

Supporting Information

Design, synthesis and evaluation of acetylcholinesterase and butyrylcholinesterase dual-target inhibitors against Alzheimer's disease

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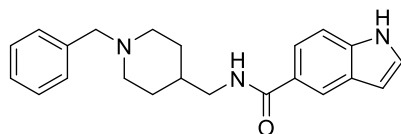
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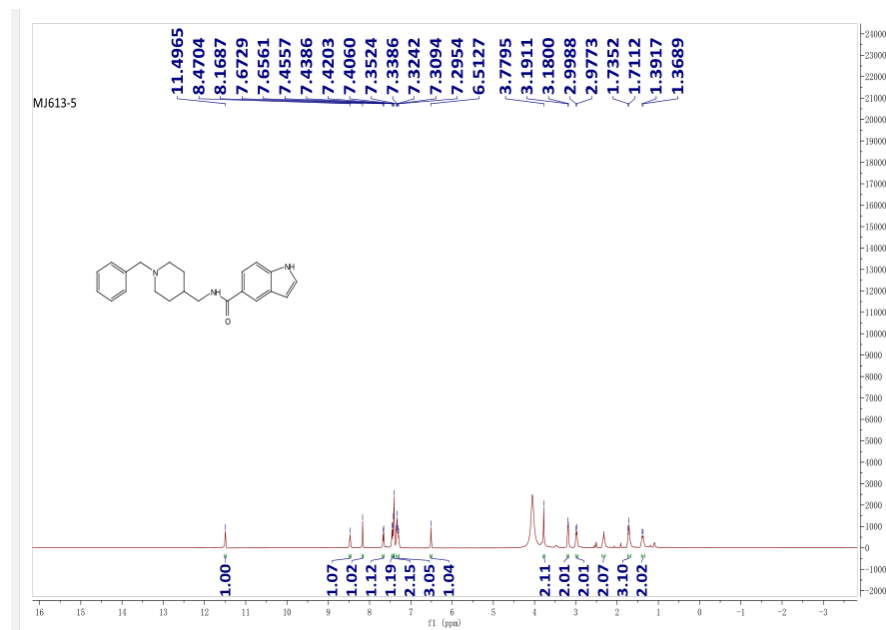
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The ^1H NMR, ^{13}C NMR and HRMS (ESI) spectrum of target compounds 6a

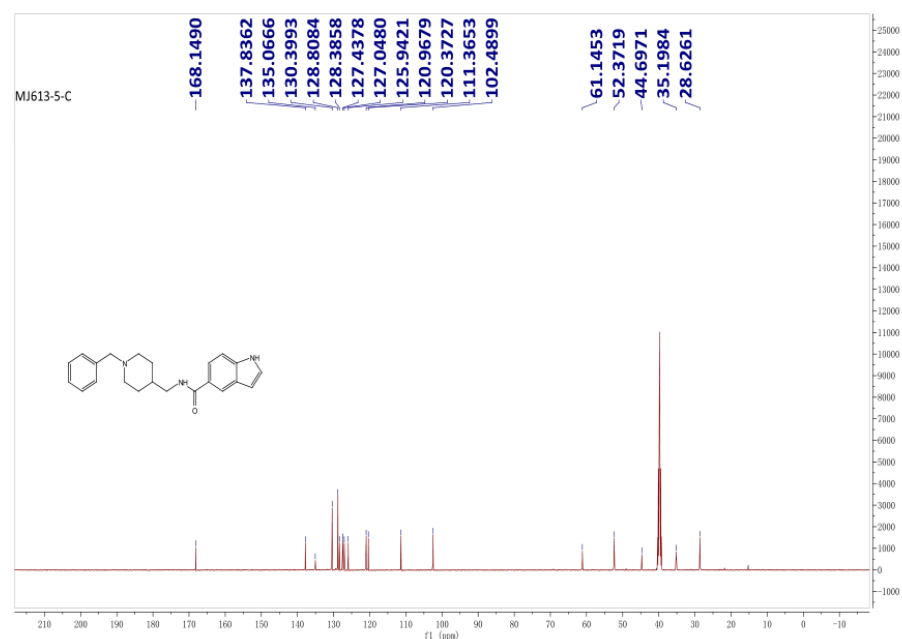


^1H NMR



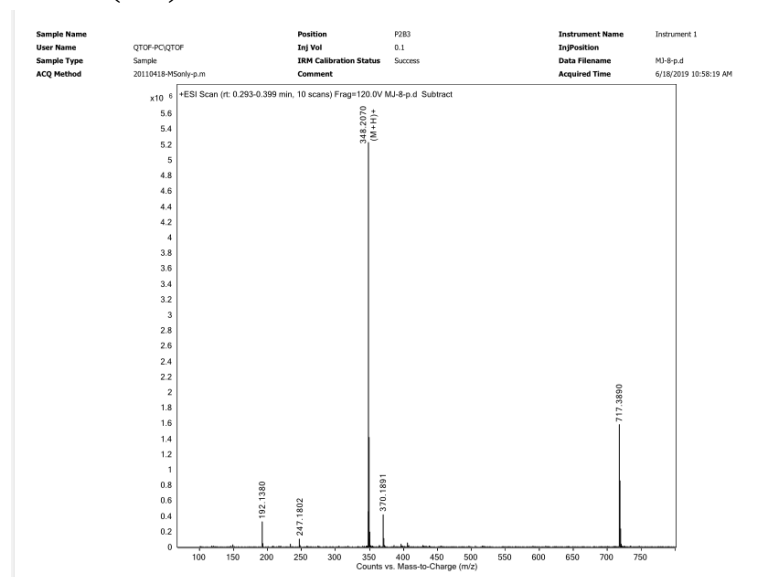
^1H NMR (500 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 7.1 Hz, 2H), 7.36 – 7.29 (m, 3H), 6.51 (s, 1H), 3.78 (s, 2H), 3.19 (d, J = 5.5 Hz, 2H), 2.99 (d, J = 10.8 Hz, 2H), 2.31 (d, J = 11.0 Hz, 2H), 1.72 (d, J = 12.0 Hz, 3H), 1.38 (d, J = 11.4 Hz, 2H).

^{13}C NMR

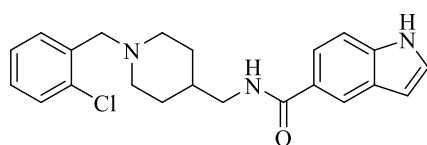


^{13}C NMR (126 MHz, DMSO- d_6) δ 168.15, 137.84, 135.07, 130.40, 128.81, 128.39, 127.44, 127.05, 125.94, 120.97, 120.37, 111.37, 102.49, 61.15, 52.37, 44.70, 35.20, 28.63.

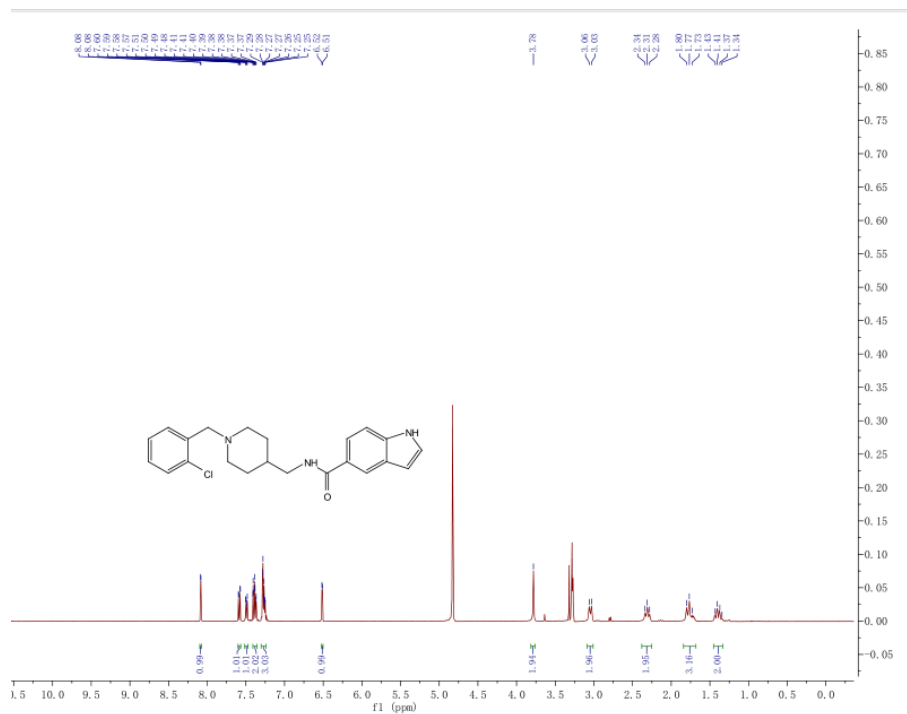
HRMS (ESI)



6b



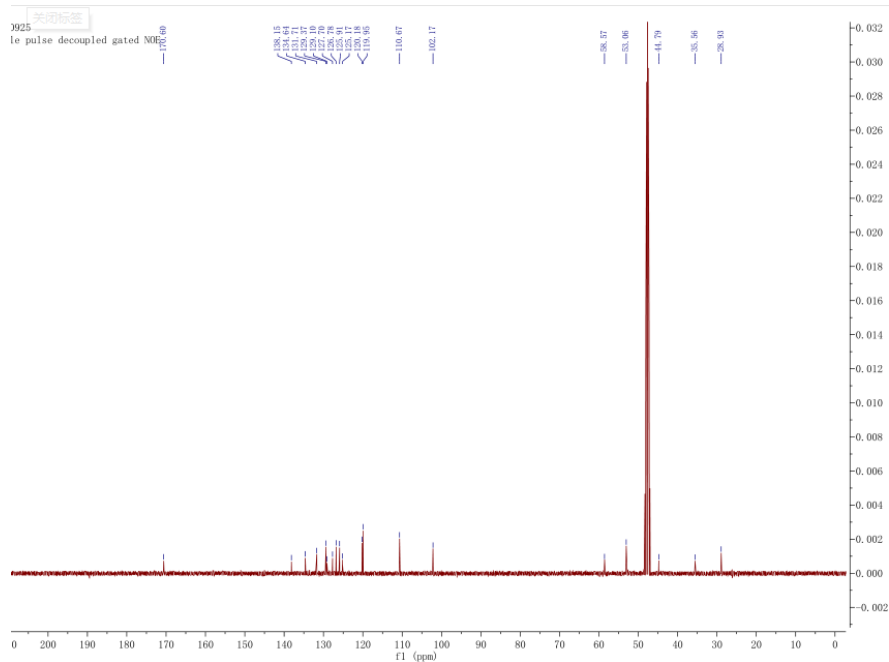
^1H NMR



^1H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 1.1 Hz, 1H), 7.58 (dd, J = 8.6, 1.8 Hz, 1H), 7.49 (dd, J = 7.1, 2.2 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.30 – 7.24 (m, 3H), 6.51 (d,

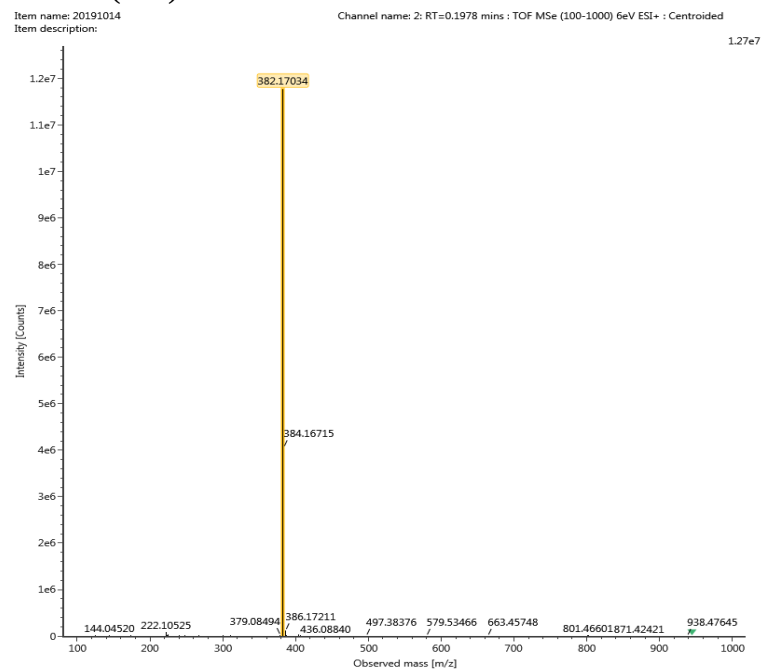
$J = 3.2$ Hz, 1H), 3.78 (s, 2H), 3.05 (d, $J = 11.7$ Hz, 2H), 2.31 (t, $J = 11.9$ Hz, 2H), 1.77 (t, $J = 14.0$ Hz, 3H), 1.45 – 1.33 (m, 2H).

^{13}C NMR

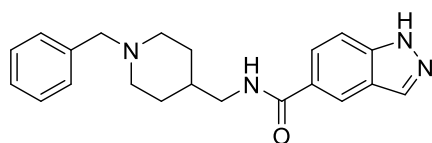


^{13}C NMR (101 MHz, CD_3OD) δ 170.60, 138.15, 134.64, 131.71, 129.37, 129.10, 127.70, 126.78, 125.91, 125.17, 120.18, 119.95, 110.67, 102.17, 58.57, 53.06, 44.79, 35.56, 28.93.

