

Supporting Information

A Bio-inspired Synthesis of Hybrid Flavonoids from 2-Hydroxychalcone Driven by Visible Light

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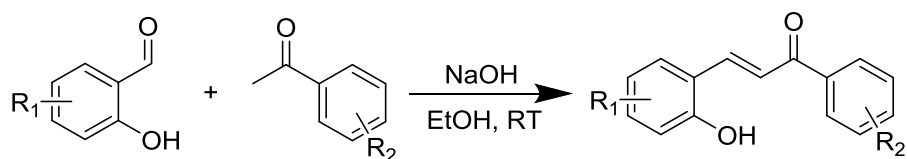
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1. General Information

Unless otherwise noted, all reagents were obtained from commercial sources and used directly without further purification. Non-aqueous reaction was conducted under inert atmosphere of argon in flame-dried glassware. Anhydrous solvents were treated as follow: chloroform was distilled from phosphorus pentoxide under argon atmosphere; tetrahydrofuran was distilled from sodium under argon atmosphere; dichloromethane and toluene were distilled from calcium hydride under argon atmosphere; ethyl acetate was distilled from magnesium sulfate under argon atmosphere. Anhydrous 2-methyltetrahydrofuran and acetonitrile (Adamas-beta, SafeDry, with molecular sieves) were commercial available. Thin layer chromatography was conducted on Merck 60 F254 pre-coated silica gel plates. Column chromatography was carried out by normal silica gel (40-60 μm , 200-400 mesh, Silicycle P60). NMR data including ^1H NMR or ^{13}C NMR spectra were recorded on Bruker AVANCE III 500MHz. All of the ^{13}C NMR spectra were broad band proton-decoupled. ^1H NMR Chemical shifts were reported in ppm relative to residual signals of the solvents (CDCl_3 : 7.26 ppm; acetone- d_6 : 2.09 ppm; CD_3CN : 1.96 ppm). ^{13}C NMR chemical shifts were reported in ppm relative to the solvent (CDCl_3 : 77.36 ppm; acetone- d_6 : 30.6 ppm; CD_3CN : 1.79 ppm). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High resolution mass spectra were obtained from IonSpec 4.7 Tesla FTMS mass spectrometer (MALDI), Bruker APEXIII 7.0 TESLA FTMS (ESI).

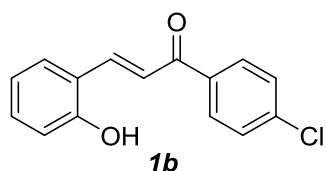
2. Preparation of Substrates

General Procedure for Synthesis of 2-Hydroxychalcone **1a-1k**^[1].



To a vigorously stirred mixture of the salicylaldehyde (1.2 equiv) and acetophenone (1.0 equiv) in absolute ethanol (20 mL) was added dropwise aqueous potassium hydroxide 40% (3 equiv) at room temperature, and using aluminium foil to wrap up the reaction flask. After stirring for 24 h, distilled H₂O (50 mL) was added and the resulting red mixture was acidified with 1M HCl. The mixture was extracted with ethyl acetate, washed with H₂O and brine. The residue was purified by column chromatography using petroleum ether /ethyl acetate (12:1) as eluent to afford pure chalcones.

The spectrum data of **1a**^[2] were consistent with the reference.

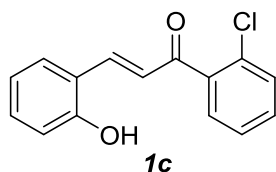


Following the general procedure for the synthesis of 2-hydroxychalcone, compound **1b** was isolated as yellow solid in 78% yield (2.02 g).

¹H NMR (500 MHz, acetone-d₆): δ 9.16 (s, 1H), 8.19 (d, J = 15.8 Hz, 1H), 8.15-8.10 (m, 2H), 7.86 (d, J = 15.7 Hz, 1H), 7.81 (dd, J = 7.8, 1.7 Hz, 1H), 7.61-7.55 (m, 2H), 7.29 (ddd, J = 8.3, 7.3, 1.7 Hz, 1H), 7.00 (dd, J = 8.2, 1.2 Hz, 1H), 6.93 (td, J = 7.6, 1.1 Hz, 1H).

¹³C NMR (126 MHz, acetone-d₆): ¹³C NMR (126 MHz, Acetone) δ 189.22, 157.98, 140.98, 139.12, 138.07, 132.79, 130.97, 129.88, 129.67, 122.86, 122.09, 120.92, 117.14.

HRMS (ESI): exact mass calcd for C₁₅H₁₁ClO₂: m/z 259.0526 [M+H]⁺, found: m/z 259.0527.

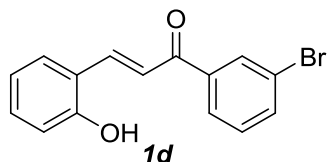


Following the general procedure for the synthesis of 2-hydroxychalcone, compound **1c** was isolated as yellow solid in 74% yield (1.91 g).

¹H NMR (500 MHz, acetone-d₆): δ 9.15 (s, 1H), 7.79 (d, J = 16.3 Hz, 1H), 7.68 (dd, J = 7.9, 1.7 Hz, 1H), 7.55-7.45 (m, 4H), 7.31-7.24 (m, 2H), 6.97 (dd, J = 8.2, 1.1 Hz, 1H), 6.92 (td, J = 7.7, 1.1 Hz, 1H).

¹³C NMR (126 MHz, acetone-d₆): δ 194.26, 157.80, 142.55, 140.62, 133.09, 132.14, 131.38, 130.90, 130.06, 129.84, 127.97, 127.02, 122.36, 121.01, 117.11.

HRMS (ESI): exact mass calcd for C₁₅H₁₁ClO₂: m/z 259.0526 [M+H]⁺, found: m/z 259.0524.

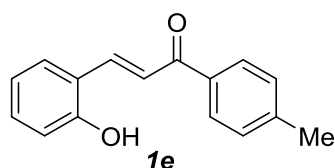


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1d** was isolated as yellow solid in 81% yield (2.46 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.13 (s, 1H), 7.76 (d, *J* = 16.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.54-7.47 (m, 2H), 7.44 (ddd, *J* = 8.0, 7.0, 2.2 Hz, 1H), 7.31-7.27 (m, 1H), 7.23 (d, *J* = 16.3 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.92 (td, *J* = 7.6, 0.9 Hz, 1H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 195.12, 157.80, 142.80, 142.72, 134.08, 133.10, 132.14, 129.94, 129.83, 128.47, 126.85, 122.39, 121.02, 119.69, 117.14.

HRMS (ESI): exact mass calcd for C₁₅H₁₁BrO₂: *m/z* 303.0020 [M+H]⁺, found: *m/z* 303.0022.

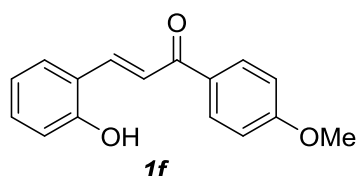


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1e** was isolated as yellow solid in 69% yield (1.64 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.12 (s, 1H), 8.17 (d, *J* = 15.8 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 15.8 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 1H), 7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.93 (td, *J* = 7.6, 1.1 Hz, 1H), 2.42 (s, 3H).

¹³C NMR (126 MHz, acetone-*d*₆): ¹³C NMR (126 MHz, Acetone) δ 189.83, 157.83, 144.11, 140.05, 136.97, 132.48, 130.11, 129.76, 129.34, 123.08, 122.58, 120.89, 117.10, 21.55.

HRMS (ESI): exact mass calcd for C₁₆H₁₄O₂: *m/z* 239.1072 [M+H]⁺, found: *m/z* 239.1071.

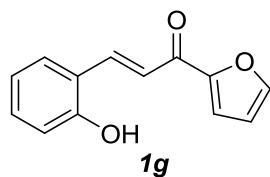


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1f** was isolated as yellow solid in 60% yield (1.53 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.11 (s, 1H), 8.21-8.06 (m, 3H), 7.89 (d, *J* = 15.7 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.27 (ddd, *J* = 8.2, 7.2, 1.6 Hz, 1H), 7.09-7.04 (m, 2H), 6.99 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 3.90 (s, 3H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 188.57, 164.31, 157.75, 139.54, 132.35, 132.30, 131.46, 129.70, 123.16, 122.42, 120.86, 117.06, 114.68, 55.93.

HRMS (ESI): exact mass calcd for C₁₆H₁₄O₃: *m/z* 255.1021 [M+H]⁺, found: *m/z* 255.1019.

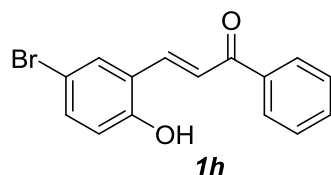


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1g** was isolated as yellow solid in 64% yield (1.37 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.18 (s, 1H), 8.18 (d, *J* = 15.9 Hz, 1H), 7.91-7.84 (m, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.72 (d, *J* = 15.8 Hz, 1H), 7.50 (d, *J* = 3.5 Hz, 1H), 7.28 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.92 (td, *J* = 7.6, 1.2 Hz, 1H), 6.71 (dd, *J* = 3.5, 1.7 Hz, 1H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 178.21, 157.90, 154.86, 147.88, 139.37, 132.67, 129.76, 122.73, 122.10, 120.89, 118.19, 117.11, 113.24.

HRMS (ESI): exact mass calcd for C₁₃H₁₀O₃: *m/z* 215.0708 [M+H]⁺, found: *m/z* 215.0710.

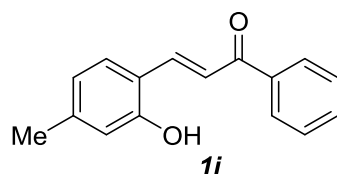


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1h** was isolated as yellow solid in 85% yield (2.58 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.44 (s, 1H), 8.17-8.08 (m, 3H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.96 (d, *J* = 15.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 190.11, 156.97, 139.24, 138.55, 134.93, 133.67, 131.70, 129.57, 129.36, 125.31, 123.65, 119.13, 112.55.

HRMS (ESI): exact mass calcd for C₁₅H₁₁BrO₂: *m/z* 303.0020 [M+H]⁺, found: *m/z* 303.0019.

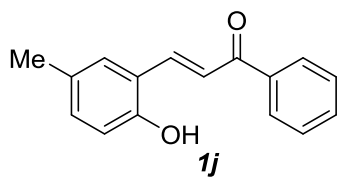


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1i** was isolated as yellow solid in 77% yield (1.83 g).

¹H NMR (500 MHz, acetone-*d*₆): δ 9.06 (s, 1H), 8.15 (d, *J* = 15.7 Hz, 1H), 8.11-8.08 (m, 2H), 7.83 (d, *J* = 15.8 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 6.83 (s, 1H), 6.76 (dd, *J* = 7.5, 1.2 Hz, 1H), 2.29 (s, 3H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 190.37, 157.92, 143.39, 140.64, 139.65, 133.29, 129.81, 129.46, 129.12, 121.96, 121.46, 120.35, 117.60, 21.51.

HRMS (ESI): exact mass calcd for C₁₆H₁₄O₂: *m/z* 239.1072 [M+H]⁺, found: *m/z* 239.1070.

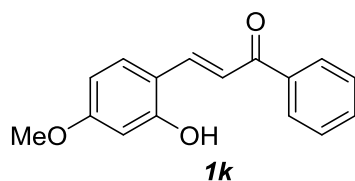


Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1j** was isolated as yellow solid in 71% yield (1.69 g).

¹H NMR (500 MHz, acetone-d₆): δ 8.96 (s, 1H), 8.20 (d, *J* = 15.8 Hz, 1H), 8.15-8.12 (m, 2H), 7.91 (d, *J* = 15.8 Hz, 1H), 7.70-7.65 (m, 2H), 7.62-7.56 (m, 2H), 7.14 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 2.32 (s, 3H).

¹³C NMR (126 MHz, acetone-d₆): δ 191.10, 156.57, 141.36, 140.31, 134.13, 134.10, 130.59, 130.57, 130.24, 129.92, 123.37, 122.95, 117.77, 21.18.

HRMS (ESI): exact mass calcd for C₁₆H₁₄O₂: *m/z* 239.1072 [M+H]⁺, found: *m/z* 239.1072.



Following the general procedure for the synthesis of 2-hydroxylchalcone, compound **1k** was isolated as yellow solid in 73% yield (1.86 g).

¹H NMR (500 MHz, acetone-d₆): δ 9.27 (s, 1H), 8.18 (d, *J* = 15.7 Hz, 1H), 8.13-8.10 (m, 2H), 7.83-7.77 (m, 2H), 7.66-7.64 (m, 1H), 7.60-7.56 (m, 2H), 6.60-6.58 (d, 2H), 3.85 (s, 3H).

¹³C NMR (126 MHz, acetone-d₆): δ 190.99, 164.72, 160.23, 141.35, 140.58, 133.91, 132.05, 130.18, 129.82, 120.64, 116.96, 108.23, 103.00, 56.47.

HRMS (ESI): exact mass calcd for C₁₆H₁₄O₃: *m/z* 255.1021 [M+H]⁺, found: *m/z* 255.1023.

3. Optimization of Reaction Conditions.

General Procedure

2-Hydroxylchalcone (0.1 mmol), nucleophile (0.12 mmol), acid (10 mol%) and acetonitrile (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred with irradiation by 24W CFL at room temperature under argon and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel to yield **4aa**, **4ba** or **4ca**.

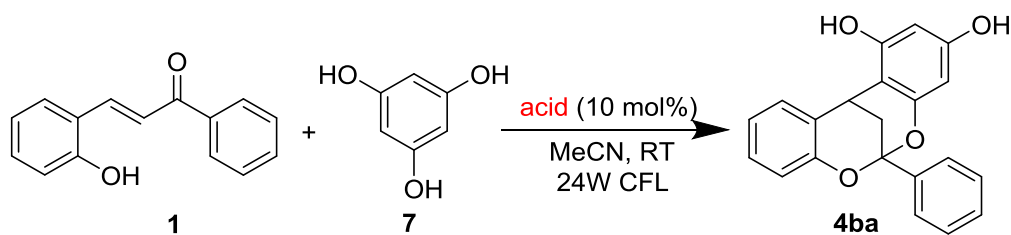
Table S1. The Screening of Solvent for the Reaction of Indole with 2-Hydroxylchalcone

entry	catalyst	solvent	time (h)	yield (%)
1	biphenyl phosphate	MeCN	30	98
2	biphenyl phosphate	THF	19	98
3	biphenyl phosphate	DCM	72	61
4	biphenyl phosphate	toluene	69	60
5	biphenyl phosphate	EA	40	85
6	biphenyl phosphate	EtOH	40	90

Table S2. The Screening of Acid for the Model Reaction of 1, 3-Cyclohexanedione with 2-Hydroxylchalcone

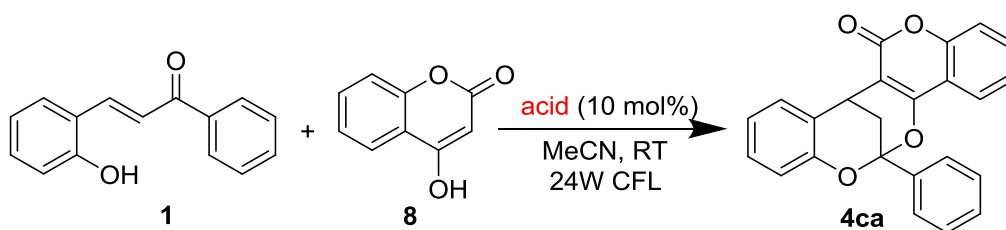
Entry	Acid	Time (h)	Yield (%)
1	None	24	trace
2	HCl	10	96
3	TsOH	10	80
4	Diphenyl phosphate	34	93
5	(±) CSA	10	62
6	HBF ₄	17	53
7	HOTf	15	47
8	HNTf ₂	12	41
9	Benzoic acid	24	trace
10	(±) CPA	18	75

Table S3. The Screening of Acid for the Model Reaction of Phloroglucinol with 2-Hydroxylchalcone



Entry	Acid	Time (h)	Yield (%)
1	None	21	39
2	HCl	20	44
3	TsOH	24	80
4	TFA	35	0
5	(±) CPA	15	63

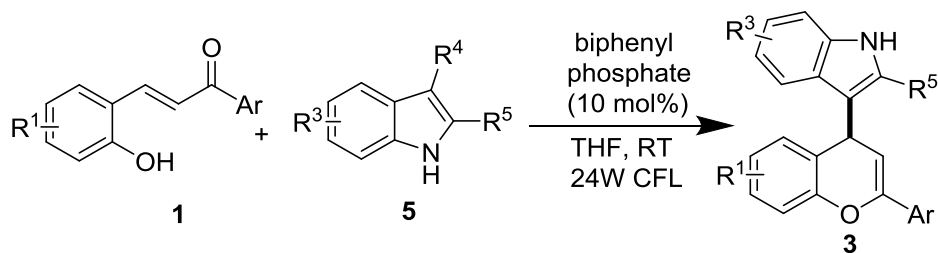
Table S4. The Screening of Acid for the Model Reaction of 4-Hydroxycoumarin with 2-Hydroxylchalcone



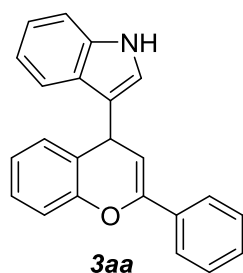
Entry	Acid	Time (h)	Yield (%)
1	None	24	trace
2	HCl	25	75
3	TsOH	33	65
4	Diphenyl phosphate	35	68
5	(±) CSA	35	55
6	(±) CPA	15	75

4. Substrate Scope of the Synthesis of Hybrid Flavonoids

4.1 General Procedure for the Synthesis of Flavonoids 3aa-3ax.



2-Hydroxychalcone (0.1 mmol), indole (0.12 mmol), biphenyl phosphate (0.01 mmol) and THF (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxychalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 15) to yield the desired products.

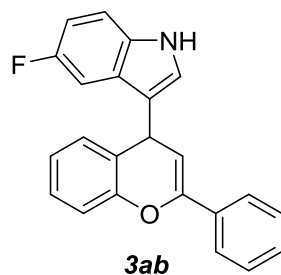


Following the general procedure, compound **3aa** was isolated as red oil in 98% yield (31.7 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.94 (s, 1H), 7.79 – 7.72 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.22 – 7.12 (m, 4H), 7.08 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.97 – 6.92 (m, 1H), 5.71 (d, J = 4.0 Hz, 1H), 5.19 (d, J = 3.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.47, 148.09, 136.98, 134.74, 129.82, 128.69, 128.63, 127.86, 126.68, 125.06, 123.72, 122.47, 122.41, 121.90, 119.97, 119.72, 116.83, 111.56, 101.38, 32.46.

HRMS (ESI): exact mass calcd for C₂₃H₁₇NO: m/z 324.1388 [M+H]⁺, found: m/z 324.1385.

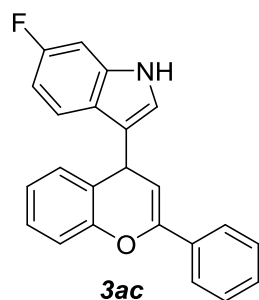


Following the general procedure, compound **3ab** was isolated as red oil in 85% yield (29.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.03 (s, 1H), 7.77-7.69 (m, 2H), 7.41-7.31 (m, 3H), 7.27-7.22 (m, 2H), 7.21-7.12 (m, 2H), 7.12-7.05 (m, 2H), 6.97-6.88 (m, 2H), 5.65 (d, J = 4.1 Hz, 1H), 5.11 (d, J = 4.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 158.02 (d, J = 234.7 Hz), 151.46, 148.33, 134.62, 133.52, 129.68, 128.79, 128.66, 128.02, 126.97 (d, J = 8.9 Hz), 125.08, 124.11, 123.79, 123.34, 122.03 (d, J = 4.7 Hz), 116.98, 112.16 (d, J = 9.6 Hz), 110.94 (d, J = 26.5 Hz), 104.68 (d, J = 23.6 Hz), 100.92, 32.49.

HRMS (ESI): exact mass calcd for C₂₃H₁₆FNO: m/z 340.1138 [M-H]⁻, found: m/z 340.1133.

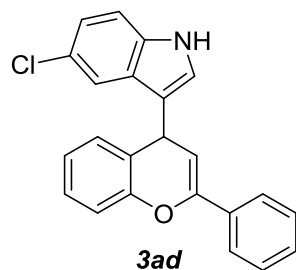


Following the general procedure, compound **3ac** was isolated as red oil in 78% yield (26.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.99 (s, 1H), 7.76-7.68 (m, 2H), 7.51-7.47 (m, 1H), 7.42-7.32 (m, 3H), 7.21-7.13 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 9.6, 2.3 Hz, 1H), 6.97-6.92 (m, 1H), 6.85-6.77 (m, 1H), 5.66 (d, *J* = 4.0 Hz, 1H), 5.13 (d, *J* = 3.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 160.30 (d, *J* = 237.9 Hz), 151.43, 148.22, 136.97 (d, *J* = 12.4 Hz), 134.62, 129.71, 128.79, 128.67, 127.98, 125.05, 123.78, 123.45, 123.22, 122.52 (d, *J* = 3.5 Hz), 121.79, 120.48 (d, *J* = 10.0 Hz), 116.89, 108.74 (d, *J* = 24.4 Hz), 101.16, 97.84 (d, *J* = 26.1 Hz), 32.52.

HRMS (ESI): exact mass calcd for C₂₃H₁₆FNO: m/z 340.1138 [M-H]⁻, found: m/z 340.1134.

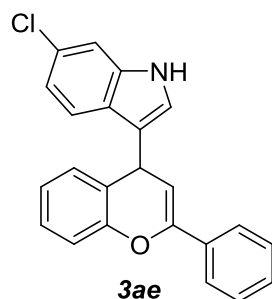


Following the general procedure, compound **3ad** was isolated as red oil in 79% yield (28.3 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.05 (s, 1H), 7.77-7.71 (m, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.42-7.32 (m, 3H), 7.27-7.24 (m, 1H), 7.22-7.18 (m, 1H), 7.17-7.07 (m, 3H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.95 (td, *J* = 7.4, 1.5 Hz, 1H), 5.65 (d, *J* = 4.0 Hz, 1H), 5.13 (d, *J* = 4.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.45, 148.37, 135.29, 134.62, 129.64, 128.80, 128.67, 128.05, 127.72, 125.71, 125.09, 123.96, 123.81, 123.35, 122.86, 121.78, 119.09, 117.00, 112.58, 100.93, 32.28.

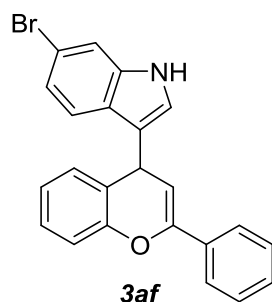
HRMS (ESI): exact mass calcd for C₂₃H₁₆ClNO: m/z 358.0998 [M+H]⁺, found: m/z 358.0994.



Following the general procedure, compound **3ae** was isolated as red oil in 77% yield (27.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.97 (s, 1H), 7.78-7.71 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43-7.34 (m, 3H), 7.32 (d, *J* = 1.6 Hz, 1H), 7.23-7.15 (m, 2H), 7.11-7.07 (m, 1H), 7.04-6.99 (m, 2H), 6.99-6.92 (m, 1H), 5.66 (d, *J* = 4.0 Hz, 1H), 5.13 (d, *J* = 4.0 Hz, 1H).

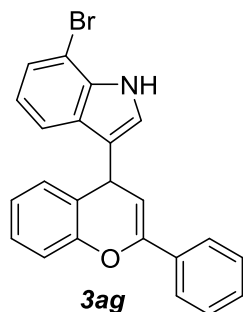
¹³C NMR (126 MHz, CDCl₃): δ 151.41, 148.27, 137.36, 134.58, 129.68, 128.81, 128.67, 128.43, 128.02, 125.22, 125.06, 123.80, 123.37, 122.90, 121.92, 120.71, 120.59, 116.92, 111.50, 101.03, 32.44.
HRMS (ESI): exact mass calcd for C₂₃H₁₆ClNO: m/z 358.0998 [M+H]⁺, found: m/z 358.0995.



Following the general procedure, compound **3af** was isolated as red oil in 86% yield (34.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.01 (s, 1H), 7.78-7.68 (m, 2H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.41-7.32 (m, 3H), 7.21-7.12 (m, 3H), 7.09-7.02 (m, 2H), 6.96-6.91 (m, 1H), 5.64 (d, *J* = 4.0 Hz, 1H), 5.13 (d, *J* = 3.9 Hz, 1H).

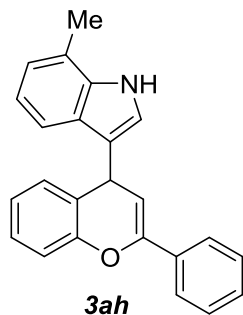
¹³C NMR (126 MHz, CDCl₃): δ 151.40, 148.29, 137.81, 134.58, 129.68, 128.81, 128.67, 128.02, 125.54, 125.06, 123.80, 123.35, 123.28, 122.85, 121.99, 120.98, 116.92, 116.08, 114.50, 101.00, 32.44.
HRMS (ESI): exact mass calcd for C₂₃H₁₆BrNO: m/z 402.0493 [M+H]⁺, found: m/z 402.0488.



Following the general procedure, compound **3ag** was isolated as red oil in 78% yield (31.4 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.19 (s, 1H), 7.77-7.70 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.42-7.31 (m, 4H), 7.22-7.13 (m, 3H), 7.11-7.07 (m, 1H), 6.97-6.91 (m, 2H), 5.66 (d, *J* = 4.0 Hz, 1H), 5.15 (d, *J* = 3.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.41, 148.30, 135.67, 134.59, 129.73, 128.81, 128.66, 128.04, 127.85, 125.07, 124.81, 123.81, 123.27, 123.03, 122.86, 121.18, 119.04, 116.93, 105.19, 100.94, 32.72.
HRMS (ESI): exact mass calcd for C₂₃H₁₆BrNO: m/z 402.0493 [M+H]⁺, found: m/z 402.0491.

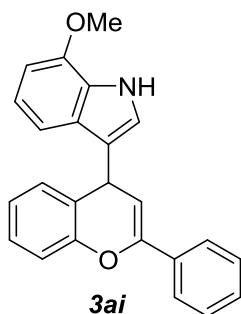


Following the general procedure, compound **3ah** was isolated as red oil in 83% yield (28.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.94 (s, 1H), 7.77-7.72 (m, 2H), 7.53-7.49 (m, 1H), 7.42-7.32 (m, 3H), 7.21-7.13 (m, 3H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.03-6.98 (m, 2H), 6.96-6.92 (m, 1H), 5.70 (d, *J* = 4.0 Hz, 1H), 5.18 (d, *J* = 3.9 Hz, 1H), 2.48 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 151.44, 148.01, 136.51, 134.74, 129.83, 128.66, 128.61, 127.82, 126.19, 125.03, 123.76, 123.71, 123.00, 122.39, 122.15, 120.72, 120.20, 117.44, 116.81, 101.41, 32.52, 16.91.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO: *m/z* 336.1389 [M-H]⁻, found: *m/z* 336.1392.

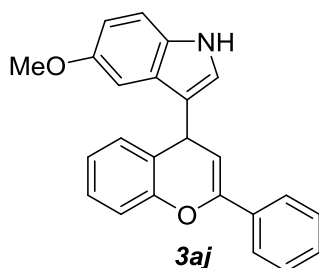


Following the general procedure, compound **3ai** was isolated as red oil in 88% yield (31.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.23 (s, 1H), 7.78-7.68 (m, 2H), 7.42-7.31 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20-7.09 (m, 3H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.96-6.91 (m, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 5.69 (d, *J* = 4.0 Hz, 1H), 5.16 (d, *J* = 3.9 Hz, 1H), 3.94 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 151.45, 148.05, 146.54, 134.79, 129.86, 128.65, 128.61, 128.02, 127.82, 127.52, 125.07, 123.80, 123.70, 122.37, 121.98, 120.37, 116.81, 112.47, 102.33, 101.44, 55.65, 32.55.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO₂: *m/z* 352.1338 [M-H]⁻, found: *m/z* 352.1334.

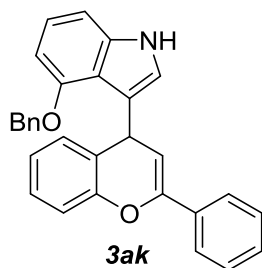


Following the general procedure, compound **3aj** was isolated as red oil in 84% yield (29.7 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.92 (s, 1H), 7.76-7.71 (m, 2H), 7.41-7.31 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.20-7.12 (m, 3H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.97-6.93 (m, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.68 (d, *J* = 4.0 Hz, 1H), 5.13 (d, *J* = 3.9 Hz, 1H), 3.75 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 154.27, 151.52, 148.18, 134.76, 132.14, 129.84, 128.68, 128.62, 127.86, 127.10, 125.04, 123.76, 123.72, 123.09, 121.60, 116.77, 112.57, 112.25, 101.54, 101.35, 56.10, 32.49.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO₂: *m/z* 354.1494 [M+H]⁺, found: *m/z* 354.1489.

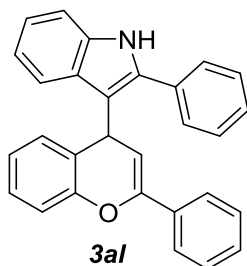


Following the general procedure, compound **3ak** was isolated as red oil in 79% yield (34.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.89 (s, 1H), 7.71-7.65 (m, 2H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.39-7.28 (m, 7H), 7.23-7.18 (m, 1H), 7.14-7.09 (m, 2H), 7.01-6.95 (m, 2H), 6.70-6.60 (m, 2H), 5.90 (d, *J* = 4.4 Hz, 1H), 5.62 (d, *J* = 4.1 Hz, 1H), 5.34-5.26 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 153.93, 151.66, 147.04, 138.33, 137.62, 134.99, 130.38, 128.89, 128.50, 128.37, 128.09, 127.60, 127.54, 124.88, 124.77, 123.39, 123.13, 122.37, 116.78, 116.70, 105.13, 102.76, 101.17, 70.26, 32.56.

HRMS (ESI): exact mass calcd for C₃₀H₂₃NO₂: *m/z* 430.1807 [M+H]⁺, found: *m/z* 430.1805.

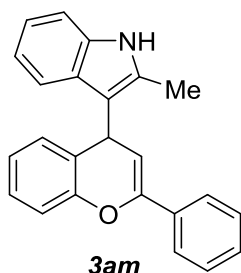


Following the general procedure, compound **3al** was isolated as red oil in 84% yield (33.5 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.07 (s, 1H), 7.77-7.71 (m, 2H), 7.67-7.62 (m, 2H), 7.53-7.32 (m, 8H), 7.20-7.13 (m, 3H), 7.01-6.94 (m, 2H), 6.91-6.86 (m, 1H), 5.64 (d, *J* = 3.5 Hz, 1H), 5.41 (d, *J* = 3.4 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.39, 148.00, 136.30, 135.08, 134.41, 132.84, 129.30, 129.01, 128.60, 128.36, 128.30, 128.24, 127.83, 127.60, 124.78, 123.51, 123.34, 122.36, 120.48, 119.87, 116.40, 116.38, 110.82, 101.32, 31.45.

HRMS (ESI): exact mass calcd for C₂₉H₂₁NO: *m/z* 400.1701 [M+H]⁺, found: *m/z* 400.1697.

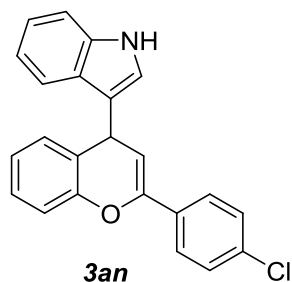


Following the general procedure, compound **3am** was isolated as red oil in 83% yield (27.9 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.79-7.75 (m, 2H), 7.73 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.44-7.34 (m, 3H), 7.28-7.25 (m, 1H), 7.22-7.15 (m, 2H), 7.14-7.09 (m, 1H), 7.04-6.98 (m, 2H), 6.95-6.90 (m, 1H), 5.61 (d, *J* = 3.8 Hz, 1H), 5.23 (d, *J* = 3.7 Hz, 1H), 2.40 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 151.55, 148.00, 135.47, 134.73, 131.76, 129.74, 128.62, 128.17, 127.76, 124.98, 123.75, 123.64, 121.38, 119.76, 118.90, 116.64, 116.31, 110.52, 101.23, 31.32, 12.22.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO: *m/z* 336.1389 [M-H]⁻, found: *m/z* 336.1385.

