SUPPORTING INFORMATION

A Combination of Selective PARP3 and PARP16 Inhibitory Analogs of Latonduine A Corrects F508del-CFTR Trafficking

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Synthetic Chemistry Experimental Procedures

All non-aqueous reactions were carried out in oven dried Pyrex® glassware under an Ar atmosphere unless otherwise noted. Air and moisture sensitive reagents were manipulated using airtight dry syringes. Anhydrous solvents were all obtained from commercial sources and all reagents were obtained from commercial sources without further purification. All $^1$H and $^{13}$C NMR spectra were recorded at 600 and 150 MHz, respectively, as indicated and referenced to the internal residual solvent peak denoted in the experimental description. Flash chromatography was performed using silica gel (230–400 mesh) with the solvent system indicated. All UV reactions were performed in a photo-reactor with a water-cooled Pyrex® filtered 450 W medium pressure mercury lamp.

General Procedure for Schmidt reaction:

A vigorously stirring flask containing tetralone (0.5 g, 1 eq) in concentrated HCl (0.3 M) was cooled to 0 °C. To this mixture was added in several small aliquots NaN₃ (2 eq) over 5 minutes. The mixture was left to stir open to air for 2 hours at 0 °C and then allowed to slowly warm to room temp and stir for another 2 hours. The reaction mixture was then poured over ice and treated with 2 mL of a 10% solution of ceric ammonium nitrate (CAN). Once bubbling had ceased, the reaction mixture was neutralized with a saturated K₂CO₃ solution and the ice was allowed to melt. The reaction mixture was then extracted with (3 X ~10 mL) EtOAc, the organic layers were combined dried over MgSO₄, filtered, and concentrated to give crude products. Purification of the three possible products namely the tetrazole, and two regio-isomeric azepines was accomplished using flash silica gel chromatography as described.
Preparation of 7-amino-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (10) and 6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepin-9-amine (11):

Scheme S1:

Using general procedure above (SI page 3) with 6-amino-3, 4-dihydro-1(2H)-naphthalenone (0.5 g, 3.1 mmol). The crude reaction mixture was obtained as described above. Purification of the crude using flash silica gel chromatography (eluting with 1:3, 1:1, 4:1 and 1:0 (EtOAc/Hex) (200 mL each) (4 X 10 cm column) gave purified starting material (0.291 g), 11 (0.152 g, 51.3% BRSM), and 10 (0.062 g, 23.8% BRSM).

Characterization of 7-amino-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one:

10: \( ^1H\) NMR (600 MHz, acetone-\(d_6\)) \(\delta\) 7.34 (d, \(J = 6.5\) Hz, 1H), 6.83 (bs, 1H), 6.56 (dd, \(J = 8.2, 2.3\) Hz, 1H), 6.46 (s, 1H), 4.99 (bs, 2H), 3.06 (dd, \(J = 14.2, 6.27\) Hz, 2H), 2.67 (dd, \(J = 8.2, 7.1\) Hz, 2H), 1.89 (m, 2H); \(^{13}C\) NMR (150 MHz, acetone-\(d_6\)) \(\delta\) 173.8, 151.9, 140.8, 131.1, 124.9, 114.3, 112.6, 40.0, 31.5, 31.1; positive ion TOFHRESIMS [M+H]+ \(m/z\) 177.1023 (calcd. for \(C_{10}H_{13}N_2O\), 177.1028).

Characterization of 6, 7-dihydro-5H-benzo[c]tetrazolo[1, 5-a]azepin-9-amine (11):

1H NMR (600 MHz, acetone-\(d_6\)) \(\delta\) 8.01 (d, \(J = 8.8\) Hz, 1H), 6.68 (dd, \(J = 8.5, 2.2\) Hz, 1H), 6.61 (d, \(J = 1.8\) Hz, 1H), 5.26 (bs, 2H), 4.61 (dd, \(J = 7.5, 6.3\) Hz, 2H), 2.95 (dd, \(J = 5.8, 7.7\) Hz 2H), 2.32 (m, 2H); \(^{13}C\) NMR (150 MHz, acetone-\(d_6\)) \(\delta\) 155.2, 152.2, 142.7, 132.2, 115.5, 113.3, 111.7, 50.0, 34.3, 26.1; positive ion TOFHRESIMS [M+H]+ \(m/z\) 202.1091 (calcd. for \(C_{10}H_{12}N_5\), 202.1093).

Preparation of 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (12), 7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (13), and 9,10-dimethoxy-6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepine (14):

Scheme S2:
Using the general procedure above (SI page 3) with 6, 7-dimethoxytetralone (0.5 g, 2.4 mmol). Purification of the crude reaction mixture by flash silica gel (eluting with 1:3, 1:1, 3:1 and 1:0 EtOAc/Hex, 200 mL each, 4 X 10 cm column) gave purified starting material (0.164 g), 14 (0.143 g, 35.4 %, BRSM), 13 (0.054 g, 15 %, BRSM), and 12 (0.077 g, 21.4 %, BRSM).

**Characterization of 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (12):** 1H NMR (600 MHz, DMSO-d_6) δ 7.89 (bt, J = 5.5 Hz, 1H), 7.04 (s, 1H), 6.86 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.91 (dd, J = 7.0, 6.3 Hz, 2H), 2.68 (dd, J = 8.21, 6.8 Hz, 2H), 1.86 (m, 2H); 13C NMR (150 MHz, DMSO-d_6) δ 173.3, 147.4, 145.6, 131.4, 125.5, 113.2, 106.5, 55.7, 55.6, 32.8, 29.3, 28.3; positive ion TOFHRESIMS [M+H]^+ m/z 222.1131 (calcd. for C_{12}H_{16}NO_3, 222.1130).

**Characterization of 7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (13):** 1H NMR (600 MHz, DMSO-d_6) δ 9.23 (s, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.60 (dd, J = 7.8, 7.2 Hz, 2H), 2.10 (obs, 2H), 2.07 (m, 2H); 13C NMR (150 MHz, DMSO-d_6) δ 173.3, 147.4, 145.6, 131.4, 125.5, 113.2, 106.5, 55.7, 55.6, 32.8, 29.3, 28.3; positive ion TOFHRESIMS [M+H]^+ m/z 222.1131 (calcd. for C_{12}H_{16}NO_3, 222.1130).

**Characterization of and 9,10-dimethoxy-6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepine (14):** 1H NMR (600 MHz, DMSO-d_6) δ 7.74 (s, 1H), 7.00 (s, 1H), 4.64 (dd, J = 7.0, 6.29 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.01 (dd, J = 5.5, 2.9 Hz, 2H), 2.10 (m, 2H); 13C NMR (150 MHz, DMSO-d_6) δ 153.6, 150.9, 147.3, 145.6, 131.4, 125.5, 113.2, 106.5, 55.6, 55.62, 49.4, 32.4, 24.8; positive ion TOFHRESIMS [M+H]^+ m/z 247.1199 (calcd. for C_{12}H_{16}N_4O_2, 247.1195).

**Preparation of 8-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (15), 8-fluoro-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (16), 10-fluoro-6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepine (17):**

**Scheme S3:**

![Scheme S3](image-url)
Using the general procedure above (SI page 3) with 7-fluoro-tetralone (0.5 g, 3.0 mmol) as starting material. Purification of the crude by flash silica gel chromatography (eluting with 1:4, 1:2, 1:1, 4:1, 1:0, EtOAc/Hex, 200 mL each, 4 X 10 cm column) gave purified starting material (0.2 g), 17 (0.126 g, 33.7 %, BRSM), 16 (0.063 g, 19.4 %, BRSM), and 15 (0.047 g, 14.6 %, BRSM).