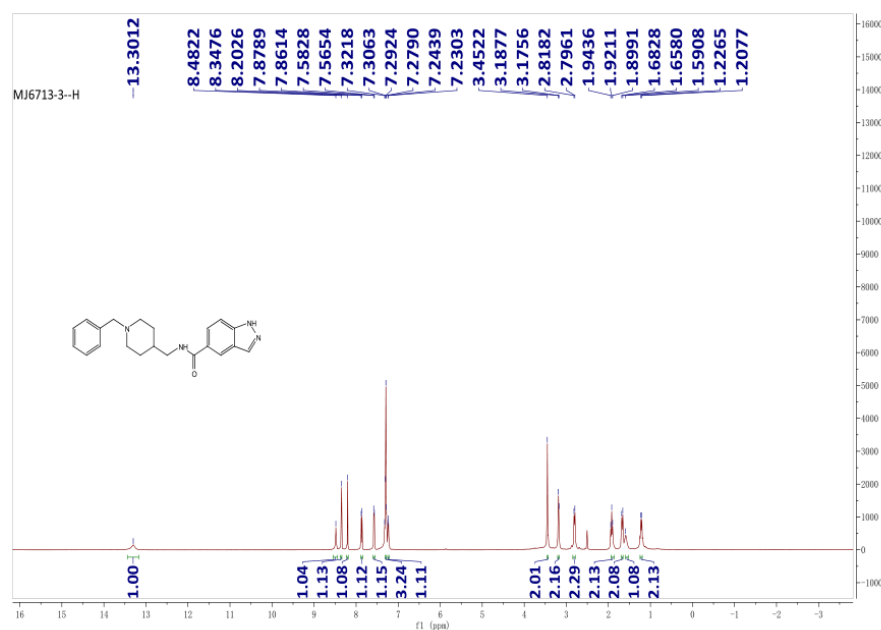
HRMS (ESI)



6c

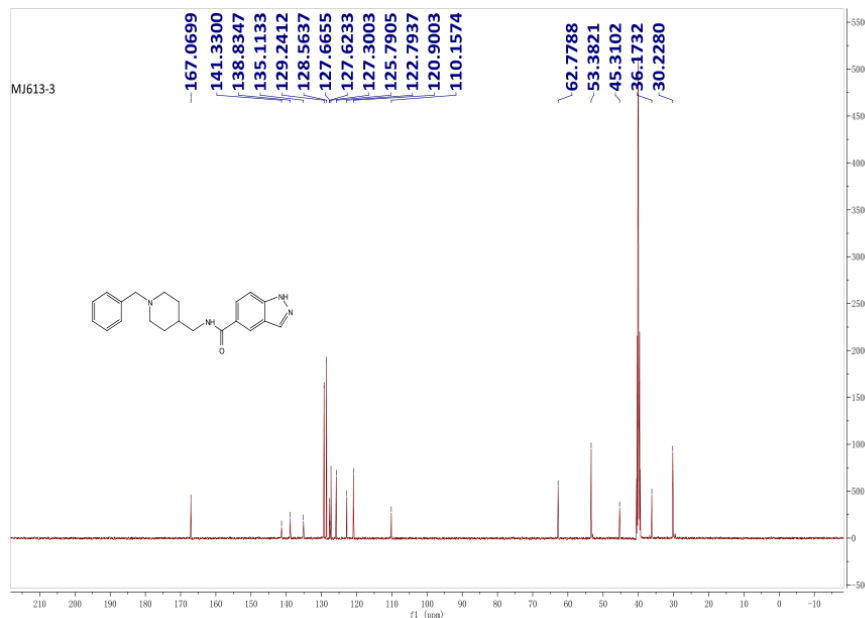


¹H NMR



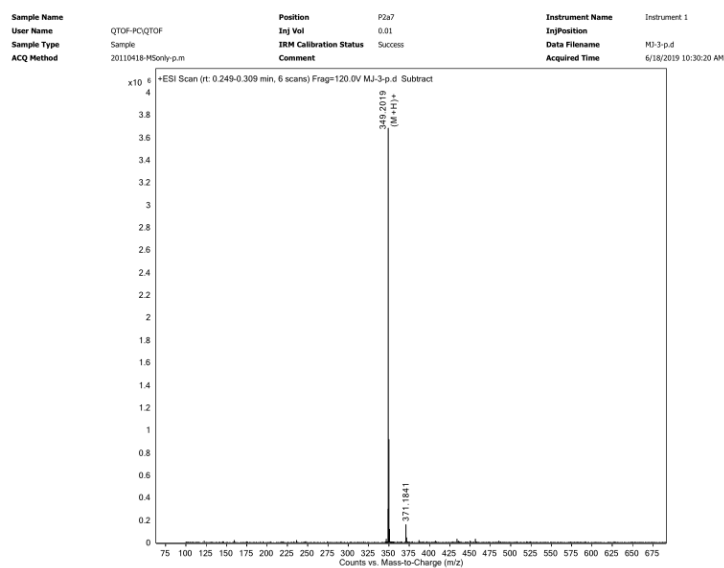
¹H NMR (500 MHz, DMSO-d₆) δ 13.30 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.24 (d, *J* = 6.8 Hz, 1H), 3.45 (s, 2H), 3.18 (d, *J* = 6.0 Hz, 2H), 2.81 (d, *J* = 11.1 Hz, 2H), 1.92 (t, *J* = 11.1 Hz, 2H), 1.67 (d, *J* = 12.4 Hz, 2H), 1.59 (s, 1H), 1.22 (d, *J* = 9.4 Hz, 2H).

¹³C NMR

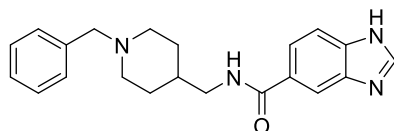


¹³C NMR (126 MHz, DMSO-d₆) δ 167.07, 141.33, 138.83, 135.11, 129.24, 128.56, 127.67, 127.62, 127.30, 125.79, 122.79, 120.90, 110.16, 62.78, 53.38, 45.31, 36.17, 30.23.

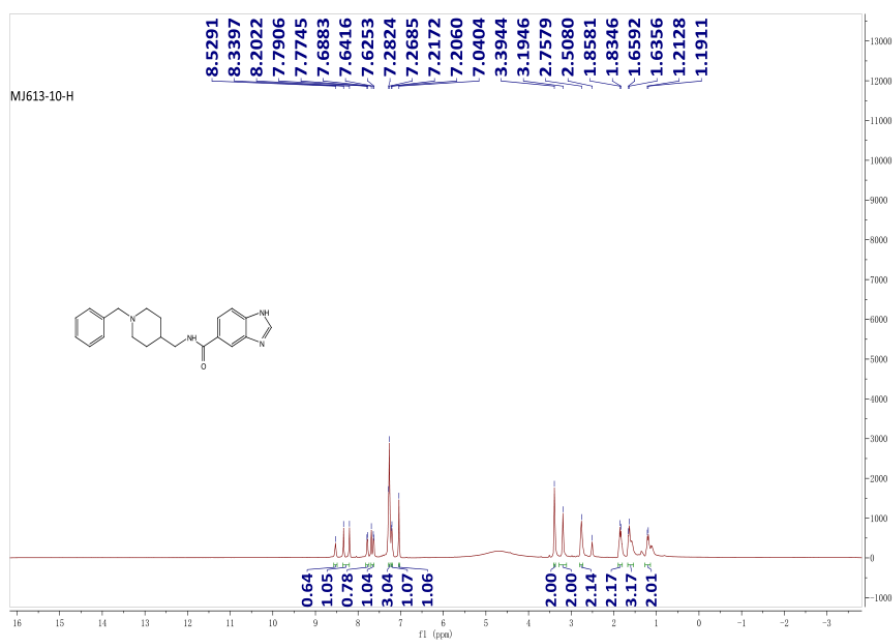
HRMS (ESI)



6d

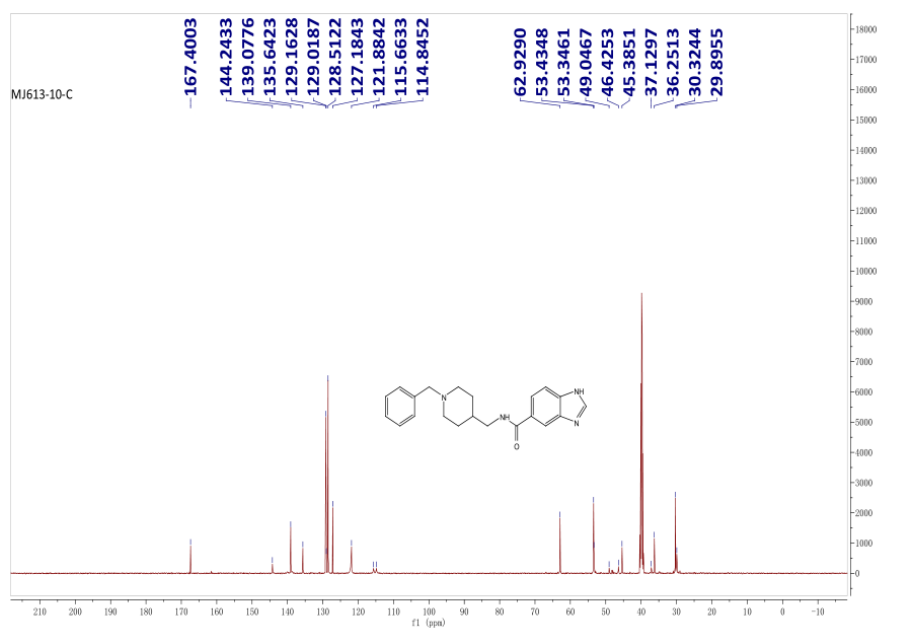


^1H NMR



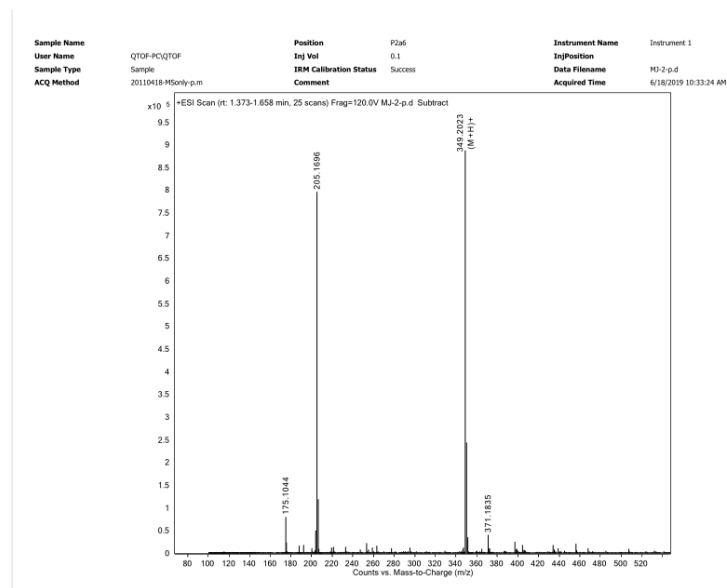
^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.27 (d, $J = 68.8$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.70 – 7.61 (m, 1H), 7.28 (d, $J = 6.9$ Hz, 3H), 7.21 (d, $J = 5.6$ Hz, 1H), 7.04 (s, 1H), 3.39 (s, 2H), 3.19 (s, 2H), 2.76 (s, 2H), 1.85 (d, $J = 11.8$ Hz, 2H), 1.65 (d, $J = 11.8$ Hz, 3H), 1.20 (d, $J = 10.9$ Hz, 2H).

^{13}C NMR

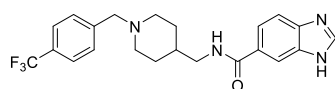


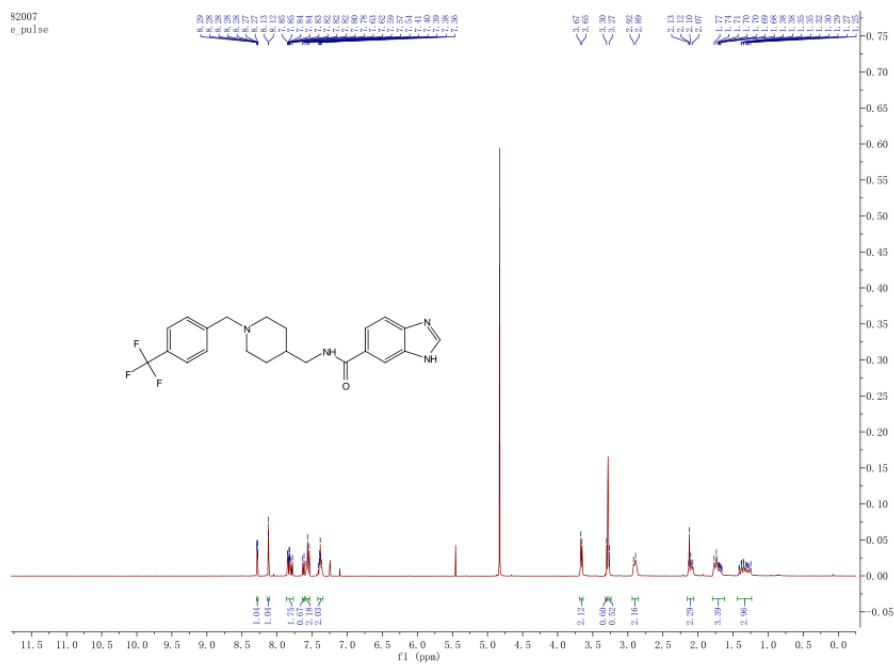
¹³C NMR (126 MHz, DMSO-d₆) δ 167.40, 144.24, 139.08, 135.64, 129.16, 129.02, 128.51, 127.18, 121.88, 115.66, 114.85, 62.93, 53.43, 53.35, 49.05, 46.43, 45.39, 37.13, 36.25, 30.32, 29.90.

