Supporting Information for

Study on the Synthesis of Anti-insomnia Drug Suvorexant

Experimental procedure and Characterization of products

Synthesis of tert-butyl (2-oxoethyl) carbamate (3)

3-Aminopropane-1, 2-diol (5.5 g, 60.1 mmol) was dissolved in DCM (10 mL) and methanol (50 mL), and triethylamine (1 mL, 7.17 mmol) was added. In another flask, dissolve di-tert-butyl dicarbonate (15.7 g, 71.9 mmol) in DCM (90 mL), and add with a dropping funnel over 30 min. The colorless solution was stirred at room temperature. After the reaction was completed, the resulting mixture was concentrated in vacuo to obtain a crude product as a colorless oil (11.26 g, yield 98%). The next reaction is carried out without purification.

tert-Butyl (2, 3-dihydroxypropyl) carbamate (10 g, 52 mmol) was suspended in H_2O (85 mL), and the single-necked bottle was covered with aluminum foil to prevent $NaIO_4$ from being affected by light. Then $NaIO_4$ (13.4 g, 62.8 mmol) was added to the stirred system, the reaction was stirred for 1 h in the dark, and the aqueous layer was extracted with DCM (3×50 mL). The obtained organic phases were combined and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain compound **3** as a yellow oil (7.7 g, 93% yield), which was used immediately without further purification.

Synthesis of tert-butyl (*R*)-(2-((1-phenylethyl) amino)ethyl)carbamate (4)

Compound **3** (7.0 g, 44 mmol) and (*R*)-1-phenylethylamine (8.0 g, 66 mmol) were dissolved in DCM (500 mL), and to the stirred solution was added sodium triacetoxyborohydride (28.0 g, 132 mmol), and the reaction was stirred at room temperature overnight. The mixture was diluted with DCM (300 mL) and then washed with water (2×200 mL) and saturated brine (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, which was then separated and purified to obtain compound **4** as a white solid (10.6 g, yield 91%), Mp: 81.9 ℃-83.2 ℃. $[\alpha]_D^{18}$= + 28.5 (*c* = 1.0, Chloroform). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.34-7.26 (m, 4H), 7.26-7.18 (m, 1H), 4.95 (s, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 3.22-3.07 (m, 2H), 2.65-2.58 (m, 1H), 2.56-2.48 (m, 1H), 1.44 (s, 9H), 1.34 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.09, 145.49, 128.45, 126.94, 126.49, 79.09, 57.96, 46.98, 40.57, 28.41, 24.36. HRMS (ESI) *m/e* calcd for $C_{15}H_{24}N_2O_2^+$ $(M+H)^+$, 265.19105, found 265.19101.

Synthesis of methyl (*R*) - 3 -((2-((*tert*-butoxycarbonyl) amino) ethyl) ((*R*) -1-phenylethyl) amino) butanoate (6)

Under N_2 protection, compound **4** (5.8 g, 22 mmol) was dissolved in THF (80 mL) and then cooled to 0 °C. A solution of n-butyllithium in hexane (30.0 mL, 44 mmol) was slowly added to the system, the resulting solution was stirred for 30 min, and then cooled to -78 ℃, Then a solution of compound **5** (2.0 g, 20 mmol) dissolved in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at -78 °C for 1.5 h., Saturated aqueous NH_4Cl (20 mL) was added dropwise to quenching the reaction, and the resulting solution was slowly warmed to room temperature. The system was extracted with EtOAc (2×30 mL). The obtained organic phases were combined, dried with anhydrous $MgSO_4$, and then distilled under reduced pressure. Then it was purified to obtain compound **6** as a colorless liquid (6.9 g, yield 95%). $[\alpha]_D^{18}$= +25.5(*c*=1.0, Chloroform) ^{1}H NMR (500 MHz, $CDCl_3$) δ7.34-7.27 (m, 4H), 7.23-7.16 (m, 1H), 5.25-5.13 (m, 1H), 3.85 (q, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 3.20-3.01 (m, 2H), 2.68-2.54 (m, 2H), 2.47-2.31 (m, 1H), 2.21-2.07 (m, 1H), 1.42 (s, 9H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 1H), 0.70 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.94, 156.19, 144.50, 128.19, 127.55, 126.98, 78.69, 58.18, 51.48, 50.76, 50.32, 44.37, 40.93,

28.45, 19.67, 17.42, 16.12. HRMS (ESI) m/e calcd for $C_{20}H_{32}N_2O_4^+(M+H)^+$, 365.24348, found 365.24343.

Synthesis of (*R*)-7-methyl-1-((*R*)-1-phenylethyl)-1,4-diazepan-5-one (7)

A solution of compound **6** (3.6 g, 10 mmol) dissolved in DCM (20 mL) was added saturated HCl/ EtOAc (20 mL), and the reaction was stirred for 4 h. The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$ and extracted with DCM. The concentrated organic phase was dried over anhydrous $MgSO_4$. Under N_2 protection, the resulting compound was dissolved in anhydrous MeOH (40 mL), CH_3ONa (0.65 g, 12 mmol) was added, and stirred at room temperature, quenched with saturated aqueous NH_4Cl (15 mL), and then the reaction system was poured into a solution containing 5% Na_2CO_3 in a separatory funnel of the aqueous solution, it was thoroughly shaken and extracted with DCM (2×20 mL). The organic phases were combined, dried with $MgSO_4$, and concentrated in vacuo to obtain compound **7** as a white solid (2.1 g, 90% yield in two steps). Mp: 161.8 ℃-168.4 ℃. $[\alpha]_D^{18}$=+15(*c*=1.0, Chloroform) ^{1}H NMR (500 MHz, $CDCl_3$) δ7.40-7.27 (m, 4H), 7.27-7.18 (m, 1H), 6.78 (s, 1H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.55-3.42 (m, 1H), 3.19-3.10 (m, 1H), 3.09-3.00 (m, 1H), 2.95-2.83 (m, 2H), 2.81-2.72 (m, 1H), 2.27 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.87, 145.72, 128.48, 126.94, 126.88, 60.45, 48.30, 44.74, 44.02, 42.90, 22.01, 10.72. HRMS (ESI) m/e calcd for $C_{14}H_{20}N_2O^+(M+H)^+$, 233.16484, found 233.16489.

Synthesis of (*R*)-7-methyl-1-((*R*)-1-phenylethyl)-1,4-diazepane (8)

Compound **7** was dissolved in THF (60 mL), and the temperature of the system was reduced to about 0°C. $LiAlH_4$ (1.4 g, 36.0 mmol) was added in portions to treat the substrate (1.4 g, 6.0 mmol). Then, the reaction was slowly warmed to room temperature. After the reaction was completed, the reaction was cooled to -10 °C, and the reaction was quenched with water (1.5 mL), 15% NaOH (1.5 mL), and then water (4.5 mL) was added to quench. An appropriate amount of $MgSO_4$ was added, the mixture was stirred for 1 hour, and then filtered. The filtrate was concentrated to obtain compound **8** as a yellow oil (1.1 g, yield 84%). $[\alpha]_D^{18}$=+13.1 (*c*=1.0, Chloroform) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.24-7.18 (m, 1H), 3.93 (q, *J* = 6.5 Hz, 1H), 3.03-2.60 (m,

7H), 1.98-1.88 (m, 1H), 1.57-1.44 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 1H),, 0.96 (d, *J* = 6.3 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 145.85, 128.61, 127.07, 127.01, 60.58, 48.43, 44.87, 44.15, 43.03, 34.08, 22.14, 10.85. HRMS (ESI) m/e calcd for $C_{14}H_{20}N_2^+(M+H)^+$, 219.18557, found 219.18563.

