Supplementary Information

Site-Selective Rhodium Carbene Transfer of 2-Hydroxy-β-Nitrostyrenes with Diazo Compounds En Route to 2-Alkylated Benzofurans

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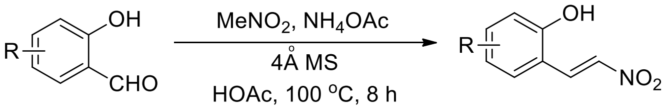
Contents

I. General

NMR spectra were recorded on JEOL 400 NMR (^{1}H 400 MHz; ^{13}C 100 MHz) in either $CDCl_3$, CD_3OD or DMSO-d_6. Abbreviations for data quoted are s, singlet; brs, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm; d_6-DMSO: δ_H = 2.50 ppm, δ_C = 39.52 ppm). Mass spectra and high-resolution mass spectra were measured on an agilent TOF-G6230B mass spectrometer and Thermo-DFS mass spectrometer. Thin-layer chromatographies were done on pre-coated silica gel 60 F254 plates (Merck). Silica gel 60H (200-300 mesh) and preparative TLC (200x200 mm, 0.2-0.25 mm in thickness) manufactured by Qingdao Haiyang Chemical Group Co. (China) were used for general chromatography. $[Cp^*IrCl_2]_2$, $[Cp^*RhCl_2]_2$, [Ru(*p*-cymene)$Cl_2]_2$ and CsOAc were purchased from Aldrich and used without further purification. Diazo compounds[S1] were synthesized according to published procedures. Other chemicals were purchased from commercial suppliers and were dried and purified when necessary. No attempts were made to optimize yields for substrate synthesis.

II. Experimental Information and Characterization Data

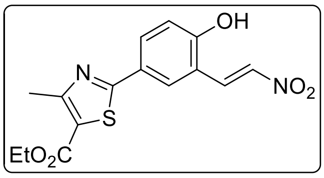
General procedure for the synthesis of 2-hydroxy-β-nitrostyrenes 1:



The synthesis of 2-hydroxy-β-nitrostyrenes **1** was conducted following a published procedure:[S2] To a 25 mL flask were added nitromethane (2.67 mL), NH_4OAc (10.0 mmol) and acetic acid (10.0 mL) under the nitrogen atmosphere. The mixture was stirred at 100 °C after the addition of 2-hydroxybenzaldehyde (10.0 mmol). The reaction mixture was heated at 100 °C for 8 h. After cooling to ambient temperature, the reaction was filter and the filtrate was extracted with EA and brine. The desired 2-hydroxy-β-nitrostyrenes **1** was purified by column chromatography on silica gel.

Substrates **1a-n** were known compounds and the characteristic data were in agreement with previous literature.[S2]

ethyl-2-(4-hydroxy-3-(2-nitrovinyl)phenyl)-4-methylthiazole-5-carboxylate (1o)



This compound was obtained in 28% yield (0.9377 g) as yellow solid. Eluent: PE/EA = 5/1. R_f = 0.2. m.p.: 203-205 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 11.65 (brs, 1H), 8.50-8.11 (m, 3H), 7.90 (s, 1H), 7.04-7.02 (m, 1H), 4.37-4.19 (m, 2H), 2.62 (s, 3H), 1.30 (t, J = 6.9 Hz, 3H).

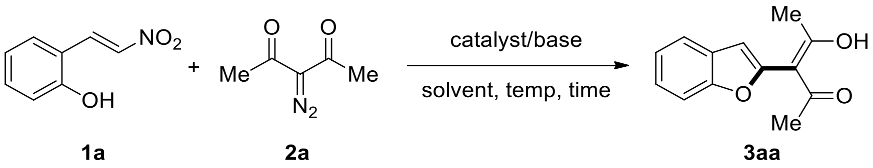
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 168.2, 161.4, 160.7, 160.1, 138.4, 134.5, 131.3, 130.3, 124.1, 120.3, 117.5, 116.8, 61.0, 17.2, 14.1.

HRMS (ESI) calculated for $C_{15}H_{15}N_2O_5S$ ($[M+H]^+$): 335.0696; found: 335.0696.

Optimization studies:

The mixture of 2-hydroxy-β-nitrostyrene **1a** (0.1 mmol, 1.0 equiv), 3-diazopentane-2,4-dione **2a** (0.11 mmol, 1.1 equiv), catalyst (x mol %) and base (1 equiv) in the solvent was stirred in an oil bath without exclusion of air or moisture. Afterwards, it was diluted with EtOAc and filtered through a short silica gel column to remove the metal residues. Then, the reaction mixture was concentrated and purified by preparative TLC (eluent: PE/EA = 10/1) to afford the corresponding product **3aa**.

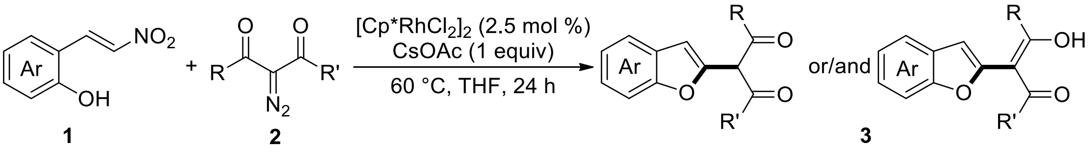
Table S1. Conditions Screening for the Synthesis of **3aa**.[a]



#	catalyst (mol %)	base	solvent	temp	time	yield (%)[b]
catalyst screening						
1	$Mn(CO)_5Br$ (5)	CsOAc	THF	60 °C	24 h	nd
2	$Ni(dppp)Cl_2$ (5)	CsOAc	THF	60 °C	24 h	nd
3	$Pd(dppf)Cl_2$ (5)	CsOAc	THF	60 °C	24 h	nd
4	$[Cp^*IrCl_2]_2$ (2.5)	CsOAc	THF	60 °C	24 h	nd
5	[Ru(*p*-cymene)$Cl_2]_2$ (2.5)	CsOAc	THF	60 °C	24 h	nd
6	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	THF	60 °C	24 h	80
7	$RhCl_3\cdot 3H_2O$ (5)	CsOAc	THF	60 °C	24 h	nd
8	$Rh_2(OAc)_4$ (2.5)	CsOAc	THF	60 °C	24 h	nd
9	$Rh(cod)BF_4$ (5)	CsOAc	THF	60 °C	24 h	nd
10	$Pd(OAc)_2$ (5)	CsOAc	THF	60 °C	24 h	nd
catalyst loading screening						
11	$[Cp^*RhCl_2]_2$ (1.5)	CsOAc	THF	60 °C		52
12	$[Cp^*RhCl_2]_2$ (3.5)	CsOAc	THF	60 °C		57
base screening						
13	$[Cp^*RhCl_2]_2$ (2.5)	NaOAc	THF	60 °C	24 h	43
14	$[Cp^*RhCl_2]_2$ (2.5)	KOAc	THF	60 °C	24 h	61
15	$[Cp^*RhCl_2]_2$ (2.5)	KOPiv	THF	60 °C	24 h	65
16	$[Cp^*RhCl_2]_2$ (2.5)	CsOPiv	THF	60 °C	24 h	33
solvent screening						
17	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	1,4-dioxane	60 °C	24 h	50
18	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	toluene	60 °C	24 h	58
19	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	MeOH	60 °C	24 h	nd
20	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	CH_2Cl_2	60 °C	24 h	17
21	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	EtOAc	60 °C	24 h	47
22	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	acetone	60 °C	24 h	39
reaction temperature screening						
23	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	THF	40 °C	24 h	61
24	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	THF	80 °C	24 h	56
reaction time screening						
25	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	THF	60 °C	18 h	25
26	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc	THF	60 °C	30 h	69

[a] Reaction Conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst (5 mol % based on metal), base (1.0 equiv), solvent (0.5 mL), temperature, time, under air. [b] Isolated yields.

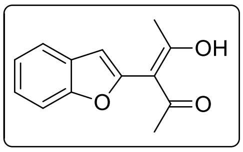
General procedure for the Rh(III)-catalysed carbene transfer reaction:



The mixture of 2-hydroxy-β-nitrostyrenes **1** (0.2 mmol, 1.0 equiv), diazo compounds **2** (0.22 mmol, 1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %) and CsOAc (1.0 equiv) in THF (1.0 mL) was stirred at 60 ºC for 24 h without exclusion of air or moisture. Afterwards, the mixture was diluted with EtOAc and filtered through a short silica gel column to remove the metal residues. Then, the reaction mixture was concentrated and purified by preparative TLC to give the desired benzofuran derivatives **3**.

Characterization of products:

3-(benzofuran-2-yl)-4-hydroxypent-3-en-2-one (3aa)



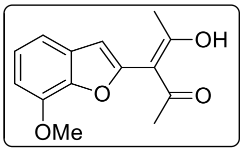
This compound was obtained in 80% yield (35.0 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.7. m.p.: 140-141 ℃.

^{1}H NMR (400 MHz, CD_3OD): δ 7.59 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 6.75 (s, 1H), 2.04 (s, 6H).

^{13}C NMR (100 MHz, CD_3OD): δ 194.1, 156.3, 153.5, 130.0, 125.5, 123.9, 122.0, 112.0, 109.3, 106.8, 24.0.

HRMS (ESI) calculated for $C_{13}H_{13}O_3$ ($[M+H]^+$): 217.0895; found: 217.0895.

4-hydroxy-3-(7-methoxybenzofuran-2-yl)pent-3-en-2-one (3ba)



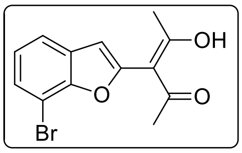
This compound was obtained in 74% yield (36.6 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.6. m.p.: 76-77 ℃.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.17 (m, 2H), 6.84-6.81 (m, 1H), 6.64 (s, 1H), 4.02 (s, 3H), 2.07 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 193.3, 151.6, 144.9, 143.5, 129.9, 123.6, 113.1, 108.4, 106.8, 105.2, 55.7, 23.8.

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ ($[M+H]^+$): 247.0965; found: 247.0963.

3-(7-bromobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3ca)



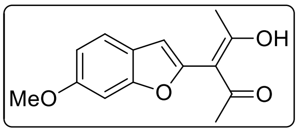
This compound was obtained in 60% yield (35.3 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.7. m.p.: 50-52 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (d, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.71 (s, 1H), 2.11 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.5, 153.4, 152.2, 129.8, 127.6, 124.3, 120.2, 108.8, 105.3, 104.2, 24.2.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_3$ ([M+H]$^+$): 294.9965; found: 294.9962.

4-hydroxy-3-(6-methoxybenzofuran-2-yl)pent-3-en-2-one (3da)



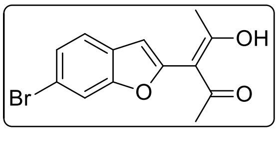
This compound was obtained in 72% yield (35.3 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.8. m.p.: 55-57 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.55 (s, 1H), 3.87 (s, 3H), 2.08 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.5, 158.2, 156.0, 151.3, 121.9, 121.1, 112.0, 107.8, 105.9, 95.9, 55.9, 24.1.

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ ([M+H]$^+$): 247.0965; found: 247.0960.

3-(6-bromobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3ea)



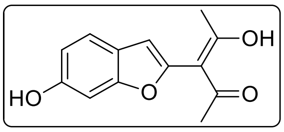
This compound was obtained in 71% yield (41.7 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.7. m.p.: 84-86 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.62 (s, 1H), 2.07 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.4, 155.3, 153.2, 127.7, 126.4, 121.9, 117.8, 114.8, 107.9, 105.4, 24.1.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_3$ ($[M+H]^+$): 294.9965; found: 294.9962.

4-hydroxy-3-(6-hydroxybenzofuran-2-yl)pent-3-en-2-one (3fa)



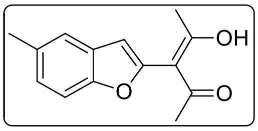
This compound was obtained in 55% yield (25.5 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.8. m.p.: 93-95 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 77.40 (d, *J* = 7.2 Hz, 1H), 6.99 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.55 (s, 1H), 5.77 (brs, 1H), 2.08 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.7, 155.9, 154.1, 151.3, 122.1, 121.2, 112.1, 107.9, 105.9, 98.4, 24.1.

HRMS (ESI) calculated for $C_{13}H_{13}O_4$ ($[M+H]^+$): 233.0809; found: 233.0808.

4-hydroxy-3-(5-methylbenzofuran-2-yl)pent-3-en-2-one (3ga)



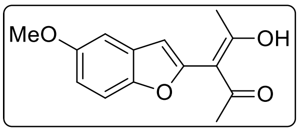
This compound was obtained in 93% yield (42.9 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.7. m.p.: 62-63 ℃.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38-7.35 (m, 2H), 7.12 (d, *J* = 10.2 Hz, 1H), 6.56 (s, 1H), 2.46 (s, 2H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.4, 153.4, 152.4, 132.4, 128.8, 125.7, 120.8, 110.9, 107.8, 105.9, 24.1, 21.5.

HRMS (ESI) calculated for $C_{14}H_{15}O_3$ ($[M+H]^+$):231.1016 ; found:231.1014 .

4-hydroxy-3-(5-methoxybenzofuran-2-yl)pent-3-en-2-one (3ha)



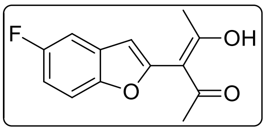
This compound was obtained in 87% yield (43 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.7. m.p.: 58-60 ℃.

^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 7.46 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 6.92-6.88 (m, 2H), 3.78 (s, 1H), 2.05 (s, 1H).

^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 193.2, 155.6, 152.4, 149.2, 128.9, 113.0, 111.6, 108.3, 105.4, 103.5, 55.6, 23.8.

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ ($[M+H]^+$): 247.0965; found: 247.0964.

3-(5-fluorobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3ia)



This compound was obtained in 69% yield (32.3 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.8. m.p.: 45-46 ℃.

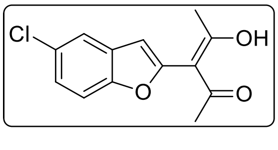
^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 7.63-7.55 (m, 1H), 7.45 (dd, *J* = 8.1, 5.4 Hz, 1H), 7.14 (dd, *J* = 9.5, 6.8 Hz, 1H), 6.96 (s, 1H), 2.05 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 193.2, 158.6 (d, *J* = 236.1 Hz), 153.7, 150.7, 129.3 (d, *J* = 11.1 Hz), 112.2, 112.1, 111.9 (d, *J* = 26.3 Hz), 108.4, 106.5 (d, *J* = 24.7 Hz), 105.2, 23.8.

^{19}F NMR (376 MHz, DMSO-*d$_6$*): δ -120.6.

HRMS (ESI) calculated for $C_{13}H_{12}FO_3$ ($[M+H]^+$): 235.0765; found: 235.0760.

3-(5-chlorobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3ja)



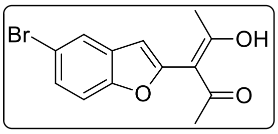
This compound was obtained in 77% yield (38.3 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.8. m.p.: 75-77 ℃.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.70 (d, *J* = 3.7 Hz, 1H), 7.60-7.57 (m, 1H), 7.35-7.28 (m, 1H), 6.94 (s, 1H), 2.05 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 193.2, 153.4, 152.8, 129.9, 127.3, 124.3, 120.5, 112.6, 107.9, 105.0, 23.8.

HRMS (ESI) calculated for $C_{13}H_{12}ClO_3$ ($[M+H]^+$): 251.0470; found: 251.0466.

3-(5-bromobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3ka)



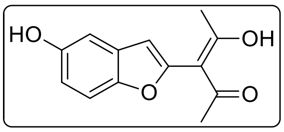
This compound was obtained in 58% yield (34 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.6. m.p.: 90-91 ℃.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.42-7.34 (m, 2H), 6.60 (s, 1H), 2.08 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 193.4, 153.9, 153.7, 130.6, 127.4, 123.6, 116.0, 112.8, 107.5, 105.5, 24.1.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_3$ ($[M+H]^+$): 294.9965; found: 294.9965.

4-hydroxy-3-(5-hydroxybenzofuran-2-yl)pent-3-en-2-one (3la)



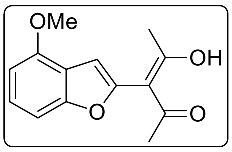
This compound was obtained in 53% yield (24.6 mg) as yellow solid. Eluent: PE/EA = 10/1. R_f = 0.2. m.p.: 136-138 ℃.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.19 (s, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.80-6.72 (m, 2H), 2.14-2.11 (m, 1H), 2.04 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 193.2, 153.4, 152.0, 148.5, 129.1, 113.0, 111.3, 108.0, 105.6, 105.3, 23.8.

HRMS (ESI) calculated for $C_{13}H_{13}O_4$ ($[M+H]^+$): 233.0809; found: 233.0805.

4-hydroxy-3-(4-methoxybenzofuran-2-yl)pent-3-en-2-one (3ma)



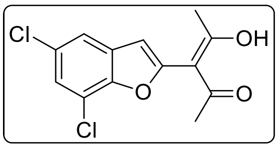
This compound was obtained in 81% yield (40 mg) as light yellow solid. Eluent: PE/EA = 10/1. R_f = 0.75. m.p.: 61-62 ℃.

^{1}H NMR (400 MHz, DMSO-*d_6*): δ 7.26 (t, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.92 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d_6*): δ 193.3, 155.4, 152.9, 150.2, 125.3, 118.2, 105.4, 105.2, 104.2, 103.7, 55.4, 23.8.

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ ($[M+H]^+$): 247.0965; found: 247.0961.

3-(5,7-dichlorobenzofuran-2-yl)-4-hydroxypent-3-en-2-one (3na)



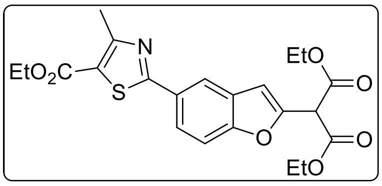
This compound was obtained in 50% yield (28.4 mg) as brownish red solid. Eluent: PE/EA = 10/1. R_f = 0.75. m.p.: 85-87 ℃.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 1.9 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 6.64 (s, 1H), 2.10 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 155.1, 149.5, 130.9, 128.9, 124.8, 119.3, 117.5, 108.3, 105.0, 24.2.

HRMS (ESI) calculated for $C_{13}H_{11}Cl_2O_3$ ($[M+H]^+$): 285.0080; found: 285.0076.

diethyl 2-(5-(5-(ethoxycarbonyl)-4-methylthiazol-2-yl)benzofuran-2-yl)malonate (3oa)



This compound was obtained in 62% yield (55.2 mg) as yellow solid. Eluent: PE/acetone = 5/1. R_f = 0.5. m.p.: 73-75 ℃.

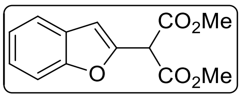
^{1}H NMR (400 MHz, DMSO-*d_6*): δ 8.20 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* =

8.7 Hz, 1H), 6.92 (s, 1H), 4.92 (s, 1H), 4.40-4.27 (m, 6H), 2.79 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.34-1.29 (m, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 170.3, 165.7, 162.5, 161.1, 156.5, 150.5, 128.9, 128.6, 123.9, 121.6, 120.1, 112.1, 106.8, 62.7, 61.4, 52.6, 17.7, 14.5, 14.1.

HRMS (ESI) calculated for $C_{22}H_{24}NO_3S$ ([M+H]$^+$): 446.1268; found: 446.1257.

dimethyl 2-(benzofuran-2-yl)malonate (3ab)



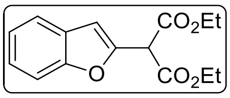
This compound was obtained in 77% yield (38.3 mg) as yellow oil. Eluent: PE/EA = 10/1. R$_f$ = 0.6.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.66 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.02 (s, 1H), 5.54 (s, 1H), 3.78 (s, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 166.3, 154.4, 149.0, 127.7, 124.7, 123.1, 121.3, 111.1, 106.6, 53.0, 51.4.

HRMS (ESI) calculated for $C_{13}H_{13}O_5$ ([M+H]$^+$): 249.0758; found: 249.0753.

diethyl 2-(benzofuran-2-yl)malonate (3ac)



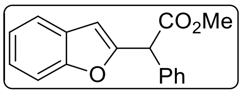
This compound was obtained in 75% yield (41.4 mg) as yellow solid. Eluent: PE/EA = 10/1. R$_f$ = 0.4. m.p.: 51-53 ℃.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 5.43 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 4H), 1.21 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 165.8, 154.4, 149.3, 127.7, 124.6, 123.1, 121.3, 111.1, 106.4, 61.9, 51.9, 13.8.

HRMS (ESI) calculated for $C_{15}H_{17}O_5$ ([M+H]$^+$): 277.1071; found: 277.1067.

methyl 2-(benzofuran-2-yl)-2-phenylacetate (3ad)



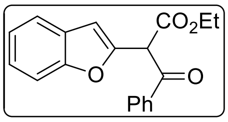
This compound was obtained in 55% yield (29.3 mg) as yellow oil. Eluent: PE/EA = 10/1. R_f = 0.6.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.59 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.46-7.38 (m, 4H), 7.37-7.32 (m, 1H), 7.30-7.18 (m, 2H), 6.68 (s, 1H), 5.50 (s, 1H), 3.71 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 170.3, 154.9, 154.3, 135.7, 128.8, 128.7, 127.9, 127.8, 124.3, 122.9, 121.1, 111.0, 105.0, 52.6, 50.4.

HRMS (ESI) calculated for $C_{17}H_{14}NaO_3$ ($[M+Na]^+$): 289.0835; found: 289.0831.

ethyl 2-(benzofuran-2-yl)-3-oxo-3-phenylpropanoate (3ae)



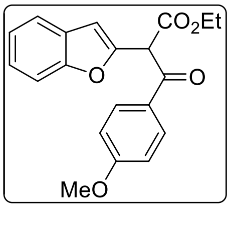
This compound was obtained in 65% yield (39.9 mg) as yellow oil. Eluent: PE/EA = 10/1. R_f = 0.6.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.70-7.59 (m, 3H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.59 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 191.6, 167.0, 154.4, 150.1, 134.9, 134.2, 129.0, 128.8, 127.8, 124.5, 123.0, 121.3, 111.1, 106.8, 61.6, 54.2, 13.9.

HRMS (ESI) calculated for $C_{19}H_{17}O_4$ ($[M+H]^+$): 309.1122; found: 309.1115.

ethyl 2-(benzofuran-2-yl)-3-(4-methoxyphenyl)-3-oxopropanoate (3af)



This compound was obtained in 89% yield (60 mg) as yellow oil. Eluent: PE/EA =

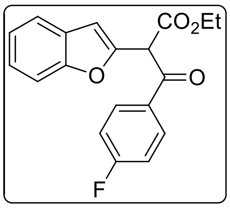
10/1. $R_f = 0.5$.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.31-7.21 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.92 (s, 1H), 6.51 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 189.8, 167.2, 163.9, 154.4, 150.6, 131.4, 127.9, 127.7, 124.5, 123.0, 121.3, 114.3, 111.1, 106.6, 61.5, 55.7, 53.9, 13.9.

HRMS (ESI) calculated for $C_{20}H_{19}O_5$ ($[M+H]^+$): 339.1227; found: 339.1222.

ethyl 2-(benzofuran-2-yl)-3-(4-fluorophenyl)-3-oxopropanoate (3ag)



This compound was obtained in 64% yield (41.7 mg) as yellow oil. Eluent: PE/EA = 10/1. $R_f = 0.55$.

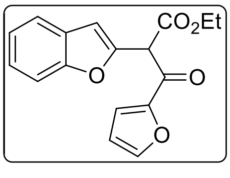
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.19 (d, *J* = 3.8 Hz, 1H), 8.13 (d, *J* = 5.0 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.38-7.17 (m, 4H), 7.01 (s, 1H), 6.48 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 190.0, 166.6, 165.3 (d, *J* = 253.9 Hz), 154.2, 149.7, 131.7 (d, *J* = 9.7 Hz), 131.4 (d, *J* = 1.6 Hz), 127.5, 124.3, 122.8, 121.0, 115.9 (d, *J* = 22.1 Hz), 110.8, 106.6, 61.4, 53.9, 13.6.

^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ -106.03.

HRMS (ESI) calculated for $C_{19}H_{16}FO_4$ ($[M+H]^+$): 327.1027; found: 327.1028.

ethyl 2-(benzofuran-2-yl)-3-(furan-2-yl)-3-oxopropanoate (3ah)



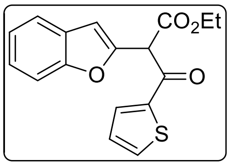
This compound was obtained in 76% yield (45.3 mg) as yellow oil. Eluent: PE/EA = 10/1. $R_f = 0.45$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, *J* = 0.9 Hz, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.64 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.33-7.22 (m, 2H), 6.97 (s, 1H), 6.79 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.21 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 179.0, 166.4, 154.4, 150.4, 149.8, 149.5, 127.8, 124.6, 123.1, 121.4, 121.3, 113.2, 111.1, 106.7, 61.8, 54.0, 13.9.

HRMS (ESI) calculated for $C_{17}H_{15}O_5$ ([M+H]$^+$): 299.0914; found: 299.0910.

ethyl 2-(benzofuran-2-yl)-3-oxo-3-(thiophen-2-yl)propanoate (3ai)



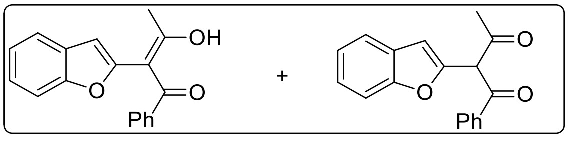
This compound was obtained in 83% yield (52.1 mg) as yellow oil. Eluent: PE/EA = 10/1. R$_f$ = 0.6.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20-8.16 (m, 1H), 8.12-8.08 (m, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.31-7.19 (m, 3H), 7.00 (s, 1H), 6.47 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 184.1, 166.5, 154.4, 150.1, 141.8, 137.1, 135.6, 129.1, 127.8, 124.6, 123.0, 121.3, 111.1, 106.8, 61.7, 54.6, 13.9.

HRMS (ESI) calculated for $C_{17}H_{15}O_4S$ ([M+H]$^+$): 315.0686; found: 315.0681.

2-(benzofuran-2-yl)-3-hydroxy-1-phenylbut-2-en-1-one (3aj) & 2-(benzofuran-2-yl)-1-phenylbutane-1,3-dione (3aj')



This compound was obtained in 65% yield (36.3 mg) as yellow oil. Eluent: PE/EA = 10/1. R$_f$ = 0.6. An inseparable mixture of two tautomers was isolated, and the ratio was determined to be **3aj/3aj'** = 1/0.3 by ^{1}H-NMR analysis.

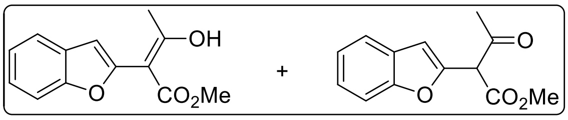
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (brs, 0.3 H), 8.05 (d, *J* = 8.0 Hz, 0.6 H), 7.66

(t, *J* = 7.2 Hz, 0.3 H), 7.61 (d, *J* = 7.6 Hz, 0.3 H), 7.58-7.53 (m, 3H), 7.42-7.38 (m, 3H), 7.30-7.20 (m, 4.8H), 6.88 (s, 0.3H), 6.80 (s, 1H), 6.68 (s, 0.3H), 2.30 (s, 0.9H), 2.16 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 201.3, 197.1, 193.4, 185.9, 154.5, 154.1, 151.5, 150.6, 135.4, 135.3, 134.1, 131.6, 129.0, 128.8, 128.2, 128.0, 127.9, 124.5, 124.4, 123.0, 122.9, 121.2, 121.1, 111.2, 111.1, 108.7, 106.8, 104.2, 61.0, 29.6, 24.7.

