Ar), 7.72-7.79 (6H, m Ar), 7.98 (1H, d, J = 7.4, Ar), 8.33 (1H, d, J = 16.3, HC=C), 8.57 (1H, s, HC=N), 8.80 (2H, br s, Pyr), 8.87 (1H, s, Pyr), 12.25 (1H, s, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ −4.53 (SiMe₂), 17.95 (SiC), 18.93 (Me), 25.48 (Me₃), 26.75 (Me₃), 115.46 (C=CH), 119.88 (Ar), 121.45 (Ar), 121.95 (Ar), 124.53 (Ar), 127.98 (Ph), 128.14 (Ar), 129.94 (Ar), 130.66 (Ar), 132.86 (Ar), 134.98 (Ph), 142.20 (C=N), 150.32 (Pyr), 154.44 (C=O). [Found (ESI+) 785.3625 [M+H]+, C₄₅H₅₃N₄O₅Si₂ requires 785.3554].
(E)-5-((tert-butyldiphenylsilyloxy)methyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2,4-bis(tert-butyldimethylsilyloxy)phenyl)acrylate (119)

A mixture of 109 (565 mg, 1.06 mmol) and a catalytic amount of anhydrous DMF (3 drops) was treated with 2 M oxalyl chloride solution in DCM (0.8 mL, 1.6 mmol) at 0°C under an argon atmosphere. The reaction mixture was allowed to warm to RT and stirred for 3 h, after which time the solvent was evaporated off. The resulting residue was treated with a solution of 105 (400 mg, 0.76 mmol) and DMAP (2 mg) in anhydrous pyridine (0.1 mL) and anhydrous DMF (5 mL) and stirred at RT for 3 days. The solvent was evaporated off and the resulting residue was dissolved in DCM (10 mL) and washed with saturated NH₄Cl solution (2 × 10 mL) and water (3 × 10 mL). The organic layer was dried (MgSO₄), filtered, and the solvent evaporated off to give the crude product. Purification by column chromatography eluting with 4% acetone in DCM + 0.1% pyridine gave 107 as a yellow solid (347 mg, 50%). Rₚ = 0.27 (30% EtOAc in petroleum ether). Mp = 84-89 ºC. ¹H NMR (DMSO-d₆, 400 MHz) δ 0.29 (12H, s, 2 × SiMe₂), 1.01 (18H, s, 2 × Me₃), 1.16 (9H, s, Me₃), 2.42 (3H, s, Pyr-Me), 5.34 (2H, s, CH₂), 6.42 (1H, d, J = 2.3, Ar), 6.66 (1H, dd, J = 8.4, 1.9, Ar), 6.85 (1H, d, J = 16.2, C=CH), 7.48-7.50 (8H, m, Ar), 7.72-7.79 (6H, m, Ar), 7.90 (1H, d, J = 8.2, Ar), 8.25 (1H, d, J = 16.2, C=CH), 8.56 (1H, s, HC=N), 8.81 (2H, br s, Pyr), 8.88 (1H, s, Ar), 12.25 (1H, s, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ -4.53, 18.91, 24.07, 25.46, 25.78, 26.52, 62.85, 110.88, 112.92, 114.55, 121.47, 127.98, 129.52, 129.92, 134.97, 141.97, 142.08, 144.24, 150.32. IR (KBr) 2954s (C-H), 2934s (C-H), 1681s (C=N), 1258s (C=O), 836s (Si-C). [Found (ESI+) 915.4423 [M+H]+, C₅₁ H₆₇N₄O₆Si₃ requires 915.4368].
(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)-methyl)-2-methylpyridin-3-yl- 3-(2-hydroxyphenyl)acrylate (120)

A solution of TBAF trihydrate (643 mg, 2.0 mmol) and AcOH (0.9 mL) in DMF (3 mL) was stirred at 0 °C for 1 h. The reaction mixture was then treated with a solution of 118 (200 mg, 0.25 mmol) in DMF (3 mL), allowed to warm to RT and stirred for a further 2 h. DMF was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (15 mL) and washed with water (2 × 10 mL). The organic layers were combined and volatiles removed under reduced pressure to give the crude product as a yellow solid (176 mg) which was purified by column chromatography eluting with 2-7% MeOH in DCM + 0.1% pyridine to give 120 as a yellow solid (52 mg, 48%). R\textsubscript{f} = 0.39 (8% MeOH in DCM). Mp = 208-212 °C. UV (EtOH): λ\textsubscript{max} 285 (28159). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) \(\delta\) 2.43 (3H, s, Me), 4.84 (2H, d, J = 6.0, CH\textsubscript{2}), 5.43 (1H, t, J = 6.0, OH), 6.95 (1H, t, J = 7.5, Ar), 7.02-7.09 (2H, m, Ar), 7.37 (1H, t, J = 7.8, Ar), 7.80 (1H, d, J = 7.4, Ar), 7.86 (2H, d, J = 5.5, Pyr), 8.21 (1H, d, J = 16.1, C=CH), 8.64 (1H, s, Pyr), 8.66 (1H, s, HC=N), 8.83 (2H, br s, Pyr), 10.52 (1H, s, OH), 12.51 (1H, s, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) \(\delta\) 19.02 (Me), 60.13 (CH\textsubscript{2}), 114.89 (C=CH), 116.34 (Ar), 119.54 (Ar), 120.33 (Ar), 121.53 (Pyr), 129.70 (Ar), 131.53 (Ar), 132.64 (Ar), 134.00 (Ar), 139.75 (Pyr), 142.37 (Pyr), 143.58 (HC=C), 146.15 (HC=N), 150.39 (Pyr), 150.72 (Ar), 157.37 (Ar), 162.16 (C=O), 164.97 (Ar). IR (KBr) 3438s (N-H), 3294 (O-H), 1685s (C=N). [Found (ESI+) 433.1512 [M+H]\textsuperscript{+}. C\textsubscript{23}H\textsubscript{20}N\textsubscript{4}O\textsubscript{5} requires 433.151197].
(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2,4-dihydroxyphenyl) acrylate (121)

A solution of TBAF trihydrate (345 mg, 1.10 mmol) and AcOH (50 μL) in THF (7.5 mL) was treated with 119 (200 mg, 0.22 mmol). The reaction mixture was stirred at RT for 48 h, after which DOWEX 50WX-8-400 ion-exchange resin (770 mg), CaCO$_3$ (254 mg) and MeOH (8 mL) were added, and the mixture stirred for an additional 2 h at RT. The ion-exchange resin and other insoluble material were removed by filtering the reaction mixture through celite, and the celite pad washed thoroughly with EtOAc and MeOH. Volatiles were removed from the filtrate under reduced pressure to give the crude product (350 mg) as a yellow oil which was purified by column chromatography eluting with 6-10% MeOH in DCM + 0.1% pyridine to give 121 as a yellow solid (30 mg, 30%). $R_f = 0.26$ (10% MeOH in DCM). Mp = 210-212 °C. UV (EtOH): $\lambda_{max}$ 302 (30362). $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 2.41 (3H, s, Me), 4.84 (2H, d, J = 6.2 CH$_2$), 5.42 (1H, t, J = 6.2, OH), 6.39 (1H, dd, J = 8.5, 2.3, Ar), 6.46 (1H, d, J = 2.3, Ar), 6.81 (1H, d, J = 16.0, C=CH), 7.61 (1H, d, J = 8.5, Ar), 7.87 (2H, d, J = 4.5, Pyr), 8.11 (1H, d, J = 16.0, C=CH), 8.63 (1H, s, Pyr), 8.64 (1H, s, HC=N), 8.84 (1H, br s, Pyr), 10.14 (1H, br s, OH), 10.44 (1H, br s, OH), 12.55 (1H, br s, NH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 19.01 (Me), 60.21 (CH$_2$), 102.51 (Ar), 108.16 (Ar), 110.27 (C=C) 112.38 (Ar), 121.75 (Pyr), 131.44 (Ar), 131.62 (Ar), 133.90 (Ar), 142.48 (C=N) 144.10 (C=C), 145.96 (Pyr), 150.39 (Pyr), 159.36 (Ar), 161.90 (C=O), 165.39 (C=O). IR (KBr) 3424s (N-H), 3285s (O-H), 1676 (C=N). [Found (ESI-) 447.1324 [M-H]$^-$, C$_{23}$H$_{19}$N$_4$O$_6$ requires 447.1305].
(E)-isopropyl-3-(2-(tert-butyldimethylsilyloxy)phenyl)acrylate (122a)

A mixture of 103 (800 mg, 2. mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2 M oxalyl chloride solution in DCM (1.3 mL, 2.6 mmol). The reaction mixture was allowed to warm to RT and stirred for 3.5 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with a solution of isopropanol (125 μL, 1.62 mmol) and pyridine (0.1 mL) in anhydrous DCM (5 mL) and stirred at RT overnight. The reaction mixture was diluted with DCM, washed with water (2 × 10 mL) and brine (15 mL), dried over MgSO₄ and evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography eluting with 1-2% EtOAc in petroleum ether to give 122a as a clear oil (450 mg, 87%). Rᵣ = 0.68 (5% EtOAc in petroleum ether). ¹H NMR (CDCl₃, 400 MHz) δ 0.23 (6H, s, SiMe₂), 1.05 (9H, s, Me₃), 1.30 (6H, d, J = 6.3, Me₂), 5.13 (1H, sp, J = 6.3, OCH), 6.35 (1H, d, J = 16.2, C=CH), 6.83 (1H, dd, J = 8.0, 1.0, Ar), 6.96 (1H, td, J = 8.0, 1.0, Ar), 7.23 (1H, td, J = 7.8, 1.7, Ar), 7.54 (1H, dd, J = 7.8, 1.7, Ar), 8.06 (1H, d, J = 16.2, C=CH). ¹³C NMR (CDCl₃, 100 MHz) δ -4.37 (SiMe₂), 18.25 (Si-C), 21.91 (Me₂), 25.71 (Me₃), 67.39 (OCH), 118.36 (C=C), 119.87 (Ar), 121.49 (Ar), 126.02 (Ar), 127.13 (Ar), 131.08 (Ar), 139.42 (C=C), 154.47 (Ar), 166.52 (C=O). IR (KBr) 3029w (Ar), 2950m (C-H), 2857m (C-H), 1258s (C=O), 833s (Si-C). [Found (ESI+) 321.1890 [M+H]+, C₁₈H₂₉O₃Si requires 321.1886].

(E)-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)-3-(2-(tert-butyldimethylsilyloxy)phenyl)acrylate (122b)

A mixture of 103 (500 mg, 1.27 mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2 M oxalyl chloride solution in DCM (0.8 mL, 1.6 mmol). The reaction mixture was allowed to warm to RT and stirred for
2.5 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with a solution of (1R,2S,5R)-(-)-menthol (160 mg, 1.02 mmol) and pyridine (0.1 mL) in anhydrous DCM (4 mL) and stirred at RT for 3 h. The reaction mixture was diluted with DCM, washed with water (2 x 10 mL) and brine (15 mL) and evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography eluting with 1-2% EtOAc in petroleum ether to give 122b as a clear oil (270 mg, 64%). Rf = 0.86 (5% EtOAc in petroleum ether). 1H NMR (CDCl3, 400 MHz) δ 0.22 (3H, s, SiMe), 0.23 (3H, s, SiMe), 0.78 (3H, d, J = 7.1, Me), 0.89-0.92 (7H, m, 2 × Me + CH), 1.04 (9H, s, Me3), 1.40-1.46 (1H, m, CH), 1.51-1.53 (1H, m, CH), 1.67-1.71 (2H, m, 2 × CH), 1.95 (1H, pentet of doublets, J = 7.1, 2.5, CH), 2.04-2.09 (1H, m, CH), 4.80 (1H, td, J = 10.9, 4.4, OCH), 6.37 (1H, d, J = 16.2, C=CH), 6.83 (1H, dd, J = 8.1, 1.0, Ar), 6.94 (1H, t, J = 8.1, Ar), 7.23 (1H, td, J = 7.7, 1.7, Ar), 7.55 (1H, dd, J = 7.7, 1.7, Ar), 8.05 (1H, d, J = 16.2, C=CH). 13C NMR (CDCl3, 100 MHz) δ -4.39 (SiMe), -4.31 (SiMe), 16.28 (Me), 18.26 (Si-C), 20.79 (Me), 22.01 (Me), 23.38 (CH2), 25.72 (Me3), 26.18 (CH), 31.37 (CH), 34.30 (CH2), 41.00 (CH2), 47.20 (CH), 73.93 (OCH), 118.31 (C=C), 119.86 (Ar), 121.50 (Ar), 125.97 (Ar), 127.18 (Ar), 131.12 (Ar), 139.34 (C=C), 154.45 (Ar), 166.65 (C=O). IR (CHCl3 cell) 3031m (Ar), 2959vs (C-H), 2866s (C-H), 1704s (C=O). [Found (ESI+) 439.2680 [M+Na]+, C25H40NaO3Si requires 439.2644].

(E)-isopropyl-3-(2-hydroxyphenyl)acrylate (123a)

A solution of TBAF trihydrate (670 mg, 2.12 mmol) and AcOH (96 μL) in THF (16 mL) was treated with 122a (340 mg, 1.06 mmol) and stirred at RT for 9 h, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with saturated NH4Cl solution (20 mL), water (2 × 20 mL) and brine (20 mL) and then dried over Na2SO3. Removal of solvent under reduced pressure gave the crude product which was purified by column chromatography eluting with 2-4% EtOAc in petroleum ether to give a clear oil, which precipitated to give 123a as a white solid upon trituration with hexane (189 mg, 86%). Rf = 0.24 (10% EtOAc in petroleum ether). Mp = 87-89 ºC (lit. 89 ºC).[191] 1H NMR (CDCl3, 400 MHz) δ 1.33 (6H, d, J = 6.3, Me2), 5.18 (1H, sp, J = 6.3, OCH), 6.65 (1H,
(E)-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)-3-(2-hydroxyphenyl)acrylate (123b)

A solution of TBAF trihydrate (360 mg, 1.15 mmol) and AcOH (57 μL) in THF (15 mL) was treated with 122b (240 mg, 0.58 mmol) and stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with saturated NH₄Cl solution (20 mL), water (2 × 20 mL) and brine (20 mL) and then dried over Na₂SO₃. Removal of solvent under reduced pressure gave the crude product which was purified by column chromatography eluting with 4-5% EtOAc in petroleum ether to give 123b as a clear oil (130 mg, 74%). Rf = 0.56 (15% EtOAc in petroleum ether). ¹H NMR (CDCl₃, 400 MHz) δ 0.80 (3H, d, J = 7.0, Me), 0.90-0.93 (7H, m, 2 × Me + CH), 1.09 (2H, m, 2 × CH), 1.44-1.56 (2H, m, 2 × CH), 1.71 (2H, m, 2 × CH), 1.94 (1H, pentet of doublets, J = 7.0, 2.5, CH), 2.06-2.09 (1H, m, CH), 4.88 (1H, td, J = 10.9, 4.4, OCH), 6.69 (1H, d, J = 16.2, C=CH), 6.87-6.92 (2H, m, Ar), 7.23 (1H, t, J = 7.6, 1.5, Ar), 7.46 (1H, dd, J = 7.6, 1.5, Ar), 7.82 (1H, s, OH), 8.09 (1H, d, J = 16.2, C=CH). ¹³C NMR (CDCl₃, 100 MHz) δ 16.39 (Me), 20.73 (Me), 22.03 (Me), 23.46 (CH₂), 26.26 (CH), 31.39 (CH), 34.23 (CH₂), 40.94 (CH₂), 47.12 (CH), 74.69 (OCH), 116.49 (Ar), 118.29 (C=C), 120.32 (Ar), 121.66 (Ar), 129.22 (Ar), 131.41 (Ar), 141.15 (C=C), 155.92 (Ar), 168.75 (C=O). IR (CHCl₃ cell) 2959s (C-H), 2866s (C-H), 1698 (C=O), 1198 (C=O) [Found (ESI−) 301.1810 [M−H]−, C₁₉H₂₅O₃ requires 301.1804].
(E)-phenethyl-3-(2,4-bis(tert-butyldimethylsilyloxy)phenyl)acrylate (124)

A mixture of 109 (500 mg, 0.96 mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2 M oxalyl chloride solution in DCM (0.6 mL, 1.15 mmol). The reaction mixture was allowed to warm to RT and stirred for 2.5 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with a solution of 2-phenylethanol (0.1 mL, 0.80 mmol) and pyridine (0.1 mL) in anhydrous DCM (2 mL) and stirred at RT for 3 h. The reaction mixture was diluted with DCM, washed with water (2 × 10 mL) and brine (15 mL) and evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography eluting with 0.5-1% EtOAc in petroleum ether to give 124 as a clear oil (342 mg, 83%). Rf = 0.64 (5% EtOAc in petroleum ether). ¹H NMR (CDCl₃, 400 MHz) δ 0.21 (6H, s, SiMe₂), 0.23 (6H, s, SiMe₂), 0.97 (9H, s, Me₃), 1.03 (9H, s, Me₃), 3.00 (2H, t, J = 6.9, PhCH₂), 4.40 (2H, t, J = 6.9, OCH₂), 6.28 (1H, d, J = 16.1, C=CH), 6.52 (1H, d, J = 2.4, Ar), 6.48 (1H, dd, J = 8.6, 2.4, Ar), 7.21-7.27 (4H, m, Ph), 7.29-7.33 (1H, m, Ph), 7.41 (1H, d, J = 8.6, Ar), 7.99 (1H, d, J = 16.1, C=CH). ¹³C NMR (CDCl₃, 100 MHz) δ -4.39 (SiMe₂), -4.29 (SiMe₂), 18.22 (Si-C), 18.29 (Si-C), 25.57 (Me₃), 25.72 (Me₃), 35.20 (PhCH₂), 64.66 (OCH₂), 111.43 (Ar), 114.12 (Ar), 115.11 (C=C), 119.46 (Ar), 126.44 (Ph), 128.30 (Ar), 128.44 (Ph), 128.87 (Ph), 137.97 (Ph), 139.95 (C=C), 155.84 (Ar), 158.66 (Ar), 167.43 (C=O). IR (KBr) 3025s (Ar), 2957s (C-H), 2939s (C-H), 1708s (C=O), 836s (Si-C). [Found (ESI+) 513.2900 [M+H]⁺, C₂₉H₄₅O₄Si₂ requires 513.2856].

