Supporting Information

"One pot" synthesis of quinazolinone-[2,3]-fused polycyclic scaffolds in a three-step reaction sequence

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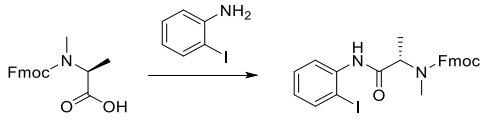
General Chemistry Information

The chemicals and reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagent Group Co. Ltd., P. R. China, and used without further purification. Anhydrous solvents (THF, MeOH, DMF, DCM, and CH_3CN) used in the reactions were dried and freshly distilled before use. Petroleum ether (PE) used had a boiling range of 60-90 ℃. All the reactions were carried out under Ar atmosphere, otherwise stated else. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions *in vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under high vacuum (0.1 - 0.2 mm Hg). The progress of the reactions was monitored by TLC (silica-coated glass plates) and visualized under UV light, and by using iodine, ceric ammonium molybdate stain or phosphomolybdic acid. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a 400 MHz Varian Instrument at 25 ℃ or 600 MHz Bruke Instrument at 25 ℃, using TMS as an internal standard, respectively. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, and m for multiplet. Coupling constants (*J*) are reported in Hertz. ^{13}C NMR spectra were completely hetero-decoupled and measured at 150 MHz. HRMS spectra were recorded on Finnigan-Mat-95 mass spectrometer, equipped with ESI source.

Optimization of Reaction Conditions for the Synthesis of 3a-Fmoc

Table S1. Coupling of *o*-iodo-benzenamine with L-Boc(Me)-alanine

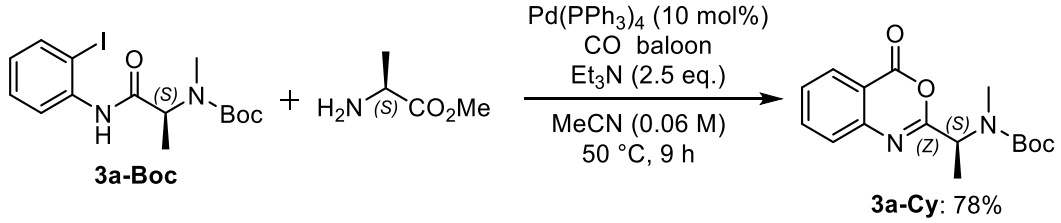


Entry	Acid	Amine	Reaction Condition	Yield
1	1.0 mmol.	2.0 eq.	HATU (2.0 eq.), TEA(2.0 eq.), THF (10 mL), r.t., 15 h	trace
2	1.0 mmol.	1.1 eq.	HOBT (1.1 eq.), DCC (1.1 eq.), THF (10 mL), r.t., 10 h	trace
3	1.0 mmol.	1.2 eq.	TCFH (1.1 eq.), NMI (2.1 eq.), MeCN (10 mL), r.t., 10 h	trace
4	1.0 mmol.	1.1 eq.	HOBT (1.1 eq.), DCC (1.1 eq.), THF (10 mL), 50 ^{o}C, 23 h	trace
5	1.0 mmol.	1.2 eq.	TCFH (1.1 eq.), NMI (2.1 eq.), MeCN (10 mL), 50 ^{o}C, 23 h	trace
6	1.2 mmol.	1.0 eq.	Isopropyl Chloroacetate (1.2 eq.), TEA (2.4 eq.), THF (10 mL), r.t., 40 h	30%
7	1.0 mmol	1.0 eq.	Triphosgen (0.33 eq.), 2,4,6-collidine (2.0 eq.), THF (10 mL), r.t., 9 h	97%

Synthesis

Synthesis of 3a-Cy

tert-Butyl (S)-methyl[1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl]carbamate (3a-Cy)

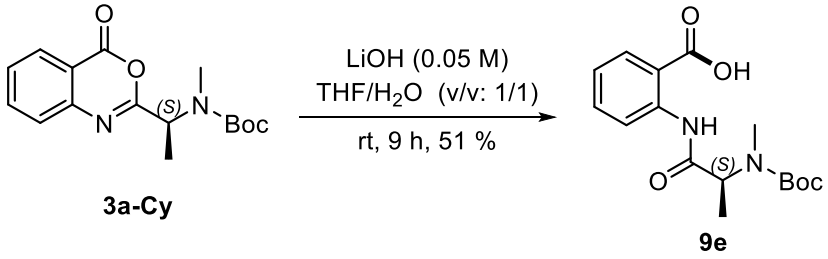


To a flame dried round bottom flask containing **3a-Boc** (0.243 g, 0.60 mmol, 1.0 eq.) were added anhydrous MeCN (10 mL), methyl L-alaninate (0.084 g, 0.60 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (0.069 g, 0.06 mmol, 0.10 eq.) and TEA (0.21 mL, 1.50 mmol, 2.50 eq.). The reaction mixture was stirred at 50 ^oC under CO atmosphere (1 atm.) for 9 h, after which sat. NH_4Cl aq. (20 mL) was added to quench the reaction. The aqueous phase was extracted with EA (20 mL×3). The combined organic phase was washed with water (100 mL×1) and brine (100 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **3a-Cy** in white solid (0.143 g, 78%). **TLC**：R_f=0.21 (PE/EA=8/1). ^{1}H NMR (600 MHz, DMSO-d_6, 95 ^oC) δ 8.13 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.94-7.90 (m, 1H, Ar*H*), 7.64-7.59 (m, 2H, Ar*H*), 4.97 (m, 1H, NC*H*), 2.87 (s, 3H, NCH_3), 1.53 (d, *J* = 7.2 Hz, 3H, CHCH_3), 1.38 (s, 9H, C(CH_3)$_3$).^{13}C NMR (600 MHz, DMSO-d_6, 25 ^oC) δ 161.5 (rotamer), 158.9, 154.9 (rotamer), 145.6, 137.0 (rotamer), 128.8, 128.0, 126.7, 116.8 (rotamer), 79.3, 54.8 (rotamer), 31.8 (rotamer), 27.8 (rotamer), 15.2 (rotamer). ESI-MS (m/z): 305.34 $[M+H]^+$

Known Compound. Data consistent with the previous report.[1]

Synthesis of 9e

(S)-2-{2-[(tert-Butoxycarbonyl)(methyl)amino]propanamido}benzoic acid (9e)



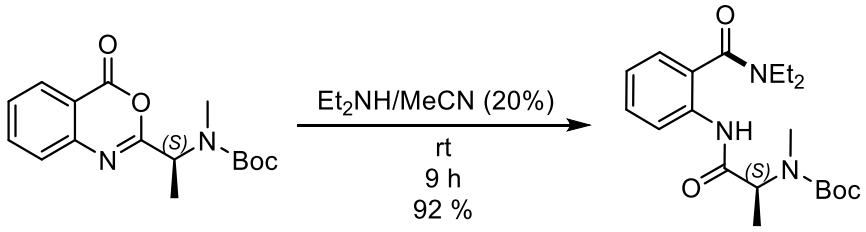
To a flame dried round bottom flask containing **3a-Cy** (0.100 g, 0.33 mmol, 1.0 eq.) were added THF/H_2O=1/1 (8 mL) and LiOH (0.010 g). The reaction mixture was allowed to stir at room temperature for 9 h, after which sat. NH_4Cl aq. (10 mL) was added to quench the reaction. The aqueous phase was extracted with EA (10 mL×3). The combined organic phase was washed with water (30 mL×1) and brine (30 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **9e** in white solid (0.052 g, 51%). **TLC**：R_f=0.27 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.53 (s, 1H, O*H*, rotamer), 8.74 (d, *J* = 8.8 Hz, 1H, Ar*H*), 8.11 (m, 1H, Ar*H*), 7.56 (m, 1H, Ar*H*), 7.21 (brs, 1H, N*H*), 7.09 (m, 1H, Ar*H*), 4.81 (m, 1H, NC*H*CH$_3$,

rotamer), 2.94 (s, 3H, NCH_3), 1.47 (ms, 9H, C(CH_3)$_3$, rotamer), 1.41 (m, 3H, NCHCH_3, rotamer). **ESI-MS** (m/z): 345.26 $[M+Na]^+$

Synthesis of 9f

tert-Butyl

(S)-(1-{[2-(diethylcarbamoyl)phenyl]amino}-1-oxopropan-2-yl)(methyl)carbamate (9f)



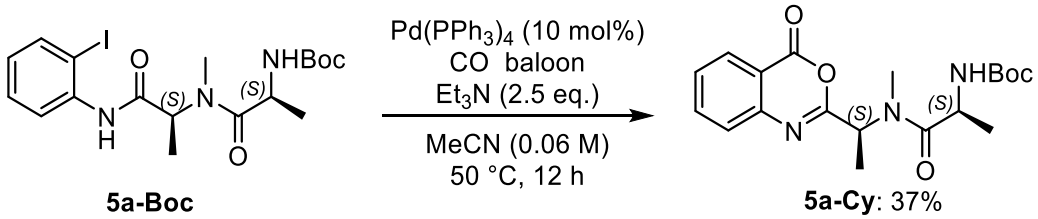
3a-Cy **9f**

To a flame dried round bottom flask containing **3a-Cy** (0.100 g, 0.33 mmol, 1.0 eq.) were added anhydrous MeCN (4 mL) and Et_2NH (2 mL). The reaction mixture was stirred at room temperature for 9 h, after which sat. NH_4Cl aq. (10 mL) was added to quench the reaction. The aqueous phase was extracted with EA (10 mL×3). The combined organic phase was washed with water (30 mL×1) and brine (30 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **9f** in white solid (0.110 g, 92%). **TLC**：R_f=0.64 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.14 (s, 1H, CON*H*), 8.24 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.36 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.20 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.07 (t, *J* = 7.6 Hz, 1H, Ar*H*), 4.74 (m, 1H, NC*H*CH_3, rotamer), 3.38 (m, 4H, 2NC$H_2$$CH_3$), 2.75 (s, 3H, NC$H_3$), 1.47 (s, 9H, C(C$H_3$)$_3$), 1.39 (d, *J* = 7.2 Hz, 3H, NCHCH_3), 1.28-1.04 (m, 6H, 2$NCH_2C$$H_3$). **ESI-MS** (m/z): 400.29 $[M+Na]^+$

Synthesis of 5a-Cy

tert-Butyl

((S)-1-{methyl[(S)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl]amino}-1-oxopropan-2-yl)carbamate (5a-Cy)



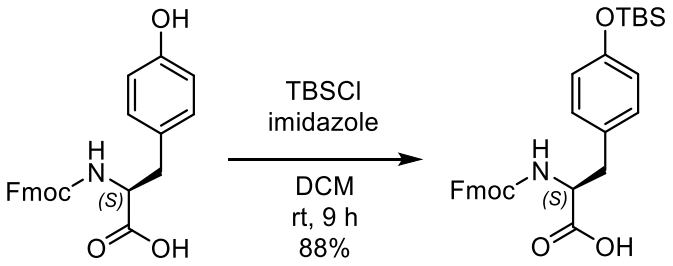
5a-Boc **5a-Cy**: 37%

To a flame dried round bottom flask containing **5a-Boc** (0.285 g, 0.60 mmol, 1.0 eq.) were added anhydrous MeCN (10 mL), $Pd(PPh_3)_4$ (0.069 g, 0.06 mmol, 0.10 eq.) and TEA (0.21 mL, 1.50 mmol, 2.50 eq.). The reaction mixture was stirred at 50 ^oC under CO atmosphere (1 atm.) for 12 h, after which sat. NH_4Cl aq. (10 mL) was added to quench the reaction. The aqueous phase was extracted with EA (10 mL×3). The combined organic phase was washed with water (30 mL×1) and brine (30 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **5a-Cy** in white solid (0.083 g, 37%). **TLC**：R_f=0.25 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H, Ar*H*), 7.81-7.77 (m, 1H, Ar*H*), 7.59-7.50 (m, 2H, Ar*H*), 5.68 (q, *J* = 7.2 Hz, 1H, MeNC*H*CH_3), 5.48 (d, *J* = 8.4 Hz, 1H, N*H*CO), 4.70 (m, 1H, NHC*H*CH_3),

3.07 (s, 3H, NCH_3, rotamer), 1.59 (d, J = 7.2 Hz, 3H, MeNCHCH_3, rotamer), 1.43 (s, 9H, C(CH_3)$_3$), 1.40 (d, J = 6.8 Hz, 3H, HNCHCH_3). **ESI-MS** (m/z): 398.20 $[M+Na]^+$

Synthesis of 2l-Fmoc

(S)-2-({[(9H-Fluoren-9-yl)methoxy]carbonyl}amino)-3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}propanoic acid (2l-Fmoc)



2l-Fmoc

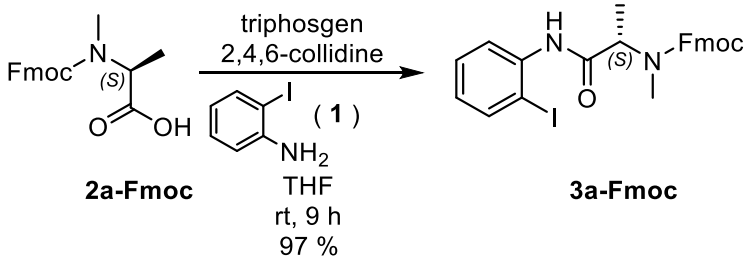
To a flame dried round bottom flask containing Fmoc-L-tyrosine (1.614 g, 4.00 mmol, 1.0 eq.) was added anhydrous DCM (15 mL), imidazole (0.545 g, 8.00 mmol, 2.0 eq.) and TBSCl (0.904 g, 6.00 mmol, 1.5 eq.) under ice bath. The reaction mixture was then warmed to room temperature and allowed to react for another 9 h until completion of conversion as indicated by monitoring of thin layer chromatography, after which sat. NH_4Cl aq. (30 mL) was added to quench the reaction. The aqueous phase was extracted with DCM (40 mL×3). The ccombined organic phase was washed with water (150 mL×1) and brine (150 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **2l-Fmoc** in yellow oil (1.822 g, 88%). $[\alpha]_D^{20}$=16.4 (c=1.00, $CHCl_3$); **TLC**：R_f=0.37 (DCM/MeOH=15/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.71 (d, J = 8.0 Hz, 2H, Ar*H*), 7.48 (m, 2H, Ar*H*), 7.34 (m, 2H, Ar*H*), 7.23 (m, 2H, Ar*H*), 6.99 (d, J = 8.0 Hz, 2H, Ar*H*), 6.71 (d, J = 8.4 Hz, 2H, Ar*H*), 5.37 (s, 1H, CON*H*), 4.58-4.13 (m, 4H, C*H*CH$_2$O, CHCH_2O, NHC*H*), 3.14-2.99 (m, 2H, CH_2Ar), 0.95 (s, 9H, C(CH_3)$_3$), 0.13 (s, 6H, Si(CH_3)$_2$). **ESI-MS** (m/z): 540.39 $[M+Na]^+$

Known Compound. Data consistent with the previous report.[2]

Representative procedure for the synthesis of 3-Fmoc

(9H-Fluoren-9-yl)methyl

(S)-{1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}(methyl)carbamate (3a-Fmoc)

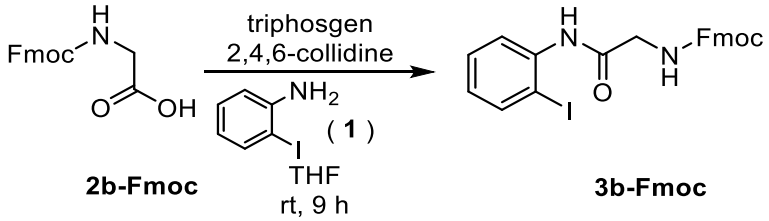


2a-Fmoc **3a-Fmoc**

To a flame dried round bottom flask containing **2a-Fmoc** (2.928 g, 9.00 mmol, 1.0 eq.) was added anhydrous THF 50 mL. The mixture was cooled to 0 °C, and was added triphosgen (0.890 g, 3.00 mmol, 0.33 eq.) and 2,4,6-collidine (2.40 mL, 18.00 mmol, 2.0 eq.) under ice bath. The mixture was allowed to stir at 0 °C for another 10 min, after which amine **1** (1.971 g, 9.00 mmol, 1.0 eq.) was added to the reaction mixture. The mixture was warmed to room temperature and was allowed to react for another 9 h until completion of reaction as indicated

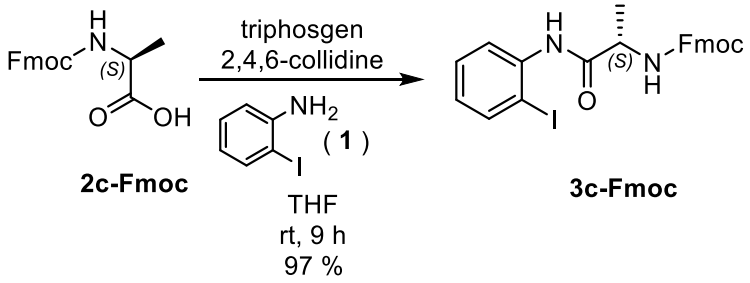
by monitoring of thin layer chromatography. Afterwards, 100 mL sat. NH_4Cl aq. was added to the mixture. The aqueous phase was extracted with EA (150 mL×3) and the combined organic phase was washed with brine (300 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **3a-Fmoc** in white powder (4.595 g, 97%). $[a]_D^{20}$ = -30.1 (c=2.00, $CHCl_3$); **TLC**: R_f=0.32 (PE/EA=5/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.18 (d, *J* = 6.4 Hz, 1H, Ar*H*), 8.11 (brs, 1H, CON*H*), 7.75 (m, 3H, Ar*H*), 7.59 (m, 2H, Ar*H*), 7.36 (m, 3H, Ar*H*), 7.28 (m, 2H, Ar*H*), 6.88-6.81 (m, 1H, Ar*H*), 5.01 (m, 1H, C*H*CH_3), 4.58 (d, *J* = 6.4 Hz, 2H, OCH_2CH), 4.28 (t, *J* = 6.4 Hz, 1H, OCH_2CH), 2.88 (s, 3H, NCH_3), 1.42 (d, *J* = 7.2 Hz, 3H, CHCH_3). **^{13}C NMR** (150 MHz, Chloroform-d) δ 169.4, 143.8, 143.8, 141.5, 141.4, 138.9, 129.3, 127.9, 127.9, 127.2, 126.2, 124.9, 122.0, 120.1, 120.1, 90.4, 68.0, 55.6, 47.3, 30.1, 13.4. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{25}H_{24}IN_2O_3^+$: 527.0826, found: 527.0806.

(9H-Fluoren-9-yl)methyl {2-[(2-iodophenyl)amino]-2-oxoethyl}carbamate (3b-Fmoc)



Similar to the synthesis of **3a-Fmoc**. The crude white powder (4.472g, 100%) obtained after concentration was subjected to the next step without further purification.

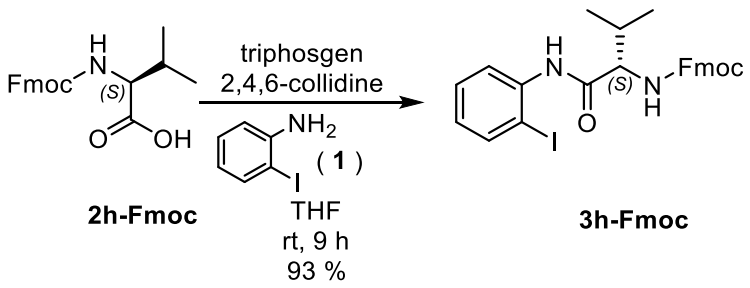
(9H-Fluoren-9-yl)methyl (S)-{1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}carbamate (3c-Fmoc)



white powder (4.472g, 100%). $[a]_D^{20}$ = -2.14 (c=0.700, $CHCl_3$); **TLC**: R_f=0.46 (PE/EA=3/1).**^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.28 (s, 1H, CON*H*Ph), 7.89 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.86 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.77-7.69 (m, 3H, Ar*H*, CON*H*CH), 7.56 (d, *J* = 9.6 Hz, 1H, Ar*H*), 7.44-7.35 (m, 3H, Ar*H*), 7.33 (m, 2H, Ar*H*), 6.96 (m, 1H, Ar*H*), 4.33 (d, *J* = 7.2 Hz, 2H, OCH_2CH), 4.25-4.23 (m, 2H, C*H*CH_3, OCH_2CH), 1.38 (d, *J* = 7.2 Hz, 3H, CHCH_3).**^{13}C NMR** (150 MHz, DMSO-d_6) δ 171.5, 155.9, 143.9, 143.8, 140.8, 139.0, 138.9, 128.8, 127.7, 127.4, 127.1, 125.9, 125.3, 120.2, 95.0, 65.8, 50.7, 46.7, 17.9. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{24}H_{22}IN_2O_3^+$: 513.0670, found: 513.0665.

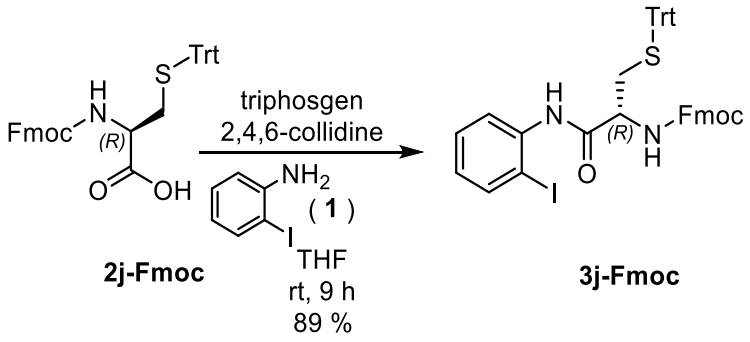
(9H-Fluoren-9-yl)methyl

(S)-{1-[(2-iodophenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (3h-Fmoc)



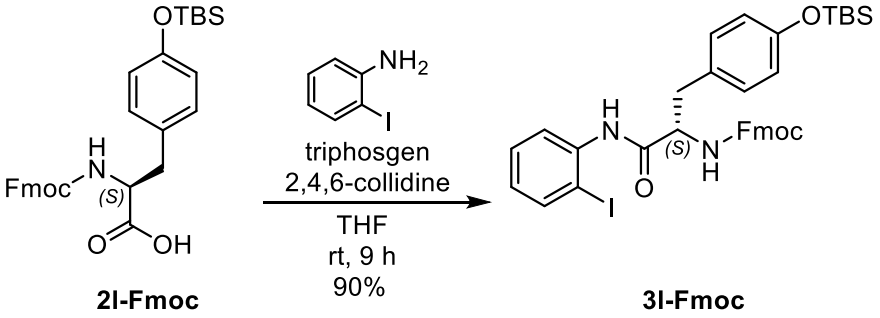
yellow solid (1.507 g, 93%). $[a]_D^{20}$= -14.0 (c=0.500, $CHCl_3$); **TLC**: R_f=0.47 (PE/EA=6/1). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.37 (s, 1H, CON*H*Ph), 7.89 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.87 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.80-7.75 (m, 2H,Ar*H*), 7.61 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.49 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.44-7.34 (m, 3H, Ar*H*, CON*H*CH), 7.34-7.29 (m, 2H, Ar*H*), 6.99-6.95 (m, 1H, Ar*H*), 4.36-4.28 (m, 2H, OCH_2CH), 4.25 (t, *J* = 7.2 Hz, 1H, OCH$_2$C*H*), 4.15-4.09 (m, 1H, C*H*NHFmoc), 2.21 (m, 1H, C*H*(CH$_3$)$_2$), 1.00 (d, *J* = 6.6 Hz, 3H, CH(CH_3)$_2$), 0.96 (d, *J* = 6.6 Hz, 3H, CH(CH_3)$_2$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 169.7, 156.6, 143.8, 141.5, 139.0, 137.8, 129.4, 127.9, 127.3, 126.5, 125.1, 122.2, 120.2, 90.5, 67.3, 61.5, 47.3, 30.8, 19.6. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{26}H_{26}IN_2O_3^+$: 541.0983, found: 541.0978. HRMS (ESI) m/z: $[M+Na]^+$ calculated for $C_{26}H_{25}IN_2O_3Na^+$: 563.0802, found: 563.0797.

(9H-Fluoren-9-yl)methyl
(R)-{1-[(2-iodophenyl)amino]-1-oxo-3-(tritylthio)propan-2-yl}carbamate (3j-Fmoc)



white foamy solid (2.112 g, 89%). $[a]_D^{20}$ = -2.55 (c=1.80, $CHCl_3$); **TLC**: R_f=0.23 (PE/EA=10/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.4 Hz, 1H, Ar*H*), 8.11 (s, 1H, CON*H*Ar), 7.80-7.70 (m, 3H, Ar*H*), 7.59-7.16 (m, 18H, Ar*H*), 6.83 (m, 1H, Ar*H*), 4.93 (d, *J* = 7.2 Hz, 1H, C*H*NHFmoc), 4.48 (d, *J* = 6.4 Hz, 2H, OCH_2CH), 4.22 (t, *J* = 6.4 Hz, 1H, OCH$_2$C*H*), 4.10 (m, 1H, N*H*Fmoc), 2.80 (m, 2H, SCH_2CH). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 168.4, 156.2, 144.3, 143.7, 143.7, 141.5, 141.5, 138.9, 137.6, 129.6, 129.3, 128.3, 127.9, 127.2, 127.1, 126.4, 125.1, 125.0, 122.0, 120.2, 90.4, 67.7, 67.2, 55.1, 47.2, 33.6. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{43}H_{35}IN_2O_3SNa^+$: 809.1305, found: 809.1328.

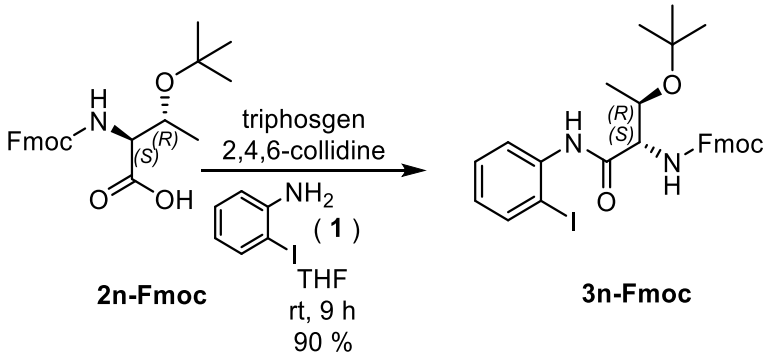
(9H-Fluoren-9-yl)methyl
(S)-(3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl)carbamate (3l-Fmoc)



2l-Fmoc **3l-Fmoc**

white solid (1.377 g, 90%). $[a]_D^{20}$=-13.0 (c=1.40, $CHCl_3$); **TLC**: R_f=0.24 (PE/EA=10/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.20 (d, *J* = 10.0 Hz, 1H, Ar*H*), 7.97 (s, 1H, CON*H*Ar), 7.79-7.70 (m, 3H, Ar*H*), 7.54 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.40-7.28 (m, 5H, Ar*H*), 7.07 (d, *J* = 6.8 Hz, 2H, Ar*H*), 6.88-6.82 (m, 1H, Ar*H*), 6.77 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.30 (brs, 1H, N*H*Fmoc), 4.56 (m, 1H, C*H*NHFmoc), 4.45 (m, 2H, CHCH_2O), 4.21 (t, *J* = 6.8 Hz, 1H, C*H*CH$_2$O), 3.14 (m, 2H, CH_2Ar), 0.97 (s, 9H, C(CH_3)$_3$), 0.16 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 169.4, 156.1, 155.1, 143.8, 141.5, 138.9, 137.7, 130.4, 129.4, 127.9, 127.2, 126.4, 125.1, 122.0, 120.7, 120.2, 120.2, 90.4, 67.5, 57.3, 47.2, 37.5, 25.8, 18.3, -4.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{36}H_{40}IN_2O_4Si^+$: 719.1797, found: 719.1799.

(9H-Fluoren-9-yl)methyl {(2S,3R)-3-(tert-butoxy)-1-[(2-iodophenyl)amino]-1-oxobutan-2-yl}carbamate (3n-Fmoc)

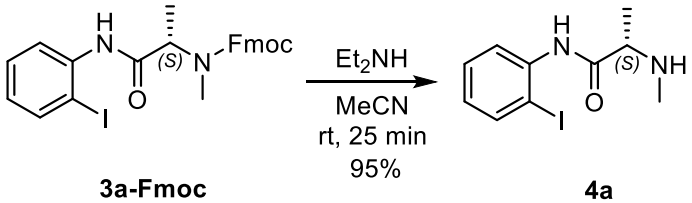


2n-Fmoc **3n-Fmoc**

grey solid (1.615 g, 90%). $[a]_D^{20}$=-3.90 (c=1.00, $CHCl_3$); **TLC**: R_f=0.33 (PE/EA=10/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H, CON*H*Ph), 8.08 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.79 (m, 3H, Ar*H*), 7.68-7.58 (m, 2H, Ar*H*), 7.45-7.30 (m, 5H, Ar*H*), 6.91-6.85 (m, 1H, Ar*H*), 6.05 (d, *J* = 6.0 Hz, 1H, N*H*Fmoc), 4.52-4.42 (m, 2H, OCH_2CH), 4.39-4.30 (m, 2H, C*H*NHFmoc, OC*H*CH$_3$), 4.26 (m, 1H, OCH$_2$C*H*), 1.33 (s, 9H, C(CH_3)$_3$), 1.20 (d, *J* = 6.4 Hz, 3H, CHCH_3). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 168.4, 156.3, 143.9, 143.8, 141.4, 139.2, 138.3, 129.1, 127.9, 127.2, 126.5, 125.3, 125.2, 123.3, 120.2, 120.1, 90.7, 76.0, 67.2, 67.1, 60.3, 47.3, 28.6, 18.1. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{29}H_{32}IN_2O_4^+$: 599.1401, found: 599.1407.

Representative procedure for the synthesis of 4

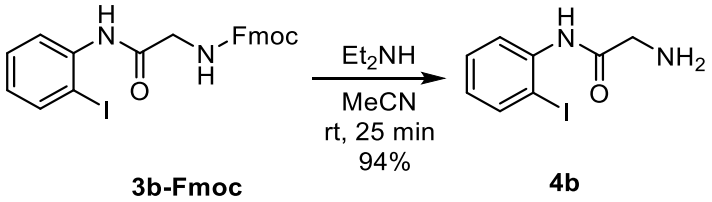
(S)-N-(2-Iodophenyl)-2-(methylamino)propanamide (4a)



3a-Fmoc **4a**

To a flame dried round bottom flask containing **3a-Fmoc** (5.263 g, 10.00 mmol, 1.0 eq.) was added anhydrous MeCN (30 mL) and Et_2NH (15 mL). The reaction mixture was allowed to stir at room temperature for 25 min. After completion of reaction as indicated by monitoring of thin layer chromatography, sat. NH_4Cl aq. (50 mL) was added to quench the reaction. The aqueous phase was extracted with EA (80 mL×3). The combined organic phase was washed with water (200 mL×1) and brine (200 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **4a** in colorless oil (2.888 g, 95%). $[a]_D^{20}$ = -21.9 (c=3.20, $CHCl_3$); **TLC**: R_f=0.12 (PE/EA=5/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 9.79 (s, 1H, CON*H*Ph), 8.24 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.68 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.24 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.72 (t, *J* = 7.8 Hz, 1H, Ar*H*), 3.08 (m, 1H, C*H*CH_3), 2.42 (d, *J* = 2.0 Hz, 3H, NHC*H*$_3$), 1.50 (brs, 1H, N*H*CH_3), 1.31 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.5, 138.9, 138.5, 129.1, 125.5, 121.3, 89.3, 61.2, 35.7, 19.6. **ESI-MS** (m/z): 305.08 $[M+H]^+$

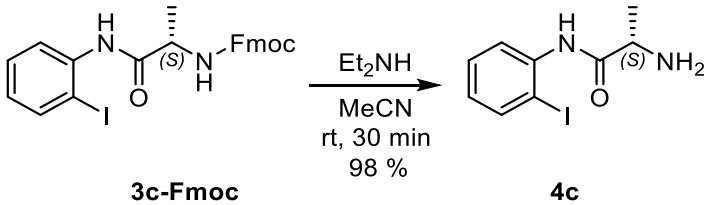
2-Amino-N-(2-iodophenyl)acetamide (4b)



3b-Fmoc **4b**

colorless oil (1.037 g, 94%). **TLC**: R_f=0.36 (DCM/MeOH=3/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.89 (s, 1H, CON*H*Ph), 8.34 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.78 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.37-7.30 (m, 1H, Ar*H*), 6.86-6.79 (m, 1H, Ar*H*), 3.52 (s, 2H, NH_2CH_2), 1.70 (s, 2H, NH_2CH_2). **^{13}C NMR** (150 MHz, Chloroform-d) δ 171.4, 139.1, 138.5, 129.3, 125.8, 121.4, 89.3, 45.6. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_8H_{10}IN_2O^+$: 276.9832, found: 276.9831.

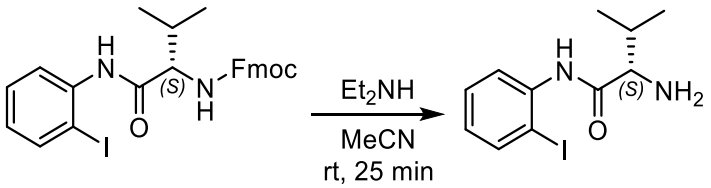
(S)-2-Amino-N-(2-iodophenyl)propanamide (4c)



3c-Fmoc **4c**

yellow oil (2.481 g, 98%). $[a]_D^{20}$ = 10.8 (c=4.20, $CHCl_3$); **TLC**: R_f=0.15 (PE/EA=3/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.93 (s, 1H, CON*H*Ph), 8.30 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar*H*), 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar*H*), 7.51-7.17 (m, 1H, Ar*H*), 6.99-6.70 (m, 1H, Ar*H*), 3.63 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 1.76 (s, 2H, NH_2CH), 1.43 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.3, 139.0, 138.5, 129.1, 125.6, 121.3, 89.5, 51.5, 21.7. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_9H_{12}IN_2O^+$: 290.9989, found: 290.9987.

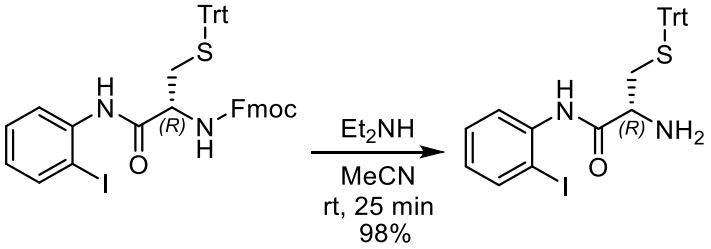
(S)-2-Amino-N-(2-iodophenyl)-3-methylbutanamide (4h)



3h-Fmoc **4h**

yellow oil (0.839 g, 96%). $[a]_D^{20}$= -23.6 (c=2.13, $CHCl_3$); **TLC**：R_f=0.45 (DCM/MeOH=15/1) **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.95 (s, 1H, CON*H*Ph), 8.33 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.77 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (m, 1H, Ar*H*), 6.80 (m, 1H, Ar*H*), 3.42 (d, *J* = 3.6 Hz, 1H, NH_2CH), 2.43 (m, 1H, NH_2CHCH), 1.57 (s, 2H, NH_2CH), 1.05 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.90 (d, *J* = 7.2 Hz, 3H, $CHCH_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.1, 139.0, 138.6, 129.1, 125.6, 121.4, 89.5, 30.9, 19.9, 16.1. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{16}IN_2O^+$: 319.0302, found: 319.0301.

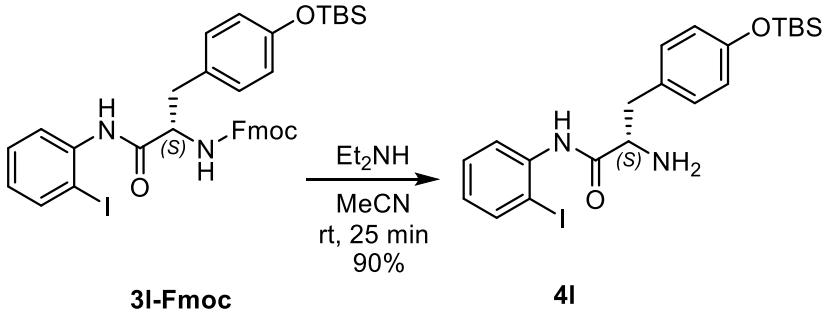
(R)-2-Amino-N-(2-iodophenyl)-3-(tritylthio)propenamide (4j)



3j-Fmoc **4j**

white foamy solid (1.105 g, 98%). $[a]_D^{20}$= 21.8 (c=2.63, $CHCl_3$); **TLC**：R_f=0.39 (PE/EA=5/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.78 (s, 1H, CON*H*Ph), 8.25 (d, *J* = 9.8 Hz, 1H, Ar*H*), 7.73 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.51-7.43 (m, 6H, Ar*H*), 7.29 (m, 7H, Ar*H*), 7.25-7.15 (m, 3H, Ar*H*), 6.78 (m, 1H, Ar*H*), 3.21 (m, 1H, NH_2CH), 2.87 (m, 1H, SCH_2), 2.65 (m, 1H, SCH_2). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.7, 144.6, 139.0, 138.4, 129.7, 129.1, 128.1, 127.0, 125.8, 121.3, 89.5, 67.2, 54.8, 37.1. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{28}H_{25}IN_2OSNa^+$: 587.0625, found: 587.0630.

(S)-2-Amino-3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-N-(2-iodophenyl)propenamide (4l)

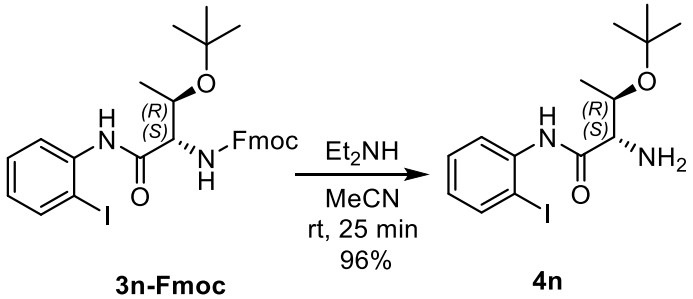


3l-Fmoc **4l**

colorless oil (1.071 g, 90%). $[a]_D^{20}$= -38.5 (c=1.10, $CHCl_3$); **TLC**：R_f=0.24 (PE/EA=6/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.92 (s, 1H, CON*H*Ph), 8.36 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.79 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.39-7.32 (m, 1H, Ar*H*), 7.12 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.84 (d, *J* = 7.9 Hz, 1H, Ar*H*), 6.80 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.73 (dd, *J* = 9.6, 4.0 Hz, 1H, NH_2CH), 3.31 (dd, *J* = 14.0, 4.0 Hz, 1H, $CHCH_2$), 2.76 (dd, *J* = 14.0, 9.6 Hz, 1H, $CHCH_2$), 0.98 (s, 9H, $C(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.2, 154.8, 139.1,

138.6, 130.4, 130.2, 129.3, 125.8, 121.5, 120.5, 89.6, 57.4, 40.1, 25.9, 18.3, -4.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{21}H_{30}IN_2O_2Si^+$: 497.1116, found: 497.1119.

(2S,3R)-2-Amino-3-(tert-butoxy)-N-(2-iodophenyl)butanamide (4n)

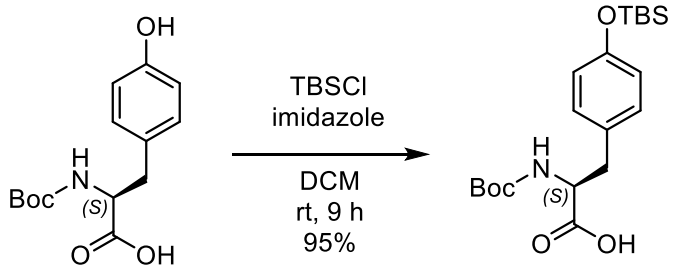


3n-Fmoc **4n**

yellow liquid (1.084 g, 96%). **TLC：** Rf=0.24 (PE/EA=5/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H, CON*H*Ph), 8.26 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.79 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.33 (m, 1H, Ar*H*), 6.86-6.79 (m, 1H, Ar*H*), 4.30 (m, 1H, OC*H*CH_3), 3.26 (d, *J* = 2.4 Hz, 1H, OCHC*H*), 1.85 (s, 2H, NH_2CH), 1.25 (d, *J* = 6.4 Hz, 3H, CHCH_3), 1.14 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 172.9, 139.1, 138.9, 129.2, 125.7, 121.7, 89.6, 74.1, 67.3, 61.1, 28.7, 21.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{22}IN_2O_2^+$: 377.0721, found: 377.0723.

Synthesis of 4k

(S)-2-[(tert-Butoxycarbonyl)amino]-3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}propanoic acid (4k)



4k

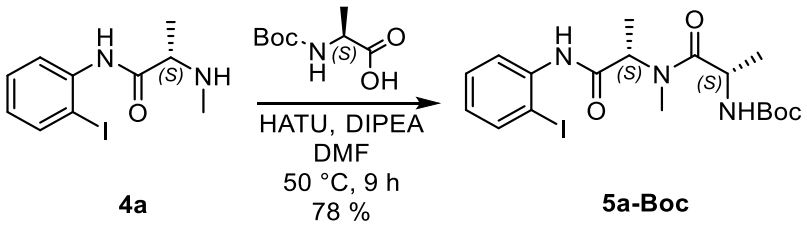
To a flame dried round bottom flask containing (tert-Butoxycarbonyl)-L-tyrosine (1.125 g, 4.00 mmol, 1.0 eq.), was added anhydrous DCM (15 mL), imidazole (0.545 g, 8.00 mmol, 2.0 eq.) and TBSCl (0.904 g, 6.00 mmol, 1.5 eq.) under ice bath. The reaction mixture was warmed to room temperature and allowed to stir for 9 h until completion of conversion as indicated by monitoring of thin layer chromatography, after which sat. NH_4Cl aq. (30 mL) was added to quench the reaction. The aqueous phase was extracted with DCM (40 mL×3). The combined organic phase was washed with water (150 mL×1) and brine (150 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **4k** in yellow oil (1.499 g, 95%). $[a]_D^{20}$=19.9 (c=1.30, $CHCl_3$); **TLC：** R_f=0.35 (DCM/MeOH=15/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.04 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.92 (d, *J* = 8.4 Hz, 1H, CON*H*), 4.58-4.53 (m, 1H, C*H*NHBoc), 3.15-2.98 (m, 2H, CH_2Ph), 1.40 (s, 9H, OC(CH_3)$_3$), 0.97 (s, 9H, SiC(CH_3)$_3$), 0.17 (s, 6H, Si(CH_3)$_2$). **ESI-MS** (m/z): 418.22 $[M+Na]^+$

Known Compound. Data consistent with the previous report.[3]

Representative procedure for the synthesis of 5-Boc

tert-Butyl

{(S)-1-[{(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}(methyl)amino]-1-oxopropan-2-yl}carbamate (5a-Boc)

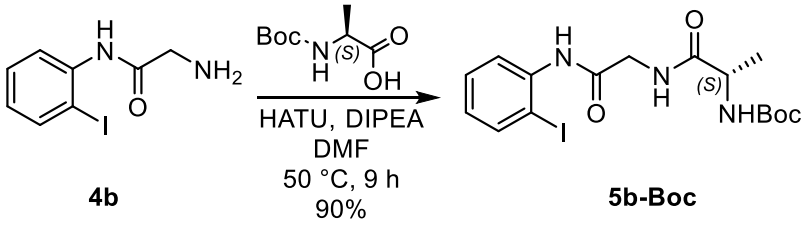


4a **5a-Boc**

To a flame dried round bottom flask containing (tert-butoxycarbonyl)-L-alanine (2.838 g, 15.00 mmol, 1.5 eq.) was added anhydrous DMF (30 mL). The reaction mixture was heated to 50 ^{o}C, and was added DIPEA (8.70 mL, 50.00 mmol, 5.0 eq.) and HATU (7.605 g, 20.00 mmol, 2.0 eq.). After stirring at 50 ^{o}C for 10 min, **4a** (3.041 g, 10.00 mmol, 1.0 eq.) was added to the reaction mixture. The reaction mixture was allowed to stir at 50 ^{o}C for another 9 h, until completion of conversion as indicated by monitoring of thin layer chromatography, after which sat. NH_4Cl aq. (50 mL) was added to quench the reaction. The organic phase was extracted with EA (80 mL ×3). The combined organic phase was washed with H_2O (300 mL ×1) and brine (300 mL ×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford **5a-Boc** in colorless oil (3.603 g, 78%). $[a]_D^{20}$ = -74.4 (c=2.26, $CHCl_3$); **TLC**：R_f=0.31 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.13 (d, *J* = 10.0 Hz, 1H, Ar*H*), 8.01 (m, 1H, N*H*), 7.74 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.35-7.27 (m, 1H, Ar*H*), 6.82 (t, *J* = 7.2 Hz, 1H, Ar*H*), 5.50 (m, 1H, N*H*Boc, rotamers), 5.39 (m, 1H, C*H*CH_3, rotamers), 4.80-4.58 (m, 1H, C*H*CH_3, rotamers), 3.15-2.98 (m, 3H, N*C*H_3, rotamers), 1.48-1.33 (m, 15H, C(C*H*$_3$)$_3$, CHC*H*$_3$, CHC*H*$_3$, rotamers). **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{18}H_{27}IN_3O_4^+$: 476.1041, found: 476.1057.

tert-Butyl

(S)-[1-({2-[(2-iodophenyl)amino]-2-oxoethyl}amino)-1-oxopropan-2-yl]carbamate (5b-Boc)

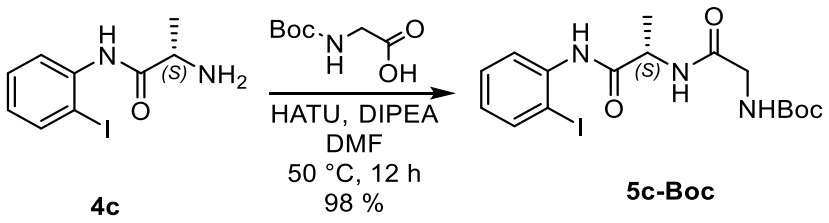


4b **5b-Boc**

yellow oil (1.456 g, 90%). $[a]_D^{20}$=-9.19 (c=1.53, $CHCl_3$); **TLC**：R_f=0.33 (PE/EA=1/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.19 (brs, 1H, CON*H*Ar), 7.99 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.74 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.48 (brs, 1H, CON*H*), 7.28 (m, 1H, Ar*H*), 6.83 (m, 1H, Ar*H*), 5.35 (brs, 1H, N*H*Boc), 4.33 (m, 1H, CON*H*CH), 4.11 (m, 2H, NHC*H*$_2$), 1.41-1.30 (m, 12H, CHC*H*$_3$, C(C*H*$_3$)$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 174.0, 167.6, 155.8, 139.1, 137.9, 129.2, 126.8, 123.3, 91.4, 80.5, 50.3, 44.4, 28.4, 18.7. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{16}H_{22}IN_3O_4Na^+$: 470.0547, found: 470.0552.

tert-Butyl

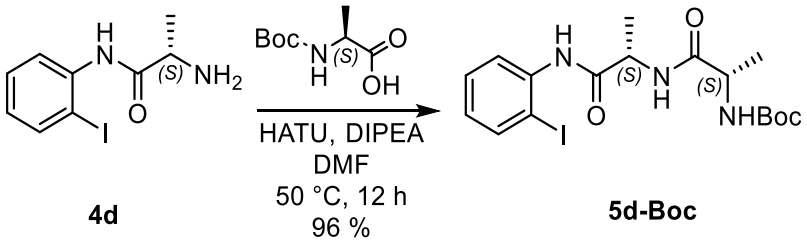
(S)-[2-({1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-2-oxoethyl]carbamate (5c-Boc)



4c **5c-Boc**

yellow solid (0.442 g, 98%). $[a]_D^{20}$ = -19.7 (c=1.15, $CHCl_3$); **TLC**：R_f=0.27 (PE/EA=2/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.17 (s, 1H, CON*H*Ar), 8.03 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.76 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.30 (m, 1H, Ar*H*), 7.05 (s, 1H, CON*H*CH), 6.84 (m, 1H, Ar*H*), 5.33 (t, *J* = 6.0 Hz, 1H, N*H*CH_2), 4.67-4.74 (m, 1H, C*H*CH_3), 3.89 (s, 2H, COC*H*$_2$), 1.50 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.43 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 170.5, 170.0, 156.3, 139.1, 138.0, 129.2, 126.7, 123.2, 91.3, 80.6, 49.8, 44.5, 28.5, 17.9. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{23}IN_3O_4^+$: 448.0728, found: 448.0725.

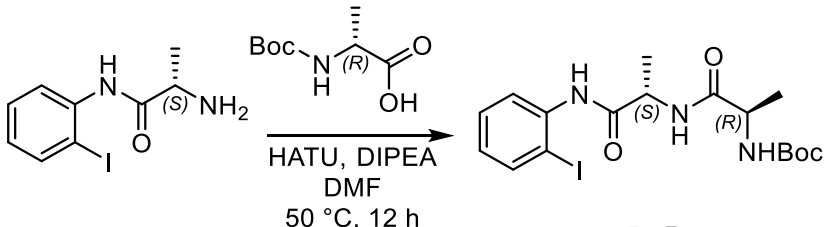
tert-Butyl [(S)-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5d-Boc)



4d **5d-Boc**

white solid (0.444 g, 96%). $[a]_D^{20}$ = -46.4 (c=1.15, $CHCl_3$); **TLC**：R_f=0.28 (PE/EA=2/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.16 (s, 1H, CON*H*Ar), 8.08 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.77 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.35-7.29 (m, 1H, Ar*H*), 7.07 (s, 1H, N*H*COCHCH$_3$), 6.88-6.81 (m, 1H, Ar*H*), 5.08 (d, *J* = 7.6 Hz, 1H, CON*H*CHCH$_3$), 4.66 (m, 1H, NHCOC*H*CH$_3$), 4.26 (m, 1H, CONHC*H*CH$_3$), 1.49 (d, *J* = 7.2 Hz, 3H, NHCOCHC*H*$_3$), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (d, *J* = 7.2 Hz, 3H, CONHCHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.1, 170.4, 155.9, 139.1, 138.1, 129.3, 126.6, 123.0, 91.0, 80.6, 50.1, 49.9, 28.4, 18.1, 17.9. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{25}IN_3O_4^+$: 462.0884, found: 462.0884.

tert-Butyl [(R)-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5e-Boc)

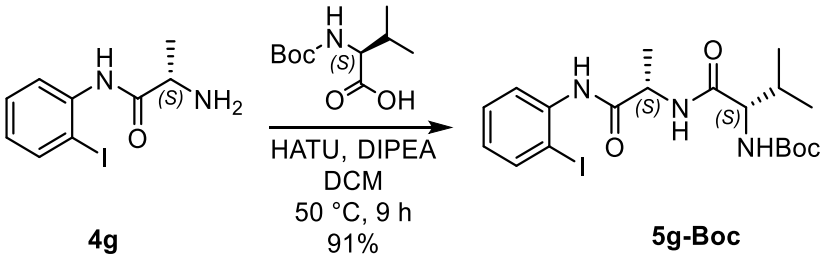


4e **5e-Boc**

white solid (0.429 g, 93%). $[a]_D^{20}$ = -6.81 (c=1.10, $CHCl_3$); **TLC**：R_f=0.24 (PE/EA=2/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.20 (s, 1H, CON*H*Ar), 8.01 (d, *J* = 8.4 Hz, 1H, Ar*H*),

7.76 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.30 (m, 1H, Ar*H*), 7.04 (s, 1H, N*H*COCHCH$_3$), 6.84 (m, 1H, Ar*H*), 5.14 (d, *J* = 7.6 Hz, 1H, CON*H*CHCH$_3$), 4.68 (m, 1H, NHCOC*H*CH$_3$), 4.26 (m, 1H, CONHC*H*CH$_3$), 1.50 (d, *J* = 7.2 Hz, 3H, NHCOCHC*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 1.38 (d, *J* = 7.2 Hz, 3H, CONHCHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.2, 170.5, 155.7, 139.1, 138.1, 129.2, 126.7, 123.3, 91.3, 80.6, 50.4, 49.9, 28.4, 18.5, 17.8. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{25}IN_3O_4^+$: 462.0884, found: 462.0887.

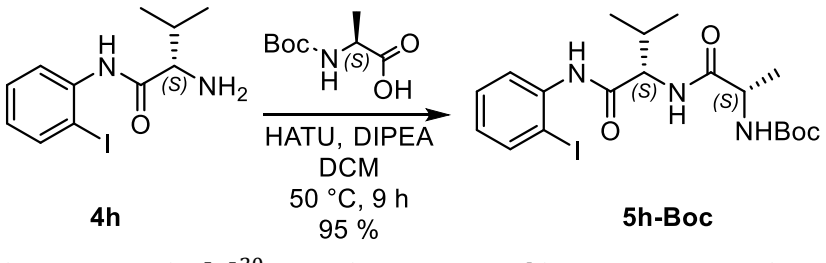
tert-Butyl [(S)-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-3-methyl-1-oxobutan-2-yl]carbamate (5g-Boc)



4g **5g-Boc**

yellow solid (0.445 g, 91%). $[a]_D^{20}$ = -32.2 (c=0.950, $CHCl_3$); **TLC**：R_f=0.41 (PE/EA=5/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.12 (s, 1H, CON*H*Ar), 7.96 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.71 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.25 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.96 (s, 1H, N*H*COCHCH$_3$), 6.78 (t, *J* = 7.8 Hz, 1H, Ar*H*), 5.13 (d, *J* = 8.0 Hz, 1H, C*H*CH(C*H*$_3$)$_2$), 4.65 (m, 1H, C*H*CH$_3$), 3.97 (s, 1H, CON*H*CHCH$_3$), 2.11 (m, 1H, C*H*(CH$_3$)$_2$), 1.43 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.2, 170.4, 139.1, 138.1, 129.2, 126.6, 123.1, 91.0, 80.3, 60.0, 49.8, 30.9, 28.4, 19.6, 18.0, 17.9. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{19}H_{29}IN_3O_4^+$: 490.1197, found: 490.1195.

tert-Butyl [(S)-1-({(S)-1-[(2-iodophenyl)amino]-3-methyl-1-oxobutan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5h-Boc)

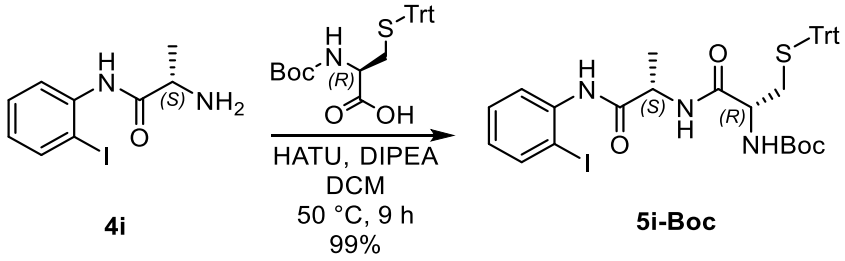


4h **5h-Boc**

white solid (0.943 g, 95%). $[a]_D^{20}$=-284 (c=0.900, $CHCl_3$); **TLC**：R_f=0.26 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.14 (d, *J* = 8.0 Hz, 1H, Ar*H*), 8.07 (s, 1H, CON*H*Ar), 7.77 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (t, *J* = 6.8 Hz, 1H, Ar*H*), 7.12 (s, 1H, N*H*COCHCH$_3$), 6.84 (m, 1H, Ar*H*), 5.08 (d, *J* = 7.2 Hz, 1H, C*H*CH(CH$_3$)$_2$), 4.51-4.42 (m, 1H, C*H*CH$_3$), 4.28 (s, 1H, CON*H*CHCH$_3$), 2.45-2.29 (m, 1H, C*H*(CH$_3$)$_2$), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.07-0.96 (m, 6H, CH(C*H*$_3$)$_2$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.3, 169.6, 156.0, 139.0, 138.0, 129.3, 126.5, 122.7, 90.7, 80.6, 59.6, 50.2, 30.6, 28.4, 19.6, 17.7. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{19}H_{28}IN_3O_4Na^+$: 512.1017, found: 512.1023.

tert-Butyl

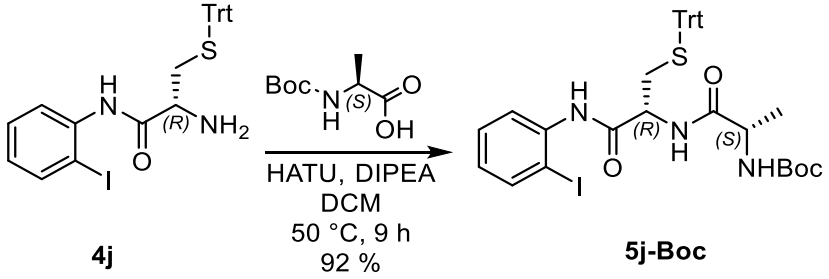
[(R)-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxo-3-(tritylthio)propan-2-yl]carbamate (5i-Boc)



white foamy solid (0.727 g, 99%). $[a]_D^{20}$ = -12.0 (c=1.05, $CHCl_3$); **TLC**： R_f=0.52 (PE/EA=5/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.09 (s, 1H, CON*H*Ar), 8.02 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.75 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.40 (m, 6H, Ar*H*), 7.30-7.25 (m, 7H, Ar*H*), 7.21 (m, 3H, Ar*H*), 6.87-6.80 (m, 1H, Ar*H*), 6.71 (s, 1H, N*H*CHCH$_3$), 4.83 (m, 1H, C*H*CH$_3$), 4.59 (m, 1H, SCH$_2$C*H*), 3.92 (s, 1H, OCOC*H*), 2.74-2.60 (m, 2H, SC*H*$_2$CH), 1.45 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.41 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 171.0, 170.0, 155.7, 144.4, 139.0, 138.1, 129.7, 129.2, 128.3, 127.1, 126.6, 123.0, 91.3, 80.8, 67.4, 53.7, 50.0, 33.5, 28.4, 17.7. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{36}H_{38}IN_3O_4SNa^+$: 758.1520, found: 758.1526.

tert-Butyl

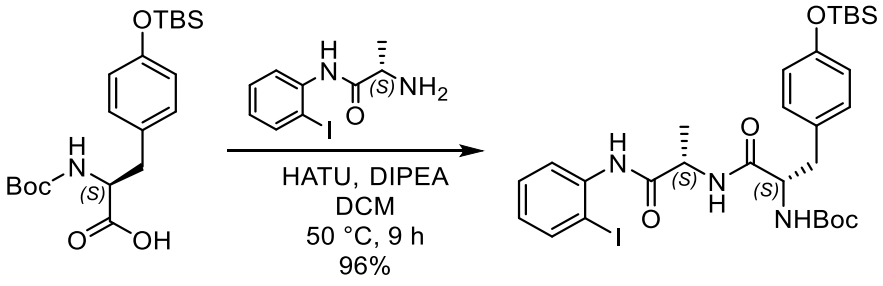
[(S)-1-({(R)-1-[(2-iodophenyl)amino]-1-oxo-3-(tritylthio)propan-2-yl}amino)-1-oxopropan-2-yl}carbamate (5j-Boc)



white solid (1.550 g, 92%). $[a]_D^{20}$=-15.5 (c=1.70, $CHCl_3$); **TLC**： R_f=0.17 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04-8.00 (m, 2H, , CON*H*Ar, Ar*H*), 7.75 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.45-7.43 (m, 6H, Ar*H*), 7.30-7.27 (m, 6H, Ar*H*), 7.23-7.20 (m, 3H, Ar*H*), 6.83 (m, 1H, Ar*H*), 6.73 (s, 1H, N*H*CO), 4.95 (d, *J* = 7.2 Hz, 1H), 4.28 (m, 1H, SCH$_2$C*H*), 4.19 (s, 1H), 2.86-2.72 (m, 2H, SC*H*$_2$CH), 1.39 (s, 9H, C(C*H*$_3$)$_3$), 1.34 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 173.0, 168.3, 155.6, 144.4, 139.1, 138.0, 129.7, 129.1, 128.2, 127.1, 126.7, 123.1, 91.1, 80.6, 67.5, 60.5, 53.2, 50.2, 33.3, 28.4. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{36}H_{38}IN_3O_4SNa^+$: 758.1520, found: 758.1540.

tert-Butyl

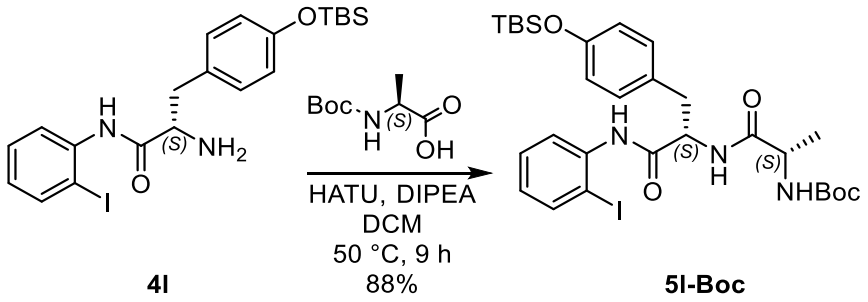
[(S)-3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5k-Boc)



4k **5k-Boc**

yellow solid (1.326 g, 96%). $[a]_D^{20}$= -12.5 (c=1.60, $CHCl_3$); **TLC**：R_f=0.37 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H, CON*H*Ar), 8.05 (d, *J* = 6.8 Hz, 1H, Ar*H*), 7.78 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.32 (m, 1H, Ar*H*), 7.03 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.90-6.82 (m, 1H, Ar*H*), 6.73 (s, 1H, CON*H*CHCH$_3$), 6.68 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.04 (m, 1H, C*H*CH$_2$), 4.65 (m, 1H, C*H*CH$_3$), 4.38 (s, 1H, OCON*H*), 3.13-2.94 (m, 2H, CHC*H*$_2$), 1.43 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.39 (s, 9H, OC(C*H*$_3$)$_3$), 0.95 (s, 9H, Si(C*H*$_3$)$_3$), 0.15 (s, 6H, Si(CH$_3$)$_2$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.9, 170.1, 155.7, 154.8, 139.1, 138.1, 130.4, 129.2, 128.9, 126.6, 123.0, 120.4, 91.0, 80.6, 55.9, 49.9, 37.4, 28.4, 25.8, 18.3, 17.7, -4.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{29}H_{43}IN_3O_5Si^+$: 668.2011, found: 668.2018.

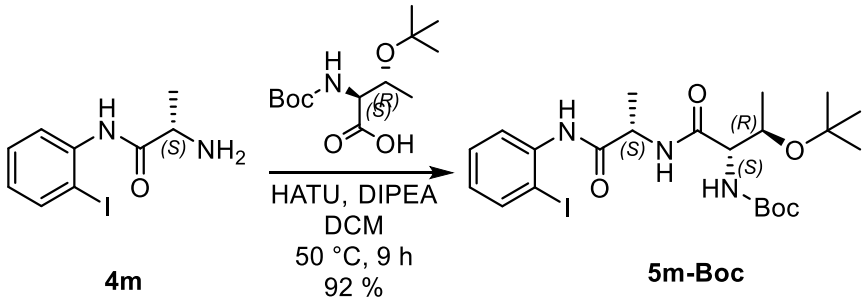
tert-Butyl [(S)-1-({(S)-3-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5l-Boc)



4l **5l-Boc**

white solid (0.984 g, 88%). $[a]_D^{20}$= -28.7 (c=1.40, $CHCl_3$); **TLC**：Rf=0.38 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.04 (s, 1H, CON*H*Ar), 8.00 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.72 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.28 (m, 1H, Ar*H*), 7.08 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.97 (s, 1H, CON*H*CHCH$_2$), 6.82 (m, 1H, Ar*H*), 6.74 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.12 (m, 1H, C*H*CH$_2$), 4.81 (m, 1H, C*H*CH$_3$), 4.21 (s, 1H, OCON*H*), 3.22-3.04 (m, 2H, CHC*H*$_2$), 1.40 (s, 9H, OC(C*H*$_3$)$_3$), 1.25 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 9H, Si(C*H*$_3$)$_3$), 0.15 (s, 6H, Si(C*H*$_3$)$_2$)). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.3, 169.5, 155.6, 154.9, 139.0, 137.9, 130.4, 129.2, 128.9, 126.7, 123.1, 120.5, 91.3, 80.4, 55.4, 50.3, 37.0, 28.5, 25.8, 18.7, 18.3, -4.3. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{29}H_{42}IN_3O_5SiNa^+$: 690.1831, found: 690.1853.

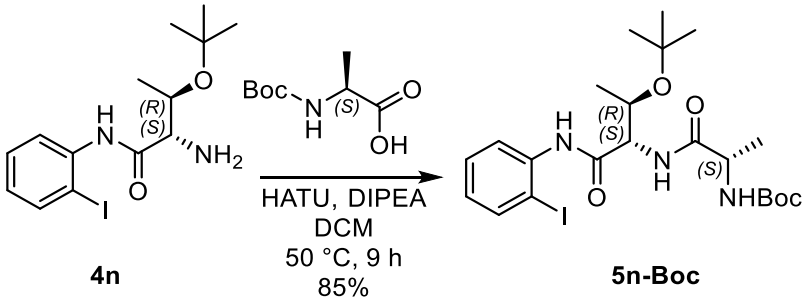
tert-Butyl [(2S,3R)-3-(tert-butoxy)-1-({(S)-1-[(2-iodophenyl)amino]-1-oxopropan-2-yl}amino)-1-oxobutan-2-yl]carbamate (5m-Boc)



4m 5m-Boc

white solid (0.503 g, 92%). $[a]_D^{20}$ = -0.130 (c=1.53, $CHCl_3$); **TLC**: R_f=0.27 (PE/EA=6/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.14 (s, 1H, CON*H*Ar), 8.05 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.78 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.53 (s, 1H, CON*H*CHCH$_3$), 7.32 (m, 1H, Ar*H*), 6.87-6.80 (m, 1H, Ar*H*), 5.57 (d, *J* = 6.0 Hz, 1H, CON*H*CHCH), 4.64 (m, 1H, NHC*H*CH$_3$), 4.18 (m, 2H, CONHC*HCH*), 1.50 (d, *J* = 7.2 Hz, 3H, NHCHC*H*$_3$), 1.44 (s, 9H, COOC(C*H*$_3$)$_3$), 1.25 (s, 9H, CHOC(C*H*$_3$)$_3$), 1.07 (d, *J* = 6.0 Hz, 3H, OCHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 170.7, 170.2, 155.8, 139.1, 138.2, 129.2, 126.5, 123.1, 91.0, 80.1, 75.4, 67.1, 58.9, 50.0, 28.5, 28.5, 18.2, 17.8. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{22}H_{35}IN_3O_5^+$: 548.1616, found: 548.1611.

tert-Butyl [(S)-1-({(2S,3R)-3-(tert-butoxy)-1-[(2-iodophenyl)amino]-1-oxobutan-2-yl}amino)-1-oxopropan-2-yl]carbamate (5n-Boc)



4n 5n-Boc

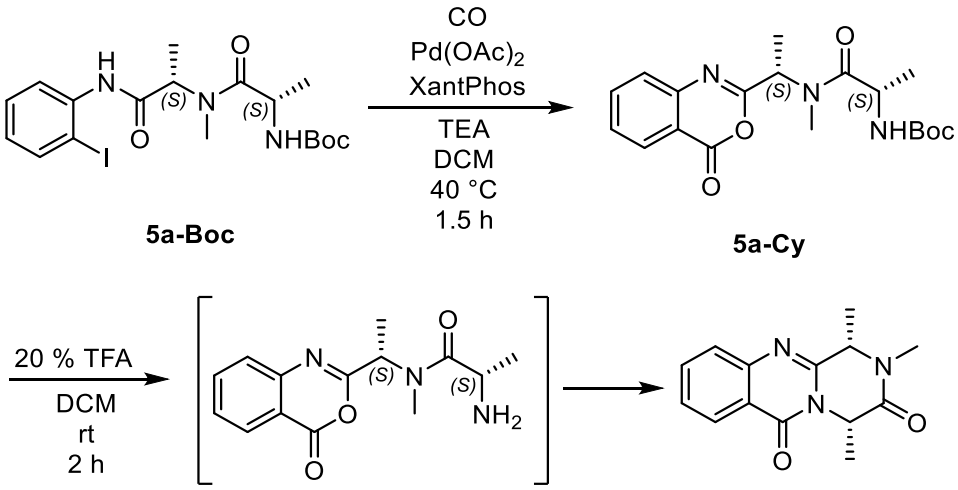
yellow solid (1.298 g, 85%). $[a]_D^{20}$= -5.33 (c=0.900, $CHCl_3$); **TLC**: R_f=0.24 (PE/EA=5/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H, CON*H*Ar), 8.01 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.80 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.39-7.30 (m, 1H, Ar*H*), 7.22 (s, 1H, CON*H*CHCH), 6.91-6.81 (m, 1H, Ar*H*), 5.07 (s, 1H, CON*H*CHCH$_3$), 4.51 (m, 1H, COC*H*CH$_3$), 4.29 (m, 2H, CONHC*HCH*), 1.45 (s, 9H, COOC(C*H*$_3$)$_3$), 1.40 (d, *J* = 7.2 Hz, 3H, COCHC*H*$_3$), 1.33 (s, 9H, CHOC(C*H*$_3$)$_3$), 1.13 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 172.9, 168.2, 155.5, 139.3, 138.3, 129.0, 126.6, 123.6, 90.8, 80.2, 76.1, 66.6, 58.9, 50.3, 28.6, 28.5, 18.5, 17.8. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{22}H_{35}IN_3O_5^+$: 548.1616, found: 548.1621.

