Supporting Information

Ligand-controlled product selectivity in palladium-catalyzed domino post-Ugi construction of (spiro)polyheterocycles

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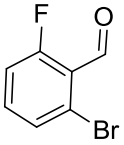
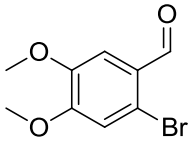
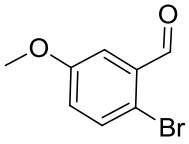
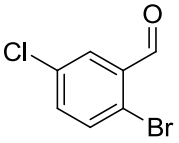
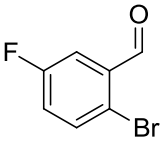
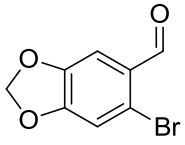
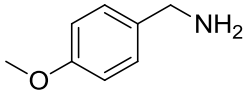
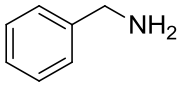
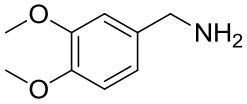
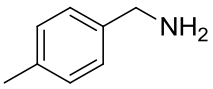
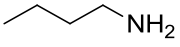
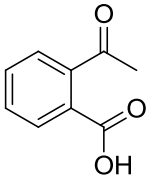
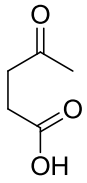
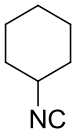
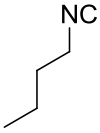
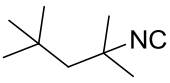
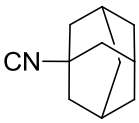
General Experimental Methods

NMR spectra were recorded on a 300 MHz or a 600 MHz instrument using $CDCl_3$ and DMSO-d_6 as solvent unless and otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The notation bs is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). For the Mass spectrometry, ion source temperature was 150-250°C. High-resolution EI or ESI-mass spectra were performed with a resolution of 10,000. Thin layer chromatography was carried out using plates coated with 70-230 mesh silica gels. Commercially available reagents were used without additional purification, unless otherwise stated. Sealed tubes were dried in oven for overnight and cooled at room temperature prior to use.

Table S1: Starting materials for Ugi reaction

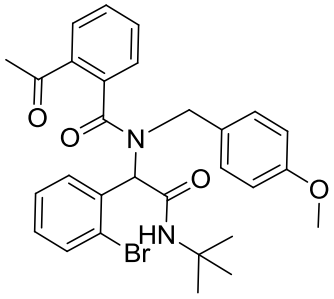
Aldehydes	Amines	Acids	Isonitriles
 **A1**  **A6**  **A2**  **A7**  **A3**  **A4**  **A5**	 **B1**  **B2**  **B3**  **B4**  **B5**	 **C1**  **C2**	 **D1**  **D2**  **D3**  **D4**  **D5**

General procedure for syntheses of Ugi products (1a-r and **4a-f)**

To a solution of aldehyde (**A1-A7**; 200 mg) in methanol (3 mL) were added successively Na_2SO_4 (0.3 g), amine (**B1-B5**; 1.2 equiv), acid (**C1-C2**; 1.2 equiv) and isonitrile (**D1-D5**; 1.2 equiv) in a screw capped vial equipped with a magnetic stir bar. The reaction mixture was stirred at room temperature for 24-48 h in closed vial. After completion of the reaction, the mixture was diluted with dichloromethane (100 mL) and extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtained residue which was subjected to silica gel column chromatography (10-30 % EtOAc in heptane) to afford the desired product **1a-r and 4a-f.**

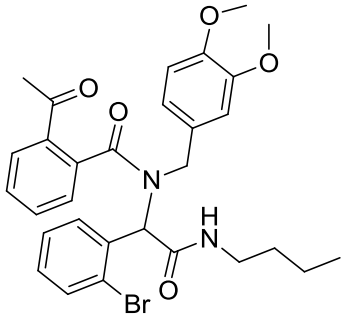
Ugi products appear as mixture of two rotamers, so ^{1}H and ^{13}C NMR spectra are not very characteristic. Only representative data for one compound is given.

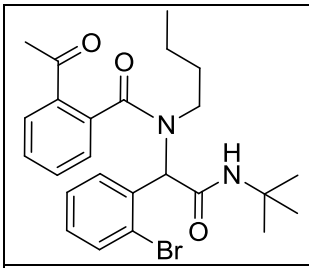
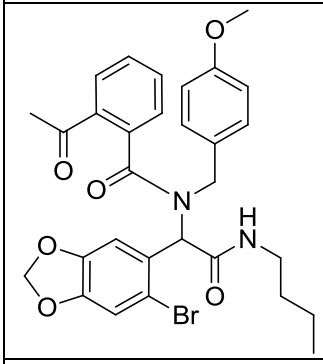
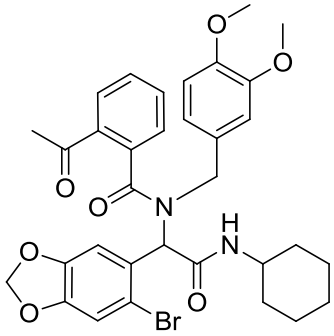
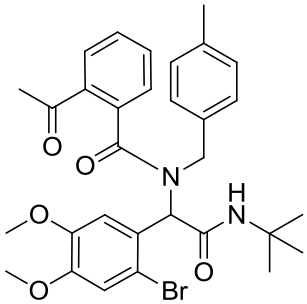
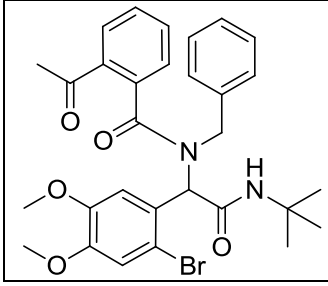
2-acetyl-*N*-(1-(2-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1a**)

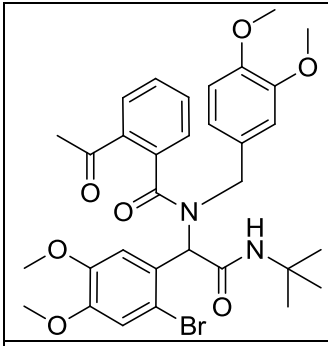
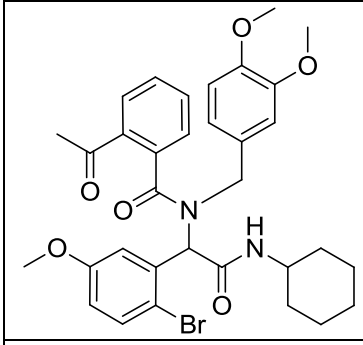
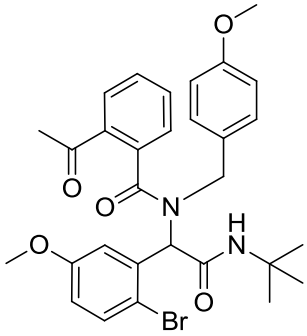
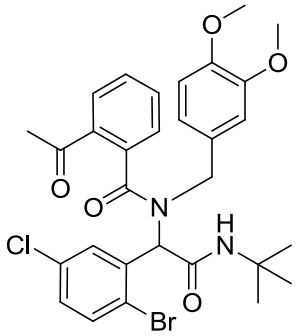
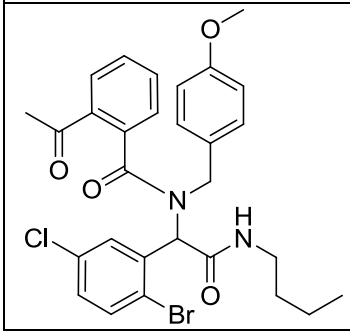


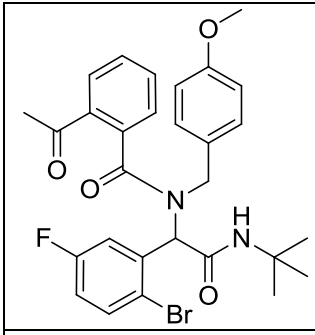
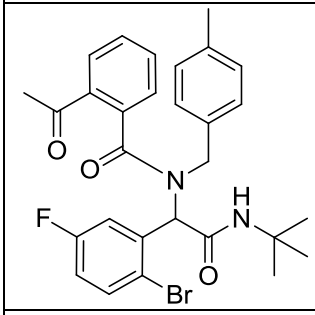
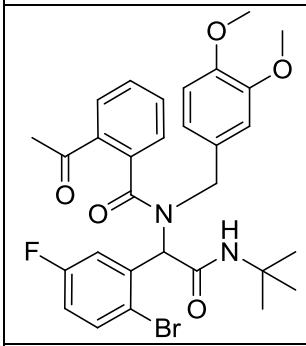
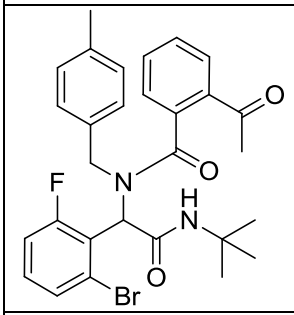
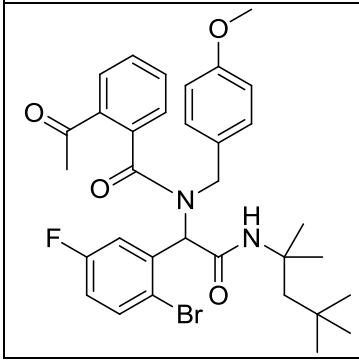
Offwhite solid, Yield 80%, Melting point: 151-152^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.86-7.83 (m, 1H), 7,74-7.66 (m, 1H), 7.56-7.33 (m, 5H), 7.17-7.11 (m, 1H), 6.92-6.86 (m, 2H), 6.80-6.61 (m, 3H), 5.76 (s, 0.71H), 4.98 (s,0.30H), 4.42-4.19 (m, 2H), 3.78-3.73 (m, 3H), 2.73-2.64 (m, 3H), 1.38-1.17 (m, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 198.9, 173.2, 172.1, 167.5, 165.4, 158.9, 158.6, 137.3, 136.6, 136.4, 135.6, 135.4, 134.9, 134.2, 132.8, 132.6, 130.0, 129.9, 129.7, 129.5, 129.3, 129.2, 129.1, 128.9, 128.0, 127.9, 127.7, 127.4, 127.2, 127.0, 125.8, 123.7, 122.4, 113.7, 113.5, 68.7, 64.7, 55.3, 55.2, 52.9, 51.7, 51.5, 48.5, 45.7, 28.8, 28.2, 28.0, 27.6. HRMS (EI) calculated for $C_{24}H_{27}BrN_2O_3$550.1467, found 451.0823(M-100).

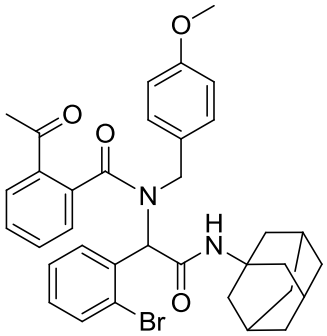
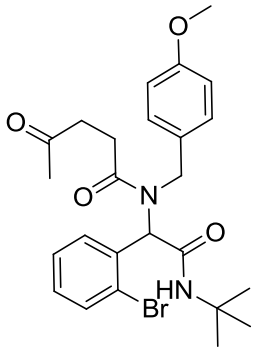
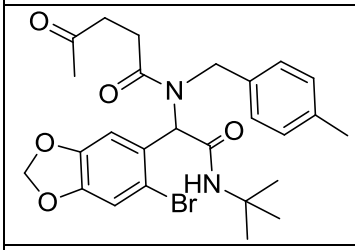
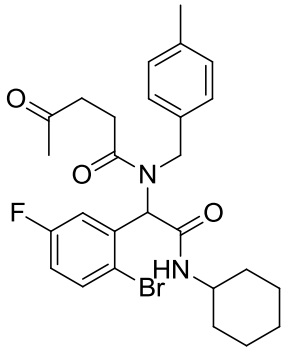
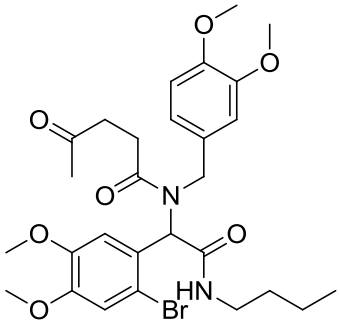
Table S2. Ugi products **1a-r and 4a-f.**

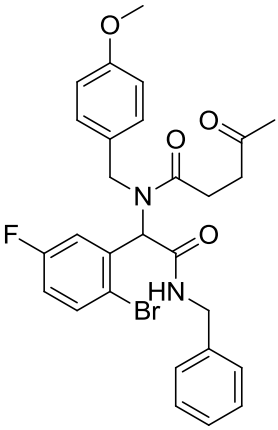
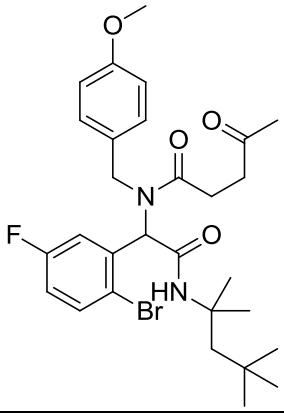
Structure	Data
	2-acetyl-*N*-(1-(2-bromophenyl)-2-(butylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide (**1b**) Offwhite solid, Yield 55%, Melting point: 52-54^{o}C. **HRMS** (EI) calculated for $C_{30}H_{33}BrN_2O_5$ 580.1573, found 580.1574.

	2-acetyl-*N*-(1-(2-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-butylbenzamide (**1c**) Yellow solid, Yield 36%, Melting point: 89-90 ^{o}C. **HRMS** (EI) calculated for $C_{25}H_{31}BrN_2O_3$ 486.1518, found 386.0772(M-100).
	2-acetyl-*N*-(1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-2-(butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1d**) Brown oil, Yield 44%. **HRMS** (EI) calculated for $C_{30}H_{31}BrN_2O_6$ 594.1365, found 515.2246(M-Br).
	2-acetyl-*N*-(1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide (**1e**) Yellow solid, Yield 64%, Melting point: 69-71 ^{o}C. **HRMS** (EI) calculated for $C_{33}H_{35}BrN_2O_7$ 650.1628, found 571.2533(M-Br).
	2-acetyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methylbenzyl)benzamide (**1f**) Yellow oil, Yield 82%. **HRMS** (EI) for $C_{31}H_{35}BrN_2O_5$ calculated 594.1729, found 594.1758.
	2-acetyl-*N*-benzyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(tert-butylamino)-2-oxoethyl)benzamide (**1g**) Yellow solid, Yield 83%, Melting point: 58-60^{o}C. **HRMS** (EI) calculated for $C_{30}H_{33}BrN_2O_5$ 580.1573, found 501.2400(M-Br).

	2-acetyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide (**1h**) Offwhite solid, Yield 80%, Melting point: 66-68^{o}C. **HRMS** (EI) calculated for $C_{32}H_{37}BrN_2O_7$ 640.1784, found 640.1799.
	2-acetyl-*N*-(1-(2-bromo-5-methoxyphenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide (**1i**) White solid, Yield 67%, Melting point: 152-154^{o}C. **HRMS** (EI) calculated for $C_{33}H_{37}BrN_2O_6$ 636.1835, found 557.2626(M-Br).
	2-acetyl-*N*-(1-(2-bromo-5-methoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1j**) White solid, Yield 79%, Melting point: 134-136^{o}C. **HRMS** (EI) calculated for $C_{30}H_{33}BrN_2O_5$ 580.1573, found 501.2378(M-Br).
	2-acetyl-*N*-(1-(2-bromo-5-chlorophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide (**1k**) Offwhite solid, Yield 71%, Melting point: 77-78^{o}C. **HRMS** (EI) calculated for $C_{30}H_{32}BrClN_2O_5$ 614.1183, found 515.0469(M-Br).
	2-acetyl-*N*-(1-(2-bromo-5-chlorophenyl)-2-(butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1l**) White solid, Yield 49%, Melting point: 96-97^{o}C. **HRMS** (EI) calculated for $C_{29}H_{30}BrClN_2O_4$ 584.1077, found 439.0605(M-147).

	2-acetyl-*N*-(1-(2-bromo-5-fluorophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1m**) White solid, Yield 51%, Melting point: 147-149^{o}C. **HRMS** (EI) calculated for $C_{29}H_{30}BrFN_2O_4$ 568.1373, found 469.0722(M-100).
	2-acetyl-*N*-(1-(2-bromo-5-fluorophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methylbenzyl)benzamide **(1n)** White solid, Yield 39%, Melting point: 131-132^{o}C. **HRMS** (EI) calculated for $C_{29}H_{30}BrFN_2O_3$ 552.1424, found 405.0989(M-147).
	2-acetyl-*N*-(1-(2-bromo-5-fluorophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)benzamide **(1o)** Yellow solid, Yield 81%, Melting point: 61-62^{o}C. **HRMS** (EI) calculated for $C_{30}H_{32}BrFN_2O_5$ 598.1479, found 598.1465.
	2-acetyl-*N*-(1-(2-bromo-6-fluorophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methylbenzyl)benzamide (**1p**) White solid, Yield 78%, Melting point: 140-141^{o}C. **HRMS** (EI) calculated for $C_{29}H_{30}BrFN_2O_3$ 552.1424, found 452.9835(M-100)
	2-acetyl-*N*-(1-(2-bromo-5-fluorophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-*N*-(4-methoxybenzyl)benzamide (**1q**) Yellow solid, Yield 66%, Melting point: 50-52^{o}C. **HRMS** (ESI) calculated for $C_{33}H_{39}BrFN_2O_4$ ($[M+H]^+$) 625.2072, found 625.2075.

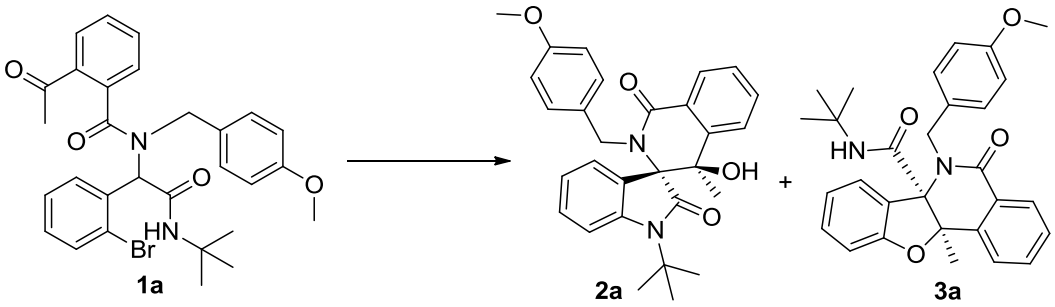
	2-acetyl-*N*-(2-(adamantan-1-ylamino)-1-(2-bromophenyl)-2-oxoethyl)-*N*-(4-methoxybenzyl)benzamide (**1r**) White solid, Yield 66%, Melting point: 170-171^{o}C. **HRMS** (ESI) calculated for $C_{35}H_{38}BrN_2O_4$ ($[M+H]^+$) 629.2010, found 629.2004.
	*N*-(1-(2-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)-4-oxopentanamide (**4a**) Colorless oil, Yield 84%. **HRMS** (EI) calculated for $C_{25}H_{31}BrN_2O_4$ 502.1467, found 403.1027(M-100).
	*N*-(1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methylbenzyl)-4-oxopentanamide (**4b**) White solid, Yield 48%, Melting point: 186-188^{o}C. **HRMS** (EI) calculated for $C_{26}H_{31}BrN_2O_5$ 530.1416, found 430.0648(M-100).
	*N*-(1-(2-bromo-5-fluorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(4-methylbenzyl)-4-oxopentanamide (**4c**) White solid, Yield 48%, Melting point: 165-166^{o}C. **HRMS** (EI) calculated for $C_{27}H_{32}BrFN_2O_3$ 530.1580, found 431.1139(M-100).
	*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(butylamino)-2-oxoethyl)-*N*-(3,4-dimethoxybenzyl)-4-oxopentanamide (**4d**) Yellow oil, Yield 76%. **HRMS** (EI) calculated for $C_{28}H_{37}BrN_2O_7$ 592.1784, found 493.1322(M-100).

	*N*-(2-(benzylamino)-1-(2-bromo-5-fluorophenyl)-2-oxoethyl)-*N*-(4-methoxybenzyl)-4-oxopentanamide (**4e**) Offwhite solid, Yield 66%, Melting point: 141-143^{o}C. **HRMS** (EI) calculated for $C_{28}H_{28}BrFN_2O_4$ 554.1216, found 456.9801(M-100).
	*N*-(1-(2-bromo-5-fluorophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-*N*-(4-methoxybenzyl)-4-oxopentanamide (**4f**) Colorless oil solid, Yield 76%. **HRMS** (ESI) calculated for $C_{29}H_{39}BrFN_2O_4$ ($[M+H]^+$) 577.2072, found 577.2061.

General procedure for the synthesis of spirocyclic oxindoles *via* Buchwald-Hartwig/Aldol reaction sequence

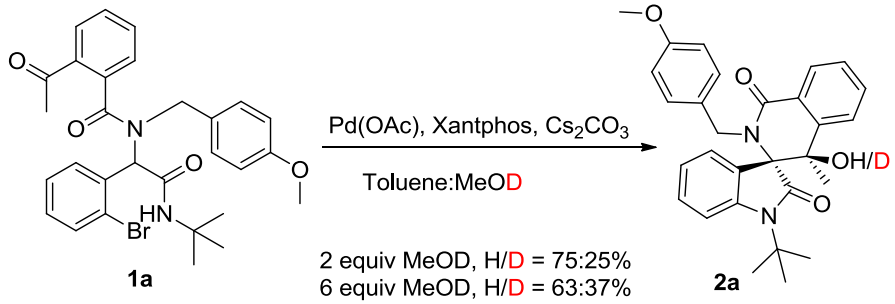
To a dry screw capped glass vial $Pd(OAc)_2$ (5 mol%), Xantphos (7.5 mol%), Cs_2CO_3 (2 equiv.) were loaded along with dry toluene (2 mL). Ugi product **1a-p and 4a-f (**0.2 mmol**)** was added. The reaction vial was evacuated, backfilled with nitrogen (4 cycles) and was stirred at 120°C for 24 hours. After completion, the reaction mixture was cooled, directly loaded over a silica gel column and chromatographed (10-30% EtOAc in heptane) to afford compounds **2a-p and 5a-f**. The structures of the compounds were confirmed by NMR and HRMS data.

Table S2: Effect of different conditions on domino cyclization



	$Pd(OAc)_2$	Ligand	Solvent	Cs_2CO_3	Yield % 2a/3a
a)	-	-	Toluene (2 mL)	2 equiv	0/0
b)	-	Xantphos (7.5 mol%)	Toluene (2 mL)	2 equiv	0/0
c)	5 mol%	-	Toluene (2 mL)	2 equiv	0/0
d)	-	-	Toluene:MeOH[a]	2 equiv	0/0
e)	5 mol%	Xantphos (7.5 mol%)	Toluene:MeOH[a]	2 equiv	77[b]/22
f)	5 mol%	BINAP (7.5 mol%)	Toluene:MeOH[a]	2 equiv	traces/72
g)	-	BINAP (7.5 mol%)	Toluene:MeOH[a]	2 equiv	0/0
h)	5 mol%	-	Toluene:MeOH[a]	2 equiv	0/0

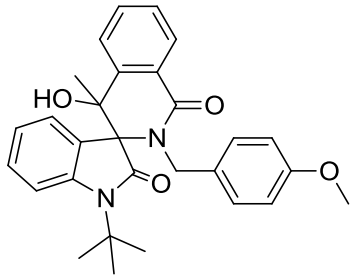
[a] 1.95 mL: 0.05 mL; [b] dr = 64:36



Scheme 1

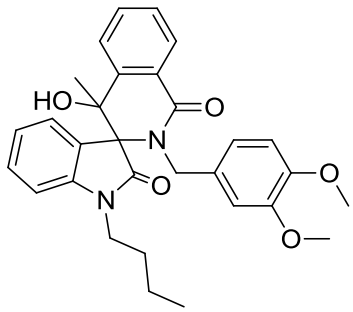
Characterization data for spiro-oxindoles (2a-p and 5a-f)

1-(*tert*-butyl)-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2a**)



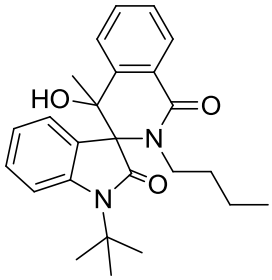
White solid, Yield 97% (*dr*: 75:25), Melting point: 180-182^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.11-8.08 (m, 0.75H), 7.96 (d, *J* = 6.8 Hz, 0.25H), 7.66 -7.33 (m, 5H), 7.23-7.17 (m, 1H), 7.11-7.06 (m, 1H), 6.62-6.42 (m, 4H), 6.02 (s, 0.75H), 5.68 (s, 0.25H), 5.40-5.23 (m, 1H), 3.95-3.87 (m, 1H), 3.63 (s, 4H), 1.23 (s, 6.6H), 1.22 (s, 3H), 1.14 (s, 2.4H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 175.0, 174.0, 165.3, 165.0 158.3, 145.9, 144.5, 144.4, 140.6, 131.9, 131.7, 129.8, 129.6, 129.3, 128.6, 128.4(2), 128.2, 128.1, 127.9, 127.7, 127.2, 126.8, 126.5, 124.6, 124.3, 123.9, 123.8(2), 120.2, 119.9, 113.1, 113.0, 112.8, 74.1, 71.6, 71.2, 71.1, 56.7, 56.2, 54.9(2), 46.1, 45.6, 45.2, 29.0, 28.3, 28.2 21.78, 20.5. **HRMS** (EI) calculated for $C_{29}H_{30}N_2O_4$ 470.2206, found 470.2212.

1-butyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2b**)



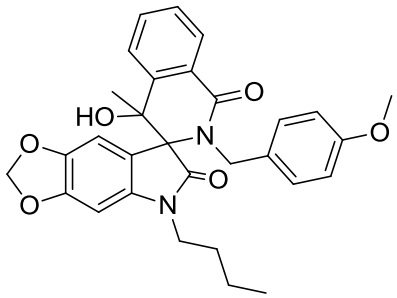
Yellow solid, Yield 68% (*dr*: 66:34), Melting point: 175-177^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ8.15-7.96 (m, 1H), 7.63 -7.30 (m, 5H), 7.20 -7.02 (m, 2H), 6.86-6.82 (m, 1H), 6.63-6.59 (m, 1H), 6.22-6.19 (m, 0.68H), 6.13 (s, 0.66H), 6.00 (s, 0.31H), 5.72 (s, 0.34H), 5.32-5.14 (m, 1H), 4.02-3.92 (m, 1H), 3.70-3.68 (m, 3H), 3.49-3.47 (m, 3H), 3.23-3.12 (m, 1H), 3.02-2.92 (m, 1H), 1.25-0.99 (m, 7H), 0.90 -0.59 (m, 3H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 174.3, 173.2, 164.7, 147.8, 147.7, 145.3, 144.0, 132.0, 131.86, 129.79, 128.59, 128.01, 127.71, 127.36, 126.68, 124.26, 123.80, 123.64, 121.46, 120.69, 120.6, 120.5, 120.0, 111.8, 111.0, 108.5, 108.4, 74.2, 73.6, 71.6, 71.3, 55.4, 55.3, 54.9, 46.3, 28.7, 19.5, 19.3, 13.4. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2328.

1-(*tert*-butyl)-2'-butyl-4'-hydroxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2c**)



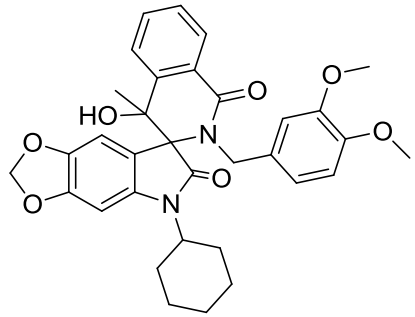
White solid, Yield 74% (*dr*: 65:35), Melting point: 116-117^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 7.99 (dd, *J* = 7.9, 1.4 Hz, 0.65H), 7.86 (dd, *J* = 7.7, 1.0 Hz, 0.35H), 7.57-7.26 (m, 6H), 7.12-7.02 (m, 1H), 5.95 (s, 0.65H), 5.74 (s, 0.35H), 3.69-3.51 (m, 1H), 2.96-2.88 (m, 1H), 1.59-1.56 (m, 9H), 1.50 (s, 1H), 1.26 (s, 2H), 1.19-0.83 (m, 4H), 0.61 (m, 3H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 176.0, 174.7, 164.8, 164.4, 145.3, 144.2, 144.0, 141.1, 131.8, 131.7, 129.4, 1281, 127.7, 127.5, 126.9, 126.8, 126.6, 126.3, 125.7, 124.6, 124.1, 123.7, 121.2, 120.5, 113.4, 113.1, 99.5, 73.8, 72.1, 71.9, 71.2, 57.3, 56.8, 43.6, 29.4, 29.2, 28.43, 28.4, 21.5, 19.5, 19.5, 13.4. **HRMS** (EI) calculated for $C_{25}H_{30}N_2O_3$ 406.2256, found 406.2231.

5-butyl-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'*H*-spiro[[1,3]dioxolo[4,5-*f*]indole-7,3'-isoquinoline]-1',6(2'*H*,4'*H*,5*H*)-dione (**2d**)



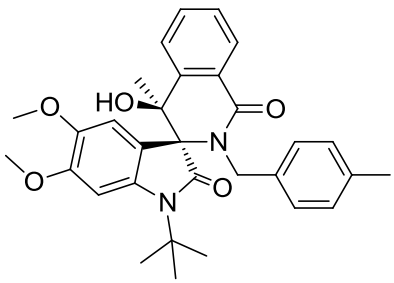
Offwhite solid, Yield 89% (*dr*: 67:33), Melting point: 135-137^{o}C. **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.08 (d, *J* = 7.7 Hz, 0.67H), 7.95 (d, *J* = 7.2 Hz, 0.33H), 7.62 -7.33 (m, 3H), 7.13 (s, 0.33H), 6.87 (s, 0.67H), 6.72-6.65 (m, 6H), 6.09-6.01 (m, 2.67H), 5.62 (s, 0.33H), 5.22-5.02 (m, 1H), 4.07-3.97 (m, 1H), 3.69-3.55 (m, 3H), 3.11-2.96 (m, 2H), 1.26- 0.91 (m, 7H), 0.79-0.73 (m, 3H). **^{13}C NMR (300 MHz, DMSO-d_6)** δ 174.5, 173.4, 165.1, 164.7, 158.2, 148.3, 144.6, 141.8, 141.5, 140.3, 138.9, 132.0, 131.8, 129.5, 129.3, 128.6, 128.4, 128.1, 127.7, 127.3, 126.6, 124.3, 123.8, 114.6, 113.0, 113.0, 109.3, 101.1, 99.5, 92.5, 92.3, 73.6, 71.9, 71.7, 71.0, 54.9, 54.9, 46.0, 45.5, 28.9, 28.4, 19.4, 19.3, 13.5(2). **HRMS** (EI) calculated for $C_{30}H_{30}N_2O_6$ 514.2104, found 514.2119.

5-cyclohexyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-4'-methyl-1'*H*-spiro[[1,3]dioxolo[4,5-*f*]indole-7,3'-isoquinoline]-1',6(2'*H*,4'*H*,5*H*)-dione (**2e**)



Offwhite solid, Yield 96% (*dr*: 68:32), Melting point: 77-79^{o}C. **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.13- 8.05 (m, 0.68H), 7.96 (d, *J* = 7.7 Hz, 0.32H), 7.87-7.28 (m, 3H), 7.18-6.80 (s, 1H), 6.70-6.59 (m, 1H), 6.36-5.97 (m, 3.70H), 5.58 (s, 0.30H), 5.43-4.89 (m, 1H), 4.06-3.95 (m, 1H), 3.66-3.47 (m, 6H), 1.74-1.48 (m, 5H), 1.18-0.82 (m, 8H). **^{13}C NMR (300 MHz, DMSO-d_6)** δ 174.5(2), 165.2, 164.9, 148.9, 148.3, 148.2, 148.0, 147.9(2), 146.9, 144.5, 141.4, 141.1, 140.8, 139.9, 138.6, 131.9, 131.7, 130.9, 129.2, 128.8, 128.3, 127.6, 127.3, 126.8, 126.6, 124.3, 123.9, 120.7, 120.4, 118.4, 116.4, 115.9, 114.8, 112.2, 112.0, 111.5, 111.4, 109.4, 101.2, 93.4, 93.1, 86.2, 78.3, 73.9, 71.7, 71.3, 71.1, 55.4, 55.4, 55.0, 54.9, 51.8, 46.1, 45.6, 28.1, 27.9, 27.7, 25.3, 25.2, 24.8, 24.5, 22.2, 20.4. **HRMS** (EI) calculated for $C_{33}H_{34}N_2O_7$ 570.2366, found 570.2376.

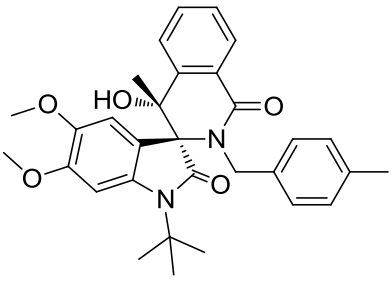
(3*S*,4'*S*)-1-(*tert*-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-2'-(4-methylbenzyl)-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2f**)



Offwhite solid, Yield 24%, Melting point: 192-194^{o}C. **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.07 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.59-7.40 (m, 3H), 7.00 (s, 1H), 6.92 (d, *J* = 7.9 Hz, 2H), 6.76 (s, 1H), 6.68 (d, *J* = 7.9 Hz, 2H), 5.90 (s, 1H), 4.76 (d, *J* = 14.0 Hz, 1H), 4.24 (d, *J* = 15.0 Hz, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 2.19 (s, 3H), 1.31 (s, 9H), 1.17 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d_6)** δ 174.4, 165.1, 149.4, 143.0, 140.8, 138.4, 135.7, 134.3, 131.7, 128.4, 128.2, 127.8, 127.5, 127.2, 124.3, 115.8, 113.6, 98.9, 72.2, 71.2, 56.8, 56.0, 55.8, 46.5, 28.4, 20.6.

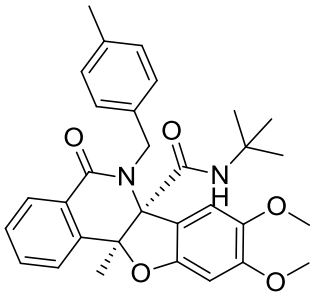
HRMS (EI) calculated for $C_{31}H_{34}N_2O_5$ 514.2468, found 514.2468.

(3*S*,4'*R*)-1-(*tert*-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-2'-(4-methylbenzyl)-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2f'**)



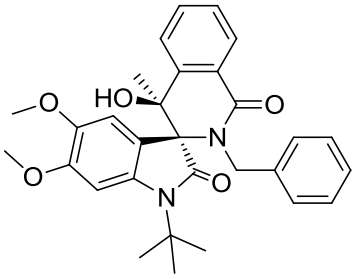
Brown oil, Yield 18%; **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 7.94 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.57-7.44 (m, 2H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.87 (s, 1H), 6.74 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 2H), 5.60 (s, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.56 (s, 3H), 2.19 (s, 3H), 1.56 (s, 3H), 1.30 (s, 9H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 175.4, 165.5, 149.5, 144.6, 142.6, 139.9, 135.8, 134.1, 131.9, 128.2, 127.9, 126.7, 126.4, 123.8, 114.8, 113.3, 99.3, 74.0, 72.1, 56.3, 56.0, 54.9, 46.4, 28.6, 20.6. **HRMS** (EI) calculated for $C_{31}H_{34}N_2O_5$ 514.2468, found 514.2441.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-8,9-dimethoxy-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3f**)



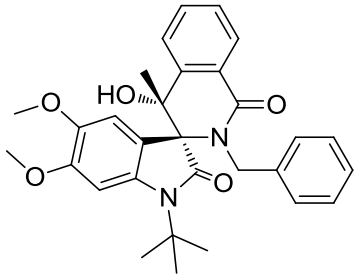
White solid, Yield 25%, Melting point: 196-198^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.10 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.69 (td, *J* = 7.6, 1.5 Hz, 1H), 7.63-7.54 (m, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 6.82 (d, *J* = 7.9 Hz, 2H), 6.66 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 4.98 (d, *J* = 16.2 Hz, 1H), 4.22 (d, *J* = 16.2 Hz, 1H), 3.70 (s, 3H), 3.48 (s, 3H), 2.13 (s, 3H), 1.76 (s, 3H), 1.28 (s, 9H). **^{13}C NMR (75 MHz, DMSO-d$_6$)** δ 165.7, 162.6, 154.9, 151.7, 143.5, 135.0, 134.9, 134.6, 132.3, 129.3, 128.0, 127.4, 127.0, 126.6, 125.7, 114.8, 113.1, 96.1, 85.9, 78.62, 56.8, 55.9, 51.9, 47.0, 27.8, 21.9, 20.5. **HRMS** (EI) calculated for $C_{31}H_{34}N_2O_5$ 514.2468, found 514.2505.

(3*S*,4'*S*)-2'-benzyl-1-(*tert*-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2g**)



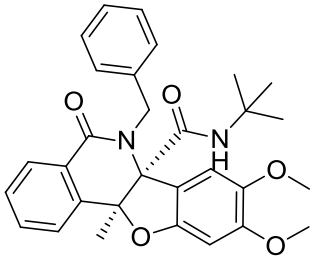
Offwhite solid, Yield 36%, Melting point: 194-196^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.07 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.56-7.44 (m, 3H), 7.17-7.08 (m, 3H), 6.98 (s, 1H), 6.86 (dd, *J* = 6.2, 2.9 Hz, 2H), 6.78 (s, 1H), 5.93 (s, 1H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.36 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.49 (s, 3H), 1.33 (s, 9H), 1.19 (s, 3H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 174.4, 165.1, 149.4, 143.0, 140.9, 138.4, 137.6, 131.7, 128.3, 127.7, 127.6, 127.1, 126.6, 124.3, 115.8, 113.5, 98.9, 72.4, 71.1, 56.9, 56.0, 55.8, 46.9, 28.5, 20.6. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2293.

(3*S*,4'*R*)-2'-benzyl-1-(*tert*-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2g'**)



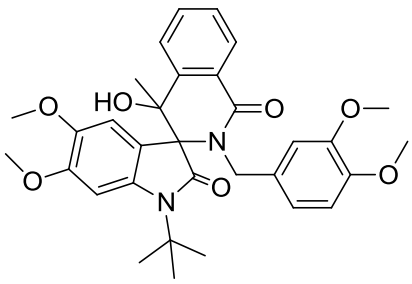
Offwhite solid, Yield 13%, Melting point: 52-53^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 7.94 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.58 -7.44 (m, 2H), 7.38 (td, *J* = 7.5, 1.5 Hz, 1H), 7.20-7.10 (m, 3H), 6.84 (s, 1H), 6.79-6.75 (m, 3H), 5.63 (s, 1H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 1.57 (s, 3H), 1.32 (s, 9H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$):** δ 175.4, 165.6, 149.5, 144.6(2), 139.8, 137.4, 132.0, 127.8, 127.7, 126.6, 126.5, 126.4, 123.9, 114.8, 113.2, 99.3, 74.0, 72.3, 56.4, 56.0, 46.9, 28.7. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2348.

(6a*S*,11a*S*)-6-benzyl-*N*-(*tert*-butyl)-8,9-dimethoxy-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3g**)



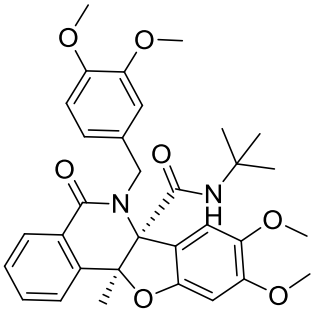
Offwhite solid, Yield 22%, Melting point: 235-237^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.11 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.70 (td, *J* = 7.6, 1.4 Hz, 1H), 7.60 (t, *J* = 7.1 Hz, 1H), 7.05 (s, 1H), 7.00 (dd, *J* = 5.1, 1.7 Hz, 3H), 6.93 (s, 1H), 6.71 (d, *J* = 3.5 Hz, 2H), 6.64 (s, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 4.24 (d, *J* = 16.5 Hz, 1H), 3.68 (s, 3H), 3.44 (s, 3H), 1.76 (s, 3H), 1.29 (s, 9H). **^{13}C NMR (75 MHz, DMSO-d$_6$)** δ 165.6, 162.6, 154.9, 151.7, 143.4, 138.0, 134.9, 132.4, 129.3, 127.5, 127.4, 127.0, 126.6, 125.7, 125.5, 114.6, 113.1, 96.0, 85.8, 78.6, 56.8, 55.8, 51.8, 47.1, 27.8, 21.8. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.23112, found 500.2305.

1-(*tert*-butyl)-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2h**)



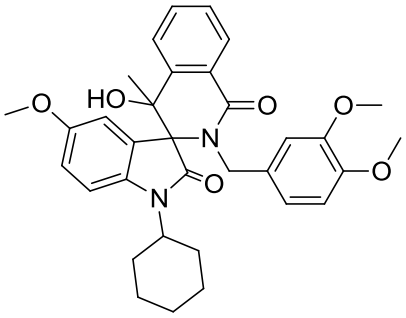
Offwhite solid, Yield 58% (*dr*: 78:22), Melting point: 198-200^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.09 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.58-7.33 (m, 3H), 7.20-7.03 (m, 1H), 6.77-6.60 (m, 2H), 6.38-6.13 (m, 2H), 5.93 (s, 0.78H), 5.59 (s, 0.22H), 5.13-4.91 (m, 1H), 4.20-3.94 (m, 1H), 3.82 (s, 3H), 3.77-3.58 (m, 6H), 3.54-3.52 (m, 3H), 1.29-1.27 (m, 9H), 1.21-1.14 (m, 3H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 175.4, 174.4, 165.5, 165.4, 165.1, 149.4, 147.9, 147.8, 144.6, 143.1, 142.7, 140.8, 140.0, 138.5, 131.9, 131.6, 129.4, 129.0, 128.5(2), 127.2, 126.8, 126.5, 124.3, 123.9, 120.6, 120.3, 115.7, 114.8, 113.8(2), 111.4, 99.2, 98.9, 74.1, 71.9, 71.7, 71.2, 56.7, 56.4, 56.2, 56.0, 56.0, 55.5, 55.4, 54.9, 54.8, 46.2, 46.0, 28.6, 28.5, 20.4. **HRMS** (EI) calculated for $C_{32}H_{36}N_2O_7$ 560.2523, found 560.2548.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-6-(3,4-dimethoxybenzyl)-8,9-dimethoxy-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3h**)



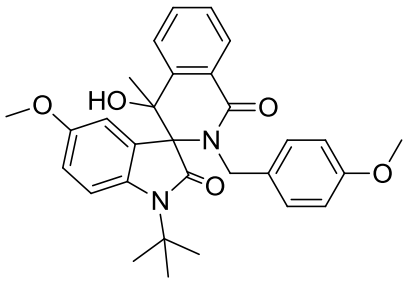
Offwhite solid, Yield 19%, Melting point: 124-126^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.10 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.69 (td, *J* = 7.6, 1.5 Hz, 1H), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H), 7.14 (s, 1H), 6.94 (s, 1H), 6.69 (s, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.36 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 15.9 Hz, 1H), 4.19 (d, *J* = 15.9 Hz, 1H), 3.70 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H), 3.44 (s, 3H), 1.76 (s, 3H), 1.29 (s, 9H). **^{13}C NMR (75 MHz, DMSO-d$_6$)** δ 165.5, 162.7, 154.9, 151.7, 148.0, 146.9, 143.5, 134.8, 132.3, 130.6, 129.3, 127.4, 127.1, 126.6, 118.4, 114.0, 113.2, 111.2, 109.7, 96.1, 85.9, 78.7, 56.8, 55.8, 55.5, 54.9, 51.86, 46.9, 27.8, 21.8. **HRMS** (EI) calculated for C32H36N2O7 560.2523, found 560.2511.

1-cyclohexyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-5-methoxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2i**)



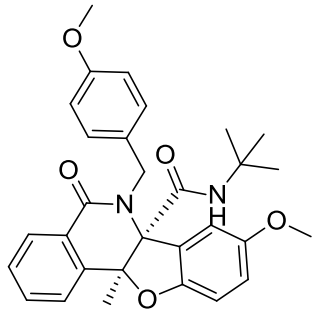
Offwhite solid, Yield 95% (*dr*: 73:27), Melting point: 161-163^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.09 (dd, *J* = 7.5, 1.5 Hz, 0.73H), 7.97 (dd, *J* = 7.6, 1.1 Hz, 0.27H), 7.59-7.35 (m, 3H), 7.15-6.78 (m, 3H), 6.67-6.62 (m, 1H), 6.32-6.05 (m, 2H), 6.02 (s,0.73H), 5.64 (s, 0.27H), 5.20-4.91 (m, 1H), 4.10-4.07 (m, 1H), 3.78 – 3.43 (m, 9H), 1.72-1.64 (m, 5H), 1.24-0.89(m, 8H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 173.8, 172.7, 166.1, 165.2, 164.8, 154.0, 153.6, 147.9, 147.9, 140.9, 136.9, 131.9, 131.7, 129.1, 128.8, 128.3, 127.7, 127.3, 126.8, 126.6, 125.7, 124.8, 124.2, 123.8, 120.7, 120.4, 115.6, 115.4, 114.3, 114.0, 112.2, 112.0, 111.4, 110.2, 109.8, 73.8, 71.8, 71.4, 71.0, 55.6, 55.4, 55.4, 55.0, 54.9, 51.5, 51.3, 46.2, 28.0, 27.8, 25.2, 24.6, 20.6. **HRMS** (EI) calculated for $C_{33}H_{36}N_2O_6$ 556.2573, found 556.2608.

1-(*tert*-butyl)-4'-hydroxy-5-methoxy-2'-(4-methoxybenzyl)-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2j**)



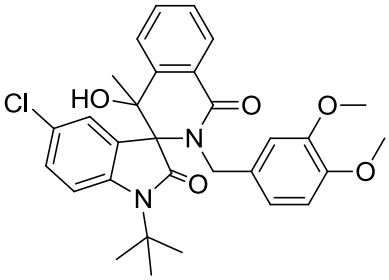
Offwhite solid, Yield 76% (*dr*: 86:14), Melting point: 192-194^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.60-7.35 (m, 3H), 7.16-7.10 (m, 1H), 7.04-7.01 (m, 1H), 6.93-6.90 (m, 1H), 6.63-6.57 (m,4H), 5.98 (s, 0.86H), 5.65 (s, 0.14H), 5.09-5.04 (m, 1H), 4.019-4.04 (m, 1H), 3.72-3.69 (m, 3H), 3.64 (s, 3H), 1.27-1.24 (m, 9H), 1.17 (s, 3H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 173.6, 165.0, 158.3, 153.5, 140.8, 137.7, 131.7, 129.4, 128.7, 128.3, 127.5, 127.2, 126.0, 124.3, 115.4, 113.8, 113.2, 113.1, 74.0, 72.0, 71.0, 56.6, 56.1, 55.4, 55.3, 54.9, 45.8, 28.3, 28.2, 20.6. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2345.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-8-methoxy-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3j**)



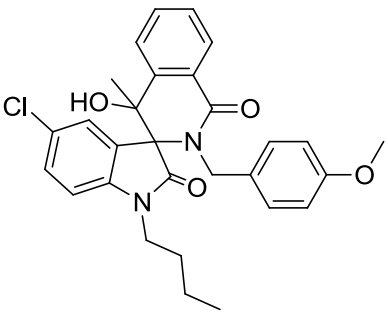
Offwhite solid, Yield 23%, Melting point: 146-126^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.10 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.69 (td, *J* = 7.6, 1.5 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 6.95 (s, 1H), 6.85-6.78 (m, 2H), 6.63-6.52 (m, 4H), 4.91 (d, *J* = 15.9 Hz, 1H), 4.21 (d, *J* = 15.9 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 1.76 (s, 3H), 1.27 (s, 9H). **^{13}C NMR (75 MHz, DMSO-d$_6$)** δ 165.1, 162.8, 157.4, 153.9, 153.8, 134.8, 132.4, 129.9, 129.4, 127.4, 127.1, 127.0, 126.5, 125.9, 116.4, 114.4, 112.9, 110.7, 85.8, 78.5, 55.9, 54.9, 51.9, 46.8, 27.8, 21.5. **HRMS** (EI) calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2339.