HRMS (ESI) calculated for $C_{18}H_{15}O_3$ ([M+H]$^+$): 279.1016; found: 279.1012.

methyl 2-(benzofuran-2-yl)-3-hydroxybut-2-enoate (3ak) & 2-(1-methoxy-1,3-dioxobutan-2-yl)benzofuran-6-ylium (3ak')



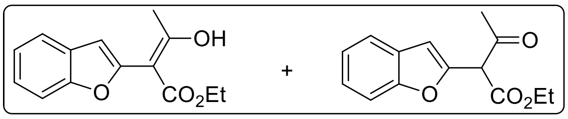
This compound was obtained in 61% yield (28.3 mg) as yellow oil. Eluent: PE/EA = 10/1. R$_f$ = 0.77. An inseparable mixture of two tautomers was isolated, and the ratio was determined to be **3ak/3ak'** = 1/0.55 by ^{1}H-NMR analysis.

^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 7.67-7.60 (m, 1.55H), 7.569-7.54(m, 1.55H), 7.34-7.21 (m, 3.1H), 6.96 (s, 0.55H), 6.84 (s, 1H), 5.56 (s, 0.55H), 3.73 (s, 1.65H), 3.71 (s, 3H), 2.26 (s, 1.65H), 2.04 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 199.4, 178.4, 171.6, 167.0, 154.4, 154.1, 150.3, 149.5, 128.3, 127.8, 124.6, 124.2, 123.1, 122.7, 121.3, 120.9, 111.1, 111.0, 107.7, 106.8, 94.7, 58.6, 52.7, 52.2, 29.0, 20.1.

HRMS (ESI) calculated for $C_{13}H_{13}O_4$ ([M+H]$^+$): 233.0809; found: 233.0807.

ethyl 2-(benzofuran-2-yl)-3-hydroxybut-2-enoate (3al) & ethyl 2-(benzofuran-2-yl)-3-oxobutanoate (3al')



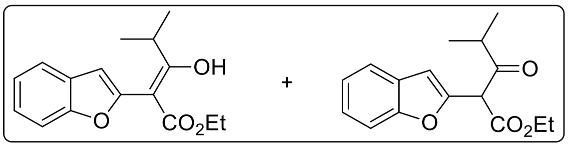
This compound was obtained in 56% yield (27.5 mg) as yellow oil. Eluent: PE/EA = 10/1. R$_f$ = 0.8. An inseparable mixture of two tautomers was isolated, and the ratio was determined to be **3al/3al'** = 1/0.6 by ^{1}H-NMR analysis.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.65-7.59 (m, 1.6H), 7.57-7.52 (m, 1.6H), 7.32-7.20 (m, 3.2H), 6.95 (s, 0.6H), 6.82 (s, 1H), 5.51 (s, 0.6H), 4.19 (q, *J* = 7.0 Hz, 3.2H), 2.26 (s, 1.8H), 2.03 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 1.8H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 199.4, 178.5, 171.3, 166.4, 154.4, 154.1, 150.3, 149.7, 128.4, 127.8, 124.5, 124.1, 123.0, 122.6, 121.2, 120.9, 111.1, 110.9, 107.5, 106.6, 94.9, 61.6, 61.1, 58.8, 28.9, 20.1, 14.0, 13.9.

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ ([M+H]$^+$): 247.0965; found: 247.0960.

ethyl 2-(benzofuran-2-yl)-3-hydroxy-4-methylpent-2-enoate (3am) & ethyl 2-(benzofuran-2-yl)-4-methyl-3-oxopentanoate (3am')



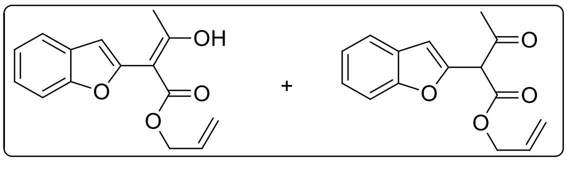
This compound was obtained in 60% yield (32.8 mg) as brownish red oil. Eluent: PE/EA = 10/1. R$_f$ = 0.8. An inseparable mixture of two tautomers was isolated, and the ratio was determined to be **3am/3am'** = 1/1 by ^{1}H-NMR analysis.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.63 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.1 Hz, 2H), 7.33-7.21 (m, 4H), 6.91 (s, 1H), 6.86 (s, 1H), 5.73 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 2.91-2.79 (m, 1H), 2.65-2.55 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.10-1.06 (m, 9H), 1.02 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 205.2, 185.2, 171.8, 166.5, 154.4, 154.2, 149.9, 149.8, 128.3, 127.8, 124.5, 124.2, 123.0, 122.7, 121.2, 120.9, 111.0, 107.7, 106.6, 93.0, 61.5, 61.1, 56.3, 31.4, 19.4, 18.1, 17.9, 14.0, 13.9.

HRMS (ESI) calculated for $C_{16}H_{19}O_4$ ([M+H]$^+$): 275.1278; found: 275.1279.

allyl 2-(benzofuran-2-yl)-3-hydroxybut-2-enoate (3an) & allyl 2-(benzofuran-2-yl)-3-oxobutanoate (3an')



This compound was obtained in 61% yield (31.5 mg) as yellow oil. Eluent: PE/EA =

10/1. R_f = 0.8. An inseparable mixture of two tautomers was isolated, and the ratio was determined to be **3an**/**3an’** = 1/0.5 by ^{1}H-NMR analysis.

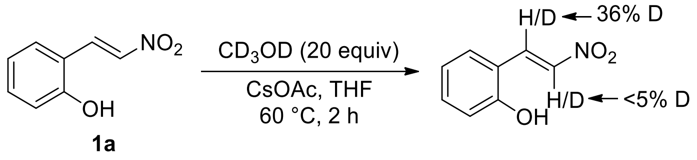
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.65 (d, *J* = 7.6 Hz, 0.5H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 0.5H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.35-7.21 (m, 3H), 6.96 (s, 0.5H), 6.85 (s, 1H), 5.97-5.82 (m, 1.5H), 5.61 (s, 1H), 5.35-5.13 (m, 3H), 4.71-4.65 (m, 3H), 2.27 (s, 1.5H), 2.06 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 199.4, 178.7, 170.8, 166.1, 154.4, 154.1, 150.3, 149.5, 132.2, 131.9, 128.3, 127.8, 124.6, 124.1, 123.1, 122.6, 121.3, 120.9, 118.2, 117.5, 111.1, 110.9, 107.5, 106.8, 94.8, 65.7, 64.9, 58.7, 29.0, 20.2.

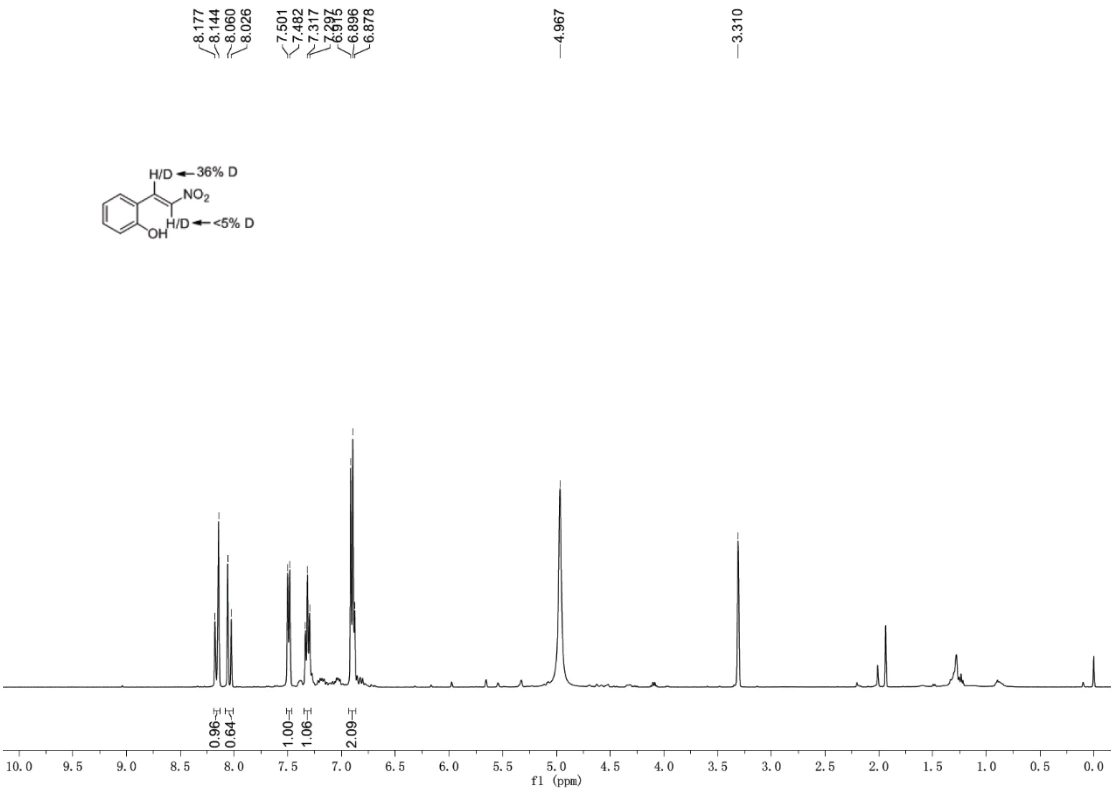
HRMS (ESI) calculated for $C_{13}H_{13}O_3$ ($[M+H]^+$): 259.0965; found: 259.0962.

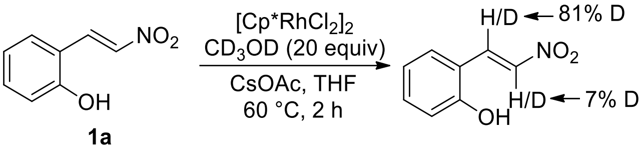
III. Experimental Mechanistic Studies

Deuterium-labeling experiment:

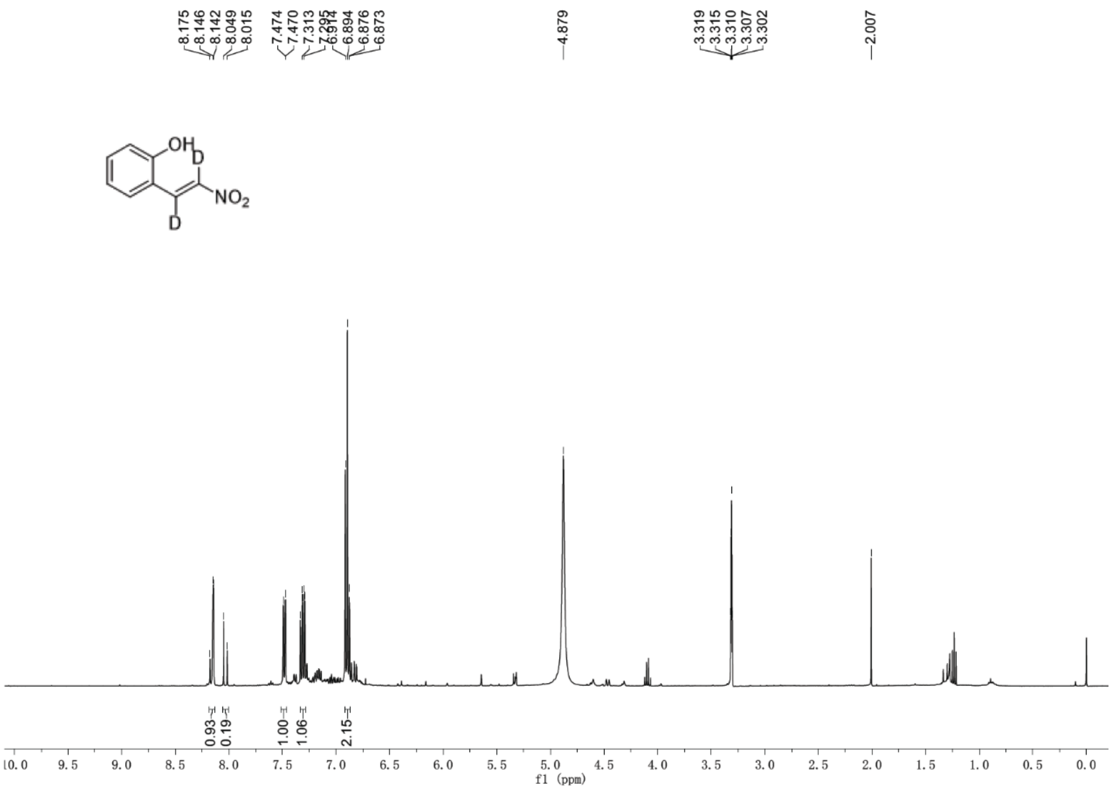


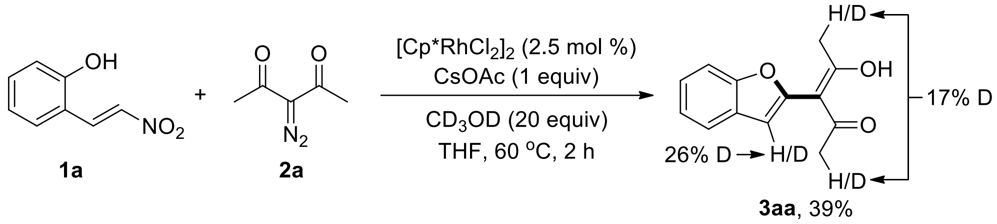
1a (0.1 mmol, 1 equiv) was dissolved in THF (0.5 mL) in the presence of CsOAc (1 equiv) and CD_3OD (20.0 equiv). The mixture was stirred at 60 ºC in an oil bath for 2 h. Afterwards, the mixture was diluted with EtOAc and transferred to a round bottom flask. The solvent was evaporated under reduced pressure and the recovered **1a** was purified by preparative TLC. The deuterium incorporation was analyzed by ^{1}H-NMR, the result showed that approximate 36% deuteration was detected at the β-position of the nitro group in **1a**, while no obvious deuterium incorporation was detected at the α-position of the nitro group.



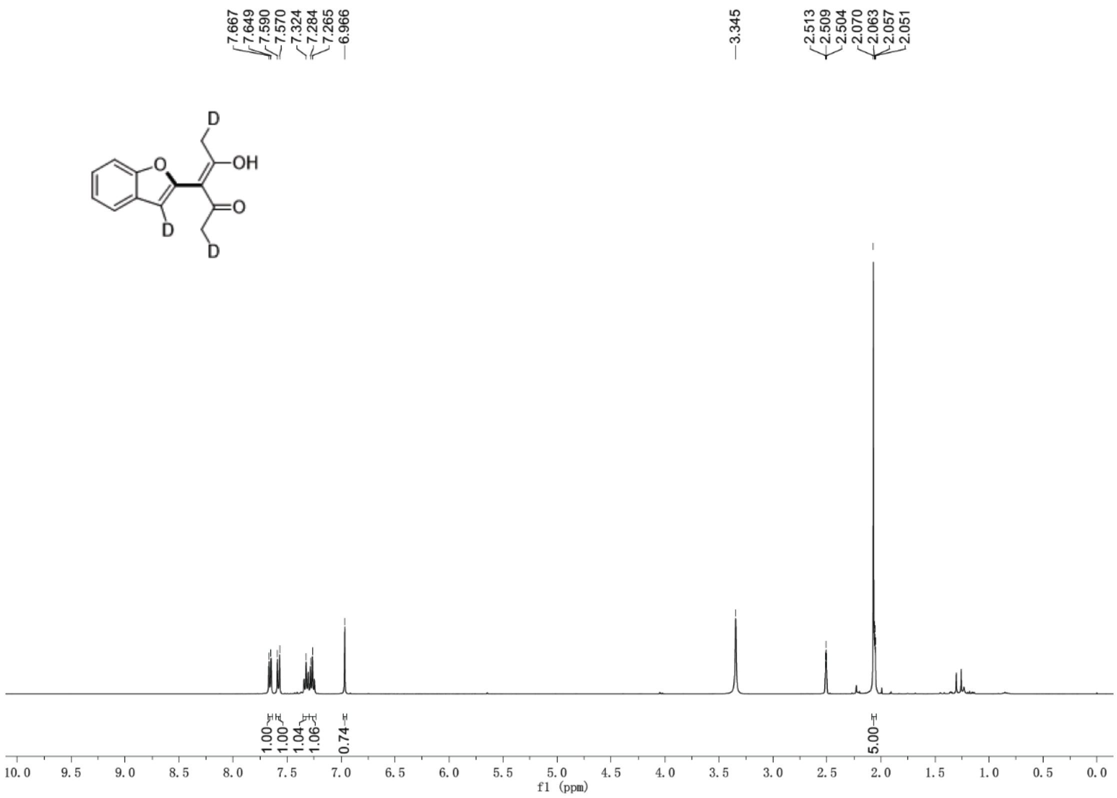


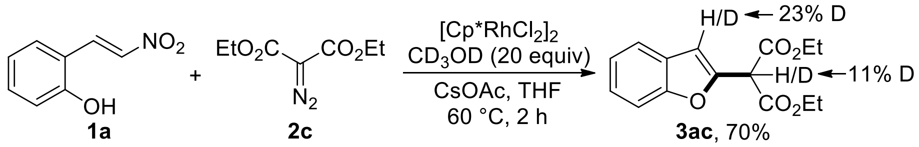
1a (0.1 mmol, 1 equiv) was dissolved in THF (0.5 mL) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (1 equiv) and CD_3OD (20.0 equiv). The mixture was stirred at 60 ºC in an oil bath for 2 h. Afterwards, the mixture was diluted with EtOAc and transferred to a round bottom flask. The solvent was evaporated under reduced pressure and the recovered **1a** was purified by preparative TLC. The deuterium incorporation was analyzed by ^{1}H-NMR, the result showed that approximate 81% deuteration (see the doublet at δ 8.03) was detected at the β-position of the nitro group in **1a**, while only 7% deuterium incorporation (see the doublet at δ 8.16) was detected at the α-position of the nitro group.





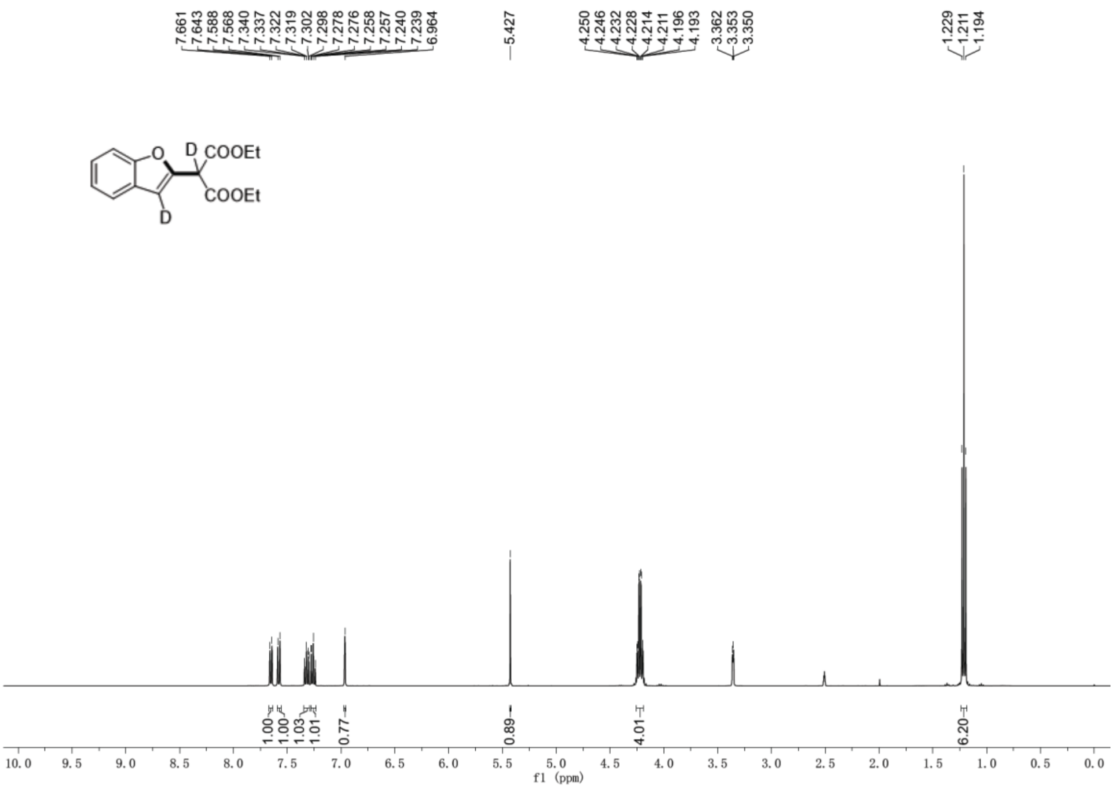
The mixture of 2-hydroxy-β-nitrostyrene **1a** (0.1 mmol, 1 equiv), diazo compound **2a** (1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (1.0 equiv) and CD_3OD (20.0 equiv) in THF (0.5 mL) was stirred at 60 °C in an oil bath for 2 h without exclusion of air or moisture. Afterwards, the solvent was removed under reduced pressure, and the resulted mixture was purified by preparative TLC to afford the corresponding product **3aa**. The deuterium incorporation was analyzed by ^{1}H-NMR. The result showed 26% (see the singlet at δ 6.96) deuteration at the C_3-position of benzofuran skeleton and 17% (see the multiplet at δ 2.07-2.05) deuteration at the methyl group.





1a **2c** **3ac**, 70%

The mixture of 2-hydroxy-β-nitrostyrene **1a** (0.1 mmol, 1 equiv), diazo compound **2c** (1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (1.0 equiv) and CD_3OD (20.0 equiv) in THF (0.5 mL) was stirred at 60 ºC in an oil bath for 2 h without exclusion of air or moisture. Afterwards, the solvent was removed under reduced pressure, and the resulted mixture was purified by preparative TLC to afford the corresponding product **3ac**. The deuterium incorporation was analyzed by ^{1}H-NMR. The result showed 23% (see the singlet at δ 6.96) deuteration at the C_3-position of benzofuran skeleton and 11% (see the singlet at δ 5.43) deuteration at the α position of the ester group.



IV. Bioactivity Assay and Molecular Docking

Identify the 2-functionalized benzofurans as tyrosinase inhibitors:

The mushroom tyrosinase inhibitory activity was determined by following the previously described method[S3] with slight modifications. Briefly, 168 μL of phosphate buffer (0.1 M, pH 6.8), 10 μL of mushroom tyrosinase (0.001 mg/mL, Sigma Chemical, USA) and 2 μL of the inhibitor solution were placed in the wells of a 96-well micro plate. After pre-incubation for 20 min at 37 ºC, 20 μL of 2.0 mg/mL L-DOPA (3,4-dihydroxyphenylalanine, Sigma Chemical, USA) was added and the enzyme activity was measured at 475 nm every 60 seconds for 180 seconds in a Microplate Reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Kojic acid was used as positive control and phosphate buffer was used as negative control. The extent of inhibition by the test compounds was expressed as the percentage of concentration necessary to achieve 50% inhibition (IC_{50}). The percentage of inhibition was calculated as follows: Inhibitory rate (%) = [Ac - At)/Ac] × 100. Ac is the absorbance of the negative control and At is the absorbance of the test compound. Each concentration was analyzed in three independent experiments run in triplicate. The IC_{50} values were determined by the data analysis software GraphPad Prism 8.

The results of the tested compounds are shown below:

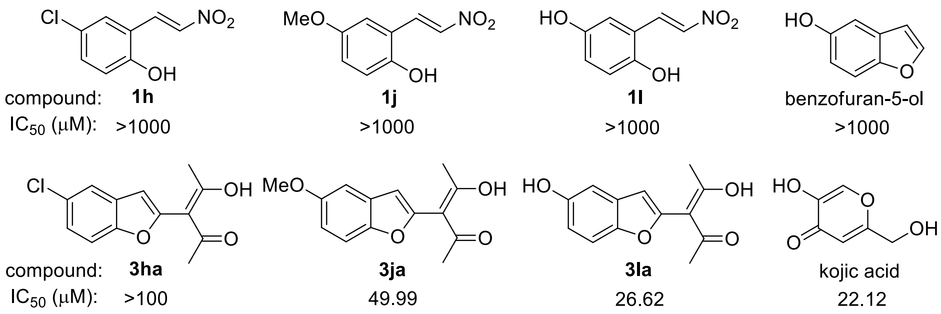


Table S2. Tyrosinase inhibiting activity assay for selected compounds

compound tyrosinase activity concentration	**3ha**	**3ja**	**3la**	**kojic acid**
100 μM	1.0776	0.1450	0.2355	0.1125
50 μM	1.3225	0.2735	0.4717	0.2677
25 μM	1.2735	0.6163	0.5588	0.4819
12.5 μM	1.3388	0.7011	0.7673	0.6250
6.25 μM	1.3714	0.8223	0.8236	0.7714
3.125 μM	1.4041	0.8836	0.9018	1.1102
1.5625 μM	1.4328	0.9469	1.0776	1.3714
IC_{50} (μM)	>100	49.99	26.62	22.12

Molecular docking between tyrosinase and compound 3la:

Molecular docking was performed on the most potent compound **3la** to explore the probable interaction model of the target compounds and the mushroom tyrosinase (PDB ID:2Y9X) active site. The most potent compound **3la** was prepared by Prepare Ligands (Discovery studio 2019) in their neutral form and their conformation optimized in the CHARMm force field. The protein structure was prepared by using one of the eight monomers from the PDB entry, and using the model of Prepara Protein (Discovery studio 2019) for adding missing residues, hydrogen atoms as well as removing water molecules and spectator ions. Then their conformation optimized in the CHARMm force field. The search grid of binding site was identified as center_x: -10.021, center_y: -28.823, and center_z: -43.596 with Radius value of 10. Molecular modeling simulations were performed with CDOCKER protocol (Discovery studio 2019), reporting the 10 top ranked poses for each ligand and generation of figure was done by PyMOL (Schrödinger).

V. X-Ray Crystallographic Data

X-ray crystallographic data of compound 3ma:

Crystal Data for $C_{14}H_{14}O_4$ (M =246.25 g/mol): monoclinic, space group C2/c (no. 15), a = 21.7556(19) Å, b = 7.6524(7) Å, c = 15.3789(14) Å, β = 108.227(10)°, V = 2431.9(4) Å^3, Z = 8, T = 149.97(10) K, μ(Mo Kα) = 0.099 mm^{-1}, $Dcalc$ = 1.345 g/cm^3, 5692 reflections measured (5.578° ≤ 2Θ ≤ 49.99°), 2142 unique (R_{int} = 0.0213, R_{sigma} = 0.0287) which were used in all calculations. The final R_1 was 0.0404 (I > 2σ(I)) and wR_2 was 0.1010 (all data).