Representative procedure for the synthesis of 8

To a flame dried round bottom flask containing **5-Boc** (0.50 mmol, 1.0 eq.) was added DCM (5 mL), $Pd(OAc)_2$ (0.011 g, 0.05 mmol, 0.10 eq.), XantPhos (0.058 g, 0.10 mmol, 0.10 eq.) and TEA (0.20 mL, 1.25 mmol, 2.50 eq.). The reaction was carried out under CO atmosphere (CO balloon, 1 atm.) at 40 ^{o}C. After stirring at 40 ^{o}C for 1.5 h, the CO balloon was removed and TFA (1 mL, TFA/DCM=20/100) was added to the reaction mixture, which was allowed to stir at room temperature for another 2 h until completion of reaction as indicated by

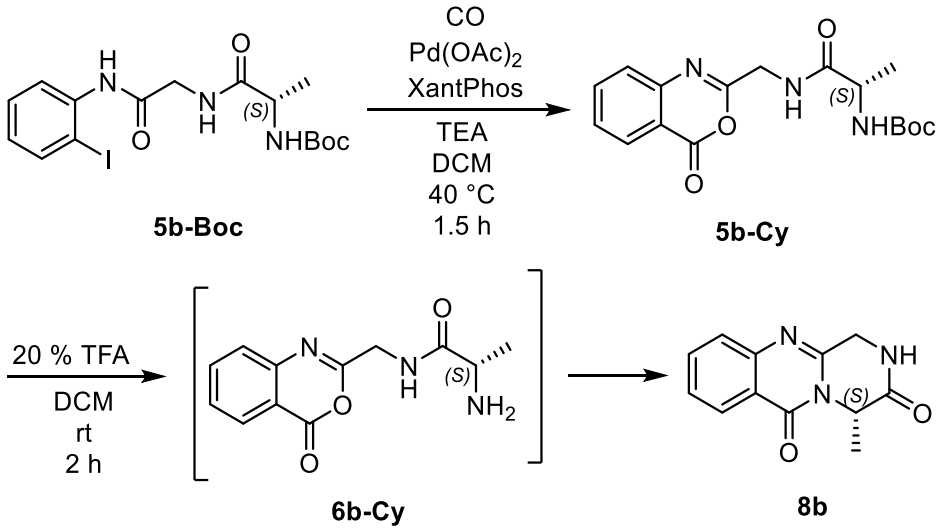
monitoring of thin layer chromatography. Sat. $NaHCO_3$ aq. (30 mL) was added to quench the reaction. The aqueous phase was extracted with EA (30 mL×3). The combined organic phase was washed with water (100 mL×1) and brine (100 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford the desired compound **8**.

(1S,4S)-1,2,4-Trimethyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8a)



white solid (0.091 g, 71%). $[a]_D^{20}$ = -89.6 (c=1.20, $CHCl_3$); **TLC**：R_f=0.21 (DCM/Et_2O=20/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.26 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.75 (m, 1H, Ar*H*), 7.61 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.49-7.45 (m, 1H, Ar*H*), 5.32 (q, *J* = 4.8 Hz, 1H, COC*H*CH_3), 4.57 (q, *J* = 4.8 Hz, 1H, NC*H*CH_3), 3.10 (s, 3H, NCH_3), 1.71 (d, *J* = 4.8 Hz, 3H, CHCH_3), 1.69 (d, *J* = 4.8 Hz, 3H, CHCH_3). **^{13}C NMR** (150 MHz, Chloroform-d) δ 166.0, 159.3, 150.5, 146.4, 133.7, 126.0, 125.9, 125.8, 119.2, 58.1, 51.1, 31.5, 20.0, 18.2. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}N_3O_2^+$: 258.1237, found: 258.1231.

(S)-4-Methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8b)

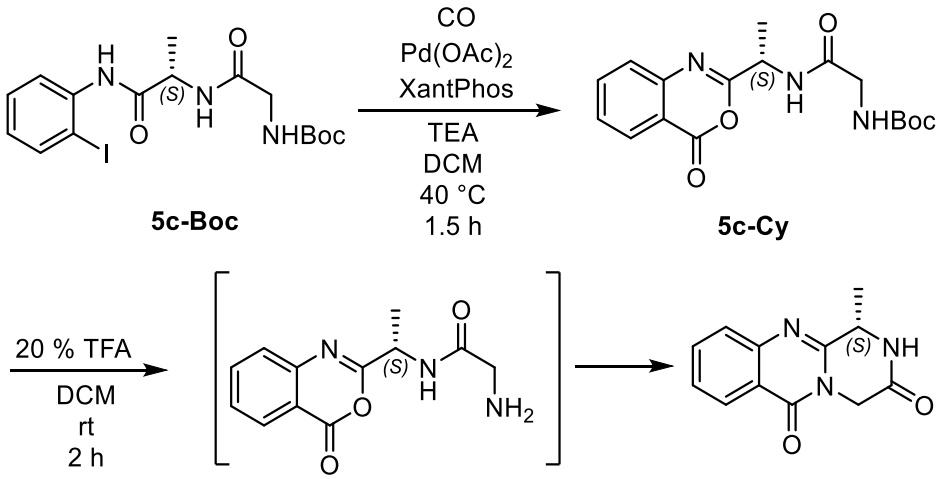


white solid (0.063 g, 55%). $[a]_D^{20}$ =33.0 (c=0.300, $CHCl_3$); **TLC**：R_f=0.40 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.30 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.65 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.51 (m, 1H, Ar*H*), 6.58 (brs, 1H, CON*H*),

5.52-5.42 (q, *J* = 7.2 Hz, 1H, C*H*CH$_3$), 4.69 (d, *J* = 16.8 Hz, 1H, NHCH_2), 4.50 (dd, *J* = 16.8, 4.8 Hz, 1H, NHCH_2), 1.66 (d, *J* = 7.2 Hz, 3H, CHCH_3). **^{13}C NMR** (150 MHz, Chloroform-d) δ 169.9, 160.3, 147.7, 147.3, 135.0, 127.5, 127.1, 120.6, 53.6, 52.0, 45.2, 17.1. **ESI-MS** (m/z): 230.11 $[M+H]^+$

Known Compound. Data consistent with the previous report.[4]

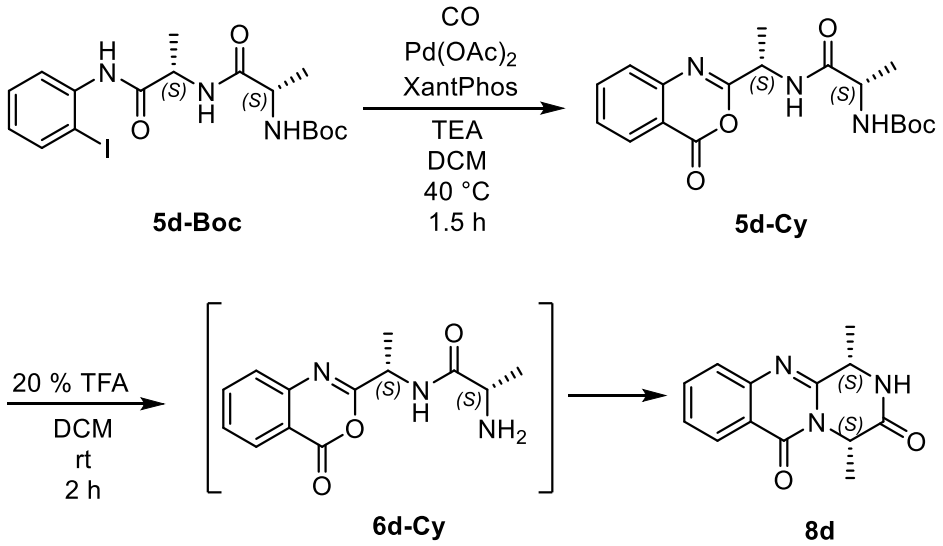
(S)-1-Methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8c)



white solid (0.065 g, 57%). $[a]_D^{20}$ = -0.067 (c=0.600, $CHCl_3$); **TLC：** R_f=0.30 (DCM/MeOH=15/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.29 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.82-7.74 (m, 1H, Ar*H*), 7.68 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.55-7.46 (m, 1H, Ar*H*), 6.95 (s, 1H, CON*H*), 4.75 (s, 2H, COCH_2), 4.70 (m, 1H, C*H*CH$_3$), 1.73 (d, *J* = 6.8 Hz, 3H, CHCH_3). **ESI-MS** (m/z): 230.13 $[M+H]^+$ (0.063 g, 55%).

Known Compound. Data consistent with the previous report.[5]

(1S,4S)-1,4-Dimethyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8d)

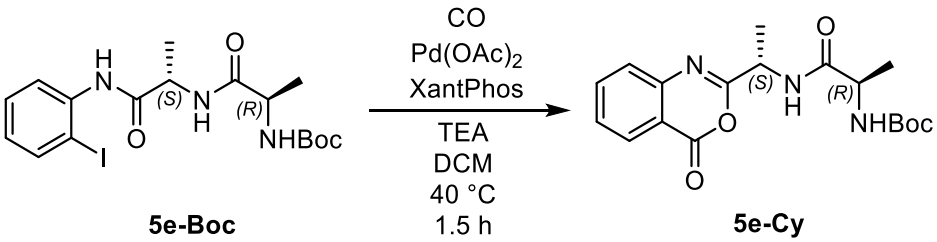


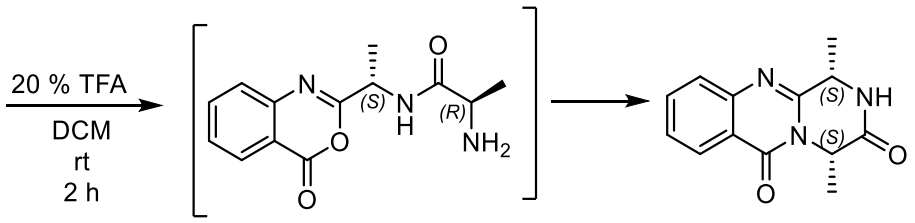
white solid (0.071 g, 58%). $[a]_D^{20}$ = 98.0 (c=0.500, $CHCl_3$); **TLC：** R_f=0.38 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.29 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.77 (m, 1H, Ar*H*), 7.64 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.50 (m, 1H, Ar*H*), 7.10 (brs, 1H, CON*H*),

5.32 (q, *J* = 7.2 Hz, 1H, COC*H*CH_3), 4.75 (m, 1H, NHC*H*CH_3), 1.76 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.75 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). **ESI-MS** (m/z): 244.16 $[M+H]^+$

Known Compound. Data consistent with the previous report.[4]

(1S,4S)-1,4-Dimethyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8e)

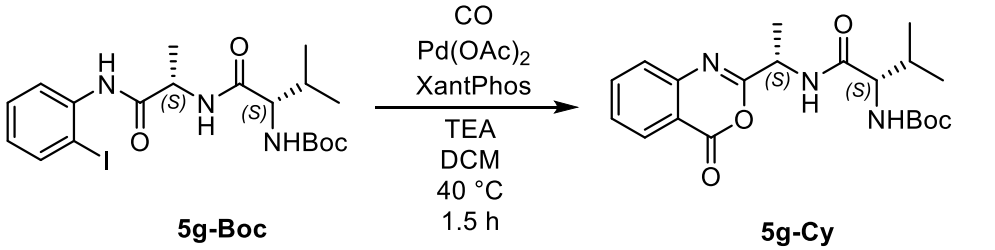


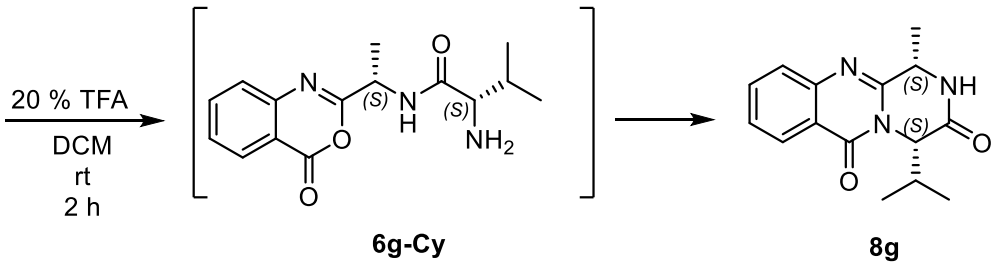


white solid (0.077 g, 64%). $[a]_D^{20}$ = -24.5 (c=0.400, $CHCl_3$); **TLC：** R_f=0.38 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.30 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.65 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.50 (m, 1H, Ar*H*), 6.56 (s, 1H, CON*H*), 5.33 (m, 1H, COC*H*CH_3), 4.75 (m, 1H, NHC*H*CH_3), 1.76 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.75 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{25}IN_3O_4^+$: 462.0884, found: 462.0887.

Known Compound. Data consistent with the previous report.[4]

(1S,4S)-4-Isopropyl-1-methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8g)



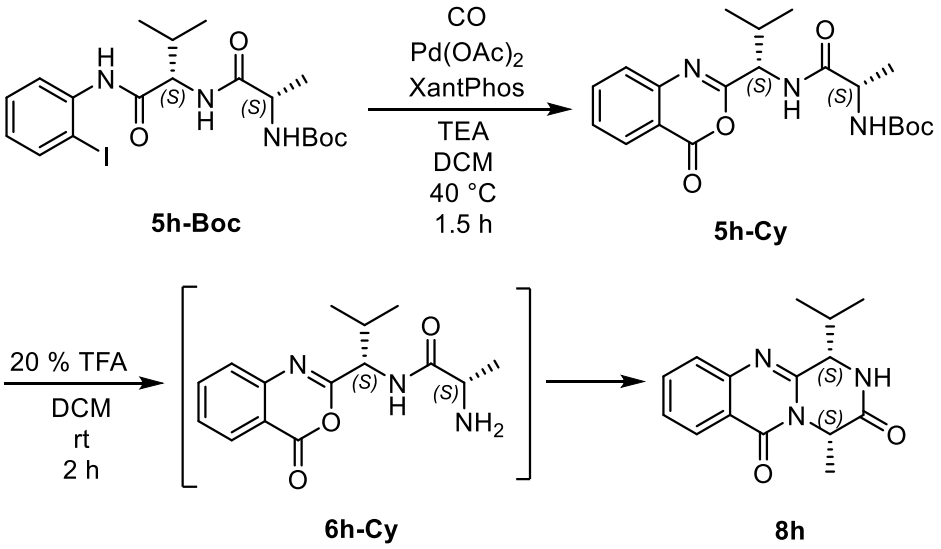


white solid (0.120 g, 89%). $[a]_D^{20}$ = 53.1 (c=1.20, $CHCl_3$); **TLC：** R_f=0.47 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.27 (d, *J* = 8.0 Hz, 1H, ArH), 7.80-7.73 (m, 1H, ArH), 7.63 (d, *J* = 8.4 Hz, 1H, ArH), 7.51-7.44 (m, 1H, ArH), 7.16 (s, 1H, CON*H*), 5.22 (d, *J* = 7.6 Hz, 1H, C*H*$CH(CH_3)_2$), 4.81-4.72 (m, 1H, C*H*CH_3), 2.26 (m, 1H,

CHC*H*$(CH_3)_2$), 1.80 (d, *J* = 7.2 Hz, 3H, CHCH(C*H*$_3)_2$), 1.19 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.07 (d, *J* = 7.2 Hz, 3H, CHCH(C*H*$_3)_2$). **ESI-MS** (m/z): 272.18 $[M+H]^+$

Known Compound. Data consistent with the previous report.[6]

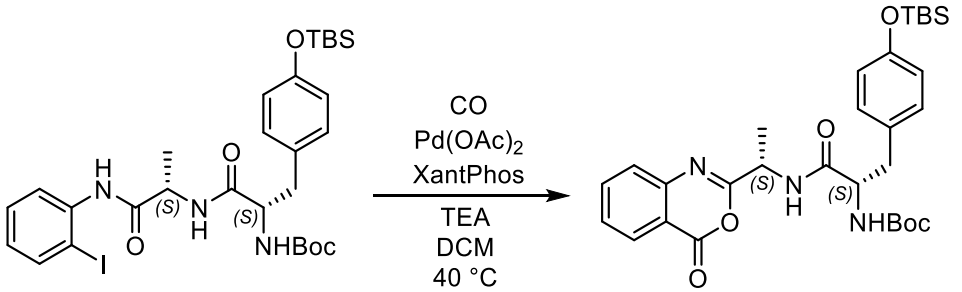
(1S,4S)-1-Isopropyl-4-methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8h)

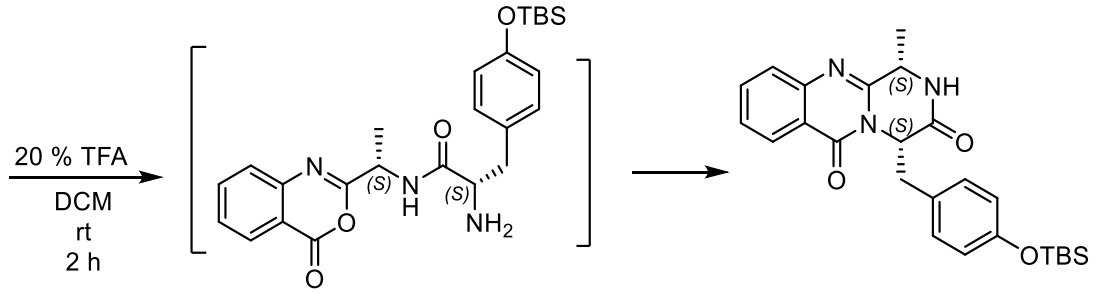


white solid (0.090 g, 67%). $[a]_D^{20}$ =52.1 (c=0.900, $CHCl_3$); **TLC :** R_f=0.46 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.28 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.76 (m, 1H, Ar*H*), 7.65 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.48 (m, 1H, Ar*H*), 7.37 (s, 1H, CON*H*), 5.26 (m, 1H, C*H*CH_3), 4.29 (m, 1H, C*H*CH$(CH_3)_2$), 2.38 (m, 1H, CHC*H*$(CH_3)_2$), 1.76 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.15 (d, *J* = 6.8 Hz, 3H, CHCH(C*H*$_3)_2$), 1.09 (d, *J* = 6.8 Hz, 3H, CHCH(C*H*$_3)_2$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 169.8, 160.9, 149.7, 147.1, 134.9, 127.2, 126.9, 120.3, 62.3, 52.1, 35.9, 19.8, 19.4, 18.7. **ESI-MS** (m/z): 272.21 $[M+H]^+$

Known Compound. Data consistent with the previous report.[7]

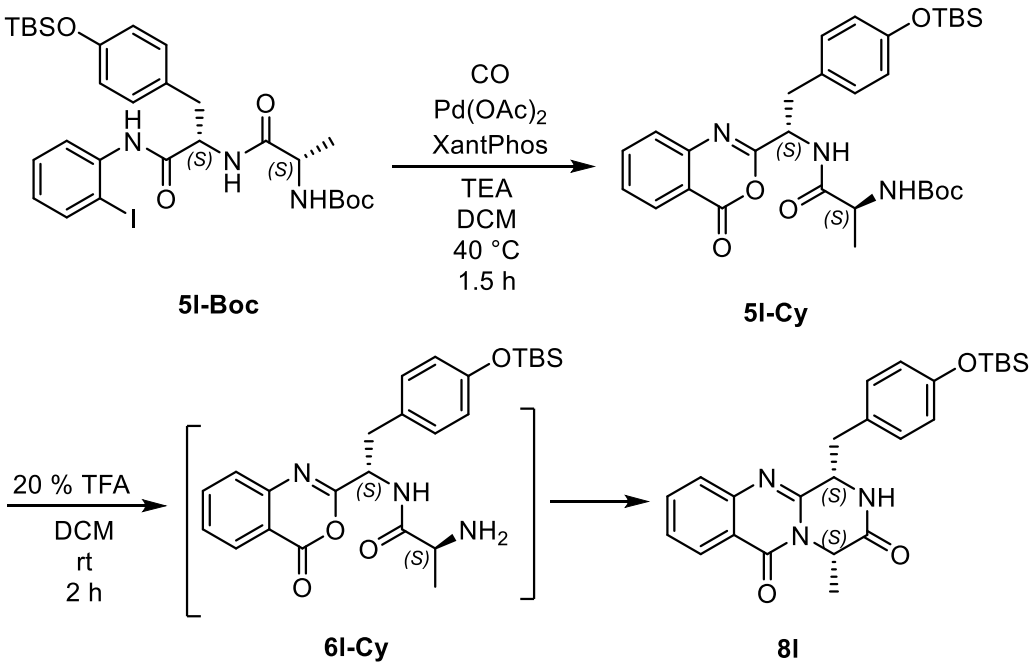
(1S,4S)-4-{4-[(tert-Butyldimethylsilyl)oxy]benzyl}-1-methyl-1,2-dihydro-6H-pyrazino[2,1-b] quinazoline-3,6(4H)-dione (8k)





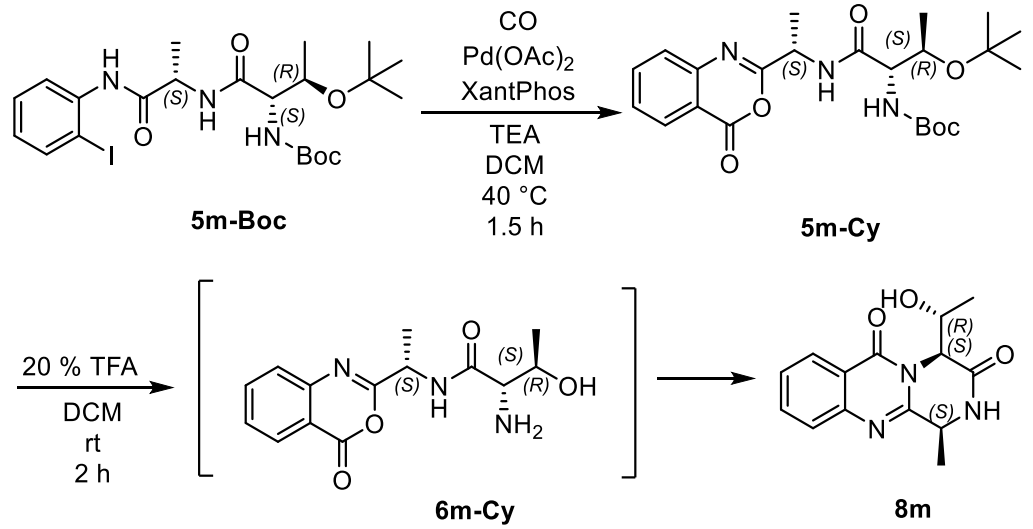
white solid (0.159 g, 71%). $[a]_D^{20}$ = 195 (c=0.600, $CHCl_3$); **TLC :** R_f=0.35 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.84-7.77 (m, 1H, Ar*H*), 7.62 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.52 (m, 1H, Ar*H*), 6.78 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.65 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.39 (s, 1H, CON*H*), 5.52-5.47 (m, 1H, COC*H*), 4.54 (m, 1H, C*H*CH_3), 3.57 (m, 1H, CHCH_2), 3.43 (m, 1H, CHCH_2), 0.93 (s, 9H, C(CH_3)$_3$), 0.80 (d, *J* = 7.2 Hz, 3H, CHCH_3), 0.11 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 166.6, 161.0, 155.5, 151.2, 147.3, 135.0, 131.4, 127.9, 127.1, 127.1, 127.0, 120.7, 120.1, 57.3, 52.3, 36.0, 25.8, 23.6, 1.2, -4.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{25}H_{32}N_3O_3^+$: 450.2207, found: 450.2210.

(1S,4S)-1-{4-[(tert-Butyldimethylsilyl)oxy]benzyl}-4-methyl-1,2-dihydro-6H-pyrazino[2,1-b] quinazoline-3,6(4H)-dione (8l)



white solid (0.154 g, 69%). $[a]_D^{20}$ = 11.3 (c=0.600, $CHCl_3$); **TLC**: R_f=0.57 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.80 (m, 1H, Ar*H*), 7.70 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.52 (m, 1H, Ar*H*), 7.09 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.81 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.30 (s, 1H, CON*H*), 5.24 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 4.77 (m, 1H, NHC*H*), 3.38 (m, 1H, NHCHCH_2), 3.13 (m, 1H, NHCHCH_2), 1.49 (d, *J* = 7.2 Hz, 3H, CHCH_3), 0.97 (s, 9H, C(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 168.7, 160.6, 155.5, 149.9, 147.3, 135.0, 130.9, 127.8, 127.3, 127.1, 127.0, 120.9, 120.4, 58.3, 52.0, 43.6, 25.8, 19.1, 18.3, -4.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{25}H_{32}N_3O_3^+$: 450.2207, found: 450.2211.

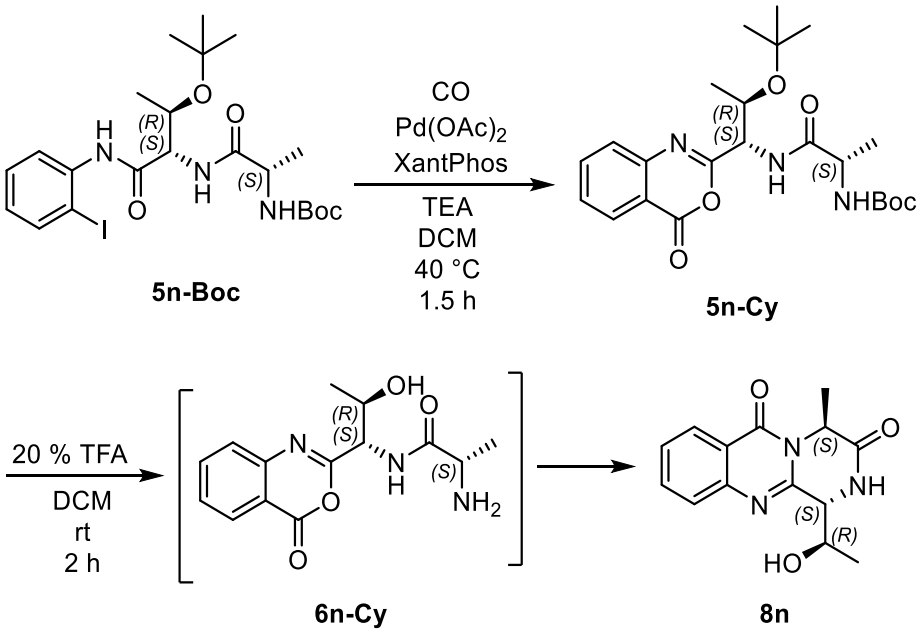
(1S,4S)-4-[(R)-1-(tert-Butoxy)ethyl]-1-methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8m)



white solid (0.069 g, 54%). $[a]_D^{20}$ = 32.8 (c=0.500, $CHCl_3$); **TLC**：R_f=0.30 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.56 (s, 1H, CON*H*), 8.14 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.88-7.82 (m, 1H, Ar*H*), 7.67 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.54 (m, 1H, Ar*H*),

5.34 (d, *J* = 5.6 Hz, 1H, CHO*H*), 5.14 (d, *J* = 4.8 Hz, 1H, C*H*CHCH$_3$), 4.98 (m, 1H, CHC*H*CH$_3$), 4.39-4.26 (m, 1H, NHC*H*CH$_3$), 1.54 (d, *J* = 6.8 Hz, 3H, NHCHC*H*$_3$), 1.10 (d, *J* = 6.4 Hz, 3H, CHCHC*H*$_3$). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 168.1, 160.6, 153.9, 146.7, 134.7, 127.1, 126.9, 126.5, 119.8, 68.5, 61.2, 49.2, 21.3, 17.4. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}N_3O_3^+$: 274.1186, found: 274.1187.

(1S,4S)-1-[(R)-1-Hydroxyethyl]-4-methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (8n)

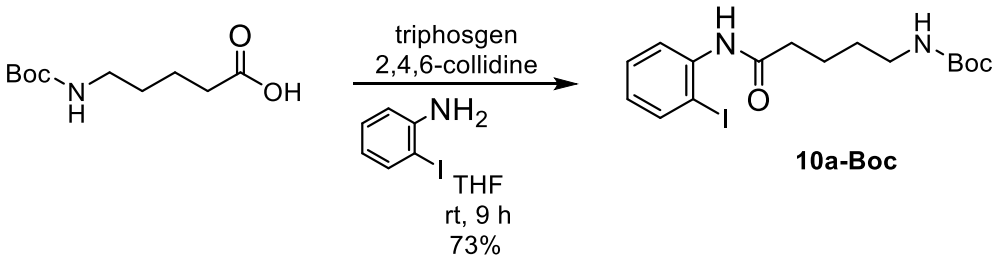


white solid (0.070 g, 51%). $[\alpha]_D^{20}$ = -422 (c=0.400, $CHCl_3$); **TLC：** R_f=0.28 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H, CON*H*), 8.27 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.76 (m, 1H, Ar*H*), 7.68 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.47 (m, 1H, Ar*H*), 6.66 (m, 1H, COC*H*CH$_3$), 5.53 (m, 1H, CHC*H*CH$_3$), 1.96 (d, *J* = 7.6 Hz, 3H, COCHC*H*$_3$), 1.67 (m, 1H, C*H*CHCH$_3$), 1.62 (d, *J* = 7.2 Hz, 3H, CHCHC*H*$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 167.5, 160.5, 147.5, 144.2, 134.9, 127.6, 127.5, 127.1, 127.0, 120.3, 114.8, 51.8, 19.2, 11.9. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}N_3O_3^+$: 274.1186, found: 274.1185.

Representative procedure for the synthesis of 10-Boc

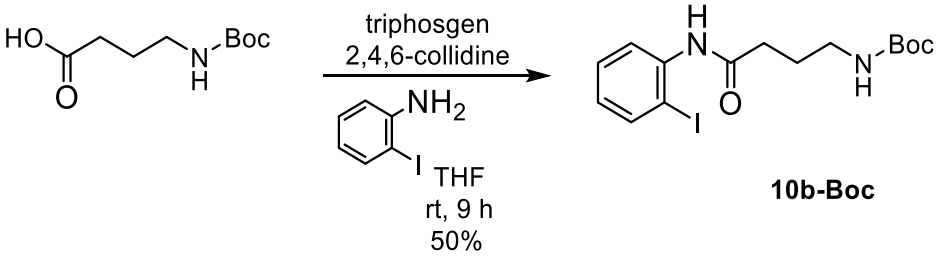
To a flame dried round bottom flask containing the carboxylic acid (1.0 eq.) was added anhydrous THF (5 mL/mmol). The mixture was cooled to 0 ^{o}C, and was added triphosgen (0.33 eq.) and 2,4,6-collidine (2.0 eq.) under ice bath. The mixture was allowed to stir at 0 ^{o}C for another 10 min, after which the amine (1.0 eq.) was added to the reaction mixture. The mixture was warmed to room temperature and was allowed to react for another 9 hours until completion of reaction as indicated by monitoring of thin layer chromatography. Afterwards, 10 mL/mmol sat. NH_4Cl aq. was added to the mixture. The aqueous phase was extracted with EA (15 mL/mmol×3) and the combined organic phase was washed with brine (30 mL/mmol×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford the desired compound **10-Boc**.

tert-Butyl {5-[(2-iodophenyl)amino]-5-oxopentyl}carbamate (10a-Boc)



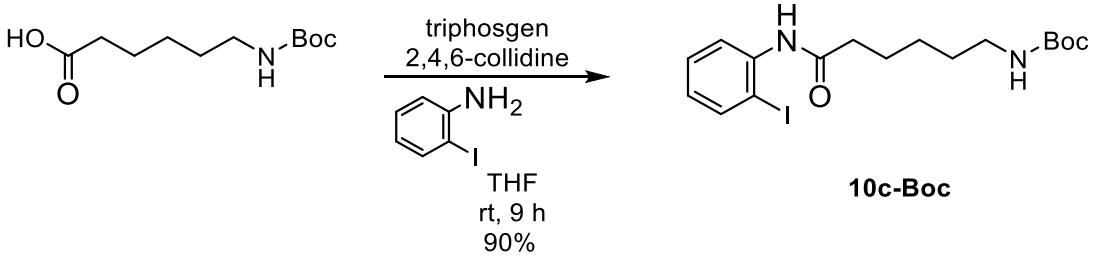
white solid (0.610 g, 73%). **TLC**：R_f=0.30 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.16 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.76 (d, *J* = 9.6 Hz, 1H, Ar*H*), 7.47 (s, 1H, CON*H*Ph), 7.32 (m, 1H, Ar*H*), 6.88-6.79 (m, 1H, Ar*H*), 4.64 (s, 1H, OCON*H*), 3.17 (m, 2H, NHCH_2), 2.45 (t, *J* = 7.2 Hz, 2H, COCH_2), 1.77 (m, 2H, COCH$_2$CH_2), 1.59 (m, 2H, NHCH$_2$CH_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 171.1, 156.2, 138.9, 138.3, 129.3, 126.2, 122.5, 90.4, 79.3, 40.1, 37.3, 29.6, 28.5, 22.6. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{24}IN_2O_3^+$: 419.0826, found: 419.0828.

tert-Butyl {4-[(2-iodophenyl)amino]-4-oxobutyl}carbamate (10b-Boc)



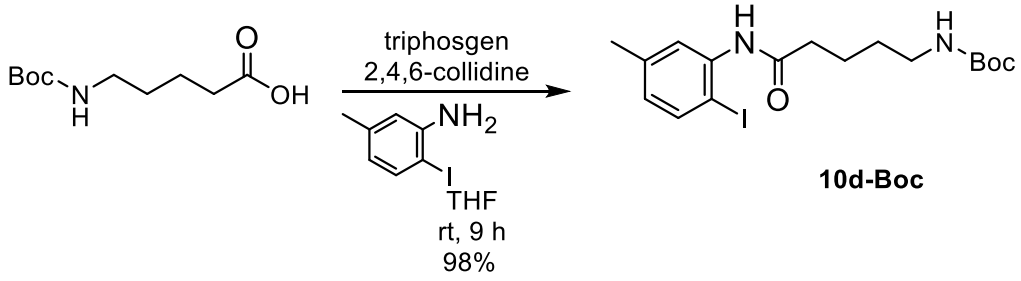
colorless oil (0.400 g, 50%). **TLC**：R_f=0.21 (PE/EA=4/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.11 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.76 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.67 (s, 1H, CON*H*Ph), 7.31 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.83 (t, *J* = 7.8 Hz, 1H, Ar*H*), 4.80 (s, 1H, OCON*H*), 3.23 (m, 2H, NHCH_2), 2.47 (m, 2H, COCH_2), 1.92 (m, 2H, CH$_2$CH_2CH$_2$), 1.41 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 174.4, 156.4, 150.4, 139.0, 129.3, 126.3, 122.8, 82.9, 79.5, 46.6, 33.1, 28.2, 17.5. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{15}H_{21}IN_2O_3Na^+$: 427.0489, found: 427.0493.

tert-Butyl {6-[(2-iodophenyl)amino]-6-oxohexyl}carbamate (10c-Boc)



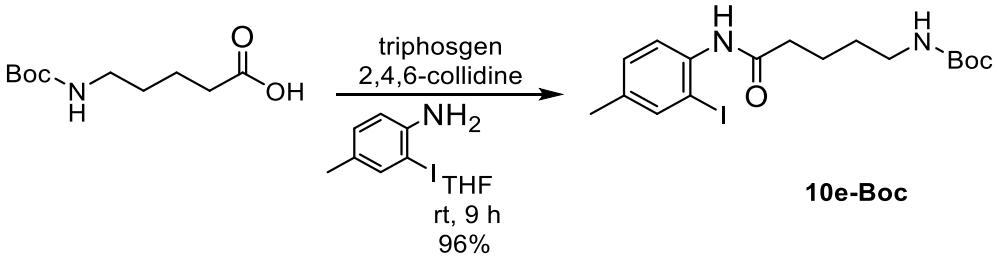
light yellow solid (0.776 g, 90%). **TLC**：R_f=0.19 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.75 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.46 (s, 1H, CON*H*Ph), 7.31 (m, 1H, Ar*H*), 6.85-6.79 (m, 1H, Ar*H*), 4.62 (s, 1H, OCON*H*), 3.11 (m, 2H, NHCH_2), 2.41 (t, *J* = 7.2 Hz, 2H, COCH_2), 1.75 (m, 2H, COCH$_2$CH_2), 1.52 (m, 2H, NHCH$_2$CH_2), 1.41 (m, 11H, C(CH_3)$_3$, CO(CH$_2$)$_2$CH_2). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.2, 156.1, 138.8, 138.2, 129.3, 126.1, 122.4, 90.4, 79.1, 40.4, 37.7, 29.9, 28.5, 26.4, 25.2. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{17}H_{25}IN_2O_3Na^+$: 455.0802, found: 455.0806.

tert-Butyl {5-[(2-iodo-5-methylphenyl)amino]-5-oxopentyl}carbamate (10d-Boc)



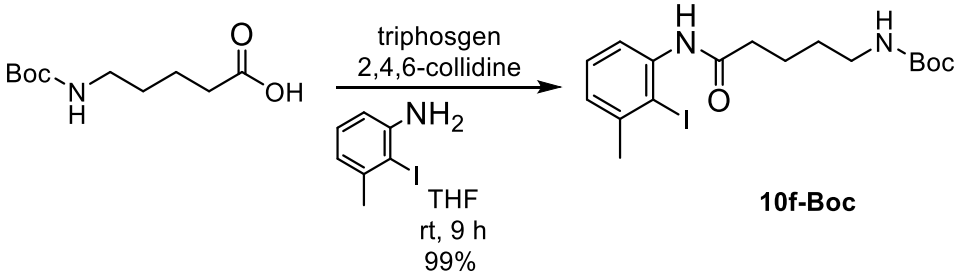
white solid (0.843 g, 98%). **TLC**：R_f=0.24 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (s, 1H, CON*H*Ph), 7.60 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.42 (s, 1H, Ar*H*), 6.66 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.66 (s, 1H, OCON*H*), 3.16 (m, 2H, N*H*CH_2), 2.43 (t, *J* = 7.2 Hz, 2H, COCH_2), 2.30 (s, 3H, PhCH_3), 1.77 (m, 2H, $COCH_2CH_2$), 1.59 (m, 2H, $NHCH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.1, 156.2, 139.6, 138.4, 137.9, 127.2, 123.2, 86.4, 79.3, 40.1, 37.3, 29.6, 28.5, 22.6, 21.3. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{17}H_{25}IN_2O_3Na^+$: 455.0802, found: 455.0804.

tert-Butyl {5-[(2-iodo-4-methylphenyl)amino]-5-oxopentyl}carbamate (10e-Boc)



white solid (0.826 g, 96%). **TLC**：R_f=0.20 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.59 (s, 1H, CON*H*Ph), 7.39 (s, 1H, Ar*H*), 7.12 (d, *J* = 8.4 Hz, 1H, Ar*H*), 4.65 (s, 1H, OCON*H*), 3.16 (m, 2H, NHCH_2), 2.43 (t, *J* = 7.2 Hz, 2H, COCH_2), 2.26 (s, 3H, PhCH_3), 1.76 (m, 2H, $COCH_2CH_2$), 1.59 (m, 2H, $NHCH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.1, 156.2, 139.1, 136.2, 135.8, 130.0, 122.4, 90.7, 79.3, 40.1, 37.2, 29.6, 28.5, 22.7, 20.4. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{17}H_{25}IN_2O_3Na^+$: 455.0802, found: 455.0806.

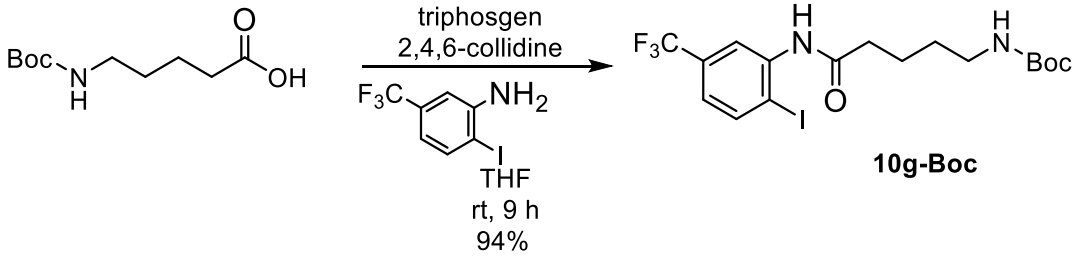
tert-Butyl {5-[(2-iodo-3-methylphenyl)amino]-5-oxopentyl}carbamate (10f-Boc)



white solid (0.863 g, 99%). **TLC**：R_f=0.19 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.62 (s, 1H, CON*H*Ph), 7.21 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.02 (d, *J* = 6.8 Hz, 1H, Ar*H*), 4.64 (s, 1H, OCON*H*), 3.17 (m, 2H, NHCH_2), 2.47 (m, 5H, COCH_2, PhCH_3), 1.79 (m, 2H, $COCH_2CH_2$), 1.60 (m, 2H, $NHCH_2CH_2$), 1.43 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.1, 156.2, 142.4, 138.4, 128.6, 126.0, 119.8, 98.1, 79.3,

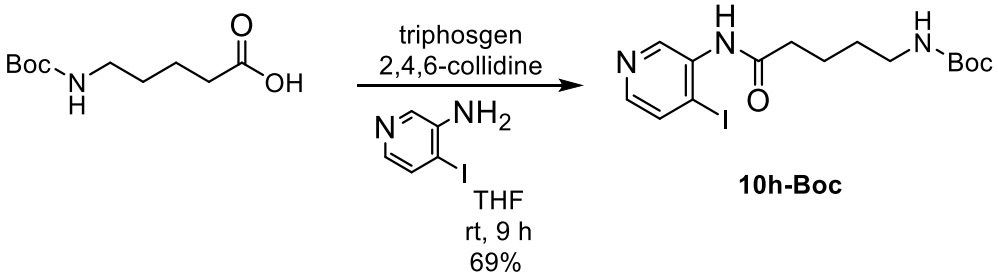
40.1, 37.4, 29.8, 29.7, 28.6, 22.7. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{17}H_{25}IN_2O_3Na^+$: 455.0802, found: 455.0805.

tert-Butyl (5-{[2-iodo-5-(trifluoromethyl)phenyl]amino}-5-oxopentyl)carbamate (10g-Boc)



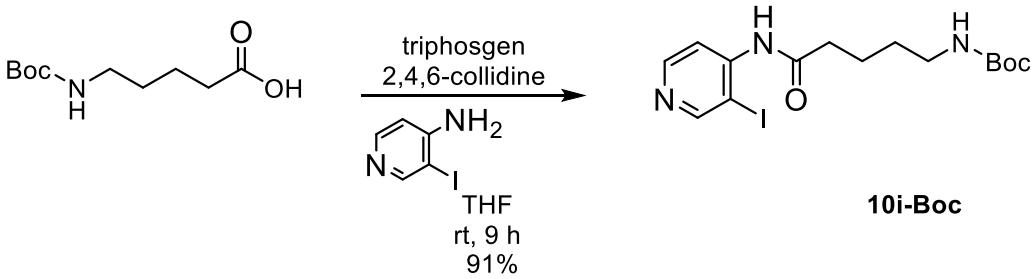
white solid (0.397 g, 94%). **TLC**：R_f=0.35 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H, CON*H*Ph), 7.89 (d, *J* = 5.6 Hz, 1H, Ar*H*), 7.60 (s, 1H, Ar*H*), 7.08 (d, *J* = 5.2 Hz, 1H, Ar*H*), 4.64 (s, 1H, OCON*H*), 3.17 (m, 2H, NHCH_2), 2.49 (t, *J* = 4.8 Hz, 2H, COCH_2), 1.83-1.76 (m, 2H, COCH$_2$CH_2), 1.59 (m, 2H, NHCH$_2$CH_2), 1.42 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 171.3, 156.2, 139.4, 139.0, 131.9 (q, *J* = 33 Hz), 123.7 (q, *J* = 273 Hz), 122.2, 118.7, 93.8, 79.4, 40.0, 37.2, 29.6, 28.6, 22.5. **^{19}F NMR** (565 MHz, Chloroform-d) δ -63.01. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{23}F_3IN_2O_3^+$: 487.0700, found: 487.0702.

tert-Butyl {5-[(4-iodopyridin-3-yl)amino]-5-oxopentyl}carbamate (10h-Boc)



yellow oil (0.560 g, 69%). **TLC**：R_f=0.16 (PE/EA=1/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.43 (s, 1H, CON*H*Ph), 8.25 (d, *J* = 5.2 Hz, 1H, Ar*H*), 7.72 (s, 1H, Ar*H*), 7.31 (d, *J* = 5.2 Hz, 1H, Ar*H*), 4.72 (s, 1H, OCON*H*), 3.16 (m, 2H, NHCH_2), 2.49 (t, *J* = 7.6 Hz, 2H, CONH_2), 1.77 (m, 2H, COCH$_2$CH_2), 1.57 (m, 2H, NHCH$_2$CH_2), 1.41 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.3, 156.3, 145.5, 144.3, 132.1, 124.0, 79.4, 60.5, 39.8, 36.7, 29.6, 28.5, 22.5. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{15}H_{22}IN_3NaO_3^+$: 442.0598, found: 442.0595.

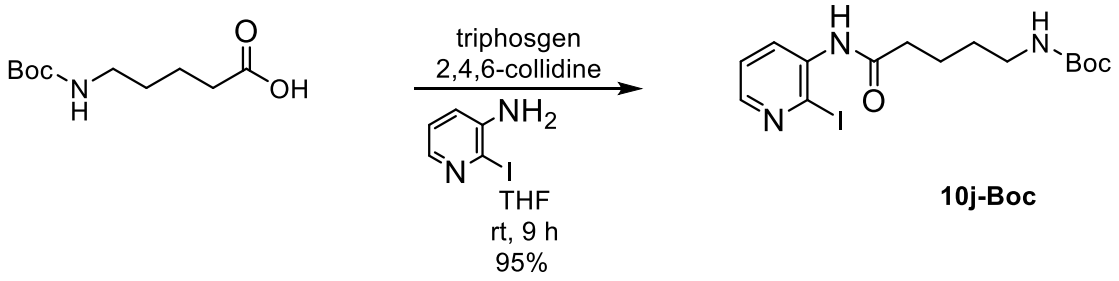
tert-Butyl {5-[(3-iodopyridin-4-yl)amino]-5-oxopentyl}carbamate (10i-Boc)



white solid (0.757 g, 91%). **TLC**：R_f=0.17 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.78 (s, 1H, CON*H*Ph), 8.37 (d, *J* = 5.2 Hz, 1H, Ar*H*), 8.28 (d, *J* = 5.6 Hz, 1H, Ar*H*), 7.64 (s, 1H, Ar*H*), 4.69 (s, 1H, OCON*H*), 3.15 (m, 2H, NHCH_2), 2.49 (t, *J* = 8.0 Hz, 2H, COCH_2),

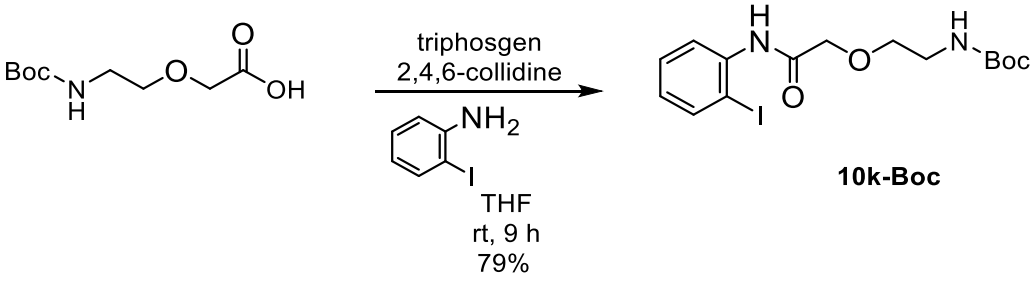
1.76 (m, 2H, $COCH_2CH_2$), 1.57 (m, 2H, $NHCH_2CH_2$), 1.41 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-d) δ 171.6, 157.4, 156.2, 150.4, 144.9, 115.2, 87.5, 79.3, 39.9, 37.4, 29.6, 28.5, 22.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{23}IN_2O_3^+$: 420.0779, found: 420.0788.

tert-Butyl {5-[(2-iodopyridin-3-yl)amino]-5-oxopentyl}carbamate (10j-Boc)



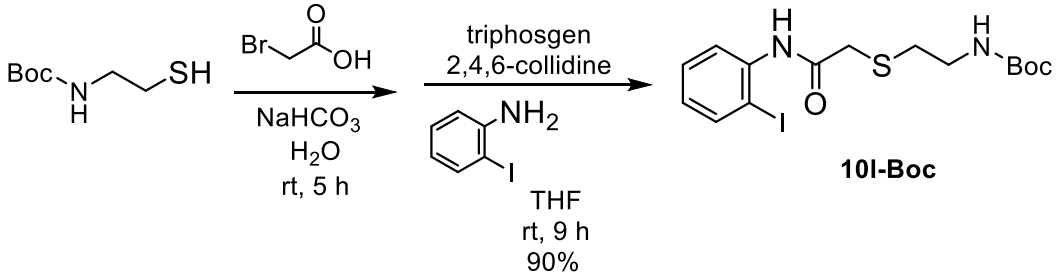
white solid (0.793 g, 95%). **TLC**：R_f=0.10 (PE/EA=3/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 8.4 Hz, 1H, Ar*H*), 8.08 (m, 1H, Ar*H*), 7.56 (s, 1H, CON*H*Ph), 7.21 (m, 1H, Ar*H*), 4.65 (s, 1H, OCON*H*), 3.17 (m, 2H, $NHCH_2$), 2.48 (t, *J* = 7.6 Hz, 2H, $COCH_2$), 1.79 (m, 2H, $COCH_2CH_2$), 1.62-1.55 (m, 2H, $NHCH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 171.5, 156.2, 146.0, 136.4, 128.4, 123.6, 114.6, 79.4, 40.0, 37.3, 29.7, 28.5, 22.5. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{23}IN_3O_3^+$: 420.0779, found: 420.0783.

tert-Butyl (2-{2-[(2-iodophenyl)amino]-2-oxoethoxy}ethyl)carbamate (10k-Boc)



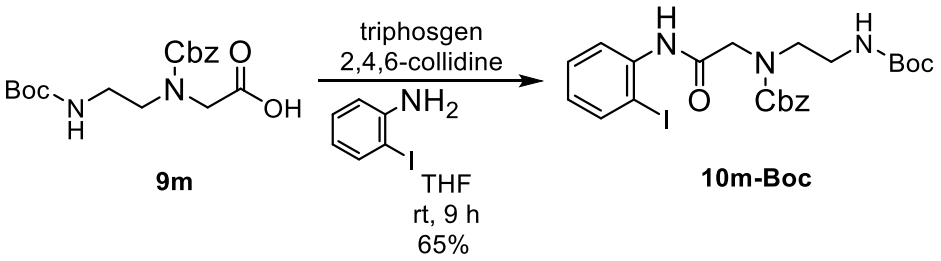
colorless oil (0.660 g, 79%). **TLC**：R_f=0.18 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.78 (s, 1H, CON*H*Ph), 8.32 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.77 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.37-7.31 (m, 1H, Ar*H*), 6.88-6.81 (m, 1H, Ar*H*), 5.04 (s, 1H, OCON*H*), 4.11 (s, 2H, OCH_2CO), 3.70 (t, *J* = 5.2 Hz, 2H, $NHCH_2CH_2$), 3.45 (m, 2H, $NHCH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 167.6, 155.9, 138.9, 137.7, 129.4, 126.2, 121.4, 89.5, 79.7, 71.1, 70.8, 40.5, 28.5. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{15}H_{21}IN_2O_4Na^+$: 443.0438, found: 443.0445.

tert-Butyl [2-({2-[(2-iodophenyl)amino]-2-oxoethyl}thio)ethyl]carbamate (10l-Boc)



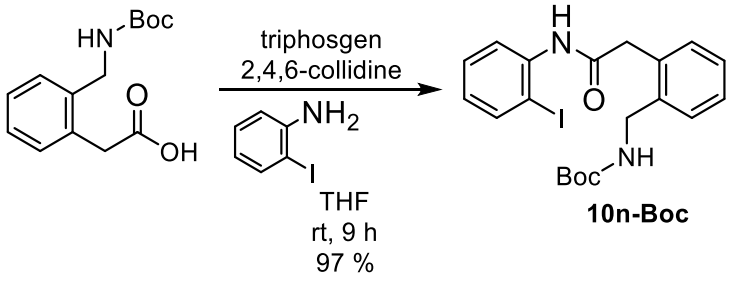
yellow oil (0.784 g, 90%). **TLC**：R_f=0.19 (PE/EA=10/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.00 (s, 1H, CON*H*Ph), 8.09 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.69 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.29-7.19 (m, 1H, Ar*H*), 6.76 (m, 1H, Ar*H*), 5.11 (s, 1H, OCON*H*), 3.34 (s, 2H, SCH_2CO), 3.29 (m, 2H, NHCH_2CH$_2$), 2.71 (t, *J* = 6.4 Hz, 2H, NHCH$_2$CH_2), 1.33 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 167.0, 155.7, 138.9, 137.8, 129.0, 126.3, 122.0, 90.0, 79.3, 39.4, 36.9, 33.4, 28.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{22}IN_2O_3S^+$: 437.0390, found: 437.0390 **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{15}H_{21}IN_2O_3SNa^+$: 459.0210, found: 459.0216.

Benzyl {2-[(tert-butoxycarbonyl)amino]ethyl}{2-[(2-iodophenyl)amino]-2-oxoethyl}carbamate (10m-Boc)



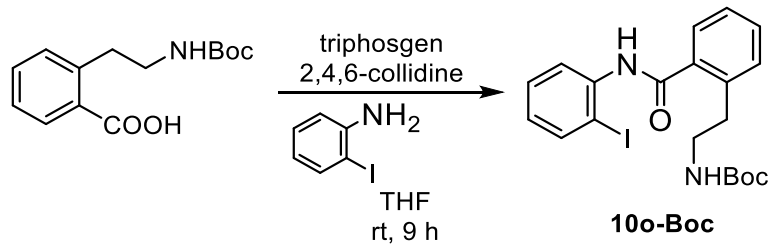
white solid (0.703 g, 65%). **TLC**：R_f=0.21 (PE/EA=3/1). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 12.6 Hz, 1H, Ar*H*), 8.08-8.00 (brs, 1H,PhN*H*), 7.74 (dd, *J* = 12.0, 2.4 Hz, 1*H*, Ar*H*), 7.33 (m, 6H, Ar*H*), 6.85 (t, *J* = 8.4 Hz, 1H, Ar*H*), 5.19 (s, 2H, COCH_2N), 5.07 (brs, 1H, CON*H*CH$_2$), 4.11 (s, 2H, CH_2Ph), 3.58-3.36 (m, 4H, NCH_2CH_2NH), 1.40 (s, 9H, OC(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 167.6, 156.9, 156.2, 138.9, 137.8, 136.1, 129.4, 128.7, 128.3, 126.5, 122.3, 122.0, 90.2, 79.6, 68.2, 53.0, 48.9, 39.3, 28.5. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{23}H_{28}IN_3O_5Na^+$: 576.0966, found: 576.0970.

tert-Butyl (2-{2-[(2-iodophenyl)amino]-2-oxoethyl}benzyl)carbamate (10n-Boc)



white solid (0.895 g, 97%). **TLC**：R_f=0.41 (PE/EA=4/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.67 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.57 (s, 1H, CON*H*Ph), 7.43-7.38 (m, 1H, Ar*H*), 7.36-7.27 (m, 4H, Ar*H*), 6.79 (t, *J* = 7.6 Hz, 1H, Ar*H*), 5.09 (s, 1H, OCON*H*), 4.37 (d, *J* = 6.0 Hz, 2H, NHCH_2), 3.83 (s, 2H, COCH_2), 1.37 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 169.2, 155.8, 138.8, 138.1, 137.9, 132.6, 131.6, 130.1, 129.1, 128.6, 128.5, 126.2, 122.1, 89.8, 79.6, 42.8, 42.1, 28.4. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{20}H_{24}IN_2O_3^+$: 467.0826, found: 467.0830.

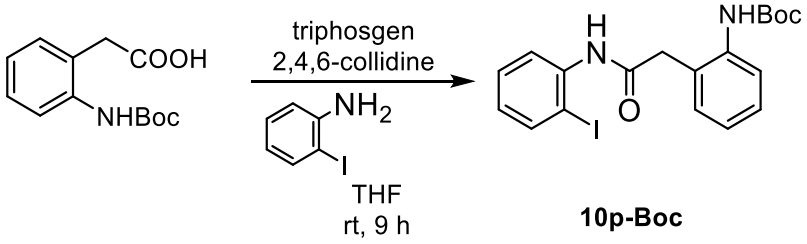
tert-Butyl {2-[(2-iodophenyl)carbamoyl]phenethyl}carbamate (10o-Boc)



10o-Boc

white solid (0.237 g, 5%). **TLC**: R_f=0.40 (PE/EA=3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.90 (s, 1H, PhN*H*CO), 7.83 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.64 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.49-7.34 (m, 4H, Ar*H*), 6.92 (t, *J* = 7.5 Hz, 1H, Ar*H*), 5.27 (s, 1H, N*H*Boc), 3.47 (m, 2H, CH_2NHBoc), 3.04 (t, *J* = 6.8 Hz, 2H, CH_2CH$_2$NHBoc), 1.38 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 156.3, 139.1, 138.9, 138.4, 136.1, 131.6, 131.1, 129.5, 127.0, 126.9, 126.7, 122.5, 90.9, 79.1, 42.3, 33.3, 28.5. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{20}H_{24}IN_2O_3^+$: 467.0826, found: 467.0823.

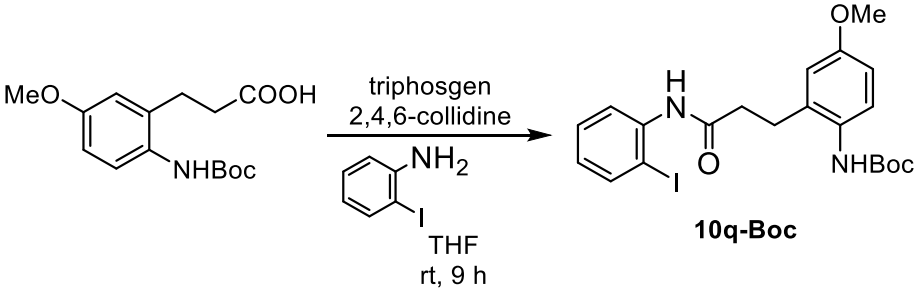
tert-Butyl (2-{2-[(2-iodophenyl)amino]-2-oxoethyl}phenyl)carbamate (10p-Boc)



10p-Boc

white solid (0.257 g, 16%). **TLC**: R_f=0.50 (PE/EA=4/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.83 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.74 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.70 (s, 1H, N*H*CO), 7.64 (s, 1H, N*H*CO), 7.36-7.28 (m, 3H, Ar*H*), 7.12 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.85 (t, *J* = 8.1 Hz, 1H, ArH), 3.75 (s, 2H, CH_2CO), 1.51 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.7, 153.7, 139.0, 137.8, 137.6, 130.8, 129.4, 128.9, 126.7, 125.6, 124.7, 124.0, 122.5, 90.5, 80.6, 42.3, 28.5. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{19}H_{21}IN_2NaO_3^+$: 475.0489, found: 475.0487.

tert-Butyl (2-{3-[(2-iodophenyl)amino]-3-oxopropyl}-4-methoxyphenyl)carbamate (10q-Boc)

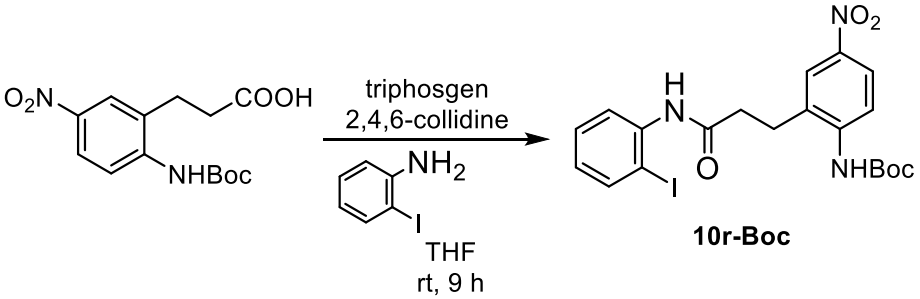


10q-Boc

white solid (3.272 g, 68%). **TLC**: R_f=0.33 (PE/EA=3/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.75 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.47-7.38 (m, 2H, N*H*CO, Ar*H*), 7.32 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.08 (s, 1H, N*H*CO), 6.83 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.77-6.73 (m, 2H, Ar*H*), 3.77 (s, 3H, OCH_3), 2.99 (t, *J* = 7.0 Hz, 2H, CH_2Ph), 2.79 (t, *J* = 7.0 Hz, 2H, COCH_2CH$_2$), 1.52 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.9, 157.2, 154.8,

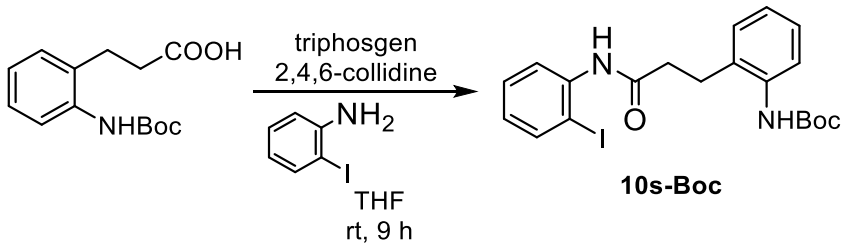
138.9, 138.1, 135.2, 129.3, 129.0, 126.9, 126.4, 122.6, 115.1, 112.4, 90.5, 80.1, 55.6, 28.3, 28.6, 26.4. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{21}H_{26}IN_2O_4^+$: 497.0932, found: 497.0939.

tert-Butyl (2-{3-[(2-iodophenyl)amino]-3-oxopropyl}-4-nitrophenyl)carbamate (10r-Boc)



light yellow solid (0.605 g, 52%). **TLC**：R_f=0.42 (PE/EA=3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, CON*H*), 8.18-8.05 (m, 4H, Ar*H*), 7.77 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.43 (s, 1H, CON*H*), 7.38-7.32 (m, 1H, Ar*H*), 6.87 (t, *J* = 7.6 Hz, 1H, Ar*H*), 3.07 (t, *J* = 6.4 Hz, 2H, CH_2Ph), 2.92 (t, *J* = 6.4 Hz, 2H, COCH_2CH$_2$), 1.56 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.7, 153.1, 143.3, 142.9, 139.1, 137.6, 130.5, 129.4, 126.7, 125.4, 123.3, 122.4, 121.3, 90.4, 81.4, 37.7, 28.4, 25.3. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{20}H_{23}IN_3O_5^+$: 512.0677, found: 512.0682.

tert-Butyl (2-{3-[(2-iodophenyl)amino]-3-oxopropyl}phenyl)carbamate (10s-Boc)



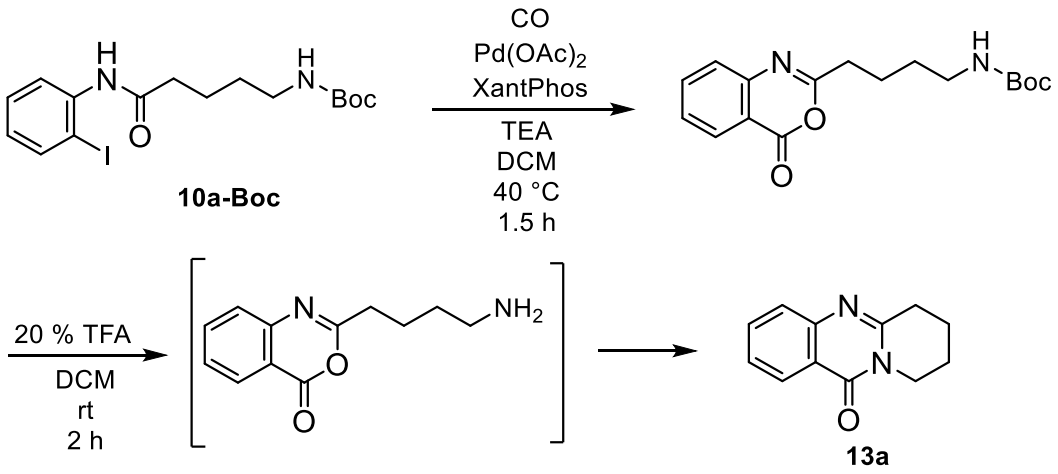
light yellow solid (0.849 g, 59%). **TLC**：R_f=0.38 (PE/EA=4/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.14 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.75 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.69 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.46 (s, 1H, CON*H*), 7.38 (s, 1H, CON*H*), 7.33 (t, *J* = 8.4 Hz, 1H, Ar*H*), 7.23-7.17 (m, 2H, Ar*H*), 7.07 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.84 (t, *J* = 7.6 Hz, 1H, Ar*H*), 3.02 (t, *J* = 6.8 Hz, 2H, CH_2Ph), 2.81 (t, *J* = 6.8 Hz, 2H, COCH_2CH$_2$), 1.53 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 154.1, 138.9, 138.0, 136.3, 131.8, 129.6, 129.4, 127.4, 126.4, 124.7, 123.9, 122.5, 90.3, 80.3, 38.3, 28.6, 25.9. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{20}H_{23}IN_2NaO_3^+$: 489.0646, found: 489.0647.

Representative procedure for the synthesis of 13

To a flame dried round bottom flask containing **10-Boc** (0.50 mmol, 1.0 eq.) was added DCM (5 mL), $Pd(OAc)_2$ (0.011 g, 0.05 mmol, 0.10 eq.), XantPhos (0.058 g, 0.10 mmol, 0.10 eq.) and TEA (0.20 mL, 1.25 mmol, 2.50 eq.). The reaction was carried out under CO atmosphere (CO balloon, 1 atm.) at 40 ^{o}C. After stirring at 40 ^{o}C for 1.5 h, the CO balloon was removed and TFA (1 mL, TFA/DCM=20/100) was added to the reaction mixture, which was allowed to stir at room temperature for another 2 h until completion of reaction as indicated by monitoring of thin layer chromatography. Sat. $NaHCO_3$ aq. (30 mL) was added to quench the reaction. The aqueous phase was extracted with EA (30 mL ×3). The combined organic phase

was washed with water (100 mL×1) and brine (100 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford the desired compound **13**.

