



Supporting Information

for

Synthesis of pyrrolidinedione-fused hexahydropyrrolo[2,1-*a*]isoquinolines via three-component [3 + 2] cycloaddition followed by one-pot *N*-allylation and intramolecular Heck reactions

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General reaction procedures, compound characterization data, and copies of NMR spectra

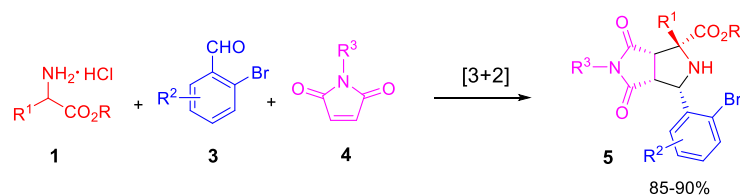
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1. General information

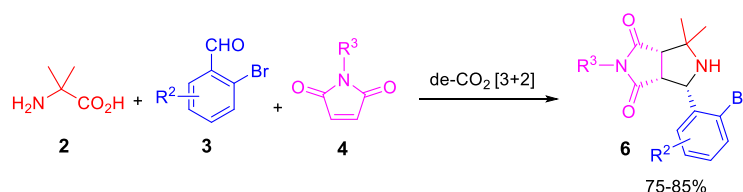
Chemicals and solvents were purchased from commercial sources and were used without further purification. ¹H (300 or 400 MHz), ¹³C NMR spectra (75 MHz) and ¹⁹F NMR (282 MHz) were recorded on Bruker NMR spectrometers. LC–MS were performed on an Agilent 2100 system with C18 column (5.0 μm, 6.0 × 50 mm). The mobile phases were MeOH and H₂O both containing 0.05% trifluoroacetic acid. A linear gradient was used to increase from 25:75 v/v MeOH/H₂O to 100% MeOH in 7.0 min at a flow rate of 0.7 mL/min. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). HRMS were performed on Agilent 6540 Q-TOF mass spectrometer (ESI). Flash column chromatography was performed using silica gel (200–300 mesh).

2. General procedures for the synthesis of pyrrolidine adducts 5



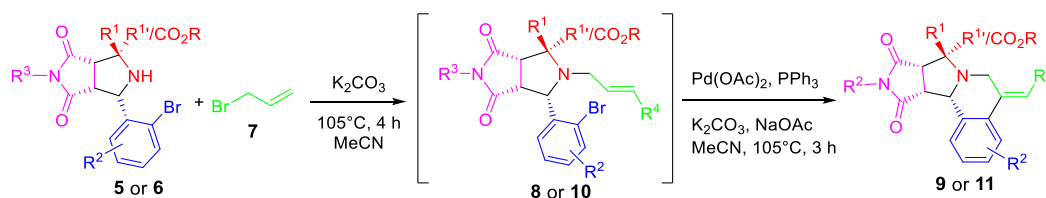
A solution of amino ester **1** (1.2 mmol), 2-bromobenzaldehyde **3** (1 mmol) and maleimide **4** (1.1 mmol) in EtOH (3 mL) with Et₃N (1.5 mmol) was heated at 110 °C for 6 h in a sealed vial. The concentrated reaction mixture was isolated by column chromatography eluted with 15:85 ethyl acetate:petroleum ether on silica gel to afford adduct **5** in 85–90% yield.

3. General procedures for the synthesis of pyrrolidine adducts 6



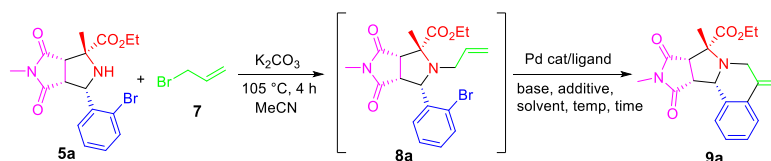
A solution of 2-aminoisobutyric acid **2** (1.2 mmol), 2-bromobenzaldehyde **3** (1 mmol) and maleimide **4** (1 mmol) in MeCN (3 mL) with AcOH (0.3 mmol) was heated at 110 °C for 6 h in a sealed vial. The concentrated reaction mixture was isolated by column chromatography eluted with 15:85 ethyl acetate:petroleum ether on silica gel to afford adduct **6** in 75%-85% yield. Selected compound characterization data for adduct **6** are listed below.

4. General procedures for the synthesis of products 9 or 11



To a solution of pyrrolidine adduct **5** or **6** (0.5 mmol), 3-bromopropene (**7**, 1.5 mmol) in MeCN (3 mL) was added K₂CO₃ (1 mmol), the mixture was heated at 105 °C for 4 h in a sealed vial. Upon the completion of reaction as monitored by HPLC or LC–MS, the mixture was evaporated under vacuum to remove unreacted 3-bromopropene to give crude *N*-allylation intermediate **8**. Without further purification, it was used for the Heck reaction with Pd(OAc)₂ (0.05 mmol), PPh₃ (0.1 mmol), K₂CO₃ (1 mmol) and NaOAc (0.5 mmol) in MeCN (3 mL) at 105 °C for 3 h under nitrogen atmosphere. After aqueous work up, the crude product was purified by flash chromatography eluted with 20:80 ethyl acetate:petroleum ether to afford product **9** or **11**.

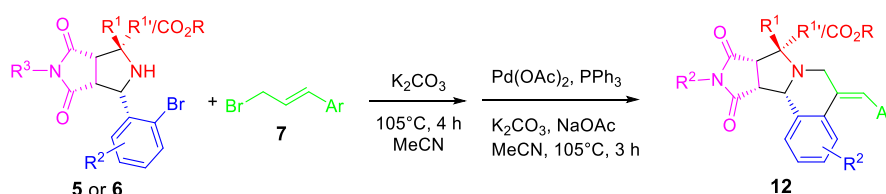
Control experiments for the synthesis of **9a**



Entry	Pd Cat.	Ligand	Base	Additive	Solvent	Temp/°C	Time/h	9a Yield/% ^d
1	Pd(OAc) ₂	-	K ₂ CO ₃	NaOAc	MeCN	105	6	Trace
2	PdCl ₂	-	K ₂ CO ₃	NaOAc	MeCN	105	6	Trace
3	-	PPh ₃	K ₂ CO ₃	NaOAc	MeCN	105	6	0
4	-	-	K ₂ CO ₃	NaOAc	MeCN	105	6	0

^a Reaction conditions: 0.5 mmol **5a** in 3 mL MeCN, **7** (3 equiv), K₂CO₃ (2 equiv) for *N*-allylation; Pd catalyst (10 mol %), ligand (20 mol %), base (2 equiv) and NaOAc (1 equiv) in 3 mL solvent under nitrogen for the Heck reaction;

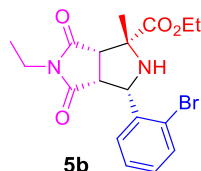
5. General procedures for the synthesis of products **12**



To a solution of pyrrolidine adduct **5** or **6** (0.5 mmol), cinnamyl bromide (1.5 mmol) in MeCN (3 mL) was added K₂CO₃ (1 mmol), the mixture was heated at 105 °C for 4 h in a sealed vial. Upon the completion of reaction as monitored by HPLC or LC–MS, the mixture was evaporated and the unreacted cinnamyl bromide was isolated to give *N*-allylation intermediate which was then used for the Heck reaction with Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), K₂CO₃ (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) at 105 °C for 3 h under nitrogen atmosphere. After aqueous work up, the crude product was purified by flash chromatography eluted with 20:80 ethyl acetate:petroleum ether to afford product **12**.

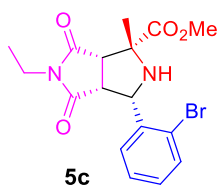
6. Characterization of selected pyrrolidine adducts **5** and **6**

Ethyl (1R,3S,3aR,6aS)-3-(2-bromophenyl)-5-ethyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (5b)



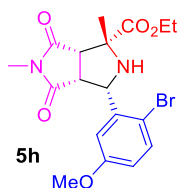
White solid, 368 mg, 90% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.27 (s, 1H), 7.17 (td, *J* = 7.6, 1.7 Hz, 1H), 5.00 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.34 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.81 (dd, *J* = 8.8, 7.7 Hz, 1H), 3.31 (ddd, *J* = 22.2, 13.5, 7.2 Hz, 3H), 2.29 (d, *J* = 4.9 Hz, 1H), 1.65 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 174.1, 172.3, 136.8, 132.5, 129.5, 127.40 (d, *J* = 2.3 Hz), 124.4, 66.8, 61.7, 60.4, 54.6, 46.9, 33.8, 24.0, 14.1, 13.1.

Methyl (1R,3S,3aR,6aS)-3-(2-bromophenyl)-5-ethyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (5c)



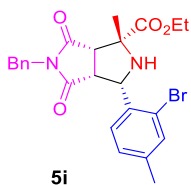
White solid, 355 mg, 90% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.17 (td, *J* = 7.6, 1.8 Hz, 1H), 5.00 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.88 (s, 3H), 3.81 (dd, *J* = 8.8, 7.7 Hz, 1H), 3.31 (ddd, *J* = 22.2, 11.0, 4.3 Hz, 3H), 2.26 (d, *J* = 6.3 Hz, 1H), 1.65 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.6, 174.0, 172.8, 136.8, 132.5, 129.5, 127.4 (d, *J* = 2.1 Hz), 124.4, 66.8, 60.42 (s), 54.6, 52.7, 46.8, 33.8, 23.9, 13.0.

Ethyl (1R,3S,3aR,6aS)-3-(2-bromo-5-methoxyphenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (5h)



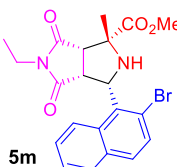
White solid, 361 mg, 85% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.47 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 6.72 (dd, *J* = 8.7, 3.1 Hz, 1H), 4.93 (d, *J* = 8.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.91 – 3.78 (m, 1H), 3.74 (s, 3H), 3.27 (d, *J* = 7.6 Hz, 1H), 2.78 (s, 3H), 2.24 (s, 1H), 1.64 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.7, 174.2, 172.3, 159.2, 138.1, 133.1, 114.5 (d, *J* = 7.1 Hz), 113.6, 66.7, 61.7, 60.3, 55.5, 54.5, 47.2, 24.8, 24.0, 14.1.

