Asymmetric Synthesis of Chaetogline A: Expedient Preparation of the Indolizino[8,7-*b*]indole Template and Optical Properties in a Push-Pull Configuration

Antoine Marchi,[a] Rayan Hachem,[a] Thibault Gallavardin,[a] Xavier Franck,[a] Julien Legros,[a] Michaël De Paolis[a,]*
[a] Univ Rouen Normandie, INSA Rouen Normandie, Univ Caen Normandie, ENSICAEN, CNRS, Institut CARMeN UMR 6064, F-76000 Rouen, France
michael.depaolis@univ-rouen.fr

General Information

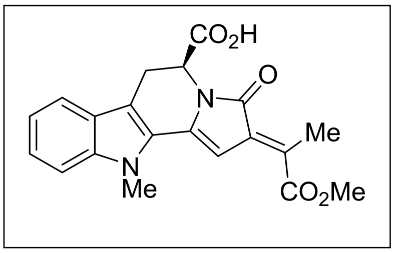
^1H NMR (400 MHz) spectra were recorded respectively on Bruker Ascend EVO 400 in deuterated chloroform $CDCl_3$ and are internally referenced to residual protic $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR (75 MHz and 101 MHz) spectra were recorded on Bruker Ascend EVO 400 in deuterated chloroform $CDCl_3$ and are internally referenced to residual protic $CDCl_3$ (δ 77.16 ppm). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J)* are given in Hertz.

High resolution mass spectra were acquired on Waters LCT Premier apparatus coupled with LC Waters Aquity device or on JEOL AccuTof 4G apparatus coupled with a GC HP Agilent 7890 device. High-resolution mass data were recorded on Q-TOF instrument with an electrospray source in API, EI or ESI mode. Infrared spectra were recorded on Perkin Elmer ATR universal sampler 100 spectrum.

Visualization of thin-layer chromatography (TLC) plates was accomplished with UV (254 nm) and ammonium molybdate staining solution (12 g of ammonium molybdate tetrahydrate, 15 mL of 95% H_2SO_4, 235 mL of distilled water). Purification were carried out by flash column chromatography on silica gel (fcc) unless otherwise mentioned.

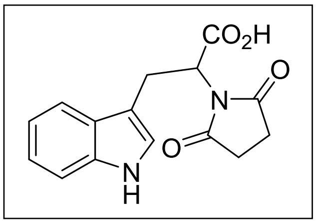
All reactions requiring anhydrous conditions were performed in dried glassware under an atmosphere of argon being purged three times through three argon-vacuum cycles. All reagents have been purchased from commercial suppliers unless otherwise stated. Dry 1,2-dichloroethane, acetonitrile, DMSO and dry methanol were purchased from Sigma Aldrich. Dry dichloromethane, THF and toluene were obtained after filtration (Mbraun SPS-800) and storage on molecular sieves (3 Å). Dry nitrobenzene, fluorobenzene and trifluorotoluene were obtained by storage over 3 Å molecular sieves for 24 h. Dry sulfolane was obtained by keeping the solvent over molecular sieves for 3 h at 40°C. Molecular sieves (3Å) was activated by storage in an oven at ~600°C for 24 h and was kept in an oven at 90°C. Pyridine was distillated on CaH_2 prior use. Acidic brine refers to a mixture of 1 mL of HCl (C= 0.1 M) in 9 mL of brine.

Chaetogline A (1)



In a 25 mL two-neck flask containing 3Å molecular sieves (300 mg/mmol) were added **3b** (60 mg, 1.00 equiv., 0.200 mmol), 1,2-dichloroethane (6 mL) and nitrobenzene (2 mL). The suspension was stirred at 400 rpm for 10 min until full solubilization. TfOH (180 µL, 10 equiv., 2.00 mmol) was slowly added with the flask kept in a water bath (15 °C). The reactor was next fitted with a condenser and was installed into an oil bath at 80 °C and stirred for 3h30 under argon atmosphere. The flask was rapidly placed into another oil bath set at 60 °C, pyrrolidine (334 µL, 4.0 mmol, 20.00 equiv.) and methyl pyruvate (54 µL, 0.60 mmol, 3.00 equiv.) were simultaneously added with two syringes and the mixture was stirred at 500 rpm at 60 °C for 30 minutes. The flask was cool down before transferring the content into a 50 mL Erlenmeyer, washing with Et_2O (15 mL) and saturated $NaHCO_3$ aqueous solution (15 mL). The biphasic system was stirred for 10 min. The organic layer was extracted with an aqueous solution of $NaHCO_3$ (2×15 mL, C= 0,1 M). The aqueous layers were combined and acidified with HCl (C= 1 M) to pH = 1 and extracted with EtOAc (3×30 mL). The combined organic layers were washed with acidic brine, dried over Na_2SO_4 and concentrated under vacuum. Reverse phase purification (PF-15SIHP, F0025; HCO_2H in water 0.1% and acetonitrile) furnished chaetogline A (39 mg) in 53% isolated yield. The *Z*-isomer (5 mg, 7% yield) was found to decompose over time. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 5.19 (d, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.77 (dd, *J* = 16.8, 1.4 Hz, 1H), 3.40 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.49 (s, 3H); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 171.8, 169.3, 169.0, 141.1, 137.2, 136.5, 131.9, 126.8, 126.4, 125.6, 121.1, 120.6, 114.1, 110.8, 98.6, 52.5, 50.5, 31.9, 24.4, 14.9; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{20}H_{17}O_5N_2$ 365.1137; found 365.1134.

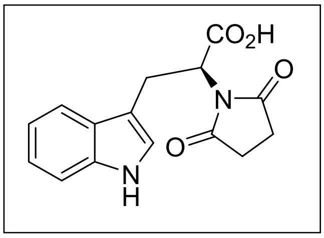
2-(2,5-dioxopyrrolidin-1-yl)-3-(1H-indol-3-yl)propanoic acid ***rac*-3a**



In a 20 mL microwave tube were added *rac*-tryptophan (807 mg, 3.95 mmol, 1.0 equiv.), succinic anhydride (395 mg, 3.95 mmol, 1.0 equiv.) and AcOH (12 mL, 0.33 M). The mixture was heated at 150 °C during 1 h under microwave irradiation and magnetic stirring. The content was transferred into a flask and concentrated under vacuum. The residue was solubilized in EtOAc (100 mL) and washed with brine (3×20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by fcc (CH_2Cl_2/MeOH/HCO_2H, 100/0/0→95/4/1) provided ***rac*-3a** (477 mg, 1.65 mmol) as a white amorphous solid in 33% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.13 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.75 – 3.54 (m, 2H), 2.63 – 2.32 (m, 4H); **^{13}C NMR** (101 MHz, CD_3OD) δ 178.9 (2C), 172.2, 137.9, 128.6, 124.3, 122.4, 119.8, 118.8, 112.3, 111.2, 55.0, 28.8 (2C), 24.6; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{15}H_{13}O_4N_2$ 285.0881; found 285.0880.

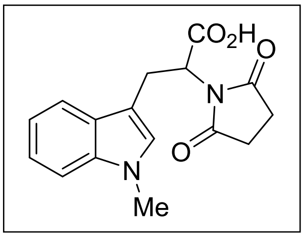
(*S*)-2-(2,5-dioxopyrrolidin-1-yl)-3-(1H-indol-3-yl)propanoic acid (**3a**)

Procedure Table 1 Entry 2: Molecular sieves 3 Å (300 mg), L-tryptophan (408 mg, 2.00 mmol, 1.00 equiv.) and succinic anhydride (202 mg, 2.02 mmol, 1.00 equiv.) were introduced in a 50 mL flask which was purged through three argon-vacuum cycles. Freshly distilled pyridine (20 mL) was added, the flask was sealed and stirred at 90 °C in an oil bath for 61 h. The flask was cool to rt and the volatiles were removed under vacuum. EtOAc (15 mL) and aq. HCl (15 mL; 0.1 M) were added and the mixture was stirred until complete solubilisation. The phases were separated and the organic layer was washed with HCl (2×15 mL, C= 0.1 M) and acidic brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by fcc (30 µm, CH_2Cl_2/MeOH/HCO_2H, 100/0/0 →100/4/1) furnished (*S*)-**3a** (63 mg, 10%, ee: 99%) as a white amorphous solid.



Procedure Table 1 Entry 6: In a 10 mL microwave tube were added **9a** and (60.9 mg, 0.191 mmol) and liquified sulfolane (2 mL) and the mixture was sonicated at 40 °C until the obtention of a homogeneous liquid solution. Then, the mixture was heated at 220 °C for 1 minutes under irradiation microwave. The mixture was then pull into water (30 mL) and extracted using EtOAc (3×10 mL). The organic phase was then washed with brine, dried over Na_2SO_4 and concentrated *in vaccuo*. The crude was then purified by reverse phase (PF-15SIHP, F0012; Water/MeCN; from 100:0 to 20:80) to furnish (*S*)-**3a** (31 mg, 52%, ee: 95%) as a white amorphous solid.

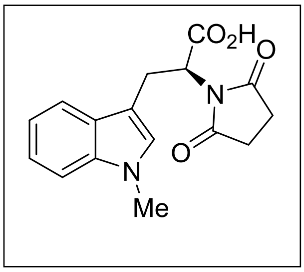
2-(2,5-dioxopyrrolidin-1-yl)-3-(1-methyl-1H-indol-3-yl)propanoic acid ***rac*-3b**



In a 100 mL flask, 1-methyl-D-tryptophan (988 mg, 4.53 mmol, 1.0 equiv.), 1-methyl-L-tryptophan (988 mg, 4.53 mmol, 1.0 equiv.), succinic anhydride (521 mg, 5.21 mmol, 1.15 equiv.) were introduced, followed by 1,2-dichlorobenzene (45 mL). The mixture was stirred at 180 °C for 1 h and poured into 200 mL of ice-cold *n*-hexanes. The solid was filtrated and washed with 200 mL of *n*-hexanes to remove 1,2-dichlorobenzene. Purification by fcc (CH_2Cl_2/MeOH/HCO_2H, 99.9/0/0.1→98.9/1/0.1) provided ***rac*-3b** (618 mg, 2.06 mmol) as a white amorphous solid in 45% yield. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.47 – 7.42 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.14 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.95 (s, 1H), 4.98 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.71 (s, 3H), 3.62 – 3.45 (m, 2H), 2.56 – 2.33 (m, 4H). **^{13}C NMR** (101 MHz, CD_3OD) δ 178.9 (2C), 172.0, 138.4, 129.2, 128.8, 122.5, 119.8, 119.1, 110.6, 110.3, 55.0, 32.7, 28.8 (2C), 24.4; **HRMS** (ESI$^+$) *m/z:* $[M+H]^+$ Calcd for $C_{16}H_{17}O_4N_2$ 301.1188; found 301.1181.

(*S*)-2-(2,5-dioxopyrrolidin-1-yl)-3-(1-methyl-1H-indol-3-yl)propanoic acid (**3b**)

In a 50 mL sealable vial was added *N*-Me-tryptophan (1.00 equiv.), succinic anhydride (1.00 equiv.) and freshly distilled pyridine. The vial was sealed with rubber septa and stirred at 80 °C in an oil bath for 45 minutes, cool to rt and concentrated under vacuum. The residue was treated with EtOAc (15 mL) and HCl (15 mL, C= 0.1 M) and the two layers were stirred until complete solubilization. After separation, the aqueous layer was extracted with EtOAc (3×15 mL) and the combined organic layers were washed with HCl aqueous solution (2×15 mL, C= 0.1 M), acidic brine, dried over Na_2SO_4 and concentrated under vacuum to give **9b** with >95% yield as a white amorphous solid (see p S11 for details).



In a 50 mL flask, (*S*)-**9b** (413 mg, 1.30 mmol, 1.00 equiv.) and DMF (13 mL) were introduced, and the mixture was stirred at 100 °C for 63 h. Once at rt, volatiles were removed and the residue was solubilized in 150 mL of EtOAc, washed with acidic brine (3 ×), dried over Na_2SO_4 and concentrated under vacuum. Purification by fcc (CH_2Cl_2/MeOH/HCO_2H, 99.9/0/0.1→98.9/1/0.1) provided **(*S*)-3b** (390 mg, 2.06 mmol) as a white amorphous solid in >95% yield (98.7:1.3 er).

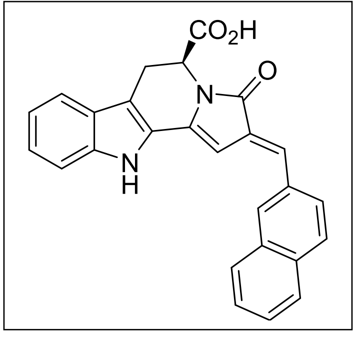
General procedure for the Bischler-Napieralski/isomerization/Mannich coupling of 3a

A 10 mL 2-neck round bottom flask fitted with a condenser and containing a magnetic stirring bar (BRAND®, PTFE, oval L 25 mm, diam. 12 mm), 3 Å molecular sieves (300 mg/mmol) and **3a** (1.0 equiv.) was purged through three argon-vacuum cycles. Under argon, 1,2-dichloroethane (3.0 mL) and fluorobenzene (1.0 mL) were added and the suspension was stirred at 250 rpm for 10 minutes until solubilization. TfOH (90 µL, 1.0 mmol, 10 equiv.) was slowly added to the flask under a water bath (15 °C) before replacing the septum with a glass stopper and installing the flask in an oil bath at 80 °C. After 2 h, the flask was removed from the oil bath to be reacted at rt with aldehydes and at 60°C in oil bath with methyl pyruvate or acetone. Pyrrolidine (170 µL, 2.0 mmol, 20 equiv.) and the electrophile were simultaneously added with two syringes and the mixture was stirred at 500 rpm for either 1 h 15 at rt or for 30 min when operating at 60°C.

A) The content was transferred into a 50 mL Erlenmeyer. EtOAc (15 mL) and HCl (15 mL, C= 0.1 M,) were used to rinse the flask and the mixture was stirred at rt. After 10 minutes, the organic layer was separated and the aqueous one was extracted with EtOAc (3×30 mL) and the combined organic layers were washed with acidic brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by fcc (CH_2Cl_2/MeOH/HCO_2H, 100/0/0→95/4/1) followed by trituration with CH_2Cl_2/Pentane (90/10; 3×4 mL) when necessary, afforded the desired products.

B) The content was transferred into a 50 mL Erlenmeyer and rinsed with Et_2O (15 mL) and 2 mL of (sat.) $NaHCO_3$ aqueous solution. The two phases were separated and the organic layer was extracted twice with 5 mL of (sat.) $NaHCO_3$ aqueous solutions. The combined aqueous layers were made acidic (pH = 1) using HCl (1 M), saturated with solid NaCl and extracted with EtOAc (3×20 mL). The organic layers were dried over Na_2SO_4 and concentrated under vacuum. Purification by trituration with CH_2Cl_2 (3×2 mL) at 0°C afforded the desired product.

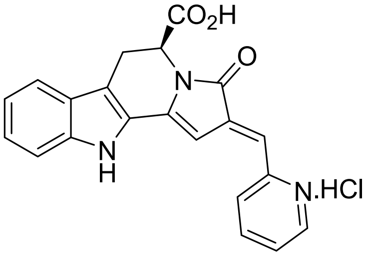
(*E*)-2-(naphthalen-2-ylmethylene)-3-oxo-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indole-5-carboxylic acid (**5a**)



Prepared following the **General procedure A** from **3a** (24.5 mg, 0.086 mmol) and 2-naphthaldehyde (28 µL, 0.178 mmol, 2.08 equiv.). **5a** was obtained in 78% yield (27.0 mg, 0.067 mmol) as an amorphous orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.29 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.98 (ddd, *J* = 9.9, 6.5, 3.5 Hz, 2H), 7.89 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.56

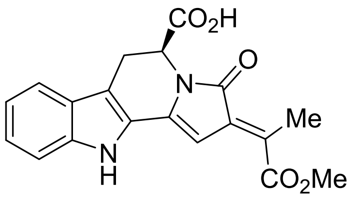
(m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.38 (s, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 3.62 (d, *J* = 16.6 Hz, 1H), 3.38 (dd, *J* = 16.6, 7.3 Hz, 1H). ^{13}**C NMR** (101 MHz, DMSO-d_6) δ 171.9, 169.1, 138.4, 136.6, 133.5, 133.1, 133.0, 130.9, 130.4, 128.9, 128.6, 128.4, 127.8, 127.4, 127.0, 126.2, 125.8, 125.0, 124.3, 119.9, 119.5, 111.8 (2C), 93.9, 50.0, 23.5; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{26}H_{17}N_2O_3$ 405.1245; found 405.1242.

(*E*)-3-oxo-2-(pyridin-2-ylmethylene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indole-5-carboxylic acid (**5b**)



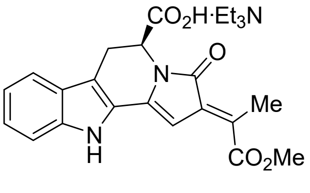
Prepared following the **General Procedure B** from **3a** (27.4 mg, 0.096 mmol) and 2-pyridinecarboxaldehyde (19 µL, 2.10 mmol, 2.10 equiv.). **5b** was obtained in 56% yield (21 mg, 0.054 mmol) as an amorphous dark-yellow solid. ^{1}**H NMR** (400 MHz, CD_3OD) δ 7.92 – 7.86 (m, 1H), 7.38 (s, 1H), 7.03 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.51 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.46 – 6.40 (m, 2H), 6.38 (s, 1H), 6.27 (dd, *J* = 7.5, 0.5 Hz, 1H), 4.36 (d, *J* = 7.1 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.60 (s, 1H).; ^{13}**C NMR** (101 MHz, DMSO-d6) δ 171.9, 169.4, 154.7, 150.2, 138.5, 137.1, 136.9, 133.3, 127.4, 126.3, 125.7, 125.0, 124.3, 123.2, 119.8, 119.5, 112.2, 111.8, 96.1, 29.6, 23.4; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{21}H_{14}N_3O_3$ 356.1035; found 356.1025.

(*E*)-2-(1-methoxy-1-oxopropan-2-ylidene)-3-oxo-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indole-5-carboxylic acid (**5c**)



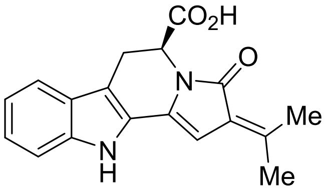
Prepared following the **General Procedure A** from **3a** (28.6 mg, 0.10 mmol) and methyl pyruvate (9 µL, 1.00 mmol, 1.0 equiv.). *E*-**5c** was obtained in 48 % yield (7 mg, 0.020 mmol) as an amorphous orange solid, along 29% yield of *E*/*Z*-**5c**. ^{1}**H NMR** (400 MHz, CD_3OD) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.84 (s, 1H), 5.10 (d, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 3.72 (d, *J* = 16.5 Hz, 1H), 3.42 – 3.34 (m, 1H), 2.49 (s, 3H); ^{13}**C NMR** (101 MHz, CD_3OD) δ 171.3, 170.0, 140.5, 138.0, 137.3, 131.8, 127.3, 126.0, 125.7, 121.1, 120.3, 114.1, 112.7, 97.5, 52.6, 24.7, 14.7; Since one carbonyl signal is overlapped, the ^{13}C spectrum of the carboxylate salt was recorded (see **5c**.Et_3N) to reveal all carbon signals; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{19}H_{15}N_2O_5$ 351.0981; found 351.0972.

Preparation of **5c.Et$_3$N** from **5c**



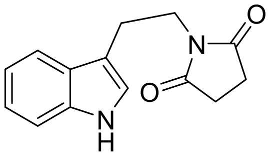
To a solution of **5c** (11 mg, 0.031 mmol, 1.00 equiv.) in CH_2Cl_2 (1 mL) was added Et_3N (10 µL, 0.072 mmol, 2.30 equiv.). The volatiles were removed under vacuum to quantitatively afford ***rac*-5c·Et$_3$N** as orange solid. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.14 – 7.03 (m, 2H), 6.94 (td, *J* = 7.0, 6.5, 1.3 Hz, 1H), 5.97 (s, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 16.3 Hz, 1H), 3.56 (s, 3H), 3.25 (dd, *J* = 16.3, 7.7 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 6H), 2.29 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 9H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 176.9, 169.9, 168.4, 139.7, 137.3, 136.3, 128.7, 126.5, 126.1, 123.8, 119.5, 118.9, 114.1, 112.1, 96.2, 52.2, 51.5, 45.2 (3C), 24.9, 14.7, 8.6 (3C).

Preparation of **5d**



Prepared following the **General Procedure A** from **3a** (28.6 mg, 0.100 mmol) and acetone (22 µL, 0.3 mmol, 3 equiv.). **5d** was obtained in 65% yield (20 mg, 0.070 mmol) as a yellow solid. **^{1}H NMR** (400 MHz, Acetone-*d*$_4$) δ 10.66 (s br, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.18 (m, 1H), 7.07 (m, 1H), 6.22 (s, 1H), 5.13 (d, *J* = 7.0 Hz, 1H), 3.70 (d, *J* = 16.3 Hz, 1H), 3.36 (dd, *J* = 16.3, 7.4 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (101 MHz, Acetone-*d*$_4$) δ 172.3, 168.3, 148.1, 139.15, 131.2, 129.3, 127.4, 124.3, 120.6, 119.7, 112.3, 112.2, 110.7, 95.0, 50.5, 24.4, 23.8, 20.3; **HRMS** (ESI$^-$) *m/z:* [M-H]$^-$ Calcd for $C_{18}H_{15}N_2O_3$ 307.1083; found 307.1091.

1-(2-(1H-indol-3-yl)ethyl)pyrrolidine-2,5-dione (**7**) [1]



Tryptamine (4.8 g, 30.0 mmol, 1.0 equiv.), succinic anhydride (3.0 g, 30.0 mmol, 1.0 equiv.), AcOH (90 mL) and toluene (30 mL) were introduced in a 250 mL flask. The mixture was stirred at 115 °C for 24 h. Once at rt, the volatiles were removed under vacuum and purification through a pad of silica gel (CH_2Cl_2/Cyclohexane, 50/50) furnished **7** as a yellow solid in 46% yield (1.1 g, 13.8 mmol). **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 10.89 – 10.78 (m, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.00 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 3.64 – 3.58 (m, 2H), 2.91 – 2.84 (m, 2H), 2.61 (s, 4H). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 177.7 (2C), 136.2, 127.1, 122.9, 121.0, 118.4, 117.9, 111.5, 110.6, 39.7, 28.1 (2C), 23.1

General procedure from tryptamine derivative 7

In a 25 mL 2-neck flask fitted with a condenser, a magnetic stirrer bar (BRAND®, PTFE, oval L 25 mm, diam. 12 mm) and containing 3 Å molecular sieves (300 mg/mmol) was introduced **7** (1.0 equiv.). The flask was purged through three argon-vacuum cycles before introducing PhCl (3 mL) and $PhCF_3$ (1 mL). The suspension was stirred at 250 rpm for 10 minutes until full solubilization. TfOH (89 µL, 1.0 mmol, 10 equiv.) was slowly added with the flask kept cool in a water bath (15 °C), then the septum was replaced by a glass stopper and the flask was installed in an oil bath at 90 °C and stirred for 30 minutes. The flask was installed into an oil bath at 25 °C and after 5 min, pyrrolidine (170 µL, 2.0 mmol, 20 equiv.), the electrophile (1.15 equiv.) were added. The reaction was stirred at 500 rpm at 25 °C for 75 minutes. Saturated $NaHCO_3$ aqueous solution (2 mL) was introduced and the content of the flask was transferred into 50 mL Erlenmeyer, rinsing with EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by fcc was followed by trituration with cold (0 °C) CH_2Cl_2/Pentane (90/10, 3×4 mL), afforded the desired products **8a-i**.

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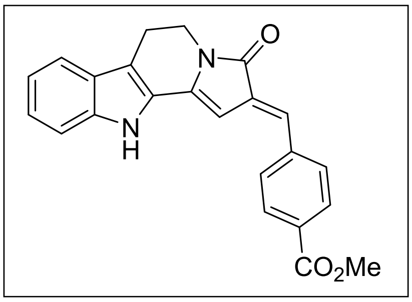
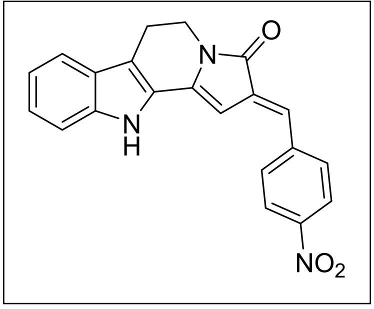
[1] I. T. Raheem, P. S. Thiara, E. A. Peterson, *J. Am. Chem. Soc.* **2007**, *129*, 13404.