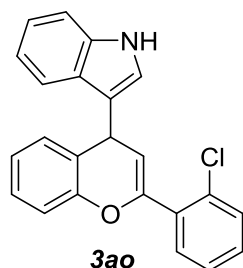


Following the general procedure, compound **3an** was isolated as red oil in 88% yield (31.5 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.00 (s, 1H), 7.69-7.64 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.38-7.33 (m, 3H), 7.22-7.11 (m, 4H), 7.10-7.05 (m, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.97-6.93 (m, 1H), 5.68 (d, *J* = 4.0 Hz, 1H), 5.17 (d, *J* = 3.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.27, 147.11, 136.96, 134.42, 133.15, 129.85, 128.78, 127.94, 126.58, 126.31, 123.88, 123.49, 122.52, 122.41, 121.61, 119.99, 119.61, 116.78, 111.62, 101.80, 32.42.

HRMS (ESI): exact mass calcd for C₂₃H₁₆ClNO: *m/z* 356.0842 [M-H]⁻, found: *m/z* 356.0839.

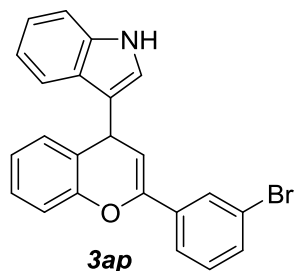


Following the general procedure, compound **3ao** was isolated as red oil in 88% yield (31.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.99 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58-7.52 (m, 1H), 7.46-7.41 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.32-7.27 (m, 2H), 7.22-7.07 (m, 6H), 6.97-6.92 (m, 1H), 5.45 (d, *J* = 3.9 Hz, 1H), 5.19 (d, *J* = 4.5 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.52, 147.44, 136.98, 134.79, 133.45, 131.07, 130.44, 130.10, 129.81, 127.87, 126.96, 126.65, 123.83, 123.67, 122.51, 122.45, 121.63, 119.92, 119.81, 116.80, 111.57, 106.31, 32.59.

HRMS (ESI): exact mass calcd for C₂₃H₁₆ClNO: *m/z* 358.0998 [M+H]⁺, found: *m/z* 358.0994.

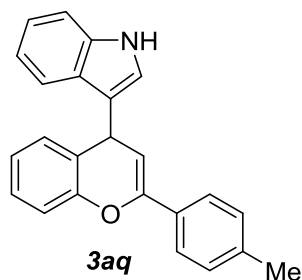


Following the general procedure, compound **3ap** was isolated as red oil in 87% yield (35.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.00 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.38-7.30 (m, 2H), 7.25-7.08 (m, 7H), 6.98-6.91 (m, 1H), 5.38 (d, *J* = 3.8 Hz, 1H), 5.19 (d, *J* = 3.7 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.50, 148.80, 136.96, 136.87, 133.61, 131.41, 130.38, 129.80, 127.87, 127.55, 126.64, 123.85, 123.70, 122.99, 122.56, 122.45, 121.61, 119.90, 119.86, 116.83, 111.57, 106.04, 32.59.

HRMS (ESI): exact mass calcd for C₂₃H₁₆BrNO: *m/z* 402.0493 [M+H]⁺, found: *m/z* 402.0491.

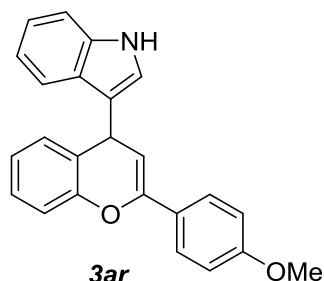


Following the general procedure, compound **3aq** was isolated as red oil in 85% yield (28.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.99 (s, 1H), 7.68-7.61 (m, 3H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.22-7.12 (m, 6H), 7.09-7.03 (m, 2H), 6.96-6.91 (m, 1H), 5.65 (d, *J* = 4.0 Hz, 1H), 5.17 (d, *J* = 3.9 Hz, 1H), 2.39 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 151.47, 148.10, 138.55, 136.94, 131.93, 129.80, 129.31, 127.79, 126.66, 124.95, 123.79, 123.61, 122.41, 122.39, 121.94, 119.90, 119.74, 116.82, 111.54, 100.51, 32.41, 21.58.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO: *m/z* 336.1389 [M-H]⁺, found: *m/z* 336.1385.

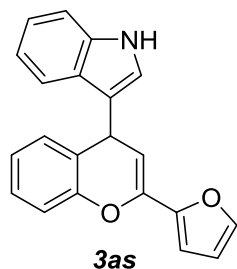


Following the general procedure, compound **3ar** was isolated as red oil in 69% yield (24.4 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.01 (s, 1H), 7.72-7.60 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.20-7.03 (m, 6H), 6.95-6.87 (m, 3H), 5.57 (d, *J* = 3.9 Hz, 1H), 5.16 (d, *J* = 3.8 Hz, 1H), 3.83 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 160.10, 151.51, 147.89, 136.98, 129.81, 127.78, 127.46, 126.69, 126.41, 123.84, 123.61, 122.42, 122.37, 122.06, 119.91, 119.76, 116.79, 114.00, 111.55, 99.71, 55.66, 32.43.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO₂: *m/z* 352.1338 [M-H]⁺, found: *m/z* 352.1339.

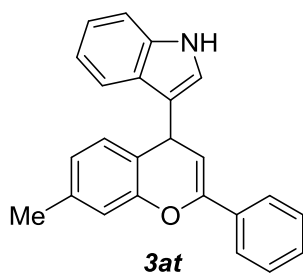


Following the general procedure, compound **3as** was isolated as red oil in 85% yield (26.6 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.00 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.39-7.33 (m, 2H), 7.20-7.05 (m, 5H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.95-6.90 (m, 1H), 6.67 (d, *J* = 3.3 Hz, 1H), 6.45 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.71 (d, *J* = 4.1 Hz, 1H), 5.15 (d, *J* = 4.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 151.04, 149.12, 142.58, 141.36, 136.96, 129.98, 127.90, 126.63, 123.81, 123.69, 122.47, 121.67, 119.95, 119.66, 116.78, 111.56, 111.49, 106.75, 100.33, 31.76.

HRMS (ESI): exact mass calcd for C₂₁H₁₅NO₂: *m/z* 312.1025 [M-H]⁺, found: *m/z* 312.1022.

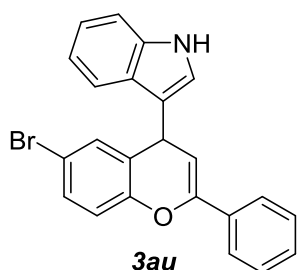


Following the general procedure, compound **3at** was isolated as red oil in 83% yield (27.9 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.99 (s, 1H), 7.77-7.71 (m, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.41-7.33 (m, 4H), 7.20-7.16 (m, 1H), 7.09-6.99 (m, 4H), 6.78-6.74 (m, 1H), 5.69 (d, *J* = 4.0 Hz, 1H), 5.14 (d, *J* = 3.9 Hz, 1H), 2.33 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 151.22, 148.01, 137.80, 136.96, 134.82, 129.52, 128.60, 126.67, 125.02, 124.64, 122.41, 122.33, 121.99, 120.67, 119.89, 119.73, 117.16, 111.54, 101.45, 32.17, 21.38.

HRMS (ESI): exact mass calcd for C₂₄H₁₉NO: *m/z* 336.1389 [M-H]⁻, found: *m/z* 336.1386.



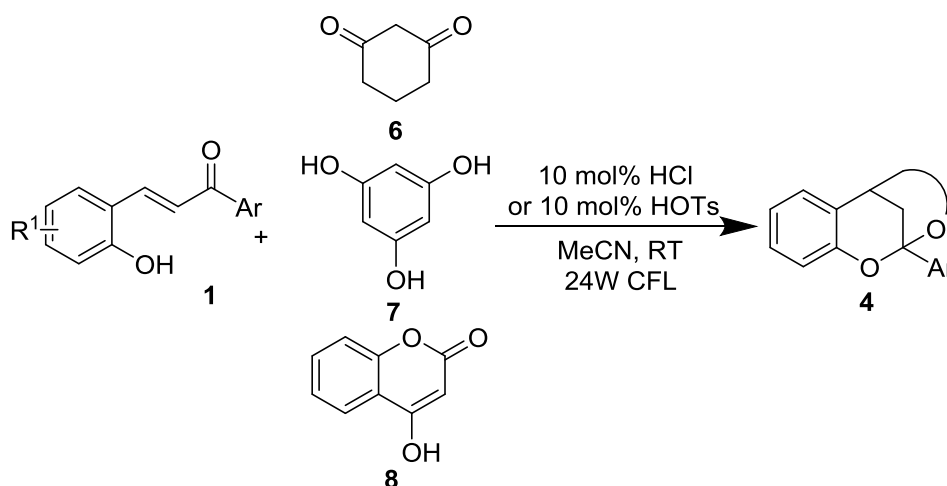
Following the general procedure, compound **3au** was isolated as red oil in 83% yield (33.3 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.98 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.41-7.30 (m, 4H), 7.27-7.15 (m, 3H), 7.07-6.95 (m, 3H), 5.64 (d, *J* = 3.7 Hz, 1H), 5.09 (d, *J* = 2.9 Hz, 1H).

¹³C NMR (126 MHz, acetone-d₆): δ 152.09, 149.12, 139.11, 135.67, 133.82, 132.18, 130.31, 130.19, 128.33, 127.99, 126.25, 124.58, 123.31, 121.40, 120.74, 120.58, 120.28, 116.74, 113.41, 102.83, 33.80.

HRMS (ESI): exact mass calcd for C₂₃H₁₆BrNO: *m/z* 402.0493 [M+H]⁺, found: *m/z* 402.0491.

4.2 General Procedure for the Bio-inspired Synthesis of Hybrid Flavonoids 4aa-4cj.

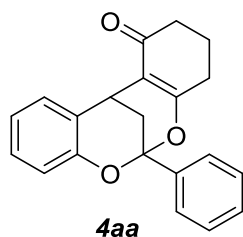


General Proceduer A

To a reaction tube equipped with a magnetic stir bar was added 2-hydroxylchalcone (0.1 mmol), nucleophile (0.12 mmol), HCl (0.01 mmol, 1M) and acetonitrile (3.0 mL). The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 8) to yield the desired products.

General Proceduer B

To a reaction tube equipped with a magnetic stir bar was added 2-hydroxylchalcone (0.1 mmol), nucleophile (0.12 mmol), HOTs (0.01 mmol) and acetonitrile (3.0 mL). The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (Acetone/DCM = 1: 20) to yield the desired products.

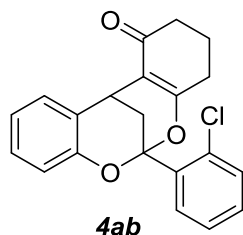


Following the **general procedure A**, compound **4aa** was isolated as white solid in 96% yield (30.5 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.75-7.58 (m, 2H), 7.50-7.36 (m, 4H), 7.16 (td, J = 8.3, 1.7 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.93 (td, J = 7.4, 1.3 Hz, 1H), 4.24 (t, J = 3.1 Hz, 1H), 2.61-2.46 (m, 2H), 2.45-2.28 (m, 2H), 2.25 (dd, J = 3.0, 13.0 Hz, 1H), 2.17 (dd, J = 3.0, 13.0 Hz, 1H), 2.06-1.92 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.31, 169.43, 151.85, 140.55, 129.39, 128.74, 128.53, 127.92, 126.90, 125.92, 121.88, 116.91, 116.30, 100.00, 36.78, 33.35, 28.16, 25.57, 21.08.

HRMS (ESI): exact mass calcd for C₂₁H₁₈O₃; m/z 319.1334 [M+H]⁺, found: m/z 319.1334.

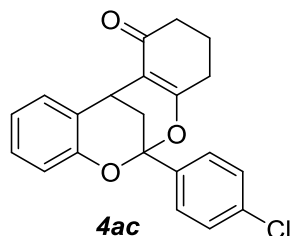


Following the **general procedure A**, compound **4ab** was isolated as white solid in 99% yield (34.9 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.05-7.96 (m, 1H), 7.50-7.43 (m, 1H), 7.41-7.33 (m, 3H), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.94 (td, *J* = 7.4, 1.2 Hz, 1H), 4.25 (t, *J* = 3.1 Hz, 1H), 2.65-2.53 (m, 1H), 2.54-2.28 (m, 5H), 2.08-1.91 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.31, 169.18, 151.35, 136.83, 132.78, 132.07, 130.72, 128.76, 128.55, 127.99, 127.24, 127.01, 122.03, 117.17, 116.52, 99.63, 36.79, 29.62, 27.92, 25.04, 21.04.

HRMS (ESI): exact mass calcd for C₂₁H₁₇ClO₃: *m/z* 353.0944 [M+H]⁺, found: *m/z* 353.0942.

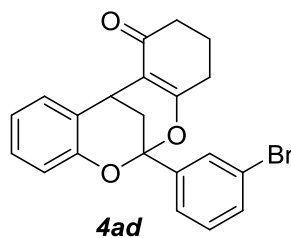


Following the **general procedure A**, compound **4ac** was isolated as white solid in 95% yield (33.4 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.64-7.56 (m, 2H), 7.46-7.36 (m, 3H), 7.16 (td, *J* = 7.8, 1.6 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.93 (td, *J* = 7.4, 1.1 Hz, 1H), 4.23 (t, *J* = 3.1 Hz, 1H), 2.59-2.45 (m, 2H), 2.44-2.28 (m, 2H), 2.21 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.13 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.05-1.92 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.29, 169.18, 151.67, 139.17, 135.44, 128.96, 128.58, 128.02, 127.51, 126.74, 122.07, 116.93, 116.28, 99.63, 36.77, 33.30, 28.12, 25.51, 21.06.

HRMS (ESI): exact mass calcd for C₂₁H₁₇ClO₃: *m/z* 375.0764 [M+Na]⁺, found: *m/z* 375.0754.

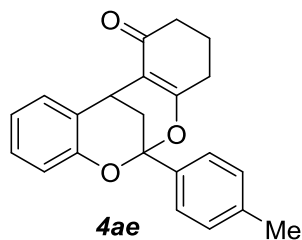


Following the **general procedure A**, compound **4ad** was isolated as white solid in 99% yield (39.2 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.06 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.73 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.50-7.43 (m, 2H), 7.31 (td, *J* = 7.7, 1.7 Hz, 1H), 7.22 (td, *J* = 7.8, 1.7 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.98 (td, *J* = 7.4, 1.2 Hz, 1H), 4.31-4.28 (m, 1H), 2.71-2.63 (m, 1H), 2.60 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.57-2.43 (m, 2H), 2.43-2.35 (m, 2H), 2.11-1.97 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.26, 169.20, 151.35, 138.17, 135.62, 130.88, 129.00, 128.50, 127.96, 127.83, 126.99, 122.01, 121.38, 117.19, 116.58, 99.95, 36.77, 29.55, 27.92, 25.01, 21.03.

HRMS (ESI): exact mass calcd for C₂₁H₁₇BrO₃: *m/z* 419.0259 [M+Na]⁺, found: *m/z* 419.0261.

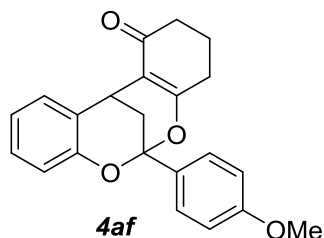


Following the **general procedure A**, compound **4ae** was isolated as white solid in 88% yield (29.3 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.58-7.53 (m, 2H), 7.40 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.92 (td, *J* = 7.4, 1.2 Hz, 1H), 4.22 (t, *J* = 3.0 Hz, 1H), 2.59-2.46 (m, 2H), 2.44-2.37 (m, 1H, overlapped), 2.40(s, 3H, overlapped), 2.36-2.28 (m, 1H), 2.24 (dd, *J* = 13.4, 2.9 Hz, 1H), 2.16 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.05-1.92 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.39, 169.56, 151.90, 139.31, 137.69, 129.40, 128.52, 127.89, 126.93, 125.82, 121.81, 116.87, 116.32, 100.06, 36.79, 33.30, 28.19, 25.60, 21.54, 21.09.

HRMS (ESI): exact mass calcd for C₂₂H₂₀O₃: *m/z* 333.1490 [M+H]⁺, found: *m/z* 333.1487.

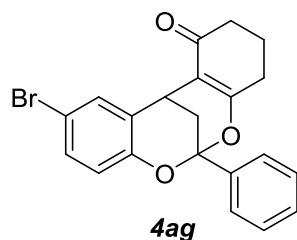


Following the **general procedure A**, compound **4af** was isolated as white solid in 95% yield (33.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.62-7.56 (m, 2H), 7.40 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.92 (td, *J* = 7.4, 1.2 Hz, 1H), 4.22 (t, *J* = 3.1 Hz, 1H), 3.85 (s, 3H), 2.58-2.45 (m, 2H), 2.44-2.27 (m, 2H), 2.23 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.16 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.05-1.91 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.36, 169.53, 160.42, 151.90, 132.81, 128.51, 127.88, 127.27, 126.92, 121.81, 116.86, 116.29, 114.02, 100.01, 55.70, 36.78, 33.35, 28.18, 25.65, 21.08.

HRMS (ESI): exact mass calcd for C₂₂H₂₀O₄: *m/z* 349.1440 [M+H]⁺, found: *m/z* 349.1440.

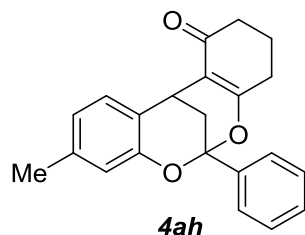


Following the **general procedure A**, compound **4ag** was isolated as white solid in 49% yield (19.5 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.66-7.61 (m, 2H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.26-7.22 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.19 (t, *J* = 3.1 Hz, 1H), 2.60-2.47 (m, 2H), 2.45-2.31 (m, 2H), 2.21 (dd, *J* = 13.5, 2.9 Hz, 1H), 2.17 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.06-1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.09, 169.51, 151.07, 140.10, 131.05, 130.85, 129.58, 128.96, 128.82, 125.85, 118.10, 116.38, 114.11, 100.00, 36.74, 32.96, 28.14, 25.46, 21.05.

HRMS (ESI): exact mass calcd for C₂₁H₁₇BrO₃: *m/z* 397.0439 [M+H]⁺, found: *m/z* 397.0436.

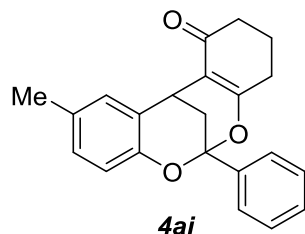


Following the **general procedure A**, compound **4ah** was isolated as white solid in 82% yield (27.3 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.69-7.64 (m, 2H), 7.48-7.40 (m, 3H), 7.29 (d, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 6.77-6.72 (m, 1H), 4.20 (t, *J* = 2.6 Hz, 1H), 2.59-2.45 (m, 2H), 2.44-2.37 (m, 1H), 2.36-2.28 (m, 1H), 2.30 (s, 3H), 2.22 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.15 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.05-1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.37, 169.37, 151.67, 140.66, 138.03, 129.36, 128.73, 128.23, 125.93, 123.97, 122.66, 117.14, 116.81, 100.00, 36.79, 33.60, 28.17, 25.22, 21.50, 21.09.

HRMS (ESI): exact mass calcd for C₂₂H₂₀O₃: *m/z* 333.1490 [M+H]⁺, found: *m/z* 333.1488.

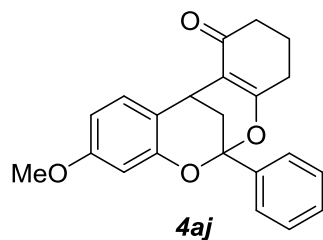


Following the **general procedure A**, compound **4ai** was isolated as white solid in 82% yield (27.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.48-7.39 (m, 3H), 7.22 (s, 1H), 6.99-6.89 (m, 2H), 4.21-4.16 (m, 1H), 2.60-2.46 (m, 2H), 2.45-2.30 (m, 2H), 2.28 (s, 3H), 2.26-2.11 (m, 2H), 2.06-1.94 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.38, 169.56, 149.61, 140.65, 131.23, 129.34, 128.87, 128.71, 128.48, 126.57, 125.91, 116.91, 116.02, 100.01, 36.82, 33.48, 28.19, 25.53, 21.08, 20.85.

HRMS (ESI): exact mass calcd for C₂₂H₂₀O₃: *m/z* 333.1490 [M+H]⁺, found: *m/z* 333.1487.

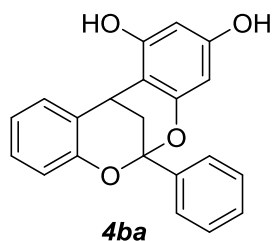


Following the **general procedure A**, compound **4aj** was isolated as white solid in 99% yield (34.4 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.68-7.64 (m, 2H), 7.48-7.40 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.18 (t, *J* = 3.1 Hz, 1H), 3.76 (s, 3H), 2.59-2.46 (m, 2H), 2.44-2.29 (m, 2H), 2.24 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.15 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.05-1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 196.37, 169.17, 159.66, 152.63, 140.57, 129.39, 128.86, 128.74, 125.90, 119.31, 117.37, 107.97, 101.98, 99.97, 55.72, 36.78, 33.69, 28.11, 24.90, 21.09.

HRMS (ESI): exact mass calcd for C₂₂H₂₀O₄: *m/z* 349.1440 [M+H]⁺, found: *m/z* 349.1438.

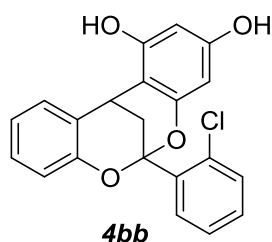


Following the **general procedure B**, compound **4ba** was isolated as brown oil in 80% yield (26.6 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.66 (s, 1H), 8.19 (s, 1H), 7.82-7.75 (m, 2H), 7.55-7.43 (m, 4H), 7.18-7.12 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.95-6.88 (m, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 4.48 (t, *J* = 3.1 Hz, 1H), 2.40-2.31 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.74, 156.33, 155.03, 154.00, 143.87, 130.13, 129.80, 129.56, 129.37, 128.91, 127.36, 122.47, 117.48, 107.46, 100.22, 97.60, 96.63, 34.89, 28.28.

HRMS (ESI): exact mass calcd for C₂₁H₁₆O₄: *m/z* 331.0971 [M-H]⁺, found: *m/z* 331.0969.

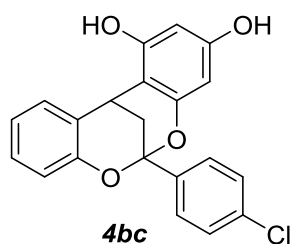


Following the **general procedure B**, compound **4bb** was isolated as brown oil in 81% yield (29.8 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.64 (s, 1H), 8.17 (s, 1H), 8.15 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.58-7.43 (m, 4H), 7.20-7.13 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.97-6.90 (m, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 4.51 (t, *J* = 3.1 Hz, 1H), 2.57 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.53 (dd, *J* = 13.2, 3.2 Hz, 1H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.78, 156.27, 154.49, 153.60, 139.88, 133.93, 133.14, 131.90, 130.27, 129.51, 129.34, 128.98, 128.65, 122.57, 117.68, 107.57, 100.04, 97.71, 96.74, 31.19, 27.82.

HRMS (ESI): exact mass calcd for C₂₁H₁₅ClO₄: *m/z* 365.0581 [M-H]⁺, found: *m/z* 365.0583.

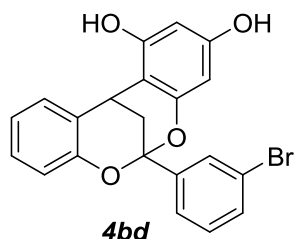


Following the **general procedure B**, compound **4bc** was isolated as brown oil in 63% yield (23.1 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.66 (s, 1H), 8.19 (s, 1H), 7.83-7.78 (m, 2H), 7.57-7.52 (m, 2H), 7.47 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.19-7.11 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.95-6.90 (m, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 4.49 (t, *J* = 3.1 Hz, 1H), 2.39-2.32 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.77, 156.33, 154.82, 153.79, 142.78, 135.62, 129.90, 129.44, 129.38, 129.33, 128.96, 122.62, 117.49, 107.37, 99.91, 97.71, 96.62, 34.66, 28.18.

HRMS (ESI): exact mass calcd for C₂₁H₁₅ClO₄: *m/z* 365.0581 [M-H]⁺, found: *m/z* 365.0579.

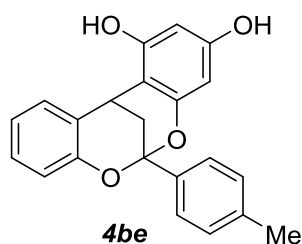


Following the **general procedure B**, compound **4bd** was isolated as brown oil in 66% yield (27.2 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.66 (s, 1H), 8.19 (s, 1H), 8.02-7.93 (m, 1H), 7.83-7.76 (m, 1H), 7.69-7.61 (m, 1H), 7.51-7.45 (m, 2H), 7.20-7.12 (m, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.98-6.88 (m, 1H), 6.11 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 4.50 (t, *J* = 3.1 Hz, 1H), 2.44-2.34 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.79, 156.32, 154.74, 153.72, 146.31, 133.24, 131.95, 130.54, 129.43, 129.39, 128.99, 126.51, 123.42, 122.69, 117.52, 107.37, 99.67, 97.77, 96.64, 34.57, 28.15.

HRMS (ESI): exact mass calcd for C₂₁H₁₅BrO₄: *m/z* 409.0076 [M-H]⁺, found: *m/z* 409.0072.

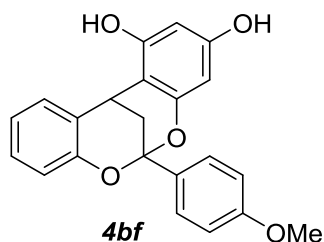


Following the **general procedure B**, compound **4be** was isolated as brown oil in 68% yield (23.6 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.60 (s, 1H), 8.14 (s, 1H), 7.71-7.62 (m, 2H), 7.46 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.17-7.11 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.94-6.88 (m, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 4.47 (t, *J* = 3.1 Hz, 1H), 2.42 (s, 3H), 2.37-2.30 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.72, 156.31, 155.11, 154.06, 141.06, 139.76, 130.37, 129.59, 129.36, 128.88, 127.30, 122.40, 117.47, 107.50, 100.25, 97.55, 96.64, 34.94, 28.32, 21.91.

HRMS (ESI): exact mass calcd for C₂₂H₁₈O₄: *m/z* 345.1972 [M-H]⁺, found: *m/z* 345.1968.

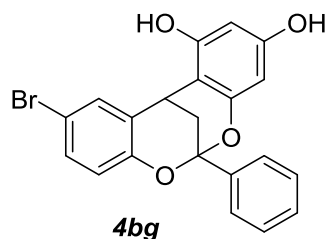


Following the **general procedure B**, compound **4bf** was isolated as brown oil in 71% yield (25.7 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.61 (s, 1H), 8.15 (s, 1H), 7.74-7.67 (m, 2H), 7.46 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.17-7.10 (m, 2H), 7.08-7.01 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.94-6.87 (m, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.06 (d, *J* = 2.3 Hz, 1H), 4.47 (t, *J* = 3.1 Hz, 1H), 3.88 (s, 3H), 2.39-2.28 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 161.61, 158.70, 156.30, 155.13, 154.08, 136.04, 129.58, 129.35, 128.86, 128.67, 122.37, 117.46, 115.04, 107.49, 100.20, 97.52, 96.62, 56.39, 34.96, 28.38.

HRMS (ESI): exact mass calcd for C₂₂H₁₈O₅: *m/z* 361.1076 [M-H]⁺, found: *m/z* 361.1079.

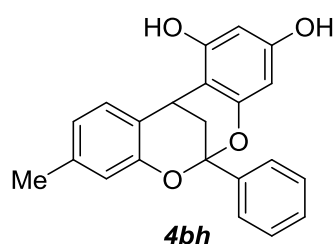


Following the **general procedure B**, compound **4bg** was isolated as brown oil in 78% yield (32.1 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.76 (s, 1H), 8.25 (s, 1H), 7.81-7.74 (m, 2H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.56-7.42 (m, 3H), 7.30 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.13 (d, *J* = 2.3 Hz, 1H), 6.09 (d, *J* = 2.2 Hz, 1H), 4.48 (t, *J* = 3.1 Hz, 1H), 2.42-2.35 (m, 2H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 159.02, 156.32, 154.86, 153.43, 143.34, 132.05, 131.68, 131.62, 130.28, 129.85, 127.32, 119.64, 113.99, 106.68, 100.46, 97.74, 96.73, 34.30, 28.19.

HRMS (ESI): exact mass calcd for C₂₁H₁₅BrO₄: *m/z* 409.0076 [M-H]⁻, found: *m/z* 409.0079.

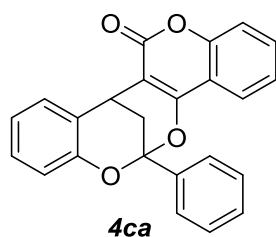


Following the **general procedure B**, compound **4bh** was isolated as brown oil in 50% yield (17.4 mg).

¹H NMR (500 MHz, acetone-*d*₆): δ 8.63 (s, 1H), 8.17 (s, 1H), 7.81-7.75 (m, 2H), 7.54-7.43 (m, 3H), 7.28 (d, *J* = 2.1 Hz, 1H), 6.95 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 4.43 (t, *J* = 3.1 Hz, 1H), 2.36-2.29 (m, 2H), 2.27 (s, 3H).

¹³C NMR (126 MHz, acetone-*d*₆): δ 158.68, 156.24, 155.14, 151.77, 143.98, 131.41, 130.07, 129.77, 129.71, 129.39, 129.19, 127.35, 117.24, 107.56, 100.14, 97.54, 96.61, 34.99, 28.26, 21.40.

HRMS (ESI): exact mass calcd for C₂₂H₁₈O₄: *m/z* 345.1972 [M-H]⁻, found: *m/z* 345.1971.

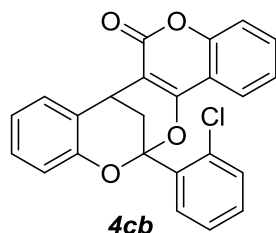


Following the **general procedure A**, compound **4ca** was isolated as white solid in 75% yield (27.5 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.88 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.82-7.72 (m, 2H), 7.57-7.46 (m, 5H), 7.33-7.25 (m, 2H), 7.23-7.18 (m, 1H), 7.07 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.02-6.96 (m, 1H), 4.40 (t, *J* = 3.0 Hz, 1H), 2.50-2.40 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 161.89, 158.57, 152.75, 151.66, 140.05, 132.33, 129.75, 128.97, 128.70, 128.55, 126.00, 125.48, 124.40, 123.10, 122.45, 117.03, 116.69, 115.43, 106.38, 100.62, 33.29, 27.53.

HRMS (ESI): exact mass calcd for C₂₄H₁₆O₄: *m/z* 369.1127 [M+H]⁺, found: *m/z* 369.1127.

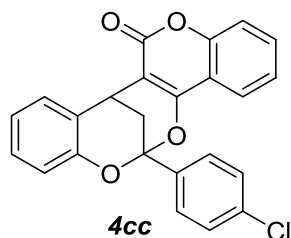


Following the **general procedure A**, compound **4cb** was isolated as white solid in 22% yield (8.9 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.13-8.09 (m, 1H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.53-7.49 (m, 2H), 7.47-7.40 (m, 2H), 7.31 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.28-7.25 (m, 1H, overlapped), 7.24-7.20 (m, 1H), 7.08 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.02-6.98 (m, 1H), 4.42 (t, *J* = 3.0 Hz, 1H), 2.79 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.54 (dd, *J* = 13.6, 2.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 161.90, 158.24, 152.80, 151.18, 136.40, 132.91, 132.29, 132.23, 131.08, 128.80, 128.75, 128.56, 127.39, 125.64, 124.40, 123.32, 122.58, 117.03, 116.84, 115.33, 106.59, 100.24, 29.61, 26.99.

