Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Facile Access to Evodiakine Enabled by Aerobic Copper-Catalyzed Oxidative Rearrangement

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[+] These authors contributed equally to this work.

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1. General Information

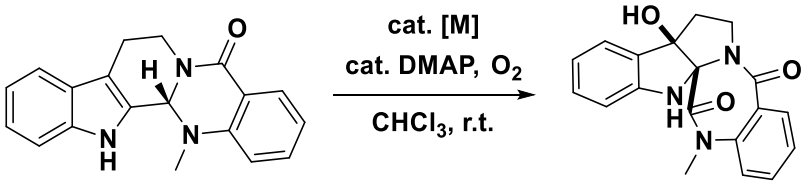
All reactions were performed under a designated atmosphere in flame-dried round bottom flasks, magnetically stirred. Preparative column chromatography was performed using silica gel 60, particle size 0.063–0.200 mm (70–230 mesh, flash). Analytical TLC was carried out employing silica gel 60 F254 plates (Merck, Darmstadt). Visualization of the developed chromatograms was performed with detection by UV (254 nm and 365 nm). Preparative thin layer chromatography (PTLC) separations were carried out on 0.20 mm Yantai Jiangyou silica gel plates (HSGF254). Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectra and Carbon Nuclear Magnetic resonance (^{13}C NMR) Spectra were recorded on a Bruker-400 (^{1}H, 400 MHz; ^{13}C, 101 MHz) spectrometer. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($CDCl_3$: δ 7.26; DMSO-d_6: 2.50). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ77.16; DMSO-d_6: 39.52). Signals are listed in ppm, and multiplicity identified as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts were expressed in ppm, and *J* values were given in Hz. High resolution mass Spectrum (HRMS) were obtained from Thermo Fisher Scientific Exactive Plus mass spectrometer. Melting point was determined using the X-4A melting point apparatus (Shanghai Yidian Co., Ltd.) and uncorrected. Concentration under reduced pressure was performed by rotary evaporation at 25–35 °C at appropriate pressure. Purified compounds were further dried under high vacuo (0.01–0.10 Torr). Yields refer to purified and spectroscopically pure compounds, unless otherwise noted. All commercially available starting materials and solvents were reagent grade, and used without further purification.

Abbreviations used: TLC = thin layer chromatography; CuBr·DMS = copper (I) bromide-dimethyl sulfide; DMAP = 4-dimethylaminopyridine; CuPc = copper phthalocyanine; $Cu(OAc)_2$ = copper (II) acetate; $Cu(acac)_2$ = copper(II) acetylacetonate; $Co(acac)_2$ = cobalt(II) acetylacetonate; $Fe(acac)_3$ = Iron(III) acetylacetonate; AcOH = acetic acid; THF = tetrahydrofuran; EtOAc = ethyl acetate; MeOH = methyl alcohol; EtOH = ethanol; DMSO = dimethyl sulfoxide; DMF = *N*,*N*-dimethylformamide; DMA = *N*,*N*-dimethylaniline; DCE = 1,2-dichloroethane; Et_3N = triethylamine; DBU = 1,8-Diazabicyclo[5,4,0]undec-7-ene; TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine; DIPEA = *N*,*N*-diisopropylethylamine; DABCO = triethylenediamine; TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl; PE = petroleum ether; TFAA = trifluoroacetic anhydride.

2. Optimization Studies

Investigation of Catalyst

Table S1: Optimization of the reaction conditions.[a]



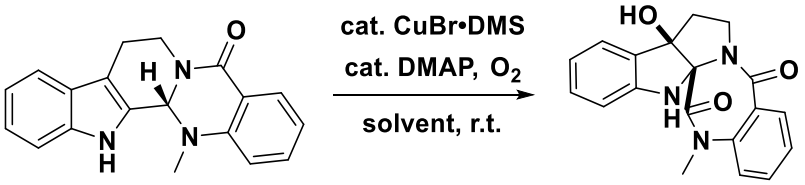
Evodiamine **Evodiakine**

Entry	Cat.	Yield (%)[b]	Entry	Cat.	Yield (%)[b]
1	CuBr·DMS	<49(46)	12	Cu(OH)Cl ·TEMDA	trace
2	CuCN	<30	13	$Cu(CH_3CN)_4 \cdot PF_6$	trace
3	CuCl	<30	14	CuPc	0
4	CuI	<30	15	CuOAc	trace
5	$CuBr_2$	<20	16	$Ce(SO_4)_2$	0
6	$CuSO_4$	trace	17	$Cu(acac)_2$	0
7	$CuCl_2$	trace	18	$Co(OAc)_2$	0
8	$Cu(OAc)_2$	trace	19	$Co(acac)_2$	0
9	$Cu(NO_3)_2$	0	20	$Fe(acac)_3$	0
10	$Cu(CF_3SO_3)_2$	trace	21	FeC_2O_4	0
11	CuO	trace	22	$Ce(NH_4)_2(NO_3)_6$	0

[a] Unless otherwise noted, all reactions were carried out with evodiamine (0.05 mmol) in 1.0 mL of $CHCl_3$, different catalyst (10 mol%) and DMAP (20 mol%) were added. The reaction mixture was stirred for 2 h at r.t. under oxygen atmosphere. [b] Conversion to the desired product by analysis of ^1H NMR spectra of unpurified reaction mixtures with dibromomethane as the internal standard. Yield of isolated production is within parentheses. CuPc = copper phthalocyanine; $Cu(OAc)_2$ = copper (II) acetate; $Cu(acac)_2$ = copper(II) acetylacetonate; $Co(acac)_2$ = cobalt(II) acetylacetonate; $Fe(acac)_3$ = Iron(III) acetylacetonate.

Investigation of Solvent

Table S2: Optimization of the reaction conditions.[a]



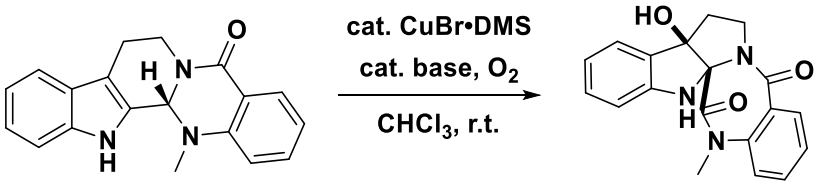
Evodiamine **Evodiakine**

Entry	Solvent	Yield (%)[b]	Entry	Solvent	Yield (%)[b]
1	CH_3CN	<30	10	DMSO	trace
2	AcOH	trace	11	DMF	<10
3	CH_2Cl_2	<30	12	CCl_4	trace
4	$CHCl_3$	<49(46%)	13	Toluene	trace
5	THF	trace	14	DMA	<10
6	EtOAc	trace	15	2-MeTHF	trace
7	Acetone	<10	16	*tert*-Butanol	trace
8	MeOH	trace	17	1,4-Dioxane	trace
9	EtOH	trace	18	DCE	<20

[a] Unless otherwise noted, all reactions were carried out with evodiamine (0.05 mmol) in 1.0 mL of different solvent, CuBr·DMS (10 mol%) and DMAP (20 mol%) were added. The reaction mixture was stirred for 2h under r.t. at oxygen atmosphere. [b] Conversion to the desired product by analysis of ^{1}H NMR spectra of unpurified reaction mixtures with dibromomethane as the internal standard. Yield of isolated production is within parentheses. AcOH = acetic acid; THF = tetrahydrofuran; EtOAc = ethyl acetate; MeOH = methyl alcohol; EtOH = ethanol; DMSO = dimethyl sulfoxide; DMF = *N*,*N*-dimethylformamide; DMA = *N*,*N*-dimethylaniline; DCE = 1,2-dichloroethane.

Investigation of Base

Table S3. Optimization of the reaction conditions.[a]

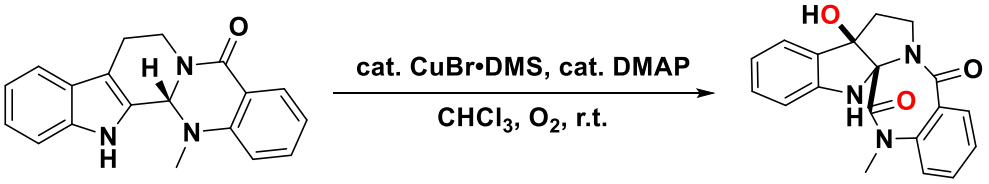


Evodiamine **Evodiakine**

Entry	Base	Yield (%)[b]	Entry	Base	Yield (%)[b]
1	DMAP	<50(46%)	10	2,6-Lutidine	0
2	Et_3N	0	11	6-Chloropicolinic acid	0
3	DBU	<30	12	Picolinic acid	0
4	Pyridine	<20	13	Pyridinium tribromide	0
5	TMEDA	<10	14	2-Methylpyridine	0
6	DIPEA	0	15	4-Acetylpyridine	0
7	DABCO	0	16	2,6-Pyridinedicarboxylic acid	0
8	4-Methylpyridine	<20	17	4-Aminopyridine	0
9	K_2CO_3	0	18	6-Chloronicotinic acid	0

[a] Unless otherwise noted, all reactions were carried out with evodiamine (0.05 mmol) in 1.0 mL of $CHCl_3$, CuBr·DMS (10 mol%) and different base (20 mol%) were added. The reaction mixture was stirred for 2 h at r.t. under oxygen atmosphere. [b] Conversion to the desired product by analysis of ^1H NMR spectra of unpurified reaction mixtures with dibromomethane as the internal standard. Yield of isolated production is within parentheses. Et_3N = triethylamine; DBU = 1,8-Diazabicyclo[5,4,0]undec-7-ene; TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine; DIPEA = *N*,*N*-diisopropylethylamine; DABCO = triethylenediamine.

3. Mechanism Studies



Evodiamine **Evodiakine**

Table S4: Investigation of the free radical inhibitor.[a]

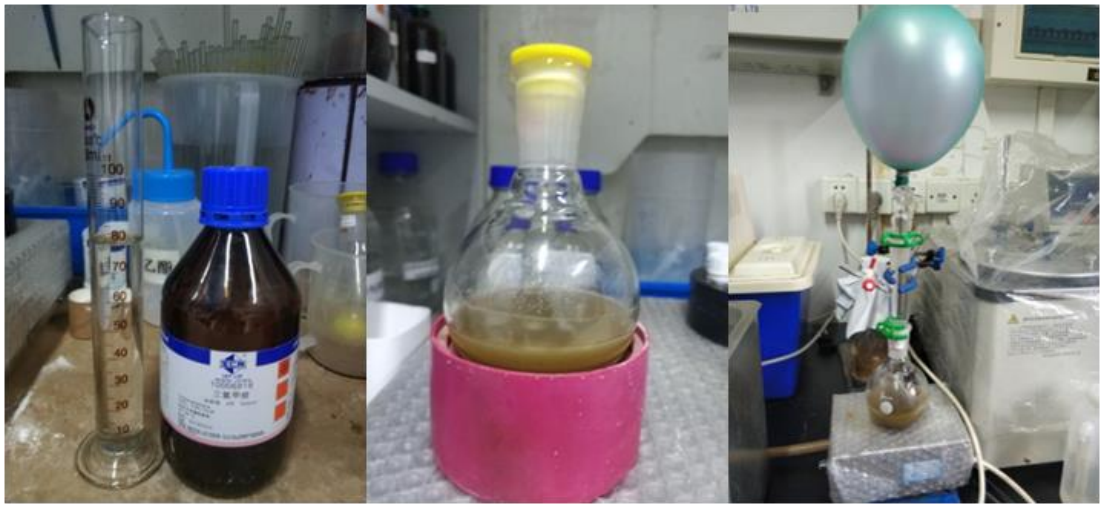
Entry	Inhibitor	Yield (%)[b]
1	Vc	0
2	TEMPO	<15

[a] Unless otherwise noted, all reactions were carried out with evodiamine (0.1 mmol) in 2.0 mL of $CHCl_3$, CuBr·DMS (10 mol%) and DMAP (20 mol%) and different free radical inhibitor (0.2 mmol) were added. The reaction mixture was stirred for 1 h at r.t. under oxygen atmosphere. [b] Conversion to the desired product by analysis of ^1H NMR spectra of unpurified reaction mixtures. Vc = ascorbic acid; TEMPO = 2,2,6,6-tetramethylpiperidinyloxy.