Methyl (*E*)-4-((3-oxo-6,11-dihydro-3H-indolizino[8,7-b]indol-2(5H) ylidene)methyl)benzoate (**8a**)



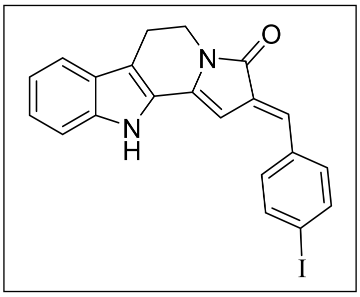
Prepared following the **General Procedure** from **7** (23.8 mg, 0.098 mmol) and 4-formylbenzoate (18.5 mg, 0.113 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8a** in 71% yield (26.0 mg, 0.07 mmol) as an amorphous orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.21 (s, 1H), 7.08 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.83 (t, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.3, 165.8, 140.5, 138.5, 138.5, 132.7, 129.8 (2C), 129.7 (2C), 129.2, 126.4, 125.7, 124.9, 124.4, 119.8, 119.7, 115.2, 111.9, 92.6, 52.3, 37.2, 20.0; **HRMS** (ESI$^+$) *m/z:* $[M-H]^+$ Calcd for $C_{23}H_{19}O_3N_2$ 371.1390; Found 371.1391.

(*E*)-2-(4-nitrobenzylidene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8b**)



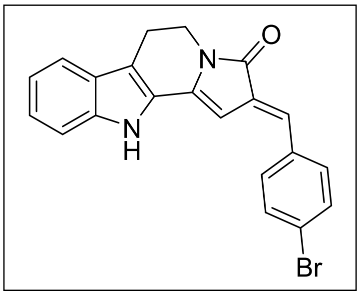
Prepared following the **General Procedure** from **7** (25.0 mg, 0.103 mmol) and 4-nitrobenzaldehyde (17.9 mg, 0.119 mmol). Purification by fcc (CH_2Cl_2/acetone 100/0→97/3) afforded **8b** (60% yield, *E*/*Z*, 96/4, 22 mg, 0.062 mmol) as an amorphous dark-red solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.64 – 7.60 (m, 1H), 7.45 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.23 (s, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.67 (d, *J* = 1.1 Hz, 1H), 3.84 (t, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.2, 146.6, 142.6, 139.4, 138.7, 133.9, 130.4 (2C), 125.7, 125.0, 124.8, 124.7, 124.1 (2C), 119.8, 119.8, 115.9, 111.9, 92.4, 37.2, 20.0; **HRMS** (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}O_3N_3$ 358.1186; Found 358.1186.

(*E*)-2-(4-iodobenzylidene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8c**)



Prepared following the **General Procedure** from **7** (23.7 mg, 0.098 mmol) and 4-iodobenzaldehyde (26.1 mg, 0.112 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8c** in 68% yield (29 mg, 0.067 mmol) as an amorphous dark-yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.89 – 7.85 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.12 (s, 1H), 7.12 – 7.04 (m, 1H), 6.61 (s, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.3, 138.4, 137.9 (2C), 137.6, 135.4, 131.5 (2C), 131.4, 127.2, 125.7, 125.0, 124.3, 119.7, 119.6, 114.8, 111.8, 96.0, 92.6, 37.2, 20.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}ON_2{}^{127}I$ 439.0302; Found 439.0302.

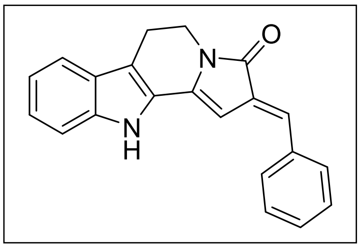
(*E*)-2-(4-bromobenzylidene)-2,5,6,11-tetrahydro-3H-



indolizino[8,7-b]indol-3-one (**8d**)

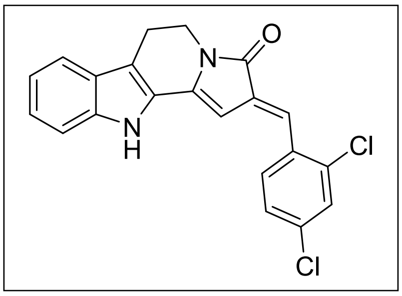
Prepared following the **General Procedure** from **7** (23.1 mg, 0.095 mmol) and 4-bromobenzaldehyde (20.3 mg, 0.11 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8d** in 38% yield (14.0 mg, 0.036 mmol) as an amorphous dark-yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.69 (q, J = 8.7 Hz, 4H), 7.61 (d, J = 8.0 Hz, 1H), 7.44 (dt, J = 8.3, 1.0 Hz, 1H), 7.24 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.16 (s, 1H), 7.08 (ddd, J = 7.9, 7.0, 1.1 Hz, 1H), 6.62 (d, J = 1.1 Hz, 1H), 3.83 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.3, 138.4, 137.6, 135.1, 132.0 (2C), 131.5, 131.4 (2C), 126.9, 125.7, 125.0, 124.3, 122.5, 119.7, 119.6, 114.8, 111.8, 92.5, 37.2, 20.0; **HRMS** (ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{16}ON_2{}^{79}Br$ 391.0441; Found 391.0443.

(*E*)-2-benzylidene-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8e**)



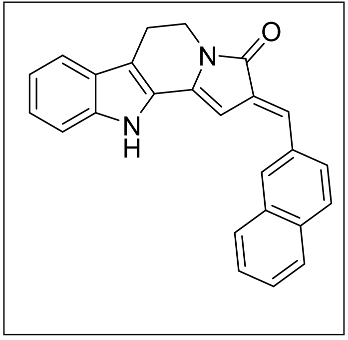
Prepared following the **General Procedure** from **7** (242 mg, 1.0 mmol) and benzaldehyde (122 mg, 1.15 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8e** in 58% yield (182 mg, 0.58 mmol) as an amorphous orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.43 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.67 (s, 1H), 3.82 (t, J = 6.4 Hz, 2H), 3.10 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.4, 138.3, 137.2, 135.9, 131.0 (2C), 129.8, 129.3 (2C), 129.1, 128.5, 125.8, 125.1, 124.1, 119.7, 119.5, 114.4, 111.8, 92.8, 37.2, 20.0; **HRMS** (ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{17}ON_2$ 313.1335; Found 313.1336.

(*E*)-2-(2,4-dichlorobenzylidene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8f**)



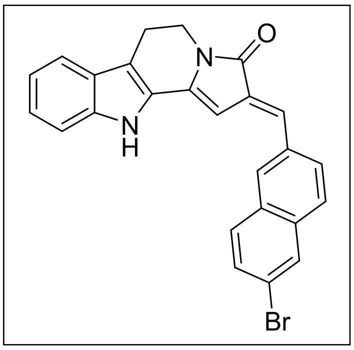
Prepared following the **General Procedure** from **7** (24.2 mg, 0.100 mmol) and 2,4-dichlorobenzaldehyde (20.1 mg, 0.115 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8f** in 67% yield (21 mg, 0.067 mmol) as an amorphous orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.5, 2.0 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.25 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.13 – 7.04 (m, 1H), 6.61 (d, J = 1.0 Hz, 1H), 3.83 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.2, 138.5, 138.3, 136.7, 132.3, 131.8, 131.2, 131.1, 130.8, 129.6, 125.7, 125.2, 124.9, 124.4, 119.8, 119.7, 115.2, 111.8, 92.2, 37.2, 19.9; **HRMS** (ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{15}ON_2{}^{35}Cl_2$ 381.0556; Found 381.0556.

(*E*)-2-(naphthalen-2-ylmethylene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8g**)



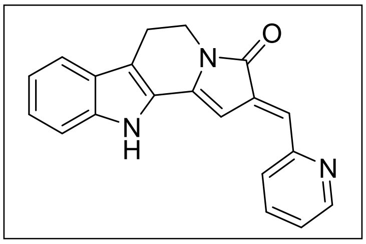
Prepared following the **General Procedure** from **7** (24.7 mg, 0.102 mmol) and 2-naphthaldehyde (18.3 mg, 0.117 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8g** in 70% yield (25.9 mg, 0.071 mmol) as an amorphous deep-orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.29 – 8.24 (m, 1H), 8.03 (d, J = 8.6 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.87 (dd, J = 8.6, 1.7 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.46 (dt, J = 8.3, 1.0 Hz, 1H), 7.36 (s, 1H), 7.24 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.08 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.81 (s, 1H), 3.85 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.9, 138.8, 137.7, 134.0, 133.6, 133.4, 131.6, 130.8, 129.0, 129.0, 128.8, 128.2, 127.7, 127.4, 126.7, 126.2, 125.6, 124.6, 120.2, 120.0, 115.0, 112.2, 93.4, 37.7, 20.4; **HRMS** (ESI^{+}) *m/z*: [M+H]$^{+}$ Calcd for $C_{25}H_{19}ON_2$ 363.1492; Found 363.1491.

(*E*)-2-((6-bromonaphthalen-2-yl)methylene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8h**)



Prepared following the **General Procedure** from **7** (24.4 mg, 0.101 mmol, 1 equiv.) and 6-bromo-2-naphthaldehyde (27.2 mg, 0.116 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→95/5) afforded **8h** in 43% yield (19.1 mg, 0.043 mmol) as amorphous deep-orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.29 (s, 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.71 (dd, J = 8.7, 2.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.33 (s, 1H), 7.24 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.78 (s, 1H), 3.85 (t, J = 6.4 Hz, 2H), 3.13 (t, J = 6.5 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.4, 138.4, 137.5, 134.2, 134.0, 131.6, 131.6, 130.5, 130.0, 129.9, 129.7, 127.9, 127.8, 127.4, 125.8, 125.1, 124.2, 120.4, 119.7, 119.6, 114.7, 111.8, 92.8, 37.2, 20.0; **HRMS** (ESI^{+}) *m/z*: [M+H]$^{+}$ Calcd for $C_{25}H_{18}ON_2{}^{79}Br$ 441.0597; Found 441.0595.

(*E*)-2-(pyridin-2-ylmethylene)-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indol-3-one (**8i**)

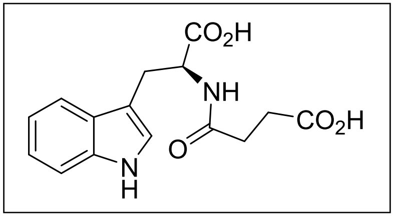


Prepared following the **General Procedure** from **7** (23.3 mg, 0.096 mmol) and 2-pyridinecarboxaldehyde (10 μL, 1.15 mmol). Purification by fcc (CH_2Cl_2/acetone, 100/0→90/10) afforded **8i** in 70% yield (21 mg, 0.067 mmol) as amorphous dark-yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.74 (dd, J = 5.0, 1.8 Hz, 1H), 7.86 (td, J = 7.7, 1.9 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.35 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.21 (s, 1H), 7.15 (s, 1H), 7.10 – 7.05 (m, 1H), 3.83 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.8, 154.8, 150.2, 138.6, 137.8, 136.9, 133.5, 127.4, 126.0, 125.7, 125.2, 124.2, 123.1, 119.7, 119.6, 115.0, 111.8, 95.4, 37.1, 20.0; **HRMS** (ESI^{+}) *m/z*: [M+H]$^{+}$ Calcd for $C_{20}H_{16}ON_3$ 314.1288; Found 314.1291.

General procedure for preparing 9a,b

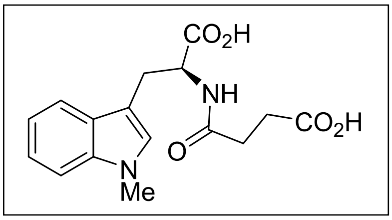
In a 50 mL sealable vial was added L-tryptophan or derivative (1.00 equiv.), succinic anhydride (1.00 equiv.) and freshly distilled pyridine. The vial was sealed with rubber septa and stirred at 80 °C in an oil bath for 45 minutes, cool to rt and concentrated under vacuum. The residue was treated with EtOAc (15 mL) and HCl (15 mL, C= 0.1 M) and the two layers were stirred until complete solubilization. After separation, the aqueous layer was extracted with EtOAc (3×15 mL) and the combined organic layers were washed with HCl aqueous solution (2×15 mL, C= 0.1 M), acidic brine, dried over Na_2SO_4 and concentrated under vacuum to give **9a,b** with >95% yield as a white amorphous solid.

(*S*)-4-((1-carboxy-2-(1H-indol-3-yl)ethyl)amino)-4-oxobutanoic acid (**9a**)



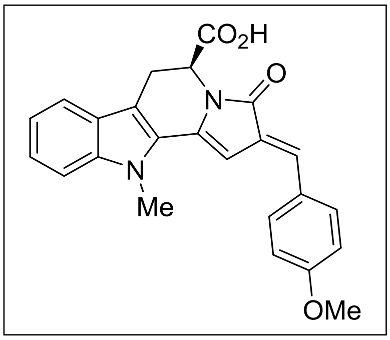
Prepared in quantitative yield following the **General Procedure** from L-tryptophan (202 mg, 0.99 mmol), succinic anhydride (99.0 mg, 0.99 mmol) in pyridine (20 mL). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.73 (dd, *J* = 7.5, 5.3 Hz, 1H), 3.36 (dd, *J* = 14.7, 5.3 Hz, 1H), 3.18 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.54 – 2.43 (m, 4H); **^{13}C NMR** (101 MHz, CD_3OD) δ 176.2, 75.2, 174.3, 138.0, 128.9, 124.4, 122.4, 119.8, 119.3, 112.2, 110.9, 54.7, 31.4, 30.1, 28.5; **HRMS** (ESI^-) *m/z:* $[M-H]^-$ Calcd for $C_{15}H_{15}N_2O_5$ 303.0981; found 303.0972.

(*S*)-4-((1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-4-oxobutanoic acid (**9b**)



Prepared following the **General Procedure** from 1-methyl-L-tryptophan (2.07 g, 9.5 mmol), succinic anhydride (0.95 g, 9.5 mmol) in pyridine (100 mL). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.60 – 7.54 (m, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.08 – 6.99 (m, 2H), 4.72 (dd, *J* = 7.5, 5.3 Hz, 1H), 3.73 (s, 3H), 3.36 (dd, *J* = 14.7, 5.3 Hz, 1H), 3.18 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.55 – 2.43 (m, 4H); **^{13}C NMR** (101 MHz, CD_3OD) δ 176.2, 175.1, 174.3, 138.5, 129.4, 128.9, 122.5, 119.8, 119.6, 110.3, 110.2, 54.9, 32.7, 31.3, 30.1, 28.3; **HRMS** (ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{17}N_2O_5$ 317.1137; found 317.1143.

(*E*)-2-(4-methoxybenzylidene)-11-methyl-3-oxo-2,5,6,11-tetrahydro-3H-indolizino[8,7-b]indole-5-carboxylic acid (**10**)

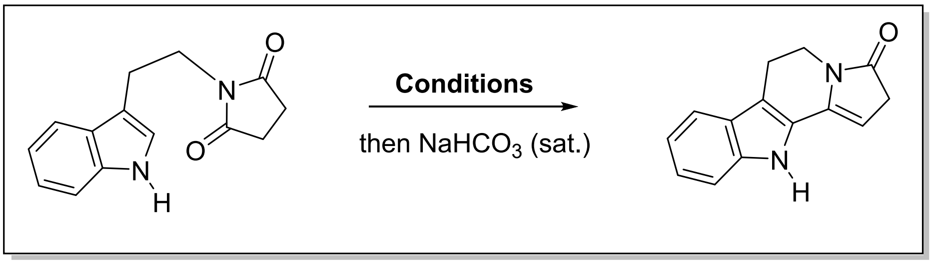


In a 25 mL two-neck flask containing 3Å molecular sieves (300 mg/mmol) were added **3b** (30 mg, 1.00 equiv., 0.100 mmol), 1,2-dichloroethane (3 mL) and nitrobenzene (1 mL). The suspension was stirred at 400 rpm for 10 min until full solubilization. TfOH (90 µL, 10 equiv., 1.00 mmol) was slowly added with the flask kept in a water bath (15 °C). The reactor was next fitted with a condenser and was installed into an oil bath at 80 °C and stirred for 3h30 under argon atmosphere. The flask was rapidly placed into another oil bath set at 60 °C, pyrrolidine (170 µL, 4.0 mmol, 10.00 equiv.) and *p*-anisaldehyde (37 µL, 0.20 mmol, 3.00 equiv.) were simultaneously added with two syringes and the mixture was stirred at 500 rpm at 60 °C for 30 minutes. The flask was cool down before transferring the content into a 50 mL Erlenmeyer, washing with Et_2O (15 mL) and saturated $NaHCO_3$ aqueous solution (15 mL). The biphasic system was stirred for 10 min. The organic layer was extracted with an aqueous solution of

$NaHCO_3$ (2×15 mL, C= 0,1 M). The aqueous layers were combined and acidified with HCl (C= 1 M) to pH = 1 and extracted with EtOAc (3×30 mL). The combined organic layers were washed with acidic brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was triturated with CH_2Cl_2/Pentane (50/50; 2×2 mL) and the solid was purified by reverse phase purification (PF-15SIHP, F0025; HCO_2H in water 0.1% and acetonitrile) to furnished **10** (26 mg) as amorphous solid with 70% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 7.27 (d, *J* = 3.9 Hz, 2H), 7.11 (m, 1H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.45 (s, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.71 (d, *J* = 16.3 Hz, 1H), 3.25 (dd, *J* = 16.3, 7.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9, 169.6, 160.9, 139.8, 134.0, 132.6, 132.2 (2C), 128.8, 128.1, 126.4, 125.6, 124.4, 120.3, 119.7, 114.6 (2C), 111.7, 109.5, 95.4, 77.4, 55.5, 31.6, 23.6; **HRMS (ESI^-)** *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O_4$ 401.1501; found 401.1486.

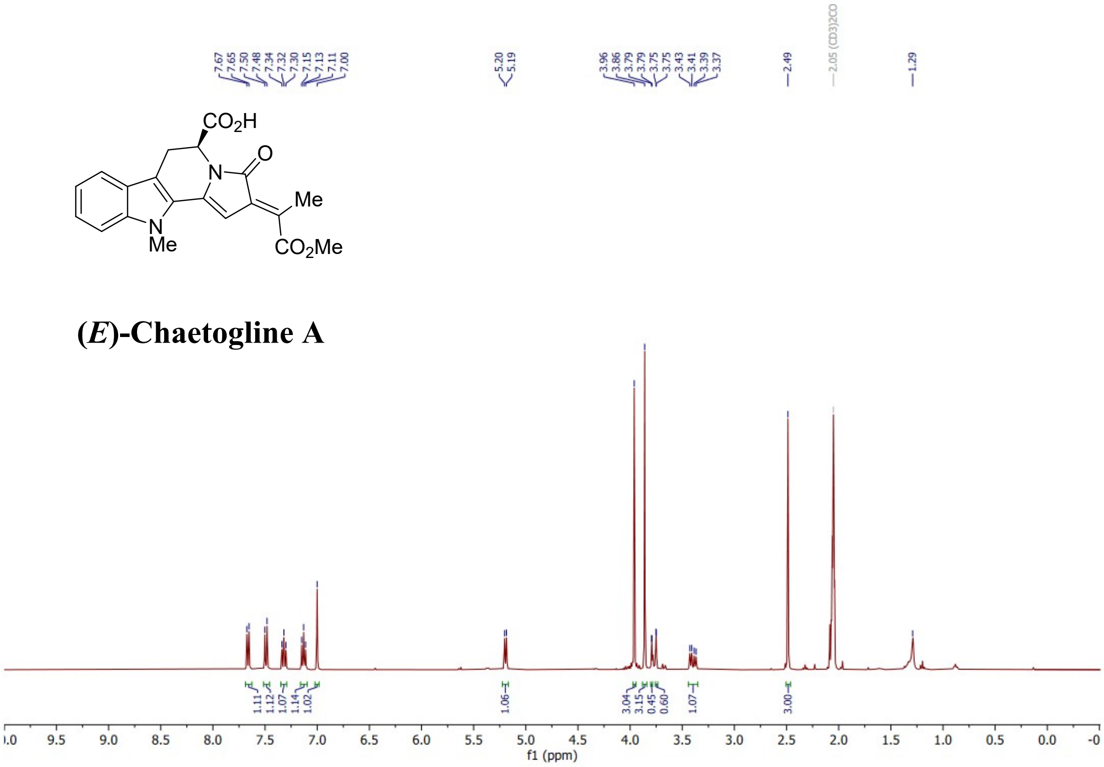
Optimization of the Bischler-Napieralski cyclization

The optimization was guided primarily by the solubilization of both the starting material and the intermediates, and eventually the compatibility with pyrrolidine for the Mannich coupling. In some cases, the solubility was partial and gummy material was observed on the sides of the flask. Conditions of Entry 9 gave the best result in terms of solubility and reproducibility. Less TfOH induced an incomplete conversion (Entry 10).

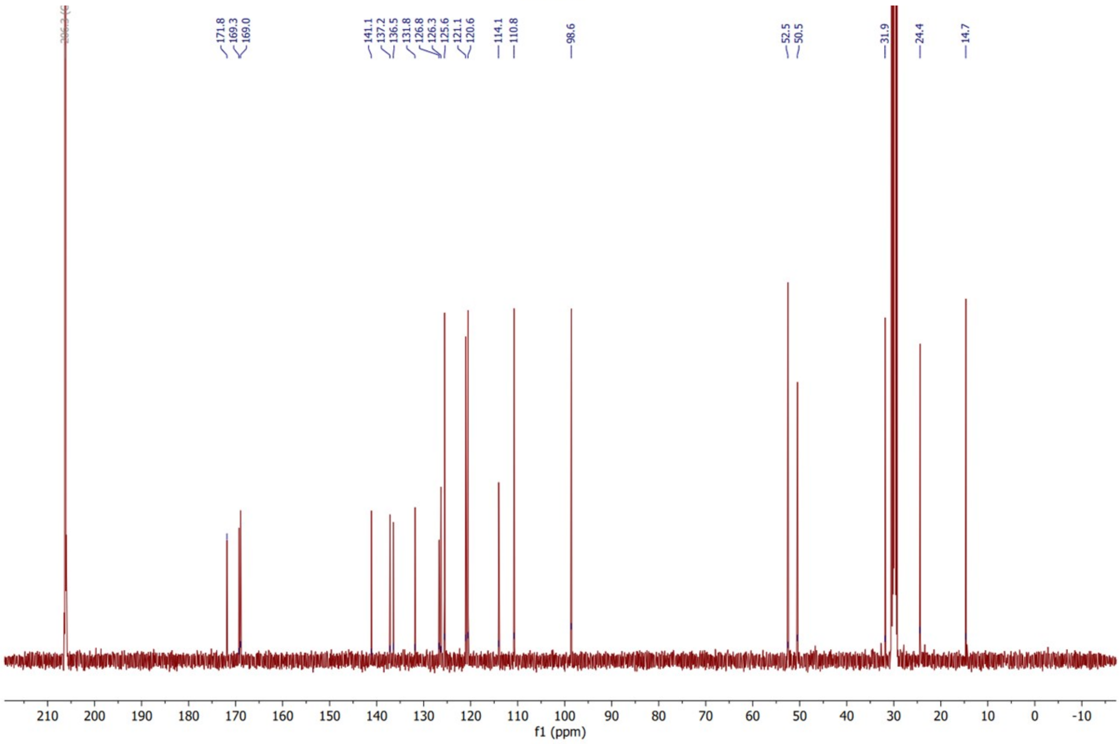


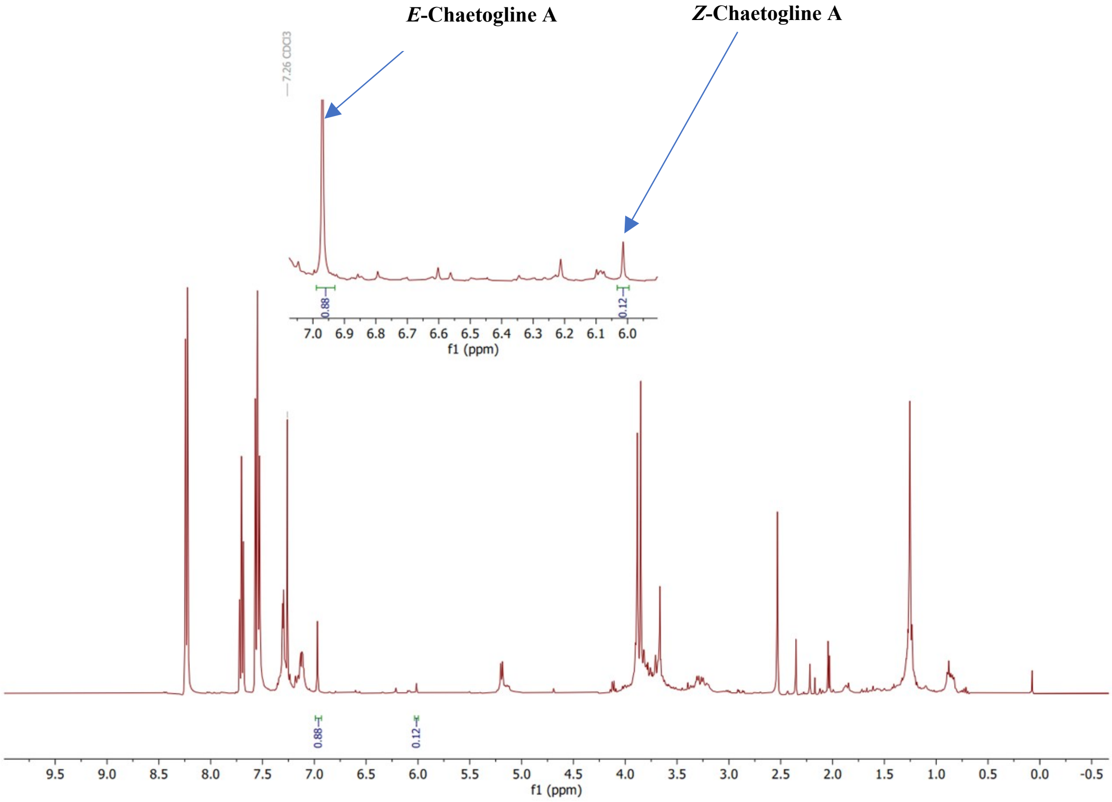
Entry	**Conditions**	**Conversion**	**Observations**
1	TfOH (4.0 equiv.), CH_2Cl_2 (0.14 M), Air, r.t. 0.5 h	10%	partially soluble
2	TfOH (5.3 equiv.), CH_2Cl_2 (0.14 M), Air, r.t. **16 h**	10%	partially soluble
3	TfOH **(10 equiv.)**, CH_2Cl_2 **(0.02 M),** MS (3 Å), Ar, rt, 15h	38%	partially soluble
4	TfOH (10 equiv.), CH_2Cl_2 **(0.01 M)**, MS (3 Å), Ar, **50 °C**, 15 h	100%[a]	partially soluble, degradation
5	TfOH (10 equiv.), CH_2Cl_2 (0.01 M), MS (3 Å), Ar, 50 °C, **2 h**	21%	partially soluble
6	TfOH (10 equiv.), **$CHCl_3$** (0.02 M), MS (3 Å), Ar, **50 °C, 2 h**	100%	not reproductible
7	TfOH (10 equiv.), $CHCl_3$ (**0.01 M**), MS (3 Å), Ar, 50 °C, **0.5 h**	22%	partially soluble
8	TfOH (10 equiv.), **$PhCl/CH_3NO_2$** (3/1; **0.03 M**), MS (3 Å), Ar, **90 °C**, 0.5 h	100%	soluble
9	TfOH (10 equiv.), PhCl/**$PhCF_3$** (3/1; 0.03 M), MS (3 Å), Ar, 90 °C, 0.5 h	100%	soluble
10	TfOH (**6 equiv.**), $PhCl/PhCF_3$ (3/1; 0.03), MS (3 Å), Ar, 90 °C, 0.5 h	75%	soluble

