Design, synthesis and evaluation of structurally diverse *ortho*-acylphenol-diindolylmethane hybrids as anticancer agents

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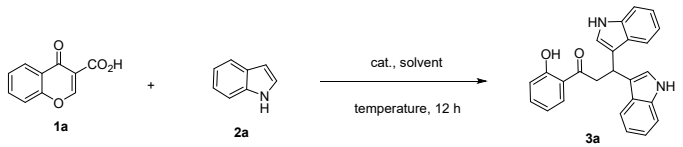
Supporting Information

1. General experimental information

The ^{1}H NMR spectra were recorded on Bruker Avance DMX 400 MHz NMR spectrometers in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. The ^{13}C NMR spectra were recorded on Bruker Avance DMX 100 MHz NMR spectrometers in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. Chemical shifts were reported as δ values (ppm). High-resolution mass spectra (HRMS-ESI) were obtained on a Micro^{TM} Q-TOF Mass Spectrometer. Melting points were uncorrected and recorded on an Electrothermal 9100 digital melting point apparatus.

All cell lines were purchased from the Chinese Academy of Sciences, Kunming Cell Bank. All of which were cultured in RPMI-1640 or DMEM medium (Gibco, USA) supplemented with 10% foetal bovine serum, 1% glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin in a humidified atmosphere with 5% CO_2 at 37°C. The synthetic compounds were placed at -20°C after dissolved in DMSO. Cisplatin purchased from Aladdin Company and bis-indole methane purchased from Macleans Reagent Company.

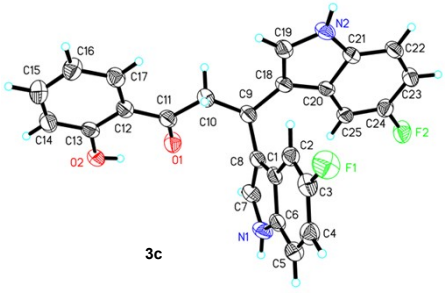
2. Table S1: optimization of reaction conditions for synthesis of compound 3[a]



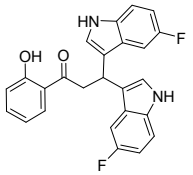
Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)
1	-	Toluene	70	57
2	AcOH (0.2 eq)	Toluene	70	61
3	CF_3CO_2H (0.2 eq)	Toluene	70	60
4	TsOH (0.2 eq)	Toluene	70	75
5	$PhSO_3H$ (0.2 eq)	Toluene	70	81
6	MsOH (0.2 eq)	Toluene	70	74
7	$PhSO_3H$ (0.2 eq)	EtOH	70	79
8	$PhSO_3H$ (0.2 eq)	CH_3CN	70	80
9	$PhSO_3H$ (0.2 eq)	Toluene	60	56
10	$PhSO_3H$ (0.2 eq)	Toluene	80	87
11	$PhSO_3H$ (0.5 eq)	Toluene	80	84

[a] A mixture of chromone-3-carboxylic acid **1a** (0.3 mmol), indole **2a** (1.5 mmol) and Cat. in 0.3 mL of solvent was stirred under specified reaction conditions for 12 h.

3. X-Ray crystal data for compound 3c and 3h



3c

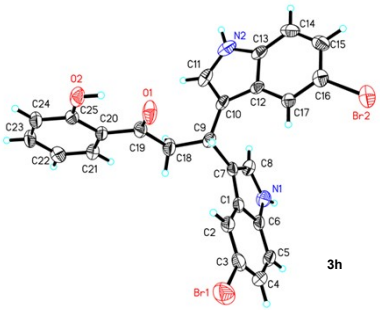


3c

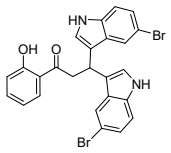
Table S2 Crystal data and structure refinement for 3c

Identification code	**3c**
Empirical formula	$C_{25}H_{18}F_2N_2O_2$
Formula weight	416.41
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å, b/Å, c/Å	11.269(3), 8.445(2), 20.524(4)
α/°, β/°, γ/°,	90, 96.54(2), 90.
Volume/Å^3	1940.5(8)
Z	4
ρ_{calc}g/cm^3	1.425
μ/mm^{-1}	0.104
F(000)	864.0
Radiation	Mo Kα (λ = 0.71073)
Crystal size/mm^3	0.13 × 0.12 × 0.11
2Θ range for data collection/°	3.996 to 49.988
Index ranges	-12 ≤ h ≤ 13, -9 ≤ k ≤ 10, -24 ≤ l ≤ 19
Reflections collected	8553
Independent reflections	3412 [R_{int} = 0.0529, R_{sigma} = 0.0604]
Data/restraints/parameters	3412/7/281
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0604, wR_2 = 0.1554
Final R indexes [all data]	R_1 = 0.0902, wR_2 = 0.1842
Largest diff. peak/hole / e Å^{-3}	0.29/-0.21

Crystal Data for $C_{25}H_{18}F_2N_2O_2$ (*M* =416.41 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 11.269(3) Å, *b* = 8.445(2) Å, *c* = 20.524(4) Å, *β* = 96.54(2)°, *V* = 1940.5(8) Å^3, *Z* = 4, *T* = 293(2) K, μ(Mo Kα) = 0.104 mm^{-1}, *Dcalc* = 1.425 g/cm^3, 8553 reflections measured (3.996° ≤ 2Θ ≤ 49.988°), 3412 unique (R_{int} = 0.0529, R_{sigma} = 0.0604) which were used in all calculations. The final R_1 was 0.0604 (I > 2σ(I)) and wR_2 was 0.1842 (all data).



3h



3h

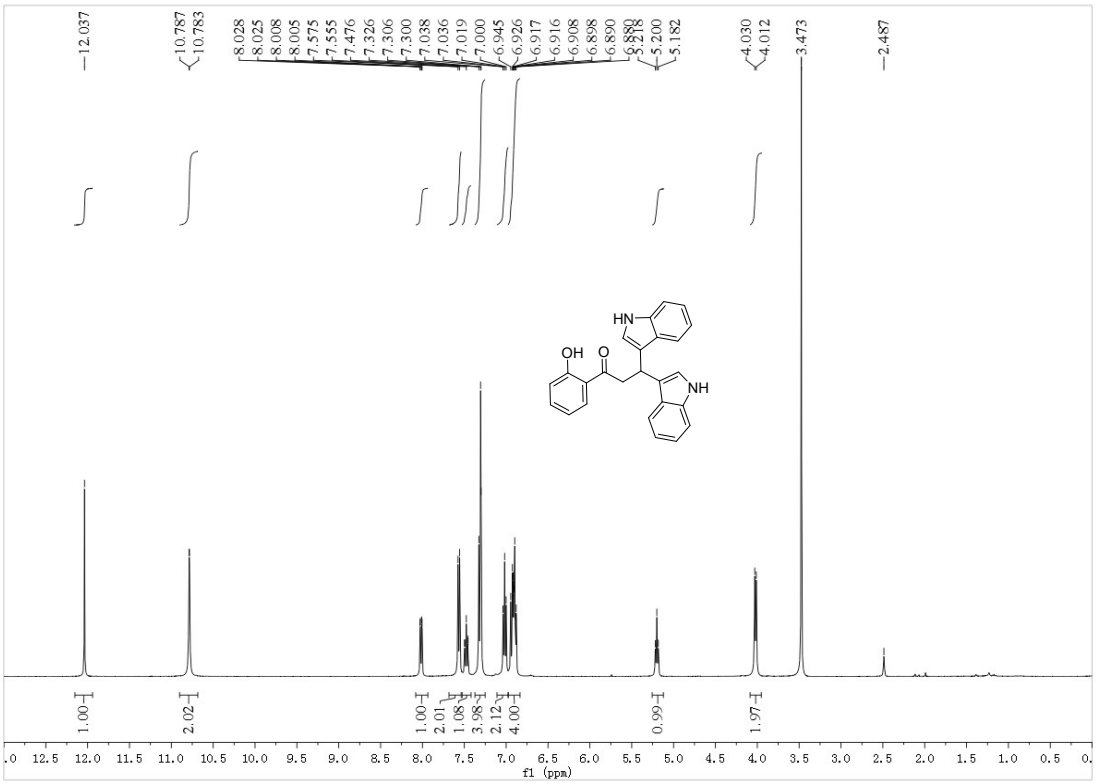
Table S3 Crystal data and structure refinement for 3h

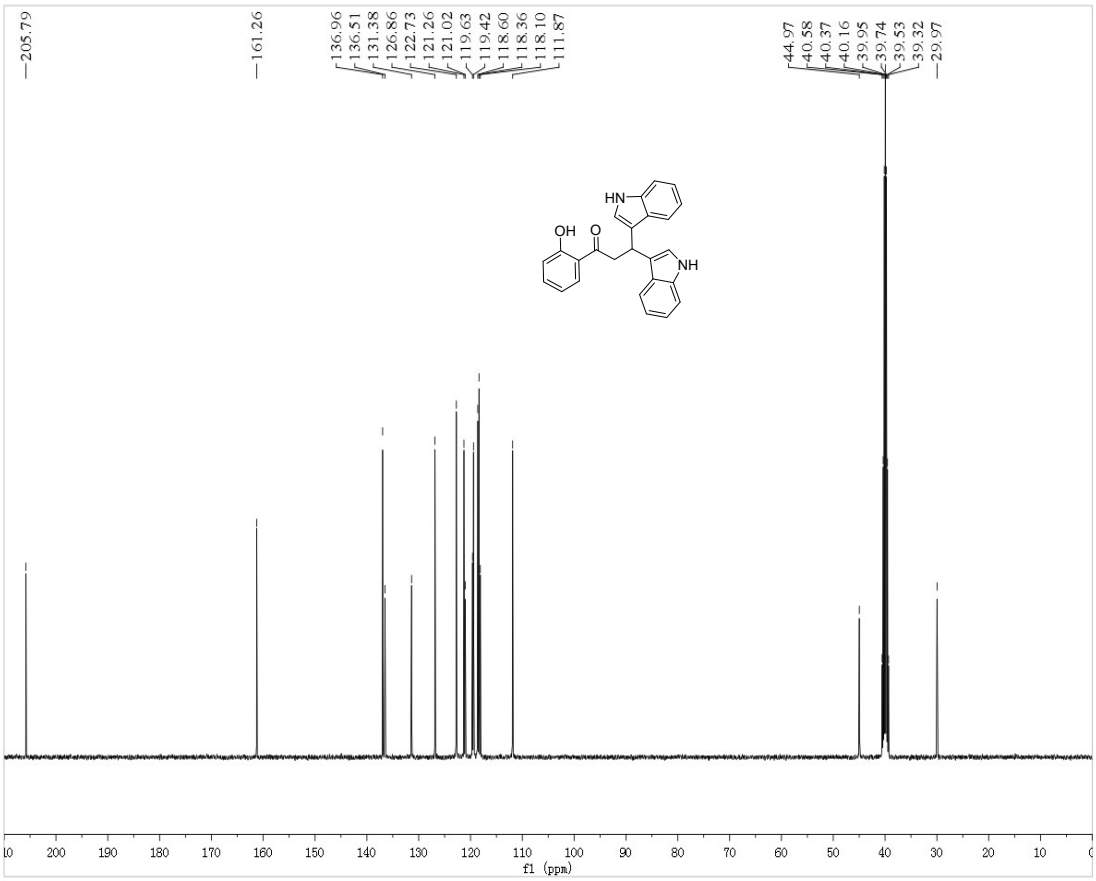
Identification code	**3h**
Empirical formula	$C_{25}H_{18}Br_2N_2O_2$
Formula weight	538.23
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	$Pna2_1$
a/Å, b/Å, c/Å	16.854(2), 22.397(2), 5.6423(5)
α/°, β/°, γ/°,	90, 90, 90.
Volume/Å^3	2129.8(4)
Z	4
ρ_{calc}g/cm^3	1.679
μ/mm^{-1}	3.832
F(000)	1072.0
Radiation	Mo Kα (λ = 0.71073)
Crystal size/mm^3	0.14 × 0.12 × 0.11
2Θ range for data collection/°	4.368 to 49.984
Index ranges	-19 ≤ h ≤ 20, -26 ≤ k ≤ 25, -6 ≤ l ≤ 5
Reflections collected	12574
Independent reflections	3466 [R_{int} = 0.0504, R_{sigma} = 0.0547]
Data/restraints/parameters	3466/1/281
Goodness-of-fit on F^2	1.016
Final R indexes [I>=2σ (I)]	R_1 = 0.0412, wR_2 = 0.0708
Final R indexes [all data]	R_1 = 0.0711, wR_2 = 0.0802
Largest diff. peak/hole / e Å^{-3}	0.35/-0.36
Flack/Hooft parameter	0.012(9)/0.047(8)

Crystal Data for $C_{25}H_{18}Br_2N_2O_2$ (*M* =538.23 g/mol): orthorhombic, space group $Pna2_1$ (no. 33), *a* = 16.854(2) Å, *b* = 22.397(2) Å, *c* = 5.6423(5) Å, *V* = 2129.8(4) Å^3, *Z* = 4, *T* = 293(2) K, μ(Mo Kα) = 3.832 mm^{-1}, *Dcalc* = 1.679 g/cm^3, 12574 reflections measured (4.368° ≤ 2Θ ≤ 49.984°), 3466 unique (R_{int} = 0.0504, R_{sigma} = 0.0547) which were used in all calculations. The final R_1 was 0.0412 (I > 2σ(I)) and wR_2 was 0.0802 (all data).

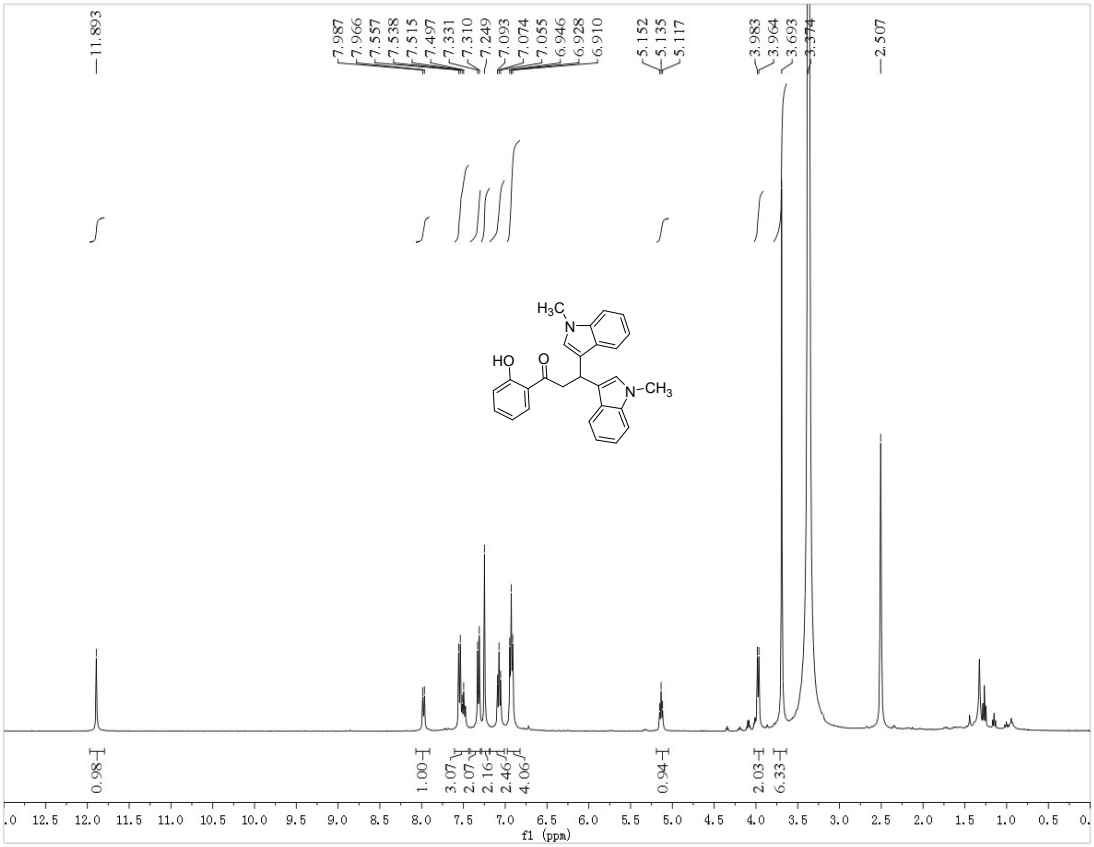
4. The copies of ^{1}H NMR, ^{13}C NMR spectra for compounds 3