Synthesis of *tert*-butyl (*R*)-5-methyl-4-((R)-1-phenylethyl)-1,4-diazepane-1-carboxylate (9)

To the flask, compound **8** (4.4 g, 20 mmol) dissolve with DCM (60 mL) and 4-dimethylaminopyridine (244 mg, 2 mmol, 10 mol%) were added. Then di-tert-butyl dicarbonate (5.1 mL, 22 mmol) was dissolved in DCM (10 ml) and slowly added under ice bath conditions. The mixture was stirred at 0 °C for 1 hour and then at room temperature overnight. The solution was washed with water and brine, then dried over anhydrous $MgSO_4$ and concentrated to give compound **9** as a yellow oil (6.0 g, yield 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.40-7.25 (m, 4H), 7.23-7.16 (m, 1H), 3.88-3.78 (m, 1H), 3.64-3.28 (m, 4H), 3.21-3.07 (m, 1H), 2.87-2.64 (m, 2H), 2.06-1.79 (m, 1H), 1.47 (s, 10H), 1.31 (dd, *J* = 9.1, 6.6 Hz, 3H), 1.07-0.92 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ155.40, 146.26, 146.05, 128.22, 127.34, 127.09, 126.62, 67.29, 59.56, 51.66, 46.70, 46.17, 44.24, 42.47, 41.67, 34.57, 34.11, 28.44, 27.76, 22.16, 14.66, 14.16. HRMS (ESI) m/e calcd for $C_{19}H_{30}N_2O_2^+(M+H)^+$, 319.23800, found 319.23806.

Synthesis of tert-butyl (*R*)-5-methyl-1,4-diazepane-1-carboxylate (10)

Compound **9** (4.8 g, 15.0 mmol) was dissolved in MeOH (60 mL). After adding a portion of 10% Pd/C (0.5 g), the reaction was placed at room temperature, stirred for 4 hours with the participation of H_2, the reaction was filtered through a pad of celite, and the filtrate was concentrated to obtain compound **10** as a yellow oil (2.8 g, yield 87%). $[\alpha]_D^{18}$=+16.2(*c*1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ3.70-3.17 (m, 4H), 3.12-2.99 (m, 1H), 2.86-2.62 (m, 2H), 2.02-1.77 (m, 2H), 1.44 (s, 9H), 1.11 (dd, *J* = 6.5, 3.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.83, 54.63, 49.75, 49.12, 48.39, 48.17, 44.99, 44.04, 37.98 ,28.47, 27.74, 23.37. HRMS (ESI) m/e calcd for $C_{11}H_{22}N_2O_2^+(M+H)^+$, 215.17540, found 215.17534.

Synthesis of *tert*-butyl (*R*)-5-methyl-4-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-1,4-diazepane-1-carboxylate (12)

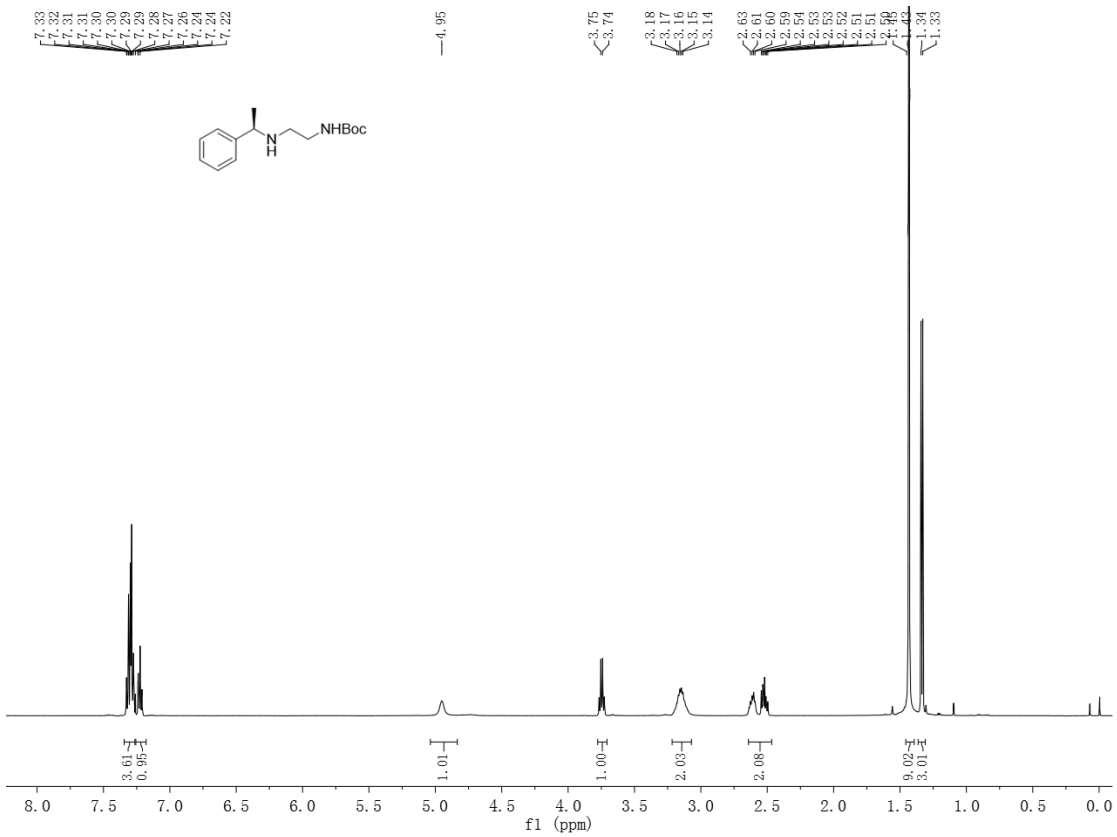
Dissolve compound **10** (1.1 g, 5 mmol) and compound **11** (1.0 g, 5 mmol) in DMF (50 mL), then EDCI (1.2 g, 6 mmol), HOBt (0.8 g, 6 mmol) and triethylamine (2.9 mL, 25 mmol)was added to the stirred solution., the reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (25 mL), the organic phase was separated after stirring well with saturated aqueous 5 % $NaHCO_3$ (25 mL), and the aqueous mixture was extracted with EtOAc (25 mL). The organic phase and extract were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was separated and purified on a silica gel chromatography column to obtain compound **12** as a colorless liquid (1.7 g, yield 85%). $[\alpha]_D^{18}$=-34.5(*c*=1.0, Chloroform). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.94-7.64 (m, 3H), 7.34-7.00 (m, 2H), 4.93-2.81 (m, 7H), 2.36 (s, 3H), 2.22-1.59 (m, 1H), 1.43 (s, 9H), 1.26-1.02 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ169.22, 169.01, 155.13, 138.41, 138.35, 138.05, 135.58, 135.56, 135.46, 135.38, 133.87, 133.51, 130.35, 129.24, 128.50, 128.37, 128.33, 128.18, 122.36, 122.13, 122.06, 52.26, 51.53, 48.44, 46.61, 45.74, 44.97, 43.62, 28.45, 28.41, 28.38, 20.96, 20.90, 16.90. HRMS(ESI) *m/e* calcd for $C_{21}H_{29}N_5O_3^+(M+H)^+$, 400.23432, found 400.23421.