HRMS (ESI)

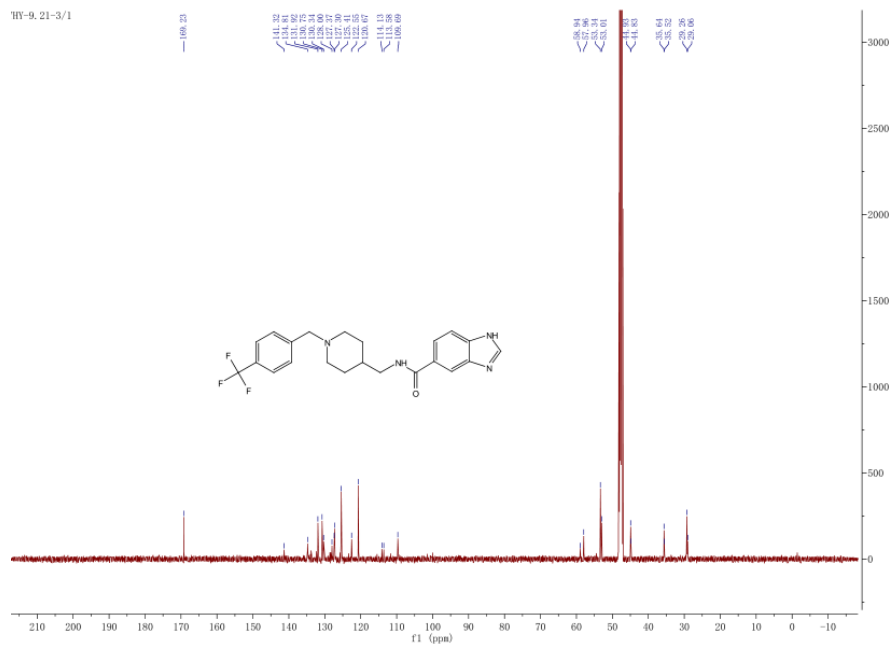


6e



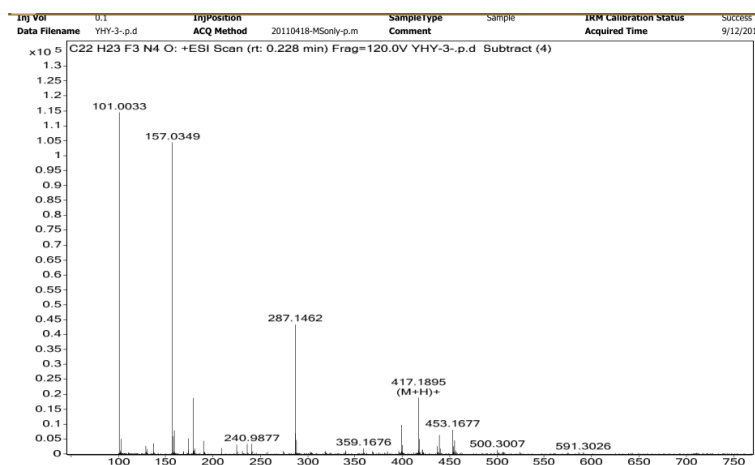
¹H NMR

¹H NMR (400 MHz, CD₃OD) δ 8.29 – 8.27 (m, 1H), 8.12 (d, *J* = 1.0 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 8.9 Hz, 2H), 7.39 (p, *J* = 5.5 Hz, 2H), 3.66 (d, *J* = 6.7 Hz, 2H), 3.30 (s, 1H), 3.27 (s, 1H), 2.90 (d, *J* = 11.4 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.79 – 1.63 (m, 3H), 1.44 – 1.24 (m, 3H).

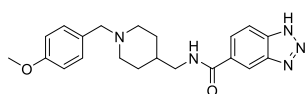
¹³C NMR

¹³C NMR (126 MHz, CD₃OD) δ 169.23, 141.32, 134.81, 131.92, 130.75, 130.34, 128.00, 127.37, 127.30, 125.41, 122.55, 120.67, 114.13, 113.58, 109.69, 58.94, 57.96, 53.34, 53.01, 44.93, 44.83, 35.64, 35.52, 29.26, 29.06.

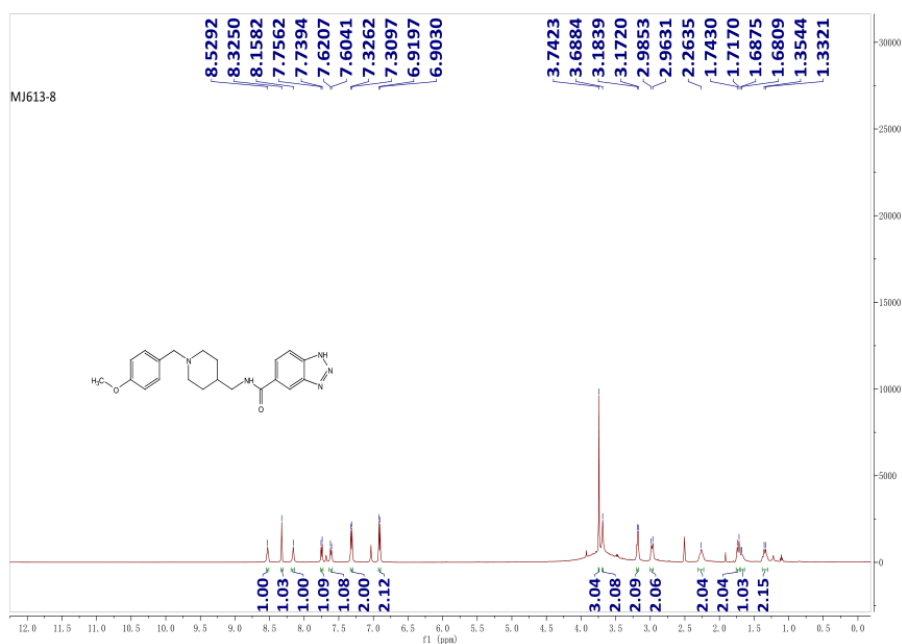
HRMS (ESI)



6f

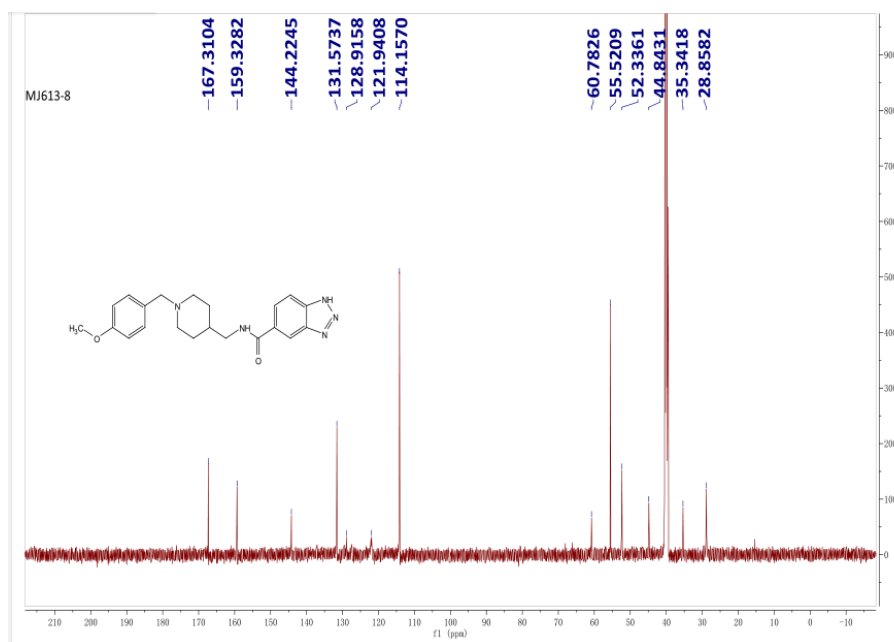


^1H NMR



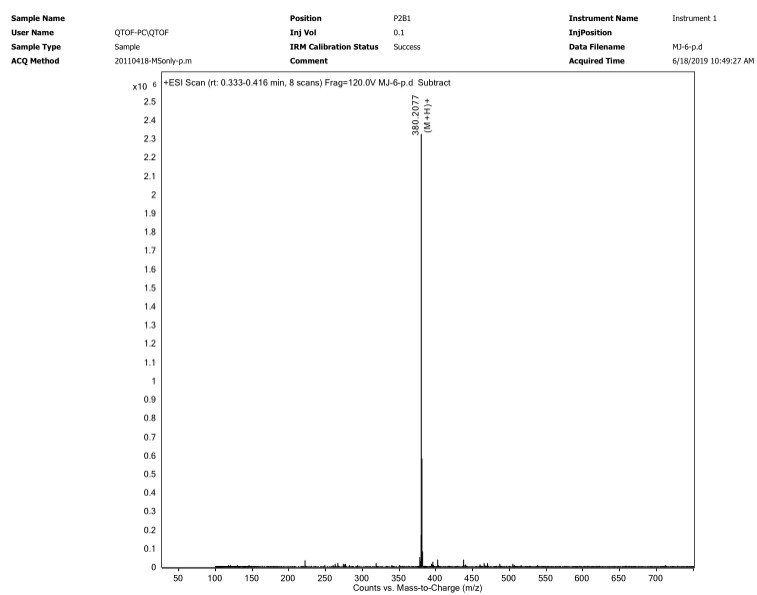
^1H NMR (500 MHz, DMSO- d_6) δ 8.53 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.3 Hz, 2H), 3.74 (s, 3H), 3.69 (s, 2H), 3.18 (d, J = 5.9 Hz, 2H), 2.97 (d, J = 11.1 Hz, 2H), 2.26 (s, 2H), 1.73 (d, J = 13.0 Hz, 2H), 1.68 (s, 1H), 1.34 (d, J = 11.2 Hz, 2H).

^{13}C NMR

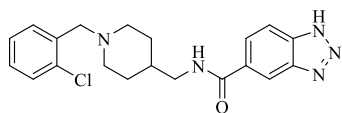


^{13}C NMR (126 MHz, DMSO- d_6) δ 167.31, 159.33, 144.22, 131.57, 128.92, 121.94, 114.16, 60.78, 55.52, 52.34, 44.84, 35.34, 28.86.

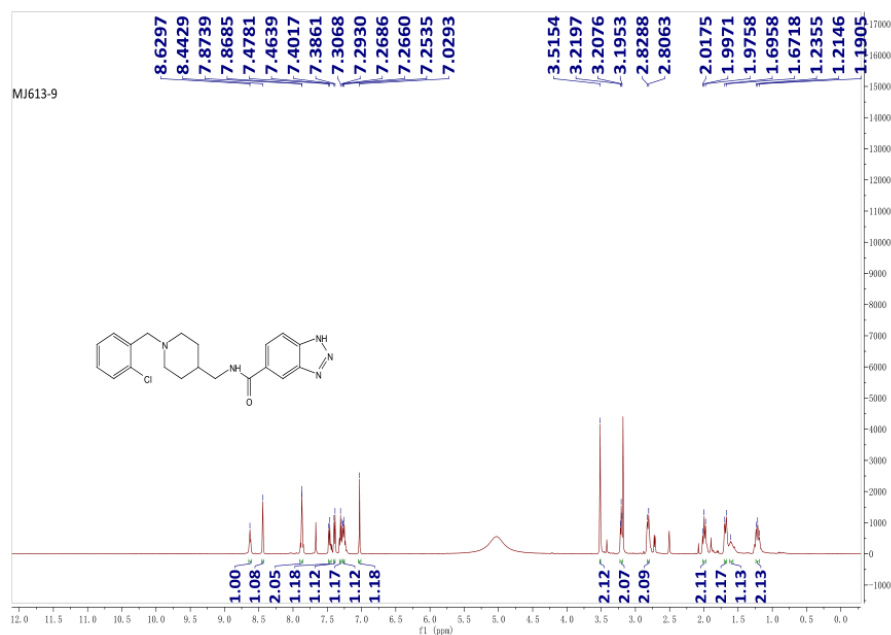
HRMS (ESI)



