Electronic Supplementary Material (ESI) for ChemComm.

Supporting information

CtD Strategy to Construct Stereochemically Complex and Structurally Diverse Compounds from Griseofulvin

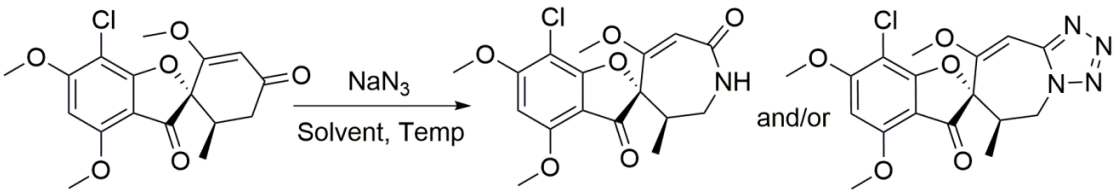
Contents

General experimental information

All chemicals and solvents used in the experiments were obtained from commercial sources and used directly without further purification. The organic solvents were treated following standard procedures before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Biospin Avance III FT-NMR spectrometer. NMR shifts are eported as delta (δ) units in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br=broad, s=single, d=doublet, t=triplet, q=quartet and m=multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent in CD_3OD (δ 3.31 ppm), in $(CD_3)_2SO$ (δ 2.50 ppm)), in $(CD_3)_2CO$ (δ 2.05 ppm). Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.1 ppm) or CD_3OD (δ 49.1 ppm) or $(CD_3)_2SO$ (δ 39.5) or $(CD_3)_2CO$ (δ 29.9 and 206.7). HMRS data for new compounds were acquired in the mass spectrometer equipped with TOF analyzer.

Optimization and proposed mechanism of schmidt reaction for griseofulvin

Table S1. Optimization of schmidt reaction for griseofulvin.



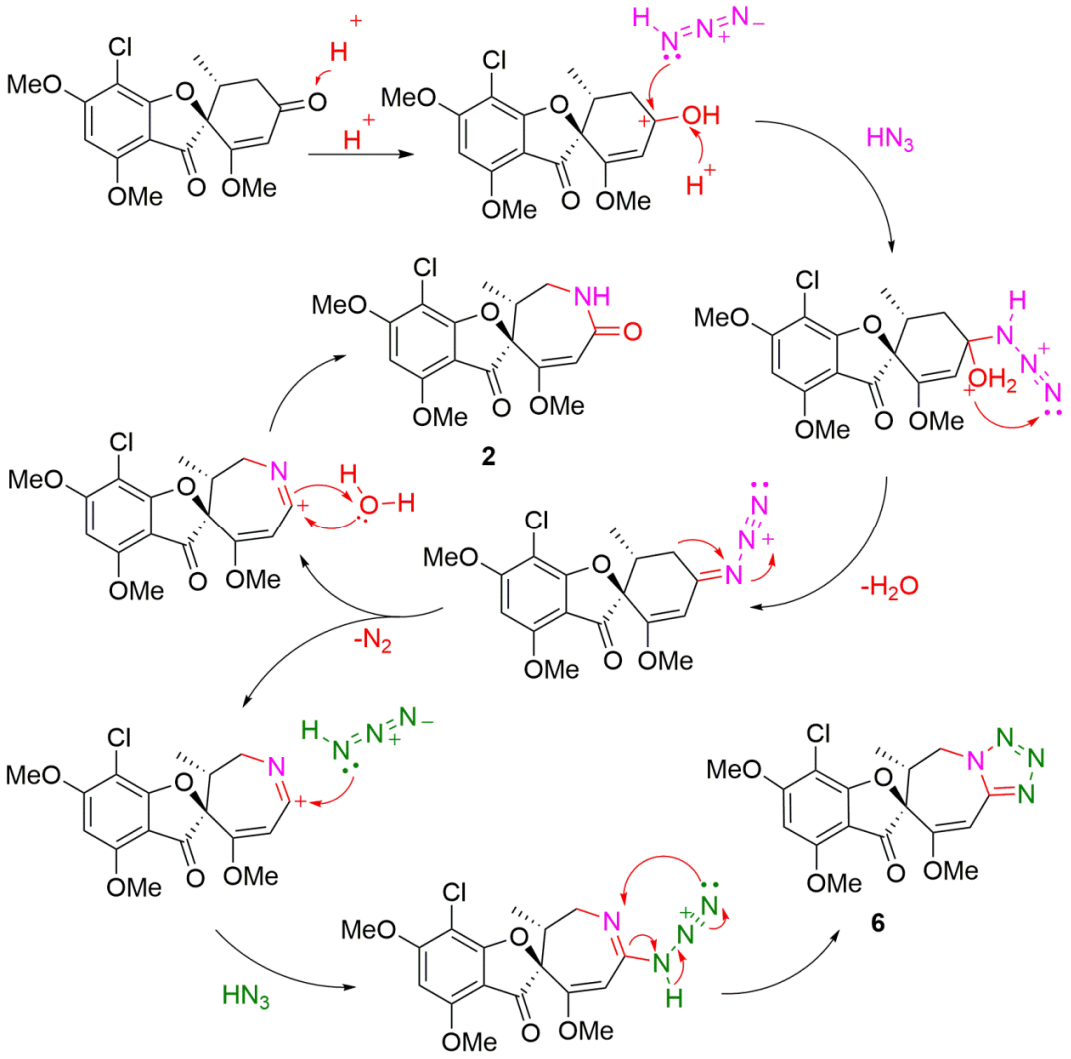
1 2 6

Entry[a]	Solvent	NaN_3 (eq.)	T (°C)	Yield (%)	**2:6**[b]
1	CCl_3COOH	1	65	7	0:10
2	CCl_3COOH	2	65	12	0:10
3	CCl_3COOH	5	65	39	0:10
4	CF_3COOH	1	65	9	0:10
5	CF_3COOH	2	65	16	0:10
6	CF_3COOH	5	65	41	0:10
7	CF_3COOH	2	r.t.	67	5.7:4.3
8[c]	CF_3COOH	5	r.t.	71	4.1:5.9
9	CF_3COOH	2	0	15	6.3:2.7
10[c]	CF_3COOH	5	0	36	3.3:6.7
11[c],[d]	$MeSO_3H$	5	r.t.	61	4.9:5.1
12[c],[e]	H_2SO_4	5	r.t.	42	0:10
13[f]	CF_3COOH	2	r.t.	65	5.2:4.8
14[c],[f]	CF_3COOH	5	r.t.	73	3.9:6.1
15[g]	CF_3COOH	2	r.t.	23	10:0
16[c],[g]	CF_3COOH	5	r.t.	48	10:0

[a]Unless otherwise noted, Griseofulvin **1** (176 mg, 0.5 mmol) was dissolved in solvent (2 ml), stirred overnight. Followed by addition of NaN_3. [b]Ratio determined from isolated yields [c]Dropwise addition of NaN_3. [d]Reaction performed in $MeSO_3H$/DCM (v/v=1/1

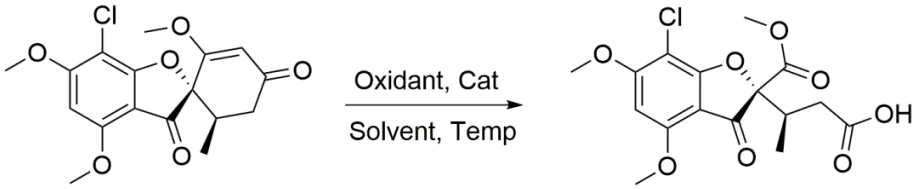
2ml). [e]Reaction performed at 0 ˚C while adding NaN_3. [f]Reaction stir for an additional 12 hours. [g]Reaction performed in solvent (2 ml), followed by addition of water (10 µl).

Scheme S1. Proposed mechanism of schmidt reaction for griseofulvin.



Optimization of oxidation reaction for griseofulvin

Table S2. Optimization of oxidation reaction for griseofulvin.



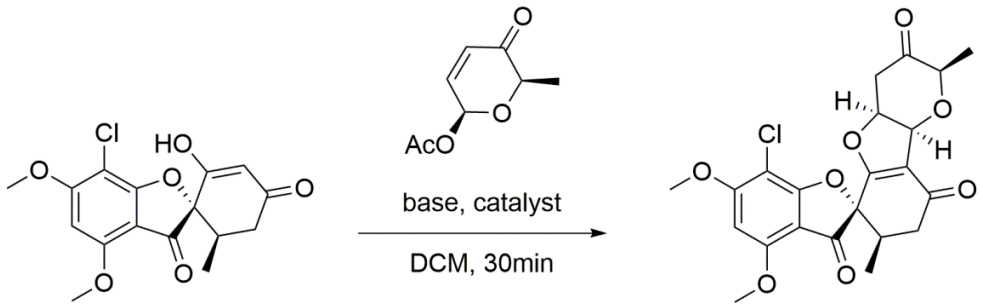
1 9

Entry[a]	Solvent	Oxidant	Catalyst	T (˚C)	Yield (%)
1	H_2O	$NaIO_4$	$KMnO_4$	reflux	0
2	*i*-PrOH	$NaIO_4$	$KMnO_4$	reflux	0
3	*t*-BuOH	$NaIO_4$	$KMnO_4$	reflux	0
4[b]	CH_3CN/H_2O	Oxone	—	r.t.	0
5	DCE	Oxone	Al_2O_3	reflux	0
6	EtOAc	Oxone	Al_2O_3	r.t.	0
7[c]	$MeOH/H_2O$	Oxone	—	r.t.	0
8	DCM	mCPBA	—	r.t.	0
9[c], [d]	DCE/H_2O	$NaIO_4$	$RuCl_3$	r.t.	0
10[e]	$DCM/CH_3CN/H_2O$	$NaIO_4$	$RuCl_3$	r.t.	0
11	$EtOAc/CH_3CN/H_2O$	$NaIO_4$	$RuCl_3$	r.t.	0
12	$THF/CH_3CN/H_2O$	$NaIO_4$	$RuCl_3$	r.t.	0
13	$CCl_4/CH_3CN/H_2O$	$NaIO_4$	$RuCl_3$	r.t.	0
14[f]	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	r.t.	17
15[g]	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	r.t.	19
16[h]	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	r.t.	17
17[i]	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	r.t.	18
18	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	60	42
19[j]	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	60	83
20	CH_3CN/H_2O	$NaIO_4$	$RuCl_3$	reflux	67

[a]Unless otherwise noted, Griseofulvin **1** (176 mg, 0.5 mmol) was dissolved in solvent, then add oxidant (5 eq, 2.5 mmol) and catalyst (5% mol, 0.025 mmol). The mixture was stirred for 6h. [b]The ratio of the solvents is 10:1. [c]The ratio of the solvents is 1:1. [d]In entry 9-20, Griseofulvin **1** (176 mg, 0.5 mmol) was dissolved in solvent, then add $NaIO_4$ (1.5 eq, 0.75 mmol) and $RuCl_3$ (3% mol, 0.015 mmol). The mixture was stirred for 6h. [e]In entry 10-13, the ratio of the solvents is 2:2:3. [f]In entry 14-20, the ratio of the solvents is 6:1. [g]Oxidant added $NaIO_4$ (3 eq, 1.5 mmol). [h]Oxidant added $NaIO_4$ (5 eq, 2.5 mmol). [i]Catalyst added $RuCl_3$ (5% mol, 0.025 mmol). [j]Reaction stir overnight.

Optimization and proposed mechanism of cascade Tsuji-Trost allylation and Oxa-Michael cyclization for griseofulvin and pyranone esters

Table S3. Optimization of cascade Tsuji-Trost allylation and Oxa-Michael cyclization for griseofulvin and Pyranone esters.



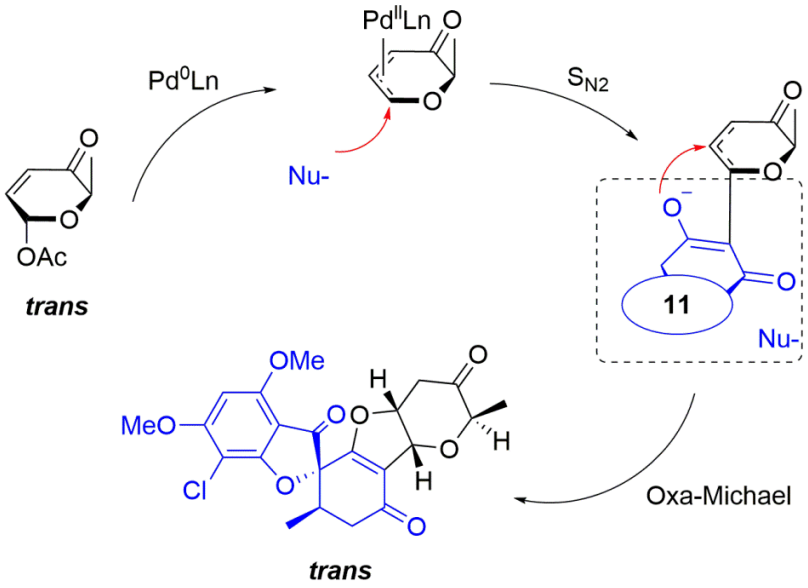
11 12a

Entry[a]	Base	Catalyst	T (˚C)	Yield (%)	***cis*:*trans***[b]
1	Et_3N	$Pd(PPh_3)_4$	r.t.	67	>30:1
2	DBU	$Pd(PPh_3)_4$	r.t.	60	>30:1
3	K_2CO_3	$Pd(PPh_3)_4$	r.t.	trace	>30:1
4	Cs_2CO_3	$Pd(PPh_3)_4$	r.t.	trace	>30:1
5	pyridine	$Pd(PPh_3)_4$	r.t.	58	>30:1
6	*t*-BuOK	$Pd(PPh_3)_4$	r.t.	trace	>30:1
7	Et_3N	$Pd(OAc)_2$	r.t.	42	>30:1
8	Et_3N	$PdCl_2$	r.t.	trace	>30:1
9	Et_3N	$Pd_2(dba)_3$	r.t.	27	>30:1
10	Et_3N	$Pd(PPh_3)_4$	reflux	67	>30:1
11	Et_3N	$Pd(PPh_3)_4$	0	61	>30:1
12[c]	Et_3N	$Pd(PPh_3)_4$	r.t.	36	>30:1
13[d]	Et_3N	$Pd(PPh_3)_4$	r.t.	58	>30:1

[a]Unless otherwise noted, Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL), add catalyst (0.011 mmol) and base (0.11 mmol), then add 17 mg (0.11 mmol) of (2S,6R)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate. The resulting

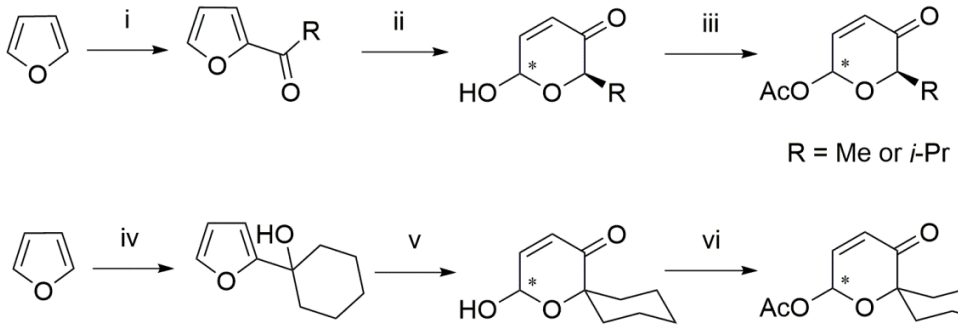
mixture was stirred at room temperature for 30 min. [b]Ratio was determined by GC-MS analysis of the crude reaction mixture. [c]Reaction performed in THF instead of DCM. [d]Reaction performed in Tol instead of DCM.

Scheme S2. Proposed mechanism of cascade Tsuji-Trost allylation and Oxa-Michael cyclization.[1]



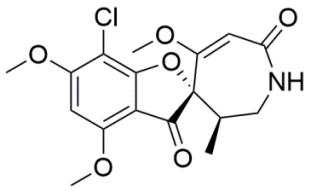
General procedure for preparation of pyranones esters

Following our procedure reported[2,3] previously, acetoxy-2-pyranones were prepared successfully, **Scheme S3**.[1-5]



i: RCOOH, *n*-BuLi, THF. ii: a) $[Cp^*RhCl_2]_2$ (0.05 mol%), (R,R)-Ts-DPEN (0.12 mol%), HCO_2Na, 40˚C; b) NBS, NaOAc, $NaHCO_3$, THF/H_2O, 40˚C. iii: Ac_2O, pyridine, DMAP, DCM. iv: cyclohexanone, *n*-BuLi, THF. v: NBS, NaOAc, $NaHCO_3$, THF/H_2O, 40˚C. vi: Ac_2O, pyridine, DMAP, DCM.

Synthetic procedures and characterization data of all synthesized products

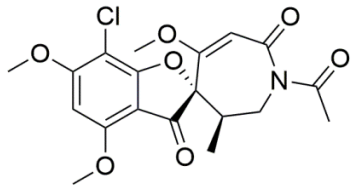


2

(3R,4S)-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4, 2'-benzofuran]-3',7(1H)-dione (2)

Griseofulvin **1** (176 mg, 0.5 mmol) was dissolved in trifluoroacetic acid (2 mL) in a 25 mL round-bottom flask. Subsequently, 10 μl of water was added dropwise, then add 65 mg (1 mmol) of sodium azide several times. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **2** (88.0 mg, 48% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.1 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 1H, ArH), 5.44 (d, *J* = 1.2 Hz, 1H, C=CH), 4.02 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.96 – 3.91 (m, 1H, CH_2), 3.54 (s, 3H, OCH_3), 3.12 (dd, *J* = 15.0, 6.3 Hz, 1H, CH_2), 2.55 – 2.44 (m, 1H, CH), 0.98 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (C=O), 168.8 (C=ON), 168.1 (C=C), 164.3 (ArO), 161.1 (ArO), 157.6 (ArO), 105.8 (C=C), 102.0 (Ar), 97.2 (Ar), 92.9 (Ar), 89.3 (C), 57.0 (OCH_3), 56.3 (OCH_3), 55.9 (OCH_3), 41.2 (CH_2), 38.8 (CH), 13.0 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{19}NO_6Cl$: 368.0901; found: 368.0896 $[M+H]^+$.

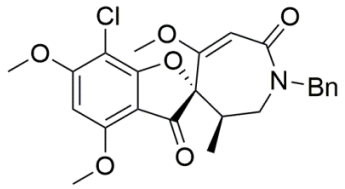


3a

(3R,4S)-1-acetyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3a)

Amide **2** (37 mg, 0.1 mmol) was dissolved in pyridine (0.5 mL) in a 5 mL round-bottom flask. Subsequently, add 0.5 ml of acetic anhydride and 2 mg (0.01 mmol) of DMAP. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, adjust the mixture to pH=1 with 1M HCl. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3a** (37.0 mg, 91% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.45 (s, 1H, C=CH), 4.13 (m, 2H , CH_2), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3), 2.59 – 2.56 (m, 1H, CH), 1.01 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1 (C=O), 173.2 (C=O), 168.5 (C=ON), 168.2 (C=C), 164.5 (ArO), 162.4 (ArO), 157.9 (ArO), 104.8 (C=C), 101.4 (Ar), 97.2 (Ar), 92.7 (Ar), 89.5 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.4 (OCH_3), 43.2 (CH_3), 40.6 (CH_2), 27.0 (CH), 13.5 (CH_3). HRMS (ESI): m/z calcd for $C_{19}H_{21}NO_7Cl$: 410.1007; found: 410.1001 $[M+H]^+$.

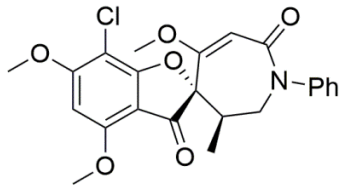


3b

(3R,4S)-1-benzyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3b)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) in a 5 mL round-bottom flask. Subsequently, cool to 0°C in an ice bath, add 5 mg (0.2 mmol) of NaH, then add 21 mg (0.12 mmol) of benzyl bromide after 30 min, and then return to room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3b** (43.0 mg, 95% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H, ArH), 6.08 (s, 1H, ArH), 5.59 (s, 1H, C=CH), 4.32 (d, *J* = 14.6 Hz, 1H, CH_2), 4.23 (dd, *J* = 15.4, 8.0 Hz, 1H, CH_2), 4.00 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.96 (t, *J* = 7.7 Hz, 2H, CH_2), 2.31 (t, *J* = 7.4 Hz, 1H, CH), 0.71 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2 (C=O), 168.9 (C=ON), 165.2 (C=C), 164.3 (ArO), 159.6 (ArO), 157.5 (ArO), 137.3 (Ar), 128.7 (Ar), 128.4 (Ar), 127.6 (Ar), 105.9 (C=C), 102.9 (Ar), 97.2 (Ar), 92.5 (Ar), 89.2 (C), 56.9 (OCH_3), 56.3 (OCH_3), 55.8, (OCH_3) 51.9 (CH_2), 47.1 (CH_2), 39.1 (CH), 13.4 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{25}NO_6Cl$: 458.1370; found: 458.1374 $[M+H]^+$.

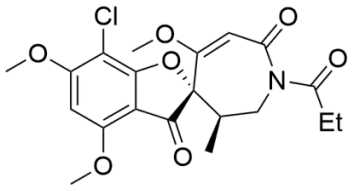


3c

(3R,4S)-1-phenyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3c)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous DMSO (1 mL) in a 5 mL round-bottom flask. Subsequently, add 2 mg (0.01 mmol) of CuI, 15 mg (0.1 mmol) of CsF and 42 mg (0.2 mmol) of iodobenzene. The resulting mixture was stirred at 130 °C overnight. The reaction was monitored by TLC, the mixture was filtered, and the filtrate was diluted with ethyl acetate. Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3c** (16.0 mg, 37% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White oil. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.33 (m, 2H, ArH), 7.27 (s, 3H, ArH), 6.12 (s, 1H, ArH), 5.62 (s, 1H, CH_2), 4.61 (dd, *J* = 15.3, 7.9 Hz, 1H, C=CH), 4.02 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.49 (d, *J* = 15.2 Hz, 1H, CH_2), 2.75 (m, 1H, CH), 1.01 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0 (C=O), 169.0 (C=ON), 164.9 (C=C), 164.4 (ArO), 160.0 (ArO), 157.6 (ArO), 144.3 (Ar), 129.2 (Ar), 126.7 (Ar), 126.3 (Ar), 105.8 (C=C), 103.2 (Ar), 97.3 (Ar), 92.6 (Ar), 89.3 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.0 (OCH_3), 51.5 (CH_2), 39.7 (CH), 13.6 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{23}NO_6Cl$: 444.1214; found: 444.1216 $[M+H]^+$.

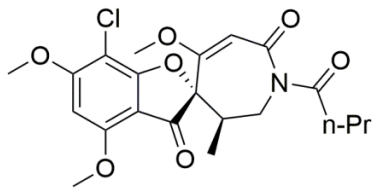


3d

(3R,4S)-1-propionyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3d)

Amide **2** (37 mg, 0.1 mmol) was dissolved in pyridine (0.5 mL) in a 5 mL round-bottom flask. Subsequently, add 0.5 ml of propionic anhydride and 2 mg (0.01 mmol) of DMAP. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, adjust the mixture to pH=1 with 1M HCl. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3d** (40.0 mg, 92% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.44 (s, 1H, C=CH), 4.14 (d, *J* = 4.9 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.03 (q, *J* = 7.2 Hz, 2H, CH_2), 2.65 – 2.50 (m, 1H, CH), 1.18 (t, *J* = 7.3 Hz, 3H, CH_3), 1.01 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2 (C=O), 177.0 (C=O), 168.5 (C=ON), 168.0 (C=C), 164.4 (ArO), 162.2 (ArO), 157.8 (ArO), 104.9 (C=C), 101.8 (Ar), 97.1 (Ar), 92.7 (Ar), 89.4 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.4 (OCH_3), 43.5 (CH_2), 40.5 (CH_2), 32.2 (CH), 13.4 (CH_3), 9.3 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{23}NO_7Cl$: 424.1163; found: 424.1171 $[M+H]^+$.

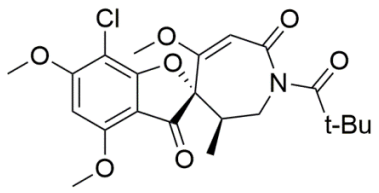


3e

(3R,4S)-1-butyryl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3e)

Amide **2** (37 mg, 0.1 mmol) was dissolved in pyridine (0.5 mL) in a 5 mL round-bottom flask. Subsequently, add 0.5 ml of butyric anhydride and 2 mg (0.01 mmol) of DMAP. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, adjust the mixture to pH=1 with 1M HCl. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3e** (40.0 mg, 92% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.46 (s, 1H, C=CH), 4.13 (d, *J* = 4.5 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.04 – 2.94 (m, 2H, CH_2), 2.56 (dd, *J* = 9.3, 7.2 Hz, 1H, CH_2), 2.32 (t, *J* = 7.4 Hz, 1H, CH_2), 1.78 – 1.61 (m, 3H, CH, CH_2), 0.99 (dd, *J* = 11.2, 8.2 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3 (C=O), 176.2 (C=O), 168.5 (C=ON), 168.0 (C=C), 164.5 (ArO), 162.2 (ArO), 157.8 (ArO), 104.9 (C=C), 101.9 (Ar), 97.1 (Ar), 92.7 (Ar), 89.4 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.4 (OCH_3), 43.3 (CH_2), 40.6 (CH_2), 40.4 (CH), 18.4 (CH_2), 13.8 (CH_3), 13.4 (CH_3). HRMS (ESI): m/z calcd for $C_{21}H_{25}NO_7Cl$: 438.1320; found: 438.1325 $[M+H]^+$.

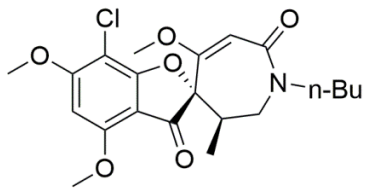


3f

(3R,4S)-1-trimethylacetyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3f)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous DCM (0.5 mL) in a 5 mL round-bottom flask. Subsequently, add 50 μl of pyridine, cool to 0 °C in an ice bath, add 200 μl of trimethylacetyl chloride dropwise. The resulting mixture was stirred at room temperature for 2h. The reaction was monitored by TLC, adjust the mixture to pH=1 with 1M HCl. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3f** (28.0 mg, 63% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White oil. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.44 (s, 1H, C=CH), 4.02 (s, 3H, OCH_3), 4.00 (m, 1H, CH_2), 3.98 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.12 (dd, *J* = 15.1, 6.3 Hz, 1H, CH_2), 2.49 (m, 1H, CH), 1.23 (m, 9H, CH_3), 0.98 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (C=O), 189.3 (C=O), 168.8 (C=ON), 166.5 (C=C), 164.4 (ArO), 161.6 (ArO), 157.7 (ArO), 105.8 (C=C), 102.6 (Ar), 97.2 (Ar), 92.9 (Ar), 89.3 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.0 (OCH_3), 51.8 (CH), 41.2 (CH_2), 28.0 (CH), 27.2 (CH_3), 13.0 (CH_3). HRMS (ESI): m/z calcd for $C_{22}H_{27}NO_7Cl$: 452.1476; found: 452.1472 $[M+H]^+$.

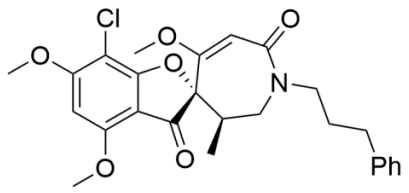


3g

(3R,4S)-1-butyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3g)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) in a 5 mL round-bottom flask. Subsequently, cool to 0°C in an ice bath, add 5 mg (0.2 mmol) of NaH, then add 16 mg (0.12 mmol) of N-butane bromide after 30 min, and then return to room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3g** (35.0 mg, 83% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.49 (s, 1H, C=CH), 4.27 (dd, *J* = 15.4, 8.1 Hz, 1H, CH_2), 4.02 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.75 – 3.62 (m, 1H, CH_2), 3.51 (s, 3H, OCH_3), 3.33 – 3.17 (m, 1H, CH_2), 2.98 (d, *J* = 15.3 Hz, 1H, CH_2), 2.48 (m, 1H, CH), 1.53 (dddd, *J* = 13.2, 8.5, 5.3, 1.8 Hz, 2H, CH_2), 1.41 – 1.31 (m, 2H, CH_2), 1.02 – 0.90 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3 (C=O), 169.0 (C=ON), 164.7 (C=C), 164.3 (ArO), 159.1 (ArO), 157.5 (ArO), 105.9 (C=C), 103.2 (Ar), 97.2 (Ar), 92.6 (Ar), 89.2 (C), 57.0 (OCH_3), 56.3 (OCH_3), 55.7 (OCH_3), 49.1 (CH_2), 48.2 (CH_2), 39.3 (CH), 30.3 (CH_2), 20.2 (CH_2), 14.0 (CH_3), 13.7 (CH_3). HRMS (ESI): m/z calcd for $C_{21}H_{27}NO_6Cl$: 424.1527; found: 424.1531 $[M+H]^+$.



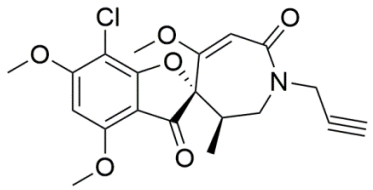
3h

(3R,4S)-1-(3-phenylpropyl)-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3h)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) in a 5 mL round-bottom flask. Subsequently, cool to 0°C in an ice bath, add 5 mg (0.2 mmol) of NaH, then add 24 mg (0.12 mmol) of 3-phenyl-1-bromopropane after 30 min, and then return to room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3h** (42.0 mg, 86% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.32 – 7.25 (m, 3H, ArH), 7.19 (s, 2H, ArH), 6.10 (s, 1H, ArH), 5.50 (s, 1H, C=CH), 4.24 (dd, *J* = 15.3, 8.0 Hz, 1H, CH_2), 4.00 (d, *J* = 1.5 Hz, 3H, OCH_3), 3.96 (d, *J* = 1.3 Hz, 3H, OCH_3), 3.72 (m, 1H, CH_2), 3.51 (s, 3H, OCH_3), 2.78 (t, *J* = 7.4 Hz, 2H, CH_2), 2.69 – 2.61 (m, 2H, CH_2), 2.46 (q, *J* = 7.4 Hz, 1H, CH), 2.17 (dq, *J* = 13.5, 6.6 Hz, 2H, CH_2), 0.94 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2 (C=O), 169.0 (C=ON), 164.9 (C=C), 164.3 (ArO), 159.3 (ArO), 157.6 (ArO), 141.6 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 126.0 (Ar), 105.9 (C=C), 103.2 (Ar), 97.2 (Ar), 92.5 (Ar), 89.2 (C), 57.0 (OCH_3), 56.3 (OCH_3), 55.7 (OCH_3), 49.0 (CH_2), 48.3 (CH_2), 39.3

(CH), 34.0 (CH_2), 33.3 (CH_2), 13.7 (CH_3). HRMS (ESI): m/z calcd for $C_{26}H_{29}NO_6Cl$: 486.1683; found: 486.1687 $[M+H]^+$.



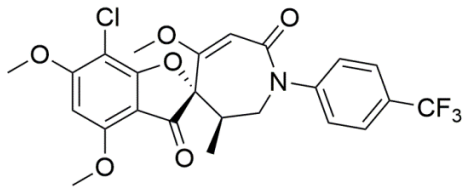
3i

(3R,4S)-1-allyl-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-Spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3i)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) in a 5 mL round-bottom flask. Subsequently, cool to 0°C in an ice bath, add 5 mg (0.2 mmol) of NaH, then add 13 mg (0.12 mmol) of 3-bromopropyne after 30 min, and then return to room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3i** (32.0 mg, 79% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (d, *J* = 1.4 Hz, 1H, ArH), 5.51 (s, 1H, C=CH), 4.71 (dt, *J* = 17.4, 2.0 Hz, 1H, CH_2), 4.33 (ddd, *J* = 15.4, 8.0, 1.4 Hz, 1H, CH_2), 4.02 (d, *J* = 1.4 Hz, 3H, OCH_3), 3.98 (d, *J* = 1.4 Hz, 3H, OCH_3), 3.53 (d, *J* = 1.3 Hz, 3H, OCH_3), 3.24 (d, *J* = 15.4 Hz, 1H, CH), 2.61 (m, 1H, CH), 0.99 (dd, *J* = 7.3, 1.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2 (C=O), 169.0 (C=ON), 164.7 (C=C), 164.4 (ArO), 160.2 (ArO), 157.6 (ArO), 105.8 (C=C), 102.4 (Ar), 97.2 (Ar), 92.5 (Ar), 89.3 (C), 78.8 (CH), 72.1 (CH), 57.0 (OCH_3),

56.4 (OCH_3), 55.9 (OCH_3), 46.9 (CH_2), 39.0 (CH_2), 37.1 (CH), 13.4 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{21}NO_6Cl$: 406.1057; found: 406.1060 $[M+H]^+$.

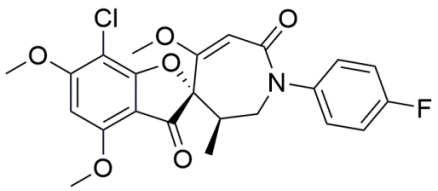


3j

(3R,4S)-1-(4-Trifluoromethylphenyl)-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3j)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous DMSO (1 mL) in a 5 mL round-bottom flask. Subsequently, add 2 mg (0.01 mmol) of CuI, 15 mg (0.1 mmol) of CsF and 48 mg (0.2 mmol) of 4-trifluoromethyl iodobenzene. The resulting mixture was stirred at 130 °C overnight. The reaction was monitored by TLC, the mixture was filtered, and the filtrate was diluted with ethyl acetate. Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3j** (16.0 mg, 31% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White oil. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 2H, ArH), 7.24 (d, *J* = 8.6 Hz, 2H, ArH), 6.12 (s, 1H, ArH), 5.61 (s, 1H, C=CH), 4.59 (dd, *J* = 15.3, 7.8 Hz, 1H, CH_2), 4.03 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.49 (d, *J* = 15.2 Hz, 1H, CH_2), 2.74 (m, 1H, CH), 1.02 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (C=O), 168.9 (C=ON), 165.1 (C=C), 164.5 (ArO), 160.4 (ArO), 157.7 (ArO), 147.2 (Ar), 142.7 (Ar), 129.9 (Ar), 127.7 (Ar), 121.8 (CF_3), 105.7 (C=C), 102.8 (Ar), 97.3 (Ar), 92.4 (Ar), 89.3 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.0 (OCH_3), 51.5 (CH_2), 39.7 (CH), 13.6 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{22}NO_6F_3Cl$: 512.1088; found: 512.1090 $[M+H]^+$.

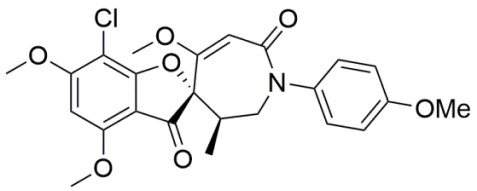


3k

(3R,4S)-1-(4-fluorophenyl)-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3k)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous DMSO (1 mL) in a 5 mL round-bottom flask. Subsequently, add 2 mg (0.01 mmol) of CuI, 15 mg (0.1 mmol) of CsF and 43 mg (0.2 mmol) of 4-fluoroiodobenzene. The resulting mixture was stirred at 130 °C overnight. The reaction was monitored by TLC, the mixture was filtered, and the filtrate was diluted with ethyl acetate. Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3k** (19.0 mg, 42% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White oil. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 2H, ArH), 7.26 – 7.13 (m, 2H, ArH), 6.12 (s, 1H, ArH), 5.60 (s, 1H, C=CH), 4.57 (dd, *J* = 15.3, 7.8 Hz, 1H, CH_2), 4.02 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (d, *J* = 15.2 Hz, 1H, CH_2), 2.73 (m, 1H, CH), 1.01 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (C=O), 168.9 (C=ON), 165.0 (C=C), 164.4 (ArO), 160.3 (ArO), 157.7 (ArO), 142.7 (Ar), 132.2 (Ar), 129.4 (Ar), 127.6 (Ar), 105.7 (C=C), 102.9 (Ar), 97.3 (Ar), 92.5 (Ar), 89.3 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.0 (OCH_3), 51.5 (CH_2), 39.7 (CH), 13.6 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{21}NO_6FNaCl$: 484.0939; found: 484.0939 $[M+Na]^+$.

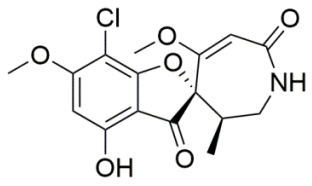


3l

(3R,4S)-1-(4-methoxyphenyl)-7'-chloro-4',5,6'-trimethoxy-3-methyl-2,3-dihydro-3'H -spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (3l)

Amide **2** (37 mg, 0.1 mmol) was dissolved in anhydrous DMSO (1 mL) in a 5 mL round-bottom flask. Subsequently, add 2 mg (0.01 mmol) of CuI, 15 mg (0.1 mmol) of CsF and 45 mg (0.2 mmol) of 4-methoxy iodobenzene. The resulting mixture was stirred at 130 °C overnight. The reaction was monitored by TLC, the mixture was filtered, and the filtrate was diluted with ethyl acetate. Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3l** (17.0 mg, 37% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.08 (m, 2H, ArH), 6.99 – 6.84 (m, 2H, ArH), 6.11 (s, 1H, ArH), 5.62 (s, 1H, C=CH), 4.57 (dd, *J* = 15.3, 7.9 Hz, 1H, CH_2), 4.02 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.46 – 3.40 (m, 1H, CH_2), 2.74 (m, 1H, CH), 1.00 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1 (C=O), 169.0 (C=ON), 165.1 (C=C), 164.4 (ArO), 159.9 (ArO), 158.1 (ArO), 157.6 (Ar), 137.3 (Ar), 127.4 (Ar), 114.5 (Ar), 105.8, 103.3 (Ar), 97.3 (Ar), 92.6 (Ar), 89.3 (C), 57.0 (OCH_3), 56.4 (OCH_3), 56.0 (OCH_3), 55.5 (OCH_3), 51.8 (CH_2), 39.7 (CH), 13.6 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{25}NO_7Cl$: 474.1320; found: 474.1324 $[M+H]^+$.

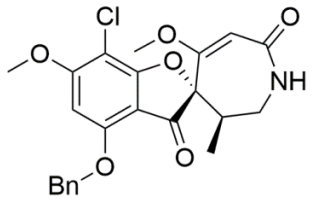


4

(3R,4S)-7'-chloro-4'-hydroxy-5,6'-dimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (4)

Amide **2** (73 mg, 0.2 mmol) was dissolved in anhydrous DCM (10 mL) in a 25 mL round-bottom flask under nitrogen atmosphere. Subsequently, cool to 0°C in an ice bath, Then add 2 ml of BBr_3 in dichloromethane solution (1M), and return to room temperature after half an hour. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium bicarbonate. The aqueous phase was extracted with DCM (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **4** (65.0 mg, 91% yield) by using mixed methanol and dichloromethane (v:v = 1:10) as eluent.

White solid. R_f = 0.2 (MeOH : DCM = 1:10). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 – 8.07 (m, 1H, OH), 7.94 – 7.86 (m, 1H, NH), 6.24 (s, 2H, ArH), 5.33 (d, J = 1.6 Hz, 1H, C=CH), 4.83 (d, J = 11.5 Hz, 1H, CH_2), 3.90 (s, 4H, OCH_3), 3.49 (s, 3H, OCH_3), 2.45 (ddd, J = 10.6, 6.8, 2.4 Hz, 1H, CH_2), 2.28 (m, 1H, CH), 0.83 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.0 (C=O), 167.8 (C=ON), 166.3 (C=C), 163.8 (ArO), 160.0 (ArO), 157.2 (ArO), 105.0 (C=C), 103.2 (Ar), 99.6 (Ar), 94.4 (Ar), 92.8 (C), 57.5 (OCH_3), 56.2 (OCH_3), 44.9(CH_2), 39.0 (CH), 12.9 (CH_3). HRMS (ESI): m/z calcd for $C_{16}H_{17}NO_6Cl$: 354.0744; found: 354.0734 $[M+H]^+$.

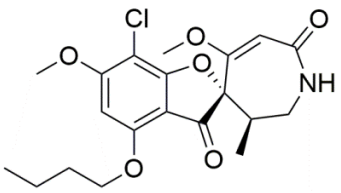


5a

(3R,4S)-7'-chloro-4'-benzyloxy-5,6'-dimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (5a)

Compound **4** (35 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 21 mg (0.12 mmol) of benzyl bromide and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **5a** (40.0 mg, 87% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.44 (m, 2H, ArH), 7.40 (t, *J* = 7.4 Hz, 2H, ArH), 7.34 (dd, *J* = 8.3, 6.1 Hz, 1H, ArH), 6.40 (t, *J* = 5.6 Hz, 1H, NH), 6.15 (s, 1H, ArH), 5.45 (d, *J* = 1.7 Hz, 1H, C=CH), 5.27 (s, 2H, CH_2), 3.98 (ddd, *J* = 15.0, 8.3, 4.7 Hz, 1H, CH_2), 3.92 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.11 (dd, *J* = 15.1, 6.3 Hz, 1H, CH_2), 2.50 (t, *J* = 7.5 Hz, 1H, CH), 1.00 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (C=O), 168.8(C=ON), 167.8 (C=C), 164.0 (ArO), 161.1 (ArO), 156.6 (ArO), 135.6 (Ar), 128.8 (Ar), 128.3 (Ar), 126.9 (Ar), 106.3 (C=C), 102.0 (Ar), 97.4 (Ar), 92.9 (Ar), 91.5 (C), 71.1 (CH_2), 56.9 (OCH_3), 56.0 (OCH_3), 41.2 (CH_2), 39.0 (CH), 13.1 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{23}NO_6Cl$: 444.1214; found: 444.1212 $[M+H]^+$.

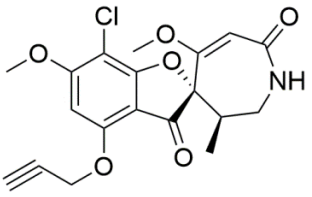


5b

(3R,4S)-7'-chloro-4'-butoxy-5,6'-dimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (5b)

Compound **4** (35 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 16 mg (0.12 mmol) of N-butane bromide and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **5b** (35.0 mg, 86% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.42 (d, *J* = 2.0 Hz, 1H, C=CH), 4.20 – 4.09 (m, 3H , CH_2), 4.00 (d, *J* = 2.1 Hz, 3H, OCH_3), 3.53 (d, *J* = 2.3 Hz, 3H, OCH_3), 3.09 (dd, *J* = 15.1, 6.3 Hz, 1H, CH_2), 2.49 (m, 1H , CH), 1.94 – 1.82 (m, 2H , CH_2), 1.53 (m, 2H, CH_2), 0.98 (m, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4 (C=O), 168.7 (C=ON), 168.1 (C=C), 164.1 (ArO), 161.2 (ArO), 157.3 (ArO), 105.9 (C=C), 101.9 (Ar), 96.8 (Ar), 92.7 (Ar), 90.2 (C), 69.2 (CH_2), 56.9 (OCH_3), 55.9 (OCH_3), 41.1 (CH_2), 39.0 (CH), 30.8 (CH_2), 19.1 (CH_2), 13.8 (CH_3), 13.1 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{25}NO_6Cl$: 410.1370; found: 410.1371 $[M+H]^+$.

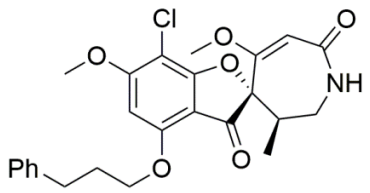


5c

(3R,4S)-7'-chloro-4'-propargyloxy-5,6'-dimethoxy-3-methyl-2,3-dihydro-3'H-spiro [azepine-4 ,2'-benzofuran] -3',7(1H)-dione (5c)

Compound **4** (35 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 13 mg (0.12 mmol) of 3-bromopropyne and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **5c** (28.0 mg, 72% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H, ArH), 5.43 (d, *J* = 1.7 Hz, 1H, C=CH), 4.91 (dd, *J* = 3.9, 2.5 Hz, 2H, CH_2), 4.02 (s, 3H, OCH_3), 3.97 – 3.88 (m, 2H, CH_2), 3.54 (s, 3H, OCH_3), 3.13 (dd, *J* = 15.1, 6.2 Hz, 1H, CH), 2.55 – 2.38 (m, 1H, CH), 0.98 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6 (C=O), 168.7 (C=ON), 167.9 (C=C), 164.0 (ArO), 160.9 (ArO), 155.2 (ArO), 106.2 (C=C), 102.2 (Ar), 98.1 (Ar), 93.0 (Ar), 91.7 (CHC), 77.5 (CHC), 57.1 (CH_2), 57.0 (OCH_3), 55.9 (OCH_3), 41.1(CH_2), 38.9 (CH), 12.9 (CH_3). HRMS (ESI): m/z calcd for $C_{19}H_{19}NO_6Cl$: 392.0901; found: 392.0899 $[M+H]^+$.