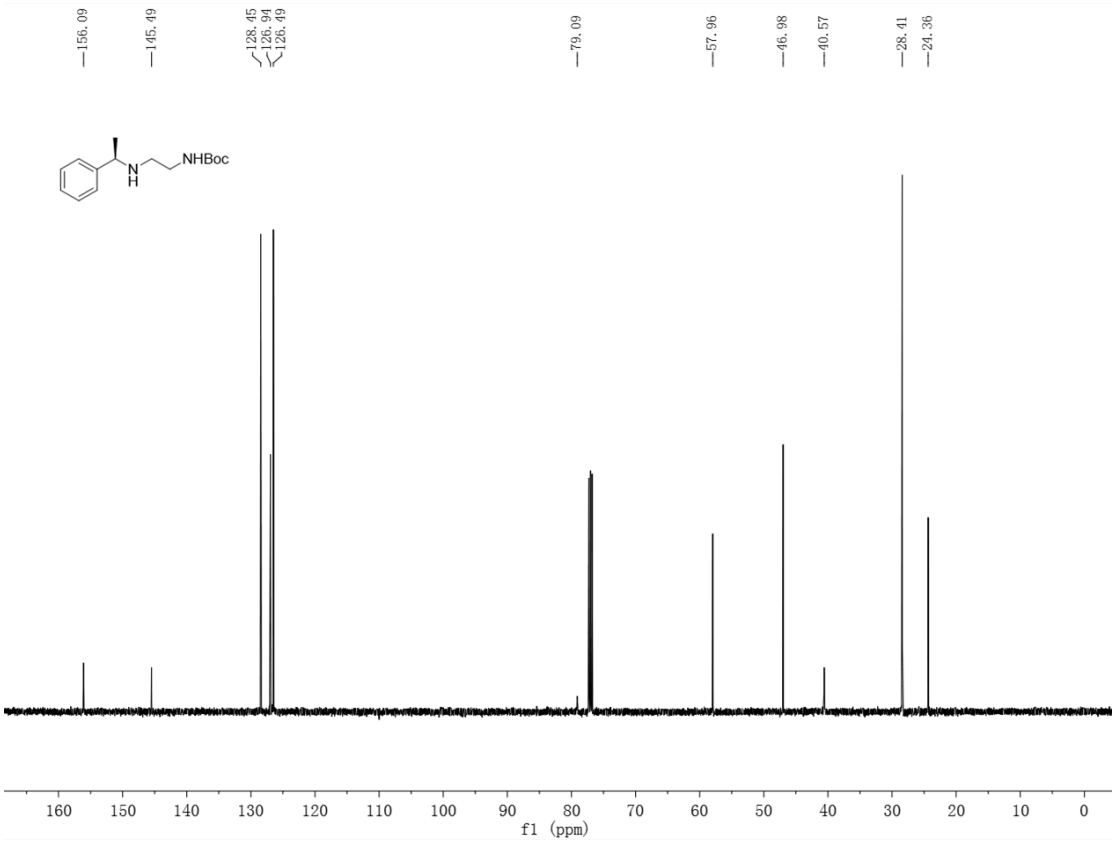
Synthesis of Suvorexant

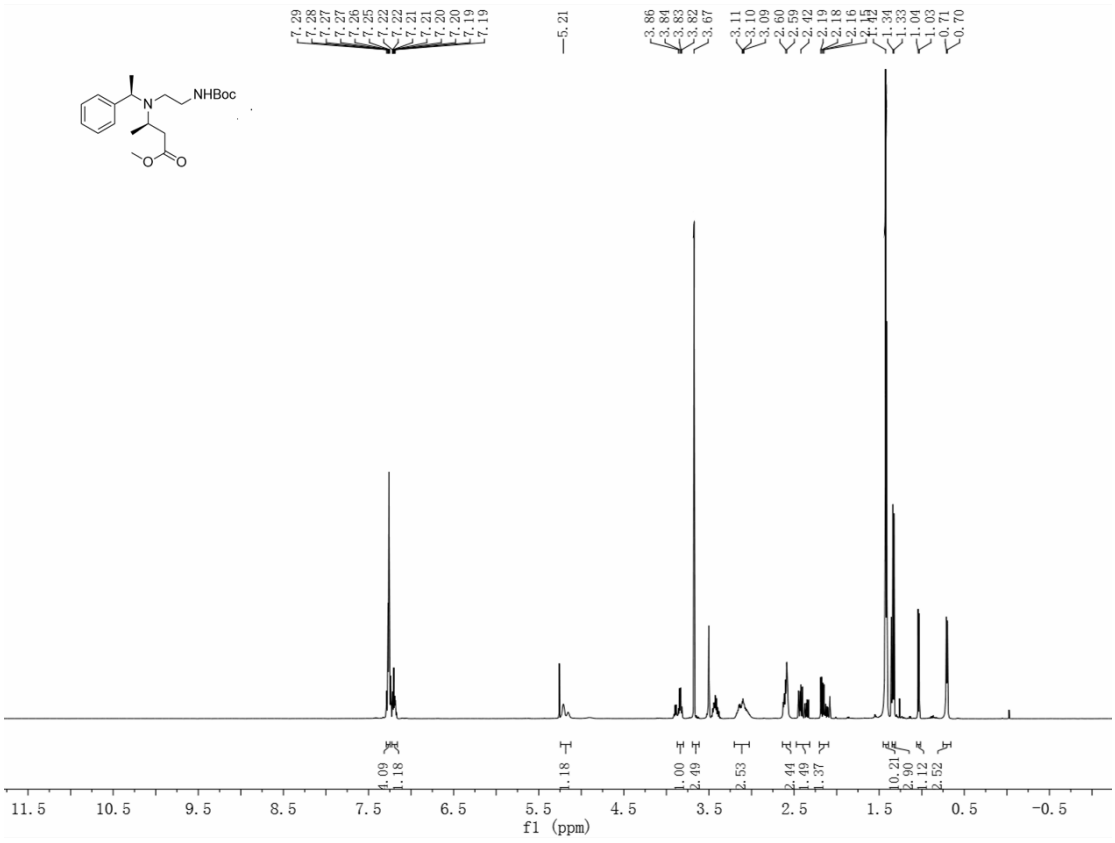
At room temperature, compound **12** (2.0 g, 5 mmol) was dissolved in DCM (50 mL), a saturated solution of HCl/ EtOAc (15 mL) was added to the stirred solution, and the resulting mixed solution was stirred until the raw materials were completely consumed. The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$ and extracted with DCM (2×20 mL). The concentrated organic phase was dried over anhydrous $MgSO_4$. The amine obtained above was dissolved in DMF (60 mL) at room temperature, compound **13** and triethylamine (1.5 g, 15 mmol) were added to the stirred solution, and the resulting mixture was stirred at 75°C for 2 h. The reaction mixture was diluted with DCM (2×50 mL) and filtered through a pad of celite, and the filtrate was concentrated in vacuo. The residue was separated and purified to obtain compound **1** (1.8 g, yield 80%). $[\alpha]_D^{25}$=-12.1(*c*=1.0, MeOH) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.62 (m, 3H), 7.35-6.88 (m, 5H), 5.05-3.31 (m, 6H), 3.23-3.02 (m, 1H), 2.45-2.24 (m, 3H), 2.14-1.39 (m, 2H), 1.31-

1.07 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ169.90, 169.39, 163.01, 162.72, 147.46, 144.71, 144.60, 144.52, 138.56, 138.54, 138.17, 135.65, 135.59, 135.54, 133.99, 133.53, 130.58, 130.57, 129.34, 129.31, 128.87, 128.64, 128.44, 128.37, 128.24, 128.05, 122.54, 122.51, 122.16, 122.07, 120.39, 120.33, 120.26, 120.23, 116.25, 116.19, 116.13, 109.32, 109.21, 109.13, 77.30, 52.18, 51.49, 48.81, 48.34, 48.08, 47.57, 47.23, 47.00, 45.53, 45.08, 44.86, 44.33, 44.01, 43.78, 40.97, 39.86, 36.22, 35.42, 34.16, 33.85, 21.00, 20.98, 20.94, 19.86, 17.88, 17.76, 16.65. HRMS (ESI) *m/e* calcd for $C_{23}H_{23}ClN_6O_2^+(M+H)^+$, 451.16438, found 451.16417.