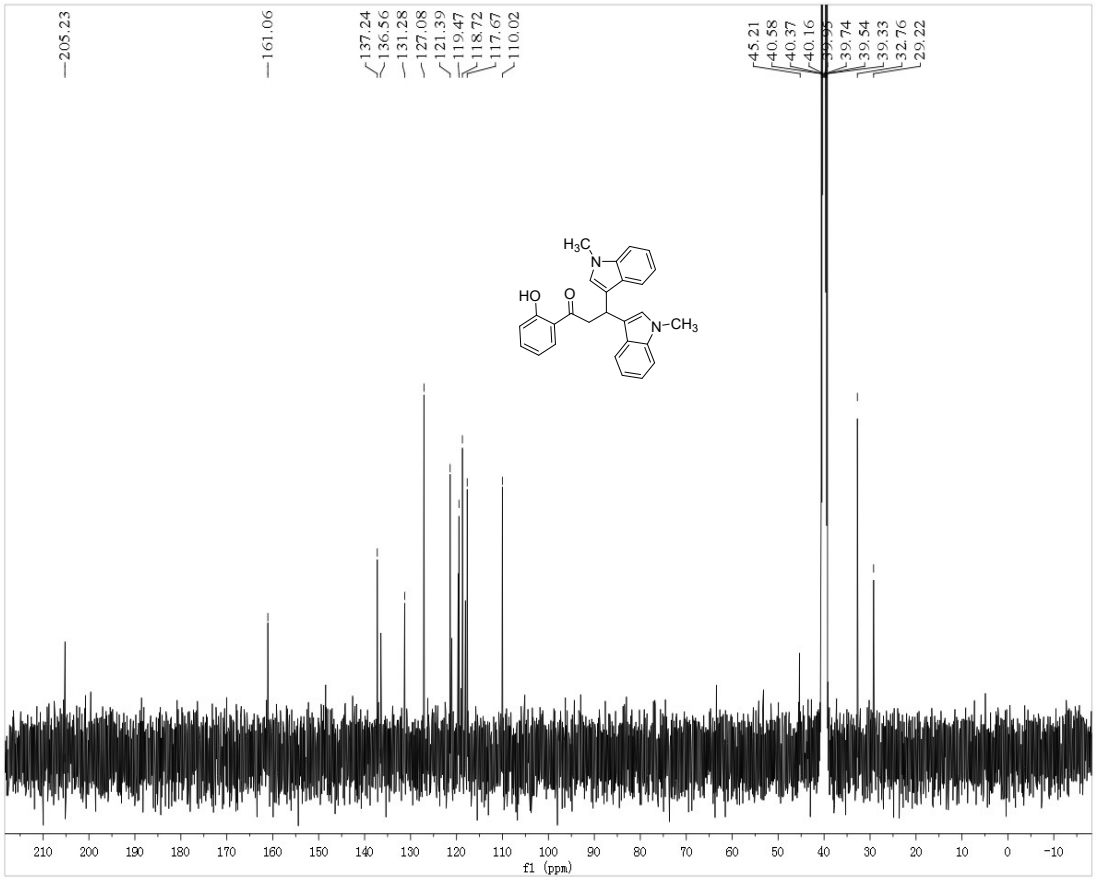
^{1}H and ^{13}C NMR of 3a



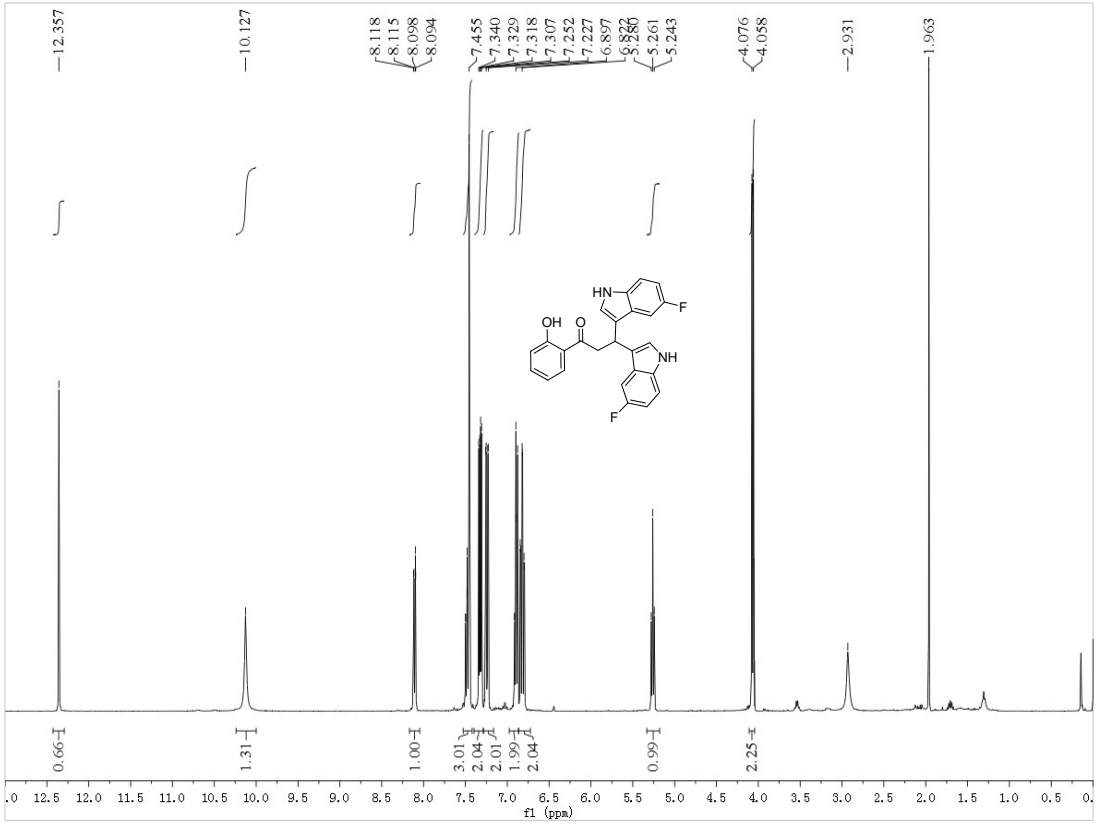


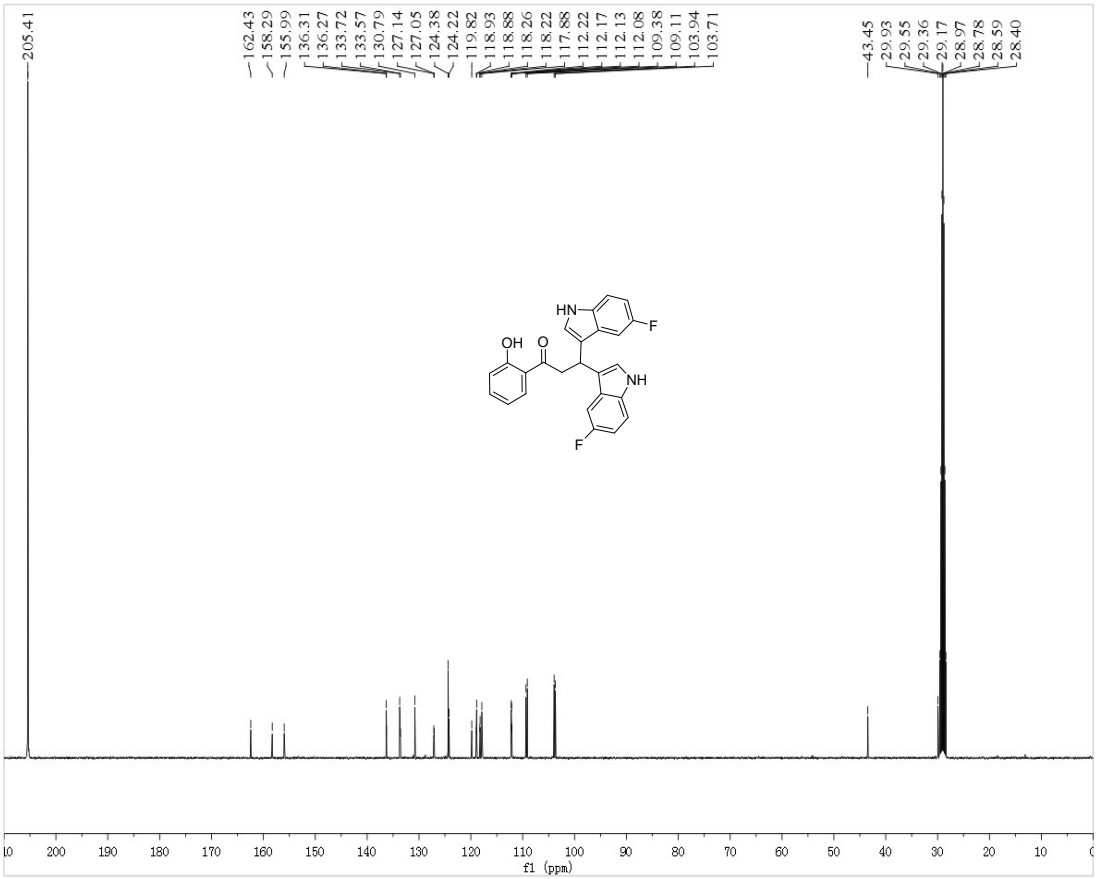
^{1}H and ^{13}C NMR of 3b



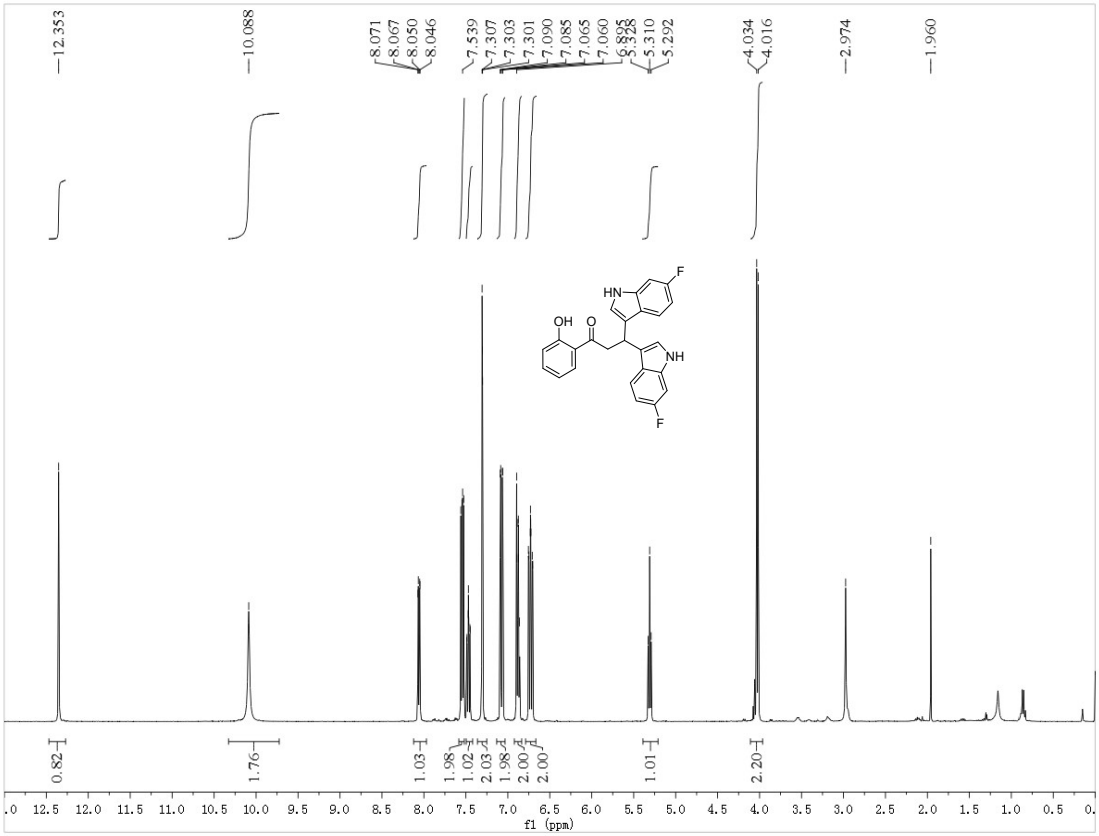


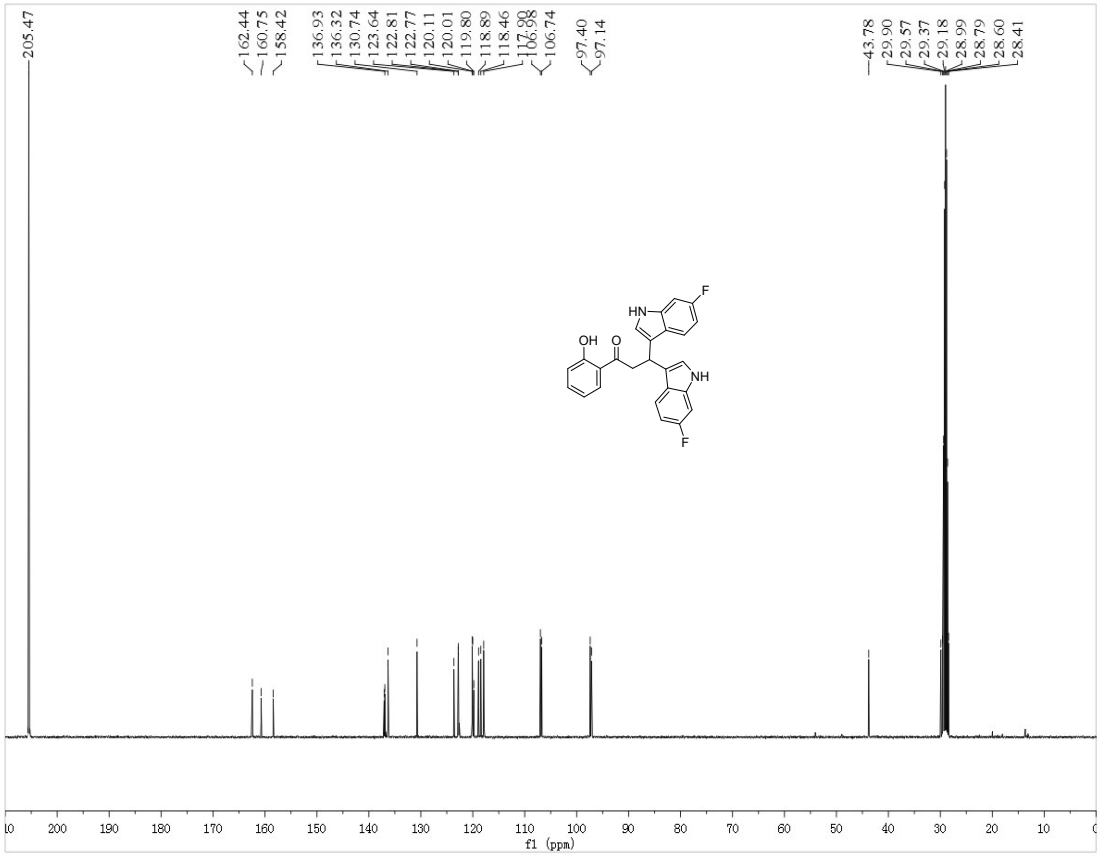
^{1}H and ^{13}C NMR of 3c



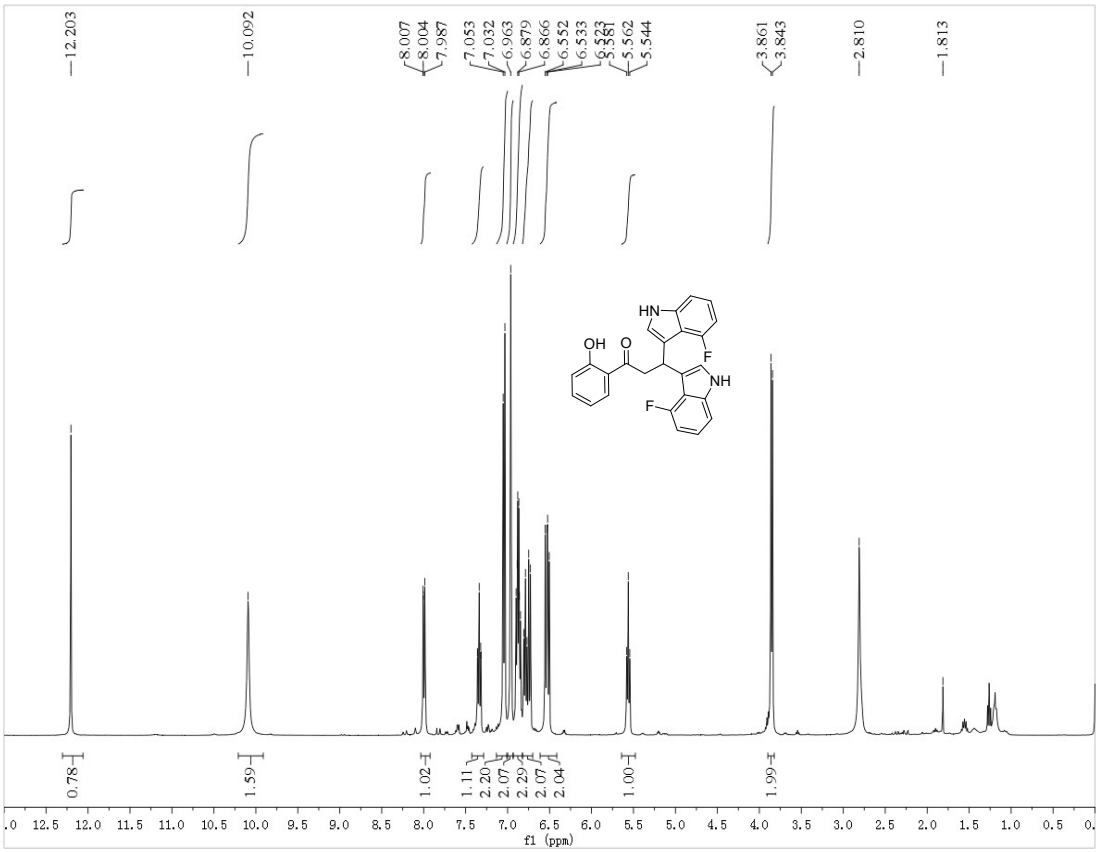