(E)-phenethyl 3-(2,4-dihydroxyphenyl)acrylate (125)

A solution of TBAF trihydrate (590 mg, 1.87 mmol) and AcOH (93 μL) in THF (15 mL) was treated with 125 (320 mg, 0.62 mmol) and stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved
in EtOAc. The mixture was washed with water (2 × 20 mL), saturated NH₄Cl solution (20 mL), and brine (20 mL) and then dried over Na₂SO₃. Removal of solvent under reduced pressure gave the crude product which was purified by column chromatography eluting with 2% MeOH in DCM to give 125 as a white solid (151 mg, 86%). Rᵣ = 0.32 (5% MeOH in DCM). Mp = 120-121 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 3.00 (2H, t, J = 6.9, CH₂), 4.36 (2H, t, J = 6.9, OCH₂), 6.32 (1H, dd, J = 8.6, 2.4, Ar), 6.40 (1H, d, J = 16.1, C=CH), 6.41 (1H, d, J = 2.4, Ar), 7.28 (1H, t, J = 6.8, Ph), 7.32-7.39 (4H, m, Ph), 7.46 (1H, d, J = 8.6, Ar), 7.81 (1H, d, J = 16.1, C=CH), 9.95 (1H, br s, OH), 10.21 (1H, br s, OH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 34.51 (PhCH₂), 64.08 (OCH₂), 102.39 (Ar), 107.77 (Ar), 112.48 (Ar), 112.71 (C=C), 126.32 (Ph), 128.35 (Ph), 128.86 (Ph), 130.41 (Ar), 138.14 (Ph), 140.58 (C=C), 158.51 (Ar), 160.98 (Ar), 167.09 (C=O). IR (KBr) 3340vs (OH), 3030w (Ar), 1180s (C=O). [Found (ESI-) 283.0973 [M–H]−. C₁₇H₁₅O₄ requires 283.0976].

![Image of compound 126](image.png)

(E)-2-methoxy-4-(((E)-8-methylnon-6-enamido)methyl)phenyl-3-(2-(tert-butyl-dimethylsilyloxy)phenyl)acrylate (126)

**Method A:**
A mixture of 103 (70 mg, 0.17 mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2M oxalyl chloride solution in DCM (0.1 mL). The reaction mixture was allowed to warm to RT and stirred for 2.5 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with a solution of capsaicin (40 mg, 0.13 mmol) and pyridine (0.1 mL) in anhydrous DCM (2 mL) and stirred at RT overnight. TLC analysis showed starting material still remaining but also the emergence of a new spot with a middle Rᵣ value. The reaction mixture was diluted with DCM, washed with water (2 × 10 mL) and brine (15 mL), dried over MgSO₄ and evaporated to dryness under reduced pressure to
give a residue which was purified by column chromatography eluting with 10-40% EtOAc in petroleum ether. This gave a mixture of compounds by $^1$H NMR spectra.

**Method B:**

A mixture of 103 (100 mg, 0.24 mmol) and anhydrous DMF (2 drops) under argon atmosphere was chilled to 0 °C and treated with 2M oxalyl chloride solution in DCM (0.15 mL). The reaction mixture was allowed to warm to RT and stirred for 2.5 h, after which volatiles were removed under reduced pressure. The resulting residue was treated with DMAP (2 mg), followed by a solution of capsaicin (50 mg, 0.16 mmol) and pyridine (0.2 mL) in anhydrous DCM (3 mL) and stirred at RT overnight. TLC analysis showed that most starting material was consumed and the emergence of a new spot with a middle $R_f$ value. The reaction mixture was diluted with DCM, washed with water (2 $\times$ 10 mL) and brine (15 mL), dried over MgSO$_4$ and evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography eluting with 5-40% EtOAc in petroleum ether to give 126 as a clear oil (78 mg, 84%). $R_f = 0.37$ (30% EtOAc in petroleum ether). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.23 (6H, s, SiMe$_2$), 0.95 (6H, d, $J = 6.8$, Me$_2$), 1.02 (9H, s, Me$_3$), 1.40 (2H, qn, $J = 7.7$, CH$_2$), 1.67 (2H, qn, $J = 7.7$, CH$_2$), 2.00 (2H, q, $J = 6.8$, CH$_2$), 2.19-2.23 (3H, m, CH$_2$/CH), 3.81 (3H, s, OMe), 4.42 (2H, d, $J = 5.7$, NCH$_2$), 5.28-5.41 (2H, m, C=CH), 5.70 (1H, br s, NH), 6.60 (1H, d, $J = 16.2$, C=CH), 6.86 (2H, dd, $J = 8.2$, 1.2, Ar), 6.92 (1H, d, 1.8, Ar), 6.99 (1H, t, $J = 7.8$, Ar), 7.05 (1H, d, $J = 8.0$, Ar), 7.28 (1H, td, $J = 7.8$, 1.7, Ar), 7.61 (1H, dd, $J = 7.8$, 1.7, Ar), 8.27 (1H, d, $J = 16.2$, C=CH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ -4.34 (SiMe$_2$), 18.25 (Si-C), 22.59 (Me$_2$), 25.19 (CH$_2$), 25.68 (Me$_3$), 29.25 (CH$_2$), 30.90 (CH), 32.16 (CH$_2$), 36.63 (CH$_2$), 43.47 (NCH$_2$), 55.87 (OMe), 112.24 (Ar), 116.30 (C=CH), 120.02 (Ar), 121.57 (Ar), 123.00 (Ar), 125.76 (Ar), 126.42 (C=CH), 127.49 (Ar), 131.65 (Ar), 137.09 (Ar), 138.05 (C=CH), 139.30 (Ar), 142.07 (C=CH), 151.44 (Ar), 154.83 (Ar), 165.21 (C=O), 172.75 (NC=O). IR (CHCl$_3$ cell) 3449w (N-H), 2958s (C-H), 1667 (C=O), 1509 (C=O). [Found (ESI+) 566.3330 [M+H]$^+$, C$_{33}$H$_{48}$NO$_5$Si requires 566.3302].
(E)-2-methoxy-4-(((E)-8-methylnon-6-enamido)methyl)phenyl-3-(2-hydroxy phenyl)acrylate (127).

A solution of TBAF trihydrate (33 mg, 0.11 mmol) and AcOH (5 μL) in THF (1 mL) was treated with 126 (20 mg, 0.04 mmol) and stirred at RT for 2.5 h, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with saturated NH₄Cl solution (2 × 10 mL), water (10 mL) and brine (10 mL). Removal of solvent under reduced pressure gave the crude product which was purified by column chromatography eluting with 2% MeOH in DCM to give 127 as a clear residue (12 mg, 76%). R₇ = 0.29 (5% MeOH in DCM). ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (6H, d, J = 6.7, Me₂), 1.40 (2H, qn, J = 7.7, CH₂), 1.70 (2H, qn, J = 7.7, CH₂), 1.98 (2H, q, J = 6.8, CH₂), 2.18-2.23 (3H, m, CH₂/CH), 3.78 (3H, s, OMe), 4.43 (2H, d, J = 5.8, NCH₂), 5.28-5.39 (2H, m, 2 × C=CH), 5.91 (1H, t, J = 5.8, NH), 6.80 (1H, d, J = 16.2, C=CH), 6.84-6.93 (4H, m, Ar), 7.05 (1H, d, J = 7.9, Ar), 7.23 (1H, td, J = 7.7, 1.7, Ar), 7.50 (1H, dd, J = 7.7, 1.7, Ar), 8.13 (1H, d, J = 16.2, C=CH). ¹³C NMR (CDCl₃, 100 MHz) δ 22.58 (Me₂), 25.19 (CH₂), 29.20 (CH₂), 30.88 (CH), 32.12 (CH₂), 36.62 (CH₂), 43.52 (NCH₂), 55.87 (OMe), 112.18 (Ar), 116.46 (Ar), 117.05 (C=CH), 119.99 (Ar), 120.45 (Ar), 121.44 (Ar), 123.02 (Ar), 126.35 (C=CH), 129.53 (Ar), 131.68 (Ar), 136.91 (Ar), 138.09 (C=CH), 139.26 (Ar), 142.53 (C=CH), 151.42 (Ar), 156.01 (Ar), 161.92 (C=O), 173.44 (C=O). IR (CHCl₃ cell) 3446s (N-H), 3022s (Ar), 2964s (O-H), 2865m (C-H), 1664s (C=O), 1514s (C=O). [Found (ESI+) 452.2448 [M+H]⁺, C₂₇H₃₄NO₅ requires 452.2437].
2,4-bis(tert-butyl(dimethyl)silyloxy)-5-methoxybenzaldehyde (129)
A solution of 2,4-dihydroxy-5-methoxybenzaldehyde (300 mg, 1.78 mmol) and imidazole (250 mg, 3.74 mmol) in anhydrous DMF (6 mL) was treated with TBSCl (670 mg, 4.45 mmol) added portionwise and stirred at RT under N₂ atmosphere overnight. The reaction mixture was concentrated under reduced pressure, dissolved in DCM (30 mL) and washed with water (3 × 20 mL). The organic layer was dried over MgSO₄, concentrated and purified by column chromatography eluting with 2.5-3% EtOAc in petroleum ether to give 129 as a clear oil (450 mg, 64%). Rf = 0.46 (10% EtOAc in petroleum ether). 

1H NMR (CDCl₃, 400 MHz) δ (0.19, 6H, s, SiMe₂), 0.24 (6H, s, SiMe₂), 0.99 (9H, s, Me₃), 1.00 (9H, s, Me₃), 3.79 (3H, s, OMe), 6.36 (1H, s, Ar), 7.25 (1H, s, Ar), 10.27 (1H, s, H=C=O). 13C NMR (CDCl₃, 100 MHz) δ -4.66 (SiMe₂), -4.42 (SiMe₂), 18.27 (Si-C), 18.42 (Si-C), 25.50 (Me₃), 25.61 (Me₃), 55.64 (OMe), 109.18 (Ar), 112.54 (Ar), 120.95 (Ar), 146.44 (Ar), 152.36 (Ar), 154.61 (Ar), 188.56 (C=O).

(E)-ethyl-3-(2,4-bis(tert-butyl(dimethyl)silyloxy)-5-methoxyphenyl)acrylate (130)
A solution of 129 (430 mg, 1.08 mmol) and ECMTP (453 mg, 1.30 mmol) in anhydrous toluene (18 mL) was stirred under argon atmosphere at 60 °C overnight. Removal of the solvent under reduced pressure gave the crude product as a yellow oil which was purified by column chromatography eluting with 1-3% EtOAc in petroleum ether to give 130 as a white solid (343 mg, 68%). Rf = 0.39 (5% EtOAc in petroleum ether). Mp = 54-56 °C. 

1H NMR (CDCl₃, 400 MHz) δ 0.17 (6H, s, SiMe₂), 0.19 (6H, s, SiMe₂), 0.99 (9H, s, Me₃), 1.03 (9H, s, Me₃), 1.31 (3H, t, J = 7.1, Me), 3.77 (3H, s, OMe), 4.23 (2H, q, J = 7.1, OCH₂), 6.22 (1H, d, J = 16.2, C=CH), 6.36 (1H, s, Ar), 6.98 (1H, s, Ar), 8.01 (1H, d, J = 16.2, C=CH). 13C NMR (CDCl₃, 100 MHz) δ -4.68 (SiMe₂), -4.41 (SiMe₂), 14.26 (Me), 18.23 (Si-C), 18.38 (Si-C), 25.56 (Me₃), 25.72 (Me₃), 55.95 (OMe), 60.04 (OCH₂), 109.62 (Ar), 112.91 (Ar), 115.02...
(C=CH), 118.66 (Ar), 139.67 (C=CH), 146.19 (Ar), 148.42 (Ar), 167.37 (C=O). IR (KBr) 3019w (Ar), 2959s (C-H), 2937s (C-H), 1258 (C=O), 836 (Si-C).

[Found (ESI+) 489.2477 [M+Na]+, C_{24}H_{42}NaO_{5}Si_{2} requires 489.2468].

(E)-3-(2,4-bis((tert-butyldimethylsilyl)oxy)-5-methoxyphenyl)acrylic acid (131)

Method A:
A solution of 130 (10 mg, 0.02 mmol) in a 1:1 mixture of THF/water (1 mL) and chilled to 0 °C was treated with LiOH (1 mg, 0.04 mmol) and stirred for 20 min, after which the reaction mixture was diluted with water (2 mL), adjusted to pH 5 with 1M HCl and extracted with DCM (3 × 3mL). The combined organic layers were washed with brine (4 mL) and the solvent removed under reduced pressure to give a residue which was purified by column chromatography eluting with DCM. ^1H NMR analysis of the isolated compound however suggested that monodesilylation had occurred while the ethyl ester remained intact, and thus the expected carboxylic acid was not observed.

Method B:
A solution of 130 (50 mg, 0.11 mmol) in tetrahydrothiophene (1 mL) under argon atmosphere was treated with AlCl₃ (96 mg, 0.22 mmol) added portionwise over 30 min and stirred at RT overnight. TLC showed no reaction progression.

2,4,5-tris((tert-butyldimethylsilyl)oxy)benzaldehyde (133)
A solution of 2,4,5-trihydroxybenzaldehyde (100 mg, 0.65 mmol) and imidazole (150 mg, 2.3 mmol) in anhydrous DMF (3 mL) and under argon atmosphere was treated with TBSCI (440mg, 3.0 mmol) and stirred at RT overnight. Removal of DMF under reduced pressure gave an oil which was diluted with water (20 mL), extracted with DCM (3 × 20 mL) and the combined organic layers washed with brine (20 mL).
Removal of volatiles under reduced pressure gave the crude product which was purified by column chromatography eluting with 0-2% EtOAc in petroleum ether to give 133 as a clear oil (193 mg, 60%). Rf = 0.69 (5% EtOAc in petroleum ether). 1H NMR (CDCl3, 400 MHz) δ 0.19 (6H, s, SiMe2), 0.24 (6H, s, SiMe2), 0.25 (6H, s, SiMe2), 0.97 (9H, s, Me3), 0.99 (9H, s, Me3), 1.00 (9H, s, Me3), 6.34 (1H, s, Ar), 7.25 (1H, s, Ar), 10.24 (1H, s, HC=O).

13C NMR (CDCl3, 100 MHz) δ -4.41 (SiMe2), -4.28 (SiMe2), -4.10 (SiMe2), 18.25 (Si-C), 18.30 (Si-C), 18.48 (Si-C), 25.60 (Me3), 25.72 (Me3), 25.82 (Me3), 111.84 (Ar), 118.22 (Ar), 121.02 (Ar), 142.05 (Ar), 154.06 (Ar), 154.27 (Ar), 188.43 (C=O).

\( \text{(E)-}\text{tert-butyl-3-(2,4,5-tris(tert-butylidimethylsilyloxy)phenyl)acrylate (134)} \)

A solution of 133 (190 mg, 0.38 mmol) and BCMTP (172 mg, 0.46 mmol) in anhydrous toluene (4 mL) under N2 atmosphere was stirred at 60 °C for 5 h. Removal of toluene under reduced pressure gave the crude product which was purified by column chromatography eluting with 1-2% EtOAc in petroleum ether + 0.1% pyridine to give 134 as a clear oil (133 mg, 59%). Rf = 0.55 (5% EtOAc in petroleum ether). 1H NMR (CDCl3, 400 MHz) δ 0.17 (6H, s, SiMe2), 0.19 (6H, s, SiMe2), 0.21 (6H, s, SiMe2), 0.97 (9H, s, Me3), 0.97 (9H, s, Me3), 1.02 (9H, s, Me3), 1.51 (9H, s, Me3), 6.05 (1H, d, J = 16.1, C=CH), 6.33 (1H, s, Ar), 6.97 (1H, s, Ar), 7.83 (1H, d, J = 16.1, C=CH). 13C NMR (CDCl3, 100 MHz) δ -5.36 (SiMe2), -5.22 (SiMe2), -5.08 (SiMe2), 17.25 (Si-C), 17.36 (Si-C), 17.49 (Si-C), 24.78 (Me3), 24.82 (Me3), 24.89 (Me3), 27.23 (Me3), 78.83 (tBuC-O), 111.23 (Ar), 116.34 (C=C), 117.09 (Ar), 117.91 (Ar), 137.38 (C=C), 140.56 (Ar), 148.10 (Ar), 148.56 (Ar), 165.72 (C=O).
(E)-tert-butyldimethylsilyl-3-(2,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl) acrylate (135)

A solution of 134 (120 mg, 0.2 mmol) in anhydrous DCM (0.5 mL), under argon atmosphere and chilled to 0 °C was treated with TBDMS-OTf (50 µL, 0.22 mmol) and stirred for 2.5 h, after which 2,6-lutidine (25 µL, 0.22 mmol) was added, and the reaction mixture stirred at 0 °C for a further 3 h. TLC showed disappearance of starting material with emergence of new spot with low Rf. The reaction mixture was quenched by addition of sat. NaHCO₃ solution (10 mL), then diluted with EtOAc and extracted (2 × 10 mL). The combined organic layers were dried over MgSO₄ and volatiles removed under reduced pressure. The expected compound was not detected by ¹H NMR analysis, and a desilylated derivative was instead observed.