Spectral Data



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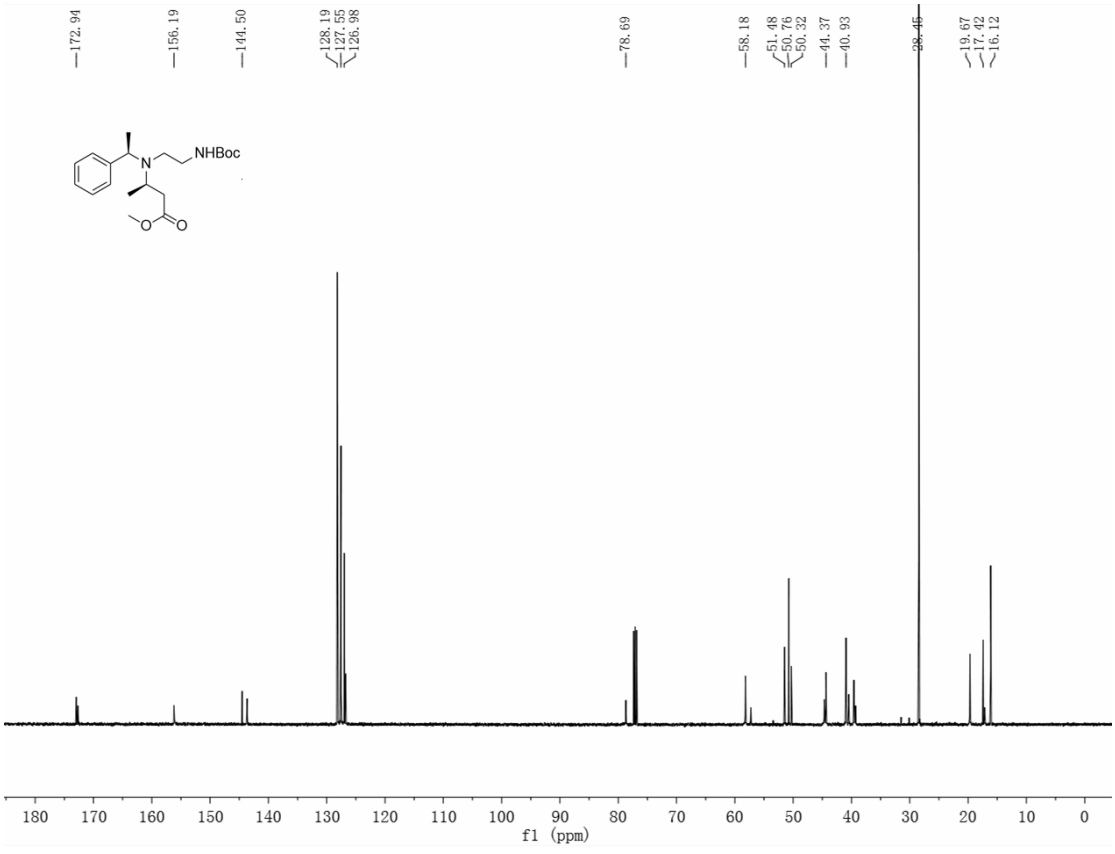
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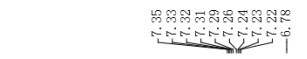
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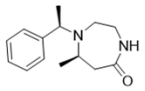
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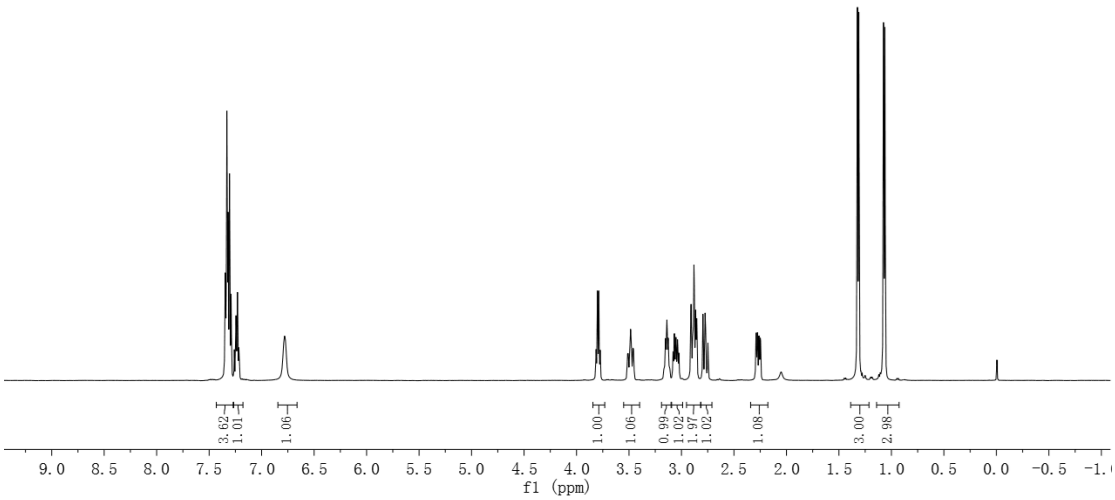