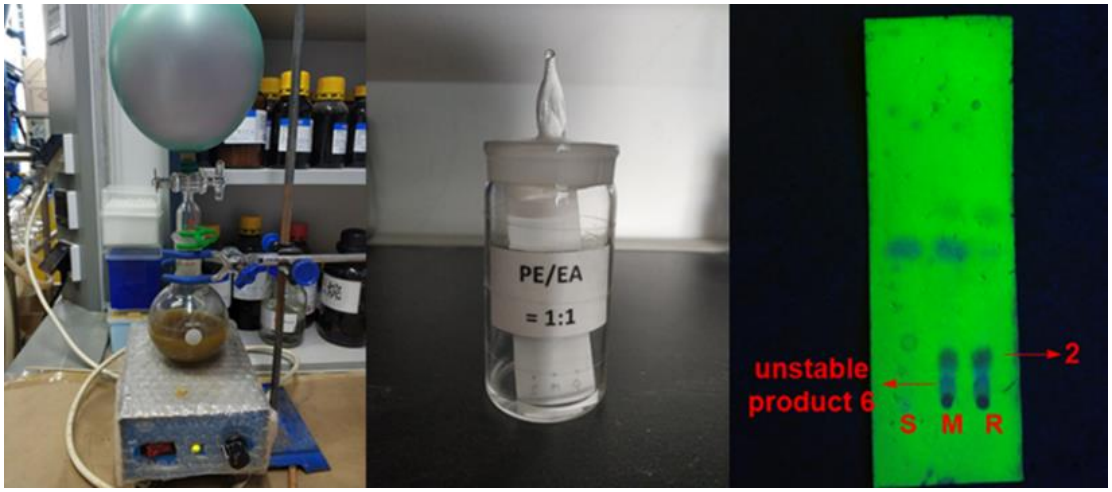
Note: Adding a radical inhibitor has a significant influence on the reaction, suggesting that this reaction might undergo radical process.

4. Graphical Procedure for Gram Preparation of evodiakine

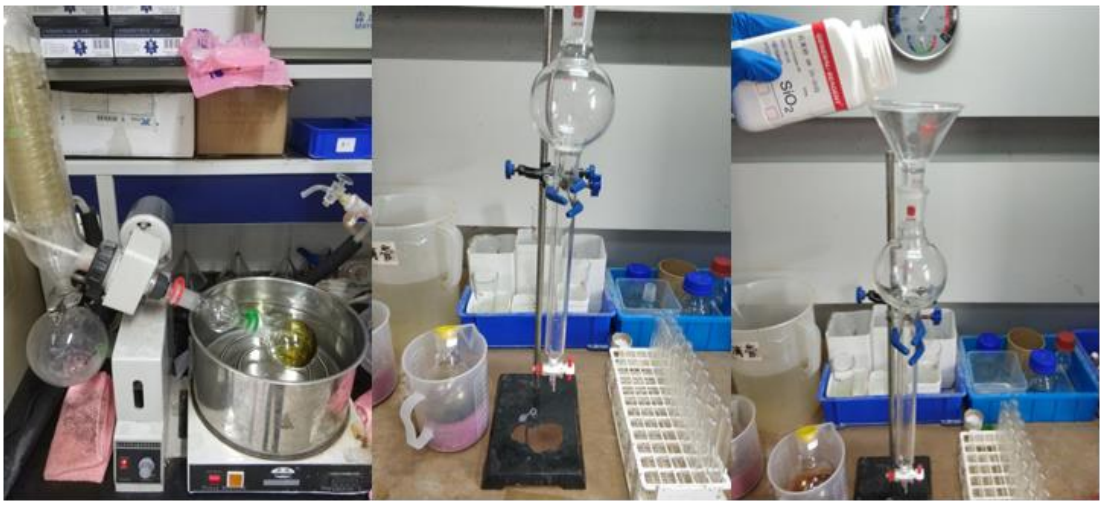
(Left) Evodiamine (1.996 g, 6.6 mmol); (Center) CuBr·DMS (0.135 g, 0.66 mmol); (Right) DMAP (0.1615g, 1.32 mmol).



(Left) $CHCl_3$ (150 mL); (Center) Dissolved in solvent; (Right) Oxygen replace air.

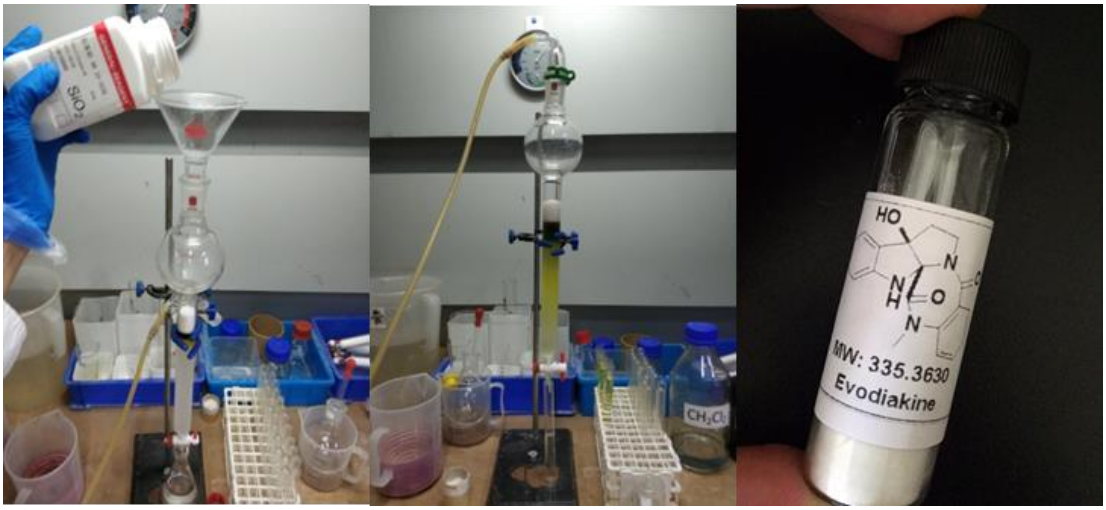


(Left) Stirred at r.t. for 2 h; (Center) Reaction progress was monitored by TLC; (Right) TLC under UV (PE/EtOAc = 1 : 1).



(Left) Concentration of the solvent; (Center) Addition of cotton to the bottom of the glass column; (Right) addition of a small amount of quartz sand.

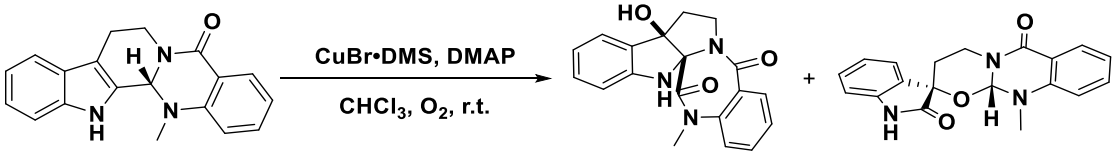
(Left) Addition of silica gel; (Center) CH_2Cl_2 was pouring into the column; (Right) Addition of the crude mixture.



(Left) Addition of quartz sand; (Center) Purified by chromatography on silica gel (CH_2Cl_2/MeOH = 100:1); (Right) Evodiakine obtained after column chromatography.

5. General Procedures

Evodiakine (2)



Evodiamine (1) Evodiakine (2) Unstable product (7)

***8a-Hydroxy-15-methyl-7,8,8a,13-tetrahydro-5H-benzo[5',6'][1,4]diazepino[1',2':1,2]pyrrolo [2,3-b]indole-5,14(15H)-dione* (2)**

To a solution of evodiamine (**1**) (607 mg, 2.0 mmol) in $CHCl_3$ (50 mL) was added CuBr·DMS (41 mg, 0.2 mmol) and DMAP (49 mg, 0.4 mmol). The mixture was stirred under r.t. for 2 h at oxygen atmosphere. The solution was concentrated under reduced pressure to afford crude product. Then the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 100:1) to give the desired product (evodiakine) (310 mg, 46 %) as a white solid and the crude, unstable rearrangement product (226 mg, 34 %) as a pale yellow solid.

Gram-scale reaction: To a solution of evodiamine (**1**) (2.00 g, 6.6 mmol) in $CHCl_3$ (150 mL) was added CuBr·DMS (136 mg, 0.66 mmol) and DMAP (161 mg, 1.32 mmol). The mixture was stirred under r.t. for 2 h at oxygen atmosphere. The solution was concentrated under reduced pressure to afford crude product. Then the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 100:1) to give the desired product (evodiakine) (1.0 g, 45 %) as a white solid and unstable rearrangement product (0.82 g, 37%)

Physical State: white solid.

Melting Point: 215.9 - 216.7 ^oC.

TLC: R_f = 0.30 (PE/EtOAc = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.50 (s, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.96 (s, 1H), 3.48 (s, 3H), 3.36 – 3.29 (m, 1H), 2.75 – 2.68 (m, 1H), 2.58 – 2.49 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.82, 164.45, 146.91, 138.29, 133.10, 131.11, 130.24, 128.97, 128.66, 126.82, 123.39, 122.49, 121.29, 111.00, 91.13, 79.06, 46.27, 36.40, 33.98.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (t, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.46 (s, 1H), 5.93 (s, 1H), 3.91 – 3.81 (m, 1H), 3.42 (s, 3H), 3.15 – 3.06 (m, 1H), 2.68 – 2.59 (m, 1H), 2.38 – 2.29 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 169.04, 164.65, 148.54, 138.69, 133.19, 130.55, 130.49, 130.16, 128.37, 126.52, 123.67, 123.54, 120.26, 112.22, 91.59, 79.41, 46.20, 36.77, 33.61.

HRMS (ESI): calcd for $C_{19}H_{17}N_3O_3$ $[M-H]^-$ *m/z* 334.1197, found 334.1151.

Unstable product (7)

***11'-Methyl-3',4',11',11a'-tetrahydro-6'H-spiro[indoline-3,2'-[1,3]oxazino[2,3-b]quinazoline]-2,6'-dione* (6)**

Physical State: pale yellow solid.

Melting Point: 258.1 - 259.0 °C.

TLC: R_f = 0.31 (PE/EtOAc = 1:2)

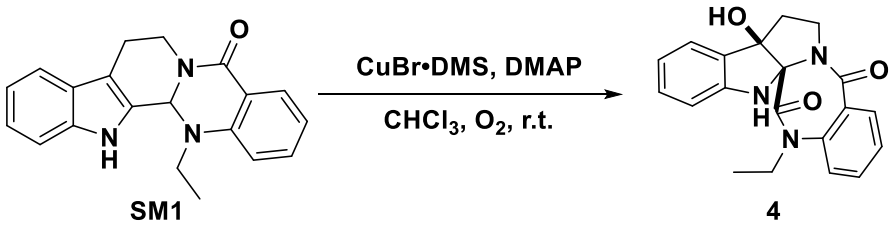
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.89 – 4.82 (m, 1H), 3.92 (s, 1H), 3.04 (s, 3H), 2.37 – 2.29 (m, 1H), 1.75 (d, *J* = 14.2 Hz, 1H), 1.25 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 178.35, 161.77, 144.92, 141.54, 134.81, 130.50, 129.72, 128.13, 124.58, 122.72, 118.78, 113.82, 112.59, 110.35, 91.45, 77.47, 38.64, 35.33, 30.28.

HRMS (ESI): calcd for $C_{19}H_{17}N_3O_3$ $[M + H]^+$ *m/z* 336.1343, found 336.1359.

Note: *The whole purification process should be done as soon as possible. This undesired product is unstable in all kind of solvents, but it can be kept in the refrigerator in solid form for more than a month.*

Compound 4



***(8a)-15-Ethyl-8a-hydroxy-7,8,8a,13-tetrahydro-5H-benzo[5',6'][1,4]diazepino[1',2':1,2]pyrrolo[2,3-b]indole-5,14(15H)-dione* (4)**

To a solution of *14-ethyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one* (95 mg, 0.3 mmol) in $CHCl_3$ (6 mL) was added CuBr·DMS (6.1 mg, 0.03 mmol) and DMAP (7.3 mg, 0.06 mmol). The mixture was stirred under r.t. for 0.5 h at oxygen atmosphere. The solution was concentrated under reduced pressure to afford crude product. Then the residue was purified by silica gel chromatography (PE/EtOAc = 2:1) to give the desired product (36 mg, 34 %) as a pale yellow solid.

Physical State: pale yellow solid.

Melting Point: 106.4 – 107.2 °C.