^{1}H NMR (400 MHz, Acetone-d_6), ^{13}C NMR (101 MHz, Acetone-d_6) and crude of the reaction ($CDCl_3$)

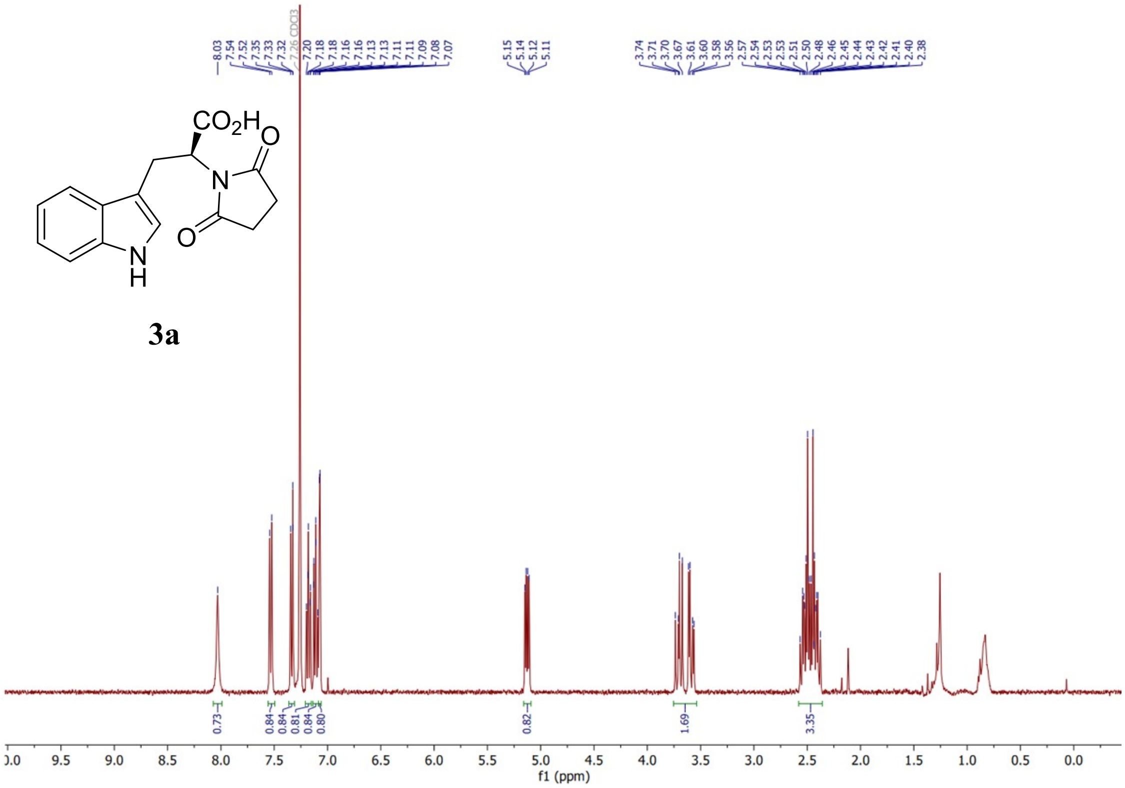


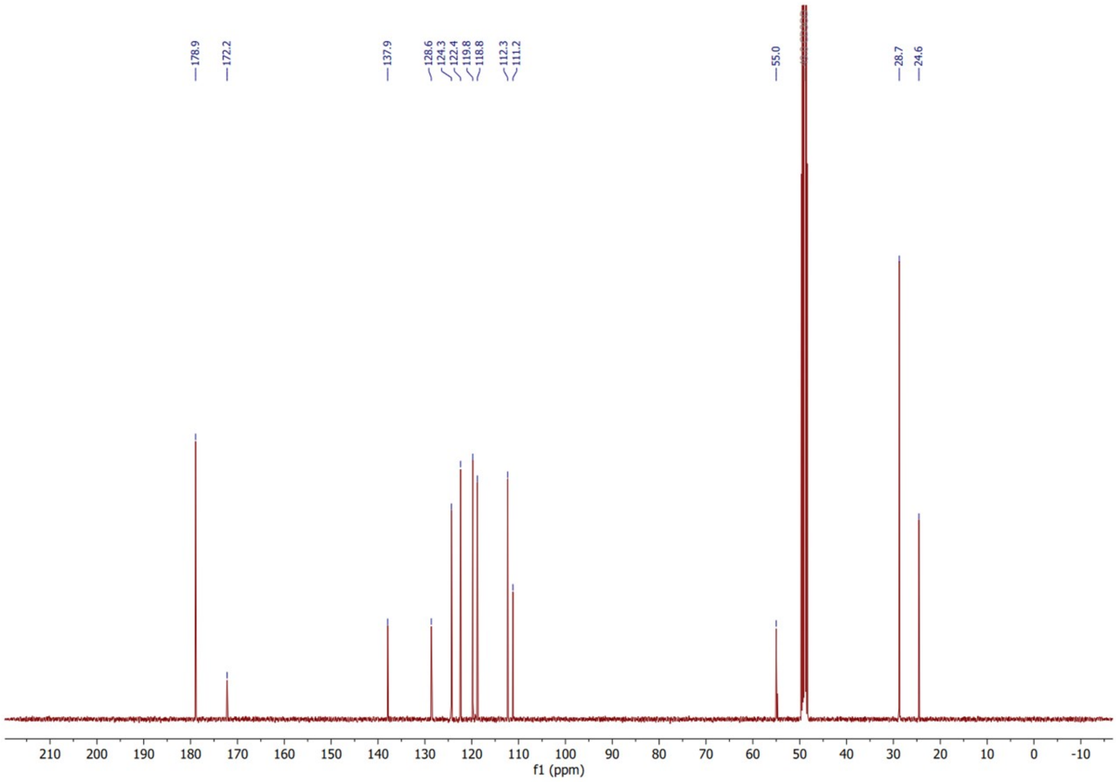
(*E*)-Chaetogline A



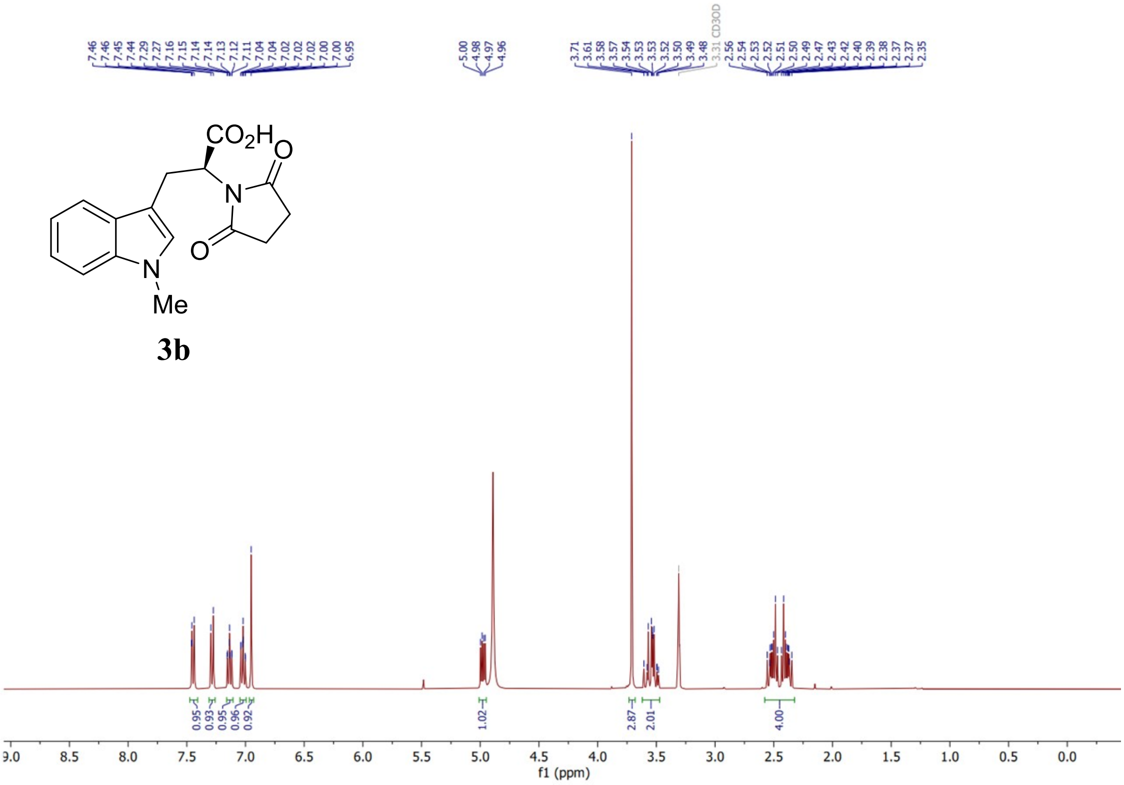

E-Chaetogline A
Z-Chaetogline A
7.26 CDCl3
0.88
0.12
7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0
f1 (ppm)
0.88
0.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

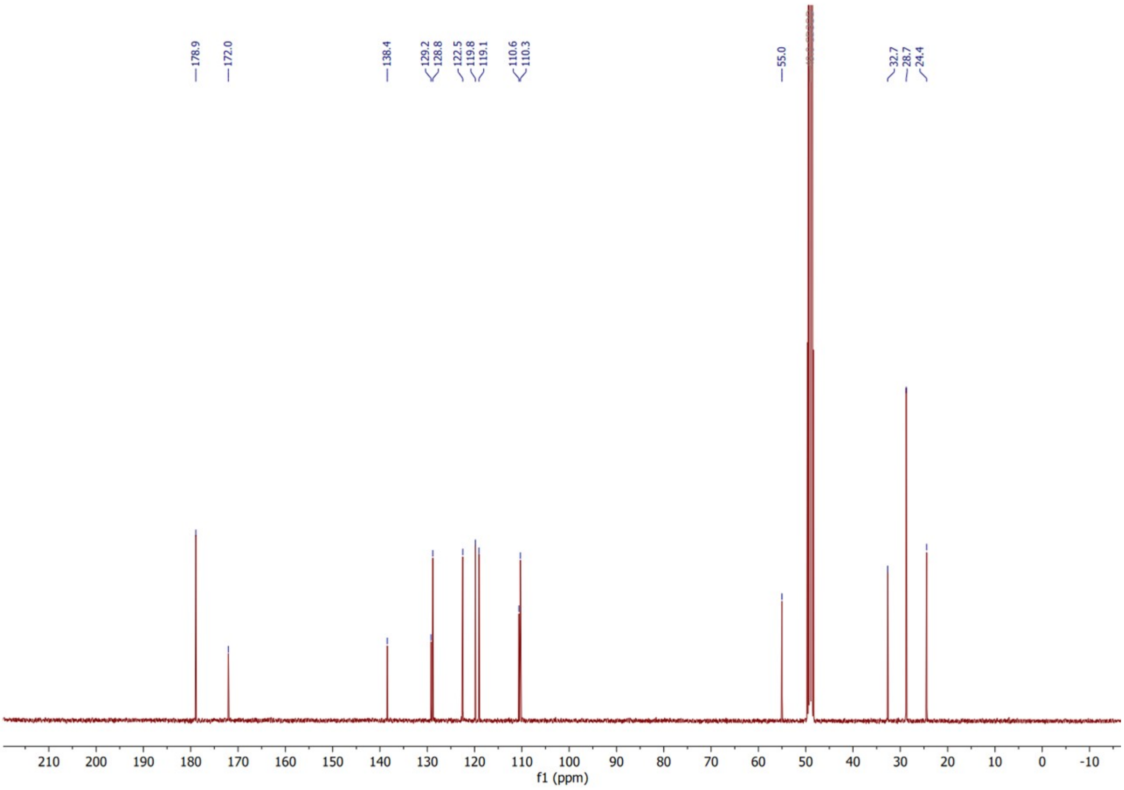
^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, Methanol-d_4)



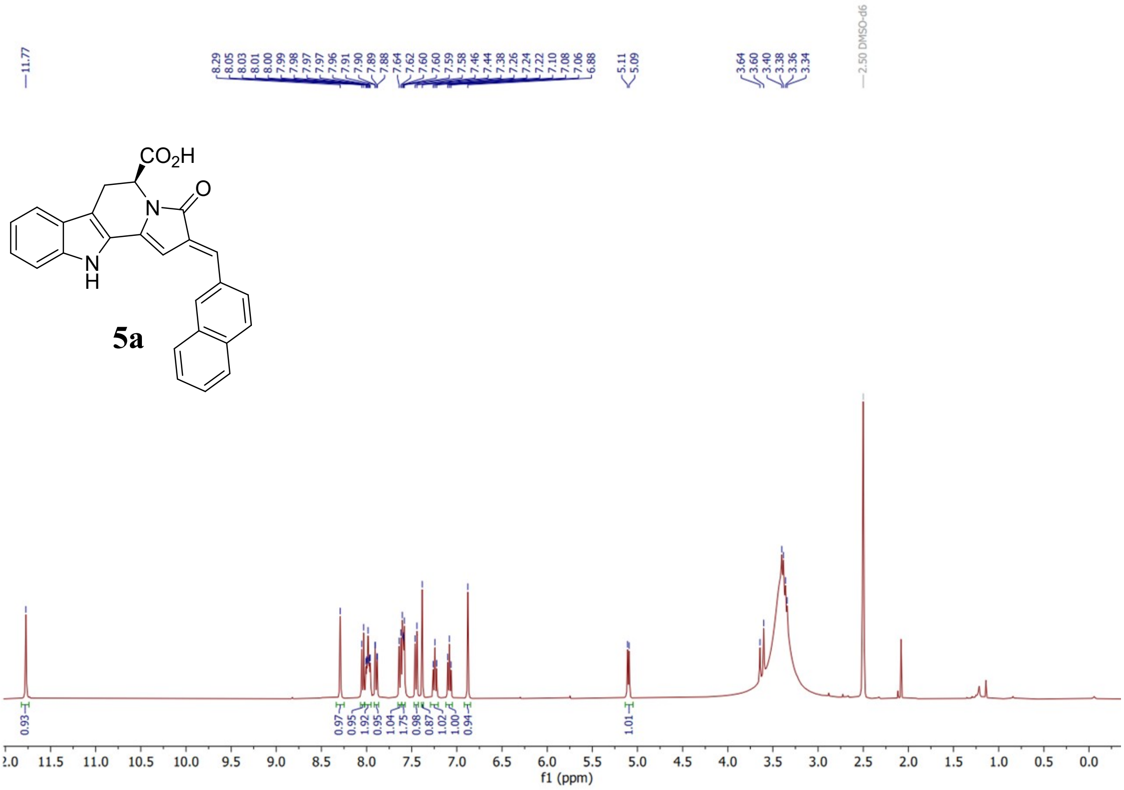


^{1}H NMR (400 MHz, Methanol-d_4) and ^{13}C NMR (101 MHz, Methanol-d_4)

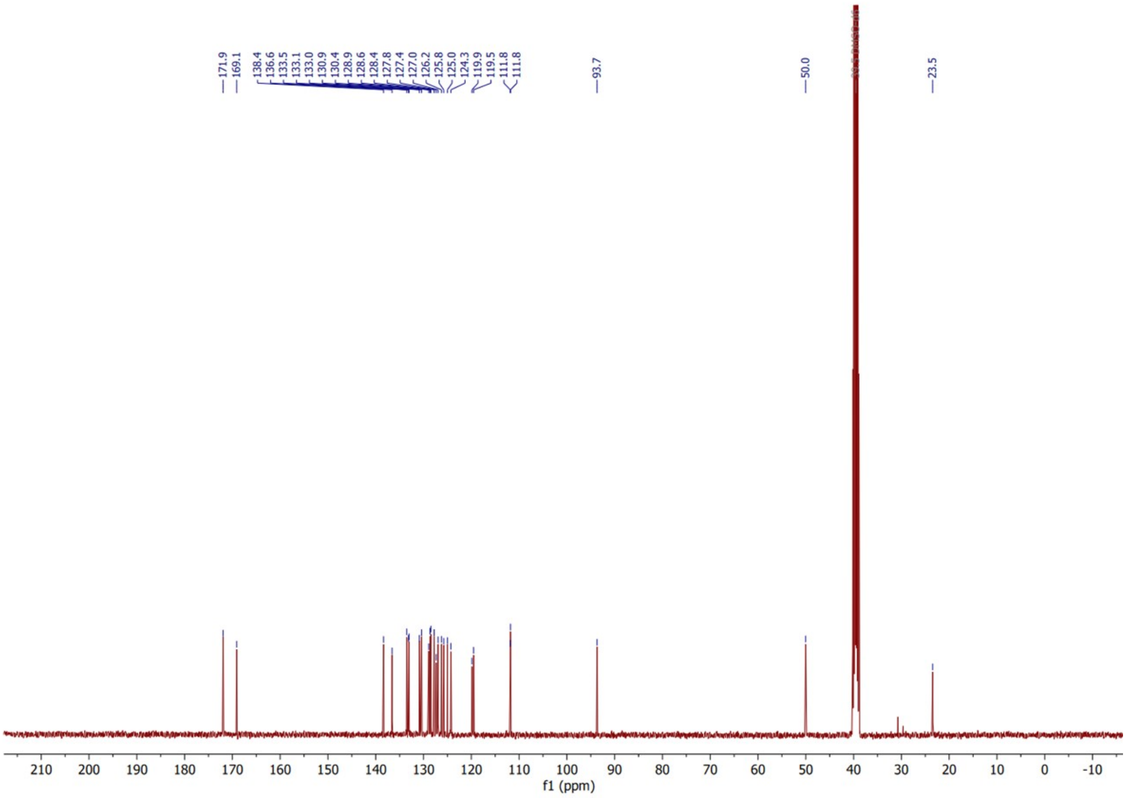




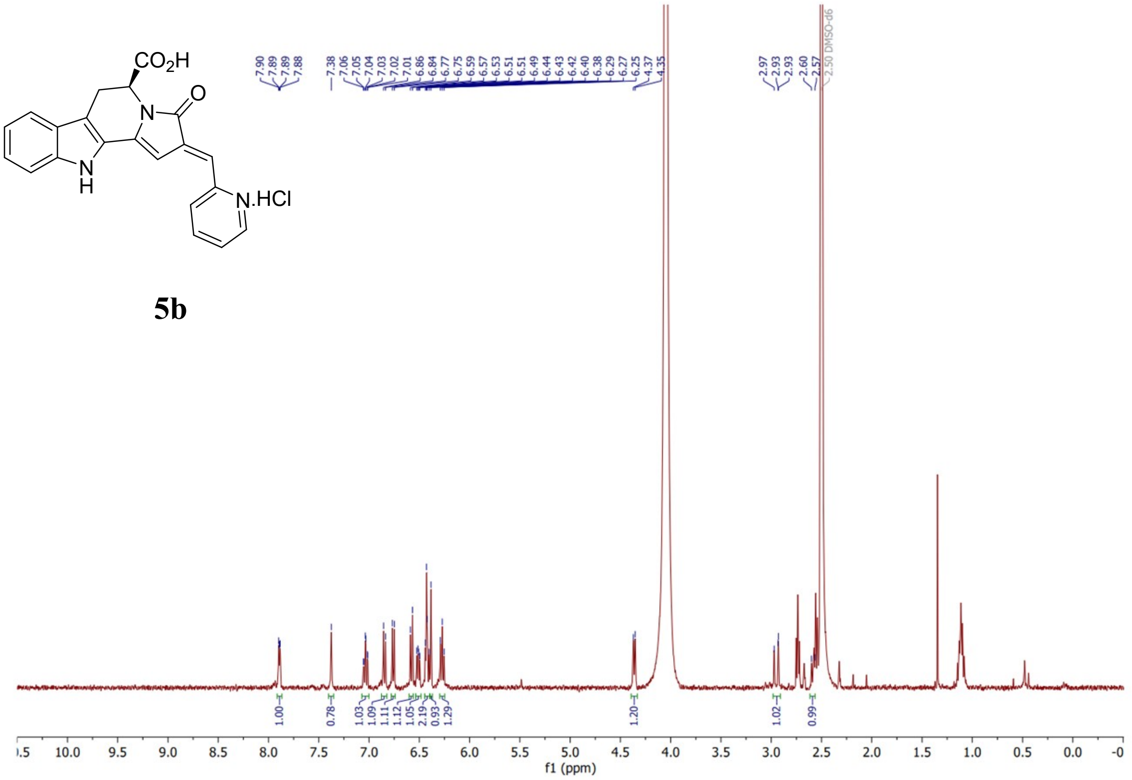
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