1-(*tert*-butyl)-5-chloro-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2k**)



White solid, Yield 63% (*dr*: 81:19), Melting point: 180-181^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.12 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.76-7.36 (m, 6H), 7.23-7.15 (m, 1H), 7.03 – 6.86 (m, 1H), 6.66-6.61 (m, 1H), 6.45 (s, 0.30H), 6.24-6.23 (m, 0.70H), 6.20-6.18(m, 0.82H), 6.15 (s, 0.81H), 6.10-6.07 (m, 0.20H), 5.75 (s, 0.19H), 5.36-3.96 (m, 2H), 3.72-3.62 (m, 6H), 1.25 (s, 7H), 1.21 (s, 1H), 1.16 (s, 2H), 1.01 (s, 2H). **^{13}C NMR (300 MHz, DMSO-*d*$_6$)** δ 174.8, 173.7, 168.5, 168.0, 165.2, 164.8, 148.7, 148.1, 148.0(2), 147.9, 144.6, 144.1, 143.3, 140.4, 132.2, 132.0, 131.9, 130.6, 130.0, 128.9, 128.6, 128.5, 128.1, 127.8, 127.3, 126.8, 126.7, 126.6 126.0, 125.2, 124.4, 123.8, 123.1, 121.3, 120.9, 120.6, 120.4, 114.1, 112.2, 111.9, 111.7, 111.3, 111.2, 74.2, 71.6, 71.4, 71.2, 69.7, 57.1, 56.5, 55.5, 55.4(2), 54.9, 50.6, 46.1, 43.5, 28.2, 28.0, 27.8, 22.0, 20.6. **HRMS** (EI) calculated for $C_{30}H_{31}ClN_2O_5$ 534.1921, found 534.1908. [The corresponding benzofuro-isoquinoline carboxamide is obtained in an isolated yield of 19**%** as byproduct].

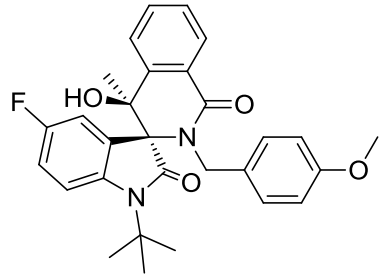
1-butyl-5-chloro-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2l**)



Offwhite solid, Yield 71% (*dr*: 77:23), Melting point: 202-204^{o}C. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 8.11 (d, *J* = 7.7 Hz, 0.78H), 7.98 (d, *J* = 7.7 Hz, 0.22H), 7.64-7.13 (m, 6H), 6.97-6.79 (m, 1H), 6.68-6.48 (m, 4H), 6.17 (s, 0.77H), 5.79 (s, 0.23H), 5.17-4.86 (m, 1H), 4.20-4.03 (m, 1H), 3.67-3.62 (m, 2H), 3.26-2.86 (m, 2H), 1.47-0.94 (m, 7H), 0.90 -0.68 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 174.0, 172.8, 165.0, 164.6, 158.3(2), 144.3, 142.8, 132.1, 129.6, 129.5, 129.3, 128.1, 128.0, 127.9, 127.8, 127.4, 126.7, 125.6, 125.3, 124.9, 124.3, 113.1, 110.0, 73.6, 71.8, 71.7, 71.0, 54.9, 46.1, 28.7, 19.4, 13.5. HRMS (EI) calculated for

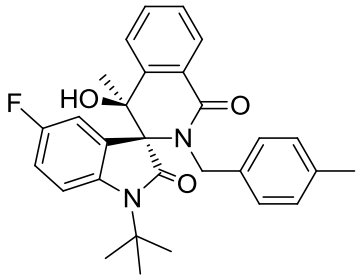
$C_{29}H_{29}ClN_2O_4$ 504.1816, found 504.1823.

(3*S*,4'*S*)-1-(tert-butyl)-5-fluoro-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (**2m**)



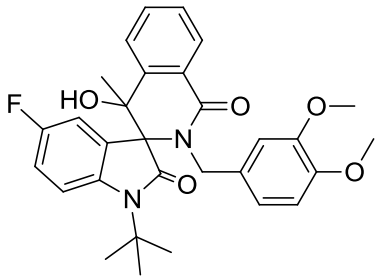
White solid, Yield 58% (*dr*: 97:3), Melting point: 210-212^{o}C. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 8.11 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.62-7.52 (m, 1H), 7.60-7.46 (M, 2H), 7.24-7.17 (m, 3H), 6.68-6.58 (m, 4H), 6.10 (s, 1H), 5.70 (s, 1H), 5.16 (d, *J* = 13.6 Hz, 1H), 4.04 (d, *J* = 13.6 Hz, 1H), 3.65 (s, 3H), 1.26 (s, 9H), 1.17 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 173.8, 164.8, 158.4, 155.2, 140.7, 140.6, 140.5, 131.9, 129.5, 128.3, 128.2, 127.7, 127.3, 126.7, 126.6, 124.4, 116.0, 116.0, 115.4, 113.7, 113.6, 113.2, 71.7, 71.1, 56.9, 55.0, 54.9, 45.7, 28.1, 20.6. **HRMS** (EI) calculated for $C_{29}H_{29}FN_2O_4$ 488.2111, found 488.2097. [The corresponding benzofuro-isoquinoline carboxamide **3m** is obtained in an isolated yield of 23% as byproduct]

(3*S*,4'*S*)-1-(*tert*-butyl)-5-fluoro-4'-hydroxy-4'-methyl-2'-(4-methylbenzyl)-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2n)**



White solid, Yield 67% (*dr*: 92:8), Melting point: 216-218^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.10 (d, *J* = 7.7 Hz, 0.92H), 7.96 (d, *J* = 7.7 Hz, 0.08H), 7.59 -7.40 (m, 3H), 7.29-7.12 (m, 3H), 6.90-6.86 (m, 2H), 6.61-6.41 (m, 2H), 6.11 (s, 0.92H), 5.72 (s, 0.08H), 5.28-5.13 (m, 1H), 4.15-3.95 (m, 1H), 2.17 (s, 3H), 1.24 (s, 8.3H), 1.20 (s,0.7H), 1.16 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 173.8, 164.8, 158.4, 155.2, 140.6, 140.5, 136.0, 133.5, 131.9, 128.4, 128.3, 128.1, 127.7, 127.3, 126.6, 126.5, 124.4, 116.0, 115.7, 115.4, 113.7, 113.6, 74.1, 71.8, 71.1, 56.9, 56.4, 46.2, 28.0, 20.6. **HRMS** (EI) calculated for $C_{29}H_{29}FN_2O_3$ 472.2162, found 472.2148. [The corresponding benzofuro-isoquinoline carboxamide **3n** is obtained in an isolated yield of 23% as byproduct]

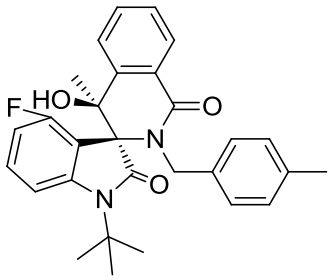
1-(*tert*-butyl)-2'-(3,4-dimethoxybenzyl)-5-fluoro-4'-hydroxy-4'-methyl-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2o**)



White solid, Yield 62% (*dr*: 65:35), Melting point: 160-161^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.12 (d, *J* = 6.8 Hz, 0.65H), 7.98 (d, *J* = 7.3 Hz, 0.35H), 7.66-7.20 (m, 6H), 6.65-6.60 (m, 1H), 6.23-6.12 (m, 2.65H), 5.71 (s, 0.35H), 5.44-526 (m, 1H), 4.00-3.92 (m, 1H), 3.63-3.53 (m, 6H), 1.36-0.94 (m, 12H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 173.8, 165.2, 164.9, 158.4, 147.9, 147.8, 144.2, 142.0, 140.7, 140.4, 132.0, 131.8, 128.5, 128.2, 128.1, 127.8, 127.3, 126.7, 126.7, 126.6, 126.6, 124.4, 123.8, 120.9, 120.6, 116.0, 115.8, 115.6, 115.5, 115.3, 115.1, 113.6, 113.5, 112.2, 112.0, 111.3, 111.1, 74.2, 71.7, 71.4, 71.2, 56.9, 56.3, 55.4(2) ,54.9, 46.0(2), 30.7, 28.2, 28.1, 20.4. **HRMS** (EI) calculated

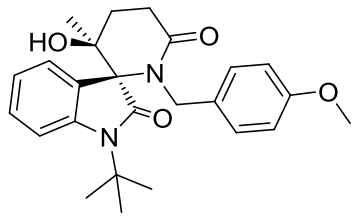
for $C_{30}H_{31}FN_2O_5$ 518.2217, found 518.2249. [The corresponding benzofuro-isoquinoline carboxamide is obtained in an isolated yield of 25% as byproduct]

(3*S*,4'*S*)-1-(*tert*-butyl)-4-fluoro-4'-hydroxy-4'-methyl-2'-(4-methylbenzyl)-1'*H*-spiro[indoline-3,3'-isoquinoline]-1',2(2'*H*,4'*H*)-dione (**2p**)



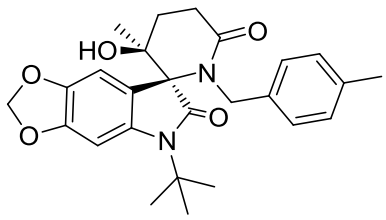
White solid, Yield 88% (*dr*: 98:2), Melting point: 197-199 ^{o}C. **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.12 (d, *J* = 7.3 Hz, 1H), 7.58-7.34 (m, 4H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.53 (d, *J* = 7.9 Hz, 2H), 6.13 (s, 1H), 5.67 (d, *J* = 15.0 Hz, 1H), 3.71 (d, *J* = 15.0 Hz, 1H), 2.15 (s, 3H), 1.21 (s, 3H), 1.19 (s, 9H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ 173.5, 164.5, 160.9, 157.6, 146.3, 146.2, 140.5, 136.3, 133.1, 131.7, 131.4, 131.3, 128.7, 128.3, 128.2, 127.5, 127.3, 124.5, 111.6, 111.4, 110.0, 109.7, 109.436, 73.8(2), 72.3, 57.1, 46.7, 28.0, 21.2, 20.6. **HRMS** (EI) calculated for $C_{29}H_{29}FN_2O_3$ 472.2162, found 472.2122.

(2'*S*,3'*S*)-1-(*tert*-butyl)-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (**5a**)



Colorless oil, Yield 65% (*dr* > 95:5), ^{1}H **NMR (75 MHz, DMSO-d_6)** δ 7.37-7.26 (m, 3H), 6.98-6.93 (m, 3H), 6.72-6.50 (m, 4H), 5.25 (s, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 3.80 (d, *J* = 15.0 Hz, 1H), 2.84-2.32 (m, 3H), 1.41 (s, 9H), 0.72 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6):** δ 175.4, 171.0, 158.1, 143.8, 129.2, 129.1, 128.9, 128.3, 125.2, 120.8, 113.0, 112.8, 72.8, 69.7, 57.0, 54.9, 46.0, 29.1, 28.3, 24.0. **HRMS** (EI) calculated for $C_{25}H_{30}N_2O_4$ 422.2206, found 422.2178.

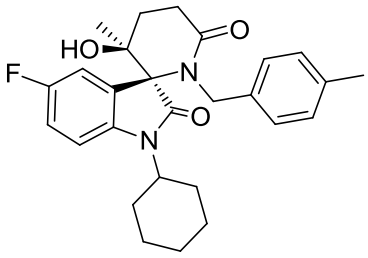
(2'*S*,3'*S*)-5-(*tert*-butyl)-3'-hydroxy-3'-methyl-1'-(4-methylbenzyl)spiro[[1,3]dioxolo[4,5-*f*]indole-7,2'-piperidine]-6,6'(5*H*)-dione (**5b**)



Offwhite solid, Yield 55% (*dr* > 95:5), Melting point: 182-184^{o}C. **^{1}H NMR (300 MHz, DMSO-d_6)** δ 7.03 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.76 (s, 1H), 6.66 (d, *J* = 7.9 Hz, 2H), 5.97 (d, *J* = 6.6 Hz, 2H), 5.24 (s, 1H), 4.19 (d, *J* = 15.1 Hz, 1H), 4.02 (d, *J* = 15.1 Hz, 1H), 2.84-2.64 (m, 1H), 2.60-2.54 (m, 1H), 2.42-2.35 (m, 1H), 2.20 (s, 3H), 1.65-1.54 (m, 1H), 1.41 (s, 9H), 0.75 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d_6):** δ 175.5, 171.0, 147.5, 141.2, 138.0, 135.4, 134.7, 128.1, 127.6, 117.4, 109.2, 101.0, 96.2, 73.0, 69.8, 57.1, 46.5, 29.1, 28.4, 24.0, 20.60. **HRMS** (EI) calculated for $C_{26}H_{30}N_2O_5$ 450.2155, found 450.2137.

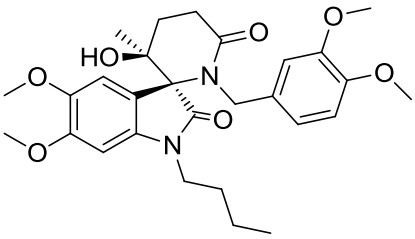
.

(2'*S*,3'*S*)-1-cyclohexyl-5-fluoro-3'-hydroxy-3'-methyl-1'-(4-methylbenzyl)spiro[indoline-3,2'-piperidine]-2,6'-dione (**5c**)



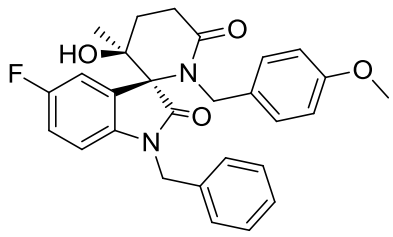
Offwhite solid, Yield 74% (*dr* > 95:5), Melting point: 58-60°C. **^{1}H NMR (300 MHz, DMSO-d$_6$)** δ 7.19-7.09 (m, 2H), 6.96 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 7.9 Hz, 2H), 5.41 (s, 1H), 4.17 (d, *J* = 15.3 Hz, 1H), 4.01 (d, *J* = 15.3 Hz, 1H), 3.87-3.80 (m, 1H), 2.80–2.73 (m, 1H), 2.67-2.58 (m, 1H), 2.50-2.40 (m, 1H), 2.19 (s, 3H), 2.13-2.04 (m, 1H), 1.96–1.69 (m, 5H), 1.31-1.13(m, 5H), 0.70 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d$_6$)** δ 174.3, 170.8, 158.8, 155.7, 139.0, 135.6, 134.5, 128.1, 127.3, 126.6, 126.5, 116.4, 116.1, 115.8, 115.5, 110.3, 110.2, 73.0, 69.4, 52.0, 46.7, 29.2, 28.1, 28.0, 27.9, 25.2, 24.7, 23.9, 20.5. **HRMS** (EI) calculated for $C_{27}H_{31}FN_2O_3$ 450.2319, found 450.2309.

(2'*S*,3'*S*)-1-butyl-1'-(3,4-dimethoxybenzyl)-3'-hydroxy-5,6-dimethoxy-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (**5d**)



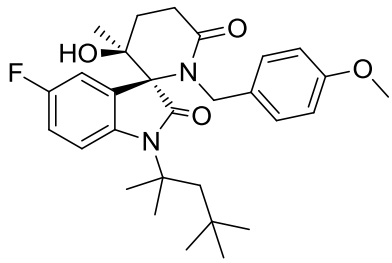
Offwhite solid, Yield 82% (*dr* > 95:5), Melting point: 54-56°C. **^{1}H NMR (300 MHz, DMSO-d$_6$)** δ 6.80 (s, 1H), 6.72-6.69 (m, 2H), 6.33 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.26 (d, *J* = 1.8 Hz, 1H), 5.27 (s, 1H), 4.19 (d, *J* = 15.1 Hz, 1H), 3.88 (d, *J* = 15.1 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.57 (s, 3H), 3.47 (s, 3H), 3.44-3.37 (m, 2H), 2.84-2.69 (m, 2H), 2.45-2.38 (m, 1H), 1.61-1.55 (m, 1H), 1.42-1.35 (m, 2H), 1.29-1.24 (m, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.71 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d$_6$)** δ 174.9, 170.8, 150.2, 147.8, 147.4, 143.4, 137.3, 130.4, 119.7, 115.3, 113.7, 111.6, 111.2, 94.5, 73.2, 69.4, 56.0, 55.6, 55.5, 55.0, 46.6, 29.2, 28.3, 24.1, 19.6, 13.6. **HRMS** (EI) calculated for $C_{28}H_{36}N_2O_7$ 512.2523, found 512.2527.

(2'*S*,3'*S*)-1-benzyl-5-fluoro-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (**5e**)



Offwhite solid, Yield 81% (*dr* = 92:8), Melting point: 154-155°C. **^{1}H NMR (300 MHz, DMSO-d$_6$)** δ 7.31-7.28 (m, 5H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.99-6.94 (m, 2H), 6.71-6.60 (m, 2H), 5.47 (s, 1H), 4.68 (d, *J* = 15.4 Hz, 1H), 4.55 (d, *J* = 15.3 Hz, 1H), 4.15 (d, *J* = 15.3 Hz, 1H), 3.95 (d, *J* = 15.2 Hz, 1H), 3.69 (s, 3H), 2.81-2.75 (m, 1H), 2.67-2.63 (m, 1H), 2.60-2.43 (m, 1H), 1.67-1.62 (m, 1H), 0.68 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d$_6$)** δ 174.6, 170.5, 157.8, 138.9, 135.9, 135.7, 129.2, 128.6, 128.4, 127.6, 127.4, 126.2, 115.8, 113.0, 112.8, 109.6, 73.4, 73.1, 69.5, 69.3, 55.0, 54.8, 46.3, 43.2, 29.2, 28.0, 23.8. **HRMS** (EI) calculated for $C_{28}H_{27}FN_2O_4$ 474.1955, found 474.1950.

(2'*S*,3'*S*)-5-fluoro-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methyl-1-(2,4,4-trimethylpentan-2-yl)spiro[indoline-3,2'-piperidine]-2,6'-dione (**5f**)



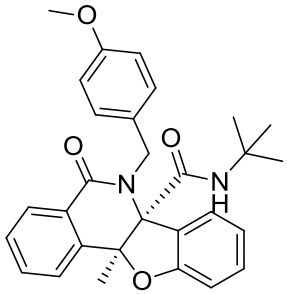
Offwhite solid, Yield 50% (*dr* = 95:5), Melting point: 117-119^{o}C. **^{1}H NMR (300 MHz, DMSO-d$_6$)** δ 7.37 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.08 (td, *J* = 9.0, 3.0 Hz, 1H), 6.79 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.70 (s, 4H), 5.37 (s, 1H), 4.43 (d, *J* = 15.2 Hz, 1H), 3.68 (s, 3H), 3.41 (d, *J* = 15.2 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.70-2.64 (m, 1H), 2.43– 2.37 (m, 1H), 1.98-1.93 (m, 1H), 1.73 (s, 3H), 1.61-1.56 (m, 2H), 1.56 (s, 3H), 0.96 (s, 9H), 0.81 (s, 3H). **^{13}C NMR (300 MHz, DMSO-d$_6$)** δ 176.0, 171.1, 158.4, 157.9, 155.2, 140.1, 140.0, 130.1, 128.0, 127.3, 127.2, 116.1, 115.7, 115.3, 115.0, 114.4, 114.3, 113.1, 74.2, 69.8, 61.5, 54.9, 50.0, 47.4, 31.2, 31.0, 29.8, 29.3, 29.1, 28.1, 24.3. **HRMS** (EI) calculated for $C_{29}H_{37}FN_2O_4$ 496.2737, found 496.2724.

General procedure for the synthesis of benzofuro-isoquinoline carboxamides

To a dry screw capped glass vial $Pd(OAc)_2$ (5 mol%), BINAP (7.5 mol%), Cs_2CO_3 (2 equiv.) were loaded along with the mixture of toluene and MeOH (1.95 mL:0.05 mL). Ugi product **1a-p and 4a-f (**0.2 mmol**)** was added. The reaction vial was evacuated, backfilled with nitrogen (4 cycles) and was stirred at 120°C for 24 hours. After completion, the reaction mixture was cooled, directly loaded over a silica gel column and chromatographed (10-30 % EtOAc in heptane) to afford compounds 3. The structures of the compounds were confirmed by NMR and HRMS data.

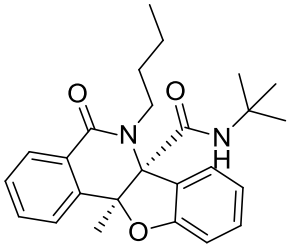
Characterization data for benzofuro-isoquinoline carboxamides (3a-i)

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3a**)



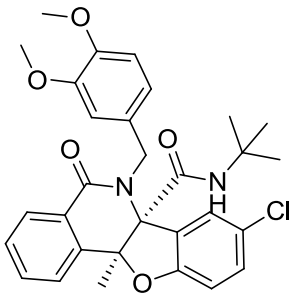
White solid, Yield 72%, Melting point: 194-196°C. **^{1}H NMR (300 MHz, $CDCl_3$)** ***δ*** 8.34 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.74 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.65 (td, *J* = 7.6, 1.5 Hz, 1H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.27-7.21 (m, 1H), 6.91-6.85 (m, 2H), 6.80-6.77 (m, 2H), 6.64-6.61 (m, 2H), 5.77 (s, 1H), 4.88 (d, *J*= 15.6Hz, 1H), 4.48 (d, *J*= 15.6, 1H), 3.68 (s, 3H), 1.79 (s, 3H), 1.21 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 165.7, 163.0, 159.9, 158.2, 134.7, 132.8, 131.0, 129.9, 129.4, 128.9, 127.8, 127.7, 127.1, 126.0, 125.9, 121.4, 113.5, 111.5, 86.3, 78.6, 55.2, 52.2, 47.8, 28.3. **HRMS** (EI) calculated for $C_{29}H_{30}N_2O_4$ 470.2206, found 470.2214.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-6-butyl-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3c**)



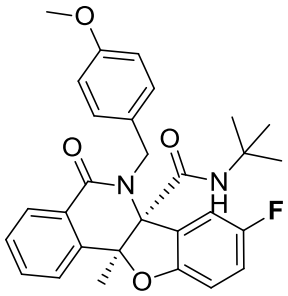
Offwhite solid, Yield 63%, Melting point: 97-99 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** *δ* 8.31 (d, *J* = 7.7 Hz, 1H), 7.72-7.53 (m, 4H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.67 (s, 1H), 3.73-3.63 (m, 1H), 3.20-3.11 (m, 1H), 1.76 (s, 3H), 1.68-1.48 (m, 2H), 1.27 (s, 9H), 1.24-1.13 (m, 1H), 0.81 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** *δ* 166.0, 162.0, 159.7, 134.67, 132.7, 130.8, 129.9, 128.6, 127.4, 127.2, 126.2, 126.0, 121.2, 111.4, 86.0, 78.1, 52.1, 45.8, 29.6, 28.3, 21.6, 20.3, 13.7. **HRMS** (ESI) calculated for $C_{25}H_{31}N_2O_3$ ($[M+H]^+$) 407.2329, found 407.2338.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-8-chloro-6-(3,4-dimethoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3k**)



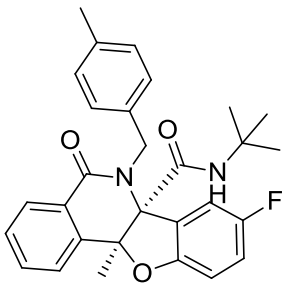
White solid, Yield 65%, Melting point: 53-55^{o}C. 1**H NMR (600 MHz, DMSO-*d*$_6$)** δ 8.12 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 10.9, 4.4 Hz, 1H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.10 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 1H), 6.23 (s, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 4.09 (d, *J* = 16.0 Hz, 1H), 3.61(s, 3H), 3.51 (m, 1H), 1.79 (s, 3H), 1.29 (s, 9H). **^{13}C NMR (600 MHz, DMSO-*d*$_6$)** δ 164.7, 162.8, 158.5, 148.1, 146.9, 134.2, 132.5, 130.4, 129.6, 128.9, 127.6, 127.4, 127.0, 126.6, 124.7, 118.0, 111.7, 111.4, 109.7, 78.3, 55.5, 55.1, 52.1, 47.0, 27.8. **HRMS** (EI) calculated for $C_{30}H_{31}ClN_2O_5$ 534.1921, found 534.1958.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-8-fluoro-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3m**)



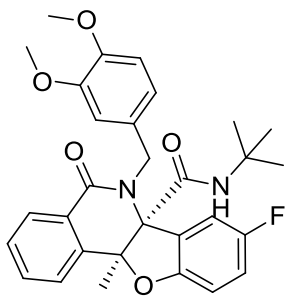
White solid, Yield 54%, Melting point: 146-148^{o}C. ^{1}**H NMR (600 MHz, DMSO-*d*$_6$)** δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.06-7.02 (m, 2H), 6.89 (dd, *J* = 8.7, 4.2 Hz, 1H), 6.58 (s, 4H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 3.61 (s, 3H), 1.79 (s, 3H), 1.28 (s, 9H). **^{13}C NMR (600 MHz, DMSO-*d*$_6$)** δ 164.8, 162.8, 157.4, 155.9, 155.2, 134.4, 132.5, 129.8, 129.5, 127.5, 127.0, 126.8, 126.7, 126.6, 117.2, 116.9, 116.1, 115.8, 112.9, 111.1, 110.9, 86.4, 78.4, 52.07, 46.8, 27.8, 21.4. **HRMS** (EI) calculated for $C_{29}H_{29}FN_2O_4$ 488.2111, found 488.2116.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-8-fluoro-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3n**)



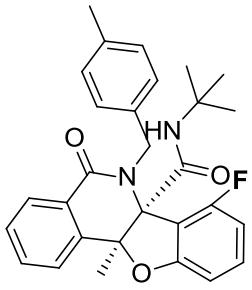
White solid, Yield 69%, Melting point: 177-178^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.10 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H), 7.61 (t, *J* = 7.1 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.06 (s, 1H), 7.04-6.99 (m, 1H), 6.93-6.86 (m, 1H), 6.82 (d, *J* = 7.9 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 5.00 (d, *J* = 16.2 Hz, 1H), 4.15 (d, *J* = 16.2 Hz, 1H), 2.13 (s, 3H), 1.79 (s, 3H), 1.29 (s, 9H). ^{13}C **NMR (75 MHz, DMSO-*d*$_6$)** δ 164.8, 162.7, 158.3, 155.9, 155.2, 134.9, 134.7, 134.5, 132.5, 129.5, 128.0, 127.5, 126.9, 126.7, 126.6, 125.5, 117.2, 116.9, 116.1, 115.7, 111.0, 110.9, 86.4, 78.4, 52.1, 47.1, 27.8, 21.5, 20.5. **HRMS** (EI) calculated for $C_{29}H_{29}FN_2O_3$ 472.2162, found 472.2155.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-6-(3,4-dimethoxybenzyl)-8-fluoro-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3o**)



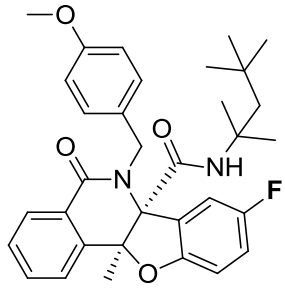
White solid, Yield 81%, Melting point: 161-162^{o}C. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.11 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.71 (td, *J* = 7.6, 1.3 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.63-7.57 (m, 2H), 7.10-7.03 (m, 2H), 6.93-6.89 (m, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.26-6.21(m, 2H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.12 (d, *J* = 16.0 Hz, 1H), 3.61 (s, 3H), 3.48 (s, 3H), 1.79 (s, 3H), 1.29 (s, 9H). ^{13}C **NMR (75 MHz, DMSO-*d*$_6$)** δ 164.8, 162.8, 158.4, 156.0, 155.2, 148.0, 146.9, 134.4, 132.5, 130.5, 129.6, 127.5, 127.0, 126.8, 126.7, 126.6, 118.0, 117.3, 116.9, 116.3, 115.9, 111.3, 111.1, 111.0, 109.7, 86.4, 78.4, 55.5, 55.1, 52.1, 47.1, 27.8, 21.5. **HRMS** (EI) calculated for $C_{30}H_{31}FN_2O_5$ 518.2217, found 518.2187.

(6a*S*,11a*S*)-*N*-(*tert*-butyl)-7-fluoro-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3p)**



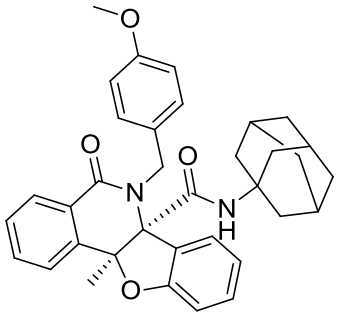
White solid, Yield 83%, Melting point: 168-169^{o}C. **^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.37 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.66 (td, *J* = 7.5, 1.6 Hz, 1H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H), 7.09 (td, *J* = 8.2, 5.7 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.62 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.46-6.32 (m, 1H), 5.88 (s, 1H), 5.22 (d, *J* = 16.2 Hz, 1H), 4.32 (d, *J* = 16.2 Hz, 1H), 2.17 (s, 3H), 1.83 (s, 3H), 1.27 (s, 9H). **^{13}C NMR (75 MHz, CDCl$_3$)** δ 164.6, 162.9, 161.6, 161.5, 160.5, 157.2, 135.7, 134.2, 133.9, 132.9, 132.6, 132.5, 130.1, 129.1, 128.6, 127.0, 126.0, 125.6, 113.7, 113.5, 109.3, 109.0, 107.4, 107.4, 86.9, 79.6, 79.5, 52.4, 48.5, 48.4, 28.3, 21.5, 21.0. **HRMS** (ESI) calculated for $C_{29}H_{30}FN_2O_3$ ($[M+H]^+$) 473.2235, found 473.2238.

(6a*S*,11a*S*)-8-fluoro-6-(4-methoxybenzyl)-11a-methyl-5-oxo-N-(2,4,4-trimethylpentan-2-yl)-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3q**)



White solid, Yield 64%, Melting point: 143-145^{o}C. **^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.34 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 6.9 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.86-6.80 (m, 3H), 6.74-6.70 (m, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.73 (s, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 15.6 Hz, 1H), 3.70 (s, 3H), 1.82 (s, 3H), 1.41 (s, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 0.78 (s, 9H). **^{13}C NMR (75 MHz, CDCl$_3$)** δ 166.4, 165.0, 162.4, 158.6, 158.2, 155.7, 155.6, 134.8, 133.2, 130.1, 129.1, 129.0, 128.0, 127.5, 127.3, 127.2, 127.0, 126.6, 126.1, 117.1, 116.8, 116.0, 115.7, 113.6, 111.4, 111.3, 86.7, 78.7, 56.5, 55.2, 54.0, 48.1, 31.4, 31.3, 27.9, 27.2, 21.3, 14.1. **HRMS** (ESI) calculated for $C_{33}H_{38}FN_2O_4$ ($[M+H]^+$) 545.2810, found 545.2801.

(6a*S*,11a*S*)-*N*-(adamantan-1-yl)-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-*c*]isoquinoline-6a-carboxamide (**3r**)



White solid, Yield 75%, Melting point: 230-231^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.33 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.91-6.84 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.66 (s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.48 (d, *J* = 15.5 Hz, 1H), 3.69 (s, 3H), 2.02 (s, 3H), 1.88-1.54 (m, 16H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 165.3, 163.0, 159.9, 158.2, 134.6, 132.7, 131.0, 129.8, 129.4, 128.9, 127.8, 127.7, 127.1, 126.0, 125.8, 121.4, 113.5, 111.5, 86.2, 78.6, 55.2, 52.8, 47.79, 41.1, 36.1, 29.2, 22.0. **HRMS** (ESI) calculated for $C_{35}H_{37}N_2O_4$ ($[M+H]^+$) 549.2748, found 549.2756.

Crystallographic data for compound 2p, 2n and 3a

Single crystals of **2p**, **2n** and **3a** suitable for X-ray diffraction were obtained by slow evaporation from acetonitrile at room temperature. X-ray intensity data were collected at 100K on an Agilent Supernova diffractometer, equipped with an Atlas CCD detector, using Mo Kα radiation (λ = 0.71073 Å). The images were interpreted and integrated with the CrysAlisPro software from Rigaku Oxford Diffraction.[1] Using Olex2,[2] the structures were solved with the ShelxS[3] structure solution program using Direct Methods and refined with the ShelxL[3] refinement package using full-matrix least squares minimization on F^2. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times U_{eq} of the parent atoms (1.5 for methyl groups). Respectively, CCDC 1435833, 1435835 and 1435834 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystallographic data

2p $C_{31}H_{32}FN_3O_3$, M =513.60 g mol^{-1}, monoclinic, $P2_1/c$ (no. 14), a = 9.0851(3) Å, b = 16.6480(5) Å, c = 17.5220(5) Å, β = 98.553(3)°, V = 2620.71(14) Å^3, T = 100.01(10) K, Z = 4, ρ_{calcd} = 1.302 g cm^{-3}, μ(Mo Kα) = 0.089 mm^{-1}, F(000) = 1088, crystal size 0.2 x 0.2 x 0.1 mm^3, 5353 reflections measured, 4678 unique which were used in all calculations. The final wR_2 was 0.1096 (all data) and R_1 was 0.0475 (>2sigma(I)).

3a $C_{29}H_{30}N_2O_4$, M =470.55 g mol^{-1}, monoclinic, $P2_1/c$ (no. 14), a = 15.2680(8) Å, b = 11.6042(4) Å, c = 15.6622(8) Å, β = 115.596(7)°, V = 2502.6(2) Å^3, T = 100.00(10) K, Z = 4, ρ_{calcd} = 1.249 g cm^{-3}, μ(Mo Kα) = 0.083 mm^{-1}, F(000) = 1000, crystal size 0.2 x 0.2 x 0.2 mm^3, 5115 reflections measured, 4350 unique which were used in all calculations. The final wR_2 was 0.1053 (all data) and R_1 was 0.0420 (>2sigma(I)).

2n $C_{31}H_{32}FN_3O_3$, M =513.60 g mol^{-1}, monoclinic, $P2_1/c$ (no. 14), a = 9.0977(4) Å, b = 16.6165(7) Å, c = 17.6000(8) Å, β = 96.066(4)°, V = 2645.7(2) Å^3, T = 100.01(10) K, Z = 4, ρ_{calcd} = 1.289 g cm^{-3}, μ(Mo Kα) = 0.088 mm^{-1}, F(000) = 1088, crystal size 0.2 x 0.2 x 0.1 mm^3, 5412 reflections measured, 4584 unique which were used in all calculations. The final wR_2 was 0.1047 (all data) and R_1 was 0.0421 (>2sigma(I)).

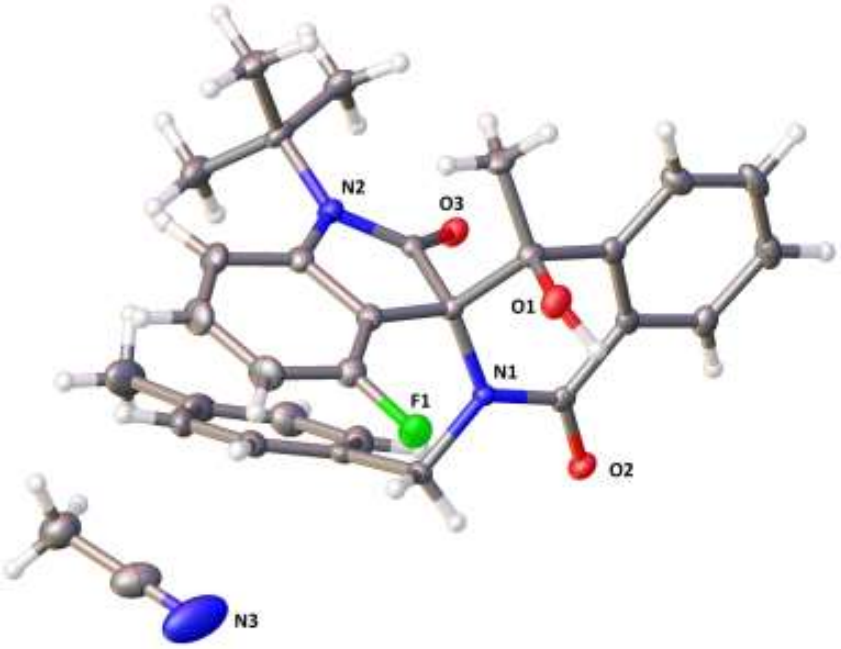


Figure 1 Asymmetric unit of **2p**. Thermal ellipsoids are drawn at 50% probability level.

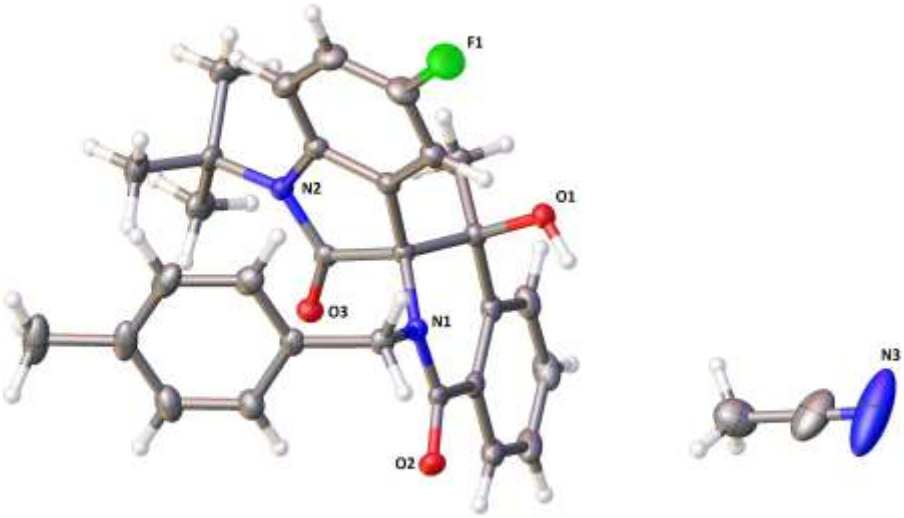


Figure 2 Asymmetric unit of **2n**. Thermal ellipsoids are drawn at 50% probability level.

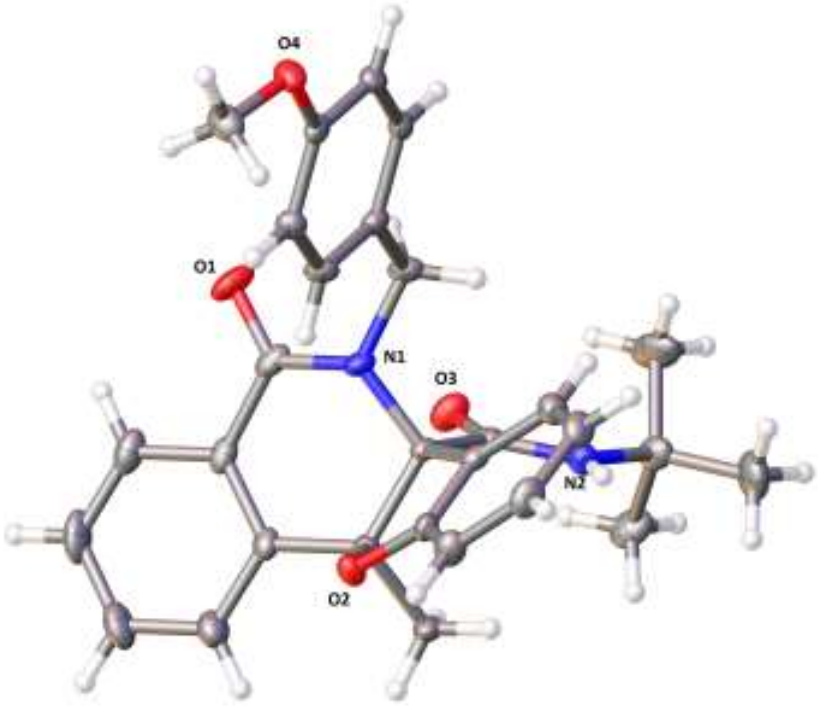


Figure 3 Asymmetric unit of **3a**. Thermal ellipsoids are drawn at 50% probability level.

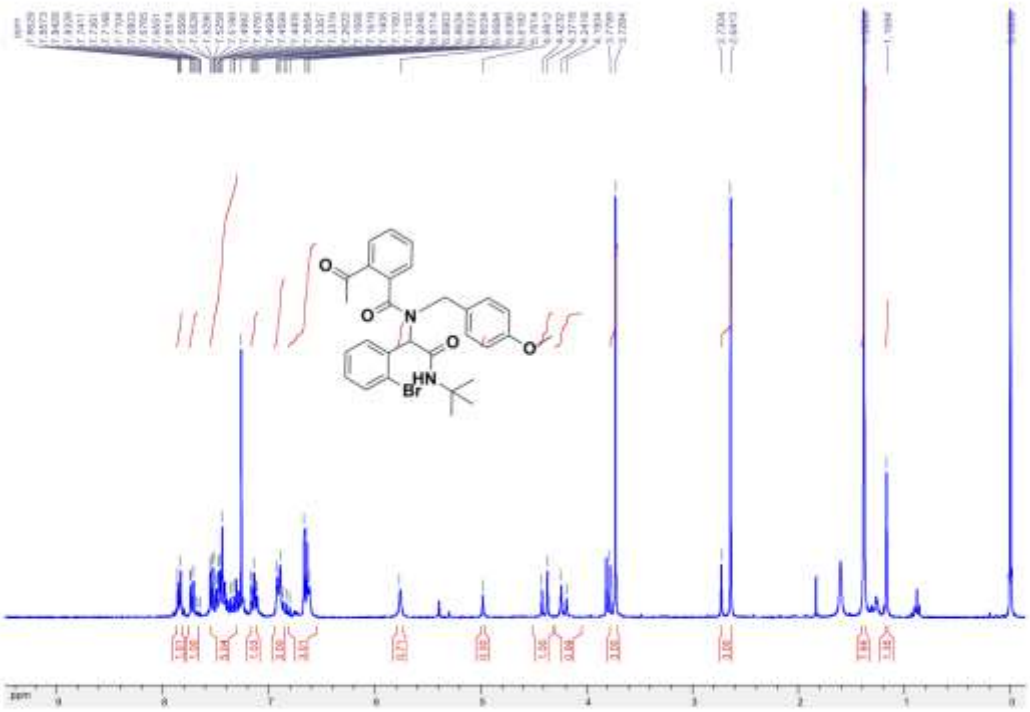
References:

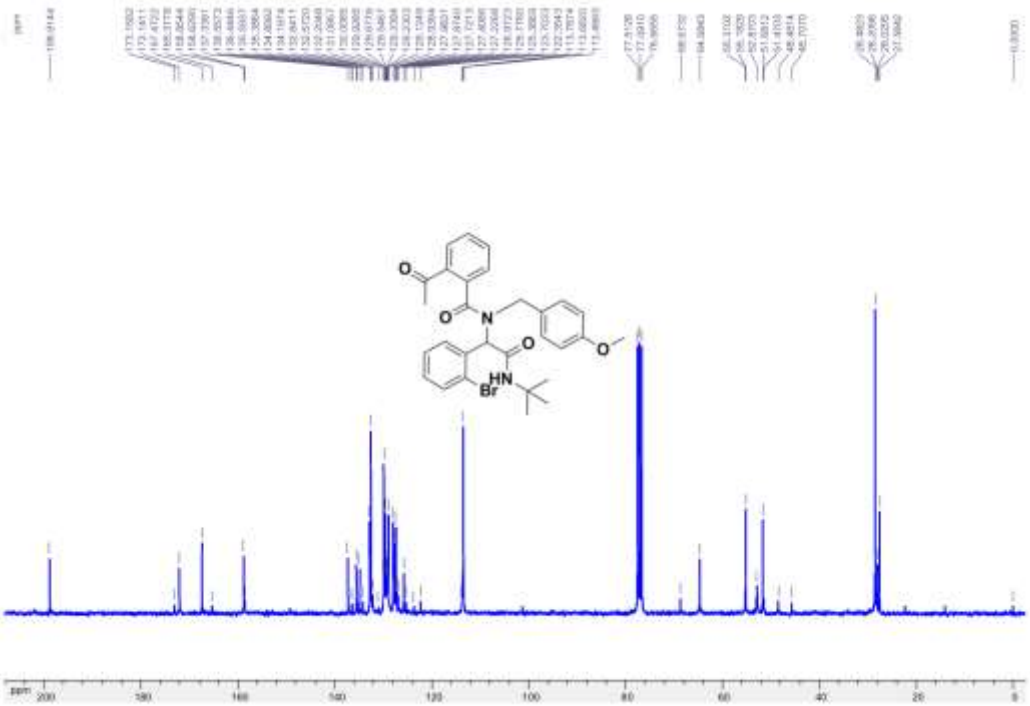
[1] CrysAlis PRO (**2012**). Agilent Technologies UK Ltd, Yarnton, Oxfordshire, England.

[2] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (**2009**). 42, 339-341.