Ethyl (1R,3S,3aR,6aS)-5-benzyl-3-(2-bromo-4-methylphenyl)-1-methyl-4,6-dioxooctahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (5i)



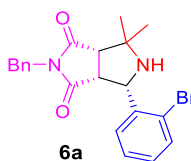
White solid, 422 mg, 87% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, *J* = 0.8 Hz, 1H), 7.25 (d, *J* = 1.1 Hz, 5H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.00 – 4.90 (m, 1H), 4.41 (d, *J* = 4.9 Hz, 2H), 4.33 (q, *J* = 6.9 Hz, 2H), 3.81 – 3.74 (m, 1H), 3.27 (d, *J* = 7.6 Hz, 1H), 2.27 (d, *J* = 7.2 Hz, 4H), 1.63 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 174.0, 172.2, 139.3, 135.6, 133.1 (d, *J* = 18.1 Hz), 129.0, 128.4 (d, *J* = 12.9 Hz), 127.8, 126.9, 123.9, 66.9, 61.8, 60.5, 54.9, 47.2, 42.4, 23.9, 20.8, 14.1.

Methyl (1R,3S,3aR,6aS)-3-(2-bromonaphthalen-1-yl)-5-ethyl-1-methyl-4,6-dioxooctahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (5m)



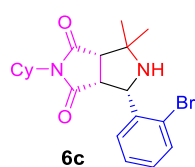
White solid, 382 mg, 86% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 5.33 (d, *J* = 4.4 Hz, 1H), 3.94 – 3.83 (m, 4H), 3.35 (dd, *J* = 13.7, 6.9 Hz, 1H), 3.27 (dd, *J* = 12.8, 7.2 Hz, 2H), 2.30 (s, 1H), 1.69 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.6, 174.0, 172.9, 134.7, 134.4, 132.2, 128.3, 127.8, 127.5 (d, *J* = 15.9 Hz), 126.7, 124.6, 124.4, 66.9, 61.3, 54.4, 52.6, 46.8, 33.9, 24.0, 13.0.

(3aS,6S,6aR)-2-Benzyl-6-(2-bromophenyl)-4,4-dimethyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (6a)



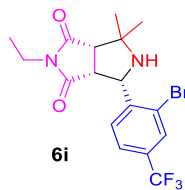
White solid, 343 mg, 83% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.59 – 7.52 (m, 1H), 7.27 (s, 7H), 7.11 (pd, *J* = 7.3, 4.0 Hz, 2H), 4.95 (d, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 2.6 Hz, 2H), 3.76 (t, *J* = 7.9 Hz, 1H), 2.90 (d, *J* = 7.8 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.3, 174.9, 137.8, 136.0, 132.3, 129.0, 128.7, 128.4, 128.1, 127.7, 127.2, 124.1, 60.3, 59.8, 53.6, 47.6, 42.1, 29.0, 26.5.

(3*aS*,6*S*,6*aR*)-6-(2-Bromophenyl)-2-cyclohexyl-4,4-dimethyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3*aH*)-dione (**6c**)



White solid, 332 mg, 82% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.58 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.24 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.15 (td, *J* = 7.6, 1.8 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 3.79 (ddd, *J* = 12.3, 8.4, 3.9 Hz, 1H), 3.68 (t, *J* = 7.9 Hz, 1H), 2.82 (d, *J* = 7.8 Hz, 1H), 2.04 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.90 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.73 (d, *J* = 12.9 Hz, 2H), 1.57 (d, *J* = 10.6 Hz, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.32 – 1.05 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.7, 175.3, 138.2, 132.3, 129.0, 128.1, 127.1, 124.2, 60.3, 59.8, 53.1, 51.6, 47.1, 29.1, 28.7 (d, *J* = 3.0 Hz), 26.5, 25.8 (d, *J* = 3.7 Hz), 24.9.

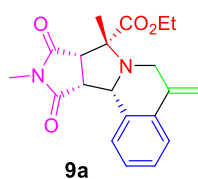
(3*aS*,6*S*,6*aR*)-6-(2-Bromo-4-(trifluoromethyl)phenyl)-2-ethyl-4,4-dimethyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3*aH*)-dione (**6i**)



White solid, 314 mg, 75% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 2.1 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.41 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 3.75 (t, *J* = 8.0 Hz, 1H), 3.43 – 3.29 (m, 2H), 2.88 (d, *J* = 7.8 Hz, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.1, 174.9, 139.8, 132.8, 129.9, 129.5, 128.0, 125.7 (d, *J* = 3.9 Hz), 125.1 (d, *J* = 3.8 Hz), 122.1, 59.9 (d, *J* = 6.5 Hz), 53.2, 47.2, 33.5, 29.0, 26.4, 13.1.

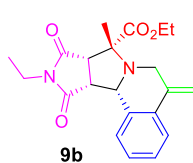
7. Characterization of products 9, 11 and 12

Ethyl (8*R*,8*aS*,11*aR*,11*bS*)-8,10-dimethyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9a**)



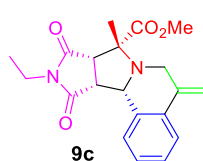
Orange solid, 138 mg, 78% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H), 7.25 (dt, *J* = 11.7, 3.9 Hz, 1H), 5.56 (d, *J* = 1.4 Hz, 1H), 4.97 (d, *J* = 1.2 Hz, 1H), 4.39 (d, *J* = 7.1 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.21 – 4.11 (m, 1H), 3.70 (t, *J* = 7.4 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.82 (s, 3H), 1.46 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 174.7, 171.3, 139.0, 132.3 (d, *J* = 4.9 Hz), 128.4, 127.0 (d, *J* = 13.5 Hz), 124.0, 108.4, 69.8, 62.0, 61.6, 54.4, 50.6, 45.6, 25.1, 14.6, 14.1. HRMS (ESI) calcd for C₂₀H₂₃N₂O₄ ([M+H]⁺): 355.1652, found 355.1655.

Ethyl (8*R*,8*aS*,11*aR*,11*bS*)-10-ethyl-8-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9b**)



Orange solid, 141 mg, 77% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.27 – 7.22 (m, 1H), 5.55 (s, 1H), 4.96 (s, 1H), 4.39 (d, *J* = 7.0 Hz, 1H), 4.33 – 4.26 (m, 1H), 4.17 – 4.08 (m, 1H), 3.68 (t, *J* = 7.4 Hz, 1H), 3.47 (d, *J* = 11.9 Hz, 1H), 3.38 (q, *J* = 7.1 Hz, 2H), 3.22 – 3.14 (m, 2H), 1.46 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.3, 174.5, 171.2, 139.1, 132.4 (d, *J* = 8.3 Hz), 128.4, 127.0, 126.8, 124.0, 108.2, 69.9, 61.9, 61.6, 54.3, 50.6, 45.6, 34.0, 14.7, 14.1, 12.7. HRMS (ESI) calcd for C₂₁H₂₅N₂O₄ ([M+H]⁺): 369.1809, found 369.1807.

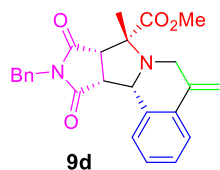
Methyl (8*R*,8*aS*,11*aR*,11*bS*)-10-ethyl-8-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9c**)



Orange solid, 141 mg, 80% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 5.57 (s, 1H), 4.98 (s, 1H), 4.39 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.68 (t, *J* = 7.4 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.42 – 3.33 (m, 2H), 3.20 (d, *J* = 12.0 Hz, 1H), 3.16 (d, *J* = 7.7 Hz, 1H), 1.47 (s, 3H),

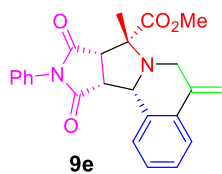
1.01 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.4, 174.4, 171.7, 138.9, 132.2 (d, $J = 8.8$ Hz), 128.4, 126.9 (d, $J = 18.0$ Hz), 124.0, 108.4, 70.0, 62.0, 54.3, 52.6, 50.6, 45.5, 34.1, 14.6, 12.6. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 355.1652, found 355.1655.

Methyl (8*R*,8*aS*,11*aR*,11*bS*)-10-benzyl-8-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9d**)



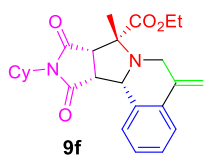
Orange solid, 158 mg, 76% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.65 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.32 – 7.23 (m, 2H), 7.18 (d, $J = 4.4$ Hz, 5H), 5.60 (s, 1H), 5.02 (s, 1H), 4.49 (d, $J = 4.8$ Hz, 2H), 4.41 (d, $J = 7.3$ Hz, 1H), 3.68 (t, $J = 7.4$ Hz, 1H), 3.58 (s, 3H), 3.52 (d, $J = 11.8$ Hz, 1H), 3.19 (dd, $J = 9.6, 6.5$ Hz, 2H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.2, 174.3, 171.7, 139.2, 135.2, 132.3 (d, $J = 15.1$ Hz), 128.4 (d, $J = 8.7$ Hz), 128.1, 127.5, 127.0 (d, $J = 15.6$ Hz), 124., 108.4, 70.1, 62.1, 54.3, 52.4, 50.6, 45.5, 42.4, 14.5. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 417.1809, found 417.1804.

Methyl (8*R*,8*aS*,11*aR*,11*bS*)-8-methyl-5-methylene-9,11-dioxo-10-phenyl-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9e**)



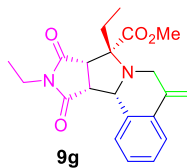
Orange solid, 159 mg, 79% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.65 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 7.37 – 7.31 (m, 2H), 7.28 (t, $J = 4.9$ Hz, 2H), 7.23 (d, $J = 7.4$ Hz, 1H), 7.13 (dd, $J = 5.5, 3.4$ Hz, 2H), 5.57 (d, $J = 1.1$ Hz, 1H), 4.99 (d, $J = 0.8$ Hz, 1H), 4.45 (d, $J = 6.7$ Hz, 1H), 3.84 (dd, $J = 7.6, 6.9$ Hz, 1H), 3.76 (s, 3H), 3.50 (d, $J = 12.0$ Hz, 1H), 3.30 (d, $J = 7.8$ Hz, 1H), 3.25 (d, $J = 11.9$ Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 173.8, 173.2, 171.8, 139.0, 132.2 (d, $J = 4.9$ Hz), 131.8, 128.9, 128.4 (d, $J = 11.6$ Hz), 126.9 (d, $J = 8.3$ Hz), 126.6, 124.0, 110.9, 108.4, 70.7, 62.1, 54.4, 53.5, 52.7, 50.5, 45.9, 14.9. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 403.1652, found 403.1656.