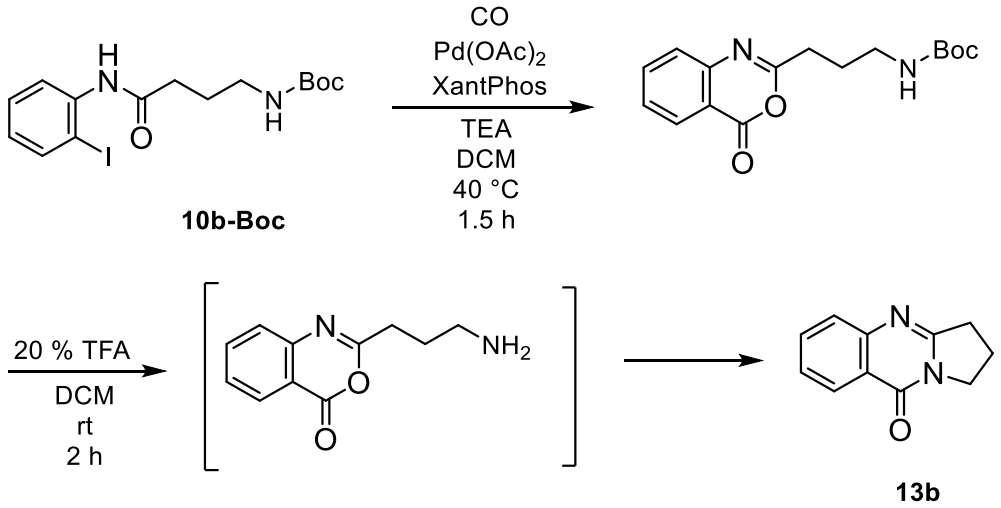
6,7,8,9-Tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (13a)



white solid (0.84 g, 84%). **TLC**: R_f=0.37 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.25 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.73-7.67 (m, 1H, Ar*H*), 7.59 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.41 (m, 1H, Ar*H*), 4.07 (t, *J* = 6.2 Hz, 2H, NCH_2), 2.99 (t, *J* = 6.8 Hz, 2H, N$(CH_2)_3$CH_2), 2.01 (m, 2H, NCH_2CH_2), 1.94 (m, 2H, N$(CH_2)_2$CH_2). **^{13}C NMR** (150 MHz, Chloroform-d) δ 162.3, 155.0, 147.5, 134.3, 126.8, 126.5, 126.2, 120.5, 42.5, 32.1, 22.2, 19.5. **ESI-MS** (m/z): 201.06 $[M+H]^+$

Known Compound. Data consistent with the previous report.[8]

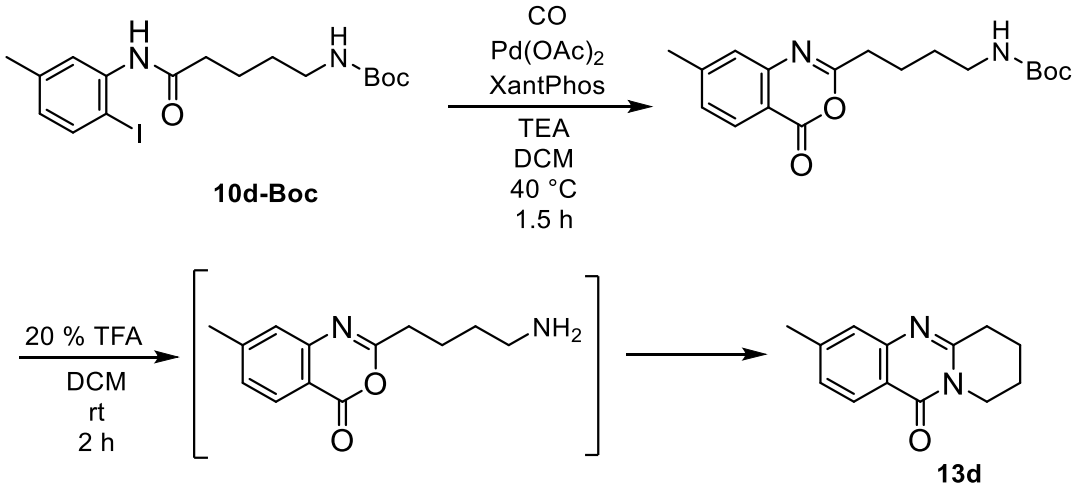
2,3-Dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (13b)



white solid (0.066 g, 71%). **TLC**: R_f=0.45 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.29 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.76-7.70 (m, 1H, Ar*H*), 7.65 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.49-7.42 (m, 1H, Ar*H*), 4.24-4.19 (m, 2H, N$(CH_2)_2$CH_2), 3.19 (t, *J* = 8.0 Hz, 2H, NCH_2), 2.33-2.25 (m, 2H, NCH_2CH_2). **ESI-MS** (m/z): 187.05 $[M+H]^+$

Known Compound. Data consistent with the previous report.[9]

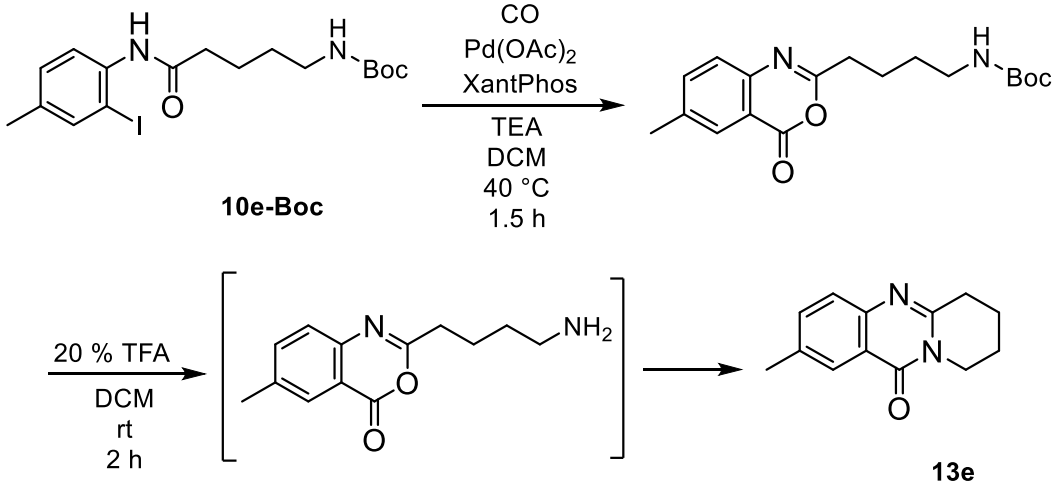
3-Methyl-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (13d)



light yellow solid (0.092 g, 86%). **TLC**：R_f=0.19 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.38 (s, 1H, Ar*H*), 7.23 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.06 (t, *J* = 6.0 Hz, 2H, NCH_2), 2.98 (t, *J* = 6.8 Hz, 2H, N$(CH_2)_3$CH_2), 2.47 (s, 3H, CH_3Ph), 2.04-1.97 (m, 2H, NCH_2CH_2), 1.96-1.90 (m, 2H, N$(CH_2)_2$CH_2). **ESI-MS** (m/z): 215.12 $[M+H]^+$

Known Compound. Data consistent with the previous report.[10]

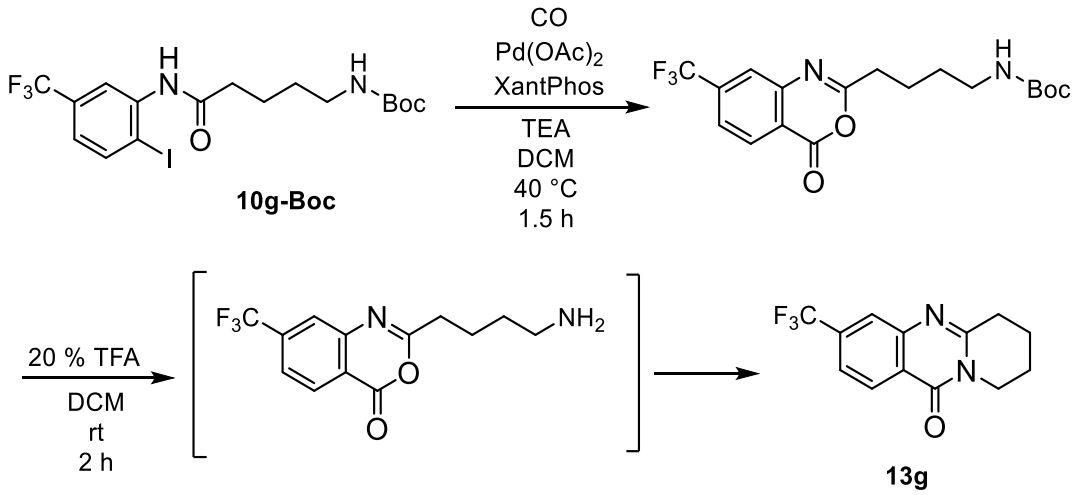
2-Methyl-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (13e)



light yellow solid (0.088 g, 83%). **TLC**：R_f=0.25 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H, Ar*H*), 7.53 (m, 1H, Ar*H*), 7.50 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.08 (t, *J* = 6.4 Hz, 2H, NCH_2), 2.98 (t, *J* = 6.8 Hz, 2H, N$(CH_2)_3$CH_2), 2.47 (s, 3H, CH_3Ph), 2.01 (m, 2H, NCH_2CH_2), 1.97-1.91 (m, 2H, N$(CH_2)_2$CH_2). **ESI-MS** (m/z): 215.14 $[M+H]^+$

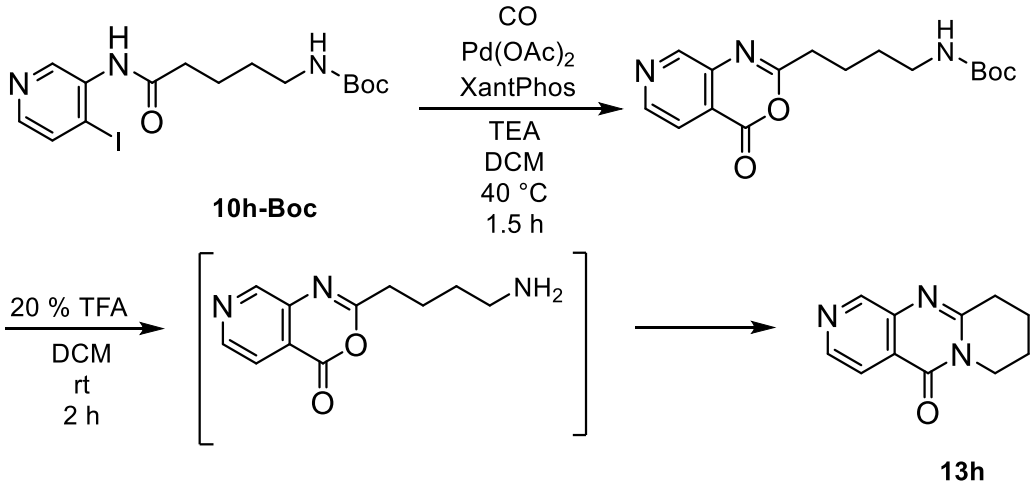
Known Compound. Data consistent with the previous report.[11]

3-(Trifluoromethyl)-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (13g)



white solid (0.071 g, 53%). **TLC**：R_f=0.19 (DCM/MeOH=20/1). **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.33 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.88 (s, 1H, Ar*H*), 7.60 (d, *J* = 8.4 Hz, 1H, Ar*H*), 4.07 (t, *J* = 6.6 Hz, 2H, NCH_2), 3.03 (t, *J* = 6.6 Hz, 2H, N$(CH_2)_3$CH_2), 2.03 (m, 2H, NCH_2CH_2), 1.96 (m, 2H, N$(CH_2)_2$CH_2). **^{13}C NMR** (150 MHz, Chloroform-d) δ 161.3, 157.0, 146.8, 136.0 (q, *J* = 33 Hz), 128.0, 123.5 (q, *J* = 273 Hz), 123.7 (q, *J* = 4 Hz), 122.6, 122.3(q, *J* = 4 Hz), 42.9, 31.7, 22.0, 19.2. **^{19}F NMR** (565 MHz, Chloroform-d) δ -63.29. **HRMS** (ESI) m/z: $[M+H]^+$calculated for $C_{13}H_{12}F_3N_2O^+$: 269.0896, found: 269.0897.

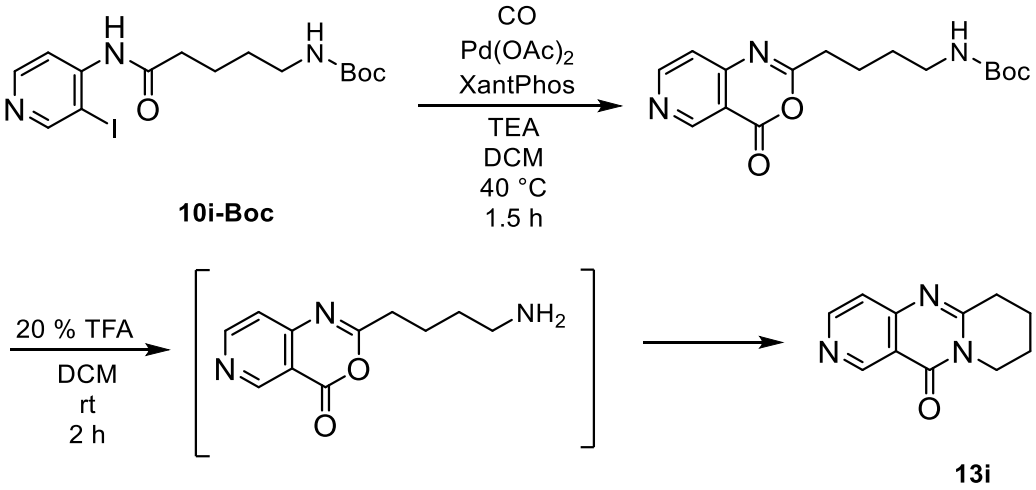
7,8,9,10-Tetrahydro-5H-dipyrido[1,2-a:3',4'-d]pyrimidin-5-one (13h)



white solid (0.072 g, 72%). **TLC**：R_f=0.51 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.06 (s, 1H, Ar*H*), 8.63 (d, *J* = 5.2 Hz, 1H, Ar*H*), 8.02 (d, *J* = 5.2 Hz, 1H, Ar*H*), 4.09 (t, *J* = 6.4 Hz, 2H, NCH_2), 3.05 (t, *J* = 6.8 Hz, 2H, N$(CH_2)_3$CH_2), 2.04 (m, 2H, NCH_2CH_2), 2.00-1.95 (m, 2H, N$(CH_2)_2$CH_2). **ESI-MS** (m/z): 202.14 $[M+H]^+$

Known Compound. Data consistent with the previous report.[12]

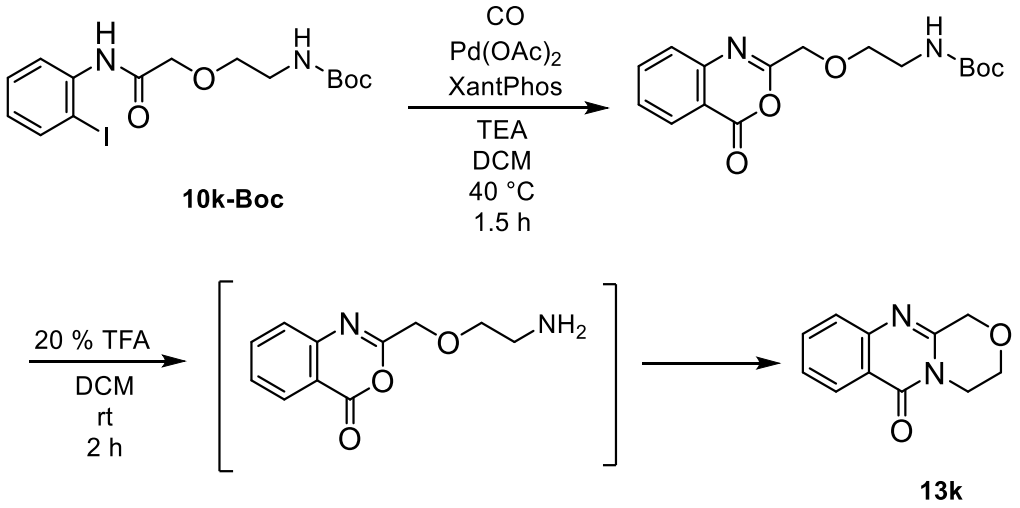
6,7,8,9-Tetrahydro-11H-dipyrido[1,2-a:4',3'-d]pyrimidin-11-one (13i)



white solid (0.085 g, 85%). **TLC**：R_f=0.37 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.47 (s, 1H, Ar*H*), 8.78 (d, *J* = 5.6 Hz, 1H, Ar*H*), 7.41 (d, *J* = 5.6 Hz, 1H, Ar*H*), 4.08 (t, *J* = 6.4 Hz, 2H, NCH_2), 3.02 (t, *J* = 6.8 Hz, 2H, N(CH_2)$_3$CH_2), 2.08-2.01 (m, 2H, NCH$_2$CH_2), 1.97 (m, 2H, N(CH_2)$_2$CH_2). **ESI-MS** (m/z): 202.15 $[M+H]^+$

Known Compound. Data consistent with the previous report.[13]

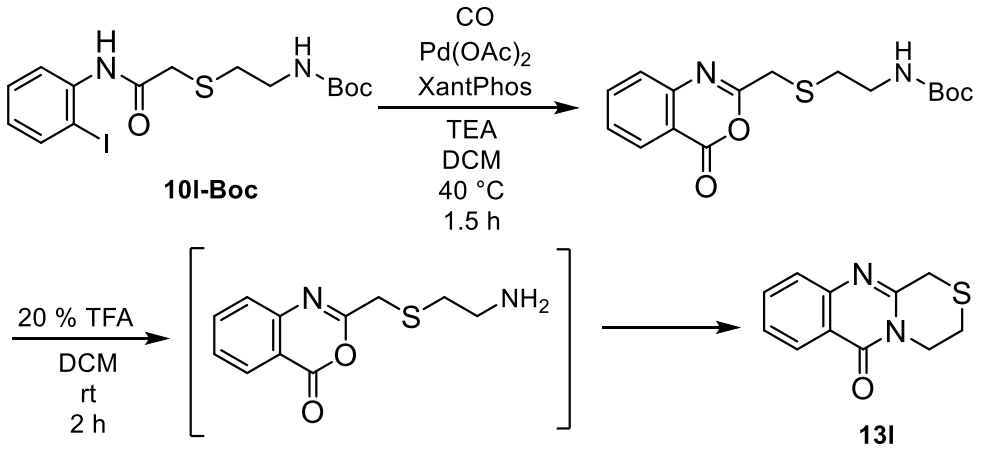
3,4-Dihydro-[1,4]oxazino[3,4-b]quinazolin-6(1H)-one (13k)



light yellow solid (0.053 g, 52%). **TLC**：R_f=0.36 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.74 (m, 1H, Ar*H*), 7.61 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.49-7.44 (m, 1H, Ar*H*), 4.77 (s, 2H, OCH_2C), 4.15-4.12 (m, 2H, NCH$_2$CH_2), 4.09-4.05 (m, 2H, NCH_2). **ESI-MS** (m/z): 203.10 $[M+H]^+$

Known Compound. Data consistent with the previous report.[14]

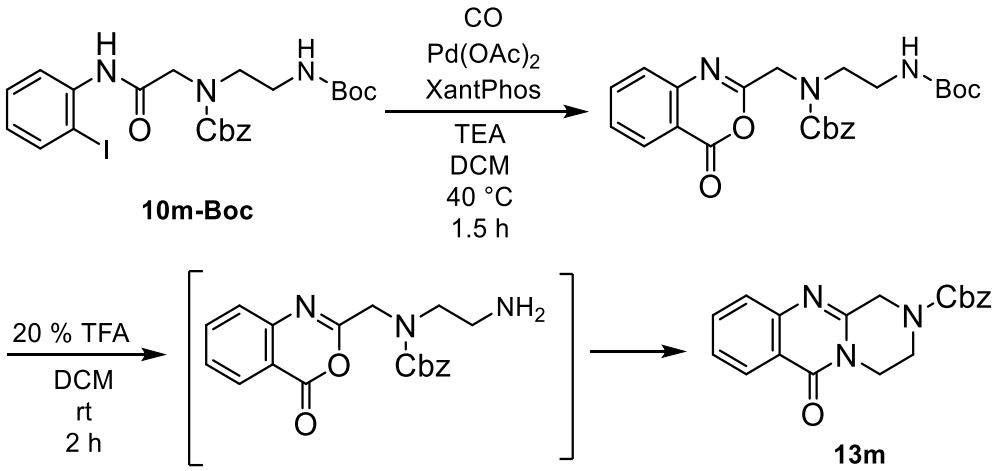
3,4-Dihydro-[1,4]thiazino[3,4-b]quinazolin-6(1H)-one (13l)



colorless oil (0.010 g, 10%). **TLC**: R_f=0.55 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.79-7.73 (m, 1H, Ar*H*), 7.65 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.51-7.46 (m, 1H, Ar*H*), 4.54-4.51 (m, 2H, NCH_2), 3.84 (s, 2H, SCH_2C), 3.13-3.09 (m, 2H, NCH_2CH_2). **ESI-MS** (m/z): 219.10 $[M+H]^+$

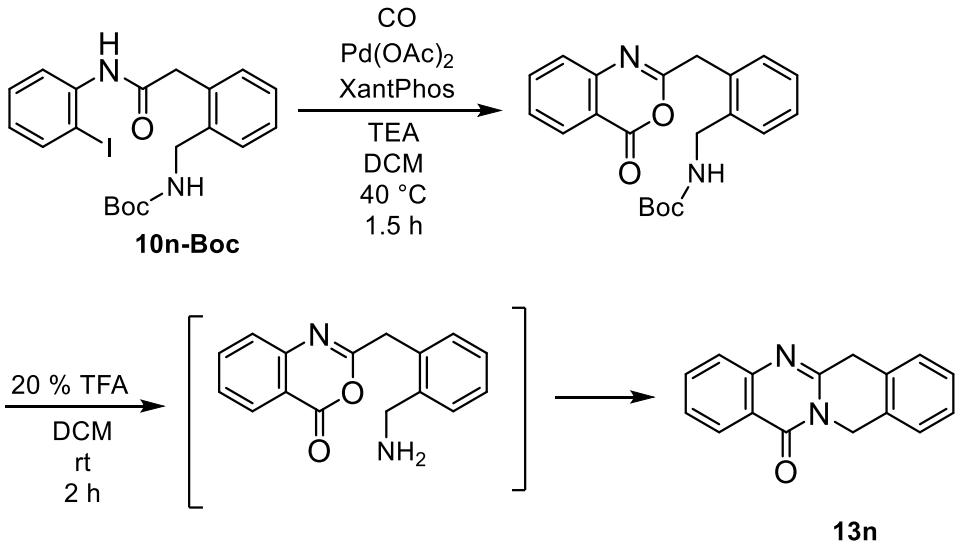
Known Compound. Data consistent with the previous report.[15]

Benzyl 6-oxo-1,3,4,6-tetrahydro-2H-pyrazino[2,1-b]quinazoline-2-carboxylate (13m)



white solid (0.063 g, 38%). **TLC**: R_f=0.33 (DCM/MeOH=20/1). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.27 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.79-7.71 (m, 1H, Ar*H*), 7.62 (m, 1H, Ar*H*), 7.47 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.41-7.32 (m, 5H, Ar*H*), 5.20 (s, 2H, OCH_2), 4.75 (s, 2H, NCH_2C), 4.23 (t, *J* = 5.6 Hz, 2H, PhCONCH_2), 3.86 (t, *J* = 6.0 Hz, 2H, $PhCONCH_2CH_2$). **ESI-MS** (m/z): 336.41 $[M+H]^+$

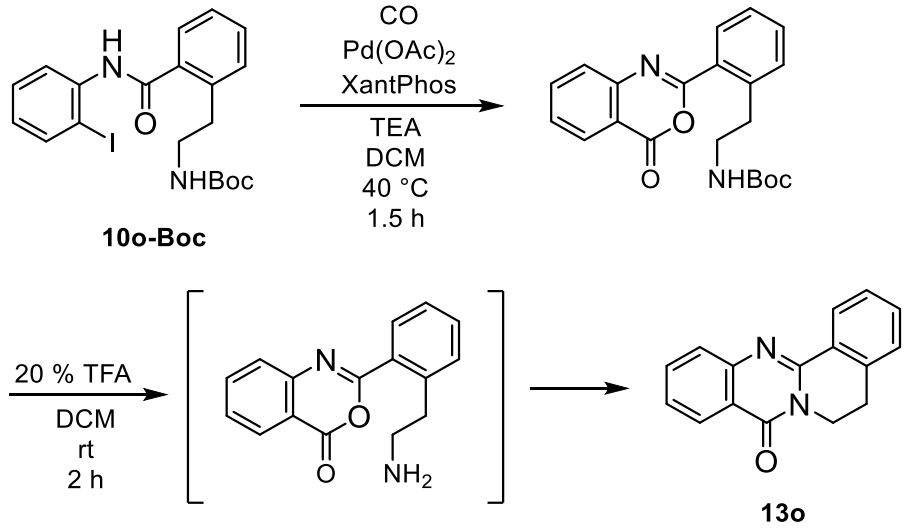
6,11-Dihydro-13H-isoquinolino[3,2-b]quinazolin-13-one (13n)



white solid (0.105 g, 85%). **TLC**：R_f=0.37 (DCM/MeOH=20/1). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.75 (t, *J* = 8.4 Hz, 1H, Ar*H*), 7.67 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.41-7.31 (m, 4H, Ar*H*), 5.29 (s, 2H, NCH_2), 4.17 (s, 2H, NCCH_2). **ESI-MS** (m/z): 249.16 $[M+H]^+$

Known Compound. Data consistent with the previous report.[16]

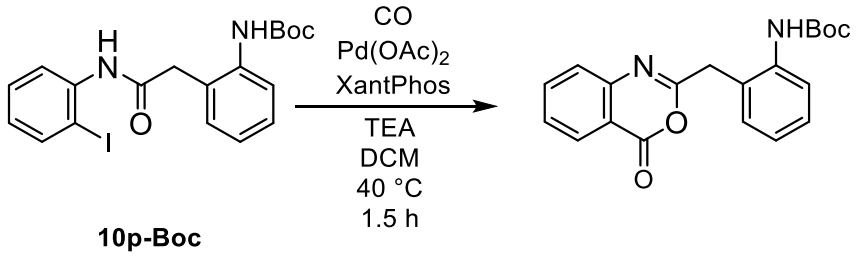
5,6-Dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (13o)

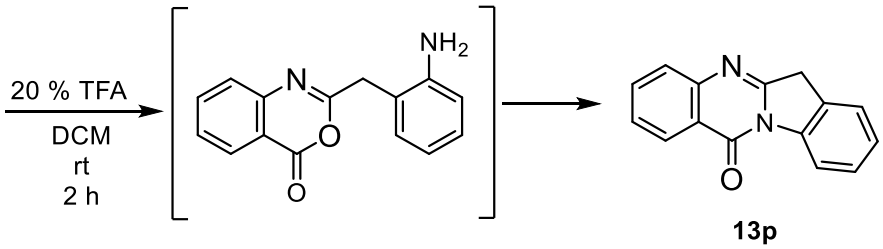


white solid (0.107 g, 86%). **TLC**：Rf=0.53 (DCM/MeOH=40/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.7 Hz, 1H, Ar*H*), 8.32 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.80-7.73 (m, 2H, Ar*H*), 7.51-7.42 (m, 3H, Ar*H*), 7.30 (d, *J* = 7.4 Hz, 1H, Ar*H*), 4.43 (t, *J* = 6.5 Hz, 2H, CH_2N), 3.11 (t, *J* = 6.5 Hz, 2H, CH_2Ph). **HRMS** (ESI) m/z: $[M+H]^+$calculated for $C_{16}H_{13}N_2O^+$: 249.1022, found: 249.1023.

Known Compound. Data consistent with the previous report.[9]

Indolo[2,1-b]quinazolin-12(6H)-one (13p)





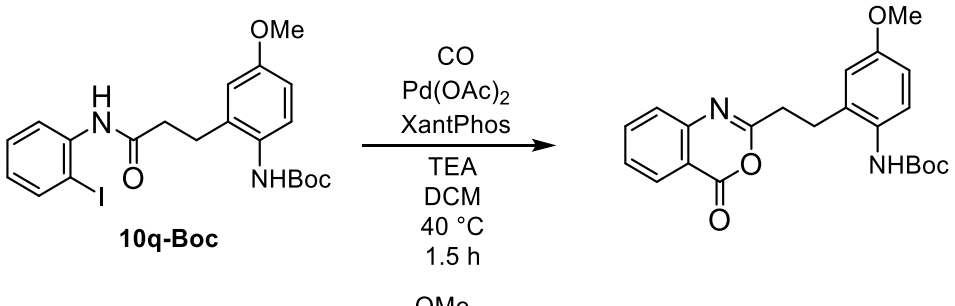
light green solid (0.058 g, 50%). **TLC**：Rf=0.45 (DCM/EA=10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (m, 1H, Ar*H*), 8.44 (m, 1H, Ar*H*), 7.80-7.74 (m, 2H, Ar*H*), 7.58-7.44 (m, 3H, Ar*H*), 7.34 (m, 1H, Ar*H*), 4.27 (s, 2H, CH_2). **ESI-MS** (m/z): 235.1 $[M+H]^+$

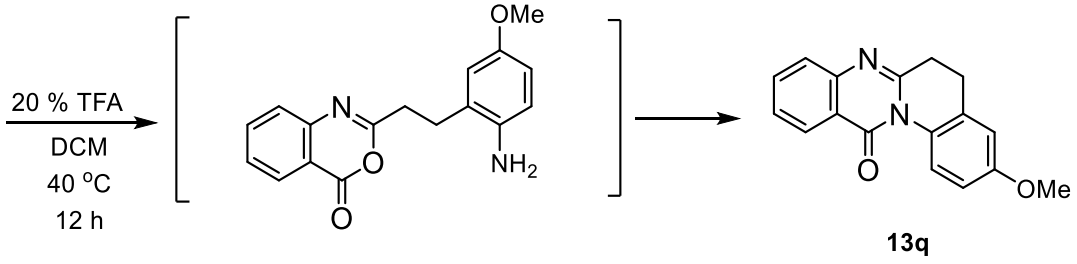
Known Compound. Data consistent with the previous report.[17]

Synthesis of 13q/r

To a flame dried round bottom flask containing **10-Boc** (0.50 mmol, 1.0 eq.) was added DCM (5 mL), $Pd(OAc)_2$ (0.011 g, 0.05 mmol, 0.10 eq.), XantPhos (0.058 g, 0.10 mmol, 0.10 eq.) and TEA (0.20 mL, 1.25 mmol, 2.50 eq.). The reaction was carried out under CO atmosphere (CO balloon, 1 atm.) at 40 ^oC. After stirring at 40 ^oC for 1.5 h, the CO balloon was removed and TFA (1 mL, TFA/DCM=20/100) was added to the reaction mixture, which was allowed to stir at 40 ^oC for another 12 h. Sat. $NaHCO_3$ aq. (30 mL) was added to quench the reaction. The aqueous phase was extracted with EA (30 mL×3). The combined organic phase was washed with water (100 mL×1) and brine (100 mL×1), dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue obtained was purified by silica gel chromatography to afford the desired compound **13**.

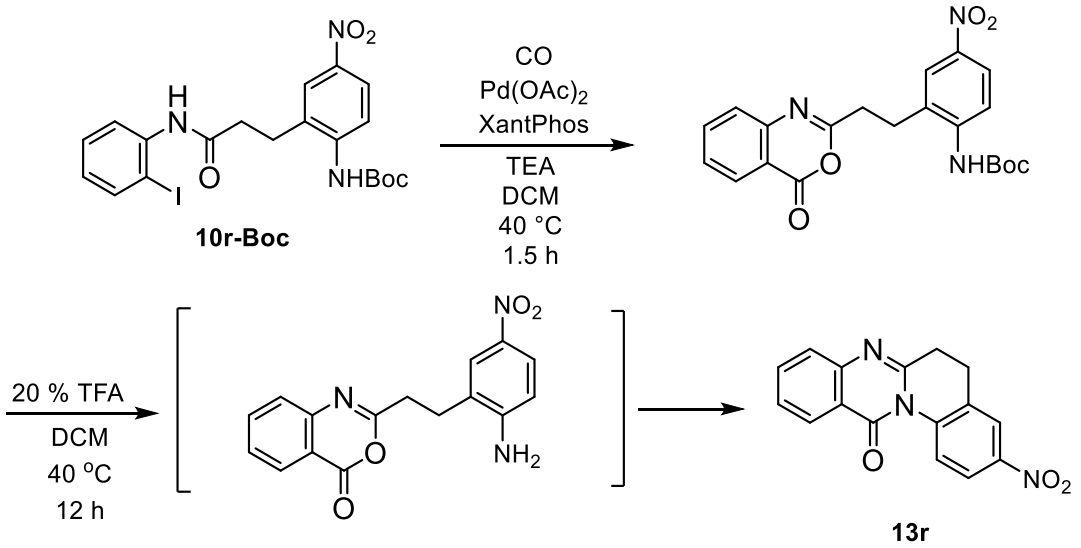
3-Methoxy-5,6-dihydro-12H-quinolino[2,1-b]quinazolin-12-one (13q)





light red solid (0.103 g, 74%). **TLC**: R_f=0.43 (DCM/MeOH=20/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1H, Ar*H*), 8.17 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.74 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.63 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.87 (dd, *J* = 9.0, 2.9 Hz, 1H, Ar*H*), 6.80 (d, *J* = 2.9 Hz, 1H, Ar*H*), 3.85 (s, 3H, OCH_3), 3.09 (m, 2H, CH_2Ph), 2.93 (m, 2H, CH_2CH_2Ph). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.0, 158.0, 154.8, 146.4, 134.5, 133.7, 127.7, 127.6, 126.8, 126.7, 125.4, 122.1, 113.1, 111.7, 55.6, 33.9, 26.3. **HRMS** (ESI) m/z: $[M+H]^+$calculated for $C_{17}H_{15}N_2O_2^+$: 279.1128, found: 279.1130.

3-Nitro-5,6-dihydro-12H-quinolino[2,1-b]quinazolin-12-one (13r)



white solid (0.033 g, 22%). **TLC**: R_f=0.69 (DCM/MeOH=25/1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.0 Hz, 1H, Ar*H*), 8.36 (d, *J* = 7.9 Hz, 1H, Ar*H*), 8.24-8.19 (m, 2H, Ar*H*), 7.81 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.67 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.53 (t, *J* = 7.0 Hz, 1H, Ar*H*), 3.15 (m, 2H, CH_2Ph), 3.09 (m, 2H, CH_2CH_2Ph). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.9, 153.3, 146.1, 145.5, 139.8, 135.4, 133.6, 127.9, 127.5, 127.1, 125.2, 123.0, 122.5, 121.8, 33.3, 26.0. **HRMS** (ESI) m/z: $[M+H]^+$calculated for $C_{16}H_{12}N_3O_3^+$: 294.0873, found: 294.0875.

Reference

1 S. B. Baravkar, M. A. Wagh, D. Paul, M. Santra and G. J. Sanjayan, *Tetrahedron Letters*, 2018, **59**, 3473–3476.

2 C. Proulx, É. Picard, D. Boeglin, P. Pohankova, S. Chemtob, H. Ong and W. D. Lubell, *J. Med. Chem.*, 2012, **55**, 6502–6511.

3 Y. Cui, M. Zhang, H. Xu, T. Zhang, S. Zhang, X. Zhao, P. Jiang, J. Li, B. Ye, Y. Sun, M. Wang, Y. Deng, Q. Meng, Y. Liu, Q. Fu, J. Lin, L. Wang and Y. Chen, *J. Med. Chem.*, 2022, **65**, 2971–2987.

4 M.-C. Tseng and Y.-H. Chu, *Tetrahedron*, 2008, **64**, 9515–9520.

5 M.-C. Tseng, H.-Y. Yang and Y.-H. Chu, *Org. Biomol. Chem.*, 2009, **8**, 419–427.

6 F. Hernández, V. Morales, F. L. Buenadicha, M. Söllhuber and C. Avendaño, *Tetrahedron: Asymmetry*, 2004, **15**, 3045–3058.

7 F. Hernández, F. L. Buenadicha, C. Avendaño and M. Söllhuber, *Tetrahedron: Asymmetry*, 2002, **12**, 3387–3398.

8 A. M. Ghouse and S. M. Akondi, *Org. Biomol. Chem.*, 2023, **21**, 5351–5355.

9 X. Chen, L. Jin, Y. Wang, H. Yang, Z. Le and Z. Xie, *Org. Biomol. Chem.*, 2023, **21**, 3863–3870.

10 A. Kamal, N. Markandeya, N. Shankaraiah, C. R. Reddy, S. Prabhakar, C. S. Reddy, M. N. Eberlin and L. Silva Santos, *Chemistry – A European Journal*, 2009, **15**, 7215–7224.

11 K. C. Jahng, S. I. Kim, D. H. Kim, C. S. Seo, J.-K. Son, S. H. Lee, E. S. Lee and Y. Jahng, *Chemical and Pharmaceutical Bulletin*, 2008, **56**, 607–609.

12 A. D. Dunn, K. I. Kinnear and R. Norrie, *Zeitschrift für Chemie*, 1986, **26**, 290–292.

13 I. Hermecz, J. Kökösi, B. Podányi and Z. Liko, *Tetrahedron*, 1996, **52**, 7789–7796.

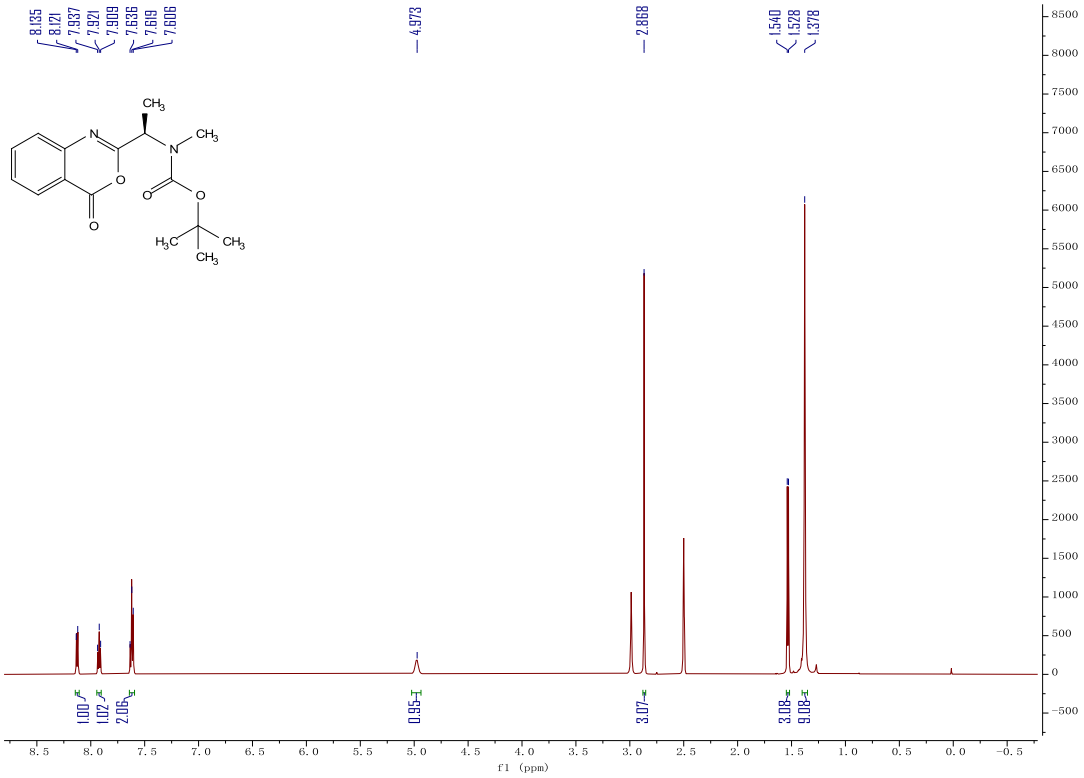
14 L. Ôrfi, J. Kökösi, G. Szász, I. Kövesdi, M. Mák, I. Teplán and G. Kéri, *Bioorganic & Medicinal Chemistry*, 1996, **4**, 547–551.

15 A. Dunn and R. Norrie, *ZEITSCHRIFT FUR CHEMIE*, 1990, **30**, 211–212.

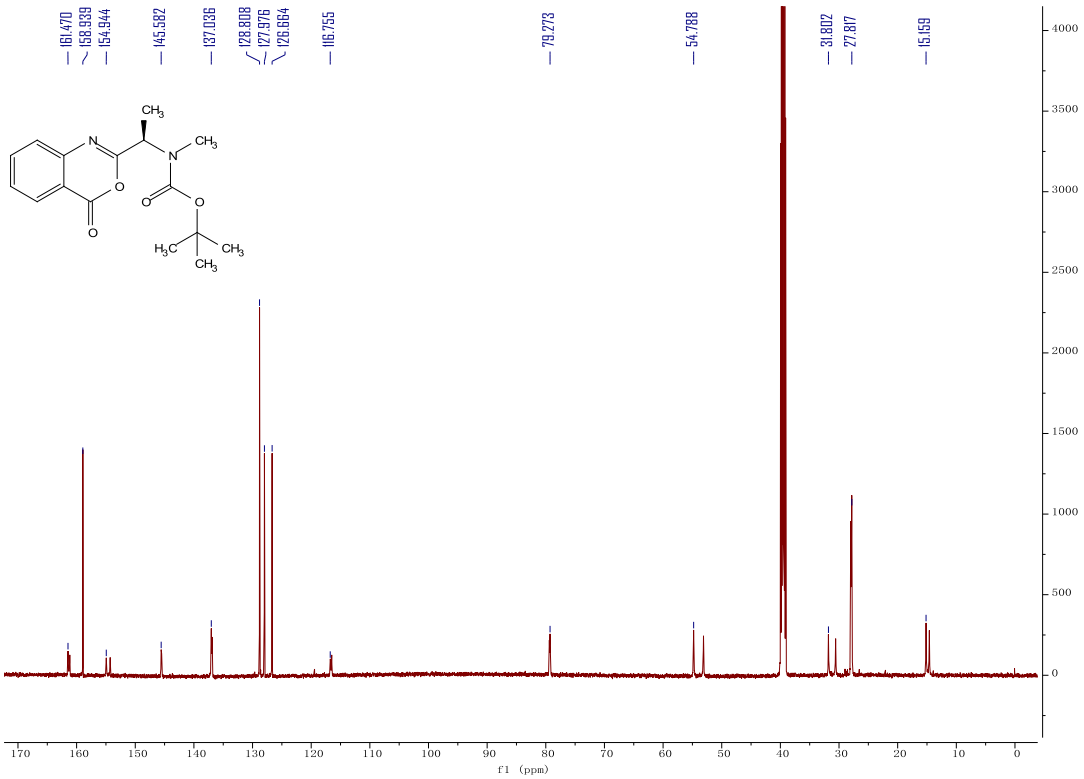
16 L. M. Potikha, *Chem Heterocycl Compd*, 2007, **43**, 759–768.

17 C. Tsukano, M. Okuno, H. Nishiguchi and Y. Takemoto, *Advanced Synthesis & Catalysis*, 2014, **356**, 1533–1538.

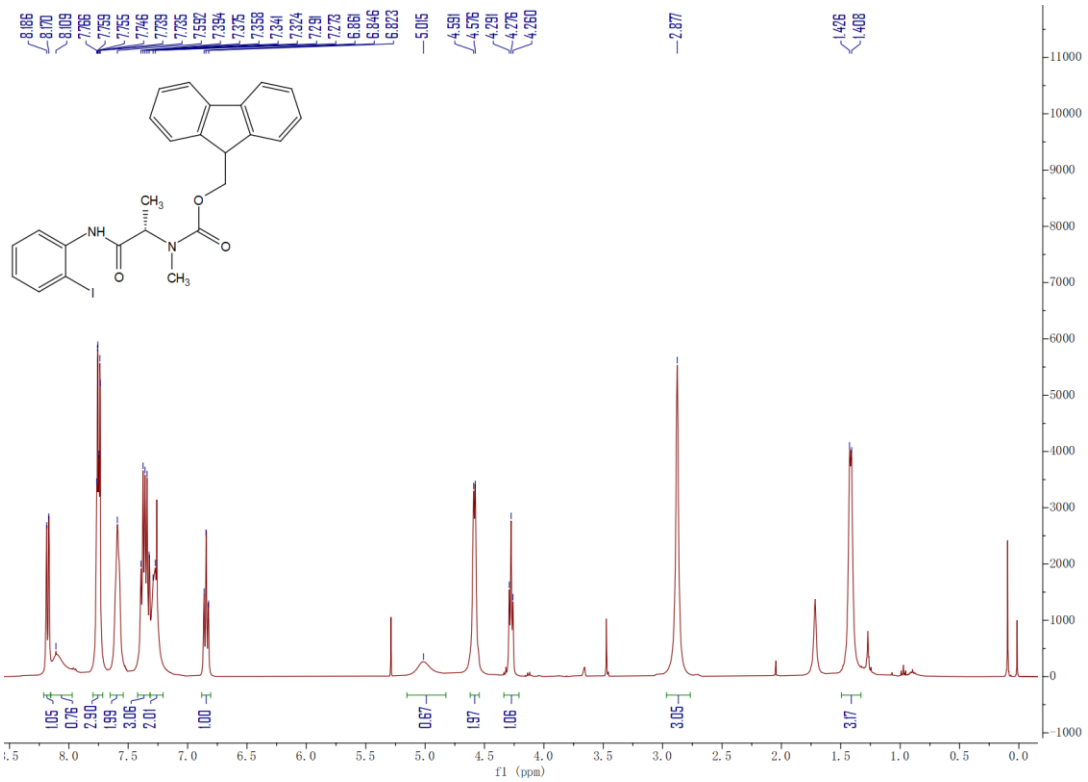
[1]H and [13]C NMR Spectra of Compounds



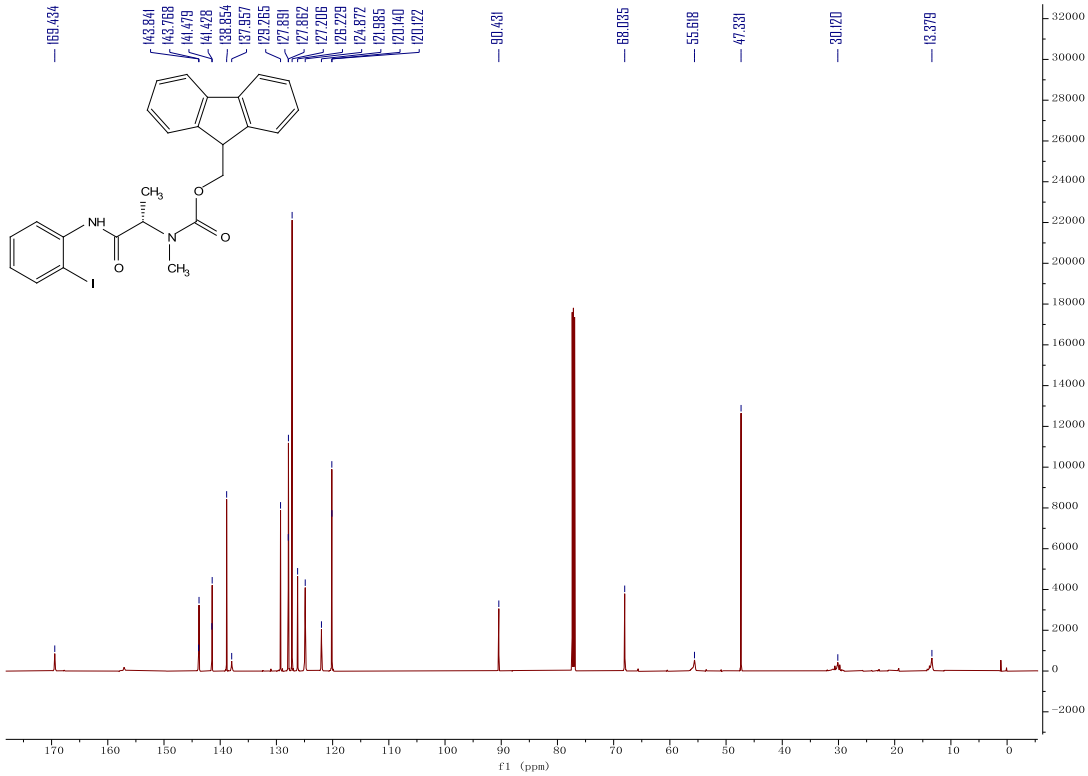
[1]H NMR spectrum of compound 3a-cy (600 MHz, DMSO-d_6, 95 °C)



[13]C NMR spectrum of compound 3a-cy (150 MHz, DMSO-d_6, 25 °C)



^{1}H NMR spectrum of compound 3a-Fmoc (400 MHz, $CDCl_3$)



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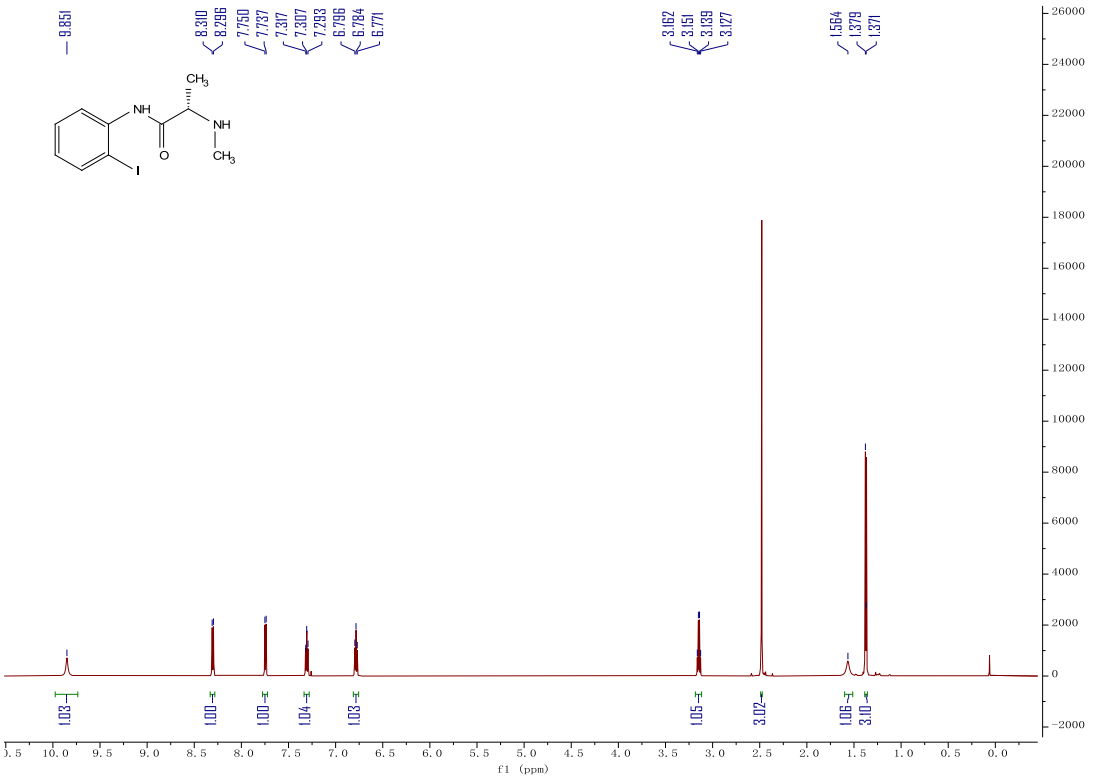
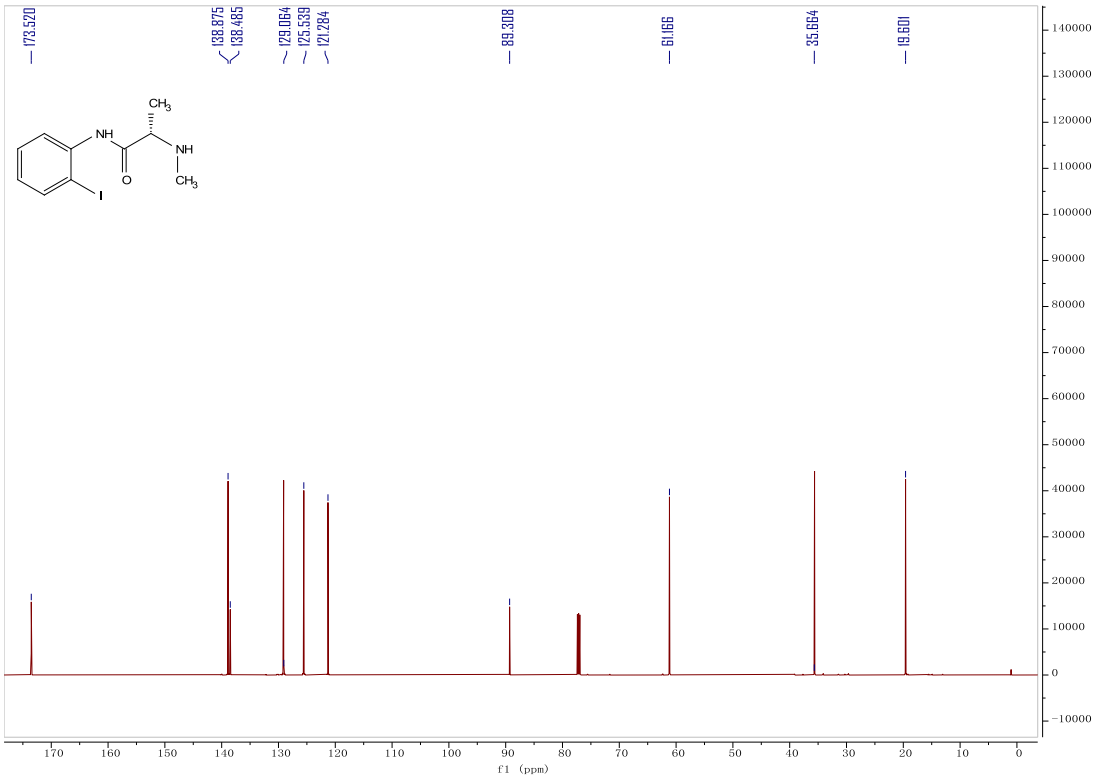
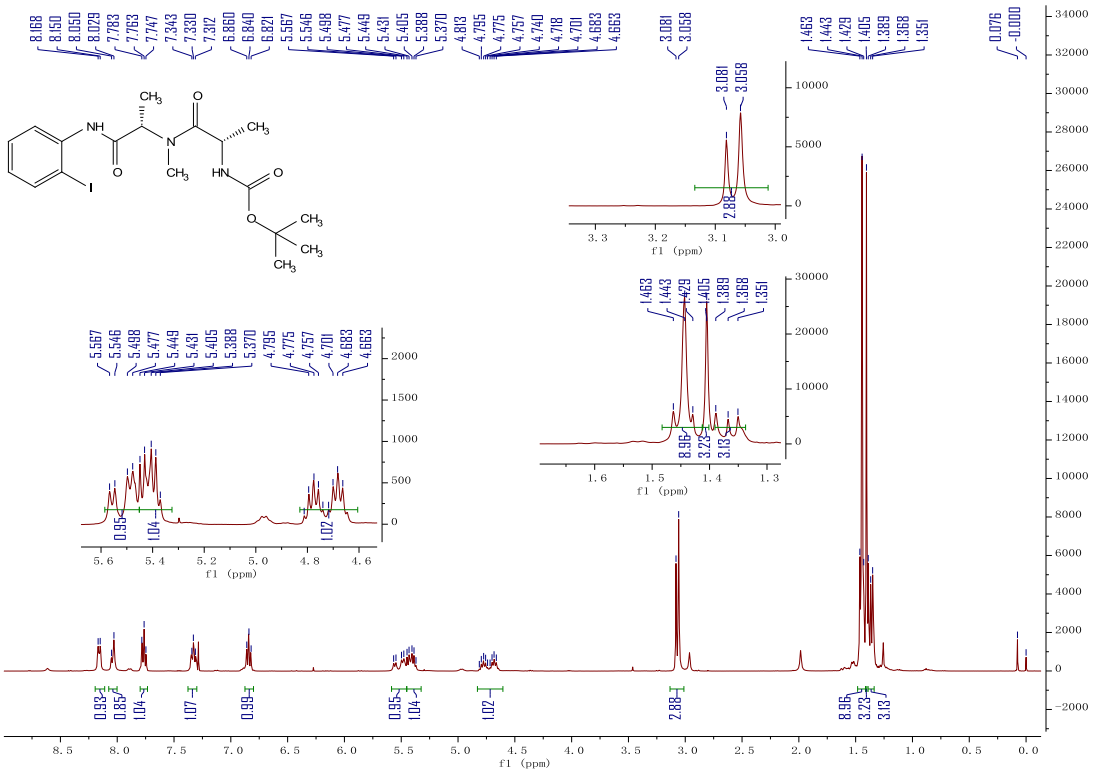


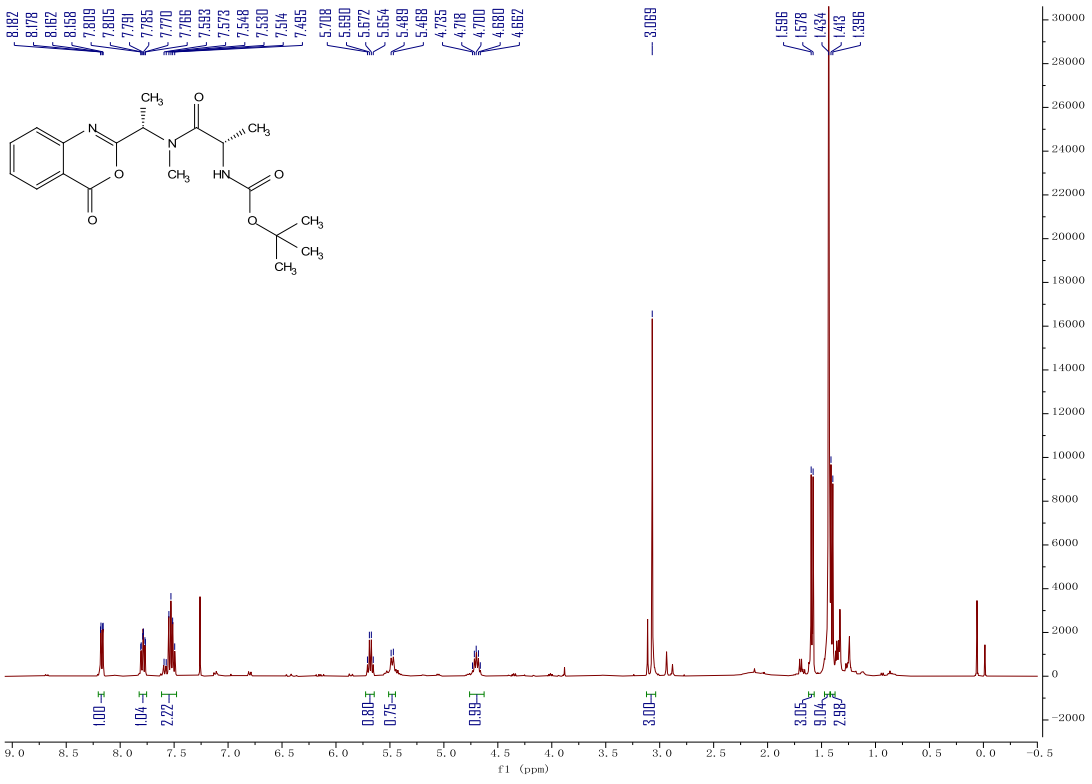
^{1}H NMR spectrum of compound 4a (600 MHz, $CDCl_3$)



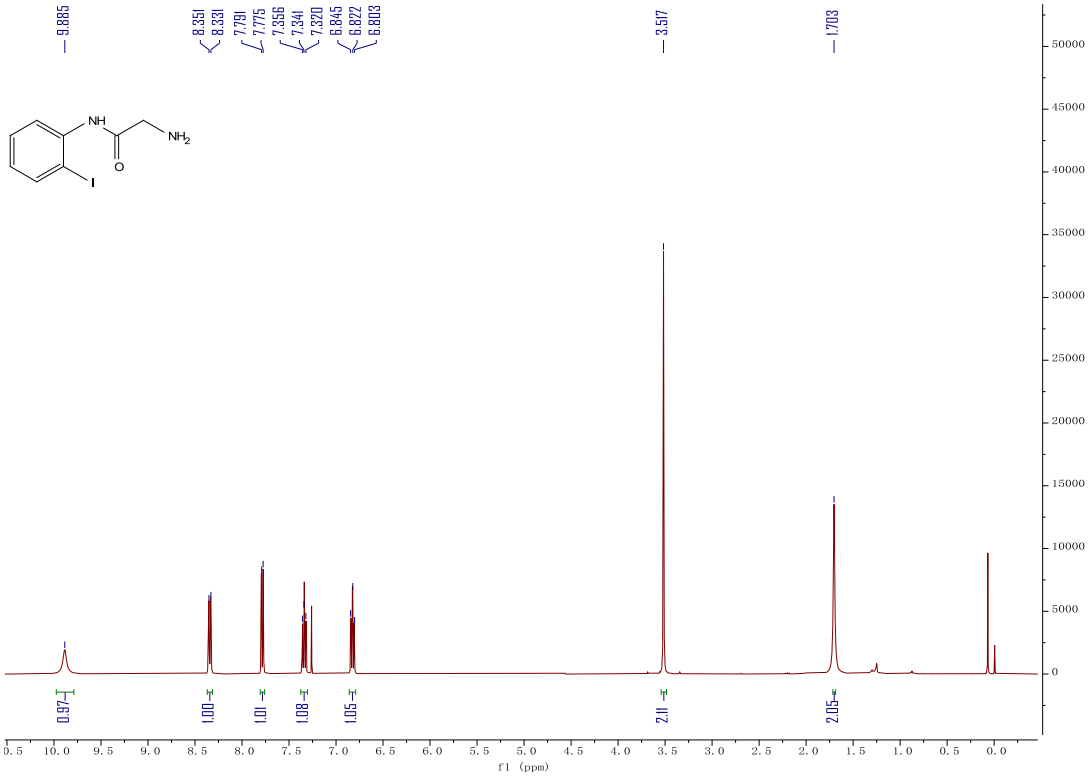
^{13}C NMR spectrum of compound 4a (150 MHz, $CDCl_3$)



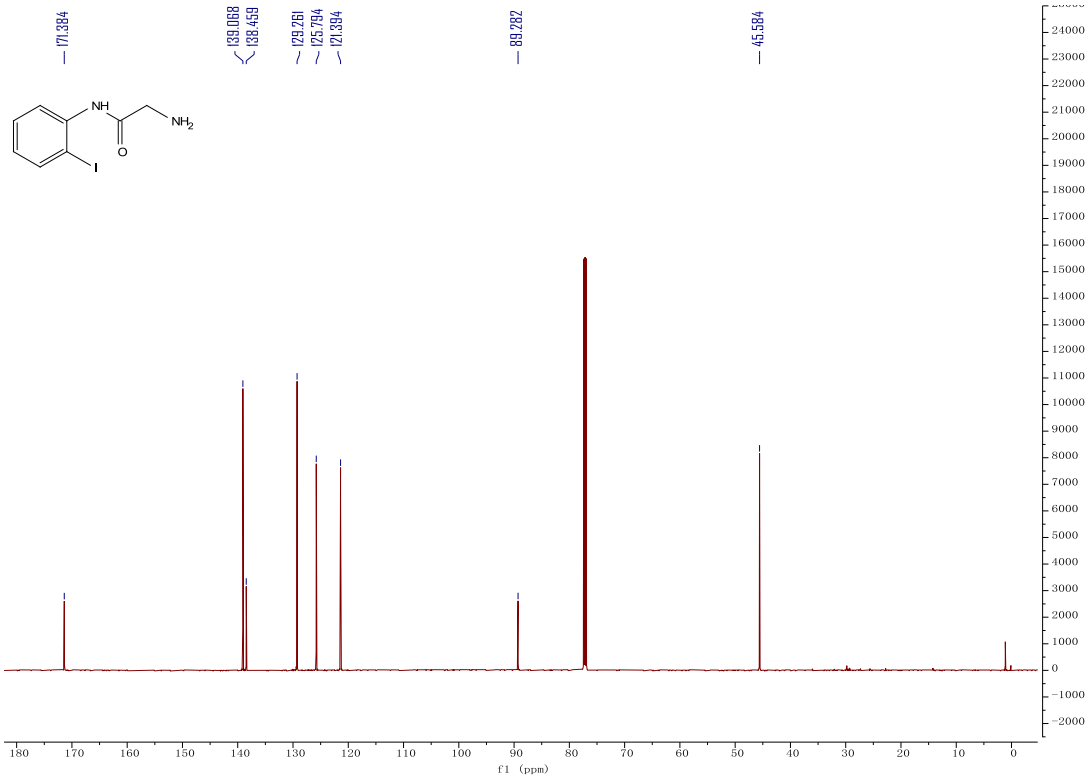
^{1}H NMR spectrum of compound 5a-Boc (400 MHz, $CDCl_3$)



^{1}H NMR spectrum of compound 5a-Cy (400 MHz, $CDCl_3$)

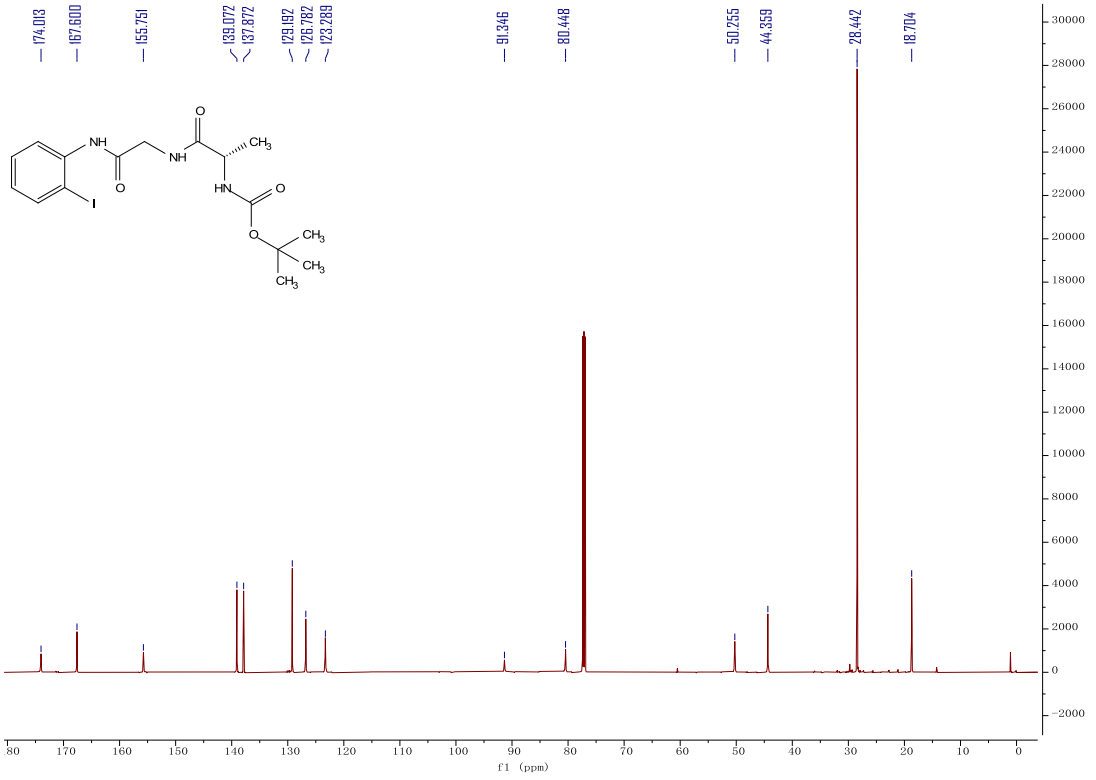


^{1}H NMR spectrum of compound 4b (400 MHz, $CDCl_3$)

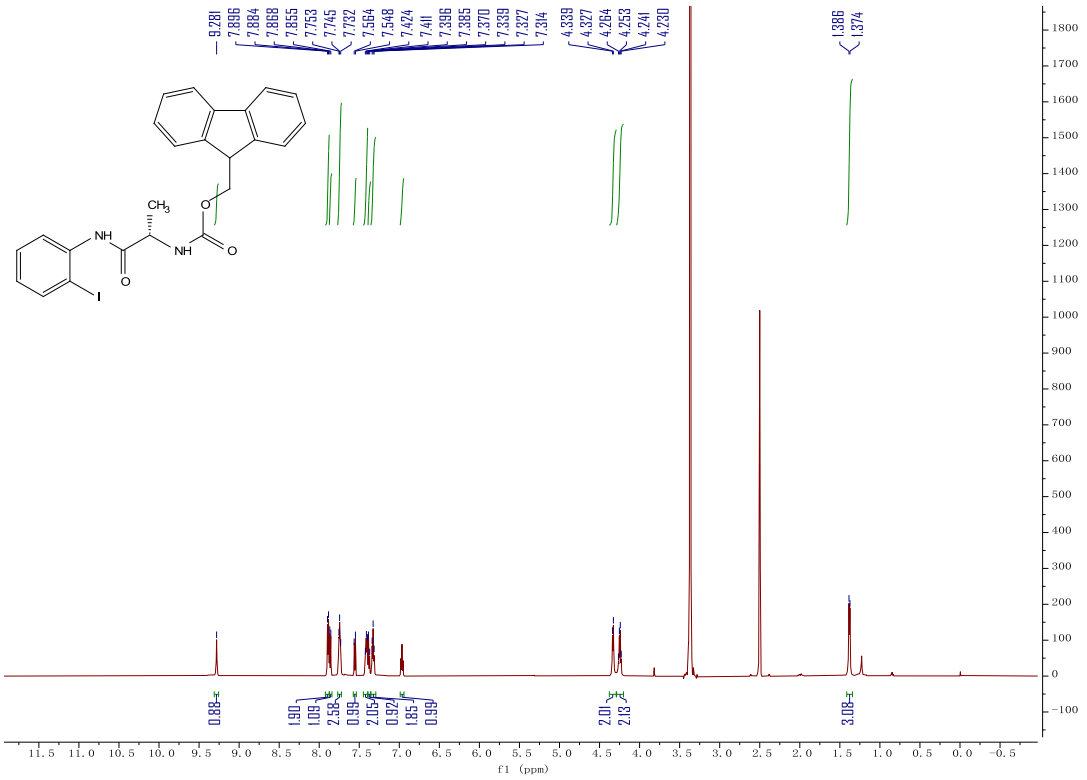


^{13}C NMR spectrum of compound 4b (150 MHz, $CDCl_3$)

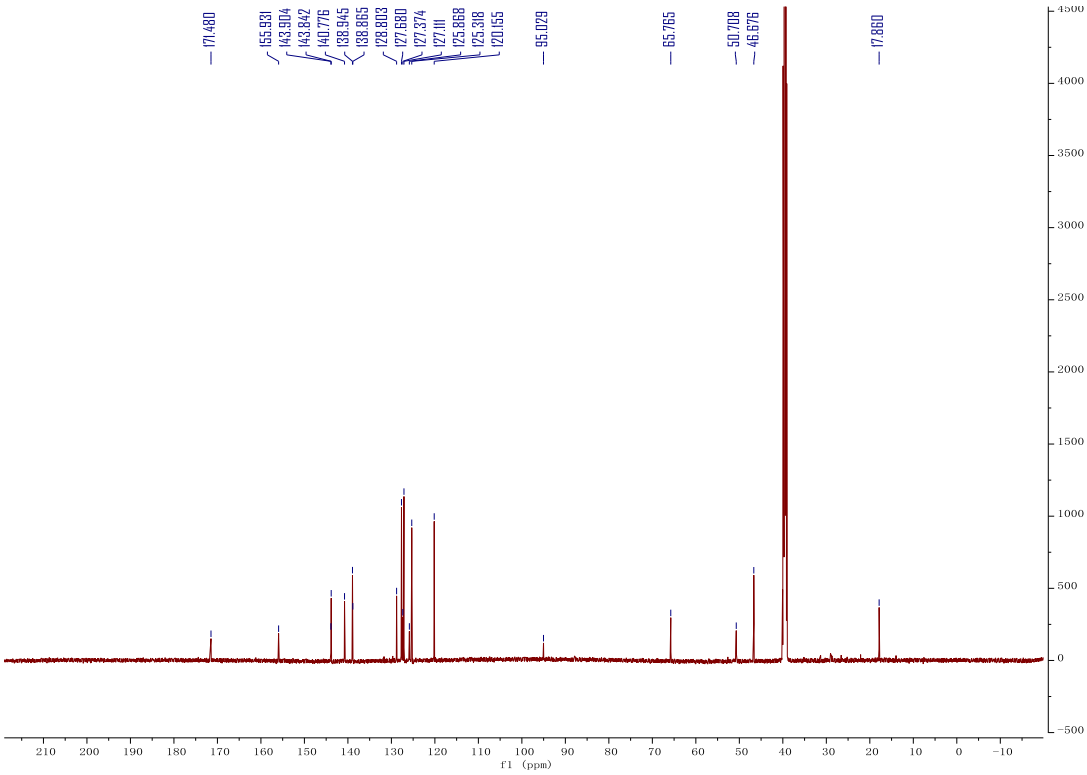
^{1}H NMR spectrum of compound 5b-Boc (400 MHz, $CDCl_3$)