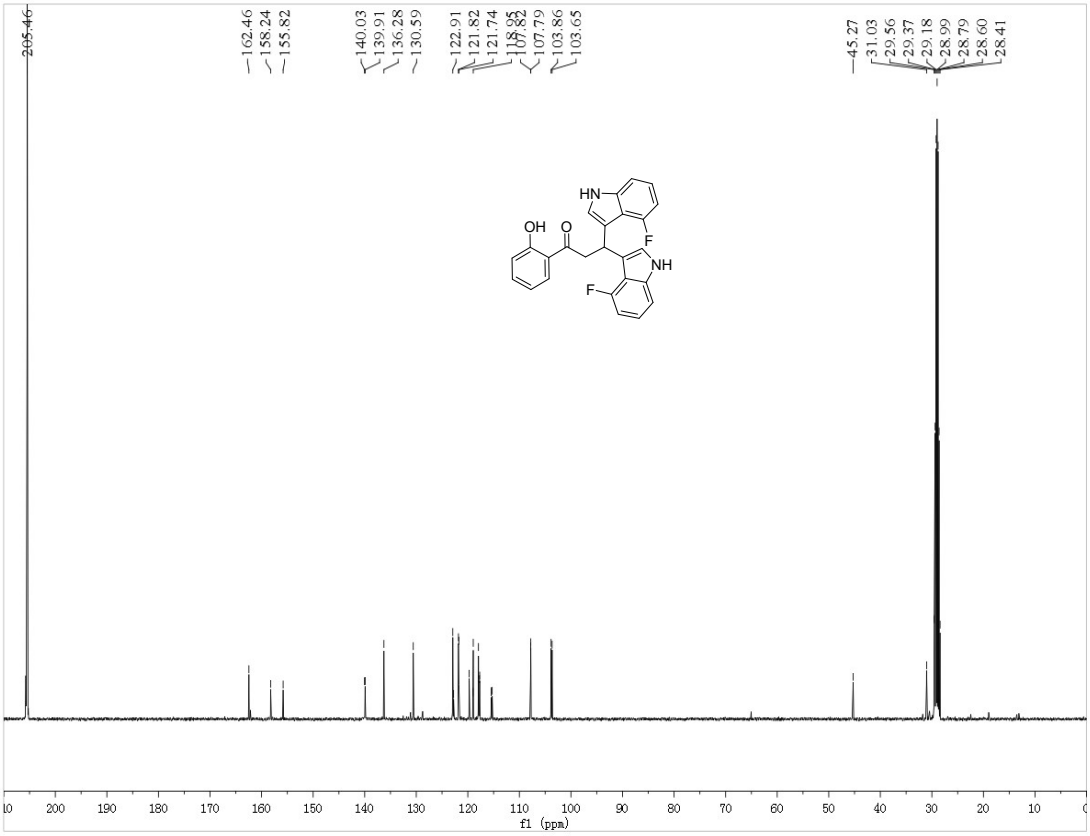
^{1}H and ^{13}C NMR of 3d



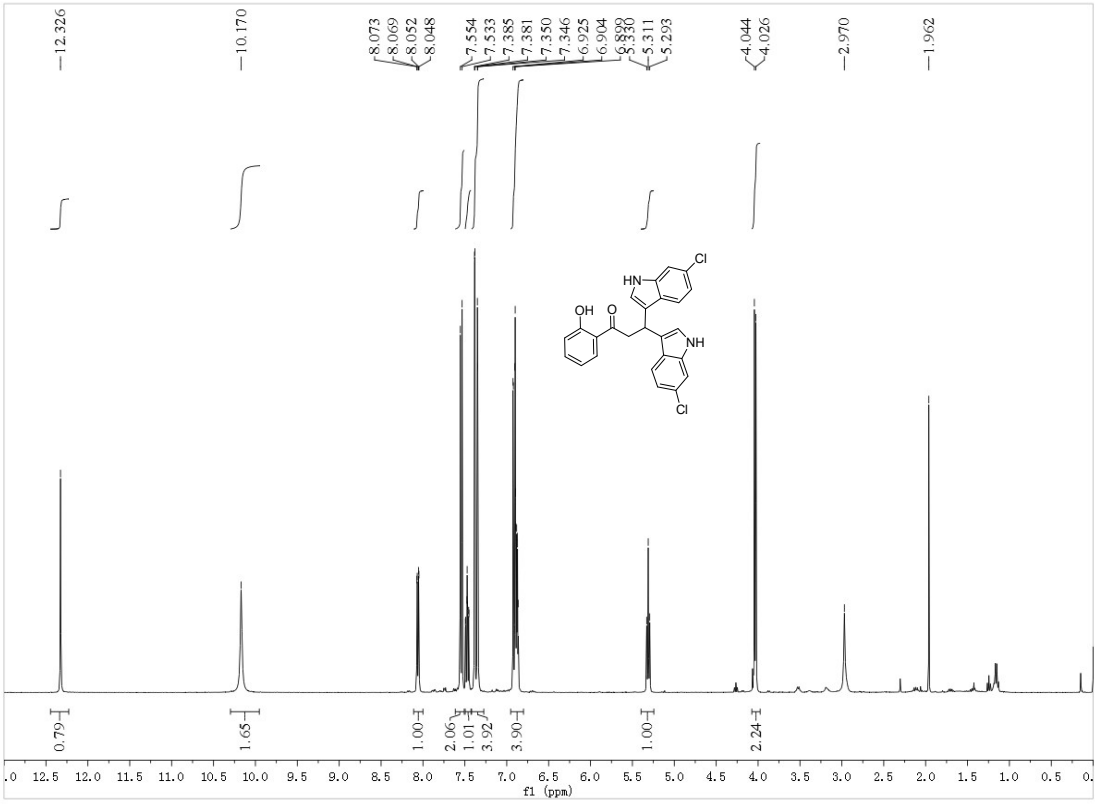


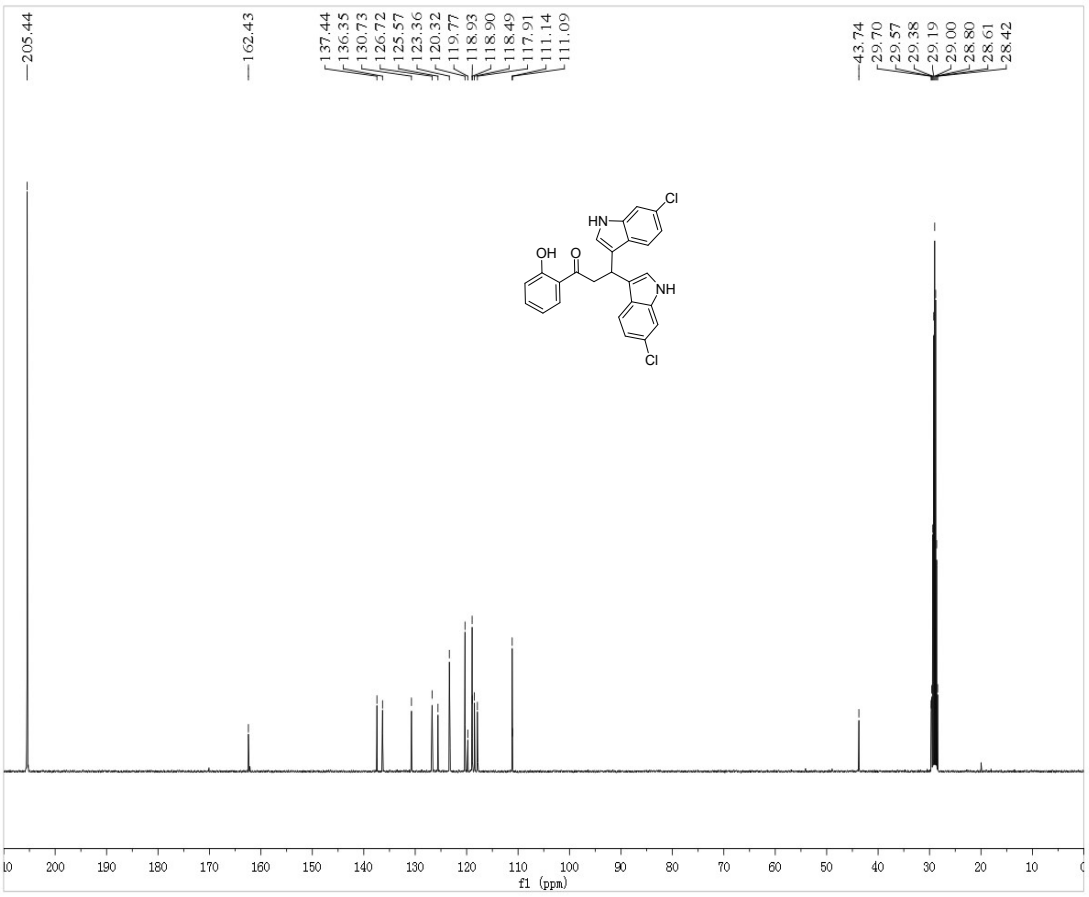
^{1}H and ^{13}C NMR of 3e



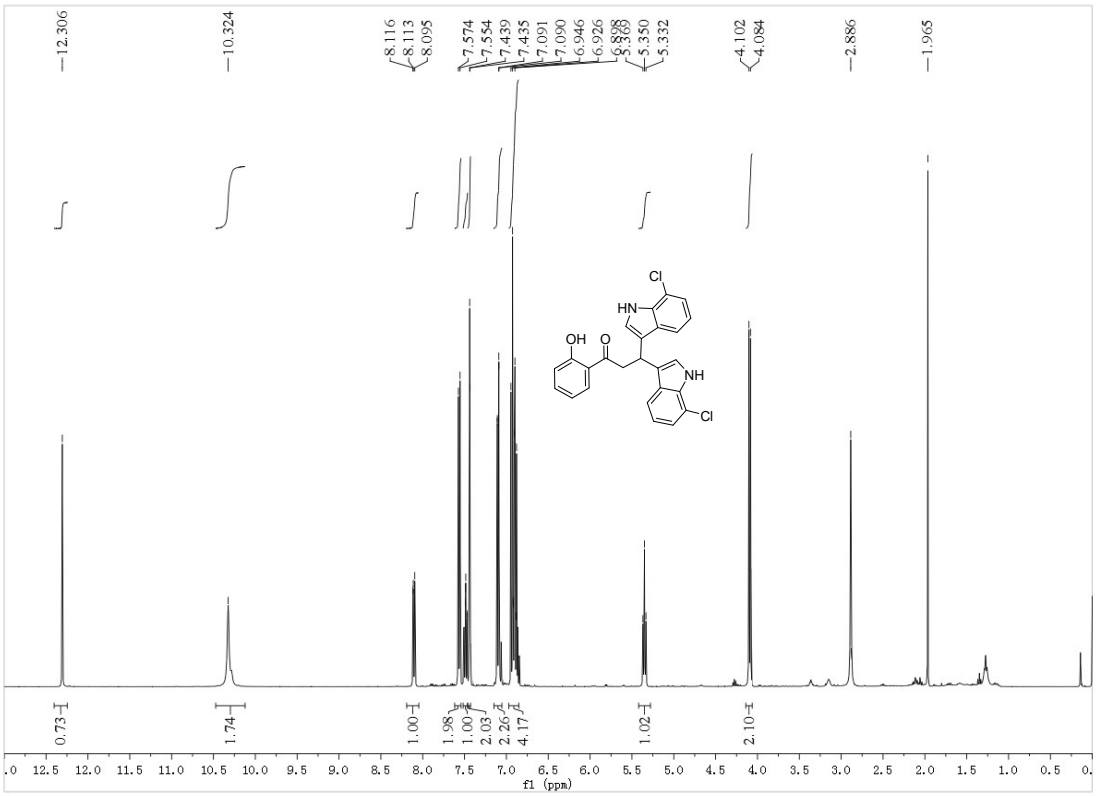


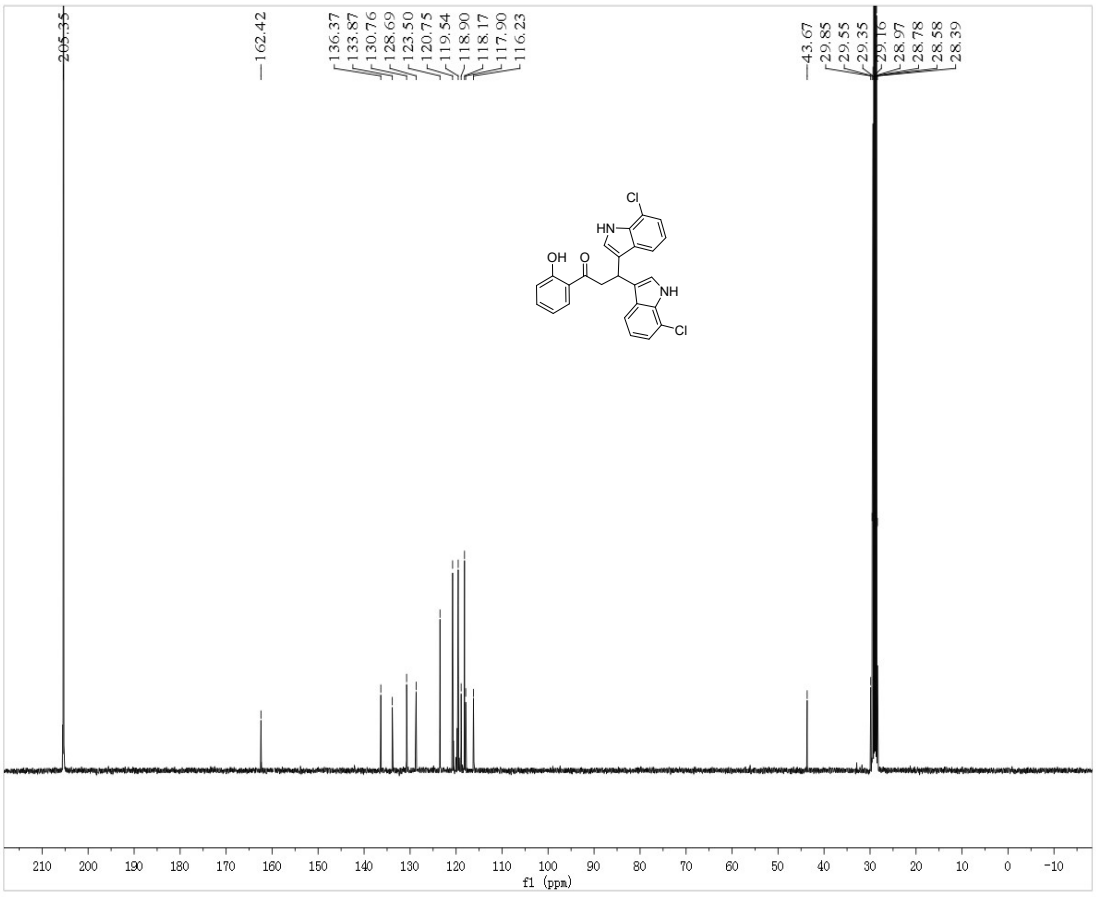
^{1}H and ^{13}C NMR of 3f



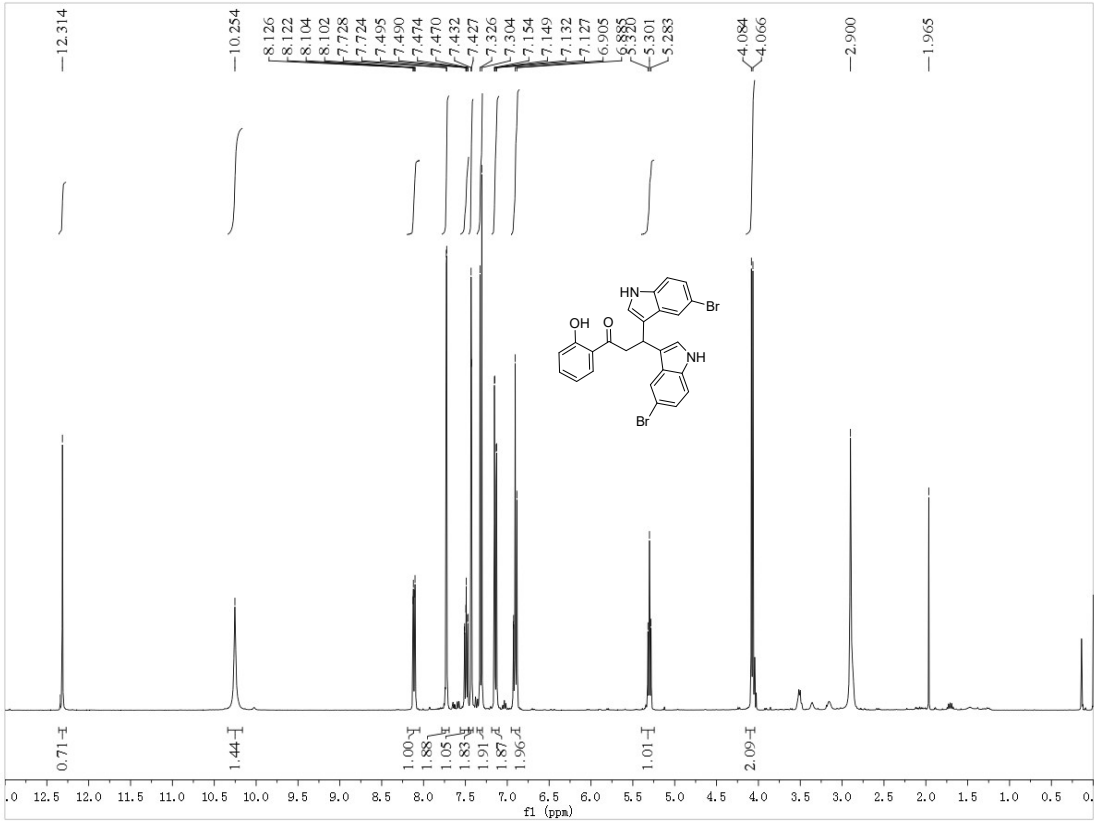


