Supporting Information

Rapidly Modular Synthesis of Indole Ethers via Dehydrogenative Cross-Coupling Reaction of Indoles and Alcohols

Mao-Gui Huang,[†] Xiao-Hong Chen,[†] Hai-Bing Xu[†], Yue-Jin Liu*[†]

[†]Collaborative Innovation Center for Advanced Organic Chemical Materials Co-constructed by the Province and Ministry, Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules. College of Chemistry and Chemical Engineering, Hubei University, Wuhan, 430062, China.

*liuyuejin@hubu.edu.cn.

Contents

1. General Information

Solvents: Dichloromethane was distilled from CaH_2 and other solvents used in this manuscript were purchased from commercial suppliers.

Reagents: All commercial materials, purchased from Alfa-Aesar, Macklin, Adamas, Bidepharm and Aladdin and used as received.

Reactions: All sample preparation reactions were performed in oven-dried glassware under an atmosphere of oxygen unless.

Chromatography: Thin layer chromatography (TLC) was carried out on silica gel 60 F254 pre-coated glass plates. Visualization was detected by irradiation with UV light (254 nm), or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography was carried out on 200 – 300 mesh silica gel, eluting with a mixture of petroleum ether (b.p. 60 – 90 °C) , ethyl acetate and dichloromethane.

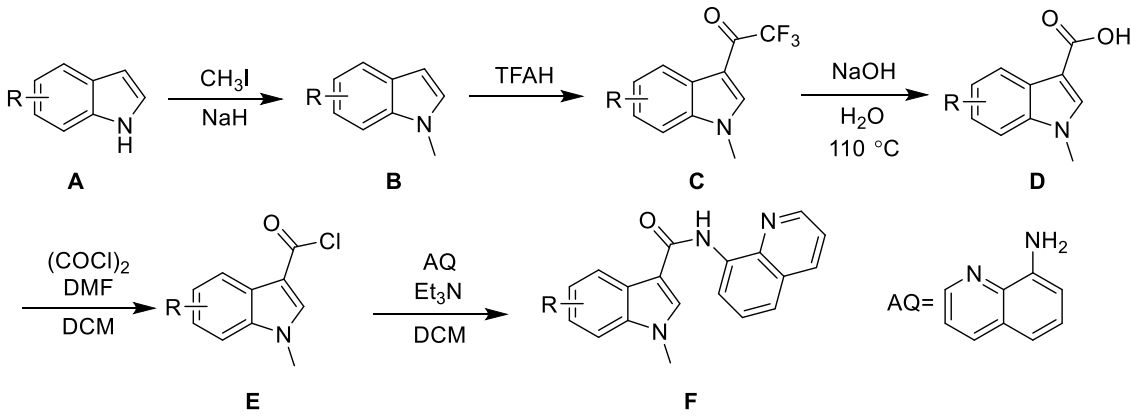
NMR Spectroscope: ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Mercury Plus 400 MHz NMR spectrometers. Chemical shifts (δ) were given in parts per million (ppm), and referenced relative to residual solvent $CHCl_3$ (7.26 ppm) in $CDCl_3$, or tetramethylsilane (0.00 ppm) as an internal standard for ^{1}H NMR spectra and deuterated solvent $CDCl_3$ (77.16 ppm) for ^{13}C NMR spectra. Coupling constants (*J*) were reported in hertz (Hz). The following abbreviations are used to indicate the multiplicity of the signals: s = singlet, d = doublet, t = triplet, m = multiplet, and associated combinations, e.g. dd = doublet of doublets.

Mass Spectrometry: High resolution mass spectra (HRMS) were recorded on the Thermo Scientific Exactive Plus (orbitrap) equipped with ESI ionization source.

Crystallography: Single crystals of 3aa suitable for X-ray diffraction were grown by layering hexane on the dichloromethane solutions and Co-2 suitable for X-ray diffraction were grown by layering MeCN on the DMF solutions. The diffraction data of crystals were collected on a Rigaku XtaLAB Synergy CCDC diffractometer with graphite monochromated Cu-Ka radiation (λ = 1.54056 Å) at 293 or 100 K. Absorption corrections were applied by SADABS. The ellipsoid contour is 50% probability in the caption for the image of the 3aa and Co-2. All the structures were solved by direct methods and refined by full-matrix least-squares method on F2 using Olex-2. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms of the ligand were generated geometrically.

2. Experimental Procedures

2.1 Preparation of indole-3-carboxamides substrates



Methylation of indoles were done according to the literature procedure[1].

To a solution of indole **A** (10 mmol) in anhydrous THF (30 mL) at 0 ℃ was added NaH (0.60 g, 60 % dispersion in mineral oil, 15 mmol). the heterogeneous mixture was stirred at 0 ℃ for 15 minutes and 1 h at room temperature. The mixture was then cooled to 0 ℃, treated with iodomethane (14 mmol), and allow to warm to room temperature. After 3 hour, the reaction mixture was cooled to 0 ℃, quenched with saturated NH_4Cl (40 mL), and extracted with ether (3 x 50 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (eluent: petroleum ether/EtOAc 10:1) to provide indole **B** as a colorless oil.

Typical procedure for synthesis of trifluoromethyl indol-3-yl ketones indoles **C**. Indole **B** (0.2 mmol) and trifluoroacetic anhydride (3 equiv) were refluxed in a 100 ℃ oil bath in 2 mL of DCE in an air atmosphere, and the progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. Water (2 x 5 mL) was added, the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 5/1) to afford the corresponding products **C**.

A 100 mL round bottom flask was charged with 2,2,2-trifluoro-1-(1-methylindol-3-yl)ethan-1-one **C** (1.135 g, 5.0 mmol), NaOH (5 M,

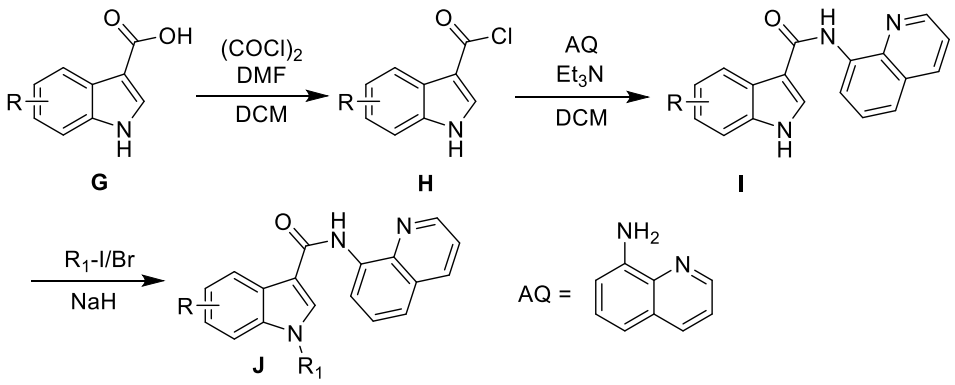
30.0 mL), methanol (10 mL), and a magnetic stirring bar. The reaction mixture was refluxed for 12 h and then cooled to room temperature, and H_2O (10 mL) was added. The layers were separated, and the organic layer was extracted with 1 M aqueous NaOH (10 mL). The combined aqueous phases were acidified to PH = 1 with 12 M aqueous HCl, then the solution has been turned into suspension. the solid were filtered from this suspension. The solid was dried to afford the corresponding product **D**.

Procedures were done according to the literature procedure [2].

To an oven-dried 100 mL bottom flask, the benzoic acid **D** (20 mmol), DMF (5 drops) and anhydrous DCM (40 mL) were added under a Ar atmosphere. Oxalyl chloride (2 mL, 24 mmol, 1.2 equiv.) was added dropwise at 0 °C resulting in vigorous bubbling. The mixture was stirred for 5 h at room temperature, and the solvent was then removed in vacuo. The resulting acid chloride **E** was used immediately without further purification.

To another oven-dried 100 mL three-necked flask, 8-aminoquinoline (3.75 g, 26 mmol, 1.3 equiv.), Et_3N (5.6 mL, 40 mmol, 2 equiv.) and anhydrous DCM (40 mL) were added. A solution of the acid chloride **E** in anhydrous DCM (20 mL) was added dropwise to the solution at 0 °C, and the solution was then warmed to room temperature. After stirring overnight, the reaction system was quenched with sat. aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with 1 M HCl aq. (40 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo.The obtained crude amide was purified by column chromatography on silica gel (petroleum ether/DCM/EtOAc 2/1/1) to afford the desired amide **F**.

2.2 General procedures for substrate 3m, 3n, 3o, 4m, 4o, 4q, 4r, 6.



Procedures G to I were done according to the literature procedure[2]

To an oven-dried 100 mL bottom flask, the 1H-indole-3-carboxylic acid **G** (20 mmol), DMF (5 drops) and anhydrous DCM (40 mL) were added under a Ar atmosphere. Oxalyl chloride (2 mL, 24 mmol, 1.2 equiv.) was added dropwise at 0 °C resulting in vigorous bubbling. The mixture was stirred for 5 h at room temperature, and the solvent was then removed in vacuo. The resulting acid chloride **H** was used immediately without further purification.

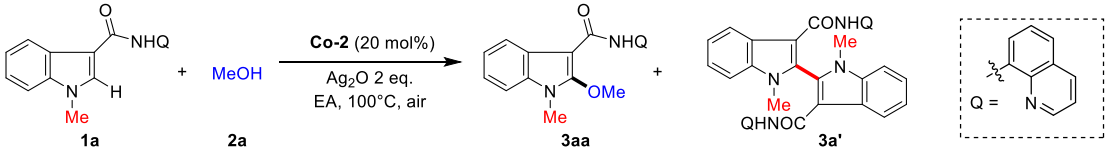
To another oven-dried 100 mL three-necked flask, 8-aminoquinoline (3.75 g, 26 mmol, 1.3 equiv.), Et_3N (5.6 mL, 40 mmol, 2 equiv.) and anhydrous DCM (40 mL) were added. A solution of the acid chloride **H** in anhydrous DCM (20 mL) was added dropwise to the solution at 0 °C, and the solution was then warmed to room temperature. After stirring overnight, the reaction system was quenched with sat. aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with 1 M HCl aq. (40 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo.The obtained crude amide was purified by column chromatography on silica gel (petroleum ether/DCM/EtOAc 2/1/1) to afford the desired amide **I**.

Procedures I to J were done according to the literature procedure[2].

To a solution of indole **I** (10 mmol) in anhydrous DCM (30 mL) at 0 °C was added NaH (0.60 g, 60 % dispersion in mineral oil, 15 mmol). the heterogeneous mixture was stirred at 0 °C for 15 minutes and 1 h at room temperature. The mixture was then cooled to 0 °C, treated with alkyl -Br or alkyl -I (14 mmol), and allow to warm to room temperature. After 3 hour, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (40 mL), and extracted with ether (3 x 50 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude amide was purified by flash chromatography (eluent: petroleum ether/EtOAc 3:1) to provide indole **J** as a solid product.

2.3 Optimization of Conditions

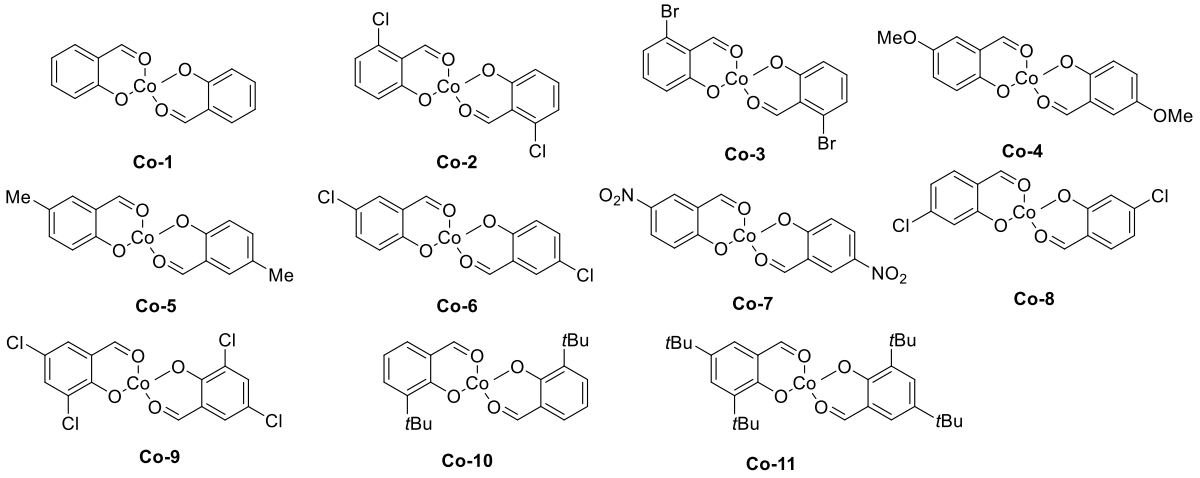
Table S1. Optimization of Conditions



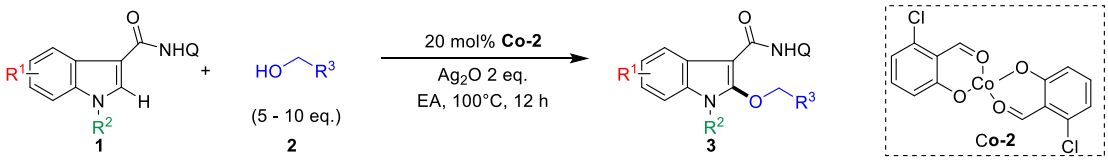
Entry	Catalyst	Oxidant	Base	Solvent	Yield 3aa:3a'[%][a]
1	Co-2	Ag_2O	KH_2PO_4	2-MeTHF	28 % : < 5 %
2	Co-2	Ag_2O	KH_2PO_4	MeCN	16 % : < 5 %
3	Co-2	Ag_2O	KH_2PO_4	Dioxane	20 % : 20 %
4	Co-2	Ag_2O	KH_2PO_4	THF	25 % : < 5 %
5	Co-2	Ag_2O	KH_2PO_4	Phe-OMe	33 % : 10 %
6	Co-2	Ag_2O	KH_2PO_4	EA	60 % : 0 %
7	Co-2	Ag_2O	KH_2PO_4	DCE	55 % : < 5 %
8	Co-2	Ag_2O	K_3PO_4	EA	22 % : 8 %
9	Co-2	Ag_2O	K_2CO_3	EA	10 % : 16 %
10	Co-2	Ag_2O	KOAc	EA	40 % : < 5 %
11	Co-2	Ag_2O	CF_3COOK	EA	60 % : < 5 %
12	Co-2	Ag_2O	$KHCO_3$	EA	56 % : < 5 %
13	Co-2	Ag_2O	K_2HPO_4	EA	29 % : < 5 %
14	Co-2	Ag_2O	$CsCO_3$	EA	0 % : 30 %
15	Co-2	Ag_2O	$KHSO_4$	EA	45 % : < 5 %
16	**Co-2**	**Ag_2O**	**------**	**EA**	**85 % : < 5 %**
17	Co-2	Ag_2CO_3	------	EA	76 % : 0 %
18	Co-2	$Mn(OAc)_2$	------	EA	0 % : < 5 %
19	Co-2	MnO_2	------	EA	0 % : < 5 %
20	Co-2	$Mn(OAc)_3$	------	EA	20 % : < 5 %
21	Co-1	Ag_2O	------	EA	53 % : < 5 %

22	Co-3	Ag_2O	------	EA	79 % : < 5 %
23	Co-4	Ag_2O	------	EA	56 % : < 5 %
24	Co-5	Ag_2O	------	EA	66 % : < 5 %
25	Co-6	Ag_2O	------	EA	70 % : < 5 %
26	Co-7	Ag_2O	------	EA	68 % : < 5 %
27	Co-8	Ag_2O	------	EA	72 % : < 5 %
28	Co-9	Ag_2O	------	EA	73 % : < 5 %
29	Co-10	Ag_2O	------	EA	15 % : 8 %
30	Co-11	Ag_2O	------	EA	17 % : 10 %
31	$Co(NO_2)_3{\cdot}6H_2O$	Ag_2O	------	EA	0 % : 0 %
32	$Pd(OAc)_2$ (10 mol%)	Ag_2O	------	EA	0 % : 0 %
33	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%)	Ag_2O	------	EA	0 % : 0 %
34	$Co(acac)_2$	Ag_2O	------	EA	55 % : < 5 %
35	$Co(OAc)_2$	Ag_2O	------	EA	< 5 % : < 5 %
36	$Cu(acac)_2$	Ag_2O	------	EA	< 5 % : < 5 %
37	$Cu(OAc)_2$ (20 mol%)	Ag_2O	------	EA	40 % : < 5 %
38	$Cp^*Co(CO)I_2$	Ag_2O	------	EA	51 % : < 5 %

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (10 equiv), Catalyst (20 mol%), base (2 equiv), oxidant (2 equiv) and EA (1 mL), at 100 °C for 12 h under air. Yield were determined by ^1H NMR analysis and CH_2Br_2 were added as an inner standard.

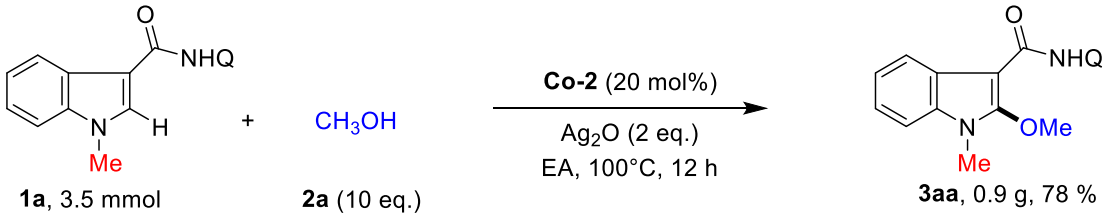


2.4 General procedures for Co-catalyzed alkoxylation of indolyl amides with primary alcohol



In a 25 mL sealed tube, 1 mL EA was added to a mixture of **1** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), alcohol **2** (5-10 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was purified by preparative chromatography with a gradient eluent of petroleum ether, ethyl acetate and dichloromethane to give the corresponding products.

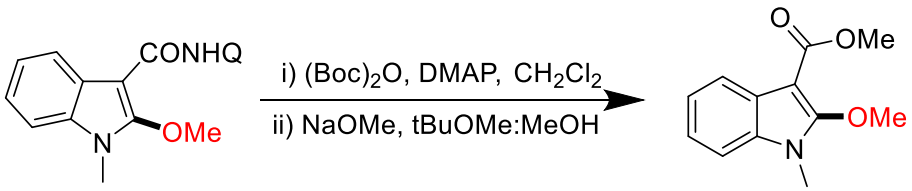
2.5 General procedure for large-scale reaction



In a 150 mL sealed tube, 30 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (3.5 mmol, 1.0 equiv.), Co-2 (270 mg, 20 mol%), Ag_2O (1617 mg, 2.0 equiv.), CH_3OH **2a** (10 equiv.) under

air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C in oil bath for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the crude product was purified by column chromatography on silica gel (R_f = 0.5, petroleum ether/DCM/EtOAc 4/1/1) affording the pure product **3aa** (yellow solid, 0.9 g, 78% yield).

2.6 General procedure for futher diversification of product 5a

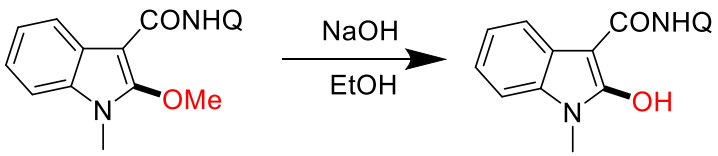


Procedures were done according to the literature procedure[3].

Step 1: To an ice-water cooled solution of compound 2-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3aa, 33 mg, 0.1 mmol, 1 equiv) and DMAP (3 equiv) in anhydrous CH_2Cl_2 (1 mL) was added Boc_2O (5 equiv). The reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by silica gel flash chromatography.

Step 2: To a solution of N-Boc-protected amide (0.1 mmol) in t-BuOMe:MeOH (3:1, 1 mL) was added NaOMe (3equiv) in one portion. The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous NH_4Cl solution, extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired methyl ester **5a** (13 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 1H), 7.24 (dd, *J* = 6.0, 4.0 Hz, 3H), 4.23 (s, 3H), 3.93 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 131.7, 125.2, 122.2, 122.1, 121.4, 109.1, 90.8, 63.4, 51.0, 27.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}NO_3^+$): 220.0968, found: 220.0964.

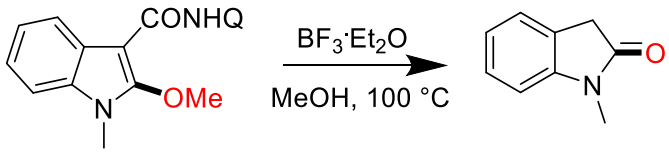
2.7 General procedure for futher diversification of product 5b



Procedures were done according to the literature procedure[4].

A solution of 2-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3aa, 33 mg, 0.1 mmol, 1 equiv) and NaOH (40 mg, 10 equiv) in ethanol (1 mL) was heated at 100 °C for 12 h. After this period, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL).The aqueous layer was acidified with 1 N HCl and extracted with ether(2 × 10 mL). The combined organic layers were dried over Na_2SO_4, and then the solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the product **5b** (24 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.98 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.79 (dd, *J* = 6.14, 2.8 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.47 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.41 – 737 (m, 1H), 7.23 – 719 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.64 (s, 1H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 162.6, 149.0, 143.9, 139.3, 136.3, 134.6, 129.0, 128.2, 127.3, 127.1, 123.34, 122.3, 121.8, 117.2, 108.5, 52.1, 26.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{16}N_3O_2^+$): 318.1237, found: 318.1234.

2.8 General procedure for futher diversification of product 5c

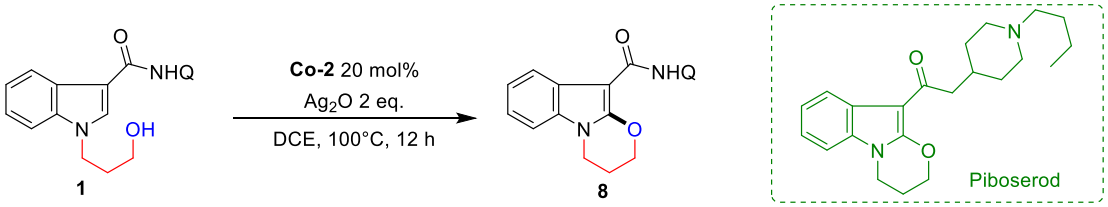


Procedures were done according to the literature procedure[5].