HRMS (ESI): exact mass calcd for C₂₄H₁₅ClO₄: *m/z* 403.0737 [M+H]⁺, found: *m/z* 403.0736.

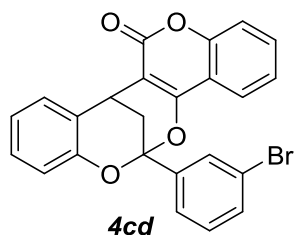


Following the **general procedure A**, compound **4cc** was isolated as white solid in 42% yield (17.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.84 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.73-7.68 (m, 2H), 7.57-7.47 (m, 4H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.23-7.18 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.02-6.98 (m, 1H), 4.40 (t, *J* = 3.0 Hz, 1H), 2.47-2.38 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 161.77, 158.37, 152.74, 151.46, 138.64, 135.84, 132.43, 129.20, 128.78, 128.59, 127.56, 125.33, 124.46, 122.99, 122.63, 117.09, 116.65, 115.29, 106.40, 100.25, 33.20, 27.46.

HRMS (ESI): exact mass calcd for C₂₄H₁₅ClO₄: *m/z* 403.0737 [M+H]⁺, found: *m/z* 403.0733.

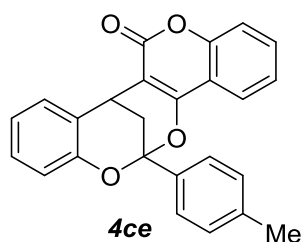


Following the **general procedure A**, compound **4cd** was isolated as white solid in 16% yield (7.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.12 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.56-7.48 (m, 3H), 7.36-7.30 (m, 2H), 7.29-7.25 (m, 1H, overlapped), 7.24-7.20 (m, 1H), 7.08 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.02-6.98 (m, 1H), 4.42 (t, *J* = 3.0 Hz, 1H), 2.84 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.54 (dd, *J* = 13.6, 2.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 161.90, 158.28, 152.80, 151.19, 137.80, 135.81, 132.29, 131.25, 129.05, 128.74, 128.53, 127.99, 125.65, 124.39, 123.49, 122.58, 121.47, 117.03, 116.91, 115.30, 106.63, 100.58, 29.57, 26.96.

HRMS (ESI): exact mass calcd for C₂₄H₁₅BrO₄: m/z 447.0232 [M+H]⁺, found: m/z 447.0228.

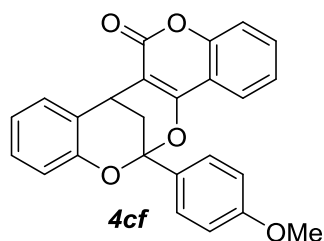


Following the **general procedure A**, compound **4ce** was isolated as white solid in 76% yield (29.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.87 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.68-7.63 (m, 2H), 7.55 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.53-7.48 (m, 1H), 7.34-7.29 (m, 3H), 7.28-7.24 (m, 1H, overlapped), 7.22-7.17 (m, 1H), 7.06 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.01-6.96 (m, 1H), 4.40 (t, *J* = 3.0 Hz, 1H), 2.49-2.40 (m, 5H).

¹³C NMR (126 MHz, CDCl₃): δ 161.91, 158.62, 152.73, 151.71, 139.70, 137.18, 132.28, 129.60, 128.64, 128.53, 125.90, 125.50, 124.35, 123.11, 122.37, 117.00, 116.69, 115.45, 106.34, 100.69, 33.25, 27.56, 21.59.

HRMS (ESI): exact mass calcd for C₂₅H₁₈O₄: m/z 383.1283 [M+H]⁺, found: m/z 383.1286.

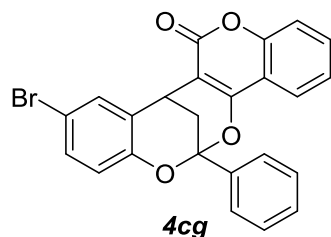


Following the **general procedure A**, compound **4cf** was isolated as white solid in 85% yield (33.8 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.86 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.72-7.67 (m, 2H), 7.55 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.52-7.47 (m, 1H), 7.30 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.27-7.23 (m, 1H, overlapped), 7.22-7.17 (m, 1H), 7.07-6.96 (m, 4H), 4.39 (t, *J* = 3.0 Hz, 1H), 3.88 (s, 3H), 2.49-2.39 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 161.88, 160.67, 158.61, 152.72, 151.71, 132.26, 128.63, 128.52, 127.36, 125.50, 124.34, 123.08, 122.36, 116.99, 116.66, 115.44, 114.22, 106.33, 100.65, 55.74, 33.30, 27.62.

HRMS (ESI): exact mass calcd for C₂₅H₁₈O₅: m/z 399.1232 [M+H]⁺, found: m/z 399.1234.

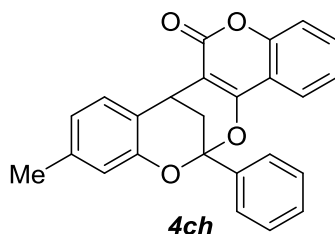


Following the **general procedure A**, compound **4cg** was isolated as white solid in 47% yield (21.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.76-7.70 (m, 2H), 7.70-7.65 (m, 1H), 7.56-7.47 (m, 4H), 7.33-7.25 (m, 3H, overlapped), 6.93 (d, *J* = 8.6 Hz, 1H), 4.36 (t, *J* = 2.9 Hz, 1H), 2.45-2.40 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 161.65, 158.61, 152.77, 150.85, 139.56, 132.54, 131.58, 130.97, 129.90, 129.02, 127.49, 125.90, 124.48, 123.08, 118.43, 117.09, 115.19, 114.61, 105.75, 100.58, 32.89, 27.36.

HRMS (ESI): exact mass calcd for C₂₄H₁₅BrO₄: m/z 447.0232 [M+H]⁺, found: m/z 447.0230.

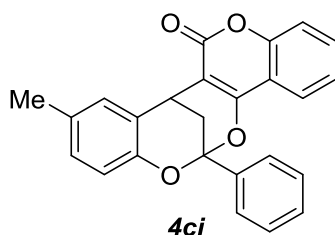


Following the **general procedure A**, compound **4ch** was isolated as white solid in 58% yield (22.1 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78-7.74 (m, 2H), 7.54-7.46 (m, 4H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.32-7.24 (m, 2H, overlapped), 6.90 (s, 1H), 6.82 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.37 (t, *J* = 3.0 Hz, 1H), 2.48-2.39 (m, 2H), 2.31 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 161.91, 158.50, 152.72, 151.48, 140.16, 138.91, 132.26, 129.70, 128.94, 128.23, 126.00, 124.36, 123.22, 123.07, 122.56, 117.17, 117.00, 115.48, 106.63, 100.61, 33.52, 27.20, 21.52.

HRMS (ESI): exact mass calcd for C₂₅H₁₈O₄: m/z 383.1283 [M+H]⁺, found: m/z 383.1284.

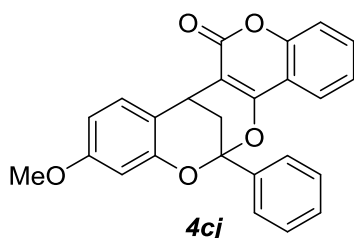


Following the **general procedure A**, compound **4ci** was isolated as white solid in 58% yield (22.0 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.79-7.72 (m, 2H), 7.54-7.45 (m, 4H), 7.36 (s, 1H), 7.33-7.24 (m, 2H), 7.03-6.93 (m, 2H), 4.35 (t, *J* = 3.8 Hz, 1H), 2.48-2.37 (m, 2H), 2.31 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 161.93, 158.66, 152.74, 149.41, 140.17, 132.28, 131.93, 129.69, 129.25, 128.94, 128.83, 126.00, 125.16, 124.37, 123.11, 117.00, 116.43, 115.48, 106.42, 100.66, 33.41, 27.53, 20.85.

HRMS (ESI): exact mass calcd for C₂₅H₁₈O₄: m/z 383.1283 [M+H]⁺, found: m/z 383.1281.



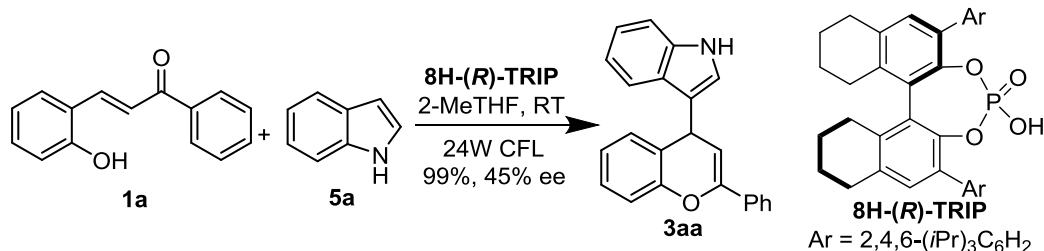
Following the **general procedure A**, compound **4cj** was isolated as white solid in 33% yield (13.2 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80-7.74 (m, 2H), 7.56-7.46 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.33-7.24 (m, 2H, overlapped), 6.63 (d, *J* = 2.5 Hz, 1H), 6.56 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.35 (t, *J* = 3.0 Hz, 1H), 3.76 (s, 3H), 2.50-2.38 (m, 2H).

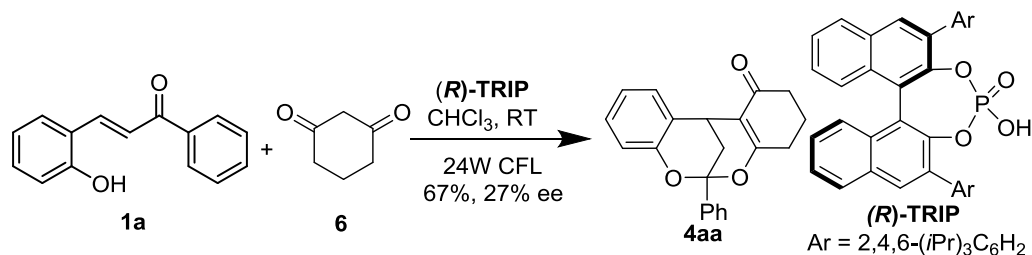
¹³C NMR (126 MHz, CDCl₃): δ 161.91, 160.20, 158.30, 152.71, 152.48, 140.06, 132.24, 129.73, 128.96, 128.92, 125.98, 124.37, 123.04, 117.82, 117.01, 115.45, 108.55, 106.84, 102.33, 100.57, 55.80, 33.62, 26.88.

HRMS (ESI): exact mass calcd for C₂₅H₁₈O₅: m/z 399.1232 [M+H]⁺, found: m/z 399.1230.

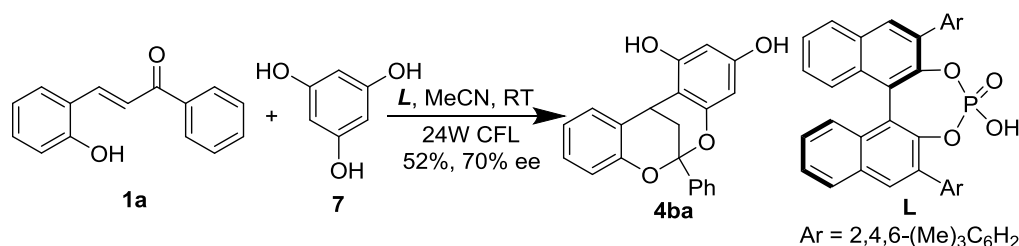
5. Chiral Phosphoric Acid Catalyzed Enantioselective Coupling of 2-Hydroxychalcone.



2-Hydroxychalcone (0.1 mmol, 22.4 mg), indole (0.12 mmol, 14.1 mg), **8H-(R)-TRIP** (10 mol%, 7.6 mg) and 2-methyltetrahydrofuran (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxychalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 15) to afford **3aa** in 99% yield (31.9 mg). Enantiomeric excess was found to be 45% by chiral HPLC (ChiralPak OD column, hexane/*i*-PrOH = 85: 15, 210 nm, 1.0 mL/min, $t_{\text{major}} = 11.49$ min, $t_{\text{minor}} = 13.79$ min).



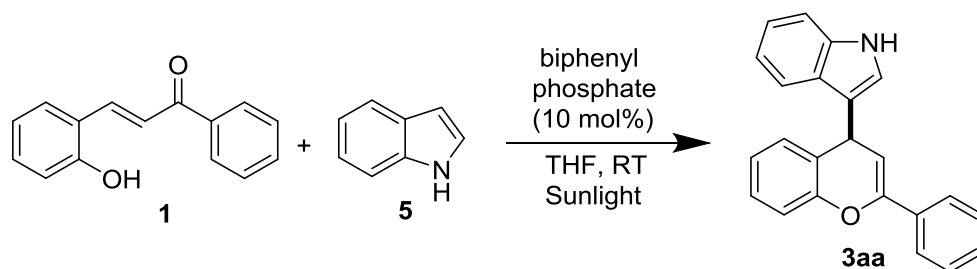
2-Hydroxychalcone (0.1 mmol, 22.4 mg), 1, 3-cyclohexanedione (0.12 mmol, 13.5 mg), **(R)-TRIP** (10 mol%, 7.5 mg) and chloroform (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxychalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 8) to afford **4aa** in 67% yield (21.3 mg). Enantiomeric excess was found to be 27% by chiral HPLC (ChiralPak IC column, hexane/*i*-PrOH = 8: 2, 214 nm, 1.0 mL/min, $t_{\text{major}} = 11.34$ min, $t_{\text{minor}} = 12.16$ min).



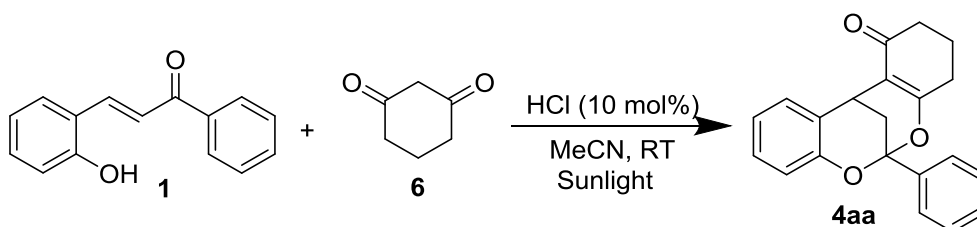
2-Hydroxychalcone (0.1 mmol, 22.4 mg), phloroglucinol (0.12 mmol, 15.1 mg), chiral phosphoric acid **L** (10 mol%, 5.8 mg) and acetonitrile (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred under the irradiation of 24W CFL at room temperature under argon overnight and monitored by TLC. After 2-hydroxychalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (Acetone/DCM = 1: 20) to afford **4ba** in 52% yield (17.3 mg).

Enantiomeric excess was found to be 70% by chiral HPLC (ChiralPak IC column, hexane/i-PrOH = 95:5, 214 nm, 1.0 mL/min, $t_{\text{major}} = 12.26$ min, $t_{\text{minor}} = 31.06$ min).

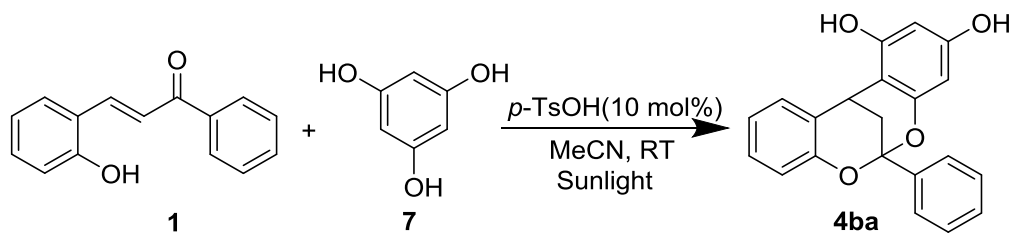
6. Sunlight powered reactions



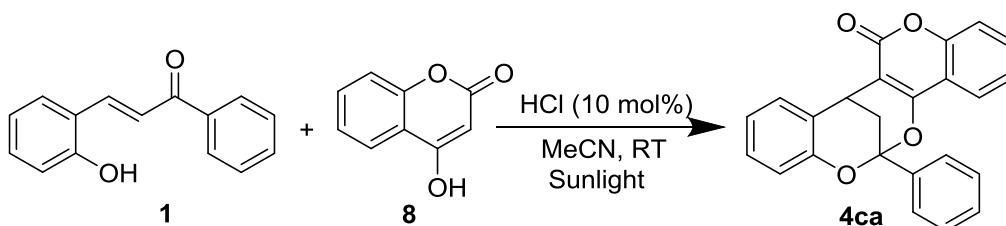
2-Hydroxylchalcone (0.1 mmol, 22.4 mg), indole (0.12 mmol, 14.1 mg), biphenyl phosphate (0.01 mmol, 2.5 mg) and THF (3.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was exposed to sunlight and stirred under air and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 15) to yield **3aa** in 94% yield (30.4 mg).



To a reaction tube equipped with a magnetic stir bar was added 2-hydroxylchalcone (0.1 mmol, 22.4 mg), 1, 3-cyclohexanedione (0.12 mmol, 13.5 mg), HCl (0.01 mmol, 1M) and acetonitrile (3.0 mL). The mixture exposed to sunlight and stirred under air and monitored by TLC.. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 8) to yield **4aa** in 91% yield (28.9 mg).



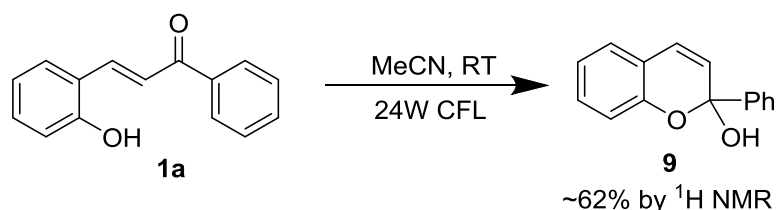
To a reaction tube equipped with a magnetic stir bar was added 2-hydroxylchalcone (0.1 mmol, 22.4 mg), phloroglucinol (0.12 mmol, 15.1 mg), HOTs (0.01 mmol, 1.7 mg) and acetonitrile (3.0 mL). The mixture was exposed to sunlight and stirred under air and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (Acetone/DCM = 1: 20) to yield **4ba** in 69% yield (23.0 mg).



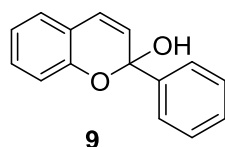
To a reaction tube equipped with a magnetic stir bar was added 2-hydroxylchalcone (0.1 mmol, 22.4 mg), 4-hydroxycoumarin (0.12 mmol, 19.5 mg), HCl (0.01 mmol, 1M) and acetonitrile (3.0 mL). The mixture was exposed to sunlight and stirred under air and monitored by TLC. After 2-hydroxylchalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 8) to yield **4ca** in 66% yield (24.3 mg).

7. Mechanistic Studies

The Synthesis of Flav-3-en-2-ol (**9**)



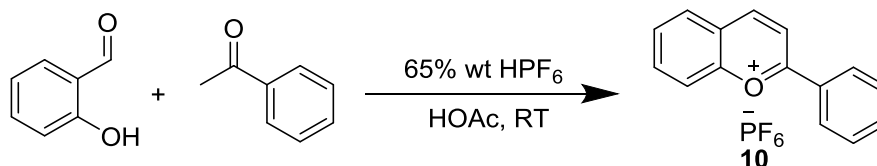
2-Hydroxychalcone (0.1 mmol, 22.4 mg) and acetonitrile (1.0 mL) were added to a reaction tube equipped with a magnetic stir bar. The mixture was stirred under the irradiation of 24W CFL at room temperature under argon for 24h and monitored by TLC. After the 2-hydroxychalcone was consumed completely, the solvent was removed by rotary evaporator. The residue was flav-3-en-2-ol (**9**) in 62% yield by ^1H NMR through adding dimethyl sulfoxide as the interior label.



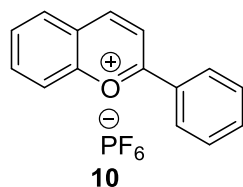
The spectrum data of **9** were consistent with the reference^[3].

^1H NMR (500 MHz, CD_3CN): δ 7.62 (d, J = 7.0 Hz, 2H), 7.47-7.36 (m, 3H), 7.31-7.25 (m, 2H), 7.02 (t, J = 7.1 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.74 (d, J = 9.5 Hz, 1H), 5.89 (d, J = 9.6 Hz, 1H), 5.09 (s, 1H).

The Synthesis of Benzopyrylium Salts^[4]



To a solution of 2-hydroxybenzaldehyde (5 mmol, 0.5 mL) and acetophenone (5 mmol, 0.6 mL) in a minimum of acetic acid was added excess of aqueous hexafluorophosphoric acid (5.61 g, 65 % in water). After stirred for 48h at room temperature under argon, the mixture was pluned into diethyl ether (20 mL per mmol). The resulting powder was collected through filtration and washed with diethyl ether to afford the desired benzopyrylium salt **10** in 59% yield (1.04 g).

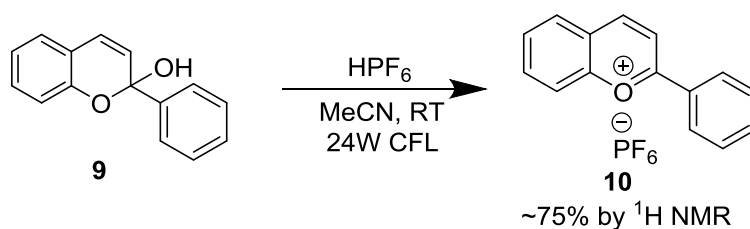


The spectrum data of **10** were consistent with the reference^[5].

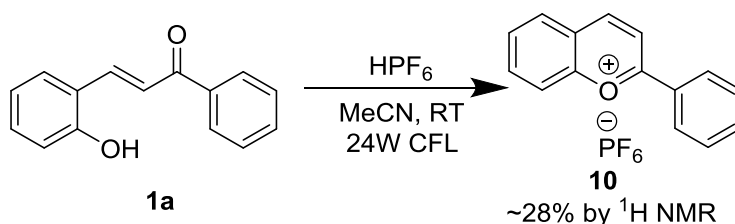
^1H NMR (500 MHz, CD_3CN): δ 9.51 (d, J = 8.9 Hz, 1H), 8.74 (d, J = 8.9 Hz, 1H), 8.62-8.56 (m, 2H), 8.44-8.37 (m, 3H), 8.09-8.03 (m, 1H), 7.99 (t, J = 7.5 Hz, 1H), 7.84 (t, J = 7.9 Hz, 2H).

^{13}C NMR (126 MHz, CD_3CN): δ 177.06, 159.05, 157.86, 141.43, 138.93, 131.86, 131.79, 131.61, 131.46, 129.85, 125.92, 120.49, 119.11.

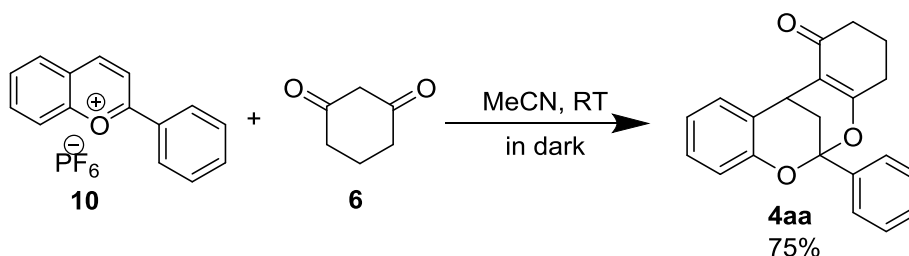
HRMS (ESI): exact mass calcd for $\text{C}_{15}\text{H}_{11}\text{O}^+$: m/z 207.0804 $[\text{M}]^+$, found: m/z 207.0801.



To a solvent of Flav-3-en-2-ol(**9**) (0.1 mmol, 22.4 mg) in acetonitrile (1.0 mL) was added aqueous hexafluorophosphoric acid 65% (0.1 mmol, 23.0 mg) at room temperature under argon, and irradiated by LED bulb. After stirring for 48 h, the solvent was removed by rotary evaporator. The crude was identified directly by the NMR spectrum and contained **10**, and the yield of **10** was confirmed to be 75% through adding dimethyl sulfone as the interior label.



To a solvent of **1a** (0.1 mmol, 22.4 mg) in acetonitrile (1.0 mL) was added aqueous hexafluorophosphoric acid 65% (0.1 mmol, 23.0 mg) at room temperature under argon, and irradiated by LED bulb. After stirring for 48 h, the solvent was removed by rotary evaporator. The crude was identified directly by the NMR spectrum and contained **10**, and the yield of **10** was confirmed to be 28% through adding dimethyl sulfone as the interior label.

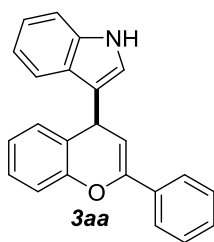


To a reaction tube equipped with a magnetic stir bar was added the benzopyrylium salt (0.12 mmol, 42.2 mg), 1,3-cyclohexanedione (0.1 mmol, 11.2 mg) and acetonitrile (3.0 mL). The mixture was stirred in dark, using aluminium foil to wrap up the reaction flask, at room temperature under argon overnight and monitored by TLC. After 1,3-cyclohexanedione was consumed, the solvent was removed by rotary evaporator. The residue was directly purified by column chromatography on silica gel (EtOAc/petroleum ether = 1: 8) to afford **4aa** in 75% yield (23.9 mg).

8. Reference

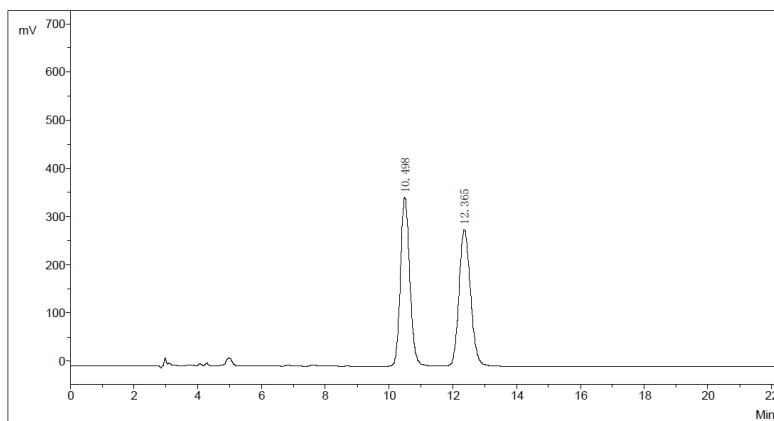
- [1] Rouh H., Liu Y., Katakam N., Pham L. Zhu Y. L..*J. Org. Chem.* **2018**, 83, 15372.
- [2] Ant únez D. J. B., Greenhalgh M. D., FallC., Slawin A. M. Z., Andrew D. Smith A. D..*Org. Biomol. Chem.*.. **2016**, 14, 7268.
- [3] Horiuchi H., Yokawa A., Okutsu T., Hiratsuka H..*Bull. Chem. Soc. Jpn.* **1999**, 71, 2429.
- [4] Yang Z, He Y., Toste F. D.. *J. A. Chem. Soc.* **2016**, 138, 9775.
- [5] Fichtner C., Remennikov G., Mayr H..*Eur. J. Org. Chem.* **2001**, 23, 4451.

