Strategic Diastereoselective C1 Functionalization in the Aza-Rocaglamide Scaffold toward Natural Product-Inspired eIF4A Inhibitors

Christian Nilewski*, Theodore D. Michels, Alan X. Xiang, Garrick K. Packard, Paul A. Sprengeler, Boreth Eam, Sarah Fish, Peggy A. Thompson, Christopher J. Wegerski, Justin T. Ernst, Siegfried H. Reich

eFFECTOR Therapeutics, 11180 Roselle Street, Suite A, San Diego, CA 92121, United States

Supporting Information

Table of contents

1 General Methods

All reagents and solvents were used as purchased from commercial sources unless otherwise noted. Silvestrol ((–)-**1**) was purchased from MedChemExpress (Monmouth Junction, NJ, USA). Rocaglamide ((–)-**2**) was synthesized and QCed at Julilant Life Sciences (Uttar Pradesh, India). Cycloheximide was purchased from Sigma-Aldrich (St. Louis, MO).

Microwave reactions were performed with a Biotage Initiator focused beam microwave reactor.

Reactions were monitored by TLC (Merck, TLC silica gel 60 F254) or LCMS using the following instruments: Shimadzu LC-10AD liquid chromatograph system equipped with a PE SCIEX API 2000 mass spectrometer, a Shimadzu SCL-10A System controller and SPD-10A UV/Vis detector, a Perkin Elmer Series 200 Autosampler and a Phenomenex Gemini NX-C18 column (3 μm, 30 x 4.6 mm) (mobile phase: 15-95% MeCN/water + 0.1% TFA); or an Agilent 1100 series LCMS system equipped with a PE SCIEX API 150EX mass spectrometer and a Phenomenex Gemini NX-C18 column (3 μm, 30 x 4.6 mm) (mobile phase: 15-95% MeCN/water + 0.1% TFA).

Flash column chromatography was performed with a Teledyne ISCO CombiFlash Rf200+ system or a Yamazen Smart Flash EPLC W-Prep 2XY system using normal-phase silica columns (230–400 mesh).

HPLC purification was performed using a Gilson automated purification system equipped with a Gilson 215 liquid handler and 333 and 334 pumps using Phenomenex Gemini NX-C18 columns (10 μm, 250 x 30 mm or 10 μm, 250 x 50 mm).

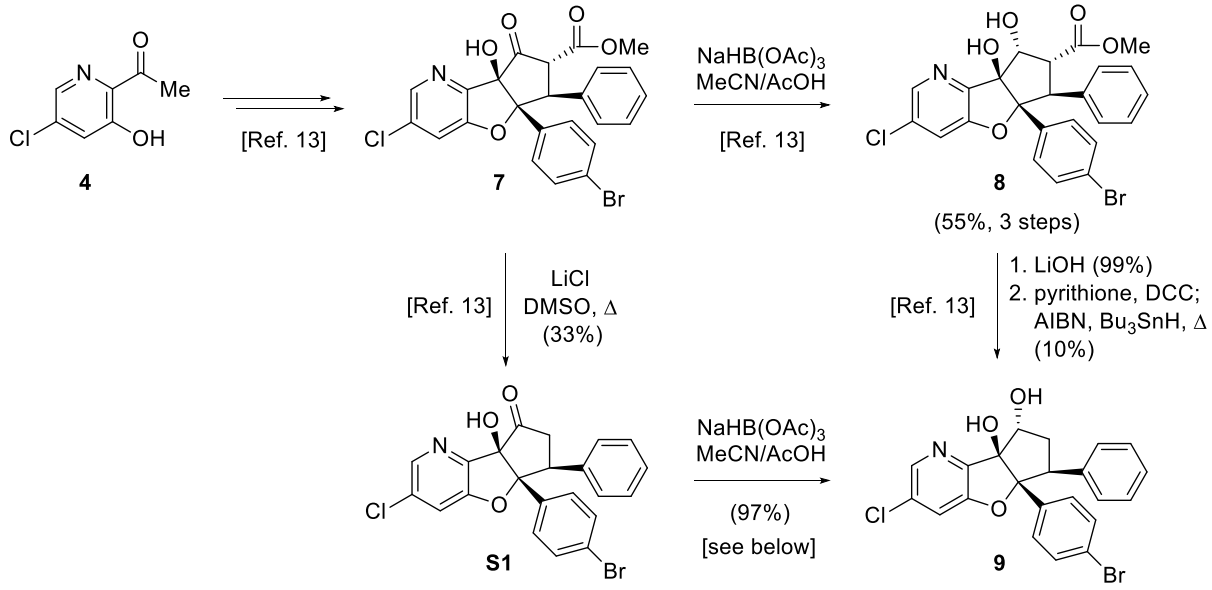
1D (^{1}H,^{13}C) and 2D NMR (COSY, HSQC, HMBC, NOESY) spectra were recorded on Agilent MR400 and Varian VX 500 spectrometers. Coupling constants (*J*) are reported in hertz (Hz). Chemical shifts (δ) of NMR spectra are reported in parts per million (ppm) and are calibrated using residual undeuterated solvent for ^{1}H NMR [^{1}H = 7.26 ($CHCl_3$), 2.50 (D_5H-DMSO), 3.31 (CD_2HOD) ppm] and ^{13}C deuterated solvent for ^{13}C NMR [77.16 ($CDCl_3$), 39.52 (DMSO-d6), 49.00 (CD_3OD) ppm] as an internal reference at 298 K.[1] The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

[1] Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Golberg, K. I. *Organometallics* **2010**, *29*, 2176.

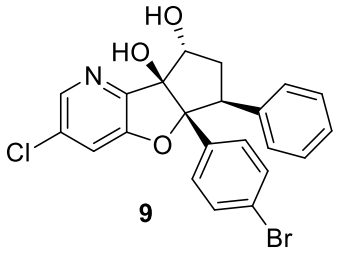
Electrospray ionization (ESI) mass spectrometry was performed on PE SCIEX API 2000 and PE SCIEX API 150EX mass spectrometers. High resolution mass spectrometry (HRMS) was performed using a Triple TOF 5600+ mass spectrometer (hybrid quadrupole time-of-flight platform; AB Sciex) connected to a 1290 UHPLC system (Agilent). The mass spectrometer was operated in electrospray positive ionization mode (ESI+). Acquisition was a full scan from m/z 100 to 1000 with a pulser frequency of 18.092 kHz and accumulation time of 250 ms. Unless otherwise noted, monoisotopic masses of the $[M+H^+]$ peaks are reported. All observed isotope patterns were in agreement with calculated isotope patterns.

2 Experimental procedures and analytical data

Synthetic scheme for the synthesis of compounds 8 and 9:



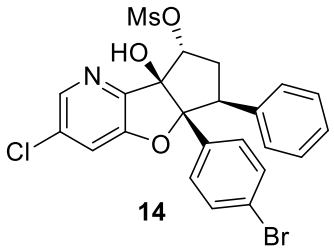
***rac*-(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diol (9)**



rac-(5a*R*,6*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-6,7-dihydrocyclopenta[4,5]furo[1,2-b]pyridin-8-one (**S1**) (150 mg, 0.328 mmol) was dissolved in acetic acid (1.4 mL) and MeCN (1.4 mL), and sodium triacetoxyborohydride (0.71 g, 3.4 mmol) was added. The mixture was stirred at room temperature. After 20 min water (ca. 10 mL) was carefully added. The mixture was extracted (3 x ca. 15 mL DCM), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (SiO_2, 0-50% EtOAC/Hexane) gave product **9** as a white solid. Yield: 146 mg (0.318 mmol, 97%). **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}BrClNO_3^+$ 458.0153; Found 458.0147; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.20 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.15-6.99 (m, 7H), 5.85 (s, 1H), 5.12 (b, 1H), 4.48 (d, *J* = 4.2 Hz, 1H), 4.23 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.80 (ddd, *J* = 13.3, 13.3, 4.2, 1H), 2.14 (dd, *J* = 13.3, 6.1 Hz, 1H); **^{13}C NMR (101 MHz, d^6-DMSO)** δ / ppm = 153.1,

149.7, 140.4, 138.6, 135.8, 130.7, 129.4, 129.3, 128.0, 127.7, 126.1, 119.8, 116.9, 103.1, 91.8, 77.6, 53.9, 37.7.

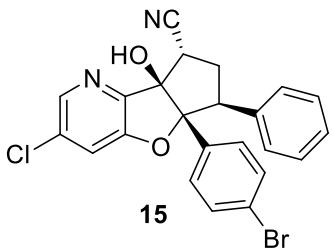
rac-(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridin-8-yl methanesulfonate (14)



14

To a solution of *rac*-(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridine-8,8a-diol (**9**) (50 mg, 0.11 mmol) in pyridine (1 mL) was added methanesulfonyl chloride (10 uL, 15 mg, 0.13 mmol) and the mixture was stirred at rt. After 22h another 3 uL MsCl added, and the mixture was stirred for two more hours. Then the reaction was quenched with NH_4Cl(aq) and the mixture was extracted with DCM (3 x ca. 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 0-50% EtOAc/hexane) gave *rac*-(5aR,6S,8R,8aS)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridin-8-yl methanesulfonate (**14**) as a white solid. Yield: 44 mg (0.082 mmol, 75%). **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}BrClNO_5S^+$ 535.9929; Found 535.9916; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.33 (d, *J* = 2.0, 1H), 7.82 (d, *J* = 2.0, 1H), 7.30 (d, *J* = 8.8, 2H), 7.17-7.03 (m, 7H), 6.52 (s, 1H), 5.48 (dd, *J* = 5.1, 1.3, 1H), 4.02 (dd, *J* = 14.3, 6.6, 1H), 3.24 (s, 3H), 3.08 (ddd, *J* = 14.3, 14.3, 5.1, 1H), 2.39 (ddd, *J* = 14.3, 6.6, 1.3); **^{13}C NMR (101 MHz, d^6-DMSO)** δ / ppm = 152.7, 147.3, 141.6, 137.0, 134.3, 131.8, 129.7, 129.4, 127.9, 127.8, 126.7, 120.5, 118.3, 102.4, 90.0, 87.0, 53.4, 38.1, 35.3.

rac-(5a*R*,6*S*,8*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-8-carbonitrile (15)

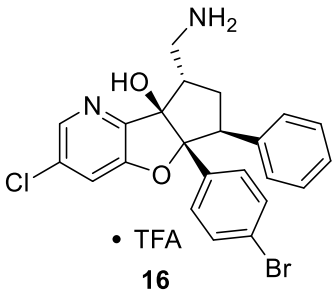


15

To a solution of *rac*-[(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridin-8-yl] methanesulfonate (**14**) (570 mg, 1.06 mmol) in DMSO (10 mL) was added potassium cyanide (142.5 mg, 2.19 mmol) and the mixture was stirred at rt under argon. After 1.5 h the mixture was diluted with EtOAc and washed brine (2x), then dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 0-40% EtOAc/hexane) yielded 496 mg (contained

ca. 0.55 eq. of EtOAc, 0.965 mmol, 91%) of **15** as an off-white solid. An analytically pure sample was obtained upon dissolving the material in $CDCl_3$, concentrating and drying under vacuum. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}BrClN_2O_2^+$ 467.0156; Found 467.0145; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.38 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.17-7.08 (m, 5H), 7.04-7.00 (m, 2H), 6.53 (bs, 1H), 4.06 (dd, *J* = 8.8, 3.5 Hz, 1H), 3.87 (dd, *J* = 12.7, 7.0 Hz, 1H), 3.00 (ddd, *J* = 13.7, 12.7, 8.8 Hz, 1H), 2.40 (ddd, *J* = 13.7, 7.0, 3.5 Hz, 1H); **^{13}C NMR (101 MHz, d^6-DMSO)** δ / ppm = 151.9, 148.3, 141.8, 137.0, 134.0, 132.2, 129.8, 129.5, 128.0, 127.8, 126.9, 120.7, 119.7, 118.8, 102.4, 87.9, 54.8, 39.7*, 31.9. * = determined by HSQC.

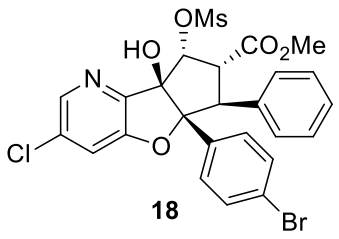
***rac*-(5a*R*,6*S*,8*S*,8a*R*)-8-(aminomethyl)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridin-8a-ol (TFA salt) (16)**



16

To a solution of *rac*-(5a*R*,6*S*,8*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo-[1,2-b]pyridine-8-carbonitrile (**15**) (20 mg, 0.043 mmol) in THF (0.5 mL) at 0ºC was added lithium aluminum hydride (3.4 mg, 0.090 mmol) and the mixture was stirred at rt. After 1h 0.02 mL water were added at 0ºC, followed by 0.02 mL 12.5% NaOH (aq) and ca. 60 mg of Na_2SO_4. The mixture was stirred for 10 min at rt, then filtered through celite (rinsed with DCM) and concentrated. The crude product (ca. 19 mg, yellow foam) was purified by repeated HPLC (C18, MeCN/H_2O + 0.1% TFA) to yield 5.3 mg (0.0091 mmol, 21%) of **16** as a white solid; **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}BrClN_2O_2^+$ 471.0469; Found 471.0469; **^{1}H NMR (400 MHz, d^6-DMSO, TFA salt)** δ / ppm = 8.30 (d, *J* = 2.0 Hz, 1H), 8.01 (b, 3H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.16–7.08 (m, 5H), 6.96–6.92 (m, 2H), 6.01 (s, 1H), 3.74 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.56–3.47 (m, 1H), 3.20–3.10 (m, 1H), 3.08–2.97 (m, 1H), 2.60 (ddd, *J* = 14.0, 9.9, 9.9 Hz, 1H), 1.86 (ddd, *J* = 14.0, 8.5, 6.2, 1H); **^{13}C NMR (101 MHz, d^6-DMSO, TFA salt)** δ / ppm = 152.5, 149.5, 140.9, 138.2, 134.2, 132.1, 129.9, 129.4, 128.1, 127.8, 126.7, 120.5, 119.2, 103.0, 87.5, 52.7, 46.1, 41.1, 29.7.

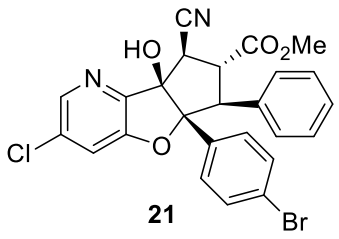
***rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-((methyl-sulfonyl)-oxy)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (18)**



18

To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridine-7-carboxylate (**8**) (800 mg, 1.55 mmol) in pyridine (15 mL) was added methanesulfonyl chloride (0.15 mL, 0.22 g, 1.9 mmol) and the mixture was stirred at rt. After 23.5h another 0.08 mL (0.1 g, 1 mmol) methanesulfonyl chloride added, and the mixture was stirred for another 3.5h. Another 0.1 mL (0.1 g, 1 mmol) methanesulfonyl chloride were added, and the mixture was stirred for ca. another 1h. Then the reaction was quenched with NH_4Cl (aq) and the mixture was extracted with DCM thrice. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 0-50% ethyl acetate/hexane) to yield 775 mg (1.30 mmol, 84%) of **18** as a yellowish foam; **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{25}H_{22}BrClNO_7S^+$ 593.9983; Found 593.9960; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.35 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.13-7.04 (m, 3H), 7.00-6.96 (m, 2H), 6.76 (s, 1H), 5.69 (d, *J* = 6.1 Hz, 1H), 4.46 (dd, *J* = 14.5, 6.1 Hz, 1H), 4.26 (d, *J* = 14.5 Hz, 1H), 3.57 (s, 3H), 3.15 (s, 3H); **^{13}C NMR (101 MHz, d6-DMSO)** δ / ppm = 168.3, 152.9, 147.0, 141.7, 135.7, 133.5, 132.2, 129.7, 129.7, 127.9, 127.7, 126.9, 120.6, 118.7, 101.1, 89.2, 86.4, 55.4, 52.1, 49.1, 38.6.

***rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (21)**

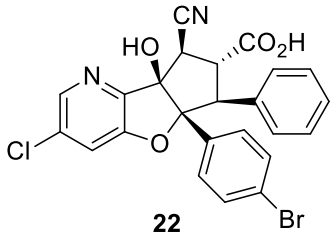


21

To a solution of *rac*-methyl (5a*R*,6S,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-methylsulfonyloxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridine-7-carboxylate (**18**) (775 mg, 1.30 mmol) in DMSO (13 mL) was added potassium cyanide (189 mg, 2.90 mmol) and the mixture was stirred at rt under argon. After stirring for 16 h the mixture was diluted with EtOAc and washed brine (2 x), then dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 0-45% ethyl acetate/hexane) yielded 469 mg (0.892 mmol, 68%) of **21** as a yellowish foam; **HRMS (ESI)**

m/z: $[M+H]^+$ Calcd for $C_{25}H_{19}BrClN_2O_4^+$ 525.0211; Found 525.0219; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.36 (d, *J* = 1.9 Hz, 1H), 7.85 (d, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 8.9 Hz, 2H), 7.10-7.06 (m, 3H), 6.96-6.90 (m, 2H), 6.83 (s, 1H), 4.22 (d, *J* = 10.5 Hz, 1H), 4.15 (dd, *J* = 13.1, 10.5 Hz, 1H), 3.75 (d, *J* = 13.1 Hz, 1H), 3.53 (s, 3H). **^{13}C NMR (101 MHz, d6-DMSO)** δ / ppm = 170.5, 151.1, 149.7, 142.3, 134.8, 133.2, 132.5, 130.2, 129.6, 128.1, 127.9, 127.3, 121.1, 119.6, 117.4, 101.4, 83.9, 57.0, 52.7, 47.7, 41.2.

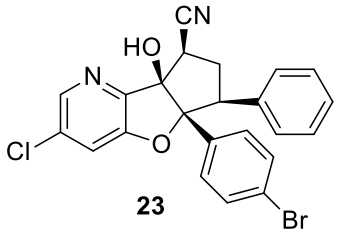
***rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (22)**



22

To *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta-[4,5]furo-[1,2-b]pyridine-7-carboxylate (**21**) (460 mg, 0.875 mmol) in methanol (4.5 mL) and THF (4.5 mL) at rt was added LiOH (aq) (2M, 6.3mL, 12.6 mmol) and the mixture was stirred at 40^{o}C (water bath). After 1h the mixture was cooled down to rt, and stirred for another 15 min, then acidified with 2M HCl (aq) (7 mL) and diluted with EtOAc and water. The aq. phase was extracted thrice, and the combined organic phases were dried (Na_2SO_4), filtered and concentrated to give 417 mg (0.815 mmol, 93%) of **22**. The crude product was directly used in the next step without further purification. An analytically pure sample could be obtained by purification by reverse phase HPLC (C18, MeCN/water+0.1%TFA). **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{24}H_{17}BrClN_2O_4^+$ 511.0055; Found 511.0051; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 13.11 (b, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.11-7.08 (m, 3H), 6.97-6.90 (m, 2H), 6.81 (s, 1H), 4.11 (d, *J* = 10.8 Hz, 1H), 3.98 (dd, *J* = 13.4, 10.8 Hz, 1H), 3.70 (d, *J* = 13.4 Hz, 1H); **^{13}C NMR (101 MHz, d6-DMSO)** δ / ppm = 171.5, 151.0, 149.7, 142.1, 134.7, 133.2, 132.3, 130.1, 129.5, 128.1, 127.7, 127.2, 121.0, 119.5, 117.3, 101.5, 83.8, 57.2, 48.2, 41.4.

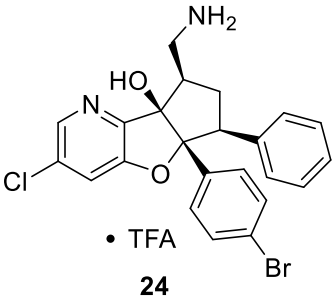
***rac*-(5a*R*,6*S*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-8-carbonitrile (23)**



23

In a screw-cap vial, crude *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta-[4,5]furo[1,2-b]pyridine-7-carboxylic acid (**22**) (387 mg, 0.756 mmol) and 1-hydroxypyridine-2-thione (144 mg, 1.13 mmol) were suspended in chloroform (7.5 mL). 2-methylpropane-2-thiol (2.1 mL, 0.168 g, 18.6 mmol) was added, the mixture was irradiated (light source: HDX XG-1026 lamp, 250 W halogen bulb), and DCC (175 mg, 0.848 mmol) in 1.5 mL $CHCl_3$ was added dropwise under argon. The mixture was irradiated for 15 min with vigorous stirring without additional external heating. The mixture was then concentrated and dried *in vacuo*. Purification by repeated column chromatography (first column: SiO_2, 0-25% ethyl acetate/hexane; second column: SiO_2, 0-20% ethyl acetate/hexane) yielded 136 mg (0.291 mmol, 38%) of **23** as an off-white foam; **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}BrClN_2O_2^+$ 467.0156; Found 467.0144; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.32 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.15-7.05 (m, 5H), 6.98-6.93 (m, 2H), 6.55 (1H), 3.98 (dd, *J* = 11.2, 7.5 Hz, 1H), 3.62 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.80-2.69 (m, 1H), 2.58-2.52 (m, 1H); **^{13}C NMR (101 MHz, d6-DMSO)** δ / ppm = 151.3, 150.3, 142.0, 136.8, 134.0, 132.3, 130.1, 129.7, 128.0, 128.0, 127.1, 120.9, 119.2, 119.1, 102.0, 85.5, 54.0, 37.3, 32.2.

***rac*-(5a*R*,6*S*,8*R*,8a*R*)-8-(aminomethyl)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridin-8a-ol (TFA salt) (24)**

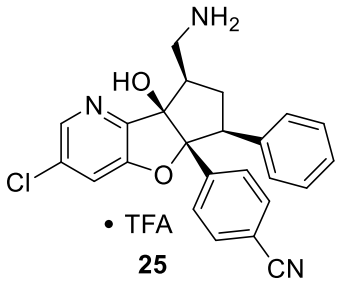


24

To a solution of *rac*-(5a*R*,6*S*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo-[1,2-b]pyridine-8-carbonitrile (**23**) (134 mg, 0.286 mmol) in THF (2.9 mL) at 0 °C was added lithium aluminum hydride (27.2 mg, 0.716 mmol) and the mixture was stirred at rt. After 30 min 0.1 mL water were added at 0 °C, followed by 0.1 mL 12.5% NaOH (aq) and ca. 200 mg of Na_2SO_4. The mixture was stirred for 10 min at rt, then filtered through celite (rinsed with DCM) and concentrated. The crude product was taken up in 2 mL DCM and treated with trifluoroacetic acid (0.03 mL, 0.39000 mmol), then concentrated, to give 176 mg of the crude product. 80 mg of

this crude product were purified by preparative HPLC (C18, MeCN/water+0.1%TFA) for analytical purposes, providing 22 mg (0.037 mmol, 28%) of **24**. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}BrClN_2O_2^+$ 471.0469; Found 471.0474; **^{1}H NMR (400 MHz, d^6-DMSO, TFA salt)** δ / ppm = 8.29 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.84–7.73 (b, 3H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.15–7.04 (m, 5H), 6.99–6.95 (m, 2H), 6.15 (s, 1H), 3.70–3.62 (m, 1H), 3.45–3.35 (m, 1H), 3.24–3.13 (m, 1H), 2.87–2.75 (m,1 H), 2.40–2.23 (m, 2H); **^{13}C NMR (101 MHz, d^6-DMSO, TFA salt)** δ / ppm = 151.9, 151.1, 141.3, 137.7, 134.7, 131.6, 129.7, 129.6, 127.8, 127.7, 126.6, 120.4, 118.8, 103.2, 86.0, 54.6, 44.1, 32.0.

4-((5a*R*,6*S*,8*R*,8a*R*)-8-(aminomethyl)-3-chloro-8a-hydroxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]pyridin-5a-yl)benzonitrile (TFA salt) (25)



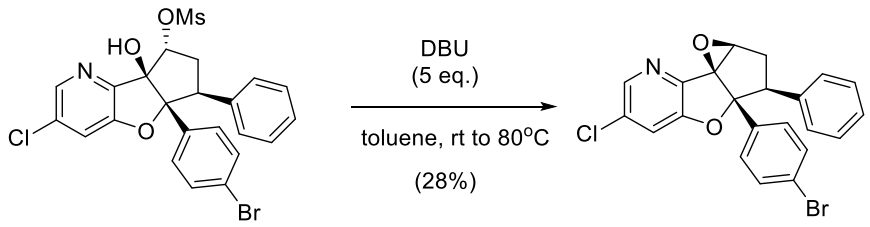
25

In a 2 mL microwave vial *rac*-(5a*R*,6*S*,8*R*,8a*R*)-8-(aminomethyl)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridin-8a-ol (TFA salt) (**24**) (48 mg, 0.082 mmol) was dissolved in DMF (0.7 mL) and water (0.07 mL). Zinc cyanide (39 mg, 0.33 mmol) and zinc (3 mg, 0.05 mmol) were added, and the mixture was degassed by bubbling argon through it for 5 min. Dppf (14.0 mg, 0.0253 mmol) and $Pd_2(dba)_3$ (10.8 mg, 0.0118 mmol) were added and the mixture was degassed for another 5 min, then incubated at 100ºC for 2.25 h in total (Biotage Initiator focused beam microwave reactor). The mixture was then filtered, diluted with MeCN, DMSO and water and subjected to purification by preparative HPLC (C18, MeCN/water+0.1%TFA) to give compound **25**. **Yield:** 13.8 mg (0.0259 mmol, 33% over two steps), white solid. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}ClN_3O_2^+$ 418.1317; Found 418.1335; **^{1}H NMR (400 MHz, d^6-DMSO, TFA salt)** δ / ppm = 8.30 (d, *J* = 2.0 Hz, 1H), 7.97–7.87 (b, 3H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16–7.02 (m, 3H), 7.02–6.90 (m, 2H), 6.22 (bs, 1H), 3.79–3.70 (m, partially obscured by water peak, 1H expected), 3.47–3.35 (m, 1H), 3.27–3.13 (m, 1H), 2.89–2.77 (m, 1H), 2.48–2.36 (m, 1H), 2.36–2.24 (m, 1H); **^{13}C NMR (126 MHz, d^6-DMSO, TFA salt)** δ / ppm = 151.7, 151.1, 141.7, 141.2, 137.5, 131.9, 130.9, 128.5, 128.0, 127.8, 126.9, 119.1, 118.9, 109.8, 103.4, 86.5, 55.2, 44.6, 32.1.

3 Mechanistic investigations of stereoretentive and stereoinvertive displacements

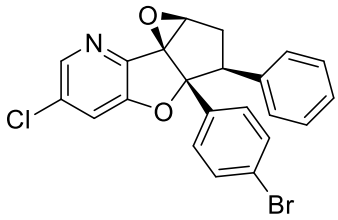
3.1 Mechanistic investigation of the stereoretentive displacement **14→16**

3.1.1 **S**ynthesis and characterization of epoxide **17**



14 **17**

***rac*-(1a*S*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-3-phenyl-1a,2,3,3a-tetrahydrooxireno[2'',3'':1',5']cyclopenta[1',2':4,5]furo[3,2-b]pyridine (17)**



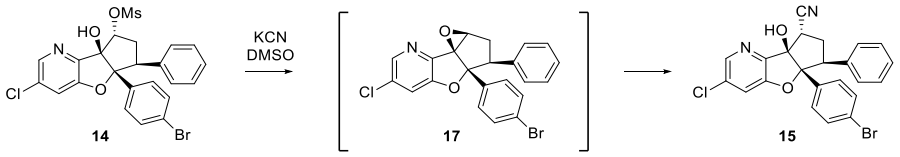
17

In a flame dried vial, [(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo-[1,2-b]pyridin-8-yl] methanesulfonate (**14**) (17.7 mg, 0.0330 mmol) was dissolved in toluene (0.5 mL). DBU (25 uL, 26 mg, 0.17 mmol) was added, and the mixture was stirred at 50 °C in a heating block. After 20 min ca. 50% conversion was observed by TLC. After another 25 min the mixture warmed up to 65°C. After another 45 min the mixture wss warmed up to 80 °C. After another 45 min another 25 µL DBU were added. Stirring at 80 °C was continued for 15 min, after which the mixture was cooled down to rt. The reaction was quenched with NH_4Cl(aq) and extracted (3 x DCM). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 0-30% ethyl acetate/hexane) followed by preparative TLC (SiO_2, EtOAc/Hex = 1/1) gave 4.0 mg (0.0091 mmol, 28% yield) of epoxide **17** as a white solid. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}BrClNO_2^+$ 440.0047 $[M+H]^+$; Found 440.0034; **^{1}H NMR (400 MHz, $CDCl_3$)** δ / ppm = 8.17 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.23-7.03 (m, 9H), 4.60 (dd, *J* = 12.2, 9.3 Hz, 1H), 4.27 (d, *J* = 3.8 Hz, 1H), 2.72 (dd, *J* = 14.8, 9.3, 3.8 Hz, 1H), 2.57 (dd, *J* = 14.8, 12.2 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ / ppm = 155.7, 142.6, 141.7, 136.9, 135.3, 133.1, 130.8, 129.0, 128.4, 128.2, 127.2, 122.1, 118.1, 95.3, 78.7, 67.2, 63.6, 32.7.

3.1.2 LCMS studies

The conversion of **14** to **15** was studied by LCMS. Samples of the reaction mixture were taken at different time points from t = 0 min to t = 1.5h and analyzed. LCMS chromatograms of compounds **14**, **17**, and **15** were obtained and used as references. The results are in agreement with the reaction pathway shown below.

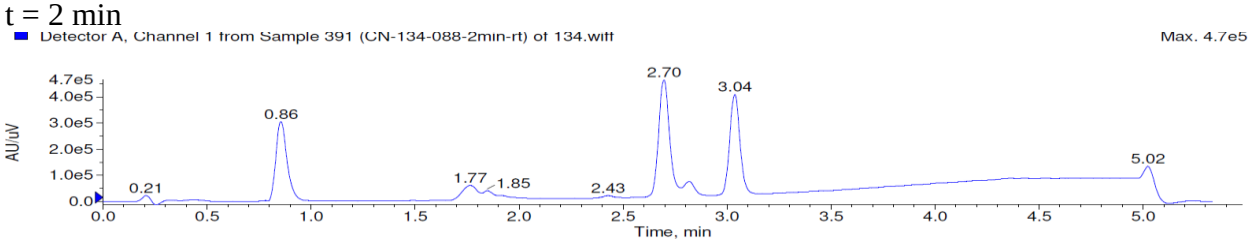
Proposed reaction pathway:



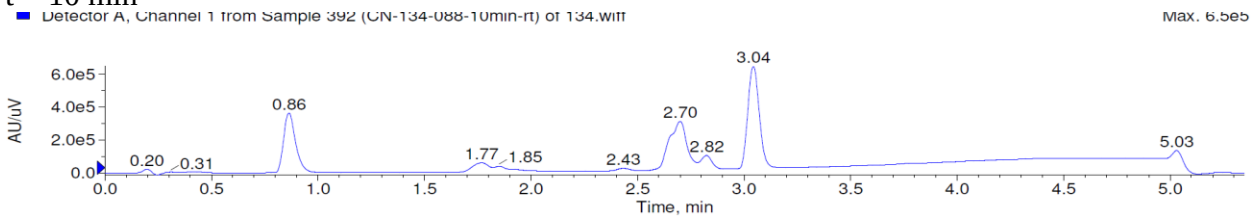
t_R(LCMS) = 2.70 min t_R(LCMS) = 3.04 min t_R(LCMS) = 2.65 min

LCMS of reaction mixture at different timepoints:

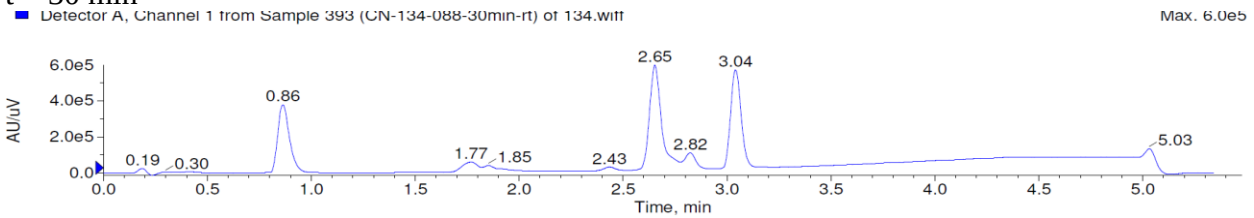
t = 2 min



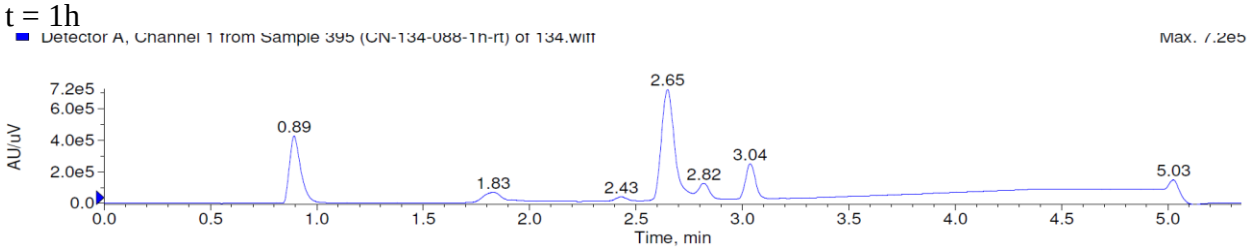
t = 10 min



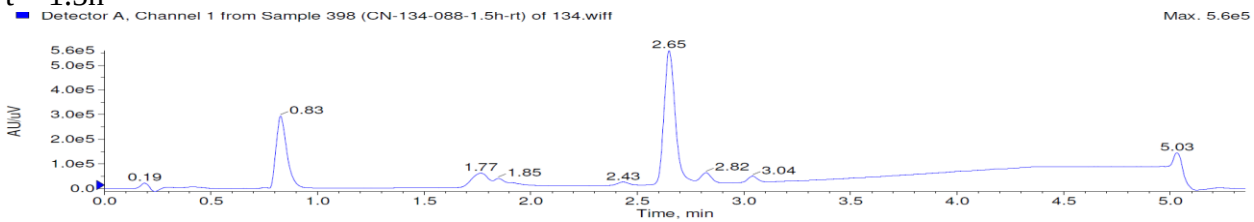
t = 30 min



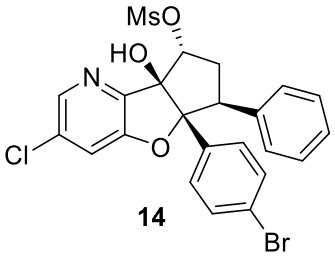
t = 1h



t = 1.5h

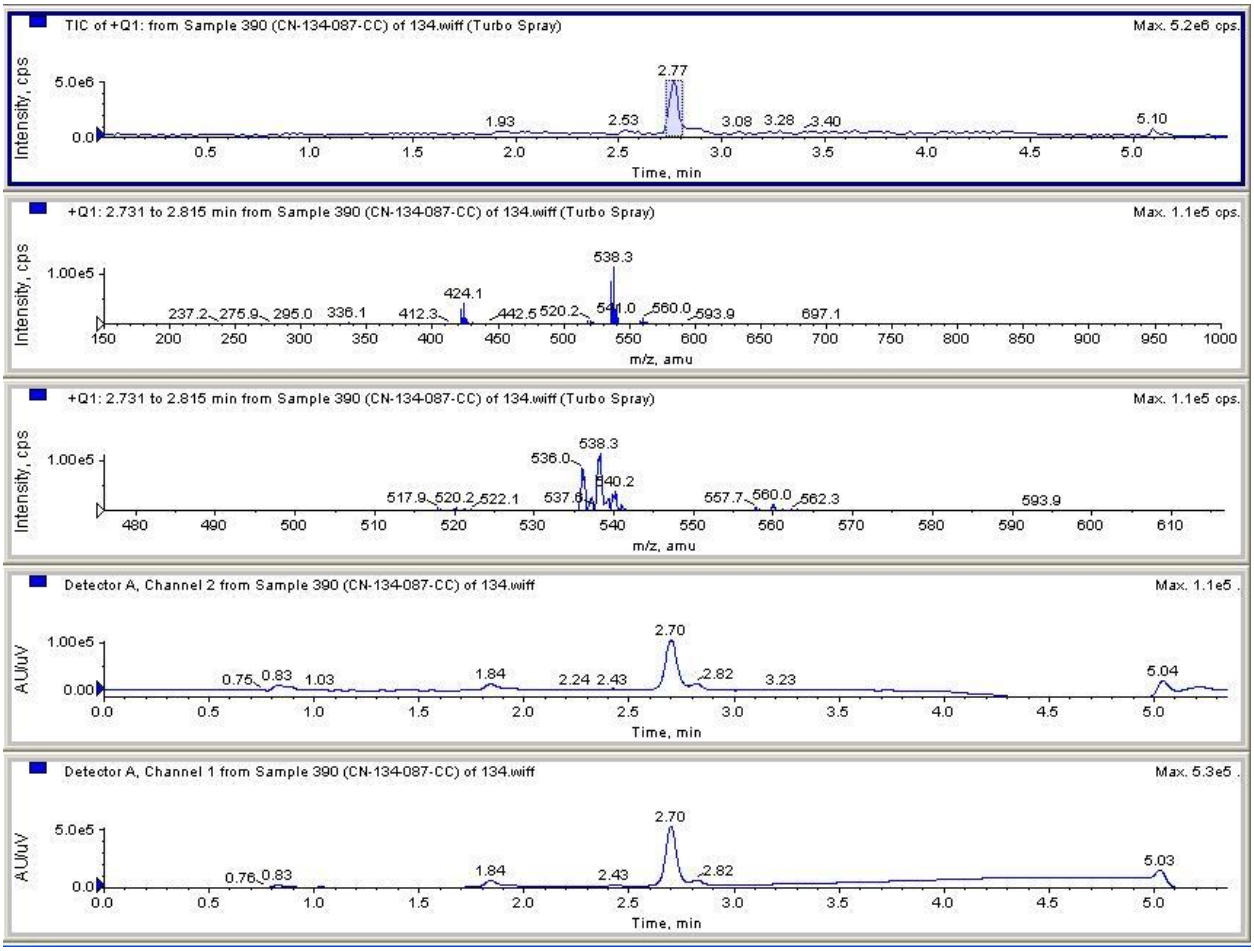


*LCMS of **14** (starting material):*

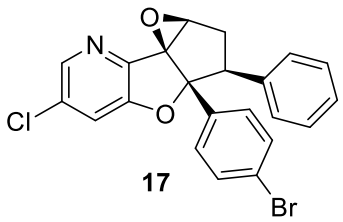


14

Chemical Formula: $C_{23}H_{19}BrClNO_5S$
Exact Mass: 534.9856

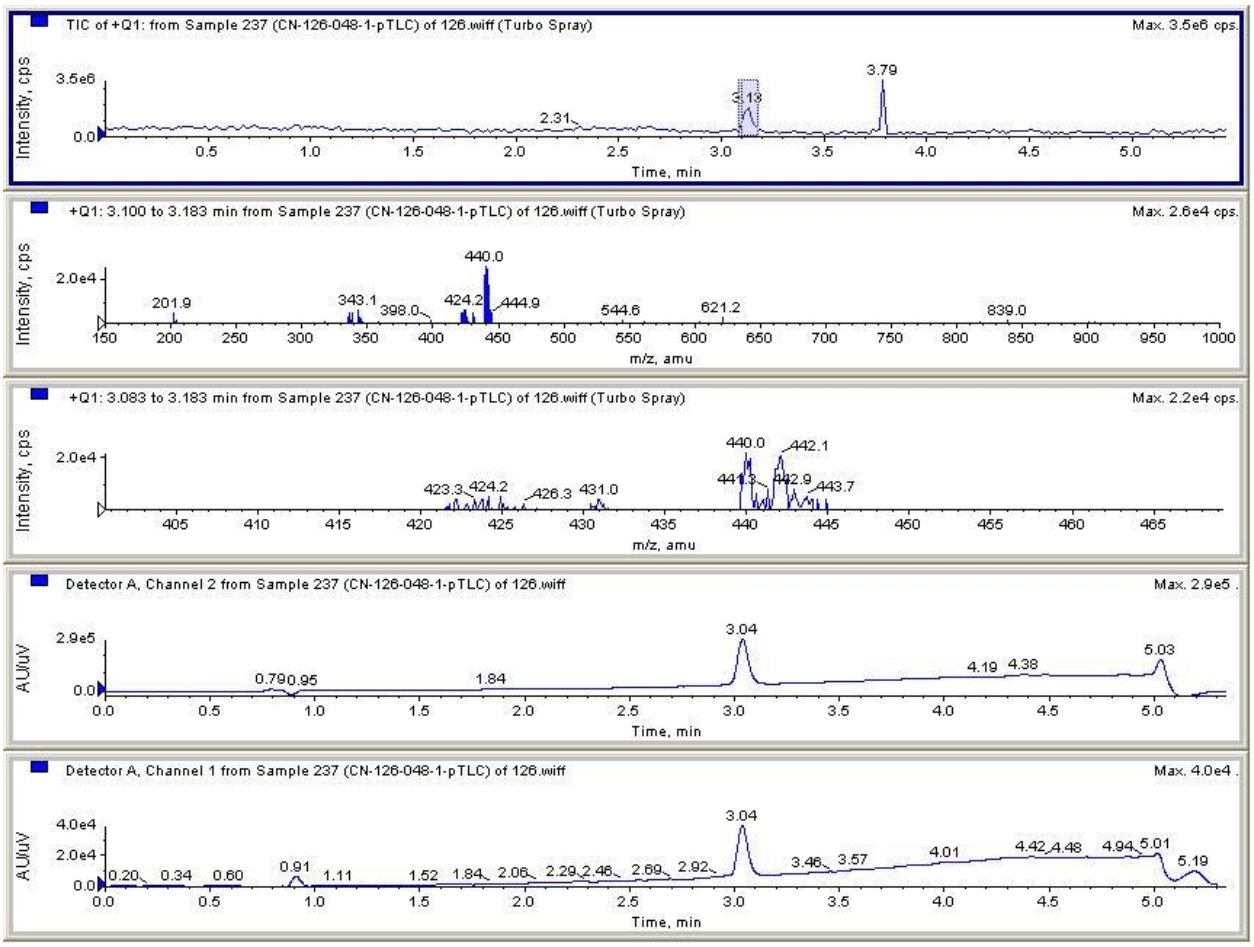


*LCMS of **17** (separately synthesized and characterized by LCMS and NMR):*

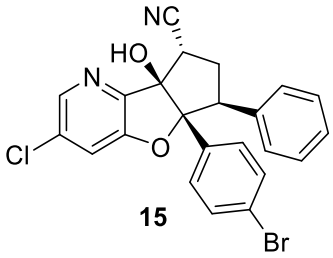


17

Chemical Formula: $C_{22}H_{15}BrClNO_2$
Exact Mass: 438.9975

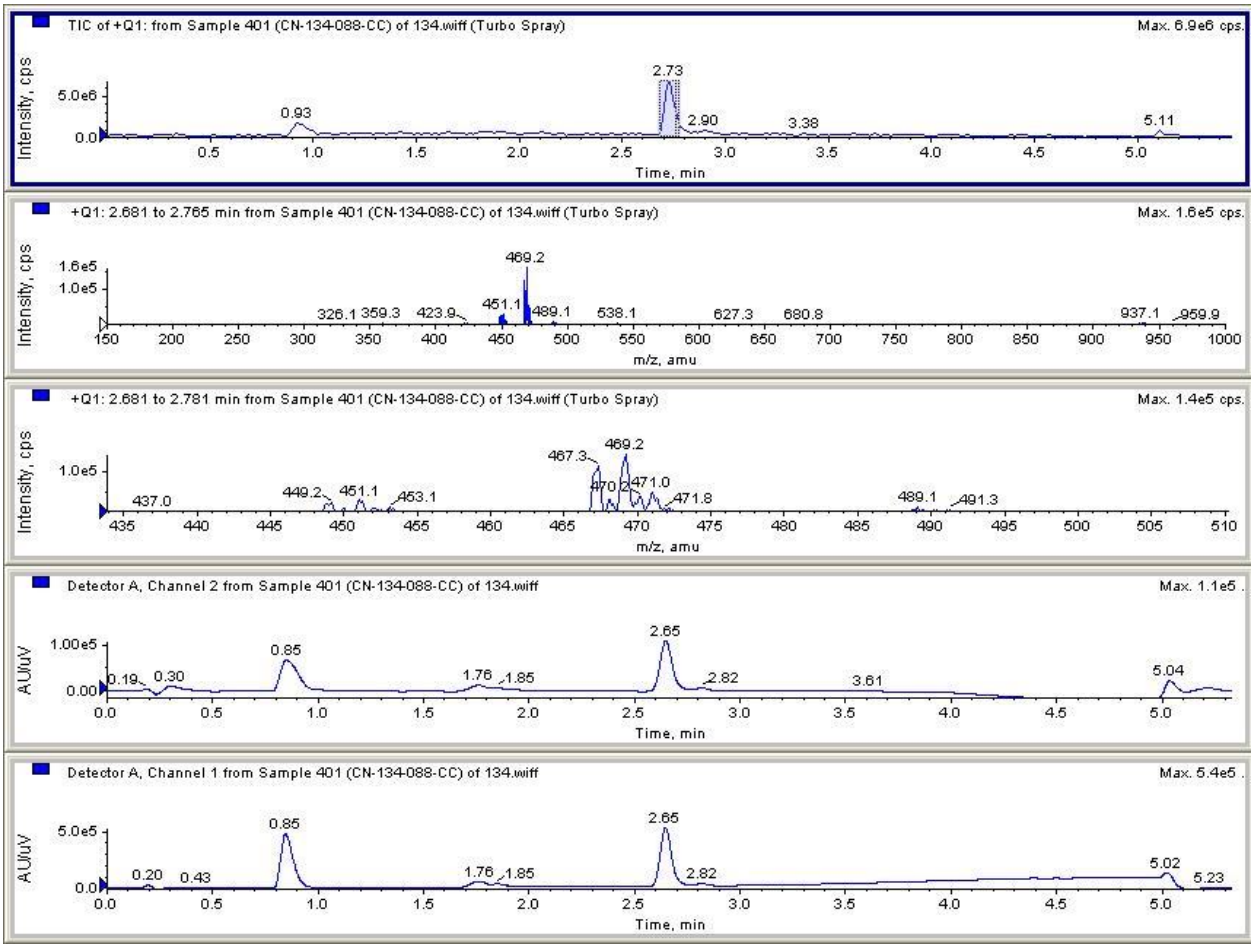


*LCMS of **15** (product):*



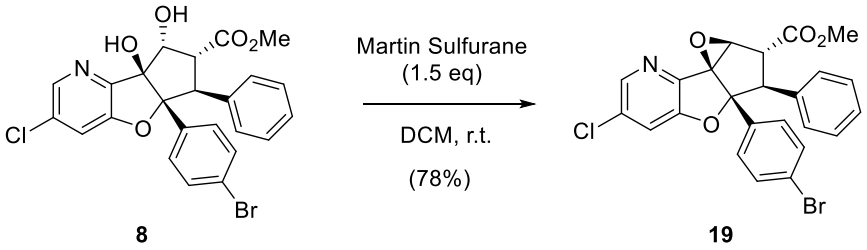
15

Chemical Formula: $C_{23}H_{16}BrClN_2O_2$
Exact Mass: 466.0084



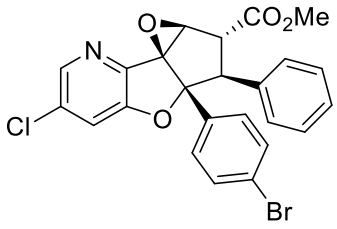
3.2 Mechanistic investigation of the stereoinvertive displacement **18→21**

3.2.1 Synthesis and characterization of epoxide **19**



8 **19**

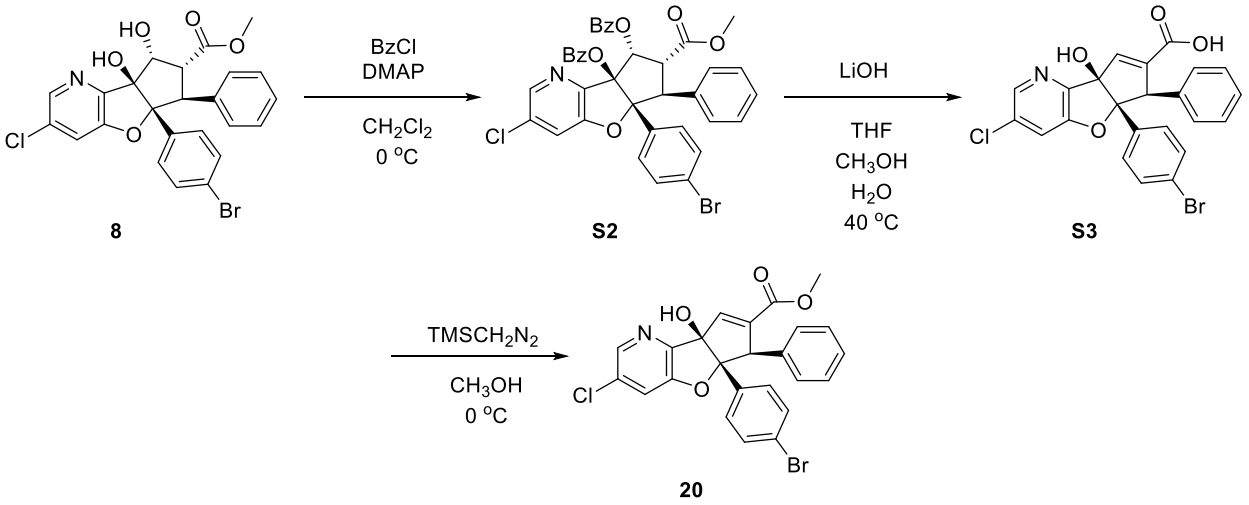
***rac*-methyl (1a*S*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-3-phenyl-1a,2,3,3a-tetrahydro-oxireno[2'',3'':1',5']cyclopenta[1',2':4,5]furo[3,2-b]pyridine-2-carboxylate (19)**



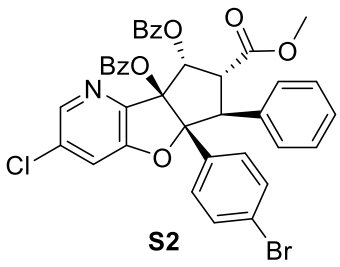
19

rac-Methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridine-7-carboxylate (**8**) (42 mg, 0.081 mmol) was dissolved in DCM (0.6 mL) under argon. Martin sulfurane (82 mg, 0.12 mmol) was added, and the mixture was stirred at rt. The mixture turned dark red. After 6 h the reaction was quenched with NH_4Cl(aq). The mixture was extracted with DCM (3x), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by repeated column chromatography (SiO_2, 0-30% ethyl acetate/hexane, then 0-20% ethyl acetate/hexane) yielded 29.6 mg (0.0594 mmol, 73%) of **19** as a light orange solid; **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{24}H_{18}BrClNO_4^+$ 498.0102; Found 498.0082; **^{1}H NMR (400 MHz, $CDCl_3$)** δ / ppm = 8.17 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.23–7.19 (m, 2H), 7.15–7.10 (m, 5H), 7.05–7.00 (m, 2H), 4.91 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 0.6 Hz, 1H), 3.72 (s, 3H), 3.72 (dd, *J* = 11.8, 0.6 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ / ppm = 171.1, 155.6, 142.8, 140.7, 135.2, 135.0, 133.5, 130.9, 128.9, 128.5, 128.2, 127.7, 122.4, 118.3, 94.7, 78.1, 68.4, 67.4, 53.0, 50.0.

3.2.2 Synthesis and characterization of enoate **20**



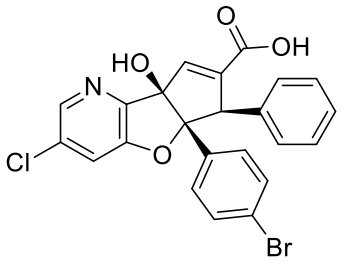
***rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(methoxycarbonyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diyl dibenzoate (S2)**



rac-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-b]pyridine-7-carboxylate (**8**) (150.0 mg, 0.2903 mmol) was dissolved in dichloromethane (1.5 mL) and the solution was cooled to 0 °C. Triethylamine (0.45 mL, 0.33 g, 3.2 mmol), benzoyl chloride (0.15 mL, 0.18 g, 1.3 mmol), and 4-dimethylaminopyridine (19.5 mg, 0.160 mmol) were added sequentially. After 20 min the reaction mixture was warmed to room temperature. After 2 h the reaction mixture was poured mixture onto saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined organic material was washed with brine, dried over magnesium sulfate and concentrated. Purification via silica gel chromatography (0-100 % ethyl acetate in dichloromethane) afforded the desired product **S2** as a tan resin. Yield: 173 mg (238 mmol, 82 %); **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{38}H_{28}BrClNO_7^+$ 724.0732; Found *m/z* 724.0695; **^{1}H NMR (400 MHz, $CDCl_3$ + TMS)** δ / ppm = 7.90 (d, *J* = 2.0 Hz, 1H), 7.86– 7.82 (m, 2H), 7.82–7.77 (m, 2H), 7.59–7.53 (m, 1H), 7.53–7.48 (m, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.43–7.37 (m, 2H), 7.37–7.31 (m, 2H), 7.19–7.06 (m, 7H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.90–6.86 (m, 2H), 4.39 (d, *J* = 14.7 Hz, 1H), 4.18 (dd, *J* = 14.7, 7.4 Hz, 1H), 3.50 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$ + TMS)** δ / ppm =168.4, 165.2, 163.7, 154.0,

143.8, 142.5, 134.7, 133.6, 133.6, 133.6, 133.5, 130.9, 129.9, 129.8, 129.2, 129.1, 128.5, 128.5, 128.3, 127.8, 127.7, 127.4, 122.1, 118.6, 100.5, 94.1, 78.4, 57.2, 52.6, 48.6.

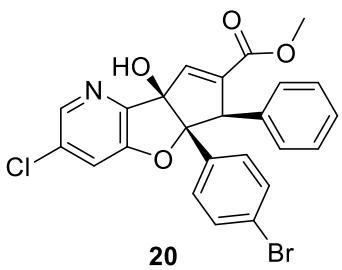
rac-(5a*R*,6*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,8a-dihydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (S3)



S3

rac-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(methoxy-carbonyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo-[3,2-b]pyridine-8,8a-diyl dibenzoate **(S2)** (80.0 mg, 0.110 mmol) was dissolved in THF (1.5 mL), water (1.5 mL), and methanol (1.5 mL). Solid lithium hydroxide (5.0 mg, 0.22 mmol) was added at room temperature and the mixture subsequently stirred at 40 °C in a heating block. After 18 h the reaction mixture was cooled to room temperature. The solvent was removed *in vacuo* and the residue taken up in a 1:1 mixture of methanol and DMSO with 1 drop of TFA. Purification via preparative HPLC (C18, MeCN/water+0.1%TFA) afforded the desired product **S3** as a white solid. Yield: 25 mg (52 mmol, 47 %); **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}BrClNO_4^+$ 483.9946; Found 483.9919; **^{1}H NMR (400 MHz, CD$_3$OD)** δ / ppm = 8.12 (bs, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.16-7.11 (m, 5H), 7.09-7.05 (m, 2H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.98-6.94 (m, 2H), 4.72 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR (101 MHz, CD$_3$OD)** δ / ppm = 167.0, 154.5, 150.1, 142.7, 142.4, 141.4, 138.7, 135.6, 133.9, 130.9, 130.7, 130.3, 129.1, 128.3, 122.5, 119.5, 104.5, 91.7, 63.7.

rac-methyl (5a*R*,6*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,8a-dihydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (20)



20

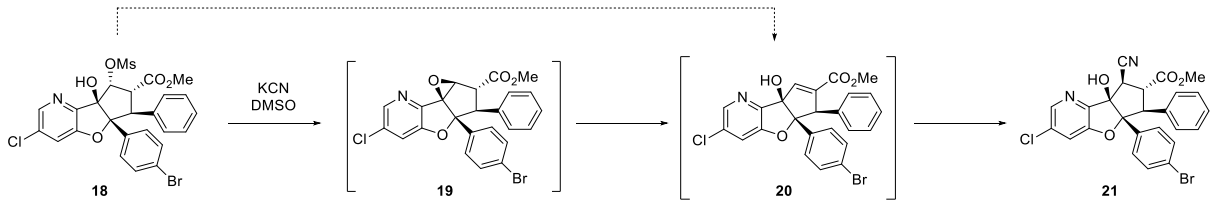
rac-(5a*R*,6*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-6H-cyclopenta[4,5]-furo[1,2-b]pyridine-7-carboxylic acid (**S3**) (8.0 mg, 0.016 mmol) was dissolved in methanol (1 mL) and stirred at 0 °C while trimethylsilyl diazomethane (2M in ether, 0.03 mL, 0.06 mmol) was added dropwise. After 30 min the mixture was warmed to room temperature. More trimethylsilyl diazomethane (2M in ether) was added every 30 min (0.03 mL, 0.06 mmol each time) until the starting material was consumed as judged by LCMS. The solvent was removed *in vacuo* and purification via preparative

HPLC (C18, MeCN/water+0.1%TFA) afforded the desired product **20** as a white solid. Yield 5.7 mg (11 mmol, 69%); **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{24}H_{18}BrClNO_4^+$ 498.0102; Found 498.0091; **^{1}H NMR (400 MHz, d^6-DMSO)** δ / ppm = 8.22 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.18–7.11 (m, 3H), 7.05 (d, *J*= 8.8 Hz, 2H), 6.98–6.92 (m, 4H), 4.67 (d, *J* = 1.6 Hz, 1H), 3.59 (s, 3H); **^{13}C NMR (101 MHz, d^6-DMSO)** δ / ppm = 163.7, 152.3, 148.9, 141.9, 141.5, 137.9, 136.9, 134.3, 131.4, 129.8, 129.4, 128.9, 128.0, 127.2, 120.8, 118.0, 102.4, 89.8, 61.4, 52.0.

3.2.3 LCMS studies

The conversion of **18** to **21** was studied by LCMS. Samples of the reaction mixture were taken at different time points from t = 0 min to t = 17.5h and analyzed. LCMS chromatograms of compounds **18**, **19**, **20**, and **21** were obtained and used as references. The results are in agreement with the reaction pathway shown below.

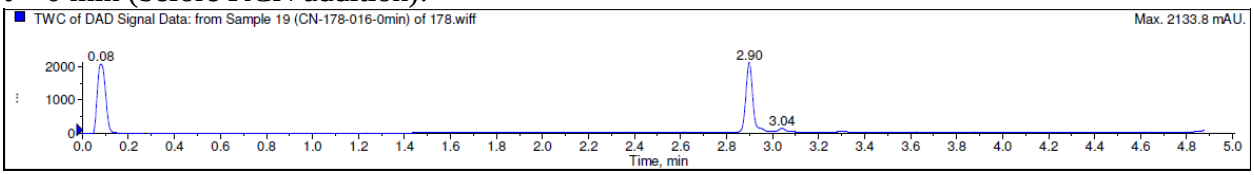
Proposed reaction pathway:



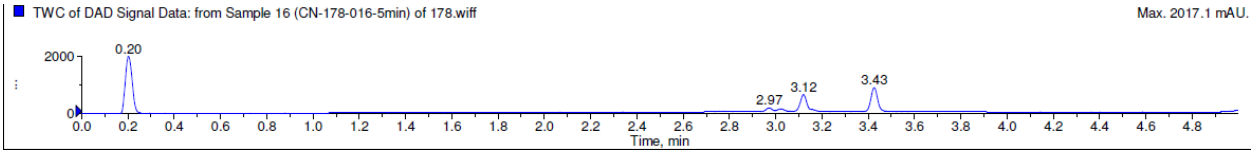
t_R(LCMS) = 2.90 min t_R(LCMS) = 3.42 min t_R(LCMS) = 3.11 min t_R(LCMS) = 3.04 min

LCMS of reaction mixture at different timepoints:

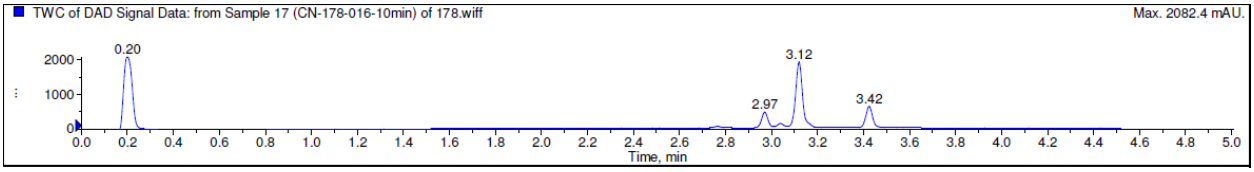
t = 0 min (before KCN addition):



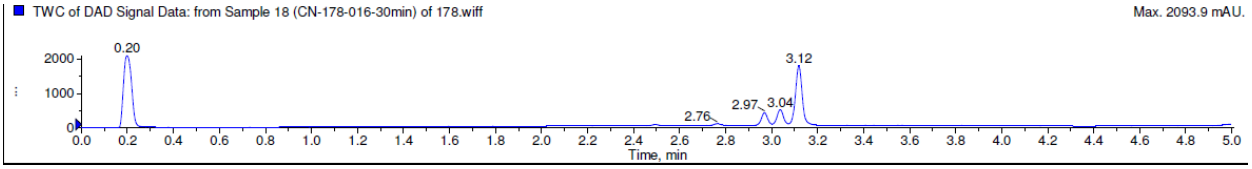
t = 5 min:



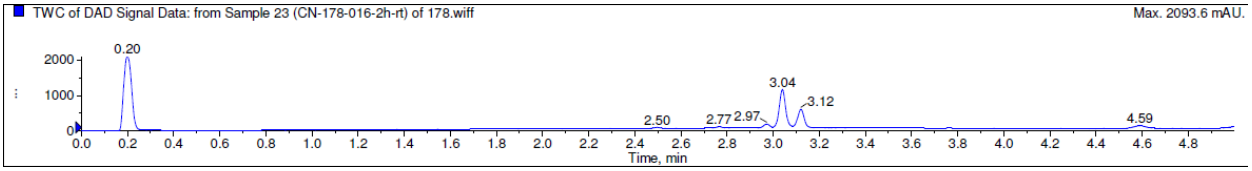
t = 10 min:



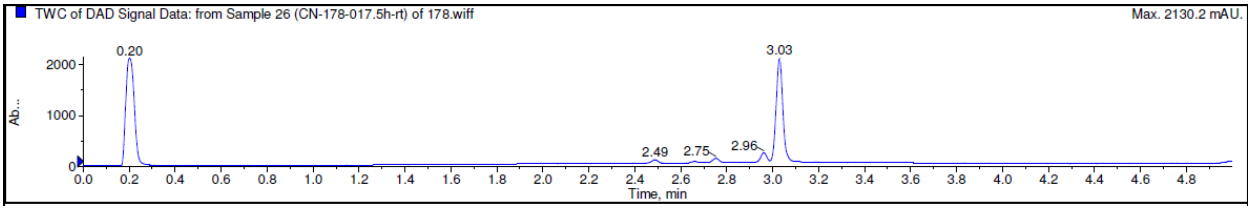
t = 30 min:



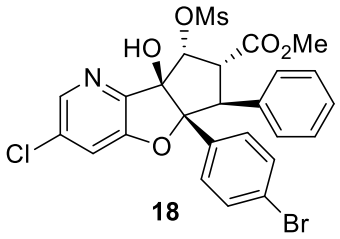
t = 2 h:



t = 17.5 h:

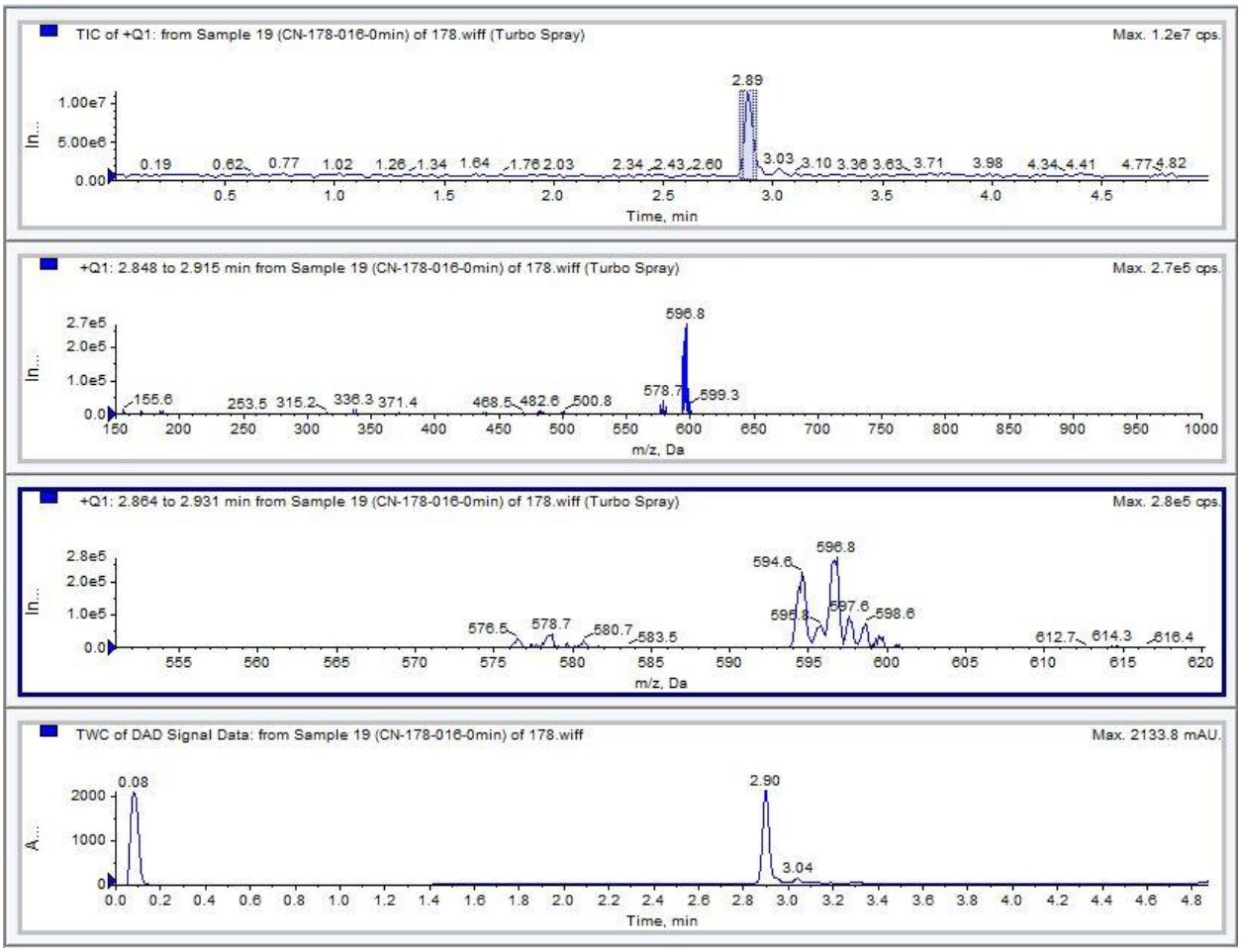


*LCMS of **18** (starting material) in DMSO before KCN addition:*

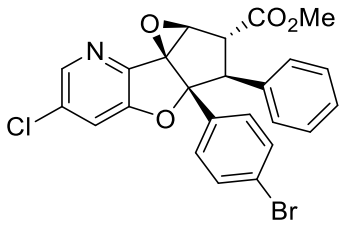


18

Chemical Formula: $C_{25}H_{21}BrClNO_7S$
Exact Mass: 592.9911

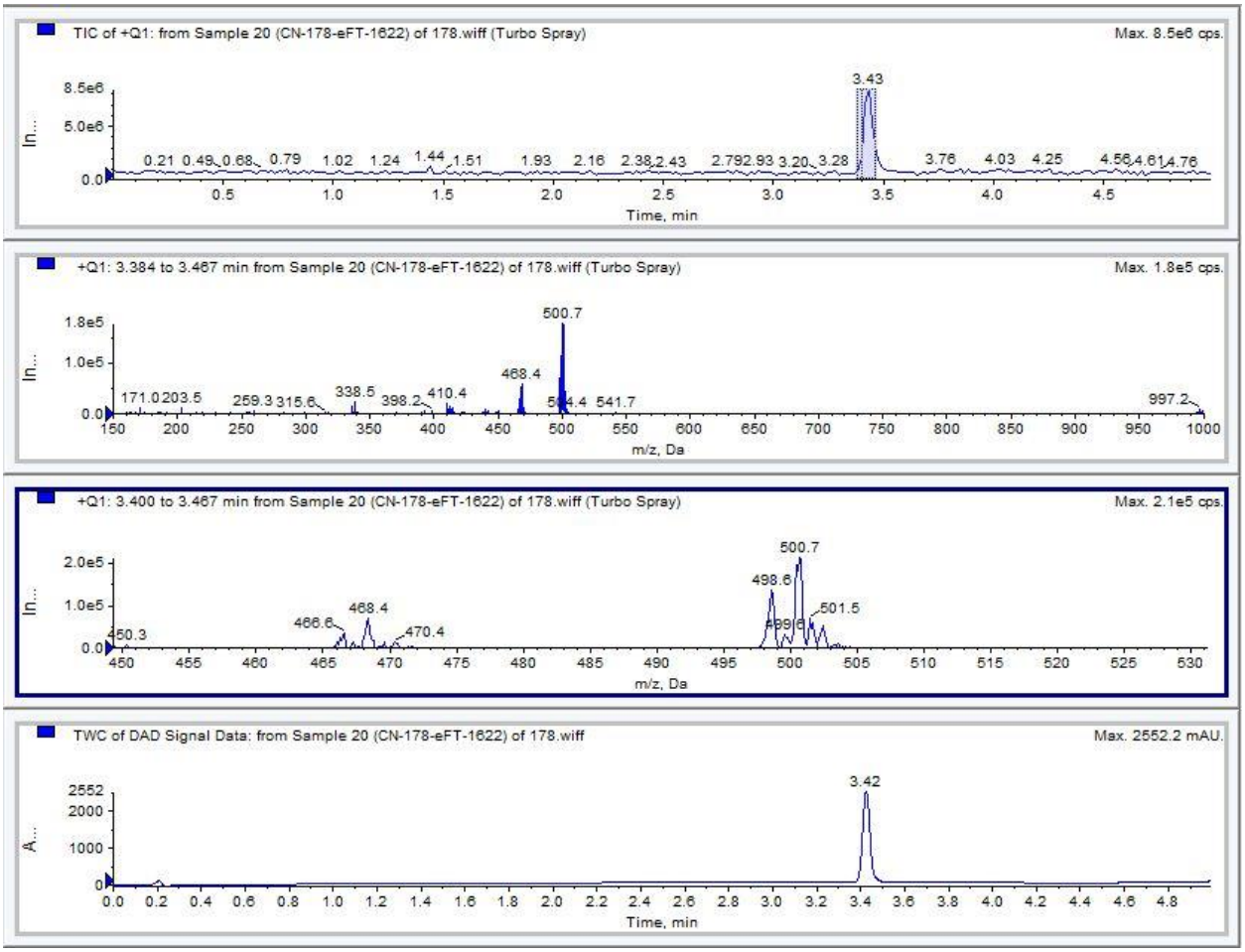


*LCMS of **19** (separately synthesized and characterized by LCMS and NMR):*

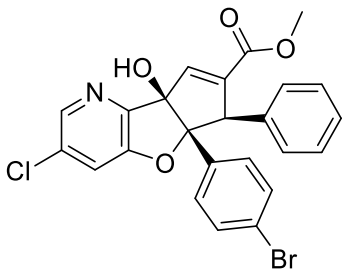


19

Chemical Formula: $C_{24}H_{17}BrClNO_4$
Exact Mass: 497.0029

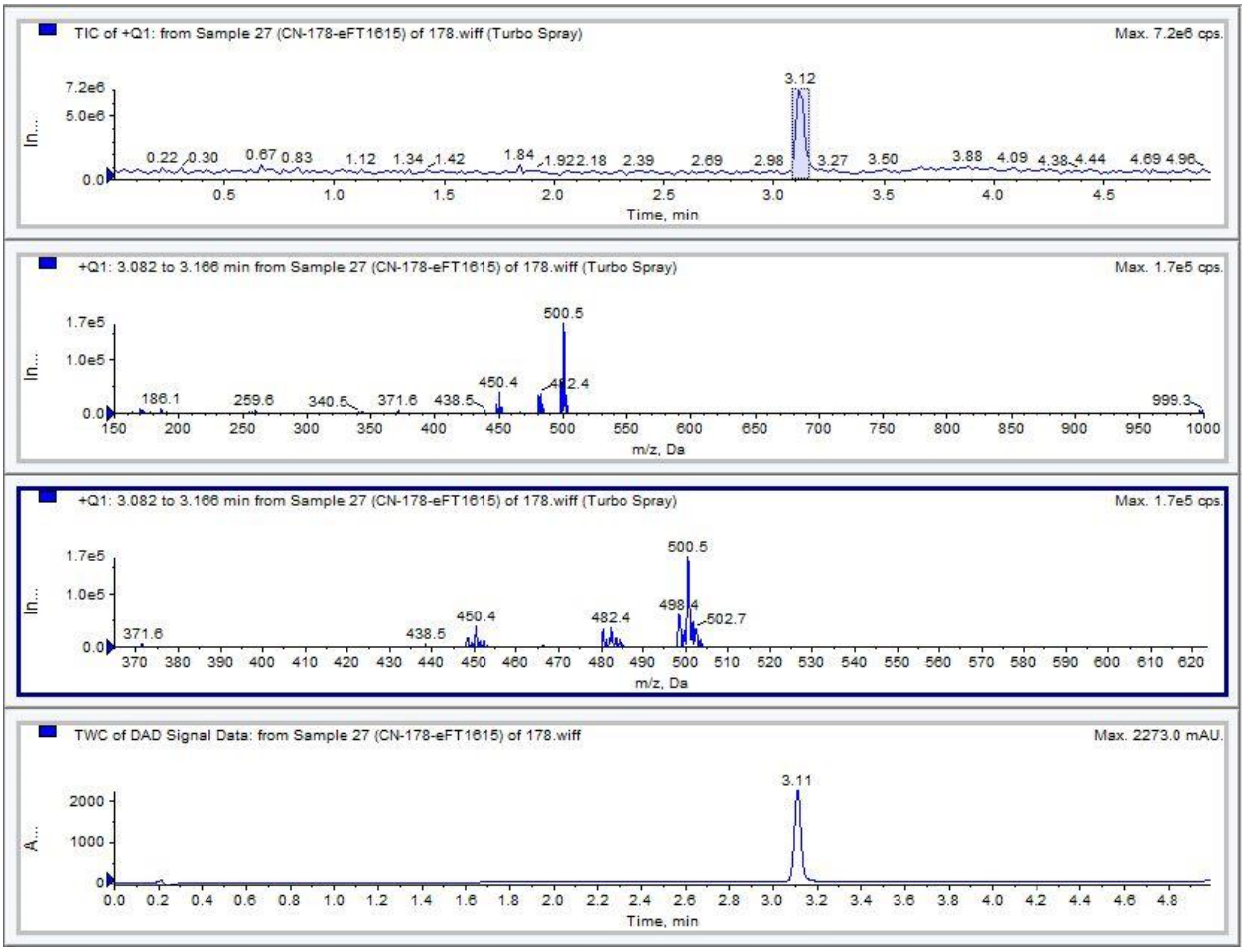


*LCMS of **20** (separately synthesized and characterized by LCMS and NMR):*

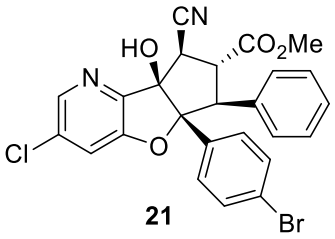


20

Chemical Formula: $C_{24}H_{17}BrClNO_4$
Exact Mass: 497.0029

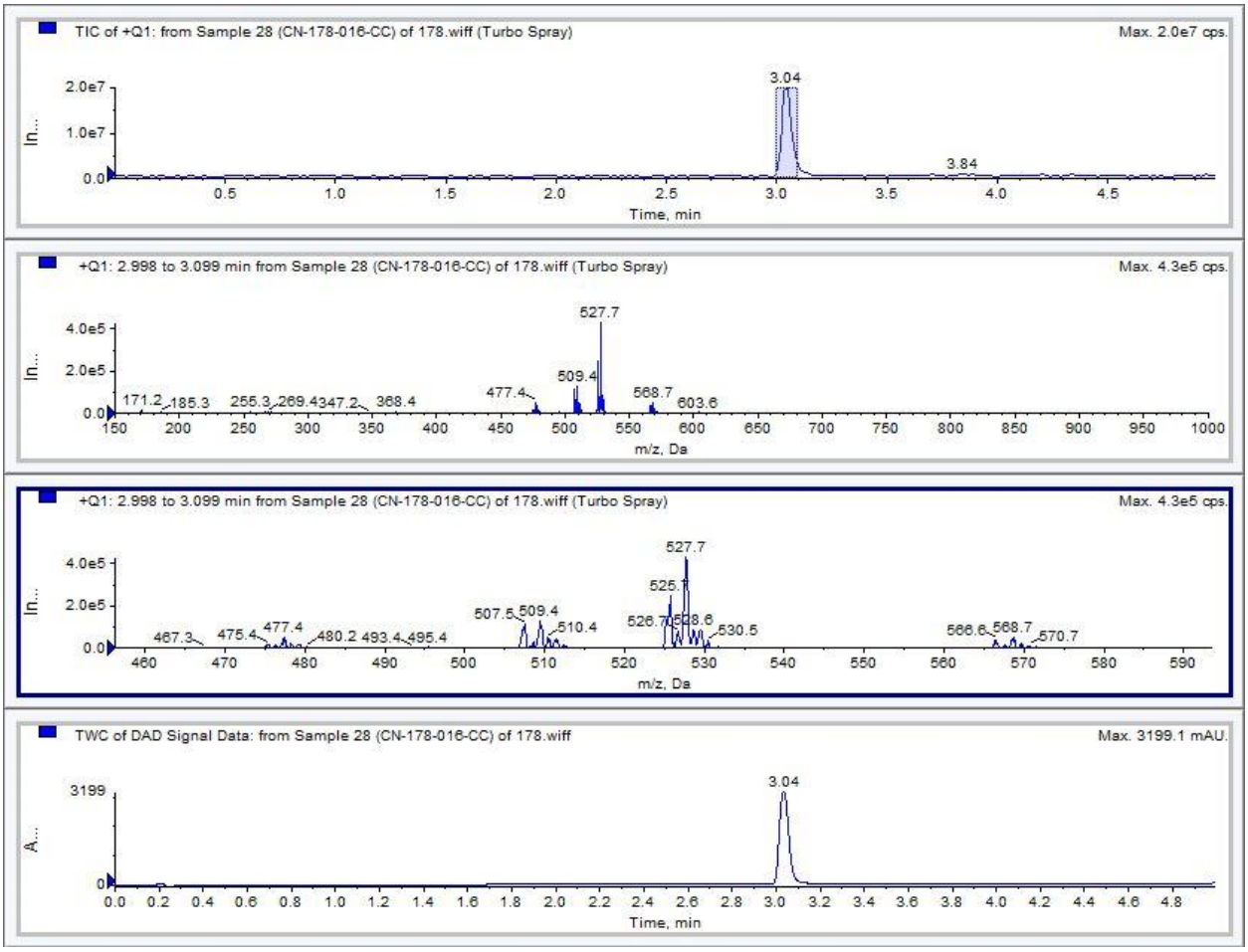


*LCMS of **21** (product):*

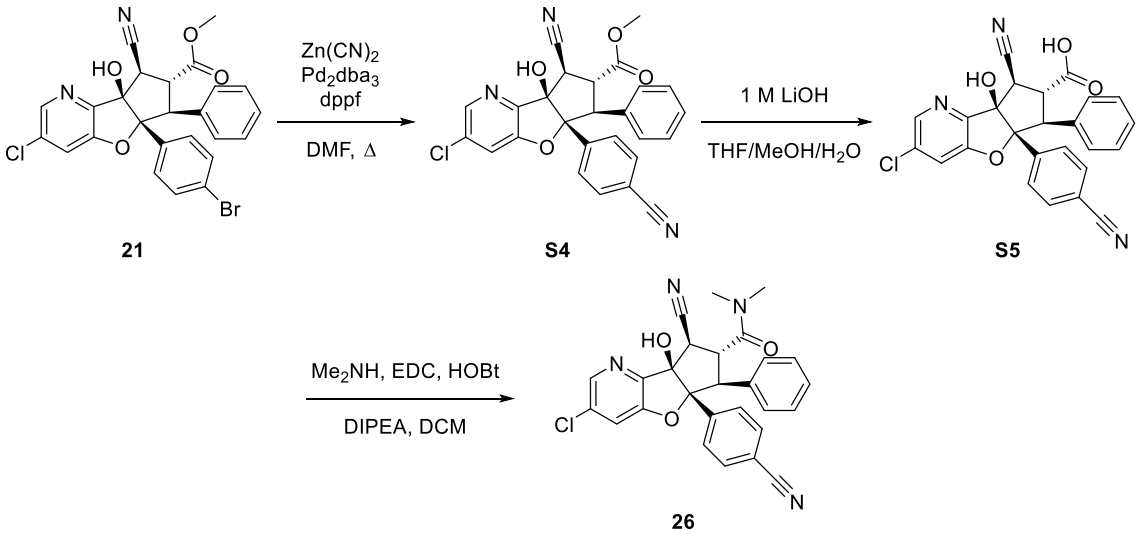


21

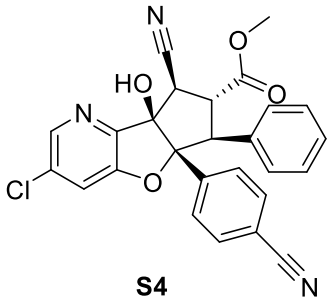
Chemical Formula: $C_{25}H_{18}BrClN_2O_4$
Exact Mass: 524.0138



3.2.4 Synthesis of compound **26**

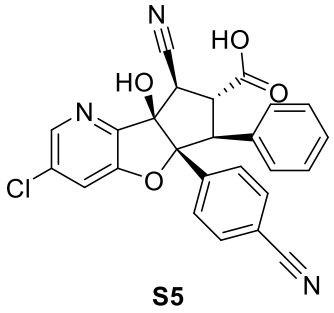


***rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (S4)**



A suspension of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-7,8-dihydro-6H-cyclopenta[4,5]furo[1,2-b]pyridine-7-carboxylate (**21**) (184 mg, 0.350 mmol), zinc cyanide (247 mg, 2.10 mmol), zinc (23 mg, 0.35 mmol), $Pd_2(dba)_3$ (32 mg, 0.035 mmol) and dppf (38.8 mg, 0.0700 mmol) in DMF (3 mL) and water (0.3 mL) was purged with argon for 5 min. The reaction was stirred at 120 ^oC for 6 h in a heating block. The resulting mixture was cooled to room temperature, diluted with DCM and filtered through a pad of celite. The filtrate was washed with water. The combined organics were dried over magnesium sulfate, filtered and concentrated. The crude product was purified via flash chromatography (silica, ethyl acetate/hexanes = 0-30%) to afford **S4** as a white solid. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{26}H_{19}ClN_3O_4^+$ 472.1059; Found 472.1053; **^{1}H NMR (400 MHz, DMSO-d6)** δ / ppm = 8.38 (d, *J* = 2.0 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.68-7.63 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.11-7.05 (m, 3H), 6.99-6.92 (m, 2H), 6.89 (s, 1H), 4.33-4.24 (m, 2H), 3.89-3.80 (m, 1H), 3.54 (s, 3H); **^{13}C NMR (101 MHz, DMSO-d6)** δ / ppm = 170.3, 150.9, 149.4, 142.3, 139.3, 134.6, 132.3, 131.0, 128.4, 127.9, 127.8, 127.2, 119.5, 118.6, 117.2, 110.1, 101.3, 84.0, 57.1, 52.6, 47.4, 41.2.

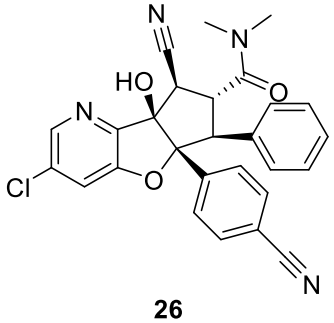
***rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (S5)**



S5

To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S4**) (15 mg, 0.032 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL) was added 2 M lithium hydroxide (1 mL, 2 mmol). The reaction was stirred at room temperature for 5 min. The reaction was acidified with 1 M hydrochloric acid and the organic volatiles were evaporated. The mixture was diluted with water and extracted with dichloromethane. The combined organics were dried over magnesium sulfate, filtered and concentrated. The crude product **S5** was used for next step without further purification. Yield: 15 mg, crude; **HRMS (ESI)** m/z: $[M+H]^+$ Calcd for $C_{25}H_{17}ClN_3O_4^+$ 458.0902; Found 458.0888.

***rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (26)**



26

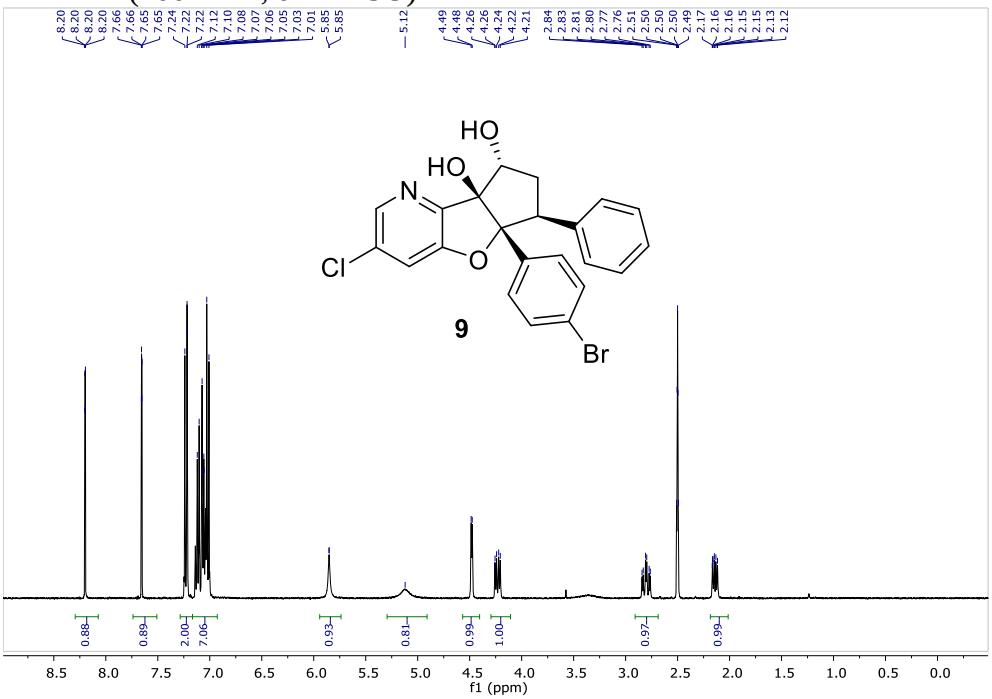
To a solution of crude *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (**S5**) (30 mg), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (39 mg, 0.20 mmol), 1-hydroxybenzotriazole hydrate (31 mg, 0.20 mmol) in dichloromethane (4 mL) at 0 ^oC were added N,N-diisopropylethylamine (0.08 mL, 0.46 mmol) and N-methylmethanamine hydrochloride (11 mg, 0.13 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted with dichloromethane and washed with aqueous saturated sodium bicarbonate solution. The combined organics were dried over magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography (silica, ethyl acetate/hexane = 0-60%), followed by preparative HPLC (C18, MeCN/water+0.1%TFA) to afford *rac*-(5aR,6S,7R,8R,8aR)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (**26**) as a white solid. Yield: 13.7 mg (0.0277 mmol, 43% over two steps); **HRMS (ESI)** m/z: $[M+H]^+$ Calcd

for $C_{27}H_{22}ClN_4O_3^+$ 485.1375; Found 485.1359; **^{1}H NMR (400 MHz, DMSO-d6)** δ / ppm = 8.37 (d, *J* = 2.0 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.11-7.07 (m, 3H), 6.91 (d, *J* = 0.6 Hz, 1H), 6.89-6.83 (m, 2H), 4.49 (dd, *J* = 12.6, 10.4 Hz, 1H), 3.92 (d,*J* = 12.6 Hz, 1H), 3.90 (dd, *J* = 10.4, 0.6 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); **^{13}C NMR (101 MHz, d6-DMSO)** δ / ppm = 168.5, 150.9, 149.4, 142.3, 139.6, 134.4, 132.4, 131.1, 128.6, 127.98, 127.96, 127.4, 119.5, 118.6, 117.1, 110.2, 101.5, 84.7, 58.8, 44.1, 42.4, 37.3, 35.8.

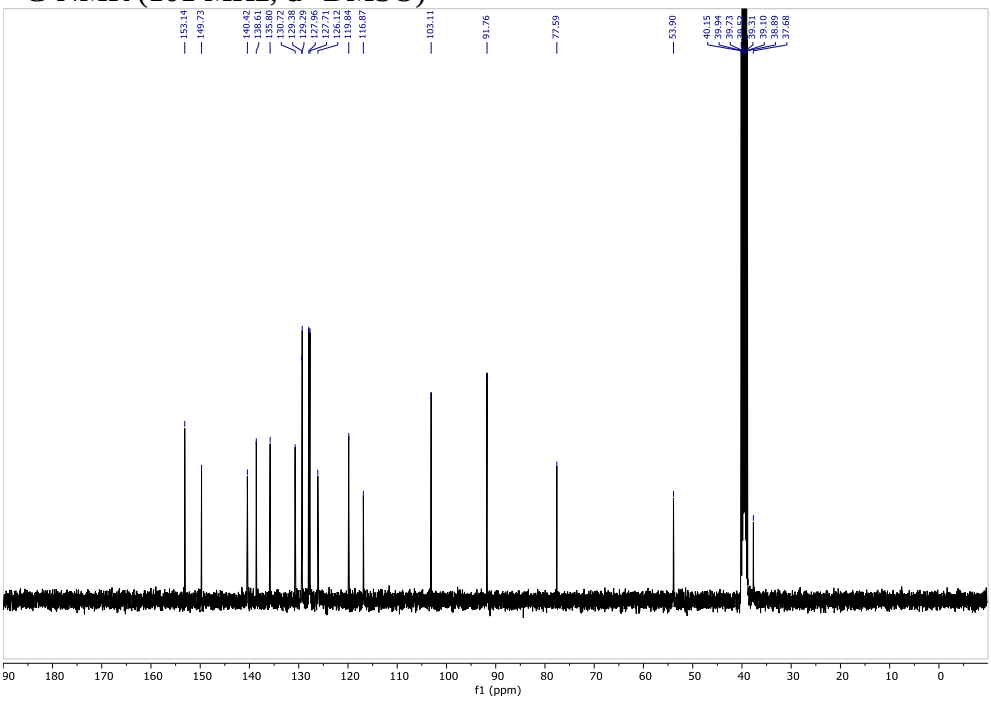
4 1D and 2D NMR spectra

rac-(5a_R_,6_S_,8_R_,8a_S_)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diol (9)

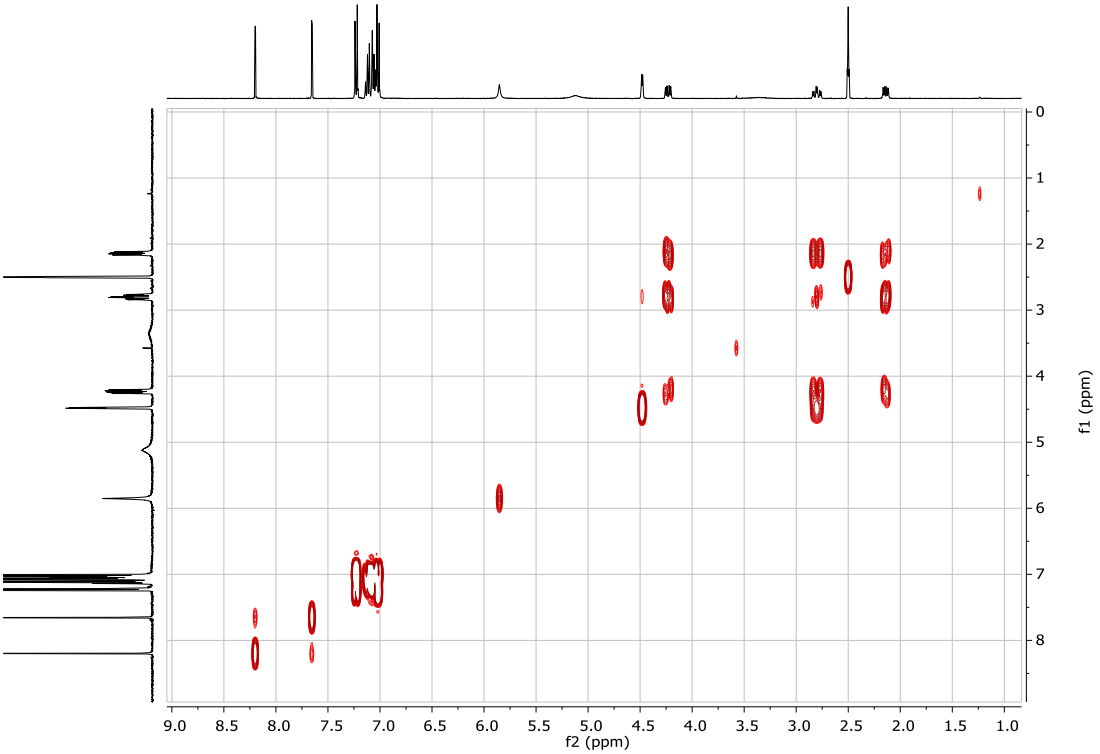
^{1}H-NMR (400 MHz, d^{6}-DMSO)



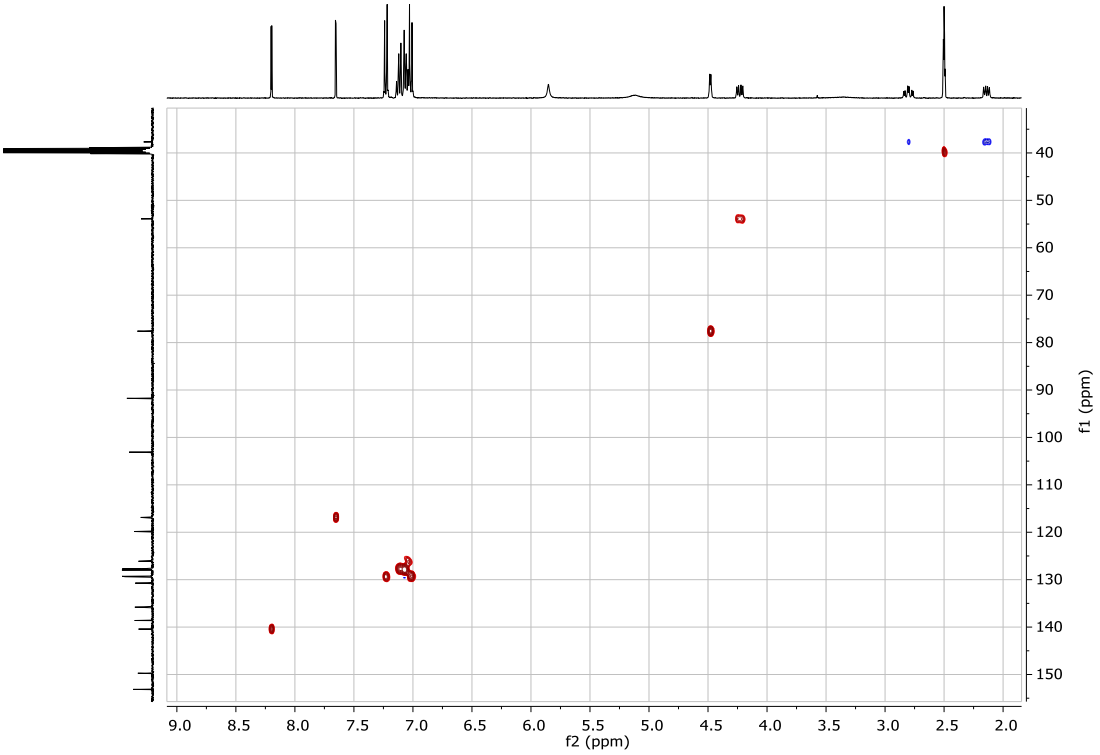
^{13}C-NMR (101 MHz, d^{6}-DMSO)



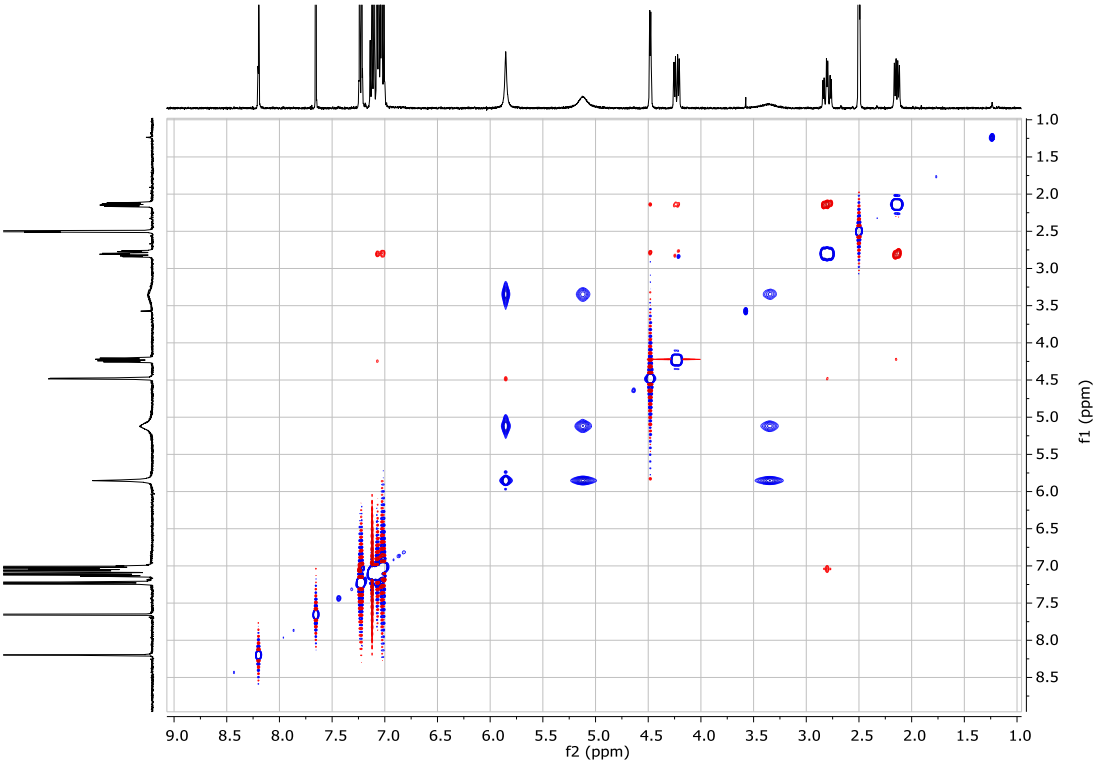
$^{1}H,^{1}H$-COSY (d^{6}-DMSO)



$^{1}H,^{13}C$-HSQC (d^{6}-DMSO)

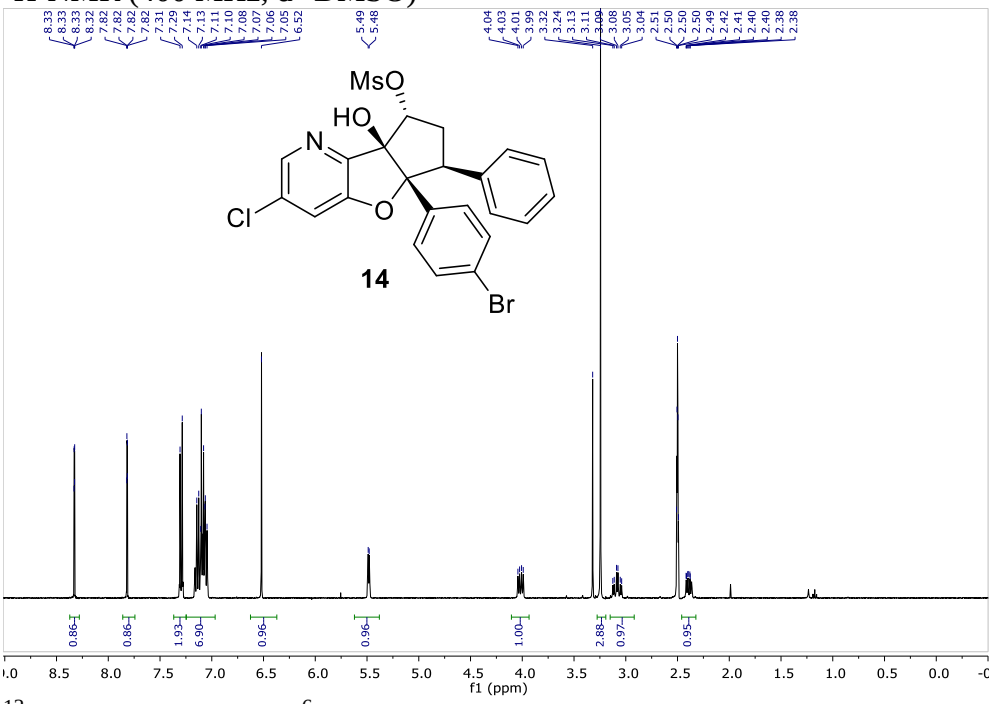


$^{1}H,^{1}H$-NOESY (d^{6}-DMSO)

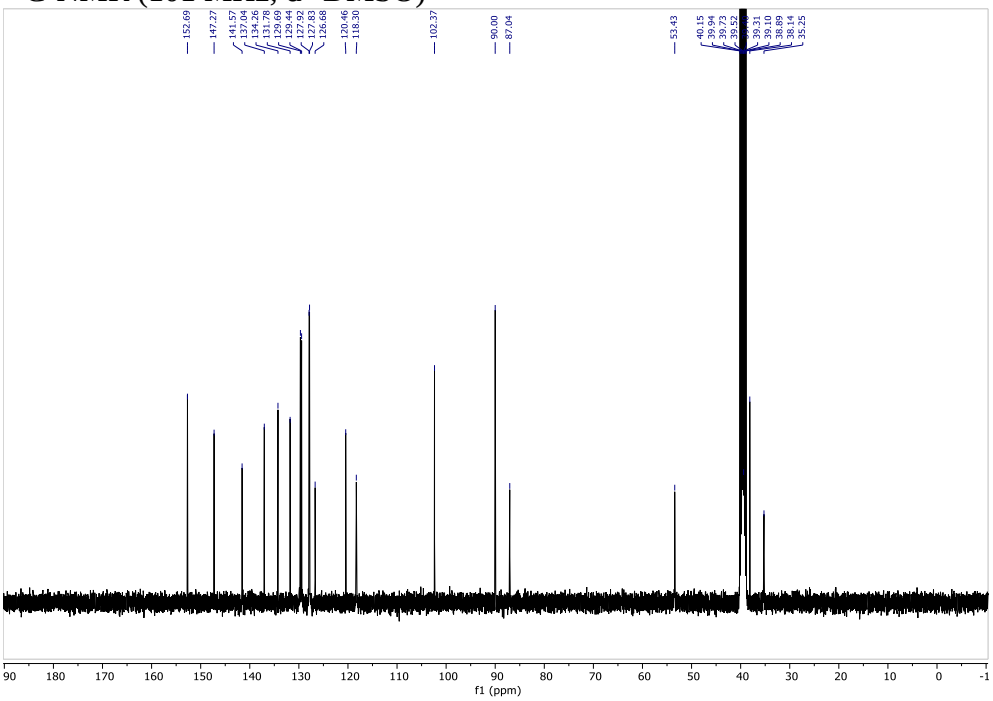


rac-(5a_R_,6_S_,8_R_,8a_S_)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridin-8-yl methanesulfonate (14)

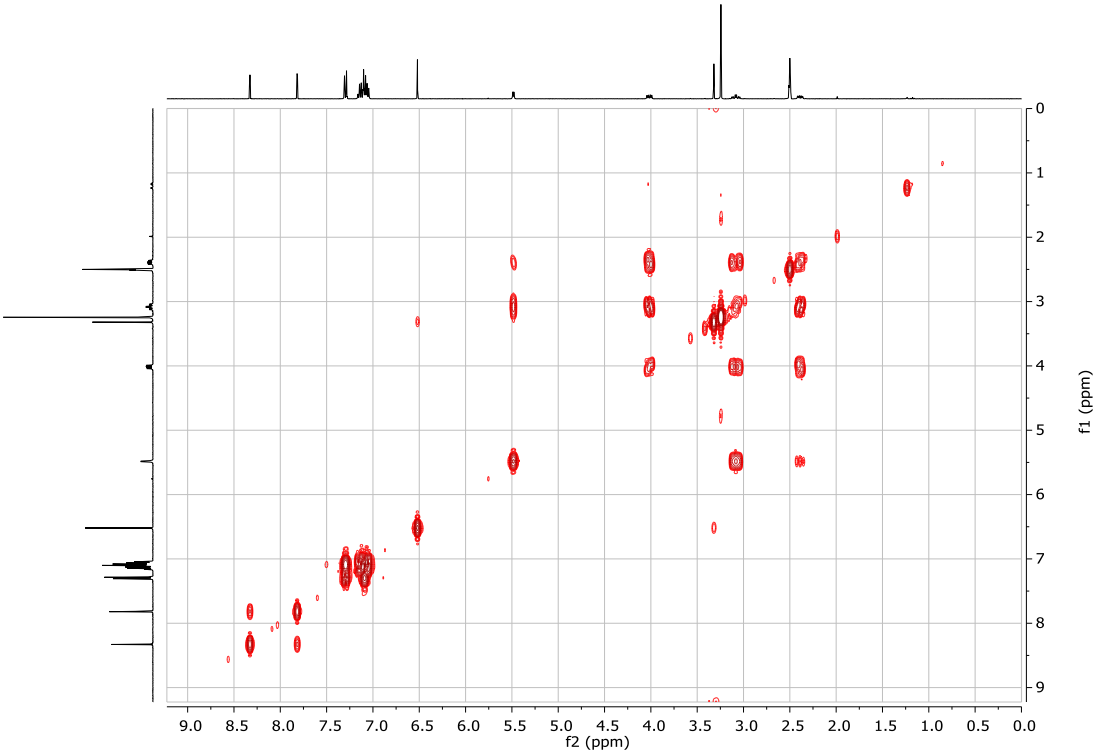
^{1}H-NMR (400 MHz, d^{6}-DMSO)