Characterization of 8-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (15): \(^{1}\)H NMR (600 MHz, acetone-\(d_6\)) \(\delta 7.38\) (bs, 1H), \(7.29\) (m, 2H), \(7.18\) (td, \(J = 8.6, 2.8\) Hz, 1H), \(3.09\) (dd, \(J = 14.6, 6.4\) Hz, 2H), \(2.82\) (dd, \(J = 8.3, 7.1\) Hz, 2H), \(1.96\) (m, 2H); \(^{13}\)C NMR (150 MHz, acetone-\(d_6\)) \(\delta 171.8, 162.5\) (d, \(J = 247.3\) Hz), \(139.2\) (d, \(J = 8.0\) Hz), \(135.2\) (d, \(J = 3.7\) Hz), \(131.5\) (d, \(J = 7.5\) Hz), \(118.1\) (d, \(J = 21.0\) Hz), \(115.8\) (d, \(J = 23.0\) Hz), 39.7, 31.1, 30.1; positive ion TOFHRESIMS \([\text{M+H}]^+\) \(m/z\) 180.0824 (calcd. for \(\text{C}_{10}\text{H}_{11}\text{NOF}\), 180.0825).

Characterization of 8-fluoro-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (16): \(^{1}\)H NMR (600 MHz, acetone-\(d_6\)) \(\delta 8.74\) (bs, 1H), \(7.28\) (bt, \(J = 7.0\) Hz, 1H), \(6.88\) (td, \(J = 8.6, 2.4\) Hz, 1H), \(2.76\) (dd, \(J = 9.0, 7.2\) Hz, 2H), \(2.26\) (dd, \(J = 9.0, 7.2\) Hz, 2H), \(2.15\) (m, 2H); \(^{13}\)C NMR (150 MHz, acetone-\(d_6\)) \(\delta 173.9, 162.7\) (d, \(J = 251.7\) Hz), \(141.6\) (d, \(J = 12.6\) Hz), \(131.9\) (d, \(J = 10.1\) Hz), \(131.0, 112.0\) (d, \(J = 21.4\) Hz), \(109.4\) (d, \(J = 21.4\) Hz), 33.7, 30.4, 29.0; positive ion TOFHRESIMS \([\text{M+H}]^+\) \(m/z\) 180.0826 (calcd. for \(\text{C}_{10}\text{H}_{11}\text{NOF}\), 180.0825).

Characterization of 10-fluoro-6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepine (17): \(^{1}\)H NMR (600 MHz, acetone-\(d_6\)) \(\delta 7.97\) (dd, \(J = 10.0, 3.4\) Hz, 1H), \(7.45\) (d, \(J = 6.1\) Hz, 1H), \(7.27\) (td, \(J = 8.7, 3.4\) Hz, 1H), \(4.74\) (dd, \(J = 7.8, 6.1\) Hz, 2H), \(3.12\) (dd, \(J = 7.6, 5.9\) Hz, 2H), \(2.42\) (m, 2H); \(^{13}\)C NMR (150 MHz, acetone-\(d_6\)) \(\delta 163.0\) (d, \(J = 240.5\) Hz), \(154.0\) (d, \(J = 2.6\) Hz), \(137.9\) (d, \(J = 3.1\) Hz), \(133.5\) (d, \(J = 7.3\) Hz), \(126.1\) (d, \(J = 9.9\) Hz), \(118.9\) (d, \(J = 20.0\) Hz), \(116.7\) (d, \(J = 24.8\) Hz), 50.5, 33.1, 26.2; positive ion TOFHRESIMS \([\text{M+H}]^+\) \(m/z\) 205.0891 (calcd. for \(\text{C}_{10}\text{H}_{10}\text{N}_{4}\text{F}\), 205.0891).

Preparation of 6-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (18) and 6-hydroxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (19):
Scheme S4:

Using general methodology above (SI page 3) with 5-hydroxy-1-tetralone (0.5 g, 3.1 mmol). Purification of the crude reaction mixture by flash silica gel chromatography (eluting with 1:3, 1:1, 4:1 and 1:0 EtOAc/Hex, 200 mL each, 4 X 10 cm column) gave purified starting material (0.216 g), 19 (0.114 g, 36.8 % BRSM), and 18 (0.078 g, 22 % BRSM).

Characterization of 6-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (18): $^1$H NMR (600 MHz, DMSO-$d_6$) δ 9.55 (s, 1H), 7.91 (bs, 1H), 7.09 (t, $J = 8.0$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 2H), 2.86 (d, $J = 12.6$, 6.3 Hz, 2H), 2.73 (d, $J = 8.3$, 7.0 Hz, 2H), 1.78 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 171.9, 153.8, 137.7, 126.9, 123.7, 118.6, 117.0, 38.5, 29.2, 20.8; positive ion TOF-HRESIMS [M+H]$^+$ m/z 178.0865 (calcd. for C$_{10}$H$_{12}$NO$_2$, 178.0868).

Characterization of 6-hydroxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (19): $^1$H NMR (600 MHz, DMSO-$d_6$) δ 9.44 (s, 1H), 9.41 (s, 1H), 6.96 (t, $J = 7.9$ Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 6.43 (d, $J = 7.9$ Hz, 1H), 2.66 (dd, $J = 8.3$, 7.6 Hz, 2H), 2.12 (dd, $J = 7.7$, 7.0 Hz, 2H), 2.02 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 173.4, 155.1, 140.3, 126.7, 119.8, 112.6, 111.4, 33.2, 27.3, 21.7; positive ion TOF-HRESIMS [M+H]$^+$ m/z 178.0869 (calcd. for C$_{10}$H$_{12}$NO$_2$, 178.0868).

Preparation of 2-(2-(trimethylsilyl)ethyl)isoindoline-1,3-dione (20):

Scheme S5:

To a round bottom flask was added a solution of phthalimide (1 g, 6.8 mmol), Cs$_2$CO$_3$ (2.215 g, 6.8 mmol) and DMF (19 mL) under Ar atmosphere and stirred for 1 hour at room temperature. The mixture was then cooled to 0 °C and bromoethyltrimethylsilane (0.903 mL, 5.7 mmol) was added dropwise over 5 min.
The reaction mixture was heated to 80 °C for 18 hours. The reaction was then poured into (~200 mL) H₂O and extracted with EtOAc (2 X 75 mL). The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product. Purification was accomplished with flash silica gel chromatography (eluting with EtOAc/Hex (1:1 then 2:1)) to give 2-(2-(trimethylsilyl)ethyl)isoindoline-1,3-dione (20), as a white solid (0.210 g, 15%). ¹H NMR (600 MHz, CDCl₃) δ 7.81 (dd, J = 5.3, 2.8 Hz, 2H), 7.67 (dd, J = 5.3, 2.8 Hz, 2H), 3.70 (m, 2H), 1.00 (m, 2H), 0.05 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 169.5, 134.0, 132.5, 123.3, 34.7, 17.3, -1.6; positive ion LRESIMS [M+Na]⁺ m/z 270.0 (calcd. for C₁₃H₁₇NO₂SiNa, 270.0).33

Preparation of 3,4-dihydro-1H-benzo[c]azepine-1,5(2H)-dione (21):

Scheme S6:

![Scheme S6](image)

To a Pyrex® test tube was added 20 (0.05 g, 0.2 mmol), and 22.4 mL of a 35%(v/v) H₂O/ACN solution. The tube was sealed using a rubber septa and degassed using N₂. The tube was then irradiated with UV light for 2 hours in an ice bath. The reaction mixture was then concentrated under reduced pressure and partitioned between H₂O (30 mL) and EtOAc (3 X 10 mL). The organic layers were combined, dried with MgSO₄, filtered and concentrated. Subsequent silica gel chromatography (eluting with 10% MeOH/EtOAc) gave starting material (0.017 g) and 3, 4-dihydro-1H-benzo[c]azepine-1,5(2H)-dione (21) (13.5 mg, 58% BRSM). It should be noted that the literature procedure performed the UV irradiation in a Vycor reaction vessel.33

¹H NMR (600 MHz, DMSO-d₆) δ 7.85 (d, J = 8.0 Hz, 1H), 7.71 (td, J = 7.1, 1.4 Hz, 1H), 7.65 (m, 2H), 3.56 (dd, J = 11.1, 6.0 Hz, 2H), 2.96 (dd, J = 6.7, 4.8 Hz, 2H); ¹³C NMR (150 MHz, DMSO-d₆) δ 203.4, 170.5, 137.5, 134.2, 133.2, 132.3, 130.8, 128.9, 47.1, 37.7; positive ion TOFHRESIMS, [M+H]⁺ m/z 176.0708 (calcd. for C₁₀H₁₀NO₂, 176.0712).33
Preparation of (+/-)-5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (22):

**Scheme S7:**

To a stirred solution of **21** (0.01 g, 0.06 mmol) and MeOH (1.5 mL) in a round bottom flask under Ar was added NaBH₄ (0.002 g, 0.06 mmol) in one portion. After 2 hours the reaction was stopped by the addition of 1 mL H₂O and concentrated under a stream of nitrogen. Crude product purified using silica gel chromatography (eluting with MeOH/EtOAc (1:9)) to give (+/-)-5-hydroxy-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (22) as a white solid (0.009 g, 89%).