9. HPLC Data



HPLC Report

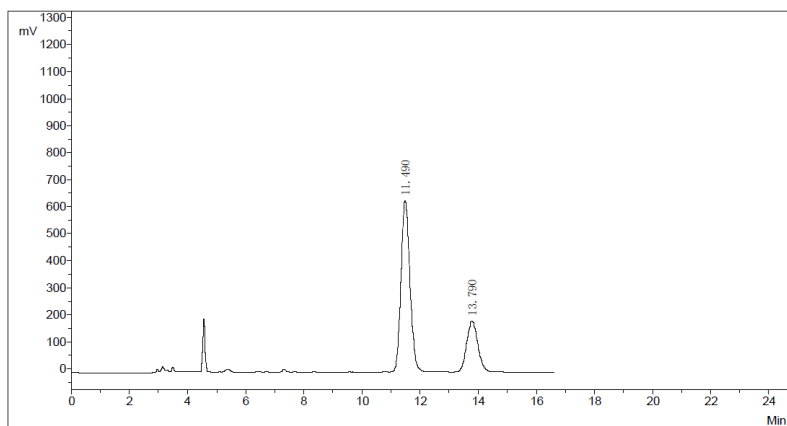
Sample Name: GYQ-I-33-2 OD-H 8515 210 1.0 Recording Time: 2016.05.04 22:46



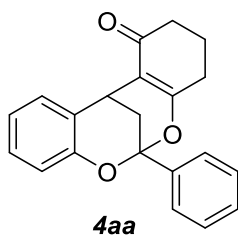
No.	PeakNo	ID. Name	R. Time	PeakHeight	PeakArea	Conc
1	1		10.498	349079.4	7089994.6	50.0990
2	2		12.365	282440.0	7061978.4	49.9010
Total				631519.4	14151973.0	100.0000

HPLC Report

Sample Name: GYQ-I-37-2 OD-H 8515 210 1.0 Recording Time: 2016.05.11 11:11



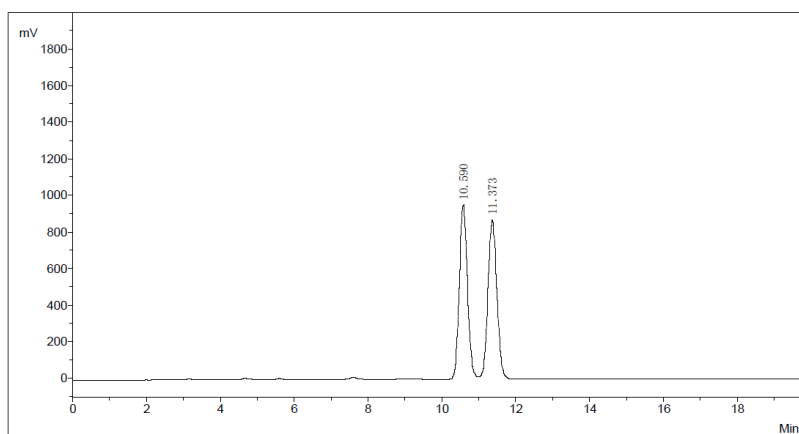
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1	1		11.490	634597.0	13634076.1	72.7437
2	2		13.790	191024.1	5108557.8	27.2563
Total				825621.1	18742634.0	100.0000



HPLC Report

Sample Name:GYQ-II-29 IC 8020 214 1.0

Recording Time:2016.12.03 15:52

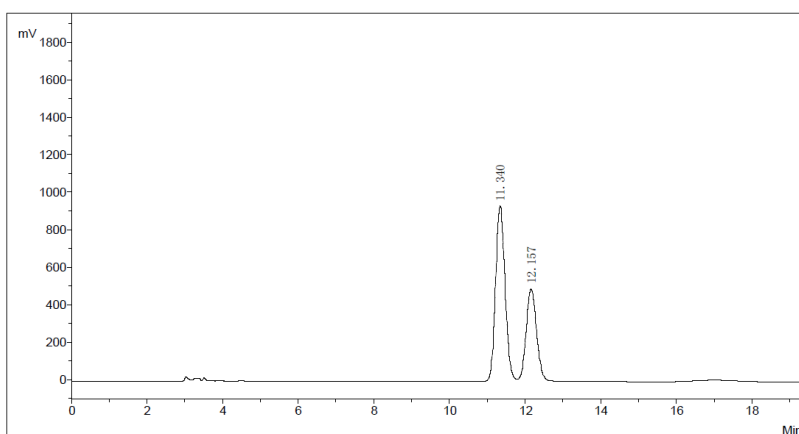


No.	PeakNo	ID. Name	R. Time	PeakHeight	PeakArea	Conc
1	1		10.590	952712.0	14765126.7	50.0107
2	2		11.373	872709.2	14758792.1	49.9893
Total				1825421.2	29523918.8	100.0000

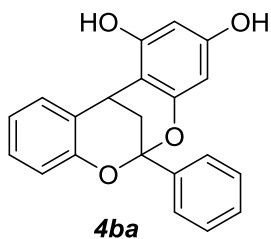
HPLC Report

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Recording Time:2017.12.08 11:10



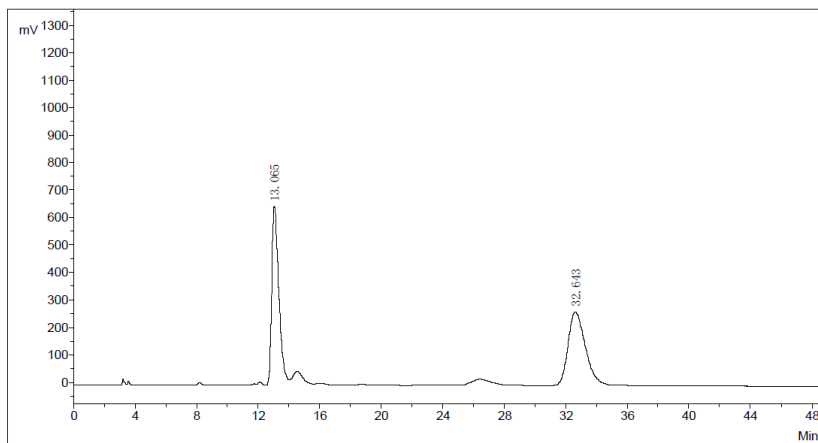
No.	PeakNo	ID. Name	R. Time	PeakHeight	PeakArea	Conc
1	1		11.340	934845.3	16385771.0	63.3001
2	2		12.157	494817.7	9500061.9	36.6999
Total				1429662.9	25885832.9	100.0000



HPLC Report

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Recording Time:2016.05.24 17:36

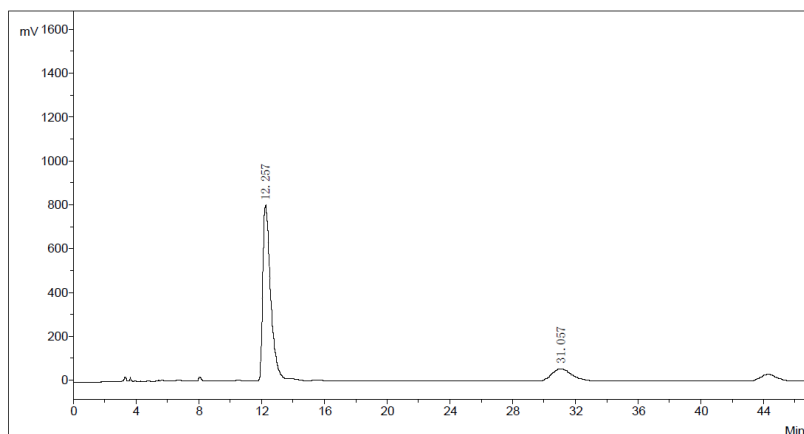


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1	1		13.065	642351.3	19992812.6	50.4016
2	2		32.643	262489.7	19674187.0	49.5984
Total				904840.9	39666999.6	100.0000

HPLC Report

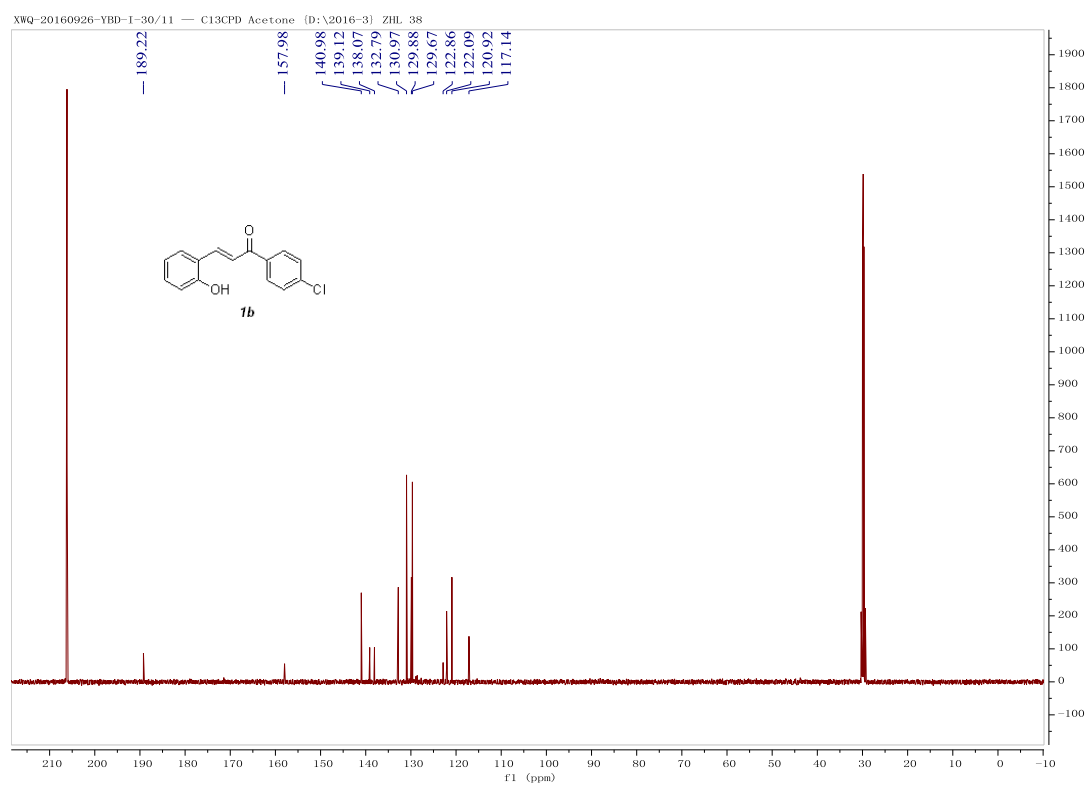
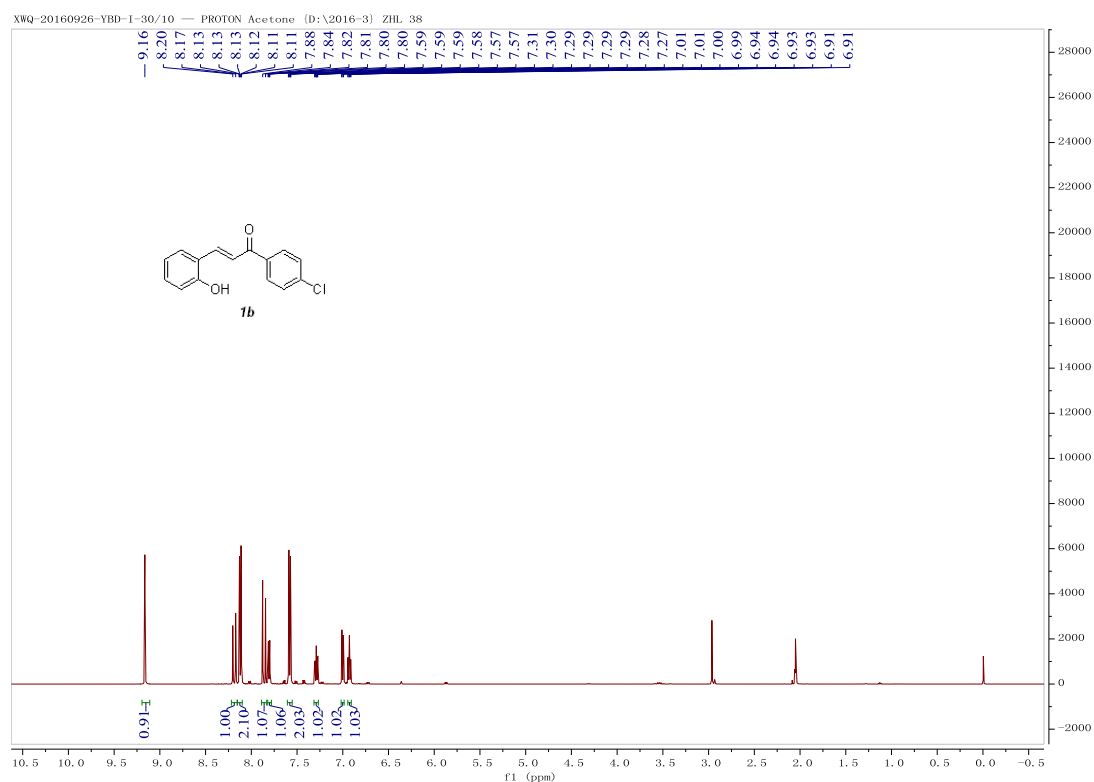
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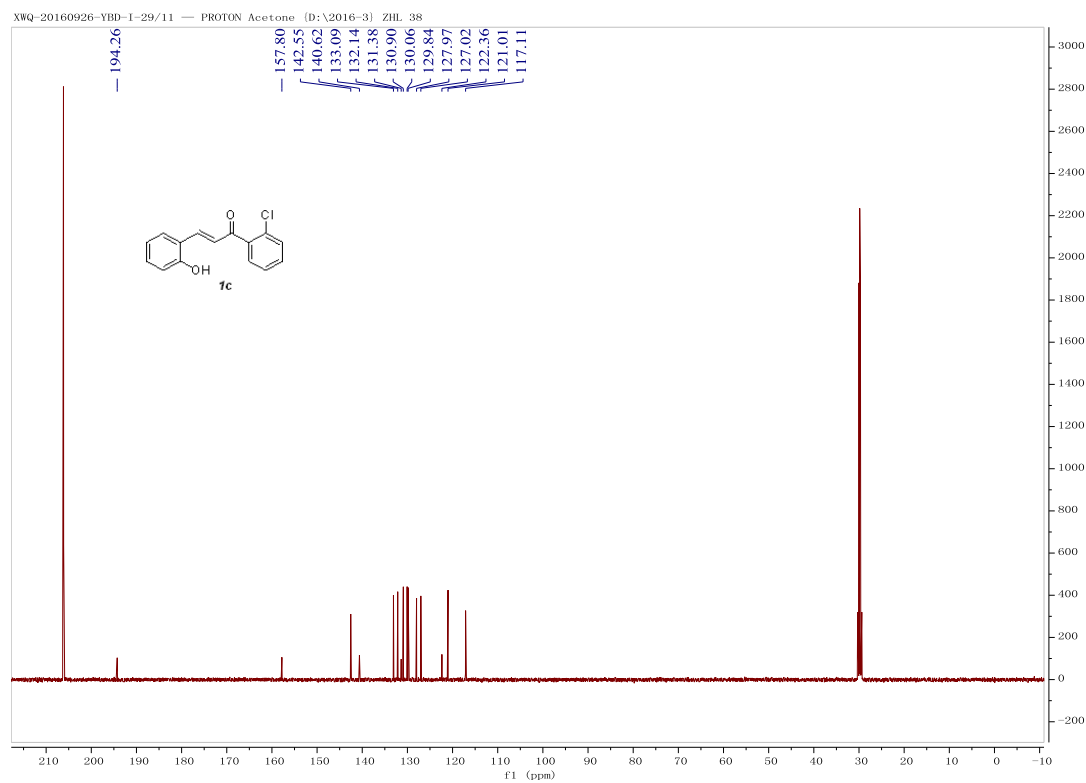
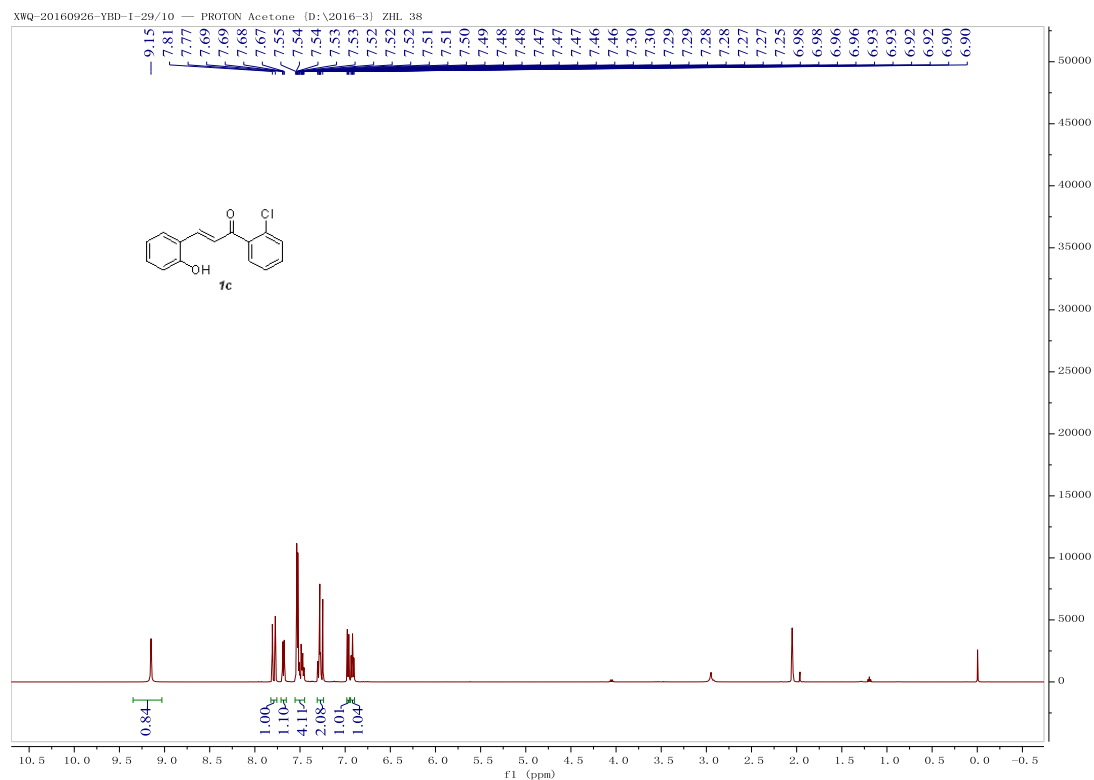
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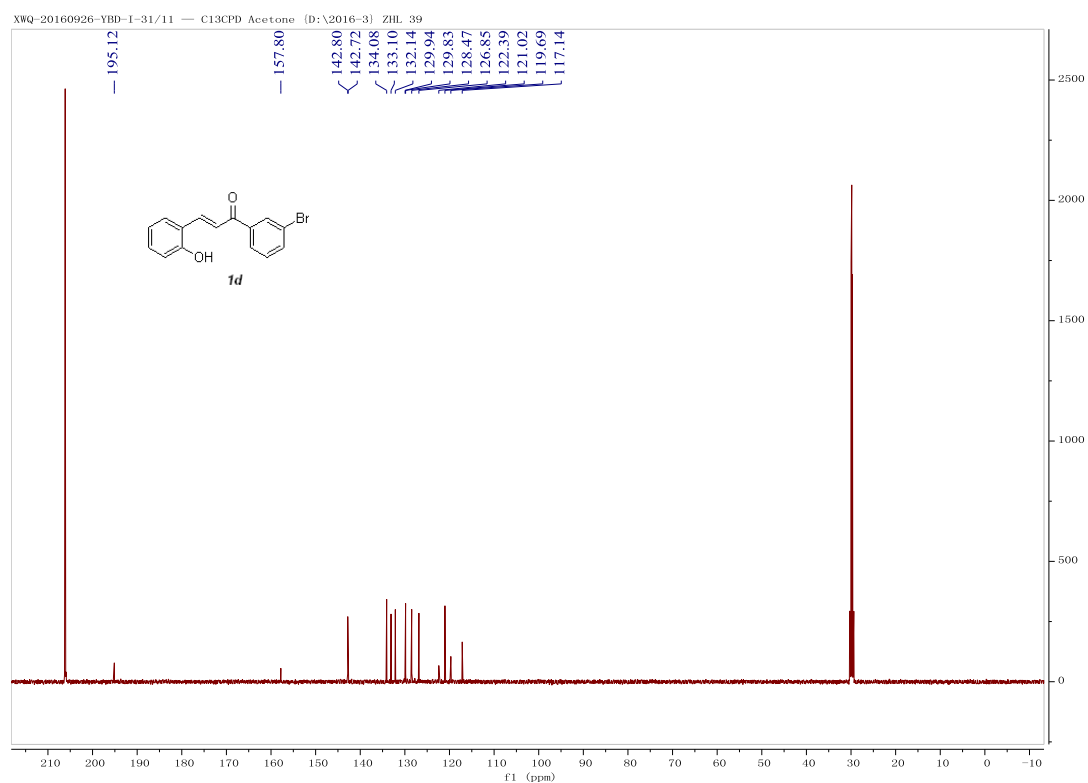
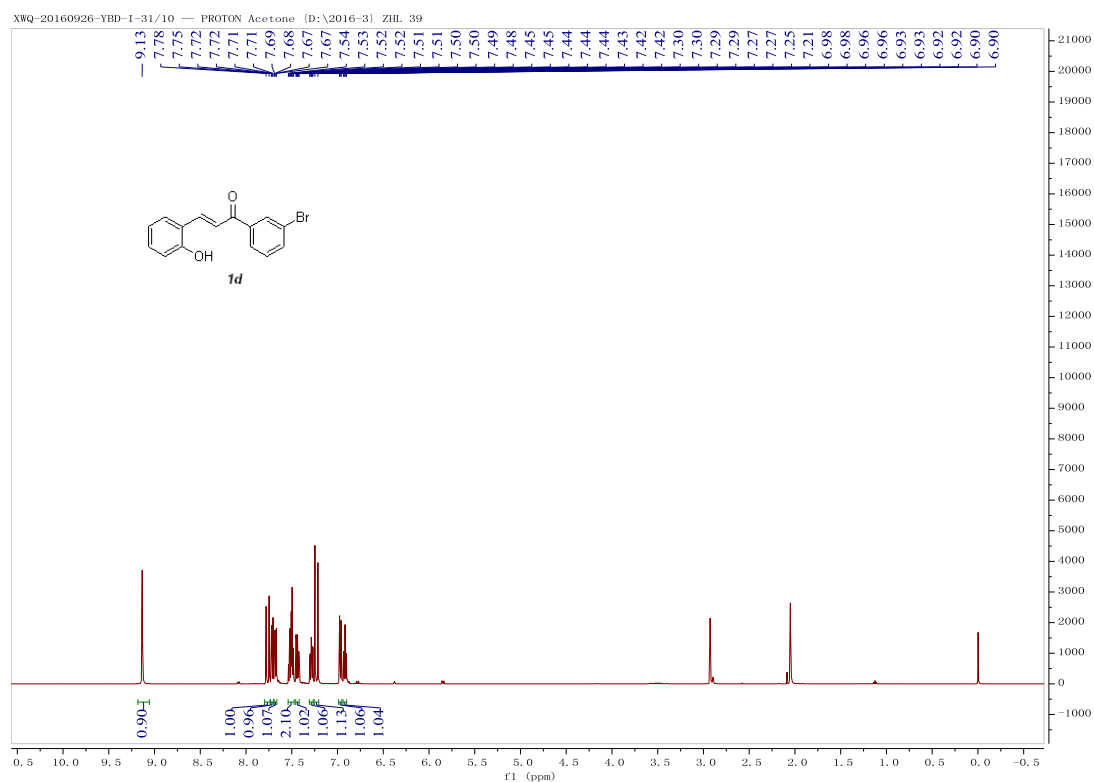


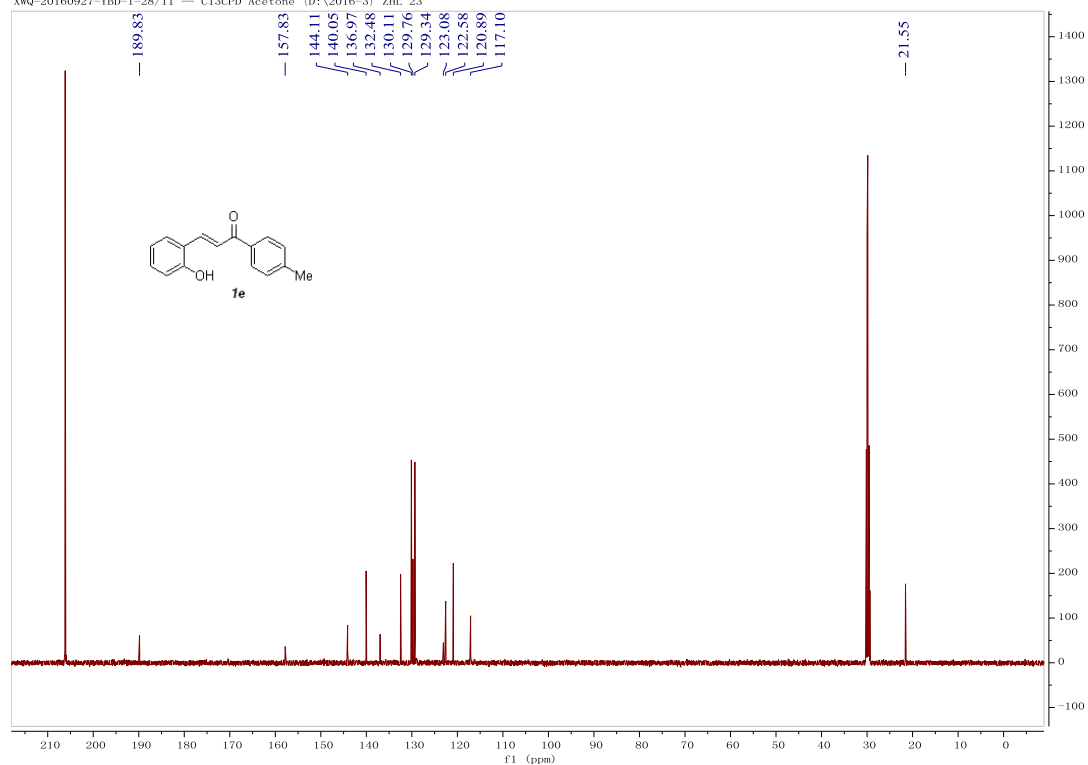
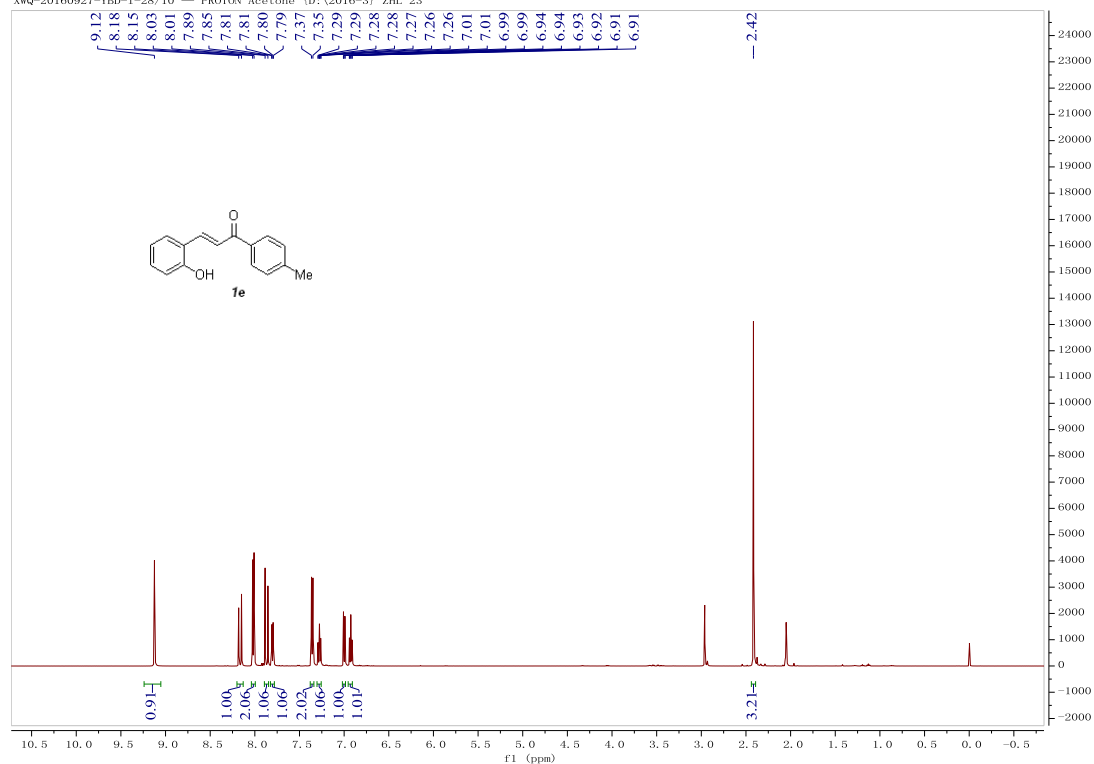
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2	2		31.057	56359.5	4922067.0	15.1446
Total				856817.8	32500513.3	100.0000

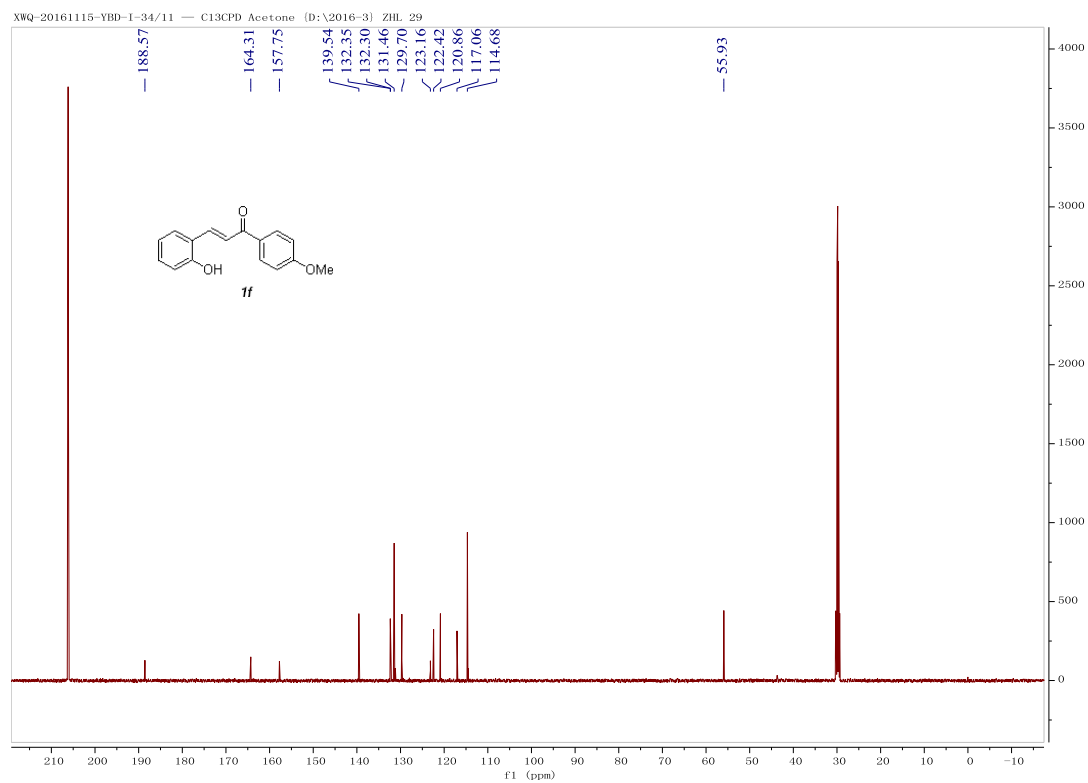
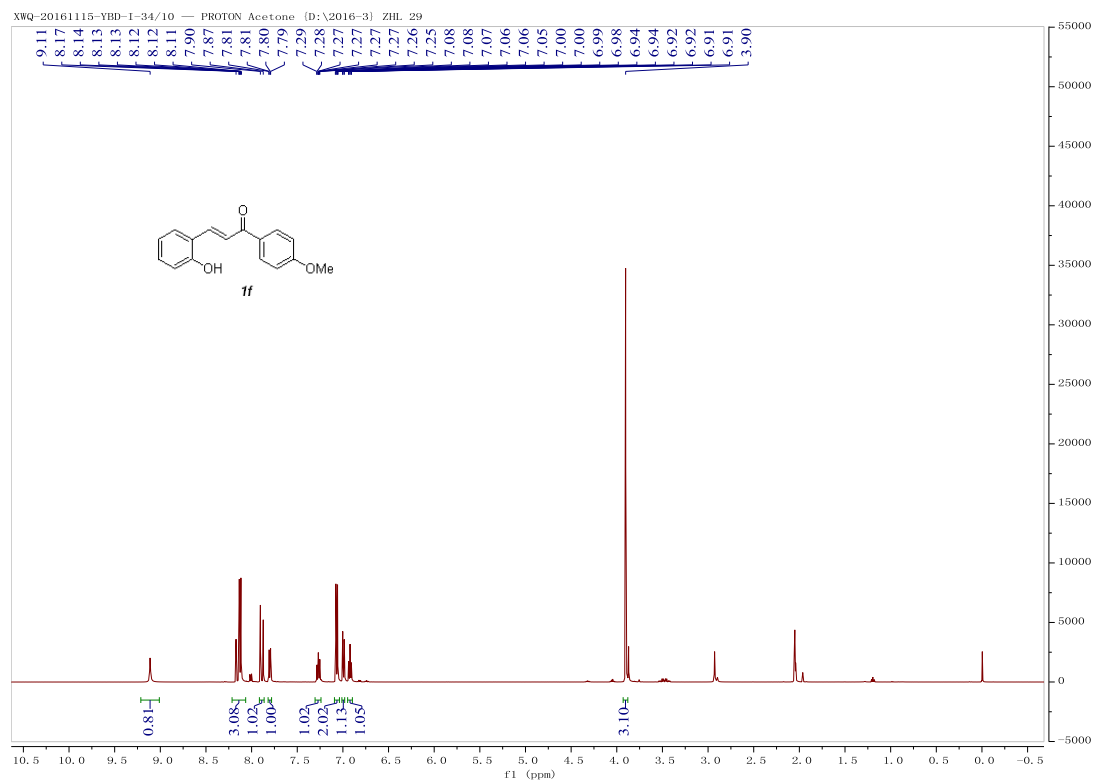
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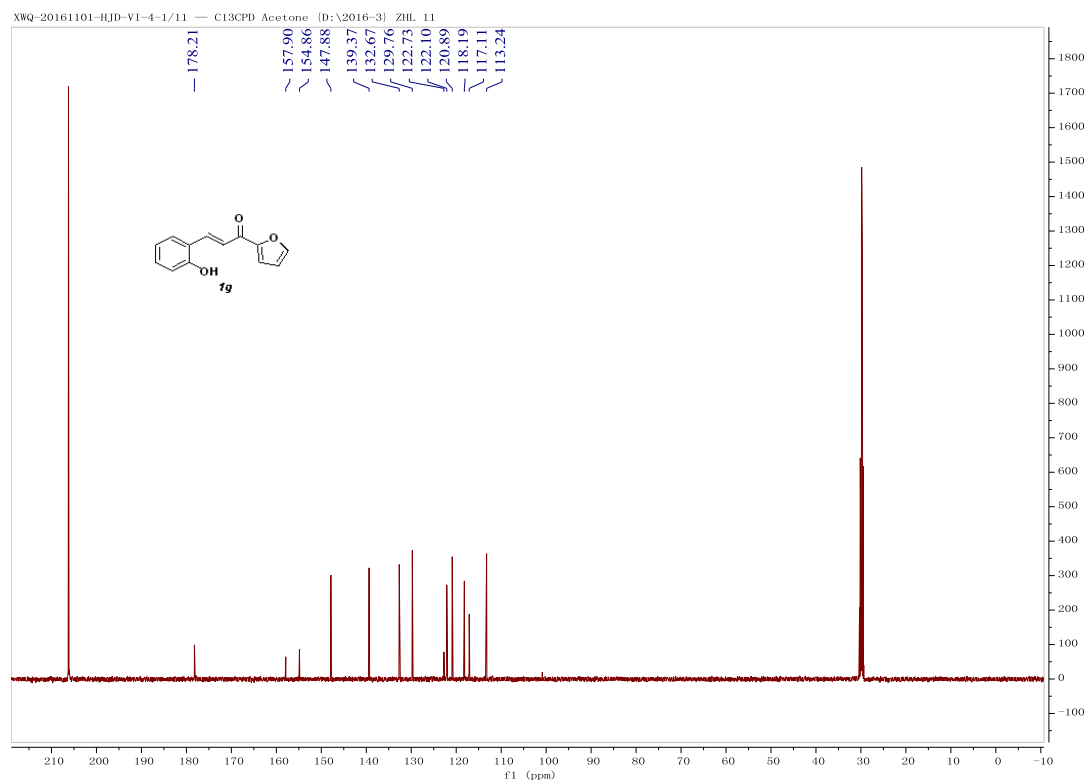
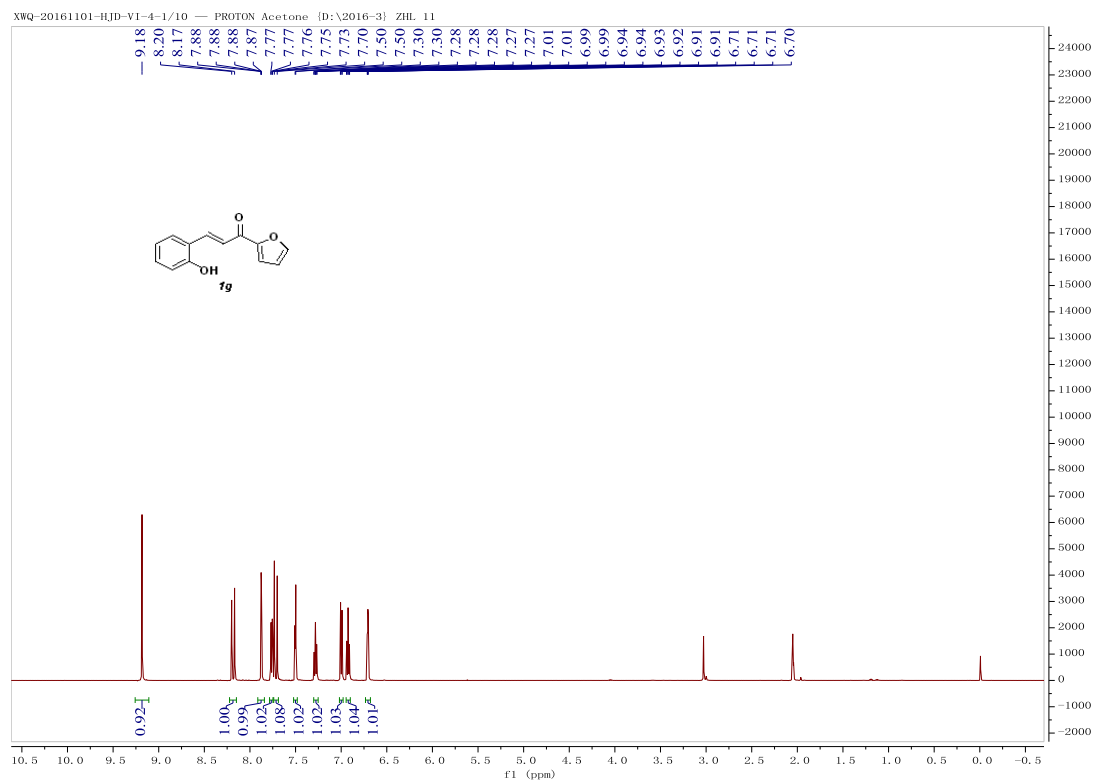