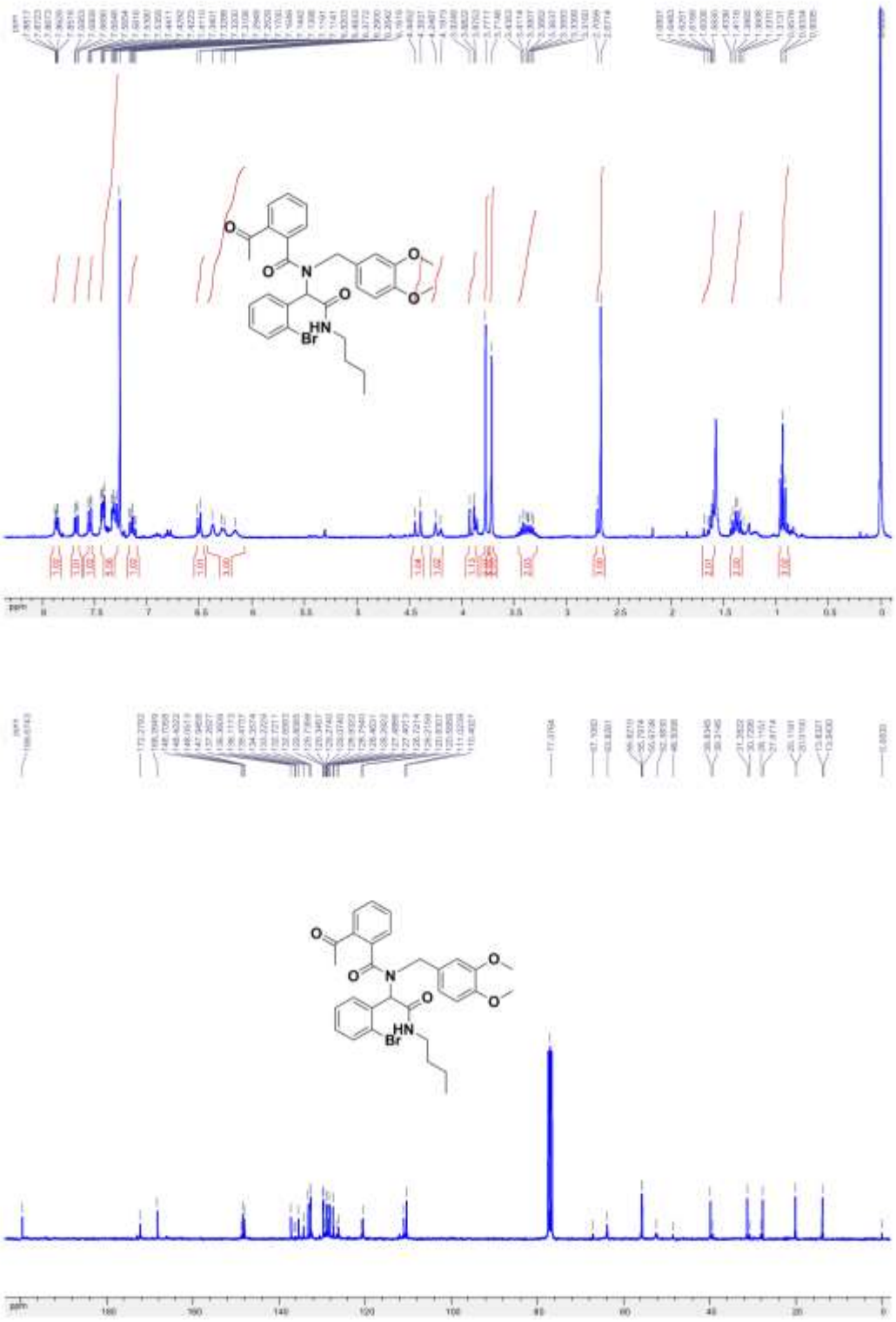
[3] G.M. Sheldrick, Acta Cryst. (**2008**). A64, 112-122

^{1}H and ^{13}C NMR spectra of compound **1a** (300 MHz, $CDCl_3$)

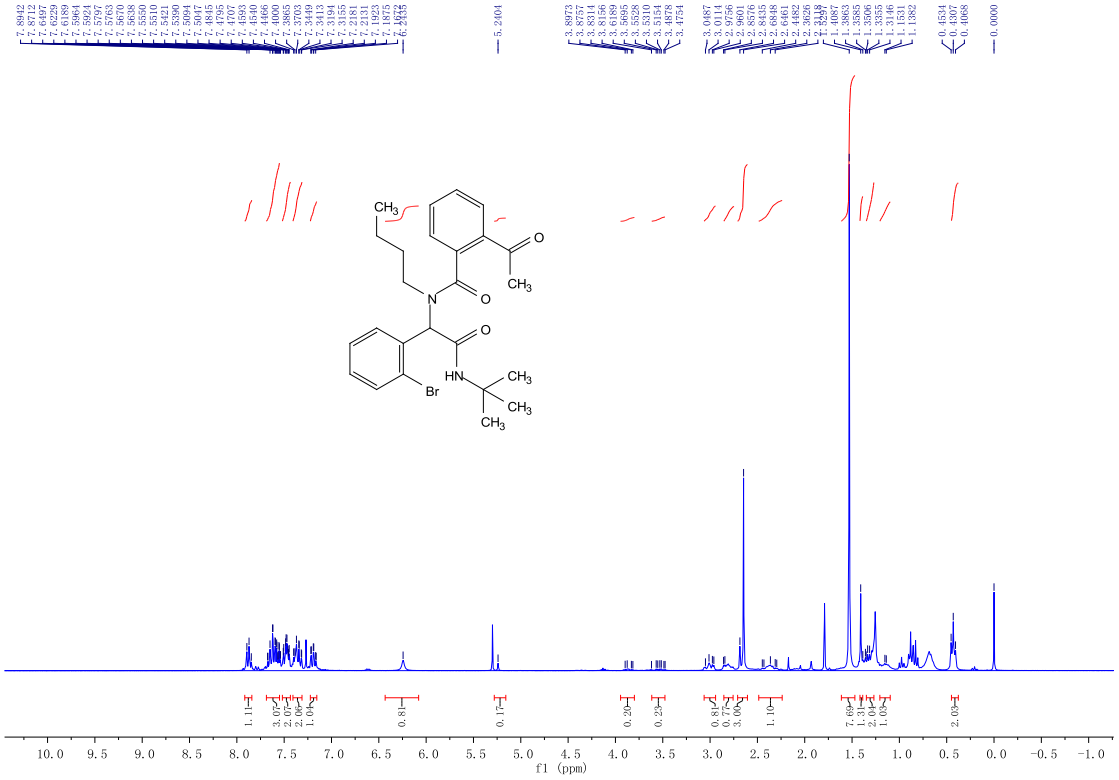


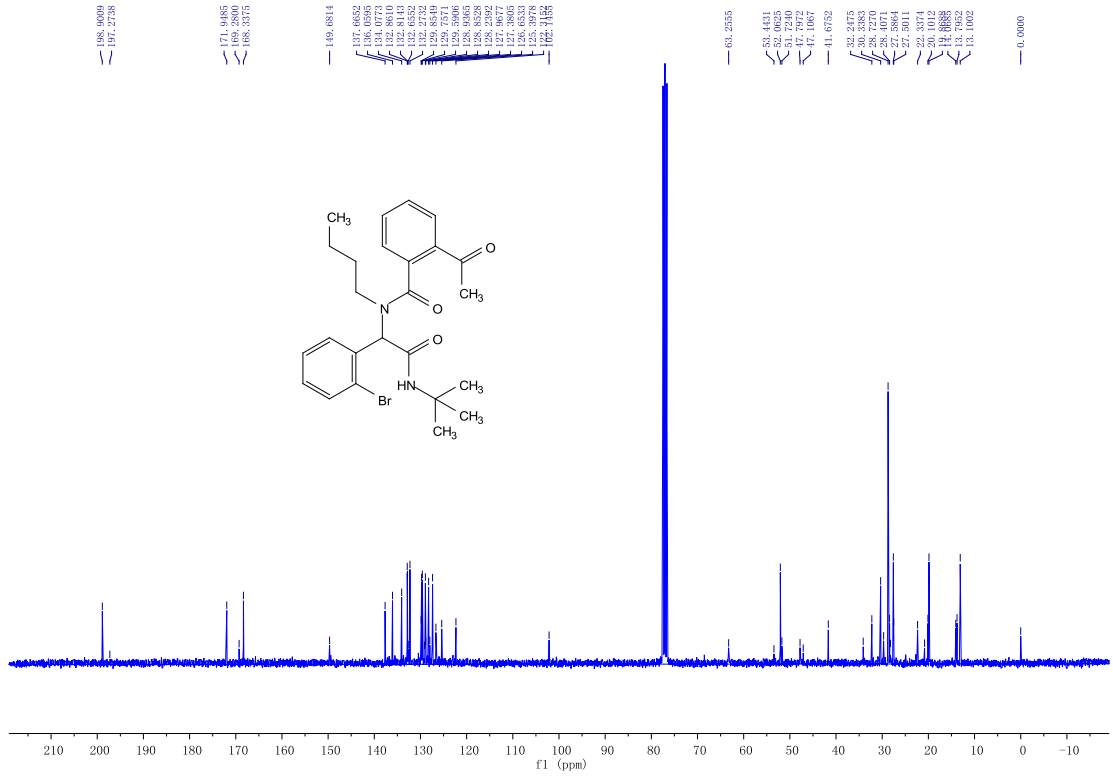


^{1}H and ^{13}C NMR spectra of compound **1b** (300 MHz, $CDCl_3$)

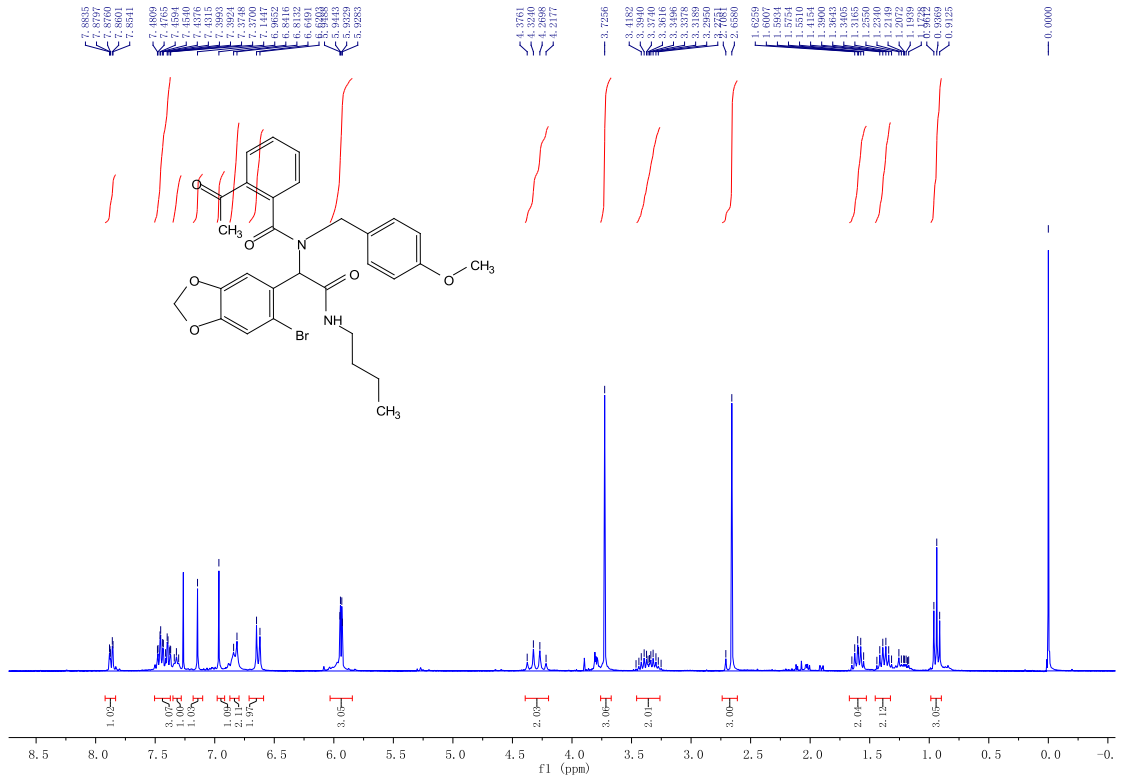


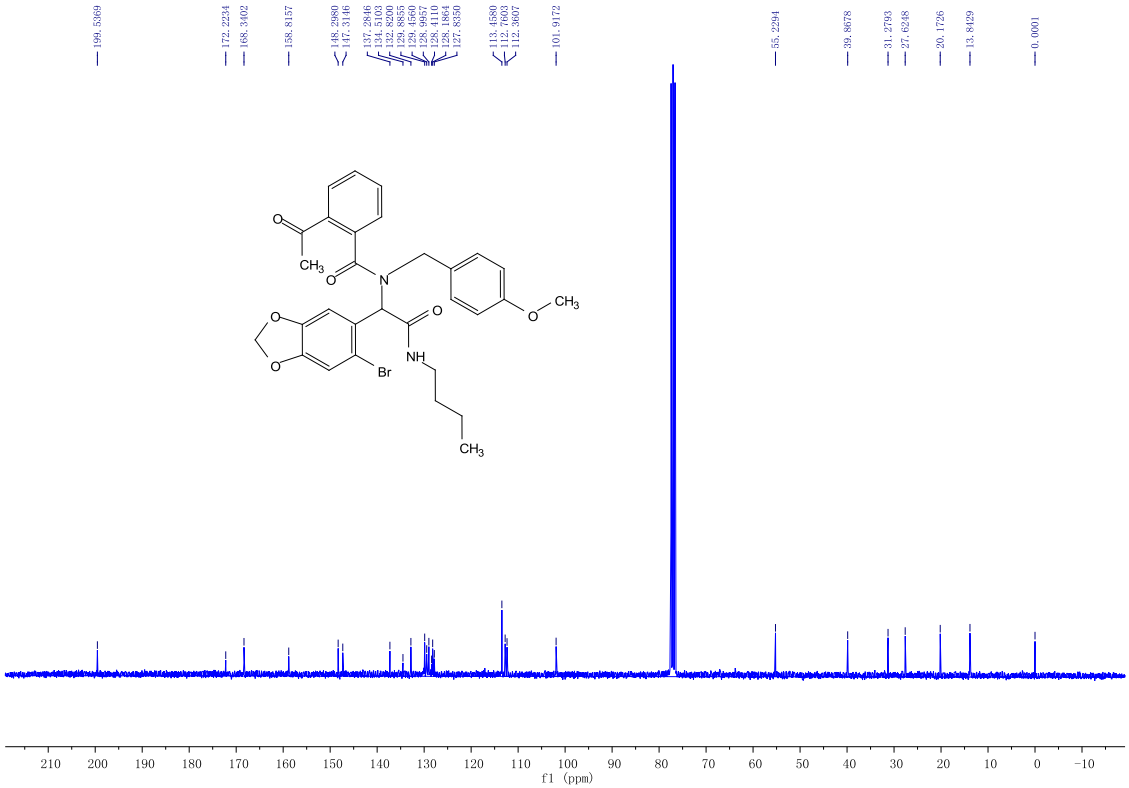
^{1}H and ^{13}C NMR spectra of compound **1c** (300 MHz, $CDCl_3$)



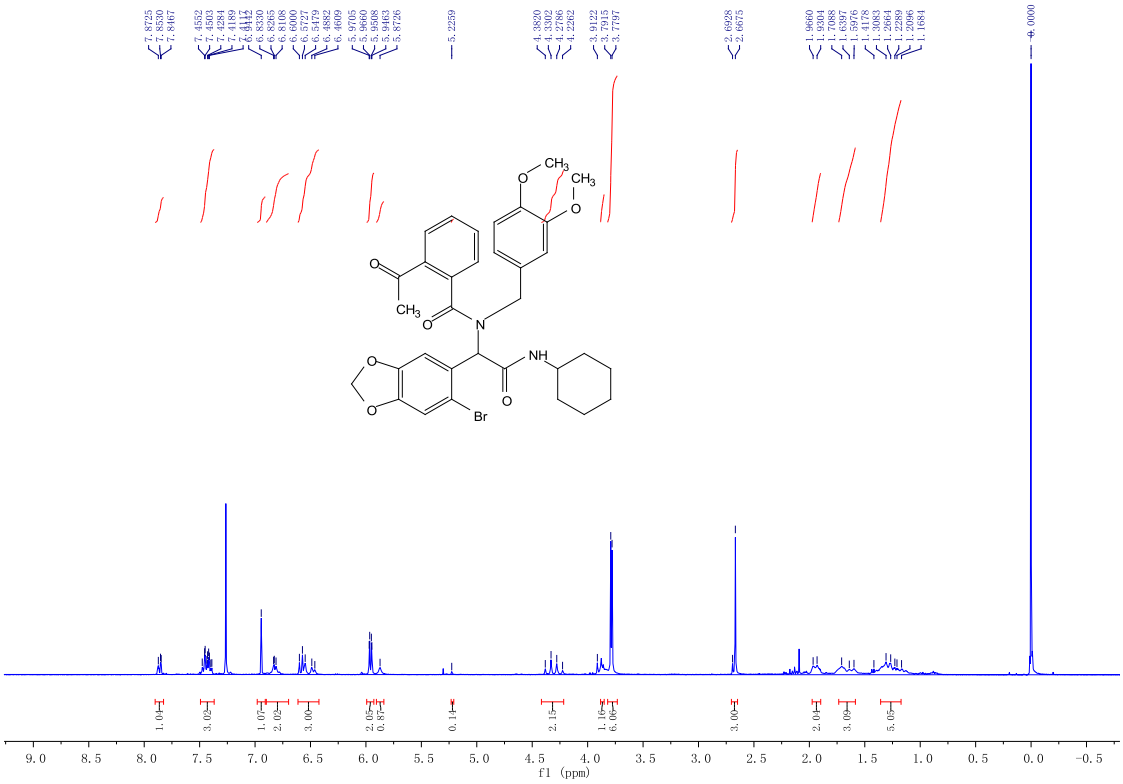


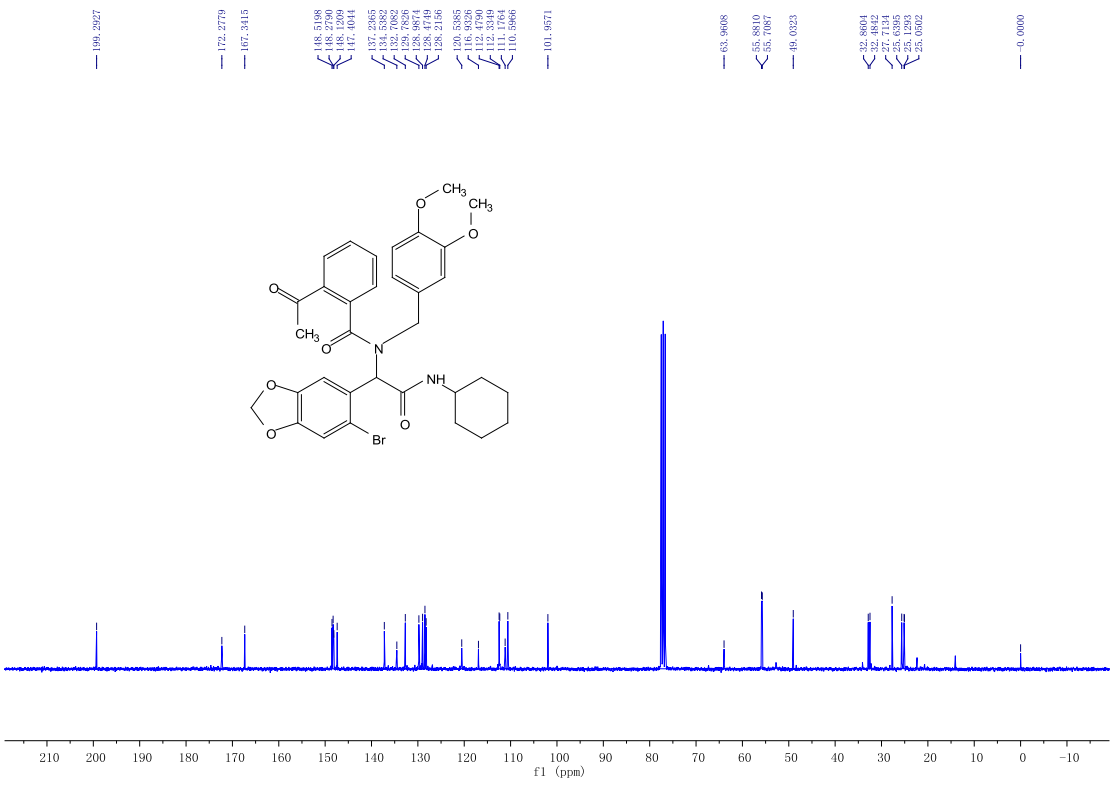
^{1}H and ^{13}C NMR spectra of compound **1d** (300 MHz, $CDCl_3$)



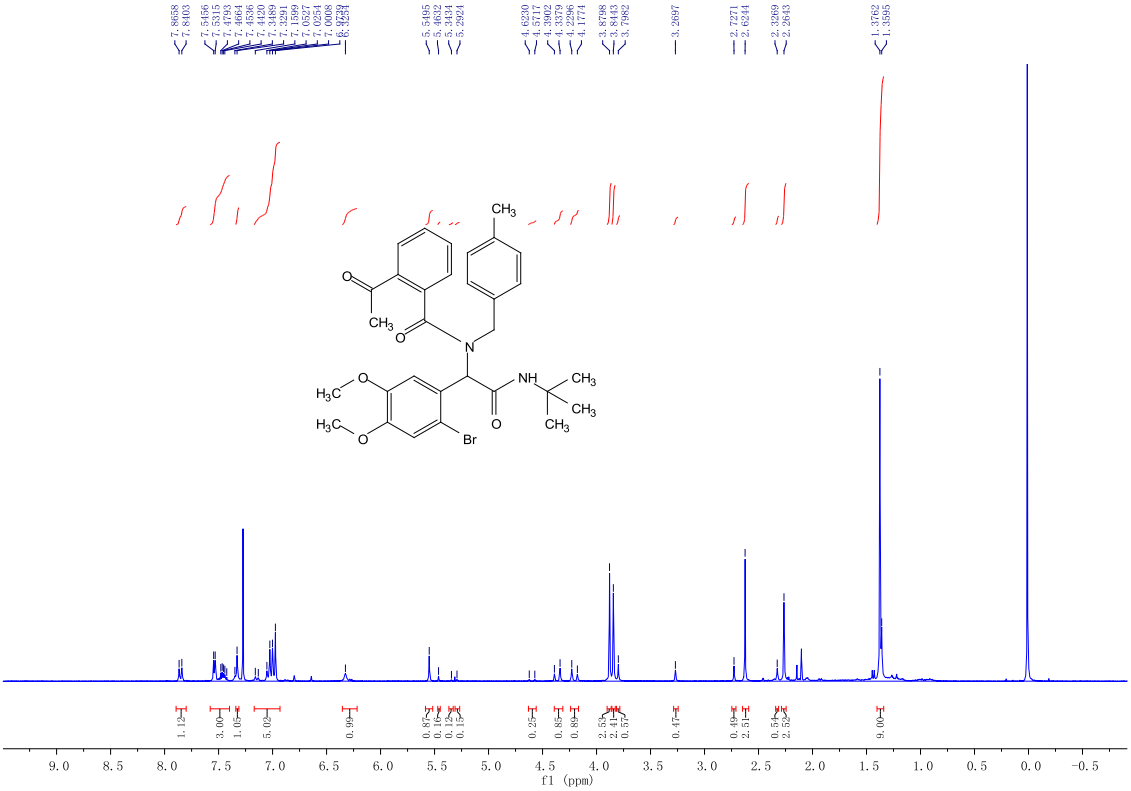


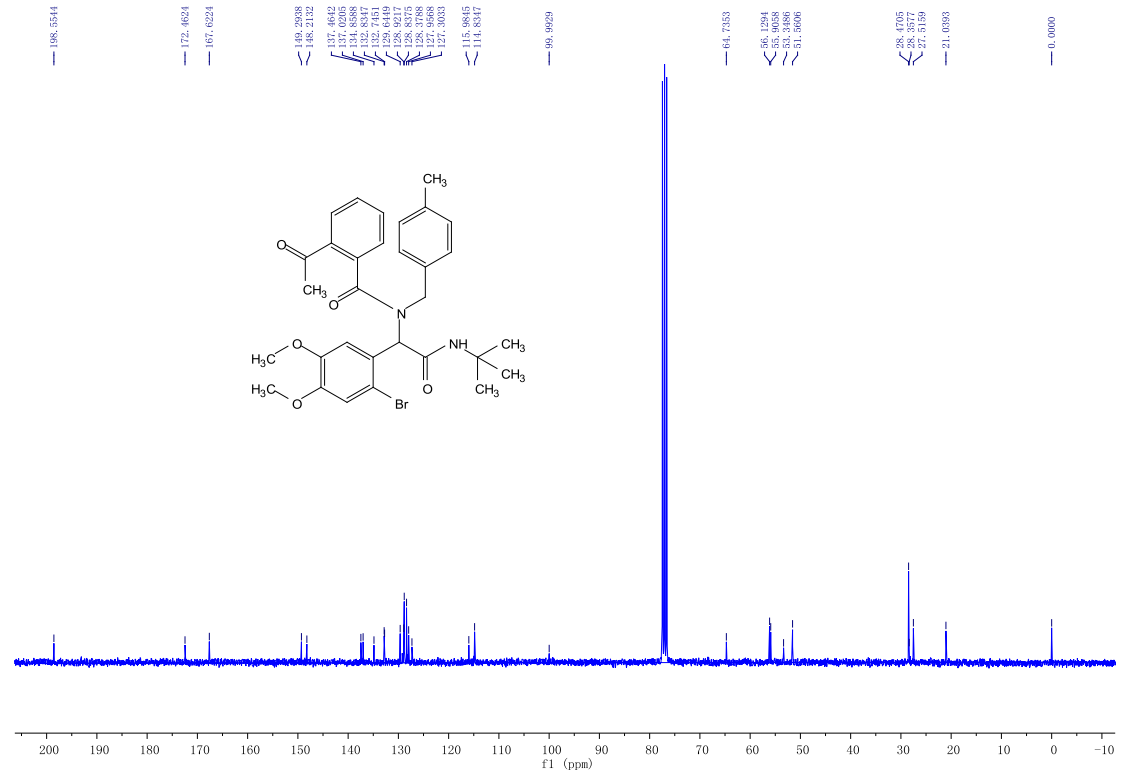
^{1}H and ^{13}C NMR spectra of compound **1e** (300 MHz, $CDCl_3$)



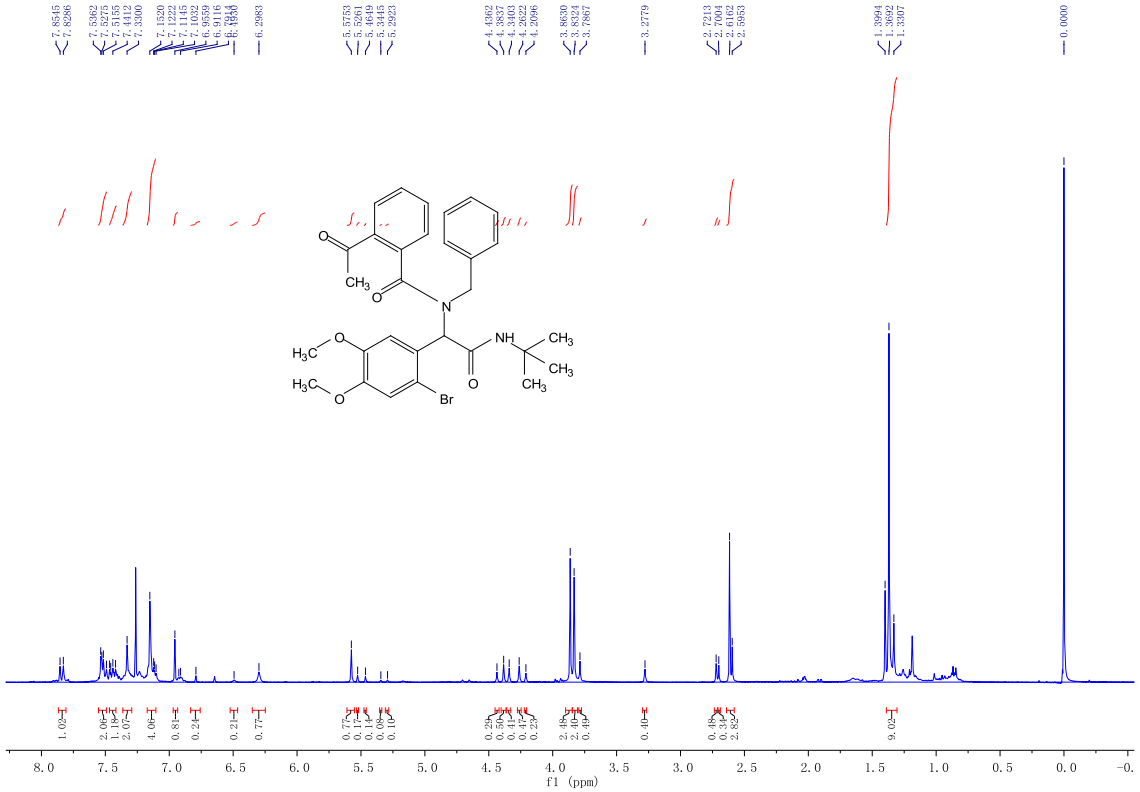


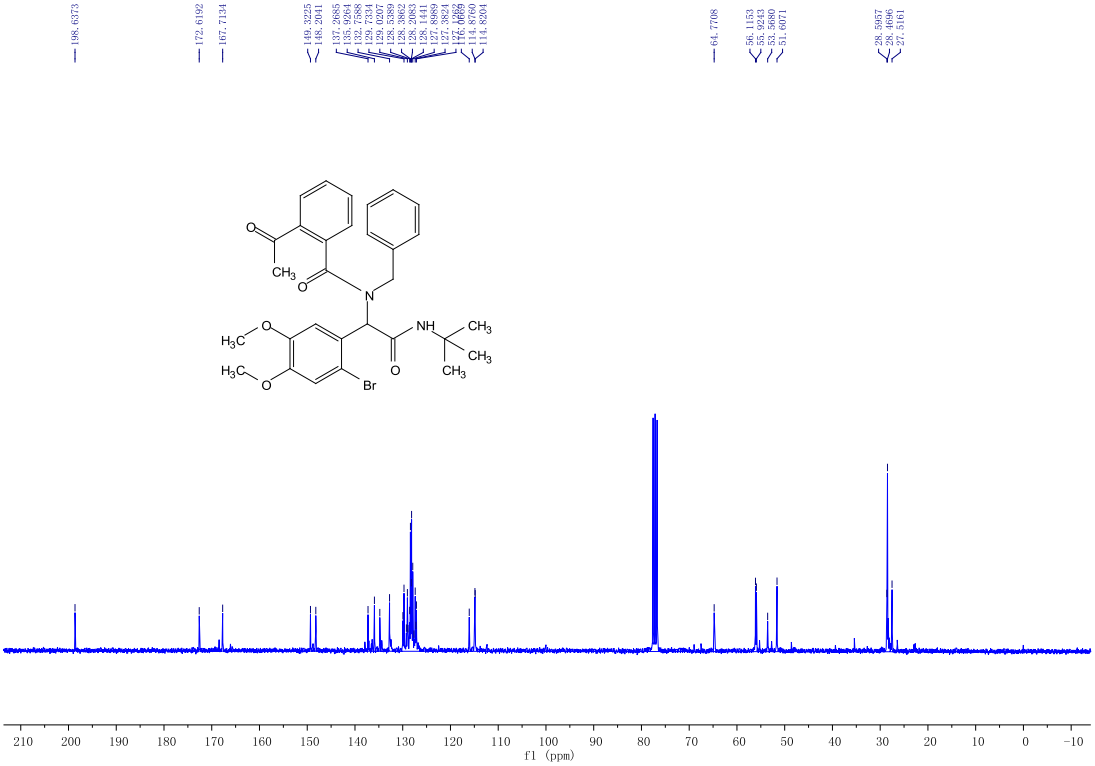
^{1}H and ^{13}C NMR spectra of compound **1f** (300 MHz, $CDCl_3$)



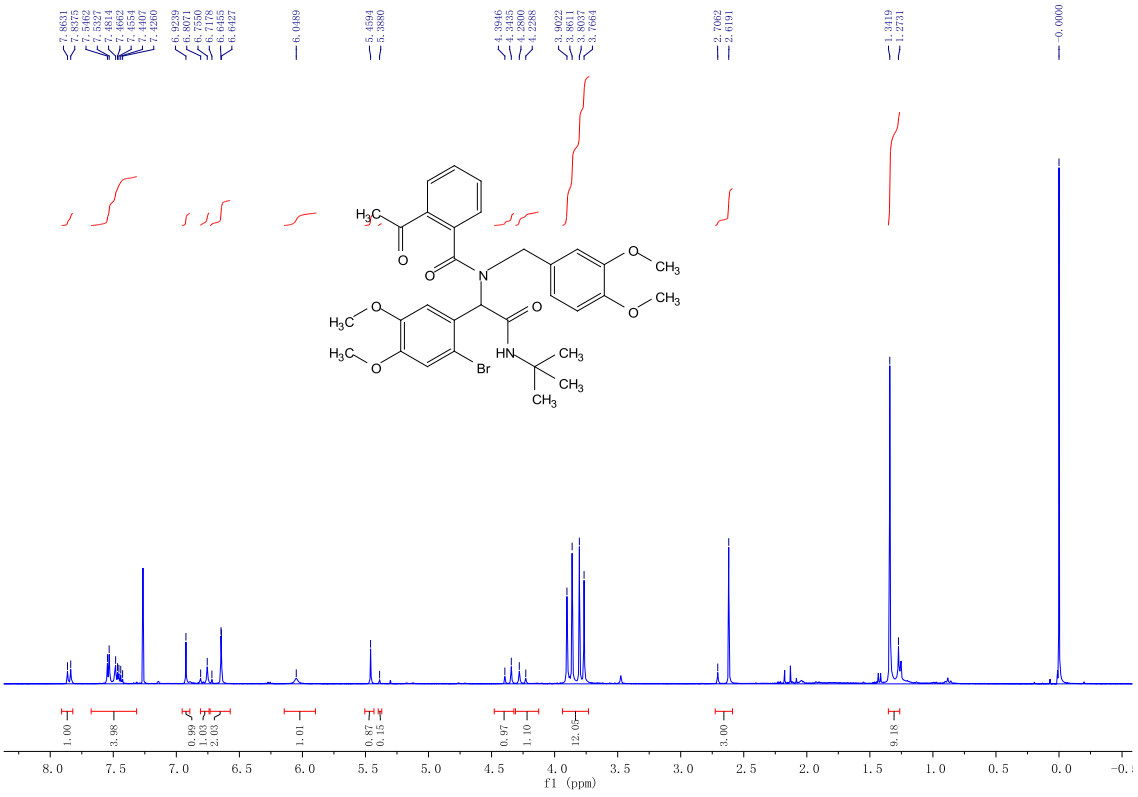


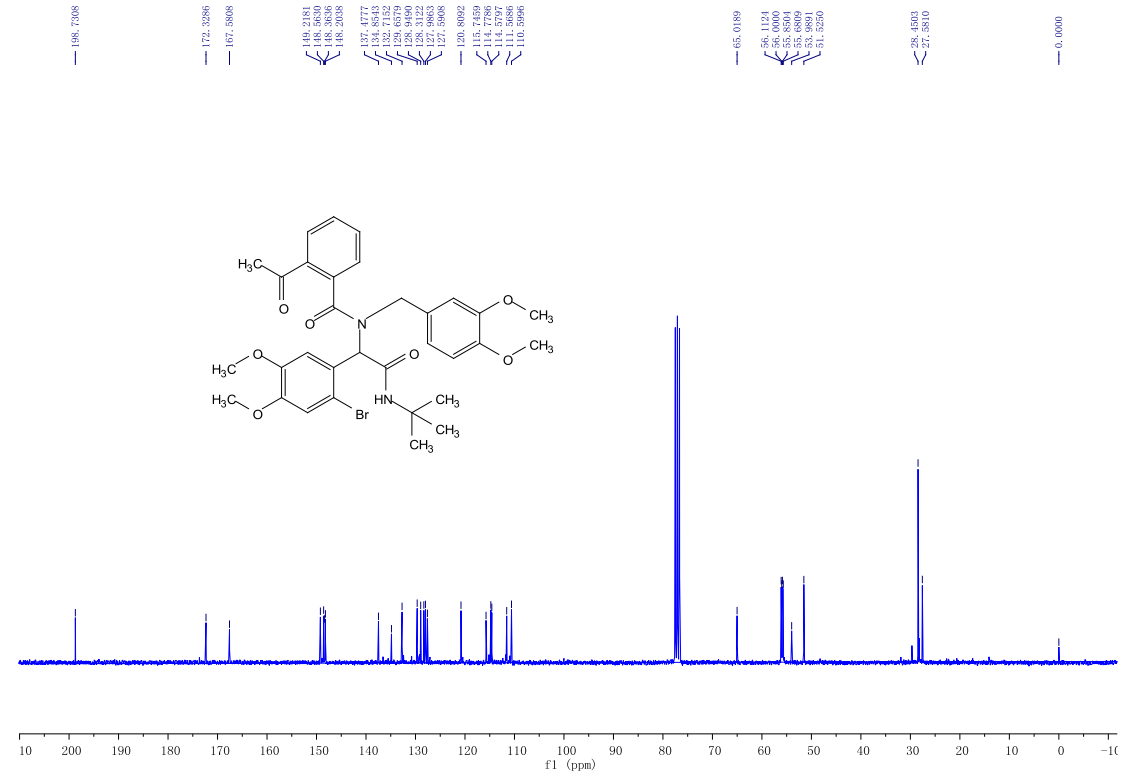
^{1}H and ^{13}C NMR spectra of compound **1g** (300 MHz, $CDCl_3$)



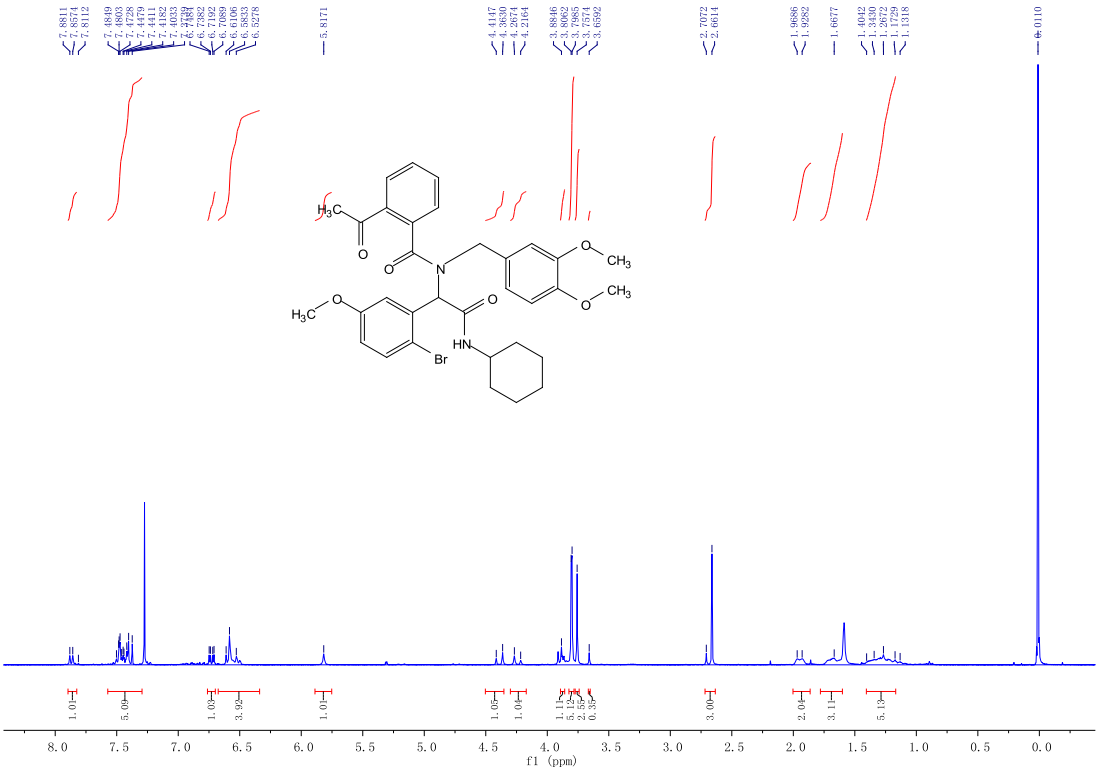


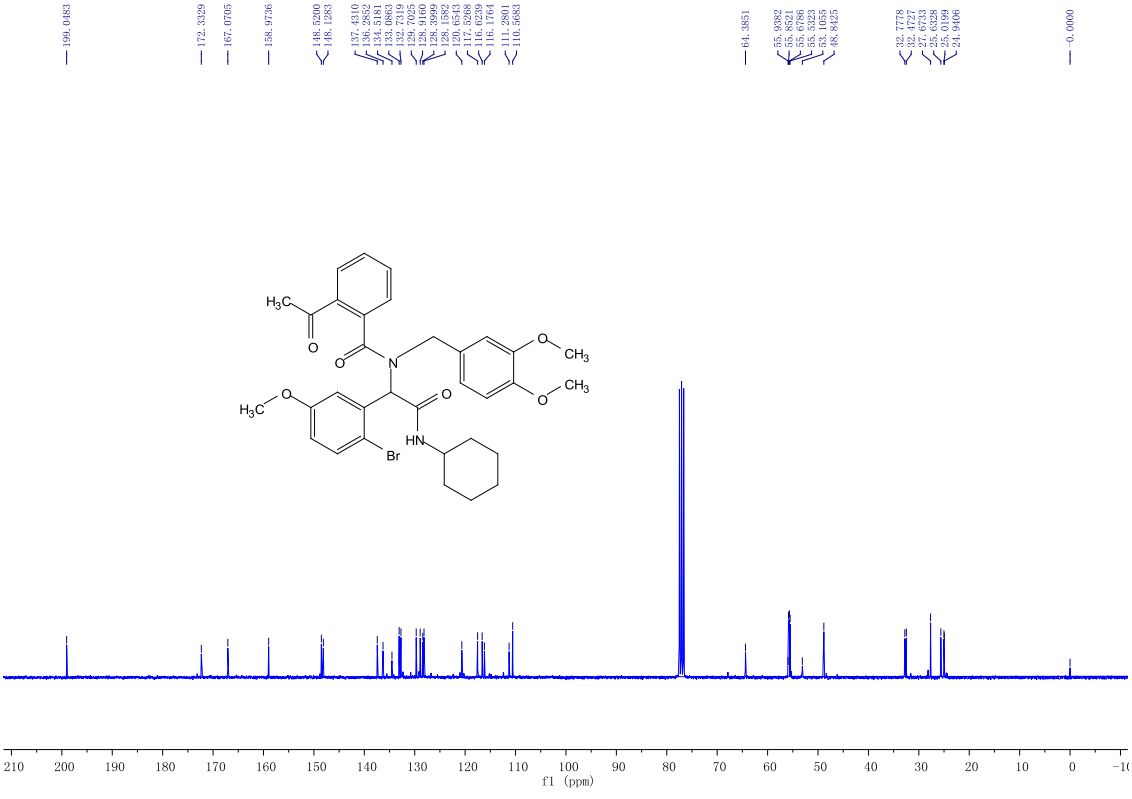
^{1}H and ^{13}C NMR spectra of compound **1h** (300 MHz, $CDCl_3$)



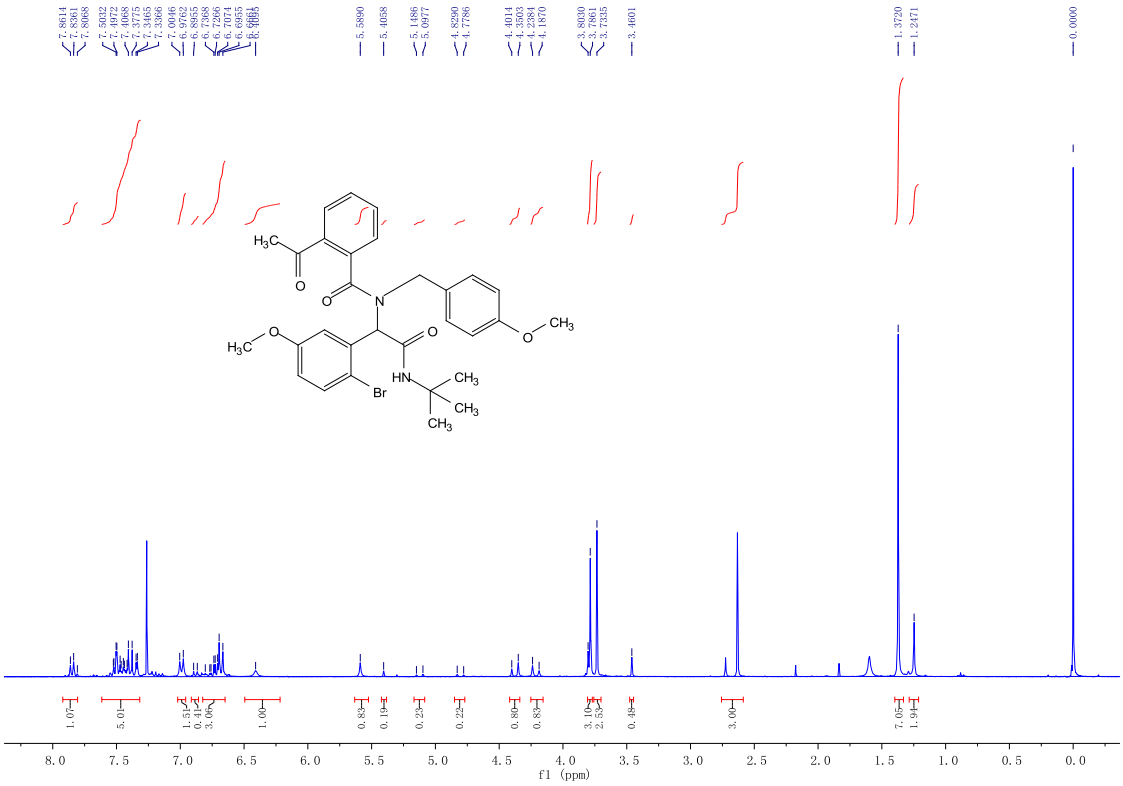


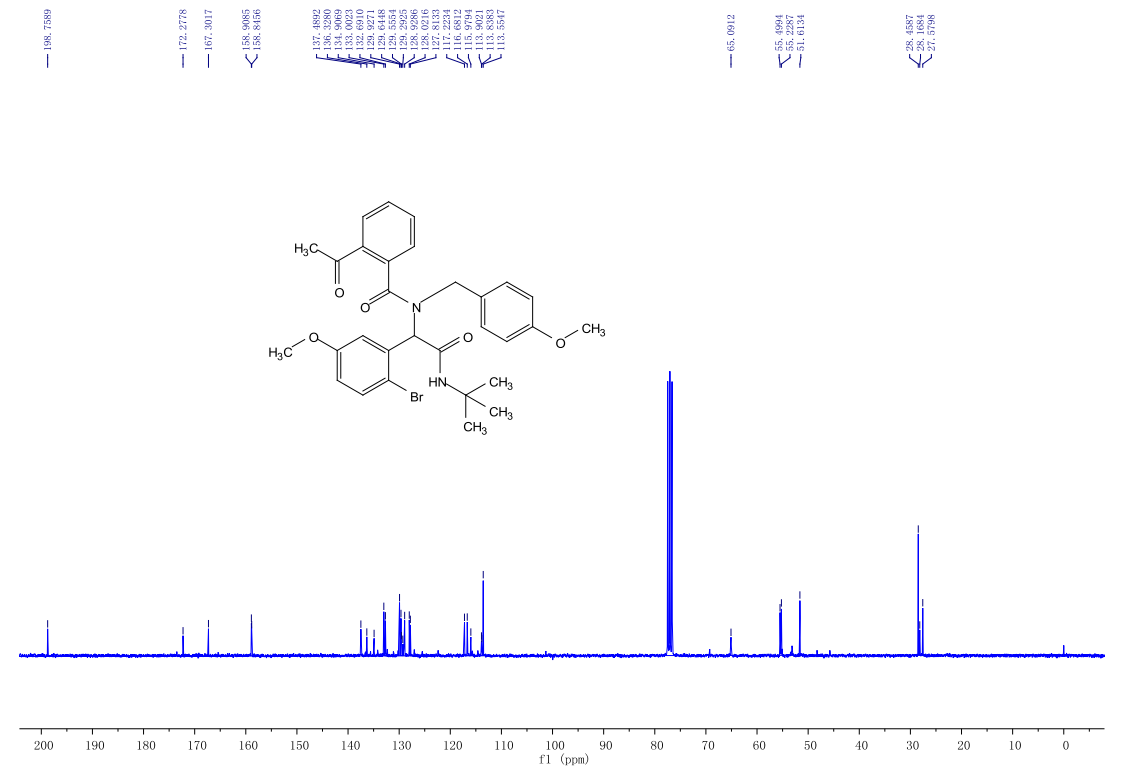
^{1}H and ^{13}C NMR spectra of compound **1i** (300 MHz, $CDCl_3$)



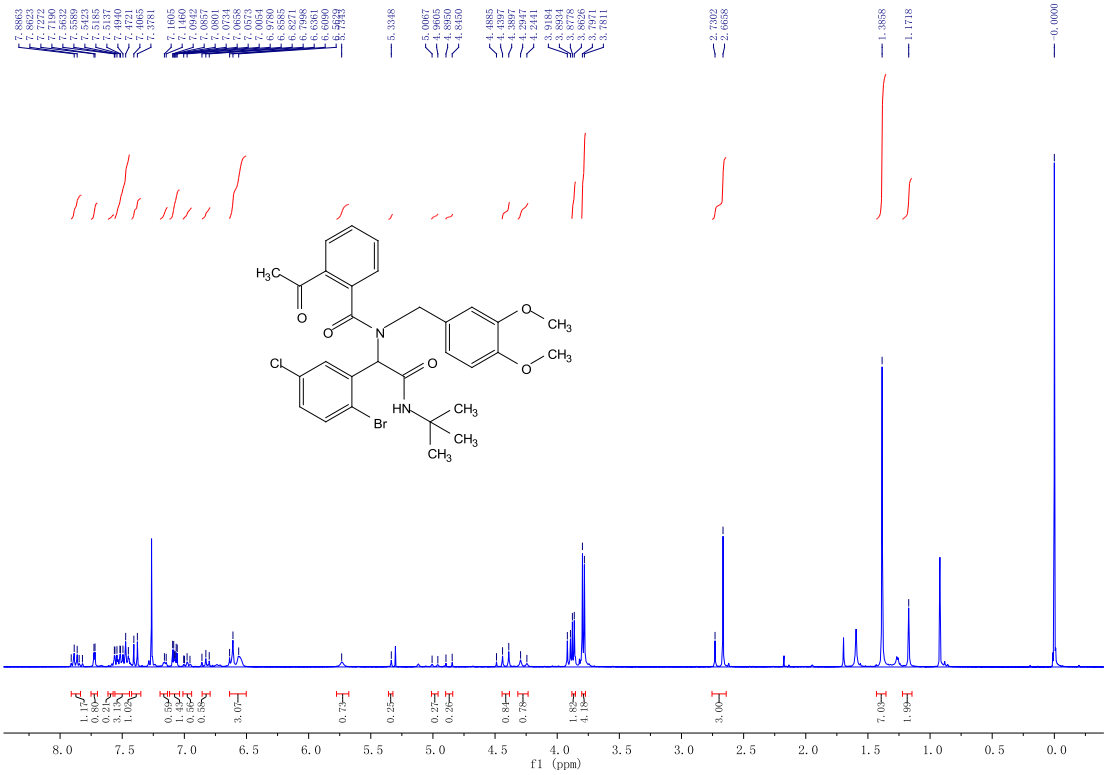


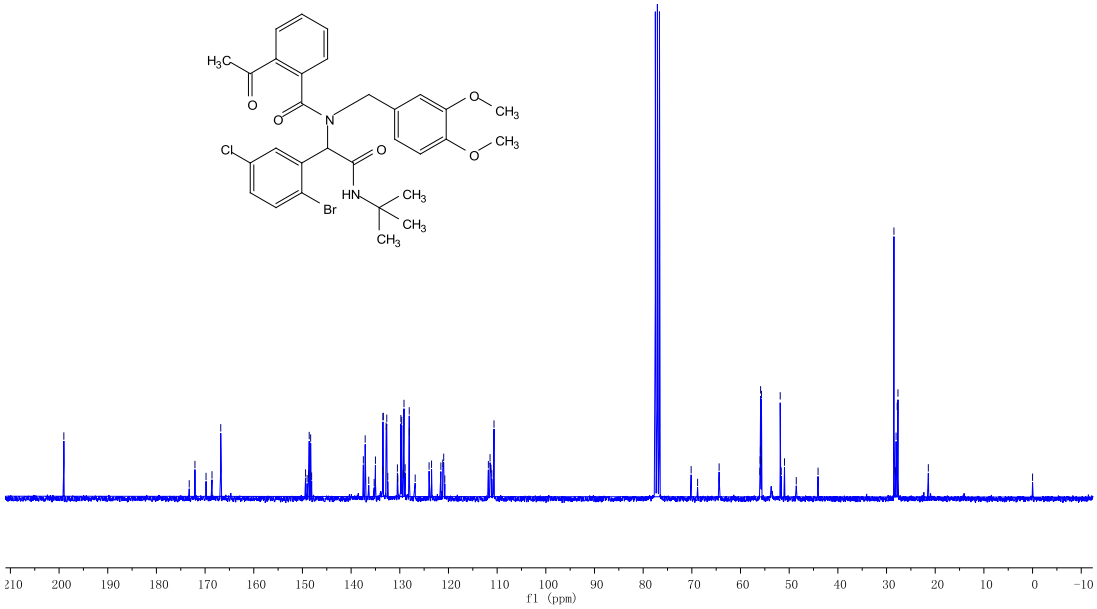
^{1}H and ^{13}C NMR spectra of compound **1j** (300 MHz, $CDCl_3$)