1H NMR (600 MHz, DMSO-d₆) δ8.00 (bt, J = 5.7 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.48 (td, J = 7.2, 1.3 Hz, 1H), 7.44 (dd, J = 7.5, 1.0 Hz, 1H), 7.32 (td, J = 7.6 Hz, 1H), 5.42 (d, J = 4.8 Hz, 1H), 4.77 (m, 1H), 2.98 (m, 1H), 2.71 (m, 1H), 2.34 (m, 1H), 1.55 (m, 1H); 13C NMR (150 MHz, DMSO-d₆) δ 171.2, 141.9, 133.1, 130.4, 127.6, 126.9, 123.9, 68.3, 39.3, 37.6; positive ion TOFHRRESIMS [M+H]+ m/z 178.0870 (calcd. for C₁₀H₁₂NO₂, 178.0868).

Preparation of 5,6-dichloro-2-(2-(trimethylsilyl)ethyl)isoindoline-1,3-dione (23):

**Scheme S8:**

A solution of 4, 5-dichlorophthalimide (1 g, 4.6 mmol) and Cs₂CO₃ (1.49 g, 4.6 mmol) under Ar atmosphere was stirred for 1 hour at room temperature in a round bottom flask. The mixture was then cooled to 0 °C and bromoethyltrimethylsilane (0.61 mL, 3.8 mmol) was added dropwise over 5 minutes. The reaction mixture was then heated to 80 °C for 18 hours. After this the reaction was poured into (~200 mL) H₂O and extracted with EtOAc (2 X 75 mL). The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product. The crude was purified via silica gel chromatography (eluting with EtOAc/Hex (3:20)) to give 5, 6-dichloro-2-(2-(trimethylsilyl)ethyl)isoindoline-1, 3-dione (23), as an off-white solid (0.253 g,
21.1%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$7.89 (s, 2H), 3.68 (m, 2H), 0.97 (m, 2H), 0.05 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$166.4, 138.9, 131.7, 125.4, 35.3, 17.2, -1.5; positive ion LRESIMS [M+H]$^+$ m/z 316.2 (calcd. for C$_{13}$H$_{16}$NO$_2$SiCl, 316.0).

**Preparation of 7,8-dichloro-3,4-dihydro-1H-benzo[c]azepine-1,5(2H)-dione (24):**

**Scheme S9:**

![Scheme S9](image)

To a Pyrex® test tube was added 23 (0.221g, 0.702 mmol) in 25 mL of (1:4) H$_2$O/ACN (ACN content increased for 23 solubility). The tube was sealed using a rubber septa and degassed using N$_2$. The tube was irradiated with UV light for 2 hours at 0°C. The reaction mixture was then concentrated under reduced pressure and partitioned between H$_2$O (30 mL) and EtOAc (3 X 10 mL). The organic layers were combined, dried with MgSO$_4$, filtered and concentrated. The crude product was purified using silica gel chromatography (eluting with 5% MeOH/EtOAc) to give 7,8-dichloro-3, 4-dihydro-1H-benzo[c]azepine-1, 5(2H)-dione (24) as a white solid (0.063 g, 37%). It should be noted that the literature procedure performed the UV irradiation in a Vycor reaction vessel $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$8.74 (t, $J$ = 5.9 Hz, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 3.37 (m, 2H), 2.92 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$200.6, 167.0, 135.6, 135.4, 134.3, 131.8, 129.9, 45.7, 36.1; positive ion HRESIMS [M+H]$^+$ 243.9927 (calcd. for C$_{10}$H$_8$NO$_2$Cl$_2$, 243.9932).

**Preparation of (+/-)-7,8-dichloro-5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine-1-one (25):**

**Scheme S10:**

![Scheme S10](image)

A solution of 24 (0.02 g, 0.08 mmol) and NaBH$_4$ (0.003 g, 0.08 mmol), in 2 mL absolute MeOH was assembled in a small glass vial under Ar atmosphere. After 2 hours the reaction was stopped by the addition of 1 mL H$_2$O and concentrated under a stream of nitrogen. The product was purified using silica gel chromatography
(eluting with MeOH/EtOAc (1:9)) to give (+/-)-7,8-dichloro-5-hydroxy-2, 3, 4, 5-
tetrahydro-1H-benzo[c]azepin-1-one (25), as a light tan solid (0.018 g, 90%). $^1$H
NMR (600 MHz, DMSO-$d_6$) $\delta$8.26 (bt, $J = 4.9$ Hz, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 5.75
(bs, 1H), 4.78 (t, $J = 8.6$ Hz, 1H), 3.04 (m, 1H), 2.80 (m, 1H), 2.39 (m, 1H), 1.59 (m,
1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$168.8, 142.9, 133.5, 133.1, 129.8, 126.3, 67.6,
38.7, 37.4; positive ion HRESIMS [M+H]$^+$ $m/z$ 246.0093 (calcd. for C$_{10}$H$_{10}$NO$_2$Cl$_2$,
246.0089).

**General Procedure for reactions of the following type:**

**Scheme S11:**

Following a procedure from Suau et al.,$^{32}$ to a Pyrex® Erlenmeyer flask containing
140 mL of ACN with 25 mL of H$_2$O, was added phthalimide (1 g, 6.8 mmol), and NaOH
(1M, 2 mL). The reaction vessel was capped with a rubber septum, and styrene or substituted styrene derivative (2 eq) was added and the reaction mixture
was degassed using a stream of N$_2$. The reaction was subsequently irradiated for 2
hours in an ice bath after which point the reaction was acidified using 1M HCl. The
mixture was then concentrated under reduced pressure and (~50 mL) H$_2$O was
added. The mixture was then extracted with EtOAc (3 X 20 mL). The organic layers
were combined, washed with brine, dried over MgSO$_4$, filtered, and concentrated
under reduced pressure. The mixture was purified using flash silica gel chromatography as described below.

**Preparation of (+/-)-4-(pyridin-2-yl)-3,4-dihydro-1H-benzo[c]azepine-1,5(2H)-dione
(27):**

**Scheme S12:**
Using general procedure above (SI page 11) substituting 2-vinyl pyridine (2.5 eq, 1.44 mL) for styrene. Purified using flash silica gel chromatography (eluting with a step gradient Hex/EtOAc (3:4), EtOAc, and 5 % MeOH/EtOAc) to give (+/-)-4-(pyridin-2-yl)-3, 4-dihydro-1H-benzo[c]azepine-1, 5(2H)-dione (27) (0.087 g, 5.1 %) as a yellow solid. Given the broad signals for the methylene on the azepine ring it is thought that the compound exists in dynamic equilibrium with the enol tautomer. $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.58 (t, $J = 6.8$ Hz, 1H), 8.50 (d, $J = 4.8$ Hz, 1H), 7.97 (td, $J = 8.7$, 1.0 Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.82 (d, $J = 7.7$ Hz, 1H), 7.65 (m, 2H), 7.57 (t, $J = 7.7$ Hz, 1H), 7.26 (dd, $J = 7.7$, 5.8 Hz, 1H), 4.05 (bs, 1H), 3.61 (bs, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 168.7, 163.8, 155.8, 143.9, 138.8, 134.9, 133.9, 130.6, 129.5, 129.4, 127.2, 119.4, 118.6, 107.2, 36.9; positive ion TOFHIRSIMS [M+H]$^+$ m/z 253.0975 (calcd. for C$_{15}$H$_{13}$N$_2$O$_2$, 253.0977).