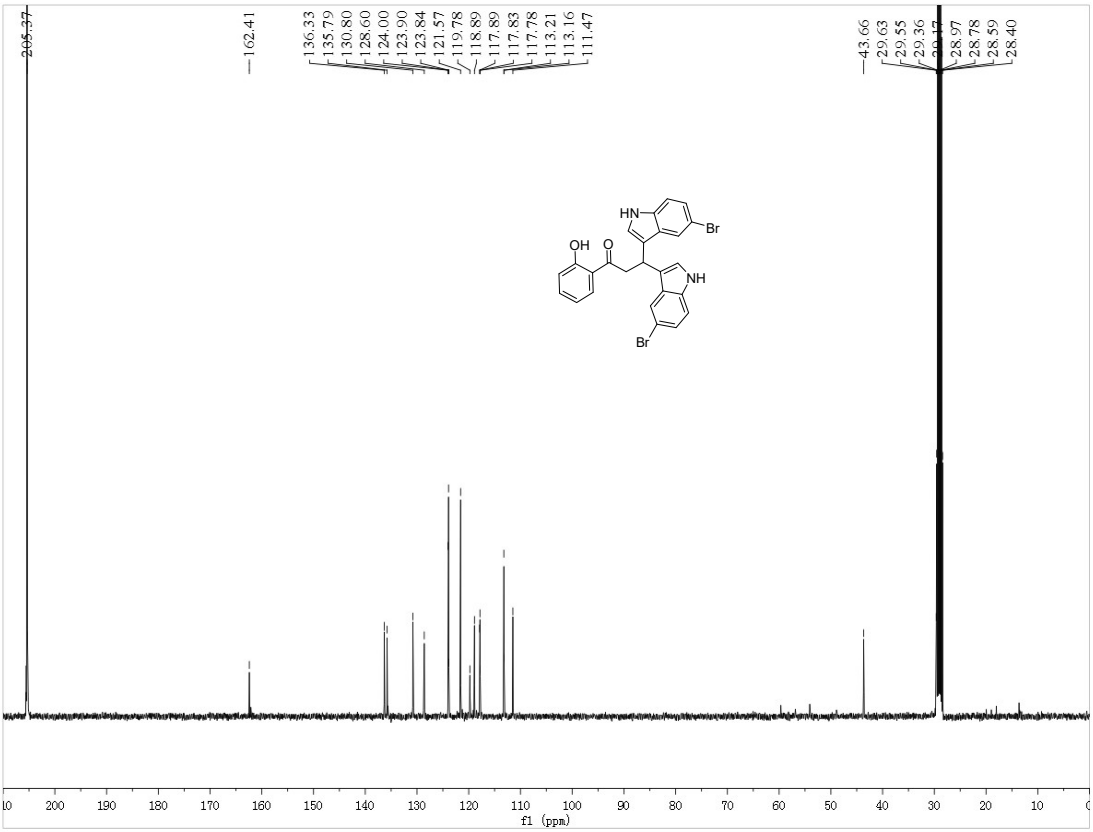
^{1}H and ^{13}C NMR of 3g



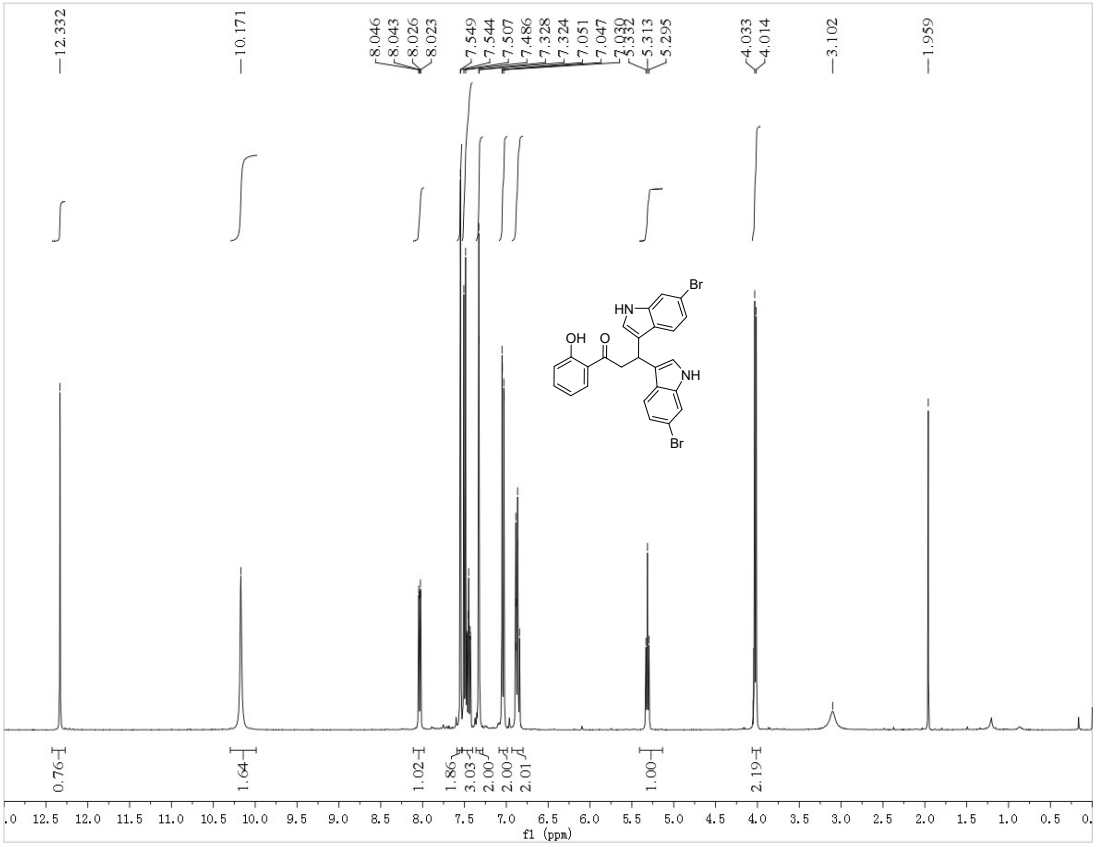


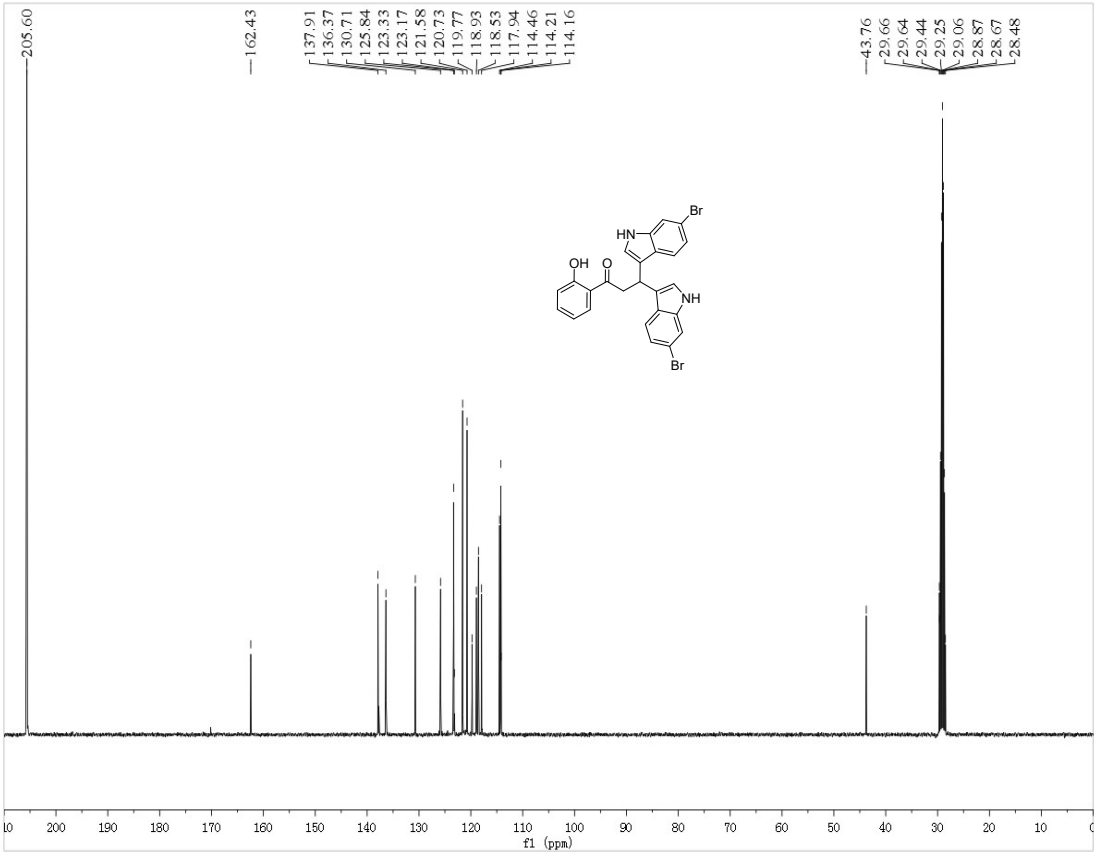
^{1}H and ^{13}C NMR of 3h



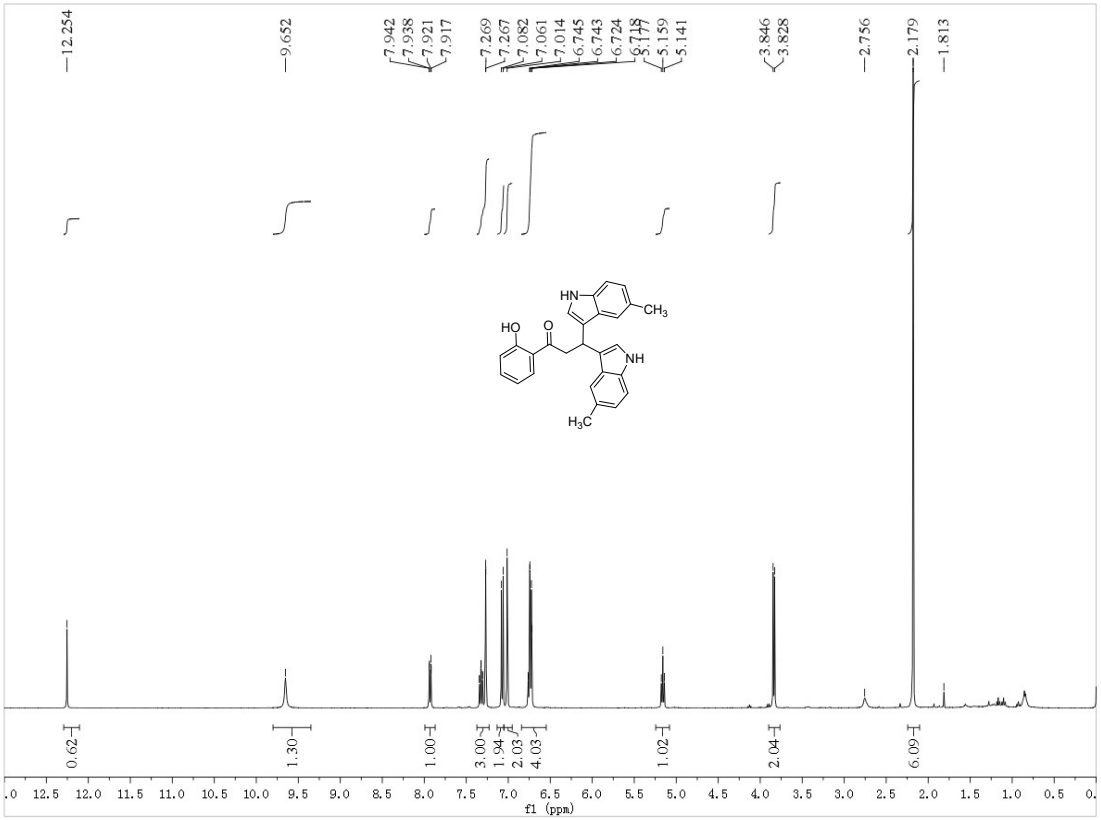


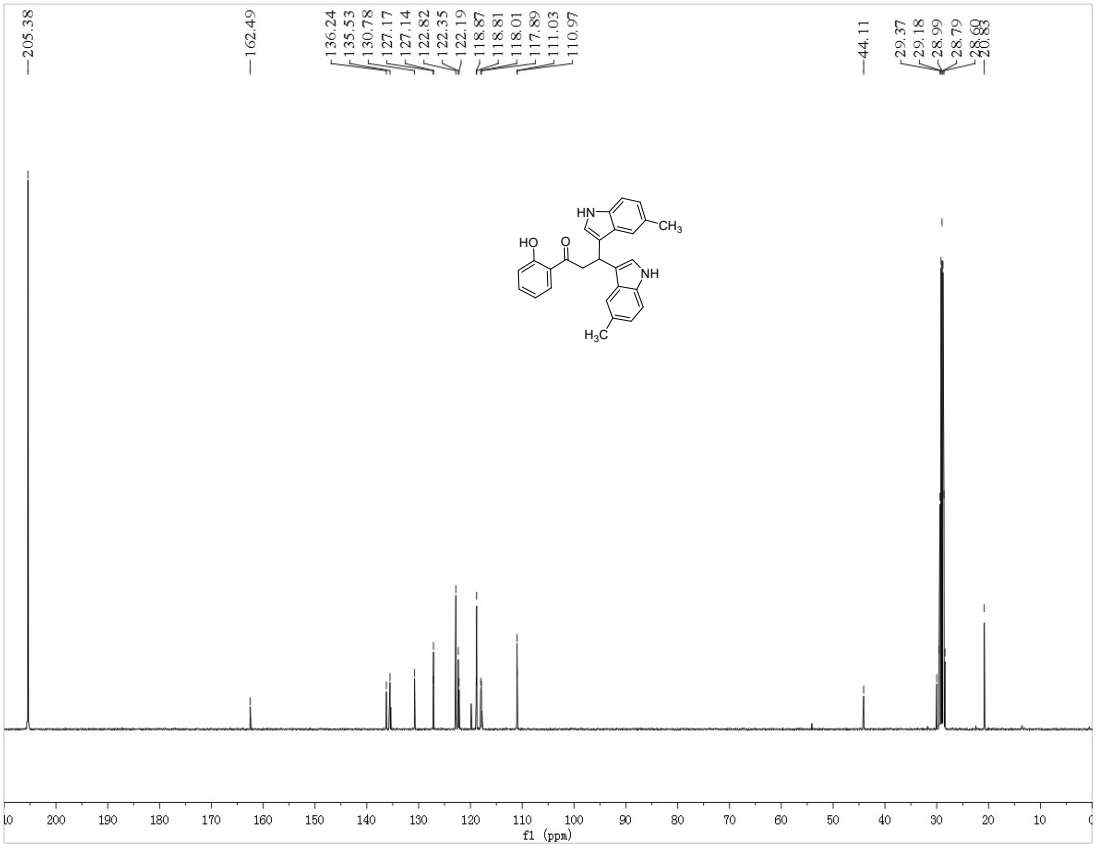
^{1}H and ^{13}C NMR of 3i



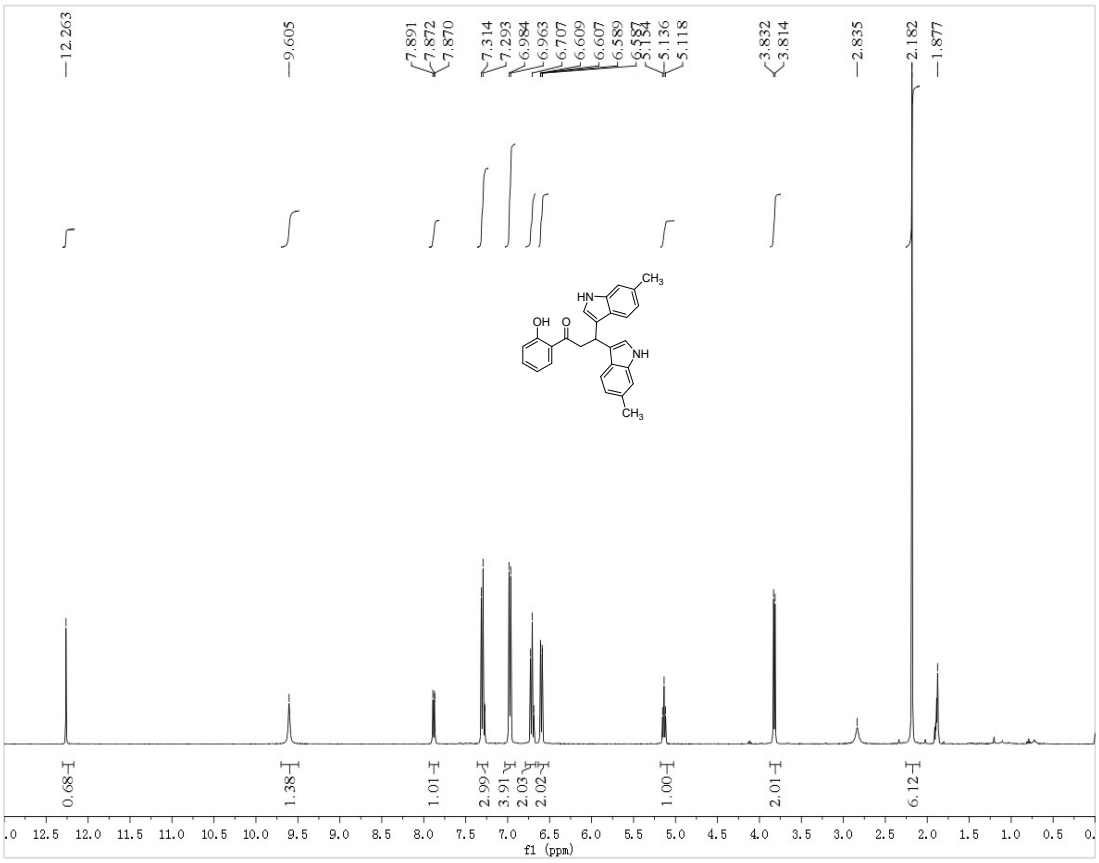