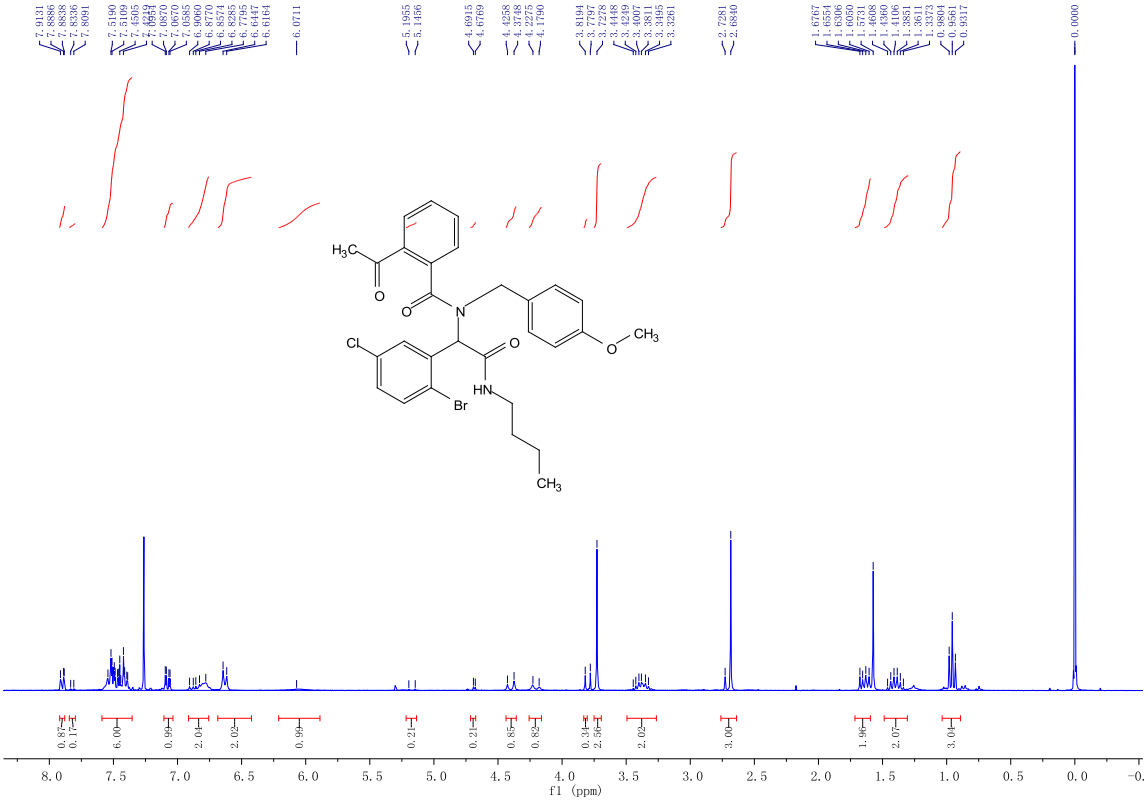


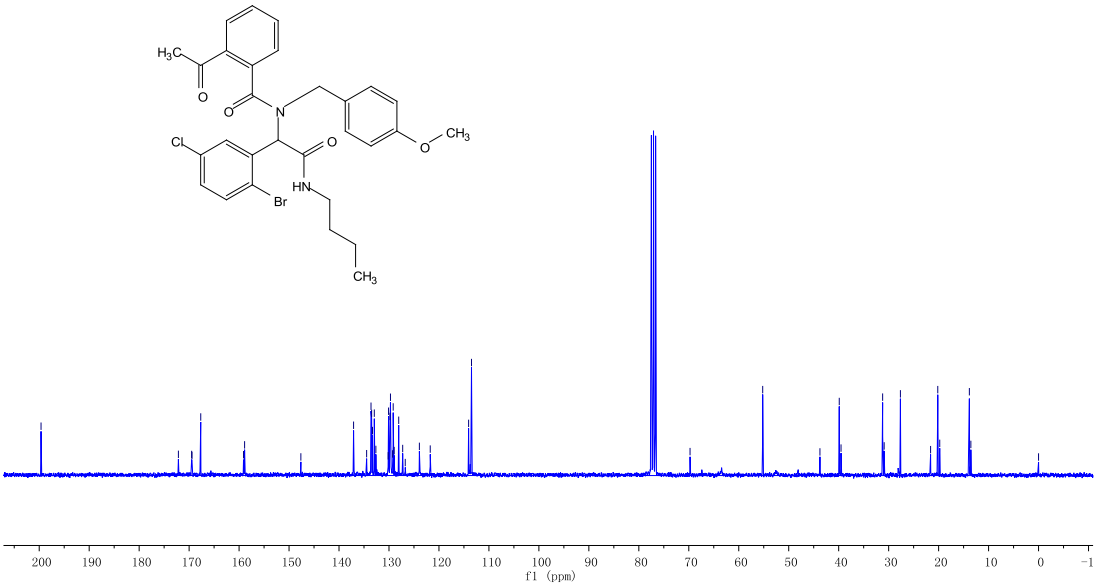
^{1}H and ^{13}C NMR spectra of compound **1k** (300 MHz, $CDCl_3$)



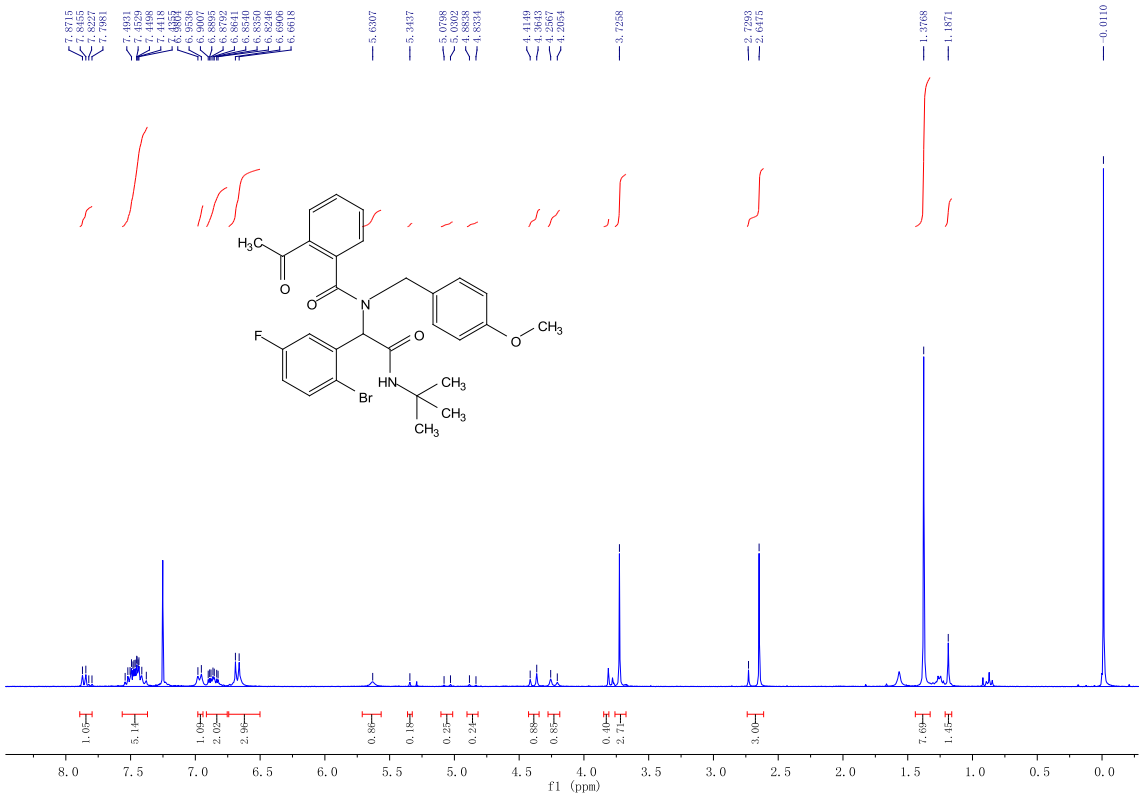


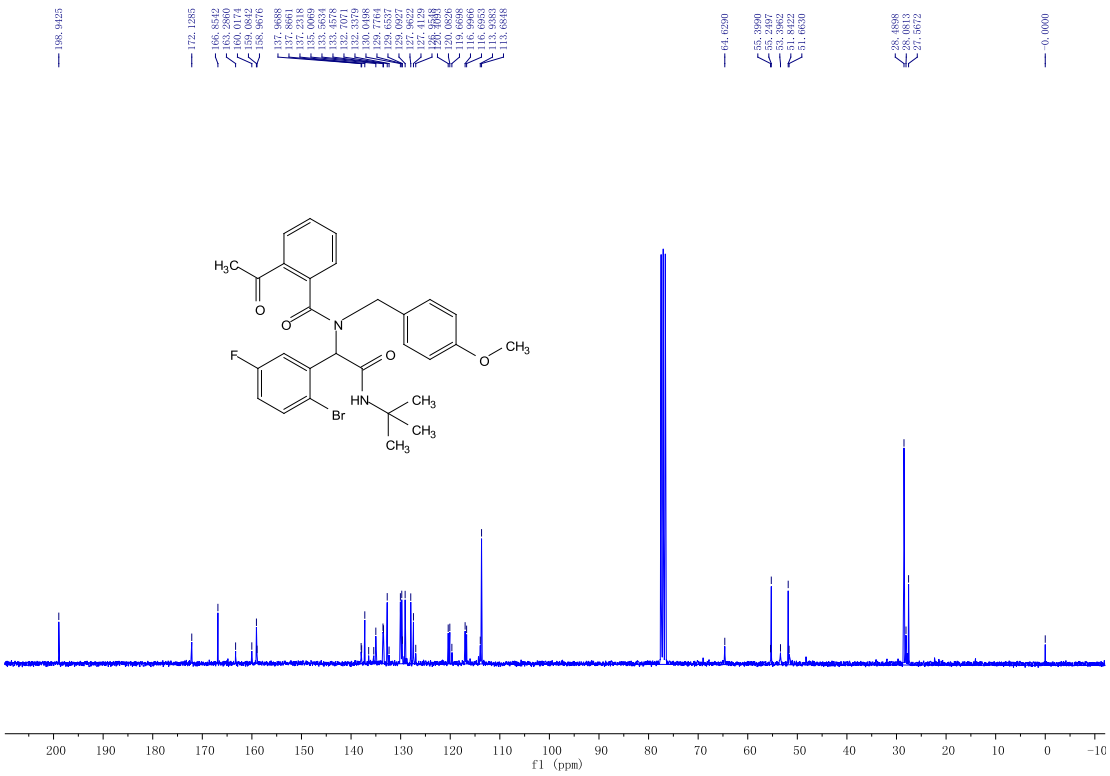
^{1}H and ^{13}C NMR spectra of compound **1l** (300 MHz, $CDCl_3$)



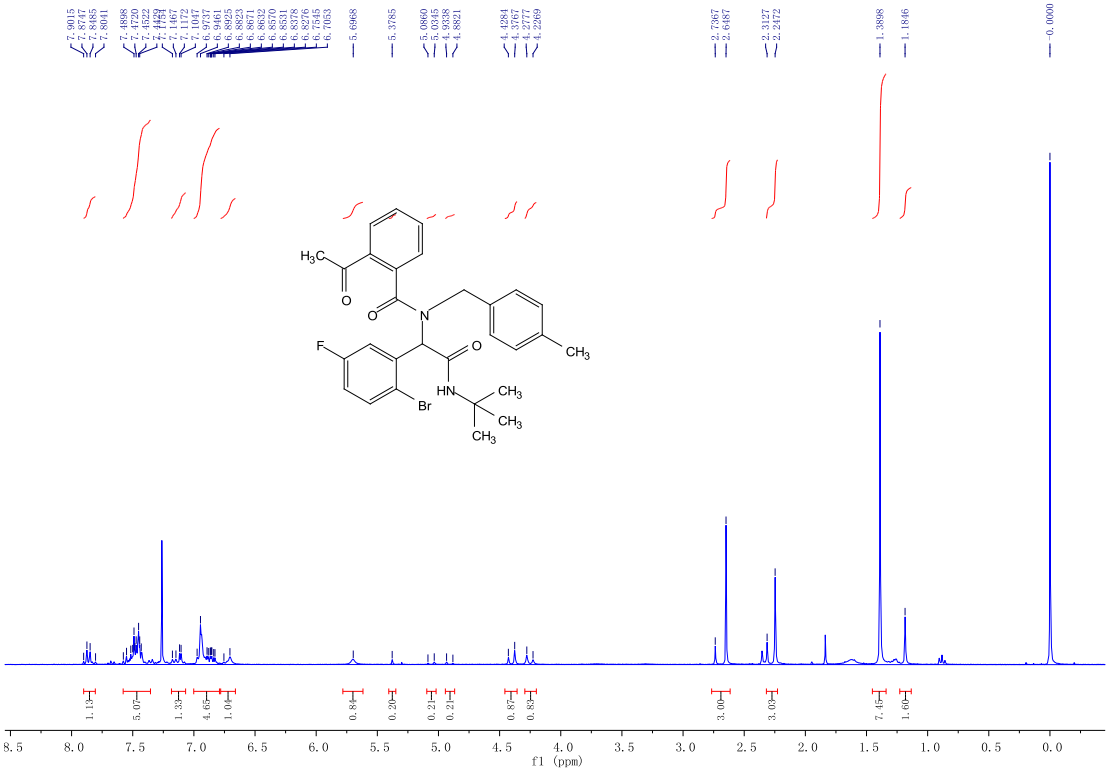


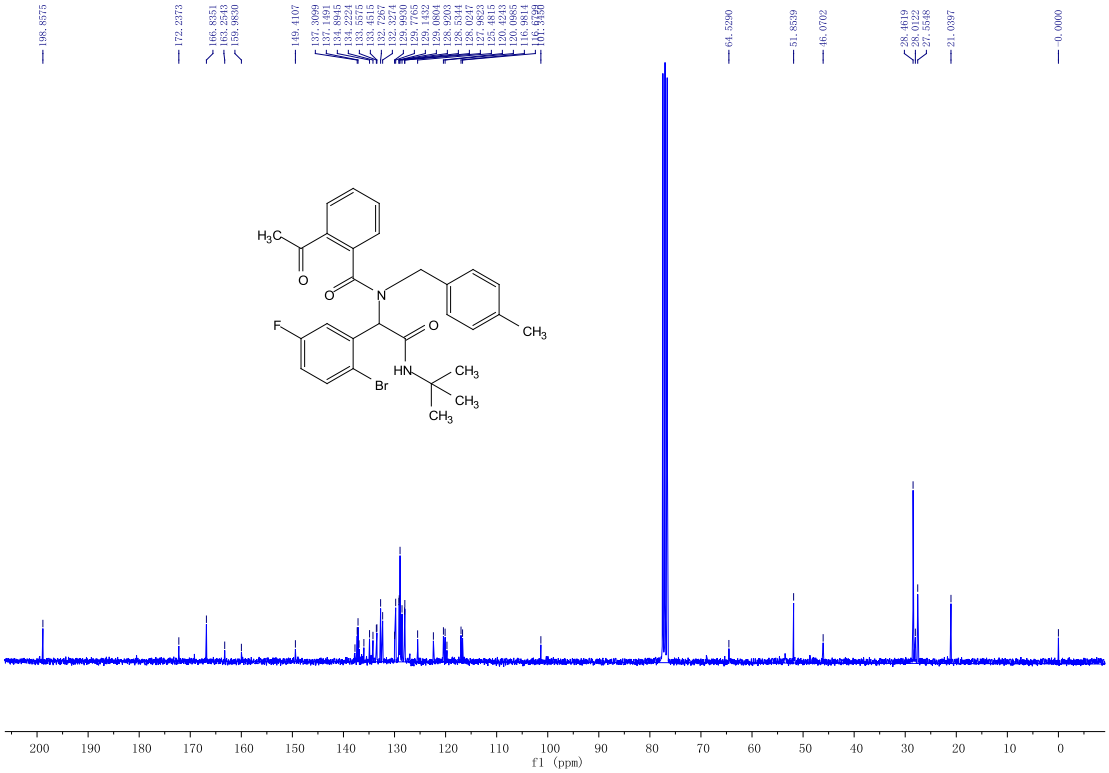
^{1}H and ^{13}C NMR spectra of compound **1m** (300 MHz, $CDCl_3$)



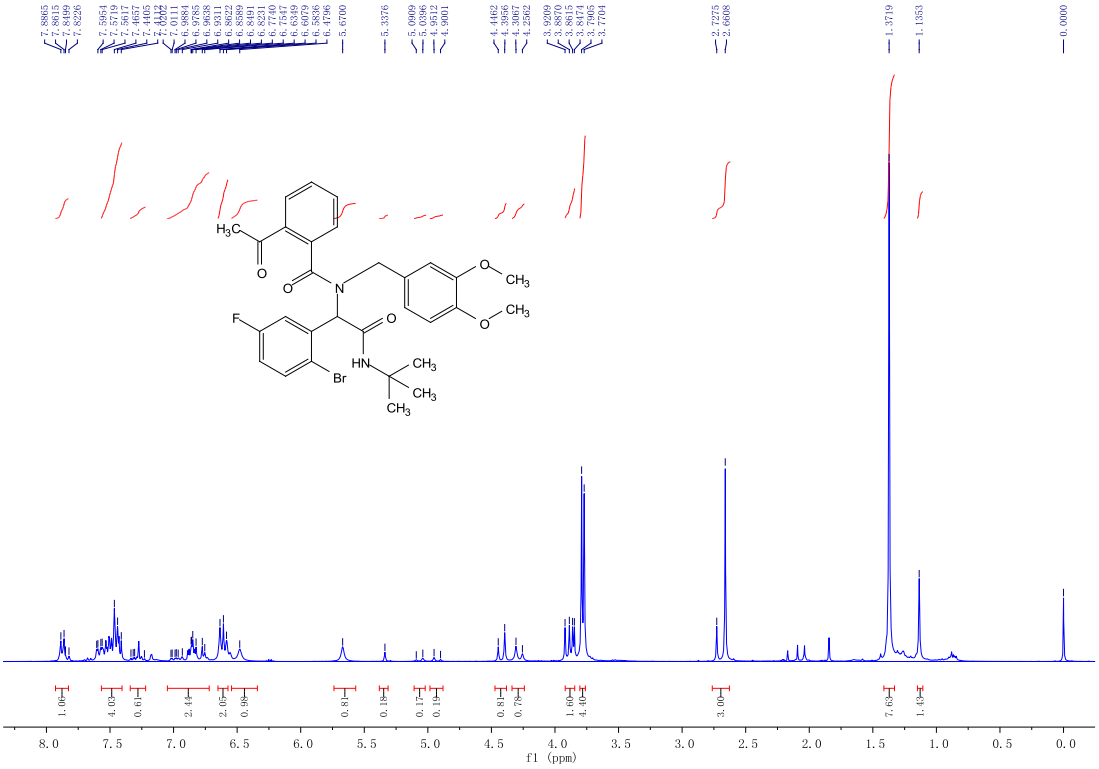


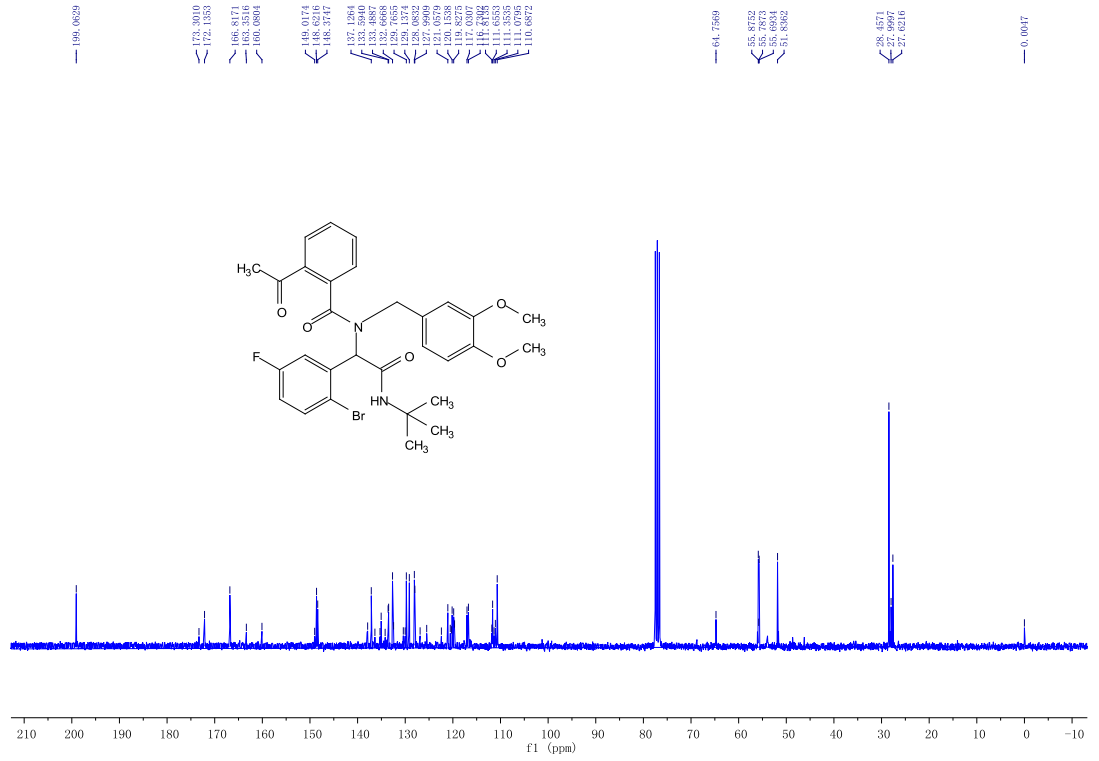
^{1}H and ^{13}C NMR spectra of compound **1n** (300 MHz, $CDCl_3$)



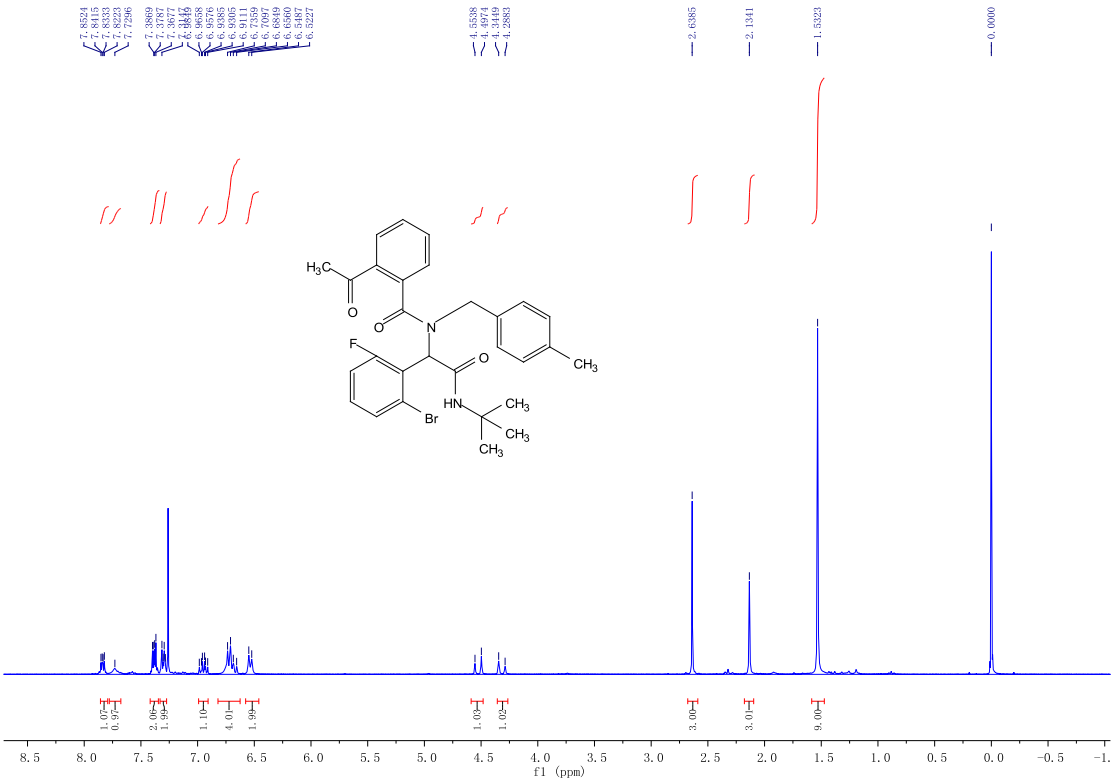


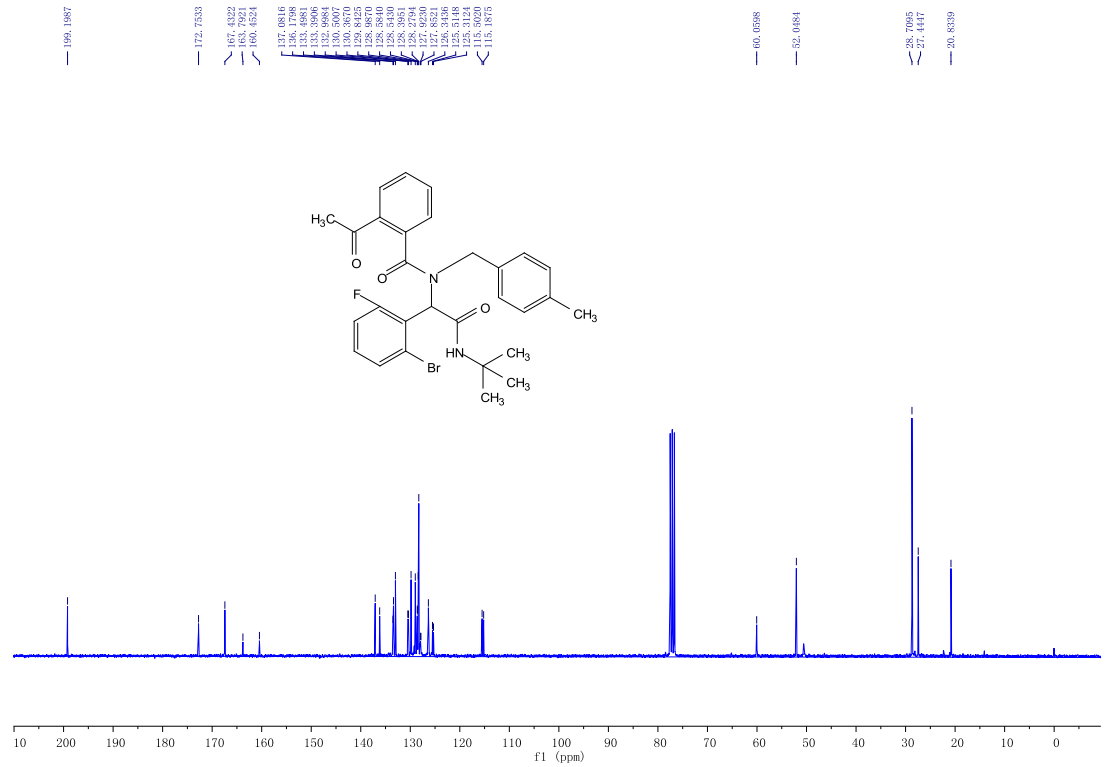
^{1}H and ^{13}C NMR spectra of compound **1o** (300 MHz, $CDCl_3$)



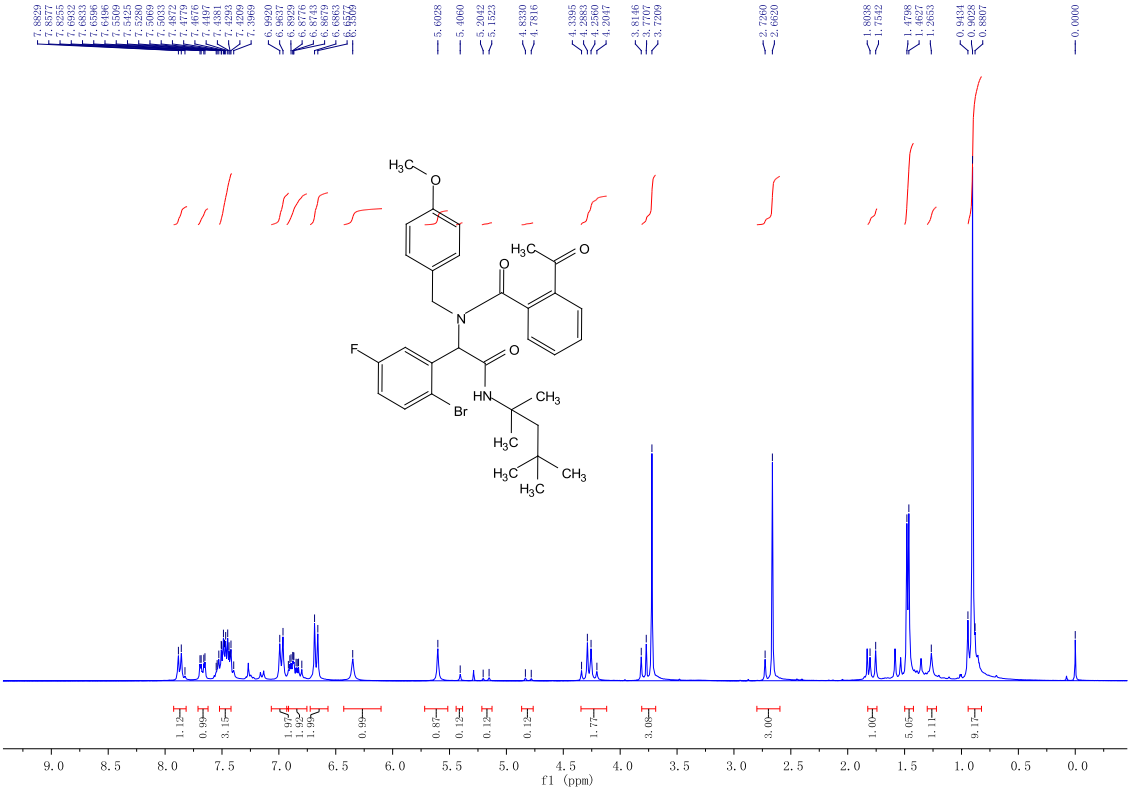


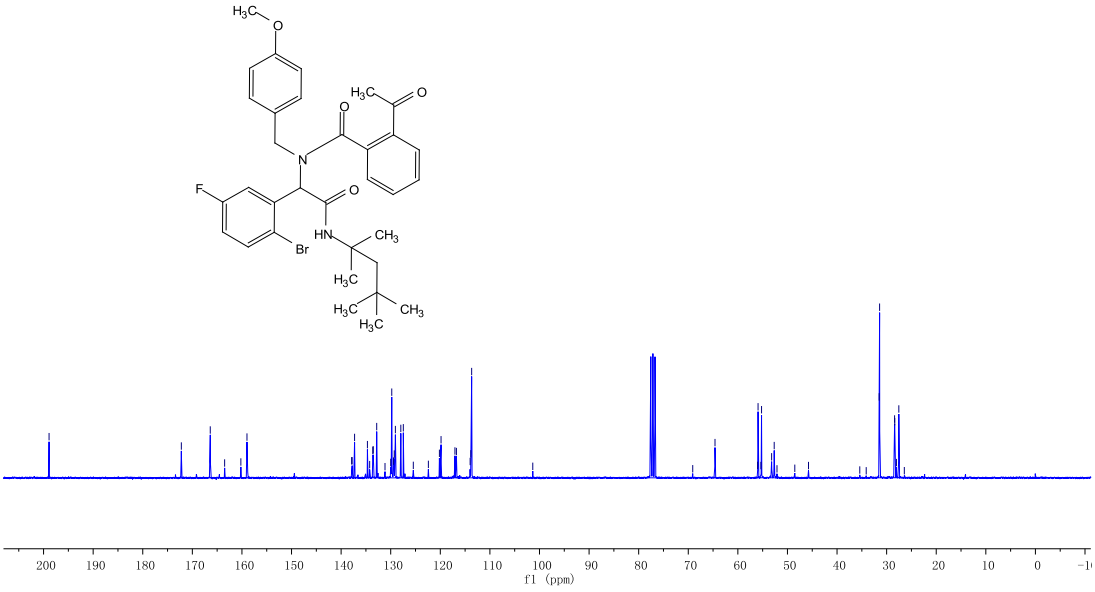
^{1}H and ^{13}C NMR spectra of compound **1p** (300 MHz, $CDCl_3$)



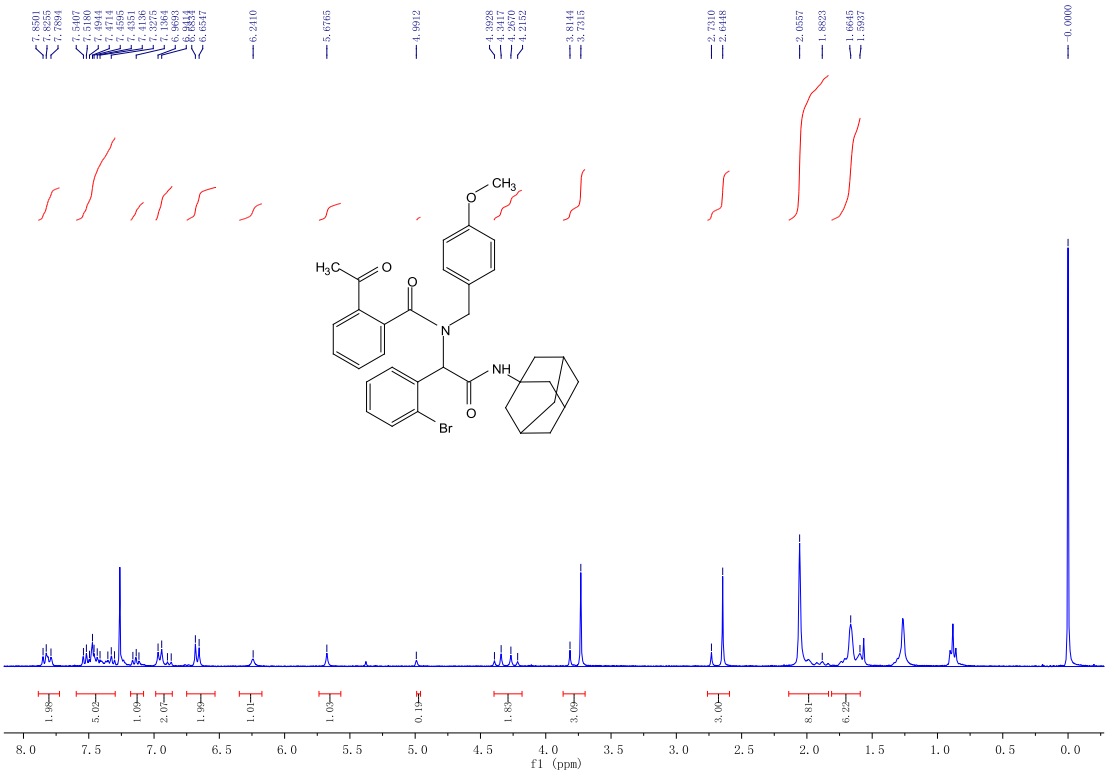


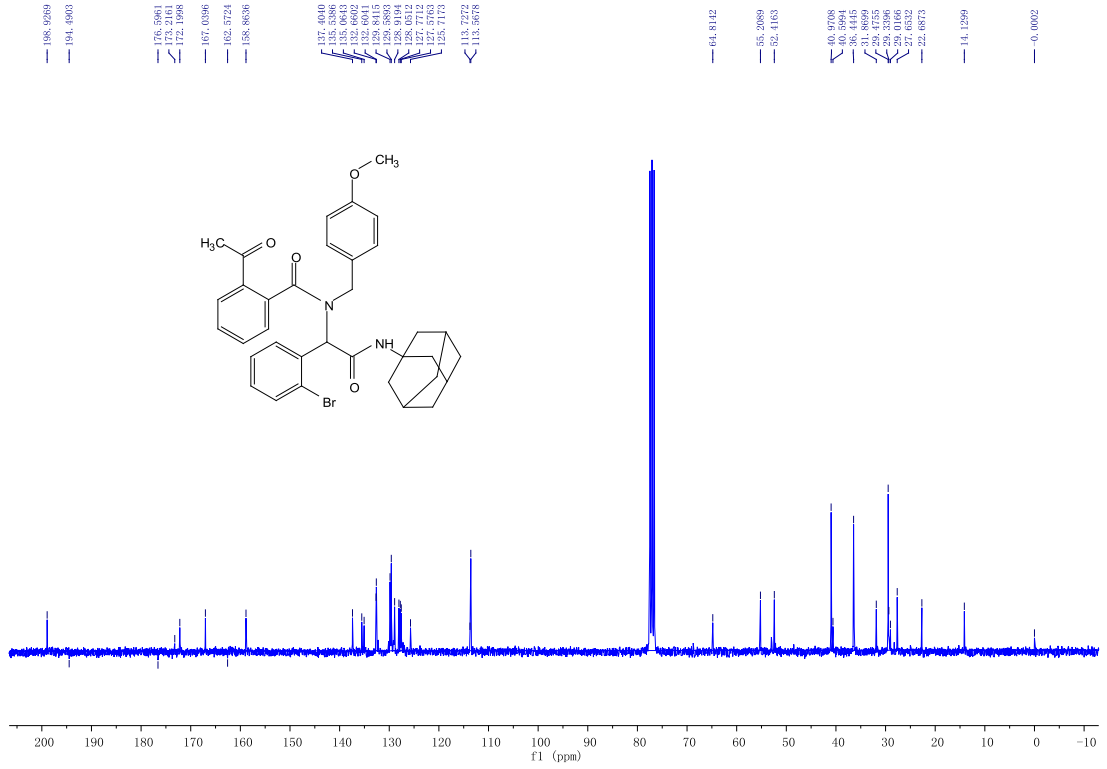
^{1}H and ^{13}C NMR spectra of compound **1q** (300 MHz, $CDCl_3$)



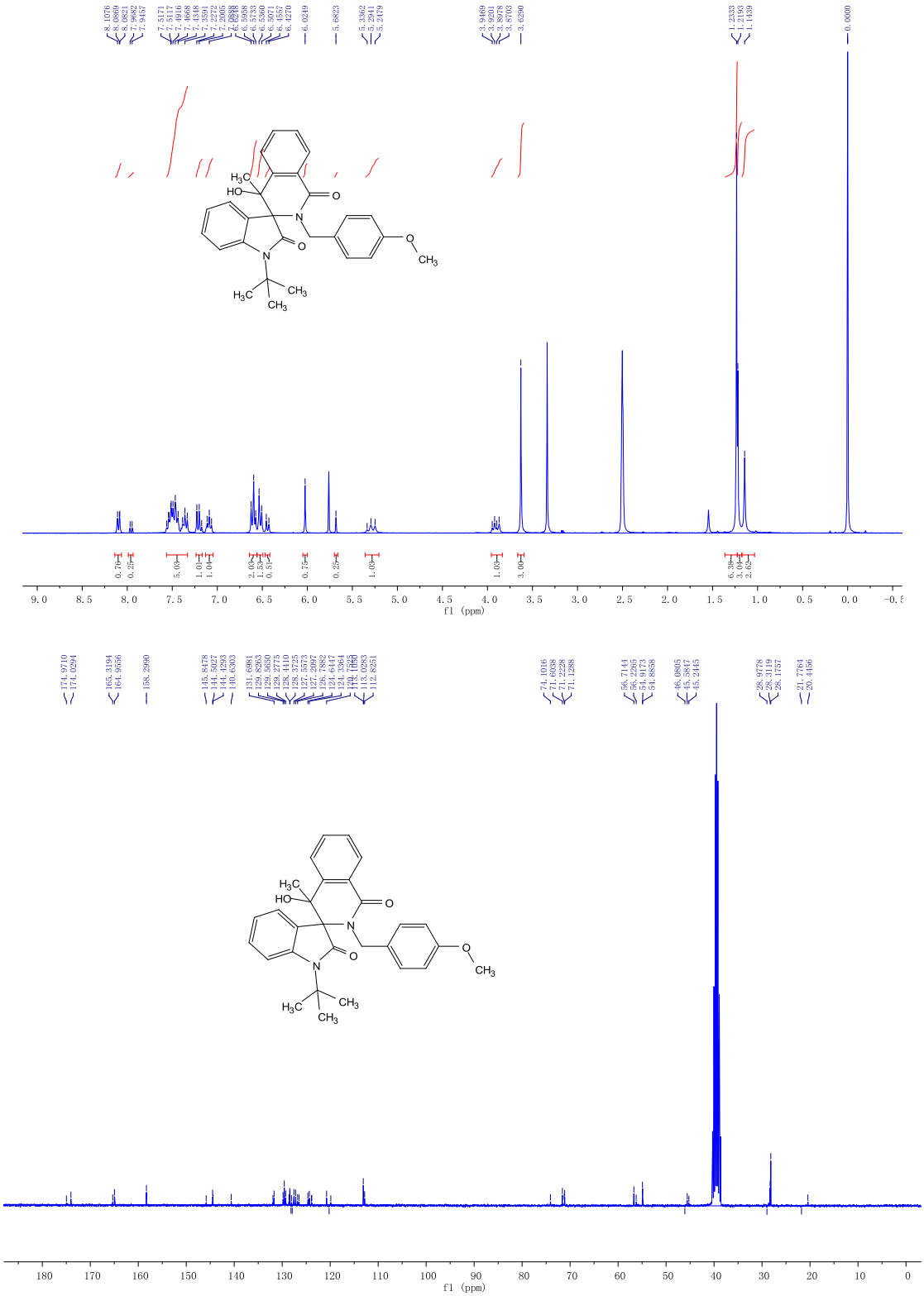


^{1}H and ^{13}C NMR spectra of compound **1r** (300 MHz, $CDCl_3$)

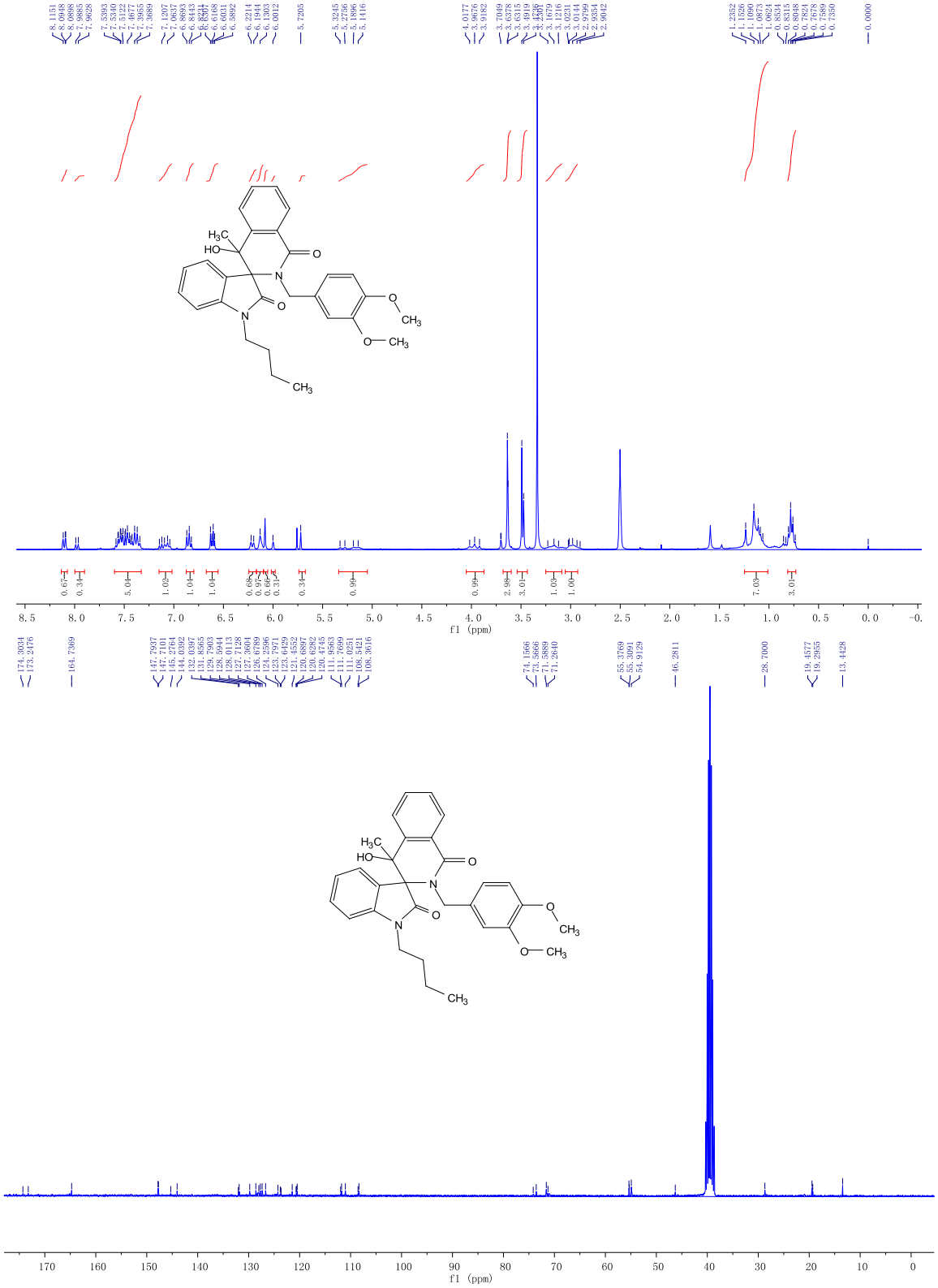




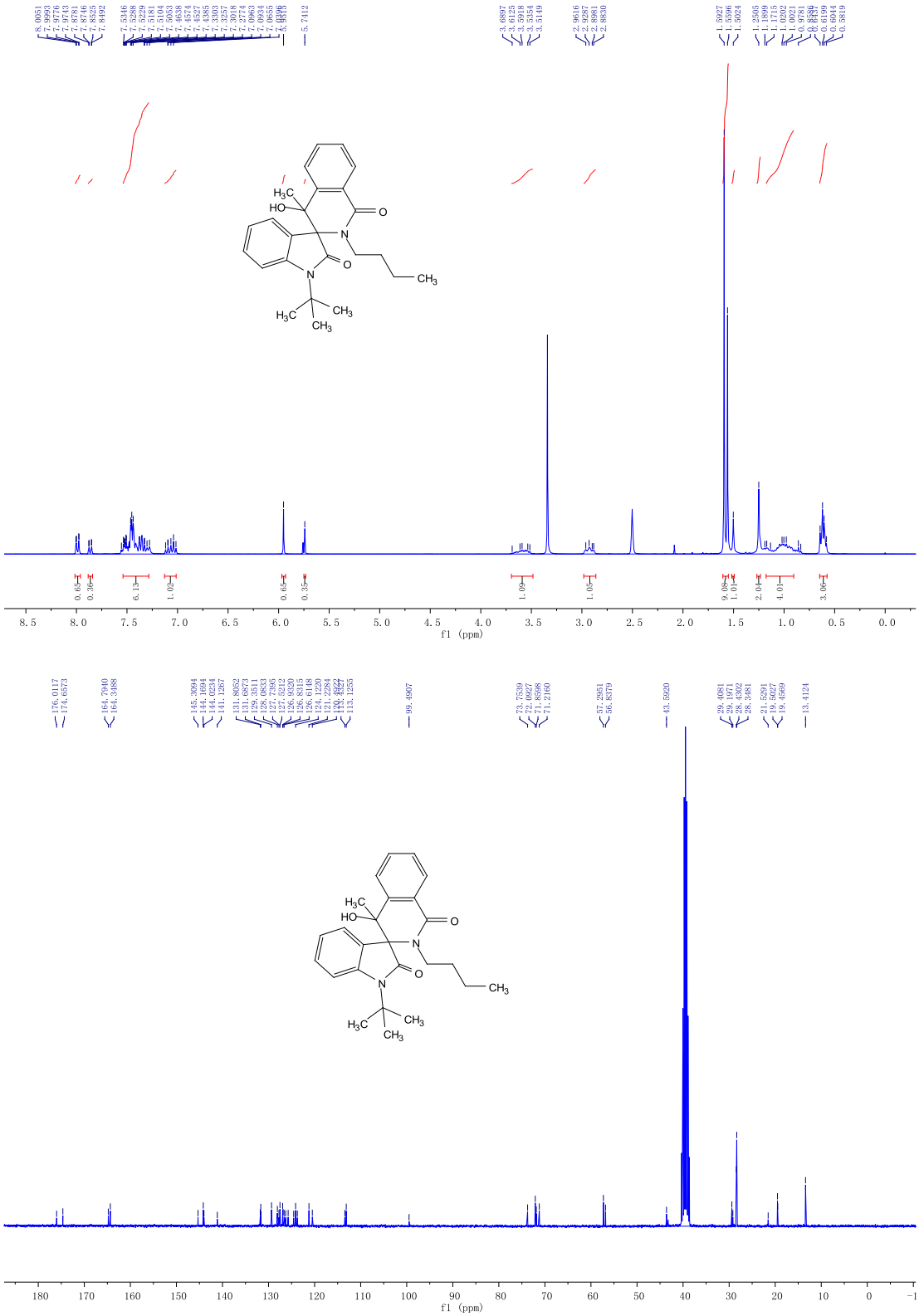
^{1}H and ^{13}C NMR spectra of compound **2a** (300 MHz, DMSO-d_6)