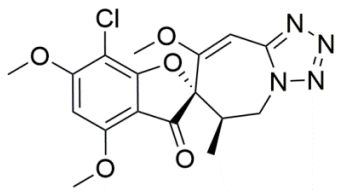


5d

(3R,4S)-7'-chloro-4'-(3-phenylpropoxy)-5,6'-dimethoxy-3-methyl-2,3-dihydro-3'H-spiro[azepine-4 ,2'-benzofuran] -3',7(1H)-dione (5d)

Compound **4** (35 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 24 mg (0.12 mmol) of 3-phenyl-1-bromopropane and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **5d** (38.0 mg, 83% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 3H, ArH), 7.19 (s, 2H, ArH), 6.01 (s, 1H, ArH), 5.43 (d, *J* = 1.4 Hz, 1H, C=CH, CH_2), 4.09 (t, *J* = 6.4 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.10 (dd, *J* = 15.0, 6.3 Hz, 1H, CH_2), 2.58 – 2.41 (m, 1H, CH), 2.20 (q, *J* = 6.9 Hz, 2H, CH_2), 0.99 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (C=O), 168.7 (C=ON), 167.9 (C=C), 164.1 (ArO), 162.6 (ArO), 161.2 (Ar), 157.1 (ArO), 140.9 (Ar), 128.6 (Ar), 128.5 (Ar), 126.1 (Ar), 106.0 (Ar), 102.0 (Ar), 97.0 (Ar), 92.8 (Ar), 90.3(C), 68.1, 56.9 (OCH_3), 55.9 (OCH_3), 41.1 (CH_2), 39.0 (CH), 31.6 (CH_2), 30.1 (CH_2), 13.1 (CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{27}NO_6Cl$: 472.1527; found: 472.1534 $[M+H]^+$.

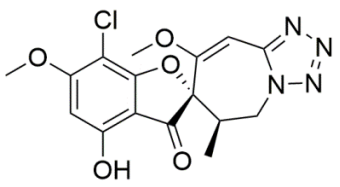


6

(2S,6'R)-7-chloro-4,6,8'-trimethoxy-6'-methyl-5',6'-dihydro-3H-spiro[benzofuran-2, 7 '-tetrazole [1,5-a] azepine]-3-one (6)

Griseofulvin **1** (176 mg, 0.5 mmol) was dissolved in trifluoroacetic acid (2 mL) in a 25 mL round-bottom flask. Subsequently, add 163 mg (2.5 mmol) of sodium azide several times. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **6** (82.0 mg, 42% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (s, 1H, ArH), 6.16 (s, 1H, C=CH), 4.92 (dd, *J* = 14.7, 7.3 Hz, 1H, CH_2), 4.69 (dd, *J* = 14.7, 1.3 Hz, 1H, CH_2), 4.04 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.64 – 2.48 (m, 1H, CH), 1.07 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6 (C=O), 168.1 (C=C), 164.7 (ArO), 159.8 (ArO), 158.0 (ArO), 149.7 (C=N), 105.0 (C=C), 97.5 (Ar), 90.9 (Ar), 90.3 (C), 89.7 (Ar), 57.1 (OCH_3), 56.6 (OCH_3), 56.5 (OCH_3), 47.6 (CH_2), 34.8 (CH), 11.3 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{18}N_4O_5Cl$: 393.0966; found: 393.0973 $[M+H]^+$.

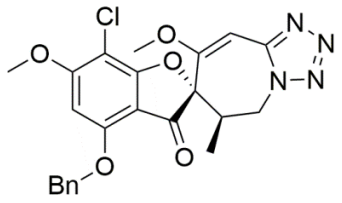


7

(2S,6'R)-7-chloro-4-hydroxy-6,8'-dimethoxy-6'-methyl-5',6'-dihydro-3H-spiro[benzofuran-2,7 '-tetrazole [1,5-a] azepine]-3-one (7)

Compound **6** (78 mg, 0.2 mmol) was dissolved in anhydrous DCM (10 mL) in a 25 mL round-bottom flask under nitrogen atmosphere. Subsequently, cool to 0°C in an ice bath, Then add 2 ml of BBr_3 in dichloromethane solution (1M), and return to room temperature after half an hour. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium bicarbonate. The aqueous phase was extracted with DCM (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **7** (70.0 mg, 93% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 1H, ArH), 6.26 (s, 1H, C=CH), 4.89 (dd, *J* = 14.8, 6.6 Hz, 1H, CH_2), 4.75 (dd, *J* = 14.7, 1.5 Hz, 1H, CH_2), 3.99 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.58 (m, 1H, CH), 1.08 (d, *J* = 7.2 Hz, 3H , CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6 (C=O), 165.8 (C=C), 165.5 (ArO), 159.2 (ArO), 156.4 (ArO), 149.6 (C=N), 103.7 (C=C), 96.8 (Ar), 94.1 (Ar), 91.5 (C), 90.6 (Ar), 57.3 (OCH_3), 56.8 (OCH_3), 48.1 (CH_2), 34.5 (CH), 10.9 (CH_3). HRMS (ESI): m/z calcd for $C_{16}H_{16}N_4O_5Cl$: 379.0809; found: 379.0812 $[M+H]^+$.

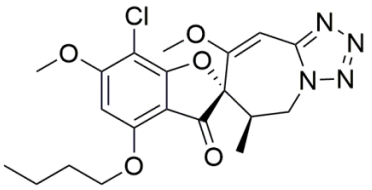


8a

(2S,6'R)-7-chloro-4-benzyloxy-6,8'-dimethoxy-6'-methyl-5',6'-dihydro-3H-spiro[benzofuran-2,7 '-tetrazole [1,5-a] azepine]-3-one (8a)

Compound **7** (47 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 21 mg (0.12 mmol) of benzyl bromide and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **8a** (40.0 mg, 68% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:3) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.3 Hz, 2H, ArH), 7.41 (t, *J* = 7.4 Hz, 2H, ArH), 7.35 (d, *J* = 7.2 Hz, 1H, ArH), 6.31 (s, 1H, ArH), 6.19 (s, 1H, C=CH), 5.30 (d, *J* = 2.2 Hz, 2H, OCH_2), 4.94 (dd, *J* = 14.7, 7.4 Hz, 1H, CH_2), 4.69 (dd, *J* = 14.7, 1.5 Hz, 1H, CH_2), 3.94 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.64 – 2.53 (m, 1H, CH), 1.09 (d, *J* = 7.2 Hz, 3H , CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2 (C=O), 168.4 (C=C), 164.4 (ArO), 159.9 (ArO), 156.9 (ArO), 149.8 (C=N), 135.4 (ArC), 128.9 (Ar), 128.4 (Ar), 126.8 (Ar), 105.5 (C=C), 97.6 (Ar), 91.8 (Ar), 90.9 (C), 90.2 (Ar), 71.2(OCH_2), 57.0 (OCH_3), 56.6 (OCH_3), 47.6 (CH_2), 34.8 (CH), 11.4 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{22}N_4O_5Cl$: 469.1279; found: 469.1282 $[M+H]^+$.

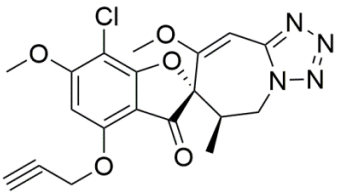


8b

(2S,6'R)-7-chloro-4-butoxy-6,8'-dimethoxy-6'-methyl-5',6'-dihydro-3H-spiro[benzo furan-2,7 '-tetrazole [1,5-a] azepine]-3-one (8b)

Compound **7** (47 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 16 mg (0.12 mmol) of N-butane bromide and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **8b** (35.0 mg, 64% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:3) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (s, 1H, ArH), 6.16 (s, 1H, C=CH), 4.94 (dd, *J* = 14.7, 7.5 Hz, 1H, CH_2), 4.69 (dd, *J* = 14.8, 1.8 Hz, 1H, CH_2), 4.14 (t, *J* = 6.7 Hz, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.59 (t, *J* = 7.4 Hz, 1H, CH), 1.98 – 1.80 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.08 (dd, *J* = 7.3, 1.3 Hz, 3H, CH_3), 1.00 (td, *J* = 7.4, 1.5 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1 (C=O), 168.1 (C=C), 164.5 (ArO), 160.0 (ArO), 157.7 (ArO), 149.8 (C=N), 105.1 (C=C), 97.0 (Ar), 90.7 (Ar), 90.5 (C), 90.0 (Ar), 69.3 (OCH_2), 57.0 (OCH_3), 56.6 (OCH_3), 47.6 (CH_2), 34.8 (CH), 30.8 (CH_2), 19.1 (CH_2), 13.8 (CH_3), 11.5 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{24}N_4O_5Cl$: 435.1435; found: 435.1440 $[M+H]^+$.

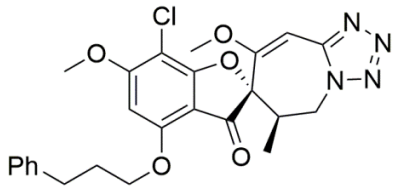


8c

(2S,6'R)-7-chloro-4-propargyloxy-6,8'-dimethoxy-6'-methyl-5',6'-dihydro-3H-spiro [benzofuran-2,7 '-tetrazole [1,5-a] azepine]-3-one (8c)

Compound **7** (47 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 13 mg (0.12 mmol) of 3-bromopropyne and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **8c** (28.0 mg, 54% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:3) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (d, *J* = 1.6 Hz, 1H, ArH), 6.30 (t, *J* = 2.4 Hz, 1H, C=CH), 5.04 – 4.85 (m, 1H, CH_2), 4.70 (dt, *J* = 14.7, 2.0 Hz, 1H, CH_2), 4.05 (d, *J* = 2.4 Hz, 2H, CH_2), 3.70 (d, *J* = 2.7 Hz, 1H, CHC), 2.69 (d, *J* = 2.5 Hz, 1H, CH_2), 2.64 – 2.48 (m, 1H, CH_2), 1.10 – 1.00 (m, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3 (C=O), 168.0(C=C), 164.4 (ArO), 159.7 (ArO), 155.6 (ArO), 149.7 (C=N), 105.3 (C=C), 98.2 (Ar), 92.0 (Ar), 90.9 (C), 90.3 (Ar), 77.7 (CHC), 76.9 (CHC), 57.2 (CH_2), 57.1 (OCH_3), 56.6 (OCH_3), 47.7 (CH_2), 34.7 (CH), 11.3 (CH_3). HRMS (ESI): m/z calcd for $C_{19}H_{18}N_4O_5Cl$: 417.0966; found: 417.0975 $[M+H]^+$.

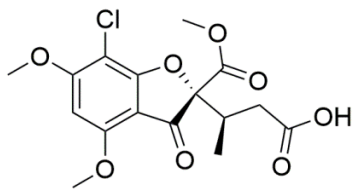


8d

(2S,6'R)-7-chloro-4-(3-phenylpropoxy)-6,8'-dimethoxy-6'-methyl-5',6'-dihydro-3H-spiro[benzofuran-2,7 '-tetrazole [1,5-a] azepine]-3-one (8d)

Compound **7** (47 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) in a 5 mL round-bottom flask. Subsequently, add 24 mg (0.12 mmol) of 3-phenyl-1-bromopropane and 28 mg (0.2 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **8d** (38.0 mg, 61% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:3) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 2H, ArH), 7.21 – 7.15 (m, 3H, ArH), 6.29 (d, *J* = 2.9 Hz, 1H, ArH), 6.08 (s, 1H, C=CH), 4.93 (ddd, *J* = 14.8, 7.4, 2.7 Hz, 1H, CH_2), 4.76 – 4.61 (m, 1H, CH_2), 4.13 (tt, *J* = 6.5, 3.6 Hz, 2H, CH_2), 3.95 (d, *J* = 1.7 Hz, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.92 – 2.78 (m, 2H, CH_2), 2.58 (tt, *J* = 7.4, 2.0 Hz, 1H, CH), 2.34 – 2.17 (m, 2H, CH_2), 1.08 (dd, *J* = 7.2, 2.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2 (C=O), 168.0 (C=C), 164.5 (ArO), 160.0 (ArO), 157.5 (ArO), 149.8 (C=N), 140.9 (Ar), 128.6 (Ar), 128.5 (Ar), 126.1 (Ar), 105.1 (C=C), 97.1 (Ar), 90.8 (C), 90.7 (Ar), 90.0 (Ar), 68.2 (CH_2), 57.1 (OCH_3), 56.6 (OCH_3), 47.6 (CH_2), 34.8 (CH), 31.6 (CH_2), 30.1 (CH_2), 11.4 (CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{26}N_4O_5Cl$: 497.1592; found: 497.1585 $[M+H]^+$.

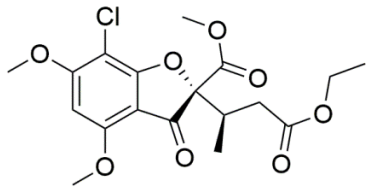


9

(R)-3-((R)-7-chloro-4,6-dimethoxy-2-(methoxycarbonyl)-3-oxo-2,3-dihydrobenzo furan-2-yl)butanoic acid (9)

Griseofulvin **1** (211 mg, 0.6 mmol) was dissolved in mixed acetonitrile and water (v:v = 6:1) (3.5 mL) in a 25 mL round-bottom flask. Subsequently, add 193 mg (0.9 mmol) of sodium periodate and 5 mg (0.02 mmol) of ruthenium trichloride. The resulting mixture was stirred at 60 °C overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium thiosulfate. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **9** (185.0 mg, 83% yield) by using mixed ethyl acetate and petroleum ether (v:v = 3:1) as eluent.

White solid. R_f = 0.1 (EtOAc : prtroleum ether = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H, COOH), 6.14 (s, 1H, ArH), 4.10 – 3.99 (m, 3H, OCH_3), 3.96 (dd, *J* = 4.0, 1.9 Hz, 3H, OCH_3), 3.77 (dd, *J* = 4.2, 2.0 Hz, 3H, OCH_3), 3.19 (ddq, *J* = 10.1, 6.3, 3.1 Hz, 1H, CH), 2.32 (ddt, *J* = 16.1, 5.7, 3.0 Hz, 1H, CH_2), 2.13 (dddd, *J* = 15.8, 13.7, 6.1, 3.4 Hz, 1H, CH_2), 1.20 (td, *J* = 6.9, 6.3, 2.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C=O), 176.9(COO), 168.8(COO), 165.5 (ArO), 164.9 (ArO), 158.0 (ArO), 104.4 (Ar), 97.7 (Ar), 95.3 (Ar), 89.9(C), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 34.8 (CH), 14.6 (CH_3). HRMS (ESI): m/z calcd for $C_{16}H_{17}O_8NaCl$: 395.0510; found: 395.050 $[M+Na]^+$.

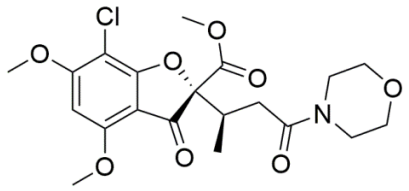


10a

Methyl (R)-7-chloro-2-((R)-4-ethoxy-4-oxobutan-2-yl)-4,6-dimethoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10a)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 92 mg (2 mmol) of ethanol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10a** (134.0 mg, 88% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 1H, ArH), 4.02 (qd, *J* = 7.1, 4.3 Hz, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.15 (dtd, *J* = 13.6, 6.8, 3.2 Hz, 1H, CH), 2.20 (dd, *J* = 15.5, 3.2 Hz, 1H, CH_2), 2.03 (dd, *J* = 15.4, 10.9 Hz, 1H, CH_2), 1.14 (t, *J* = 7.1 Hz, 3H, CH_3), 1.12 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C=O), 171.2 (COO), 168.9 (COO), 165.5 (ArO), 164.8 (ArO), 157.9 (ArO), 104.5 (Ar), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 60.6 (OCH_3), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_2), 35.0 (CH_2), 35.0 (CH), 14.6 (CH_3), 14.1 (CH_3). HRMS (ESI): m/z calcd for $C_{18}H_{21}O_8NaCl$: 423.0823; found: 423.0820 $[M+Na]^+$.

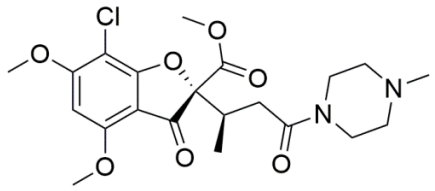


10b

methyl (R)-7-chloro-4,6-dimethoxy-2-((R)-4-morpholino-4-oxobutan-2-yl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10b)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 36 mg (0.4 mmol) of morpholine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10b** (114.0 mg, 72% yield) by using mixed ethyl acetate and petroleum ether (v:v = 2:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.64 (d, *J* = 4.4 Hz, 4H, CH_2), 3.61 – 3.53 (m, 2H, CH_2), 3.41 (d, *J* = 4.9 Hz, 2H, CH_2), 3.22 – 3.13 (m,2H, CH_2), 2.36 (d, *J* = 14.4 Hz, 1H, CH), 2.20 – 2.10 (m, 2H, CH_2), 1.17 (dd, *J* = 6.8, 2.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 169.2 (C=ON), 168.9 (COO), 165.7 (ArO),, 164.9 (ArO),, 157.9 (ArO),, 104.5 (Ar), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 66.9 (OCH_2), 66.7 (OCH_2), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 46.1 (CH_2), 42.0 (CH_2), 35.0 (CH_2), 33.5 (CH_2), 14.4 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{25}NO_8Cl$: 442.1269; found: 442.1269 $[M+H]^+$.

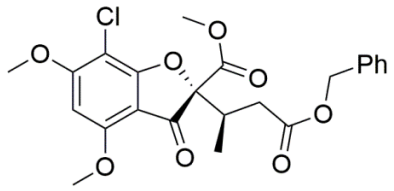


10c

methyl (R)-7-chloro-4,6-dimethoxy-2-((R)-4-(4-methylpiperazin-1-yl)-4-oxobutan-2-yl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10c)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 40 mg (0.4 mmol) of 1-methylpiperazine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10c** (159.0 mg, 92% yield) by using mixed methanol and dichloromethane (v:v = 1:30) as eluent.

White solid. R_f = 0.3 (MeOH : DCM = 1:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (dtd, *J* = 18.7, 12.9, 7.0 Hz, 2H, CH_2), 3.44 (tq, *J* = 14.2, 9.0, 7.0 Hz, 2H, CH_2), 3.18 (ddd, *J* = 11.1, 8.4, 2.9 Hz, 1H, CH), 2.43 – 2.33 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 2.15 (dd, *J* = 14.3, 11.3 Hz, 2H, CH_2), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 168.9 (C=ON), 165.7 (ArO), 164.8 (ArO), 157.9 (ArO), 104.6 (Ar), 97.8 (Ar), 95.6 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 55.2 (OCH_3), 54.7 (CH_2), 53.4 (CH_2), 46.0 (CH_2), 45.6 (CH_2), 41.6 (CH_2), 35.1 (CH), 33.7 (CH_3), 14.4 (CH_3). HRMS (ESI): m/z calcd for $C_{21}H_{28}N_2O_7Cl$: 455.1585; found: 455.1586 $[M+H]^+$.

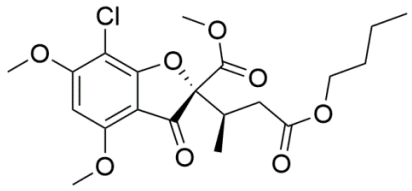


10d

methyl (R)-7-chloro-4,6-dimethoxy-2-((R)-4-(4-methylpiperazin-1-yl)-4-oxobutan-2-yl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10d)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 216 mg (2 mmol) of phenylmethanol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10d** (92.0 mg, 53% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.4 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H, ArH), 6.10 (s, 1H, ArH), 5.13 – 4.99 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.75 (s,3H, OCH_3), 3.25 (qd, *J* = 6.5, 6.0, 2.6 Hz, 1H, CH_2), 2.33 (dd, *J* = 15.7, 3.3 Hz, 1H, CH_2), 2.17 (ddd, *J* = 15.5, 10.7, 1.4 Hz, 1H, CH), 1.19 (dd, *J* = 6.9, 1.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C=O), 171.1 (COO), 168.9 (COO), 165.5(ArO), 164.8(ArO), 158.0(ArO), 135.6 (Ar), 128.6 (Ar), 128.3 (Ar), 127.0 (Ar), 104.4 (Ar), 97.7 (Ar), 95.5 (Ar), 89.8 (C), 66.5 (CH_2), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 35.0 (CH), 14.6 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{23}O_8NaCl$: 485.0979; found: 485.0977 $[M+Na]^+$.

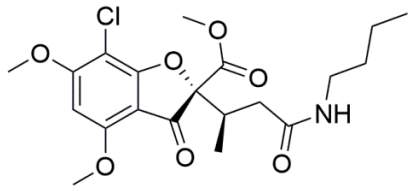


10e

methyl (R)-2-((R)-4-butoxy-4-oxobutan-2-yl)-7-chloro-4,6-dimethoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10e)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 148 mg (2 mmol) of butan-1-ol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10e** (74.0 mg, 57% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.5 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 1H, ArH), 4.07 – 4.04 (m, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.29 – 3.15 (m, 1H, CH_2), 2.28 (dd, *J* = 15.5, 3.2 Hz, 1H, CH_2), 2.11 (dd, *J* = 15.4, 11.0 Hz, 1H, CH), 1.63 – 1.50 (m, 2H, CH_2), 1.34 (q, *J* = 7.5 Hz, 2H, CH_2), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C=O), 171.3 (COO), 168.9 (COO), 165.5 (ArO), 164.8 (ArO), 157.9 (ArO), 104.4 (Ar), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 64.5 (CH_2), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 35.0 (CH), 34.9 (CH_2), 30.6 (CH_2), 19.1 (CH_2), 14.6 (CH_3), 13.7 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{25}O_8NaCl$: 451.1136; found: 451.1134 $[M+Na]^+$.

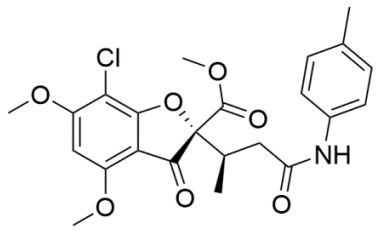


10f

methyl (R)-2-((R)-4-(butylamino)-4-oxobutan-2-yl)-7-chloro-4,6-dimethoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10f)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 29 mg (0.4 mmol) of butan-1-amine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10f** (142.0 mg, 93% yield) by using mixed ethyl acetate and petroleum ether (v:v = 2:1) as eluent.

White solid. R_f = 0.25 (EtOAc : prtroleum ether = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H, ArH), 5.49 (t, *J* = 5.3 Hz, 1H, NH), 4.02 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.24 – 3.18 (m, 2H, CH_2), 3.16 – 3.12 (m, 1H, CH), 2.20 (dd, *J* = 13.9, 3.3 Hz, 1H, CH_2), 1.90 (dd, *J* = 13.9, 11.2 Hz, 1H, CH_2), 1.49 – 1.38 (m, 2H, CH_2), 1.37 – 1.25 (m, 2H, CH_2), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3), 0.90 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2 (C=O), 170.3 (C=ON), 168.9 (COO), 165.7 (ArO), 164.8 (ArO), 157.9 (ArO), 104.6 (=CC=O), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 39.3 (CH), 37.1 (CH_2), 36.0 (CH_2), 31.6 (CH_2), 20.0 (CH_2), 14.3 (CH_3), 13.7 (CH_3). HRMS (ESI): m/z calcd for $C_{20}H_{27}NO_7Cl$: 428.1476; found: 428.1471 $[M+H]^+$.

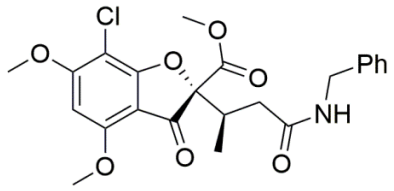


10g

methyl (R)-7-chloro-4,6-dimethoxy-3-oxo-2-((R)-4-oxo-4-(p-tolylamino)butan-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (10g)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 43 mg (0.4 mmol) of *p*-toluidine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10g** (140.0 mg, 88% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.2 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, NH), 7.34 (d, *J* = 3.1 Hz, 2H, ArH), 7.09 (d, *J* = 8.3 Hz, 2H, ArH), 6.12 (s, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.28 (ddp, *J* = 10.5, 6.7, 3.3 Hz, 1H, CH), 2.44 (dd, *J* = 14.1, 3.8 Hz, 1H, CH_2), 2.29 (s, 3H, CH_3), 2.11 (dd, *J* = 14.1, 10.6 Hz, 1H, CH_2), 1.22 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5 (C=O), 168.9 (C=ON), 168.5 (COO), 165.7 (ArO), 164.9 (ArO), 158.0 (ArO), 135.2 (Ar), 133.9 (Ar), 129.4 (Ar), 119.8 (Ar), 104.7 (Ar), 97.8 (Ar), 95.3 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 53.5 (OCH_3), 38.2 (CH), 35.9 (CH_2), 20.9 (CH_3), 14.5 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{25}NO_7Cl$: 462.1320; found: 462.1321 $[M+H]^+$.

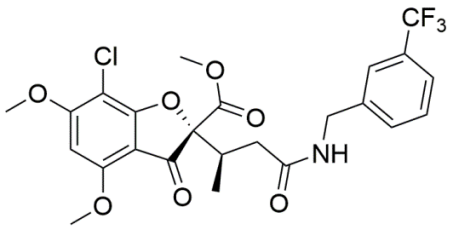


10h

methyl (R)-2-((R)-4-(benzylamino)-4-oxobutan-2-yl)-7-chloro-4,6-dimethoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10h)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 43 mg (0.4 mmol) of phenylmethanamine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10h** (126.0 mg, 72% yield) by using mixed ethyl acetate and petroleum ether (v:v = 2:1) as eluent.

White solid. R_f = 0.25 (EtOAc : prtroleum ether = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 1H, ArH), 7.33 – 7.27 (m, 2H, ArH), 7.26 – 7.20 (m, 2H, ArH), 6.11 (s, 1H, ArH), 5.83 (s, 1H, ArH), 4.48 – 4.29 (m, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.29 – 3.11 (m, 1H, CH), 2.24 (dd, *J* = 14.1, 3.2 Hz, 1H, CH_2), 1.95 (dd, *J* = 14.1, 11.1 Hz, 1H, CH_2), 1.18 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 170.3 (C=ON), 168.9 (COO), 165.7 (ArO), 164.9 (ArO), 158.0 (ArO), 138.0 (Ar), 128.7 (Ar), 127.8 (Ar), 127.5 (Ar), 104.5 (Ar), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 53.5 (OCH_3), 43.7 (CH_2), 37.0 (CH), 35.9 (CH_2), 14.4 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{25}NO_7Cl$: 462.1320; found: 462.1317 $[M+H]^+$.

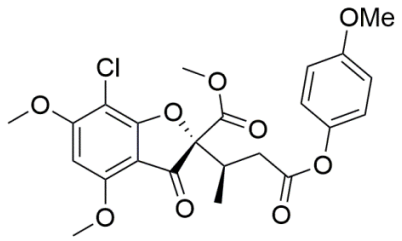


10i

methyl (R)-7-chloro-4,6-dimethoxy-3-oxo-2-((R)-4-oxo-4-((3-(trifluoromethyl) benzyl)amino)butan-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (10i)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DMF (2 mL) in a 5 mL round-bottom flask. Subsequently, add 100 mg (0.76 mmol) of DIPEA and 218 mg (0.57 mmol) of HATU. After stirring for half an hour, add 60 mg (0.4 mmol) of (3-(trifluoromethyl)phenyl)methanamine. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with ethyl acetate (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10i** (151.0 mg, 75% yield) by using mixed ethyl acetate and petroleum ether (v:v = 2:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.50 (m, 1H, ArH), 7.48 (s, 1H, ArH), 7.46 – 7.39 (m, 2H, ArH), 6.12 (s, 1H, ArH), 5.99 (t, *J* = 6.0 Hz, 1H, NH), 4.54 – 4.36 (m, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.32 – 3.08 (m, 1H, CH), 2.28 (dd, *J* = 14.1, 3.3 Hz, 1H, CH_2), 1.99 (dd, *J* = 14.1, 10.9 Hz, 1H, CH_2), 1.18 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 170.6 (C=ON), 168.9 (COO), 165.6 (ArO), 165.0 (ArO), 158.0 (ArO), 139.2 (Ar), 131.2 (Ar), 131.2 (Ar), 129.2 (Ar), 124.4 (CF_3), 124.4 (Ar), 124.3 (Ar), 104.5 (Ar), 97.8 (Ar), 95.4 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 53.5 (OCH_3), 43.1 (CH_2), 37.0 (CH), 35.9 (CH_2), 14.4 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{24}NO_7ClF_3$: 530.1193; found: 530.1190 $[M+H]^+$.

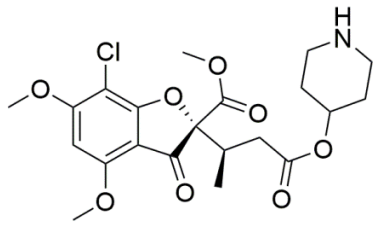


10j

methyl (R)-7-chloro-4,6-dimethoxy-2-((R)-4-(4-methoxyphenoxy)-4-oxobutan-2-yl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (10j)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 248 mg (2 mmol) of 4-methoxyphenol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10j** (93.0 mg, 53% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.25 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.92 (m, 2H, ArH), 6.89 – 6.83 (m, 2H, ArH), 6.13 (s, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.35 (ddt, *J* = 10.3, 6.9, 3.4 Hz, 1H, CH), 2.54 (dd, *J* = 15.7, 3.3 Hz, 1H, CH_2), 2.34 (dd, *J* = 15.7, 10.8 Hz, 1H, CH_2), 1.29 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C=O), 170.2 (COO), 168.9 (COO), 165.5 (ArO), 164.9 (ArO), 158.0 (ArO), 157.3 (Ar), 144.0 (Ar), 122.2 (Ar), 114.4 (Ar), 104.5 (Ar), 97.9 (Ar), 95.4 (Ar), 89.8 (C), 57.1 (OCH_3), 56.4 (OCH_3), 55.6 (OCH_3), 53.5 (OCH_3), 35.0 (CH), 35.0 (CH_2), 14.7 (CH_3). HRMS (ESI): m/z calcd for $C_{23}H_{23}O_9NaCl$: 501.0928; found: 501.0926 $[M+Na]^+$.

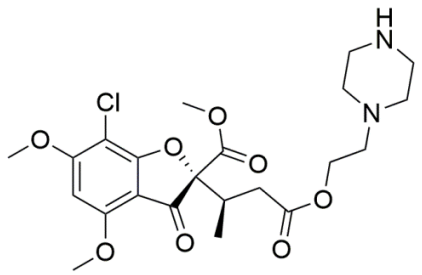


10k

methyl (R)-7-chloro-4,6-dimethoxy-3-oxo-2-((R)-4-oxo-4-(piperidin-4-yloxy)butan-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (10k)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 202 mg (2 mmol) of piperidin-4-ol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10k** (99.0 mg, 58% yield) by using mixed methanol and dichloromethane (v:v = 1:30) as eluent.

White solid. R_f = 0.25 (MeOH : DCM = 1:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H, ArH), 4.14 – 4.04 (m, 1H, CH_2), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.91 (tq, *J* = 7.9, 4.3, 3.8 Hz, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.73 – 3.59 (m, 1H, CH_2), 3.32 – 3.05 (m, 3H, CH_2), 2.38 (dd, *J* = 14.5, 3.0 Hz, 1H, CH), 2.15 (ddd, *J* = 13.8, 11.2, 2.0 Hz, 1H, CH_2), 1.94 – 1.78 (m, 2H, CH_2), 1.57 – 1.38 (m, 2H, CH_2), 1.16 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 168.9 (C=ON), 165.8 (COO), 164.8 (ArO), 157.9 (ArO), 149.2 (ArO), 106.6 (Ar), 104.6 (Ar), 97.8 (Ar), 95.6 (Ar), 89.8 (C), 67.1 (CH_2), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (OCH_3), 43.0 (CH_2), 39.1 (CH), 35.1 (CH), 34.7 (CH_2), 33.9 (CH_2), 14.4 (CH_3). HRMS (ESI): m/z calcd for $C_{21}H_{27}NO_8Cl$: 456.1425; found: 456.1419 $[M+H]^+$.



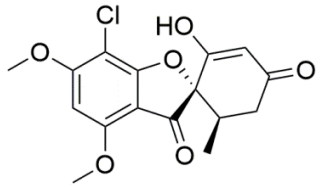
10l

methyl (R)-7-chloro-4,6-dimethoxy-3-oxo-2-((R)-4-oxo-4-(2-(piperazin-1-yl)ethoxy) butan-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (10l)

Compound **9** (142 mg, 0.38 mmol) was dissolved in anhydrous DCM (2 mL) in a 5 mL round-bottom flask. Subsequently, add 480 mg (1.9 mmol) of EDCI and 6 mg (0.05 mmol) of DMAP. After stirring for half an hour, add 260 mg (2 mmol) of 2-(piperazin-1-yl)ethan-1-ol. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **10l** (83.0 mg, 52% yield) by using mixed methanol and dichloromethane (v:v = 1:30) as eluent.

White solid. R_f = 0.25 (MeOH : DCM = 1:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.63 (t, *J* = 5.3 Hz, 2H, CH_2), 3.58 (dd, *J* = 6.5, 3.9 Hz, 1H, CH_2), 3.51 – 3.36 (m, 2H, CH_2), 3.26 (q, *J* = 7.2 Hz, 1H, CH_2), 3.17 (dqd, *J* = 13.6, 6.9, 3.0 Hz, 1H, CH), 2.56 (t, *J* = 5.4 Hz, 2H, CH_2), 2.52 – 2.44 (m, 4H, CH_2), 2.43 – 2.30 (m, 1H, CH_2), 2.15 (dd, *J* = 14.4, 11.3 Hz, 1H, CH_2), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (C=O), 168.9 (C=ON), 165.7 (COO), 164.8 (ArO), 157.9 (ArO), 149.7 (ArO), 104.6 (Ar), 97.8 (Ar), 95.5 (Ar), 89.8 (C), 59.3 (OCH_3), 57.1 (OCH_3), 56.4 (OCH_3), 53.4 (CH_2), 53.2

(CH_2), 52.6 (CH_2), 45.7 (CH_2), 45.5 (CH_2), 41.7 (CH_2), 35.0 (CH), 33.7 (CH_2), 14.3 (CH_3). HRMS (ESI): m/z calcd for $C_{22}H_{30}N_2O_8Cl$: 485.1691; found: 485.1692 $[M+H]^+$.

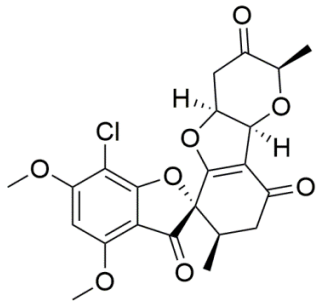


11

(2S,6'R)-7-chloro-2'-hydroxy-4,6-dimethoxy-6'-methyl-3H-spiro[benzofuran-2,1'-cyclohexan]-2'-ene-3,4'-dione (11)

Griseofulvin **1** (390 mg, 1.1 mmol) was dissolved in glacial acetic acid (4 mL) in a 25 mL round-bottom flask. Subsequently, add 2M H_2SO_4 (1 ml). The resulting mixture was stirred at 80 °C for 45 min. The reaction was monitored by TLC, the mixture was returned to room temperature. The mixture was filtered, then washed with ice water, and then with ice ethyl acetate. The filter cake is dried to obtain a crude product **11** (369.0 mg, 99% yield), which can be directly used for the next step without any purification.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.45 (s, 1H, ArH),), 5.32 (s, 1H, C=CH), 4.03 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.91 – 2.66 (m, 2H, CH_2), 2.46 (d, J = 2.9 Hz, 1H, CH), 0.85 (d, J = 6.1 Hz, 3H, CH_3). HRMS (ESI): m/z calcd for $C_{16}H_{16}O_6Cl$: 339.0635; found: 339.0633 $[M+H]^+$.

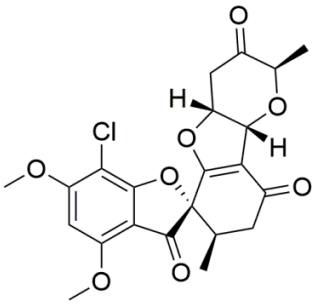


12a

(2S,2'R,4a'S,7'R,9b'S)-7-chloro-4,6-dimethoxy-2',7'-dimethyl-4a',7',8',9b'-tetrahydro-2'H,3H,9'H-spiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran]-3,3',9'(4'H)-trione (12a)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 17 mg (0.1 mmol) of (2S,6R)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **12a** (30.0 mg, 67% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H, ArH), 5.48 (d, *J* = 7.6 Hz, 1H, CH), 5.32 – 5.26 (m, 1H, CH), 4.03 (s, 3H, OCH_3), 4.01 – 3.97 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.16 (dd, *J* = 17.9, 11.7 Hz, 1H, CH_2), 2.99 (td, *J* = 17.6, 17.1, 3.2 Hz, 2H, CH_2), 2.93 – 2.86 (m, 1H, CH_2), 2.55 (ddd, *J* = 17.9, 5.6, 1.4 Hz, 1H, CH), 1.25 (d, *J* = 6.8 Hz, 3H, CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8 (C=O), 191.7 (C=O), 184.3 (C=O), 181.2 (ArO), 169.8 (ArO), 164.6 (C=C), 157.8 (ArO), 110.1 (C=C), 104.8 (Ar), 97.3 (Ar), 95.3 (Ar), 89.6 (C), 84.0 (CH), 73.3 (CH), 73.2 (CH), 57.1 (OCH_3), 56.3 (OCH_3), 38.4 (CH_2), 36.1 (CH_2), 28.0 (CH), 15.9 (CH_3), 14.9 (CH_3). HRMS (ESI): m/z calcd for $C_{22}H_{22}O_8Cl$: 449.1003; found: 449.0999 $[M+H]^+$.



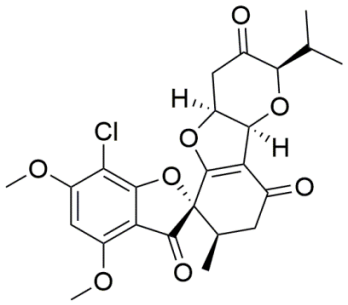
12b

(2S,2'R,4a'R,7'R,9b'R)-7-chloro-4,6-dimethoxy-2',7'-dimethyl-4a',7',8',9b'-tetrahydro-2'H,3H,9'H-spiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran]-3,3',9'(4'H)-trione (12b)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 17 mg (0.1 mmol) of (2R,6R)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **12b** (29.0 mg, 65% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (s, 1H, ArH), 5.02 (m, 1H, CH), 4.87 (d, *J* = 6.3 Hz, 1H, CH), 4.02 (s, 3H, OCH_3), 3.96 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.24 – 2.83 (m, 4H, CH_2), 2.66 (dd, *J* = 17.6, 5.2 Hz, 1H, CH), 1.35 (d, *J* = 7.0 Hz, 3H, CH_3), 1.06 (d, *J* = 6.5 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1 (C=O), 192.2 (C=O), 183.8 (C=O), 181.4 (ArO), 170.1 (ArO), 164.7 (C=C), 157.7 (ArO), 112.2 (C=C), 105.1 (Ar), 97.5 (Ar), 95.5 (Ar), 89.5 (C), 84.0 (CH), 79.1 (CH), 75.6 (CH), 57.0 (OCH_3), 56.3 (OCH_3), 39.6 (CH_2), 35.6 (CH_2),

28.3 (CH), 16.8 (CH_3), 14.7 (CH_3). HRMS (ESI): m/z calcd for $C_{22}H_{22}O_8Cl$: 449.1003; found: 449.0995 $[M+H]^+$.



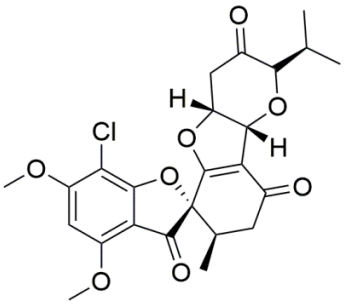
12c

(2S,2'R,4a'S,7'R,9b'S)-7-chloro-2'-isopropyl-4,6-dimethoxy-7'-methyl-4a',7',8',9b'-tetrahydro-2'H,3H,9'H-spiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran]-3,3',9'(4'H)-trione (12c)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 20 mg (0.1 mmol) of (2S,6R)-6-isopropyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **12c** (34.0 mg, 72% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H, ArH), 5.04 – 4.89 (m, 1H, CH), 4.79 (d, *J* = 6.3 Hz, 1H, CH), 4.02 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.64 (d, *J* = 3.7 Hz, 1H, CH), 3.18 – 2.99 (m, 3H, CH, CH_2), 2.92 (dd, *J* = 13.7, 8.9 Hz, 1H, CH_2), 2.67 (dd, *J* = 17.0, 4.6 Hz, 1H, CH_2), 2.17 (ddp, *J* = 10.6, 6.9, 3.5 Hz, 1H, CH), 1.07 (d, *J* = 6.4 Hz, 3H, CH_3), 1.02 (d, *J* = 6.9 Hz, 3H, CH_3), 0.91 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.6 (C=O), 192.2

(C=O), 183.5 (C=O), 181.2 (ArO), 170.0 (ArO), 164.6 (C=C), 157.7 (ArO), 112.2 (C=C), 105.1 (Ar), 97.5 (Ar), 95.7 (Ar), 89.5 (C), 86.9 (CH), 84.3 (CH), 75.6 (CH), 57.0 (OCH_3), 56.3 (OCH_3), 41.9 (CH_2), 35.6 (CH_2), 31.3 (CH), 28.3 (CH), 18.6 (CH_3), 16.8 (CH_3), 14.7 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{26}O_8Cl$: 477.1316; found: 477.1308 $[M+H]^+$.



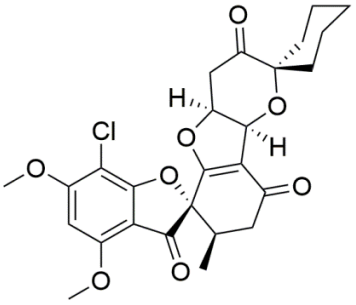
12d

(2S,2'R,4a'R,7'R,9b'R)-7-chloro-2'-isopropyl-4,6-dimethoxy-7'-methyl-4a',7',8',9b'-tetrahydro-2'H,3H,9'H-spiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran]-3,3',9'(4'H)-trione (12d)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 20 mg (0.1 mmol) of (2R,6R)-6-isopropyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **12d** (37.0 mg, 78% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, ArH), 5.54 (d, *J* = 7.7 Hz, 1H, CH), 5.36 – 5.24 (m, 1H, CH), 4.01 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.75 (d, *J* = 2.7 Hz, 1H, CH), 3.14 (dd, *J* = 17.9, 11.7 Hz, 1H,

CH_2), 2.99 – 2.79 (m, 3H, CH_2, CH), 2.55 (dd, J = 18.0, 5.7 Hz, 1H, CH_2), 2.41 – 2.21 (m, 1H, CH), 1.03 (d, J = 6.7 Hz, 3H, CH_3), 0.79 (d, J = 6.9 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8 (C=O), 191.7 (C=O), 184.1 (C=O), 181.2 (ArO), 169.8 (ArO), 164.6 (C=C), 157.9 (ArO), 109.9 (C=C), 104.8 (Ar), 97.3 (Ar), 95.4 (Ar), 89.8 (C), 84.13 (CH), 80.63 (CH), 73.13 (CH), 57.1 (OCH_3), 56.3 (OCH_3), 40.1 (CH_2), 35.8 (CH_2), 29.1 (CH), 28.0 (CH), 18.6 (CH_3), 15.9 (CH_3), 14.9 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{26}O_8Cl$: 477.1316; found: 477.1314 $[M+H]^+$.