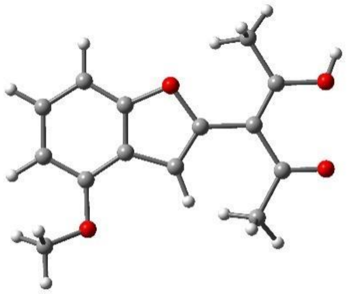


Table S3. Crystal data and structure refinement for ZHM632

Identification code	ZHM632
Empirical formula	$C_{14}H_{14}O_4$
Formula weight	246.25
Temperature/K	149.97(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	21.7556(19)
b/Å	7.6524(7)
c/Å	15.3789(14)
α/°	90

β/°	108.227(10)
γ/°	90
Volume/Å^3	2431.9(4)
Z	8
ρ_{calc}g/cm^3	1.345
μ/mm^{-1}	0.099
F(000)	1040.0
Crystal size/mm^3	0.14 × 0.13 × 0.12
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.578 to 49.99
Index ranges	$-25 \le h \le 23$, $-7 \le k \le 9$, $-18 \le l \le 18$
Reflections collected	5692
Independent reflections	2142 [R_{int} = 0.0213, R_{sigma} = 0.0287]
Data/restraints/parameters	2142/0/167
Goodness-of-fit on F^2	1.088
Final R indexes [I>=2σ (I)]	R_1 = 0.0404, wR_2 = 0.0966
Final R indexes [all data]	R_1 = 0.0485, wR_2 = 0.1010
Largest diff. peak/hole / e Å^{-3}	0.22/-0.23

VI. References

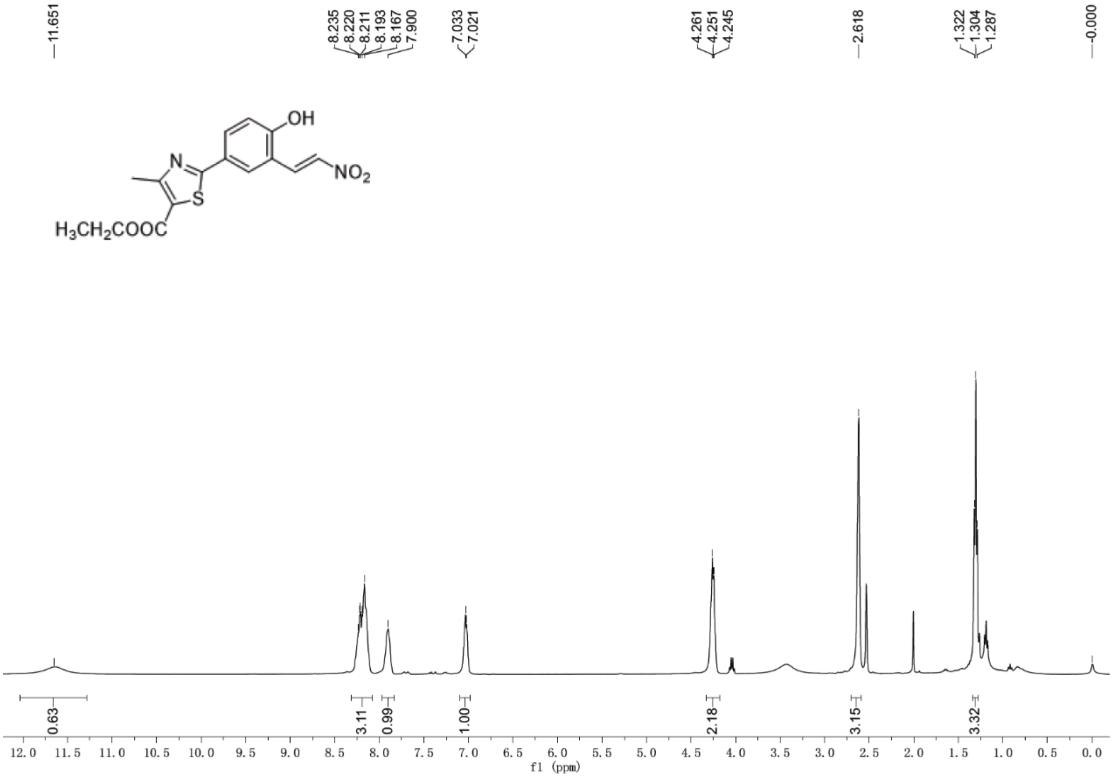
[S1] (a) L. Song, X. Tian, C. Han, M. Amanpur, F. Rominger and A. S. K. Hashmi, *Org. Chem. Front.*, 2021, **8**, 3314; (b) Z. Jiang, J. Zhou, H. Zhu, H. Liu and Y. Zhou, *Org. Lett.*, 2021, **23**, 4406.

[S2] (a) H. Zhang, J. He, Y. Chen, C. Zhuang, C. Jiang, K. Xiao, Z. Su, X. Ren and T. Wang, *Angew. Chem. Int. Ed*, 2021, **60**, 19860; (b) Y. Liu, Y. Wang, H. Song, Z. Zhou and C. Tang, *Adv. Synth. Catal.*, 2013, **355**, 2544.

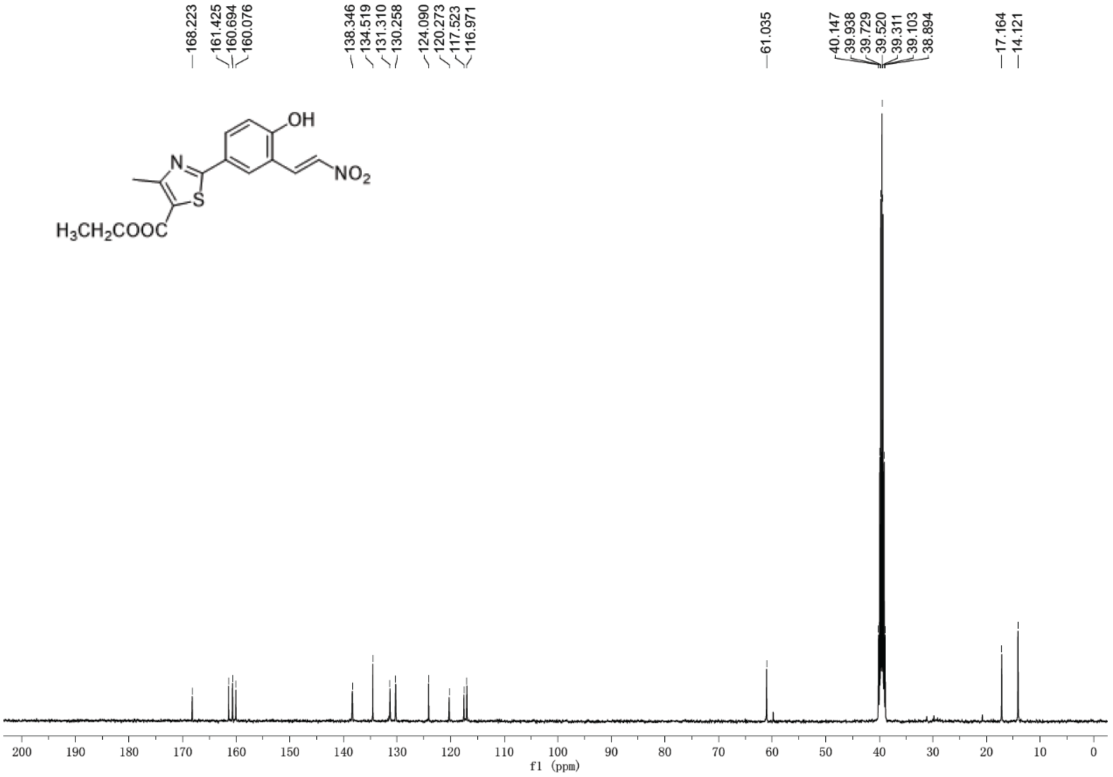
[S3] M. N. Mustafaa, A. Saeeda, P. A. Channara, F. A. Larika, M. Zain-ul abideena, G. Shabira, Q. Abbasc, M. Hassanb, H. Razab, S.-Y. Seob, *Bioorg. Chem.*, 2019, **90**, 103063.

VII. Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra

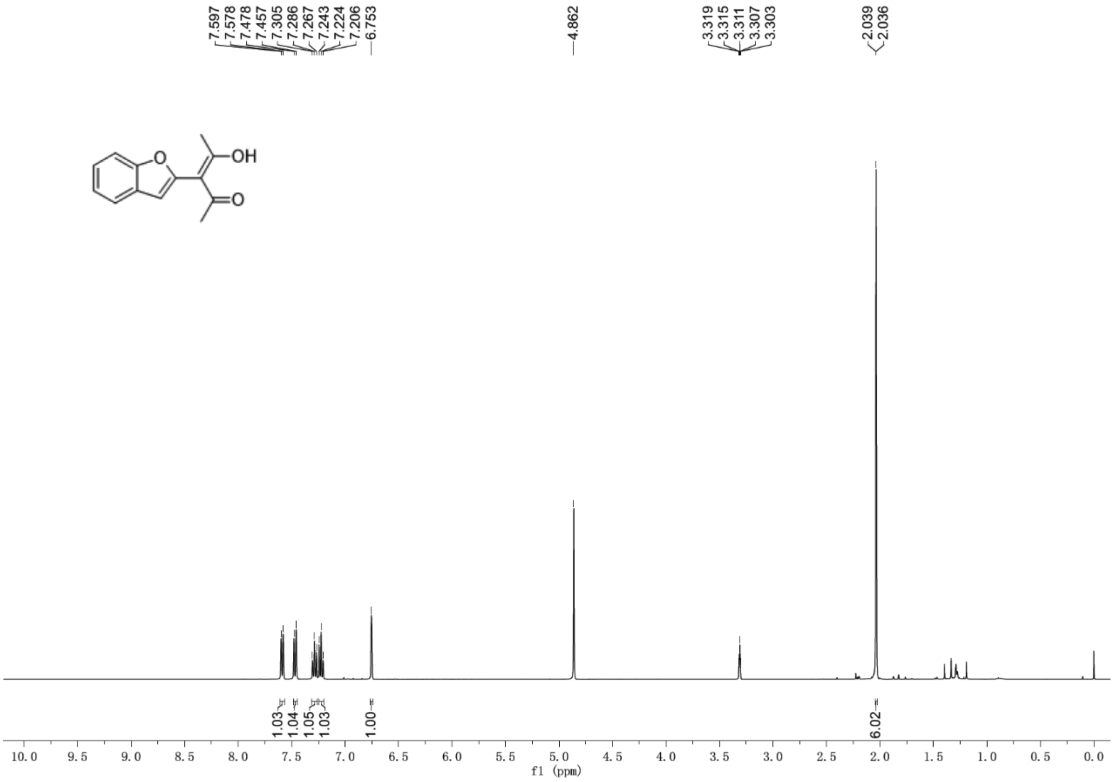
1o-^{1}H NMR (400 MHz, CDCl$_3$)



1o-^{13}C NMR (100 MHz, DMSO-*d*$_6$)



3aa-^{1}H NMR (400 MHz, CD$_3$OD)



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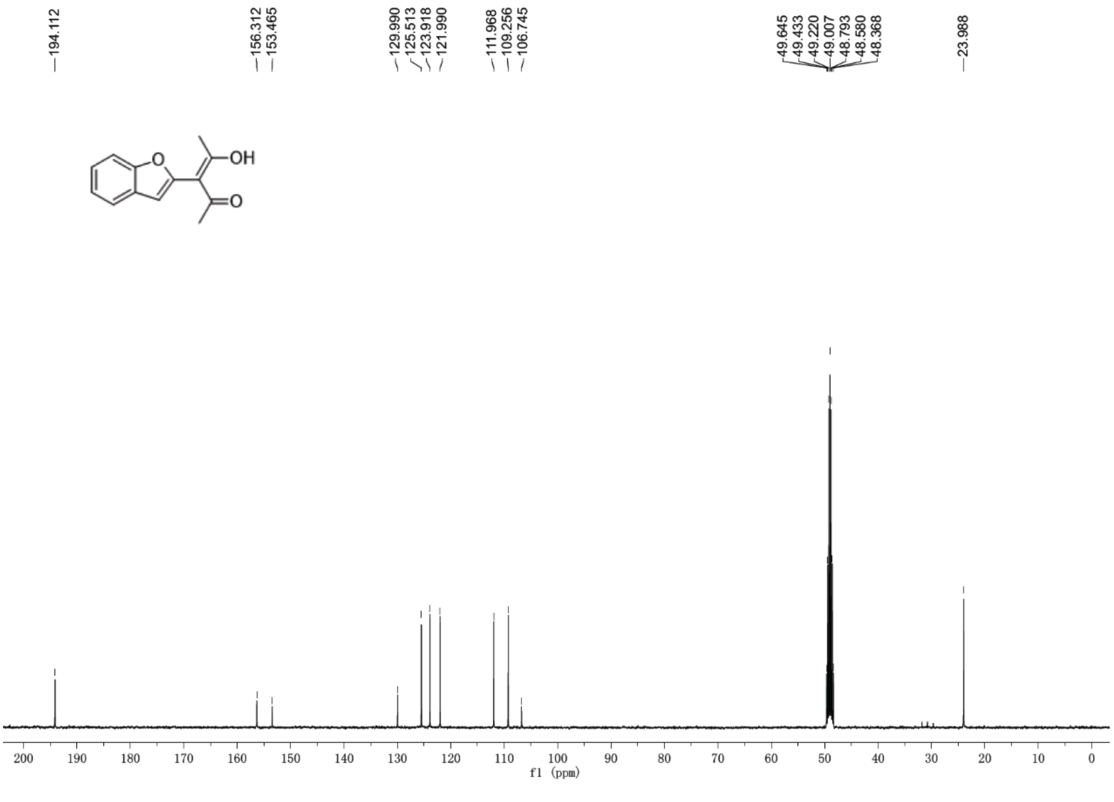

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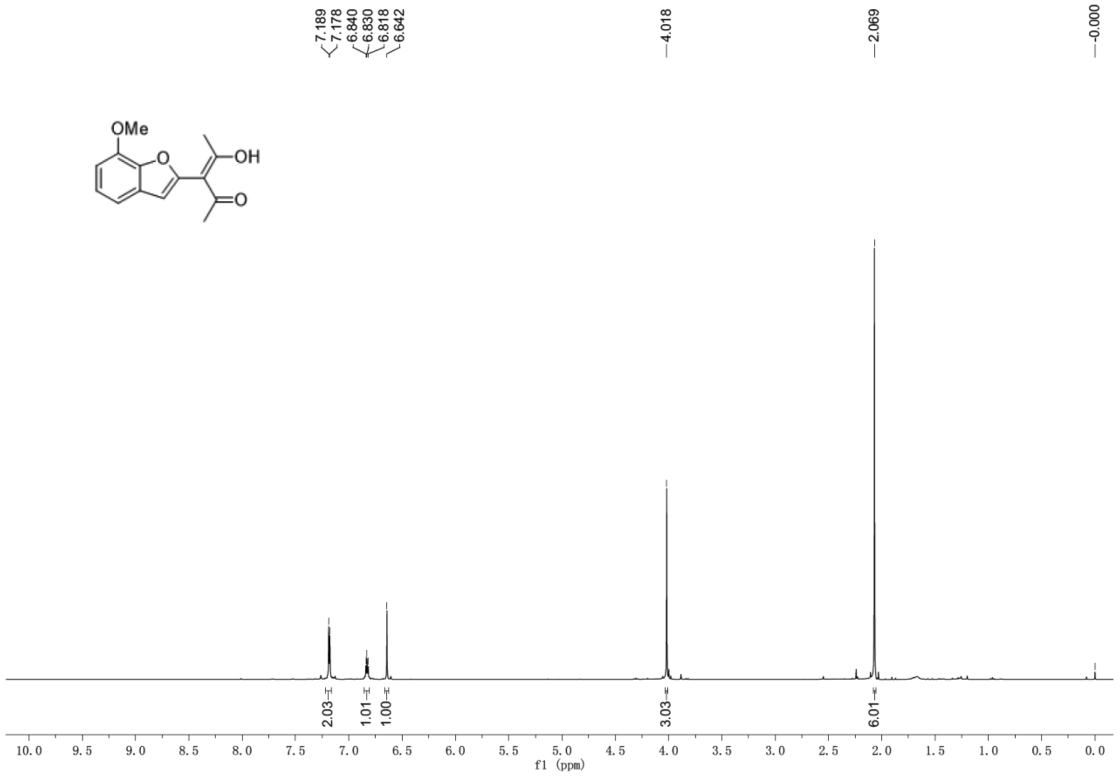

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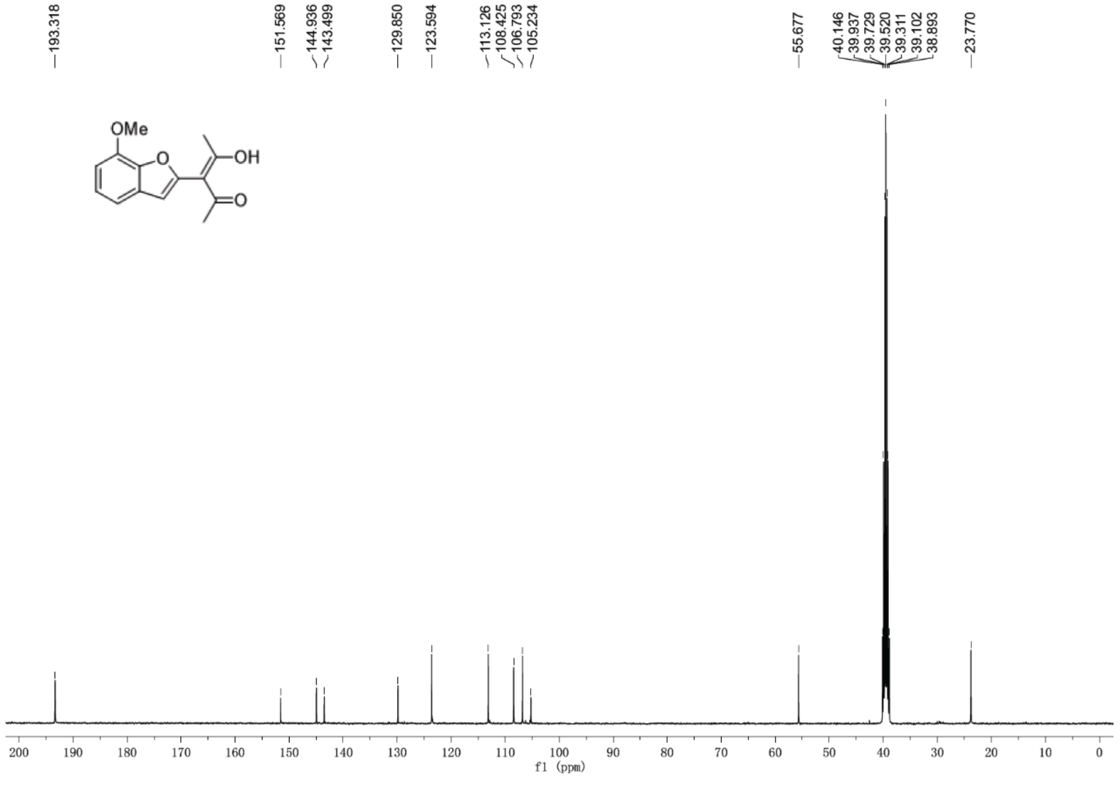

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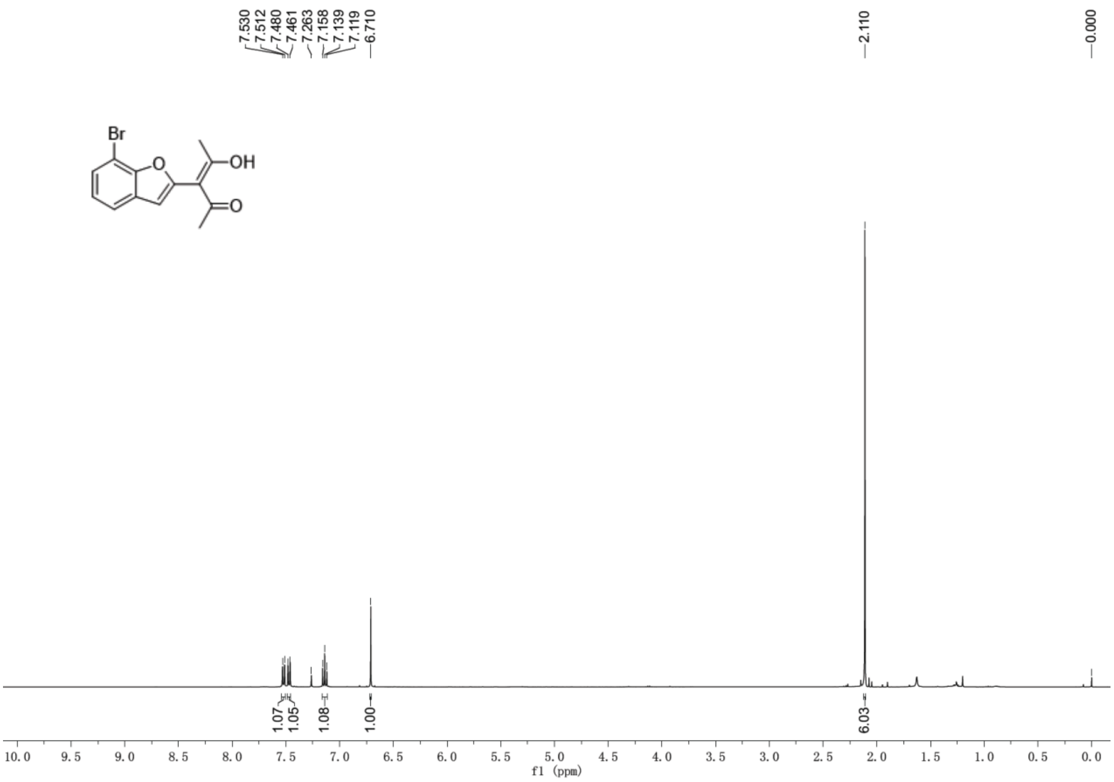

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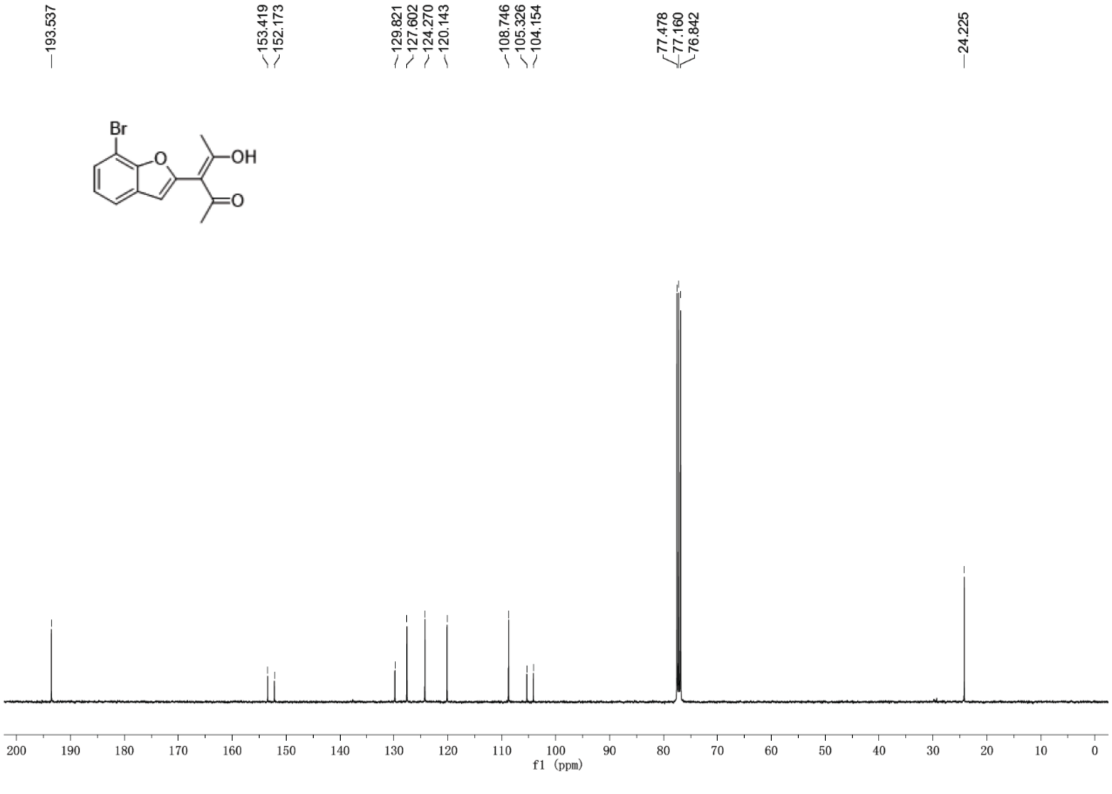

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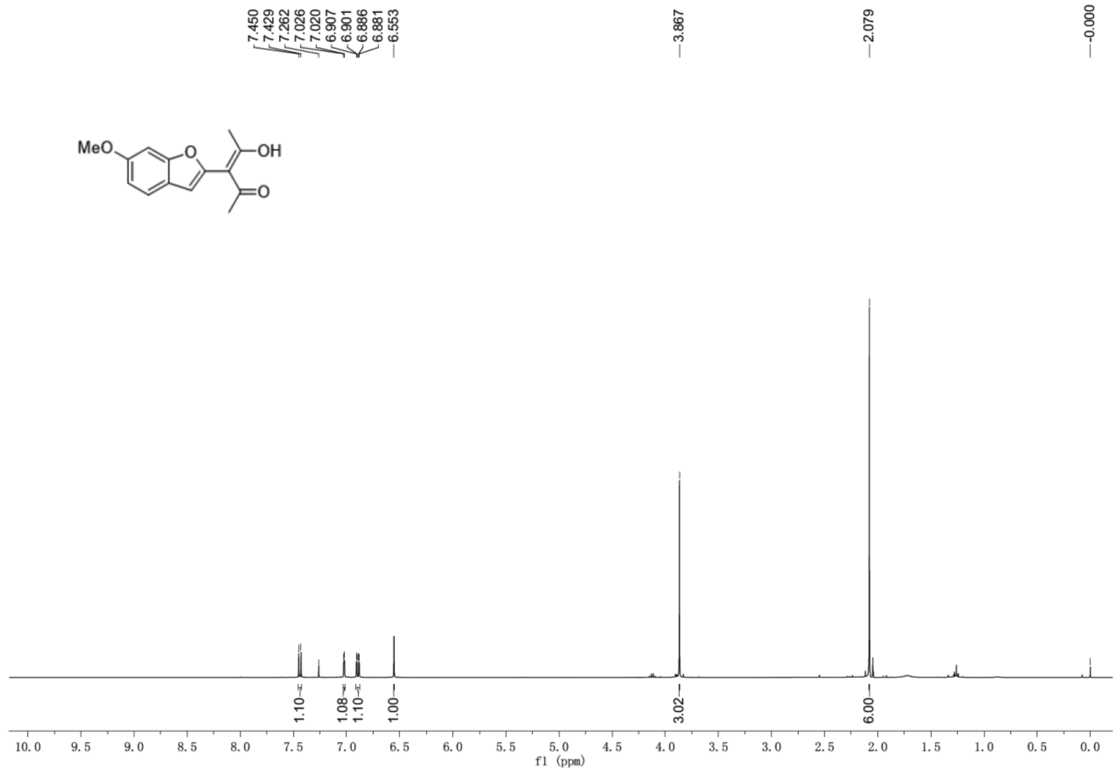

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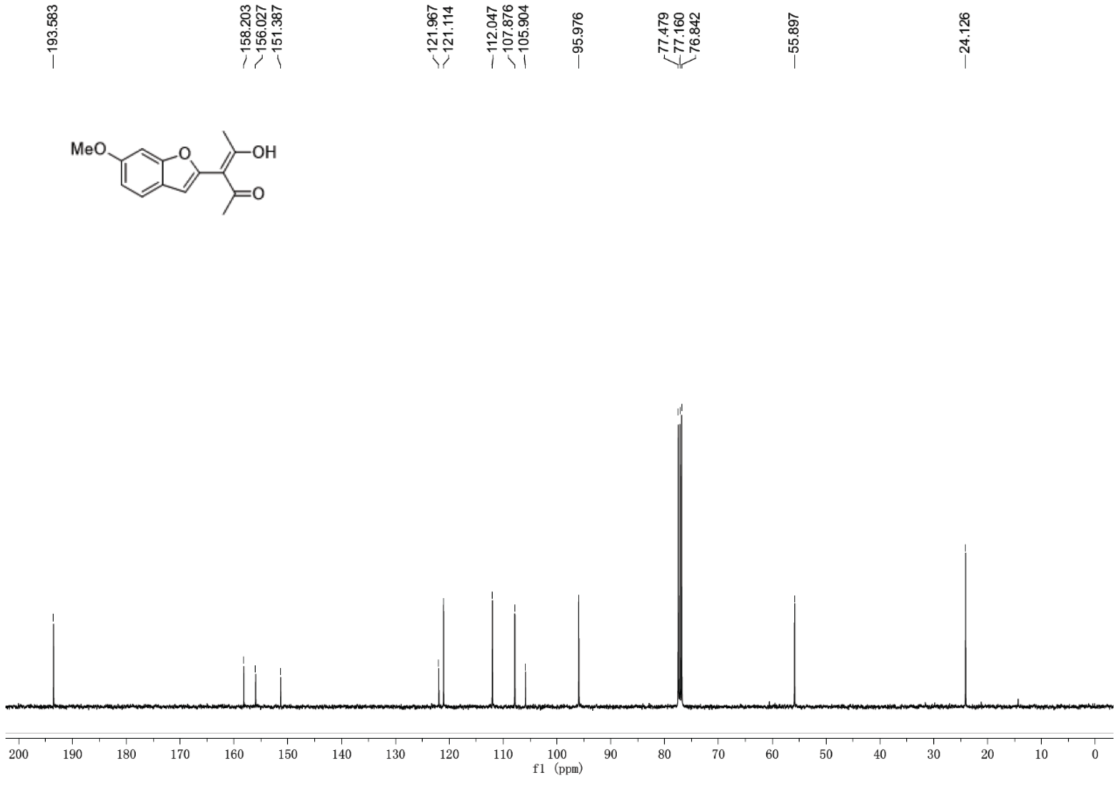