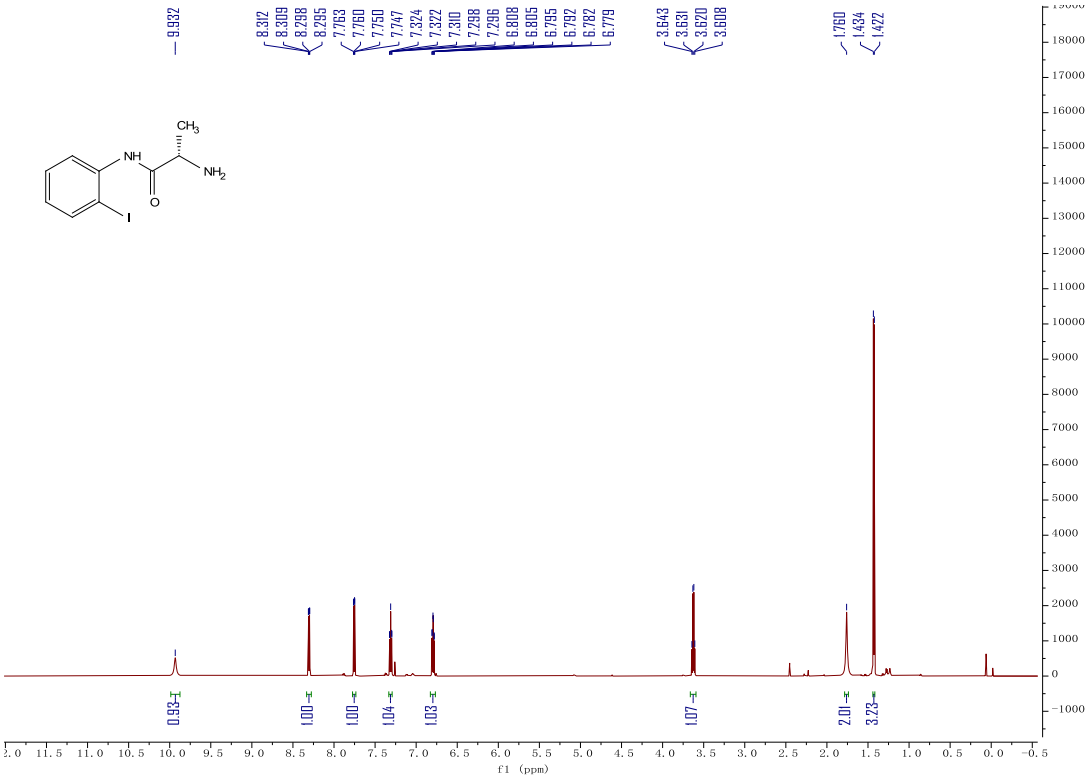
^{13}C NMR spectrum of compound 5b-Boc (150 MHz, $CDCl_3$)



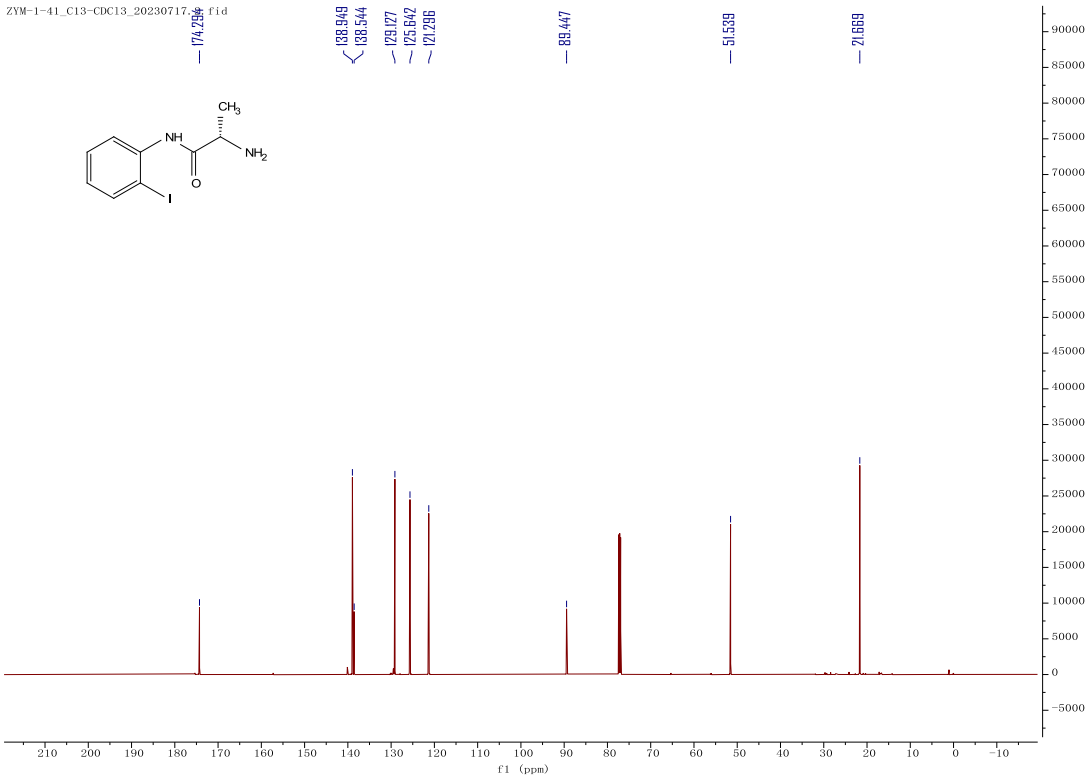
^{1}H NMR spectrum of compound of 3c-Fmoc (600 MHz, DMSO-d_6)



^{13}C NMR spectrum of compound 3c-Fmoc (150 MHz, DMSO-d_6)

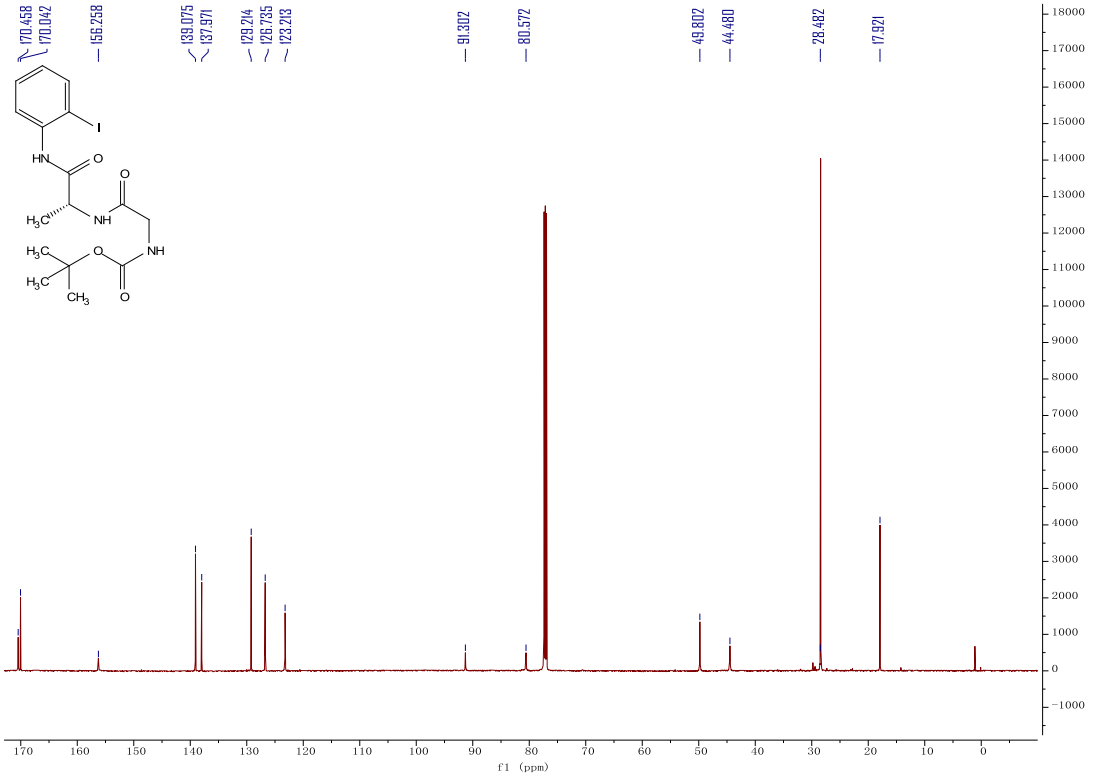


^{1}H NMR spectrum of compound 4c (600 MHz, $CDCl_3$)2



^{13}C NMR spectrum of compound 4c (150 MHz, $CDCl_3$)

^{1}H NMR spectrum of compound 5c-Boc (400 MHz, $CDCl_3$)



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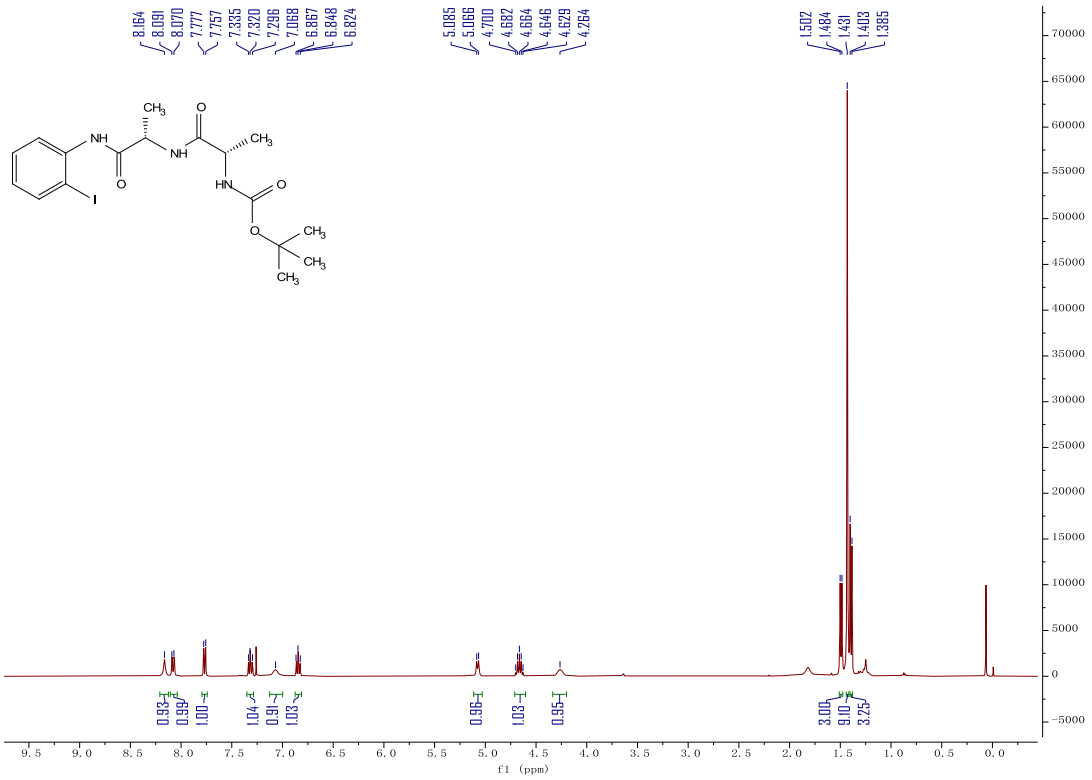

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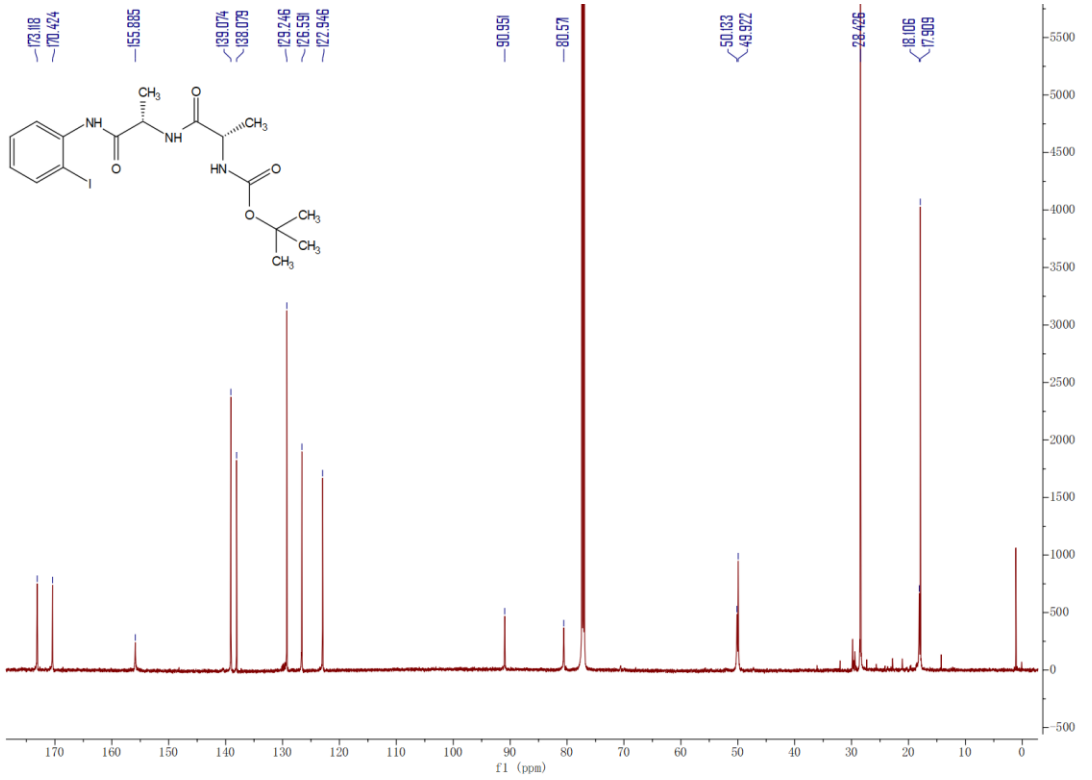

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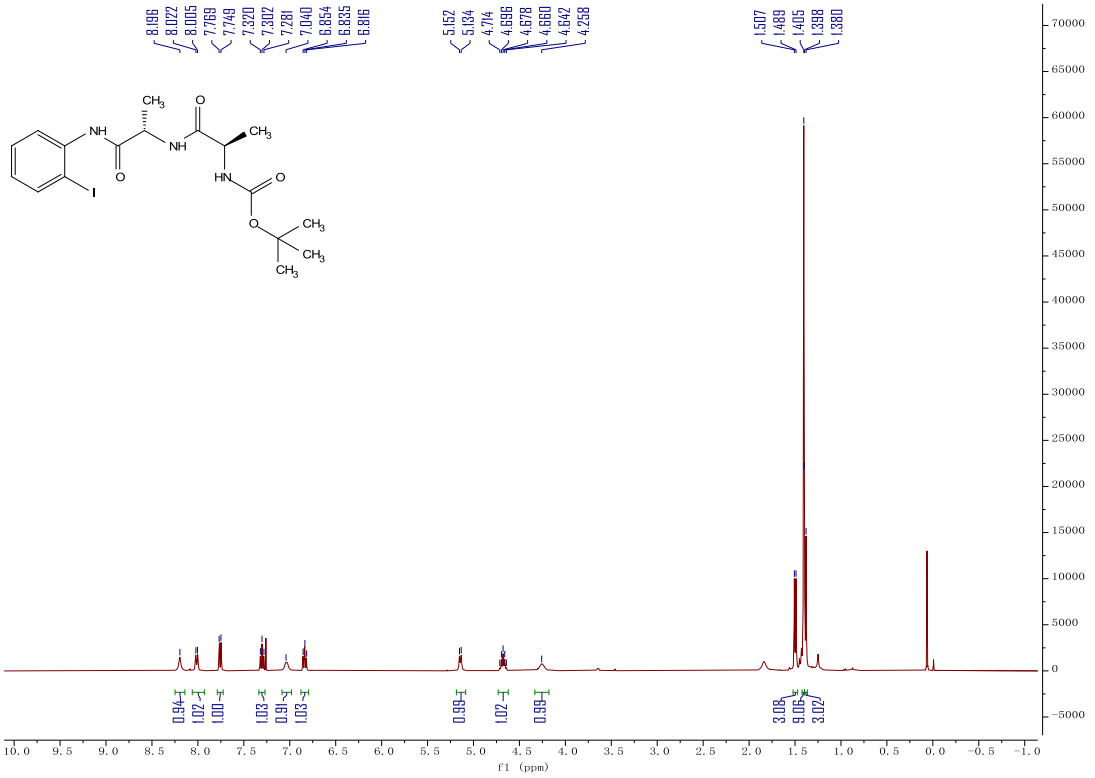

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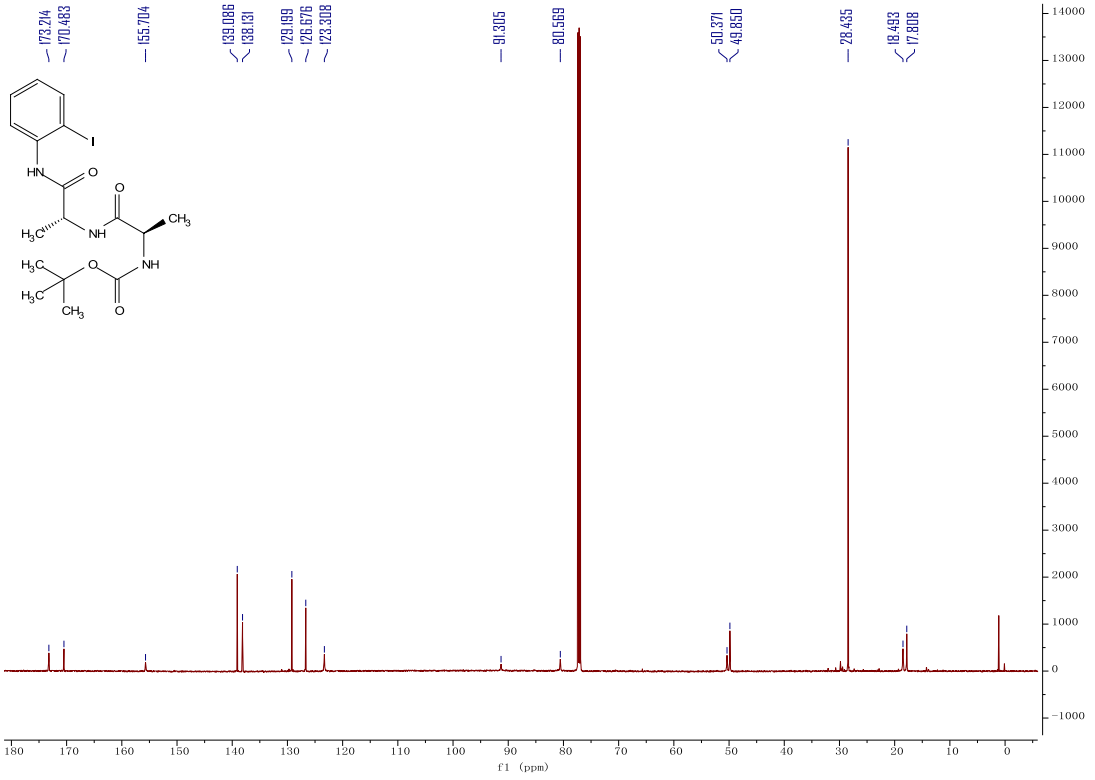

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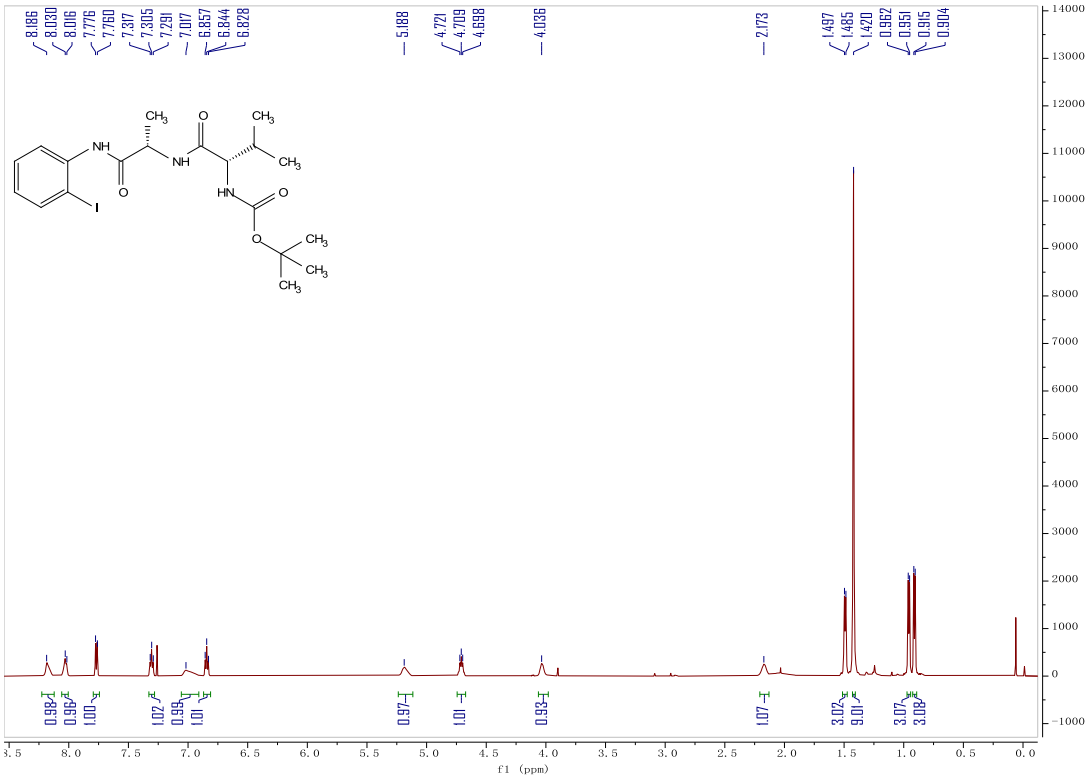
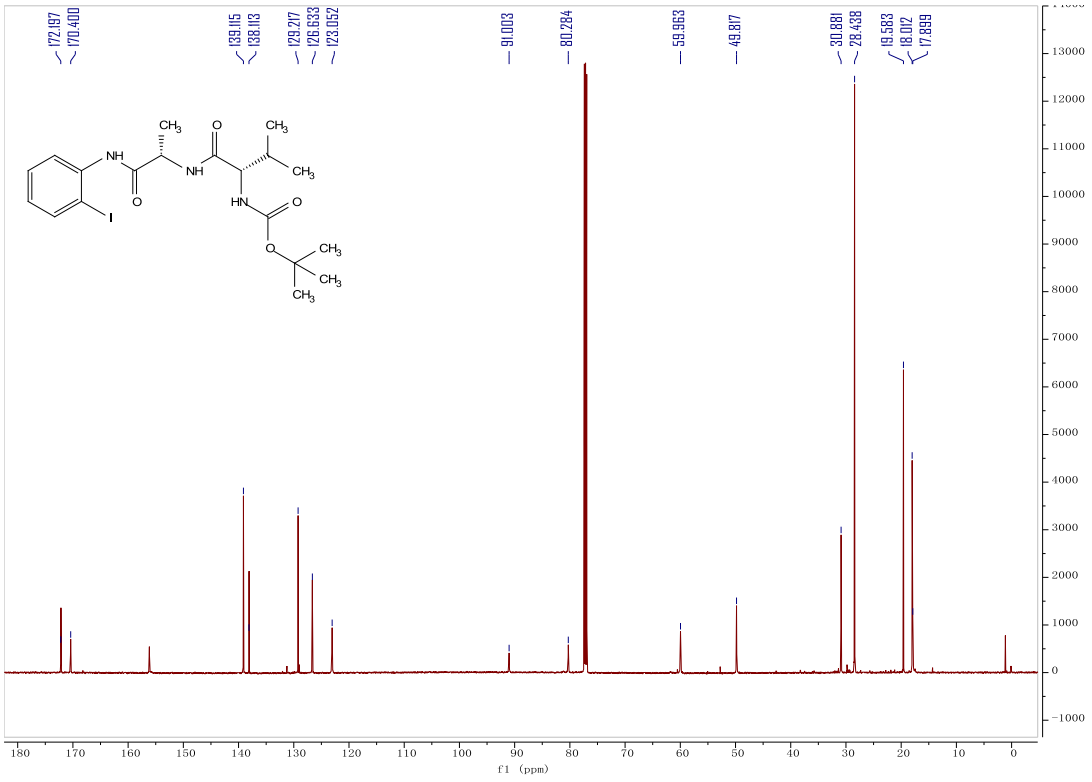
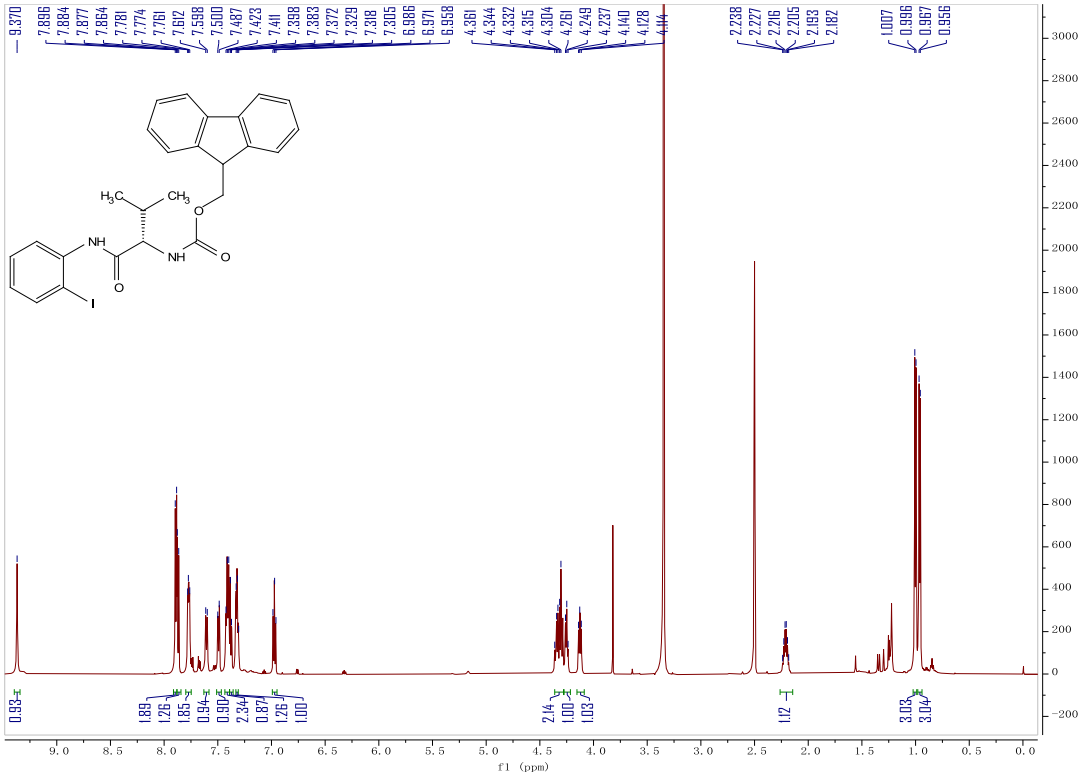


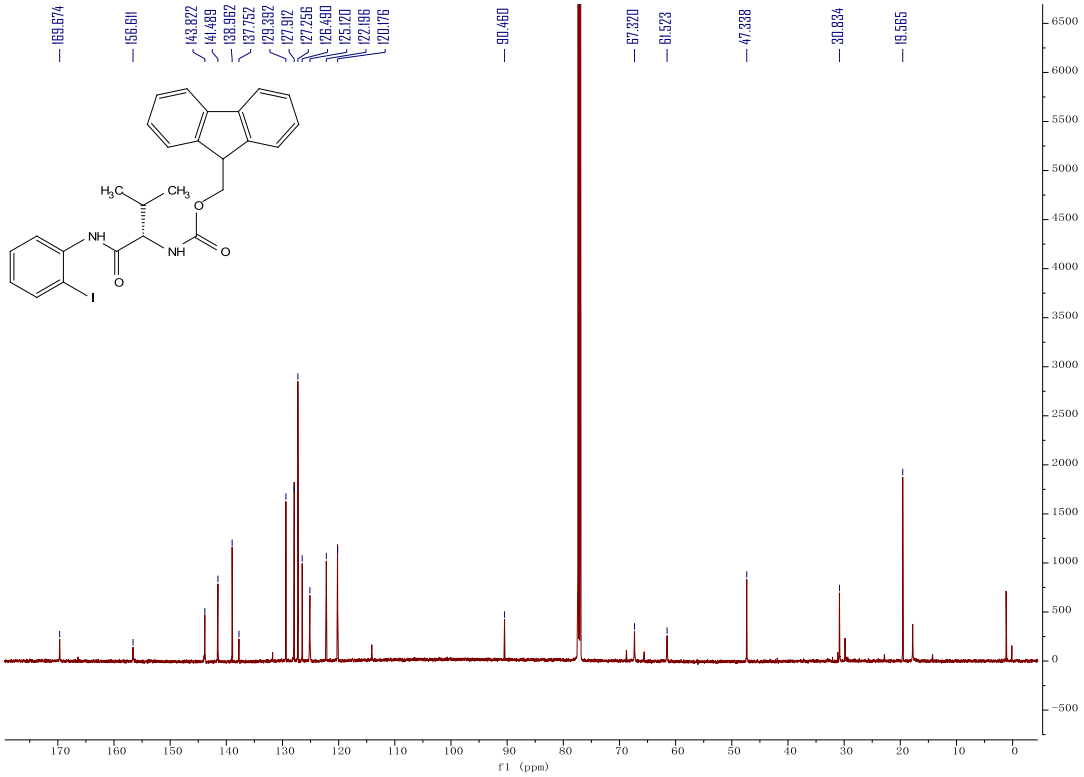
^{1}H NMR spectrum of compound 5g-Boc (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of compound 5g-Boc (150 MHz, $CDCl_3$)



^{1}H NMR spectrum of compound 3h-Fmoc (600 MHz, DMSO-d_6)



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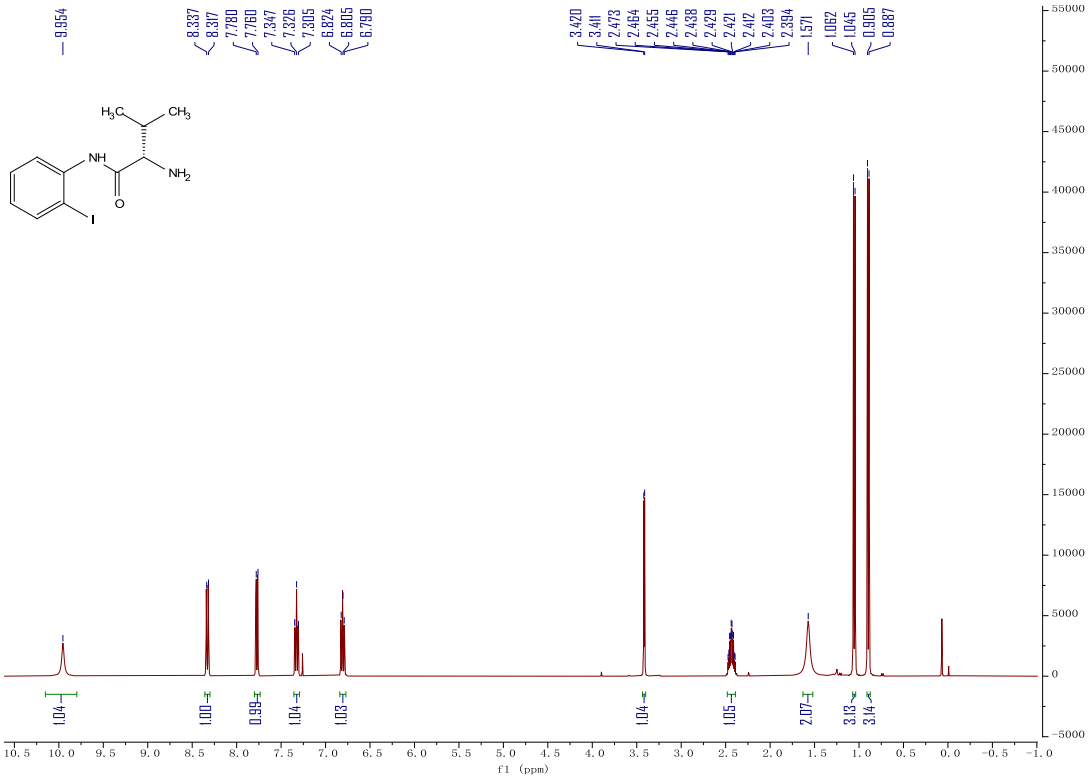

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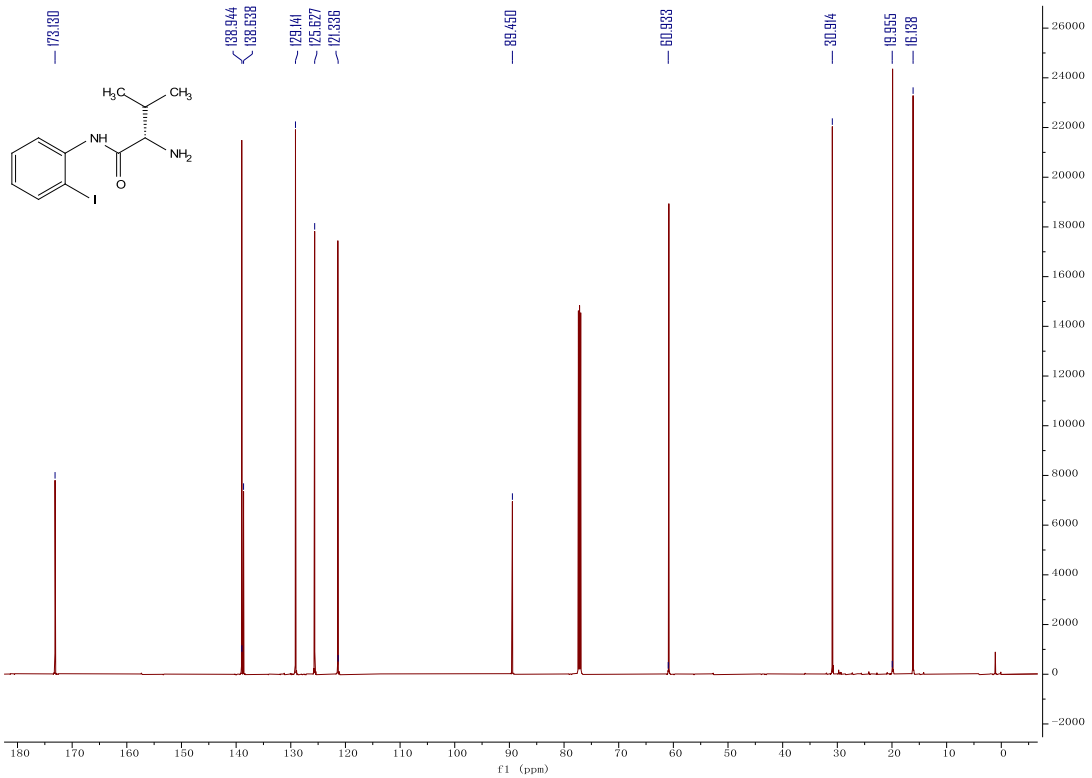

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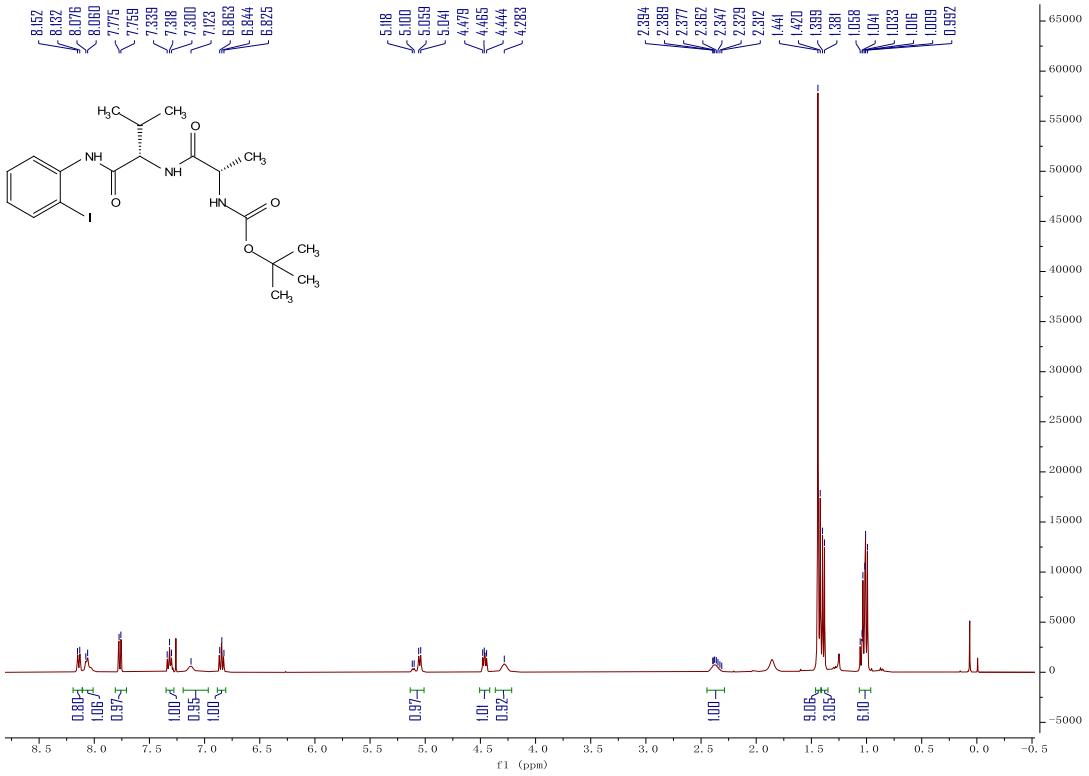
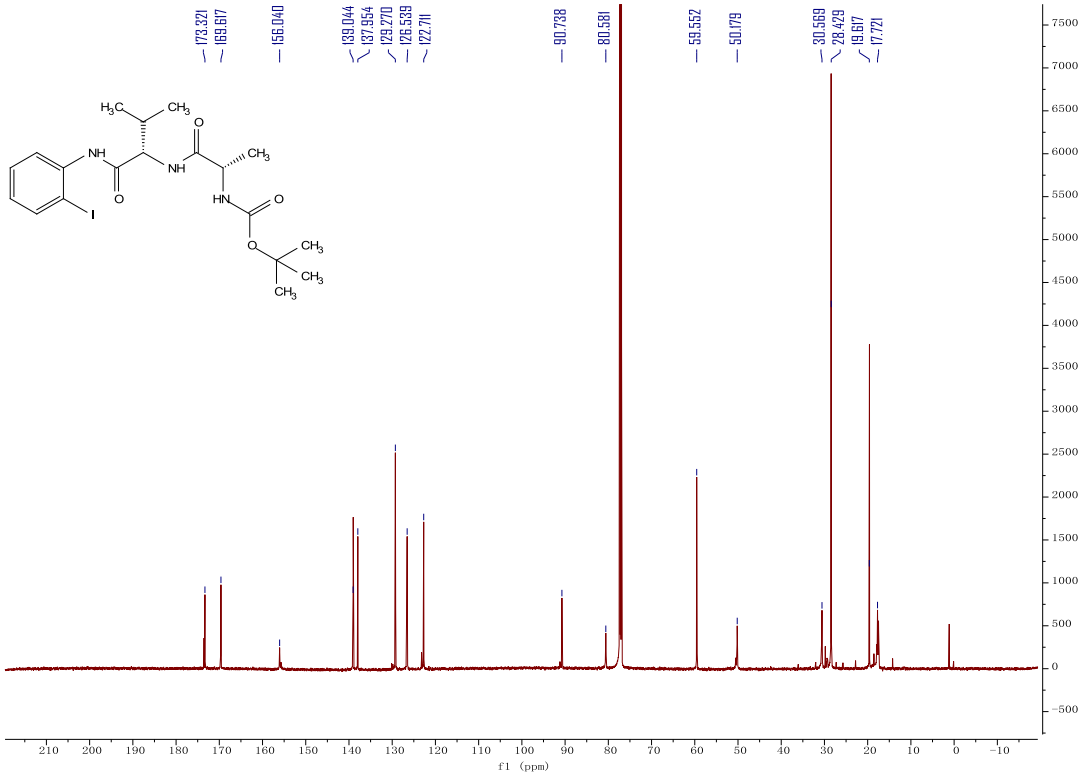


^{1}H NMR spectrum of compound 5h-Boc (400 MHz, $CDCl_3$)



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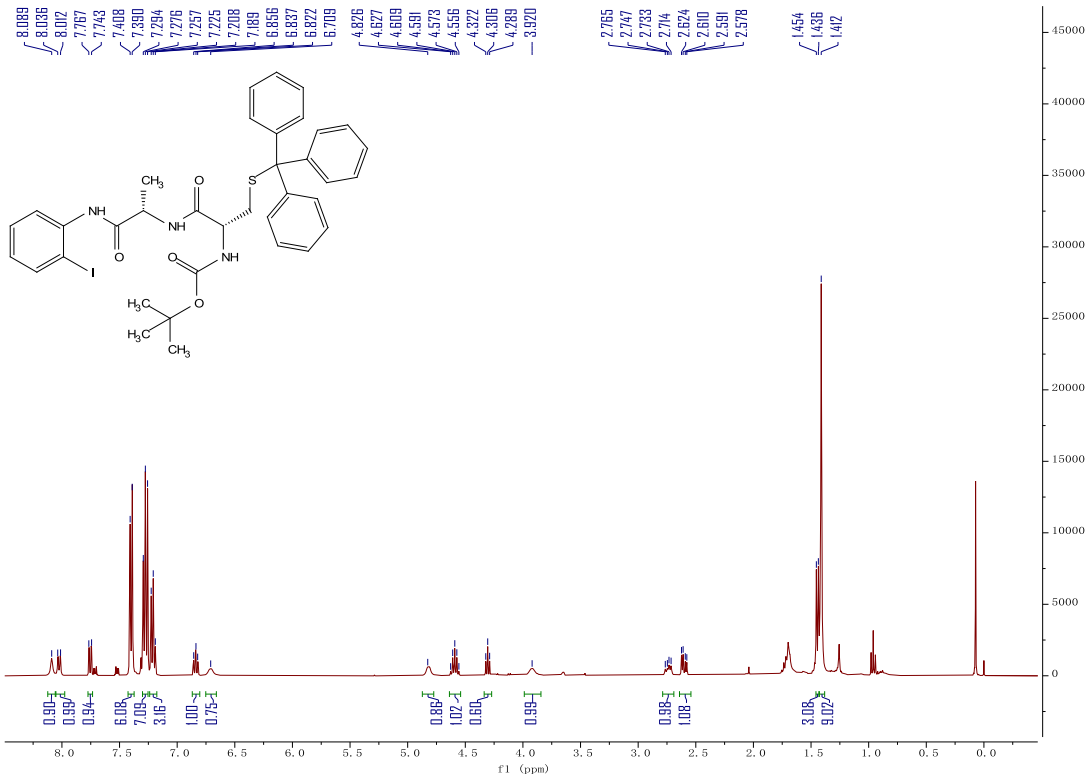

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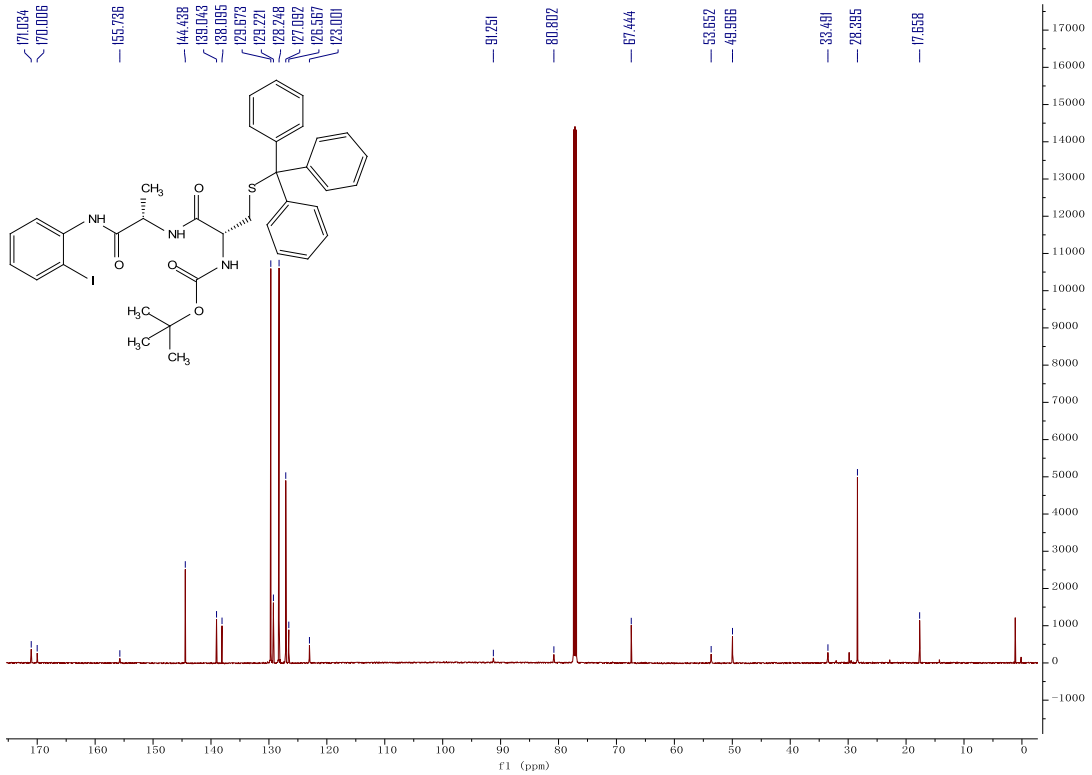

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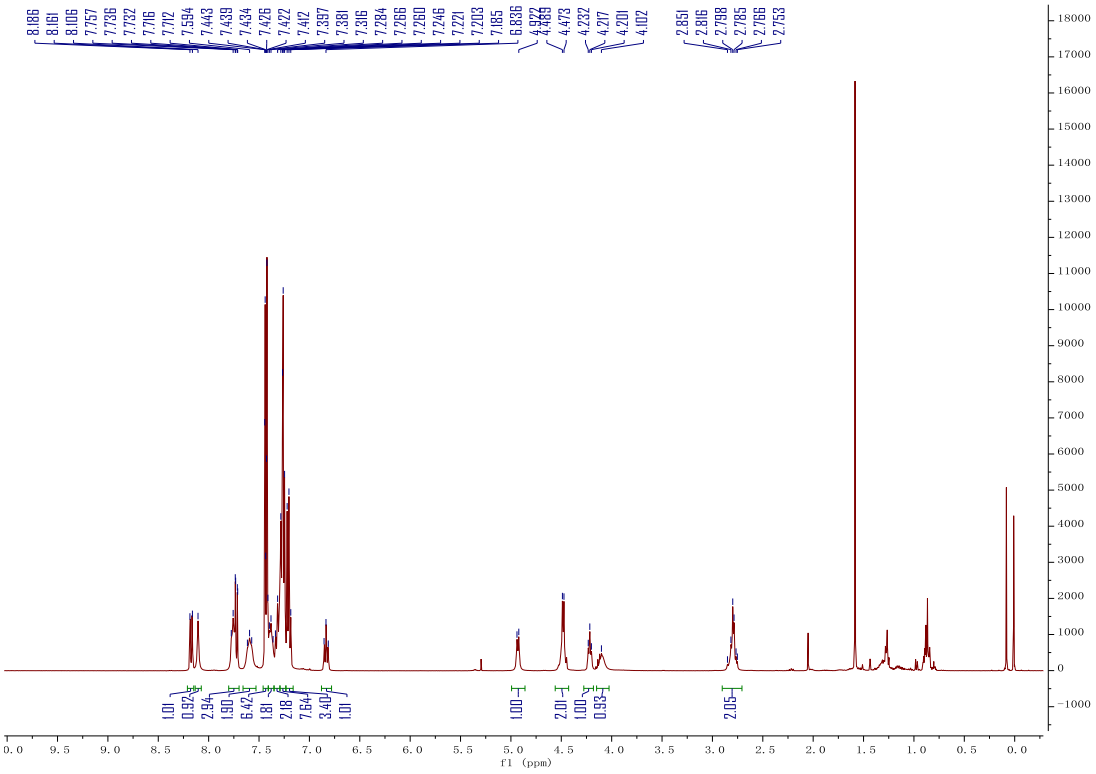

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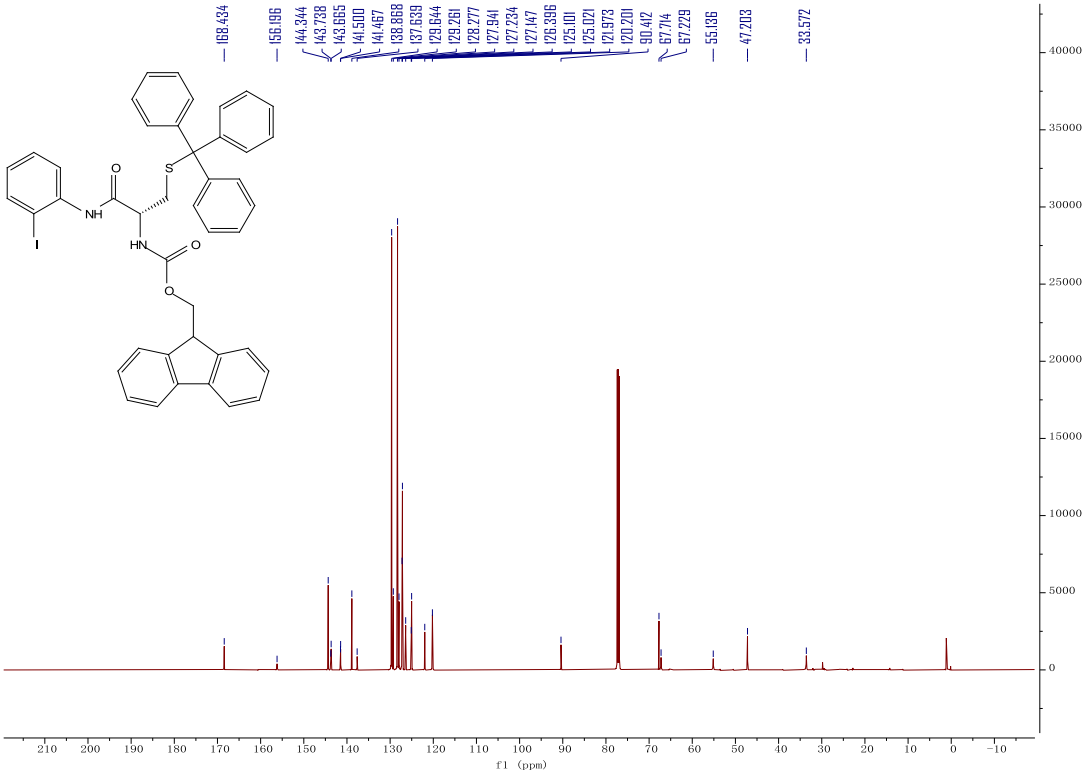

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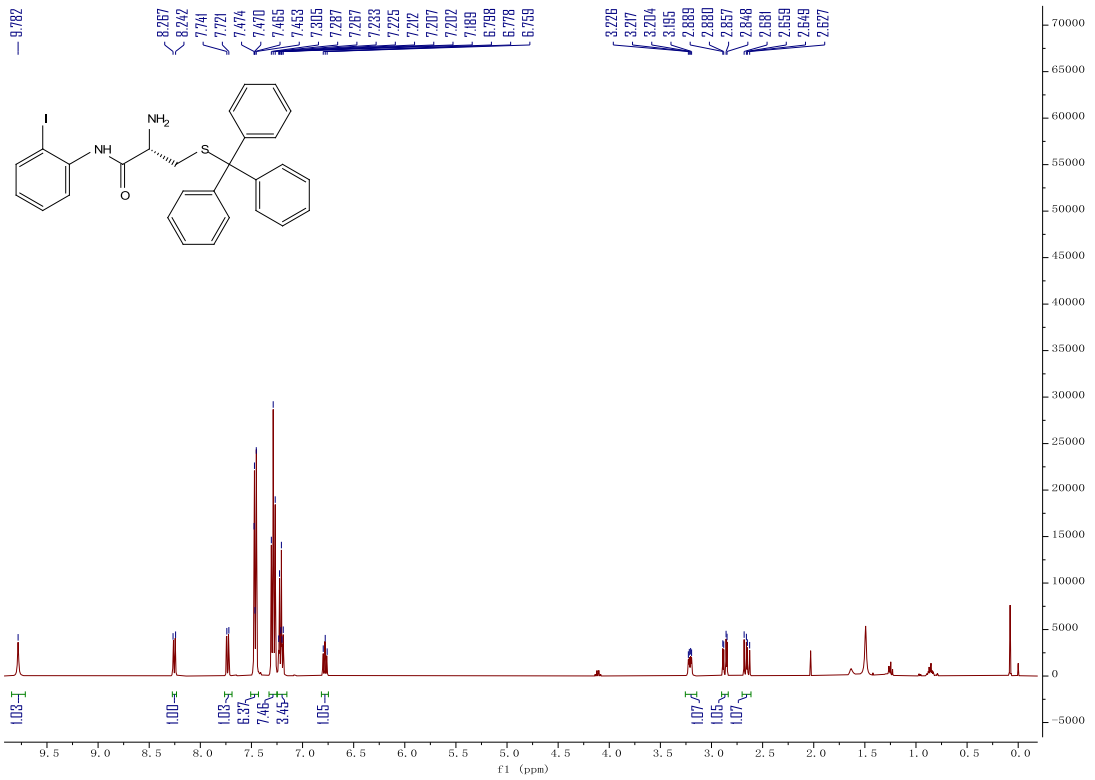

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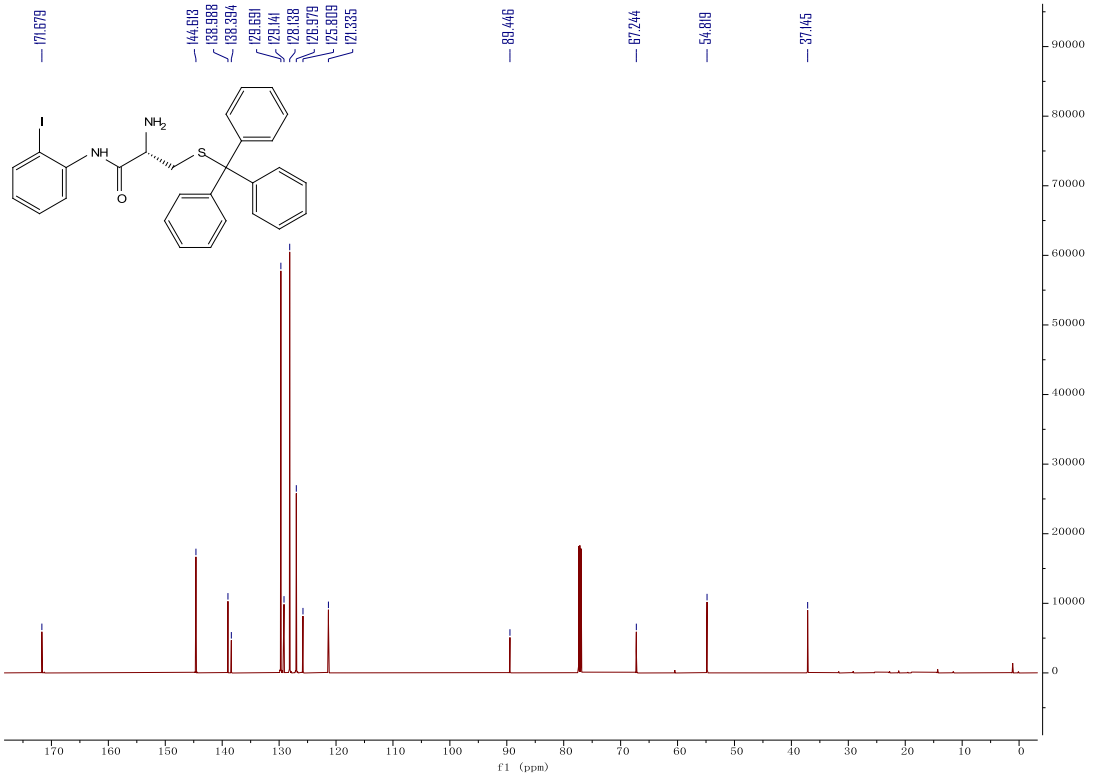

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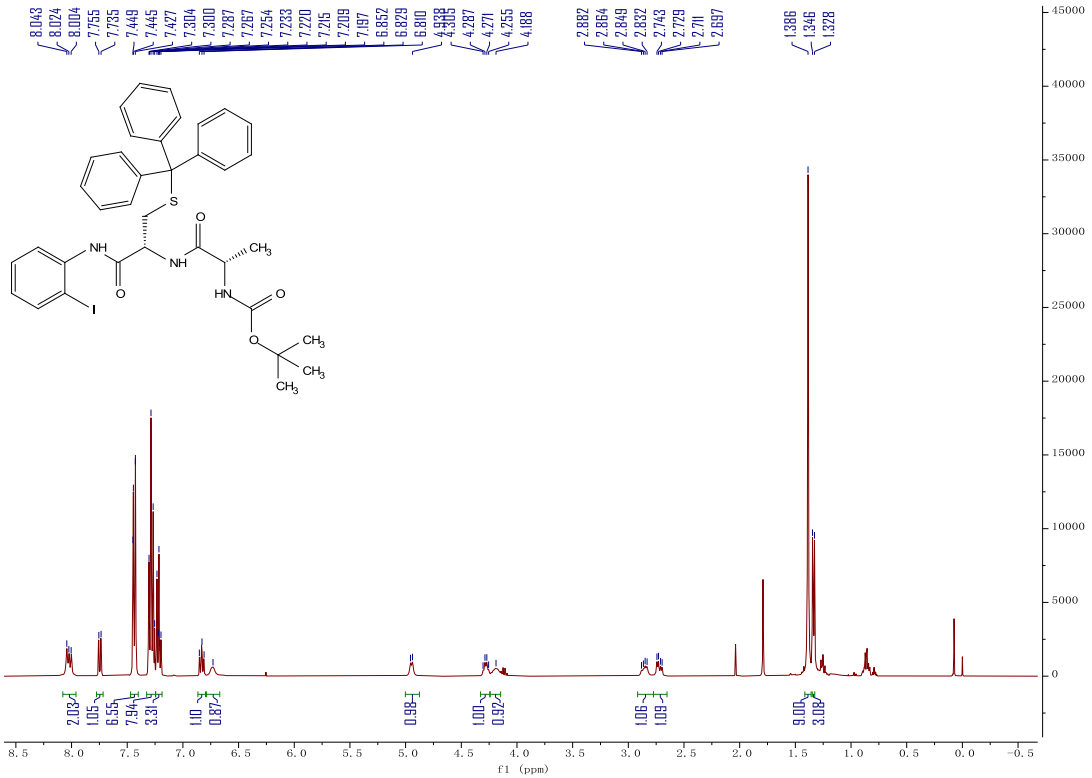

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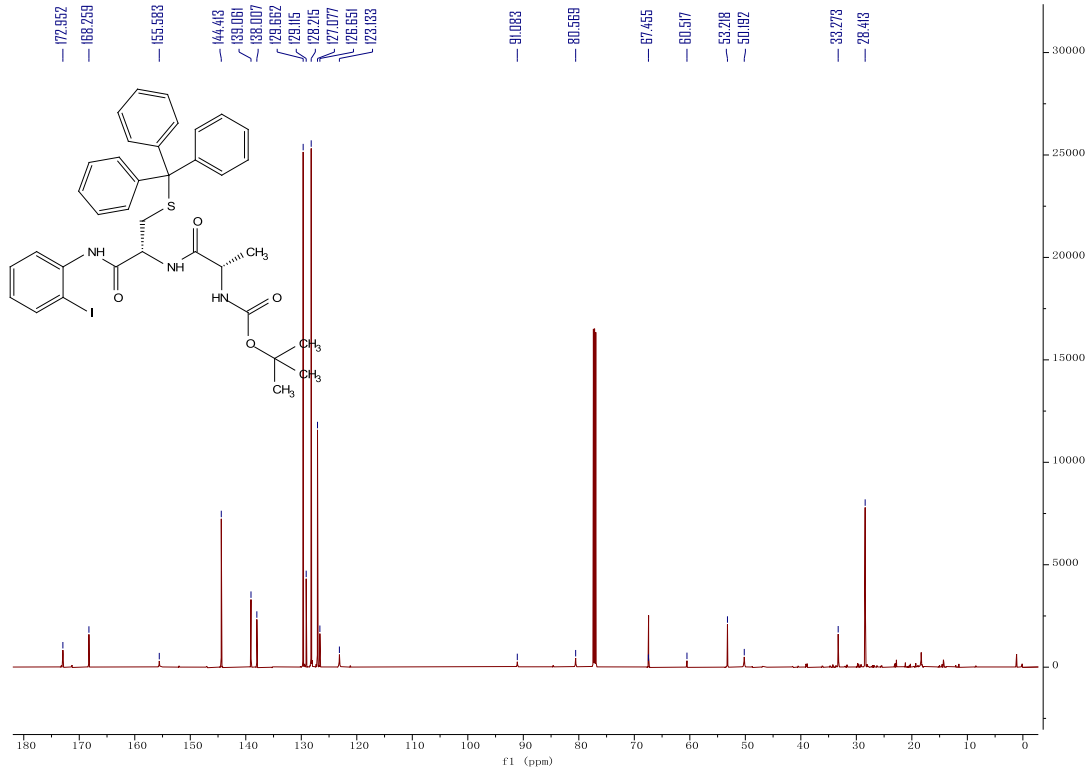

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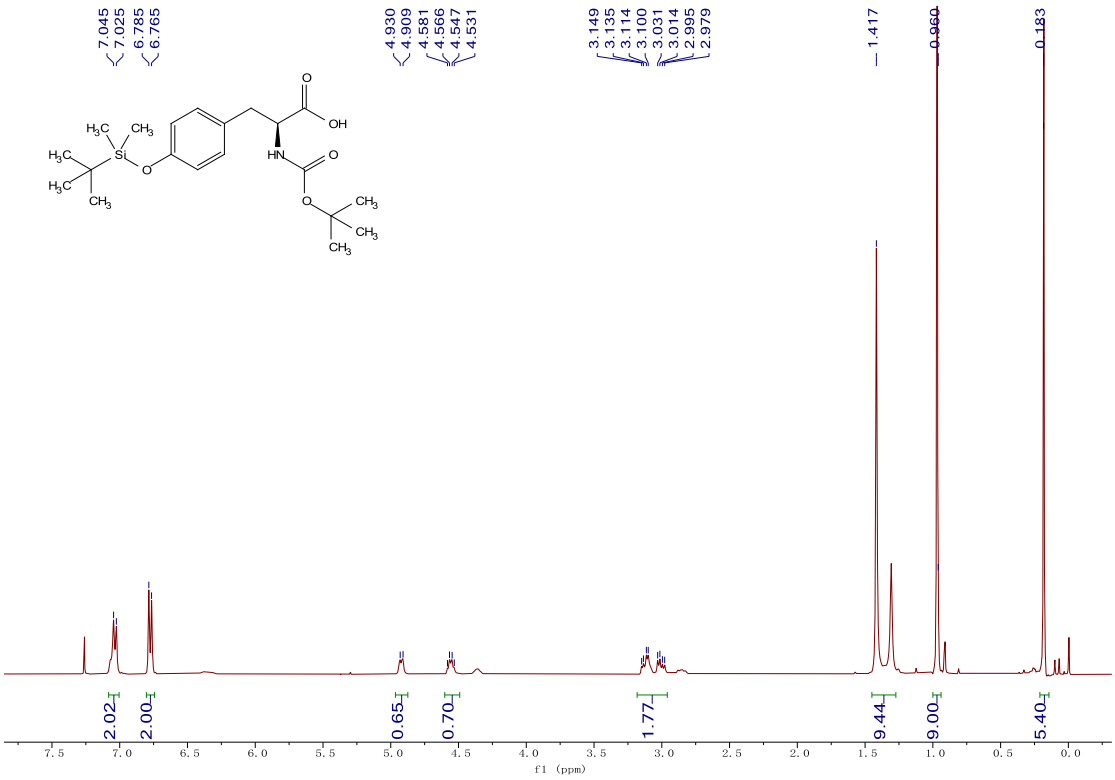
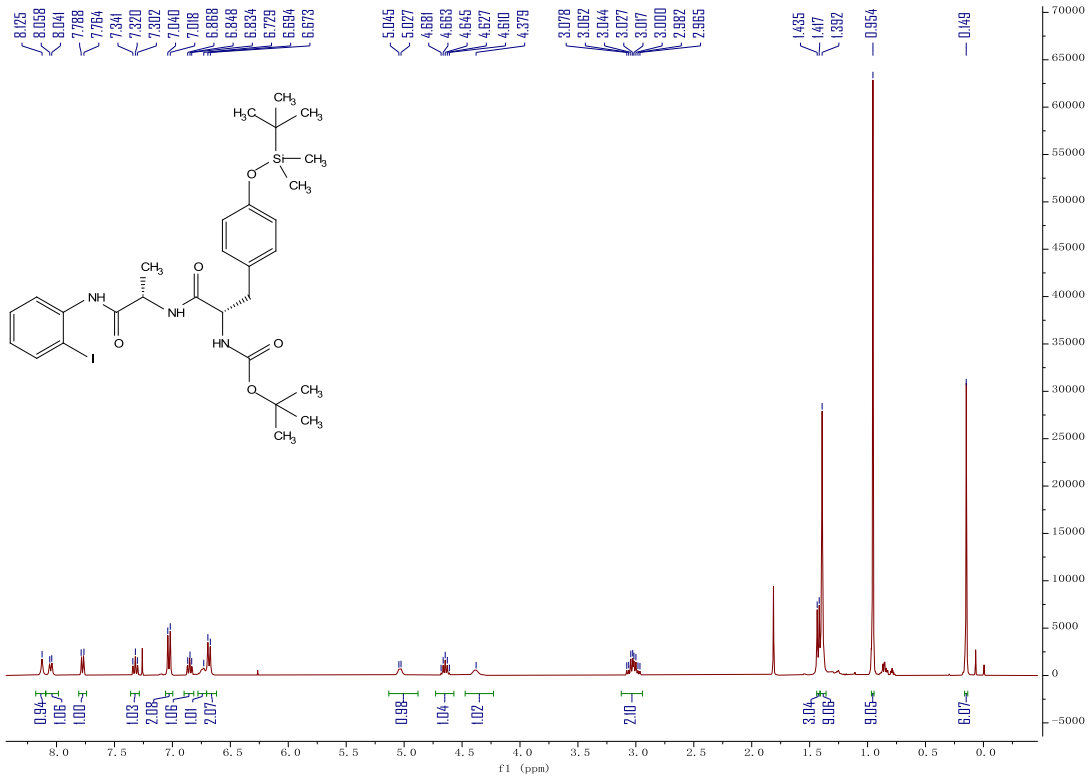


^{1}H NMR spectrum of compound 4k (400 MHz, $CDCl_3$)