To a solution of 2-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carbox -amide 3aa (33 mg, 0.1 mmol, 1 equiv) in dry methanol (1 mL) was added BF_3·Et_2O (0.1 mL, 6 equiv) dropwise. Then the resulting mixture was stirred at 100°C for 12 h and allowed to attain rt. Et_3N (1 mL) was added dropwise to the reaction mixture with stirring, and then the solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the product **5c** (13 mg, 86%).^{1}H

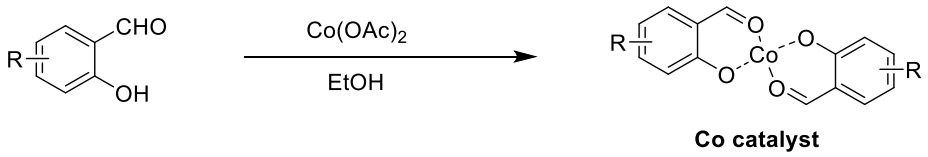
NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.07 – 7.02 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 3.53 (s, 2H), 3.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 145.4, 128.0, 124.6, 124.5, 122.5, 108.2, 35.9, 26.3. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_9H_{10}N_3O^+$): 148.0757, found: 148.0754.

2.9 Synthesis of 5-HT4-receptor antagonist analogue



In a 25 mL sealed tube, 1 mL DCE was added to a mixture of 1-(3-hydroxypropyl)-N-(quinolin-8-yl)-1H-indole-3-carboxamide **1** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was purified by preparative chromatography with a gradient eluent of petroleum ether, ethyl acetate and dichloromethane to give the corresponding products **8 (41 %)**. ^1H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.96 (d, *J* = 7.6 Hz, 1H), 8.70 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.32 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.29 (dd, *J* = 10.0, 4.4 Hz, 3H), 4.70 – 4.62 (m, 2H), 4.53 – 4.49 (m, 2H), 2.57 – 2.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 150.3, 148.0, 139.0, 136.4, 136.4, 131.6, 127.9, 126.0, 122.5, 121.3, 121.1, 121.1, 120.2, 116.4, 107.9, 90.5, 67.1, 39.2, 21.4. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}N_3O^+$): 344.1394, found: 344.1391.

2.10 General procedure for synthesis of Co catalyst



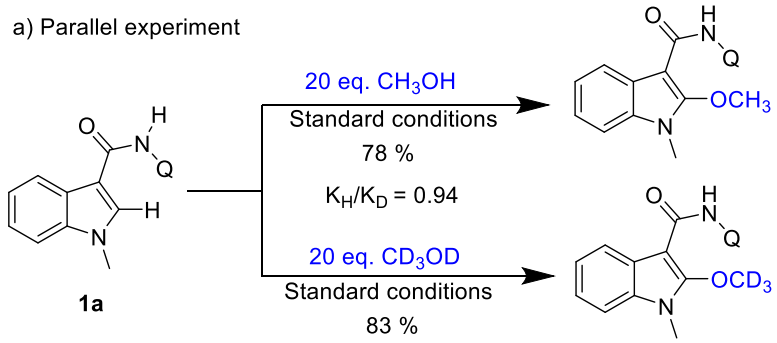
Co catalyst

Procedures were done according to the literature procedure[6].

The metal acetate of Co (6.0 mmol) was dissolved in ethanol (10 mL) in a 100 mL

round-bottomed fask, and it added the solution of salicylaldehyde (2.94 g, 24.0 mmol) in ethanol (40 mL). The solution was stirred at 80 ºC in an oil bath for 24 h. Cobalt formed a yellow precipitate. The precipitate was fltered and washed with DCM. The residue was dried at 100 ºC in an air oven for 24 h to get a pure **Co catalyst**.

2.11 Mechanism investigations



In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CH_3OH (10 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was subject to ^1H NMR test to determine the yield of **3aa**. Yield were determined by ^1H NMR analysis and CH_2Br_2 were added as an inner standard.

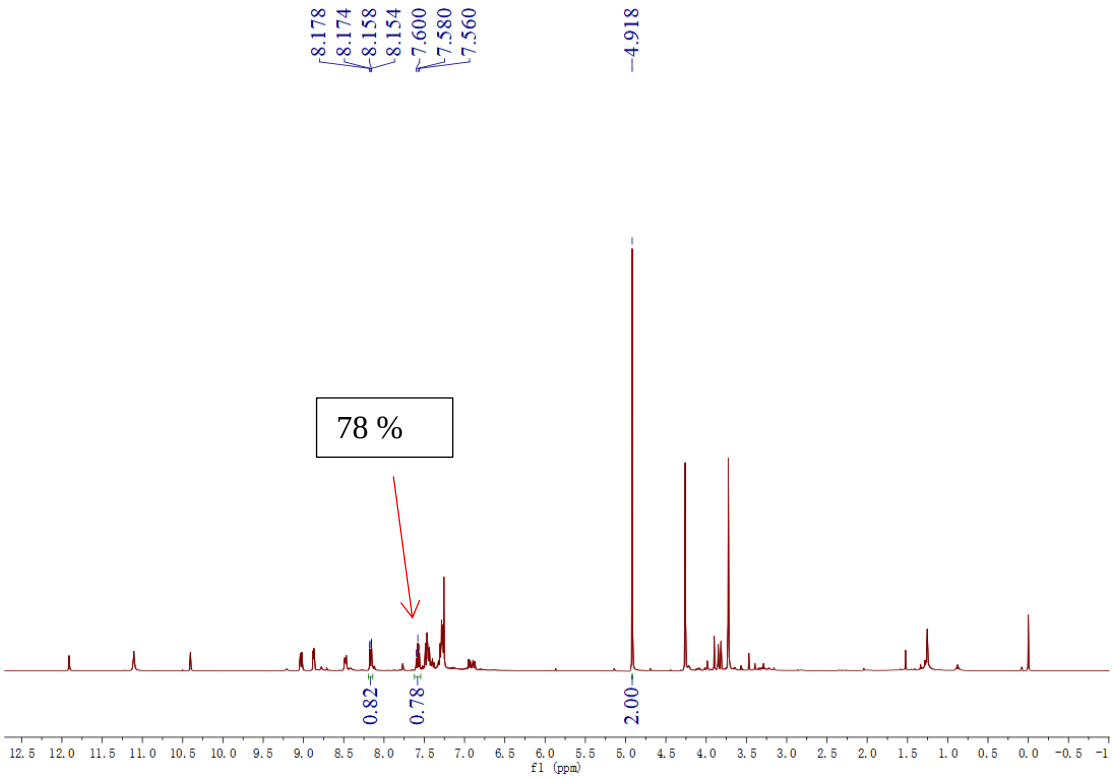


Figure S1. ^{1}H NMR spectrum of the mixture system of 3aa

In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CD_3OD (10 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was subject to ^{1}H NMR test to determine the ratio of **3ap**. Yield were determined by ^{1}H NMR analysis and CH_2Br_2 were added as an inner standard.

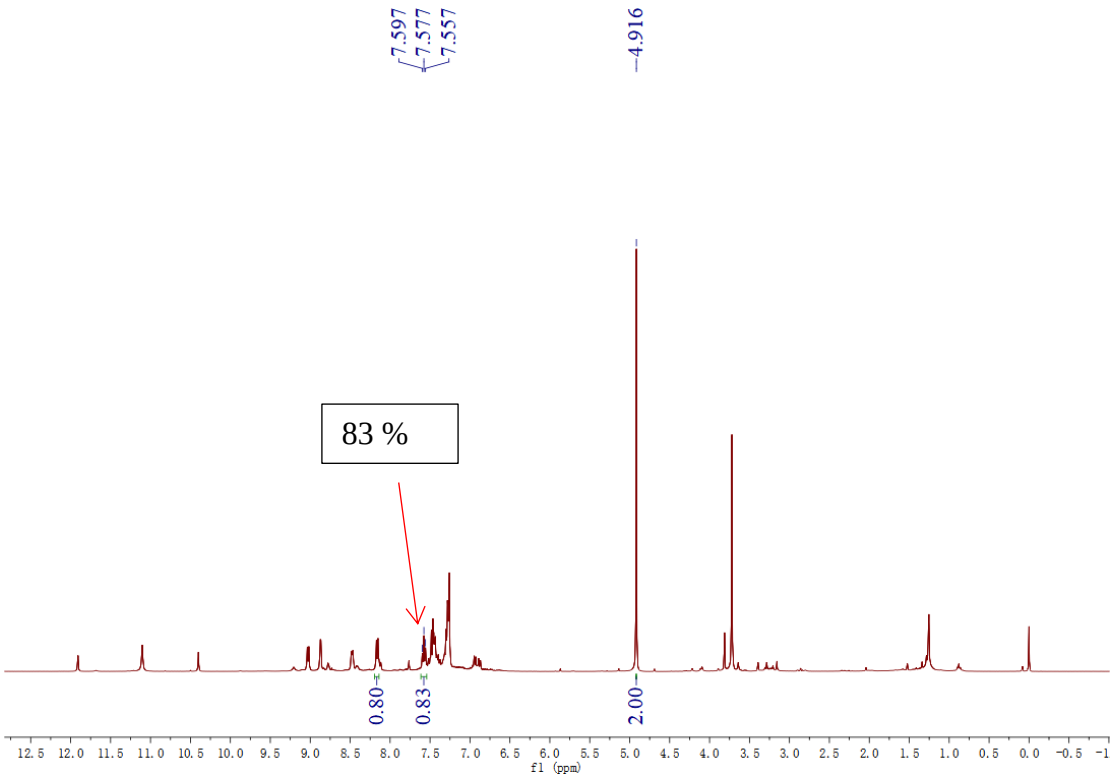
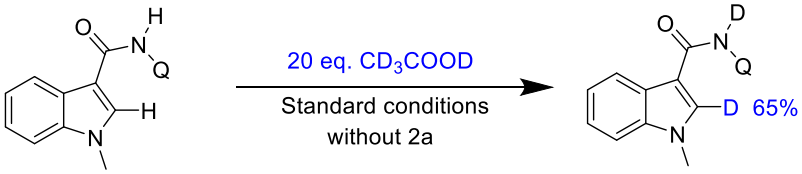


Figure S2. ^{1}H NMR spectrum of the mixture system of 3ap



In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-1 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CD_3COOD (20 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was sub*J*ect to ^{1}H NMR test to determine the ratio of **3aa-D.**

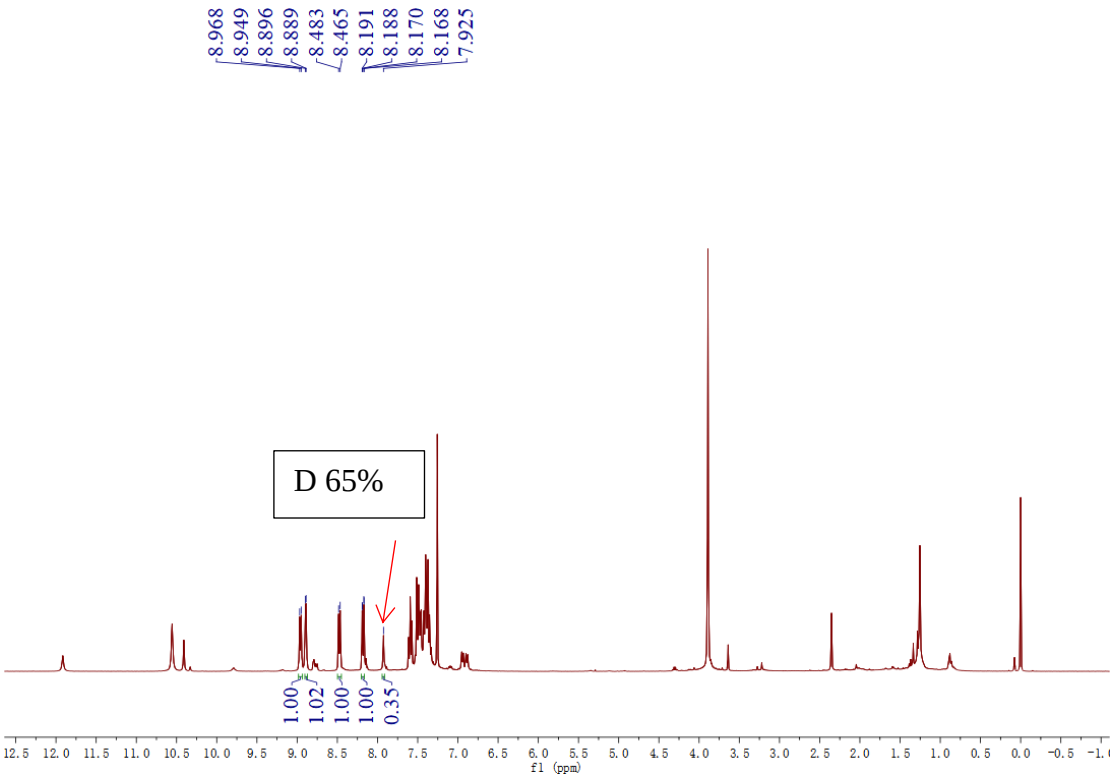
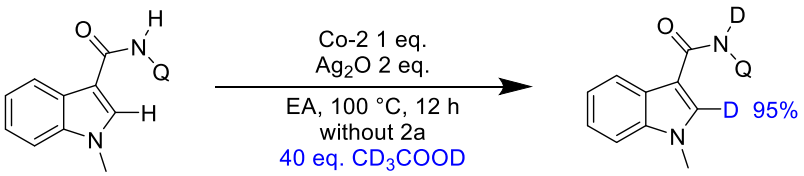


Figure S3. ^{1}H NMR spectrum of the mixture system of 3aa-D



In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-2 (38.4 mg,1 equiv), Ag_2O (46.3 mg, 2.0 equiv.), CD_3COOD (40 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was subJect to ^{1}H NMR test to determine the ratio of **1a-D**.

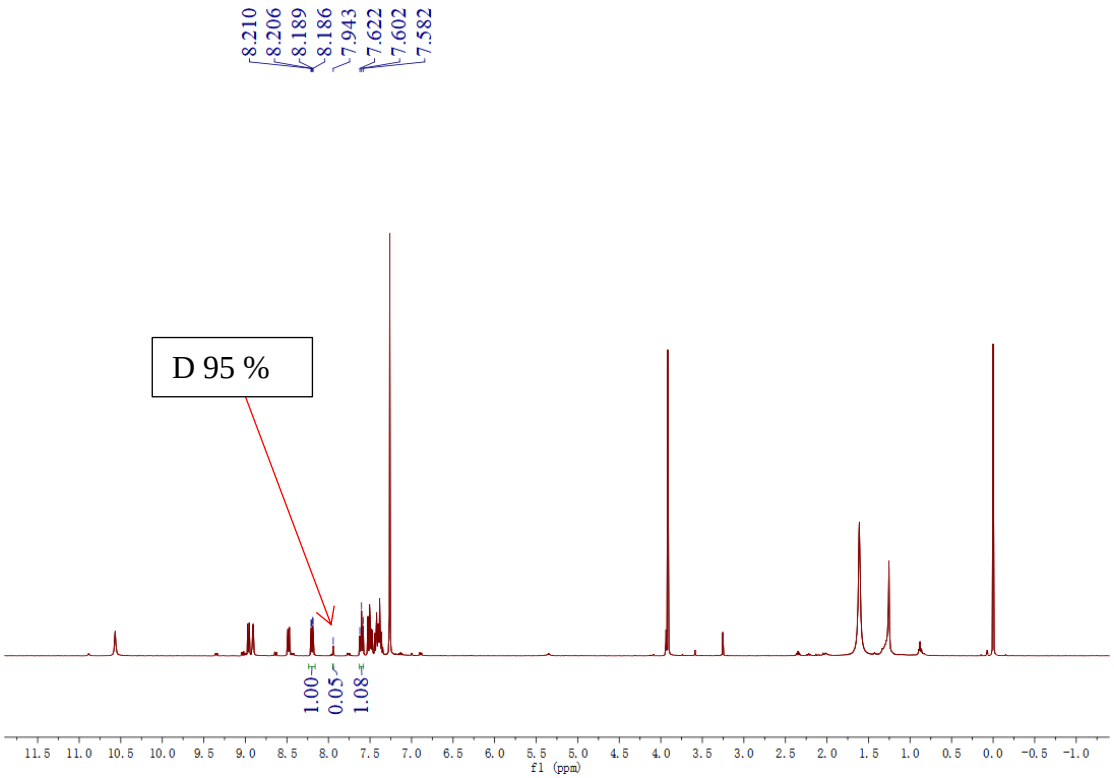
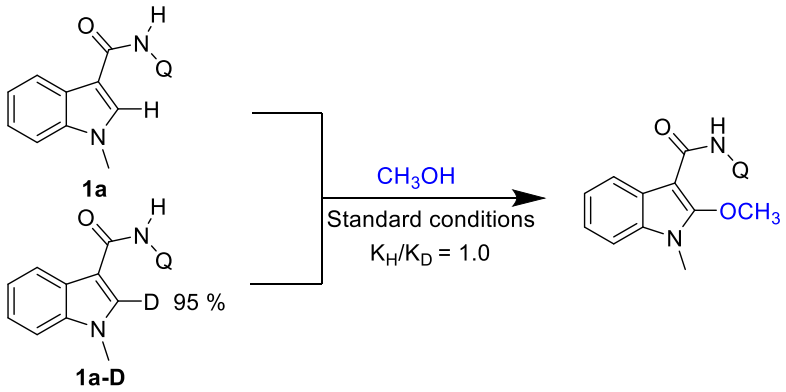


Figure S4. ^{1}H NMR spectrum of the mixture system of 1a-D



In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CH_3OH (10 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was subject to ^{1}H NMR test to determine the ratio of **3aa**. Yield were determined by ^{1}H NMR analysis and CH_2Br_2 were added as an inner standard.

In a 25 mL sealed tube, 1 mL EA was added to a mixture of **1a-D** (0.1 mmol, 1.0 equiv.), Co-2 (7.7 mg, 20 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CH_3OH (10 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was

stirred at 100 °C by heating metal mantle for 12 h. After cooling to room temperature, the mixture was filtered over celite, concentrated under vacuum and the residue was subject to ^{1}H NMR test to determine the ratio of **3aa**. Yield were determined by ^{1}H NMR analysis and CH_2Br_2 were added as an inner standard.

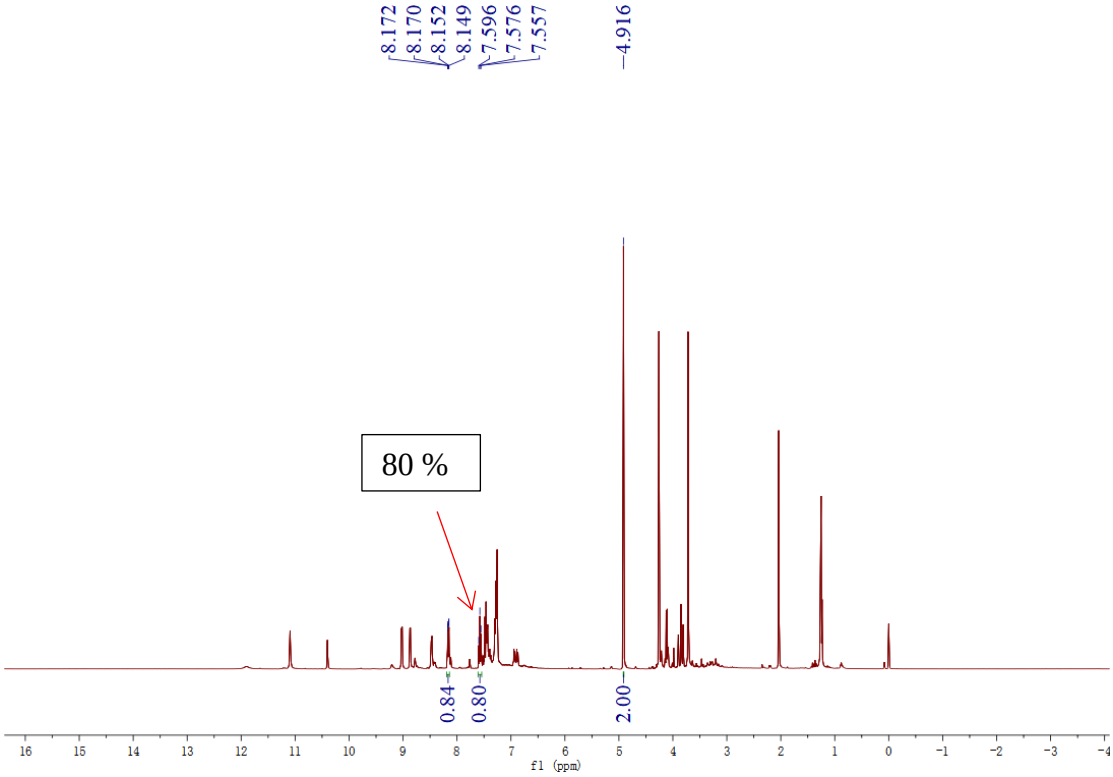


Figure S5. ^{1}H NMR spectrum of the 1a mixture system of 3aa

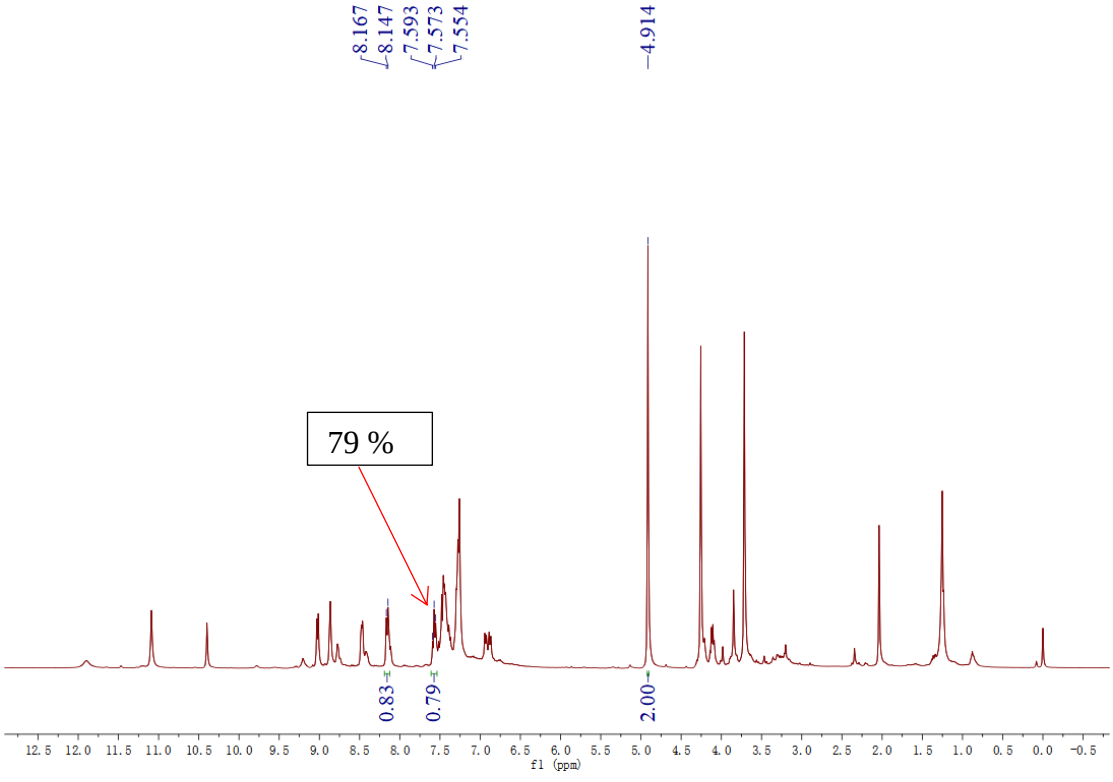
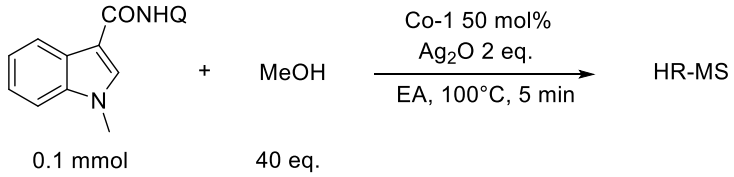


Figure S6. ^{1}H NMR spectrum of the 1a-D mixture system of 3aa



In a 25 mL sealed tube, 1 mL EA was added to a mixture of 1-methyl-N-(quinolin-6-yl)-1H-indole-3-carboxamide **1a** (0.1 mmol, 1.0 equiv.), Co-1 (18.4 mg, 50 mol%), Ag_2O (46.3 mg, 2.0 equiv.), CH_3OH (40 equiv) under air. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C by heating metal mantle for 5 minute. After cooling to room temperature, Take out the appropriate reaction solution for HR-MS test, and then analyze and fit the spectrogram.