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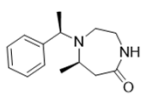
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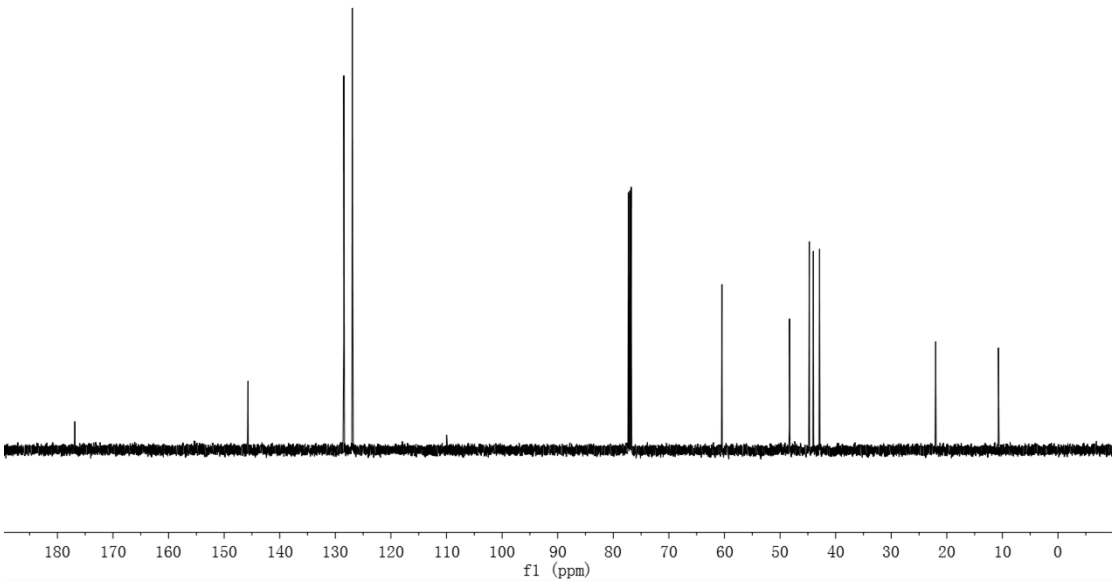
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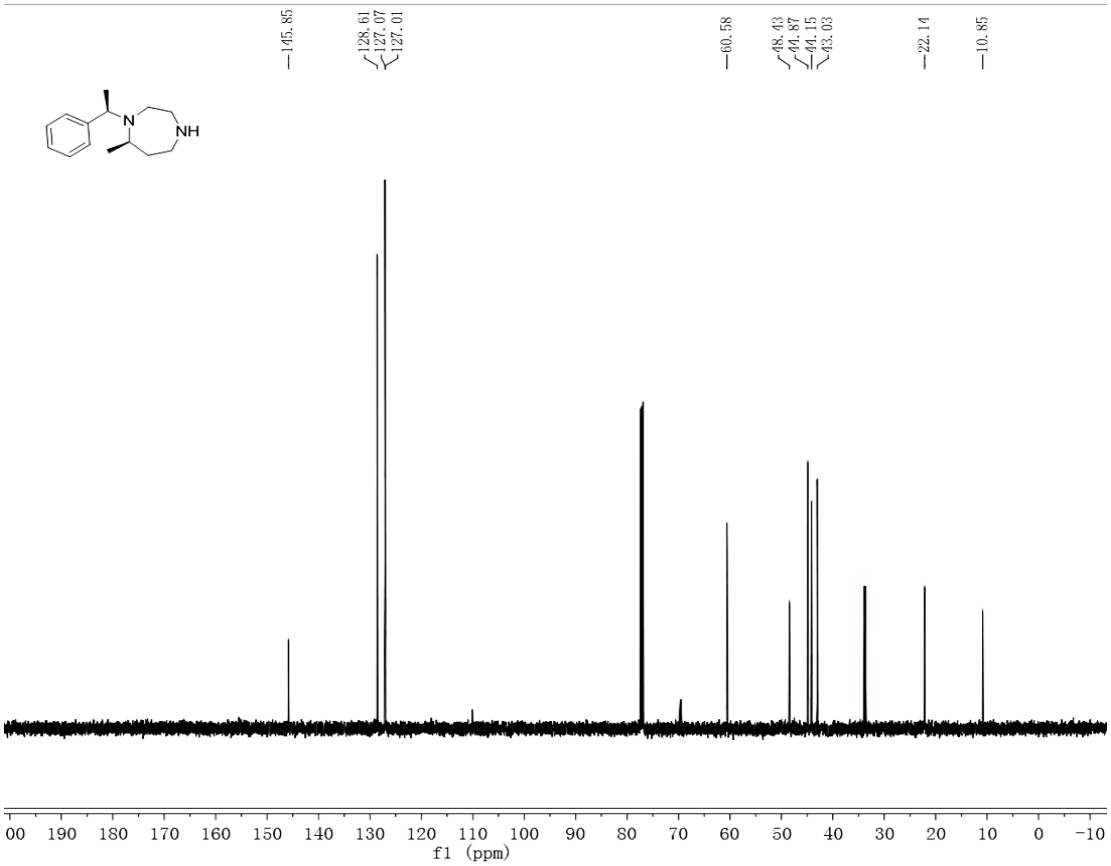
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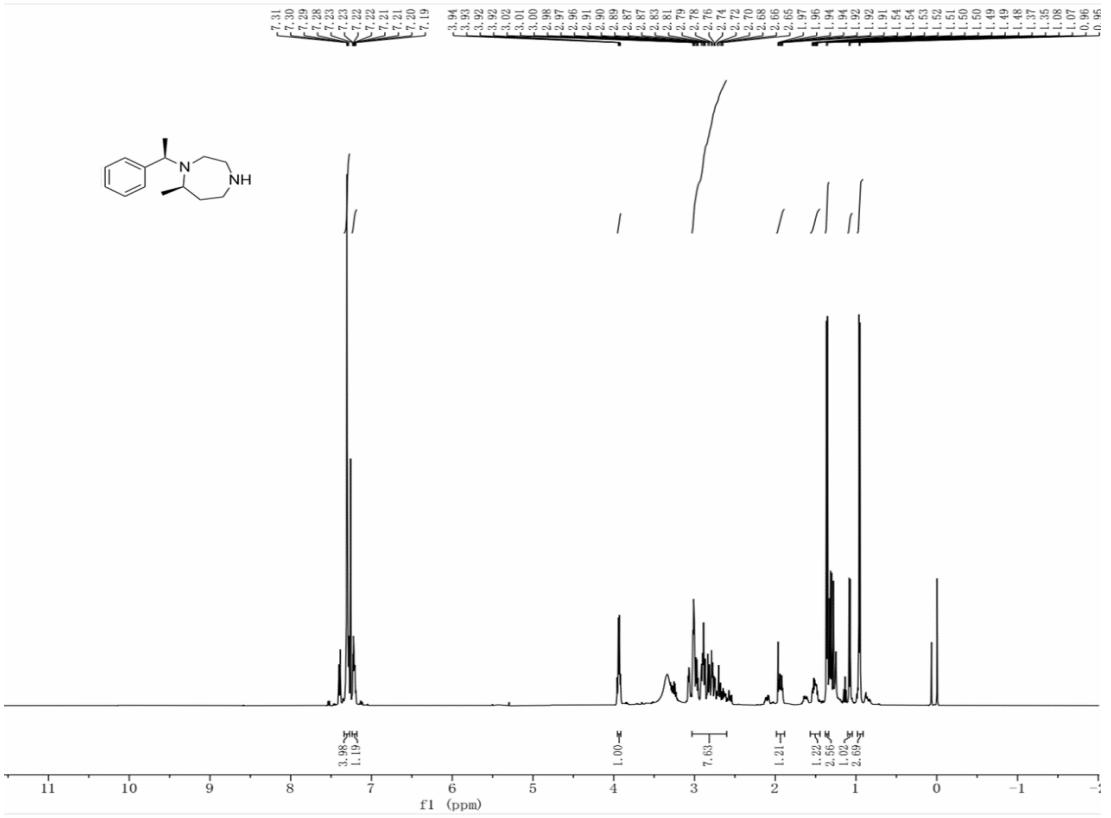