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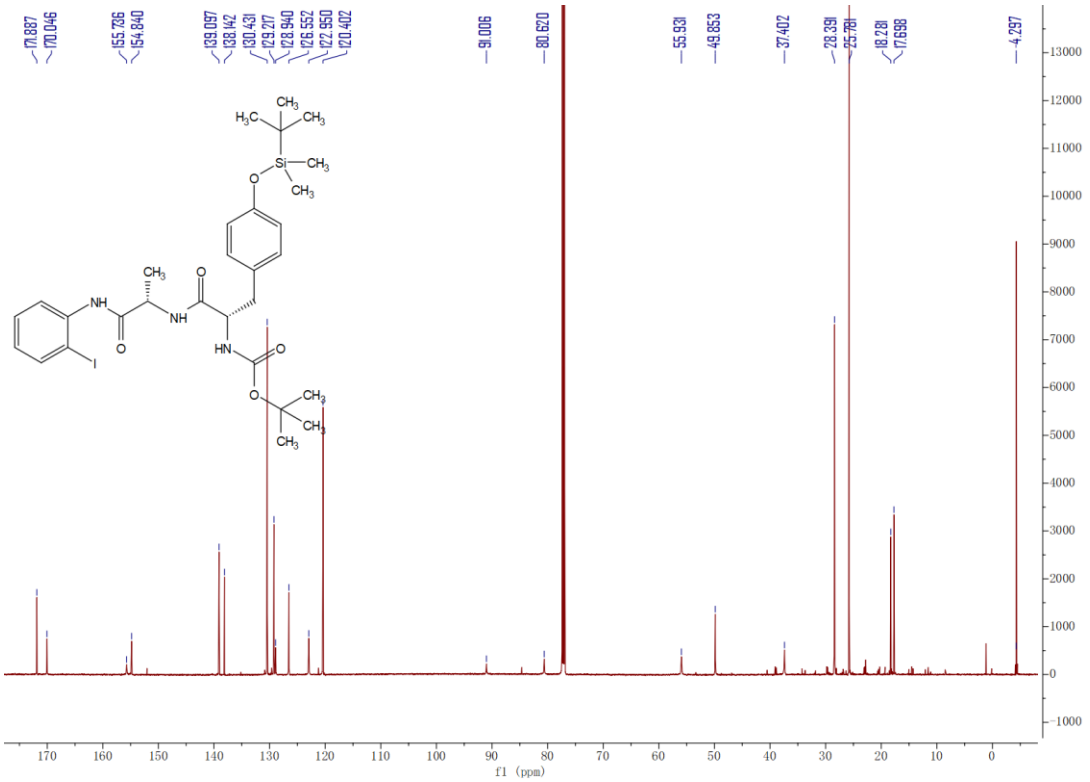
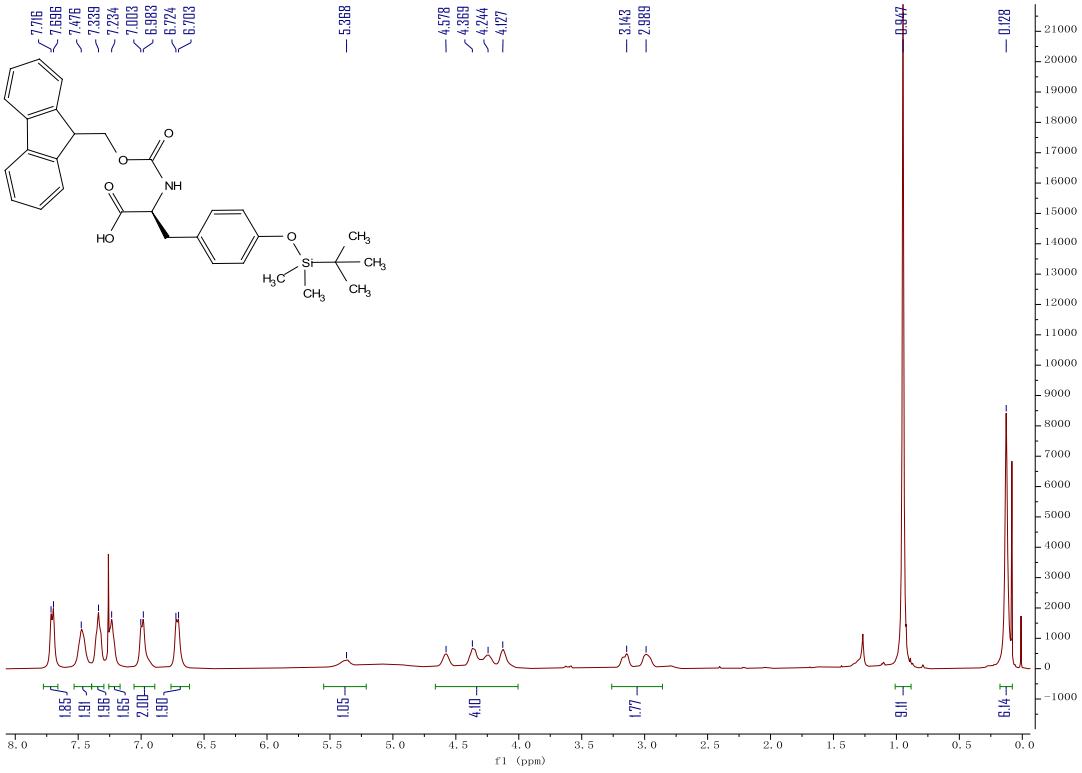
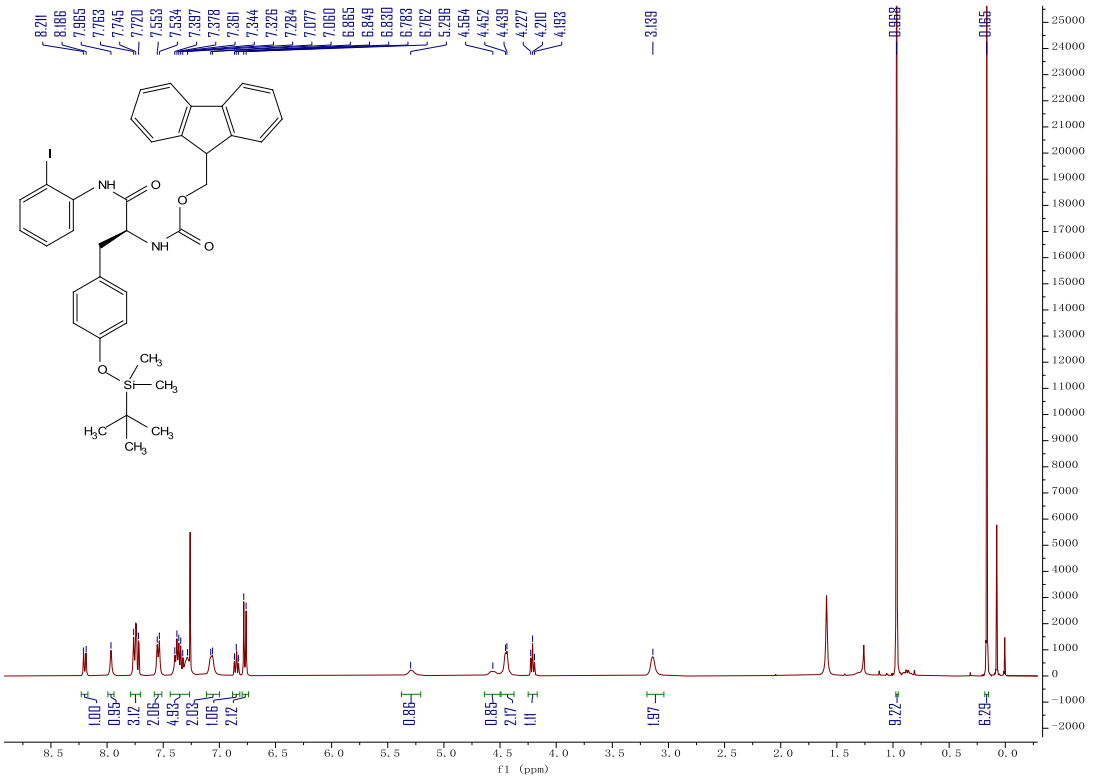


^{13}C NMR spectrum of compound 5k-Boc (150MHz, $CDCl_3$)



^{1}H NMR spectrum of compound 2l-Fmoc (400 MHz, $CDCl_3$)



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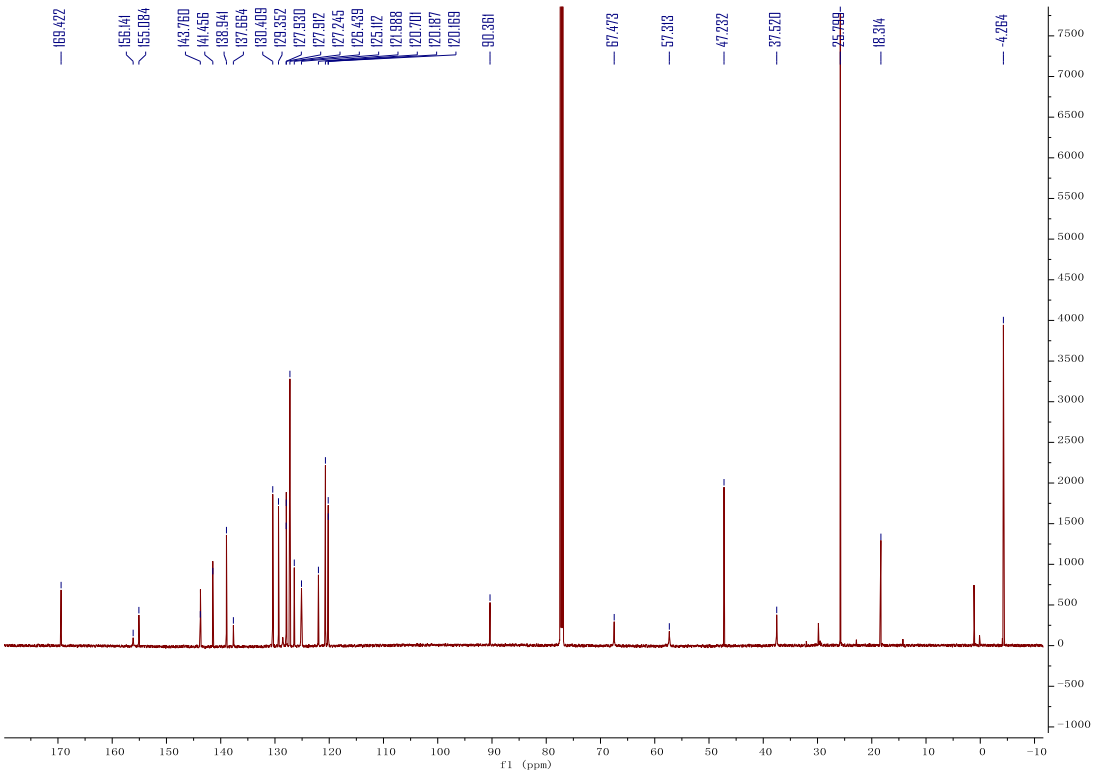
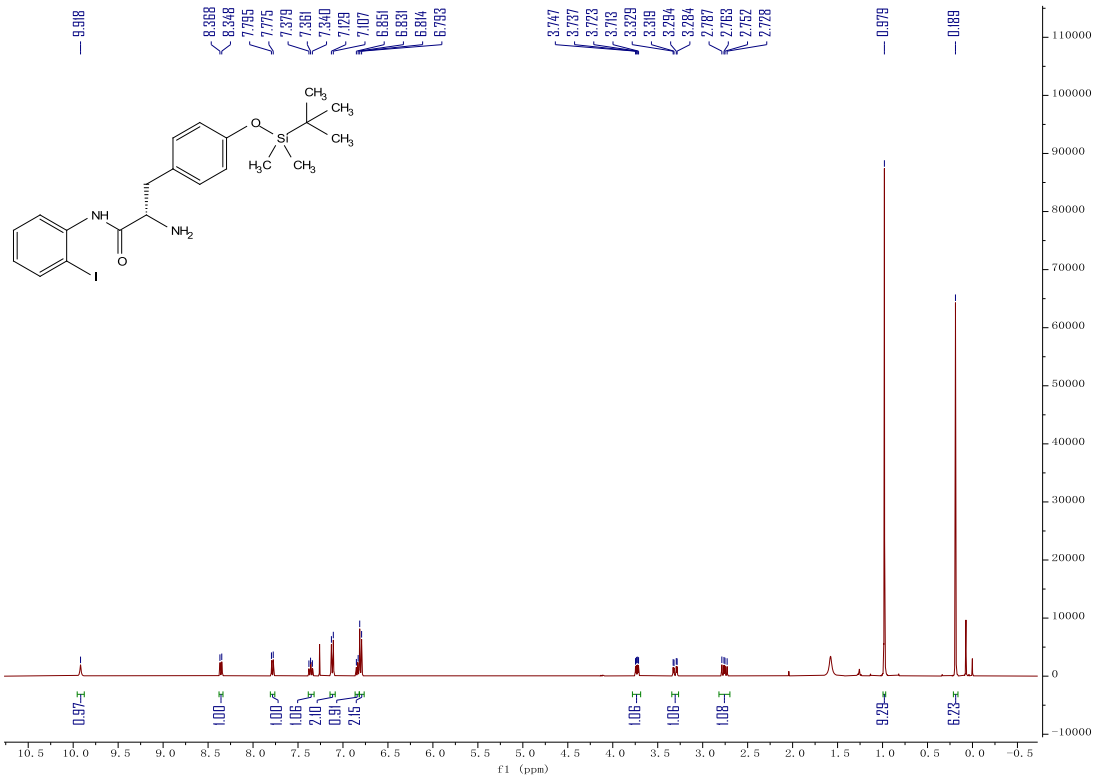
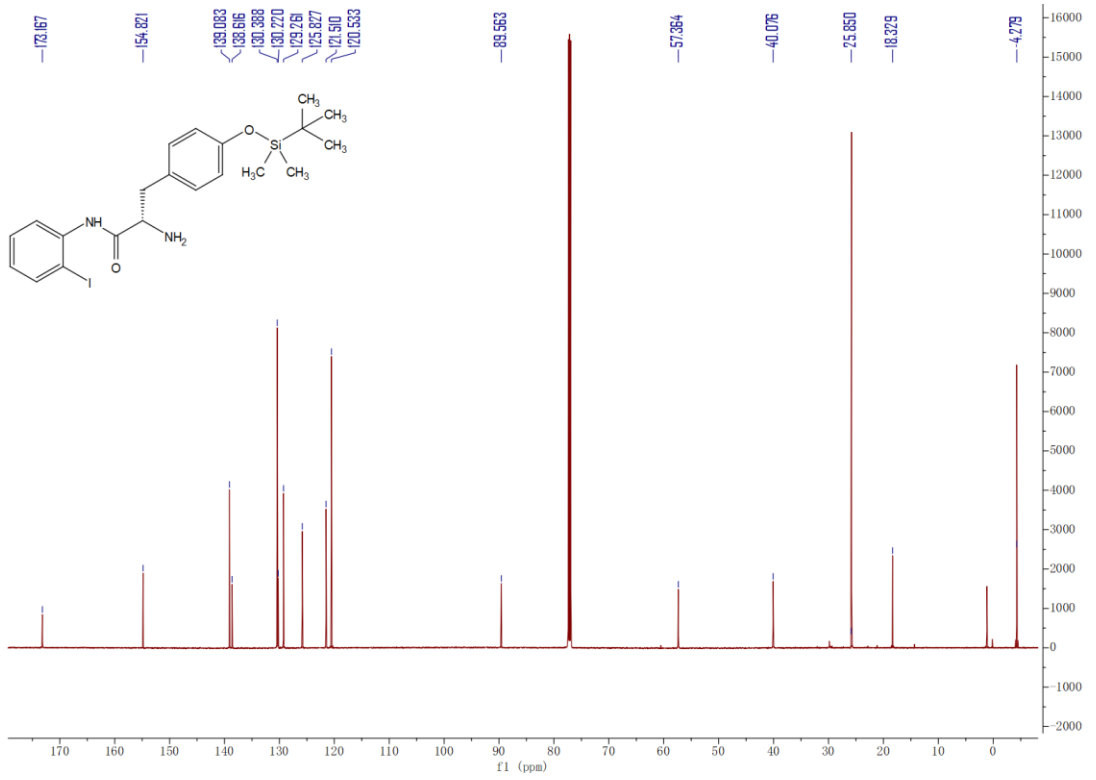


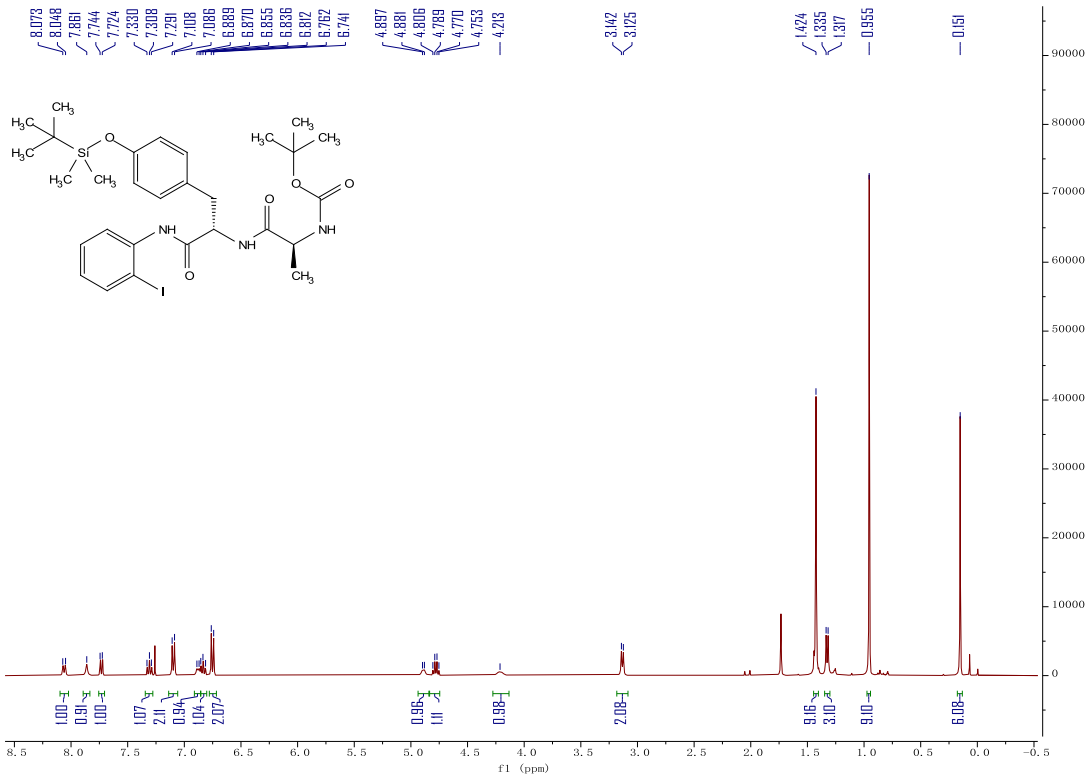
^{13}C NMR spectrum of compound 3l-Fmoc (150 MHz, $CDCl_3$)



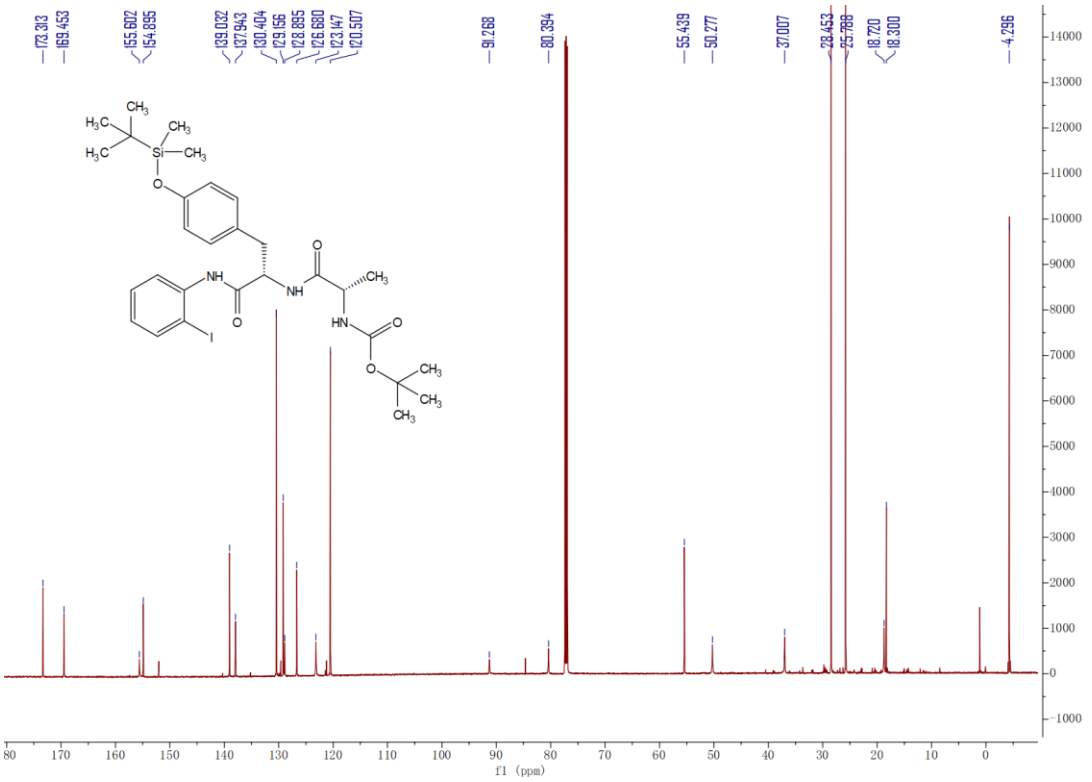
^{1}H NMR spectrum of compound 4l (400 MHz, $CDCl_3$)



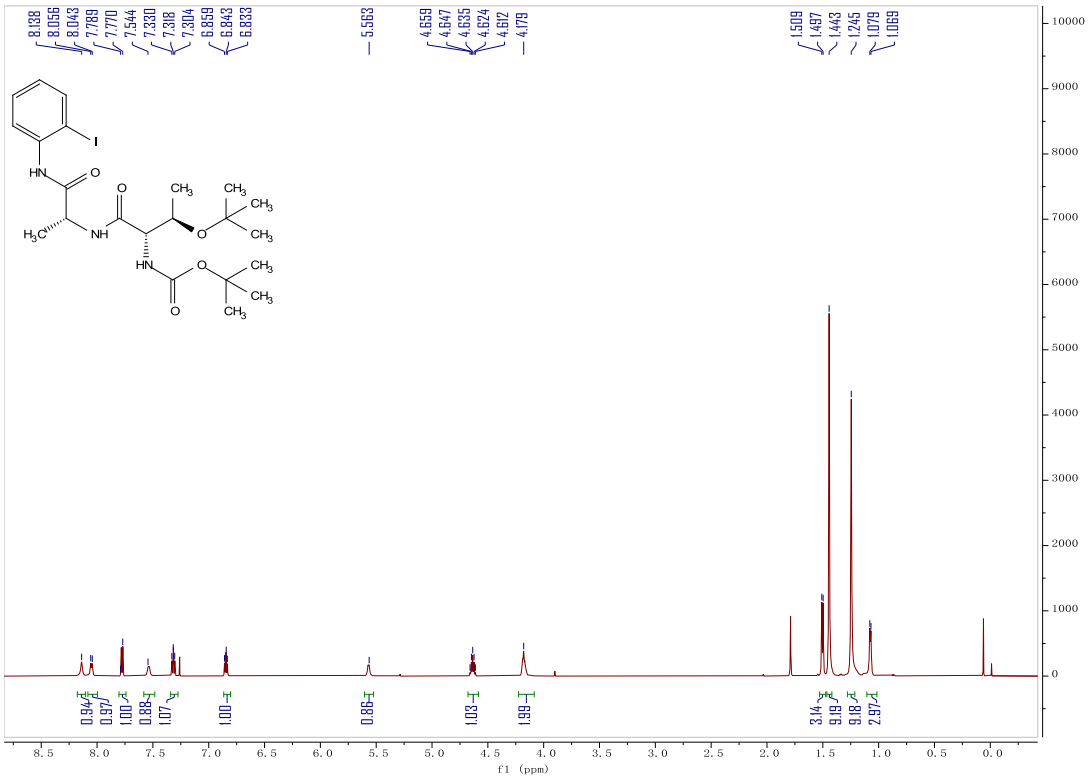
^{13}C NMR spectrum of compound 4l (150 MHz, $CDCl_3$)



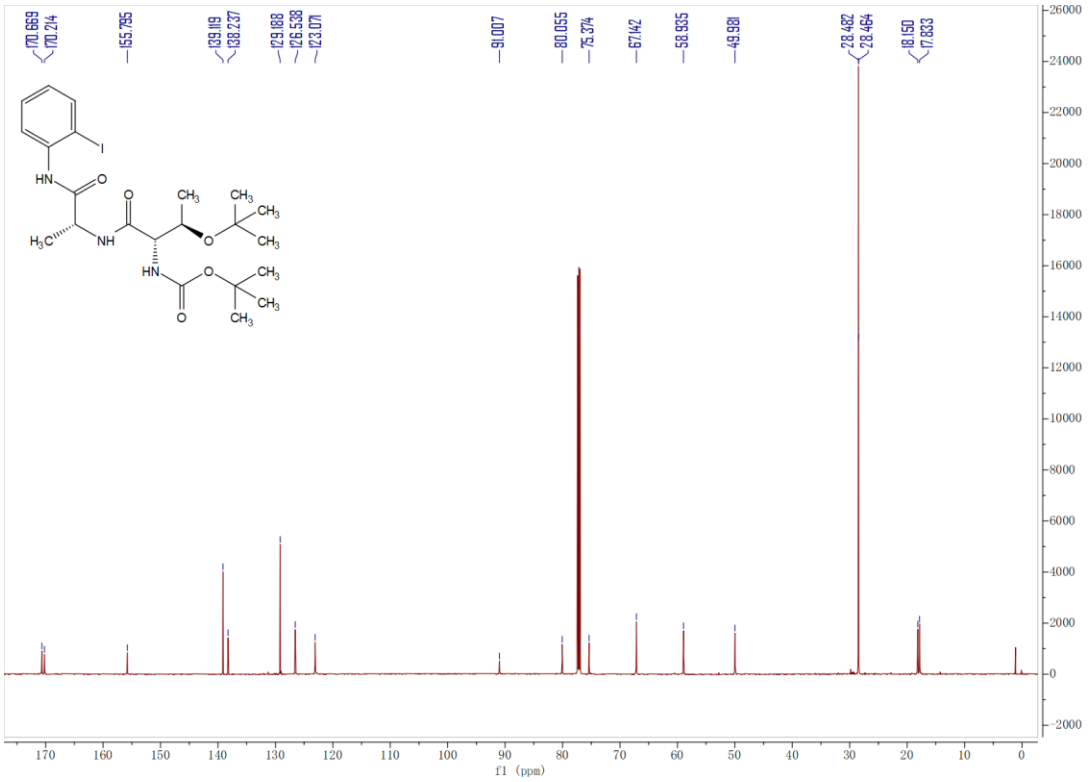
^{1}H NMR spectrum of compound 5l-Boc (400 MHz, $CDCl_3$)



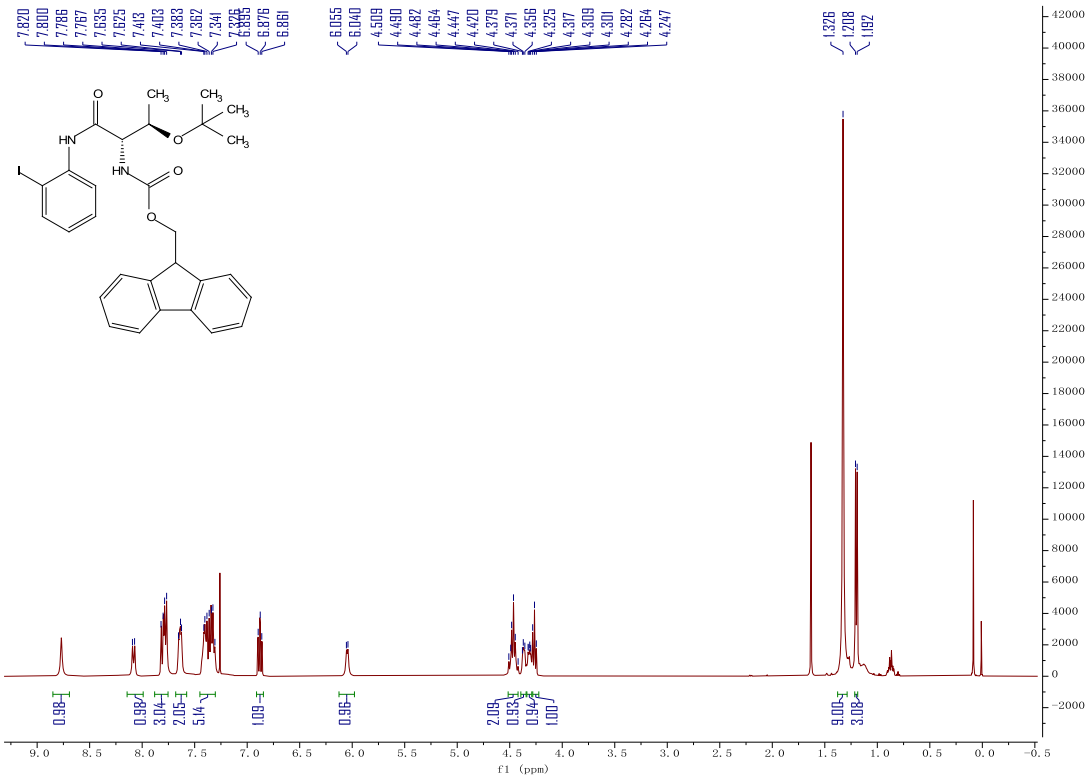
^{13}C NMR spectrum of compound 5l-Boc (150 MHz, $CDCl_3$)



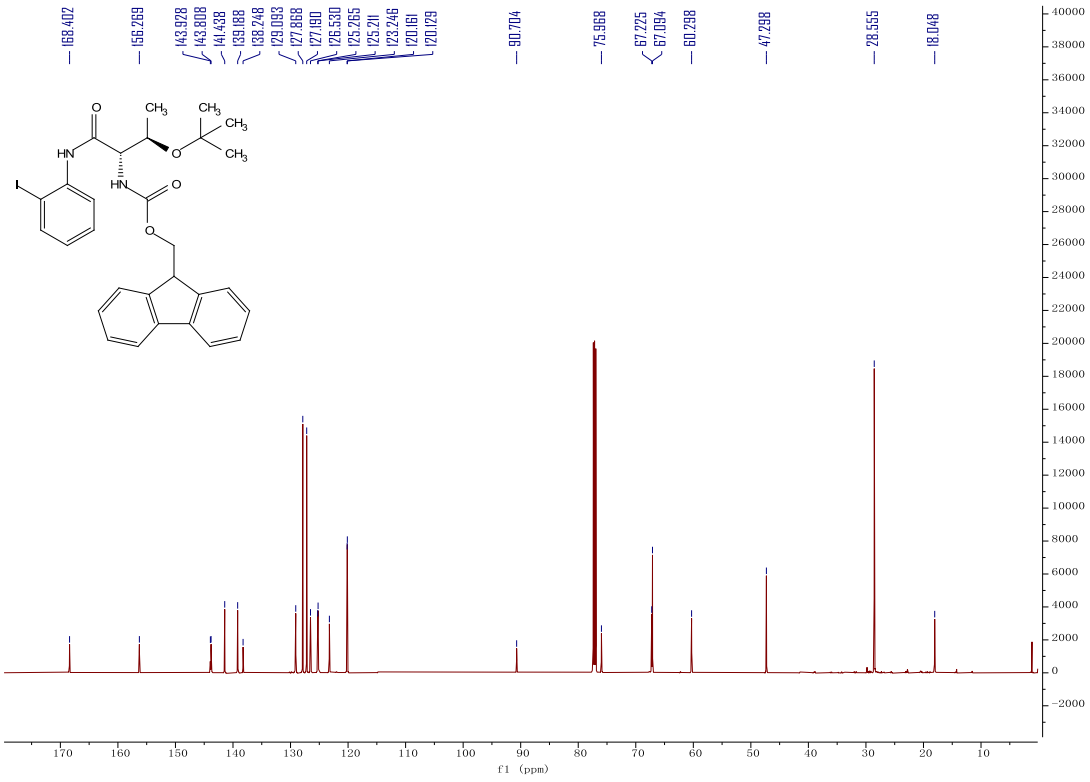
^{1}H NMR spectrum of compound 5m-Boc (600 MHz, $CDCl_3$)



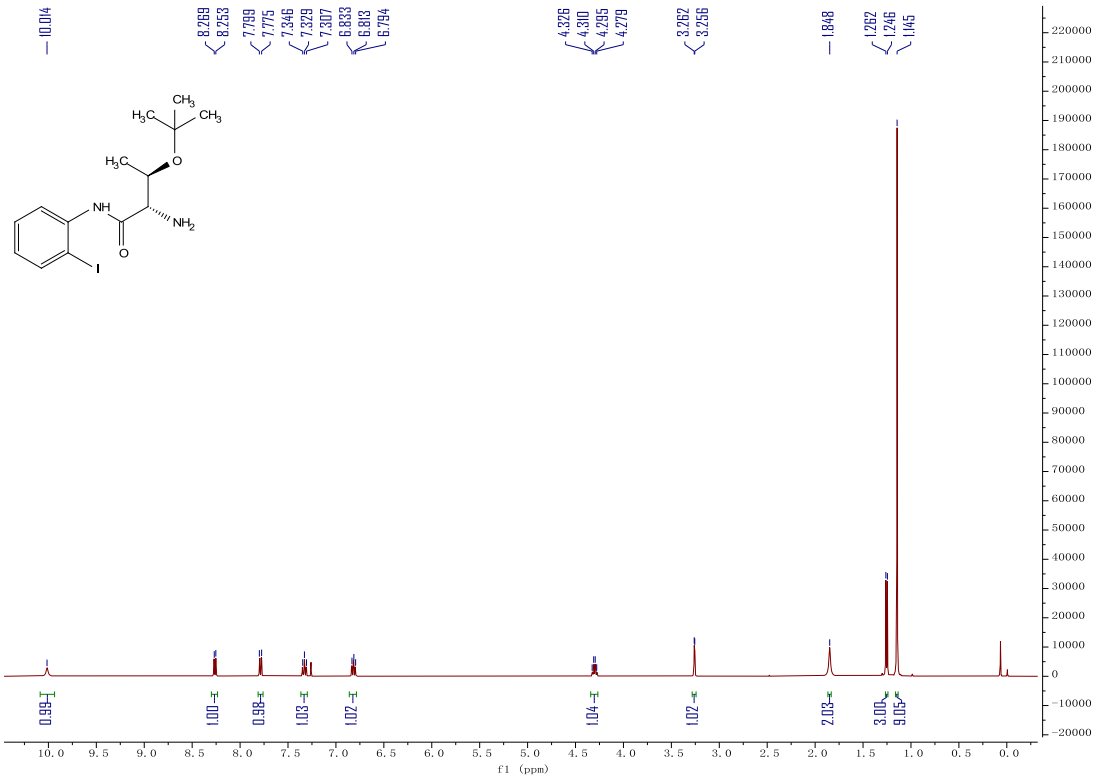
^{13}C NMR spectrum of compound 5m-Boc (150 MHz, $CDCl_3$)



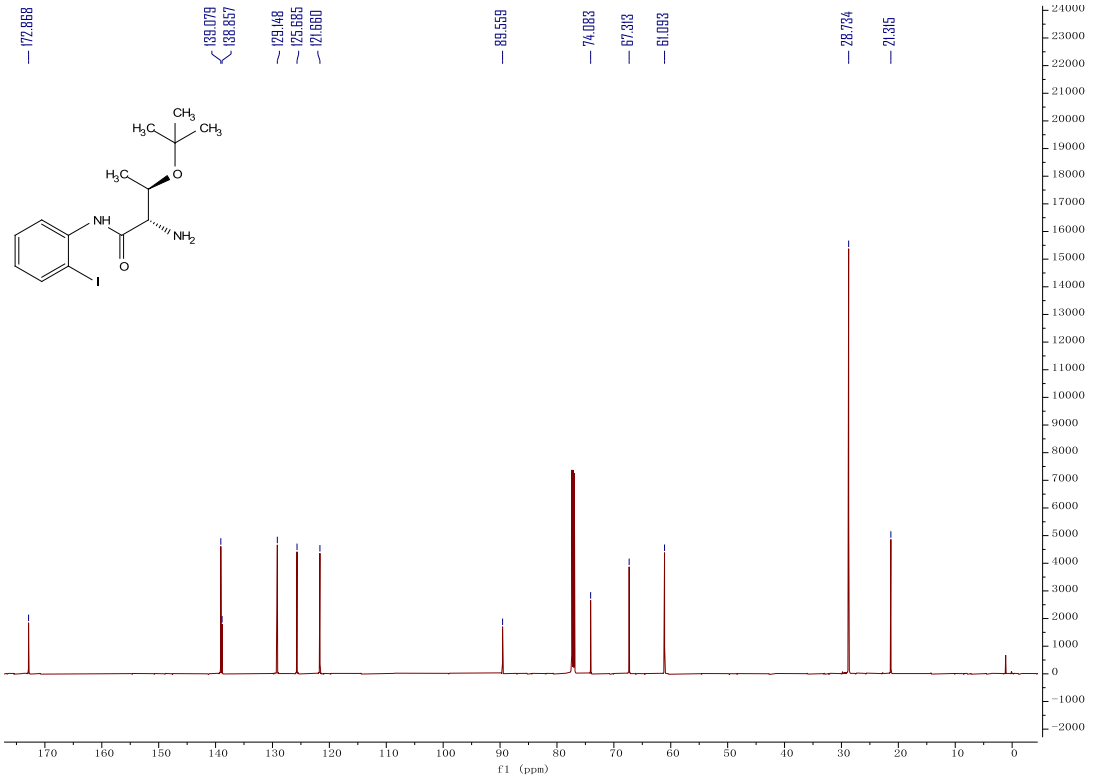
^{1}H NMR spectrum of compound 3n-Fmoc (400 MHz, $CDCl_3$)



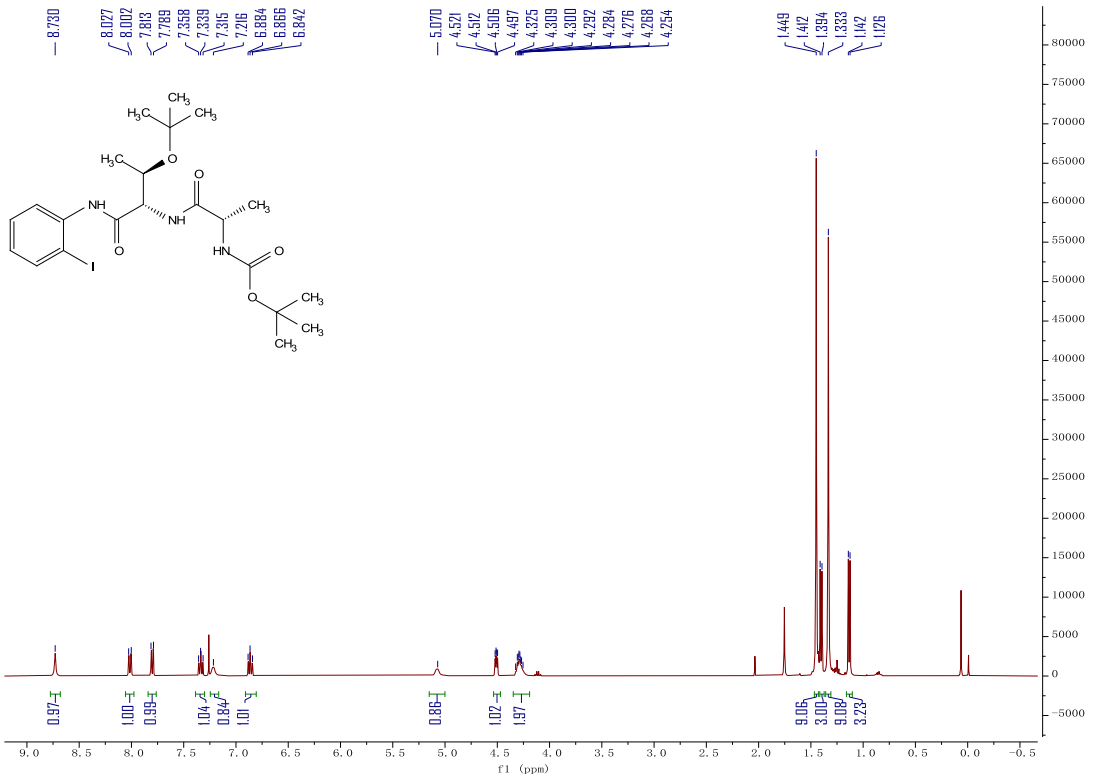
^{13}C NMR spectrum of compound 3n-Fmoc (150 MHz, $CDCl_3$)



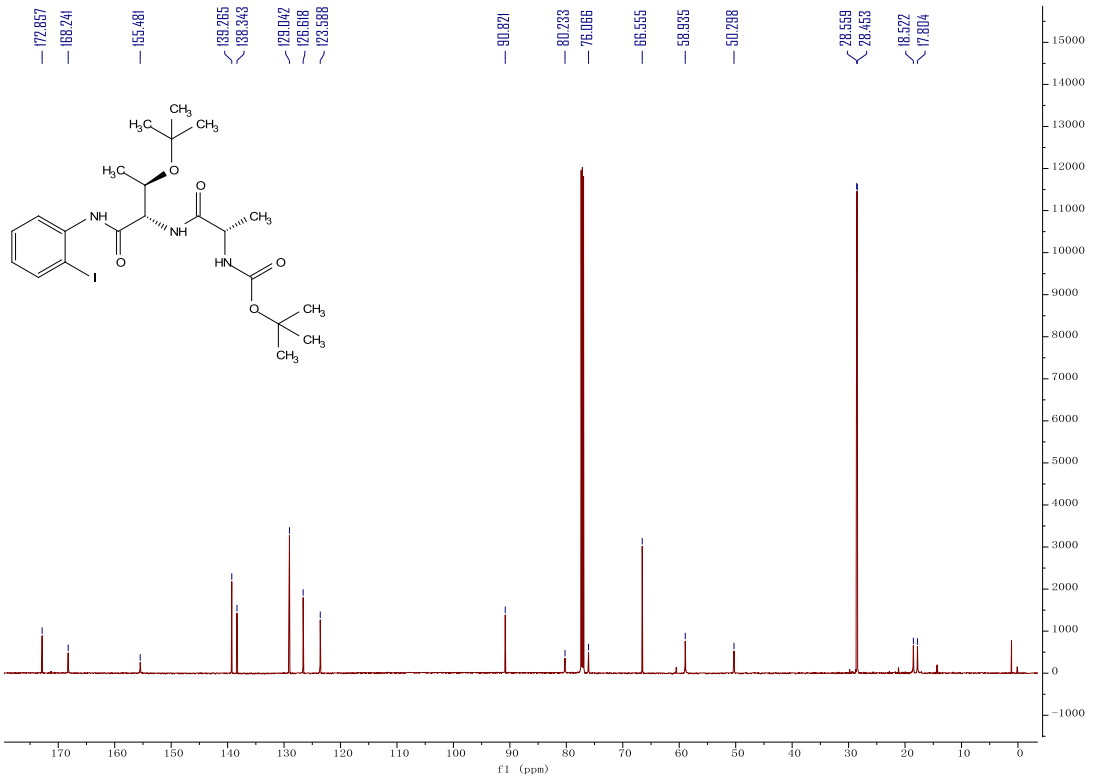
^{1}H NMR spectrum of compound 4n (400 MHz, $CDCl_3$)



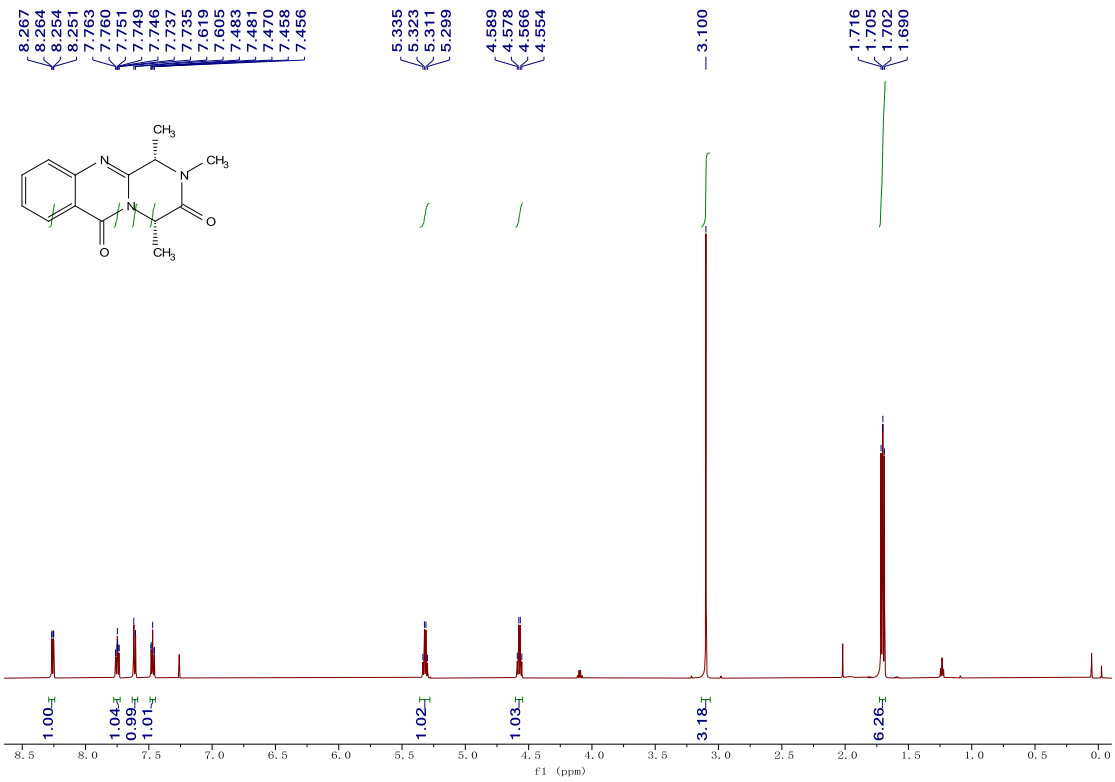
^{13}C NMR spectrum of compound 4n (150 MHz, $CDCl_3$)



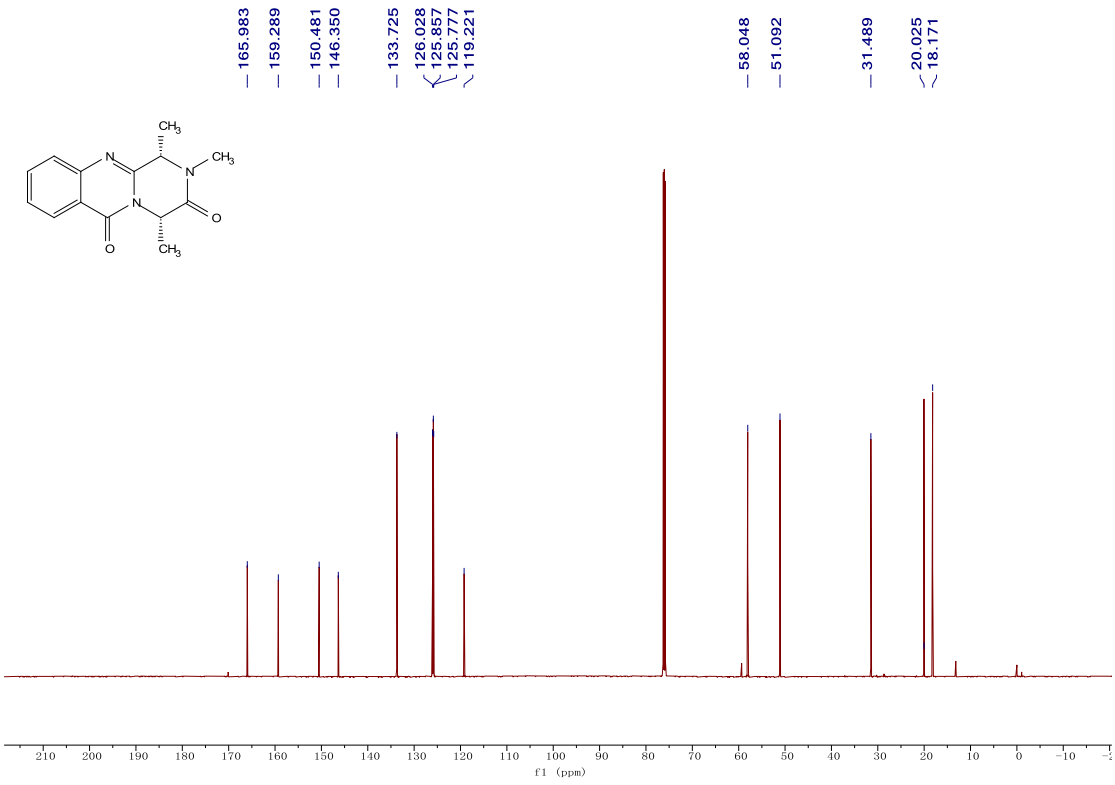
^{1}H NMR spectrum of compound 5n-Boc (400 MHz, $CDCl_3$)



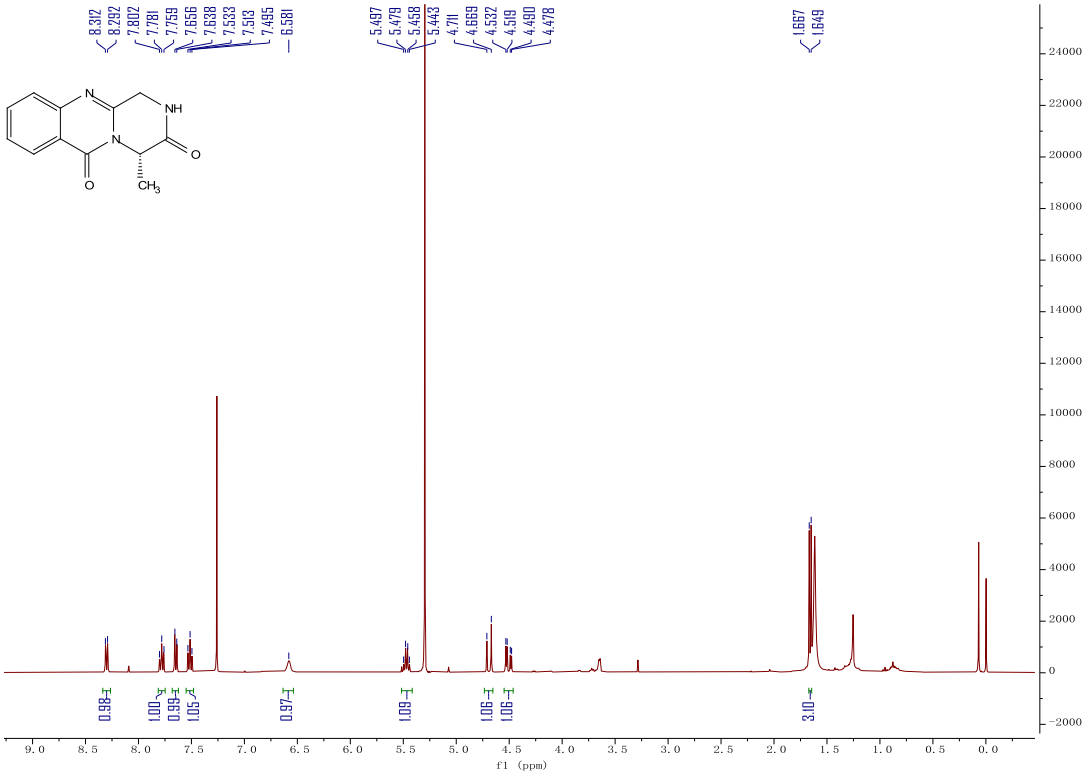
^{13}C NMR spectrum of compound 5n-Boc (150 MHz, $CDCl_3$)



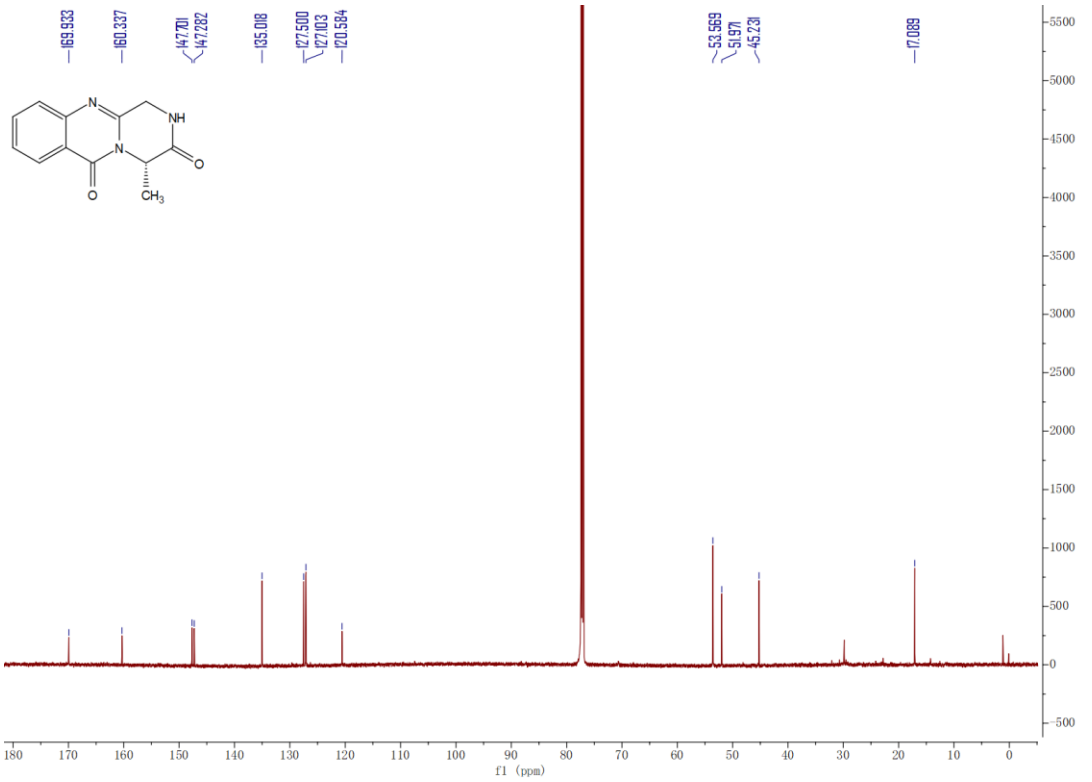
^{1}H NMR spectrum of compound 8a (600 MHz, $CDCl_3$)



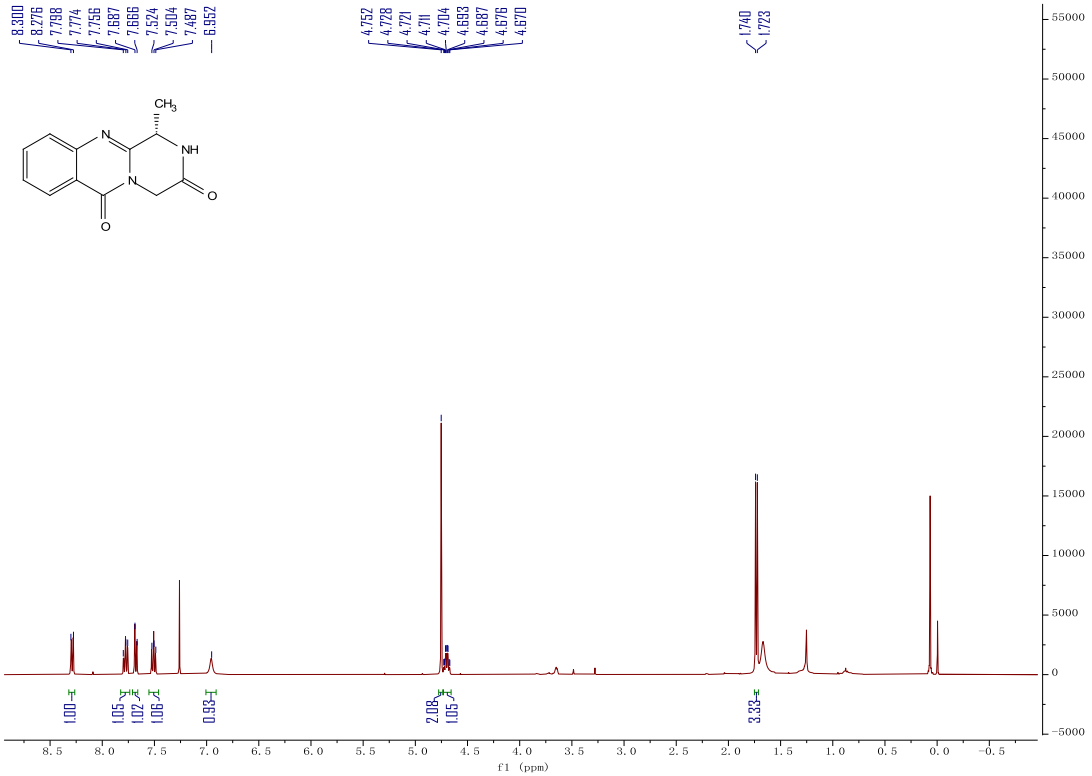
^{13}C NMR spectrum of compound 8a (150 MHz, $CDCl_3$)



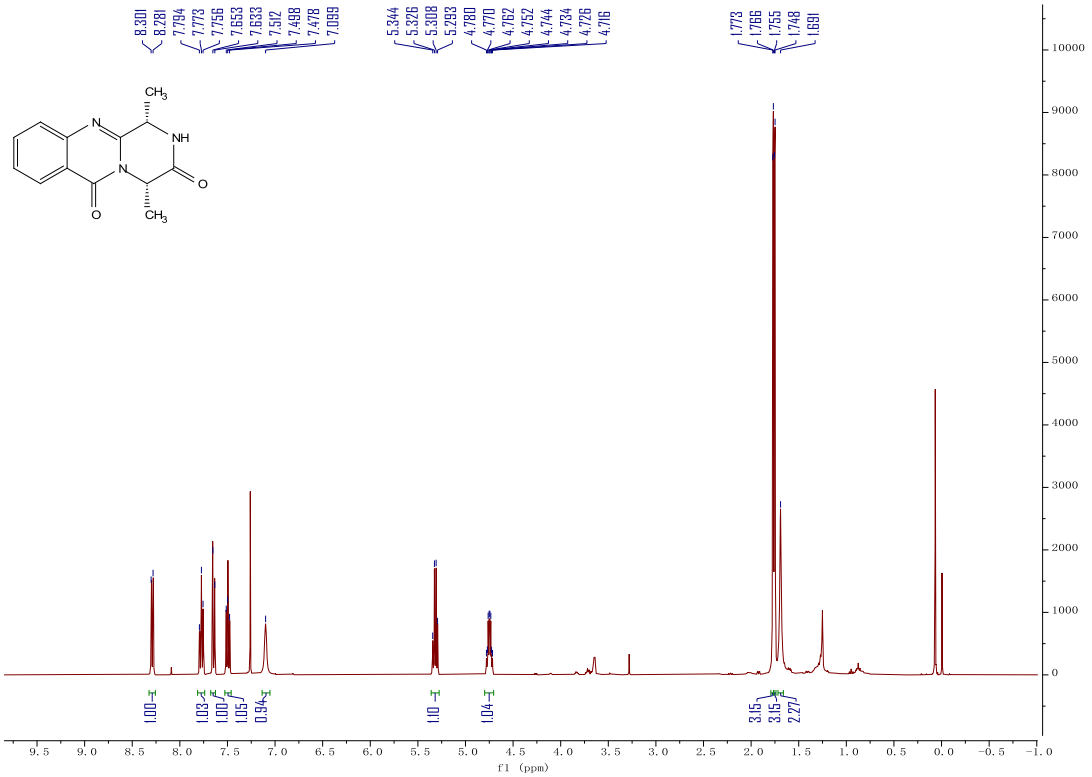
^{1}H NMR spectrum of compound 8b (400 MHz, $CDCl_3$)



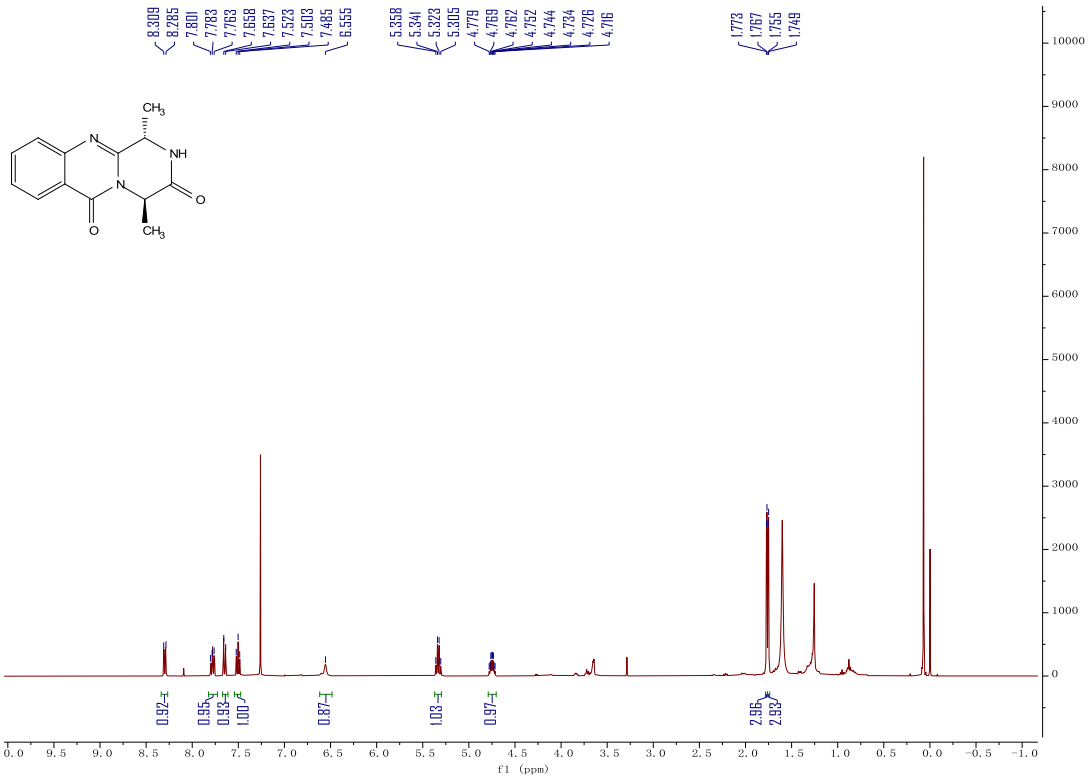
^{13}C NMR spectrum of compound 8b (150 MHz, $CDCl_3$)



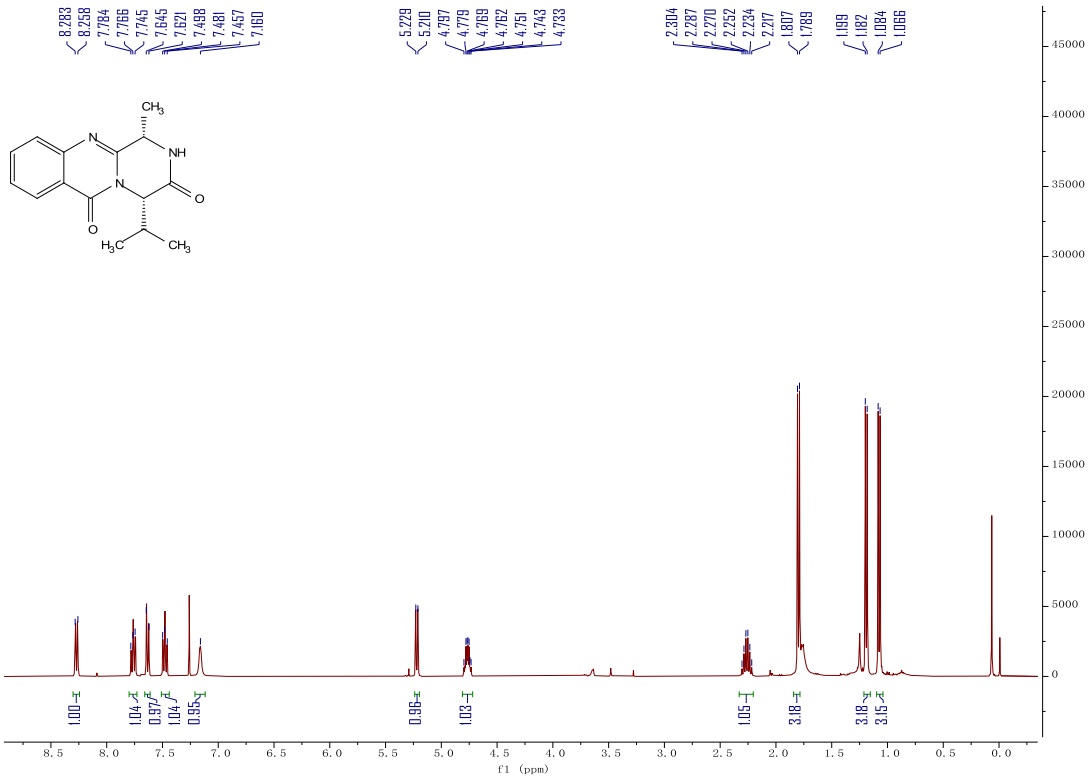
^{1}H NMR spectrum of compound 8c (400 MHz, $CDCl_3$)



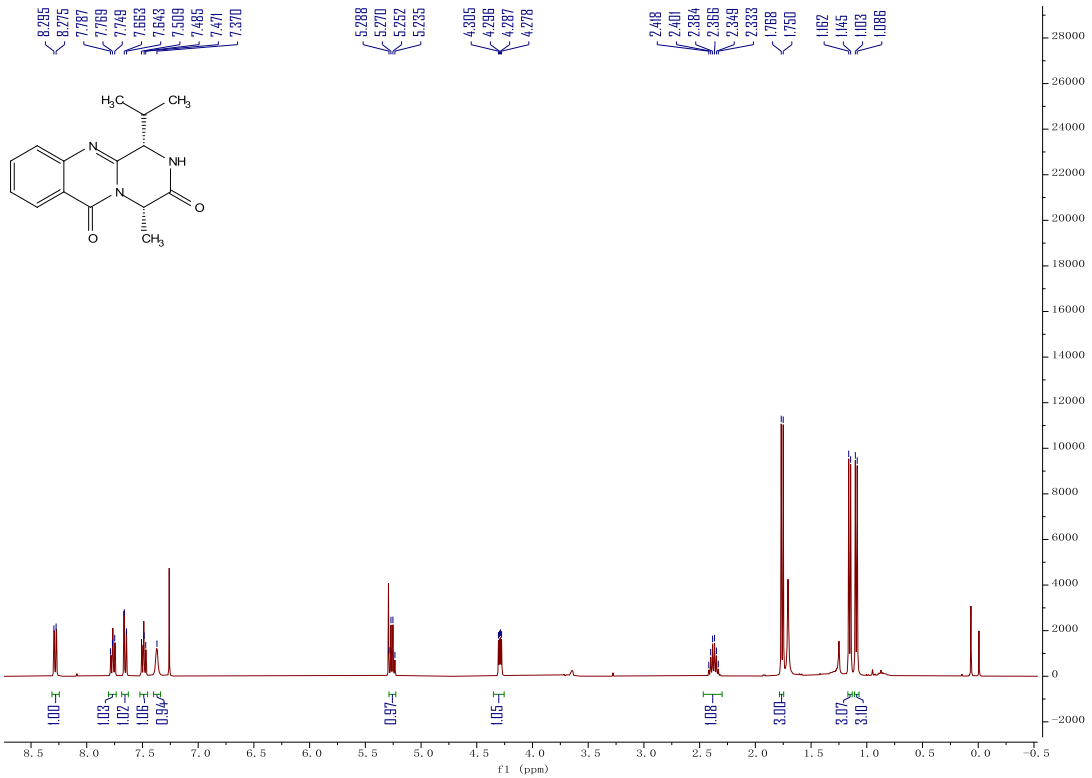
^{1}H NMR spectrum of compound 8d (400 MHz, $CDCl_3$)



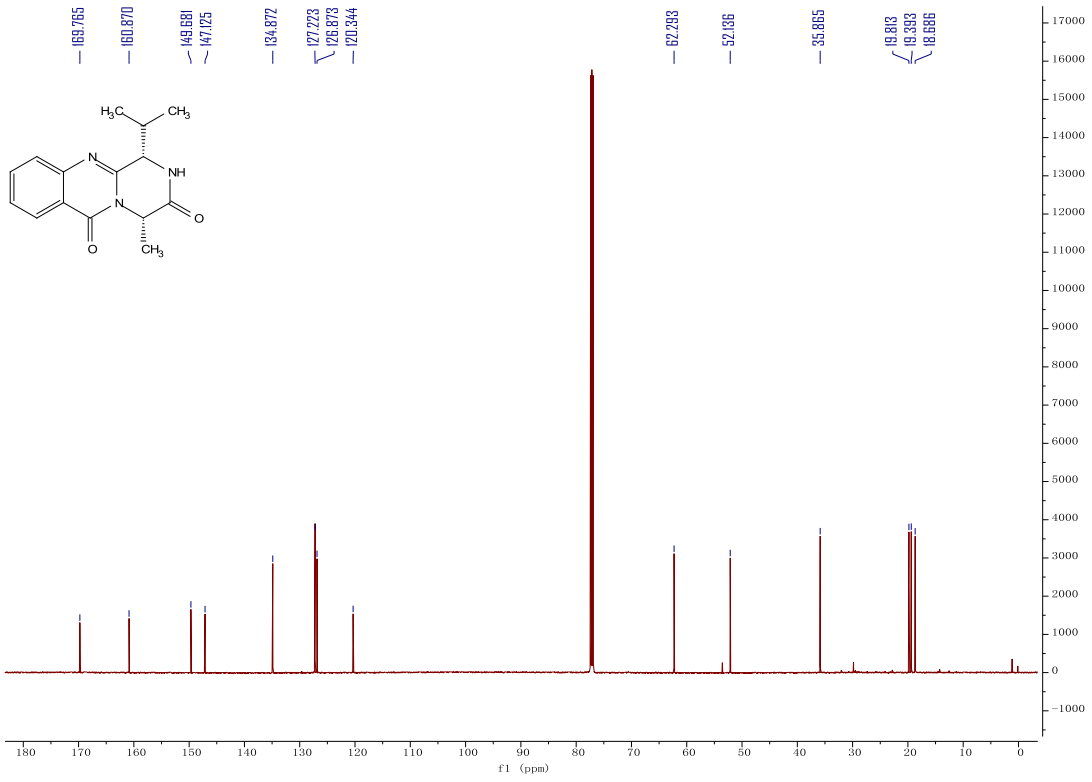
^{1}H NMR spectrum of compound 8e(400 MHz, $CDCl_3$)



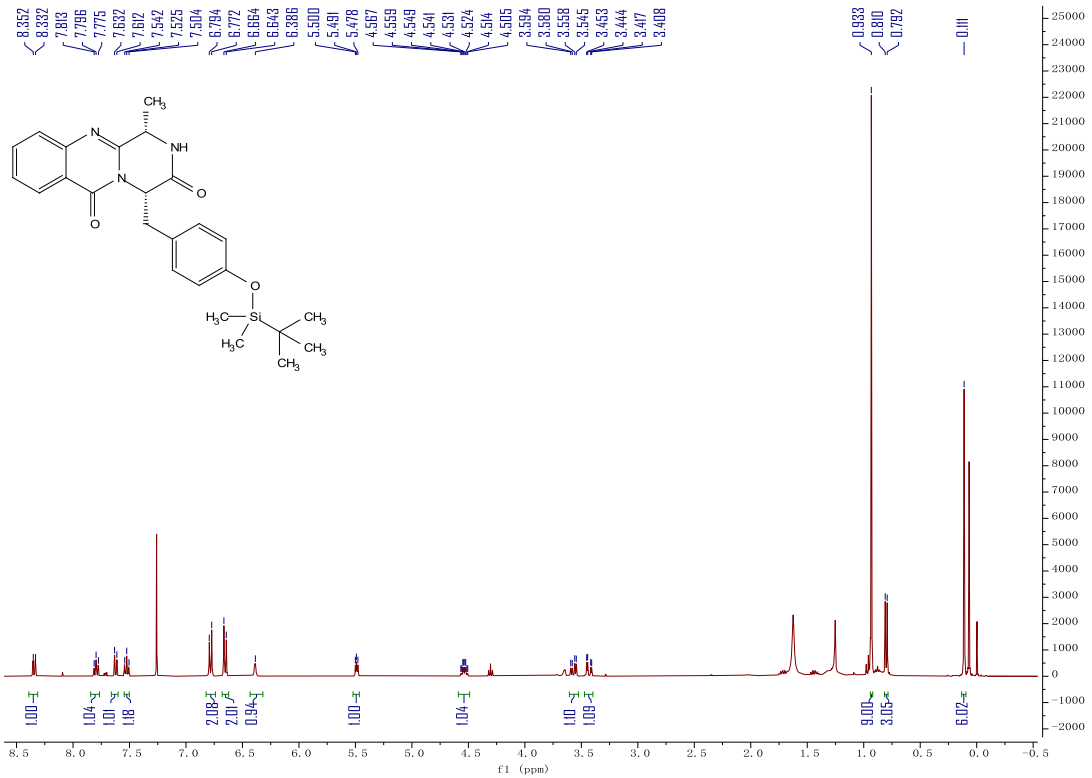
^{1}H NMR spectrum of compound 8g (400 MHz, $CDCl_3$)