Ethyl (8*R*,8*aS*,11*aR*,11*bS*)-10-cyclohexyl-8-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9f**)



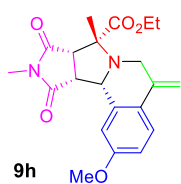
Orange solid, 154 mg, 73% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.64 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.54 – 7.49 (m, 1H), 7.30 (td, $J = 7.5, 1.5$ Hz, 1H), 7.26 – 7.20 (m, 1H), 5.52 (d, $J = 1.0$ Hz, 1H), 4.93 (s, 1H), 4.37 – 4.26 (m, 2H), 4.15 – 4.03 (m, 1H), 3.83 – 3.68 (m, 1H), 3.60 (dd, $J = 7.6, 7.0$ Hz, 1H), 3.47 – 3.41 (m, 1H), 3.17 (d, $J = 11.8$ Hz, 1H), 3.07 (d, $J = 7.7$ Hz, 1H), 2.01 – 1.87 (m, 2H), 1.70 (d, $J = 10.4$ Hz, 2H), 1.53 (dd, $J = 7.1, 3.7$ Hz, 2H), 1.44 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H), 1.22 – 1.04 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.5, 174.8, 171.2, 139.4, 132.5 (d, $J = 13.8$ Hz), 128.4, 126.8 (d, $J = 16.4$ Hz), 124.0, 108.0, 70.0, 61.9, 61.4, 53.9, 51.9, 50.4, 45.2, 28.6, 28.3, 25.8 (d, $J = 3.5$ Hz), 24.9, 14.8, 14.1. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 423.2278, found 423.2275.

Methyl (8*R*,8*aS*,11*aR*,11*bS*)-8,10-diethyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9g**)



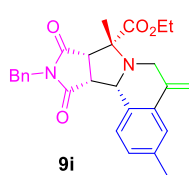
Orange solid, 134 mg, 73% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.62 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.32 – 7.21 (m, 2H), 5.50 (s, 1H), 4.96 (d, $J = 0.9$ Hz, 1H), 4.56 (d, $J = 7.3$ Hz, 1H), 3.74 (d, $J = 11.5$ Hz, 4H), 3.64 (t, $J = 7.5$ Hz, 1H), 3.44 – 3.31 (m, 3H), 3.26 (d, $J = 7.7$ Hz, 1H), 2.11 (dt, $J = 14.3, 7.2$ Hz, 1H), 1.93 – 1.79 (m, 1H), 1.14 (t, $J = 7.4$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.6, 174.5, 171.2, 139.3, 132.50 (d, $J = 16.5$ Hz), 128.5, 126.85 (d, $J = 17.8$ Hz), 124.1, 108.0, 73.4, 61.9, 52.32 (d, $J = 16.7$ Hz), 51.4, 46.0, 34.0, 23.7, 12.7, 10.6. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 369.1809, found 369.1813.

Ethyl (8R,8aS,11aR,11bS)-2-methoxy-8,10-dimethyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (9h)



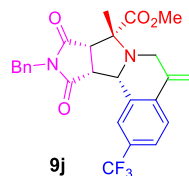
Orange solid, 123 mg, 64% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.59 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 8.8, 2.3 Hz, 1H), 5.42 (s, 1H), 4.86 (s, 1H), 4.36 (d, J = 7.2 Hz, 1H), 4.30 – 4.23 (m, 1H), 4.17 (dd, J = 10.7, 7.1 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 1H), 3.46 (d, J = 12.0 Hz, 1H), 3.20 (s, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.83 (s, 3H), 1.46 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.4, 174.7, 171.3, 158.3, 138.6, 133.7, 125.25 (d, J = 11.7 Hz), 113.8, 112.9, 106.4, 69.8, 62.3, 61.6, 55.4, 54.4, 50.8, 45.6, 25.2, 14.6, 14.1. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$): 385.1758, found 385.1761.

Ethyl (8R,8aS,11aR,11bS)-10-benzyl-3,8-dimethyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (9i)



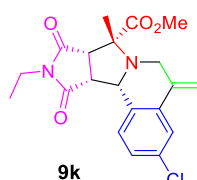
Orange solid, 144 mg, 65% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.18 (s, 5H), 7.12 (d, J = 7.9 Hz, 1H), 5.57 (s, 1H), 4.98 (s, 1H), 4.50 (s, 2H), 4.38 (d, J = 7.2 Hz, 1H), 4.25 – 4.17 (m, 1H), 3.96 (dq, J = 10.7, 7.1 Hz, 1H), 3.65 (t, J = 7.4 Hz, 1H), 3.50 (d, J = 11.7 Hz, 1H), 3.19 (s, 1H), 3.16 (d, J = 3.9 Hz, 1H), 2.33 (s, 3H), 1.45 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.1, 174.5, 171.2, 139.5, 136.5, 135.2, 132.3, 129.4, 128.35 (d, J = 5.2 Hz), 128.00 (d, J = 3.3 Hz), 127.5, 124.5, 107.9, 69.9, 62.0, 61.5, 54.4, 50.6, 45.6, 42.3, 29.7, 21.4, 14.5, 14.0. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 445.2122, found 445.2127.

Methyl (8R,8aS,11aR,11bS)-10-benzyl-8-methyl-5-methylene-9,11-dioxo-2-(trifluoromethyl)-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (9j)



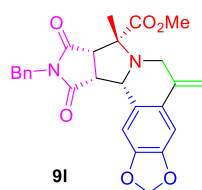
Orange solid, 162 mg, 67% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.81 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.18 (s, 5H), 5.69 (s, 1H), 5.15 (s, 1H), 4.50 (d, J = 2.3 Hz, 2H), 4.43 (d, J = 7.5 Hz, 1H), 3.73 (dd, J = 8.7, 6.2 Hz, 1H), 3.62 – 3.51 (m, 4H), 3.23 (d, J = 2.1 Hz, 1H), 3.20 (d, J = 6.6 Hz, 1H), 1.47 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ -62.48 (s). ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 173.9, 171.4, 138.2, 135.8, 135.0, 132.7, 128.69 (d, J = 21.5 Hz), 128.4, 127.9, 127.5, 125.94 (d, J = 3.8 Hz), 124.6, 123.68 (d, J = 3.7 Hz), 110.7, 70.0, 61.9, 54.2, 52.5, 50.2, 45.2, 42.4, 29.7, 14.5. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 485.1683, found 485.1687.

Methyl (8R,8aS,11aR,11bS)-3-chloro-10-ethyl-8-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (9k)



Orange solid, 120 mg, 62% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 5.56 (s, 1H), 5.03 (s, 1H), 4.33 (d, J = 7.0 Hz, 1H), 3.77 (s, 3H), 3.66 (t, J = 7.4 Hz, 1H), 3.49 (d, J = 12.0 Hz, 1H), 3.39 (dd, J = 14.1, 6.9 Hz, 2H), 3.17 (d, J = 7.9 Hz, 2H), 1.47 (s, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.2, 174.3, 171.5, 137.9, 134.1, 133.0, 130.7, 129.9, 126.9, 124.0, 109.7, 70.0, 61.6, 54.2, 52.6, 50.3, 45.3, 34.1, 14.7, 12.7. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{ClN}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 389.1263, found 389.1260.

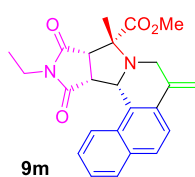
Methyl (8*R*,8*aS*,11*aR*,11*bS*)-10-benzyl-8-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**9l**)



9l

Orange solid, 138 mg, 60% yield. ¹H NMR (300 MHz, DMSO) δ 7.24 – 7.20 (m, 2H), 7.19 (d, *J* = 1.8 Hz, 2H), 7.13 (dd, *J* = 7.0, 2.6 Hz, 2H), 7.07 (s, 1H), 6.00 (d, *J* = 6.5 Hz, 2H), 5.49 (s, 1H), 4.88 (s, 1H), 4.47 (d, *J* = 15.5 Hz, 1H), 4.37 (d, *J* = 15.5 Hz, 1H), 4.29 (d, *J* = 7.1 Hz, 1H), 3.97 (t, *J* = 7.3 Hz, 1H), 3.47 (s, 3H), 3.38 (d, *J* = 3.4 Hz, 2H), 3.07 (d, *J* = 11.9 Hz, 1H), 1.37 (s, 3H). ¹³C NMR (75 MHz, DMSO) δ 176.0, 175.5, 171.9, 146.8, 146.6, 139.8, 135.9, 128.6, 128.1, 127.4 (d, *J* = 11.0 Hz), 126.5, 109.0, 107.2, 103.6, 101.4, 70.0, 61.8, 54.5, 52.4, 50.4, 45.9, 41.6, 14.9. HRMS (ESI) calcd for C₂₆H₂₅N₂O₆ ([M+H]⁺): 461.1707, found 461.1703.

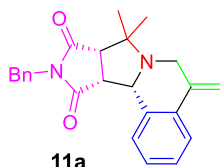
Methyl(10*R*,10*aS*,13*aR*,13*bS*)-12-ethyl-10-methyl-7-methylene-11,13-dioxo-7,10,10*a*,11,12,-13,13*a*,13*b*-octahydro-8*H*-benzo[*h*]pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-10-carboxylate (**9m**)



9m

Orange solid, 141 mg, 70% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.56 – 8.47 (m, 1H), 7.87 – 7.80 (m, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.49 – 7.40 (m, 2H), 5.64 (s, 1H), 5.51 (s, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 3.75 – 3.67 (m, 1H), 3.50 (d, *J* = 10.3 Hz, 1H), 3.38 (q, *J* = 7.2 Hz, 2H), 3.29 (d, *J* = 10.3 Hz, 1H), 3.15 (d, *J* = 7.5 Hz, 1H), 1.47 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.6, 174.8, 171.8, 138.2, 133.4, 130.71 – 130.21 (m), 128.6, 126.9, 126.1, 125.8 – 125.2 (m), 116.9, 70.2, 62.7, 54.2, 52.5 (d, *J* = 2.7 Hz), 45.7, 34.0, 14.7, 12.7. HRMS (ESI) calcd for C₂₄H₂₅N₂O₄ ([M+H]⁺): 405.1809, found 405.1814.