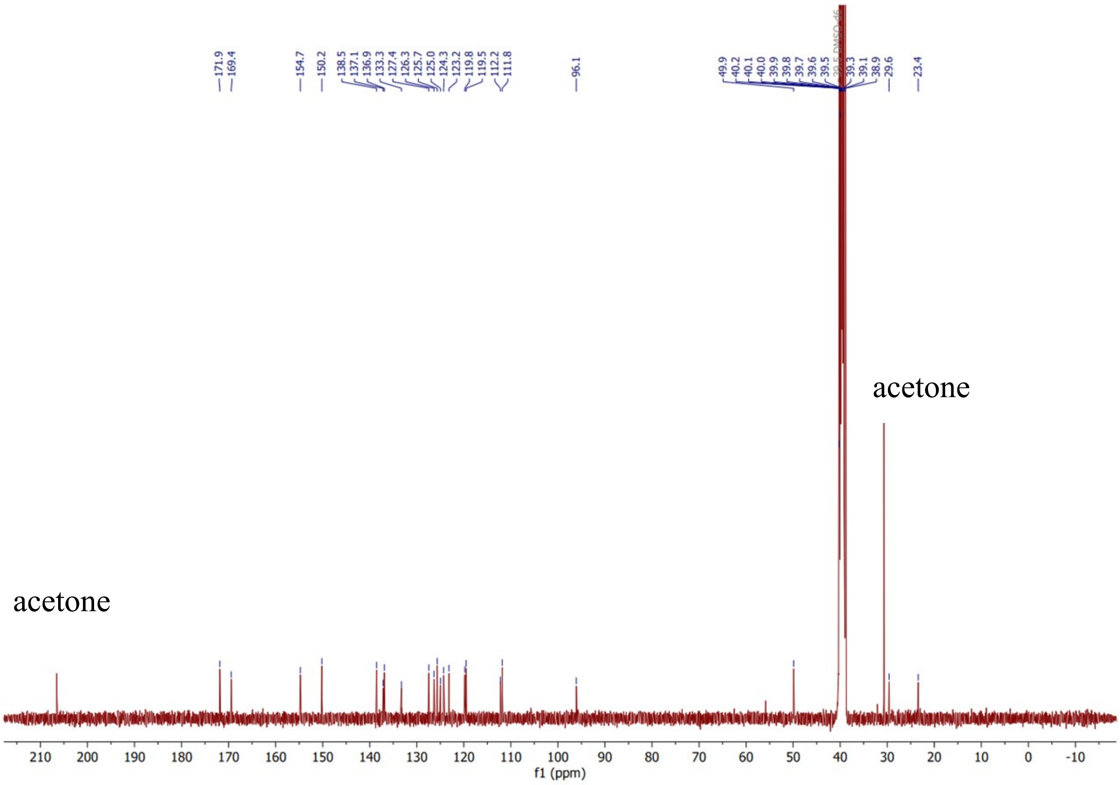
5a



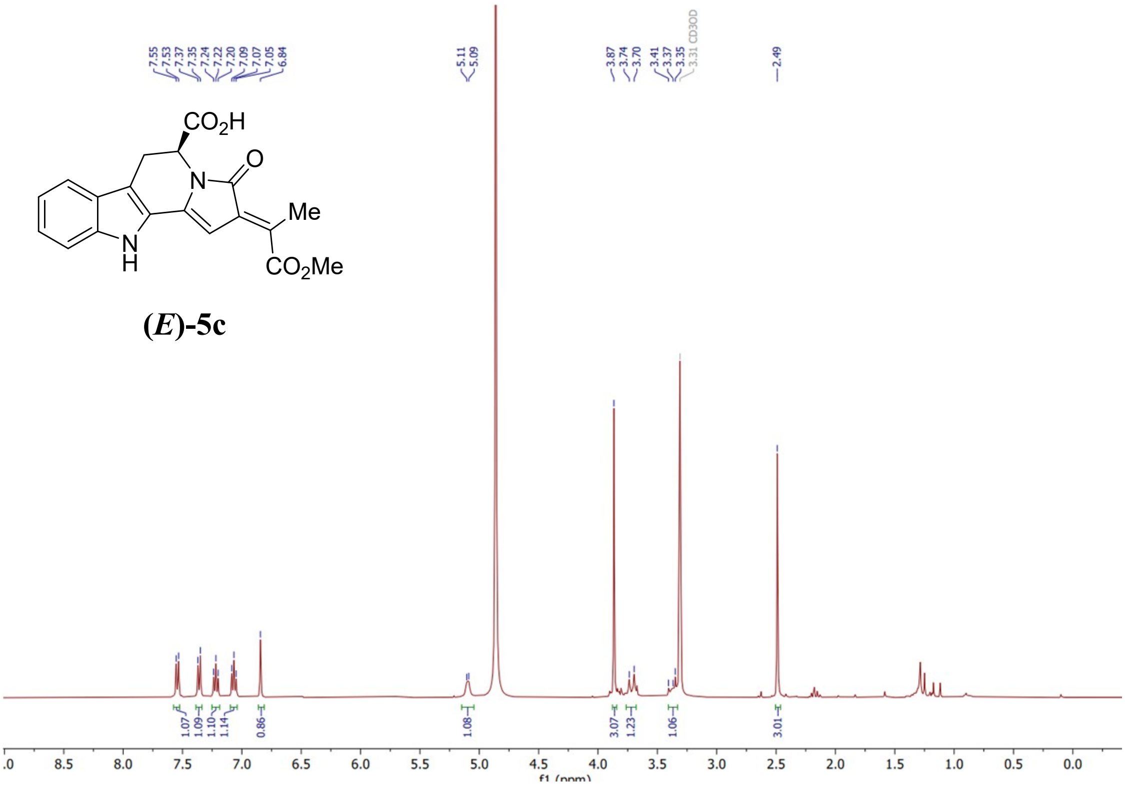
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



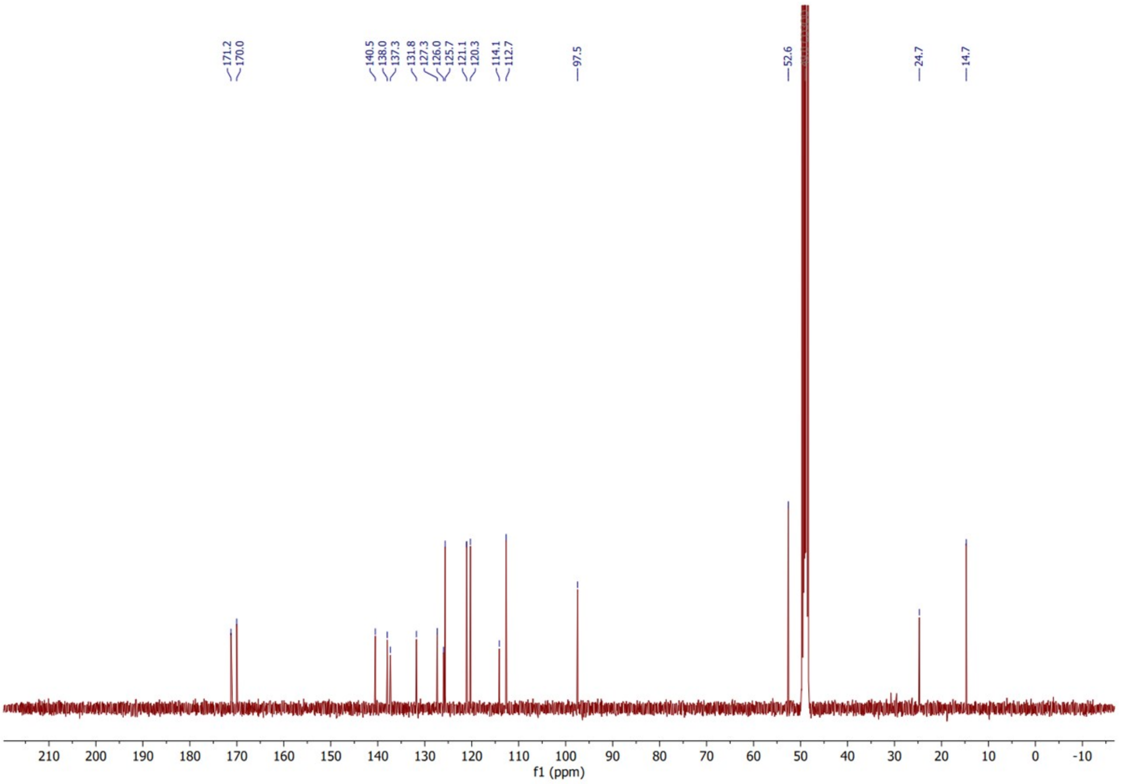
5b



^{1}H NMR (400 MHz, Methanol-d_4) and ^{13}C NMR (101 MHz, Methanol-d_4)

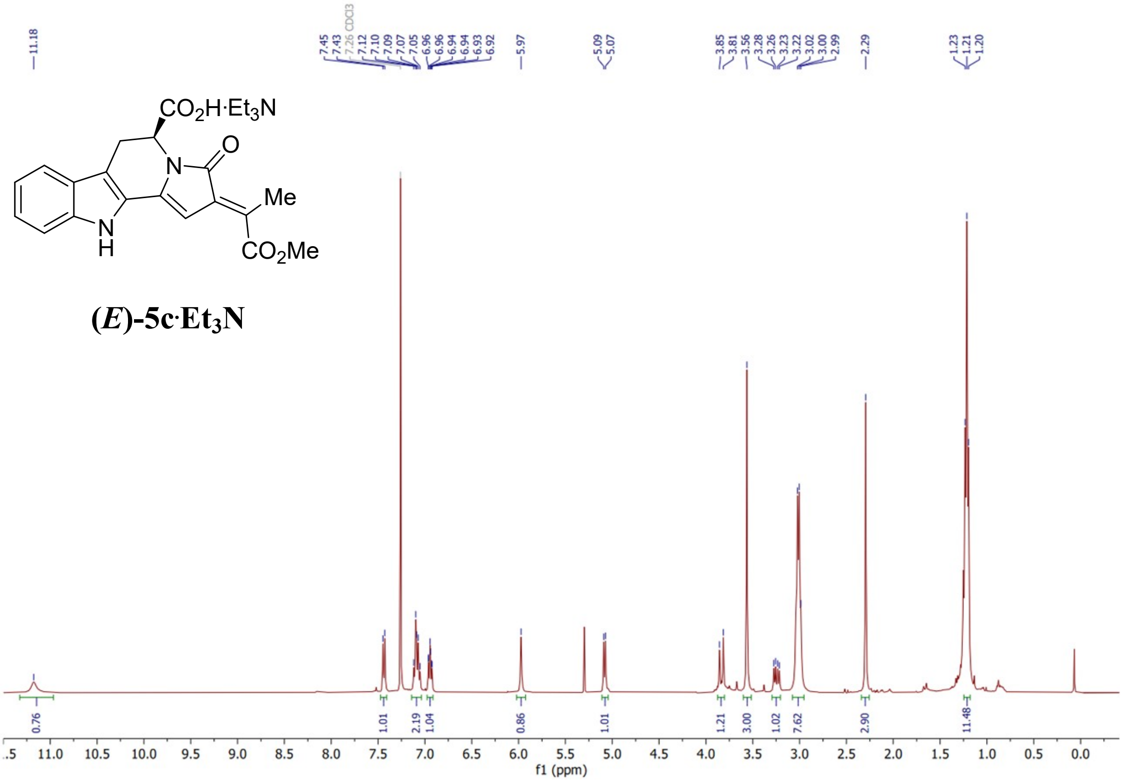


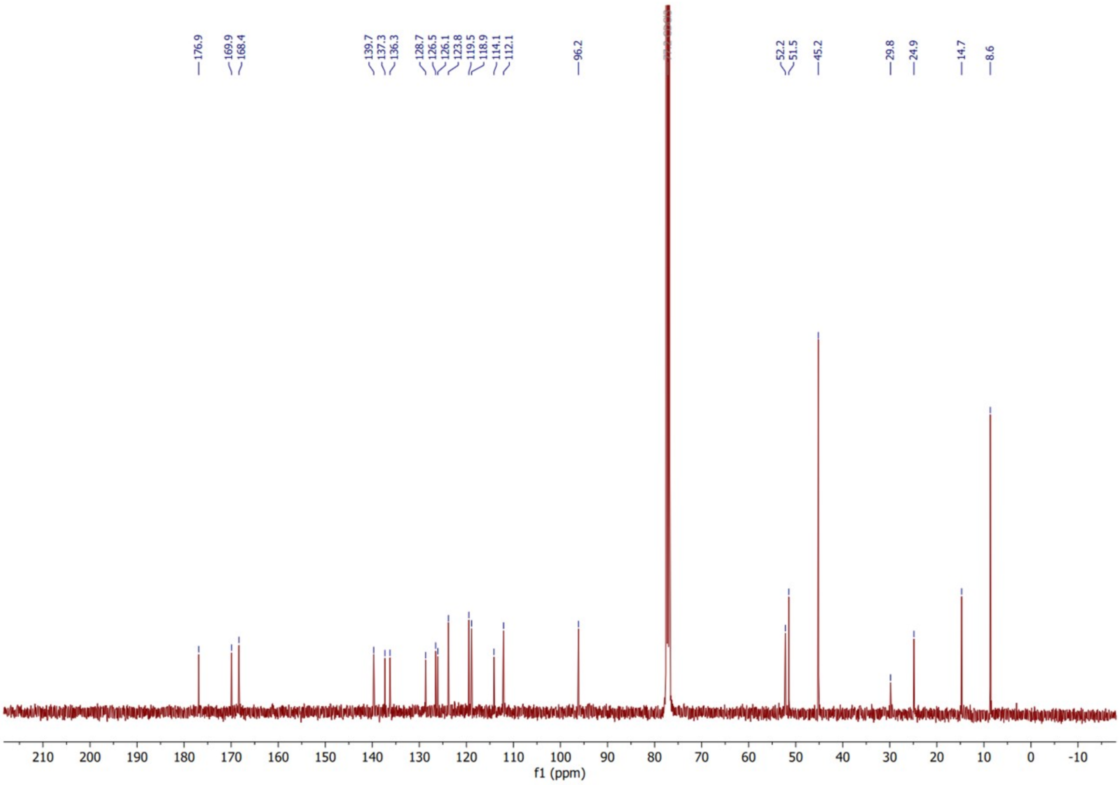
(*E*)-5c



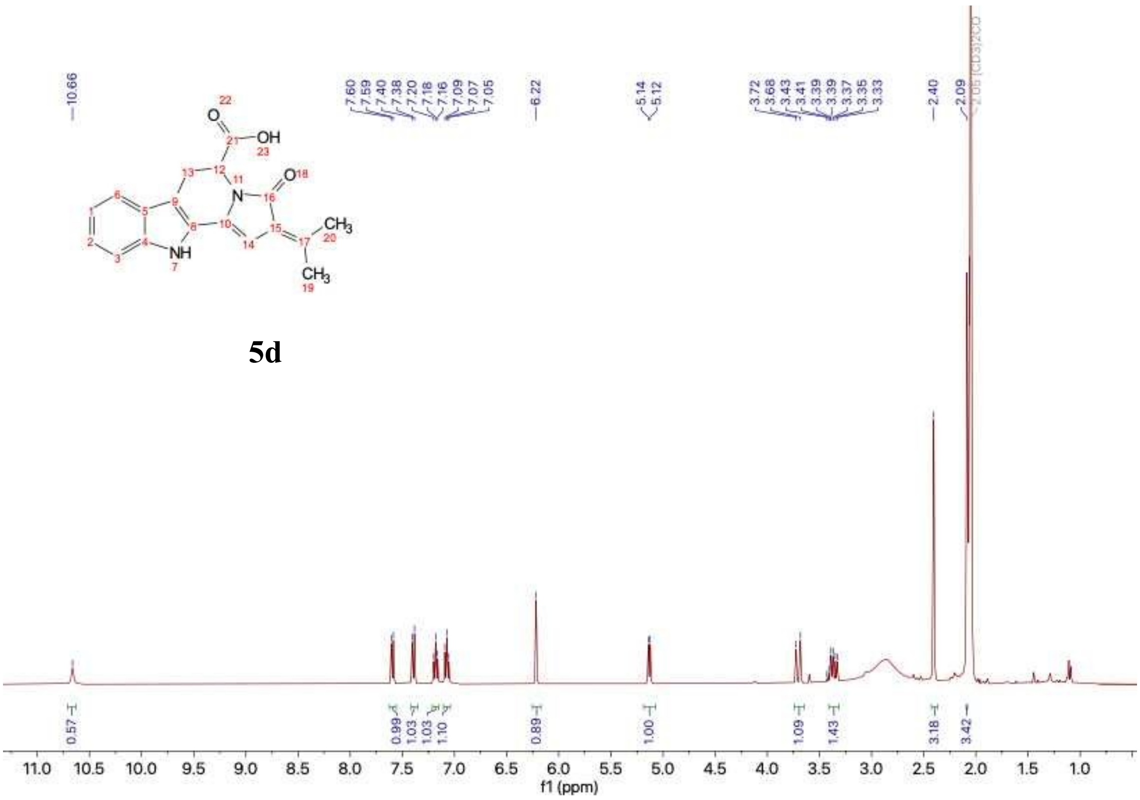
^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$)

(*E*)-5c·Et$_3$N

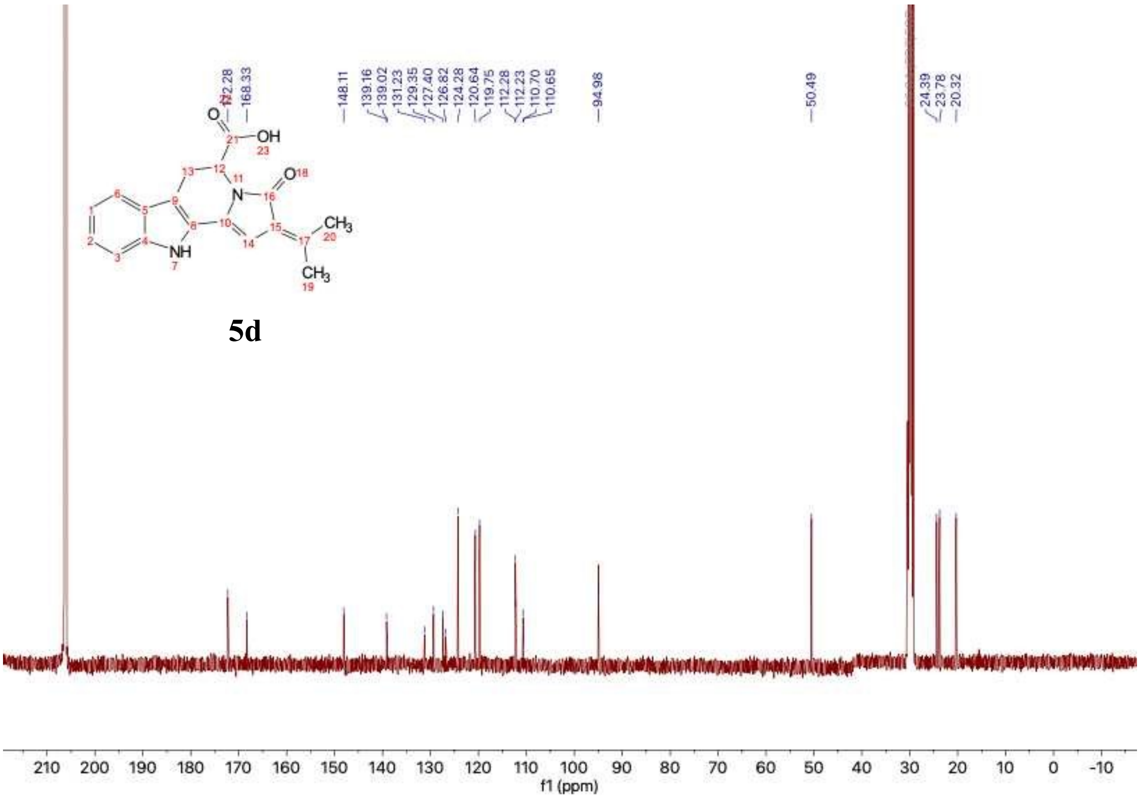




^{1}H NMR (400 MHz, acetone-*d_6*) and ^{13}C NMR (101 MHz, acetone-*d_6*)

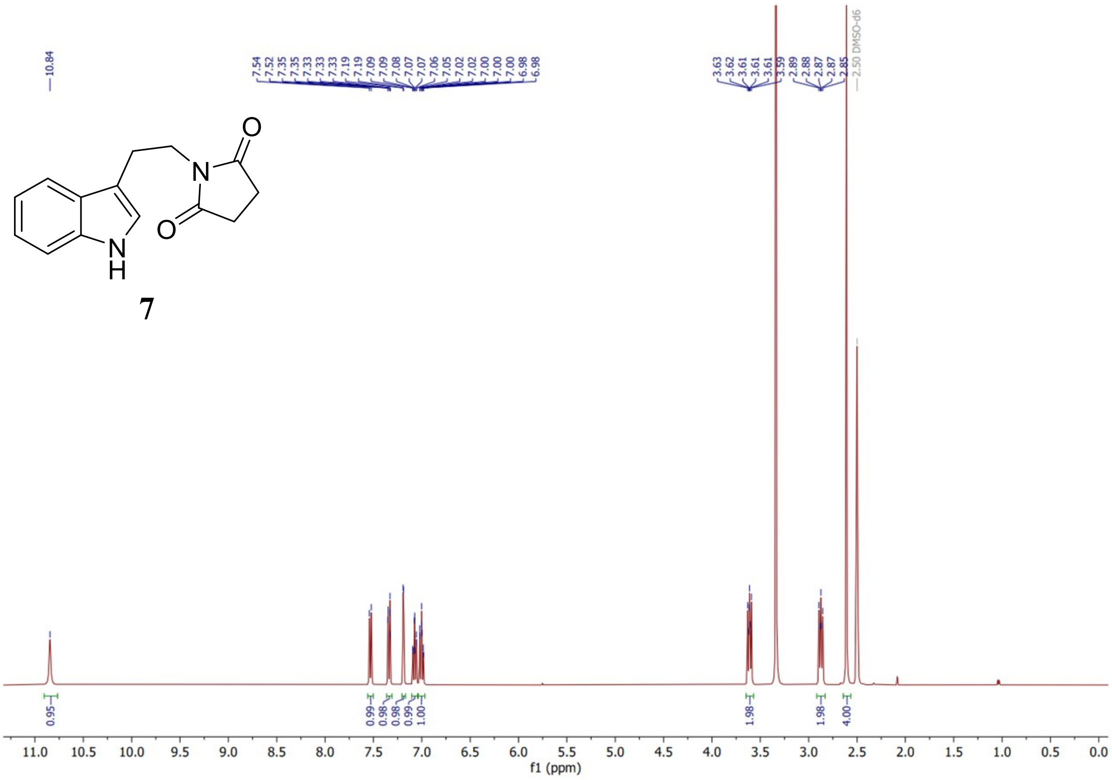


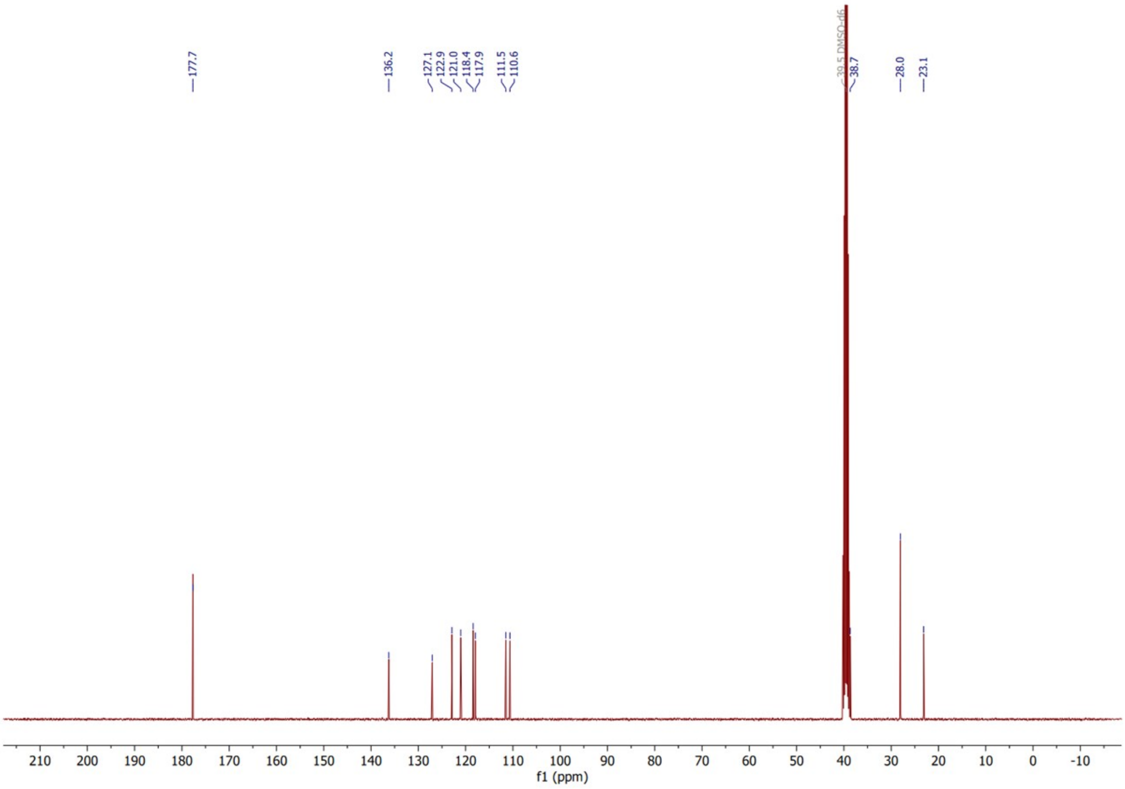
5d



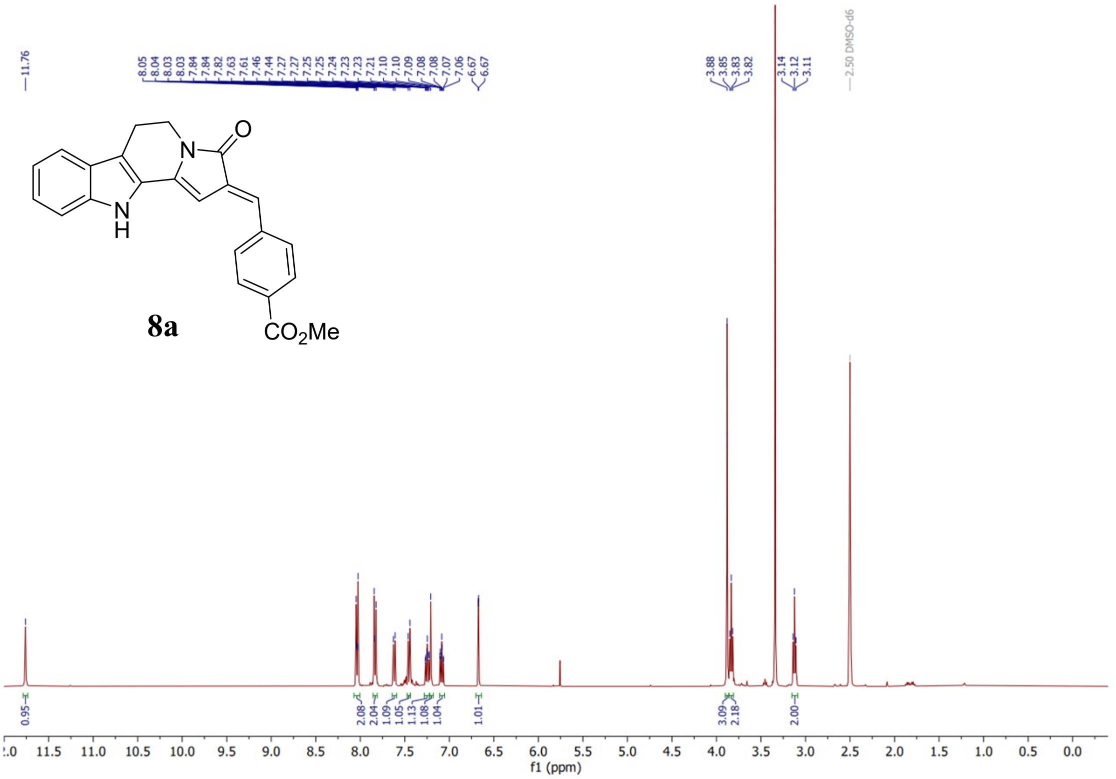
5d

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)