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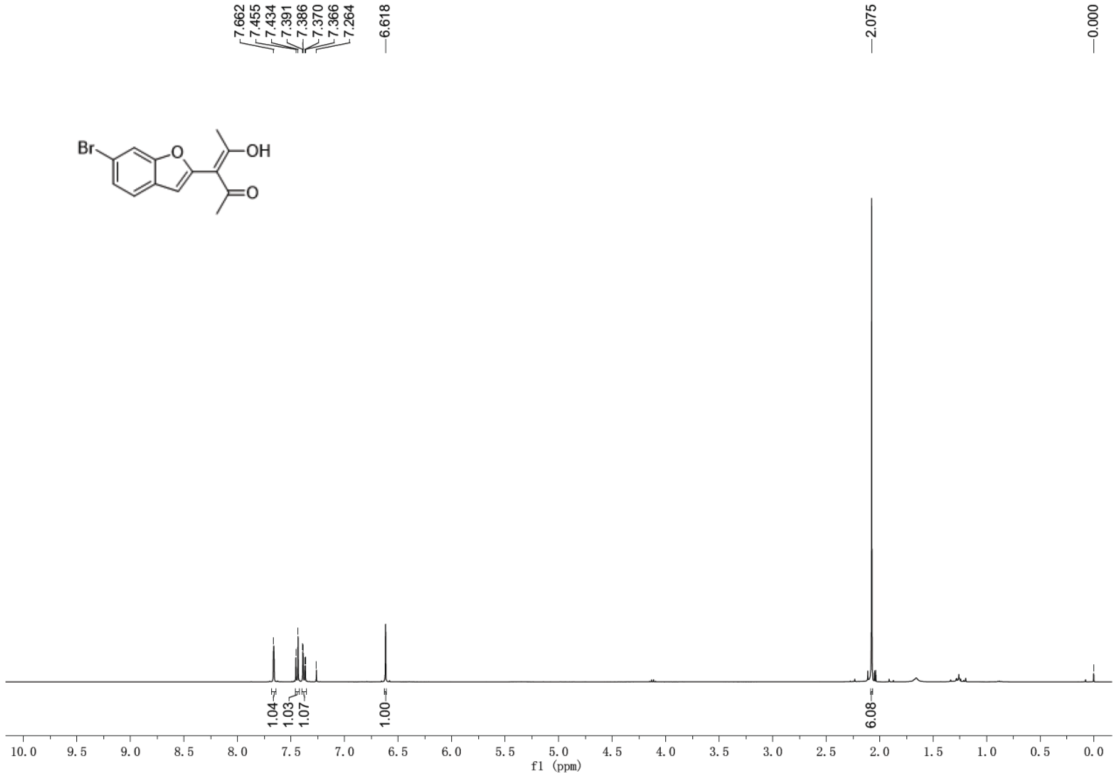

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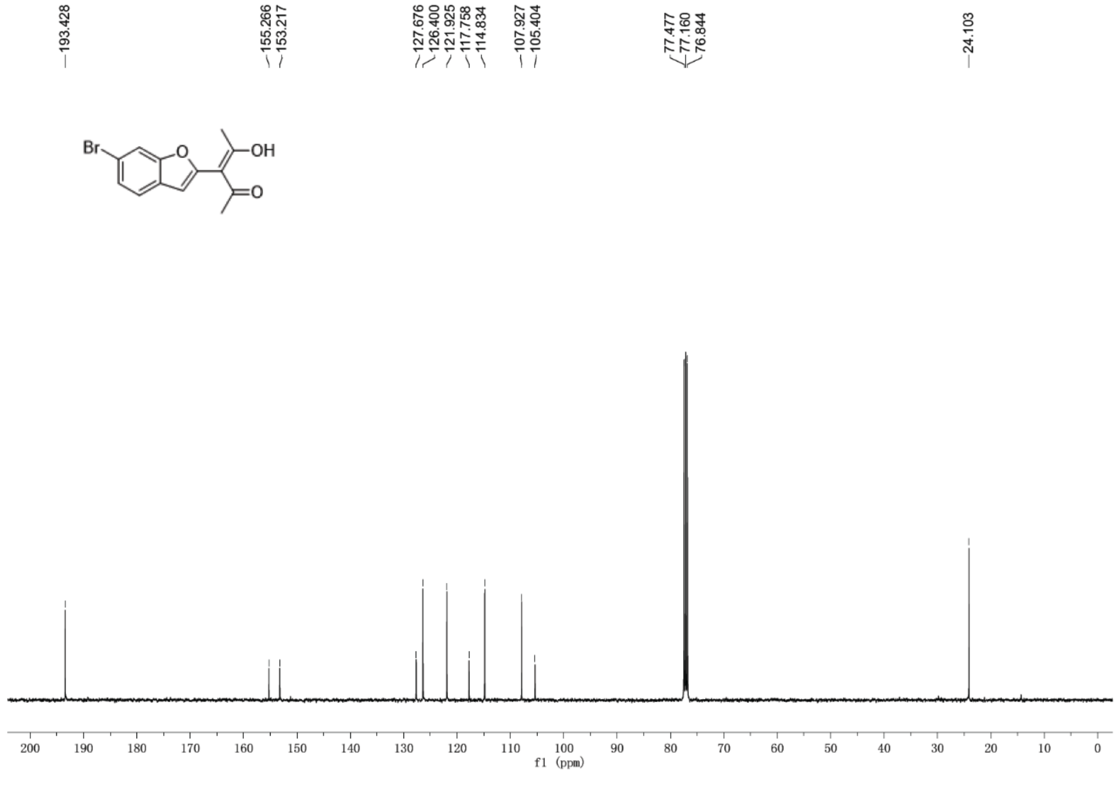

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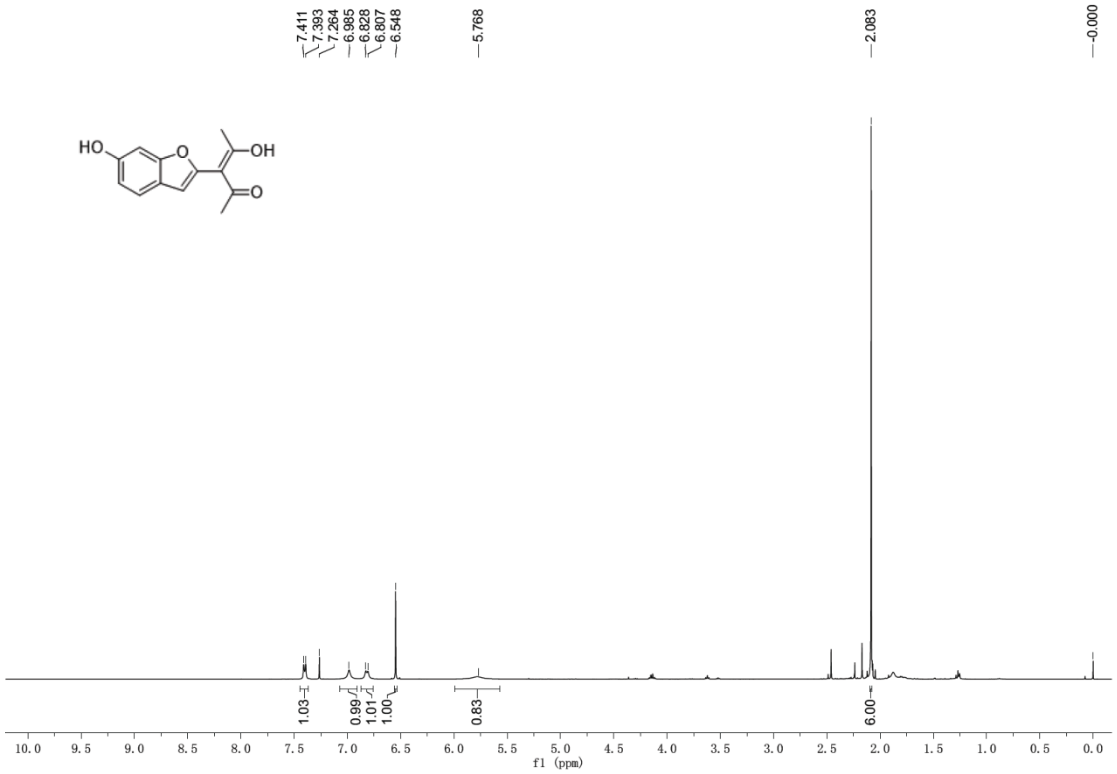

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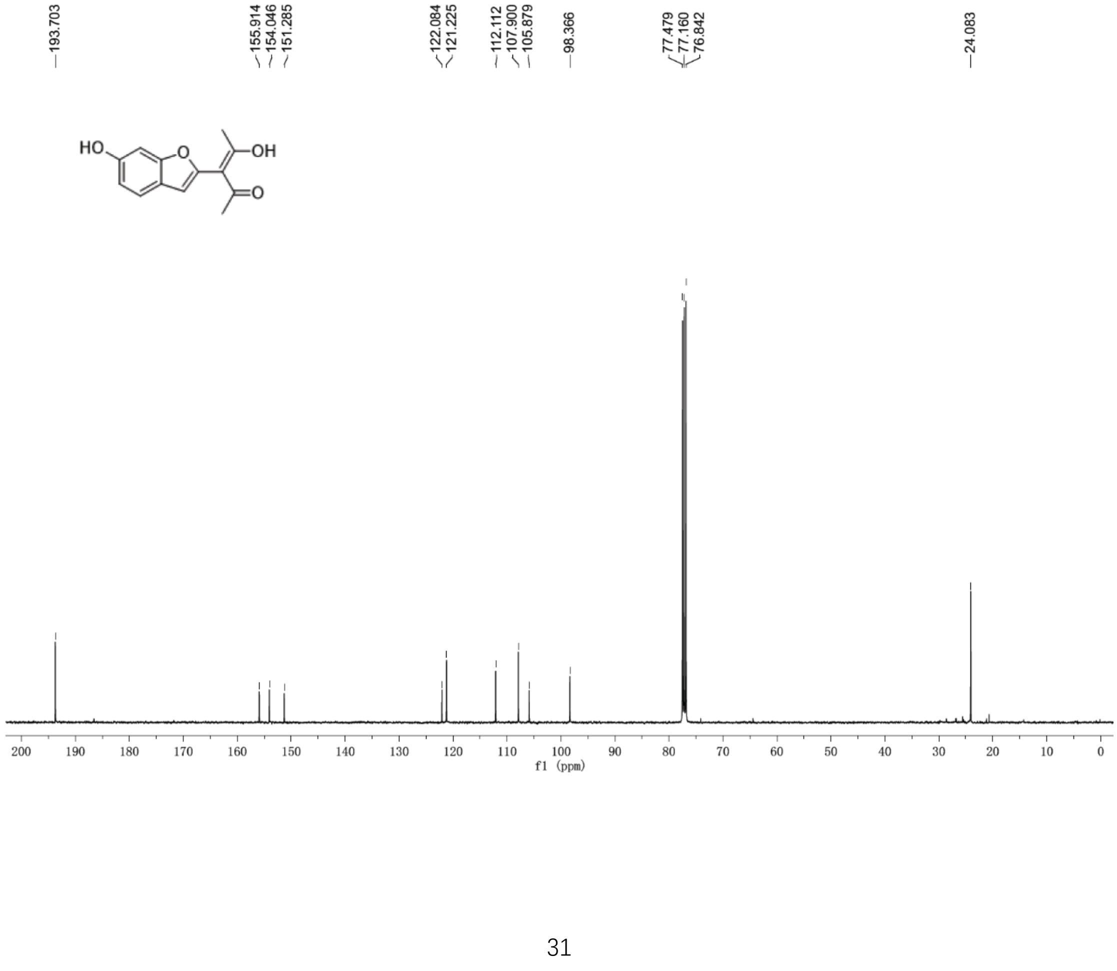

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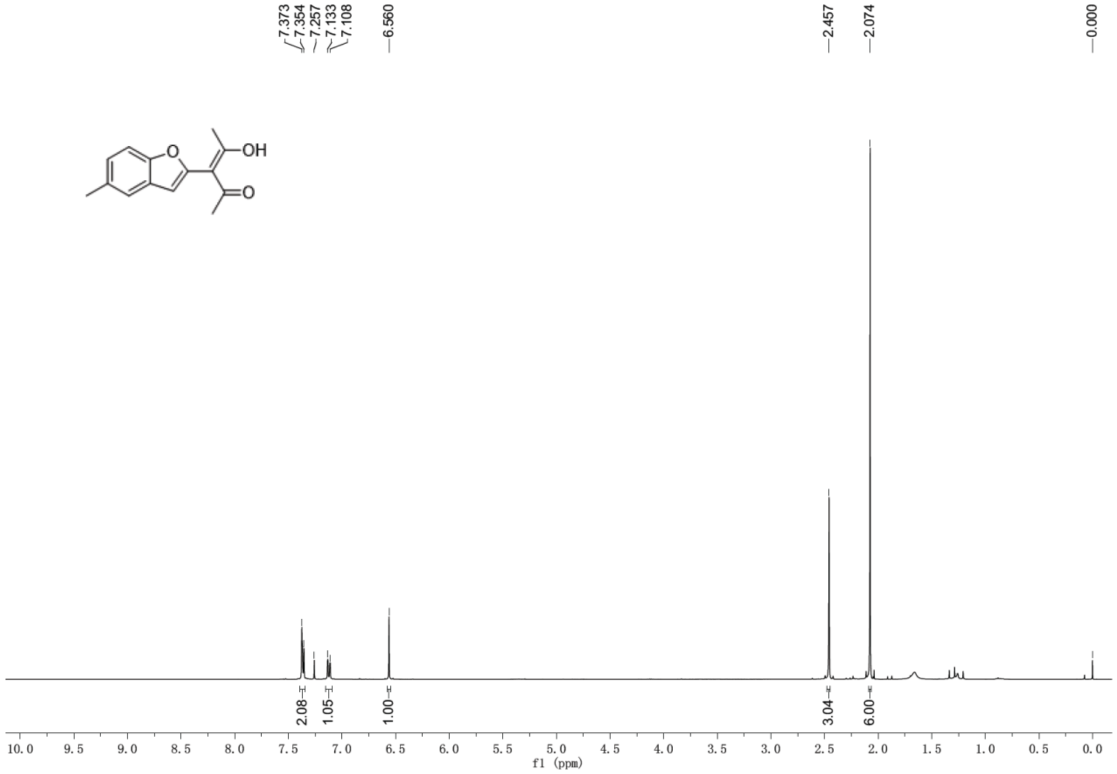

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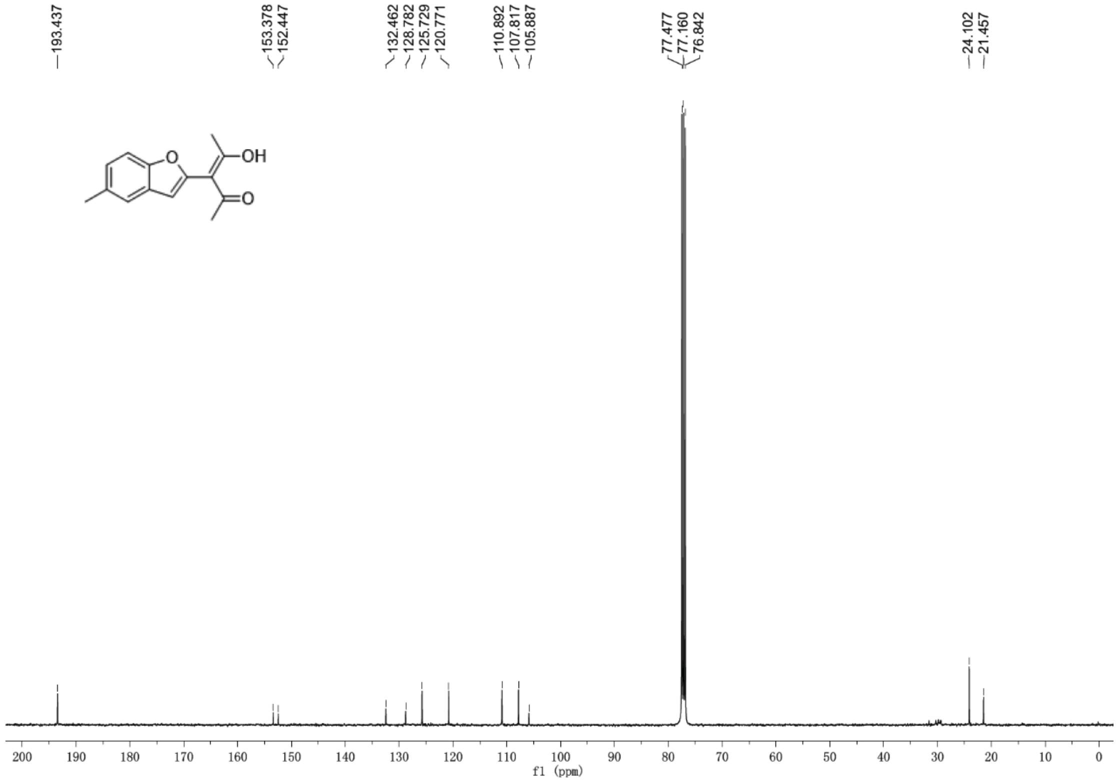

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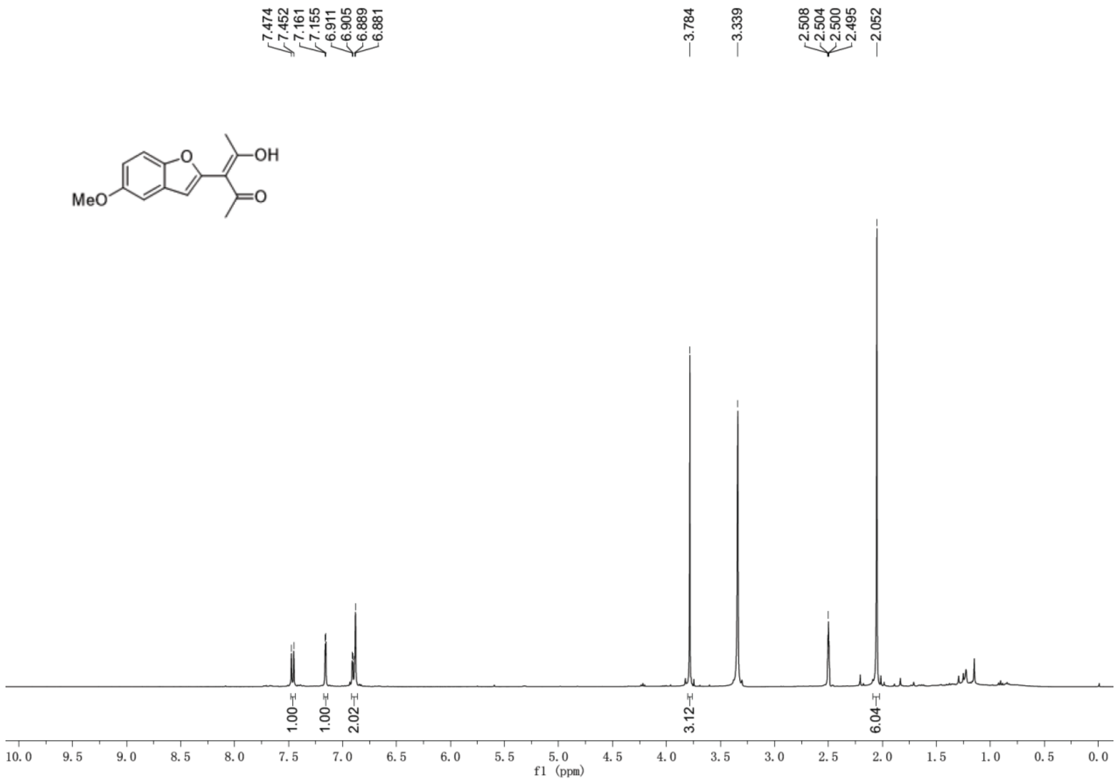

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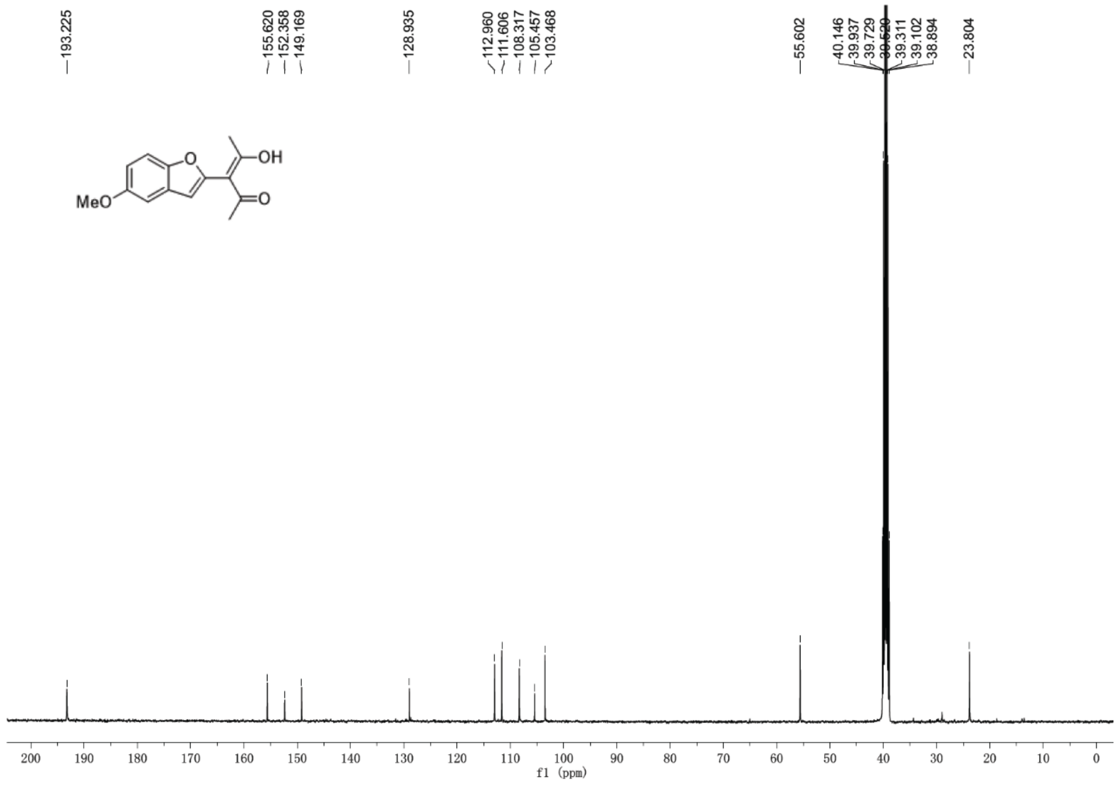

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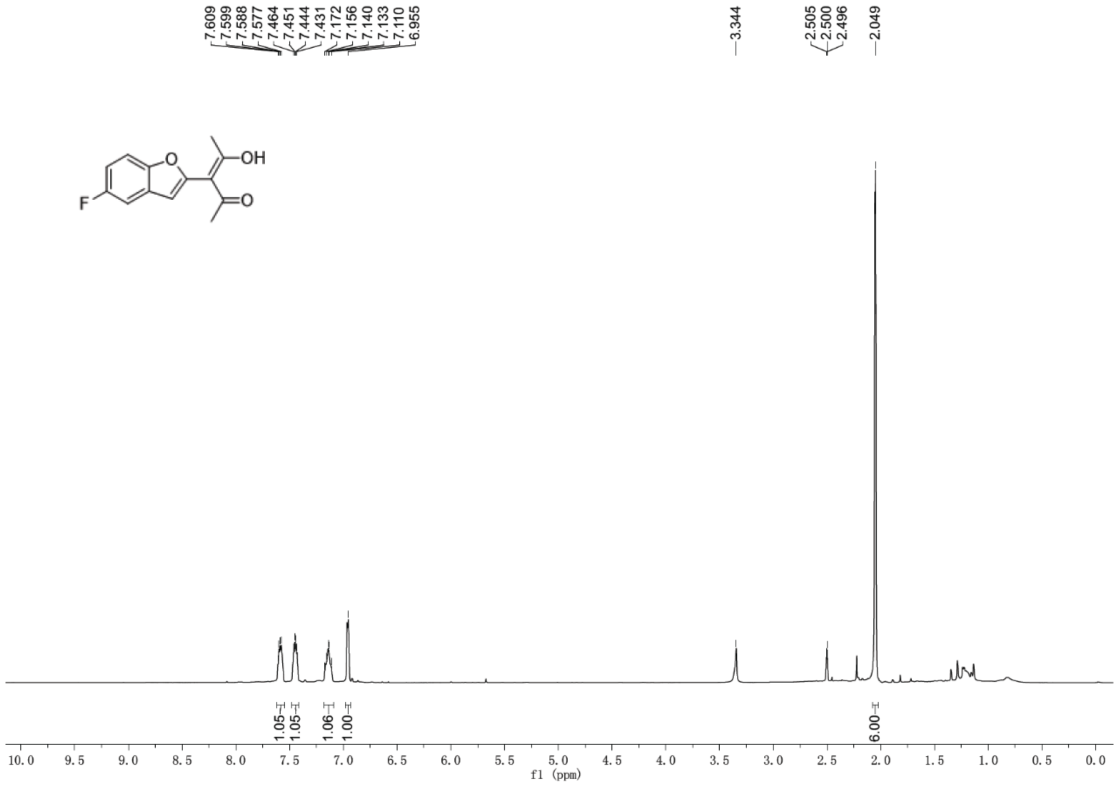