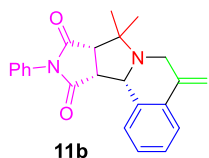
(8*aS*,11*aR*,11*bS*)-10-Benzyl-8,8-dimethyl-5-methylene-5,6,8,8*a*,11*a*,11*b*-hexahydro-9*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11a**)



11a

Orange solid, 139 mg, 75% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.25 (dd, *J* = 5.5, 2.5 Hz, 1H), 7.22 – 7.17 (m, 5H), 5.57 (s, 1H), 5.00 (s, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.46 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 6.5 Hz, 1H), 3.67 – 3.58 (m, 1H), 3.49 (d, *J* = 12.0 Hz, 1H), 3.14 (d, *J* = 11.9 Hz, 1H), 2.93 (d, *J* = 7.6 Hz, 1H), 1.26 (s, 3H), 1.14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.2, 175.3, 140.2, 135.6, 133.2, 132.4, 128.4, 128.1, 127.5, 126.9 (d, *J* = 1.3 Hz), 124.0, 107.8, 62.4, 61.9, 53.9, 49.1, 46.0, 42.1, 24.1, 19.6. HRMS (ESI) calcd for C₂₄H₂₅N₂O₂ ([M+H]⁺): 373.1911, found 373.1914.

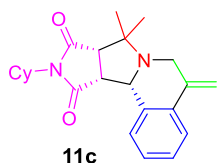
(8*aS*,11*aR*,11*bS*)-8,8-Dimethyl-5-methylene-10-phenyl-5,6,8,8*a*,11*a*,11*b*-hexahydro-9*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11b**)



11b

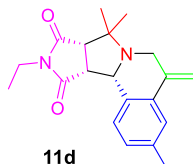
Orange solid, 140 mg, 78% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.64 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.37 – 7.21 (m, 5H), 7.18 – 7.13 (m, 2H), 5.55 (d, *J* = 1.2 Hz, 1H), 4.99 (d, *J* = 1.1 Hz, 1H), 4.39 (d, *J* = 6.1 Hz, 1H), 3.78 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.54 (d, *J* = 12.2 Hz, 1H), 3.18 (d, *J* = 12.0 Hz, 1H), 3.07 (d, *J* = 7.7 Hz, 1H), 1.42 (s, 3H), 1.21 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.8, 174.6, 140.0, 133.2, 132.3, 131.8, 128.9, 128.3 (d, *J* = 3.5 Hz), 126.9 (d, *J* = 5.8 Hz), 126.5, 123.9, 107.8, 62.6, 62.4, 54.0, 49.4, 46.2, 45.2, 24.5, 20.1. HRMS (ESI) calcd for C₂₃H₂₃N₂O₂ ([M+H]⁺): 359.1754, found 359.1757.

(8a*S*,11a*R*,11b*S*)-10-Cyclohexyl-8,8-dimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11c**)



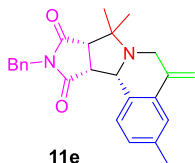
Orange solid, 131 mg, 72% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.27 (ddd, *J* = 18.4, 10.9, 6.6 Hz, 2H), 5.53 (s, 1H), 4.95 (s, 1H), 4.28 (d, *J* = 6.0 Hz, 1H), 3.79 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.55 (dd, *J* = 7.4, 6.3 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 3.13 (d, *J* = 12.1 Hz, 1H), 2.83 (d, *J* = 7.6 Hz, 1H), 2.14 – 1.89 (m, 2H), 1.71 (d, *J* = 11.0 Hz, 2H), 1.55 (d, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 12.1 Hz, 2H), 1.29 (s, 3H), 1.21 – 1.06 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 176.9, 175.8, 140.2, 133.6, 132.2, 128.2, 126.8, 123.9, 107.6, 62.4, 61.9, 53.6, 51.6, 49.3, 45.7, 29.0, 28.3, 25.8 (d, *J* = 3.5 Hz), 25.0, 24.2, 20.2. HRMS (ESI) calcd for C₂₃H₂₉N₂O₂ ([M+H]⁺): 365.2224, found 365.2222.

(8a*S*,11a*R*,11b*S*)-10-Ethyl-3,8,8-trimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11d**)



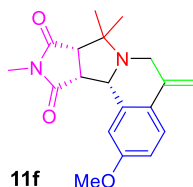
Orange solid, 118 mg, 73% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.53 (s, 1H), 4.94 (s, 1H), 4.26 (d, *J* = 6.0 Hz, 1H), 3.59 (t, *J* = 6.8 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 3.42 – 3.30 (m, 2H), 3.11 (d, *J* = 12.0 Hz, 1H), 2.90 (d, *J* = 7.5 Hz, 1H), 2.35 (s, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.02 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 176.5, 175.6, 140.2, 136.2, 132.0, 130.6, 128.2, 127.9, 124.3, 107.5, 62.2, 61.8, 53.9, 49.4, 46.0, 33.6, 24.3, 21.4, 19.9, 12.9. HRMS (ESI) calcd for C₂₀H₂₅N₂O₂ ([M+H]⁺): 325.1911, found 325.1914.

(8a*S*,11a*R*,11b*S*)-10-Benzyl-3,8,8-trimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11e**)



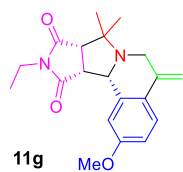
Orange solid, 135 mg, 70% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.20 (s, 5H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.55 (s, 1H), 4.98 (s, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.46 (d, *J* = 14.5 Hz, 1H), 4.31 (d, *J* = 6.4 Hz, 1H), 3.60 (t, *J* = 7.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.11 (d, *J* = 11.9 Hz, 1H), 2.91 (d, *J* = 7.5 Hz, 1H), 2.34 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 176.3, 175.4, 140.4, 136.3, 135.7, 132.2, 130.4, 128.2 (dd, *J* = 25.0, 11.9 Hz), 127.5, 124.4, 107.5, 62.3, 61.9, 53.9, 49.2, 46.1, 42.1, 24.2, 21.4, 19.6. HRMS (ESI) calcd for C₂₅H₂₇N₂O₂ ([M+H]⁺): 387.2067, found 387.2071.

(8a*S*,11a*R*,11b*S*)-2-Methoxy-8,8,10-trimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11f**)



Orange solid, 115 mg, 71% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.86 (d, *J* = 1.1 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 1H), 3.86 (s, 3H), 3.62 (t, *J* = 7.2 Hz, 1H), 3.47 (d, *J* = 12.2 Hz, 1H), 3.11 (d, *J* = 12.2 Hz, 1H), 2.94 (d, *J* = 7.7 Hz, 1H), 2.82 (s, 3H), 1.33 (s, 3H), 1.14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.6, 175.6, 158.4, 139.5, 134.7, 125.1 (d, *J* = 10.0 Hz), 113.6, 112.9, 105.8, 62.7, 61.8, 55.4, 54.0, 49.5, 45.8, 24.8, 24.3, 19.6. HRMS (ESI) calcd for C₁₉H₂₃N₂O₃ ([M+H]⁺): 327.1703, found 327.1701.

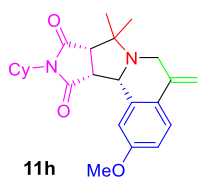
(8a*S*,11a*R*,11b*S*)-10-Ethyl-2-methoxy-8,8-dimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11g**)



11g

Orange solid, 115 mg, 68% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.40 (s, 1H), 4.85 (s, 1H), 4.28 (d, *J* = 6.5 Hz, 1H), 3.86 (s, 3H), 3.60 (t, *J* = 7.1 Hz, 1H), 3.46 (d, *J* = 12.2 Hz, 1H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.11 (d, *J* = 12.1 Hz, 1H), 2.91 (d, *J* = 7.7 Hz, 1H), 1.32 (s, 3H), 1.15 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 176.4, 175.3, 158.4, 139.6, 134.7, 125.2, 113.4, 112.9, 105.6, 62.6, 61.8, 55.4, 53.9, 49.5, 45.9, 33.7, 24.3, 19.8, 12.9. HRMS (ESI) calcd for C₂₀H₂₅N₂O₃ ([M+H]⁺): 341.1860, found 341.1864.

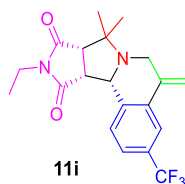
(8a*S*,11a*R*,11b*S*)-10-Cyclohexyl-2-methoxy-8,8-dimethyl-5-methylene-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11h**)



11h

Orange solid, 128 mg, 65% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.8 Hz, 1H), 6.99 (s, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 5.38 (s, 1H), 4.84 (s, 1H), 4.25 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.79 (t, *J* = 12.3 Hz, 1H), 3.53 (t, *J* = 6.8 Hz, 1H), 3.43 (d, *J* = 12.1 Hz, 1H), 3.11 (d, *J* = 12.1 Hz, 1H), 2.82 (d, *J* = 7.6 Hz, 1H), 2.03 (dq, *J* = 36.3, 12.1 Hz, 2H), 1.72 (d, *J* = 10.7 Hz, 2H), 1.55 (d, *J* = 11.2 Hz, 1H), 1.46 (d, *J* = 11.8 Hz, 2H), 1.29 (s, 3H), 1.20 (s, 1H), 1.13 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.8, 175.6, 158.3, 139.8, 134.9, 125.2, 113.4, 112.7, 105.5, 62.6, 61.9, 55.3, 53.5, 51.6, 49.4, 45.6, 29.0, 28.4, 25.8 (d, *J* = 3.2 Hz), 25.0, 24.2, 20.1. HRMS (ESI) calcd for C₂₄H₃₁N₂O₃ ([M+H]⁺): 395.2329, found 395.2327.

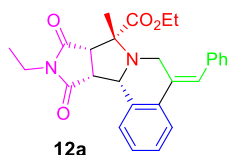
(8a*S*,11a*R*,11b*S*)-10-Ethyl-8,8-dimethyl-5-methylene-3-(trifluoromethyl)-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(10*H*)-dione (**11i**)



11i

Orange solid, 136 mg, 72% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.72 (m, 2H), 7.47 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 5.10 (s, 1H), 4.32 (d, *J* = 6.3 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 1H), 3.52 (d, *J* = 12.3 Hz, 1H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.15 (d, *J* = 12.2 Hz, 1H), 2.94 (d, *J* = 7.6 Hz, 1H), 1.33 (s, 3H), 1.17 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ¹⁹F NMR (282 MHz, CDCl₃) δ -62.52 (s). ¹³C NMR (101 MHz, CDCl₃) δ 176.2, 175.1, 139.0, 133.9, 124.4, 123.4, 110.1, 62.2, 61.9, 53.8, 53.4, 49.0, 45.6, 33.7, 29.7, 24.2, 19.8, 12.9. HRMS (ESI) calcd for C₂₀H₂₂F₃N₂O₂ ([M+H]⁺): 379.1628, found 379.1631.