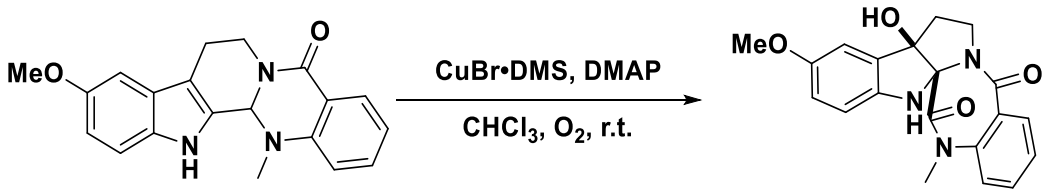
TLC: R_f = 0.32 (PE/EtOAc = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 10.2 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.45 (s, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 4.15 – 4.03 (m, 3H), 3.97 – 3.89 (m, 2H), 3.31 – 3.21 (m, 1H), 2.80 – 2.68 (m, 1H), 2.61 – 2.50 (m, 1H), 1.30 (t, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.89, 164.39, 147.05, 137.41, 133.13, 131.26, 130.28, 129.51, 128.78, 127.02, 123.48, 122.62, 121.26, 110.96, 90.93, 79.09, 46.10, 44.80, 33.96, 13.31.

HRMS (ESI): calcd for $C_{20}H_{19}N_3O_3$ $[M + H]^+$ *m/z* 350.1499, found 350.1500.

Compound 5



SM2 5

(8a)-8a-Hydroxy-10-methoxy-15-methyl-7,8,8a,13-tetrahydro-5H-benzo[5',6'][1,4]diazepino[1',2':1,2]pyrrolo[2,3-b]indole-5,14(15H)-dione **(5)**

To a solution of *10-methoxy-14-methyl-8,13,13b,14-tetrahydroindolo[2',3':3,4] pyrido[2,1-b]quinazolin-5(7H)-one* (333 mg, 1.0 mmol) in $CHCl_3$ (15 mL) was added CuBr·DMS (20.6 mg, 0.1 mmol) and DMAP (24.5 mg, 0.2 mmol). The mixture was stirred under r.t. for 1 h at oxygen atmosphere. The solution was concentrated under reduced pressure to afford crude product. Then the residue was purified by chromatography on silica gel (PE/EtOAc = 2:1) to give the desired product (133 mg, 37 %) as a yellow solid.

Physical State: yellow solid.

Melting Point: 194.5 – 195.6 °C.

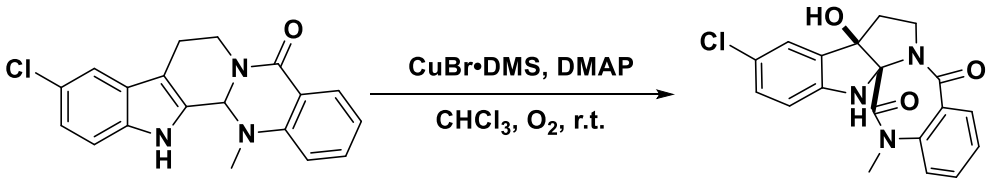
TLC: R_f = 0.45 (PE/EtOAc = 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 6.95 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.53 (s, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.76 (s, 3H), 3.48 (s, 3H), 3.38 – 3.30 (m, 1H), 2.71 – 2.63 (m, 1H), 2.56 – 2.47 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.97, 164.47, 155.08, 140.49, 138.32, 133.05, 131.07, 130.24, 128.62, 126.77, 122.43, 116.19, 112.04, 109.02, 91.35, 79.74, 55.95, 46.15, 36.41, 34.00.

HRMS (ESI): calcd for $C_{20}H_{19}N_3O_4$ $[M + H]^+$ *m/z* 366.1448, found 366.1449.

Compound 6



SM3 7

(8aR)-10-chloro-8a-hydroxy-15-methyl-7,8,8a,13-tetrahydro-5H-benzo[5',6'][1,4]diazepino[1',2':1,2]pyrrolo[2,3-b]indole-5,14(15H)-dione **(6)**

To a solution of *10-chloro-14-methyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one* (338 mg, 1.0 mmol) in $CHCl_3$ (15 mL) was added CuBr·DMS (20.6 mg, 0.1 mmol) and DMAP (24.5 mg, 0.2 mmol). The mixture was stirred under r.t. for 4 h at oxygen atmosphere. The solution was concentrated under reduced pressure to afford crude product. Then the residue was purified by chromatography on silica gel (PE/EtOAc = 2:1) to give the desired product (192 mg, 52 %) as a pale yellow solid.

Physical State: pale yellow solid.

Melting Point: 228.5 – 229.4 °C.

TLC: R_f = 0.28 (PE/EtOAc = 2:1)

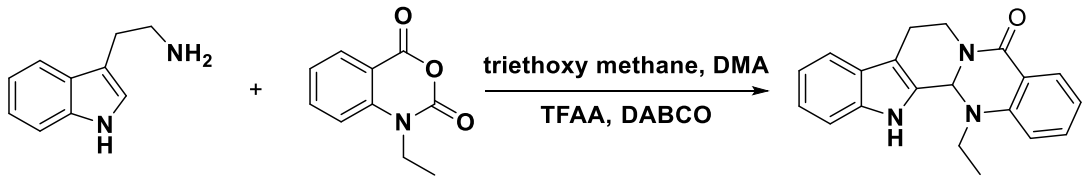
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.39 – 6.34 (m, 1H), 4.13 – 4.06 (m, 1H), 4.00 (s, 1H), 3.51 (s, 3H), 3.43 – 3.37 (m, 1H), 2.70 – 2.63 (m, 1H), 2.59 – 2.51 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.22, 131.21, 130.15, 128.54, 126.96, 126.08, 123.80, 122.46, 112.00, 46.29, 36.46, 34.04.

HRMS (ESI): calcd for $C_{19}H_{16}ClN_3O_3$ $[M + H]^+$ *m/z* 370.0953, found 370.0965.

6. Preparation of Substrates

Compound SM1[1]



tryptamine 1-ethyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione SM1

14-ethyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one **(SM1)**

A mixture of tryptamine (320 mg, 2.0 mmol), *1-ethyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione*[2] (382 mg, 2.0 mmol), TFAA (278 μL, 2.0 mmol) in triethoxymethane (4.0 mL) and DMA (2.0 mL) were added in a pressure vessel, then DABCO (3.0 mmol) was added and stirred at 100 °C for 5 h. Then 100 mL water and 60 mL saturated brine solution were added to the mixture and extracted with EtOAc 3 times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2) to afford the desired product (126 mg, 20 %) as white solid.

Physical State: white solid.

Melting Point: 299 – 300 °C.

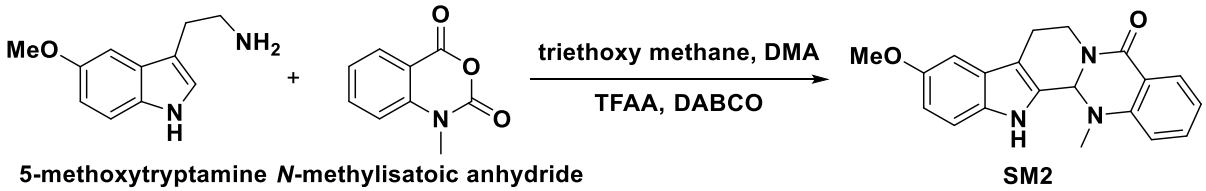
TLC: R_f = 0.44 (PE/EtOAc = 2:1)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.07 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.36 – 7.33 (m, 1H), 7.14 – 7.09 (m, 2H), 7.00 – 6.94 (m, 2H), 6.16 (s, 1H), 4.64 – 4.60 (m, 1H), 3.32 – 3.16 (m, 3H), 2.96 – 2.91 (m, 1H), 2.81 – 2.76 (m, 1H), 1.05 – 1.02 (m, 3H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 165.01, 147.53, 136.78, 133.69, 131.54, 128.48, 126.65, 122.21, 120.74, 120.69, 119.32, 118.93, 118.61, 112.11, 111.52, 69.35, 45.24, 41.57, 19.81, 13.95.

HRMS (ESI): calcd for $C_{20}H_{19}N_3O$ $[M + H]^+$ *m/z* 318.1601, found 318.1599.

Compound SM2[1]



5-methoxytryptamine *N*-methylisatoic anhydride SM2

10-methoxy-14-methyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one **(SM2)**

A mixture of 5-methoxytryptamine (190 mg, 1.0 mmol), *N*-methylisatoic anhydride (177 mg, 1.0 mmol), TFAA (139 μL, 1.0 mmol) in triethoxymethane (2.0 mL) and DMA (1.0 mL) were added in a pressure vessel, then DABCO (1.5 mmol) was added and stirred at 100 °C for 5 h. Then 50 mL water and 30 mL saturated brine solution were added to the mixture and extracted with EtOAc 3 times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 200: 1) to afford the desired product (184 mg, 55 %) as white solid.

Physical State: white solid.

Melting Point: 312 – 314 °C.

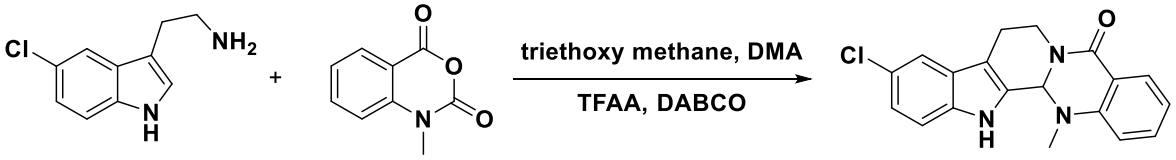
TLC: R_f = 0.58 (PE/EtOAc = 2:1)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.87 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.98 – 6.93 (m, 2H), 6.77 – 6.73 (m, 1H), 6.10 (s, 1H), 4.65 – 4.60 (m, 1H), 3.75 (s, 3H), 3.20 – 3.15 (m, 1H), 2.88 (s, 4H), 2.78 – 2.73 (m, 1H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) ^{13}C NMR (101 MHz, DMSO) δ 164.59, 153.76, 149.11, 133.79, 131.91, 131.62, 128.37, 126.67, 120.55, 119.57, 117.69, 112.71, 112.34, 111.68, 100.45, 70.21, 55.73, 41.31, 36.76, 19.96.

HRMS (ESI): calcd for $C_{20}H_{19}N_3O_2$ $[M + H]^+$ *m/z* 334.1550, found 334.1551.

Compound SM3[1]



5-chlorotryptamine *N*-methylisatoic anhydride SM3

***10-chloro-14-methyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one* (SM3)**

A mixture of 5-chlorotryptamine (194 mg, 1.0 mmol), *N*-methylisatoic anhydride (177 mg, 1.0 mmol), TFAA (139 μL, 1.0 mmol) in triethoxymethane (2.0 mL) and DMA (1.0 mL) were added in a pressure vessel, then DABCO (1.5 mmol) was added and stirred at 100 °C for 5 h. Then 50 mL water and 30 mL saturated brine solution were added to the mixture and extracted with EtOAc 3 times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product (85 mg, 25 %) as white solid.

Physical State: white solid.

Melting Point: 312.2 – 313.3 °C.

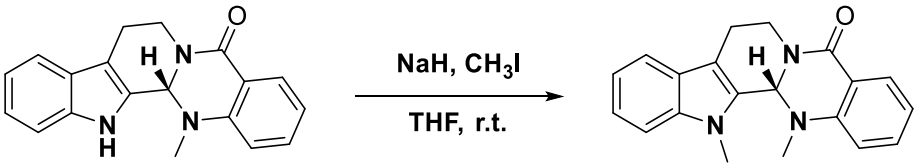
TLC: R_f = 0.32 (PE/EtOAc = 2:1)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.26 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.53 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.15 (s, 1H), 4.65 – 4.59 (m, 1H), 3.23 – 3.17 (m, 1H), 2.92 – 2.86 (m, 4H), 2.81 – 2.76 (m, 1H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 164.65, 149.06, 135.36, 134.00, 133.19, 128.46, 127.59, 124.06, 122.24, 120.75, 119.52, 118.08, 117.83, 113.64, 111.85, 70.23, 41.35, 37.09, 19.78.

HRMS (ESI): calcd for $C_{19}H_{17}ClN_3O$ $[M + H]^+$ *m/z* 338.1055, found 338.1051.

Compound 8



Evodiamine 8

***13,14-dimethyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one* (8)**

To a solution of evodiamine (2.0 g, 6.6 mmol) in THF (20 mL) was added NaH (475.2 mg, 19.8 mmol), CH_3I (822 uL, 13.20 mmol) in the ice bath. Then the ice bath was removed and the mixture was stirred under r.t. for 12 h. The solution was concentrated under reduced pressure, washed with H_2O (50 mL) and EtOAc (100 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 4:1) give the desired product (1.15 g, 55 %) as a yellow solid.

Physical State: yellow solid.

Melting Point: 184.7 - 185.6°C.

TLC: Rf = 0.50 (PE/EtOAc = 4:1).