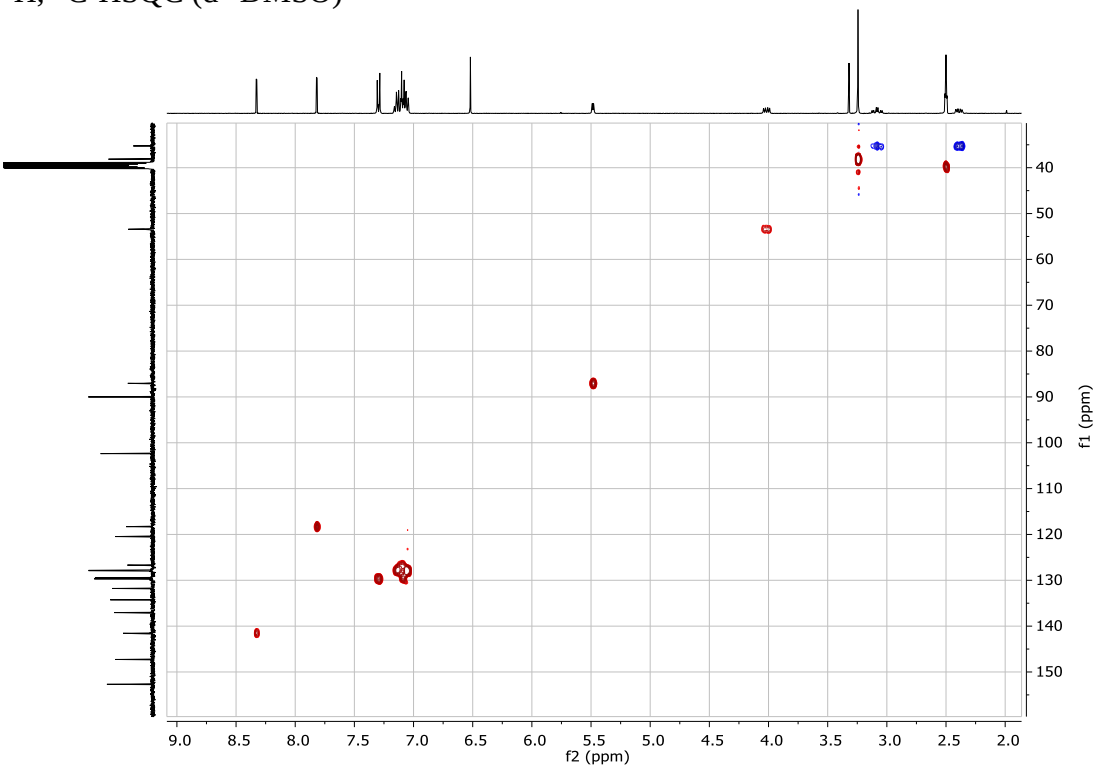
^{13}C-NMR (101 MHz, d^{6}-DMSO)



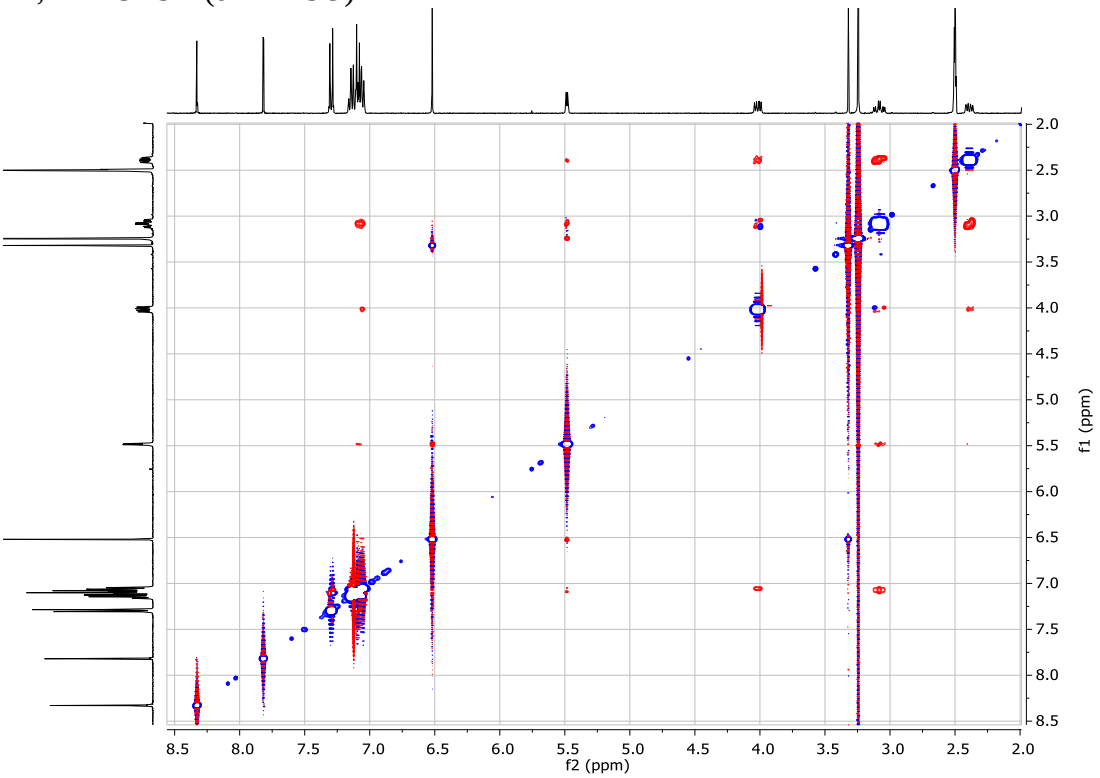
$^{1}H,^{1}H$-COSY (d^{6}-DMSO)



$^{1}H,^{13}C$-HSQC (d^{6}-DMSO)

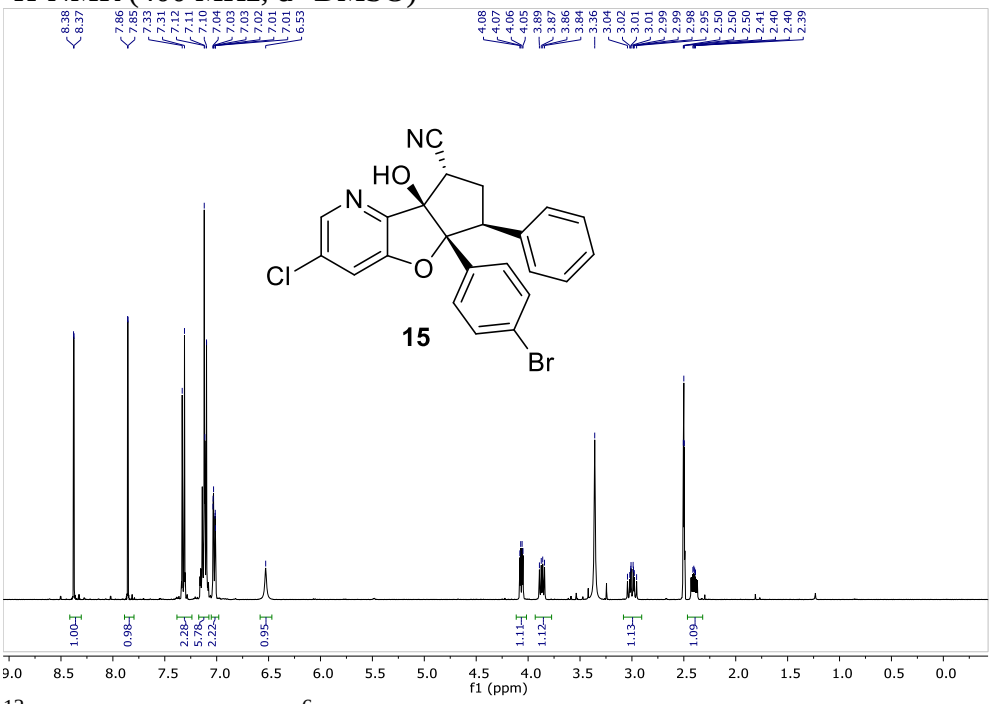


$^{1}H,^{1}H$-NOESY (d^{6}-DMSO)

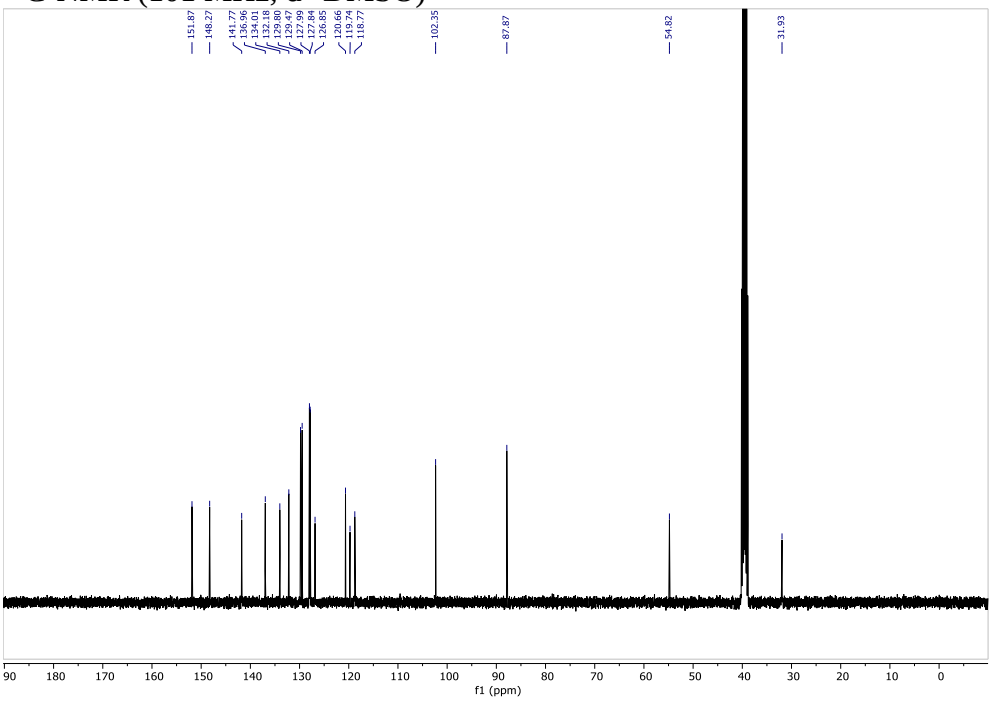


rac-(5a_R_,6_S_,8_S_,8a_R_)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-8-carbonitrile (15)

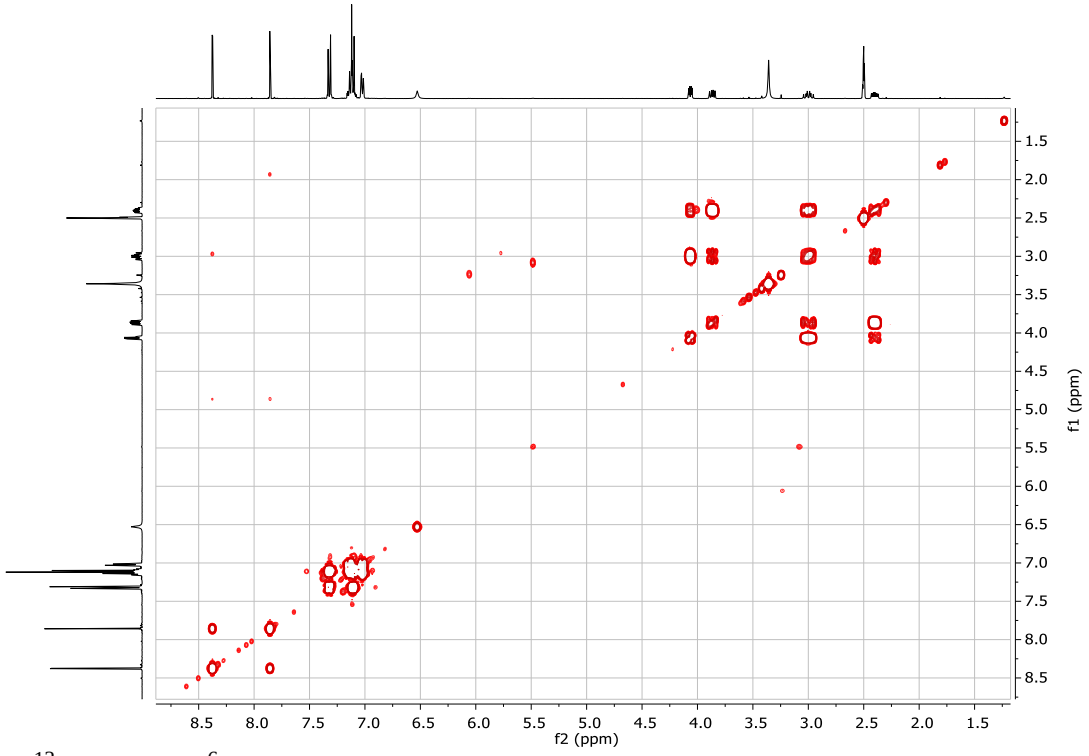
^{1}H-NMR (400 MHz, d^{6}-DMSO)



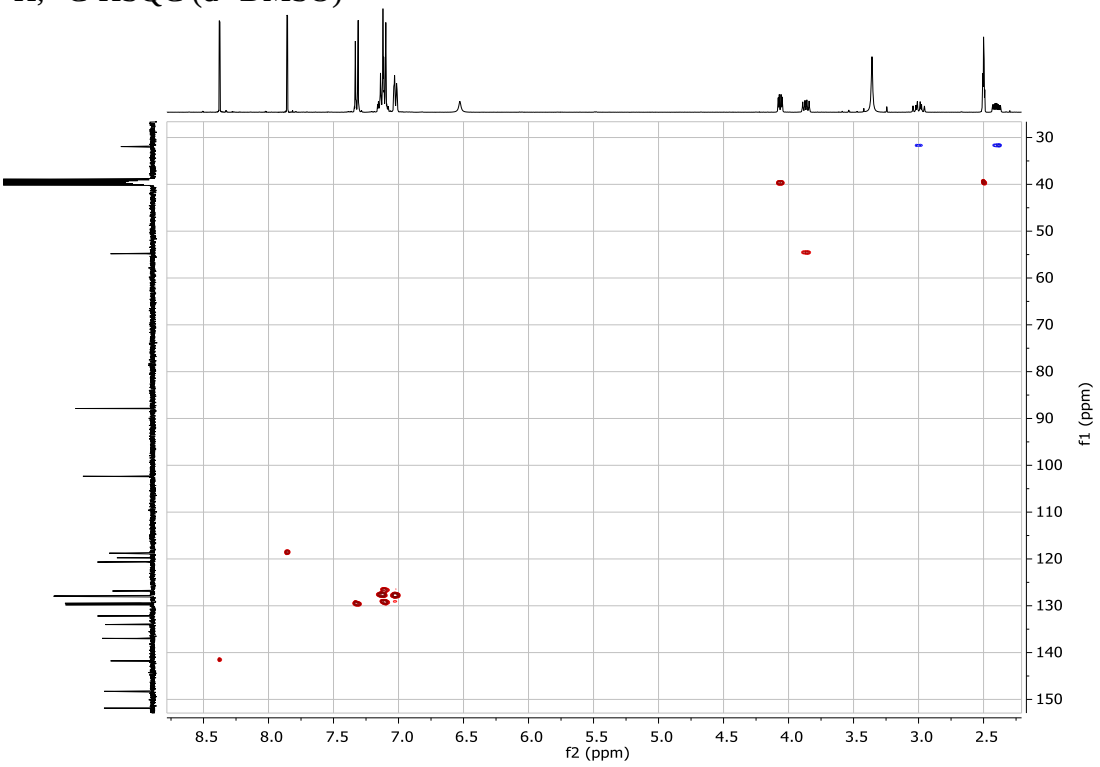
^{13}C-NMR (101 MHz, d^{6}-DMSO)



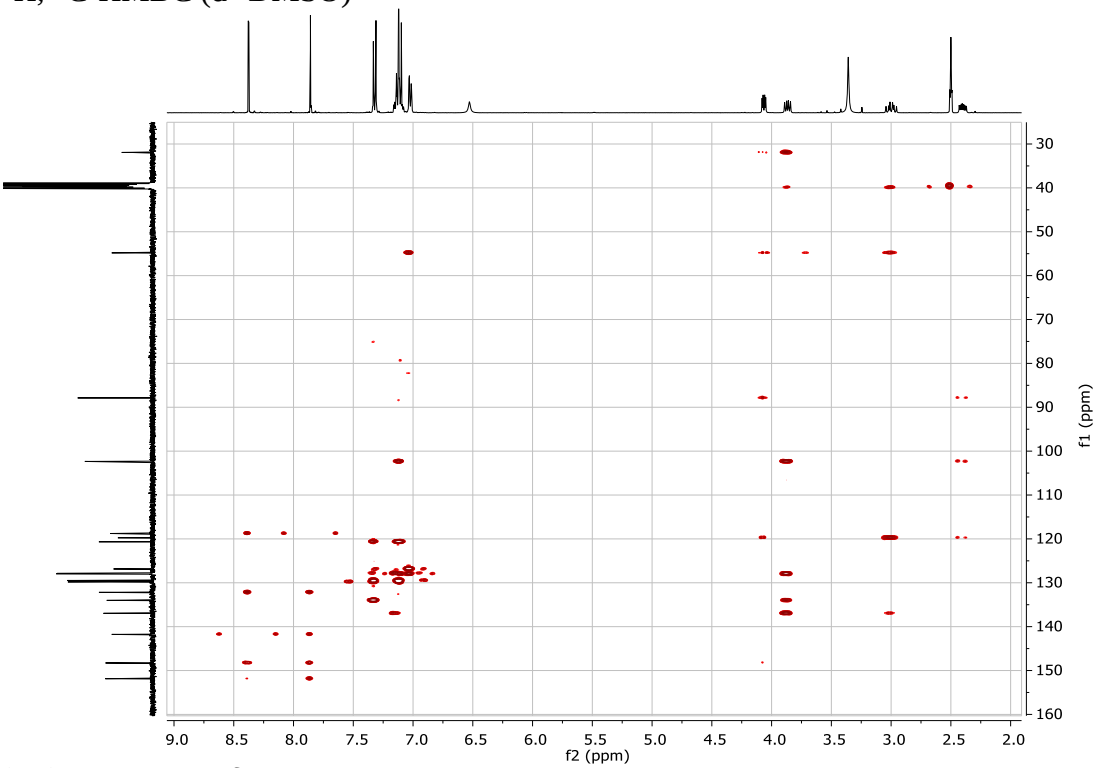
$^{1}H,^{1}H$-COSY (d^{6}-DMSO)



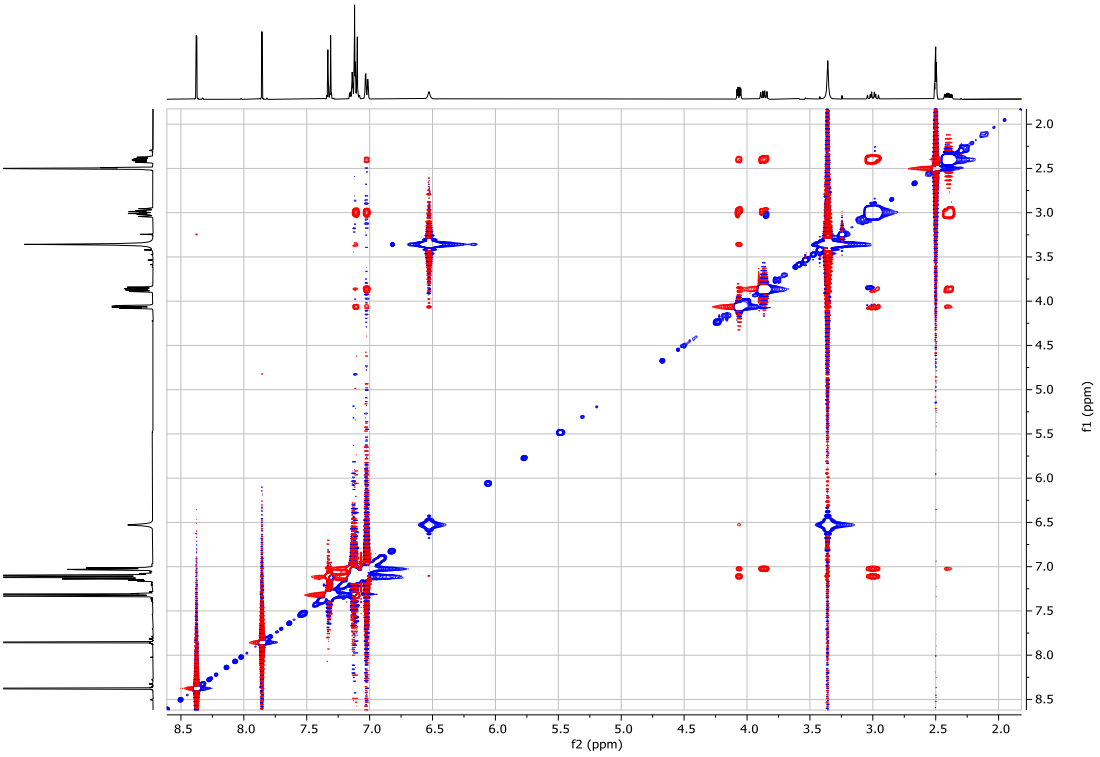
$^{1}H,^{13}C$-HSQC (d^{6}-DMSO)



$^{1}H,^{13}C$-HMBC (d^{6}-DMSO)

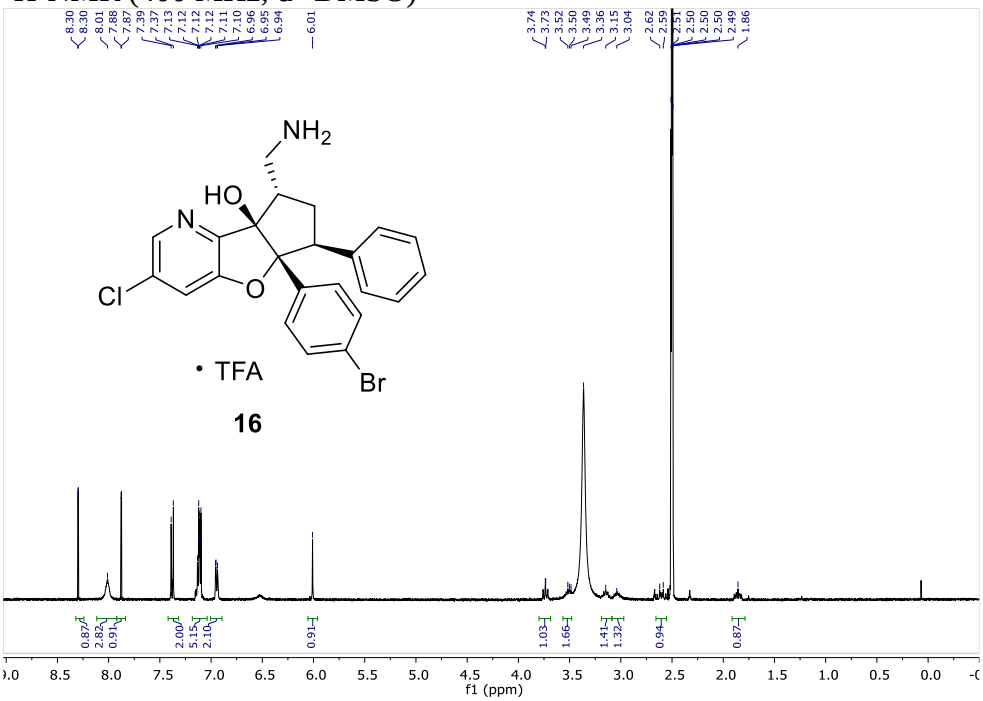


$^{1}H,^{1}H$-NOESY (d^{6}-DMSO)

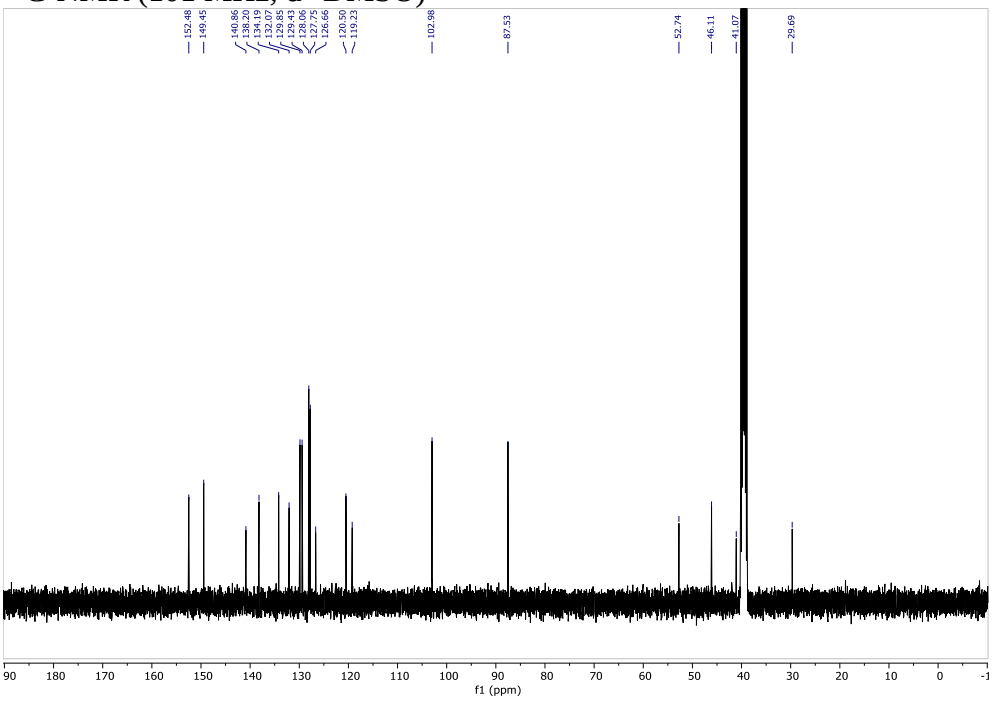


rac-(5a_R_,6_S_,8_S_,8a_R_)-8-(aminomethyl)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridin-8a-ol (TFA salt) (16)

^{1}H-NMR (400 MHz, d^{6}-DMSO)

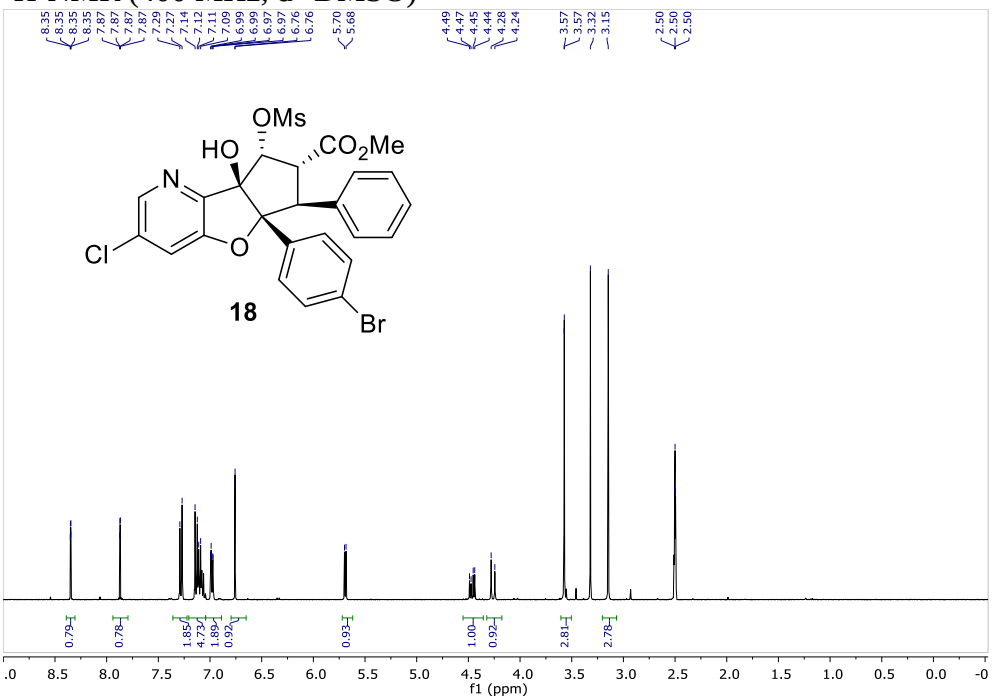


^{13}C-NMR (101 MHz, d^{6}-DMSO)

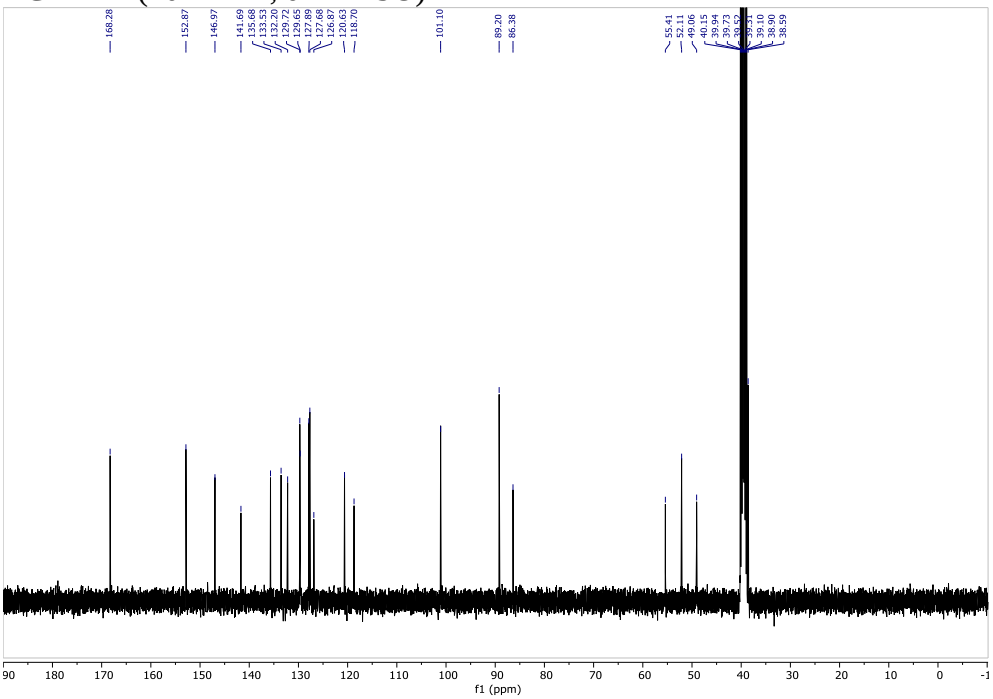


rac-methyl (5a_R_,6_S_,7_R_,8_R_,8a_S_)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-((methylsulfonyl)-oxy)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (18)

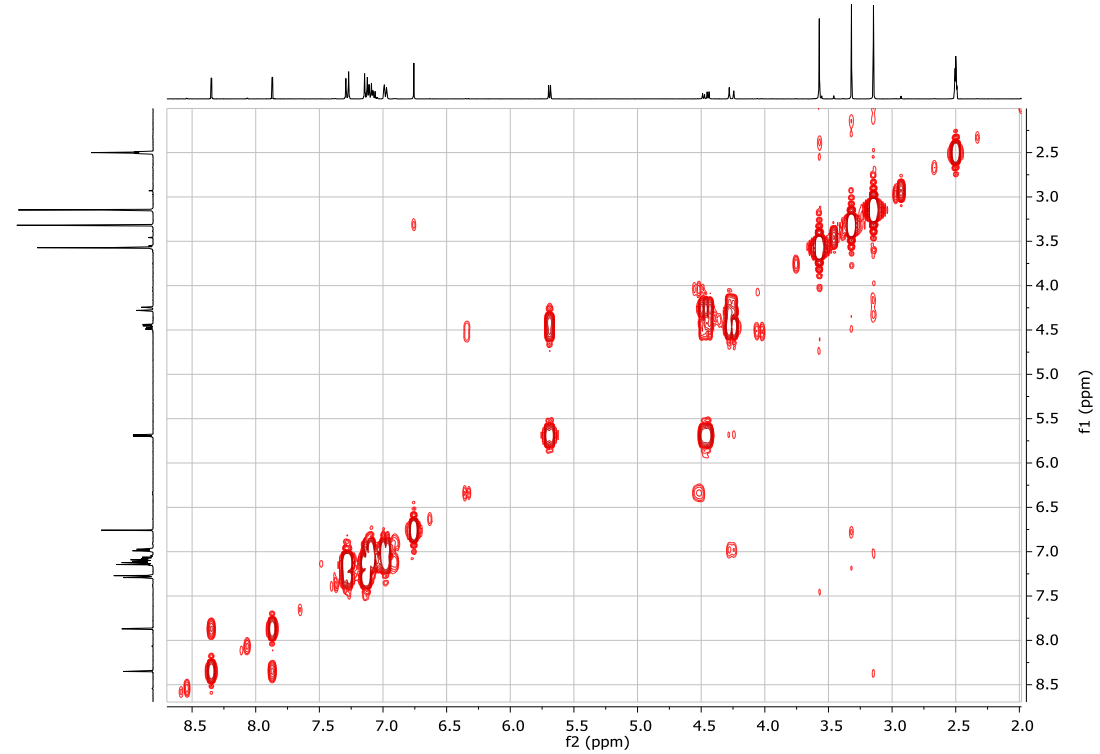
^{1}H-NMR (400 MHz, d^{6}-DMSO)



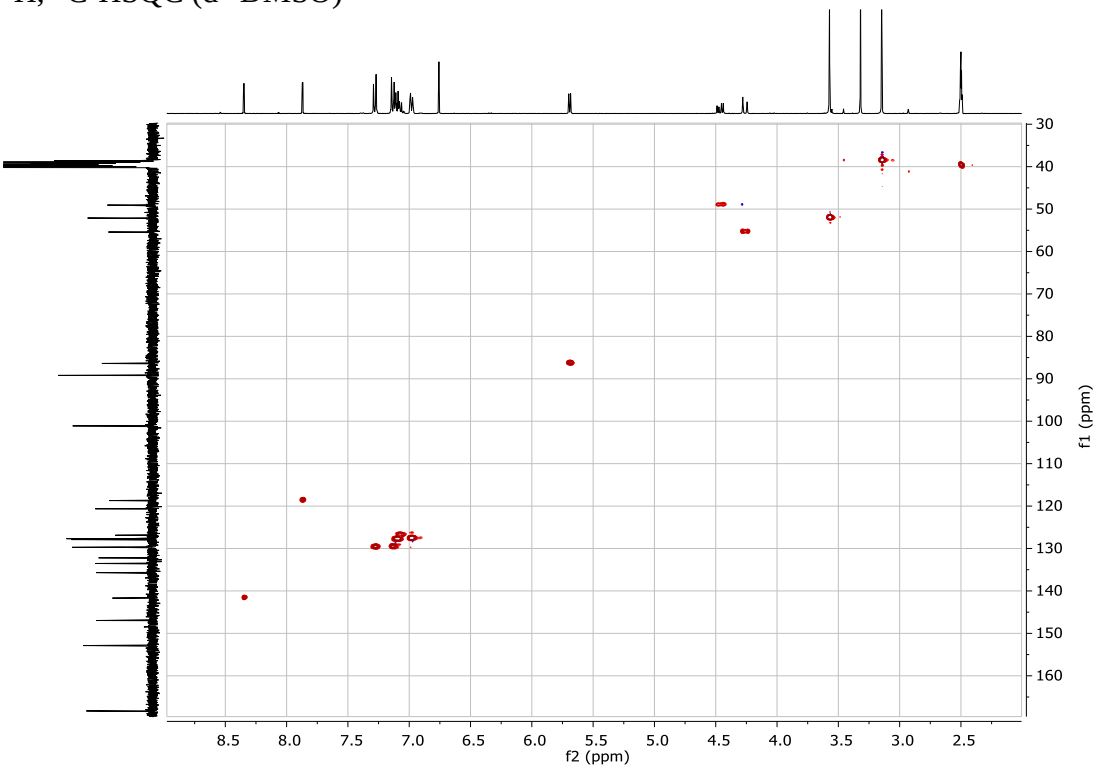
^{13}C-NMR (101 MHz, d^{6}-DMSO)