6g

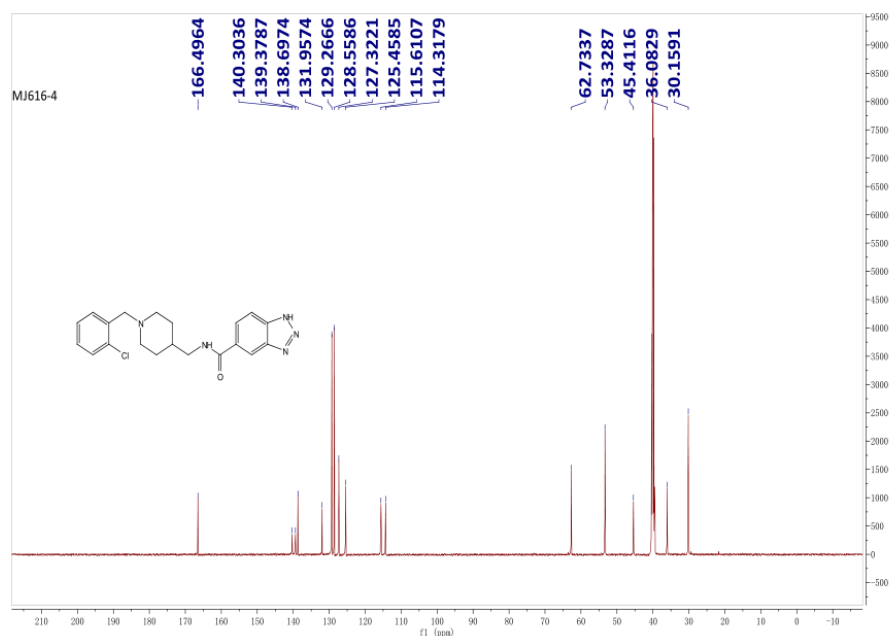


^1H NMR



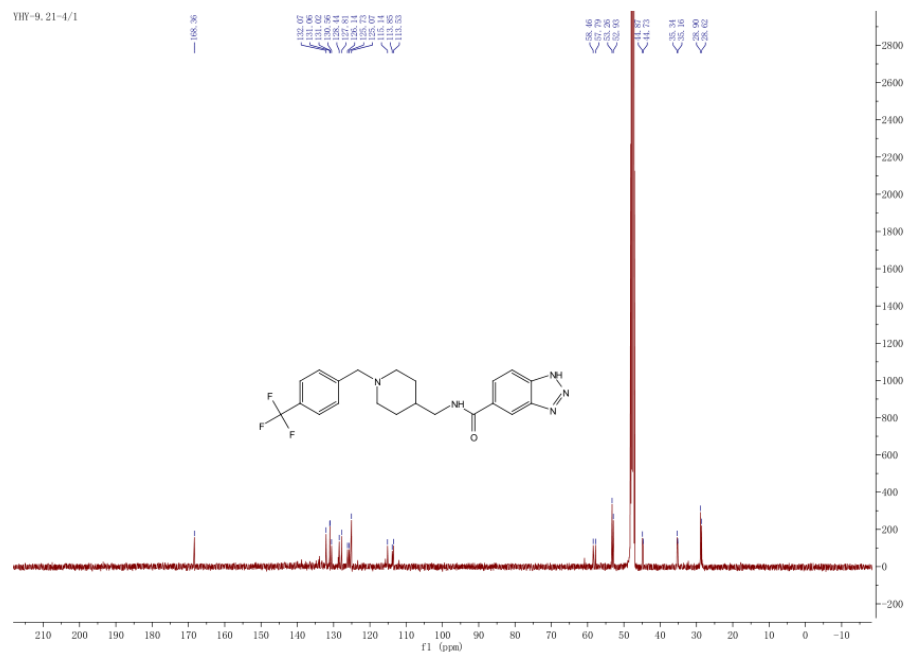
¹H NMR (500 MHz, DMSO-d₆) δ 8.63 (s, 1H), 8.44 (s, 1H), 7.87 (d, *J* = 2.7 Hz, 2H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.03 (s, 1H), 3.52 (s, 2H), 3.21 (t, *J* = 6.1 Hz, 2H), 2.82 (d, *J* = 11.3 Hz, 2H), 2.00 (t, *J* = 10.4 Hz, 2H), 1.68 (d, *J* = 12.0 Hz, 2H), 1.61 (s, 1H), 1.23 (d, *J* = 10.5 Hz, 2H).

¹³C NMR



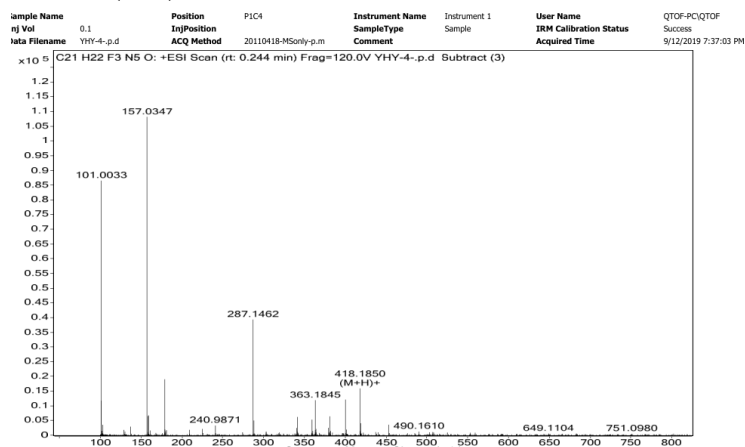
¹³C NMR (126 MHz, DMSO-d₆) δ 166.50, 140.30, 139.38, 138.70, 131.96, 129.27, 128.56, 127.32, 125.46, 115.61, 114.32, 62.73, 53.33, 45.41, 36.08, 30.16.

HRMS (ESI)

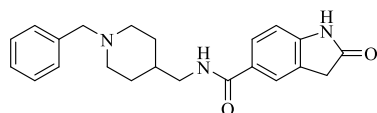


^{13}C NMR (126 MHz, CD_3OD) δ 168.36, 132.07, 131.06, 131.02, 130.56, 128.44, 127.81, 125.07, 115.14, 113.53, 58.46, 57.79, 53.26, 52.93, 44.87, 44.73, 35.34, 35.16, 28.90, 28.62.

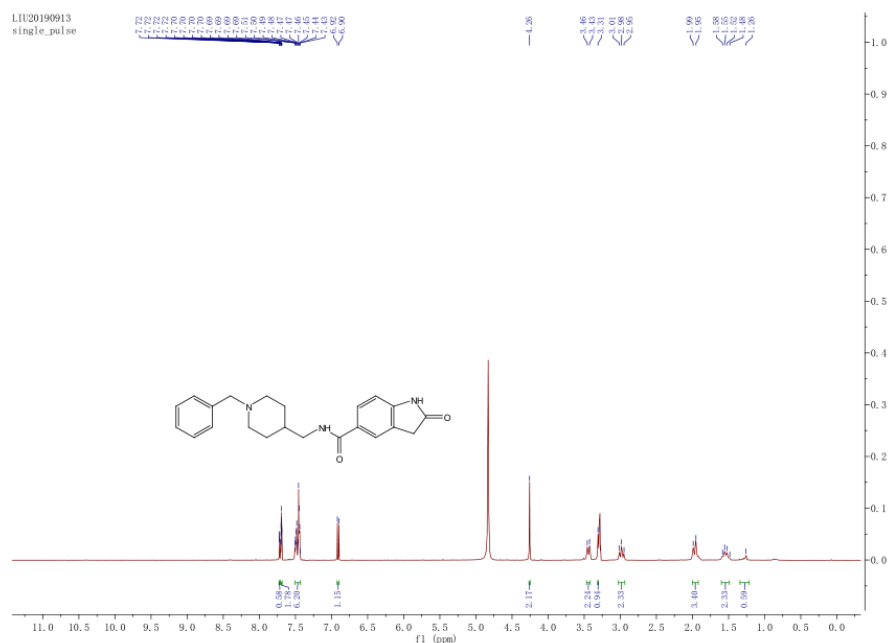
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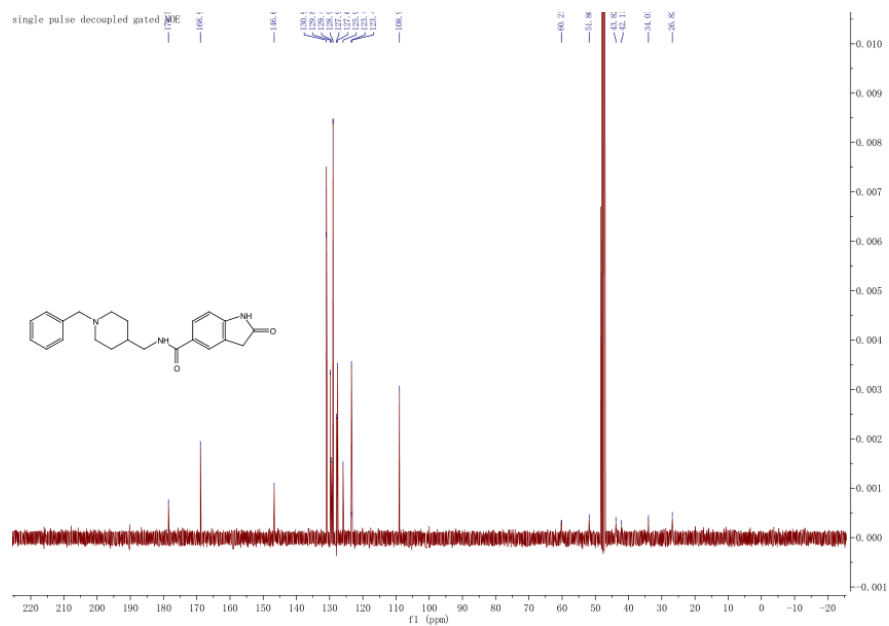
8i



^1H NMR

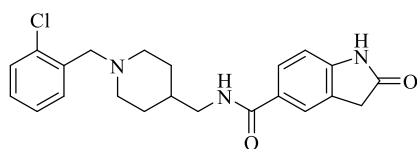


^{13}C NMR

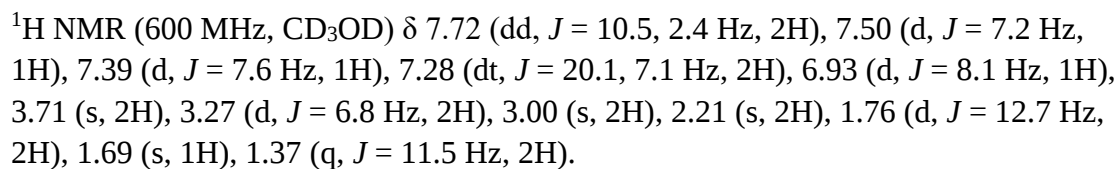


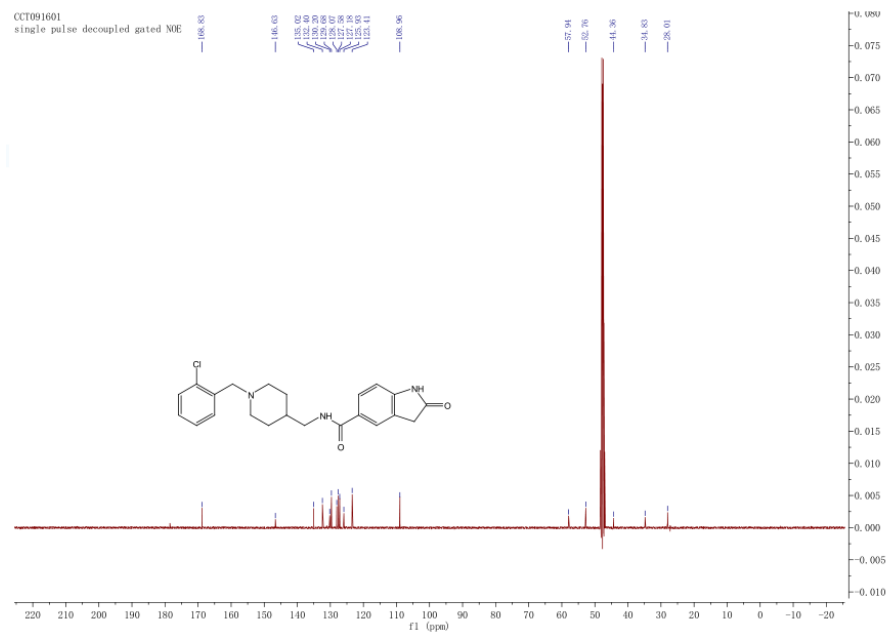
^{13}C NMR (101 MHz, CD_3OD) δ 178.52, 168.90, 146.69, 130.99, 129.80, 129.40, 128.99, 127.92, 127.60, 125.95, 123.42, 123.40, 108.97, 60.21, 51.86, 43.82, 42.11, 34.01, 26.82.