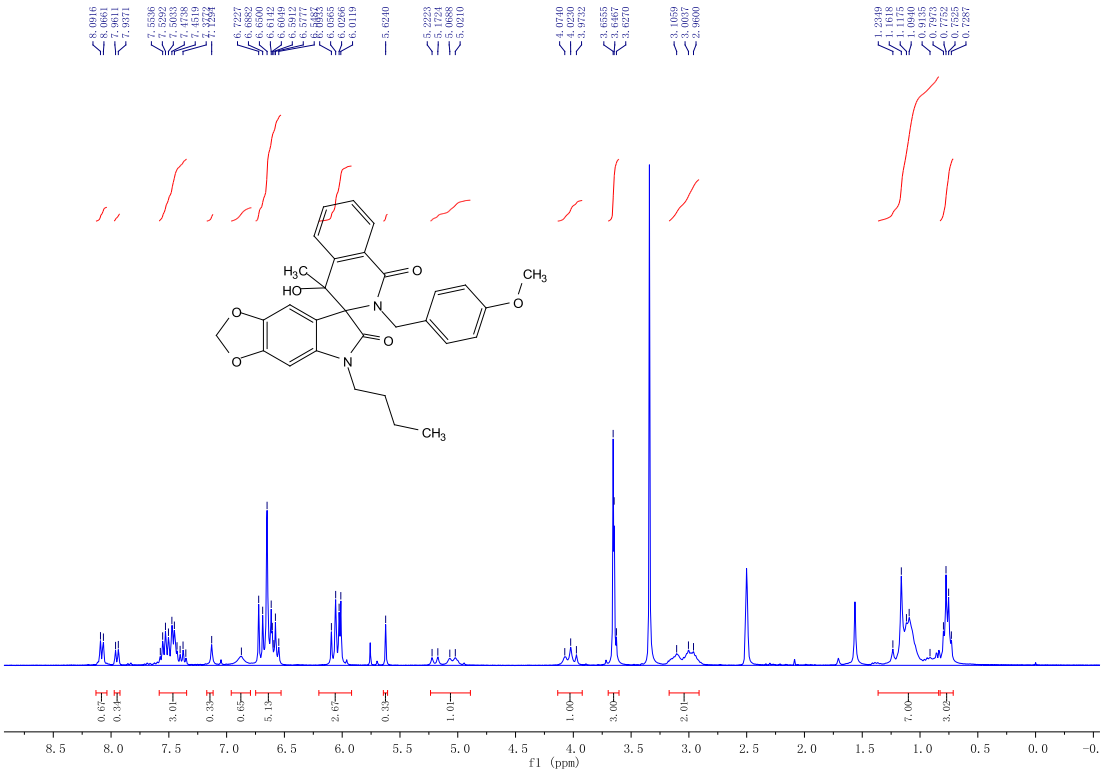
^{1}H and ^{13}C NMR spectra of compound **2b** (300 MHz, DMSO-d_6)

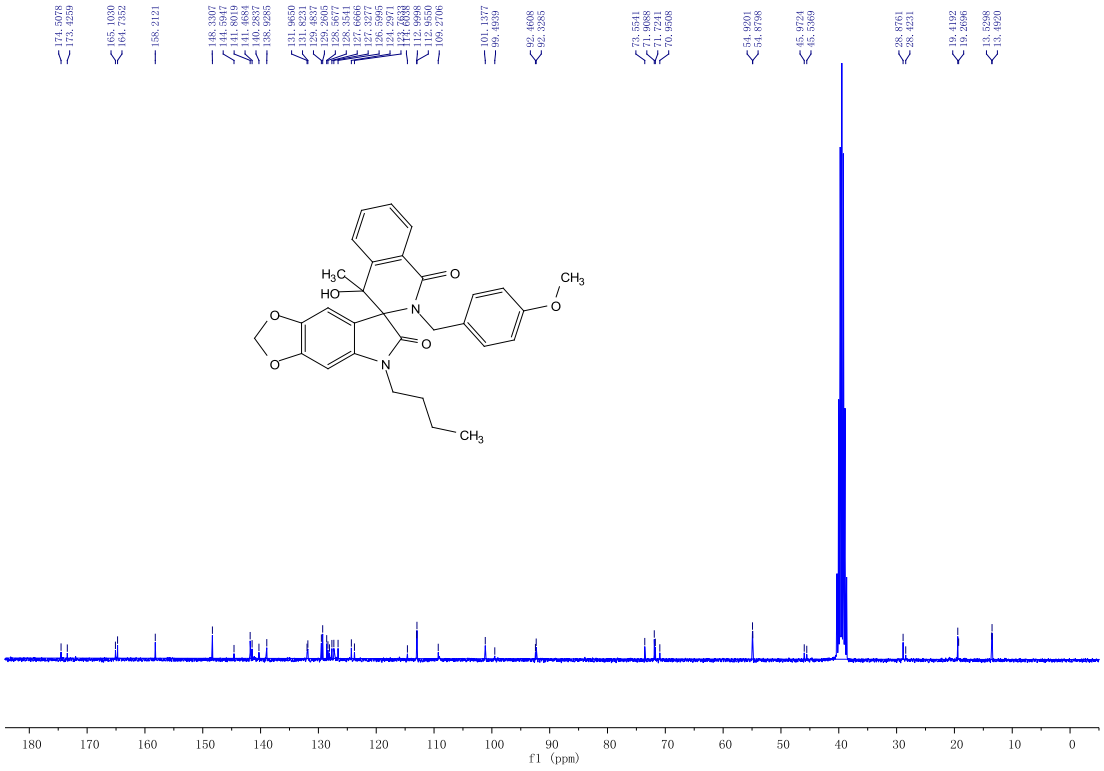


^{1}H and ^{13}C NMR spectra of compound **2c** (300 MHz, DMSO-d_6)

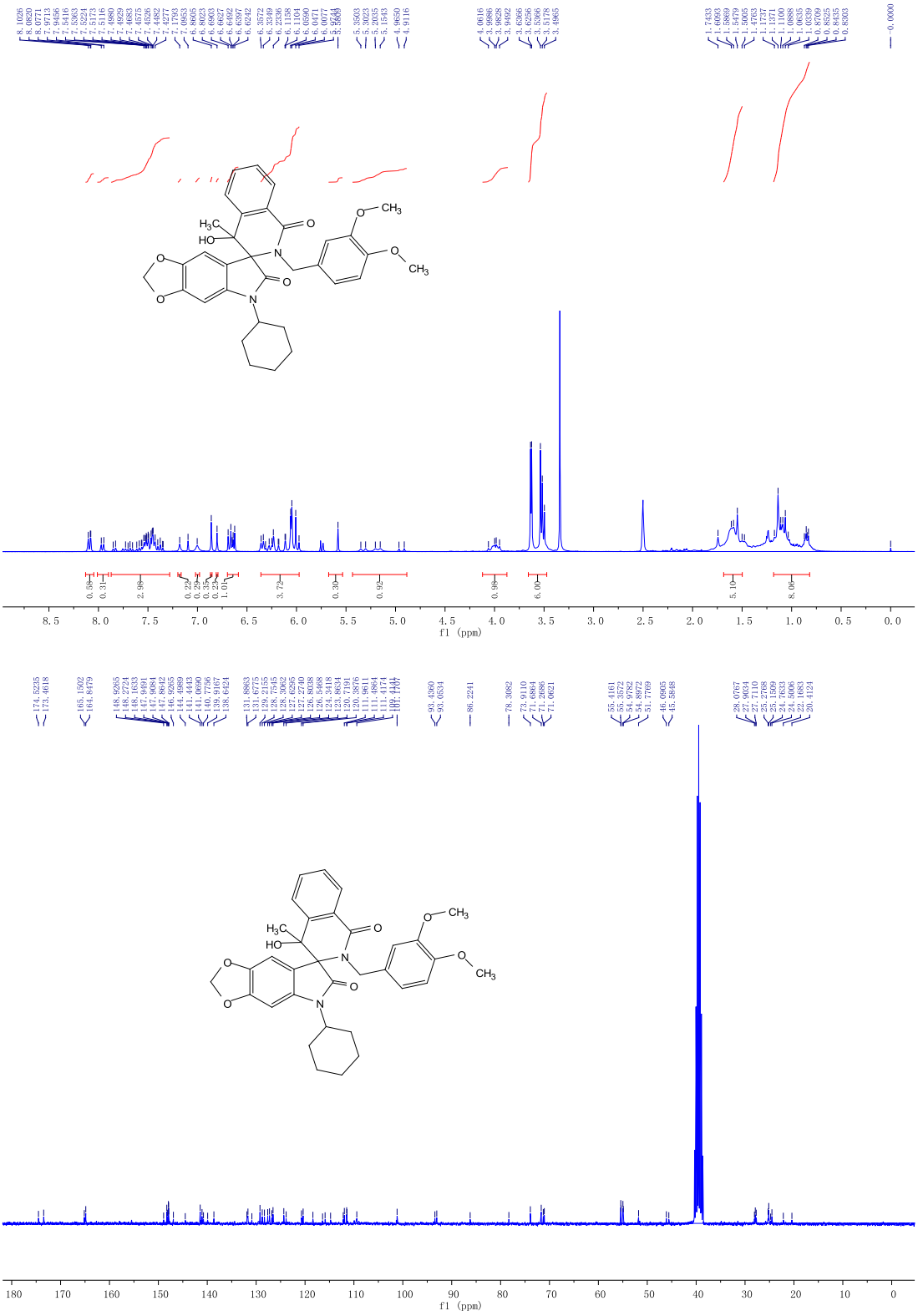


^{1}H and ^{13}C NMR spectra of compound **2d** (300 MHz, DMSO-d_6)

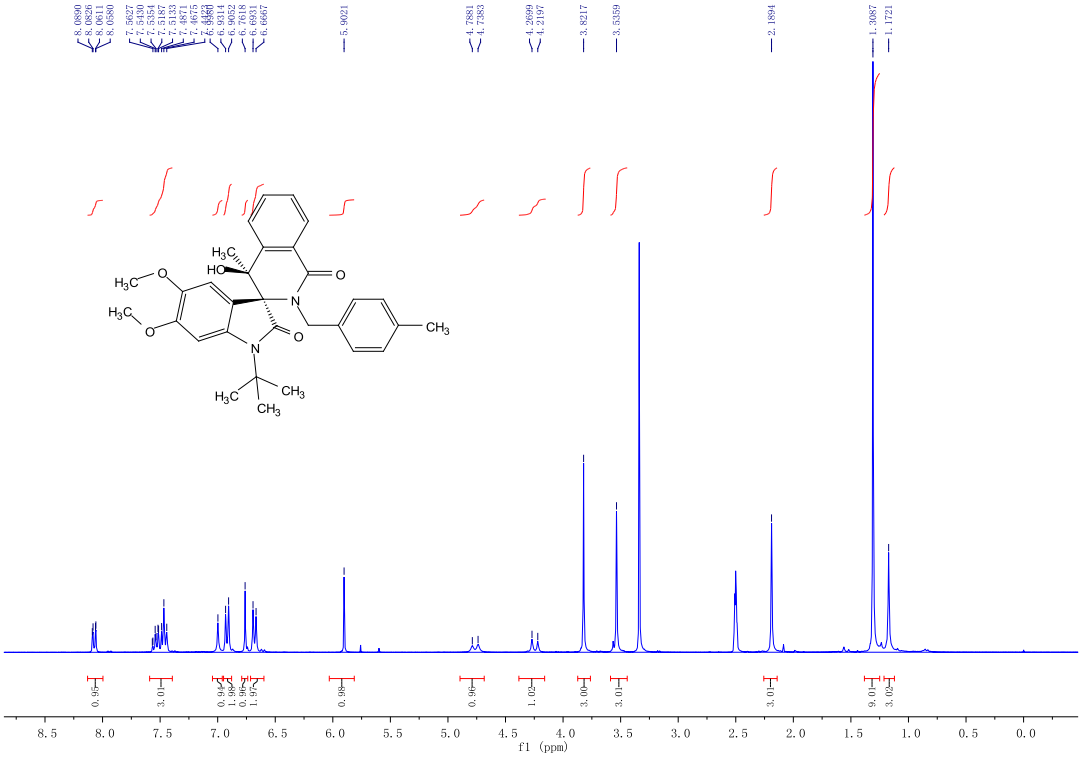


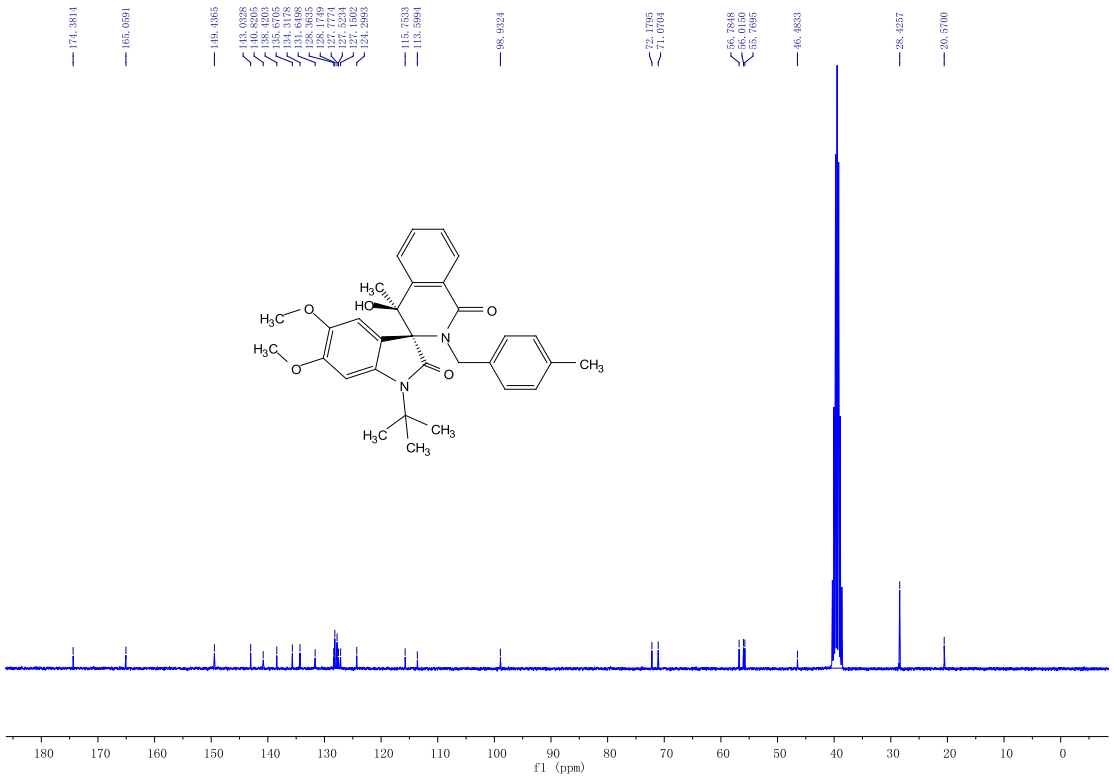


^{1}H and ^{13}C NMR spectra of compound **2e** (300 MHz, DMSO-d_6)

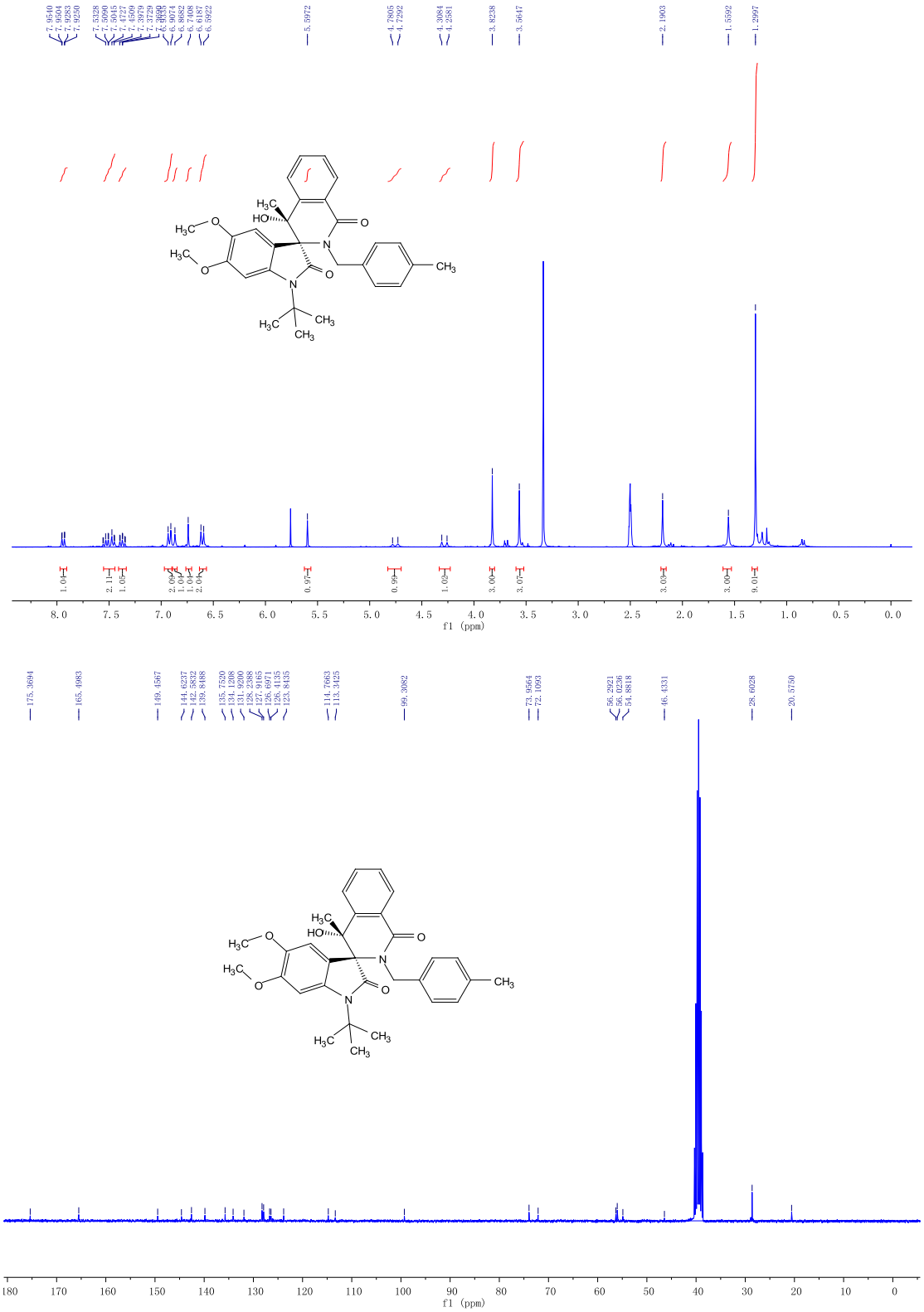


^{1}H and ^{13}C NMR spectra of compound **2f** (300 MHz, DMSO-d_6)

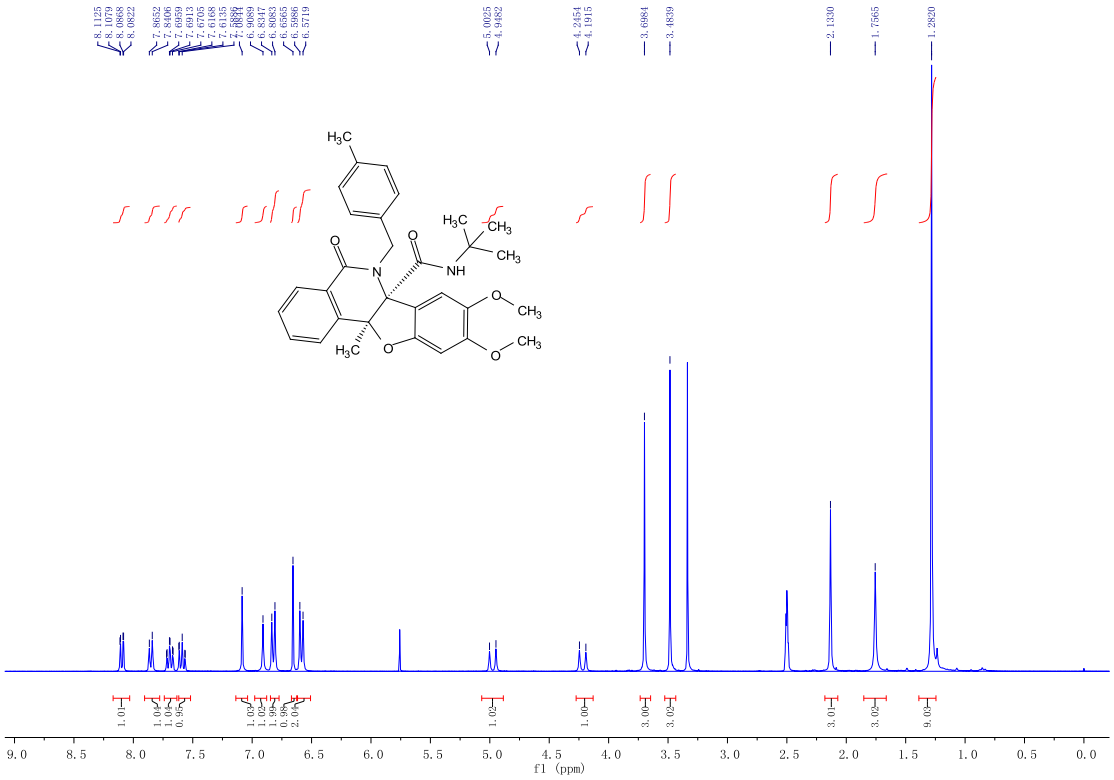


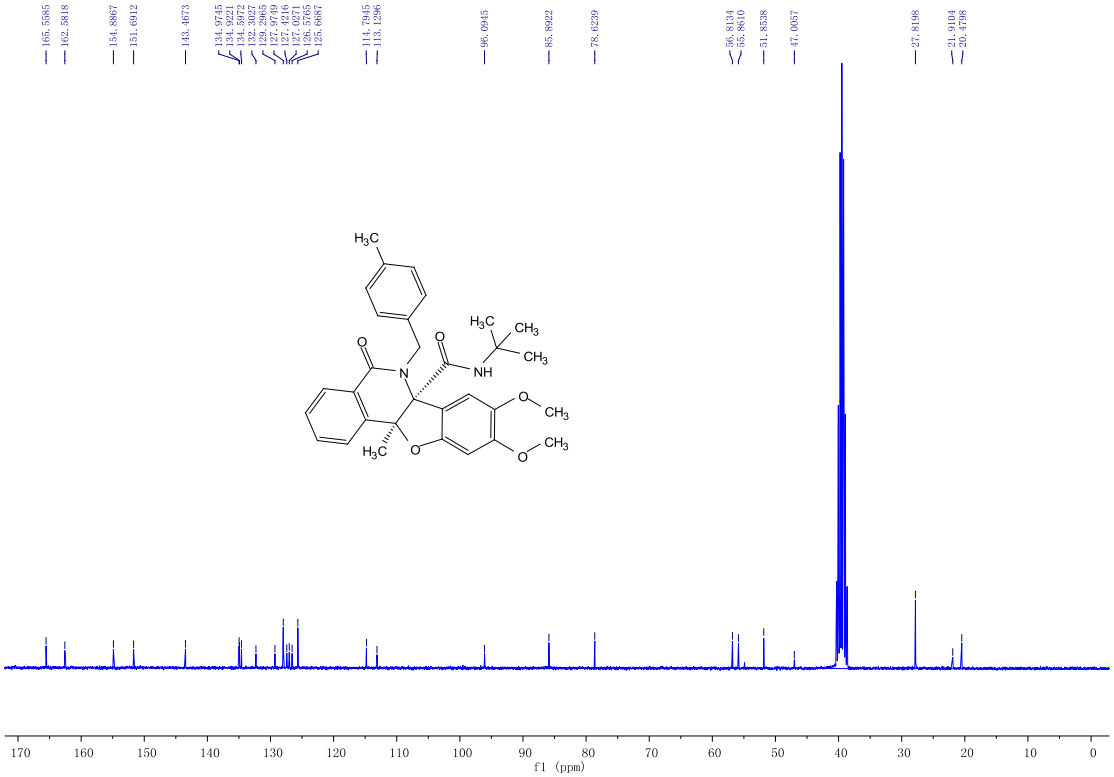


^{1}H and ^{13}C NMR spectra of compound **2f'** (300 MHz, DMSO-d_6)

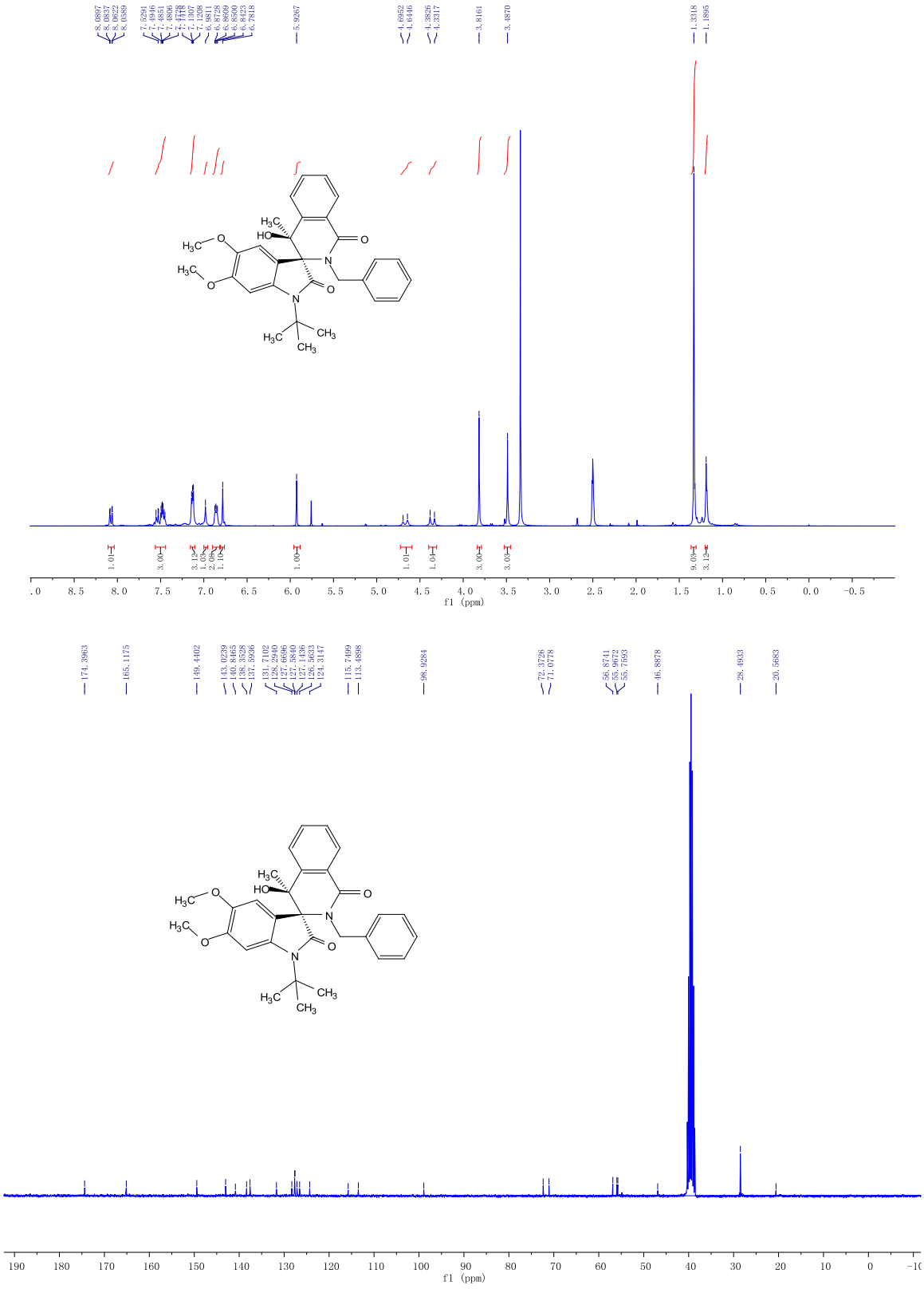


^{1}H and ^{13}C NMR spectra of compound **3f** (300 MHz, DMSO-d_6)

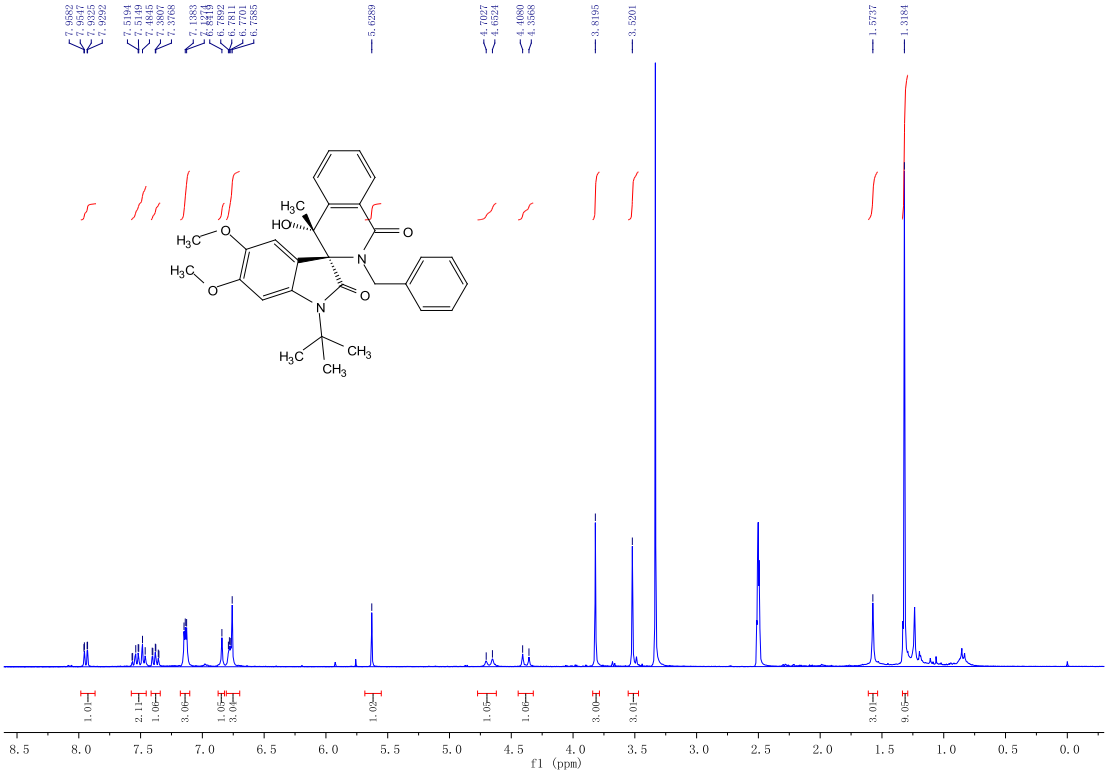


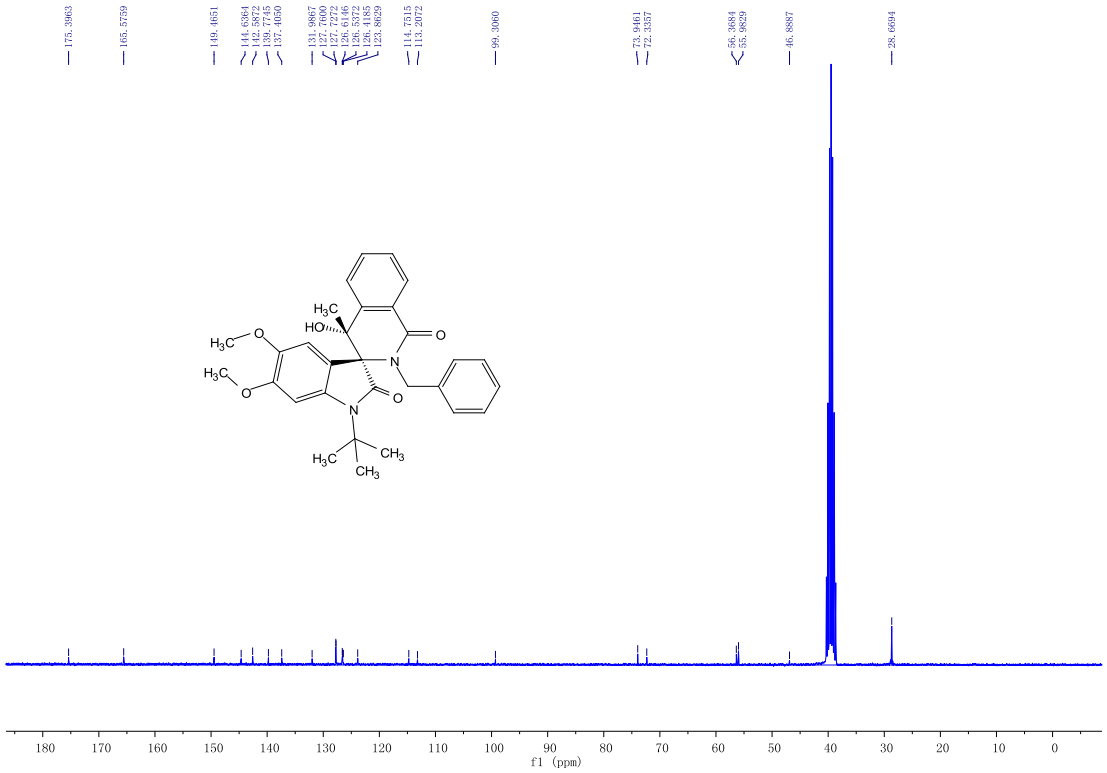


^{1}H and ^{13}C NMR spectra of compound **2g** (300 MHz, DMSO-d_6)

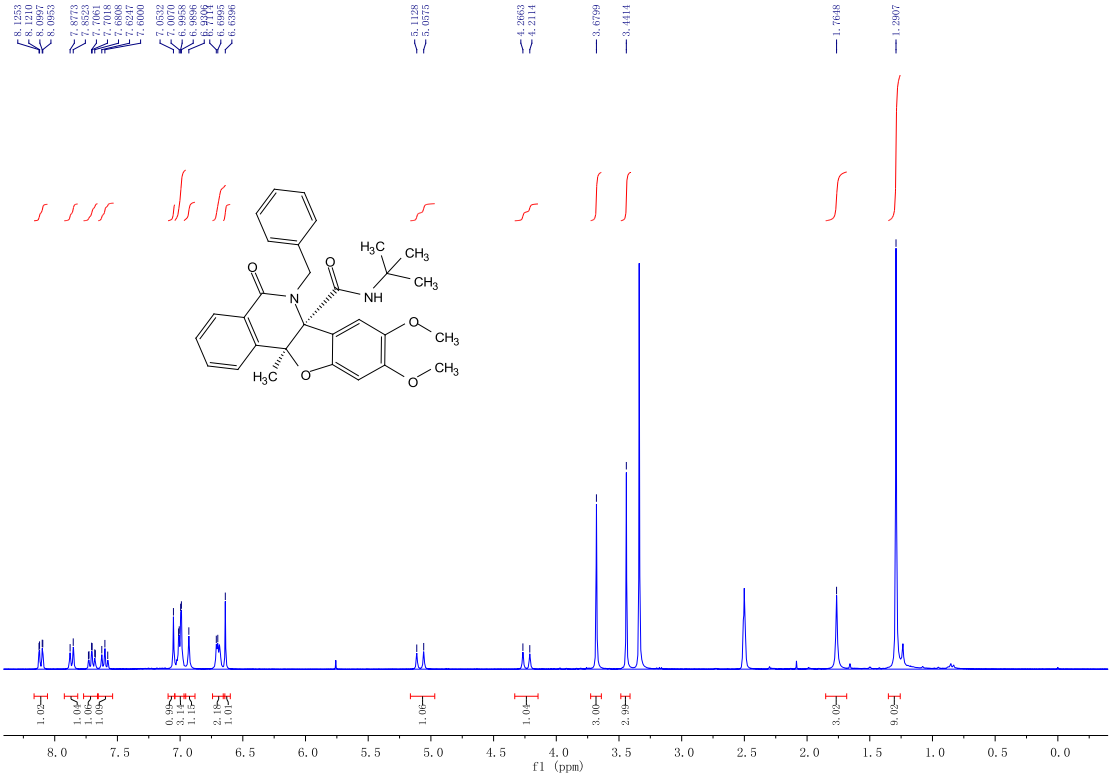


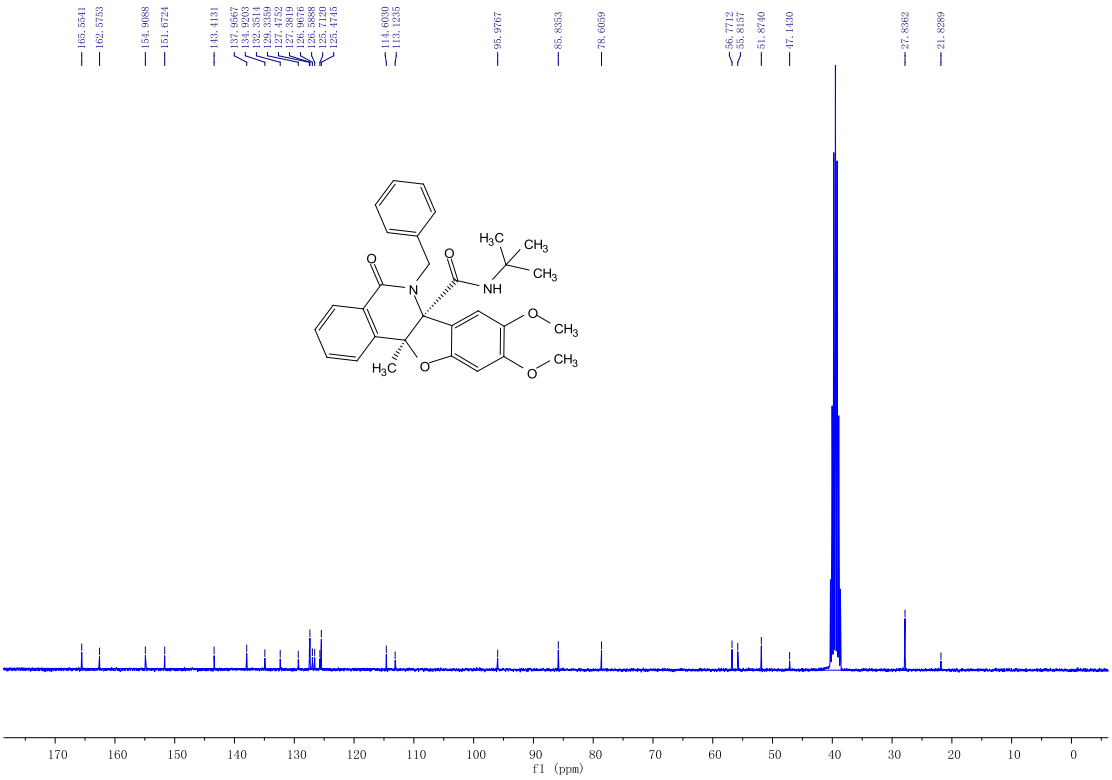
^{1}H and ^{13}C NMR spectra of compound **2g'** (300 MHz, DMSO-d_6) **Z**



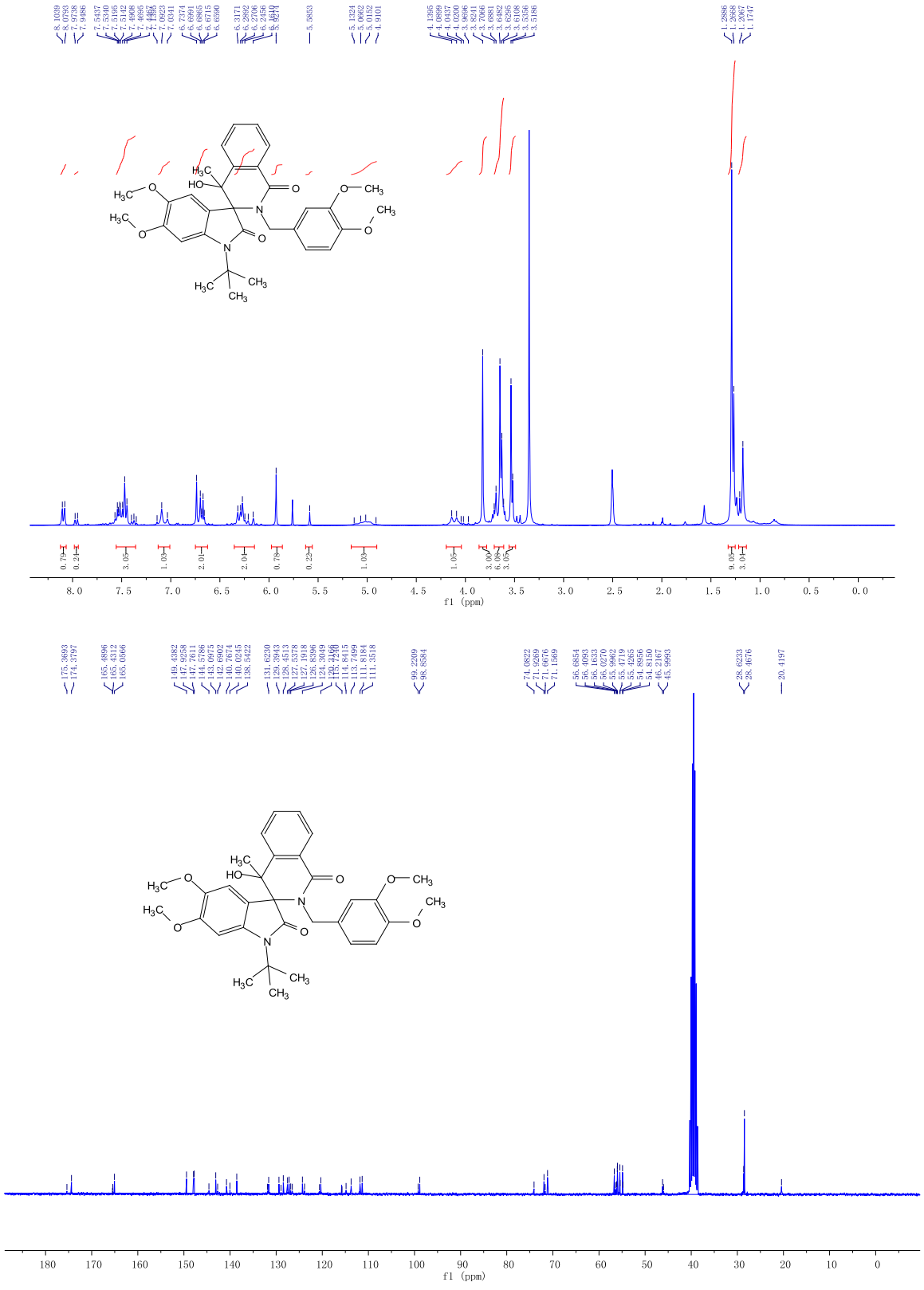


^{1}H and ^{13}C NMR spectra of compound **3g** (300 MHz, DMSO-d_6)

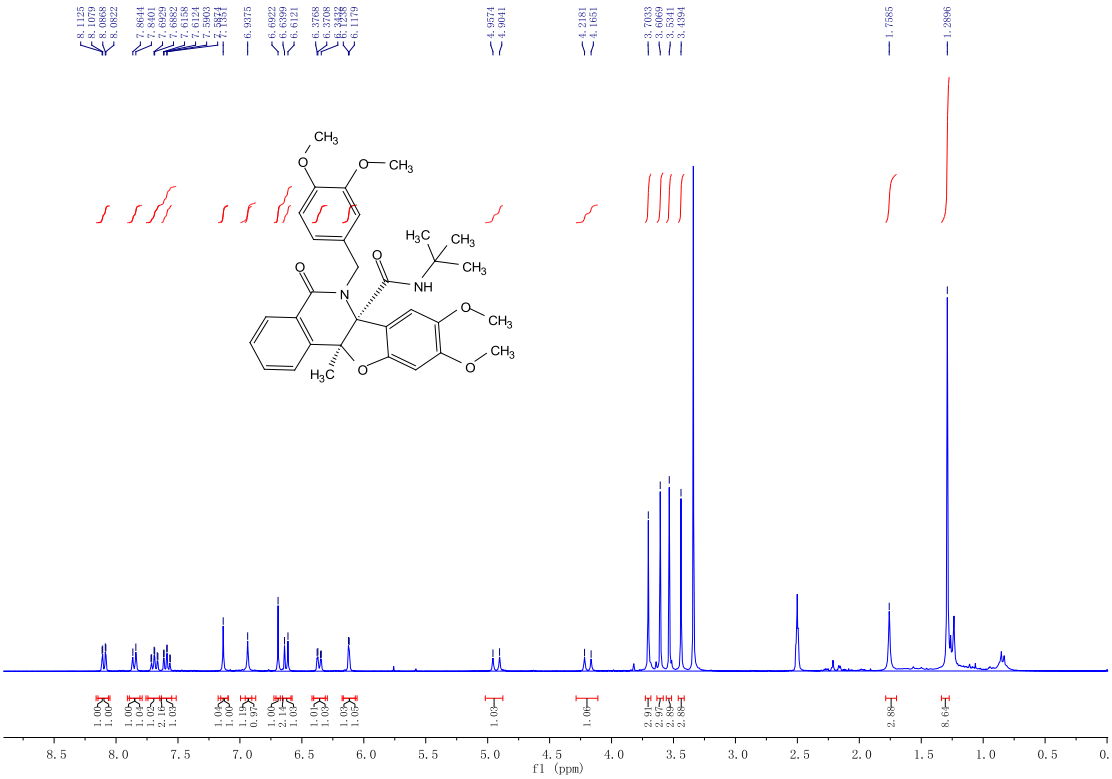


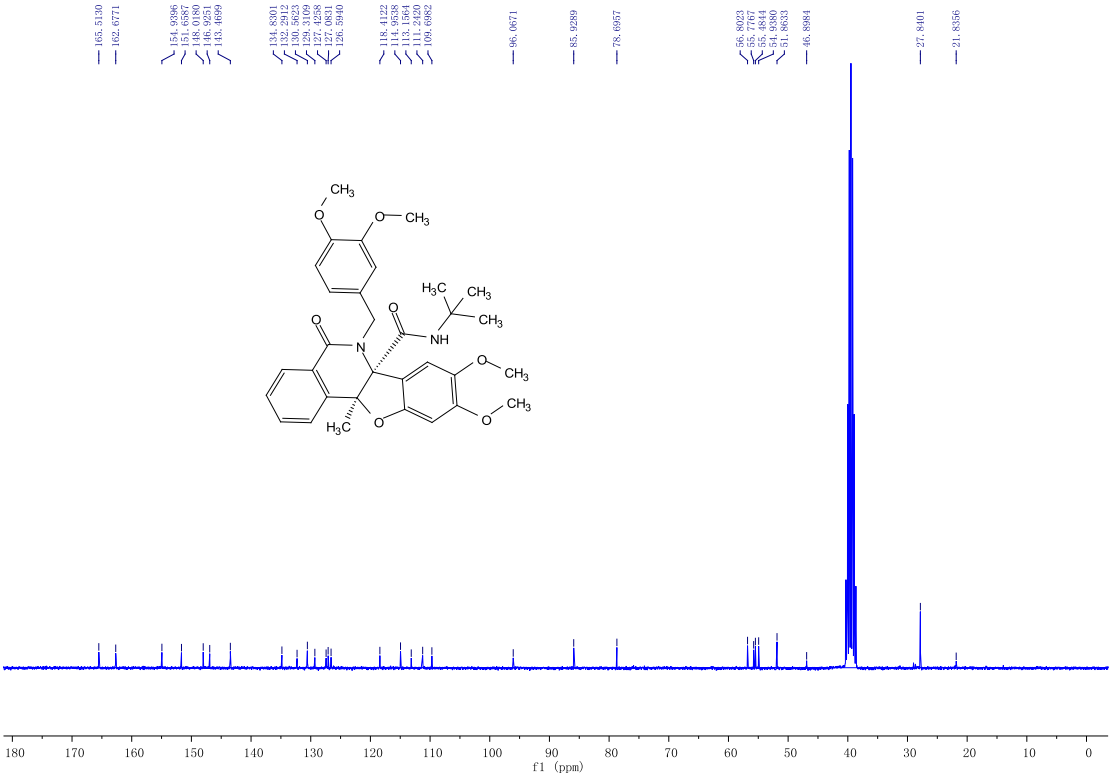


^{1}H and ^{13}C NMR spectra of compound **2h** (300 MHz, DMSO-d_6)