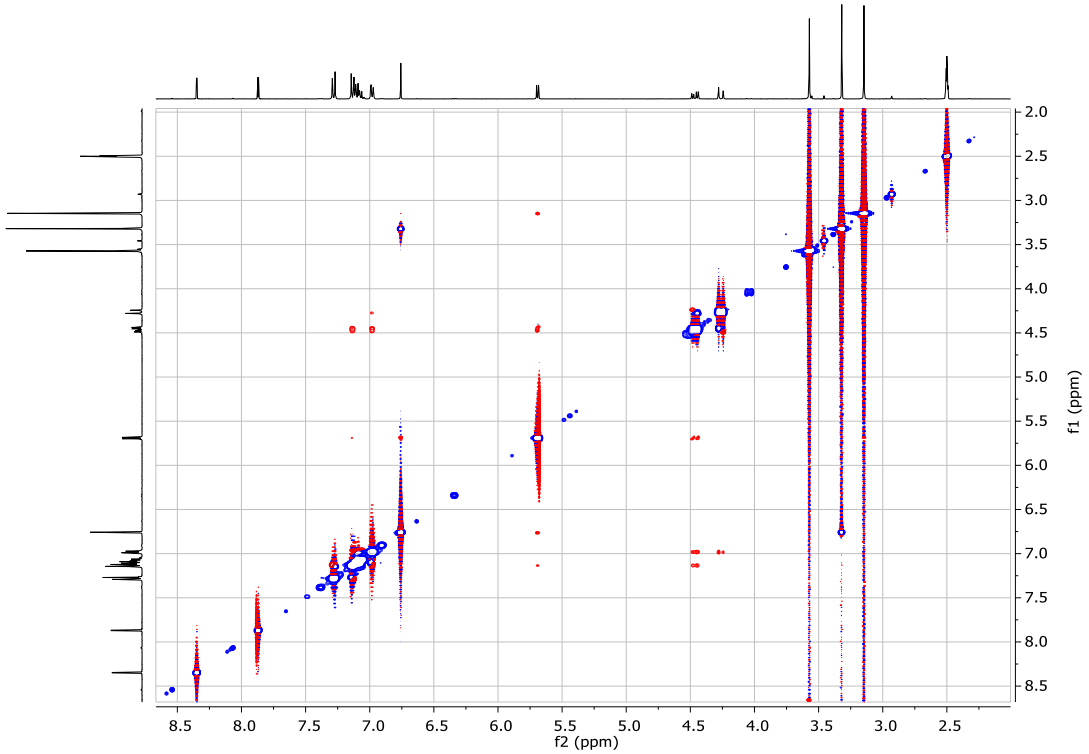
$^{1}H,^{1}H$-COSY (d^{6}-DMSO)



$^{1}H,^{13}C$-HSQC (d^{6}-DMSO)

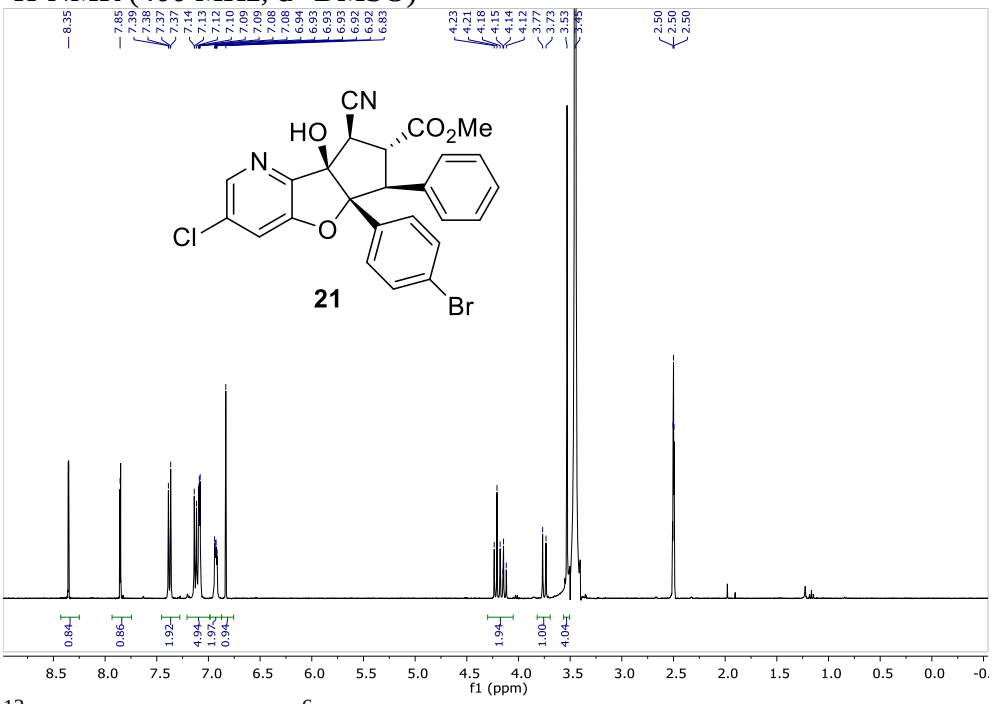


$^{1}H,^{1}H$-NOESY (d^{6}-DMSO)

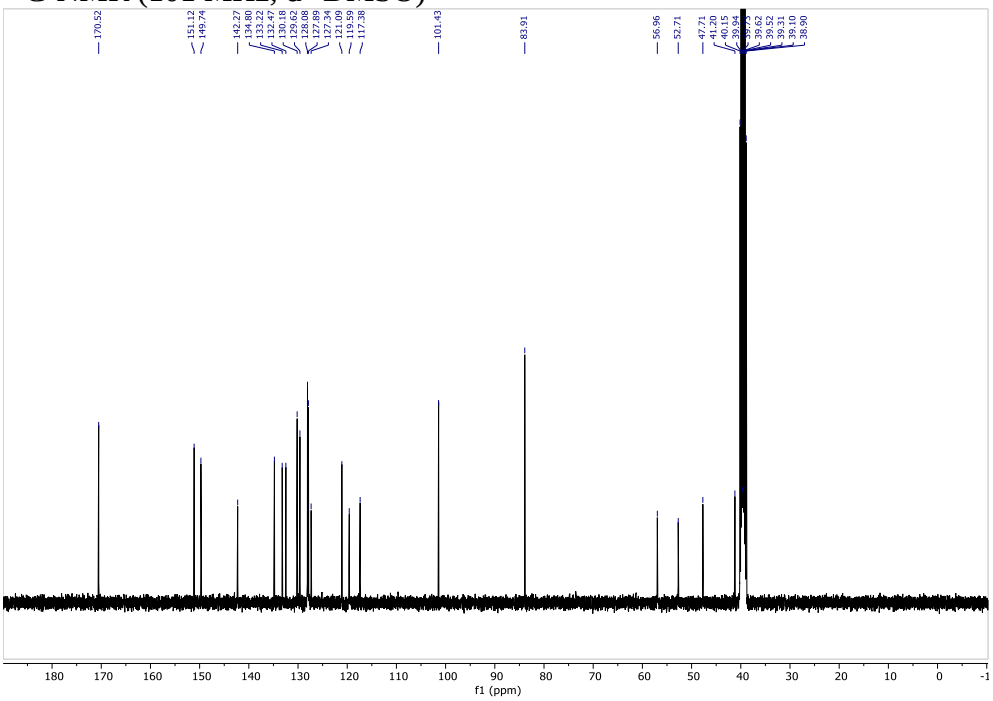


***rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (21)**

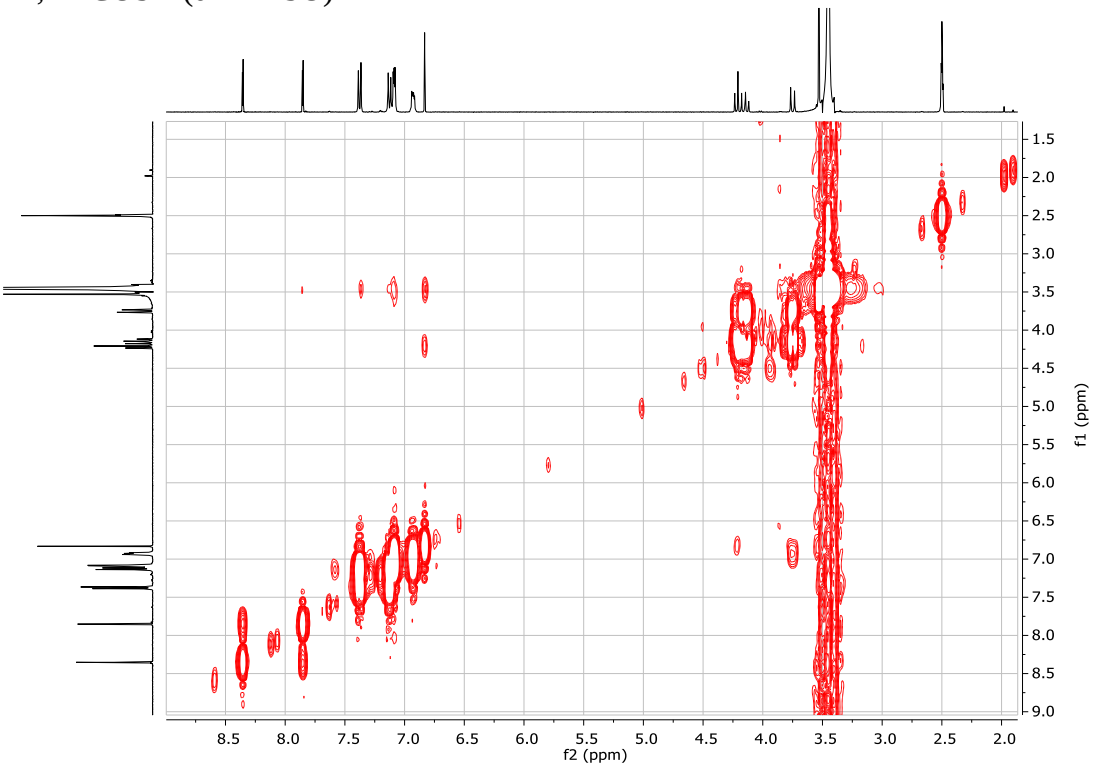
^{1}H-NMR (400 MHz, d^{6}-DMSO)



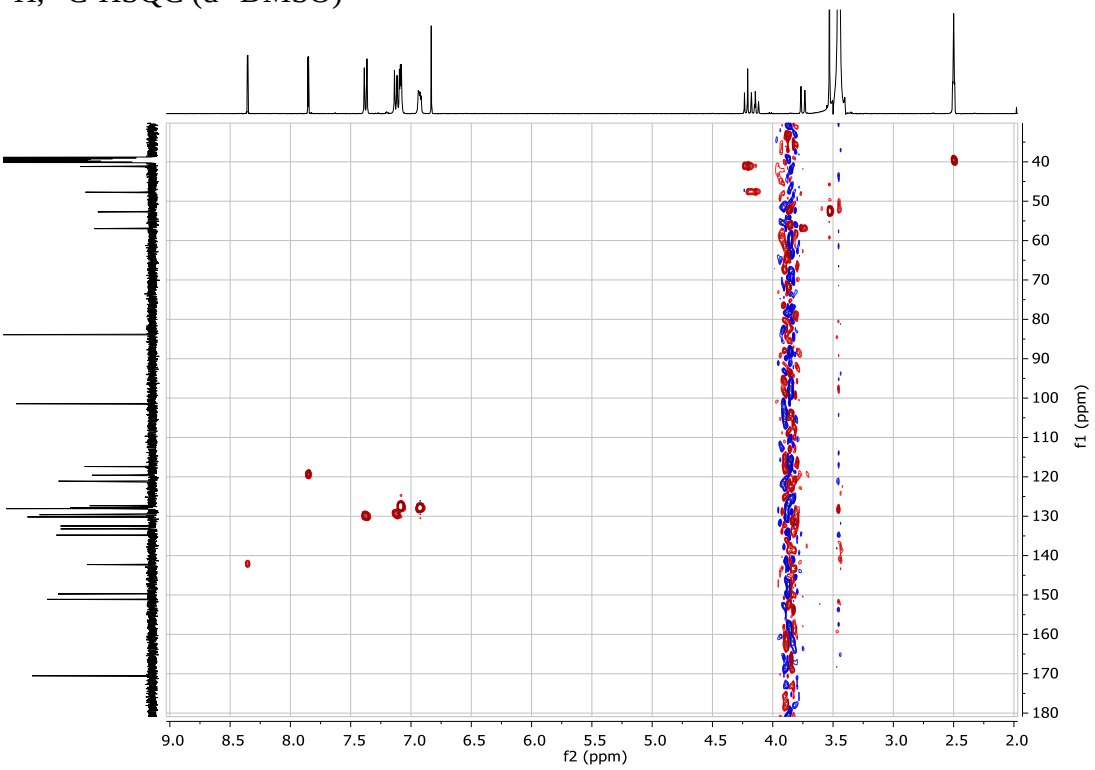
^{13}C-NMR (101 MHz, d^{6}-DMSO)



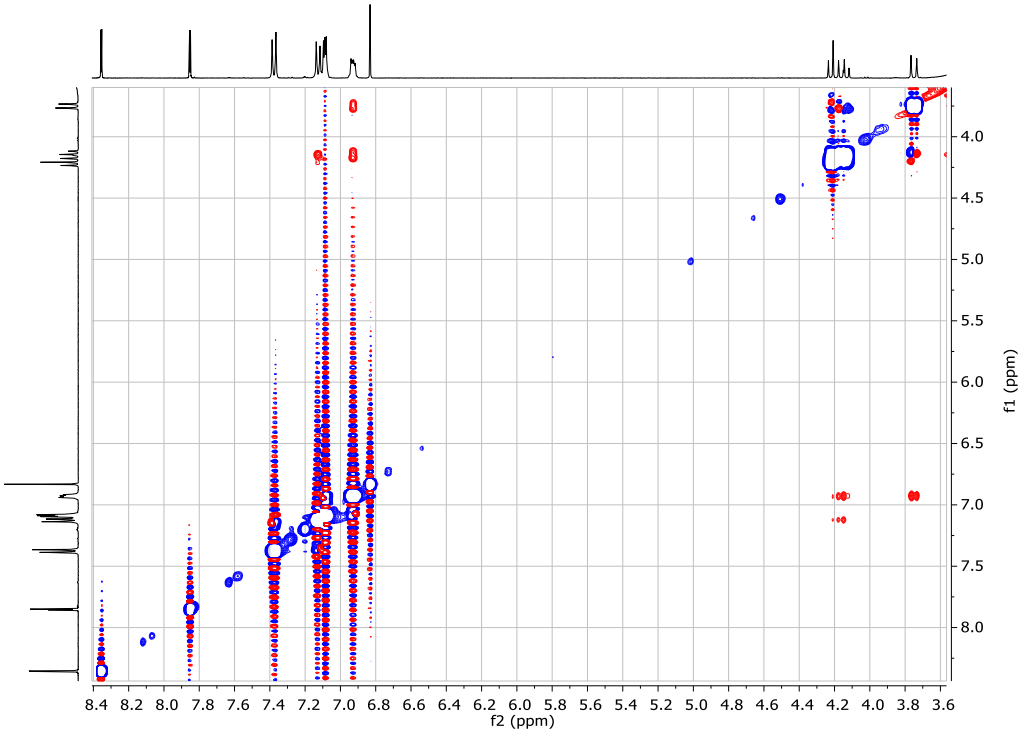
$^{1}H,^{1}H$-COSY (d^{6}-DMSO)



$^{1}H,^{13}C$-HSQC (d^{6}-DMSO)

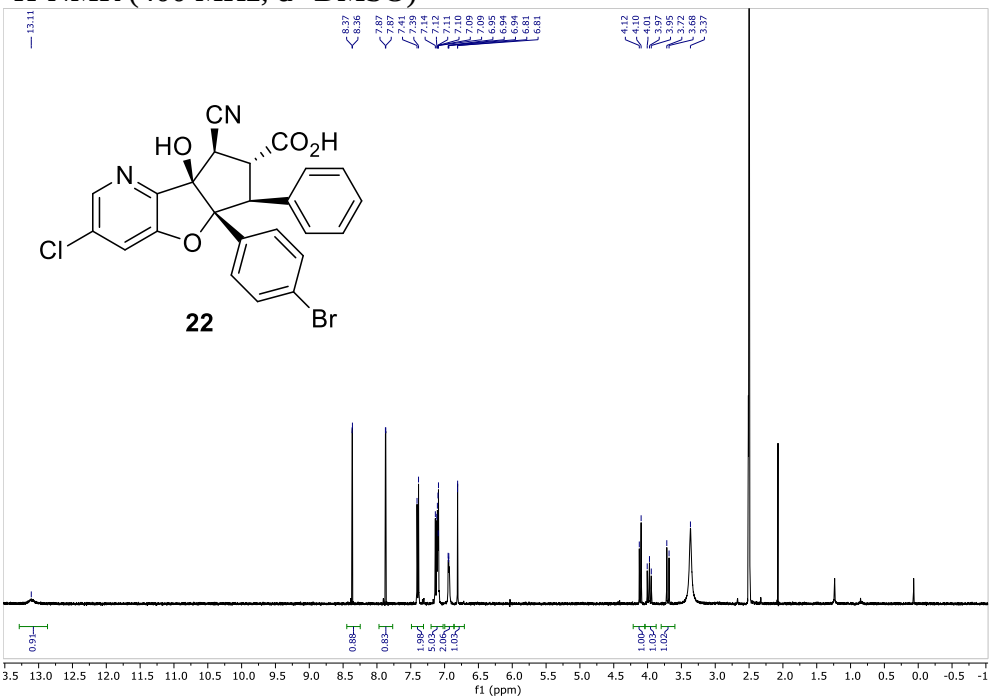


$^{1}H,^{1}H$-NOESY (d^{6}-DMSO)

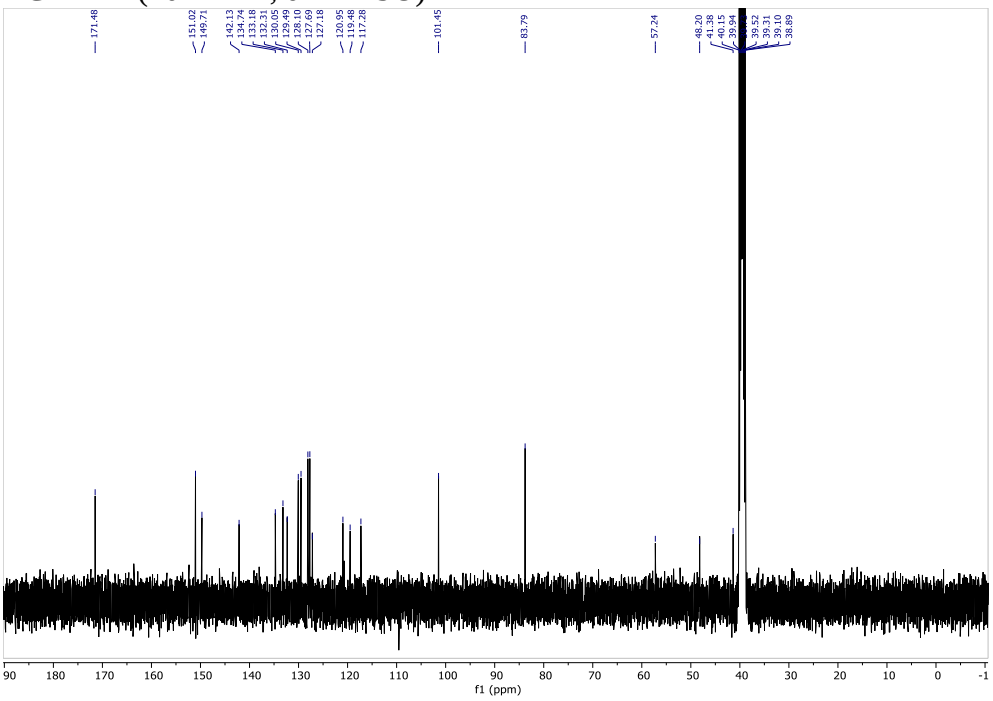


rac-(5a_R_,6_S_,7_R_,8_R_,8a_R_)-5a-(4-bromophenyl)-3-chloro-8-cyano-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (22)

^{1}H-NMR (400 MHz, d^{6}-DMSO)

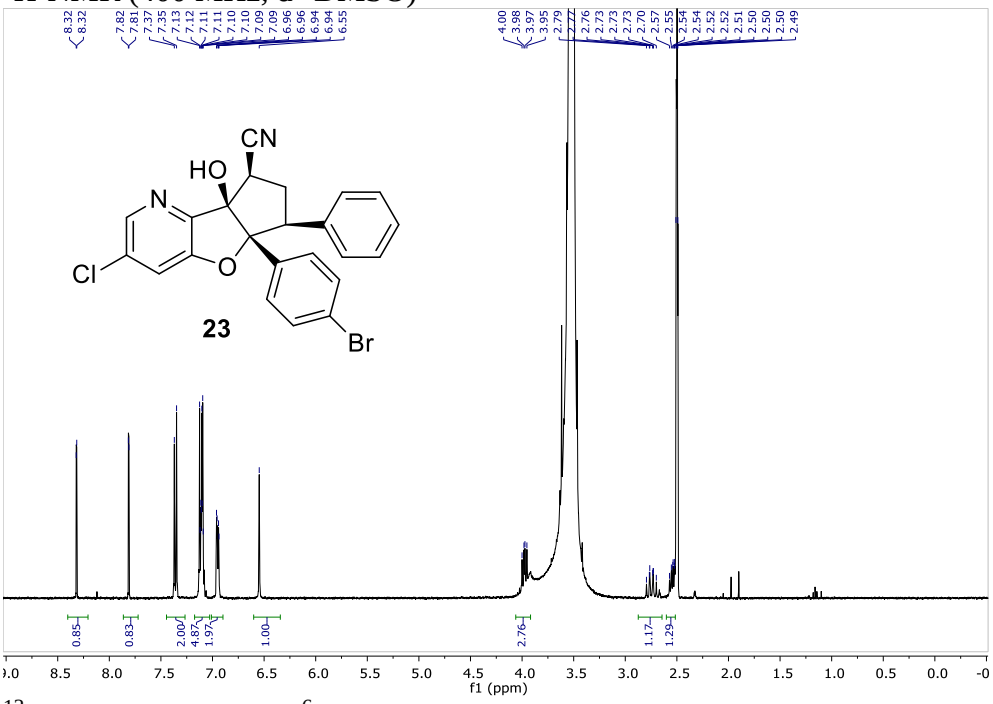


^{13}C-NMR (101 MHz, d^{6}-DMSO)

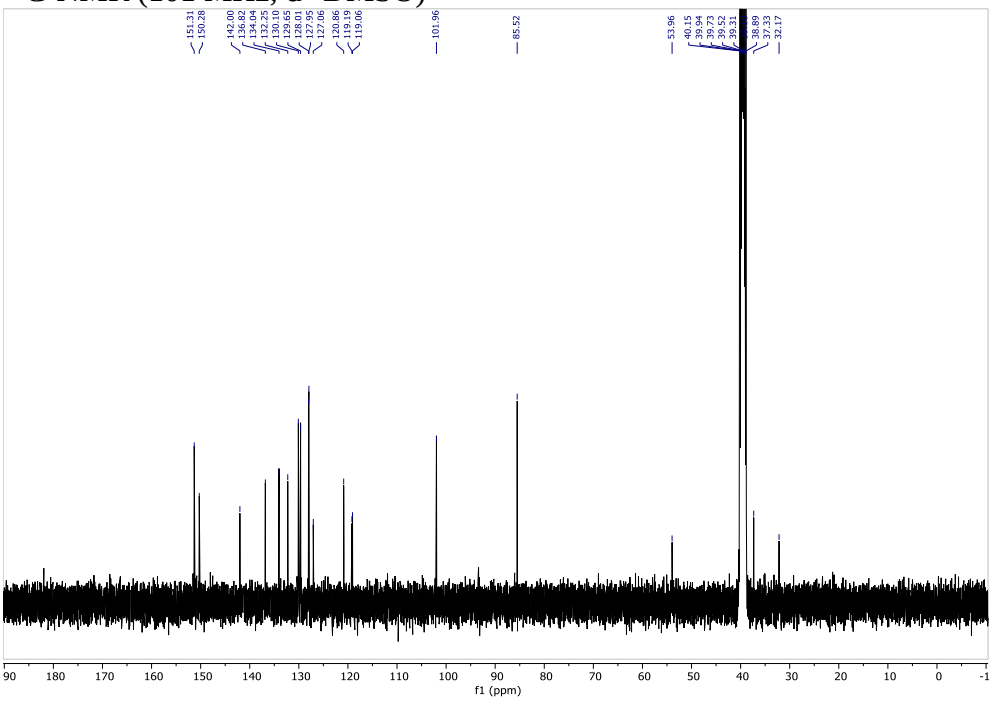


rac-(5a_R_,6_S_,8_R_,8a_R_)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-8-carbonitrile (23)

^{1}H-NMR (400 MHz, d^{6}-DMSO)

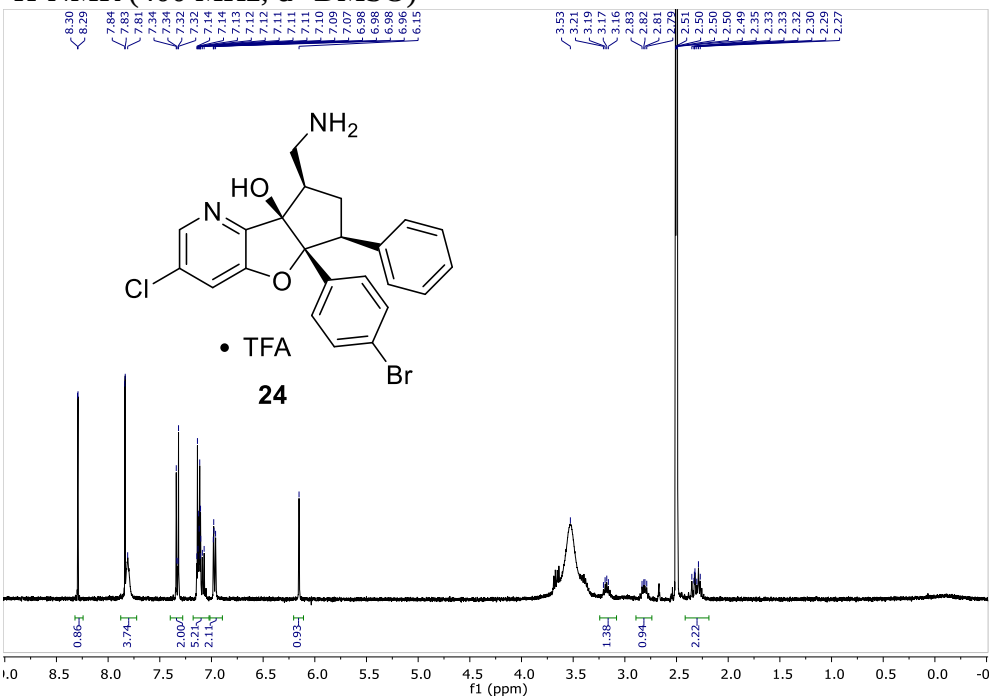


^{13}C-NMR (101 MHz, d^{6}-DMSO)

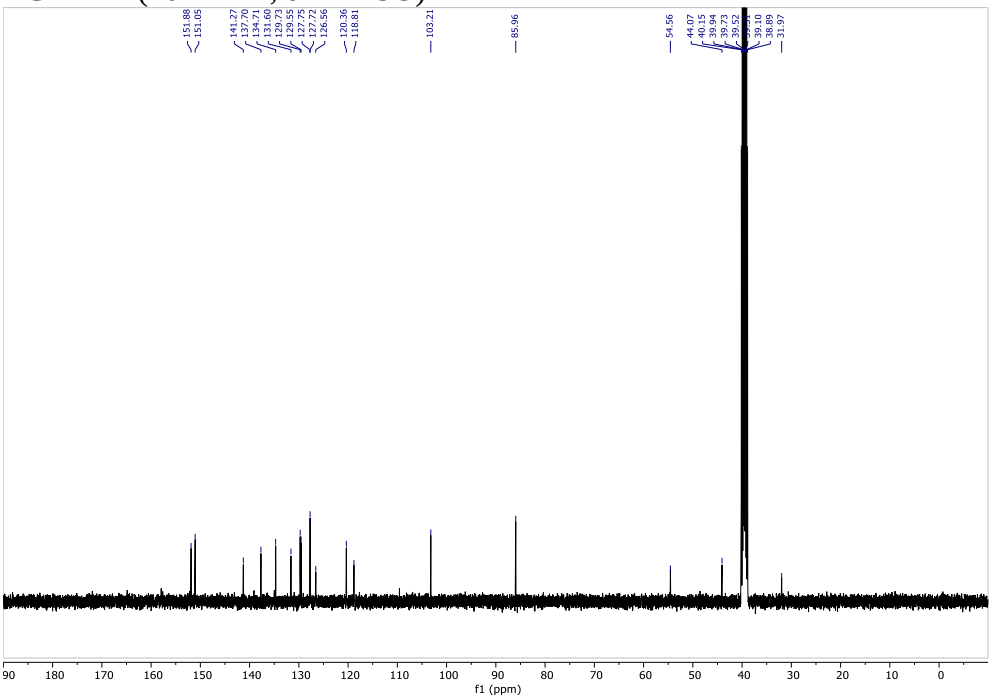


***rac*-(*5aR,6S,8R,8aR*)-8-(aminomethyl)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridin-8a-ol (TFA salt) (24)**

^{1}H-NMR (400 MHz, d^{6}-DMSO)

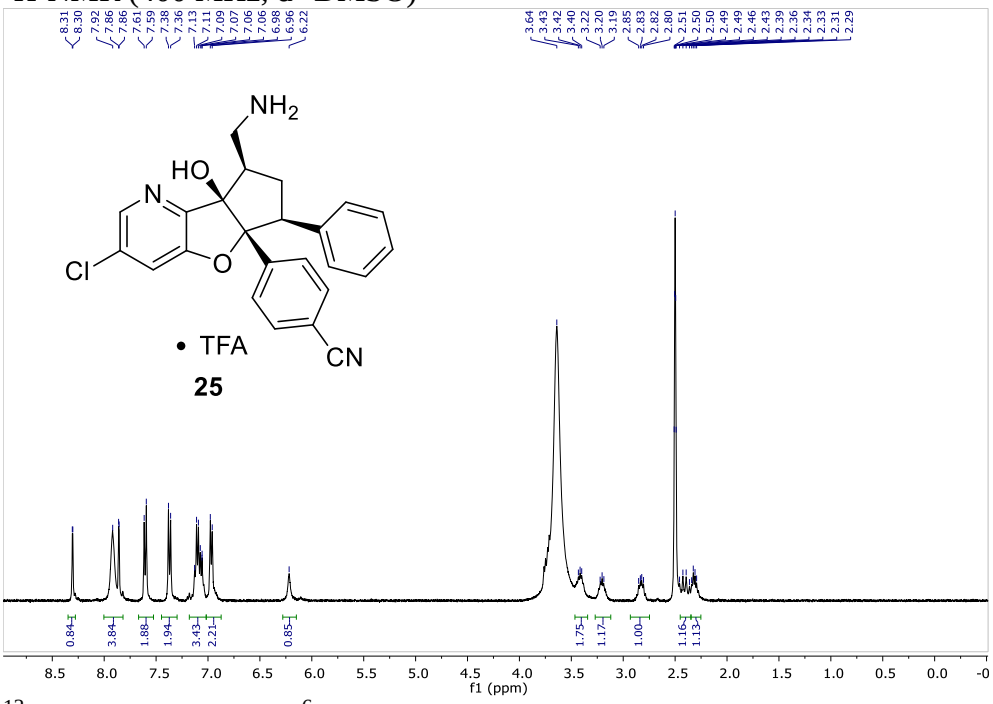


^{13}C-NMR (101 MHz, d^{6}-DMSO)

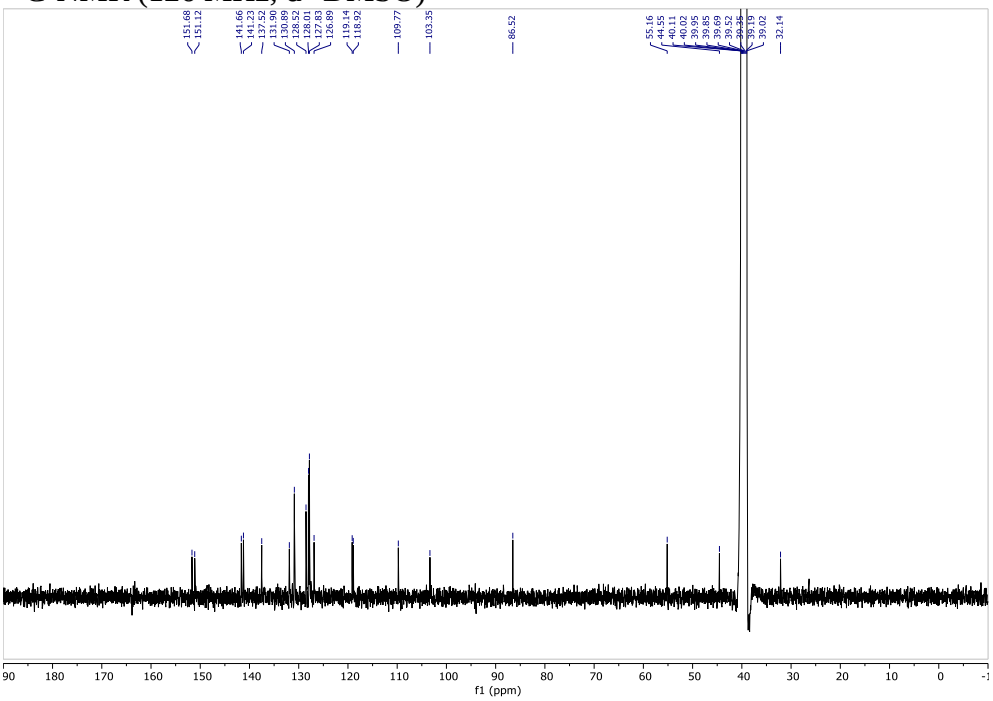


***rac*-4-((5a*R*,6*S*,8*R*,8a*R*)-8-(aminomethyl)-3-chloro-8a-hydroxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]pyridin-5a-yl)benzonitrile (TFA salt) (25)**

^{1}H-NMR (400 MHz, d^{6}-DMSO)

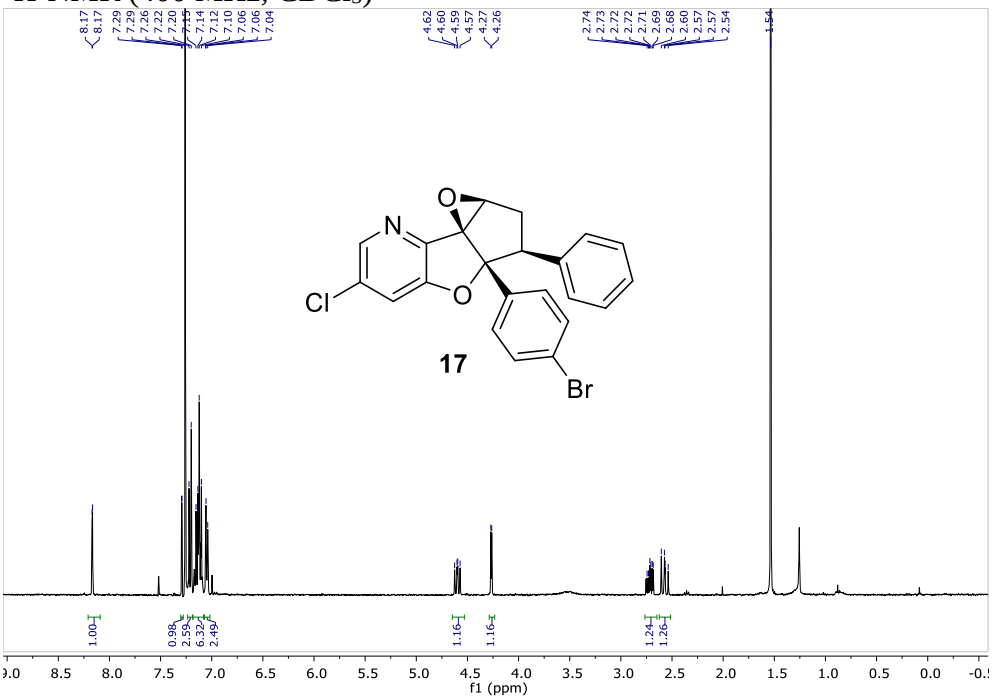


^{13}C-NMR (126 MHz, d^{6}-DMSO)