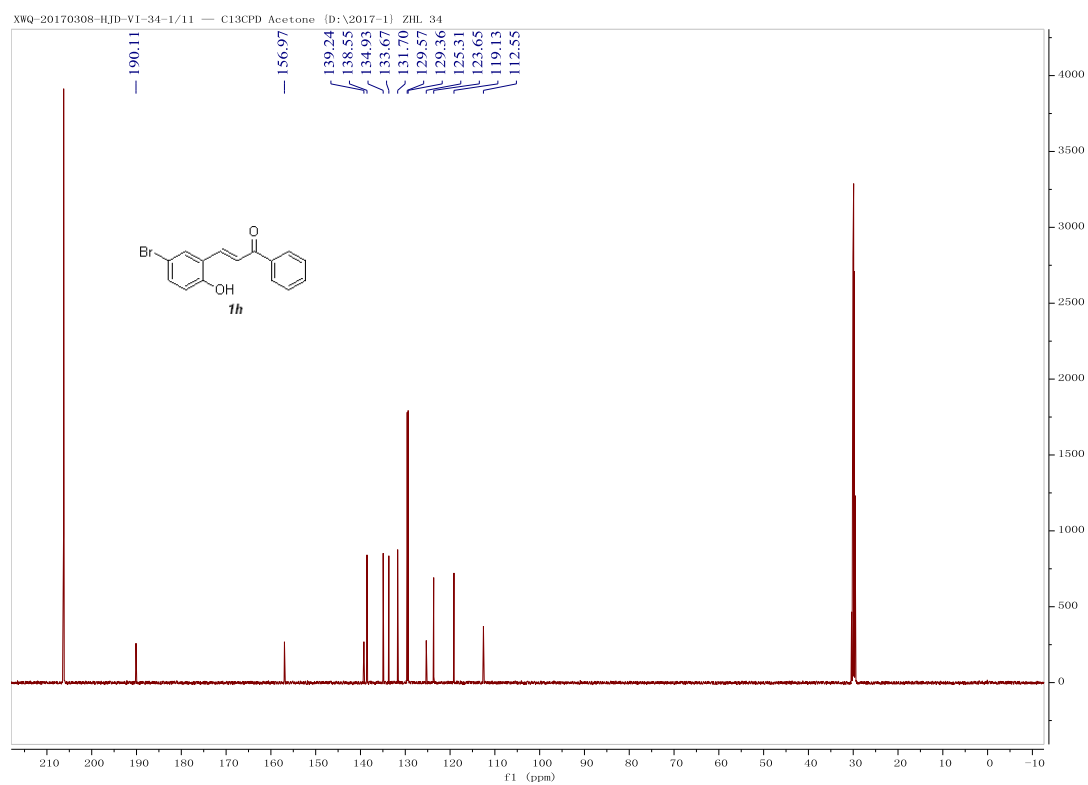
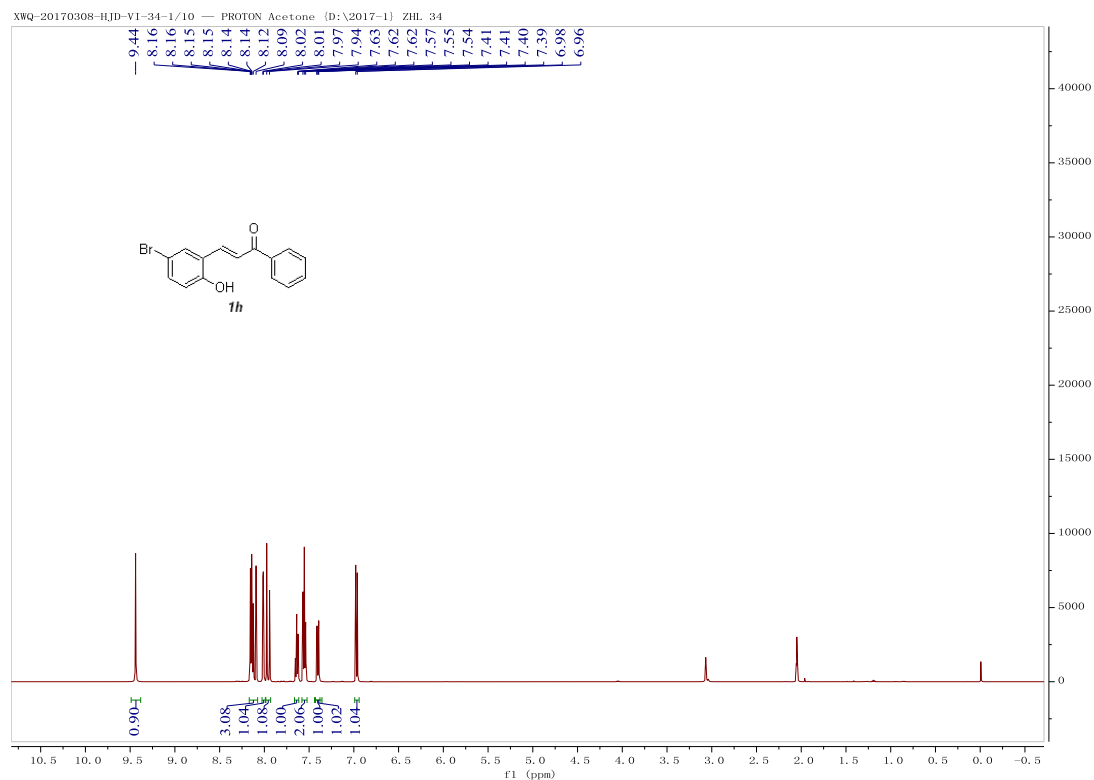


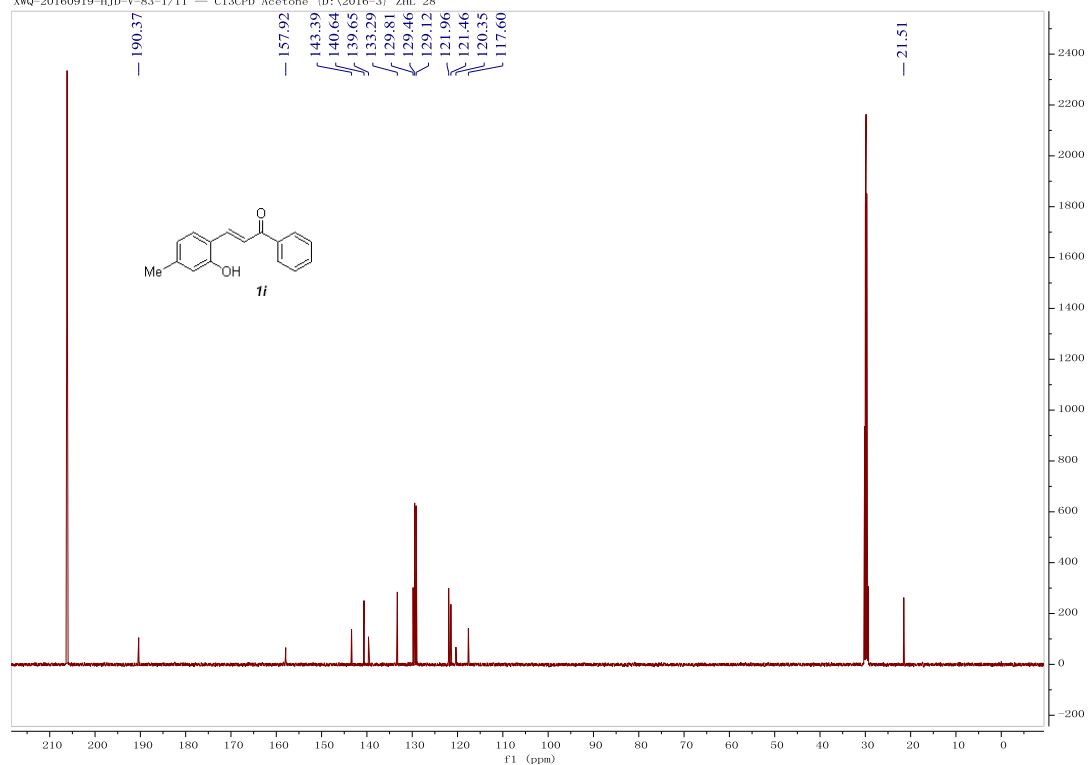
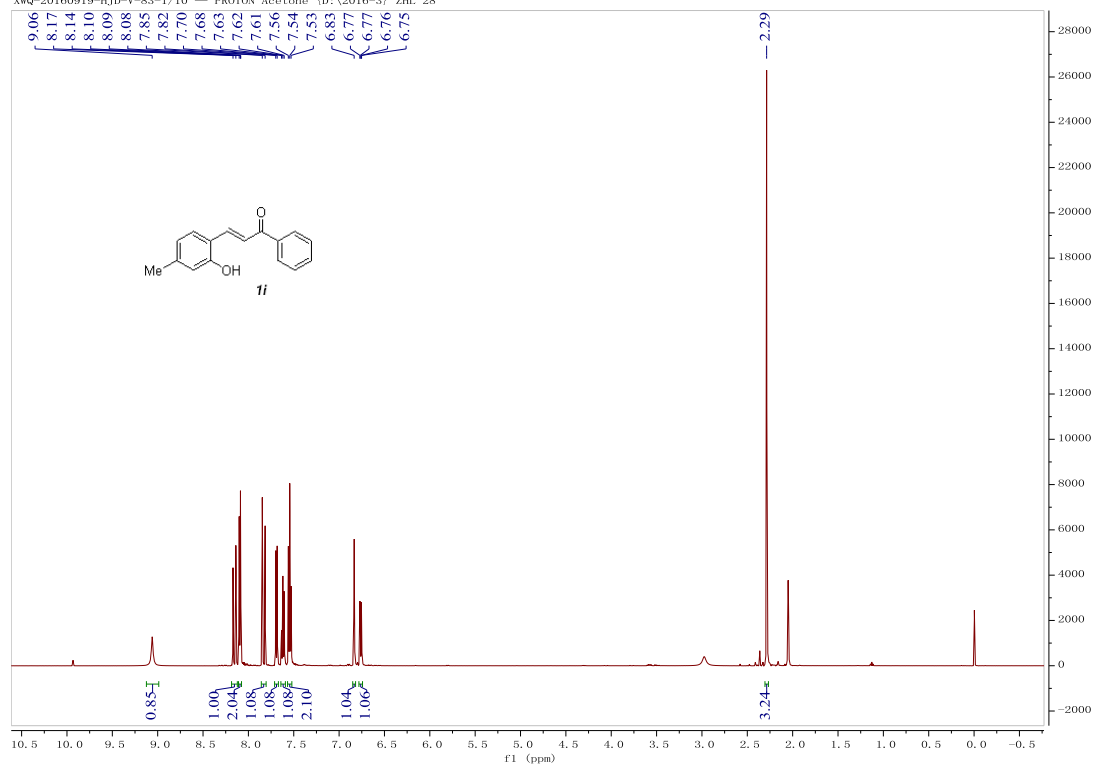


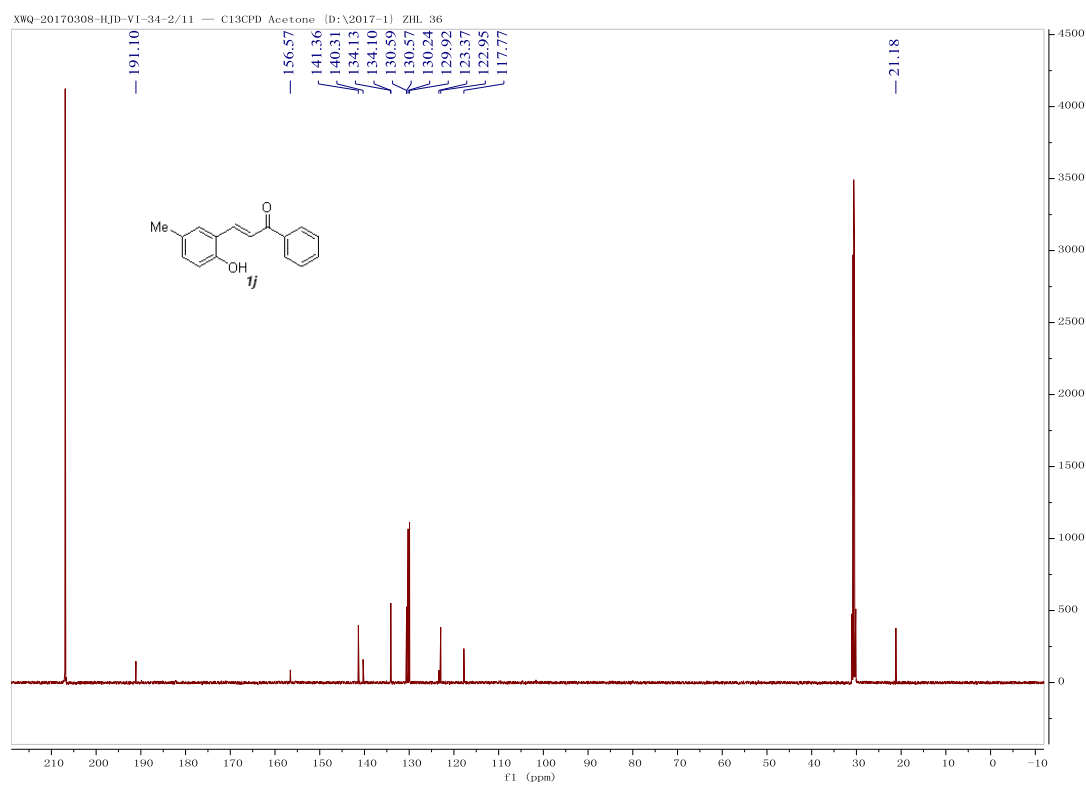
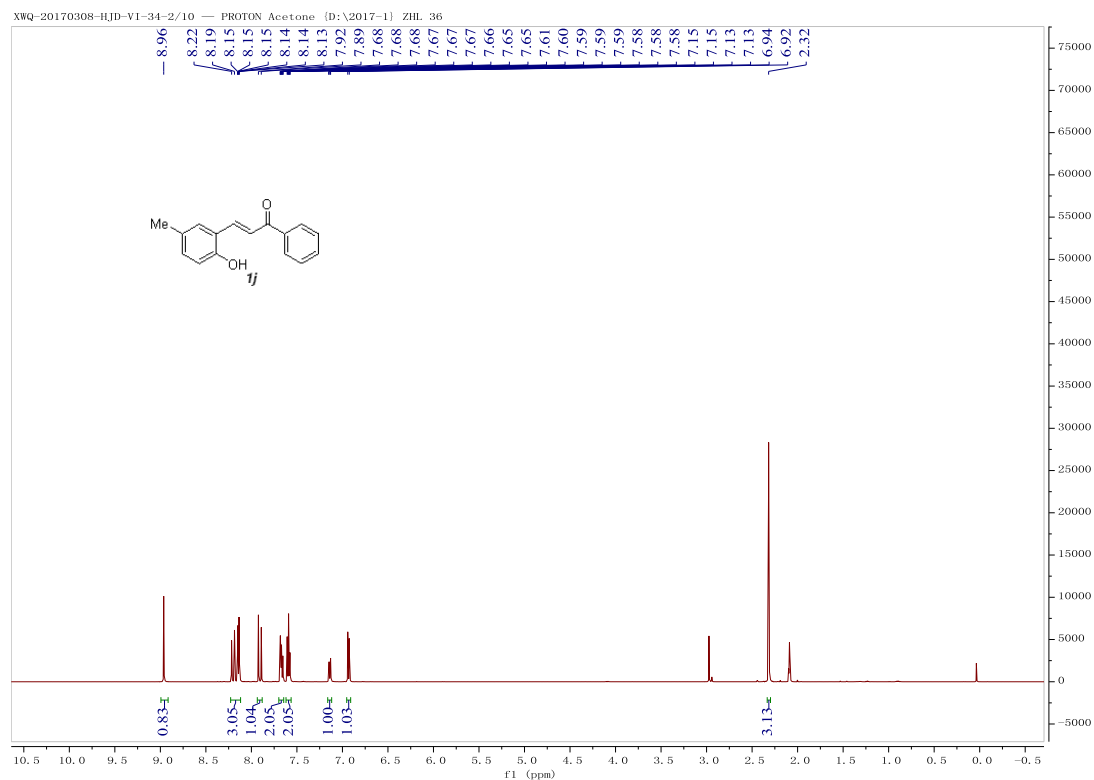


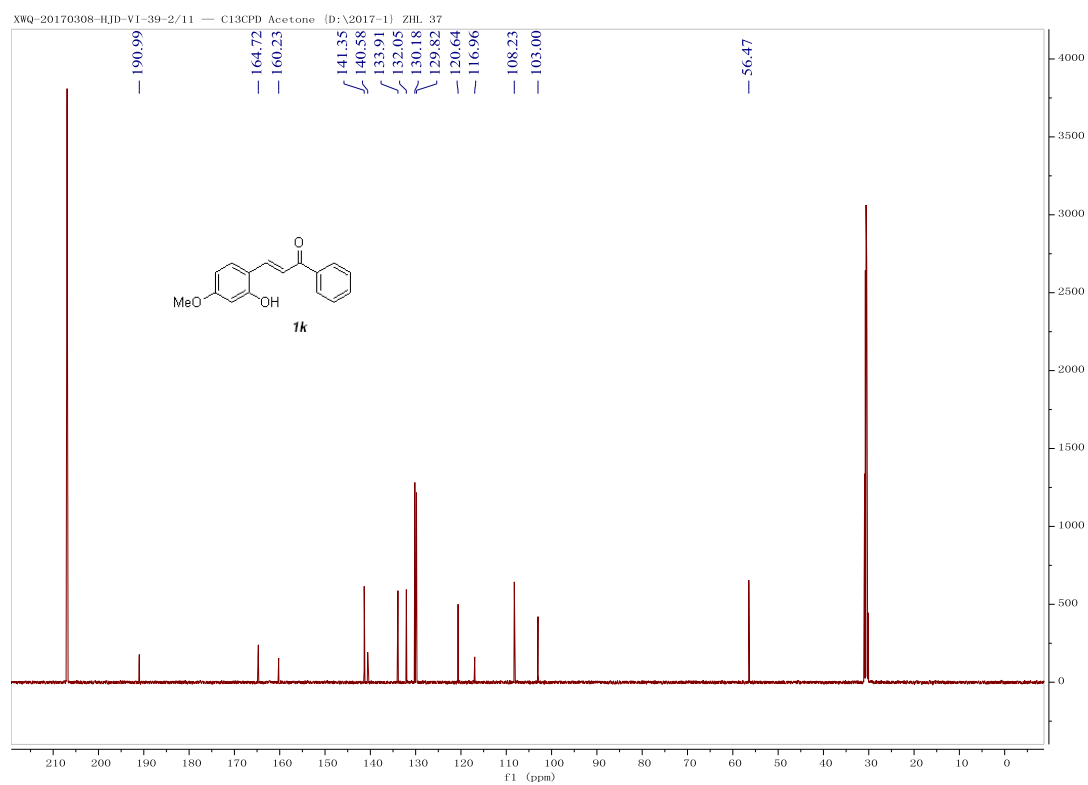
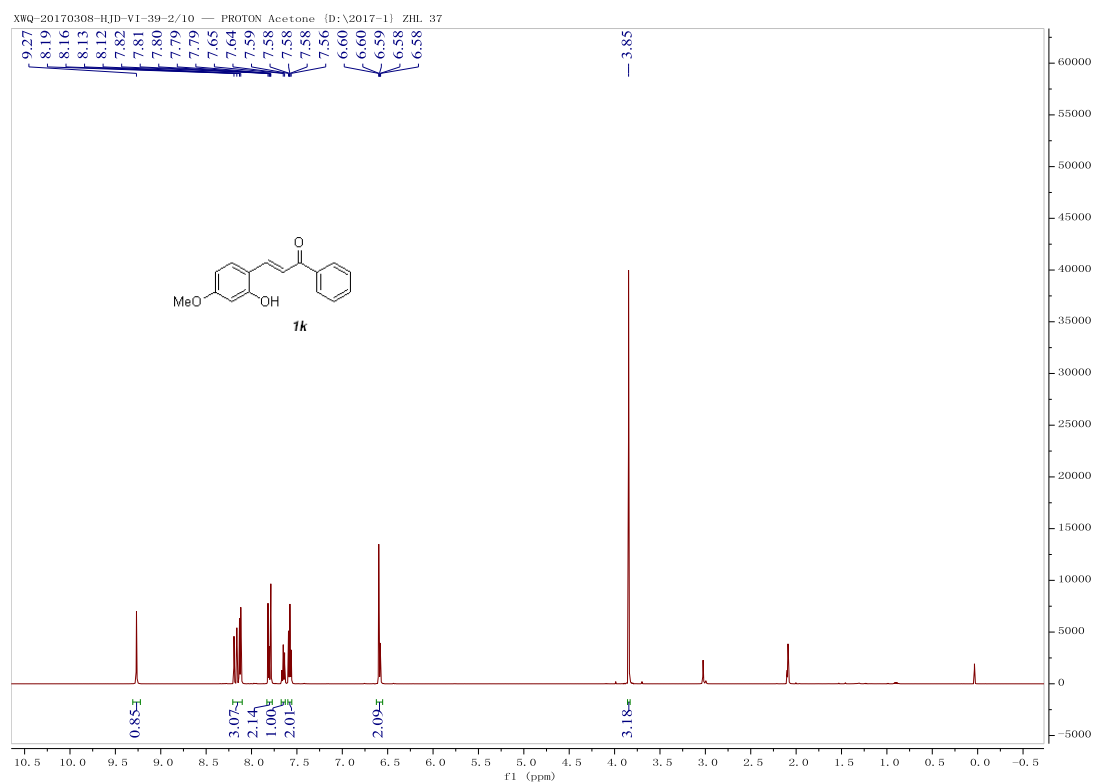


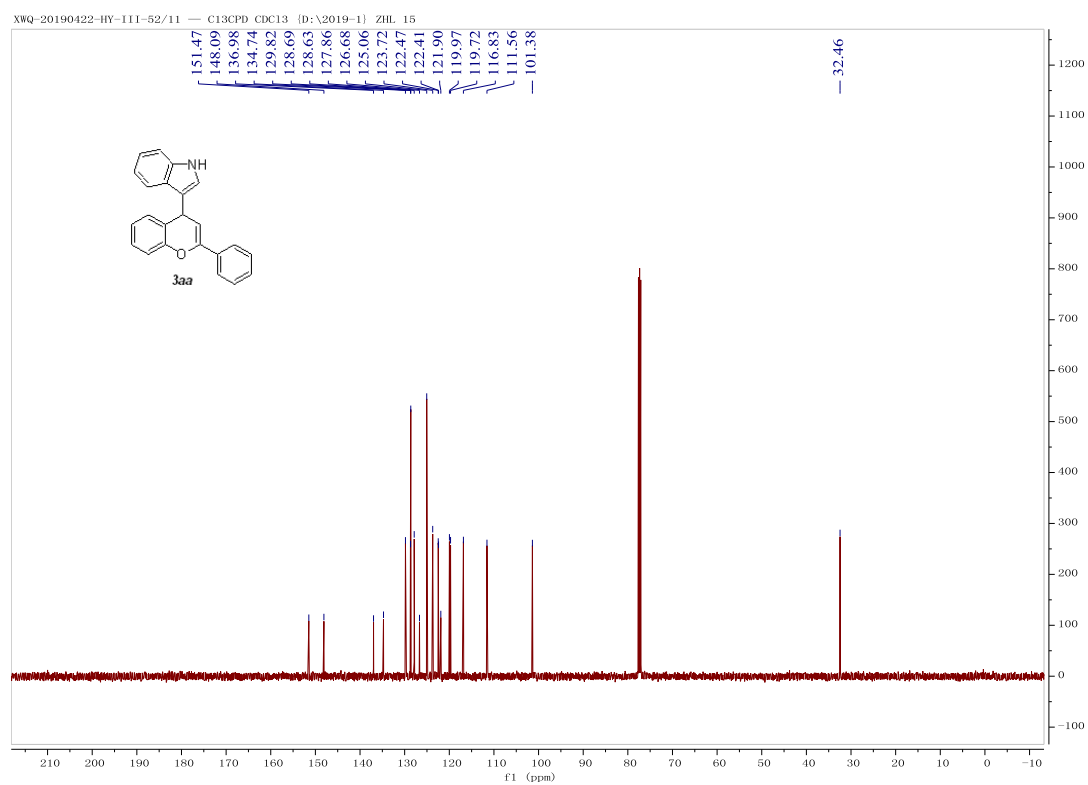
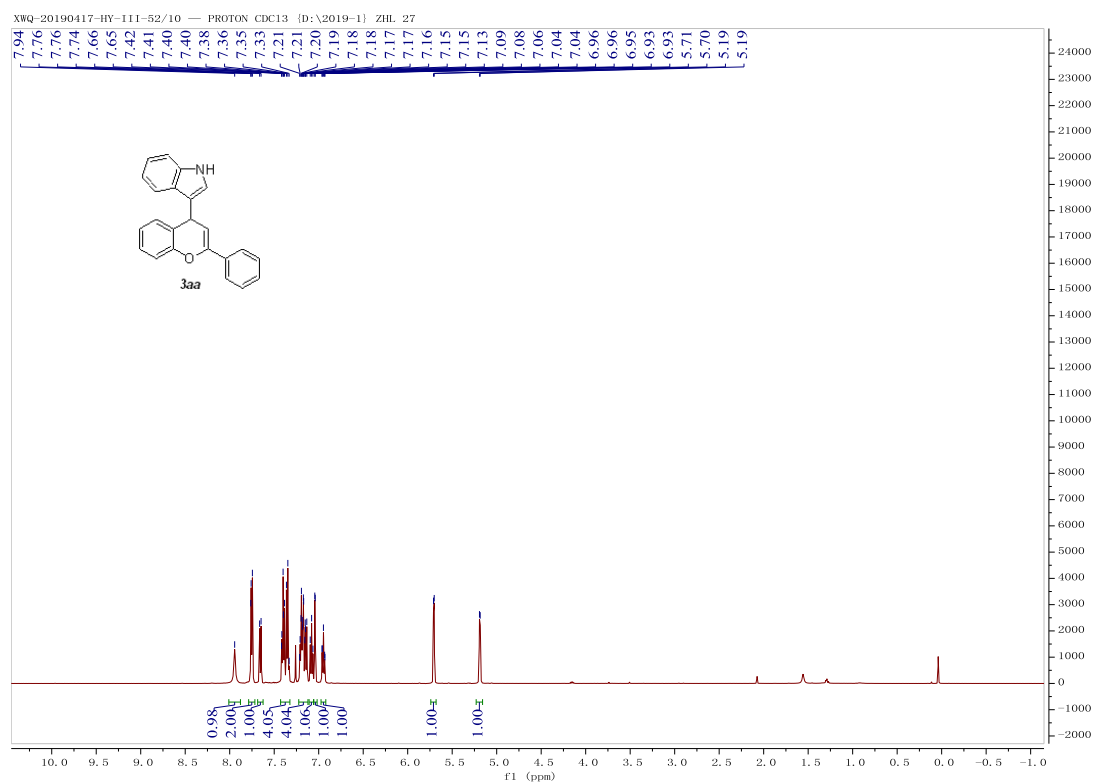