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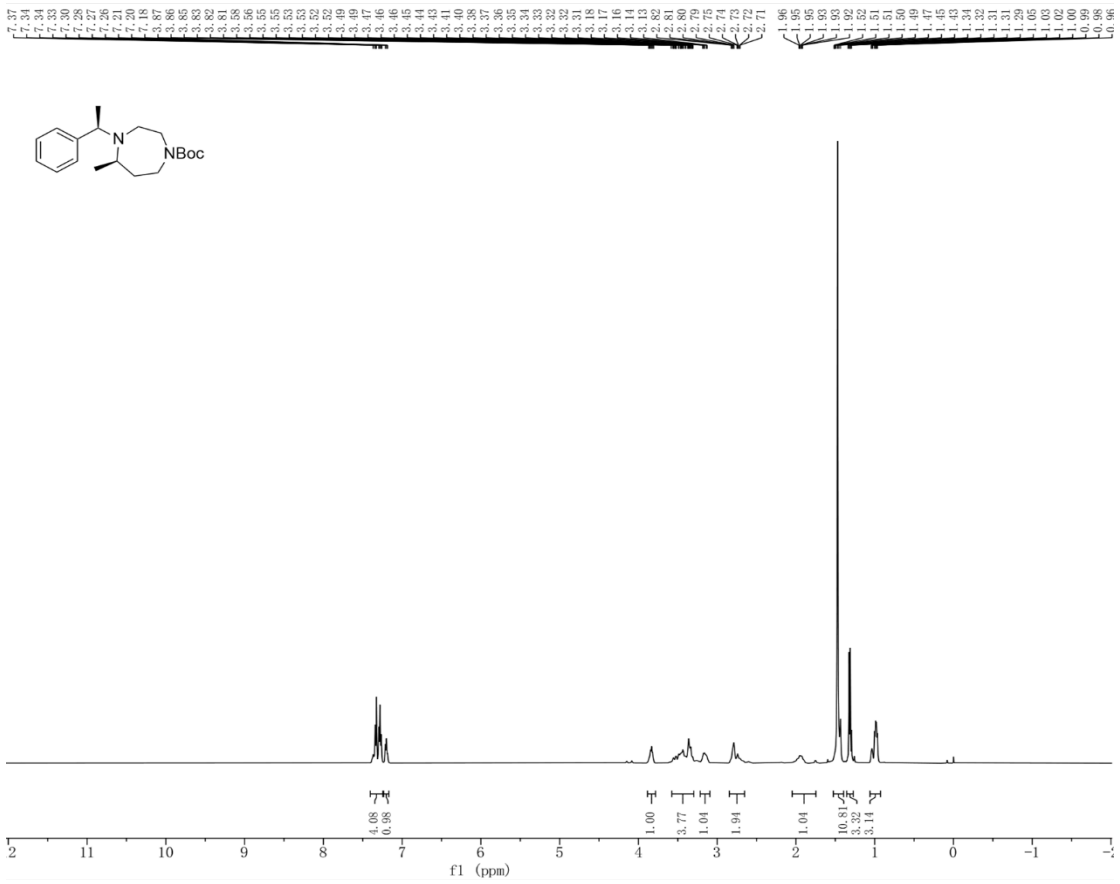
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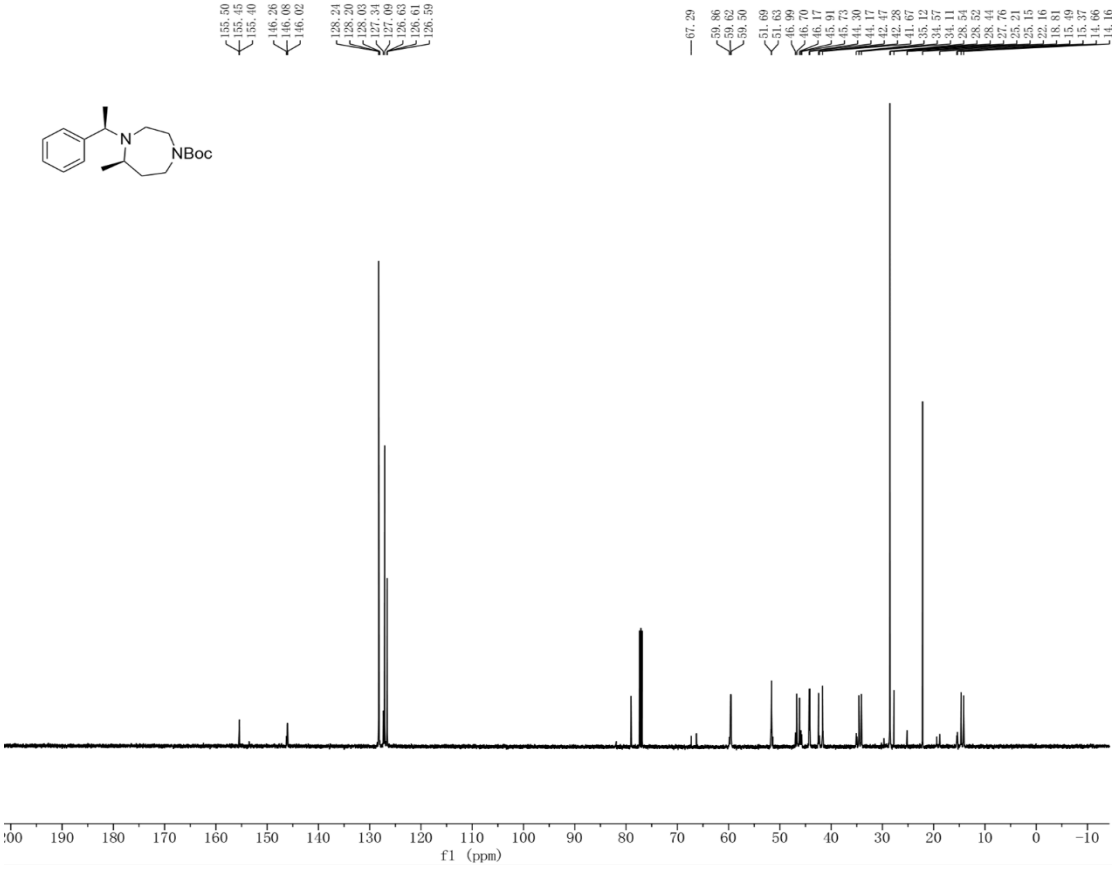
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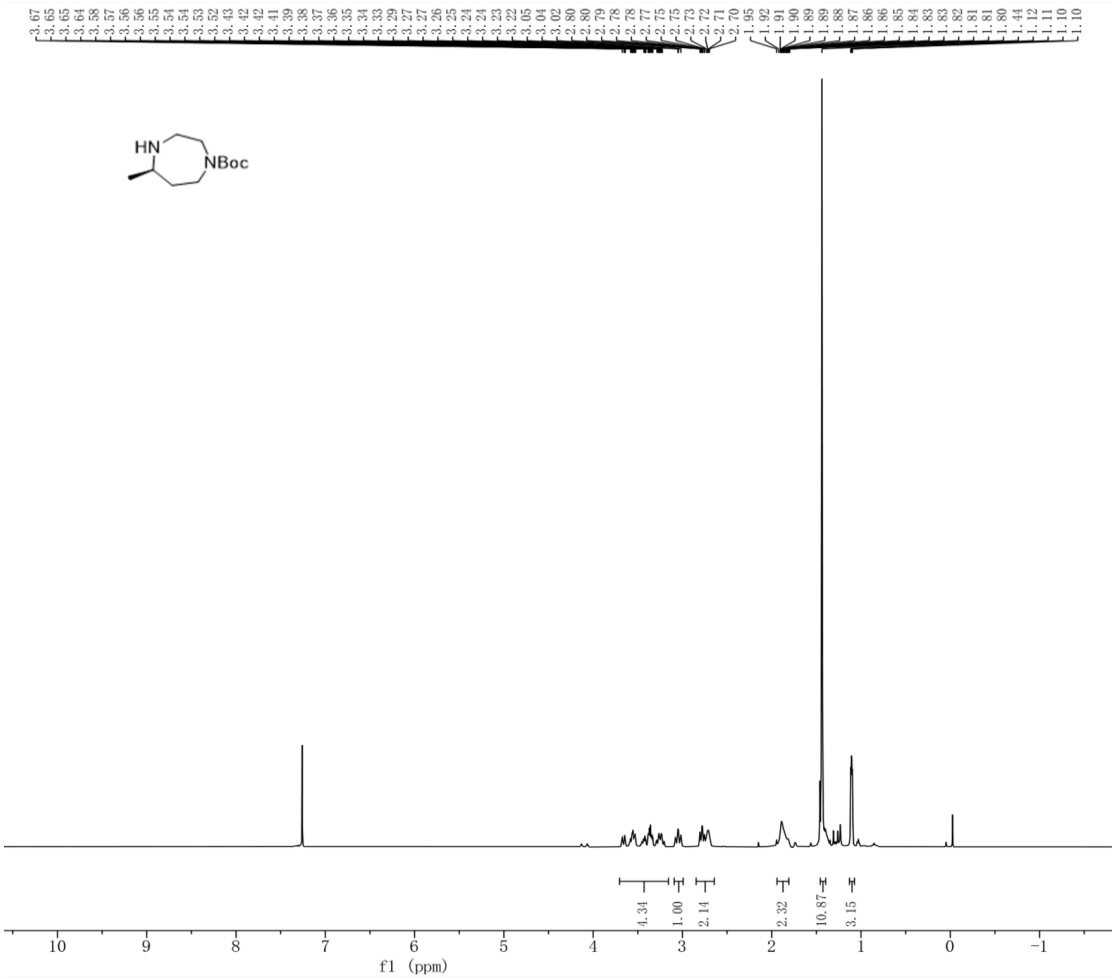
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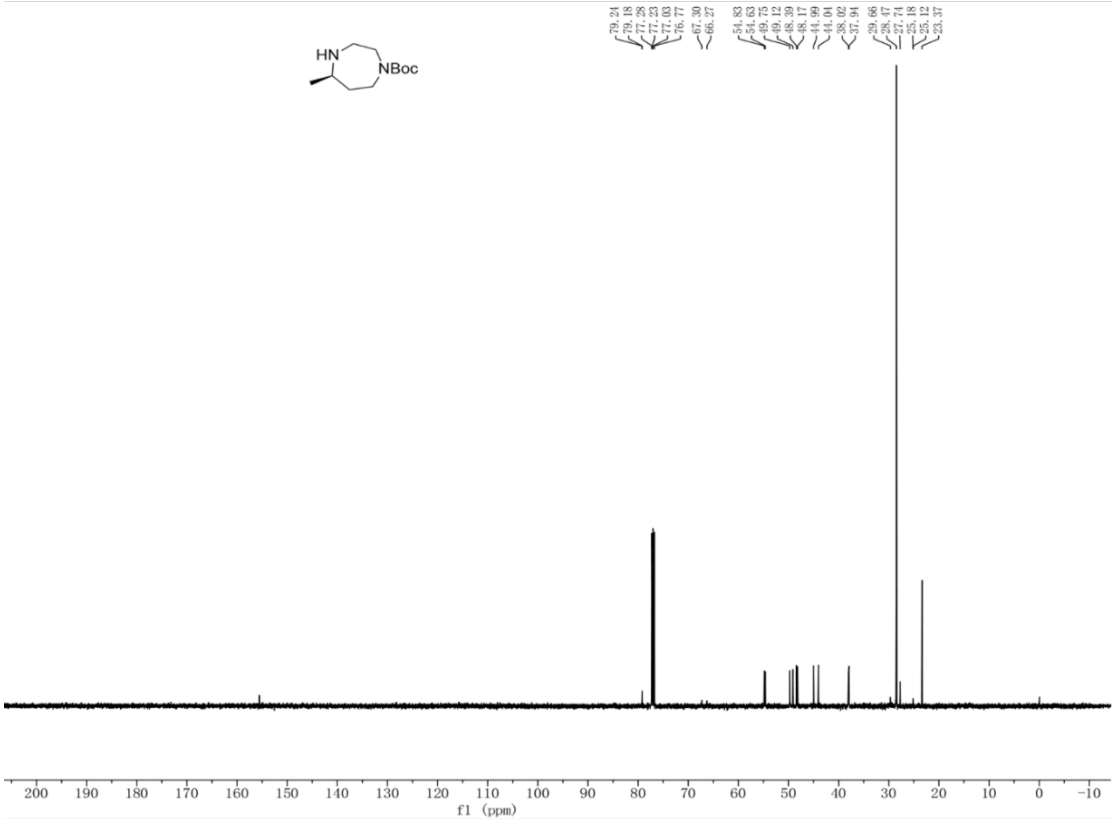