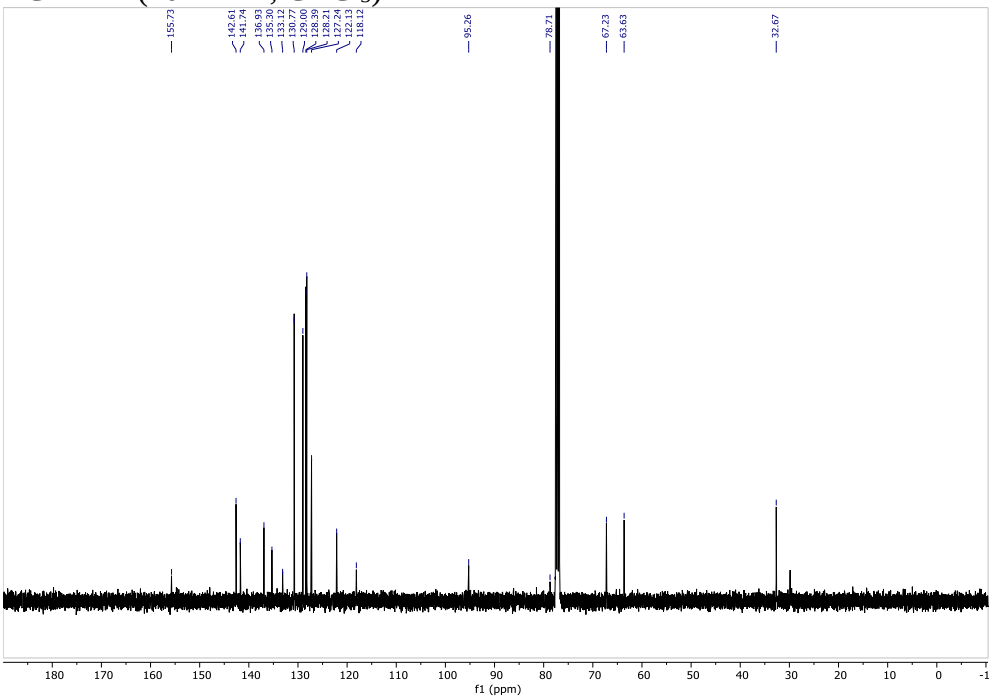


rac-(1a_S_,3_S_,3a_R_,8b_S_)-3a-(4-bromophenyl)-6-chloro-3-phenyl-1a,2,3,3a-tetrahydrooxireno[2'',3'':1',5']cyclopenta[1',2':4,5]furo[3,2-b]pyridine (17)

^{1}H-NMR (400 MHz, $CDCl_3$)

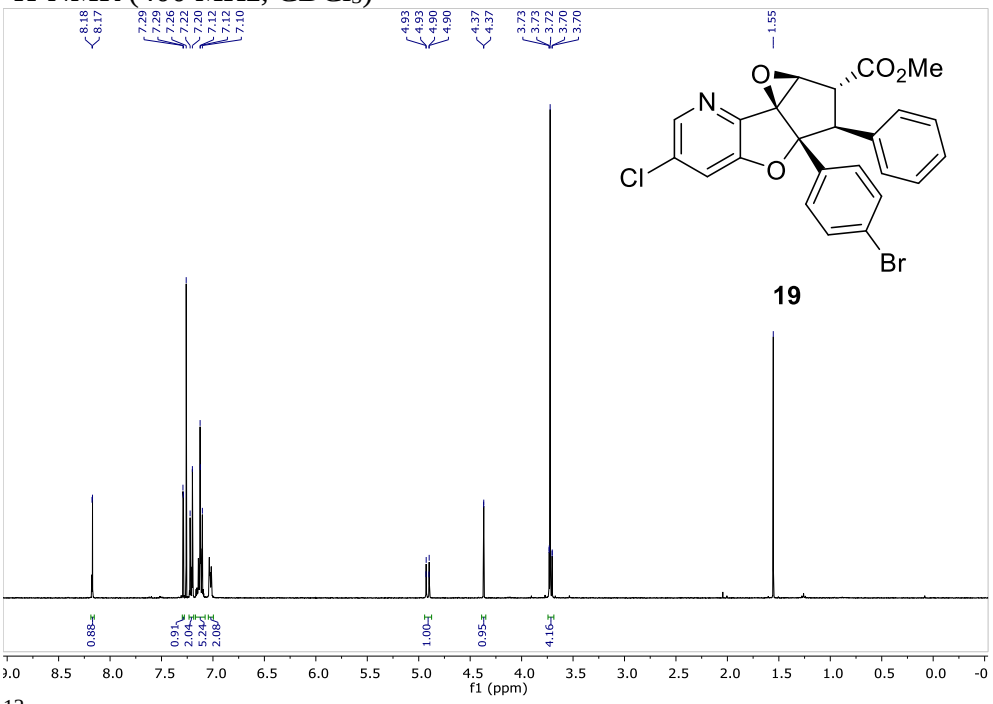


^{13}C-NMR (101 MHz, $CDCl_3$)

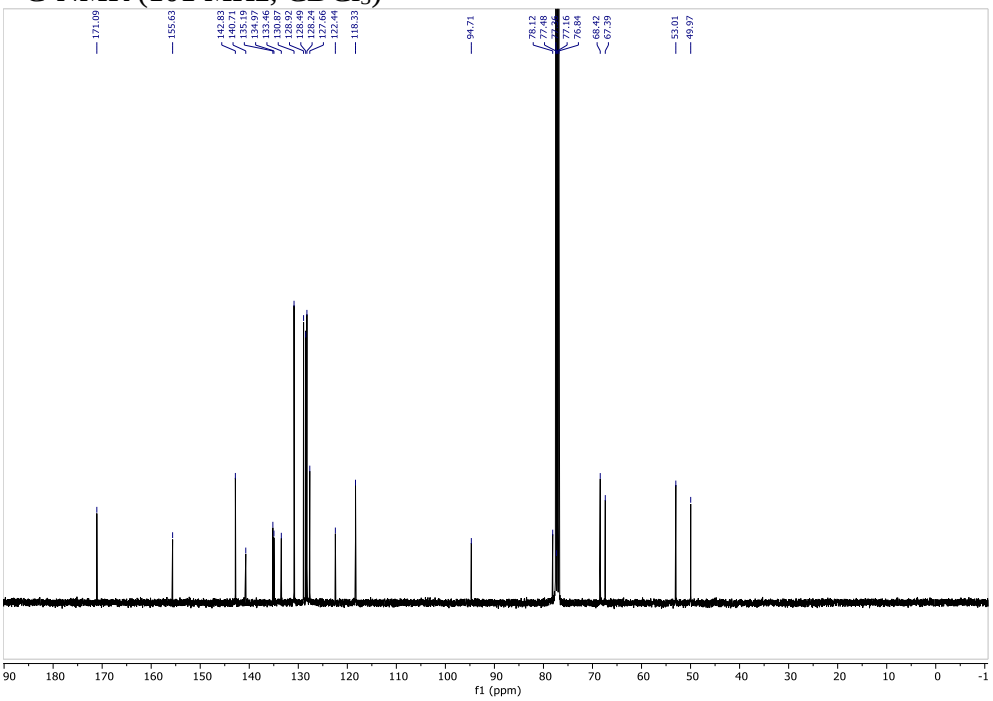


***rac*-methyl (1a*S*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-3-phenyl-1a,2,3,3a-tetra-hydro-oxireno[2'',3'':1',5']cyclopenta[1',2':4,5]furo[3,2-b]pyridine-2-carboxylate (19)**

^{1}H-NMR (400 MHz, $CDCl_3$)

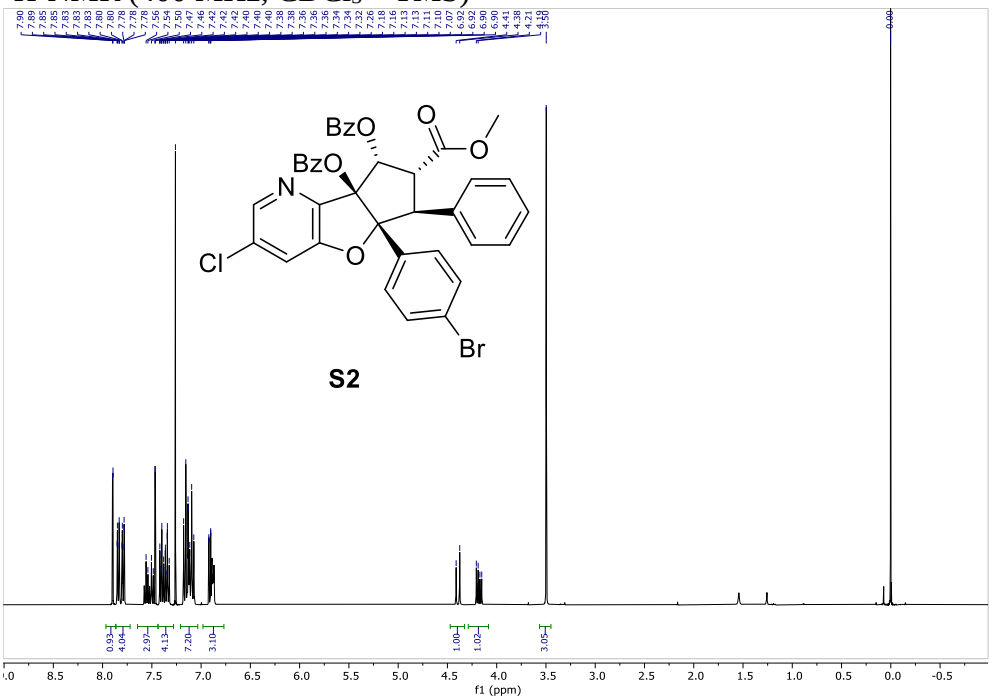


^{13}C-NMR (101 MHz, $CDCl_3$)

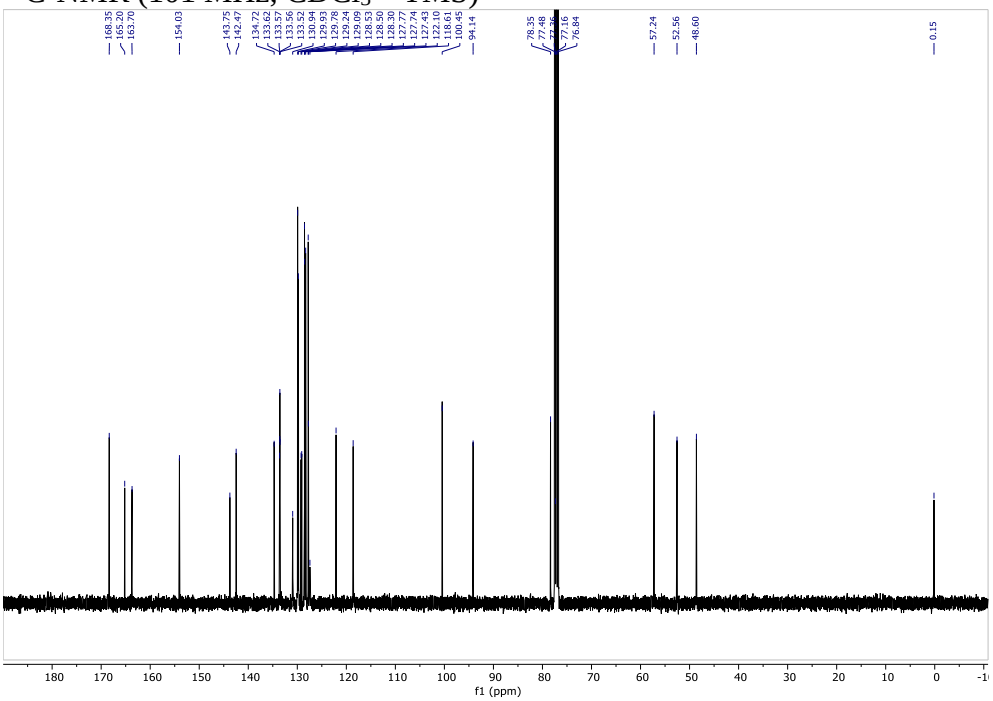


***rac*-(5aR,6S,7R,8R,8aS)-5a-(4-bromophenyl)-3-chloro-7-(methoxycarbonyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diyl dibenzoate (S2)**

^{1}H-NMR (400 MHz, $CDCl_3$ + TMS)

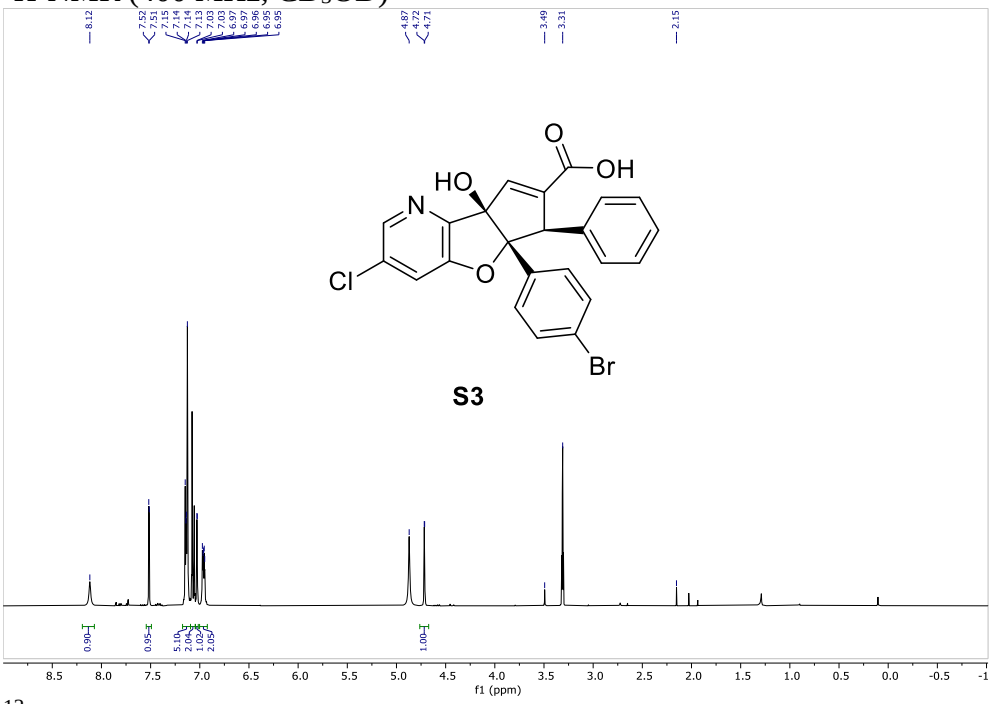


^{13}C-NMR (101 MHz, $CDCl_3$ + TMS)

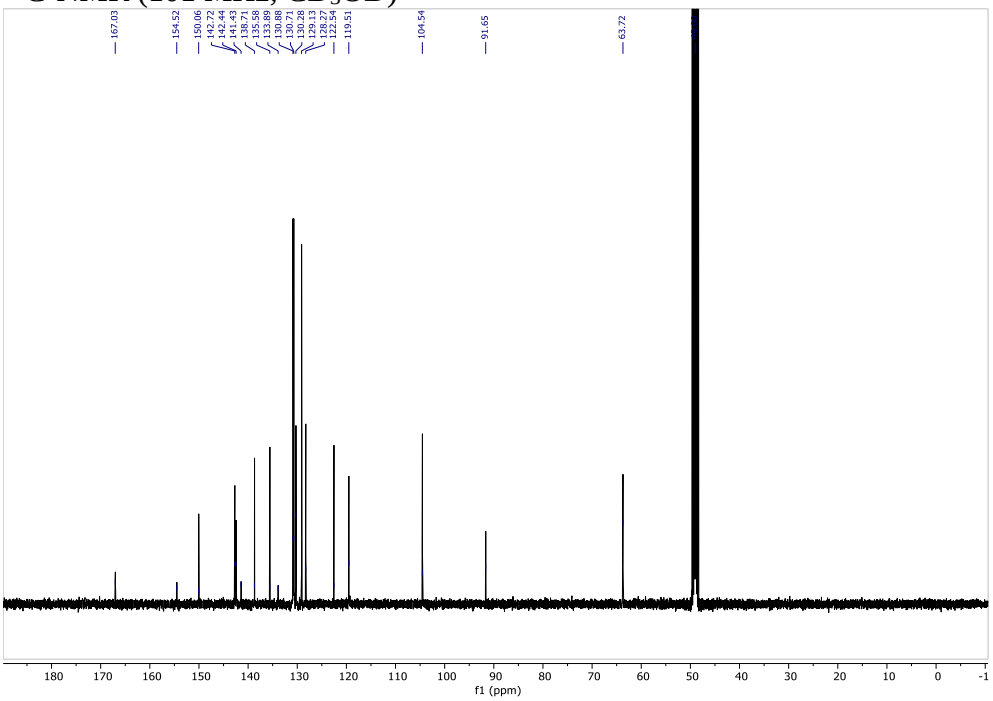


***rac*-(5a*R*,6*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,8a-dihydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic acid (S3)**

^{1}H-NMR (400 MHz, CD_3OD)

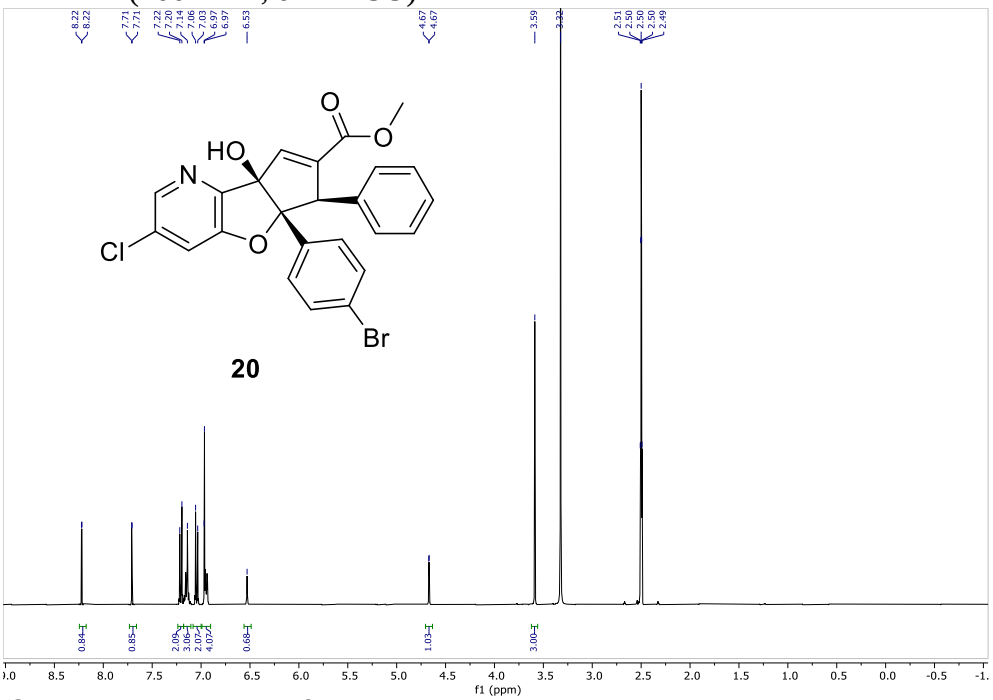


^{13}C-NMR (101 MHz, CD_3OD)

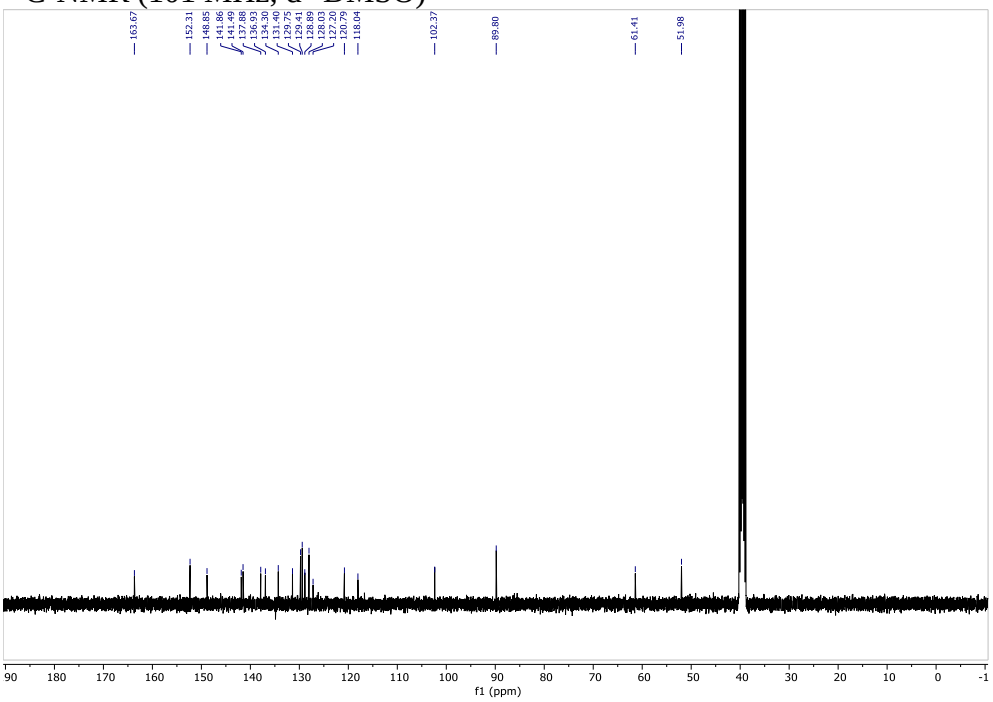


***rac*-methyl (5a*R*,6*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,8a-dihydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (20)**

^{1}H-NMR (400 MHz, d^{6}-DMSO)

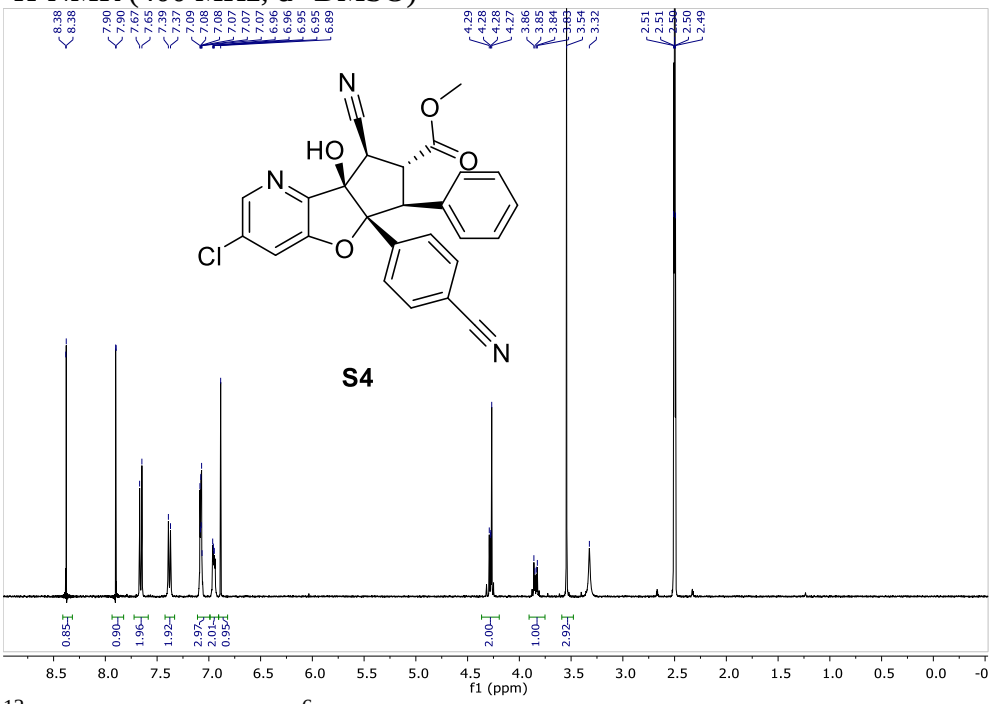


^{13}C-NMR (101 MHz, d^{6}-DMSO)

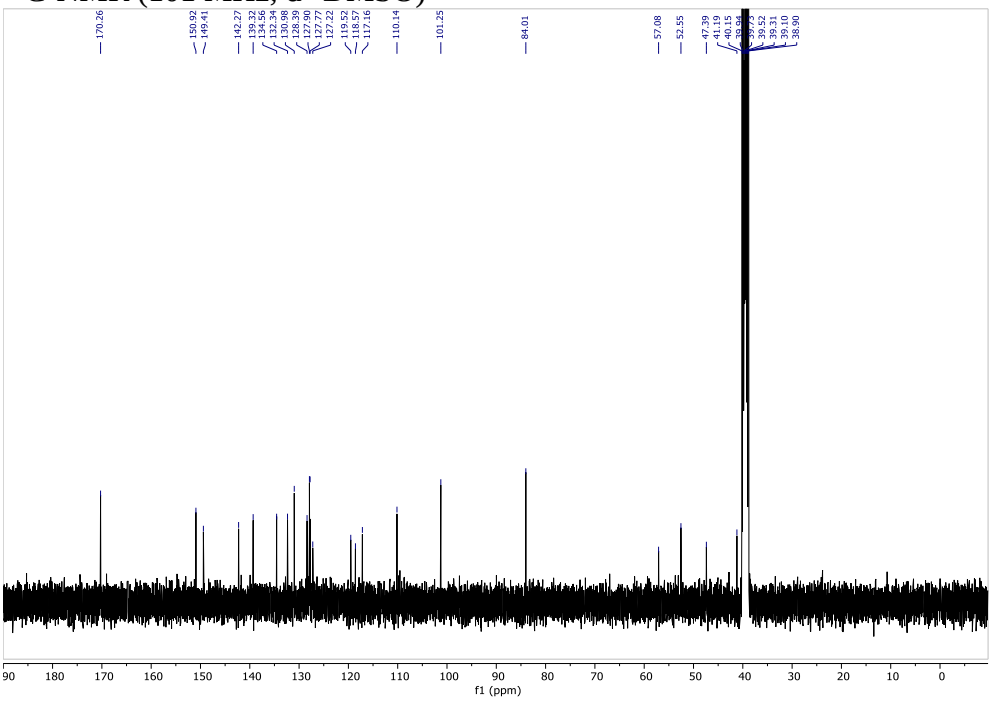


***rac*-methyl (5aR,6S,7R,8R,8aR)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (S4)**

^{1}H-NMR (400 MHz, d^{6}-DMSO)

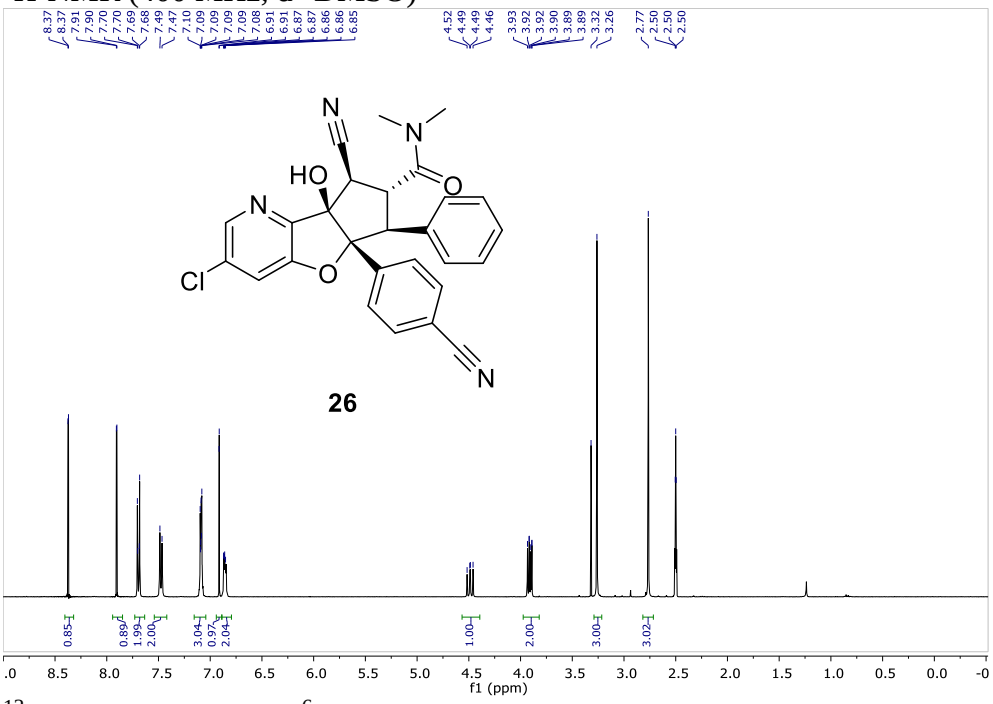


^{13}C-NMR (101 MHz, d^{6}-DMSO)

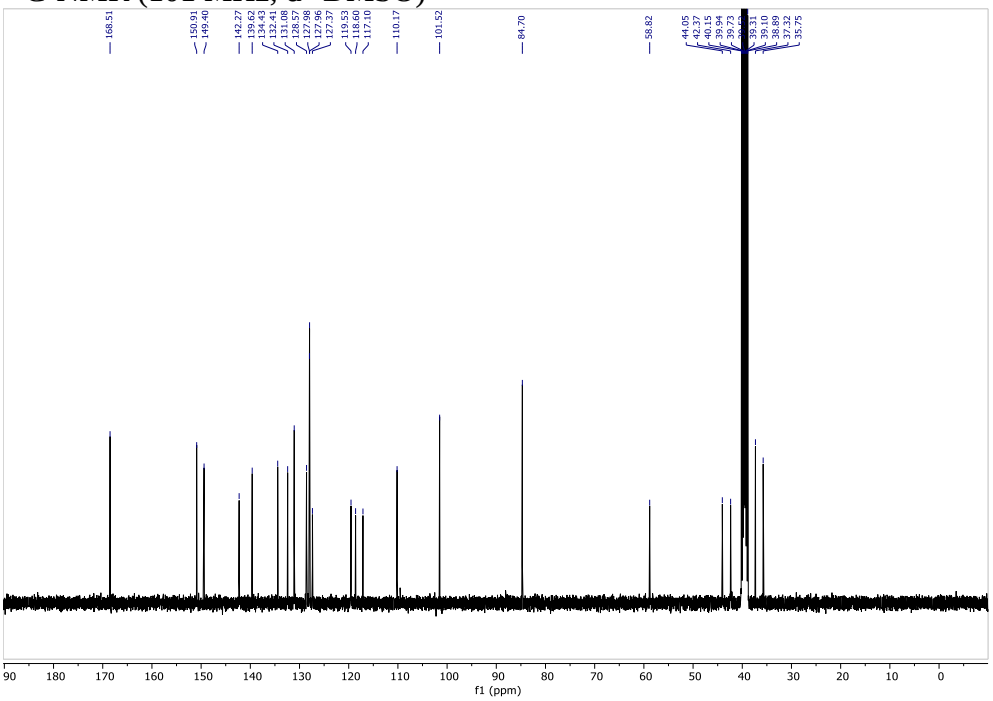


***rac*-(5a*R*,6*S*,7*R*,8*R*,8a*R*)-3-chloro-8-cyano-5a-(4-cyanophenyl)-8a-hydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (26)**

^{1}H-NMR (400 MHz, d^{6}-DMSO)



^{13}C-NMR (101 MHz, d^{6}-DMSO)



5 X-ray crystallographic data

5.1 X-ray crystallographic data of compound **15**

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Platinum-135 CCD diffractometer equipped with Cu K_α radiation (λ = 1.54178).

Crystal where used as received (grown from Metranol), A 0.20 x 0.12 x 0.06 mm colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 45 mm using exposure time 1, 2 and 4s depending on the 2Theta angle with a scan width of 1.50°. Data collection was 98.50% complete to 67.50° in θ. A total of 18696 reflections were collected covering the indices, -11<=h<=11, -12<=k<=12, -15<=l<=15. 4204 reflections were found to be symmetry independent, with a R_{int} of 0.0388. Indexing and unit cell refinement indicated a **P**rimitive, **Triclinic** lattice. The space group was found to be ***P*-1**. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

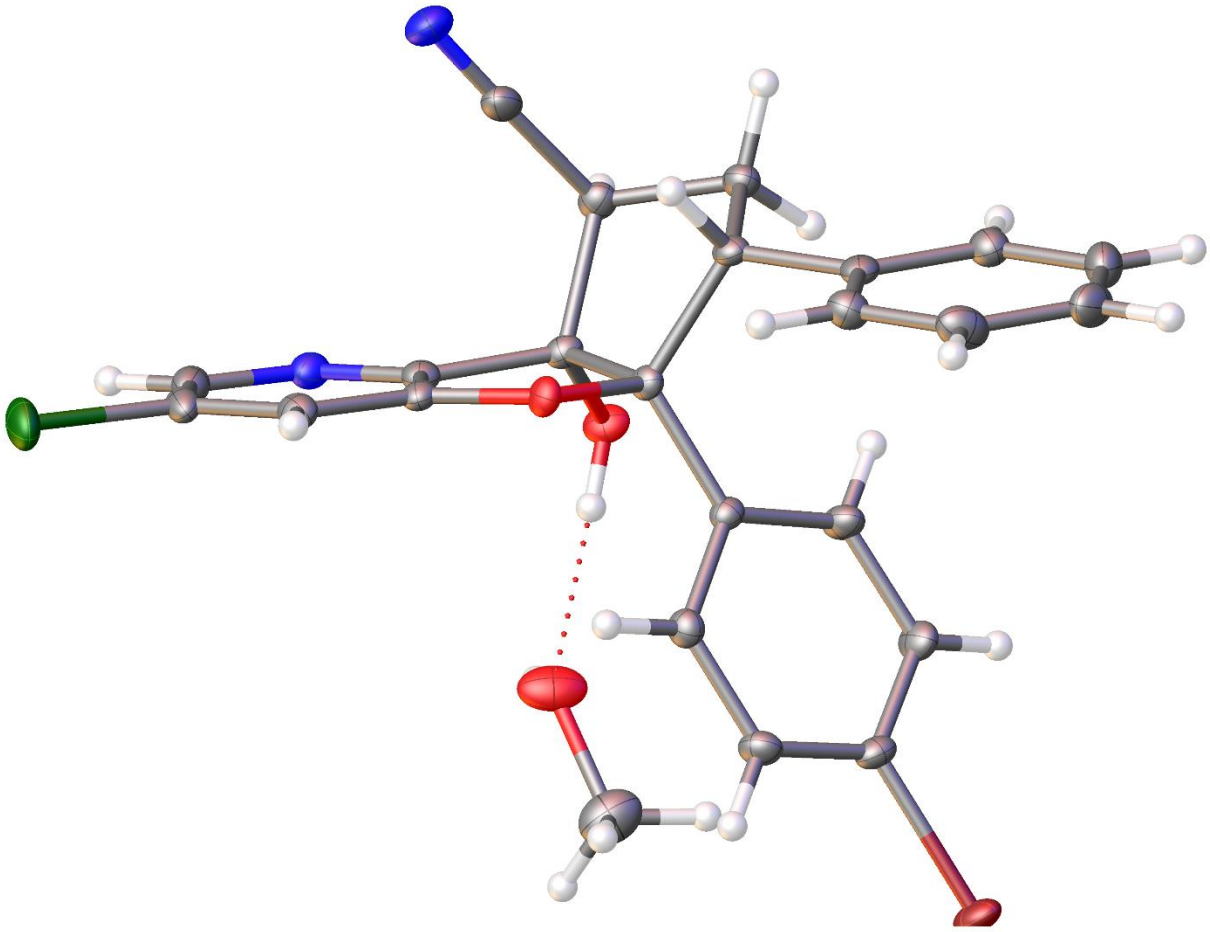
All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Position of the O-H hydrogen atom have been refined using HFIX 147 command, with thermal parameter Uiso 1.5 of parent atom.