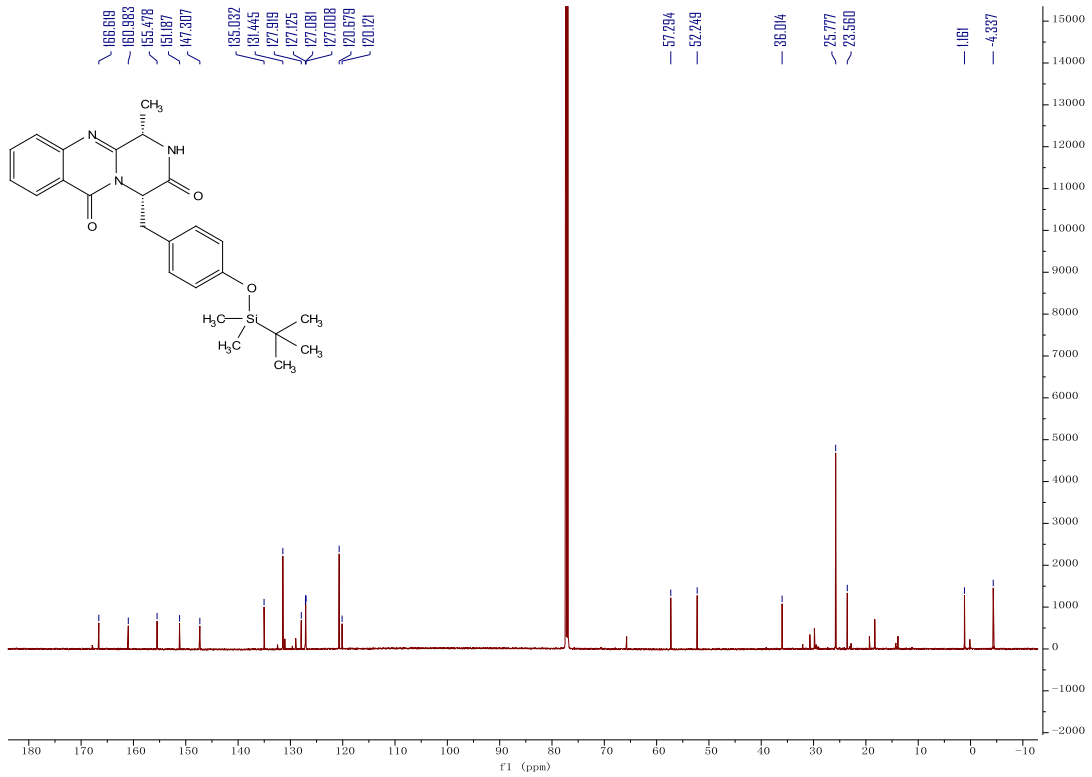
^{1}H NMR spectrum of compound 8h (400 MHz, $CDCl_3$)



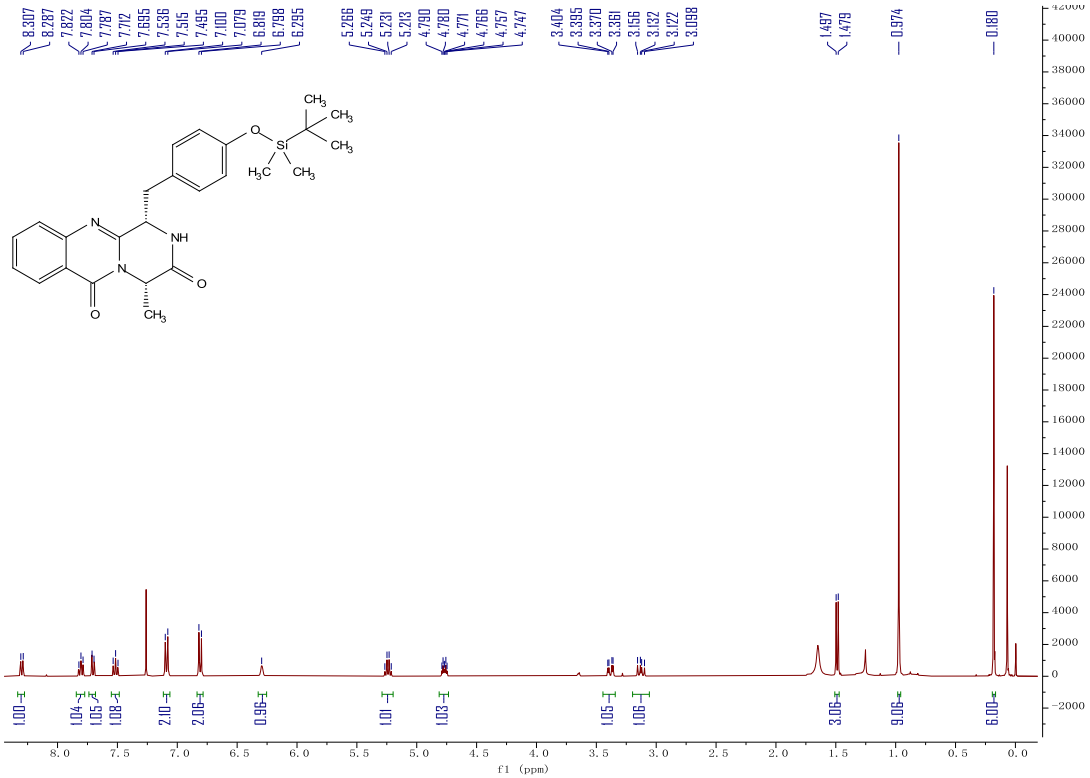
^{13}C NMR spectrum of compound 8h (150 MHz, $CDCl_3$)



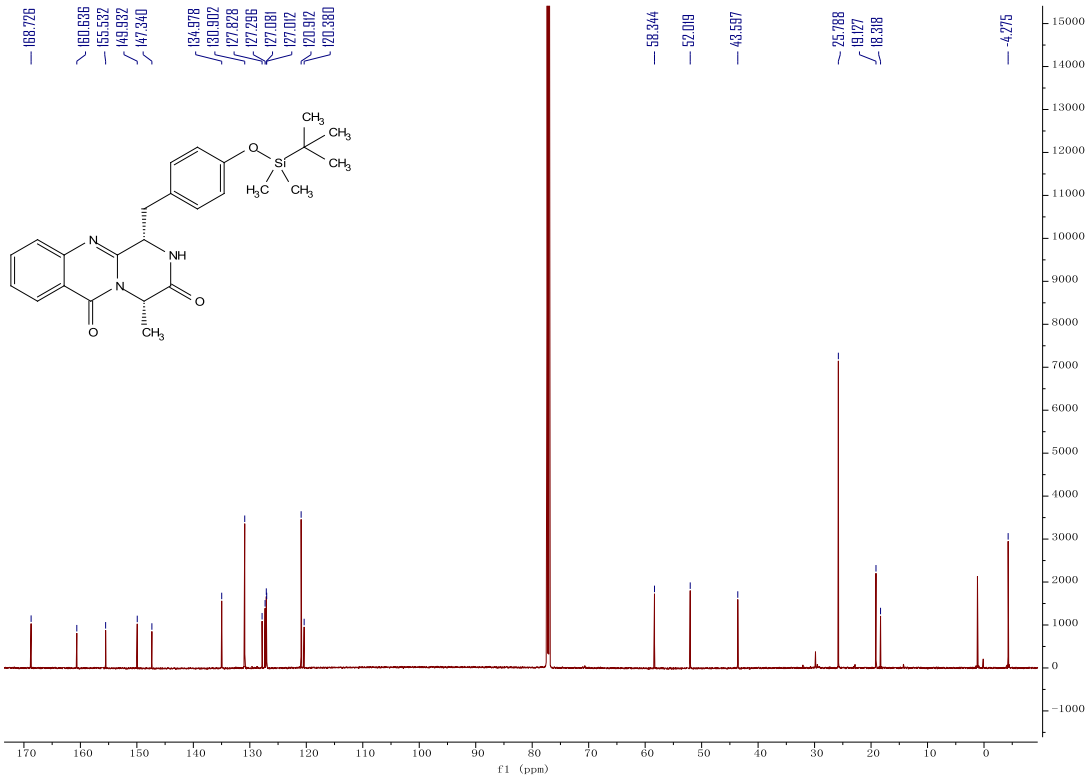
^{1}H NMR spectrum of compound 8k (400 MHz, $CDCl_3$)



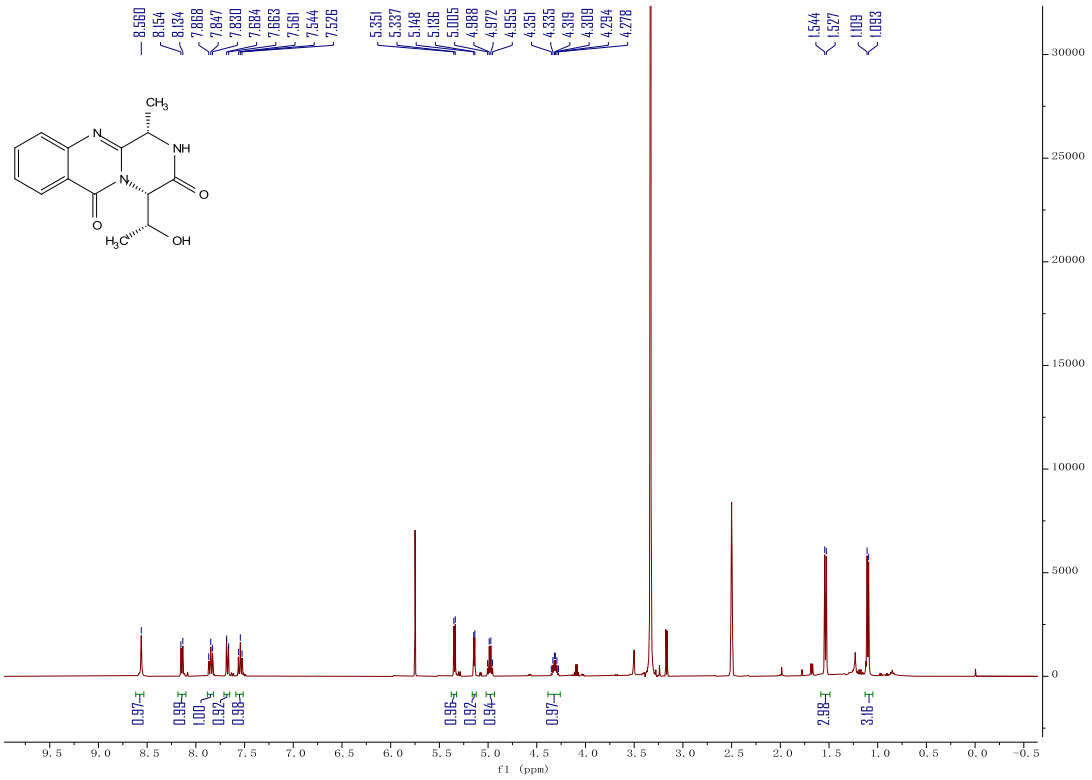
^{13}C NMR spectrum of compound 8k (150 MHz, $CDCl_3$)



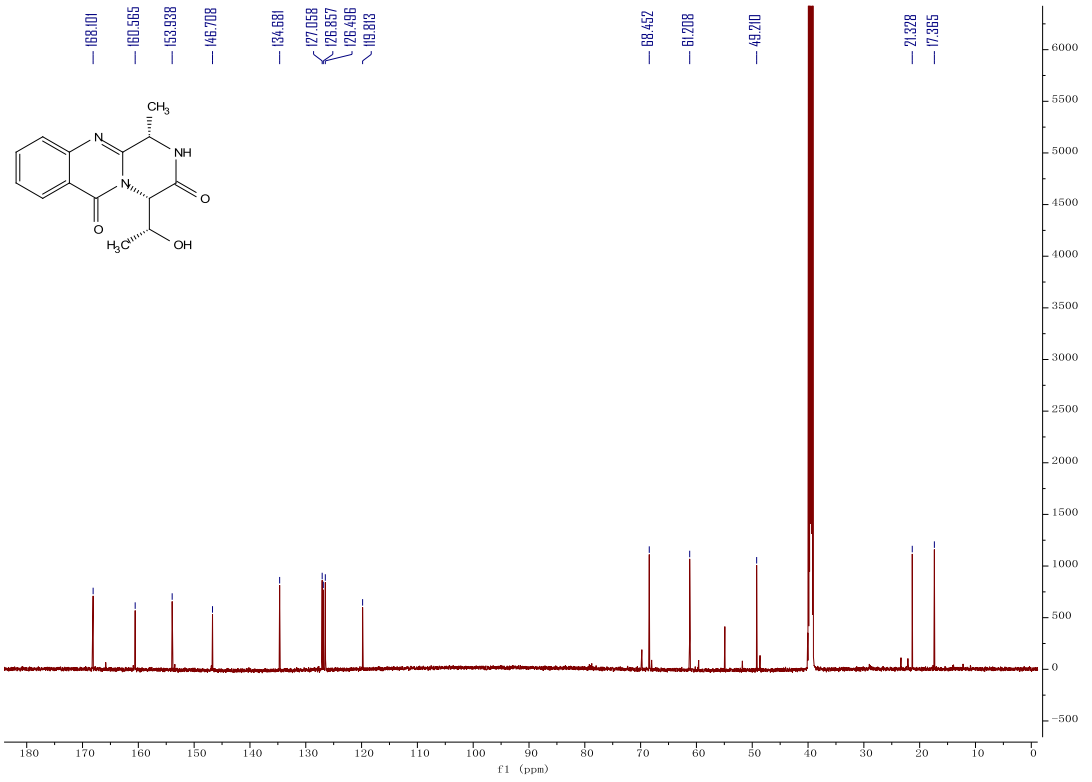
^{1}H NMR spectrum of compound 8l (400 MHz, $CDCl_3$)



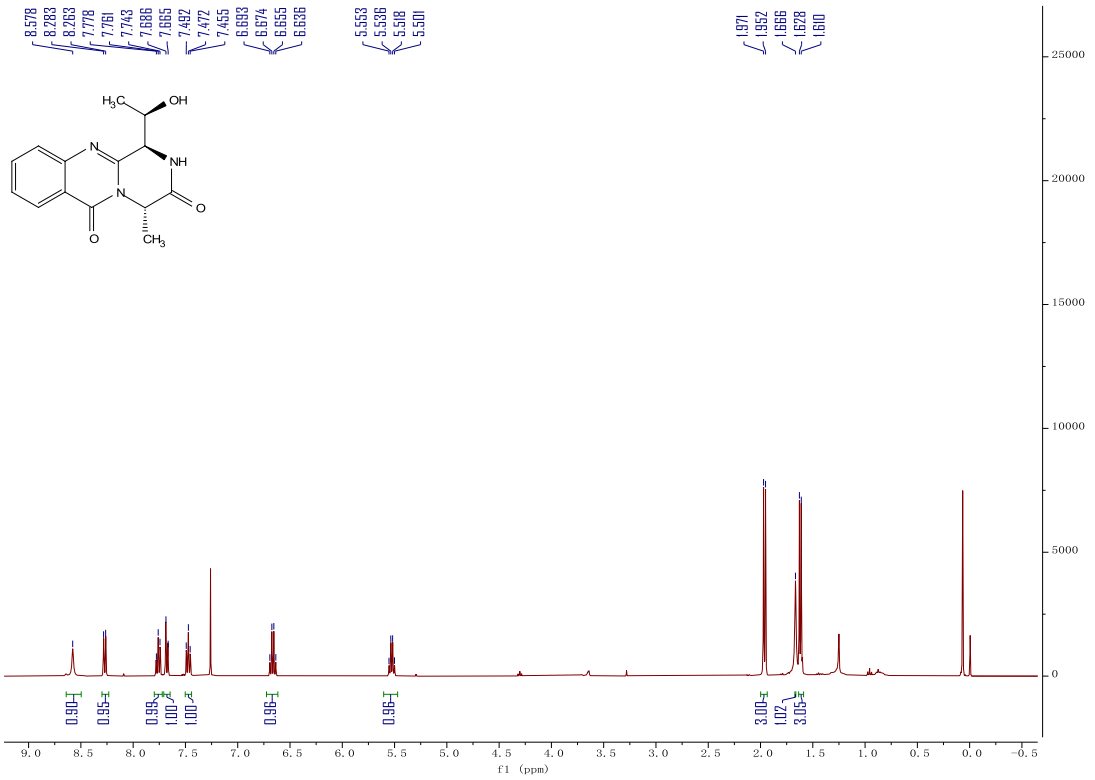
^{13}C NMR spectrum of compound 8l (150 MHz, $CDCl_3$)



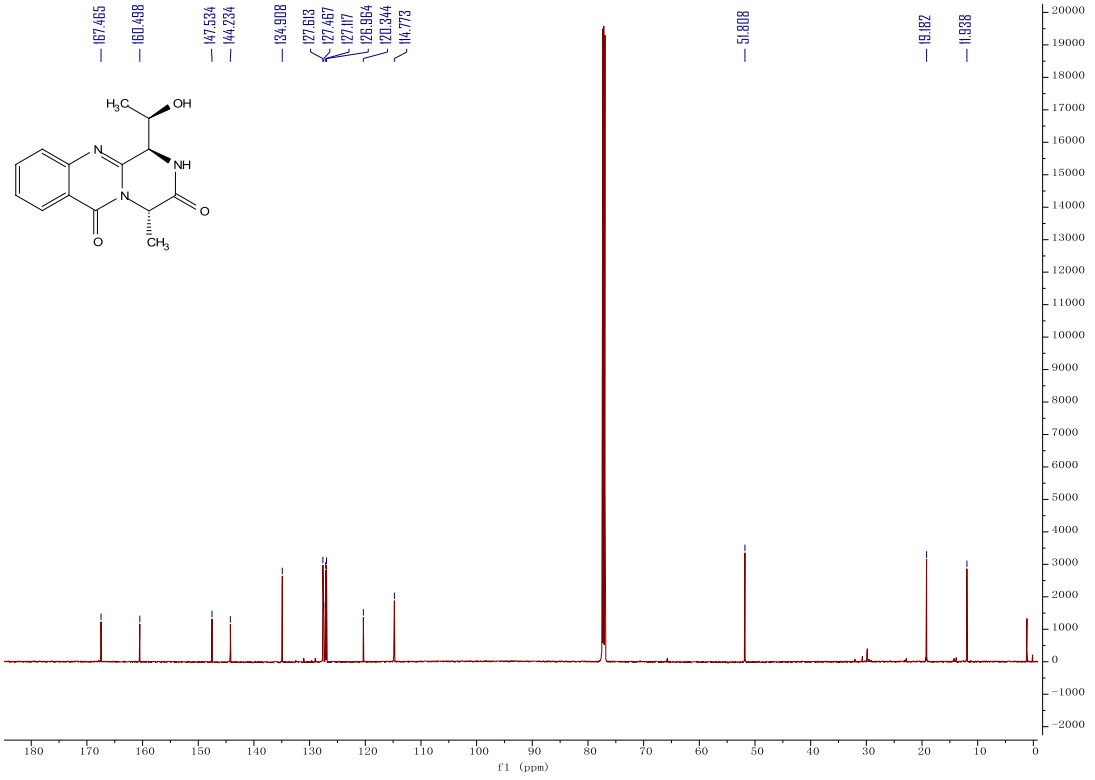
^{1}H NMR spectrum of compound 8m (400 MHz, DMSO-d_6)



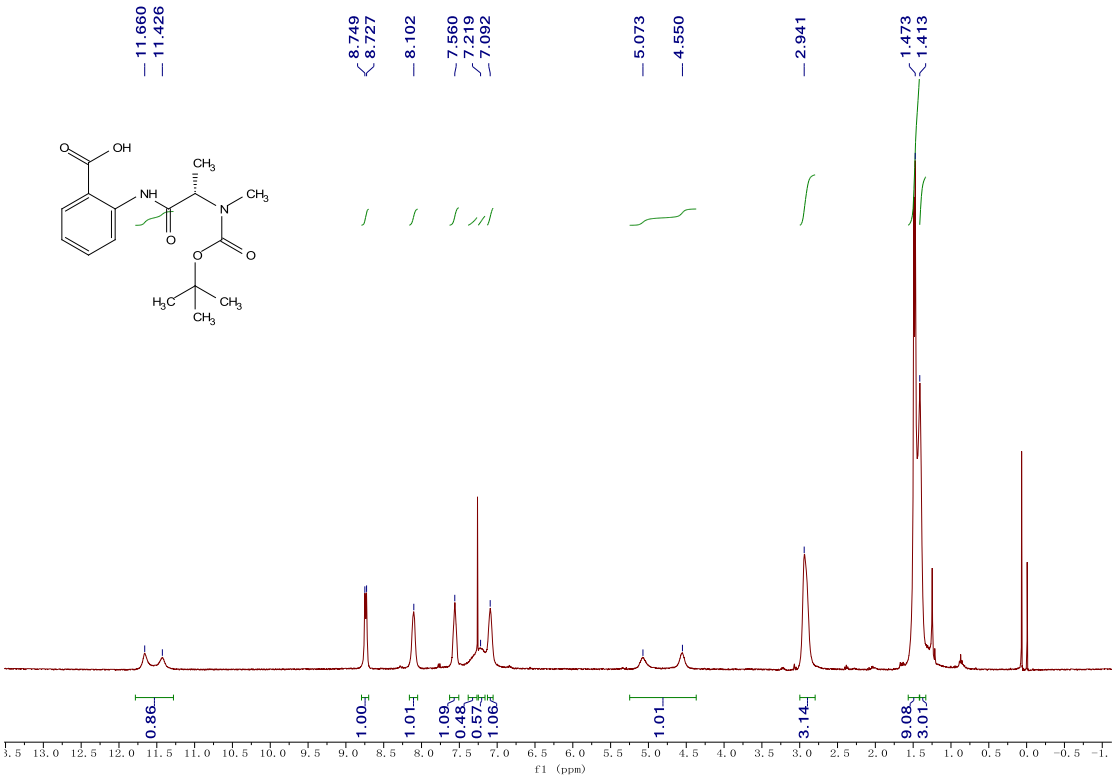
^{13}C NMR spectrum of compound 8m (150 MHz, DMSO-d_6)



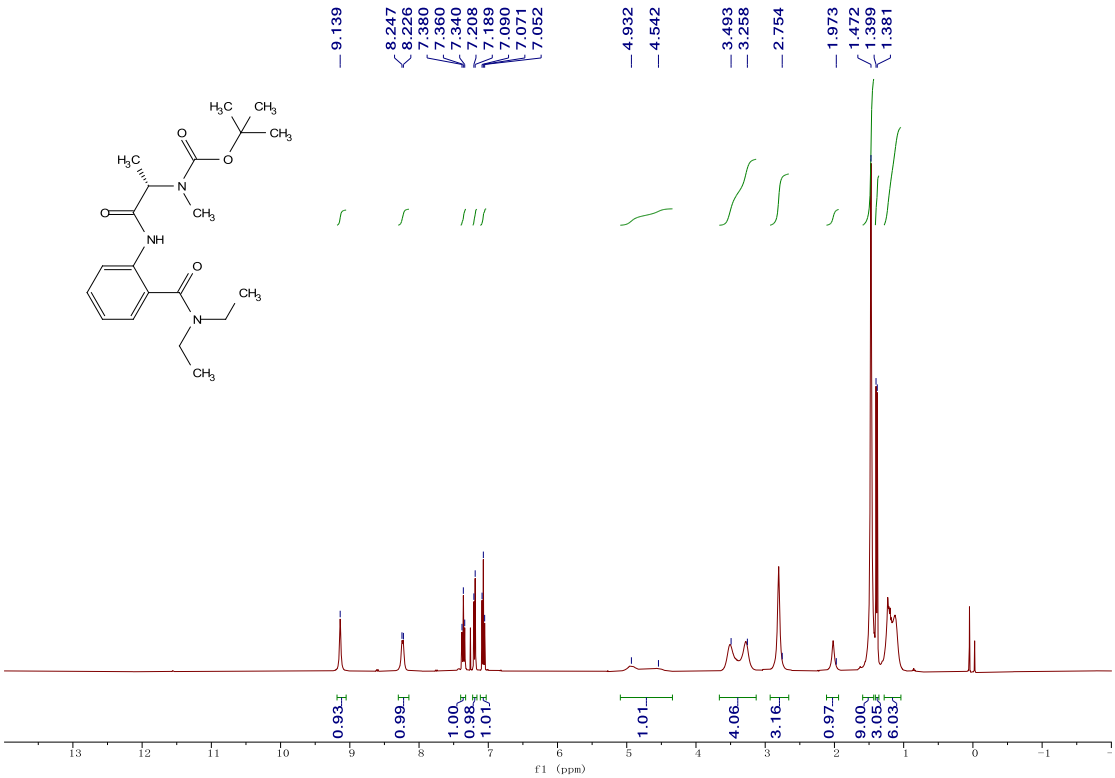
^{1}H NMR spectrum of compound 8n (400 MHz, $CDCl_3$)



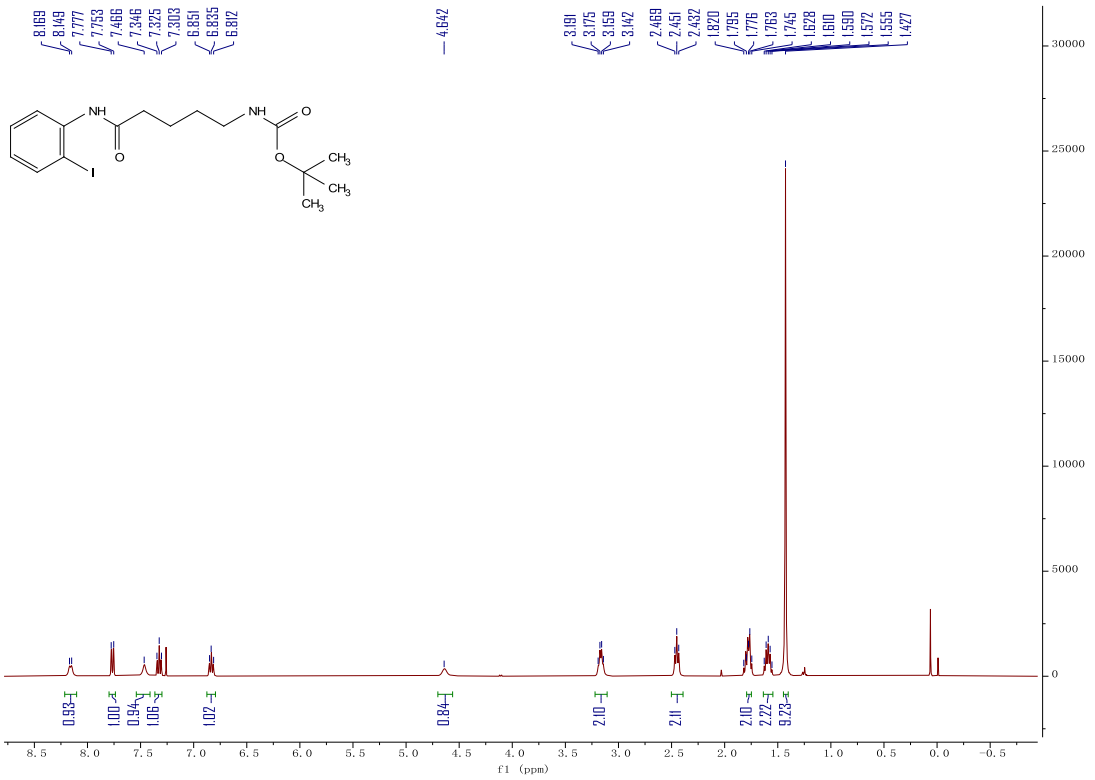
^{13}C NMR spectrum of compound 8n (150 MHz, $CDCl_3$)



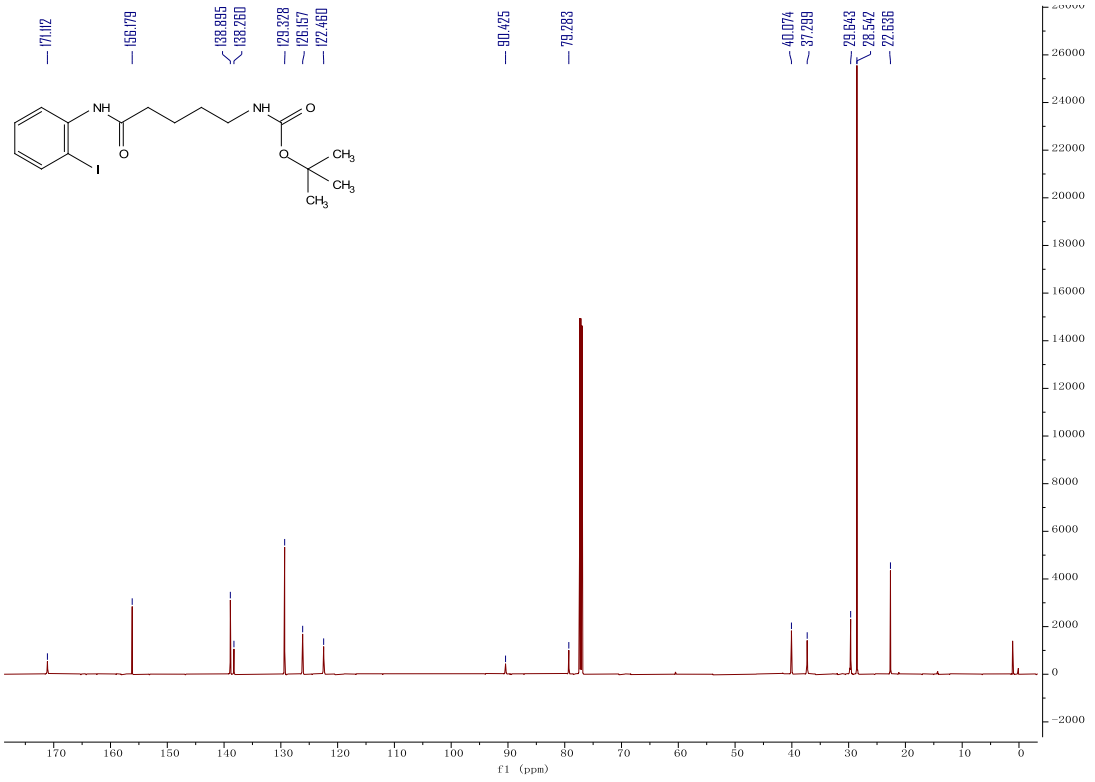
^{1}H NMR spectrum of compound 9e (400 MHz, $CDCl_3$)



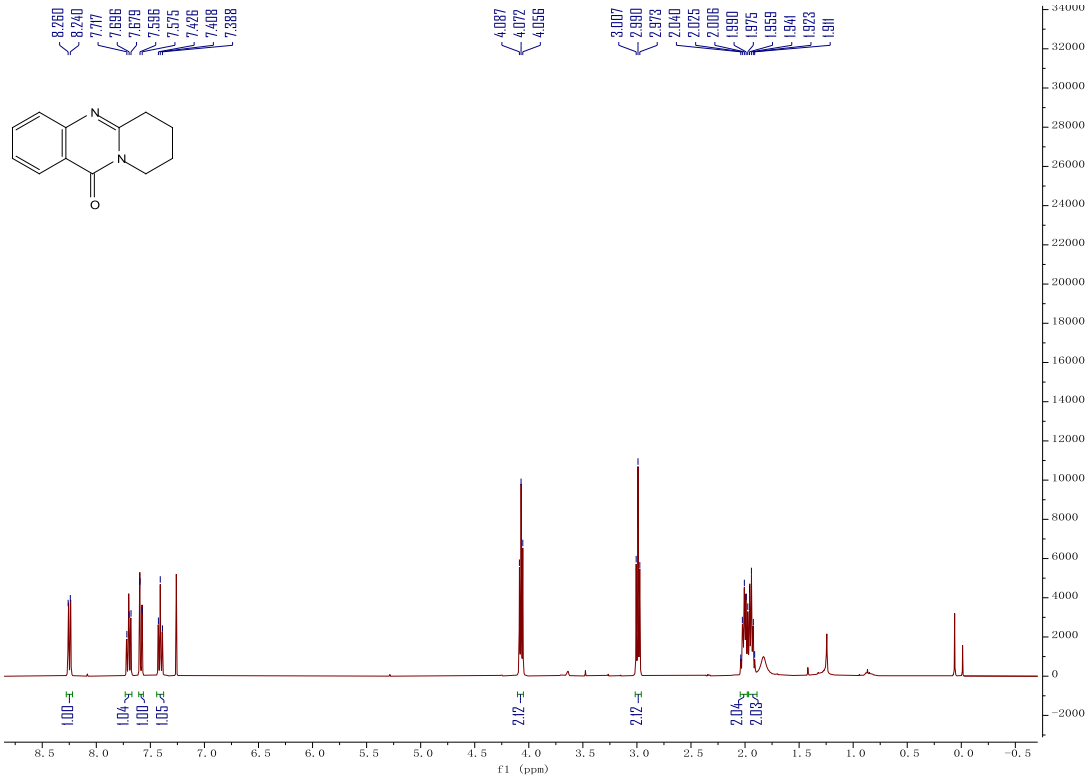
^{1}H NMR spectrum of compound 9f (400 MHz, $CDCl_3$)



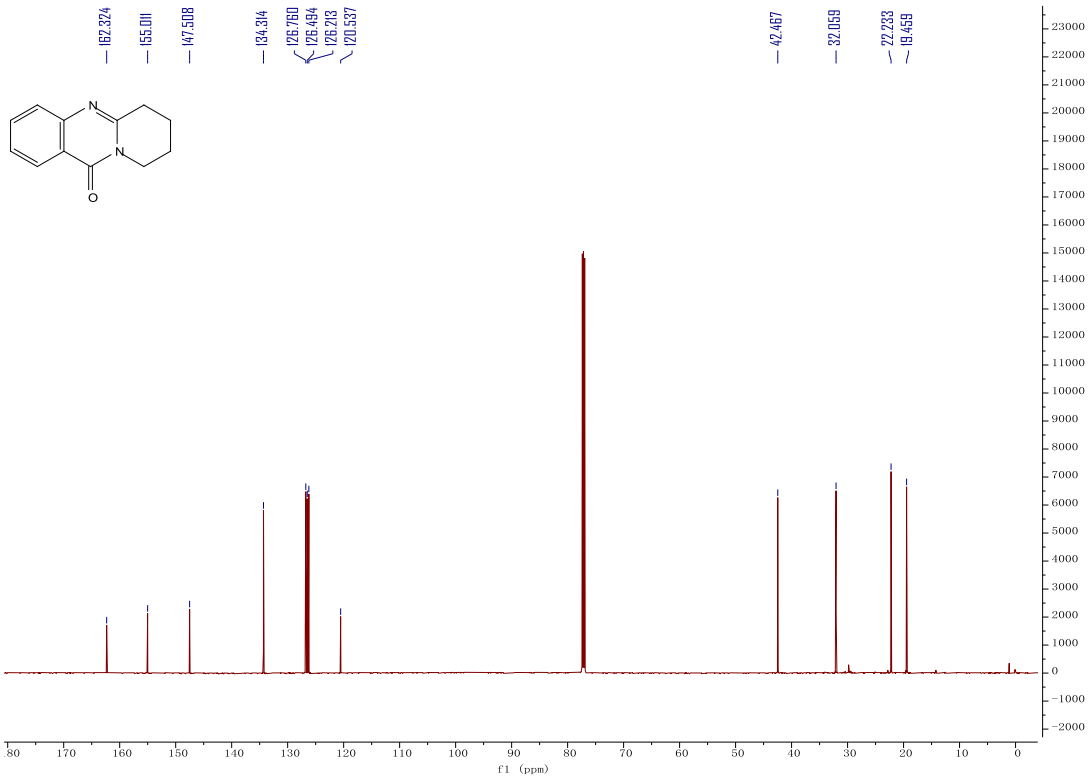
^{1}H NMR spectrum of compound 10a-Boc (400 MHz, $CDCl_3$)



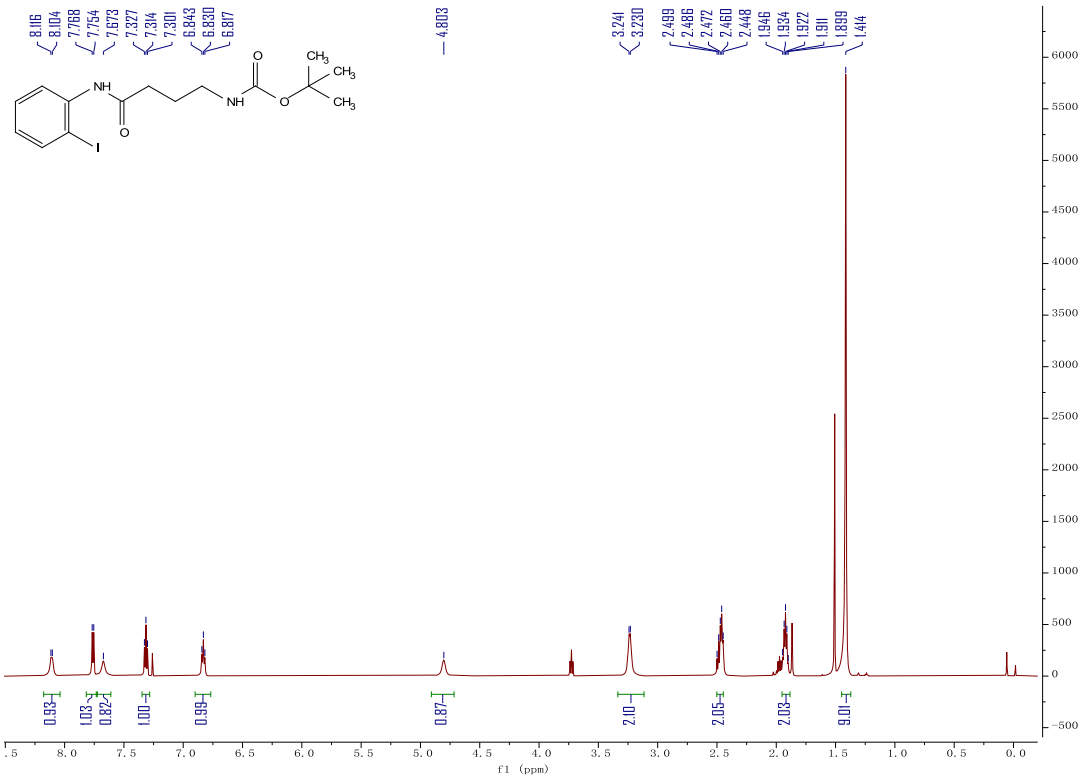
^{13}C NMR spectrum of compound 10a-Boc (150 MHz, $CDCl_3$)



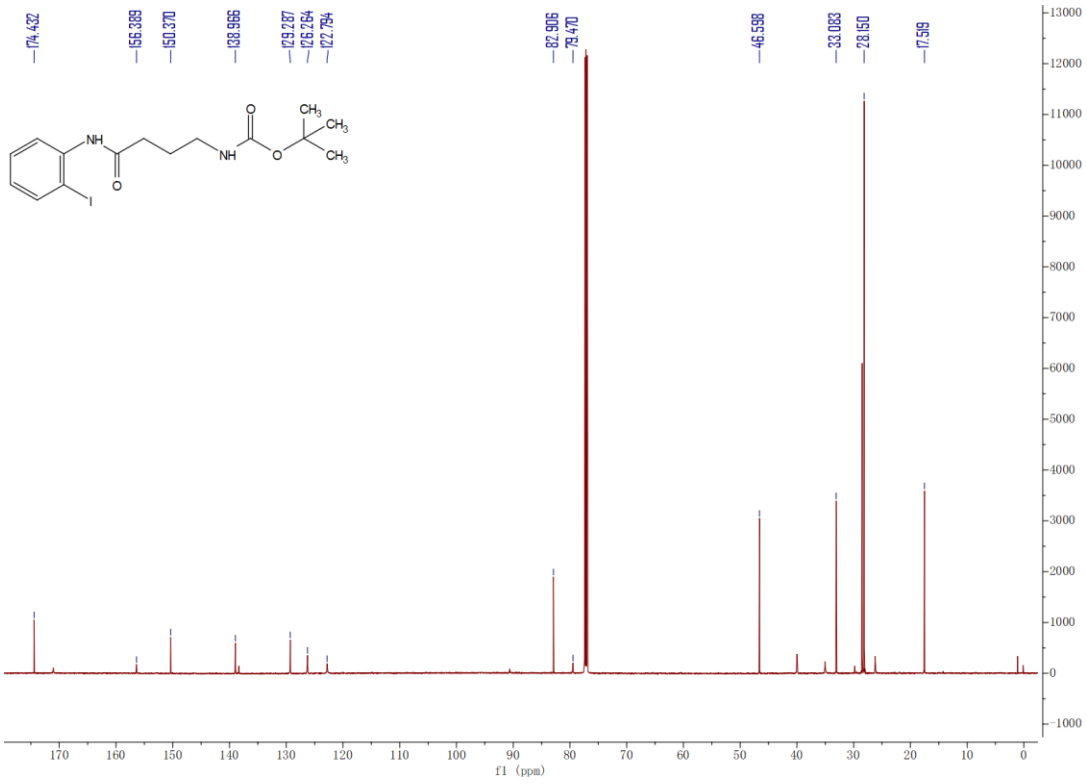
^{1}H NMR spectrum of compound 13a (400 MHz, $CDCl_3$)



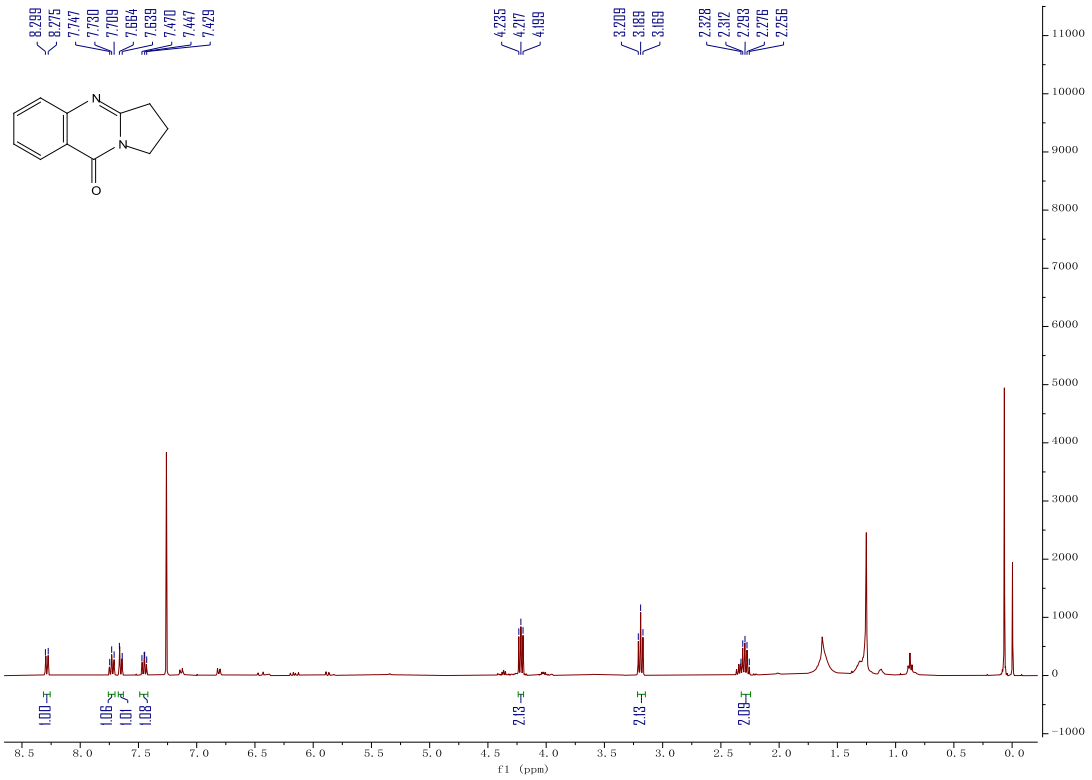
^{13}C NMR spectrum of compound 13a (150 MHz, $CDCl_3$)



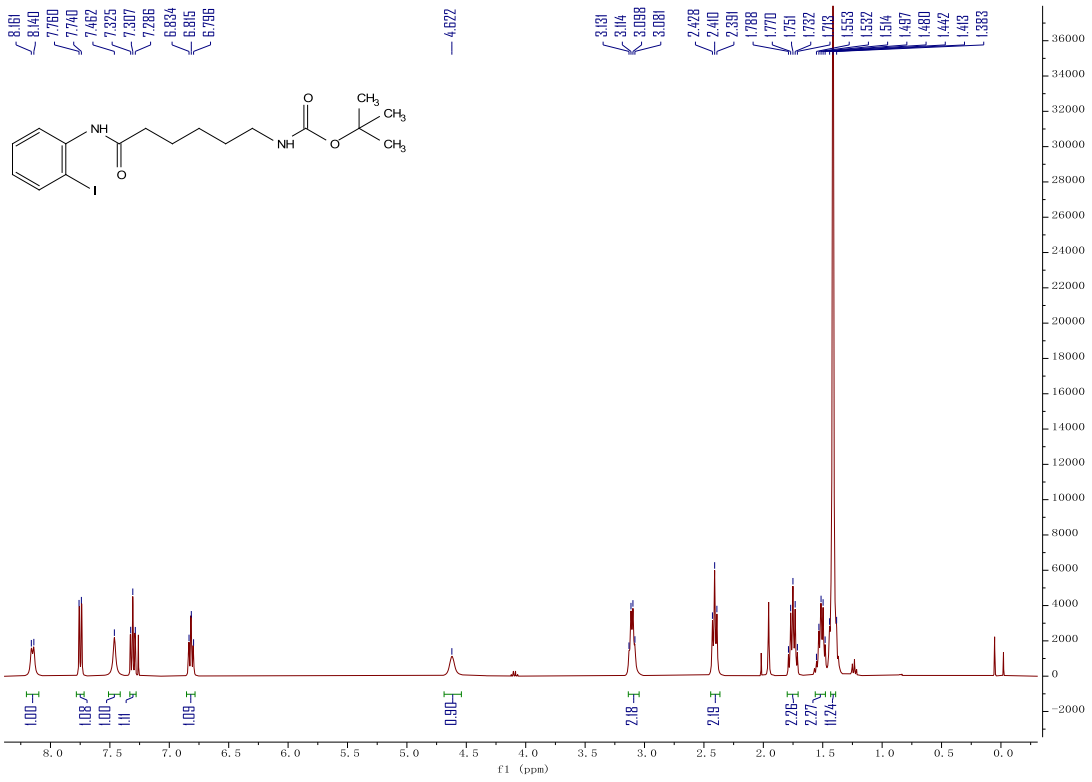
^{1}H NMR spectrum of compound 10b-Boc (600 MHz, $CDCl_3$)



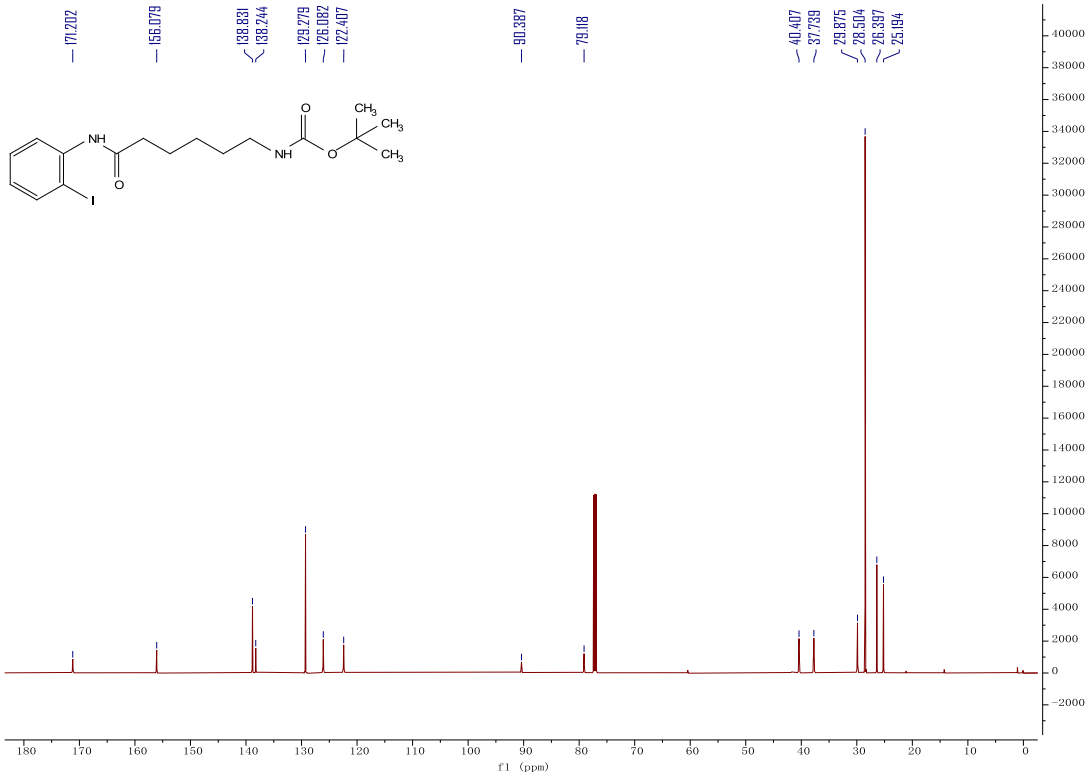
^{13}C NMR spectrum of compound 10b-Boc (150 MHz, $CDCl_3$)



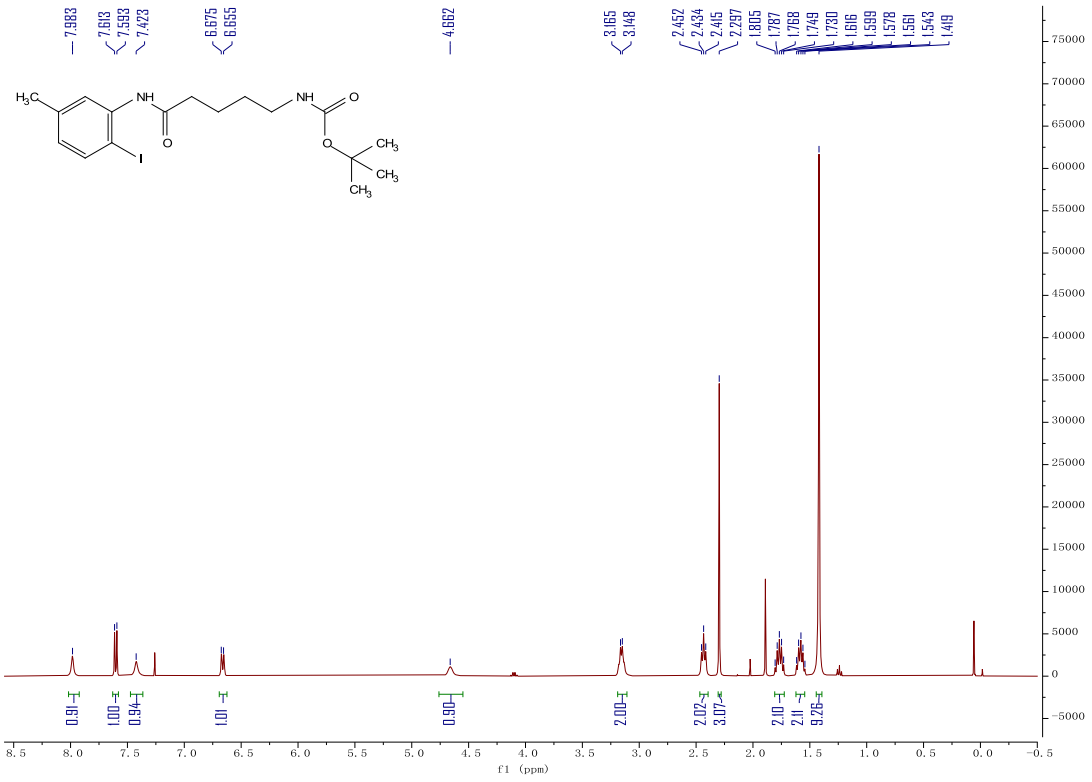
^{1}H NMR spectrum of compound 13b (400 MHz, $CDCl_3$)



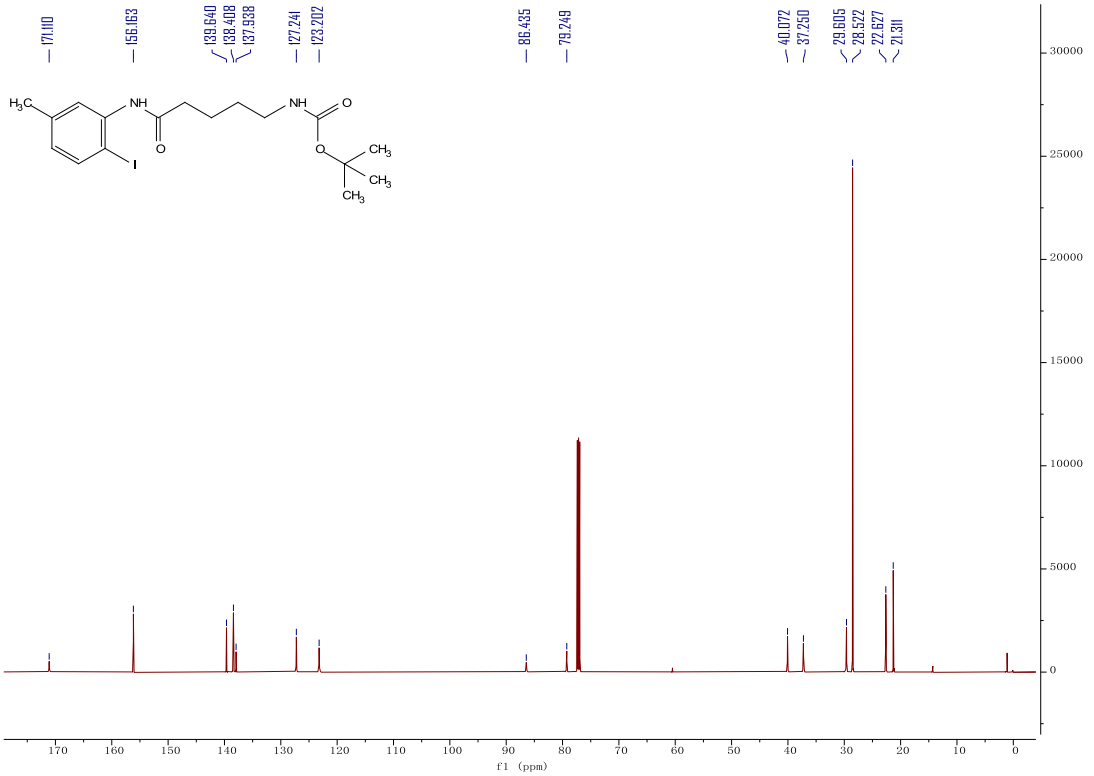
^{1}H NMR spectrum of compound 10c-Boc (400 MHz, $CDCl_3$)



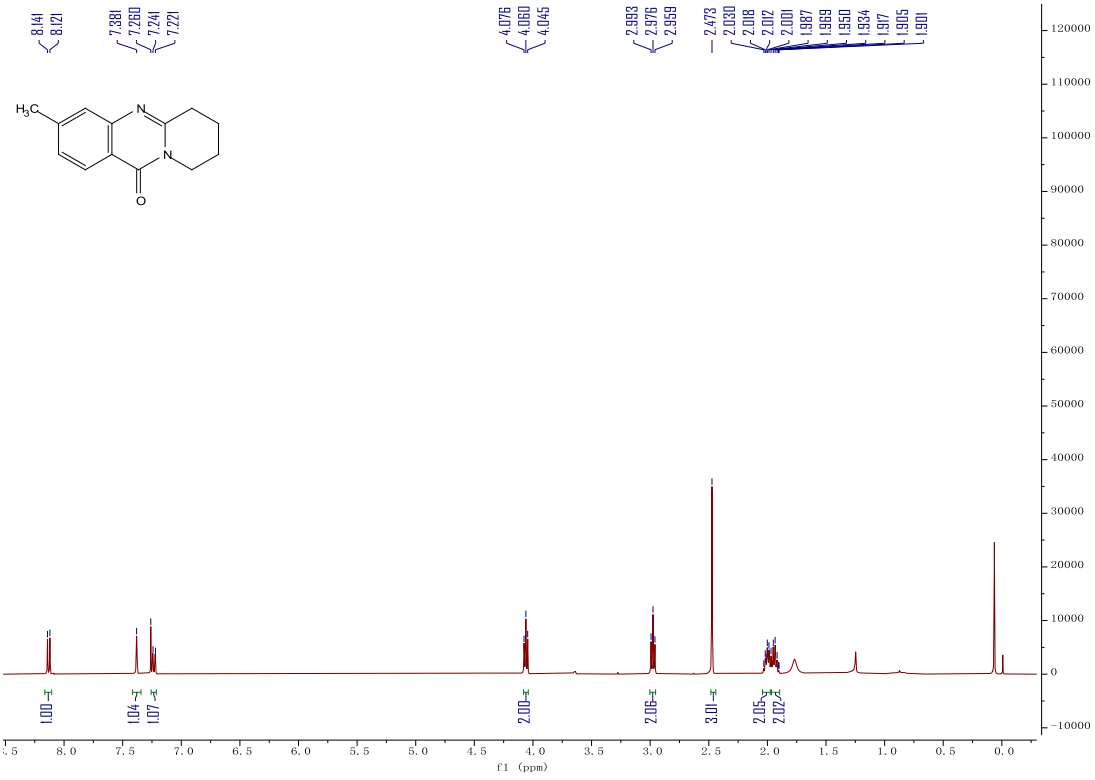
^{13}C NMR spectrum of compound 10c-Boc (150 MHz, $CDCl_3$)



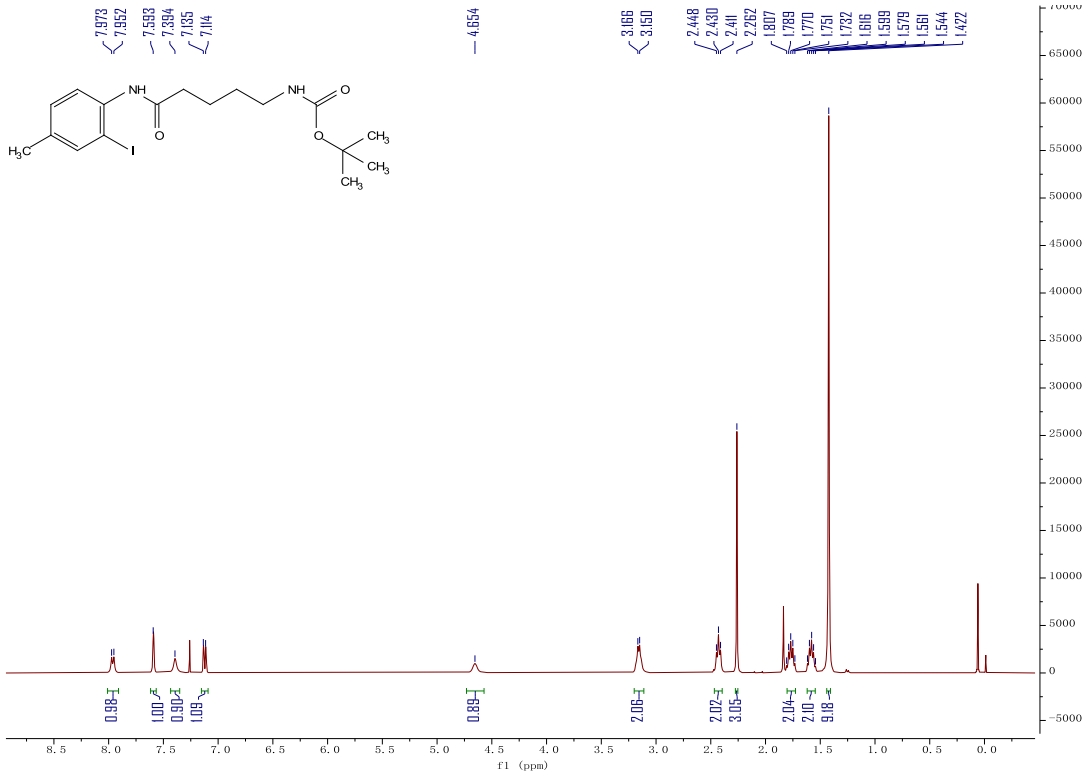
^{1}H NMR spectrum of compound 10d-Boc (400 MHz, $CDCl_3$)



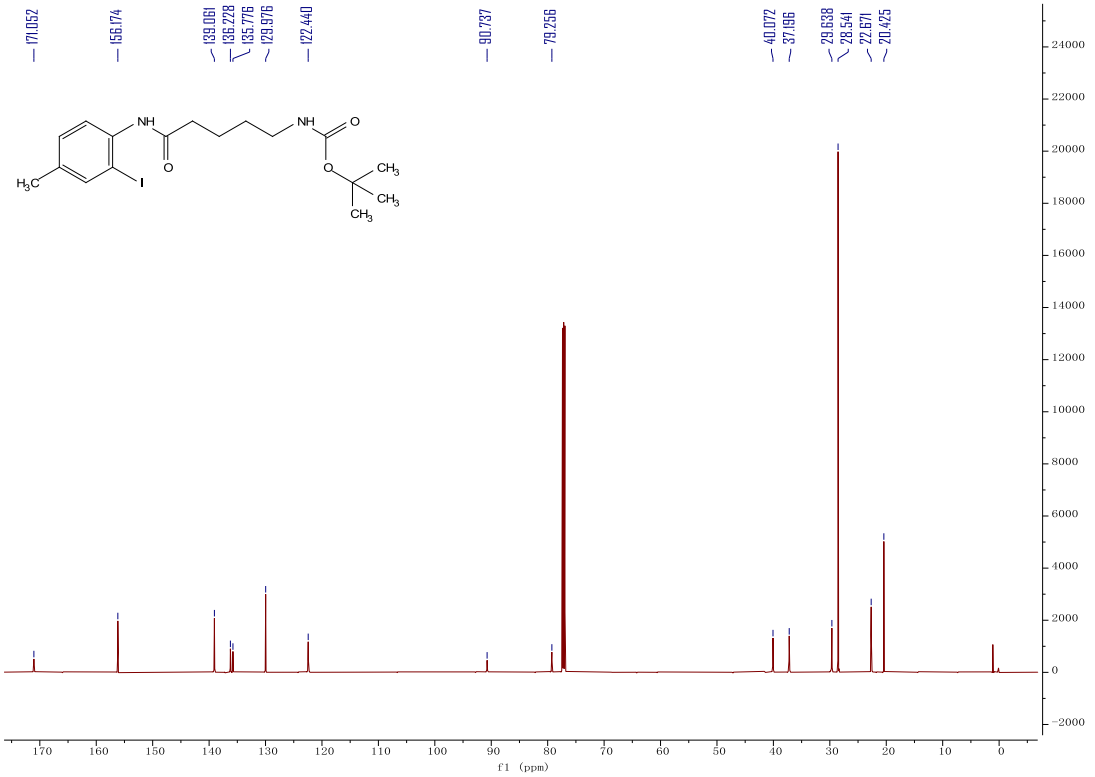
^{13}C NMR spectrum of compound 10d-Boc (150 MHz, $CDCl_3$)



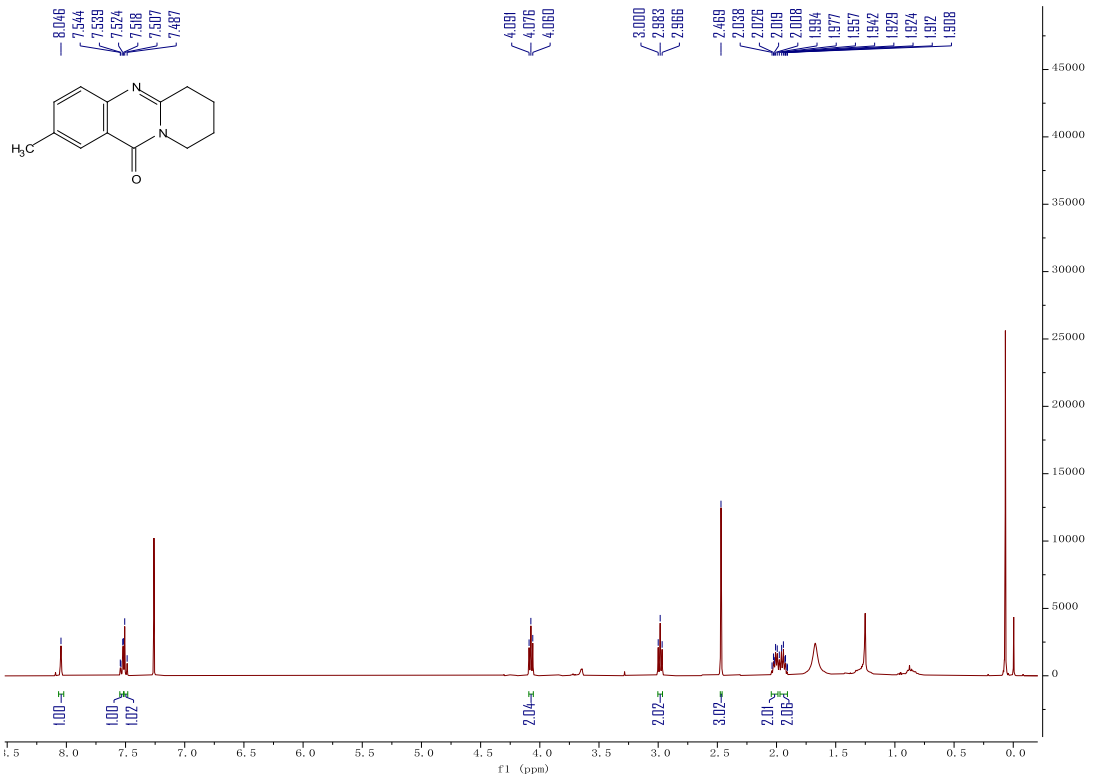
^{1}H NMR spectrum of compound 13d (400 MHz, $CDCl_3$)



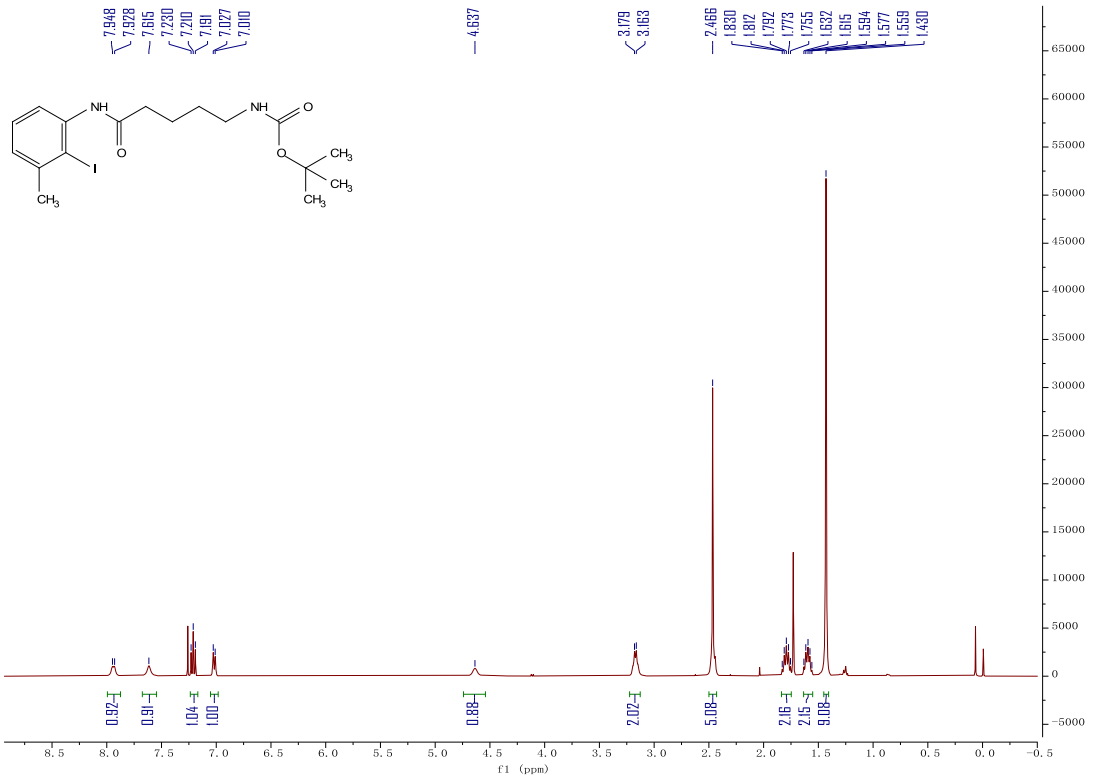
^{1}H NMR spectrum of compound 10e-Boc (400 MHz, $CDCl_3$)



