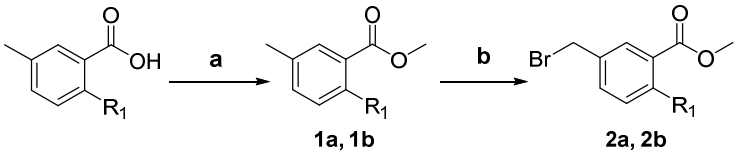
Supporting Information

Content

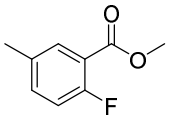
Synthesis of intermediates in Scheme S1

Scheme S1



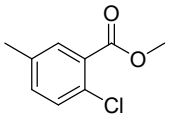
Reagents and conditions: a) $SOCl_2$, MeOH, reflux; b) NBS, AIBN, acetonitrile, tetrachloride, 70°C.

Methyl 2-fluoro-5-methylbenzoate (1a)



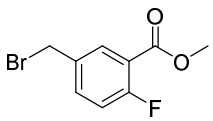
To a solution of 2-fluoro-5-methylbenzoic acid (5.06 g, 33 mmol) in methanol (110 mL), thionyl chloride (5.0 mL, 66 mmol) was added, and the mixture was stirred at reflux for 3 h. After removal of the solvent under vacuum distillation, ethyl acetate (100 mL) was added to the residue. The resulting mixture was washed with brine (40 mL × 2), and then the organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration to give compound **1a** as a light yellow oil (5.45 g, 98.3%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.72 (dd, J_1 = 7.0 Hz, J_2 = 2.5 Hz, 1H), 7.27-7.31 (m, 1H), 7.01 (dd, J_1 = 11.0 Hz, J_2 = 8.5 Hz, 1H), 3.92 (s, 3H), 2.34 (s, 3H).

Methyl 2-chloro-5-methylbenzoate (1b)



Following the preparation protocol of compound **1a**, starting from 2-chloro-5-methylbenzoic acid, the title compound **1b** was obtained as a light yellow oil (5.9 g, 97.2%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.21 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 3.92 (s, 3H), 2.34 (s, 3H).

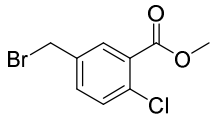
Methyl 5-(bromomethyl)-2-fluorobenzoate (2a)



To a stirred solution of methyl 2-fluoro-5-methylbenzoate (**1a**) (6.72 g, 40.0 mmol) in carbon tetrachloride (100 mL) and acetonitrile (20 mL), azodiisobutyronitrile (1.29 g, 8.0 mmol) and

N-bromosuccinimide (7.47 g, 42.0 mmol) were added. The reaction mixture was heated at reflux for 1.5 h and then the mixture was diluted with DCM (100 mL) and washed with brine (50 mL×2), dried over anhydrous magnesium sulfate. After removal of the solvent under vacuum distillation, the residue was purified with column chromatography (ethyl acetate / petroleum ether = 150:1) to give compound **2a** as a white solid (6.4 g, 65%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96-7.99 (m, 1H), 7.53-7.58 (m, 1H), 7.10-7.17 (m, 1H), 4.48 (s, 2H), 3.94 (s, 3H).

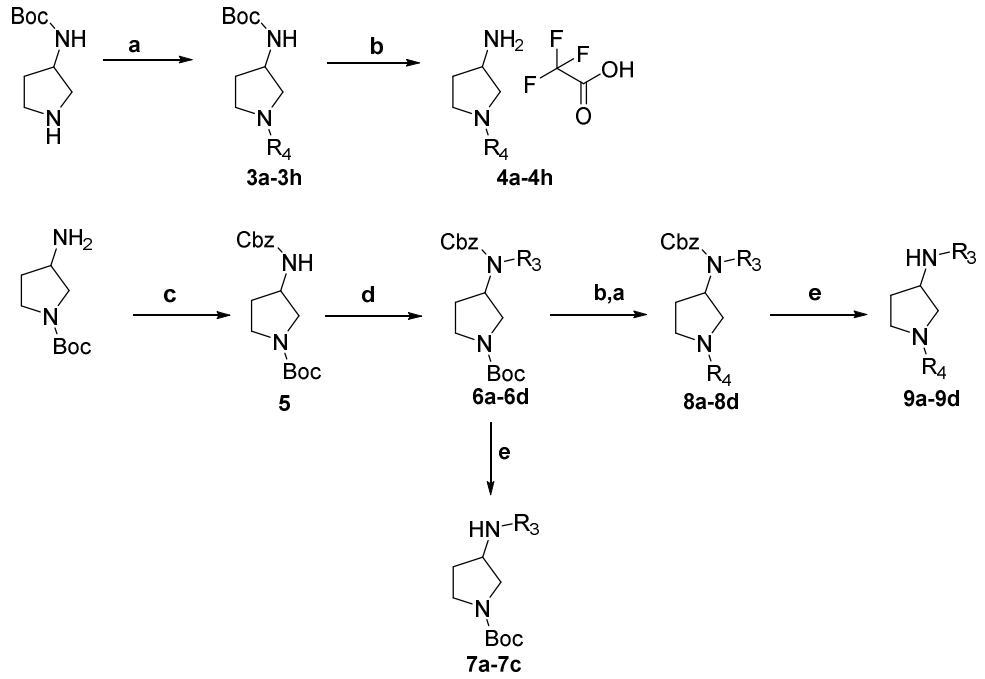
Methyl 5-(bromomethyl)-2-chlorobenzoate (2b)



Following the preparation protocol of compound **2a**, starting from methyl 2-chloro-5-methylbenzoate (**1b**), the title compound **2b** was obtained as a white soild (4.8 g, 57.8%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.97 (dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz, 1H), 7.54-7.57 (m, 1H), 7.13 (d, J = 9.5 Hz, 1H), 4.48 (s, 2H), 3.94 (s, 3H).

Synthesis of intermediates in Scheme S2

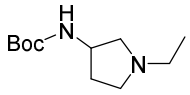
Scheme S2



Reagents and conditions: a) Haloalkane, DIEA, acetonitrile, rt or 40°C or 70°C or aldehyde or ketone, DIEA, THF,

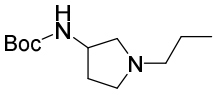
then $NaBH(OAc)_3$; b) TFA, DCM, rt; c) CBZ-Cl, Et_3N, DCM, 0°C; d) Haloalkane, NaH, DMF, rt; e) 10% Pd/C, EtOH, H_2. rt;

tert-Butyl (1-ethylpyrrolidin-3-yl)carbamate (3a)



To a solution of methyl *tert*-butyl pyrrolidin-3-ylcarbamate (651 mg, 3.5 mmol) in acetonitrile (20 mL), DIEA (0.92 mL, 5.25 mmol) and bromoethane (0.3 mL, 3.85 mmol) were added, and the mixture was stirred at room temperature for 2 h. After the removal of solvent under vacuum distillation, the residue was purified with column chromatography (methylene chloride /methanol = 40:1 to 30:1) to give compound **3a** as a light yellow solid (600 mg, 80%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.16 (d, J = 8.4 Hz, 1H), 3.87 (s, 1H), 3.70 (s, 0.5H), 3.61 (s, 0.5H), 3.10-3.30 (m, 4H), 2.42-2.56 (m, 1H), 2.22 (brs, 1H), 1.53 (t, J = 6.0 Hz, 3H), 1.42 (s, 9H).

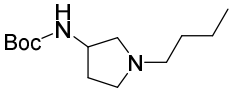
tert-Butyl (1-propylpyrrolidin-3-yl)carbamate (3b)



To a solution of methyl *tert*-butyl pyrrolidin-3-ylcarbamate (651 mg, 3.5 mmol) in acetonitrile (20 mL), DIEA (0.92 mL, 5.25 mmol) and 1-bromopropane (0.38 mL, 4.2 mmol) were added, and the mixture was stirred at 40°C for 3 h. After removal of the solvent under vacuum distillation, the residue was purified with column chromatography (methylene chloride /methanol = 40:1 to 30:1) to give compound **3b** as a light yellow solid (650 mg, 81%);

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.19 (d, J = 8.4 Hz, 1H), 4.63 (brs, 1H), 4.29 (brs, 0.5H), 3.92 (brs, 1H), 3.76 (brs, 0.5H), 3.64 (d, J = 10.0 Hz, 1H), 3.01-3.13 (m, 2H), 2.81-2.87 (m, 1H), 2.48-2.56 (m, 1H), 2.23-2.30 (m, 1H), 1.94 (brs, 2H), 1.43 (s, 9H), 1.04(t, J = 7.2 Hz, 3H).

tert-Butyl (1-butylpyrrolidin-3-yl)carbamate (3c)

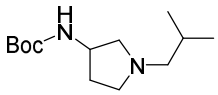


Following the preparation protocol of compound **3b**, starting from *tert*-butyl

pyrrolidin-3-ylcarbamate and 1-bromobutane, the title compound **3c** was obtained as a light yellow solid (390 mg, 53.7%);

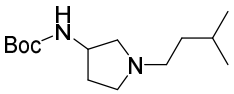
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.10 (s, 1H), 4.21 (s, 1H), 2.96 (s, 1H), 2.60-2.75 (m, 2H), 2.49 (brs, 2H), 2.25-2.37 (m, 2H), 1.69 (s, 1H), 1.48-1.55 (m, 2H), 1.42 (s, 9H), 1.31-1.36 (m, 2H), 0.91 (d, J = 7.2 Hz, 3H).

***tert*-Butyl (1-isobutylpyrrolidin-3-yl)carbamate (3d)**



Following the preparation protocol of compound **3b**, starting from *tert*-butyl pyrrolidin-3-ylcarbamate and 1-bromo-2-methylpropane, the title compound **3d** was obtained as a light yellow solid (300 mg, 35.4%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.85 (s, 1H), 4.14 (s, 1H), 2.76 (s, 1H), 2.50 (s, 2H), 2.16-2.30 (m, 4H), 1.66-1.73 (m, 1H), 1.52-1.58 (m, 1H), 1.43 (s, 9H), 0.89 (d, J = 6.4 Hz, 6H).

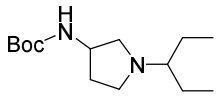
***tert*-Butyl (1-isopentylpyrrolidin-3-yl)carbamate (3e)**



Following the preparation protocol of compound **3b**, starting from tert-butyl pyrrolidin-3-ylcarbamate and1-bromo-3-methylbutane, the title compound **3e** was obtained as a light yellow solid (420 mg, 82%);

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.91 (s, 1H), 4.16 (s, 1H), 2.83 (s, 1H), 2.58 (s, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.20-2.30 (m, 2H), 1.52-1.65 (m, 2H), 1.44 (s, 9H), 1.30 -1.42 (m, 2H), 0.89 (d, J = 6.4 Hz, 6H).

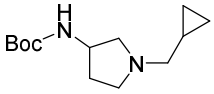
***tert*-Butyl (1-(pentan-3-yl)pyrrolidin-3-yl)carbamate (3f)**



Following the preparation protocol of compound **3b**, starting from tert-butyl pyrrolidin-3-ylcarbamate and 3-bromopentane, the title compound **3f** was obtained as a light

yellow solid (330 mg, 64%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.67 (brs, 1H), 4.33 (s, 1H), 3.30 (s, 1H), 3.04 (s, 1H), 2.95 (s, 1H), 2.68 (s, 1H), 2.48 (s, 1H), 2.32 (s, 1H), 1.94 (s, 1H), 1.65 (brs, 4H), 1.41 (s, 9H), 0.95 (t, J = 7.2 Hz, 6H).

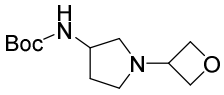
***tert*-Butyl (1-(cyclopropylmethyl)pyrrolidin-3-yl)carbamate (3g)**



Following the preparation protocol of compound **3b**, starting from tert-butyl pyrrolidin-3-ylcarbamate and (bromomethyl)cyclopropane, the title compound **3g** was obtained as a light yellow oil (510 mg, 70.7%)

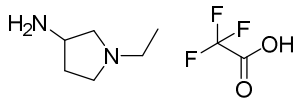
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 5.33 (brs, 1H), 4.31 (s, 1H), 3.20 (s, 1H), 2.96 (s, 1H), 2.83 (s, 1H), 2.52 (brs, 3H), 2.34 (brs, 1H), 1.83 (s, 1H), 1.44 (s, 9H), 1.01 (s, 1H), 0.61 (d, J = 8.5 Hz, 2H), 0.23 (s, 2H).

***tert*-Butyl (1-(oxetan-3-yl)pyrrolidin-3-yl)carbamate (3h)**



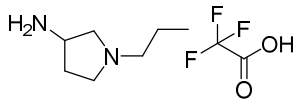
To a solution of methyl *tert*-butyl pyrrolidin-3-ylcarbamate (465 mg, 2.5 mmol) in methylene chloride (5 mL) , oxetan-3-one (0.88 mL, 15 mmol) and AcOH (0.2 mL) were added, and the mixture was stirred at room temperature for 6 h. Sodium triacetoxyborohydride ($NaBH(OAc)_3$, 3.18 g, 15.0 mmol) was added to the mixture and stirred at room temperature for 48 h and then methylene chloride (50 mL) was added. The resulting mixture was washed with brine (15 mL × 2), and dried over anhydrous $MgSO_4$. After filtration and concentration, the crude product was obtained and purified with column chromatography (methylene chloride /methanol = 60:1 to 20:1) to give compound **3h** as a white solid (45 mg, 7.5%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.92 (brs, 1H), 4.69 (t, J = 6.8 Hz, 2H), 4.61 (q, J = 6.0 Hz, 2H), 4.20 (brs, 1H), 3.60-3.66 (m, 1H), 2.82 (brs, 1H), 2.57 (brs, 2H), 2.25-2.30 (m, 2H), 1.60-1.75 (m, 1H), 1.44 (s, 9H)

1-Ethylpyrrolidin-3-amine 2,2,2-trifluoroacetate (4a)



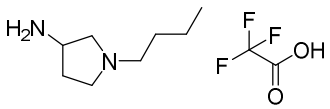
To a solution of compound **3a** (215 mg, 1.0 mmol) in DCM (10.0 mL), TFA (0.73 mL, 10.0mmol) was added and then the reaction mixture was stirred at room temperature for 4 h. Then removal of the solvent under vacuum distillation to give compound **4a** as a light yellow oil (220 mg, 96.4%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.35-8.41 (m, 3H), 3.91-4.04 (m, 1.5H), 3.44-3.71 (m, 2H), 3.08-3.22 (m, 3.5H), 2.48 (brs, 0.5H), 2.24 (brs, 0.5H), 2.13 (brs, 0.5H), 1.97 (brs, 0.5H), 1.21 (t, J = 7.2 Hz, 3H).

1-Propylpyrrolidin-3-amine 2,2,2-trifluoroacetate (4b)



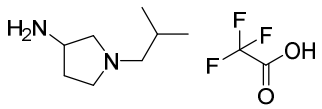
Following the preparation protocol of compound **4a**, starting from *tert*-butyl (1-propylpyrrolidin-3-yl)carbamate (**3b**), the title compound **4b** was obtained as a light yellow oil (250 mg, 98%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.33-8.41 (m, 3H), 4.04 (s, 0.5H), 3.92 (s, 1H), 3.72 (s, 0.5H), 3.61 (s, 1H), 3.46 (s, 0.5H), 3.30 (s, 0.5H), 3.13 (brs, 3H), 2.47 (brs, 0.5H), 2.24 (brs, 0.5H), 2.11 (brs, 0.5H), 1.96 (brs, 0.5H), 1.57-1.67 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H).

1-Butylpyrrolidin-3-amine 2,2,2-trifluoroacetate (4c)



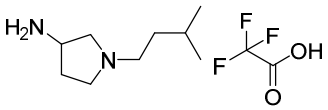
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-butylpyrrolidin-3-yl)carbamate (**3c**), the title compound **4c** was obtained as a light yellow oil (240 mg, 96%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.38-8.44 (m, 3H), 4.06(s, 0.5H), 3.94(s, 1H), 3.75 (s, 0.5H), 3.64 (s, 1H), 3.48 (s, 0.5H), 3.19-3.30 (m, 3.5H), 2.47 (brs, 0.5H), 2.23 (brs, 0.5H), 2.11 (brs, 0.5H), 1.95 (brs, 0.5H), 1.50-1.62 (m, 2H), 1.20-1.31 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).

1-Isobutylpyrrolidin-3-amine 2,2,2-trifluoroacetate (4d)



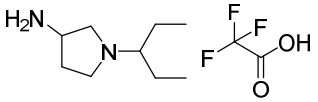
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-isobutylpyrrolidin-3-yl)carbamate (**3d**), the title compound **4d** was obtained as a light yellow oil (250 mg, 98%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.39-8.46 (m, 3H), 3.96-4.09 (m, 2H), 3.78 (s, 0.5H), 3.69 (s, 1H), 3.50 (s, 0.5H), 3.07-3.20 (m, 3H), 2.48 (brs, 0.5H), 2.26 (brs, 0.5H), 2.10 (brs, 0.5H), 0.90-1.99 (m, 1.5H), 0.92 (d, J = 6.8 Hz, 6H).

1-Isopentylpyrrolidin-3-amine 2,2,2-trifluoroacetate (4e)



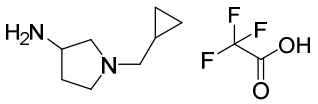
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-isopentylpyrrolidin-3-yl)carbamate (**3e**), the title compound **4e** was obtained as a light yellow oil (630 mg, 100%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.44 (brs, 3H), 3.75-4.03 (m, 2H), 3.46-3.65 (m, 1.5H), 3.10-3.30 (m, 3.5H), 2.47 (brs, 0.5H), 2.26 (brs, 0.5H), 2.15 (brs, 0.5H), 1.98 (brs, 0.5H), 1.58-1.66 (m, 1H), 1.48-1.54 (m, 2H), 0.89 (d, J = 6.8 Hz, 6H).

1-(Pentan-3-yl)pyrrolidin-3-amine 2,2,2-trifluoroacetate (4f)



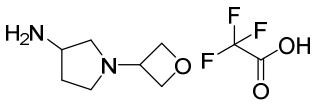
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-(pentan-3-yl)pyrrolidin-3-yl)carbamate (**3f**), the title compound **4f** was obtained as a light yellow oil (300 mg, 99%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.38-8.45 (m, 3H), 4.04 (s, 0.5H), 3.89 (s, 1H), 3.74 (s, 0.5H), 3.53-3.61 (m, 1.5H), 3.35 (s, 0.5H), 3.17 (brs, 2H), 2.44 (s, 0.5H), 2.26 (brs, 0.5H), 2.10 (brs, 0.5H), 1.99 (brs, 0.5H), 1.60-1.73 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).

1-(Cyclopropylmethyl)pyrrolidin-3-amine 2,2,2-trifluoroacetate (4g)



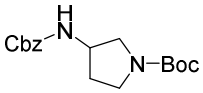
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-(cyclopropylmethyl)pyrrolidin-3-yl)carbamate (**3g**), the title compound **4g** was obtained as a brownish red oil (560 mg, 98.1%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.50 (brs, 3H), 3.96-4.07 (m, 1.5H), 3.67-3.77 (m, 1.5H), 3.53 (s, 1H), 3.35 (s, 0.5H), 3.10-3.16 (m, 3H), 2.47 (brs, 0.5H), 2.29 (brs, 0.5H), 2.14 (brs, 0.5H), 2.00 (brs, 0.5H), 1.05-1.10 (m, 1H), 0.61 (t, J = 7.6 Hz, 2H), 0.38 (d, J = 4.0 Hz, 2H).

1-(Oxetan-3-yl)pyrrolidin-3-amine 2,2,2-trifluoroacetate (4h)



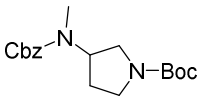
Following the preparation protocol of compound **4a**, starting from tert-butyl (1-(oxetan-3-yl)pyrrolidin-3-yl)carbamate (**3h**), the title compound **4h** was obtained as a light yellow oil (50 mg, 95%);

***tert*-Butyl 3-(((benzyloxy)carbonyl)amino)pyrrolidine-1-carboxylate (5)**



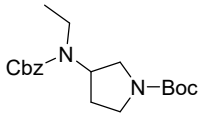
To a solution of *tert*-butyl 3-aminopyrrolidine-1-carboxylate (2.0 g, 10.75 mmol) in methylene chloride (30 mL), DIEA (2.8 mL, 16.13 mmol) and benzyl chloroformate (1.76 mL, 12.9 mmol) were added, and the mixture was stirred in ice bath for 3 h. Then the methylene chloride (50 mL) was added and washed with brine (10 mL×2), dried over anhydrous magnesium sulfate. After filtration and concentration, the crude product was obtained and purified with column chromatography (Ethyl Acetate /Petroleum ether = 1:5 to 1:3) to give compound **5** as a colorless oil (3.0 g, 87.2%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27-7.35 (m, 5H), 5.10 (s, 2H), 4.89 (brs, 1H), 4.25 (brs, 1H), 3.57-3.62 (m, 1H), 3.41 (brs, 2H), 3.15-3.20 (m, 1H), 2.11 (brs, 1H), 1.83 (brs, 1H), 1.45 (s, 9H).

tert-Butyl 3-(((benzyloxy)carbonyl)(methyl)amino)pyrrolidine-1-carboxylate (6a)



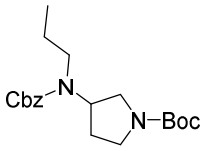
To a solution of *tert*-butyl 3-(((benzyloxy)carbonyl)amino)pyrrolidine-1-carboxylate (1.6 g, 5.0 mmol) in DMF (30 mL), NaH (300 mg, 7.5 mmol) was added and the mixture was stirred under argon at room temperature for 1 h. Then iodomethane (0.38 mL, 6 mmol) was added and the reaction mixture was stirred still at room temperature for 1 h. H_2O was added to the mixture and then the solution was extracted with ethyl acetate (50 mL × 2) and then the organic layer was washed with brine (40 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration, the crude product was obtained and purified with column chromatography (Ethyl Acetate /Petroleum ether = 1:5) to give compound **6a** as a colorless oil (1.4 g, 84.8%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27-7.36 (m, 5H), 5.14 (s, 2H), 4.80 (brs, 1H), 3.40-3.60 (m, 2H), 3.21-3.33 (m, 2H), 2.86 (s, 3H), 1.93-2.02 (m, 2H), 1.45 (s, 9H).