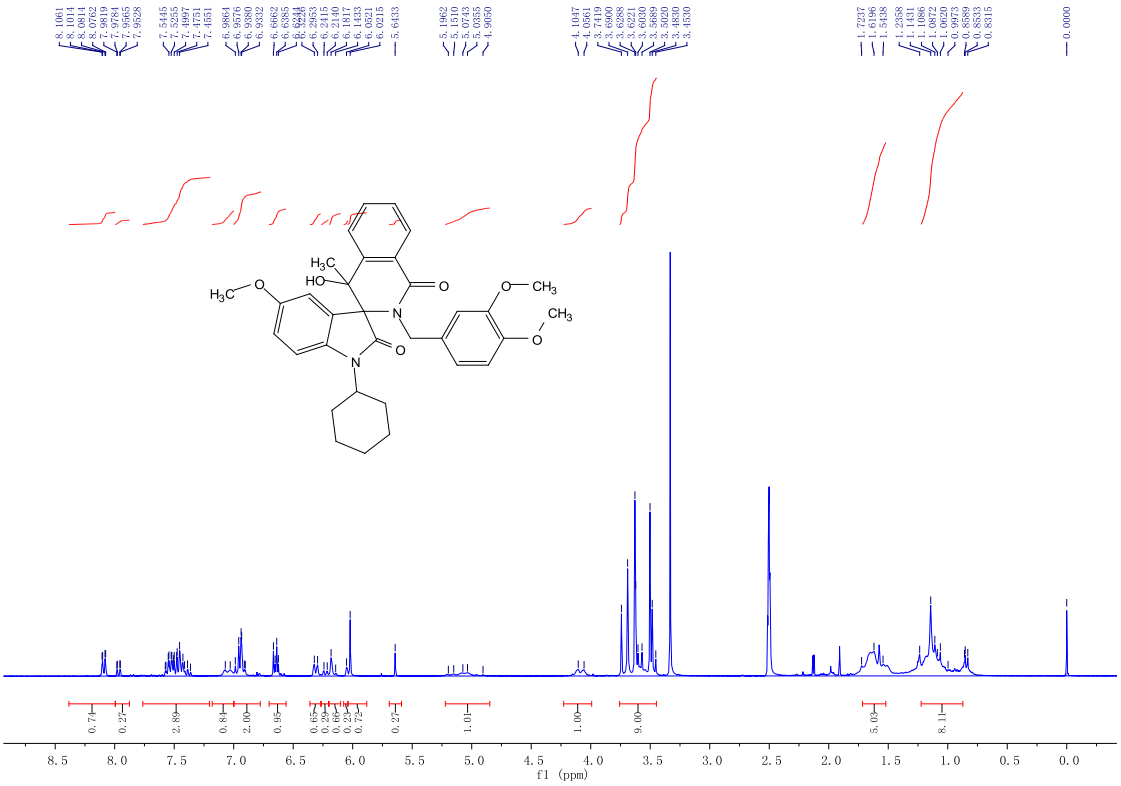


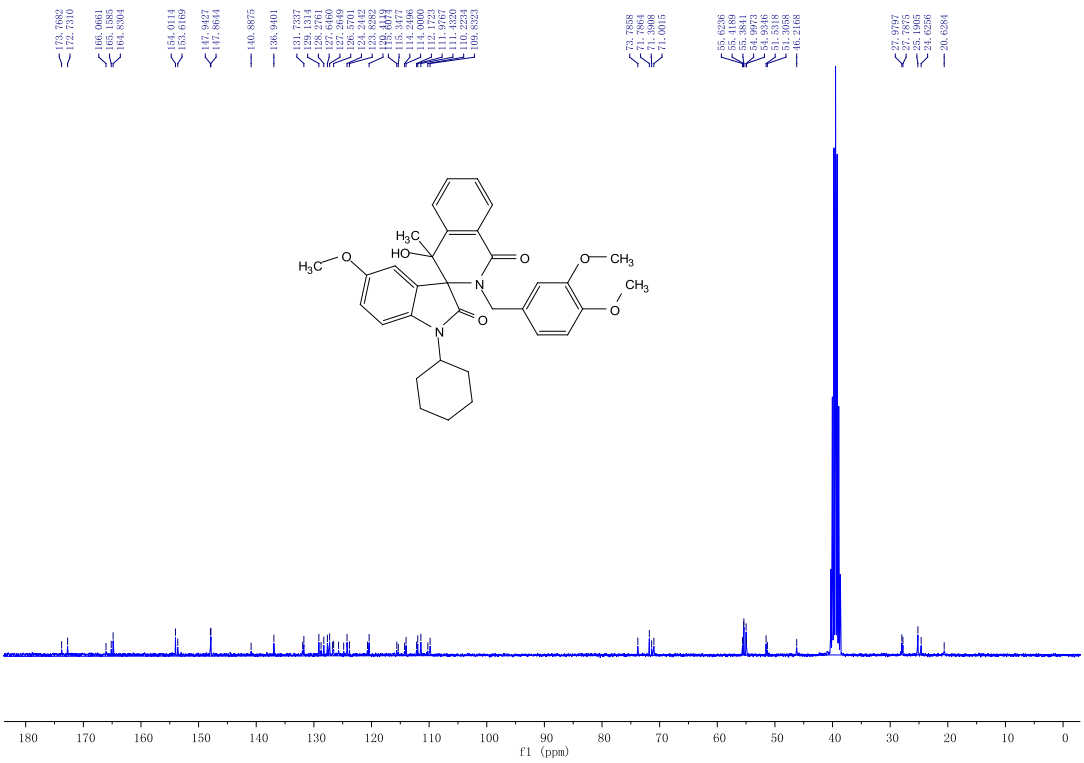
^{1}H and ^{13}C NMR spectra of compound **3h** (300 MHz, DMSO-d_6)



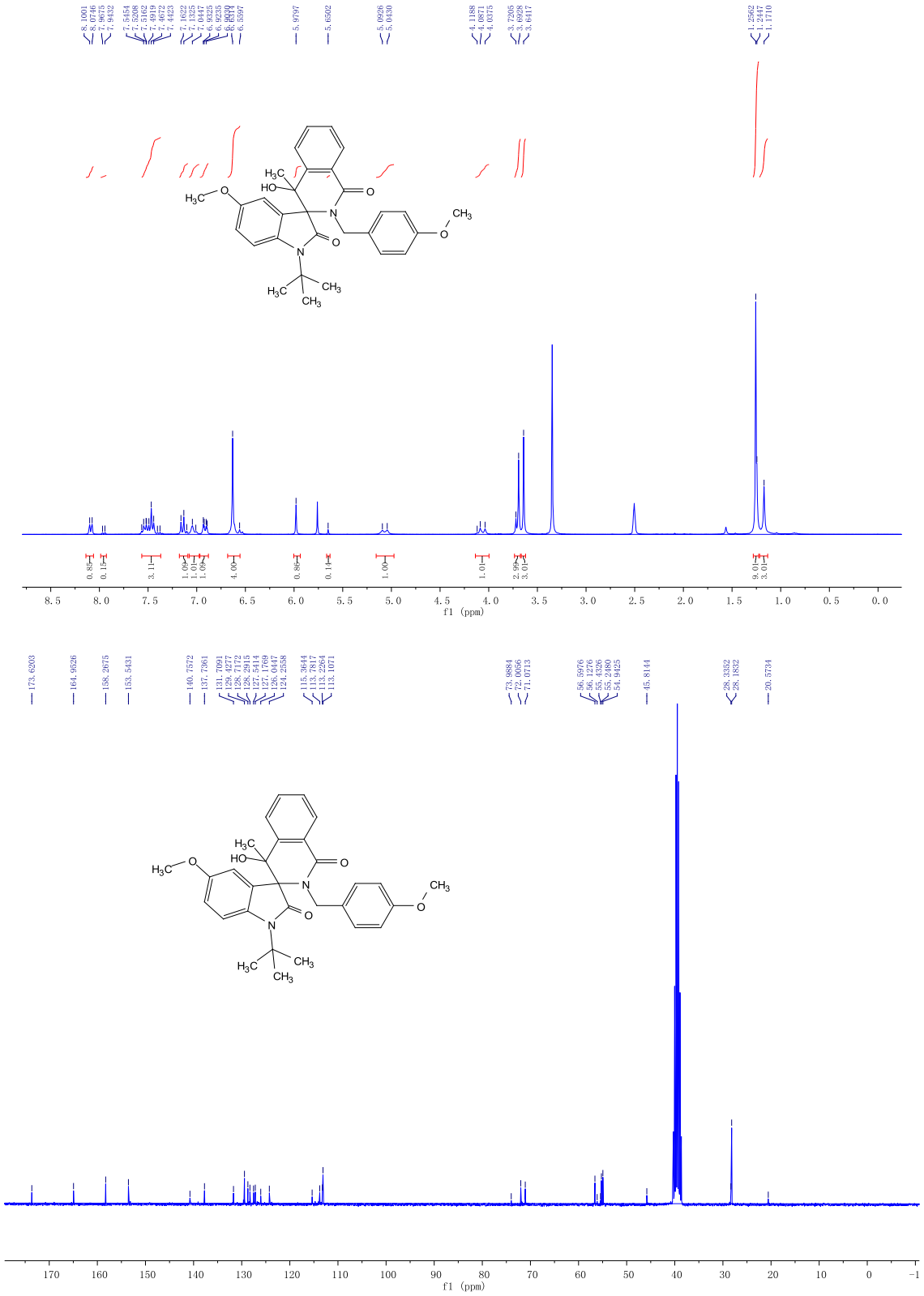


^{1}H and ^{13}C NMR spectra of compound **2i** (300 MHz, DMSO-d_6)

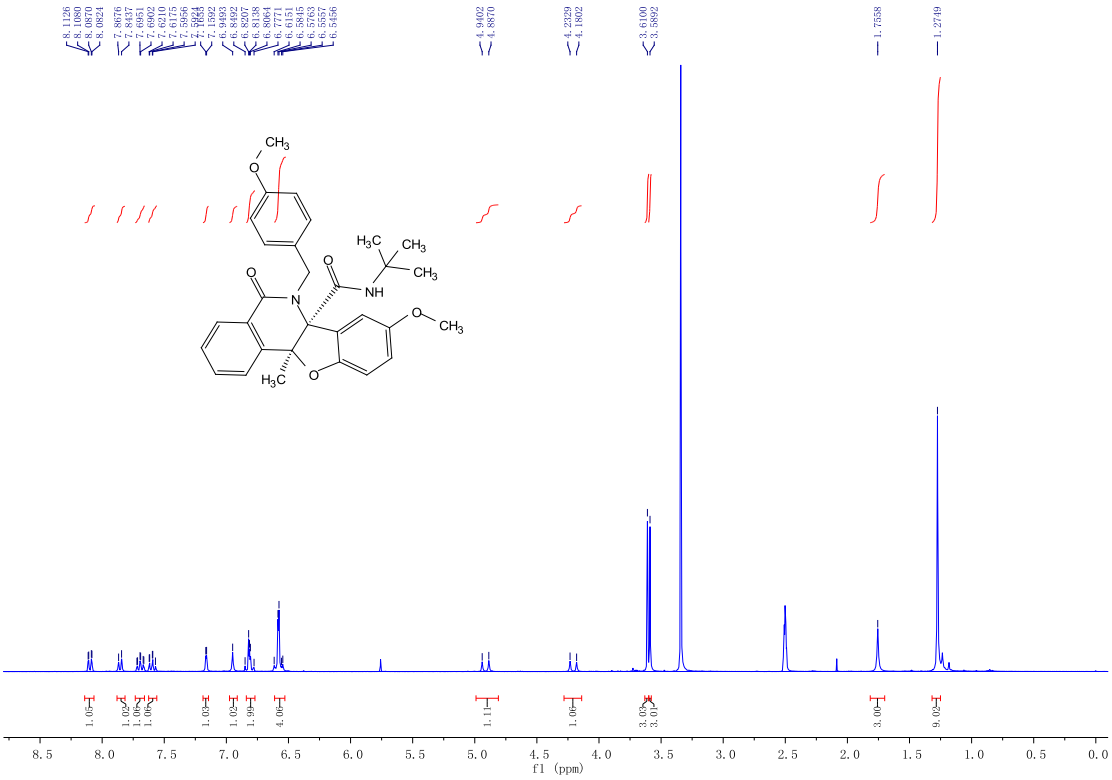


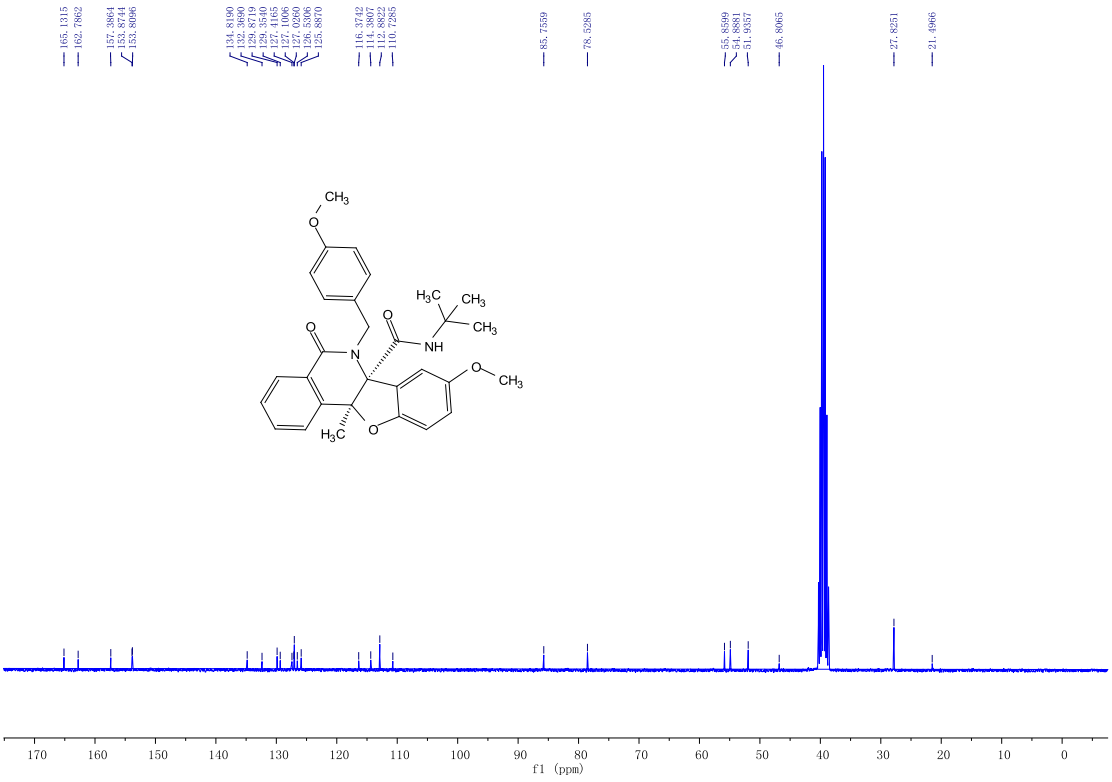


^{1}H and ^{13}C NMR spectra of compound **2j** (300 MHz, DMSO-d_6)

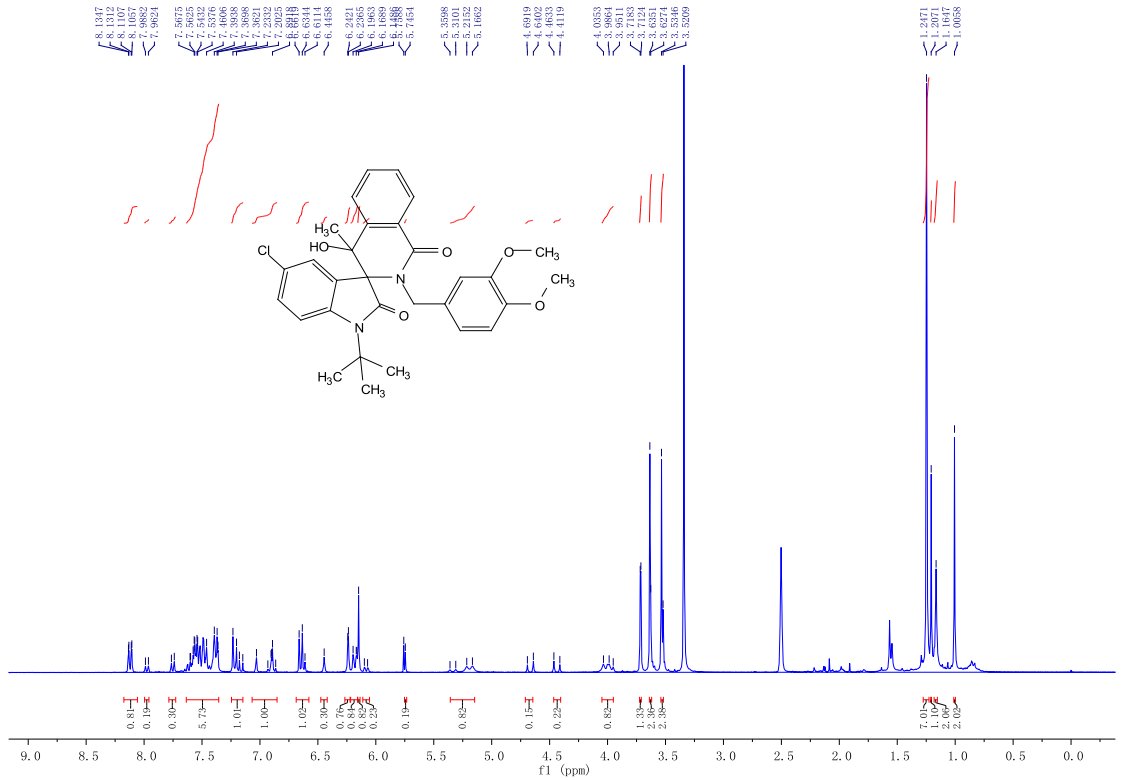


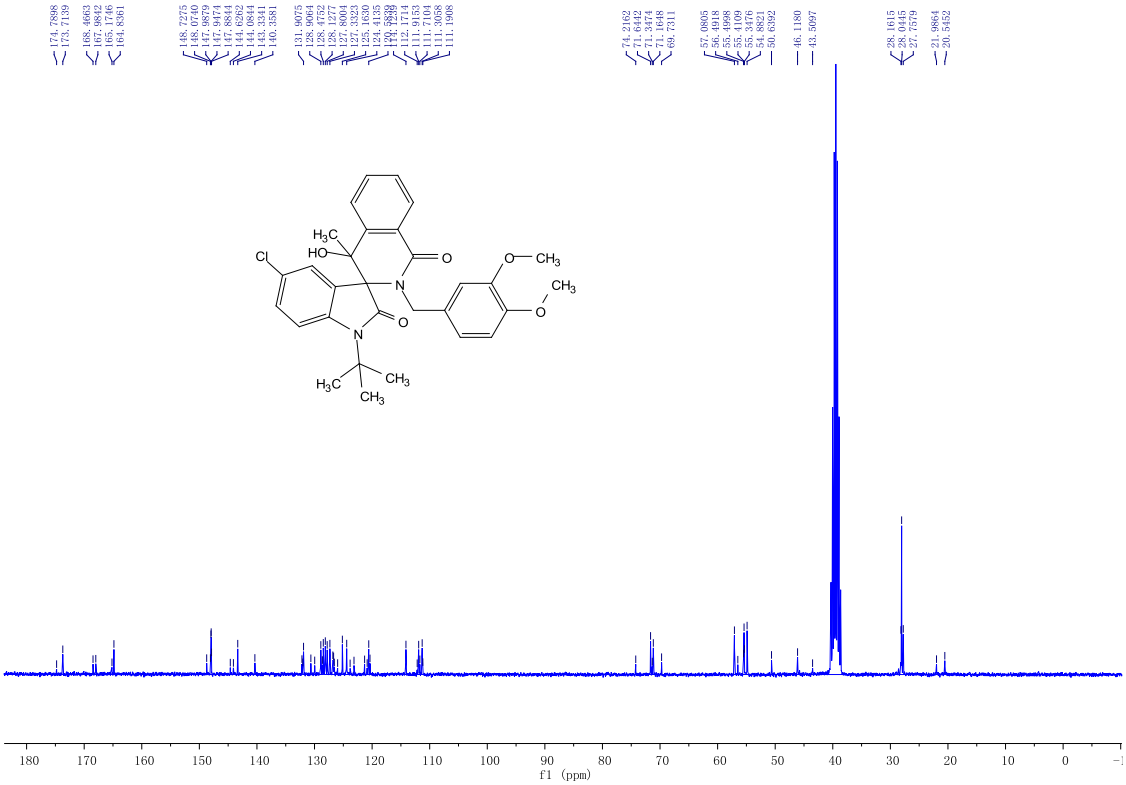
^{1}H and ^{13}C NMR spectra of compound **3j** (300 MHz, DMSO-d_6)



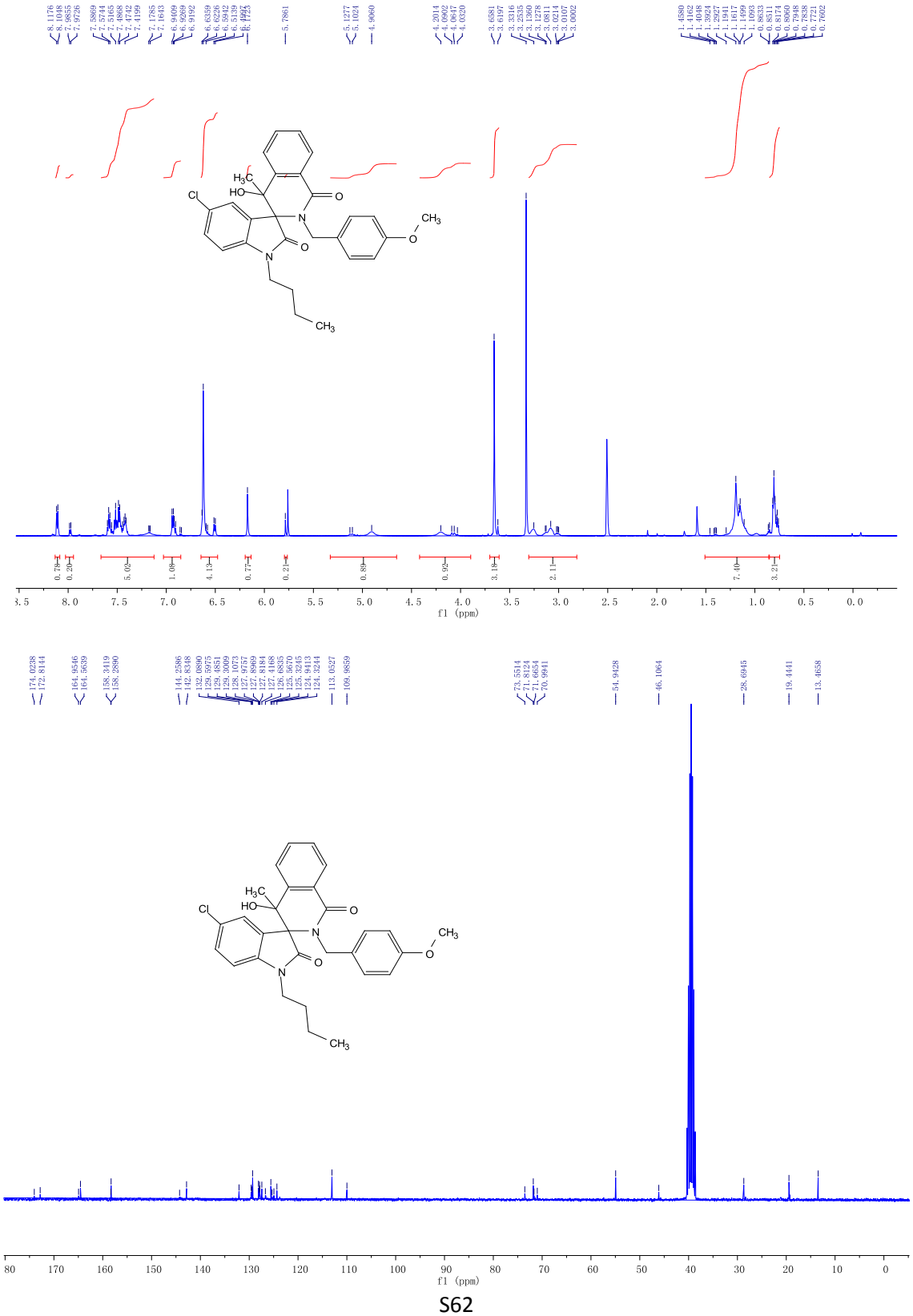


^{1}H and ^{13}C NMR spectra of compound **2k** (300 MHz, DMSO-d_6)

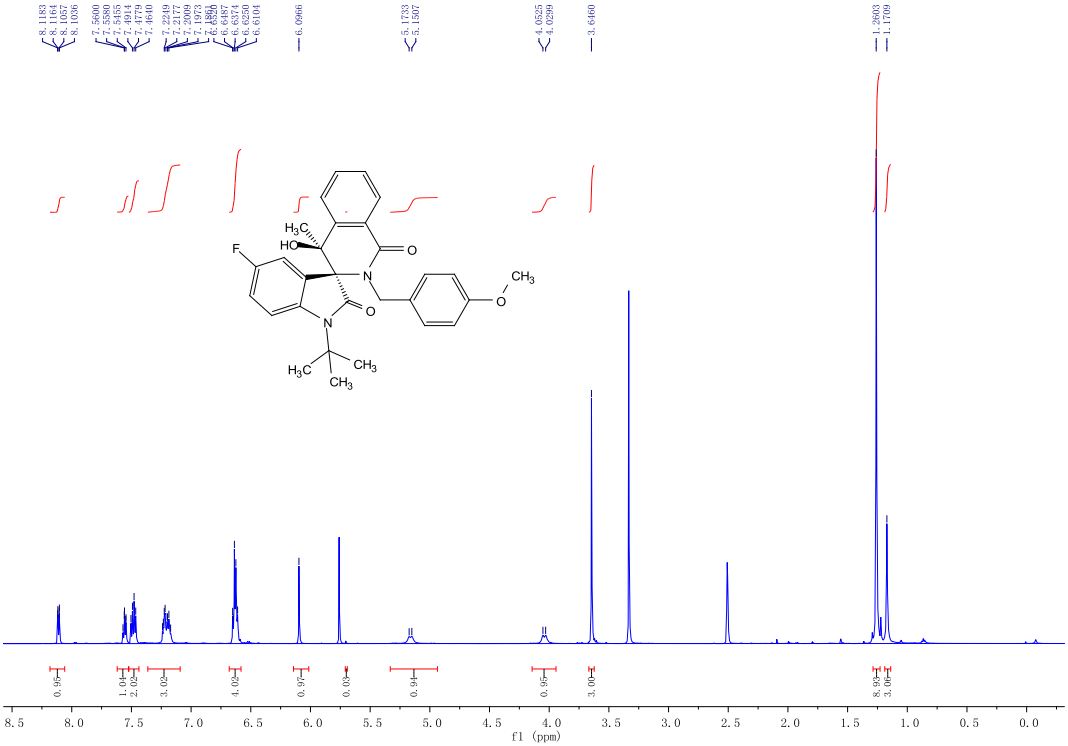


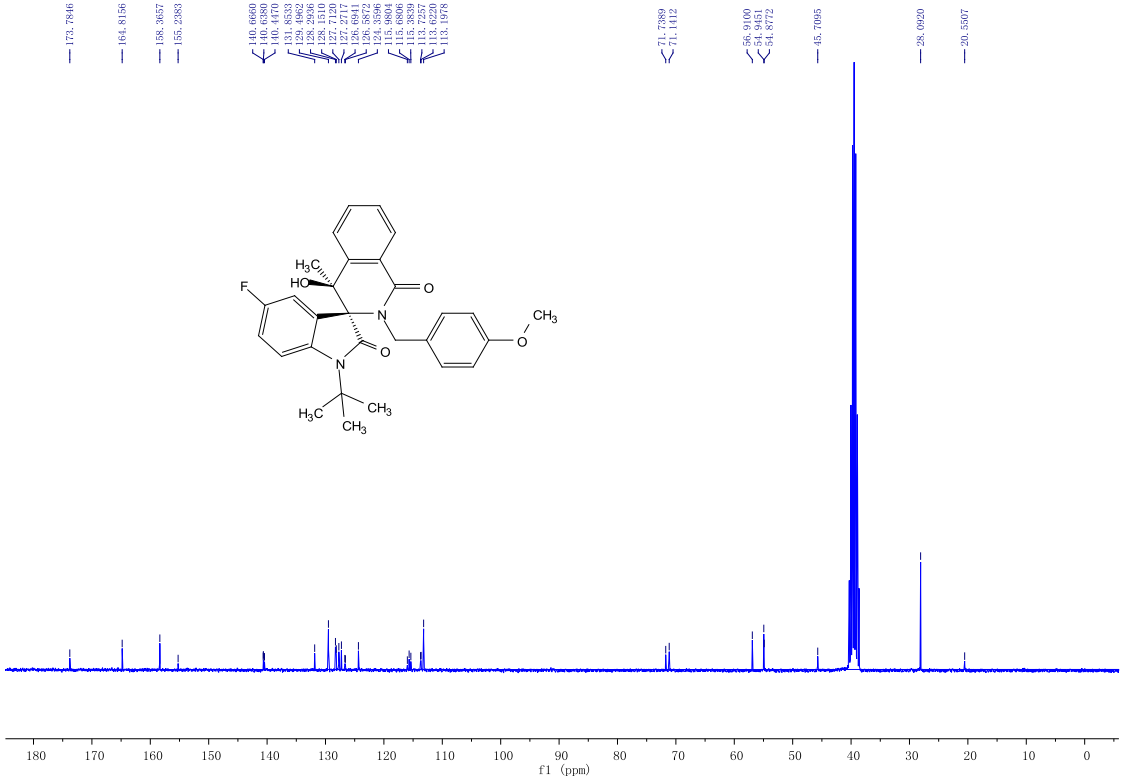


^{1}H and ^{13}C NMR spectra of compound **2l** (600 MHz, DMSO-d_6)

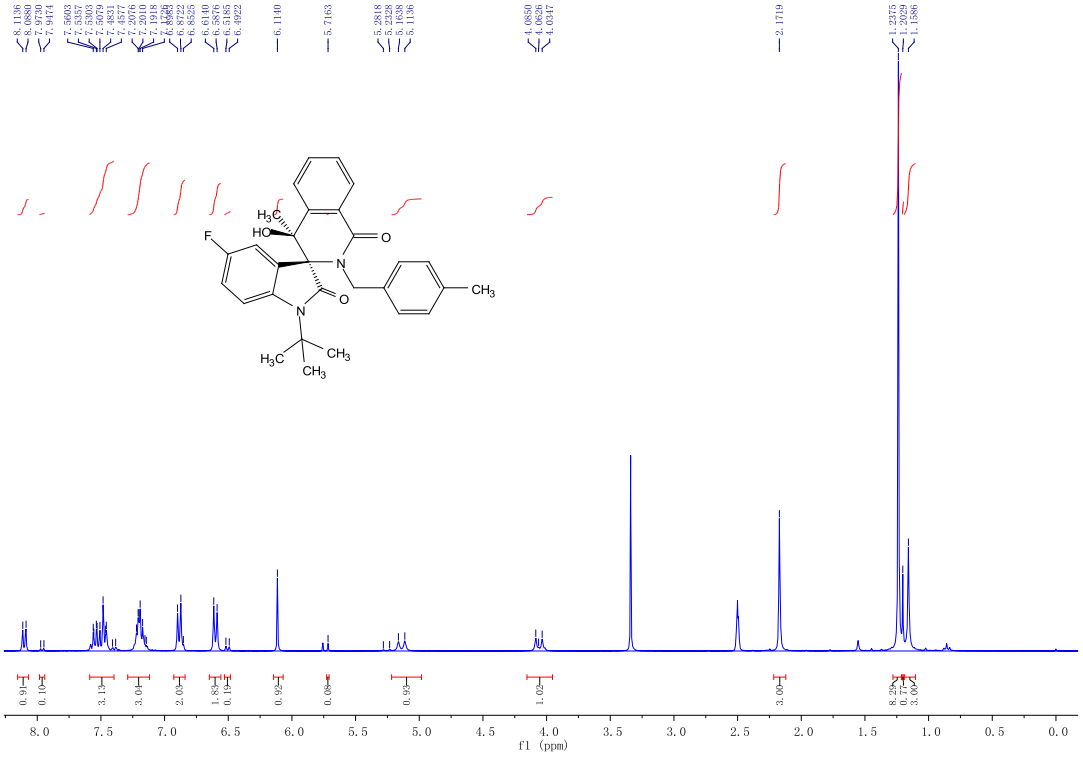


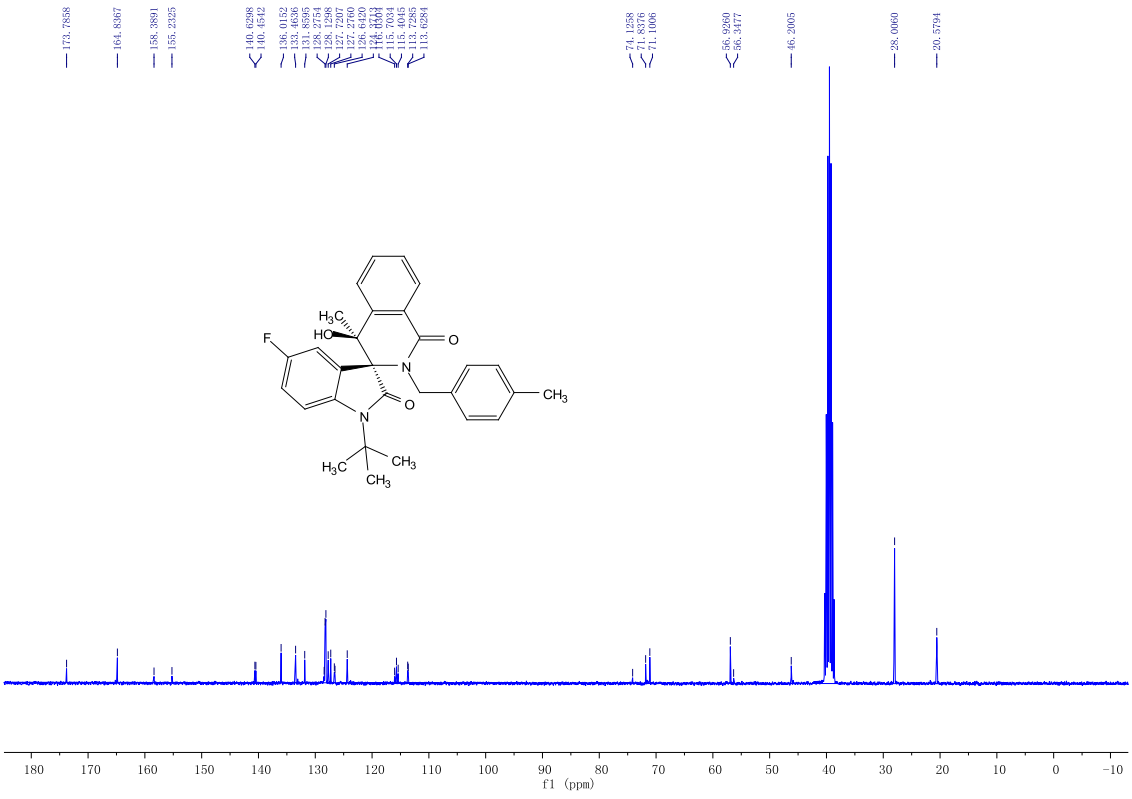
^{1}H and ^{13}C NMR spectra of compound **2m** (600 MHz, DMSO-d_6)



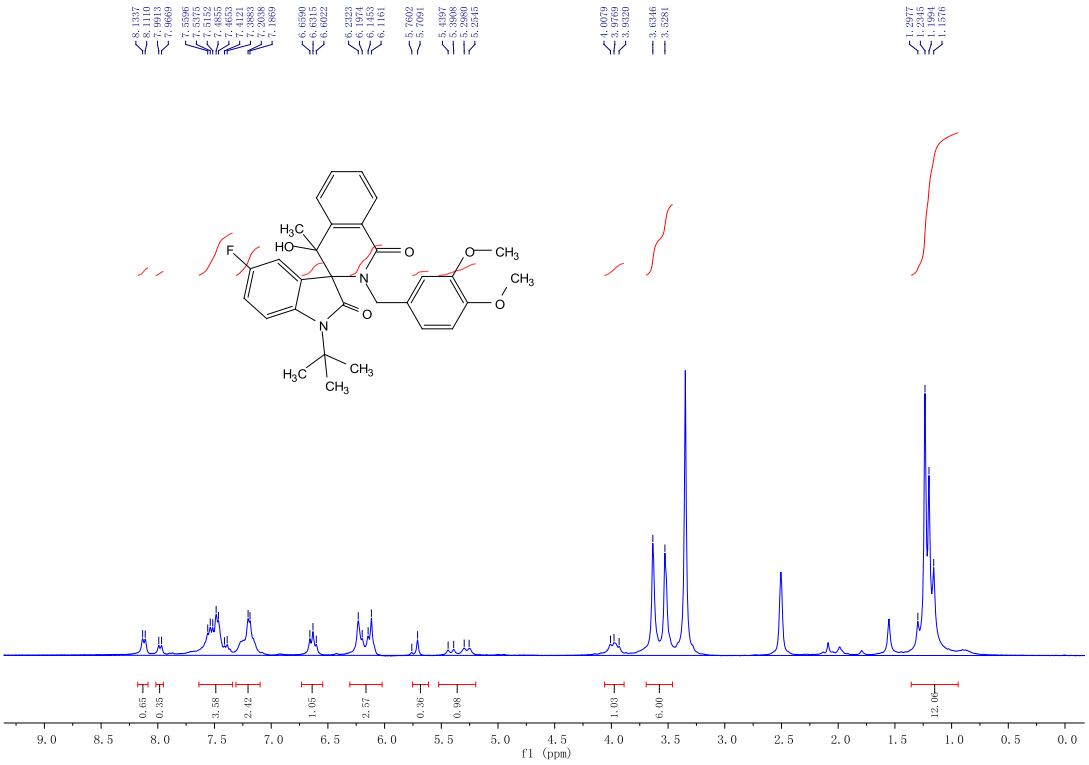


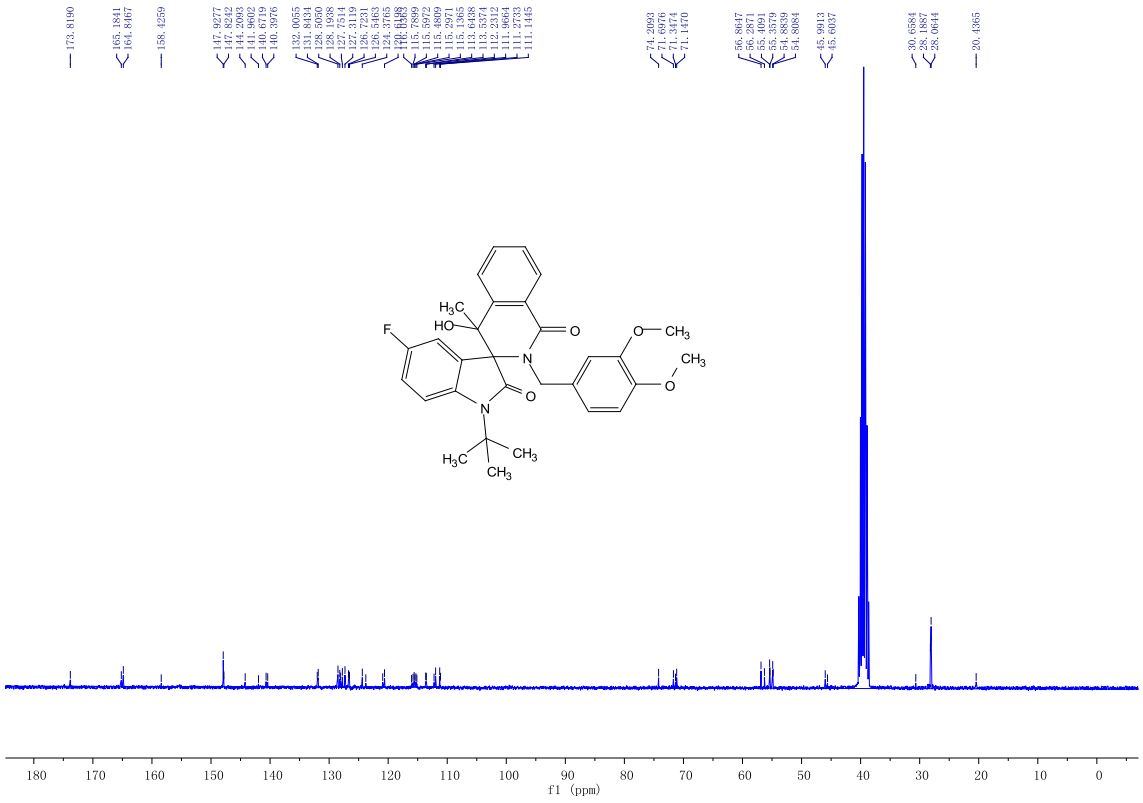
^{1}H and ^{13}C NMR spectra of compound **2n** (300 MHz, DMSO-d_6)



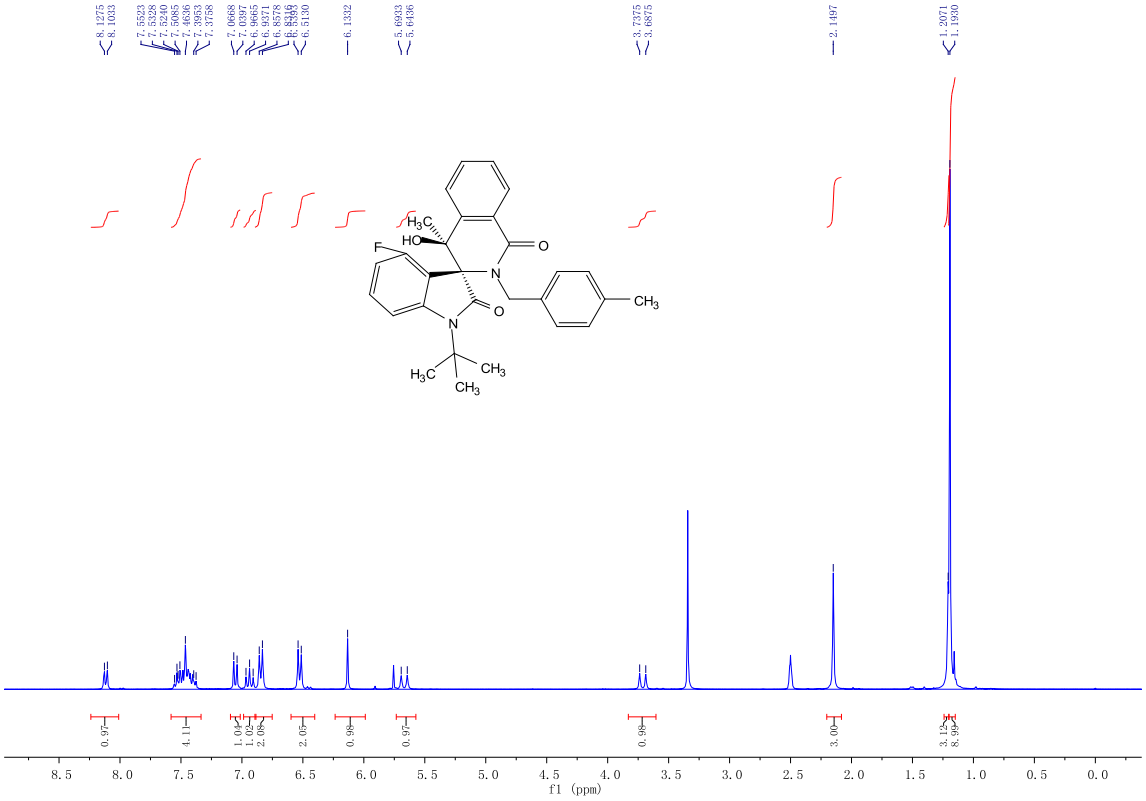


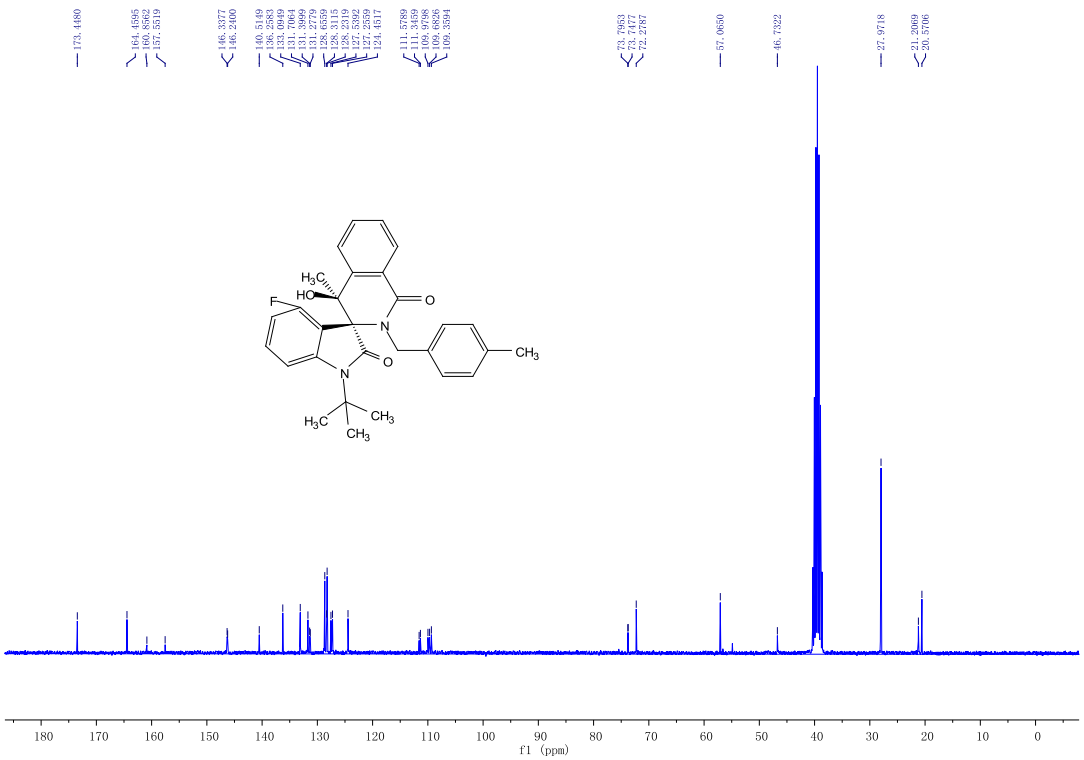
^{1}H and ^{13}C NMR spectra of compound **2o** (300 MHz, DMSO-d_6)



