Palladium-catalyzed native α-amino acid derivative-directed arylation/oxidation of benzylic C–H bonds: synthesis of 5-aryl-1,4-benzodiazepin-2-ones

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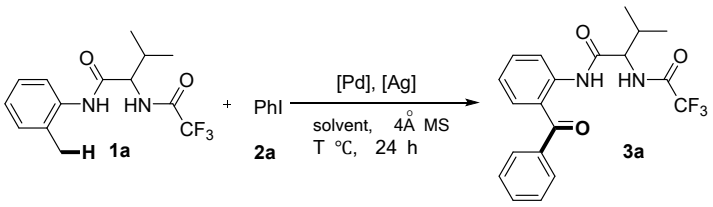
Supporting Information

Contents

1. General considerations

Unless otherwise noted, All reactions were performed under air in oven-dried glassware. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer (400/500 MHz). Chemical shifts were reported in δ units relative to internal standard TMS (δ 0) for ^{1}H NMR ($CDCl_3$ or DMSO-*d6*), ^{13}C NMR (center peak is δ 77.00 in $CDCl_3$ or δ 39.90 in DMSO-*d6*). Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), Coupling constants are reported in Hertz (Hz). The melting point is determined by Melting Point M-560. High resolution mass spectra (HRMS) were performed on a XEVO G2-XS QTOF/H-CLASS or a SCIEX TripleTOF 6600 System with ESI source. The melting points were measured on Buchi M-560. The enantiomeric ratio (er) was determined by HPLC analysis on Agilent 1260 Infinity II Prime using Daicel CHIRALPAK® column OD-H, AS-H. *N*-protected amino acid derivatives **1** were synthesized according to the literature procedure or known method.[1-3] Palladium catalysts (>98% purity) and other reagents (aryl iodides, α-amino acid derivatives, Ag salt etc.) were purchased from Energy Chemical (>95% purity) and used without further purification. Solvents were dried with according to the standard procedures and degassed with argon. Column chromatography was carried out on Tsingdao silica gel (particle size 200-300 mesh).

2. Detailed optimization of reaction conditions(Table S1)

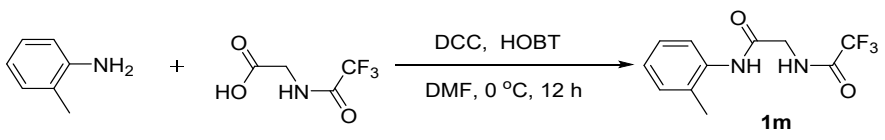


entry	[Pd]	Ag salt	Solvent	T (^{o}C)	yield (%)[b]
1	-	Ag_2CO_3	DMAC	130	N.R.
2	$PdCl_2$	Ag_2CO_3	DMAC	130	32
3	$Pd(PPh_3)_4$	Ag_2CO_3	DMAC	130	49
4	$Pd_2(dba)_3$	Ag_2CO_3	DMAC	130	Trace
5	$Pd(CH_3CN)_2Cl_2$ (10 mol %)	Ag_2CO_3	DMAC	130	38
6	$Pd(OAc)_2$ (10 mol %)	Ag_2CO_3	DMAC	130	52
7	$Pd(OAc)_2$ (15 mol %)	Ag_2CO_3	DMAC	130	71
8	$Pd(OAc)_2$ (20 mol %)	Ag_2CO_3	DMAC	130	87
9[c]	$Pd(OAc)_2$	Ag_2CO_3	DMAC	130	68

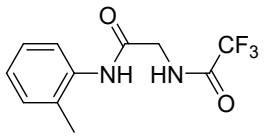
	(20 mol %)				
10	$Pd(OAc)_2$	-	DMAC	130	N.R.
11	$Pd(OAc)_2$	AgF	DMAC	130	37
12	$Pd(OAc)_2$	AgOAc	DMAC	130	N.R.
13	$Pd(OAc)_2$	Ag_2O	DMAC	130	47
14	$Pd(OAc)_2$	$AgNO_3$	DMAC	130	N.R.
15	$Pd(OAc)_2$	AgOTs	DMAC	130	N.R.
16	$Pd(OAc)_2$	CF_3COOAg	DMAC	130	N.R.
17	$Pd(OAc)_2$	Ag_2CO_3 (1.5 eq)	DMAC	130	72
18	$Pd(OAc)_2$	Ag_2CO_3 (1.0 eq)	DMAC	130	59
19	$Pd(OAc)_2$	Ag_2CO_3	xylene	130	N.R.
20	$Pd(OAc)_2$	Ag_2CO_3	1,4-dioxane	130	N.R.
21	$Pd(OAc)_2$	Ag_2CO_3	DMF	130	56
22	$Pd(OAc)_2$	Ag_2CO_3	DCE	130	N.D
23	$Pd(OAc)_2$	Ag_2CO_3	DMSO	130	20
24	$Pd(OAc)_2$	Ag_2CO_3	DMAC	140	78
25	$Pd(OAc)_2$	Ag_2CO_3	DMAC	120	70
26	$Pd(OAc)_2$	Ag_2CO_3	DMAC	110	46
27[d]	$Pd(OAc)_2$	Ag_2CO_3	DMAC	130	81
28[e]	$Pd(OAc)_2$	Ag_2CO_3	DMAC	130	73

[a]Reaction conditions: 1a (0.25 mmol), Pd catalyst (0.050 mmol), PhI (0.75 mmol, 153 mg), Ag salt (0.50 mmol), solvent (2.5 mL), 4Å MS, 130 °C, 24h. [b]Isolated yields. [c]Reaction without 4Å MS. [d](0.50 mmol, 2.0 equiv) PhI was used. [e](0.375 mmol, 1.5 equiv) PhI was used.

3. Typical procedure for preparation of *N*-protected valine derivatives 1m[1]

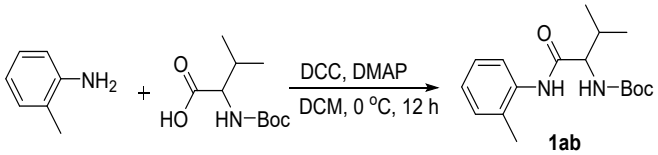


N-(2,2,2-trifluoroacetyl)-glycine (1.71 g, 10 mmol), *o*-toluidine (2.14 g, 20 mmol) was dissolved in DMF (5 mL) followed by addition of DMF (5 mL) of DCC (3.09 g, 15 mmol) and HOBT (1.35 g, 10 mmol) dropwise at 0 °C. Subsequently, the reaction was performed at room temperature for 12 h until *o*-toluidine was consumed completely. The precipitated dicyclohexyl urea (DCU) was filtered. The filtrate was diluted with ethyl acetate (30 mL), and the organic phase was washed with 1 N HCl (3 × 30 mL), brine, 1 M Na_2CO_3 solution (3 × 30 mL) and again with brine. The solvent was then dried over anhydrous Na_2SO_4 and and concentrated. The crude product was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product (EA/PE = 1:5 or 1:10,v/v).

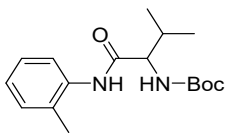


2,2,2-trifluoro-*N*-(2-oxo-2-(o-tolylamino)ethyl)acetamide (1m, CAS no. 357158-15-7). 1.04 g, 40% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5 , v/v); mp 146 – 148 °C; δ ^{1}H NMR (500 MHz, DMSO) δ 9.78 (s, 1H), 9.53 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.07 (d, *J* = 5.6 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 165.9, 156.8 (q, *J* = 36.4 Hz), 135.8, 131.7, 130.3, 126.0, 125.3, 124.9, 115.9 (q, *J* = 287.9 Hz), 42.3, 17.7. HRMS (ESI) calcd for $C_{11}H_{11}F_3N_2O_2$ $[M + H]^+$ 261.0845, found 261.0846.

4. Typical Procedure for Preparation of *N*-Boc-valine derivatives 1ab[2]



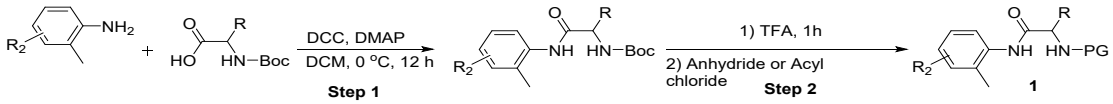
o-toluidine (2.12 g, 10 mmol), DCC (2.48 g, 12 mmol), and DMAP (0.317 g, 2.6 mmol) was dissolved in CH_2Cl_2 (30 mL) followed by addition of *N*-Boc-L-valine (2.39 g, 11 mmol) in CH_2Cl_2 (10 mL) dropwise at 0 °C. Then the reaction mixture was stirred for 12 hours at room temperature. Upon completion (monitored by TLC), the precipitated dicyclohexyl urea (DCU) was filtered. The filtrate was concentrated in vacuo to obtain the desired product (EA/PE = 1:10, v/v).



***tert*-butyl(3-methyl-1-oxo-1-(o-tolylamino)buta*N*-2-yl)carbamate (1ab, CAS no. 672959-58-9).** 2.85 g, 93% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 139 – 141 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.30 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 3.96 (t, *J* = 7.8 Hz, 1H), 2.19 (s, 3H), 2.10 – 1.96 (m, 1H), 1.40 (s, 9H), 0.94 (dd, *J* = 11.7, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, DMSO) δ 171.0, 156.1, 136.5,

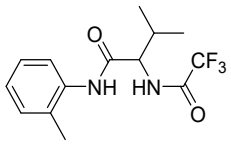
132.3, 130.7, 126.4, 125.7, 125.6, 78.5, 60.8, 30.6, 28.6, 19.8, 18.98, 18.2. HRMS (ESI) calcd for $C_{17}H_{26}N_2O_3$ $[M + H]^+$ 307.2016, found 307.2018.

5. Typical procedure for preparation of *N*-protected amino acid derivatives1a, 1ac-ae, 1n-z[3]

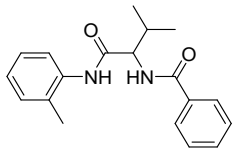


Step1: Aromatic amine (10 mmol), DCC (2.48 g, 12 mmol), and DMAP (0.317 g, 2.6 mmol) was dissolved in CH_2Cl_2 (30 mL) followed by addition of *N*-Boc-L-amino acid (11 mmol) in CH_2Cl_2 (10 mL) dropwise at 0 °C . Then the reaction mixture was stirred for 12 hours at room temperature until aromatic amine was consumed completely. After completion, the precipitated dicyclohexyl urea (DCU) was filtered. The filtrate was concentrated in vacuo to obtain the crude product.

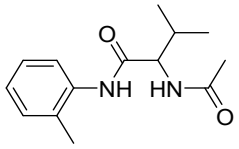
Step2: 11 mL TFA was slowly added dropwise to the above crude product at 0 °C and stirred for 1 h until the starting material had disappeared, excess TFA was removed under vacuum，20 mL CH_2Cl_2 was added for dilution, followed by the addition of Et_3N until the pH of the solution was slightly alkaline. Subsequently, 4.0 mL of anhydride or acyl chloride in CH_2Cl_2 (20 mL) was slowly added dropwise to the above system at 0 °C and stirred for 1 h. The reaction mixture was concentrated in vacuo, and then water (20 mL) was added to the reaction mixture. The solution was extracted with EtOAc (3×20 mL). The combined organic layer was washed with water (20 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to give the desired product.



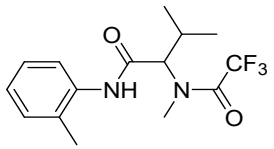
3-methyl-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)butanamide (1a, CAS no. 1808766-08-6). 2.48 g, 82% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 197– 205 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.68 (s, 1H), 9.67 (s, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.11 (t, *J* = 6.9 Hz, 1H), 4.38 (t, *J* = 8.6 Hz, 1H), 2.24 – 2.17 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.1, 157.0 (q, *J* = 36.6 Hz), 136.1, 132.5, 130.8, 126.4, 126.1, 125.8, 116.4 (q, *J* = 288.1 Hz), 60.1, 30.1, 19.5, 19.2, 18.2. HRMS (ESI) calcd for $C_{14}H_{17}F_3N_2O_2$ $[M + H]^+$ 303.1315, found 303.1324.



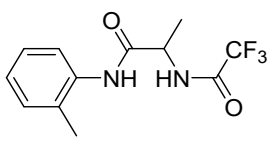
***N*-(3-methyl-1-oxo-1-(o-tolylamino)butan-2-yl)benzamide (1ac, CAS no. 1009493-81-5).** 2.42 g, 78% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 216 – 218 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.55 (s, 1H), 8.50 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.49 (t, *J* = 8.3 Hz, 1H), 2.33 – 2.14 (m, 4H), 1.04 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, DMSO) δ 170.7, 167.2, 136.5, 134.6, 132.3, 131.8, 130.8, 128.7, 128.1, 126.4, 125.7, 125.6, 60.2, 30.4, 19.9, 19.6, 18.3. HRMS (ESI) calcd for $C_{19}H_{22}N_2O_2$ $[M + H]^+$ 311.1754, found 311.1757.



2-acetamido-3-methyl-*N*-(o-tolyl)butanamide (1ad, CAS no. 1214129-69-7). 2.06 g, 83% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 229 – 231 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.44 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.28 – 7.13 (m, 2H), 7.09 (t, *J* = 7.1 Hz, 1H), 4.36 (t, *J* = 7.7 Hz, 1H), 2.20 (s, 3H), 2.06 (dd, *J* = 13.2, 6.4 Hz, 1H), 1.91 (s, 3H), 0.94 (t, *J* = 7.6 Hz, 6H). ^{13}NMR (100 MHz,) δ 170.7, 169.9, 136.5, 132.3, 130.7, 126.3, 125.7, 125.7, 58.7, 30.9, 22.9, 19.8, 18.8, 18.3. HRMS (ESI) calcd for $C_{14}H_{20}N_2O_2$ $[M + H]^+$ 249.1598, found 249.1601.

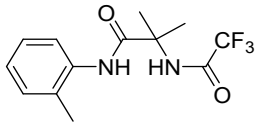


3-methyl-*N*-(o-tolyl)-2-(2,2,2-trifluoro-*N*-methylacetamido)butanamide (1ae). 1.84 g, 58% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:15, v/v); mp 83 – 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.24 – 7.16 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 3.17 (d, *J* = 1.4 Hz, 3H), 2.54 – 2.44 (m, 1H), 2.22 (s, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 158.9 (q, *J* = 36.3 Hz), 135.1, 130.6, 129.0, 126.7, 125.5, 122.7, 116.5 (q, *J* = 287.6 Hz), 65.5, 30.5, 25.5, 19.5, 18.3, 17.7. HRMS (ESI) calcd for $C_{15}H_{19}F_3N_2O_2$ $[M + H]^+$ 317.1472, found 317.1474.

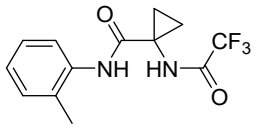


***N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)propanamide (1n, CAS no. 2210945-86-9).** 1.62 g, 59% yield; white solid after purification by column chromatography (eluent, ethyl

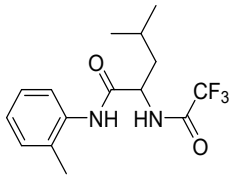
acetate/petroleum ether = 1:5, v/v); mp 162 – 164 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.56 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 4.57 (q, *J* = 7.0 Hz, 1H), 2.19 (s, 3H), 1.45 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.1, 156.7 (q, *J* = 36.5 Hz), 136.2, 132.7, 130.8, 126.4, 126.0, 125.8, 116.3 (q, *J* = 287.9 Hz), 49.9, 18.1, 17.9. HRMS (ESI) calcd for $C_{12}H_{13}F_3N_2O_2$ $[M + H]^+$ 275.1002, found 275.1001.



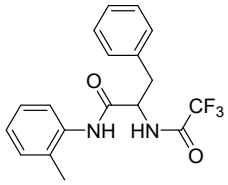
2-methyl-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)propanamide (1o, CAS no. 2341641-00-5). 1.50 g, 52% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 131 – 134 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 9.20 (s, 1H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.20 – 7.10 (m, 3H), 2.14 (s, 3H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 171.5, 156.1 (q, *J* = 36.3 Hz), 136.6, 134.3, 130.6, 127.2, 126.4, 126.3, 116.0 (q, *J* = 288.9 Hz), 57.9, 24.9, 18.0. HRMS (ESI) calcd for $C_{13}H_{15}F_3N_2O_2$ $[M + H]^+$ 289.1159, found 289.1163.



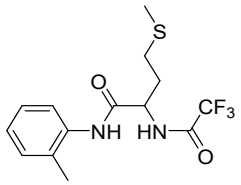
(o-tolyl)-1-(2,2,2-trifluoroacetamido)cyclopropane-1-carboxamide (1p). 1.94 g, 68% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 208 – 211 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.97 (s, 1H), 9.46 (s, 1H), 7.23 (d, *J* = 6.9 Hz, 1H), 7.18 – 7.13 (m, 3H), 2.14 (s, 3H), 1.44 (dd, *J* = 7.7, 4.5 Hz, 2H), 1.07 (dd, *J* = 7.7, 4.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 169.1, 158.4 (q, *J* = 36.7 Hz), 136.5, 134.4, 130.7, 127.1, 126.5, 126.4, 116.2 (q, *J* = 287.7 Hz), 35.1, 18.0, 16.6. HRMS (ESI) calcd for $C_{13}H_{13}F_3N_2O_2$ $[M + H]^+$ 287.1002, found 287.1009.



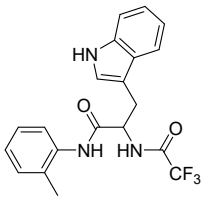
4-methyl-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)pentanamide (1q, CAS no. 2210941-17-4). 2.02 g, 64% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 134 – 145 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.74 (d, *J* = 7.7 Hz, 1H), 9.68 (s, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 6.9 Hz, 1H), 7.14 – 7.09 (m, 1H), 4.69 – 4.53 (m, 1H), 2.18 (s, 3H), 1.80 (dd, *J* = 10.2, 8.4 Hz, 1H), 1.72 – 1.60 (m, 2H), 0.94 (dd, *J* = 13.9, 6.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO) δ 170.0, 157.0 (q, *J* = 36.7 Hz), 136.2, 133.0, 130.8, 126.4, 126.2, 126.1, 116.3 (q, *J* = 288.3 Hz), 52.7, 24.9, 23.3, 21.7, 18.2.



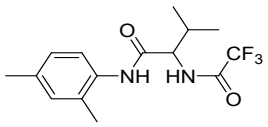
3-phenyl-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)propanamide (1r, CAS no. 2210438-10-9). 2.73 g, 78% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 189 – 191 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.87 (d, *J* = 8.1 Hz, 1H), 9.73 (s, 1H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 3H), 7.25 – 7.16 (m, 3H), 7.1 (t, *J* = 7.3 Hz, 1H), 4.88 – 4.82 (m, 1H), 3.23 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.09 (dd, *J* = 13.5, 10.3 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.0, 156.8 (q, *J* = 36.6 Hz), 137.6, 136.0, 132.8, 130.8, 129.7, 128.6, 127.1, 126.4, 126.2, 125.9, 116.2 (q, *J* = 288.0 Hz), 55.6, 37.4, 18.1. HRMS (ESI) calcd for $C_{18}H_{17}F_3N_2O_2$ [M + H]$^+$ 351.1315, found 351.1315.



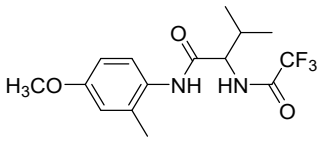
4-(methylthio)-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)butanamide (1s). 1.37 g, 41% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 150 – 153 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.76 (d, *J* = 7.5 Hz, 1H), 9.65 (s, 1H), 7.35 – 7.28 (m, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 10.6, 4.4 Hz, 1H), 7.12 (td, *J* = 7.3, 1.2 Hz, 1H), 4.69 – 4.58 (m, 1H), 2.63 – 2.54 (m, 1H), 2.53 – 2.49 (m, 1H), 2.19 (s, 3H), 2.16 – 2.10 (m, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.2, 157.1 (q, *J* = 36.5 Hz), 136.1, 132.9, 130.8, 126.5, 126.2, 126.0, 115.7 (q, *J* = 287.9 Hz), 53.6, 31.1, 30.2, 18.2, 15.0. HRMS (ESI) calcd for $C_{14}H_{17}F_3N_2O_2S$ [M + H]$^+$ 335.1036, found 335.1038.



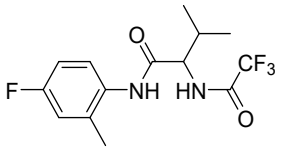
3-(1H-indol-3-yl)-*N*-(o-tolyl)-2-(2,2,2-trifluoroacetamido)propanamide (1t). 1.95 g, 49% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 192 – 193 °C; ^{1}NMR (400 MHz,) δ 10.88 (s, 1H), 9.81 (d, *J* = 7.7 Hz, 1H), 9.74 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.2, 1H), 7.25 – 7.18 (m, 2H), 7.18 – 7.15 (m, 1H), 7.12 – 7.06 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 4.96 – 4.68 (m, 1H), 3.35 – 3.27 (m, 1H), 3.21 (dd, *J* = 14.5, 9.6 Hz, 1H), 2.12 (s, 3H). ^{13}NMR (100 MHz,) δ 169.5, 156.8 (q, *J* = 42.4 Hz), 136.5, 136.1, 133.0, 130.8, 127.5, 126.4, 126.2, 126.1, 124.4, 121.5, 119.0, 118.8, 116.3 (q, *J* = 288.0 Hz), 111.8, 109.9 , 55.1, 27.7, 18.1. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_3O_2$ [M + H]$^+$ 390.1424, found 390.1424.



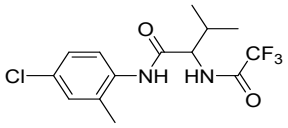
***N*-(2,4-dimethylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1u).** 2.34 g, 74% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 219 – 221 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.65 (d, 1H), 9.59 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 4.36 (t, *J* = 8.8 Hz, 1H), 2.25 (s, 3H), 2 .23 – 2.17 (m, 1H), 2.15 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.0, 157.0 (q, *J* =36.6), 135.2, 133.5, 132.5, 131.3, 126.9, 125.8, 116.3 (q, *J* = 288.1 Hz), 60.1, 30.1, 20.90, 19.5, 19.2, 18.2. HRMS (ESI) calcd for $C_{15}H_{19}F_3N_2O_2$ $[M + H]^+$ 317.1472, found 317.1472.



***N*-(4-methoxy-2-methylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1v).** 2.09 g, 63% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 219 – 221 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.64 (d, *J* = 8.3 Hz, 1H), 9.56 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.32 (t, *J* = 8.5 Hz, 1H), 3.72 (s, 3H), 2.24 – 2.18 (m, 1H), 2.16 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.1, 157.5, 157.0 (q, *J* = 36.6 Hz), 134.6, 129.0, 127.4, 116.4 (q, *J* = 286.3 Hz),115.8, 111.7, 60.0, 55.6, 30.1, 19.5, 19.2, 18.4. HRMS (ESI) calcd for $C_{15}H_{19}F_3N_2O_3$ $[M + H]^+$ 333.1421, found 333.1421.

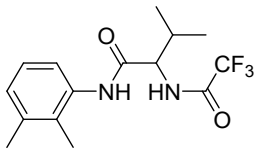


***N*-(4-fluoro-2-methylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1w)**. 2.27 g, 71% yeild; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 214 – 219 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 9.68 (s, 1H), 7.30 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.10 (dd, *J* = 9.7, 2.8 Hz, 1H), 7.01 (td, *J* = 8.6, 2.9 Hz, 1H), 4.34 (t, *J* = 8.4 Hz, 1H), 2.25 – 2.16 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.2, 160.1 (d, *J* = 241.8 Hz), 157.1 (q, *J* = 36.8 Hz), 135.6 (d, *J* = 8.3 Hz), 132.3, 127.8 (d, *J* = 8.7 Hz), 117.1 (d, *J* = 22.2 Hz), 116.4 (q, *J* = 286.3), 113.0 (d, *J* = 22.2 Hz), 60.1, 30.0, 19.5, 19.2, 18.2. HRMS (ESI) calcd for $C_{14}H_{16}F_4N_2O_2$ $[M + H]^+$ 321.1221, found 321.1224.

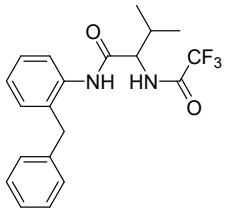


***N*-(4-chloro-2-methylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1x).** 2.42 g, 72% yeild; white solid after purification by column chromatography (eluent, ethyl

acetate/petroleum ether = 1:10, v/v); mp 230 – 232 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.70 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.36 (t, *J* = 8.4 Hz, 1H), 2.22 – 2.17 (m, 4H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.3, 157.1 (q, *J* = 36.7 Hz), 135.1, 134.9, 130.4, 129.9, 127.3, 126.3, 116.4 (q, *J* = 288.1 Hz), 60.1, 30.0, 19.5, 19.2, 18.0. HRMS (ESI) calcd for $C_{14}H_{16}ClF_3N_2O_2$ [M + H]$^+$ 337.0925, found 337.0926.

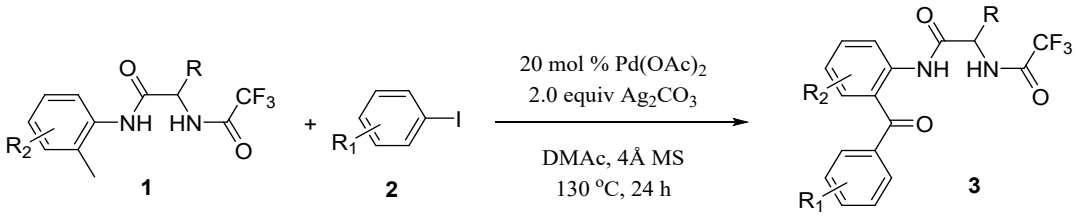


***N*-(2,3-dimethylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1y).** 2.18 g, 69% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 219 – 222 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.67 (d, *J* = 8.1 Hz, 1H), 7.11 – 7.07 (m, 1H), 7.06 – 7.01 (m, 2H), 4.37 (t, *J* = 8.4 Hz, 1H), 2.25 (s, 3H), 2.22 – 2.19 (m, 1H), 2.07 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.2, 157.0 (q, *J* = 36.5 Hz), 137.5, 135.9, 131.8, 127.7, 125.7, 124.1, 116.4 (q, *J* = 287.9 Hz), 60.1, 30.1, 20.5, 19.5, 19.3, 14.4. HRMS (ESI) calcd for $C_{15}H_{19}F_3N_2O_2$ [M + H]$^+$ 317.1472, found 317.1472.

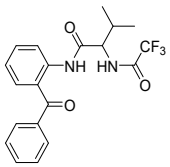


***N*-(2-benzylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (1z)**. 2.57 g, 68% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 227 – 228 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.85 (s, 1H), 9.69 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.19 (m, 3H), 7.17 – 7.14 (m, 5H),4.41 (s, 1H), 4.14 – 3.80 (m, 2H), 2.15 (dd, *J* = 14.2, 7.1 Hz, 1H), 0.92 (dd, *J* = 19.0, 6.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO) δ 169.4, 157.0 (q, *J* = 36.7 Hz), 140.7, 136.1, 135.7, 130.6, 129.2, 128.7, 126.9, 126.6, 126.4, 126.4, 116.4 (d, *J* = 288.2 Hz), 59.9, 36.8, 30.3, 19.4, 19.1. HRMS (ESI) calcd for $C_{20}H_{21}F_3N_2O_2$ [M + H]$^+$ 379.1628, found 379.1629.

6. Typical Procedure for Bifunctional Products 3a−y

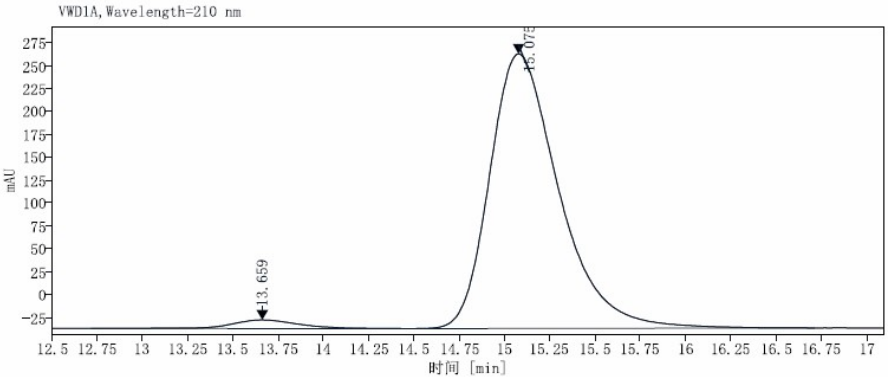


A mixture of *N*-protected amino acid derivatives **1** (0.25 mmol), aryl iodides **2** (0.75 mmol), $Pd(OAc)_2$ (0.05 mmol, 20 mol %), Ag_2CO_3 (0.5 mmol), 4 Å molecuar sieve, and DMAc (2.5 mL) was placed in a 35 mL pressure tube with PTFE cap under air. The tube was heated at 130 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (3 mL), and filtered through celite. Then, the 15 mL water was added to filtrate and the mixture was extracted with ethyl acetate (15 mL) for 3 times. The organic layers was dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product (EA/PE = 1:7 ~ 1:20, v/v).



***N*-(2-benzoylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3a).** 85 mg, 87% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 159-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.64 – 7.60 (m, 3H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.19 – 7.12 (m, 2H), 4.60 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.37 – 2.29 (m, 1H), 1.08 (dd, *J* = 12.8, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 168.4, 157.3 (q, *J* = 37.1 Hz), 139.5, 138.3, 134.5, 133.9, 132.7, 129.9, 128.4, 123.4, 123.1, 121.5, 115.8 (q, *J* = 287.6 Hz), 59.6, 32.2, 19.01, 17.8. HRMS (ESI) calcd for $C_{20}H_{19}F_3N_2O_3$ $[M + H]^+$ 393.1421, found 393.1425.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 13.7 min (minor), t_{R2} = 15.1 min (major).



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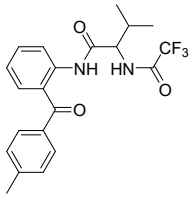
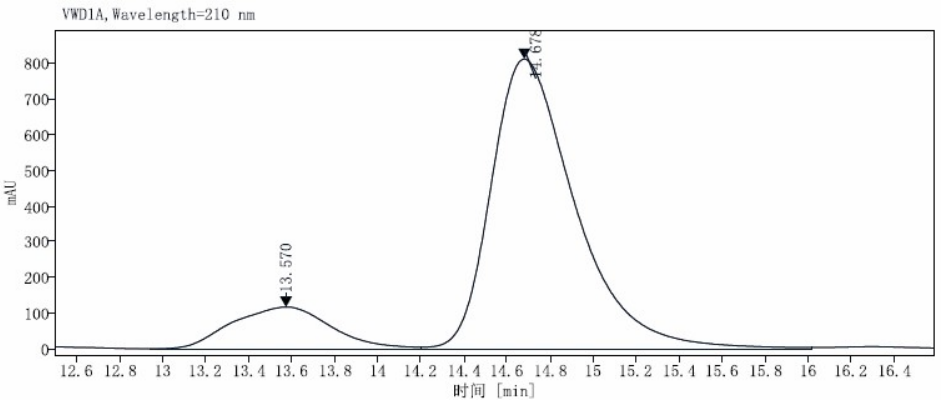
15.075	BB	2.2281	7959.6103	299.7696	97.0366



3-**methyl-*N*-(2-(4-methylbenzoyl)phenyl)-2-(2,2,2-trifluoroacetamido)butanamide (3b).** 79 mg, 78% yield; white solid after purification by column chromatography (eluent, ethyl

acetate/petroleum ether = 1:20, v/v); mp 105 – 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.52 (m, 4H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.16 (td, *J* = 7.7, 1.0 Hz, 2H), 4.59 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.46 (s, 3H), 2.38 – 2.27 (m, 1H), 1.04 (dd, *J* = 12.7, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 168.3, 157.0 (q, *J* = 37.2 Hz), 143.8, 139.3, 135.5, 134.2, 133.7, 130.2, 129.1, 123.7, 123.0, 121.5, 115.8 (q, *J* = 290.4 Hz), 59.5, 32.2, 21.7, 19.0, 17.8. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_3$ $[M + H]^+$ 407.1577, found 407.1584.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 13.6 min (minor), t_{R2} = 14.7 min (major).



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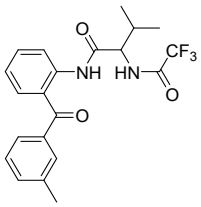
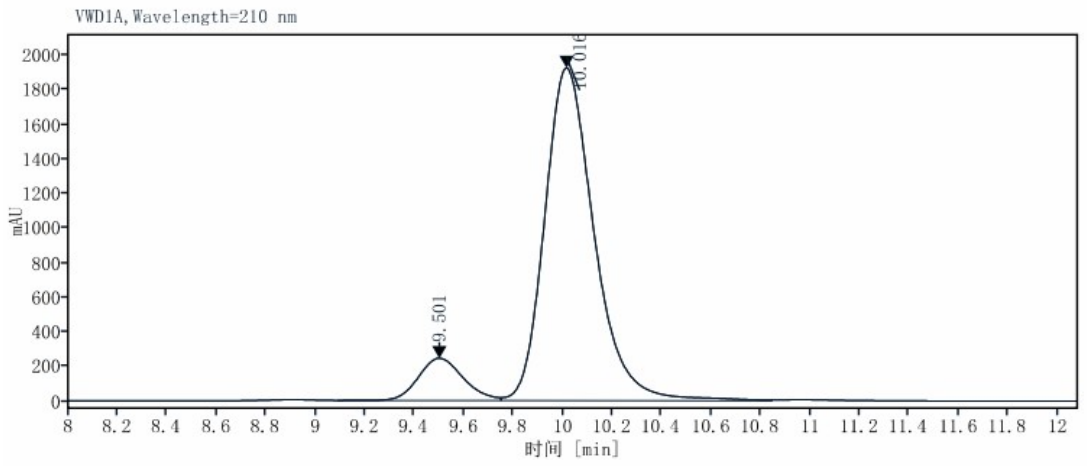
14.678	VV	1.8151	22112.9315	814.2907	85.5248



3-**methyl-*N*-(2-(3-methylbenzoyl)phenyl)-2-(2,2,2-trifluoroacetamido)butanamide (3c).** 65 mg, 64% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.60 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.52 (s, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.20 – 7.13 (m, 1H), 4.60 (dd, *J* = 8.3, 5.4 Hz, 1H), 2.43 (s, 3H), 2.39 – 2.20 (m, 1H), 1.04 (dd, *J* = 12.3, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 168.5, 157.1 (q, *J* = 37.6 Hz), 139.5, 138.4, 138.3, 134.4, 134.0, 133.5, 130.3, 128.2, 127.2, 123.5, 123.1, 121.4, 115.8 (q, *J* = 287.8 Hz), 59.6, 32.1, 21.4, 19.0, 17.8. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_3$ $[M + H]^+$ 407.1577, found 407.1581.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 9.5 min (minor), t_{R2} = 10.0 min (major).



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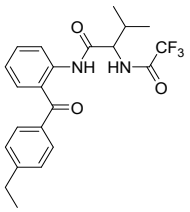
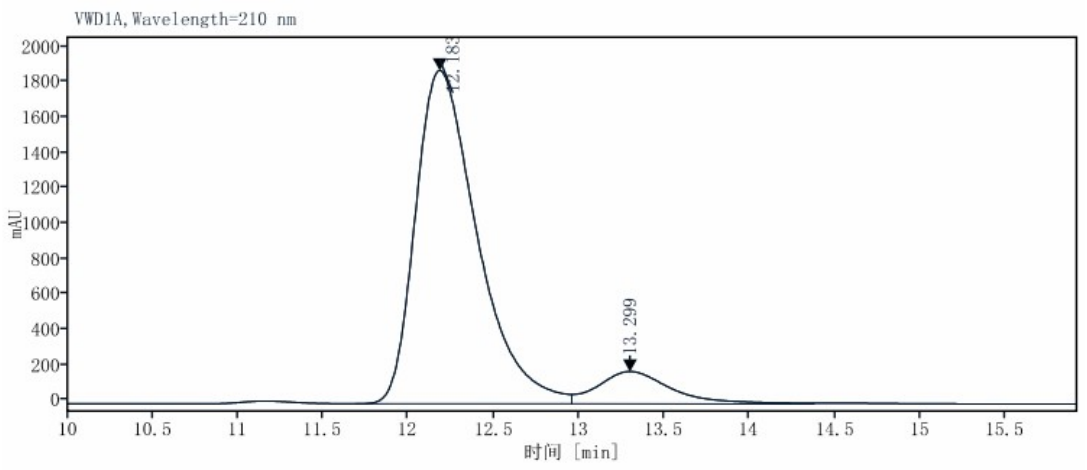
10.016	VV	1.0958	26759.6995	1923.2317	89.6855



***N*-(2-(4-ethylbenzoyl)phenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3e).** 76 mg, 72% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 113 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.54 (m, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.59 (dd, *J* = 8.4, 5.3 Hz, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.37 – 2.28 (m, 1H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.04 (dd, *J* = 12.7, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 168.4, 157.1 (q, *J* = 37.5 Hz), 149.9, 139.3, 135.7, 134.2, 133.7, 130.3, 127.9, 123.8, 123.0, 121.5, 130.8 (q, *J* = 287.8 Hz), 59.6, 32.1, 29.0, 19.0, 17.8, 15.2. HRMS (ESI) calcd for $C_{22}H_{23}F_3N_2O_3$ [M + H]$^+$ 421.1734, found 421.1739.

HPLC: Daicel Chiralcel As-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 13.3 min (minor), t_{R2} = 12.2 min (major).



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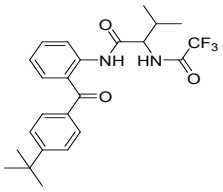
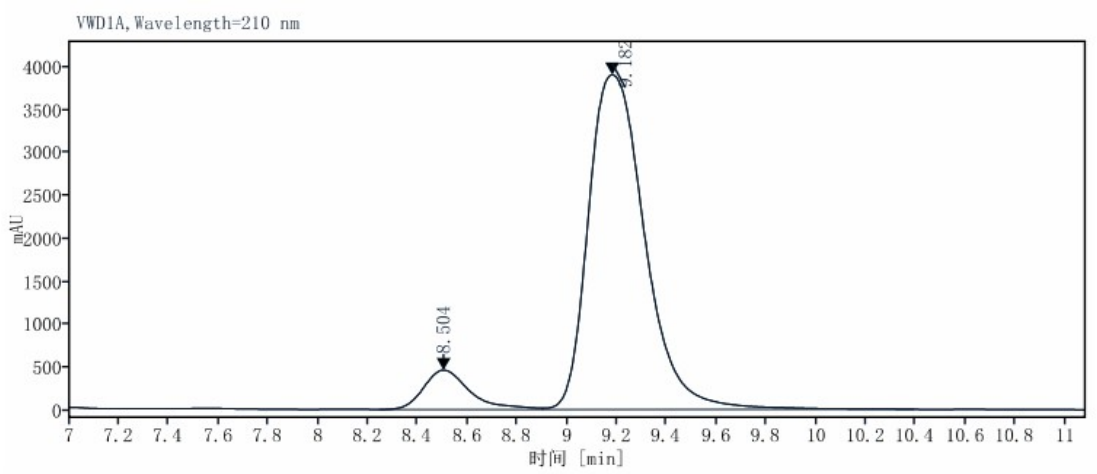
13.299	VV	1.4202	5519.8301	183.2878	10.4154



***N*-(2-(4-(tert-butyl)benzoyl)phenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3f).** 65 mg, 58% yield; yellow liquid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.64 (m, 3H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.50 (s, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.59 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.37 – 2.28 (m, 1H), 1.37 (s, 9H), 1.04 (dd, *J* = 13.0, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 168.4, 157.1 (d, *J* = 37.3 Hz), 156.7, 139.3, 135.4, 134.2, 133.8, 130.1, 125.4, 123.8, 123.0, 121.5, 115.8 (q, *J* = 287.8 Hz), 59.6, 35.2, 32.1, 31.1, 19.0, 17.8. HRMS (ESI) calcd for $C_{24}H_{27}F_3N_2O_3$ $[M + H]^+$ 449.2047, found 449.2047.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 8.5 min (minor), t_{R2} = 9.1 min (major).



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
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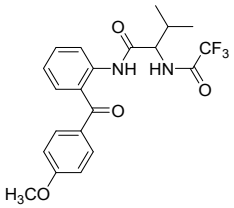
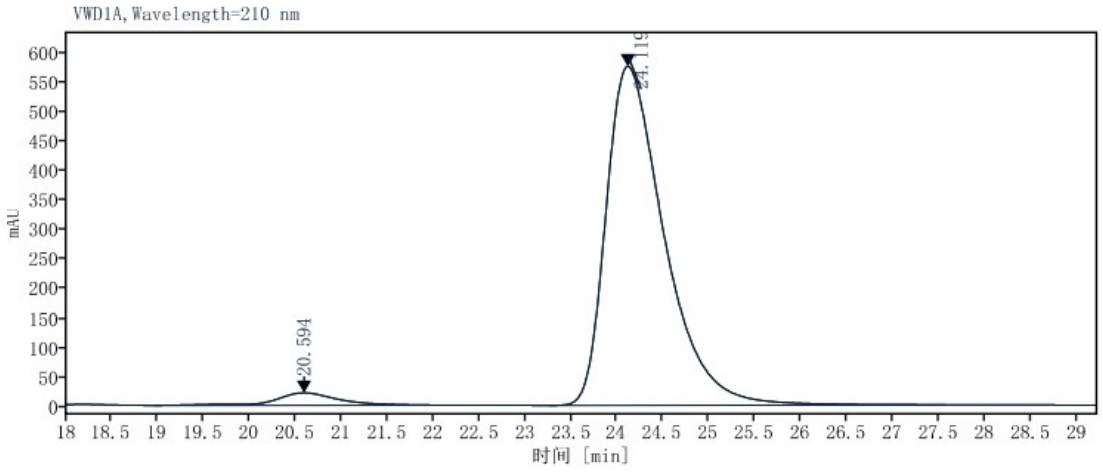
9.182	MM m	0.2478	61493.0861	3904.1775	91.2669



***N*-(2-(4-methoxybenzoyl)phenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3g).** 74 mg, 70% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 120 – 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.54 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.69 – 7.55 (m, 2H), 7.20 – 7.11 (m, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 4.57 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.91 (s, 3H), 2.36 – 2.27 (m, 1H), 1.06 (dd, *J* = 12.0, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 168.2, 163.6, 157.0 (q, *J* = 37.4 Hz), 138.9, 133.8, 133.1, 132.7, 115.8 (q, *J* = 290.4 Hz), 130.5, 124.3, 123.1, 121.6, 113.7, 59.5, 55.6, 32.2, 19.0, 17.8. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_4$ $[M + H]^+$ 423.1526, found 423.1532.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 20.6 min (minor), t_{R2} = 24.1 min (major).



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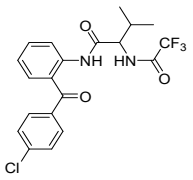
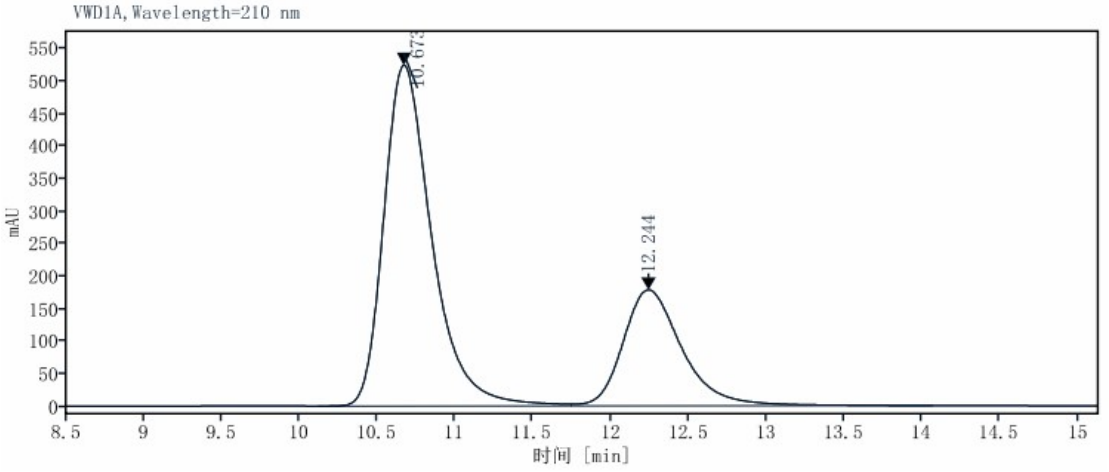
24.119	BB	4.3053	25305.2568	575.4458	96.1026



***N*-(2-(4-chlorobenzoyl)phenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3h).** 73 mg, 68% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 132 – 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.60 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.56 (m, 4H), 7.53 – 7.45 (m, 2H), 7.22 – 7.09 (m, 2H), 4.58 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.39 – 2.26 (m, 1H), 1.05 (dd, *J* = 12.2, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 168.4, 157.1 (q, *J* = 29.7 Hz), 139.5, 139.3, 136.5, 134.7, 133.6, 131.4, 128.8, 123.2, 123.1, 121.6, 111.5 (q, *J* = 278.5 Hz), 59.6, 32.1, 19.0, 17.8. HRMS (ESI) calcd for $C_{20}H_{18}ClF_3N_2O_3$ $[M + H]^+$ 427.1031, found 427.1018.

HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 12.2 min (minor), t_{R2} = 10.7 min (major).



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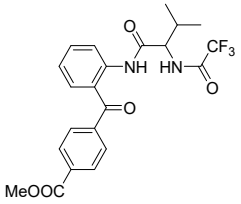
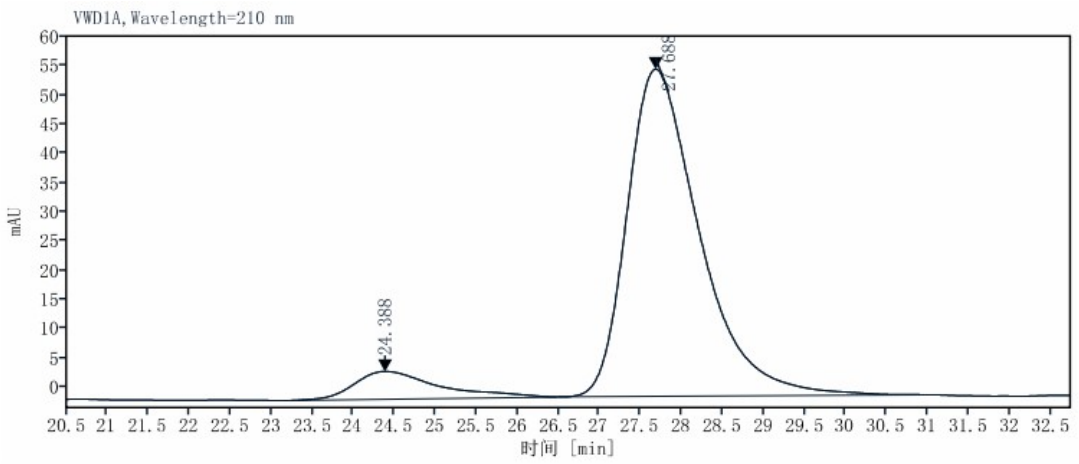
12.244	VB	2.3216	4688.9725	178.2335	29.4977



Methyl 4-(2-(3-methyl-2-(2,2,2-trifluoroacetamido)butanamido)benzoyl)benzoate (3i). 81 mg, 72% yield; white solid after purification by column chromatography (eluent, ethyl

acetate/petroleum ether = 1:15, v/v); mp 121 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.66 – 7.52 (m, 2H), 7.21 – 7.10 (m, 2H), 7.06 – 6.92 (m, 2H), 4.57 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.91 (s, 3H), 2.36 – 2.26 (m, 1H), 1.04 (dd, *J* = 12.0, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 168.2, 163.6, 157.1 (q, *J* = 37.2 Hz), 138.9, 133.8, 133.2, 132.7, 130.5, 129.2, 124.3, 123.1, 121.6, 115.8 (d, *J* = 287.2 Hz), 113.7, 59.5, 55.6, 32.2, 19.0, 17.8. HRMS (ESI) calcd for $C_{22}H_{21}F_3N_2O_5$ $[M + H]^+$ 451.1476, found 451.1480.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 24.4 min (minor), t_{R2} = 27.7 min (major).