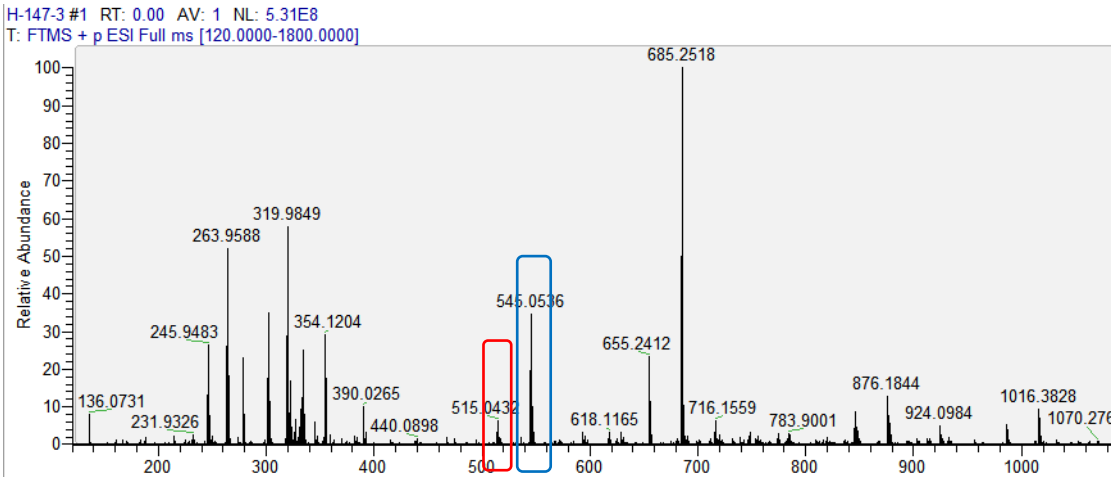


Figure S7. HR-MS of 3aa mixture system

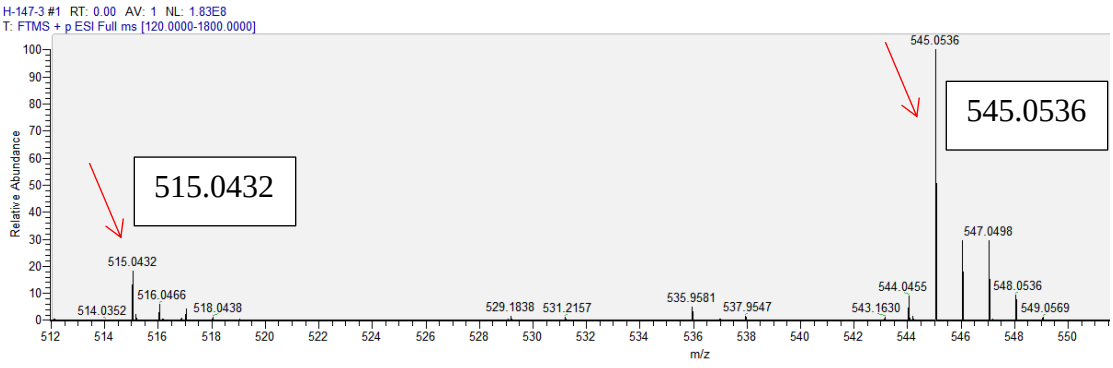


Figure S8. HR-MS of 3aa mixture system partial enlargement

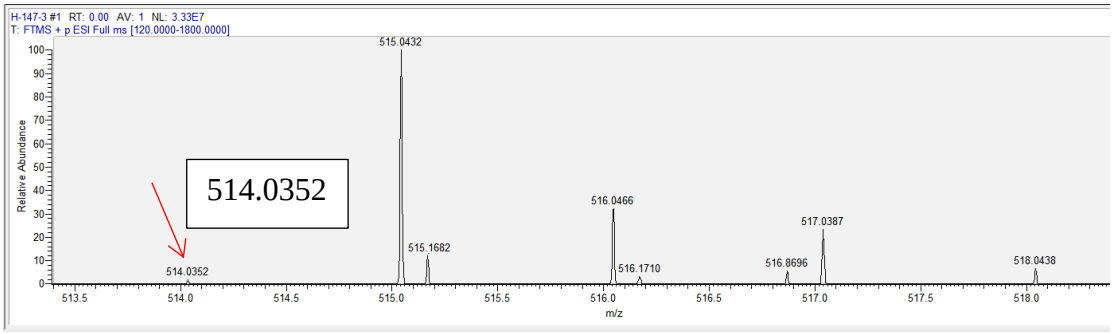
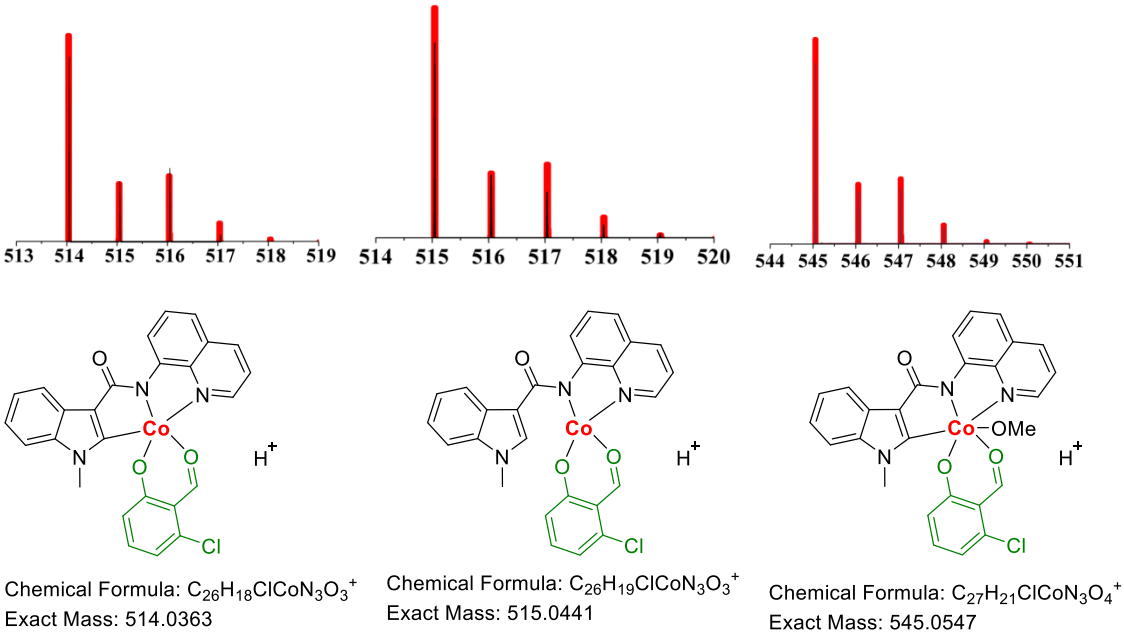


Figure S9. HR-MS of 3aa mixture system partial enlargement



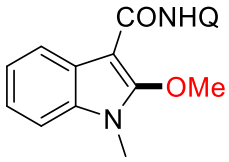
Chemical Formula: $C_{26}H_{18}ClCoN_3O_3^+$
Exact Mass: 514.0363

Chemical Formula: $C_{26}H_{19}ClCoN_3O_3^+$
Exact Mass: 515.0441

Chemical Formula: $C_{27}H_{21}ClCoN_3O_4^+$
Exact Mass: 545.0547

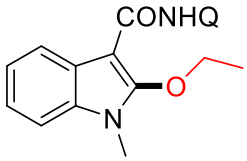
Figure S10. HRMS of origin fit spectrum

3. Characterization Data



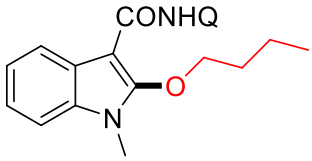
2-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3aa)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3aa** (26 mg, 80 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.88 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.50 – 8.45 (m, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.49 – 7.44 (m, 2H), 7.33 – 7.27 (m, 3H), 4.27 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 153.7, 148.2, 139.0, 136.5, 136.0, 132.2, 128.3, 127.8, 125.3, 122.5, 122.3, 121.7, 121.6, 120.7, 116.4, 109.1, 95.7, 64.0, 28.3. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}N_3O_2^+$): 332.1394, found: 332.1386.



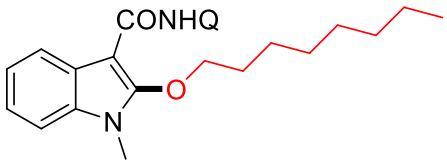
2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ba)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ba** (26 mg, 76 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 – 8.47 (m, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.49 – 7.44 (m, 2H), 7.32 – 7.26 (m, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.5, 148.0, 138.9, 136.5, 136.0, 132.3, 128.3, 127.8, 125.5, 122.4, 122.2, 121.8, 121.5, 120.6, 116.5, 109.1, 96.3, 73.5, 28.4, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}N_3O_2^+$): 346.1550, found: 346.1540.



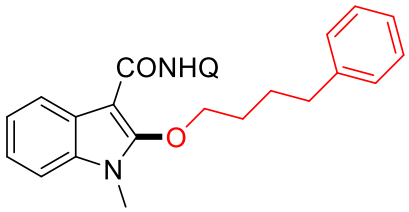
2-butoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ab)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ab** (26 mg, 71 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 9.09 – 9.04 (m, 1H), 8.85 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.50 – 8.45 (m, 1H), 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.50 – 7.44 (m, 2H), 7.31 – 7.26 (m, 3H), 4.35 (t, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 2.09 – 2.02 (m, 2H), 1.59 – 1.53 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.8, 147.9, 139.0, 136.5, 136.0, 132.3, 128.3, 127.8, 125.5, 122.3, 122.2, 121.7, 121.5, 120.7, 116.6, 109.0, 96.1, 32.0, 28.4, 19.2, 14.1. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{24}N_3O_2^+$): 374.1863 found: 374.1853.



1-methyl-2-(octyloxy)-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ac)

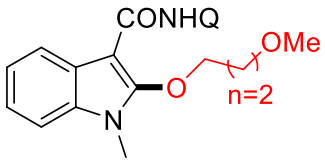
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ac** (28 mg, 66 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 9.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.50 – 8.44 (m, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.51 – 7.45 (m, 2H), 7.32 – 7.28 (m, 3H), 4.33 (t, *J* = 6.8 Hz, 2H), 3.73 (s, 3H),2.11 – 2.03 (m, 2H), 1.53 – 1.47 (m, 2H), 1.33 – 1.22 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.8, 147.9, 139.0, 136.5, 136.0, 132.3, 128.3, 127.8, 125.5, 122.4, 122.2, 121.7, 121.5, 120.7, 116.6, 109.0, 96.2, 31.9, 30.0, 29.6, 29.3, 28.4, 25.9, 22.7, 14.2. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{32}N_3O_2^+$): 430.2489, found: 430.2481.



1-methyl-2-(4-phenylbutoxy)-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ad)

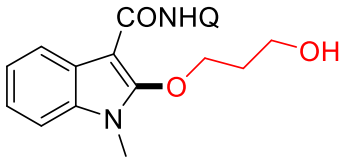
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ad** (18 mg, 40 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 9.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.57 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.49 – 8.45 (m, 1H), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H),

7.61 – 7.57 (m, 1H), 7.48 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.31 – 7.25 (m, 5H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.16 – 7.12 (m, 2H), 4.34 (t, *J* = 6.8 Hz, 2H), 3.70 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.15 – 2.08 (m, 2H), 1.92 – 1.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.7, 148.0, 141.8, 138.9, 136.4, 136.0, 132.2, 128.6, 128.3, 127.8, 126.1, 125.5, 122.4, 122.2, 121.8, 121.6, 120.7, 116.6, 109.1, 96.2, 35.9, 29.6, 28.4, 27.8. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{29}H_{28}N_3O_2^+$): 450.2176, found: 450.2168.



2-(4-methoxybutoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ae)

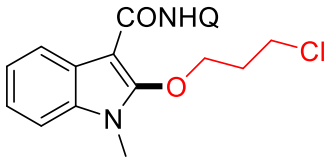
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ae** (20 mg, 49 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 9.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.49 – 8.45 (m, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.50 – 7.45 (m, 2H), 7.32 – 7.27 (m, 3H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.73 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 2H), 3.30 (s, 3H), 2.20 – 2.13 (m, 2H), 1.85 – 1.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.8, 148.0, 139.0, 136.5, 136.0, 132.3, 128.3, 127.8, 125.5, 122.4, 122.2, 121.7, 121.6, 120.7, 116.6, 109.1, 96.2, 72.4, 58.8, 28.4, 27.0, 26.2. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{26}N_3O_3^+$): 404.1969, found: 404.1957.



2-(3-hydroxypropoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ah)

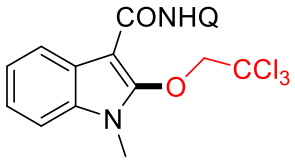
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 1/1/1) afforded the product as a solid **4ah** (13 mg, 34 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (s, 1H), 9.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.82 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.43 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.47 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.35 – 7.26 (m, 3H), 4.44 (t, *J* = 6.0 Hz, 2H), 4.00 (t, *J* = 5.6 Hz, 2H), 3.64 (s, 3H), 2.25 – 2.19 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 153.5, 148.1, 138.8,

136.5, 135.7, 132.1, 128.2, 127.8, 124.8, 122.3, 122.3, 121.6, 121.0, 120.9, 116.7, 109.4, 96.0, 74.1, 58.8, 32.7, 28.2. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_3^+$): 376.1656, found: 376.1645.



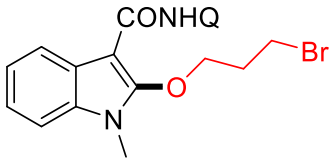
2-(3-chloropropoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ag)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ag** (20 mg, 51 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 9.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.82 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.50 – 8.45 (m, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.51 – 7.45 (m, 2H), 7.33 – 7.28 (m, 3H), 4.49 (t, *J* = 6.0 Hz, 2H), 3.95 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 2.57 – 2.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 152.2, 147.9, 138.8, 136.6, 135.9, 132.3, 128.3, 127.9, 125.3, 122.6, 122.3, 121.7, 121.6, 120.8, 116.7, 109.2, 96.3, 73.5, 41.3, 32.6, 28.4. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{21}ClN_3O_2^+$): 394.1317, found: 394.1306.



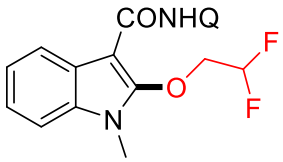
1-methyl-N-(quinolin-8-yl)-2-(2,2,2-trichloroethoxy)-1H-indole-3-carboxamide (4af)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 4/1/1) afforded the product as a solid **4af** (35 mg, 77 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.89 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.36 – 8.33 (m, 1H), 8.20 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.53 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.49 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.39 – 7.33 (m, 3H), 5.21 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 154.0, 148.5, 138.9, 136.5, 135.5, 131.7, 128.3, 127.7, 123.9, 122.4, 122.3, 121.8, 121.2, 119.8, 116.5, 109.7, 95.9, 94.4, 85.7, 28.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{17}Cl_3N_3O_2^+$): 448.0381, found: 448.0369.



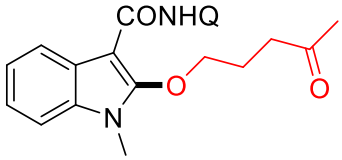
2-(3-bromopropoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4aj)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4aj** (23 mg, 53 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 9.07 (dd, J = 7.6, 1.2 Hz, 1H), 8.83 (dd, J = 4.0, 1.6 Hz, 1H), 8.49 – 8.45 (m, 1H), 8.19 (dd, J = 8.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.51 – 7.46 (m, 2H), 7.33 – 7.28 (m, 3H), 4.49 (t, J = 5.6 Hz, 2H), 3.79 (t, J = 6.4 Hz, 2H), 3.77 (s, 3H), 2.65 – 2.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 152.2, 147.9, 138.9, 136.6, 135.9, 132.3, 128.3, 127.9, 125.3, 122.6, 122.3, 121.7, 121.6, 120.8, 116.7, 109.2, 96.3, 74.6, 32.8, 29.7, 28.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{21}BrN_3O_2^+$): 438.0812, found: 438.0801.



2-(2,2-difluoroethoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ai)

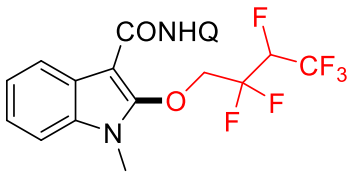
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 4/1/1) afforded the product as a solid **4ai** (26 mg, 71 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.99 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 – 8.40 (m, 1H), 8.20 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.53 – 7.47 (m, 1H), 7.36 – 7.30 (m, 3H), 6.39 4.67 (tt, *J* = 54.8, 3.6 Hz, 1H)), 4.67 (td, *J* = 13.6, 3.8 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 152.2, 148.2, 138.9, 136.6, 135.6, 132.0, 128.3, 127.8, 124.5, 122.7, 122.5, 121.7, 121.1, 121.0, 116.6, 113.4 (t, *J* = 242.4 Hz), 109.5, 95.9, 74.1 (t, *J* = 28.3 Hz), 28.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -126.23. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}F_2N_3O_2^+$): 382.1362, found: 382.1350.



1-methyl-2-((4-oxopentyl)oxy)-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ak)

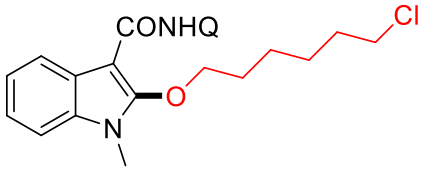
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ak** (10 mg, 26 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 9.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.48 – 8.43 (m, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.51 – 7.46 (m, 2H), 7.33 – 7.27 (m, 3H), 4.36 (t, *J* = 6.8 Hz, 2H),

3.72 (s, 3H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.38 – 2.31 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 163.0, 152.5, 148.1, 138.9, 136.6, 135.9, 132.3, 128.3, 127.9, 125.4, 122.5, 122.2, 121.6, 120.8, 116.7, 109.1, 96.2, 76.5, 39.6, 30.1, 28.5, 24.0. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}N_3O_3^+$): 402.1812, found: 402.1801.



1-methyl-N-(quinolin-8-yl)-2-(2,2,3-trifluorobutoxy)-1H-indole-3-carboxamide (4am)

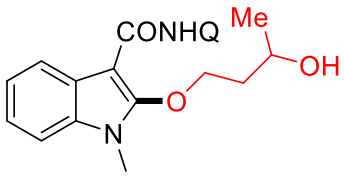
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4am** (37 mg, 79 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.95 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.37 (dd, *J* = 6.0, 2.4 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39 – 7.32 (m, 3H), 5.41 – 5.22 (m, 1H), 5.10 – 4.99 (m, 1H), 4.83 – 4.74 (m, 1H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 152.5, 148.7, 138.8, 136.6, 135.4, 131.8, 128.3, 127.7, 123.9, 122.7, 122.5, 121.8, 121.3, 120.4, 116.6, 109.7, 95.9, 85.4 – 84.5 (m), 83.2 – 82.5 (m), 72.80 – 72.23 (m), 28.28. ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.84 (dd, *J* = 21.0, 10.5 Hz), -115.74 – -115.96 (m), -116.48 – -116.74 (m), -120.90 – -121.14 (m), -121.64 – -121.87 (m), -211.8 – -212.0 (m). HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{18}F_6N_3O_2^+$): 482.1298, found:482.1286.