Preparation of (+/-)-4-(3,4-dimethoxyphenyl)-3,4-dihydro-1H-benzo[c]azepine-1,5(2H)-dione (30):

Scheme S13:

Using general procedure above substituting 3, 4-dimethoxy styrene (2.0 mL, 2 eq) for styrene. Purified using flash silica gel chromatography (eluting with 5 % MeOH/EtOAc) to give (+/-)-4-(3, 4-dimethoxyphenyl)-3, 4-dihydro-1H-benzo[c]azepine-1, 5(2H)-dione (30) (0.017 g, 0.8 %) as a yellow solid. Thought to exist as a rapidly converting mixture with enol tautomer. $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.53 (t, $J = 5.6$ Hz, 1H), 7.77 (d, $J = 9.4$ Hz, 1H), 7.71 (t, $J = 7.5$ Hz, 1H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 1H), 6.73 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.52 (bs, 1H), 3.87 (dd, $J = 14.9$, 5.2 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.22 (dd, $J = 15.0$, 6.5 Hz, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 205.9, 169.2, 148.4 (X 2), 137.0, 132.7, 132.2 (X 2), 131.5, 129.2, 127.7, 117.7, 111.3, 109.4, 83.9, 55.5, 55.3, 49.4;
$^1$H NMR (600 MHz, acetone-$d_6$) $\delta$7.87 (d, $J$ = 7.7 Hz, 1H), $\delta$7.74 (td, $J$ = 7.7, 1.5 Hz, 1H), $\delta$7.70 (td, $J$ = 7.7, 1.5 Hz, 1H), $\delta$7.66 (bs, 1H), $\delta$7.49 (d, $J$ = 7.7 Hz, 1H), $\delta$6.88 (d, $J$ = 7.9 Hz, 1H), $\delta$6.82 (d, $J$ = 1.9 Hz, 1H), $\delta$6.72 (d, $J$ = 7.9, 1.9 Hz, 1H), $\delta$4.15 (dd, $J$ = 10.5, 4.0 Hz, 1H), $\delta$3.85 (ddd, $J$ = 15.2, 10.5, 15.2, 4.8 Hz, 1H), $\delta$3.78 (s, 3H), $\delta$3.74 (s, 3H), $\delta$3.68 (ddd, $J$ = 15.2, 6.5, 4.8 Hz, 1H); $^{13}$C NMR (150 MHz, acetone-$d_6$) $\delta$205.6, 170.4, 150.5, 149.9, 138.6, 133.7, 133.0, 132.6, 131.6, 130.5, 128.9, 121.2, 113.2, 113.0, 62.4, 56.19, 56.17, 44.8; positive ion TOFHRESIMS [M+H]$^+$ m/z 312.1242 (calcd. for C$_{18}$H$_{18}$NO$_4$, 312.1236).

**General transformation scheme for reduction of the following type:**

**Scheme S14:**

To a stirred solution of azepinedione (1 eq) was added NaBH$_4$ (1.2 eq) under Ar atmosphere in absolute MeOH (~2 mL). This was stirred while monitoring by TLC with another equivalent of NaBH$_4$ added every 2 hours. Once complete consumption of starting material had been achieved, H$_2$O was added and the reaction mixture was concentrated. The reaction was then partitioned between H$_2$O (~15 mL) and EtOAc (3 X 7 mL). The organic layers were combined, concentrated, and subjected to silica gel column chromatography as described below.

**Preparation of (+/-)-5-hydroxy-4-(pyridin-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one 28:**

**Scheme S15:**

Using general procedure above 27 (0.01 g, 0.04 mmol), NaBH$_4$ (1.8 mg, 0.05 mmol) and absolute MeOH were added to a small glass vial. The crude product was purified by flash chromatography (eluting with MeOH/EtOAc (1:9)) to give (+/-)-5-hydroxy-4-(pyridin-2-yl)-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (28) as a white solid.
(0.009 g, 89%). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.33 (d, $J$ = 3.4 Hz, 1H), 8.15 (bt, $J$ = 5.6 Hz, 1H), 7.64 (t, $J$ = 6.8 Hz, 1H), 7.53 (d, $J$ = 6.8 Hz, 1H), 7.46 (t, $J$ = 6.8 Hz, 1H), 7.36 (t, $J$ = 7.9 Hz, 1H), 7.28 (d, $J$ = 6.8 Hz, 1H), 7.17 (m, 1H), 7.12 (d, $J$ = 6.8 Hz, 1H), 5.52 (bs, 1H), 5.19 (d, $J$ = 7.1 Hz, 1H), 3.81 (m, 1H), 3.33 (obs, 1H), 3.21 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 171.2, 158.6, 148.1, 140.6, 135.6, 132.9, 130.0, 127.5, 126.9, 125.4, 124.6, 121.7, 70.2, 54.3, 43.3; positive ion HRESIMS [M+H]$^+$ 255.1134 (calcd. for C$_{15}$H$_{15}$N$_2$O$_2$, 255.1134).

Preparation of (+/-)-4-(3, 4-dimethoxyphenyl)-5-hydroxy-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (31):

Scheme S16:

Using general procedure above 30 (0.01 g, 0.03 mmol), NaBH$_4$ (1.4 mg, 0.036 mmol), and absolute MeOH were added to a small glass vial. The crude product was purified using column chromatography (eluting with MeOH/EtOAc (9:1)) to give (+/-)-4-(3, 4-dimethoxyphenyl)-5-hydroxy-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (31) product as an off white solid (0.007 g, 75%). $^1$H NMR (600 MHz, acetone-$d_6$) $\delta$ 7.67 (d, $J$ = 7.7 Hz, 1H), 7.55 (m, 2H), 7.43 (m, 1H), 7.33 (bs, 1H), 6.78 (d, $J$ = 8.8 Hz, 1H), 6.53 (dd, $J$ = 8.3, 1.8 Hz, 1H), 6.45 (d, $J$ = 2.0 Hz, 1H), 5.38 (dd, $J$ = 8.2, 5.2 Hz, 1H), 4.07 (d, $J$ = 5.6 Hz, 1H), 3.78 (m, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 3.40 (m, 1H), 3.14 (m, 1H); $^{13}$C NMR (150 MHz, acetone-$d_6$) $\delta$ 172.3, 149.7, 149.5, 141.4, 134.2, 131.8, 131.1, 129.0, 128.0, 126.4, 122.7, 113.8, 112.4, 71.8, 56.0, 55.7, 54.2, 46.7; positive ion HRESIMS [M+Na]$^+$ m/z 336.1217 (calcd. for C$_{18}$H$_{19}$NO$_4$Na, 336.1212).