HRMS (ESI)



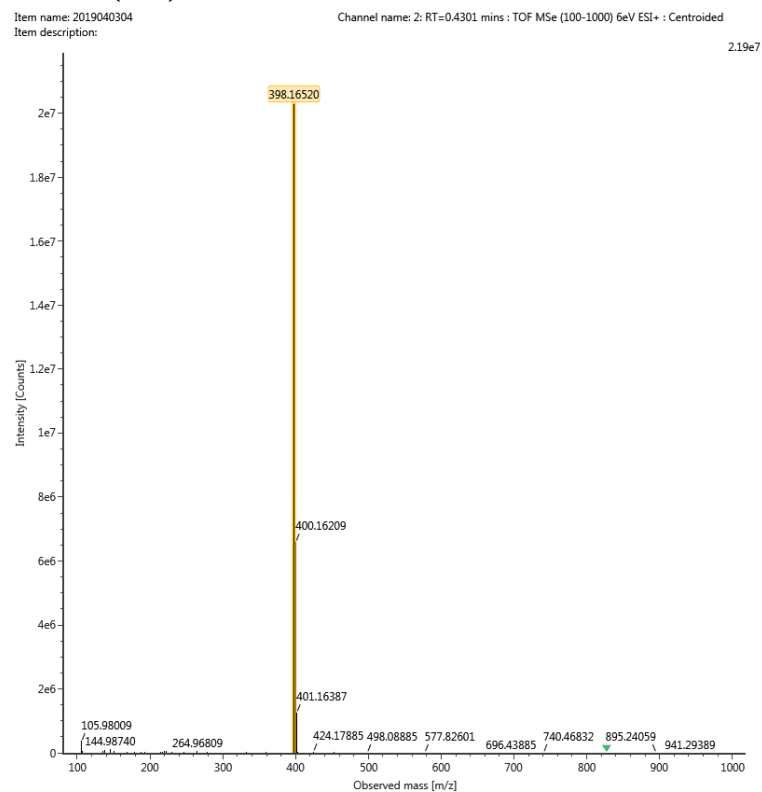
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LZL348-0474

¹³C NMR

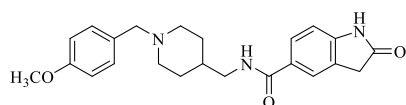


^{13}C NMR (101 MHz, CD_3OD) δ 168.83, 146.63, 135.02, 132.40, 130.20, 129.68, 128.07, 127.58, 127.18, 125.93, 123.41, 108.96, 57.94, 52.76, 44.36, 34.83, 28.01.

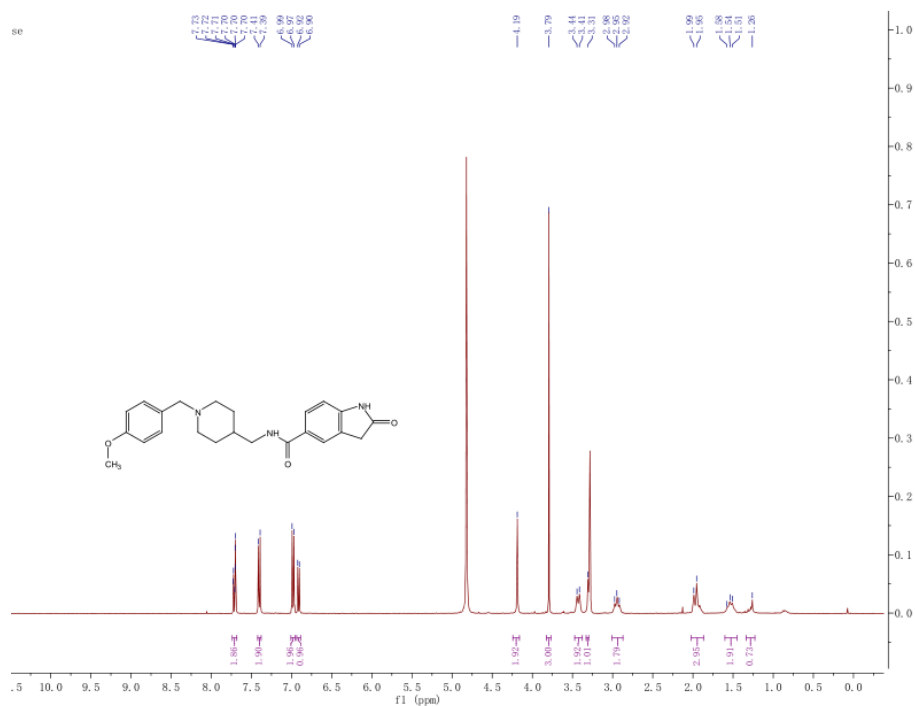
HRMS (ESI)



8k

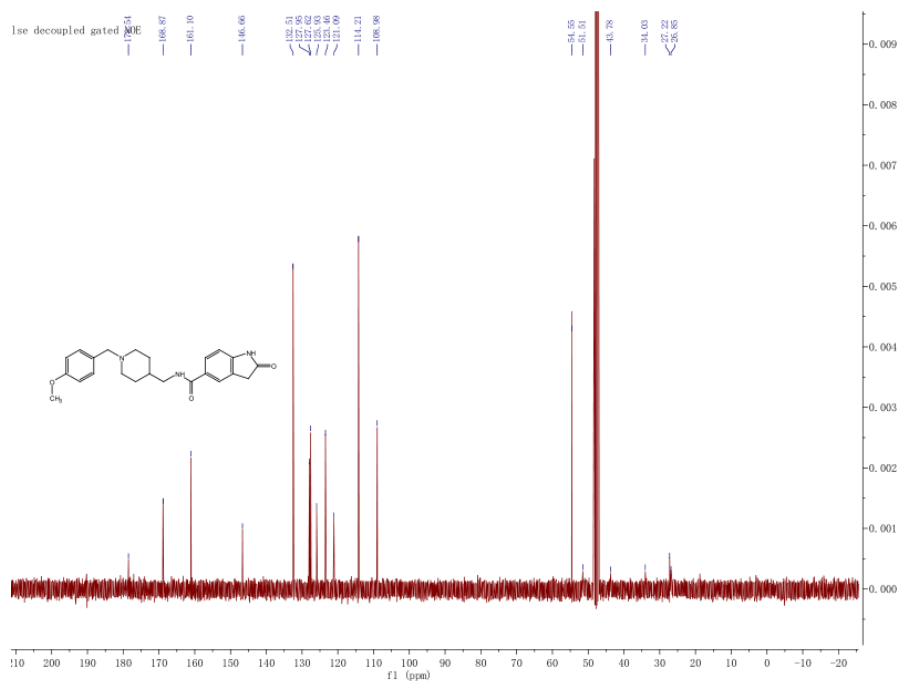


^1H NMR



¹H NMR (400 MHz, CD₃OD) δ 7.74 – 7.68 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.19 (s, 2H), 3.79 (s, 3H), 3.43 (d, *J* = 12.0 Hz, 2H), 3.31 (s, 1H), 2.95 (t, *J* = 11.7 Hz, 2H), 1.97 (d, *J* = 13.9 Hz, 3H), 1.60 – 1.45 (m, 2H), 1.26 (s, 1H).

¹³C NMR

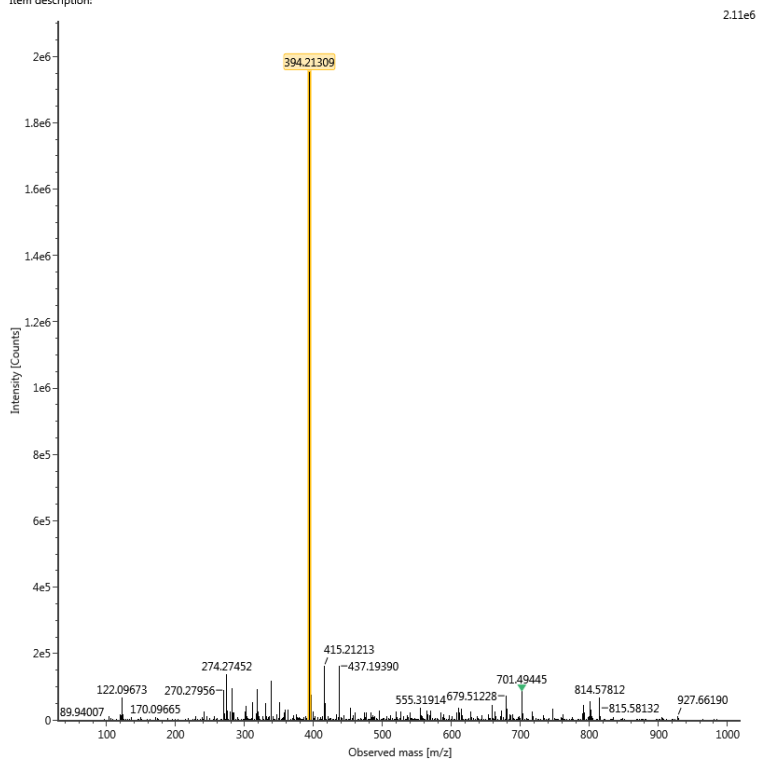


¹³C NMR (101 MHz, CD₃OD) δ 178.54, 168.87, 161.10, 146.66, 132.51, 127.95, 127.62, 125.93, 123.46, 121.09, 114.21, 108.98, 54.55, 51.51, 43.78, 34.03, 27.22, 26.85.

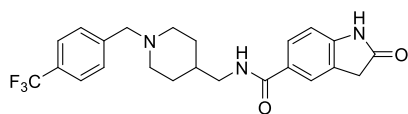
HRMS (ESI)

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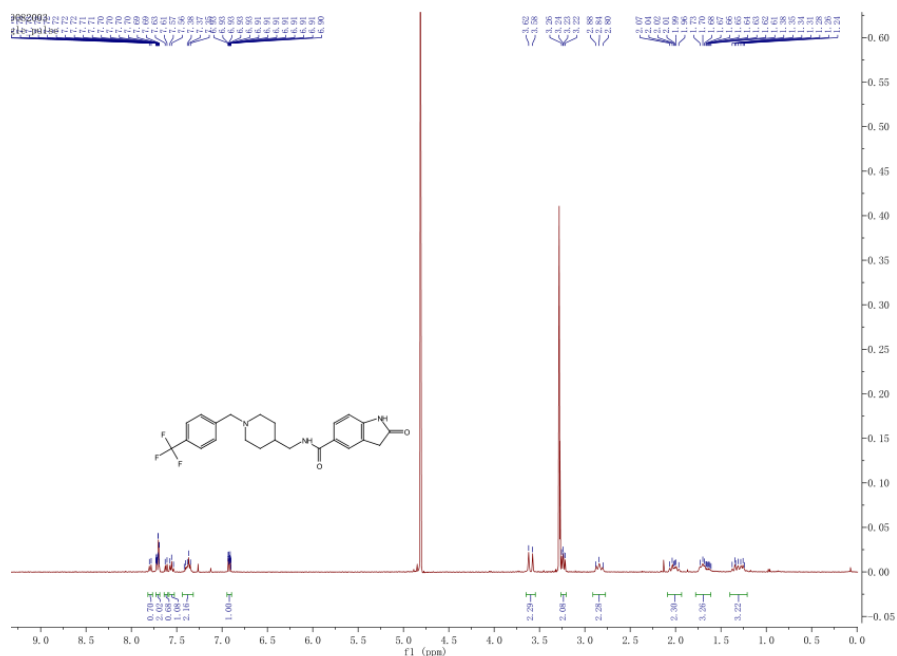
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81



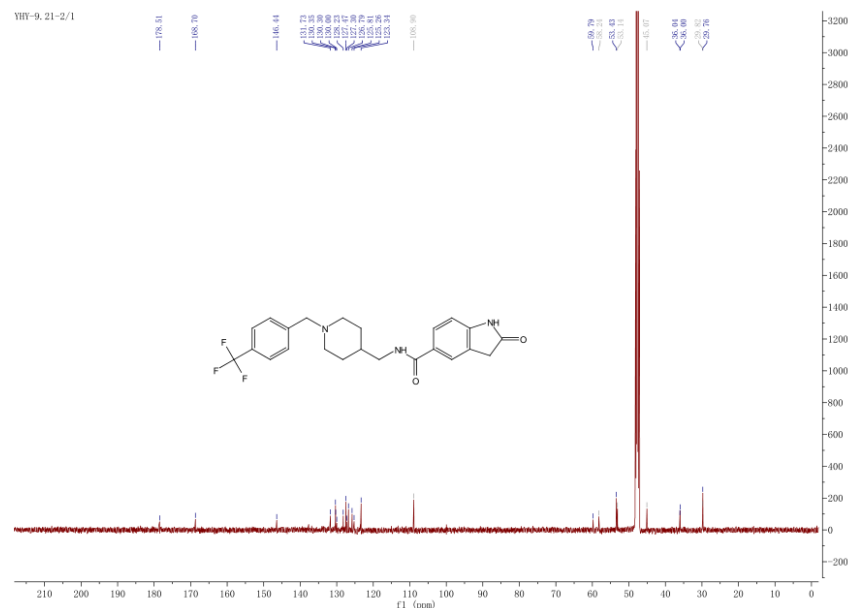
^1H NMR



^1H NMR (400 MHz, CD_3OD) δ 7.79 (d, J = 7.8 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.62 (d, J = 8.2 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.44 – 7.32 (m, 2H), 6.95 – 6.90 (m, 1H),

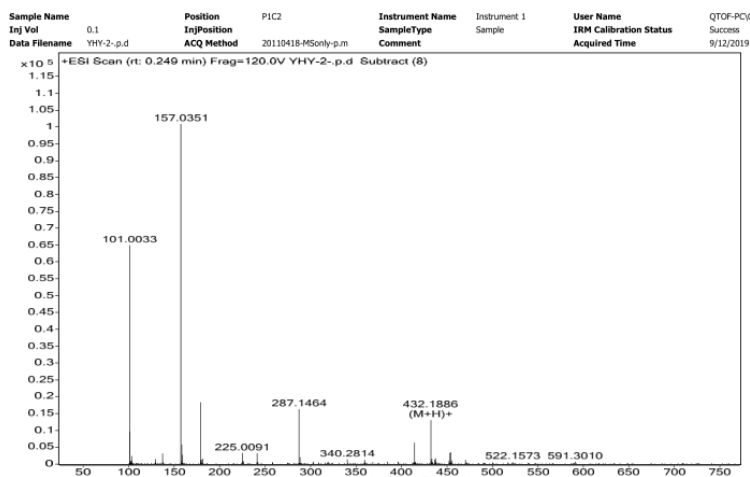
3.60 (d, $J = 17.7$ Hz, 2H), 3.24 (dd, $J = 9.1, 6.8$ Hz, 2H), 2.91 – 2.77 (m, 2H), 2.09 – 1.93 (m, 2H), 1.78 – 1.61 (m, 3H), 1.40 – 1.21 (m, 3H).