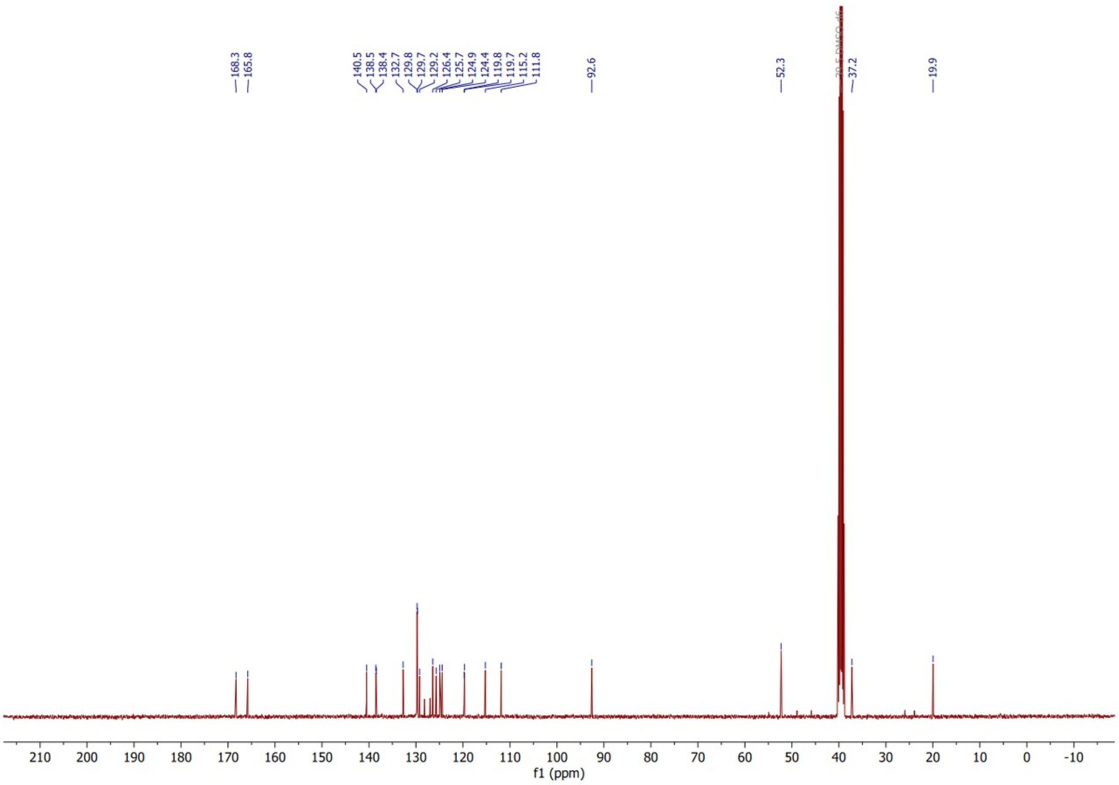




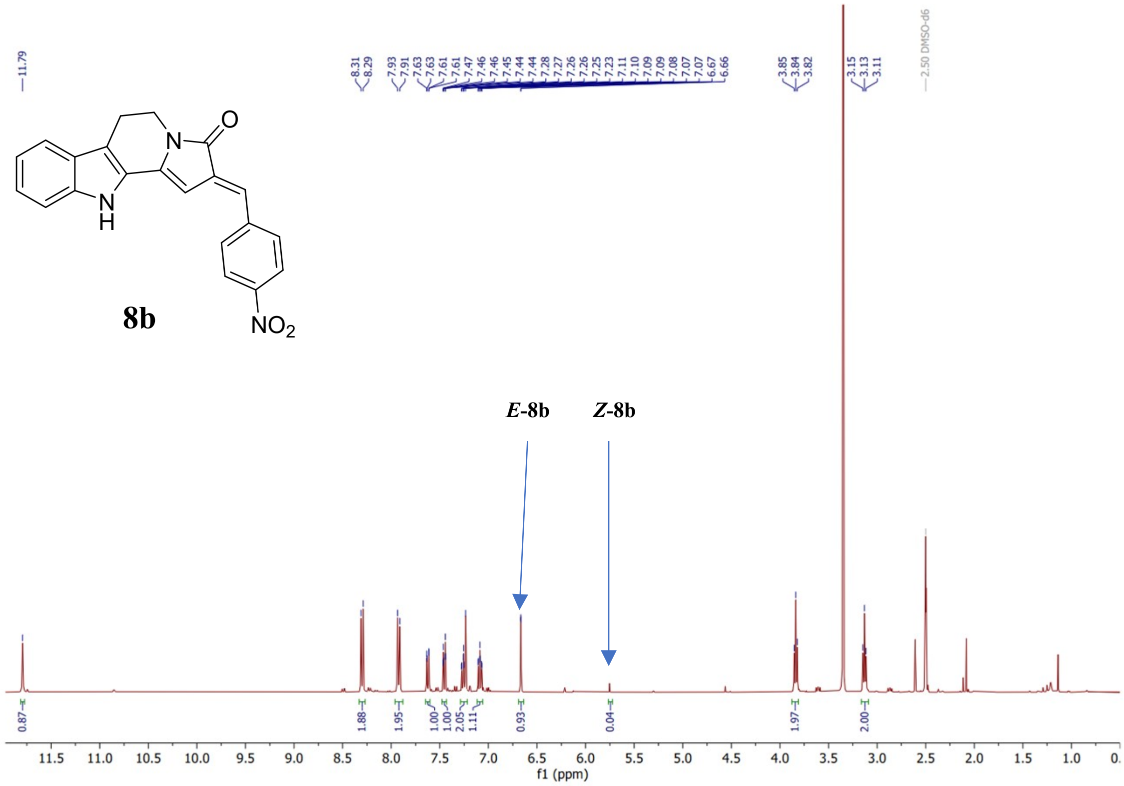
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)

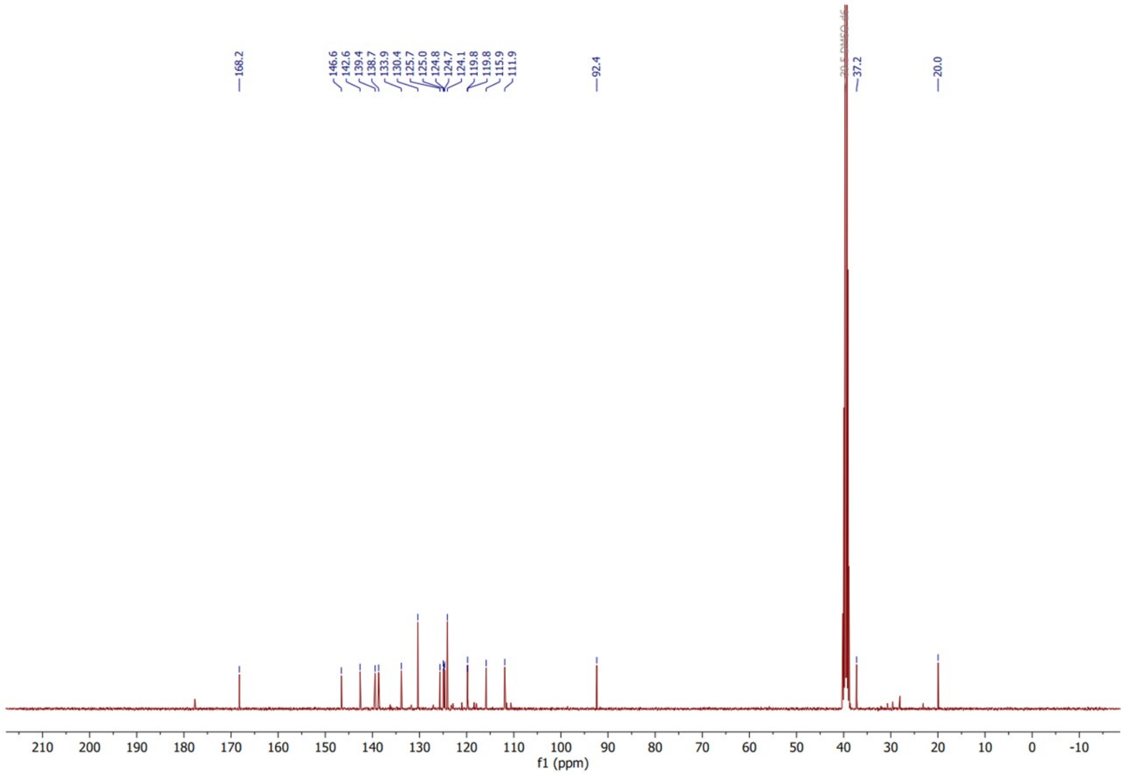


8a

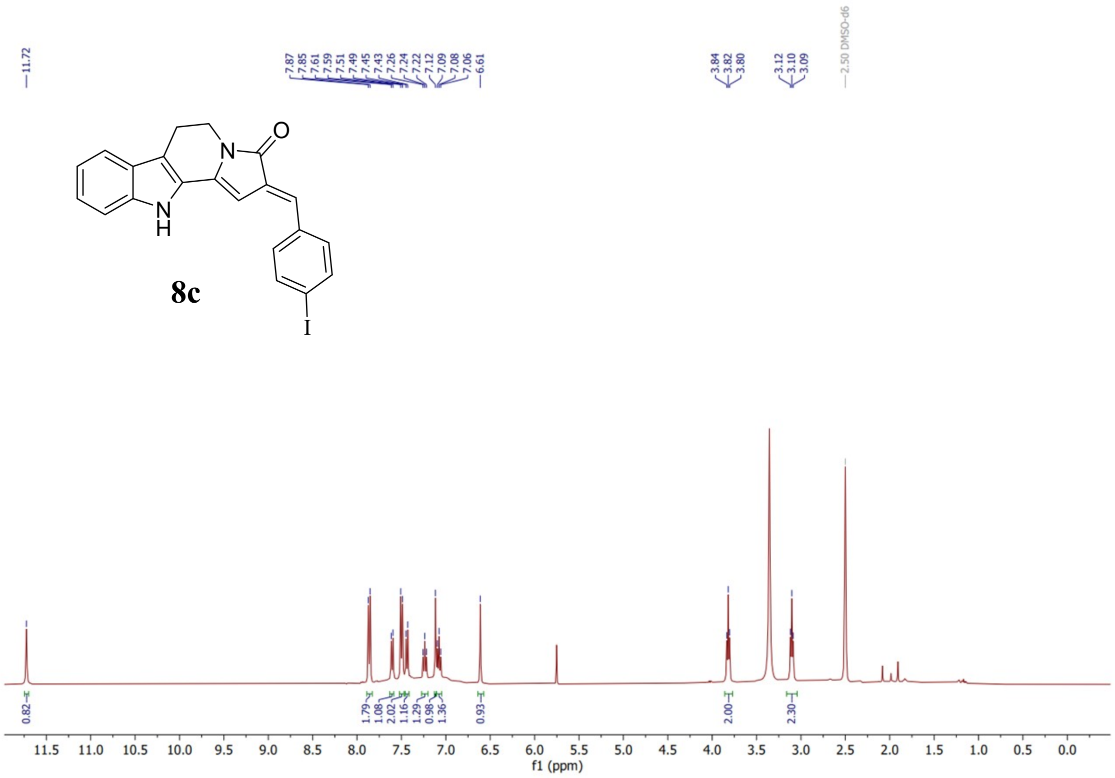


^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)

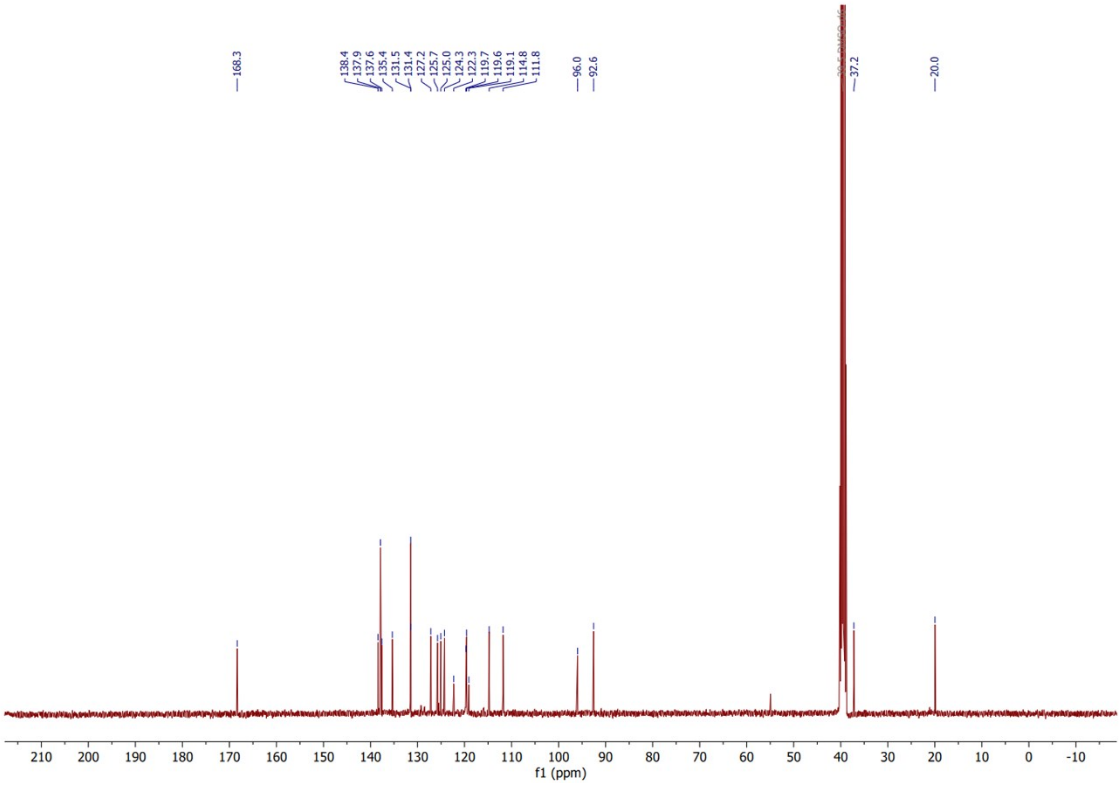




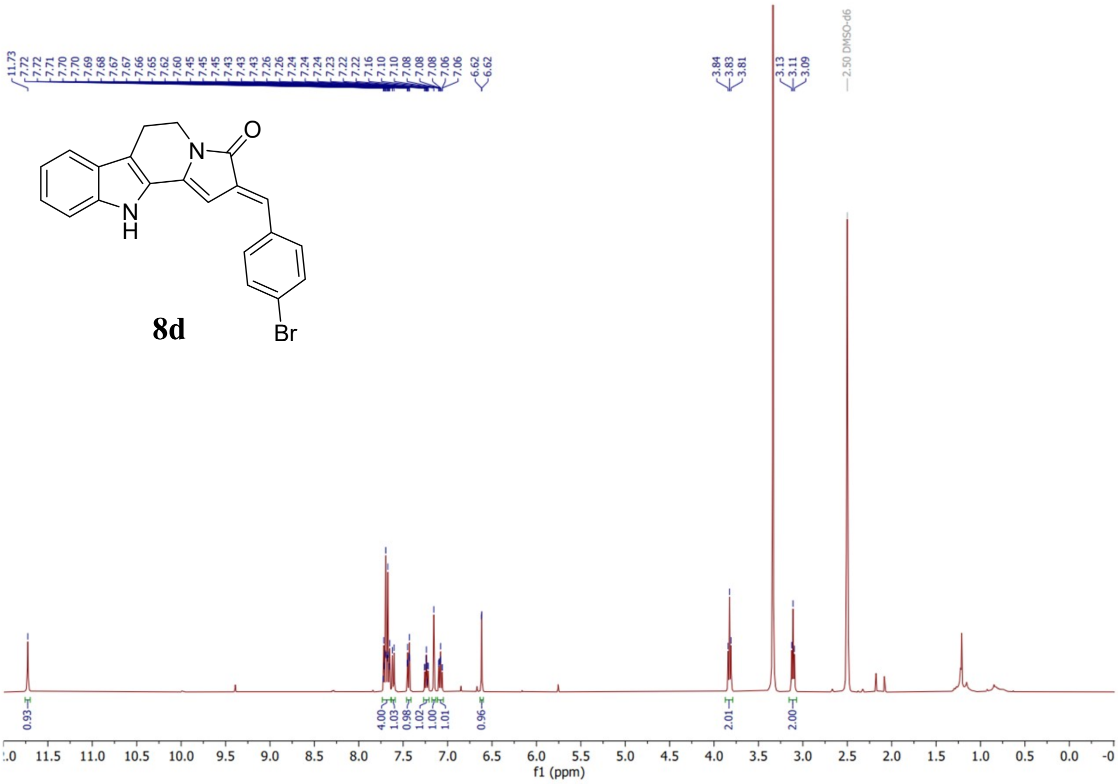
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