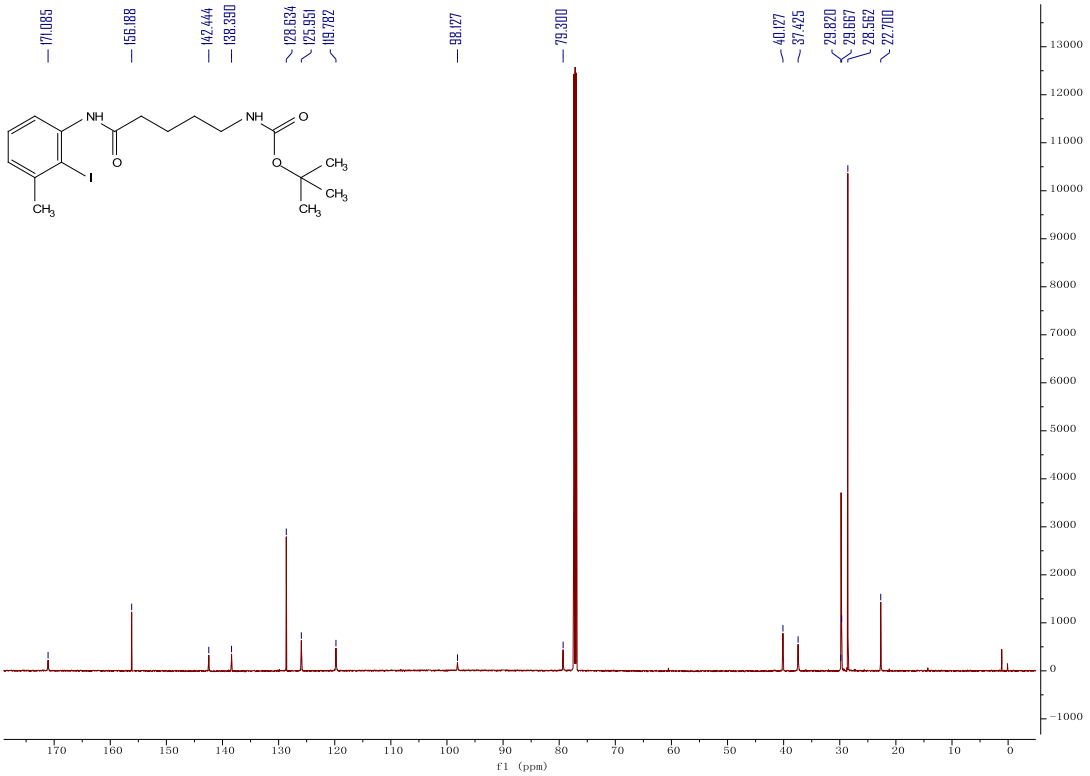
^{13}C NMR spectrum of compound 10e-Boc (150 MHz, $CDCl_3$)



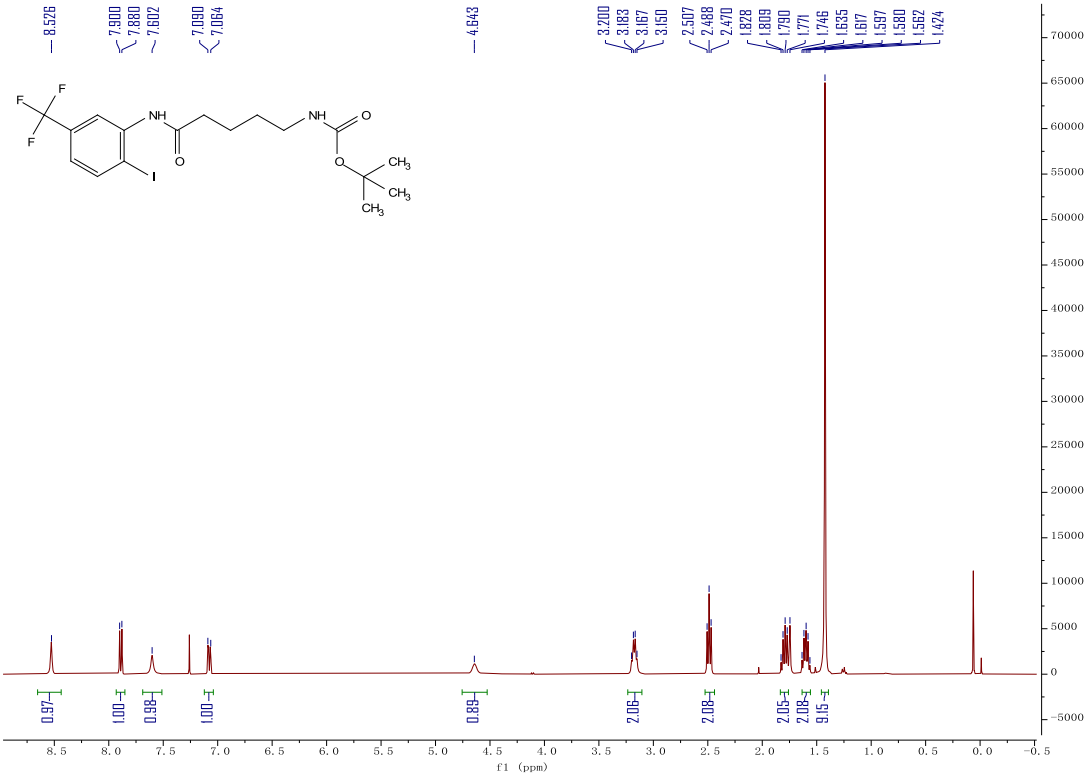
^{1}H NMR spectrum of compound 13e (400 MHz, $CDCl_3$)



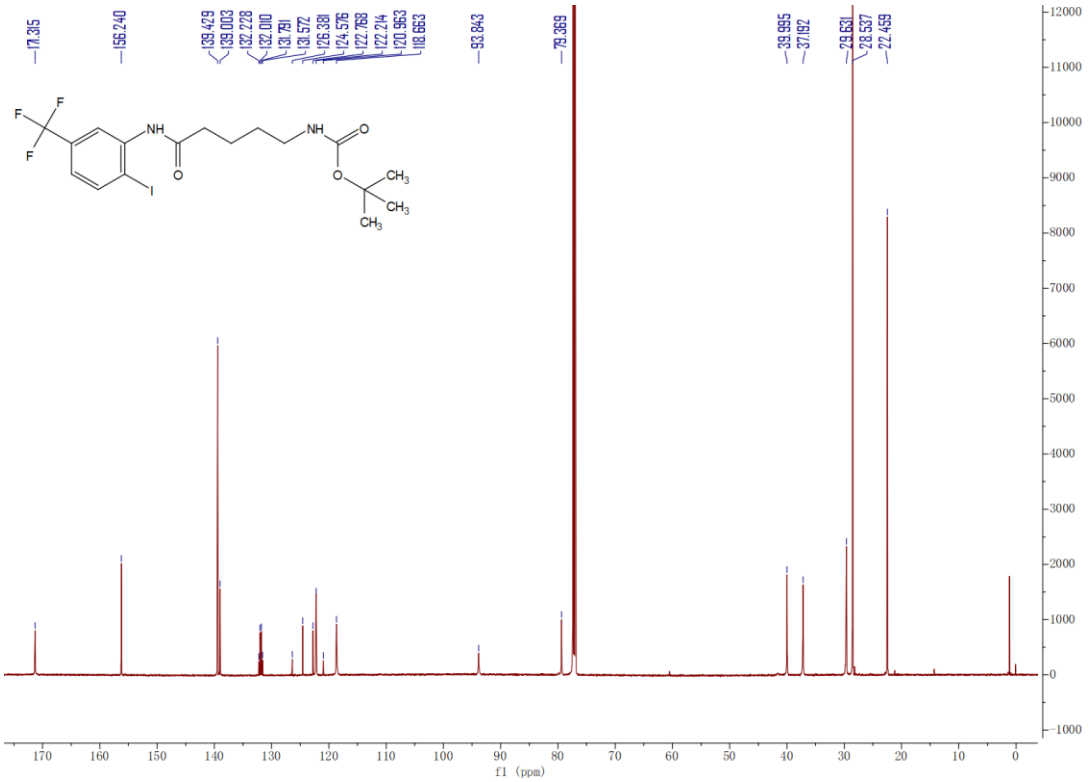
^{1}H NMR spectrum of compound 10f-Boc (400 MHz, $CDCl_3$)



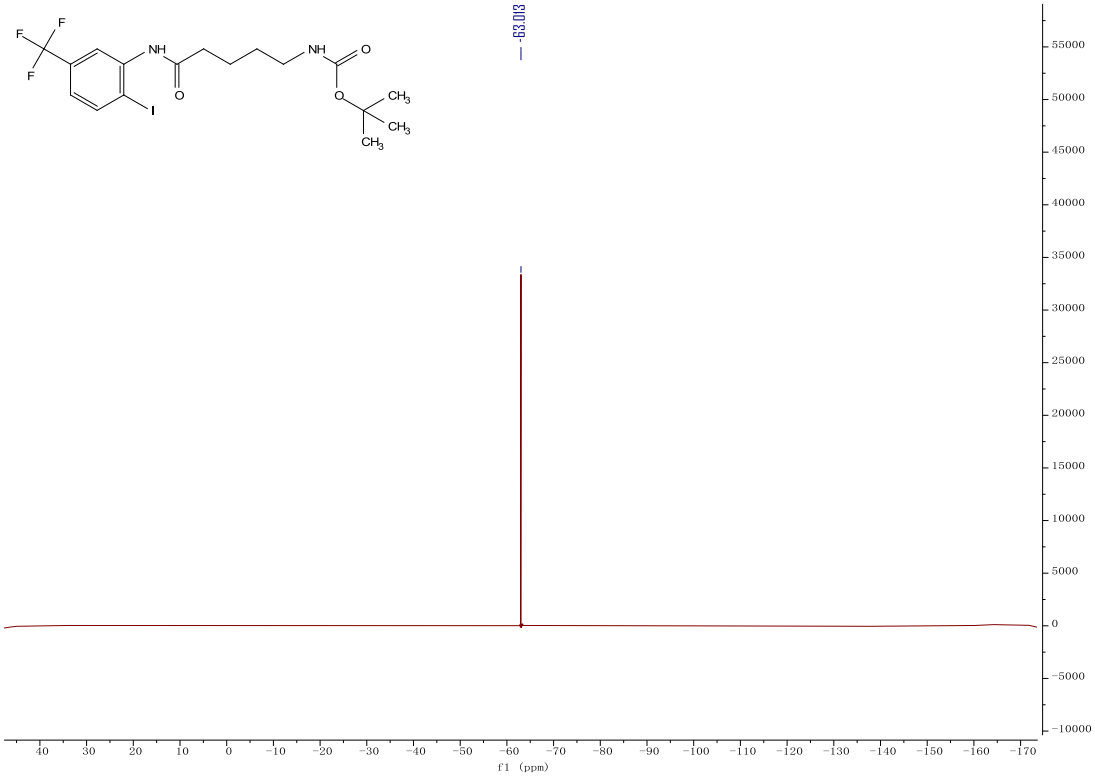
^{13}C NMR spectrum of compound 10f-Boc (150 MHz, $CDCl_3$)



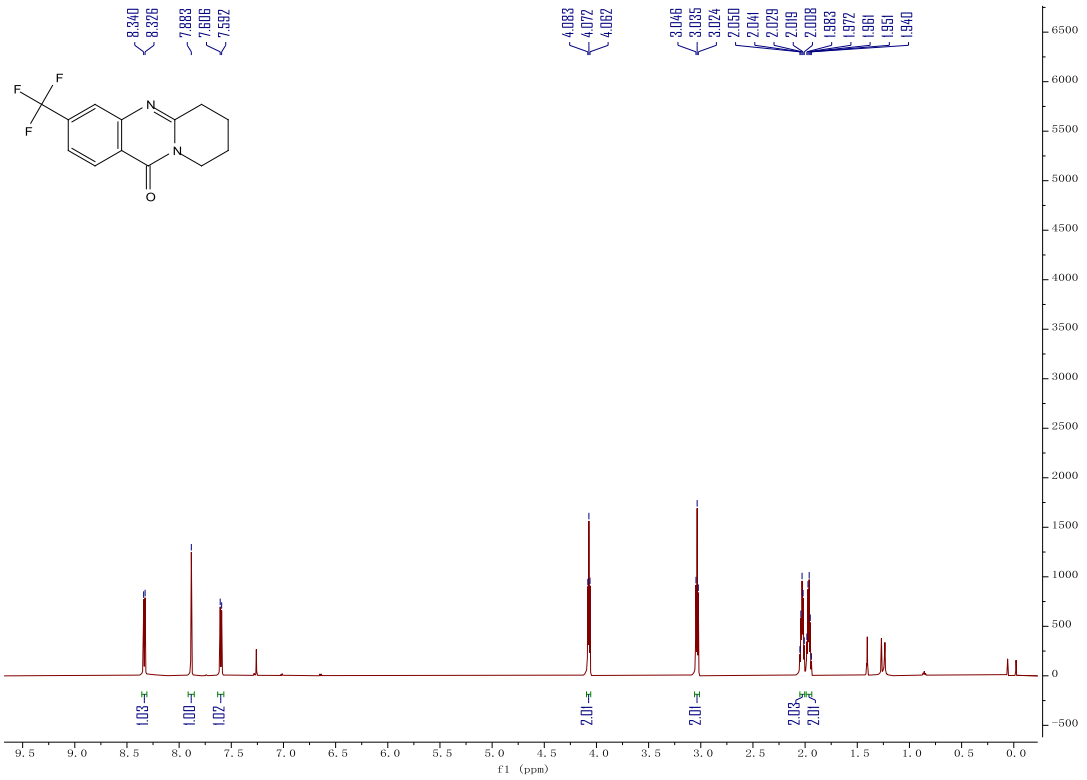
^{1}H NMR spectrum of compound 10g-Boc (400 MHz, $CDCl_3$)



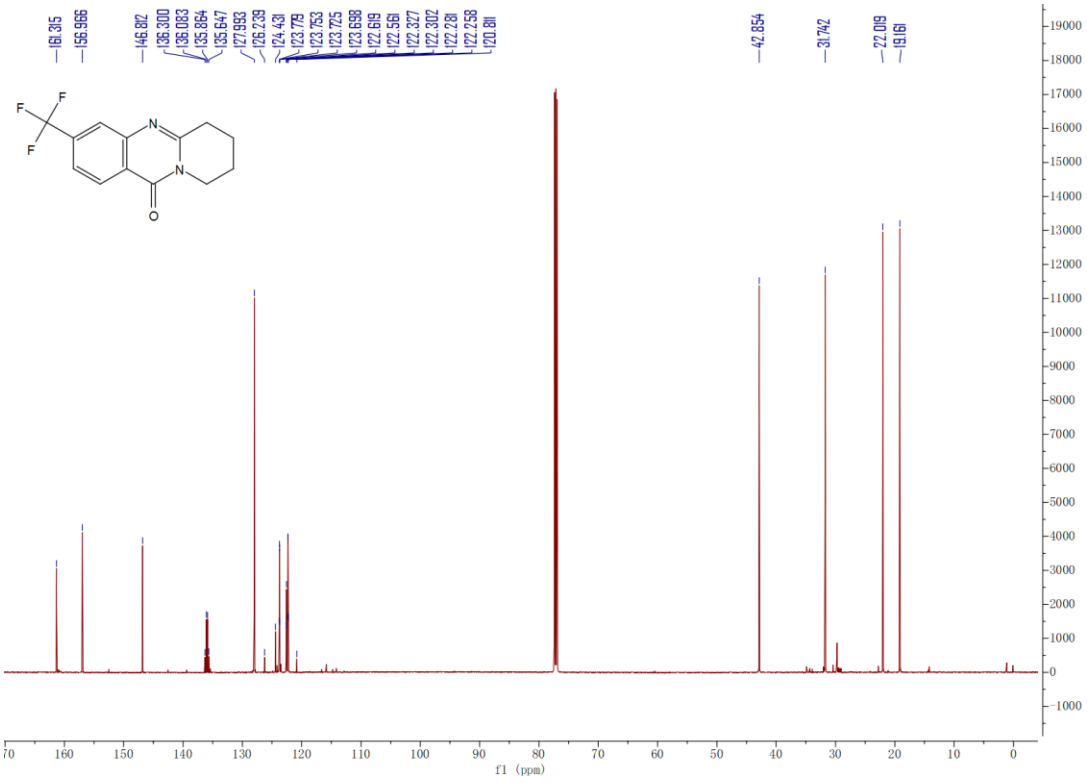
^{13}C NMR spectrum of compound 10g-Boc (150 MHz, $CDCl_3$)



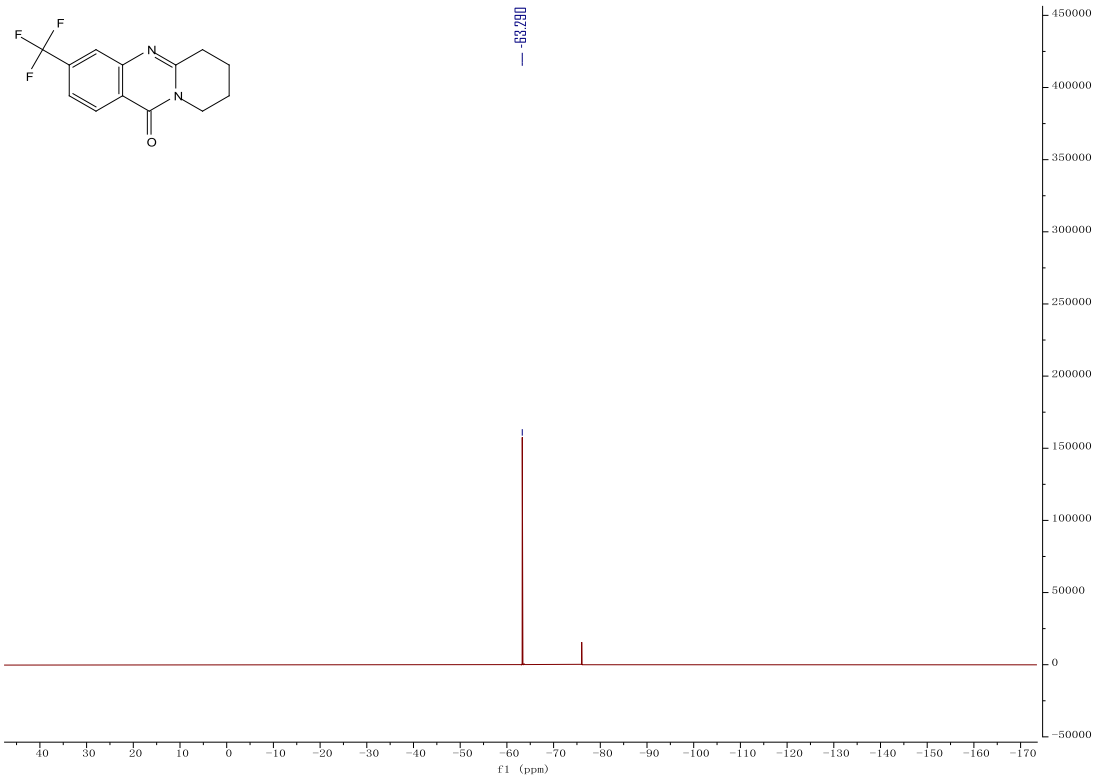
^{19}F NMR spectrum of compound 10g-Boc (565 MHz, $CDCl_3$)



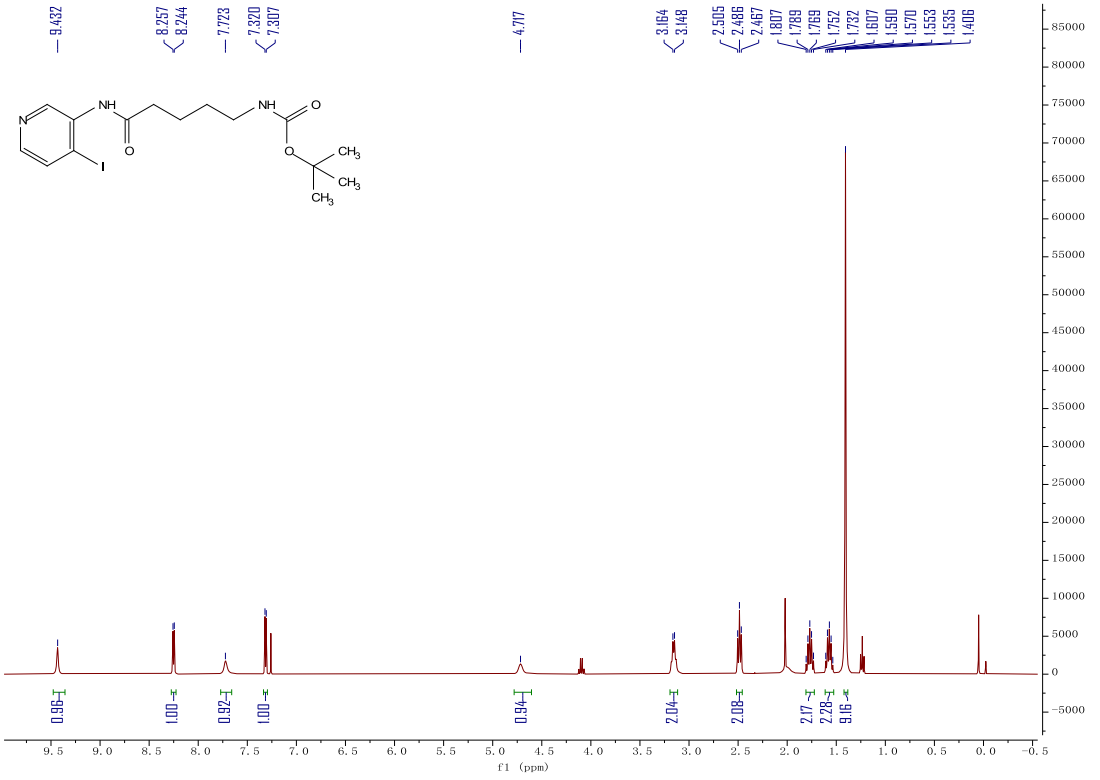
^{1}H NMR spectrum of compound 13g (600 MHz, $CDCl_3$)



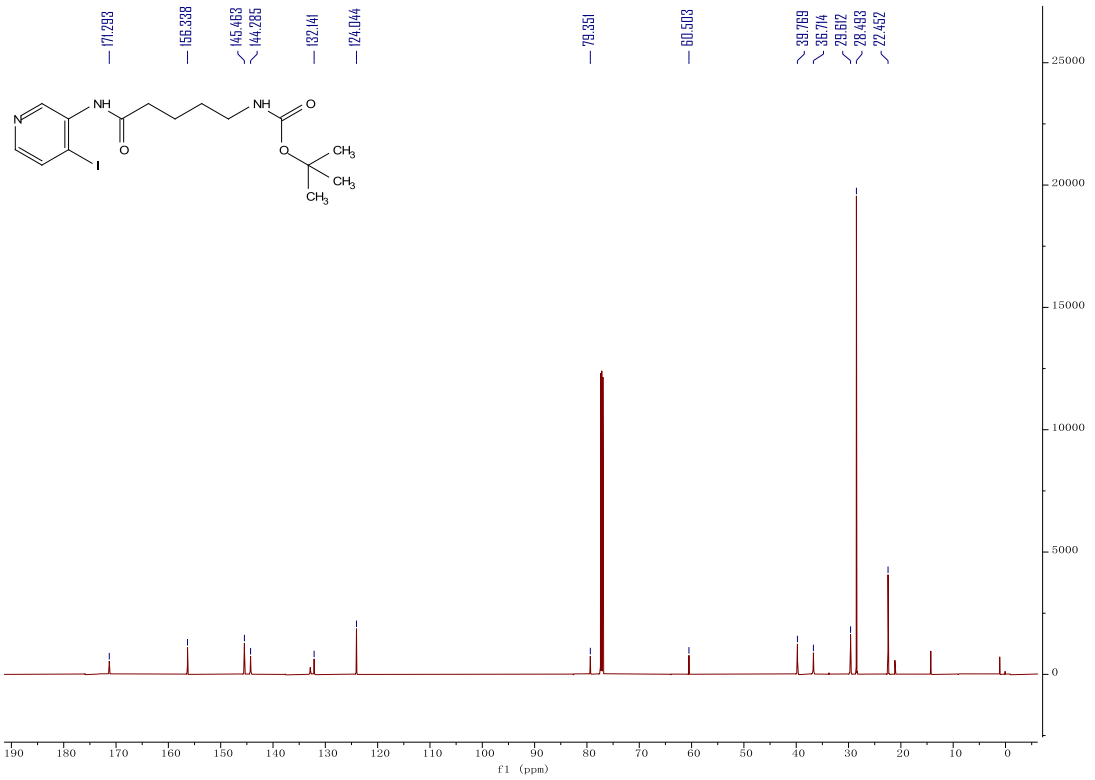
^{13}C NMR spectrum of compound 13g (150 MHz, $CDCl_3$)



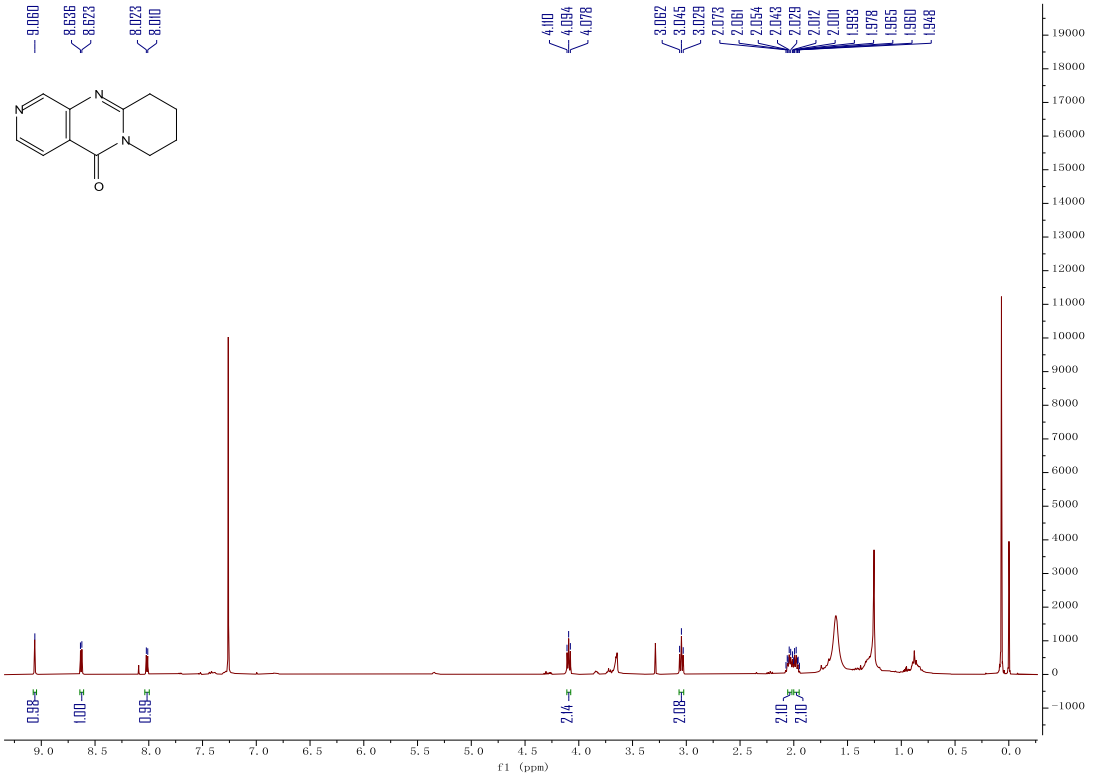
^{19}F NMR spectrum of compound 13g (565 MHz, $CDCl_3$)



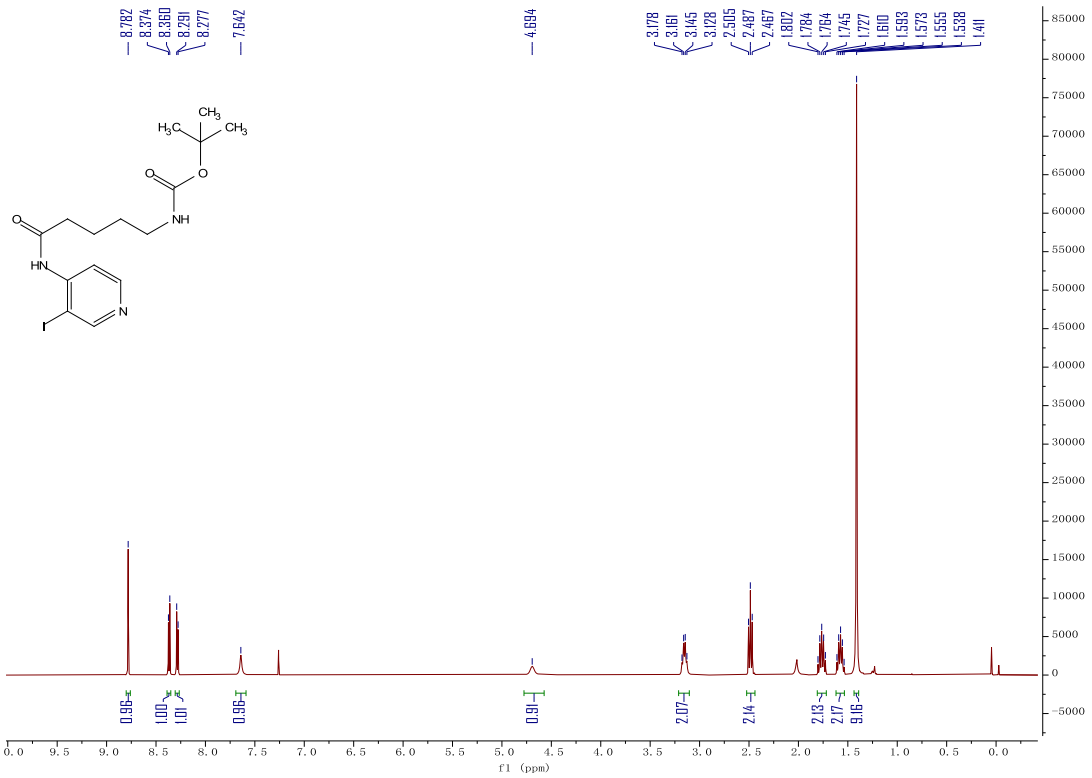
^{1}H NMR spectrum of compound 10h-Boc (400 MHz, $CDCl_3$)



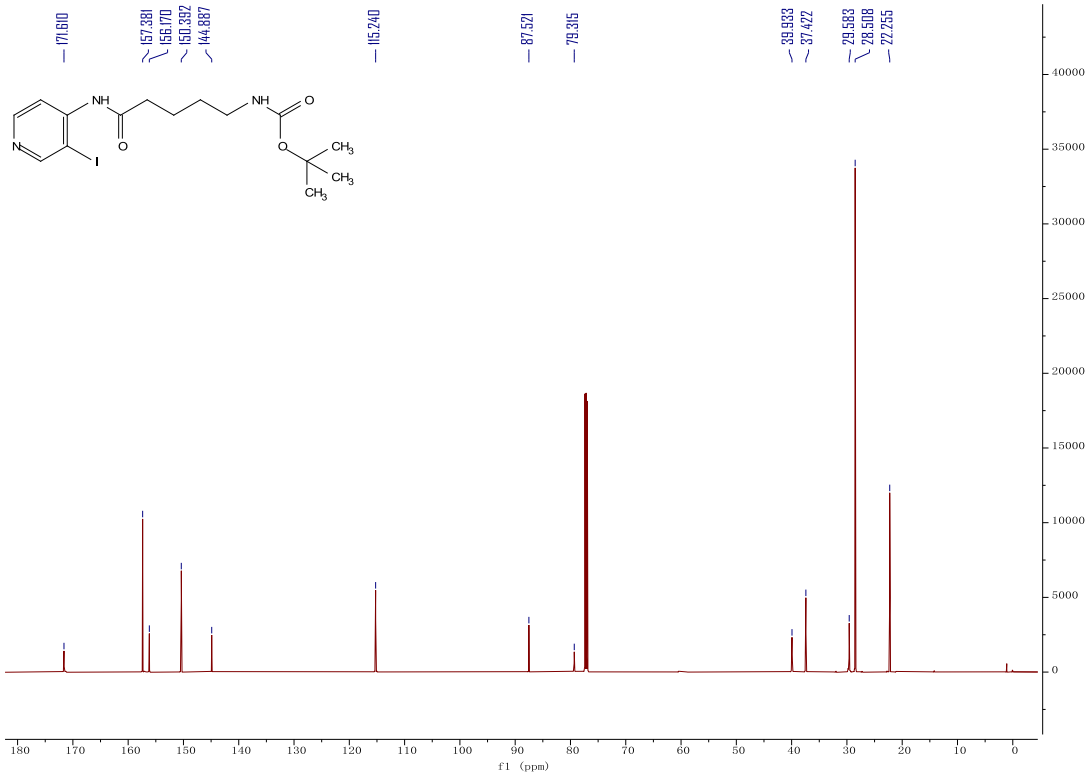
^{13}C NMR spectrum of compound 10h-Boc (150 MHz, $CDCl_3$)



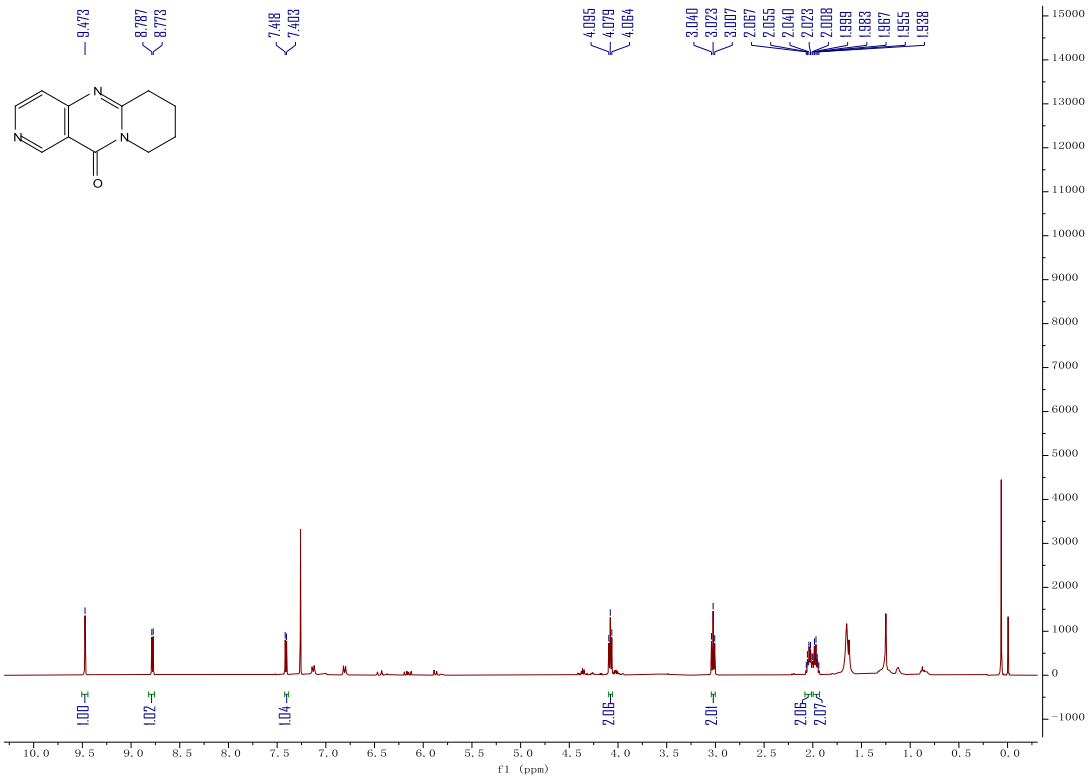
^{1}H NMR spectrum of compound 13h (400 MHz, $CDCl_3$)



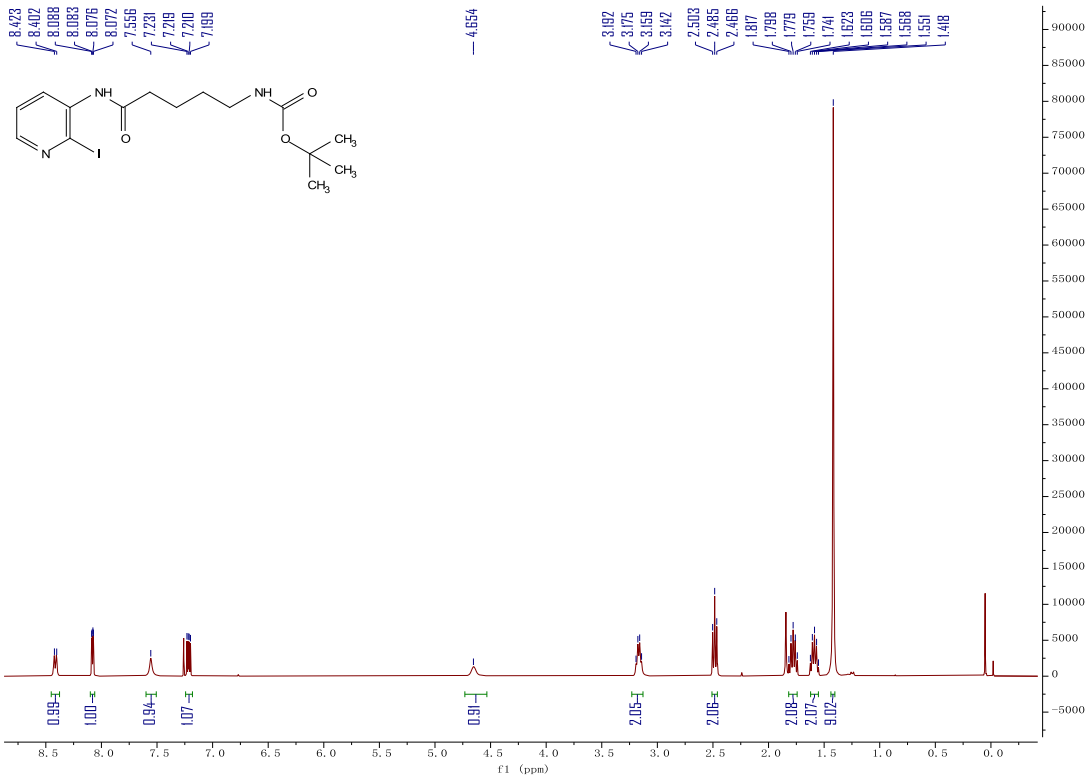
^{1}H NMR spectrum of compound 10i-Boc (400 MHz, $CDCl_3$)



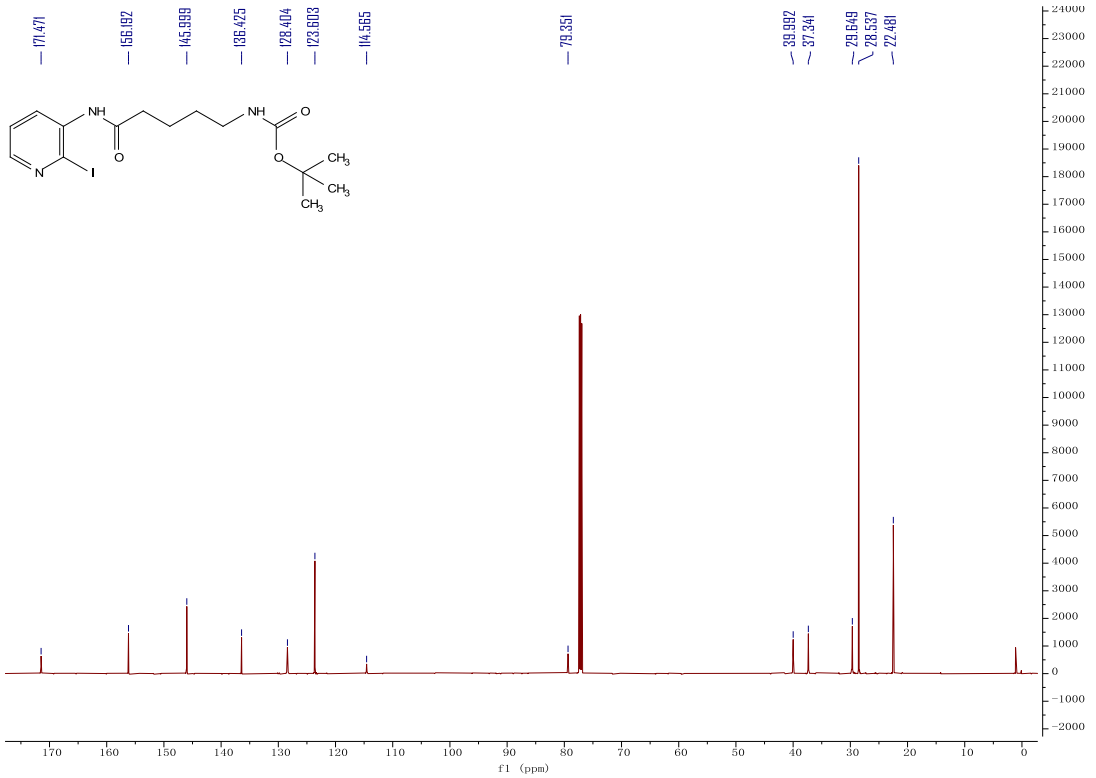
^{13}C NMR spectrum of compound 10i-Boc (150 MHz, $CDCl_3$)



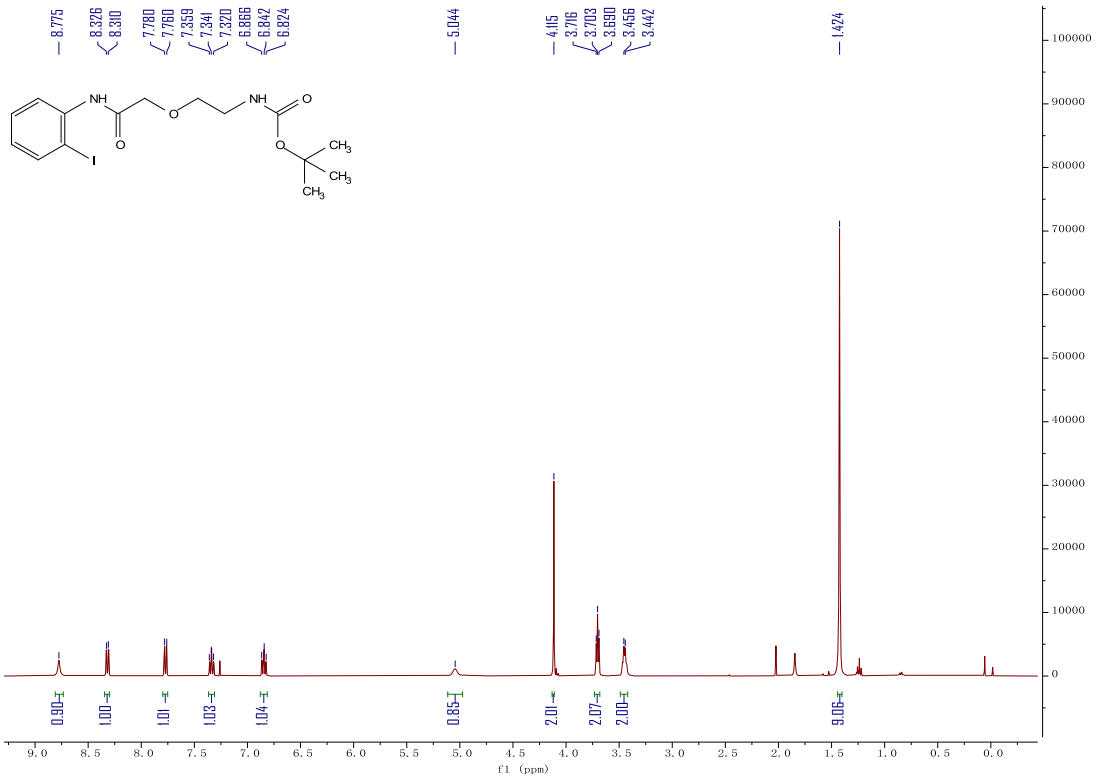
^{1}H NMR spectrum of compound 13i (400 MHz, $CDCl_3$)



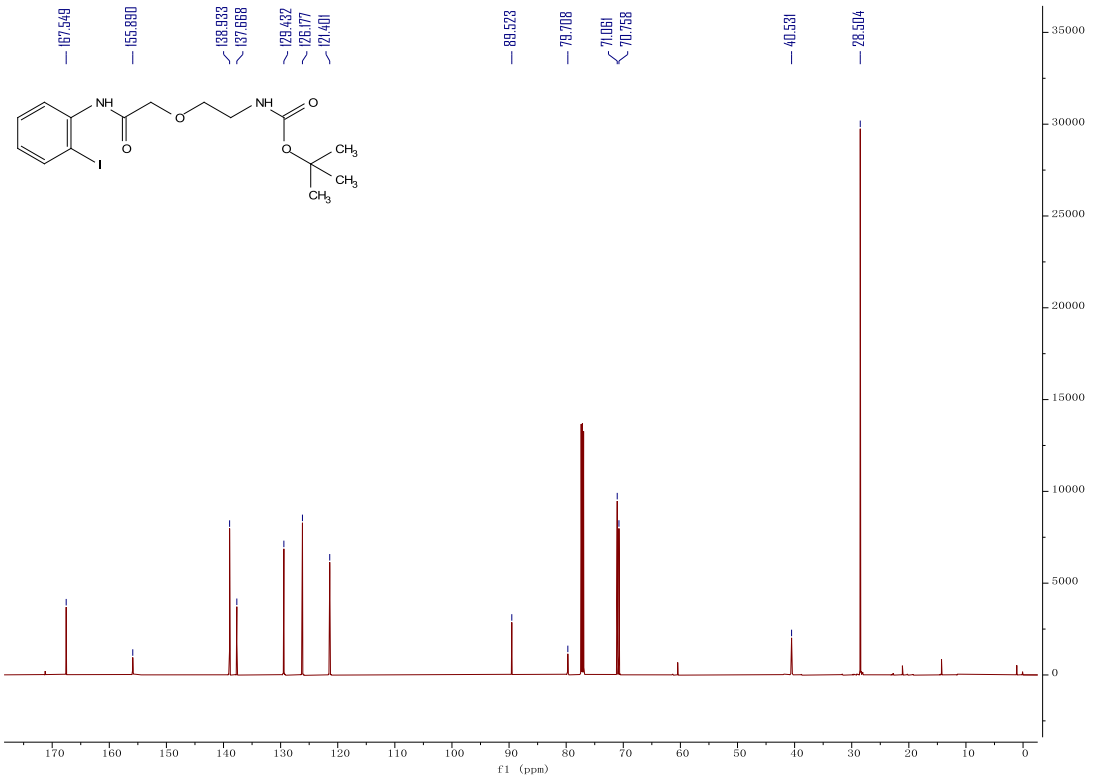
^{1}H NMR spectrum of compound 10j-Boc (400 MHz, $CDCl_3$)



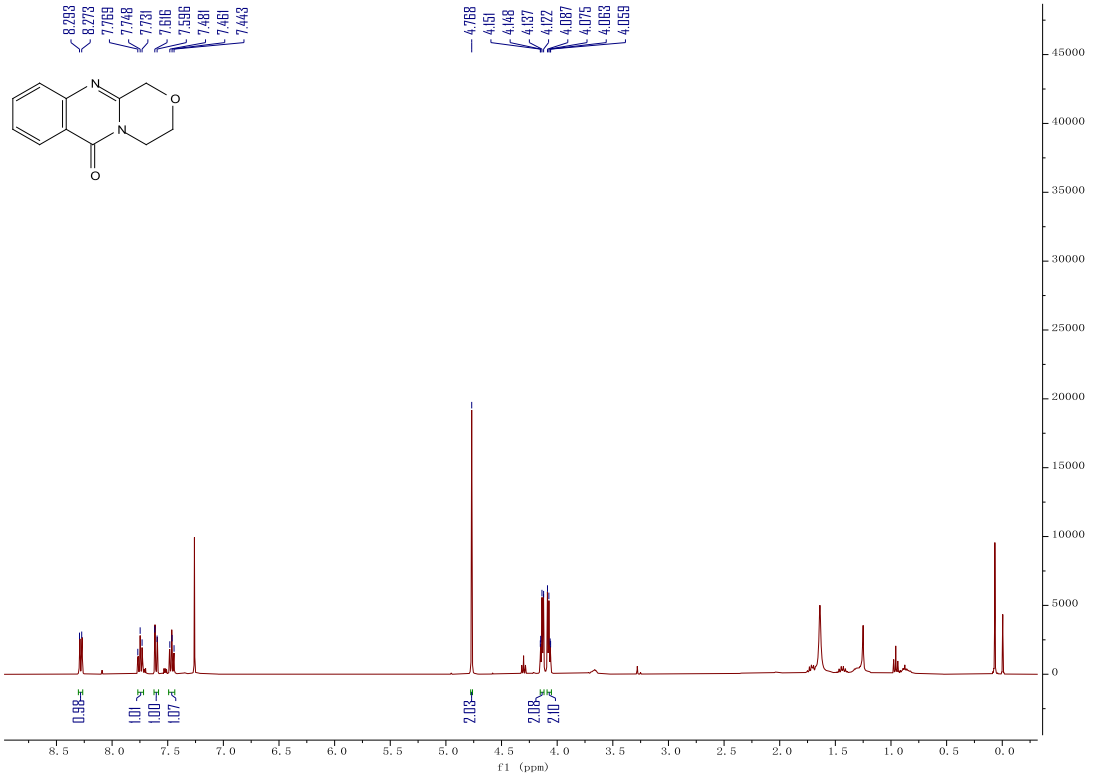
^{13}C NMR spectrum of compound 10j-Boc (150 MHz, $CDCl_3$)



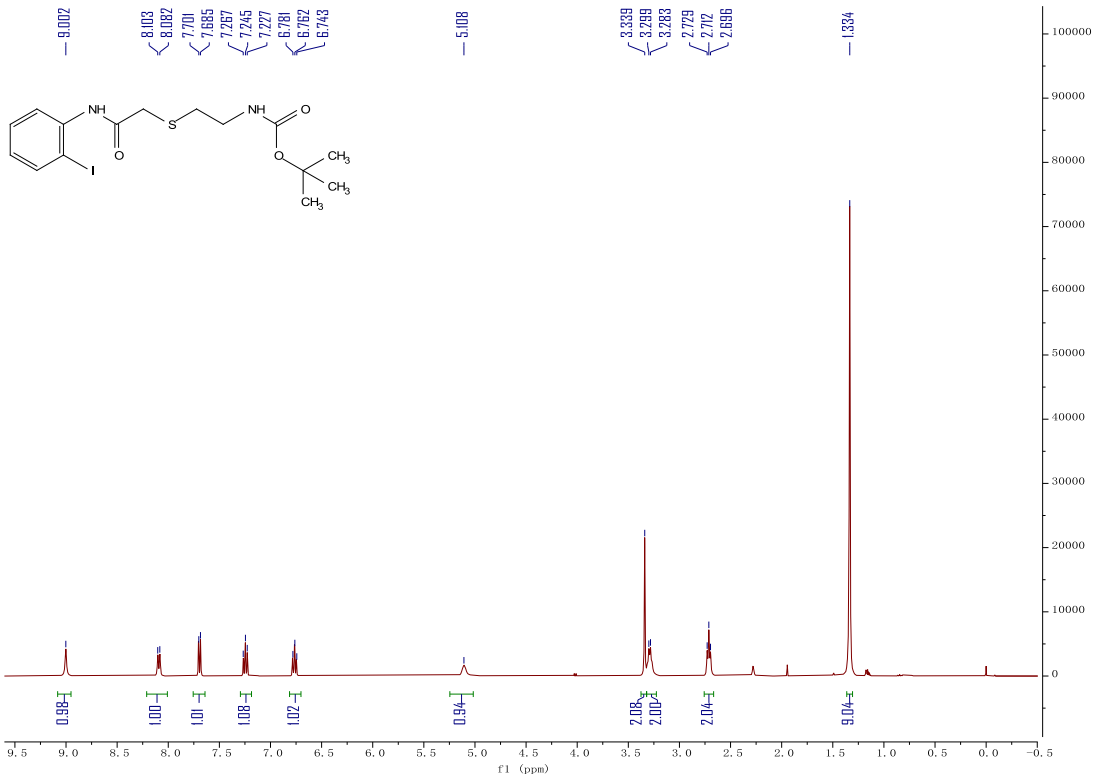
^{1}H NMR spectrum of compound 10k-Boc (400 MHz, $CDCl_3$)



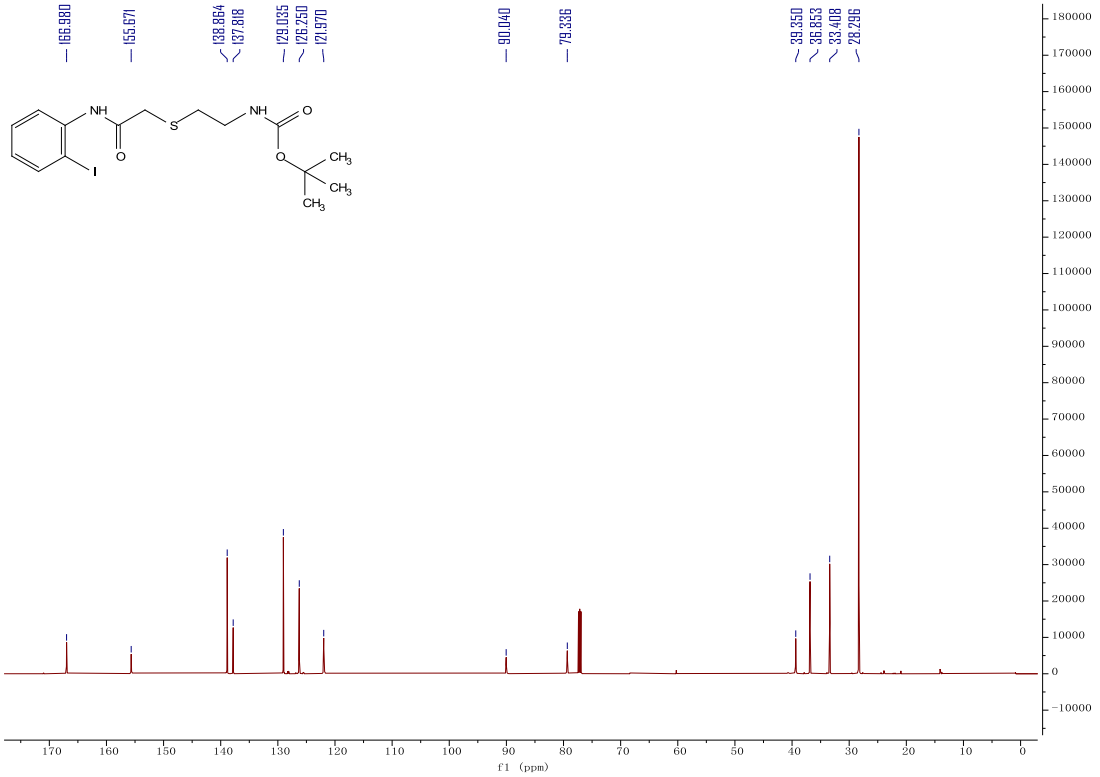
^{13}C NMR spectrum of compound 10k-Boc (150 MHz, $CDCl_3$)



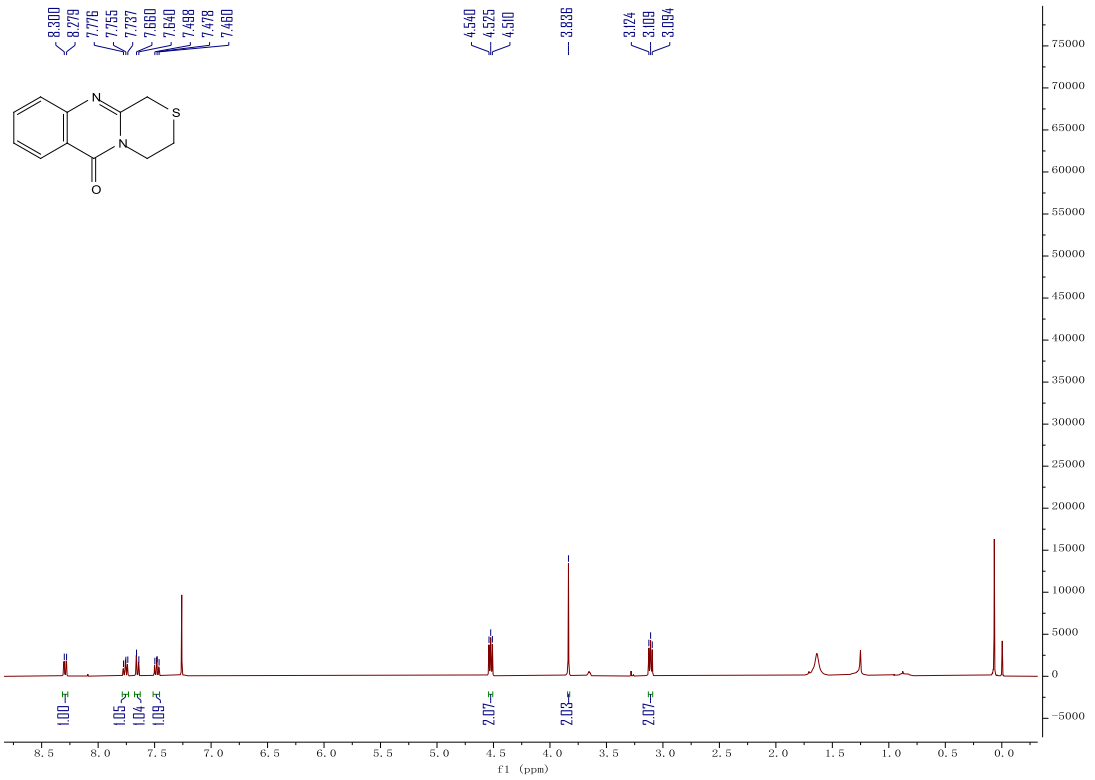
^{1}H NMR spectrum of compound 13k (400 MHz, $CDCl_3$)



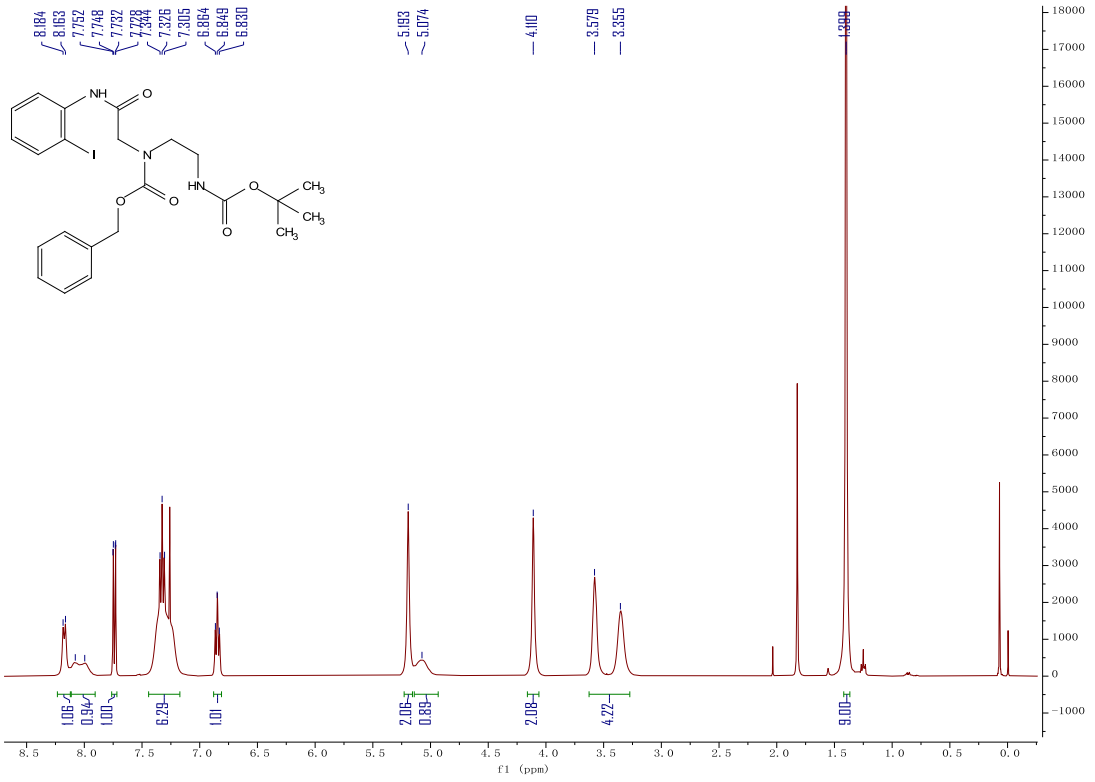
^{1}H NMR spectrum of compound 10l-Boc (400 MHz, $CDCl_3$)



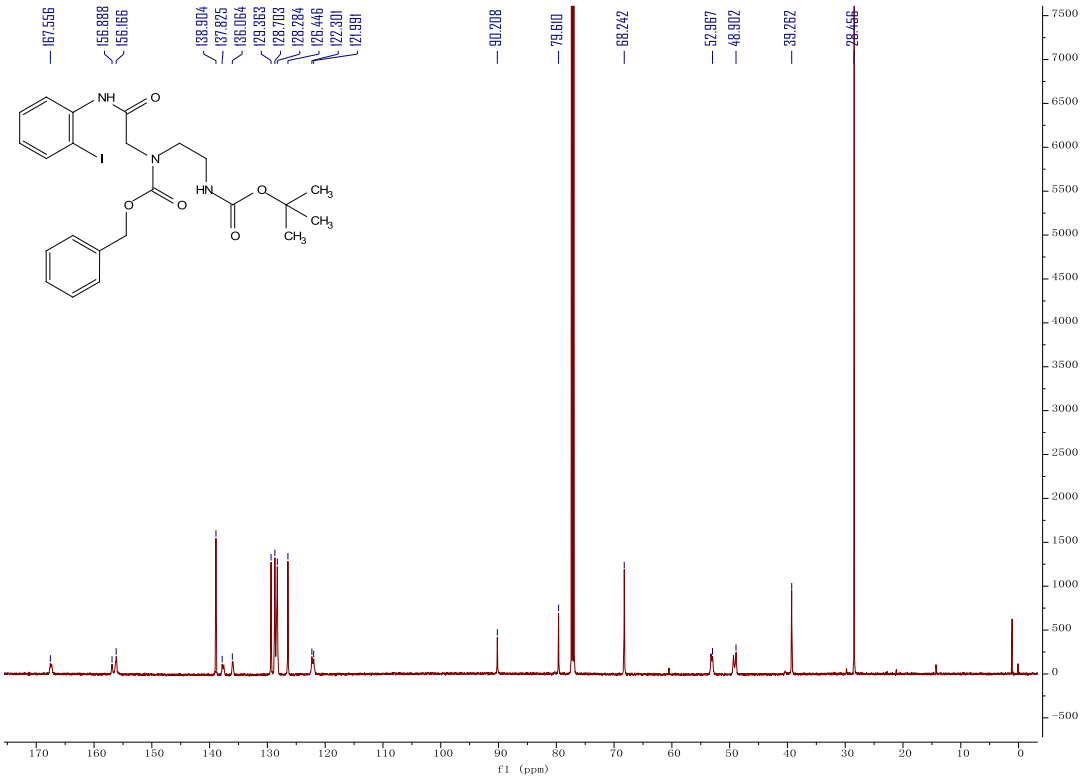
^{13}C NMR spectrum of compound 10l-Boc (150 MHz, $CDCl_3$)



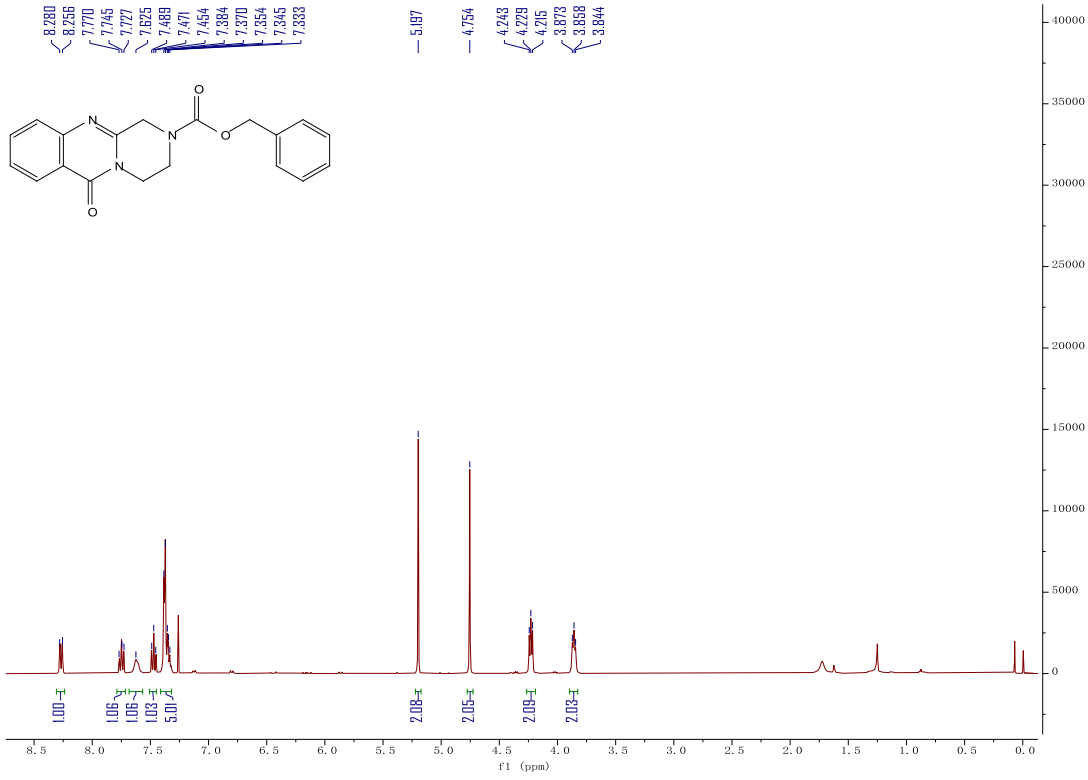
^{1}H NMR spectrum of compound 13l (400 MHz, $CDCl_3$)



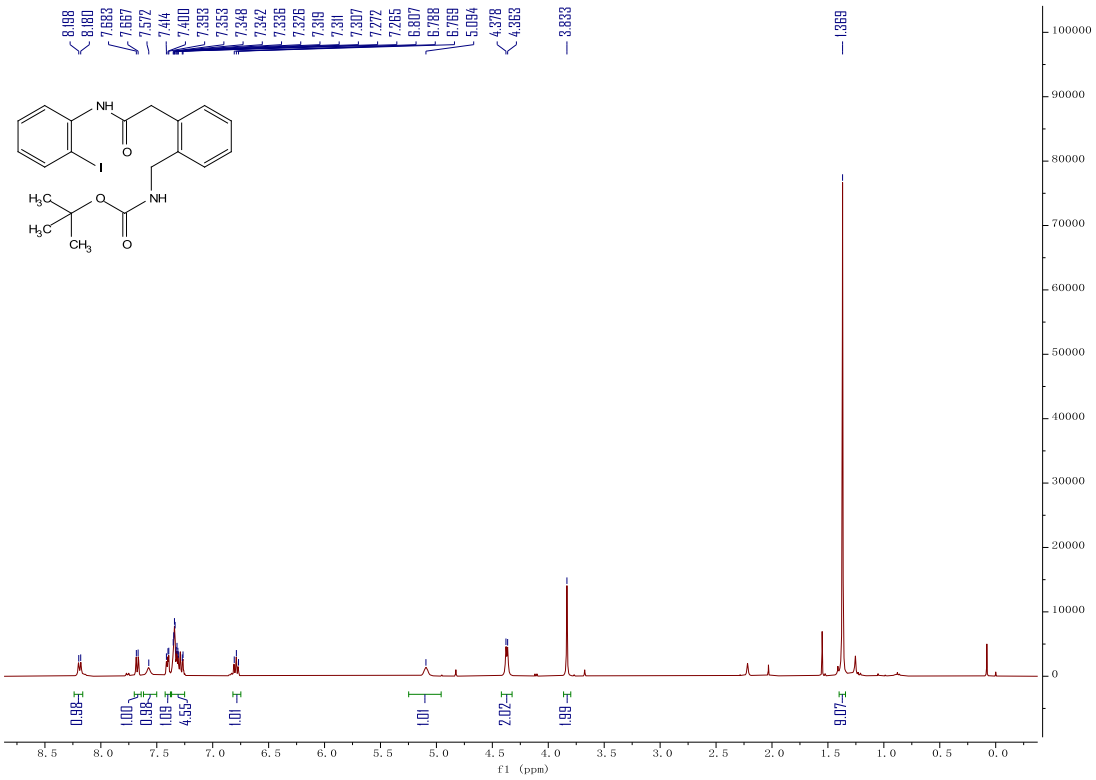
^{1}H NMR spectrum of compound 10m-Boc (600 MHz, $CDCl_3$)



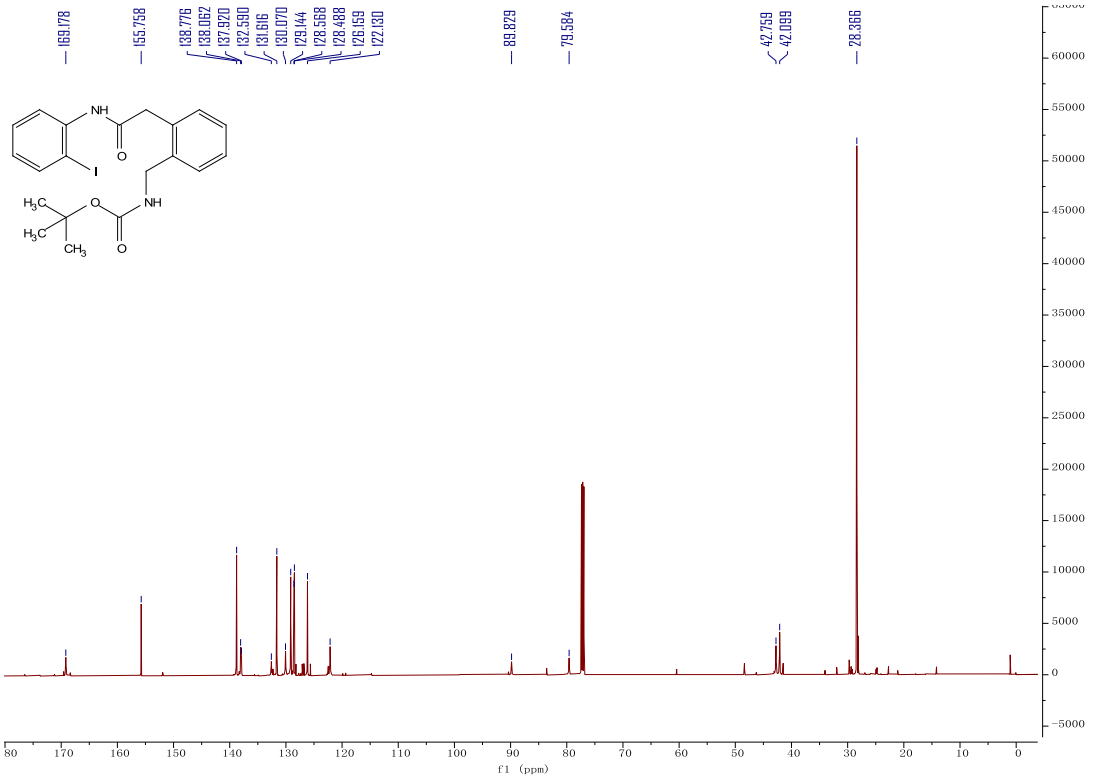
^{13}C NMR spectrum of compound 10m-Boc (150 MHz, $CDCl_3$)