2-((6-chlorohexyl)oxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4ai)

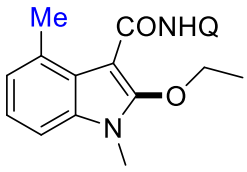
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 5/1/1) afforded the product as a solid **4ai** (20 mg, 46 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 9.06 (d, *J* = 7.6 Hz, 1H), 8.87 – 8.84 (m, 1H), 8.48 – 8.43 (m, 1H), 8.21 – 8.17 (m, 1H), 7.62 – 7.58 (m, 1H), 7.51 – 7.46 (m, 2H), 7.34 – 7.27 (m, 3H), 4.35 (t, *J* = 6.8 Hz, 2H), 3.73 (s, 3H), 3.48 (t,

J = 6.8 Hz, 2H), 2.12 – 2.05 (m, 2H), 1.75 – 1.69 (m, 2H), 1.56 – 1.46 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.7, 148.0, 138.9, 136.5, 136.0, 132.3, 128.3, 127.9, 125.5, 122.4, 122.2, 121.7, 121.6, 120.7, 116.6, 109.1, 96.2, 45.0, 32.5, 29.9, 28.4, 26.8, 25.3. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{27}ClN_3O_2^+$): 436.1786, found: 436.1772.



2-(3-hydroxybutoxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4an)

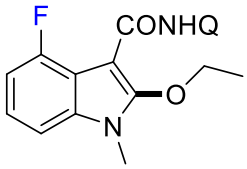
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 1/1/1) afforded the product as a solid **4an** (16 mg, 42 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 9.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.80 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.43 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.13 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.46 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.24 – 7.21 (m, 1H), 4.55 – 4.50 (m, 1H), 4.35 – 4.26 (m, 2H), 3.63 (s, 3H), 2.27 – 2.19 (m, 1H), 1.97 – 1.90 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 153.5, 148.1, 138.8, 136.5, 135.7, 132.1, 128.2, 127.7, 124.8, 122.3, 122.2, 121.6, 121.0, 120.9, 116.7, 109.3, 95.9, 74.5, 64.3, 39.0, 28.2, 23.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{24}N_3O_3^+$): 390.1812, found: 390.1808.



2-ethoxy-1,4-dimethyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ca)

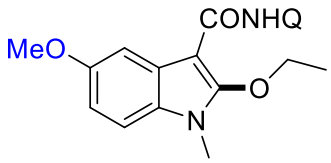
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ca** (20 mg, 56 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 9.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.82 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 2.75 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 151.9, 148.2, 138.9, 136.4, 135.7, 132.4, 131.7, 128.3, 127.8, 123.8, 123.7, 122.0,

121.6, 121.0, 116.4, 106.7, 97.7, 72.6, 28.2, 22.0, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_2^+$): 360.1707, found: 360.1705.



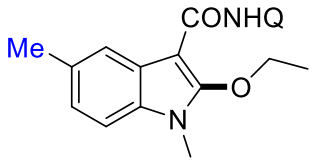
2-ethoxy-4-fluoro-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3da)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3da** (29 mg, 84 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 9.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.4., 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.49 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.06 – 7.03 (m, 1H), 6.96 (ddd, *J* = 11.6, 8.0, 0.8 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.68 (s, 3H), 1.50 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 156.2 (*J* = 249.5 Hz), 153.4, 148.1, 139.0, 136.4, 135.9, 134.5, 134.4, 128.2, 127.7, 122.6, 122.5, 121.5, 120.9, 116.8, 112.7 (*J* = 19.2 Hz), 108.1 (*J* = 22.2 Hz), 105.3, 95.5, 72.9, 28.6, 15.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.85. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}FN_3O_2^+$): 364.1456, found: 364.1444



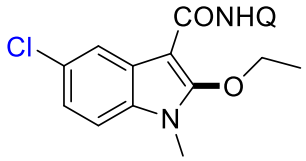
2-ethoxy-5-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ea)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ea** (32 mg, 86 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.50 – 7.44 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.41 (q, *J* = 6.8 Hz, 2H), 3.94 (s, 3H), 3.68 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 156.1, 152.5, 148.0, 139.0, 136.5, 136.0, 128.3, 127.8, 127.0, 126.1, 121.6, 120.6, 116.5, 112.7, 110.0, 103.4, 96.3, 73.5, 56.0, 28.5, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_3^+$): 376.1656, found: 376.1653.



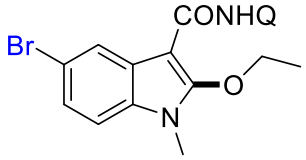
2-ethoxy-1,5-dimethyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3fa)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3fa** (24 mg, 69 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.34 – 8.30 (m, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.49 – 7.44 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 2.51 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 152.5, 148.0, 139.0, 136.5, 136.1, 131.7, 130.6, 128.3, 127.8, 125.6, 123.7, 121.7, 121.5, 120.6, 116.5, 108.8, 95.9, 76.8, 73.4, 28.4, 21.8, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_2^+$): 360.1707, found: 360.1706.



5-chloro-2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ga)

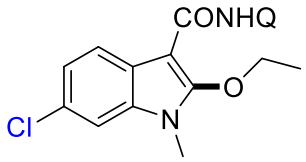
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ga** (28 mg, 75 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.03 (d, *J* = 7.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.42 – 8.37 (m, 1H), 8.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.50 – 7.44 (m, 2H), 7.27 – 7.24 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.6, 148.1, 138.9, 136.5, 135.8, 132.8, 128.3, 128.3, 127.8, 124.0, 122.9, 122.7, 121.6, 120.9, 116.6, 109.3, 96.6, 73.7, 28.5, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}ClN_3O_2^+$): 380.1160, found: 380.1156.



5-bromo-2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ha)

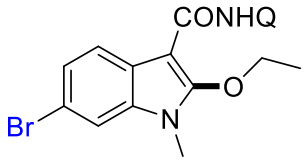
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ha** (31 mg,

76 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 9.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.85 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.65 (d, *J* = 1.6 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.49 – 7.43 (m, 2H), 7.32 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 1.63 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 152.8, 148.0, 138.9, 136.5, 135.8, 130.9, 128.3, 127.8, 127.0, 125.3, 124.3, 121.6, 120.8, 116.5, 115.6, 110.5, 96.1, 73.7, 28.5, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}BrN_3O_2^+$): 424.0655, found: 424.0652.



6-chloro-2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ia)

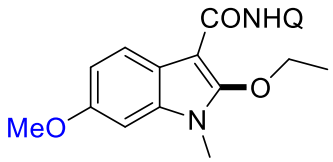
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ia** (27 mg, 72 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.03 (d, *J* = 7.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.42 – 8.37 (m, 1H), 8.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.50 – 7.44 (m, 2H), 7.27 – 7.24 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.6, 148.1, 138.9, 136.5, 135.8, 132.8, 128.3, 128.3, 127.8, 124.0, 122.9, 122.7, 121.6, 120.9, 116.6, 109.3, 96.6, 73.7, 28.5, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}ClN_3O_2^+$): 380.1160, found: 380.1164.



6-bromo-2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ja)

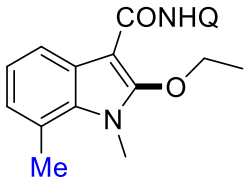
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ja** (29 mg, 71 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.03 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.58 (d, *J* =8.0 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.42 – 7.38 (m, 2H), 4.44 (q, *J* = 6.8 Hz, 2H), 3.69 (s, 3H), 1.65 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.5, 148.1, 138.9, 136.5, 135.8, 133.1, 128.3, 127.8, 125.3, 124.4, 123.2,

121.6, 120.9, 116.6, 115.8, 112.2, 96.6, 73.7, 28.5, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}BrN_3O_2^+$): 424.0655, found: 424.0649.



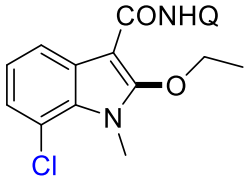
2-ethoxy-6-methoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ka)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ka** (28 mg, 76 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 9.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.60 – 7.66 (m, 1H), 7.49 – 7.44 (m, 2H), 6.95 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 156.7, 151.8, 148.0, 139.0, 136.5, 136.1, 133.1, 128.3, 127.8, 122.6, 121.5, 120.6, 119.3, 116.5, 110.7, 96.2, 93.8, 73.5, 55.9, 28.4, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_3^+$): 376.1656, found: 376.1653.



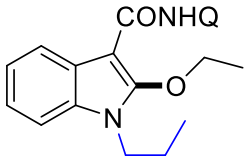
2-ethoxy-1,7-dimethyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3la)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3la** (27 mg, 79 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.51 – 7.45 (m, 2H), 7.17 – 7.14 (m, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 4.40 (q, *J* = 6.8 Hz, 2H), 3.97 (s, 3H), 2.77 (s, 3H), 1.66 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.5, 148.0, 139.0, 136.5, 136.1, 131.4, 128.3, 127.8, 126.3, 125.4, 122.0, 121.5, 120.8, 120.6, 119.1, 116.5, 96.2, 73.4, 31.3, 19.9, 15.4. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}N_3O_2^+$): 360.1707, found: 360.1704.



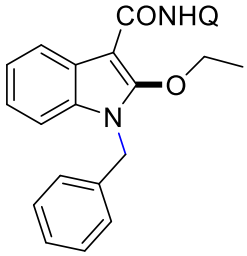
7-chloro-2-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3ma)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ma** (27 mg, 73 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.52 – 7.46 (m, 2H), 7.22 – 7.19 (m, 1H), 7.18 – 7.14 (m, 1H), 4.43 (q, *J* = 6.8 Hz, 2H), 4.07 (s, 3H), 1.67 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 153.0, 148.1, 138.9, 136.5, 135.8, 128.4, 128.3, 127.8, 124.1, 122.6, 121.6, 120.9, 120.6, 116.6, 96.8, 73.8, 31.4, 15.4. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}ClN_3O_2^+$): 380.1160, found: 380.1158.



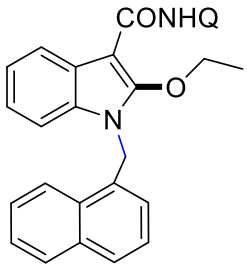
2-ethoxy-1-propyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3na)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3na** (29 mg, 79 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 9.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.50 – 8.46 (m, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.49 – 7.44 (m, 2H), 7.32 – 7.25 (m, 3H), 4.44 (q, *J* = 6.8 Hz, 2H), 4.11 – 4.05 (m, 2H), 1.91 (dt, *J* = 14.8, 7.6 Hz, 2H), 1.63 (t, *J* = 6.8 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.7, 148.0, 138.9, 136.5, 136.0, 131.5, 128.3, 127.8, 125.7, 122.2, 122.0, 121.6, 121.5, 120.6, 116.5, 109.5, 96.1, 73.4, 44.0, 23.1, 15.6, 11.7. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{24}N_3O_2^+$): 374.1863, found: 374.1860.



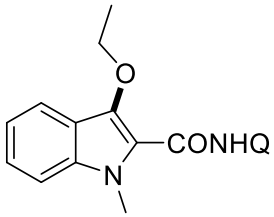
1-benzyl-2-ethoxy-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3oa)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3oa** (33 mg, 81 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 9.08 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.48 (ddd, *J* = 12.4, 8.2, 2.6 Hz, 2H), 7.35 – 7.27 (m, 4H), 7.23 – 7.14 (m, 4H), 5.37 (s, 2H), 4.33 (q, *J* = 6.8 Hz, 2H), 1.53 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.7, 148.1, 139.0, 136.7, 136.5, 136.0, 132.0, 129.1, 128.3, 127.9, 126.5, 125.7, 122.6, 122.3, 121.7, 121.6, 120.7, 116.6, 109.9, 96.7, 73.8, 45.6, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{24}N_3O_2^+$): 422.1863, found: 422.1860.



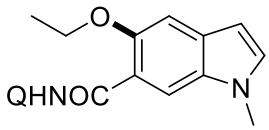
2-ethoxy-1-(naphthalen-1-ylmethyl)-N-(quinolin-8-yl)-1H-indole-3-carboxamide (3pa)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3pa** (35 mg, 76 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.10 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.19 – 8.13 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.63 – 7.59 (m, 2H), 7.50 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.0, 4.2 Hz, 1H), 7.31 (td, *J* = 8.0, 4.0 Hz, 2H), 7.20 – 7.15 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 7.2, 0.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.8, 148.0, 139.0, 136.5, 136.0, 133.8, 132.3, 131.6, 130.4, 129.3, 128.3, 128.3, 127.9, 126.9, 126.3, 125.8, 125.7, 123.2, 122.7, 122.4, 122.2, 121.9, 121.6, 120.8, 116.6, 110.0, 97.0, 74.0, 43.4, 15.5. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{31}H_{26}N_3O_2^+$): 472.2020, found: 472.2021.



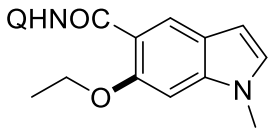
3-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-2-carboxamide (3ta)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ta** (27 mg, 80 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 9.01 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.91 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.52 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.13 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H), 4.58 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 148.2, 141.1, 139.3, 136.9, 136.4, 135.9, 128.3, 127.6, 125.1, 121.7, 121.4, 120.0, 119.8, 119.5, 118.7, 117.1, 110.5, 71.1, 32.2, 15.8. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}N_3O_2^+$): 346.1550, found: 346.1546.



5-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-6-carboxamide (3ua)

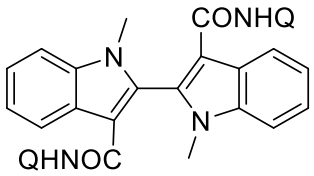
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3ua** (25 mg, 74 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 1H), 9.16 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (s, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 6.43 (dd, *J* = 2.8, 0.4 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.77 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 151.9, 147.9, 139.6, 136.5, 136.3, 132.6, 132.2, 131.9, 128.3, 127.8, 121.5, 121.4, 117.9, 117.8, 114.0, 103.1, 100.4, 65.8, 33.4, 15.3. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}N_3O_2^+$): 346.1550, found: 346.1541.



6-ethoxy-1-methyl-N-(quinolin-8-yl)-1H-indole-5-carboxamide (3va)

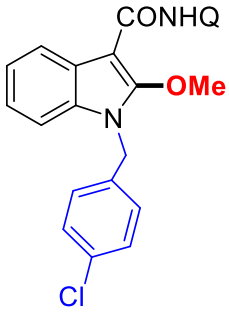
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3va** (37 mg, 52% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 10.02 (s, 1H), 9.18 (s, 1H), 9.16 (d, J = 7.6 Hz, 1H), 8.82 (dd, J = 4.0, 1.6 Hz, 1H), 8.18 (dd, J = 8.0, 1.6 Hz, 1H), 7.60 (d, J = 6.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 6.87

(s, 1H), 4.43 – 4.38 (m, 2H), 3.85 (s, 3H), 1.78 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 164.5, 155.3, 147.8, 140.5, 139.4, 138.6, 136.4, 136.3, 128.3, 127.9, 126.7, 121.5, 119.8, 119.5, 118.9, 118.0, 117.9, 93.1, 65.8, 34.0, 29.9, 15.1. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}N_3O_2^+$): 346.1550, found: 346.1543.



1,1'-dimethyl-N3,N3'-di(quinolin-8-yl)-1H,1'H-[2,2'-biindole]-3,3'-dicarboxamide (3a')

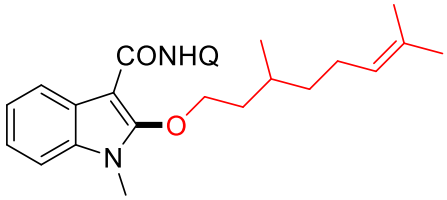
Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **3a'** (19 mg, 32 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 2H), 8.91-8.88 (m, 4H), 7.91 (dd, *J* = 8.4 Hz, 1.6 Hz, 2H), 7.52-7.40 (m, 10H), 7.32 (dd, *J* = 8.0 Hz, 0.8 Hz, 2H), 7.10 (dd, *J* = 8.0 Hz, 2.0 Hz, 2H), 3.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 148.1, 138.6, 138.5, 135.7, 135.2, 128.9, 128.0, 127.7, 127.2, 124.4, 123.4, 122.6, 121.4, 121.0, 116.2, 114.7, 110.4, 30.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{38}H_{29}N_6O_2^+$): 601.2347, found: 601.2341.



1-(4-chlorobenzyl)-2-methoxy-N-(quinolin-8-yl)-1H-indole-3-carboxamide (6)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 3/1/1) afforded the product as a solid **6** (36 mg, 81 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.04 (d, *J* = 7.6 Hz, 1H), 8.85 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.24 – 7.20 (m, 1H), 7.13 – 7.09 (m, 3H), 5.32 (s, 2H), 4.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 153.7, 148.2, 139.0, 136.5, 135.8, 135.1, 133.8, 131.6, 129.3, 128.3, 127.9, 127.8, 125.5, 122.8, 122.5, 121.7, 121.6, 120.8, 116.5,

109.7, 96.2, 64.5, 44.9. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{26}H_{21}ClN_3O_2^+$): 442.1317, found: 442.1315.



2-((3,7-dimethyloct-6-en-1-yl)oxy)-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (7)

Prepared according to general procedure **2.4**, purification of the residue by preparative chromatography (PE/DCM/EA = 6/1/1) afforded the product as a solid **7** (15 mg, 34 % yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 9.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.49 – 8.45 (m, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.50 – 7.44 (m, 2H), 7.32 – 7.27 (m, 3H), 5.05 – 5.00 (m, 1H), 4.41 – 4.36 (m, 2H), 3.72 (s, 3H), 2.18 – 2.10 (m, 1H), 2.05 – 1.83 (m, 4H), 1.65 (d, *J* = 0.8 Hz, 3H), 1.54 (s, 3H), 1.38 – 1.33 (m, 1H), 1.21 – 1.15 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.9, 148.0, 139.0, 136.5, 136.0, 132.3, 131.7, 128.3, 127.8, 125.5, 124.5, 122.4, 122.2, 121.7, 121.5, 120.7, 116.6, 109.0, 96.2, 76.5, 37.3, 36.9, 29.4, 28.4, 25.8, 25.4, 19.6, 17.8. HRMS (ESI+) exact mass calculated for $[M+H]^+$ ($C_{29}H_{34}N_3O_2^+$): 456.2646, found: 456.2639.

4. References

(1) Chen, H.; Lin, C.; Xiong, C.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2017**, *4*, 455-459.

(2) Zhang, T.-Y.; Liu, C.; Chen, C.; Liu, *J*.-X.; Xiang, H.-Y.; *J*iang, W.; Ding, T.-M.; Zhang, S.-Y. *Org. Lett.* **2018**, *20*, 220-223.

(3) Pan, J.-L.; Chen, C.; Ma, Z.-J.; Zhou, J.; Wang, L.-R.; Zhang, S.-Y. *Org. Lett.* **2017**, *19*, 5216 – 5219.

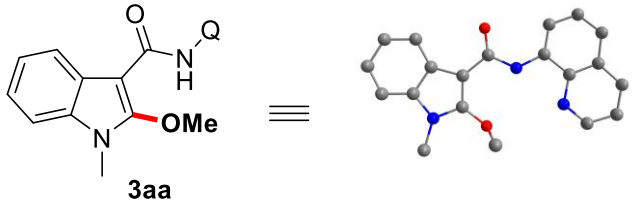
(4) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956–4959.

(5) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*., **2013**, *4*, 3906-3911.

(6) Dhinagaran, G.; Prashanna Suvaitha, S.; Muthukumaran, M.; Venkatachalamet K. *Catal Lett.* **2021**, *151*, 1361-1375.