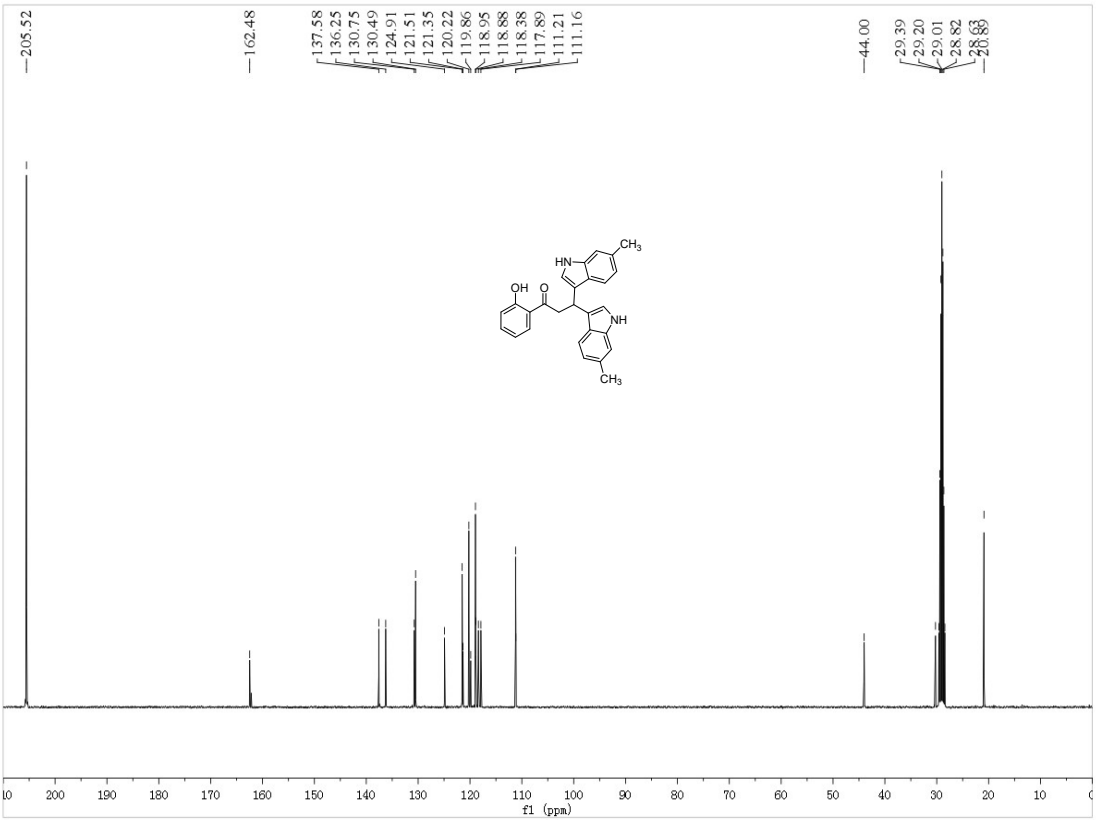
^{1}H and ^{13}C NMR of 3j



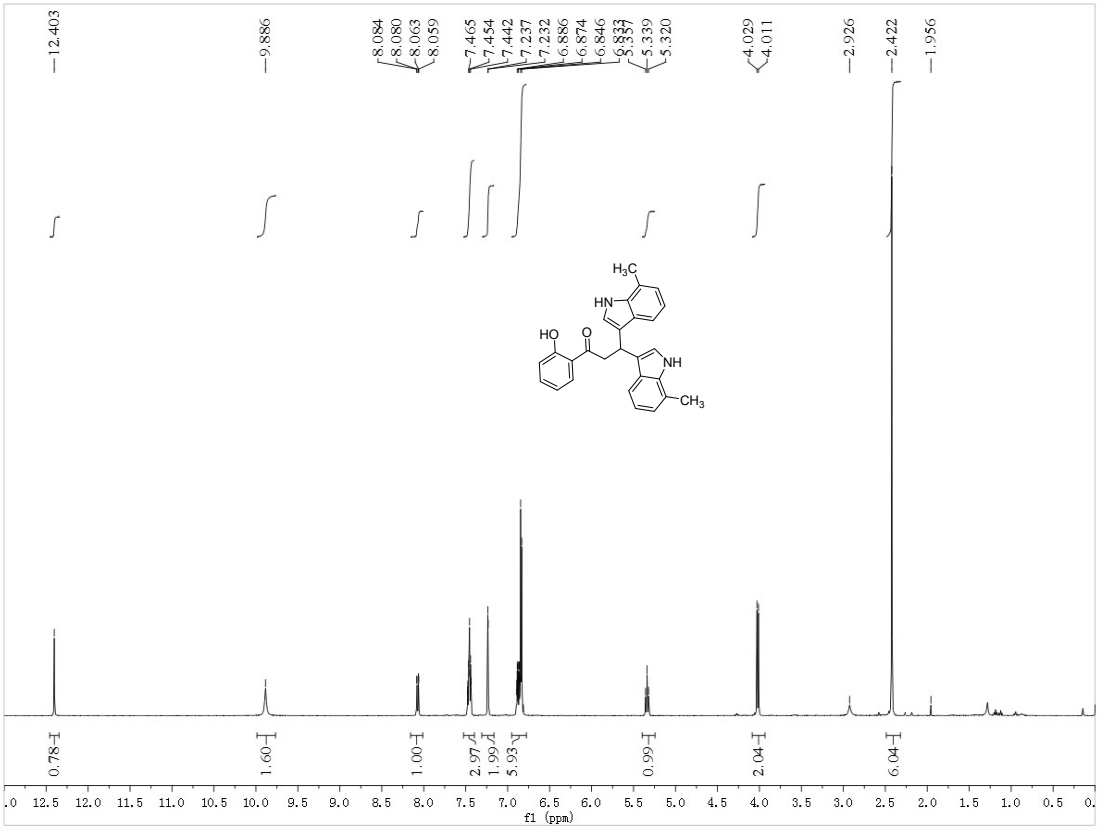


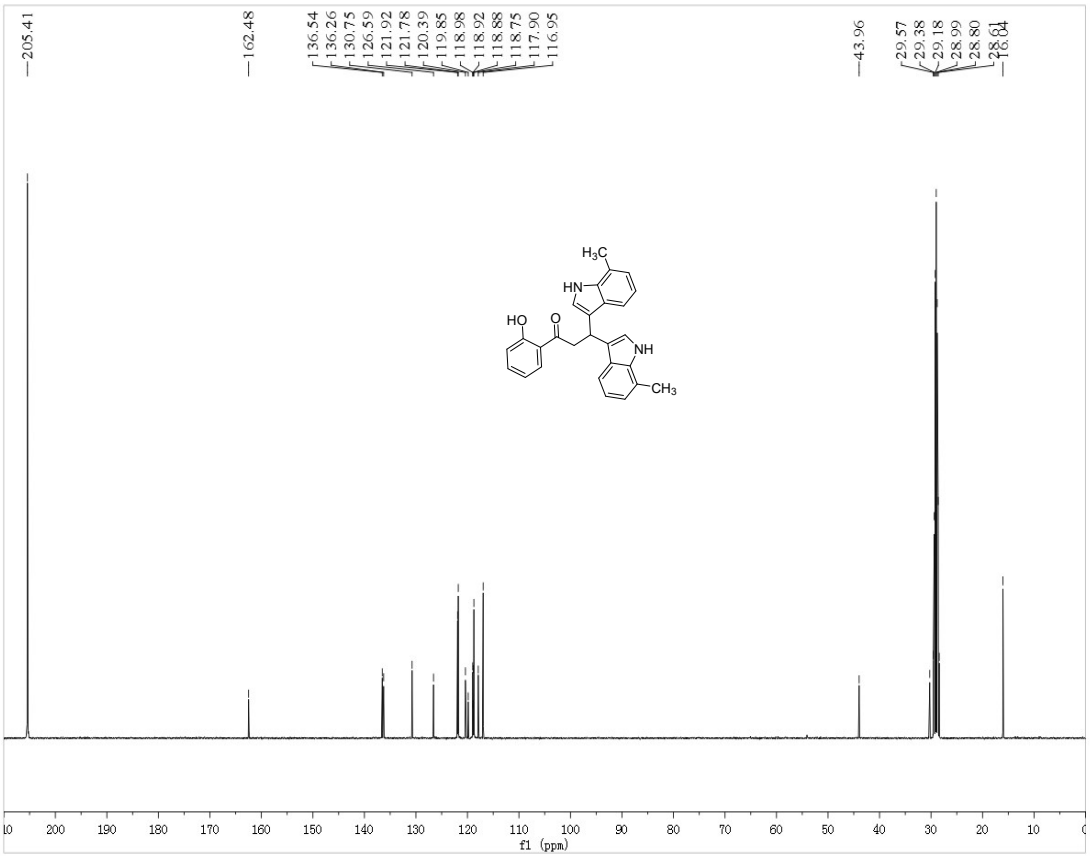
^{1}H and ^{13}C NMR of 3k



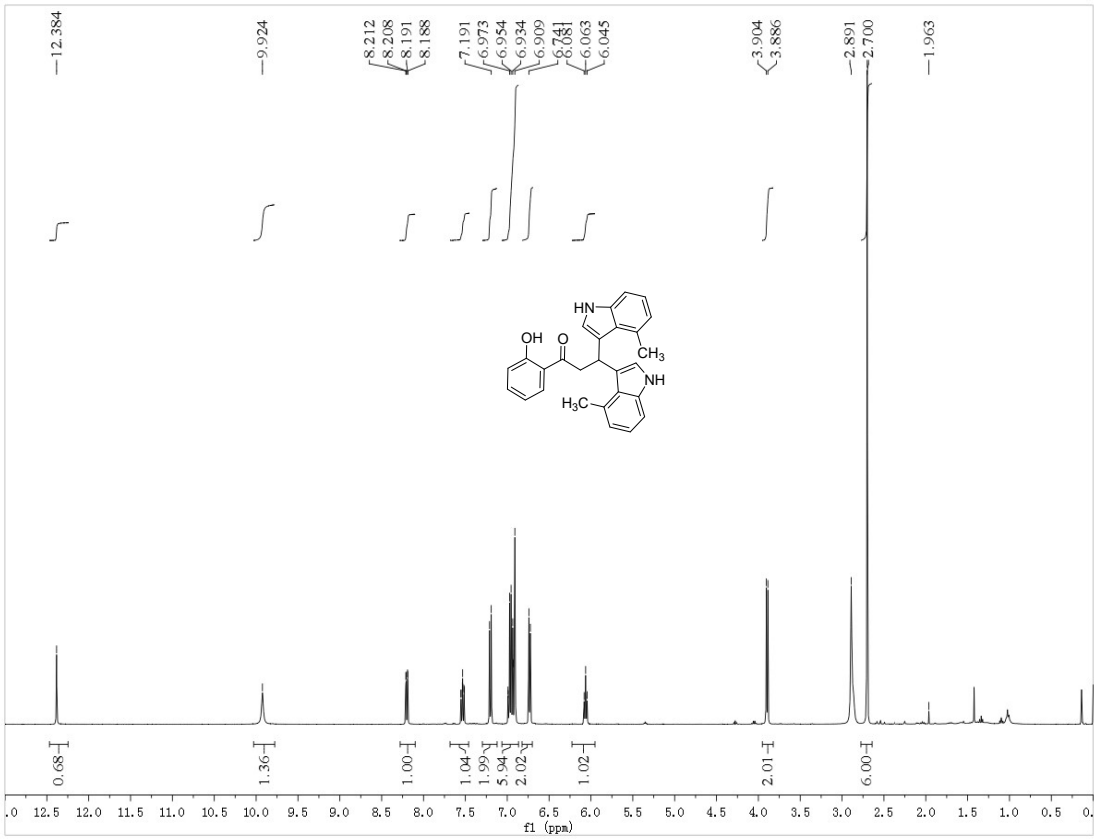


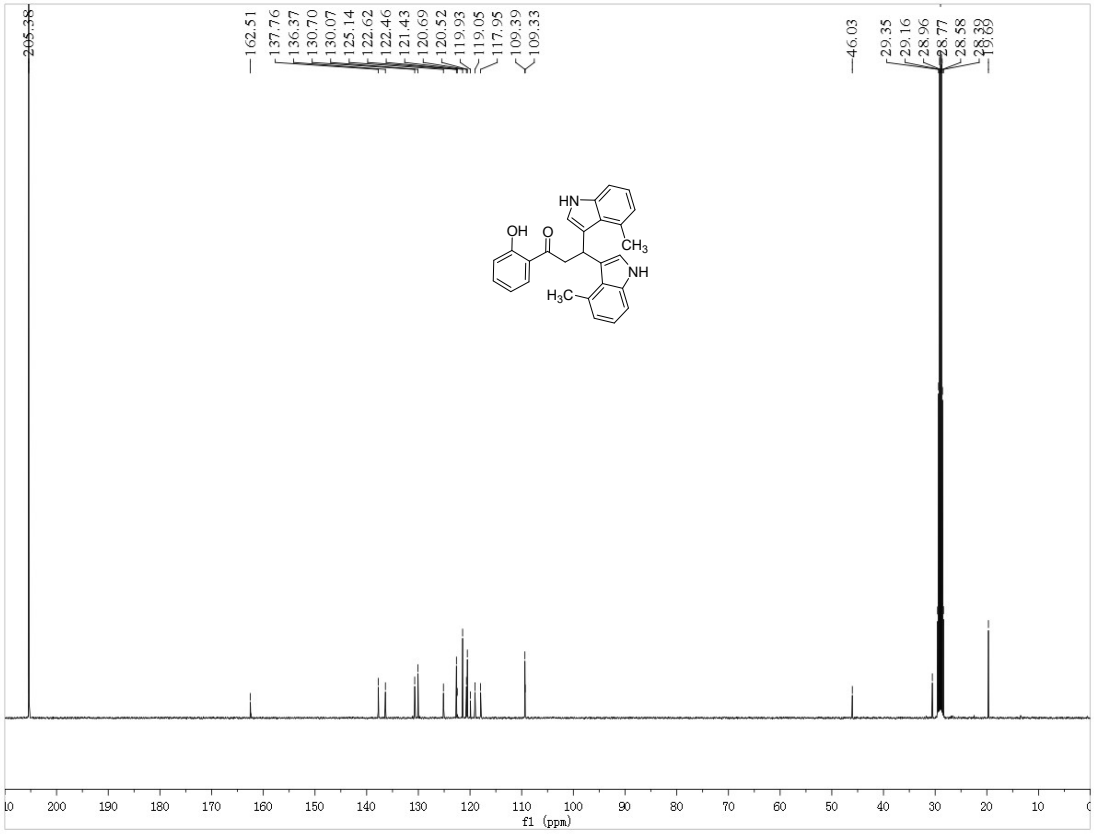
^{1}H and ^{13}C NMR of 3l



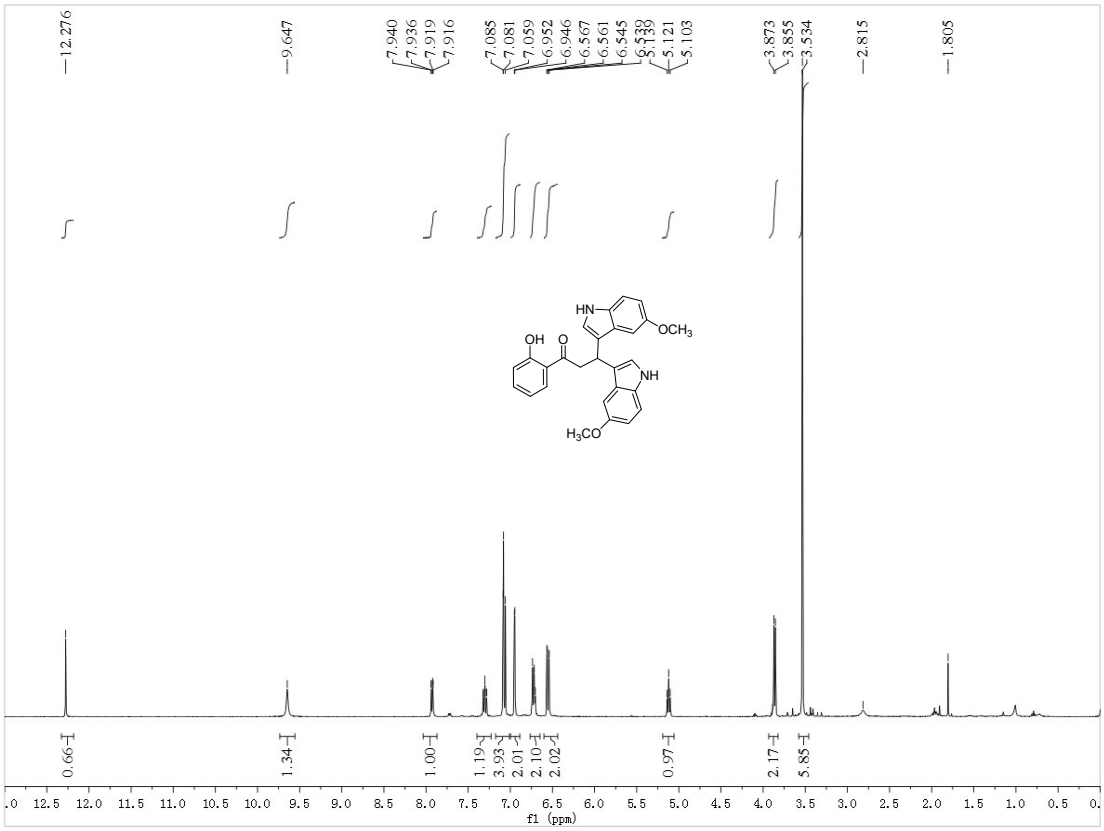