(E)-ethyl-3-(4,5-dimethoxy-2-nitropheryl)-2-methylacrylate (143a)[108]

A solution of 6-nitoveratraldehyde (4.00 g, 18.94 mmol) and ECETP (8.09 g, 22.33 mmol) in anhydrous toluene (200 mL) was heated at 85 °C under an Argon atmosphere for 19 h. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography eluting with DCM to give 143a as a yellow solid (5.36 g, 96%). Rf = 0.53 (DCM). Mp = 143-145 °C (lit. 146-147 °C).[192] IR (CHCl₃) 1074 (C=O), 1127 (C=O), 1522 (C-NO₂), 1579.5 (Ar), ¹H NMR (CDCl₃, 400 MHz) δ 1.34 (3H, t, J = 7.1, Me), 1.90 (3H, s, C=CMe), 3.91 (3H, s, OMe), 3.95 (3H, s, OMe), 4.27 (2H, q, J = 7.1, CH₂), 6.70 (1H, s, Ar), 7.72 (1H, s, Ar), 7.91 (1H, s, C=CH). ¹³C NMR (CDCl₃, 100 MHz) δ 14.08 (Me), 14.28 (Me), 56.44 (OMe), 56.50 (OMe), 61.05 (OCH₂), 107.91 (Ar), 112.38 (Ar), 126.63 (Ar), 129.49 (C=C), 136.44 (C=C), 140.39 (Ar), 148.64 (Ar), 153.03 (Ar), 167.78 (C=O).
(E)-ethyl-2-methyl-3-(6-nitrobenzo[d][1,3]dioxyl-5-yl)acrylate (143b)\[^{108}\]

A solution of 6-nitropiperonal (2.00 g, 10.25 mmol) and ECETP (4.09 g, 11.29 mmol) in anhydrous toluene (100 mL) was heated at 65°C under an Argon atmosphere for 19 h. The solvent was removed under reduced pressure and the resulting crude solid was purified by column chromatography eluting with DCM to give 143b as a bright yellow solid (1.64 g, 84%). R\(_f\) = 0.35 (DCM). Mp = 118-121 °C (lit. 115-117 °C).\[^{192}\] IR (CHCl\(_3\)), 1526 (C-NO\(_2\)), 1715 (C=O), 2902.7 (Me) \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.33 (3H, t, J = 7.1, Me), 1.89 (3H, s, MeC=C), 4.26 (2H, q, J = 7.1, CO\(_2\)CH\(_2\)), 6.15 (2H, s, H\(_2\)C), 6.69 (1H, s, Ar), 7.64 (1H, s, Ar), 7.83 (1H, s, C=CH). \(^13\)C NMR (CDCl\(_3\), 400 MHz) \(\delta\) 13.96 (Me), 14.25 (Me), 61.03 (OCH\(_2\)), 103.24 (H\(_2\)CO\(_2\)), 105.62 (Ar), 109.71 (Ar), 128.72 (Ar), 129.70 (C=C), 136.07 (C=C), 142.02 (Ar), 147.83 (Ar), 151.81 (Ar), 167.64 (C=O).

(143b)

(E)-ethyl-2-methyl-3-(2-nitrophenyl)acrylate (143c)\[^{192}\]

A solution of 2-nitrobenzaldehyde (1.0 g, 6.62 mmol) and ECETP (2.9 g, 7.94 mmol) in anhydrous toluene (40 mL) was heated at 65 °C under argon atmosphere overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography eluting with DCM to give 143c as a yellow oil (1.6 g, 99%). R\(_f\) = 0.32 (DCM). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.35 (3H, t, J = 7.2, Me), 1.89 (3H, s, Me), 4.30 (2H, q, J = 7.2, OCH\(_2\)), 7.36 (1H, d, J = 7.6, Ar), 7.50 (1H, td, J = 8.0, 0.9, Ar), 7.64 (1H, td, J = 7.6, 1.0, Ar), 7.89 (1H, s, C=CH), 8.12 (1H, dd, J = 8.0, 1.2, Ar). \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 13.88 (C=CMe), 14.18 (Me), 61.03 (OCH\(_2\)), 124.75 (Ar), 128.83 (Ar), 130.49 (C=C), 131.23 (Ar), 131.89 (Ar), 133.13 (Ar), 135.23 (C=CH), 147.78 (Ar), 167.52 (C=O).
(E)-ethyl-2-methyl-3-(2-nitro-4-(trifluoromethyl)phenyl)acrylate (143d)

A solution of 2-nitro-4-(trifluoromethyl)benzaldehyde (800 mg, 3.65 mmol) and ECETP (1.56 g, 4.4 mmol) in anhydrous toluene (35 mL) and under argon atmosphere was stirred at 65 °C overnight. The toluene was removed under reduced pressure to give the crude product which was purified by column chromatography eluting with DCM to give 143d as a yellow-orange oil (862 mg, 78%). Rf = 0.82 (DCM). 1H NMR (CDCl3, 400 MHz) δ 1.24 (3H, t, J = 7.2, Me), 1.81 (3H, d, J = 1.3, Me), 4.18 (2H, q, J = 7.2, CH2), 7.51 (1H, d, J = 8.1, Ar), 7.77 (1H , s, C=CH), 7.86 (1H, dd, J = 8.1, 1.6, Ar), 8.27 (1H, s, J = 1.3, Ar). 13C NMR (CDCl3, 100 MHz) δ 13.89 (Me), 14.07 (Me), 61.23 (CH2), 122.11 (Ar), 123.97 (CF3), 126.68 (C=C), 129.58 (Ar), 131.52 (Ar), 132.30 (Ar), 133.58 (C=C), 135.47 (Ar), 139.17 (Ar), 166.96 (C=O). IR (KBr) 3026s (Ar), 1709s (C=O), 1213s (C-F). [Found (ESI+) 304.0785 [M+H]⁺, C13H13F3NO4 requires 304.0797].

(E)-ethyl-3-(4-(dimethylamino)-2-nitrophenyl)-2-methylacrylate (143e)

A solution of 4-dimethylamino-2-nitrobenzaldehyde (1.00 g, 5.15 mmol) and ECETP (2.30 g, 6.17 mmol) in anhydrous toluene (50 mL) and under argon atmosphere was stirred at 70 °C overnight. The toluene was removed under reduced pressure to give the crude product which was purified by column chromatography eluting with DCM to give 143e as a red solid (1.47 g, 99%). Rf = 0.32 (DCM). Mp = 87-88 °C. 1H NMR (CDCl3, 400 MHz) δ 1.33 (3H, t, J = 7.1, Me), 1.95 (3H, s, Me), 3.05 (6H, s, NMe2), 4.26 (2H, q, J = 7.1, CH2), 6.88 (1H, dd, J = 8.7, 2.7, Ar), 7.21 (1H, s, Ar), 7.32 (1H, d, J = 2.7, Ar), 7.80 (1H, s, C=CH). 13C NMR (CDCl3, 100 MHz) δ 14.00 (Me), 14.23 (Me), 40.18 (NMe2), 60.75 (CH2), 106.97 (Ar), 115.64 (Ar), 118.00 (Ar), 128.18 (C=C), 131.94 (Ar), 135.58 (C=C), 149.14 (Ar), 150.15 (Ar), 168.16 (C=O). IR (KBr) 3030s (Ar), 2989s (C-H), 2907s (C-H), 1696s (C=O). [Found (ESI+) 301.1162 [M+Na]⁺, C14H18N2NaO4 requires 301.1164].
(E)-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylacrylic acid (144a)\textsuperscript{[193]}

A solution of 143a (0.9 g, 3.05 mmol) in THF (26 mL) was treated with 1M NaOH (9.2 mL) and EtOH (5 mL) and stirred at RT for 41 h. The organic solvents were removed under reduced pressure and the pH of the remaining aqueous solution was adjusted to pH 3 with 6M HCl. The resulting suspension was extracted with EtOAc (3 × 100 mL), the organic phase dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure to give 144a as a yellow solid (763 mg, 94%). R\textsubscript{f} = 0.67 (10% MeOH in DCM). Mp = 255-259 °C. IR (cm\textsuperscript{-1}): 3422 (COOH), 1682 (C=C), 1573 (C=O), 1361 (OMe), 1348 (C–NO\textsubscript{2}). \textsuperscript{1}H NMR (acetone-d\textsubscript{6}, 270 MHz) δ 1.91 (3H, s, Me), 3.98 (3H, s, OMe), 4.01 (3H, s, OMe), 7.02 (1H, s, Ar), 7.75 (1H, s, Ar), 7.92 (1H, s, C=CH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) δ 13.80 (Me), 56.13 (OMe), 56.48 (OMe), 107.82 (Ar), 112.86 (Ar), 125.73 (Ar), 129.53 (C=C), 135.43 (C=C), 139.86 (Ar), 148.25 (Ar), 152.90 (Ar), 168.71 (C=O).

(E)-2-methyl-3-(6-nitrobenzo[d][1,3]dioxyl-5-yl)acrylic acid (144b)

A solution of 143b (2.00 g, 7.16 mmol) in THF (52 mL) was treated with 1M NaOH (22 mL) and EtOH (13 mL) and stirred at RT for 22 h. The organic solvents were removed under reduced pressure and the pH of the remaining aqueous solution was adjusted to pH 4 with 6M HCl. The resulting suspension was extracted with EtOAc (3 × 100 mL), the organic phase dried over MgSO\textsubscript{4}, and the solvent removed under reduced pressure to give 144b as an orange solid (840 mg, 93%). R\textsubscript{f} = 0.61 (10% MeOH in DCM). Mp = 189-202 °C. \textsuperscript{1}H NMR (CD\textsubscript{3}OD, 270 MHz) δ 1.81 (3H, s, Me), 6.26 (2H, s, H\textsubscript{2}C), 7.07 (1H, s, Ar), 7.68 (1H, s, Ar), 7.76 (1H, s, CH=C), 11.95 (1H, s, COOH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 100 MHz) δ 13.50 (Me), 103.61 (H\textsubscript{2}CO\textsubscript{2}), 104.95 (Ar), 109.50 (Ar), 127.88 (Ar), 129.54 (C=C), 135.30 (C=C), 141.53 (Ar), 147.65 (Ar), 189.02 (C=O).
151.78 (Ar), 168.50 (C=O). IR (KBr) 3105-2635m (O-H), 1691 (O-H), 1508 (NO2). [Found (ESI-) 250.0360 [M-H]-, C11H8NO6 requires 250.0351].

(E)-2-methyl-3-(2-nitrophenyl)acrylic acid (144c)
A solution of 143c (1.4 g, 5.95 mmol) in THF (32 mL) was treated with 1M NaOH solution (21 mL) and EtOH (8 mL) and stirred at 40 ºC overnight. The organic solvents were removed under reduced pressure and the pH of the remaining aqueous solution was adjusted to pH 2 with 10% HCl solution. The resulting suspension was diluted with water (30 mL), extracted with EtOAc (2 × 80 mL) and the combined organic layers dried over MgSO4. Removal of solvent under reduced pressure gave 144c (1.2 g, 97%) as a light yellow solid. Rf = (5% MeOH in DCM). Mp = 196-201 º C. 1H NMR (DMSO-d6, 400 MHz) δ 1.87 (3H, s, Me), 7.59 (1H, d, J = 7.6, Ar), 7.70 (1H, t, 8.0, Ar), 7.81 (1H, s, C=CH), 7.86 (1H, t, J = 7.6, Ar), 8.20 (1H, d, J = 8.0, Ar), 12.75 (1H, s, COOH). 13C NMR (DMSO-d6, 100 MHz) δ 13.73 (Me), 124.60 (Ar), 129.47 (Ar), 130.52 (C=C), 130.91 (Ar), 131.33 (Ar), 133.75 (Ar), 147.56 (Ar), 168.53 (C=O).

(E)-2-methyl-3-(2-nitro-4-(trifluoromethyl)phenyl)acrylic acid (144d)
A solution of 143d (850 mg, 2.8 mmol) in THF (24 mL) was treated with 1M NaOH solution (8.4 mL) and EtOH (6 mL) and stirred at 40 ºC overnight. The organic solvents were removed under reduced pressure and the pH of the remaining aqueous solution was adjusted to pH 4 with 10% HCl. The resulting suspension was diluted with water and extracted with EtOAc (3 × 50 mL), the organic phase dried over MgSO4, and the solvent removed under reduced pressure to give 131d as a pale yellow solid (757 mg, 98%). Rf = 0.14 (4% MeOH in DCM). Mp = 144-146 ºC.
\[^{1}\text{H} \text{NMR (DMSO-}d_6, 400 \text{ MHz)} \delta 1.89 (3\text{H, s, Me}), 7.81 (3\text{H, s, C=CH}), 7.84 (1\text{H, d, J = 8.1, Ar}), 8.23 (1\text{H, dd, J = 8.2, 1.3, Ar}), 8.53 (1\text{H, d, J = 8.2, Ar}), 12.89 (1\text{H, br s, COOH}). \]^\text{13}\text{C NMR (DMSO-}d_6, 100 \text{ MHz)} \delta 13.80 (\text{Me}), 121.82 (\text{Ar}), 124.27 (\text{CF}_3), 129.27 (\text{C=C}), 129.60 (\text{Ar}), 130.04 (\text{Ar}), 132.07 (\text{Ar}), 133.32 (\text{C=C}), 135.11 (\text{Ar}), 147.78 (\text{Ar}), 168.24 (\text{C=O}). \text{ IR (KBr) 3093-2877s (O-H), 1702s (C=O), 1273s (C-F). [Found (ESI–) 274.0320 [M-H]–, C}_{11}\text{H}_{7}\text{F}_3\text{NO}_4 \text{ requires 274.0327].}

\text{(E)-3-(4-(dimethylamino)-2-nitrophenyl)-2-methylacrylic acid (144e)}

A solution of 143e (800 mg, 2.9 mmol) in THF (24 mL) was treated with 1M NaOH solution (8.6 mL) and EtOH (6 mL) and stirred at 40 °C overnight. The organic solvents were removed under reduced pressure and the pH of the remaining aqueous solution was adjusted to pH 4 with 10% HCl. The resulting suspension was diluted with water (50 mL) and extracted with EtOAc (2 × 150 mL), the organic phase dried over MgSO\(_4\), and the solvent removed under reduced pressure to give 144e as an orange solid (700 mg, 97%). \(R_f = 0.45\) (6% MeOH in DCM). Mp = 198-201 °C. \[^{1}\text{H} \text{NMR (DMSO-}d_6, 400 \text{ MHz)} \delta (1.94, 3\text{H, d, J = 1.4, Me}), 3.07 (6\text{H, s, NMe}_2), 7.11 (1\text{H, dd, J = 8.8, 2.7, Ar}), 7.32 (1\text{H, d, J = 2.7, Ar}), 7.42 (1\text{H, d, J = 8.8, Ar}), 7.65 (1\text{H, d, J = 1.4, C=CH}), 12.51 (1\text{H, br s, COOH}). \]^\text{13}\text{C NMR (DMSO-}d_6, 100 \text{ MHz)} \delta 13.87 (\text{Me}), 40.18 (\text{NMe}_2), 106.21 (\text{Ar}), 115.81 (\text{Ar}), 116.13 (\text{Ar}), 128.02 (\text{C=C}), 131.80 (\text{Ar}), 134.07 (\text{C=C}), 149.41 (\text{Ar}), 150.17 (\text{Ar}), 169.00 (\text{C=O}). \text{ [Found (ESI+) 251.1016 [M+H]^+}, \text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_4 \text{ requires 251.1032].}
(E)-3-(2-amino-4,5-dimethoxyphenyl)-2-methylacrylic acid (145a)

*Method A:*

A vigorously stirred mixture of iron powder (1.26 g, 22.3 mmol) and ferrous sulfate heptahydrate (657 mg, 2.25 mmol) in water (50 mL) was treated with 144a (600 mg, 2.25 mmol) and heated at reflux for 3 h. Upon cooling the iron was removed by filtering the mixture through celite. The filtrate was extracted with EtOAc (2 x 100 mL), the organic layers were combined and the solvent removed under reduced pressure to yield the crude product as a brown solid. The crude was purified by column chromatography eluting with 5% MeOH in DCM to give 145a as a yellow solid (295 mg, 55%). $R_f = 0.52$ (10% MeOH in DCM). $^1$H NMR (CDCl$_3$, 270 MHz) $\delta$ 2.07 (3H, s, Me), 3.81 (3H, s, OMe), 3.85 (3H, s, OMe), 5.29 (2H, s, NH$_2$), 6.30 (1H, s, Ar), 6.73 (1H, s, Ar), 7.73 (1H, s, CH=C).