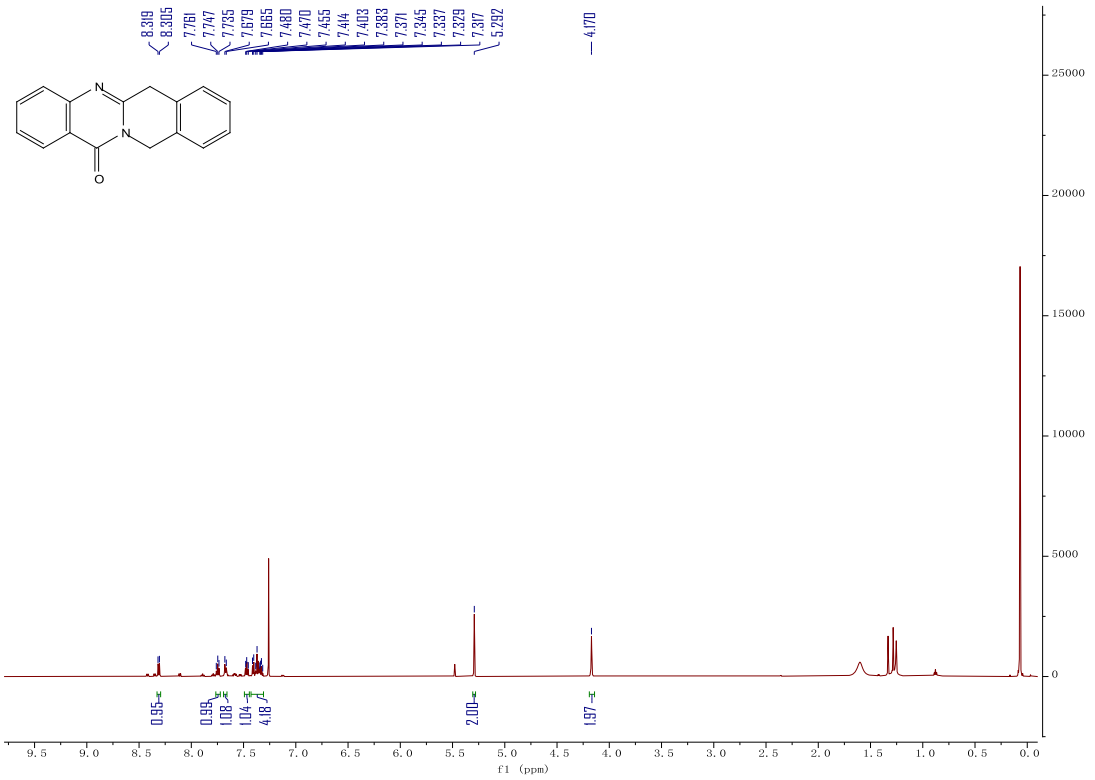
^{1}H NMR spectrum of compound 13m (400 MHz, $CDCl_3$)



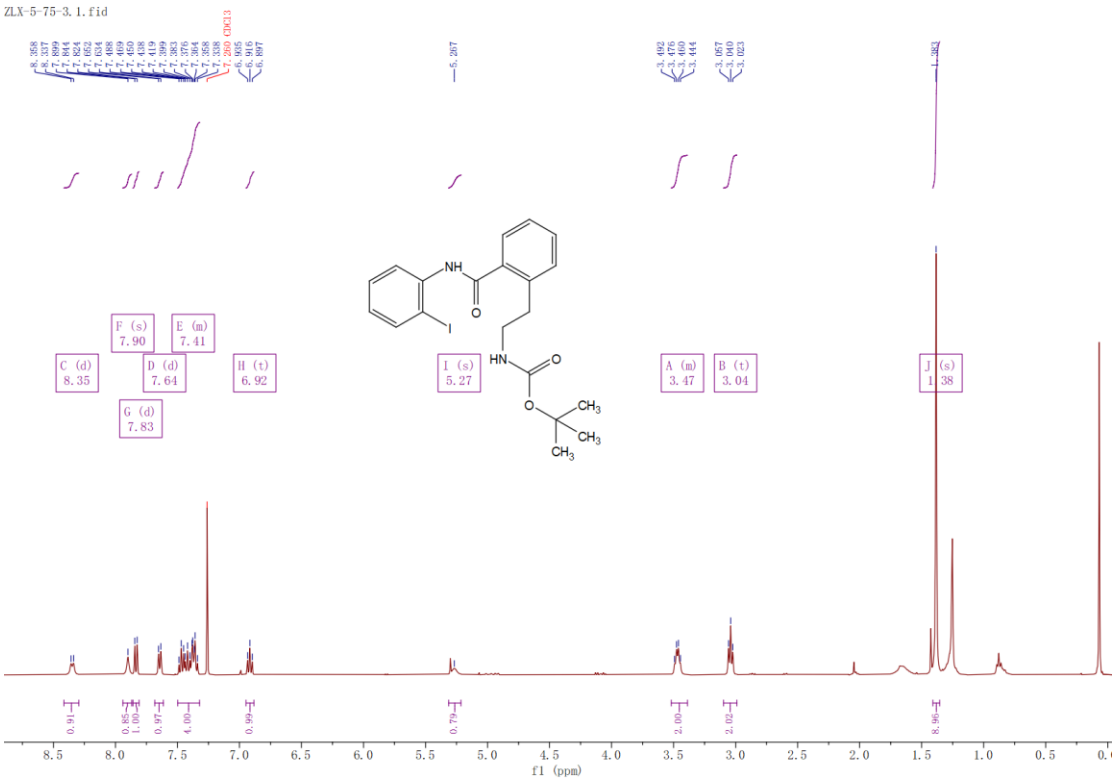
^{1}H NMR spectrum of compound 10n-Boc (400 MHz, $CDCl_3$)



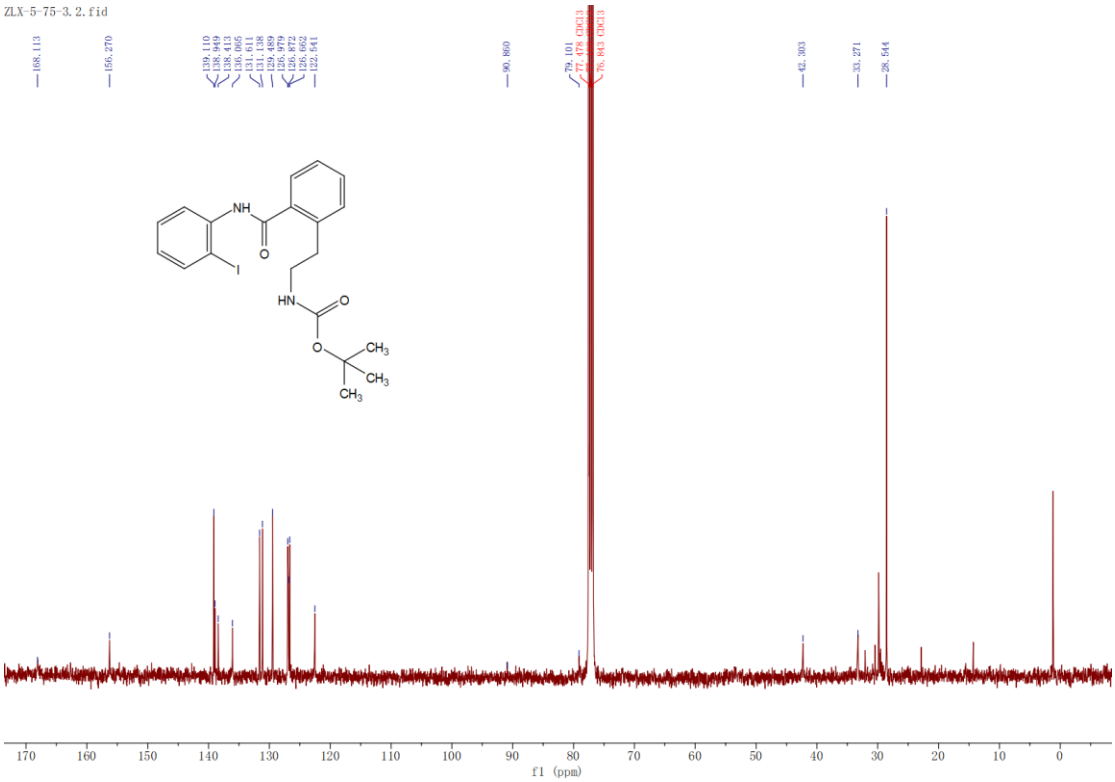
^{13}C NMR spectrum of compound 10n-Boc (150 MHz, $CDCl_3$)



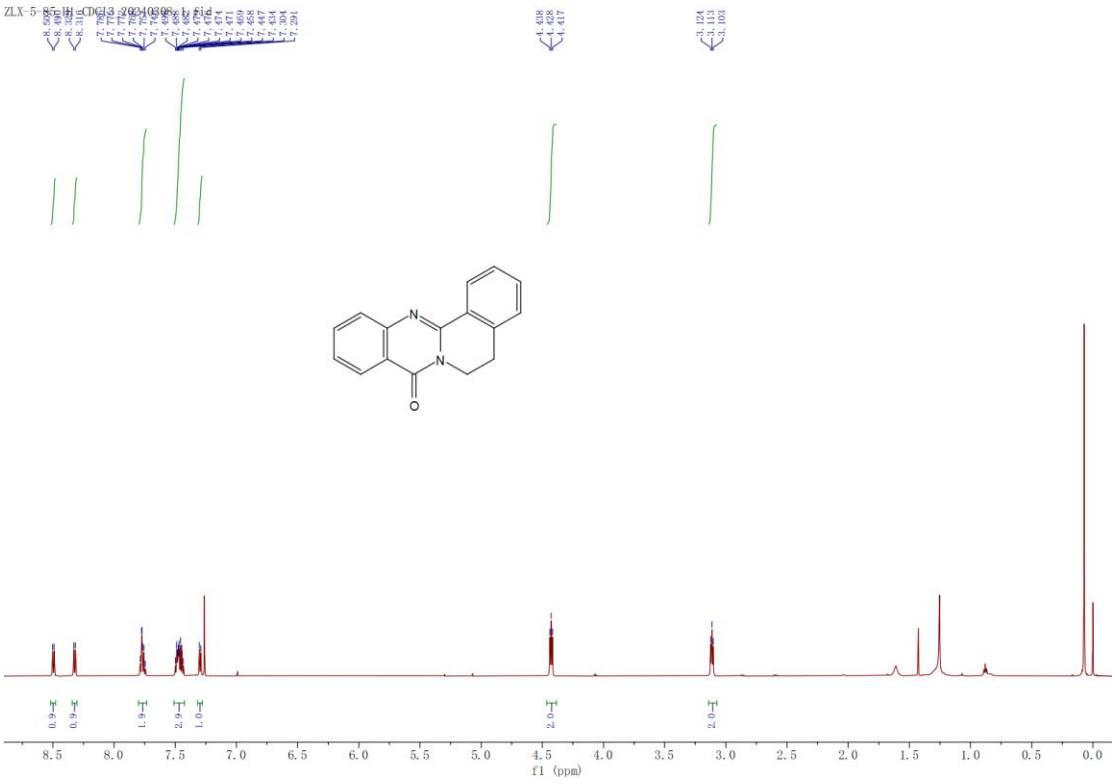
^{1}H NMR spectrum of compound 13n (600 MHz, $CDCl_3$)



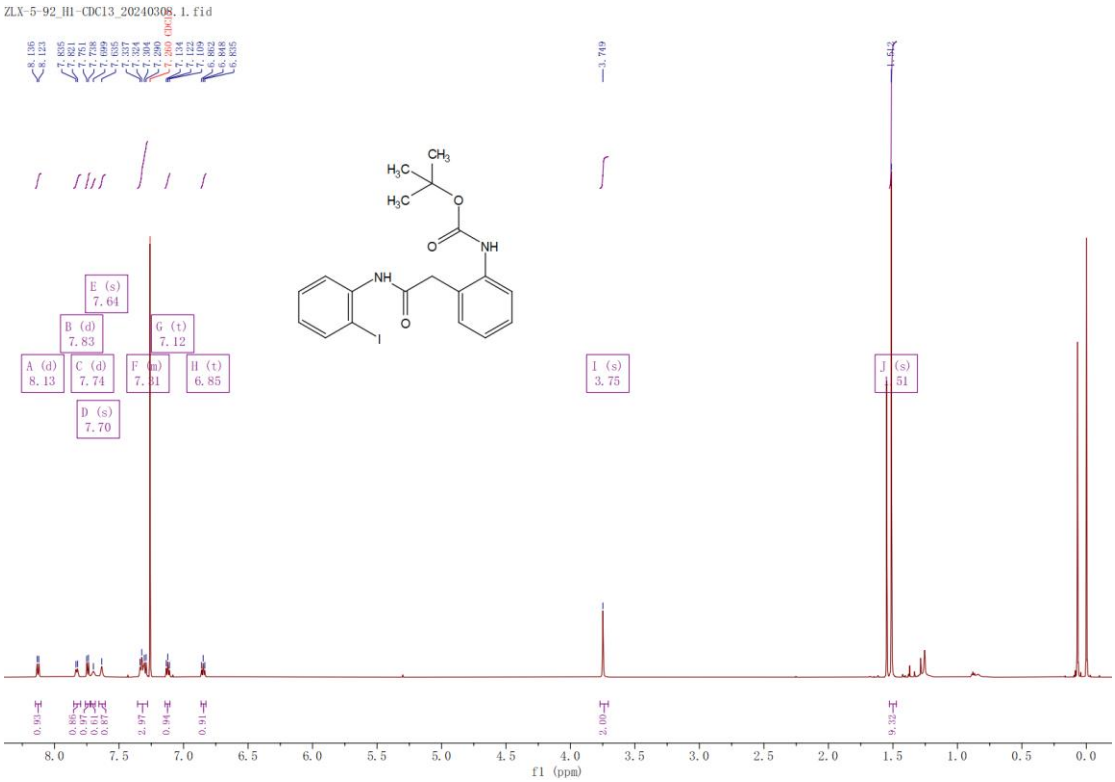
^{1}H NMR spectrum of compound 10o-Boc (400 MHz, $CDCl_3$)



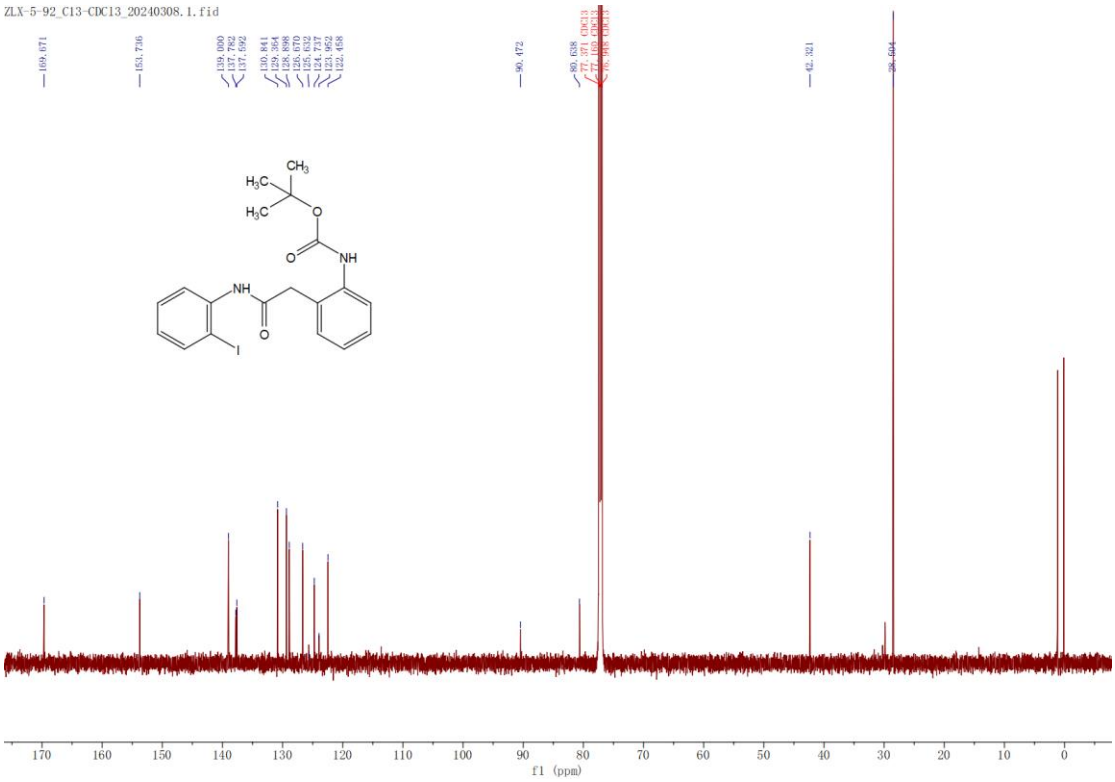
^{13}C NMR spectrum of compound 10o-Boc (100 MHz, $CDCl_3$)



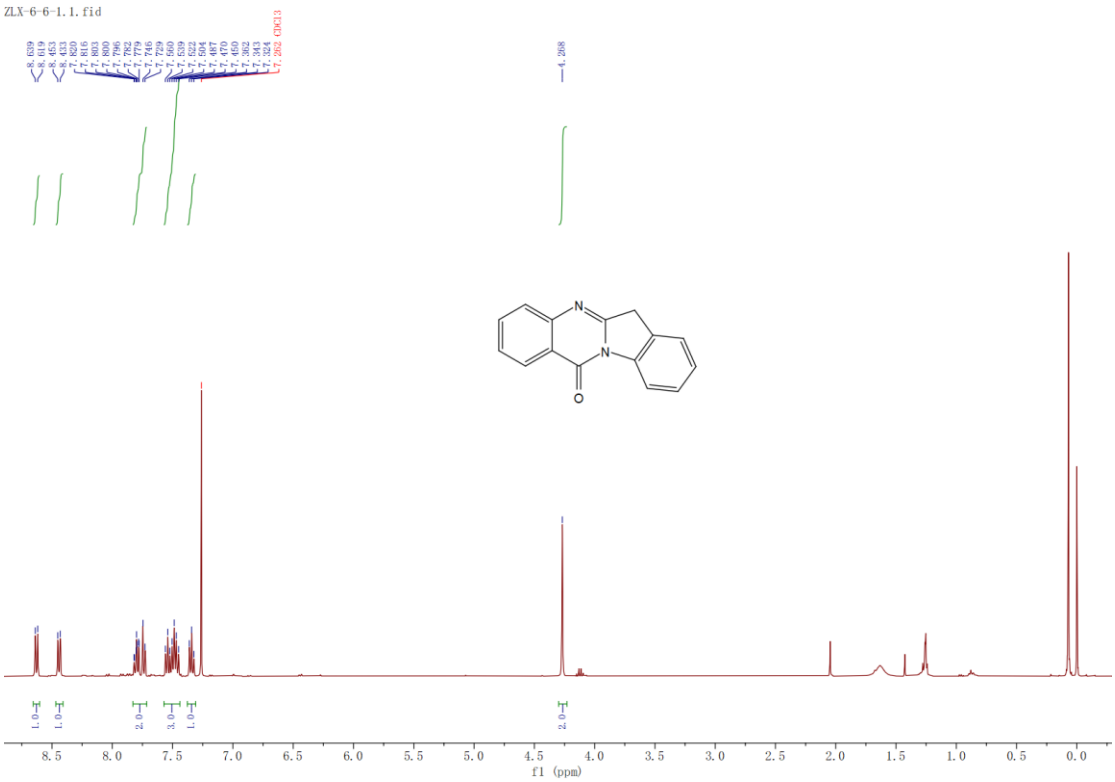
^{1}H NMR spectrum of compound 13o (600 MHz, $CDCl_3$)



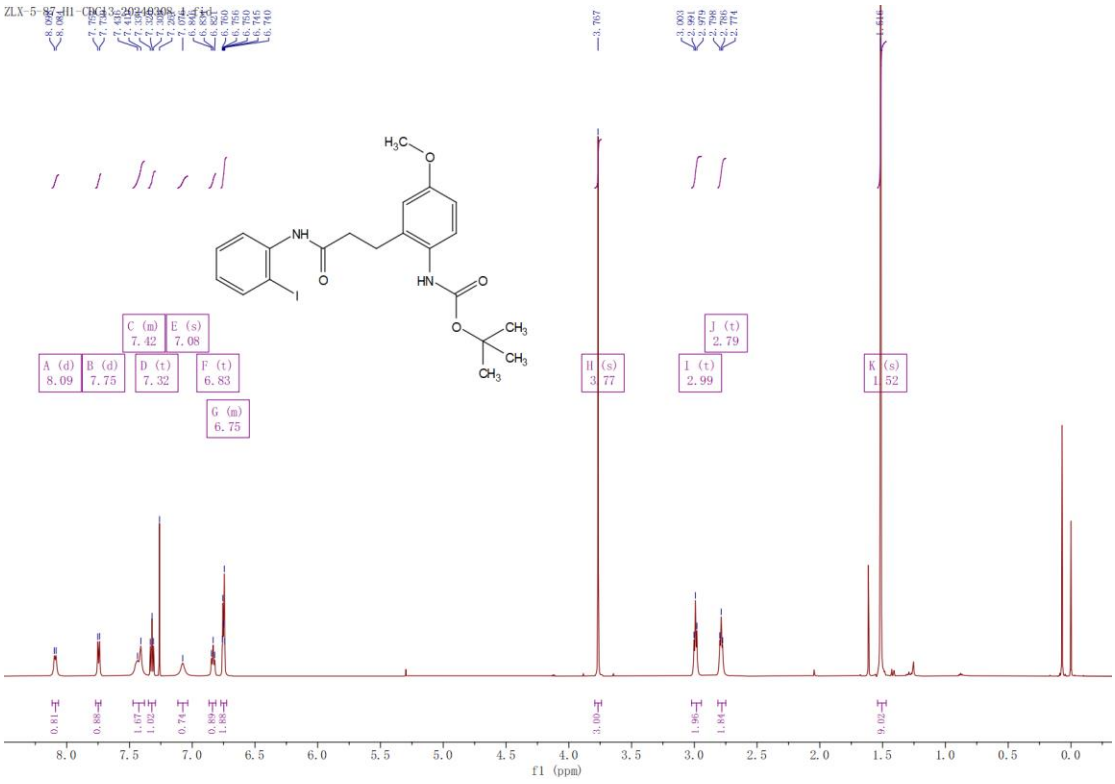
^{1}H NMR spectrum of compound 10p-Boc (600 MHz, $CDCl_3$)



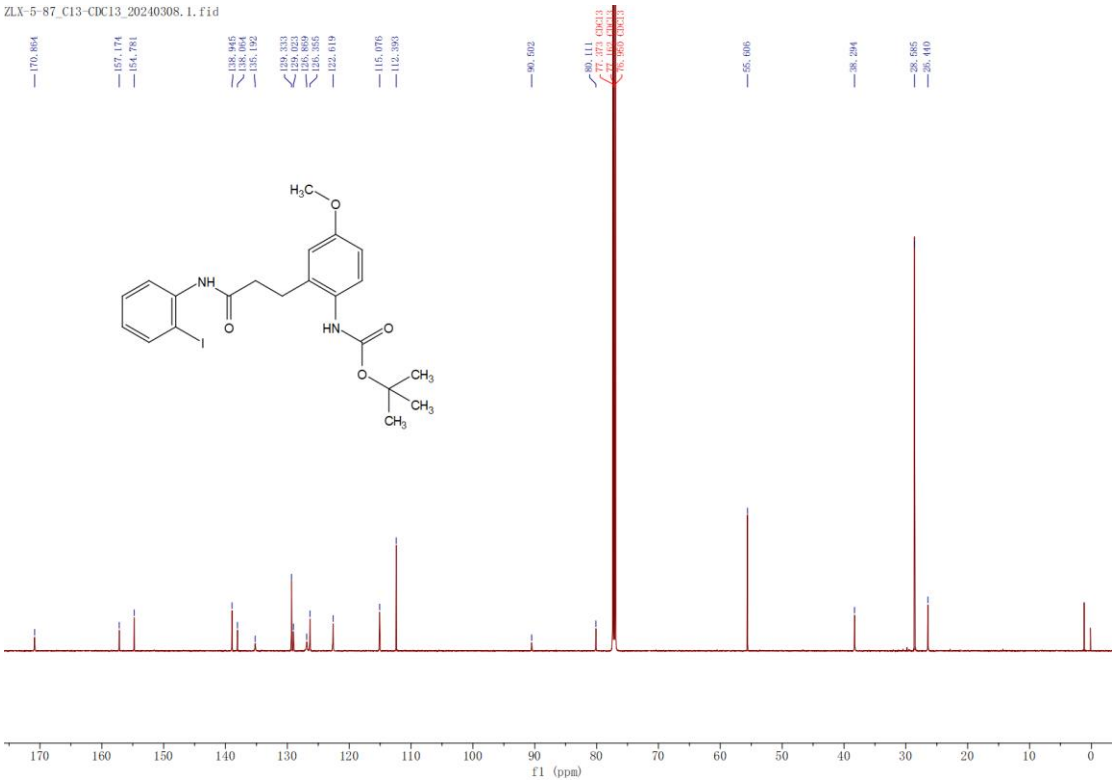
^{13}C NMR spectrum of compound 10p-Boc (150 MHz, $CDCl_3$)



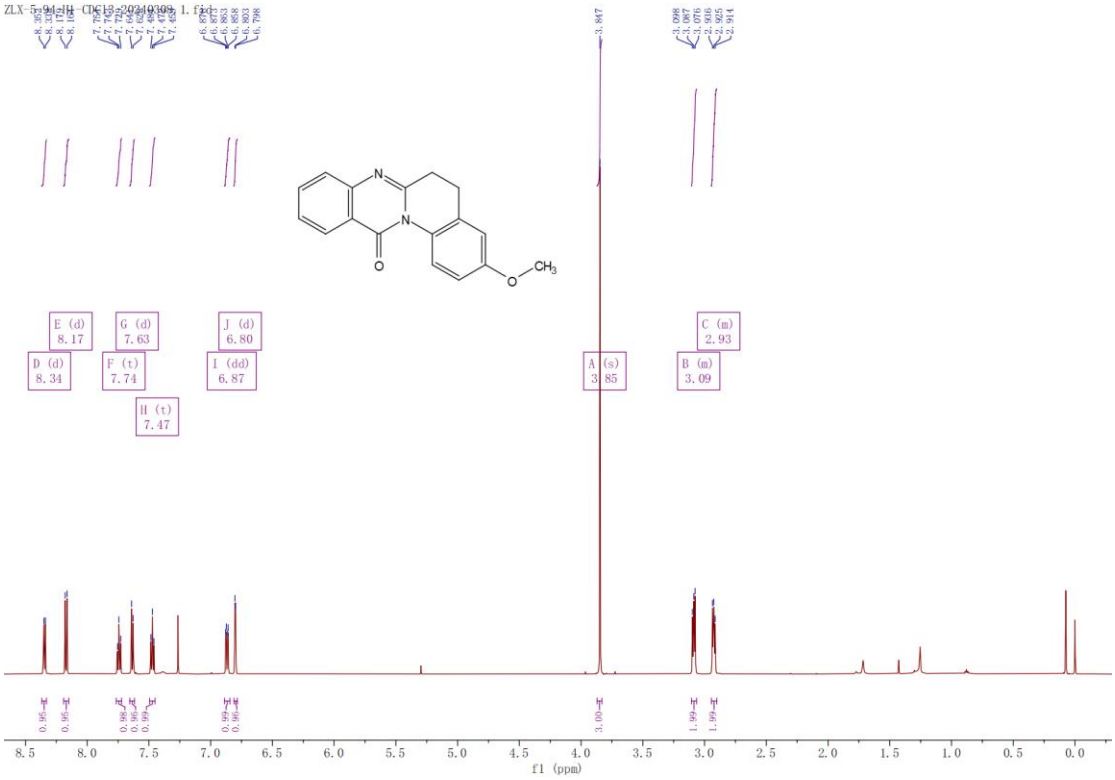
^{1}H NMR spectrum of compound 13p (400 MHz, $CDCl_3$)



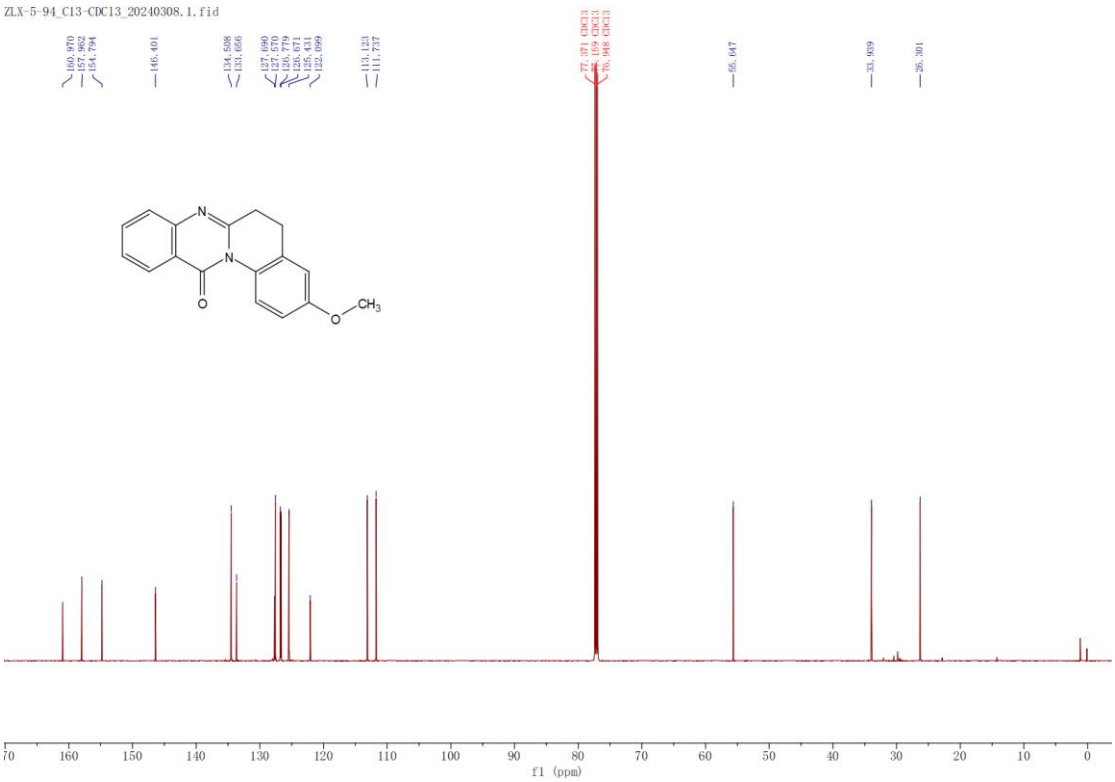
^{1}H NMR spectrum of compound 10q-Boc (600 MHz, $CDCl_3$)



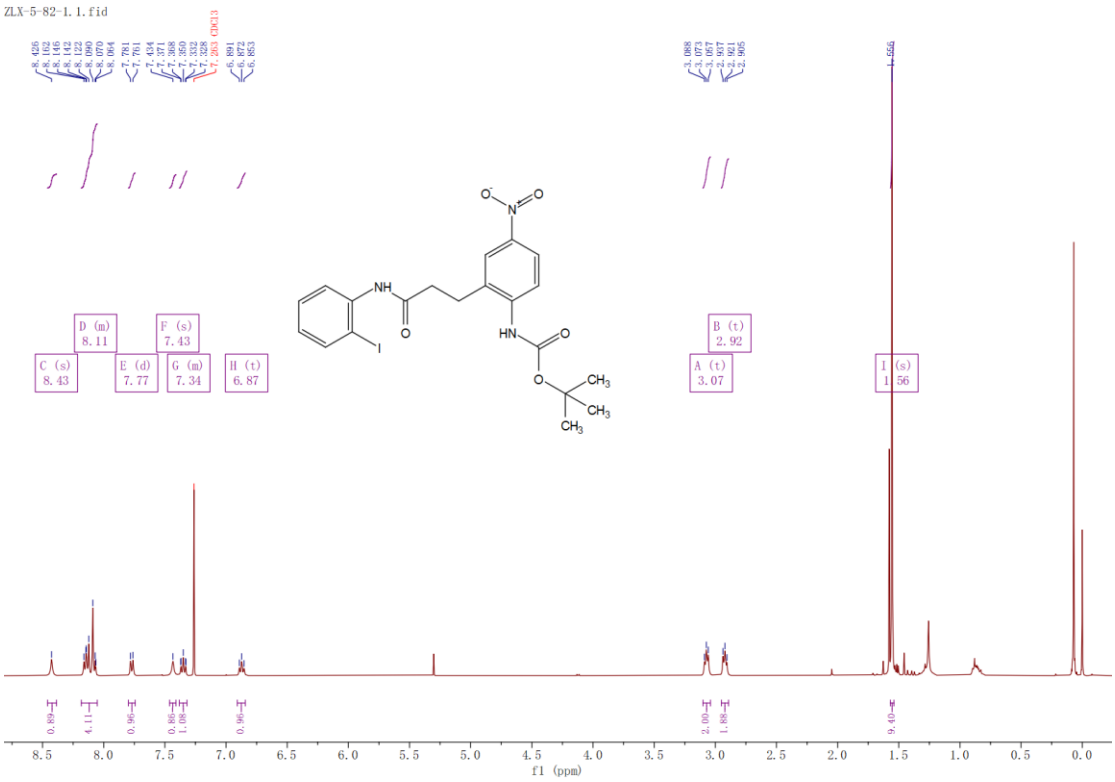
^{13}C NMR spectrum of compound 10q-Boc (150 MHz, $CDCl_3$)



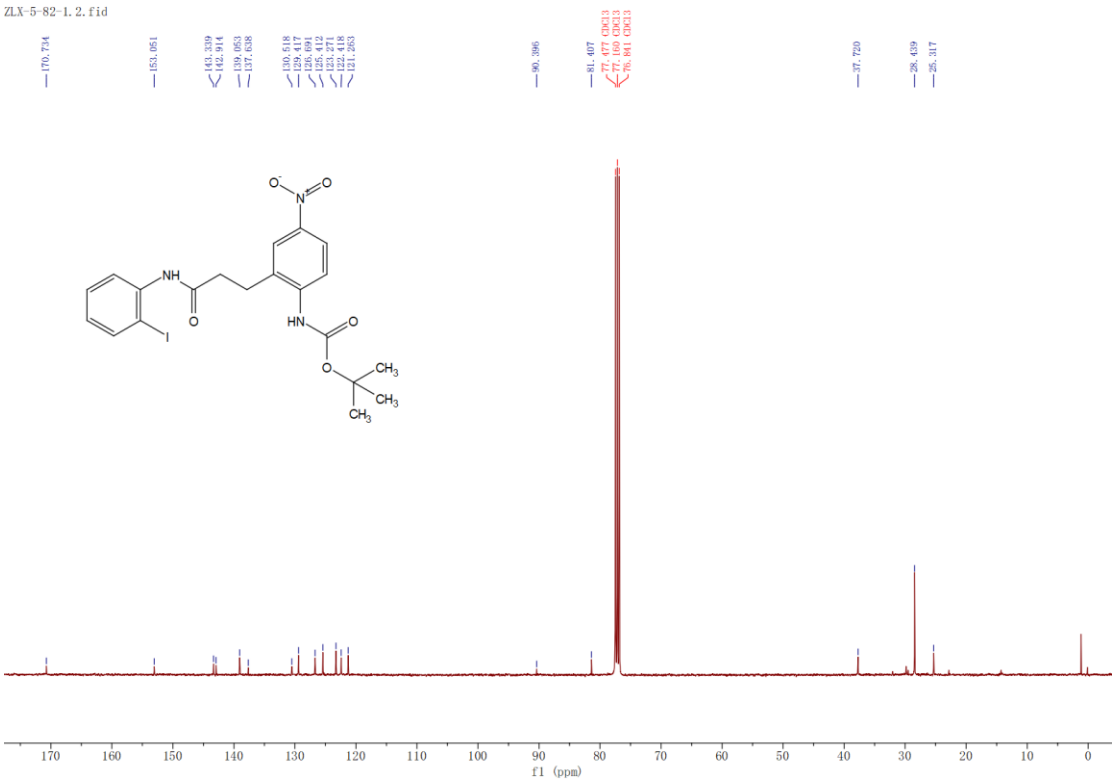
^{1}H NMR spectrum of compound 13q (600 MHz, $CDCl_3$)



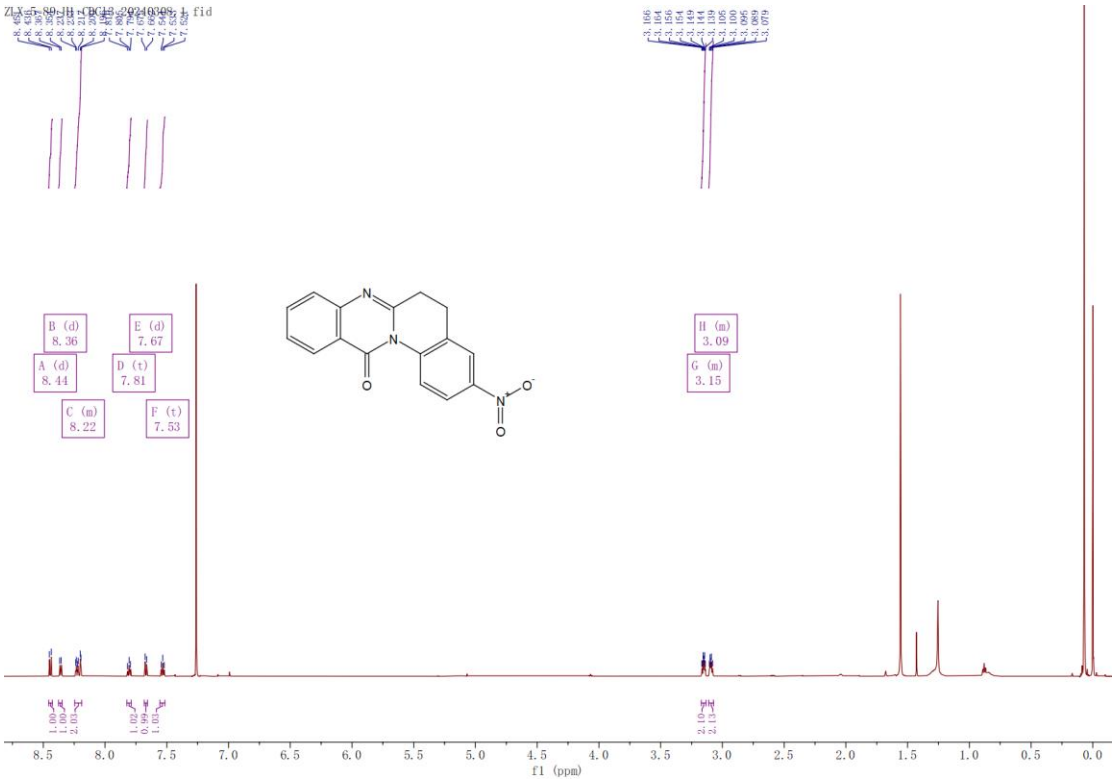
^{13}C NMR spectrum of compound 13q (150 MHz, $CDCl_3$)



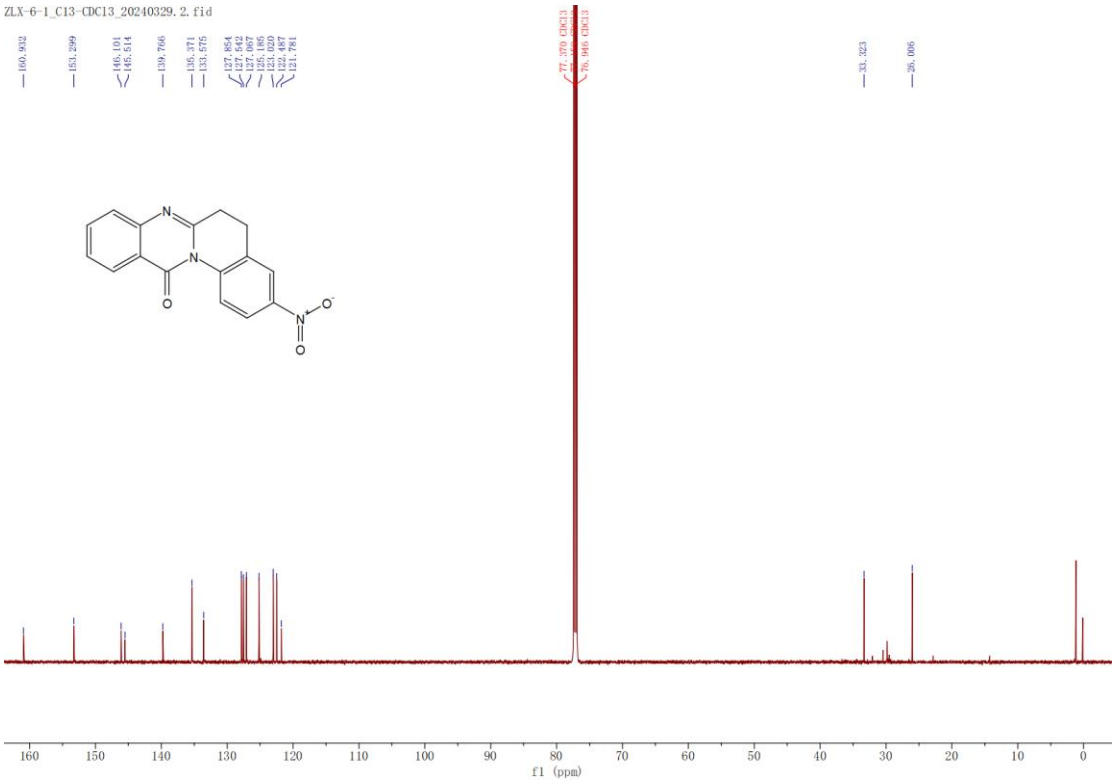
^{1}H NMR spectrum of compound 10r-Boc (600 MHz, $CDCl_3$)



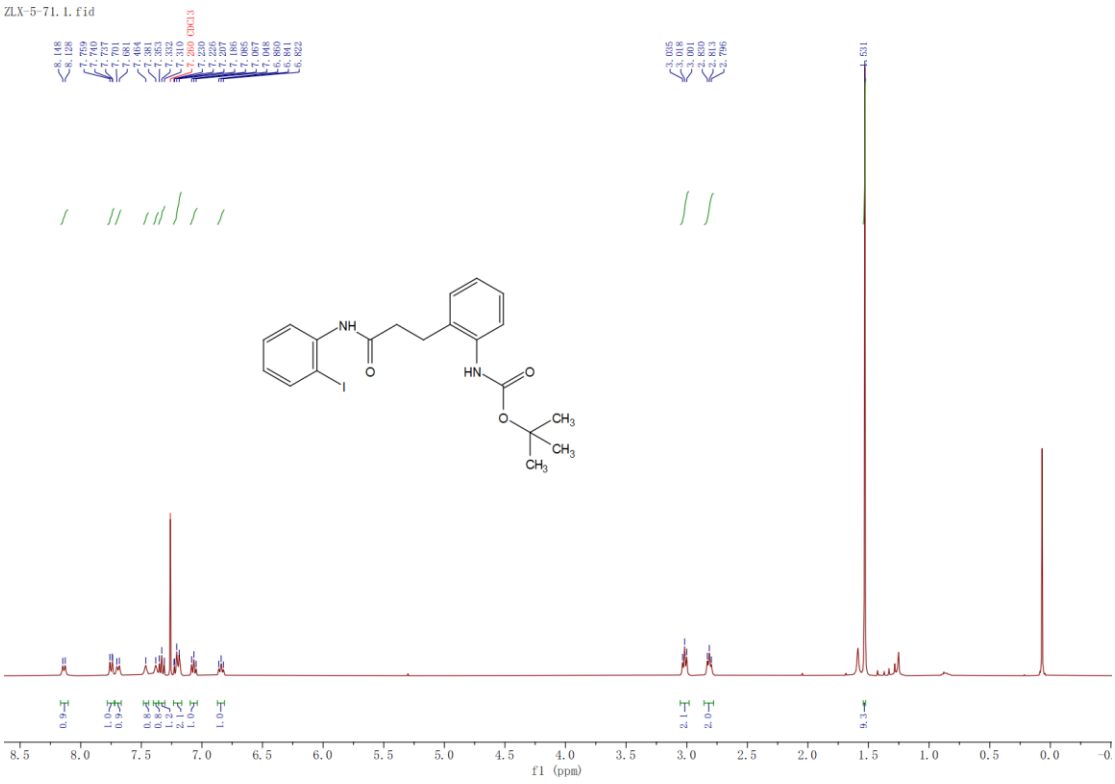
^{13}C NMR spectrum of compound 10r-Boc (150 MHz, $CDCl_3$)



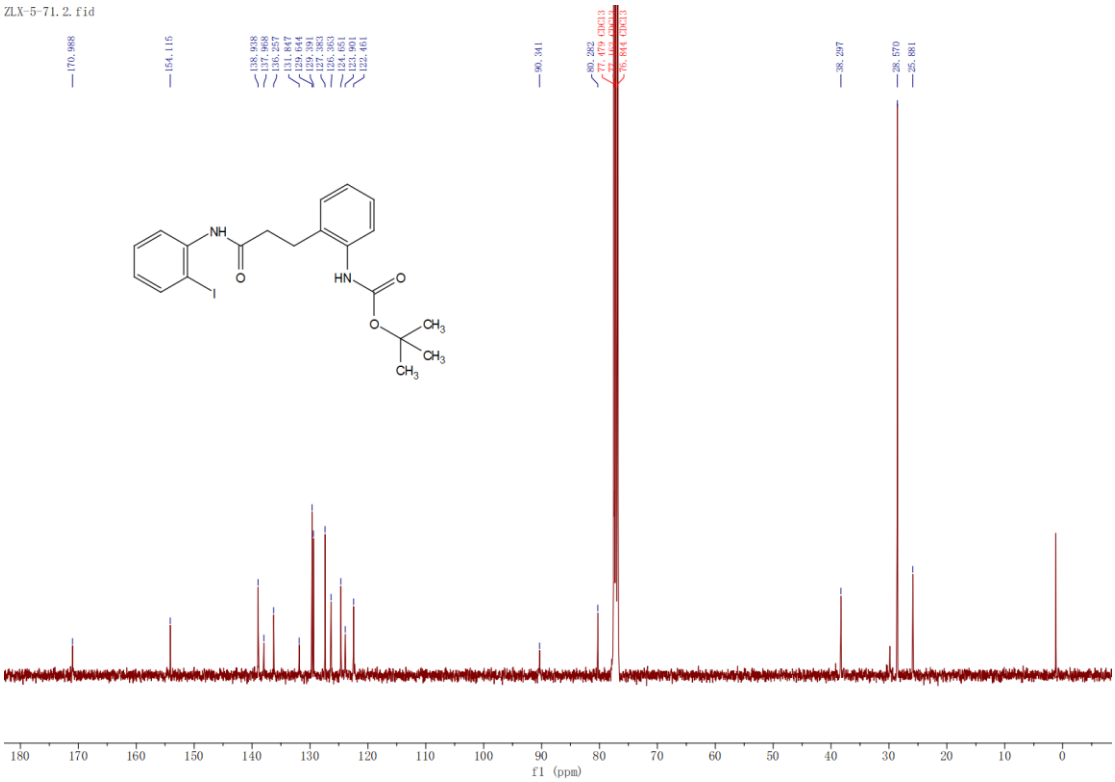
^{1}H NMR spectrum of compound 13r (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of compound 13r (150 MHz, $CDCl_3$)



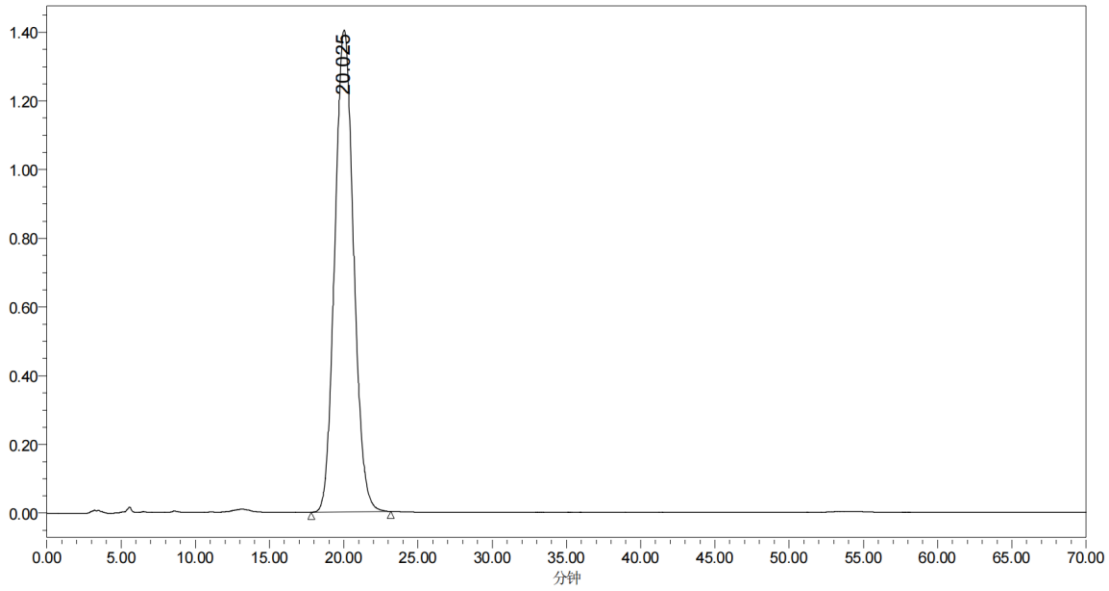
^{1}H NMR spectrum of compound 10s-Boc (400 MHz, $CDCl_3$)

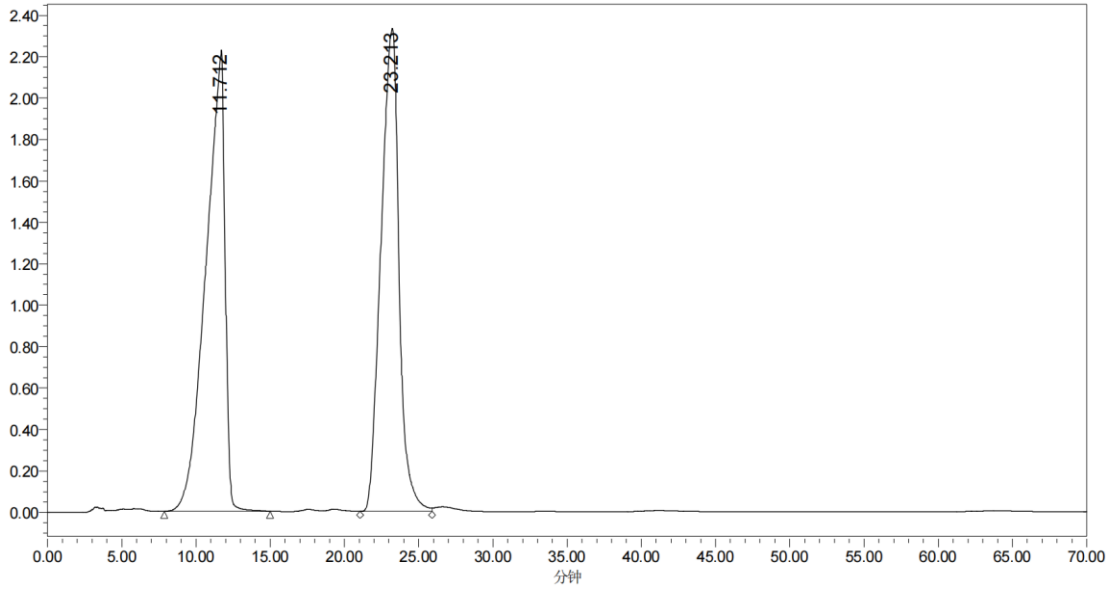


^{13}C NMR spectrum of compound 10s-Boc (100 MHz, $CDCl_3$)

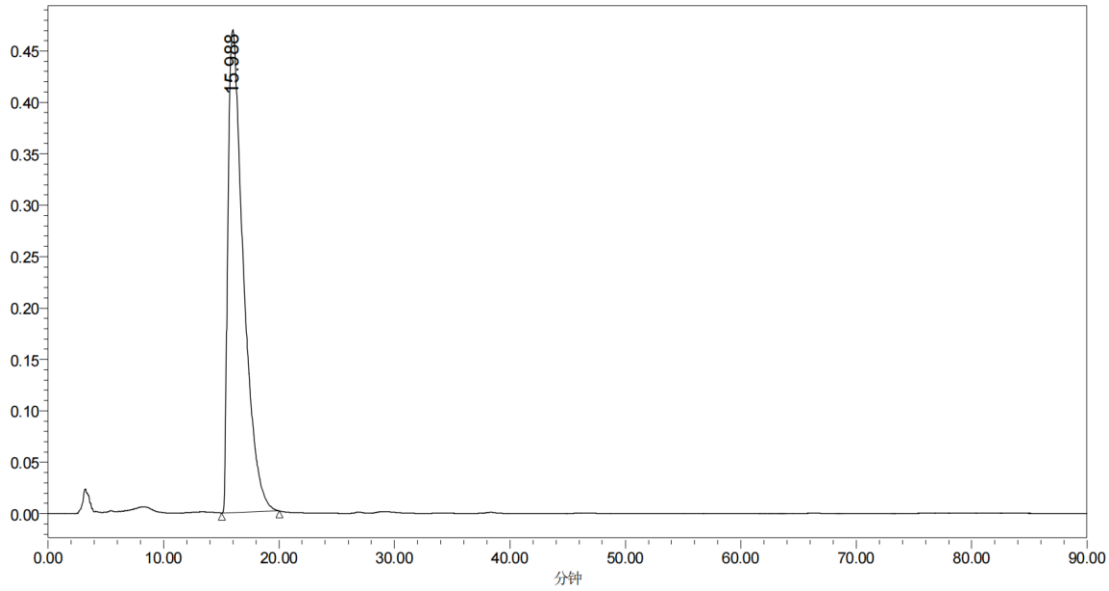
HPLC Reports

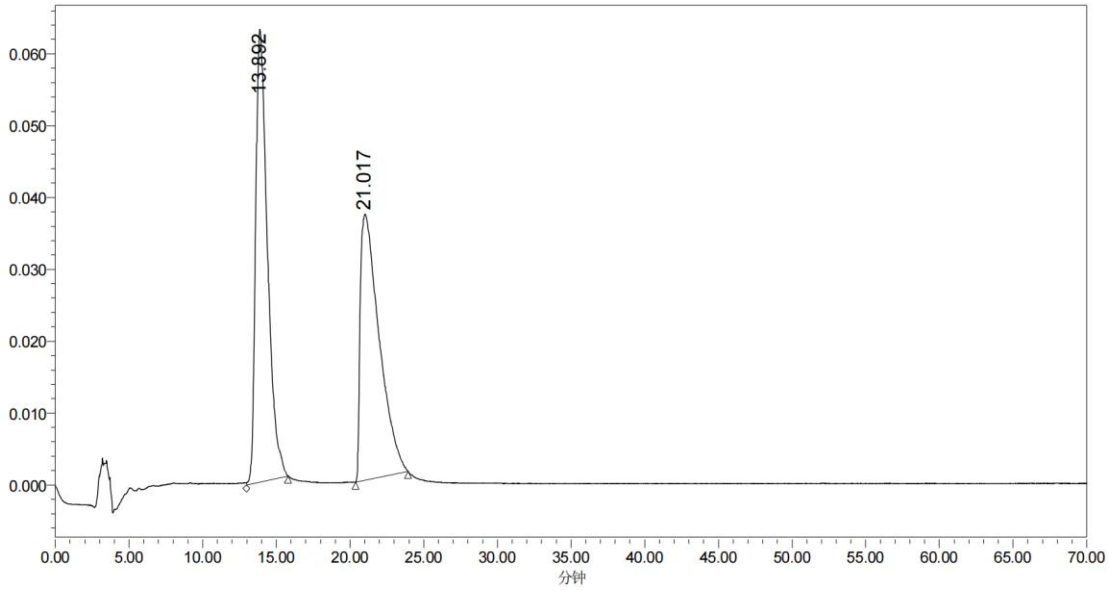
chiral HPLC (comparison to racemic products)
chiral column (Chiracel OD-H; 25 cm×0.25 mm) and UV-detection at 254 nm;
mobile phase:hexane/2-propanol (9:1) at 1 mL/min.
Waters HPLC



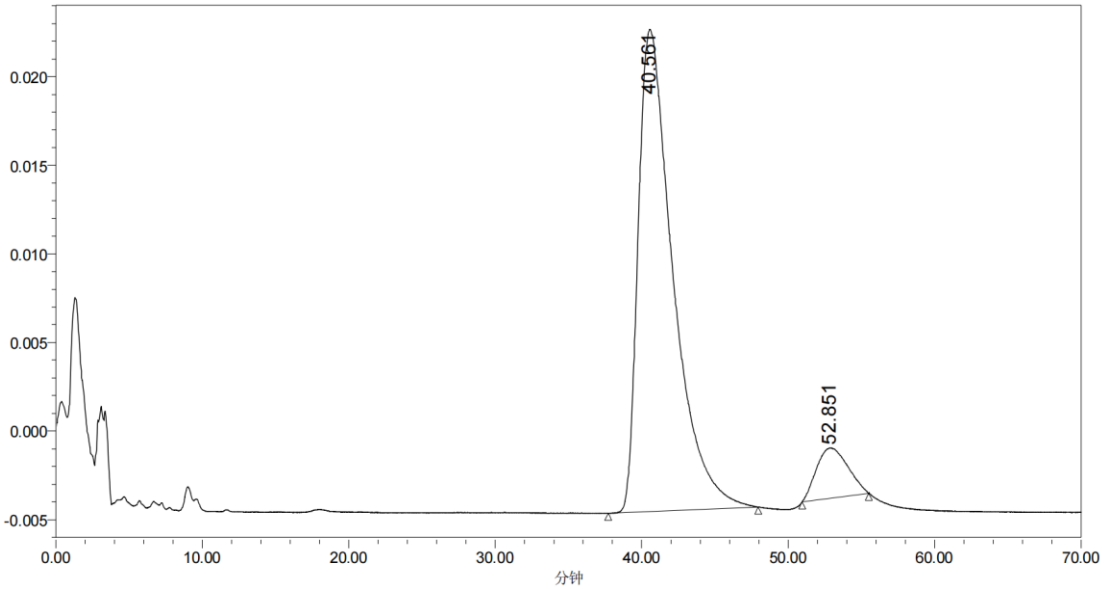


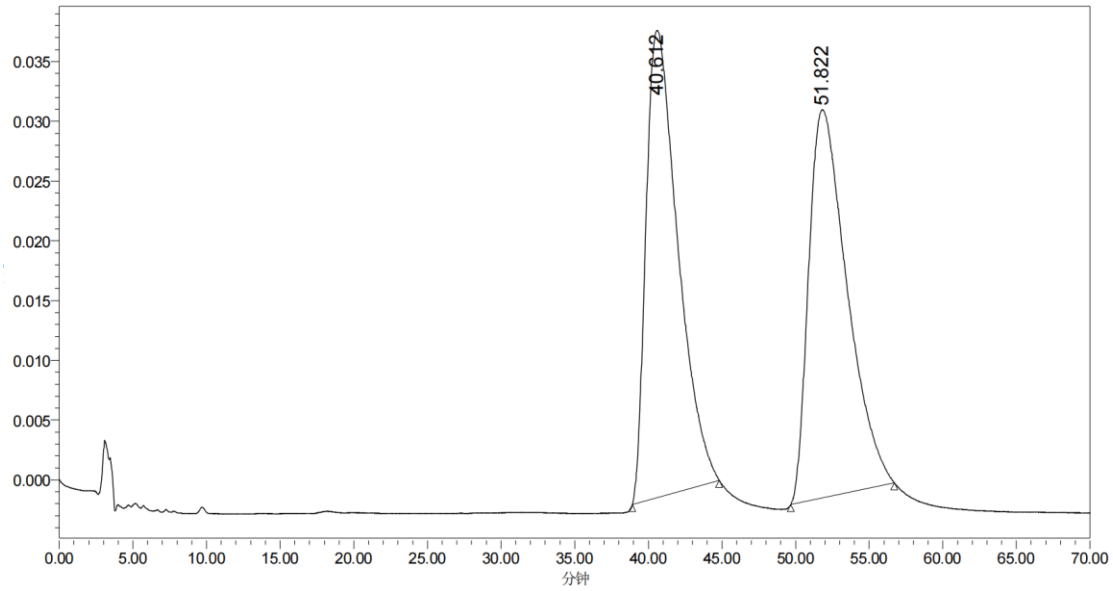
Separation of compound 5c-Boc and its enantiomer using HPLC



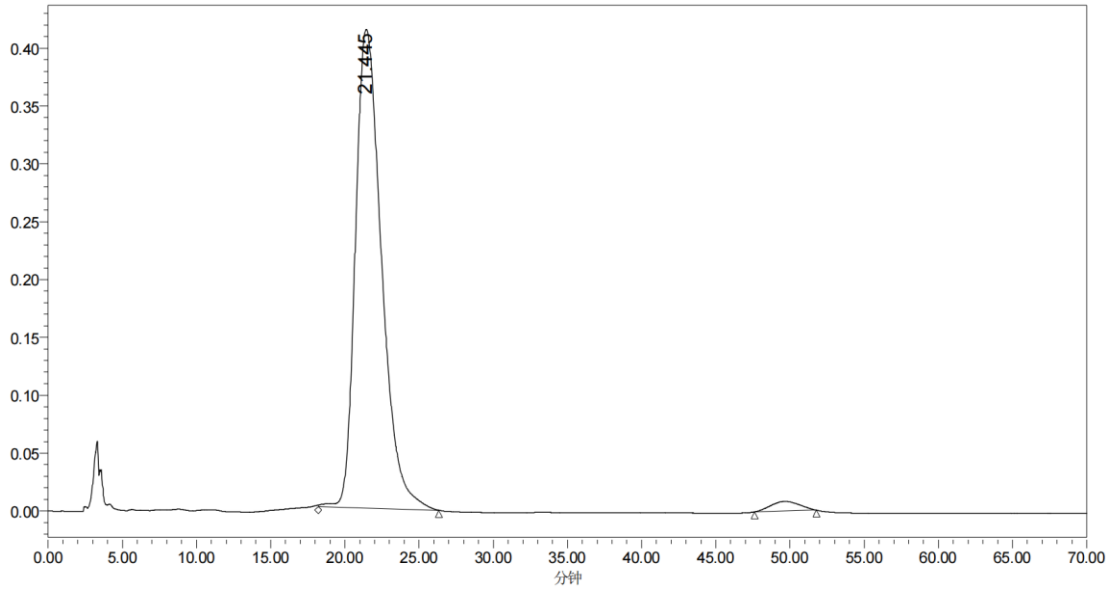


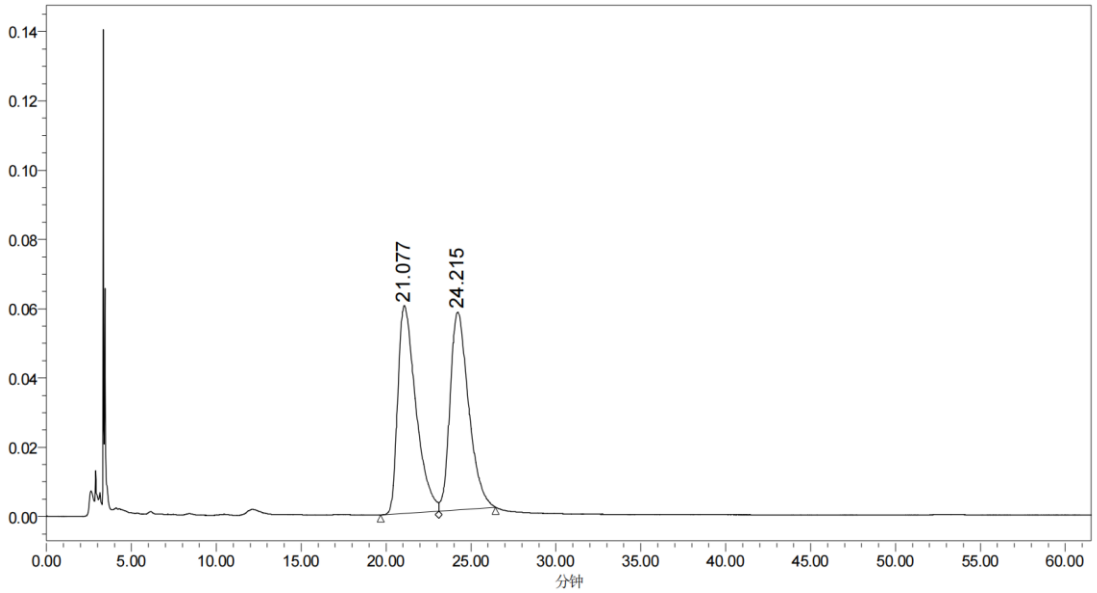
Separation of compound 8b and its enantiomer using HPLC



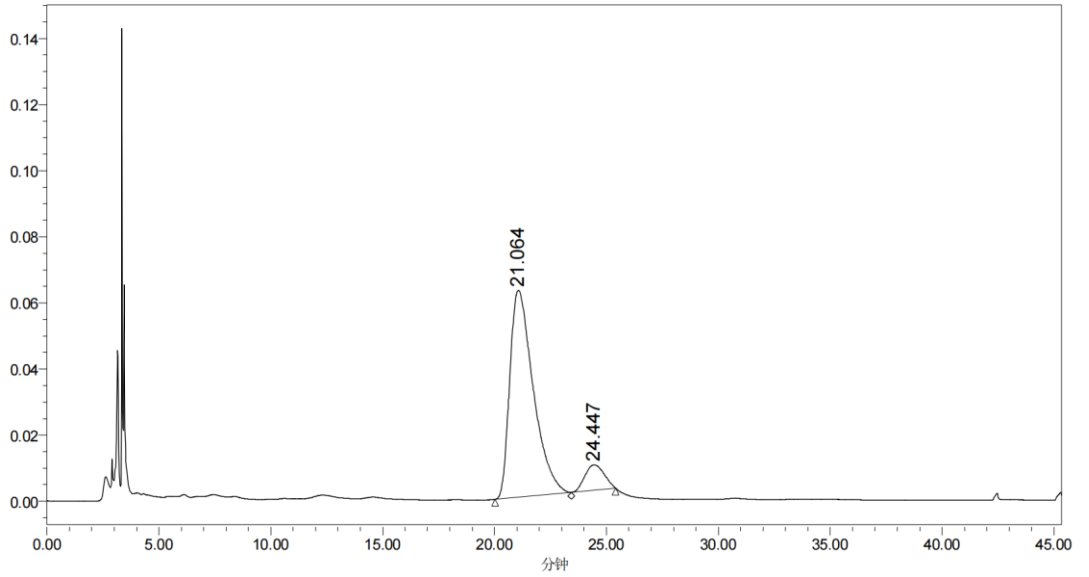


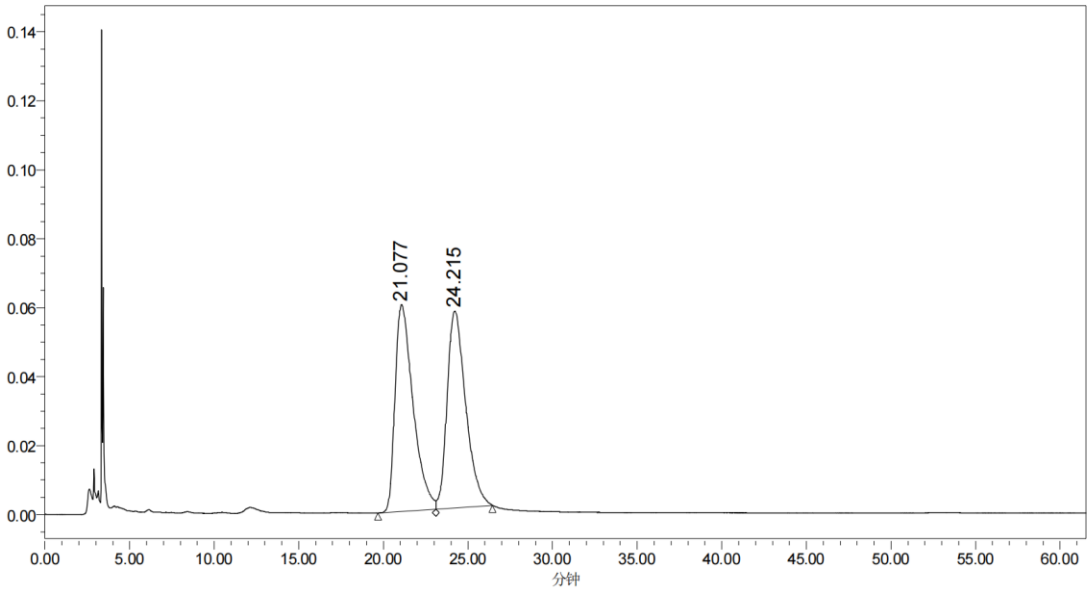
Separation of compound 8c and its enantiomer using HPLC





Separation of compound 8d and its enantiomer using HPLC





Separation of compound 8e and its enantiomer using HPLC