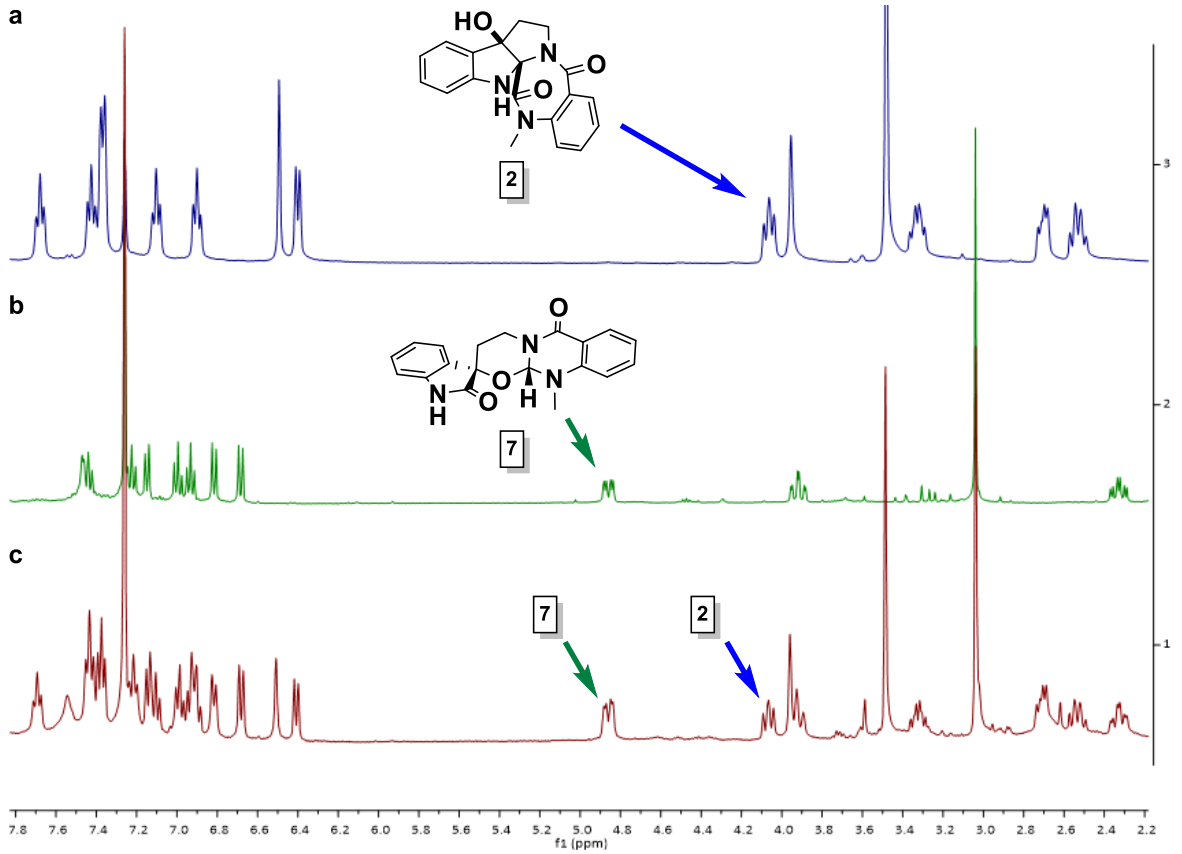
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.15 (m, 3H), 5.98 (s, 1H), 4.96 – 4.90 (m, 1H), 3.87 (s, 3H), 3.21 (t, *J* = 11.2 Hz, 1H), 3.04 (d, *J* = 14.7 Hz, 1H), 2.96 – 2.87 (m, 1H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 164.15, 150.93, 137.87, 133.42, 129.57, 128.54, 125.58, 123.56, 123.37, 122.92, 122.60, 119.61, 119.10, 112.36, 110.24, 67.69, 39.68, 36.39, 30.36, 20.32.

HRMS (ESI): calcd for $C_{20}H_{19}N_3O$ $[M + H]^+$ *m/z* 318.1599, found 318.1601.

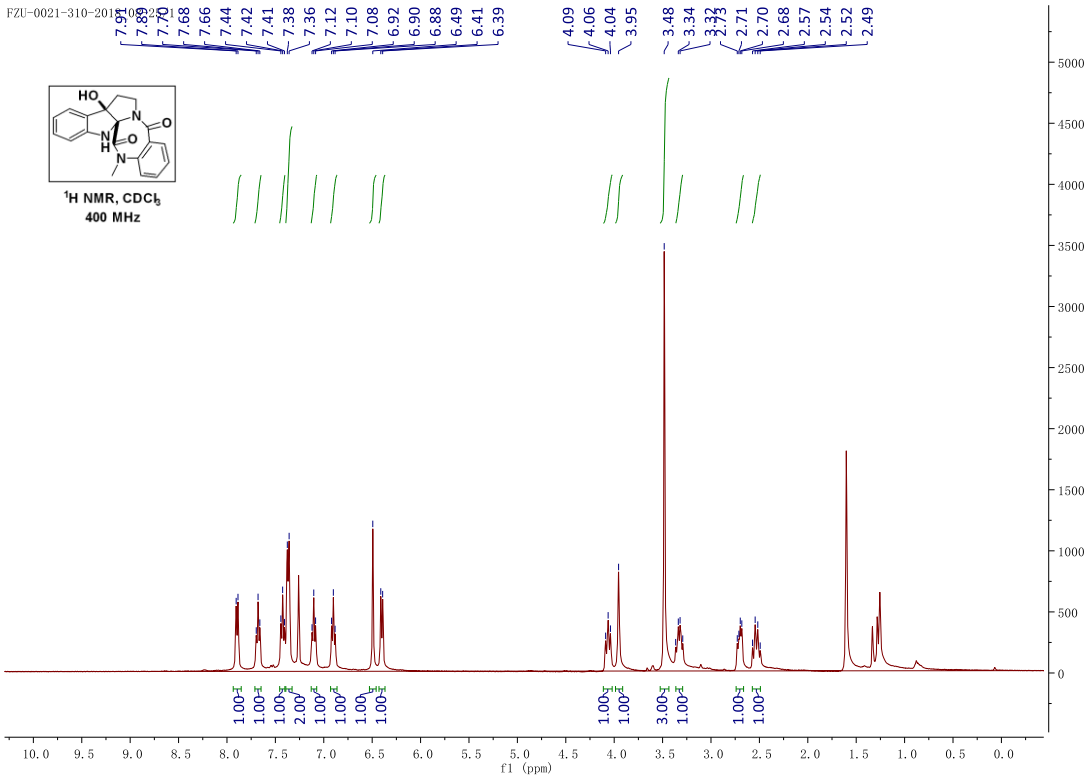
7. NMR Spectrum

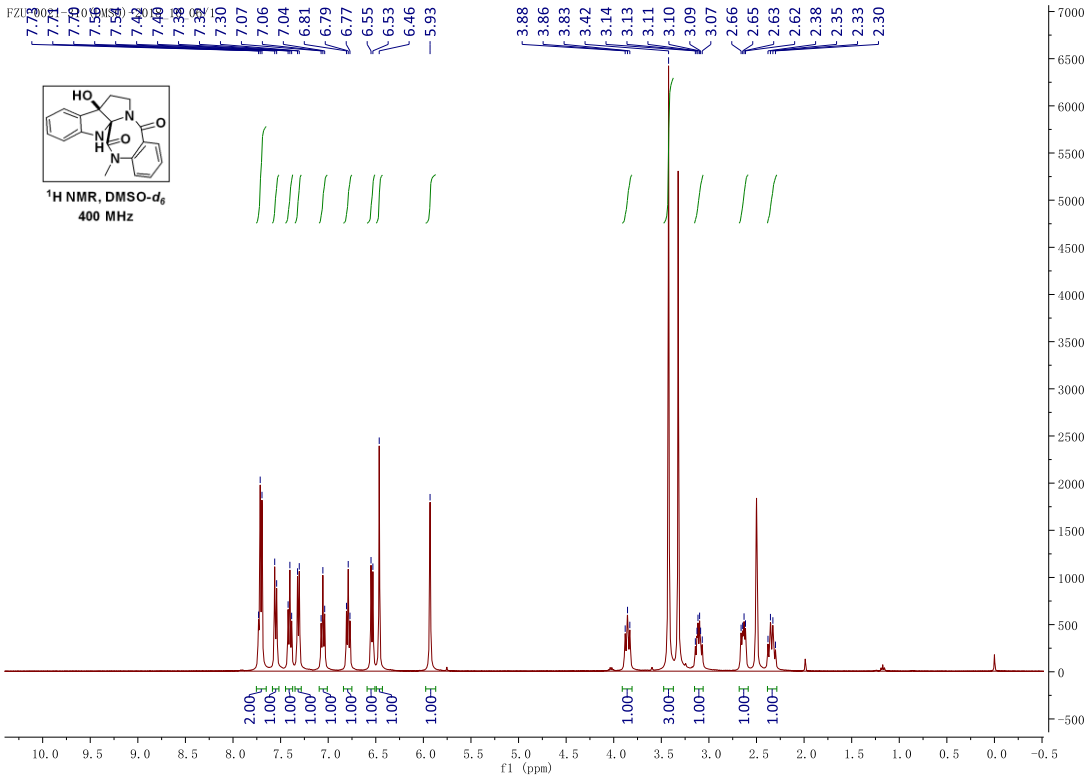
The ^{1}H NMR profiles of evodiakine (2), unstable product (7) and the crude product



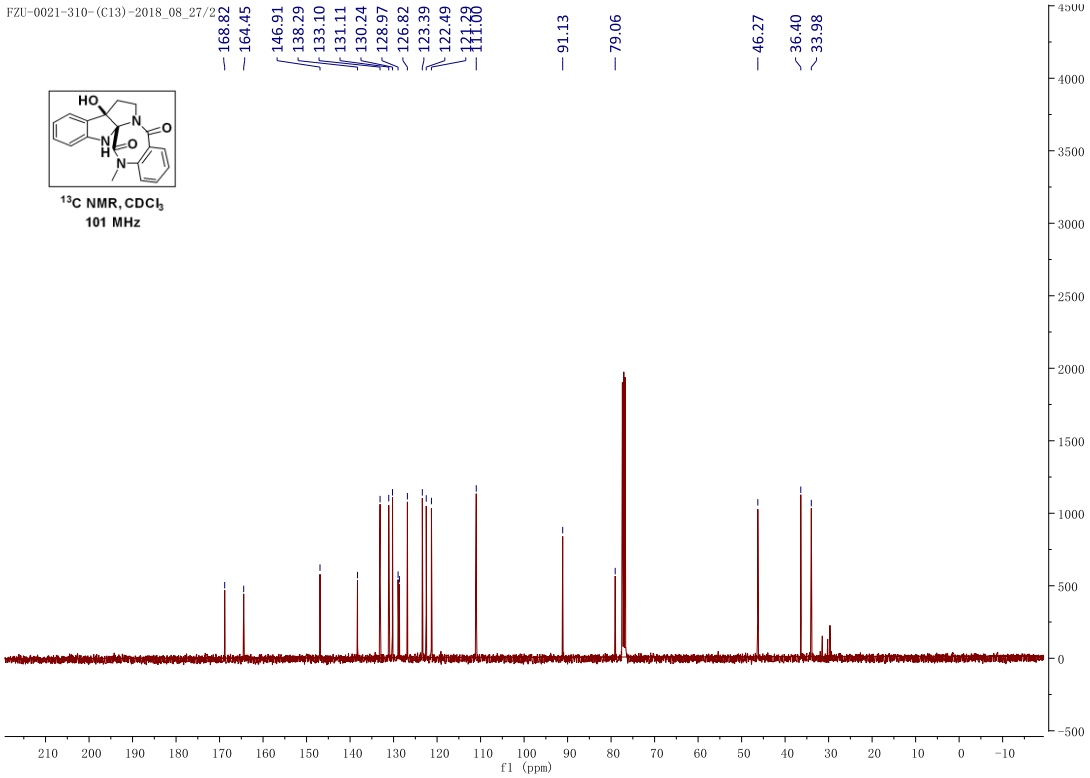
a. ^{1}H NMR spectrum of pure evodiakine (**2**); b. ^{1}H NMR spectrum of pure unstable product (**7**); c. ^{1}H NMR spectrum of the crude products.