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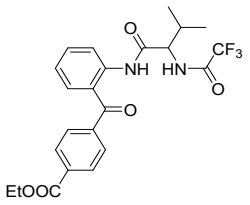
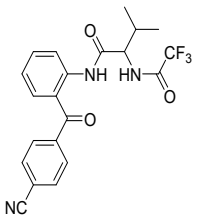
27.688	BB	4.4878	3440.3022	56.1610	90.9517

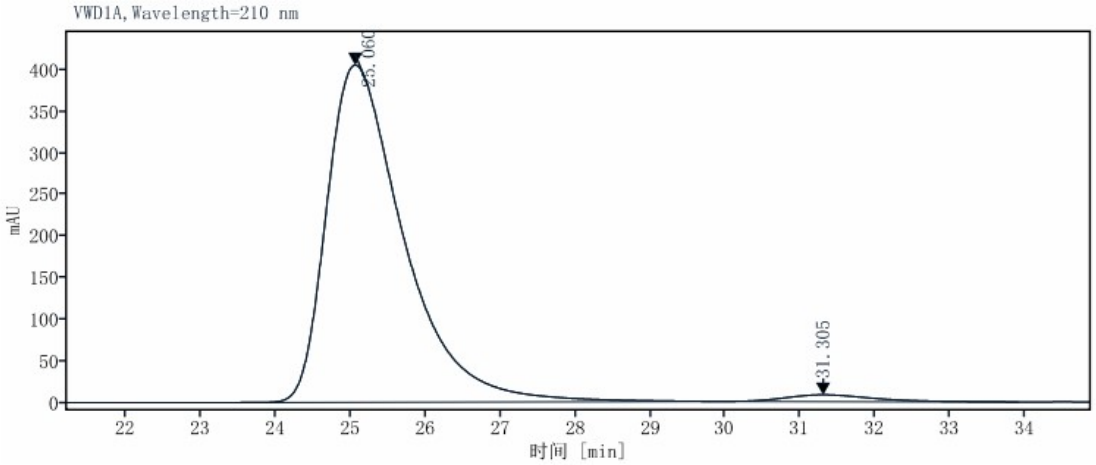


Ethyl 4-(2-(3-methyl-2-(2,2,2-trifluoroacetamido)butanamido)benzoyl)benzoate (3j). 84 mg, 72% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:15, v/v); mp 129 – 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (s, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.61 (dd, *J* = 8.2, 5.6 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.47 – 2.16 (m, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.06 (dd, *J* = 11.6, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 168.6, 165.6, 157.1 (q, *J* = 37.7 Hz), 141.9, 139.8, 135.1, 134.0, 133.8, 129.5, 129.5, 123.2, 122.8 121.5, 115.8 (q, *J* = 287.8 Hz), 61.5, 59.7, 32.0, 19.0, 17.8, 14.3. HRMS (ESI) calcd for $C_{23}H_{23}F_3N_2O_5$ $[M + H]^+$ 465.1632, found 465.1638.



***N*-(2-(4-cyanobenzoyl)phenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3k).** 73 mg, 70% yield; yellow liquid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:15, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 7.80 (q, *J* = 8.5 Hz, 4H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.23 – 7.11 (m, 2H), 4.59 (dd, *J* = 8.3, 5.4 Hz, 1H), 2.38 – 2.29 (m, 1H), 1.06 (dd, *J* = 12.1, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 168.6, 157.1 (q, *J* = 37.3 Hz), 141.9, 140.0, 135.5, 133.7, 132.2, 130.1, 123.3, 122.2, 121.7, 115.8 (q, *J* = 279.4 Hz), 117.8, 115.9, 59.7, 32.0, 19.0, 17.8. HRMS (ESI) calcd for $C_{21}H_{18}F_3N_3O_3$ $[M + H]^+$ 418.1373, found 418.1369.

HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 31.3 min (minor), t_{R2} = 25.1 min (major).



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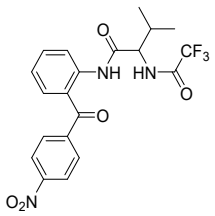
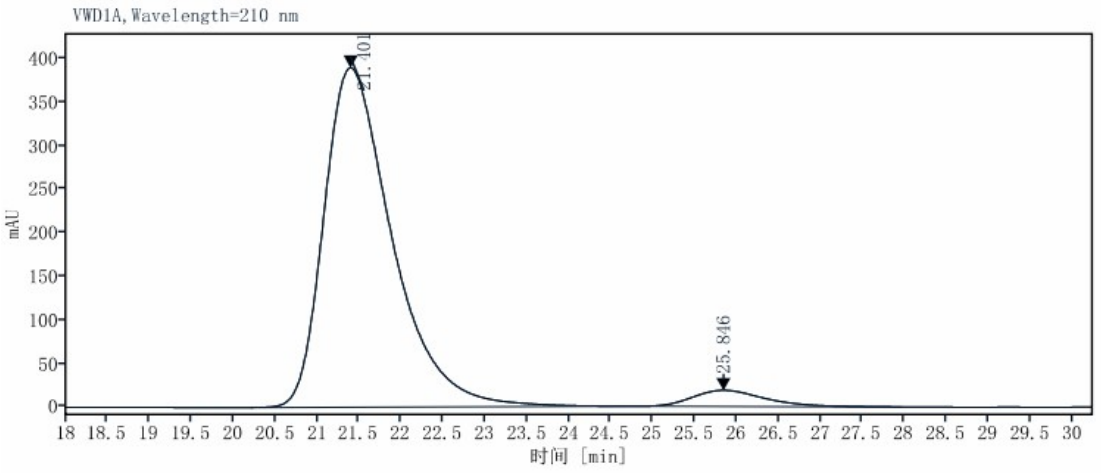
31.305	BB	4.0133	649.9764	8.1490	2.1917



3-methyl-*N*-(2-(4-nitrobenzoyl)phenyl)-2-(2,2,2-trifluoroacetamido)butanamide (3l). 71 mg, 65% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:15, v/v); mp 164 – 167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 8.68 (d, *J* = 7.8 Hz, 1H), 8.42 – 8.30 (m, 2H), 7.91 – 7.79 (m, 2H), 7.74 – 7.63 (m, 1H), 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 4.60 (dd, *J* = 8.3, 5.4 Hz,

1H), 2.39 – 2.30 (m, 1H), 1.06 (dd, J = 12.1, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 198.1, 168.6, 158.7 (q, J = 25.2 Hz), 149.9, 143.6, 140.1, 135.7, 133.8, 130.5, 123.7, 123.3, 122.1, 121.7, 115.9 (q, J = 267.5 Hz), 59.7, 32.0, 19.0, 17.8. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_3O_5$ $[M + H]^+$ 438.1272, found 438.1272.

HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 25.8 min (minor), t_{R2} = 21.4 min (major).



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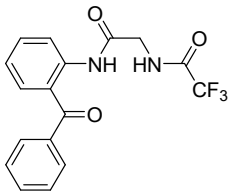
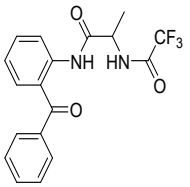
25.846	BB	3.1600	1103.5556	18.5383	4.7772



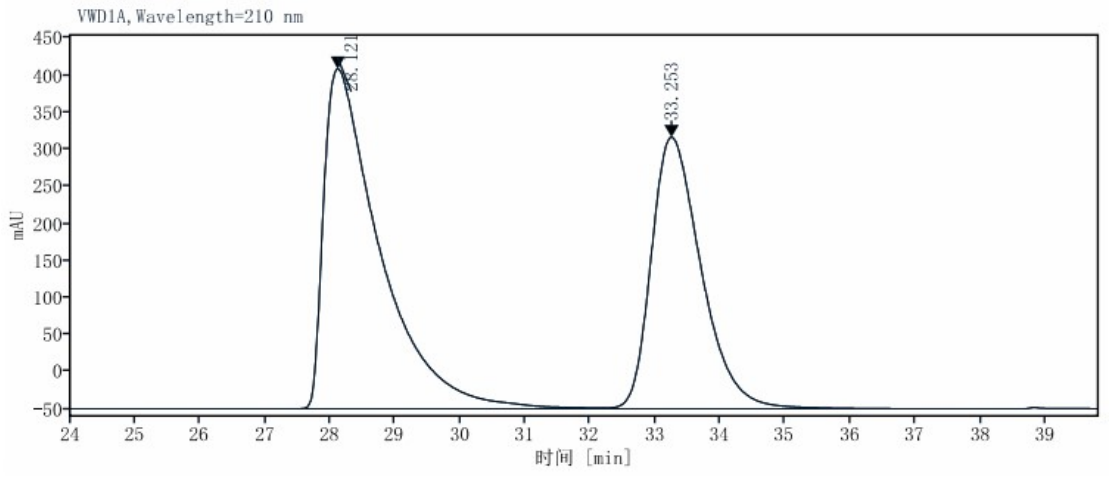
***N*-(2-((2-benzoylphenyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamide (3m).** 61 mg, 70% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:7, v/v); mp 112 – 114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.55 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.65 – 7.56 (m, 3H), 7.49 (t, J = 7.7 Hz, 2H), 7.40 (s, 1H), 7.16 (t, J = 7.6 Hz, 1H), 4.24 (d, J = 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 165.5, 157.3 (q, J = 37.8 Hz), 139.4, 138.2, 134.4, 133.8, 132.7, 129.9, 128.4, 123.4, 123.1, 121.6, 115.7 (q, J = 287.5 Hz), 43.6. HRMS (ESI) calcd for $C_{17}H_{13}F_3N_2O_3$ $[M + H]^+$ 351.0951, found 351.0959.



***N*-(2-benzoylphenyl)-2-(2,2,2-trifluoroacetamido)propanamide (3n).** 74 mg, 81% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:15, v/v); mp 141 – 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 8.58 (d, J = 8.2 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.62 (t, J = 8.0 Hz, 3H), 7.51 (t, J = 7.6 Hz, 2H), 7.39 (d, J = 5.3 Hz, 1H), 7.17 (t,

J = 7.6 Hz, 1H), 4.70 (p, J = 6.9 Hz, 1H), 1.63 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 169.4, 156.6 (q, J = 37.7 Hz), 139.7, 138.2, 134.6, 134.0, 132.7, 129.9, 128.4, 123.3, 123.1, 121.5, 115.7 (q, J = 287.5 Hz), 50.5, 18.8. HRMS (ESI) calcd for $C_{18}H_{15}F_3N_2O_3$ $[M + H]^+$ 365.1108, found 365.1107.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 33.3 min (minor), t_{R2} = 28.1 min (major).



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
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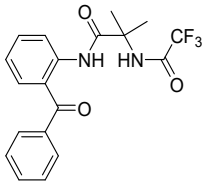
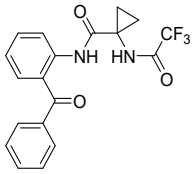
33.253	VB	5.3510	19574.3430	366.5743	41.5486

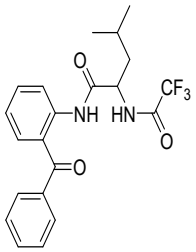


***N*-(2-benzoylphenyl)-2-methyl-2-(2,2,2-trifluoroacetamido)propanamide (3o).** 71 mg, 75% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 123 – 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 8.64 (d, J = 8.3 Hz, 1H), 7.84 (s, 1H), 7.72 – 7.68 (m, 2H), 7.68 – 7.59 (m, 3H), 7.51 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.1 Hz, 1H), 1.85 (d, J = 9.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 172.6, 156.0 (q, J = 36.8 Hz), 140.2, 138.4, 134.8, 134.8, 134.3, 132.7, 129.9, 128.4, 122.9, 121.2, 117.2 (q, J = 278.0 Hz), 58.6, 24.0. HRMS (ESI) calcd for $C_{19}H_{17}F_3N_2O_3$ $[M + H]^+$ 379.1264, found 379.1262.



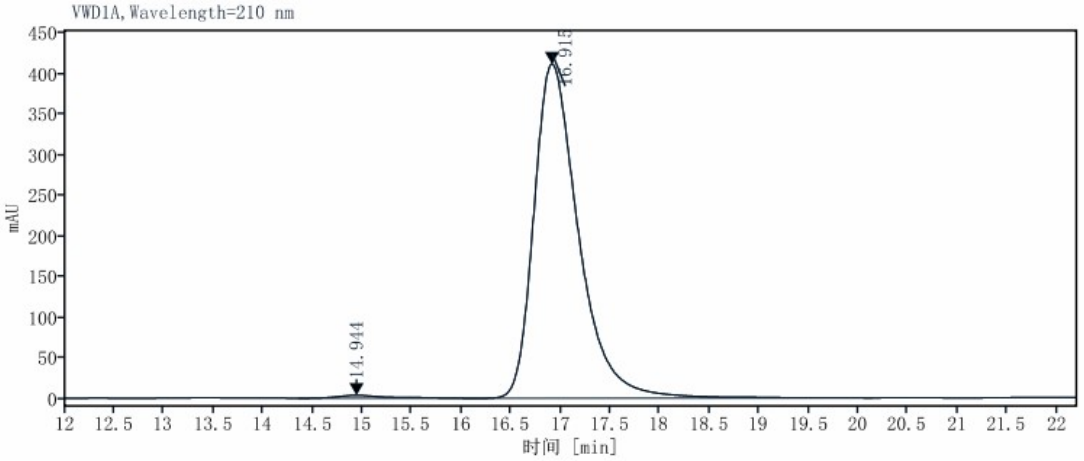
***N*-(2-benzoylphenyl)-1-(2,2,2-trifluoroacetamido)cyclopropane-1-carboxamide (3p).** 59 mg, 63% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 168 – 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s,

1H), 8.57 (d, *J* = 8.3 Hz, 1H), 7.68 – 7.61 (m, 3H), 7.60 – 7.54 (m, 2H), 7.54 – 7.48 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.11 – 6.99 (m, 1H), 1.73 (q, *J* = 5.0 Hz, 2H), 1.20 (q, *J* = 5.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 169.1, 158.5 (q, *J* = 37.8 Hz), 140.1, 138.4, 134.4, 133.8, 132.5, 129.9, 128.3, 122.8, 122.5, 120.9, 115.6 (q, *J* = 288.4 Hz), 35.9, 17.8. HRMS (ESI) calcd for $C_{19}H_{15}F_3N_2O_3$ $[M + H]^+$ 377.1108, found 377.1114.

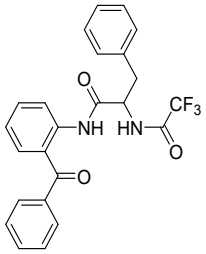


***N*-(2-benzoylphenyl)-4-methyl-2-(2,2,2-trifluoroacetamido)pentanamide (3q).** 80 mg, 79% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 161 – 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 11.31 (s, 1H), 8.57 (d, *J* = 8.3 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.66 – 7.54 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.75 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.90 – 1.68 (m, 3H), 0.98 (dd, *J* = 11.6, 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 169.8, 157.1 (q, *J* = 36.5 Hz), 139.5, 138.3, 134.4, 133.8, 132.6, 129.9, 128.4, 123.6, 123.1, 121.6, 115.8 (q, *J* = 287.9 Hz), 53.5, 41.8, 24.9, 22.8, 22.0. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_3$ $[M + H]^+$ 406.1577, found 406.1571.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 14.9 min (minor), t_{R2} = 16.9 min (major).

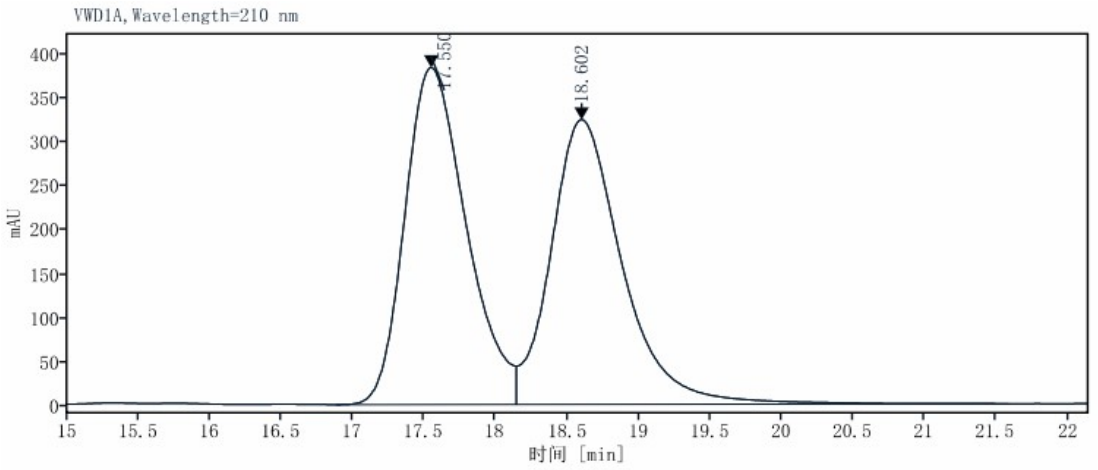


RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
14.944	BB	1.8397	122.1964	3.5892	0.9390
16.915	BB	3.9400	12890.6019	411.9440	99.0610



***N*-(2-benzoylphenyl)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamide (3r).** 95 mg, 86% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 153 – 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 7.65 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.64 – 7.60 (m, 1H), 7.60 – 7.55 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.11 (m, 6H), 7.00 (m, 1H), 4.86 (dd, *J* = 13.0, 7.3 Hz, 1H), 3.29 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.21 (dd, *J* = 13.8, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 167.9, 156.6 (q, *J* = 37.8 Hz), 139.1, 138.1, 134.6, 134.3, 133.7, 132.7, 130.0, 129.2, 128.8, 128.3, 127.5, 123.5, 123.1, 121.5, 115.6 (q, *J* = 288.0 Hz), 55.9, 38.8. HRMS (ESI) calcd for $C_{24}H_{19}F_3N_2O_3$ $[M + H]^+$ 441.1421, found 441.1420.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 17.6 min, t_{R2} = 18.6 min.



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
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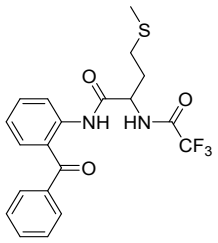
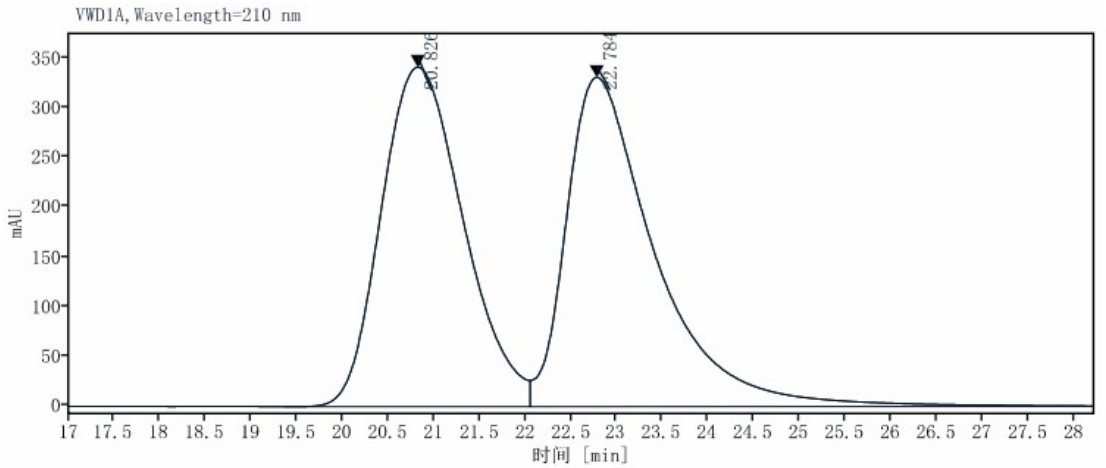
18.602	VB	3.4416	11242.4338	324.0344	49.5260



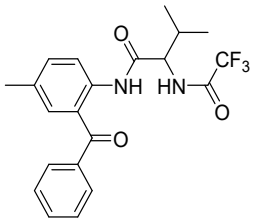
***N*-(2-benzoylphenyl)-4-(methylthio)-2-(2,2,2-trifluoroacetamido)butanamide (3s).** 55 mg, 52% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:10, v/v); mp 136 – 137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s,

1H), 8.57 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 3H), 7.50 (t, *J* = 7.7 Hz, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 4.85 (dd, *J* = 12.9, 6.6 Hz, 1H), 2.70 – 2.46 (m, 2H), 2.33 – 2.28 (m, 1H), 2.27 – 2.15 (m, 1H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 168.3, 156.9 (q, *J* = 37.8 Hz), 139.4, 138.2, 134.4, 133.8, 132.7, 130.0, 128.4 123.6, 123.2, 121.6, 115.8 (q, *J* = 287.8 Hz), 53.9, 31.7, 29.6, 15.3. HRMS (ESI) calcd for $C_{20}H_{19}F_3N_2O_3S$ $[M + H]^+$ 425.1141, found 425.1151.

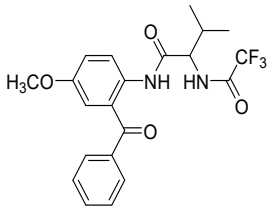
HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 20.8 min, t_{R2} = 22.8 min.



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
20.826	BV	2.6950	21307.7008	340.8439	48.8279
22.784	VB	7.2830	22330.7098	330.6041	51.1721

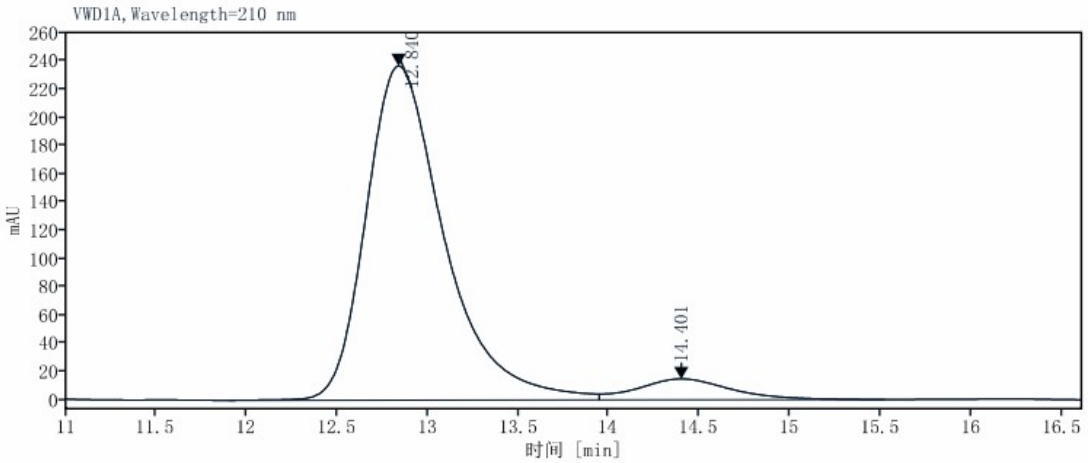


***N*-(2-benzoyl-4-methylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3u).** 80 mg, 79% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 136 – 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.47 (d, *J* = 8.3 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 10.8 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 1H), 4.57 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.47 – 2.15 (m, 4H), 1.03 (dd, *J* = 11.6, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 168.2, 157.0 (q, *J* = 37.2 Hz), 138.3, 137.0, 135.1, 134.0, 132.8, 132.6, 129.9, 128.4, 123.5, 121.5, 115.8 (q, *J* = 286.2 Hz), 59.5, 32.2, 20.8, 19.0, 17.8. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_3$ $[M + H]^+$ 407.1577, found 407.1575.



***N*-(2-benzoyl-4-methoxyphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3v).** 81 mg, 77% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.47 (d, *J* = 9.1 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.62 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 3.0 Hz, 1H), 7.15 (d, *J* = 3.0 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 4.54 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.77 (s, 3H), 2.34 – 2.25 (m, 1H), 1.03 (dd, *J* = 10.5, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 167.9, 157.0 (q, *J* = 36.9 Hz), 154.9, 138.0, 132.9, 132.4, 130.0, 128.5, 125.2, 1233, 119.3, 118.8, 115.8 (q, *J* = 287.6 Hz), 59.5, 55.7, 32.2, 19.0, 17.9. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_4$ $[M + H]^+$ 423.1526, found 423.1534.

HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 14.4 min (minor), t_{R2} = 12.8 min (major).



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
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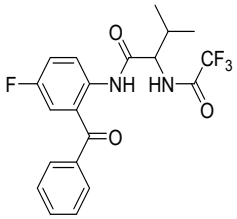
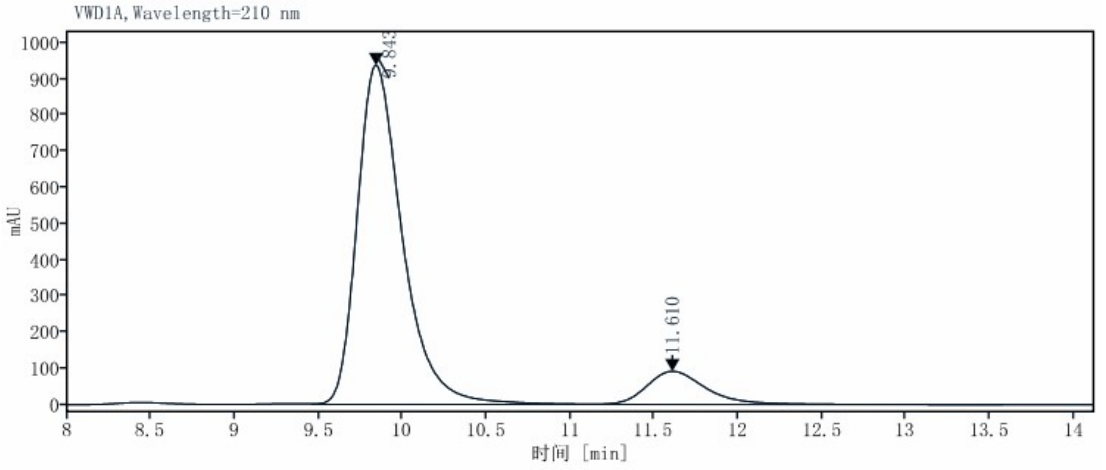
14.401	VB	1.5768	530.0518	14.8019	6.9307



***N*-(2-benzoyl-4-fluorophenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3w).** 90 mg, 88% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 159 – 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.58 (dd, *J* = 8.7, 4.9 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6

Hz, 2H), 7.38 – 7.28 (m, 2H), 7.14 (d, J = 7.6 Hz, 1H), 4.56 (dd, J = 8.2, 5.5 Hz, 1H), 2.45 – 2.26 (m, 1H), 1.04 (dd, J = 11.8, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 168.3, 157.3 (q, J = 37.3 Hz), 137.5, 135.5, 133.2, 129.9, 128.6, 125.0 (d, J = 5.9 Hz), 123.6 (d, J = 7.2 Hz), 121.2 (d, J = 22.1 Hz), 119.9, 119.6, 115.8 (q, J = 287.8 Hz), 59.5, 32.1, 19.0, 17.8. HRMS (ESI) calcd for $C_{20}H_{18}F_4N_2O_3$ $[M + H]^+$ 411.1327, found 411.1330.

HPLC: Daicel Chiralcel AS-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 11.6 min (minor), t_{R2} = 9.8 min (major).



RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
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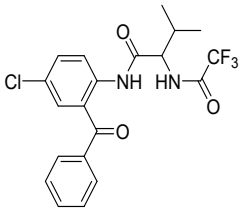
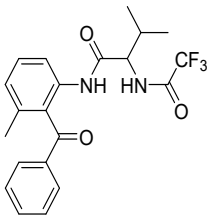
11.610	VB	2.4377	2290.5153	91.9211	11.5124

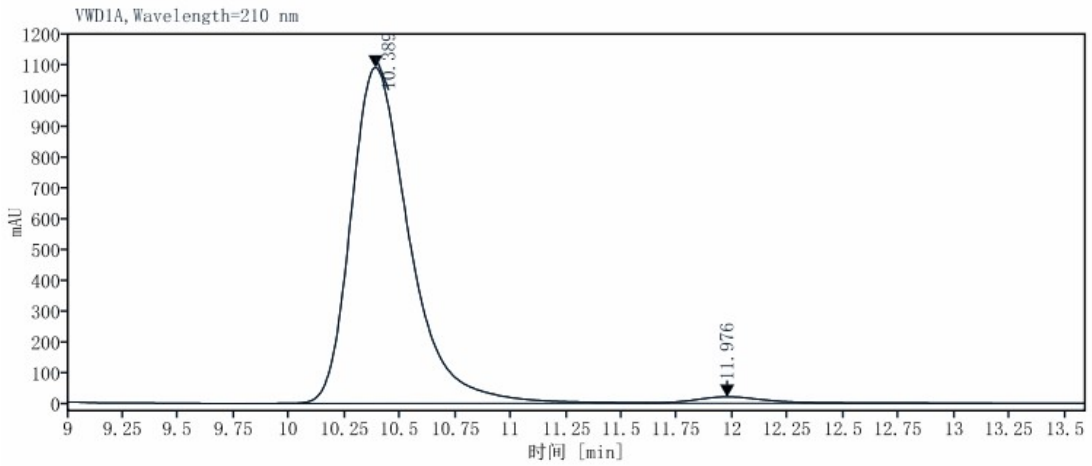


***N*-(2-benzoyl-4-chlorophenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3x).** 81 mg, 76% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 143 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.58 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 7.3 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.55 (dd, J = 16.6, 8.7 Hz, 4H), 7.15 (d, J = 8.2 Hz, 1H), 4.57 (dd, J = 8.3, 5.5 Hz, 1H), 2.30 (dt, J = 13.4, 6.7 Hz, 1H), 1.04 (dd, J = 12.2, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 168.5, 157.1 (q, J = 37.4 Hz), 137.9, 137.5, 134.2, 133.2, 133.0, 129.9, 128.7, 128.4, 124.7, 123.0, 115.8 (q, J = 287.8 Hz), 59.6, 32.0, 19.0, 17.8. HRMS (ESI) calcd for $C_{20}H_{18}ClF_3N_2O_3$ $[M + H]^+$ 427.1031, found 427.1035.



***N*-(2-benzoyl-3-methylphenyl)-3-methyl-2-(2,2,2-trifluoroacetamido)butanamide (3y).** 65 mg, 64% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:20, v/v); mp 139 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.76 (dd, *J* = 8.0, 6.7 Hz, 3H), 7.66 – 7.56 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 4.29 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.10 (s, 3H), 2.01 – 1.91 (m, 1H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 168.1, 156.9 (q, *J* = 37.5 Hz), 137.1, 136.2, 134.4, 133.5, 131.9, 130.3, 129.6, 129.0, 127.9, 121.9, 115.7 (q, *J* = 288.0 Hz), 58.8, 31.9, 20.4, 18.6, 17.5. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_2O_3$ $[M + H]^+$ 407.1577, found 407.1565.

HPLC: Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate =0.5 mL/min, uv-vis λ = 210 nm, t_{R1} = 12.0 min (minor), t_{R2} = 10.4 min (major).

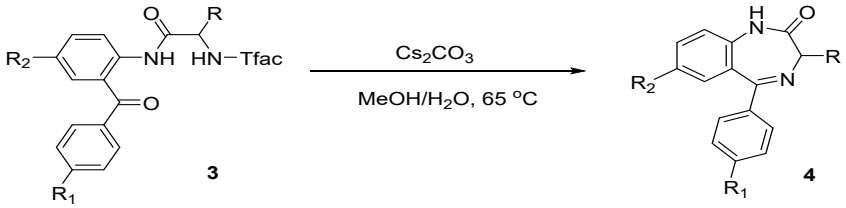


RetTime[min]	Type	Width[min]	Area[mAU*s]	Height[mAU]	Area%
10.389	BV	1.8687	20016.0412	1091.2585	97.5982
11.976	VB	1.5604	492.5695	21.1024	2.4018

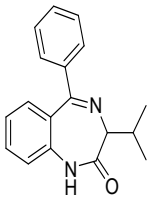
7. Typical Procedure for Bifunctional Products 3a on a one-gram scale

A mixture of *N*-protected amino acid derivatives **1a** (3.30 mmol), aryl iodides **2a** (9.90 mmol), $Pd(OAc)_2$ (0.66 mmol), Ag_2CO_3 (6.60 mmol), 4 Å molecuar sieve, and DMAc (15 mL) was placed in a 150 mL pressure tube with PTFE cap under air. The tube was heated at 130 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and filtered through celite. Then, the 30 mL water was added to filtrate and the mixture was extracted with ethyl acetate (50 mL) for 3 times. The organic layers was dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product (EA/PE = 1:20, v/v).

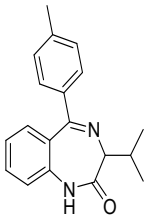
8. Typical Procedure for synthesis of the 5-aryl-1,4-Benzodiazepine-2-one derivatives 4a–j[3]



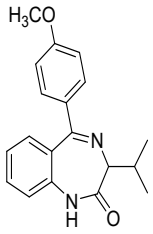
A mixture of **3** (0.11 mmol), Cs_2CO_3 (0.072 g, 0.22 mmol) and 2 mL MeOH/H_2O (1:1) was placed in a 35 mL pressure tube with PTFE cap under air. The tube was heated at 65 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (3 mL), filtered through celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product (EA/PE = 1:2 ~ 1:5).



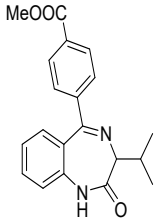
3-isopropyl-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4a, CAS no. 34124-69-1). 25 mg, 82% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 200 – 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.62 – 7.50 (m, 3H), 7.51 – 7.43 (m, 1H), 7.43 – 7.35 (m, 3H), 7.19 (t, *J* = 7.5 Hz, 2H), 3.16 (d, *J* = 9.2 Hz, 1H), 2.81 – 2.71 (m, 1H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.11 (dd, *J* = 6.5, 3.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 170.9, 168.7, 139.5, 138.4, 131.5, 131.1, 130.2, 129.8, 128.2, 127.6, 123.2, 121.1, 69.3, 29.0, 20.4, 19.1. HRMS (ESI) calcd for $C_{18}H_{18}N_2O$ $[M + H]^+$ 279.1492, found 279.1489.



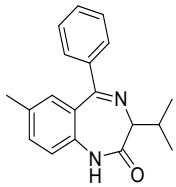
3-isopropyl-5-(p-tolyl)-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4b). 30 mg, 93% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 214 – 215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.57 – 7.48 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.18 – 7.12 (m, 4H), 3.12 (d, *J* = 9.3 Hz, 1H), 2.77 (dd, *J* = 15.5, 6.6 Hz, 1H), 2.39 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.09 (dd, *J* = 6.5, 1.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 168.5, 140.4, 138.4, 136.8, 131.4, 131.1, 129.8, 128.8, 127.8, 123.1, 121.1, 69.2, 29.0, 21.4, 20.4, 19.1. HRMS (ESI) calcd for $C_{19}H_{20}N_2O$ $[M + H]^+$ 293.1649, found 293.1646.



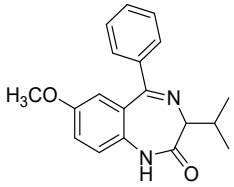
3-isopropyl-5-(4-methoxyphenyl)-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4c, CAS no. 152236-83-4). 32 mg, 94% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 227 – 228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.53 – 7.49 (m, 3H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.08 (d, *J* = 9.2 Hz, 1H), 2.83 – 2.57 (m, 1H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 168.0, 161.3, 138.5, 132.1, 131.4, 131.4, 131.1, 127.8, 123.1, 121.3, 111.5, 69.2, 55.4, 29.0, 20.4, 19.1. HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$ $[M + H]^+$ 309.1598, found 309.1621.



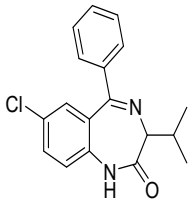
Methyl 4-(3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepi*N*-5-yl)benzoate (4d). 32 mg, 86% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:3, v/v); mp 230 – 232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 40.0 Hz, 1H), 8.07 – 7.97 (m, 2H), 7.67 – 7.46 (m, 2H) , 7.52 (t, *J* = 7.7 Hz, 1H), 7.32 – 7.19 (m, 2H), 7.15 (t, *J* = 7.1 Hz, 1H), 3.92 (s, 3H), 3.15 (d, *J* = 9.1 Hz, 1H), 2.87 – 2.7 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.09 (dd, *J* = 17.5, 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.0, 167.0, 143.4, 138.6, 131.8, 131.4, 130.7, 129.8, 129.4, 127.1, 123.3, 121.4, 69.6, 52.3, 29.0, 20.4, 19.1. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ $[M + H]^+$ 337.1547, found 337.1544.



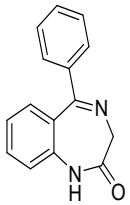
3-isopropyl-7-methyl-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4e). 29 mg, 89% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 212 – 214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.65 – 7.51 (m, 2H), 7.46 – 7.41 (m, 1H), 7.41 – 7.34 (m, 2H), 7.32 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.13 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 3.11 (d, *J* = 9.2 Hz, 1H), 2.93 – 2.67 (m, 1H), 2.32 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.07 (dd, *J* = 6.4, 4.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 139.6, 136.0, 133.1, 132.5, 131.0, 130.1, 129.8, 128.2, 127.6, 120.9, 69.3, 29.0, 20.8, 20.3, 19.1. HRMS (ESI) calcd for $C_{19}H_{20}N_2O$ $[M + H]^+$ 293.1649, found 293.1646.



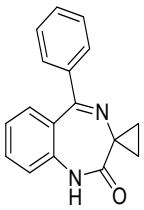
3-isopropyl-7-methoxy-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4f, CAS no. 2226130-96-5). 31 mg, 91% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 191 – 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 25.4 Hz, 1H), 7.65 – 7.52 (m, 2H), 7.46 – 7.29 (m, 3H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.81 – 6.78 (m, 1H), 3.71 (d, *J* = 2.3 Hz, 3H), 3.12 (d, *J* = 9.3 Hz, 1H), 2.81 – 2.71 (m, 1H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.08 (dd, *J* = 18.7, 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.2, 154.9, 139.3, 132.3, 130.2, 129.8, 128.5, 128.2, 122.7, 118.7, 114.2, 69.4, 55.7, 29.0, 20.4, 19.2. HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$ $[M + H]^+$ 309.1598, found 309.1585.



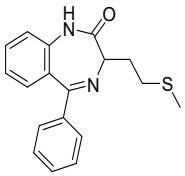
7-chloro-3-isopropyl-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4g, CAS no. 14404-96-7). 33 mg, 97% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 225 – 226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (d, *J* = 3.9 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.44 (m, 2H), 7.41 – 7.34 (m, 2H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 3.10 (d, *J* = 9.2 Hz, 1H), 2.88 – 2.60 (m, 1H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.08 (dd, *J* = 6.5, 3.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 167.6, 138.8, 137.3, 131.7, 130.5, 130.3, 129.8, 128.8, 128.5, 128.4, 122.9, 69.5, 29.0, 20.4, 19.1. HRMS (ESI) calcd for $C_{18}H_{17}ClN_2O$ $[M + H]^+$ 313.1102, found 313.1111.



5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4h, CAS no. 2898-08-0). 24 mg, 94% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:2, v/v); mp 175 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.51 (m, 3H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.11 (m, 1H), 4.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.1, 139.4, 138.8, 131.7, 131.4, 130.3, 129.7, 128.2, 127.3, 123.4, 121.1, 56.7. HRMS (ESI) calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$ 237.1023, found 237.1028.



5-phenylspiro[benzo[e][1,4]diazepine-3,1'-cyclopropan]-2(1H)-one (4i). 28 mg, 98% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:5, v/v); mp 230 – 231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.52 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.50 – 7.40 (m, 2H), 7.40 – 7.32 (m, 2H), 7.24 (t, *J* = 7.9, 1.4 Hz, 1H), 7.18 – 7.07 (m, 2H), 1.32 (q, *J* = 5.0 Hz, 2H), 0.96 (q, *J* = 5.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 174.4, 139.6, 138.7, 131.7, 130.9, 130.3, 129.6, 128.3, 128.1, 122.9, 120.8, 46.0, 12.9. HRMS (ESI) calcd for $C_{17}H_{14}N_2O$ $[M + H]^+$ 263.1179, found 263.1180.



3-(2-(methylthio)ethyl)-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepi*N*-2-one (4j，CAS no. 884492-51-7). 29 mg, 86% yield; white solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1:2, v/v); mp 147 – 149°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7. 58 – 7.48 (m, 3H), 7 .47 – 7.41 (m, 1H), 7.41 – 7.32 (m, 3H), 7. 16 (t, *J* = 8.0 Hz, 2H), 3. 79 (dd, *J* = 8.6, 5.2 Hz, 1H), 2.98 – 2.69 (m, 2H), 2.69 – 2.53 (m, 1H), 2.47 (m, 1H), 2.12 (s, 3H). ^{13}NMR (100 MHz, $CDCl_3$) δ 171.9, 169.7, 139.3, 138.3, 131.8, 131.3, 130.3, 129.8, 128.2, 127.6, 123.4, 121.04, 61.6, 30.7, 30.5, 15.5. HRMS (ESI) calcd for $C_{18}H_{18}N_2OS$ $[M + H]^+$ 311.1213, found 311.1221.

9. References

(1) Kar, S.; Drew, M. G. B.; Pramanik, A., Nano structures through self-assembly of protected hydrophobic amino acids: encapsulation of rhodamine B dye by proline-based nanovesicles. *J Mater Sci* **2012,** *47*, 1825-1835.

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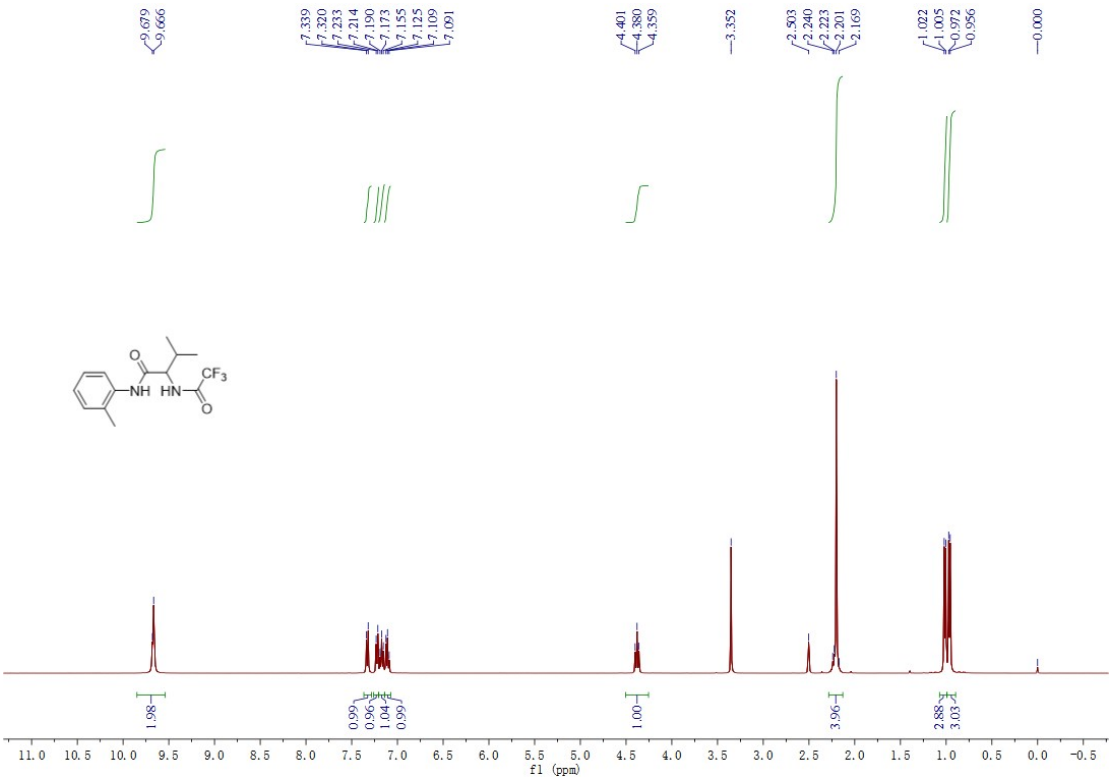
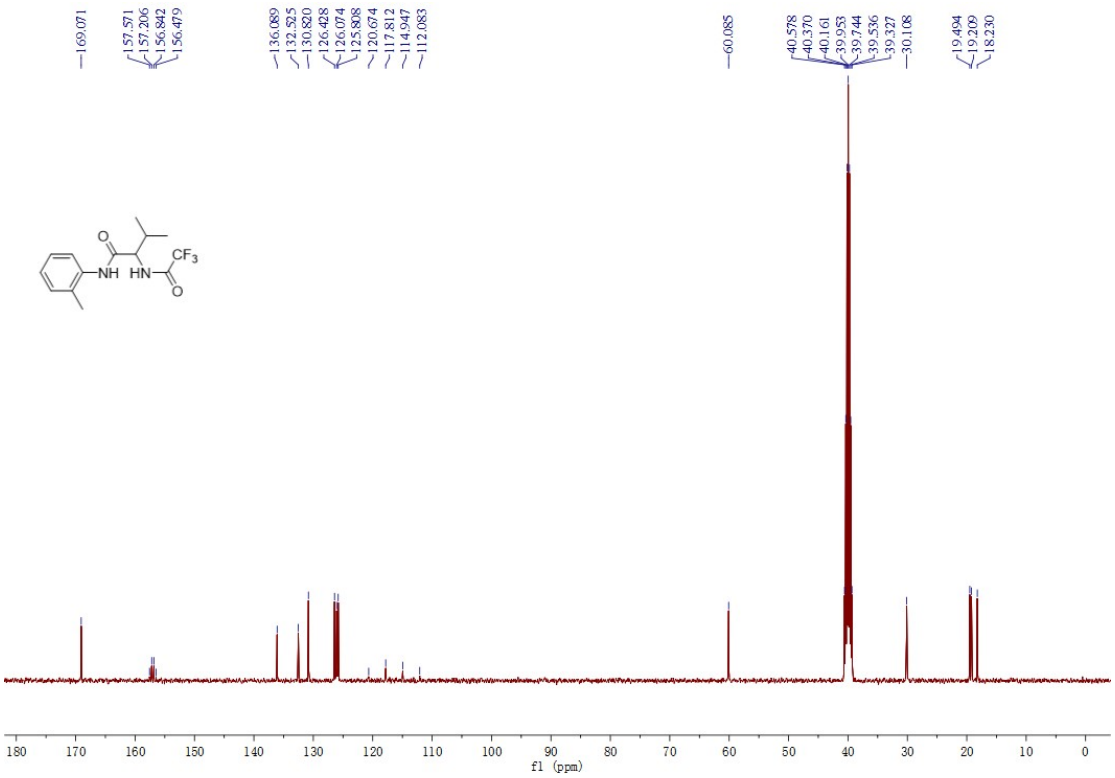
(3) Sykes, B. M.; Atwell, G. J.; Hogg, A.; Wilson, W. R.; O'Connor, C. J.; Denny, W. A., *N*-Substituted 2-(2,6-Dinitrophenylamino)propanamides: Novel Prodrugs That Release a Primary Amine via Nitroreduction and Intramolecular Cyclization. *J. Med. Chem.* **1999,** *42*, 346-355.