Crystallographic data are summarized in Table 1.

Notes:

Methanol solvate



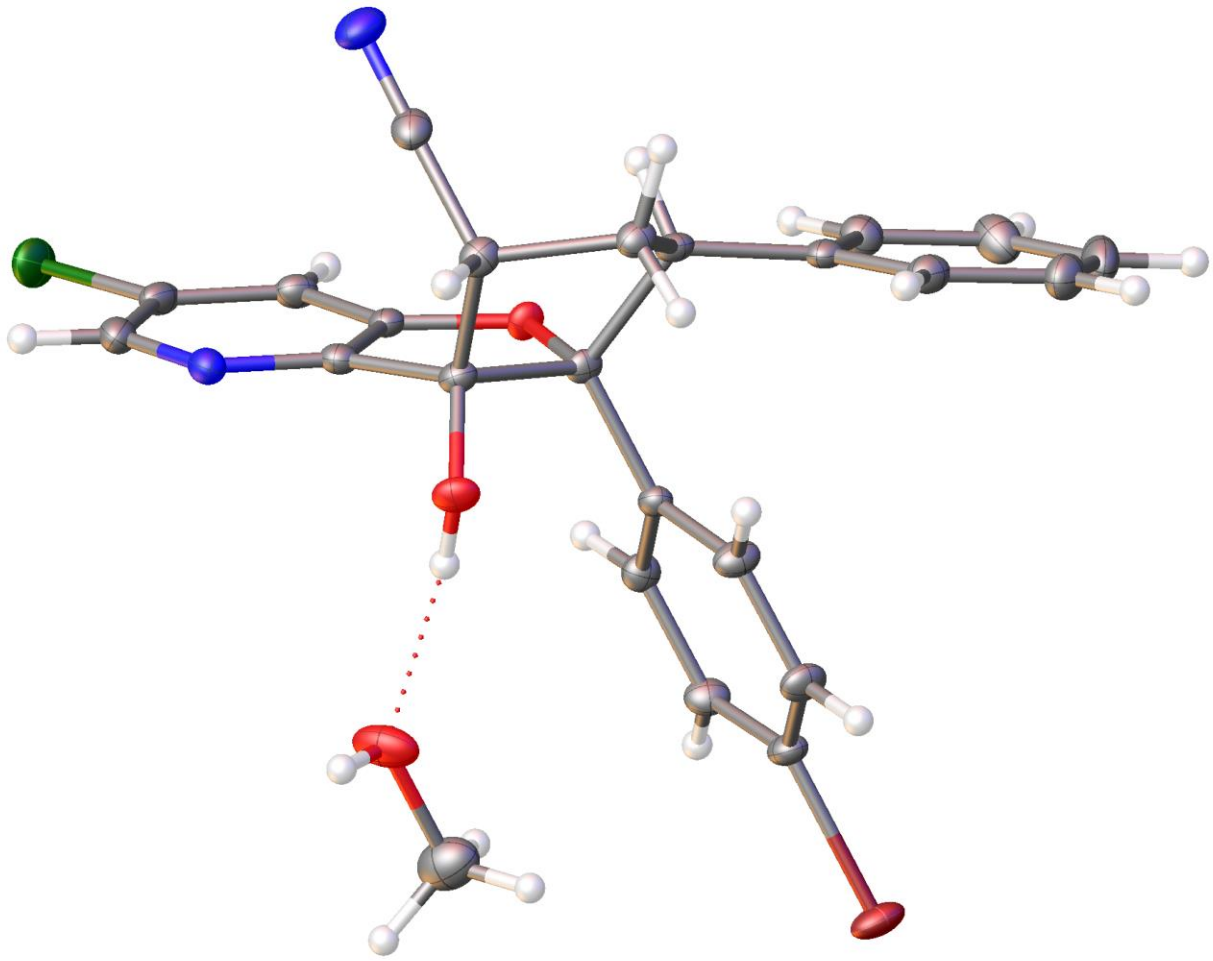


Table 1. Crystal data and structure refinement for CN_134_088.

Report date	2017-07-05	
Identification code	cn_134_088	
Empirical formula	C24 H20 Br Cl N2 O3	
Molecular formula	C23 H16 Br Cl N2 O2, C H4 O	
Formula weight	499.78	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.0883(2) Å	α= 80.9870(10)°.
	b = 9.7340(2) Å	β= 77.1700(10)°.
	c = 12.7956(3) Å	γ = 87.6970(10)°.
Volume	1090.06(4) $Å^3$	
Z	2	
Density (calculated)	1.523 Mg/m^3	
Absorption coefficient	3.939 mm^{-1}	
F(000)	508	
Crystal size	0.2 x 0.12 x 0.06 mm^3	
Crystal color, habit	colorless plank	
Theta range for data collection	3.584 to 72.758°.	
Index ranges	-11<=h<=11, -12<=k<=12, -15<=l<=15	
Reflections collected	18696	
Independent reflections	4204 [R(int) = 0.0388]	
Completeness to theta = 67.500°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5233 and 0.4092	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4204 / 0 / 283	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0688	
R indices (all data)	R1 = 0.0285, wR2 = 0.0693	
Largest diff. peak and hole	0.325 and -0.451 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for CN_134_088. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5009(1)	8897(1)	3887(1)	23(1)
Cl(1)	11313(1)	-499(1)	3026(1)	27(1)
O(1)	6300(1)	2168(1)	3084(1)	14(1)
O(2)	7320(1)	4515(1)	574(1)	17(1)
O(3)	9134(2)	6307(2)	1086(1)	30(1)
N(1)	9532(2)	2092(2)	926(1)	18(1)
N(2)	6524(2)	-207(2)	600(2)	27(1)
C(1)	10444(2)	1214(2)	1406(2)	20(1)
C(2)	10027(2)	605(2)	2488(2)	19(1)
C(3)	8640(2)	867(2)	3136(1)	17(1)
C(4)	7714(2)	1771(2)	2618(1)	14(1)
C(5)	8192(2)	2346(2)	1541(1)	15(1)
C(6)	6935(2)	3192(2)	1168(1)	14(1)
C(7)	6119(2)	2486(2)	442(1)	16(1)
C(8)	4441(2)	2835(2)	852(1)	16(1)
C(9)	4260(2)	2564(2)	2089(1)	14(1)
C(10)	5726(2)	3177(2)	2284(1)	12(1)
C(11)	6360(2)	969(2)	541(1)	19(1)
C(12)	5552(2)	4566(2)	2686(1)	12(1)
C(13)	4828(2)	5670(2)	2163(1)	18(1)
C(14)	4657(2)	6955(2)	2514(1)	18(1)
C(15)	5225(2)	7132(2)	3402(1)	16(1)
C(16)	5962(2)	6070(2)	3931(1)	17(1)
C(17)	6126(2)	4788(2)	3570(1)	15(1)
C(18)	2793(2)	2991(2)	2783(1)	16(1)
C(19)	1701(2)	3807(2)	2364(2)	19(1)
C(20)	362(2)	4144(2)	3051(2)	25(1)
C(21)	95(2)	3679(2)	4155(2)	26(1)
C(22)	1180(2)	2862(2)	4579(2)	25(1)
C(23)	2510(2)	2519(2)	3899(1)	19(1)
C(24)	9024(3)	7399(2)	1714(2)	34(1)

Table 3. Bond lengths [Å] and angles [°] for CN_134_088.

Br(1)-C(15)	1.9050(16)	C(21)-H(21)	0.9500
Cl(1)-C(2)	1.7378(18)	C(21)-C(22)	1.392(3)
O(1)-C(4)	1.359(2)	C(22)-H(22)	0.9500
O(1)-C(10)	1.4714(19)	C(22)-C(23)	1.386(3)
O(2)-H(2)	0.8400	C(23)-H(23)	0.9500
O(2)-C(6)	1.4039(19)	C(24)-H(24A)	0.9800
O(3)-H(3A)	0.8400	C(24)-H(24B)	0.9800
O(3)-C(24)	1.418(3)	C(24)-H(24C)	0.9800
N(1)-C(1)	1.341(2)		
N(1)-C(5)	1.332(2)	C(4)-O(1)-C(10)	108.44(12)
N(2)-C(11)	1.141(3)	C(6)-O(2)-H(2)	109.5
C(1)-H(1)	0.9500	C(24)-O(3)-H(3A)	109.5
C(1)-C(2)	1.392(3)	C(5)-N(1)-C(1)	116.26(15)
C(2)-C(3)	1.385(3)	N(1)-C(1)-H(1)	118.9
C(3)-H(3)	0.9500	N(1)-C(1)-C(2)	122.27(16)
C(3)-C(4)	1.389(2)	C(2)-C(1)-H(1)	118.9
C(4)-C(5)	1.383(2)	C(1)-C(2)-Cl(1)	118.11(14)
C(5)-C(6)	1.501(2)	C(3)-C(2)-Cl(1)	119.88(14)
C(6)-C(7)	1.558(2)	C(3)-C(2)-C(1)	122.00(16)
C(6)-C(10)	1.596(2)	C(2)-C(3)-H(3)	122.7
C(7)-H(7)	1.0000	C(2)-C(3)-C(4)	114.58(16)
C(7)-C(8)	1.541(2)	C(4)-C(3)-H(3)	122.7
C(7)-C(11)	1.474(2)	O(1)-C(4)-C(3)	125.13(15)
C(8)-H(8A)	0.9900	O(1)-C(4)-C(5)	114.08(14)
C(8)-H(8B)	0.9900	C(5)-C(4)-C(3)	120.78(15)
C(8)-C(9)	1.536(2)	N(1)-C(5)-C(4)	124.11(16)
C(9)-H(9)	1.0000	N(1)-C(5)-C(6)	126.18(15)
C(9)-C(10)	1.566(2)	C(4)-C(5)-C(6)	109.55(14)
C(9)-C(18)	1.511(2)	O(2)-C(6)-C(5)	116.39(13)
C(10)-C(12)	1.511(2)	O(2)-C(6)-C(7)	104.27(13)
C(12)-C(13)	1.395(2)	O(2)-C(6)-C(10)	115.38(13)
C(12)-C(17)	1.394(2)	C(5)-C(6)-C(7)	114.69(13)
C(13)-H(13)	0.9500	C(5)-C(6)-C(10)	101.18(12)
C(13)-C(14)	1.385(2)	C(7)-C(6)-C(10)	104.72(12)
C(14)-H(14)	0.9500	C(6)-C(7)-H(7)	109.7
C(14)-C(15)	1.384(2)	C(8)-C(7)-C(6)	103.60(13)
C(15)-C(16)	1.379(3)	C(8)-C(7)-H(7)	109.7
C(16)-H(16)	0.9500	C(11)-C(7)-C(6)	113.27(14)
C(16)-C(17)	1.389(2)	C(11)-C(7)-H(7)	109.7
C(17)-H(17)	0.9500	C(11)-C(7)-C(8)	110.81(14)
C(18)-C(19)	1.394(3)	C(7)-C(8)-H(8A)	111.3
C(18)-C(23)	1.399(2)	C(7)-C(8)-H(8B)	111.3
C(19)-H(19)	0.9500	H(8A)-C(8)-H(8B)	109.2
C(19)-C(20)	1.394(3)	C(9)-C(8)-C(7)	102.53(13)
C(20)-H(20)	0.9500	C(9)-C(8)-H(8A)	111.3
C(20)-C(21)	1.384(3)	C(9)-C(8)-H(8B)	111.3

C(8)-C(9)-H(9)	105.9	O(3)-C(24)-H(24A)	109.5
C(8)-C(9)-C(10)	104.36(12)	O(3)-C(24)-H(24B)	109.5
C(10)-C(9)-H(9)	105.9	O(3)-C(24)-H(24C)	109.5
C(18)-C(9)-C(8)	118.09(14)	H(24A)-C(24)-H(24B)	109.5
C(18)-C(9)-H(9)	105.9	H(24A)-C(24)-H(24C)	109.5
C(18)-C(9)-C(10)	115.70(13)	H(24B)-C(24)-H(24C)	109.5
O(1)-C(10)-C(6)	105.82(12)		
O(1)-C(10)-C(9)	108.07(12)		
O(1)-C(10)-C(12)	108.03(12)		
C(9)-C(10)-C(6)	105.01(12)		
C(12)-C(10)-C(6)	113.34(13)		
C(12)-C(10)-C(9)	116.01(13)		
N(2)-C(11)-C(7)	178.31(19)		
C(13)-C(12)-C(10)	120.28(14)		
C(17)-C(12)-C(10)	121.26(15)		
C(17)-C(12)-C(13)	118.45(15)		
C(12)-C(13)-H(13)	119.3		
C(14)-C(13)-C(12)	121.41(16)		
C(14)-C(13)-H(13)	119.3		
C(13)-C(14)-H(14)	120.7		
C(15)-C(14)-C(13)	118.55(16)		
C(15)-C(14)-H(14)	120.7		
C(14)-C(15)-Br(1)	119.00(13)		
C(16)-C(15)-Br(1)	119.34(13)		
C(16)-C(15)-C(14)	121.66(15)		
C(15)-C(16)-H(16)	120.4		
C(15)-C(16)-C(17)	119.11(15)		
C(17)-C(16)-H(16)	120.4		
C(12)-C(17)-H(17)	119.6		
C(16)-C(17)-C(12)	120.81(15)		
C(16)-C(17)-H(17)	119.6		
C(19)-C(18)-C(9)	123.32(15)		
C(19)-C(18)-C(23)	118.57(16)		
C(23)-C(18)-C(9)	118.10(15)		
C(18)-C(19)-H(19)	119.9		
C(18)-C(19)-C(20)	120.25(17)		
C(20)-C(19)-H(19)	119.9		
C(19)-C(20)-H(20)	119.6		
C(21)-C(20)-C(19)	120.79(18)		
C(21)-C(20)-H(20)	119.6		
C(20)-C(21)-H(21)	120.4		
C(20)-C(21)-C(22)	119.28(17)		
C(22)-C(21)-H(21)	120.4		
C(21)-C(22)-H(22)	119.9		
C(23)-C(22)-C(21)	120.15(18)		
C(23)-C(22)-H(22)	119.9		
C(18)-C(23)-H(23)	119.5		
C(22)-C(23)-C(18)	120.95(17)		
C(22)-C(23)-H(23)	119.5		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for CN_134_088. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	33(1)	12(1)	27(1)	-8(1)	-13(1)	3(1)
Cl(1)	19(1)	21(1)	42(1)	-2(1)	-13(1)	6(1)
O(1)	16(1)	11(1)	13(1)	1(1)	-4(1)	3(1)
O(2)	24(1)	12(1)	15(1)	2(1)	-4(1)	-3(1)
O(3)	40(1)	27(1)	22(1)	-1(1)	-2(1)	-16(1)
N(1)	15(1)	16(1)	22(1)	-6(1)	-2(1)	-2(1)
N(2)	29(1)	20(1)	37(1)	-14(1)	-10(1)	3(1)
C(1)	14(1)	17(1)	30(1)	-8(1)	-4(1)	-1(1)
C(2)	16(1)	11(1)	32(1)	-5(1)	-10(1)	1(1)
C(3)	19(1)	12(1)	21(1)	-1(1)	-7(1)	-1(1)
C(4)	14(1)	10(1)	18(1)	-4(1)	-4(1)	-1(1)
C(5)	15(1)	12(1)	18(1)	-3(1)	-4(1)	-2(1)
C(6)	17(1)	11(1)	13(1)	-2(1)	-3(1)	-1(1)
C(7)	19(1)	16(1)	14(1)	-3(1)	-6(1)	2(1)
C(8)	18(1)	15(1)	17(1)	-4(1)	-7(1)	1(1)
C(9)	16(1)	9(1)	17(1)	-3(1)	-6(1)	-1(1)
C(10)	15(1)	10(1)	12(1)	0(1)	-5(1)	1(1)
C(11)	17(1)	22(1)	20(1)	-10(1)	-6(1)	1(1)
C(12)	13(1)	10(1)	14(1)	-1(1)	-2(1)	-1(1)
C(13)	24(1)	14(1)	17(1)	-4(1)	-10(1)	1(1)
C(14)	23(1)	12(1)	22(1)	-1(1)	-10(1)	2(1)
C(15)	18(1)	11(1)	17(1)	-4(1)	-2(1)	-2(1)
C(16)	21(1)	17(1)	16(1)	-4(1)	-7(1)	-2(1)
C(17)	16(1)	14(1)	16(1)	-1(1)	-5(1)	1(1)
C(18)	16(1)	11(1)	21(1)	-5(1)	-5(1)	-2(1)
C(19)	20(1)	16(1)	24(1)	-4(1)	-8(1)	1(1)
C(20)	18(1)	22(1)	36(1)	-8(1)	-9(1)	4(1)
C(21)	16(1)	30(1)	33(1)	-16(1)	-1(1)	1(1)
C(22)	22(1)	33(1)	20(1)	-9(1)	-2(1)	-5(1)
C(23)	19(1)	20(1)	20(1)	-4(1)	-6(1)	-1(1)
C(24)	43(1)	28(1)	29(1)	-4(1)	-2(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for CN_134_088.

	x	y	z	U(eq)
H(2)	7770	4959	921	26
H(3A)	9594	6591	447	45
H(1)	11407	1001	994	24
H(3)	8347	462	3876	20
H(7)	6461	2919	-333	19
H(8A)	4215	3817	596	19
H(8B)	3778	2222	613	19
H(9)	4337	1532	2289	16
H(13)	4444	5537	1554	21
H(14)	4160	7698	2153	22
H(16)	6354	6214	4535	21
H(17)	6634	4052	3929	18
H(19)	1869	4134	1608	23
H(20)	-376	4700	2757	29
H(21)	-818	3915	4619	31
H(22)	1008	2538	5335	30
H(23)	3240	1954	4195	23
H(24A)	9987	7893	1539	51
H(24B)	8785	7011	2486	51
H(24C)	8223	8048	1552	51

5.2 X-ray crystallographic data of compound **26**

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Cu K_α radiation (λ = 1.5478). Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350μL of Dichloroethane, which was then vapor diffused with Pentane over several days. A 0.135 x 0.067 x 0.041 mm piece if a colorless rod was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm using variable exposure time (5s-20s) depending on θ with a scan width of 1.0°. Data collection was 98.8% complete to 68.00° in θ. A total of 97780 reflections were collected covering the indices, -21<=h<=22, -23<=k<=23, -24<=l<=22. 14480 reflections were found to be symmetry independent, with a R_{int} of 0.0897. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1/n$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

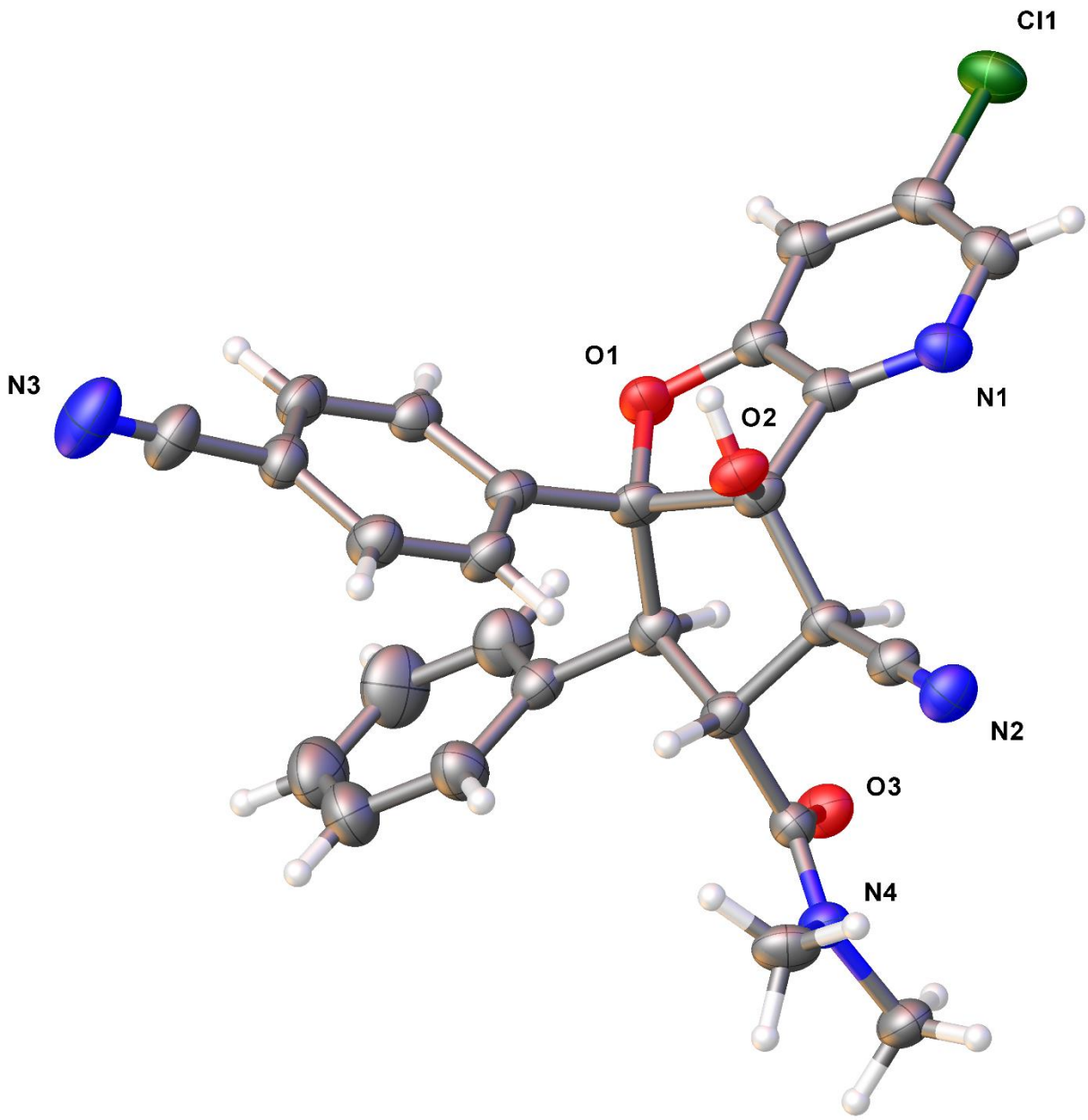

Cl1
O1
N3
N1
O2
N2
O3
N4

Table 1. Crystal data and structure refinement for eFT1605.

Report date	2016-10-20	
Identification code	eFT1605	
Empirical formula	C27 H21 Cl N4 O3	
Molecular formula	C27 H21 Cl N4 O3	
Formula weight	484.93	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 19.5956(4) Å	α= 90°.
	b = 19.9085(4) Å	β= 93.891(2)°.
	c = 20.5971(4) Å	γ = 90°.
Volume	8016.8(3) $Å^3$	
Z	12	
Density (calculated)	1.205 Mg/m^3	
Absorption coefficient	1.540 mm^{-1}	
F(000)	3024	
Crystal size	0.135 x 0.067 x 0.041 mm^3	
Crystal color, habit	Colorless Rod	
Theta range for data collection	3.012 to 68.322°.	
Index ranges	-21<=h<=22, -23<=k<=23, -24<=l<=22	
Reflections collected	97780	
Independent reflections	14480 [R(int) = 0.0897, R(sigma) = 0.0462]	
Completeness to theta = 68.000°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3201 and 0.2231	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14480 / 0 / 955	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0921	
R indices (all data)	R1 = 0.0650, wR2 = 0.1031	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.230 and -0.289 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for eFT1605. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	7872(1)	3671(1)	3443(1)	42(1)
O(1)	5421(1)	2760(1)	3486(1)	33(1)
O(2)	4999(1)	3498(1)	4947(1)	32(1)
O(3)	5491(1)	835(1)	4881(1)	37(1)
N(1)	6527(1)	3426(1)	4773(1)	34(1)
N(2)	5342(1)	2744(1)	6350(1)	38(1)
N(3)	1940(1)	4263(1)	3125(1)	64(1)
N(4)	4853(1)	980(1)	5746(1)	32(1)
C(1)	7088(1)	3570(1)	4459(1)	36(1)
C(2)	7121(1)	3456(1)	3799(1)	34(1)
C(3)	6584(1)	3182(1)	3422(1)	32(1)
C(4)	6011(1)	3032(1)	3754(1)	31(1)
C(5)	6008(1)	3162(1)	4411(1)	30(1)
C(6)	5330(1)	2967(1)	4652(1)	29(1)
C(7)	4957(1)	2652(1)	4010(1)	30(1)
C(8)	4934(1)	1882(1)	4152(1)	29(1)
C(9)	4860(1)	1846(1)	4888(1)	28(1)
C(10)	5392(1)	2372(1)	5138(1)	28(1)
C(11)	5355(1)	2588(1)	5818(1)	31(1)
C(12)	4273(1)	2956(1)	3790(1)	30(1)
C(13)	4113(1)	3111(1)	3137(1)	33(1)
C(14)	3498(1)	3416(1)	2941(1)	36(1)
C(15)	3035(1)	3566(1)	3402(1)	36(1)
C(16)	3170(1)	3377(1)	4046(1)	38(1)
C(17)	3785(1)	3075(1)	4236(1)	35(1)
C(18)	2420(1)	3946(1)	3234(1)	45(1)
C(19)	4434(1)	1485(1)	3717(1)	33(1)
C(20)	4633(1)	1257(1)	3123(1)	47(1)
C(21)	4186(2)	902(2)	2704(1)	62(1)
C(22)	3529(2)	768(1)	2867(1)	59(1)
C(23)	3324(1)	992(1)	3450(1)	52(1)
C(24)	3772(1)	1347(1)	3877(1)	44(1)

C(25)	5073(1)	1164(1)	5174(1)	28(1)
C(26)	5127(1)	374(1)	6071(1)	39(1)
C(27)	4342(1)	1337(1)	6101(1)	40(1)
Cl(1')	7265(1)	2675(1)	1606(1)	43(1)
O(1')	6493(1)	5051(1)	2184(1)	30(1)
O(2')	4921(1)	5019(1)	1471(1)	31(1)
O(3')	5089(1)	4431(1)	4048(1)	37(1)
N(1')	5494(1)	3590(1)	1811(1)	34(1)
N(2')	3483(1)	4984(1)	2152(1)	45(1)
N(3')	5592(1)	8723(1)	2044(1)	51(1)
N(4')	4225(1)	5186(1)	4061(1)	32(1)
C(1')	5985(1)	3140(1)	1694(1)	37(1)
C(2')	6674(1)	3303(1)	1735(1)	35(1)
C(3')	6903(1)	3941(1)	1903(1)	31(1)
C(4')	6393(1)	4398(1)	2015(1)	30(1)
C(5')	5715(1)	4205(1)	1960(1)	30(1)
C(6')	5270(1)	4817(1)	2055(1)	29(1)
C(7')	5829(1)	5301(1)	2366(1)	29(1)
C(8')	5771(1)	5167(1)	3110(1)	28(1)
C(9')	4998(1)	5189(1)	3162(1)	29(1)
C(10')	4740(1)	4732(1)	2583(1)	31(1)
C(11')	4040(1)	4875(1)	2333(1)	35(1)
C(12')	5782(1)	6038(1)	2198(1)	28(1)
C(13')	5148(1)	6354(1)	2102(1)	30(1)
C(14')	5100(1)	7046(1)	2050(1)	32(1)
C(15')	5695(1)	7429(1)	2081(1)	32(1)
C(16')	6334(1)	7119(1)	2151(1)	33(1)
C(17')	6372(1)	6430(1)	2211(1)	31(1)
C(18')	5641(1)	8152(1)	2054(1)	38(1)
C(19')	6221(1)	5608(1)	3551(1)	29(1)
C(20')	6033(1)	6252(1)	3726(1)	34(1)
C(21')	6491(1)	6664(1)	4075(1)	40(1)
C(22')	7140(1)	6438(1)	4264(1)	44(1)
C(23')	7332(1)	5794(1)	4107(1)	44(1)
C(24')	6874(1)	5382(1)	3752(1)	36(1)
C(25')	4764(1)	4915(1)	3802(1)	30(1)
C(26')	3990(1)	4912(1)	4669(1)	42(1)

C(27')	3789(1)	5718(1)	3773(1)	40(1)
Cl(1")	6137(1)	1170(1)	1844(1)	45(1)
O(1")	7101(1)	1406(1)	4219(1)	35(1)
O(2")	6461(1)	-65(1)	4832(1)	32(1)
O(3")	9135(1)	-46(1)	4386(1)	43(1)
N(1")	6554(1)	-53(1)	3330(1)	33(1)
N(2")	7260(1)	-1511(1)	4841(1)	46(1)
N(3")	6587(1)	2401(2)	7628(1)	77(1)
N(4")	9080(1)	-757(1)	5237(1)	37(1)
C(1")	6372(1)	205(1)	2743(1)	35(1)
C(2")	6415(1)	888(1)	2613(1)	35(1)
C(3")	6664(1)	1341(1)	3081(1)	35(1)
C(4")	6843(1)	1062(1)	3686(1)	32(1)
C(5")	6770(1)	382(1)	3790(1)	30(1)
C(6")	6984(1)	213(1)	4486(1)	30(1)
C(7")	7301(1)	909(1)	4728(1)	32(1)
C(8")	8083(1)	787(1)	4731(1)	31(1)
C(9")	8157(1)	61(1)	4982(1)	30(1)
C(10")	7596(1)	-285(1)	4539(1)	31(1)
C(11")	7402(1)	-969(1)	4721(1)	36(1)
C(12")	7101(1)	1204(1)	5368(1)	34(1)
C(13")	6968(1)	817(1)	5903(1)	38(1)
C(14")	6842(1)	1116(1)	6494(1)	45(1)
C(15")	6854(1)	1812(1)	6552(1)	47(1)
C(16")	6999(1)	2206(1)	6021(1)	45(1)
C(17")	7119(1)	1907(1)	5434(1)	39(1)
C(18")	6706(1)	2136(2)	7158(1)	59(1)
C(19")	8508(1)	1328(1)	5068(1)	33(1)
C(20")	8716(1)	1305(1)	5725(1)	38(1)
C(21")	9048(1)	1851(1)	6027(1)	48(1)
C(22")	9176(1)	2424(1)	5671(1)	55(1)
C(23")	8981(1)	2447(1)	5015(1)	54(1)
C(24")	8653(1)	1902(1)	4716(1)	41(1)
C(25")	8846(1)	-252(1)	4860(1)	33(1)
C(26")	8746(1)	-1026(1)	5796(1)	42(1)
C(27")	9705(1)	-1106(1)	5075(1)	50(1)

Table 3. Bond lengths [Å] and angles [°] for eFT1605.