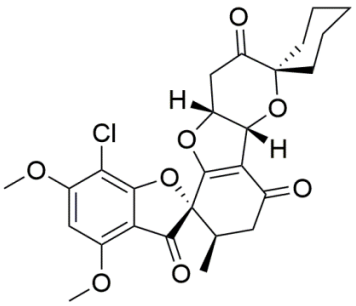


12e

(2S,4a'S,7'R,9b'S)-7-chloro-4,6-dimethoxy-7'-methyl-4a',7',8',9b'-tetrahydro-3H,9'H-dispiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran-2',1''-cyclohexane]-3,3',9'(4'H)-trione (12e)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 22 mg (0.1 mmol) of (S)-5-oxo-1-oxaspiro[5.5]undec-3-en-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **12e** (31.0 mg, 61% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H, ArH), 5.28 – 4.90 (m, 2H, CH), 4.01 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.17 – 2.81 (m, 4H, CH, CH_2), 2.72 – 2.48 (m, 1H, CH), 1.72 – 1.41 (m, 10H, CH_2), 1.08 (dd, *J* = 6.5, 1.9 Hz, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2 (C=O), 192.1 (C=O), 183.7 (C=O), 180.9 (ArO), 170.0 (ArO), 164.6 (C=C), 157.8 (ArO), 132.1 (C), 128.5 (Ar), 112.2 (C=C), 105.1 (Ar), 95.8 (Ar), 89.5 (C), 85.1 (CH), 82.7 (CH), 69.7 (CH), 57.0 (OCH_3), 56.3 (OCH_3), 39.8 (CH_2), 35.4 (CH_2), 33.7 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.1 (CH_2), 20.6 (CH_2), 20.0 (CH), 14.8 (CH_3). HRMS (ESI): m/z calcd for $C_{26}H_{28}O_8Cl$: 503.1473; found: 503.1469 $[M+H]^+$.



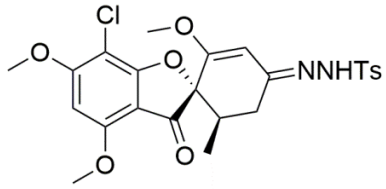
12f

(2S,4a'R,7'R,9b'R)-7-chloro-4,6-dimethoxy-7'-methyl-4a',7',8',9b'-tetrahydro-3H,9'H-dispiro[benzofuran-2,6'-pyrano[3,2-b]benzofuran-2',1''-cyclohexane]-3,3',9'(4'H)-trione (12f)

Compound **11** (37 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) in a 5 mL round-bottom flask. Subsequently, add 12 mg (0.01 mmol) of $Pd(PPh_3)_4$ and 10 mg (0.1 mmol) of triethylamine, then add 22 mg (0.1 mmol) of (R)-5-oxo-1-oxaspiro[5.5]undec-3-en-2-yl acetate. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC, the mixture was filtered, diluted with DCM (20 ml). Washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column

chromatography to give pure product **12f** (33.0 mg, 67% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H, ArH), 5.28 – 4.90 (m, 2H, CH), 4.01 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.17 – 2.81 (m, 4H, CH, CH_2), 2.72 – 2.48 (m, 1H, CH), 1.72 – 1.41 (m, 10H, CH_2), 1.08 (dd, *J* = 6.5, 1.9 Hz, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2 (C=O), 192.1 (C=O), 183.7 (C=O), 180.9 (ArO), 170.0 (ArO), 164.6 (C=C), 157.8 (ArO), 132.1 (C), 128.5 (Ar), 112.2 (C=C), 105.1 (Ar), 95.8 (Ar), 89.5 (C), 85.1 (CH), 82.7 (CH), 69.7 (CH), 57.0 (OCH_3), 56.3 (OCH_3), 39.8 (CH_2), 35.4 (CH_2), 33.7 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.1 (CH_2), 20.6 (CH_2), 20.0 (CH), 14.8 (CH_3). HRMS (ESI): m/z calcd for $C_{26}H_{28}O_8Cl$: 503.1473; found: 503.1474 $[M+H]^+$.

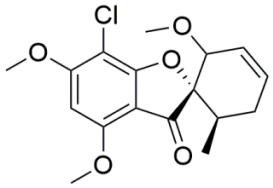


13

N'-((2S,6'R,Z)-7-chloro-2',4,6-trimethoxy-6'-methyl-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-2'-en-4'-ylidene)-4-methylbenzenesulfonohydrazide (13)

Griseofulvin **1** (353 mg, 1 mmol) was dissolved in glacial acetic acid (4 mL) in a 25 mL round-bottom flask. Subsequently, add 372 mg (2 mmol) of *p*-toluenesulfonyl hydrazide. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **13** (505.5 mg, 97% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:1) as eluent.

White solid. R_f = 0.1 (EtOAc : prtroleum ether = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 2H, ArH), 7.31 (dd, *J* = 8.2, 2.6 Hz, 2H, ArH), 6.10 (s, 1H, ArH), 5.62 (s, 1H, C=CH), 4.00 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 2.66 – 2.58 (m, 1H, CH_2), 2.58 – 2.49 (m, 1H, CH_2), 2.46 – 2.40 (m, 4H, CH_3, CH), 0.87 (t, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9 (C=O), 169.5 (C=N), 164.6 (C=C), 159.7 (ArO), 157.6 (ArO), 154.3 (ArO), 144.0 (Ar), 135.5 (Ar), 129.9 (Ar), 129.7 (Ar), 128.3 (Ar), 128.0 (Ar), 105.4 (C=C), 102.1 (Ar), 93.2 (Ar), 90.9 (Ar), 89.3 (C), 57.0 (OCH_3), 56.3 (OCH_3), 56.1 (OCH_3), 35.2 (CH), 27.7 (CH_2), 21.6 (CH_3), 14.2 (CH_3). HRMS (ESI): m/z calcd for $C_{24}H_{26}N_2O_7SCl$: 521.1149; found: 521.1148 $[M+H]^+$.

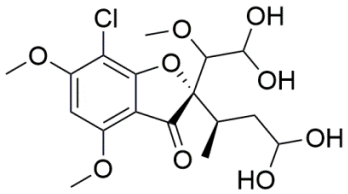


14

(2S,6'R)-7-chloro-2',4,6-trimethoxy-6'-methyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-en-3-one (14)

Compound **13** (520 mg, 1 mmol) was dissolved in anhydrous $CHCl_3$ (10 mL) in a 25 mL round-bottom flask under nitrogen atmosphere. Subsequently, cool to 0°C in an ice bath, Then add 1 ml of catechol borane in THF solution (1M), then the mixture was stirred at 0 °C for 2 h. After returning to room temperature, add 409 mg (3 mmol) of Sodium acetate trihydrate. The resulting mixture was refluxed and reacted overnight. The reaction was monitored by TLC, remove most of the solvent in the mixture. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **14** (327.9 mg, 97% yield) by using mixed ethyl acetate and petroleum ether (v:v = 1:2) as eluent.

White solid. R_f = 0.3 (EtOAc : prtroleum ether = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (s, 1H, ArH), 5.94 (d, *J* = 10.2 Hz, 1H, =CH), 5.89 – 5.76 (m, 1H, =CH), 4.06 (s, 1H, CH), 4.00 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.64 – 2.51 (m, 1H, CH), 2.35 – 2.18 (m, 1H, CH_2), 2.12 – 1.94 (m, 1H, CH_2), 1.09 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6 (C=O), 168.3 (ArO), 163.9 (ArO), 157.5 (ArO), 129.3 (Ar), 123.1 (Ar), 105.9 (Ar), 97.5 (C=C), 93.8 (C=C), 88.9 (C), 75.1 (CH), 58.8 (CH), 56.8 (OCH_3), 56.3 (OCH_3), 33.1 (OCH_3), 31.0 (CH_2), 13.8 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{20}O_5Cl$: 339.0999; found: 339.0999 $[M+H]^+$.



15

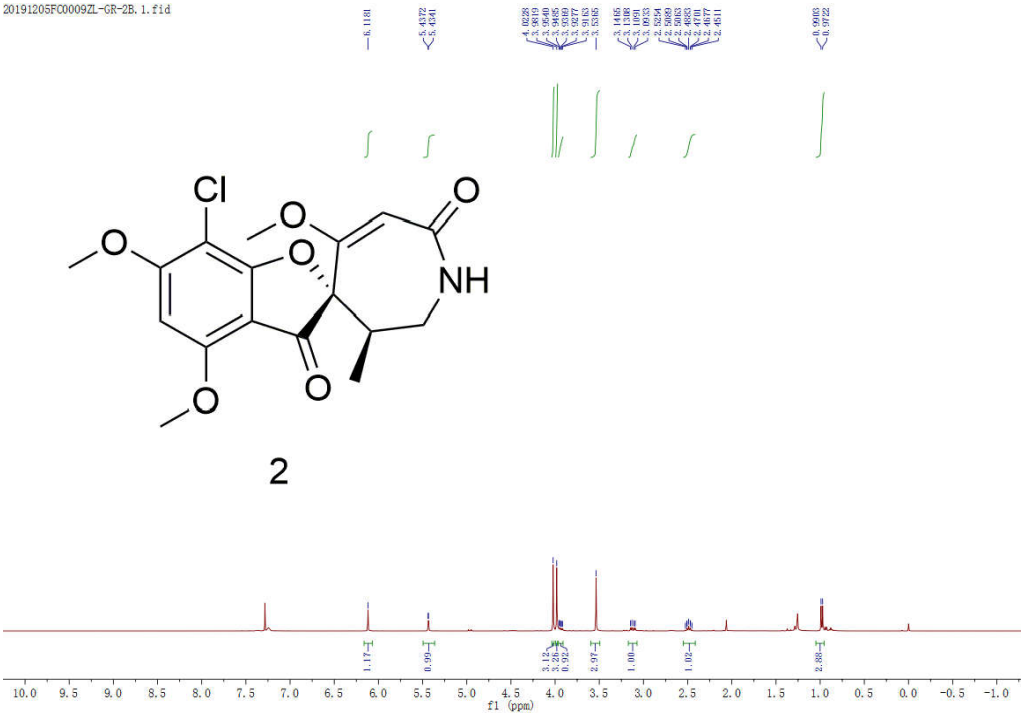
(2S)-7-chloro-2-(2,2-dihydroxy-1-methoxyethyl)-2-((R)-4,4-dihydroxybutan-2-yl)-4,6-dimethoxybenzofuran-3(2H)-one (15)

Compound **14 (**338 mg, 1 mmol) was dissolved in mixed acetonitrile and water (v:v = 6:1) (7 mL) in a 25 mL round-bottom flask. Subsequently, add 32 mg (1.5 mmol) of sodium periodate and 7 mg (0.03 mmol) of ruthenium trichloride. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC, the mixture was quenched with saturated sodium thiosulfate. The aqueous phase was extracted with ethyl acetate (10 ml x 3), the organic phases were combined, and then washed with water (20 ml x 2) and brine (10 ml x 1), dried with anhydrous sodium sulfate. The organic phase was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **15** (316.0 mg, 78% yield) by using mixed ethyl acetate and petroleum ether (v:v = 2:1) as eluent.

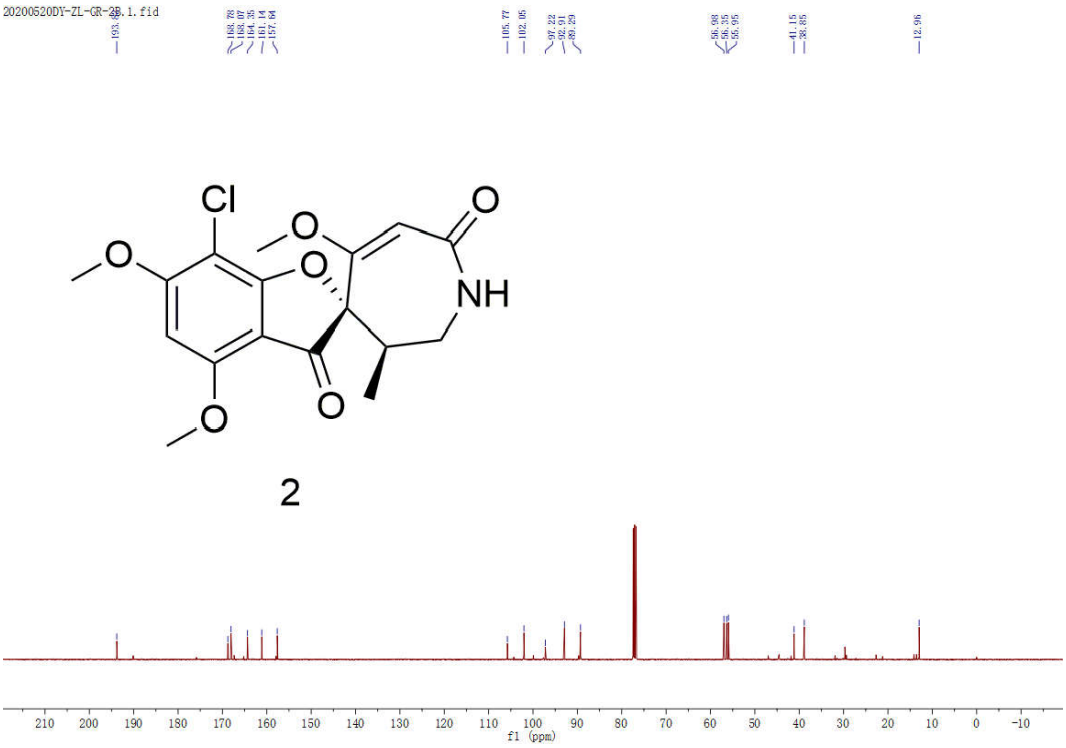
White solid. R_f = 0.1 (EtOAc : prtroleum ether = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (d, *J* = 2.0 Hz, 1H, CHO), 6.37 (s, 1H, ArH), 5.00 (d, *J* = 6.0 Hz, 1H,

OH), 4.64 (s, 1H, OH), 4.05 – 3.95 (m, 1H, CH), 3.98 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.79 (d, J = 6.2 Hz, 2H, CH), 3.28 (s, 3H, OCH_3), 1.96 – 1.76 (m, 2H, CH_2, CH), 1.67 (d, J = 14.7 Hz, 1H, CH_2), 1.18 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.3 (C=O), 167.7 (ArO), 163.9 (ArO), 157.6 (ArO), 105.5 (Ar), 96.7 (Ar), 95.8 (Ar), 90.7 (C), 79.6 (CH), 78.2 (CH), 73.1 (CH), 70.5 (CH), 61.3 (OCH_3), 57.7 (OCH_3), 56.7 (OCH_3), 35.8 (CH), 34.3 (CH_2), 16.7 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{24}O_9Cl$: 407.1109; found: 407.1116 $[M+H]^+$.

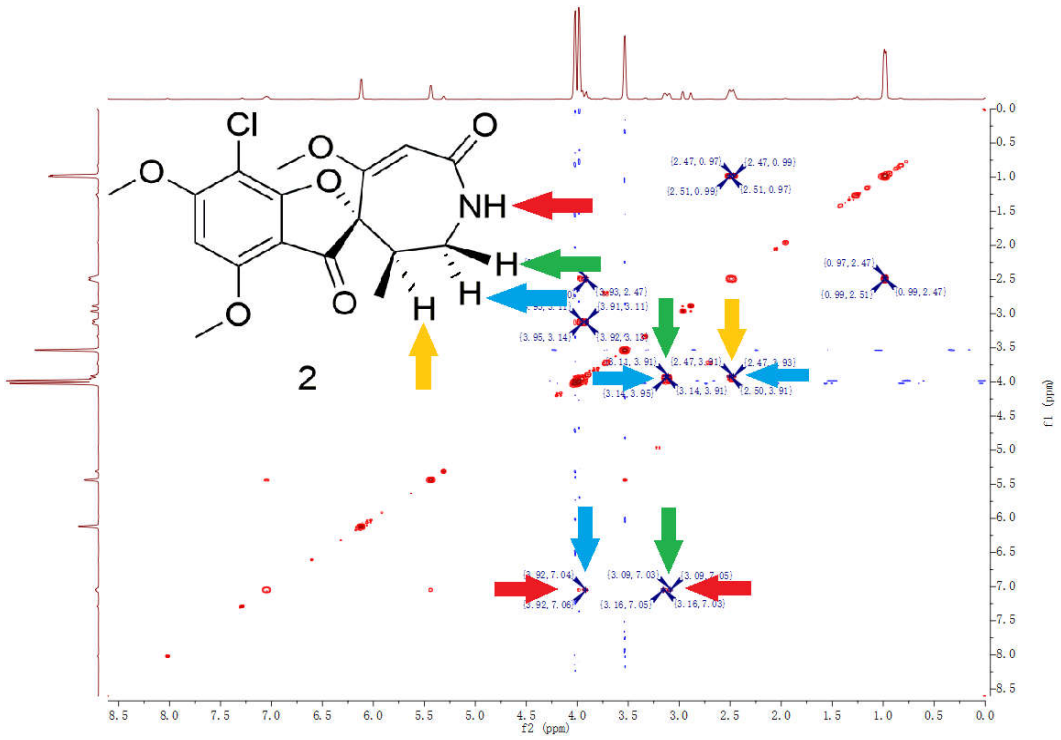
NMR spectra of all products



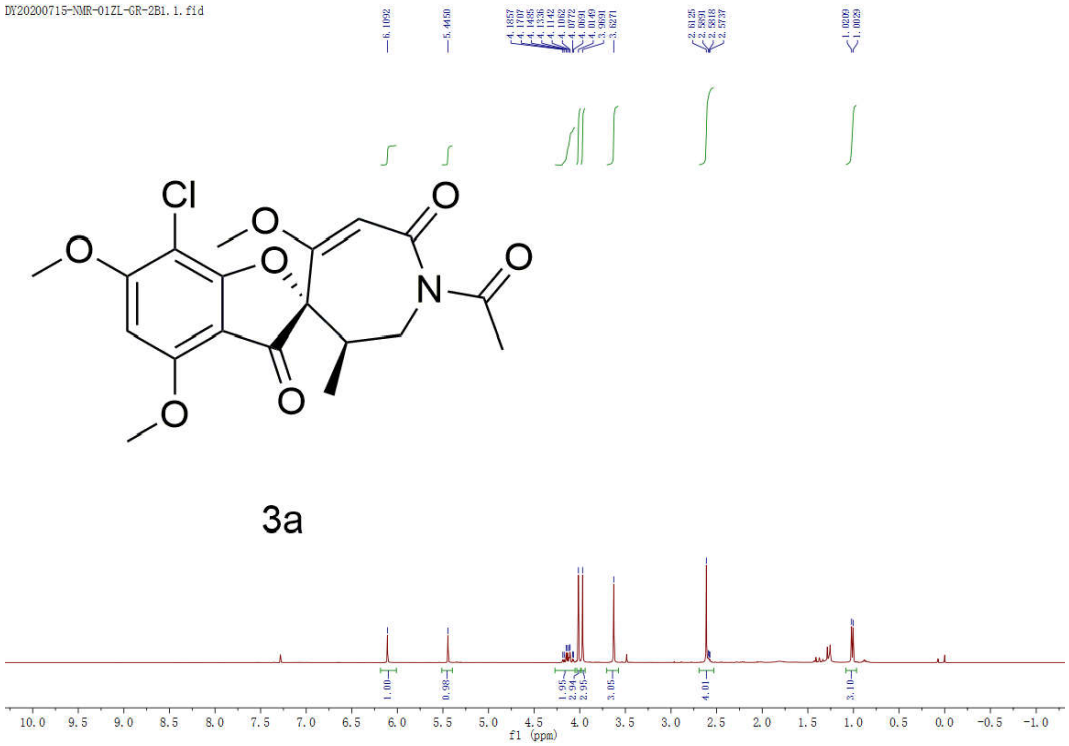
^{1}H NMR spectrum of 2 (400 MHz, $CDCl_3$)



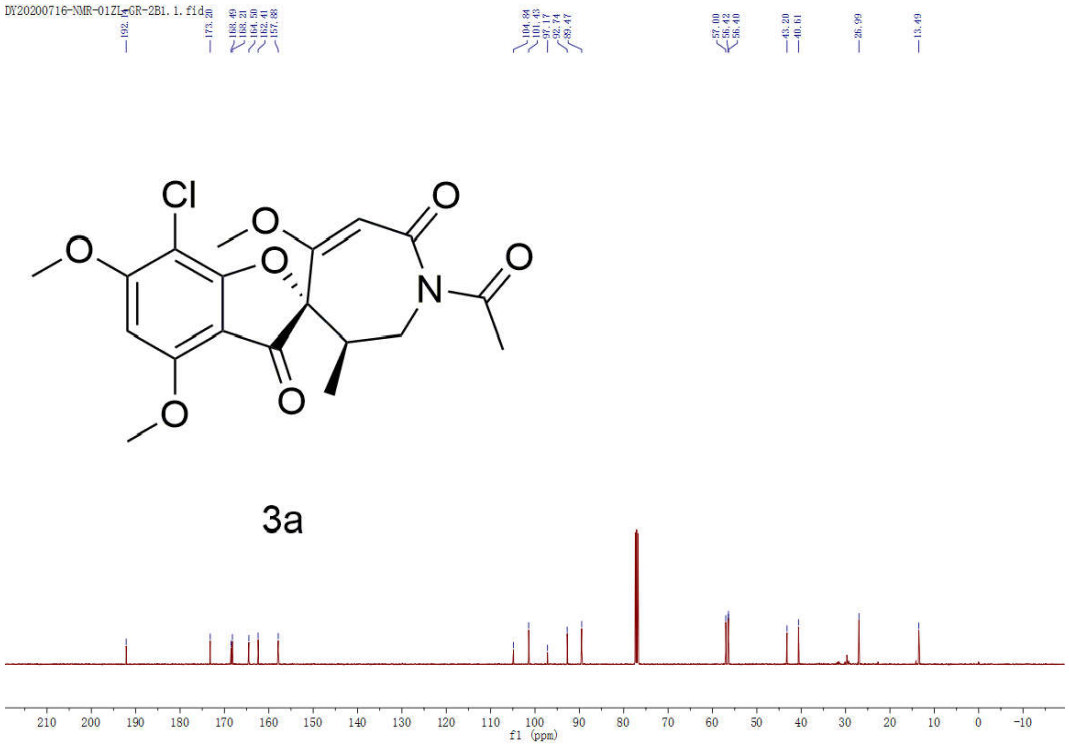
^{13}C NMR spectrum of 2 (100 MHz, $CDCl_3$)



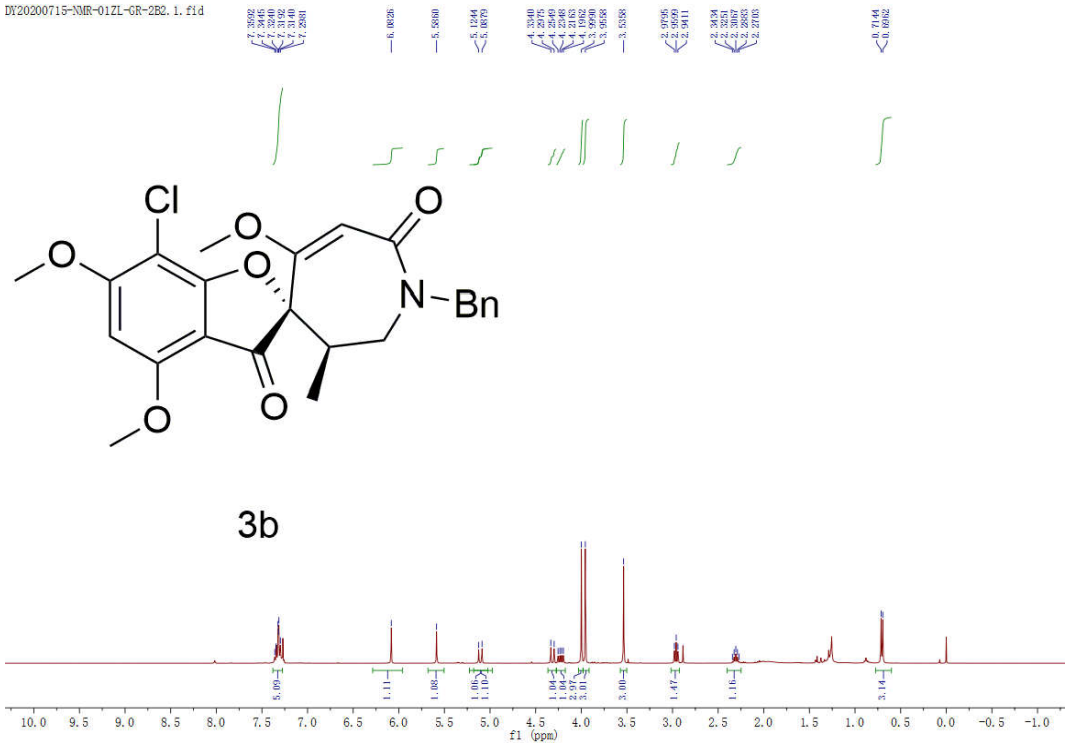
^{1}H-^{1}H COSY NMR spectrum of 2 (400 MHz, $CDCl_3$)



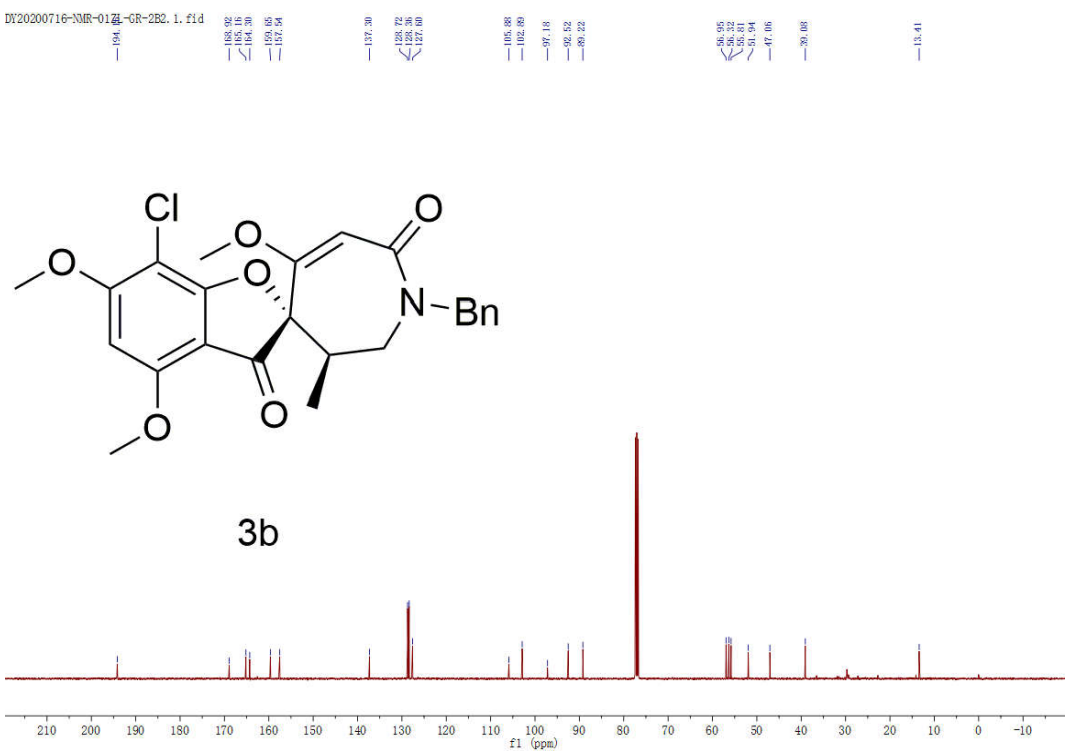
^{1}H NMR spectrum of 3a (400 MHz, $CDCl_3$)



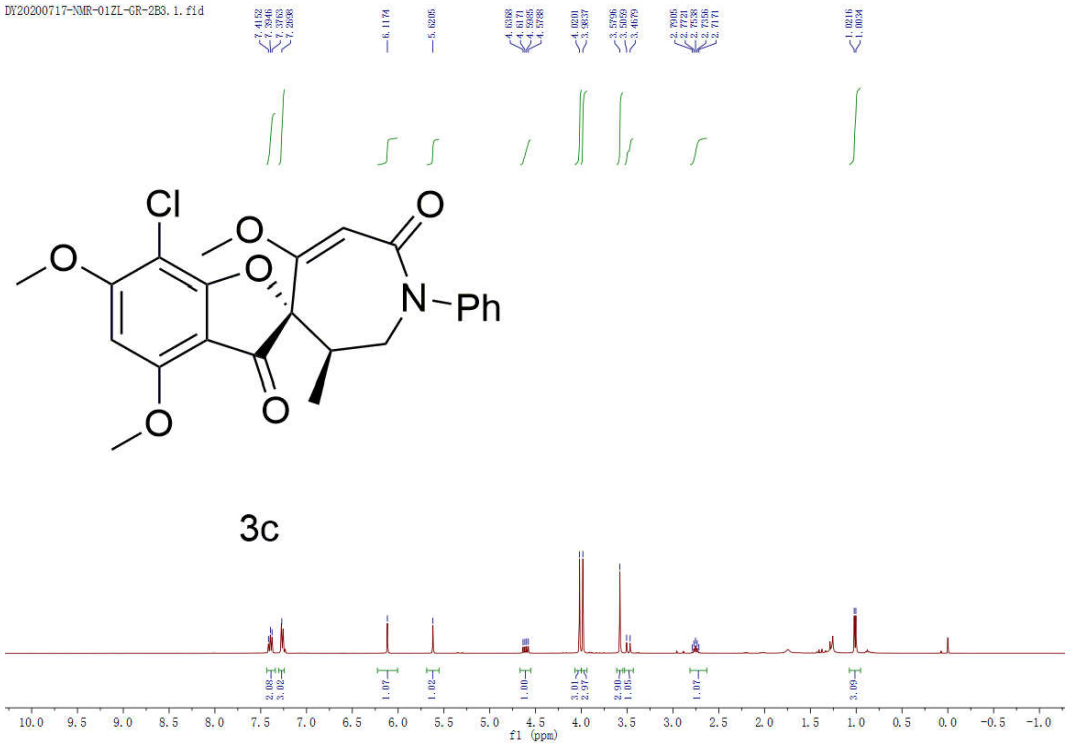
^{13}C NMR spectrum of 3a (100 MHz, $CDCl_3$)



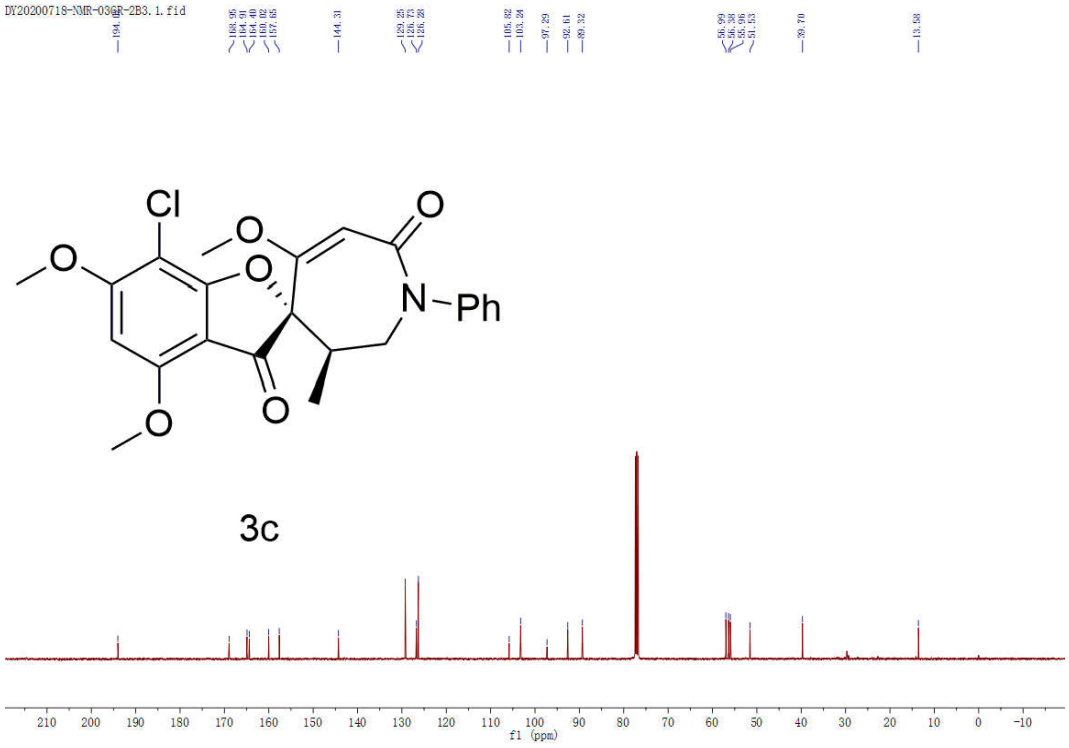
^{1}H NMR spectrum of 3b (400 MHz, $CDCl_3$)



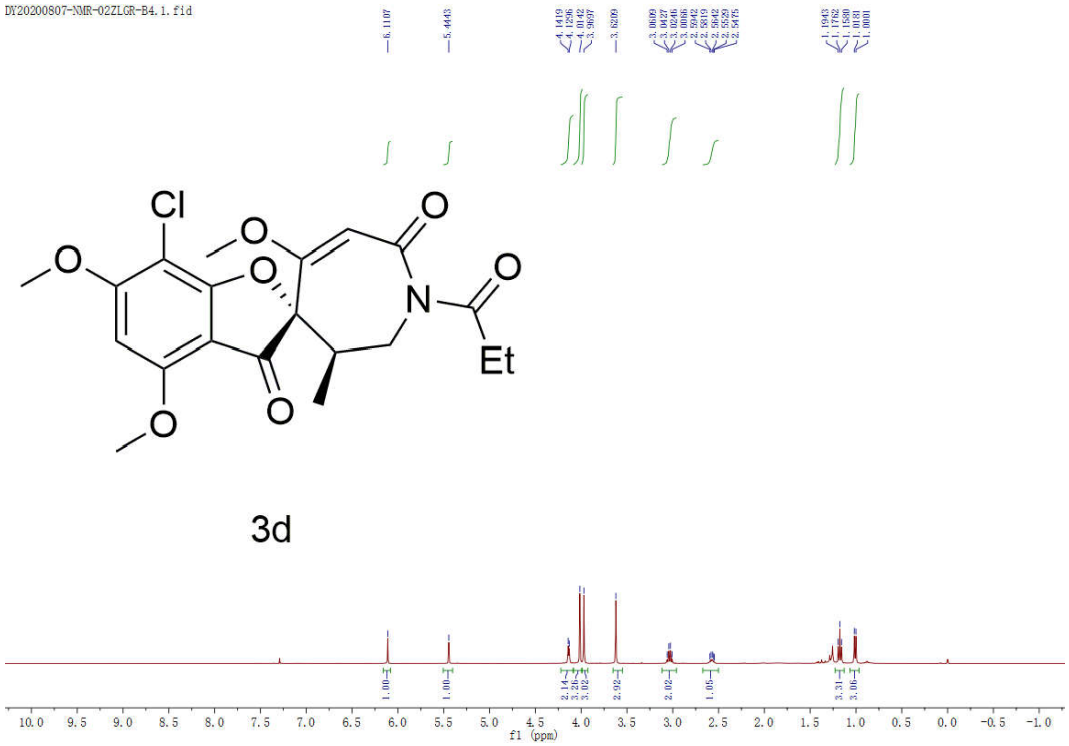
^{13}C NMR spectrum of 3b (100 MHz, $CDCl_3$)



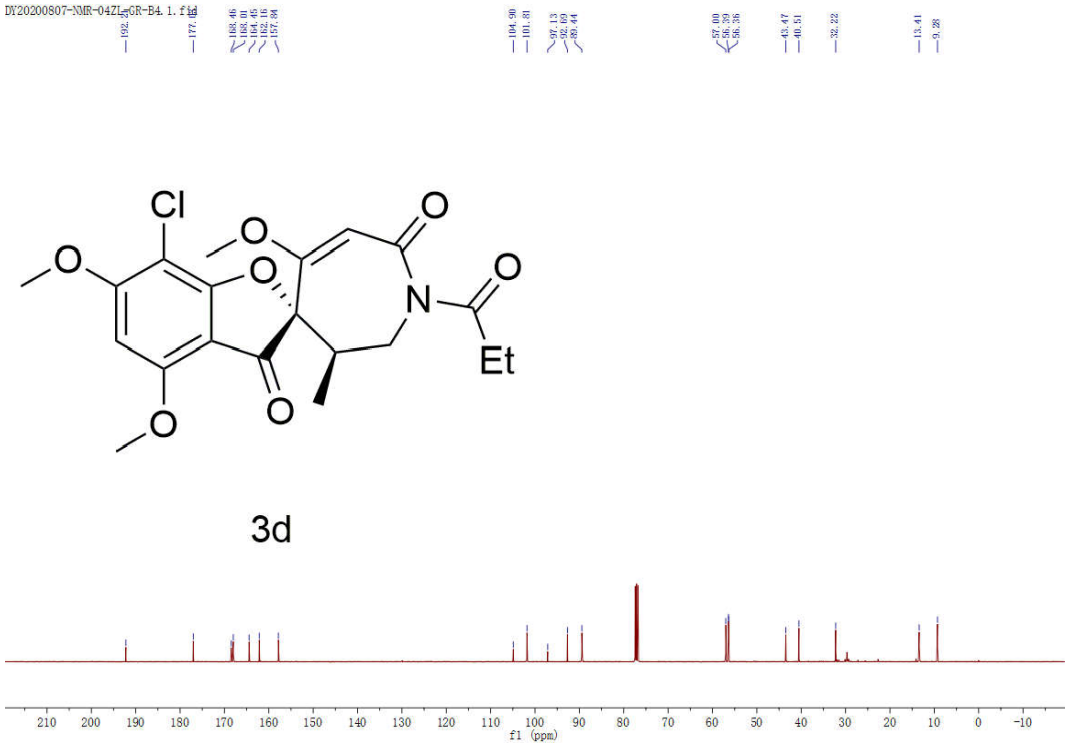
^{1}H NMR spectrum of 3c (400 MHz, $CDCl_3$)



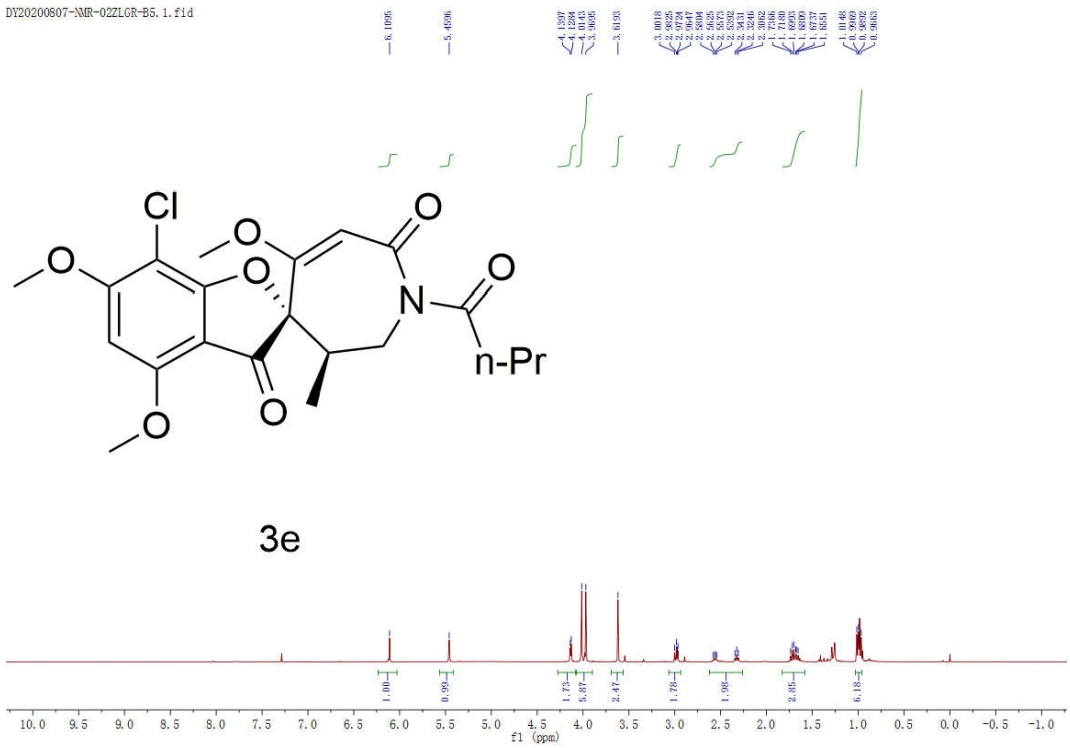
^{13}C NMR spectrum of 3c (100 MHz, $CDCl_3$)



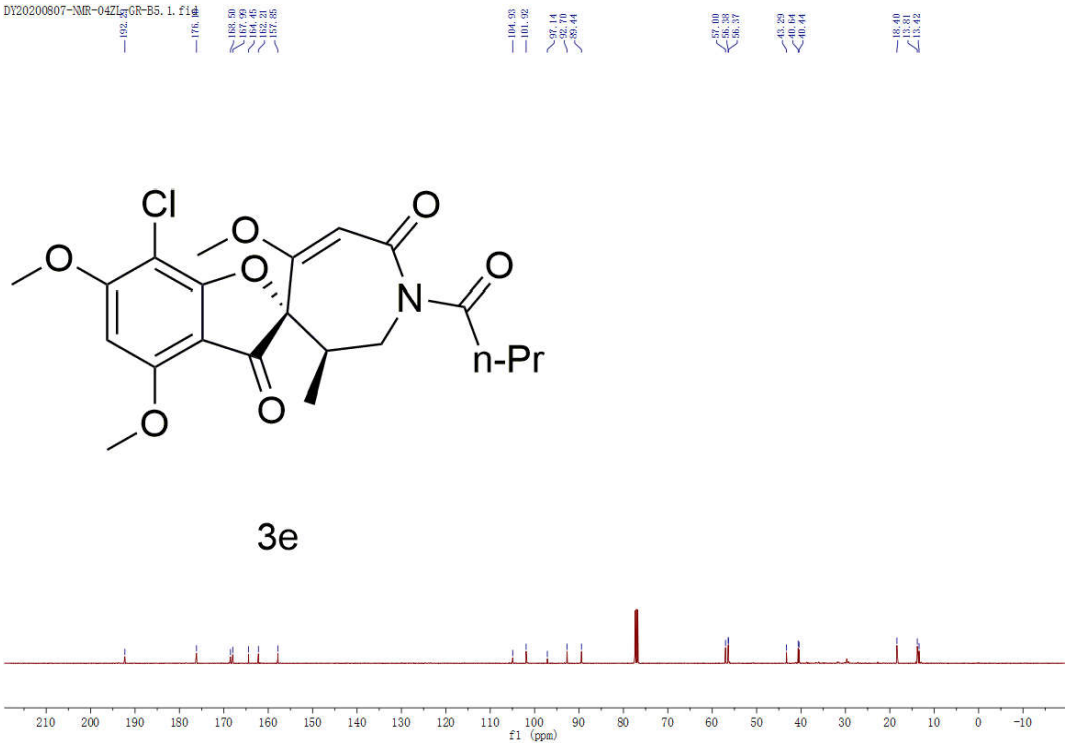
^{1}H NMR spectrum of 3d (400 MHz, $CDCl_3$)