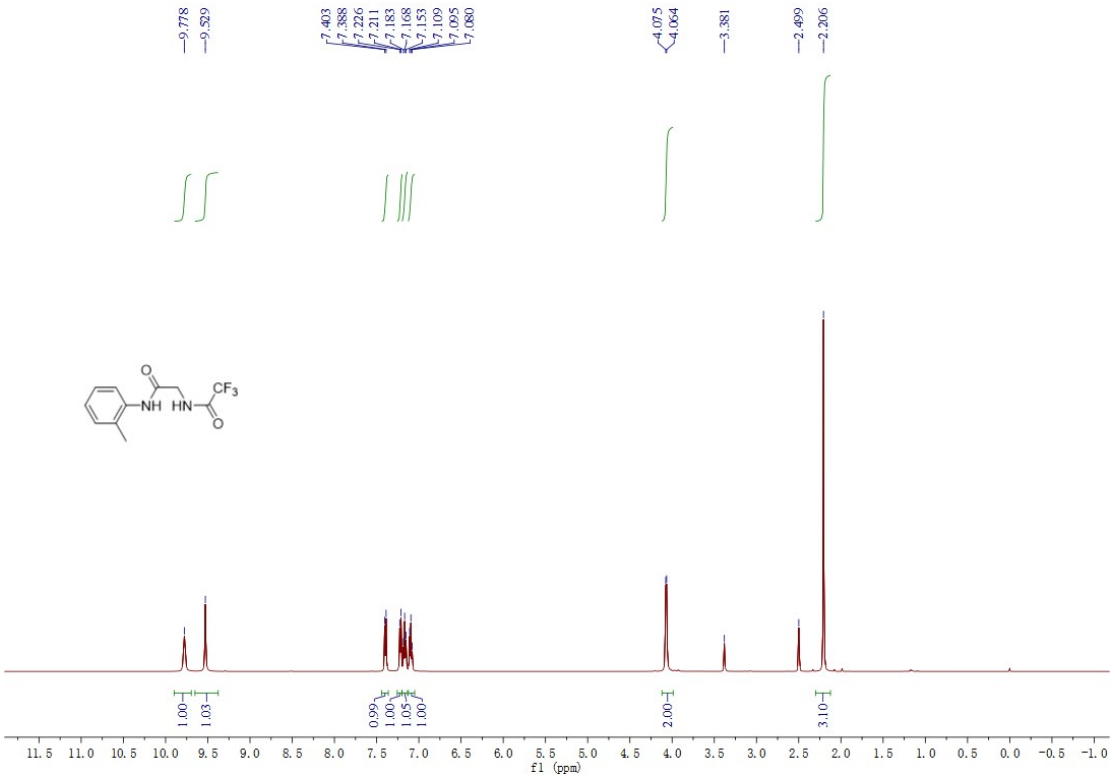
10. NMR Spectra



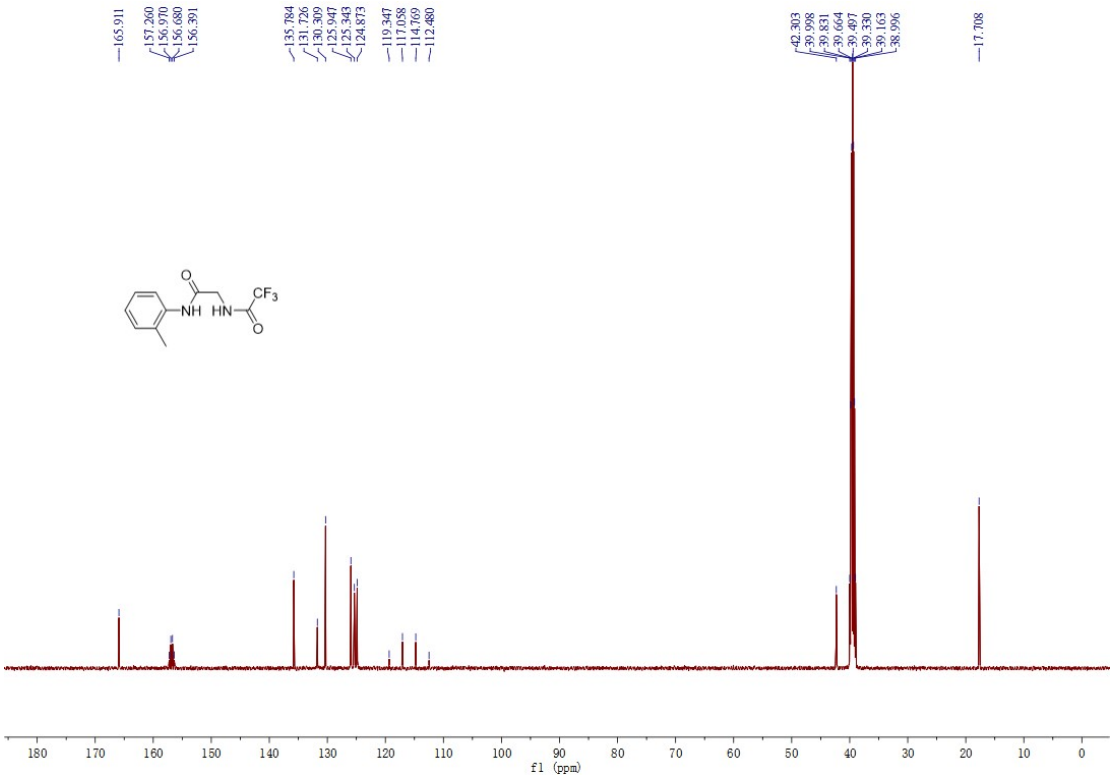
^{1}H NMR of product **1a** (DMSO-*d6*)



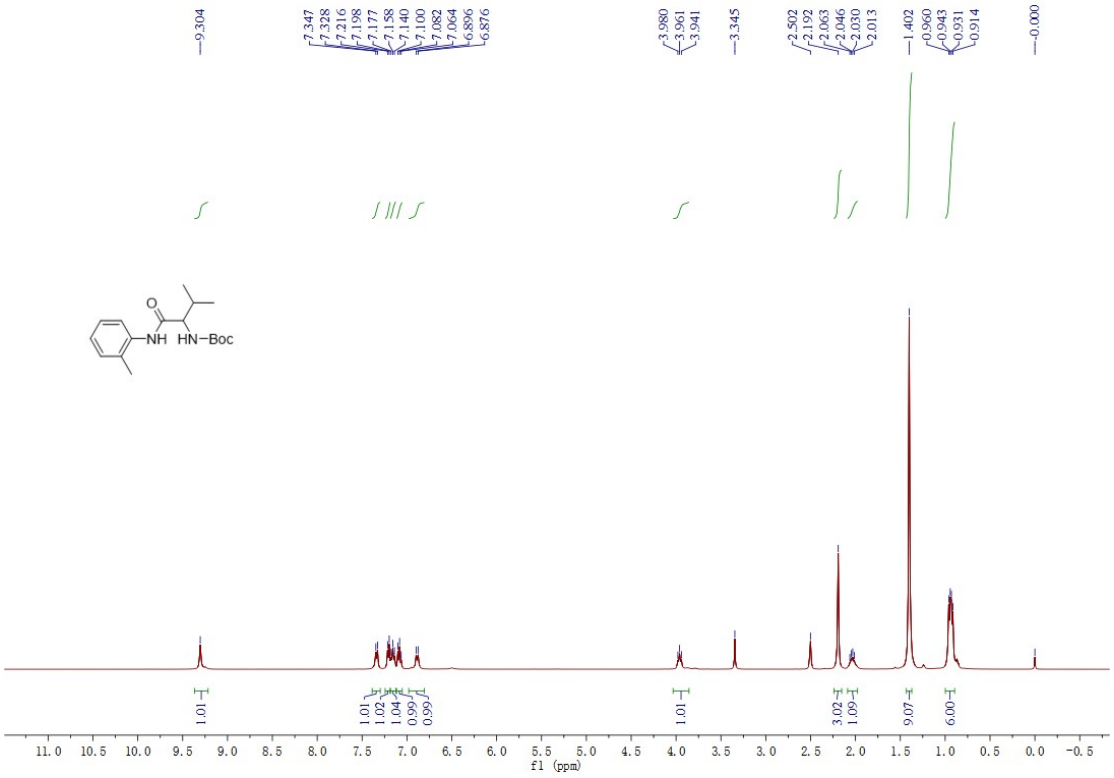
^{13}C NMR of product **1a** (DMSO-*d6*)



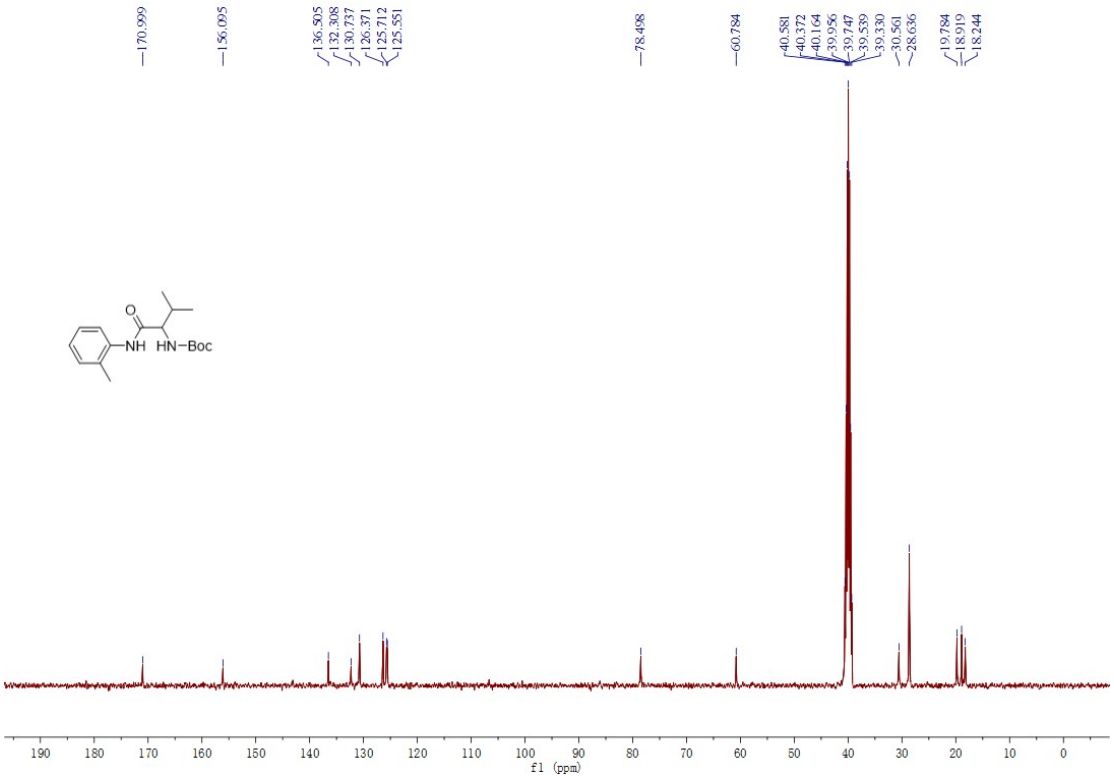
^{1}H NMR of product **1m** (DMSO-*d6*)



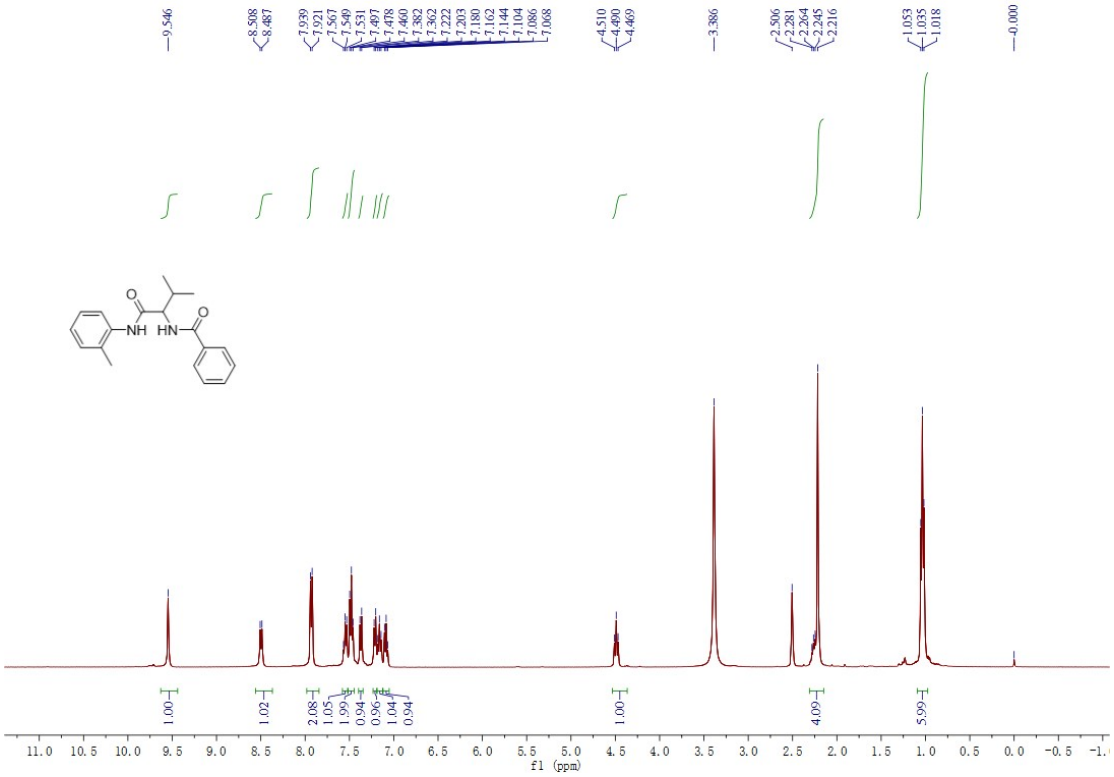
^{13}C NMR of product **1m** (DMSO-*d6*)



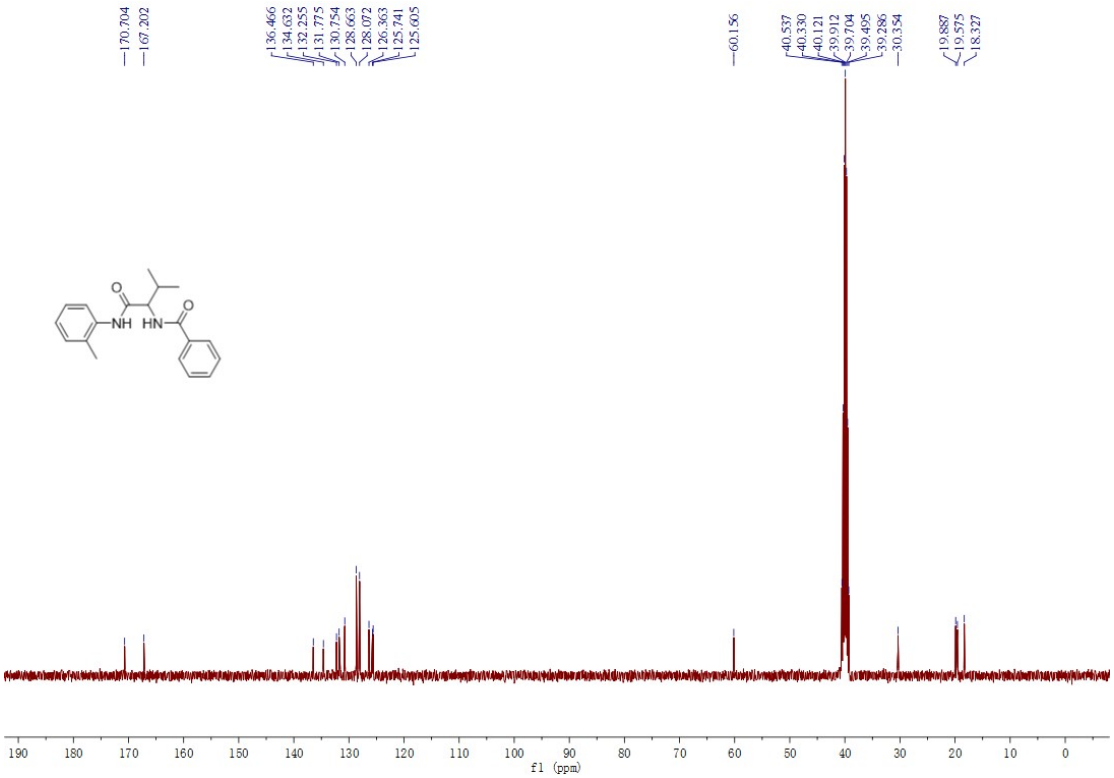
^{1}H NMR of product **1ab** (DMSO-*d6*)



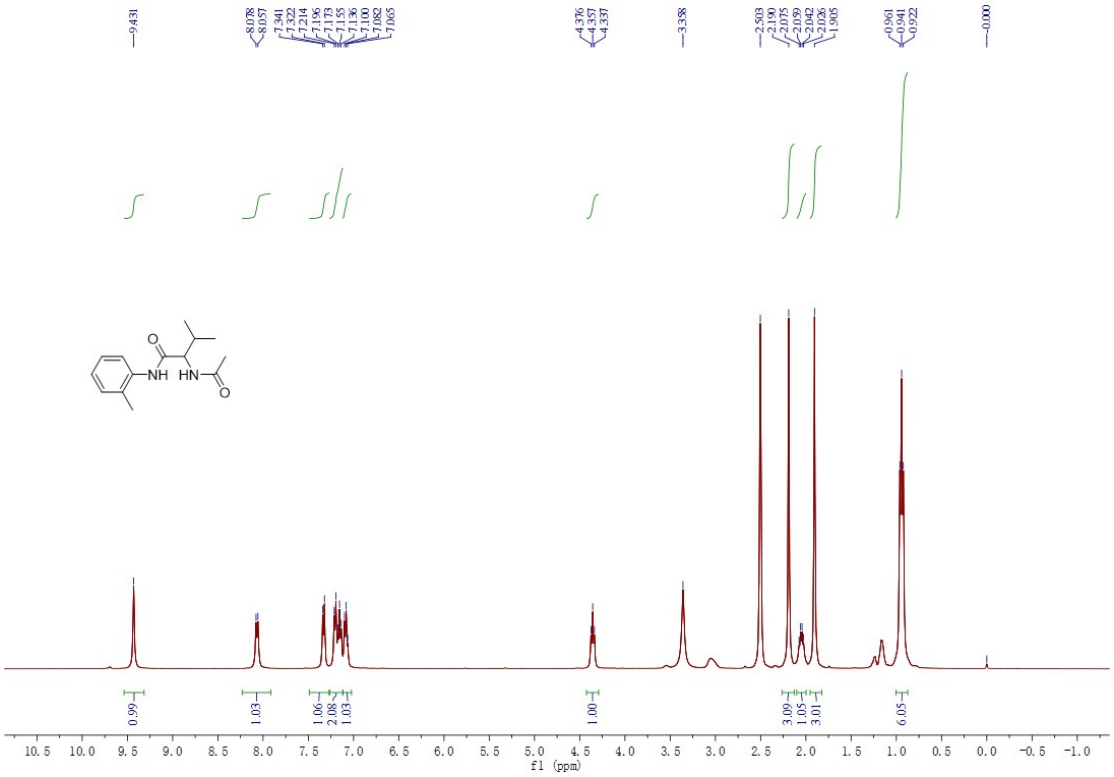
^{13}C NMR of product **1ab** (DMSO-*d6*)



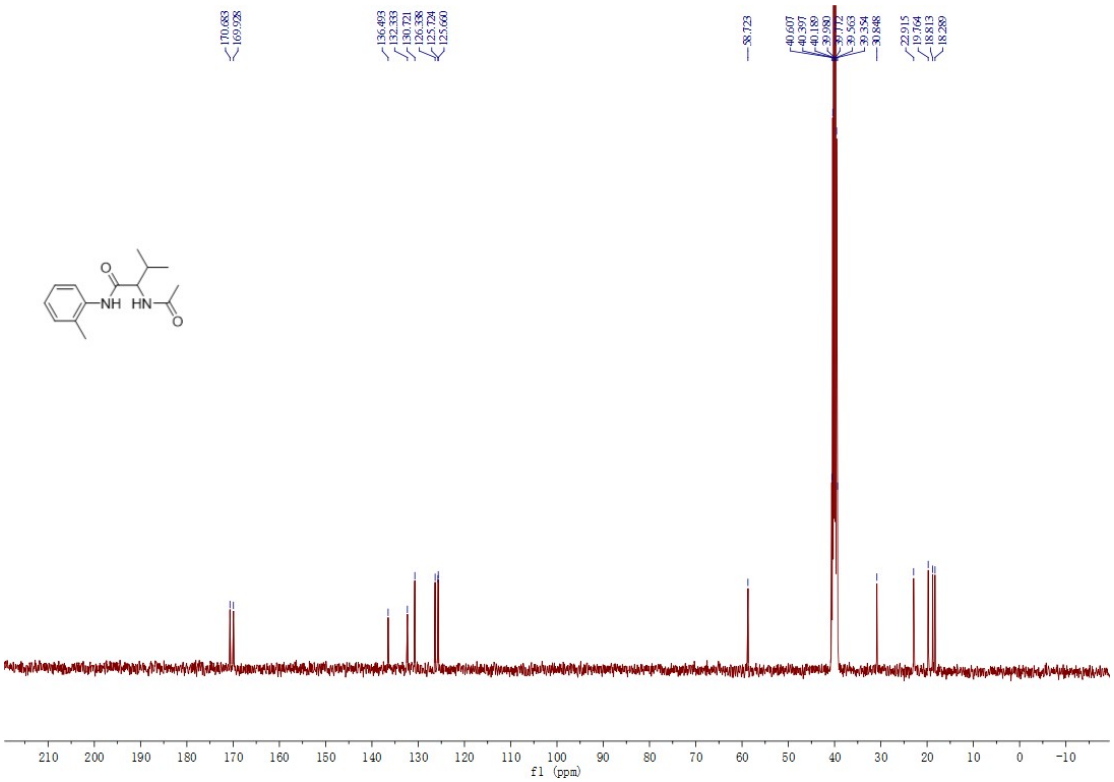
^{1}H NMR of product **1ac** (DMSO-*d6*)



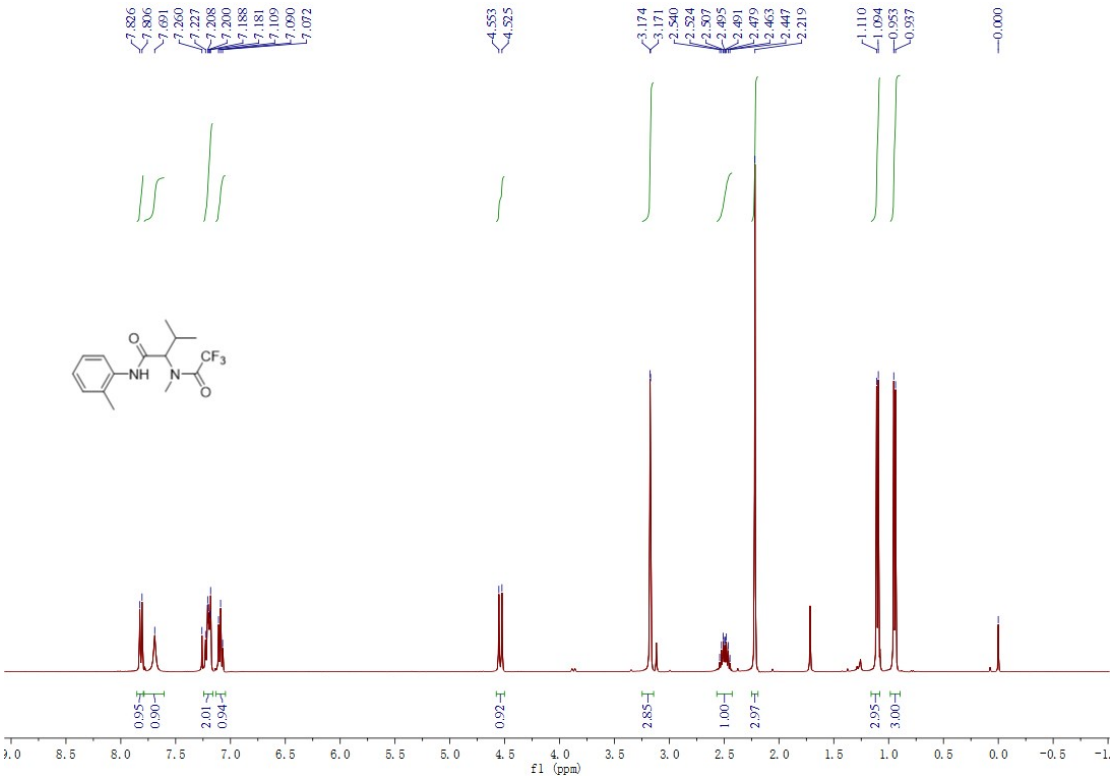
^{13}C NMR of product **1ac** (DMSO-*d6*)



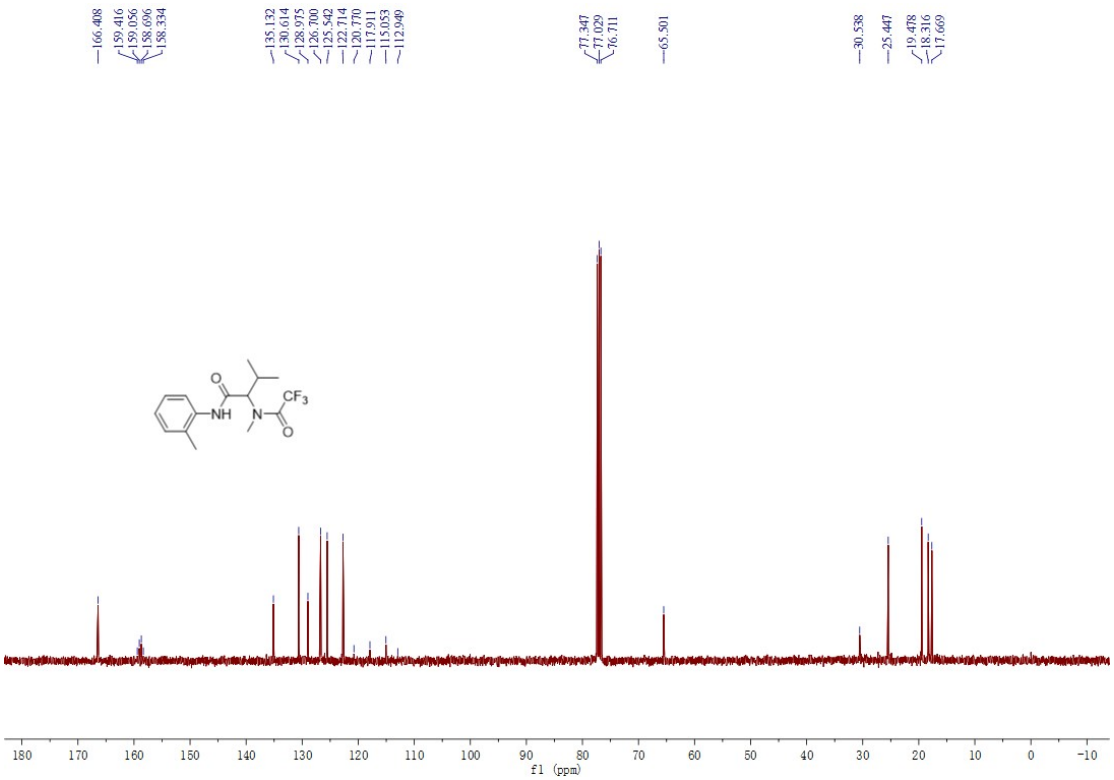
^{1}H NMR of product **1ad** (DMSO-*d6*)



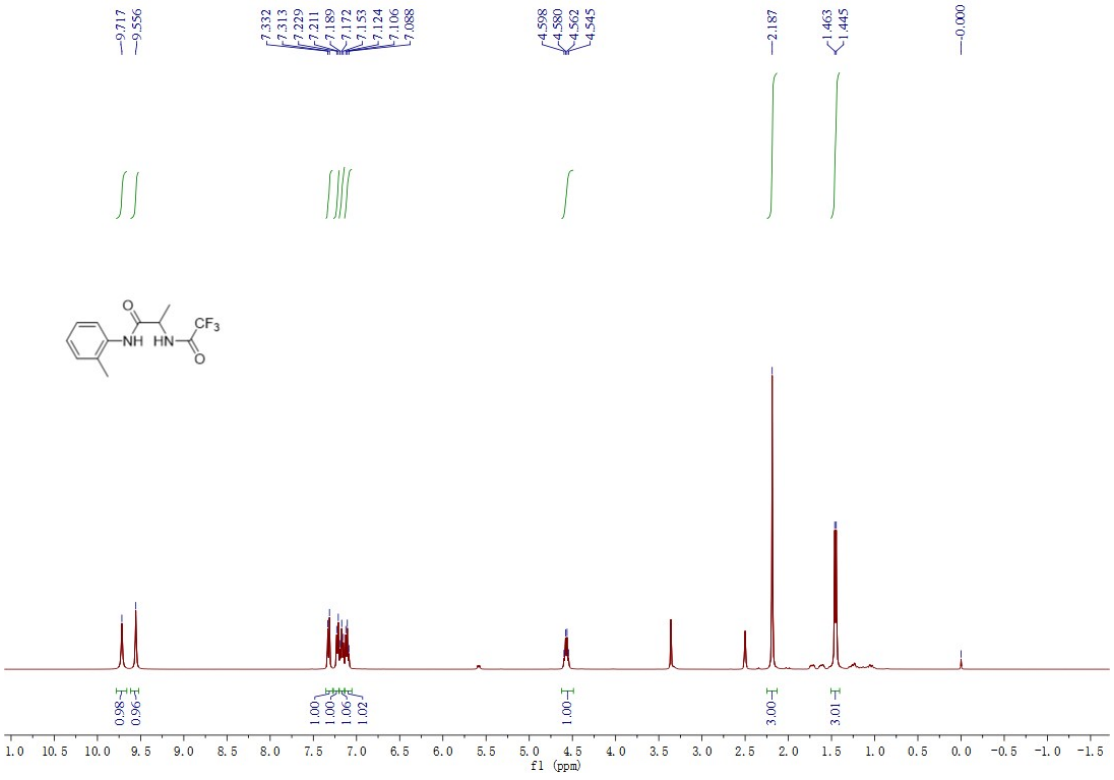
^{13}C NMR of product **1ad** (DMSO-*d6*)



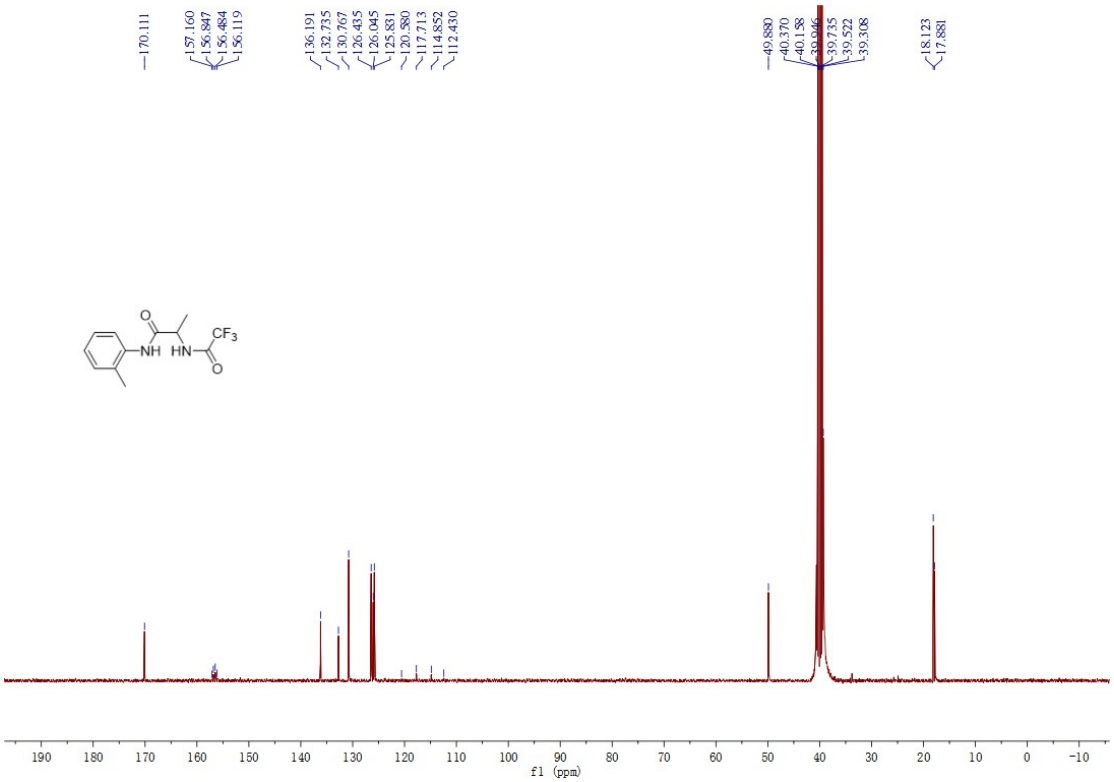
^{1}H NMR of product **1ae** (DMSO-*d6*)



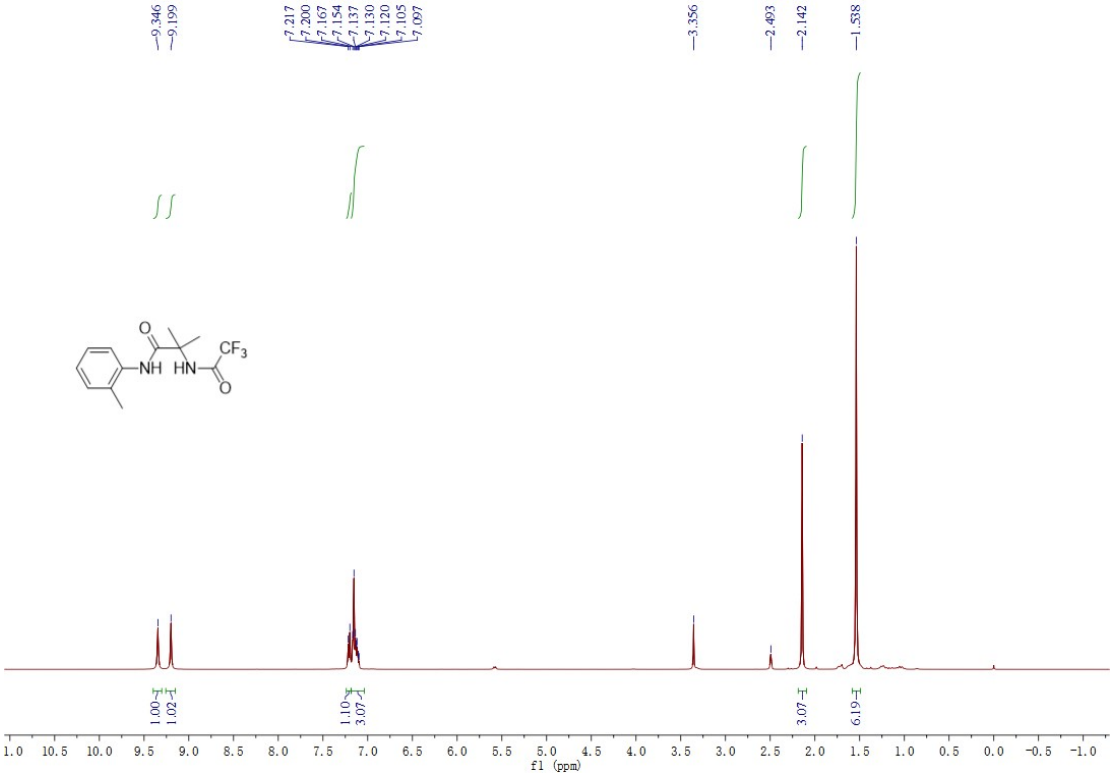
^{13}C NMR of product **1ae** (DMSO-*d6*)



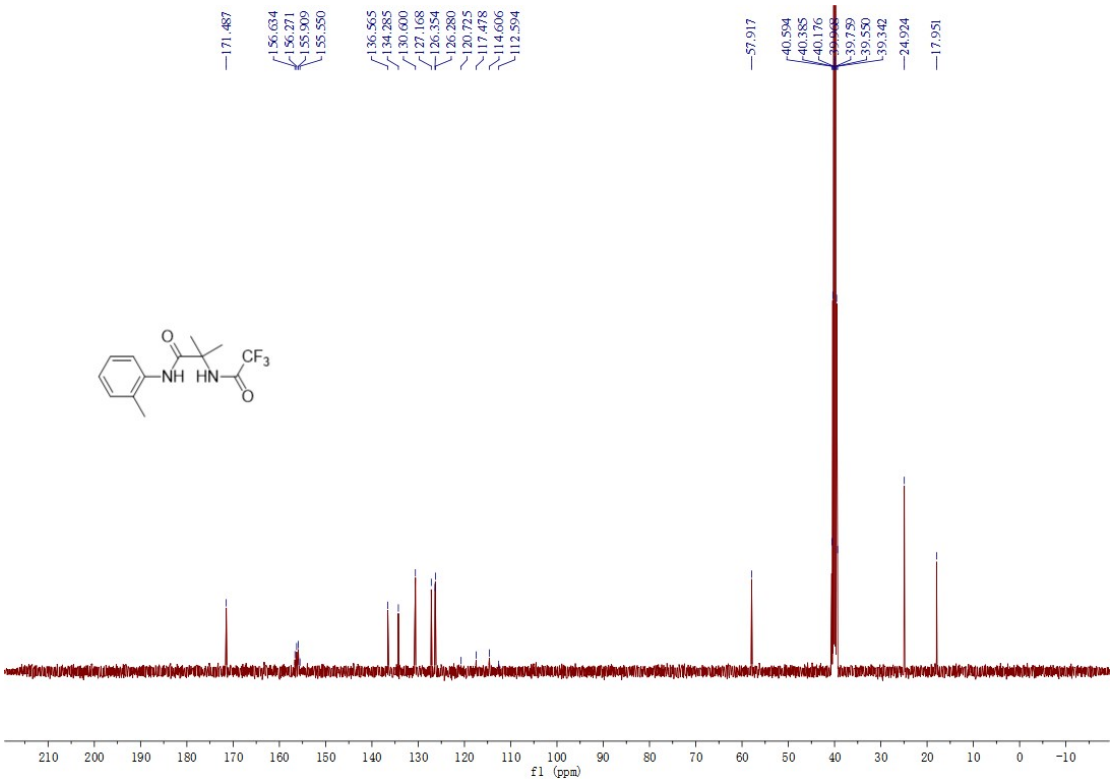
^{1}H NMR of product **1n** (DMSO-*d6*)



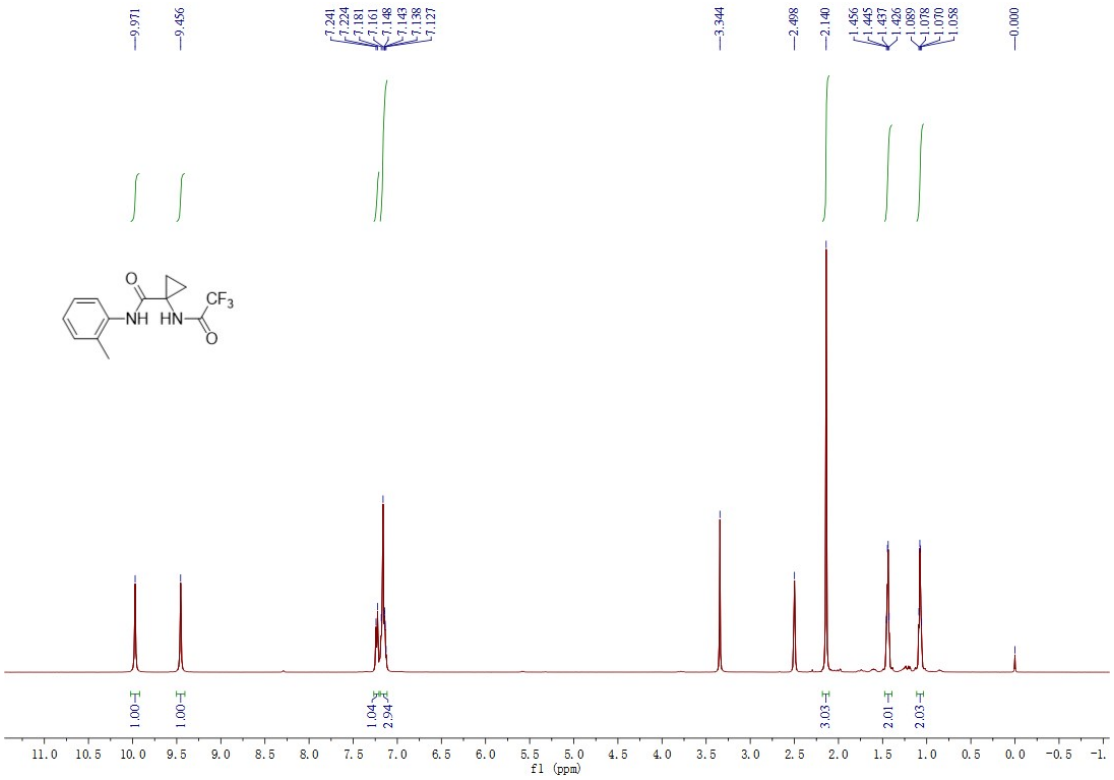
^{13}C NMR of product **1n** (DMSO-*d6*)



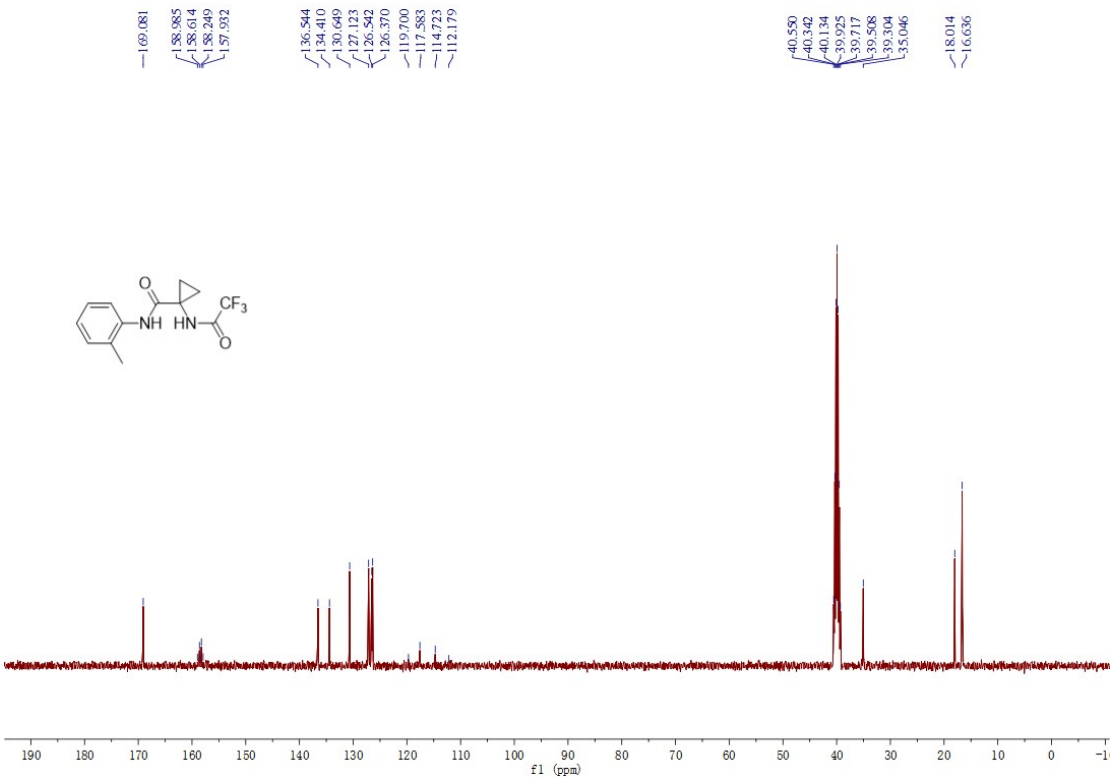
^{1}H NMR of product **1o** (DMSO-*d6*)



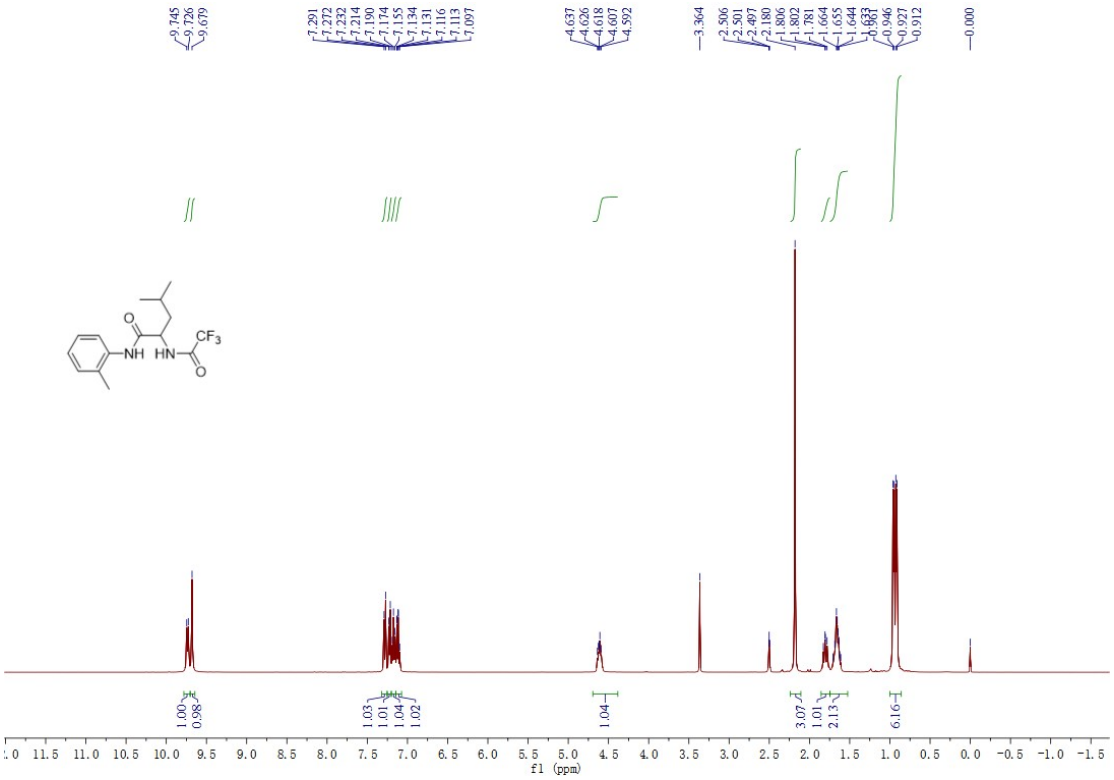
^{13}C NMR of product **1o** (DMSO-*d6*)