***tert*-Butyl 3-(((benzyloxy)carbonyl)(ethyl)amino)pyrrolidine-1-carboxylate (6b)**



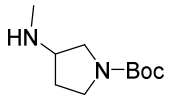
Following the preparation protocol of compound **6a**, starting from compound **5** and bromoethane, the title compound **6b** was obtained as a colorless oil (840 mg, 80.4%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27-.36 (m, 5H), 5.15 (s, 2H), 4.60 (brs, 1H), 3.45-3.65 (m, 2H), 3.10-3.30 (m, 4H), 1.95-2.03 (m, 2H), 1.45 (s, 9H), 1.14 (t, J = 6.4 Hz, 3H)

***tert*-Butyl 3-(((benzyloxy)carbonyl)(propyl)amino)pyrrolidine-1-carboxylate (6c)**



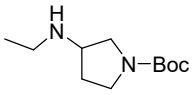
Following the preparation protocol of compound **6a**, starting from compound **5** and 1-bromopropane, the title compound **6c** was obtained as a colorless oil (300 mg, 73.7%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27-7.35 (m, 5H), 5.14 (s, 2H), 4.53 (brs, 1H), 3.50-3.60 (m, 2H), 3.11-3.29 (m, 4H), 1.97-2.04 (m, 2H), 1.53-1.61 (m, 2H), 1.45 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H).

***tert*-Butyl 3-(methylamino)pyrrolidine-1-carboxylate (7a)**



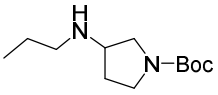
The mixture of compound **6a** (250 mg, 0.75 mmol) and 10% Pd/C (75 mg) in ethanol (10.0 mL) was hydrogenated at room temperature and 1 atm for 3 h. The reaction mixture was filtered over a pad of Celiteand and then the solution was concentrated to afford compound **7a** as a colorless oil (140 mg, 93.9%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.34-3.55 (m, 3H), 3.05-3.25 (m, 2H), 2.44 (s, 3H), 1.98-2.07 (m, 1H), 1.70 (brs, 1H), 1.46 (s, 9H).

***tert*-Butyl 3-(ethylamino)pyrrolidine-1-carboxylate (7b)**



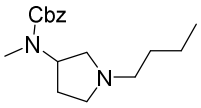
Following the preparation protocol of compound **7a**, starting from compound **6b**, the title compound **7b** was obtained as a colorless oil (440 mg, 90%).

***tert*-Butyl 3-(propylamino)pyrrolidine-1-carboxylate (7c)**



Following the preparation protocol of compound **7a**, starting from compound **6c**, the title compound **7c** was obtained as a colorless oil (160 mg, 95.8%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.43-3.62 (m, 2H), 3.25-3.32 (m, 2H), 2.99-3.13 (m, 1H), 2.57 (t, J = 6.8 Hz, 2H), 2.00-2.09 (m, 1H), 1.697 (brs, 1H), 1.48 (q, J = 7.2 Hz, 2H), 1.44 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H).

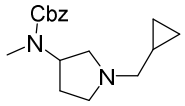
Benzyl (1-butylpyrrolidin-3-yl)(methyl)carbamate (8a)



To a solution of compound **6a** (500 mg, 1.56 mmol) in DCM (10.0 mL), TFA (1.15 mL, 15.6 mmol) was added and then the reaction mixture was stirred at room temperature for 3 h. After filtration under vacuum distillation, acetonitrile (10 mL) was added to the residue. Then the DIEA (0.53 mL, 3.44 mmol) and 1-bromobutane (0.11 mL, 1.03 mmol) were added to the mixture. The mixture was stirred at 50 °C for 4 h. After concentration, the crude product was obtained and

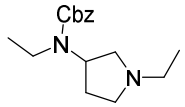
purified with column chromatography (methylene chloride /methanol = 50:1 to 40:1) to give compound **8a** as a light yellow oil (280 mg, 64.5%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.36 (m, 5H), 5.10 (s, 2H), 3.30 (brs, 3H), 2.70-2.99 (m, 6H), 2.37-2.42 (m, 1H), 2.12-2.30 (m, 2H), 1.76 (brs, 2H), 1.34-1.38 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H).

Benzyl (1-(cyclopropylmethyl)pyrrolidin-3-yl)(methyl)carbamate (8b)



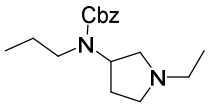
Following the preparation protocol of compound **8a**, starting from compound **6a** and (bromomethyl)cyclopropane, the title compound **8b** was obtained as a light yellow oil (206 mg, 79.8%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.36 (m, 5H), 5.07-5.15 (m, 2H), 3.25-3.65 (m, 4H), 3.00 (s, 3H), 2.87 (brs, 3H), 2.43 (brs, 1H), 2.24 (brs, 1H), 0.78-0.85 (m, 1H), 0.70 (brs, 2H), 0.38 (brs, 2H).

Benzyl ethyl(1-ethylpyrrolidin-3-yl)carbamate (8c)



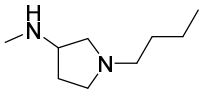
Following the preparation protocol of compound **8a**, starting from compound **6b** and bromoethane, the title compound **8c** was obtained as a light yellow oil (197 mg, 77.2%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.36 (m, 5H), 5.06-5.15 (m, 2H), 4.13 (brs, 1H), 3.10-3.85 (m, 8H), 2.61 (brs, 1H), 2.28 (brs, 1H), 1.45 (brs, 3H), 1.11 (t, J = 8.0 Hz, 3H).

Benzyl (1-ethylpyrrolidin-3-yl)(propyl)carbamate (8d)



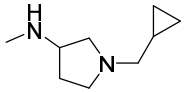
Following the preparation protocol of compound **8a**, starting from compound **6c** and bromoethane, the title compound **8d** was obtained as a light yellow oil (230 mg, 95.8%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.38 (m, 5H), 5.07-5.11 (m, 2H), 4.14 (brs, 1H), 3.79 (brs, 1H), 3.64 (brs, 1H), 3.10-3.60 (m, 6H), 2.63 (brs, 1H), 2.31 (brs, 1H), 1.40-1.60 (m, 2H), 0.80-0.95 (m, 6H).

1-Butyl-*N*-methylpyrrolidin-3-amine (9a)



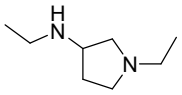
Following the preparation protocol of compound **7a**, starting from compound **8a**, the title compound **9a** was obtained as a light yellow oil (100 mg, 93.4%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.48 (brs, 1H), 3.56 (brs, 1H), 3.16-3.25 (m, 1H), 3.09-3.16 (m, 1H), 3.23 (brs, 0.5H), 3.09-3.16 (m, 1H), 2.92-3.03 (m, 2H), 2.65-2.82 (m, 2.5H), 2.49 (s, 3H), 2.18-2.32 (m, 1H), 1.95-2.05 (m, 1H), 1.61-1.71 (m, 2H), 1.35-1.39 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

1-(Cyclopropylmethyl)-*N*-methylpyrrolidin-3-amine (9b)



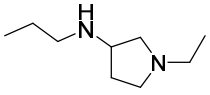
Following the preparation protocol of compound **7a**, starting from compound **8b**, the title compound **9b** was obtained as a light yellow oil (100 mg, 96%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.48 (brs, 1H), 3.56 (brs, 1H), 3.20-3.25 (m, 1H), 3.11-3.16 (m, 1H), 2.95-3.06 (m, 2H), 2.68 (d, J = 6.4 Hz, 2H), 2.51 (s, 3H), 2.29-2.34 (m, 1H), 1.93-2.03 (m, 1H), 0.80-0.90 (m, 1H), 0.63 (d, J = 7.2 Hz, 2H), 0.29 (d, J = 4.0 Hz, 2H).

***N*,1-diethylpyrrolidin-3-amine (9c)**



Following the preparation protocol of compound **7a**, starting from compound **8c**, the title compound **9c** was obtained as a light yellow oil (95 mg, 97.2%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.92 (brs, 1H), 3.58-3.63 (m, 1H), 3.38-3.44 (m, 1H), 3.30-3.40 (m, 2H), 3.10-3.15 (m, 2H), 2.89-3.00 (m, 2H), 2.46-2.52 (m, 1H), 2.35-2.45 (m, 1H), 1.38 (t, J = 7.2 Hz, 6H).

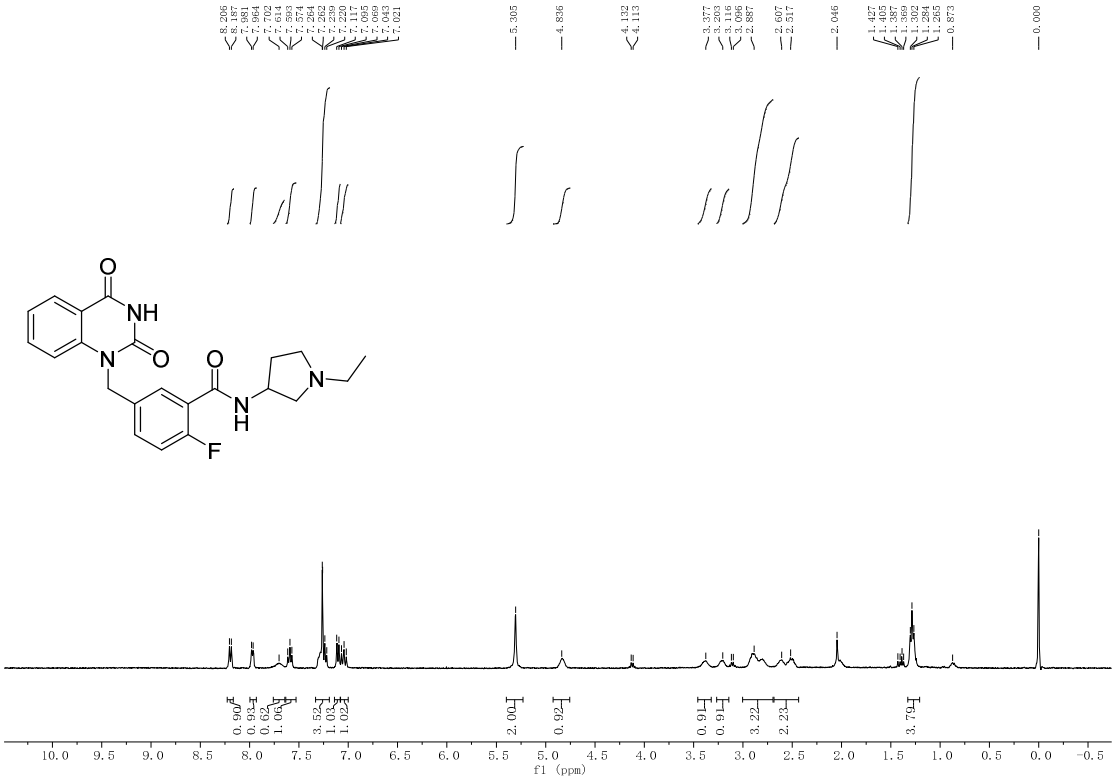
1-Ethyl-*N*-propylpyrrolidin-3-amine (9d)



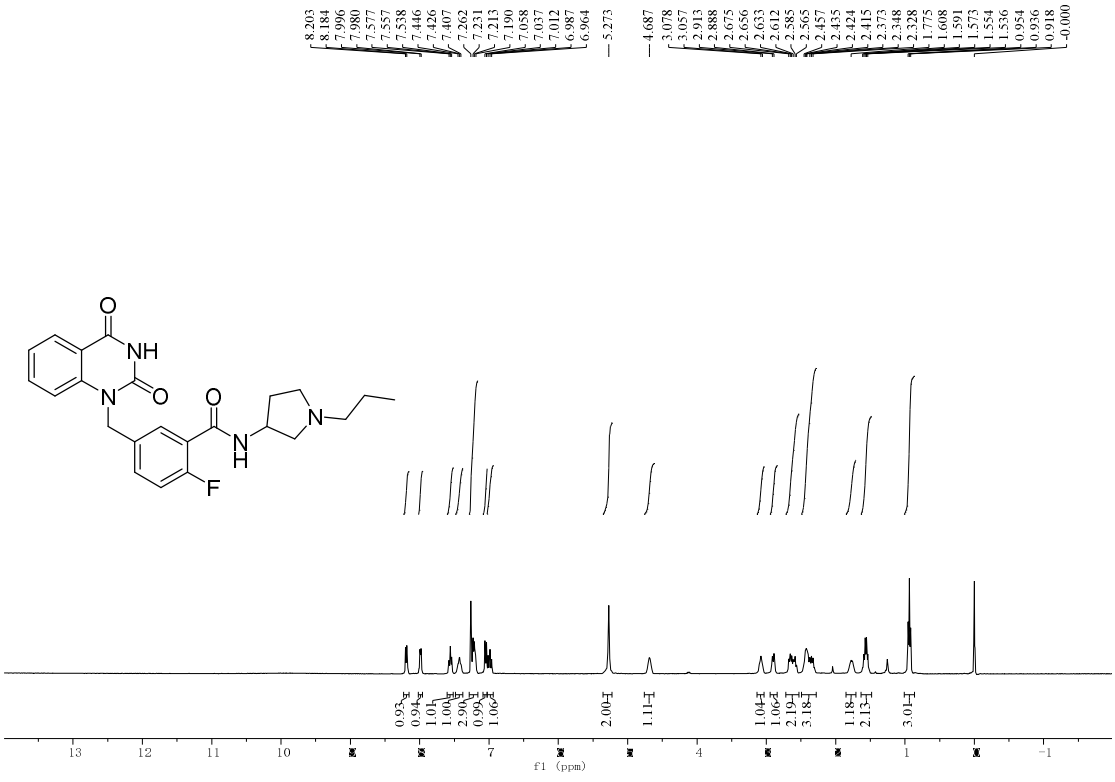
Following the preparation protocol of compound **7a**, starting from compound **8d**, the title

compound **9d** was obtained as a light yellow oil (100 mg, 86.9%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.74-3.81 (m, 1H), 3.44-3.52 (m, 1H), 3.18-3.36 (m, 3H), 3.02-3.12 (m, 2H), 2.66-2.74 (m, 2H), 2.34-2.44 (m, 1H), 2.17-2.26 (m, 1H), 1.66-1.76 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.6 Hz, 3H).