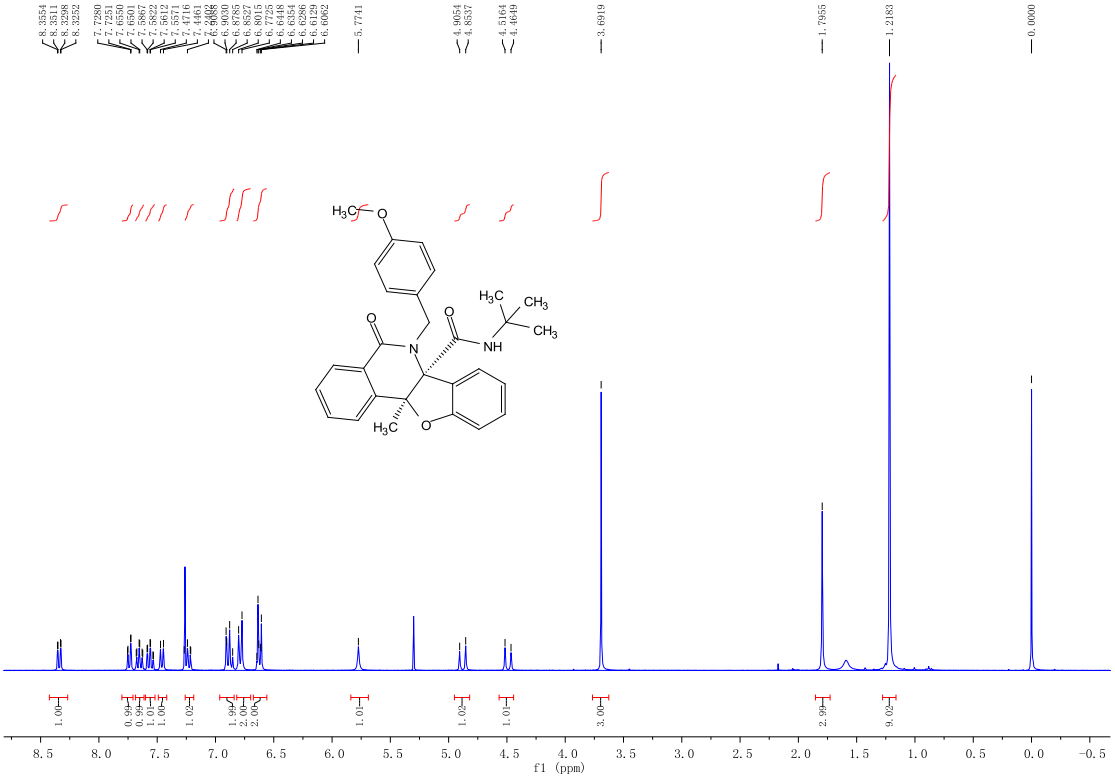


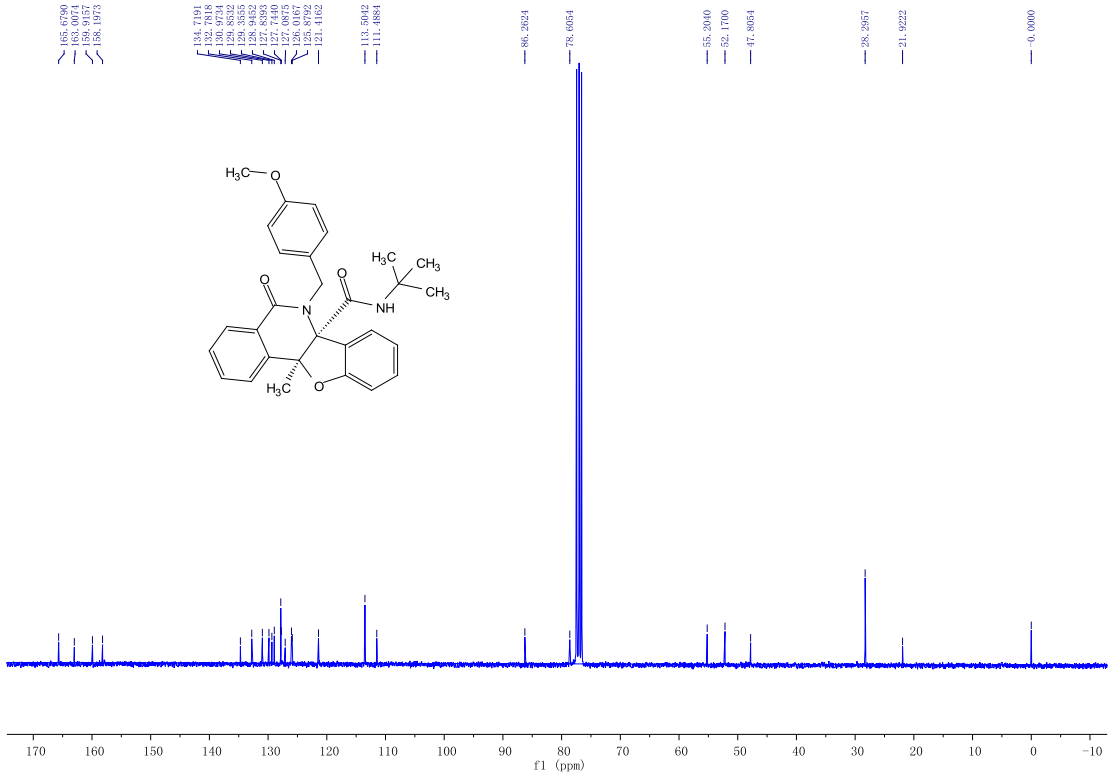
^{1}H and ^{13}C NMR spectra of compound **2p** (300 MHz, DMSO-d_6)



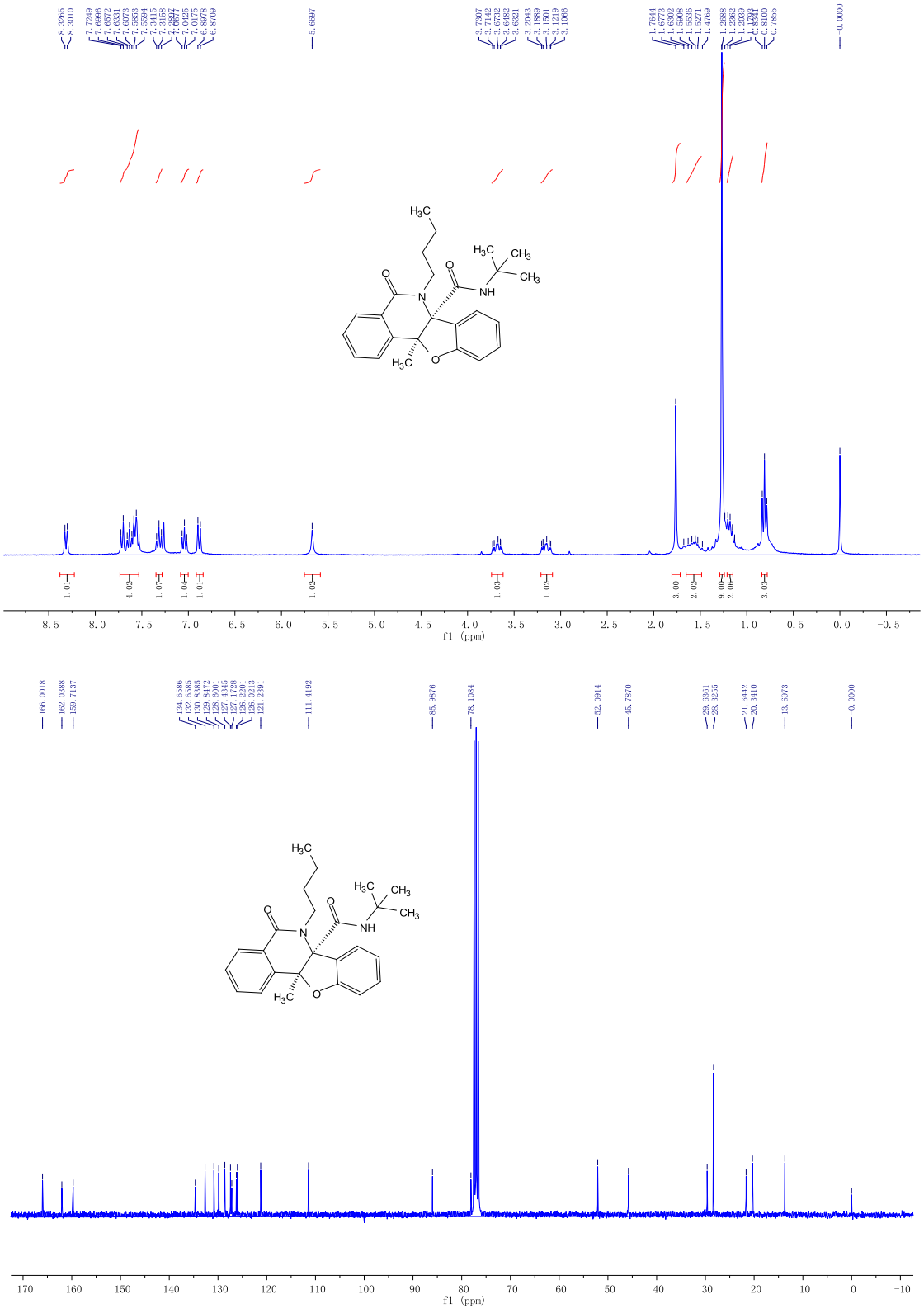


^{1}H and ^{13}C NMR spectra of compound **3a** (300 MHz, $CDCl_3$)

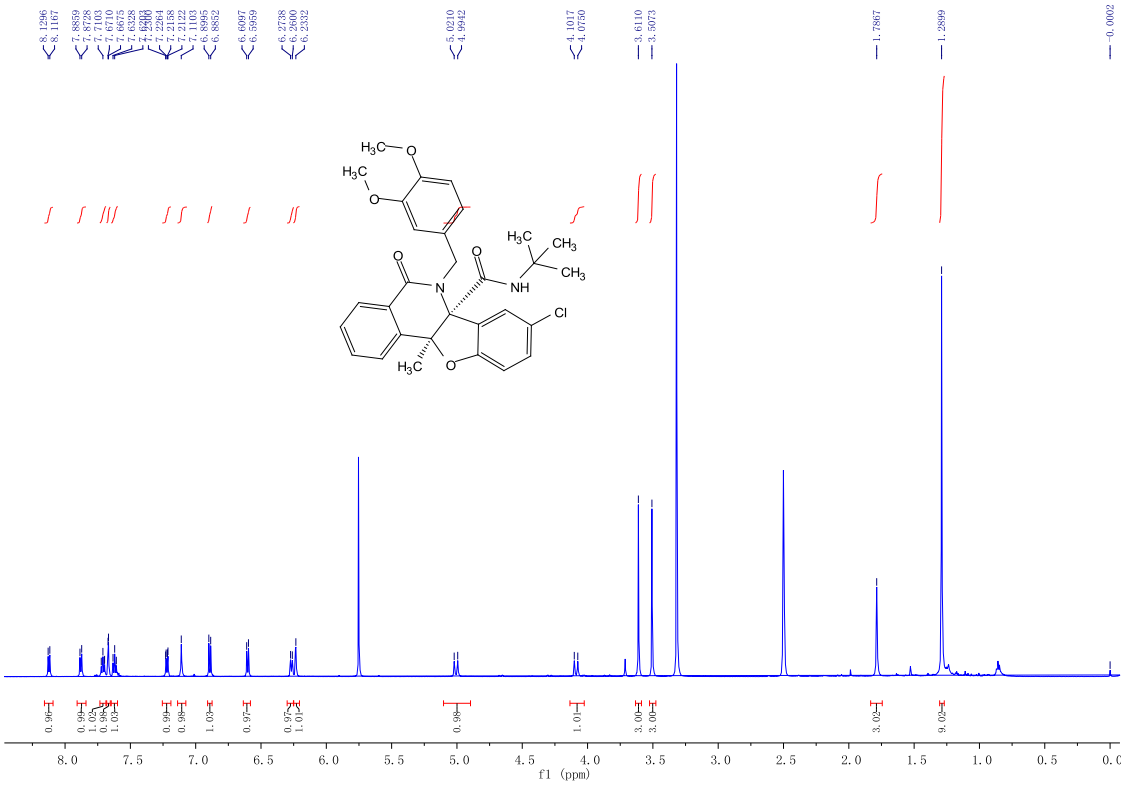


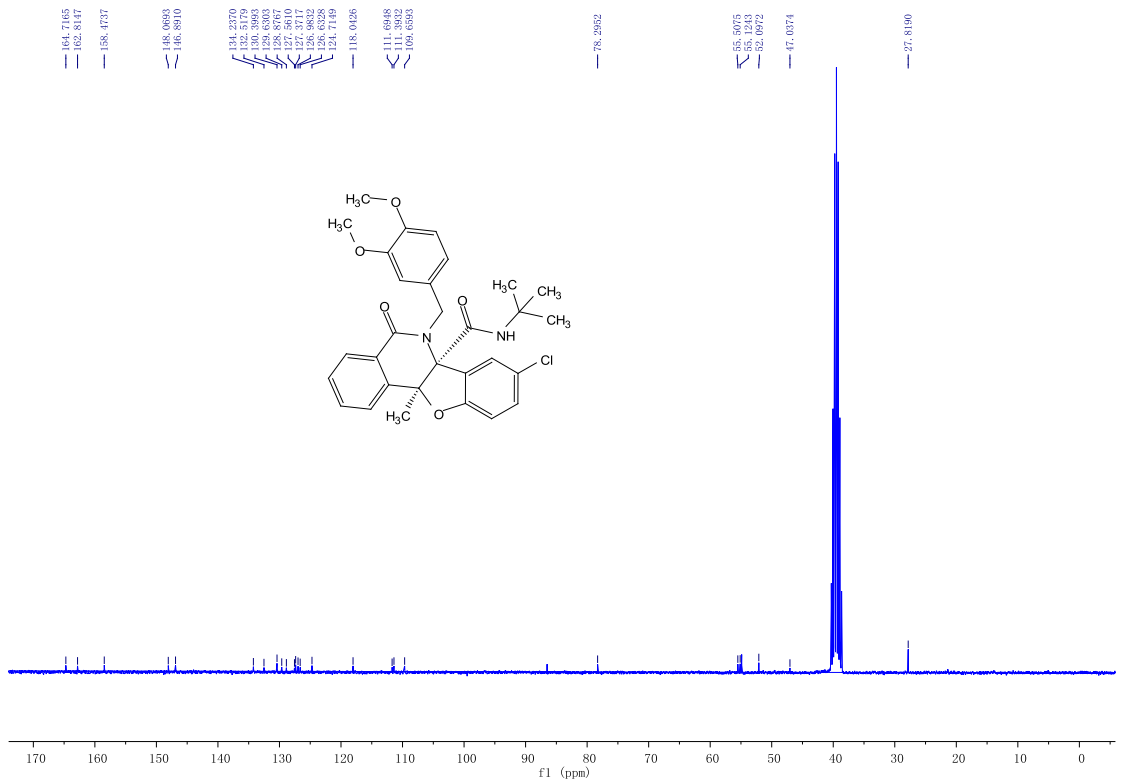


^{1}H and ^{13}C NMR spectra of compound **3c** (300 MHz, $CDCl_3$)

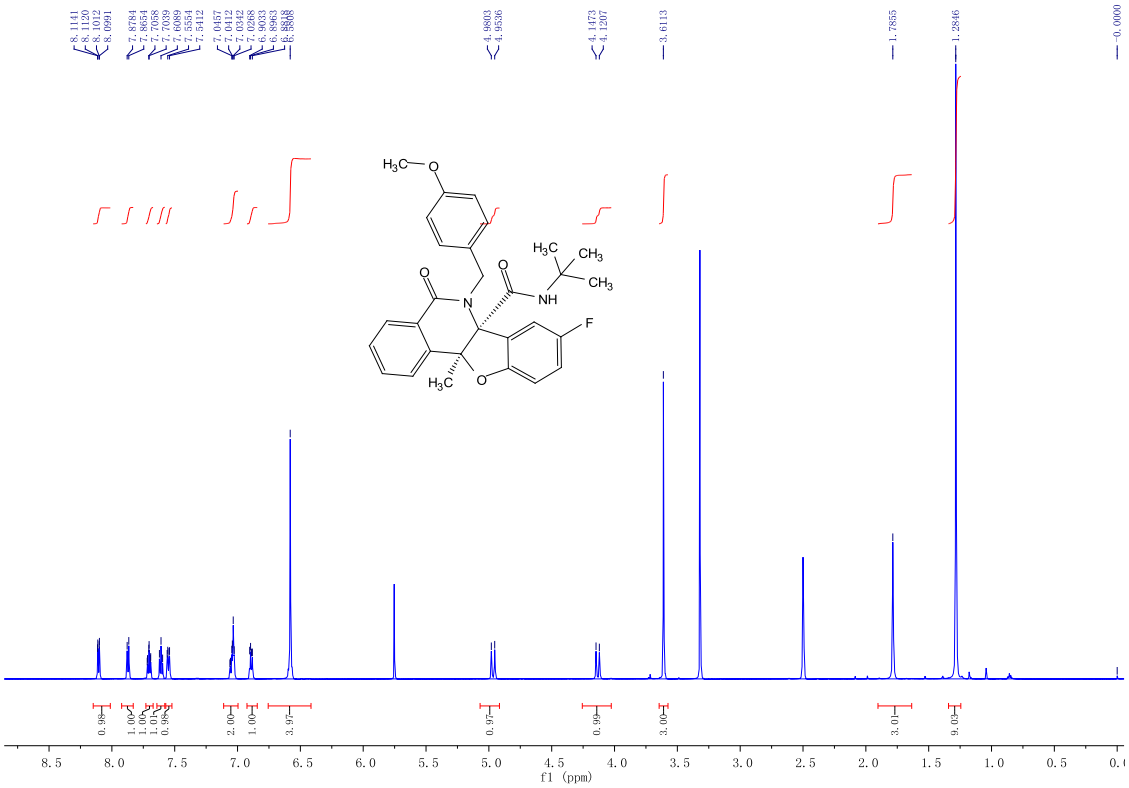


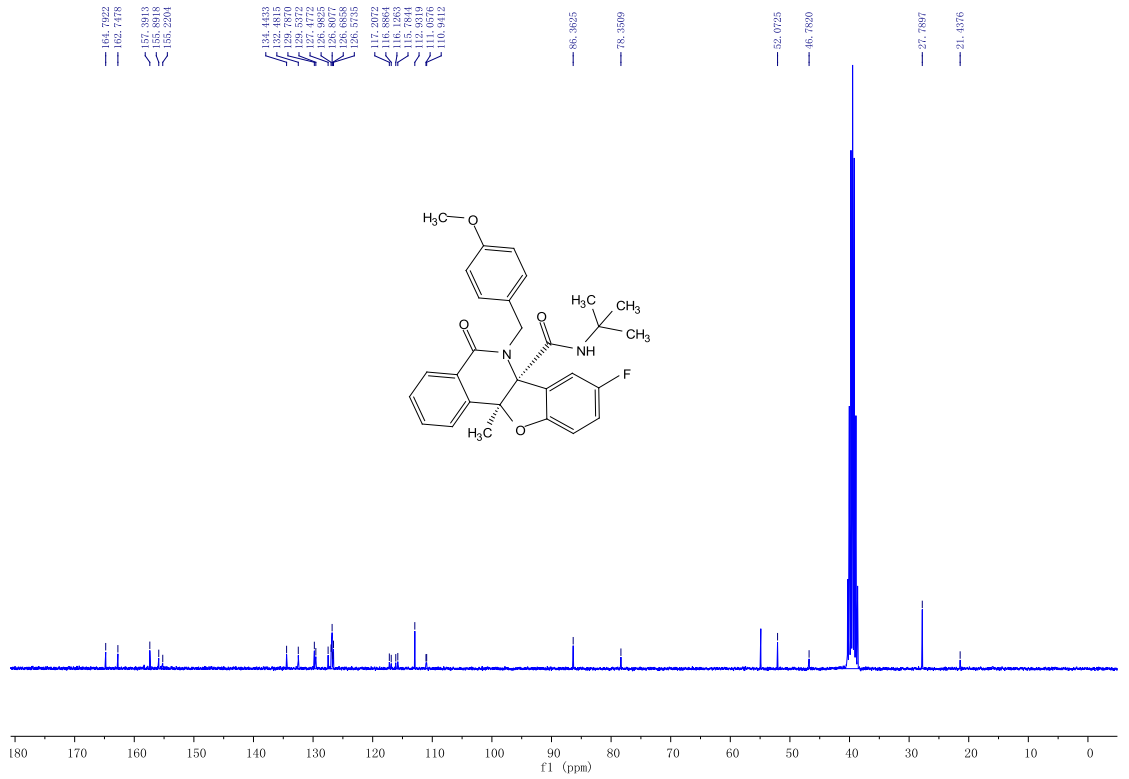
^{1}H and ^{13}C NMR spectra of compound **3k** (600 MHz, DMSO-d_6)



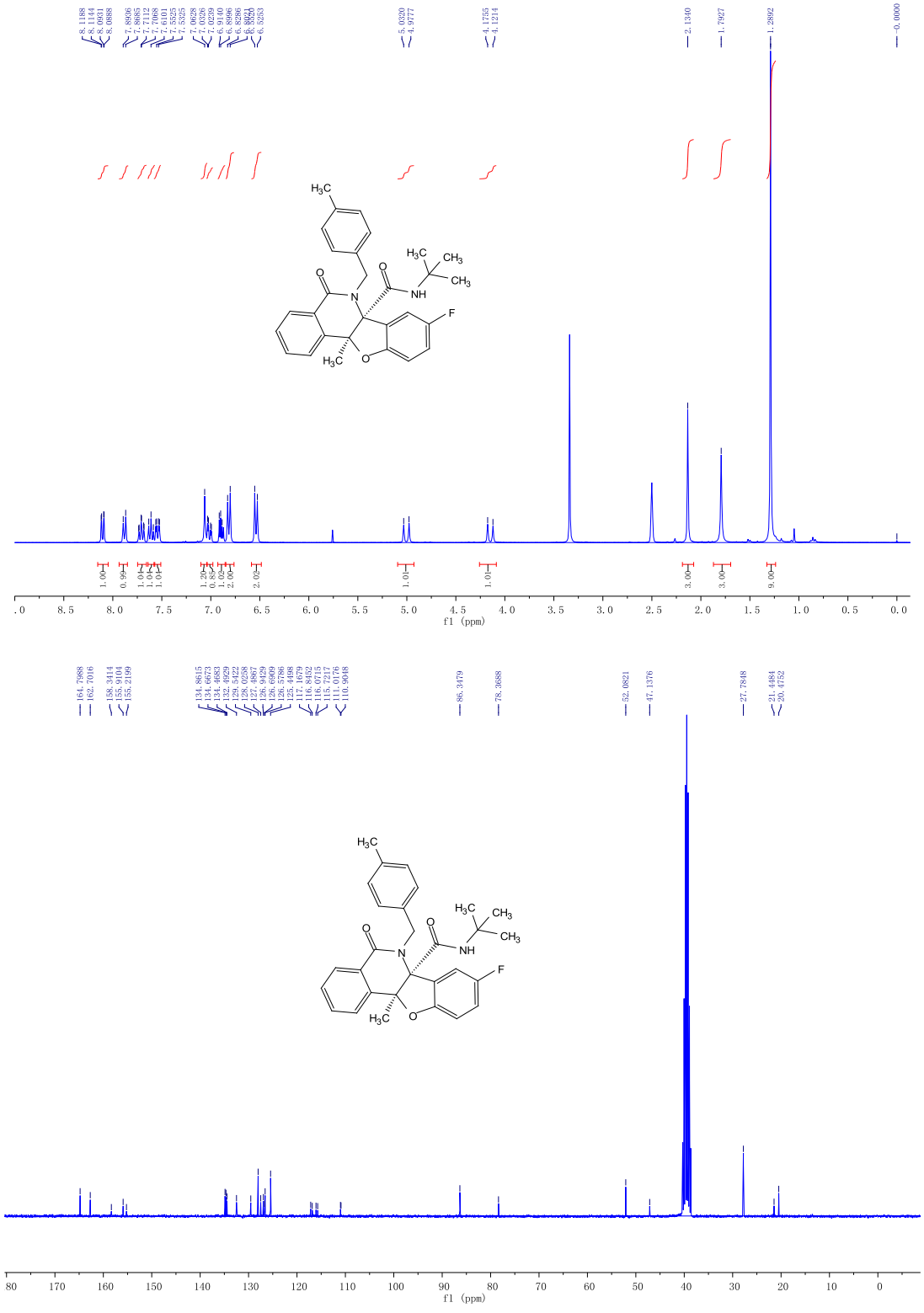


^{1}H and ^{13}C NMR spectra of compound **3m** (600 MHz, DMSO-d_6)

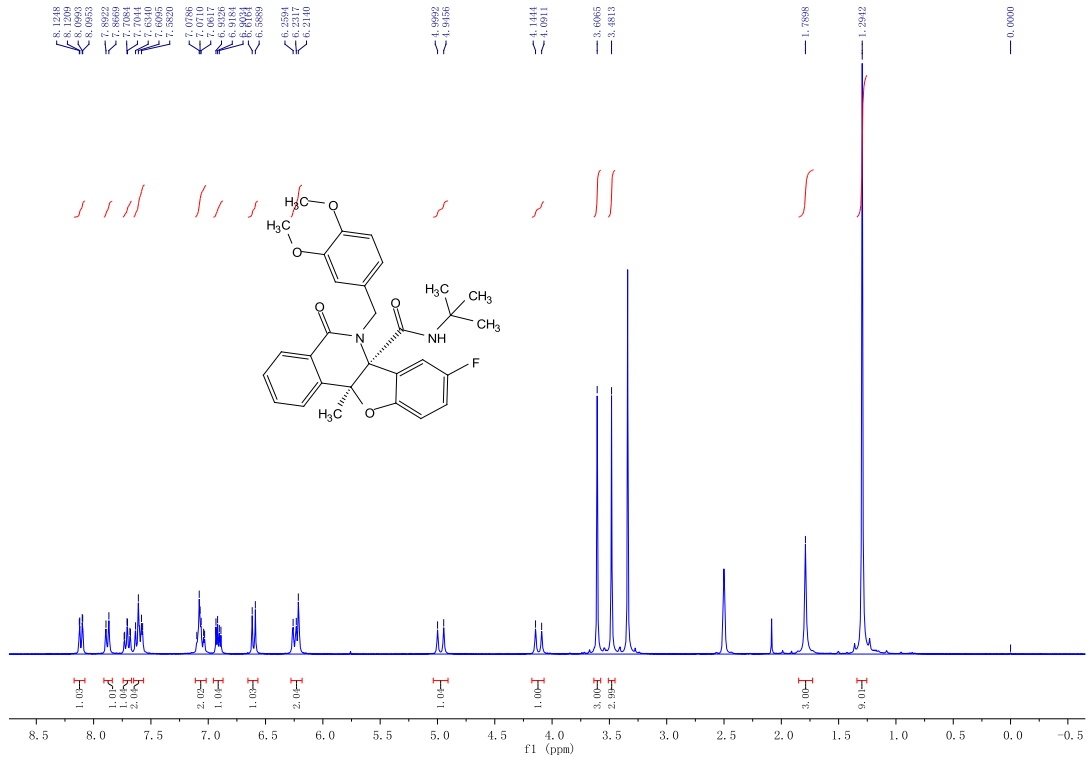


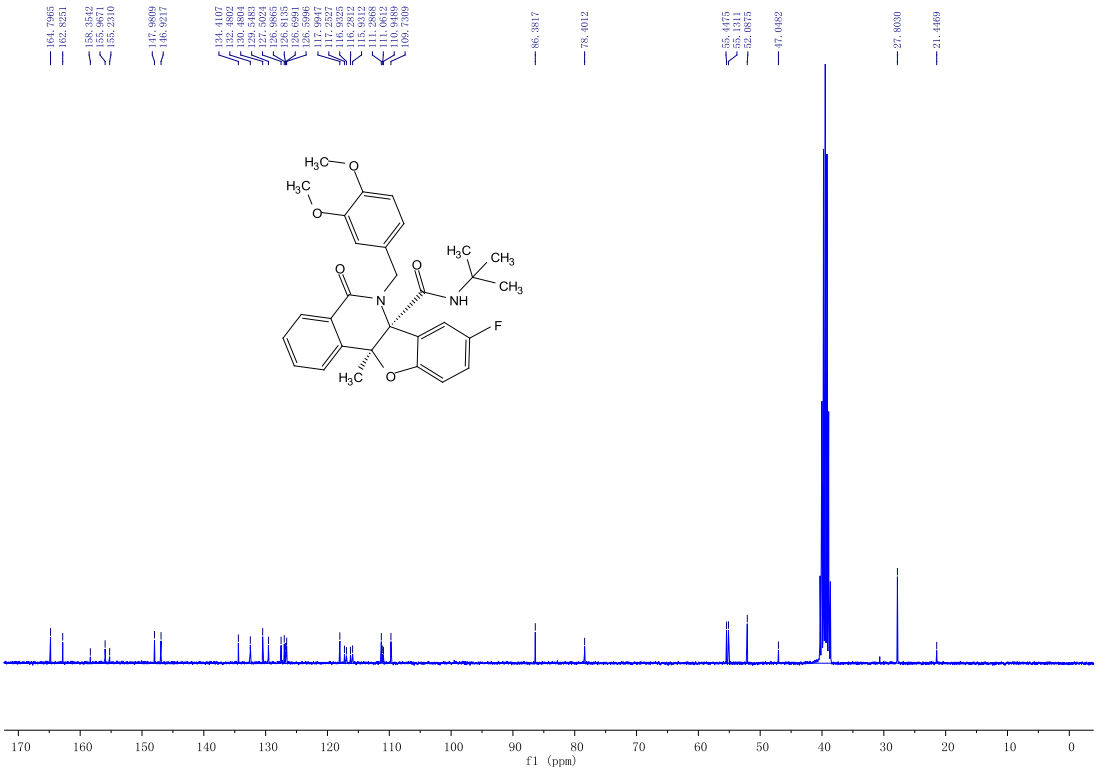


^{1}H and ^{13}C NMR spectra of compound **3n** (300 MHz, DMSO-d_6)

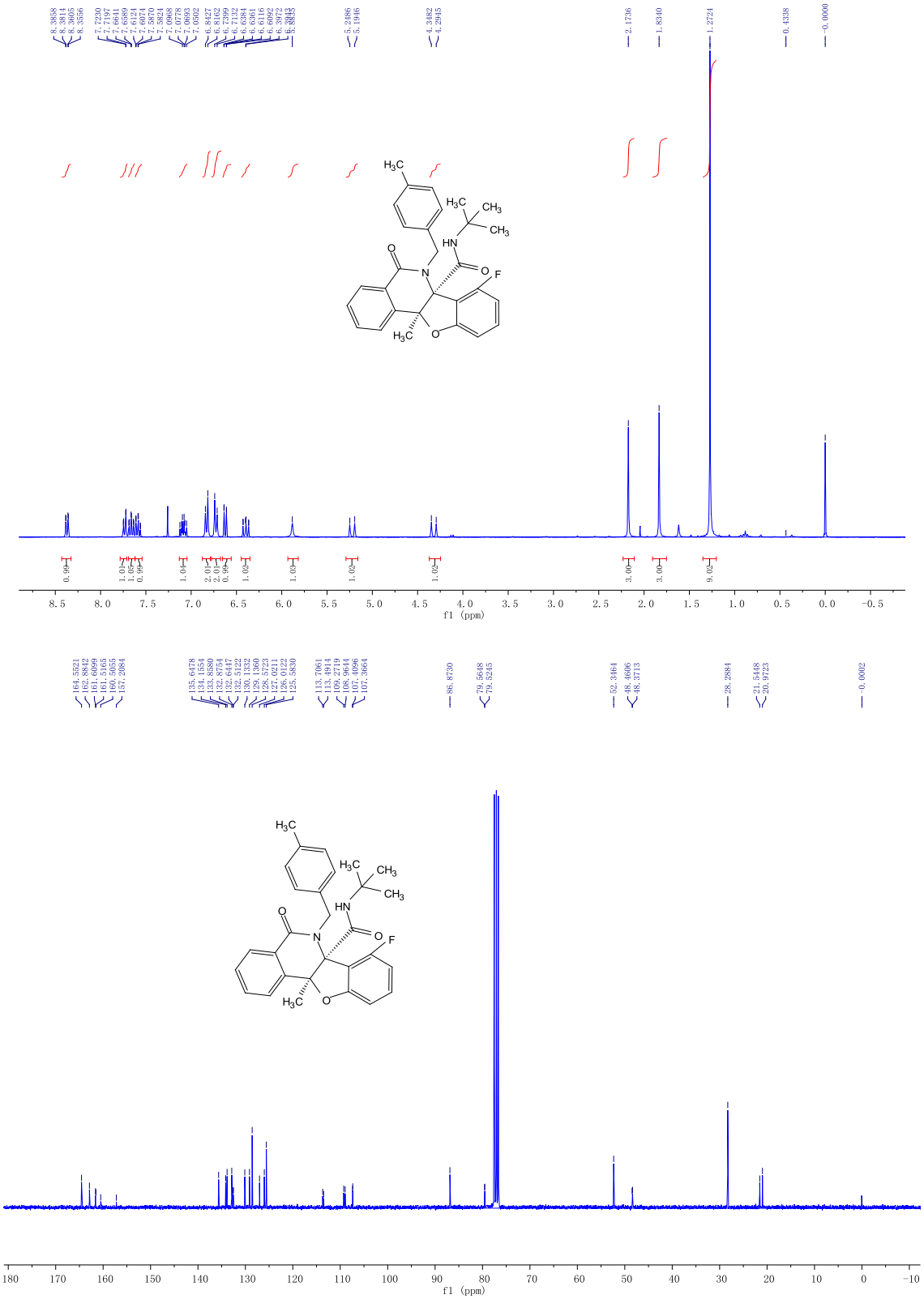


^{1}H and ^{13}C NMR spectra of compound **3o** (300 MHz, DMSO-d_6)

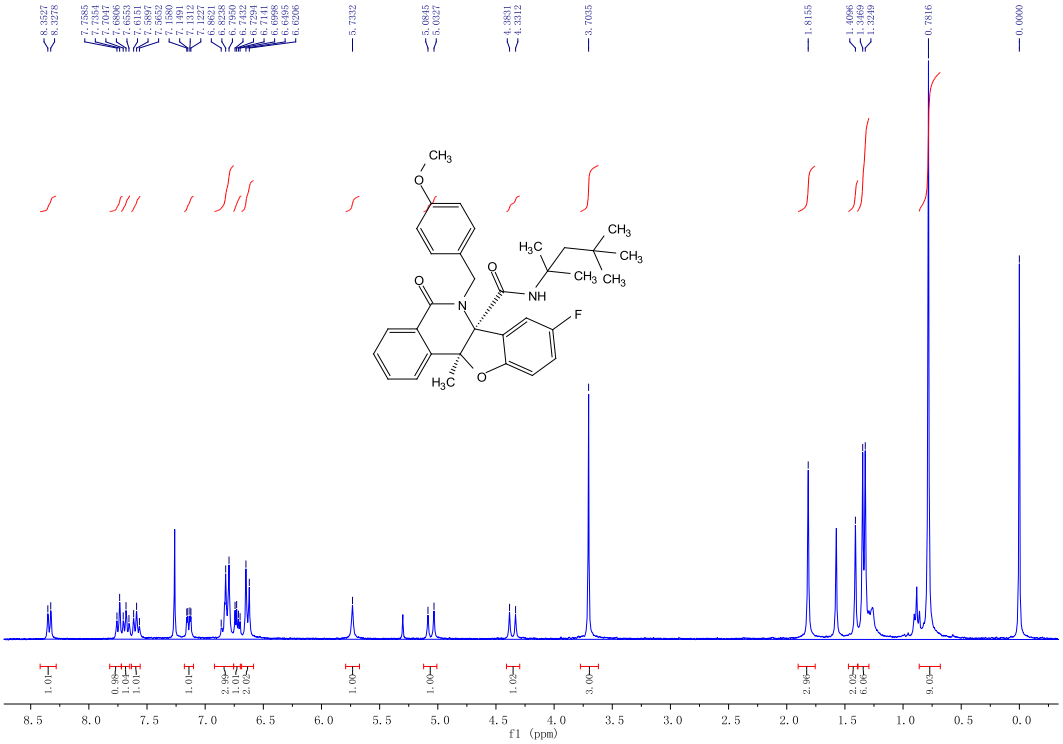


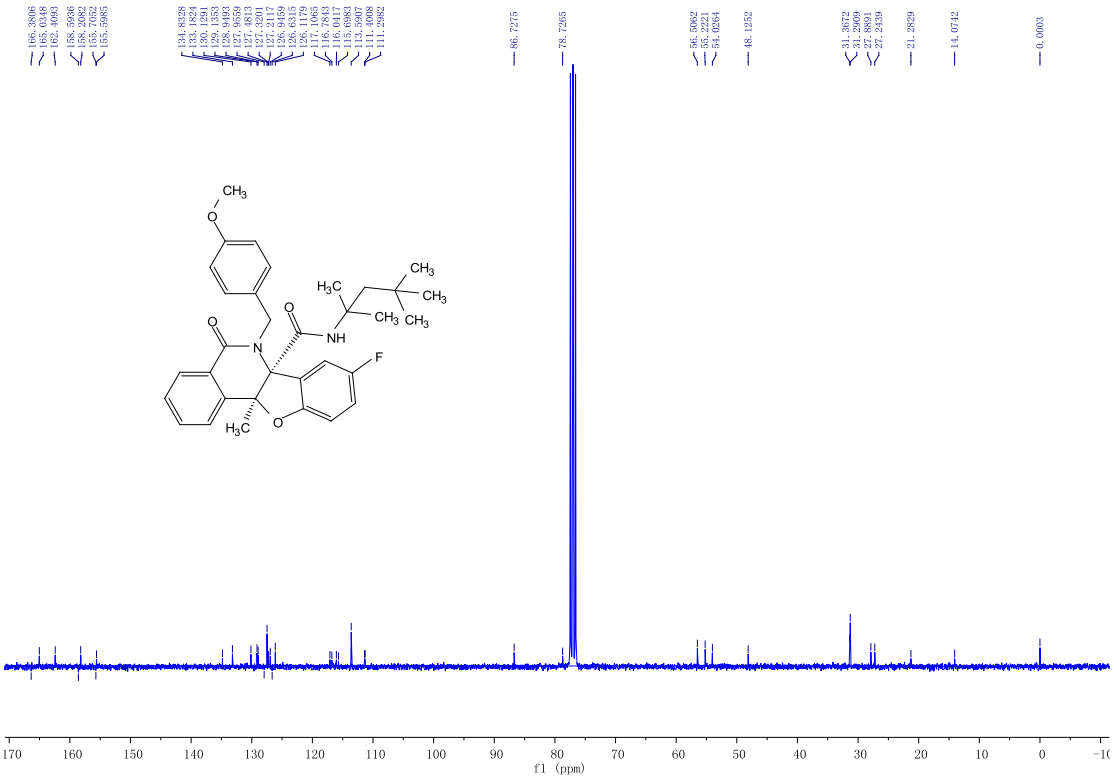


^{1}H and ^{13}C NMR spectra of compound **3p** (300 MHz, $CDCl_3$)

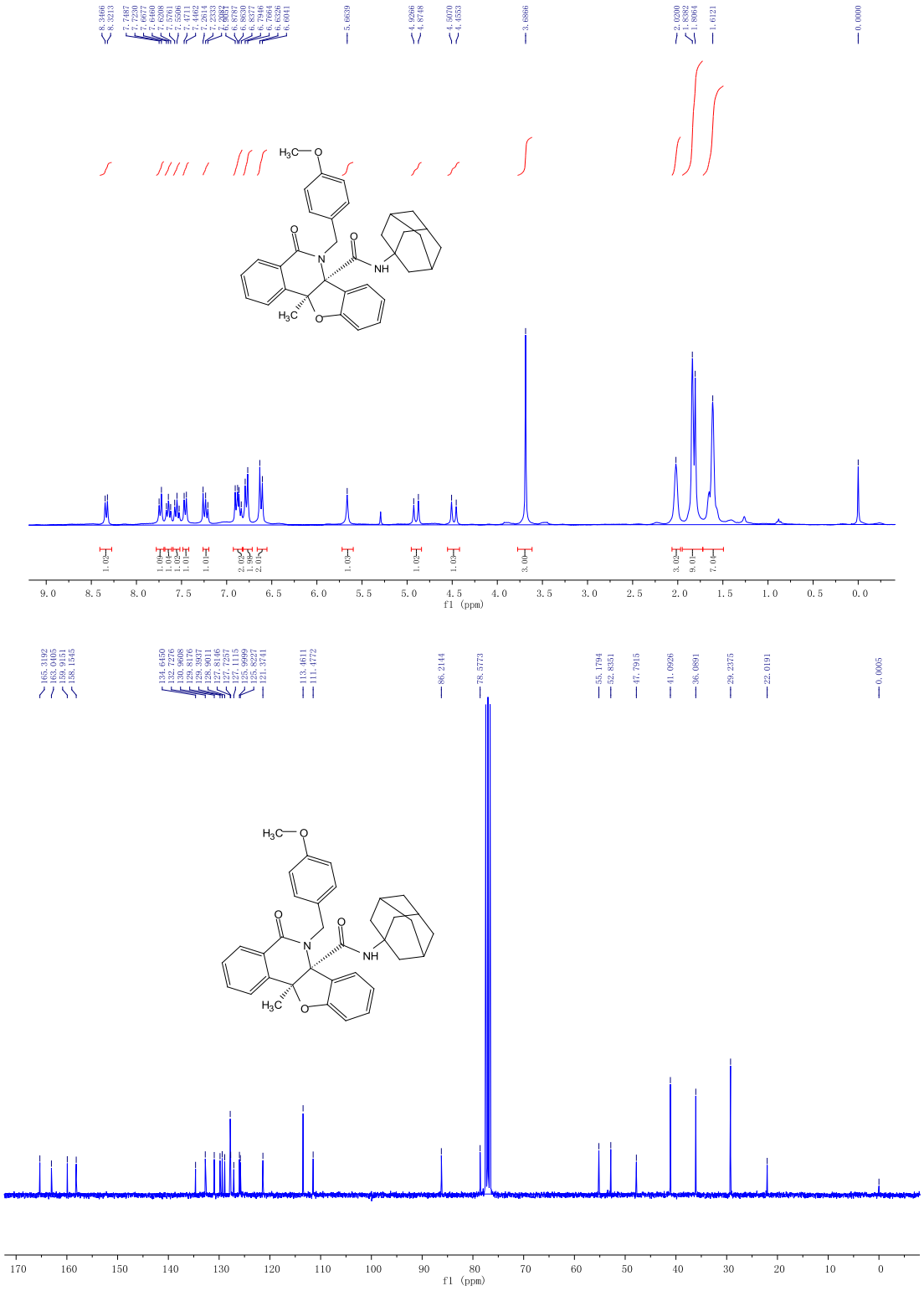


^{1}H and ^{13}C NMR spectra of compound **3q** (300 MHz, $CDCl_3$)

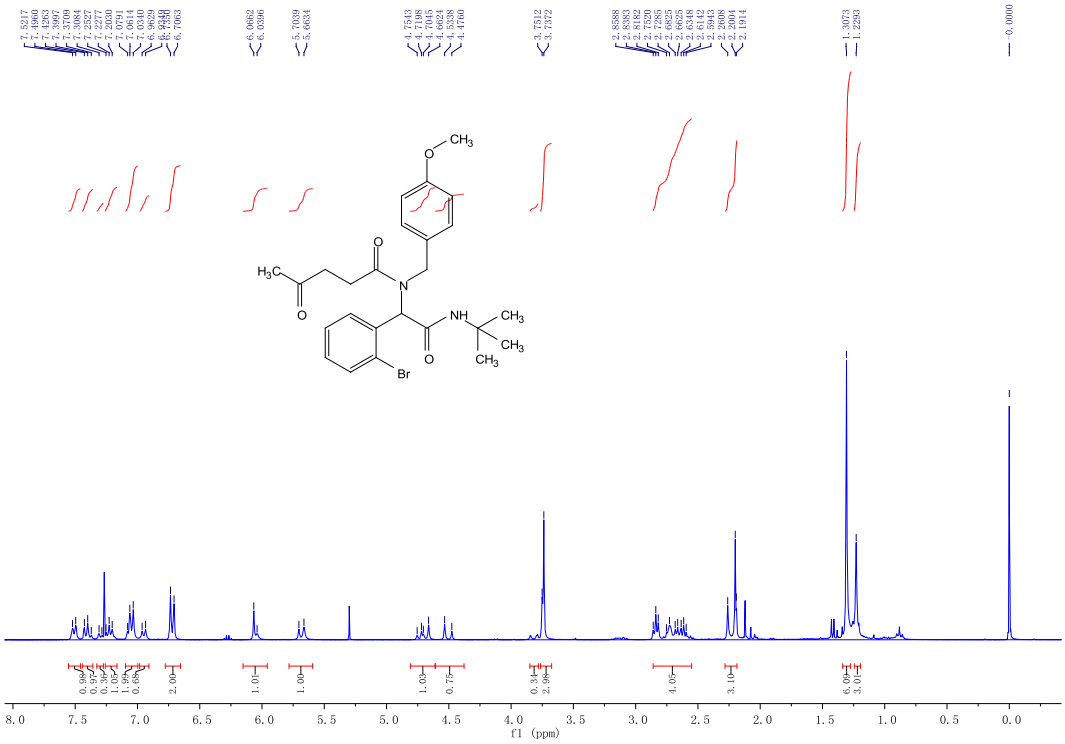


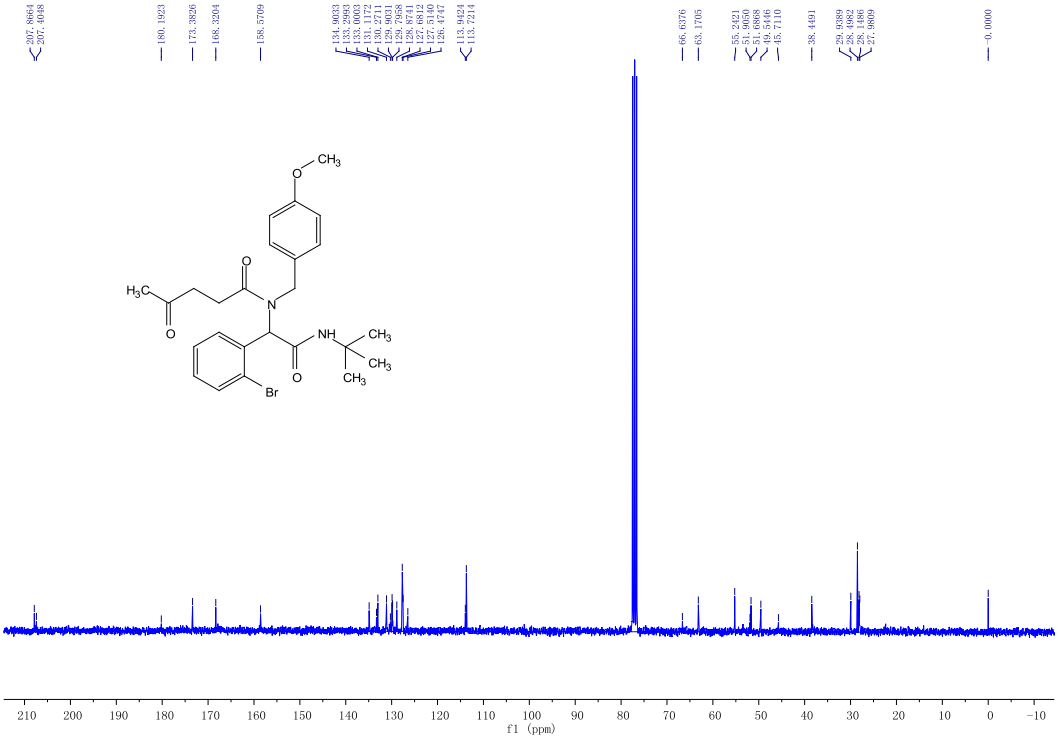


^{1}H and ^{13}C NMR spectra of compound **3r** (300 MHz, $CDCl_3$)