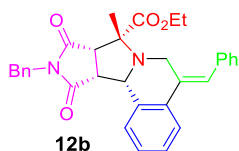
Ethyl (8*R*,8a*S*,11a*R*,11b*S*)-5-((*Z*)-benzylidene)-10-ethyl-8-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (**12a**)



12a

Orange solid, 122 mg, 55% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.76 – 7.68 (m, 1H), 7.60 – 7.53 (m, 1H), 7.32 (dd, *J* = 9.7, 4.3 Hz, 4H), 7.22 (dd, *J* = 10.2, 4.4 Hz, 3H), 7.14 (s, 1H), 4.44 (d, *J* = 6.9 Hz, 1H), 4.00 – 3.89 (m, 2H), 3.85 – 3.75 (m, 1H), 3.68 (t, *J* = 7.3 Hz, 1H), 3.36 (q, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 11.2 Hz, 2H), 1.46 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.2, 174.7, 171.3, 137.2, 133.6, 133.2, 132.6, 129.1, 128.4 (d, *J* = 18.8 Hz), 127.0 (d, *J* = 19.1 Hz), 126.6, 124.2, 123.9, 70.1, 61.7, 61.4, 54.2, 45.7, 45.3, 34.0, 14.8, 13.4, 12.7. HRMS (ESI) calcd for C₂₇H₂₉N₂O₄ ([M+H]⁺): 445.2122, found 445.2126.

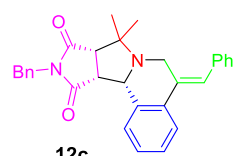
Ethyl (8R,8aS,11aR,11bS)-10-benzyl-5-((Z)-benzylidene)-8-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (12b)



12b

Orange solid, 142 mg, 56% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.55 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.37 – 7.22 (m, 7H), 7.19 (d, *J* = 7.2 Hz, 6H), 4.48 (d, *J* = 3.7 Hz, 3H), 4.03 (d, *J* = 11.9 Hz, 1H), 3.84 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.67 (t, *J* = 7.4 Hz, 1H), 3.56 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.15 (dd, *J* = 10.0, 5.5 Hz, 2H), 1.46 (s, 3H), 0.60 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 174.5, 171.2, 137.2, 135.2, 133.8, 133.4, 132.4, 129.1, 128.4 (t, *J* = 10.8 Hz), 127.9, 127.4 (d, *J* = 12.9 Hz), 127.0, 126.7, 124.4, 123.8, 70.2, 61.9, 61.4, 54.2, 45.6, 45.2, 42.2, 14.5, 13.2. HRMS (ESI) calcd for C₃₂H₃₁N₂O₄ ([M+H]⁺): 507.2278, found 507.2278.

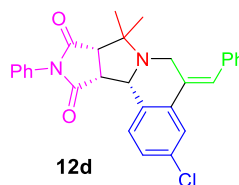
(8aS,11aR,11bS)-10-Benzyl-5-((Z)-benzylidene)-8,8-dimethyl-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione (12c)



12c

Orange solid, 116 mg, 52% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.76 – 7.71 (m, 1H), 7.54 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.27 (ddd, *J* = 10.6, 6.1, 2.4 Hz, 5H), 7.18 (t, *J* = 2.2 Hz, 5H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.46 (d, *J* = 12.9 Hz, 1H), 4.42 (d, *J* = 4.8 Hz, 1H), 4.03 (d, *J* = 12.3 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.09 (d, *J* = 12.6 Hz, 1H), 2.92 (d, *J* = 7.6 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.2, 175.4, 137.4, 135.6, 134.1, 133.7, 133.4, 129.2, 128.7 – 128.2 (m), 128.1, 127.5, 127.2 – 126.5 (m), 124.1, 123.2, 62.2 (d, *J* = 10.8 Hz), 53.9, 46.1, 43.8, 42.1, 24.1, 19.8. HRMS (ESI) calcd for C₃₀H₂₉N₂O₂ ([M+H]⁺): 449.2224, found 449.2227.

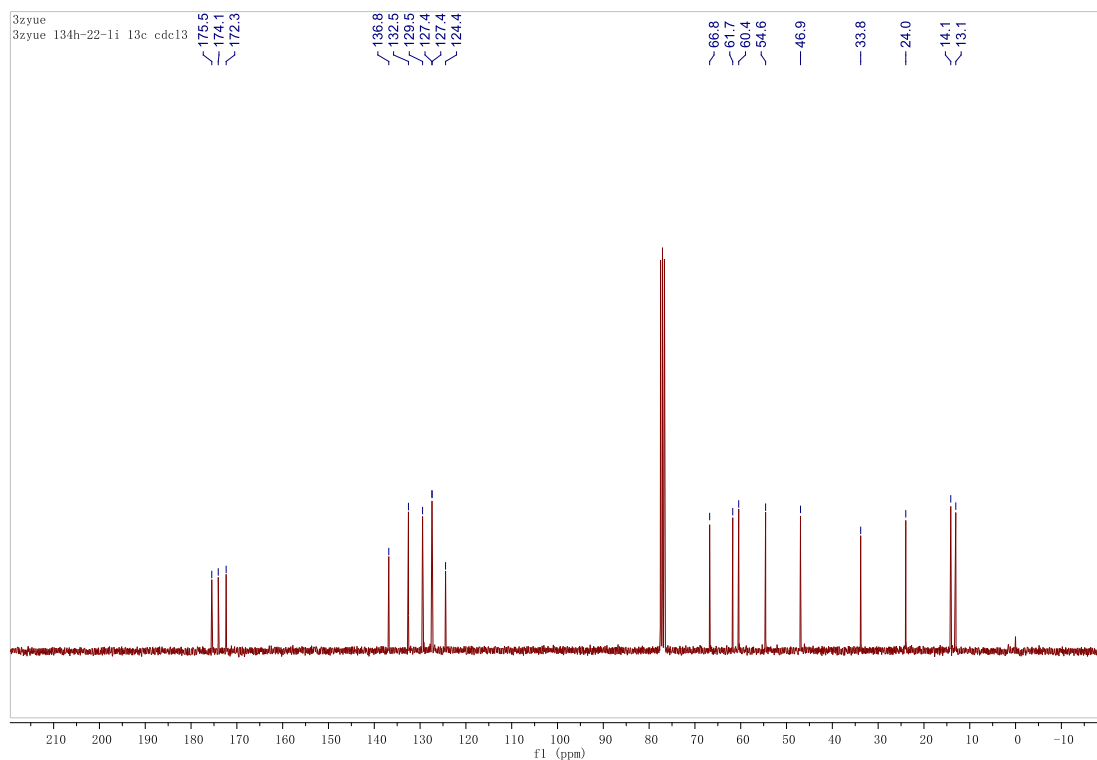
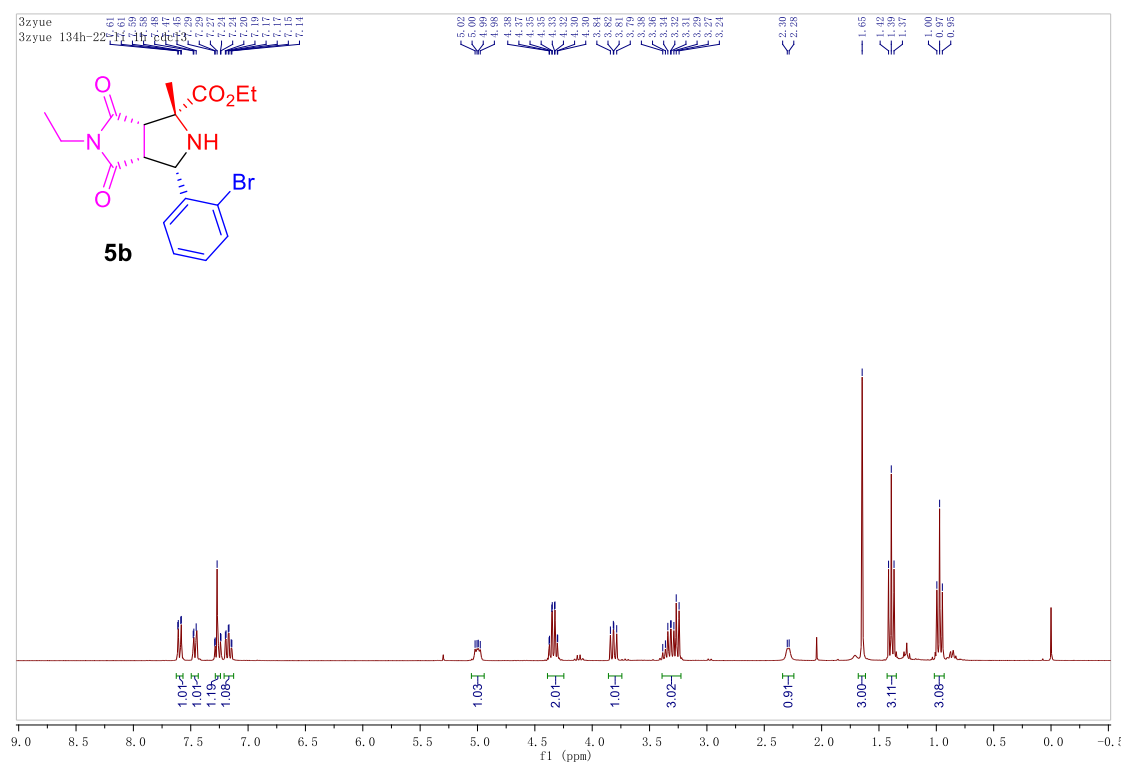
(8aS,11aR,11bS)-5-((Z)-Benzylidene)-3-chloro-8,8-dimethyl-10-phenyl-5,6,8,8a,11a,11b-hexahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione (12d)