^{13}C NMR

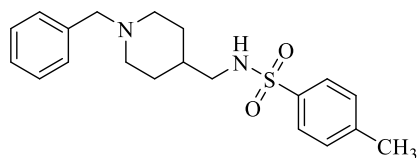


^{13}C NMR (126 MHz, CD_3OD) δ 168.70 , 146.44 , 131.73 , 130.35 , 130.30 , 128.23 , 127.47 , 127.30 , 126.79 , 125.81 , 125.26 , 123.34 , 108.90 , 59.79 , 59.79 , 58.24 , 53.43 , 53.14 , 45.07 , 36.04 , 36.04 , 36.00 , 36.00 , 29.82 , 29.76 .

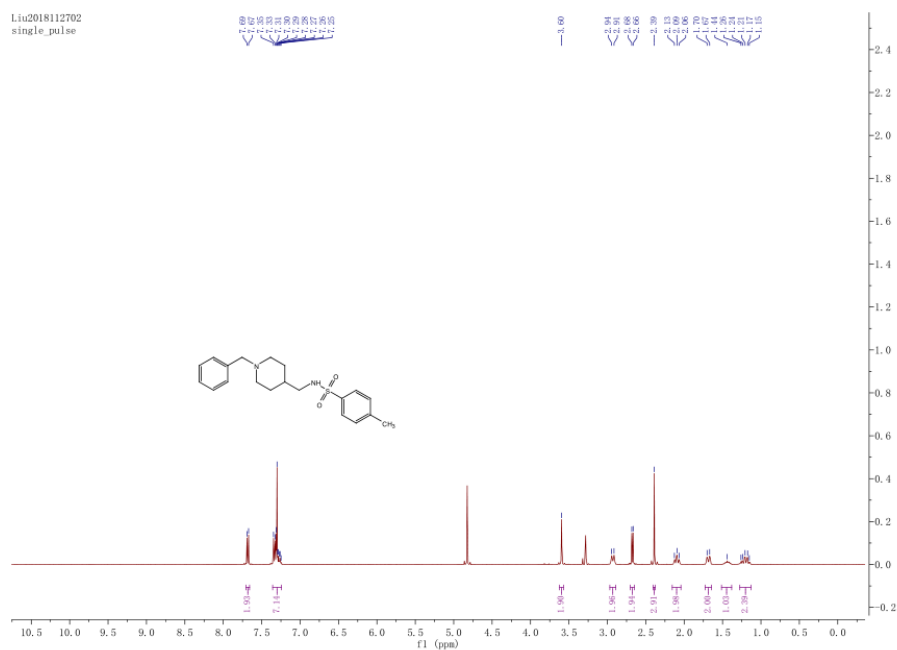
HRMS (ESI)



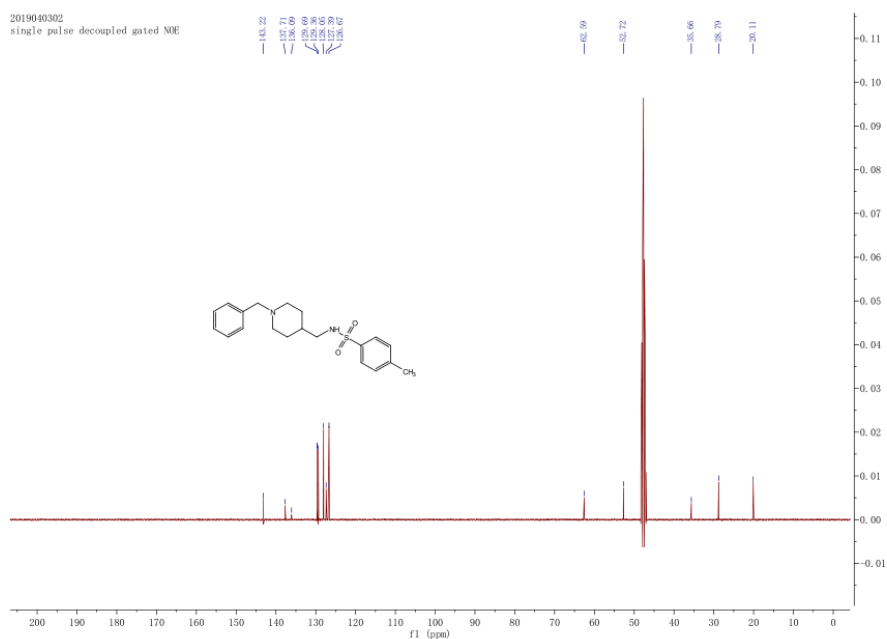
10s



^1H NMR



^{13}C NMR

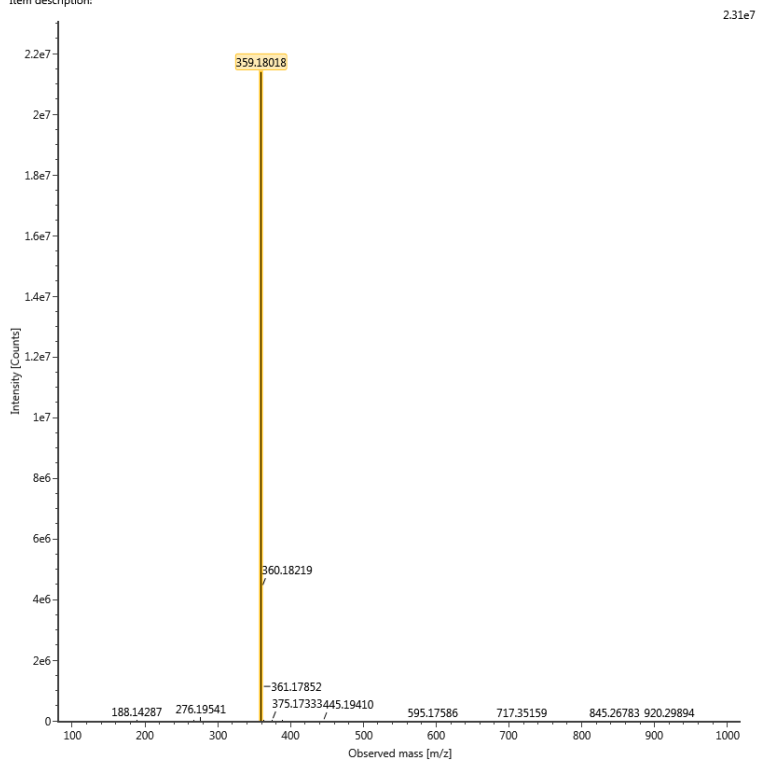


^{13}C NMR (101 MHz, CD_3OD) δ 143.22, 137.71, 136.09, 129.69, 129.36, 128.05, 127.39, 126.67, 62.59, 52.72, 35.66, 28.79, 20.11.

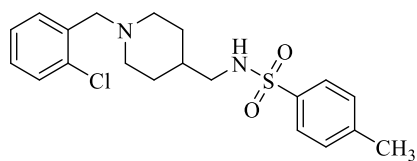
HRMS (ESI)

Item name: 2019040302
Item description:

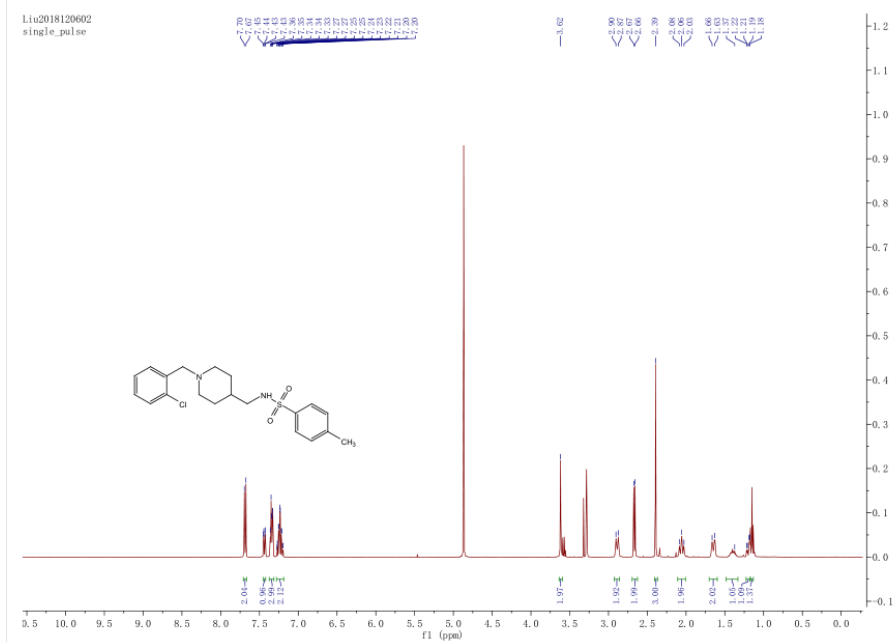
Channel name: 2: RT=0.4302 mins : TOF MSe (100-1000) 6eV ESI+ : Centroided



10t



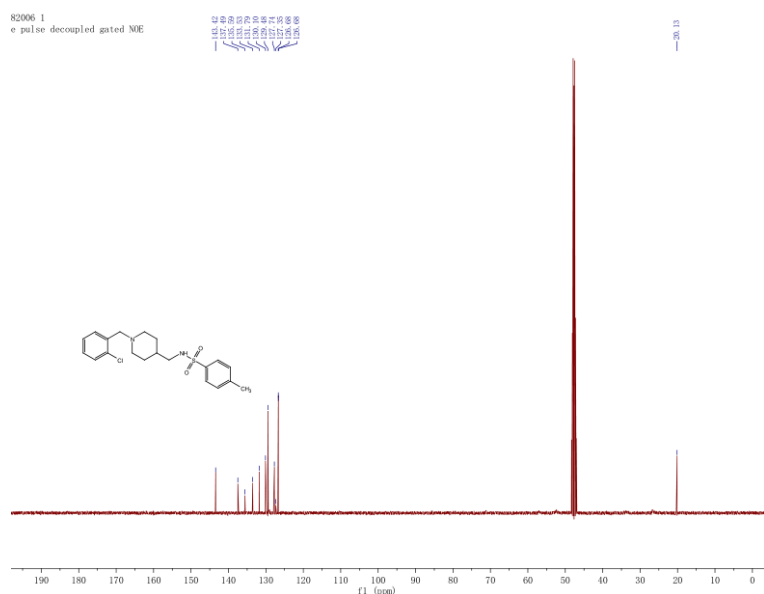
¹H NMR



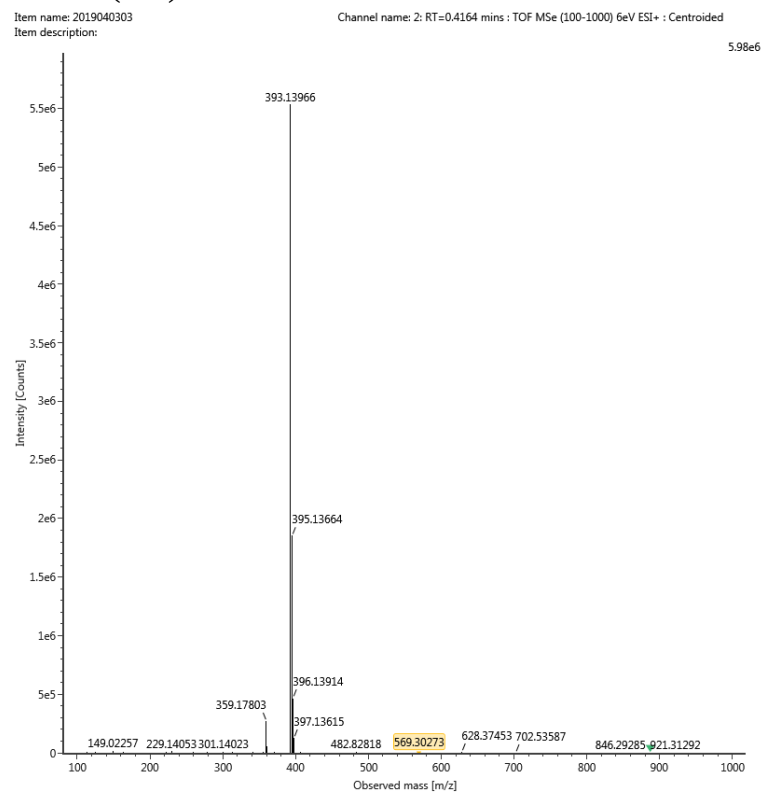
¹H NMR (400 MHz, CD₃OD) δ 7.69 (d, J = 8.3 Hz, 2H), 7.44 (dd, J = 7.4, 2.0 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.23 (td, J = 7.1, 1.9 Hz, 2H), 3.62 (s, 2H), 2.89 (d, J = 11.8

Hz, 2H), 2.67 (d, $J = 6.8$ Hz, 2H), 2.39 (s, 3H), 2.06 (t, $J = 11.7$ Hz, 2H), 1.65 (d, $J = 13.1$ Hz, 2H), 1.37 (s, 1H), 1.20 (dd, $J = 12.3, 3.6$ Hz, 1H), 1.15 (s, 1H).