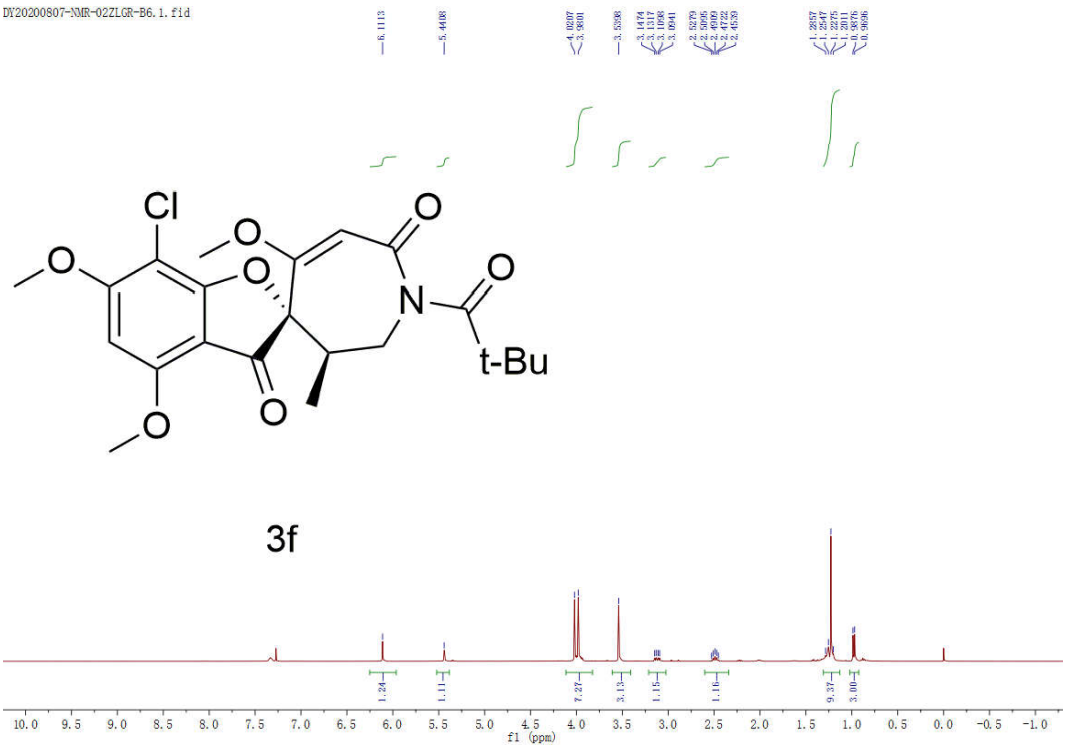
^{13}C NMR spectrum of 3d (100 MHz, $CDCl_3$)



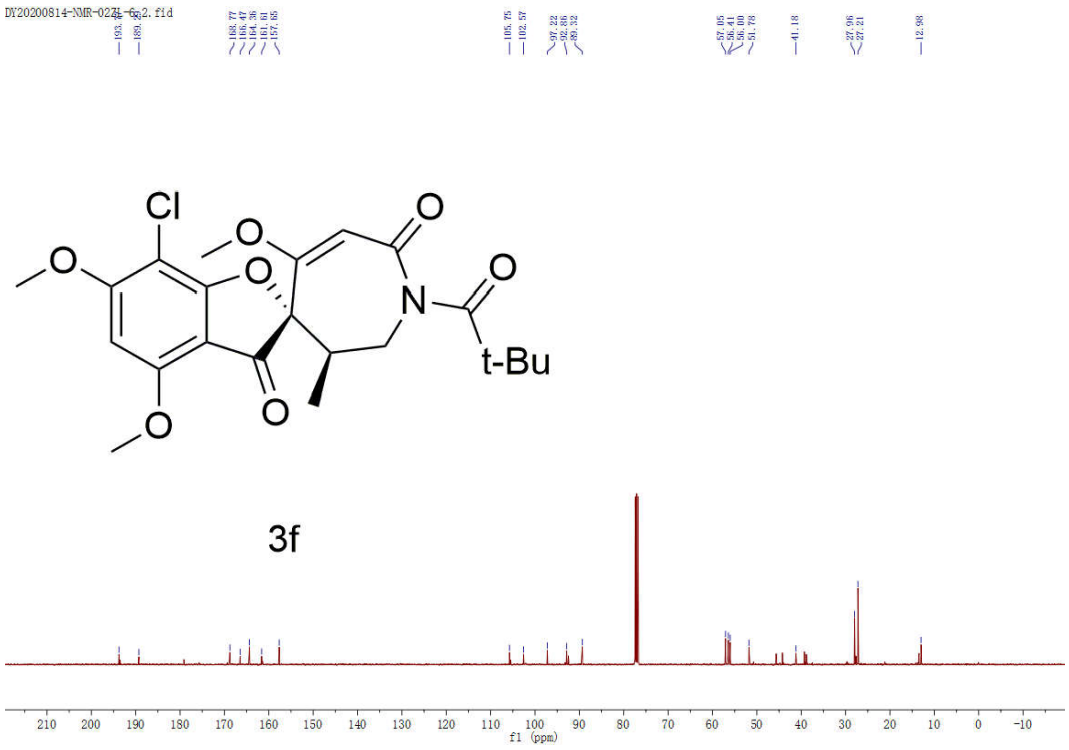
^{1}H NMR spectrum of 3e (400 MHz, $CDCl_3$)



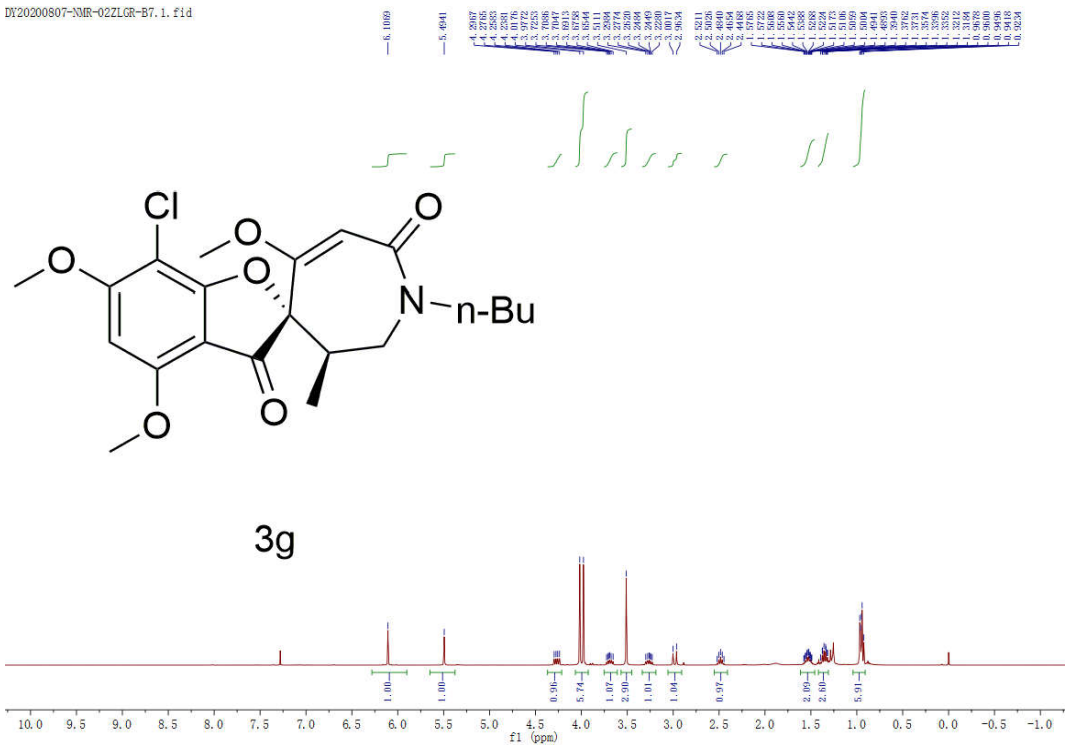
^{13}C NMR spectrum of 3e (100 MHz, $CDCl_3$)



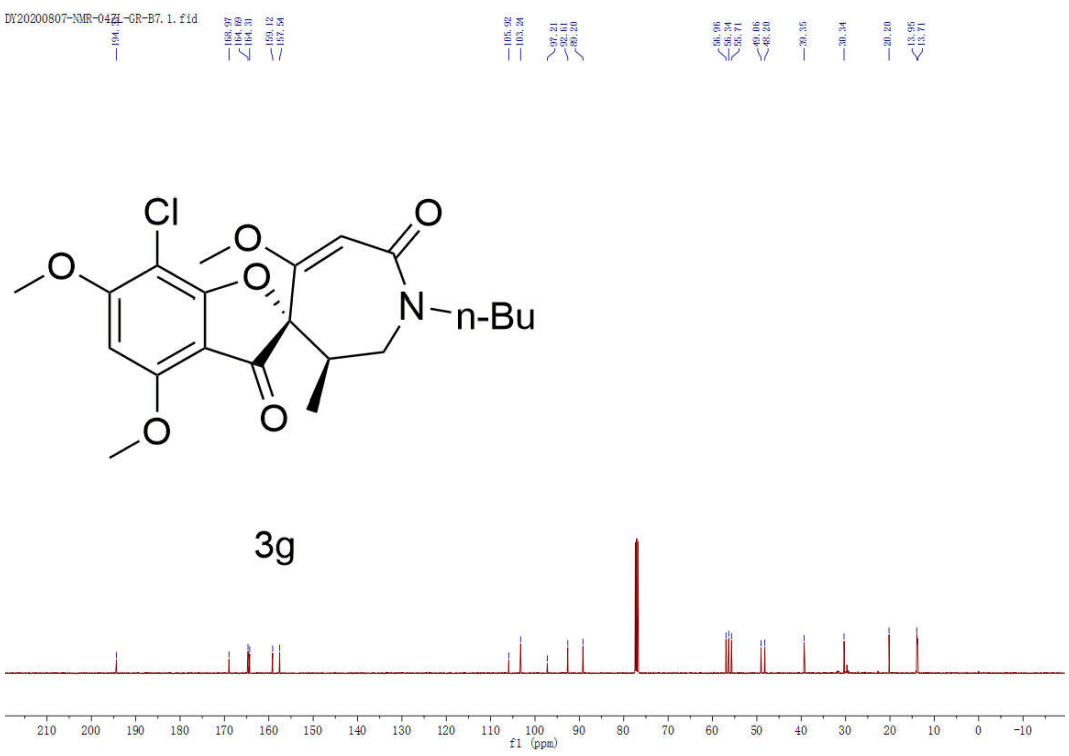
^{1}H NMR spectrum of 3f (400 MHz, $CDCl_3$)



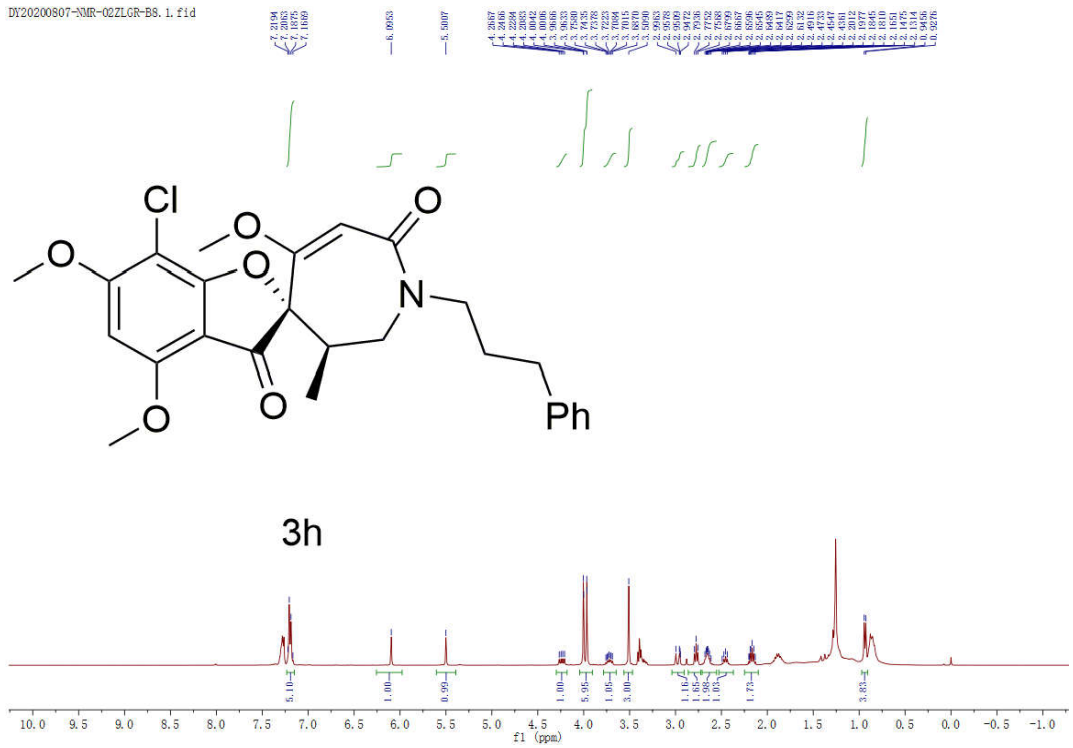
^{13}C NMR spectrum of 3f (100 MHz, $CDCl_3$)



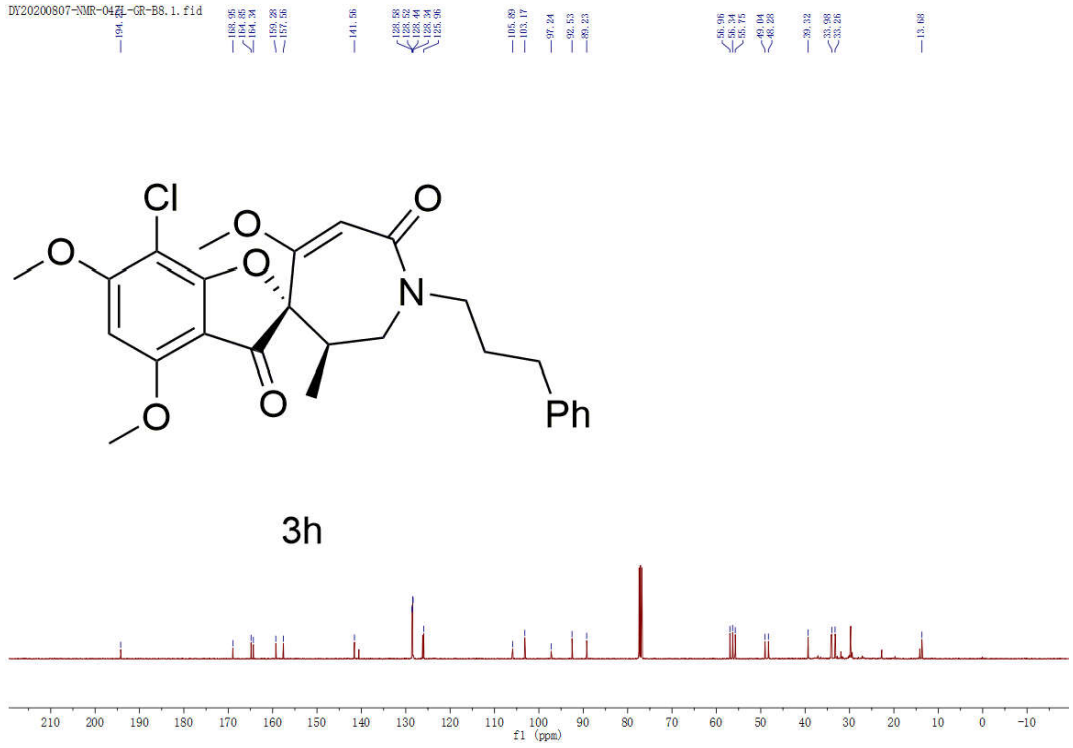
^{1}H NMR spectrum of 3g (400 MHz, $CDCl_3$)



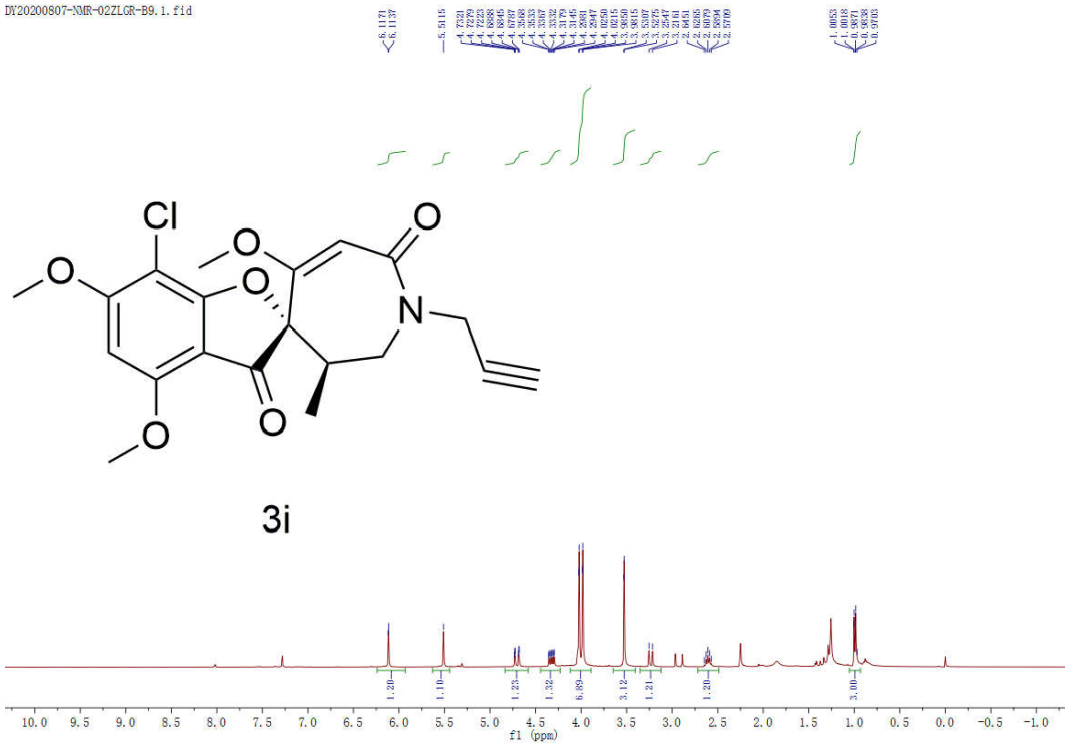
^{13}C NMR spectrum of 3g (100 MHz, $CDCl_3$)



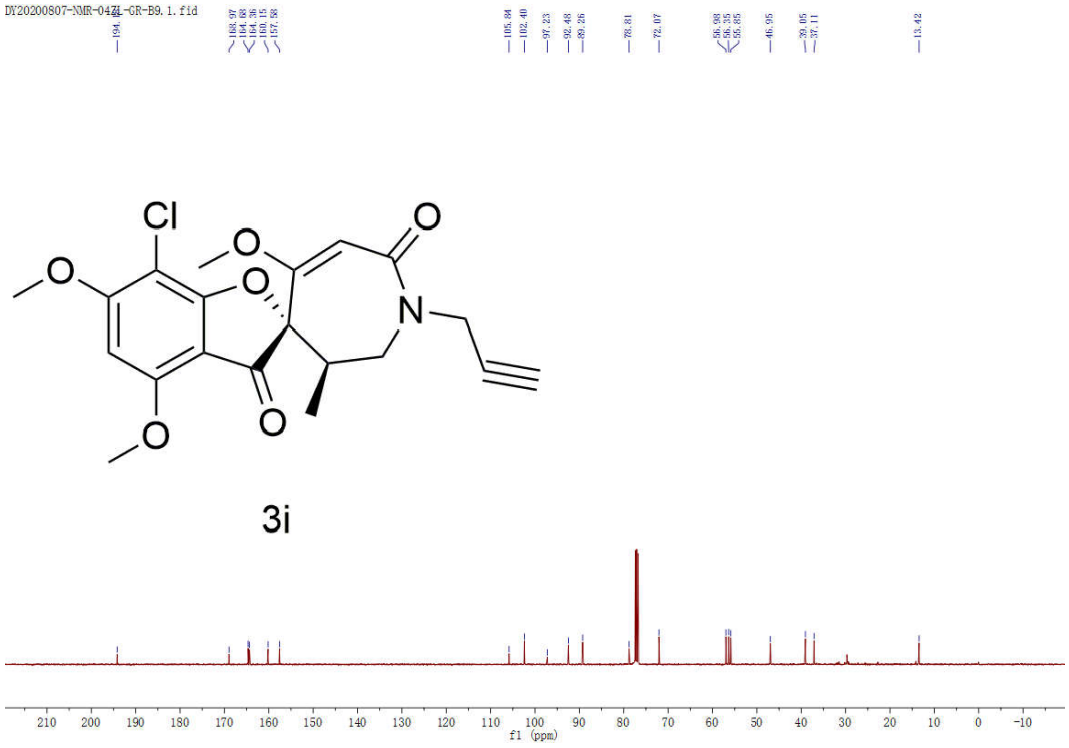
^{1}H NMR spectrum of 3h (400 MHz, $CDCl_3$)



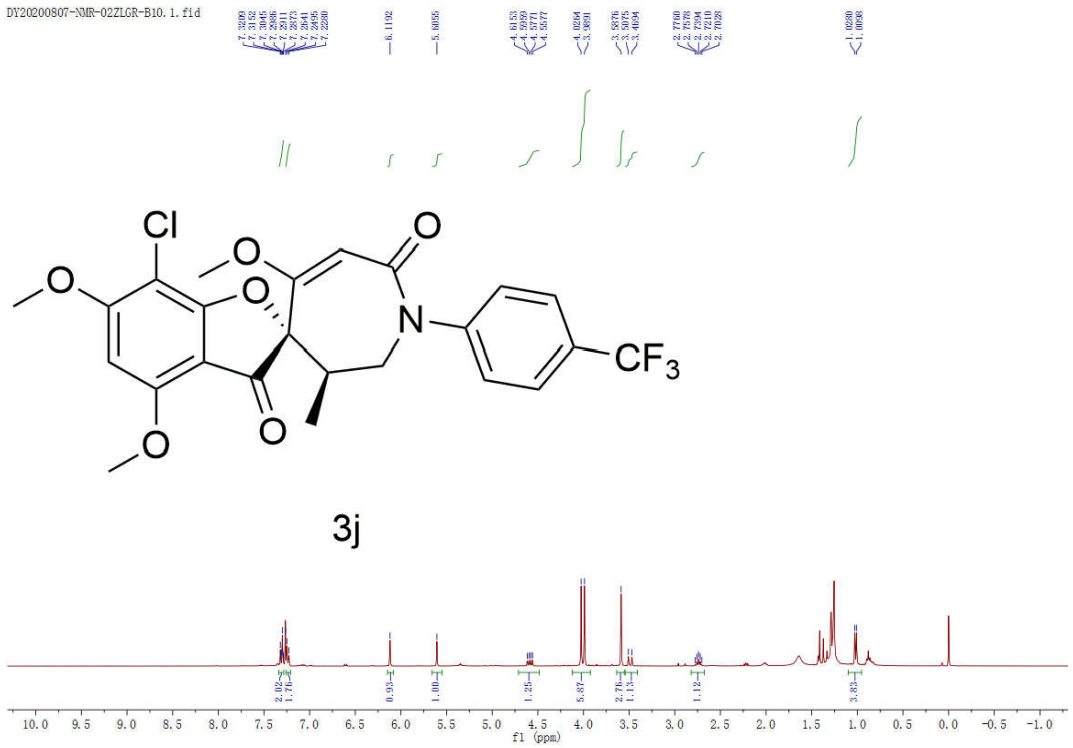
^{13}C NMR spectrum of 3h (100 MHz, $CDCl_3$)



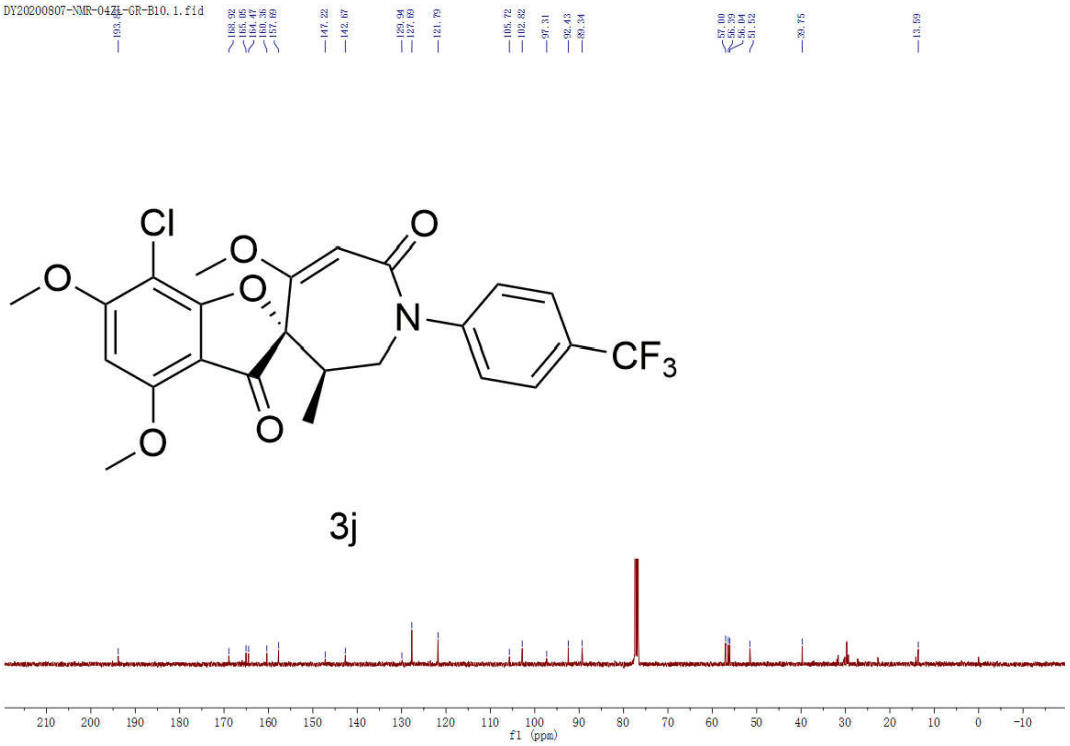
^{1}H NMR spectrum of 3i (400 MHz, $CDCl_3$)



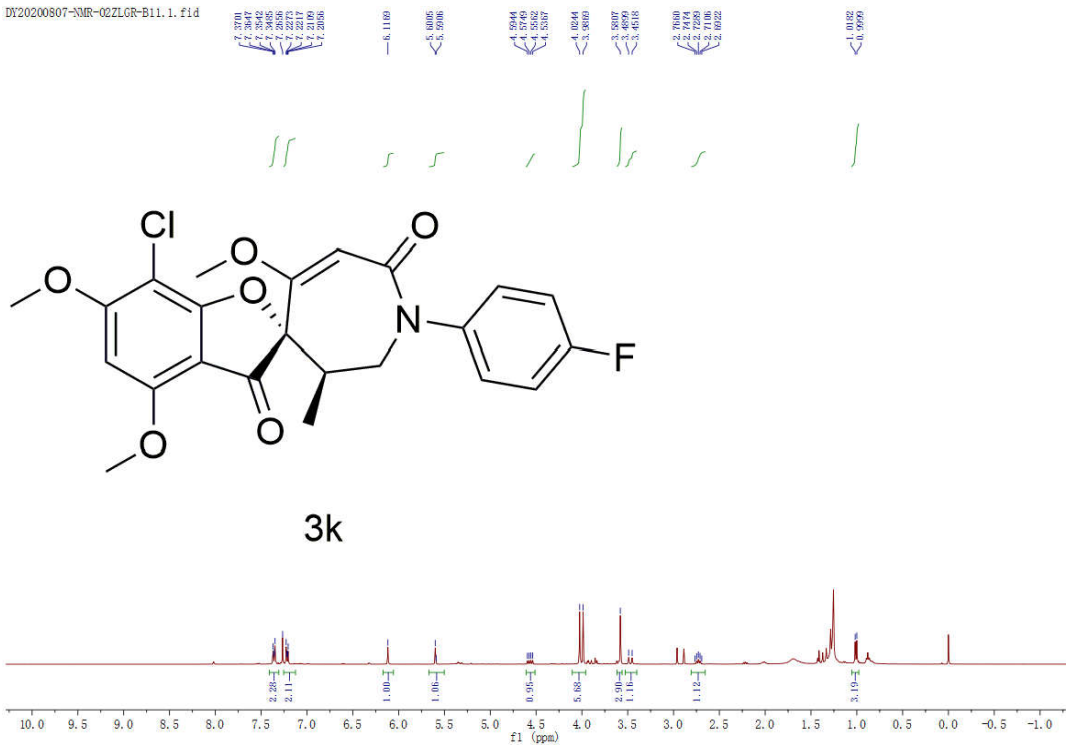
^{13}C NMR spectrum of 3i (100 MHz, $CDCl_3$)



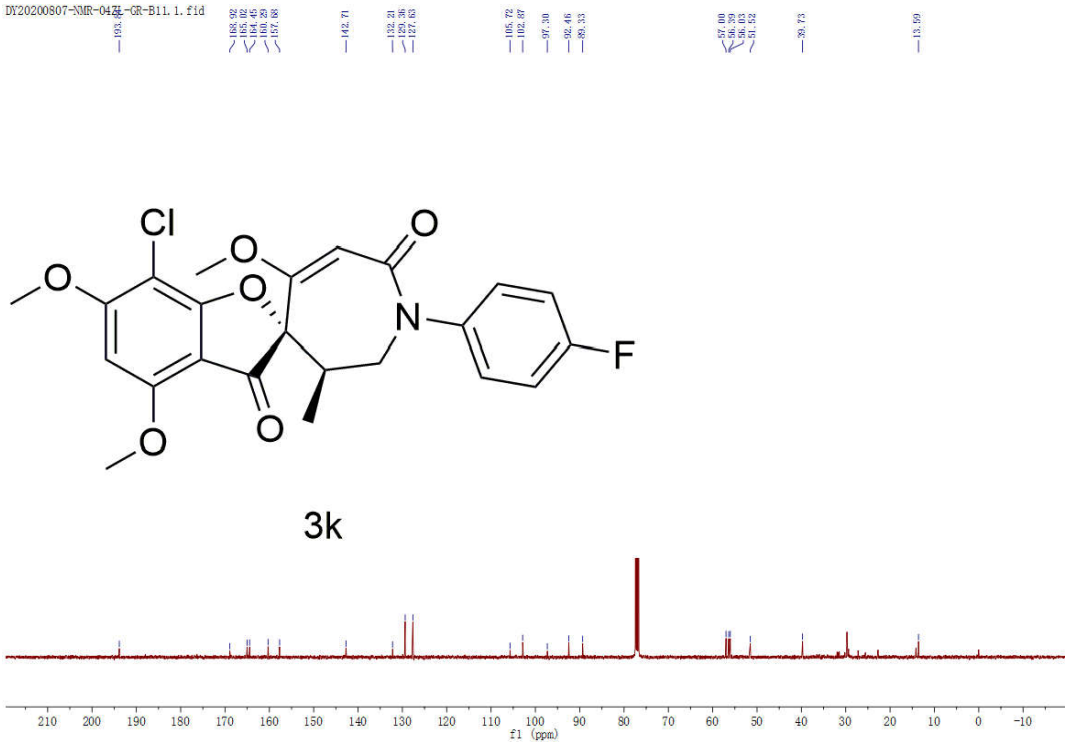
^{1}H NMR spectrum of 3j (400 MHz, $CDCl_3$)



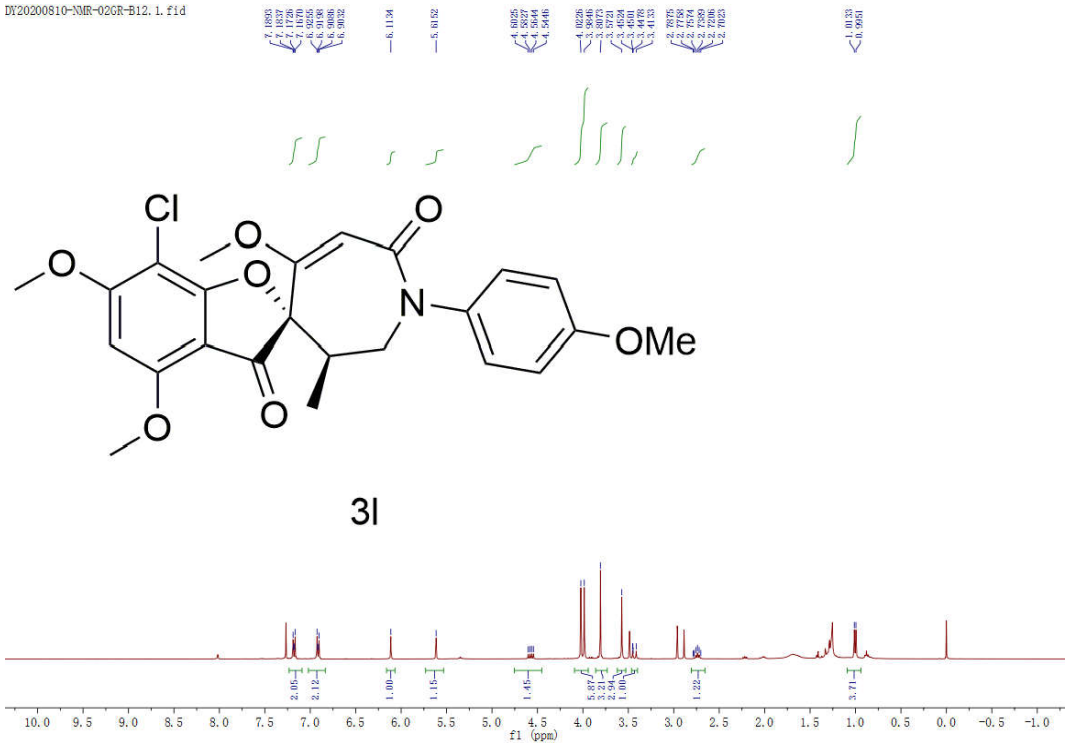
^{13}C NMR spectrum of 3j (100 MHz, $CDCl_3$)



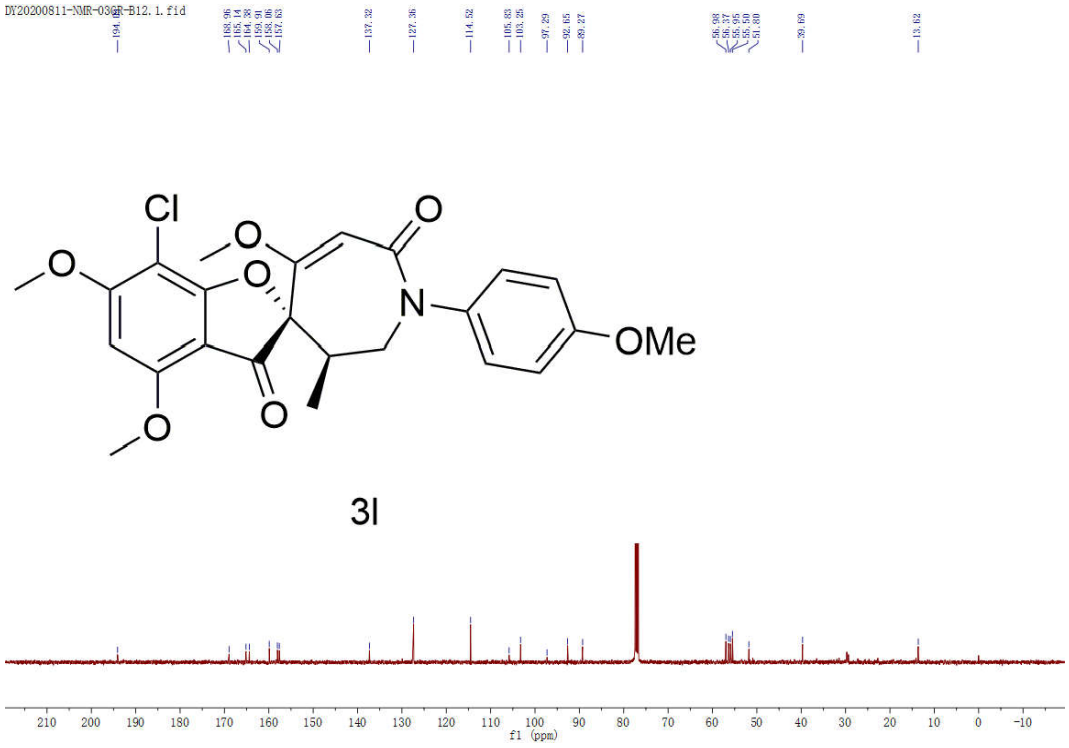
^{1}H NMR spectrum of 3k (400 MHz, $CDCl_3$)



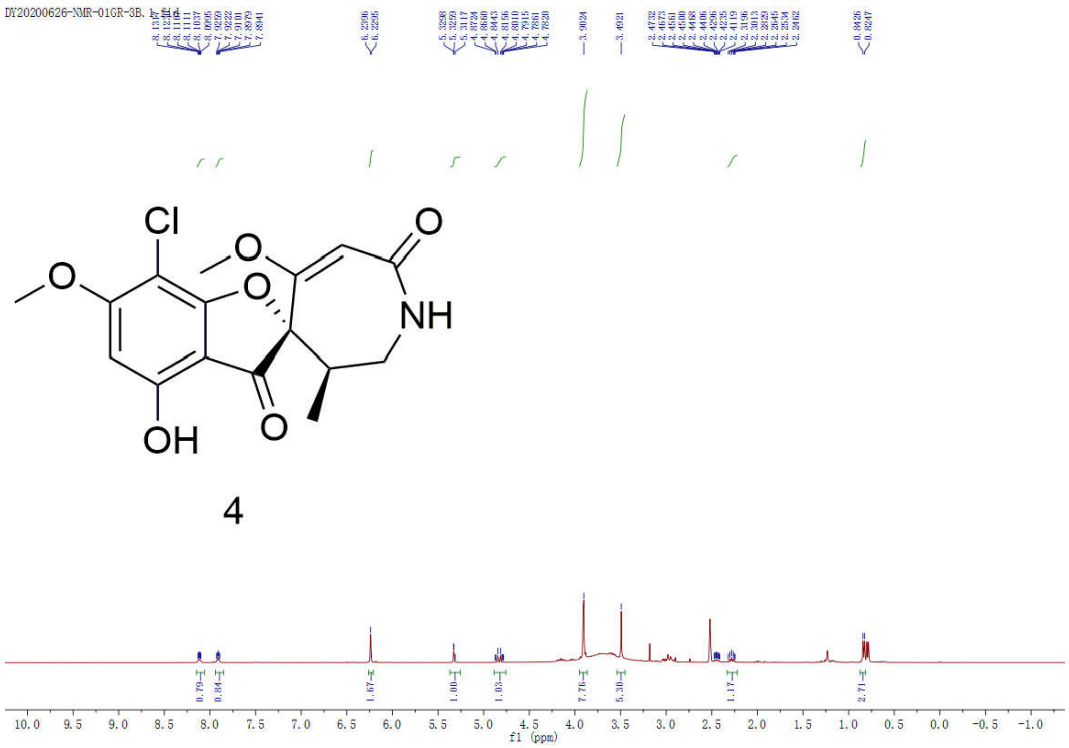
^{13}C NMR spectrum of 3k (100 MHz, $CDCl_3$)



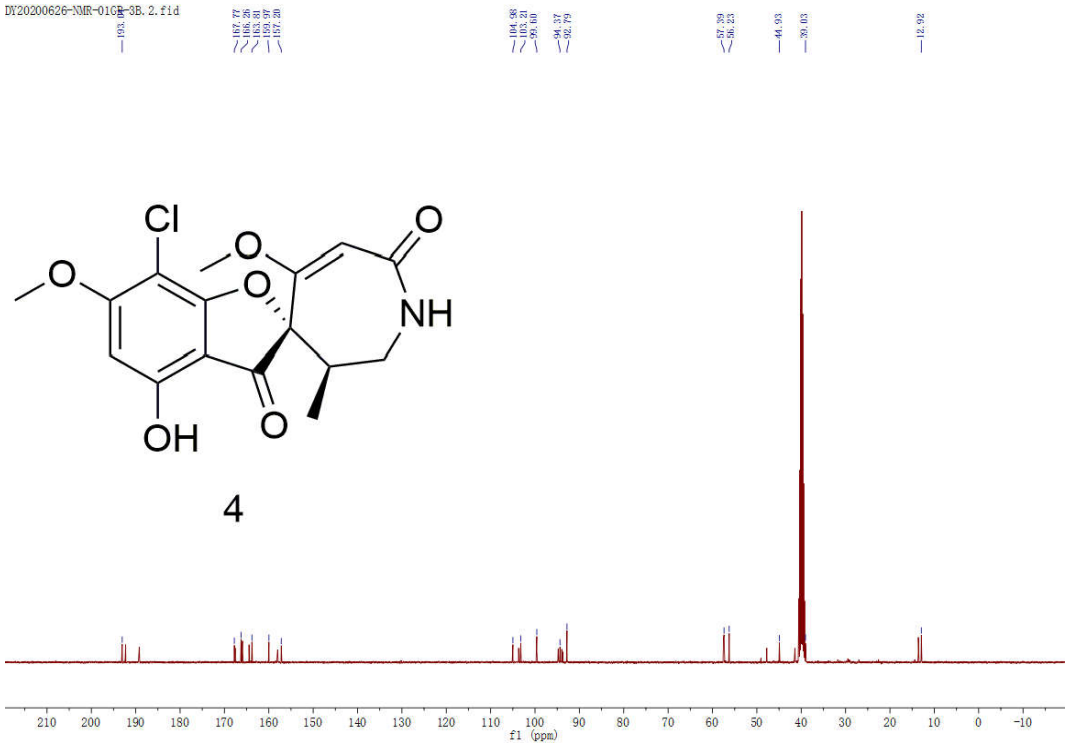
^{1}H NMR spectrum of 3l (400 MHz, $CDCl_3$)



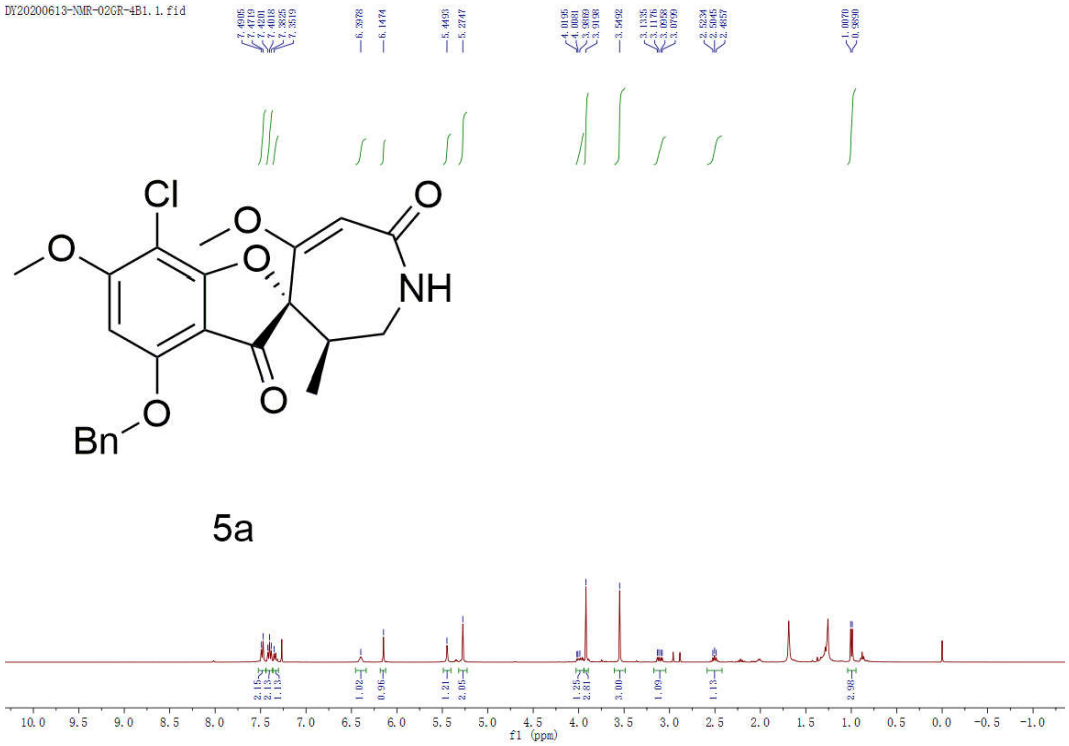
^{13}C NMR spectrum of 3l (100 MHz, $CDCl_3$)