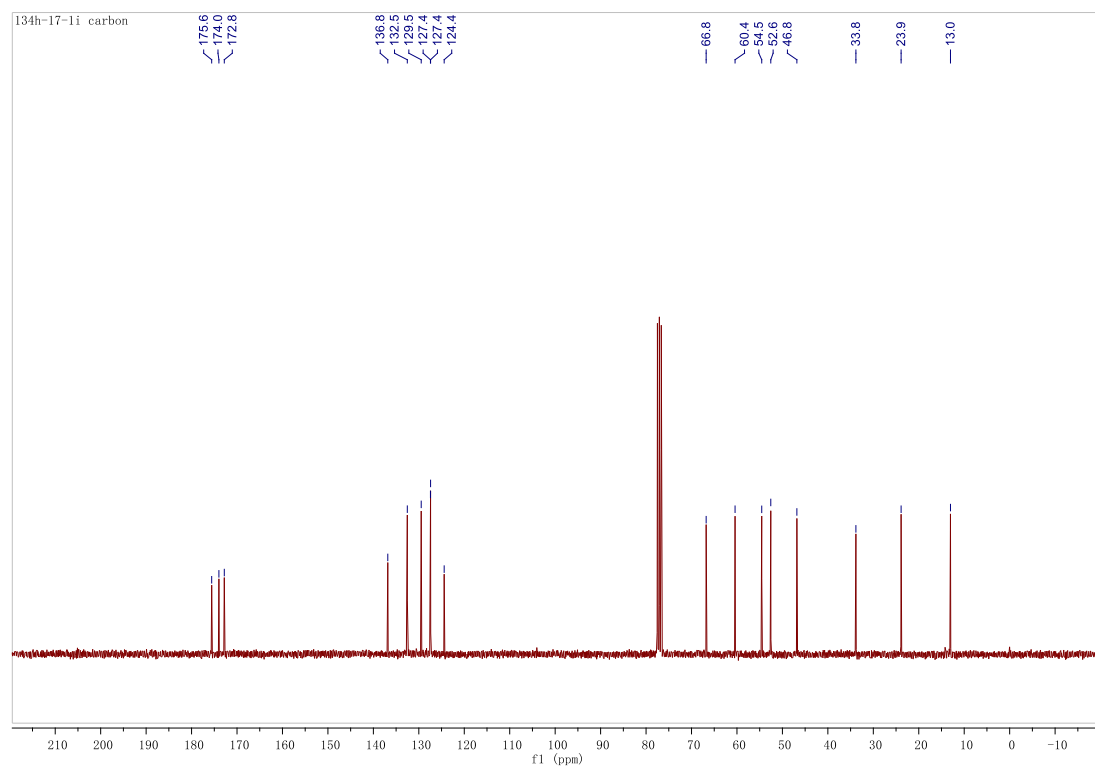
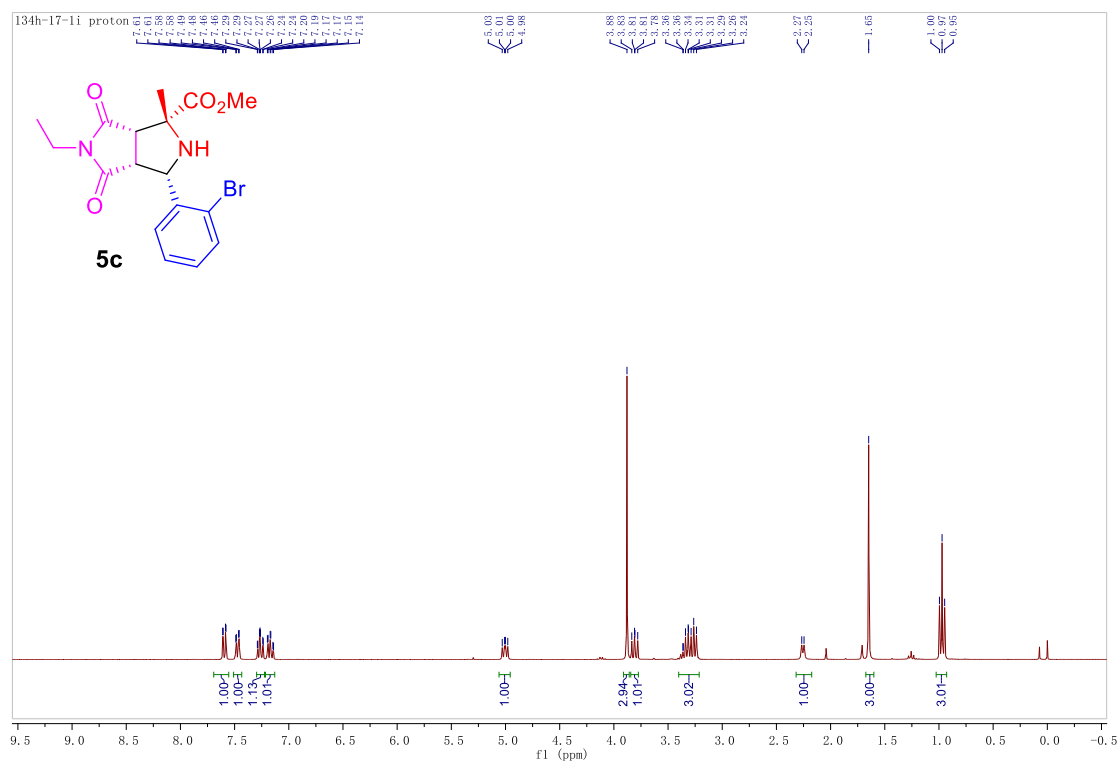


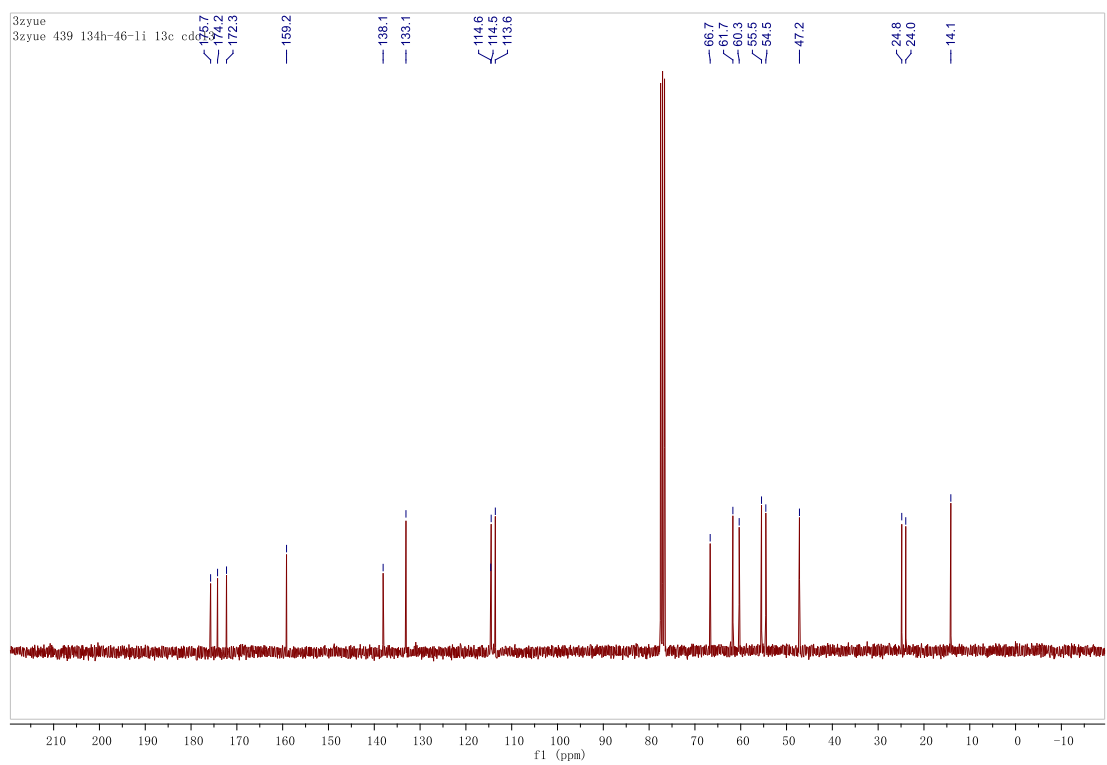
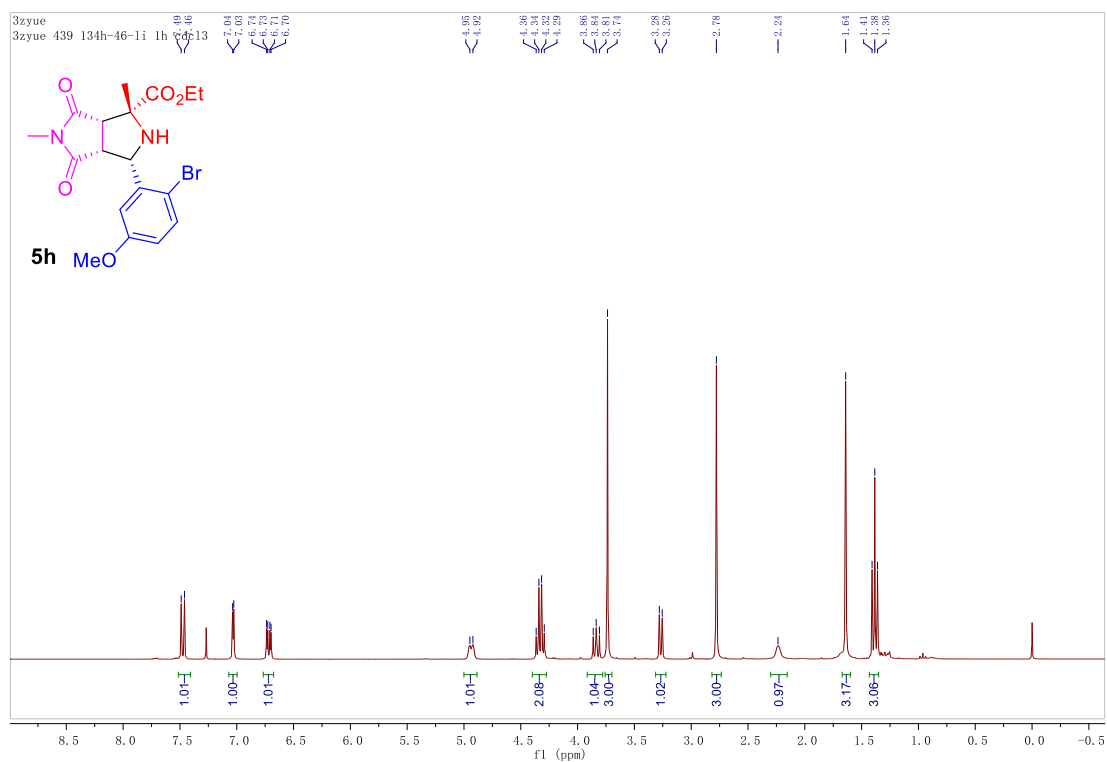
12d