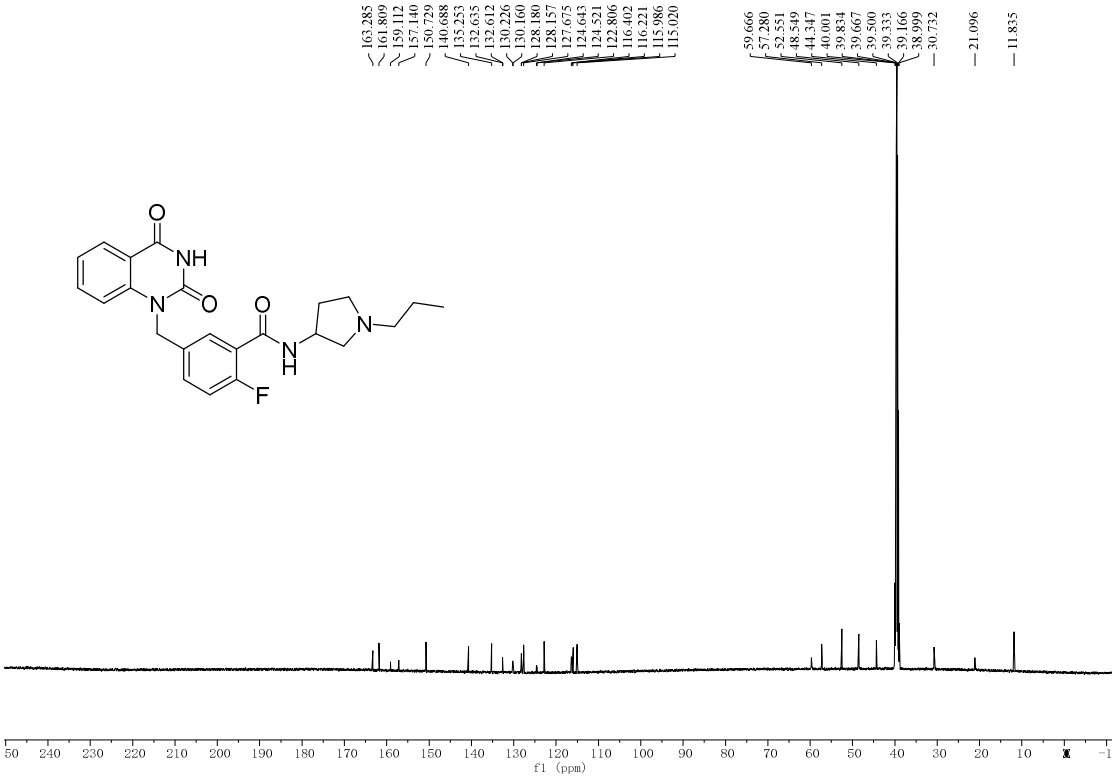
^{1}H NMR Spectrum of Compound 5



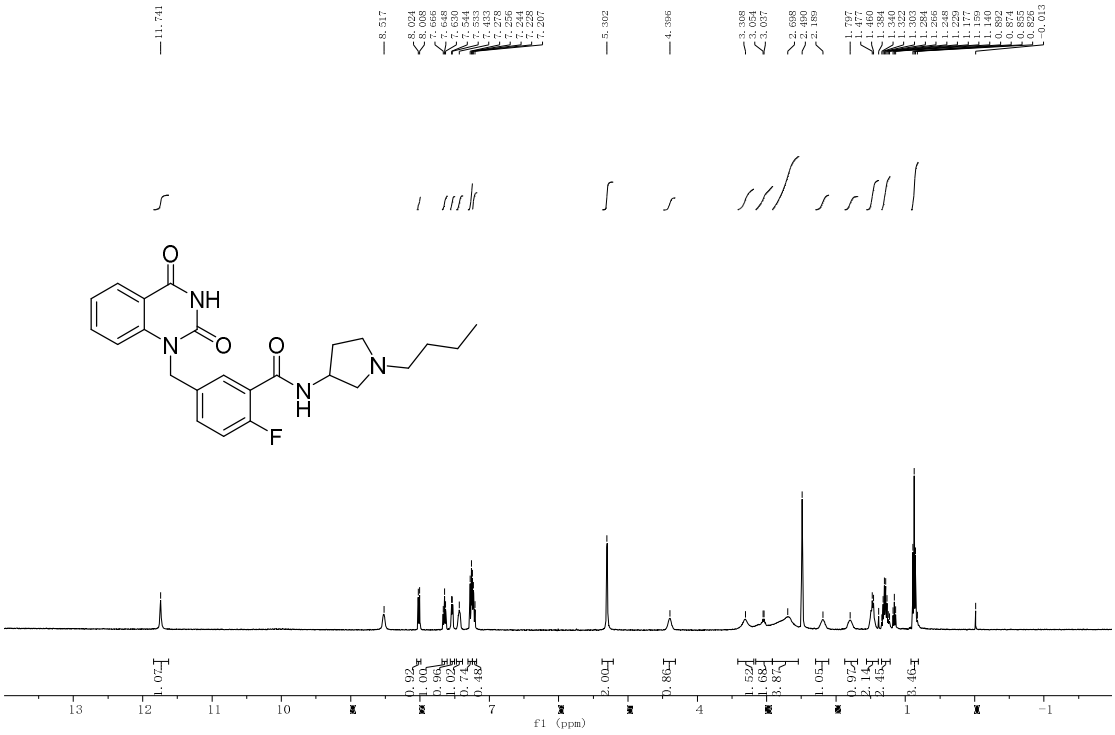
^{1}H NMR Spectrum of Compound 6



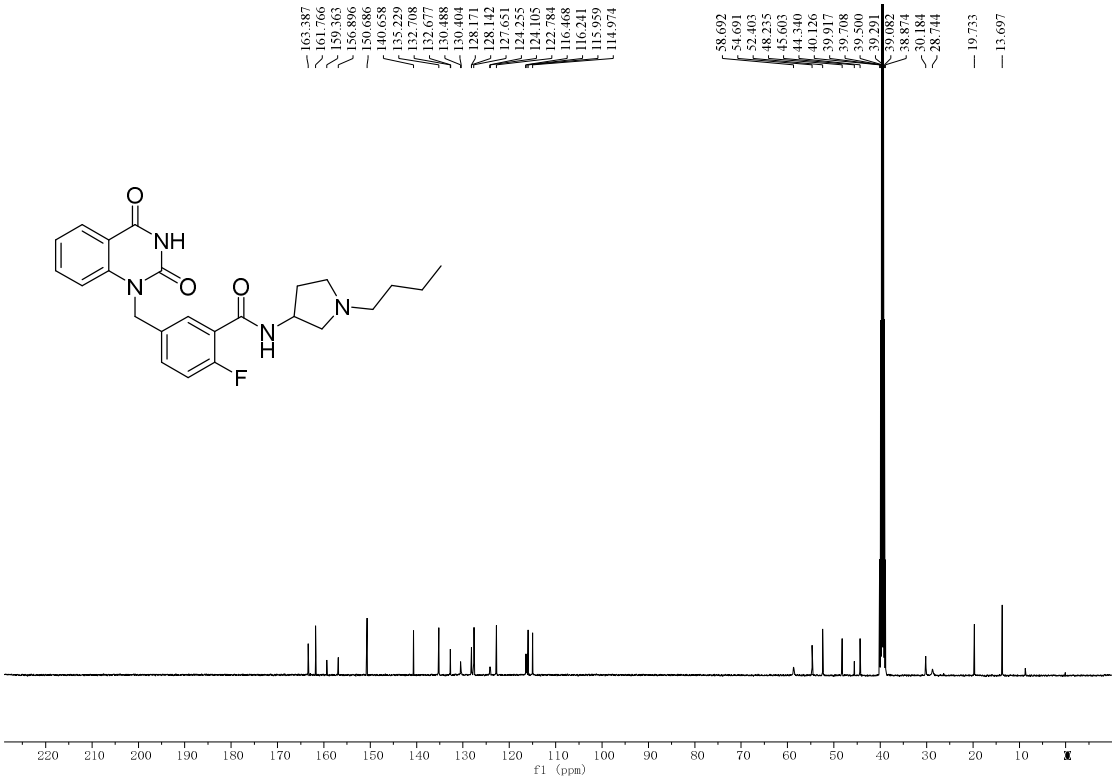
^{13}C NMR Spectrum of Compound 6



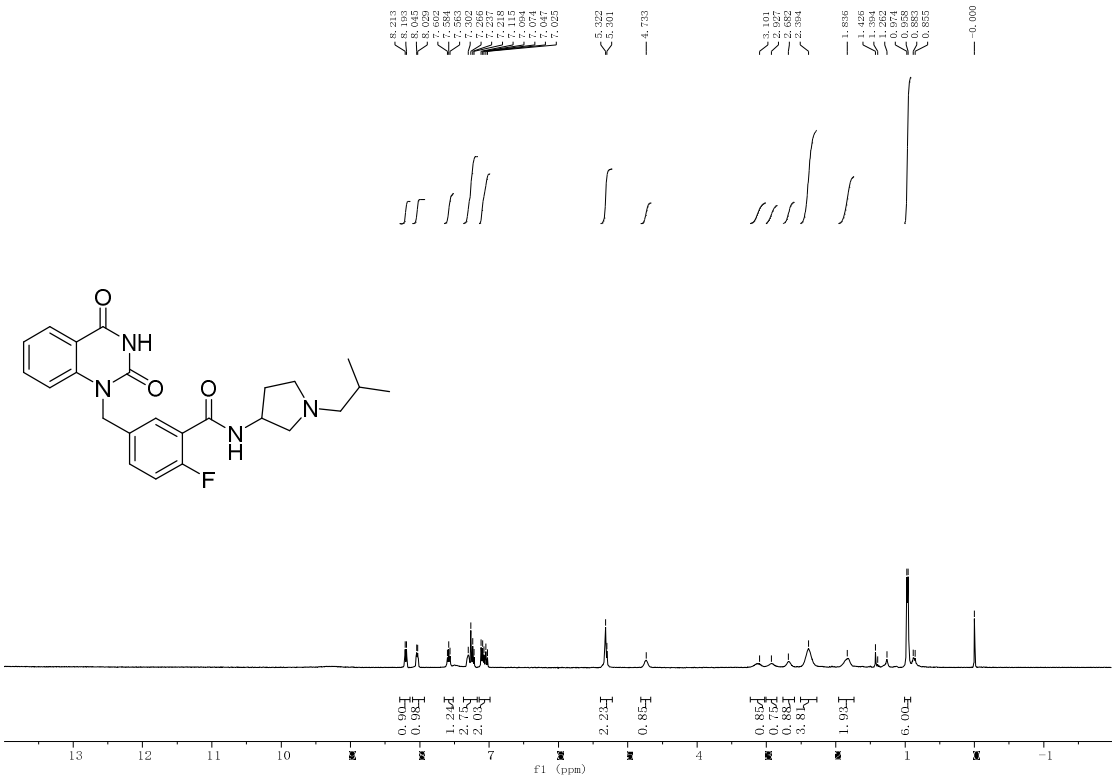
^{1}H NMR Spectrum of Compound 7



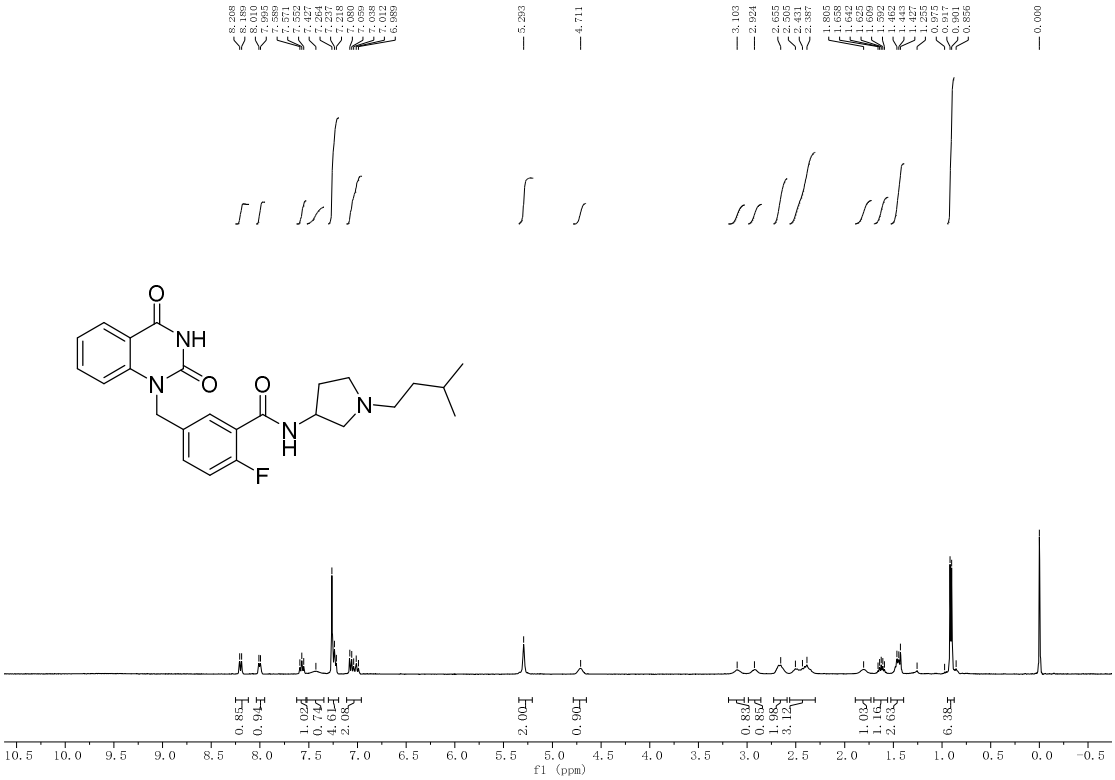
^{13}C NMR Spectrum of Compound 7



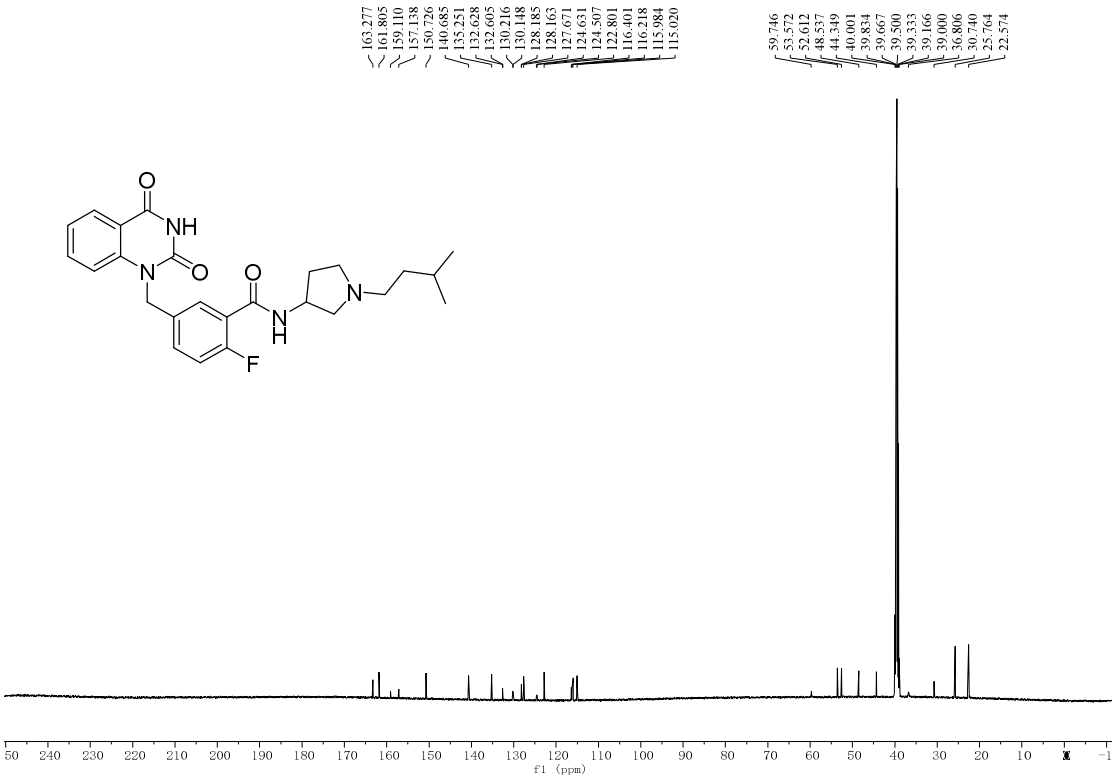
^{1}H NMR Spectrum of Compound 8



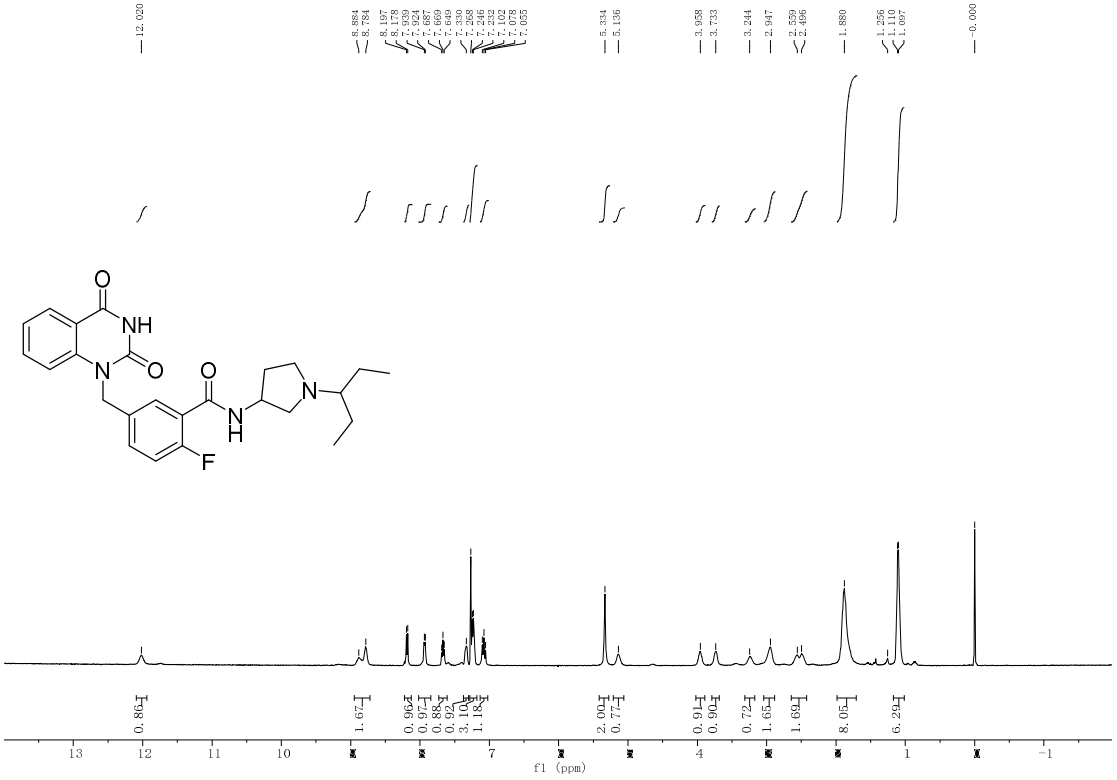
^{1}H NMR Spectrum of Compound 9



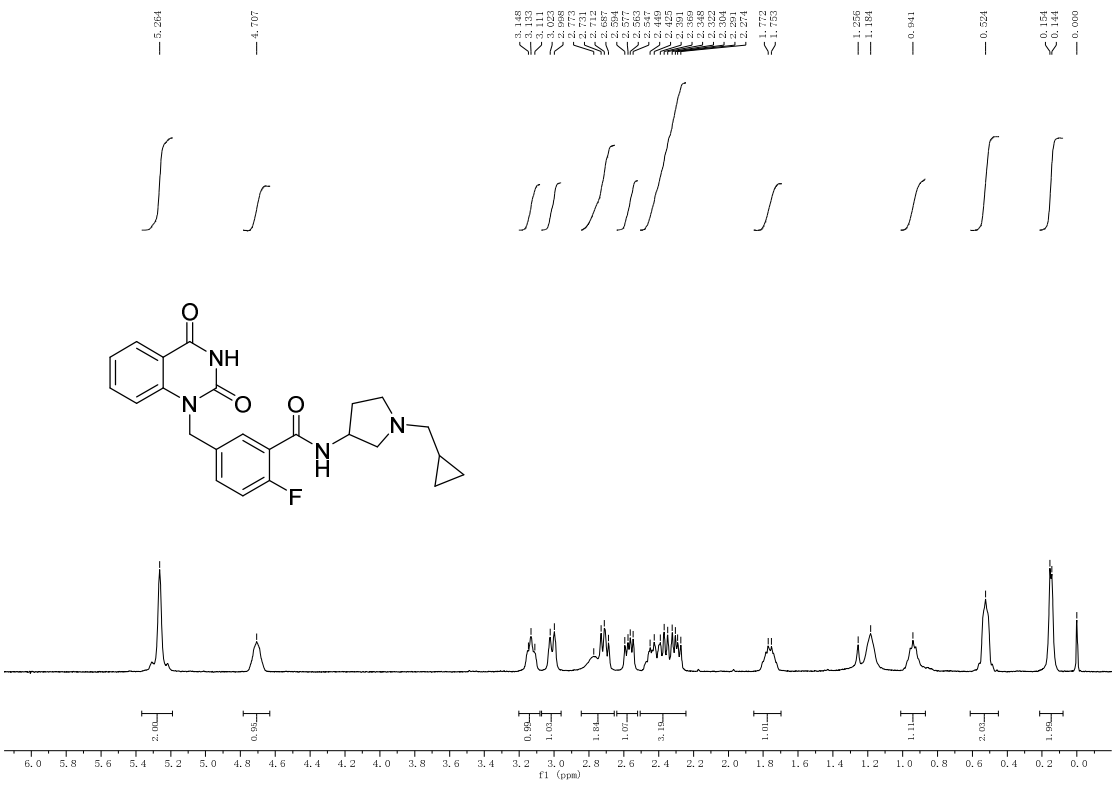
^{13}C NMR Spectrum of Compound 9



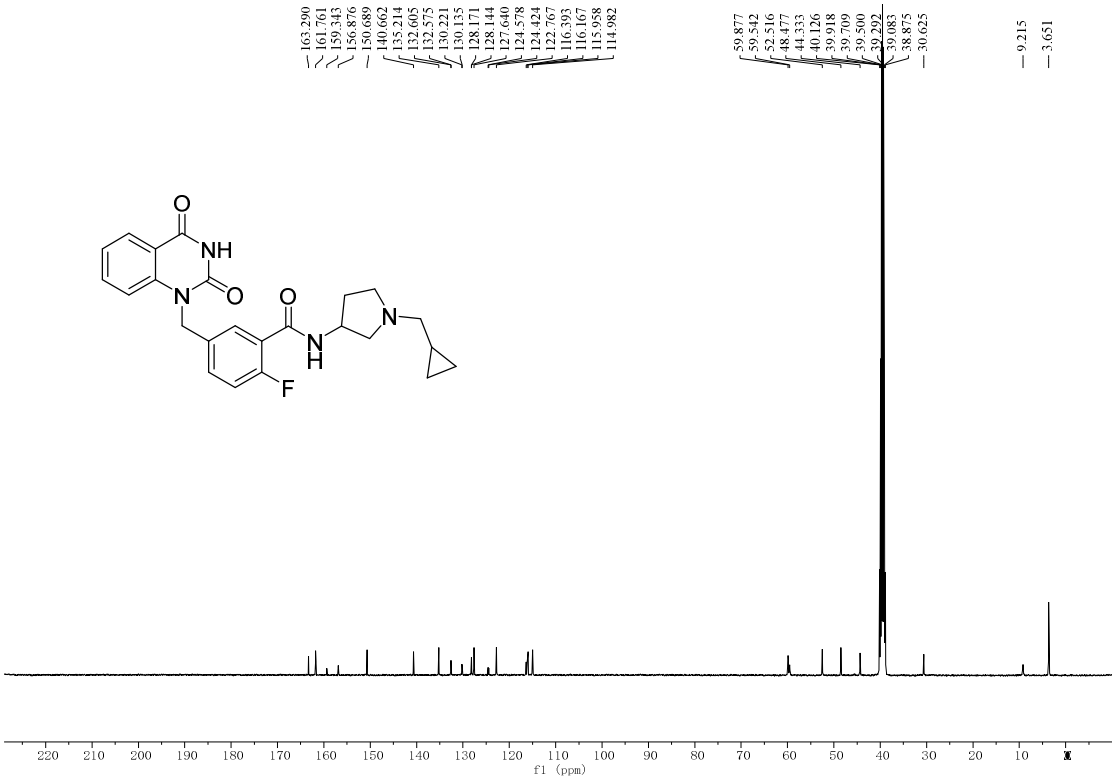
^{1}H NMR Spectrum of Compound 10



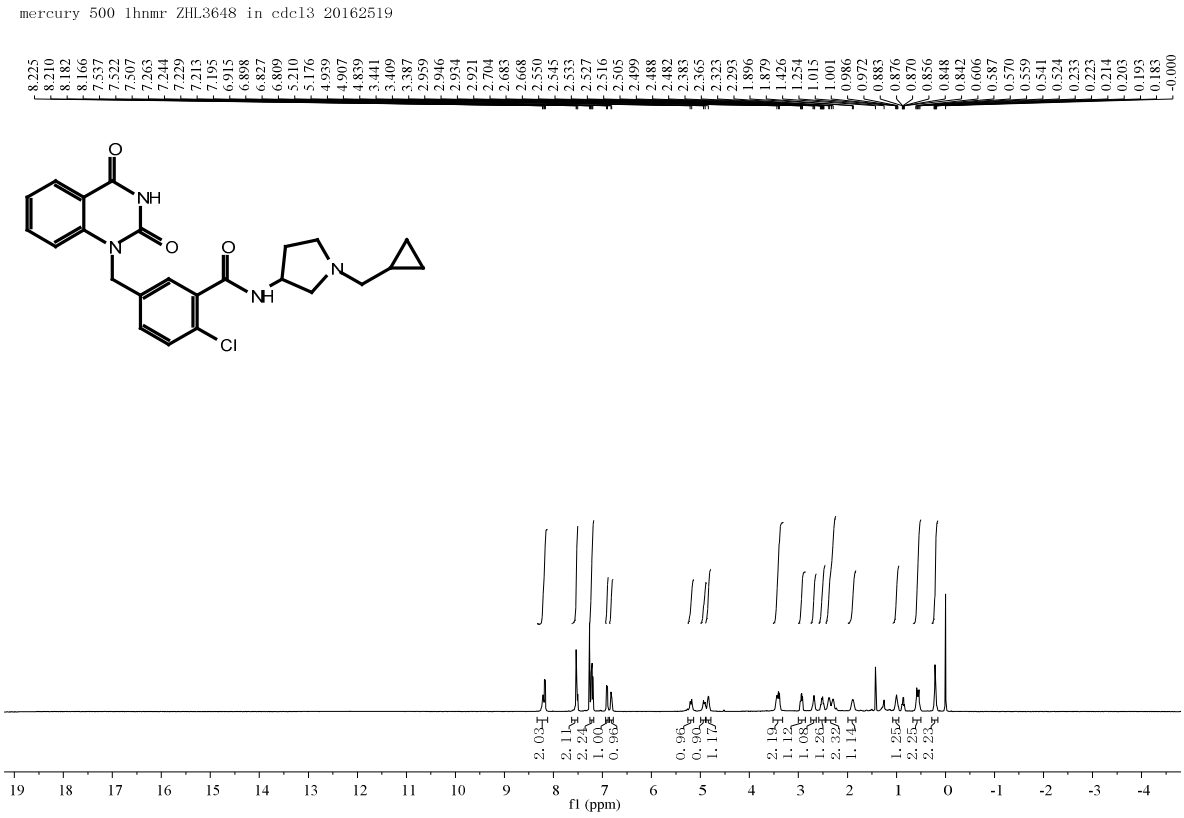
^{1}H NMR Spectrum of Compound 11



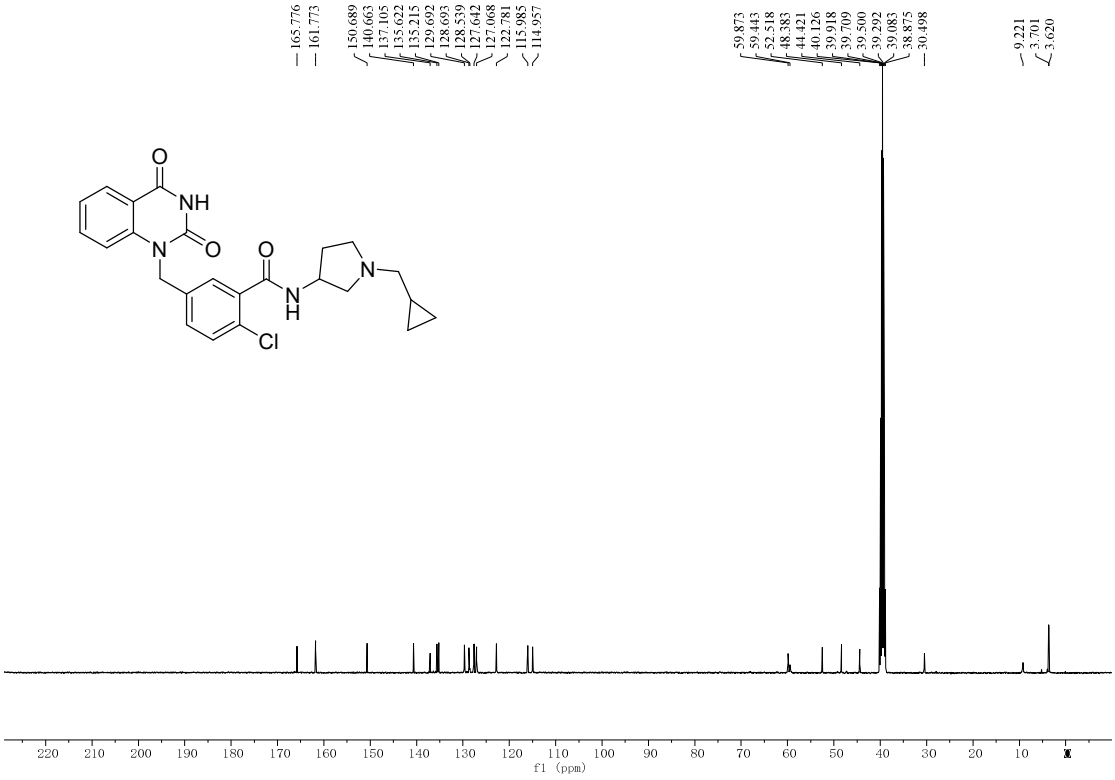