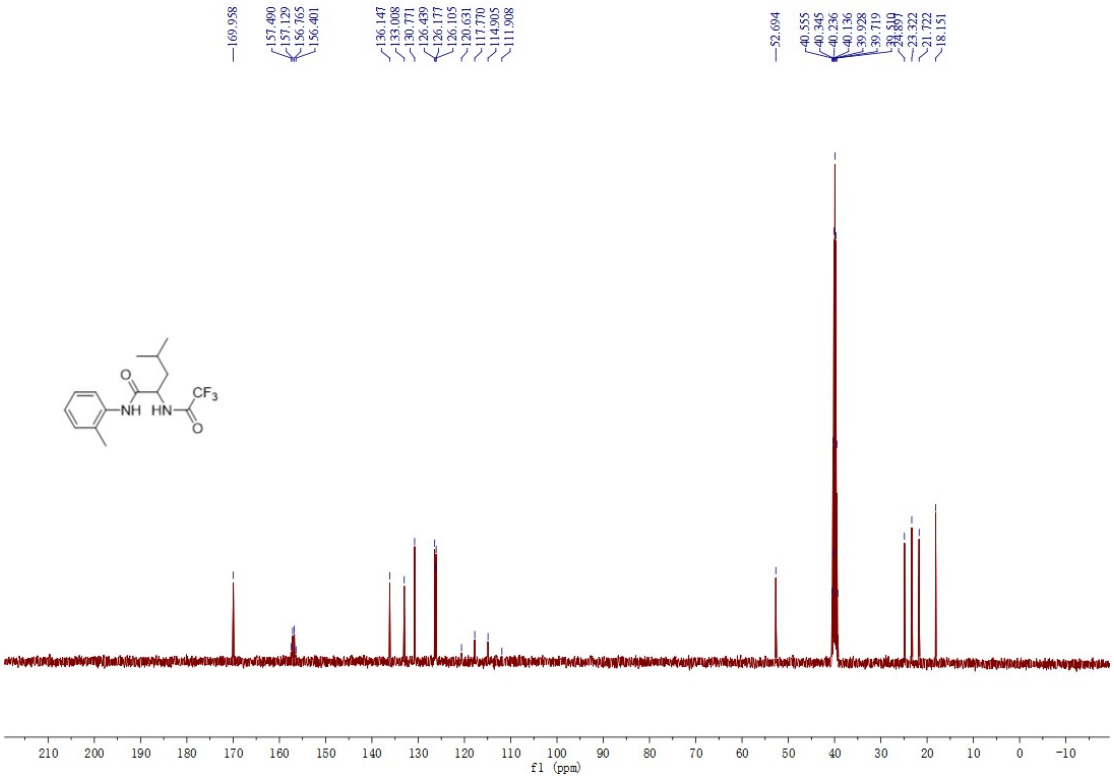
^{1}H NMR of product **1p** (DMSO-*d6*)



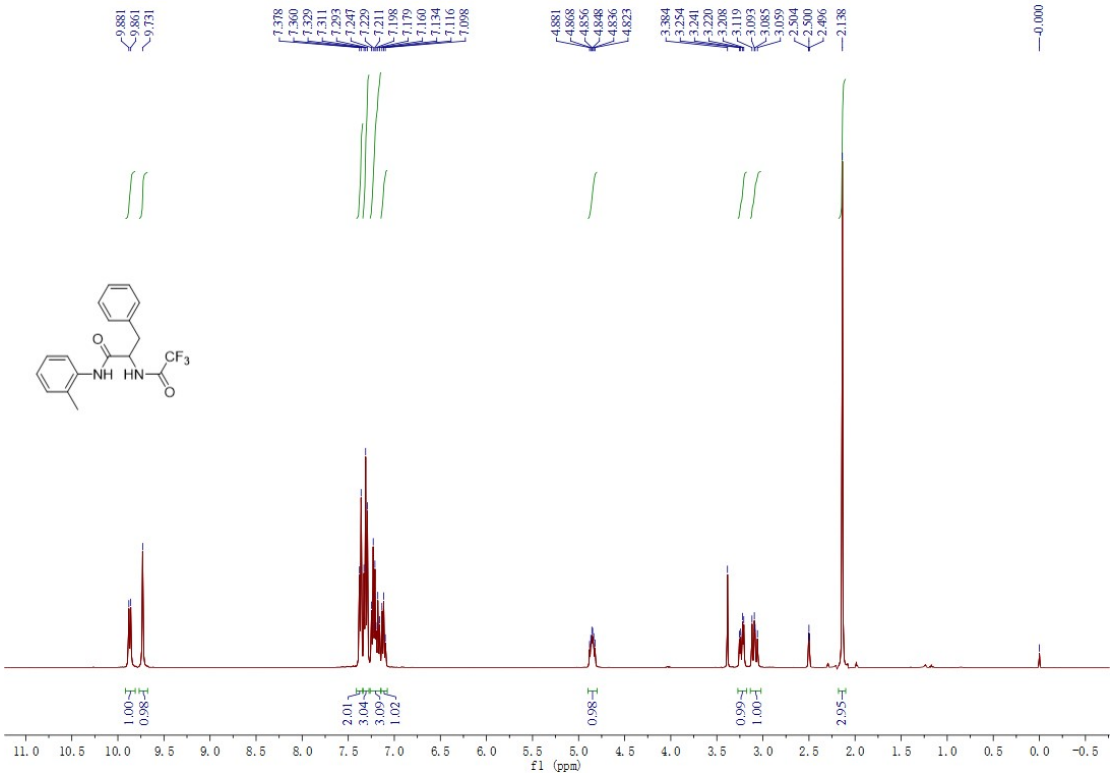
^{13}C NMR of product **1p** (DMSO-*d6*)



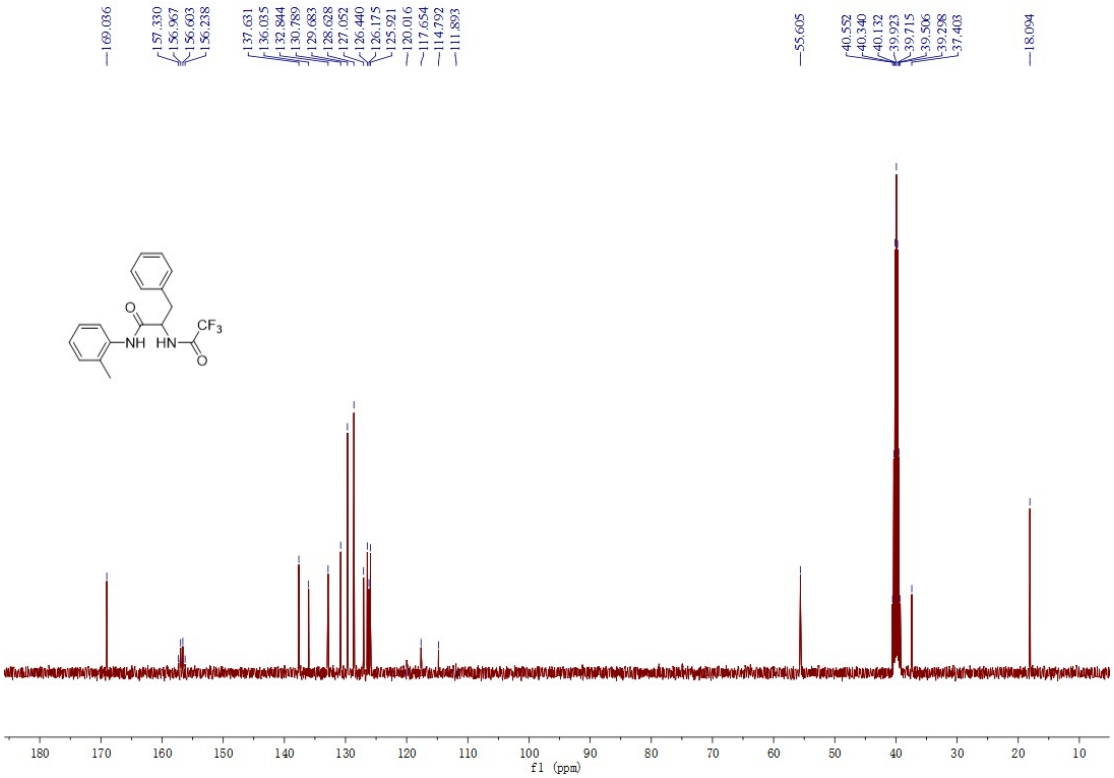
^{1}H NMR of product **1q** (DMSO-*d6*)



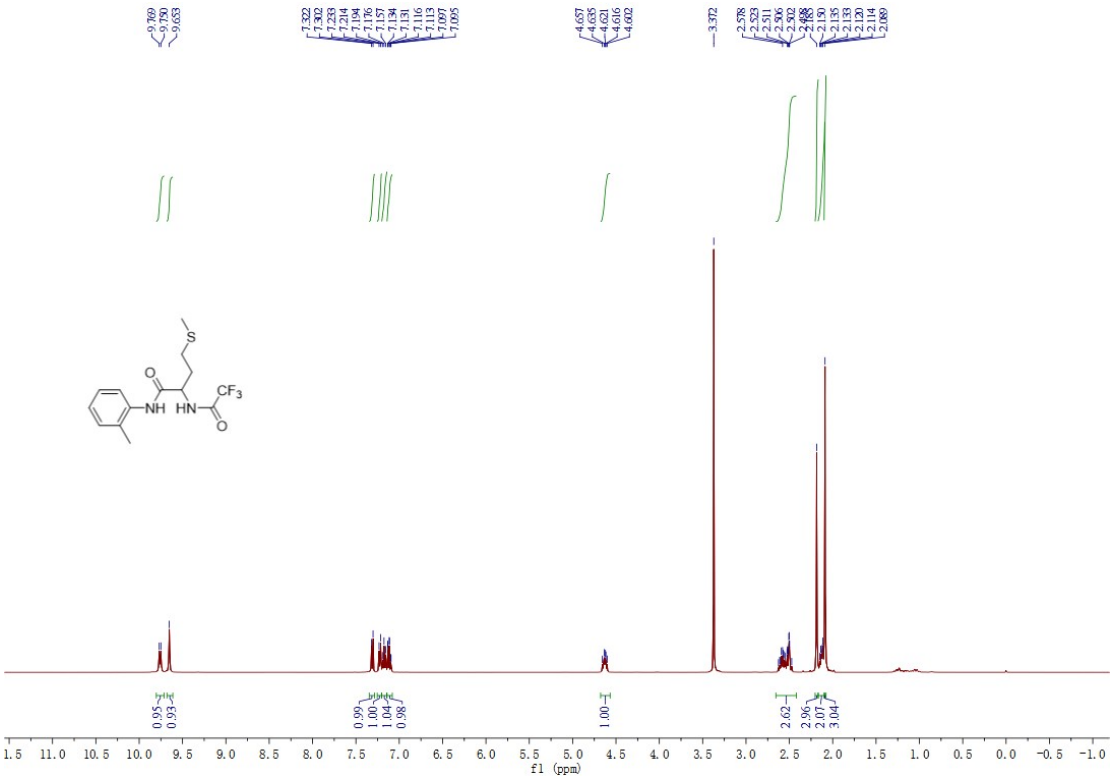
^{13}C NMR of product **1q** (DMSO-*d6*)



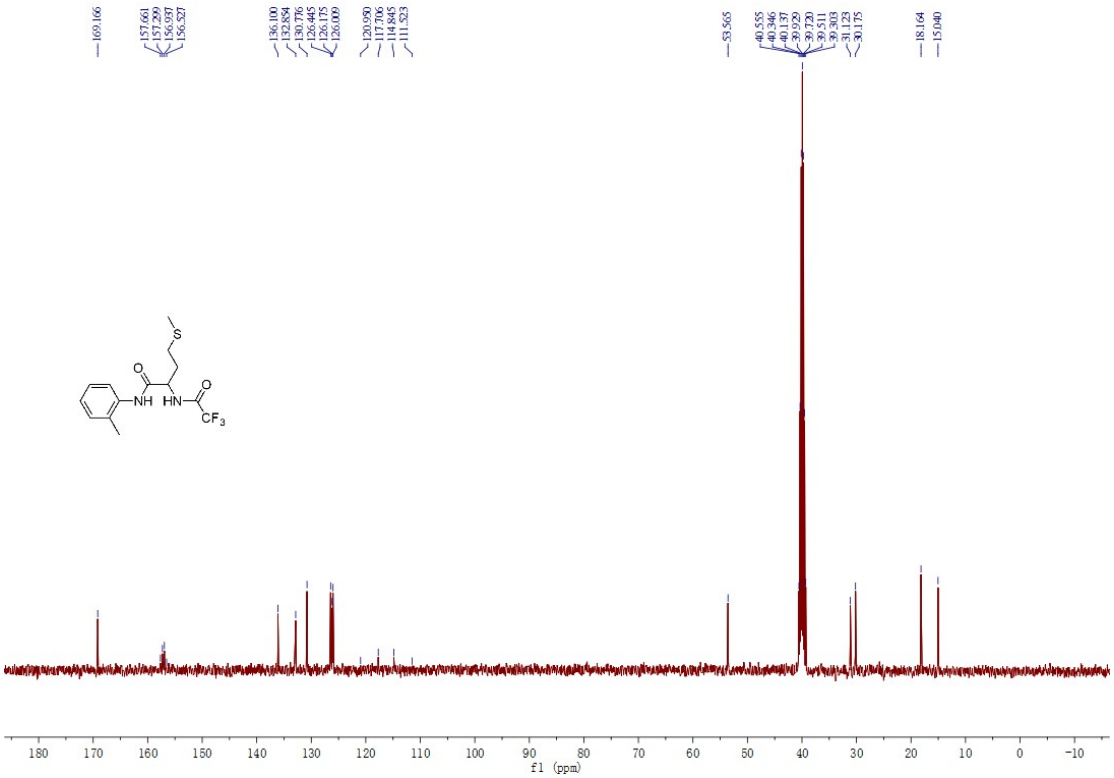
^{1}H NMR of product **1r** (DMSO-*d6*)



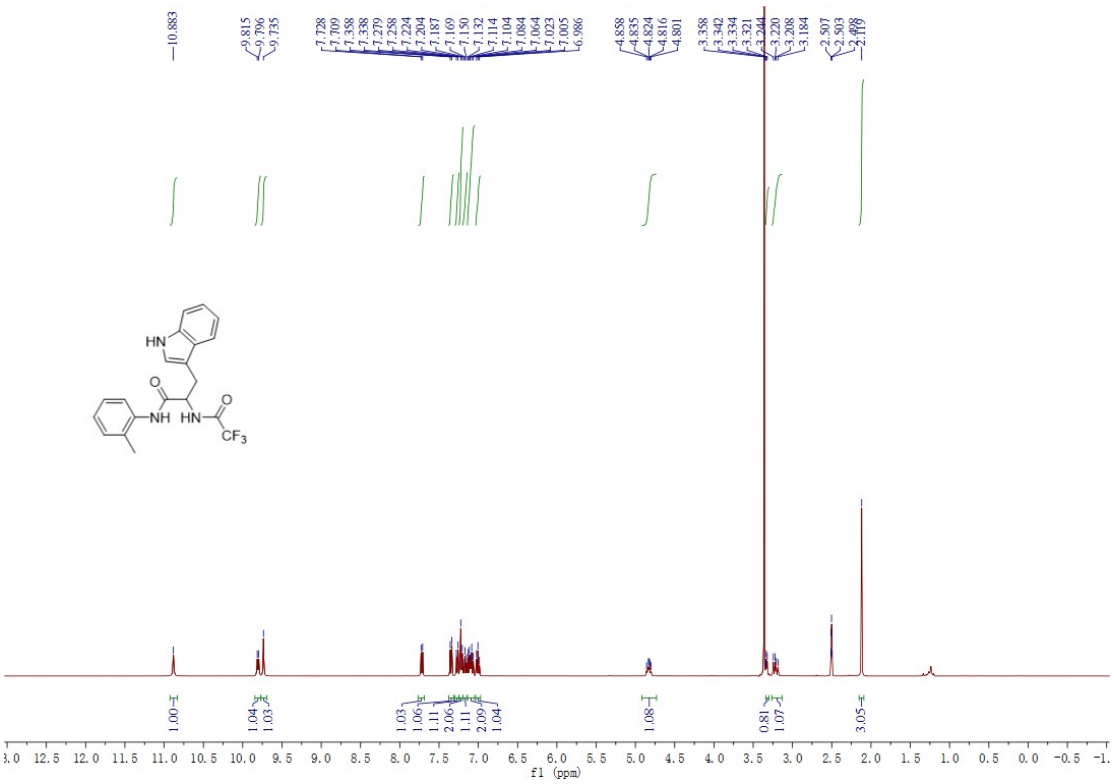
^{13}C NMR of product **1r** (DMSO-*d6*)



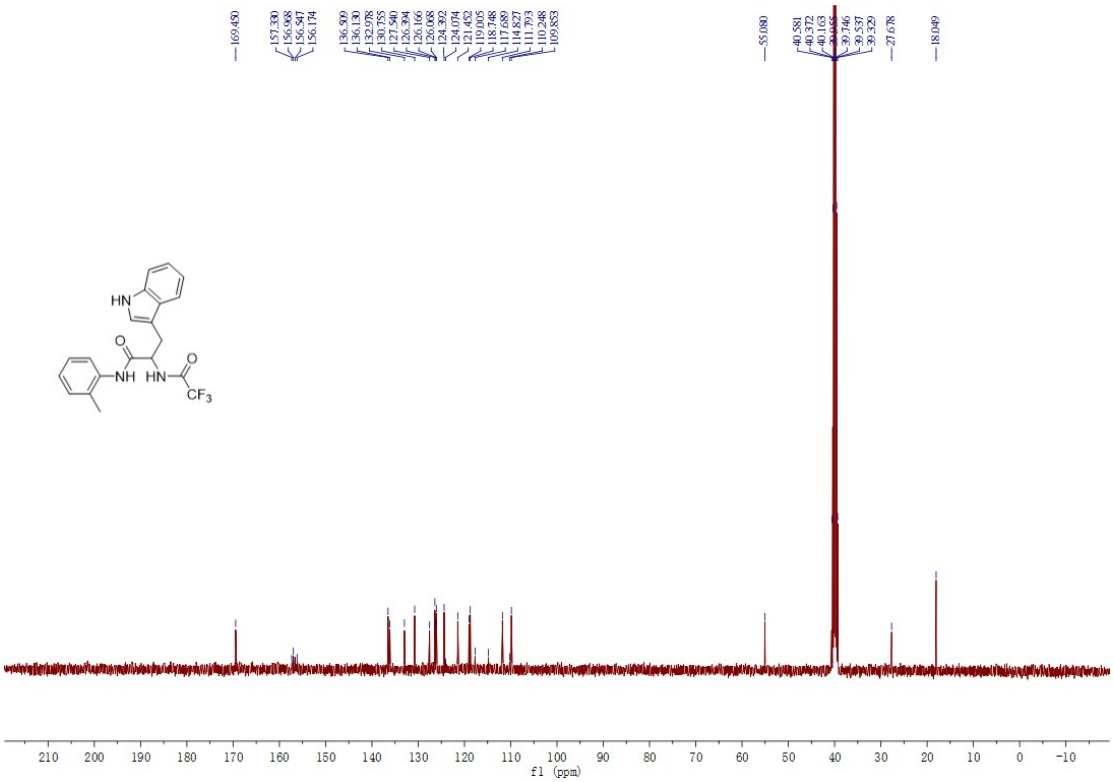
^{1}H NMR of product **1s** (DMSO-*d6*)



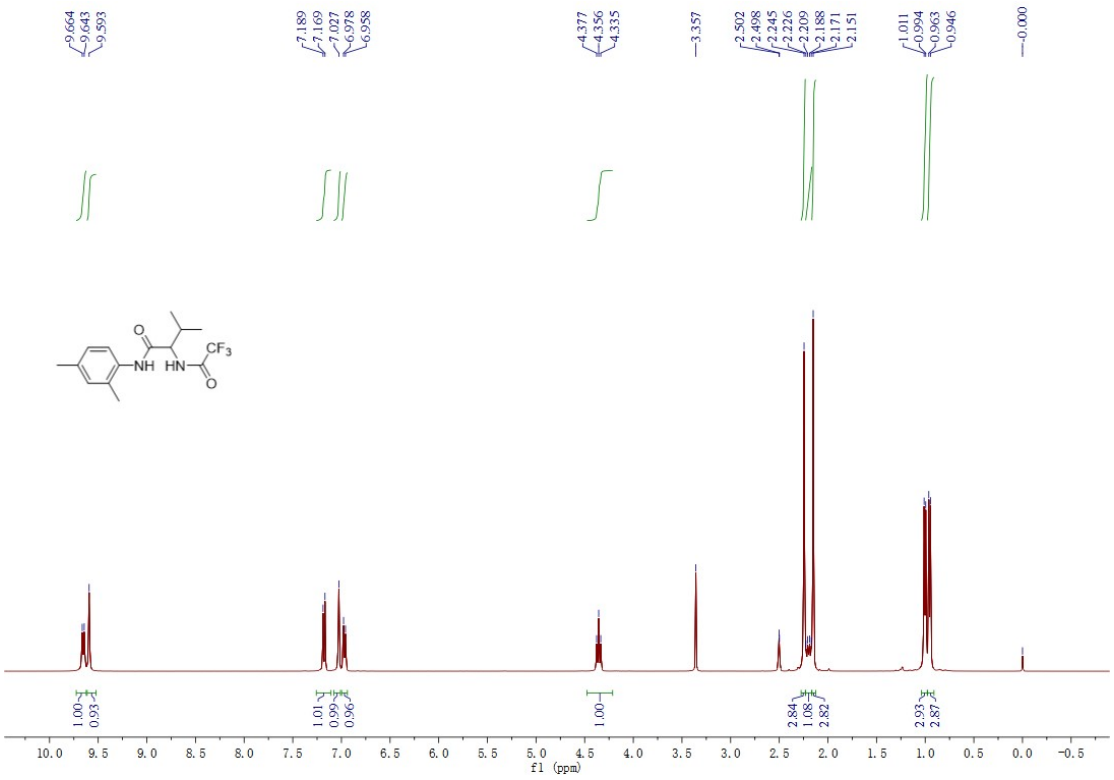
^{13}C NMR of product **1s** (DMSO-*d6*)



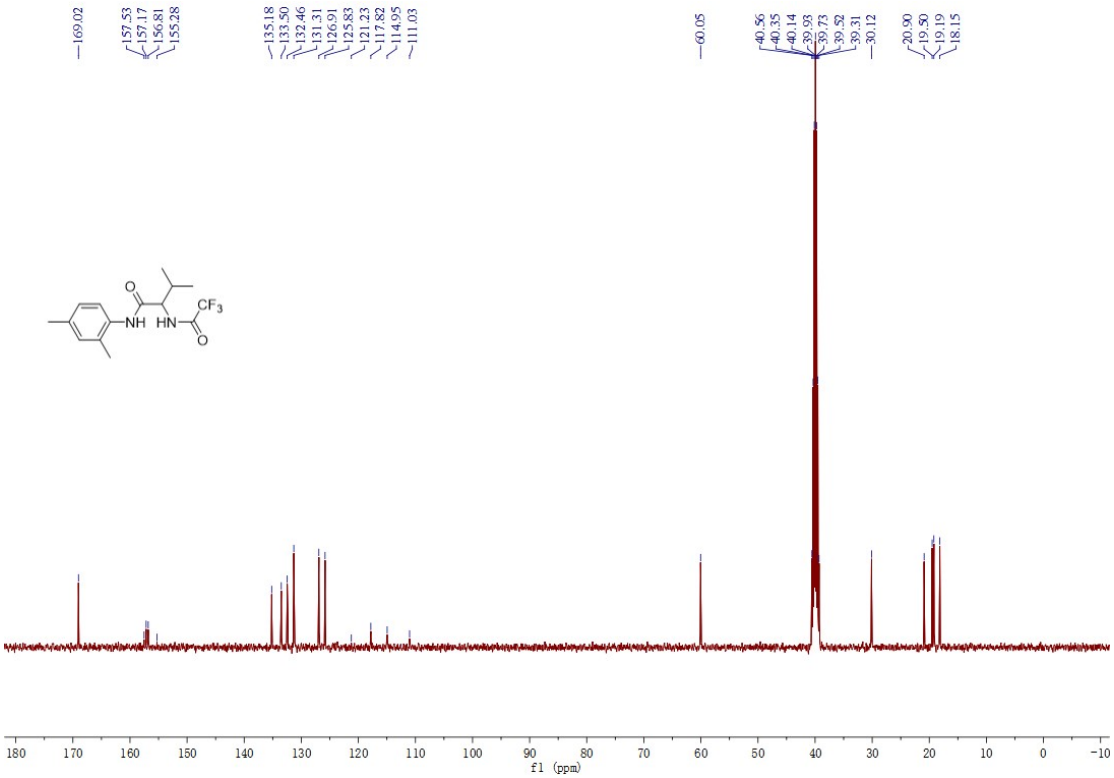
^{1}H NMR of product **1t** (DMSO-*d6*)



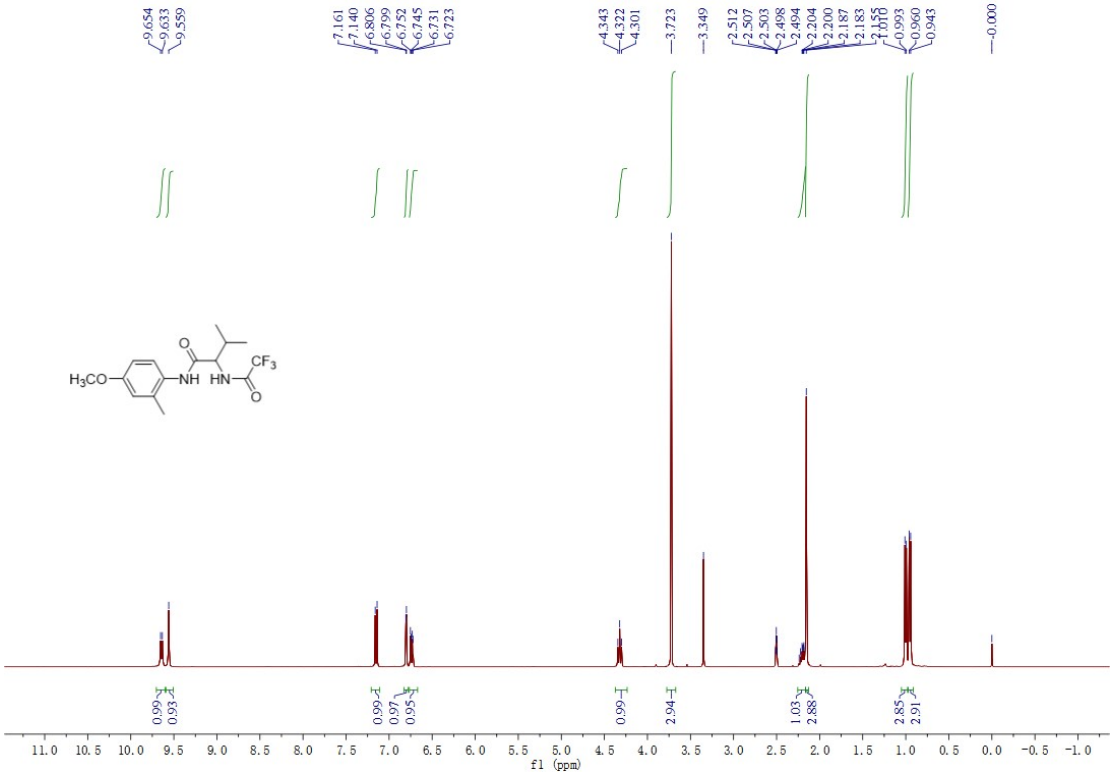
^{13}C NMR of product **1t** (DMSO-*d6*)



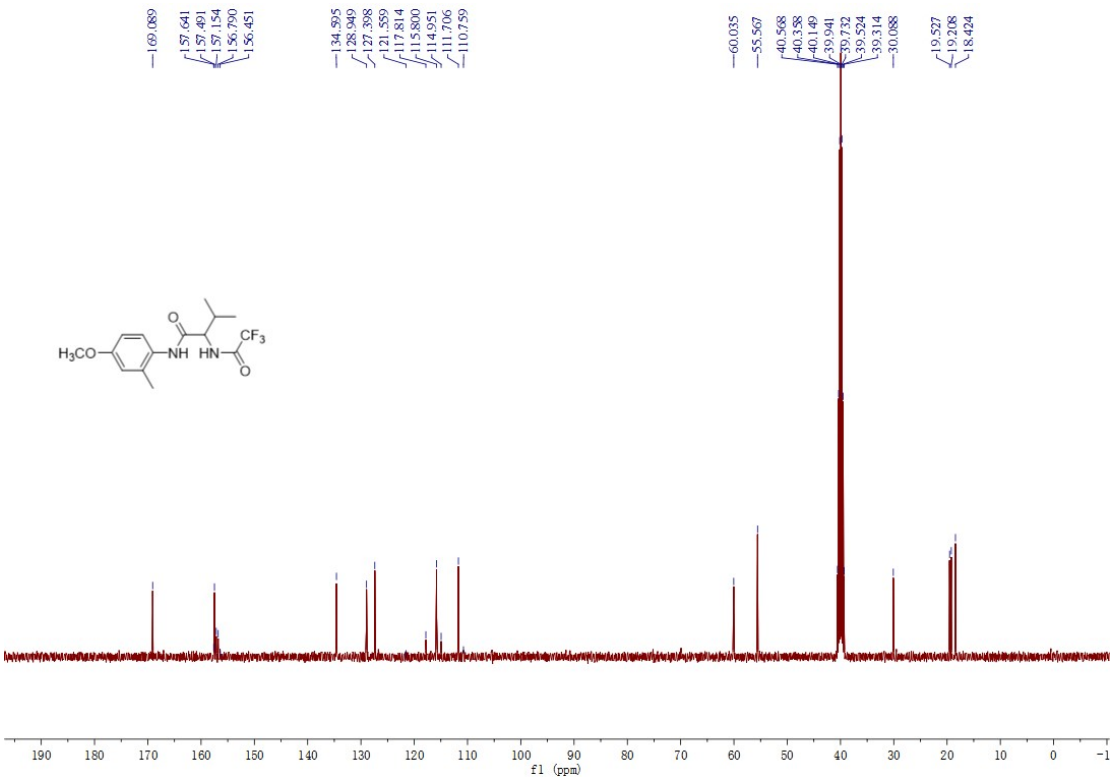
^{1}H NMR of product **1u** (DMSO-*d6*)



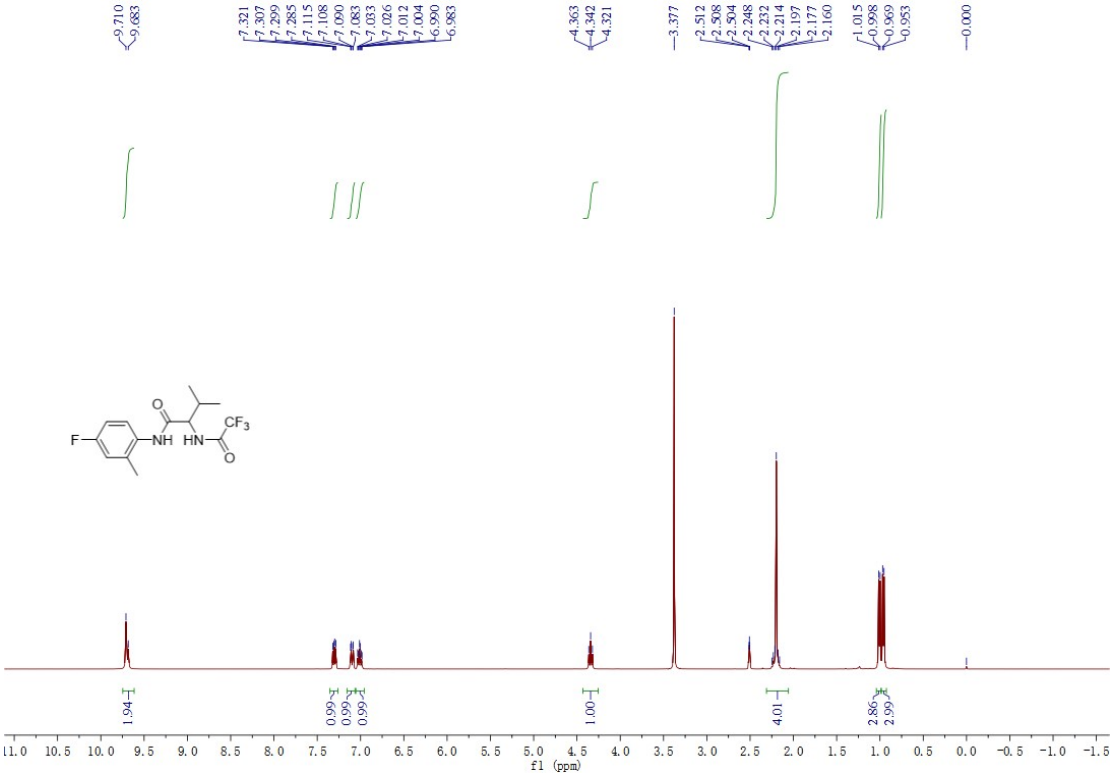
^{13}C NMR of product **1u** (DMSO-*d6*)



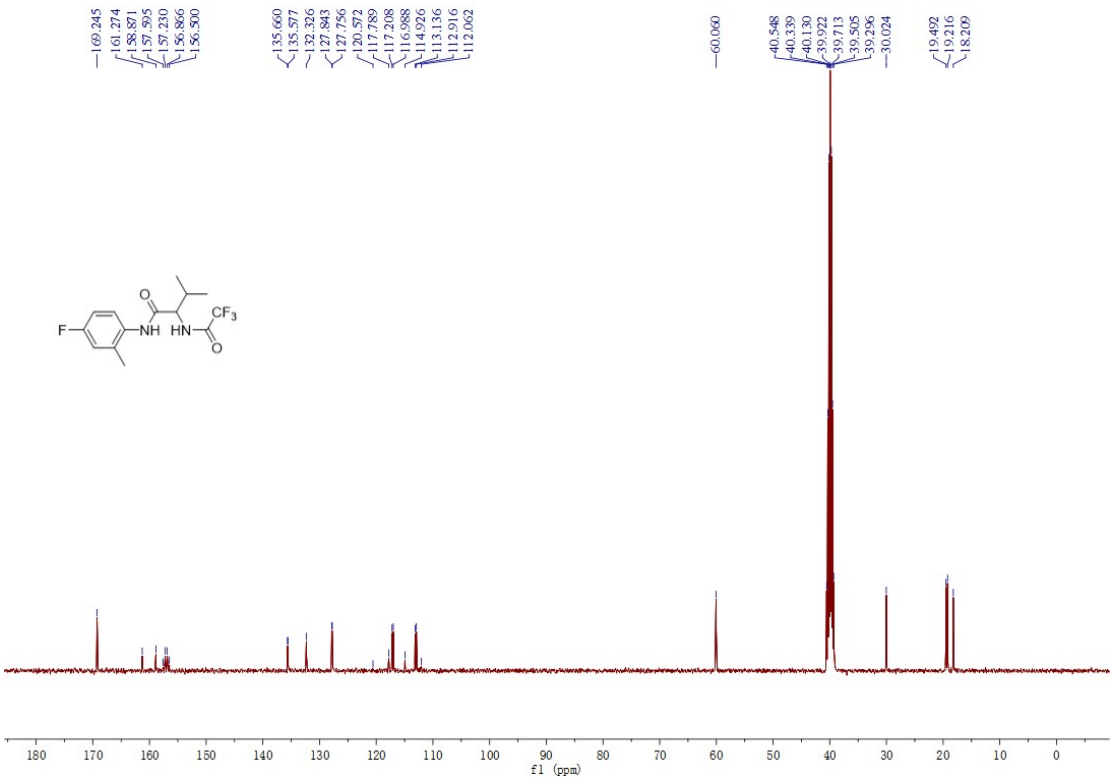
^{1}H NMR of product **1v** (DMSO-*d6*)



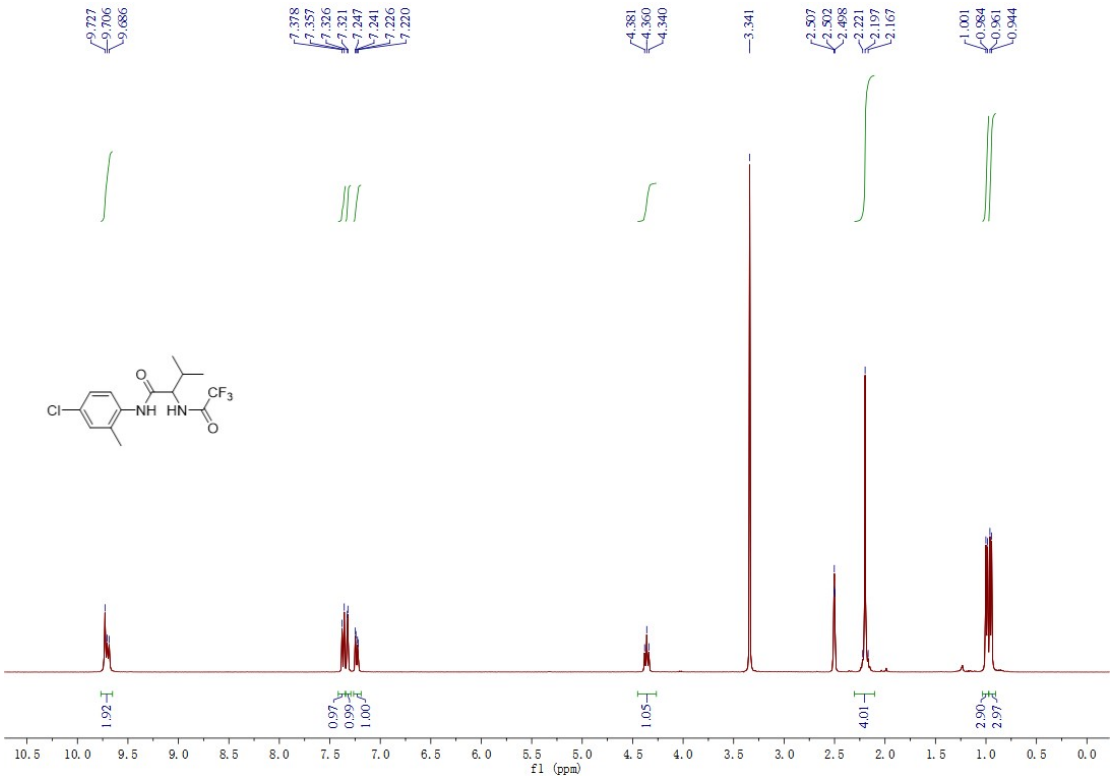
^{13}C NMR of product **1v** (DMSO-*d6*)



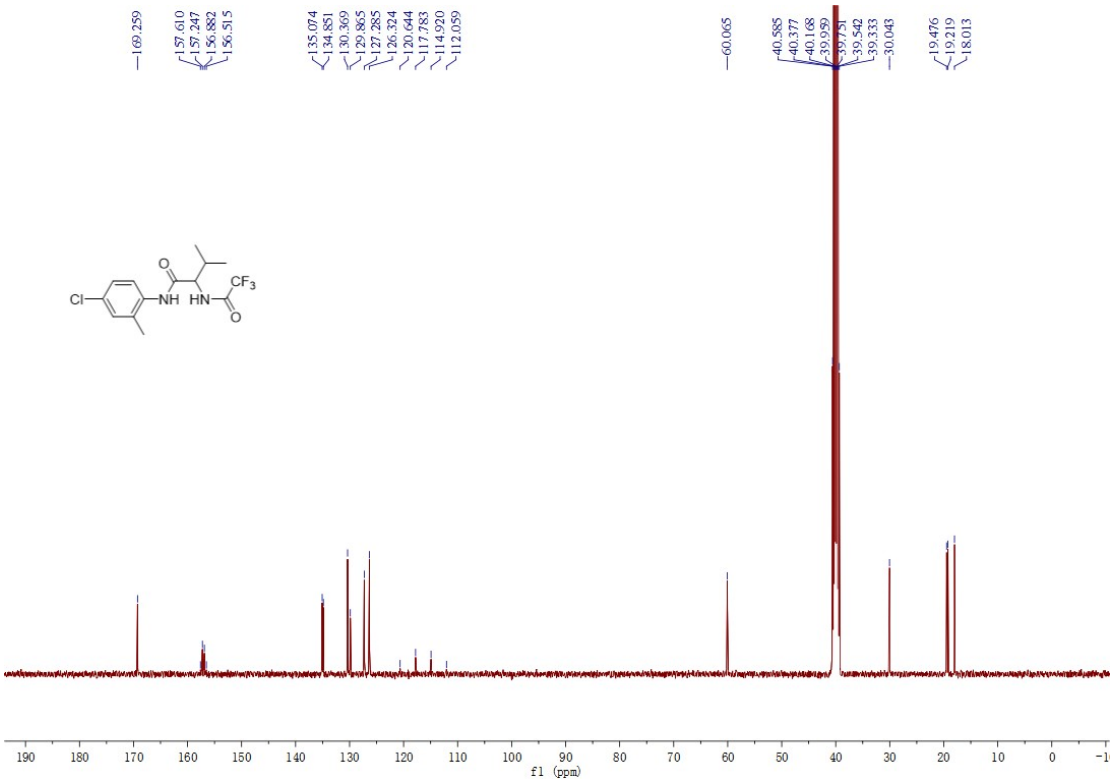
^{1}H NMR of product **1w** (DMSO-*d6*)



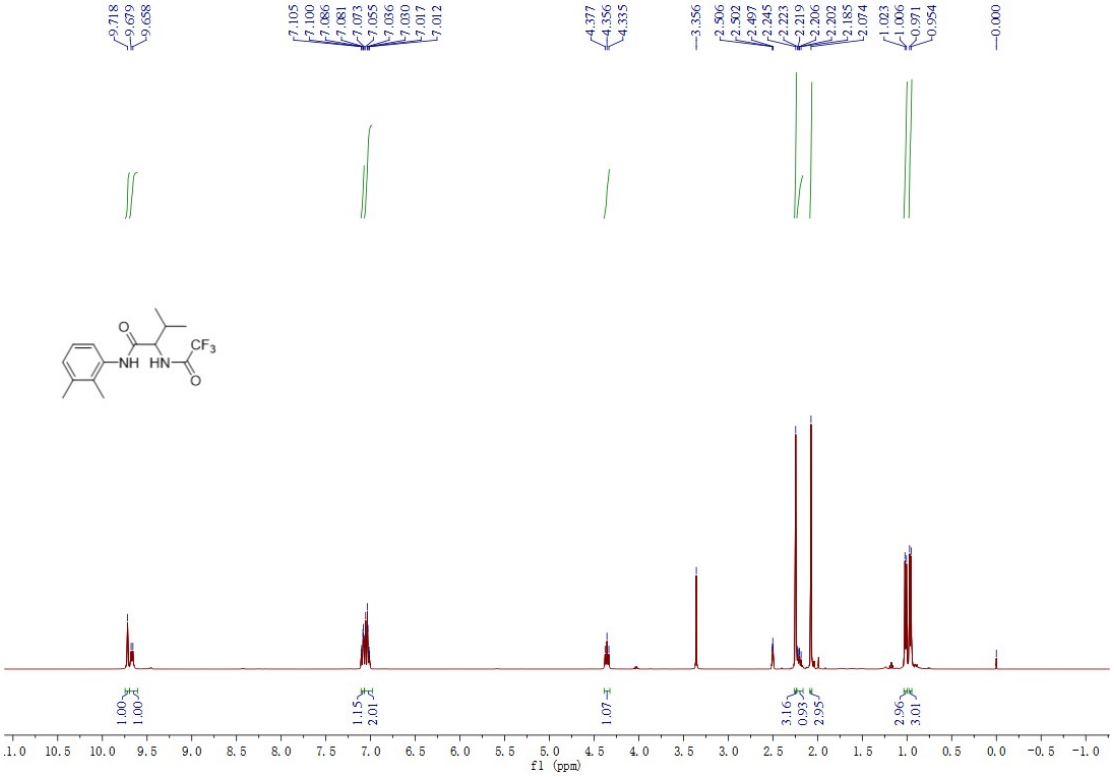
^{13}C NMR of product **1w** (DMSO-*d6*)



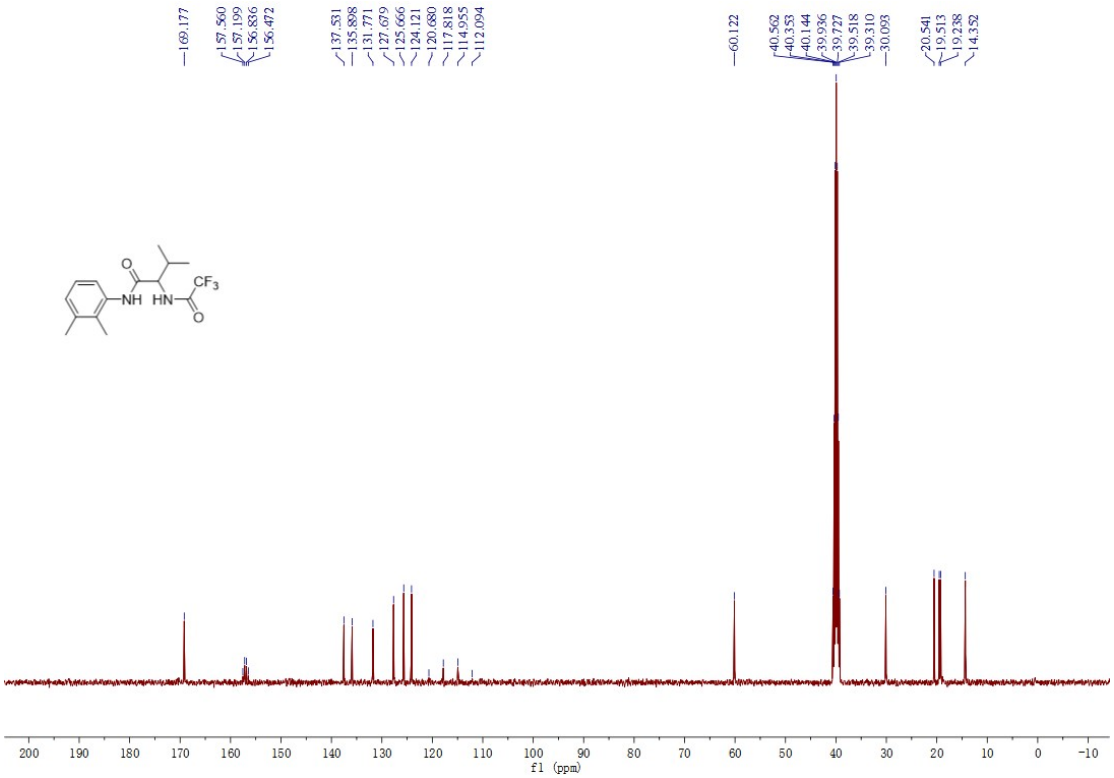
^{1}H NMR of product **1x** (DMSO-*d6*)