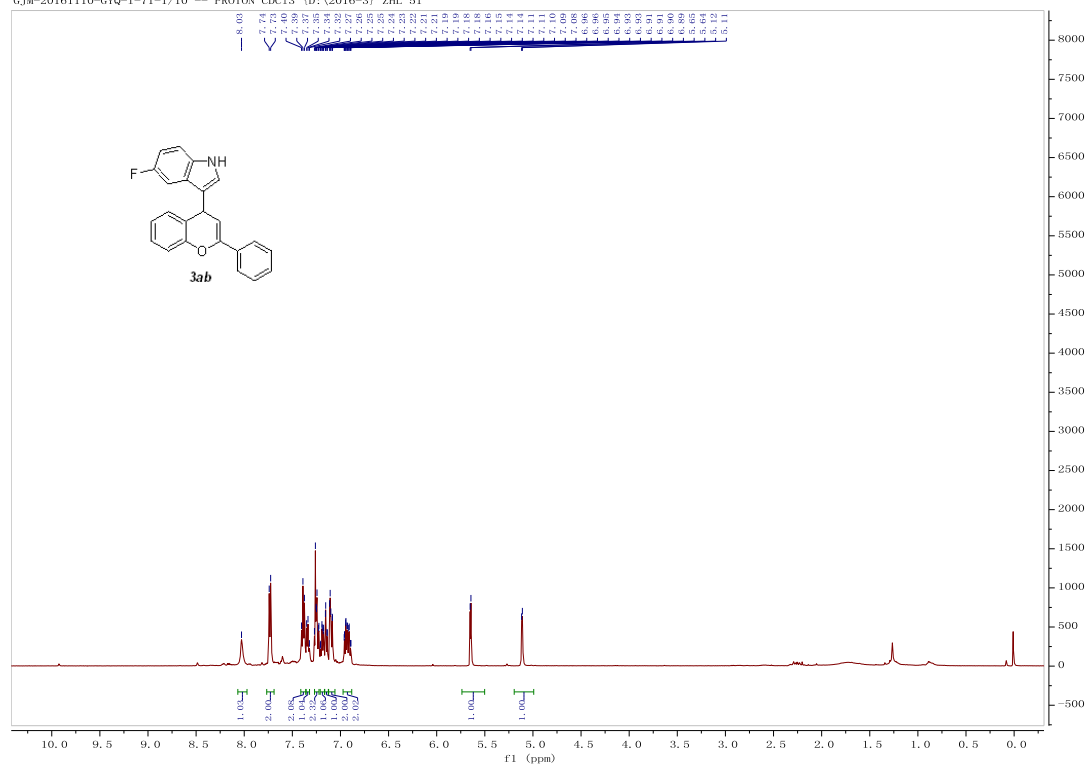




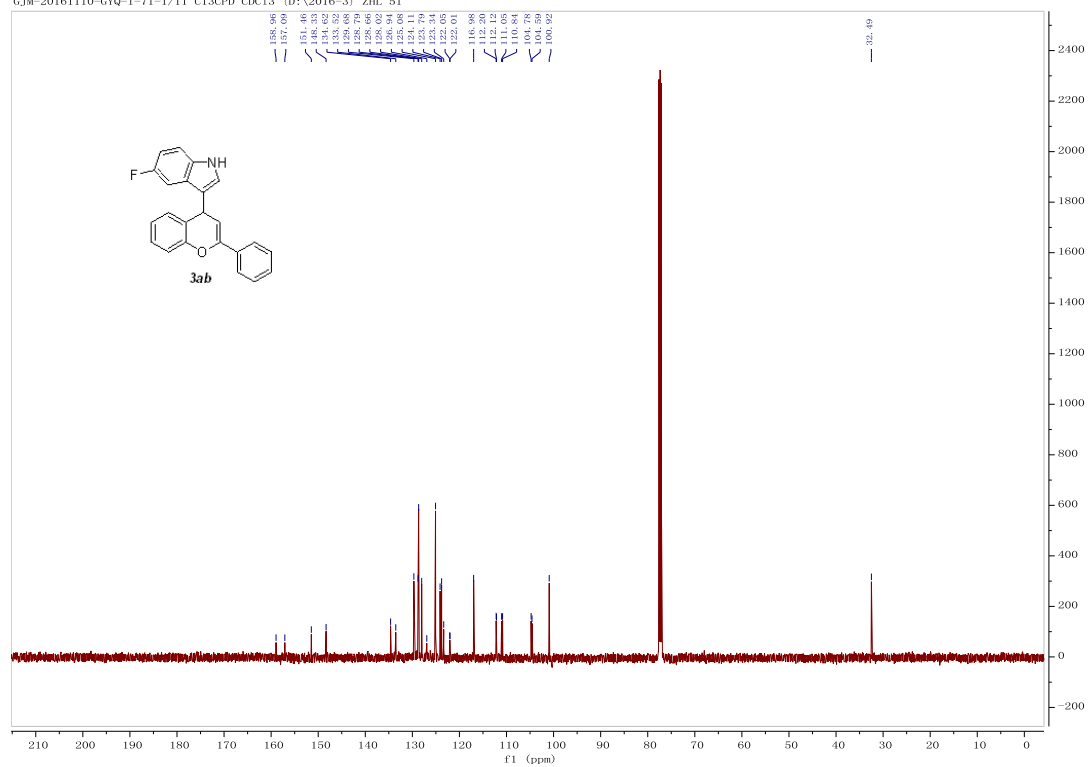


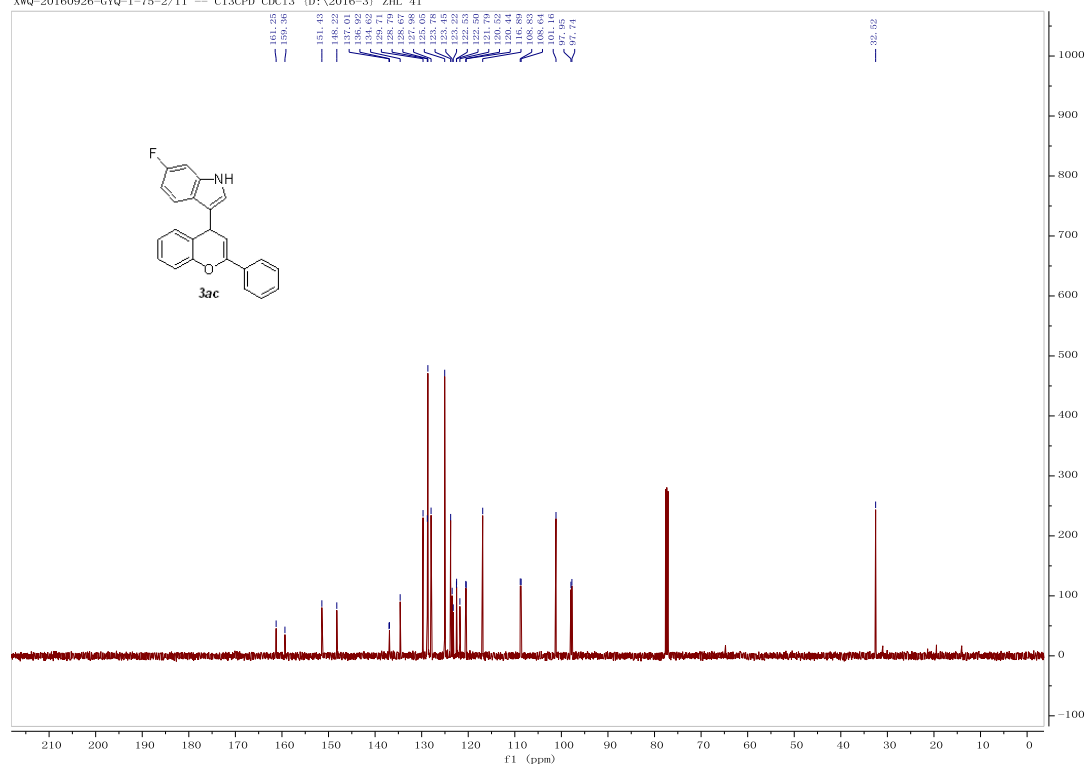
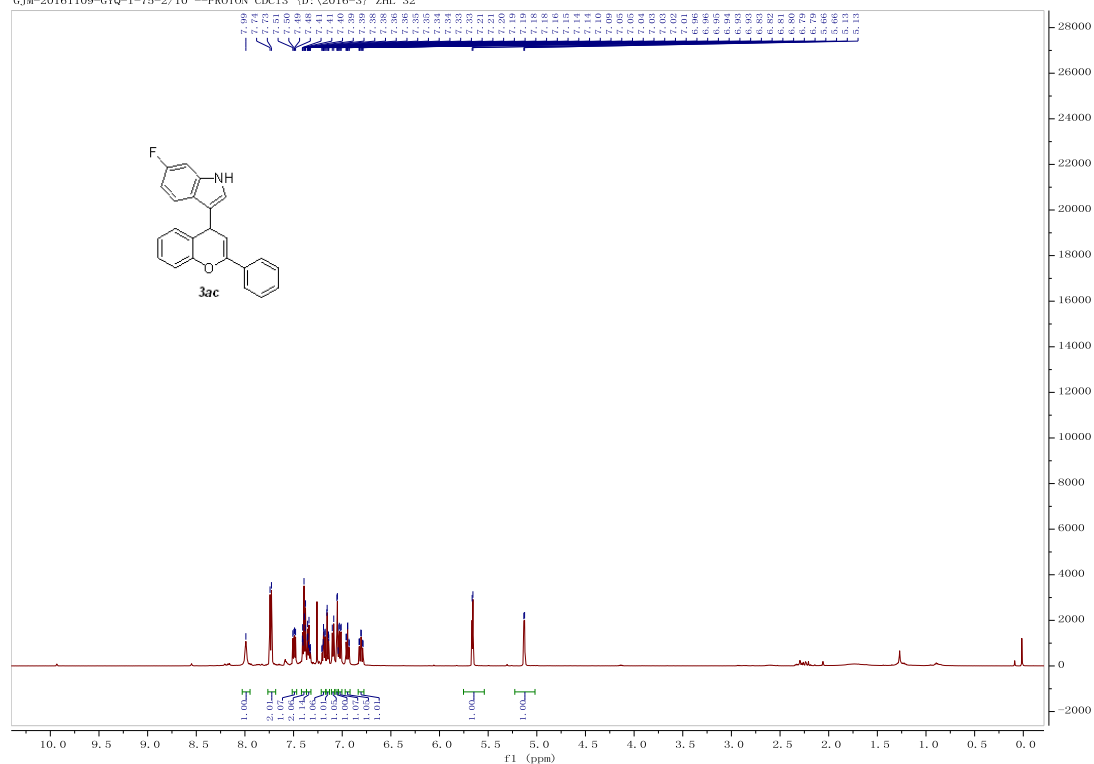


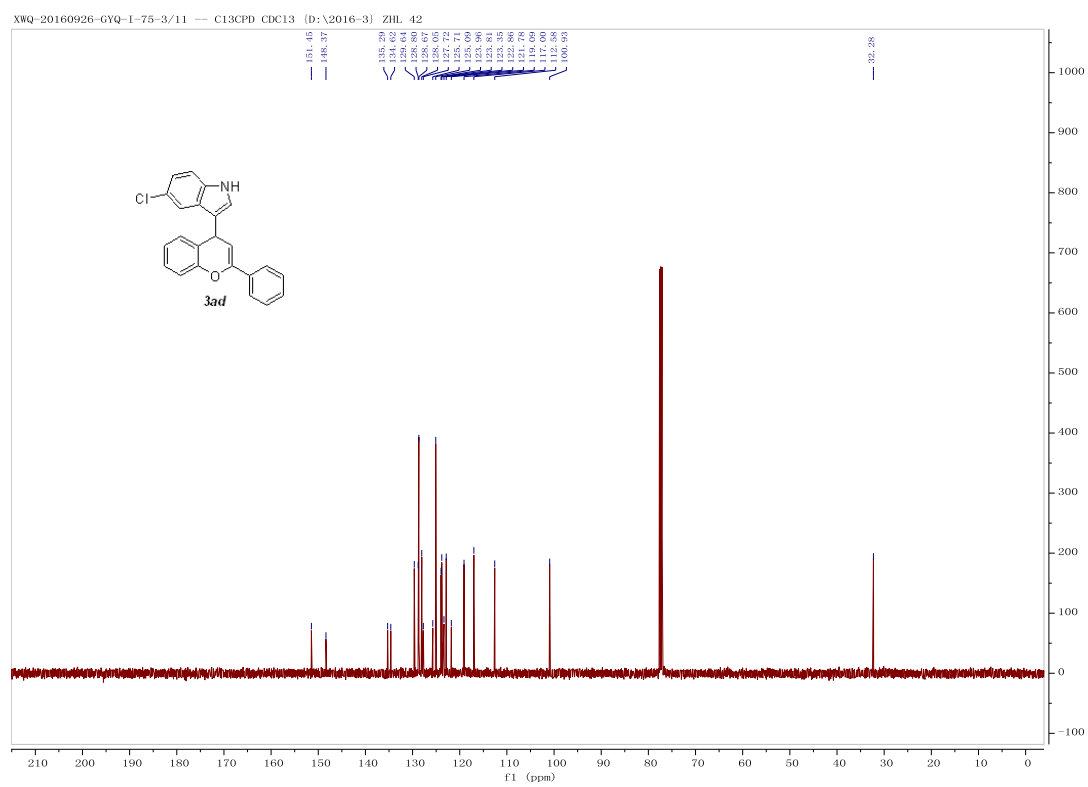
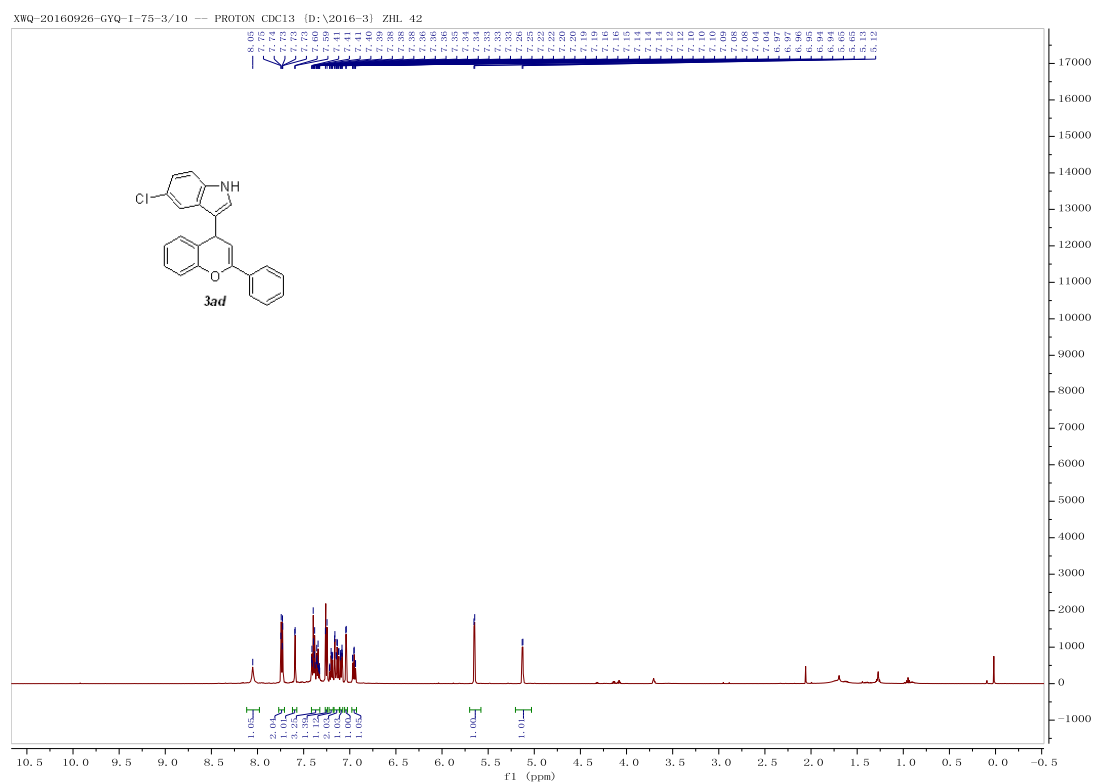
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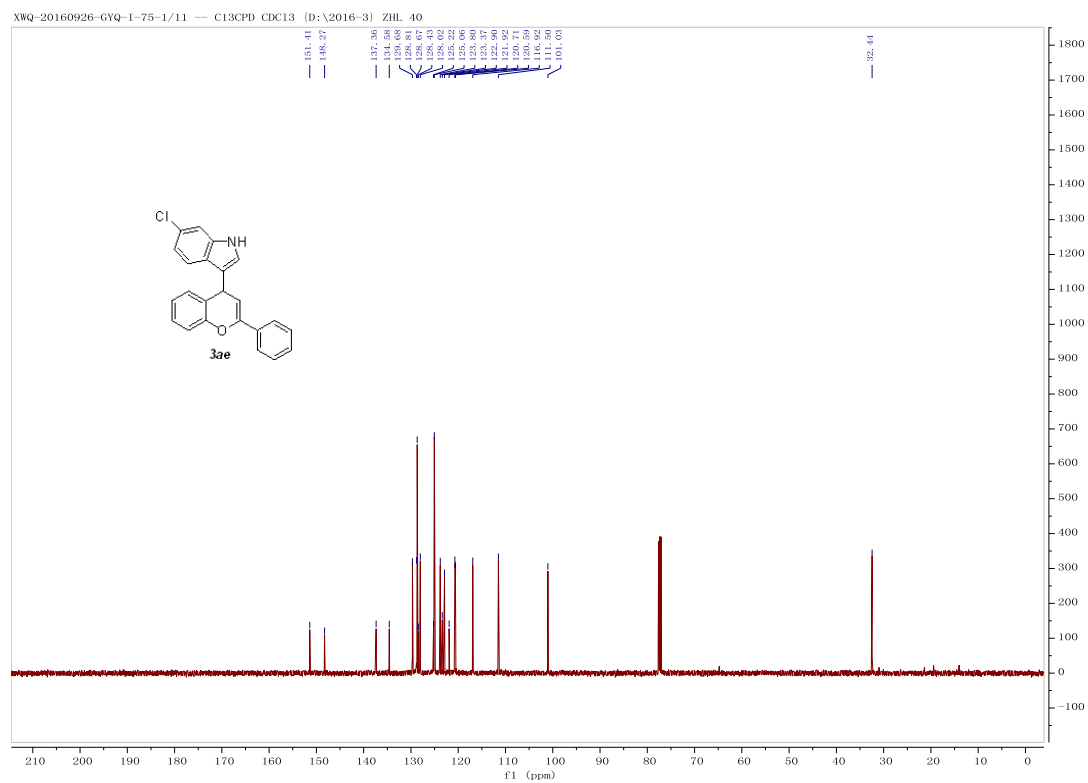
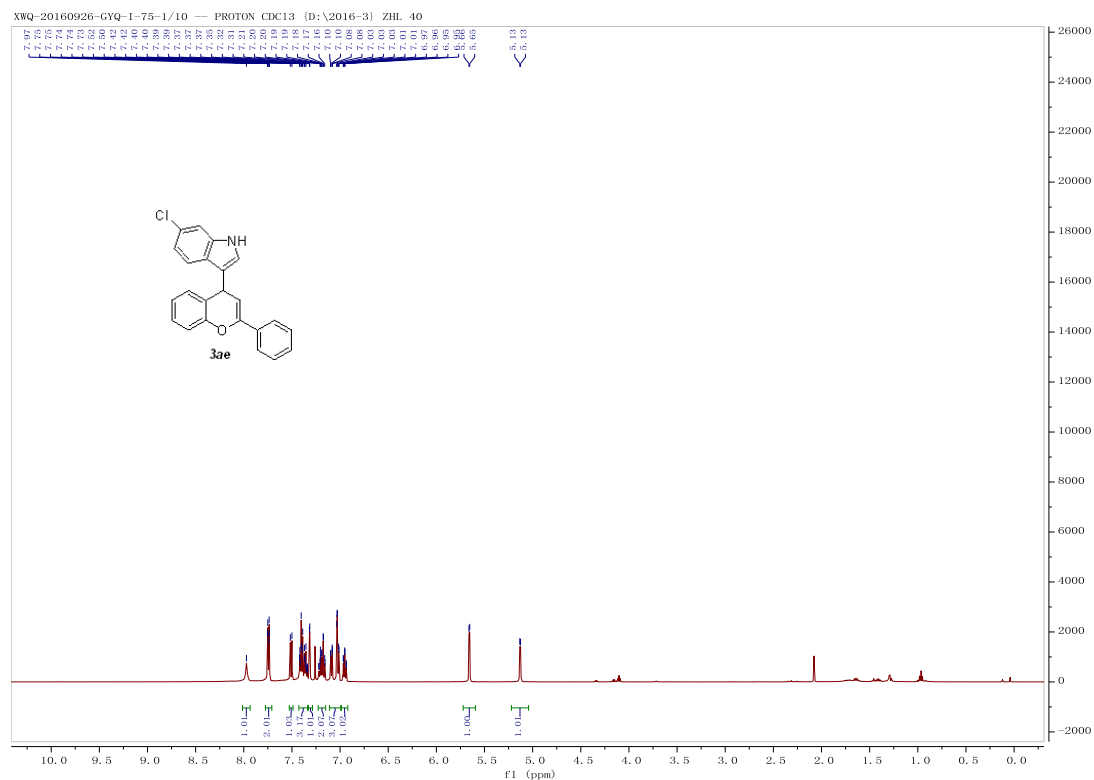


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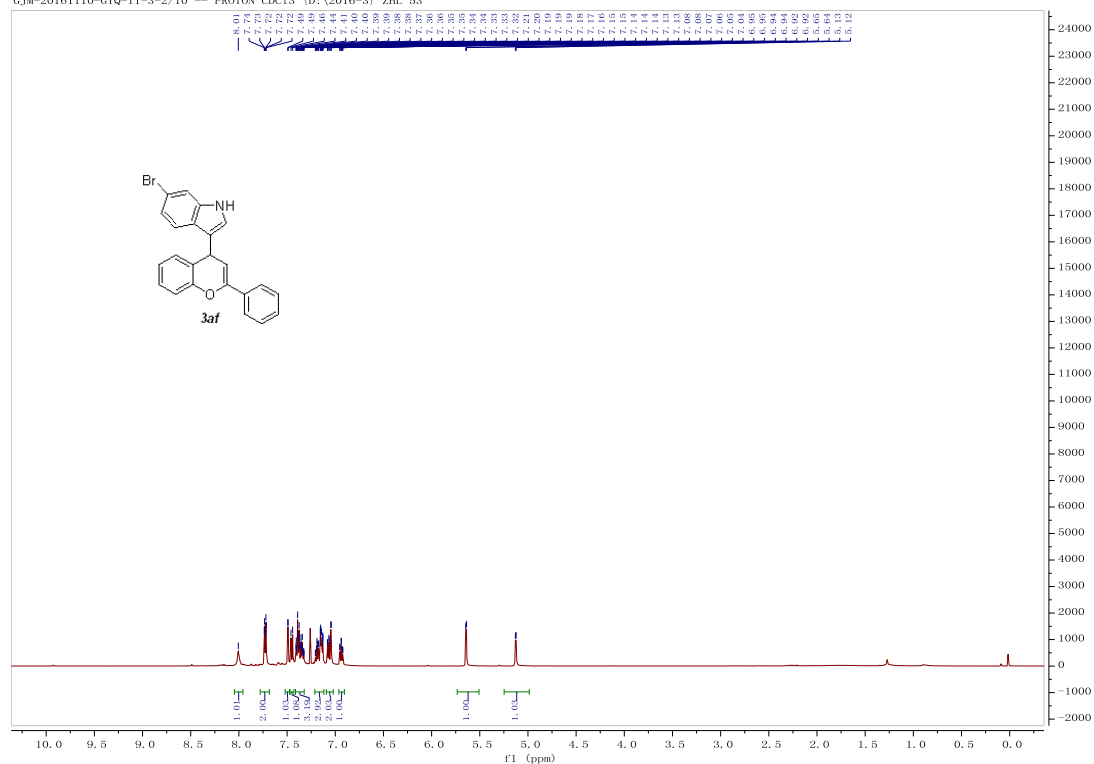




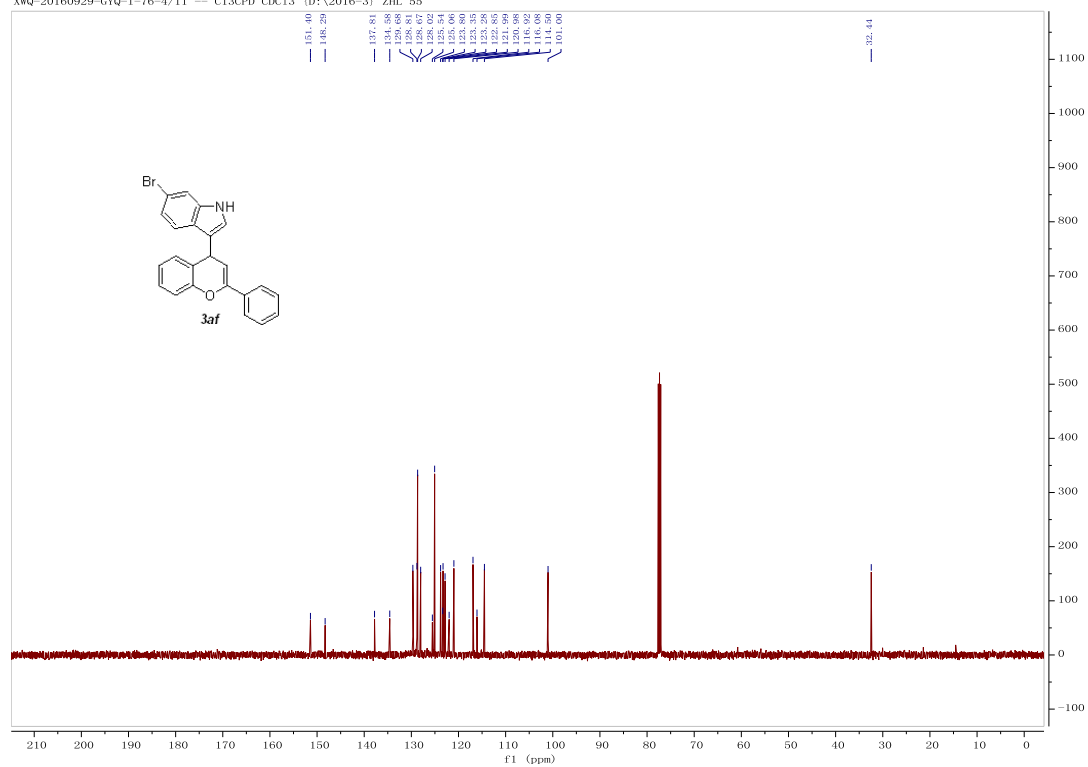




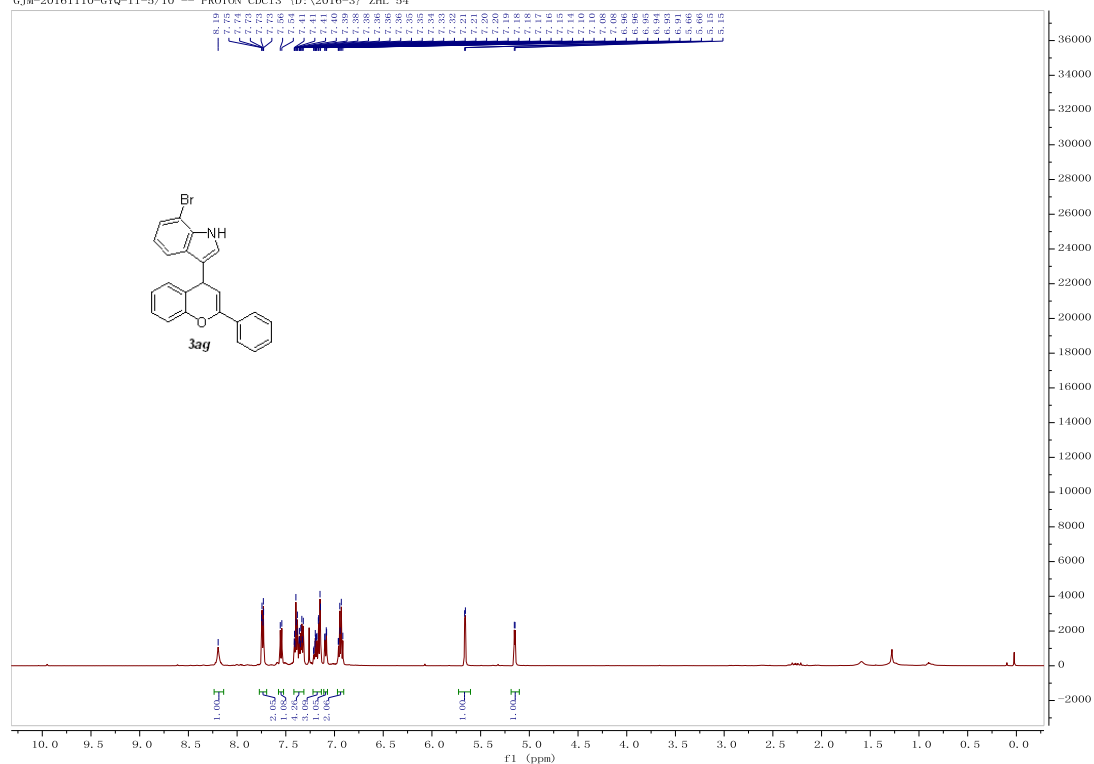
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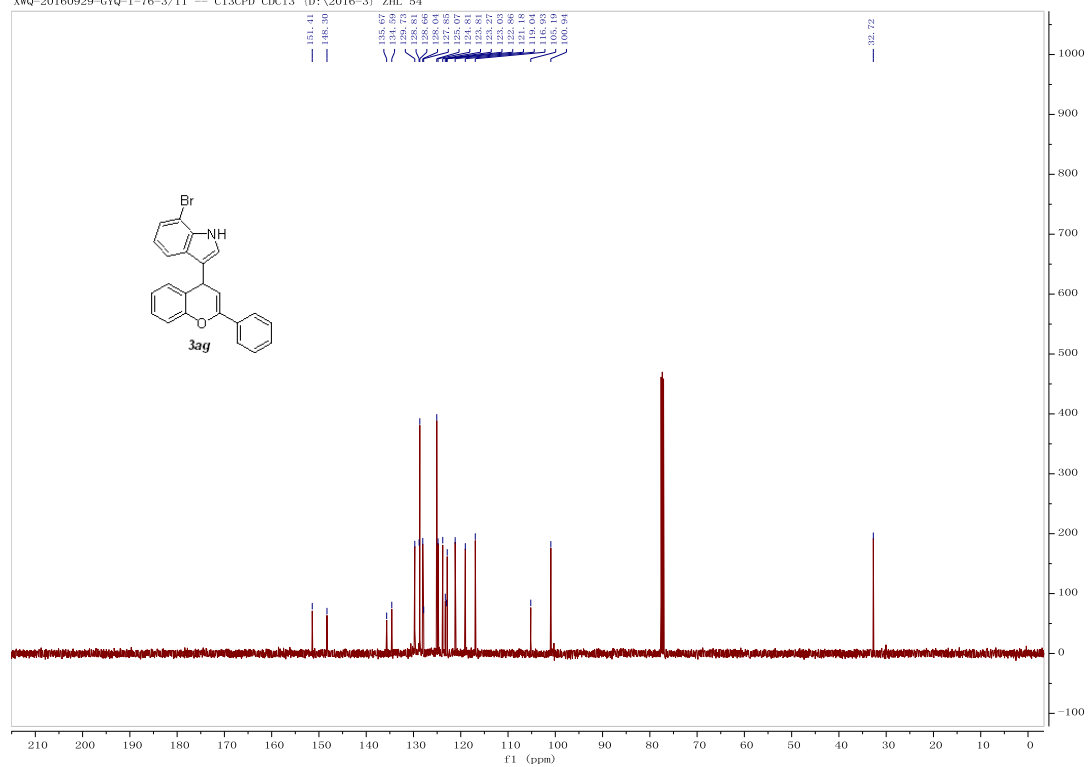
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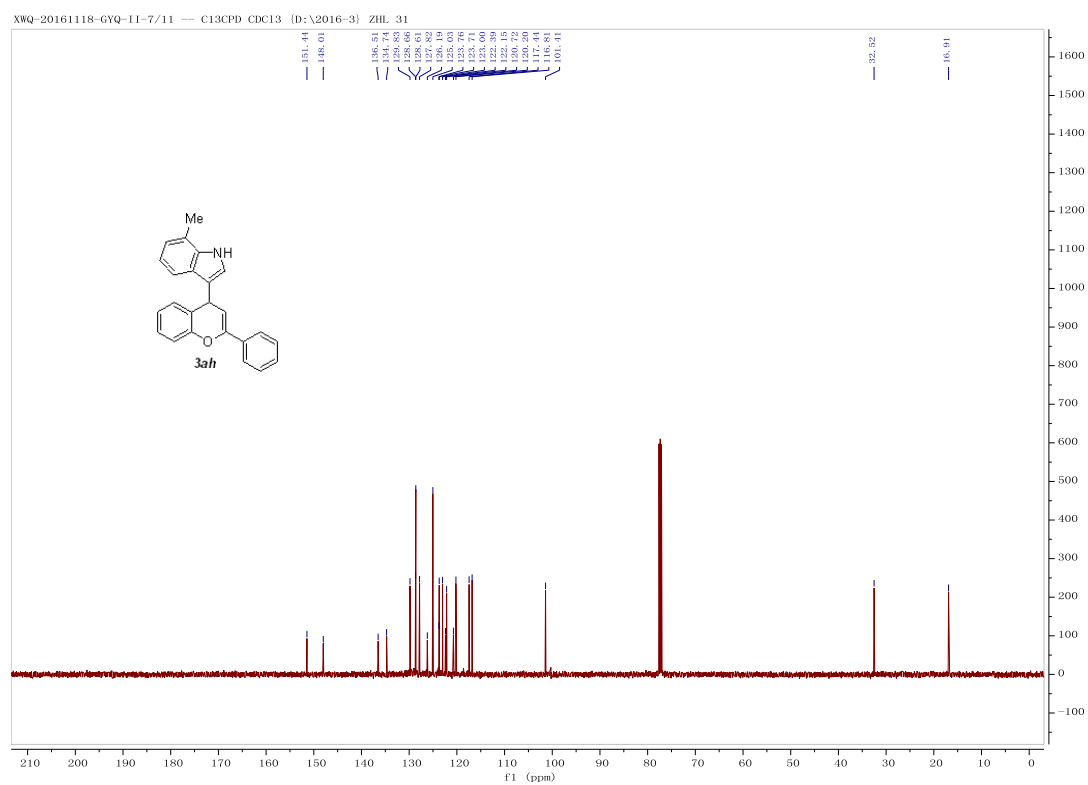
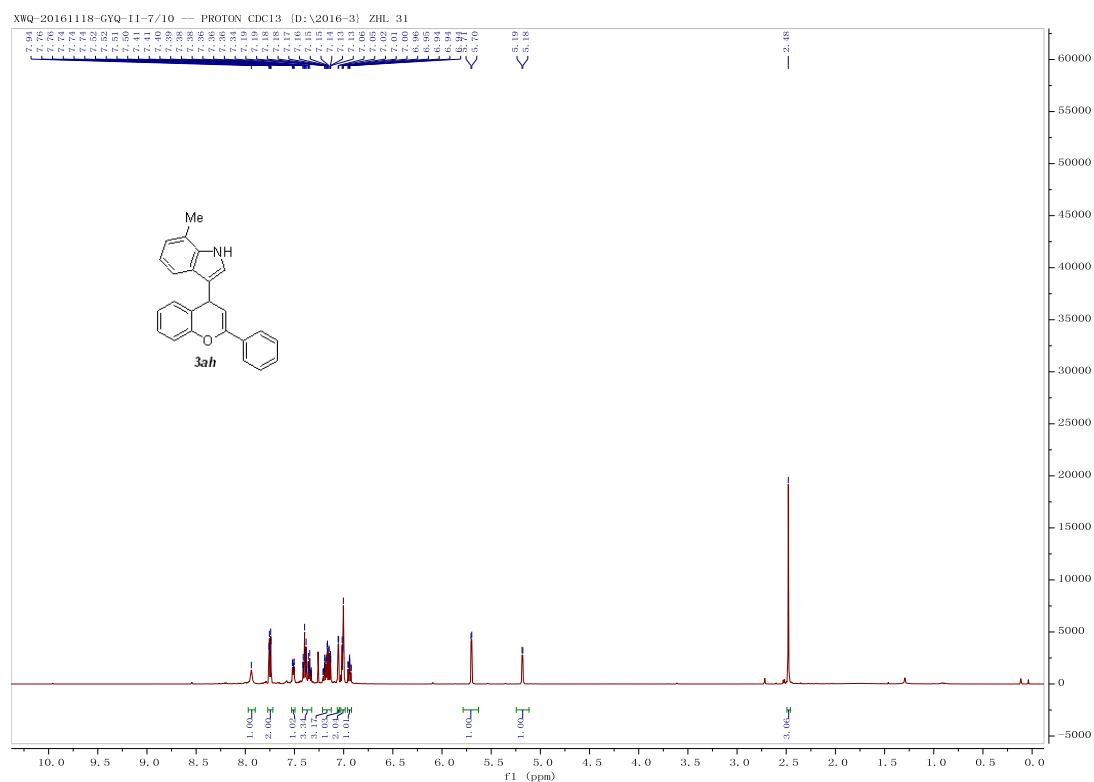