Preparation of (+/-)-3-(hydroxymethyl)-3, 4-dihydro-1H-benzo[c]azepine-1, 5(2H)-dione (32):
Scheme S17:

Following the procedure from Suau et al., a Pyrex® Erlenmeyer flask containing 140 mL of ACN with 25 mL of H₂O, phthalimide (1 g, 6.8 mmol), and NaOH (1M, 2 mL) was capped using a rubber septum, and allyl trimethylsilyl ether (2.29 mL, 13.6 mmol) was added. The reaction mixture was then degassed using a stream of N₂. The reaction was subsequently irradiated for 2hrs in an ice bath after which point the reaction was acidified using 1M HCl. The mixture was then concentrated under reduced pressure and H₂O (~50 mL) was added. The mixture was extracted with EtOAc (3 X 20 mL) and the organic layers were combined, dried over MgSO₄, filtered, and concentrated under reduced pressure. The mixture was purified using flash silica gel chromatography (eluting with Hex/EtOAc (3:4), EtOAc, and 5 % MeOH/EtOAc) to give (+/-)-3-(hydroxymethyl)-3, 4-dihydro-1H-benzo[c]azepine-1, 5(2H)-dione (32) (0.011 g, 0.8 %) as a white solid. ¹H NMR (600 MHz, DMSO-d₆) δ 8.17 (d, J = 5.4 Hz, 1H), 7.77 (dd, J = 7.7, 1.0 Hz, 1H), 7.71 (td, J = 7.6, 1.0 Hz, 2H), 7.66 (td, J = 7.6, 1.0 Hz, 1H), 7.56 (bd, 7.7 Hz, 1H), 4.88 (t, J = 5.8 Hz, 1H), 3.72 (m, 1H), 3.51 (m, 2H), 2.94 (dd, J = 18.8, 2.7 Hz, 1H), 2.79 (dd, J = 18.8, 11.6 Hz, 1H); ¹³C NMR (150 MHz, DMSO-d₆) δ 202.5, 168.5, 136.4, 133.2, 132.4, 131.4, 129.4, 127.5, 61.7, 50.6, 48.8; positive ion TOFHRESIMS [M+Na]⁺ m/z 228.0644 (calcd. for C₁₁H₁₁NO₃Na, 228.0637).

Preparation of (+/-)-(3S*, 5S*)-5-hydroxy-3-(hydroxymethyl)-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (33) and 34:

Scheme S18:
To a small vial was added 32 (0.01 g, 0.076 mmol) and NaBH$_4$ (0.003 g, 0.076 mmol) under Ar atmosphere in absolute MeOH (1.5 mL). The reaction was stirred for 2 hours at which point another aliquot of NaBH$_4$ was added. After another 2hr period, the reaction was quenched using 0.5 mL of a saturated NH$_4$Cl (sol), concentrated under a stream of N$_2$, and partitioned between H$_2$O (10 mL) and EtOAc (3 X 3 mL) to give the diasteriomeric crude alcohol in the organic layer. Purification of the crude product using C$_{18}$ reversed phase HPLC (eluting with 15 % ACN/H$_2$O) gave the *cis* (33)(2.5 mg, rt = 11 min) and *trans* (34)(5.4 mg, rt = 10 min) diastereomers as individual peaks.

**Characterization of (+/-)-(3S*, 5S*)-5-hydroxy-3-(hydroxymethyl)-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (33):** $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$7.52 (dd, $J$ = 7.4, 1.2 Hz, 1H), 7.44 (d, $J$ = 6.2 Hz, 1H), 7.41 (td, $J$ = 7.9, 1.2 Hz, 1H), 7.37 (td, $J$ = 7.9, 1.2 Hz, 1H), 7.28 (d, $J$ = 7.3 Hz, 1H), 5.23 (bs, 1H), 4.81 (d, $J$ = 4.5 Hz, 1H), 4.65 (t, $J$ = 5.6 Hz, 1H), 3.28 (obs, 2H), 3.16 (d, $J$ = 5.1 Hz, 1H) 3.03 (m, 1H), 2.09 (m, 1H), 1.88 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-d$_6$) $\delta$ 170.7, 142.3, 132.8, 130.0, 127.5, 126.8, 123.3, 70.2, 62.5, 51.8, 41.3; positive ion TOFHRESIMS [M+Na]$^+$ m/z 230.0795 (calcd. for C$_{11}$H$_{13}$NO$_3$Na, 230.0793).

**Characterization of (+/-)-(3S*, 5R*)-5-hydroxy-3-(hydroxymethyl)-2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-1-one (34):** $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$7.66 (d, $J$ = 4.6 Hz, 1H), 7.60 (d, $J$ = 7.2 Hz, 1H), 7.51 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.47 (dd, $J$ = 7.7, 1.2 Hz, 1H), 7.35 (t, $J$ = 7.5 Hz, 1H), 5.50 (d, $J$ = 6.0 Hz, 1H), 4.79 (m, 1H), 4.68 (t, $J$ = 5.3 Hz, 1H), 3.42 (m, 2H), 3.16 (d, $J$ = 5.5 Hz, 1H) 2.96 (m, 1H), 2.18 (m, 1H), 1.58 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-d$_6$) $\delta$ 170.4, 142.3, 132.8, 130.5, 127.3, 126.8, 123.2, 67.6, 62.3, 52.3, 42.4; positive ion TOFHRESIMS [M+Na]$^+$ m/z 230.0795 (calcd. for C$_{11}$H$_{13}$NO$_3$Na, 230.0793).
General NMR Acquisition Parameters

The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV-600 spectrometer with a 5 mm CPTCI cryoprobe. $^1$H chemical shifts are referenced to the residual DMSO-$d_6$, (δ 2.49 ppm), acetone-$d_6$ (δ 2.05 ppm), MeOD-$d_4$ (δ 3.31, δ 4.78 ppm), CDCl$_3$ (δ 7.24 ppm) and $^{13}$C chemical shifts are referenced to the solvent peaks for DMSO-$d_6$ (δ 39.5 ppm), Acetone-$d_6$ (δ 29.9, δ 206.7 ppm), MeOD-$d_4$ (δ 49.1 ppm), and CDCl$_3$ (δ 77.2 ppm).