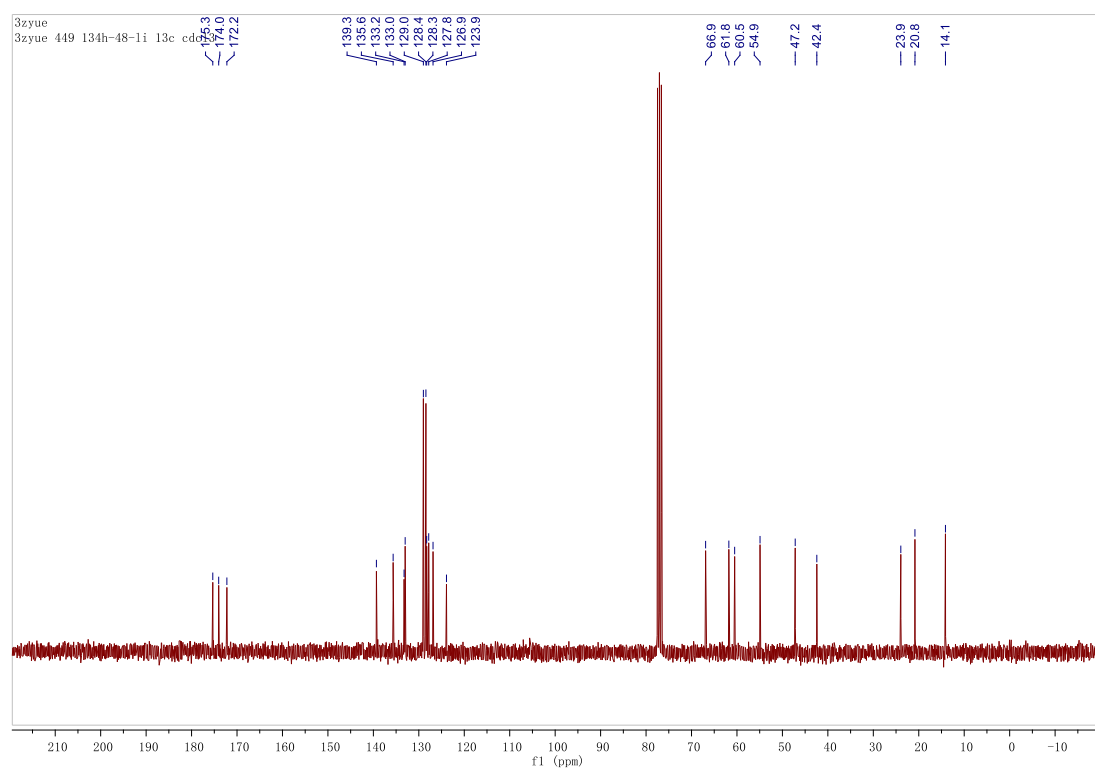
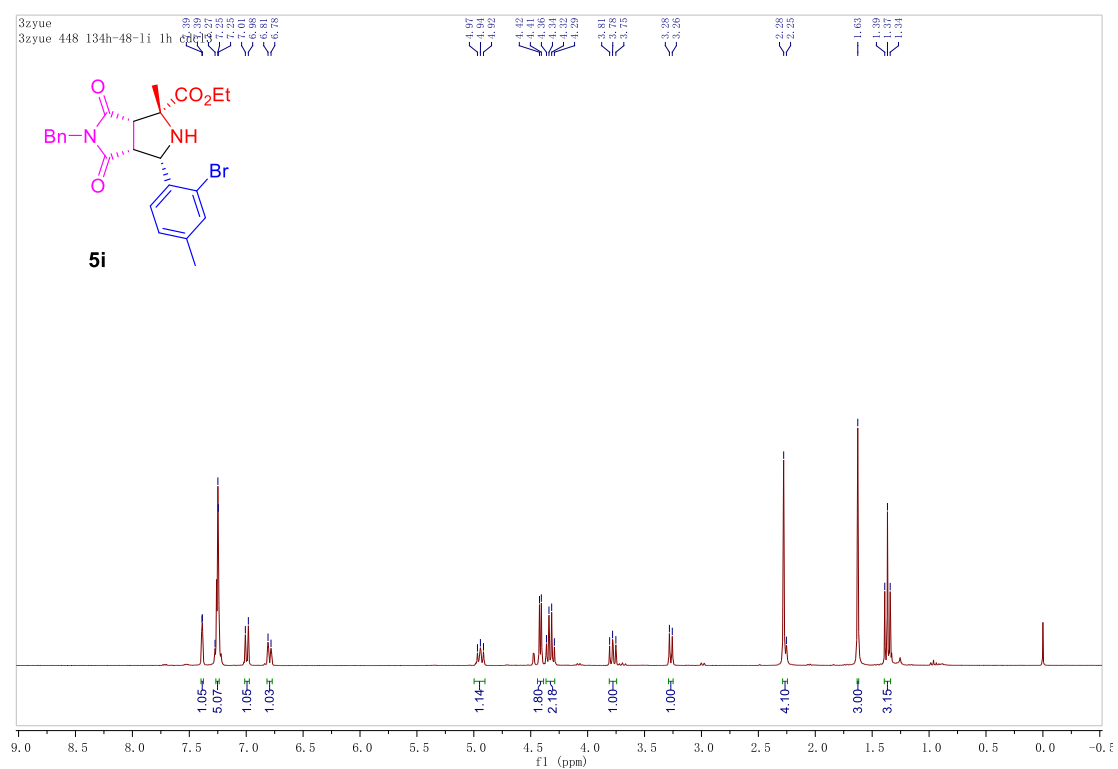
Orange solid, 117 mg, 50% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 7.2, 4.3 Hz, 3H), 7.31 – 7.21 (m, 6H), 7.13 (dd, *J* = 5.3, 3.1 Hz, 3H), 4.36 (d, *J* = 6.1 Hz, 1H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.73 (dd, *J* = 7.7, 6.2 Hz, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 3.04 (d, *J* = 7.8 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.6, 174.6, 136.9, 135.5, 132.8 (d, *J* = 13.1 Hz), 131.8 (d, *J* = 6.4 Hz), 129.9, 129.2, 128.9, 128.4, 127.2, 126.5 (d, *J* = 14.8 Hz), 124.5, 123.9, 62.6, 62.1, 53.9, 46.2, 44.0, 24.4, 20.1. HRMS (ESI) calcd for C₂₉H₂₆ClN₂O₂ ([M+H]⁺): 469.1677, found 469.1680.

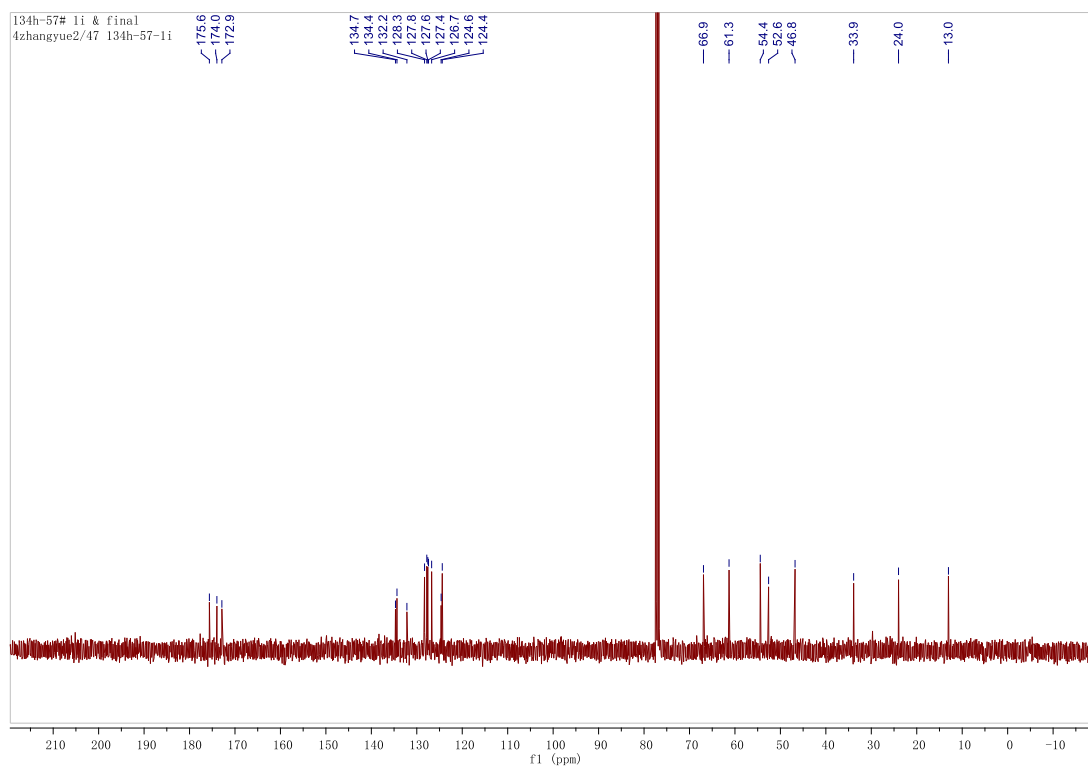
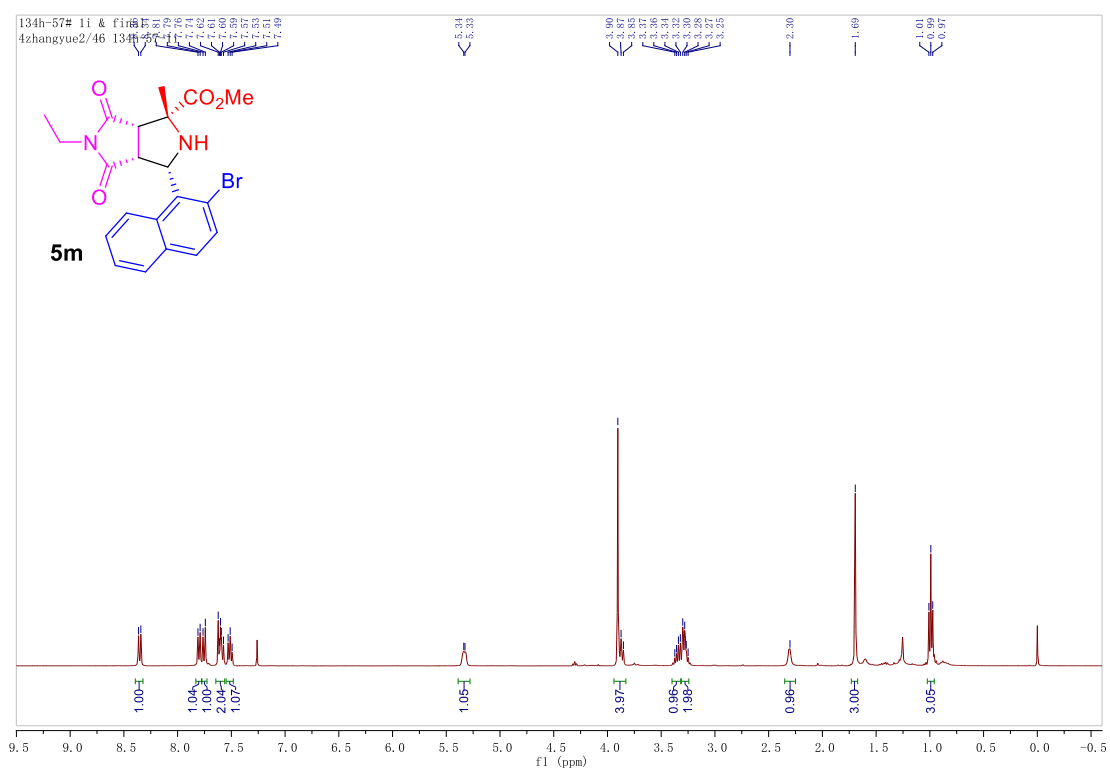
8. ^1H NMR and ^{13}C NMR of selected pyrrolidine adduct 5 and 6