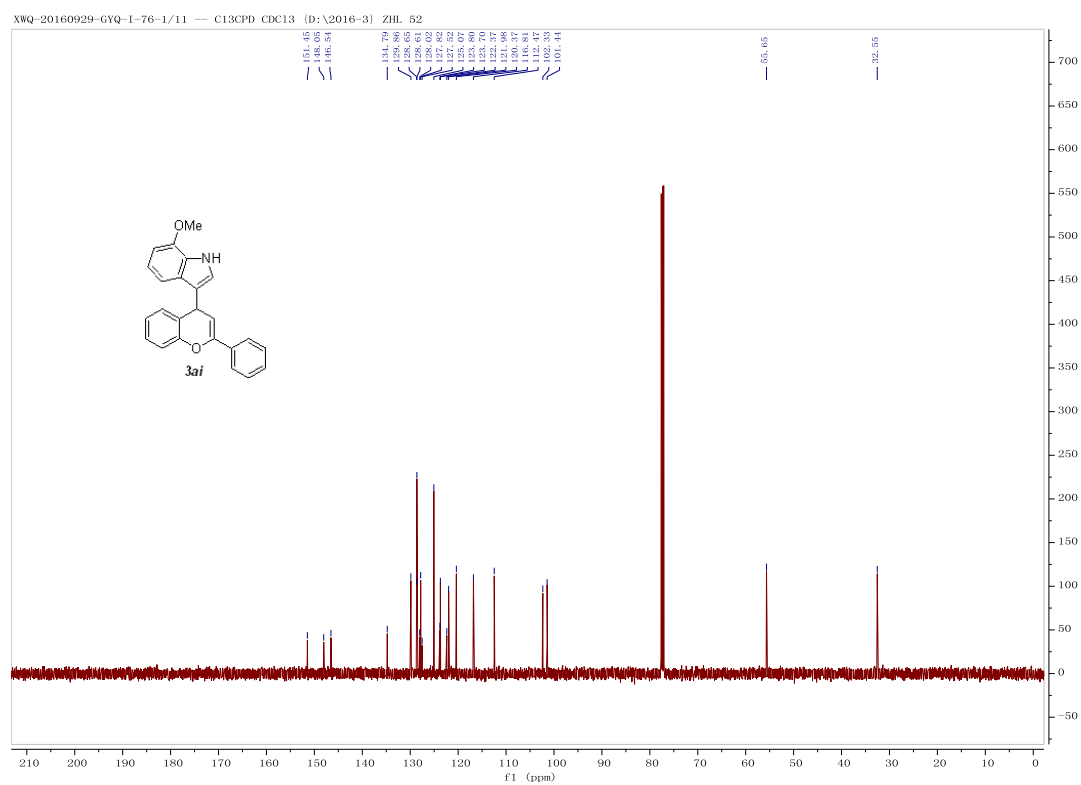
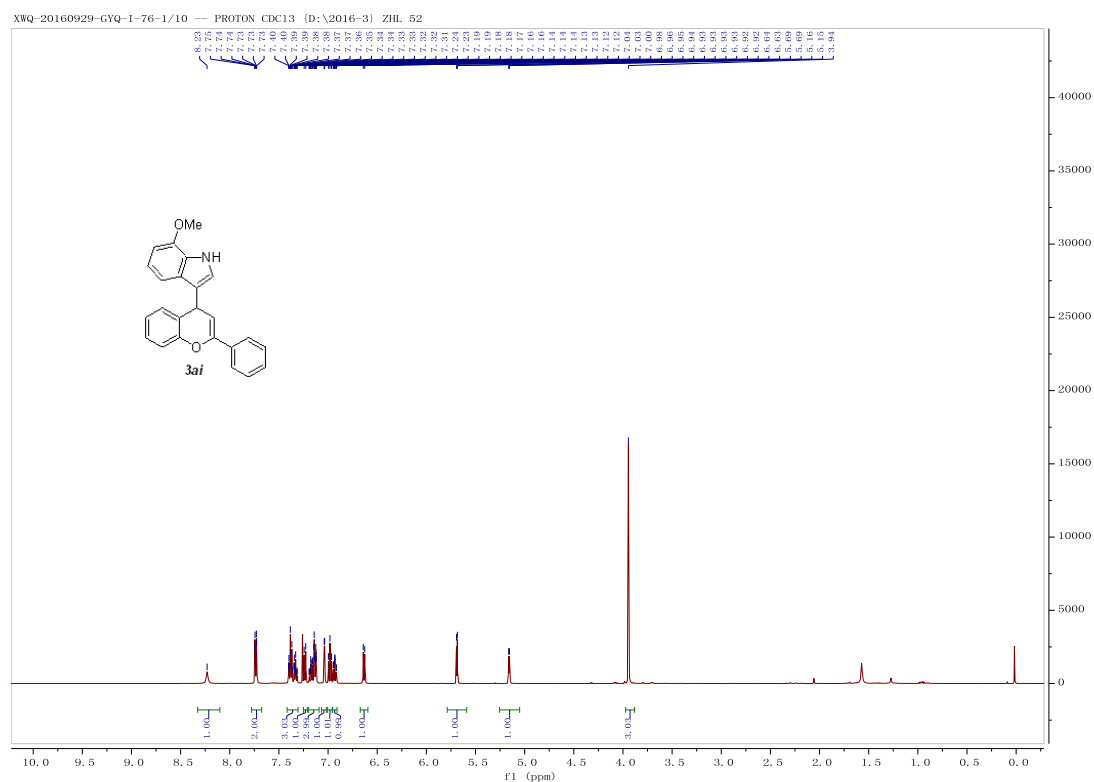
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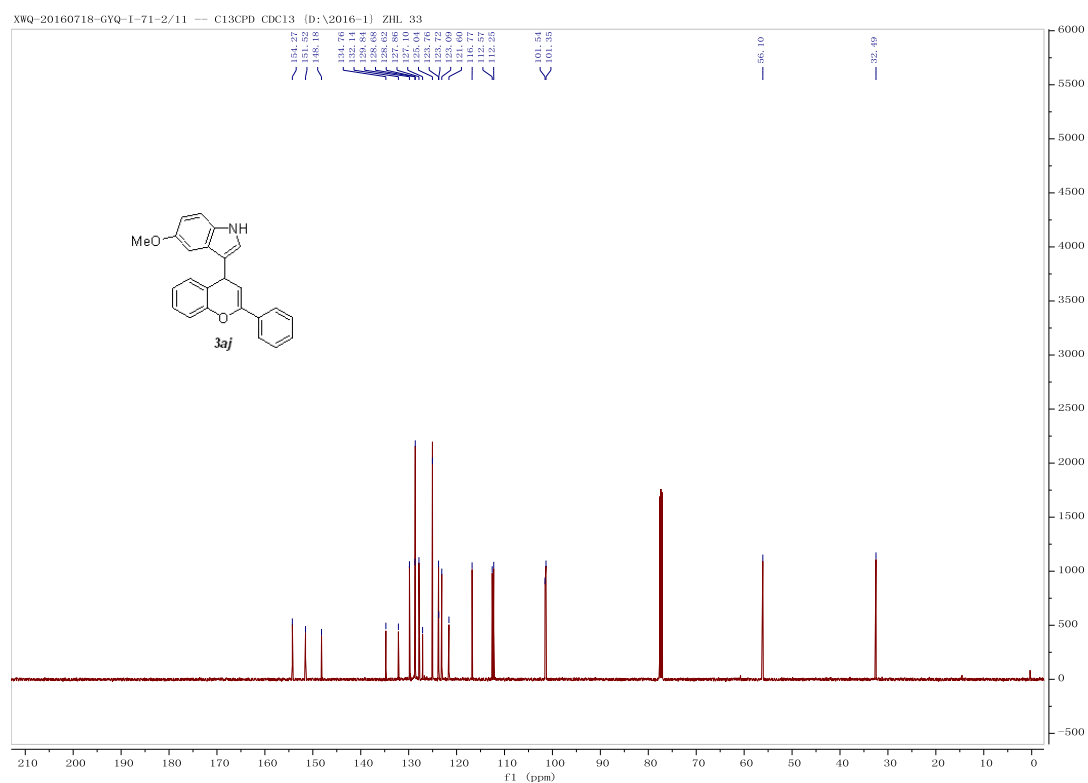
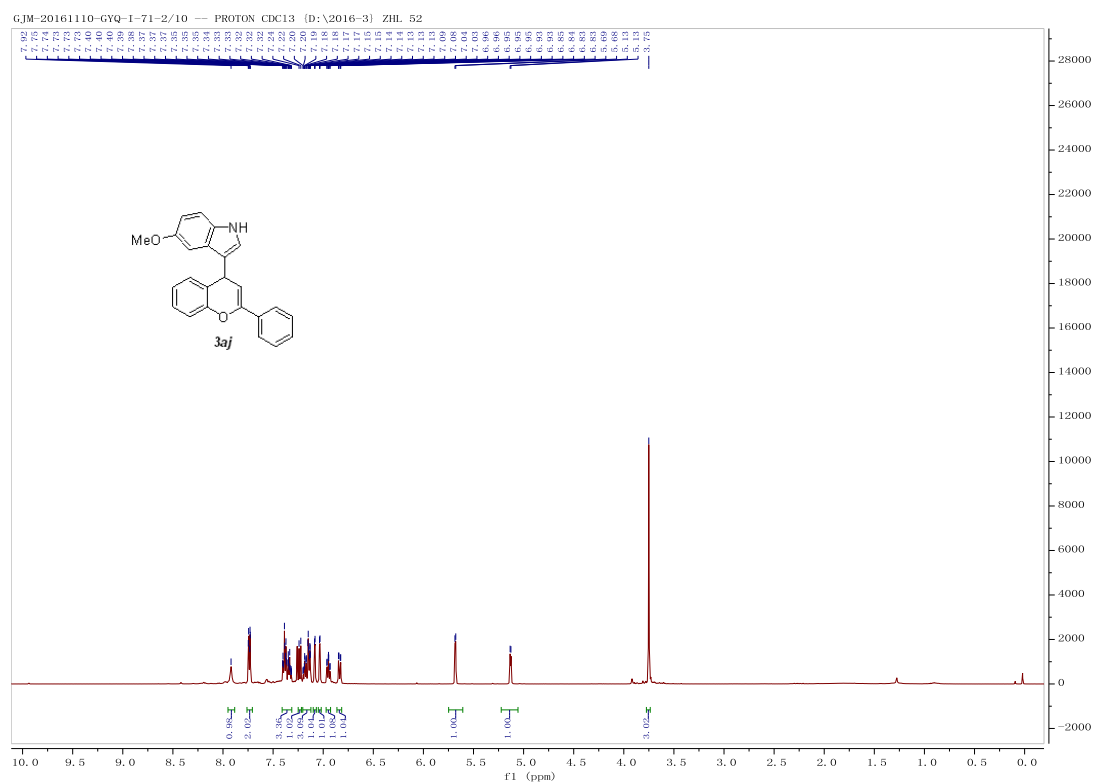


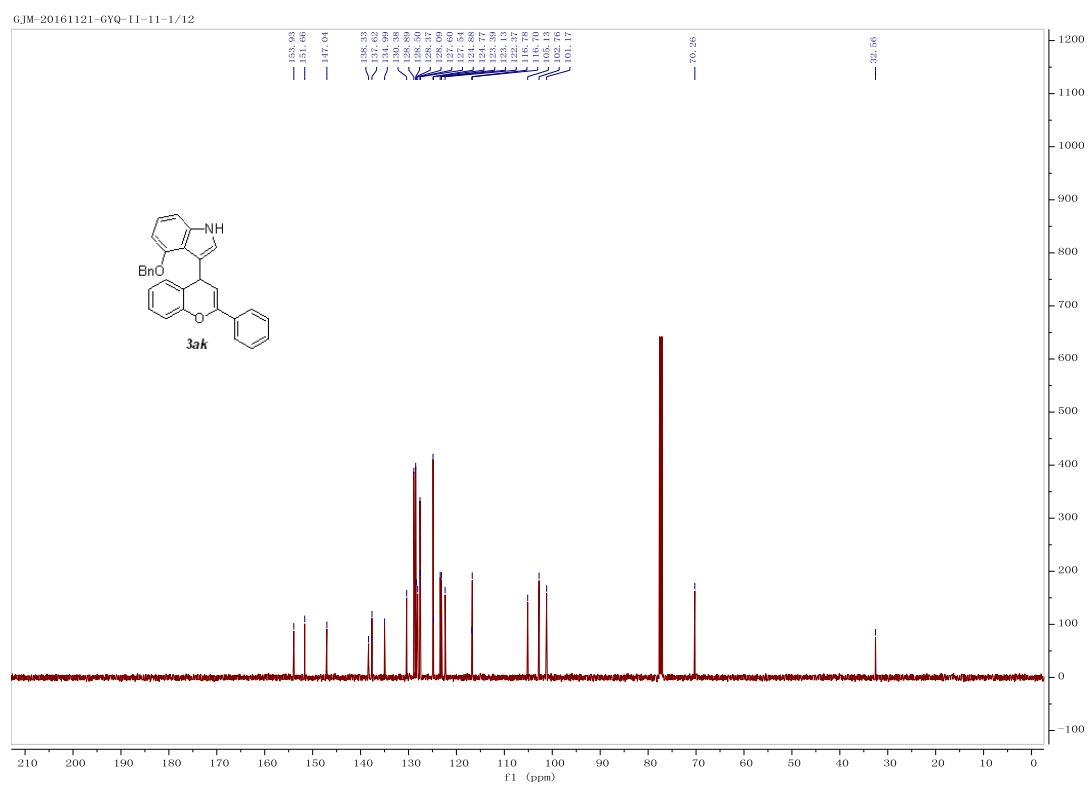
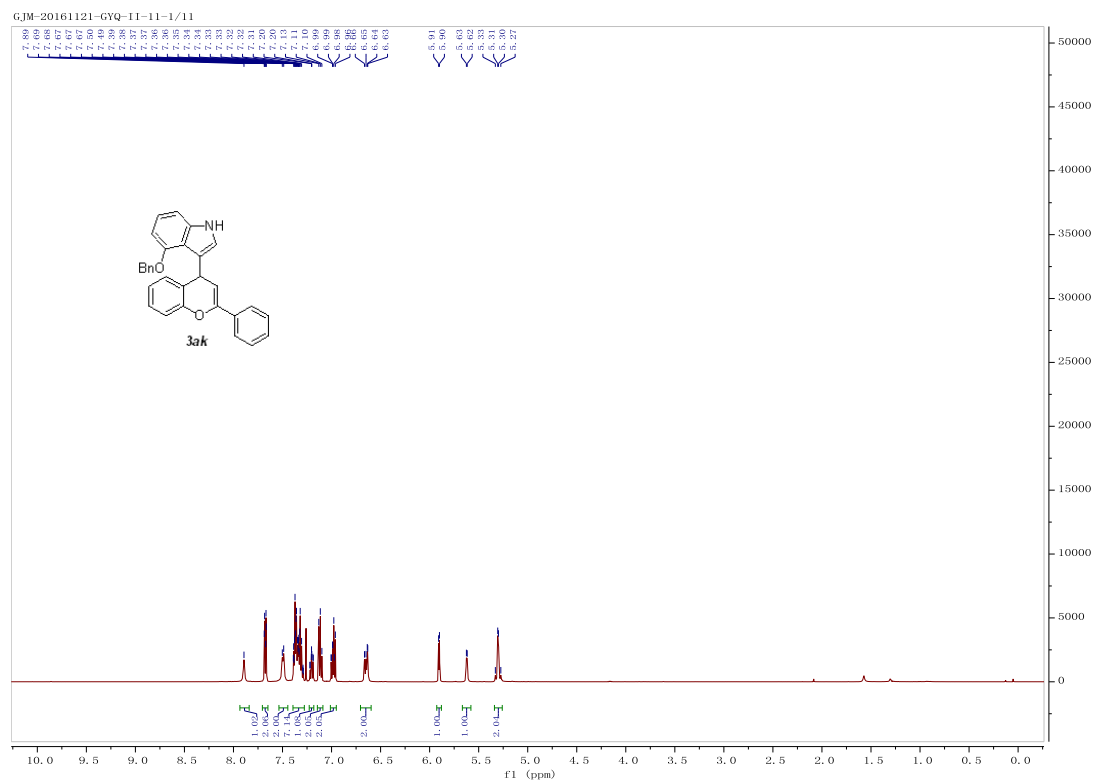
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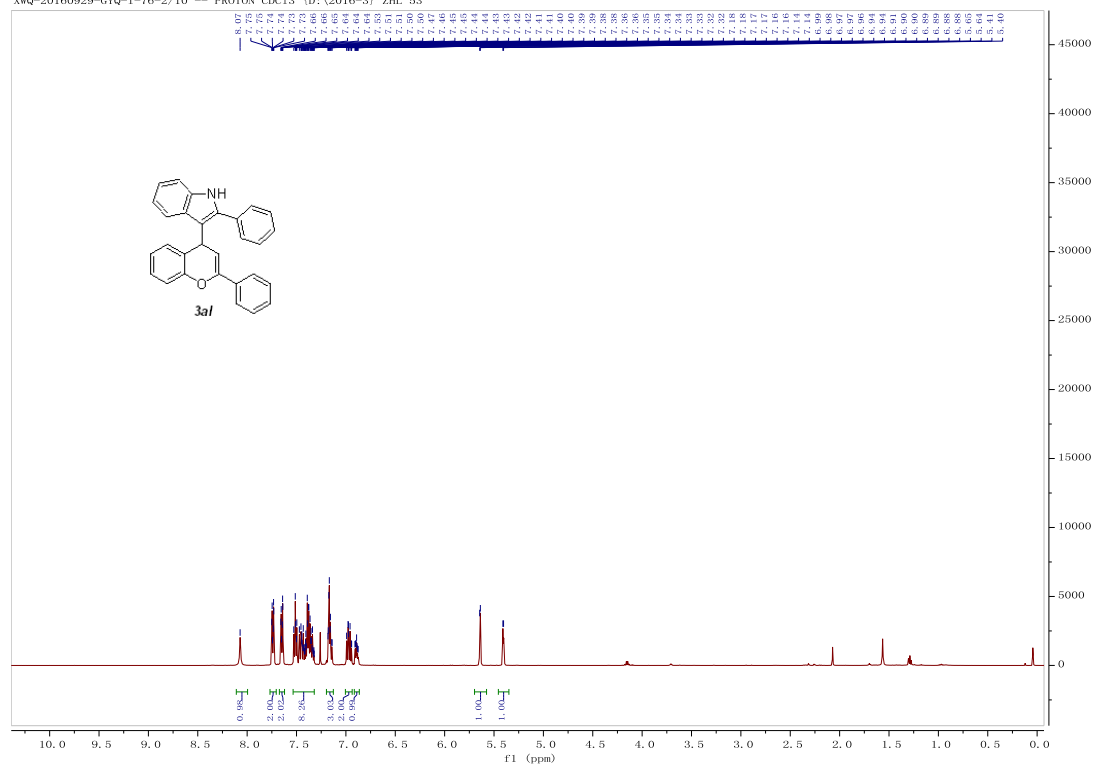


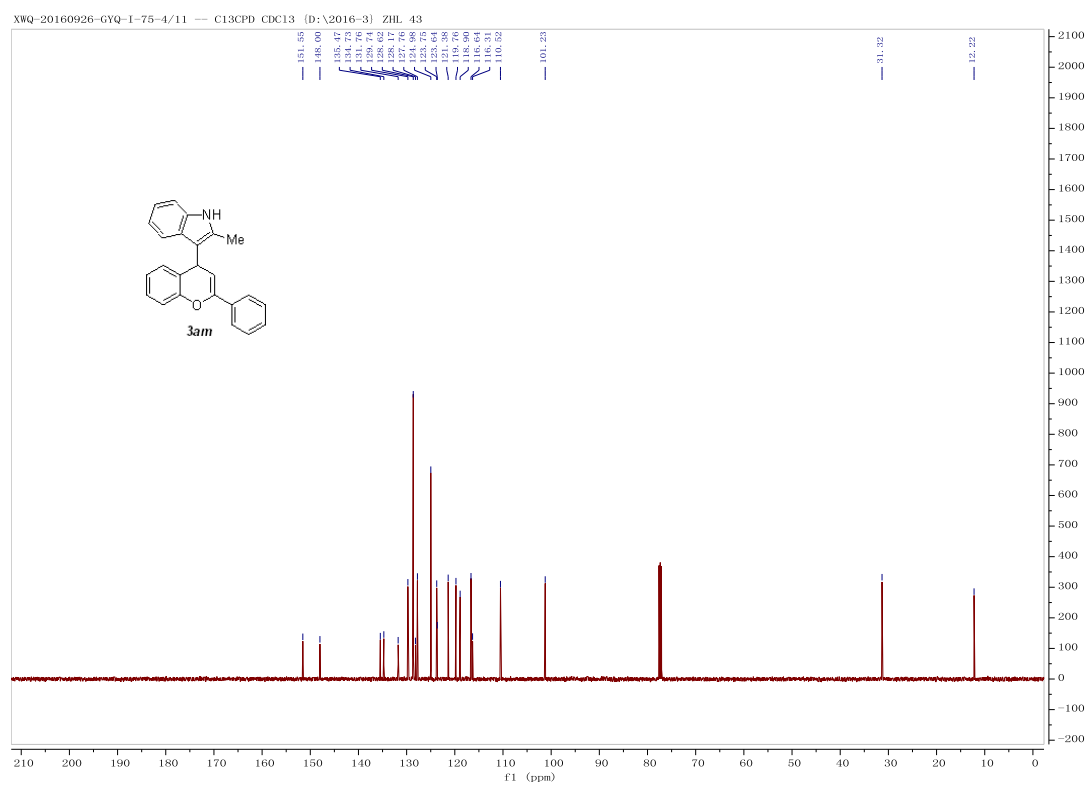
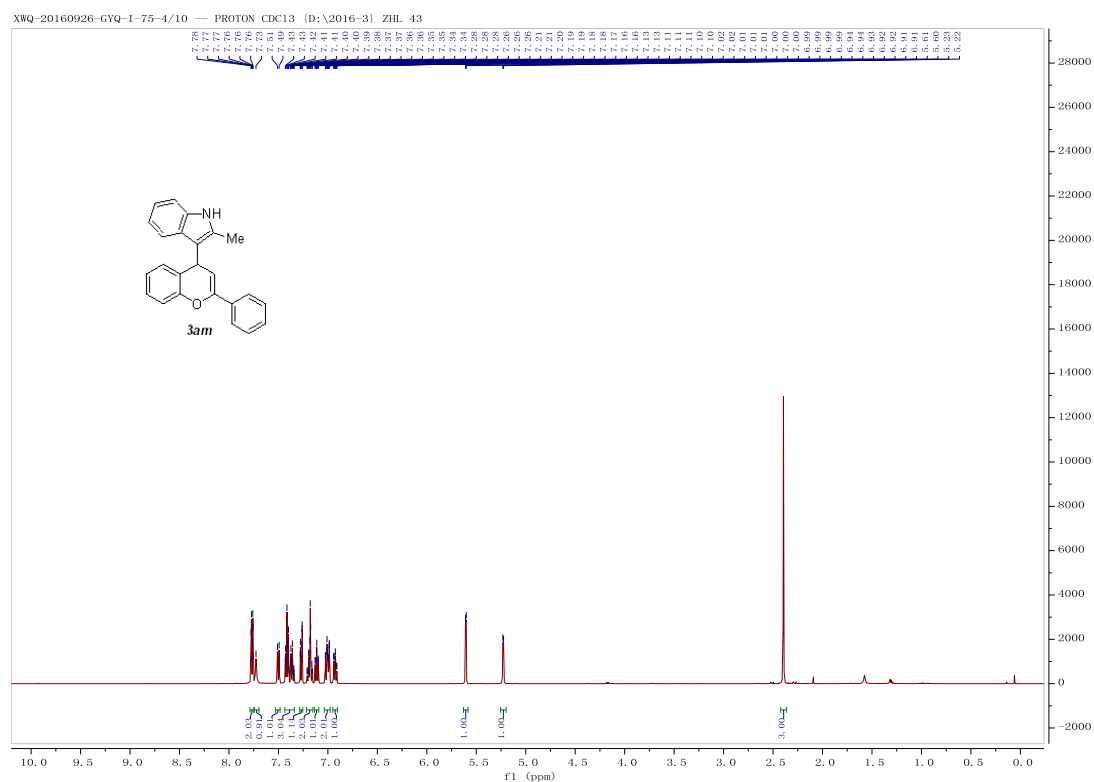


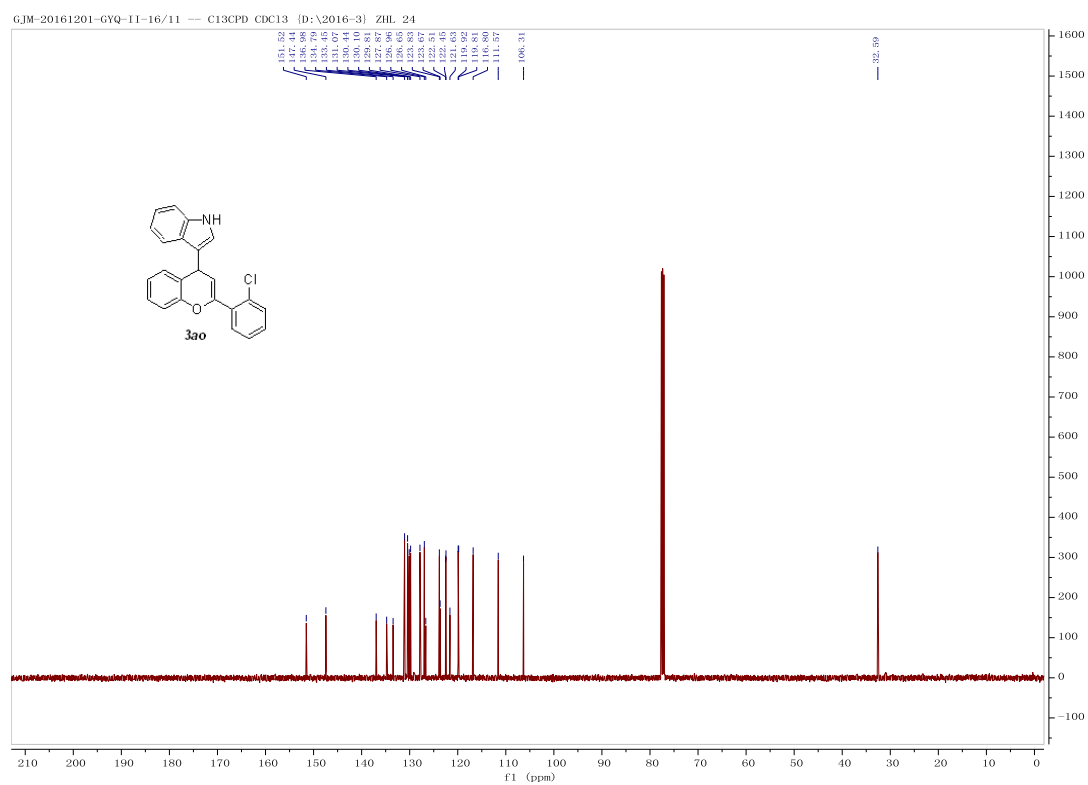
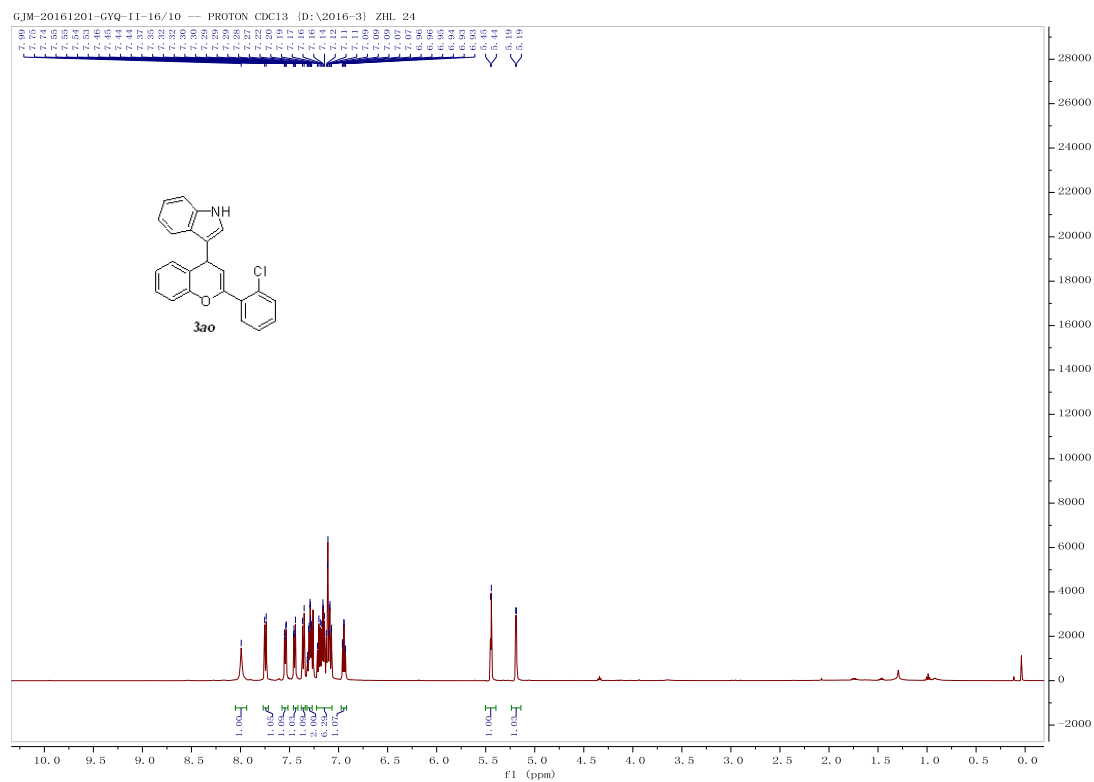