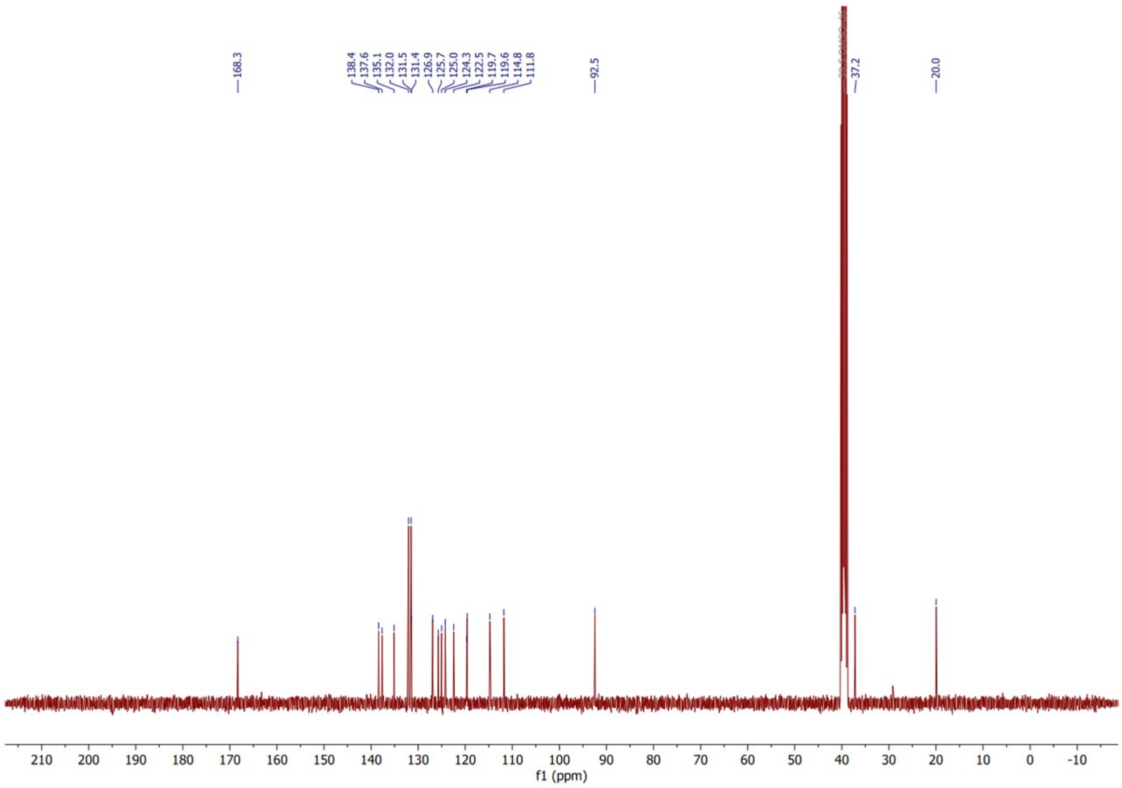
8c



^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



8d



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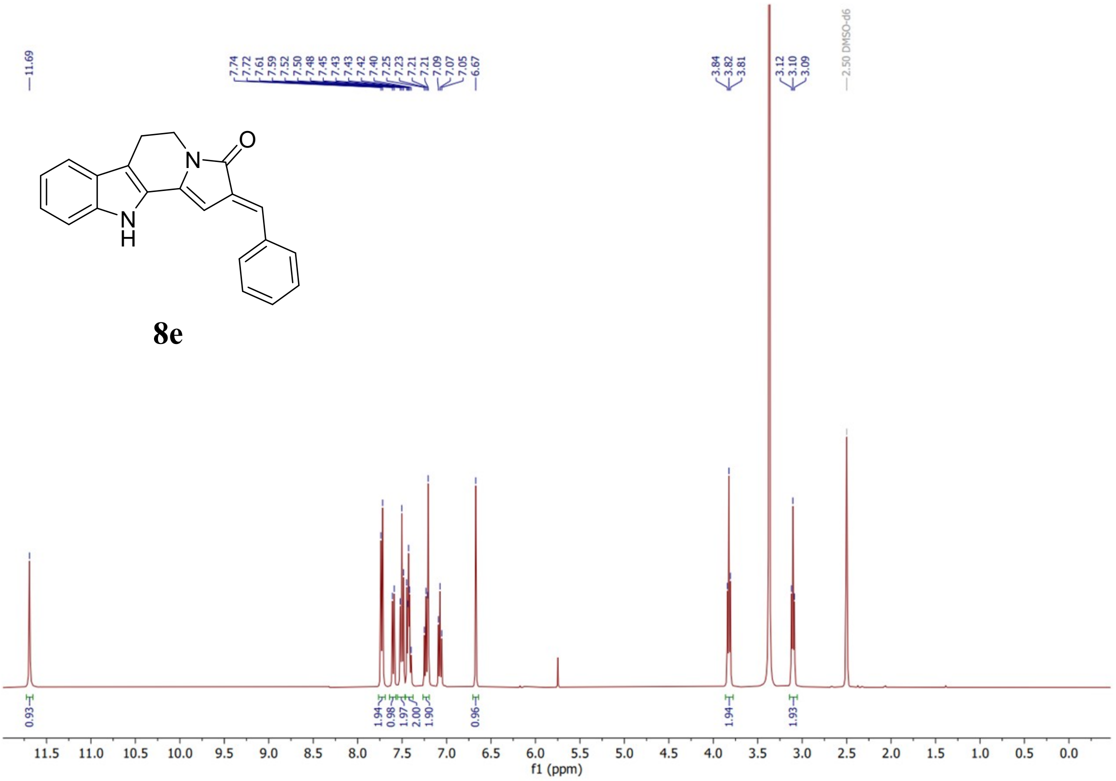
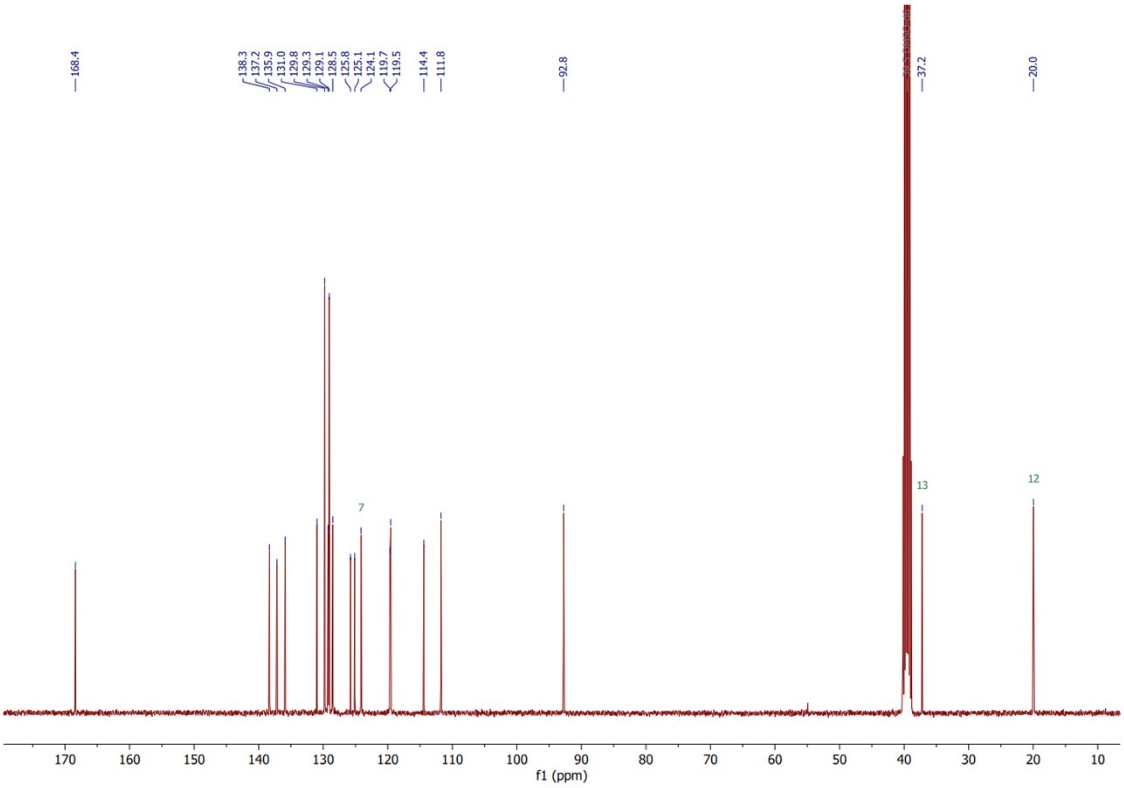
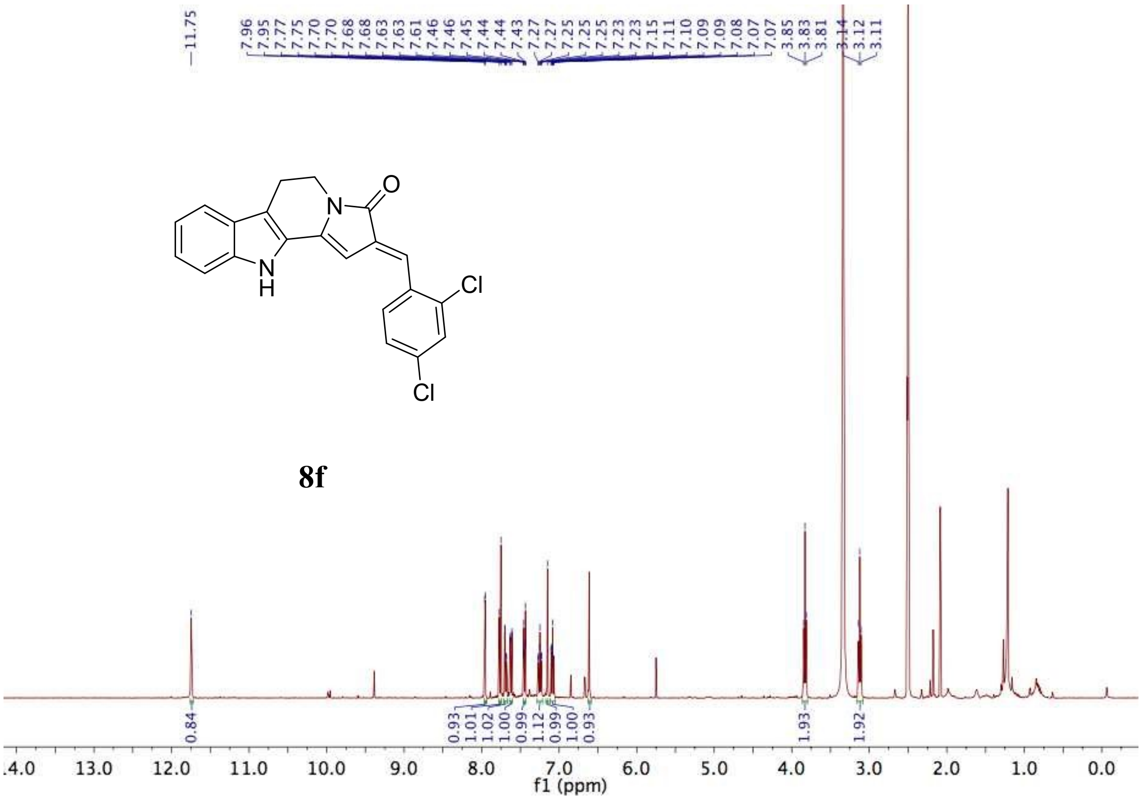
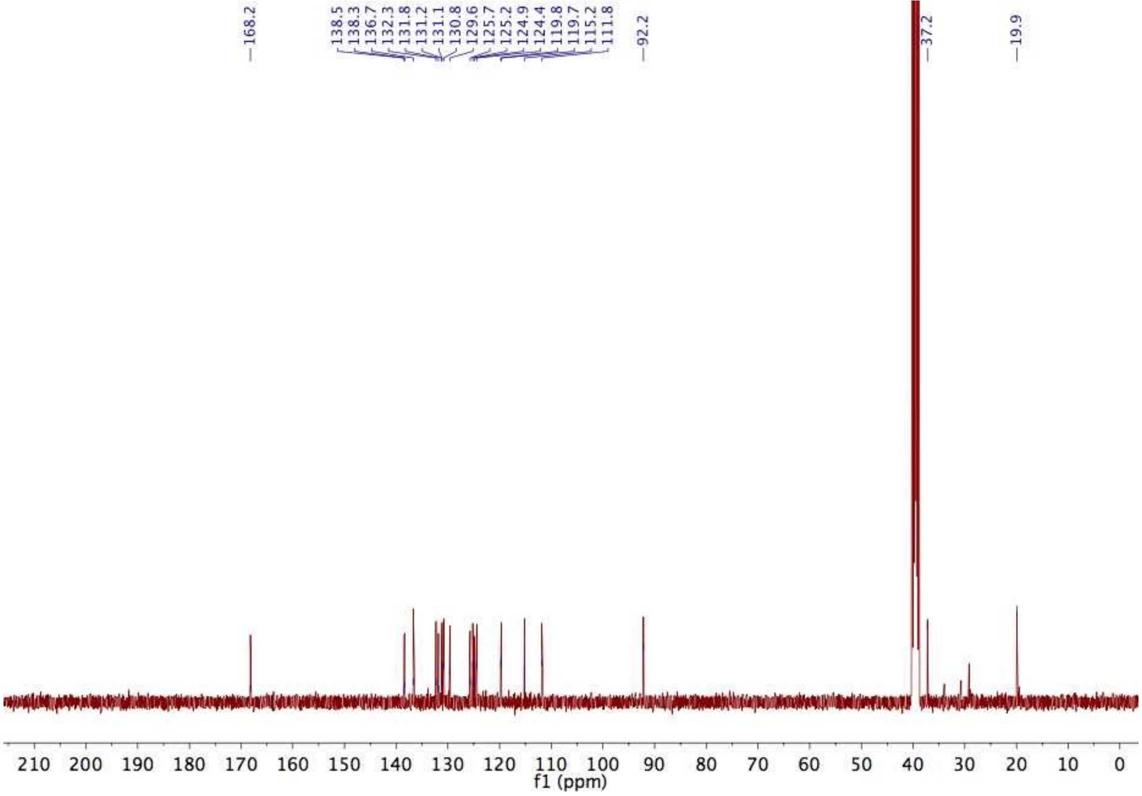




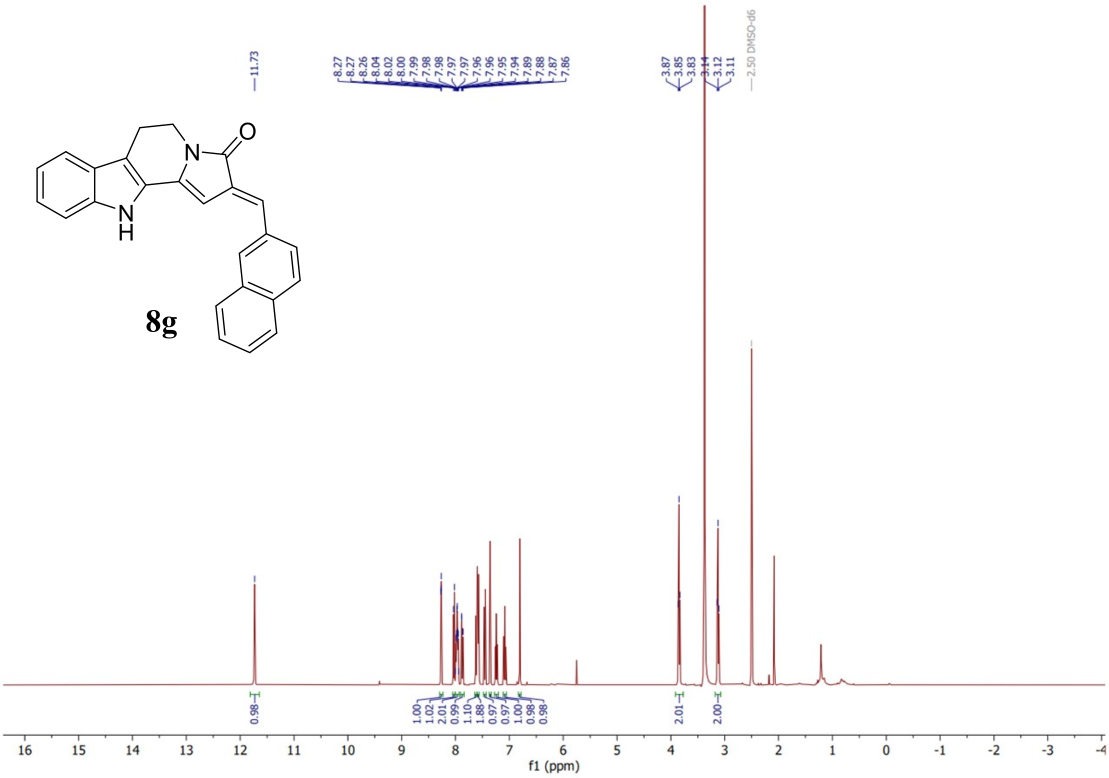
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)

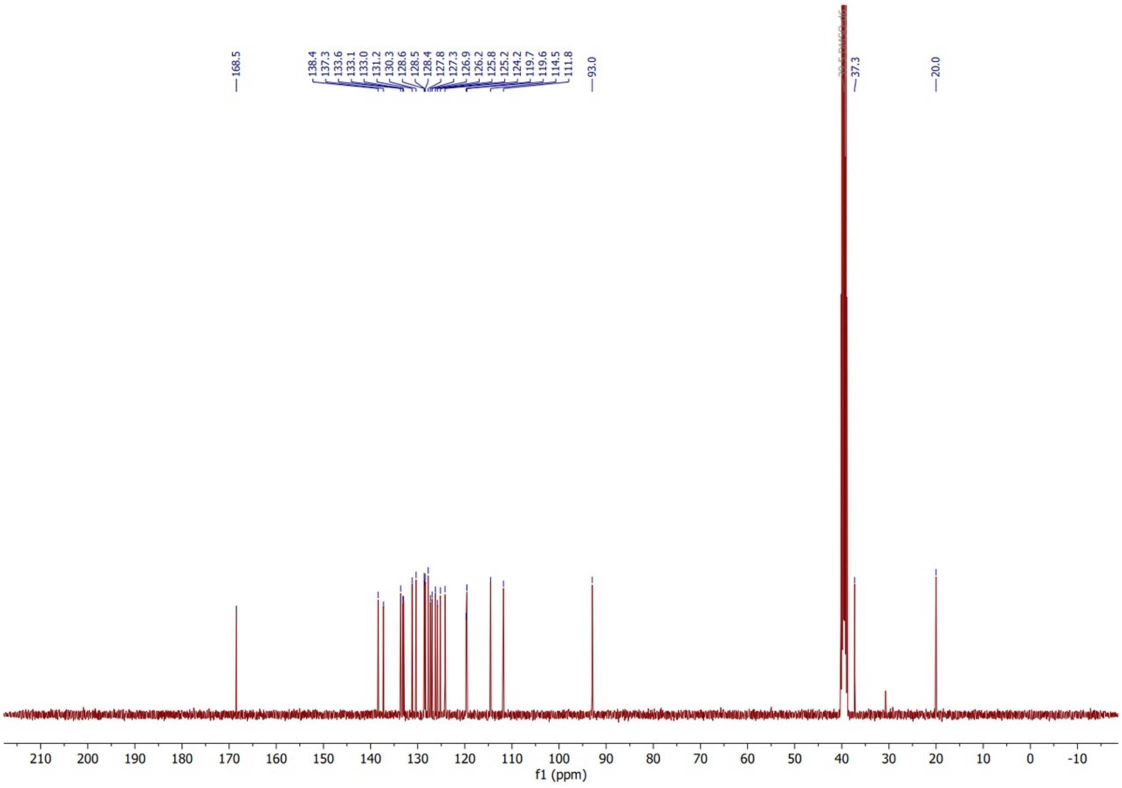


8f

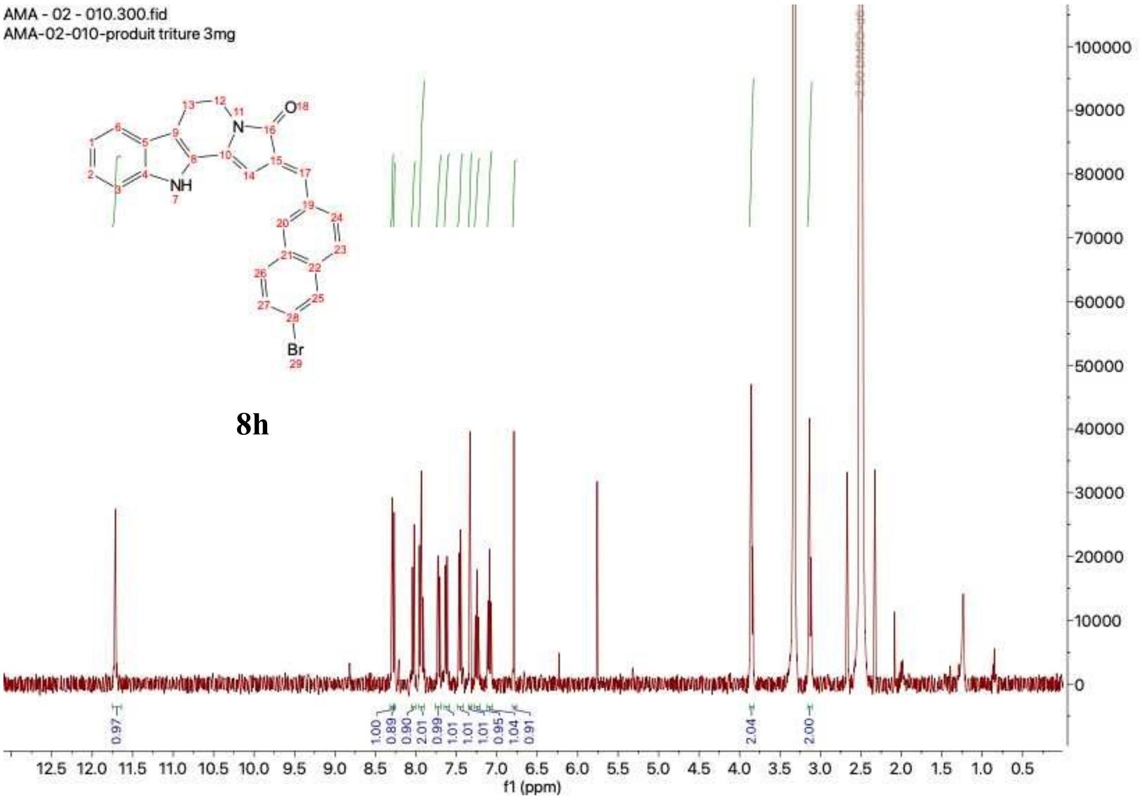


^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)

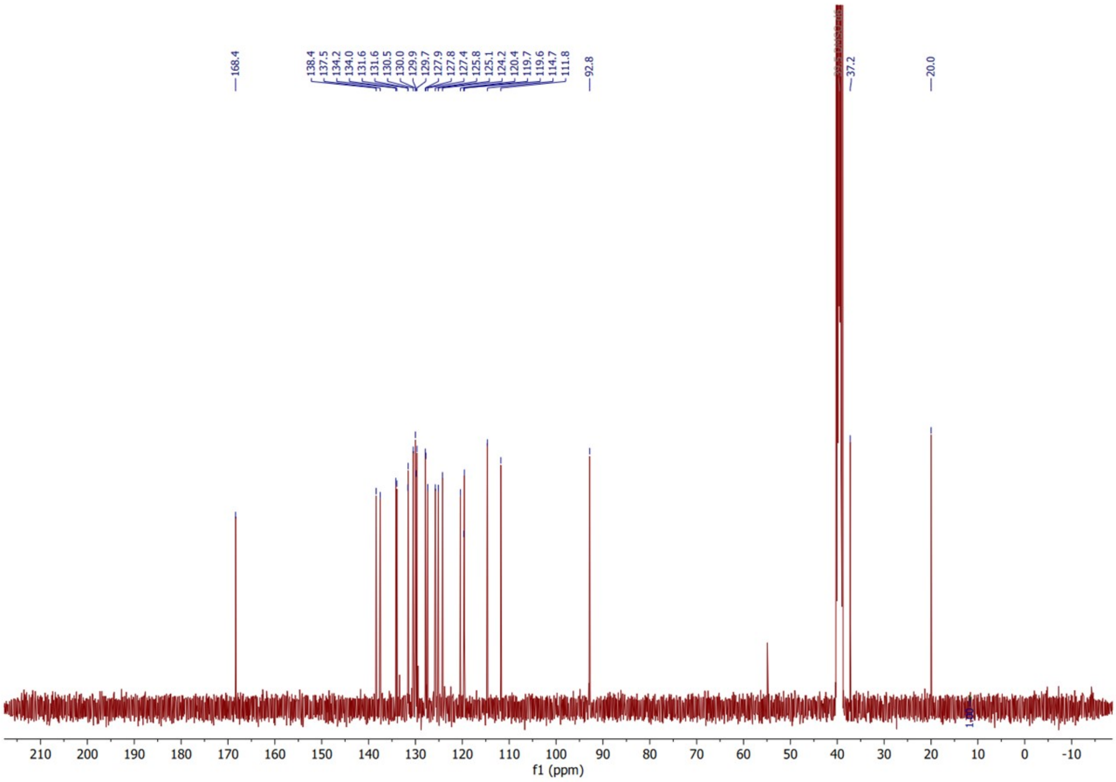




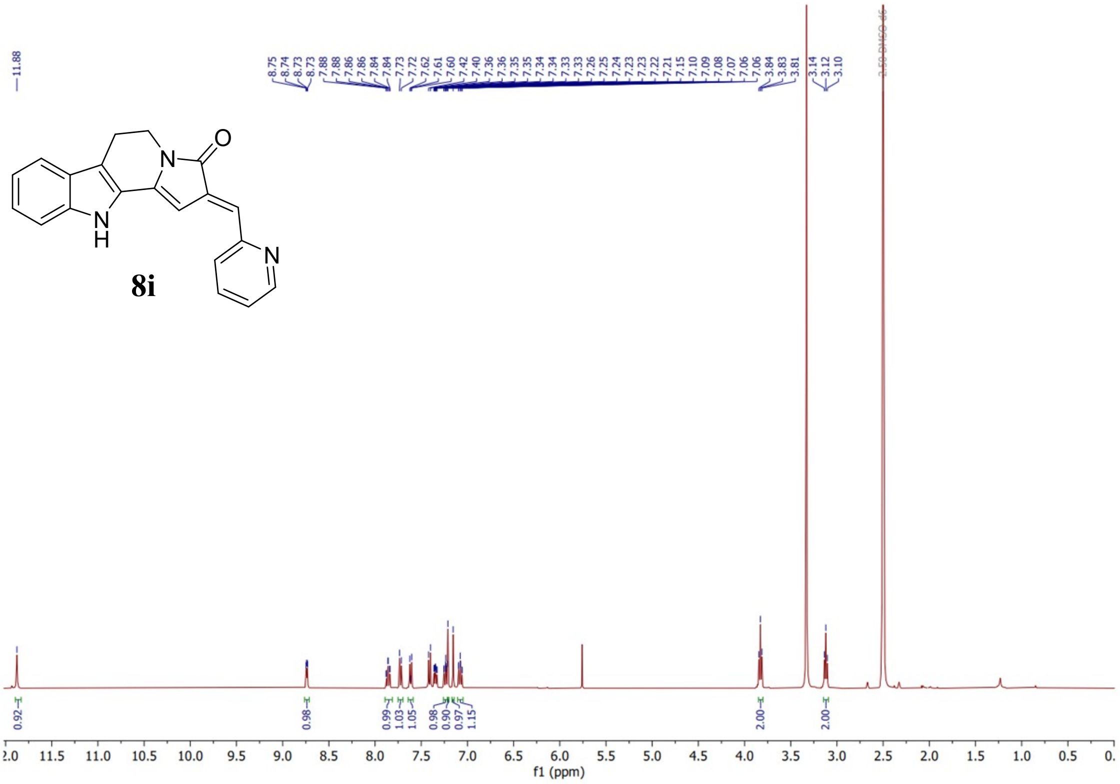
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