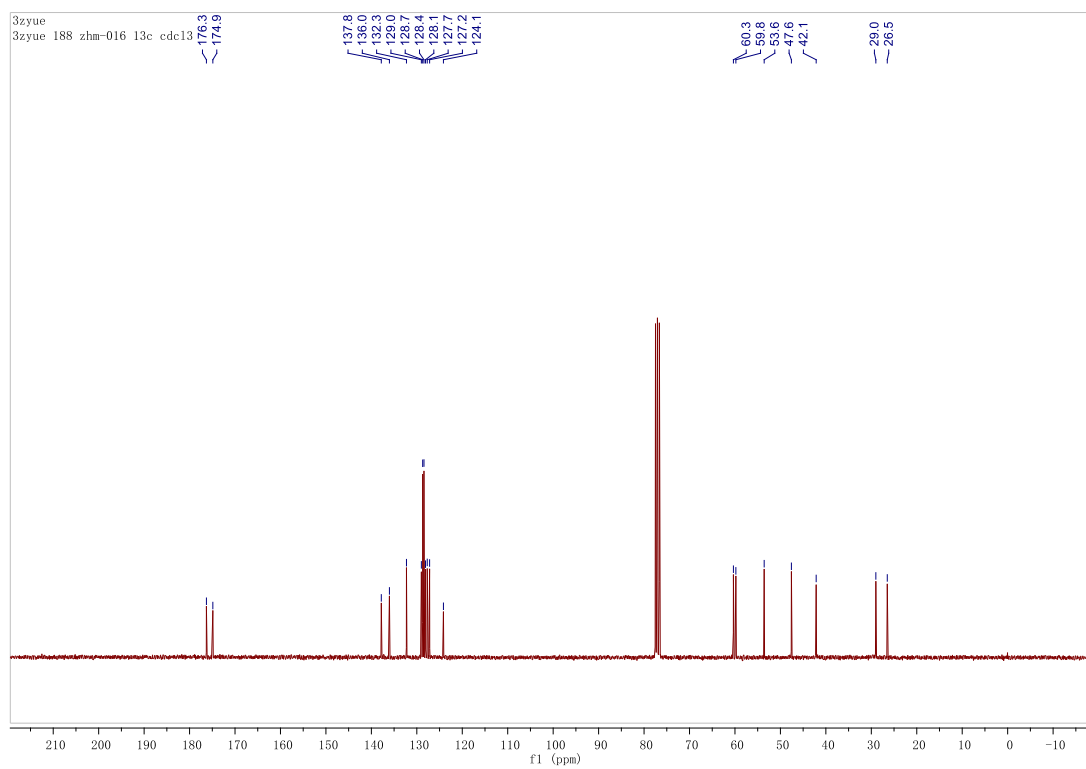
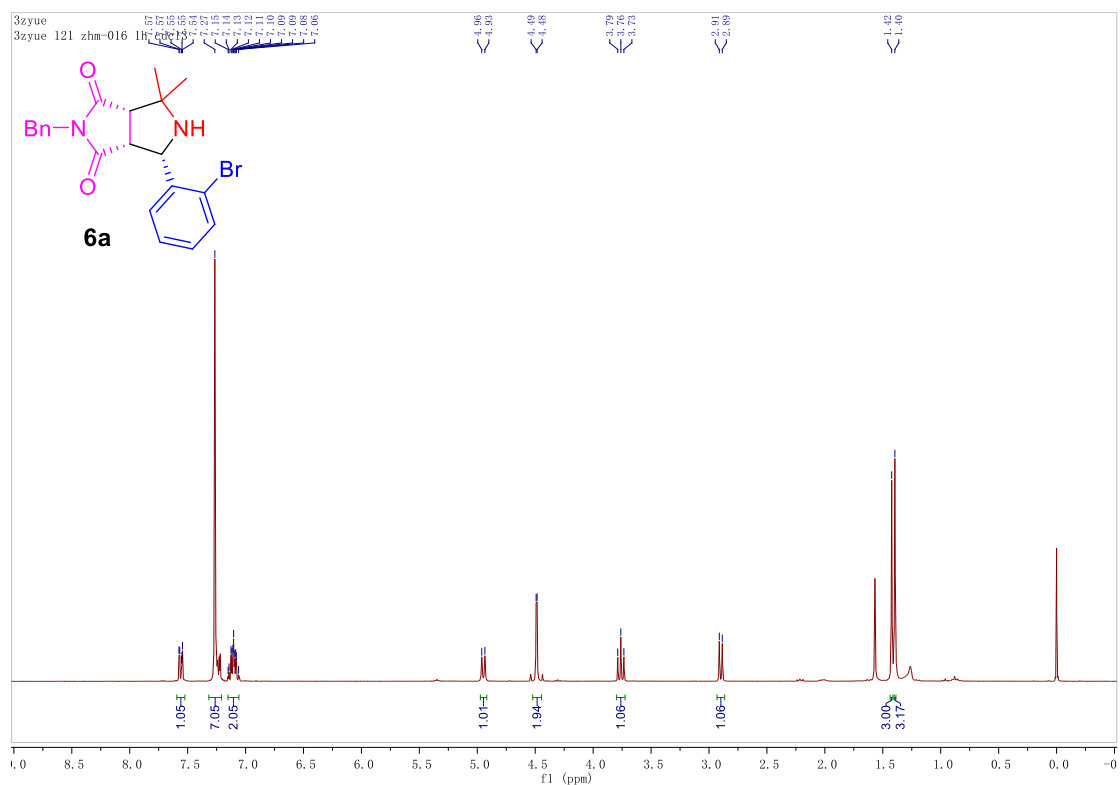


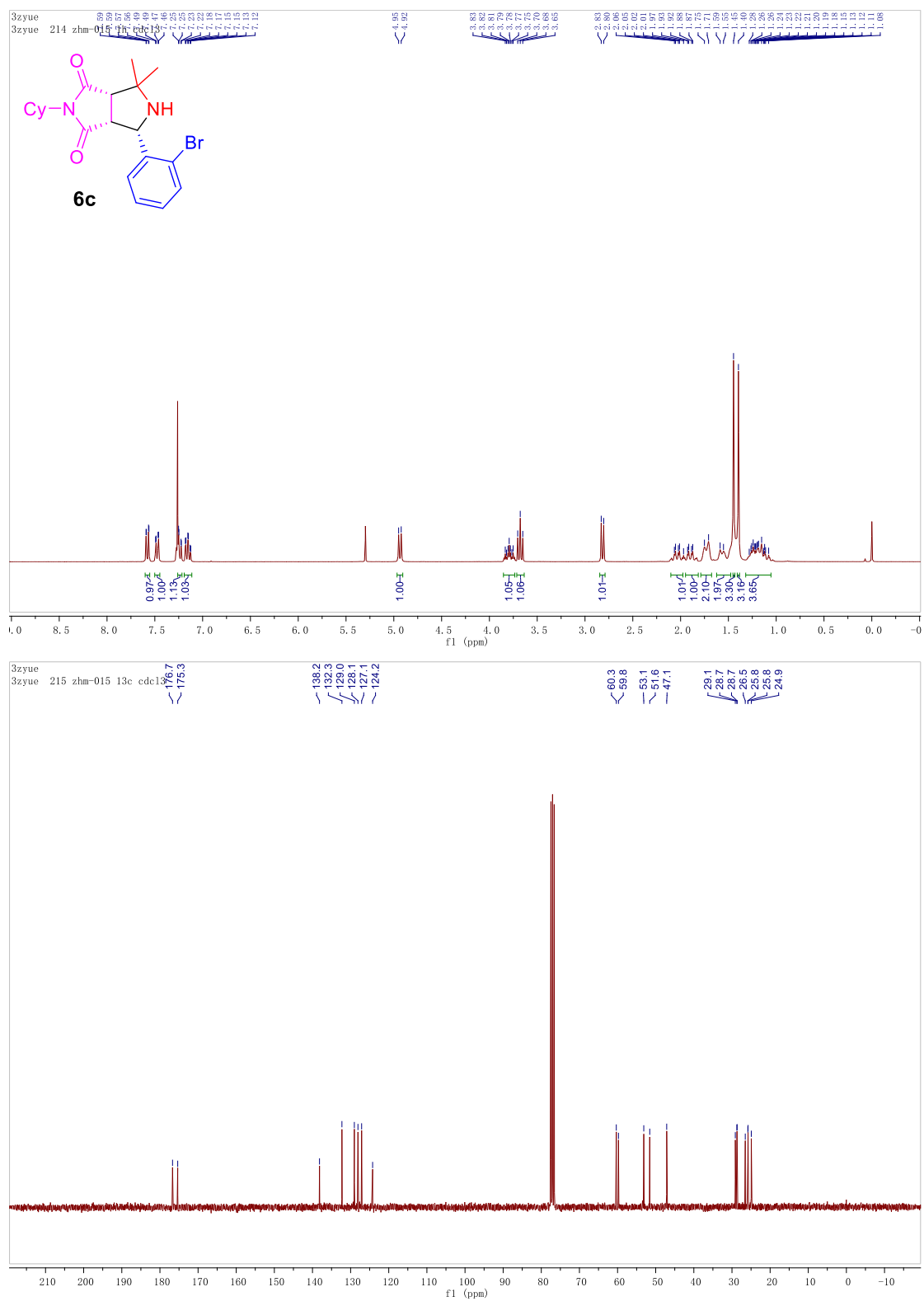












9. ^1H NMR, ^{13}C NMR and ^{19}F NMR of products 9, 11 and 12