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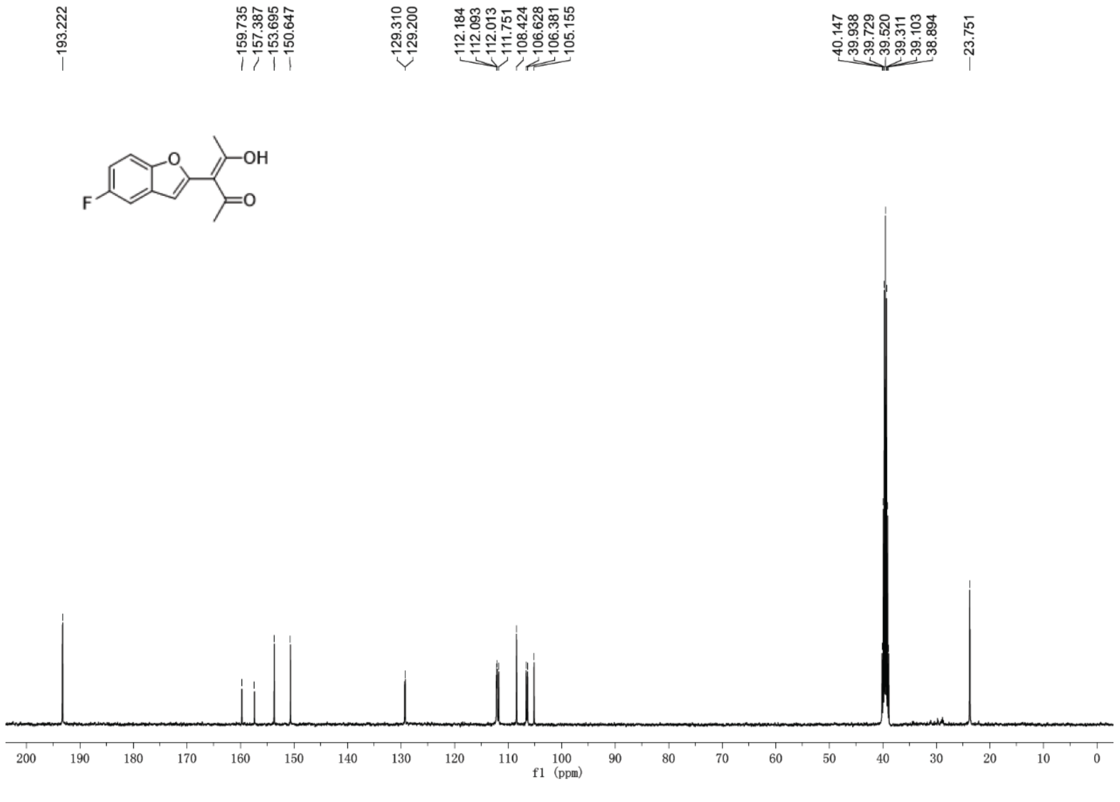

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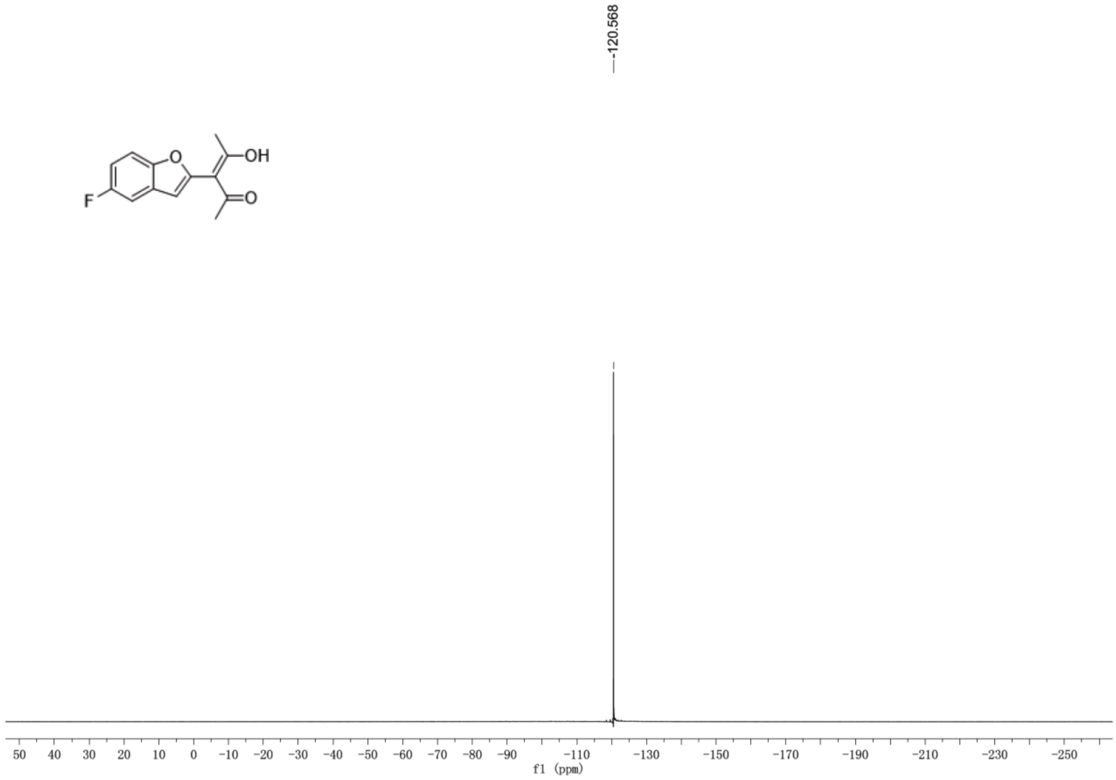

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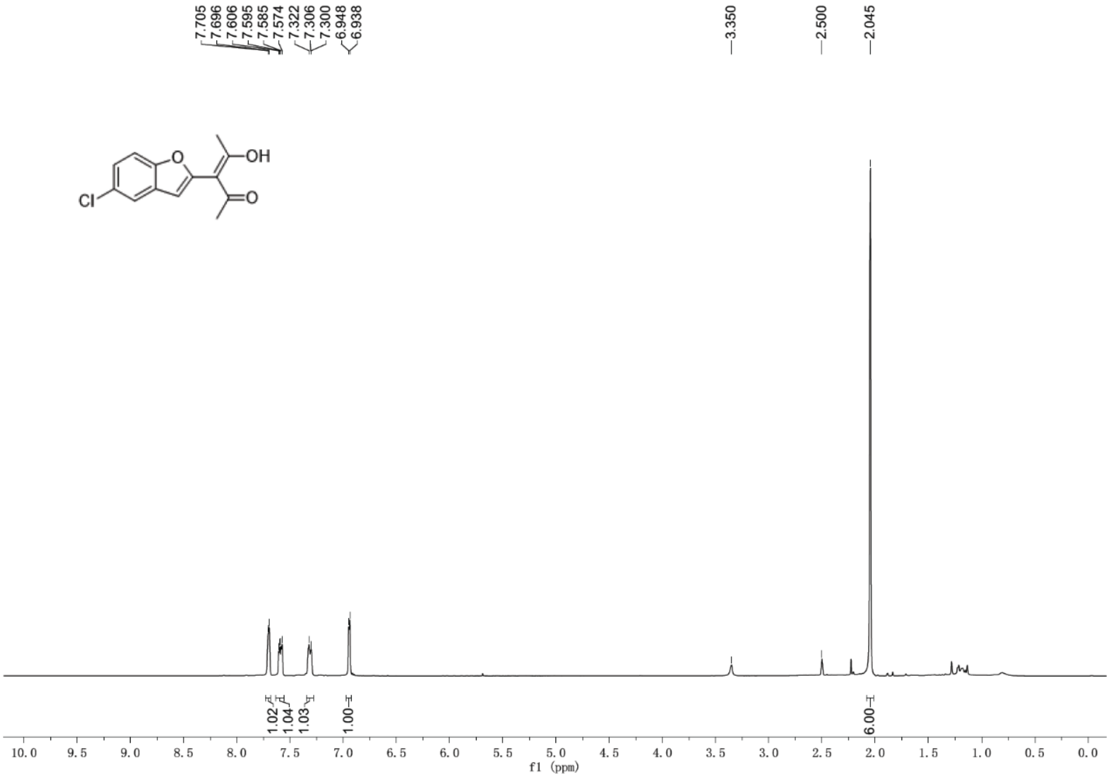

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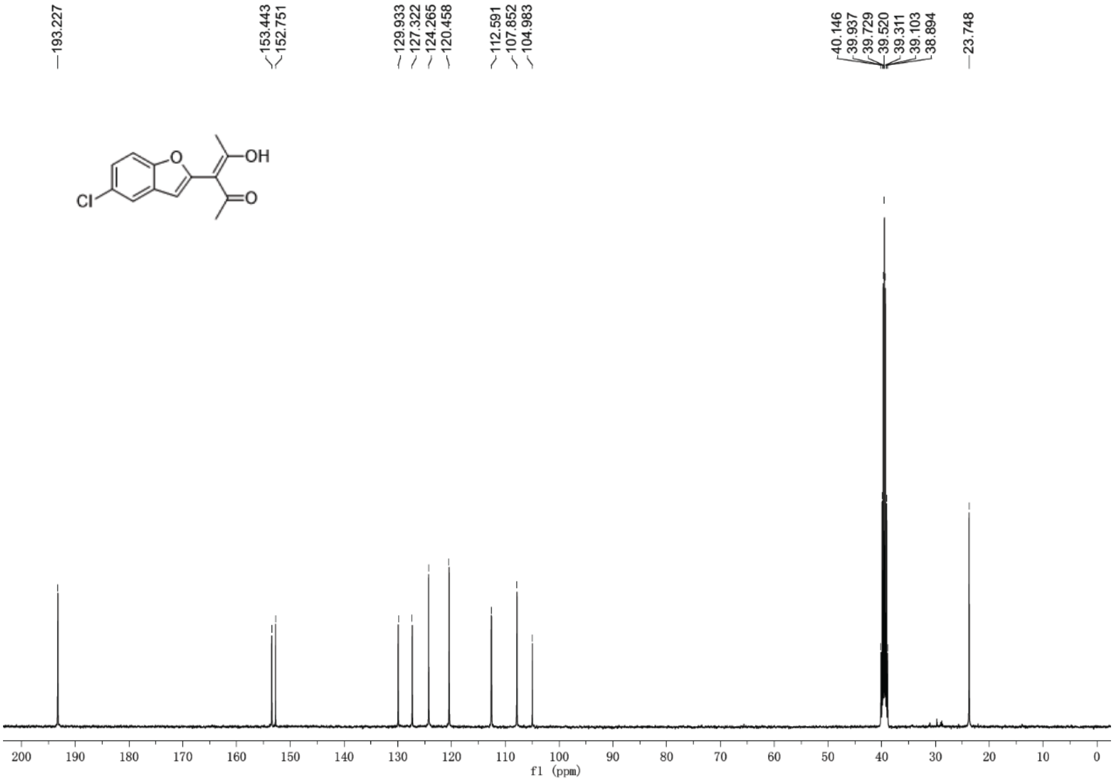

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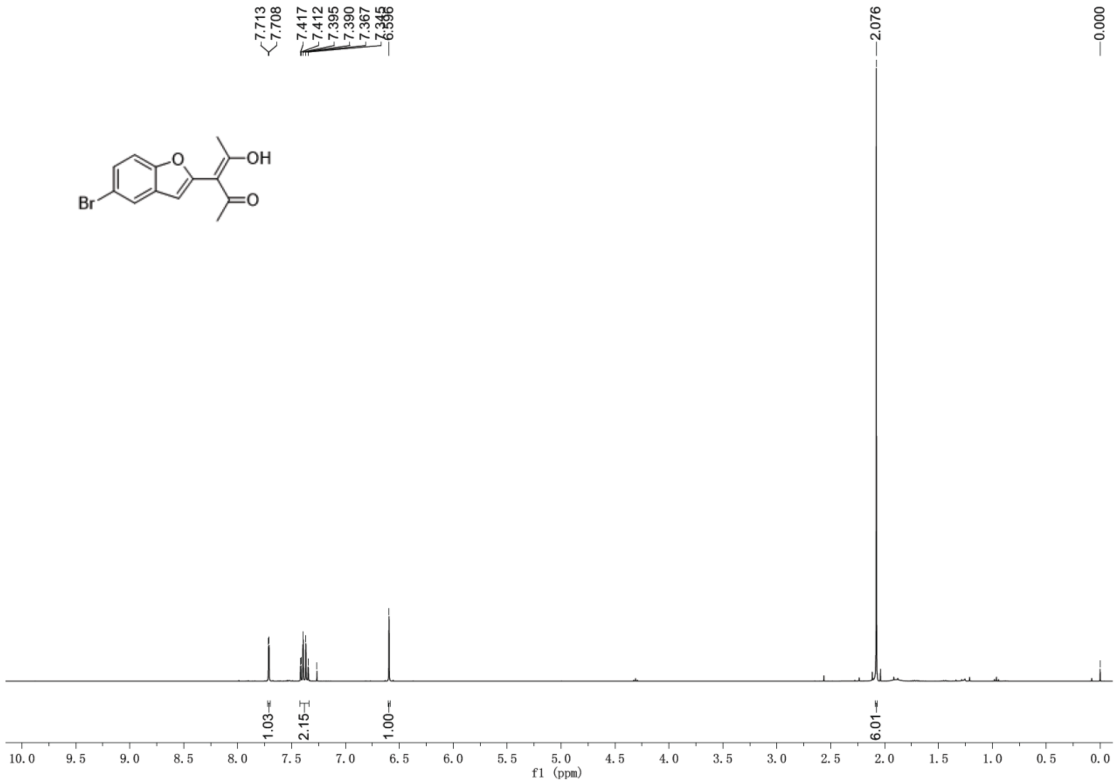

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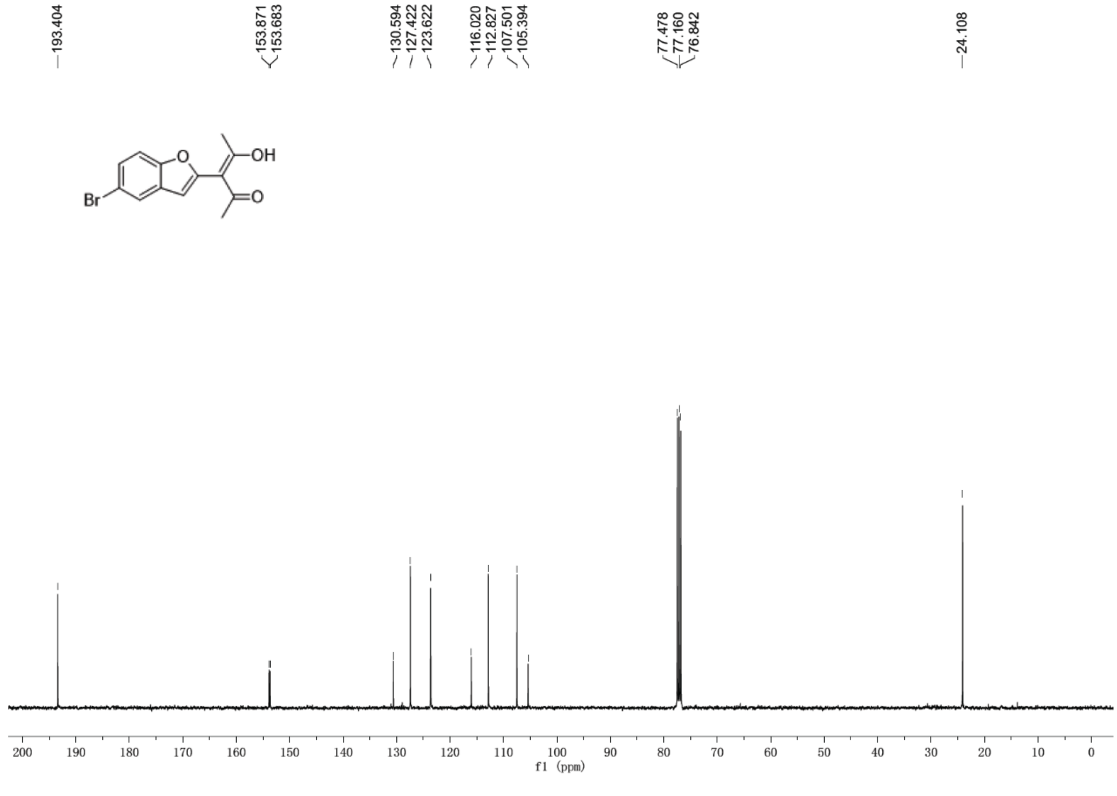

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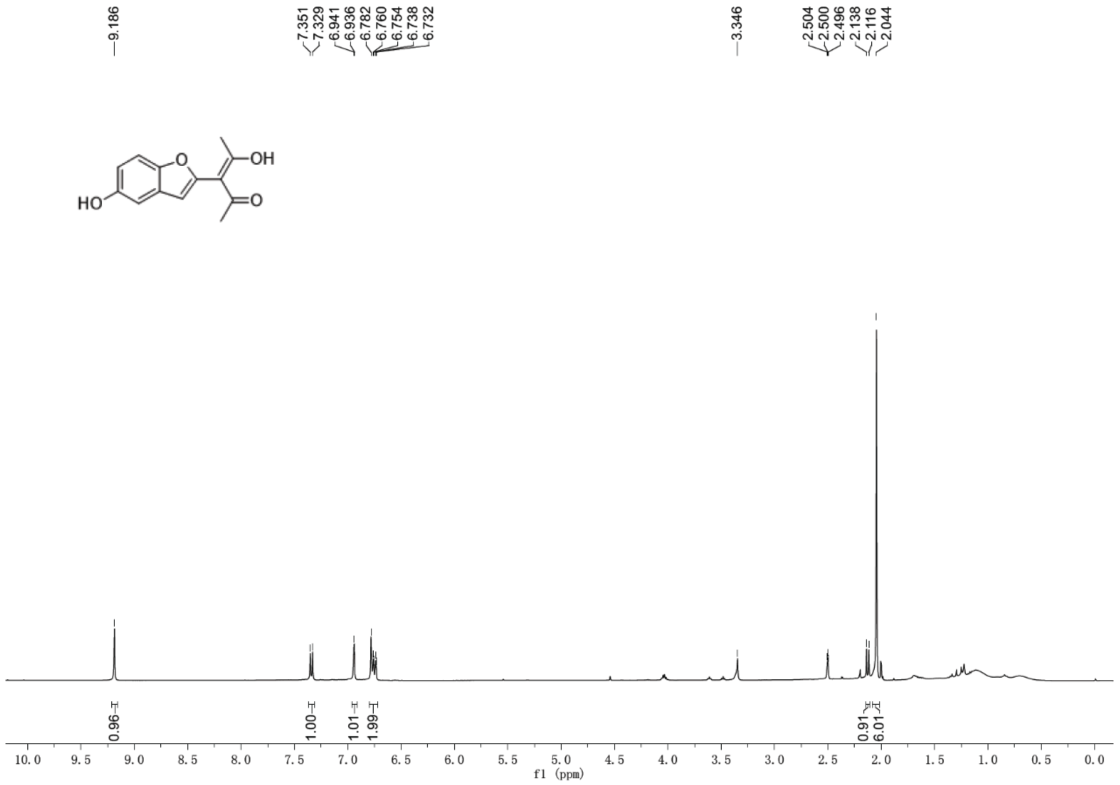

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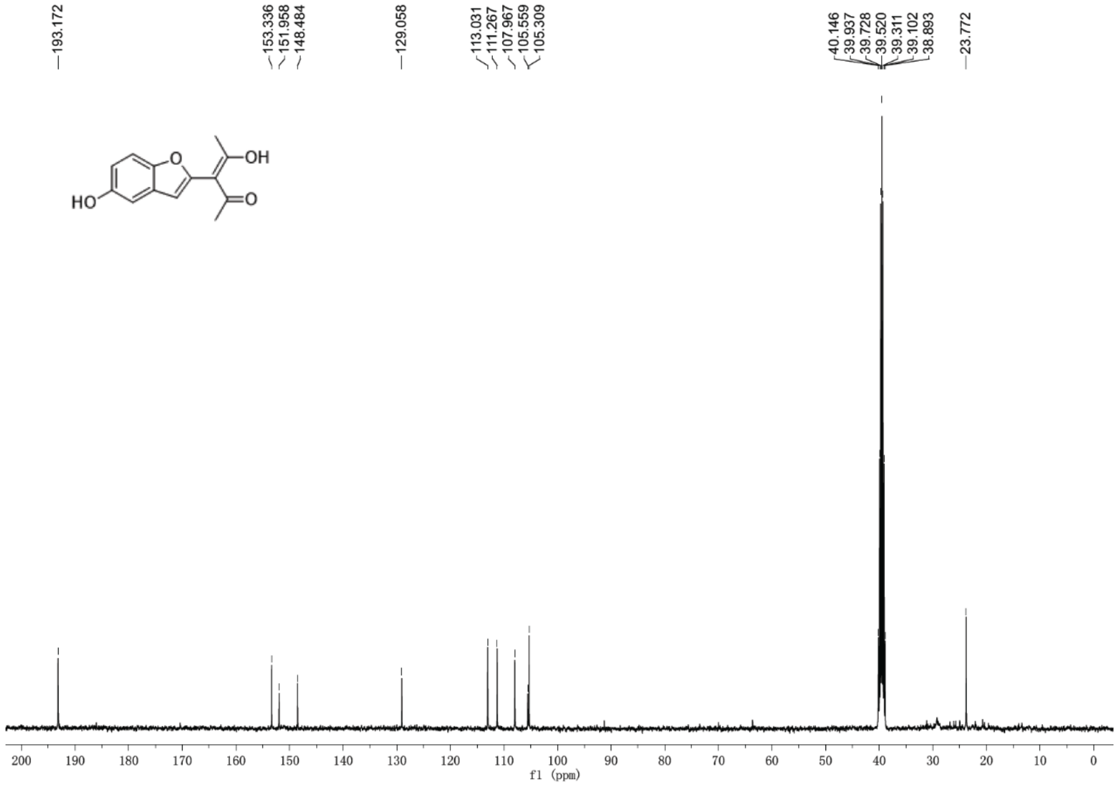

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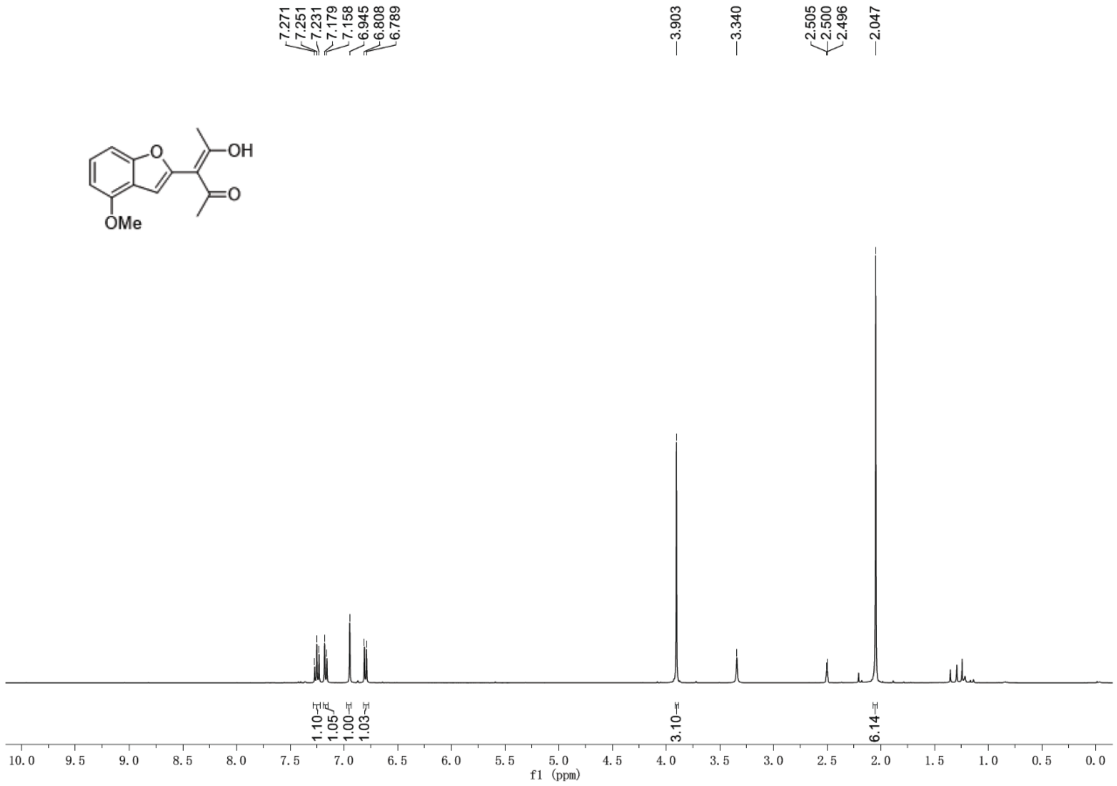

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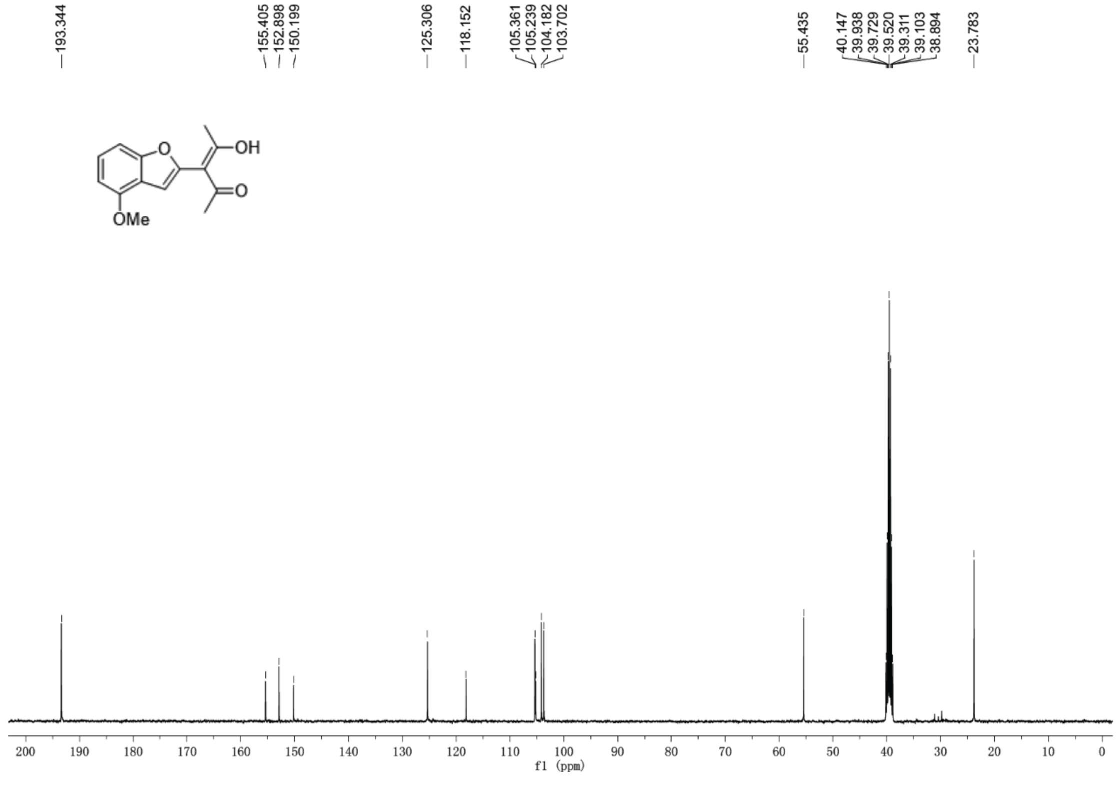