Experimental Procedures

All $^1$H and $^{13}$C NMR spectra were recorded at 600 and 150 MHz, respectively, as indicated and referenced to the internal residual solvent peak denoted in the experimental description.
Figure S1. $^1$H NMR spectrum of 5 in DMSO-$d_6$ at 600 MHz
Figure S2: $^{13}$C NMR spectrum of 5 in DMSO-$d_6$ at 150 MHz.
Figure S3: $^1$H NMR spectrum of 6 in MeOD-$d_4$ at 600 MHz.
Figure S4: $^{13}$C NMR spectrum of 6 in MeOD-$d_4$ at 150 MHz.
Figure S5: $^1$H NMR spectrum of 10 in acetone-$d_6$ at 600 MHz
Figure S6: $^{13}$C NMR spectrum of 10 in acetone-$d_6$ at 150 MHz.
Figure S7: $^1$H NMR spectrum of 11 in acetone-$d_6$ at 600 MHz.
Figure S8: $^{13}$C NMR spectrum of 11 in acetone-$d_6$ at 150 MHz.
Figure S9: $^1$H NMR spectrum of 12 in DMSO-$d_6$ at 600 MHz.
Figure S10: $^{13}$C NMR spectrum of 12 in DMSO-$d_6$ at 150 MHz.
Figure S11: $^1$H NMR spectrum of 13 in DMSO-$d_6$ at 600 MHz.
Figure S12: $^{13}$C NMR spectrum of 13 in DMSO-$d_6$ at 150 MHz.
Figure S13: $^1$H NMR spectrum of 14 in DMSO-$d_6$ at 600 MHz.
Figure S14: $^{13}$C NMR spectrum of 14 in DMSO-$d_6$ at 150 MHz.
Figure S15: $^1$H NMR spectrum of 15 in acetone-$d_6$ at 600 MHz.
Figure S16: $^{13}$C NMR spectrum of 15 in acetone-$d_6$ at 150 MHz.
Figure S17: $^1$H NMR spectrum of 16 in acetone-$d_6$ at 600 MHz.
Figure S18: $^{13}$C NMR spectrum of 16 in acetone-$d_6$ at 150 MHz.
Figure S19: $^1$H NMR spectrum of 17 in acetone-$d_6$ at 600 MHz.
Figure S20: $^{13}$C NMR spectrum of 17 in acetone-$d_6$ at 150 MHz.
Figure S21: $^1$H NMR spectrum of 18 in DMSO-$d_6$ at 600 MHz.
Figure S22: $^{13}$C NMR spectrum of 18 in DMSO-$d_6$ at 150 MHz.
Figure S23: $^1$H NMR spectrum of 19 in DMSO-$d_6$ at 600 MHz.
Figure S24: $^{13}$C NMR spectrum of 19 in DMSO-$d_6$ at 150 MHz.
Figure S25: $^1$H NMR spectrum of 22 in DMSO-$d_6$ at 600 MHz.
Figure S26: $^{13}$C NMR spectrum of 22 in DMSO-$d_6$ at 150 MHz.
Figure S27: $^1$H NMR spectrum of 23 in CDCl$_3$ at 600 MHz.
Figure S28: $^{13}$C NMR spectrum of 23 in CDCl$_3$ at 150 MHz.
Figure S29: $^1$H NMR spectrum of 24 in DMSO-$d_6$ at 600 and 150 MHz.
Figure S30: $^{13}$C NMR spectrum of 24 in DMSO-$d_6$ at 150 MHz.
Figure S31: $^1$H NMR spectrum of 25 in DMSO-$d_6$ at 600 MHz.
Figure S32: $^{13}$C NMR spectrum of 25 in DMSO-$d_6$ at 150 MHz.
Figure S33: $^1$H NMR spectrum of 26 in DMSO-$d_6$ at 600 MHz.
Figure S34: $^{13}$C NMR spectrum of 26 in DMSO-$d_6$ at 150 MHz.
Figure S35: $^1$H NMR spectrum of 27 in DMSO-$d_6$ at 600 MHz.
Figure S36: $^{13}$C NMR spectrum of 27 in DMSO-$d_6$ at 150 MHz.
Figure S37: $^1$H NMR spectrum of 28 in DMSO-$d_6$ at 600 MHz.
Figure S38: $^{13}$C NMR spectrum of 28 in DMSO-$d_6$ at 150 MHz.
Figure S39: $^1$H NMR spectrum of 29 in DMSO-$d_6$ at 600 MHz.
Figure S40: $^{13}$C NMR spectrum of 29 in DMSO-$d_6$ at 150 MHz.
Figure S41: $^1$H NMR spectrum of 30 in DMSO-$d_6$ at 600 MHz.
Figure S42: $^{13}$C NMR spectra of 30 in DMSO-$d_6$ at 150 MHz.
Figure S43: $^1$H NMR spectrum of 30 in acetone-$d_6$ at 600 MHz
Figure S44: $^{13}$C NMR spectrum of 30 in acetone-$d_6$ at 150 MHz
Figure S45: $^1$H NMR spectrum of 31 in acetone-$d_6$ at 600 MHz.
Figure S46: $^{13}$C NMR spectrum of 31 in acetone-$d_6$ at 150 MHz.
Figure S47: $^1$H NMR spectrum of 32 in DMSO-$d_6$ at 600 MHz.
Figure S48: $^{13}$C NMR spectrum of 32 in DMSO-$d_6$ at 150 MHz.
Figure S49: $^1$H NMR spectrum of 33 in DMSO-$d_6$ at 600 MHz.
Figure S50: $^{13}$C NMR spectrum of 33 in DMSO-$d_6$ at 150 MHz.
Figure S51: tROESY NMR spectra of 33 in DMSO-$d_6$ at 600 MHz
Figure S52: $^1$H NMR spectrum of 34 in DMSO-$d_6$ at 600 MHz.
Figure S53: $^{13}$C NMR spectrum of 34 in DMSO-$d_6$ at 150 MHz.
Figure S54: tROESY NMR spectrum of 34 in DMSO-$d_6$ at 600 MHz
X-ray Diffraction Analysis of (4R,5S)-7,8-dichloro-5-hydroxy-4-(pyridin-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (6):

![ORTEP Diagram of 6]

**Figure S55: ORTEP Diagram of 6.**

Data Collection

A colourless irregular crystal of C_{15}H_{12}N_{2}O_{2}Cl_{2} having approximate dimensions of 0.02 x 0.16 x 0.27 mm was mounted on a glass fiber. All measurements were made on a Bruker APEX DUO diffractometer with a TRIUMPH curved-crystal monochromator with Mo-Kα radiation.

The data were collected at a temperature of -183.0 ± 0.1°C to a maximum 2θ value of 55.8°. Data were collected in a series of φ and ω scans in 0.5° oscillations using 10.0-second exposures. The crystal-to-detector distance was 38.25 mm.
Data Reduction

Of the 11617 reflections that were collected, 3349 were unique ($R_{\text{int}} = 0.041$); equivalent reflections were merged (Friedel's pairs excluded). Data were collected and integrated using the Bruker SAINT\textsuperscript{1} software package. The linear absorption coefficient, $\mu$, for Mo-K\textalpha radiation is 4.64 cm\textsuperscript{-1}. Data were corrected for absorption effects using the multi-scan technique (SADABS\textsuperscript{2}), with minimum and maximum transmission coefficients of 0.897 and 0.991, respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods\textsuperscript{3}. All non-hydrogen atoms were refined anisotropically. H2O and H2N hydrogen atoms were located in difference maps and refined isotropically. All other hydrogen atoms were placed in calculated positions. The absolute configuration was determined on the basis of the refined Flack\textsuperscript{12} parameter, -0.02(3). The final cycle of full-matrix least-squares refinement\textsuperscript{4} on $F^2$ was based on 3349 reflections and 198 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R_1 (I>2.00\sigma(I)) = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|} = 0.033$$

$$wR_2 \text{(all data)} = \frac{\sum (w(F_o^2 - F_c^2)^2)}{\sum w(F_o^2)^2}^{1/2} = 0.068$$

The standard deviation of an observation of unit weight\textsuperscript{5} was 1.03. The weighting scheme was based on counting statistics. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.26 and $-0.27$ e$^-$/Å$^3$, respectively.
Neutral atom scattering factors were taken from Cromer and Waber\(^6\). Anomalous dispersion effects were included in Fcalc\(^7\); the values for \(\Delta f'\) and \(\Delta f''\) were those of Creagh and McAuley\(^8\). The values for the mass attenuation coefficients are those of Creagh and Hubbell\(^9\). All refinements were performed using the XL\(^{10}\) via the OLEX2\(^{11}\) interface.

**References**

(1) SAINT. Version 8.34A Bruker AXS Inc., Madison, Wisconsin, USA. (1997-2013).

(2) Krause, L.; Herbst-Irmer, R.; Stalke, D. "An empirical correction for the influence of low-energy contamination" J. Appl. Crystallogr. 2015, 48, 1907-1913.

(3) Sheldrick, G. M. "SHELXT - Integrated space-group and crystal-structure determination" Acta Cryst. 2015, A71, 3-8.

(4) Least Squares function minimized:

\[
\Sigma w(F_o^2 - F_c^2)^2
\]

(5) Standard deviation of an observation of unit weight:

\[
\left[\Sigma w(F_o^2 - F_c^2)^2/(N_o - N_v)\right]^{1/2}
\]

where:

- \(N_o\) = number of observations
- \(N_v\) = number of variables

(6) Cromer, D. T.; Waber, J. T. in International Tables for X-ray Crystallography, Vol. IV; Ibers, J.K.A. and Hamilton, J.C., Ed; The Kynoch Press: Birmingham, England, 1974; Table 2.2 A.

(7) Ibers, J. A.; Hamilton, W. C. "Dispersion corrections and crystal structure refinements" Acta Cryst. 1964, 17, 781 -782.