5. Crystallographic Data

X-ray data for 3aa



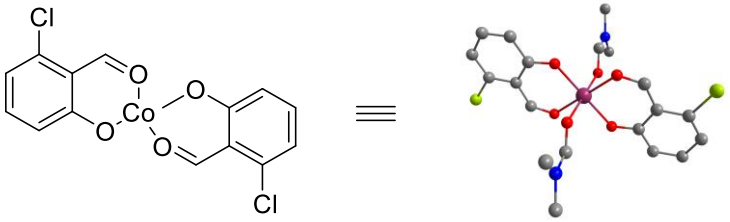
3aa

CCDC 2291138

compound	3aa
formula	$C_{20}H_{16}N_3O_2$
formula weight	330.36
T (K)	298
crystal system	monoclinic
space group	P 1 21/c 1
a (Å)	7.9810(5)
b (Å)	10.9216(9)
c (Å)	19.0174(17)
α (°)	90
β (°)	96.715(7)
γ (°)	90
V (Å^3)	1646.3(2)
Z	4
D_c.(g cm^{-3})	1.333
μ (mm^{-1})	0.713
reflns coll.	11451
independent reflns	3222
$^aR_1$ [I $\geqslant$ 2 σ (I)]	0.0696
$^bwR_2$(all data)	0.2006
GOF	1.041

$^aR_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $^bwR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^1$

X-ray data for Co-2



Co-2

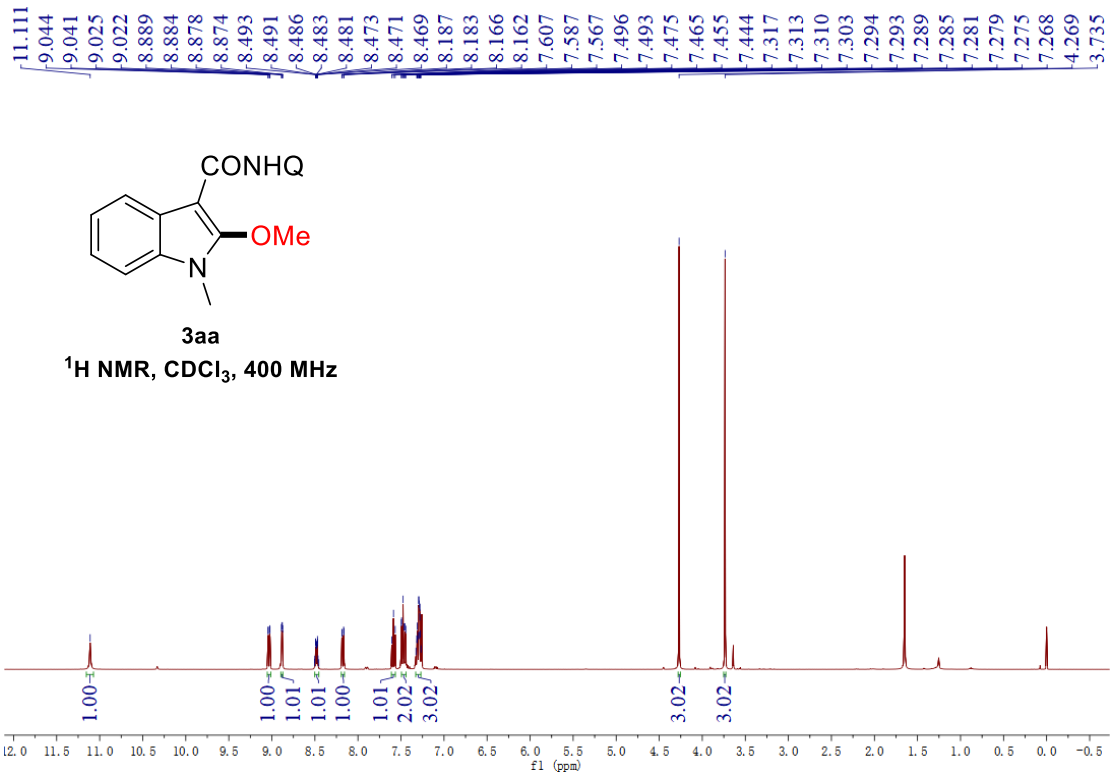
CCDC 2291139

compound	Co-2
formula	$C_{10}H_{11}ClCo_{0.5}NO_3$
formula weight	258.11
T (K)	294

crystal system	triclinic
space group	P-1
a (Å)	6.3806(2)
b (Å)	9.3454(3)
c (Å)	9.8157(2)
α (°)	91.120(2)
β (°)	98.754(2)
γ (°)	108.211(3)
V (Å^3)	548.10(3)
Z	2
D_c.(g cm^{-3})	1.564
μ (mm^{-1})	8.732
reflns coll.	9647
independent reflns	2166
$^aR_1$ [I $\geqslant$ 2 σ (I)]	0.0410
$^bwR_2$(all data)	0.1091
GOF	1.040

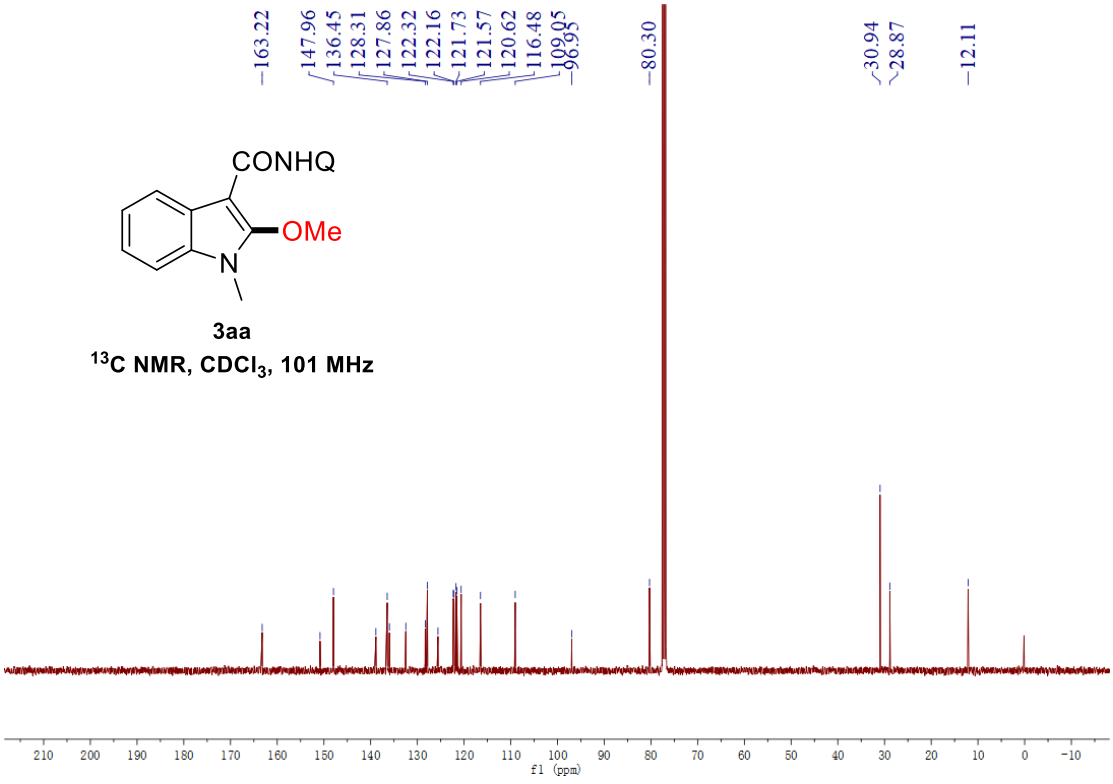
$^aR_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $^bwR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^1$

6. NMR Spectra



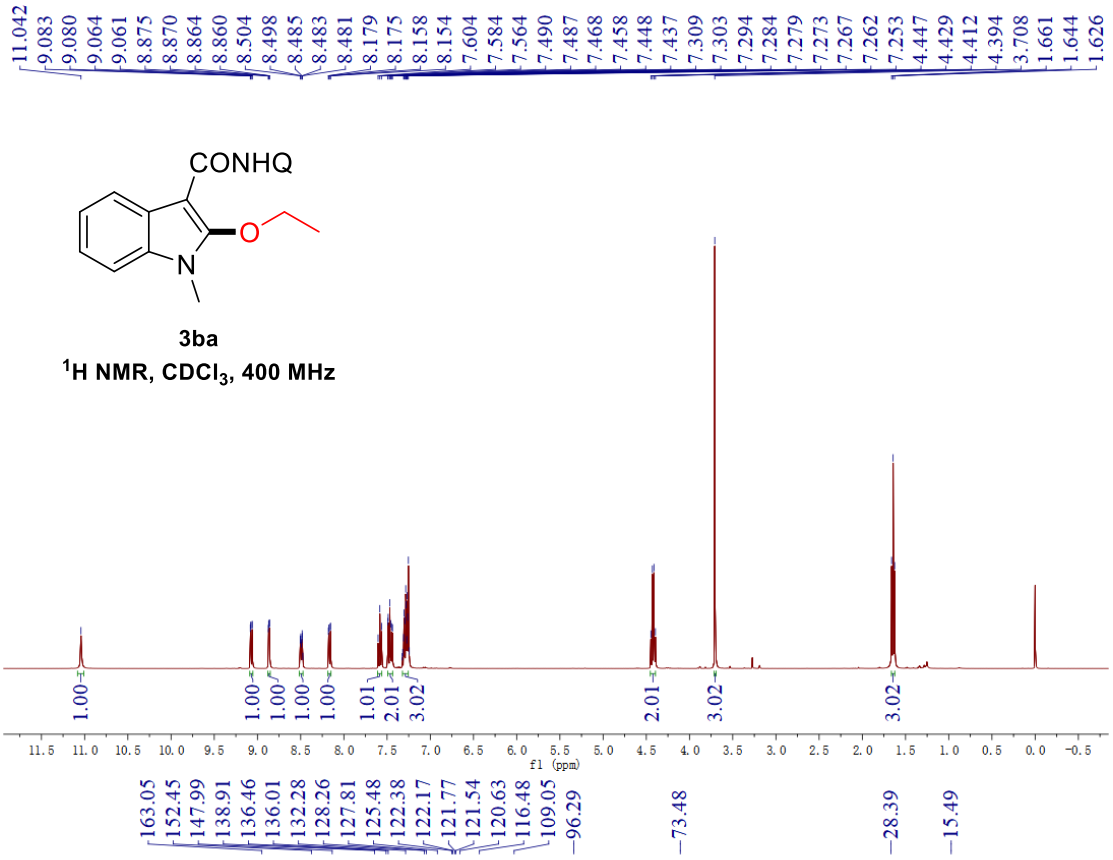
3aa

^{1}H NMR, $CDCl_3$, 400 MHz



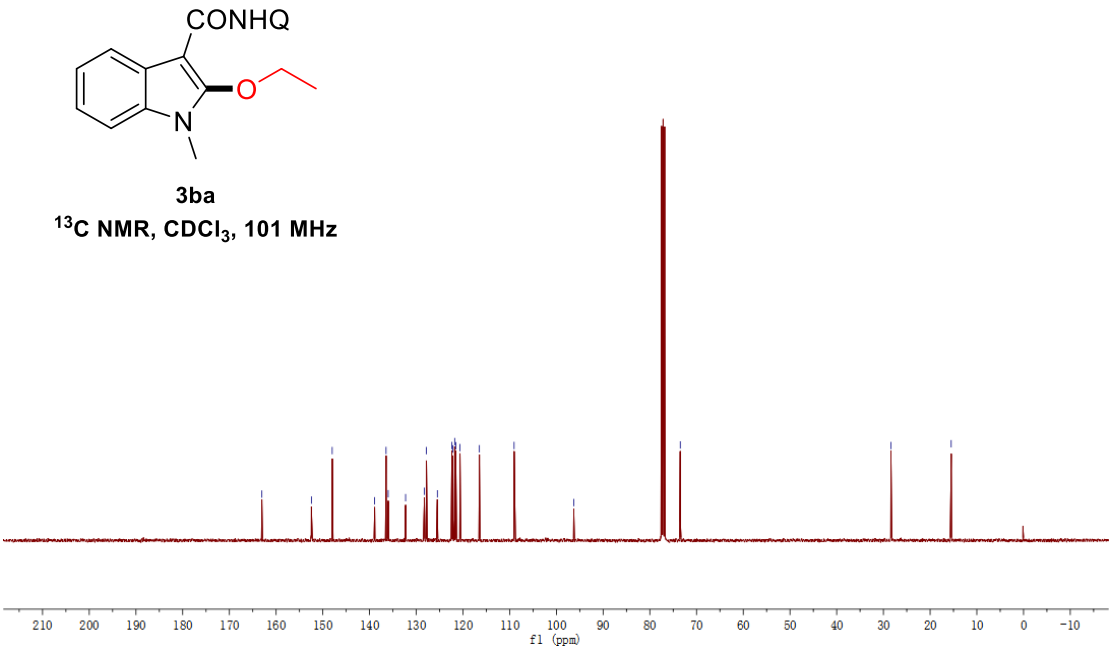
3aa

^{13}C NMR, $CDCl_3$, 101 MHz



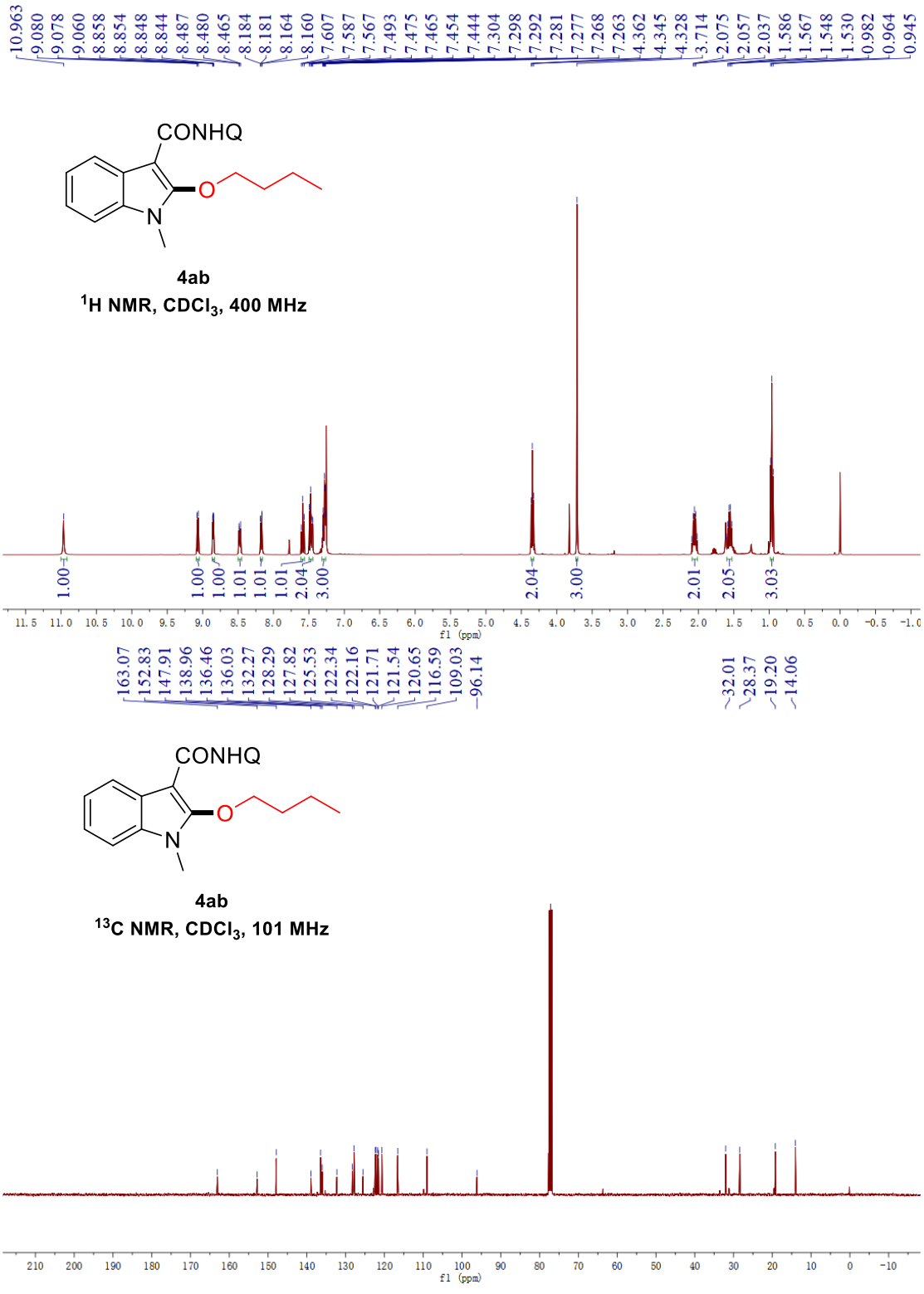
3ba

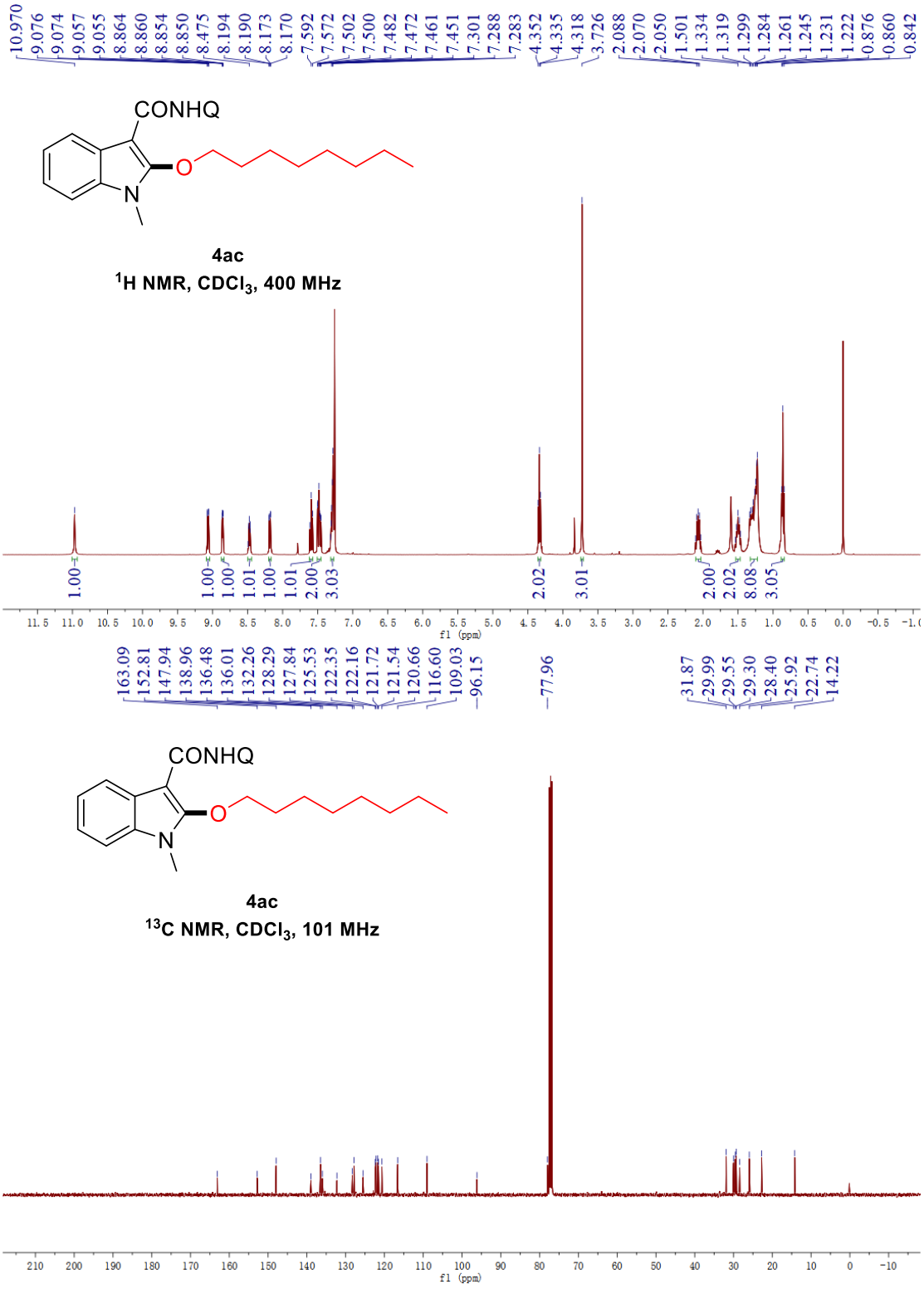
^{1}H NMR, $CDCl_3$, 400 MHz

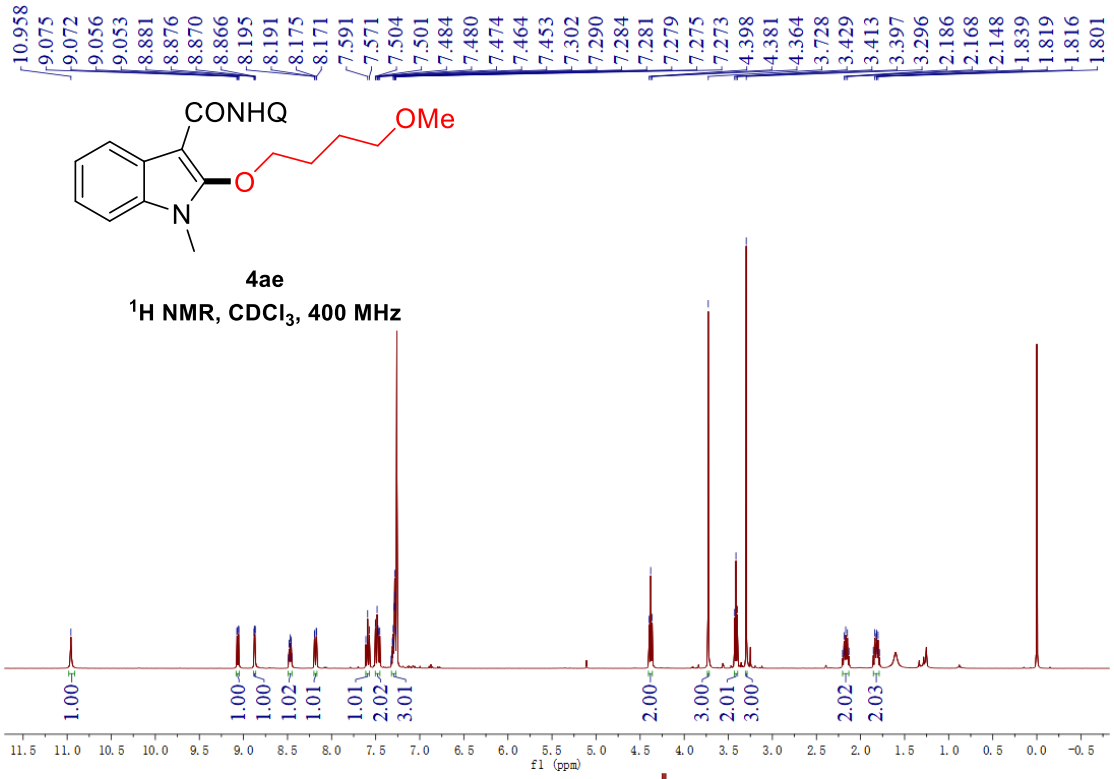


3ba

^{13}C NMR, $CDCl_3$, 101 MHz

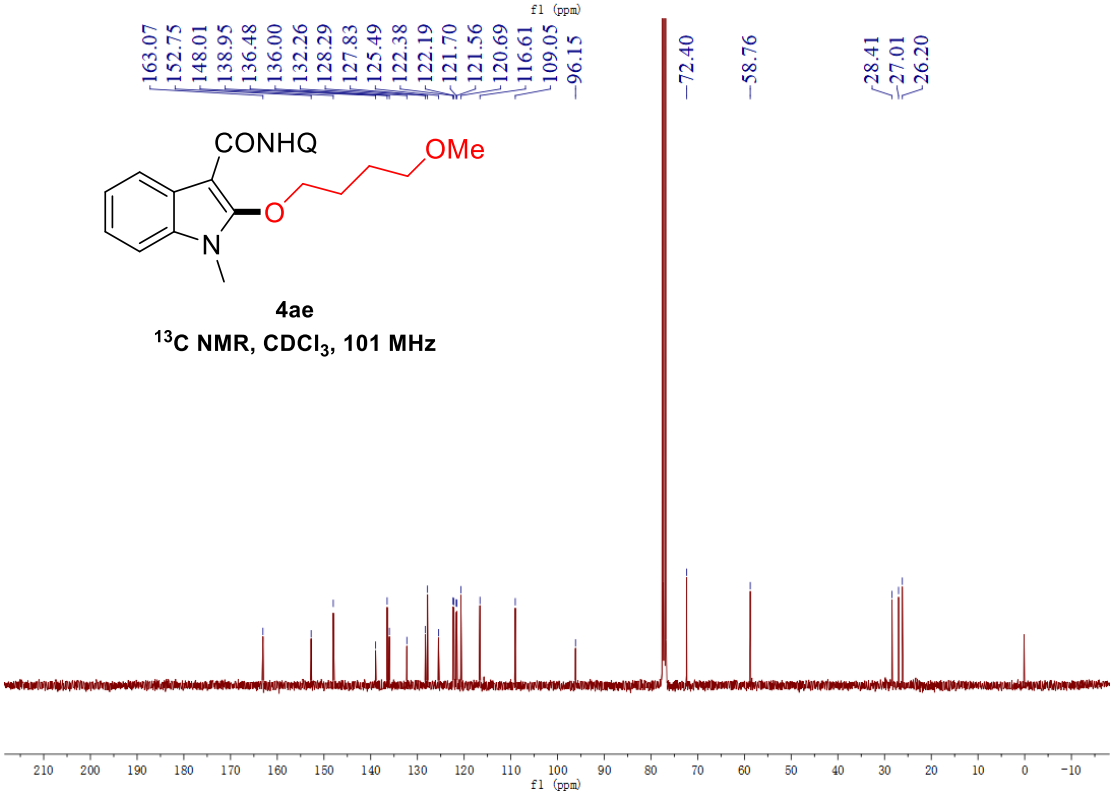

10.963
9.080
9.078
9.060
8.858
8.854
8.848
8.844
8.487
8.480
8.465
8.184
8.181
8.164
8.160
7.607
7.587
7.567
7.493
7.475
7.465
7.454
7.444
7.304
7.298
7.292
7.281
7.277
7.268
7.263
4.362
4.345
4.328
3.714
2.075
2.057
2.037
1.586
1.567
1.548
1.530
0.982
0.964
0.945
CONHQ
O
N
4ab
1H NMR, CDCl3, 400 MHz
1.00
1.00
1.00
1.01
1.01
1.01
2.04
3.00
2.04
3.00
2.01
2.05
3.03
f1 (ppm)
163.07
152.83
147.91
138.96
136.46
136.03
132.27
128.29
127.82
125.53
122.34
122.16
121.71
121.54
120.65
116.59
109.03
96.14
32.01
28.37
19.20
14.06
CONHQ
O
N
4ab
13C NMR, CDCl3, 101 MHz
f1 (ppm)