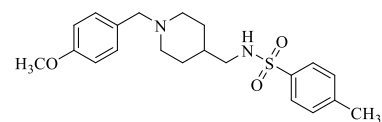
^{13}C NMR

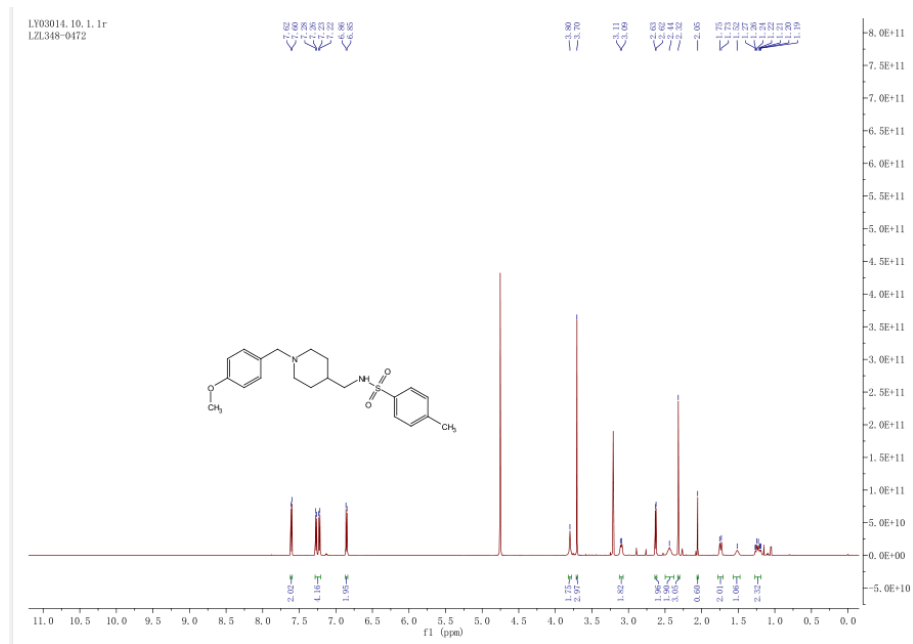


HRMS (ESI)

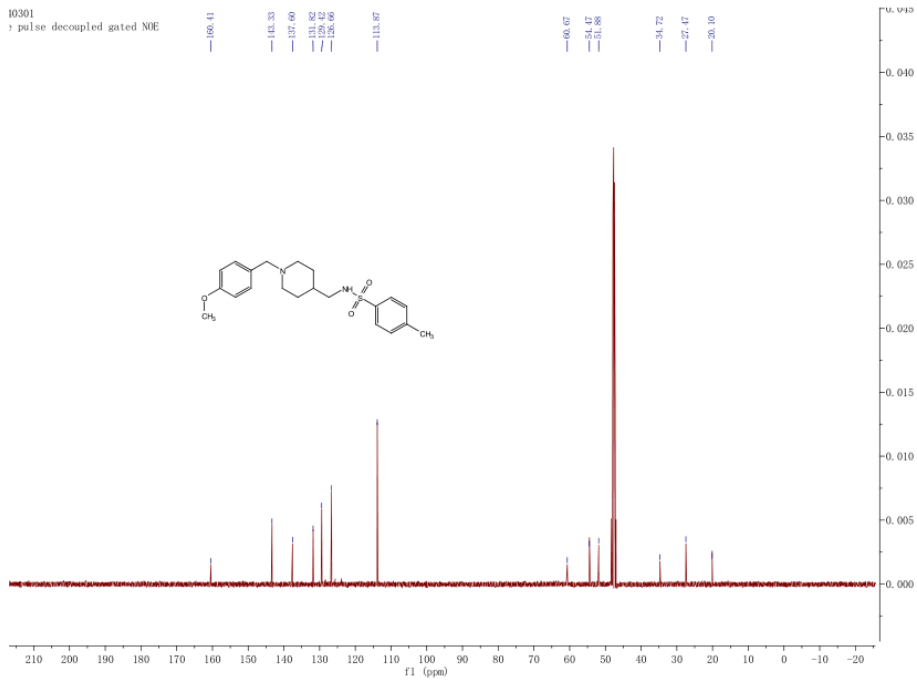


10u



¹H NMR

¹H NMR (600 MHz, CD₃OD) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.25 (dd, *J* = 27.4, 8.3 Hz, 4H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 2H), 3.70 (s, 3H), 3.10 (d, *J* = 10.7 Hz, 2H), 2.63 (d, *J* = 6.7 Hz, 2H), 2.44 (s, 2H), 2.32 (s, 3H), 2.05 (s, 1H), 1.73 (s, 2H), 1.52 (s, 1H), 1.27 – 1.19 (m, 2H).

¹³C NMR

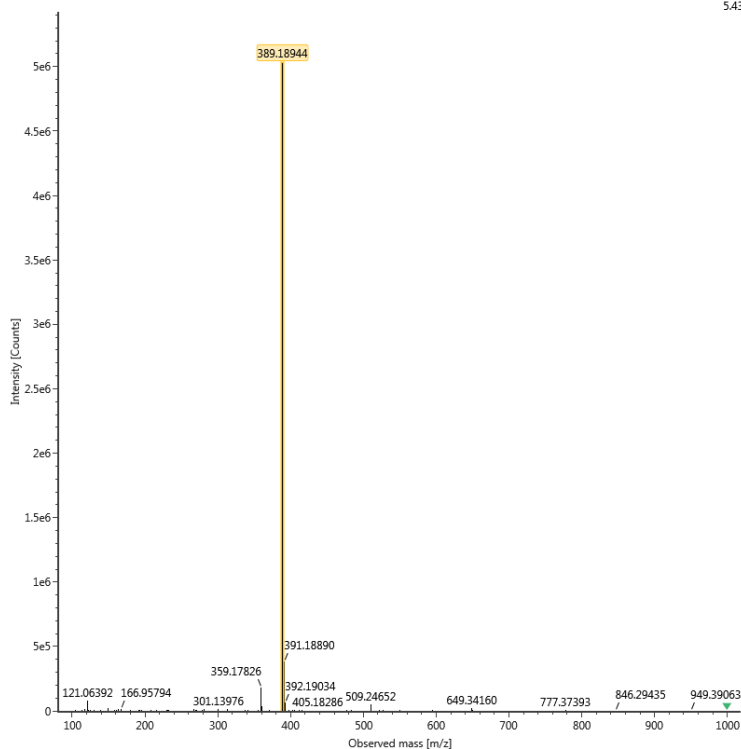
¹³C NMR (101 MHz, CD₃OD) δ 160.41, 143.33, 137.60, 131.82, 129.42, 126.66, 113.87, 60.67, 54.47, 51.88, 34.72, 27.47, 20.10.

HRMS (ESI)

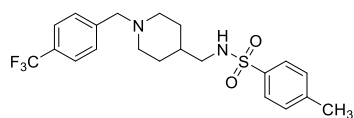
Item name: 2019040301
Item description:

Channel name: 2: RT=0.4235 mins : TOF MSE (100-1000) 6eV ESI+ : Centroided

5.43e6

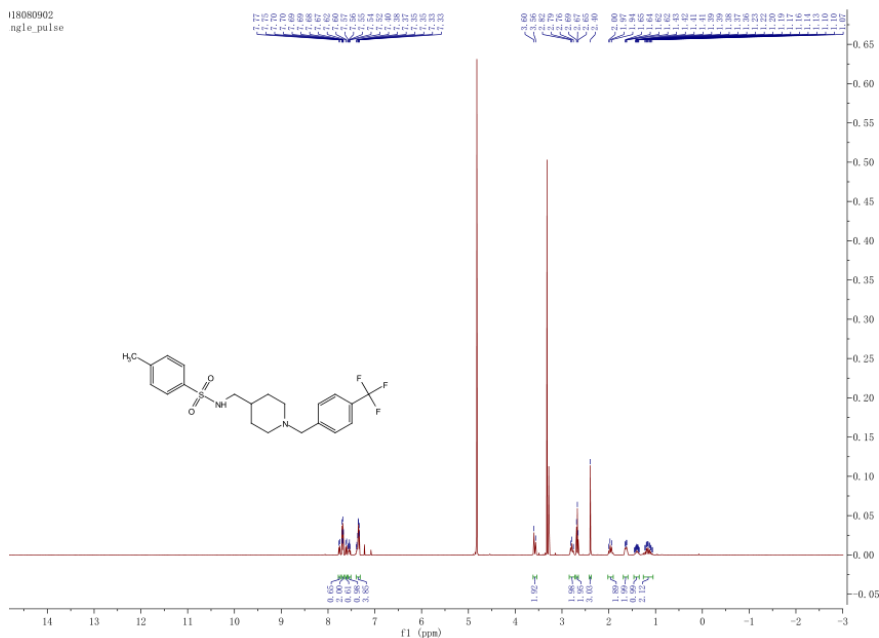


10v



^1H NMR

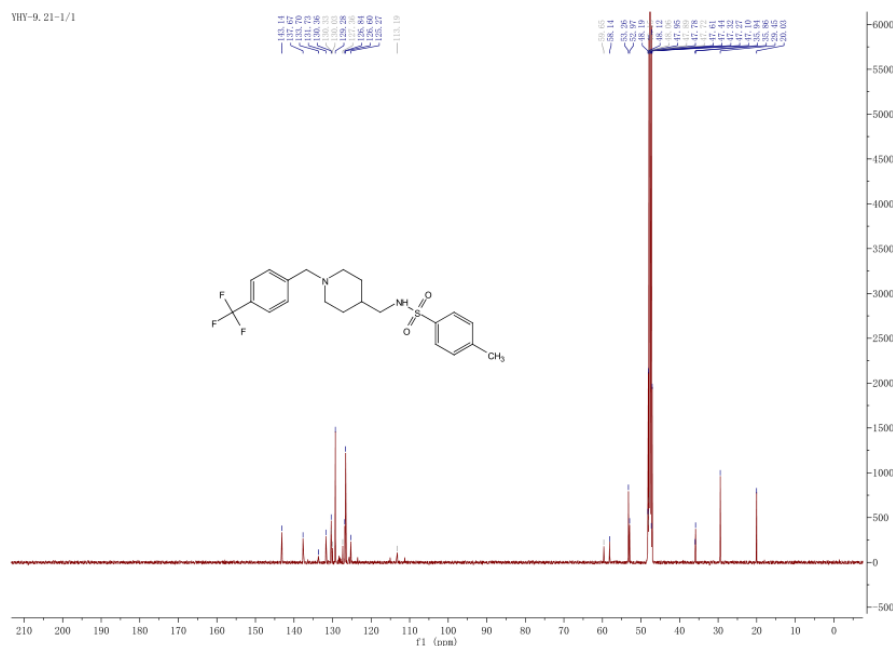
118080902
ngle_pulse



^1H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 7.8 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.40 – 7.31 (m, 4H), 3.58 (d, J = 14.0 Hz, 2H), 2.79 (t, J = 12.2 Hz, 2H), 2.67 (t, J = 6.9 Hz, 2H), 2.40 (s, 3H), 1.97 (t, J = 11.6 Hz,

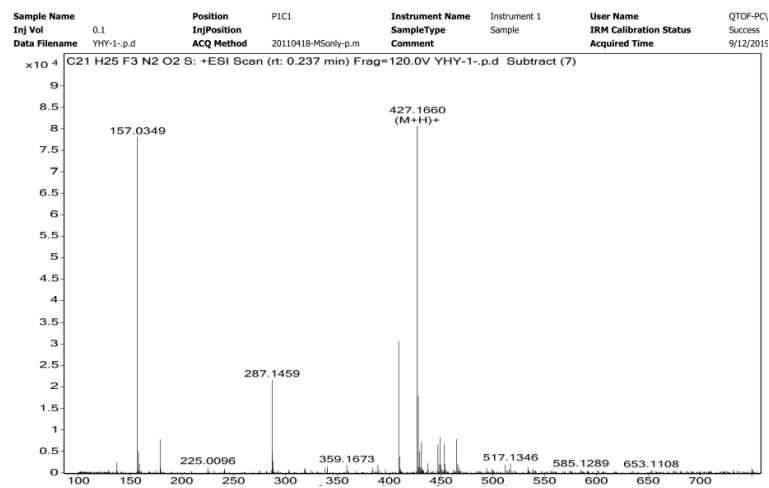
2H), 1.69 – 1.59 (m, 2H), 1.40 (dtt, $J = 14.5, 7.3, 3.2$ Hz, 1H), 1.15 (dq, $J = 24.7, 12.2, 3.7$ Hz, 2H).