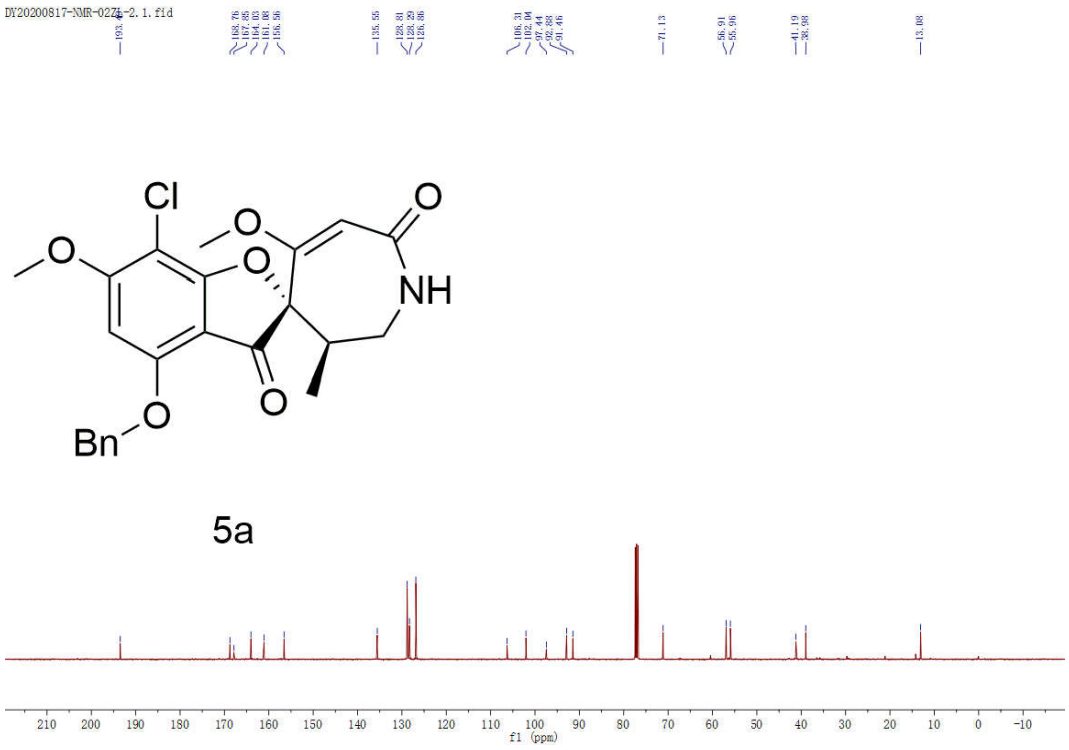
^{1}H NMR spectrum of 4 (400 MHz, DMSO-d_6)



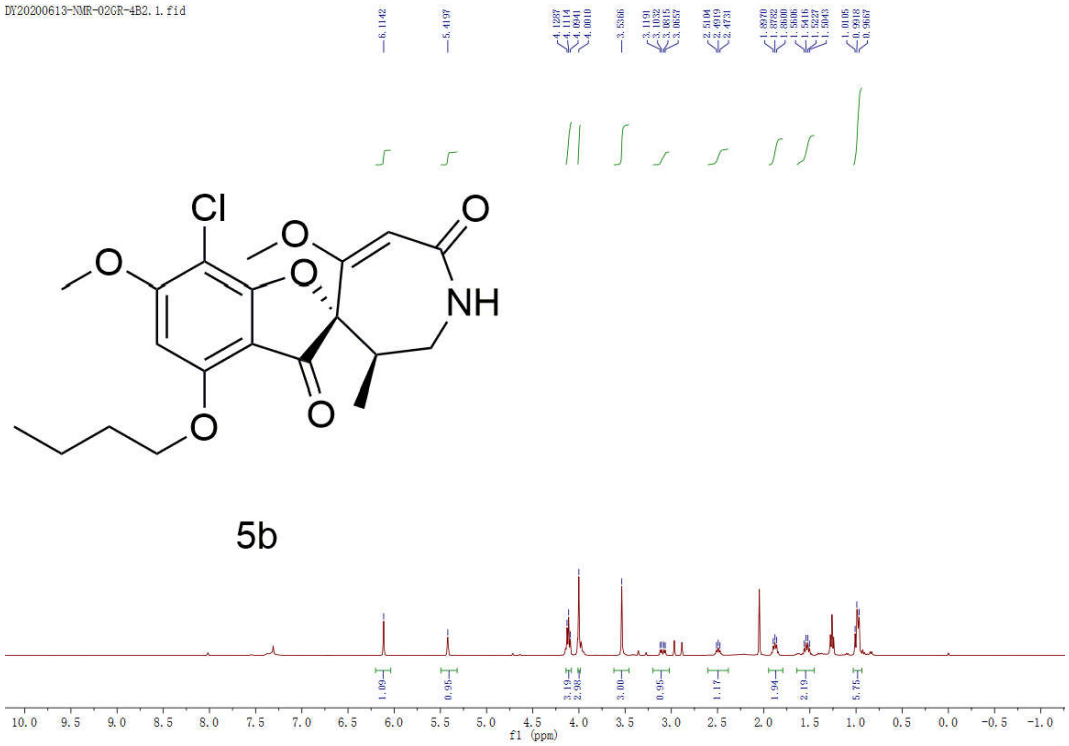
^{13}C NMR spectrum of 4 (100 MHz, DMSO-d_6)



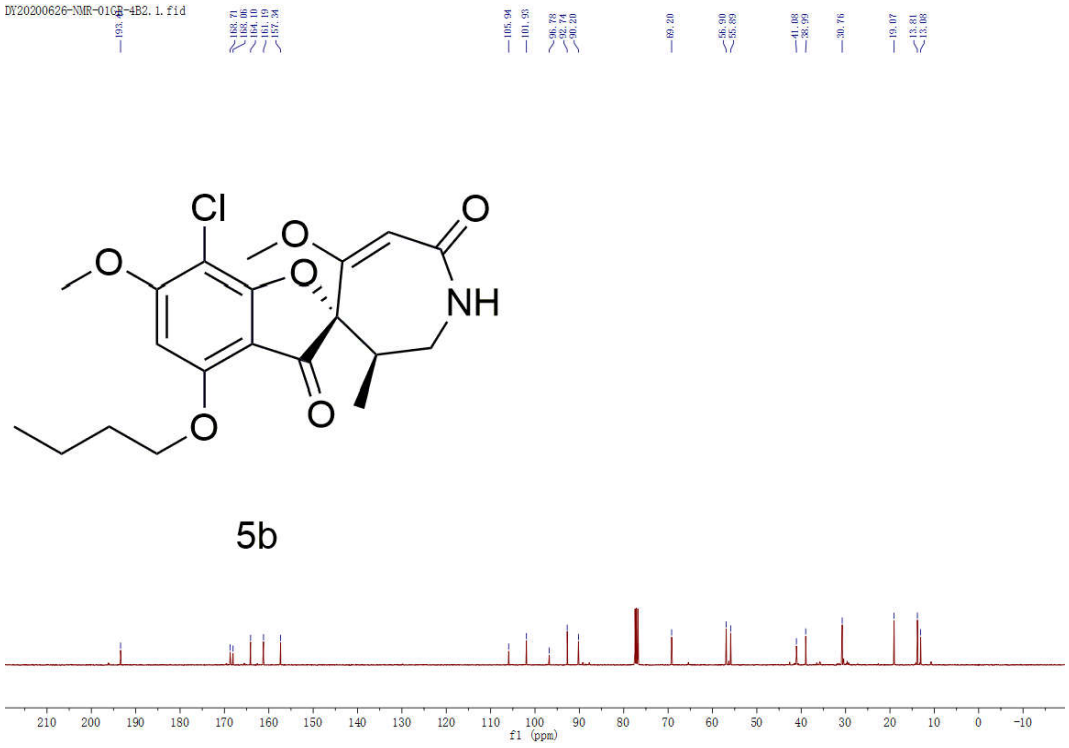
^{1}H NMR spectrum of 5a (400 MHz, $CDCl_3$)



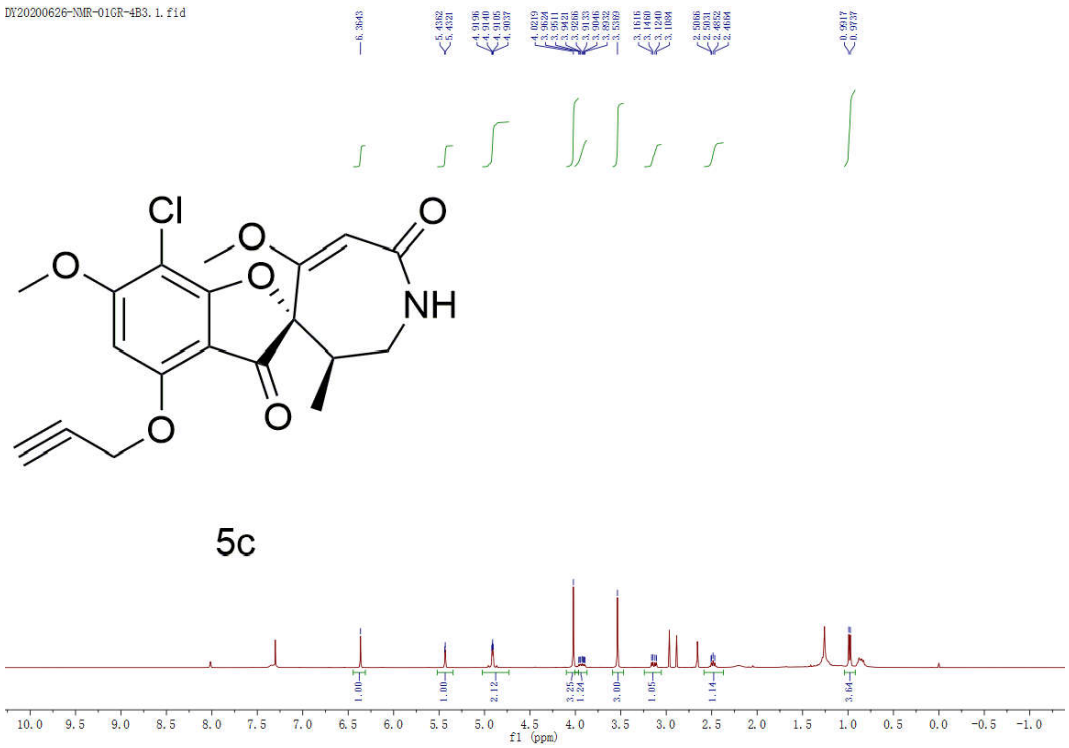
^{13}C NMR spectrum of 5a (100 MHz, $CDCl_3$)



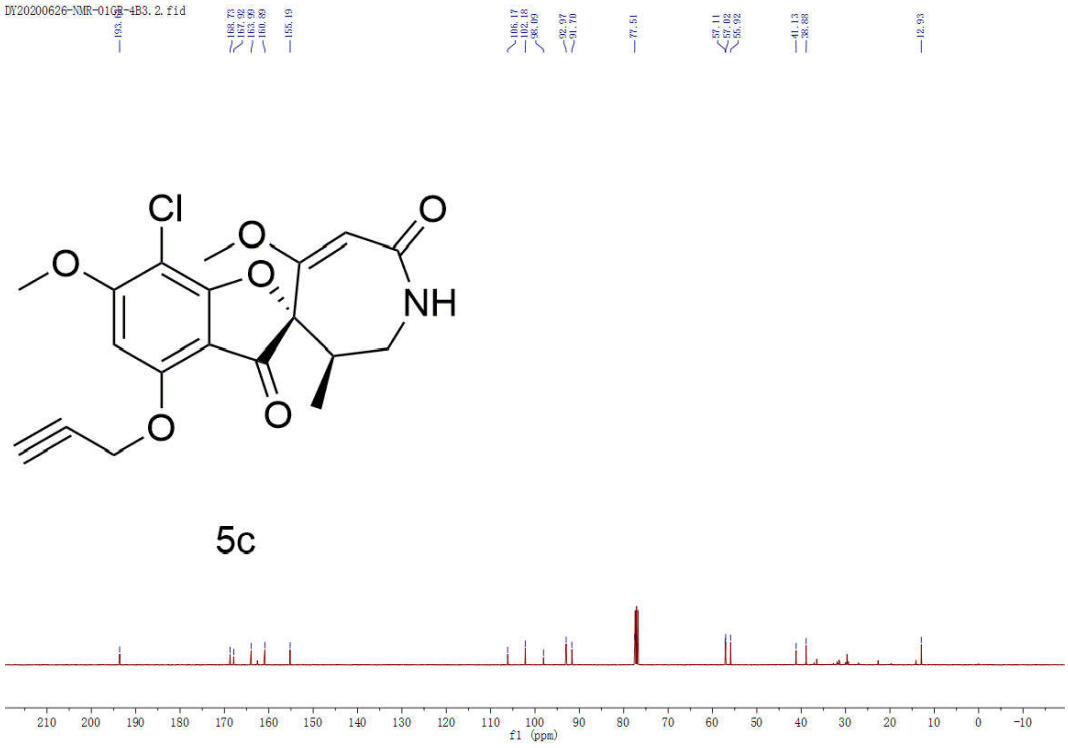
^{1}H NMR spectrum of 5b (400 MHz, $CDCl_3$)



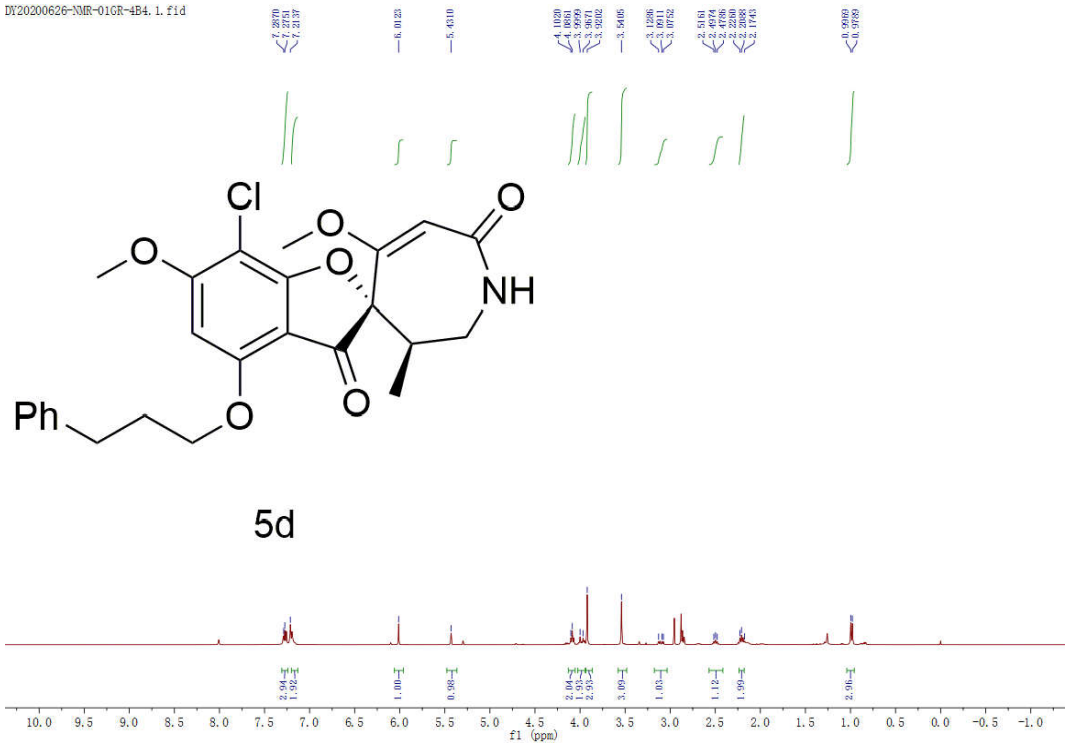
^{13}C NMR spectrum of 5b (100 MHz, $CDCl_3$)



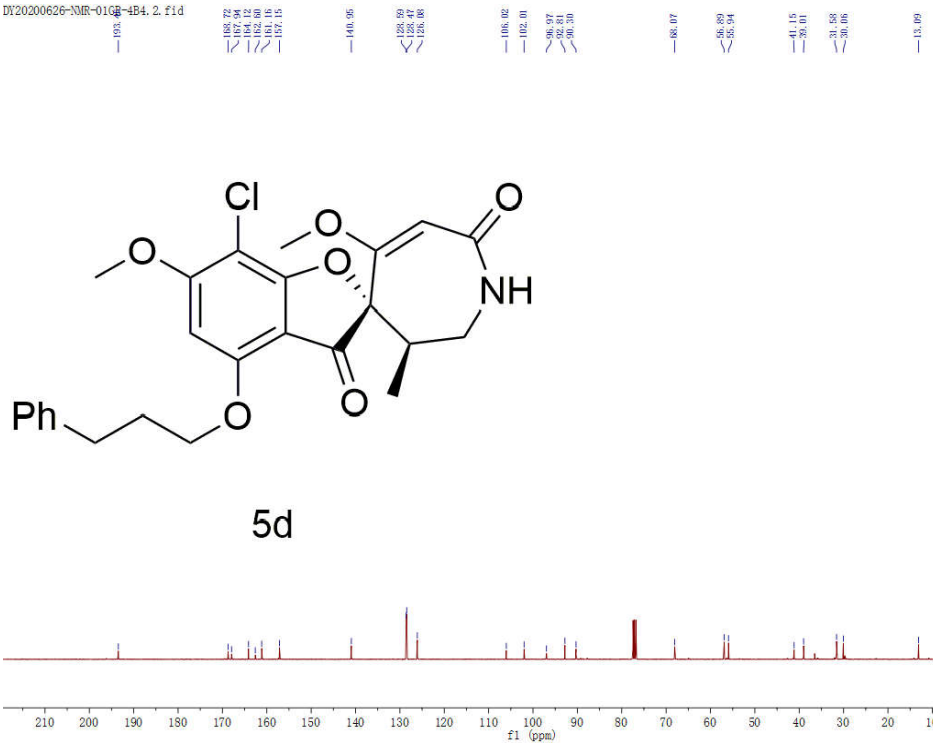
^{1}H NMR spectrum of 5c (400 MHz, $CDCl_3$)



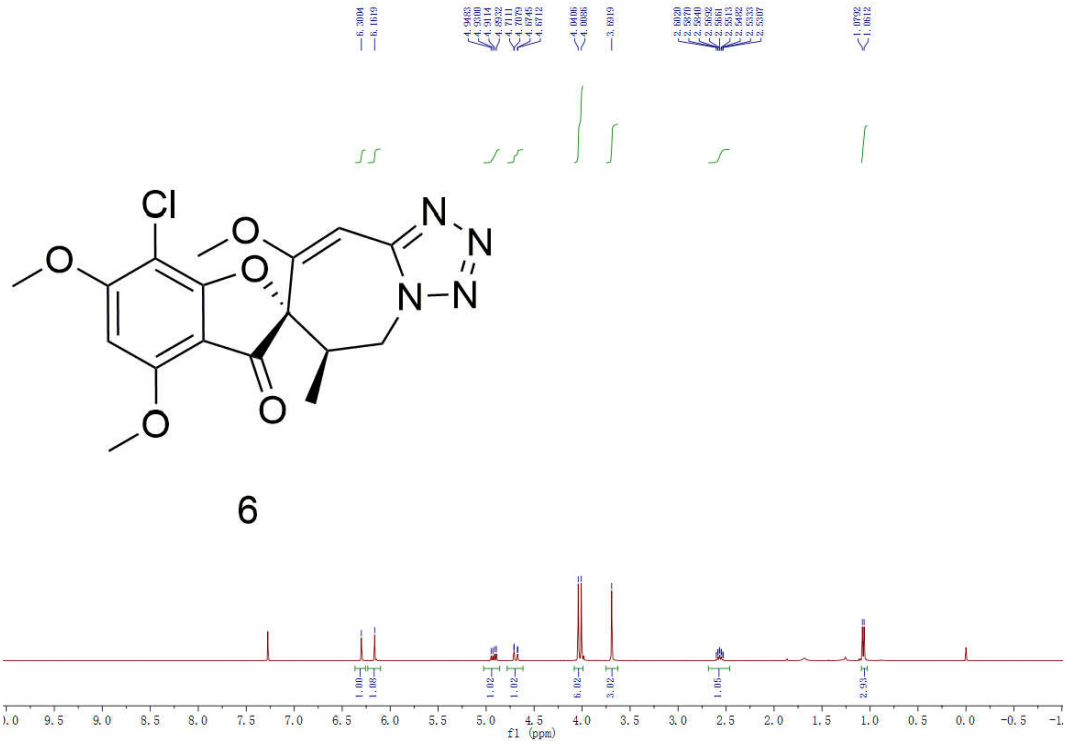
^{13}C NMR spectrum of 5c (100 MHz, $CDCl_3$)



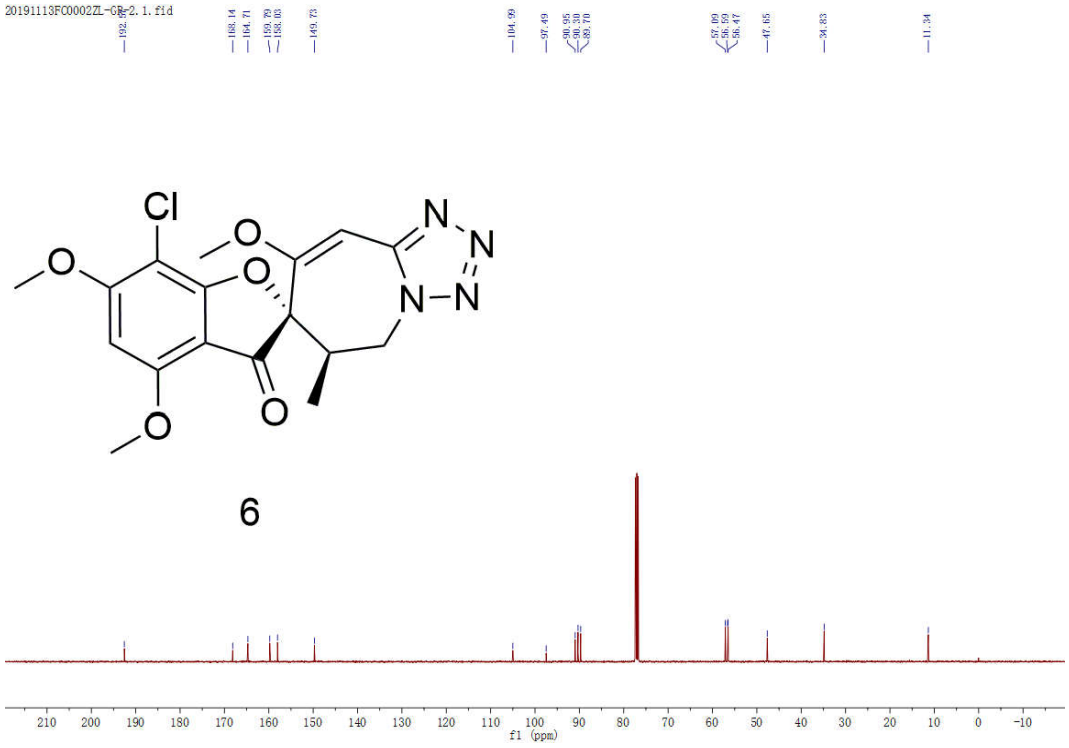
^{1}H NMR spectrum of 5d (400 MHz, $CDCl_3$)



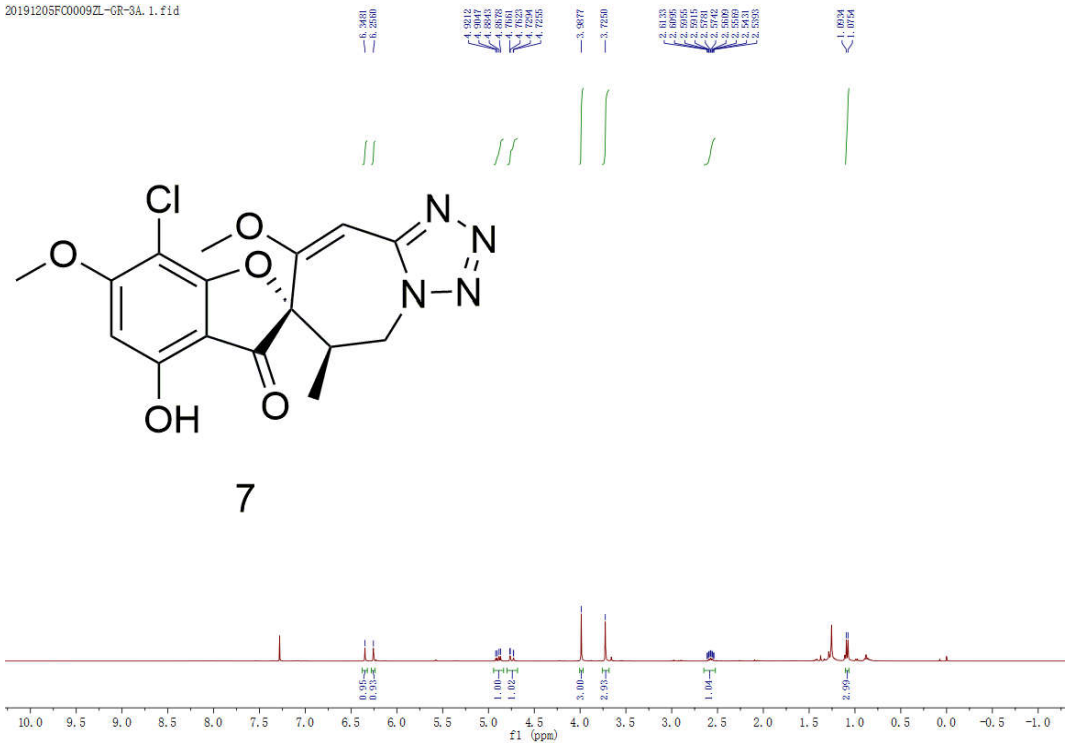
^{13}C NMR spectrum of 5d (100 MHz, $CDCl_3$)



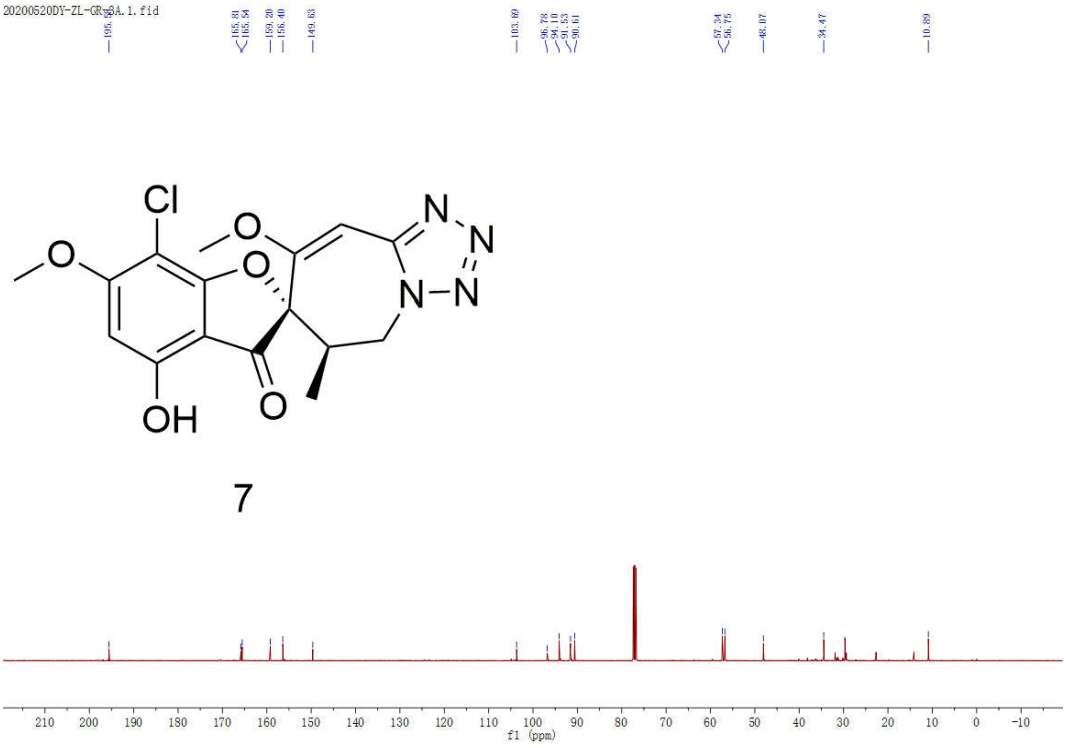
^{1}H NMR spectrum of 6 (400 MHz, $CDCl_3$)



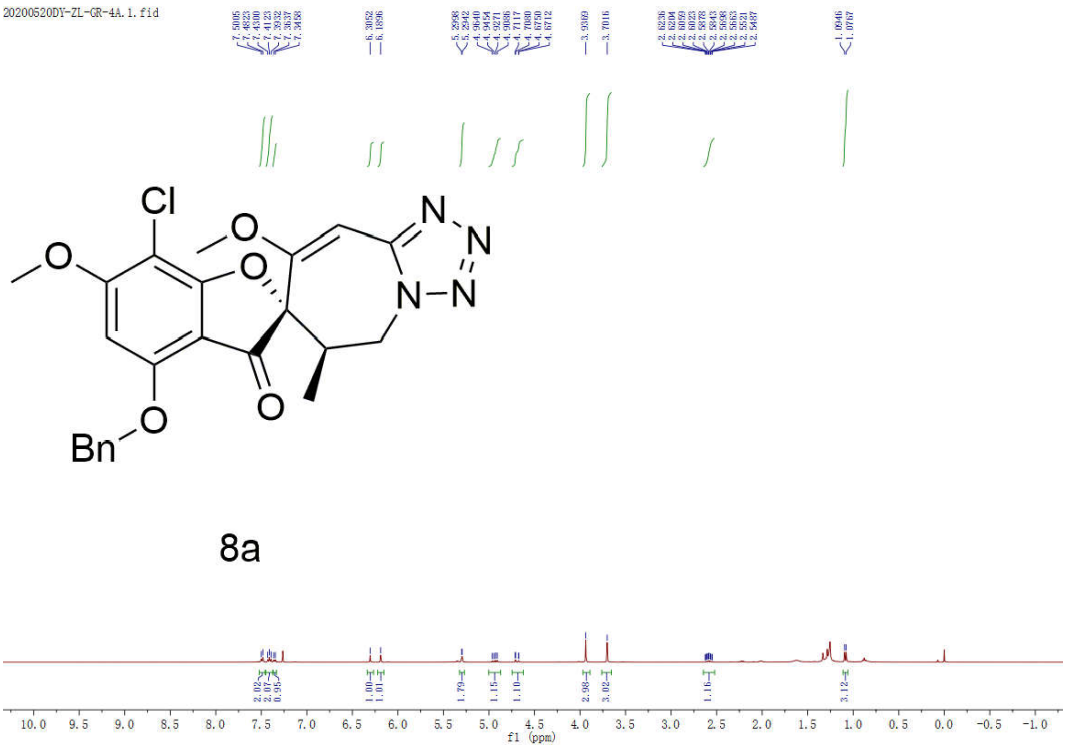
^{13}C NMR spectrum of 6 (100 MHz, $CDCl_3$)



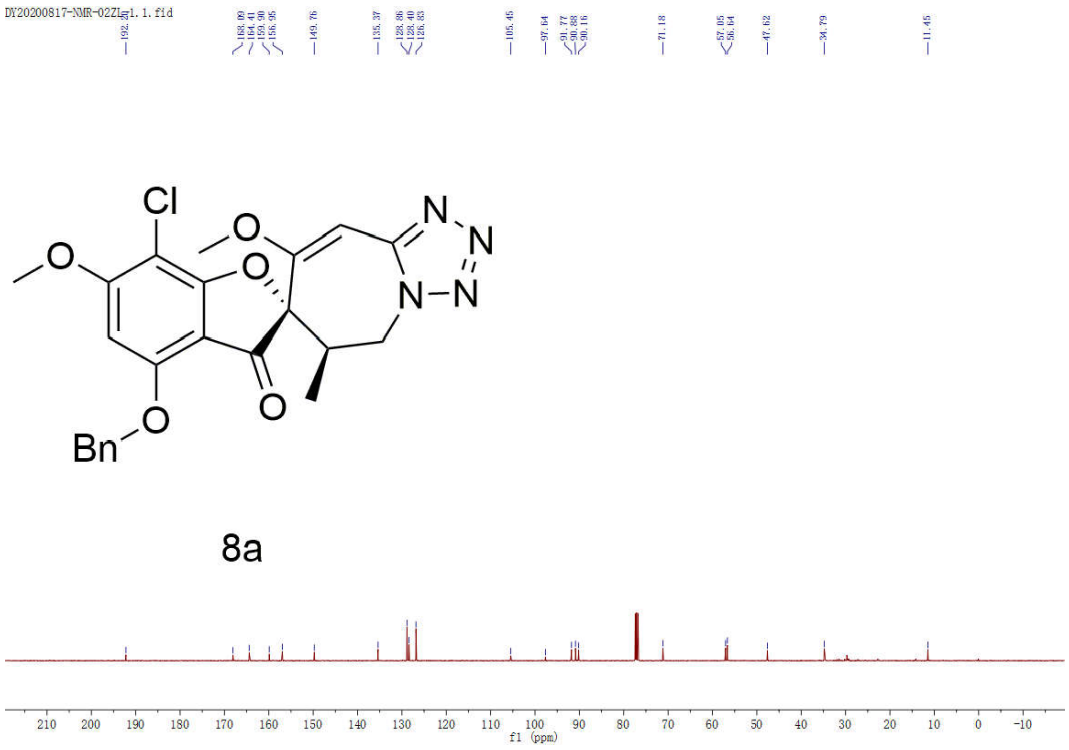
^{1}H NMR spectrum of 7 (400 MHz, $CDCl_3$)



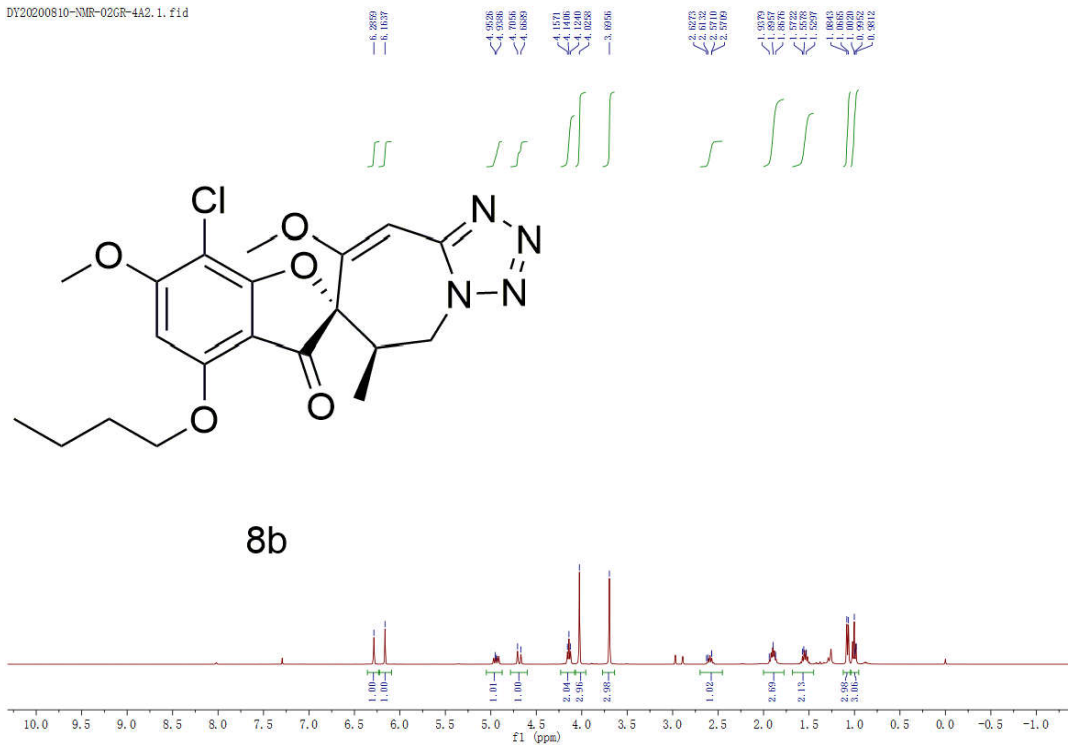
^{13}C NMR spectrum of 7 (100 MHz, $CDCl_3$)



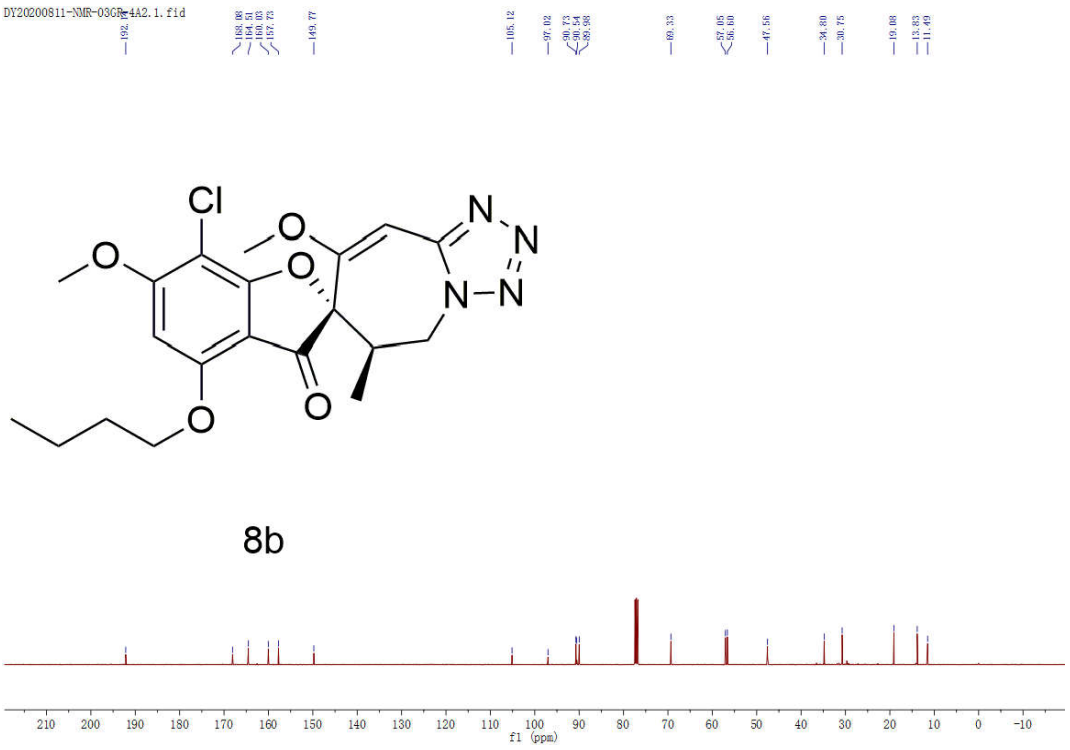
^{1}H NMR spectrum of 8a (400 MHz, $CDCl_3$)



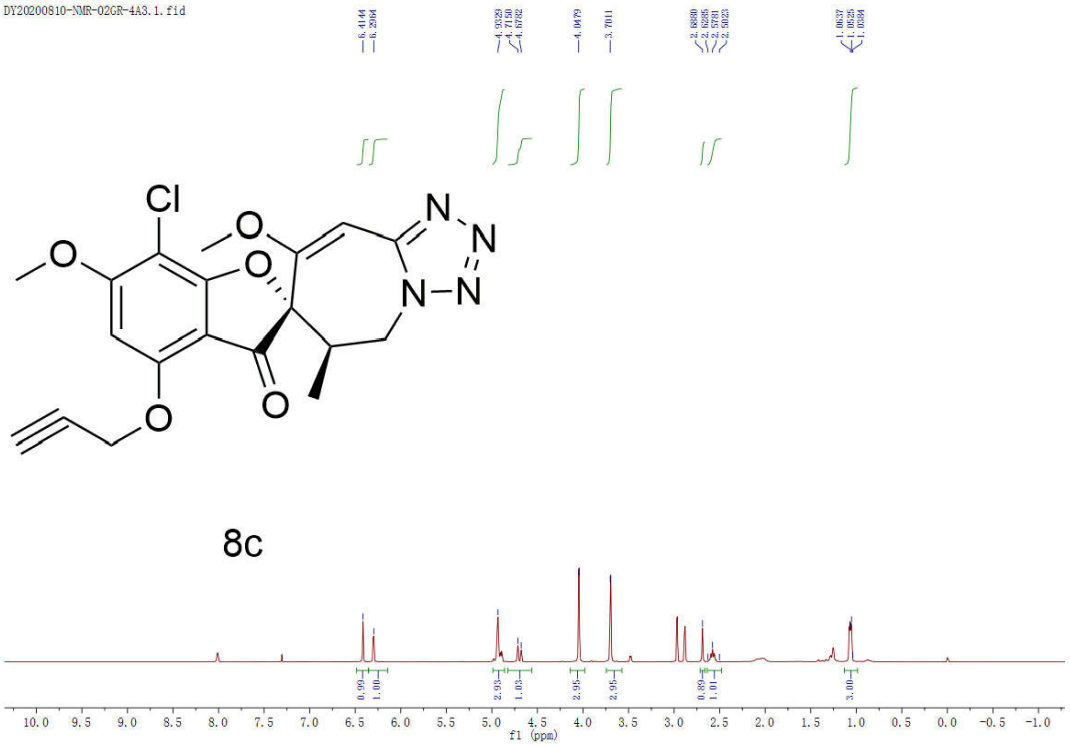
^{13}C NMR spectrum of 8a (100 MHz, $CDCl_3$)



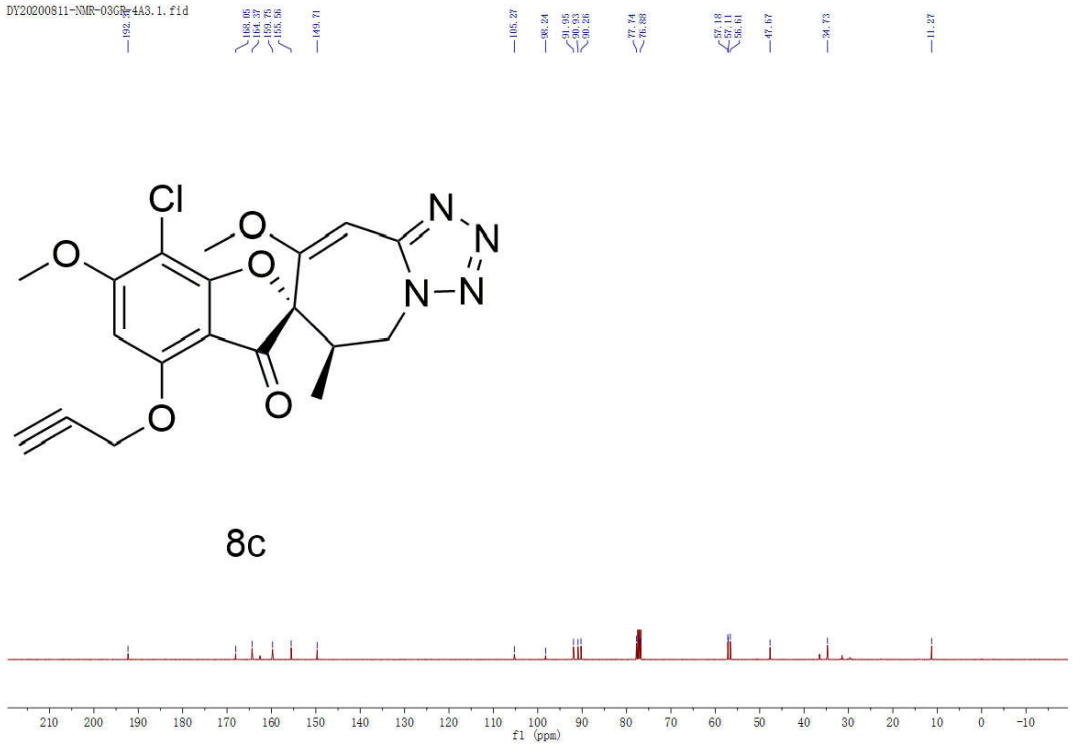
^{1}H NMR spectrum of 8b (400 MHz, $CDCl_3$)