*Method B:*

Adapted from the method according to Jung and Park. A solution of 144a (1.00 g, 3.74 mmol), iron powder (1.4 g, 26.2 mmol) and AcOH (12 mL) in 66% aqueous EtOH (18 mL) was heated at reflux for 1 h. The reaction mixture was filtered through celite and concentrated down under reduced pressure to remove the EtOH. The resulting suspension was diluted with water, extracted with EtOAc (4 $\times$ 80 mL) and the organic layer dried over MgSO$_4$. The volatiles were removed under reduced pressure to give a residue which was co-evaporated with MeCN, toluene and then CHCl$_3$ to remove traces of AcOH, which gave 145a as a dark yellow solid (521 mg, 60%). $R_f = 0.34$ (8% MeOH in DCM). $\text{Mp} = 159-161 \, ^\circ\text{C}$.$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.08 (3H, s, Me), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 6.30 (1H, s, Ar), 6.74 (1H, s, Ar), 7.73 (1H, s, HC=C). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 14.01 (Me), 55.75 (OMe), 56.57 (OMe), 100.23 (Ar), 112.28 (Ar), 113.16 (Ar), 126.50 (C=C), 136.75 (C=C), 139.87 (Ar), 141.62 (Ar), 150.89 (Ar), 173.68 (COOH). IR (KBr) 3407s (N-H), 3194-3829 (O-H). [Found (ESI+) 238.1066 [M+H]$^+$, C$_{12}$H$_{16}$NO$_4$ requires 238.1079].
(E)-3-(6-aminobenzo[d][1,3]dioxol-5-yl)-2-methylacrylic acid (145b)

**Method A:**
A vigorously stirred mixture of iron powder (3.30 g, 55.97 mmol) and ferrous sulfate heptahydrate (1.78 g, 6.42 mmol) in water (110 mL) was treated with 144b (1.51 g, 5.97 mmol) and heated at reflux for 3 h. Upon cooling the iron was removed by filtering the mixture through celite. The filtrate was extracted with EtOAc (2 x 100 mL) and the solvent removed from the organic phase to yield crude product as a brown solid. The crude was purified by column chromatography eluting with 5% MeOH in DCM to give 145b as a yellow solid (365 mg, 28%). Rf = 0.50 (10% MeOH in DCM).

\[ ^1H \text{ NMR (Acetone-d}_6, \text{ 270 MHz)} \delta 2.03 (3\text{H, s, Me}), 6.01 (2\text{H, s, H}_2\text{C}), 6.25 (1\text{H, s, Ar}), 6.93 (1\text{H, s, Ar}), 7.46 (1\text{H, s, CH=C}). \]

**Method B:**
Adapted from the method according to Jung and Park. A solution of 144b (300 mg, 1.19 mmol), iron powder (466 mg, 26.2 mmol) and AcOH (3.6 mL) in 66% aqueous EtOH (5.4 mL) was heated at reflux for 1h. The reaction mixture was filtered through celite and the EtOH removed under reduced pressure. The resulting mixture was diluted with water, extracted with EtOAc (4 x 40 mL) and the organic layer dried over MgSO₄. The volatiles were removed under reduced pressure and the residue was co-evaporated with MeCN/toluene (1:1) and then CHCl₃ to remove traces of AcOH. This gave 145b as a dark yellow solid (220 mg, 84%) which was pure by NMR. Rf = 0.10 (8% MeOH in DCM). Mp = 191-194 °C. \[ ^1H \text{ NMR (DMSO-d}_6, \text{ 400 MHz)} \delta 1.99 (3\text{H, s, Me}), 5.03 (2\text{H, s, NH}_2), 5.93 (2\text{H, s, CH}_2), 6.42 (1\text{H, s, Ar}), 6.73 (1\text{H, s, Ar}), 7.50 (1\text{H, s, HC=C}), 12.24 (1\text{H, s, COOH}). \]

\[ ^13C \text{ NMR (DMSO-d}_6, \text{ 100 MHz)} \delta 14.25 (\text{Me}), 96.80 (\text{Ar}), 100.36 (\text{CH}_2), 108.29 (\text{Ar}), 111.33 (\text{Ar}), 125.37 (\text{CH=C}), 134.74 (\text{CH=C}), 138.21 (\text{Ar}), 143.55 (\text{Ar}), 148.34 (\text{Ar}), 169.72 (\text{C=O}). \]

IR (KBr) 3418s (N–H), 3243-2900s (O–H). [Found (ESI–) 220.0613 [M–H]–, C₁₁H₁₀NO₄ requires 220.0610].
A solution of 144c (500 mg, 2.41 mmol) in glacial AcOH (6 mL) and 66% EtOH (9 mL) was treated with Iron powder (940 mg, 16.9 mmol) and stirred at reflux for 75 min. The cooled reaction mixture was filtered through celite, and the celite pad washed thoroughly with EtOH and EtOAc. Removal of volatiles under reduced pressure gave a dark brown residue to which water (70 mL) was added and the mixture was extracted with EtOAc (2 × 70 mL). The combined organic layers were dried over Na₂SO₃ and volatiles removed under reduced pressure to give 145c as a dark yellow solid (422 mg, 99%). Rᵣ = 0.32 (6% MeOH in DCM). Mp = 99-102 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 1.97 (3H, s, Me), 5.11 (2H, br s, NH₂), 6.63 (1H, t, J = 7.3, Ar), 6.76 (1H, d, J = 7.8, Ar), 7.06-7.11 (2H, m, Ar), 7.55 (1H, s, C=CH), 12.35 (1H, br s, COOH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 14.23 (Me), 115.16 (Ar), 115.67 (Ar), 119.67 (Ar), 128.00 (C=C), 129.19 (Ar), 129.37 (Ar), 134.92 (C=C), 146.90 (Ar), 169.48 (C=O).

A solution of 144d (740 mg, 2.69 mmol) in glacial AcOH (8 mL) and 66% EtOH (12 mL) was treated with Iron powder (1.05 g, 18.8 mmol) and stirred at reflux for 70 min. The cooled reaction mixture was filtered through celite, and the celite pad washed thoroughly with EtOH. Removal of volatiles under reduced pressure gave a black residue to which water (40 mL) was added and the mixture extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with water (40 mL), dried over Na₂SO₃ and the solvent removed under reduced pressure to give the crude product as a black oil which was purified by column chromatography eluting with 10% MeOH in DCM to give 145d as a dark brown solid (543 mg, 82%). Rᵣ = 0.47 (10% MeOH in DCM). Mp = 161-165 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 1.95 (3H, s, Me), 5.62 (2H, s, NH₂), 6.89 (1H, d, J = 7.1, Ar), 7.07 (1H, s, C=CH), 7.27 (1H, d, J =7.1, Ar),
7.50 (1H, s, Ar), 12.51 (1H, br s, COOH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 14.19 (Me), 110.87 (Ar), 111.28 (Ar), 123.10 (CF$_3$), 125.70 (C=C), 129.21 (Ar), 129.52 (Ar), 130.26 (Ar), 133.52 (C=C), 147.34 (Ar), 169.09 (C=O). IR (KBr) 3403s (N-H), 2985-2634s (O-H), 1680s (C=O), 1340s (C-F). [Found (ESI-) 244.0598 [M-H]$^-$, C$_{11}$H$_9$F$_3$NO$_2$ requires 244.0585].

(E)-3-(2-amino-4-(dimethylamino)phenyl)-2-methylacrylic acid (145e)

A solution of 144e (600 mg, 2.4 mmol) in glacial AcOH (7 mL) and 66% EtOH (12 mL) was treated with Iron powder (930 mg, 16.8 mmol) and stirred at reflux for 50 min. TLC analysis showed disappearance of starting material but extensive side-product formation. The cooled reaction mixture was filtered through celite, and the celite pad washed thoroughly with EtOH and EtOAc. Removal of volatiles under reduced pressure gave a dark brown residue to which water (100 mL) was added and the mixture was extracted with EtOAc (2 × 80 mL). The combined organic layers were dried over Na$_2$SO$_3$ and volatiles removed under reduced pressure to give a brown oil which was purified by column chromatography eluting with 2-6% MeOH in DCM; however analysis by $^1$H NMR showed a mixture of compounds with the expected product not observed.
(E)-2-((E)-(2-isonicotinoylhydrazono)methyl)phenyl-3-(2-amino-4,5-dimethoxy phenyl)-2-methyl acrylate (148a)

**Method A:**
A solution of 145a (150 mg, 0.63 mmol) in anhydrous DMF (5 mL) and under an N\textsubscript{2} atmosphere was chilled to 0 °C and treated with EDC hydrochloride (121 mg, 0.63 mmol) and DMAP (77 mg, 0.63 mmol). After 10 min a solution of SIH (121 mg, 0.40 mmol) in anhydrous DMF (5 mL) was added and the reaction was stirred overnight at RT under N\textsubscript{2} atmosphere. The DMF was removed under reduced pressure and the crude product was dissolved in DCM (10 mL) and purified by column chromatography, eluting with 2% MeOH in DCM + 0.1% pyridine to give 148a as a bright yellow solid (134 mg, 73%).

**Method B:**
A solution of 145a (300 mg, 1.26 mmol) in anhydrous DMF (15 mL) and under an N\textsubscript{2} atmosphere was chilled to 0 °C and treated with EDC hydrochloride (242 mg, 1.26 mmol) and DMAP (154 mg, 1.26 mmol). After 10 min a solution of SIH (200 mg, 0.84 mmol) and DIPEA (96 µL, 0.84 mmol) in anhydrous DMF (5 mL) was added and the reaction was stirred overnight at RT under N\textsubscript{2} atmosphere. The DMF was removed under reduced pressure and the crude product was dissolved in DCM (10 mL) and purified by column chromatography, eluting with 2% MeOH in DCM + 0.1% pyridine to give 148a as a bright yellow solid (305 mg, 79%). \( R_t = 0.42 \) (5% MeOH in DCM). Mp = 115-118 °C. UV (EtOH): \( \lambda_{\text{max}} \) 270 (27243), 298 (29547). \(^1\text{H} \) NMR (DMSO-\textit{d}_6, 400 MHz) \( \delta \) 2.18 (3H, s, Me), 3.66 (3H, s, OMe), 3.72 (3H, s, OMe), 5.13 (2H, s, NH\textsubscript{2}), 6.43 (1H, s, Ar), 6.81 (1H, s, Ar), 6.91-6.94 (1H, m, Ar), 7.25 (1H, d, J = 8.0, Ar), 7.30 (1H, t, J = 7.7, Ar), 7.37 (1H, t, J = 7.6, Ar), 7.52 (1H, t, J = 7.9, Ar), 7.58 (1H, d, J = 7.6, Ar), 7.87 (2H, m, Ar), 8.00 (1H, d, J = 7.8, Ar), 8.55 (1H, s, HC=C), 8.67 (1H, s, HC=N), 12.08 (1H, s, NH). \(^{13}\text{C} \) NMR (DMSO-\textit{d}_6, 100 MHz) \( \delta \) 14.60 (Me),
55.19 (OMe), 56.53 (OMe), 100.05 (Ar), 110.15 (Ar), 114.15 (Ar), 116.44 (Ar), 118.67 (Ar), 119.41 (Ar), 122.14 (Ar), 123.49 (Ar), 126.16 (Ar), 126.38 (Ar), 126.70 (Ar), 129.26 (Ar), 131.26 (Ar), 131.70 (Ar), 137.82 (Ar), 139.97 (Pyr), 143.62 (Ar), 143.71 (C=C), 149.07 (C=N), 150.08 (Ar), 151.64 (Ar), 157.48 (Ar), 161.72 (C=O), 166.90 (C=O). IR (KBr) 3371m (N-H), 2943w (C-H), 1708s (C=O).


(E)-2-((E)-(2-isonicotinoylhydrazono)methyl)phenyl-3-(6-aminobenzo[d][1,3]-dioxol-5-yl)-2-methylacrylate (148b)

Method A:
A solution of 145b (300 mg, 1.36 mmol) in anhydrous DMF (30 mL) under an N2 atmosphere was chilled to 0 ºC. EDC hydrochloride (221 mg, 1.40 mmol) and DMAP (17 mg, 0.14 mmol) were then added. After 10 min, SIH (269 mg, 1.12 mmol) was added and the reaction mixture was stirred at RT for a further 3 days. The DMF was removed under reduced pressure and the resulting crude purified by column chromatography eluting with 1-2% MeOH in DCM + 0.1% pyridine to give a mixture of SIH and coupled product 148b as a dark yellow solid (79 mg, 26%). Rf = 0.50 (5% MeOH in DCM). Mp = 201-209 ºC. 1H NMR (DMSO-d6, 400 MHz) δ 2.18 (3H, s, Me), 5.27 (2H, s, NH2), 5.94 (2H, s, CH2), 6.44 (1H, s, Ar), 6.83 (1H, s, Ar), 6.95 (1H, d, J = 9.0, Ar), 7.30 (2H, m, Ar), 7.41 (1H, t, J = 8.0, Ar), 7.56 (1H, t, J = 7.2, Ar), 7.81 (2H, d, J = 5.9, Pyr), 7.85 (1H, s, CH=H), 8.57 (1H, s, CH=H), 8.80 (2H, d, J = 5.9, Pyr), 12.1 (1H, s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 14.53 (Me), 96.87 (Ar), 100.62 (CH2), 108.07 (Ar), 110.54 (Ar), 116.44 (Ar), 118.67 (Ar), 119.41 (Ar), 121.52 (Ar), 122.49 (Ar), 123.50 (Ar), 126.17 (Ar), 131.27 (Ar), 137.75 (Ar), 138.47 (Ar), 143.61 (C=C), 144.61 (C=N), 149.06 (Ar), 149.26 (Ar), 150.37 (Ar), 157.48 (Ar), 161.33 (Ar), 161.71 (C=O), 166.84 (C=O).
Method B:

A solution of 145b (136 mg, 0.62 mmol) in anhydrous DMF (8 mL), under argon atmosphere was chilled to 0 ºC and treated with EDC hydrochloride (120 mg, 0.62 mmol) and DMAP (76 mg, 0.62 mmol). The mixture was stirred for 10 min, followed by addition of a solution of SIH (100 mg, 0.41 mmol) and DIPEA (71 μL, 0.41 mmol) in anhydrous DMF (2 mL). The resulting mixture was heated to 30 ºC and stirred for 2 days. The DMF was removed under reduced pressure, and the resulting residue dissolved in DCM (10 mL) and washed with saturated aqueous NH₄Cl solution (3 × 30 mL). The organic layer was dried over MgSO₄, concentrated down under reduced pressure and purified by column chromatography eluting with 2-4% MeOH in DCM + 0.1% pyridine to give 148b as an orange-yellow solid (130 mg, 71%). Rf = 0.39 (8% MeOH in DCM). Mp = 109-111 ºC. UV (EtOH): λmax 300 (23211). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.22 (3H, d, J = 1.1, Me), 5.36 (2H, s, NH₂), 5.82 (2H, s, CH₂), 6.47 (1H, s, Ar), 6.88 (1H, s, Ar), 7.34 (1H, d, J = 8.2, Ar), 7.46 (1H, t, J = 7.5, Ar), 7.60 (1H, td, J = 8.1, 1.7, Ar), 7.86 (2H, d, J = 6.0, Pyr), 7.90 (1H, d, J = 1.1, CH=C), 8.07 (1H, dd, J = 7.9, 1.6, Ar), 8.61 (1H, s, CH=N), 8.84 (2H, d, J = 6.0, Pyr), 12.19 (1H, s, NH). IR (KBr) 3452m (N-H), 2908m (C-H), 1721m (C=O), 1658s (C=N). [Found (ESI+) 445.1511 [M+H]+, C₂₄H₂₁N₄O₅ requires 445.1512].

(E)-5-((tert-butyldiphenylsilyloxy)methyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2-amino-4,5-dimethoxyphenyl)-2-methylacrylate (149a)

A solution of 145a (418 mg, 2.30 mmol) in anhydrous DMF (15 mL), under argon atmosphere was chilled to 0 ºC and treated with EDC hydrochloride (330 mg, 2.30 mmol) and DMAP (210 mg, 2.30 mmol). The mixture was stirred for 10 min, followed by the addition of 117 (600 mg, 1.52 mmol) in a solution of anhydrous DMF (5 mL) and DIPEA (0.2 mL, 1.52 mmol). The resulting mixture was allowed to return to RT
and stirred overnight. The DMF was removed under reduced pressure, and the resulting residue dissolved in DCM (50 mL) and washed with saturated aqueous NH₄Cl solution (3 × 50 mL). The organic layer was dried over MgSO₄, concentrated down under reduced pressure and purified by column chromatography eluting with 4-20% acetone in DCM to give 149a as yellow solid (604 mg, 53%). Rf = 0.76 (20% acetone in DCM). Mp = 112-116 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 1.15 (9H, s, Me₃), 2.14-2.29 (2H, m, Me), 2.43-2.47 (3H, m, Pyr-Me), 3.71-3.83 (6H, m, 2 × OMe), 5.28-5.31 (2H, m, CH₂), 6.45-6.50 (1H, m, Ar), 7.14 (1H, s, Ar), 7.47-7.52 (8H, m, Ar), 7.72-7.81 (7H, m, Ar), 8.56-8.60 (1H, m, HC=N), 8.82 (3H, s, Ar), 12.31-12.33 (1H, m, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 14.66 (Me), 18.92 (Pyr-Me), 19.23 (Si-C), 26.73 (Me₃), 55.10 (OMe), 56.27 (OMe), 62.81 (OCH₂), 99.85 (Ar), 109.91 (Ar), 113.77 (Ar), 121.28 (C=C), 121.55 (Pyr), 128.01 (Ph), 129.97 (Ar), 130.58 (Ar), 132.63 (Ar), 132.83 (Ar), 134.99 (Ph), 138.29 (Ar), 139.87 (Ar), 140.02 (Ar), 142.40 (Ar), 143.83 (Ar), 143.92 (Ar), 144.05 (C=N), 150.36 (Pyr), 151.04 (Ar), 151.65 (Ar), 161.73 (C=O), 166.33 (C=O). IR (KBr) 3439-3360m (N-H), 2934m (C-H), 1706s (C=O), 1609s (C=N). [Found (ESI+) 744.3224 [M+H]⁺, C₄₂H₄₆N₅O₆Si requires 744.3217]. Rₜ (HPLC) = 8.87 min.