^{13}C NMR Spectrum of Compound 11



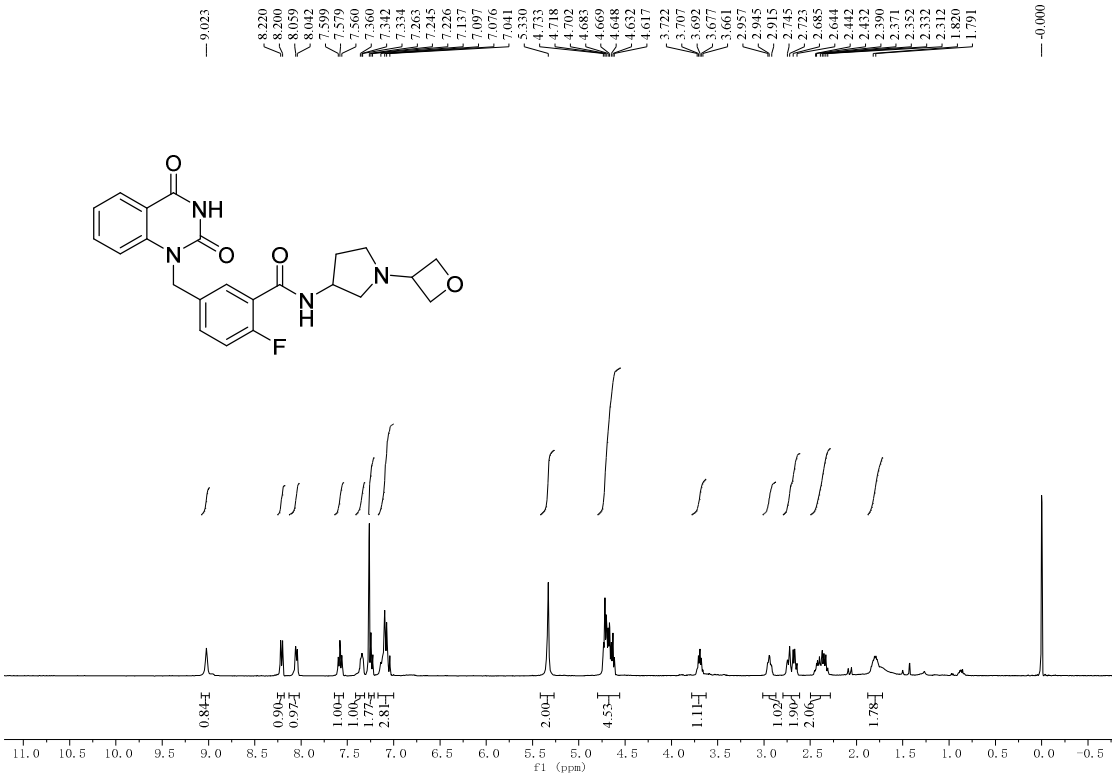
^{1}H NMR Spectrum of Compound 12



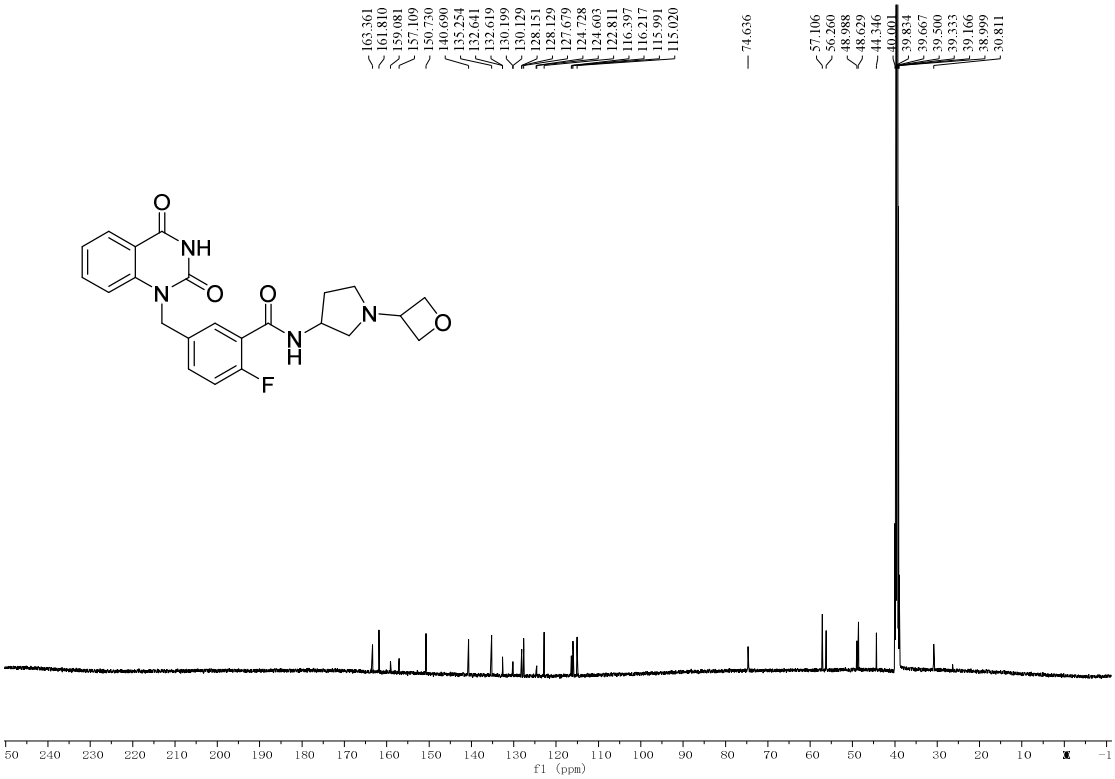
^{13}C NMR Spectrum of Compound 12



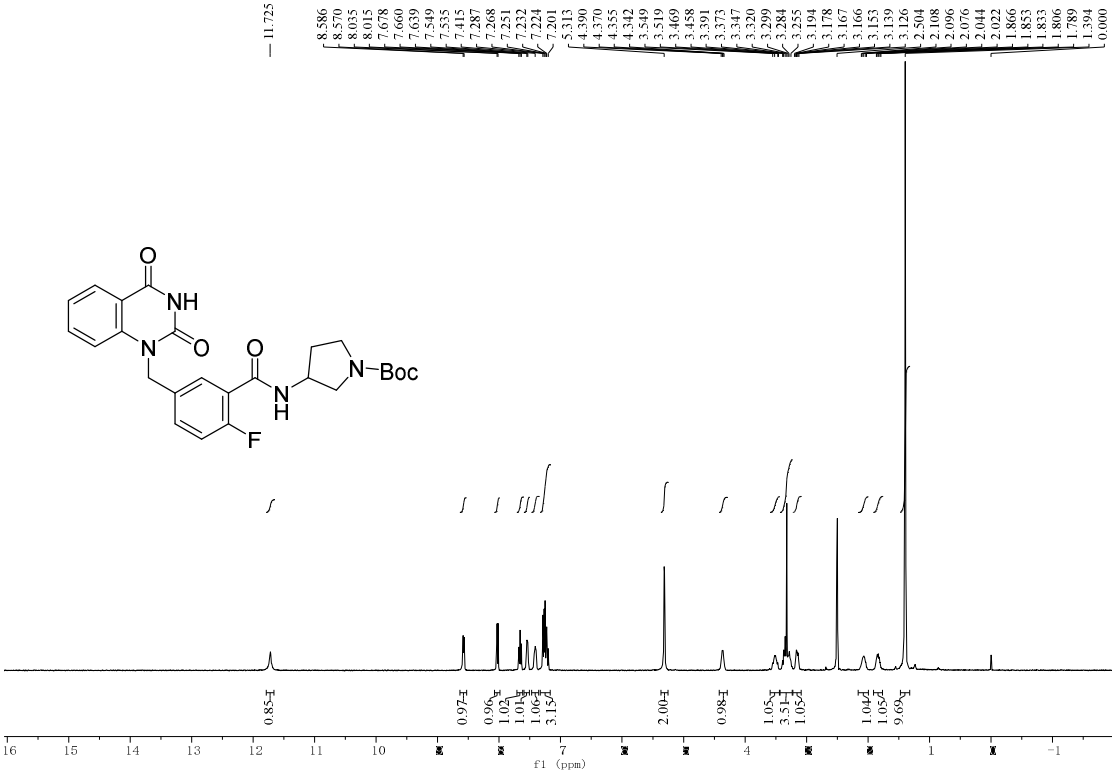
^{1}H NMR Spectrum of Compound 13



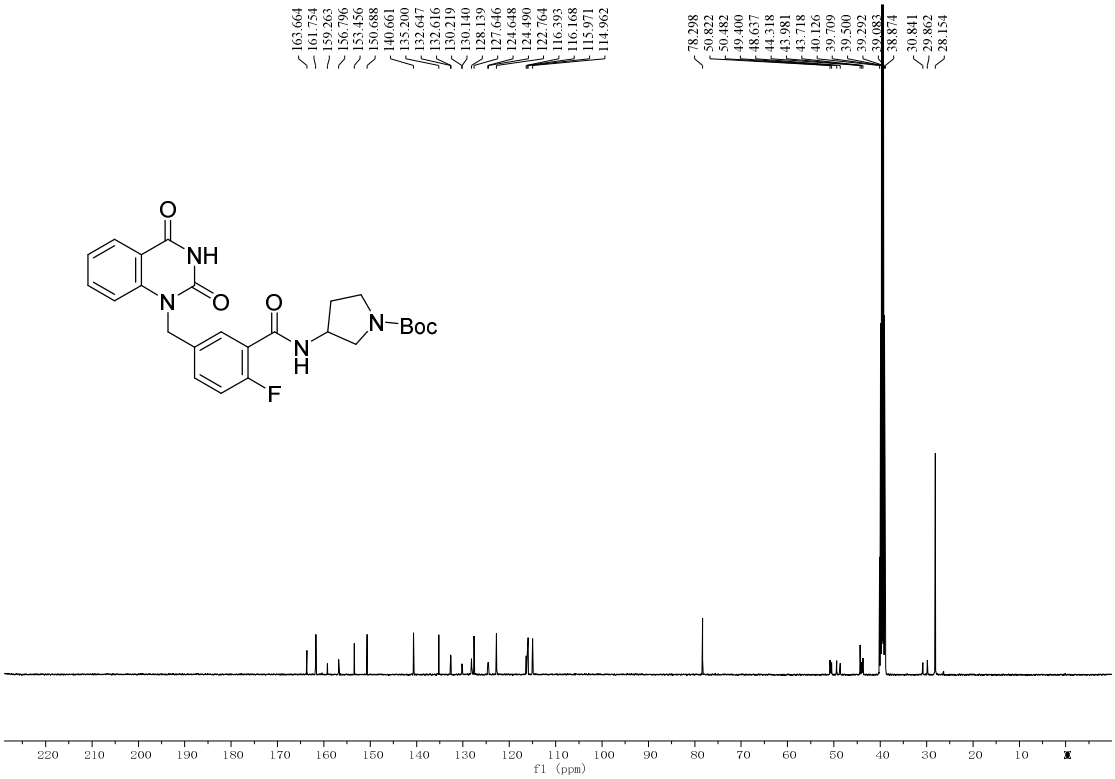
^{13}C NMR Spectrum of Compound 13



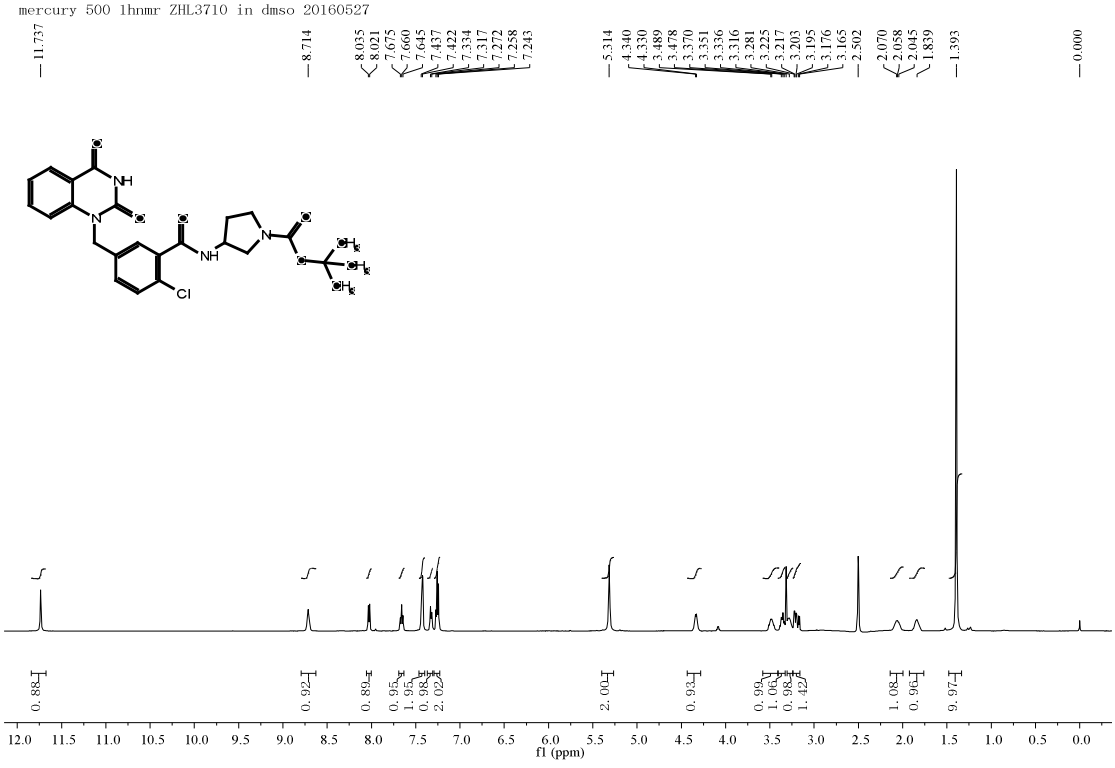
^{1}H NMR Spectrum of Compound 14



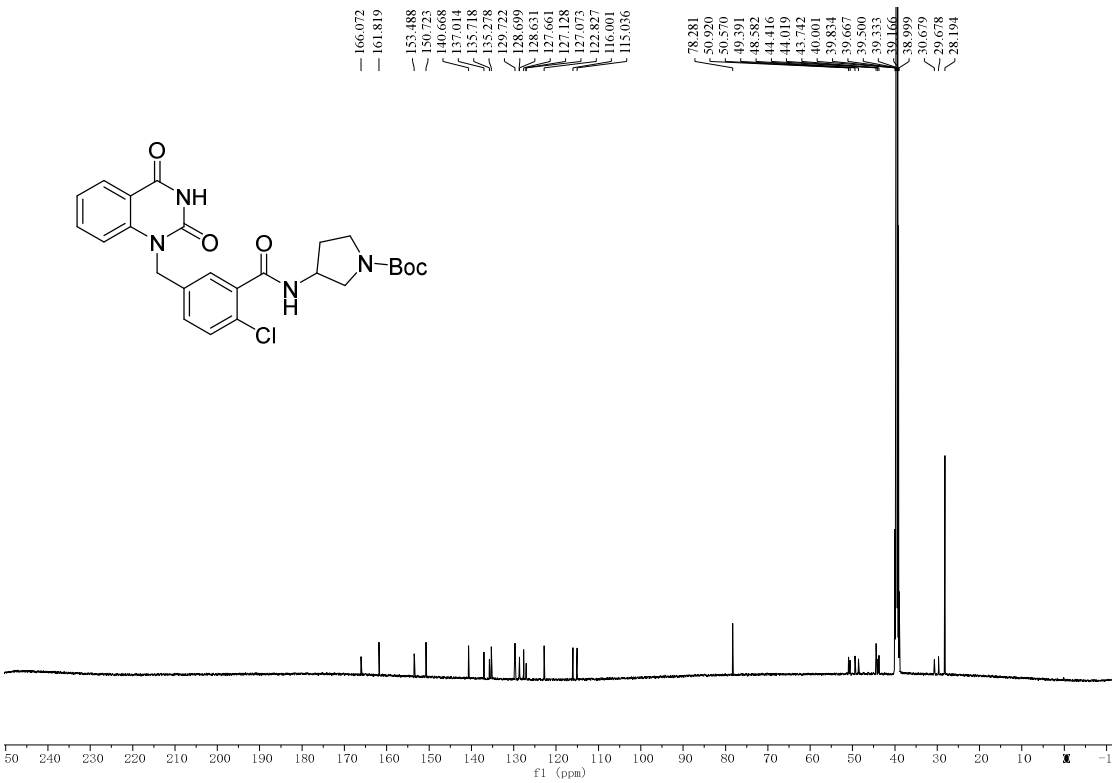
^{13}C NMR Spectrum of Compound 14



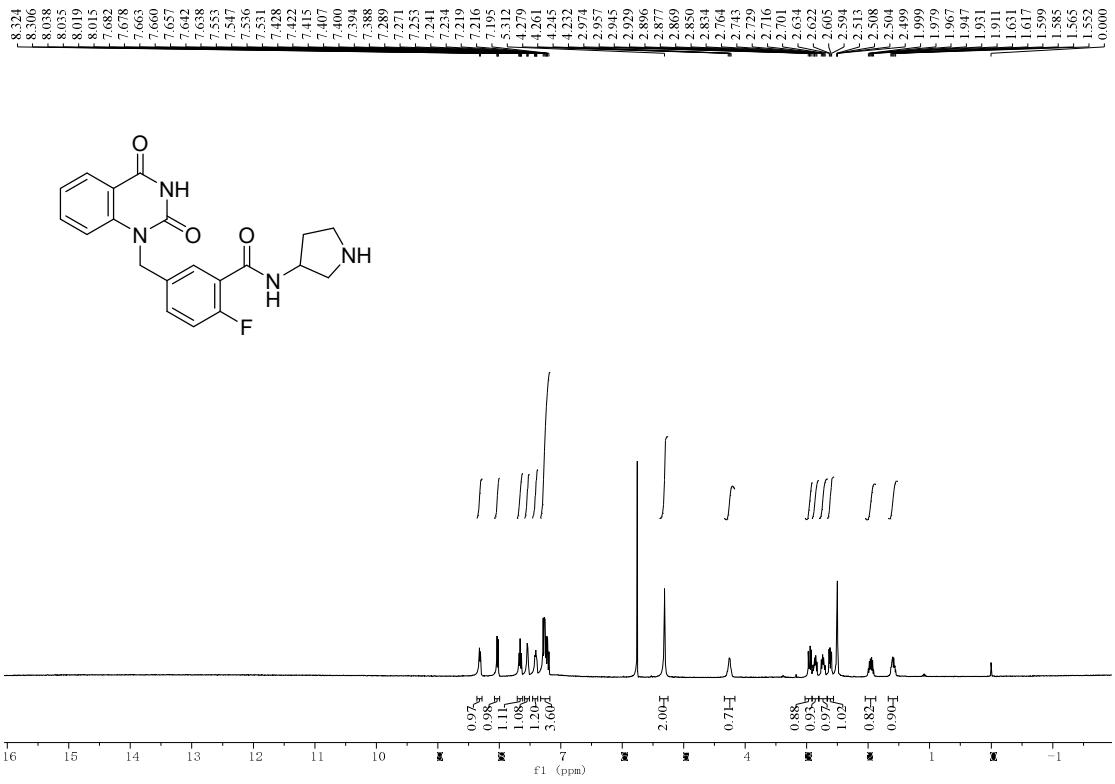
^{1}H NMR Spectrum of Compound 15



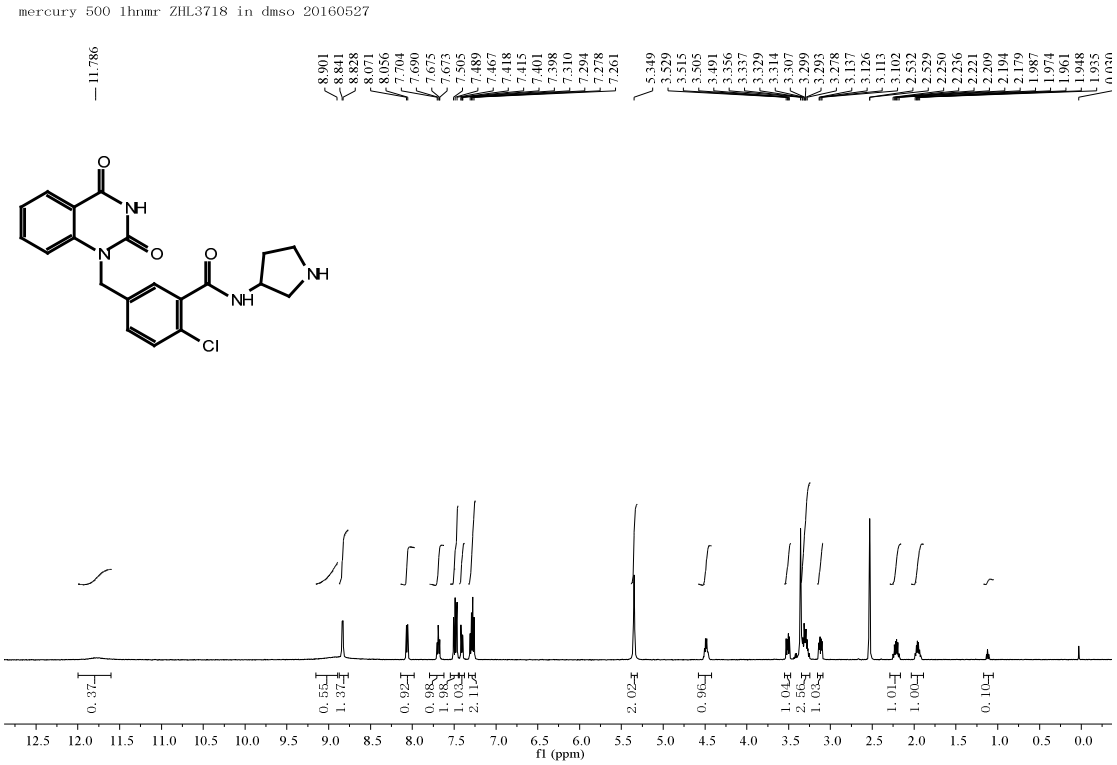
^{13}C NMR Spectrum of Compound 15



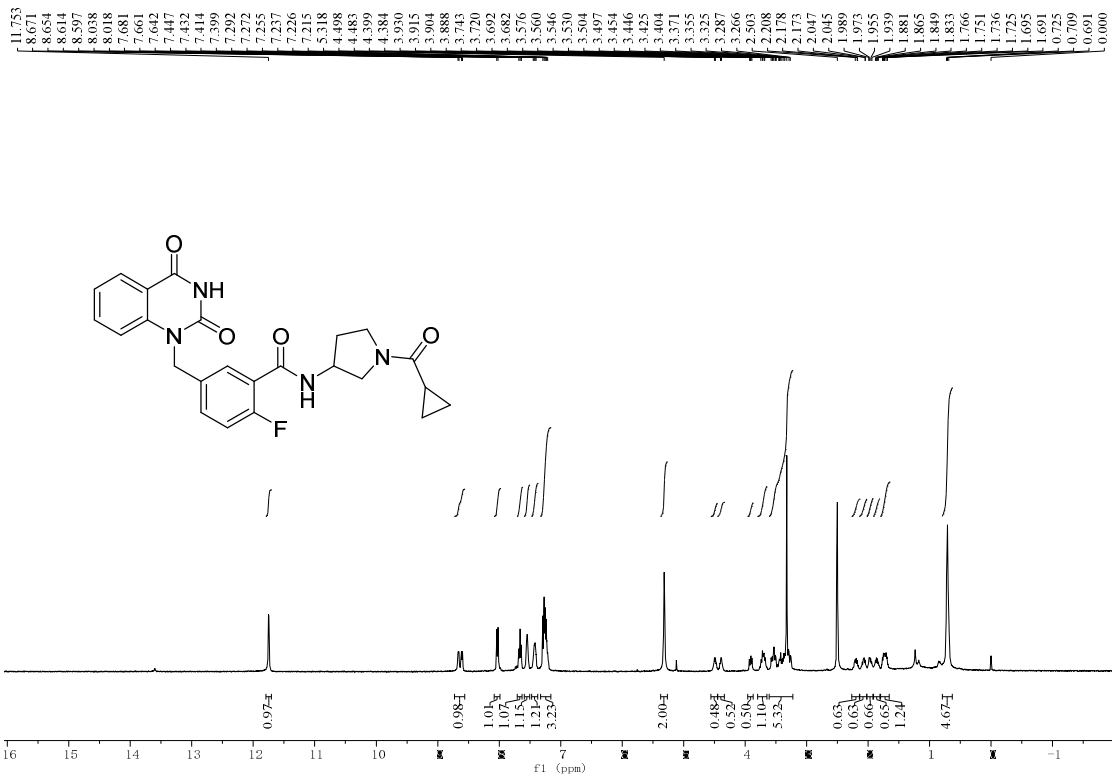
^{1}H NMR Spectrum of Compound 16



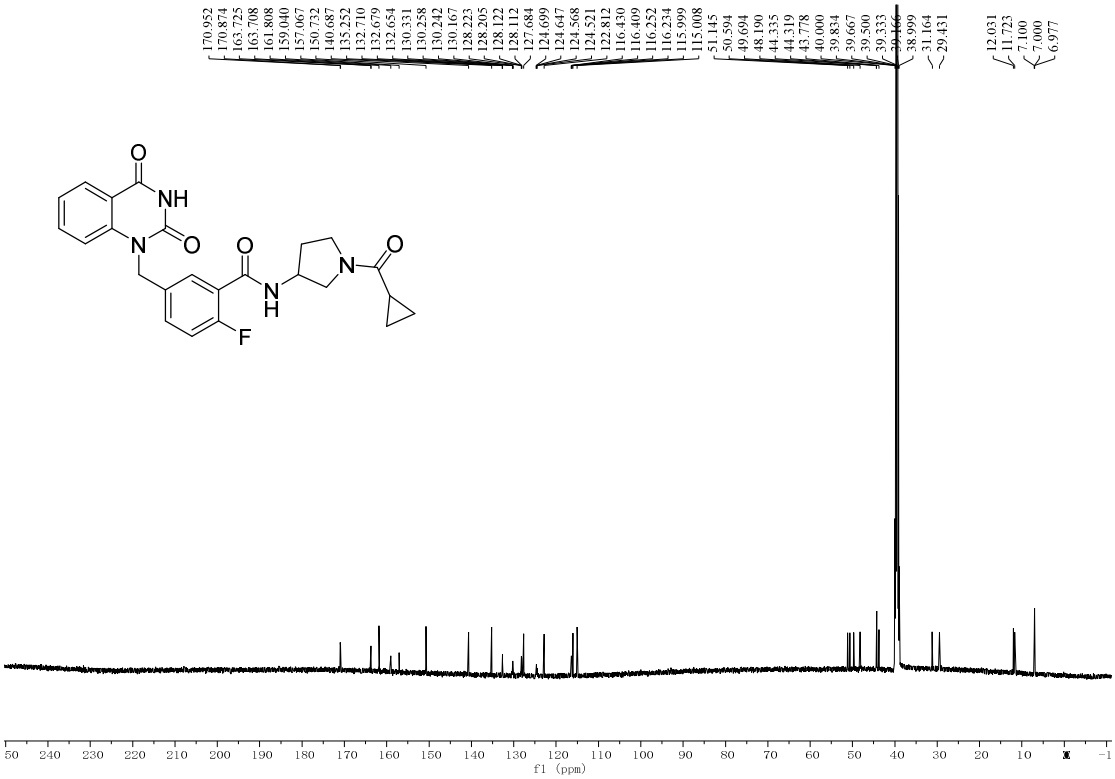
^{1}H NMR Spectrum of Compound 17