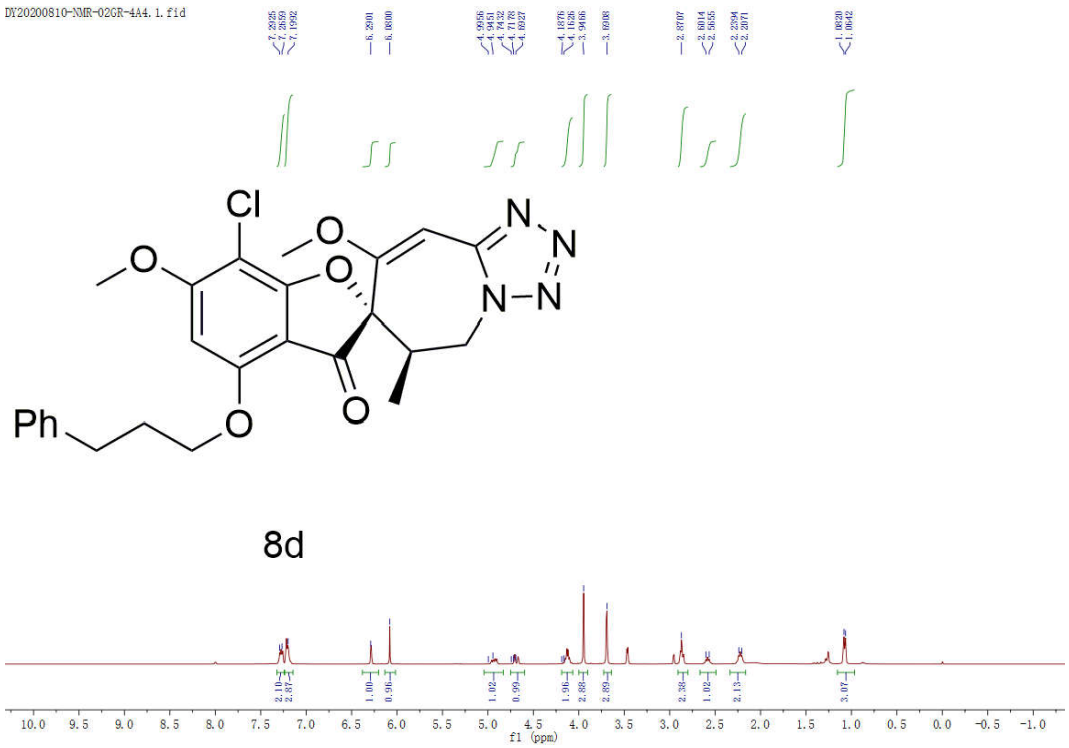
^{13}C NMR spectrum of 8b (100 MHz, $CDCl_3$)



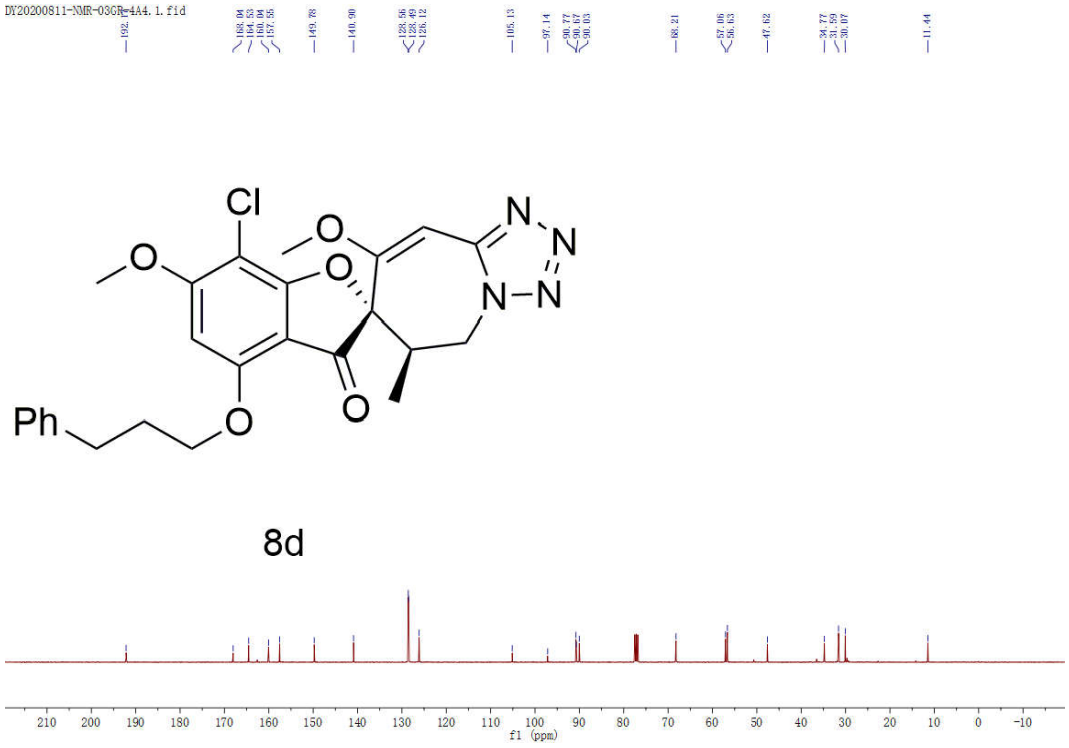
^{1}H NMR spectrum of 8c (400 MHz, $CDCl_3$)



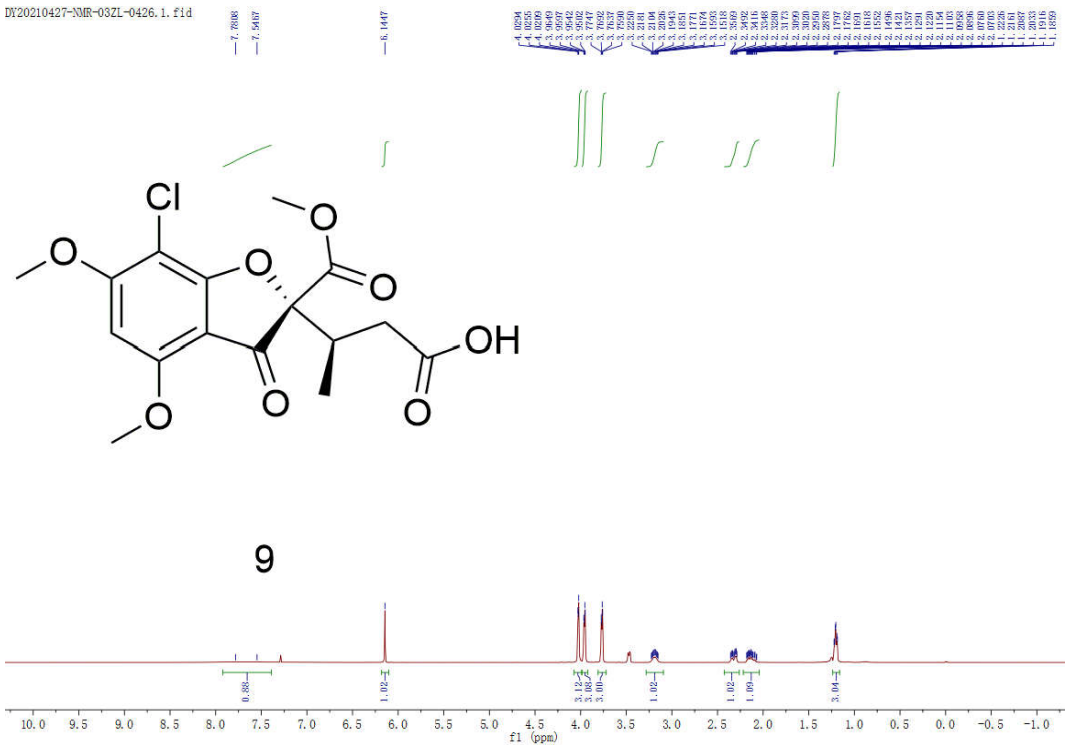
^{13}C NMR spectrum of 8c (100 MHz, $CDCl_3$)



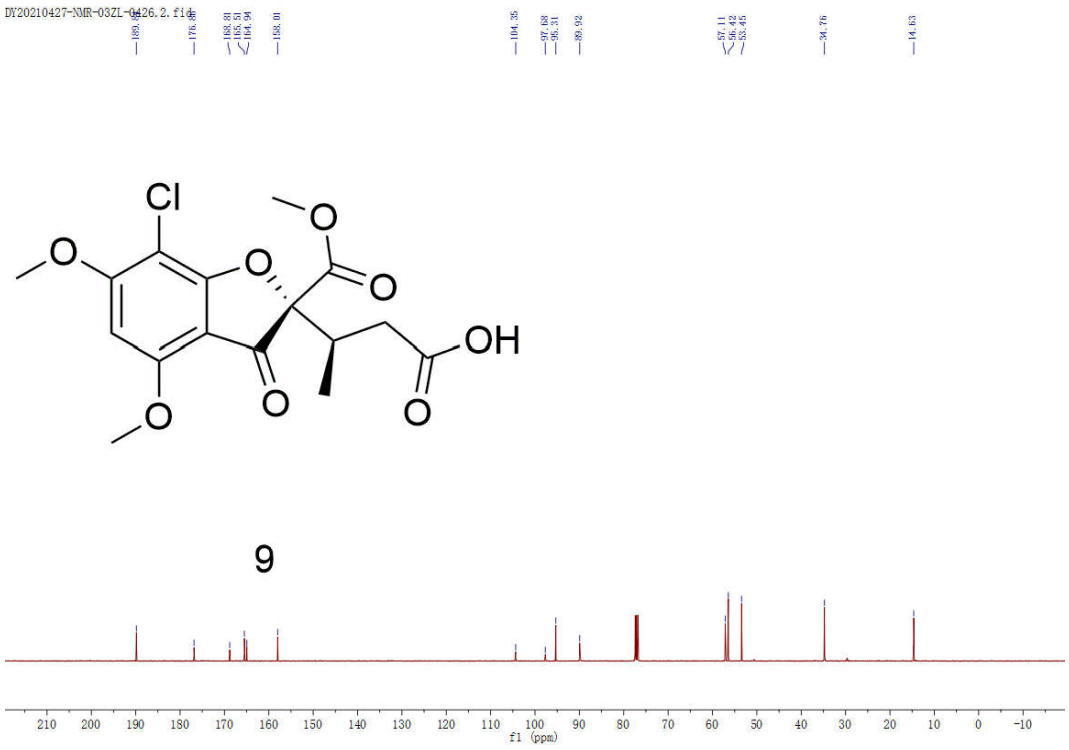
^{1}H NMR spectrum of 8d (400 MHz, $CDCl_3$)



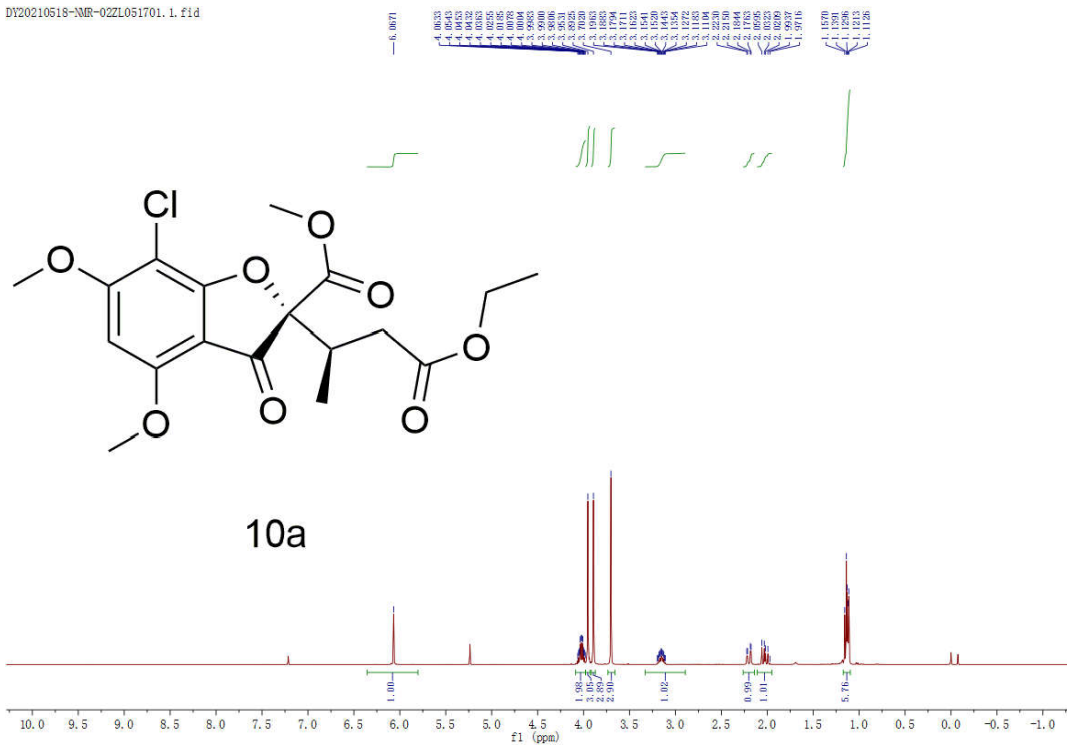
^{13}C NMR spectrum of 8d (100 MHz, $CDCl_3$)



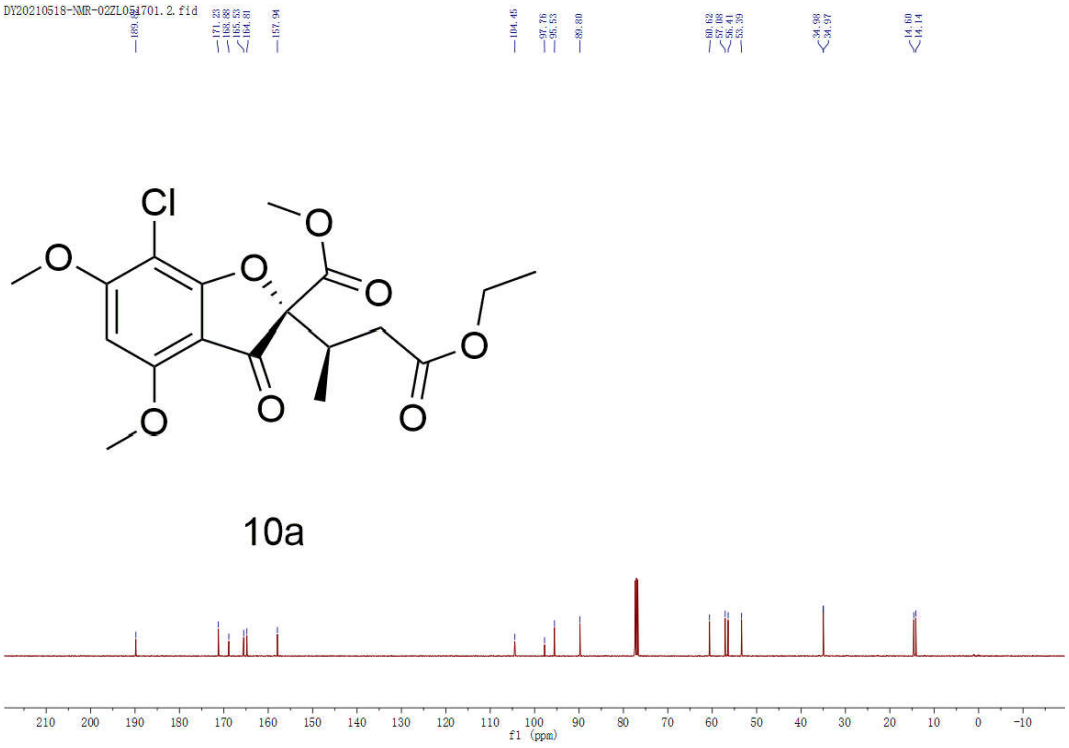
^{1}H NMR spectrum of 9 (400 MHz, $CDCl_3$)



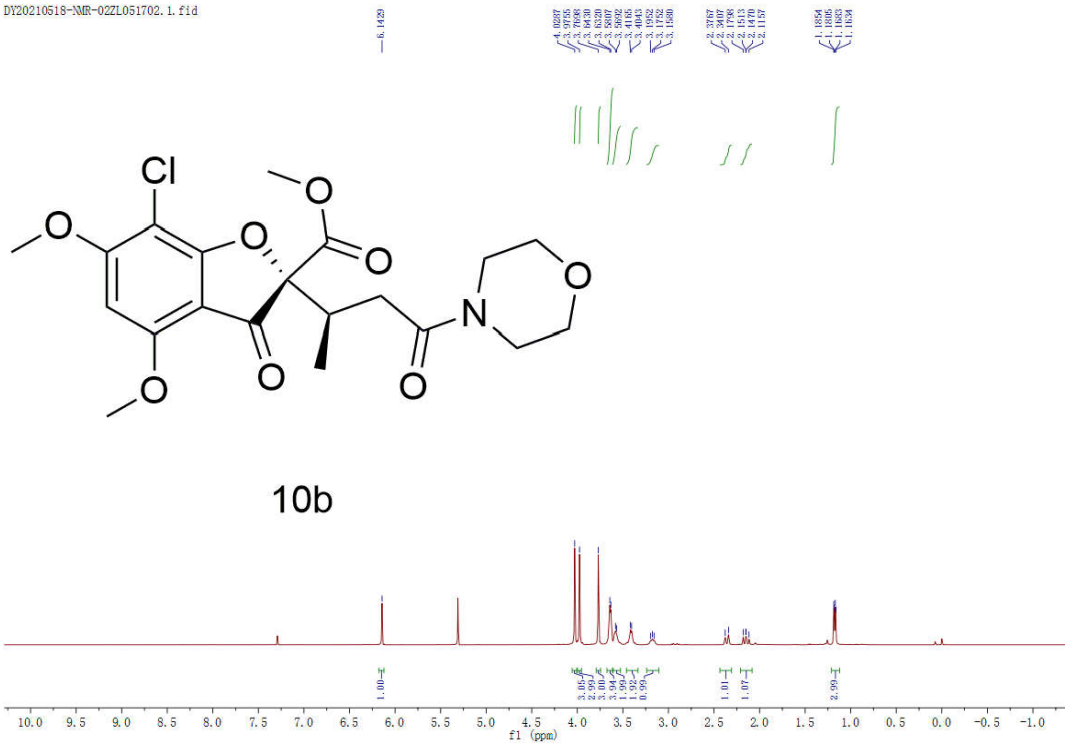
^{13}C NMR spectrum of 9 (100 MHz, $CDCl_3$)



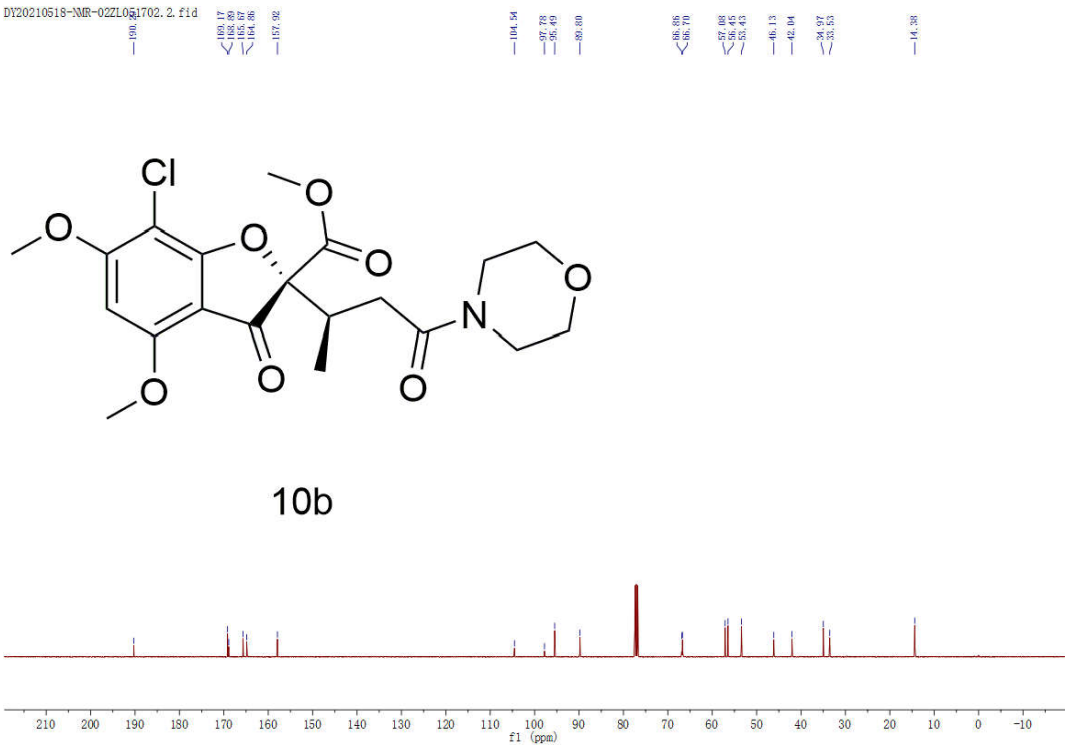
^{1}H NMR spectrum of 10a (400 MHz, $CDCl_3$)



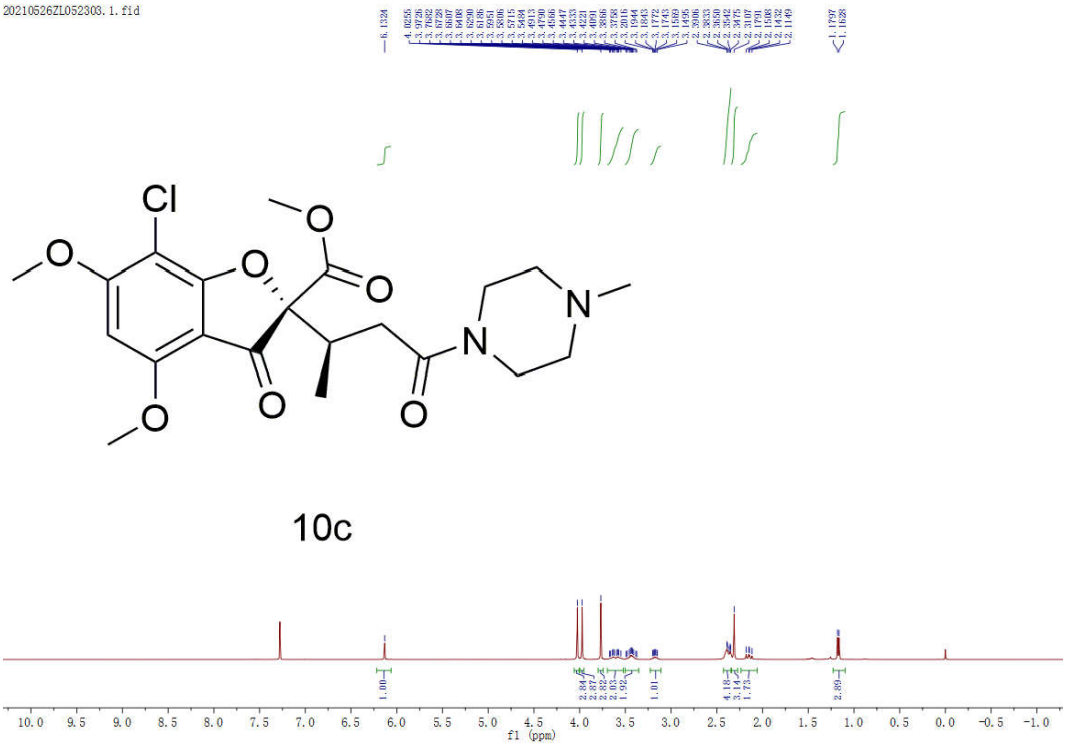
^{13}C NMR spectrum of 10a (100 MHz, $CDCl_3$)



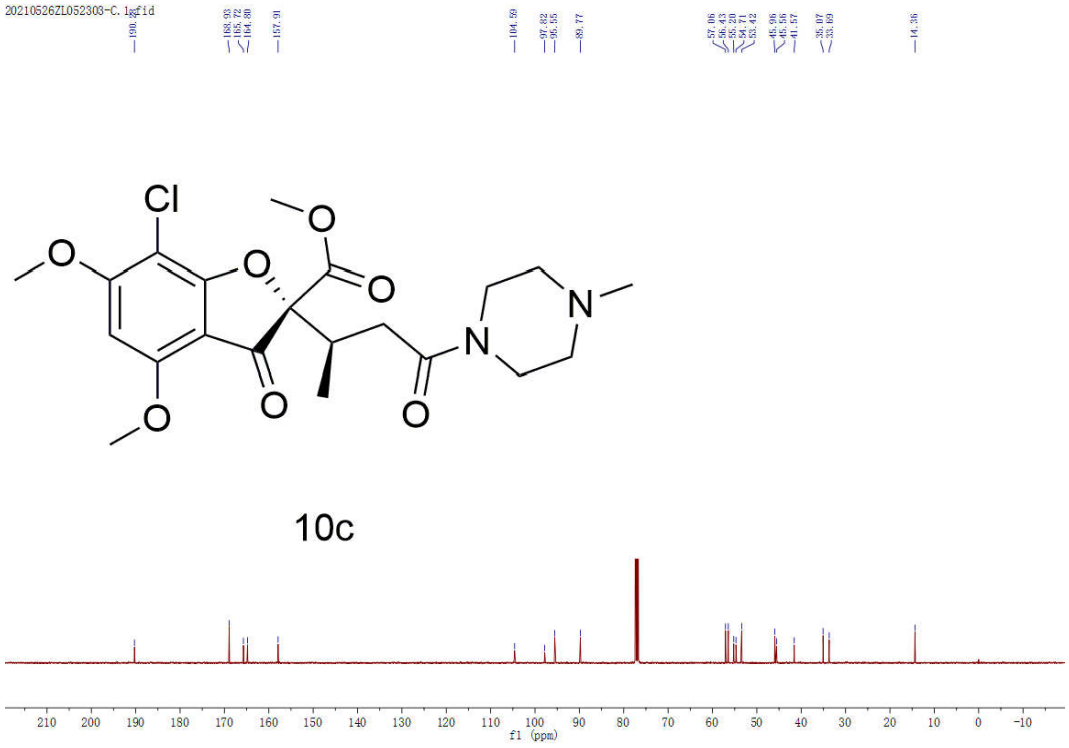
^{1}H NMR spectrum of 10b (400 MHz, $CDCl_3$)



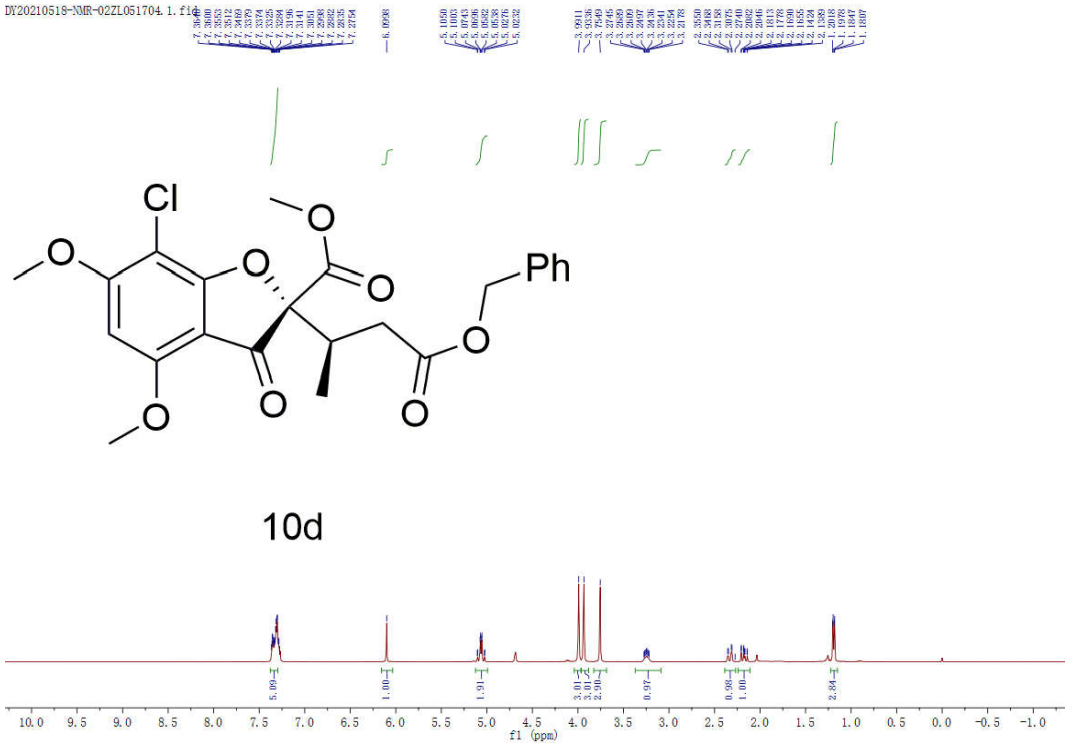
^{13}C NMR spectrum of 10b (100 MHz, $CDCl_3$)



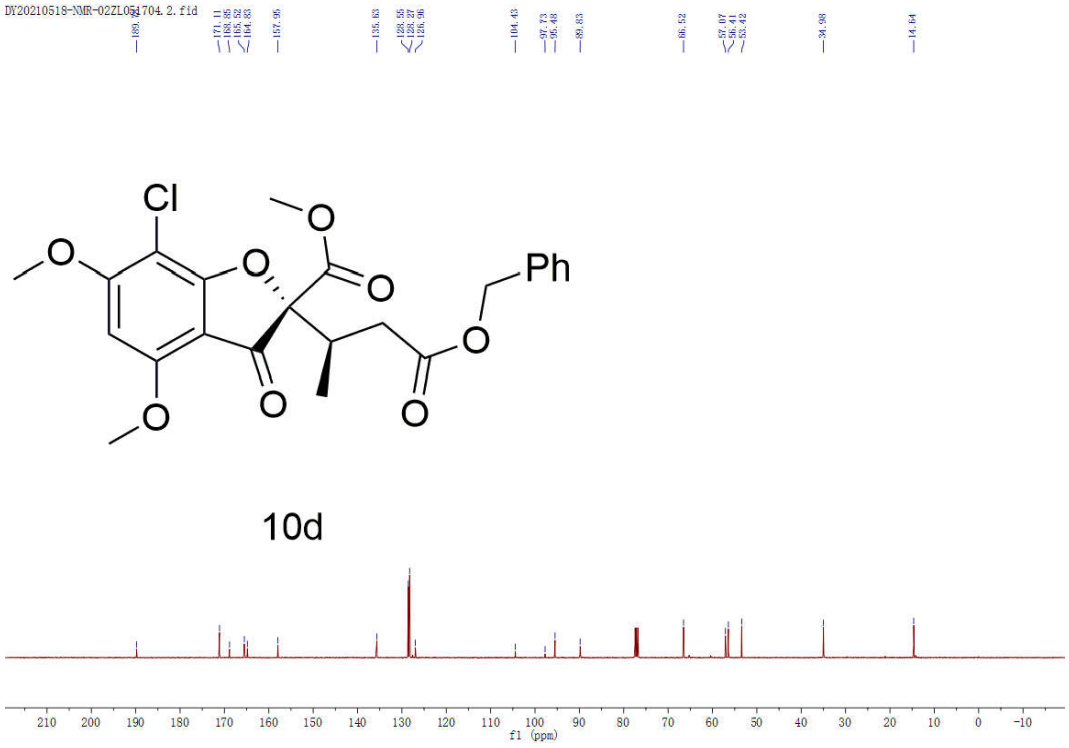
^{1}H NMR spectrum of 10c (400 MHz, $CDCl_3$)



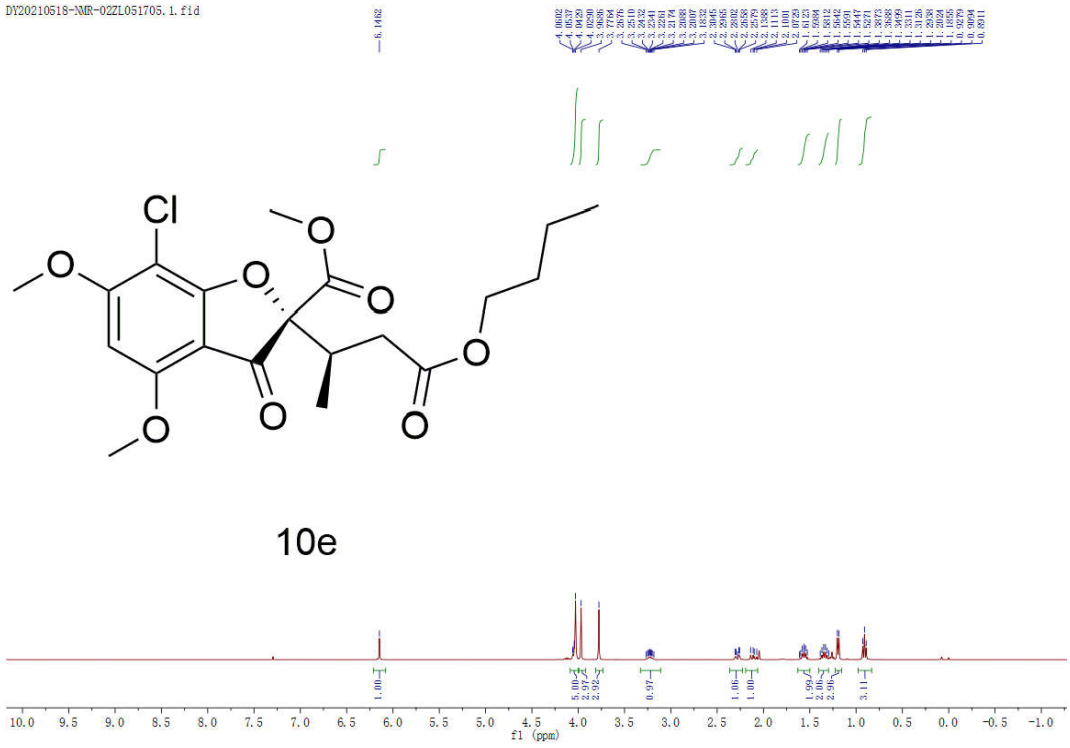
^{13}C NMR spectrum of 10c (100 MHz, $CDCl_3$)



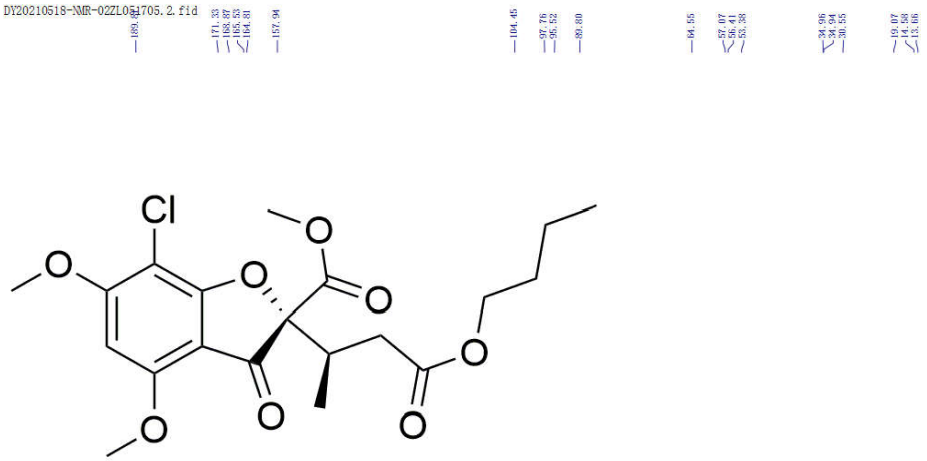
^{1}H NMR spectrum of 10d (400 MHz, $CDCl_3$)



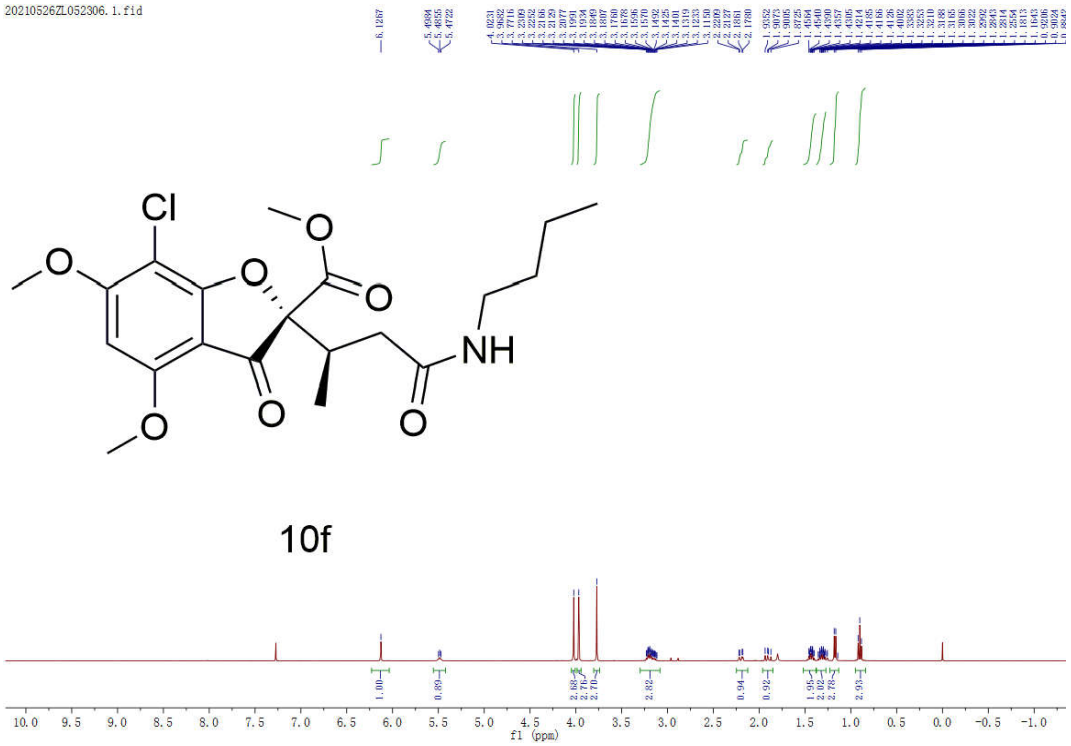
^{13}C NMR spectrum of 10d (100 MHz, $CDCl_3$)



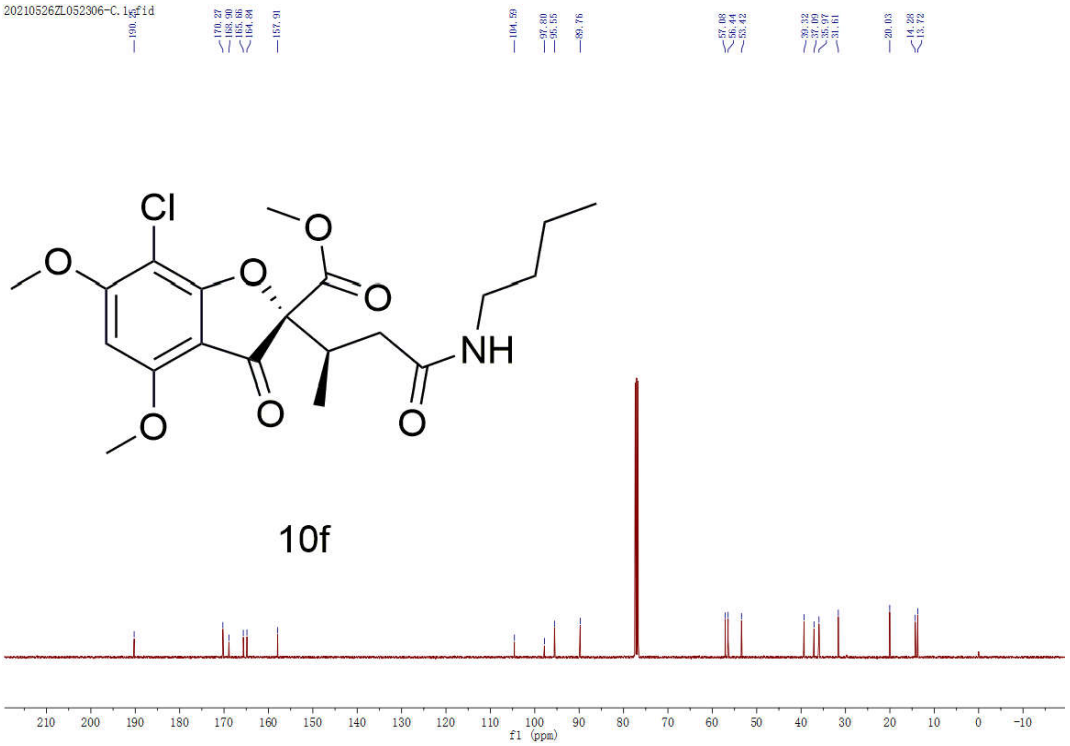
^{1}H NMR spectrum of 10e (400 MHz, $CDCl_3$)



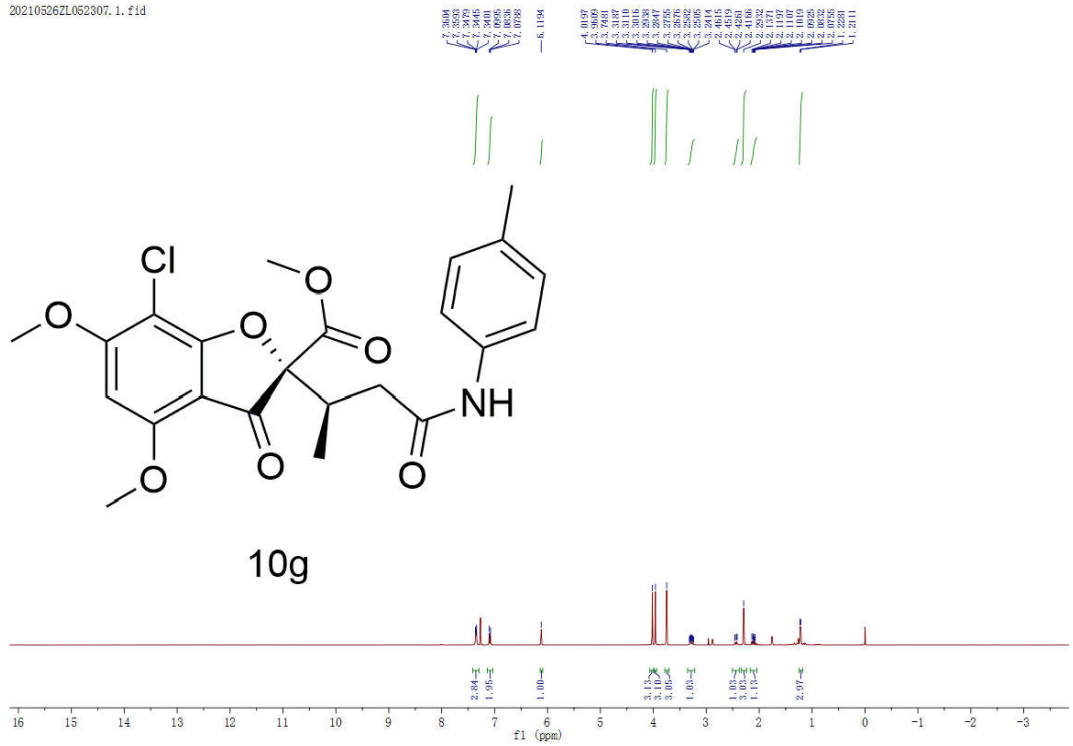
^{13}C NMR spectrum of 10e (100 MHz, $CDCl_3$)



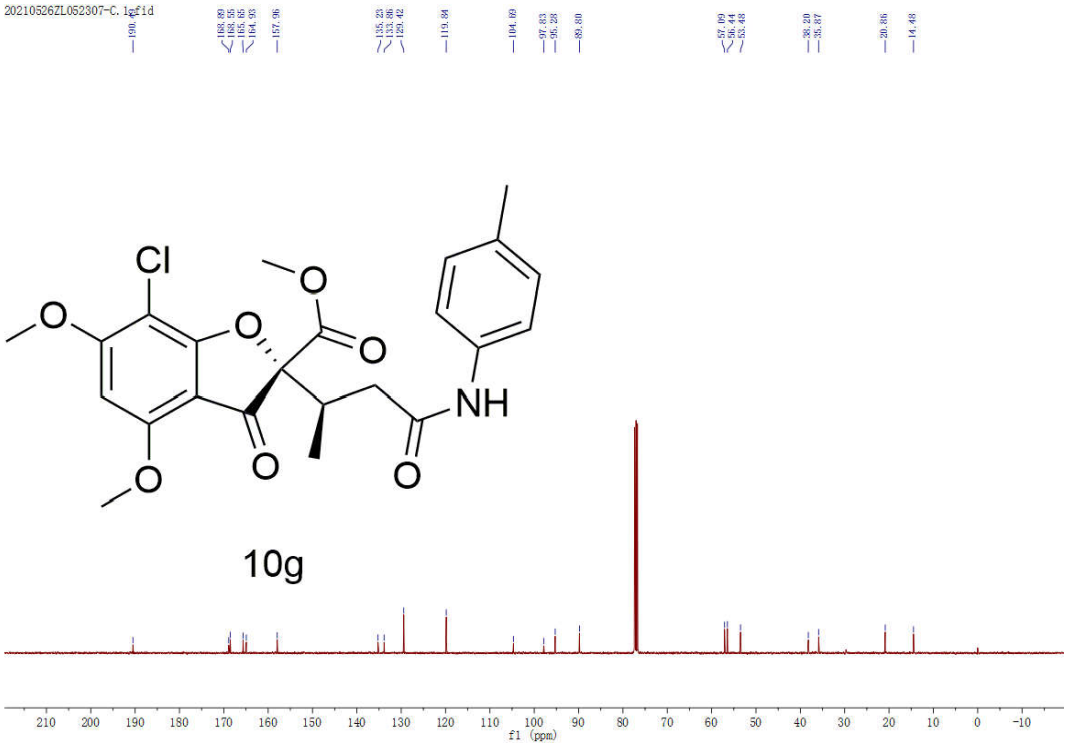
^{1}H NMR spectrum of 10f (400 MHz, $CDCl_3$)