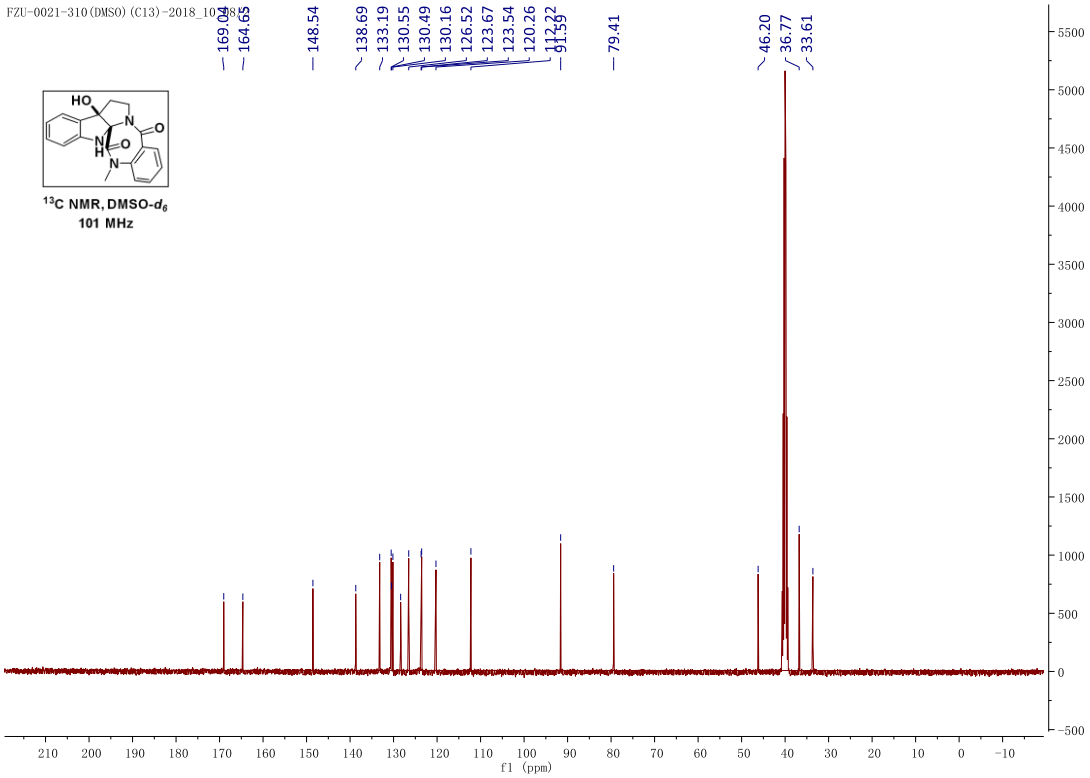
^{1}H NMR Spectrum of Evodiakine (2)



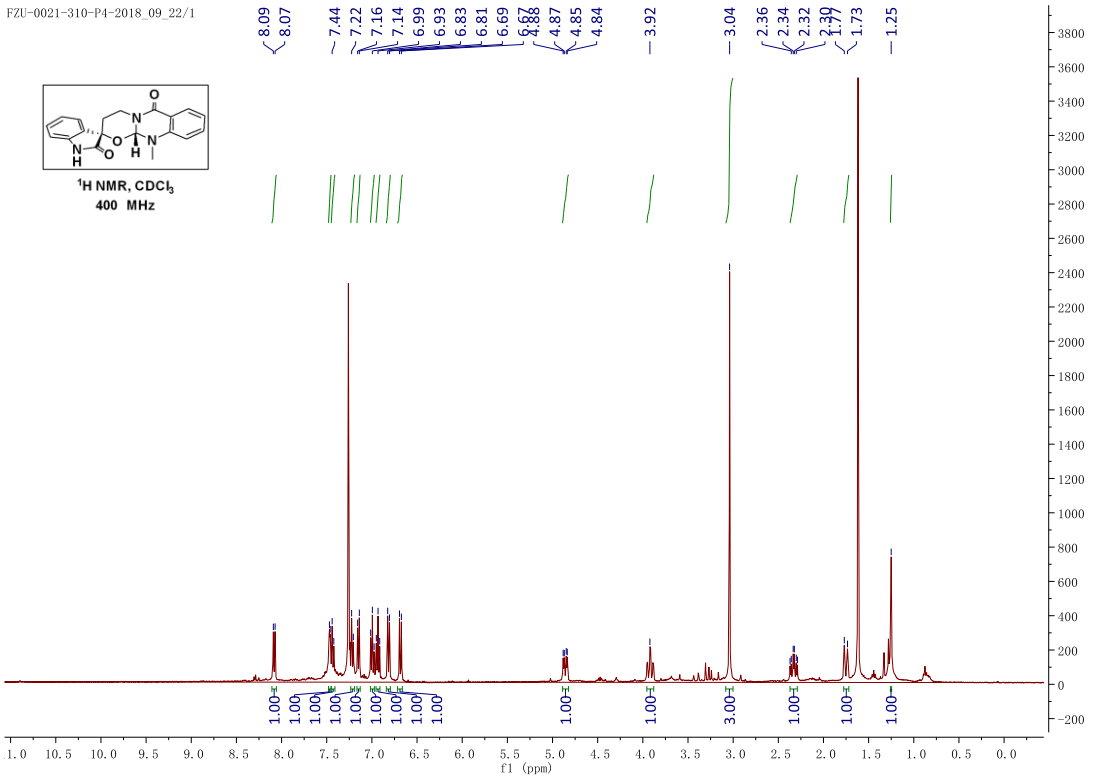


^{13}C NMR Spectrum of Evodiakine (2)

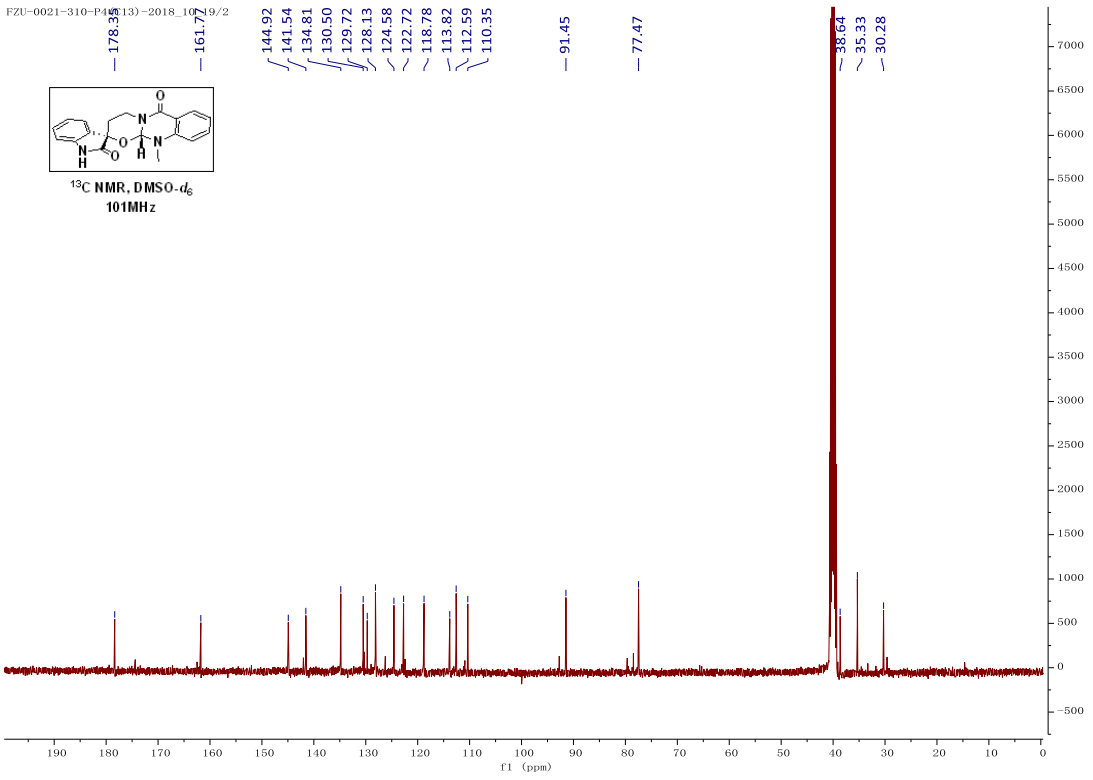




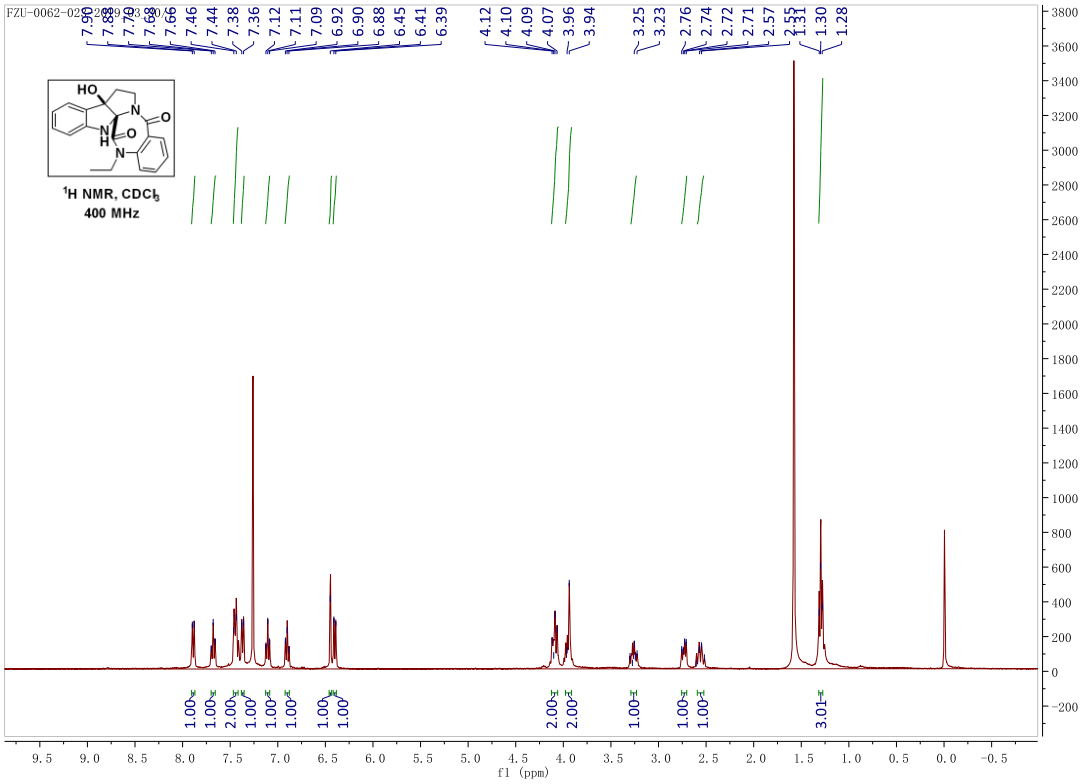
^{1}H NMR Spectrum of the unstable product (7)



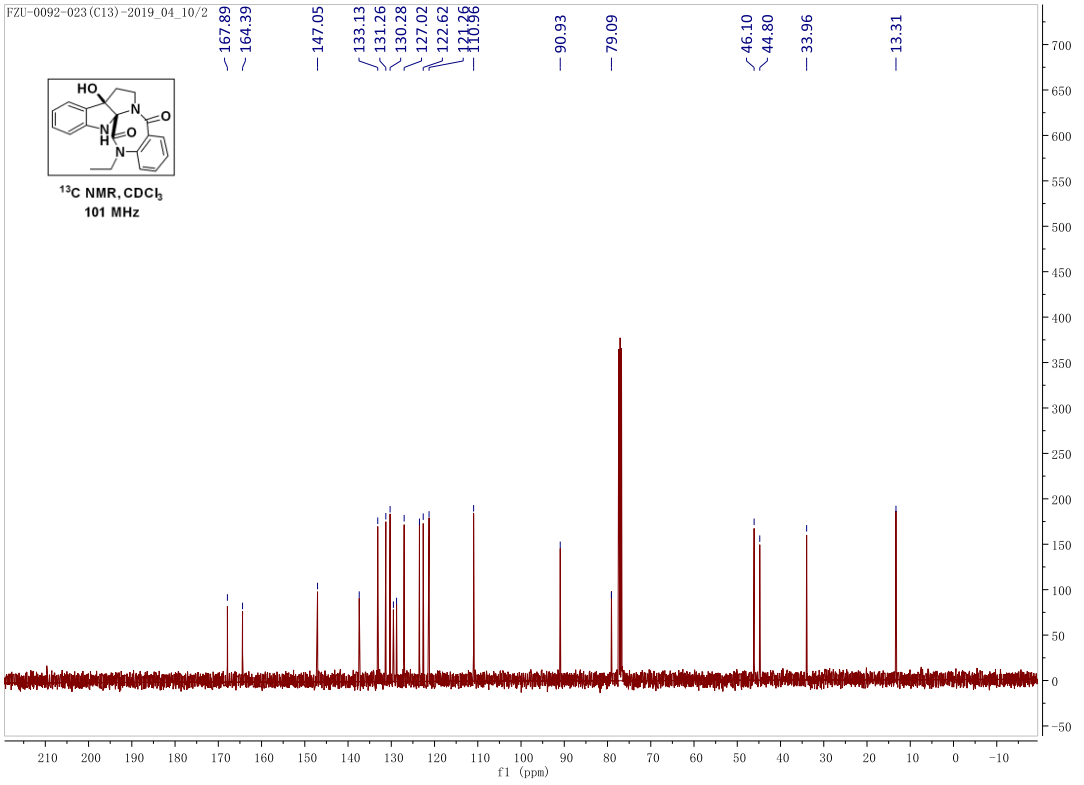
^{13}C NMR Spectrum of the unstable product (7)