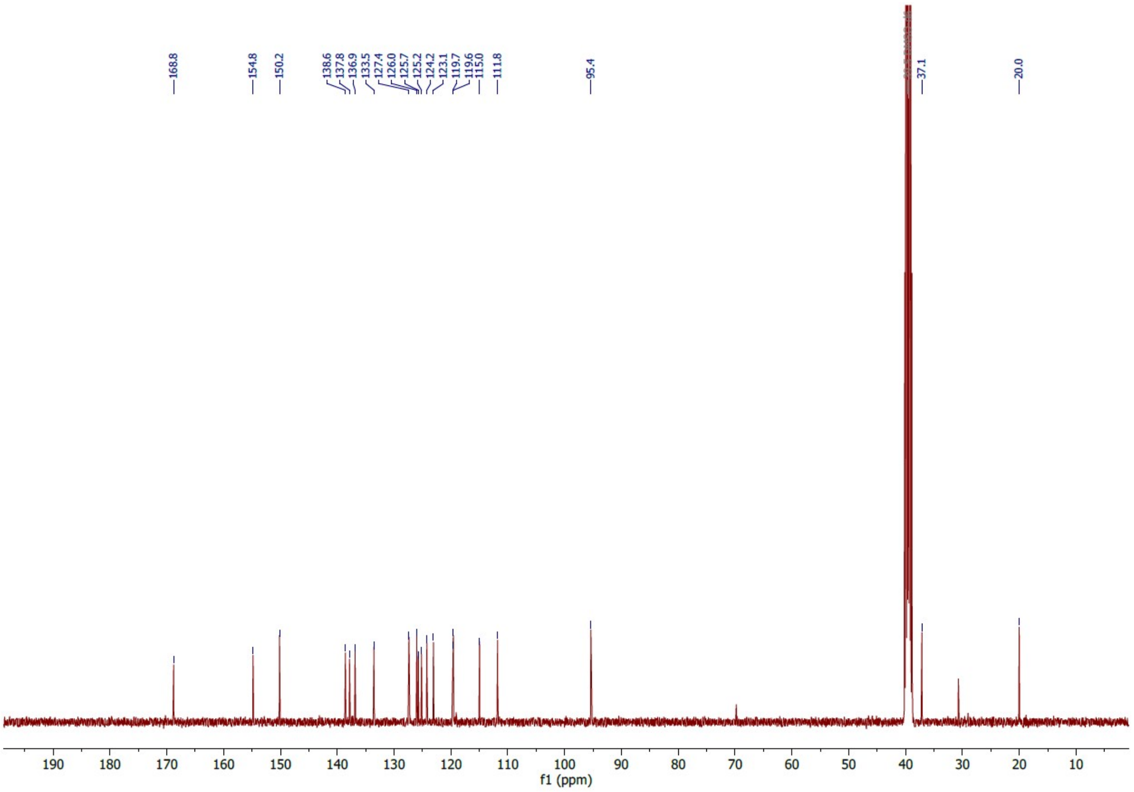
8h



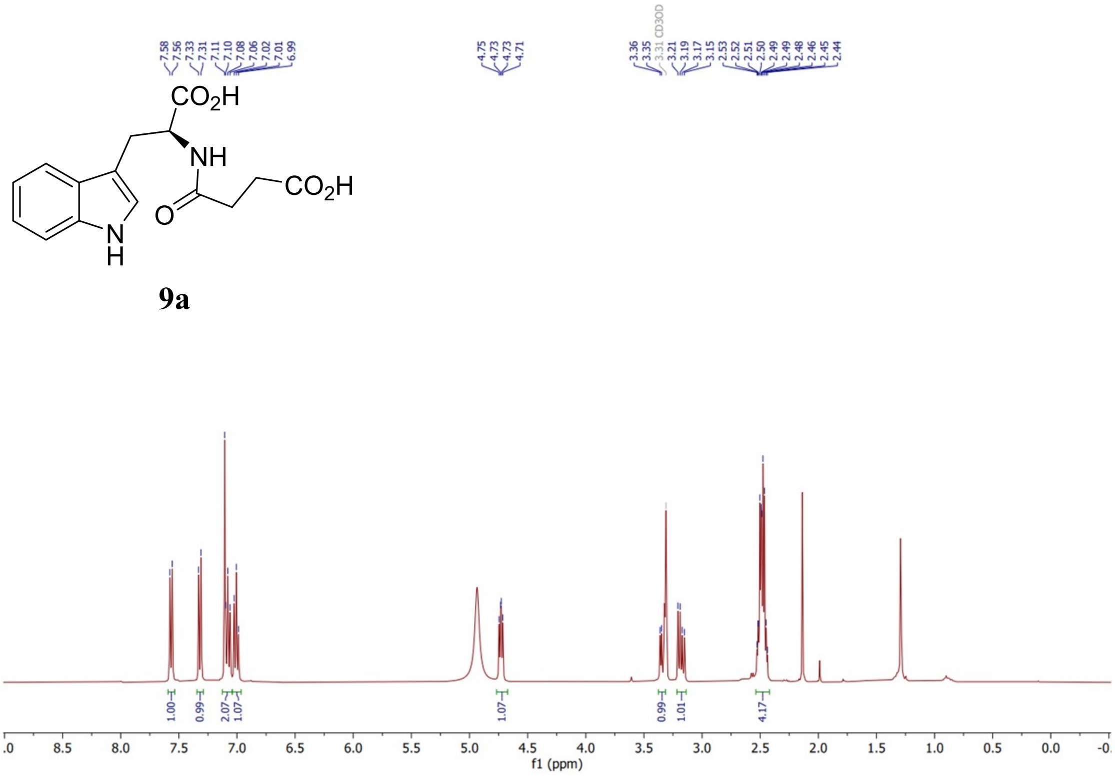
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (101 MHz, DMSO-d_6)



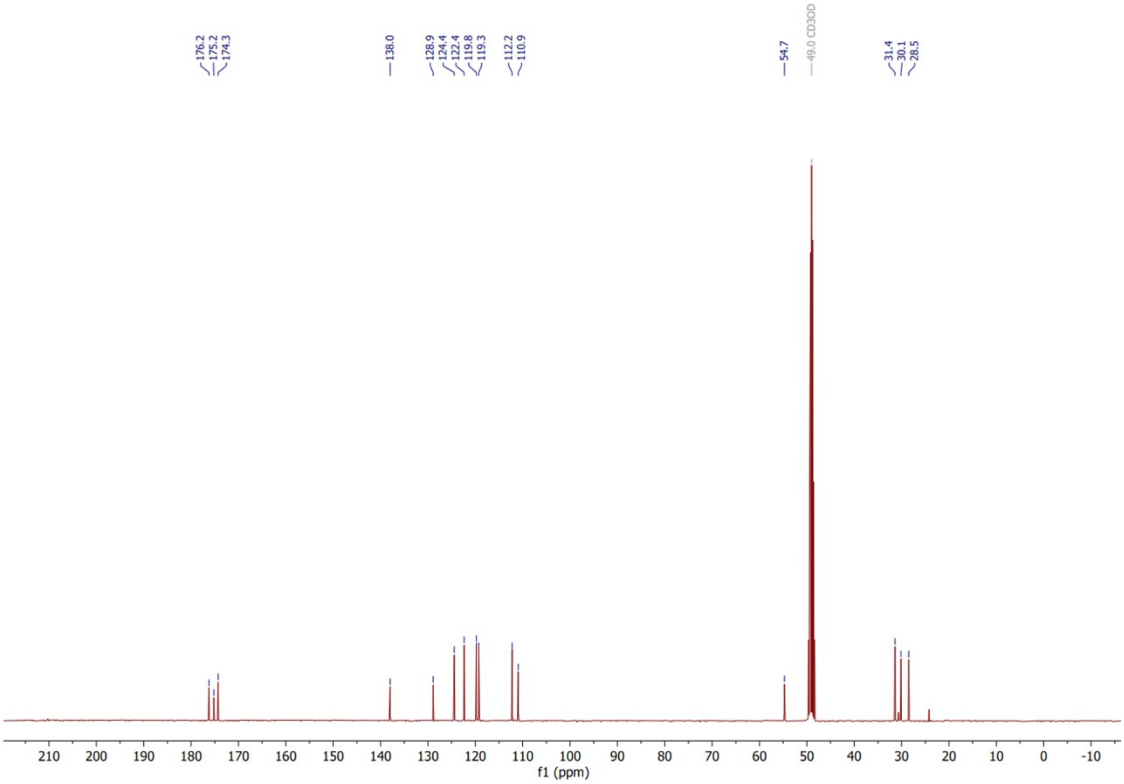
8i



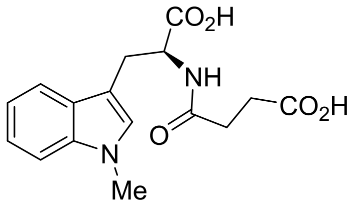
^{1}H NMR (400 MHz, Methanol-d_4) and ^{13}C NMR (101 MHz, Methanol-d_4)



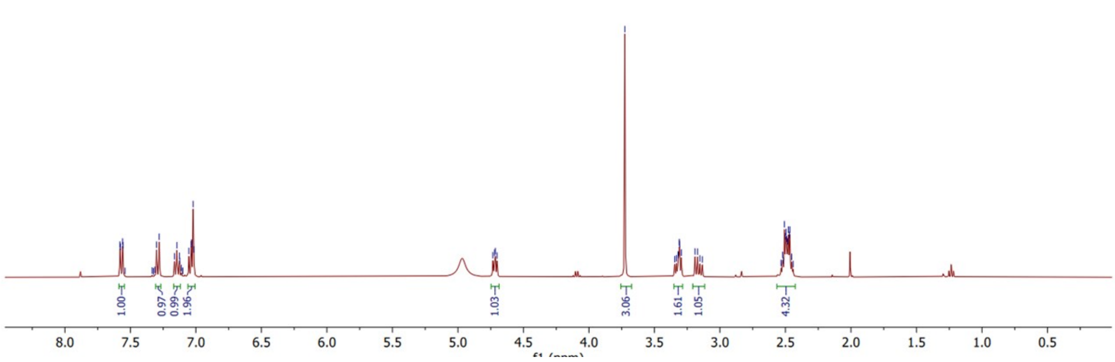
9a

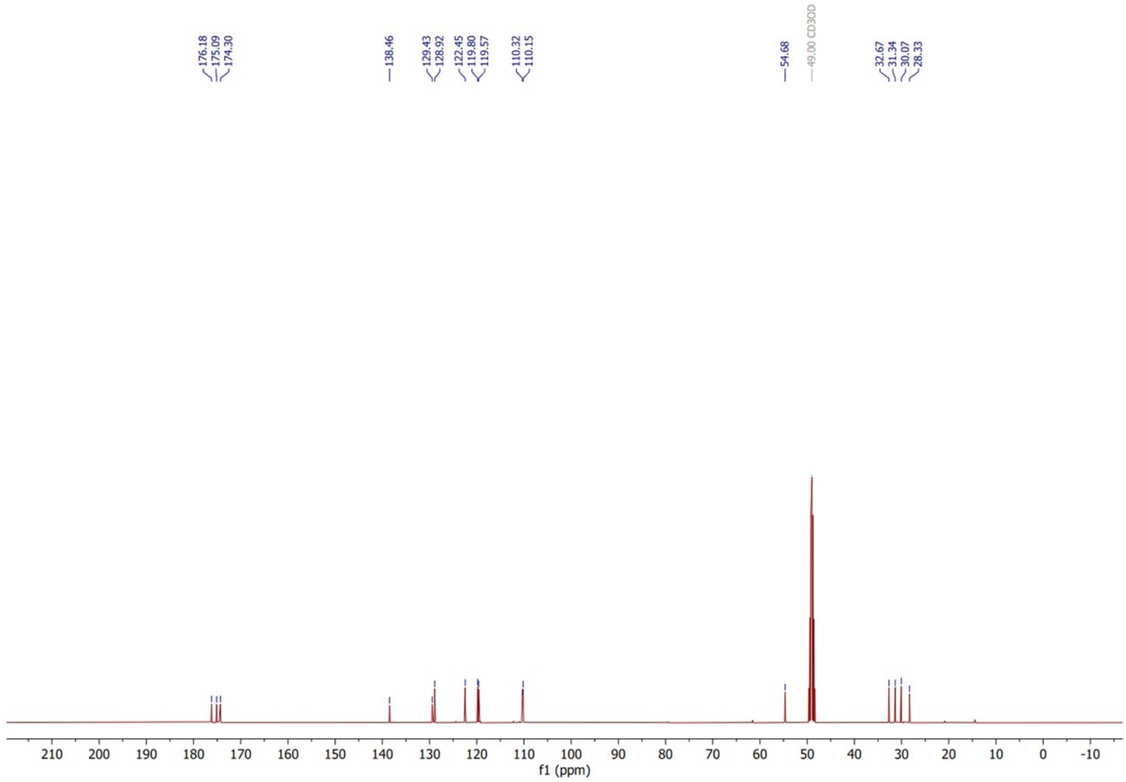


^{1}H NMR (400 MHz, Methanol-d_4) and ^{13}C NMR (101 MHz, Methanol-d_4)



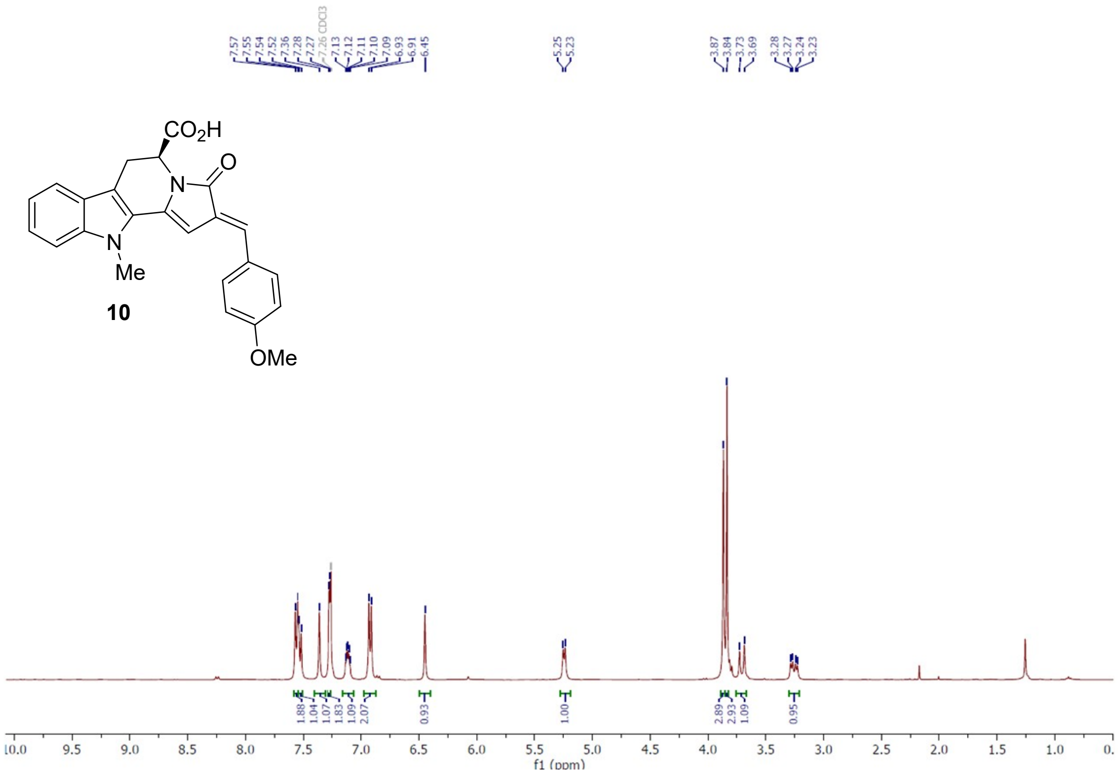
9b

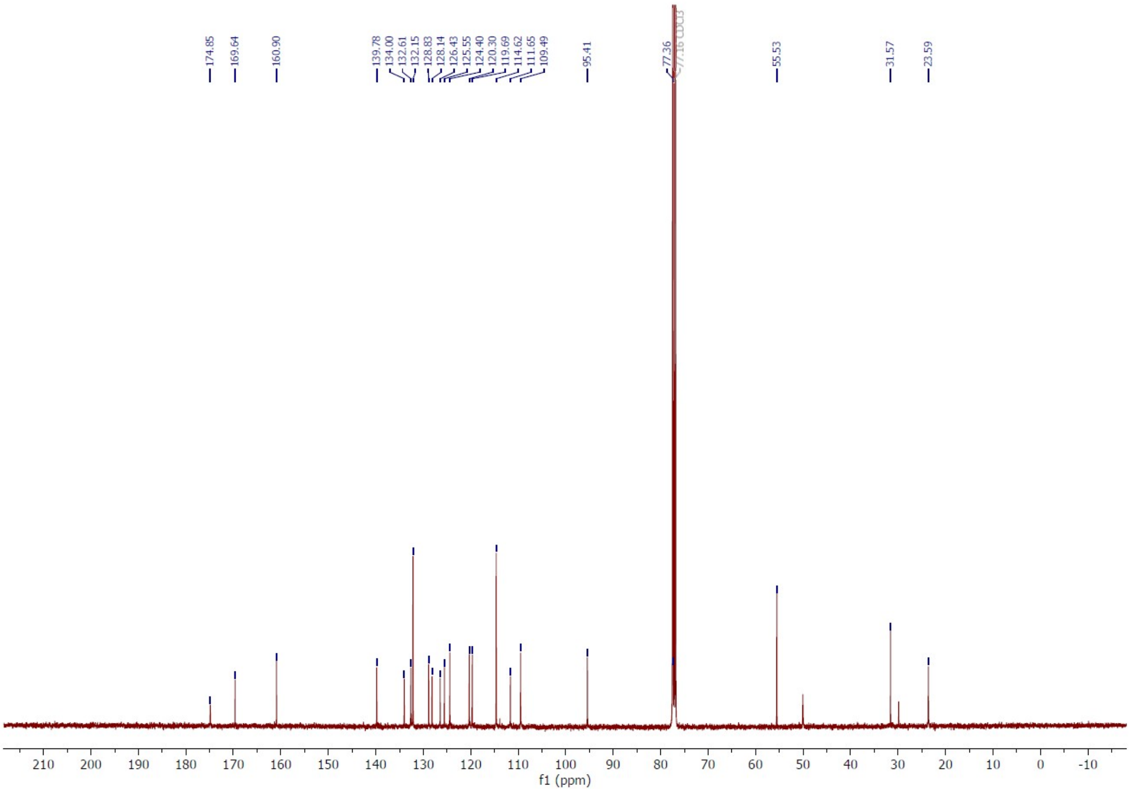




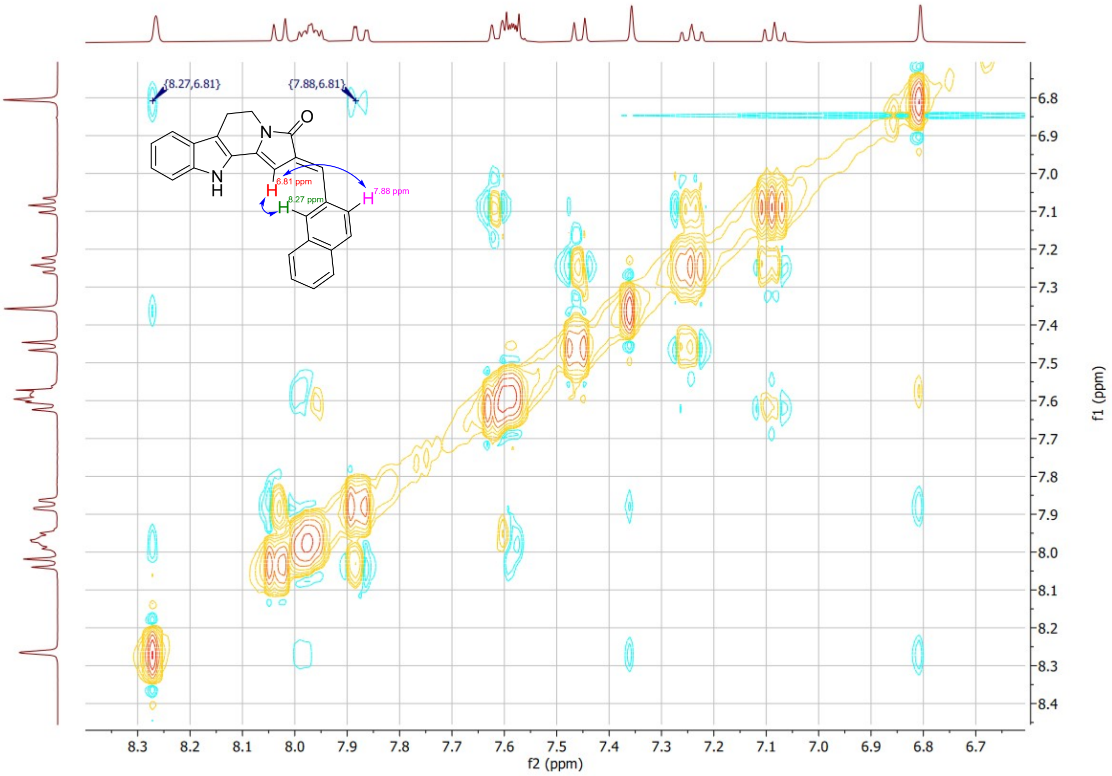
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$)