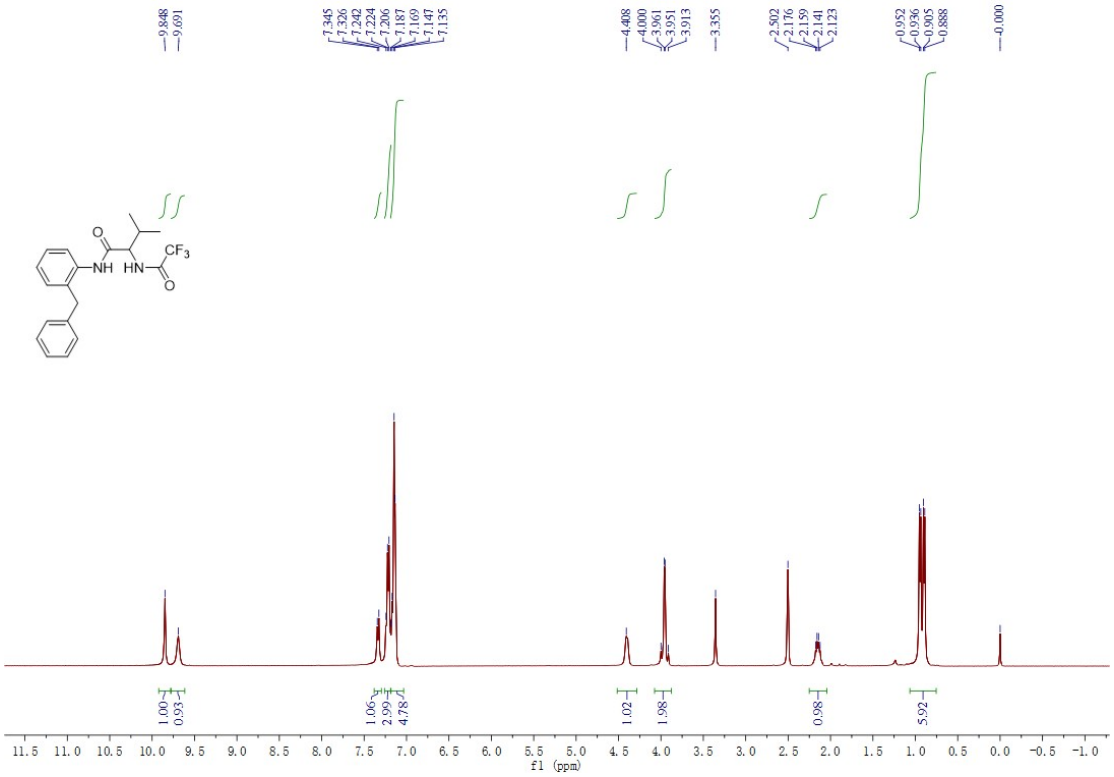
^{13}C NMR of product **1x** (DMSO-*d6*)



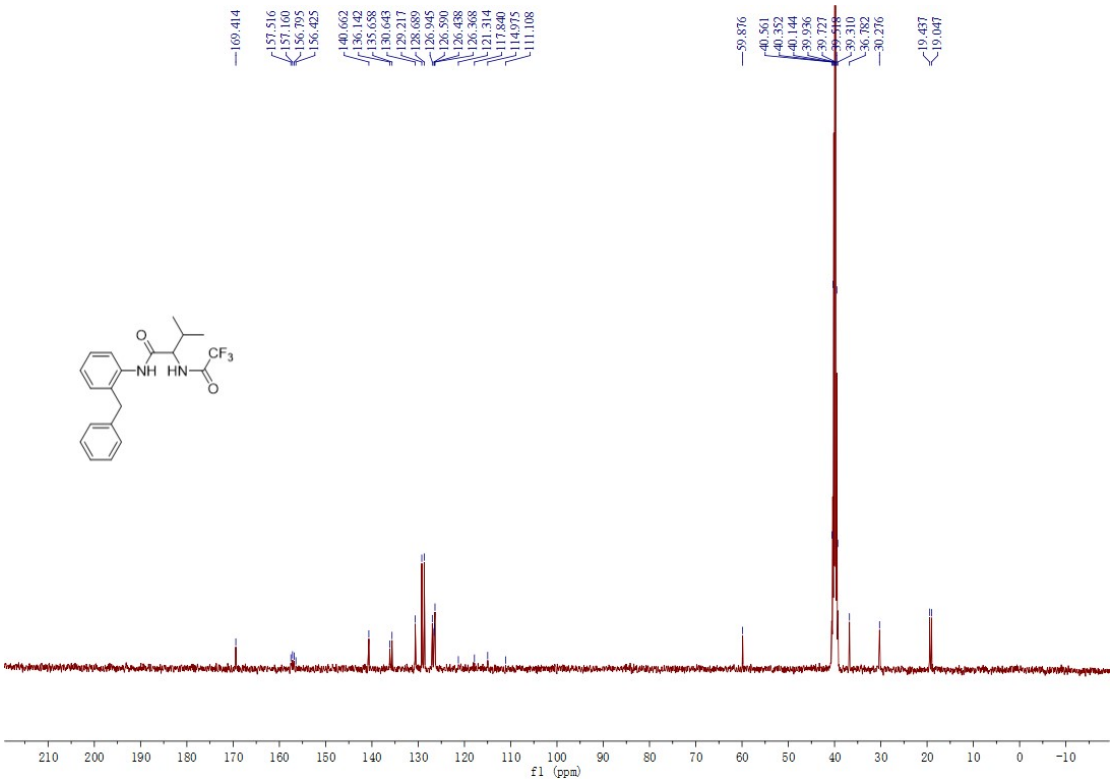
^{1}H NMR of product **1y** (DMSO-*d6*)



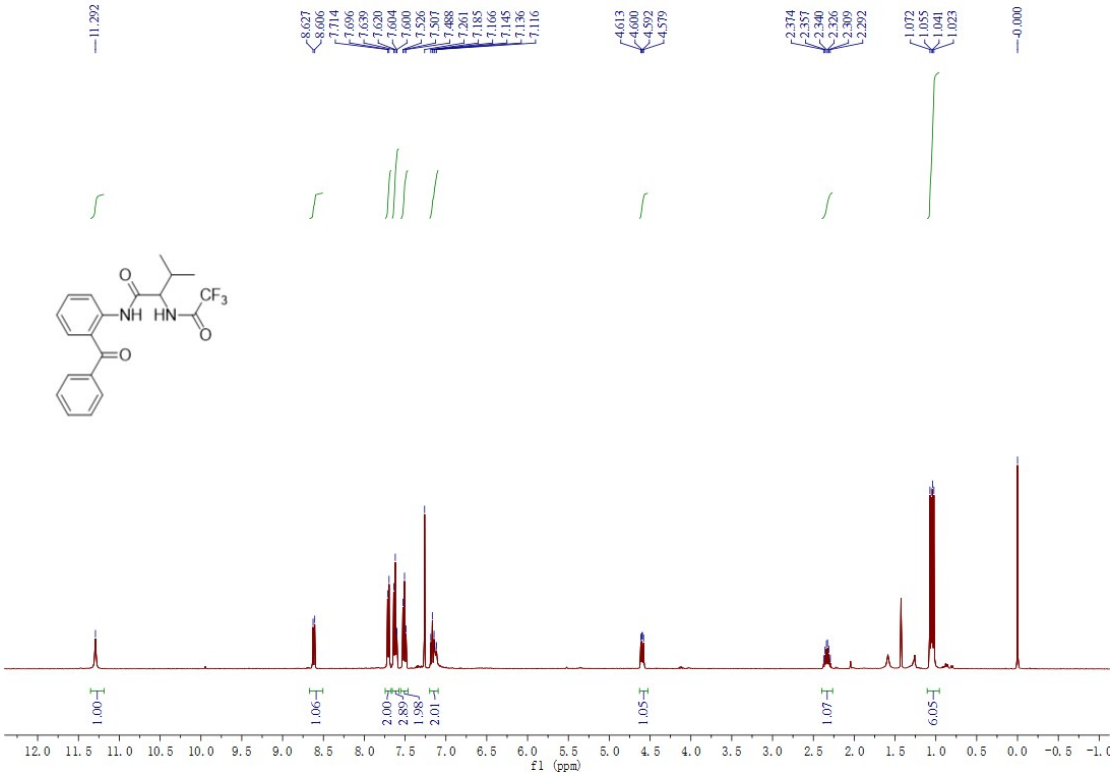
^{13}C NMR of product **1y** (DMSO-*d6*)



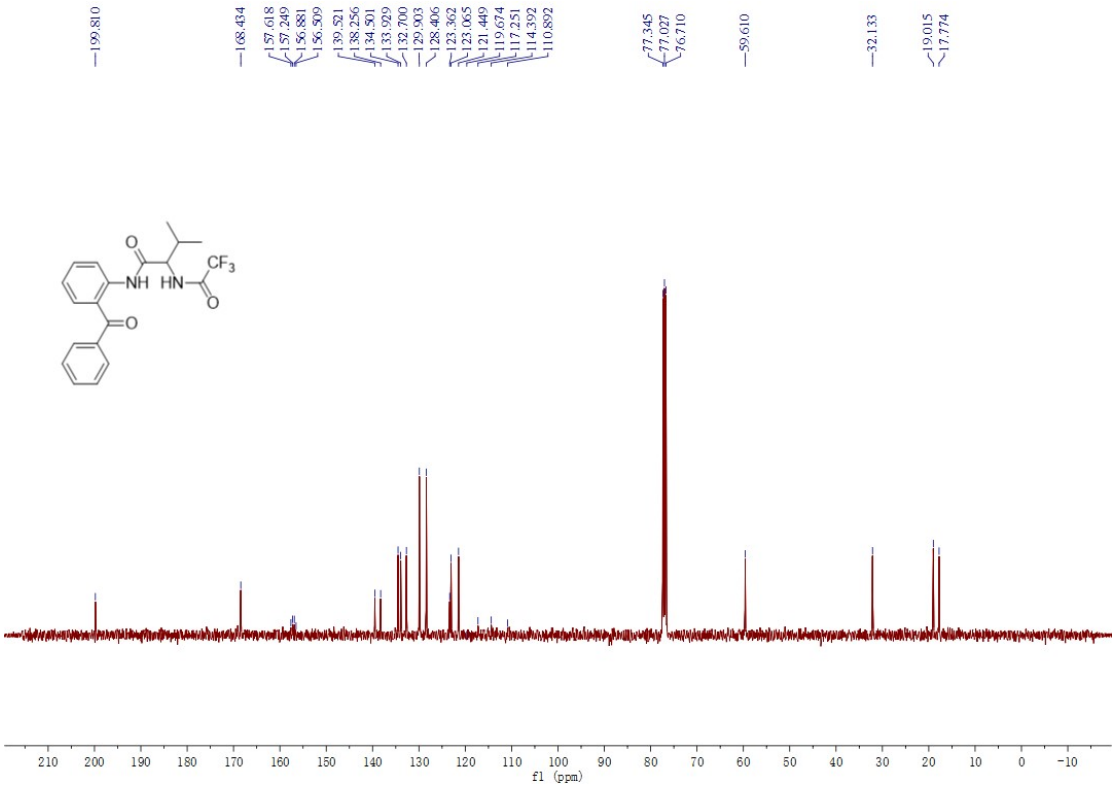
^{1}H NMR of product **1z** (DMSO-*d6*)



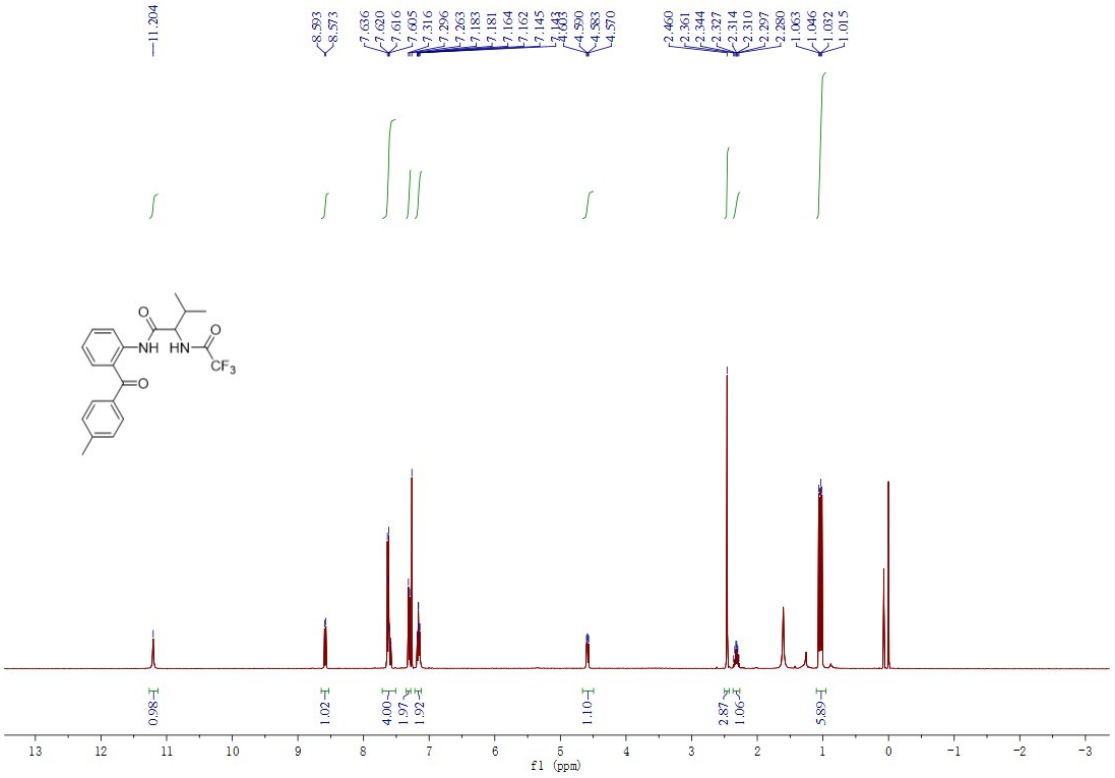
^{13}C NMR of product **1z** (DMSO-*d6*)



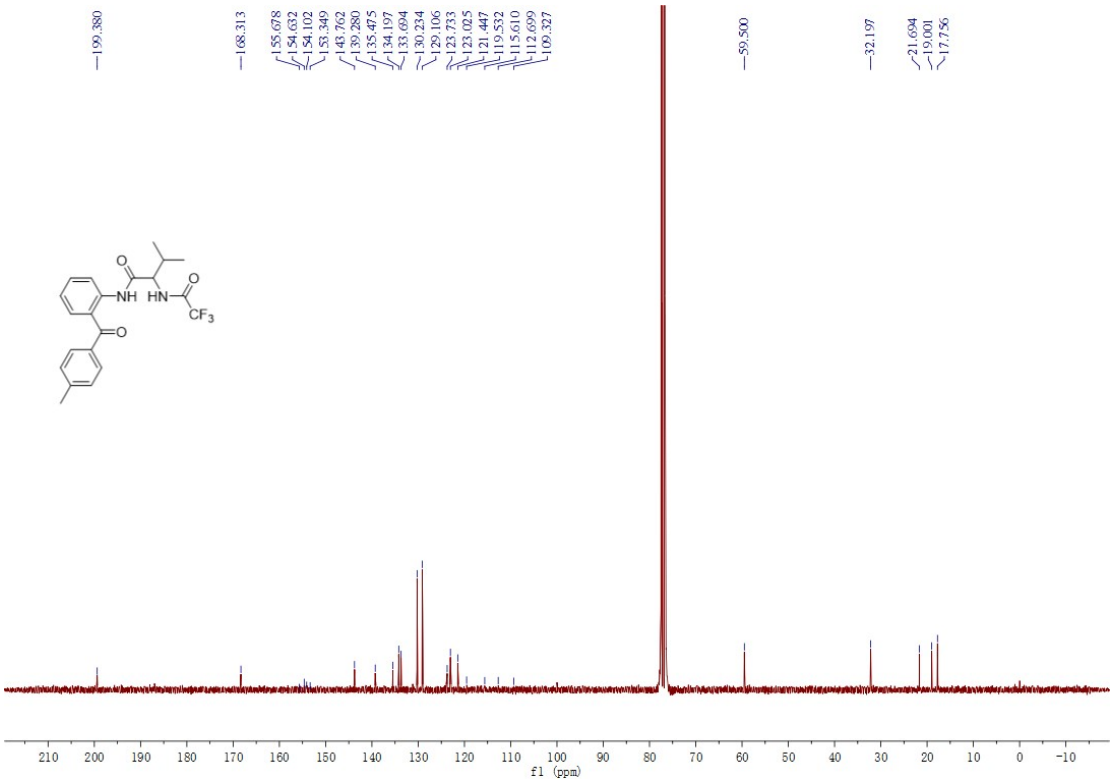
^{1}H NMR of product **3a** ($CDCl_3$)



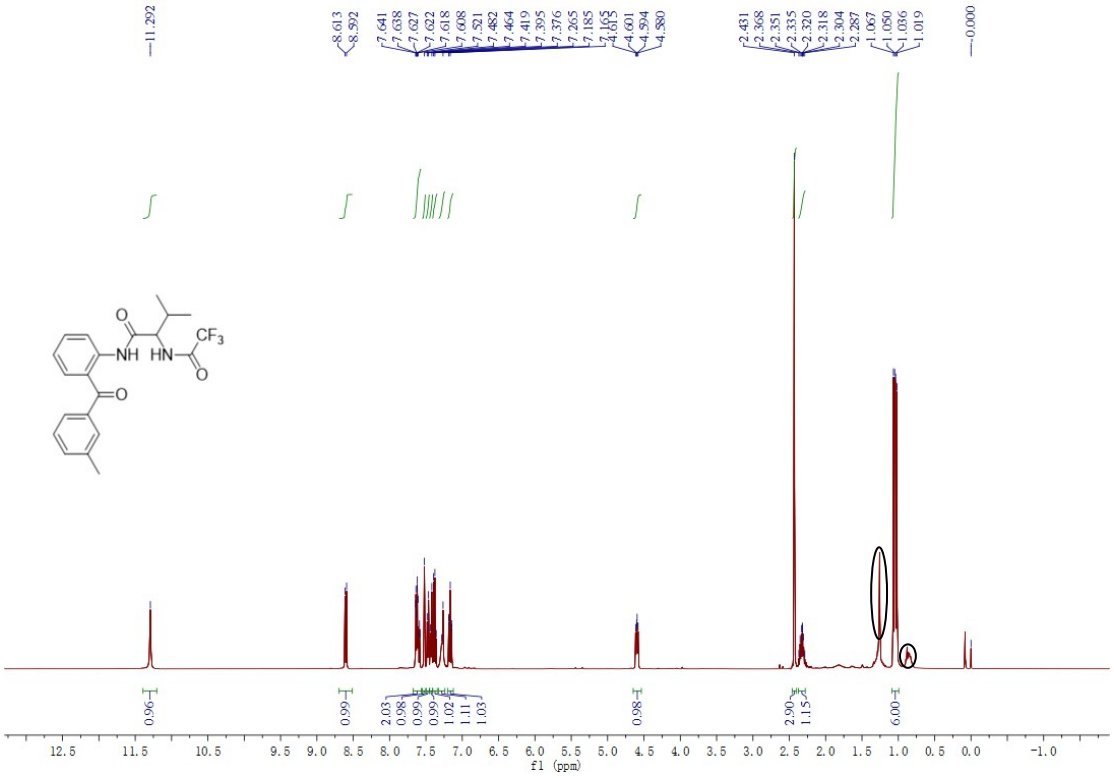
^{13}C NMR of product **3a** ($CDCl_3$)



^{1}H NMR of product **3b** ($CDCl_3$)

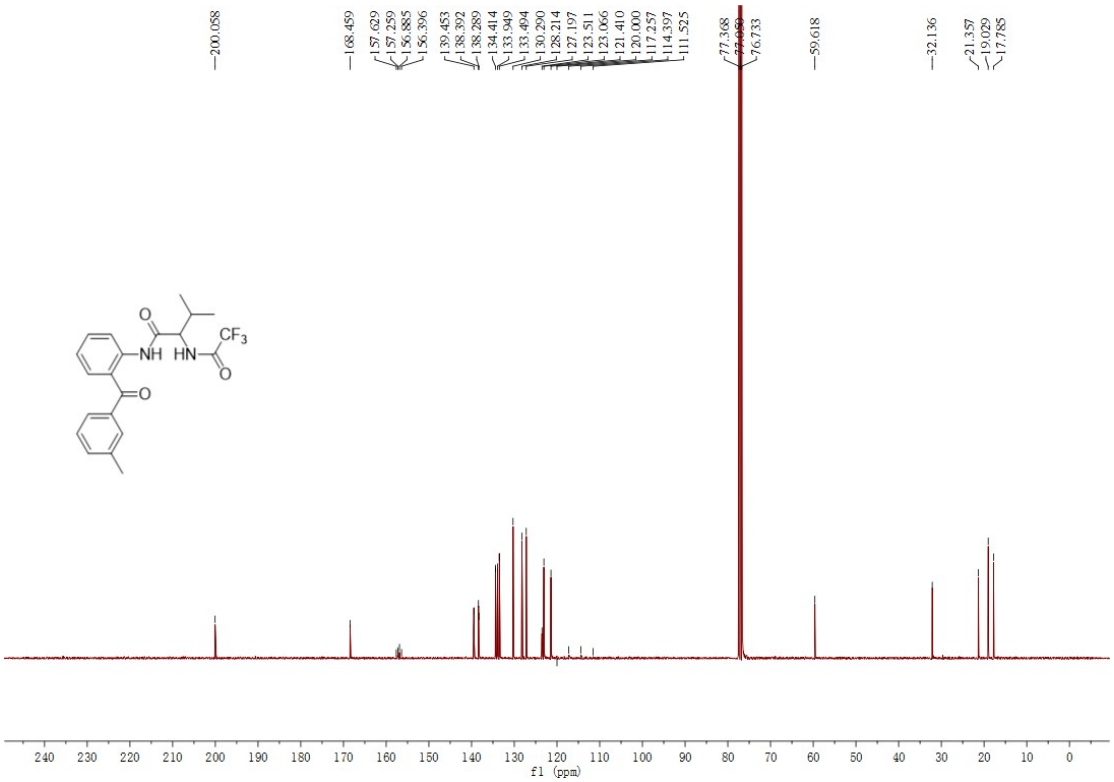


^{13}C NMR of product **3b** ($CDCl_3$)

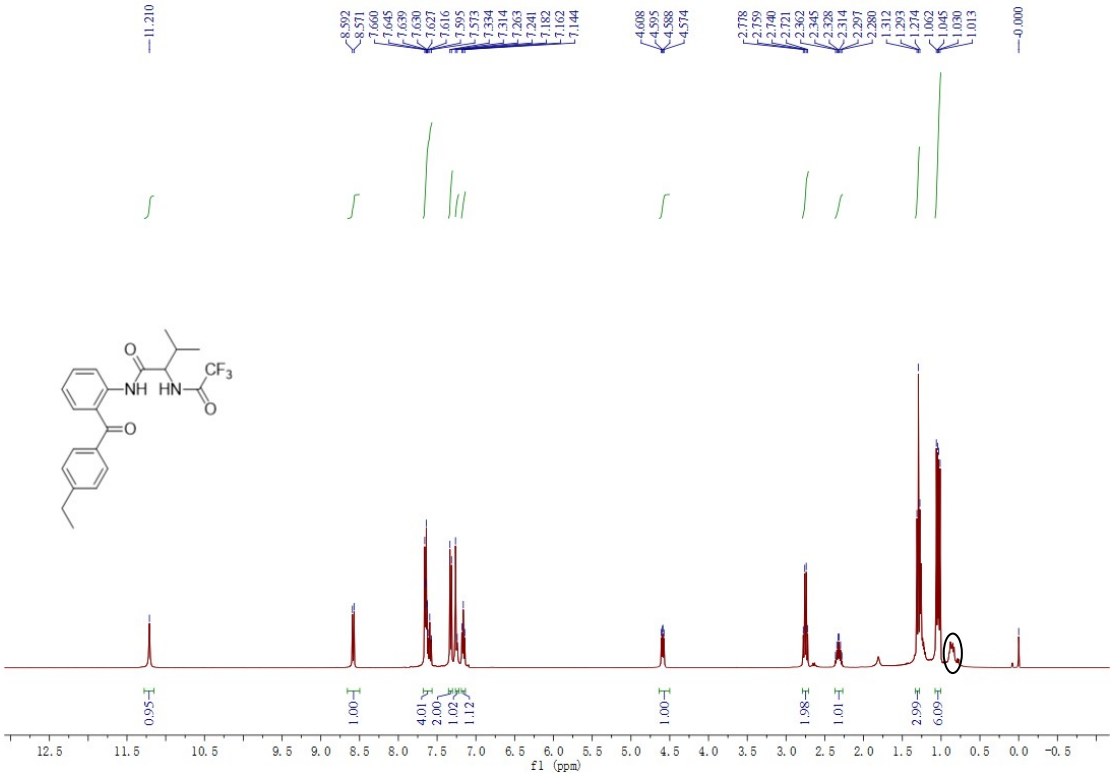


^{1}H NMR of product **3c** ($CDCl_3$)

The peak in black oval is the signal of grease.

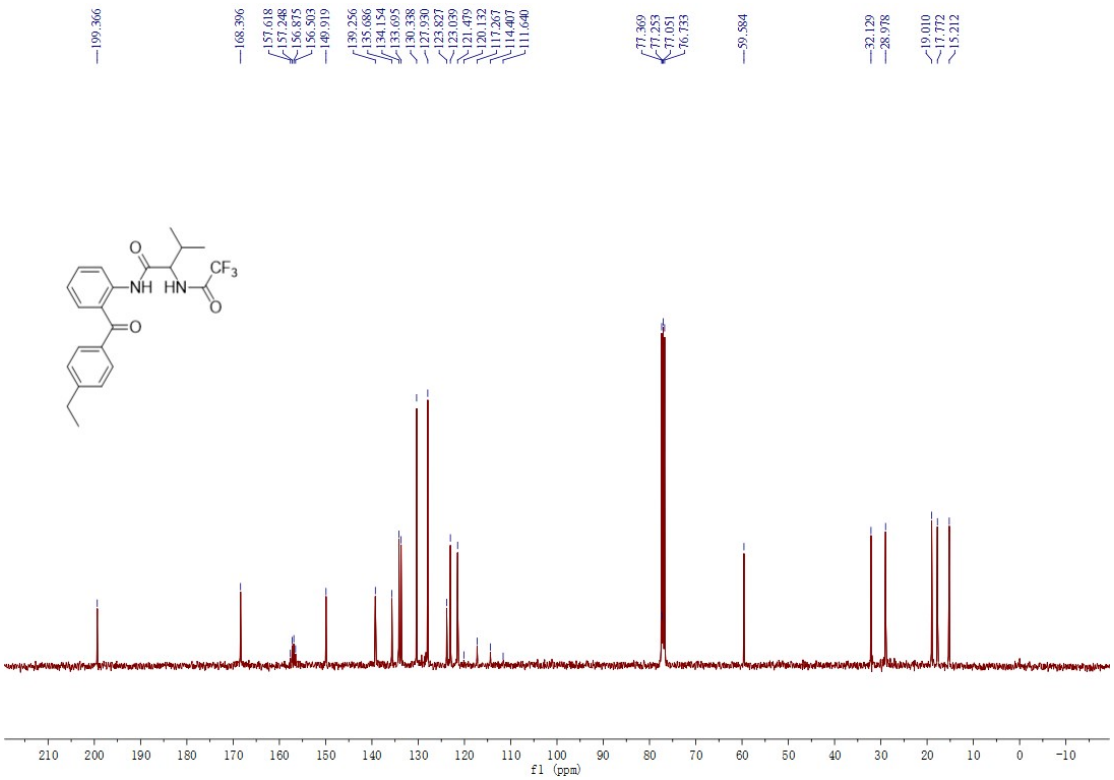


^{13}C NMR of product **3c** ($CDCl_3$)

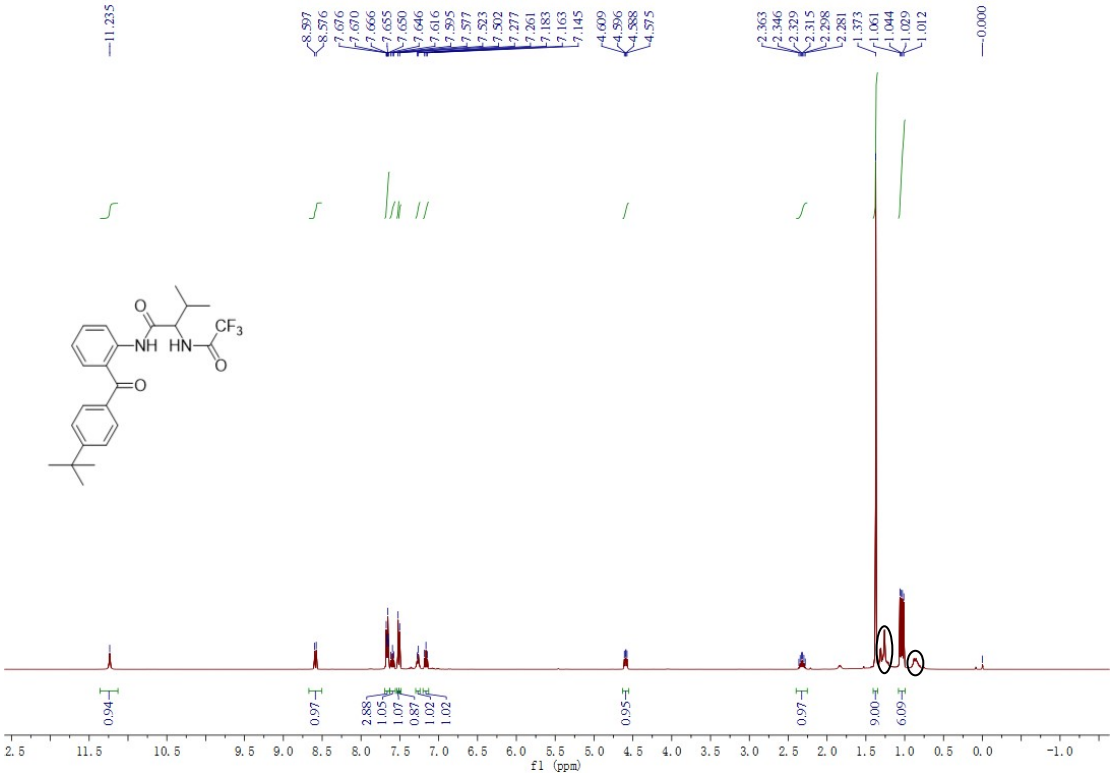


^{1}H NMR of product **3e** ($CDCl_3$)

The peak in black oval is the signal of grease.

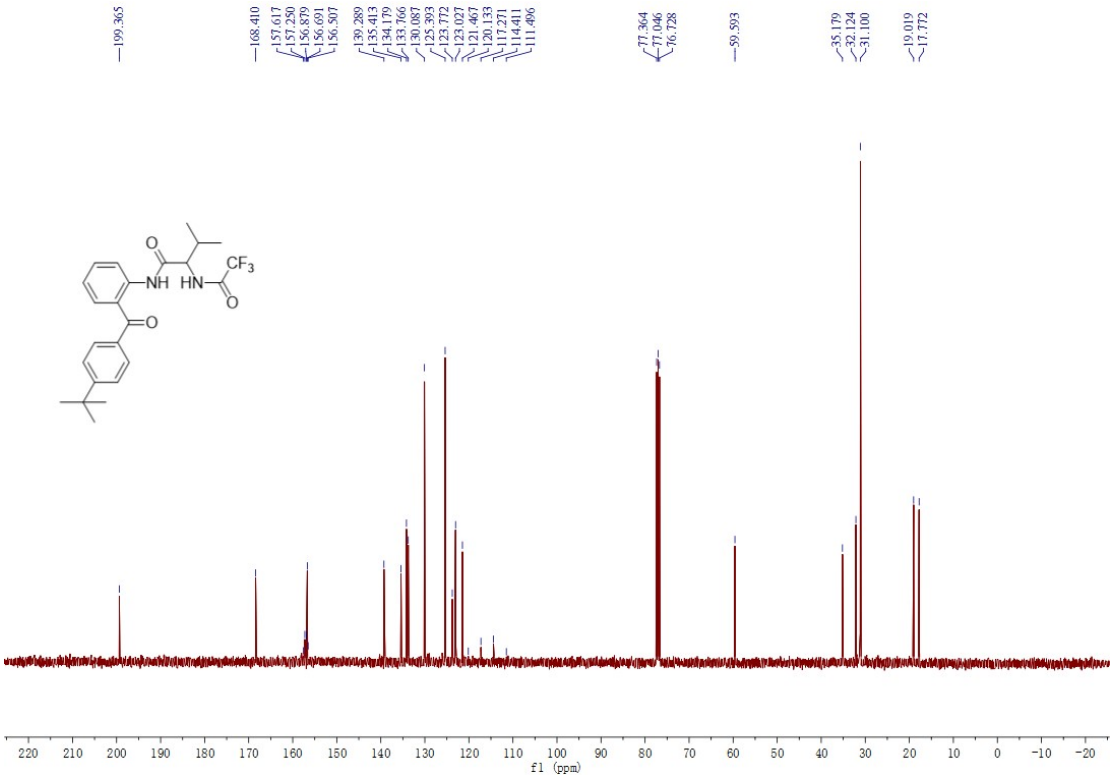


^{13}C NMR of product **3e** ($CDCl_3$)

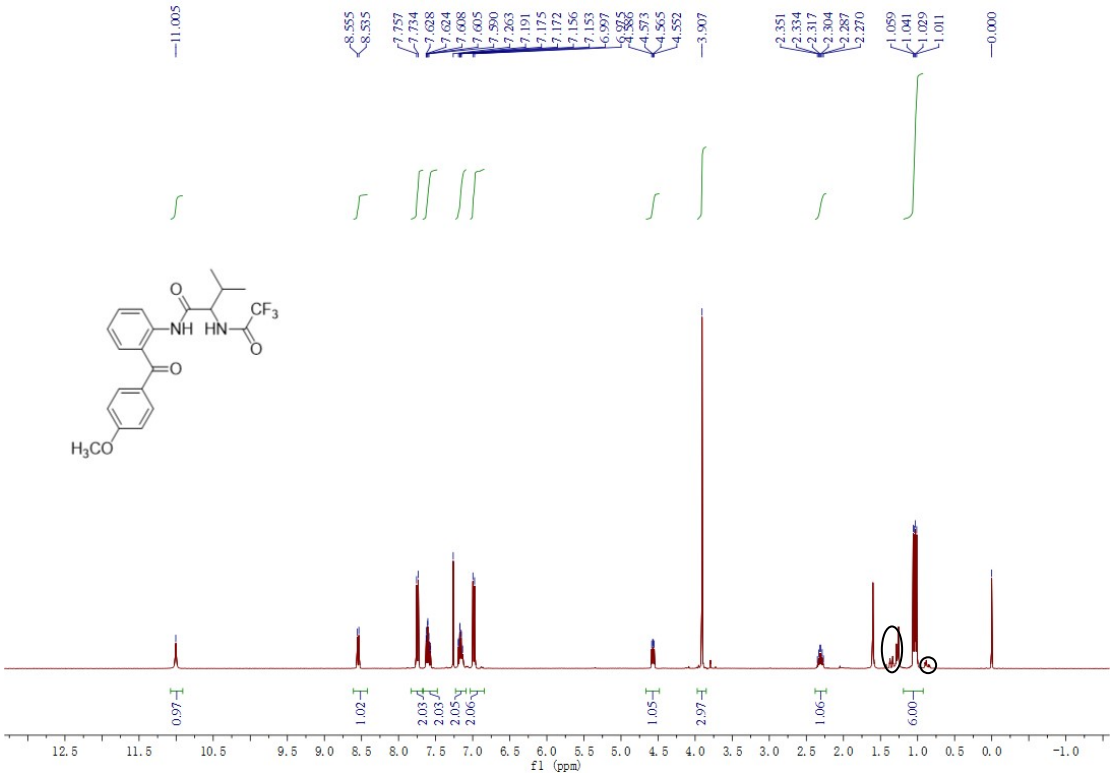


^{1}H NMR of product **3f** ($CDCl_3$)

The peak in black oval is the signal of grease.

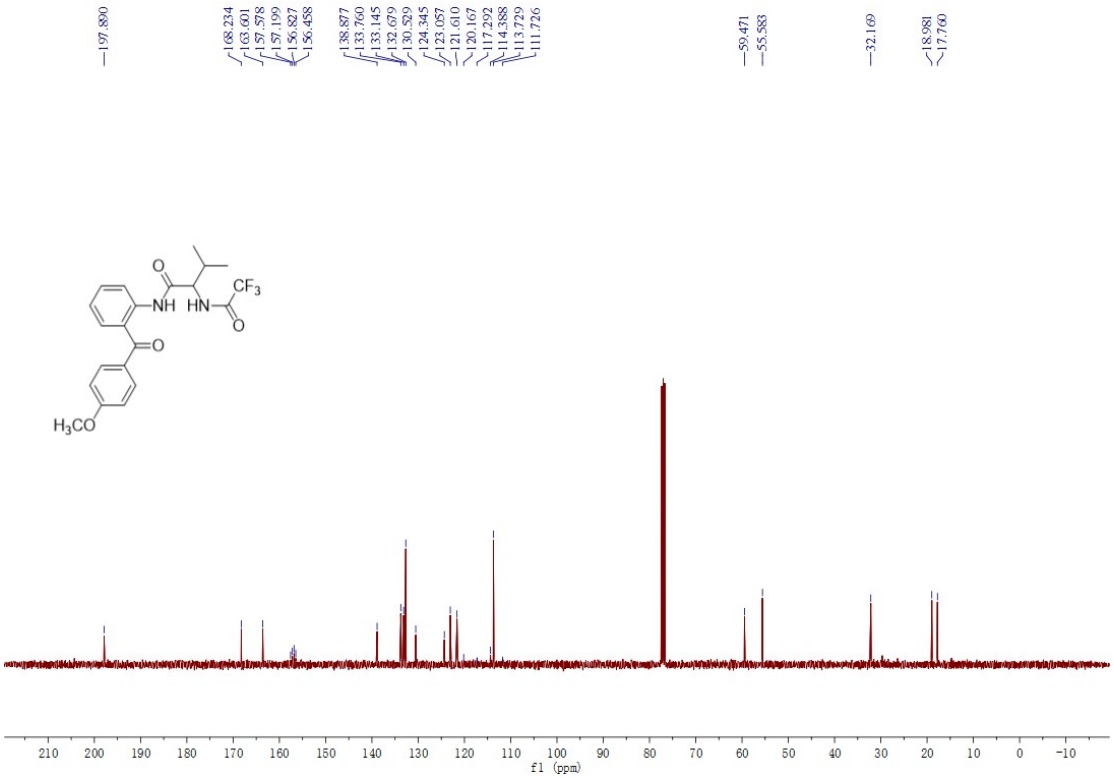


^{13}C NMR of product **3f** ($CDCl_3$)

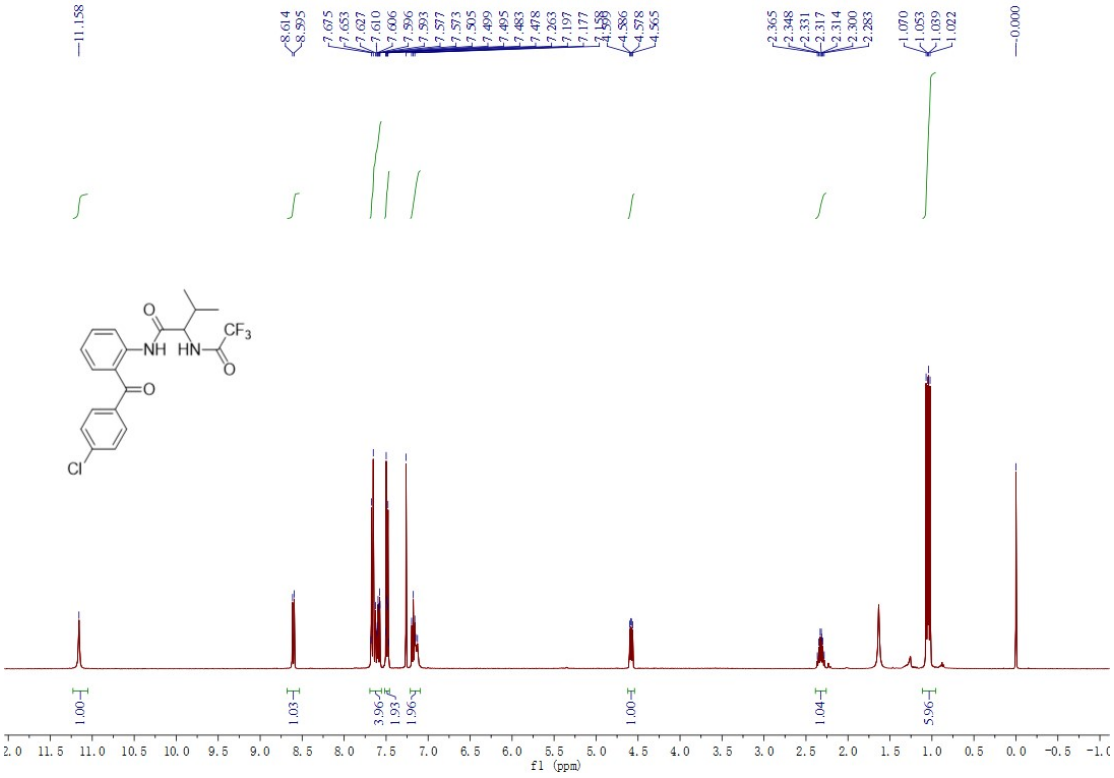


^{1}H NMR of product **3g** ($CDCl_3$)

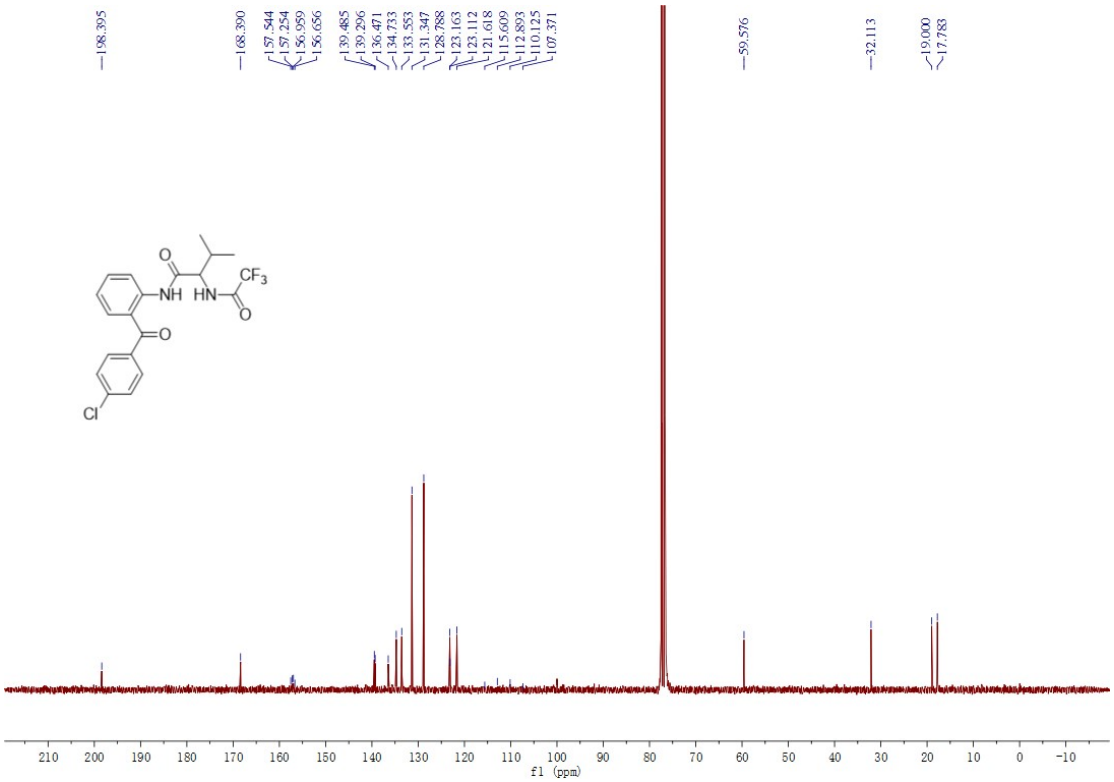
The peak in black oval is the signal of grease.