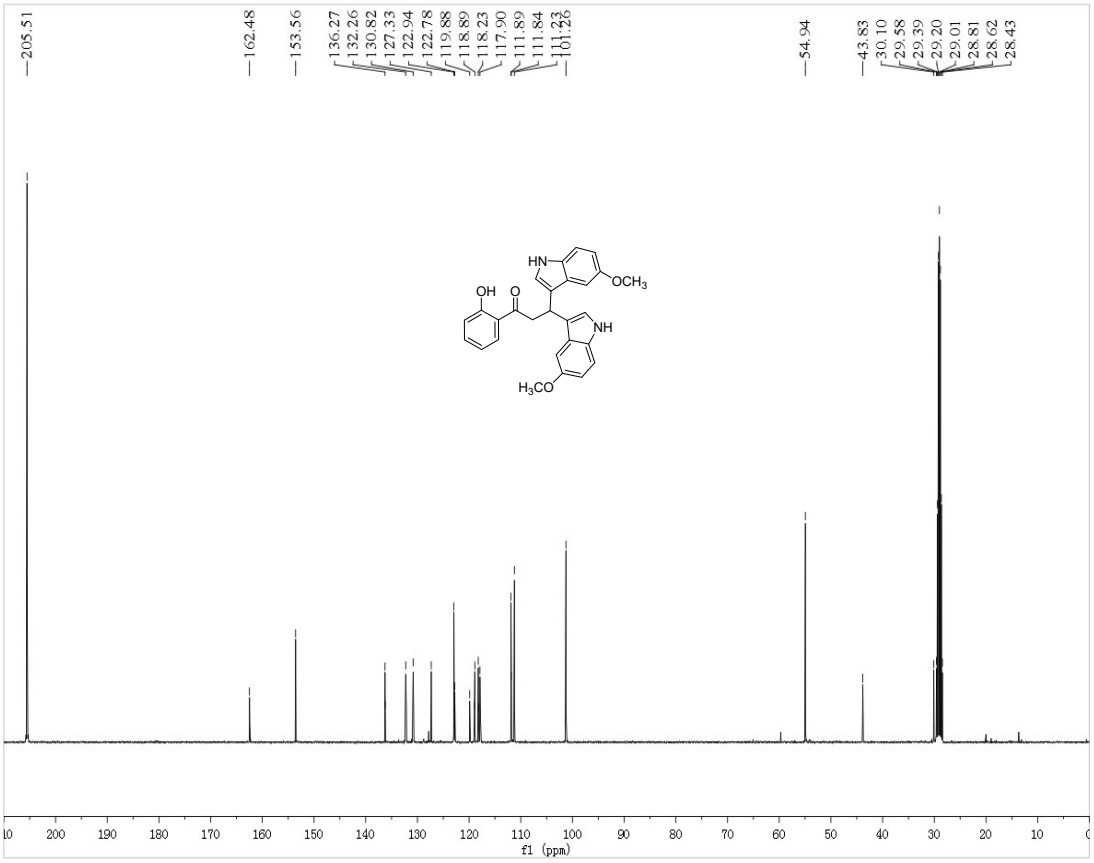
^{1}H and ^{13}C NMR of 3m



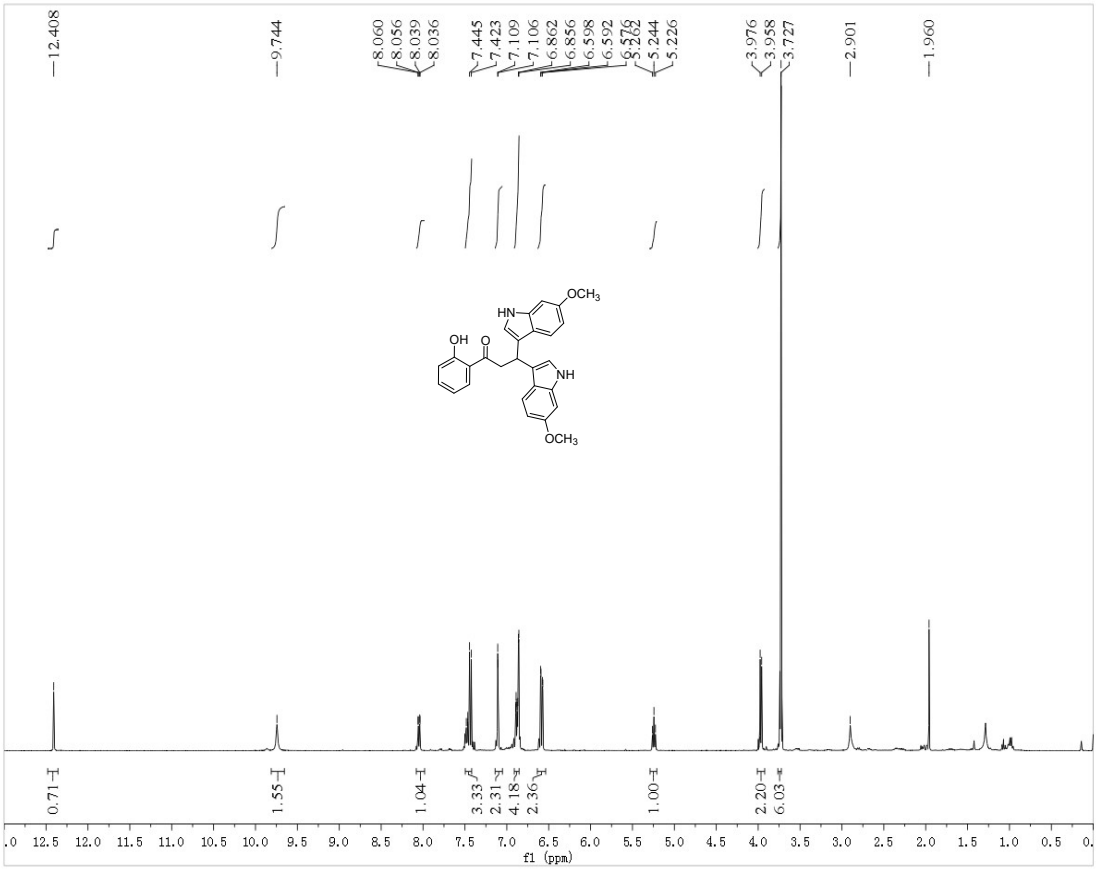


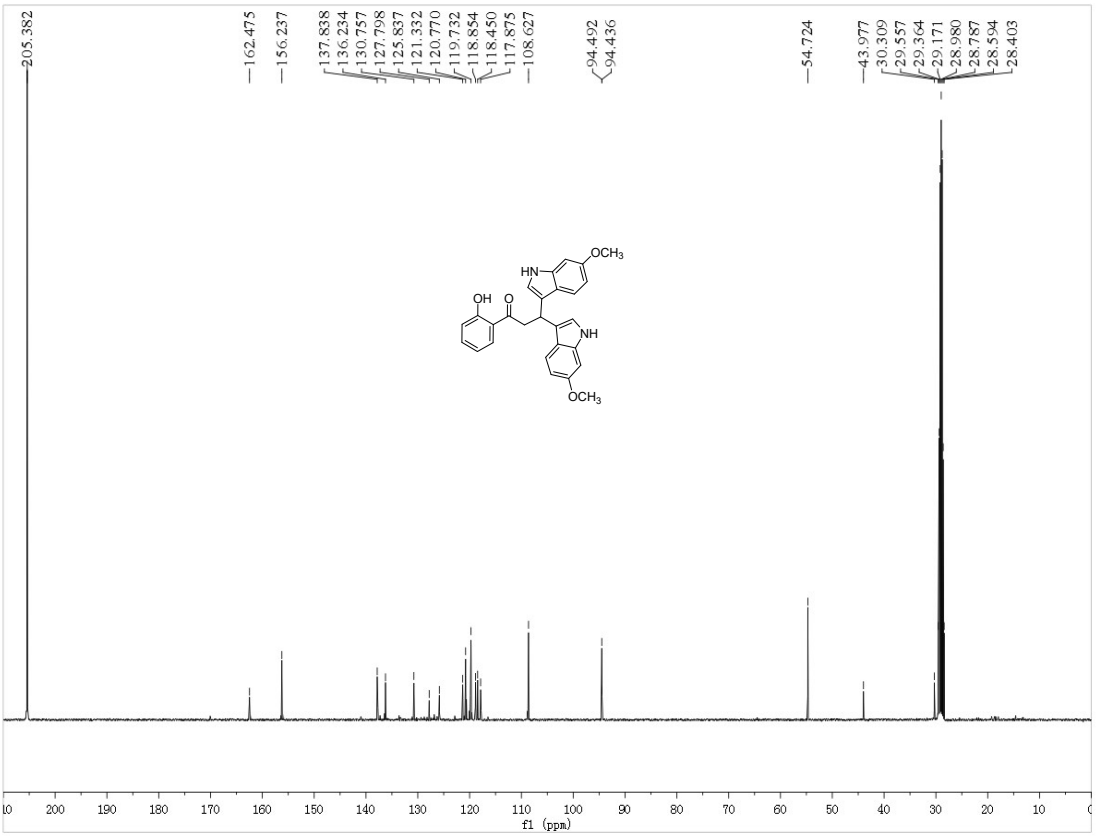
^{1}H and ^{13}C NMR of 3n



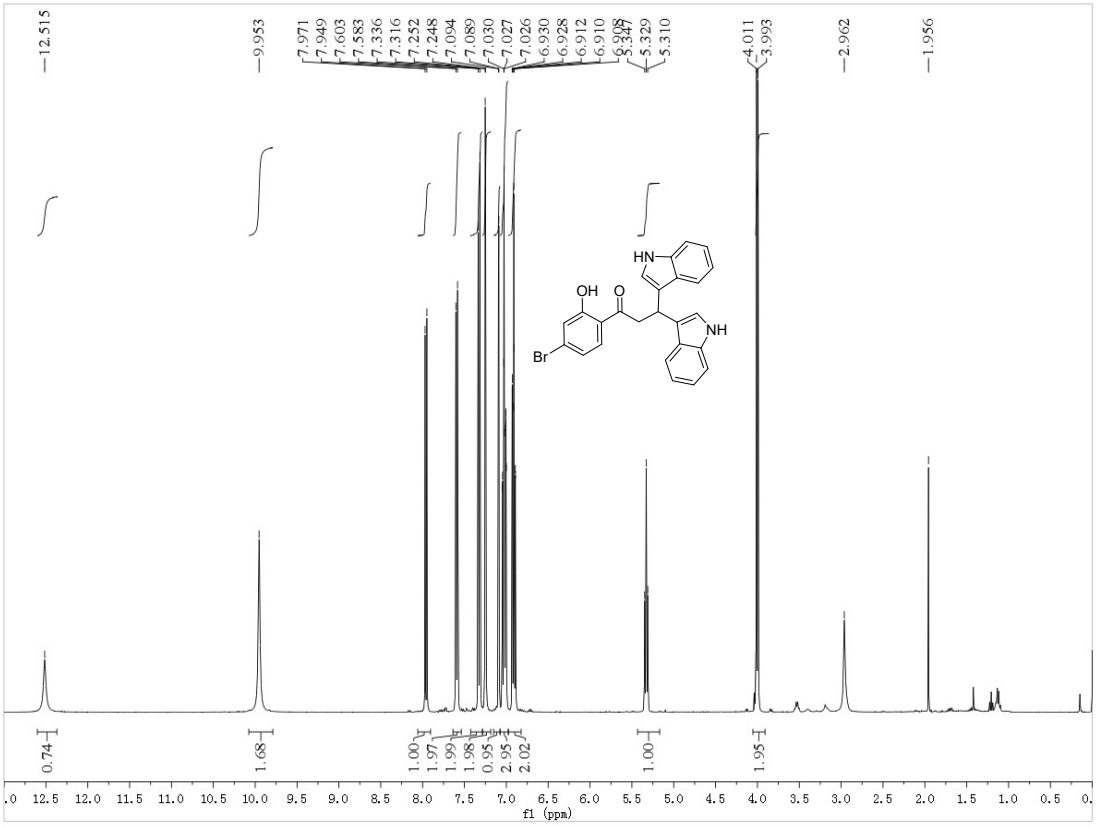


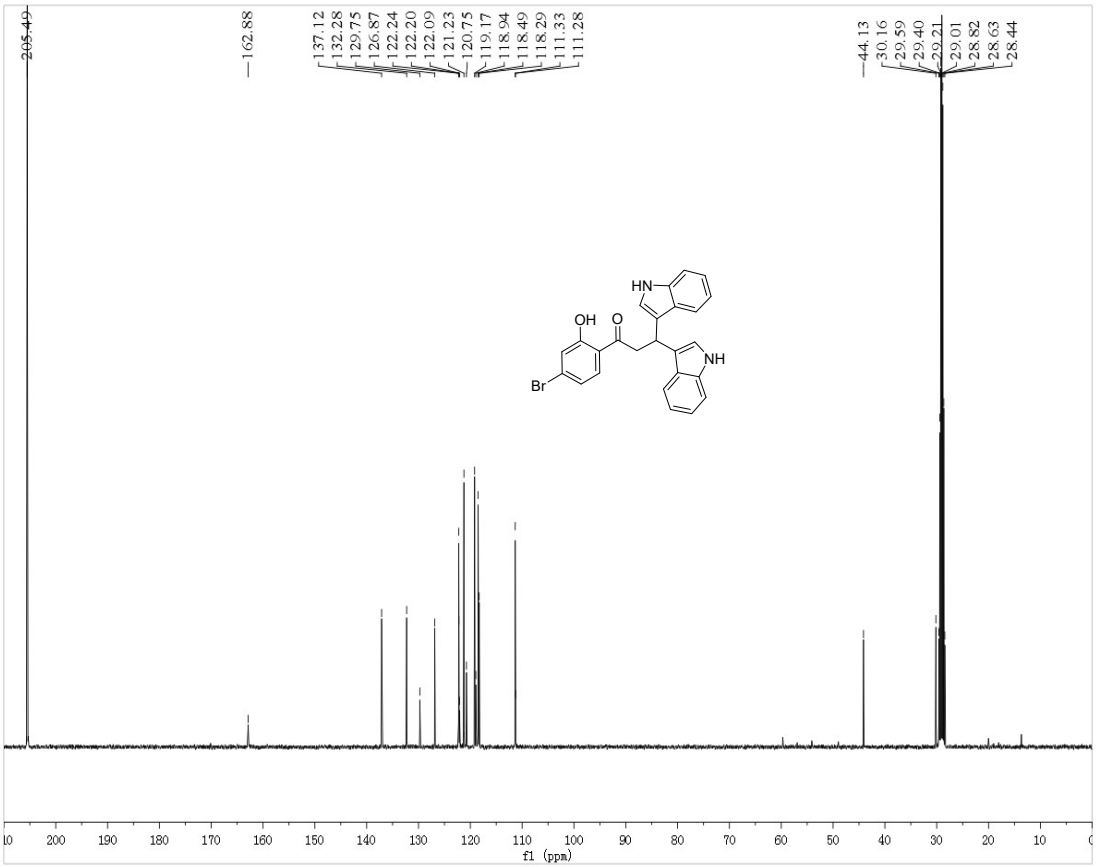
^{1}H and ^{13}C NMR of 3o



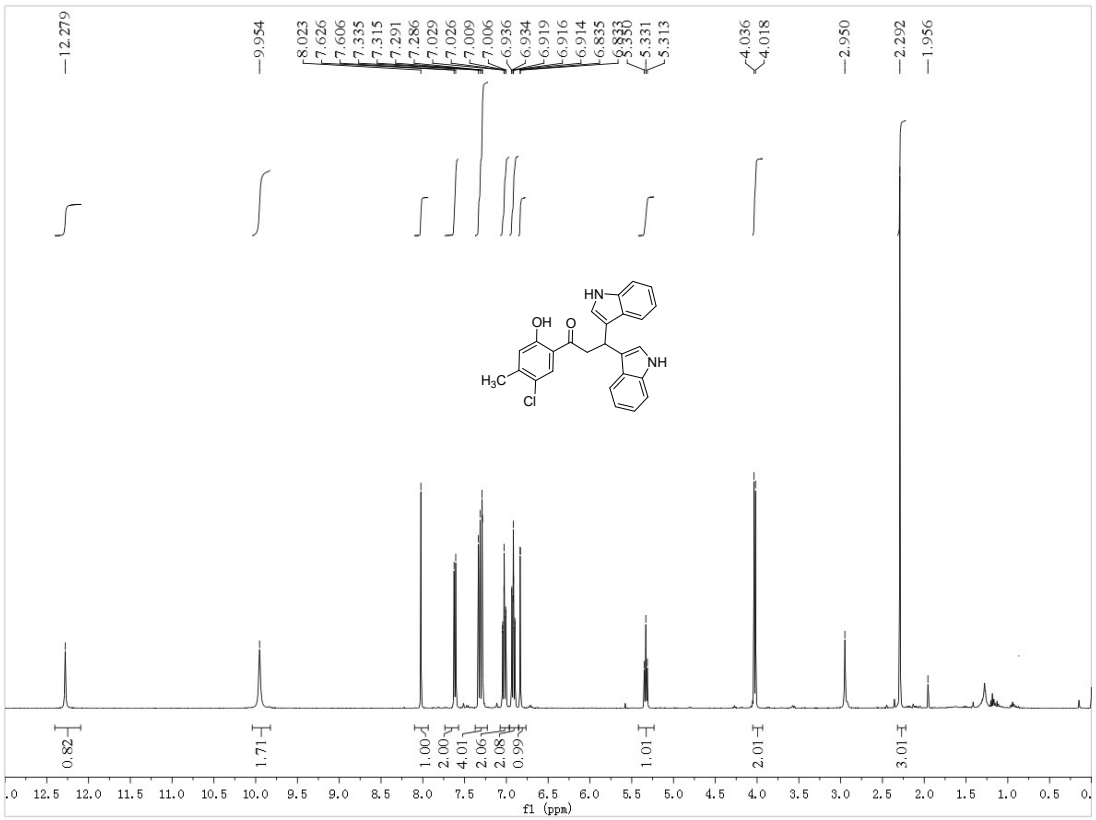