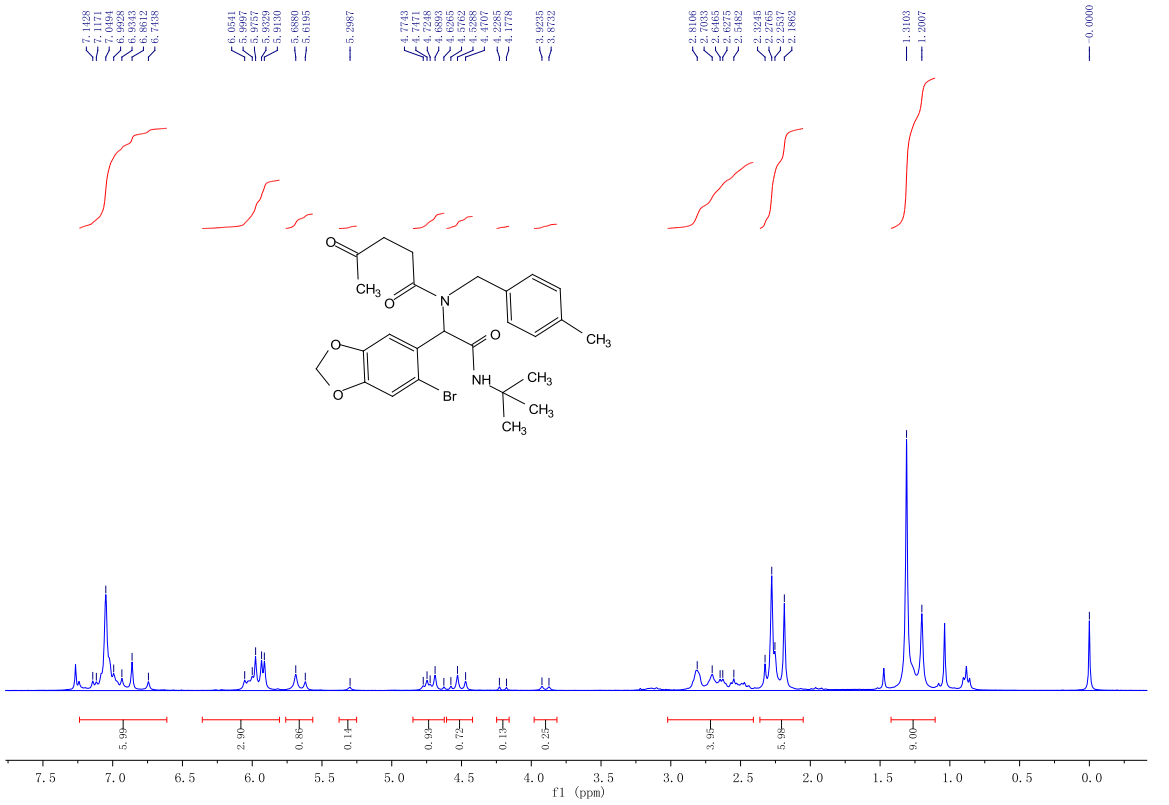


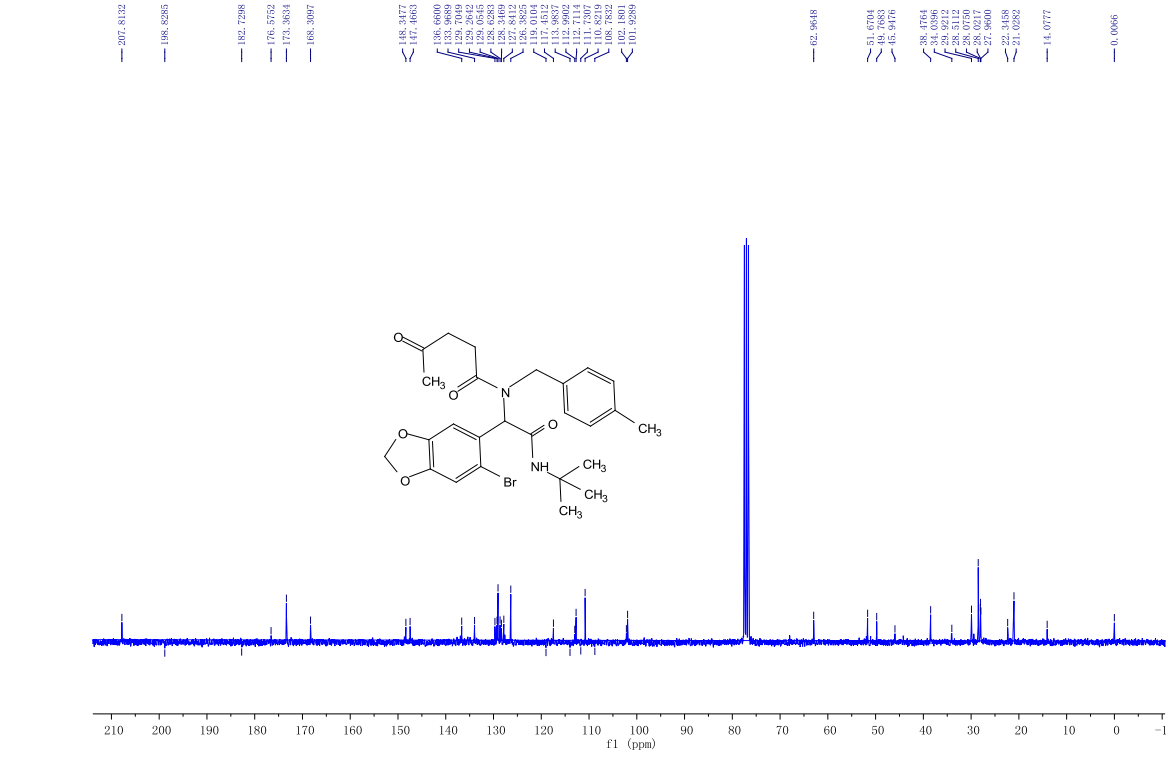
^{1}H and ^{13}C NMR spectra of compound **4a** (300 MHz, $CDCl_3$)



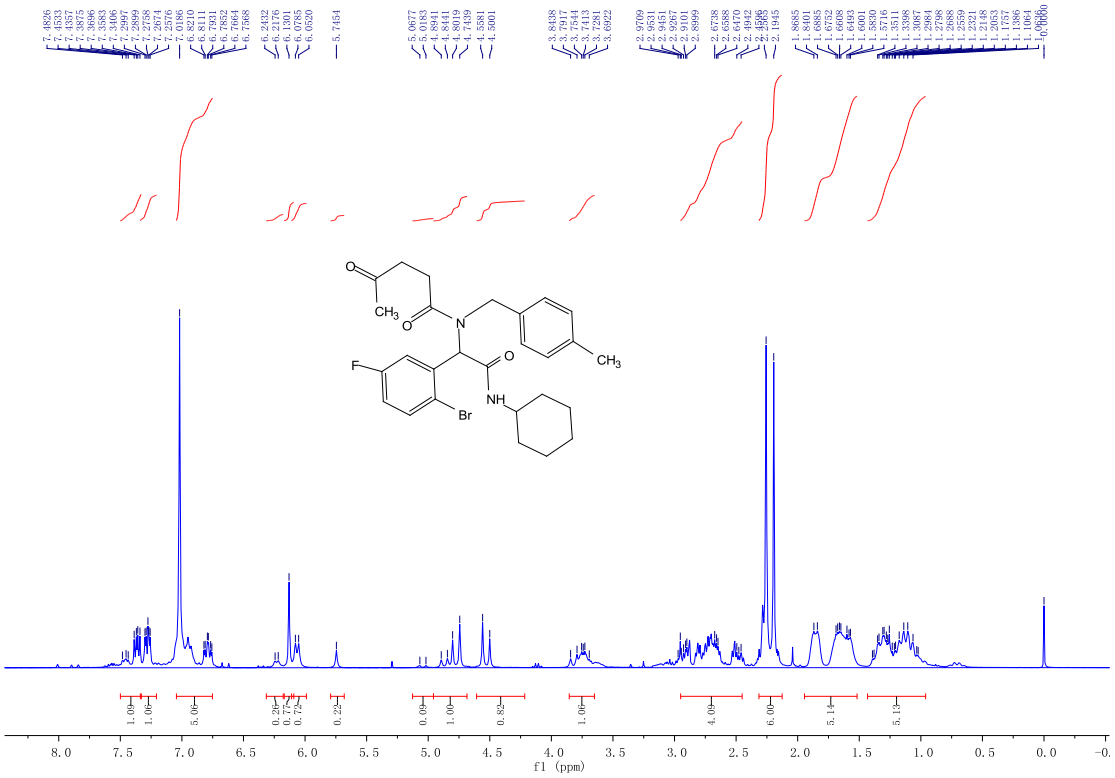


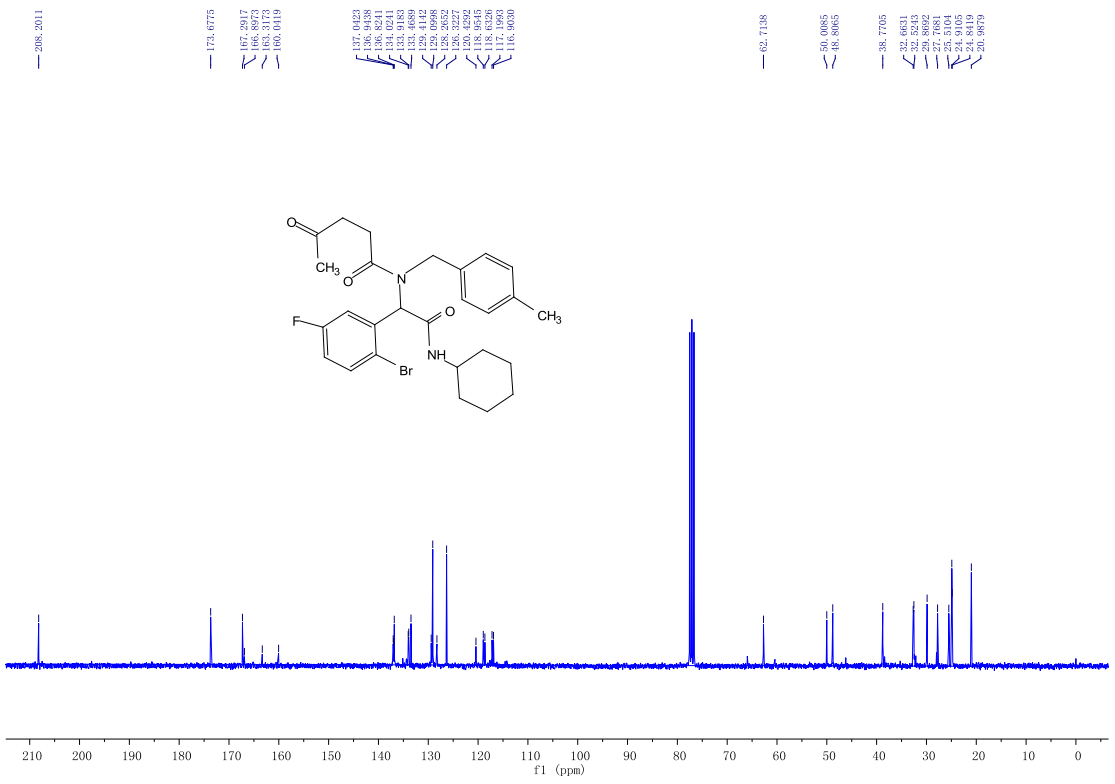
^{1}H and ^{13}C NMR spectra of compound **4b** (300 MHz, $CDCl_3$)



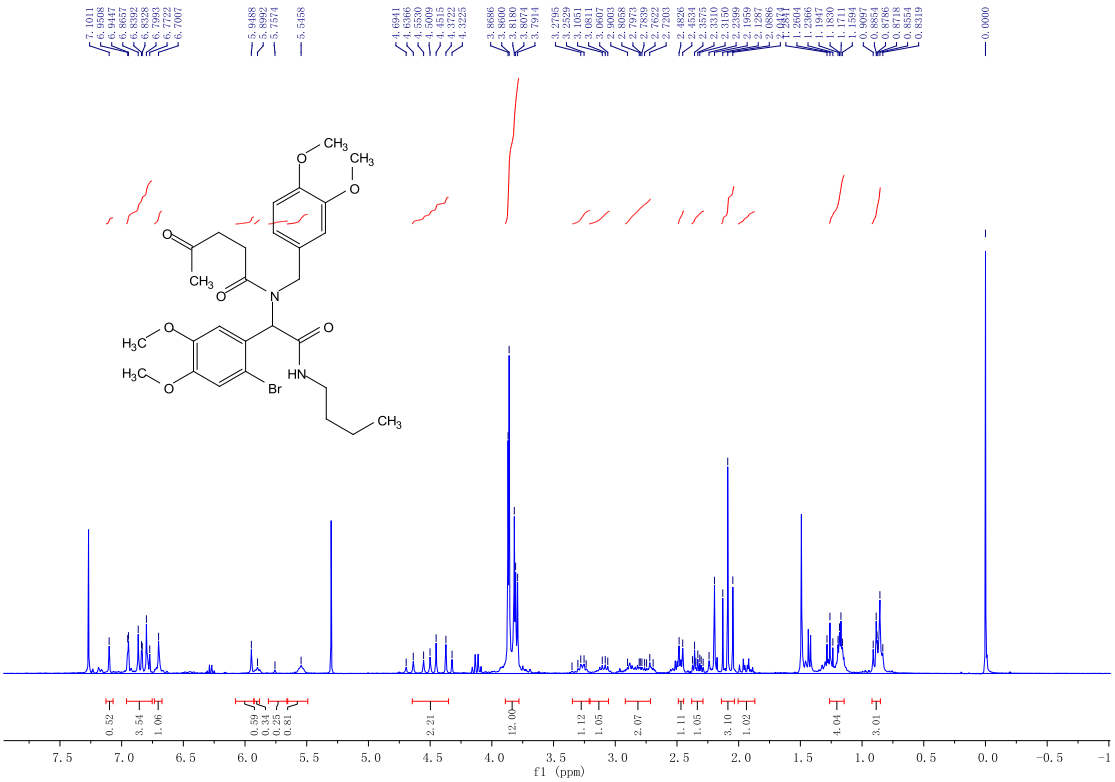


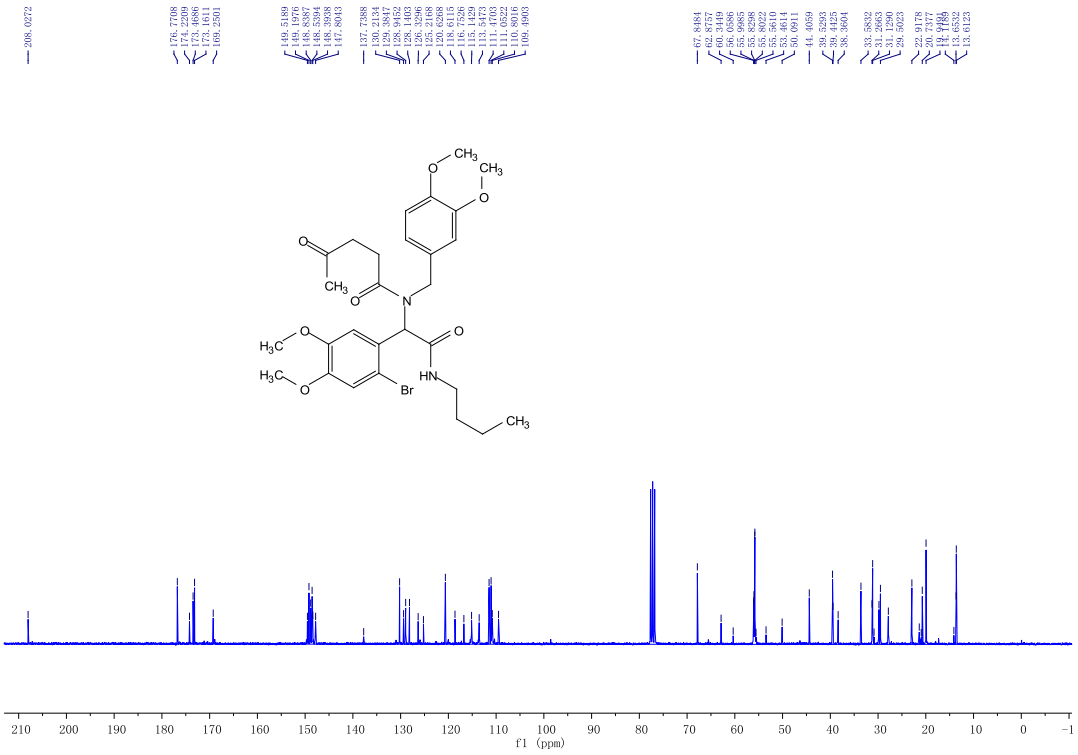
^{1}H and ^{13}C NMR spectra of compound **4c** (300 MHz, $CDCl_3$)



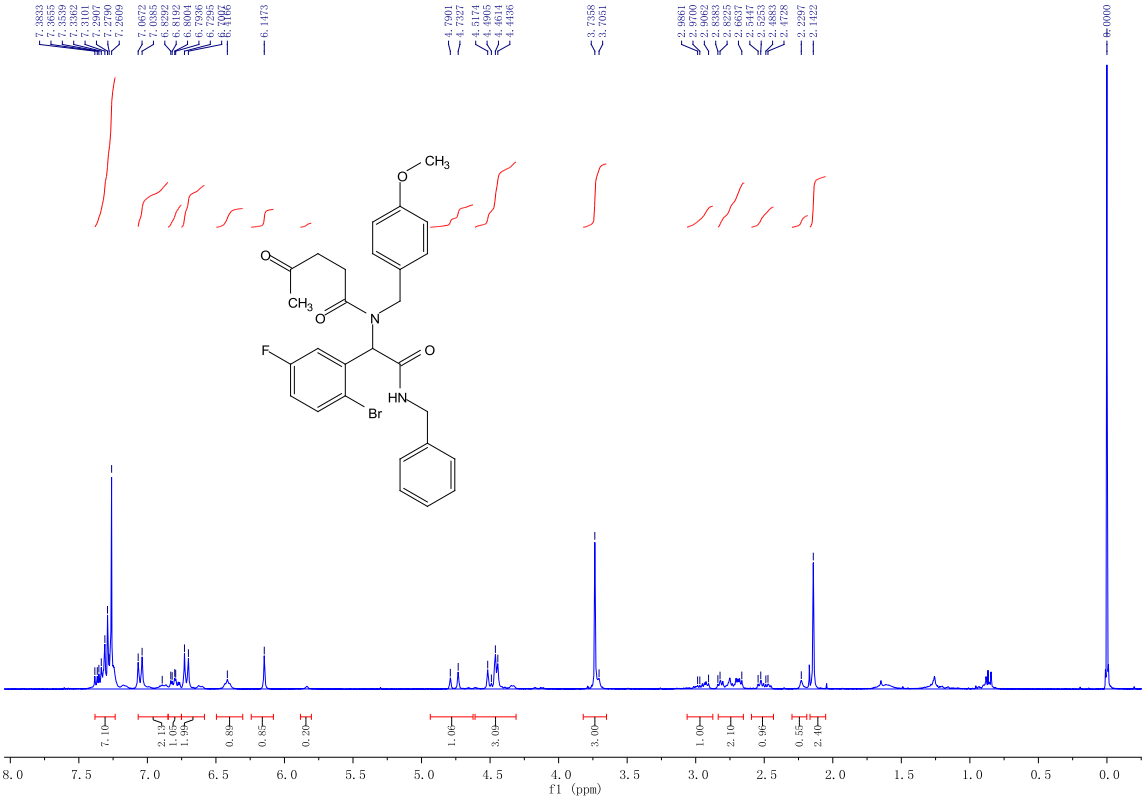


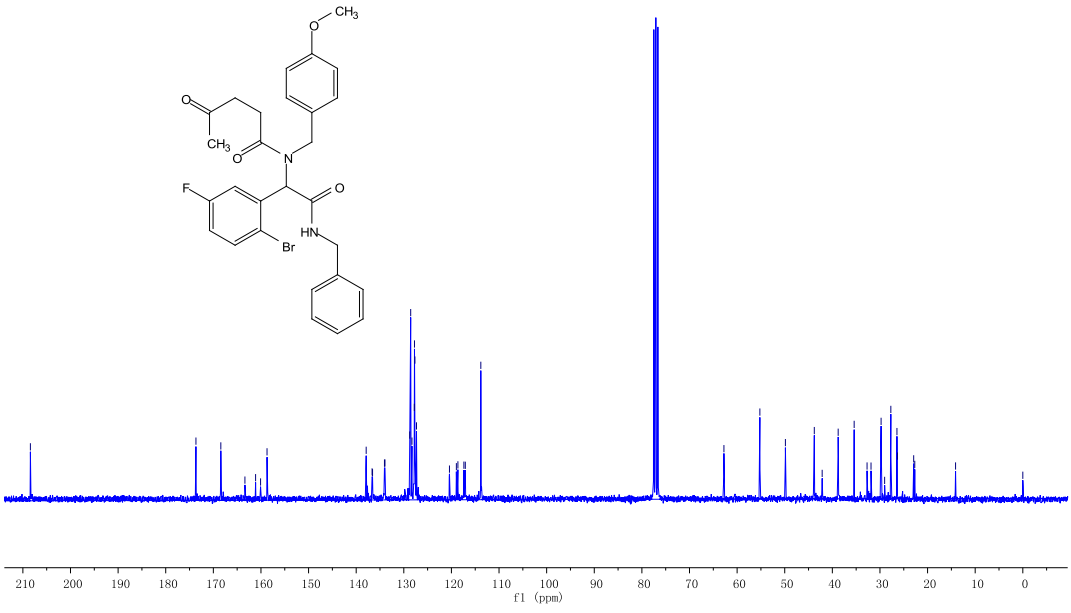
^{1}H and ^{13}C NMR spectra of compound **4d** (300 MHz, $CDCl_3$)



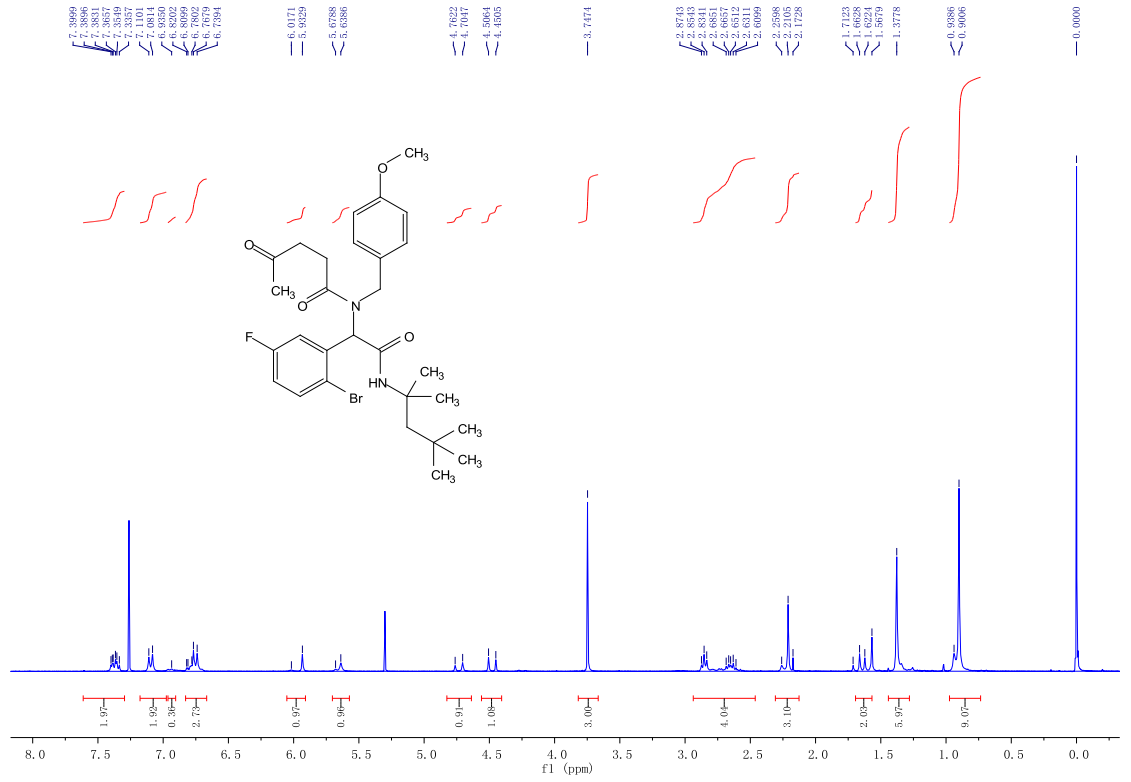


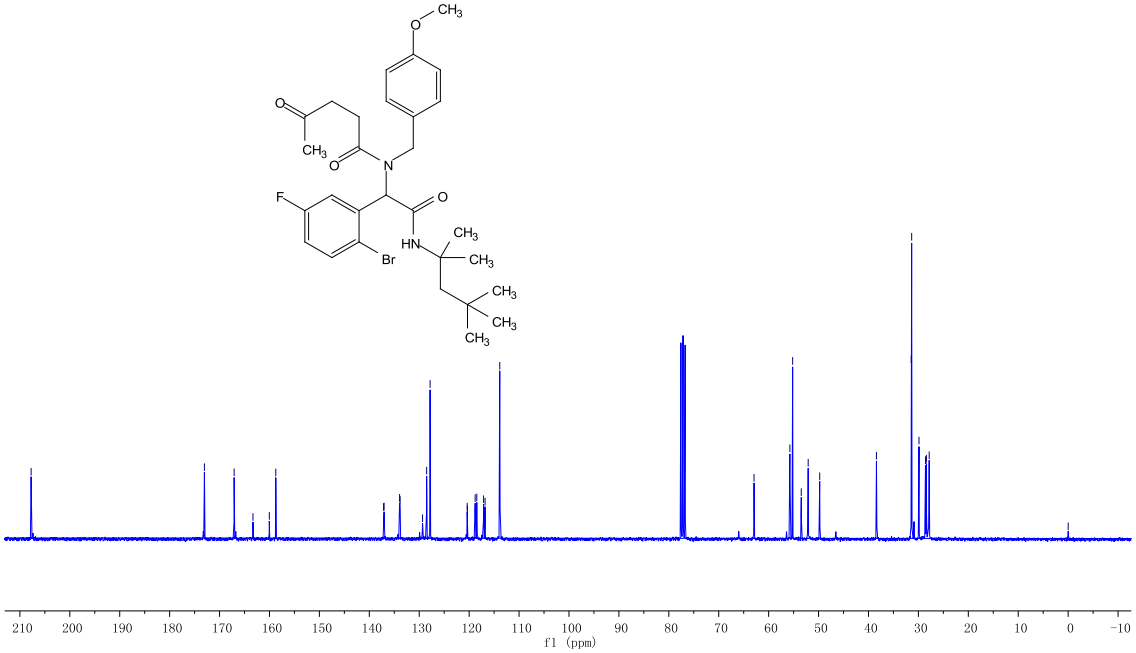
^{1}H and ^{13}C NMR spectra of compound **4e** (300 MHz, $CDCl_3$)



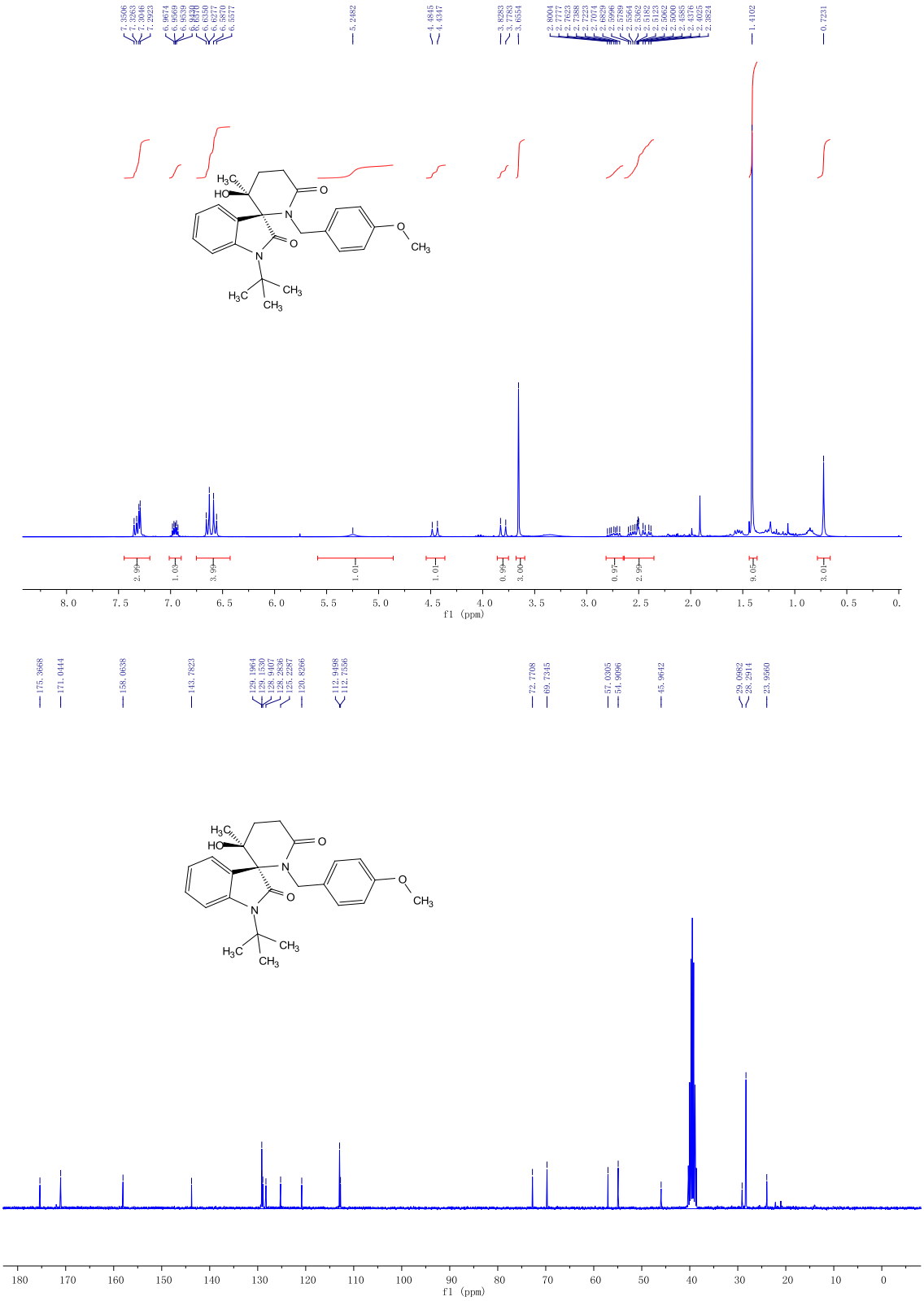


^{1}H and ^{13}C NMR spectra of compound **4f** (300 MHz, $CDCl_3$)

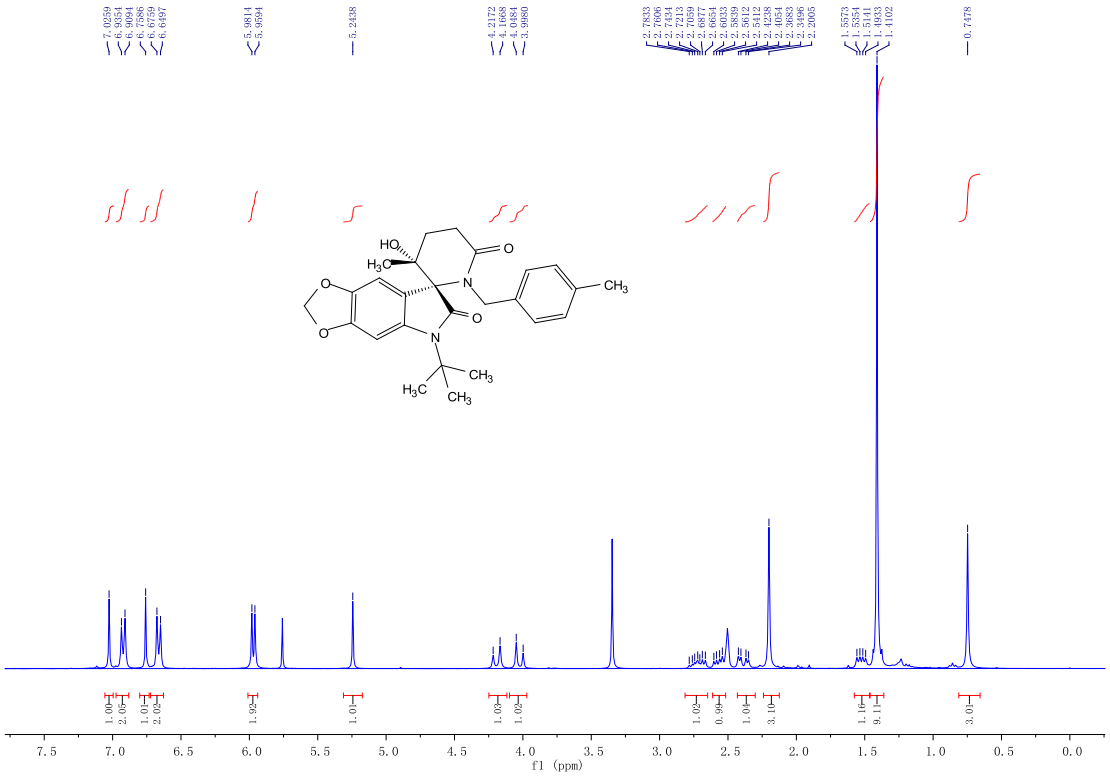


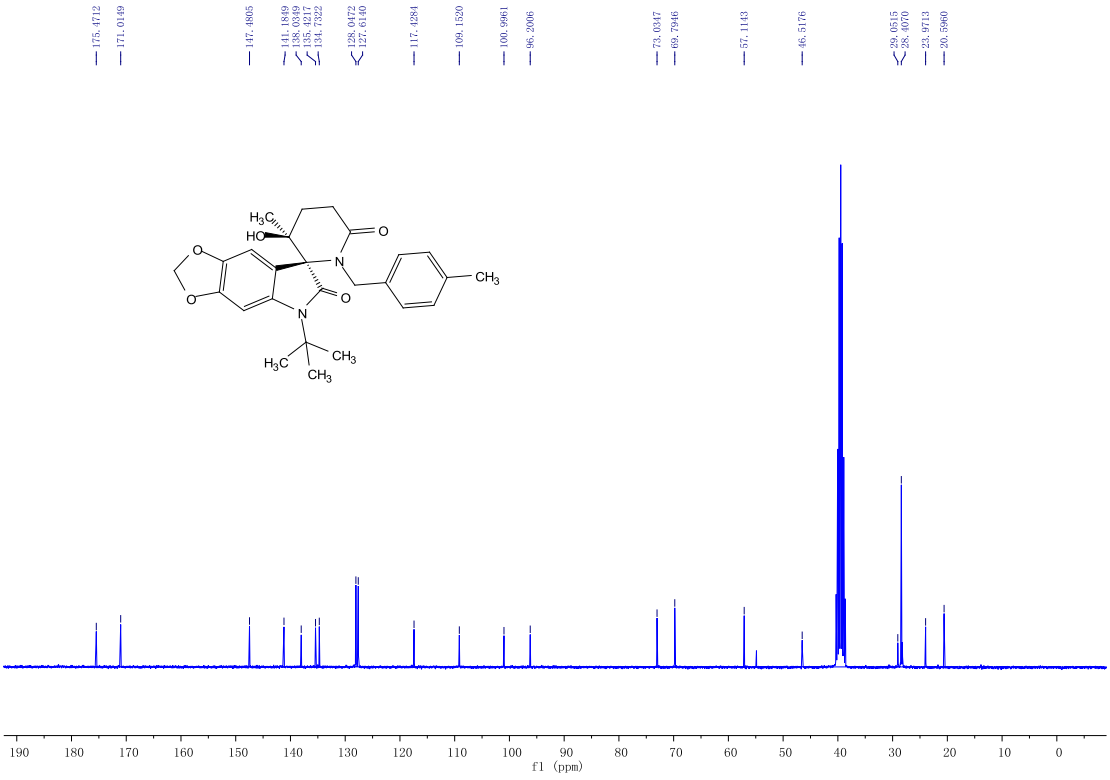


^{1}H and ^{13}C NMR spectra of compound **5a** (300 MHz, DMSO-d_6)

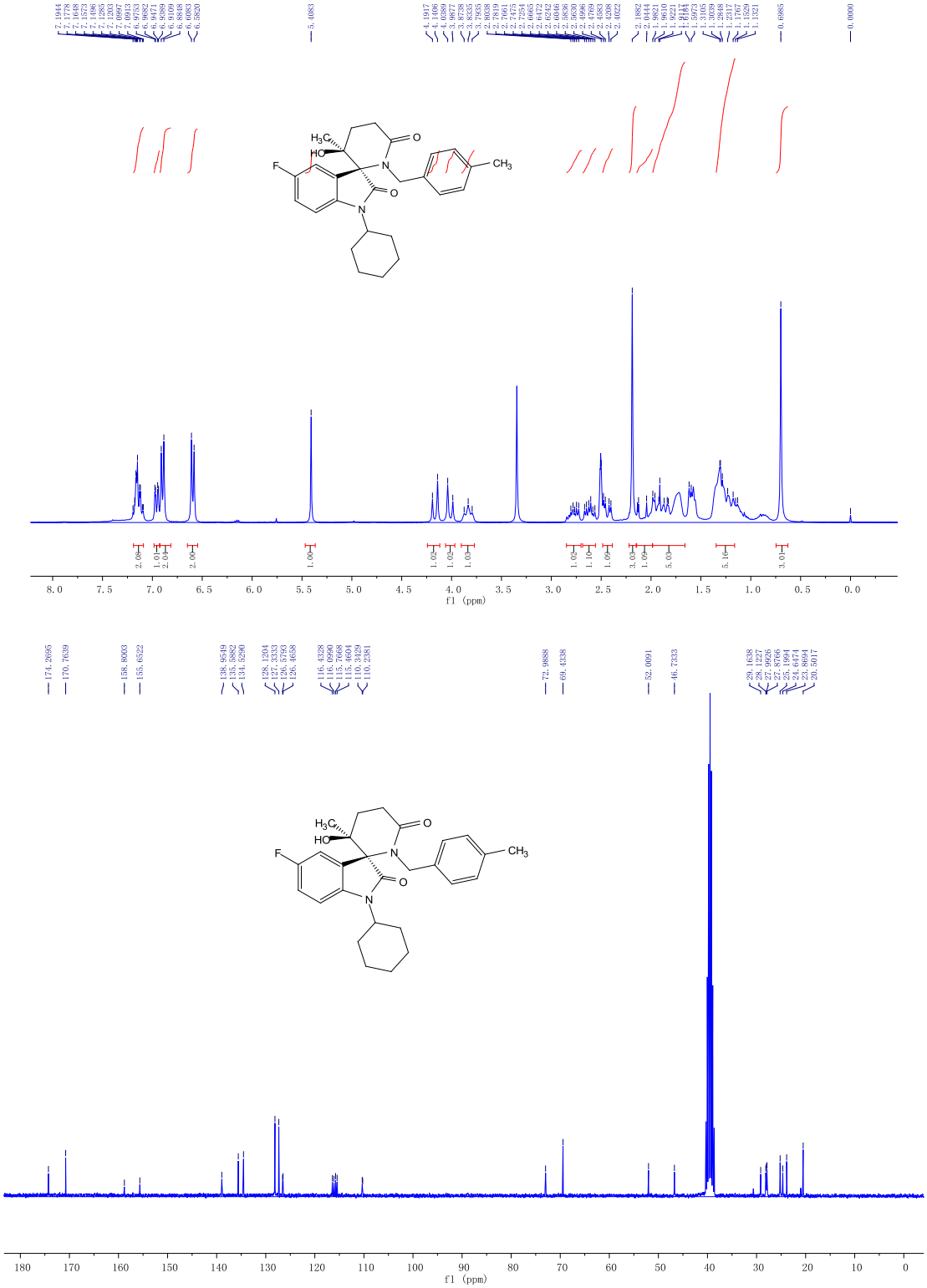


^{1}H and ^{13}C NMR spectra of compound **5b** (300 MHz, DMSO-d_6)

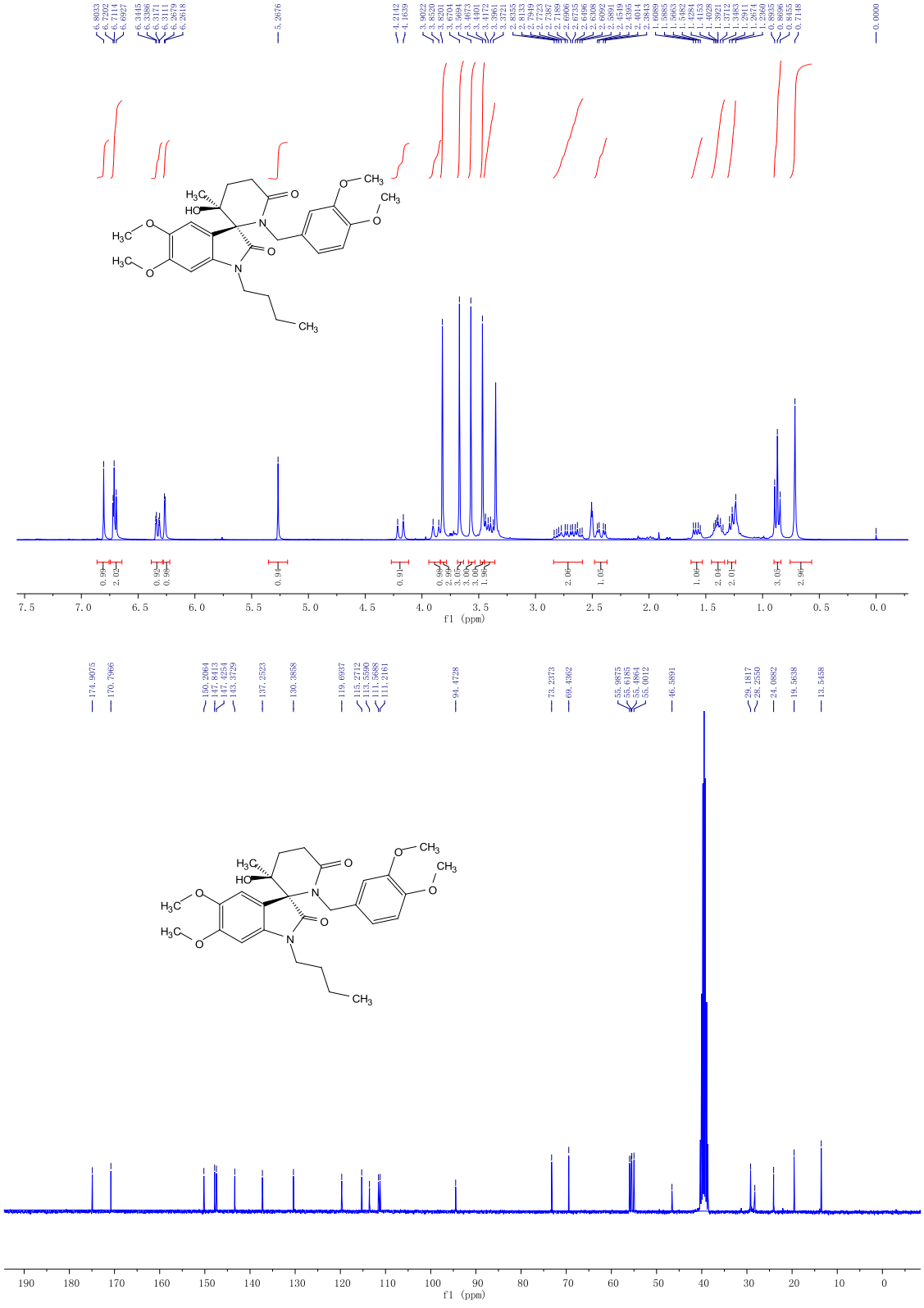




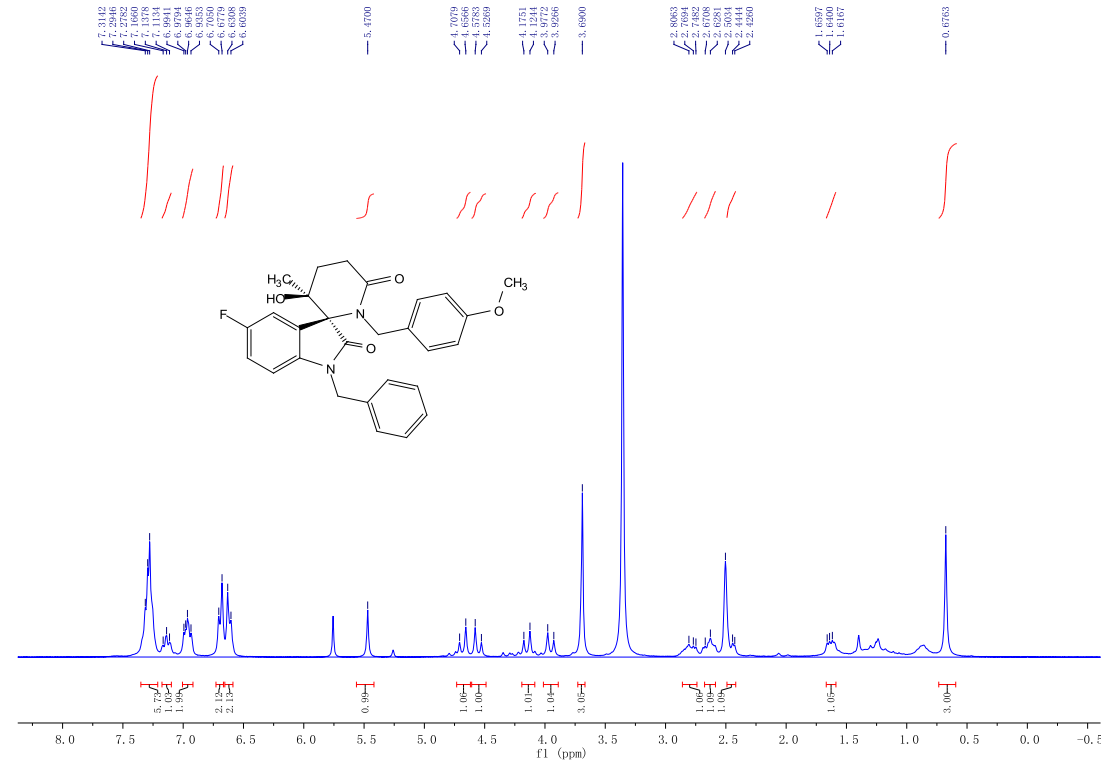
^{1}H and ^{13}C NMR spectra of compound **5c** (300 MHz, DMSO-d_6)

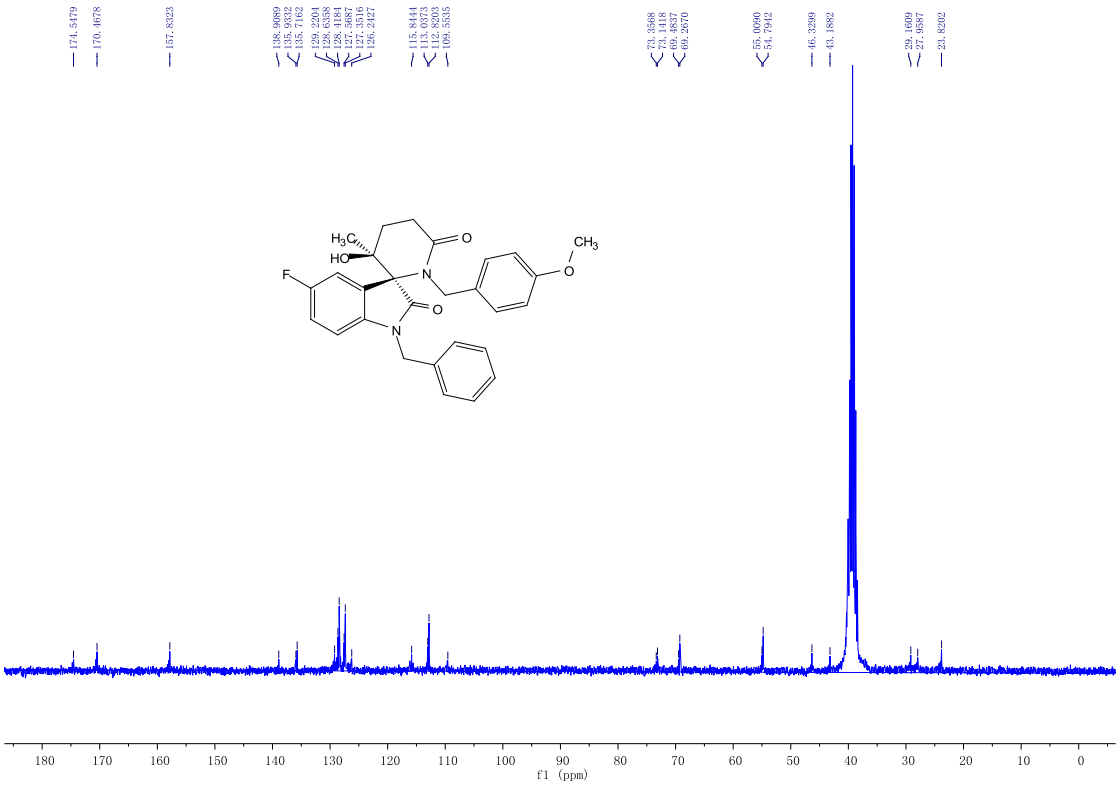


^{1}H and ^{13}C NMR spectra of compound **5d** (300 MHz, DMSO-d_6)



^{1}H and ^{13}C NMR spectra of compound **5e** (300 MHz, DMSO-d_6)





^{1}H and ^{13}C NMR spectra of compound **5f** (300 MHz, DMSO-d_6)