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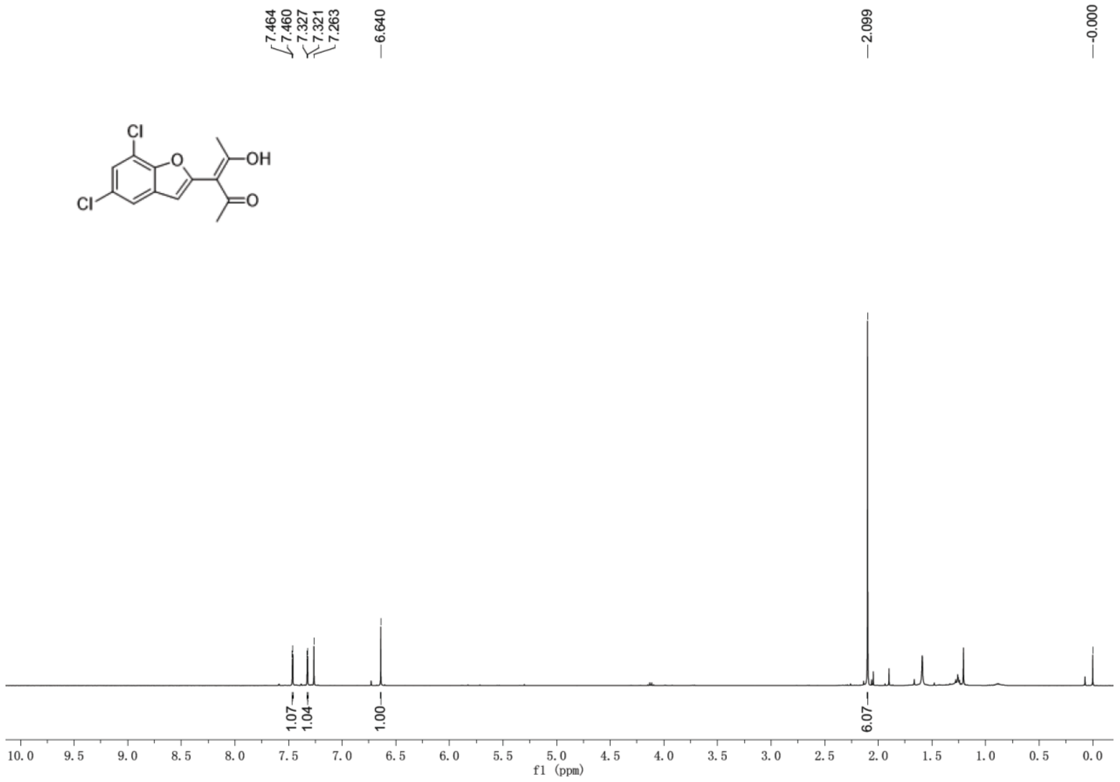

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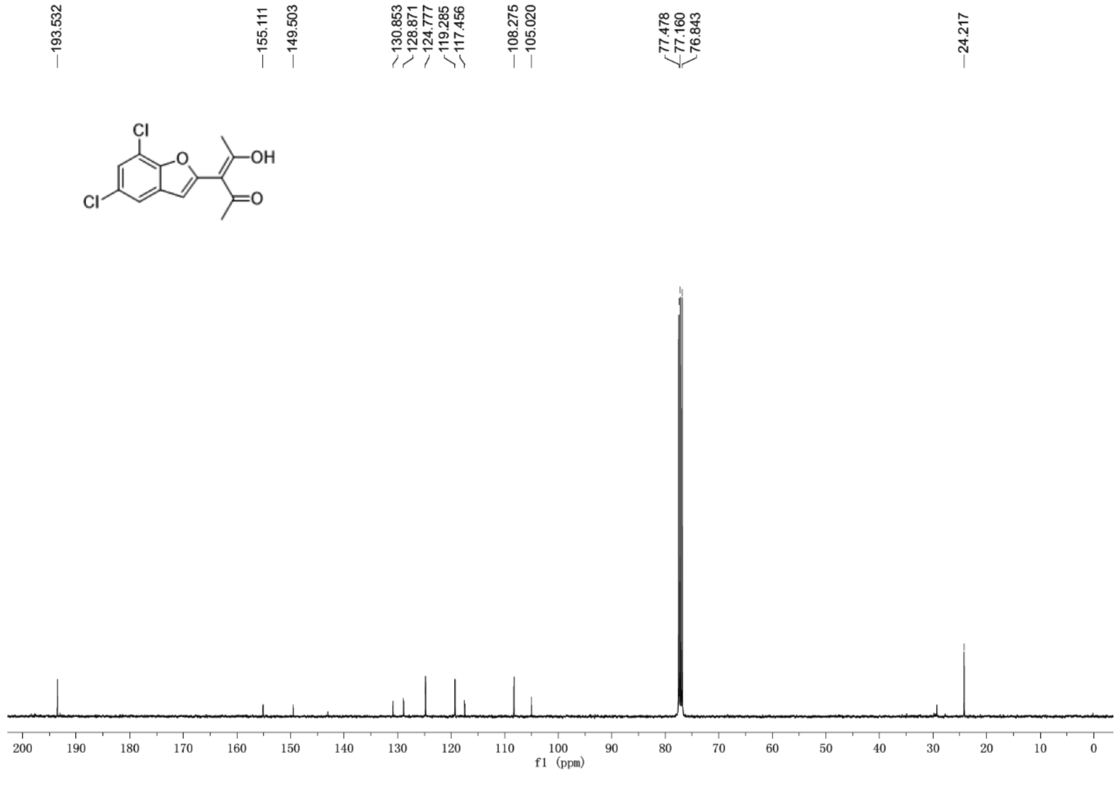

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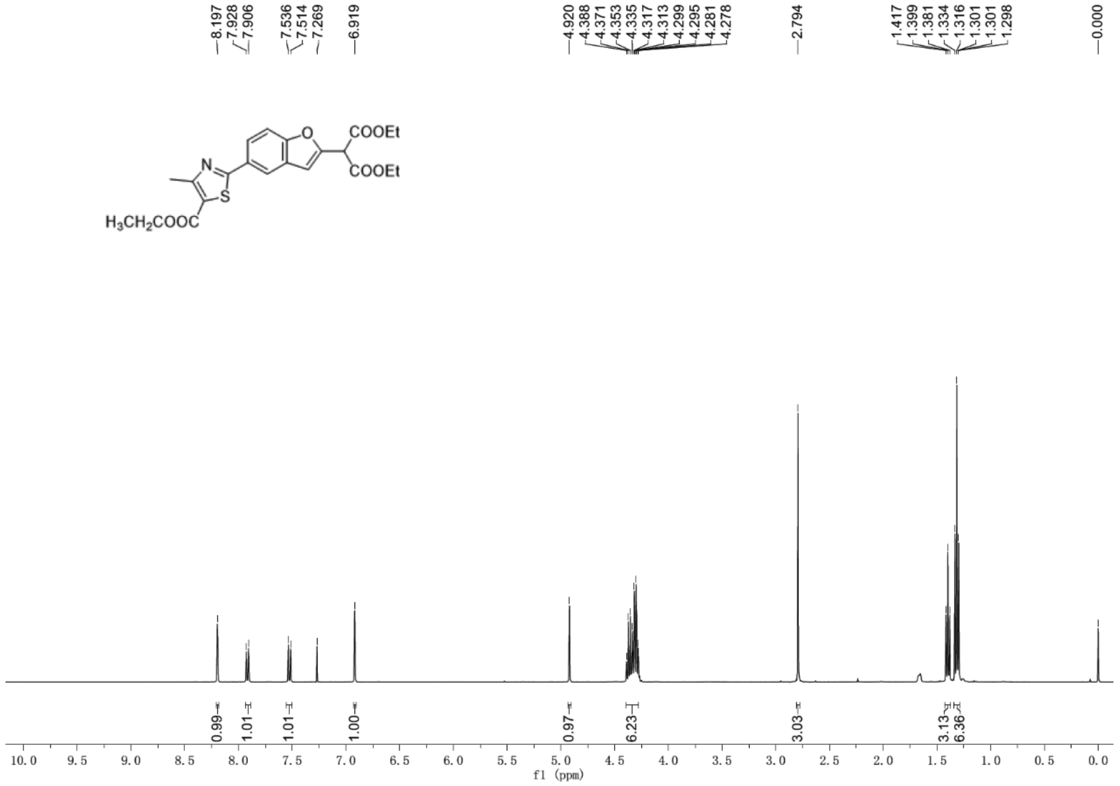

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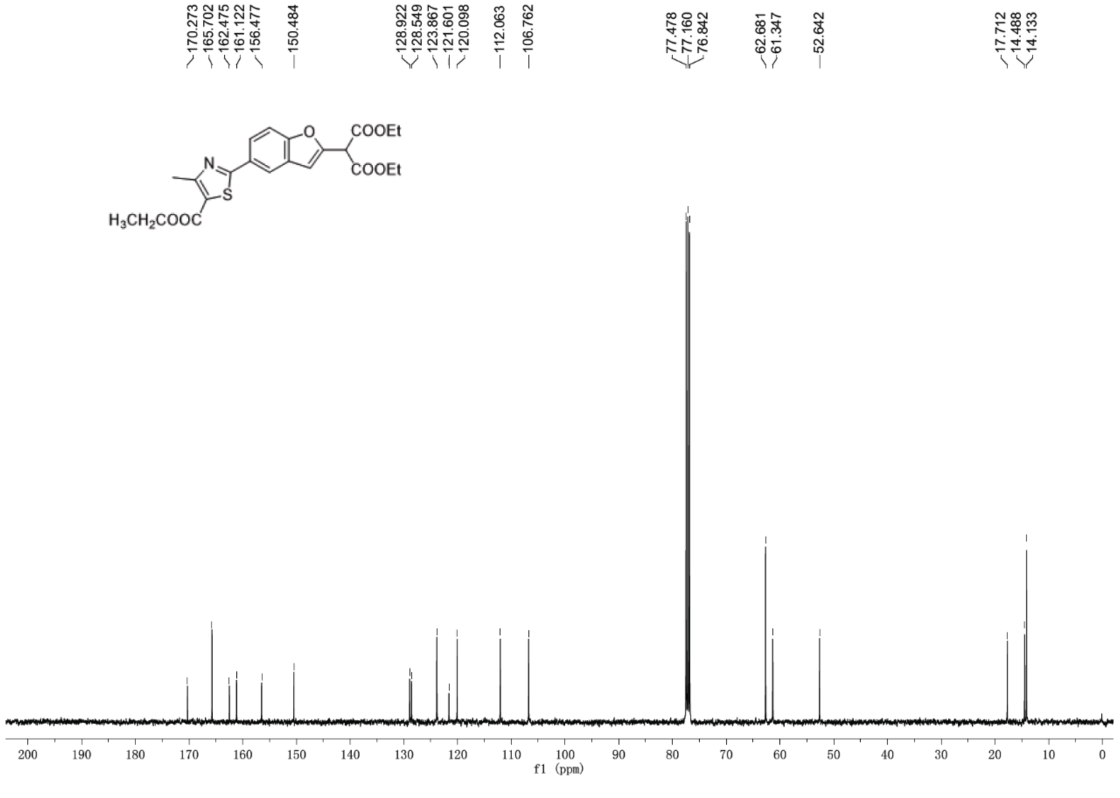

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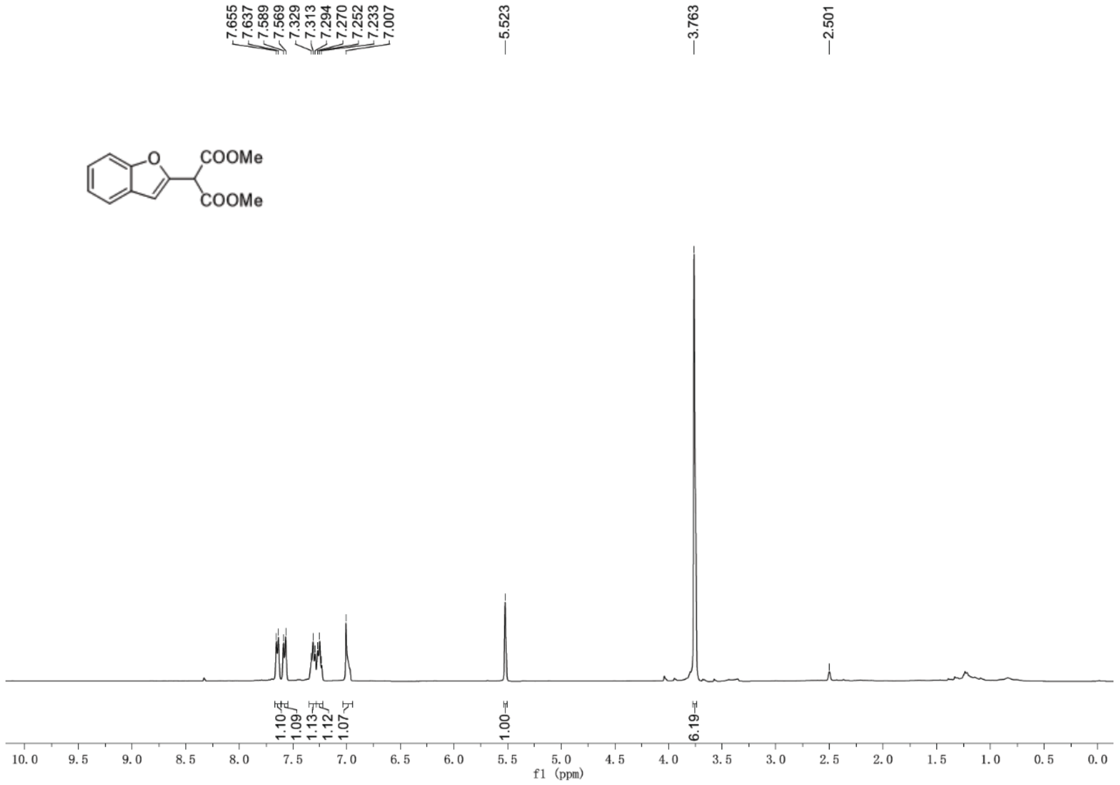

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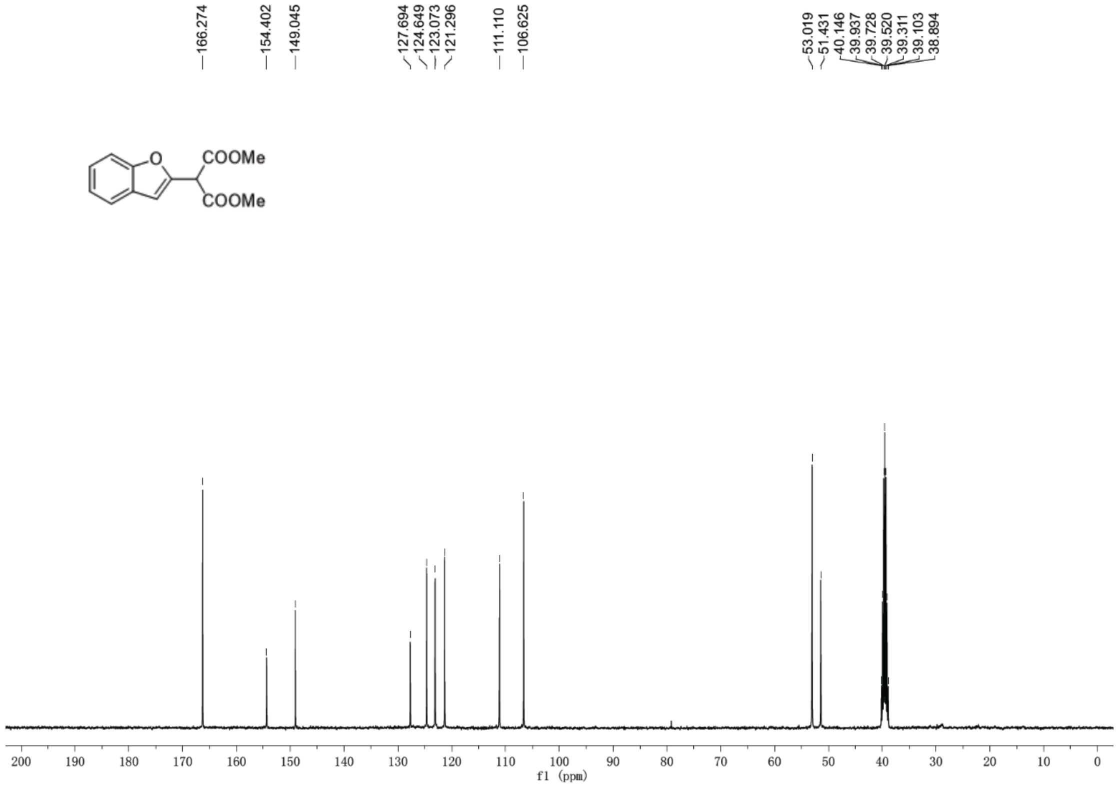

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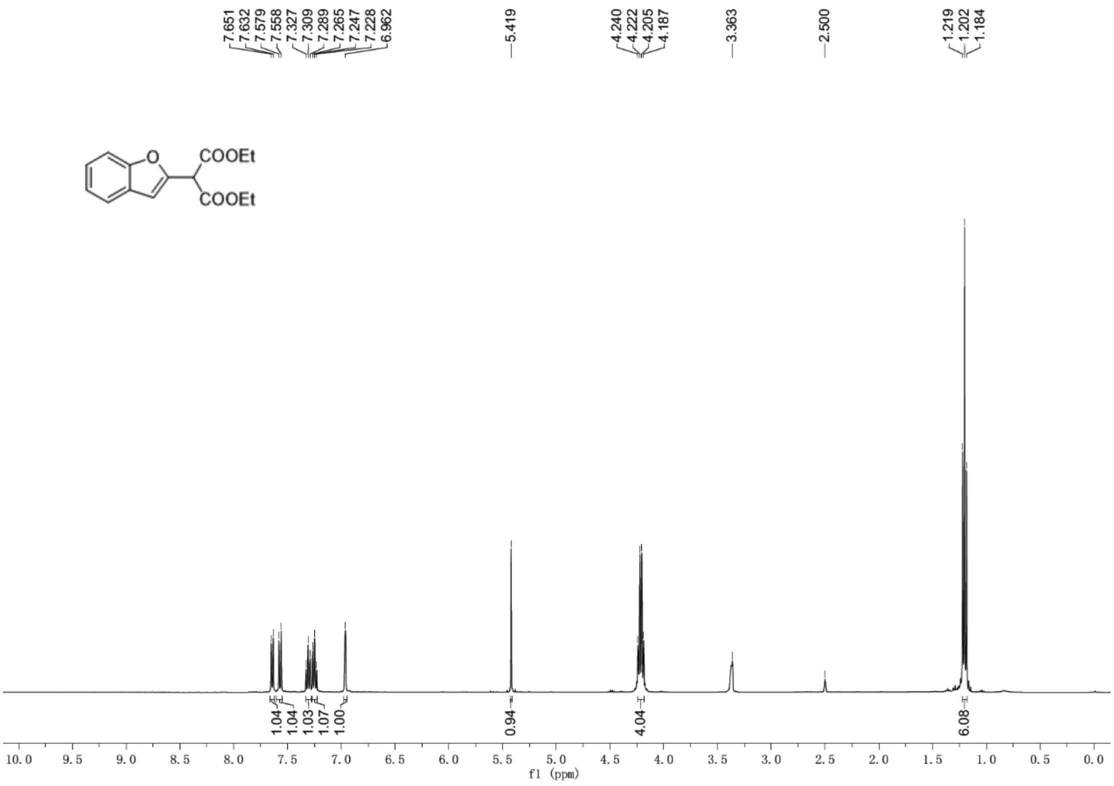

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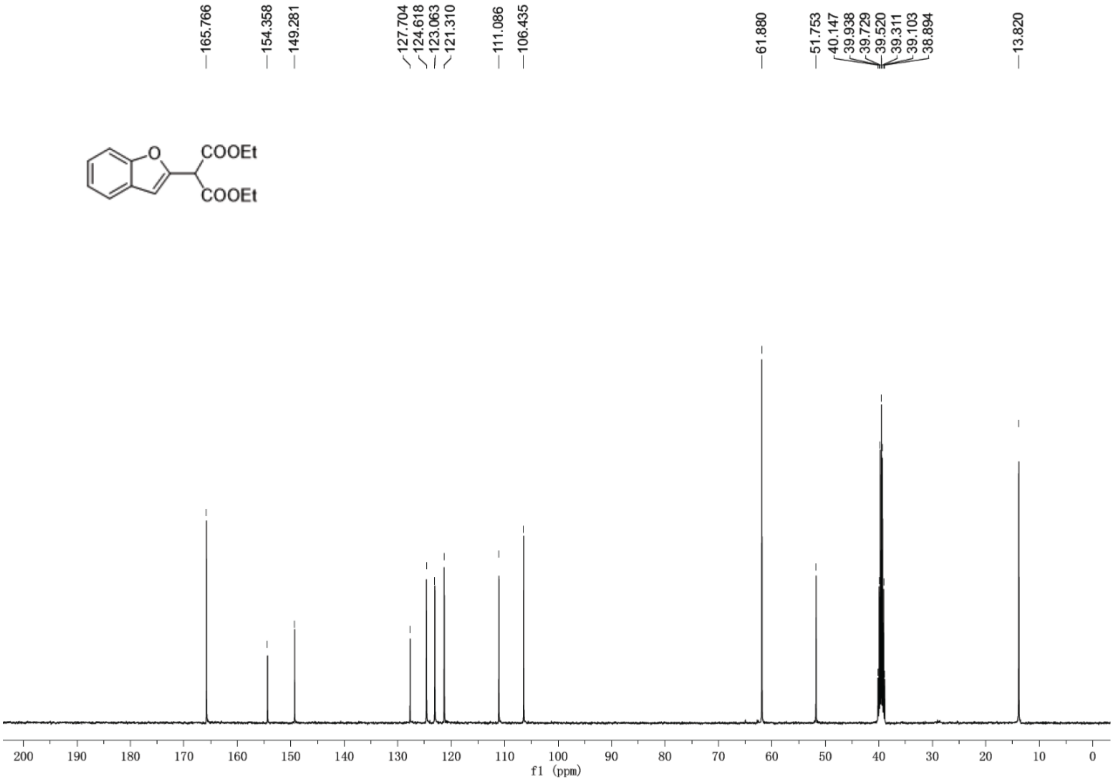
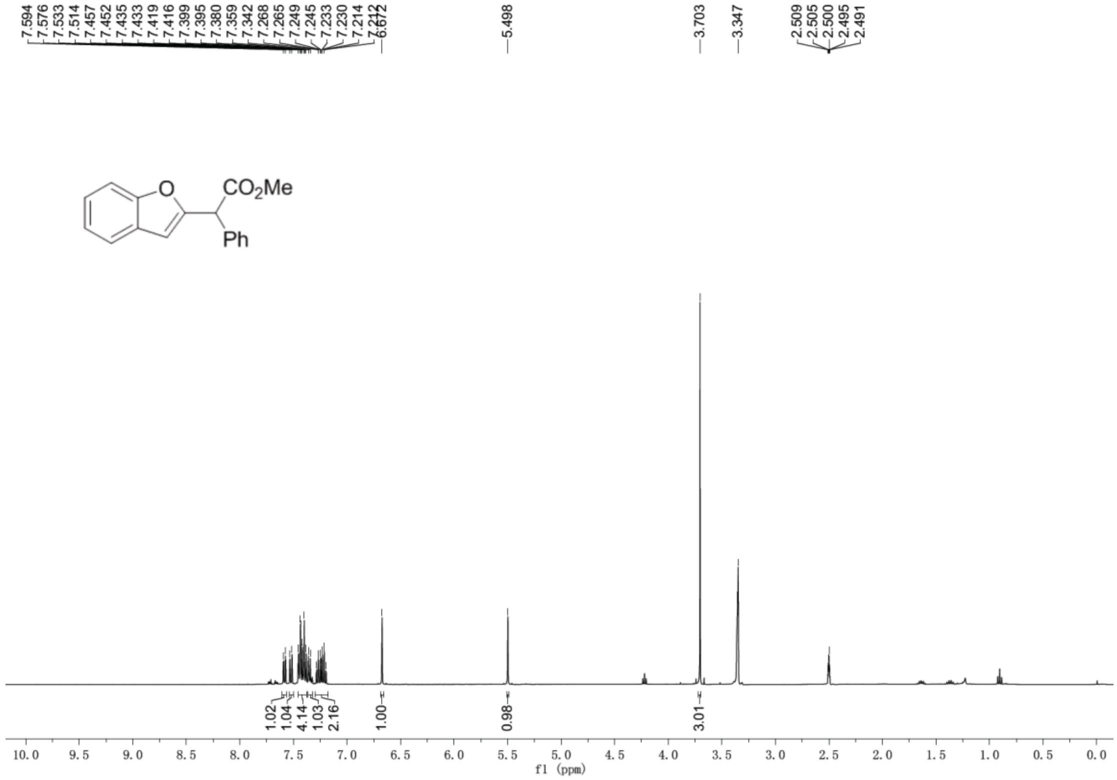
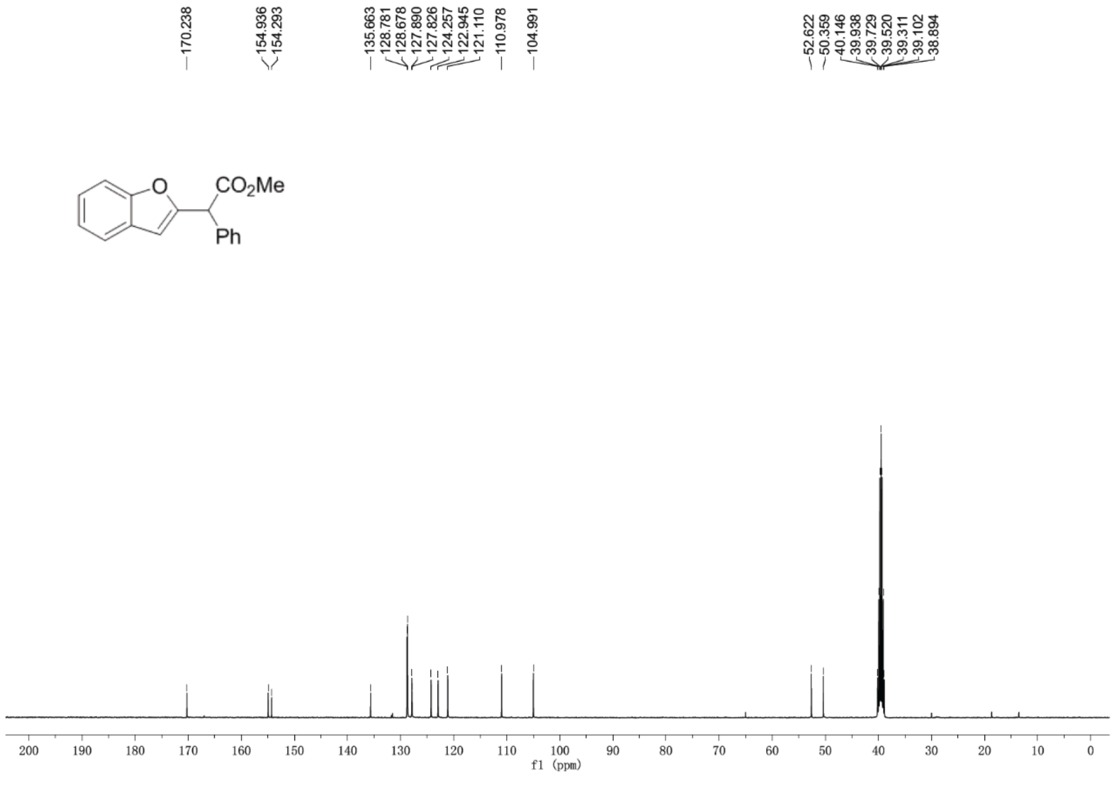