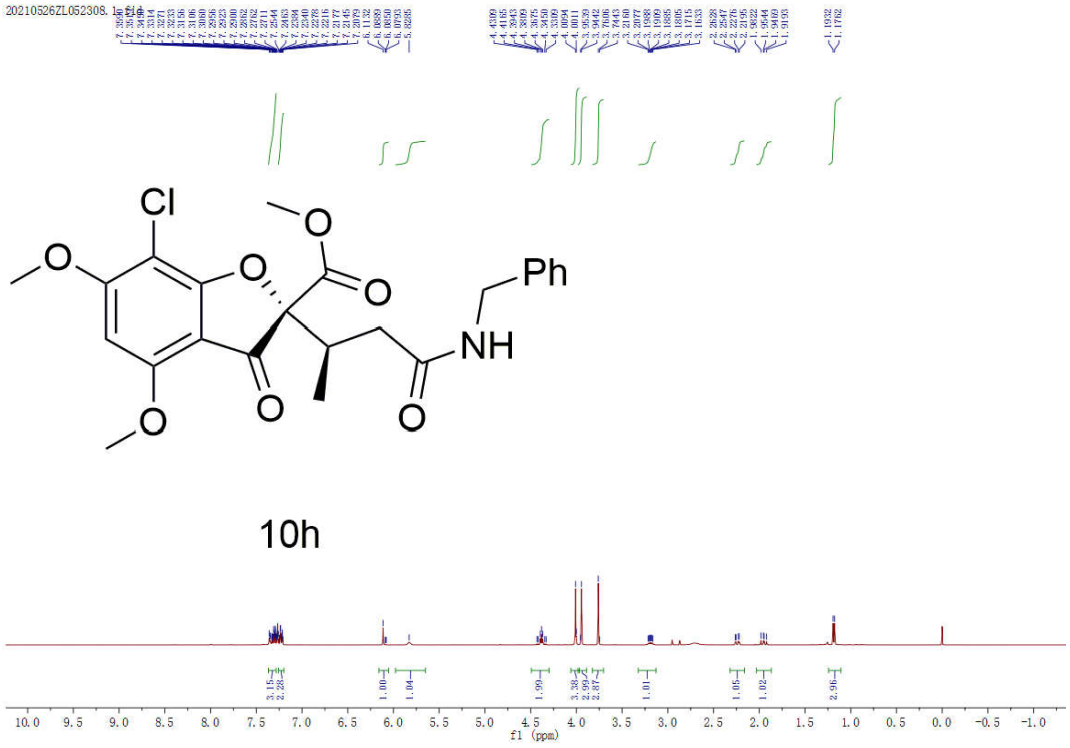
^{13}C NMR spectrum of 10f (100 MHz, $CDCl_3$)



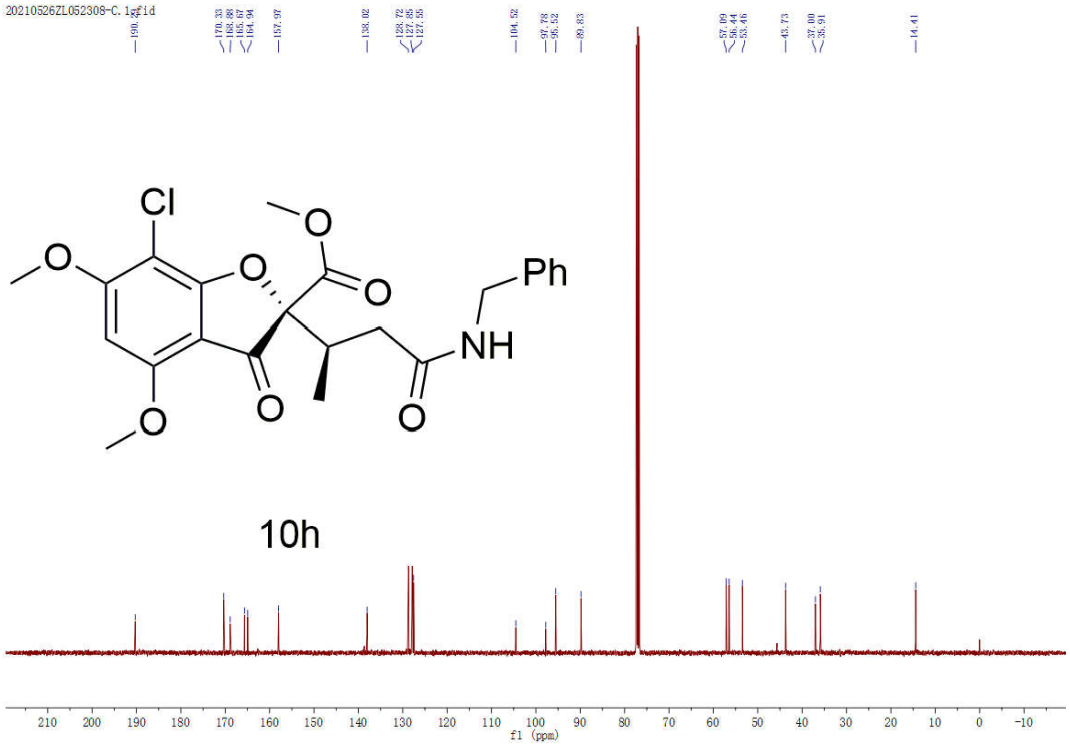
^{1}H NMR spectrum of 10g (400 MHz, $CDCl_3$)



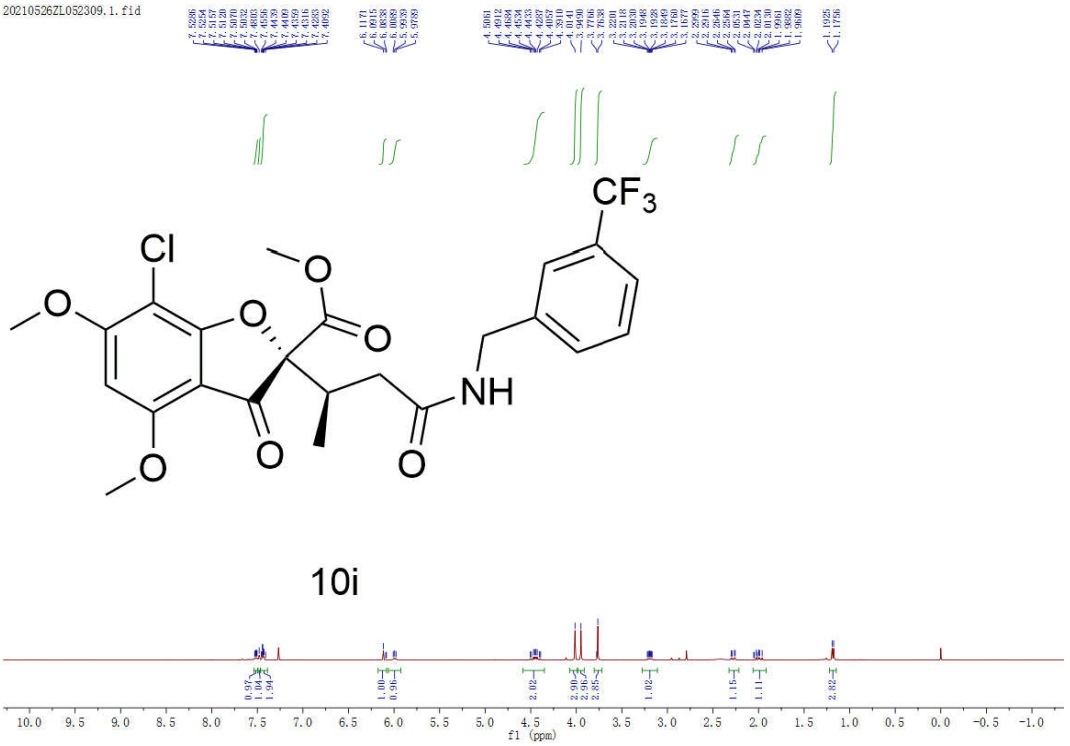
^{13}C NMR spectrum of 10g (100 MHz, $CDCl_3$)



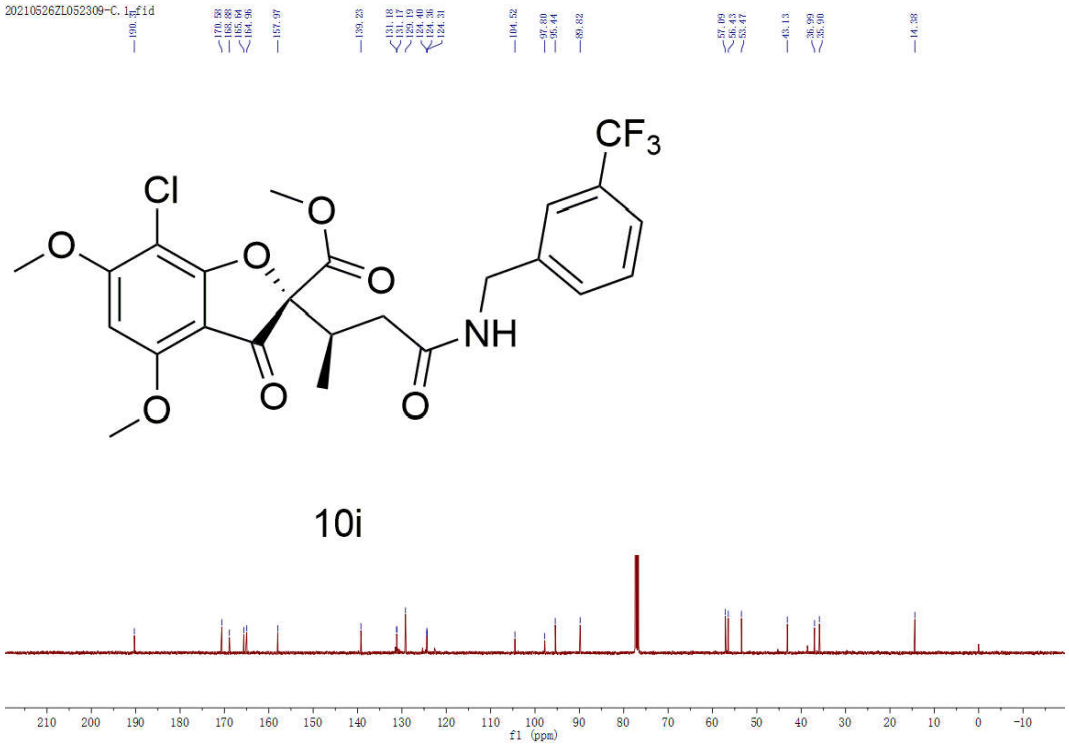
^{1}H NMR spectrum of 10h (400 MHz, $CDCl_3$)



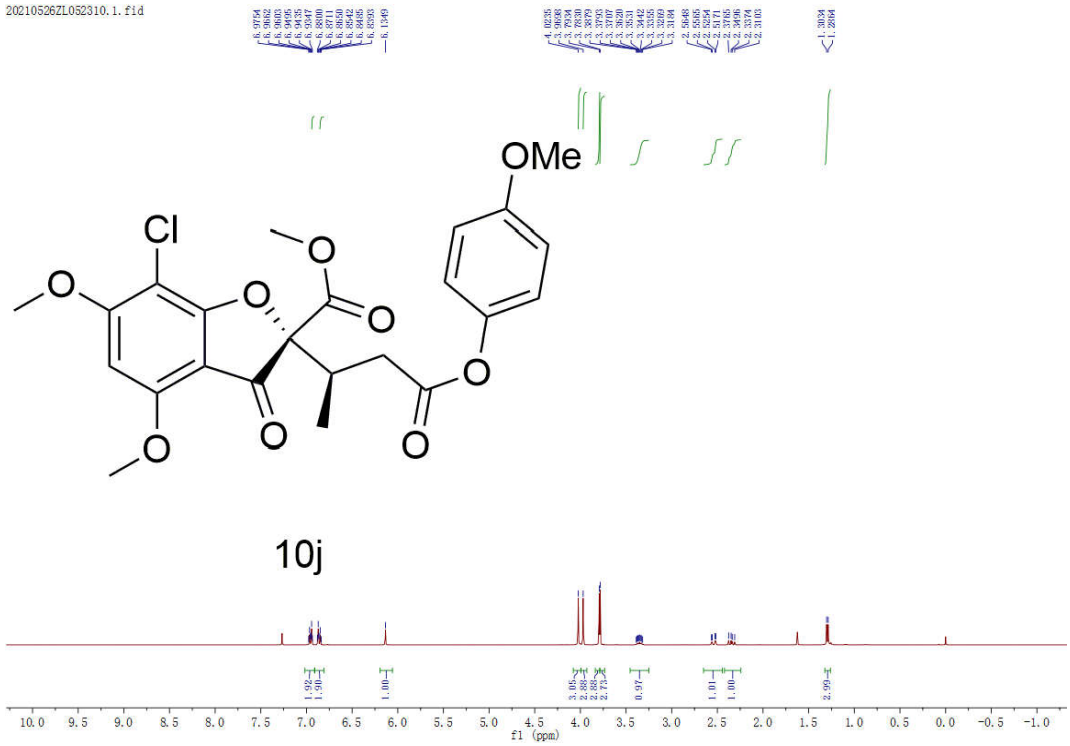
^{13}C NMR spectrum of 10h (100 MHz, $CDCl_3$)



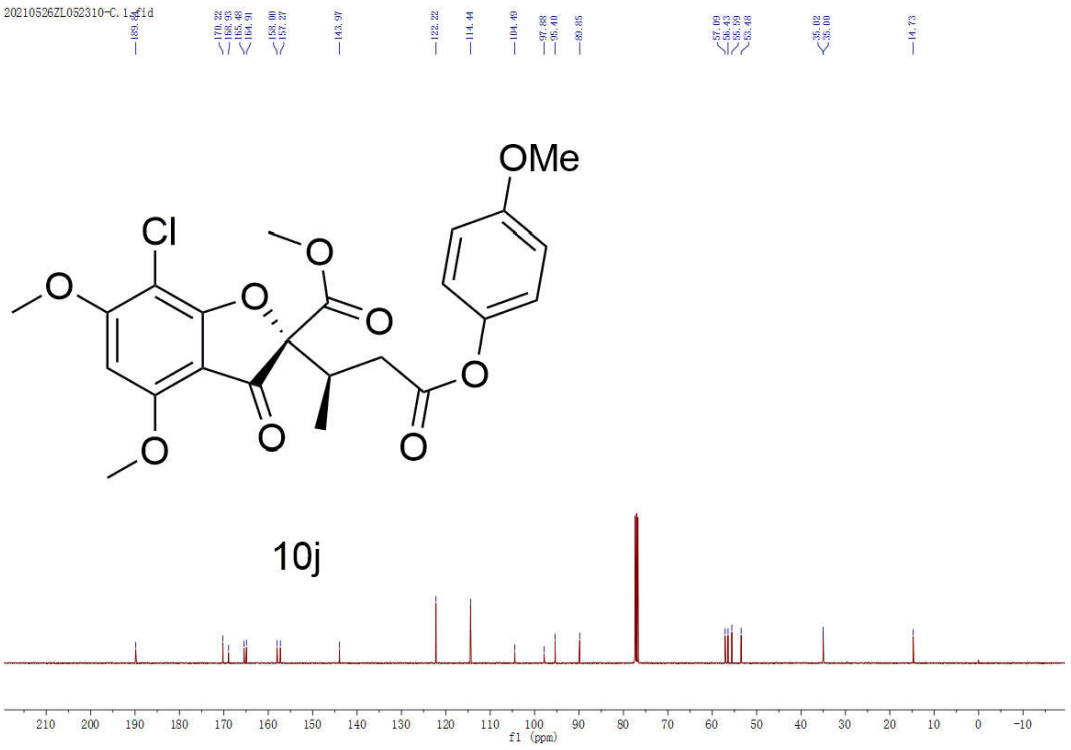
^{1}H NMR spectrum of 10i (400 MHz, $CDCl_3$)



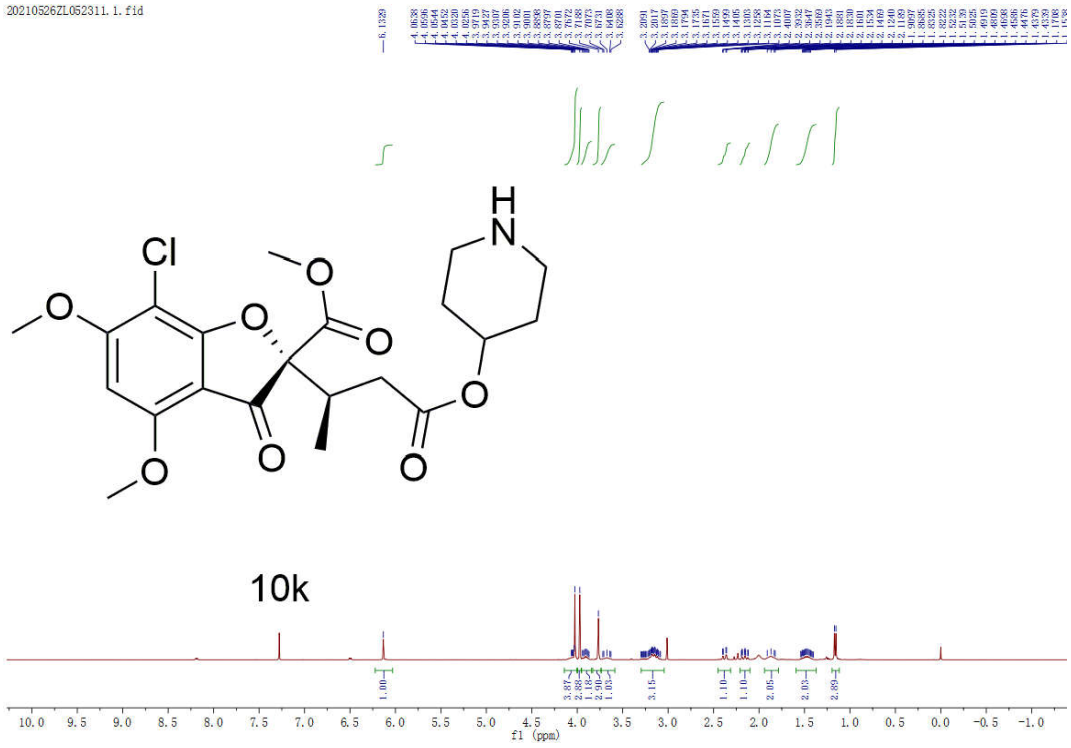
^{13}C NMR spectrum of 10i (100 MHz, $CDCl_3$)



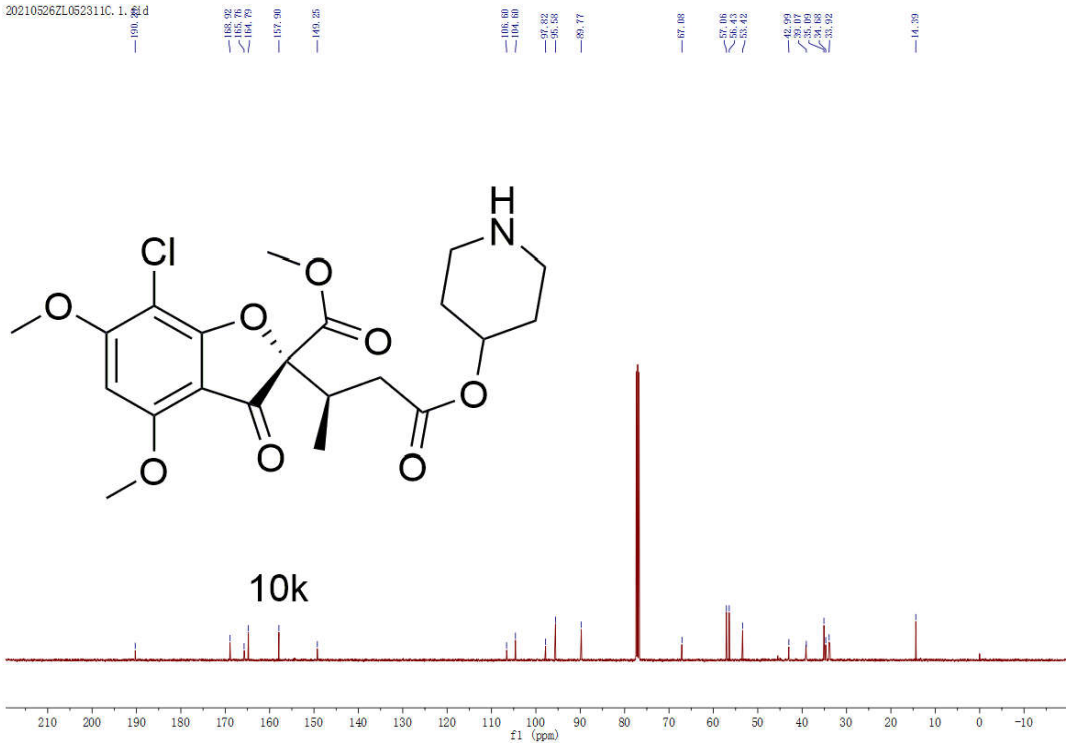
^{1}H NMR spectrum of 10j (400 MHz, $CDCl_3$)



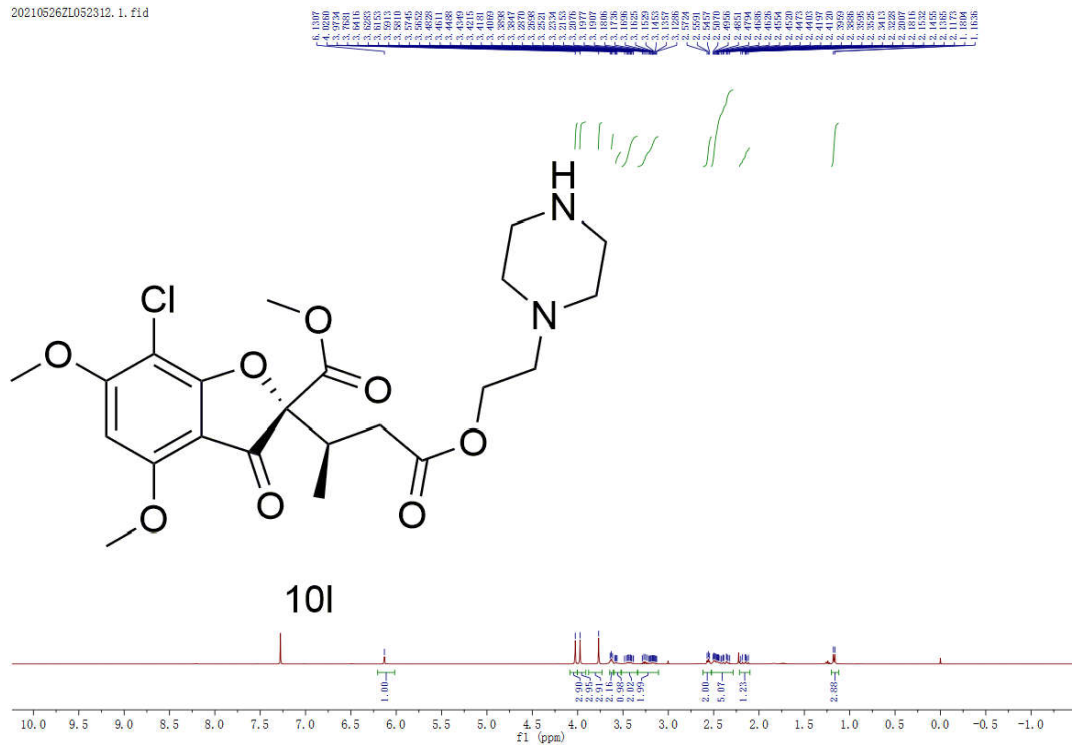
^{13}C NMR spectrum of 10j (100 MHz, $CDCl_3$)



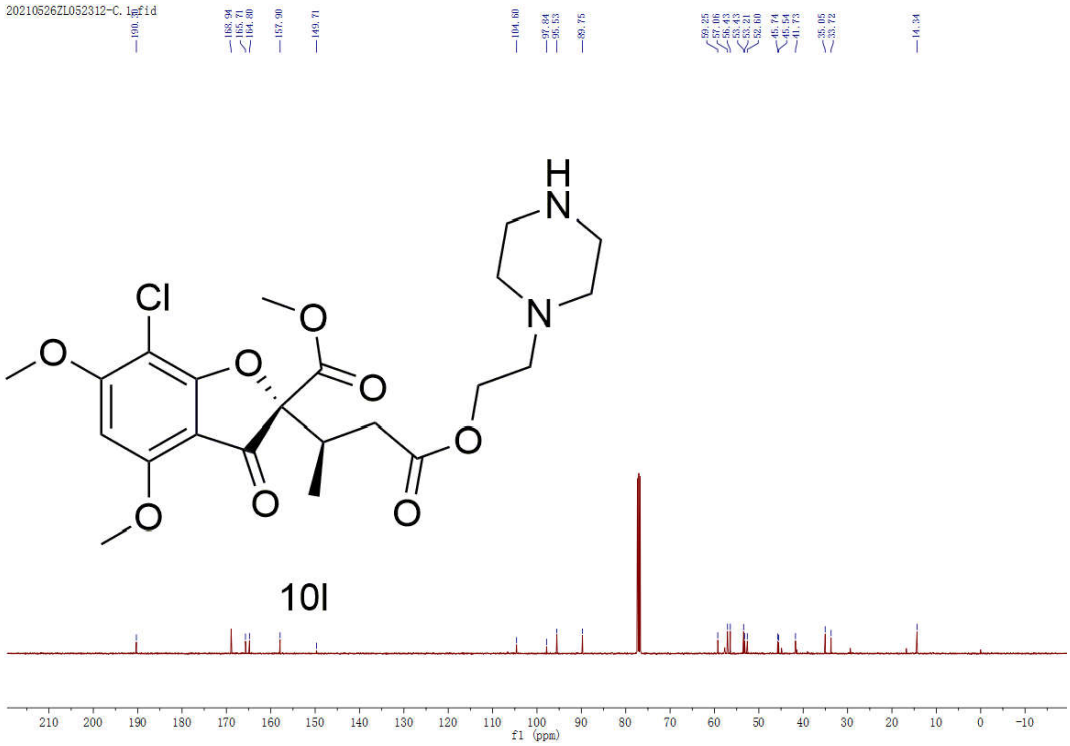
^{1}H NMR spectrum of 10k (400 MHz, $CDCl_3$)



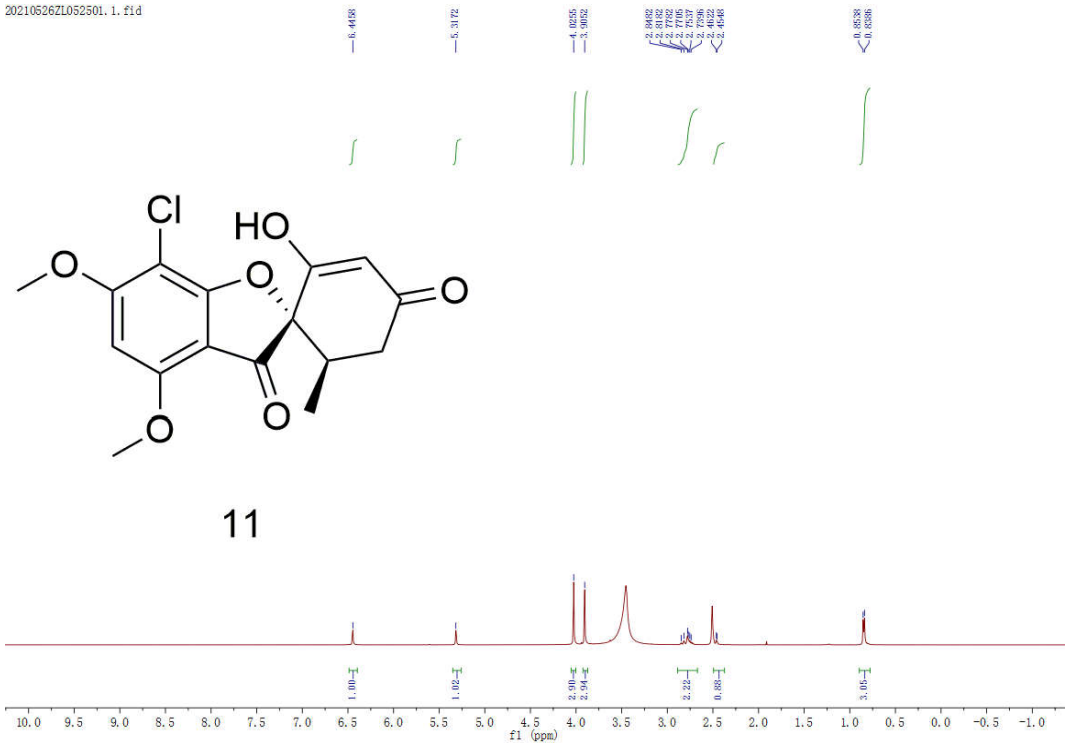
^{13}C NMR spectrum of 10k (100 MHz, $CDCl_3$)



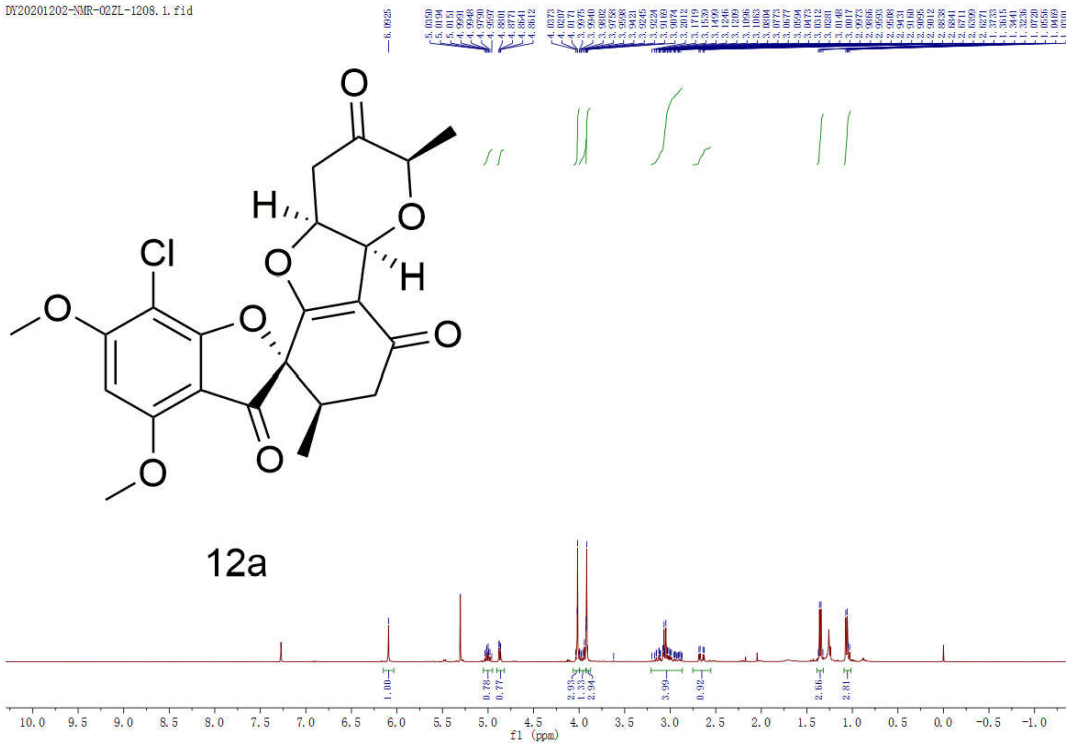
^{1}H NMR spectrum of 10l (400 MHz, $CDCl_3$)



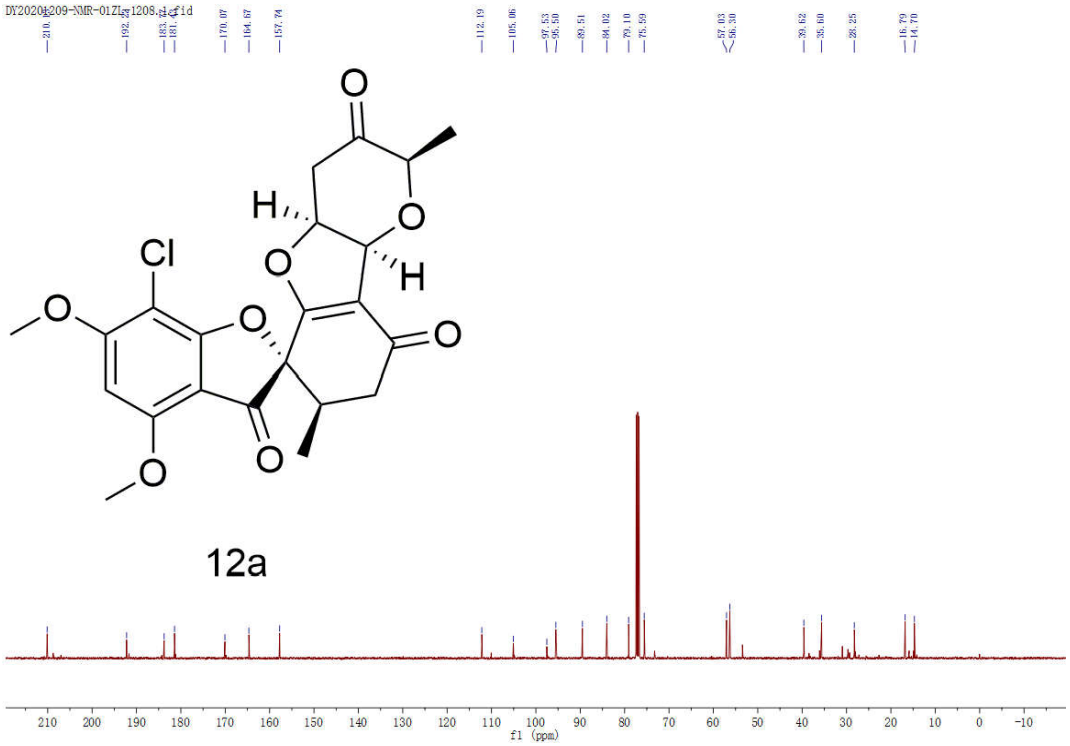
^{13}C NMR spectrum of 10l (100 MHz, $CDCl_3$)



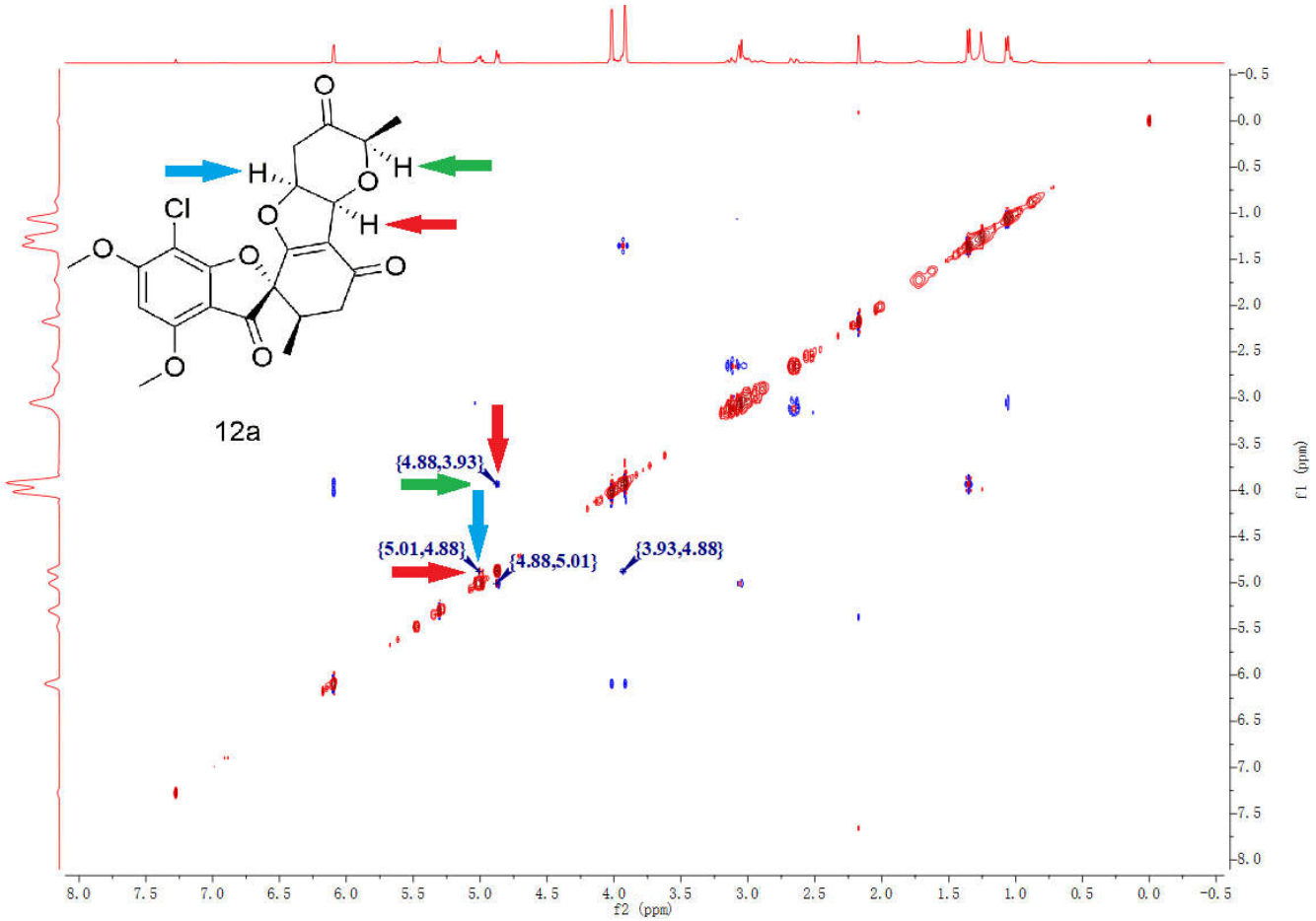
^{1}H NMR spectrum of 11 (400 MHz, DMSO-d_6)



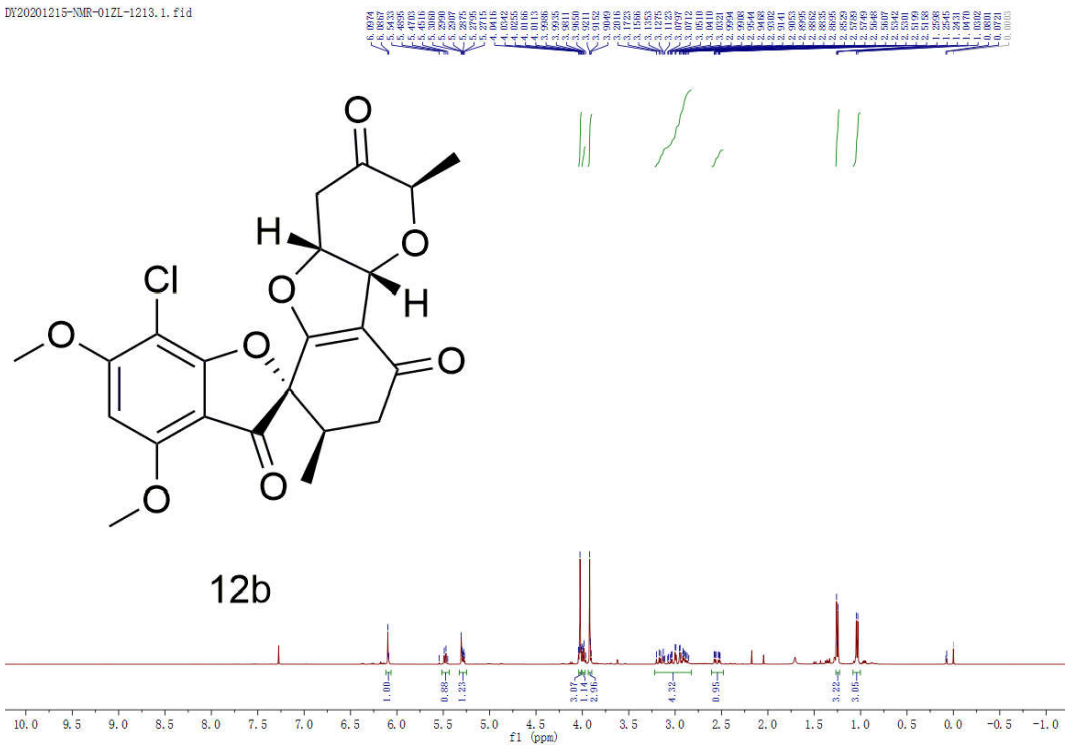
^{1}H NMR spectrum of 12a (400 MHz, $CDCl_3$)



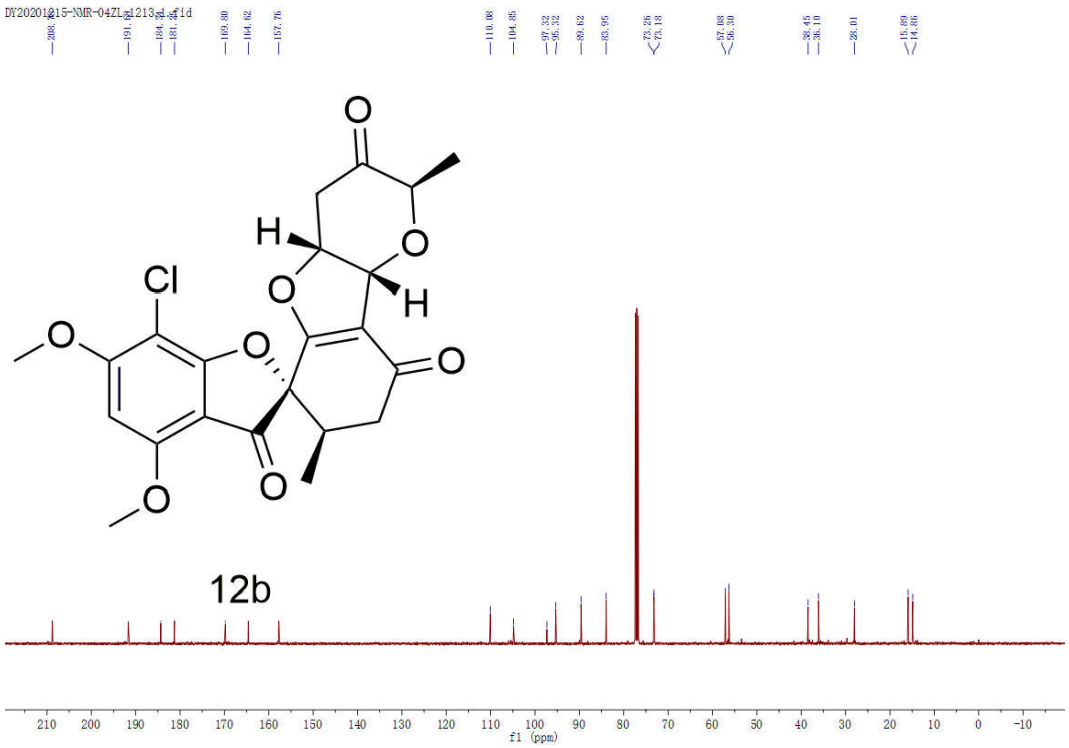
^{13}C NMR spectrum of 12a (100 MHz, $CDCl_3$)