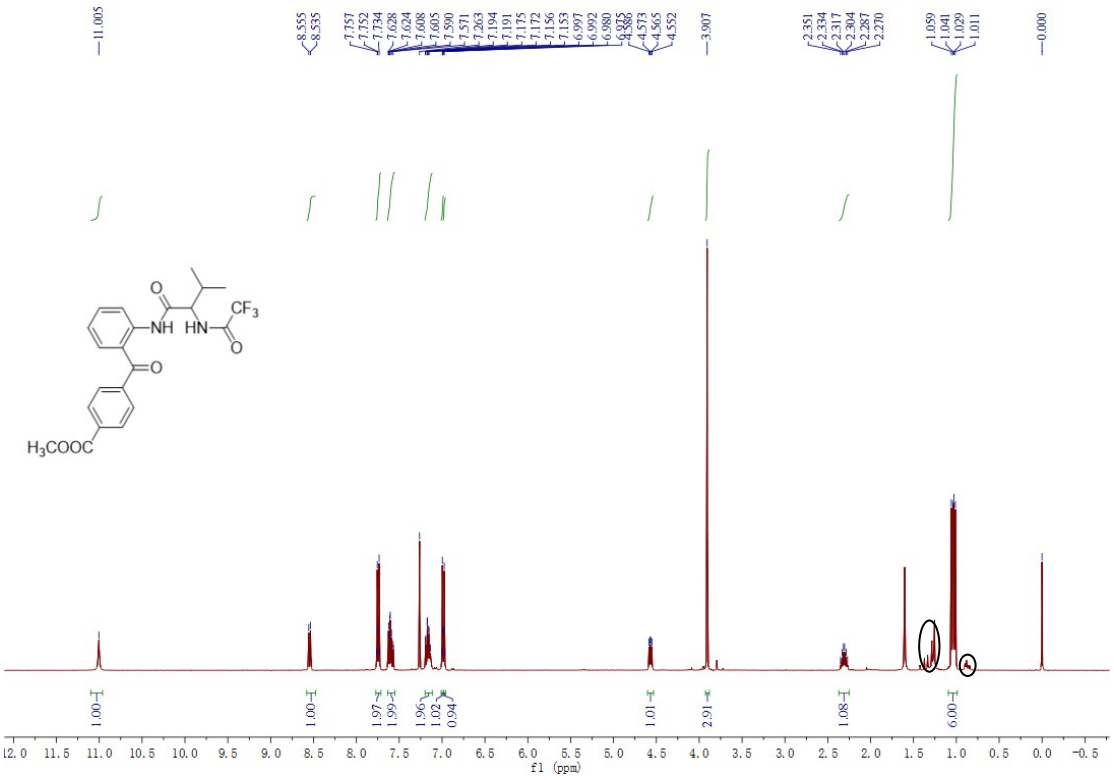
^{13}C NMR of product **3g** ($CDCl_3$)



^{1}H NMR of product **3h** ($CDCl_3$)

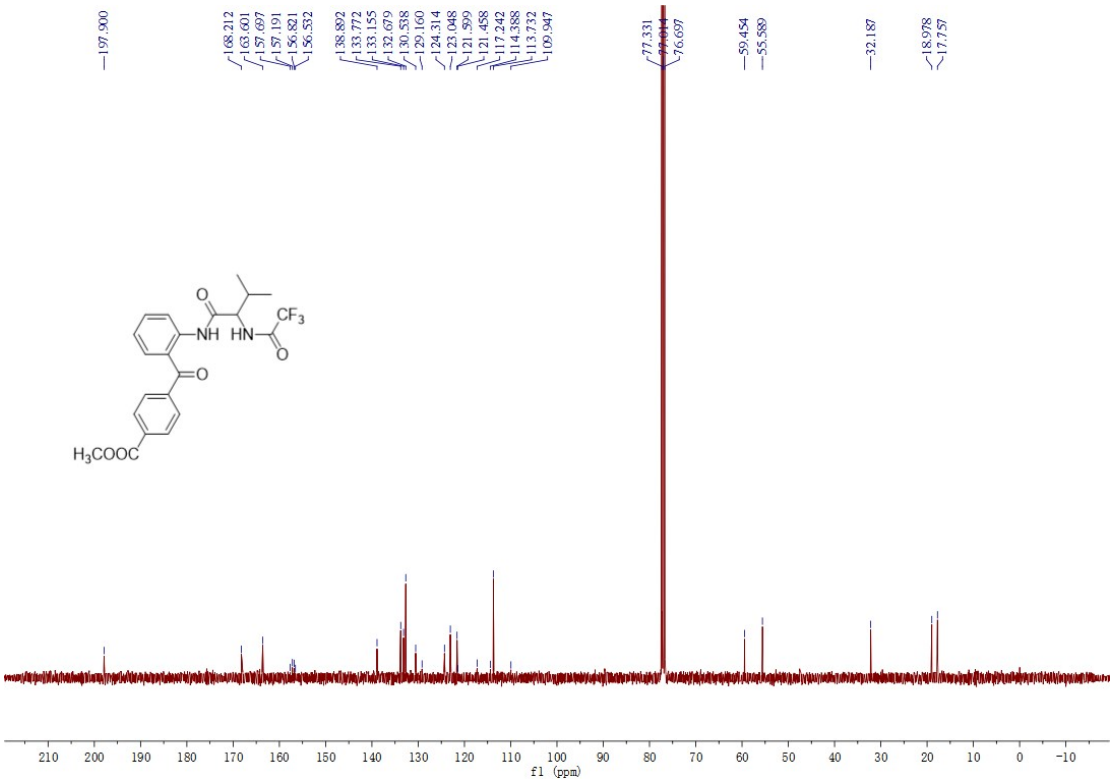


^{13}C NMR of product **3h** ($CDCl_3$)

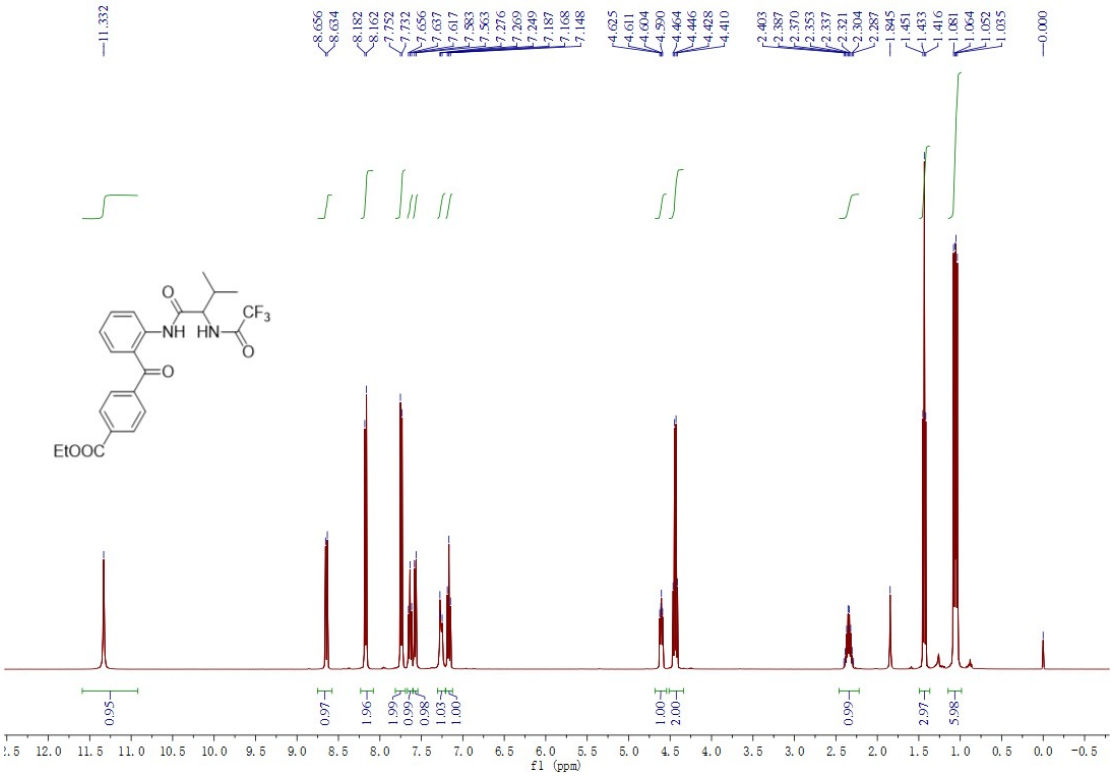


^{1}H NMR of product **3i** ($CDCl_3$)

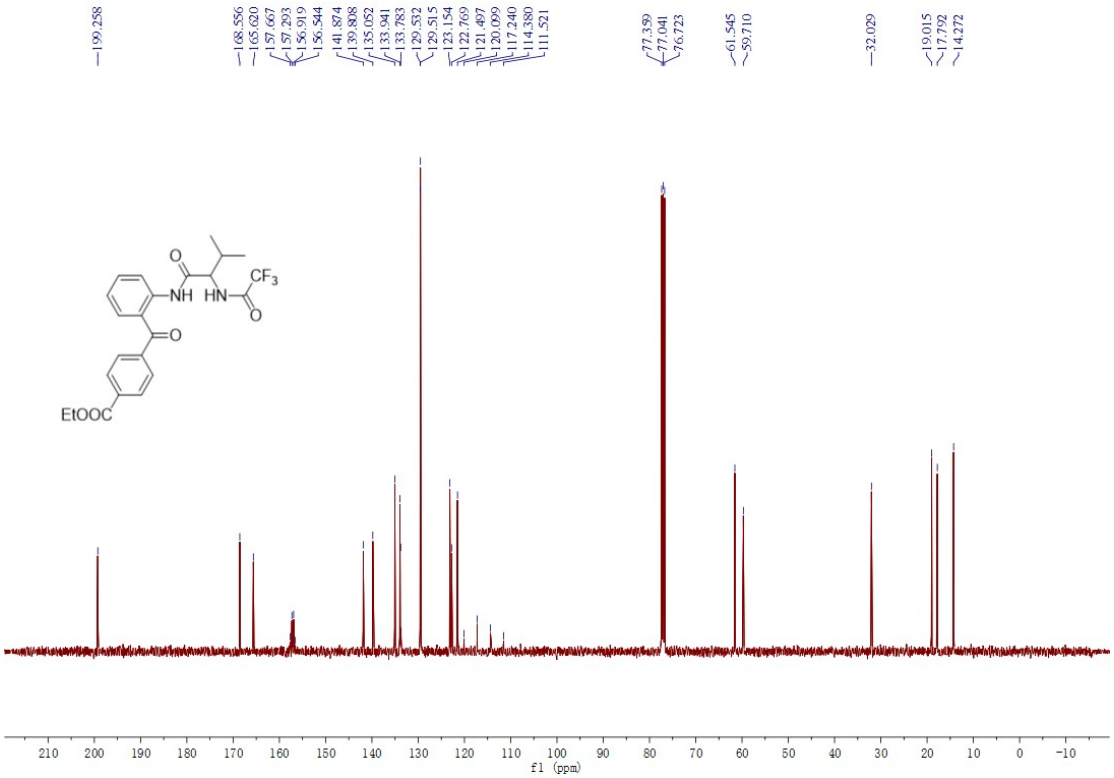
The peak in black oval is the signal of grease.



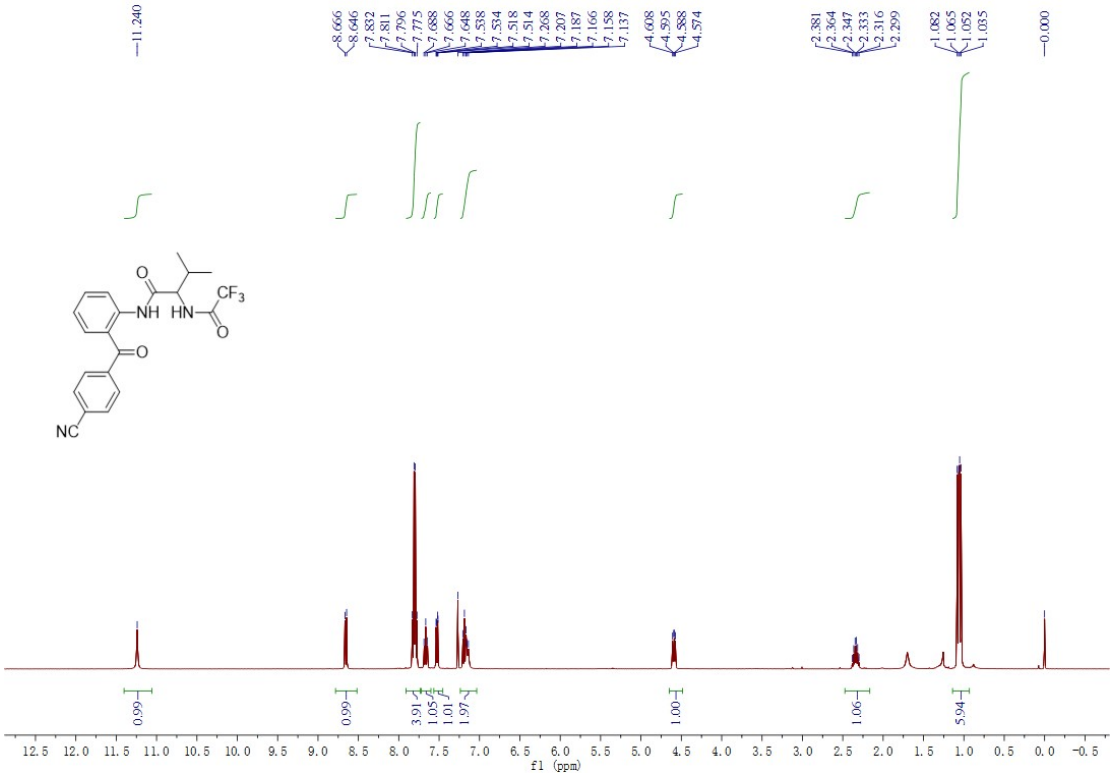
^{13}C NMR of product **3i** ($CDCl_3$)



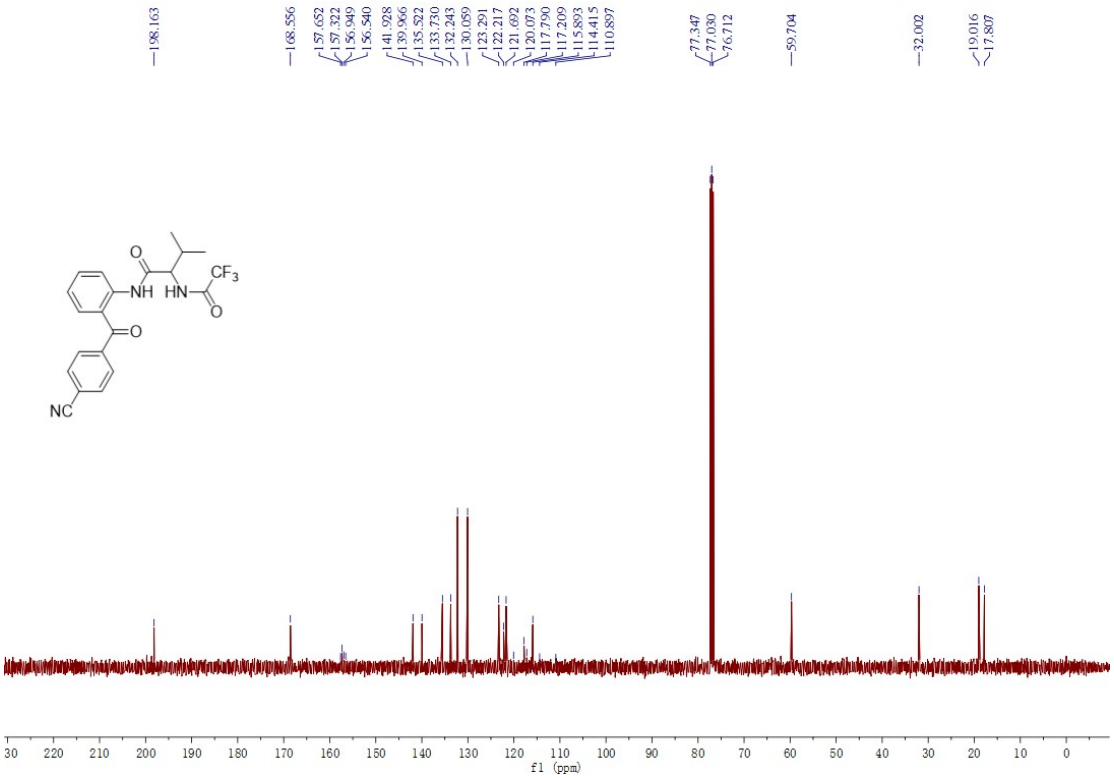
^{1}H NMR of product **3j** ($CDCl_3$)



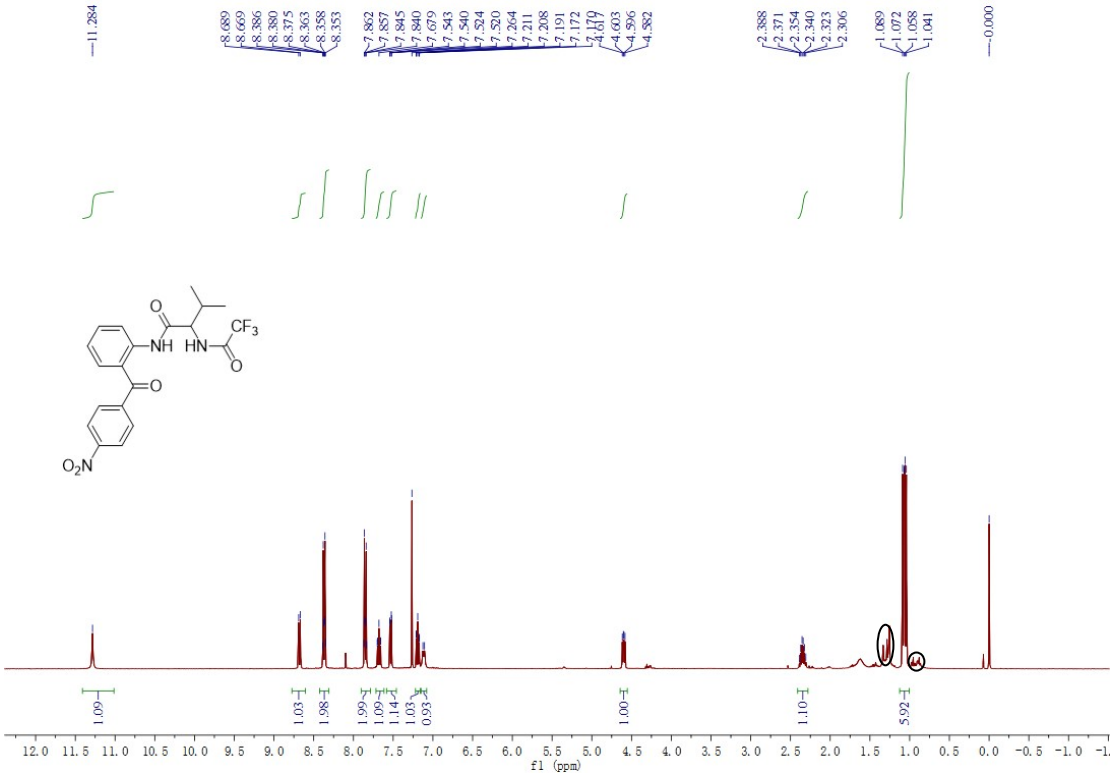
^{13}C NMR of product **3j** ($CDCl_3$)



^{1}H NMR of product **3k** ($CDCl_3$)

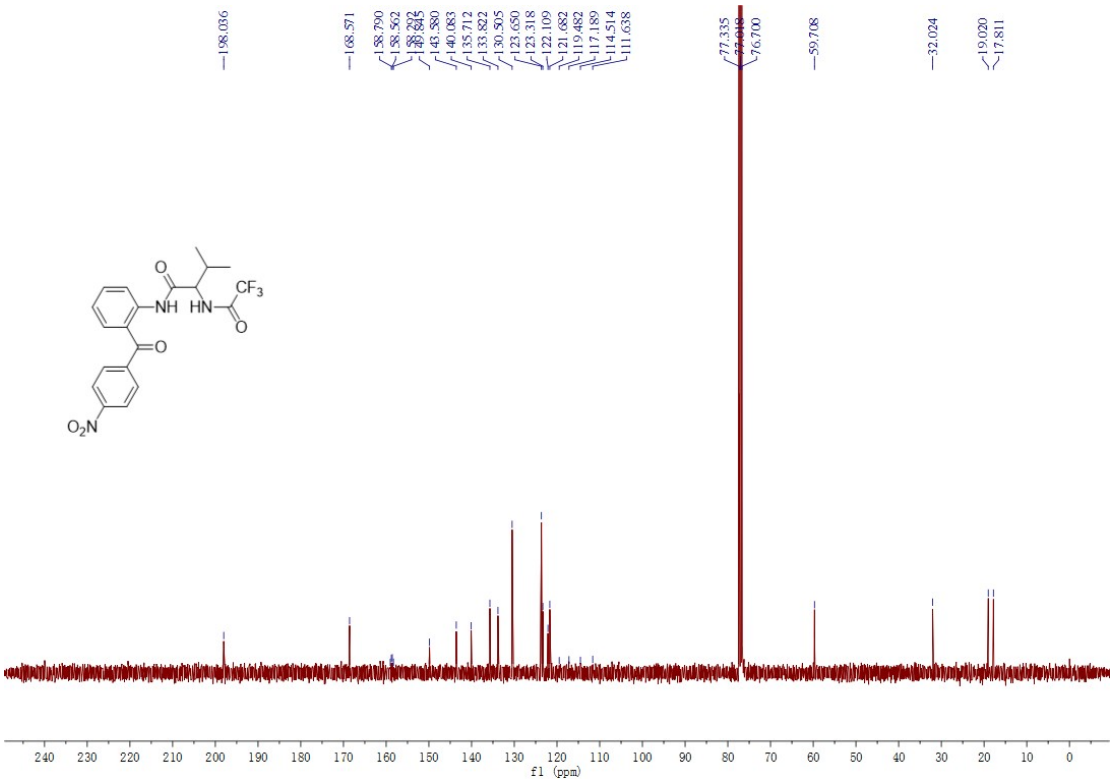


^{13}C NMR of product **3k** ($CDCl_3$)

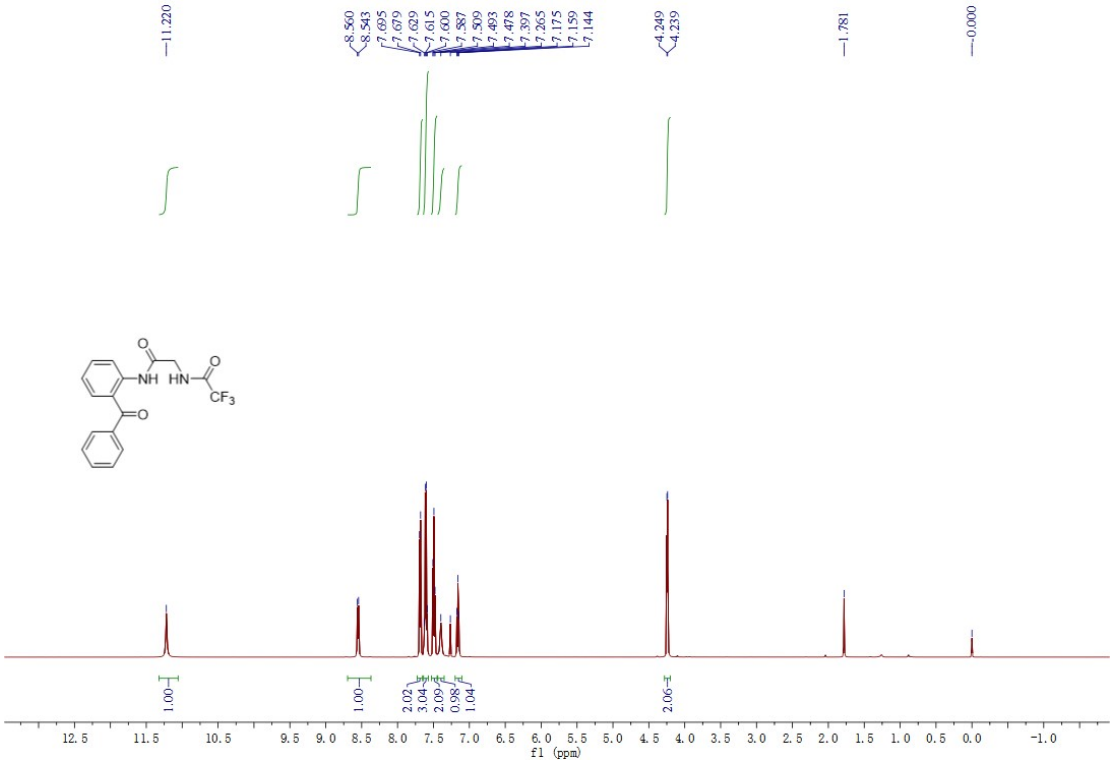


^{1}H NMR of product **3l** ($CDCl_3$)

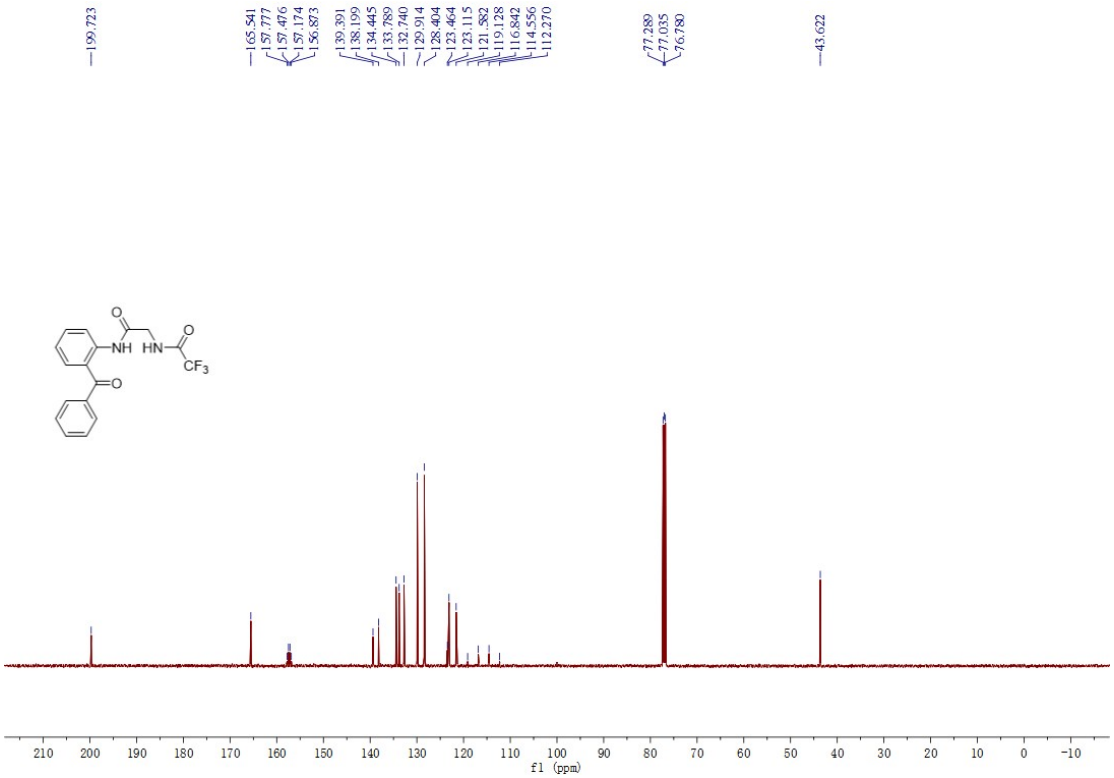
The peak in black oval is the signal of grease.



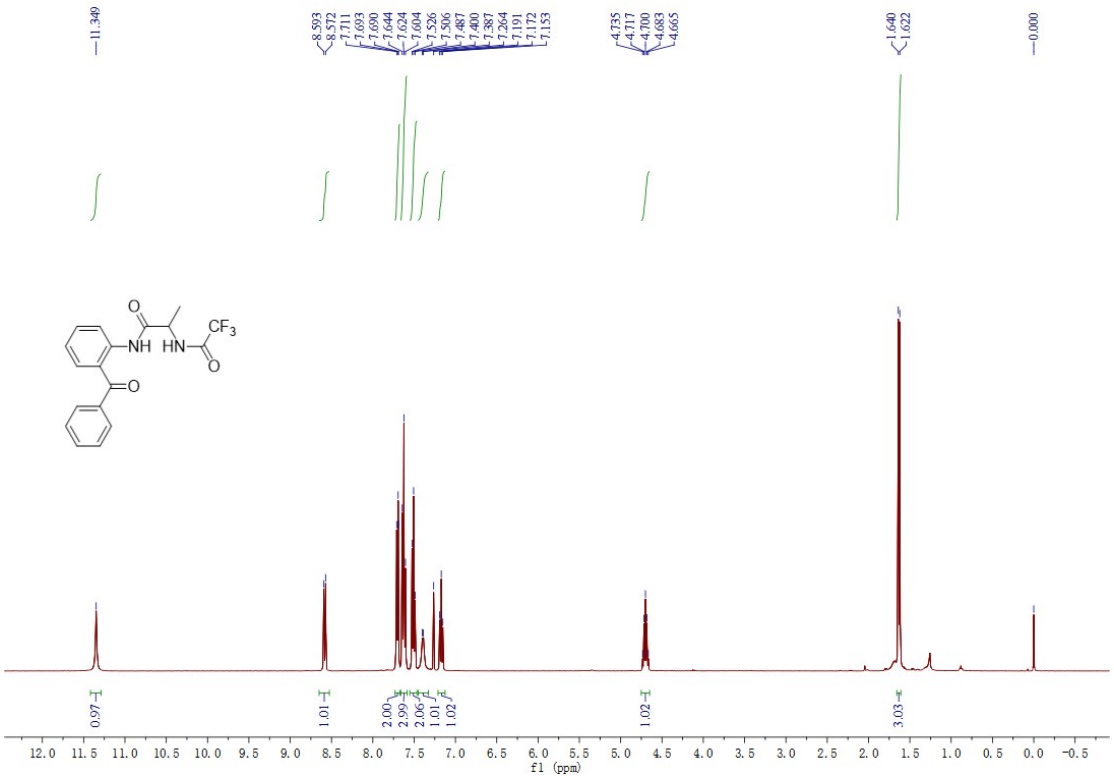
^{13}C NMR of product **3l** ($CDCl_3$)



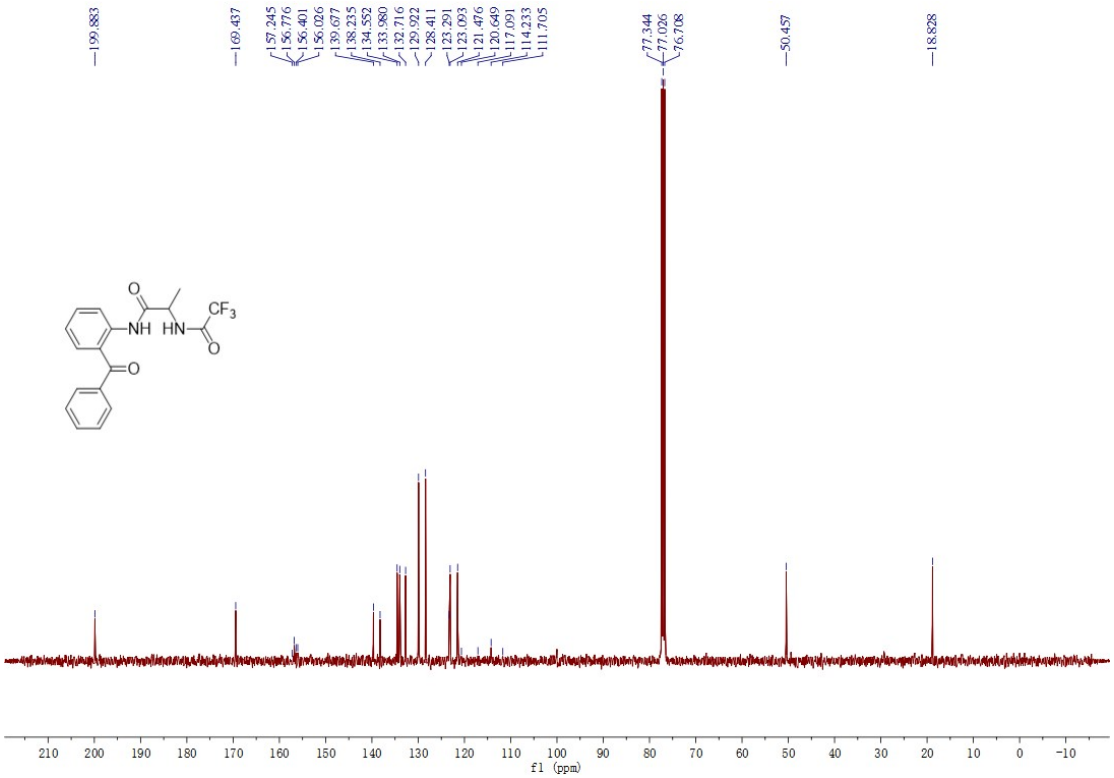
^{1}H NMR of product **3m** ($CDCl_3$)



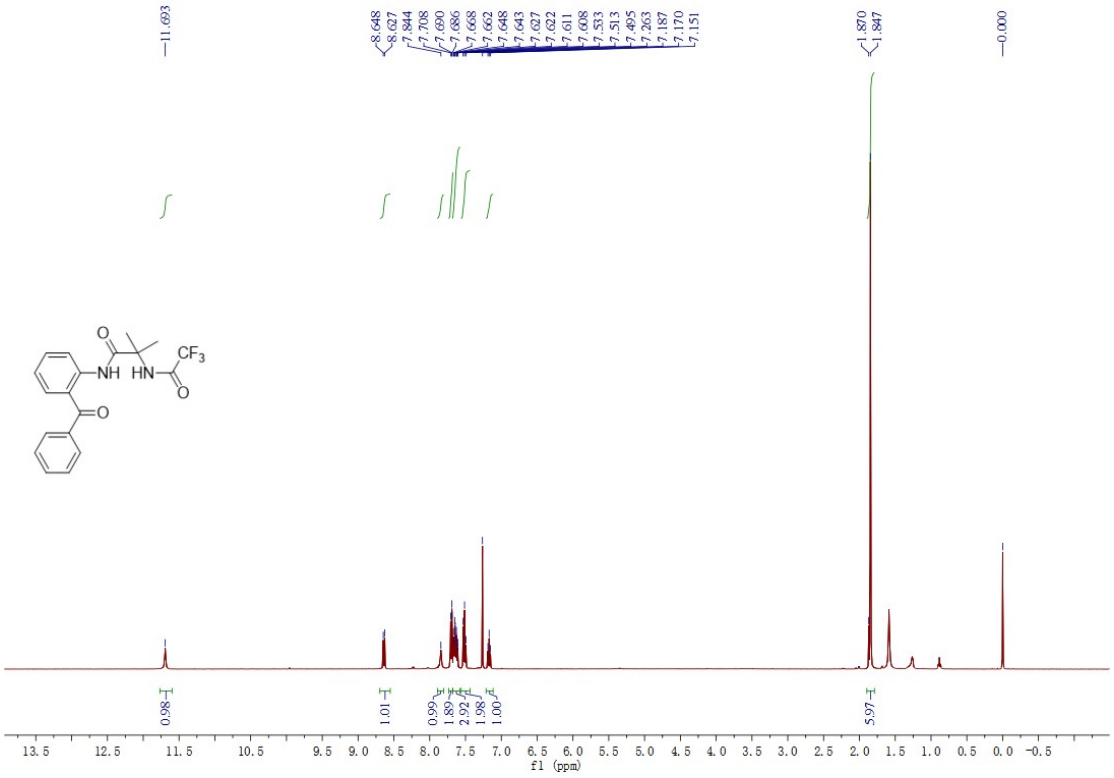
^{13}C NMR of product **3m** ($CDCl_3$)



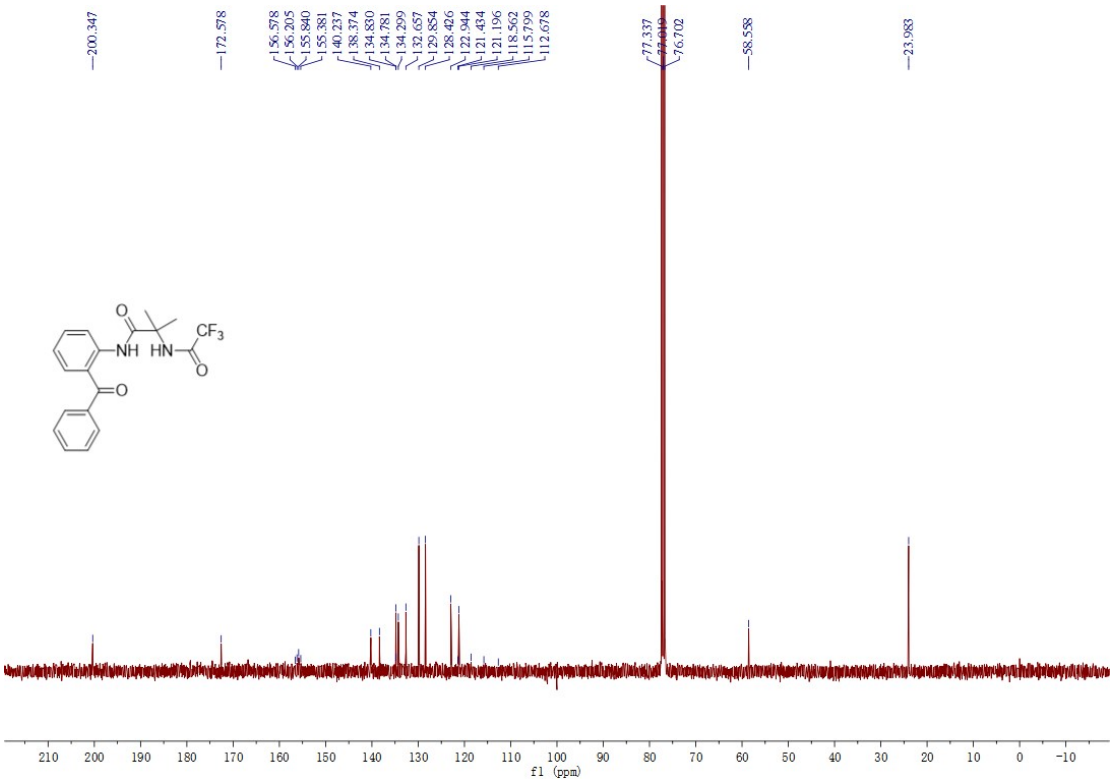
^{1}H NMR of product **3n** ($CDCl_3$)



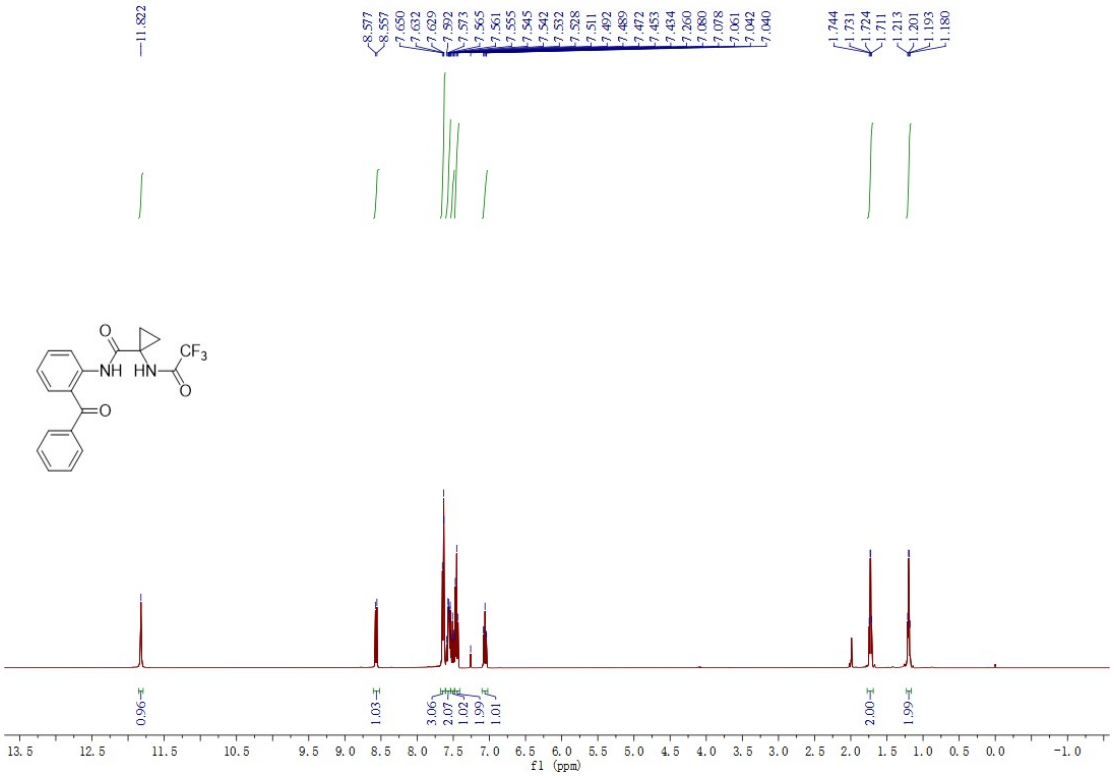
^{13}C NMR of product **3n** ($CDCl_3$)



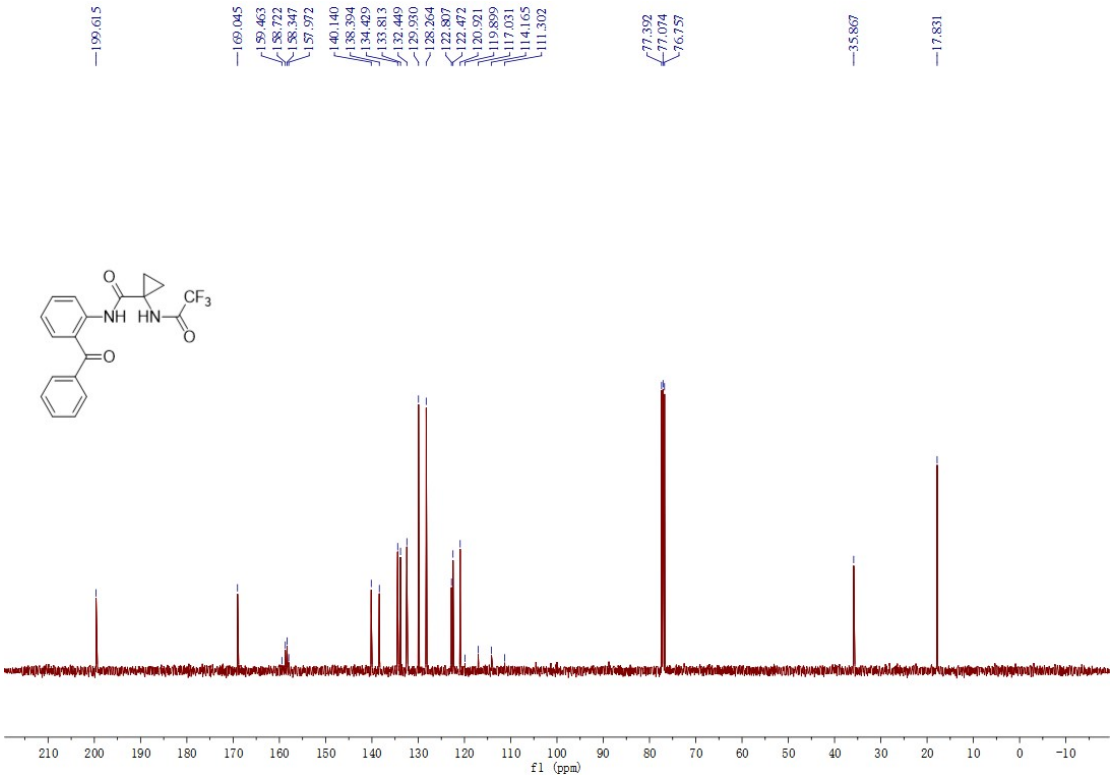
^{1}H NMR of product **3o** ($CDCl_3$)



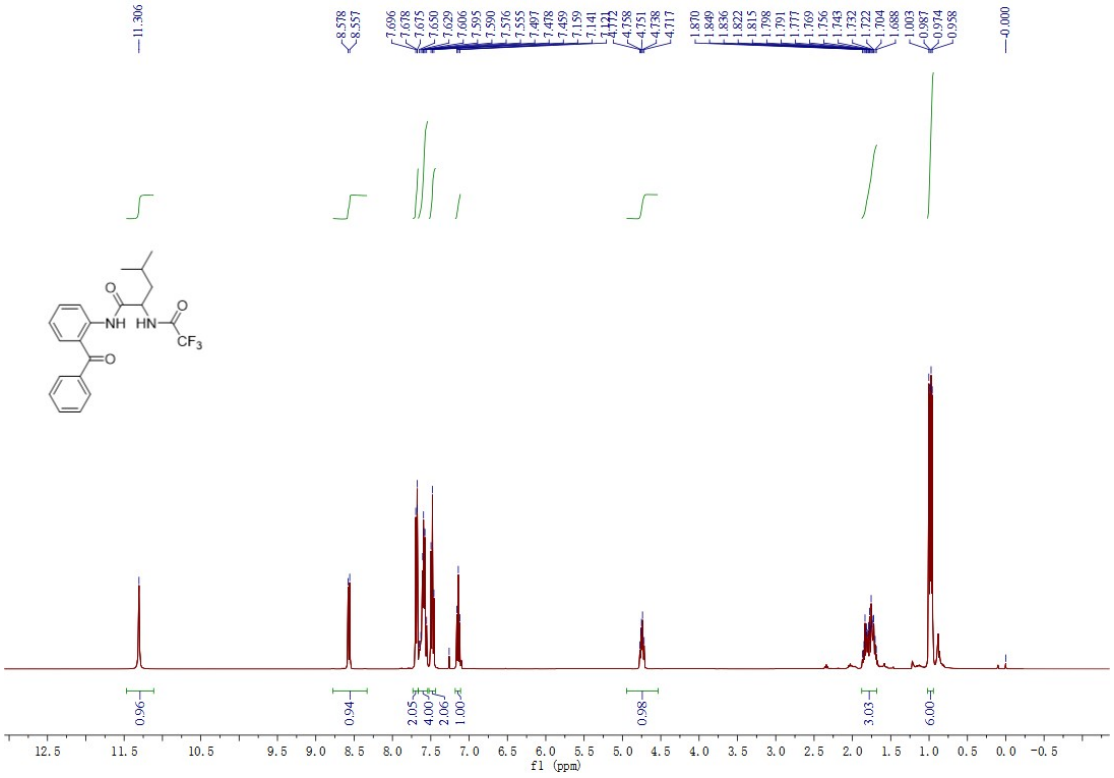
^{13}C NMR of product **3o** ($CDCl_3$)



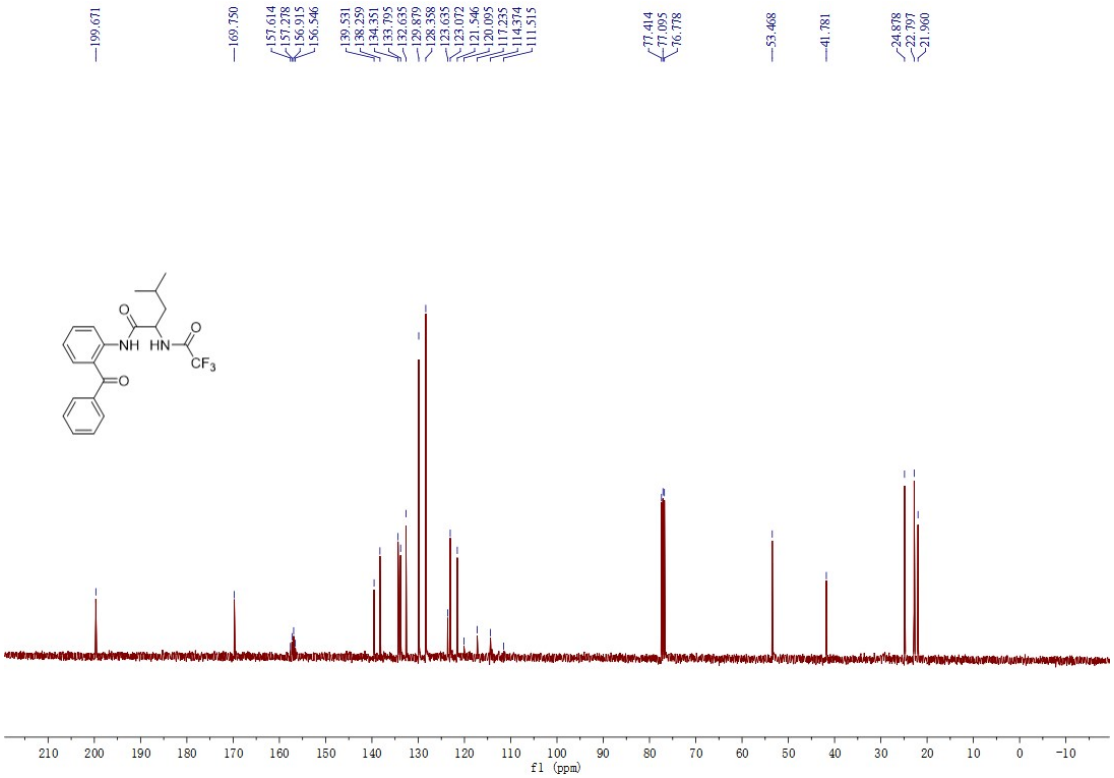
^{1}H NMR of product **3p** ($CDCl_3$)