Cl(1)-C(2)	1.740(2)	C(13)-H(13)	0.9500
O(1)-C(4)	1.360(3)	C(13)-C(14)	1.384(3)
O(1)-C(7)	1.473(2)	C(14)-H(14)	0.9500
O(2)-H(2)	0.8400	C(14)-C(15)	1.390(3)
O(2)-C(6)	1.401(2)	C(15)-C(16)	1.388(3)
O(3)-C(25)	1.238(2)	C(15)-C(18)	1.444(3)
N(1)-C(1)	1.342(3)	C(16)-H(16)	0.9500
N(1)-C(5)	1.329(3)	C(16)-C(17)	1.380(3)
N(2)-C(11)	1.141(3)	C(17)-H(17)	0.9500
N(3)-C(18)	1.143(3)	C(19)-C(20)	1.385(3)
N(4)-C(25)	1.333(2)	C(19)-C(24)	1.388(3)
N(4)-C(26)	1.463(3)	C(20)-H(20)	0.9500
N(4)-C(27)	1.464(3)	C(20)-C(21)	1.382(4)
C(1)-H(1)	0.9500	C(21)-H(21)	0.9500
C(1)-C(2)	1.384(3)	C(21)-C(22)	1.379(4)
C(2)-C(3)	1.378(3)	C(22)-H(22)	0.9500
C(3)-H(3)	0.9500	C(22)-C(23)	1.367(4)
C(3)-C(4)	1.386(3)	C(23)-H(23)	0.9500
C(4)-C(5)	1.377(3)	C(23)-C(24)	1.391(3)
C(5)-C(6)	1.501(3)	C(24)-H(24)	0.9500
C(6)-C(7)	1.595(3)	C(26)-H(26A)	0.9800
C(6)-C(10)	1.551(3)	C(26)-H(26B)	0.9800
C(7)-C(8)	1.562(3)	C(26)-H(26C)	0.9800
C(7)-C(12)	1.511(3)	C(27)-H(27A)	0.9800
C(8)-H(8)	1.0000	C(27)-H(27B)	0.9800
C(8)-C(9)	1.535(3)	C(27)-H(27C)	0.9800
C(8)-C(19)	1.506(3)	Cl(1')-C(2')	1.736(2)
C(9)-H(9)	1.0000	O(1')-C(4')	1.358(2)
C(9)-C(10)	1.541(3)	O(1')-C(7')	1.465(2)
C(9)-C(25)	1.527(3)	O(2')-H(2')	0.8400
C(10)-H(10)	1.0000	O(2')-C(6')	1.402(2)
C(10)-C(11)	1.471(3)	O(3')-C(25')	1.244(2)
C(12)-C(13)	1.394(3)	N(1')-C(1')	1.348(3)
C(12)-C(17)	1.391(3)	N(1')-C(5')	1.329(3)

N(2')-C(11')	1.148(3)	C(19')-C(24')	1.392(3)
N(3')-C(18')	1.142(3)	C(20')-H(20')	0.9500
N(4')-C(25')	1.330(3)	C(20')-C(21')	1.381(3)
N(4')-C(26')	1.469(3)	C(21')-H(21')	0.9500
N(4')-C(27')	1.460(3)	C(21')-C(22')	1.380(4)
C(1')-H(1')	0.9500	C(22')-H(22')	0.9500
C(1')-C(2')	1.386(3)	C(22')-C(23')	1.382(4)
C(2')-C(3')	1.384(3)	C(23')-H(23')	0.9500
C(3')-H(3')	0.9500	C(23')-C(24')	1.387(3)
C(3')-C(4')	1.382(3)	C(24')-H(24')	0.9500
C(4')-C(5')	1.380(3)	C(26')-H(26D)	0.9800
C(5')-C(6')	1.517(3)	C(26')-H(26E)	0.9800
C(6')-C(7')	1.563(3)	C(26')-H(26F)	0.9800
C(6')-C(10')	1.565(2)	C(27')-H(27D)	0.9800
C(7')-C(8')	1.567(2)	C(27')-H(27E)	0.9800
C(7')-C(12')	1.508(3)	C(27')-H(27F)	0.9800
C(8')-H(8')	1.0000	Cl(1")-C(2")	1.734(2)
C(8')-C(9')	1.528(3)	O(1")-C(4")	1.362(2)
C(8')-C(19')	1.504(3)	O(1")-C(7")	1.475(2)
C(9')-H(9')	1.0000	O(2")-H(2")	0.8400
C(9')-C(10')	1.557(3)	O(2")-C(6")	1.401(2)
C(9')-C(25')	1.524(3)	O(3")-C(25")	1.233(2)
C(10')-H(10')	1.0000	N(1")-C(1")	1.339(3)
C(10')-C(11')	1.461(3)	N(1")-C(5")	1.332(3)
C(12')-C(13')	1.396(3)	N(2")-C(11")	1.144(3)
C(12')-C(17')	1.394(3)	N(3")-C(18")	1.139(3)
C(13')-H(13')	0.9500	N(4")-C(25")	1.333(3)
C(13')-C(14')	1.384(3)	N(4")-C(26")	1.463(3)
C(14')-H(14')	0.9500	N(4")-C(27")	1.467(3)
C(14')-C(15')	1.390(3)	C(1")-H(1")	0.9500
C(15')-C(16')	1.394(3)	C(1")-C(2")	1.390(3)
C(15')-C(18')	1.444(3)	C(2")-C(3")	1.383(3)
C(16')-H(16')	0.9500	C(3")-H(3")	0.9500
C(16')-C(17')	1.379(3)	C(3")-C(4")	1.387(3)
C(17')-H(17')	0.9500	C(4")-C(5")	1.381(3)
C(19')-C(20')	1.389(3)	C(5")-C(6")	1.502(3)

C(6")-C(7")	1.586(3)	C(26")-H(26I)	0.9800
C(6")-C(10")	1.554(3)	C(27")-H(27G)	0.9800
C(7")-C(8")	1.553(3)	C(27")-H(27H)	0.9800
C(7")-C(12")	1.518(3)	C(27")-H(27I)	0.9800
C(8")-H(8")	1.0000		
C(8")-C(9")	1.540(3)	C(4)-O(1)-C(7)	108.10(14)
C(8")-C(19")	1.501(3)	C(6)-O(2)-H(2)	109.5
C(9")-H(9")	1.0000	C(5)-N(1)-C(1)	115.81(17)
C(9")-C(10")	1.543(3)	C(25)-N(4)-C(26)	120.08(17)
C(9")-C(25")	1.523(3)	C(25)-N(4)-C(27)	125.56(17)
C(10")-H(10")	1.0000	C(26)-N(4)-C(27)	114.35(16)
C(10")-C(11")	1.470(3)	N(1)-C(1)-H(1)	118.9
C(12")-C(13")	1.384(3)	N(1)-C(1)-C(2)	122.2(2)
C(12")-C(17")	1.404(3)	C(2)-C(1)-H(1)	118.9
C(13")-H(13")	0.9500	C(1)-C(2)-Cl(1)	118.12(17)
C(13")-C(14")	1.392(3)	C(3)-C(2)-Cl(1)	119.65(16)
C(14")-H(14")	0.9500	C(3)-C(2)-C(1)	122.23(18)
C(14")-C(15")	1.390(4)	C(2)-C(3)-H(3)	122.6
C(15")-C(16")	1.391(4)	C(2)-C(3)-C(4)	114.87(18)
C(15")-C(18")	1.452(3)	C(4)-C(3)-H(3)	122.6
C(16")-H(16")	0.9500	O(1)-C(4)-C(3)	125.46(18)
C(16")-C(17")	1.382(3)	O(1)-C(4)-C(5)	114.38(17)
C(17")-H(17")	0.9500	C(5)-C(4)-C(3)	120.15(19)
C(19")-C(20")	1.387(3)	N(1)-C(5)-C(4)	124.77(18)
C(19")-C(24")	1.392(3)	N(1)-C(5)-C(6)	125.37(17)
C(20")-H(20")	0.9500	C(4)-C(5)-C(6)	109.86(17)
C(20")-C(21")	1.391(3)	O(2)-C(6)-C(5)	113.20(16)
C(21")-H(21")	0.9500	O(2)-C(6)-C(7)	117.18(16)
C(21")-C(22")	1.388(4)	O(2)-C(6)-C(10)	108.33(14)
C(22")-H(22")	0.9500	C(5)-C(6)-C(7)	101.16(14)
C(22")-C(23")	1.380(4)	C(5)-C(6)-C(10)	112.34(16)
C(23")-H(23")	0.9500	C(10)-C(6)-C(7)	104.28(15)
C(23")-C(24")	1.385(3)	O(1)-C(7)-C(6)	106.21(15)
C(24")-H(24")	0.9500	O(1)-C(7)-C(8)	107.99(14)
C(26")-H(26G)	0.9800	O(1)-C(7)-C(12)	107.45(15)
C(26")-H(26H)	0.9800	C(8)-C(7)-C(6)	104.34(15)

C(12)-C(7)-C(6)	115.97(15)	C(12)-C(17)-H(17)	119.5
C(12)-C(7)-C(8)	114.38(16)	C(16)-C(17)-C(12)	121.02(19)
C(7)-C(8)-H(8)	106.5	C(16)-C(17)-H(17)	119.5
C(9)-C(8)-C(7)	103.68(15)	N(3)-C(18)-C(15)	176.9(3)
C(9)-C(8)-H(8)	106.5	C(20)-C(19)-C(8)	119.11(19)
C(19)-C(8)-C(7)	115.42(16)	C(20)-C(19)-C(24)	118.0(2)
C(19)-C(8)-H(8)	106.5	C(24)-C(19)-C(8)	122.91(18)
C(19)-C(8)-C(9)	117.55(16)	C(19)-C(20)-H(20)	119.5
C(8)-C(9)-H(9)	111.6	C(21)-C(20)-C(19)	121.0(2)
C(8)-C(9)-C(10)	101.04(15)	C(21)-C(20)-H(20)	119.5
C(10)-C(9)-H(9)	111.6	C(20)-C(21)-H(21)	119.7
C(25)-C(9)-C(8)	112.29(15)	C(22)-C(21)-C(20)	120.5(2)
C(25)-C(9)-H(9)	111.6	C(22)-C(21)-H(21)	119.7
C(25)-C(9)-C(10)	108.33(15)	C(21)-C(22)-H(22)	120.4
C(6)-C(10)-H(10)	107.1	C(23)-C(22)-C(21)	119.2(2)
C(9)-C(10)-C(6)	106.36(15)	C(23)-C(22)-H(22)	120.4
C(9)-C(10)-H(10)	107.1	C(22)-C(23)-H(23)	119.7
C(11)-C(10)-C(6)	112.60(15)	C(22)-C(23)-C(24)	120.6(3)
C(11)-C(10)-C(9)	116.22(16)	C(24)-C(23)-H(23)	119.7
C(11)-C(10)-H(10)	107.1	C(19)-C(24)-C(23)	120.7(2)
N(2)-C(11)-C(10)	178.1(2)	C(19)-C(24)-H(24)	119.7
C(13)-C(12)-C(7)	121.01(17)	C(23)-C(24)-H(24)	119.7
C(17)-C(12)-C(7)	120.40(17)	O(3)-C(25)-N(4)	123.40(18)
C(17)-C(12)-C(13)	118.58(19)	O(3)-C(25)-C(9)	117.11(16)
C(12)-C(13)-H(13)	119.5	N(4)-C(25)-C(9)	119.20(16)
C(14)-C(13)-C(12)	120.91(18)	N(4)-C(26)-H(26A)	109.5
C(14)-C(13)-H(13)	119.5	N(4)-C(26)-H(26B)	109.5
C(13)-C(14)-H(14)	120.3	N(4)-C(26)-H(26C)	109.5
C(13)-C(14)-C(15)	119.39(18)	H(26A)-C(26)-H(26B)	109.5
C(15)-C(14)-H(14)	120.3	H(26A)-C(26)-H(26C)	109.5
C(14)-C(15)-C(18)	121.45(19)	H(26B)-C(26)-H(26C)	109.5
C(16)-C(15)-C(14)	120.3(2)	N(4)-C(27)-H(27A)	109.5
C(16)-C(15)-C(18)	118.2(2)	N(4)-C(27)-H(27B)	109.5
C(15)-C(16)-H(16)	120.2	N(4)-C(27)-H(27C)	109.5
C(17)-C(16)-C(15)	119.62(19)	H(27A)-C(27)-H(27B)	109.5
C(17)-C(16)-H(16)	120.2	H(27A)-C(27)-H(27C)	109.5

H(27B)-C(27)-H(27C)	109.5	C(9')-C(8')-H(8')	107.0
C(4')-O(1')-C(7')	106.02(14)	C(19')-C(8')-C(7')	114.42(15)
C(6')-O(2')-H(2')	109.5	C(19')-C(8')-H(8')	107.0
C(5')-N(1')-C(1')	115.36(18)	C(19')-C(8')-C(9')	119.05(15)
C(25')-N(4')-C(26')	119.66(17)	C(8')-C(9')-H(9')	110.1
C(25')-N(4')-C(27')	126.13(16)	C(8')-C(9')-C(10')	101.64(14)
C(27')-N(4')-C(26')	114.05(16)	C(10')-C(9')-H(9')	110.1
N(1')-C(1')-H(1')	118.7	C(25')-C(9')-C(8')	114.07(16)
N(1')-C(1')-C(2')	122.58(19)	C(25')-C(9')-H(9')	110.1
C(2')-C(1')-H(1')	118.7	C(25')-C(9')-C(10')	110.60(15)
C(1')-C(2')-Cl(1')	118.61(16)	C(6')-C(10')-H(10')	108.1
C(3')-C(2')-Cl(1')	119.45(17)	C(9')-C(10')-C(6')	105.87(15)
C(3')-C(2')-C(1')	121.88(18)	C(9')-C(10')-H(10')	108.1
C(2')-C(3')-H(3')	122.6	C(11')-C(10')-C(6')	112.64(16)
C(4')-C(3')-C(2')	114.83(19)	C(11')-C(10')-C(9')	113.84(16)
C(4')-C(3')-H(3')	122.6	C(11')-C(10')-H(10')	108.1
O(1')-C(4')-C(3')	125.47(18)	N(2')-C(11')-C(10')	178.1(2)
O(1')-C(4')-C(5')	114.08(16)	C(13')-C(12')-C(7')	120.76(17)
C(5')-C(4')-C(3')	120.46(18)	C(17')-C(12')-C(7')	120.19(18)
N(1')-C(5')-C(4')	124.88(18)	C(17')-C(12')-C(13')	118.62(18)
N(1')-C(5')-C(6')	126.05(18)	C(12')-C(13')-H(13')	119.5
C(4')-C(5')-C(6')	108.96(17)	C(14')-C(13')-C(12')	121.02(18)
O(2')-C(6')-C(5')	111.83(15)	C(14')-C(13')-H(13')	119.5
O(2')-C(6')-C(7')	117.52(15)	C(13')-C(14')-H(14')	120.3
O(2')-C(6')-C(10')	108.62(15)	C(13')-C(14')-C(15')	119.32(19)
C(5')-C(6')-C(7')	98.93(15)	C(15')-C(14')-H(14')	120.3
C(5')-C(6')-C(10')	114.64(15)	C(14')-C(15')-C(16')	120.45(18)
C(7')-C(6')-C(10')	105.13(14)	C(14')-C(15')-C(18')	119.07(19)
O(1')-C(7')-C(6')	107.19(14)	C(16')-C(15')-C(18')	120.47(19)
O(1')-C(7')-C(8')	108.45(15)	C(15')-C(16')-H(16')	120.2
O(1')-C(7')-C(12')	108.19(14)	C(17')-C(16')-C(15')	119.50(18)
C(6')-C(7')-C(8')	101.64(14)	C(17')-C(16')-H(16')	120.2
C(12')-C(7')-C(6')	118.39(17)	C(12')-C(17')-H(17')	119.5
C(12')-C(7')-C(8')	112.47(15)	C(16')-C(17')-C(12')	121.02(19)
C(7')-C(8')-H(8')	107.0	C(16')-C(17')-H(17')	119.5
C(9')-C(8')-C(7')	101.63(15)	N(3')-C(18')-C(15')	178.6(2)

C(20')-C(19')-C(8')	122.67(18)	C(25")-N(4")-C(26")	125.41(17)
C(20')-C(19')-C(24')	118.45(19)	C(25")-N(4")-C(27")	119.00(18)
C(24')-C(19')-C(8')	118.69(17)	C(26")-N(4")-C(27")	115.53(18)
C(19')-C(20')-H(20')	119.7	N(1")-C(1")-H(1")	118.9
C(21')-C(20')-C(19')	120.6(2)	N(1")-C(1")-C(2")	122.26(19)
C(21')-C(20')-H(20')	119.7	C(2")-C(1")-H(1")	118.9
C(20')-C(21')-H(21')	119.8	C(1")-C(2")-Cl(1")	118.31(16)
C(22')-C(21')-C(20')	120.5(2)	C(3")-C(2")-Cl(1")	119.92(16)
C(22')-C(21')-H(21')	119.8	C(3")-C(2")-C(1")	121.76(19)
C(21')-C(22')-H(22')	120.1	C(2")-C(3")-H(3")	122.6
C(21')-C(22')-C(23')	119.8(2)	C(2")-C(3")-C(4")	114.90(18)
C(23')-C(22')-H(22')	120.1	C(4")-C(3")-H(3")	122.6
C(22')-C(23')-H(23')	120.1	O(1")-C(4")-C(3")	125.58(18)
C(22')-C(23')-C(24')	119.8(2)	O(1")-C(4")-C(5")	113.77(17)
C(24')-C(23')-H(23')	120.1	C(5")-C(4")-C(3")	120.65(19)
C(19')-C(24')-H(24')	119.5	N(1")-C(5")-C(4")	123.88(18)
C(23')-C(24')-C(19')	120.9(2)	N(1")-C(5")-C(6")	126.03(17)
C(23')-C(24')-H(24')	119.5	C(4")-C(5")-C(6")	110.08(17)
O(3')-C(25')-N(4')	123.35(17)	O(2")-C(6")-C(5")	114.04(16)
O(3')-C(25')-C(9')	116.98(16)	O(2")-C(6")-C(7")	117.96(15)
N(4')-C(25')-C(9')	119.65(17)	O(2")-C(6")-C(10")	107.40(15)
N(4')-C(26')-H(26D)	109.5	C(5")-C(6")-C(7")	100.53(15)
N(4')-C(26')-H(26E)	109.5	C(5")-C(6")-C(10")	111.96(15)
N(4')-C(26')-H(26F)	109.5	C(10")-C(6")-C(7")	104.59(16)
H(26D)-C(26')-H(26E)	109.5	O(1")-C(7")-C(6")	106.42(15)
H(26D)-C(26')-H(26F)	109.5	O(1")-C(7")-C(8")	108.72(15)
H(26E)-C(26')-H(26F)	109.5	O(1")-C(7")-C(12")	106.66(15)
N(4')-C(27')-H(27D)	109.5	C(8")-C(7")-C(6")	103.27(15)
N(4')-C(27')-H(27E)	109.5	C(12")-C(7")-C(6")	119.60(16)
N(4')-C(27')-H(27F)	109.5	C(12")-C(7")-C(8")	111.73(16)
H(27D)-C(27')-H(27E)	109.5	C(7")-C(8")-H(8")	106.9
H(27D)-C(27')-H(27F)	109.5	C(9")-C(8")-C(7")	102.58(15)
H(27E)-C(27')-H(27F)	109.5	C(9")-C(8")-H(8")	106.9
C(4")-O(1")-C(7")	107.66(14)	C(19")-C(8")-C(7")	113.97(16)
C(6")-O(2")-H(2")	109.5	C(19")-C(8")-H(8")	106.9
C(5")-N(1")-C(1")	116.48(17)	C(19")-C(8")-C(9")	118.76(17)

C(8")-C(9")-H(9")	111.5
C(8")-C(9")-C(10")	99.98(15)
C(10")-C(9")-H(9")	111.5
C(25")-C(9")-C(8")	113.09(16)
C(25")-C(9")-H(9")	111.5
C(25")-C(9")-C(10")	108.87(15)
C(6")-C(10")-H(10")	106.8
C(9")-C(10")-C(6")	105.81(15)
C(9")-C(10")-H(10")	106.8
C(11")-C(10")-C(6")	113.44(17)
C(11")-C(10")-C(9")	116.66(17)
C(11")-C(10")-H(10")	106.8
N(2")-C(11")-C(10")	177.4(2)
C(13")-C(12")-C(7")	123.27(19)
C(13")-C(12")-C(17")	118.82(19)
C(17")-C(12")-C(7")	117.61(19)
C(12")-C(13")-H(13")	119.6
C(12")-C(13")-C(14")	120.8(2)
C(14")-C(13")-H(13")	119.6
C(13")-C(14")-H(14")	120.1
C(15")-C(14")-C(13")	119.9(2)
C(15")-C(14")-H(14")	120.1
C(14")-C(15")-C(16")	119.8(2)
C(14")-C(15")-C(18")	120.9(3)
C(16")-C(15")-C(18")	119.3(2)
C(15")-C(16")-H(16")	120.0
C(17")-C(16")-C(15")	120.1(2)
C(17")-C(16")-H(16")	120.0
C(12")-C(17")-H(17")	119.7
C(16")-C(17")-C(12")	120.6(2)
C(16")-C(17")-H(17")	119.7
N(3")-C(18")-C(15")	178.8(3)
C(20")-C(19")-C(8")	123.01(19)
C(20")-C(19")-C(24")	118.5(2)
C(24")-C(19")-C(8")	118.30(19)
C(19")-C(20")-H(20")	119.7
C(19")-C(20")-C(21")	120.6(2)
C(21")-C(20")-H(20")	119.7
C(20")-C(21")-H(21")	119.9
C(22")-C(21")-C(20")	120.1(2)
C(22")-C(21")-H(21")	119.9
C(21")-C(22")-H(22")	120.1
C(23")-C(22")-C(21")	119.7(2)
C(23")-C(22")-H(22")	120.1
C(22")-C(23")-H(23")	120.1
C(22")-C(23")-C(24")	119.9(2)
C(24")-C(23")-H(23")	120.1
C(19")-C(24")-H(24")	119.4
C(23")-C(24")-C(19")	121.2(2)
C(23")-C(24")-H(24")	119.4
O(3")-C(25")-N(4")	123.60(18)
O(3")-C(25")-C(9")	117.13(18)
N(4")-C(25")-C(9")	119.10(17)
N(4")-C(26")-H(26G)	109.5
N(4")-C(26")-H(26H)	109.5
N(4")-C(26")-H(26I)	109.5
H(26G)-C(26")-H(26H)	109.5
H(26G)-C(26")-H(26I)	109.5
H(26H)-C(26")-H(26I)	109.5
N(4")-C(27")-H(27G)	109.5
N(4")-C(27")-H(27H)	109.5
N(4")-C(27")-H(27I)	109.5
H(27G)-C(27")-H(27H)	109.5
H(27G)-C(27")-H(27I)	109.5
H(27H)-C(27")-H(27I)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for eFT1605. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	38(1)	39(1)	51(1)	0(1)	20(1)	-2(1)
O(1)	35(1)	42(1)	23(1)	2(1)	7(1)	-3(1)
O(2)	41(1)	29(1)	26(1)	4(1)	10(1)	7(1)
O(3)	36(1)	36(1)	40(1)	4(1)	9(1)	9(1)
N(1)	37(1)	33(1)	33(1)	0(1)	8(1)	-2(1)
N(2)	42(1)	42(1)	30(1)	0(1)	6(1)	6(1)
N(3)	64(2)	82(2)	47(1)	13(1)	2(1)	30(1)
N(4)	32(1)	32(1)	32(1)	6(1)	4(1)	0(1)
C(1)	34(1)	36(1)	40(1)	-2(1)	8(1)	-2(1)
C(2)	34(1)	27(1)	44(1)	2(1)	13(1)	2(1)
C(3)	39(1)	30(1)	30(1)	1(1)	10(1)	3(1)
C(4)	36(1)	29(1)	29(1)	3(1)	6(1)	3(1)
C(5)	35(1)	26(1)	28(1)	2(1)	8(1)	1(1)
C(6)	33(1)	30(1)	27(1)	3(1)	6(1)	4(1)
C(7)	34(1)	34(1)	23(1)	3(1)	9(1)	1(1)
C(8)	30(1)	33(1)	25(1)	2(1)	7(1)	4(1)
C(9)	27(1)	31(1)	27(1)	4(1)	5(1)	4(1)
C(10)	30(1)	29(1)	25(1)	2(1)	5(1)	2(1)
C(11)	32(1)	30(1)	30(1)	4(1)	5(1)	4(1)
C(12)	35(1)	27(1)	27(1)	3(1)	3(1)	-1(1)
C(13)	41(1)	32(1)	25(1)	0(1)	3(1)	-2(1)
C(14)	44(1)	38(1)	26(1)	3(1)	-4(1)	-1(1)
C(15)	38(1)	35(1)	34(1)	2(1)	-5(1)	1(1)
C(16)	37(1)	42(1)	35(1)	4(1)	6(1)	5(1)
C(17)	39(1)	39(1)	27(1)	7(1)	4(1)	5(1)
C(18)	50(2)	52(1)	33(1)	6(1)	-2(1)	14(1)
C(19)	38(1)	30(1)	31(1)	3(1)	1(1)	4(1)
C(20)	49(2)	55(1)	37(1)	-9(1)	4(1)	3(1)
C(21)	73(2)	70(2)	42(1)	-21(1)	-1(1)	4(1)
C(22)	66(2)	54(2)	54(2)	-7(1)	-14(1)	-8(1)
C(23)	46(2)	55(1)	54(2)	-1(1)	-7(1)	-10(1)
C(24)	42(1)	50(1)	39(1)	-2(1)	3(1)	-6(1)

C(25)	25(1)	30(1)	29(1)	1(1)	1(1)	-2(1)
C(26)	40(1)	38(1)	40(1)	12(1)	1(1)	1(1)
C(27)	49(1)	38(1)	35(1)	3(1)	18(1)	-3(1)
Cl(1')	49(1)	36(1)	44(1)	-2(1)	12(1)	10(1)
O(1')	28(1)	30(1)	33(1)	-1(1)	10(1)	-1(1)
O(2')	30(1)	38(1)	26(1)	0(1)	7(1)	0(1)
O(3')	44(1)	34(1)	33(1)	6(1)	15(1)	4(1)
N(1')	39(1)	32(1)	32(1)	-2(1)	5(1)	-2(1)
N(2')	37(1)	58(1)	42(1)	-3(1)	8(1)	-5(1)
N(3')	48(1)	35(1)	71(1)	-2(1)	14(1)	0(1)
N(4')	37(1)	30(1)	32(1)	-1(1)	13(1)	-1(1)
C(1')	46(1)	30(1)	34(1)	-3(1)	7(1)	0(1)
C(2')	42(1)	35(1)	27(1)	2(1)	10(1)	8(1)
C(3')	32(1)	35(1)	28(1)	3(1)	8(1)	3(1)
C(4')	34(1)	32(1)	24(1)	1(1)	8(1)	-2(1)
C(5')	33(1)	32(1)	26(1)	2(1)	7(1)	0(1)
C(6')	29(1)	31(1)	27(1)	0(1)	7(1)	-2(1)
C(7')	26(1)	32(1)	29(1)	-2(1)	9(1)	0(1)
C(8')	30(1)	27(1)	28(1)	2(1)	9(1)	-1(1)
C(9')	32(1)	28(1)	28(1)	1(1)	7(1)	-1(1)
C(10')	30(1)	33(1)	31(1)	-1(1)	9(1)	-3(1)
C(11')	34(1)	41(1)	31(1)	-3(1)	10(1)	-6(1)
C(12')	31(1)	32(1)	22(1)	1(1)	8(1)	-1(1)
C(13')	30(1)	33(1)	26(1)	0(1)	6(1)	-3(1)
C(14')	34(1)	35(1)	27(1)	3(1)	6(1)	1(1)
C(15')	39(1)	30(1)	28(1)	1(1)	8(1)	0(1)
C(16')	32(1)	36(1)	32(1)	1(1)	7(1)	-6(1)
C(17')	29(1)	34(1)	29(1)	3(1)	7(1)	-1(1)
C(18')	37(1)	37(1)	42(1)	-1(1)	10(1)	-2(1)
C(19')	31(1)	33(1)	24(1)	3(1)	8(1)	-2(1)
C(20')	39(1)	36(1)	28(1)	0(1)	10(1)	-1(1)
C(21')	57(2)	37(1)	29(1)	-1(1)	11(1)	-7(1)
C(22')	54(2)	52(1)	27(1)	2(1)	7(1)	-20(1)
C(23')	39(1)	57(1)	35(1)	7(1)	1(1)	-8(1)
C(24')	35(1)	38(1)	36(1)	4(1)	4(1)	-1(1)
C(25')	34(1)	26(1)	30(1)	-1(1)	8(1)	-2(1)
C(26')	54(1)	37(1)	38(1)	0(1)	24(1)	-1(1)

C(27')	41(1)	42(1)	37(1)	-2(1)	12(1)	7(1)
Cl(1")	58(1)	44(1)	32(1)	7(1)	2(1)	1(1)
O(1")	37(1)	31(1)	35(1)	-1(1)	-3(1)	3(1)
O(2")	30(1)	33(1)	33(1)	3(1)	9(1)	5(1)
O(3")	35(1)	56(1)	38(1)	2(1)	16(1)	8(1)
N(1")	37(1)	34(1)	30(1)	1(1)	8(1)	0(1)
N(2")	47(1)	37(1)	55(1)	1(1)	9(1)	5(1)
N(3")	72(2)	104(2)	54(1)	-32(1)	-6(1)	38(2)
N(4")	32(1)	40(1)	38(1)	-3(1)	3(1)	10(1)
C(1")	40(1)	36(1)	30(1)	-1(1)	6(1)	-2(1)
C(2")	36(1)	38(1)	32(1)	2(1)	7(1)	3(1)
C(3")	36(1)	31(1)	38(1)	3(1)	6(1)	2(1)
C(4")	29(1)	34(1)	32(1)	-3(1)	4(1)	2(1)
C(5")	26(1)	33(1)	31(1)	1(1)	6(1)	2(1)
C(6")	28(1)	33(1)	29(1)	-1(1)	7(1)	3(1)
C(7")	30(1)	33(1)	32(1)	1(1)	2(1)	5(1)
C(8")	28(1)	36(1)	30(1)	1(1)	6(1)	2(1)
C(9")	29(1)	34(1)	26(1)	0(1)	8(1)	6(1)
C(10")	32(1)	34(1)	29(1)	-2(1)	7(1)	6(1)
C(11")	32(1)	38(1)	39(1)	-1(1)	6(1)	7(1)
C(12")	23(1)	42(1)	37(1)	-7(1)	2(1)	7(1)
C(13")	30(1)	48(1)	36(1)	-6(1)	4(1)	6(1)
C(14")	32(1)	67(2)	35(1)	-7(1)	3(1)	8(1)
C(15")	30(1)	66(2)	44(1)	-19(1)	-2(1)	13(1)
C(16")	31(1)	48(1)	54(1)	-17(1)	-5(1)	12(1)
C(17")	27(1)	43(1)	46(1)	-9(1)	0(1)	9(1)
C(18")	47(2)	81(2)	48(1)	-21(1)	-4(1)	25(1)
C(19")	27(1)	38(1)	36(1)	-3(1)	8(1)	4(1)
C(20")	31(1)	46(1)	39(1)	-4(1)	4(1)	5(1)
C(21")	34(1)	59(2)	50(1)	-14(1)	-3(1)	6(1)
C(22")	43(2)	52(1)	70(2)	-17(1)	-1(1)	-4(1)
C(23")	50(2)	42(1)	71(2)	-2(1)	8(1)	-6(1)
C(24")	38(1)	43(1)	43(1)	-1(1)	8(1)	-2(1)
C(25")	29(1)	42(1)	29(1)	-6(1)	6(1)	6(1)
C(26")	43(1)	44(1)	40(1)	6(1)	-3(1)	5(1)
C(27")	38(1)	51(1)	62(2)	-5(1)	5(1)	15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for eFT1605.

	x	y	z	U(eq)
H(2)	4998	3838	4705	48
H(1)	7474	3756	4698	43
H(3)	6605	3101	2970	39
H(8)	5399	1702	4078	35
H(9)	4388	1972	5000	34
H(10)	5853	2167	5101	34
H(13)	4430	3007	2823	39
H(14)	3394	3521	2495	43
H(16)	2840	3454	4356	45
H(17)	3877	2946	4677	42
H(20)	5083	1347	3002	56
H(21)	4334	748	2299	74
H(22)	3223	524	2578	71
H(23)	2871	905	3565	63
H(24)	3623	1496	4282	53
H(26A)	4763	38	6086	59
H(26B)	5300	487	6516	59
H(26C)	5500	194	5831	59
H(27A)	4573	1606	6449	60
H(27B)	4038	1011	6291	60
H(27C)	4073	1632	5802	60
H(2')	5188	5005	1169	47
H(1')	5854	2694	1580	44
H(3')	7375	4057	1938	38
H(8')	5920	4693	3196	33
H(9')	4825	5657	3090	35
H(10')	4758	4255	2737	37
H(13')	4742	6091	2072	35
H(14')	4665	7257	1993	38
H(16')	6739	7381	2157	40

H(17')	6807	6219	2262	37
H(20')	5585	6411	3605	41
H(21')	6358	7106	4186	49
H(22')	7454	6725	4502	53
H(23')	7776	5633	4242	52
H(24')	7008	4939	3643	43
H(26D)	3582	4635	4572	63
H(26E)	3878	5281	4957	63
H(26F)	4353	4636	4884	63
H(27D)	4027	5945	3432	60
H(27E)	3686	6043	4110	60
H(27F)	3362	5522	3584	60
H(2")	6141	213	4848	48
H(1")	6208	-89	2405	42
H(3")	6708	1807	2994	42
H(8")	8202	783	4266	37
H(9")	8058	29	5451	36
H(10")	7774	-315	4096	38
H(13")	6963	341	5866	45
H(14")	6749	845	6857	54
H(16")	7014	2681	6061	54
H(17")	7216	2178	5072	46
H(20")	8632	914	5970	46
H(21")	9188	1831	6477	58
H(22")	9397	2799	5879	66
H(23")	9072	2836	4768	65
H(24")	8524	1919	4264	50
H(26G)	8535	-657	6026	64
H(26H)	9086	-1251	6091	64
H(26I)	8393	-1349	5644	64
H(27G)	9592	-1567	4938	75
H(27H)	10030	-1116	5458	75
H(27I)	9911	-869	4720	75

Table 6. Hydrogen bonds for eFT1605 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(3')	0.84	1.82	2.6380(18)	166.0
O(2')-H(2')...O(3'')#1	0.84	1.81	2.6442(18)	171.3
O(2'')-H(2'')...O(3)	0.84	1.78	2.6198(19)	177.3

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,y+1/2,-z+1/2

6 Biological assays

6.1 Cell proliferation assay

MDA-MB-231 cells were cultured in DMEM media, 10% FBS and 1x penicillin/streptomycin. Exponentially growing cells were seeded at 3000 cells per well in 96-well flat bottom white polystyrene plates from Thermofisher Scientific (Waltham, MA) and cultured overnight. The following day, compound was added in a 3-fold dilution series along with a DMSO control. The final DMSO concentration was 0.1%. Cells were incubated for 72 hours at 37°C in a CO_2 incubator. Baseline viability of untreated cells was measured on the day of treatment and proliferation was measured after 72 hours of treatment using CellTiter-Glo reagent from Promega (Madison, WI) according to manufactures instructions. Dose-response curves were plotted using Prism 6 software, and EC_{50} values were calculated using a 4 parameter, variable slope non-linear regression model.

Calculation of % Inhibition:
% inhibition = 1-(((cells + inhibitor) – baseline) / ((cells + DMSO) – baseline))) X 100.

6.2 *In vitro* translation reporter assay

c-MYC or Tubulin 5'-UTRs were cloned into the luciferase reporter vector pGL3 (Promega Corp., Madison, WI) at Genewiz (San Diego). DNA templates were PCR amplified using Phusion High-fidelity PCR Master Mix (New England Biolabs, Ipswich, MA) from the reporter vector that incorporates the T7 promoter sequence for subsequent RNA transcription. Reactions were purified using the Qiagen PCR clean up kit and eluted in 50uL water. RNA was transcribed from the DNA templates using the mMESSAGE mMACHINE T7 Ultra kit (Ambion ThermoFisher, Waltham, MA). RNA was purified with the RNA Mega Clear Kit and eluted with 30 μL elution buffer (Ambion ThermoFisher, Waltham, MA). Using the manufacturer's instructions, RNA was transiently transfected into exponentially growing MDA-MB-231 cancer cells seeded into 96-well plates using the TransIT mRNA transfection kit (Mirus Bio, Madison, WI). The transfected cells were treated with various concentrations of compounds or control (DMSO) for 4 hours at 37°C.

Cells were rinsed with 100 μL PBS and lysed using 50 μL 1x passive lysis buffer (Promega Corp., Madison, WI). After shaking for 20 minutes at room temperature, 100 μL luciferase assay reagent (Promega Corp., Madison, WI) was added and luminescence was quantitated using a Victor (Perkin Elmer) plate reader. The data were fitted using GraphPad Prism (GraphPad Software, La Jolla, CA) and a four-parameter dose response equation.

See Figure S1 and Table S1 for data obtained for compounds **1**, **2**, **24**, **25** and **CHX**.

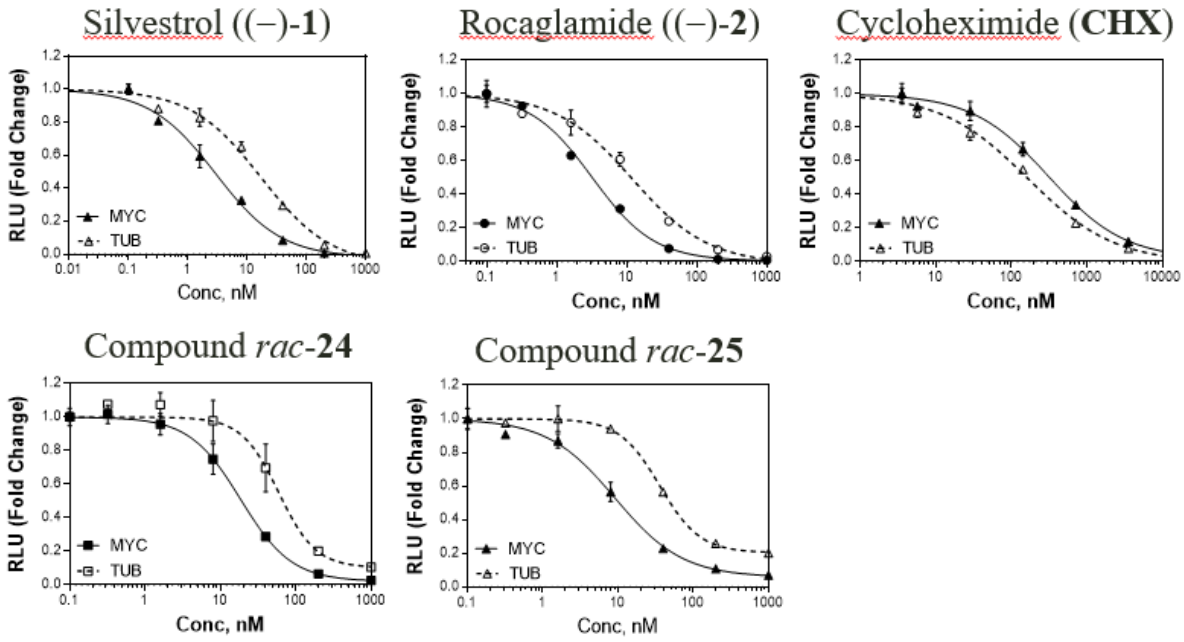


Figure S1: Cell based translation reporter assay. Relative luciferase expressed in the *in vitro* luciferase reporter assay containing either the highly structured 5'-UTR of c-MYC or the short 5'-UTR of tubulin. The luciferase reporter gene constructs were transiently transfected into the MDA-MB-231 cell line and treated with increasing concentrations of compound for 4 hours in triplicate. Data were fitted to a four-parameter dose response curve.

Table S1: Cell based translation reporter assay results for compounds **1**, **2, 24**, **25** and cycloheximide (**CHX**).

Compound	MYC IC_{50} (nM)	TUB IC_{50} (nM)
(–)-1	3	13
(–)-2	3	12
***rac*-24**	19	59
***rac*-25**	9	36
CHX	311	165