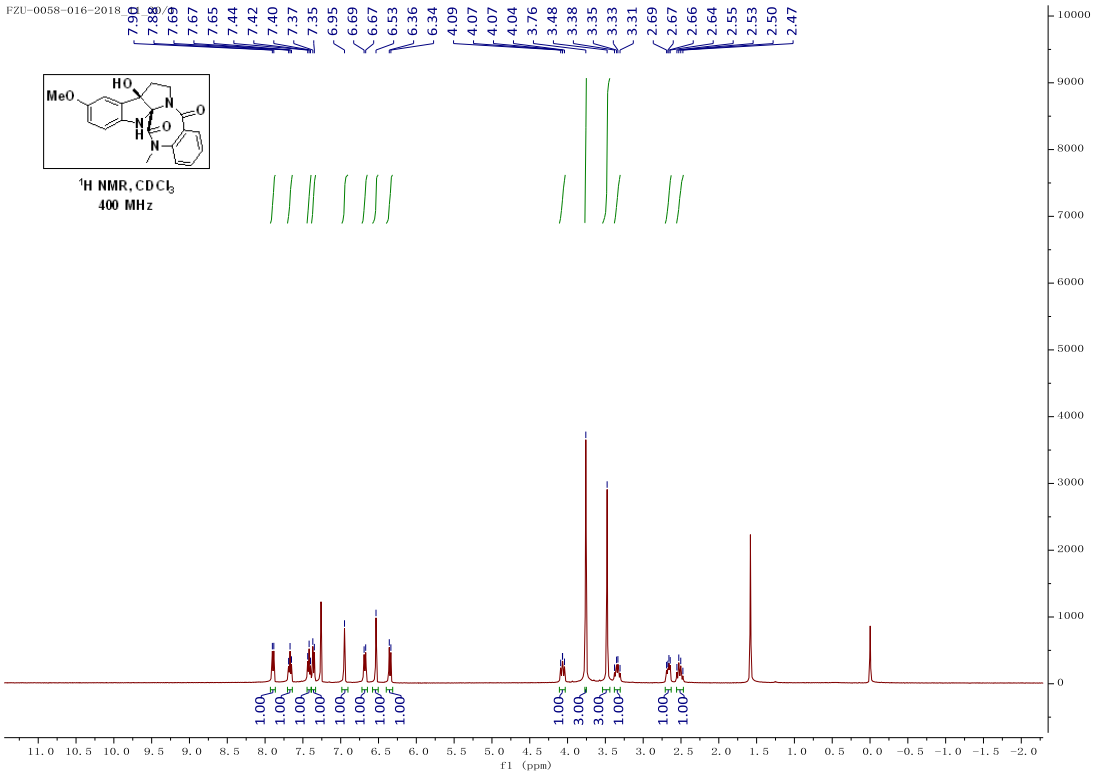
^{1}H NMR Spectrum of compound 4



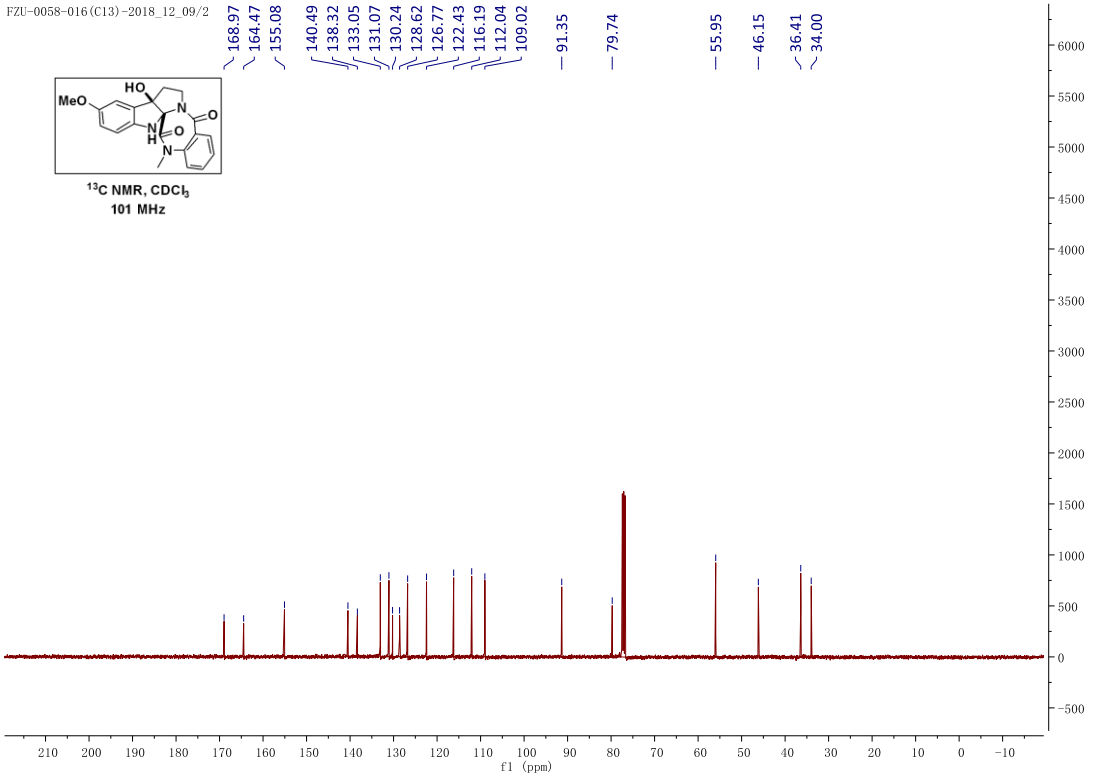
^{13}C NMR Spectrum of compound 4



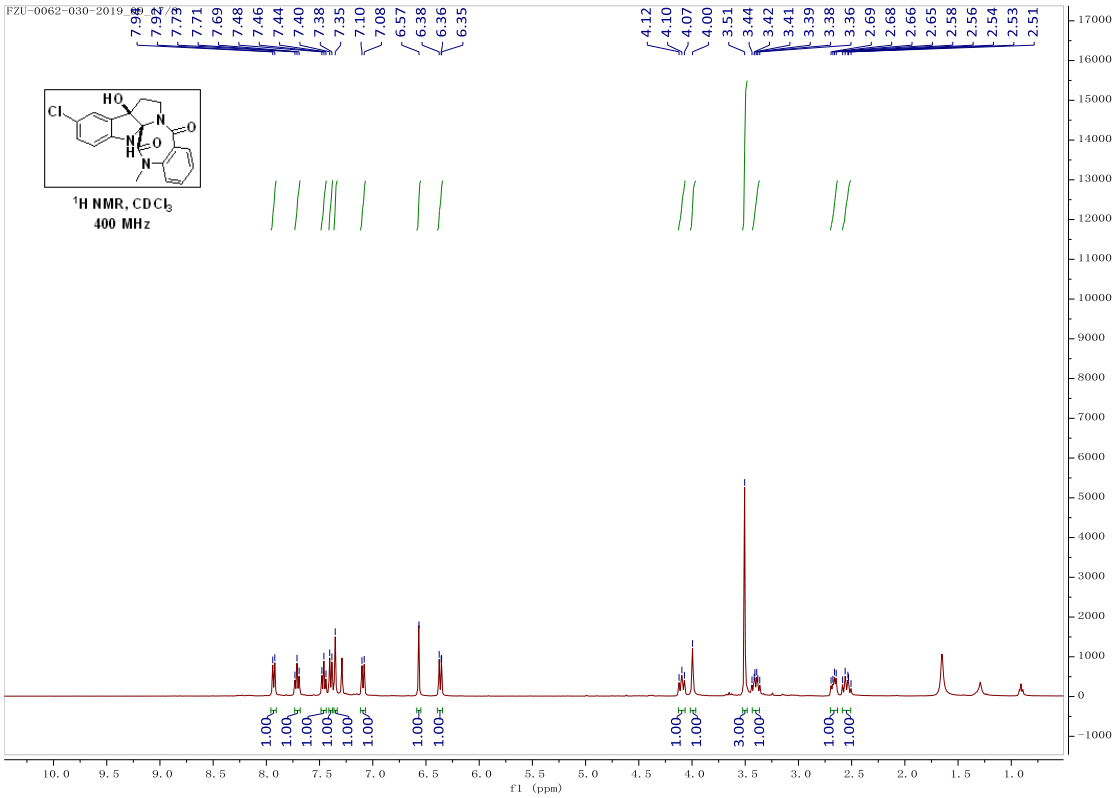
^{1}H NMR Spectrum of compound 5



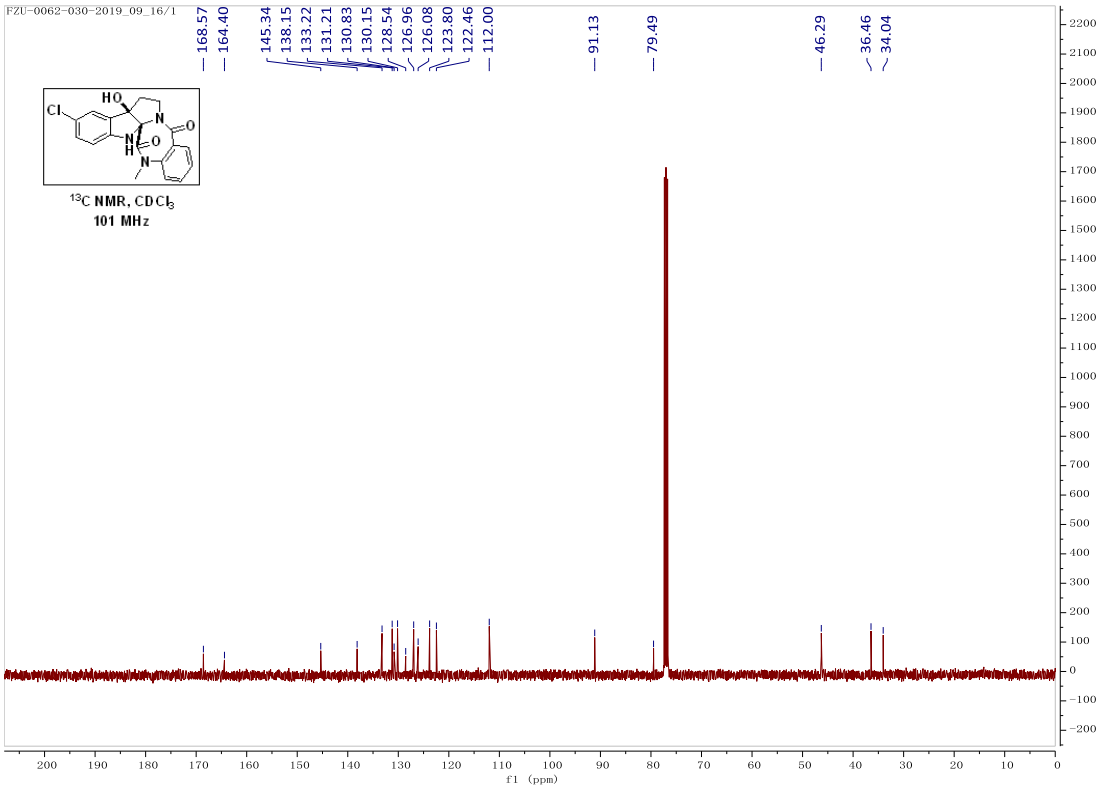
^{13}C NMR Spectrum of compound 5



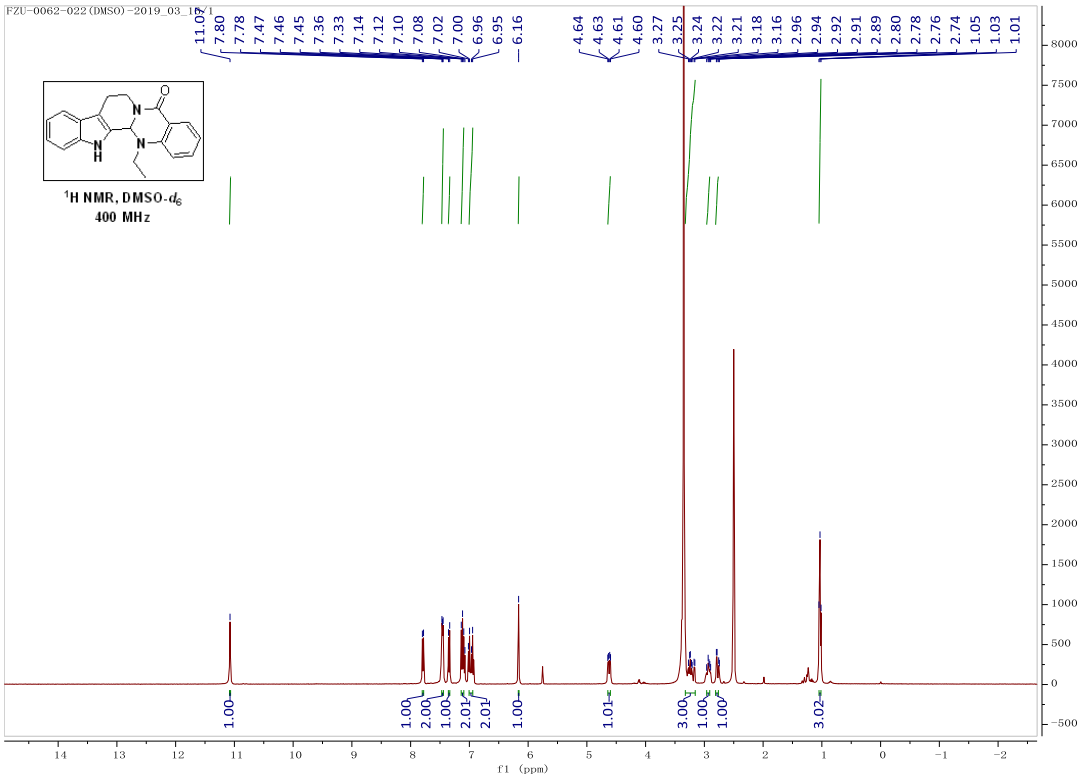
^{1}H NMR Spectrum of compound 7



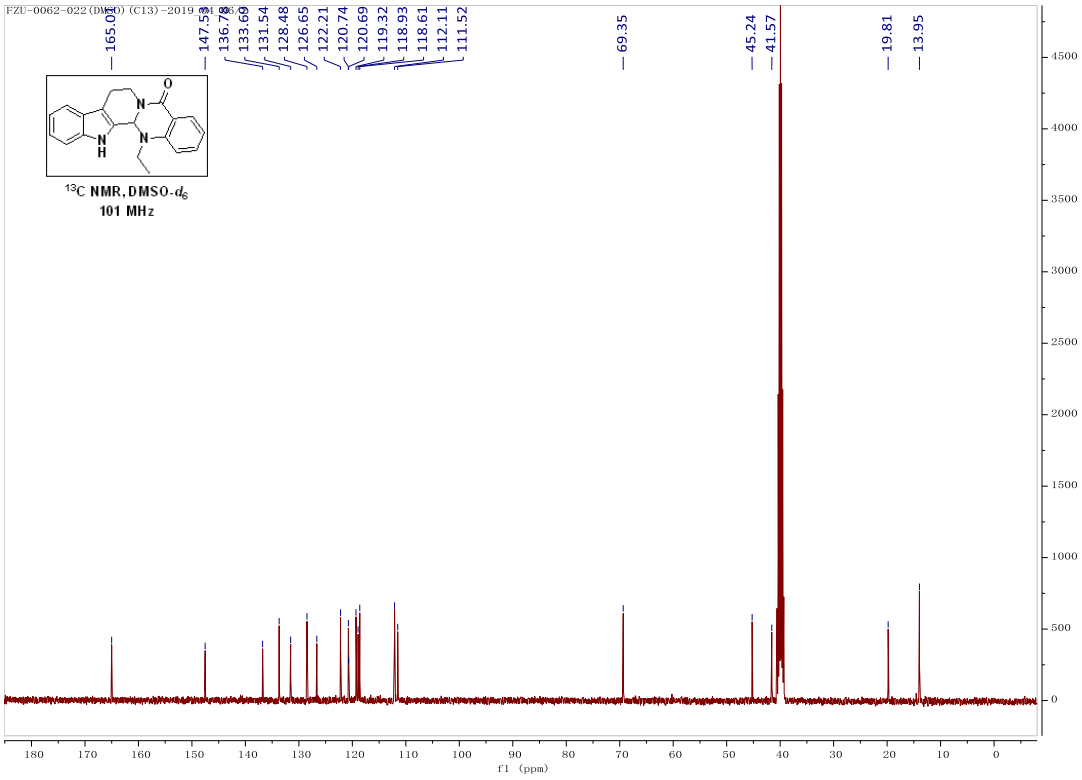
^{13}C NMR Spectrum of compound 7



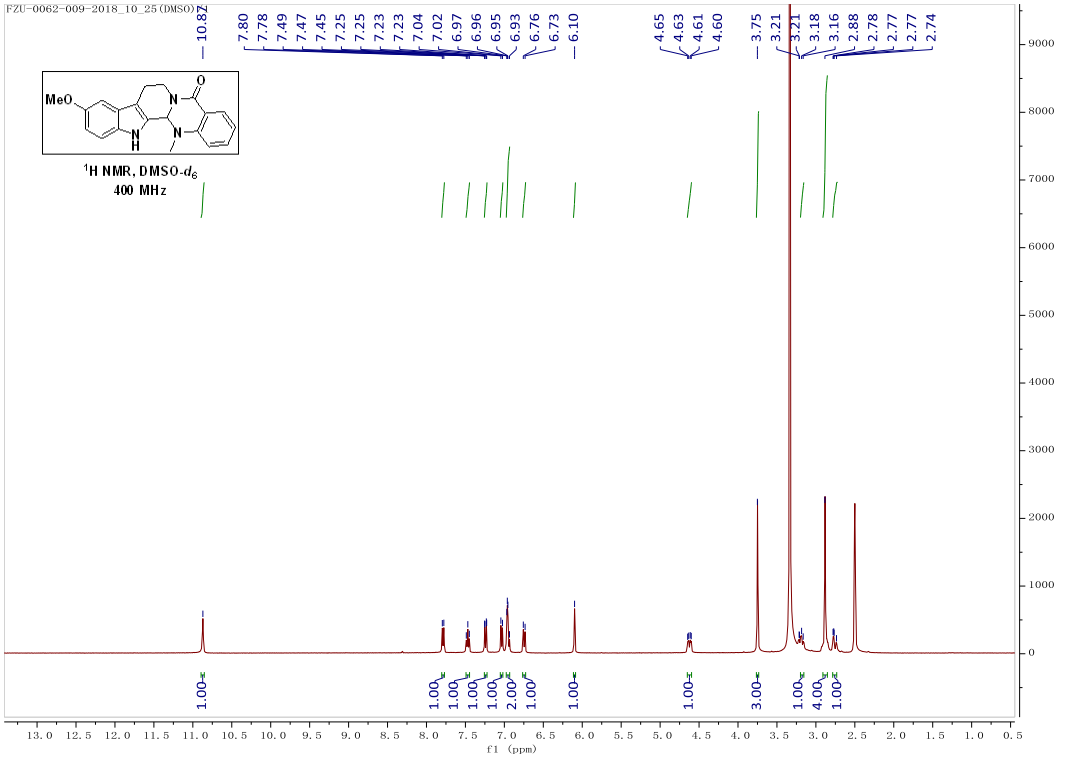
^{1}H NMR Spectrum of SM1



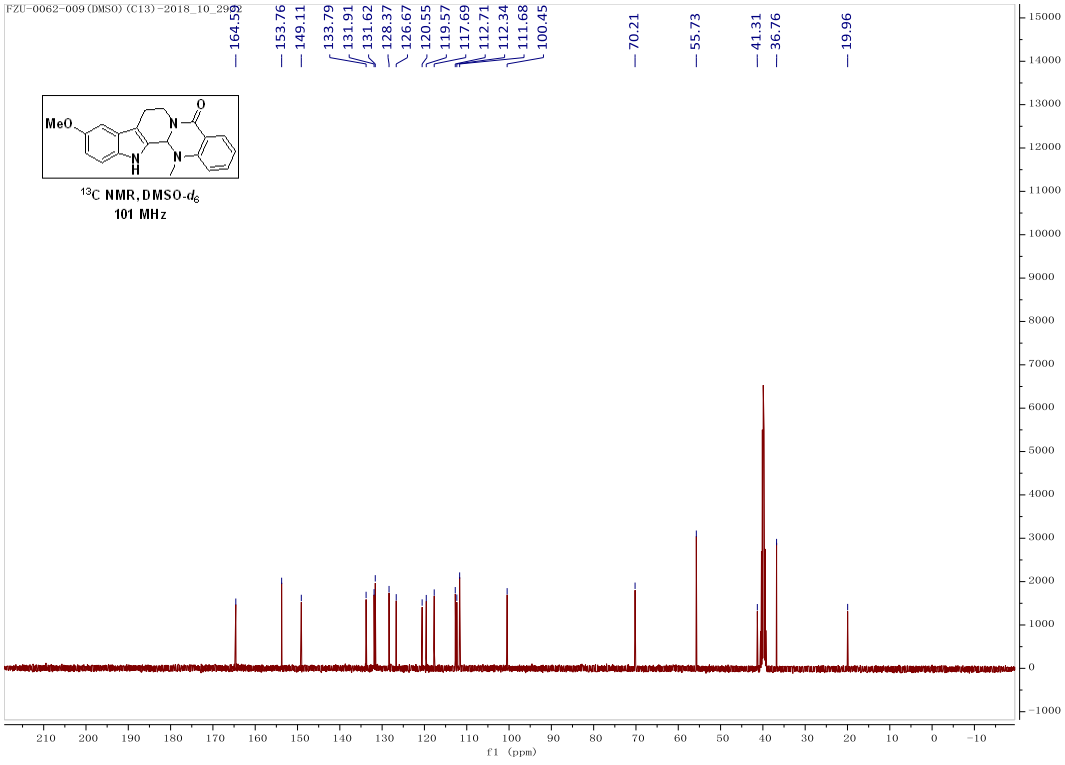
^{13}C NMR Spectrum of SM1



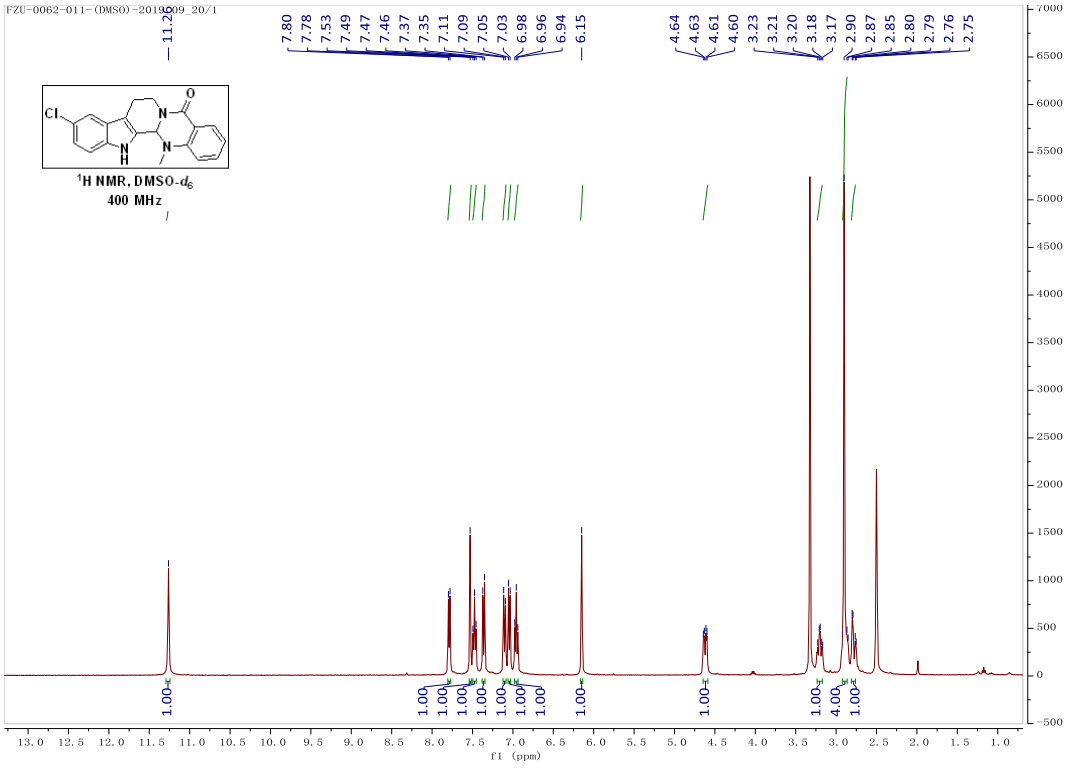
^{1}H NMR Spectrum of SM2



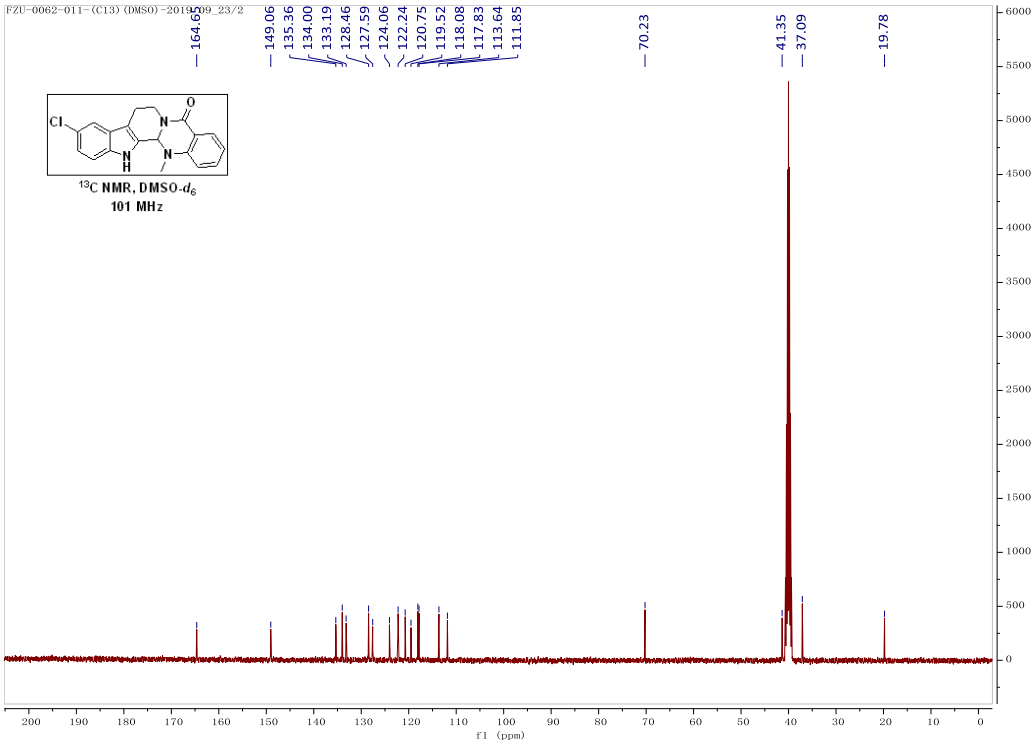
^{13}C NMR Spectrum of SM2



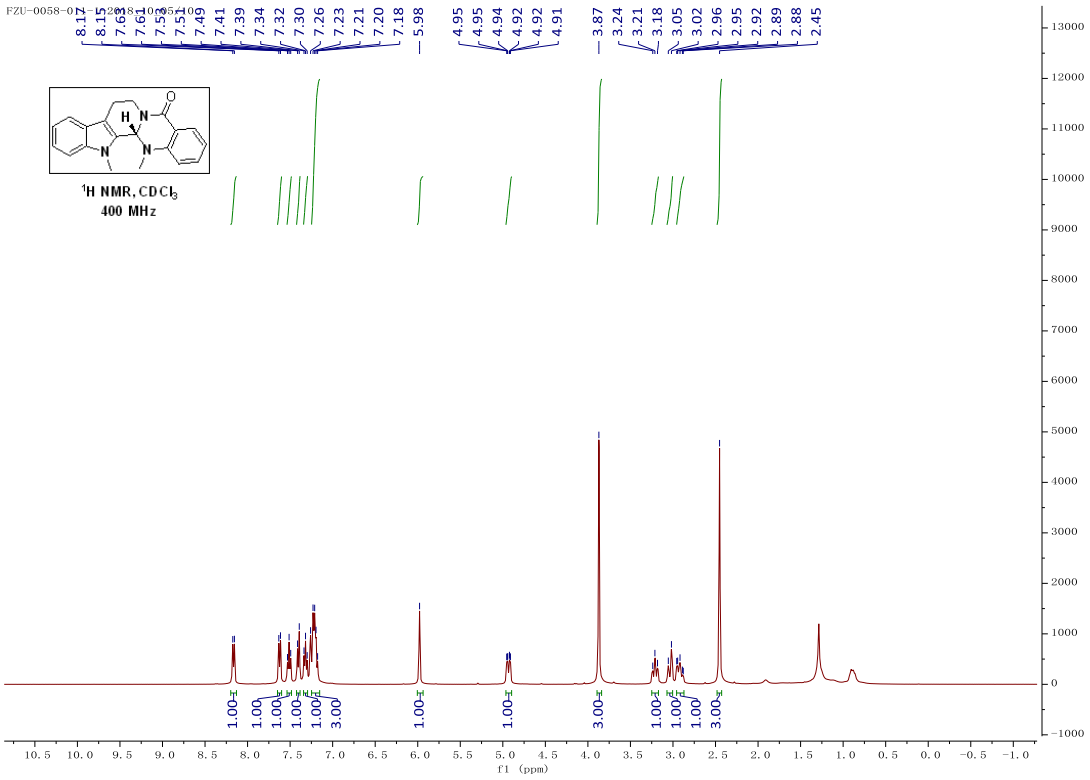
^{1}H NMR Spectrum of SM3



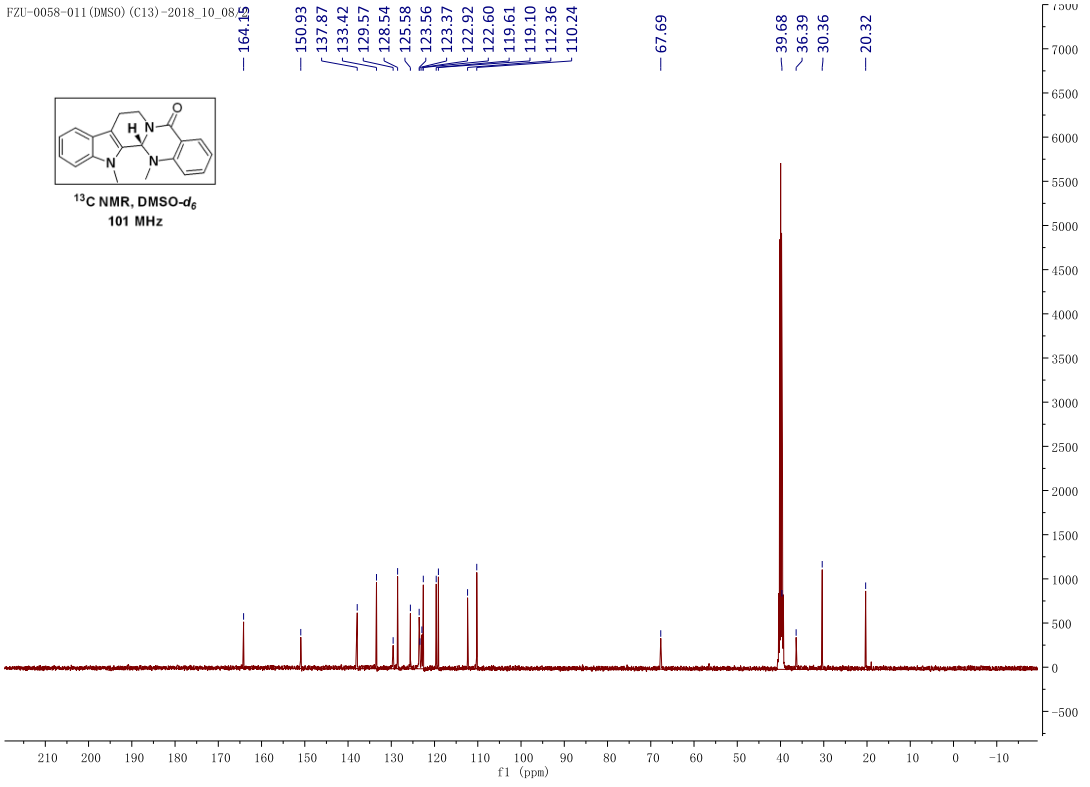
^{13}C NMR Spectrum of SM3



^{1}H NMR Spectrum of compound 8

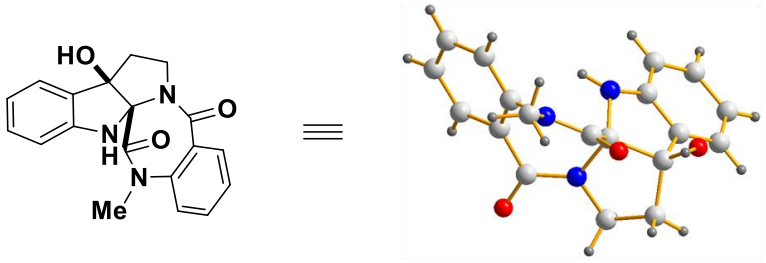


^{13}C NMR Spectrum of compound 8