CONHQ
O
N
4ac
^{1}H NMR, $CDCl_3$, 400 MHz
^{13}C NMR, $CDCl_3$, 101 MHz
f1 (ppm)



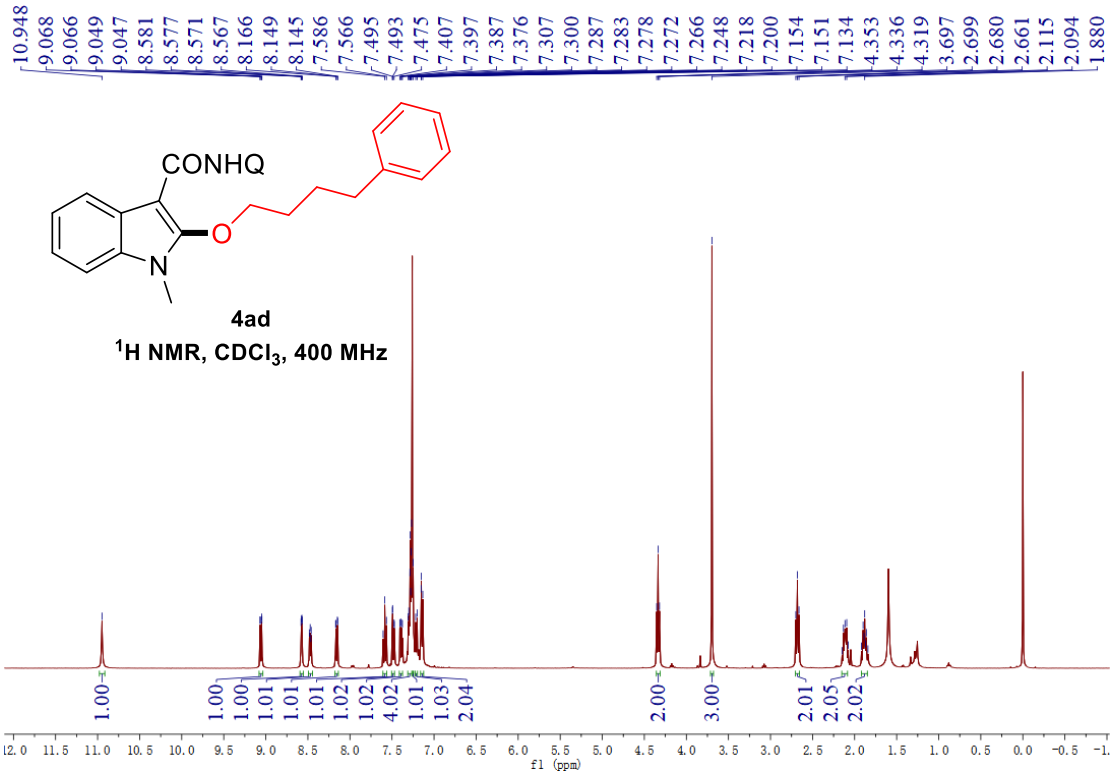
4ae

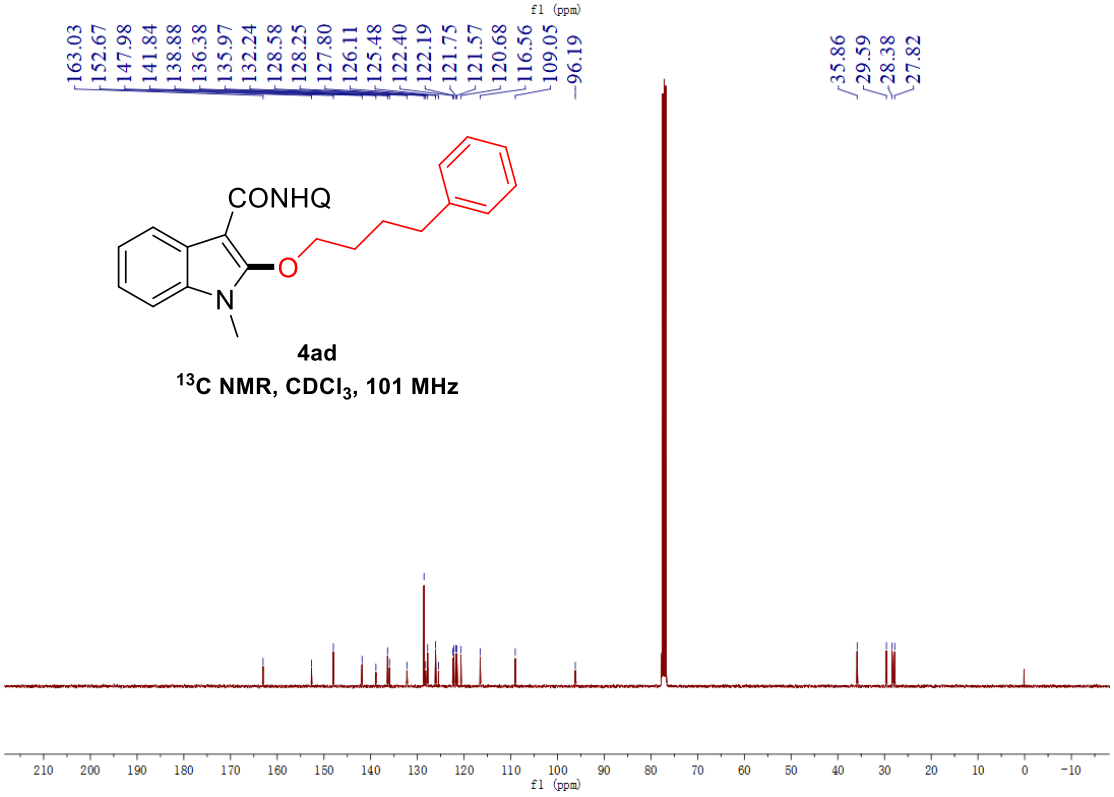
^{1}H NMR, $CDCl_3$, 400 MHz

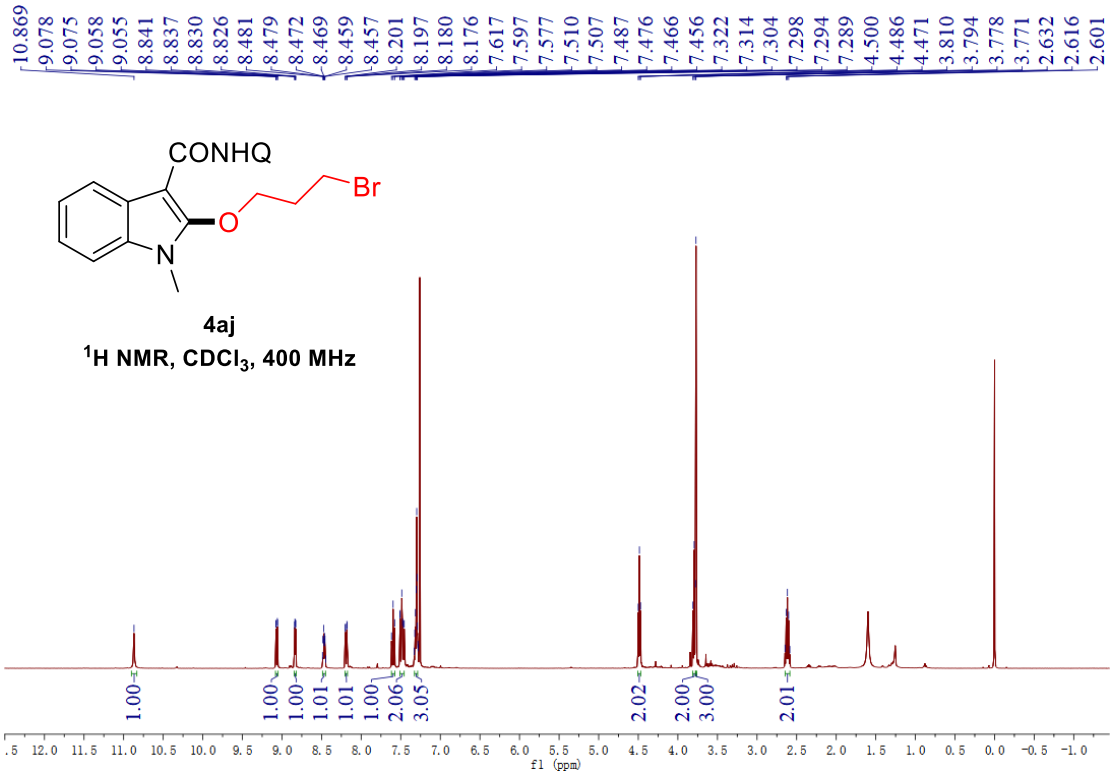


4ae

^{13}C NMR, $CDCl_3$, 101 MHz

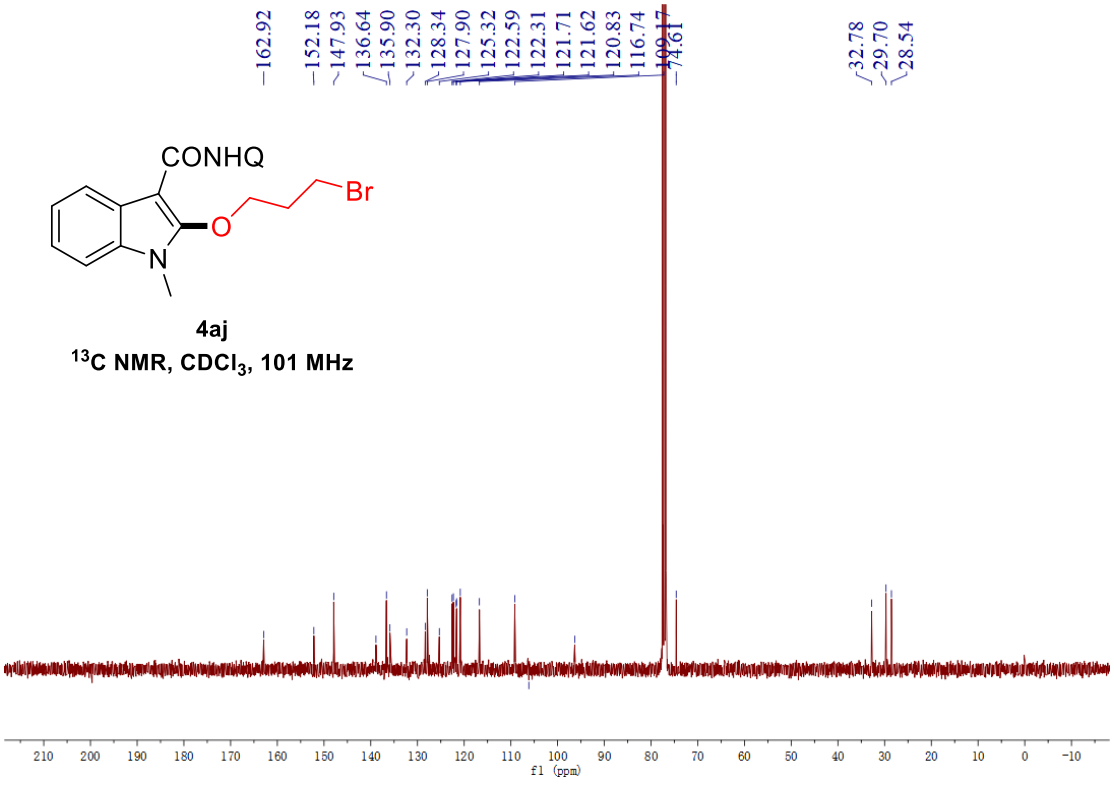

10.948
9.068
9.066
9.049
9.047
8.581
8.577
8.571
8.567
8.166
8.149
8.145
7.586
7.566
7.495
7.493
7.475
7.407
7.397
7.387
7.376
7.307
7.300
7.287
7.283
7.278
7.272
7.266
7.248
7.218
7.200
7.154
7.151
7.134
4.353
4.336
4.319
3.697
2.699
2.680
2.661
2.115
2.094
1.880
CONHQ
O
N
4ad
1H NMR, CDCl3, 400 MHz
1.00
1.00
1.00
1.01
1.01
1.01
1.02
1.02
4.02
1.01
1.03
2.04
2.00
3.00
2.01
2.05
2.02
f1 (ppm)


163.03
152.67
147.98
141.84
138.88
136.38
135.97
132.24
128.58
128.25
127.80
126.11
125.48
122.40
122.19
121.75
121.57
120.68
116.56
109.05
96.19
35.86
29.59
28.38
27.82
CONHQ
O
N
4ad
13C NMR, CDCl3, 101 MHz
f1 (ppm)