(E)-5-((tert-butyldimethylsilyloxy)methyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(6-aminobenzo[d][1,3]dioxol-5-yl)-2-methylacrylate (149b)

A solution of 145b (400 mg, 1.80 mmol) in anhydrous DMF (15 mL), under argon atmosphere was chilled to 0 °C and treated with EDC hydrochloride (340 mg, 1.80 mmol) and DMAP (220 mg, 1.80 mmol). The mixture was stirred for 10 min, followed by the addition of 117 (640 mg, 1.22 mmol) in a solution of anhydrous DMF (5 mL) and DIPEA (0.2 mL). The resulting mixture was allowed to return to RT and stirred overnight. The DMF was removed under reduced pressure, and the resulting residue
dissolved in DCM (30 mL) and washed with saturated aqueous NH₄Cl solution (3 × 30 mL). The organic layer was dried over MgSO₄, concentrated down under reduced pressure and purified by column chromatography eluting with 4-20% acetone in DCM + 0.1% pyridine to give 149b as a yellow solid (230 mg, 56%). Rᵣ = 0.72 (20% acetone in DCM). Mp = 99-103 ºC. ¹H NMR (CD₃OD, 400 MHz) δ 1.11 (9H, s, Me₃), 2.16-2.22 (3H, m, Me), 2.41-2.45 (3H, m, Pyr-Me), 5.21-5.23 (2H, m, OCH₂), 5.86 (2H, s, O₂CH₂), 6.36-6.41 (1H, m, Ar), 6.79 (1H, s, Ar), 7.36-7.42 (8H, m, Ar), 7.68 (4H, d, J = 7.5, Ar), 7.77 (2H, d, J = 5.9, Pyr), 7.97 (1H, s, C=CH), 8.55 (1H, s, Ar), 8.58 (1H, s, HC=N), 8.69 (2H, br s, Pyr). ¹³C NMR (CD₃OD, 100 MHz) δ 14.85 (Me), 19.11 (Pyr-Me), 20.17 (Si-C), 27.43 (Me₃), 63.80 (OCH₂), 98.83 (OCH₂), 102.33 (Ar), 109.46 (Ar), 113.78 (Ar), 123.19 (Pyr), 125.12 (C=C), 128.99 (Ph), 131.09 (Ar), 133.57 (Ar), 134.35 (Ar), 135.47 (Ar), 136.72 (Ph), 139.92 (C=C), 141.41 (Ar), 142.32 (Ar), 144.52 (C=N), 144.70 (Ar), 145.80 (Ar), 151.13 (Pyr), 152.79, 164.19 (C=O), 168.04 (C=O). IR (KBr) 3443-3374m (N-H), 2928m (C-H), 1718s (C=O), 1671s (C=N). [Found (ESI+) 728.2905 [M+H]⁺, C₄₁H₄₂N₅O₆Si requires 728.2905]. Rᵣ (HPLC) = 9.22 min.

(E)-5-((tert-butyldiphenylysilyloxy)methyl)-4-((E)-2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2-aminophenyl)-2-methylacrylate (149c)

A solution of 145c (150 mg, 0.85 mmol) in anhydrous DMF (5 mL), under argon atmosphere was chilled to 0 ºC and treated with EDC hydrochloride (163 mg, 0.85 mmol) and DMAP (104 mg, 0.85 mmol). The mixture was stirred for 10 min, followed by the addition of 117 (320 mg, 0.61 mmol) in a solution of anhydrous DMF (5 mL) and DIPEA (0.1 mL). The resulting mixture was stirred at RT overnight. The DMF was removed under reduced pressure, and the resulting residue dissolved in DCM (30 mL) and washed with saturated aqueous NH₄Cl solution (2 × 30 mL) and water (40 mL). The organic layer was dried over Na₂SO₄, concentrated down under
reduced pressure and purified by column chromatography eluting with 5-30% Acetone in DCM + 0.1% pyridine to give 149c as a pale yellow solid (341 mg, 82%). Rf = 0.34 (20% acetone in DCM). Mp = 81-84 °C. 1H NMR (DMSO-d6, 400 MHz) δ 1.15 (9H, s, Me3), 2.22 (3H, s, Me), 2.48 (3H, s, Pyr-Me), 5.30 (2H, s, OCH2), 5.39 (2H, s, NH2), 6.70 (1H, t, J = 7.4, Ar), 6.82 (1H, d, J = 7.8, Ar), 7.16 (1H, t, J = 7.4, Ar), 7.26 (1H, d, J = 7.8, Ar), 7.46-7.54 (6H, m, Ph), 7.73 (4H, d, J = 6.5, Ph), 7.82 (2H, d, J = 5.0, Pyr), 7.95 (1H, s, C=CH), 8.60 (1H, s, N=CH), 8.83 (2H, d, J = 5.0, Pyr), 12.28 (1H, s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 14.51 (Me), 18.90 (Pyr-Me), 19.21 (Si-C), 26.73 (Me3), 62.64 (OCH2), 115.51 (Ar), 115.74 (Ar), 118.72 (Ar), 121.53 (Pyr), 122.88 (Ar), 125.07 (C=C), 126.88 (Ar), 127.98 (Ph), 129.65 (Ar), 129.95 (Ph), 130.66 (Ar), 132.84 (Pyr), 134.99 (Ph), 138.53 (C=C), 140.04 (Pyr), 142.36 (C=N), 143.54 (Pyr), 144.35 (Pyr), 147.52 (Ar), 150.36 (Pyr), 151.06 (Pyr), 161.75 (C=O), 165.98 (C=O). IR (KBr) 3361m (N-H), 3214m (O-H), 2932m (C-H), 1727s (C=O), 1669s (C=N). [Found (ESI+) 684.3021 [M+H]+, C40H42N5O4Si requires 684.3006].

(E)-5-((tert-butyldiphenylsilyloxy)methyl)-4-((E)-2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(2-amino-4-(trifluoromethyl)phenyl)-2-methyl acrylate (149d)

A solution of 145d (280 mg, 1.14 mmol) in anhydrous DMF (8 mL), under argon atmosphere was chilled to 0 °C and treated with EDC hydrochloride (220 mg, 1.14 mmol) and DMAP (140 mg, 1.14 mmol). The mixture was stirred for 10 min, followed by the addition of 117 (400 mg, 0.76 mmol) in a solution of anhydrous DMF (7 mL) and DIPEA (0.15 mL). The resulting mixture was stirred at RT overnight. The DMF was removed under reduced pressure, and the resulting residue dissolved in DCM (40 mL) and washed with saturated aqueous NH4Cl solution (2 × 40 mL). The organic layer was dried over MgSO4, concentrated down under reduced pressure and purified by column chromatography eluting with 6-20% Acetone in DCM + 0.1%
pyridine to give 149d as a pale yellow solid (240 mg, 42%). \( R_f = 0.46 \) (20% acetone in DCM). \( \text{Mp} = 77-79 \degree \text{C}. \) \( ^1\text{H NMR (DMSO-d}_6, \text{400 MHz)} \ \delta \ 1.14 \ (9\text{H, s, Me}_3), \ 2.20 \ (3\text{H, s, Me}), \ 2.49 \ (3\text{H, s, Pyr-Me}), \ 5.27 \ (2\text{H, s, CH}_2), \ 5.84 \ (2\text{H, s, NH}_2), \ 6.95 \ (1\text{H, d, J = 8.2, Ar}), \ 7.13 \ (1\text{H, s, Ar}), \ 7.43 \ (1\text{H, d, J = 7.1, Ar}), \ 7.49-7.50 \ (6\text{H, m, Ph}), \ 7.73 \ (4\text{H, d, J = 6.5, Ph}), \ 7.82 \ (2\text{H, d, J = 4.4, Pyr}), \ 7.88 \ (1\text{H, s, C=CH}), \ 8.60 \ (1\text{H, s, HC=N}), \ 8.76 \ (1\text{H, s, Pyr}), \ 8.84 \ (2\text{H, d, J = 4.4, Pyr}), \ 12.27 \ (1\text{H, s, NH}). \) \( ^{13}\text{C NMR (DMSO-d}_6, \text{100 MHz)} \ \delta \ 14.50 \ (\text{Me}), \ 18.89 \ (\text{Pyr-Me}), \ 19.21 \ (\text{SiC}), \ 26.71 \ (\text{Me}_3), \ 62.44 \ (\text{CH}_2), \ 111.36 \ (\text{Ar}), \ 111.29 \ (\text{Ar}), \ 121.51 \ (\text{Pyr}), \ 125.61 \ (\text{C=C}), \ 127.99 \ (\text{Ph}), \ 129.71 \ (\text{Ph}), \ 130.60 \ (\text{Ar}), \ 132.79 \ (\text{Ar}), \ 134.99 \ (\text{Ph}), \ 136.94 \ (\text{C=C}), \ 142.32 \ (\text{C=N}), \ 147.68 \ (\text{Pyr}), \ 150.38 \ (\text{Pyr}), \ 162.85 \ (\text{C=O}), \ 165.57 \ (\text{C=O}). \) \( \text{IR (KBr) 3393w (N-H), 2930m (C-H), 1678s (C=O).} \) \( [\text{Found (ESI+) 776.2771 [M+Na}]^+], \text{C}_{41}\text{H}_{42}\text{F}_3\text{N}_5\text{Na}_4\text{Si} \text{requires 776.2850}]. \)

(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl 3-(2-amino-4,5-dimethoxyphenyl)-2-methylacrylate (150a)

A solution of TBAF trihydrate (378 mg, 1.20 mmol) and AcOH (55 \( \mu \text{L}) \text{ in THF (11 mL)} \text{ was treated with 149a (300 mg, 0.40 mmol). The reaction mixture was stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with water (2 \( \times \) 60 mL), and saturated NH\(_4\)Cl solution (1 \( \times \) 30 mL), and the organic layers were combined and dried over Na\(_2\)SO\(_3\). Removal of solvent under reduced pressure gave the crude product which was purified by column chromatography eluting with 3-9\% MeOH in DCM + 0.1\% pyridine to give 150a as a yellow solid (60 mg, 50\%). \( R_f = 0.19 \) (4\% MeOH in DCM). \( \text{Mp} = 189-193 \degree \text{C}. \) \( \text{UV (EtOH): } \lambda_{\text{max}} 299 \ (30103). \) \( ^1\text{H NMR (DMSO-d}_6, \text{400 MHz)} \ \delta \ 2.27 \ (3\text{H, s, Me}), \ 2.45 \ (3\text{H, s, PyrMe}), \ 3.73 \ (3\text{H, s, OMe}), \ 3.79 \ (3\text{H, s, OMe}), \ 4.82 \ (2\text{H, d, J = 6.0, CH}_2), \ 5.21 \ (2\text{H, br s, NH}_2), \ 5.45 \ (1\text{H, t, J = 6.0, OH}), \ 6.50 \ (1\text{H, s, Ar}), \ 6.91 \ (1, s, Ar), \ 7.87 \ (2\text{H, d, J = 5.2, Pyr}), \ 7.96 \ (1\text{H, s, Ar}), \ 8.62 \ (1\text{H, s, HC=N}), \ 8.67 \ (1\text{H, s, Pyr}), \ 8.86 \ (2\text{H, d, J = 5.2, Pyr}), \ 12.49 \ (1\text{H, s, NH}). \)}
13C NMR (DMSO-d6, 100 MHz) δ 14.63 (Me), 19.19 (PyrMe), 55.16 (OMe), 56.42 (OMe), 59.94 (CH2), 100.00 (Ar), 110.11 (Ar), 114.06 (Ar), 121.53 (Pyr), 121.69 (C=C), 131.55 (Pyr), 133.95 (Pyr), 138.16 (HC=C), 139.78 (Ar), 139.96 (Pyr), 142.74 (Pyr), 143.79 (Pyr), 143.85 (Pyr), 145.99 (C=N), 150.40 (Pyr), 151.20 (Pyr), 151.66 (Ar), 162.12 (C=O), 166.33 (C=O). IR (KBr) 3470-3420s (N-H), 3209s (O-H), 1721s (C=O), 1676s (C=N).

[Found (ESI+) 506.2058 [M+H]+, C26H28N5O6 requires 506.2040].

(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin-3-yl-3-(6-aminobenzo[d][1,3]dioxol-5-yl)-2-methylacrylate (150b)
A solution of TBAF trihydrate (600 mg, 1.94 mmol) and AcOH (98 μL) in THF (15 mL) was treated with 149b (470 mg, 0.65 mmol). The reaction mixture was stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with water (2 × 100 mL), and saturated NH4Cl solution (1 × 50 mL), and the organic layers were combined and dried over Na2SO3. Removal of solvent under reduced pressure gave the crude product (540 mg) which was purified by column chromatography eluting with 3-9% MeOH in DCM + 0.1% pyridine to give 150b as an orange solid (201 mg, 63%). Rf = 0.14 (4% MeOH in DCM). Mp = 157-162 ºC. UV (EtOH): λmax 299 (30362). 1H NMR (DMSO-d6, 400 MHz) δ 2.24 (3H, s, Me), 2.44 (3H, s, Pyr-Me), 4.82 (2H, d, J = 6.1, CH2), 5.31 (2H, s, NH2), 5.44 (1H, t, J = 6.1, OH), 5.98 (2H, s, H2C), 6.48 (1H, s, Ar), 6.90 (1H, s, Ar), 7.89 (2H, d, J = 5.5, Pyr), 7.92 (1H, s, HC=C), 8.61 (1H, s, Pyr), 8.66 (1H, s, HC=N), 8.85 (2H, br d, Pyr), 12.49 (1H, br s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 14.57 (Me), 19.18 (Pyr-Me), 59.95 (CH2), 96.89 (Ar), 100.64, (H2C), 108.13 (Ar), 110.54 (Ar), 121.57 (Pyr), 122.05 (C=C), 131.57 (Pyr), 133.95 (Pyr), 138.11 (C=C), 138.49, (Ar), 139.75 (Ar), 142.75 (C=N), 143.84 (Pyr), 144.74 (Ar), 146.00 (Pyr), 149.33 (Ar), 150.40 (Pyr), 151.18 (Pyr), 162.12 (C=O), 166.26 (C=O). IR (KBr) 3362s (N-H), 3223s (O-H), 1699s (C=N). [Found (ESI+) 490.1732 [M+H]+, C25H23N5O6 requires 490.1727].
(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methylpyridin -3-yl-3-(2-aminophenyl)-2-methylacrylate (150c)

A solution of TBAF trihydrate (270 mg, 0.86 mmol) and AcOH (42 μL) in THF (8 mL) was treated with 149c (200 mg, 0.29 mmol). The reaction mixture was stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with saturated NH₄Cl solution (40 mL) and water (40 mL) and the organic layers were combined and dried over Na₂SO₃. Removal of solvent under reduced pressure gave the crude product (217 mg) which was purified by column chromatography eluting with 3-6% MeOH in DCM + 0.1% pyridine to give 150c as a light yellow solid (69 mg, 53%). Rf = 0.47 (8% MeOH in DCM). Mp = 269-271 °C. UV (EtOH): λmax 286 (27412). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.22 (3H, s, Me), 2.46 (3H, s, Pyr-Me), 4.82 (2H, d, J= 5.9, CH₂), 5.40 (2H, s, NH₂), 5.46 (1H, t, J = 5.9, OH), 6.69 (1H, t, J = 7.4, Ar), 6.82 (1H, d, J = 7.8, Ar), 7.16 (1H, t, J = 7.4, Ar), 7.27 (1H, d, J = 7.8, Ar), 7.89 (2H, d, J = 5.0, Pyr), 7.95 (1H, s, C=CH), 8.62 (1H, s, N=CH), 8.69 (1H, s, Pyr), 8.86 (1H, d, J = 5.0, Pyr), 12.50 (1H, s, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 14.52 (Me), 19.18 (Pyr-Me), 59.85 (OCH₂), 115.48 (Ar), 115.73 (Ar), 118.78 (Ar), 121.56 (Pyr), 125.22 (C=C), 129.66 (Ar), 130.10 (Ar), 131.52 (Pyr), 134.02 (Pyr), 138.44 (C=CH), 139.77 (Pyr), 142.71 (C=N), 143.57 (Pyr), 146.12 (Pyr), 147.47 (Ar), 150.40 (Pyr), 151.19 (Pyr), 162.09 (C=O), 166.01 (C=O). IR (KBr) 3371m (N-H), 3249m (O-H), 1694s (C=N), 1281s (C=O). [Found (ESI+) 446.1859 [M+H]+, C₂₄H₂₄N₅O₄ requires 446.1828].
(E)-5-(hydroxymethyl)-4-((E)-(2-isonicotinoylhydrazono)methyl)-2-methyl pyridin-3-yl-3-(2-amino-4-(trifluoromethyl)phenyl)-2-methylacrylate (150d)