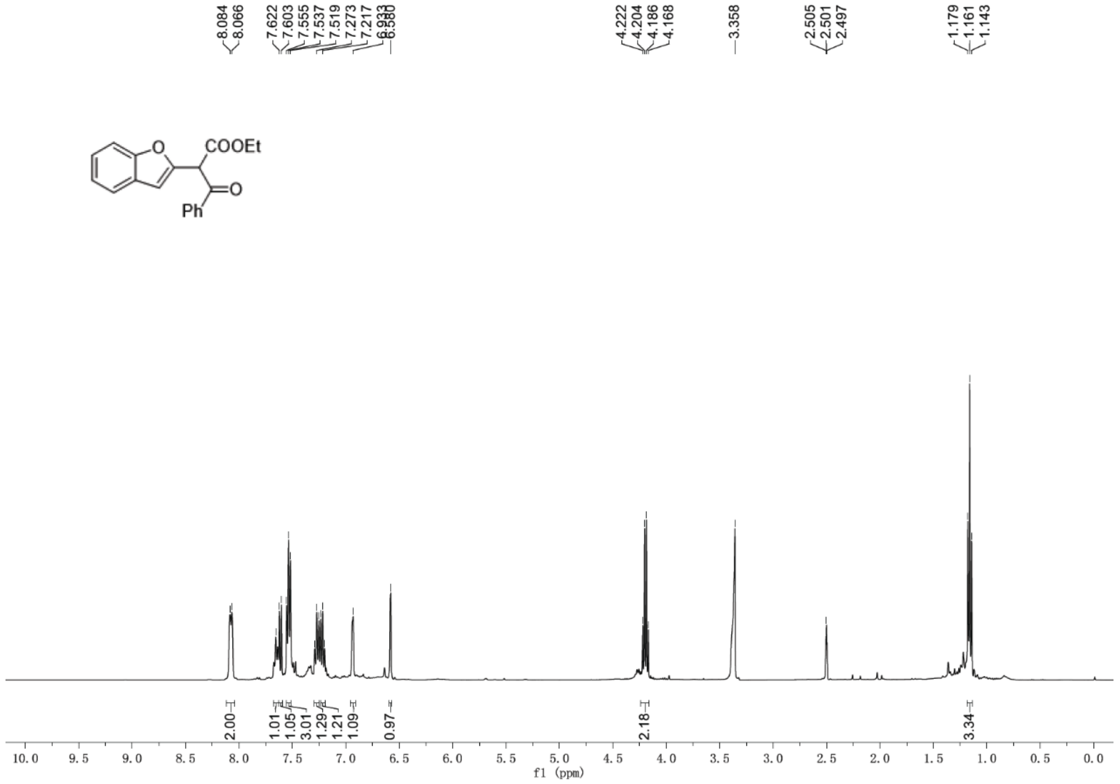
3ad-^{1}H NMR (400 MHz, DMSO-d_6)



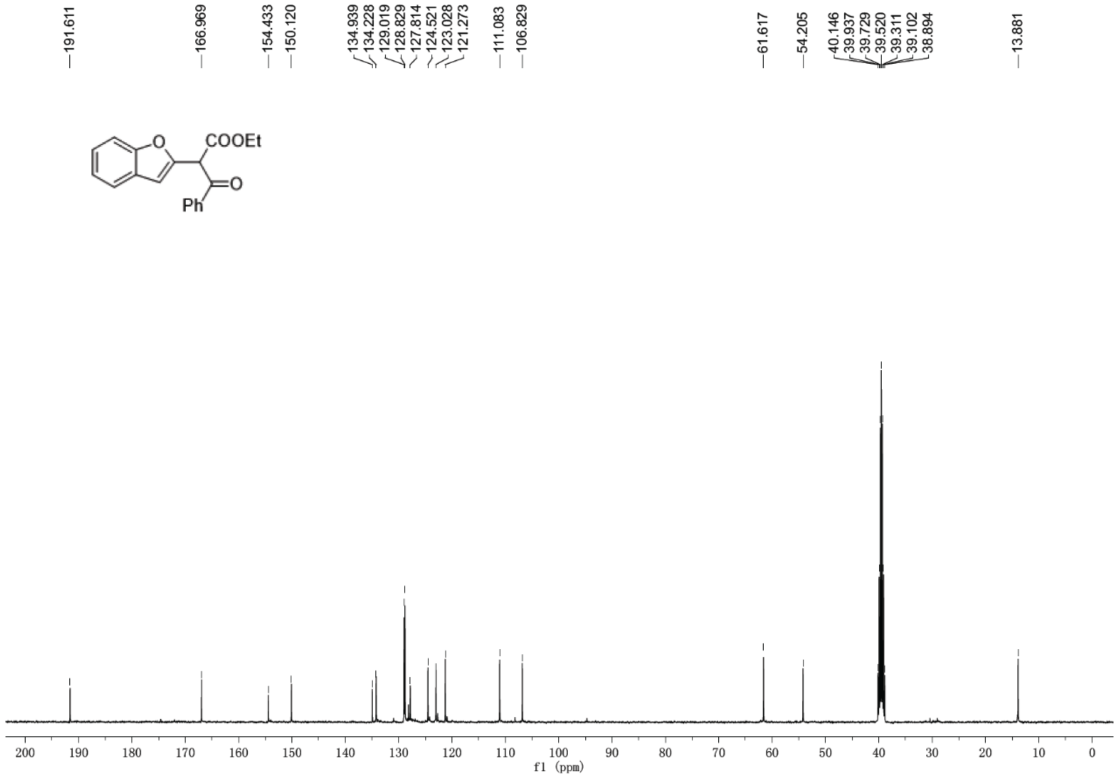
3ad-^{13}C NMR (100 MHz, DMSO-d_6)



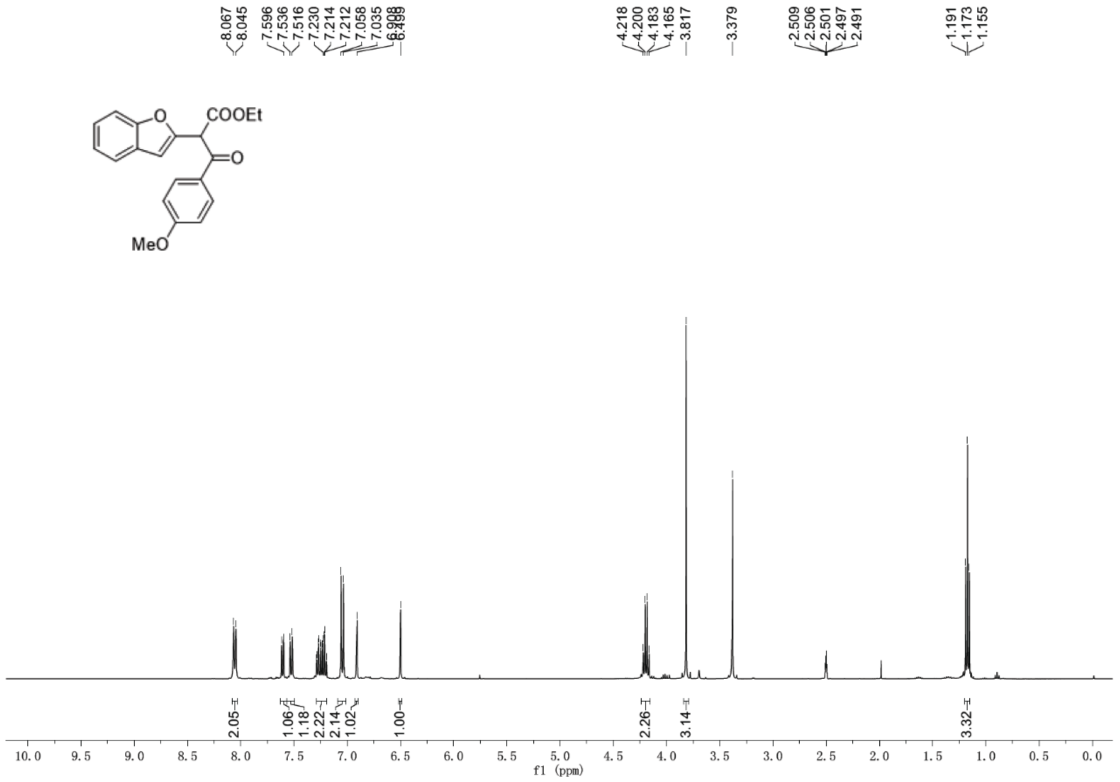
3ae-^{1}H NMR (400 MHz, DMSO-d_6)



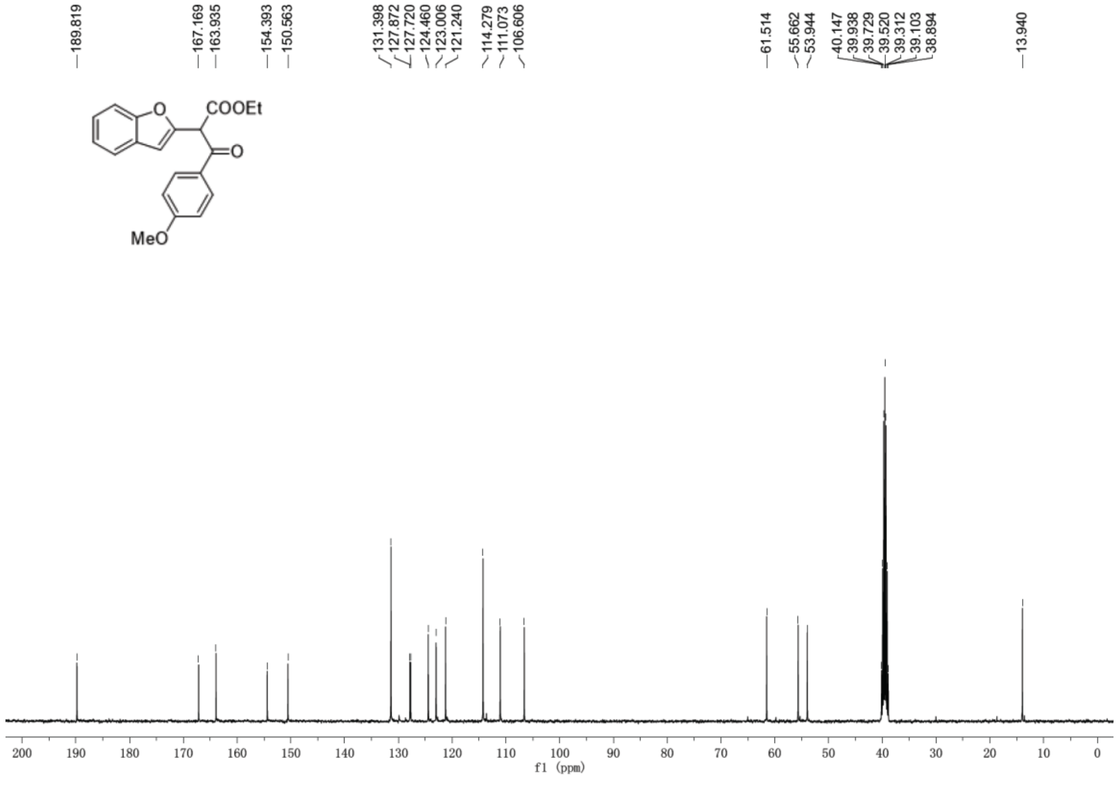
3ae-^{13}C NMR (100 MHz, DMSO-d_6)



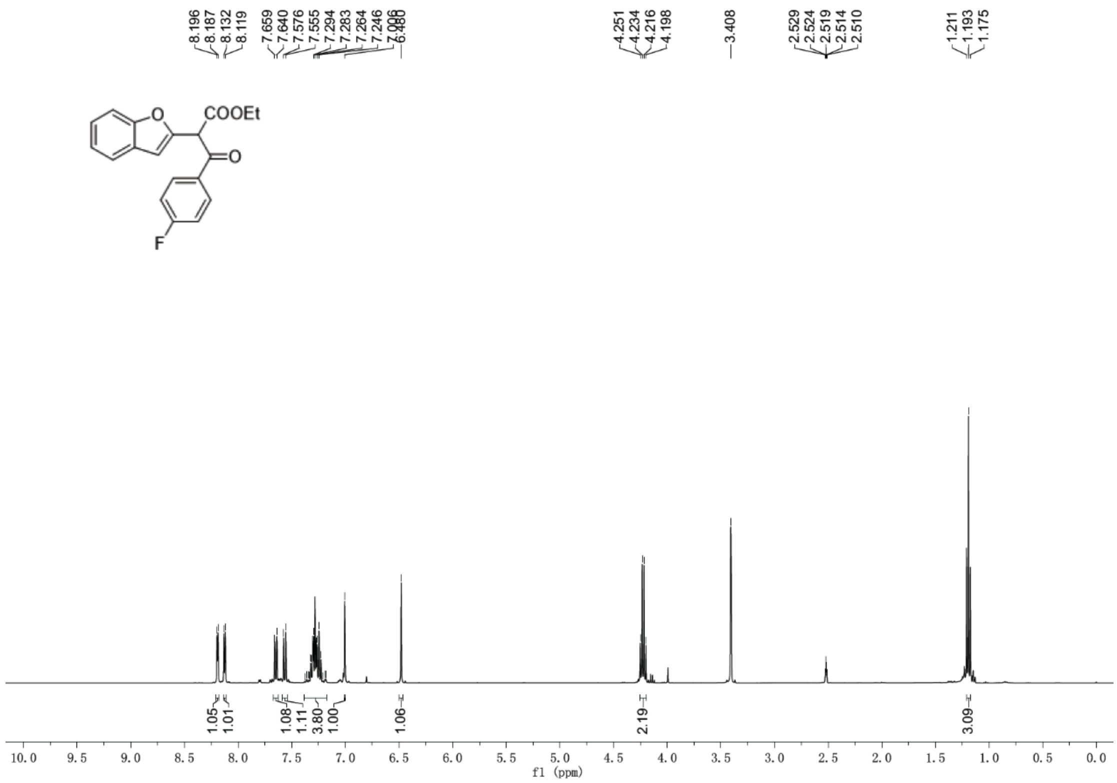
3af-^{1}H NMR (400 MHz, DMSO-d_6)



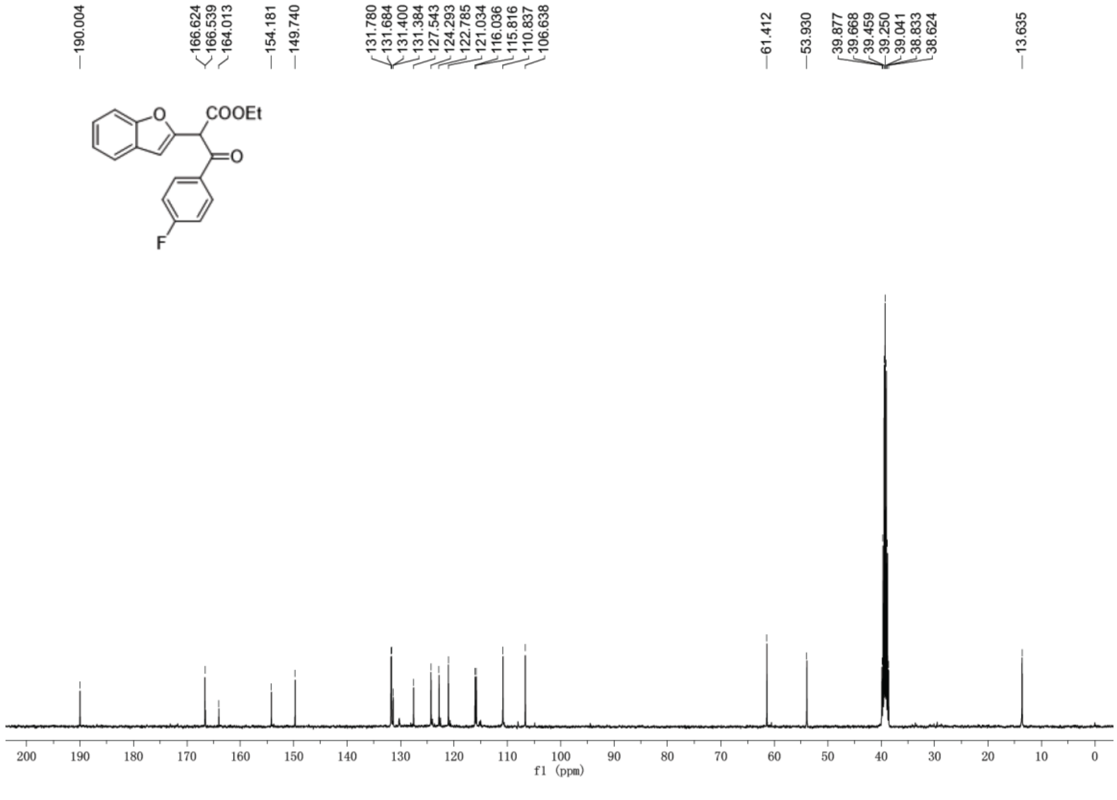
3af-^{13}C NMR (100 MHz, DMSO-d_6)



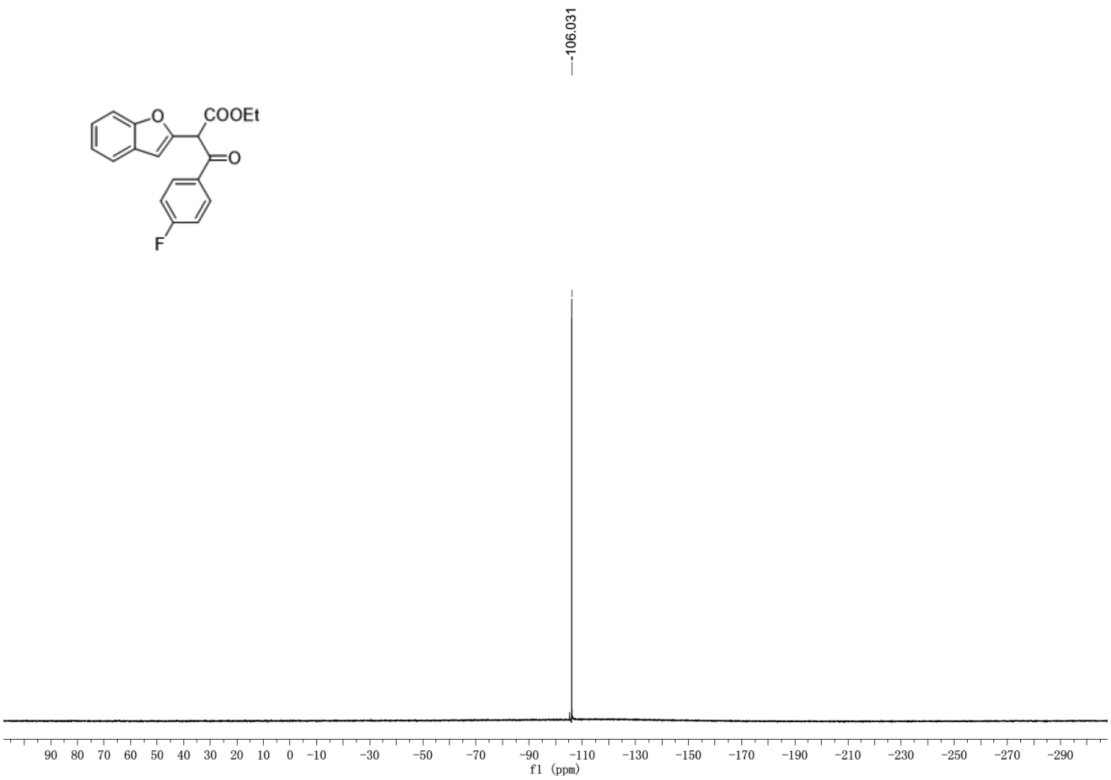
3ag-^{1}H NMR (400 MHz, DMSO-*d₆*)



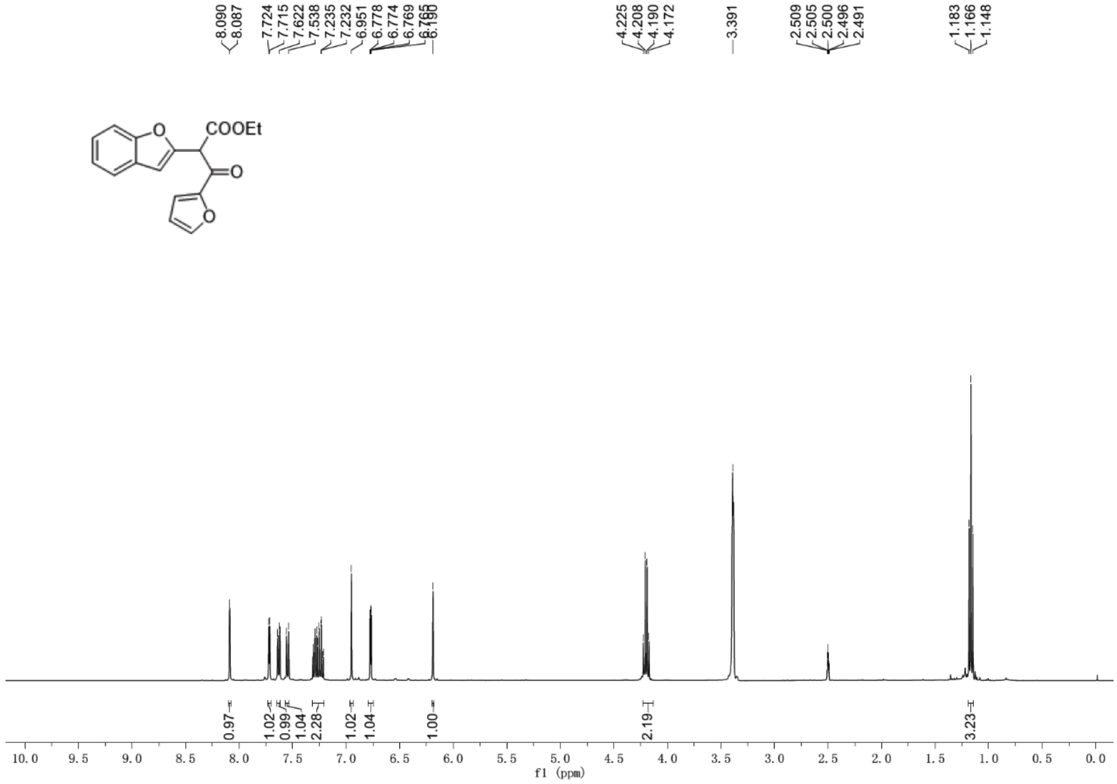
3ag-^{13}C NMR (100 MHz, DMSO-*d₆*)



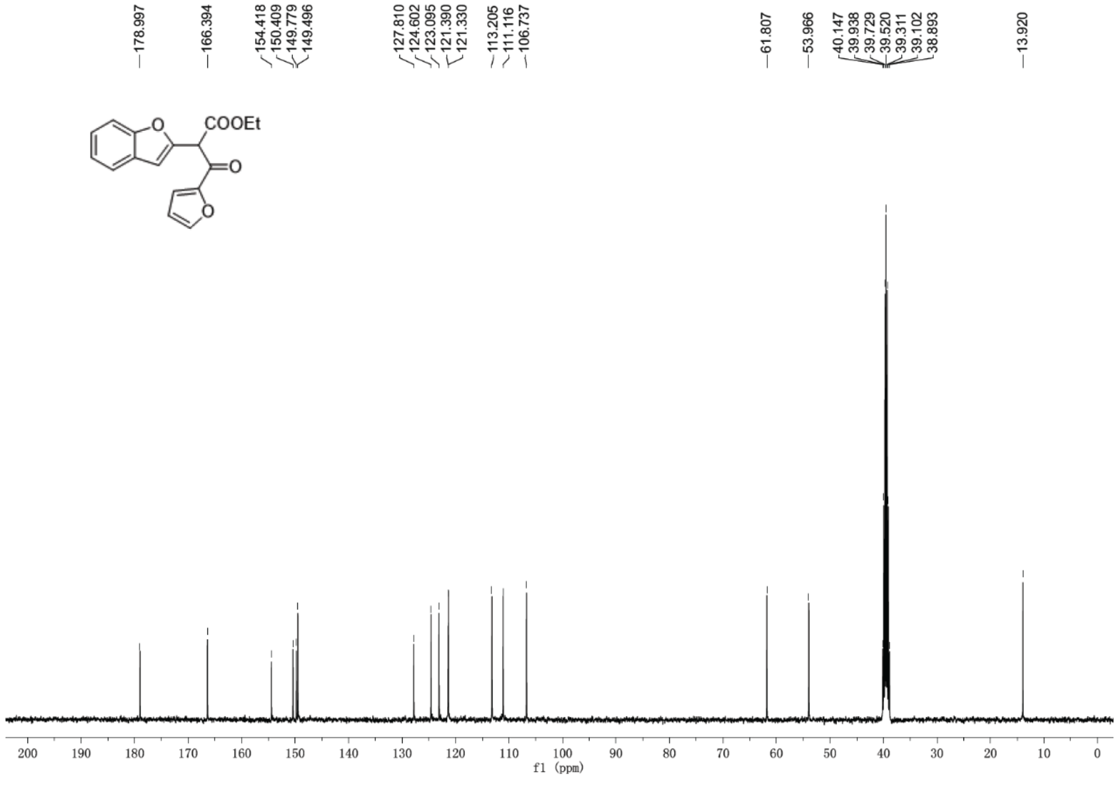
3ag-^{19}F NMR (376 MHz, CDCl$_3$)



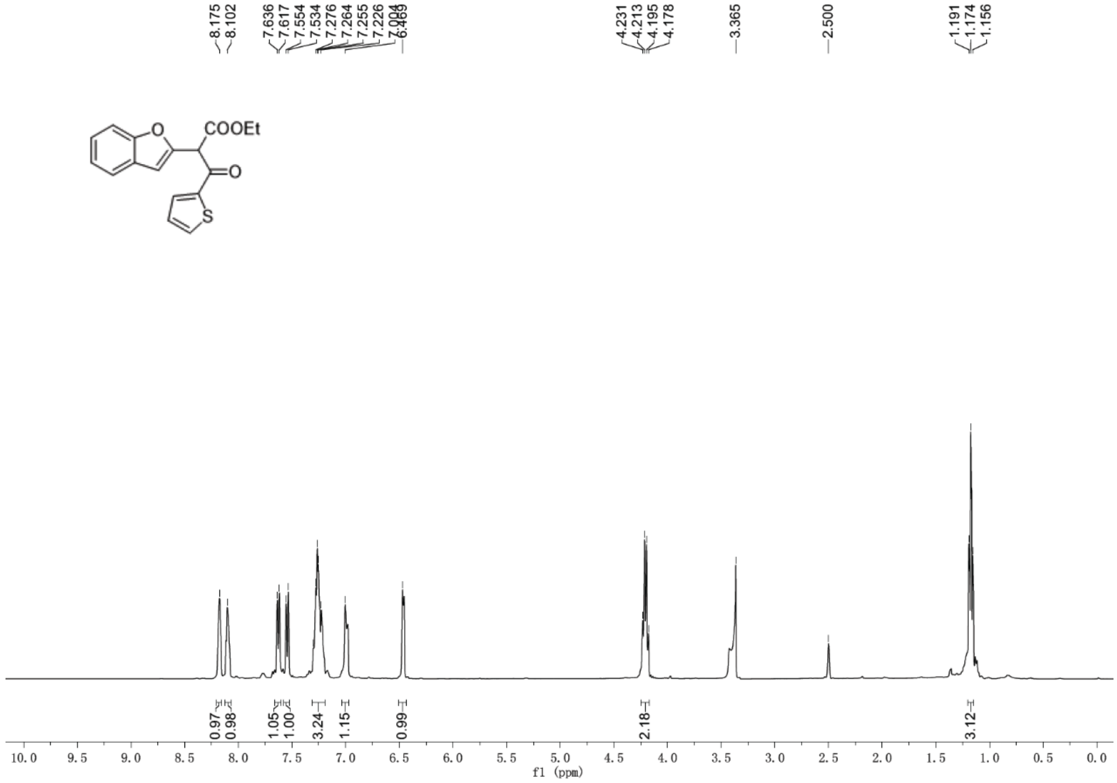
3ah-^{1}H NMR (400 MHz, DMSO-d_6)