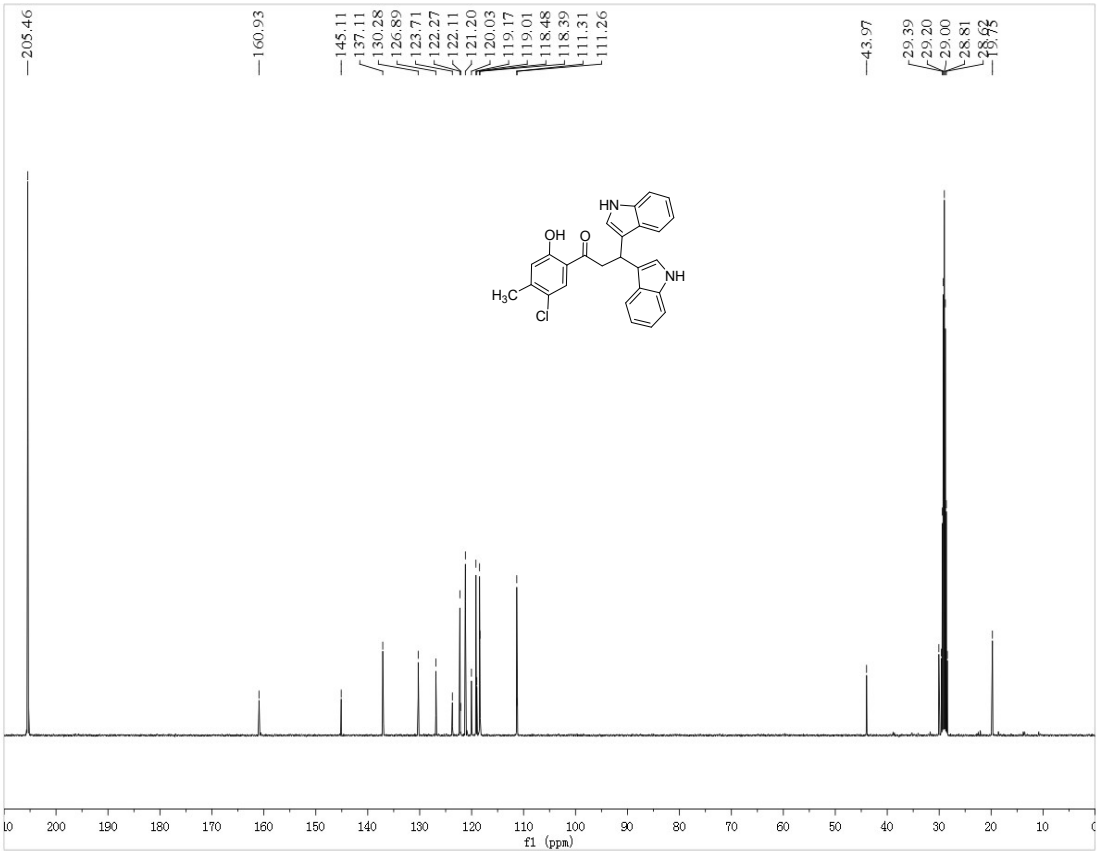
^{1}H and ^{13}C NMR of 3p



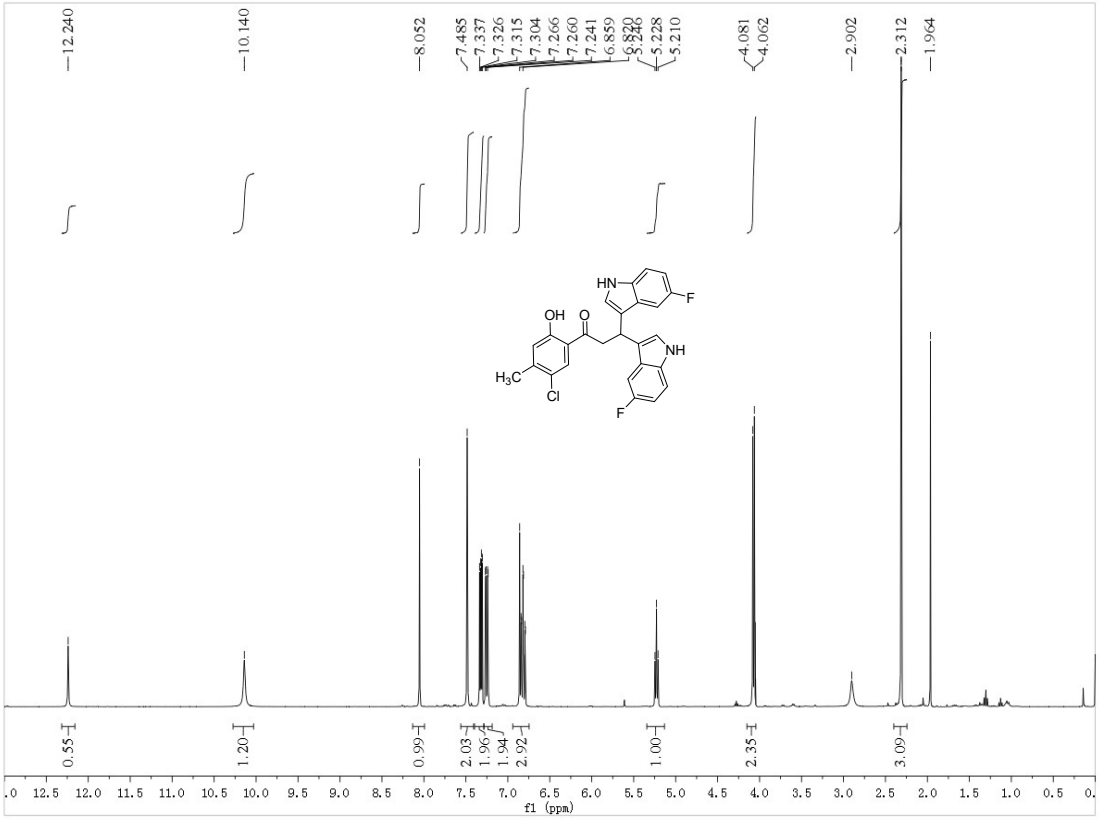


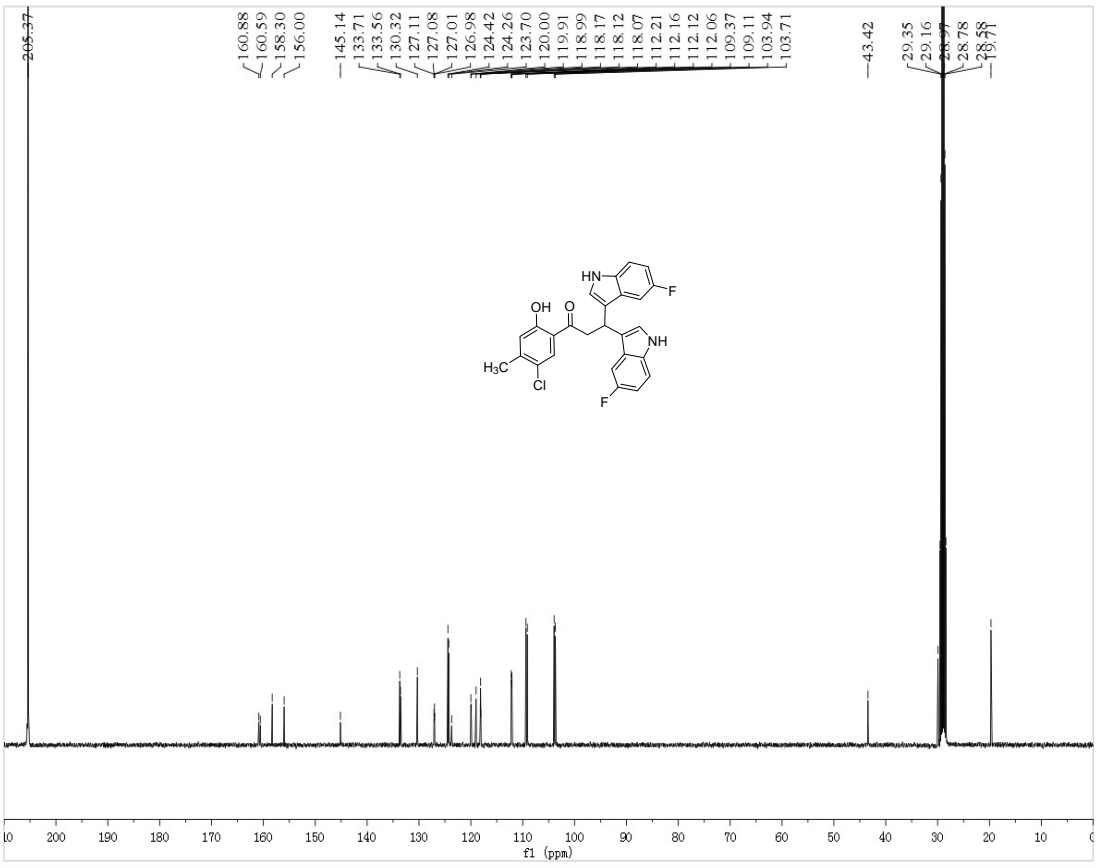
^{1}H and ^{13}C NMR of 3q



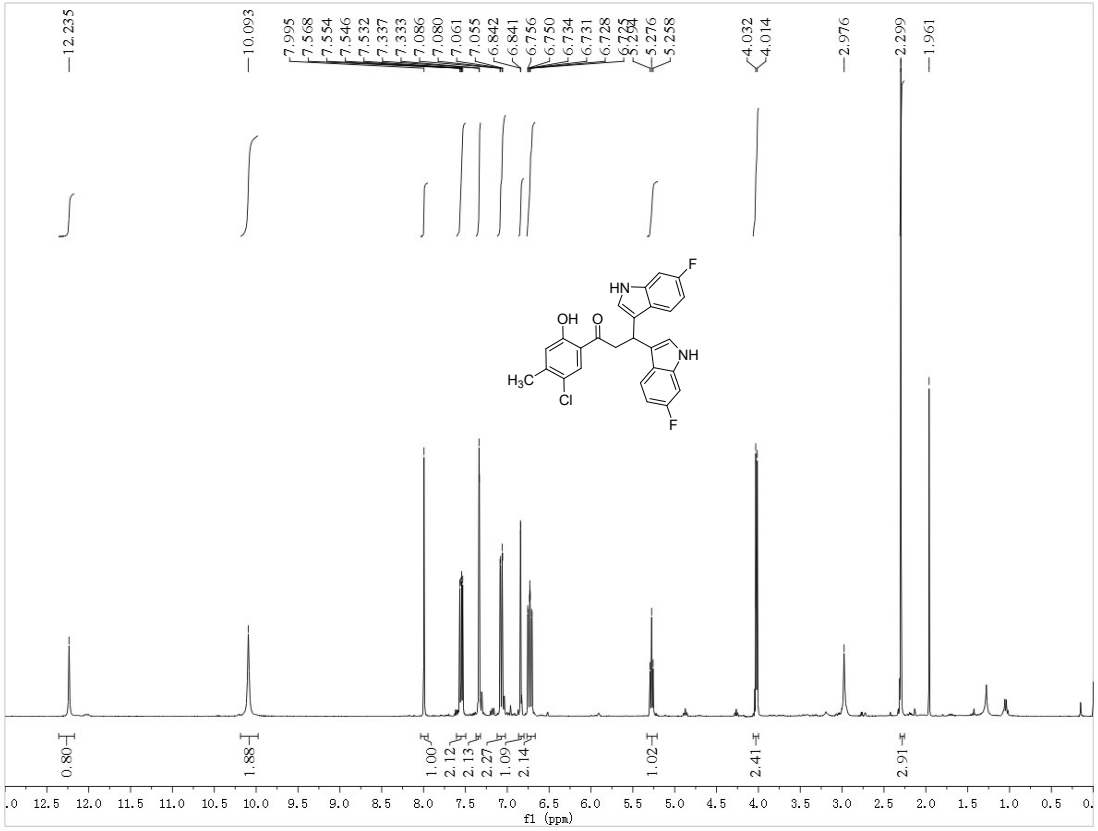


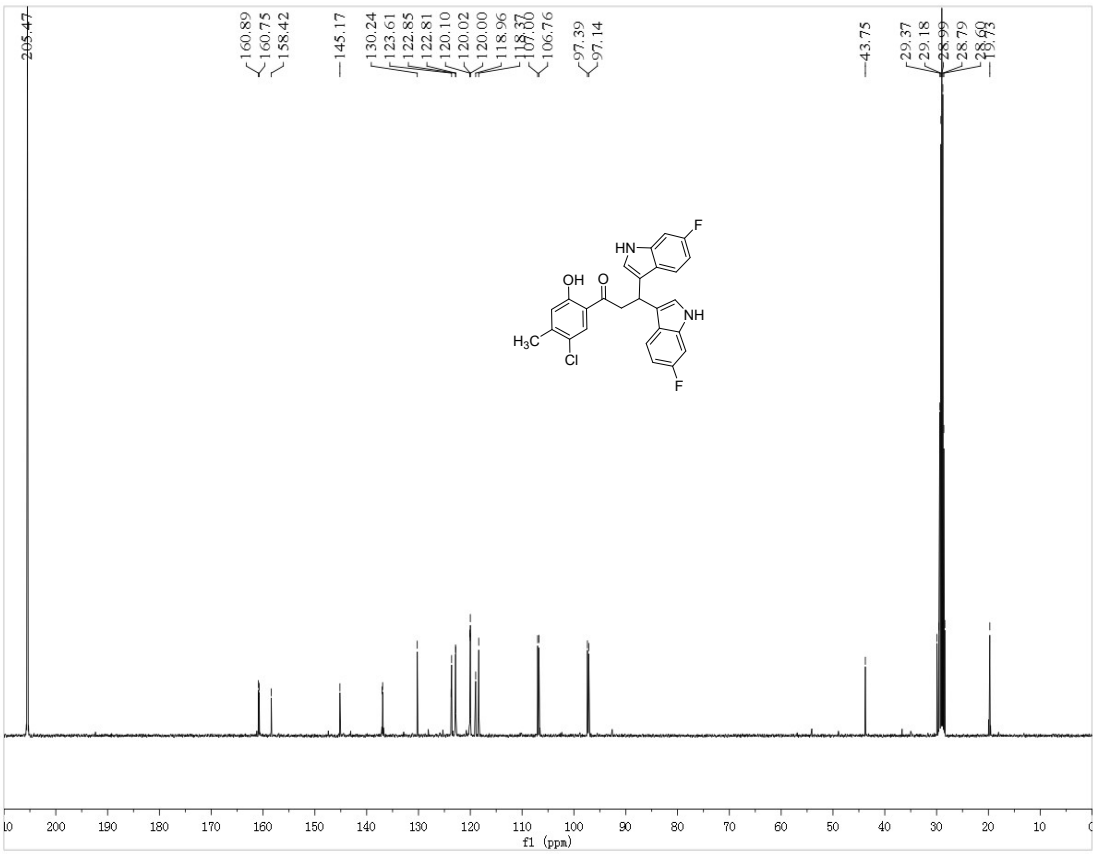
^{1}H and ^{13}C NMR of 3r



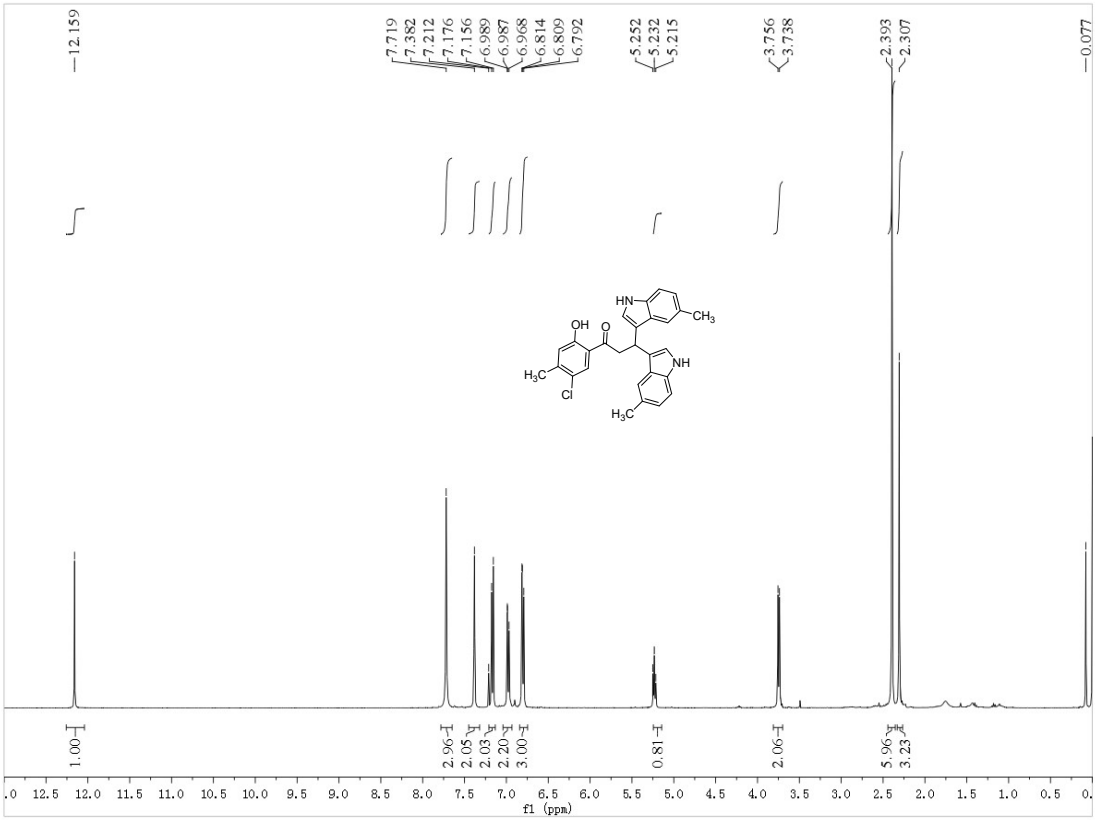