(8) Creagh, D. C.; McAuley, W.J . in International Tables for Crystallography, Vol C; Wilson, A.J.C., Ed.; Kluwer Academic Publishers: Boston, 1992; Table 4.2.6.8, pp 219-222.
EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula  
\( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O}_{2}\text{Cl}_{2} \)

Formula Weight  
323.17

Crystal Colour, Habit  
colourless, irregular

Crystal Dimensions  
0.02 x 0.16 x 0.27 mm

Crystal System  
orthorhombic

Lattice Type  
Primitive

Lattice Parameters  
\( a = 7.3051(14) \text{ Å} \)
\( b = 9.899(2) \text{ Å} \)
\( c = 19.553(4) \text{ Å} \)
\( \alpha = 90^\circ \)
\( \beta = 90^\circ \)
\( \gamma = 90^\circ \)
\( V = 1414.0(5) \text{ Å}^3 \)

Space Group  
\( P 2_12_12_1 \) (#19)

Z value  
4
D\text{calc} & 1.518 \text{ g/cm}^3 \\
F000 & 664.00 \\
\mu(\text{Mo-K}\alpha) & 4.64 \text{ cm}^{-1} \\

B. Intensity Measurements

Diffractometer & Bruker APEX DUO \\
Radiation & Mo-K\alpha (\lambda = 0.71073 \text{ Å}) \\

Data Images & 937 exposures @ 10.0 seconds \\
Detector Position & 38.25 mm \\
2\theta_{\text{max}} & 55.8^\circ \\
No. of Reflections Measured & Total: 11617 \\
 & Unique: 3349 (R_{\text{int}} = 0.041) \\
Corrections & Absorption (T_{\text{min}} = 0.897, T_{\text{max}}=0.991) \\
 & Lorentz-polarization \\

C. Structure Solution and Refinement

Structure Solution & Direct Methods (XT) \\
Refinement & Full-matrix least-squares on F^2 \\
Function Minimized & \Sigma w (F_o^2 - F_c^2)^2
Least Squares Weights

\[ w = \frac{1}{\sigma^2(F_o^2) + (0.0272P)^2 + 0.4430P} \]

Anomalous Dispersion

All non-hydrogen atoms

No. Observations (I>0.00σ(I)) 3349

No. Variables 198

Reflection/Parameter Ratio 16.91

Residuals (refined on F^2, all data): R1; wR2 0.043; 0.068

Goodness of Fit Indicator 1.03

No. Observations (I>2.00σ(I)) 2934

Residuals (calculated on F^2): R1; wR2 0.033; 0.064

Max Shift/Error in Final Cycle 0.00

Maximum peak in Final Diff. Map 0.26 e^-/Å^3

Minimum peak in Final Diff. Map -0.27 e^-/Å^3
Table S1 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\AA^2 \times 10^3$) for ra096. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$ tensor.

| Atom | $x$       | $y$       | $z$               | $U(eq)$   |
|------|-----------|-----------|-------------------|-----------|
| C(1) | 7870(3)   | 8091(3)   | 7160.7(13)        | 11.5(5)   |
| C(1')| 2164(3)   | 931(3)    | 6305.2(13)        | 11.5(5)   |
| C(2')| 943(4)    | 10010(3)  | 6290.5(14)        | 14.8(6)   |
| C(3) | 5429(4)   | 9395(3)   | 6572.1(13)        | 12.8(5)   |
| C(3')| -346(3)   | 10080(3)  | 5770.0(14)        | 16.7(6)   |
| C(4) | 3607(3)   | 8858(3)   | 6861.6(13)        | 11.4(5)   |
| C(4')| -381(3)   | 9069(3)   | 5278.1(13)        | 16.7(6)   |
| C(5) | 3934(3)   | 7440(3)   | 7184.0(13)        | 10.9(5)   |
| C(5')| 904(4)    | 8050(4)   | 5326.0(14)        | 19.3(6)   |
| C(6) | 5276(3)   | 6543(3)   | 6797.3(13)        | 10.7(5)   |
| C(7) | 4704(4)   | 5347(3)   | 6483.4(13)        | 12.4(5)   |
| C(8) | 5971(4)   | 4501(3)   | 6171.5(13)        | 14.5(6)   |
| C(9) | 7835(4)   | 4832(3)   | 6165.1(13)        | 14.3(6)   |
| C(10)| 8429(3)   | 5992(3)   | 6491.7(13)        | 13.5(6)   |
| C(11)| 7164(3)   | 6848(3)   | 6805.5(13)        | 11.5(5)   |
| Cl(1)| 5189.0(9) | 3025.7(7) | 5788.2(3)         | 19.36(16) |
| Cl(2)| 9433.2(9) | 3820.4(8) | 5753.4(4)         | 24.00(18) |
| N(2) | 6959(3)   | 9238(3)   | 7049.6(12)        | 12.7(5)   |
| N(3) | 2186(3)   | 7957(3)   | 5822.4(12)        | 16.7(5)   |
| O(1) | 9236(2)   | 8048(2)   | 7542.8(9)         | 16.0(4)   |
| O(2) | 2287(2)   | 6707(2)   | 7289.7(10)        | 14.2(4)   |
Table S2 Anisotropic Displacement Parameters (Å$^2 \times 10^3$) for ra096. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^*^2U_{11}+2hkba^*b^*U_{12}+...].$

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|------|---------|---------|---------|---------|---------|---------|
| C(1) | 6.3(11) | 14.9(15)| 13.5(12)| -2.9(11)| 4.4(9)  | -0.1(11) |
| C(1')| 8.9(11) | 13.5(15)| 12.0(12)| 2.3(11) | 1.7(9)  | -2.1(11) |
| C(2')| 13.1(12)| 14.5(16)| 16.7(13)| 0.3(11) | 2.9(11) | -0.4(11) |
| C(3) | 11.6(12)| 11.1(15)| 15.5(13)| 0.7(10) | -1.7(10)| -0.7(11)|
| C(3')| 10.6(11)| 19.3(16)| 20.3(13)| 3.6(12) | 1.2(12) | 2.5(10)  |
| C(4) | 10.1(11)| 9.9(15) | 14.1(13)| -1.1(11)| -0.8(9)| 0.8(11) |
| C(4')| 9.5(11) | 25.4(18)| 15.2(13)| 6.2(11) | -3.4(10)| -4.4(12)|
| C(5) | 7.3(11) | 12.2(15)| 13.1(12)| 0.8(10) | -0.4(9)| -2(1)   |
| C(5')| 18.8(13)| 23.3(17)| 15.7(13)| -2.6(12)| -3(1)  | -3.1(14)|
| C(6) | 9.7(11) | 12.2(14)| 10.2(11)| 1.4(9)  | -2.5(10)| 0.8(10)|
| C(7) | 11.3(12)| 13.1(15)| 12.8(12)| 2.1(10) | -1.3(10)| 0.4(11)|
| C(8) | 22.6(14)| 10.8(16)| 9.9(13) | -1(1)   | -3.4(11)| -0.9(12)|
| C(9) | 15.3(12)| 13.3(16)| 14.1(13)| -0.8(11)| 3.8(11)| 5.5(11)|
| C(10)| 9.9(11) | 15.4(16)| 15.0(13)| 0.0(11) | 0.5(10)| -0.1(11)|
| C(11)| 11.4(11)| 10.4(15)| 12.8(12)| -0.7(11)| -1.3(10)| 0.2(11)|
| Cl(1)| 27.4(3) | 11.3(3) | 19.4(3) | -3.8(3) | -3.5(3)| -1.4(3)|
| Cl(2)| 22.4(3) | 21.6(4) | 28.0(4) | -10.3(3)| 5.3(3)| 7.8(3) |
| N(2) | 7.7(10) | 12.4(14)| 18.1(12)| -4(1)   | -1.3(9)| -2.2(10)|
| N(3) | 15.8(10)| 18.3(13)| 15.9(11)| -2.3(11)| -0.9(9)| 1(1)    |
| O(1) | 7.9(8)  | 21.3(12)| 18.7(9) | -2.7(8) | -1.7(7)| 2.1(9) |
| O(2) | 7.7(8)  | 11.9(12)| 22.9(10)| 1.9(8)  | 2.5(7) | 1.2(8) |
Table S3 Bond Lengths for ra096.