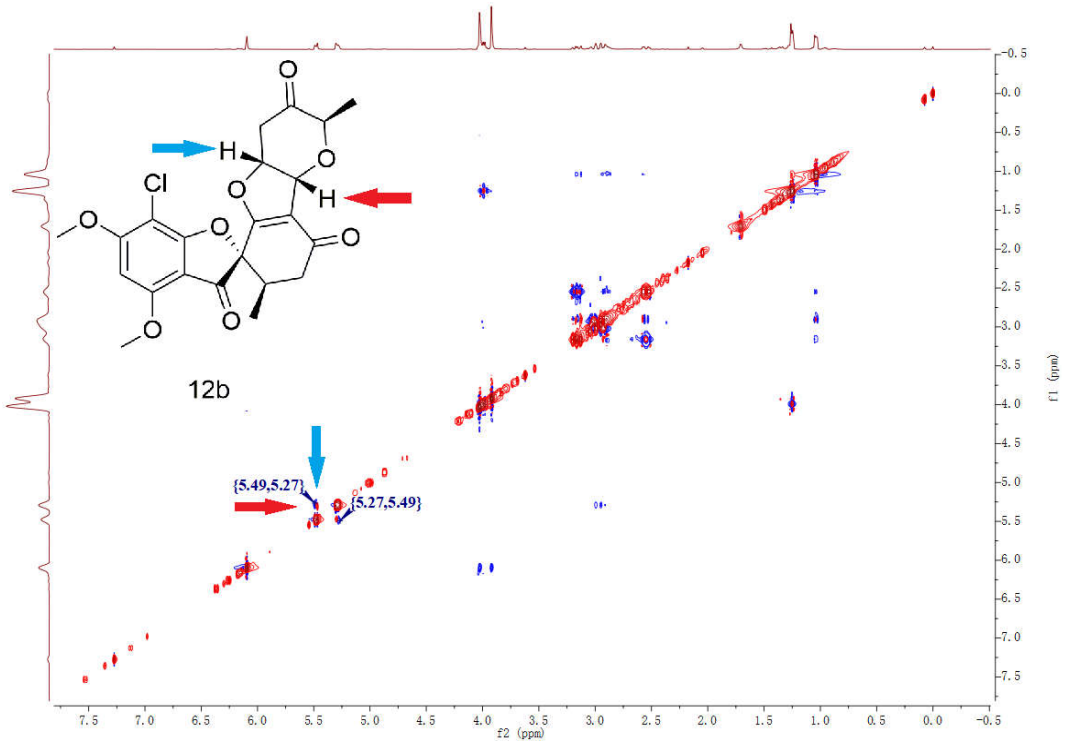
^{1}H-^{1}H NOESY NMR spectrum of 12a (100 MHz, $CDCl_3$)



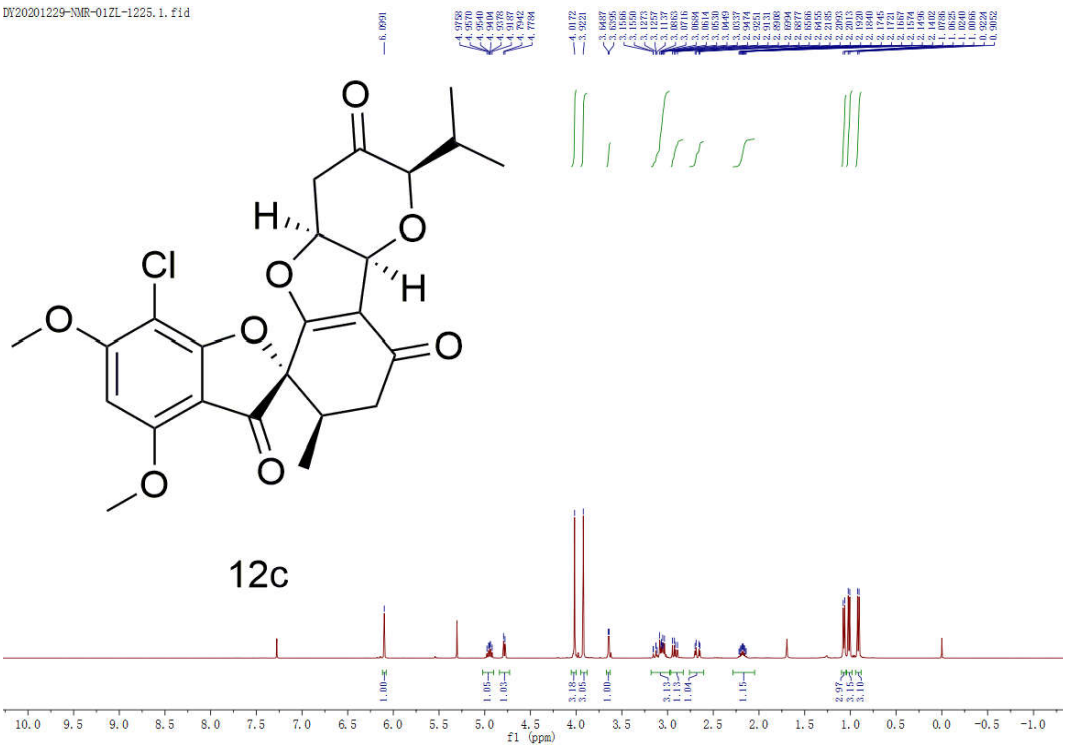
^{1}H NMR spectrum of 12b (400 MHz, $CDCl_3$)



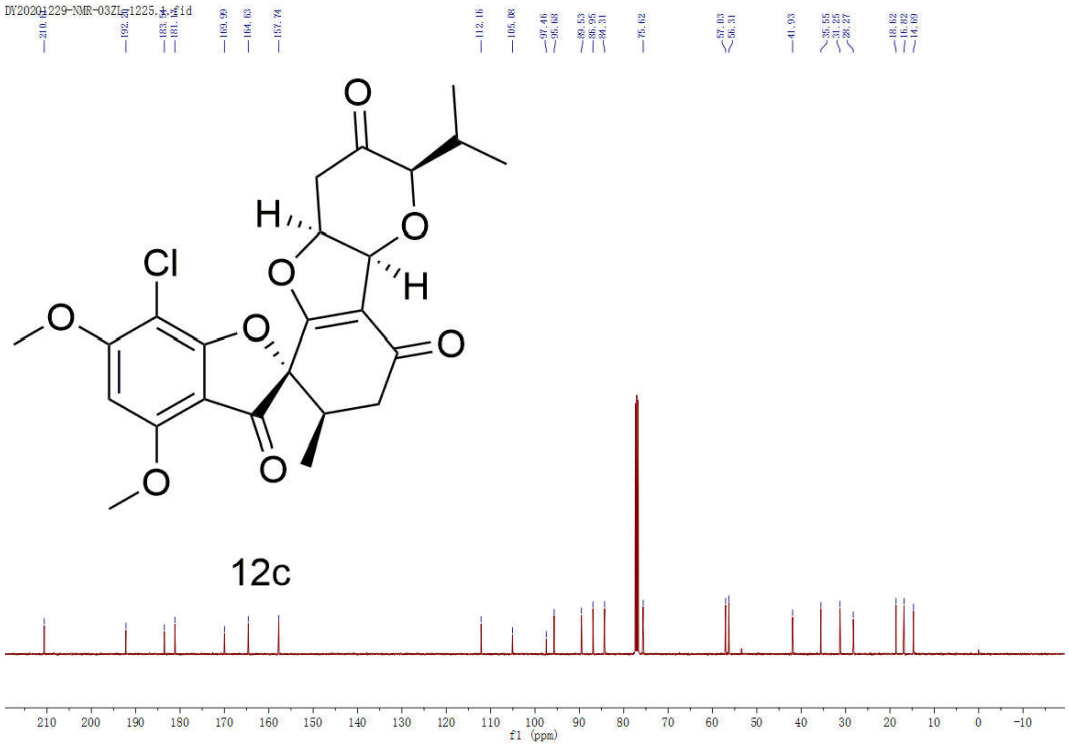
^{13}C NMR spectrum of 12b (100 MHz, $CDCl_3$)



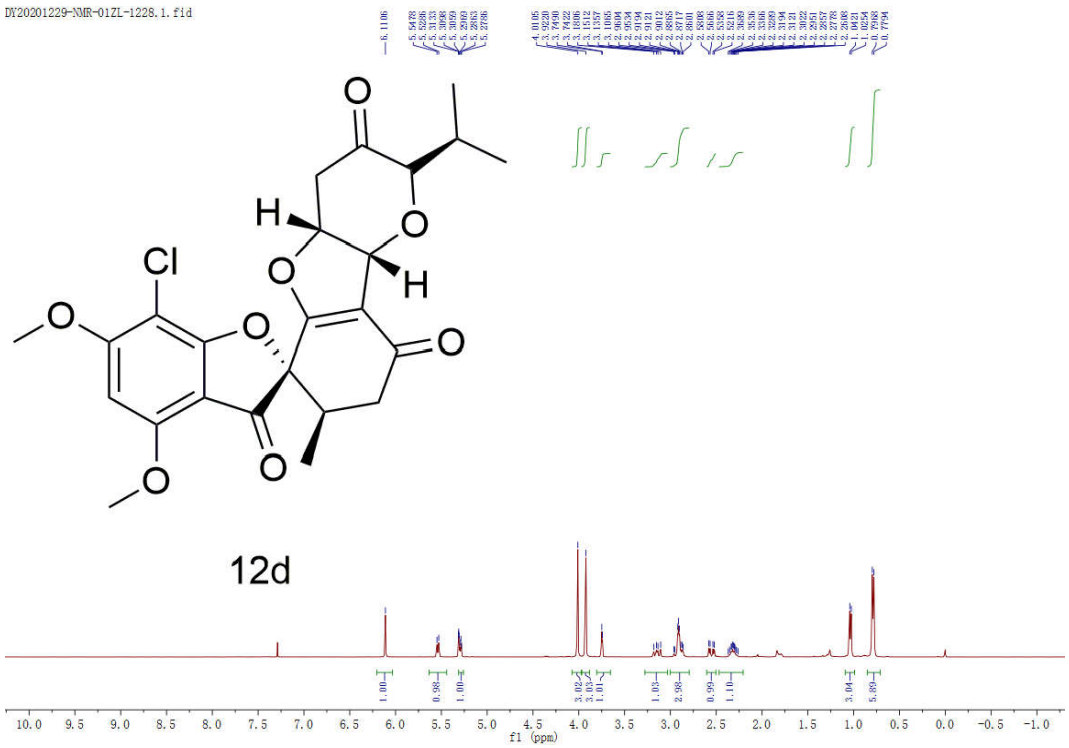
^{1}H-^{1}H NOESY NMR spectrum of 12b (100 MHz, $CDCl_3$)



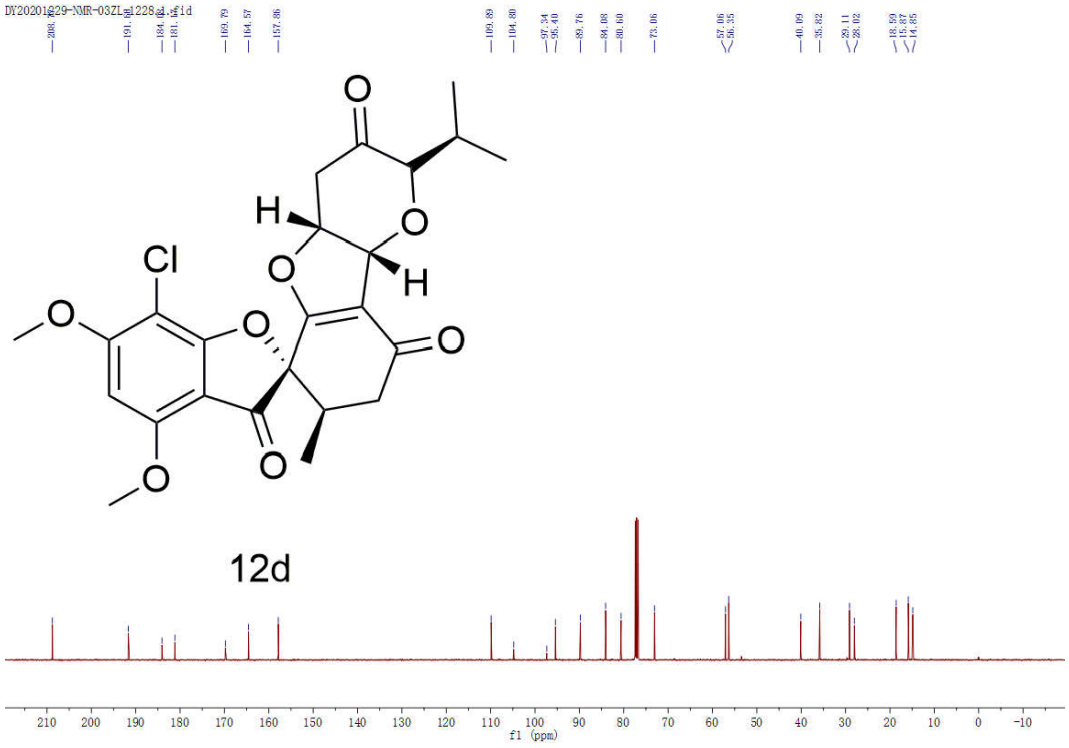
^{1}H NMR spectrum of 12c (400 MHz, $CDCl_3$)



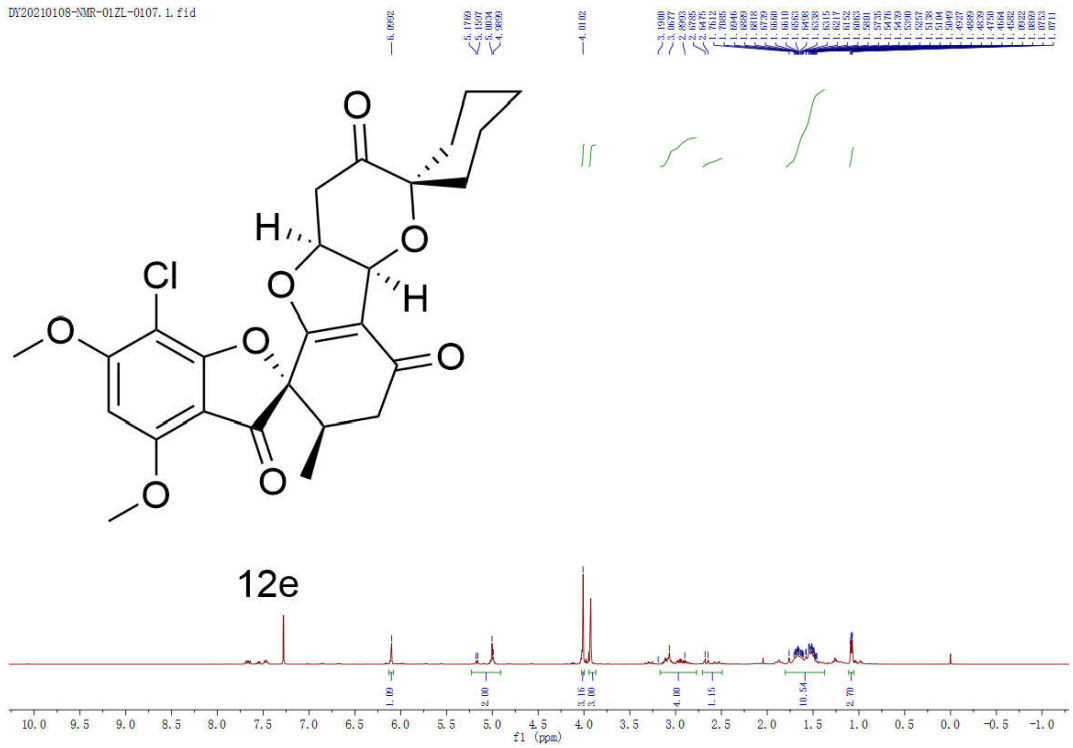
^{13}C NMR spectrum of 12c (100 MHz, $CDCl_3$)



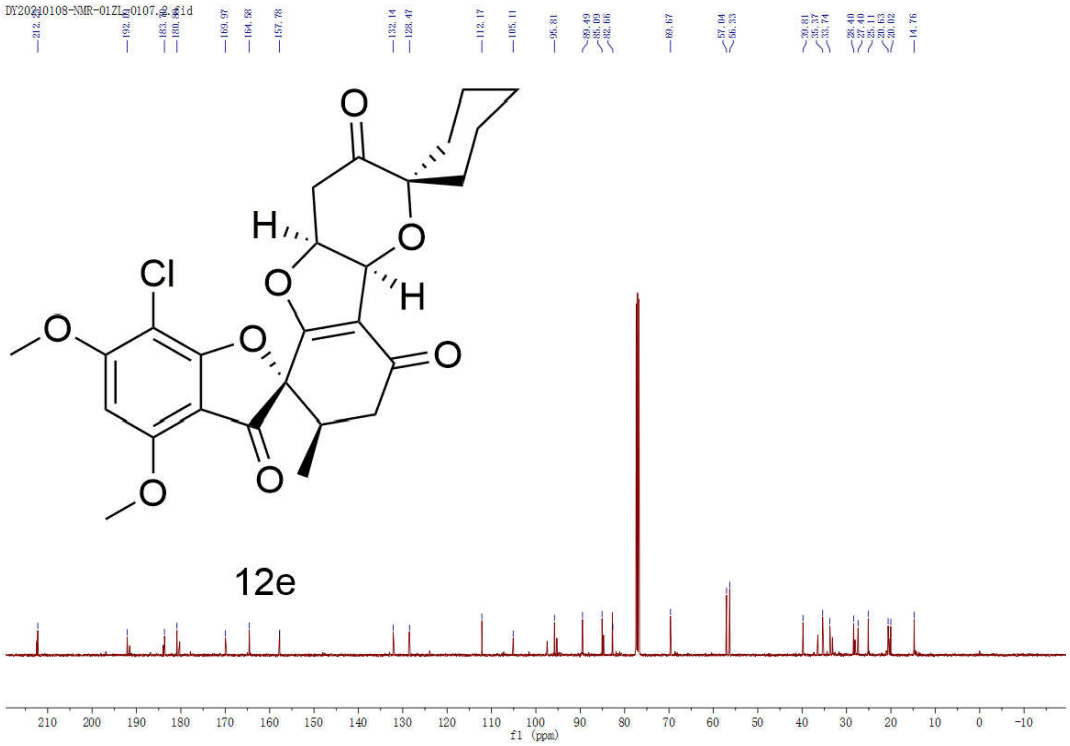
^{1}H NMR spectrum of 12d (400 MHz, $CDCl_3$)



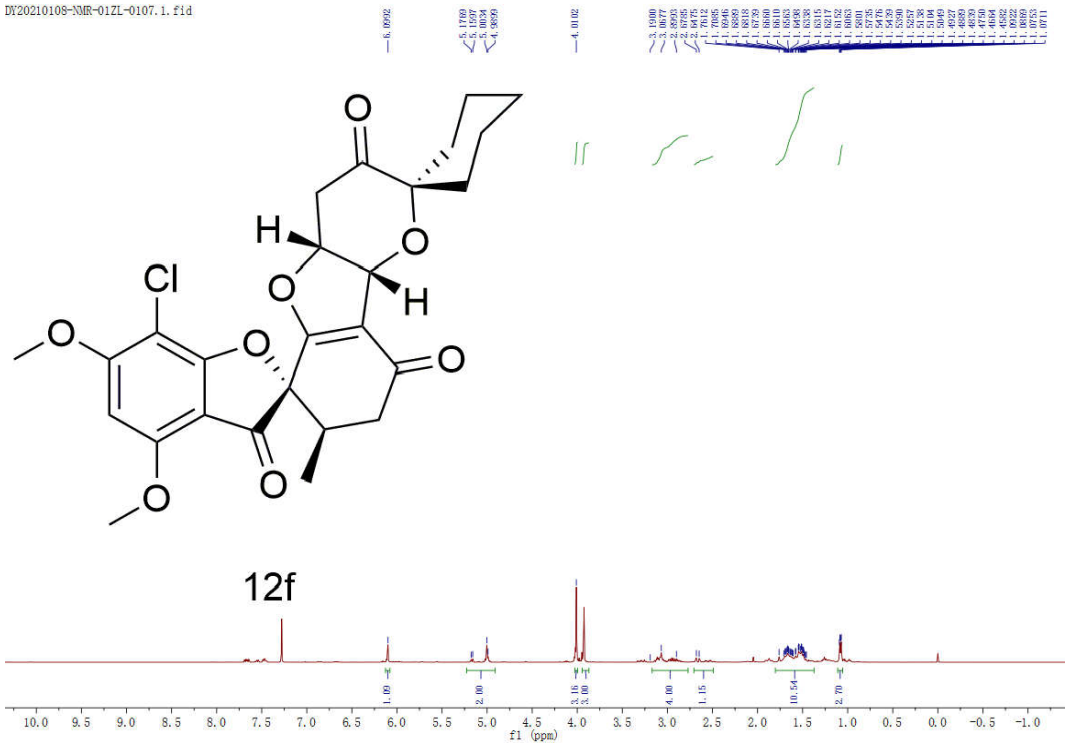
^{13}C NMR spectrum of 12d (100 MHz, $CDCl_3$)



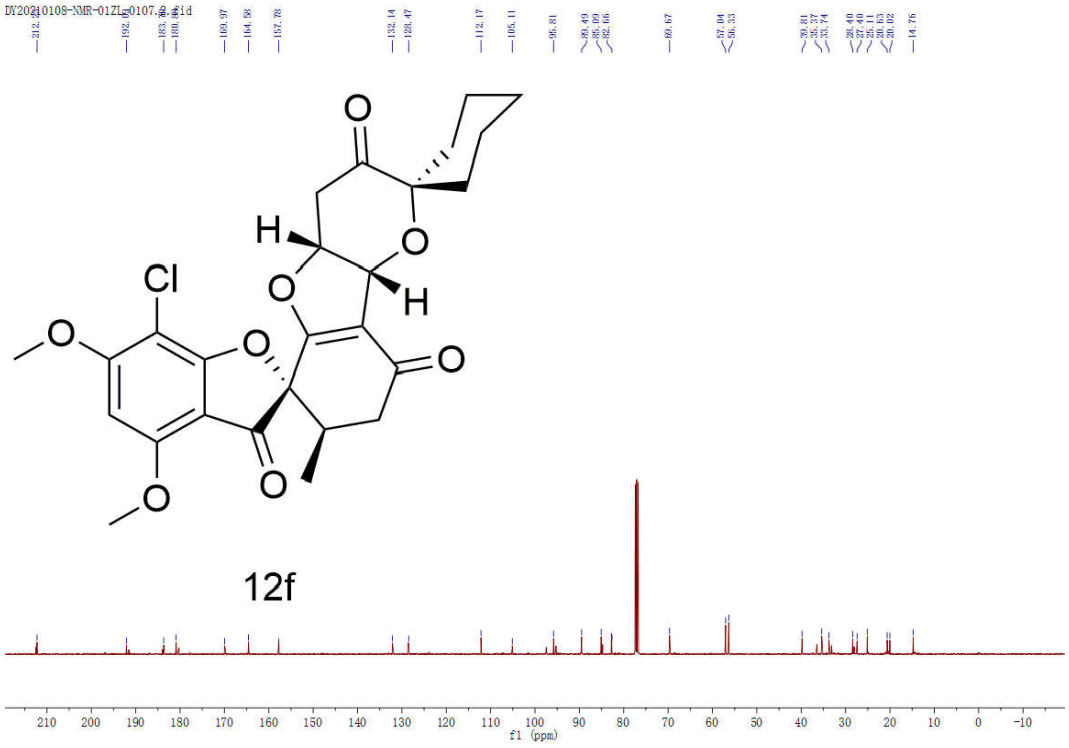
^{1}H NMR spectrum of 12e (400 MHz, $CDCl_3$)



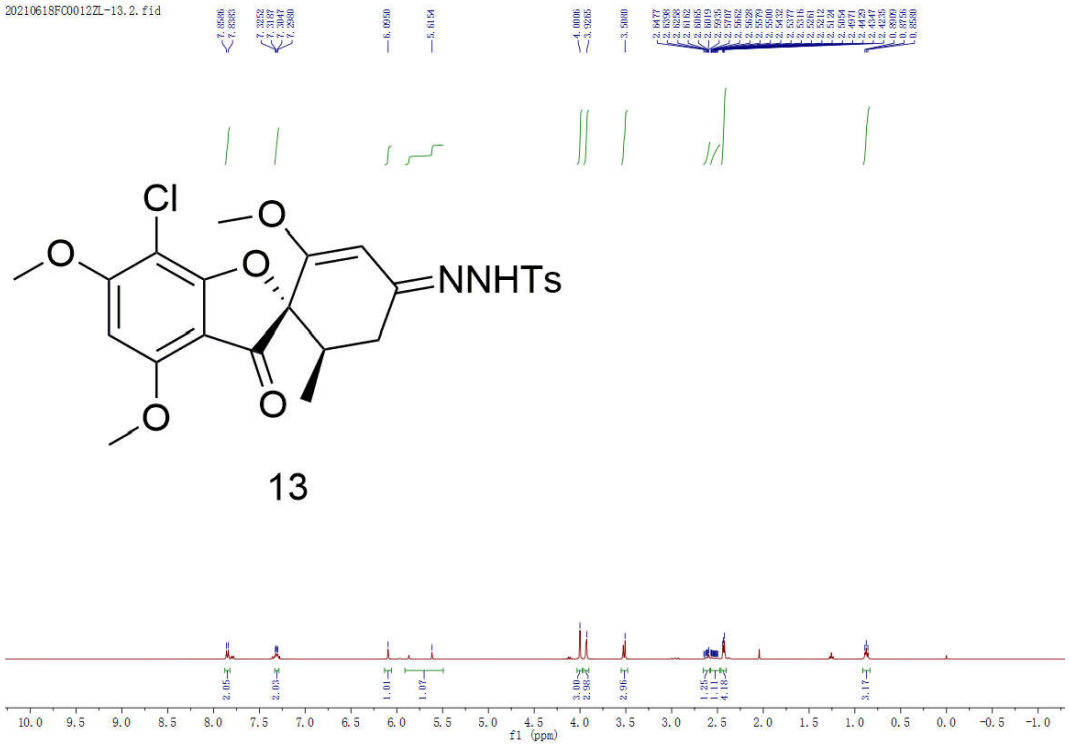
^{13}C NMR spectrum of 12e (100 MHz, $CDCl_3$)



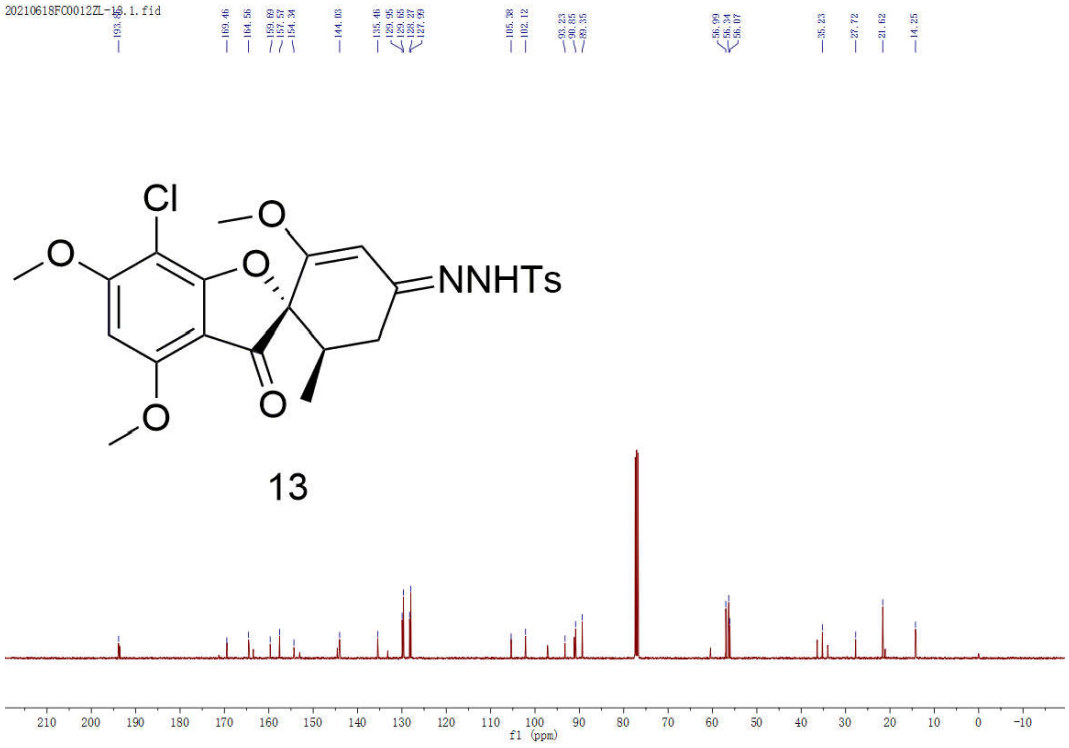
^{1}H NMR spectrum of 12f (400 MHz, $CDCl_3$)



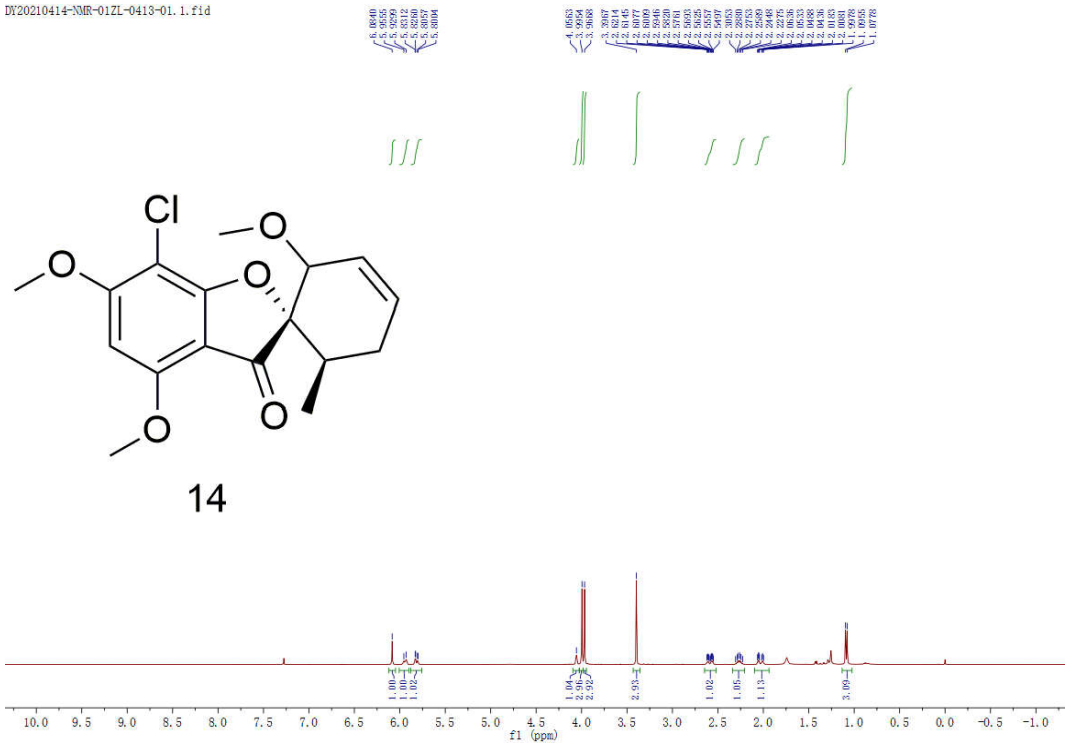
^{13}C NMR spectrum of 12f (100 MHz, $CDCl_3$)



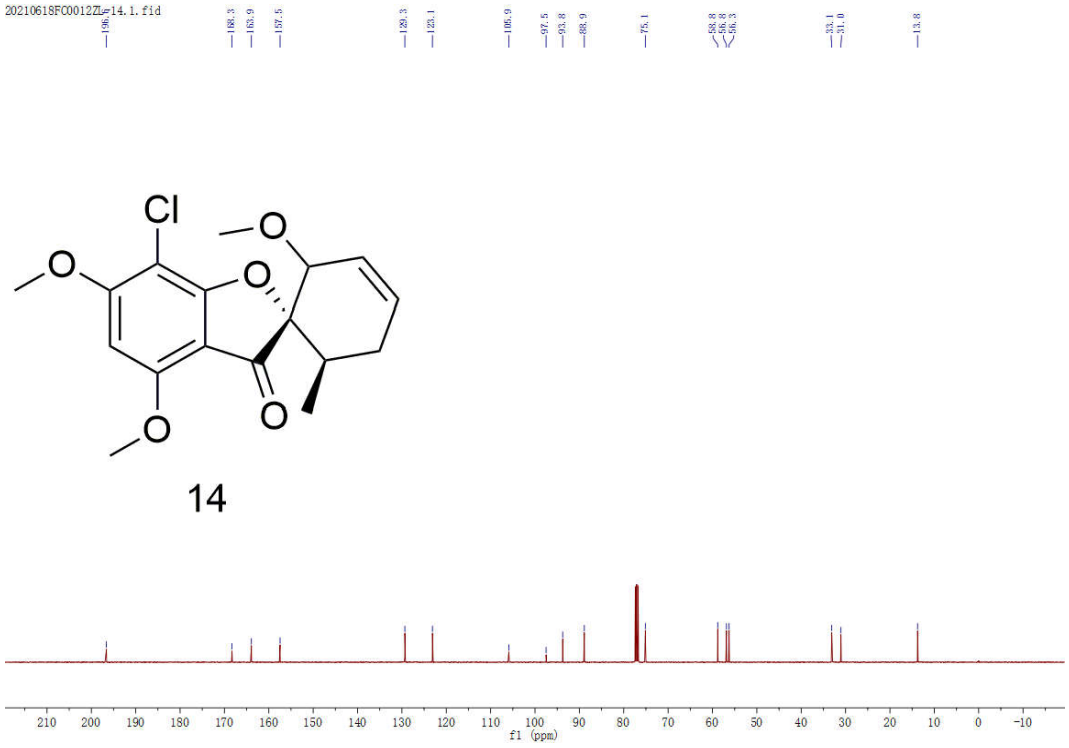
^{1}H NMR spectrum of 13 (400 MHz, $CDCl_3$)



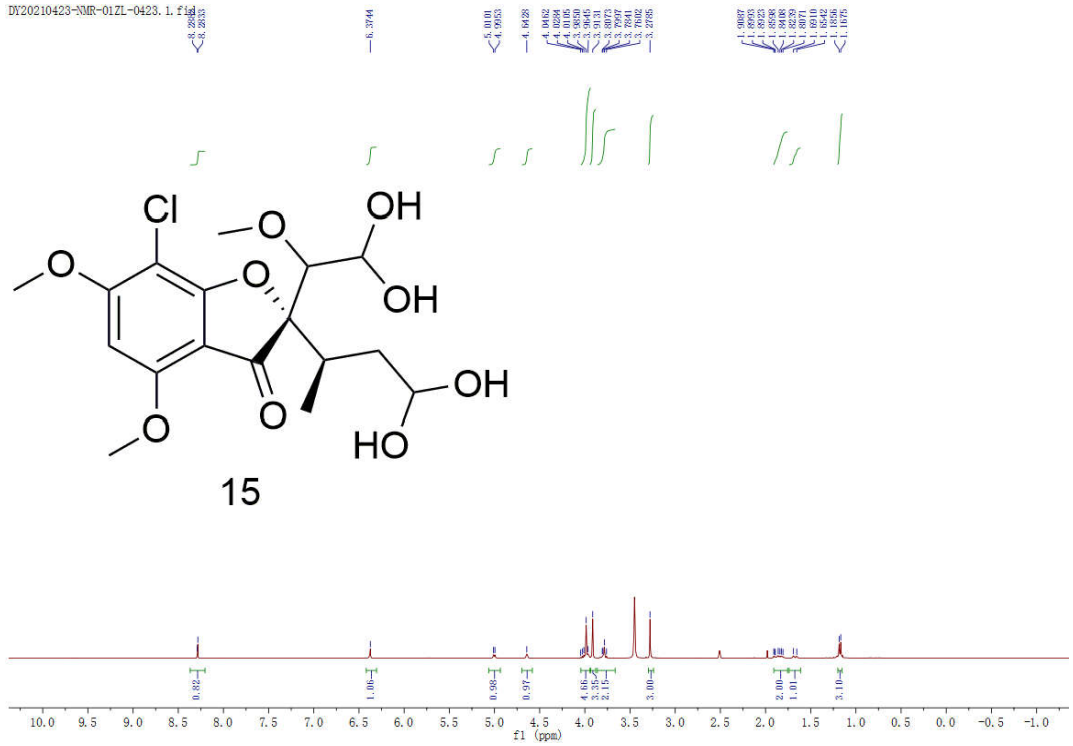
^{13}C NMR spectrum of 13 (100 MHz, $CDCl_3$)



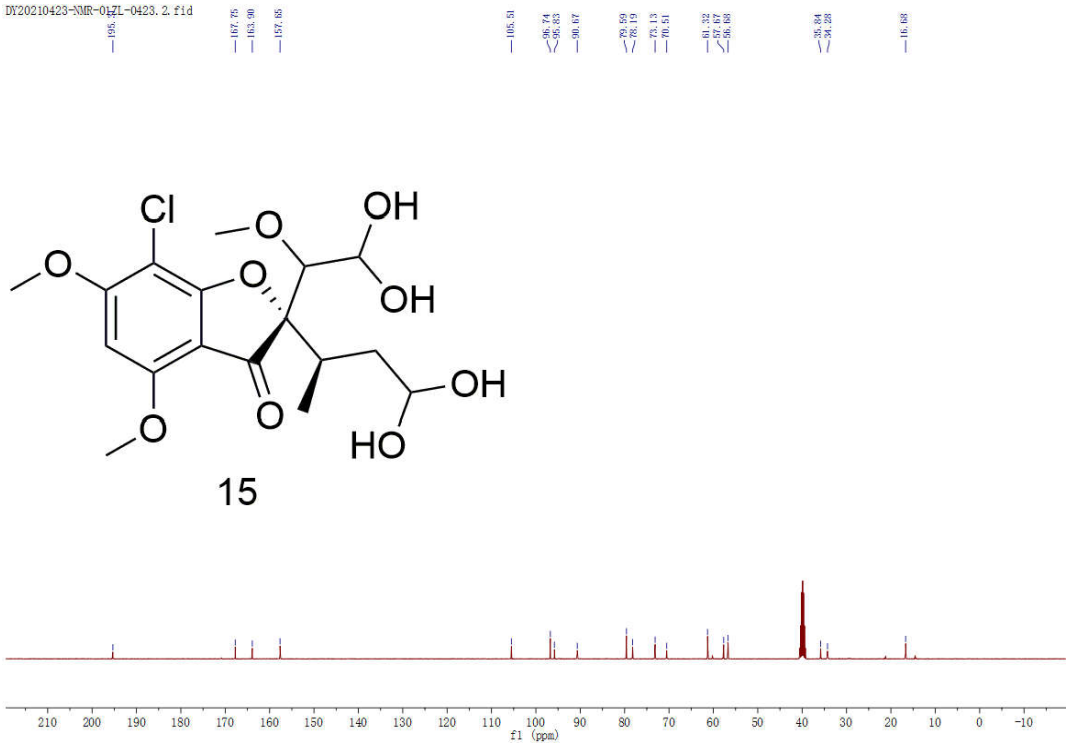
^{1}H NMR spectrum of 14 (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of 14 (100 MHz, $CDCl_3$)



^{1}H NMR spectrum of 15 (400 MHz, DMSO-d_6)



^{13}C NMR spectrum of 15 (100 MHz, DMSO-d_6)

Table 1 Crystal data and structure refinement for 8b.

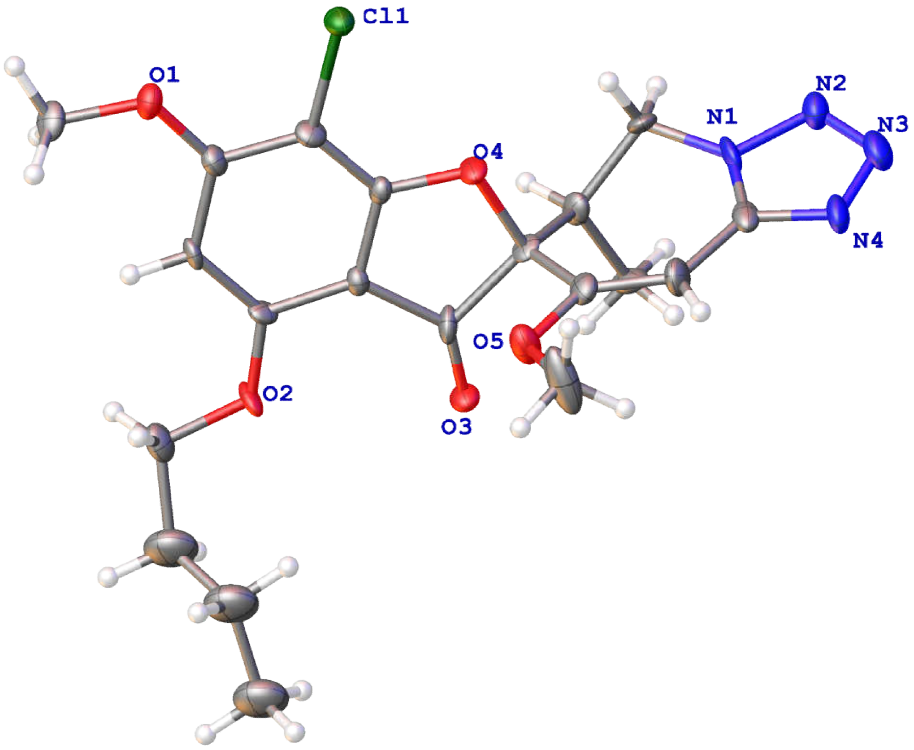
Identification code	8b
Empirical formula	$C_{20}H_{23}ClN_4O_5$
Formula weight	434.87
Temperature/K	169.99(10)
Crystal system	triclinic
Space group	P1
a/Å	10.9389(16)
b/Å	12.8371(12)
c/Å	16.8588(12)
α/°	67.975(8)
β/°	82.641(10)
γ/°	76.510(11)
Volume/Å^3	2131.9(4)
Z	4
ρ_{calc}g/cm^3	1.355
μ/mm^{-1}	0.218
F(000)	912.0
Crystal size/mm^3	0.13 × 0.1 × 0.08
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.538 to 49.994
Index ranges	$-13 \le h \le 12$, $-15 \le k \le 15$, $-20 \le l \le 19$
Reflections collected	11290
Independent reflections	11290 [R_{int} = 0.0876, R_{sigma} = 0.1352]
Data/restraints/parameters	11290/61/1098
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.1109, wR_2 = 0.2956
Final R indexes [all data]	R_1 = 0.1326, wR_2 = 0.3245
Largest diff. peak/hole / e Å^{-3}	1.29/-0.68
Flack parameter	0.05(10)

Crystal structure determination of compound 8b

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as CCDC no. CCDC-2107148. Copies of the data can be obtained, free of charge, on application to CHGC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

Crystal Data for $C_{20}H_{23}ClN_4O_5$ (M =434.87 g/mol): triclinic, space group P1 (no. 1), a = 10.9389(16) Å, b = 12.8371(12) Å, c = 16.8588(12) Å, α = 67.975(8)°, β =

82.641(10)°, γ = 76.510(11)°, V = 2131.9(4) Å^3, Z = 4, T = 169.99(10) K, μ(Mo Kα) = 0.218 mm^{-1}, *Dcalc* = 1.355 g/cm^3, 11290 reflections measured (4.538° ≤ 2Θ ≤ 49.994°), 11290 unique (R_{int} = 0.0876, R_{sigma} = 0.1352) which were used in all calculations. The final R_1 was 0.1109 (I > 2σ(I)) and wR_2 was 0.3245 (all data).



References

(1) Yu, J. X.; Ma, H. C.; Yao, H. L.; Cheng, H.; Tong, R. B., Diastereoselective and regiodivergent oxa-[3+2] cycloaddition of Achmatowicz products and cyclic 1,3-dicarbonyl compounds. *Org Chem Front* **2016,** *3*, 714-719.

(2) Lu, Y. P.; Wang, L.; Wang, X. Y.; Yuan, H. L.; Zhao, Y., Divergent de novo synthesis of 2,4,5-trideoxyhexopyranosides derivatives of podophyllotoxin as anticancer agents. *Future Med Chem* **2019,** *11*, 3015-3027.

(3) Song, W. Z.; Zhao, Y.; Lynch, J. C.; Kim, H.; Tang, W. P., Divergent de novo synthesis of all eight stereoisomers of 2,3,6-trideoxyhexopyranosides and their oligomers. *Chem Commun* **2015,** *51*, 17475-17478.

(4) Kasare, S.; Bankar, S. K.; Ramasastry, S. S. V., Expeditious Metal-Free Access to Functionalized Polycyclic Acetals under Mild Aqueous Conditions. *Org Lett* **2014,** *16*, 4284-4287.

(5) Wang, H. Y.; Yang, K.; Yin, D.; Liu, C.; Glazier, D. A.; Tang, W. P., Chiral Catalyst-Directed Dynamic Kinetic Diastereoselective Acylation of Lactols for De Novo Synthesis of Carbohydrate. *Org Lett* **2015,** *17*, 5272-5275.