8. X-ray Crystal Structure Data

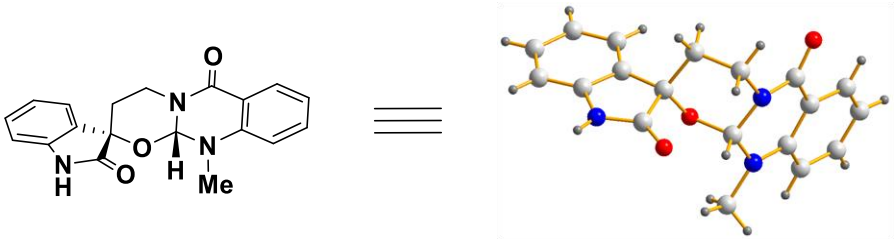
X-ray Crystal Structure Data for Evodiakine (2)



CCDC：1866987

Identification code	2
Empirical formula	$C_{19}H_{17}N_3O_3$
Formula weight	335.35
Temperature/K	169.97
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.3447(4)
b/Å	10.1160(2)
c/Å	10.7205(3)
α/°	90
β/°	109.8920(10)
γ/°	90
Volume/Å^3	1564.82(7)
Z	4
ρ_{calc}g/cm^3	1.423
μ/mm^{-1}	0.517
F(000)	704.0
Crystal size/mm^3	0.05 × 0.03 × 0.02
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	9.288 to 109.824
Index ranges	-18 ≤ h ≤ 18, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	16321
Independent reflections	2963 [R_{int} = 0.0701, R_{sigma} = 0.0470]
Data/restraints/parameters	2963/0/232
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0447, wR_2 = 0.1046
Final R indexes [all data]	R_1 = 0.0595, wR_2 = 0.1137
Largest diff. peak/hole / e Å^{-3}	0.24/-0.26

X-ray Crystal Structure Data for the unstable product (7)



CCDC:1880631

Identification code	7