| Atom Atom | Length/Å | Atom Atom | Length/Å |
|-----------|----------|-----------|----------|
| C(1) C(11) | 1.505(4) | C(5) C(6) | 1.524(4) |
| C(1) N(2) | 1.334(4) | C(5) O(2) | 1.421(3) |
| C(1) O(1) | 1.248(3) | C(5') N(3) | 1.352(3) |
| C(1') C(2') | 1.391(4) | C(6) C(7) | 1.397(4) |
| C(1') C(4) | 1.516(4) | C(6) C(11) | 1.412(4) |
| C(1') N(3) | 1.350(4) | C(7) C(8) | 1.389(4) |
| C(2') C(3') | 1.388(4) | C(8) C(9) | 1.400(4) |
| C(3) C(4) | 1.541(4) | C(8) Cl(1) | 1.738(3) |
| C(3) N(2) | 1.465(3) | C(9) C(10) | 1.384(4) |
| C(3') C(4') | 1.388(4) | C(9) Cl(2) | 1.736(3) |
| C(4) C(5) | 1.556(4) | C(10) C(11) | 1.396(4) |
| C(4') C(5') | 1.381(4) |

Table S4 Bond Angles for ra096.

| Atom Atom Atom | Angle/° | Atom Atom Atom | Angle/° |
|----------------|---------|----------------|---------|
| N(2) C(1) C(11) | 116.8(2) | C(7) C(6) C(5) | 121.3(2) |
| O(1) C(1) C(11) | 121.5(3) | C(7) C(6) C(11) | 118.6(2) |
| O(1) C(1) N(2) | 121.7(3) | C(11) C(6) C(5) | 119.8(2) |
| C(2') C(1') C(4) | 119.8(3) | C(8) C(7) C(6) | 120.3(2) |
| N(3) C(1') C(2') | 122.8(2) | C(7) C(8) C(9) | 120.7(3) |
| N(3) C(1') C(4) | 117.3(2) | C(7) C(8) Cl(1) | 118.4(2) |
| C(3') C(2') C(1') | 119.2(3) | C(9) C(8) Cl(1) | 120.8(2) |
| N(2) C(3) C(4) | 112.9(2) | C(8) C(9) Cl(2) | 121.5(2) |
| C(4') C(3') C(2') | 119.0(3) | C(10) C(9) C(8) | 119.7(2) |
| C(1') C(4) C(3) | 108.7(2) | C(10) C(9) Cl(2) | 118.8(2) |
| C(1') C(4) C(5) | 116.2(2) | C(9) C(10) C(11) | 119.9(2) |
| C(3) C(4) C(5) | 109.1(2) | C(6) C(11) C(1) | 121.0(2) |
| C(5') C(4') C(3') | 117.8(2) | C(10) C(11) C(1) | 118.2(2) |
| C(6) C(5) C(4) | 115.1(2) | C(10) C(11) C(6) | 120.8(3) |
| O(2) C(5) C(4) | 112.9(2) | C(1) N(2) C(3) | 125.1(3) |
| O(2) C(5) C(6) | 108.6(2) | C(1') N(3) C(5') | 116.5(3) |
| N(3) C(5') C(4') | 124.7(3) |

Table S5 Hydrogen Bonds for ra096.
| A    | B    | C    | D    | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A° |
|------|------|------|------|----------|----------|----------|--------|
| N(2) | H(2N)| O(2) |     | 0.79(3)  | 2.05(4)  | 2.818(3) | 166(3) |
| O(2) | H(2O)| O(1) |     | 0.82(4)  | 1.83(4)  | 2.641(3) | 172(4) |

1-X,1/2+Y,3/2-Z; 2-1+X,+Y,+Z

Table S6 Torsion Angles for ra096.

| A    | B    | C    | D    | Angle/° | A    | B    | C    | D    | Angle/° |
|------|------|------|------|---------|------|------|------|------|---------|
| C(1')| C(2')| C(3')| C(4')| 0.0(4)  | C(7) | C(8) | C(9) | C(10)| 2.1(4)  |
| C(1')| C(4) | C(5) | C(6) | 85.2(3) | C(7) | C(8) | C(9) | C(10)| -177.8(2) |
| C(1')| C(4) | C(5) | O(2) | -40.2(3)| C(8) | C(9) | C(10)| C(11)| -2.1(4)  |
| C(2')| C(1')| C(4) | C(3) | -98.5(3)| C(9) | C(10)| C(11)| C(12)| 179.4(2) |
| C(2')| C(1')| C(4) | C(5) | 138.1(3)| C(9) | C(10)| C(11)| C(12)| 0.3(4)   |
| C(2')| C(1')| N(3) | C(5')| -2.2(4) | C(11)| C(1) | N(2) | C(3) | -5.0(4)  |
| C(2')| C(3')| C(4')| C(5')| -1.2(4) | C(11)| C(6) | C(7) | C(8) | -1.7(4)  |
| C(3) | C(4) | C(5) | C(6) | -38.0(3)| C(11)| C(8) | C(9) | C(10)| -178.1(2) |
| C(3')| C(4)'| C(5')| N(3) | 0.7(4)  | C(11)| C(8) | C(9) | C(10)| 177.7(2) |
| C(4) | C(1')| C(2')| C(3')| 178.7(2)| N(2) | C(1) | C(11)| C(6) | -45.2(4) |
| C(4) | C(1')| N(3) | C(5')| -179.2(2)| N(2)| C(1) | C(11)| C(10)| 135.7(3) |
| C(4) | C(3) | N(2) | C(1) | 78.8(3) | N(2) | C(3) | C(4) | C(1')| -174.2(2) |
| C(4) | C(5) | C(6) | C(7) | -114.4(3)| N(2)| C(3) | C(4) | C(5)| -46.6(3) |
| C(4) | C(5) | C(6) | C(11)| 71.5(3) | N(3) | C(1')| C(2')| C(3')| 1.8(4)   |
| C(4')| C(5')| N(3) | C(1')| 1.0(4)  | N(3) | C(1')| C(4')| C(3)| 78.5(3)  |
| C(5) | C(6) | C(7) | C(8) | -175.9(2)| N(3)| C(1')| C(4) | C(5)| -44.9(3) |
| C(5) | C(6) | C(11)| C(1) | -3.2(4) | O(1) | C(1) | C(11)| C(6)| 134.5(3) |
| C(5) | C(6) | C(11)| C(10)| 175.9(2)| O(1) | C(1) | C(11)| C(10)| -44.7(4) |
| C(6) | C(7) | C(8) | C(9) | -0.1(4) | O(1) | C(1) | N(2) | C(3)| 175.4(2) |
| C(6) | C(7) | C(8) | Cl(1) | 179.99(19)| O(2)| C(5) | C(6) | C(7)| 13.3(3)  |
| C(7) | C(6) | C(11)| C(1) | -177.5(2)| O(2)| C(5) | C(6) | C(11)| -160.8(2) |
| C(7) | C(6) | C(11)| C(10)| 1.6(4)   |
Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for ra096.

| Atom  | x    | y    | z    | U(eq) |
|-------|------|------|------|-------|
| H(2') | 991  | 10691| 6633 | 18    |
| H(3A) | 5716 | 8907 | 6144 | 15    |
| H(3B) | 5286 | 10364| 6459 | 15    |
| H(3') | -1192| 10808| 5751 | 20    |
| H(4)  | 3220 | 9480 | 7238 | 14    |
| H(4') | -1260| 9078 | 4920 | 20    |
| H(5)  | 4478 | 7600 | 7646 | 13    |
| H(5') | 886  | 7365 | 4986 | 23    |
| H(7)  | 3443 | 5111 | 6483 | 15    |
| H(10) | 9697 | 6205 | 6502 | 16    |
| H(2N) | 7350(40) | 9890(40) | 7230(15) | 9(8) |
| H(2O) | 1400(50) | 7180(40) | 7382(17) | 28(10) |