A solution of TBAF trihydrate (290 mg, 0.92 mmol) and AcOH (47 μL) in THF (5 mL) was treated with 149d (230 mg, 0.31 mmol). The reaction mixture was stirred at RT overnight, after which volatiles were removed under reduced pressure and the resulting residue dissolved in EtOAc. The mixture was washed with water (3 × 40 mL), and saturated NH₄Cl solution (1 × 40 mL), and the organic layers were combined and dried over Na₂SO₃. Removal of solvent under reduced pressure gave the crude product (240 mg) which was purified by column chromatography eluting with 3-10% MeOH in DCM + 0.1% pyridine to give 150d as a yellow solid (85 mg, 53%). Rᶠ = 0.41 (10% MeOH in DCM). Mp = 220-222 °C. UV (EtOH): λₘₐₓ 239 (28272), 281 (24210). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.16 (3H, s, Me), 2.43 (3H, s, Pyr-Me), 4.76 (2H, d, J = 6.0, CH₂), 5.45 (1H, t, J = 6.0, OH), 5.82 (2H, s, NH₂), 6.91 (1H, d, J = 7.9, Ar), 7.08 (1H, s, Ar), 7.39 (1H, d, J = 7.9, Ar), 7.83 (1H, s, C=CH), 7.84 (2H, d, J = 5.2, Pyr), 8.57 (1H, s, HC=N), 8.64 (1H, s, Pyr), 8.82 (2H, d, J = 5.2, Pyr), 12.44 (1H, s, NH). ¹³C NMR (DMSO-d₆, 100 MHz) δ 14.55 (Me), 19.21 (Pyr-Me), 59.69 (CH₂), 111.17 (Ar), 111.32 (Ar), 121.57 (Pyr), 122.20 (Ar), 125.37 (CF₃), 128.00 (C=C), 130.64 (Ar), 131.40 (Ar), 134.12 (Pyr), 136.85 (C=N), 139.77 (Pyr), 142.74 (C=C), 143.19 (Pyr), 146.26 (Pyr), 147.67 (Ar), 150.43 (Pyr), 151.26 (Pyr), 162.05 (C=O), 165.62 (C=O). IR (KBr) 3375m (N-H), 3267s (O-H), 1699s (C=N), 1339s (C-F). [Found (ESI+) 514.1706 [M+H]+, C₂₅H₂₃F₃N₅O₄ requires 514.1702].
Prepared according to the method reported by Jung and Park. A solution of 6-nitoveratraldehyde (1.00 g, 4.73 mmol), iron powder (1.85 g, 33.1 mmol) and AcOH (12 mL) in 66% aqueous EtOH (18 mL) was stirred at reflux for 5 min and then at RT for a further 15 min. The reaction mixture was filtered through celite, the filtrate diluted with water (60 mL) and then extracted with EtOAc (2 × 60 mL). The organic layer was washed with Sat. NaHCO₃ solution (2 × 60 mL), dried over MgSO₄ and the solvent removed under reduced pressure to give 151a as an orange oil (761 mg, 89%) which was used for the next step without further purification. Rᵣ = 0.15 (DCM). IR 1654 (C=O), 3026 (NH₂). ¹H NMR (CDCl₃, 400 MHz) δ 3.79 (3H, s, OMe), 3.82 (3H, s, OMe), 6.07 (1H, s, Ar), 6.10 (2H, br s, NH₂), 6.83 (1H, s, Ar), 9.64 (1H, s, HC=O). ¹³C NMR (CDCl₃, 100 MHz) δ 55.83 (OMe), 56.50 (OMe), 98.38 (Ar), 111.29 (Ar), 116.15 (Ar), 140.95 (Ar), 147.30 (Ar), 156.17 (Ar), 191.23 (C=O).

A solution of 6-nitropiperonal (2.5 g, 12.8 mmol), iron powder (4.9 g, 89.7 mmol) and AcOH (30 mL) in 66% aqueous EtOH (45 mL) was heated at reflux for 20 min. The reaction mixture was twice filtered through celite, and the filtrate was concentrated down under reduced pressure and then diluted with water (250 mL). The pH was adjusted to pH8 with 1M NaOH and extracted with EtOAc (3 × 100 mL). The organic layer was washed with Sat. NaHCO₃ solution (3 × 150 mL), dried over MgSO₄ and the solvent removed under reduced pressure to give 151b as a dark yellow solid (2.01 g, 95%) which was used for the next step without further purification. Rᵣ = 0.16 (DCM). Mp = 103-107 °C. ¹H NMR (CDCl₃, 400 MHz) δ 5.92 (2H, s, CH₂), 6.13 (1H, s, Ar), 6.27 (2H, s, NH₂), 6.81 (1H, s, Ar), 9.59 (1H, s, HC=O). ¹³C NMR (CDCl₃, 100 MHz) δ 95.91 (Ar), 101.43 (CH₂), 111.48 (Ar), 111.76 (Ar), 139.33 (Ar), 149.16 (Ar), 153.94 (Ar), 190.91 (C=O).
N-(2-formyl-4,5-dimethoxyphenyl)propionamide (152a)\textsuperscript{[171]}

A solution of 151a (54 mg, 0.29 mmol) and anhydrous pyridine (35 µL, 0.41 mmol) in toluene (2.5 mL) was slowly treated with propionyl chloride (38 µL, 0.41 mmol). The reaction mixture was stirred at RT for 20 min and then extracted with 20% HCl (4 × 15 mL). The organic layer was dried over MgSO\textsubscript{4} and removal of volatiles under reduced pressure gave the crude product (61 mg), which was purified by column chromatography eluting with 15-30% EtOAc in petroleum ether to give 152a as a pale yellow solid (66 mg, 96%). R\textsubscript{f} = 0.52 (30% EtOAc in petroleum ether). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 1.26 (3H, t, J = 7.6, Me), 2.48 (2H, q, J = 7.6, CH\textsubscript{2}), 3.90 (3H, s, OMe), 3.98 (1H, s, OMe), 7.08 (1H, s, Ar), 8.50 (1H, s, Ar), 9.74 (1H, s, HC=O), 11.32 (1H, s, NH). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 8.37 (Me), 30.45 (CH\textsubscript{2}), 55.15 (OMe), 55.40 (OMe), 101.90 (Ar), 113.35 (Ar), 115.22 (Ar), 136.69 (Ar), 143.25 (Ar), 154.46 (Ar), 172.60 (C=O) 192.26 (NHCO).

N-(2-formyl-4,5-methylenedioxyphenyl)propionamide (152b)\textsuperscript{[171]}

A solution of 151b (400 mg, 2.42 mmol) and anhydrous pyridine (0.32 mL, 3.64 mmol) in toluene (20 mL) was slowly treated with propionyl chloride (0.3 mL, 3.64 mmol). The reaction mixture was stirred at RT for 20 min and then extracted with 20% HCl (4 × 40 mL). The organic layer was dried over MgSO\textsubscript{4} and removal of volatiles under reduced pressure gave 152b as a pale brown solid (440 mg, 82%) which was pure by NMR. R\textsubscript{f} = 0.52 (30% EtOAc in petroleum ether). Mp = 98-102 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 1.26 (3H, t, J = 7.6, Me), 2.47 (2H, q, J = 7.6, CH\textsubscript{2}), 6.06 (2H, s, O\textsubscript{2}CH\textsubscript{2}), 7.00 (1H, s, Ar), 8.39 (1H, s, Ar), 9.67 (1H, s, HC=O), 11.49 (1H, s, NH). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 8.45 (Me), 30.25 (CH\textsubscript{2}), 100.07 (Ar), 101.29 (O\textsubscript{2}CH\textsubscript{2}), 111.87 (Ar), 114.44 (Ar), 138.44 (Ar), 141.99 (Ar), 153.04 (Ar), 172.41 (NHCO), 191.83 (C=O).
2-(((trimethylsilyl)oxy)methyl)aniline (154)\(^{[172]}\)
A solution of 2-aminobenzyl alcohol (300 mg, 2.44 mmol) and Et\(_3\)N (0.36 mL, 2.56 mmol) in anhydrous THF (8 mL) was treated with chlorotrimethylsilane (0.32 mL, 2.56 mmol) and stirred at RT under N\(_2\) atmosphere overnight. Volatiles were removed under reduced pressure, then the residue was partitioned by addition of EtOAc (40 mL) and water (40 mL). The organic layer was collected, washed with brine (2 × 30 mL) and dried over MgSO\(_4\). Removal of solvent under reduced pressure gave 154 as a yellow-brown liquid (417 mg, 87%). \(R_f = 0.85\) (30% EtOAc in petroleum ether). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.13 (9H, s, SiMe\(_3\)), 4.15 (2H, br s, NH\(_2\)), 4.66 (2H, s, CH\(_2\)), 6.67 (2H, m, Ar), 7.04 (1H, d, J = 7.6, Ar), 7.10 (1H, td, J = 7.6, 1.6, Ar). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 0.00 (SiMe\(_3\)), 64.68 (OCH\(_2\)), 116.16 (Ar), 118.34 (Ar), 125.28 (Ar), 129.11 (Ar), 129.24 (Ar), 146.53 (Ar).

N-(2-(hydroxymethyl)phenyl)acrylamide (155)\(^{[172]}\)
A solution of 154 (1.90 g, 2.05 mmol) in anhydrous DCM (30 mL) was chilled to 0 ºC and treated with Et\(_3\)N (1.3 mL, 9.70 mmol) and acryloyl chloride (0.9 mL, 10.7 mmol). After stirring under argon atmosphere for 30 min, the volatiles were removed under reduced pressure and to the residue was added MeOH (30 mL) and K\(_2\)CO\(_3\) (1.60 g, 11.6 mmol). After stirring at RT for a further 1.5 h, the solvent was removed under reduced pressure, and the resulting residue was partitioned with EtOAc (100 mL) and water (100 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (100 mL), and the combined organic layers were dried over MgSO\(_4\). The crude product was purified by column chromatography eluting with 20-30% EtOAc in petroleum ether to give 155 as a white solid (930 mg, 66%). \(R_f = 0.35\) (50% EtOAc in petroleum ether). Mp = 117-119 ºC. \(^1\)H NMR (DMSO-d\(_6\), 400 MHz) \(\delta\) 4.56 (2H, d, J = 5.5, CH\(_2\)), 5.34 (1H, t, J = 5.5, OH), 5.81 (1H, dd, J = 10.2, 1.9,
C=CH), 6.29 (1H, dd, J = 17.0, 1.9, C=CH), 6.53 (1H, dd, J = 17.0, 10.2, C=CH), 7.23 (1H, t, J = 7.5, 1.1, Ar), 7.30 (1H, td, J = 7.5, 1.6, Ar), 7.49 (1H, dd, J = 7.0, 1.1, Ar), 7.65 (1H, d, J = 7.8, Ar), 9.56 (1H, br s, NH).

$^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 60.01 (CH$_2$), 123.88 (Ar), 124.87 (Ar), 126.59 (C=C), 126.94 (Ar), 127.34 (Ar), 131.87 (C=C), 134.84 Ar), 135.06 (Ar), 163.28 (C=O).

N-(2-(bromomethyl)phenyl)acrylamide (156a)$^{[172]}$

**Method A:**

A solution of 155 (120 mg, 0.68 mmol) in anhydrous DCM (8 mL) and under argon atmosphere was chilled to 0 °C and treated with PBr$_3$ (60 $\mu$L, 0.68 mmol) added dropwise. The reaction mixture was stirred for 30 min, after which the reaction was quenched by addition of water (10 mL), extracted with DCM (3 x 30 mL) and dried over Na$_2$SO$_4$. Removal of volatiles under reduced pressure gave the crude product which was purified by column chromatography eluting with 20% EtOAc in petroleum ether to give 156a as a white solid (33 mg, 21%) which was found to decompose if stored overnight at RT or in chloroform solution. $R_f = 0.57$ (50% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 4.51 (2H, s, CH$_2$Br), 5.82 (1H, dd, J = 9.5, 1.1, HC=C), 6.33 (1H, dd, J = 17.0, 10.1, HC=C), 6.45 (1H, dd, J = 17.0, 1.1, HC=C), 7.15 (1H, t, J = 7.6, Ar), 7.33 (1H, dd, J = 7.0, 1.2, Ar), 7.37 (1H, td, J = 7.6, 1.4, Ar), 7.64 (1H, s, NH), 7.94 (1H, s, Ar).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 31.49 (CH$_2$Br), 124.48 (Ar), 125.49 (Ar), 128.00 (C=C), 130.08 (Ar), 130.13 (Ar), 131.15 (C=C), 136.20 (Ar), 163.65 (C=O).

**Method B:**

A solution of 155 (50 mg, 0.28 mmol) in anhydrous DCM (4 mL) and under argon atmosphere was chilled to 0 °C and treated with PPh$_3$ (84 mg, 0.32 mmol). After stirring for 10 min, N-bromosuccinimide (57 mg, 0.32 mmol) was added portionwise over 5 min. TLC monitoring indicated no reaction progress at 20 min or 3 h. After stirring at 40 °C overnight TLC indicated no further progression.
Method C:
A light-protected solution of 155 (50 mg, 0.28 mmol) and PPh₃ (110 mg, 0.42 mmol) in anhydrous DCM (5 mL) was treated with CBr₄ (140 mg, 0.42 mmol) and stirred for 1 h. TLC monitoring indicated partial disappearance of starting material and emergence of a higher-running spot. The reaction mixture was purified by column chromatography eluting with 20% EtOAc in petroleum ether; however ¹H NMR spectra of the isolated compound did not show the expected benzyl bromide product.

\[ \text{N-(2-(chloromethyl)phenyl)acrylamide (156b)} \]
A solution of 155 (300 mg, 1.69 mmol) in anhydrous DCM (20 mL) which was chilled to –10 ºC was treated with SOCl₂ (0.14 mL, 1.86 mmol) and stirred at –10 ºC for 30 min, then at 30 ºC for an additional 4 h under N₂ atmosphere. The reaction mixture was washed with water (40 mL), 5% NaHCO₃ solution (40 mL) and brine (40 mL), and dried over MgSO₄ to give the crude product which was purified by column chromatography eluting with 15-30% EtOAc in petroleum ether to give 156b as an off-white solid (220 mg, 67%). Rᵣ = 0.52 (30% EtOAc in petroleum ether). Mp = 115-117 ºC. ¹H NMR (DMSO-d₆, 400 MHz) δ 4.87 (2H, s, CH₂Cl), 5.84 (1H, dd, J = 10.2, 2.0, C=CH), 6.33 (1H, dd, J = 17.0, 2.0 C=CH), 6.60 (1H, dd, J = 17.0, 10.2, C=CH), 7.28 (1H, td, J = 7.5, 1.2, Ar), 7.42 (1H, td, J = 7.5, 1.5, Ar), 7.54 (1H, dd, J = 7.7, 1.5, Ar), 7.62 (1H, d, J = 7.7, Ar), 9.74 (1H, br s, NH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 44.13 (CH₂Cl), 124.41 (Ar), 125.44 (Ar), 127.82 (H₂C=C), 128.16 (Ar), 129.99 (Ar), 130.00 (Ar), 131.12 (C=CH), 136.24 (Ar), 163.73 (C=O). IR (KBr) 3412m (N-H), 3026vs (C-H), 1694s (C=O). [Found (ESI+) 196.0530 [M+H]⁺, C₁₀H₁₁ClNO requires 196.0529].
N-acetyl-N-(2-(chloromethyl)phenyl)acrylamide (157)
A solution of 156b (300 mg, 1.53 mmol) and C₆H₄ (200 mg, 4.60 mmol) in anhydrous THF (15 mL) and under argon atmosphere was treated with AcCl (0.35 mL, 4.60 mmol) and stirred at RT for 72 h. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography eluting with 5-8% EtOAc in petroleum ether to give 157 as a pale-brown oil (186 mg, 51%). Rf = 0.67 (15% EtOAc in petroleum ether). ¹H NMR (CDCl₃, 400 MHz) δ 2.48 (3H, s, Me), 4.42 (2H, s, CH₂Cl), 5.70 (1H, dd, J = 10.1, 1.8, HC=C), 6.34 (1H, dd, J = 16.8, 10.1, HC=C), 6.46 (1H, dd, J = 16.8, 1.8, HC=C), 7.11 (1H, dd, J = 6.8, 2.3, Ar), 7.43-7.46 (2H, m, Ar), 7.56 (1H, dd, J = 6.8, 2.3, Ar). ¹³C NMR (DMSO-d₆, 100 MHz) δ 26.39 (Me), 42.07 (CH₂Cl), 129.66 (CH₂), 129.89 (Ar), 130.17 (Ar), 130.24 (CH), 130.66 (Ar), 131.23 (Ar), 135.10 (Ar), 137.49 (Ar), 167.06 (C=O), 172.66 (C=O). IR (KBr) 2952w (C-H), 1702s (C=O), 1612m (C=C), 971m (C=C). [Found (ESI+) 238.0657 [M+H]⁺, C₁₂H₁₃ClNO₂ requires 238.0629].

3-methylquinolin-2-(1H)-one (140c)[¹⁷²]
A solution of 157 (180 mg, 0.76 mmol), Pd₂(dba)₃ (18 mg, 2.5mol%), DPPF (20 mg, 5.0mol%) and Et₃N (0.3 mL, 2.2 mmol) in anhydrous MeCN (4 mL) and under N₂ atmosphere was stirred at reflux for 5 h, after which DBU (0.1 mL, 0.76 mmol) was added and the mixture stirred at reflux for a further 3 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography eluting with 10-40% EtOAc in petroleum ether to give 140c as an off-white solid (17 mg, 14%). Rf = 0.11 (20% EtOAc in petroleum ether). Mp > 230 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 2.14 (3H, s, Me), 7.19 (1H, t, J = 7.7, 1.1, Ar), 7.34 (1H, d, J = 8.0, Ar), 7.47 (1H, t, J = 7.7, 1.4, Ar), 7.62(1H, d, J = 8.0, 1.1, Ar), 7.80 (1H, s, C=CH), 11.76
$^1$H NMR (DMSO-d$_6$, 100 MHz) $\delta$ 16.49 (Me), 114.70 (Ar), 119.44 (Ar), 121.57 (Ar), 126.88 (Ar), 129.01 (Ar), 129.82 (C=C), 136.29 (C=C), 137.88 (Ar), 162.39 (C=O). [Found (ESI+) 160.0769 [M+H]$^+$, C$_{10}$H$_{10}$NO requires 160.0762].