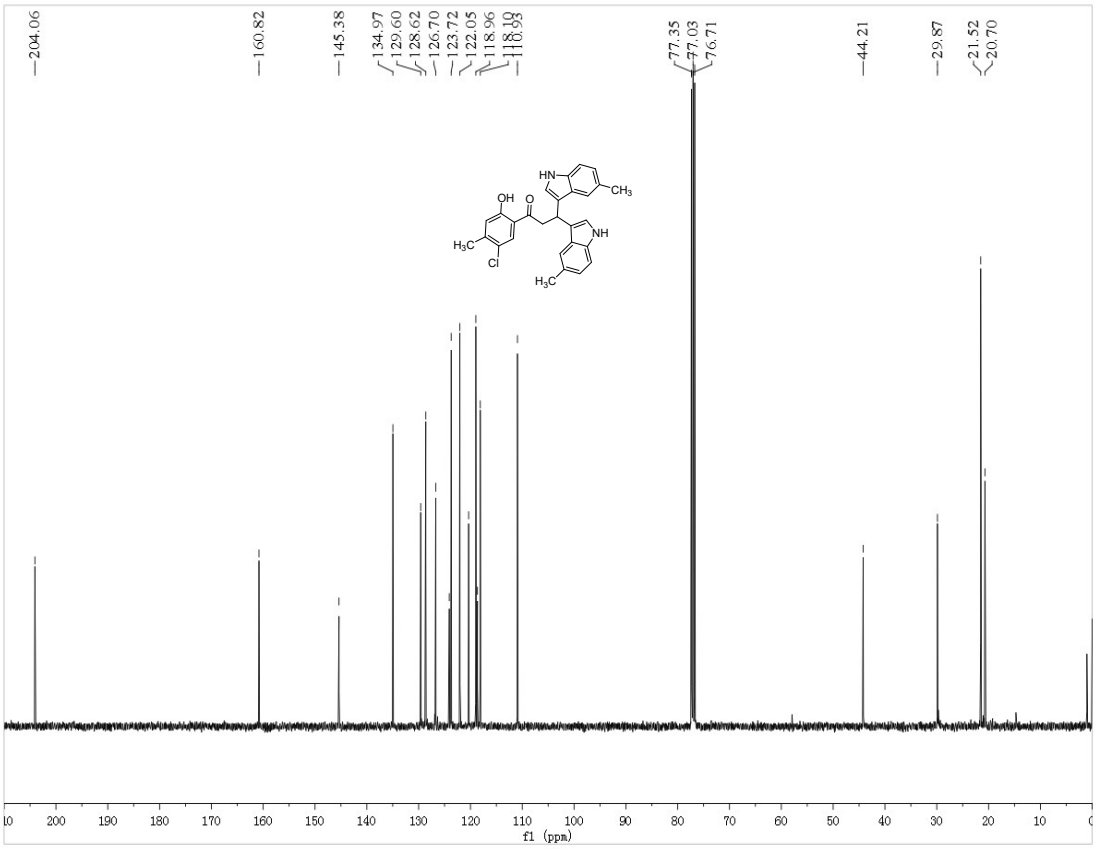
^{1}H and ^{13}C NMR of 3s



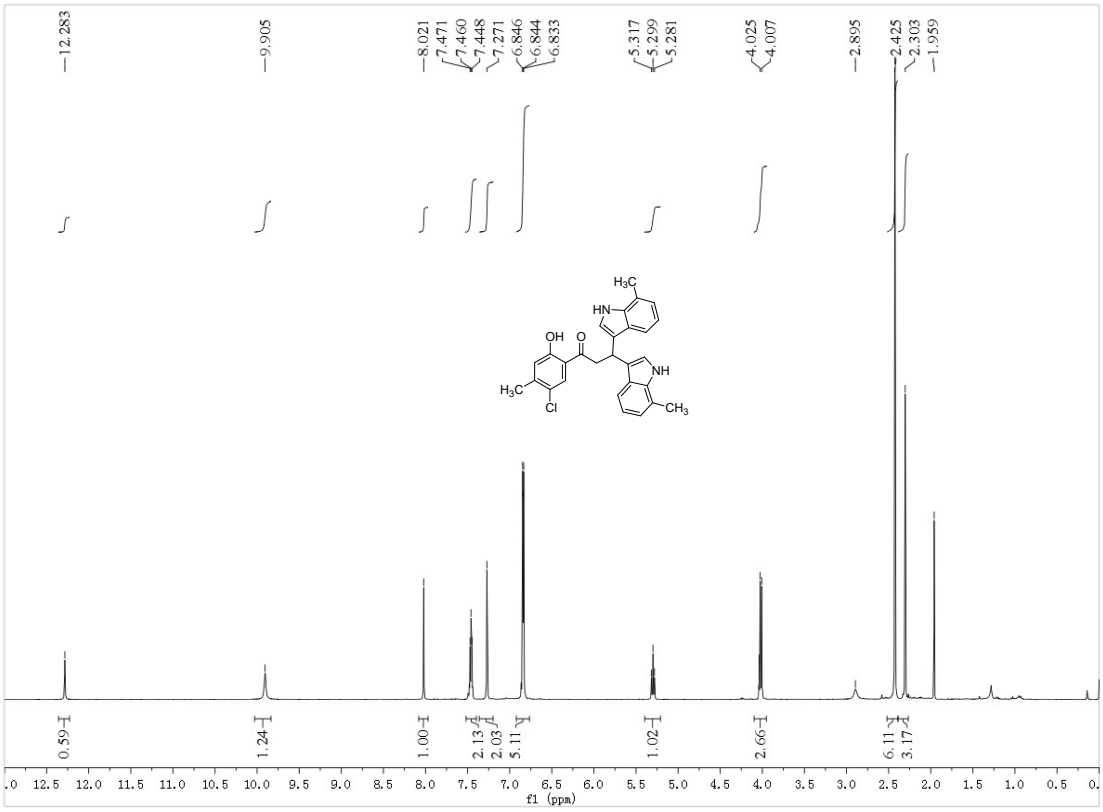


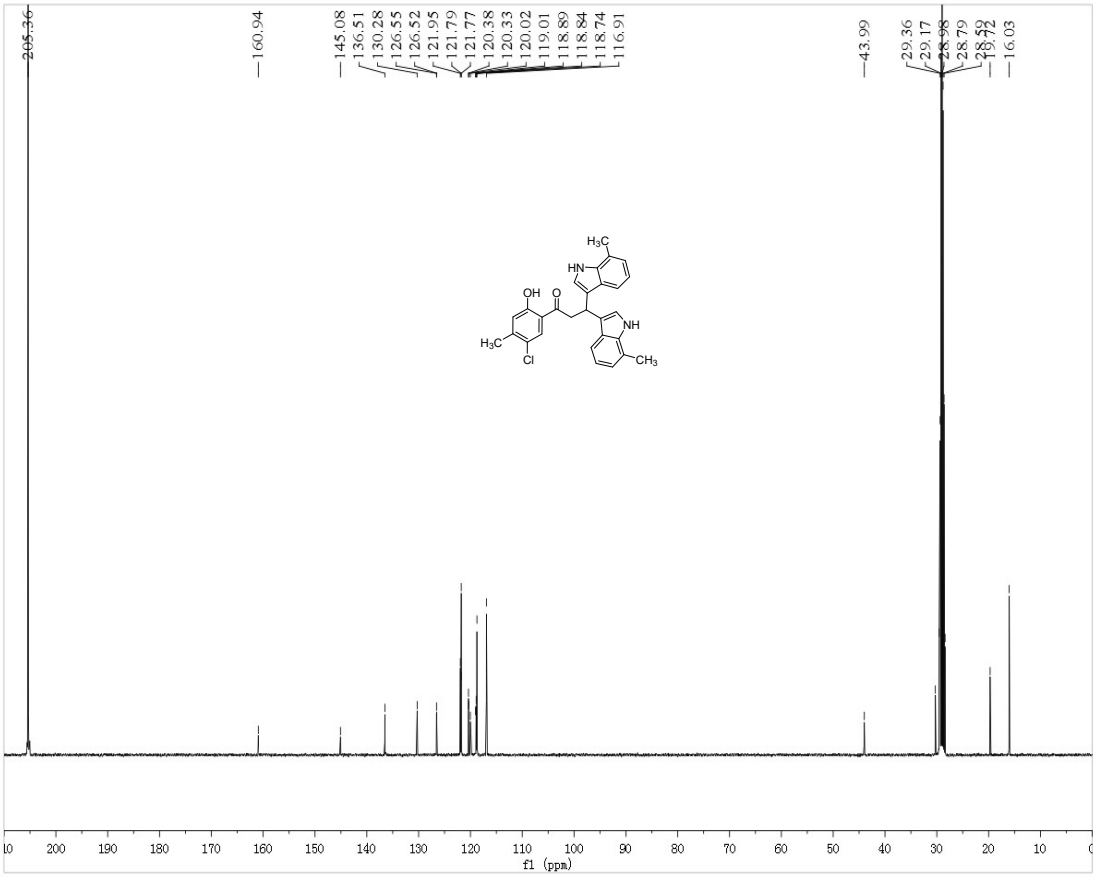
^{1}H and ^{13}C NMR of 3t



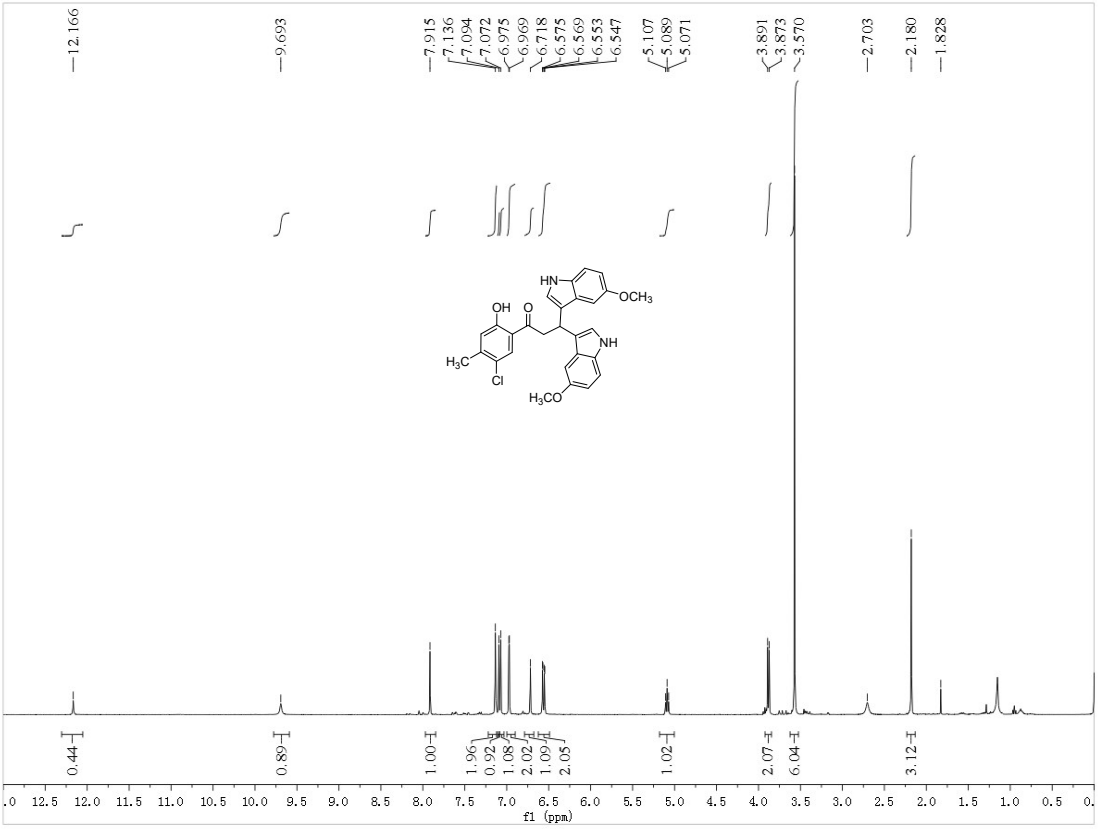


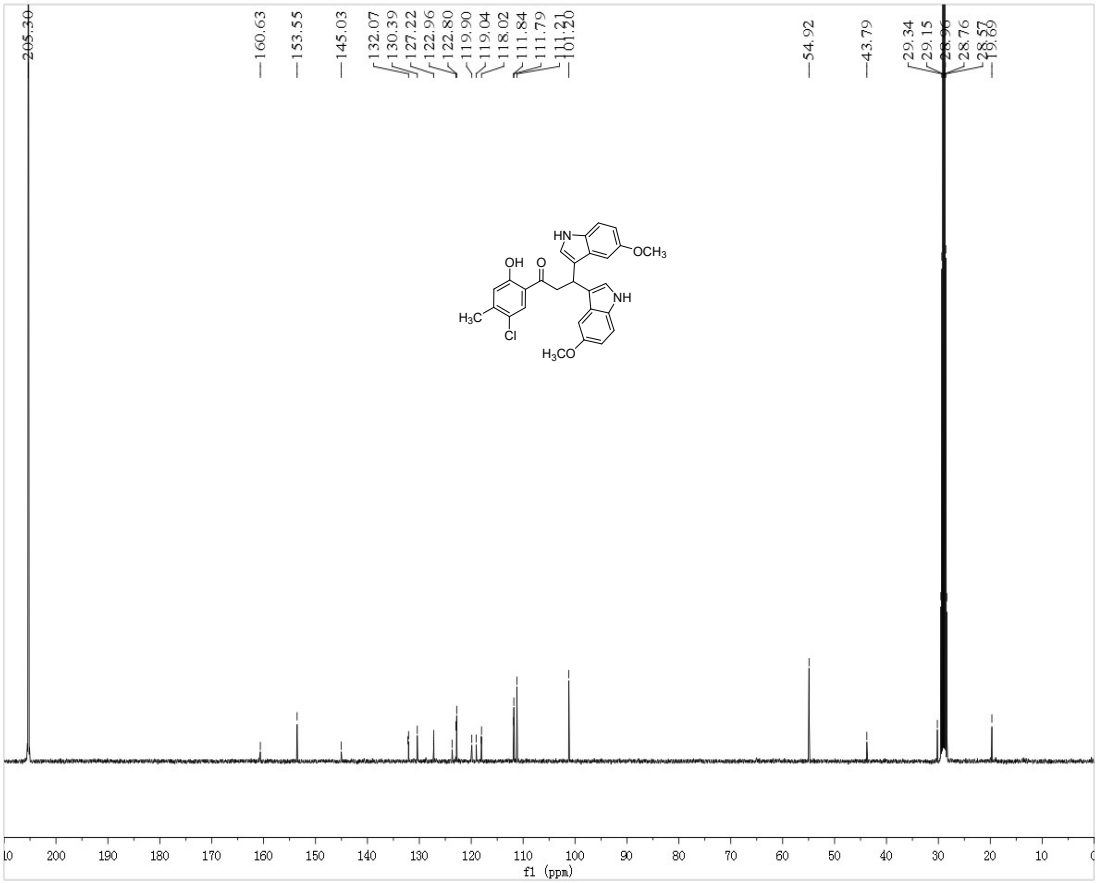
^{1}H and ^{13}C NMR of 3u





^{1}H and ^{13}C NMR of 3v





^{1}H and ^{13}C NMR of 3w