^{13}C NMR



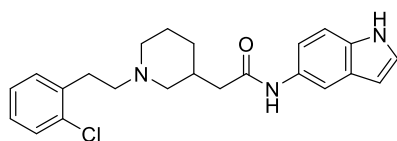
^{13}C NMR (126 MHz, CD_3OD) δ 143.14, 137.67, 131.73, 130.36, 130.33, 130.03, 129.28, 127.36, 126.84, 126.60, 125.27, 59.65, 58.14, 53.26, 52.97, 35.94, 35.86, 29.45, 20.03.

HRMS (ESI)



16a

^1H NMR



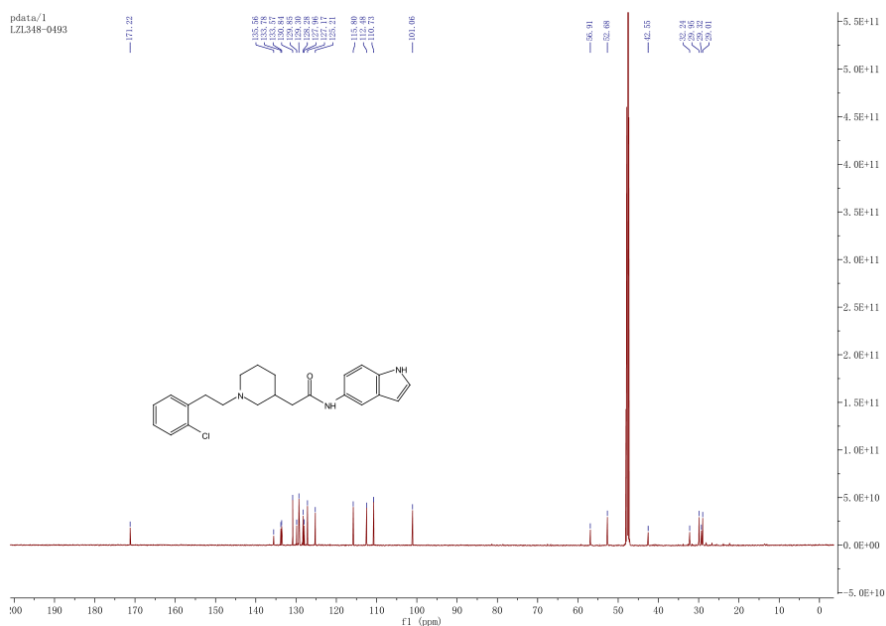
¹H NMR spectrum (CDCl₃) of 2-(2-chlorophenyl)-2-(2,3-dihydro-1H-indolizin-5(1H)-yl)ethan-1-ol.

Chemical structure: Clc1ccccc1CN(CCC(=O)Nc2c[nH]c3ccccc23)CCO

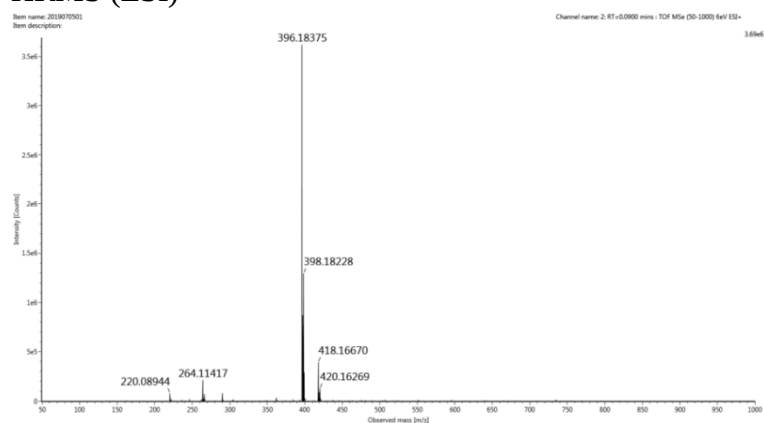
Peak Data:

Chemical Shift (ppm)	Integration
7.75 (d)	0.94
7.55 (m)	3.12
7.45 (m)	2.12
7.35 (m)	1.05
6.55 (d)	0.94
4.80 (s)	1.99
3.45 (m)	0.94
3.25 (m)	0.94
3.15 (m)	0.94
2.55 (m)	2.05
2.15 (m)	1.07
1.95 (m)	1.07
1.55 (m)	2.12

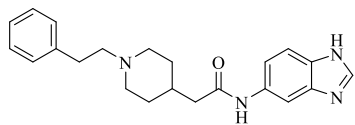
¹³C NMR



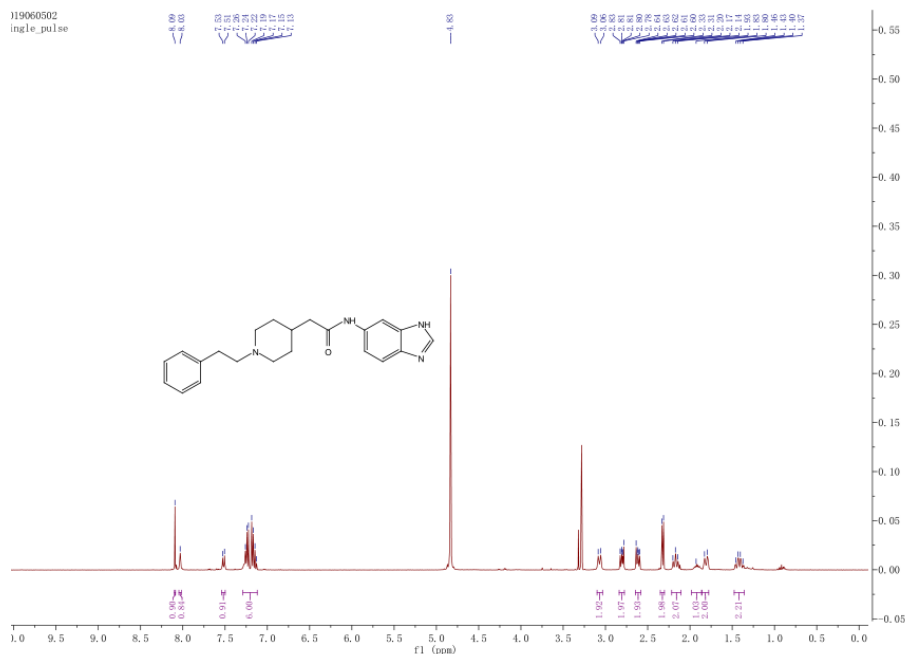
HRMS (ESI)



16c



^1H NMR

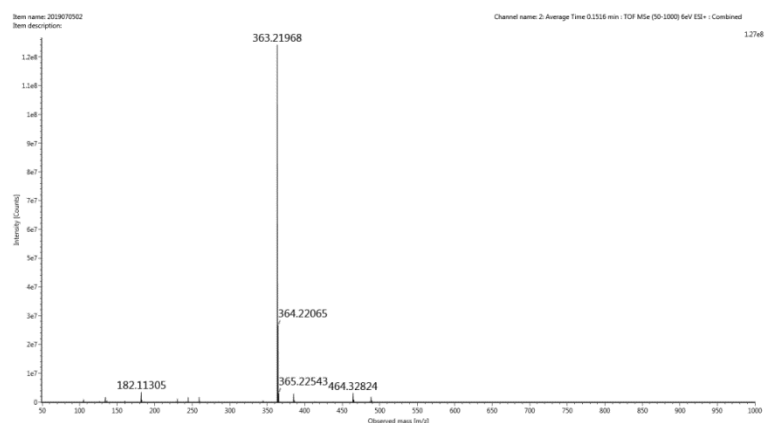


¹³C NMR

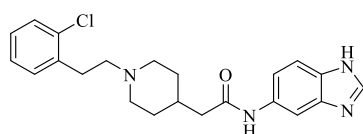


¹³C NMR (101 MHz, CD₃OD) δ 171.84, 141.67, 139.67, 133.93, 128.33, 128.21, 128.20, 125.93, 116.32, 60.33, 53.19, 47.89, 43.30, 33.27, 32.51, 31.15.

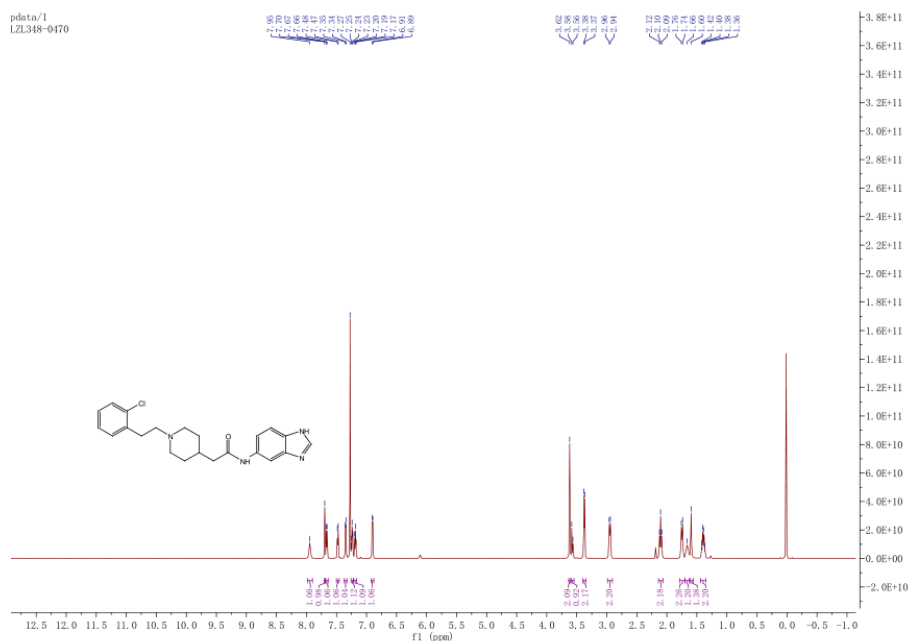
HRMS (ESI)



16d

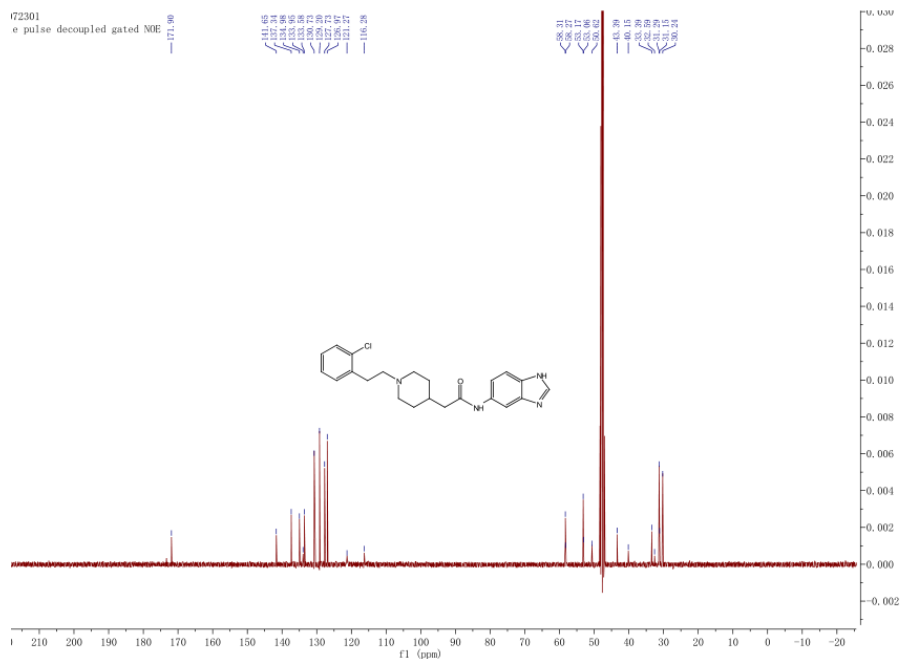


¹H NMR



¹H NMR (600 MHz, CDCl₃) δ 7.95 (s, 1H), 7.70 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 3.62 (s, 2H), 3.57 (d, J = 11.7 Hz, 1H), 3.37 (d, J = 6.5 Hz, 2H), 2.95 (d, J = 11.2 Hz, 2H), 2.10 (t, J = 11.3 Hz, 2H), 1.75 (d, J = 12.4 Hz, 2H), 1.66 (s, 1H), 1.60 (s, 1H), 1.39 (q, J = 11.5 Hz, 2H).

¹³C NMR



HRMS (ESI)