![159](image)

**N-(2-formyl-4,5-dimethoxyphenyl)acrylamide (159)**

A solution of 151a (750 mg, 4.14 mmol) in anhydrous DCM (12 mL) was chilled to 0 °C and treated with Et$_3$N (0.6 mL, 4.56 mmol) and acryloyl chloride (0.4 mL, 4.97 mmol). After stirring under argon atmosphere for 25 min the reaction mixture was quenched by addition of water (30 mL) and the organic layer collected. The aqueous layer was extracted further with DCM (2 × 30 mL) and the combined organic layers were then washed with brine and dried over MgSO$_4$. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography eluting with 20-30% EtOAc in petroleum ether to give 159 as a light yellow solid (435 mg, 45%). $R_f = 0.32$ (30% EtOAc in petroleum ether). $Mp = 139$-141 °C. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.92 (3H, s, OMe), 4.00 (3H, s, OMe), 5.81 (1H, dd, J = 10.1, 1.2, C=CH), 6.32 (1H, dd, J = 17.0, 10.1, C=CH), 6.44 (1H, dd, J = 17.0, 1.2, C=CH), 7.06 (1H, s, Ar), 8.59 (1H, s, Ar), 9.77 (1H, s, HC=O), 11.55 (1H, br s, NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 56.22 (OMe), 56.37 (OMe), 103.21 (Ar), 114.72 (Ar), 116.51 (Ar), 127.73 (CH$_2$), 131.95 (CH), 137.52 (Ar), 144.66 (Ar), 155.54 (Ar), 164.57 (NC=O), 193.22 (HC=O). IR (KBr) 3245m (N-H), 2935m (C-H), 2840m (C-H), 1649s (C=O). [Found (ESI+) 258.0711 [M+Na]$^+$, C$_{12}$H$_{13}$NNaO$_4$ requires 258.0737].
N-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)acrylamide (160)
A solution of 159 (1.20 g, 5.10 mmol) in isopropyl alcohol (200 mL) was treated with NaBH₄ (290 mg, 7.65 mmol) and stirred at RT for 30 min, after which the reaction mixture was concentrated under reduced pressure, diluted with water (100 mL) and the pH adjusted to pH 6 with 1M HCl. The resulting solution was extracted with EtOAc (3 × 100 mL) and the combined organic layers were then washed with brine (100 mL), dried over Na₂SO₄ and the solvent removed under reduced pressure to give 160 138 as an off-white solid (1.13 g, 91%). Rᵢ = 0.42 (EtOAc). Mp = 135-136 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 3.77 (3H, s, OMe), 3.81 (3H, s, OMe), 4.46 (2H, d, J = 5.6, CH₂), 5.20 (1H, t, J = 5.6, OH), 5.78 (1H, dd, J = 10.2, 1.9, CH), 6.27 (1H, dd, J = 17.1, 1.9, CH), 6.51 (1H, dd, J = 17.1, 10.2, CH) 7.07 (1H, s, Ar), 7.21 (1H, s, Ar), 9.48 (1H, br s, NH). ¹³C NMR (CDCl₃, 125 MHz) δ 56.06 (OMe), 56.20 (OMe), 64.15 (OCH₂), 106.91 (Ar), 112.07 (Ar), 122.09 (Ar), 127.41 (CH₂), 130.66 (Ar), 131.50 (COCH), 145.55 (Ar), 148.94 (Ar), 163.91 (C=O). IR (KBr) 3477s (O-H), 3227s (N-H), 2937m (C-H), 1606 (C=O). [Found (ESI –) 236.0922 [M-H]– C₁₂H₁₄NO₄ requires 236.0923].

N-(2-(chloromethyl)-4,5-dimethoxyphenyl)acrylamide (161)
A solution of 160 (50 mg, 0.21 mmol) in anhydrous DCM (3 mL) under argon atmosphere and chilled to 0 °C was treated with SOCl₂ (23 µL, 0.31 mmol), allowed to warm to RT and stirred for 4 h. TLC analysis showed starting material still remaining but emergence of several new spots. Reaction mixture was washed with water (20 mL) and 5% NaHCO₃ solution (2 × 20 mL) and purified by column chromatography eluting with 10-20% EtOAc in petroleum ether + 0.1% pyridine to give 161 as a clear residue (4 mg, 3.7%).
**N-(3,4-dimethoxyphenyl)acetamide (163a)[195]**

A solution of 3,4-dimethoxyaniline (500 mg, 3.26 mmol) and Et₃N (0.5 mL, 3.91 mmol) in anhydrous DCM (4 mL) under N₂ atmosphere was treated with acetyl chloride (0.3 mL, 3.91 mmol) added dropwise and stirred at RT for 20 minutes. The reaction mixture was then washed with saturated NH₄Cl solution (2 × 10 mL) and brine (15 mL), dried over Na₂SO₄ and evaporated to dryness under reduced pressure to give **163a** as a grey solid (477 mg, 75%). Rᵣ = 0.30 (80% EtOAc in petroleum ether). Mp = 131-133 °C (lit. 130-131 °C).[195] ¹H NMR (CDCl₃, 400 MHz) δ 2.12 (3H, s, Me), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 6.76 (1H, d, J = 8.6, Ar), 6.87 (1H, dd, J = 8.6, 2.4, Ar), 7.28 (1H, d, J = 2.4, Ar), 7.62 (1H, br s, NH). ¹³C NMR (CDCl₃, 100 MHz) δ 24.34 (Me), 55.78 (OMe), 56.00 (OMe), 105.00 (Ar), 111.15 (Ar), 111.98 (Ar), 131.54 (Ar), 145.71 (Ar), 148.86 (Ar), 168.44 (C=O).

**N-(3,4-methylenedioxyphenyl)acetamide (163b)[196]**

A solution of 3,4-methylenedioxyaniline (1.00 g, 7.3 mmol) and Et₃N (1.1 mL, 8.8 mmol mmol) in anhydrous DCM (8 mL) under N₂ atmosphere was treated with acetyl chloride (0.7 mL, 8.8 mmol) added slowly and stirred at RT for 15 minutes. The reaction mixture was then washed with water (20 mL), saturated NH₄Cl solution (20 mL) and brine (20 mL). The combined organic layers were dried over MgSO₄ and evaporated to dryness under reduced pressure to give **163b** as a grey-brown solid (912 mg, 70%). Rᵣ = 0.59 (EtOAc). Mp = 135-137 °C (lit. 135-136 °C).[196] ¹H NMR (CDCl₃, 400 MHz) δ 2.12 (3H, s, Me), 5.92 (2H, s, H₂CO₂), 6.70 (1H, d, J = 8.3, Ar), 6.76 (1H, dd, J = 8.3, Ar), 7.17 (1H, d, J = 2.0, Ar), 7.56 (1H, br s, NH). ¹³C NMR (CDCl₃, 100 MHz) δ 24.34 (Me), 101.19 (H₂CO₂), 103.03 (Ar), 107.95 (Ar), 113.30 (Ar), 132.04 (Ar), 144.22 (Ar), 147.67 (Ar), 168.47 (C=O).
2-chloro-6,7-dimethoxyquinoline-3-carbaldehyde (164a)\[197\]
A mixture of 163a (450 mg, 2.30 mmol) and anhydrous DMF (0.5 mL, 6.92 mmol) chilled to 0 °C and under N\(_2\) atmosphere was treated with POCl\(_3\) (2.5 mL, 27.6 mmol) added dropwise and stirred at 85 °C for 4 h. The reaction mixture was poured into ice-cold water and stirred for a further 10 min after which the resulting orange-brown precipitate was collected by suction filtration, washed with water and recrystallised from MeCN to give 164a as a light brown solid (140 mg, 24%). The filtrate was extracted with EtOAc (2 × 20 mL), dried over MgSO\(_4\) and the resulting crude product (150 mg) purified by column chromatography eluting with EtOAc to give 151a as a light brown solid (90 mg); total yield = 230 mg, 40%. \(R_f = 0.801\) (EtOAc). Mp = 219-221 °C (lit. 215 °C).\[197\] \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 3.97 (3H, s, OMe), 4.04 (3H, s, OMe), 7.47 (1H, s, Ar), 7.67 (1H, s, Ar), 8.76 (1H, s, Ar), 10.38 (1H, s, HC=O). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 55.93 (OMe), 56.28 (OMe), 106.76 (Ar), 106.76 (Ar), 122.06 (Ar), 124.08 (Ar), 138.33 (Ar), 146.65 (Ar), 147.11 (Ar), 150.33 (Ar), 155.66 (Ar), 189.29 (C=O).

2-chloro-6,7-methylenedioxyquinoline-3-carbaldehyde (164b)\[197\]
A mixture of 163b (850 mg, 4.74 mmol) and anhydrous DMF (1.0 mL, 14.2 mmol) chilled to 0 °C and under N\(_2\) atmosphere was treated with POCl\(_3\) (5.2 mL, 57.0 mmol) added dropwise and stirred at 85 °C for 4 h. The reaction mixture was poured into ice-cold water and stirred for a further 10 min after which the resulting orange-brown precipitate was collected by suction filtration, washed with water and MeCN and dried under reduced pressure to give 164b as a light brown solid (680 mg, 61%). \(R_f = 0.95\) (EtOAc). Mp = 232-233 °C \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) 6.37 (2H, s, CH\(_2\)), 7.48 (1H, s, Ar), 7.67 (1H, s, Ar), 8.77 (1H, s, Pyr), 10.37 (1H, s, HC=O). \(^{13}\)C NMR (DMSO-\(d_6\), 100 MHz) \(\delta\) 103.17 (CH\(_2\)), 104.20 (Ar), 104.28 (Ar), 123.69 (Ar), 124.25 (Ar), 138.77 (Ar), 147.43 (Ar), 148.06 (Ar), 148.81 (Ar), 154.19 (Ar), 189.31 (HC=O).
6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (165a)[197]

A solution of 164a (200 mg, 0.79 mmol) in 70% aqueous AcOH (8 mL) was stirred under reflux for 8 h and allowed to cool, after which water (10 mL) was added. The resulting precipitate was collected by suction filtration, washed with water and EtOAc and dried under vacuum to give 165a as a yellow solid (112 mg, 61%). Rf = 0.48 (EtOAc). Mp = >230 ºC. 1H NMR (DMSO-d6, 400 MHz) δ 3.81 (3H, s, OMe), 3.88 (3H, s, OMe), 6.87 (1H, s, Ar), 7.43 (1H, s, Ar), 8.39 (1H, s, Ar), 10.19 (1H, s, HC=O), 12.08 (1H, br s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 55.72 (OMe), 55.87 (OMe), 97.21 (Ar), 110.26 (Ar), 111.66 (Ar), 122.46 (Ar), 138.40 (Ar), 141.48 (Ar), 145.54 (Ar), 155.08 (Ar), 161.53 (NC=O), 189.32 (HC=O).

6,7-methylenedioxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (165b)

A solution of 164b (250 mg, 1.06 mmol) in 70% AcOH (10 mL) was stirred at 130 ºC overnight, after which the reaction mixture was allowed to cool, diluted with chilled 10% NaHCO3 solution. The resulting precipitate was collected by suction filtration, washed with water and allowed to air dry to give 165b as a dark yellow solid (190 mg, 83%). Rf = 0.68 (EtOAc). Mp = >230 ºC. 1H NMR (DMSO-d6, 400 MHz) δ 6.22 (2H, s, CH2), 6.89 (1H, s, Ar), 7.45 (1H, s, Ar), 8.41 (1H, s, Ar), 10.22 (1H, s, HC=O), 12.24 (1H, br s, NH). 13C NMR (DMSO-d6, 100 MHz) δ 94.95 (Ar), 102.52 (CH2), 106.82 (Ar), 112.76 (Ar), 122.39 (Ar), 140.09 (Ar), 141.59 (Ar), 144.04 (Ar), 153.31 (Ar), 161.51 (NC=O), 189.36 (HC=O). [Found (ESI+) 218.0442 [M+H]+, C11H8NO4 requires 218.0453].
6,7-dimethoxy-3-methylquinolin-2(1H)-one (140a)

A solution of 165a (100 mg, 0.43 mmol) in CF$_3$COOH (2 mL) chilled to 0 ºC and under N$_2$ atmosphere was treated with Et$_3$SiH (0.2 mL, 1.3 mmol) and stirred at RT overnight, after which the reaction mixture was poured into ice-water, extracted with DCM (2 × 10 mL) and the combined organic layers dried over MgSO$_4$. Removal of volatiles under reduced pressure gave the crude product which was purified by column chromatography eluting with 2% MeOH in DCM to give 140a as a peach solid (56 mg, 59%). $R_t = 0.29$ (5% MeOH in DCM). Mp = >230 ºC. UV (EtOH): $\lambda_{max}$ 235 (29056), 341 (14485). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.27 (3H, s, Me), 3.92 (3H, s, OMe), 3.99 (3H, s, OMe), 6.82 (1H, s, Ar), 6.88 (1H, s, Ar), 7.56 (1H, s, C=CH), 11.76 (1H, s, NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 16.65 (Me), 56.11 (OMe), 56.14 (OMe), 97.79 (Ar), 107.28 (Ar), 113.60 (Ar), 127.01 (Ar), 132.95 (Ar), 137.08 (Ar), 145.55 (Ar), 151.38 (Ar), 164.27 (C=O). [Found (ESI+) 220.0952 [M+H]$^+$, C$_{12}$H$_{14}$NO$_3$ requires 220.0974].

6,7-methylenedioxy-3-methylquinolin-2(1H)-one (140b)

A solution of 165b (100 mg, 0.46 mmol) in CF$_3$COOH (2 mL) chilled to 0 ºC and under N$_2$ atmosphere was treated with Et$_3$SiH (0.2 mL, 1.3 mmol) and stirred at RT overnight, after which the reaction mixture was poured into ice-water, extracted with DCM (3 × 10 mL) and the combined organic layers washed with brine (20 mL) and dried over MgSO$_4$. Removal of volatiles under reduced pressure gave the crude product which was purified by column chromatography eluting with 2% MeOH in DCM to give 140b as an off-white solid (45 mg, 48%). $R_t = 0.29$ (5% MeOH in DCM). Mp = >230 ºC. UV (EtOH): $\lambda_{max}$ 236.5 (16531), 343 (27473). $^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 2.08 (3H, s, Me), 6.11 (2H, s, CH$_2$), 6.84 (1H, s, Ar), 7.14 (1H, s, Ar), 7.67 (1H, s, C=CH), 11.70 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$, 100 MHz) $\delta$ 16.37 (Me),
94.83 (Ar), 101.47 (CH$_2$), 104.61 (Ar), 113.55 (Ar), 126.65 (Ar), 134.38 (Ar), 136.30 (C=C), 142.92 (Ar), 148.89 (Ar), 162.13 (C=O). [Found (ESI+) 204.0674 [M+H]$^+$, C$_{11}$H$_{10}$NO$_3$ requires 204.0660].

![Structure 15a](image)

**2-(dipyridin-2-ylmethylene)-N,N-dimethylhydrazinecarbothioamide (15a)**

A solution of di-2-pyridyl ketone (772 mg, 4.19 mmol) and 4,4-dimethyl-3-thiosemicarbazide (500 mg, 4.19 mmol) in EtOH (20 mL) was heated at reflux for 24 h. The solvent was removed under reduced pressure and the crude product recrystallized from EtOH/H$_2$O (1:1) to give 15a as a yellow solid (406 mg, 34%). R$_f$ = 0.35 (4% MeOH in DCM). Mp = 143-145 °C. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.47 (6H, s, NMe$_2$), 7.29 (1H, ddd, J = 7.5, 4.9, 1.1, Pyr), 7.36 (1H, ddd, J = 6.0, 3.7, 1.1, Pyr), 7.72 (1H, d, J = 8.2, Pyr), 7.82 (2H, tdd, J = 8.0, 3.4, 1.8, Pyr), 8.11 (1H, d, J = 7.8, Pyr), 8.57 (1H, d, J = 4.7, Pyr), 8.69 (1H, d, J = 4.8, Pyr), 15.05 (1H, s, NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 41.86 (NMe$_2$), 123.32 (Pyr), 123.84 (Pyr), 124.69 (Pyr), 126.96 (Pyr), 137.21 (Pyr), 142.98 (Pyr), 147.11 (Pyr), 148.08 (Pyr), 152.04 (Pyr), 156.38 (C=N) 181.33 (C=S).

![Structure 15b](image)

**2-(dipyridin-2-ylmethylene)-N-phenylhydrazinecarbothioamide (15b)**

A solution of di-2-pyridyl ketone (500 mg, 2.71 mmol) and 4-phenyl-3-thiosemicarbazide (500 mg, 3.00 mmol) was heated at reflux in EtOH (15 mL) for 7 h. The crystalline product which formed upon cooling was collected by suction filtration, washed with chilled EtOH and dried under vacuum to yield 15b as yellow crystals (573 mg, 63%). R$_f$ = 0.43 (4% MeOH in DCM). Mp = 140-141 °C. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.22 (1H, t, J = 7.4, Ph), 7.36-7.41 (4H, m, Ph), 7.57 (1H, d, J = 8.1, Ph),
7.70 (2H, d, J = 7.7, Ph), 7.78-7.87 (3H, m, Ar), 8.66 (1H, dt, J = 4.7, 2.5, Pyr), 8.83 (1H, d, J = 4.4, Pyr), 9.52 (1H, s, NH), 14.47 (1H, s, NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 123.78 (Ar), 124.06 (Ar), 124.17 (Ar), 124.37 (Ar), 125.96 (Ar), 126.87 (Ar), 128.73 (Ar), 137.04 (Ar), 137.15 (Ar), 138.08 (Ar), 140.61 (Ar), 148.19 (Ar), 148.86 (Ar), 148.86 (Ar), 151.65 (Ar), 155.89 (C=N), 176.68 (C=S).