Empirical formula	$C_{19}H_{17}N_3O_3$
Formula weight	335.35
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.6547(7)
b/Å	13.5081(6)
c/Å	16.2182(7)
α/°	90
β/°	117.9680(10)
γ/°	90
Volume/Å^3	3222.5(2)
Z	8
ρ_{calc}g/cm^3	1.382
μ/mm^{-1}	0.096
F(000)	1408.0
Crystal size/mm^3	0.160 × 0.100 × 0.060
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.024 to 52
Index ranges	-18 ≤ h ≤ 20, -16 ≤ k ≤ 16, -19 ≤ l ≤ 20
Reflections collected	31796
Independent reflections	6314 [R_{int} = 0.0645, R_{sigma} = 0.0582]
Data/restraints/parameters	6314/0/454
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0545, wR_2 = 0.1119
Final R indexes [all data]	R_1 = 0.1184, wR_2 = 0.1468
Largest diff. peak/hole / e Å^{-3}	0.17/-0.17

Reference

[1] Z. X. Wang, J. C. Xiang, M. Wang, J. T. Ma, Y. D. Wu, A. X. Wu, *Org. Lett.* **2018**, *20*, 6380-6383.

[2] R. L. Clark, C. J. Clements, M. P. Barrett, S. P. Mackay, R. P. Rathnam, G. Owusu-Dapaah, J. Spencer, J. K. Huggan, *Bioorg. Med. Chem.* **2012**, *20*, 6019-6033.