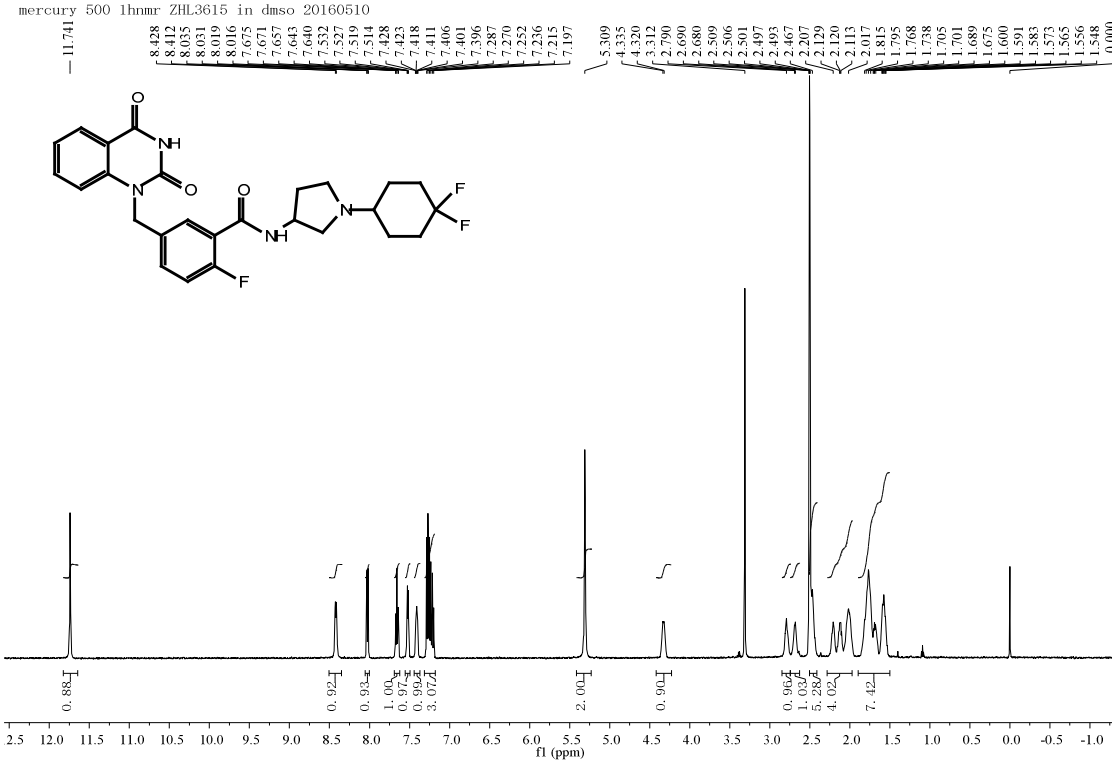
^{1}H NMR Spectrum of Compound 18



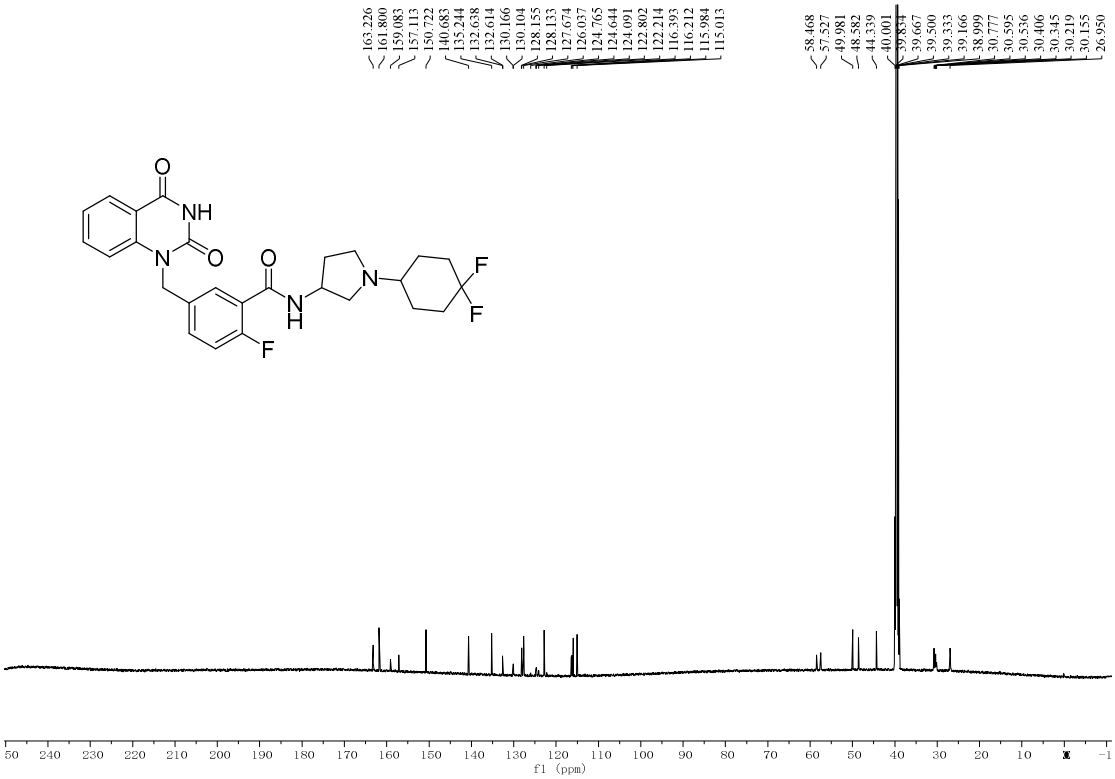
^{13}C NMR Spectrum of Compound 18



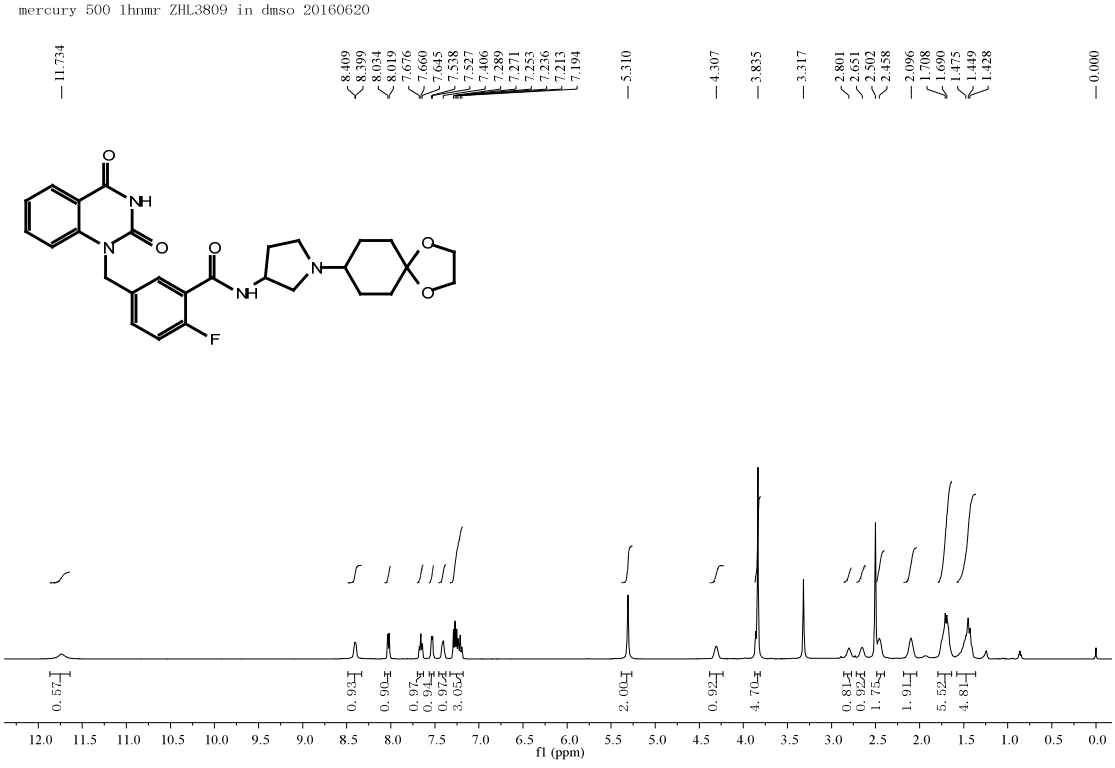
^{1}H NMR Spectrum of Compound 19



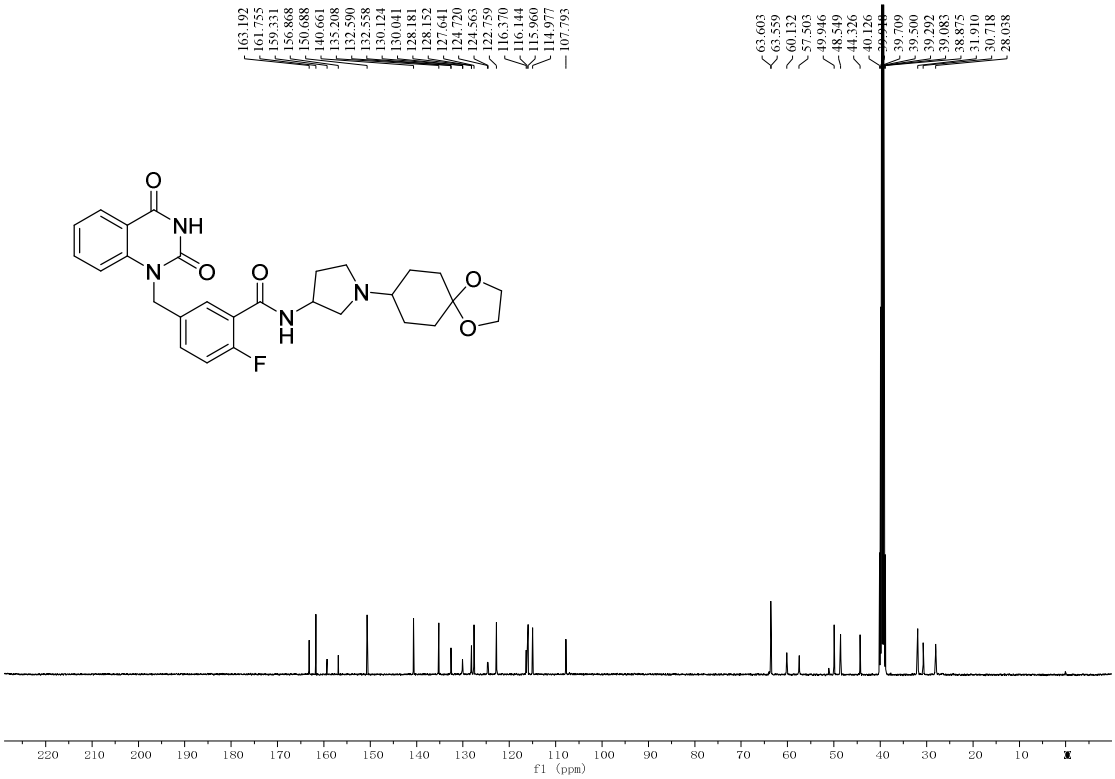
^{13}C NMR Spectrum of Compound19



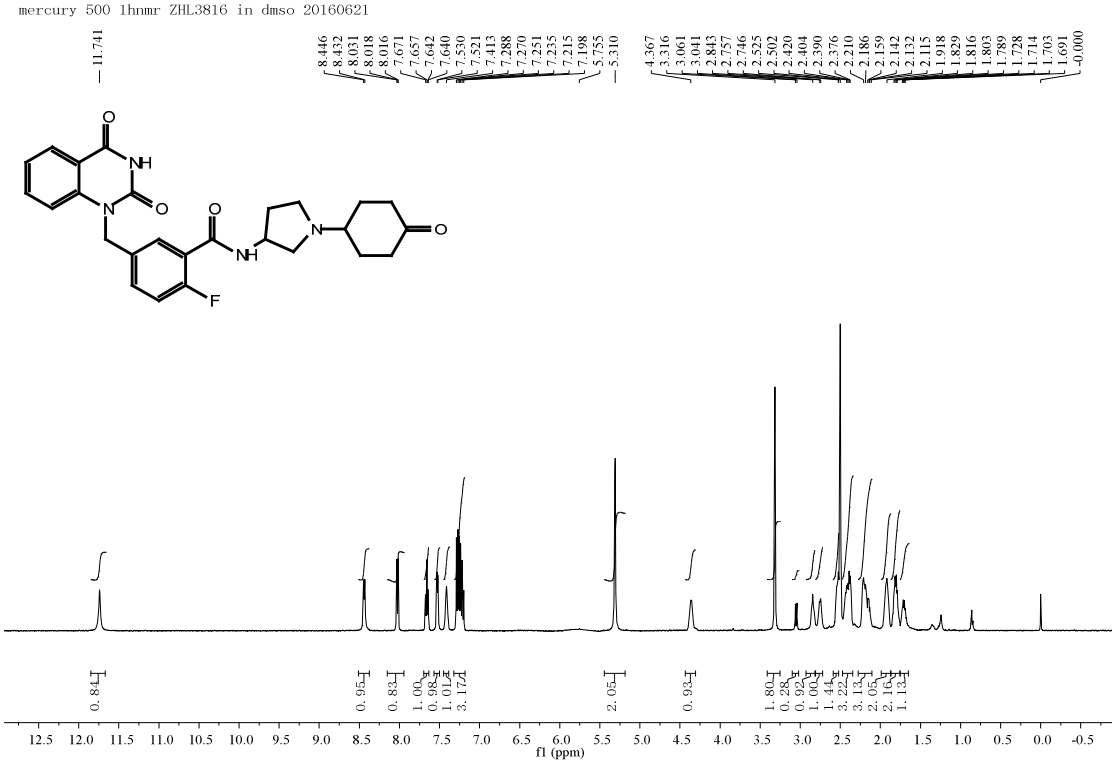
^{1}H NMR Spectrum of Compound 20



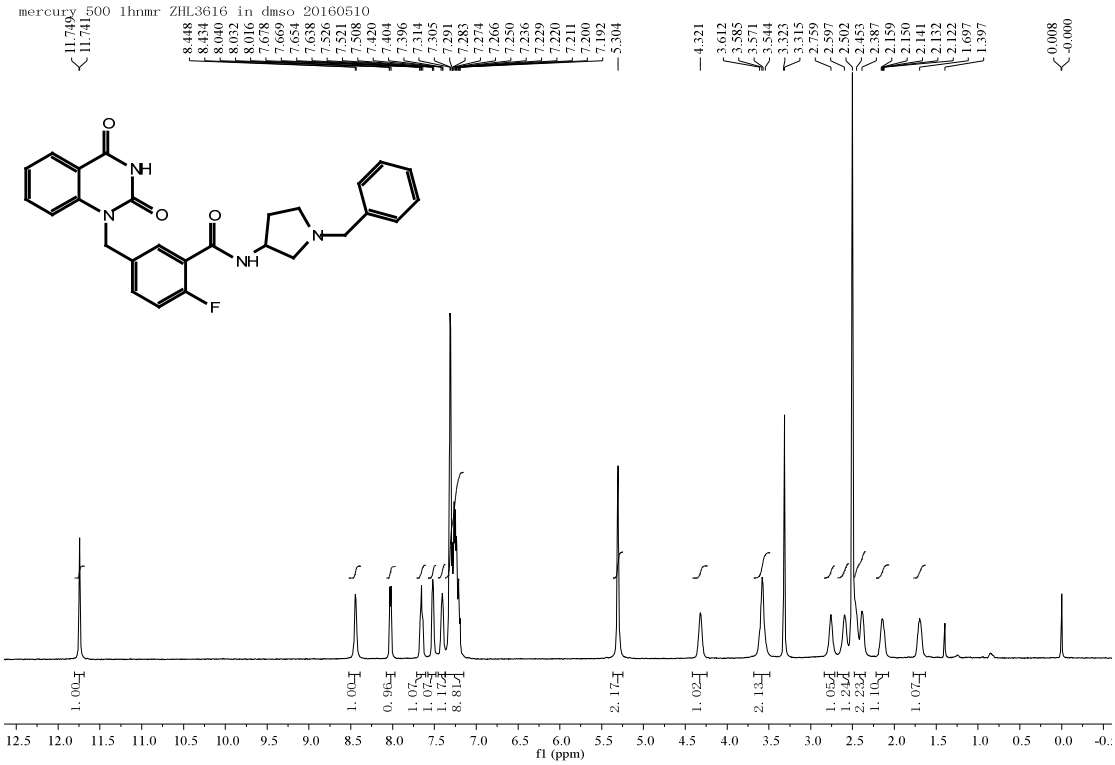
^{13}C NMR Spectrum of Compound 20



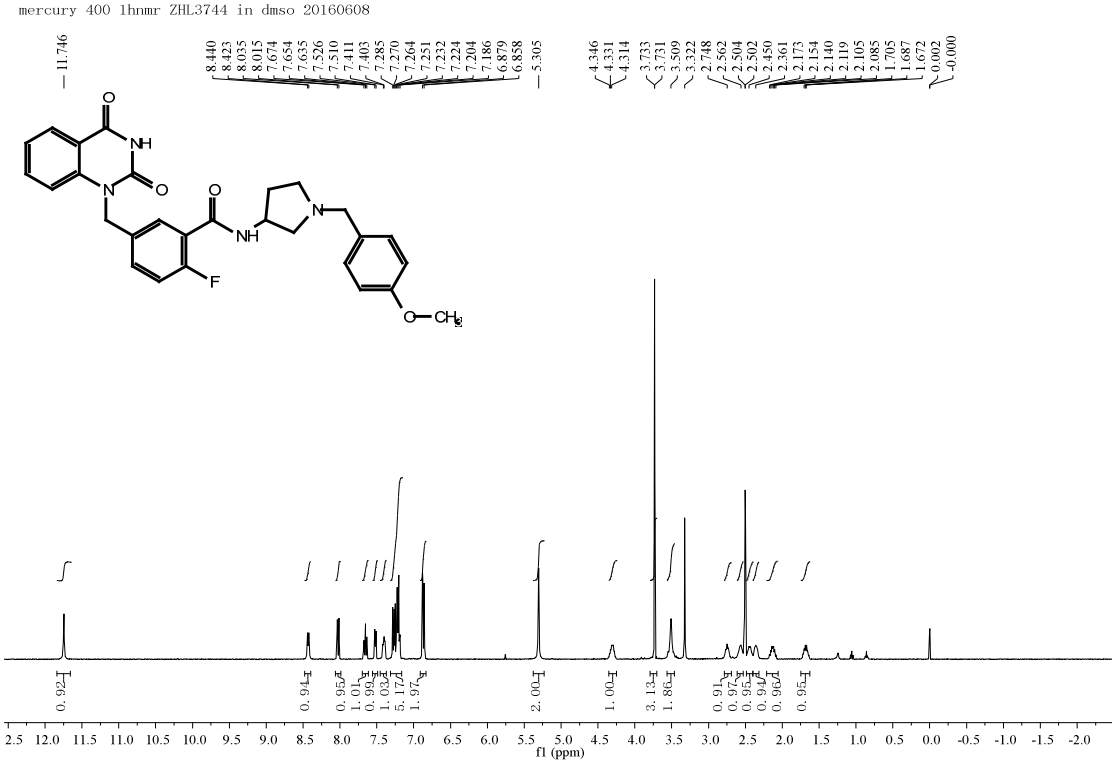
^{1}H NMR Spectrum of Compound 21



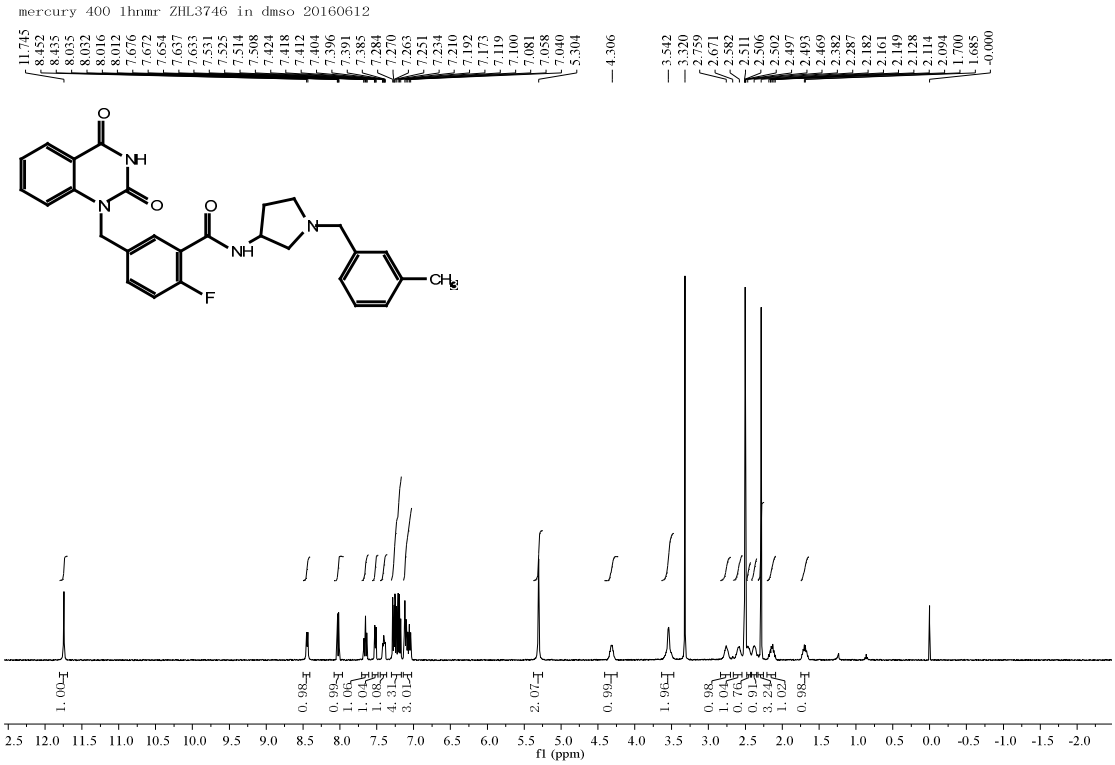
^{1}H NMR Spectrum of Compound 22



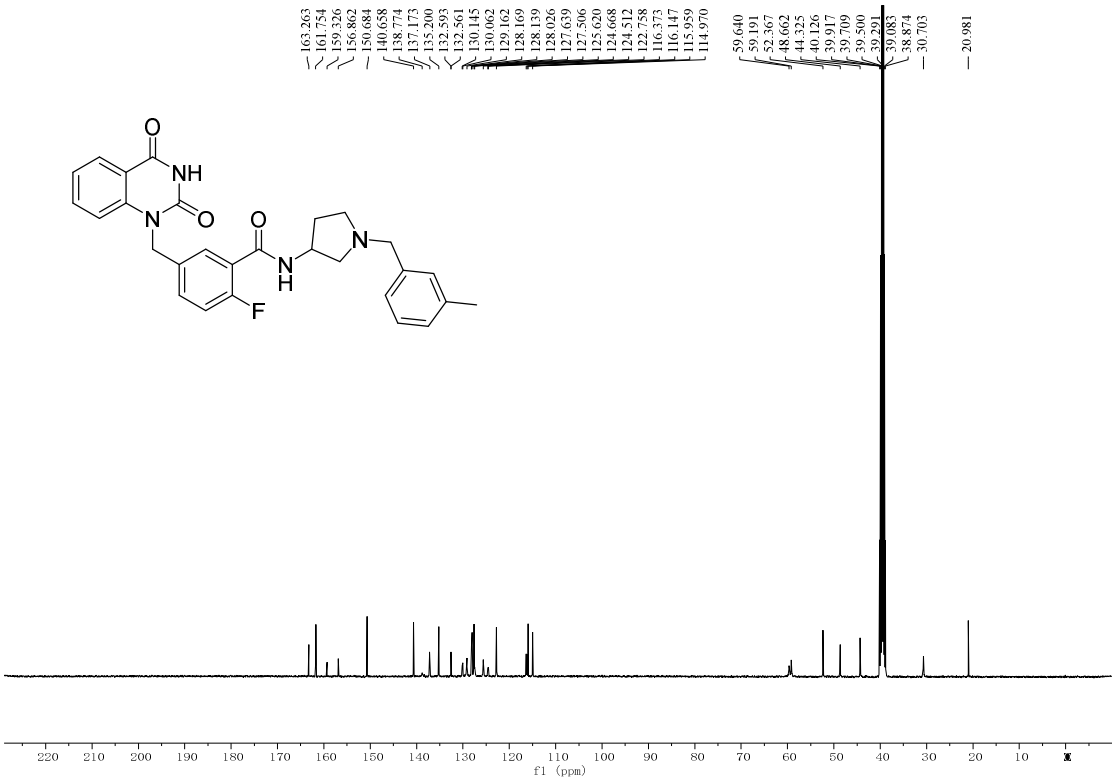
^{1}H NMR Spectrum of Compound 23



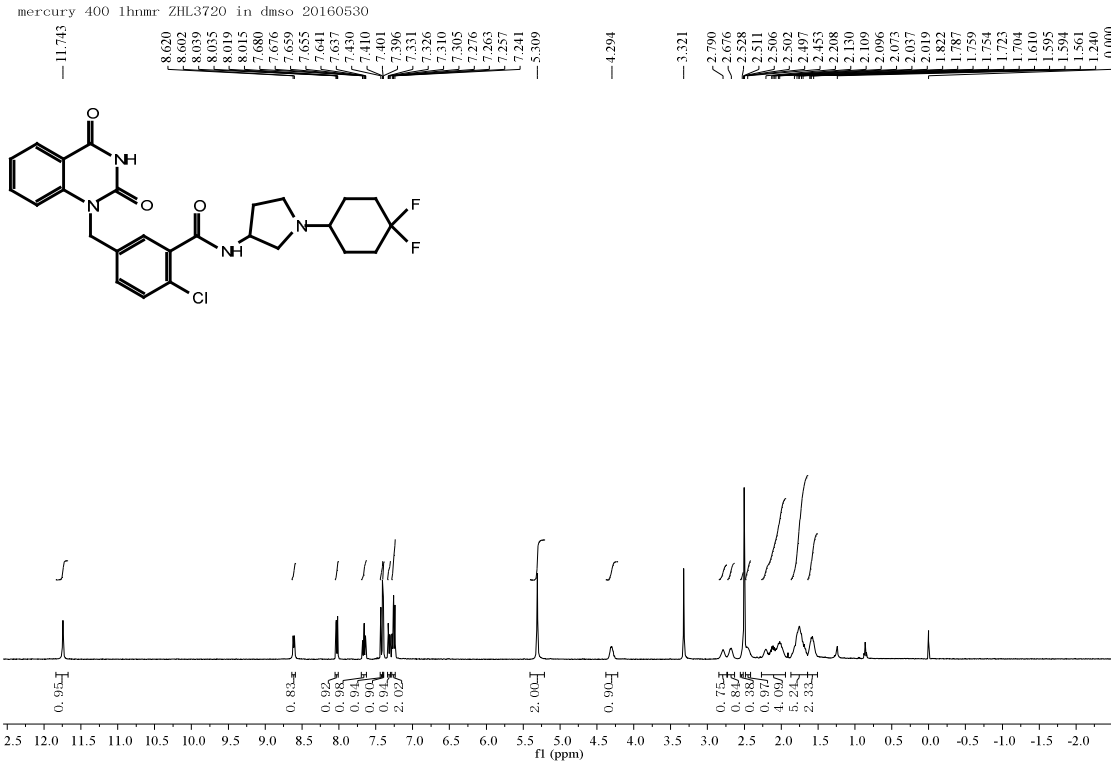
[1]H NMR Spectrum of Compound 24



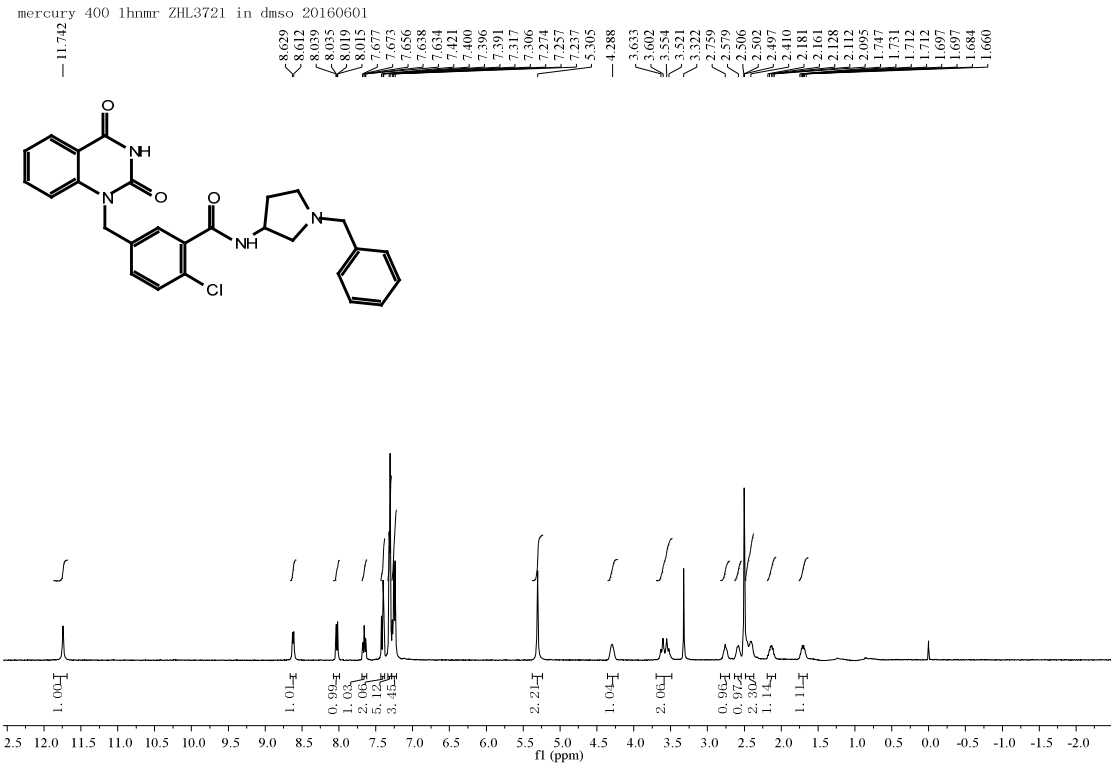