10

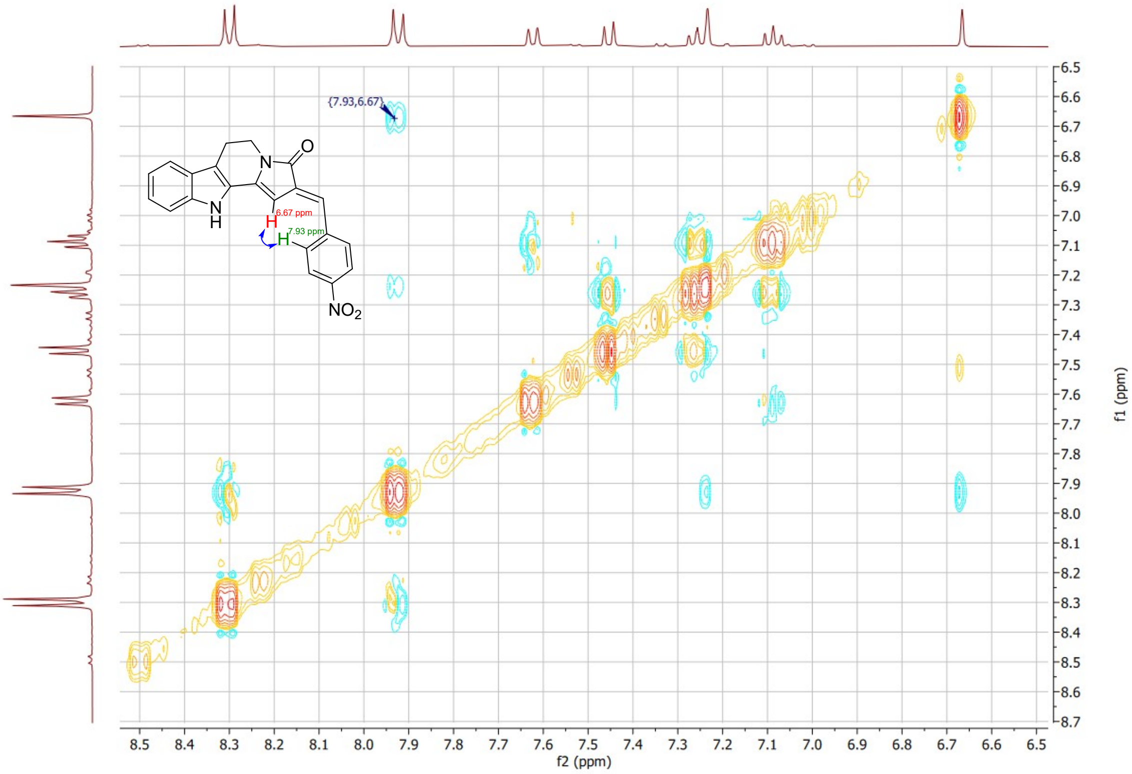




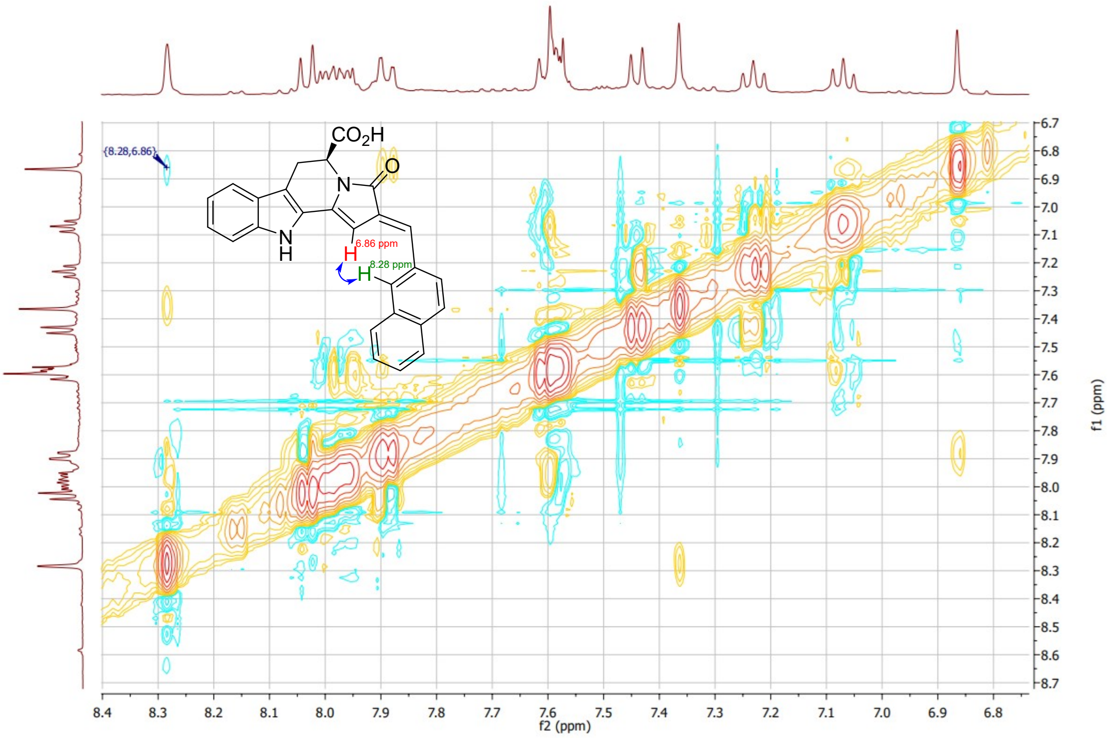
NOESY analysis of 8f



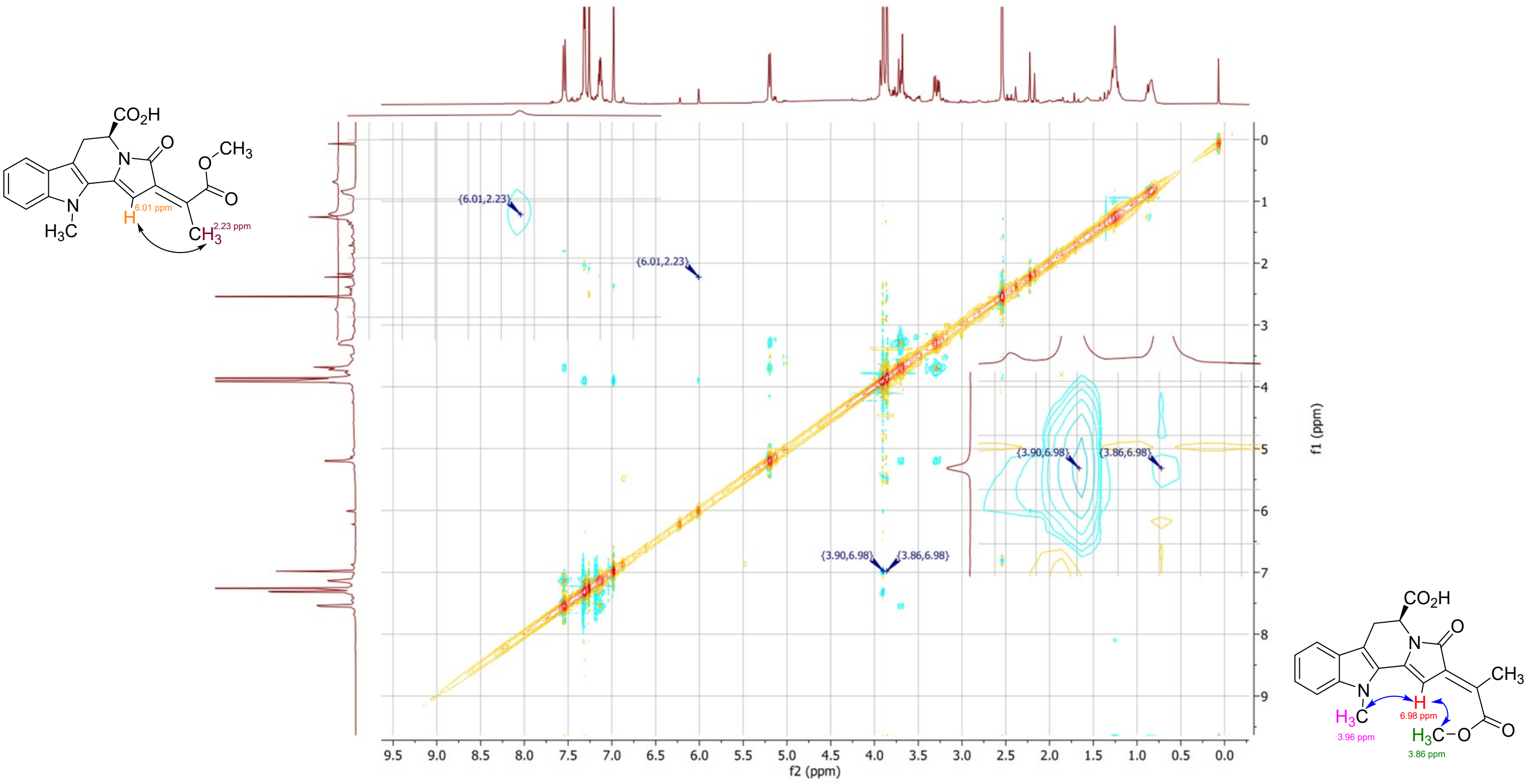
NOESY analysis of 8b



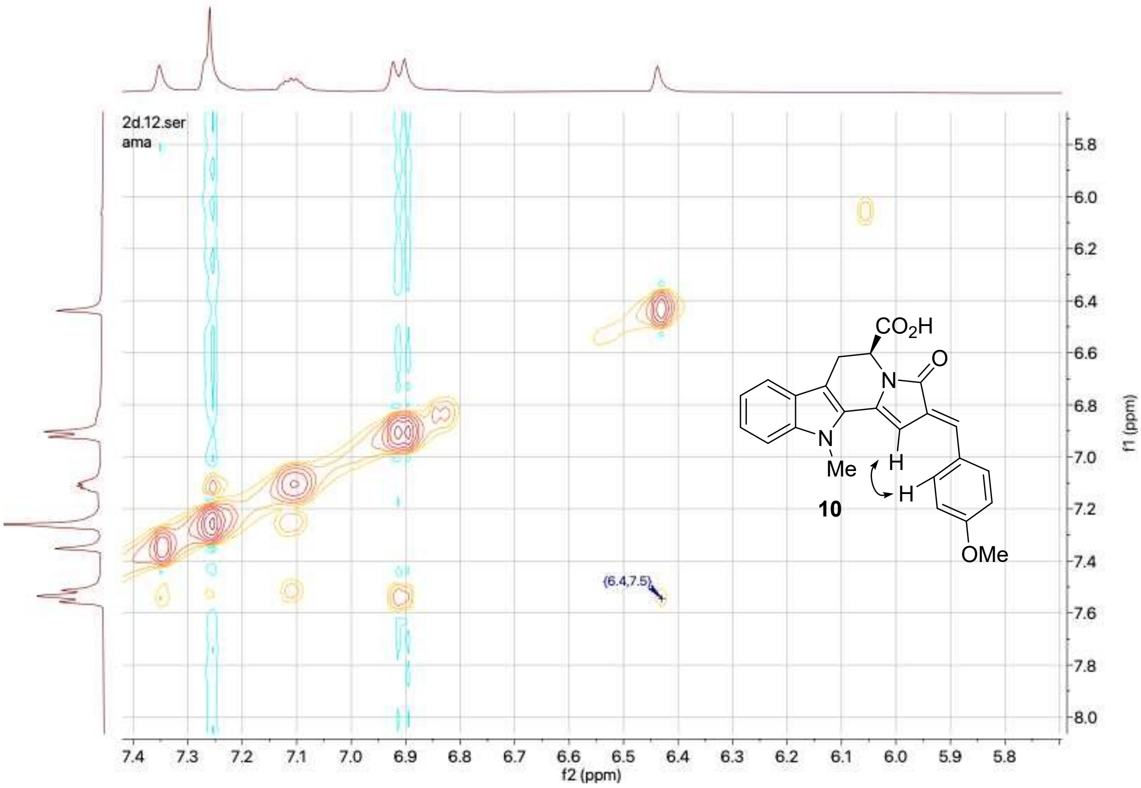
NOESY analysis of 5a



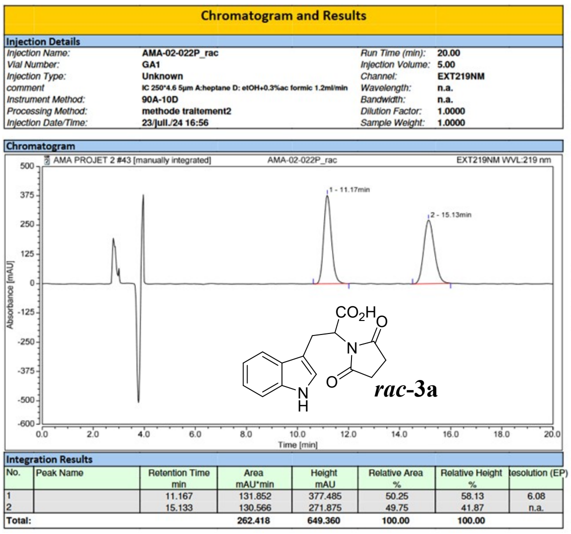
NOESY analysis of mixture of *(E)*-(Z) Chaetogline A



NOESY analysis of 10



HPLC traces



Chromatogram and Results

Injection Details

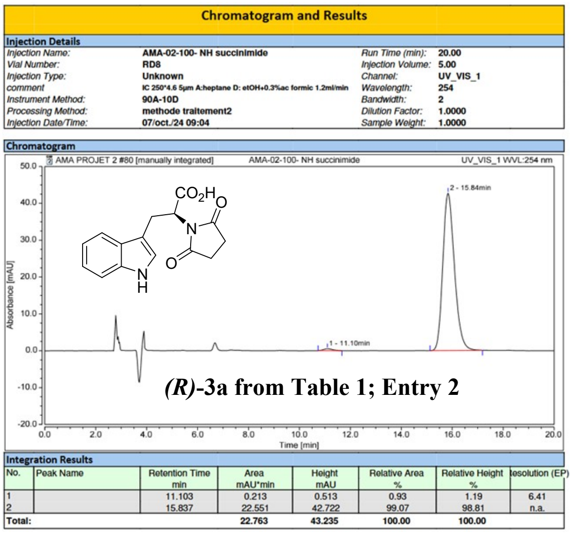
Injection Name: AMA-02-022P_rac
Vial Number: GA1
Injection Type: Unknown
comment IC 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.2ml/min
Instrument Method: 90A-10D
Processing Method: methode traitement2
Injection Date/Time: 23/juil./24 16:56
Run Time (min): 20.00
Injection Volume: 5.00
Channel: EXT219NM
Wavelength: n.a.
Bandwidth: n.a.
Dilution Factor: 1.0000
Sample Weight: 1.0000

Chromatogram

***rac*-3a**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Resolution (EP)
1		11.167	131.852	377.485	50.25	58.13	6.08
2		15.133	130.566	271.875	49.75	41.87	n.a.
Total:			262.418	649.360	100.00	100.00	



Chromatogram and Results

Injection Details

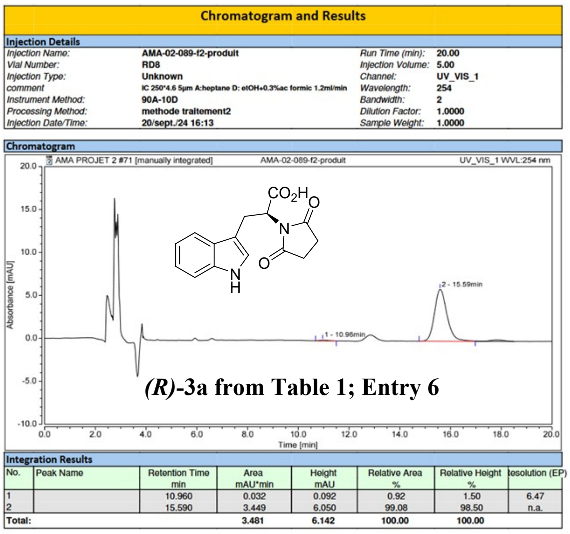
Injection Name: AMA-02-100- NH succinimide
Vial Number: RD8
Injection Type: Unknown
comment IC 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.2ml/min
Instrument Method: 90A-10D
Processing Method: methode traitement2
Injection Date/Time: 07/oct./24 09:04
Run Time (min): 20.00
Injection Volume: 5.00
Channel: UV_VIS_1
Wavelength: 254
Bandwidth: 2
Dilution Factor: 1.0000
Sample Weight: 1.0000

Chromatogram

***(R)*-3a from Table 1; Entry 2**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Resolution (EP)
1		11.103	0.213	0.513	0.93	1.19	6.41
2		15.837	22.551	42.722	99.07	98.81	n.a.
Total:			22.763	43.235	100.00	100.00	



Chromatogram and Results

Injection Details

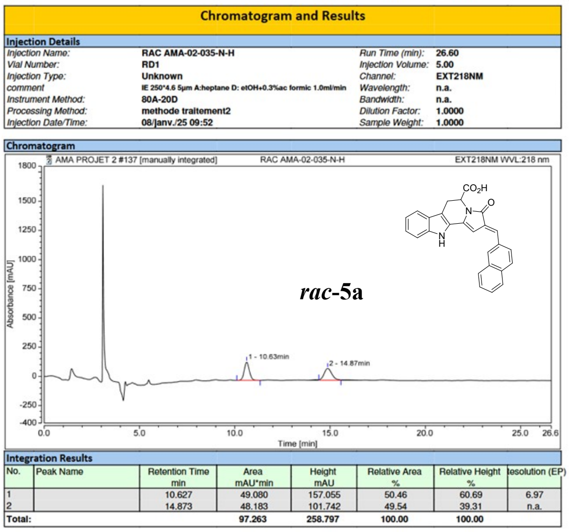
Injection Name: AMA-02-089-f2-produit
Vial Number: RD8
Injection Type: Unknown
comment IC 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.2ml/min
Instrument Method: 90A-10D
Processing Method: methode traitement2
Injection Date/Time: 20/sept./24 16:13
Run Time (min): 20.00
Injection Volume: 5.00
Channel: UV_VIS_1
Wavelength: 254
Bandwidth: 2
Dilution Factor: 1.0000
Sample Weight: 1.0000

Chromatogram

***(R)*-3a from Table 1; Entry 6**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Resolution (EP)
1		10.960	0.032	0.092	0.92	1.50	6.47
2		15.590	3.449	6.050	99.08	98.50	n.a.
Total:			3.481	6.142	100.00	100.00	



Chromatogram and Results

Injection Details

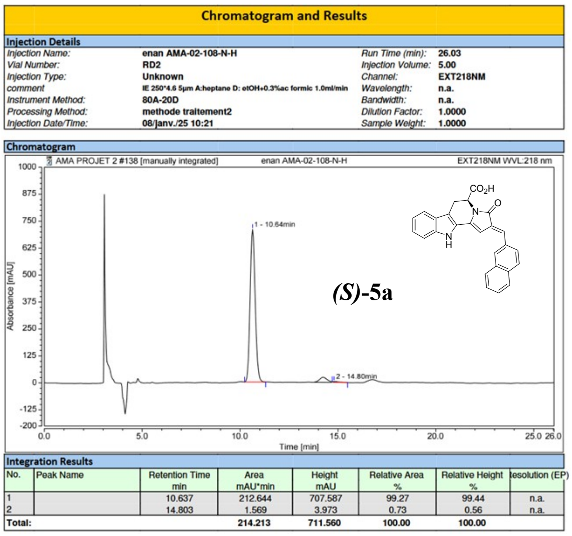
Injection Name: RAC AMA-02-035-N-H
Vial Number: RD1
Injection Type: Unknown
comment IE 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.0ml/min
Instrument Method: 80A-20D
Processing Method: methode traitement2
Injection Date/Time: 08/janv./25 09:52
Run Time (min): 26.60
Injection Volume: 5.00
Channel: EXT218NM
Wavelength: n.a.
Bandwidth: n.a.
Dilution Factor: 1.0000
Sample Weight: 1.0000

Chromatogram

***rac*-5a**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Resolution (EP)
1		10.627	49.080	157.055	50.46	60.69	6.97
2		14.873	48.183	101.742	49.54	39.31	n.a.
Total:			97.263	258.797	100.00	100.00	



Chromatogram and Results

Injection Details

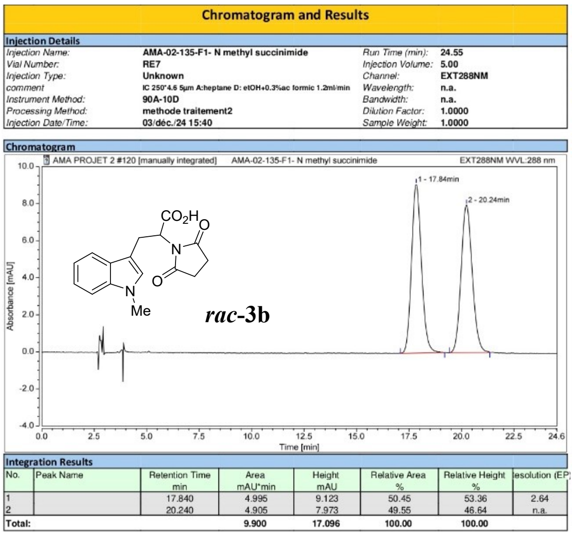
Injection Name: enan AMA-02-108-N-H
Vial Number: RD2
Injection Type: Unknown
comment IE 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.0ml/min
Instrument Method: 80A-20D
Processing Method: methode traitement2
Injection Date/Time: 08/janv./25 10:21
Run Time (min): 26.03
Injection Volume: 5.00
Channel: EXT218NM
Wavelength: n.a.
Bandwidth: n.a.
Dilution Factor: 1.0000
Sample Weight: 1.0000

Chromatogram

***(S)*-5a**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Resolution (EP)
1		10.637	212.644	707.587	99.27	99.44	n.a.
2		14.803	1.569	3.973	0.73	0.56	n.a.
Total:			214.213	711.560	100.00	100.00	



Chromatogram and Results

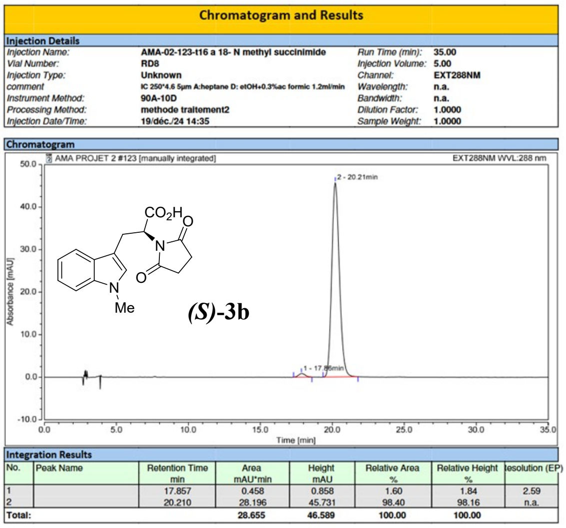
Injection Details

Injection Name:	**AMA-02-135-F1- N methyl succinimide**	*Run Time (min):*	**24.55**
Vial Number:	**RE7**	*Injection Volume:*	**5.00**
Injection Type:	**Unknown**	*Channel:*	**EXT288NM**
comment	**IC 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.2ml/min**	*Wavelength:*	**n.a.**
Instrument Method:	**90A-10D**	*Bandwidth:*	**n.a.**
Processing Method:	**methode traitement2**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**03/déc./24 15:40**	*Sample Weight:*	**1.0000**

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	esolution (EP)
1		17.840	4.995	9.123	50.45	53.36	2.64
2		20.240	4.905	7.973	49.55	46.64	n.a.
Total:			**9.900**	**17.096**	**100.00**	**100.00**	



Chromatogram and Results

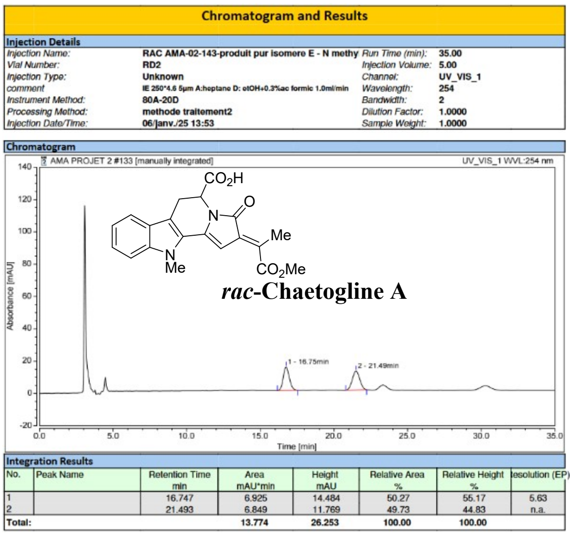
Injection Details

Injection Name:	**AMA-02-123-t16 a 18- N methyl succinimide**	*Run Time (min):*	**35.00**
Vial Number:	**RD8**	*Injection Volume:*	**5.00**
Injection Type:	**Unknown**	*Channel:*	**EXT288NM**
comment	**IC 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.2ml/min**	*Wavelength:*	**n.a.**
Instrument Method:	**90A-10D**	*Bandwidth:*	**n.a.**
Processing Method:	**methode traitement2**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/déc./24 14:35**	*Sample Weight:*	**1.0000**

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	esolution (EP)
1		17.857	0.458	0.858	1.60	1.84	2.59
2		20.210	28.196	45.731	98.40	98.16	n.a.
Total:			**28.655**	**46.589**	**100.00**	**100.00**	



Chromatogram and Results

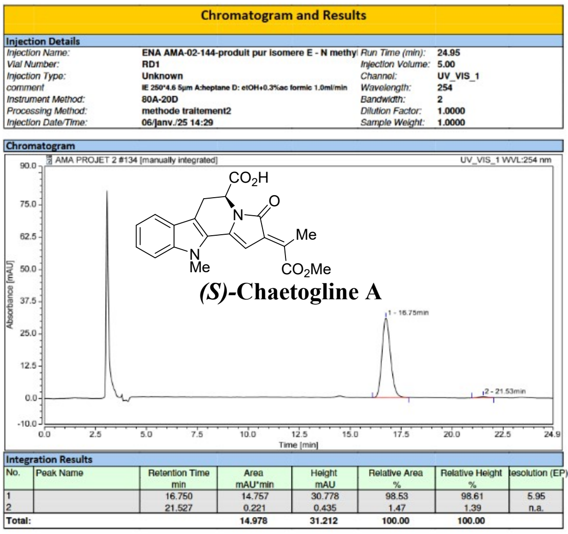
Injection Details

Injection Name:	**RAC AMA-02-143-produit pur isomere E - N methy**	*Run Time (min):*	**35.00**
Vial Number:	**RD2**	*Injection Volume:*	**5.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
comment	**IE 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.0ml/min**	*Wavelength:*	**254**
Instrument Method:	**80A-20D**	*Bandwidth:*	**2**
Processing Method:	**methode traitement2**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**06/janv./25 13:53**	*Sample Weight:*	**1.0000**

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	esolution (EP)
1		16.747	6.925	14.484	50.27	55.17	5.63
2		21.493	6.849	11.769	49.73	44.83	n.a.
Total:			**13.774**	**26.253**	**100.00**	**100.00**	



Chromatogram and Results

Injection Details

Injection Name:	**ENA AMA-02-144-produit pur isomere E - N methy**	*Run Time (min):*	**24.95**
Vial Number:	**RD1**	*Injection Volume:*	**5.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
comment	**IE 250*4.6 5µm A:heptane D: etOH+0.3%ac formic 1.0ml/min**	*Wavelength:*	**254**
Instrument Method:	**80A-20D**	*Bandwidth:*	**2**
Processing Method:	**methode traitement2**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**06/janv./25 14:29**	*Sample Weight:*	**1.0000**

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	esolution (EP)
1		16.750	14.757	30.778	98.53	98.61	5.95
2		21.527	0.221	0.435	1.47	1.39	n.a.
Total:			**14.978**	**31.212**	**100.00**	**100.00**	

Optical measurement methods

UV-visible absorption spectra were recorded using a Cary 60 (Agilent) spectrophotometer, applying a baseline correction, in 1 cm path length quartz cuvettes. Steady state fluorescence spectra were measured with a Fluorolog 3–21 (Horiba, Hamamatsu photomultiplier tube R13456) using diluted samples O.D.< 0.1 in 3.5 mL cuvettes. A correction factor was applied

Fluorescence quantum yields (φf) were measured following the equation:

$$\varphi F = \varphi Fc \times \left(\frac{F}{F_c}\right) \times \left(\frac{1-10^{-A}}{1-10^{-Ac}}\right) \times \left(\frac{n}{n_c}\right)^2$$

Were "F" is the integrated fluorescence signal of the dye, "Fc" is the integrated fluorescence signal of the reference (coumarin 153 in ethanol, φFc = 0.54 described by Rurack); A and Ac are the absorbances the dye and the coumarin 153 respectively; n and nc the refractive index of the solvents: dye (dichloromethane) and reference (ethanol).

Fluorescence lifetimes were measured by TCSPC using an EPL 405 nm LASER diode (5 mW, pulse width 56.3 ps, repetition rate 200 ns, Edimburgh Instrument) and a Fluorolog 3–21 (Horiba, Hamamatsu photomultiplier tube R13456) using diluted samples O.D.< 0.1 in 3.5 mL cuvettes. The measurement stopped when the maximum number of counts reached 10 000.

Figure S 1 Solvatochromism of ***5a***

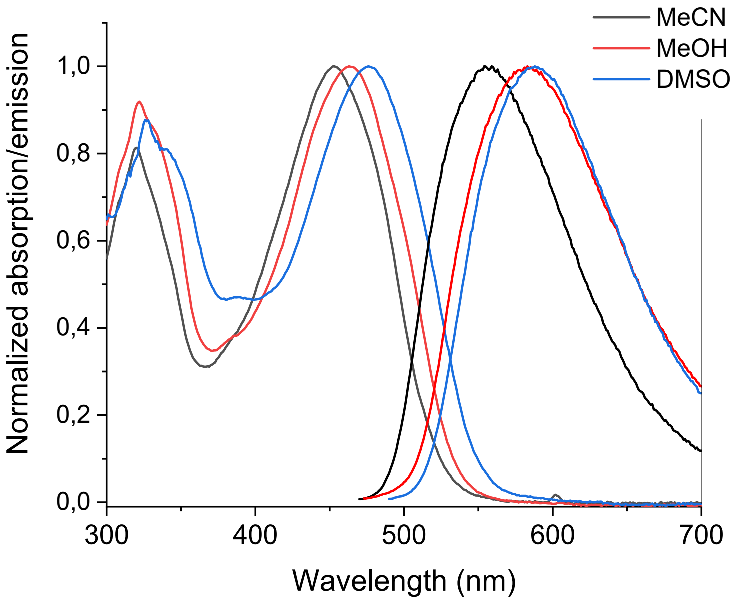


Figure S 2 Solvatochromism of ***5b***