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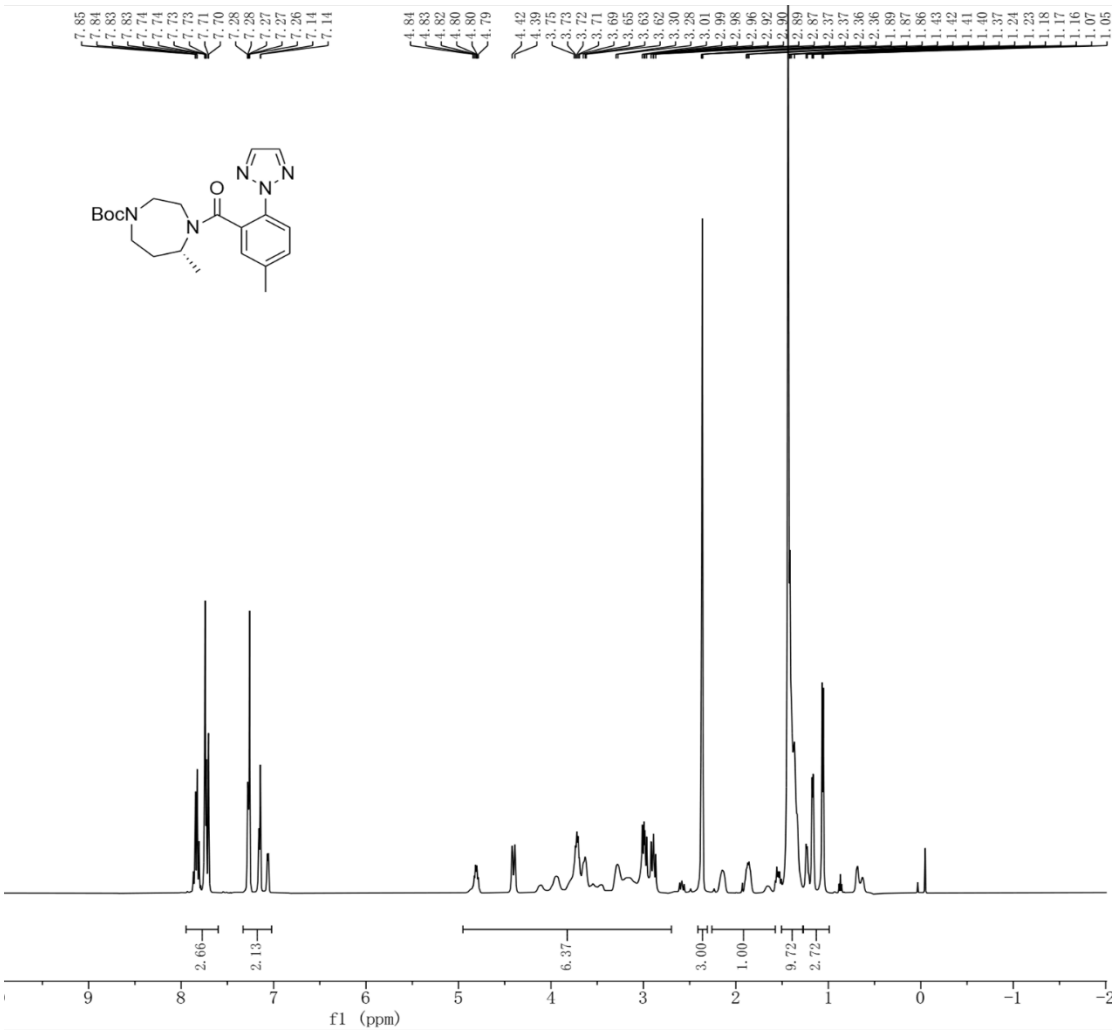
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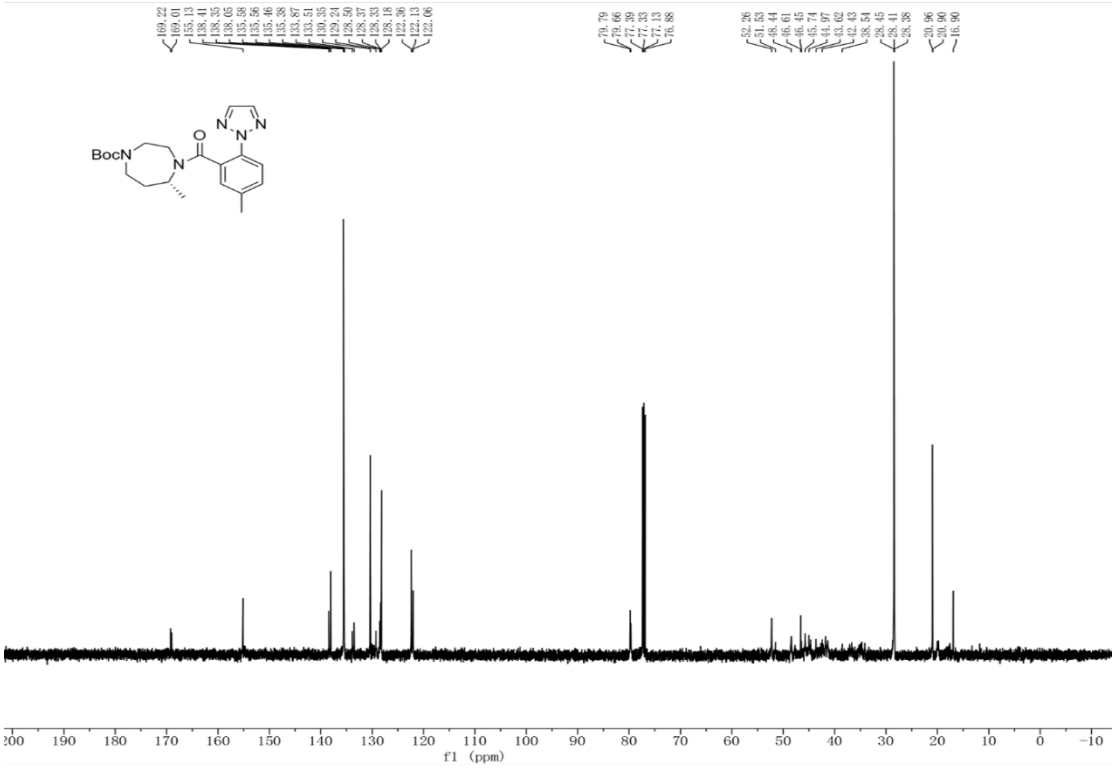
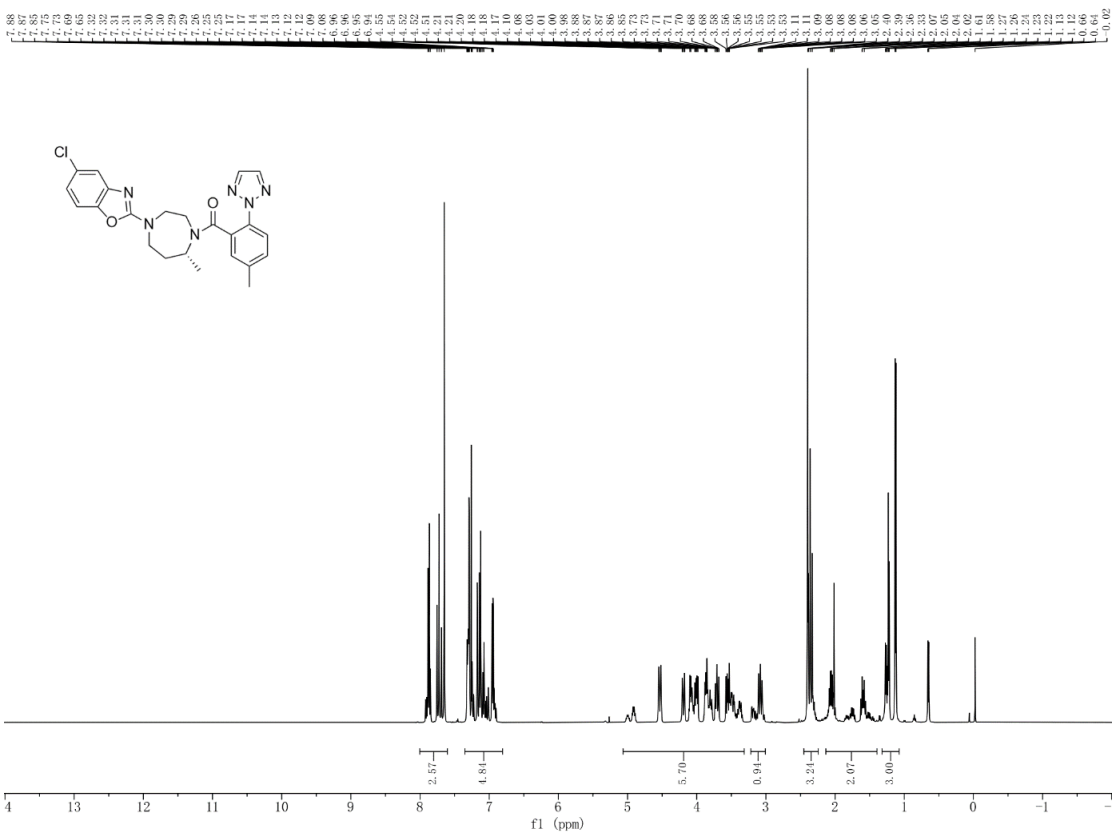
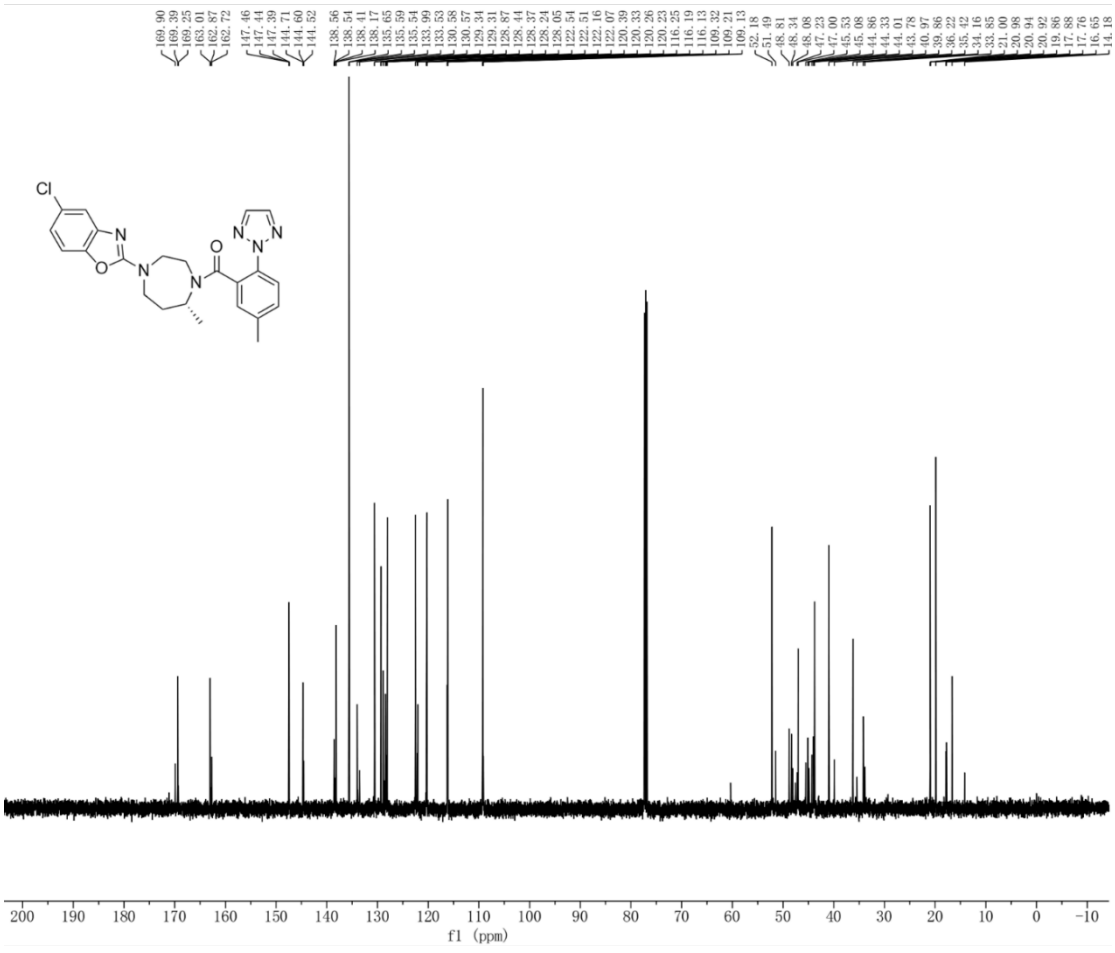
BocN
O
N
2.66 2.13 6.37 3.00 1.00 9.72 2.72
f1 (ppm)


169.22 169.01 155.13 138.41 138.35 138.05 135.58 135.56 135.46 135.38 133.57 133.51 130.35 129.24 128.50 128.37 128.33 128.18 122.36 122.13 122.06
79.79 79.66 77.39 77.33 77.13 76.88
52.26 51.53 46.44 46.01 45.45 45.74 44.97 43.62 42.43 38.54 28.45 28.41 28.38 20.96 20.90 16.90
BocN
O
N
f1 (ppm)


Cl
N
O
N
O
N
N
N
2.57
4.84
5.70
0.94
3.24
2.07
3.00
f1 (ppm)


Cl
N
O
N
O
N
N
N
f1 (ppm)