[13]C NMR Spectrum of Compound 24



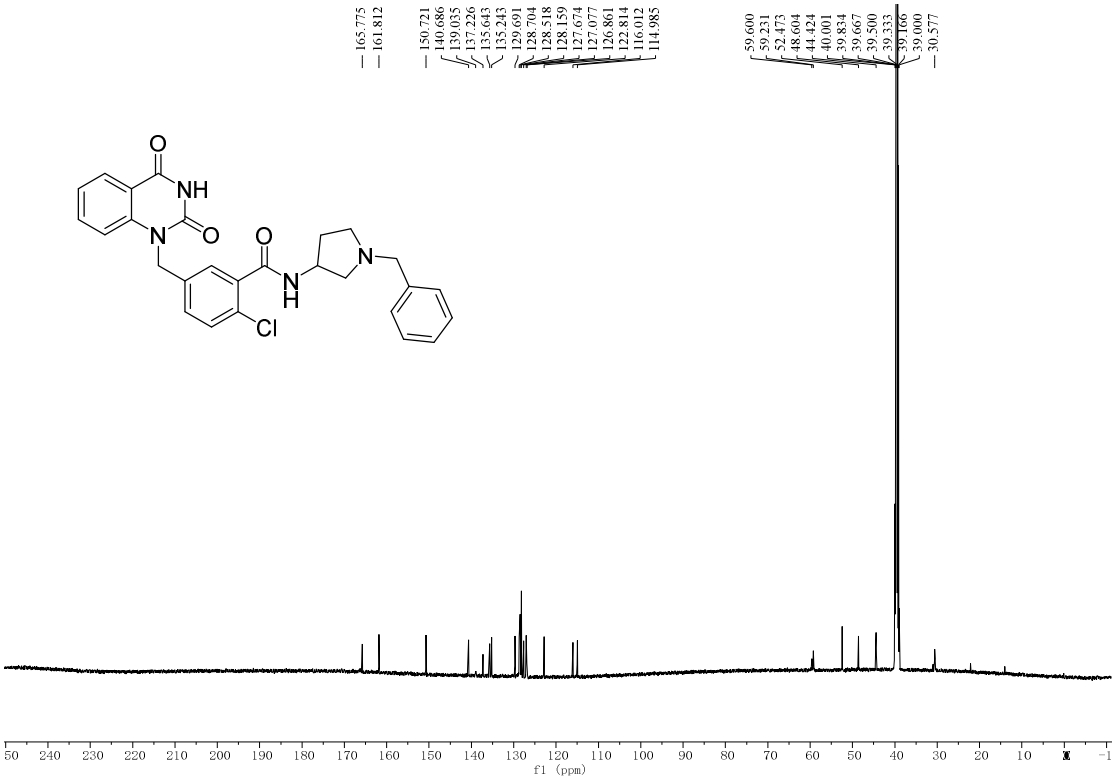
^{1}H NMR Spectrum of Compound 25



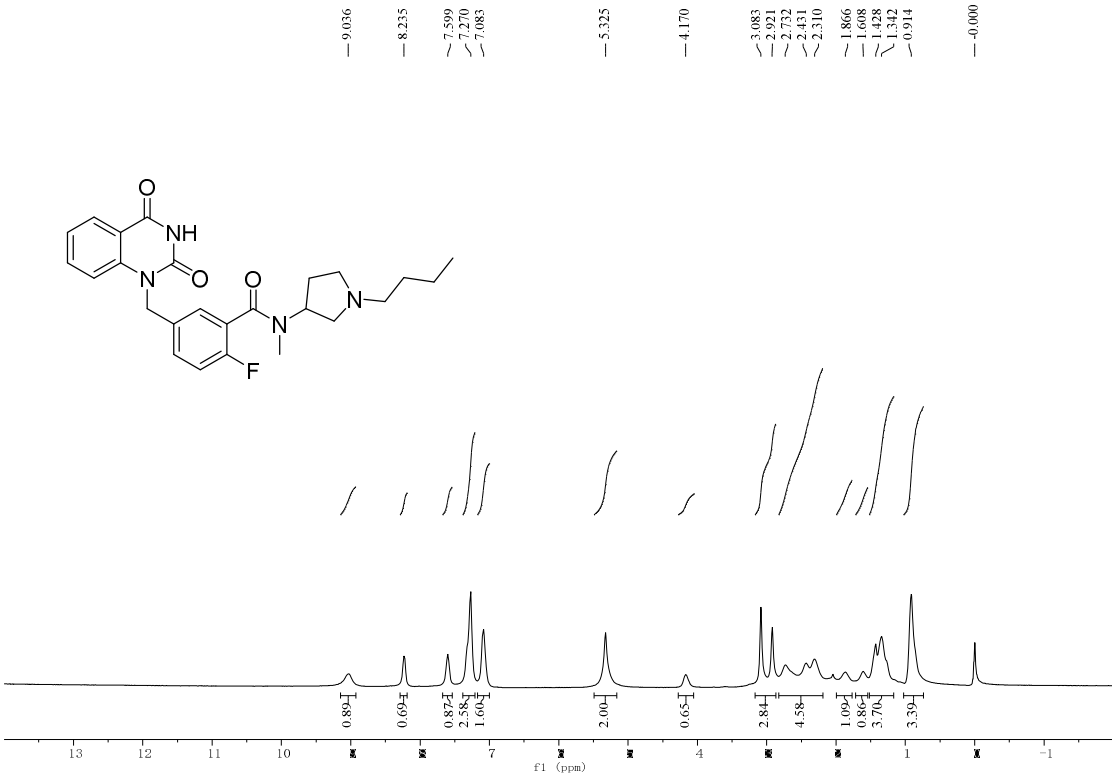
^{1}H NMR Spectrum of Compound 26



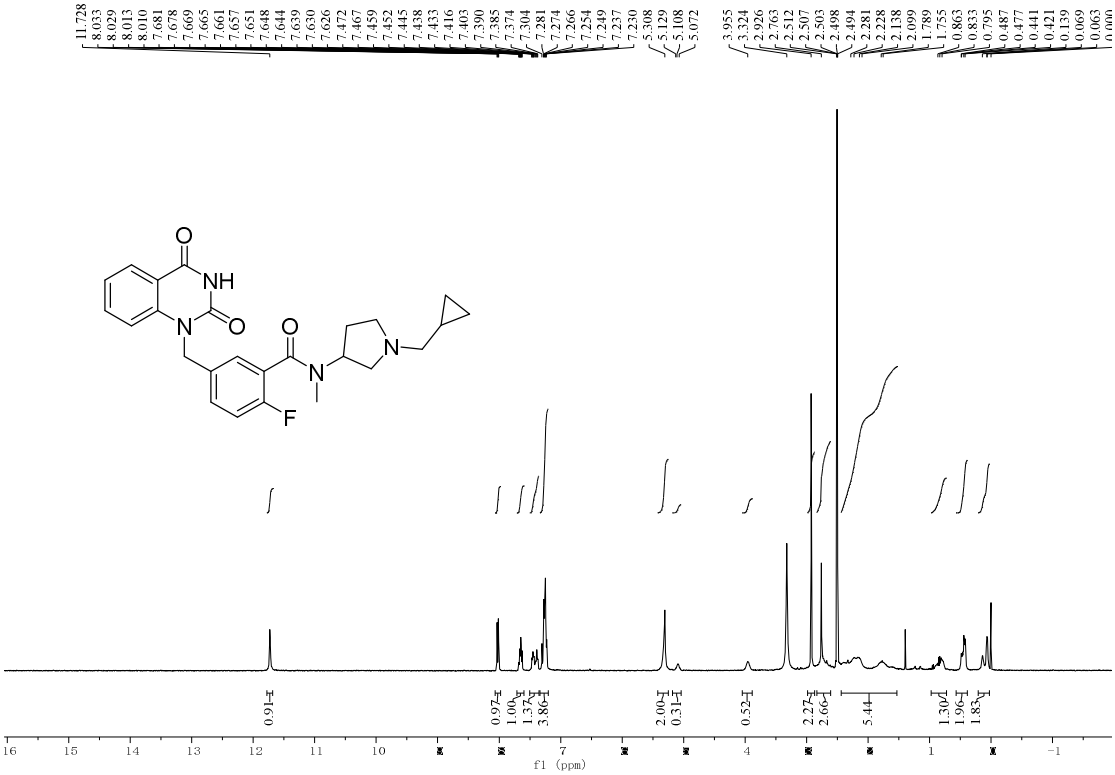
^{13}C NMR Spectrum of Compound 26



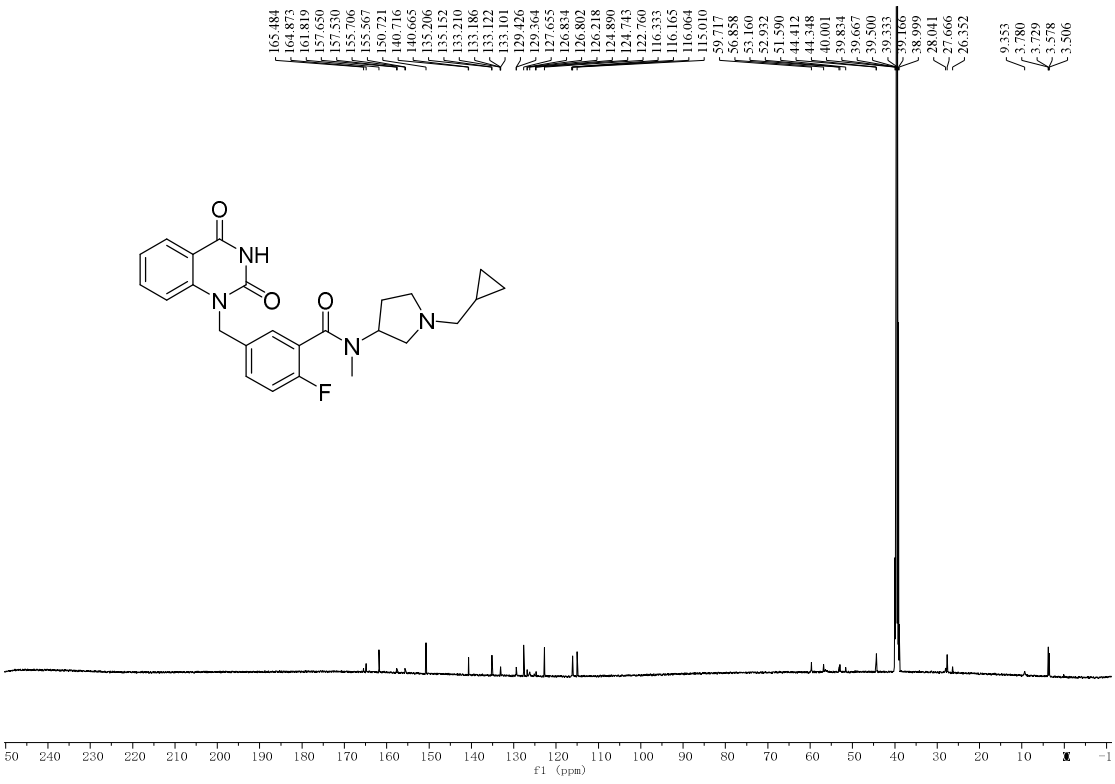
^{1}H NMR Spectrum of Compound 27



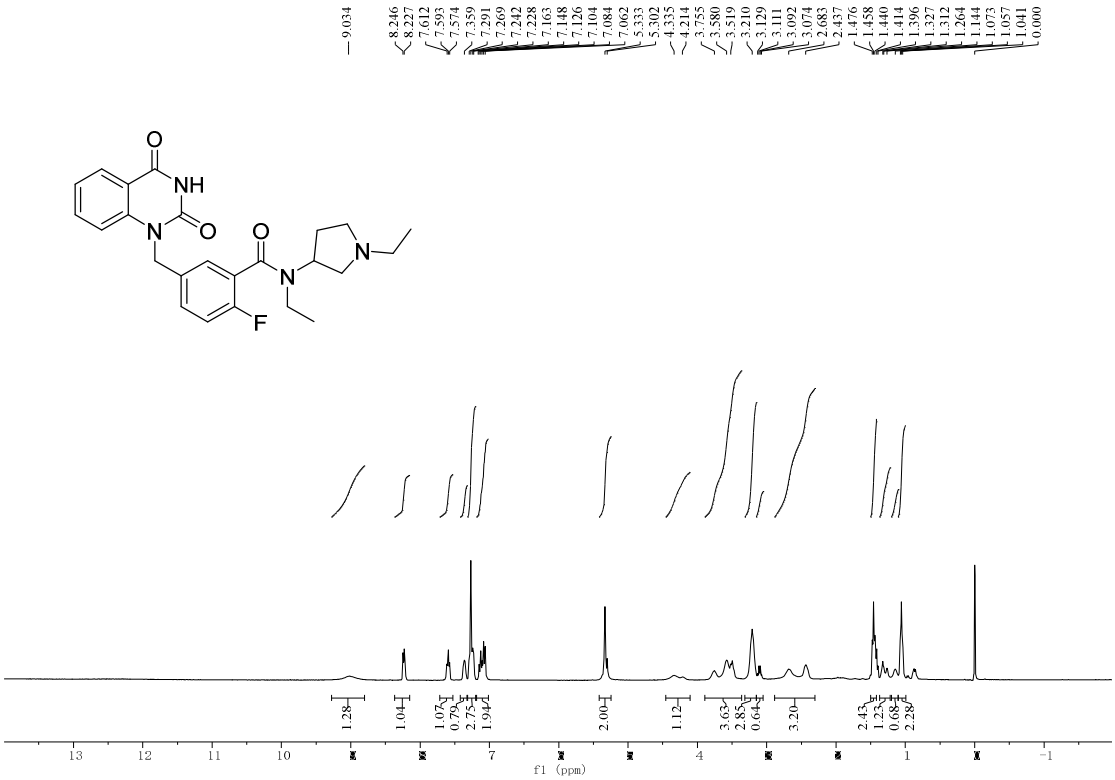
^{1}H NMR Spectrum of Compound28



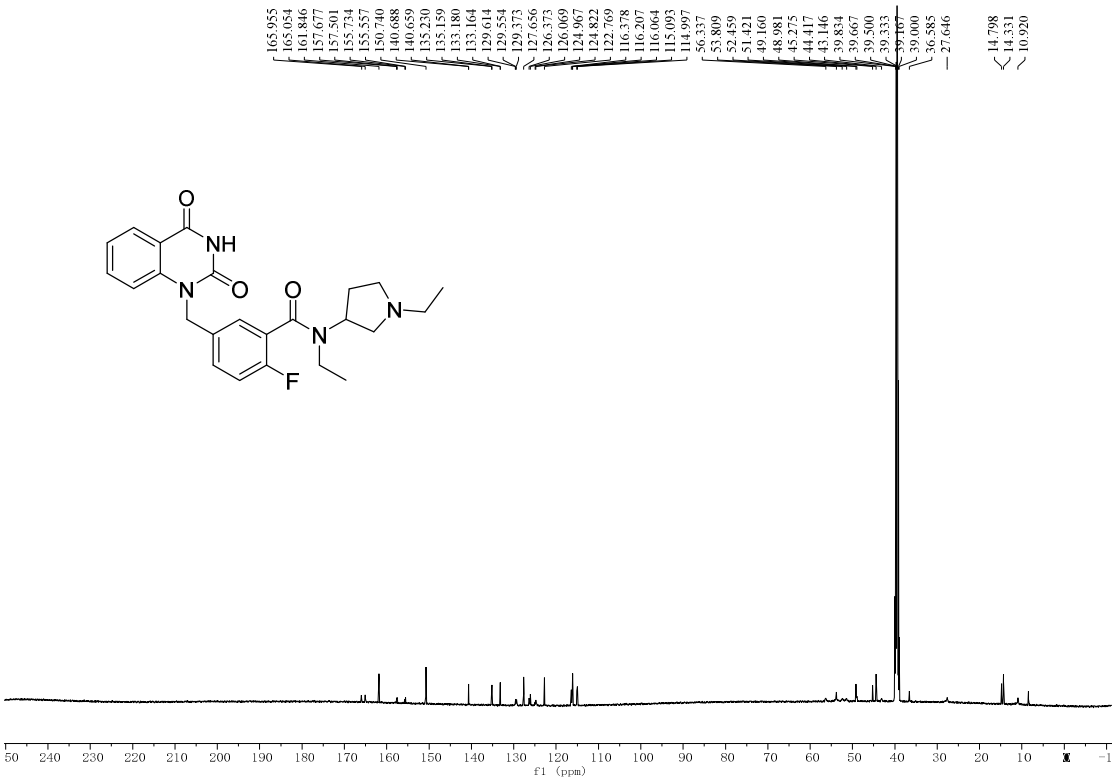
^{13}C NMR Spectrum of Compound 28



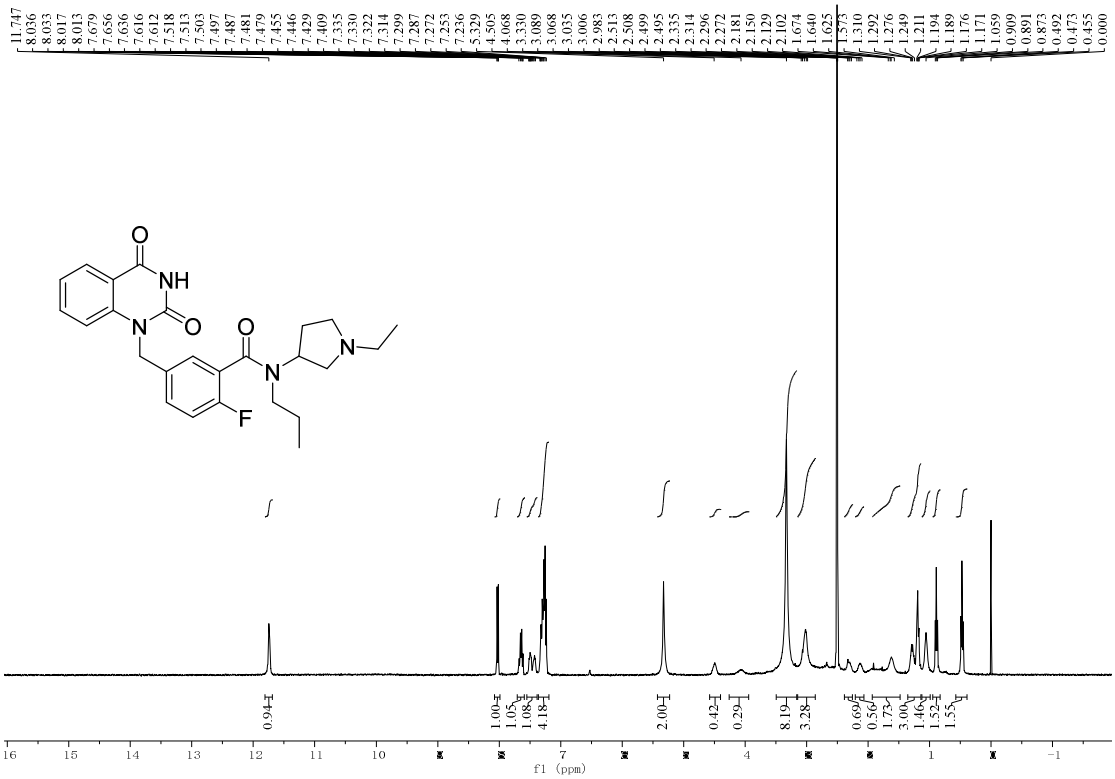
^{1}H NMR Spectrum of Compound 29



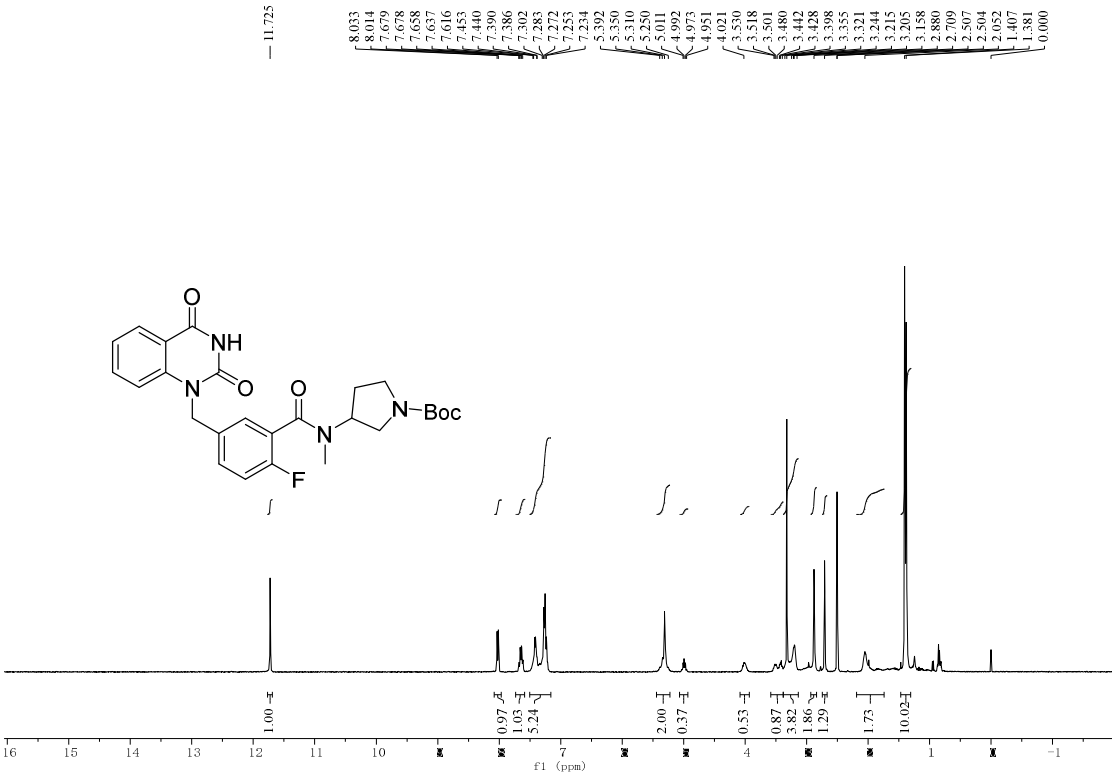
^{13}C NMR Spectrum of Compound 29



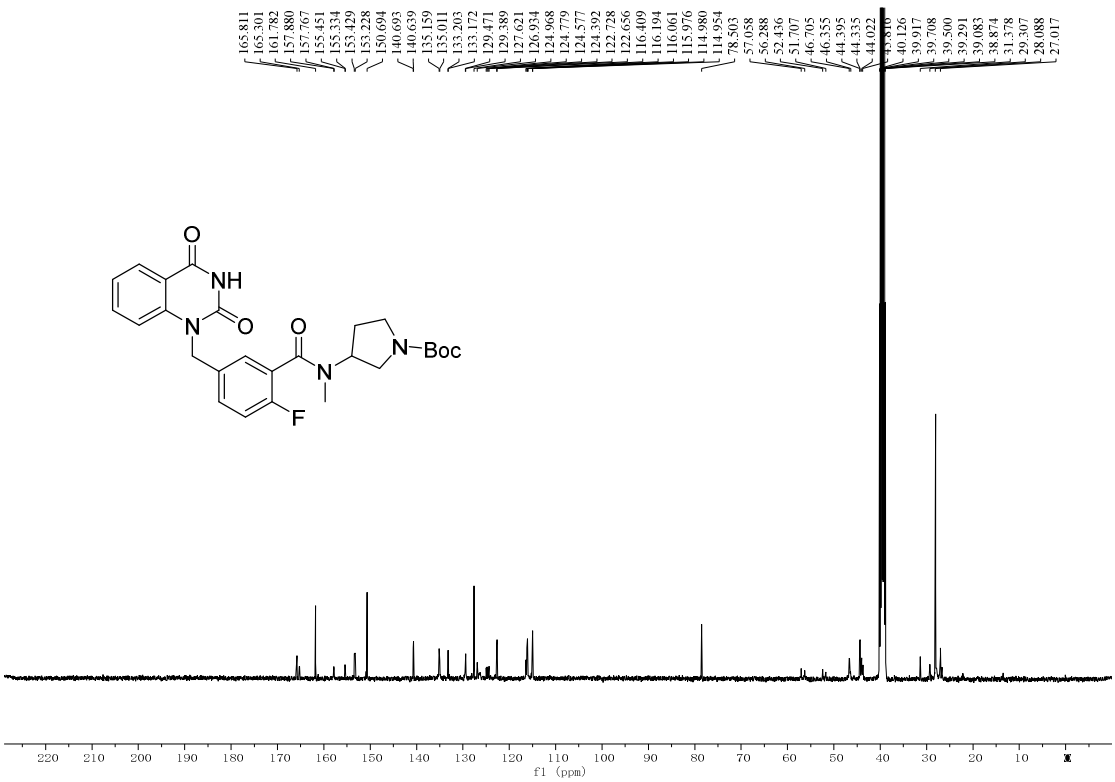
^{1}H NMR Spectrum of Compound 30



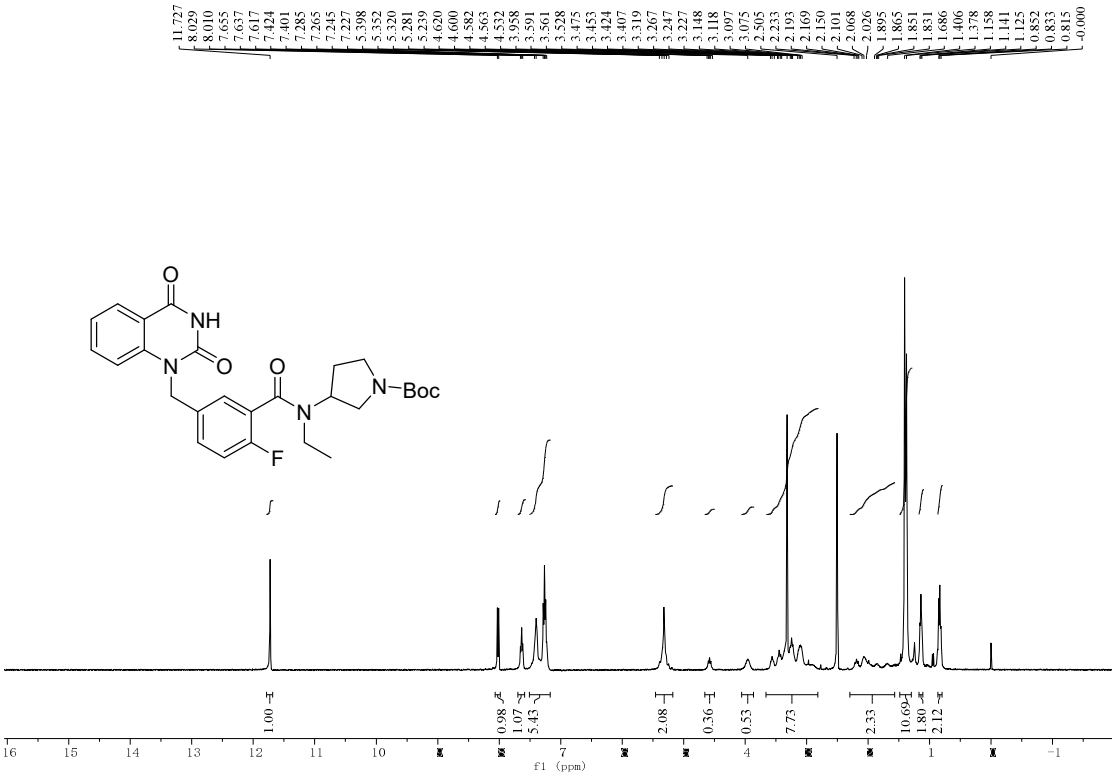
^{1}H NMR Spectrum of Compound 31