N-(dipyridin-2-ylmethylene)benzothiohydrazide (15c)$^{[86]}$

A solution of di-2-pyridyl ketone (400 mg, 2.17 mmol) and 12 (362 mg, 2.39 mmol) was heated at reflux in EtOH (5 mL) for 14 h. The crystalline product which formed upon cooling was collected by suction filtration, washed with chilled EtOH and dried under vacuum to yield 15c as dark red crystals (348 mg, 50%). Rf = 0.72 (4% MeOH in DCM). Mp = 147-149 °C. $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.28 (2H, td, J = 6.7, 1.0, Ph), 7.34-7.42 (3H, m, Ar), 7.55 (2H, dd, J = 7.8, 1.7, Pyr), 7.78-7.85 (4H, m, Ar), 8.48 (2H, d, J = 4.3, Pyr), 9.18 (1H, s, NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 121.53, 122.63, 126.98, 128.49, 129.63, 131.32, 136.91, 147.28, 148.61, 161.74.

N-ethyl-2-(phenyl(pyridin-2-yl)methylene)hydrazinecarbothioamide (16d)$^{[87]}$

A solution of 2-benzoylpyridine (1.00 g, 5.46 mmol) in EtOH (15 mL) was treated with a solution of 4-ethylthiosemicarbazide (651 mg, 5.46 mmol) in water (7.5 mL), followed by AcOH (3 drops) and stirred at 90 °C overnight. The EtOH was removed from the reaction mixture under reduced pressure and the resulting aqueous suspension was adjusted to pH 9-10 with 1M NaOH and extracted with DCM (2 x 30mL). The organic extracts were combined, the reaction mixture concentrated down under reduced pressure and the crude residue purified by column
chromatography eluting with 1% MeOH in DCM + 0.1% pyridine. This gave 16d as a pale orange solid after 2 columns (73 mg, 5%). \( R_f = 0.39 \) (2% MeOH in DCM). Mp = 112-121 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.34 (3H, t, J = 7.2, Me), 3.75-3.82 (2H, m, J = 7.2, CH\(_2\)), 7.27-7.31 (3H, m, Ar), 7.55 (4H, dt, J = 7.2, 1.4, Aryl), 7.72 (2H, m, Ar), 7.90 (1H, m, Ar), 8.59 (1H, dt J = 4.7, 1.4, Ar), 8.74 (1H, s, NH\(_2\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 14.46 (Me), 39.19 (CH\(_2\)), 124.10 (Pyr), 126.12 (Pyr), 128.50 (Ph), 129.14 (Ph), 137.12 (Ar), 137.77 (Ar), 148.69 (Pyr), 142.42 (Pyr), 155.22 (C=N), 178.22 (C=S).

1-(2-nitrophenyl)ethyl-N'-dipyridin-2-ylmethylen-N,N-dimethylcarbamo hydrazonothioate (170a)

A solution of 15a (290 mg, 1.00 mmol) and 49 (250 mg, 1.10 mmol) in acetone (9 mL) was stirred at 85 °C overnight and volatiles removed under reduced pressure. The crude product was purified by column chromatography eluting with 0-40% acetone in DCM + 0.1% pyridine to give 170a as a brown oil (128 mg, 29%). \( R_f = 0.24 \) (80% DCM in petroleum ether). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.70 (3H, d, J = 6.3, Me), 2.84 (6H, s, NMe\(_2\)), 5.47 (1H, q, J = 6.3, CH), 7.18-7.20 (2H, m, Ar), 7.28 (1H, td, J = 4.9, 1.1, Ar), 7.31 (1H, dd, J = 5.0, 1.1, Ar), 7.49 (1H, td, J = 4.9, 1.1, Pyr), 7.66-7.68 (2H, m, Ar), 7.73 (1H, td, J = 4.9, 1.1, Ar), 7.83 (1H, d, J = 5.0, 1.1, Ar), 8.15 (1H, d, J = 8.2, Ar), 8.51 (1H, dd, J = 4.7, 1.1, Pyr), 8.65 (1H, dd, J = 4.8, 1.1, Pyr). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 22.92 (Me), 39.90 (NMe\(_2\)), 41.26 (CH), 122.16 (Ar), 122.22 (Ar), 122.94 (Ar), 123.76 (Ar), 125.55 (Ar), 127.72 (Ar), 129.97 (Ar), 132.63 (Ar), 134.92 (Ar), 135.97 (Ar), 138.17 (Ar), 148.87 (Ar), 148.90 (Ar), 148.98 (Ar), 155.73 (Ar), 156.74 (Ar), 158.27 (N=C=S), 160.68 (C=N). [Found (ESI+) 457.1422 [M+H]\(^+\), \( C_{22}H_{23}N_6O_2S \) requires 457.1402].
1-(2-nitrophenyl)ethyl-N-(dipyridin-2-ylmethylene)-N-phenylhydrazinecarbimido thiothioate (170b)

A solution of 15b (50.9 mg, 0.15 mmol) and 49 (41.3 mg, 0.16 mmol) in acetone (1 mL) was heated at reflux for 18 h. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography eluting with 55% EtOAc in petroleum ether. This gave 170b as an off-white solid (20 mg, 28%). Rf = 0.71 (80% EtOAc in petroleum ether). Mp = 198-200 °C. IR (cm⁻¹) 1355 (NO₂), 1519 (Ph), 1534 (C=S), 1580 (NO₂), 1589 (Ph), 1604 (C=N), 3448-3546 (>N–H). ¹H NMR (CDCl₃, 400 MHz) δ 1.82 (3H, d, J = 7.2, Me), 5.50 (1H, q, J = 7.2, CH), 6.74 (2H, d, J = 7.4, Ar), 7.13-7.06 (2H, m, Ar), 7.25-7.32 (4H, m, Ar), 7.55 (1H, t, J = 7.3, Ar), 7.68-7.67 (2H, m, Ar), 7.74 (1H, dd, J = 8.1, 1.2, Ar), 7.81 (1H, td, J = 7.7, 5.9, 1.7, Ar), 7.86 (1H, d, J = 7.8, Ar), 7.94-7.92 (2H, m, Ar), 8.54 (1H, d, J = 2.4, Ar), 14.39 (1H, s, NH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 156.31 (C=N), 154.69 (S–C), 151.56 (Ar), 150.18 (Ar), 149.31 (Ar), 148.05 (Ar), 146.58 (Ar), 140.62 (Ar), 138.77 (Ar), 136.93 (Ar), 136.63 (Ar), 132.45 (Ar), 129.73 (Ar), 129.04 (Ar), 126.91 (Ar), 125.86 (Ar), 123.89 (Ar), 123.29 (Ar), 132.22 (Ar), 122.96 (Ar), 122.90 (Ar), 121.52 (Ar), 53.42 (Ar), 38.00 (Ar), 22.62 (S–CH), 21.39 (Me). [Found (ESI⁺) 483.1590 [M+H⁺] C₂₆H₂₃N₆O₂S requires 483.1603].
(Z)-(7-(diethylamino)-2-oxo-2H-chromen-4-yl)methyl 2-(dipyridin-2-ylmethylene)-N-phenylhydrazinecarbimidothioate (171)

A solution of 15b (250 mg, 0.75 mmol) and 73 (260 mg, 0.84 mmol) in acetone (6 mL) was stirred at reflux for 8 hours and volatiles removed under reduced pressure. The crude product purified by column chromatography eluting with 0.5-1% MeOH in DCM + 0.1% pyridine to give 171 as a yellow solid (380 mg, 90%). Rf = 0.48 (5% MeOH in DCM). Mp = 88-90 °C. ¹H NMR (CDCl₃, 400 MHz) δ 1.20 (6H, t, J = 7.1, 2 × Me), 3.40 (4H, q, J = 7.1, 2 × NCH₂), 4.44 (2H, s, SCH₂), 6.31 (1H, s, C=CH), 6.51 (1H, d, J = 2.6, Ar), 6.60 (1H, dd, J = 9.0, Ar), 7.05 (2H, dd, J = 8.4, 1.1, Ar), 7.15-7.20 (2H, m, Ar), 7.25-7.28 (1H, m, Ar), 7.43 (2H, t, J = 7.8 Ar), 7.66 (1H, d, J = 9.0, Ar), 7.69-7.71 (2H, m, Ar), 7.78 (1H, td, J = 7.6, 1.8, Ar), 7.89 (1H, d, J = 8.0, Pyr), 7.95 (1H, d, J = 4.8, Pyr), 8.54 (1H, dq, J = 4.9, 0.8, Pyr), 14.68 (1H, s, NH). ¹³C NMR (CDCl₃, 125 MHz) δ 12.45 (2 × Me), 29.83 (SCH₂), 44.70 (2 × NCH₂), 97.77 (Ar), 107.81 (Ar), 108.46 (Ar), 109.28 (C=C), 121.72 (Ar), 123.03 (Ar), 123.23 (Ar), 123.36 (Ar), 123.94 (Ar), 125.58 (Ar), 125.84 (Ar), 126.02 (Ar), 129.41 (Ar), 136.72 (Ar), 136.97 (Ar), 139.24 (Ar), 146.51 (Ar), 147.97 (Ar), 149.40 (Ar), 150.58 (Ar), 151.45 (Ar), 152.43 (Ar), 155.29 (Ar), 156.03 (Ar), 156.44 (Pyr), 162.13 (C=O). [Found (ESI+) 563.2245 [M+H]+, C₃₂H₃₁N₆O₂S requires 563.2229].
[Fe(2-(dipyridin-2-ylmethylene)-N,N-dimethylhydrazinecarbothioamide)₂]ClO₄·H₂O (175).[^86]

A solution of 15a (30 mg, 0.11 mmol) in EtOH (2 mL) was treated with Et₃N (14 μL) and Fe(ClO₄)₃ hydrate (20 mg, 0.06 mmol) and stirred at reflux for 25 min, after which the reaction mixture was allowed to cool. The resulting precipitate was collected by suction filtration and washed with EtOH and Et₂O to give 175 as a brown powder (11 mg).

[^86]: Reference number
6.3. UV absorption assays

Stock solutions of each compound in EtOH were prepared at a concentration of 0.2 mM. Serial dilutions of each stock resulted in solutions of 40μM, 30μM, 20μM and 10μM, and the absorbance spectrum of each solution was recorded. This procedure was repeated in triplicate and an average value recorded. A plot of concentration versus maximum absorbance intensity ($\lambda_{\text{max}}$) gave a linear line from which the molar extinction coefficient ($\varepsilon$) was obtained.

6.4. Biological assays

6.4.1. General

Cell culture materials were obtained from Gibco (Germany), except for Foetal Bovine Serum (FBS) which is purchased from PAA laboratories (Austria). *MilliQ* water (Millipore, MA, USA) was used to prepare phosphate-buffered saline (PBS) to minimise transition metal levels.

6.4.2. Stock solutions

Stock solutions of all compounds under investigation, including parental ICs and CICs described in Chapters 2-5 (except PIH) were prepared in DMSO at a concentration of 100 mM. An exception to this was NT44mT, the stock solution of which was prepared at a concentration of 50 mM in DMSO, as it was only partially-soluble at higher concentrations. Aliquots were kept at -20 °C until required. Stock solutions of PIH were prepared by dissolving PIH powder in 1M HCl at a concentration of 500 mM, then diluted in PBS to obtain a 25 mM stock solution.

6.4.3. Cell culture

Cytotoxicity evaluation was undertaken on human spontaneously immortalised skin keratinocytes (HaCaT). These non-tumorigenic cells are derived from keratinocytes found in epidermal tissue, and demonstrate a high level of resistance to UVA damage.[142] Cells were cultured in 10% FBS-DMEM (high-glucose Dulbecco’s modified eagles medium) containing 2mM glutamine and 50 IU/mL penicillin-
streptomycin. HaCaT cells were passaged twice a week and seeded at a density of $2 \times 10^4$ cells per 3 cm plate in 2.5 mL media, and grown for 48 h prior to treatment with compounds for 24, 48 or 72 h depending on the experimental requirement.

A number of assays were also conducted in FEK4 fibroblasts, which are human primary skin fibroblasts. These cells are more susceptible to the effects of UVA radiation because of a higher level of intracellular LI compared to HaCaT cells.[18] This makes them particularly useful as a cell model for evaluating the photoprotective effects of compounds, or as an alternative cell line to HaCaT cells for the cytotoxicity of ICs. FEK4 cells were cultured in 15% FCS-EMEM containing 0.25% NaHCO$_3$, 2mM glutamine and 50 IU/mL penicillin-streptomycin. FEK4 cells were passaged once a week and seeded as follows:

- For MTT and clonogenic assays: $2 \times 10^4$ cells per 3 cm plate in 3 mL media
- For flow cytometry: $12 \times 10^4$ cells per 10 cm plate in 12 mL media

6.4.4. MTT assay

MTT stock solution was prepared in PBS at 5 mg/mL, which was sterilised by filtration through a 0.2 µM filter (Ministart®, Germany) and stored at $-20$ °C. Fresh MTT solution in serum free media (SFM) was prepared from the stock solution at a final concentration of 0.5 mg/mL.

The assay was performed at 24, 48 and 72 hours post-treatment with the parent uncaged (or ‘naked’) arylhydrazones PIH 8, SIH 10, and NIH 11, the NT compounds 54a-b and thiohydrazone analogue H$_2$PTBH (56). After washing each plate with PBS cells were incubated with MTT/SFM (500 µL) for 3 h at 37 °C, after which the MTT/SFM solution was aspirated and DMSO (500 µL) was added to each plate. The plates were swirled on a 3D rocking platform (Stuart Scientific, UK) for 5-10 minutes, after which 20 µL (24 and 48 h) or 10 µL (72 h) of each sample was added in triplicate to a 96 well plate and diluted with DMSO (up to 100 µL). Colorimetric absorbance values were obtained by a VERSAmaxTM plate-reader which scans at 570 nm.
6.4.5. Annexin V / Propidium iodide Dual Staining Assay

This work was undertaken by Dr. Asma Aroun and Dr. Olivier Reelfs in the Pourzand laboratory. After relevant treatments and incubation treatment times, cells were collected and washed with incubation buffer containing 10mM HEPES, 5 M NaCl and 100 mM CaCl₂. Cells were then resuspended in incubation buffer containing Annexin-VFLUOS (20 µL/mL) and PI (20 µg/mL) at a concentration of $5 \times 10^5$ cells / 100 µL. The mixture was then incubated for 20 min at RT in the dark in a polystyrene round-bottom tube, after which 400 µL incubation buffer was added. Data analysis was performed using FACSDiva software (Becton-Dickinson, Erembodegem, Belgium).

6.4.6. ROS assay

This work was undertaken by Dr. Olivier Reelfs and Dr. Asma Aroun. Staining agent CM-H₂DCFDA was freshly-prepared on the day of incubation with the cells (5mM stock solution in DMSO) and maintained under Argon atmosphere and protected from light during storage and use.

FEK4 cells were seeded in 35mm culture dishes and grown for 48h, after which cells were treated with SIH or the CIC 135a or left untreated (control) and incubated for 18 h. Cells were then irradiated with UVA, and immediately after irradiation, cells were treated with CM-H₂DCFDA, (freshly diluted 5 µM solution in PBS) and incubated for 20 mins at 37 °C. Cells were washed with PBS and the cells were trypsinized and resuspended in FACS tubes in 200-300µl PBS containing 0.1% BSA. Propidium iodide (5 µM solution in PBS) was added to the cell suspension just before analysis by flow cytometry on a Beckton Dickinson (BD) Canto II instrument. Cells were gated to exclude debris and PI-positive cells. ROS-mediated fluorescence emitted solely from intact (PI-negative) cells was recorded as the Median Fluorescence intensity.

6.4.7. BrdU assay: cell pulsing and staining

Cells were pulsed by incubating with BrdU (10 µL / well) for 1 h at 37 °C, after which cells were washed with PBS, harvested with 0.25 %w/v trypsin and centrifuged at
1000 rpm for 8 min. The supernatant was removed and cells were permeabilised by ice-cold 70% aq. EtOH solution, added dropwise whilst vortexing to avoid clump formation. Pulsed cells were then stored at 4 °C.

Cells were centrifuged at 2000 rpm and washed twice with PBS, after which cellular DNA was denatured by resuspending the cell suspension in 2M HCl for 30 min with occasional mixing. The acid was removed from the mixture by centrifugation (1000 rpm) and the cells washed with PBS containing BSA and Tween-20 (0.1% and 0.2% respectively). Cells were then stained with the anti-BrdU primary antibody for 20 min at RT in the dark, after which they were washed again with BSA/Tween-20 in PBS and incubated with FITC-conjugated secondary antibody for 20 min in the dark at RT. Cells were then washed with PBS/Tween-20 in PBS and treated with RNase for 15 min at RT, followed by treatment with PI after which cells were incubated at RT in the dark for a further 30 min. Cells were then analysed by flow cytometry, detecting at 515-545 nm for FITC antibody and >580 nm for PI. 20000 events were collected at a low flow rate setup.

6.4.8. Colony forming assay

Cells were seeded at different densities (500-5000 cells/well) and grown for 48 h. Cells were then treated with compounds as described above for 72 h, after which the cell media was removed. Cells were washed with PBS and fresh media was added. Cells were then allowed to grow for 12 days, after which media was removed and colonies were fixed and stained by addition of crystal violet solution (0.2% in EtOH containing paraform aldehyde 2%). Plates were washed with PBS and colonies were counted. Data are expressed as percent survival relative to the control.