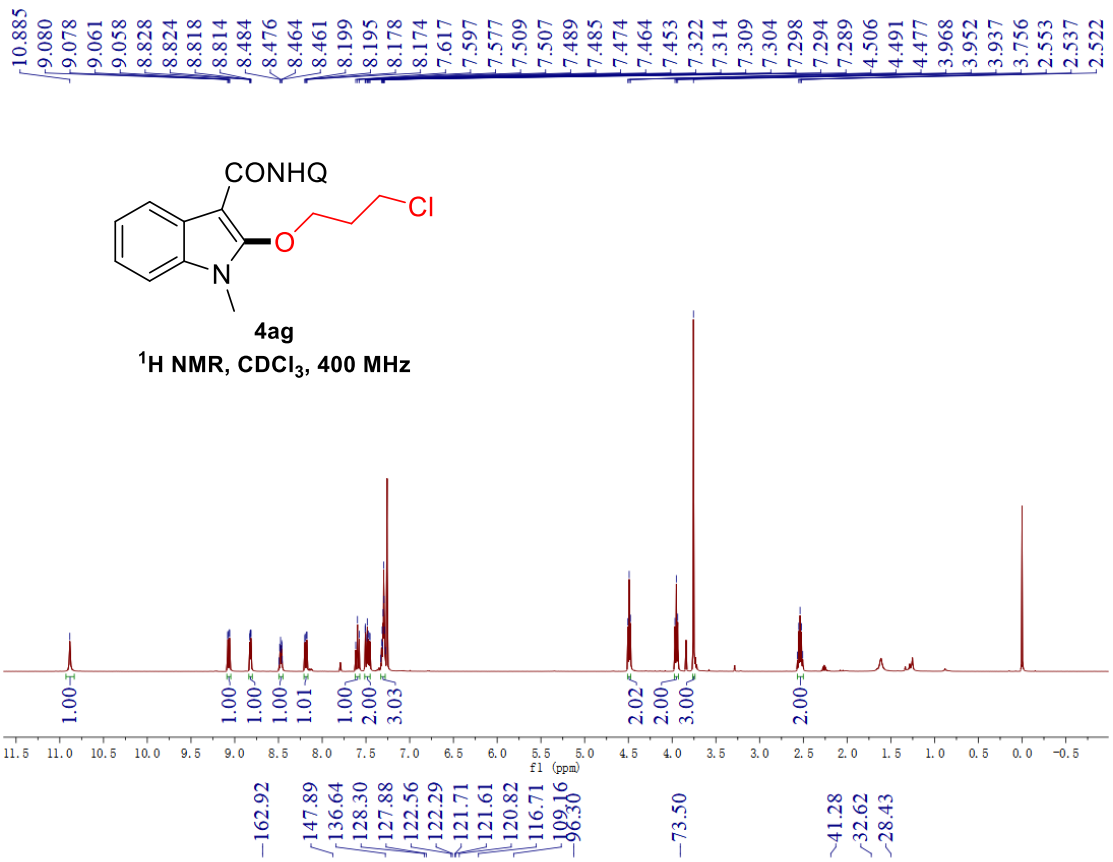
4aj

^{1}H NMR, $CDCl_3$, 400 MHz



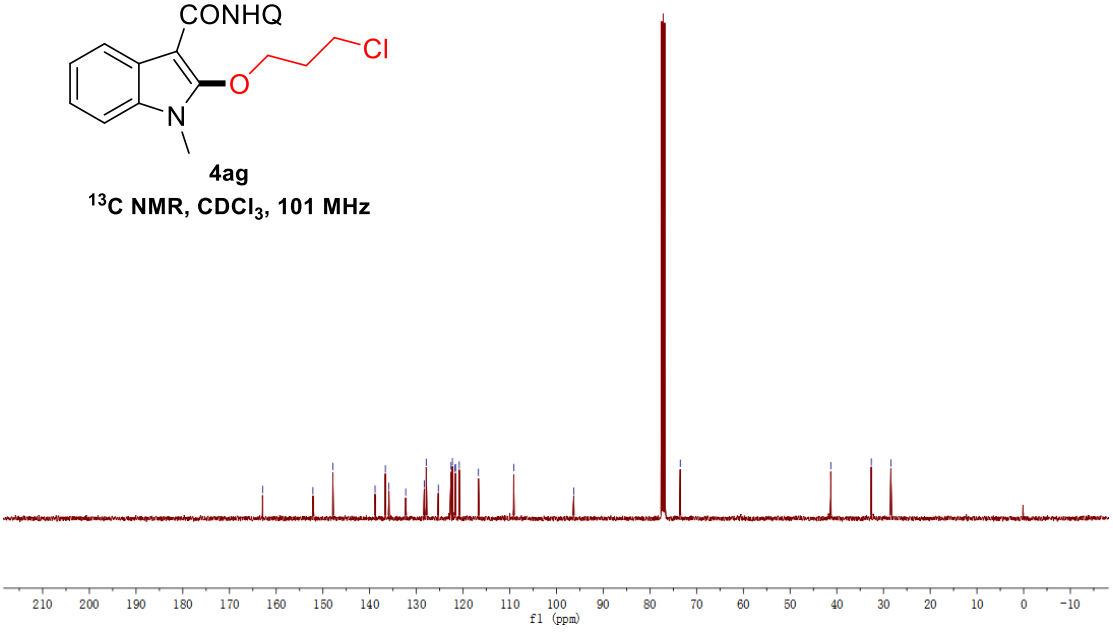
4aj

^{13}C NMR, $CDCl_3$, 101 MHz



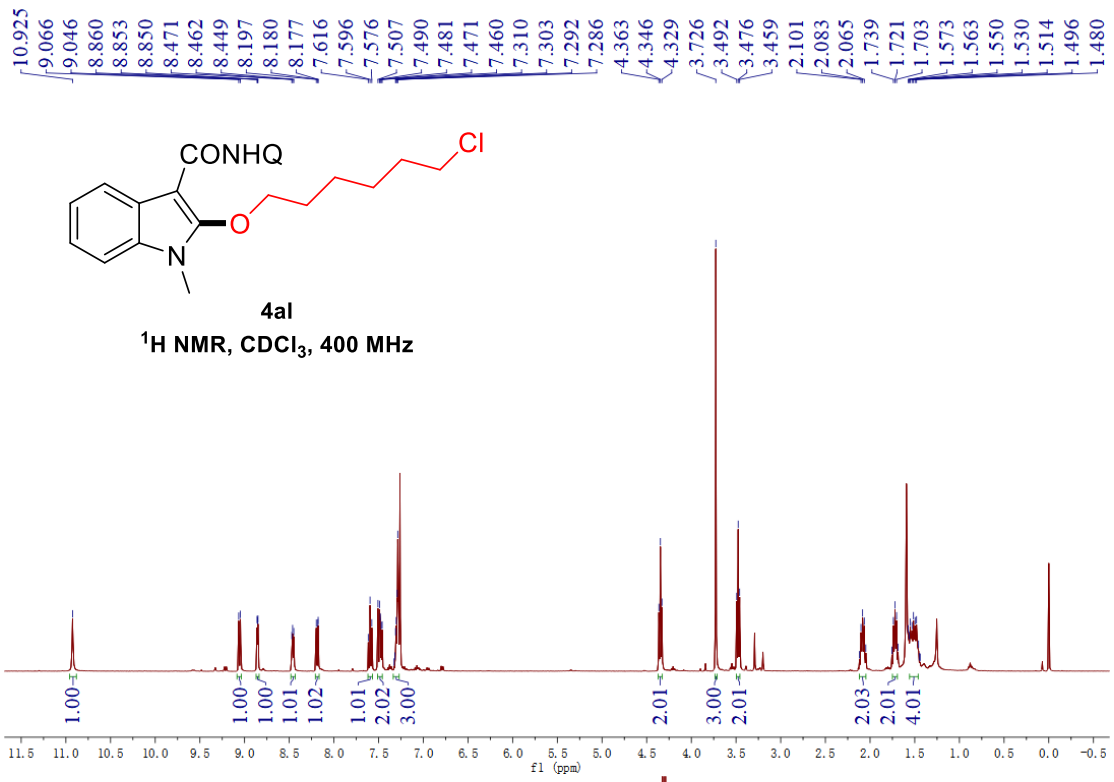
4ag

^{1}H NMR, $CDCl_3$, 400 MHz



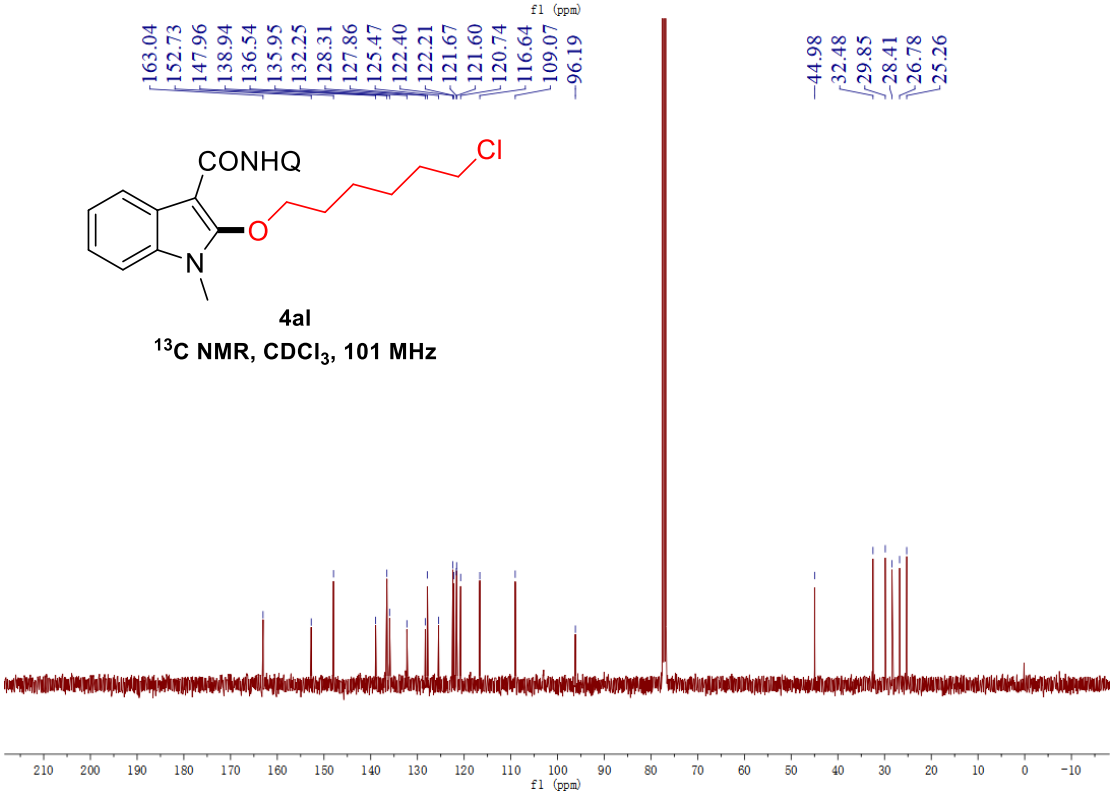
4ag

^{13}C NMR, $CDCl_3$, 101 MHz



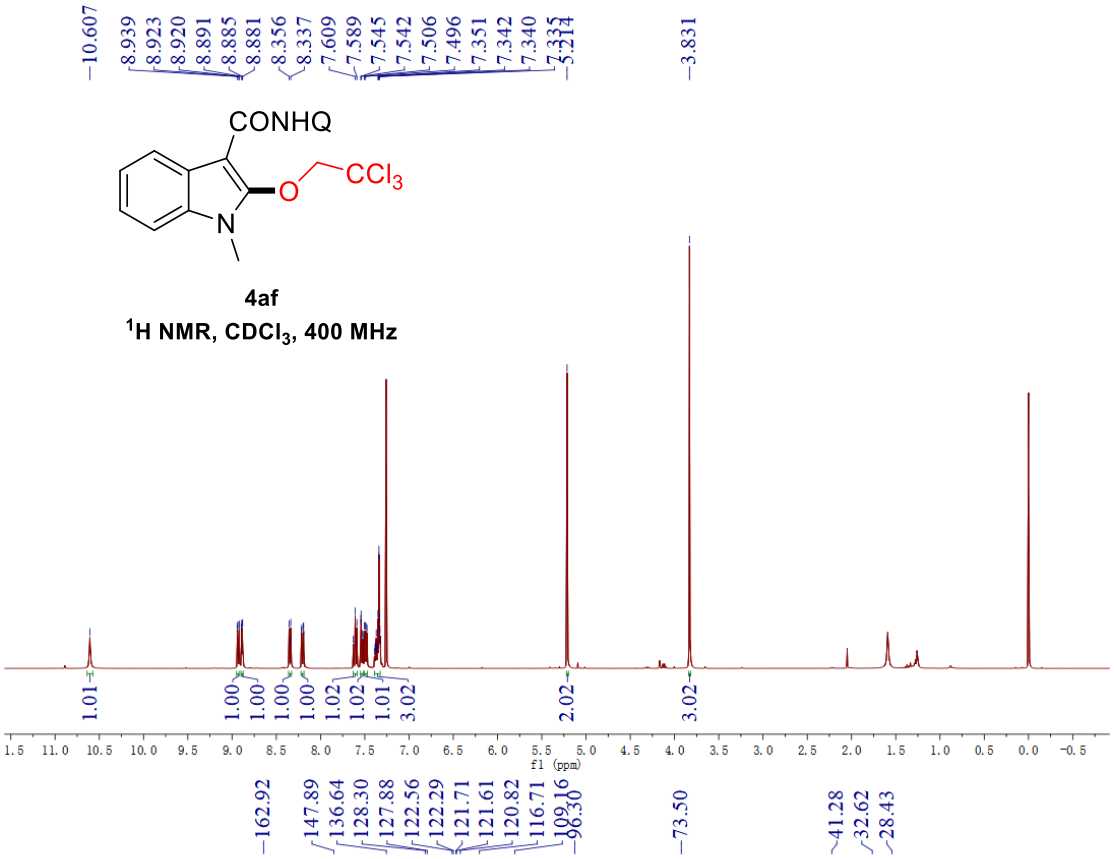
4al

^{1}H NMR, $CDCl_3$, 400 MHz



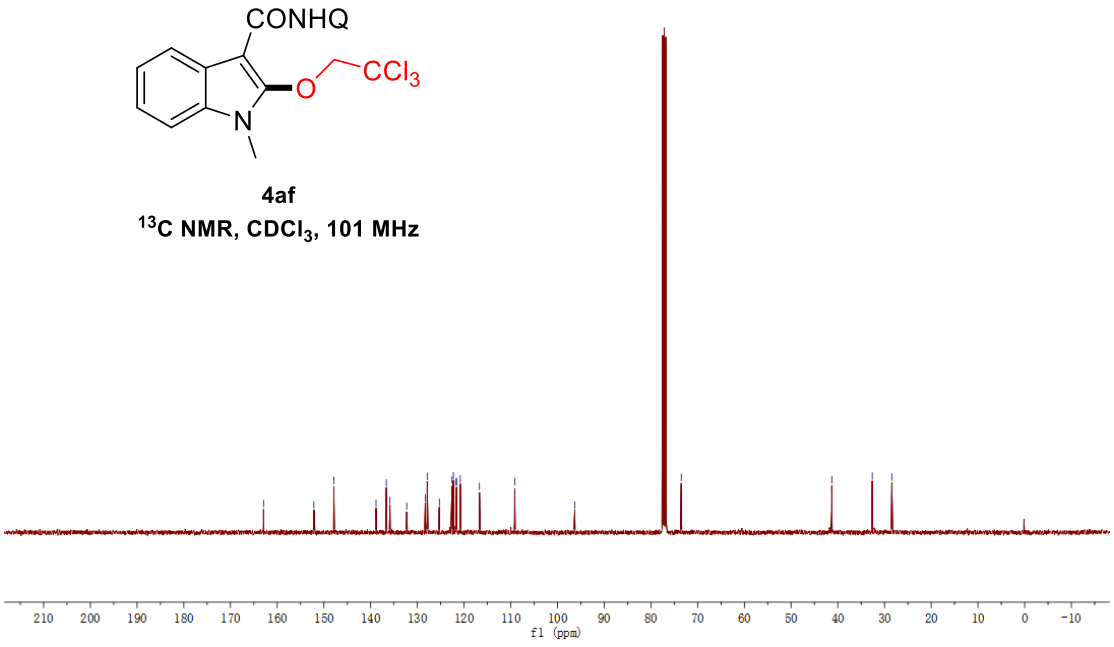
4al

^{13}C NMR, $CDCl_3$, 101 MHz



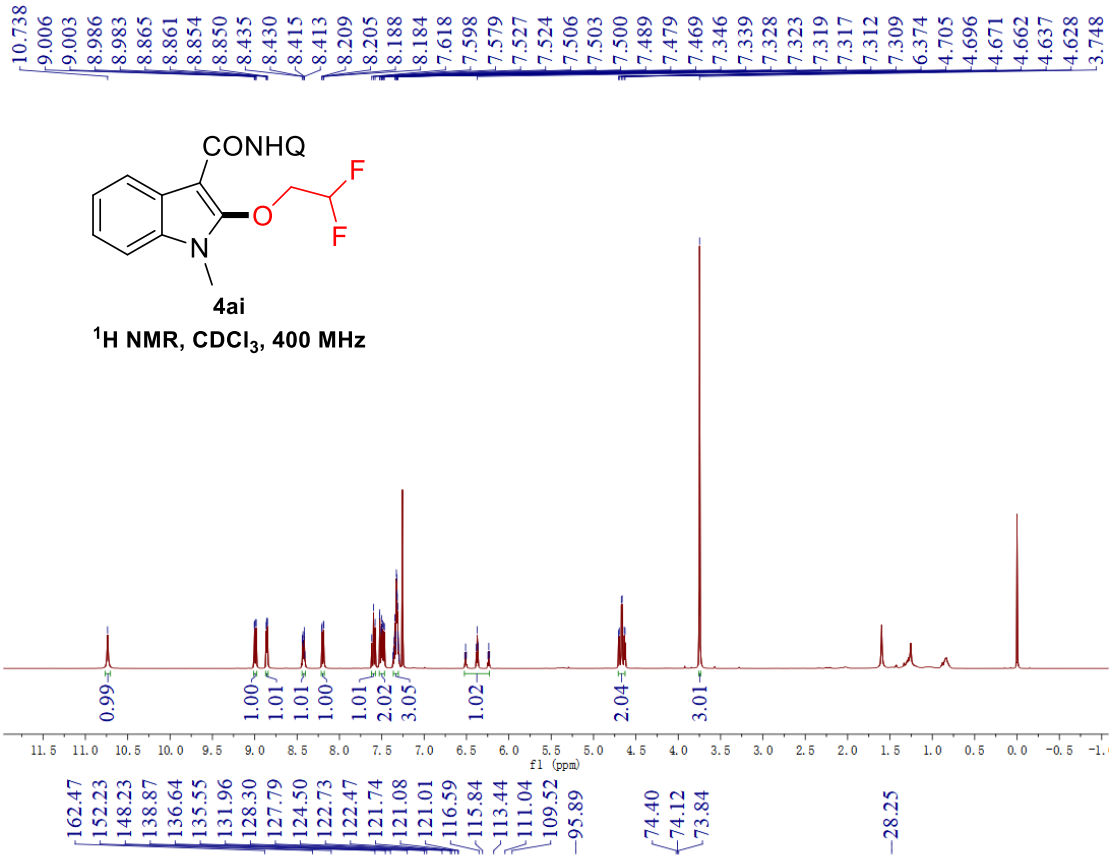
4af

^{1}H NMR, $CDCl_3$, 400 MHz



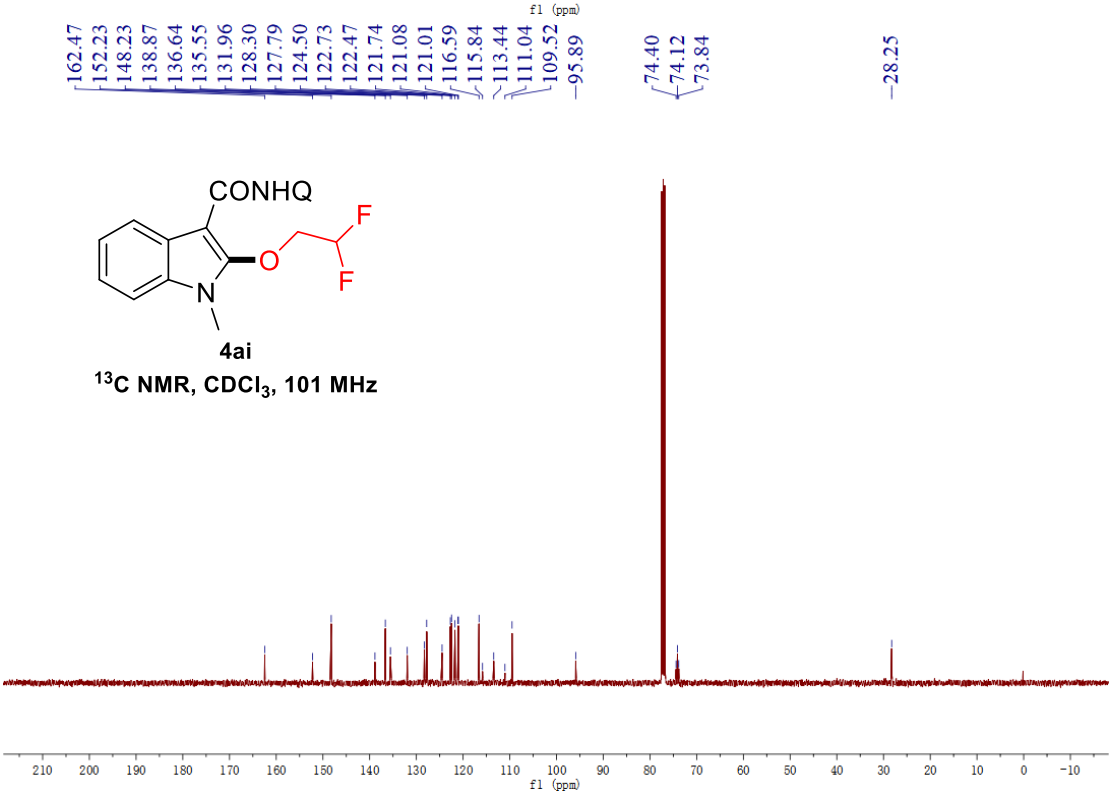
4af

^{13}C NMR, $CDCl_3$, 101 MHz



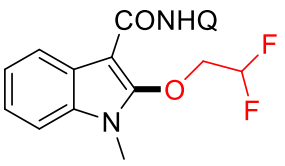
4ai

^{1}H NMR, $CDCl_3$, 400 MHz



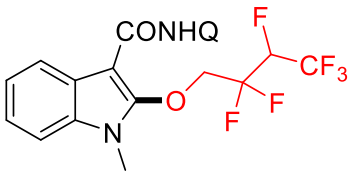
4ai

^{13}C NMR, $CDCl_3$, 101 MHz



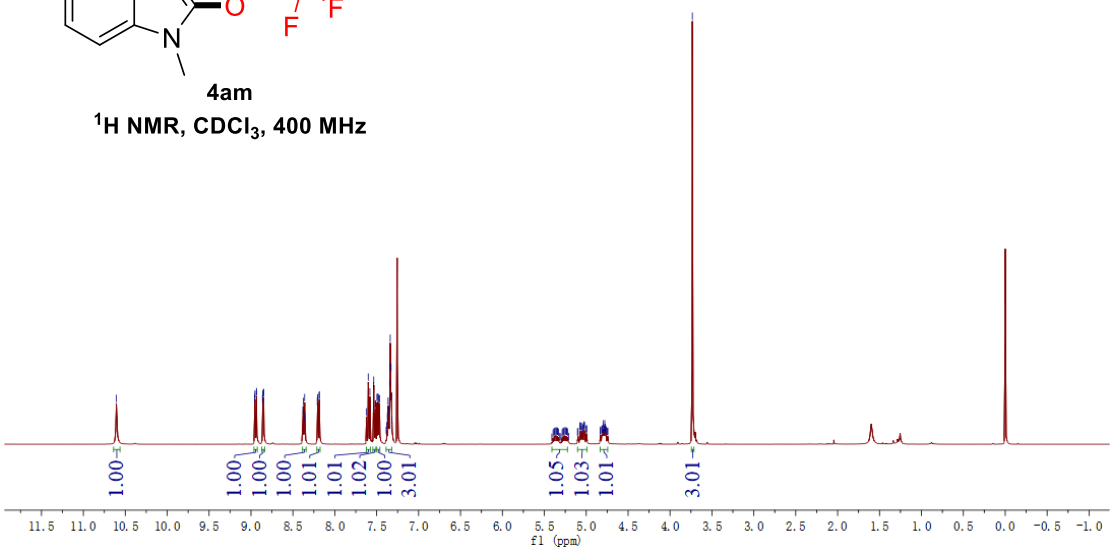