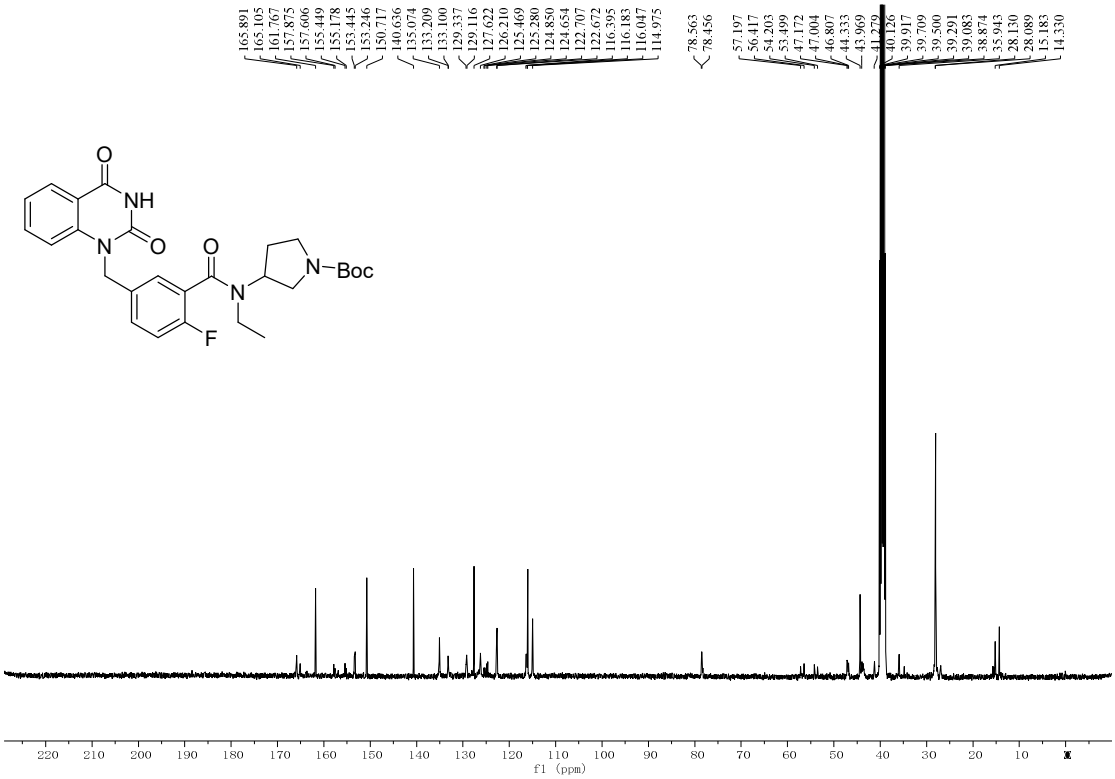
^{13}C NMR Spectrum of Compound 31



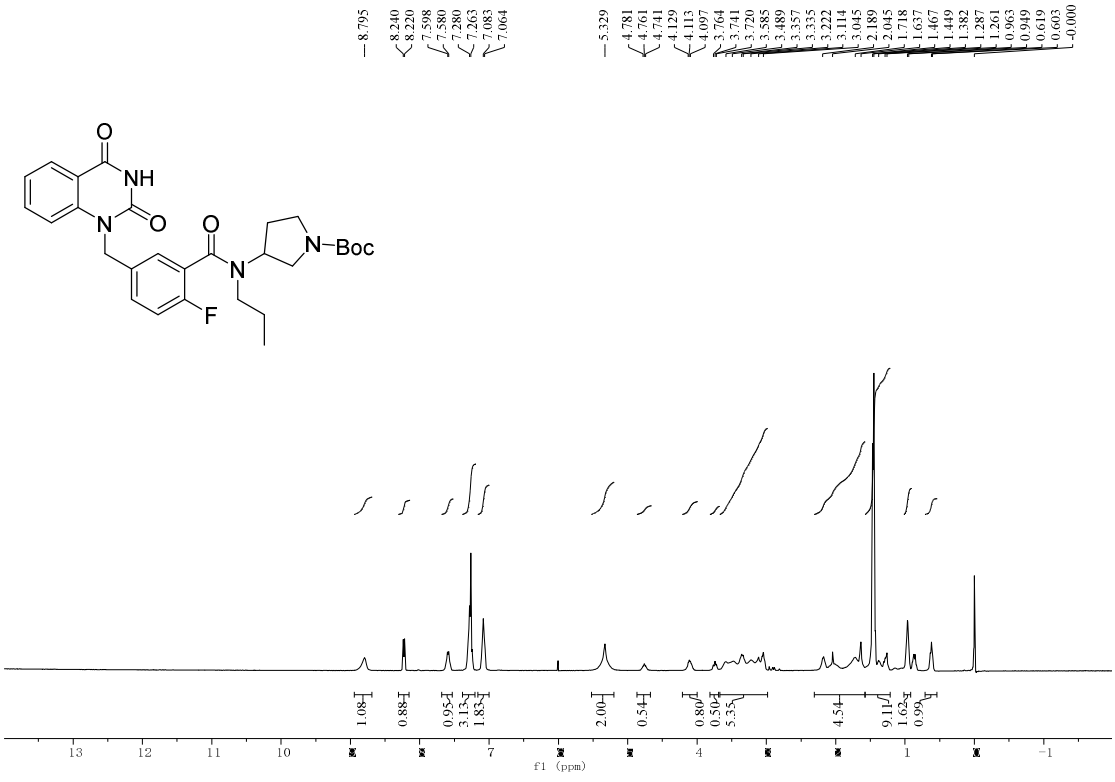
^{1}H NMR Spectrum of Compound 32



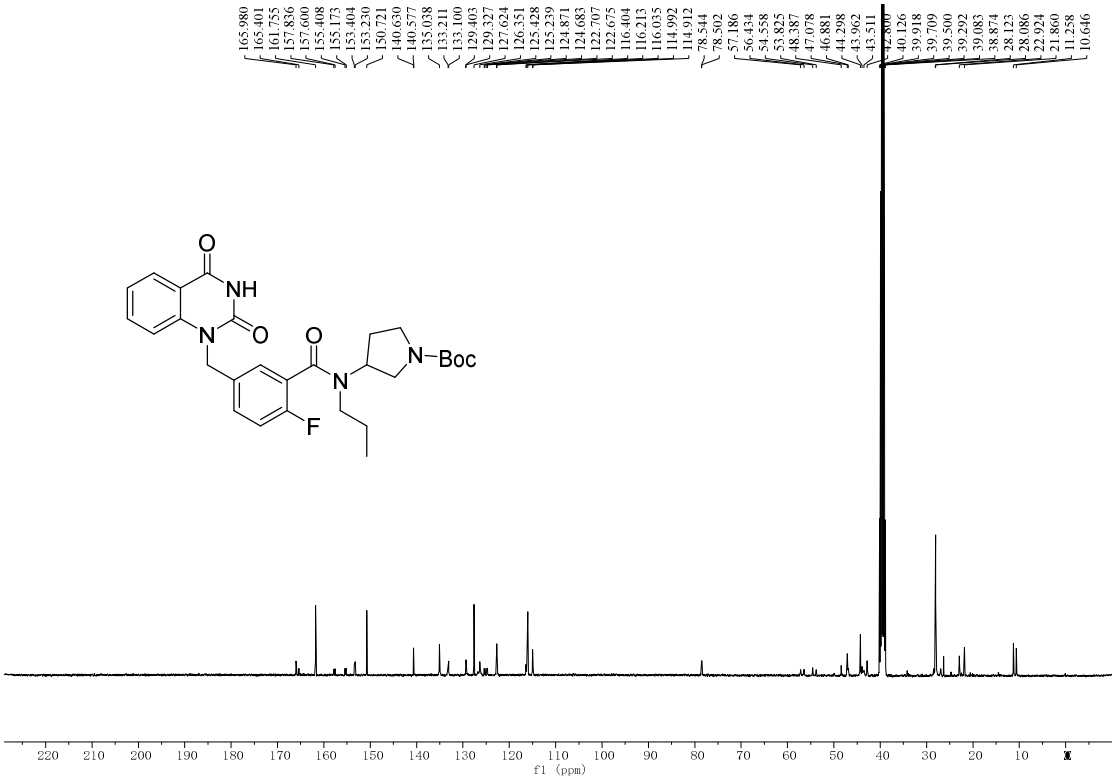
^{13}C NMR Spectrum of Compound 32



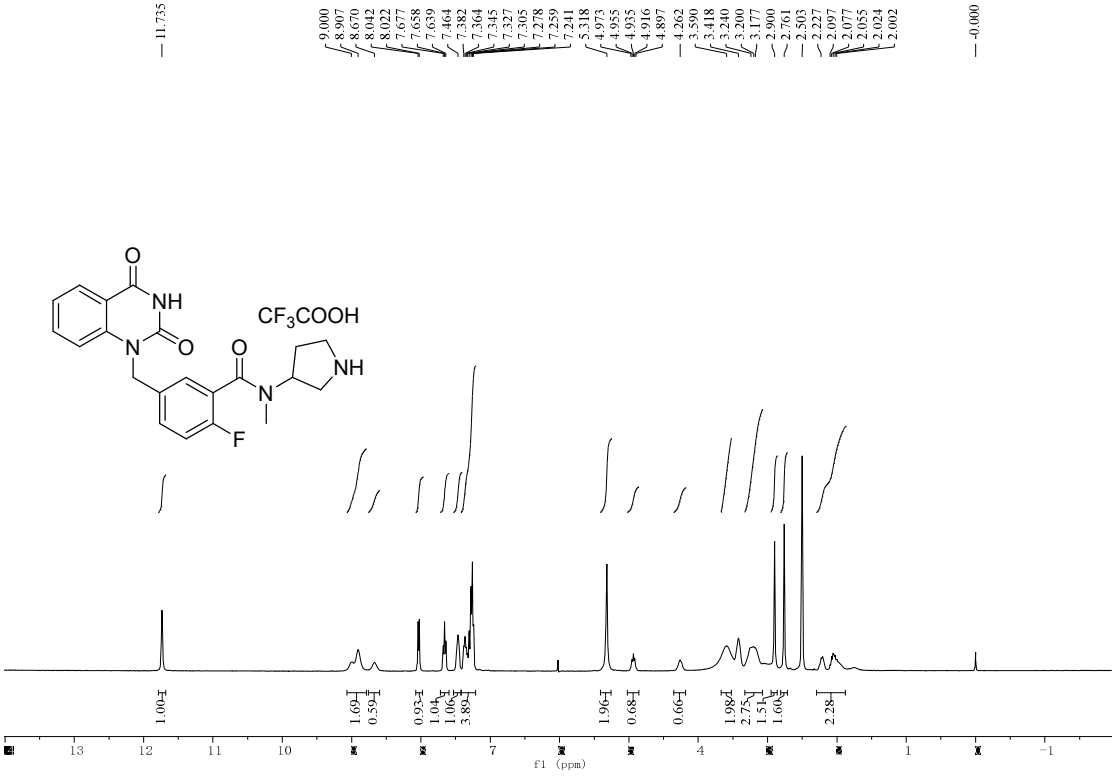
^{1}H NMR Spectrum of Compound 33



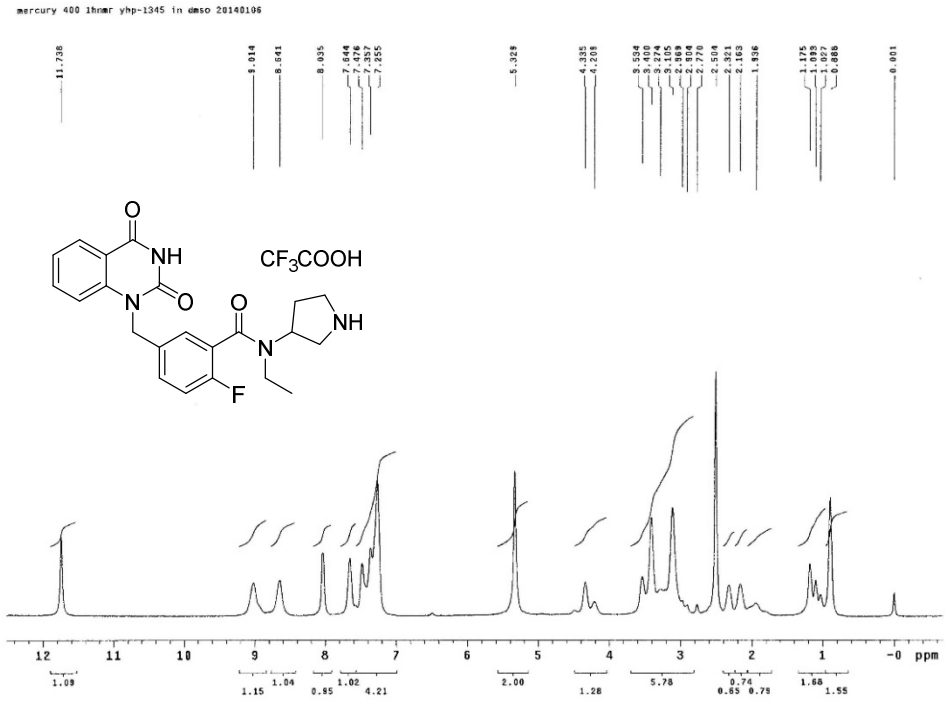
^{13}C NMR Spectrum of Compound 33



^{1}H NMR Spectrum of Compound 34



^{1}H NMR Spectrum of Compound 35



^{1}H NMR Spectrum of Compound 36

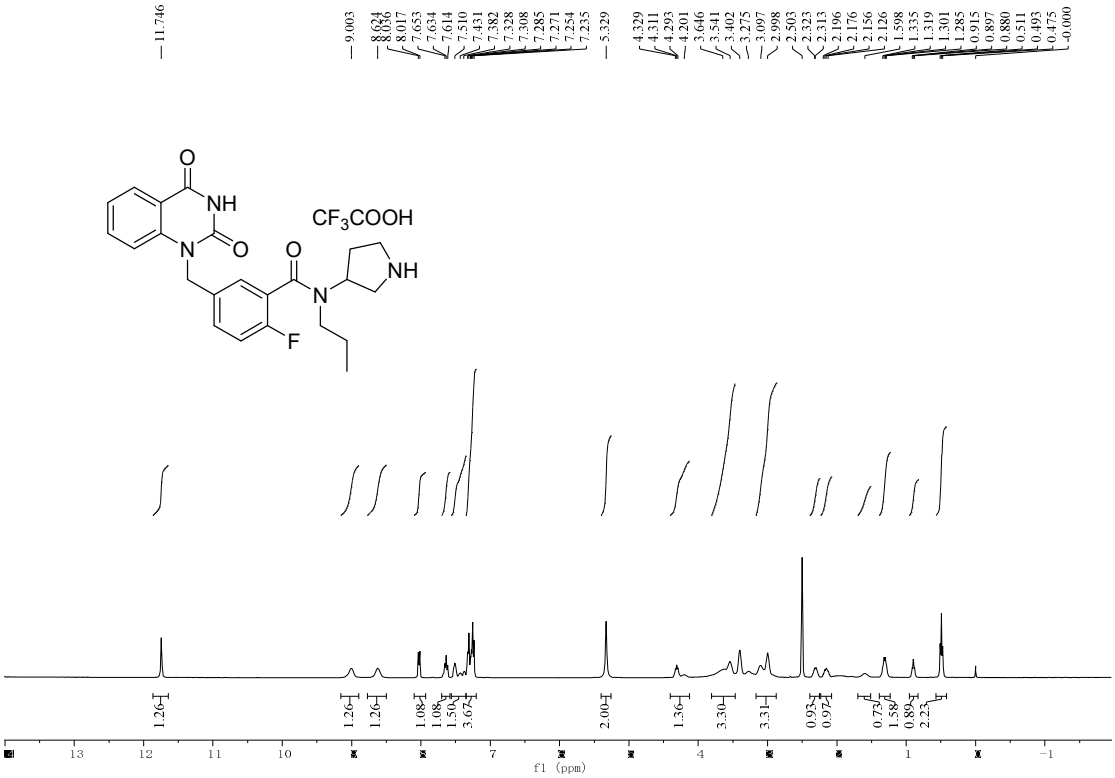


Table S1. The data collection and refinement statistics of co-crystal structure of PARP-1 in complex with **11**.

Data collection	
Space group	P21 21 21
Cell dimensions	a=48.63, b=92.31, c=164.08; =90°, =90°, =90°
Wavelength (Å)	0.9784
Resolution range (Å)[a]	92.31-2.03 (2.14-2.03)
Unique reflections	48854 (7005)
Redundancy	11.9 (11.9)
I/σ	17.7 (7.7)
Completeness (%)	99.9 (99.8)
R_{merge}[b]	0.103 (0.330)
Structure refinement	
Resolution range (Å)	81.72-2.03
No. reflections	62596
No. heavy atoms	5612
R_{work}[c]	0.2535
R_{free}[d]	0.2974
Rms Deviations	
Bond length (Å)	0.0081
Bond angles (°)	1.2002

[a]Values in parentheses are for the data in the highest resolution shell.

[b]$R_{merge} = \Sigma|I_i - I_m|/\Sigma I_i$, where I_i is the intensity of the measured reflection and I_m is the mean intensity of all symmetry related reflections.

[c]$R_{work} = \Sigma|F_o - F_c|/\Sigma F_o$, where F_o and F_c are the observed and calculated structure factor amplitudes.

[d]R_{free} is the same as R_{work}, but calculated on 5% reflections not used in refinement.