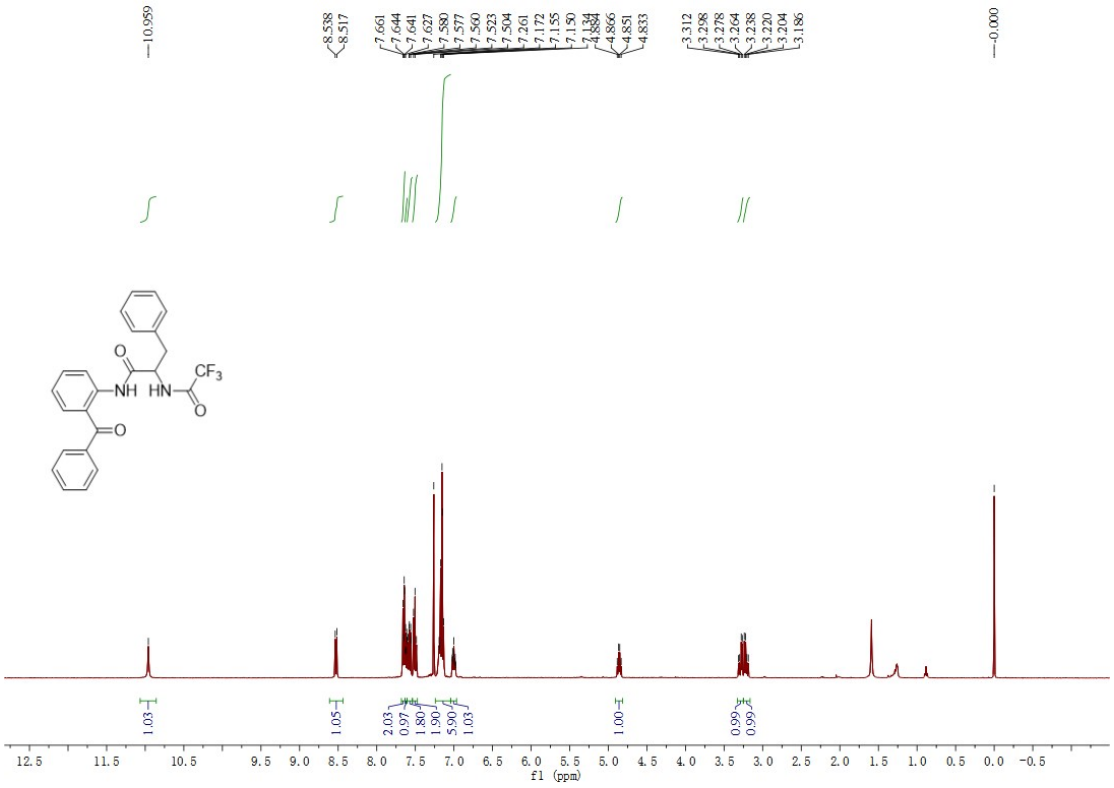
^{13}C NMR of product **3p** ($CDCl_3$)



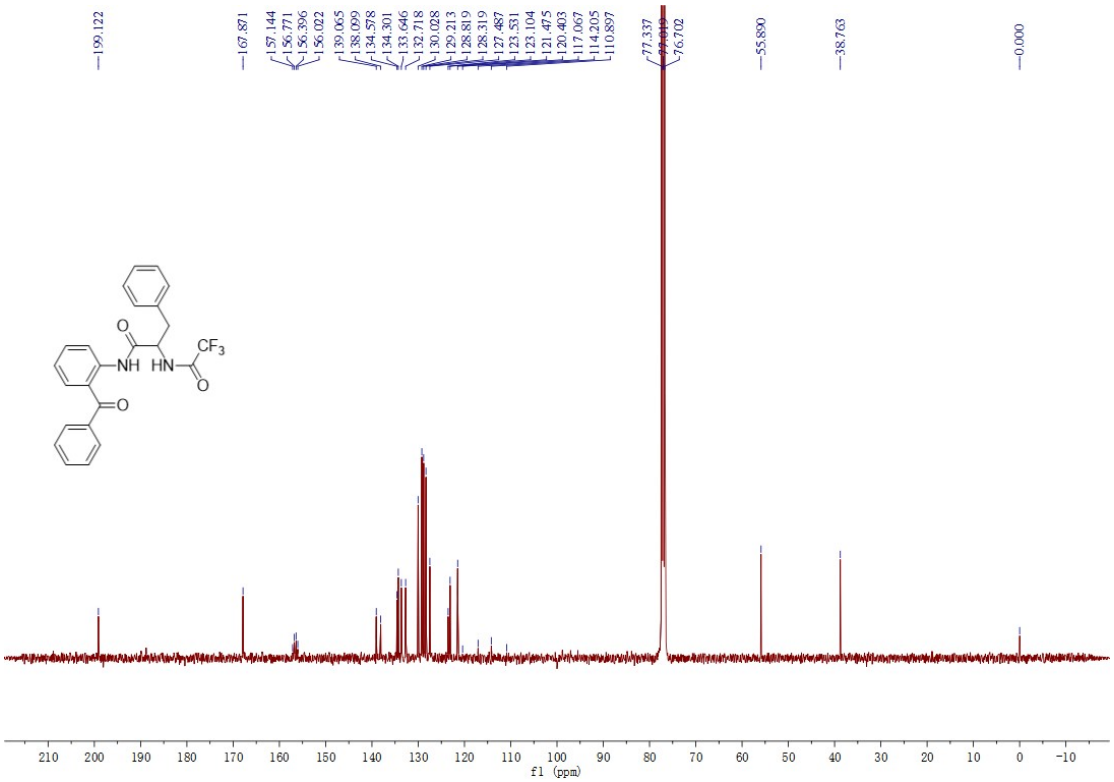
^{1}H NMR of product **3q** ($CDCl_3$)



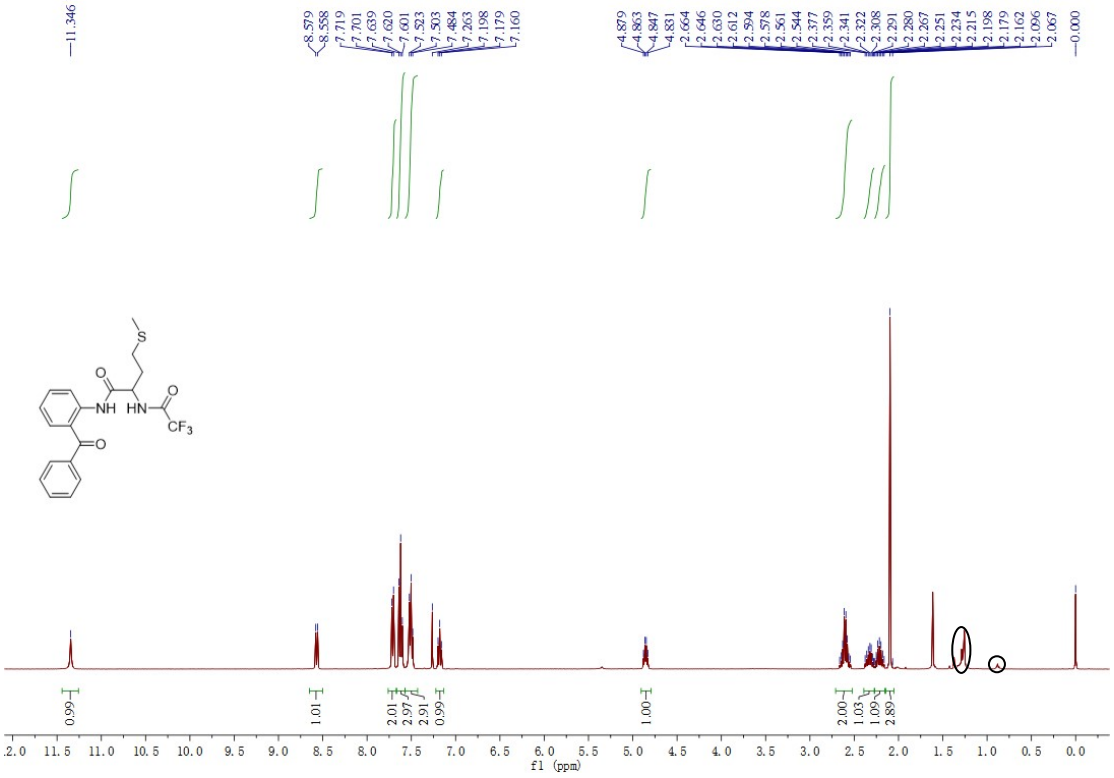
^{13}C NMR of product **3q** ($CDCl_3$)



^{1}H NMR of product **3r** ($CDCl_3$)

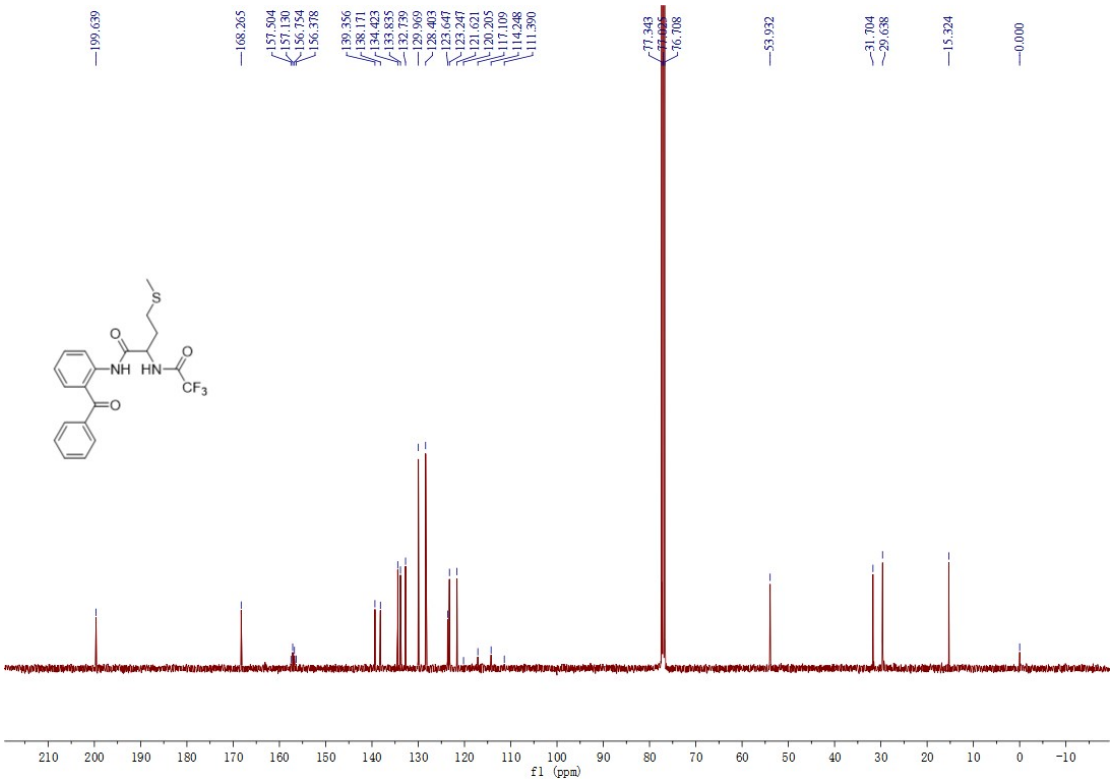


^{13}C NMR of product **3r** ($CDCl_3$)

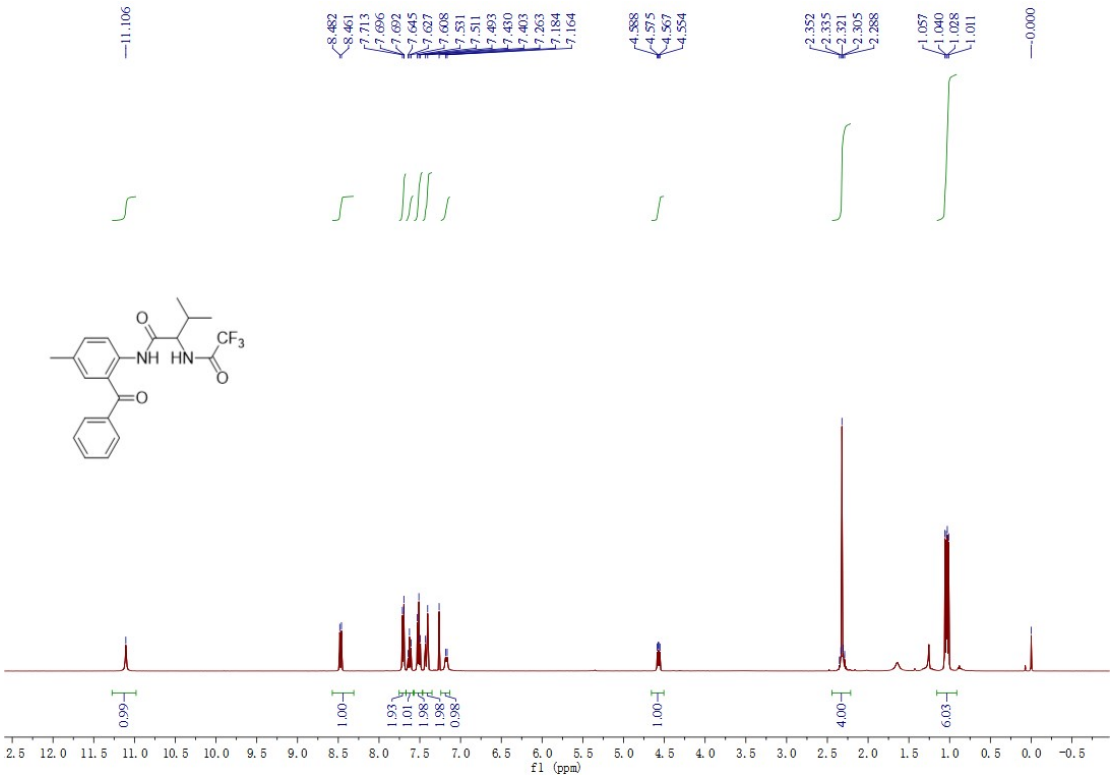


^{1}H NMR of product **3s** ($CDCl_3$)

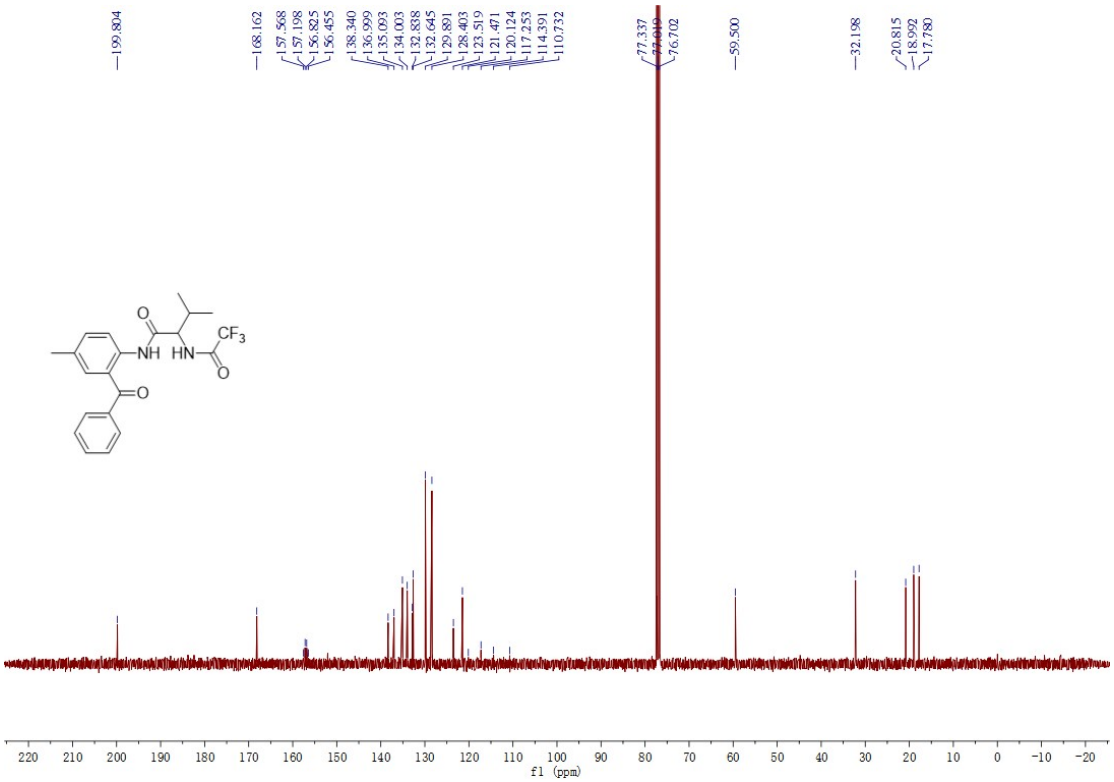
The peak in black oval is the signal of grease.



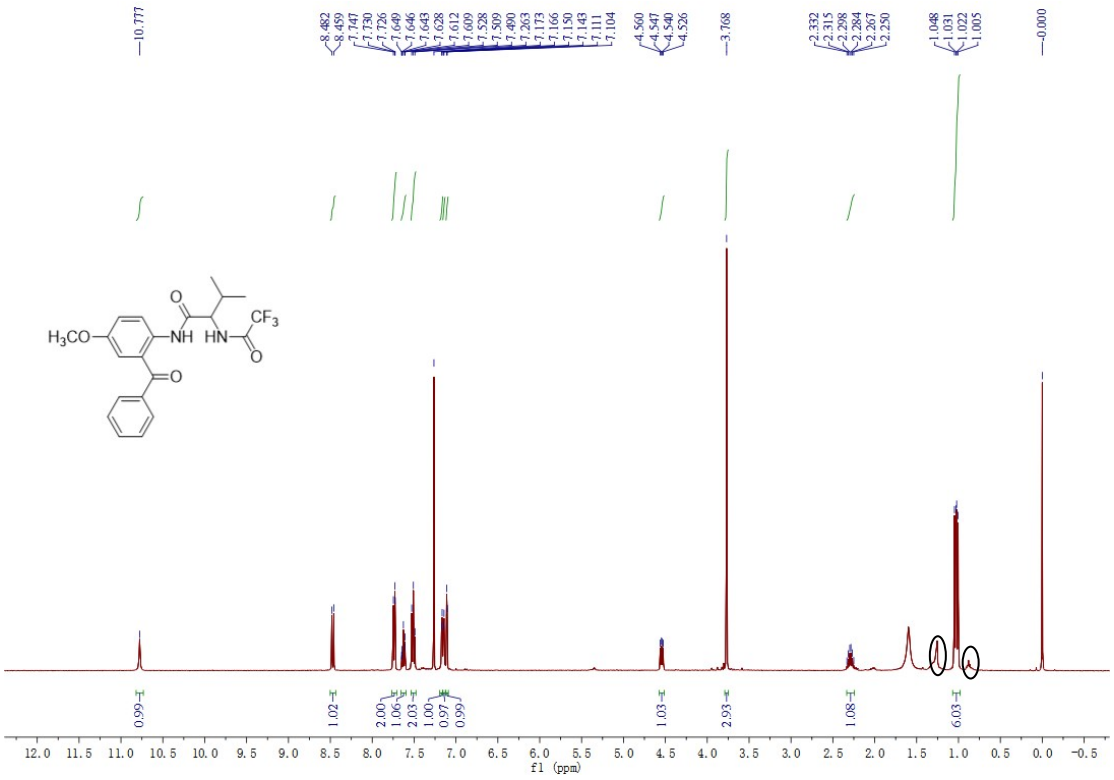
^{13}C NMR of product **3s** ($CDCl_3$)



^{1}H NMR of product **3u** ($CDCl_3$)

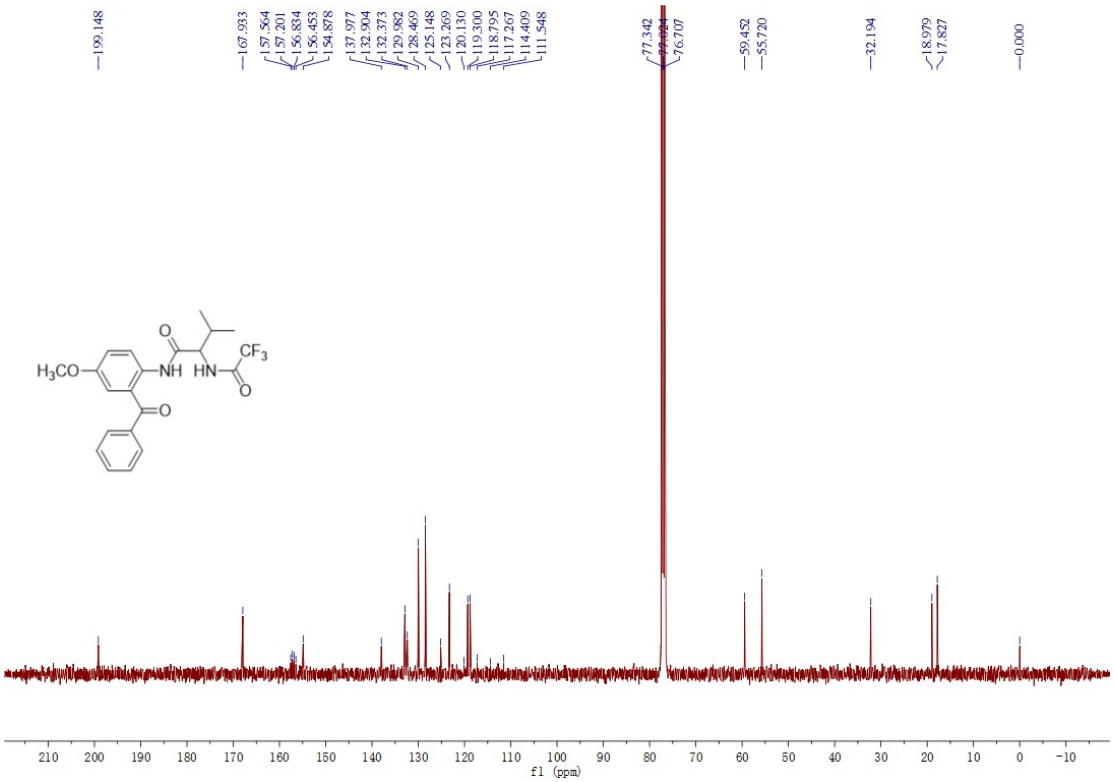


^{13}C NMR of product **3u** ($CDCl_3$)

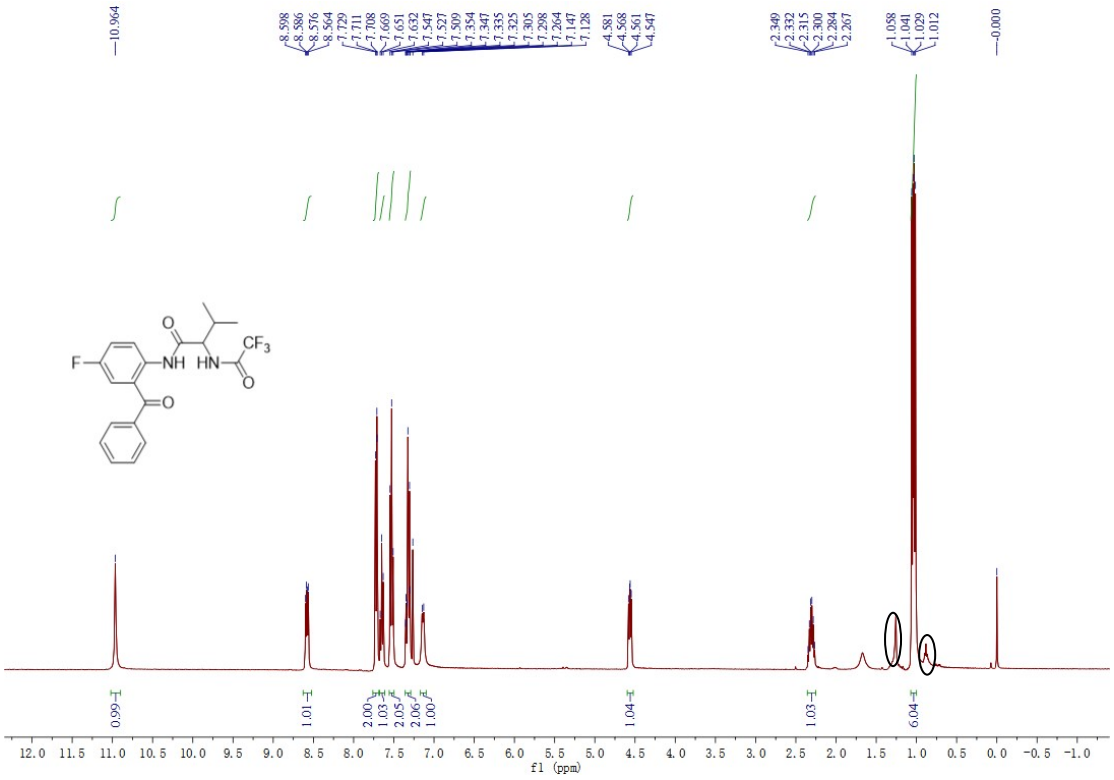


^{1}H NMR of product **3v** ($CDCl_3$)

The peak in black oval is the signal of grease.

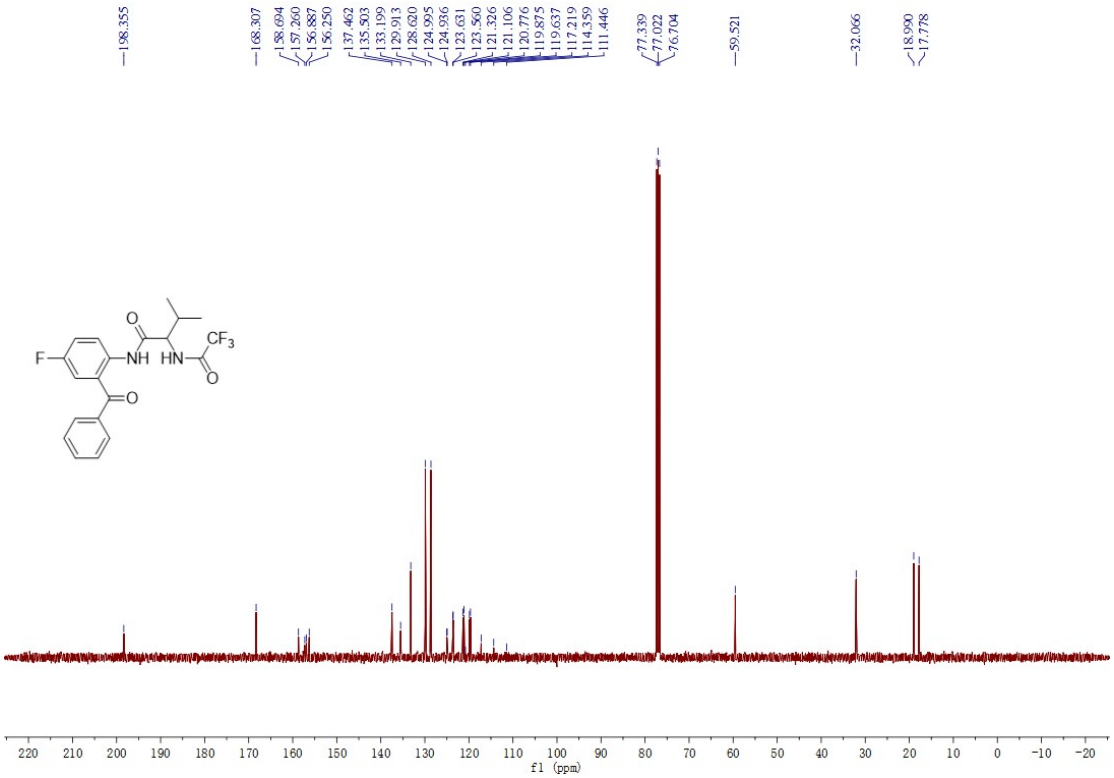


^{13}C NMR of product **3v** ($CDCl_3$)

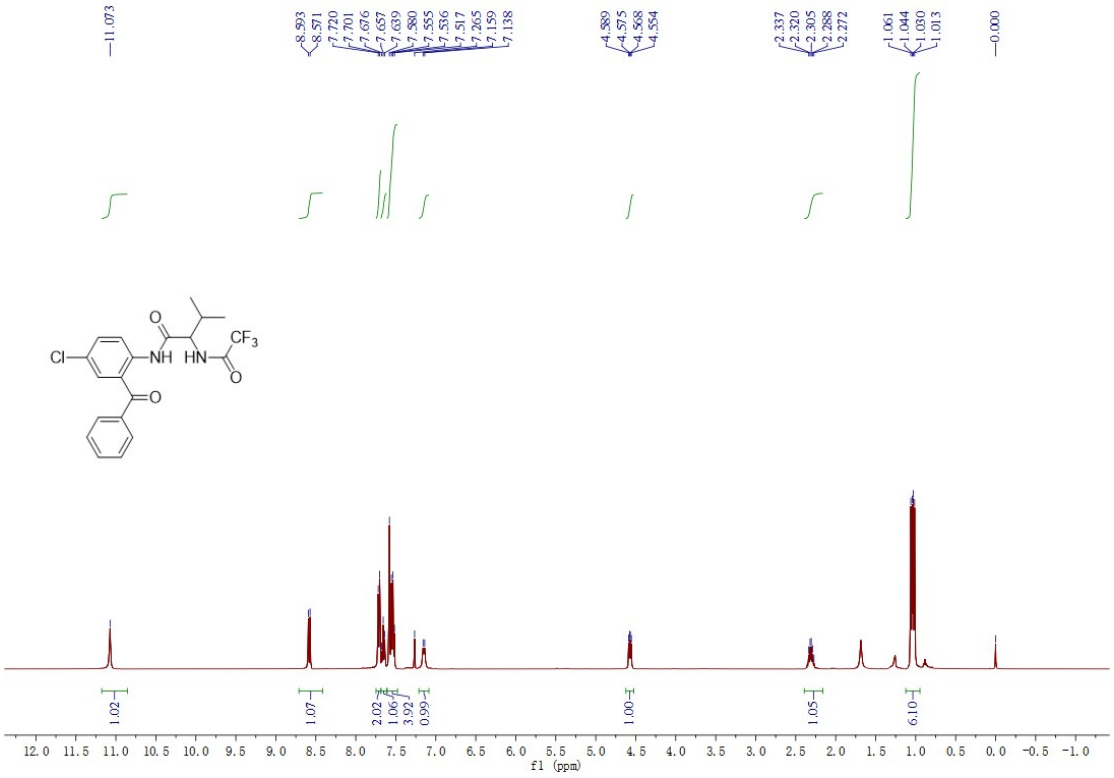


^{1}H NMR of product **3w** ($CDCl_3$)

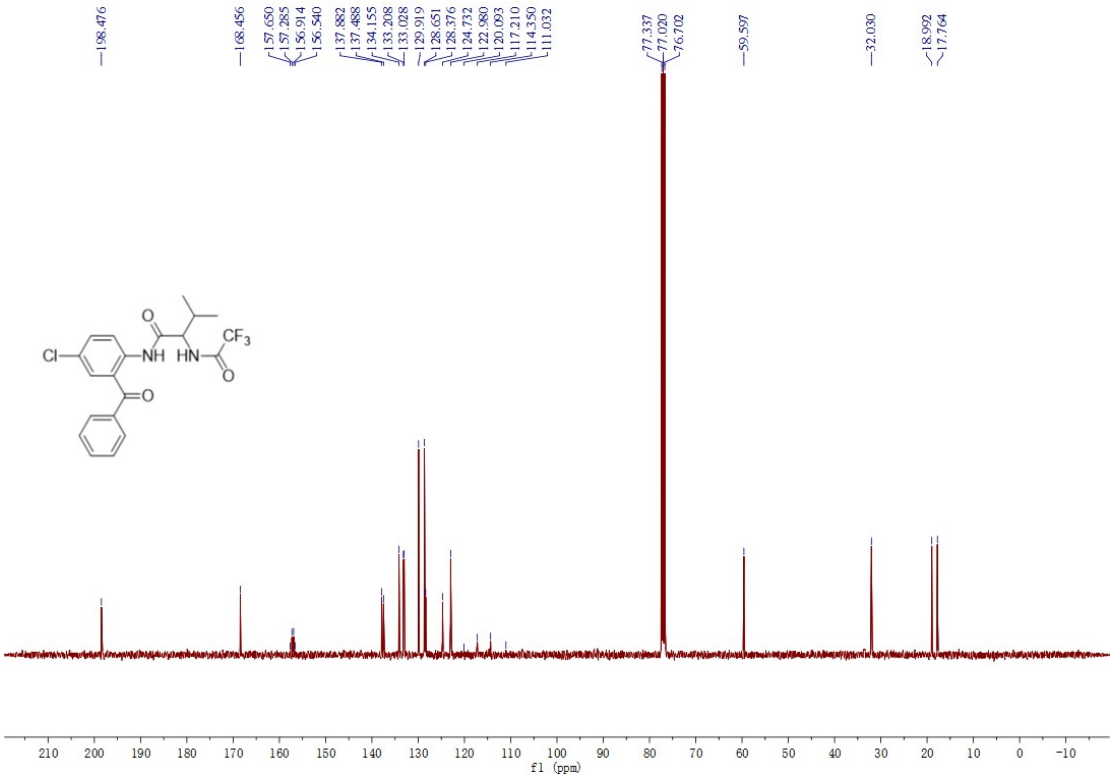
The peak in black oval is the signal of grease.



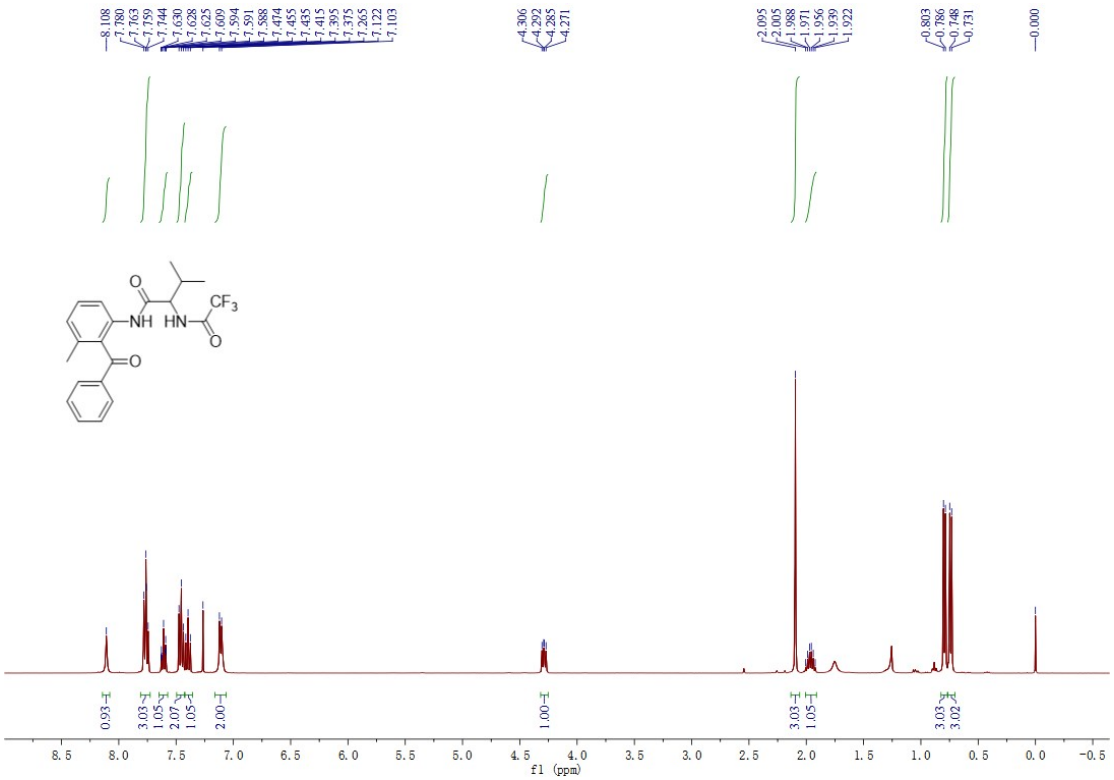
^{13}C NMR of product **3w** ($CDCl_3$)



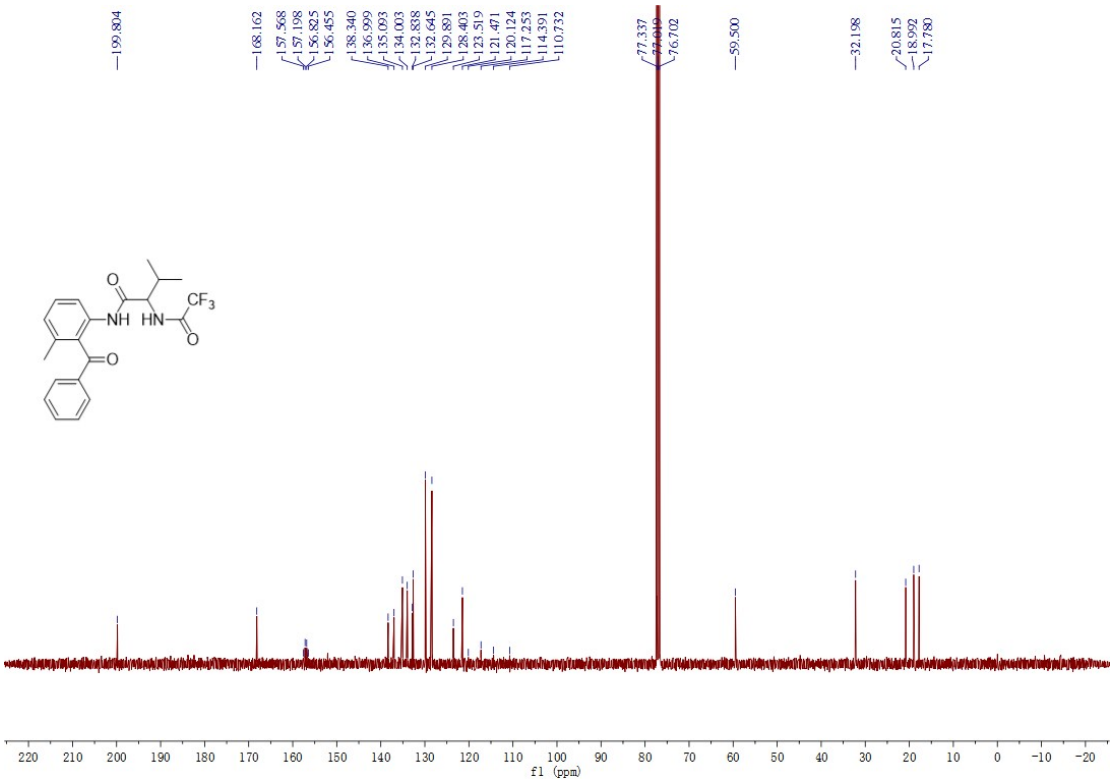
^{1}H NMR of product **3x** ($CDCl_3$)



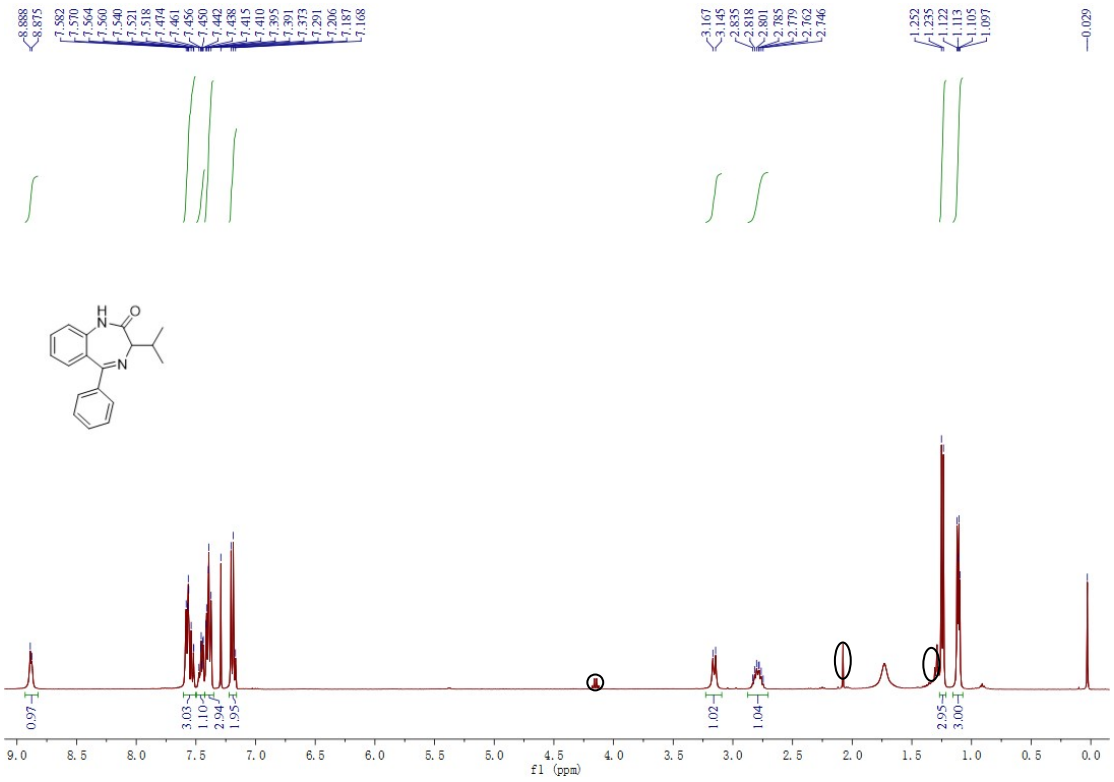
^{13}C NMR of product **3x** ($CDCl_3$)



^{1}H NMR of product **3y** ($CDCl_3$)

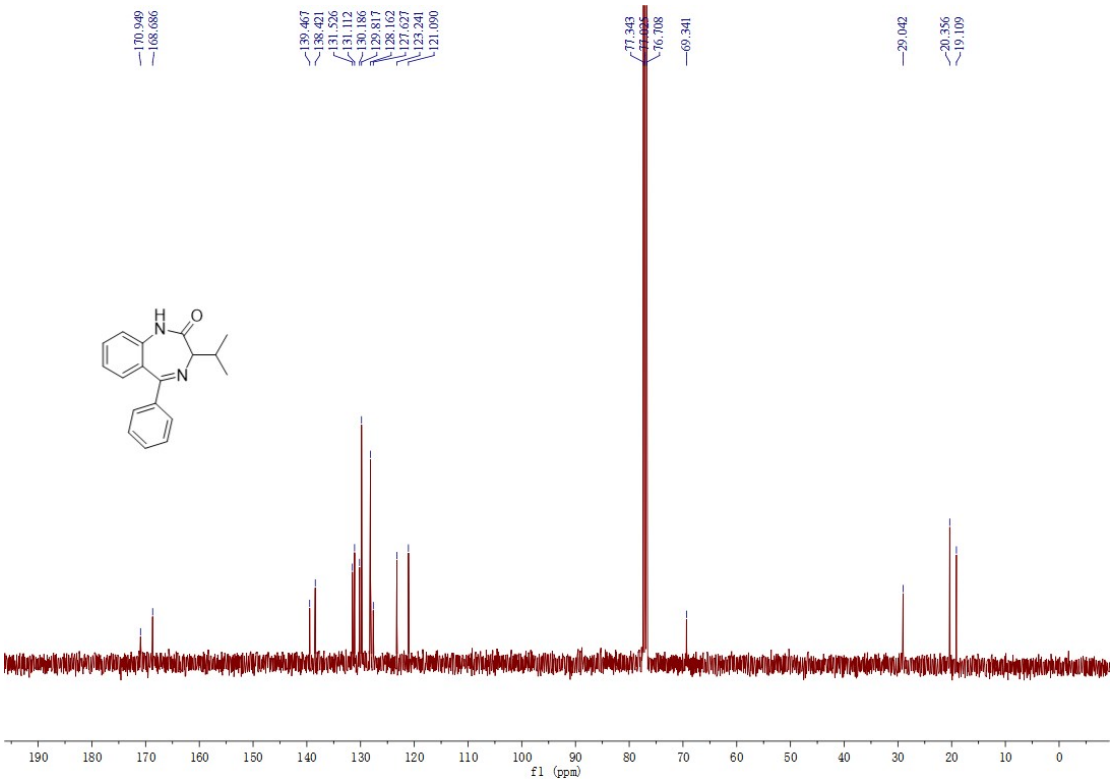


^{13}C NMR of product **3y** ($CDCl_3$)

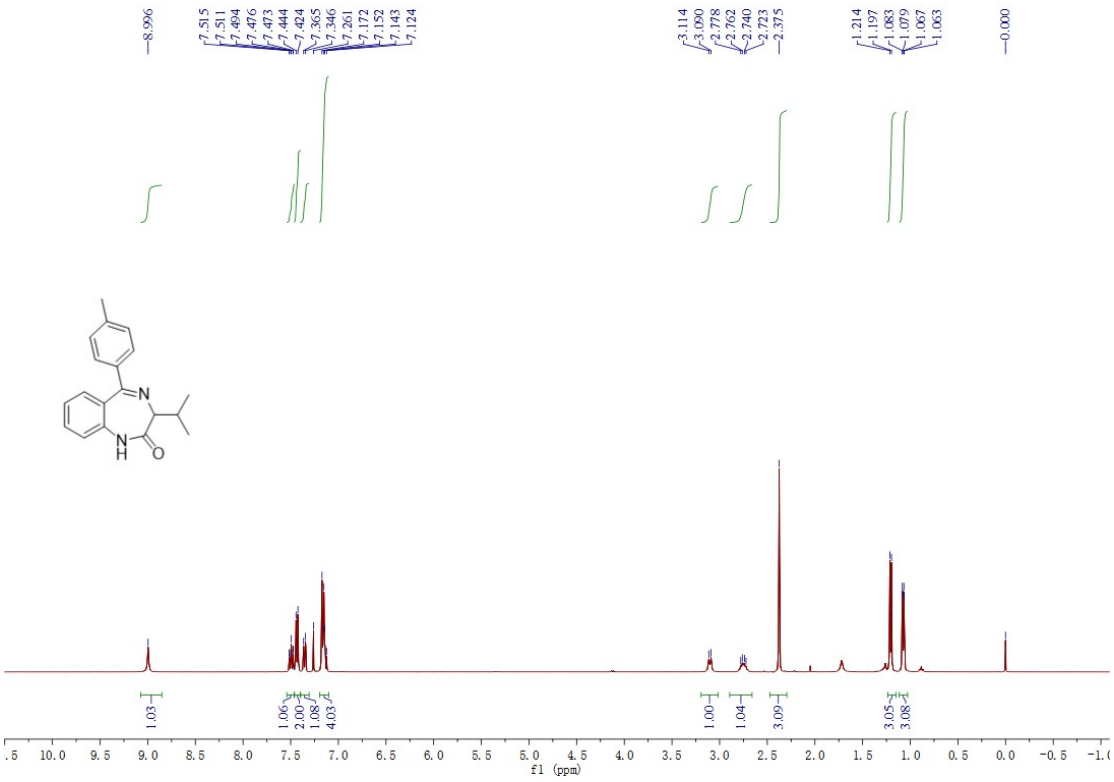


^{1}H NMR of product **4a** ($CDCl_3$)

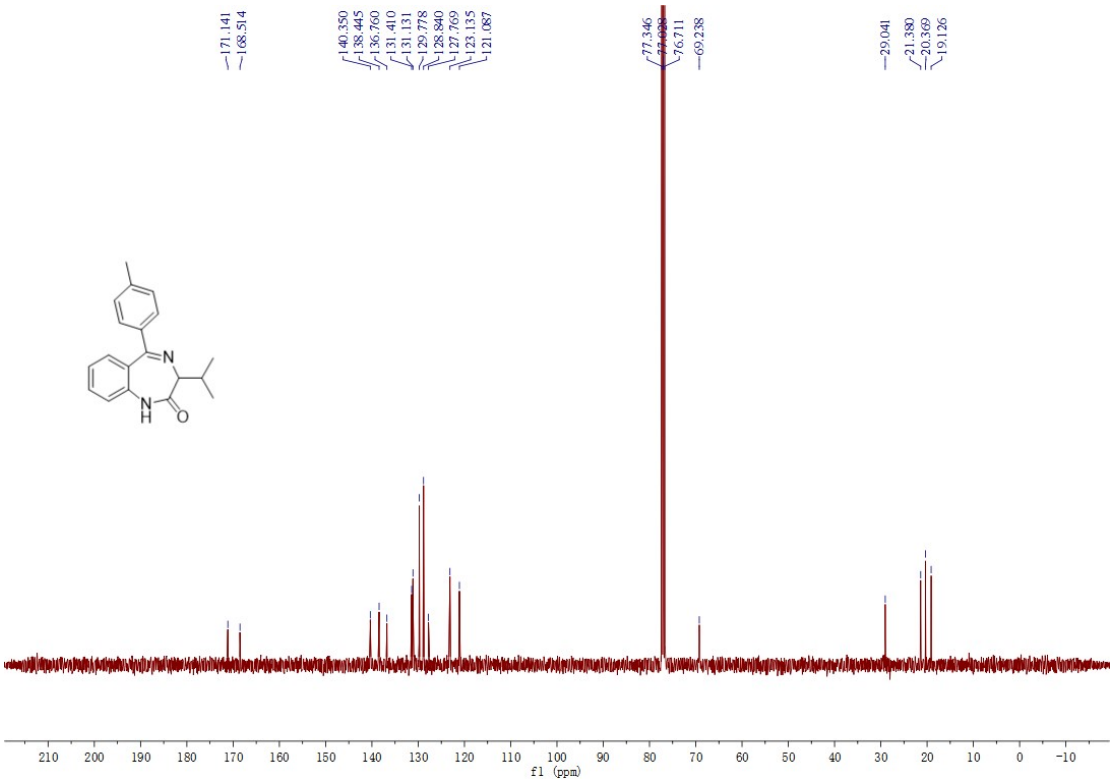
The peak in black oval is the signal of ethyl acetate.