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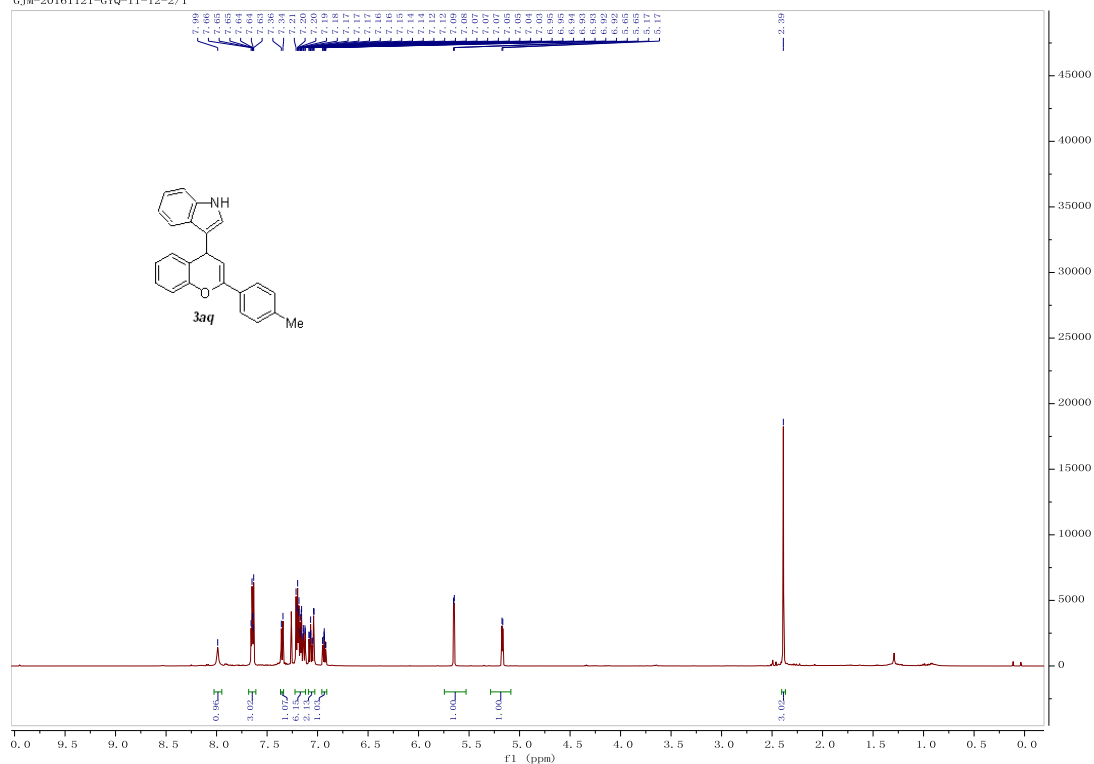




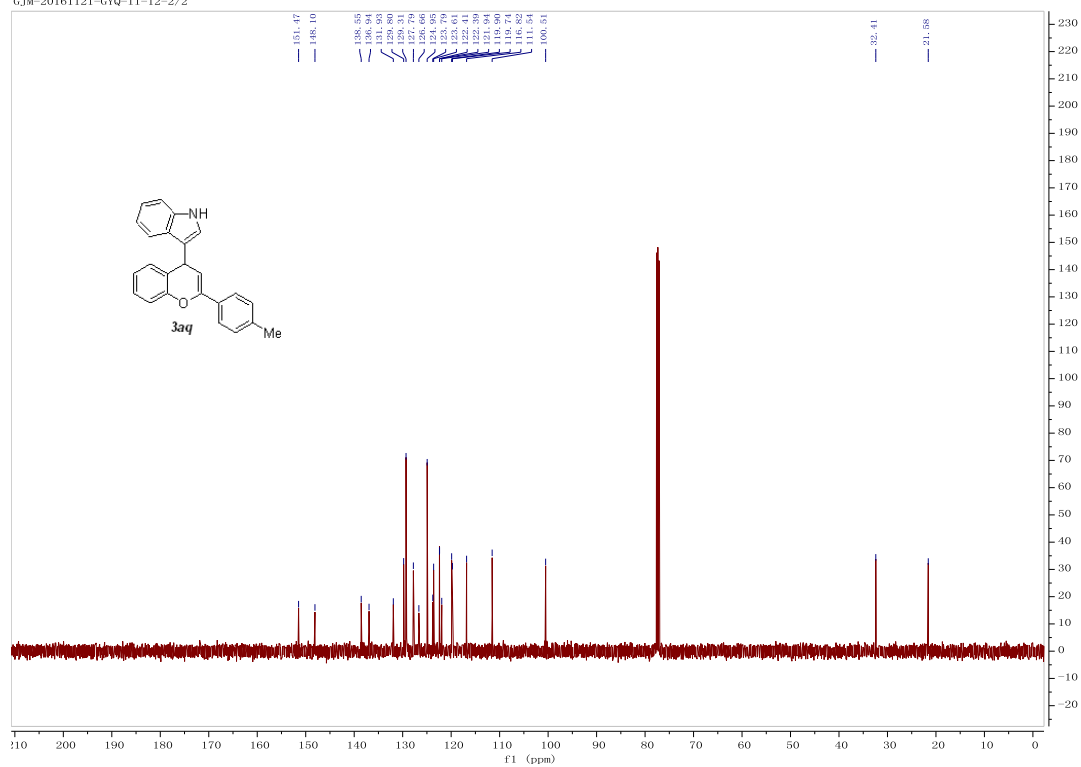




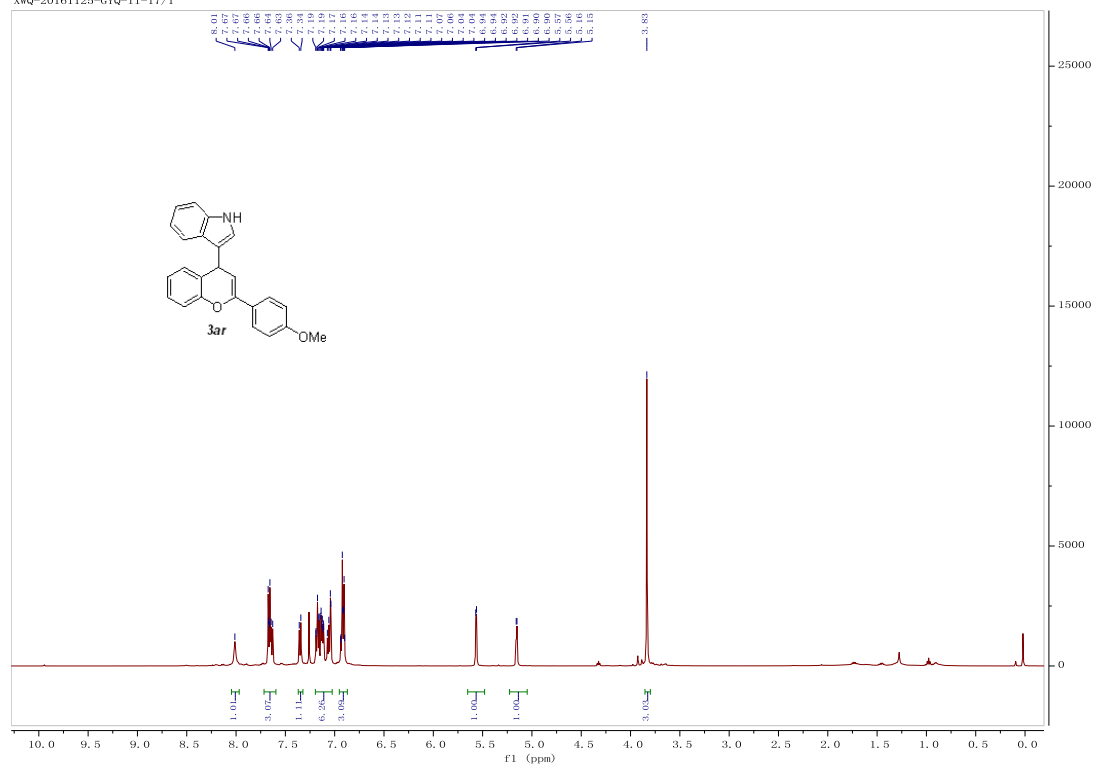
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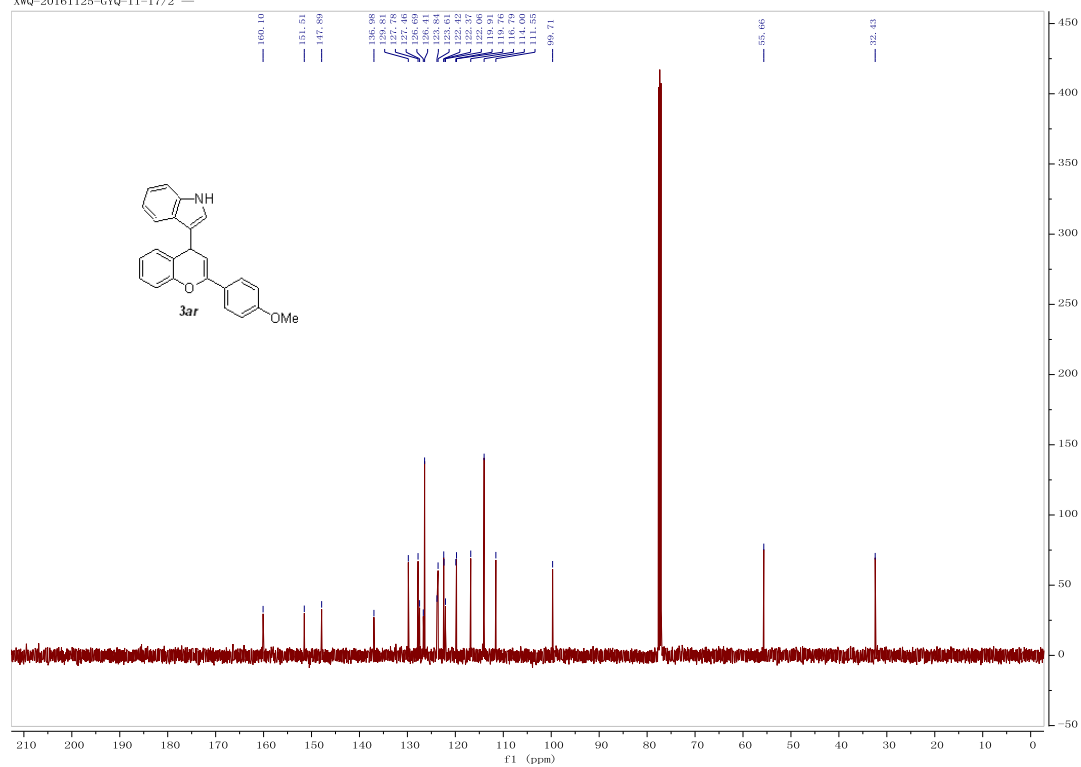
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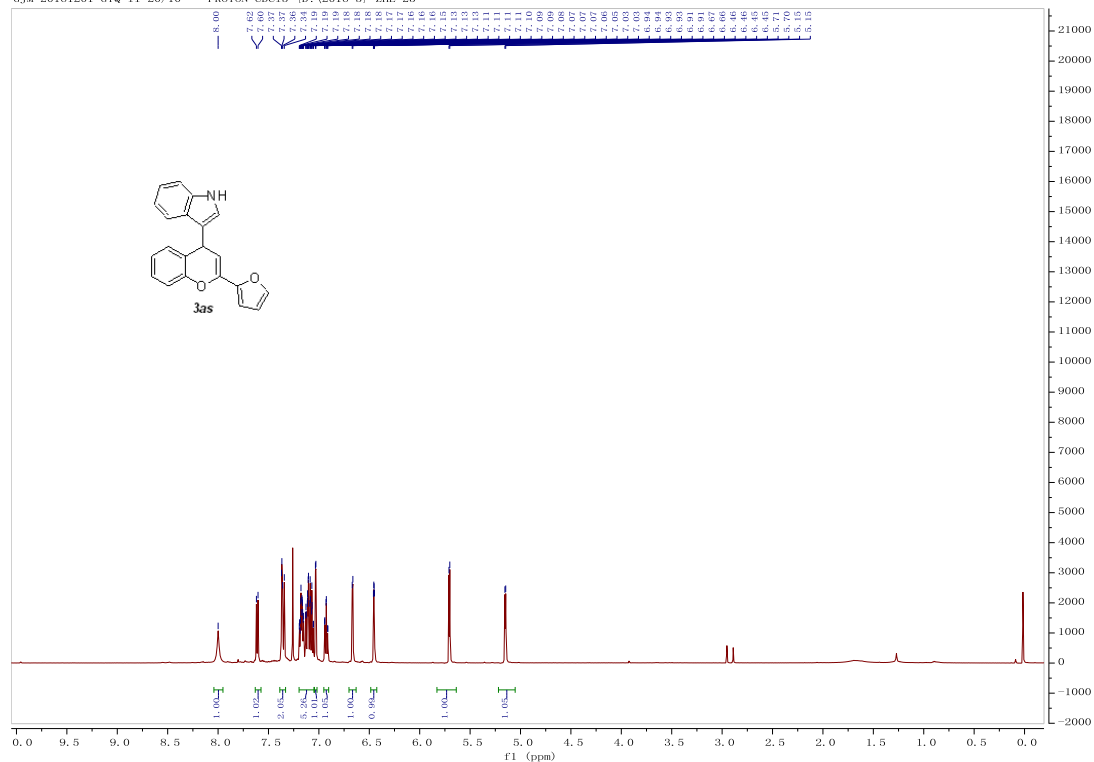
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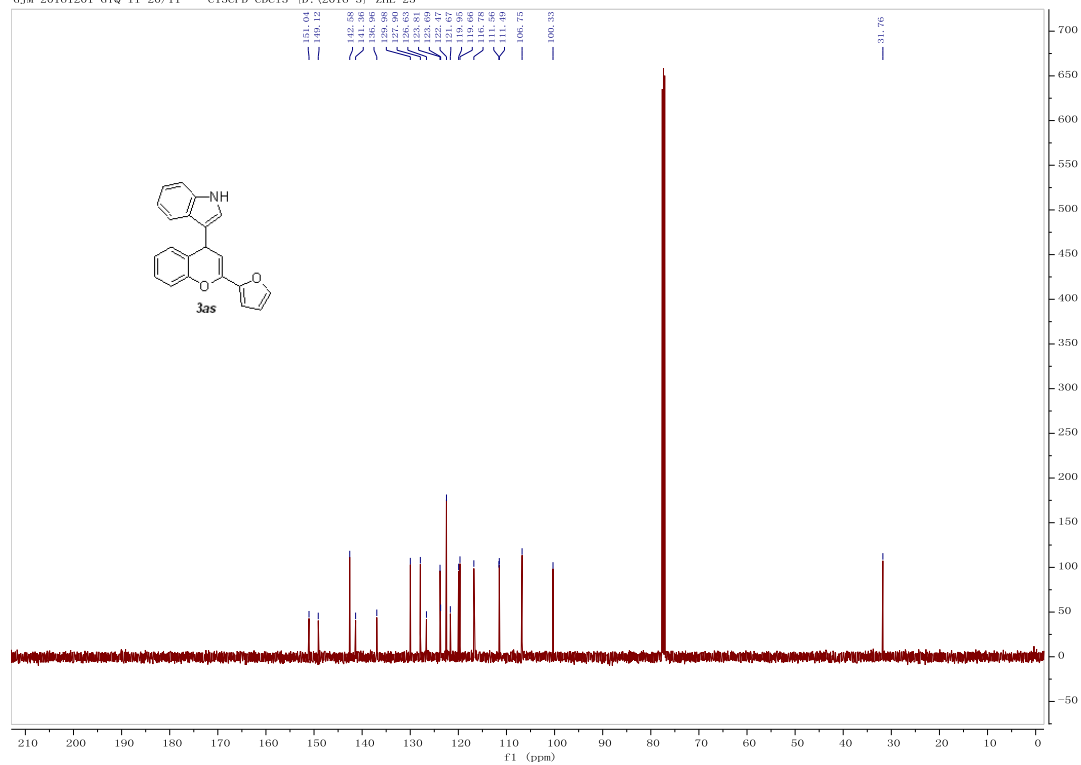
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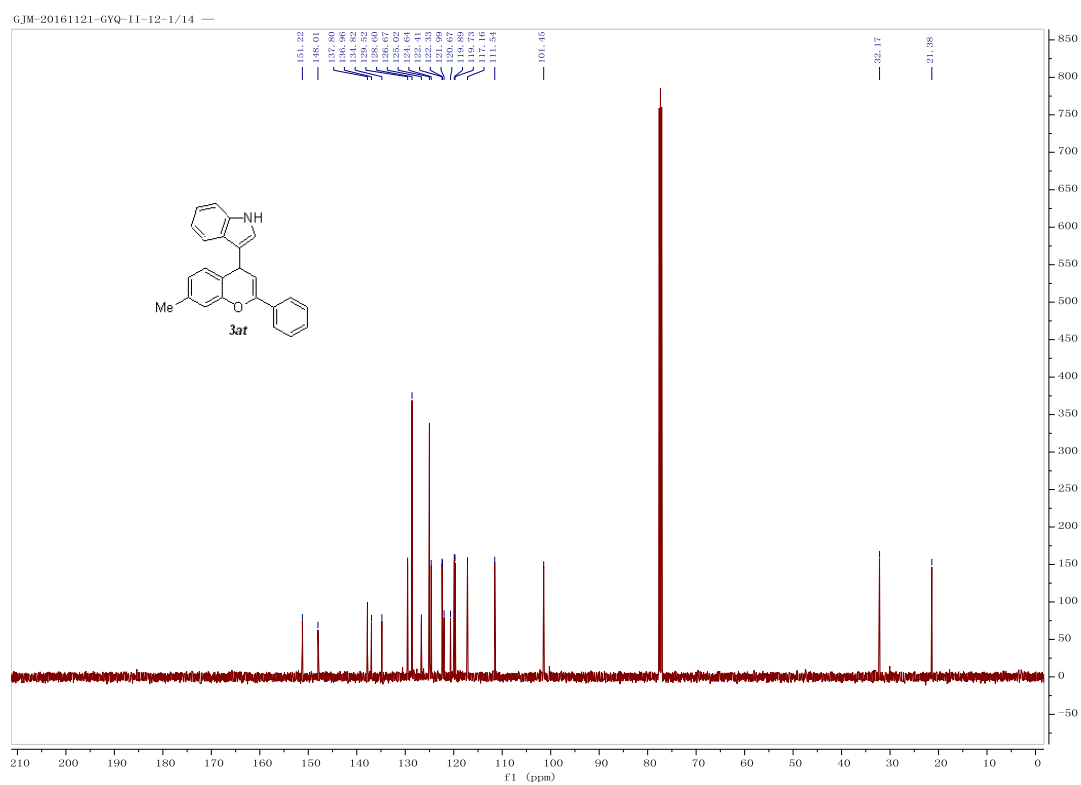
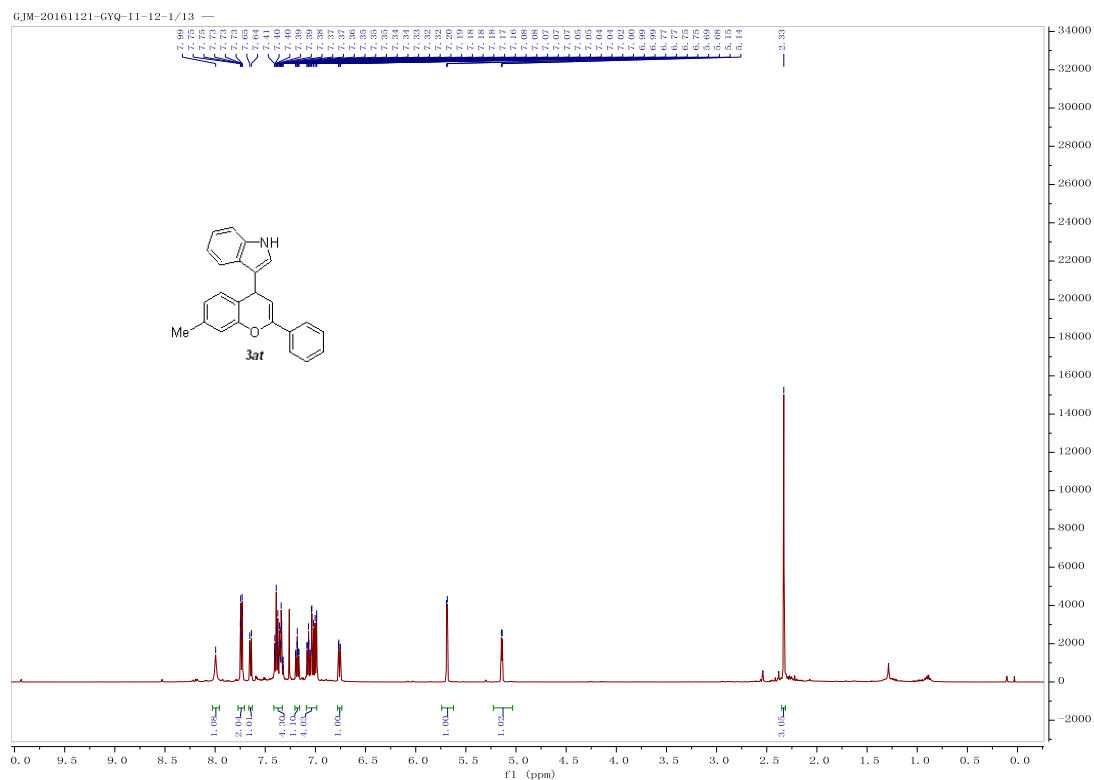


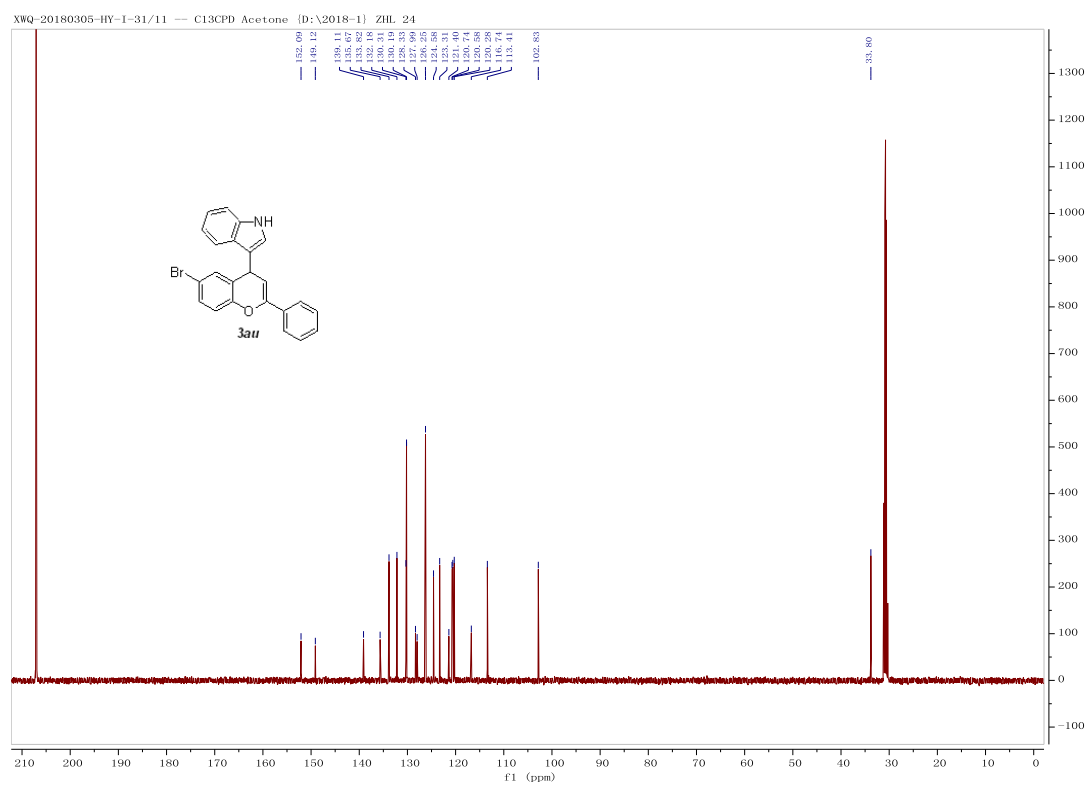
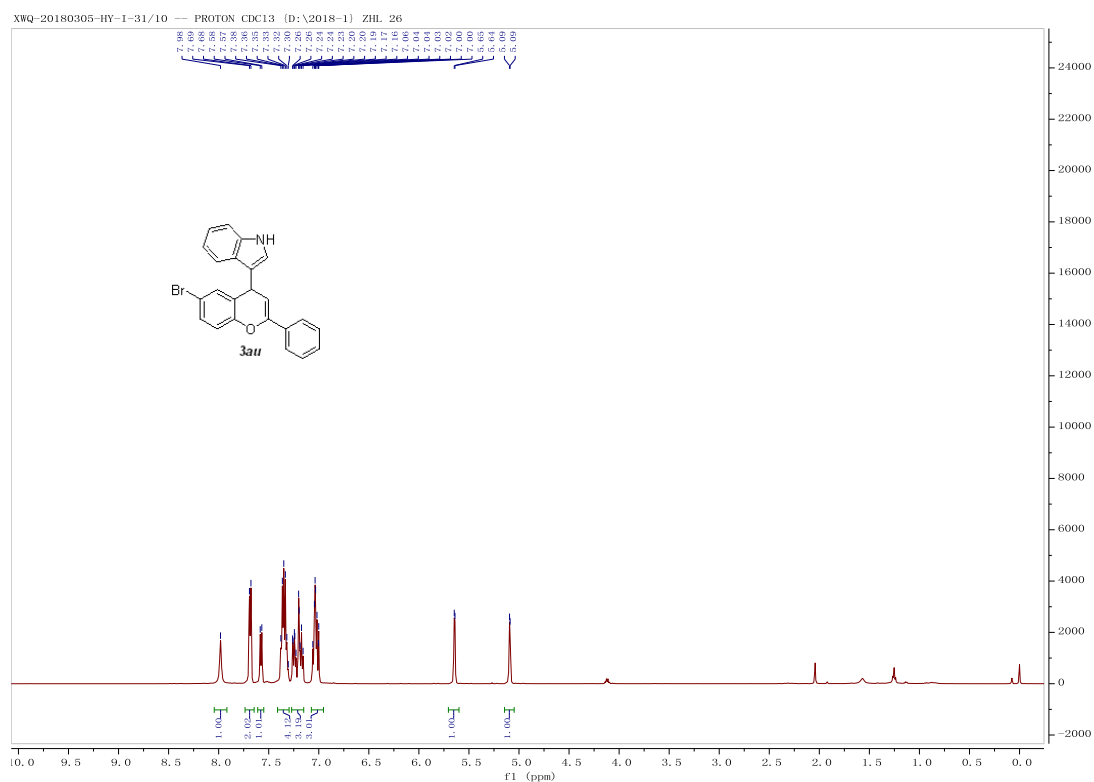
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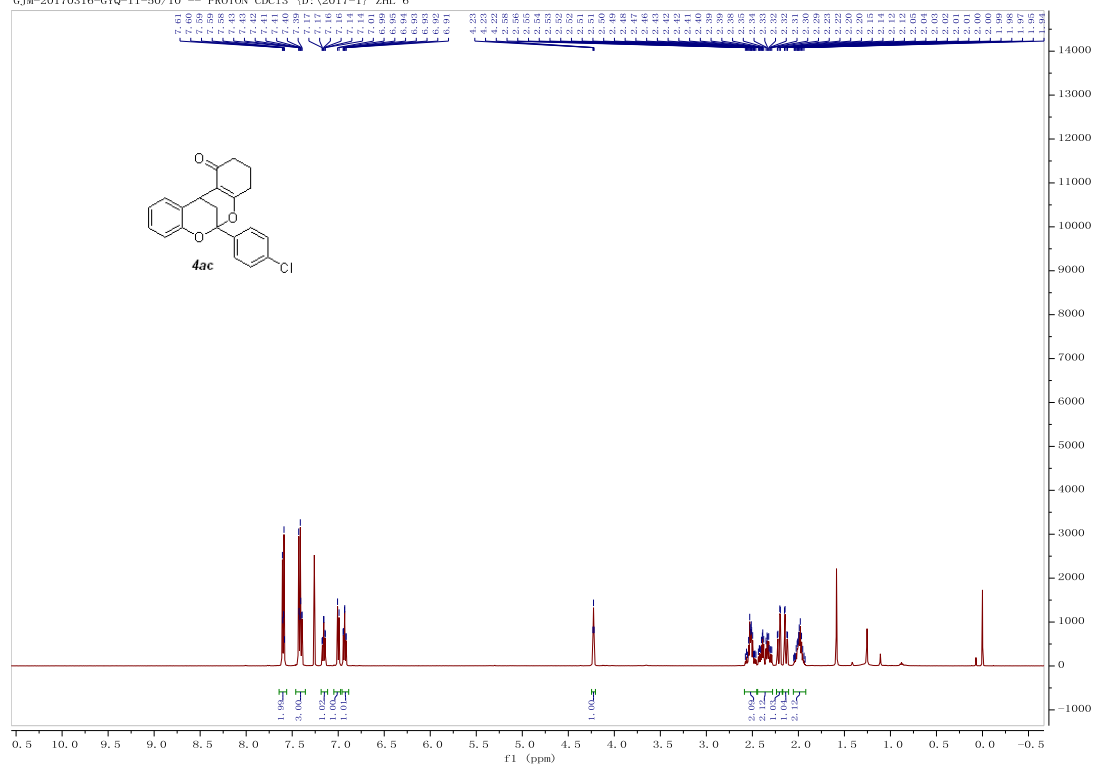
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GJM-20170316-GYQ-11-50/11 -- C13CPD CDC13 [D:\2017-1] ZHL 6