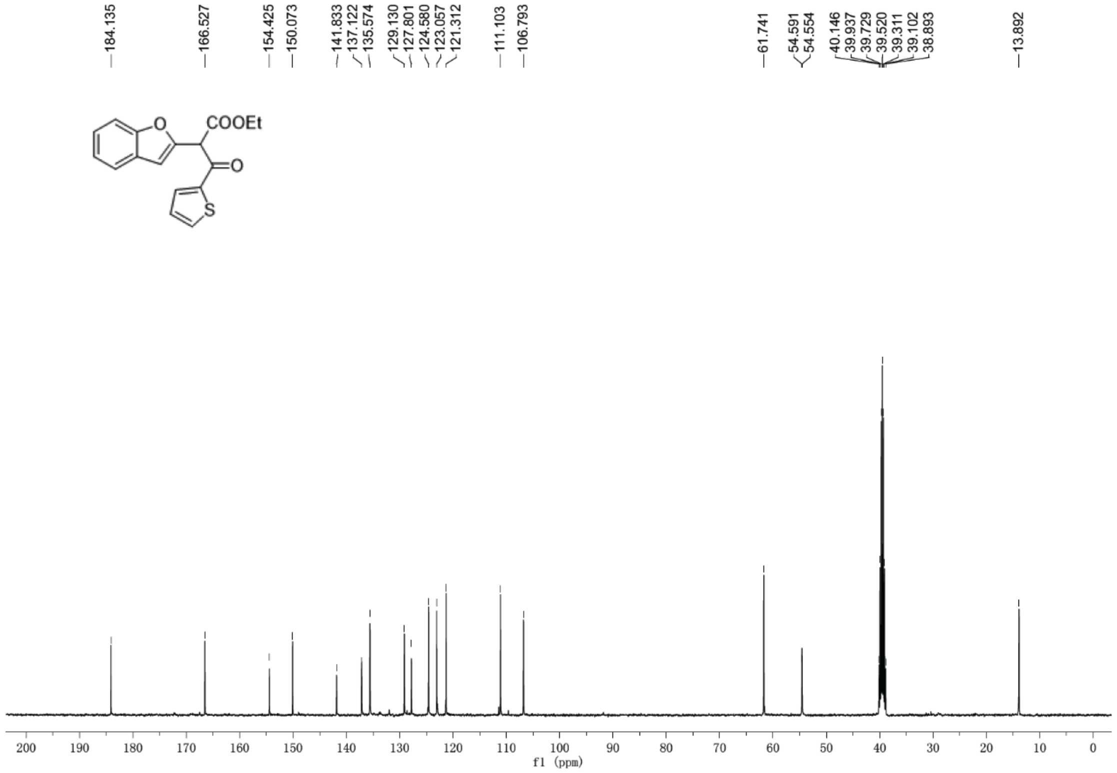
3ah-^{13}C NMR (100 MHz, DMSO-d_6)



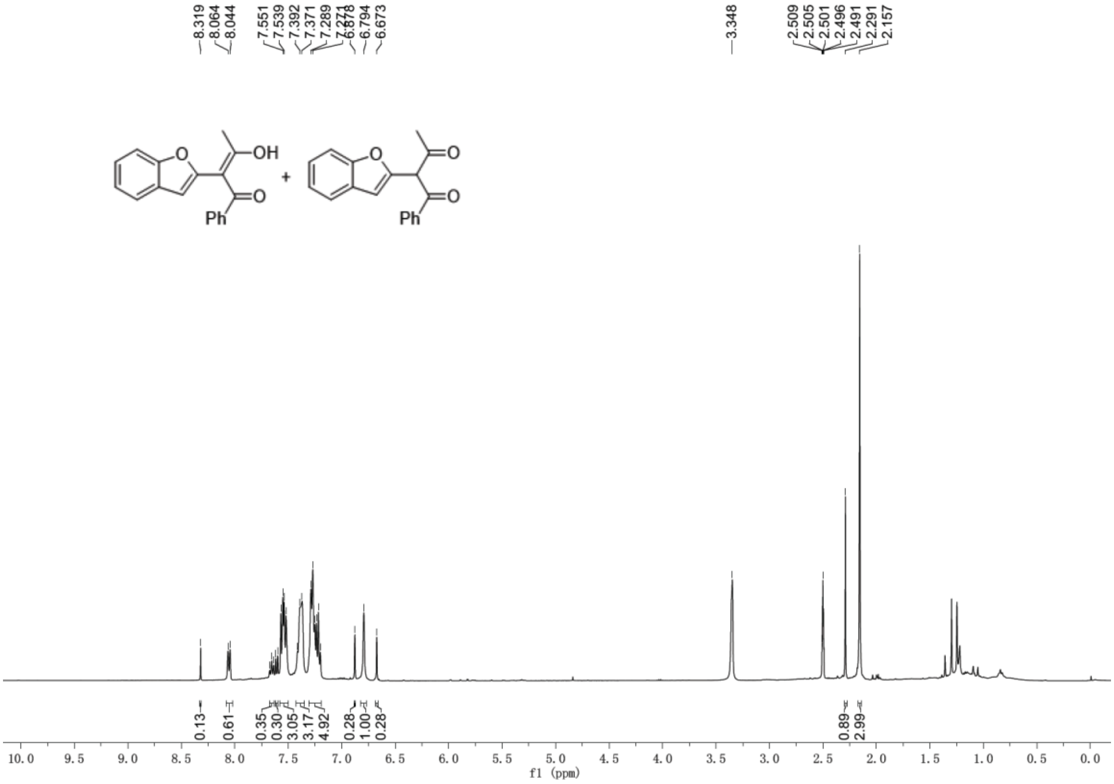
3ai-^{1}H NMR (400 MHz, DMSO-*d*$_6$)



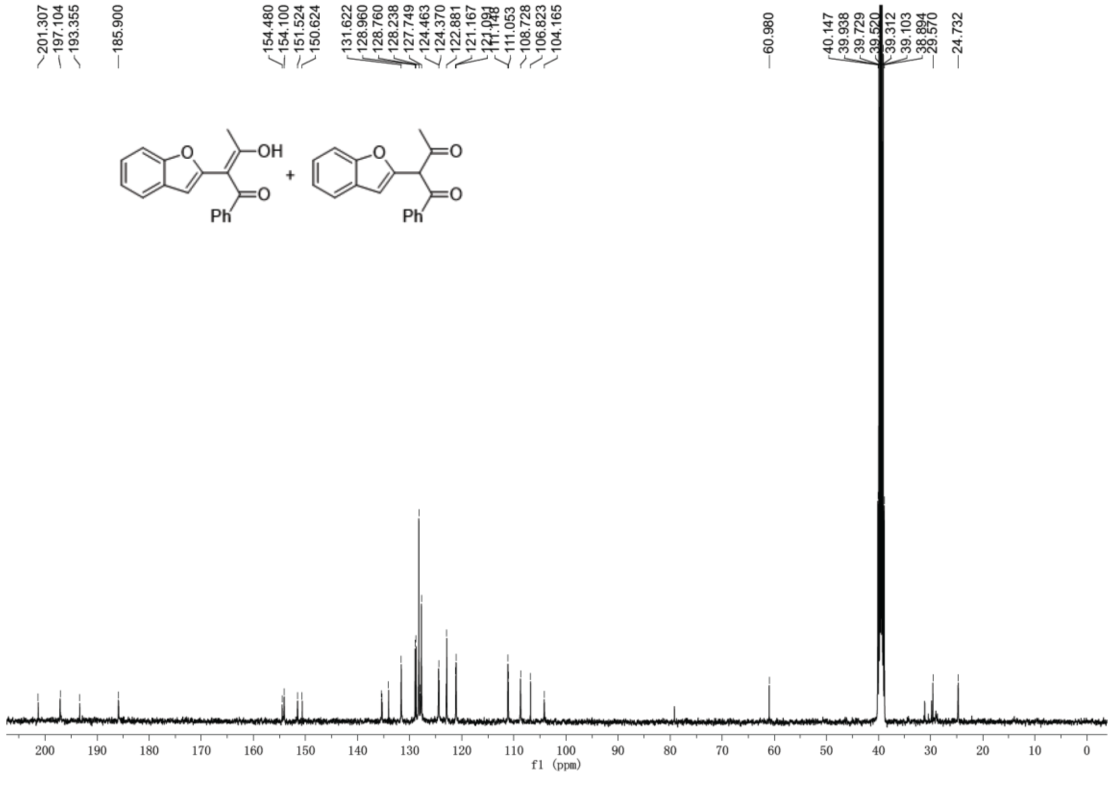
3ai-^{13}C NMR (100 MHz, DMSO-*d*$_6$)



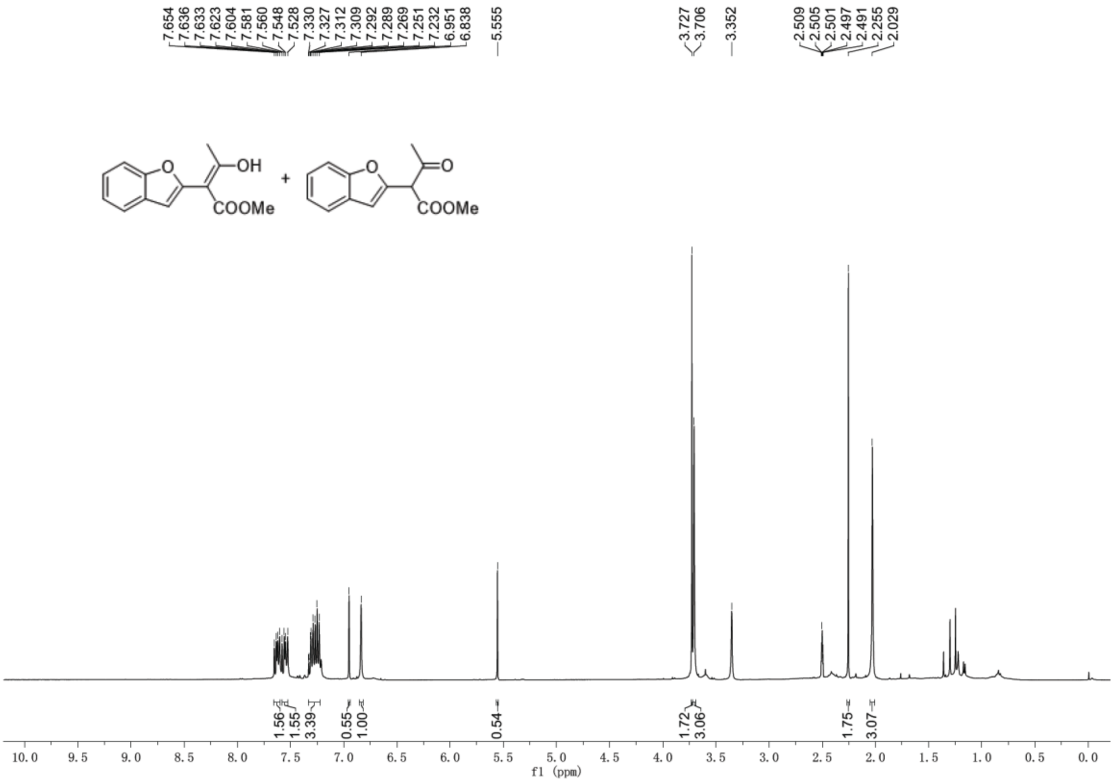
3aj/3aj'-^{1}H NMR (400 MHz, DMSO-*d$_6$*)



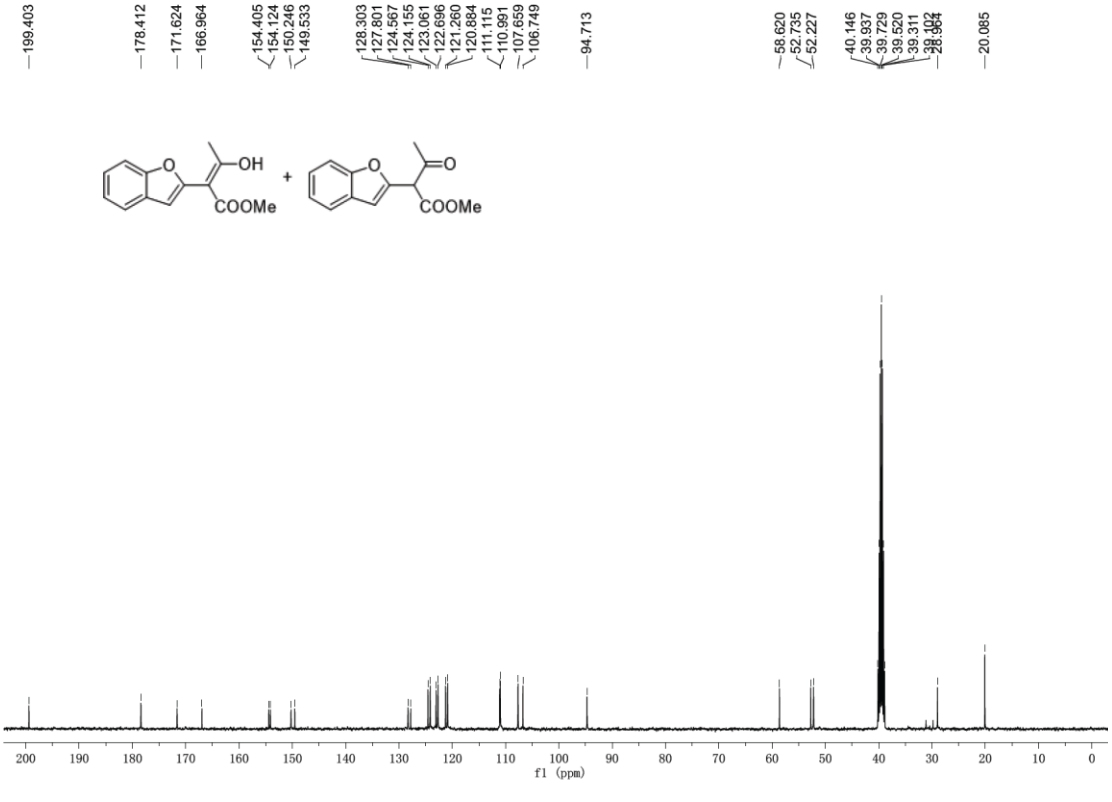
3aj/3aj'-^{13}C NMR (100 MHz, DMSO-*d$_6$*)



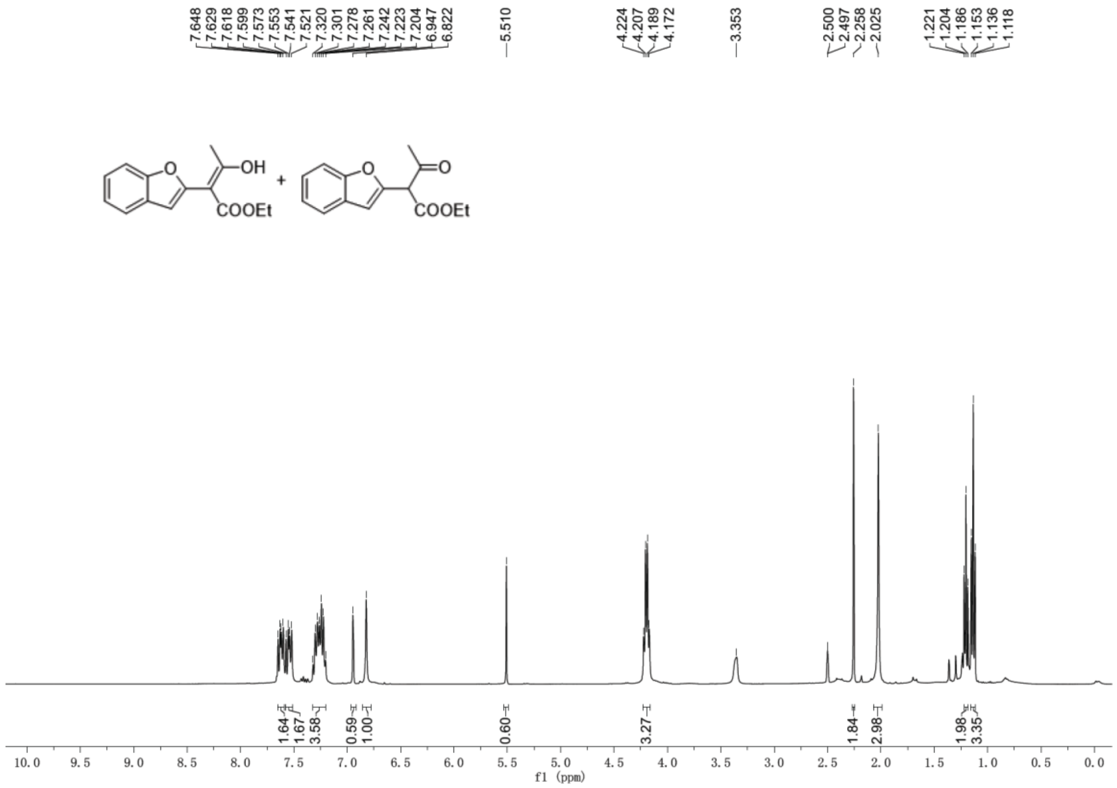
3ak/3ak’-^{1}H NMR (400 MHz, DMSO-d_6)



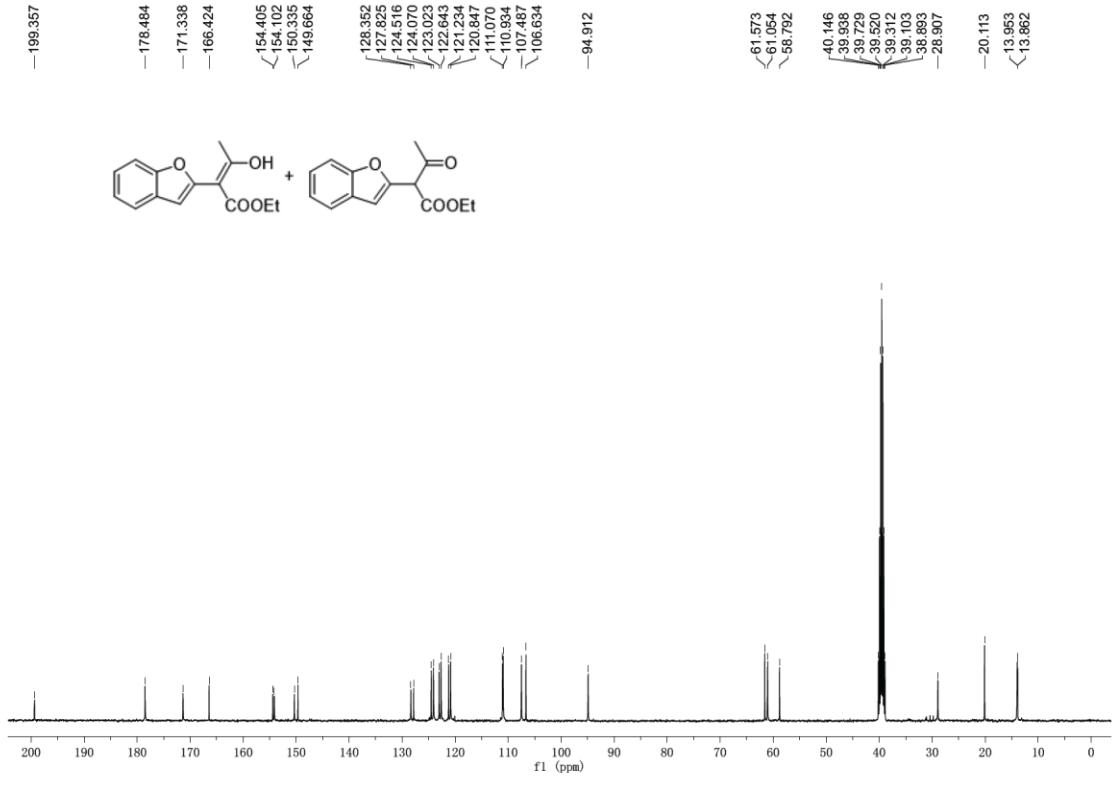
3ak/3ak’-^{13}C NMR (100 MHz, DMSO-d_6)



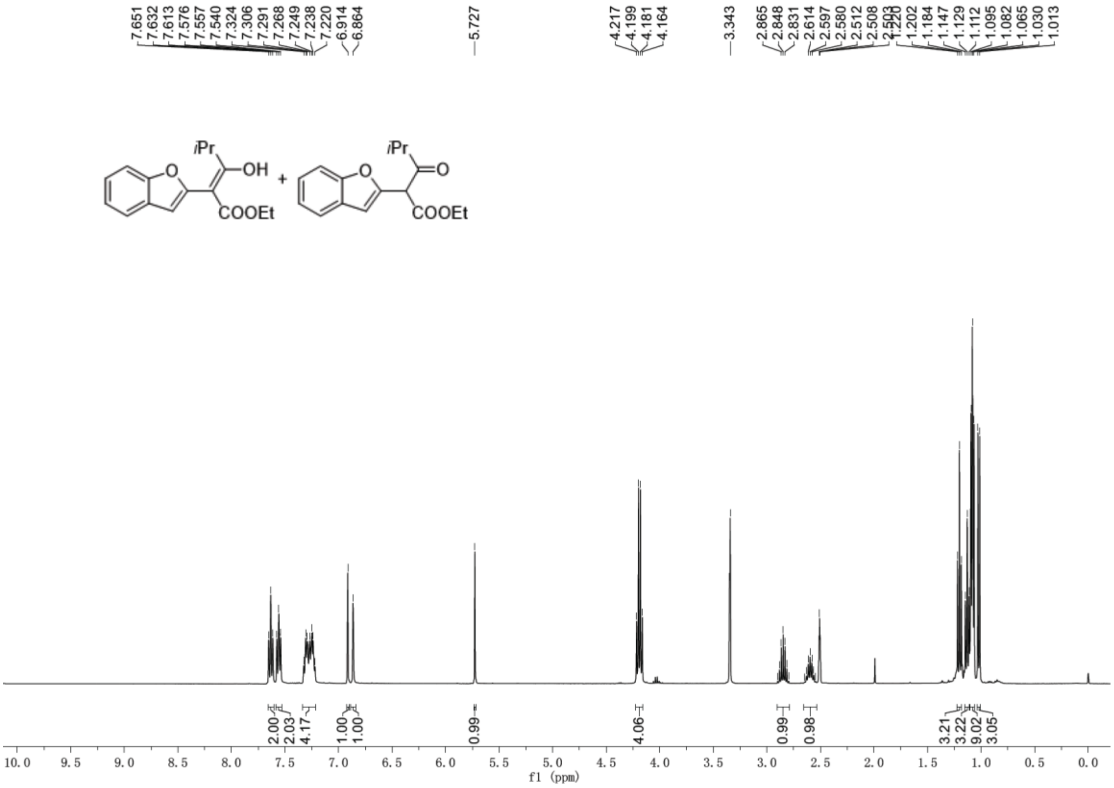
3al/3al’-^{1}H NMR (400 MHz, DMSO-d_6)



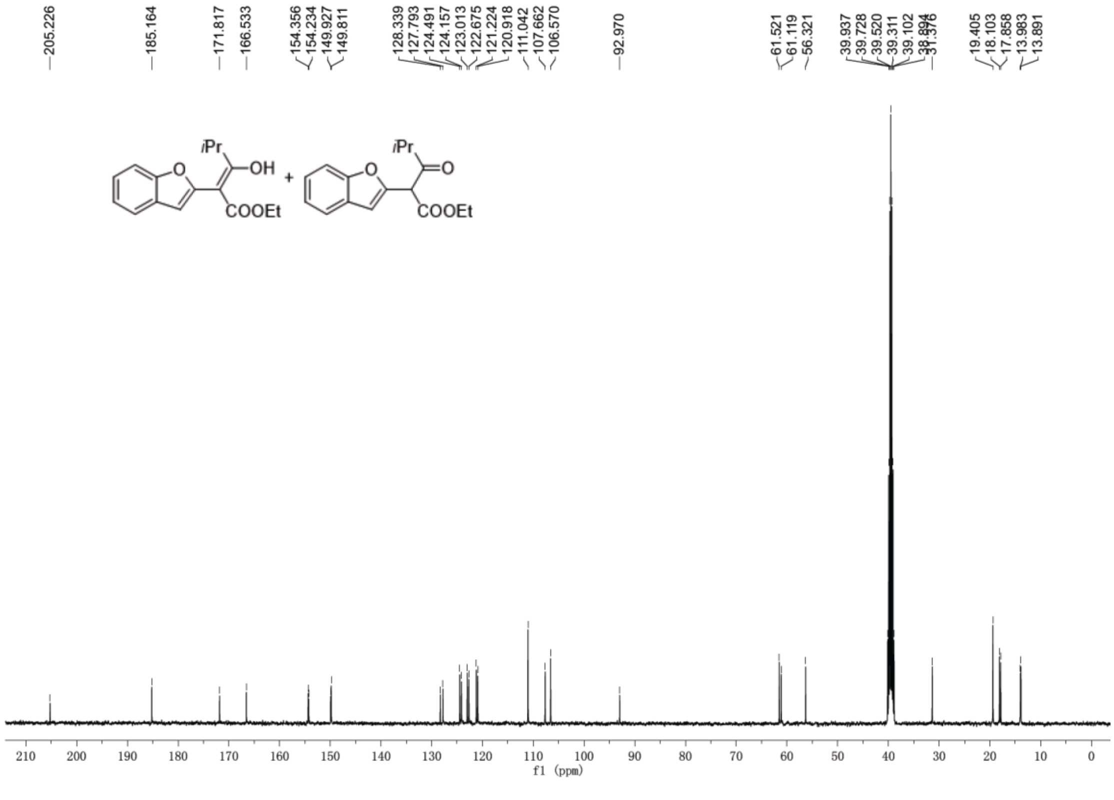
3al/3al’-^{13}C NMR (100 MHz, DMSO-d_6)



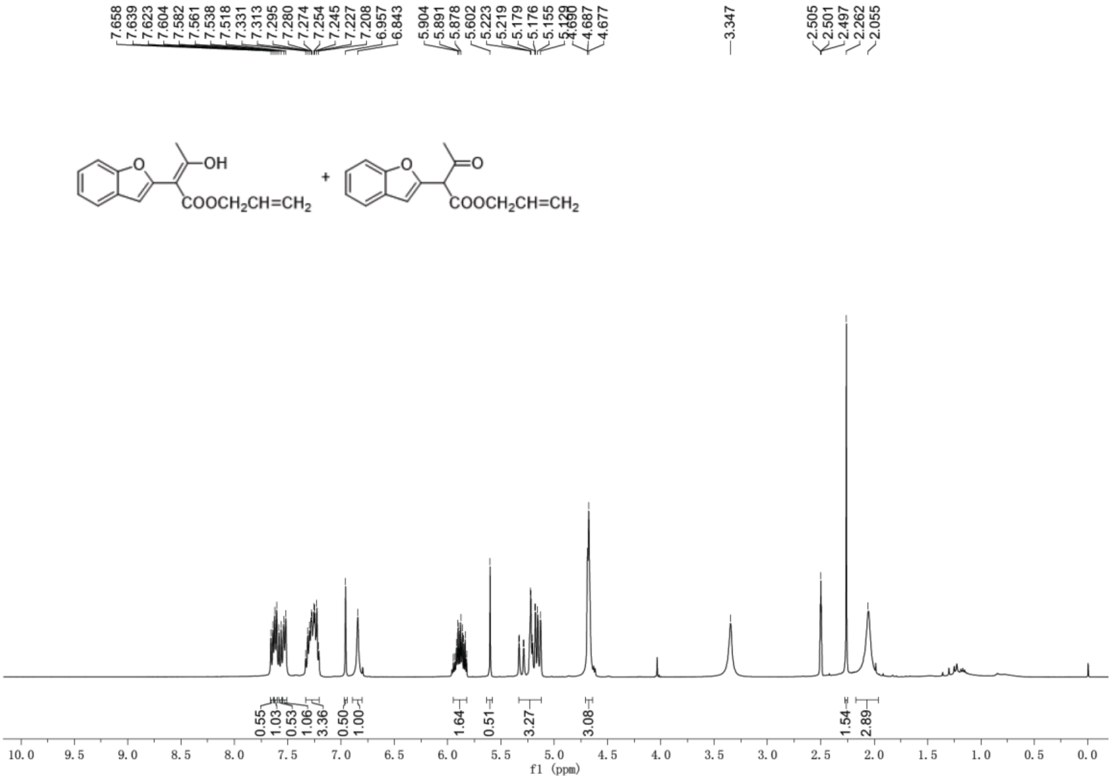
3am/3am'-^{1}H NMR (400 MHz, DMSO-d_6)



3am/3am'-^{13}C NMR (100 MHz, DMSO-d_6)



3an/3an'-^{1}H NMR (400 MHz, DMSO-d_6)



3an/3an'-^{13}C NMR (100 MHz, DMSO-d_6)