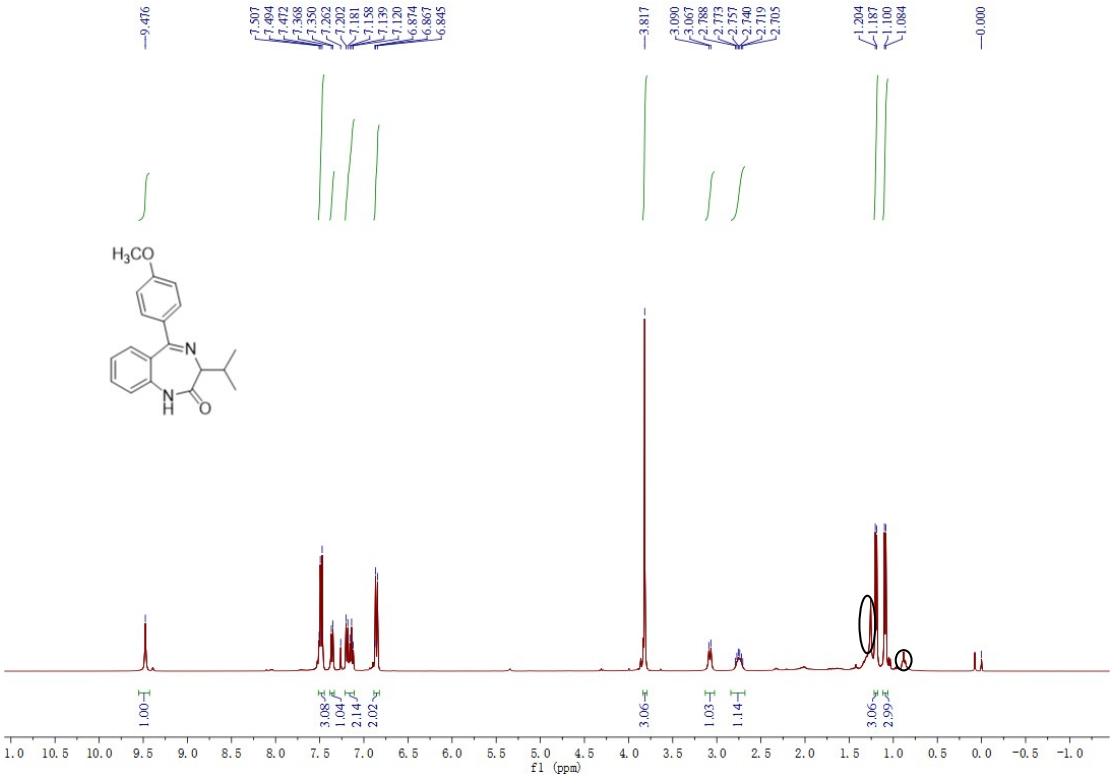
^{13}C NMR of product **4a** ($CDCl_3$)



^{1}H NMR of product **4b** ($CDCl_3$)

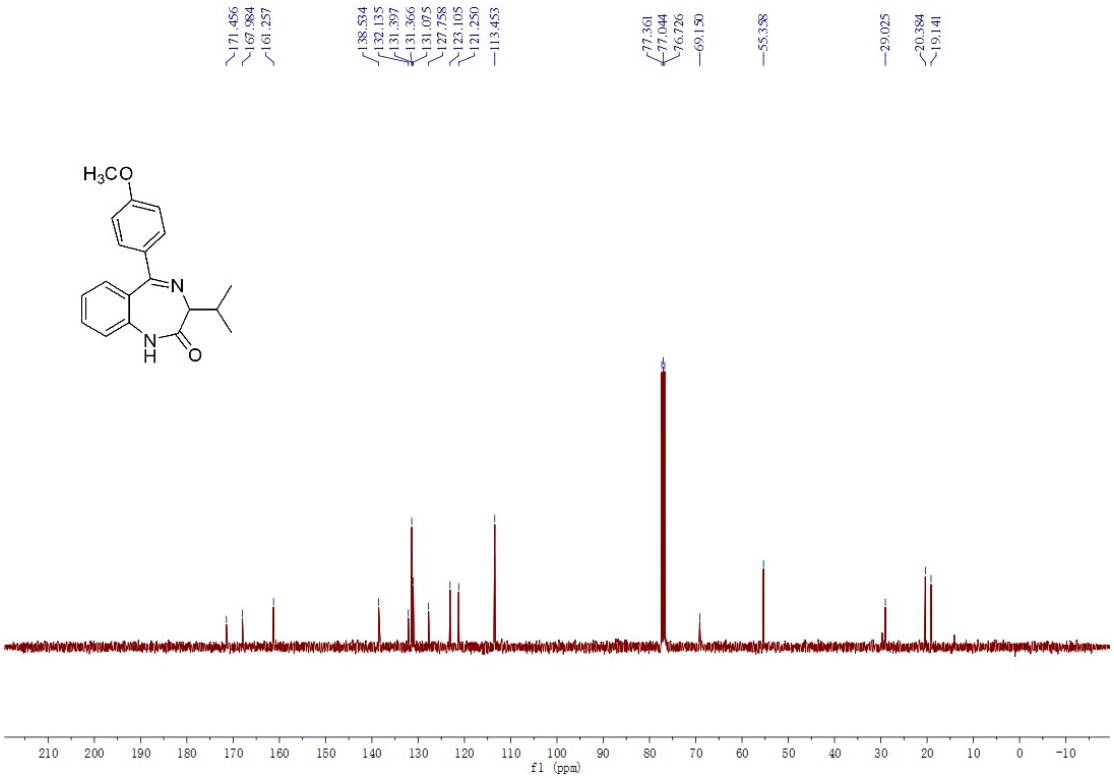


^{13}C NMR of product **4b** ($CDCl_3$)

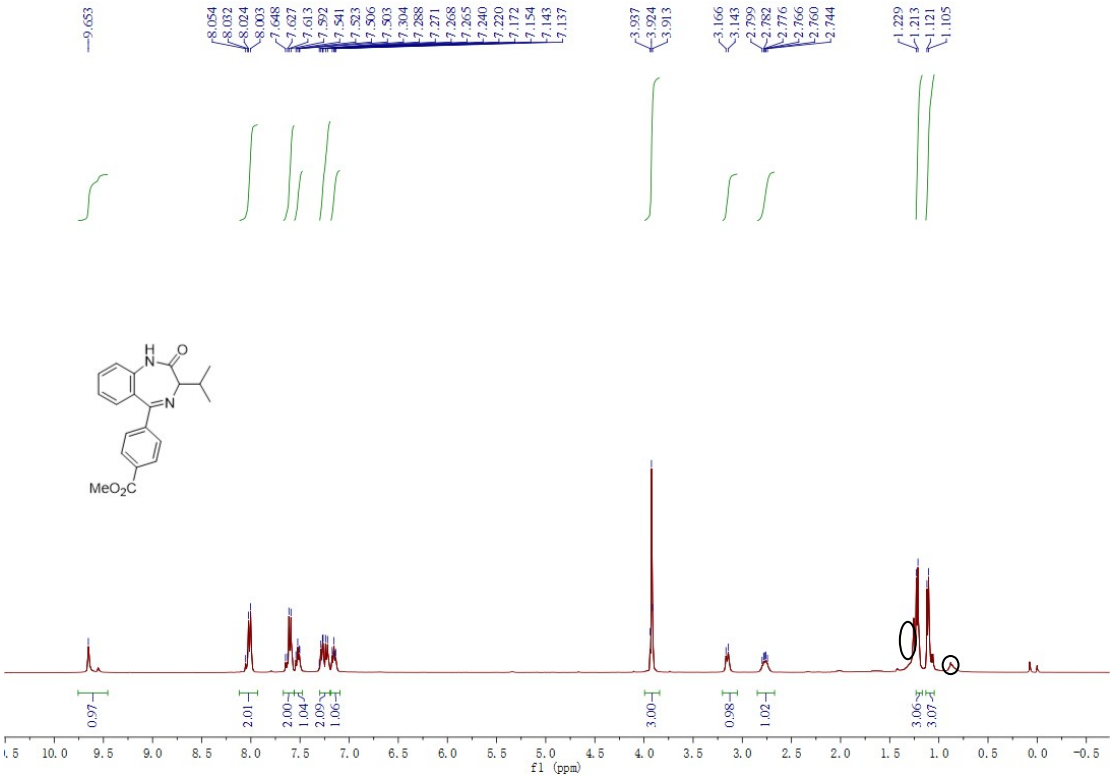


^{1}H NMR of product **4c** ($CDCl_3$)

The peak in black oval is the signal of grease.

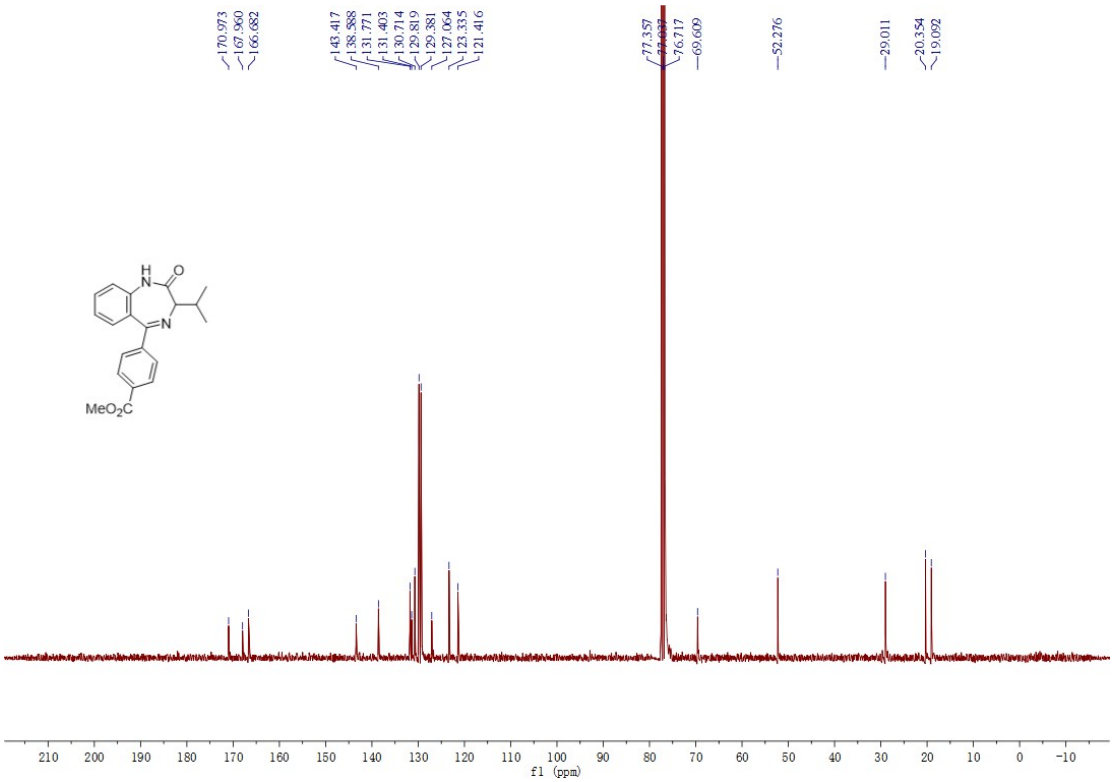


^{13}C NMR of product **4c** ($CDCl_3$)

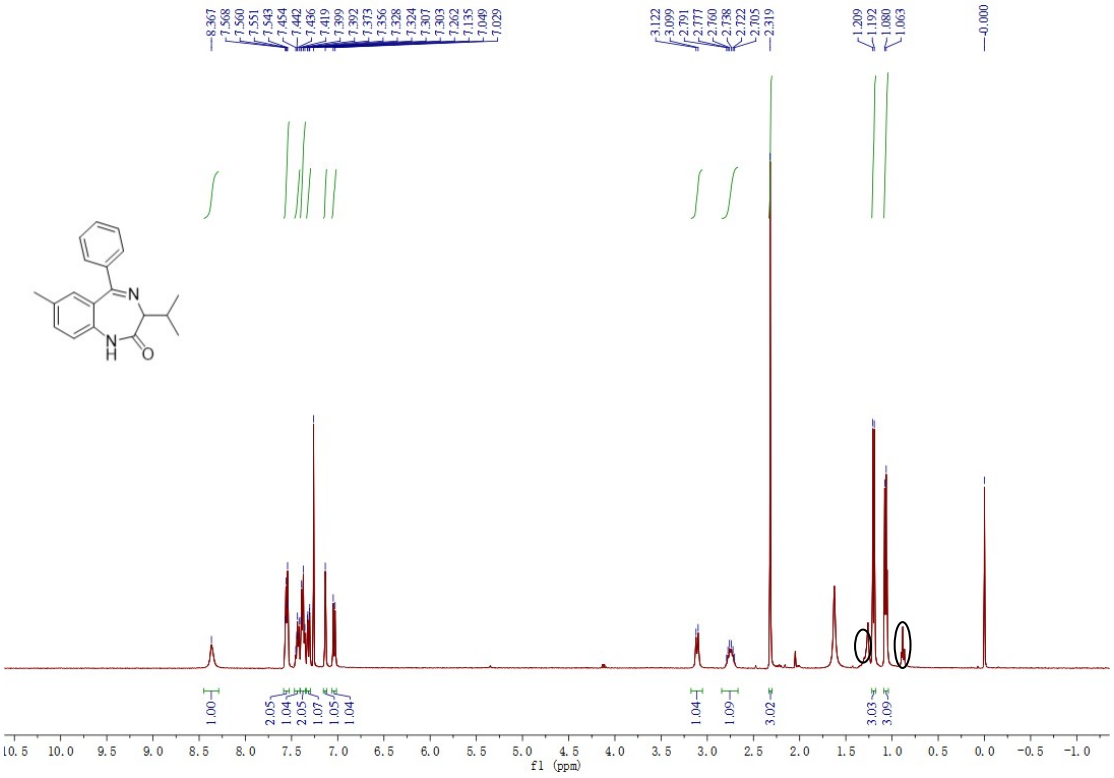


^{1}H NMR of product **4d** ($CDCl_3$)

The peak in black oval is the signal of grease.

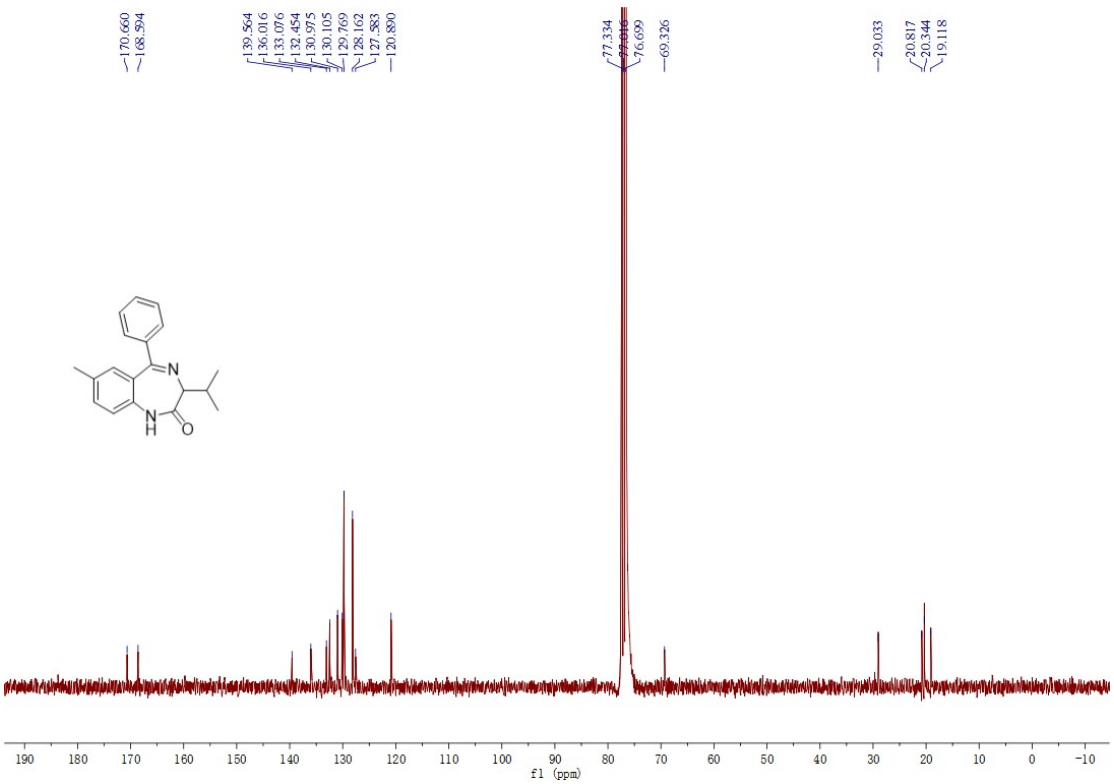


^{13}C NMR of product **4d** ($CDCl_3$)

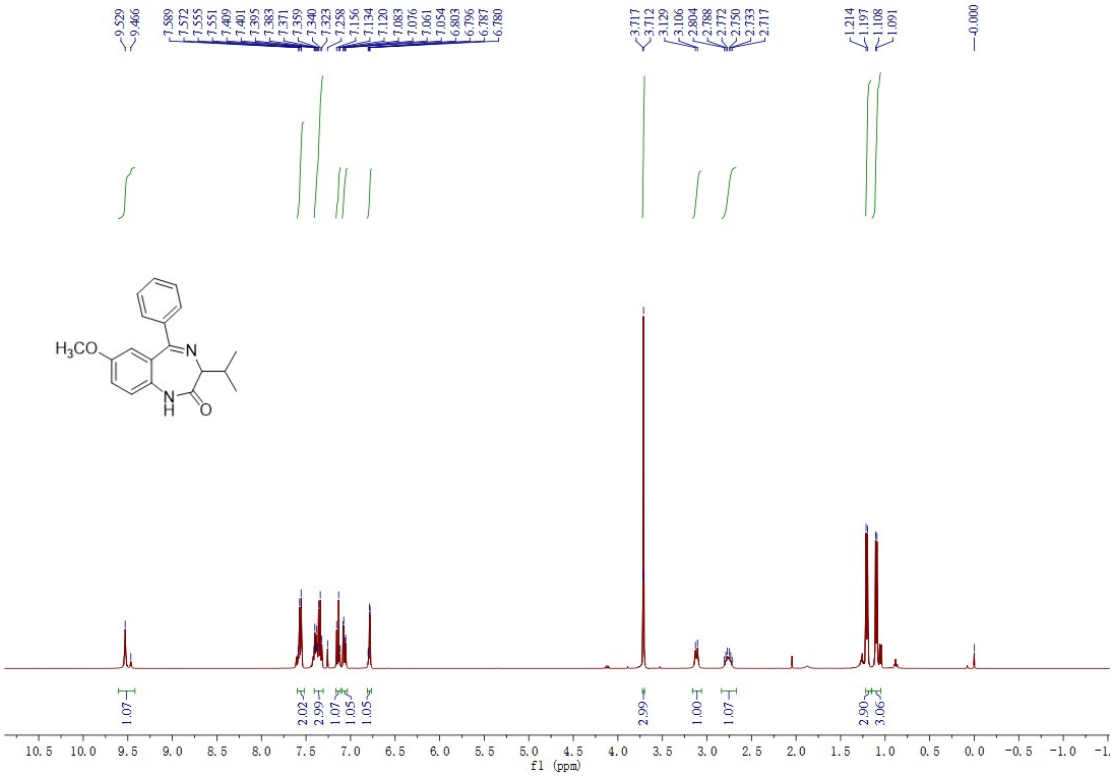


^{1}H NMR of product **4e** ($CDCl_3$)

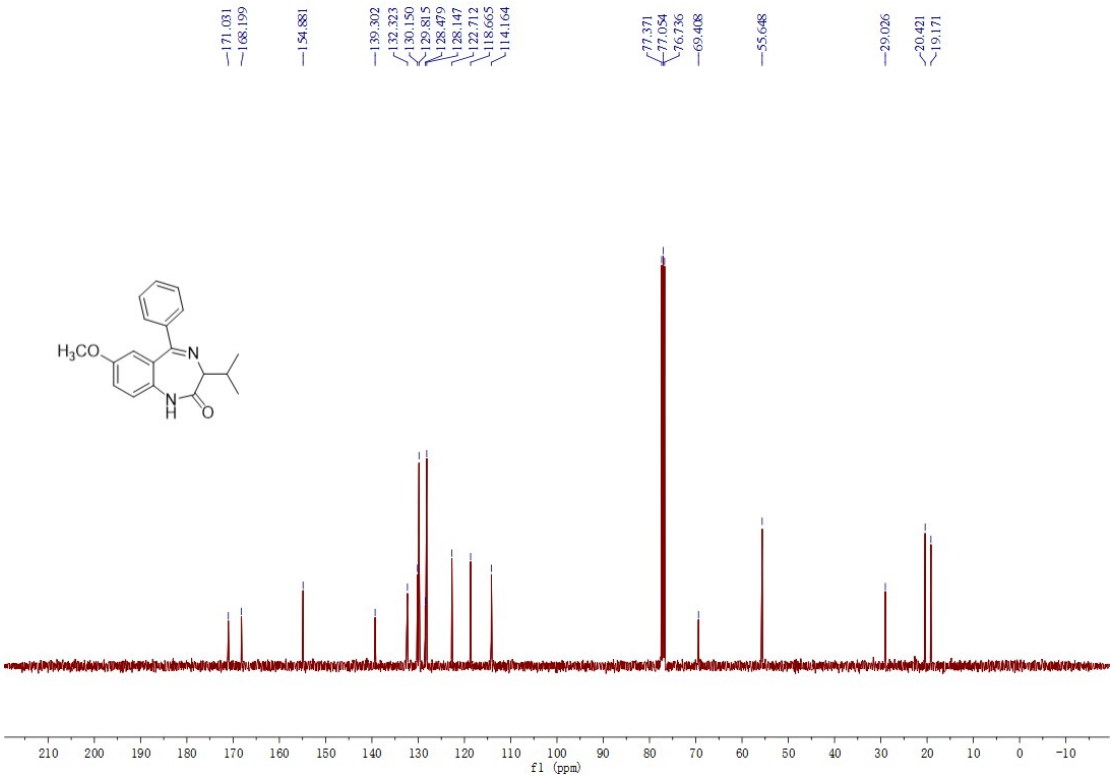
The peak in black oval is the signal of grease.



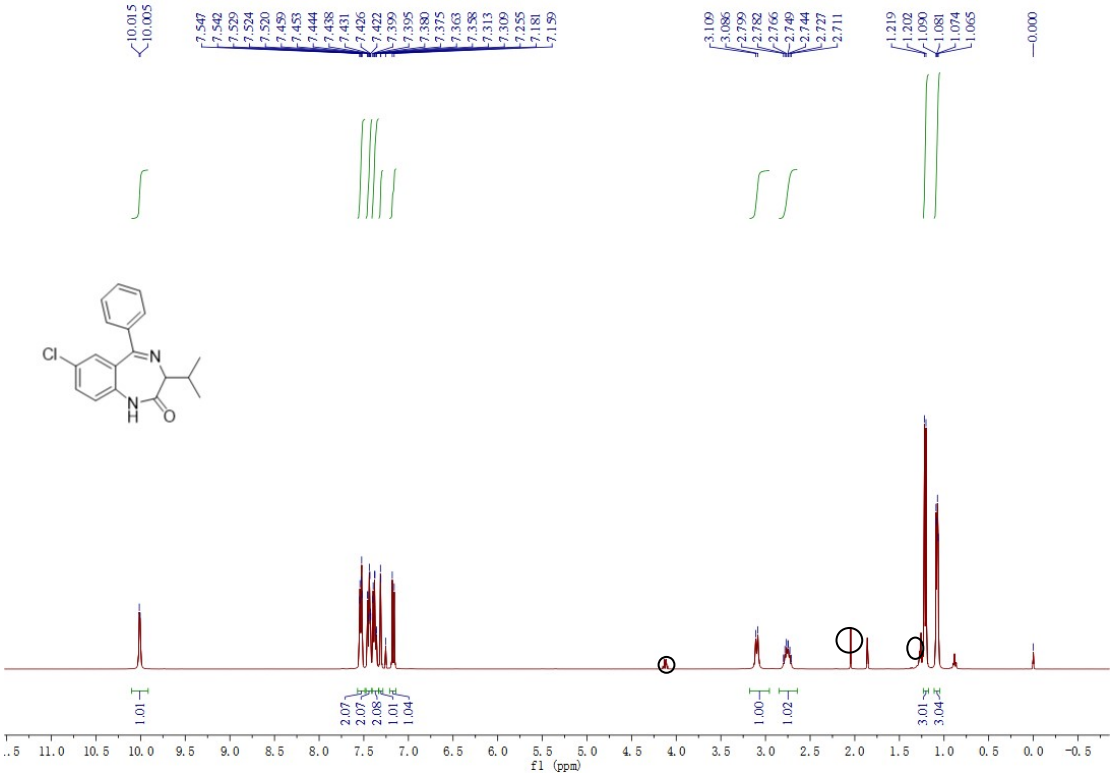
^{13}C NMR of product **4e** ($CDCl_3$)



^{1}H NMR of product **4f** ($CDCl_3$)

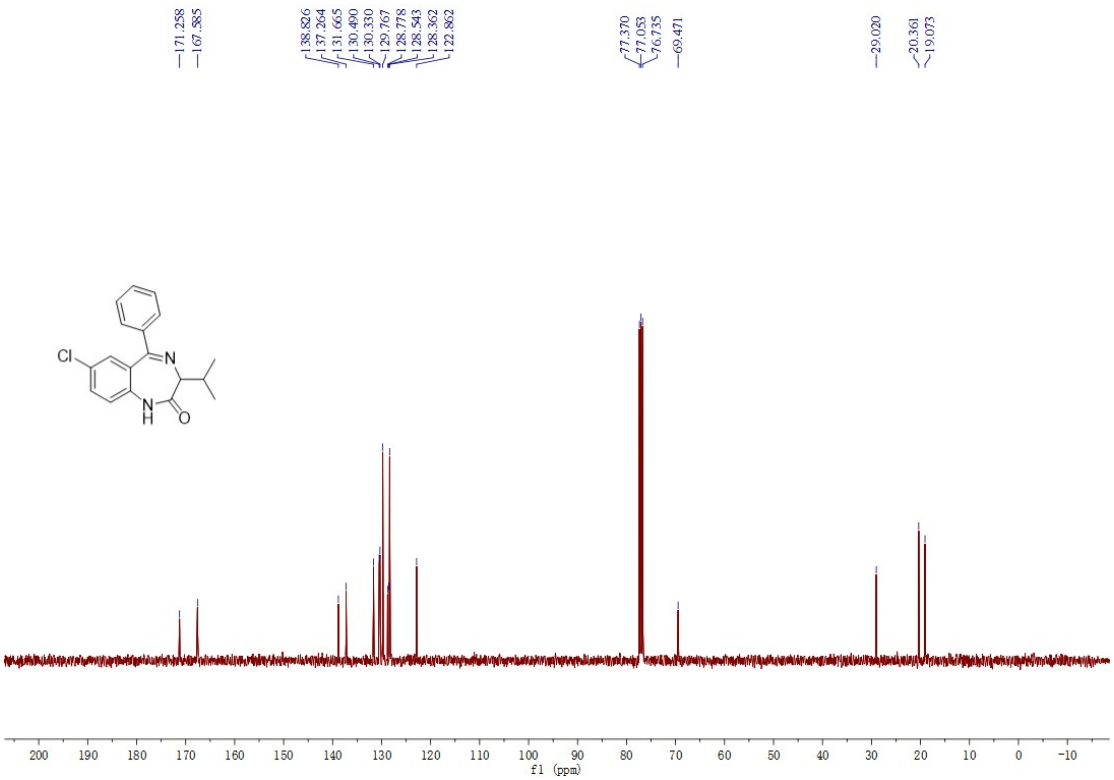


^{13}C NMR of product **4f** ($CDCl_3$)

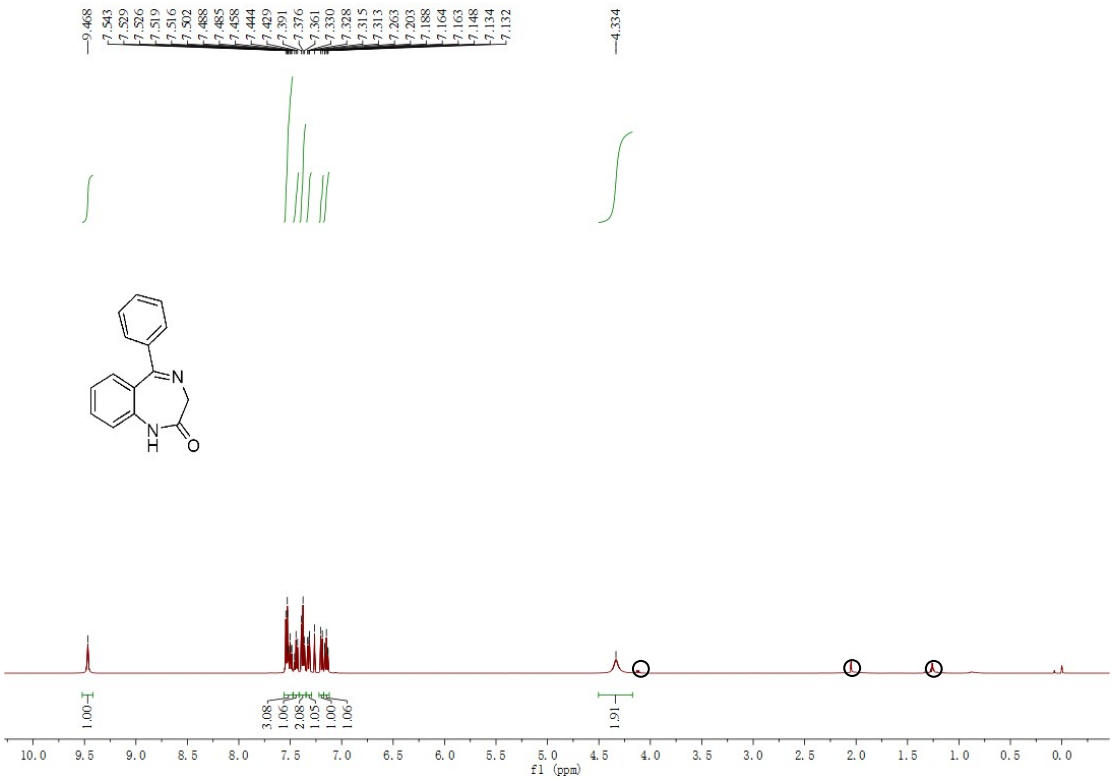


^{1}H NMR of product **4g** ($CDCl_3$)

The peak in black oval is the signal of ethyl acetate.

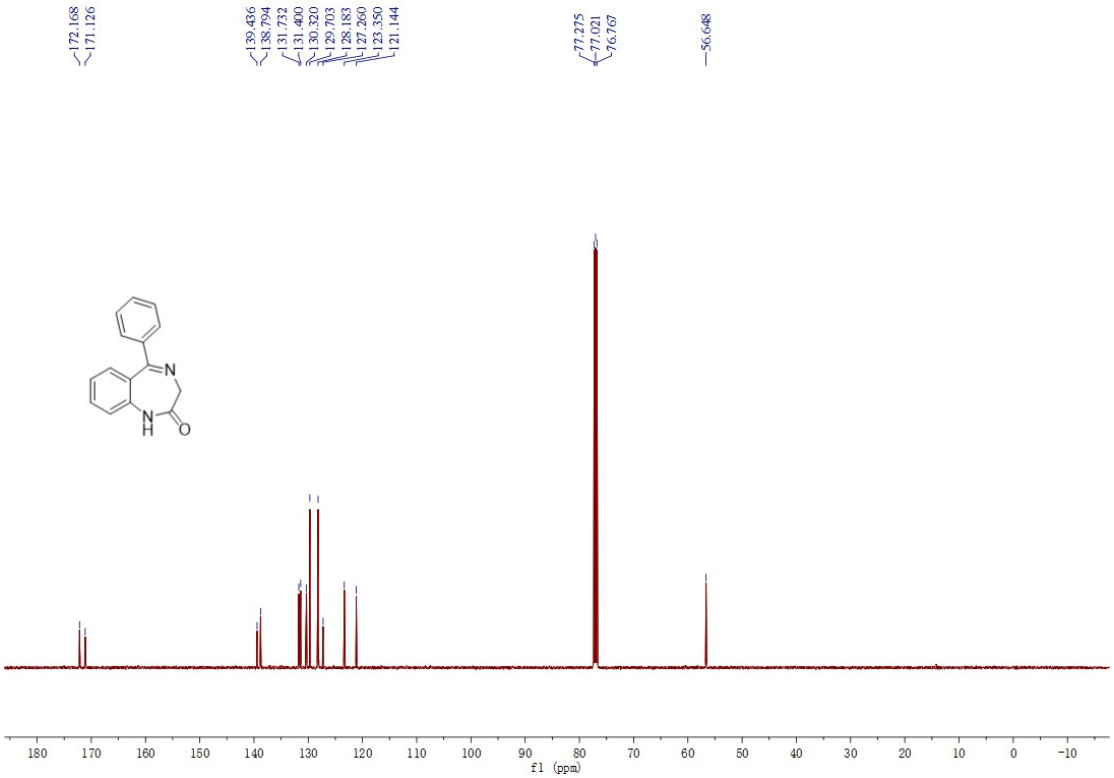


^{13}C NMR of product **4g** ($CDCl_3$)

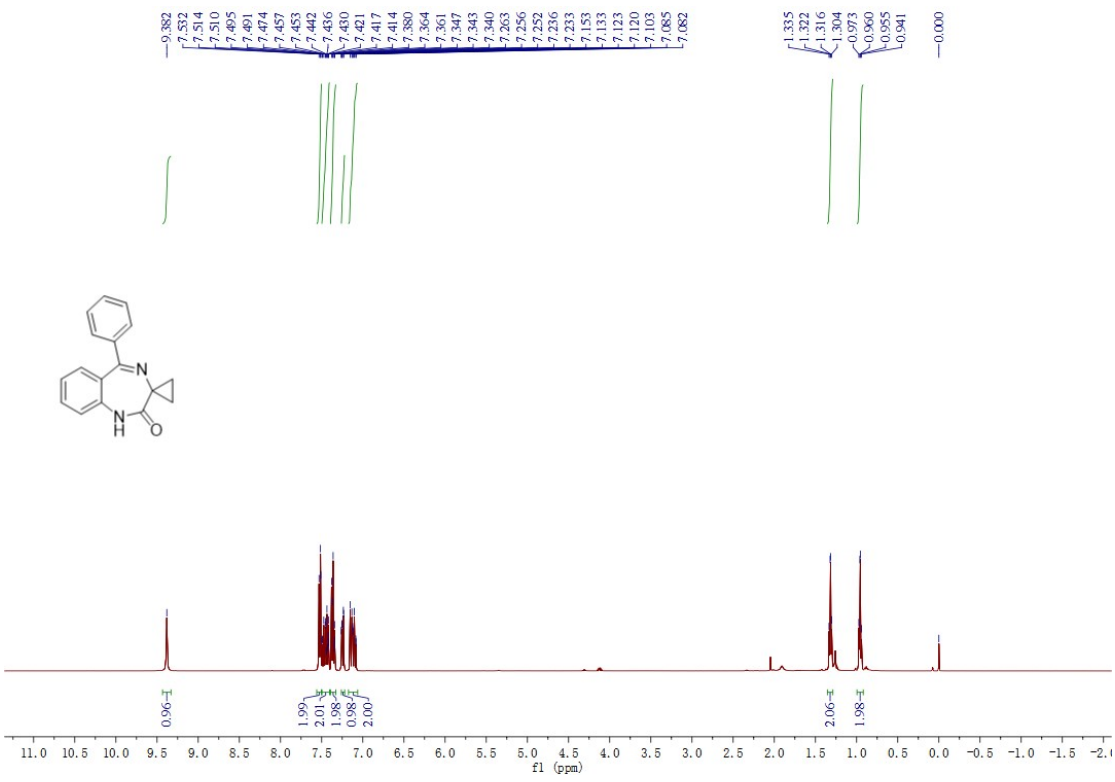


^{1}H NMR of product **4h** ($CDCl_3$)

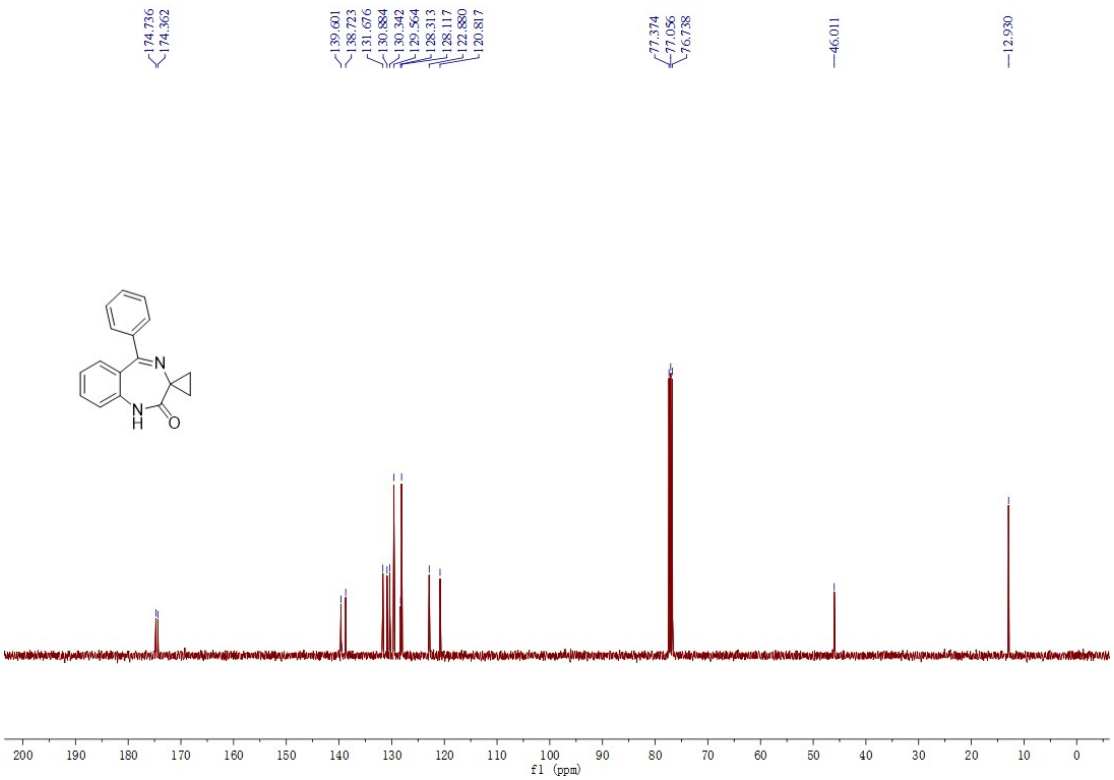
The peak in black oval is the signal of ethyl acetate.



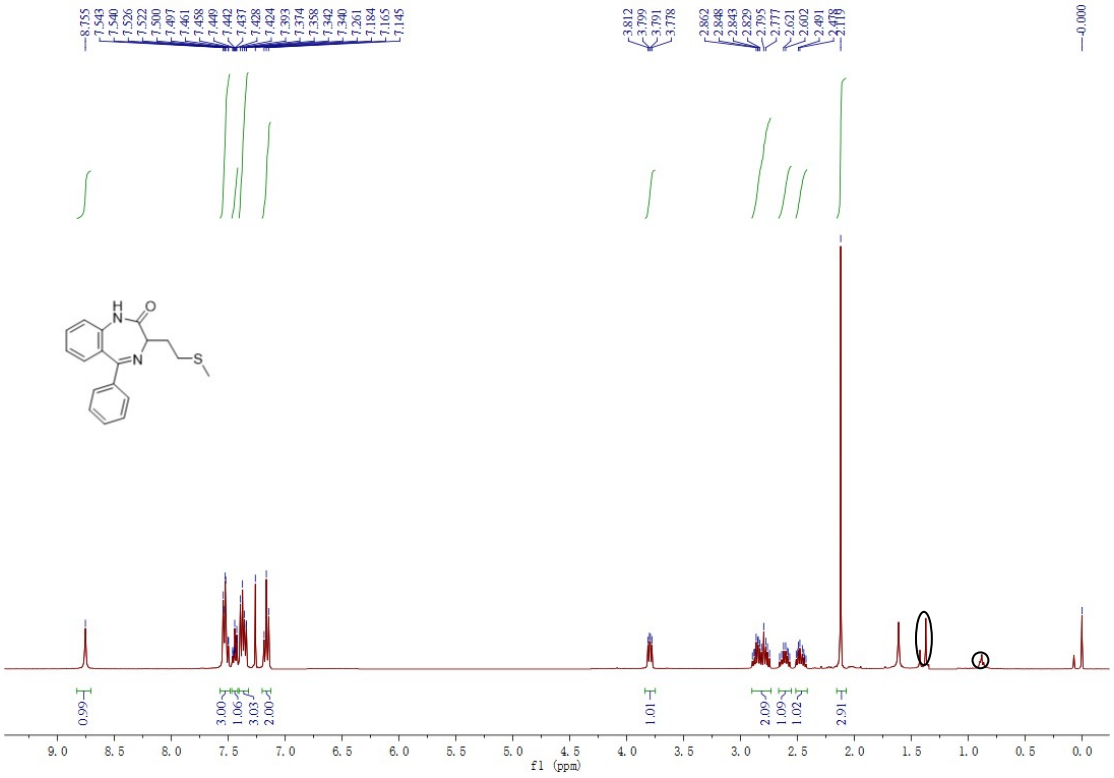
^{13}C NMR of product **4h** ($CDCl_3$)



^{1}H NMR of product **4i** ($CDCl_3$)

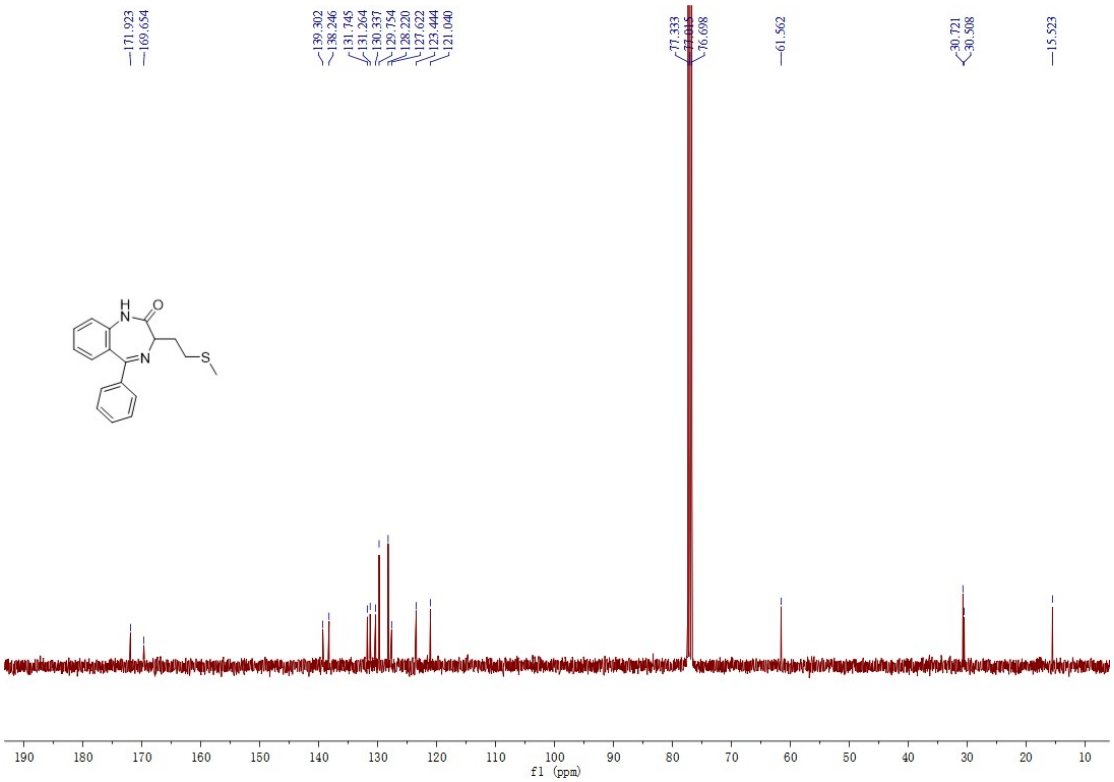


^{13}C NMR of product **4i** ($CDCl_3$)



^{1}H NMR of product **4j** ($CDCl_3$)

The peak in black oval is the signal of grease.



^{13}C NMR of product **4j** ($CDCl_3$)