4ai

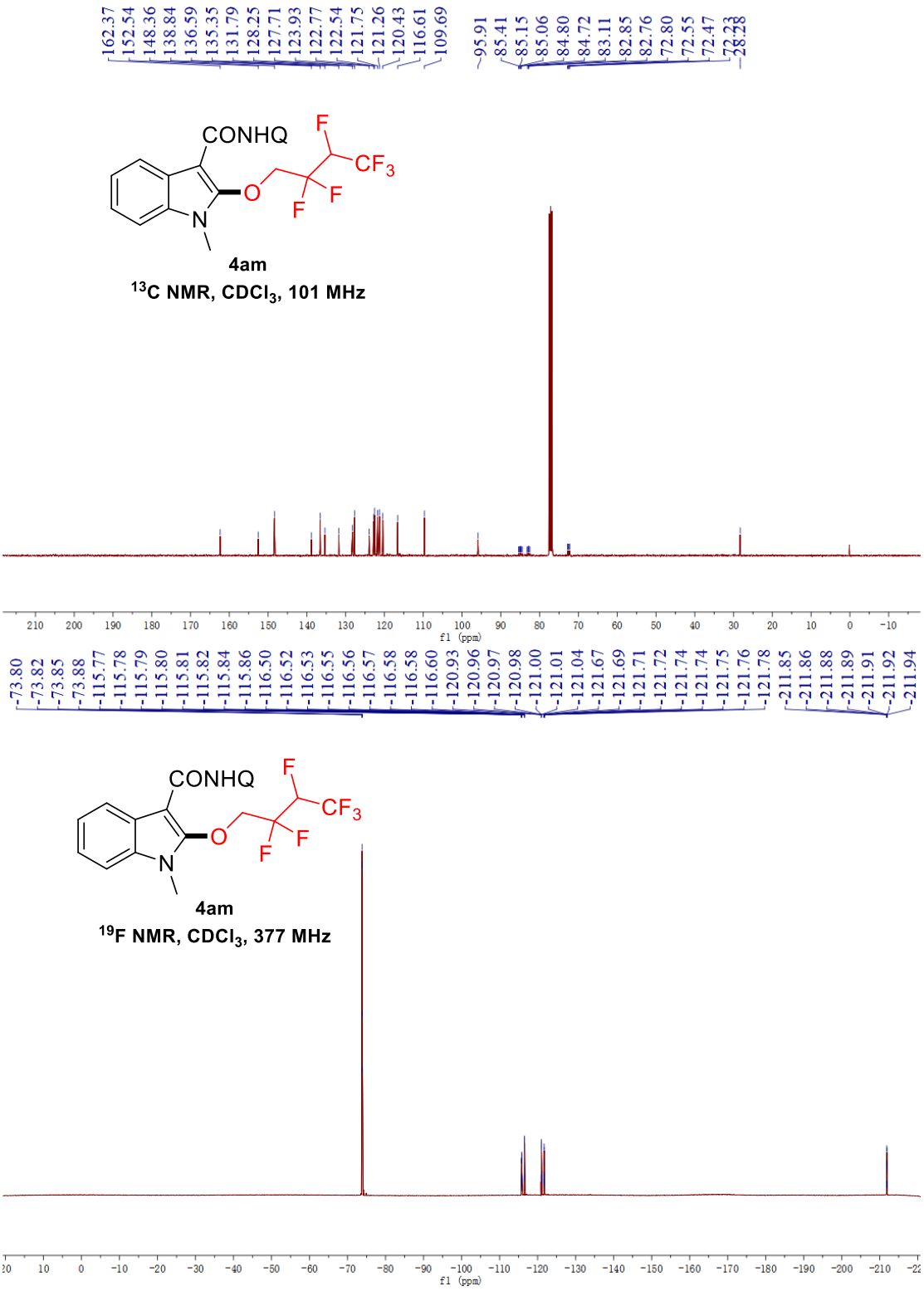
^{19}F NMR, $CDCl_3$, 377 MHz

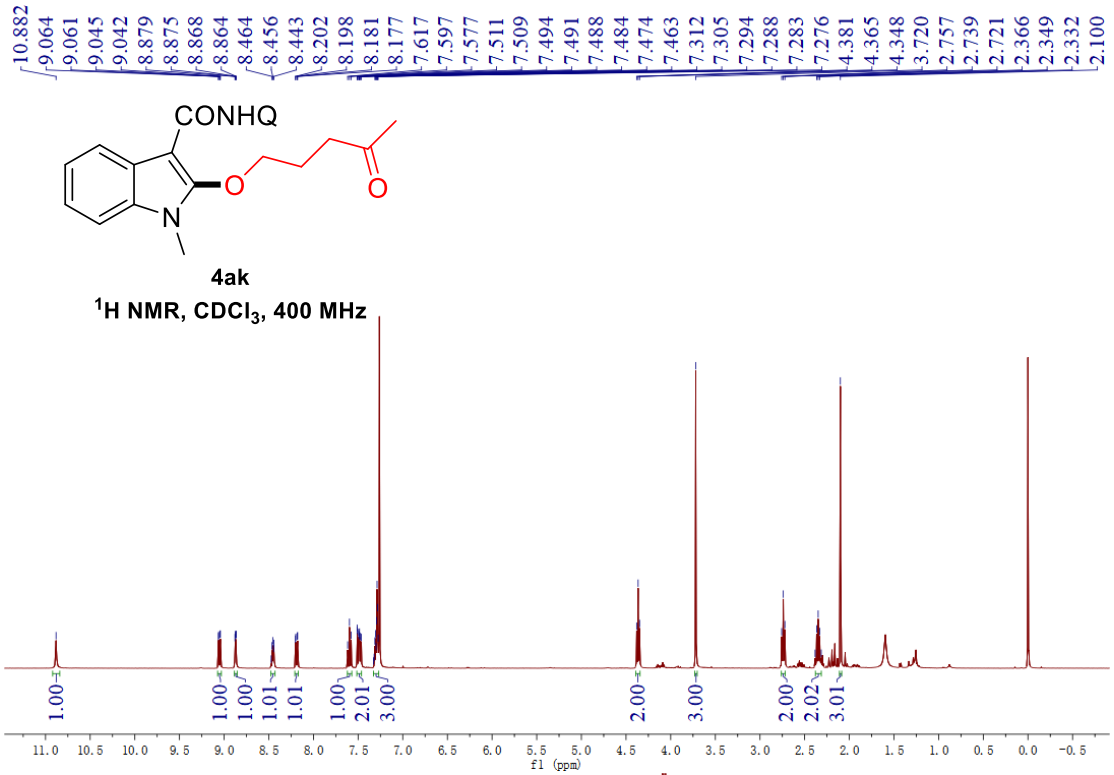


4am

^{1}H NMR, $CDCl_3$, 400 MHz

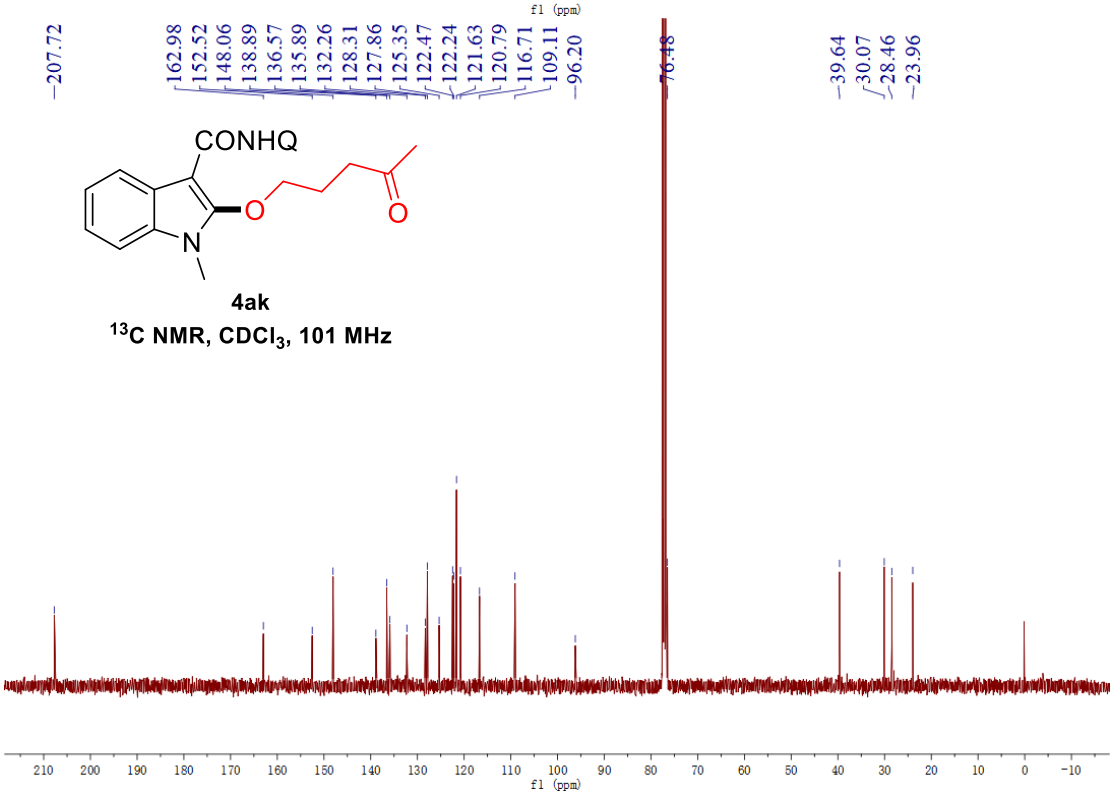



CONHQ
F
CF3
O
F
F
N
4am
13C NMR, CDCl3, 101 MHz
CONHQ
F
CF3
O
F
F
N
4am
19F NMR, CDCl3, 377 MHz



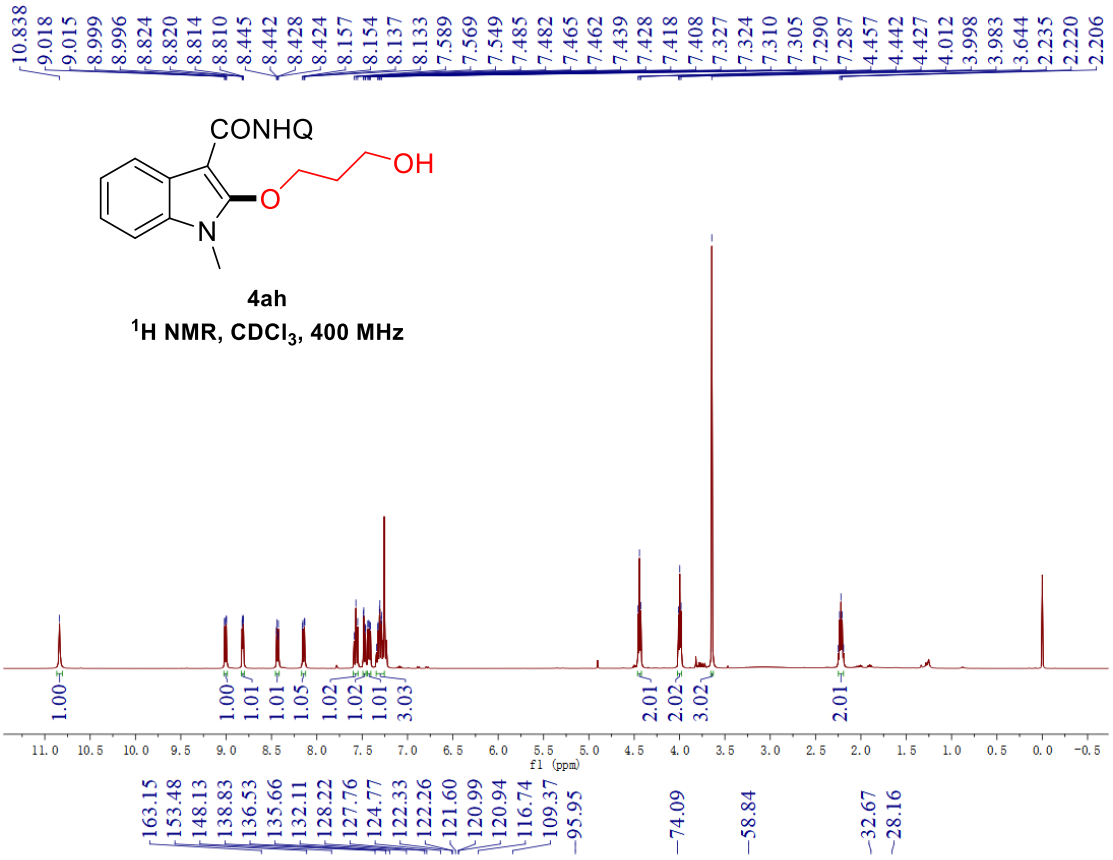
4ak

^{1}H NMR, $CDCl_3$, 400 MHz



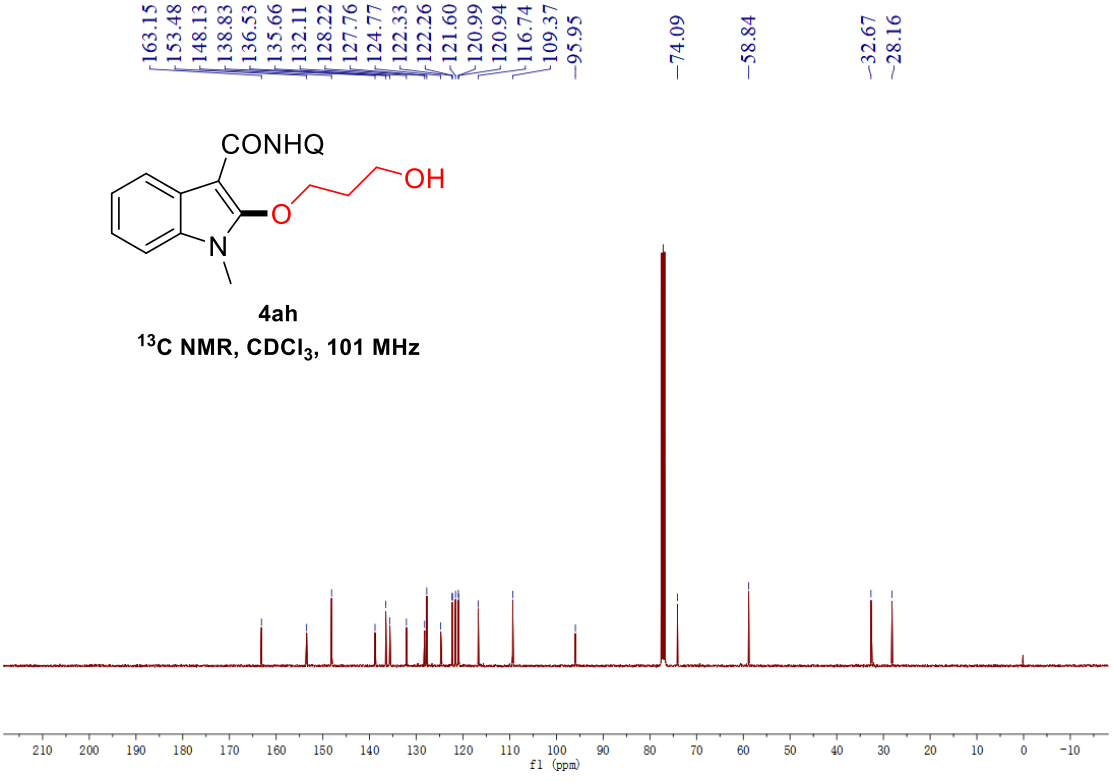
4ak

^{13}C NMR, $CDCl_3$, 101 MHz



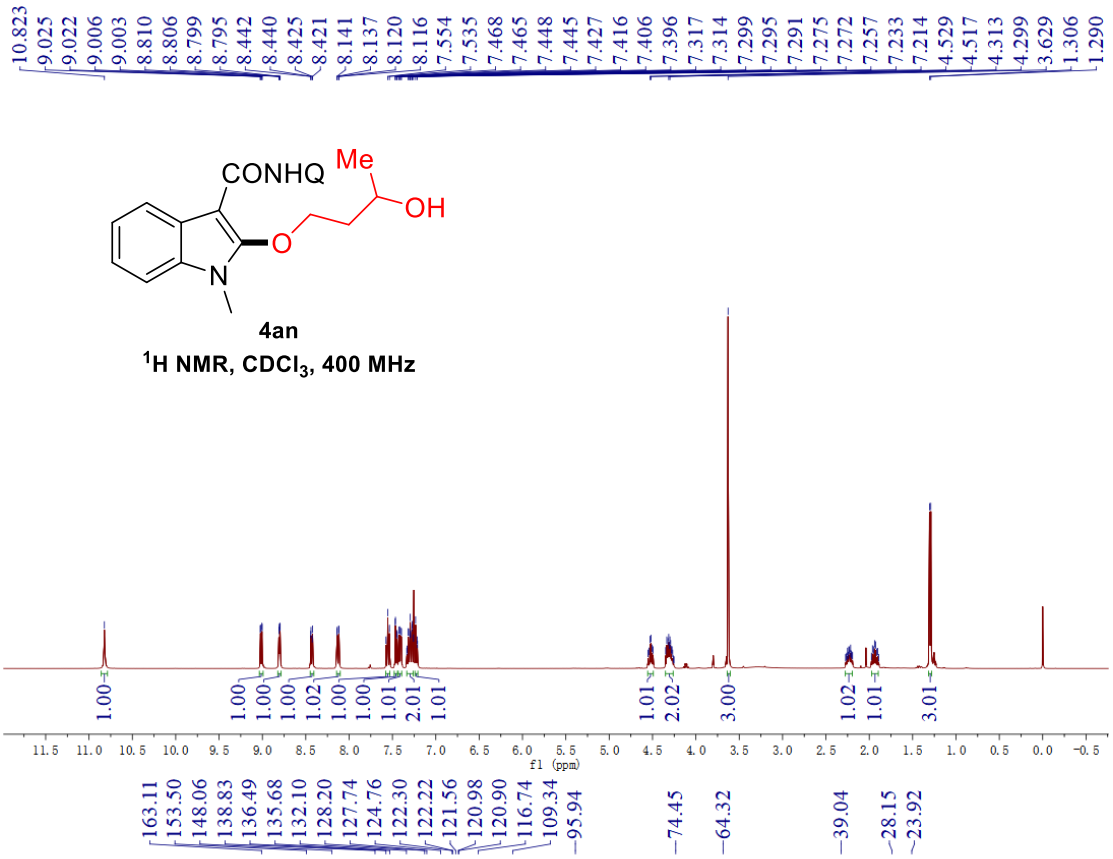
4ah

^{1}H NMR, $CDCl_3$, 400 MHz



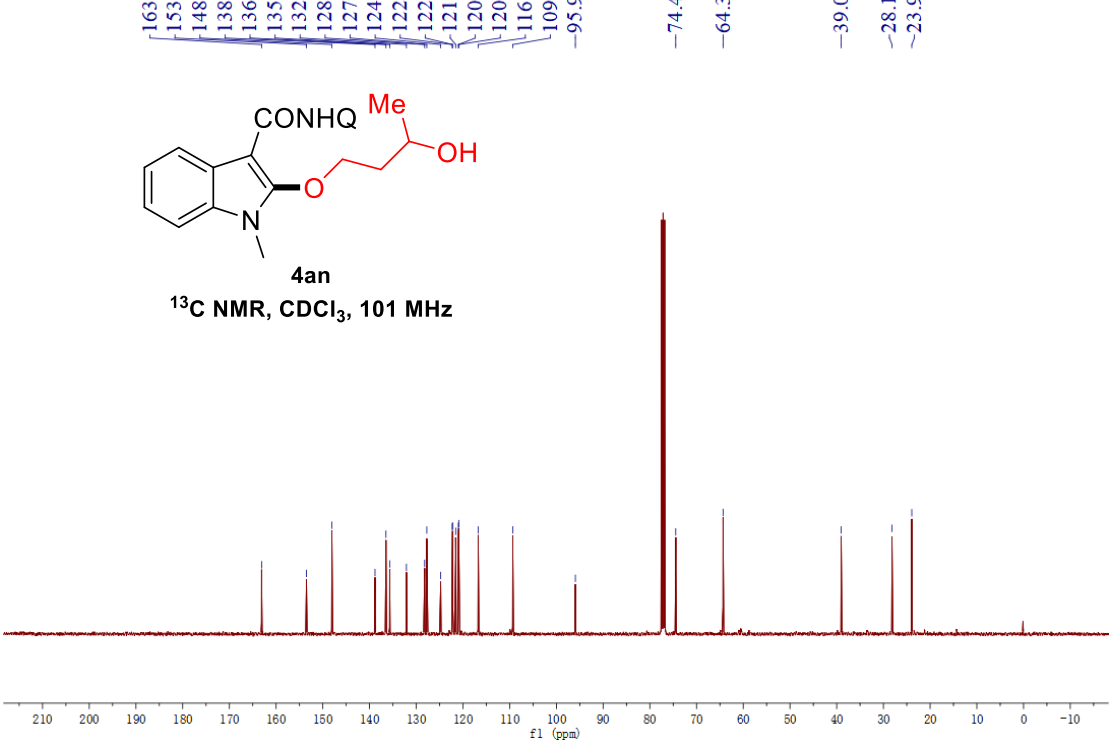
4ah

^{13}C NMR, $CDCl_3$, 101 MHz



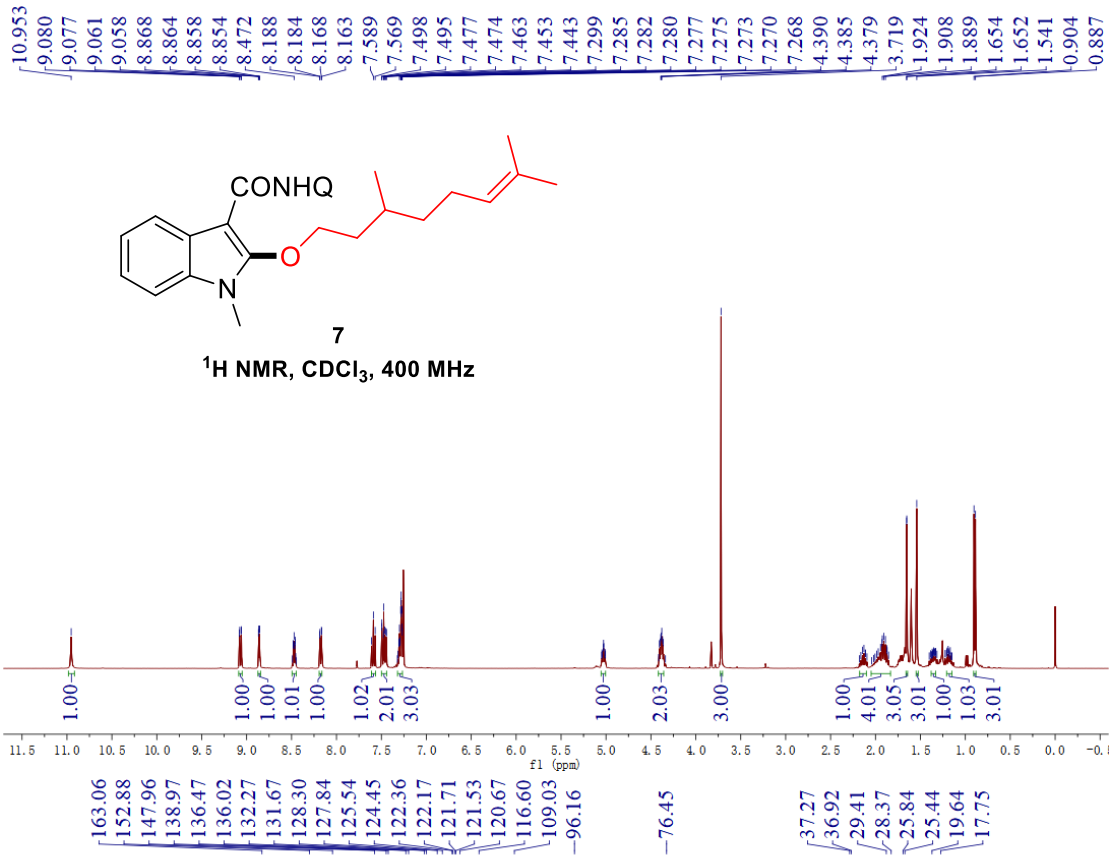
4an

^{1}H NMR, $CDCl_3$, 400 MHz



4an

^{13}C NMR, $CDCl_3$, 101 MHz

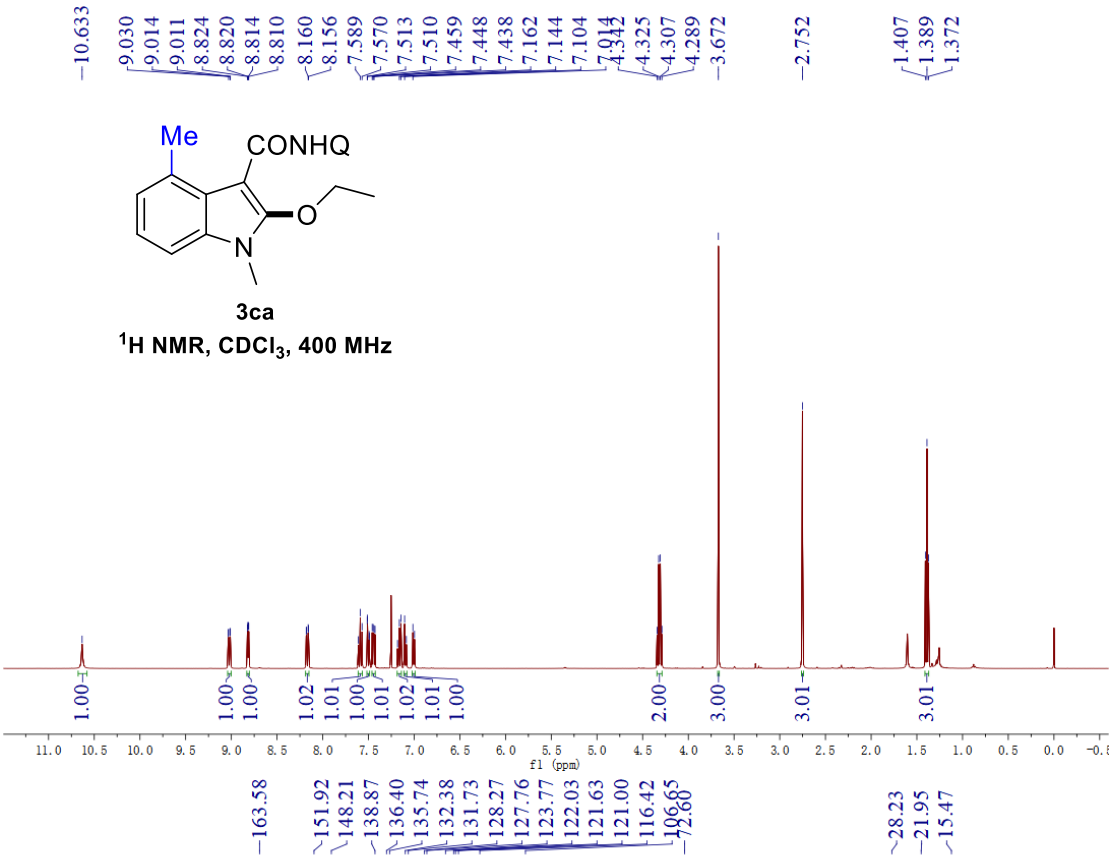


7

^{1}H NMR, $CDCl_3$, 400 MHz

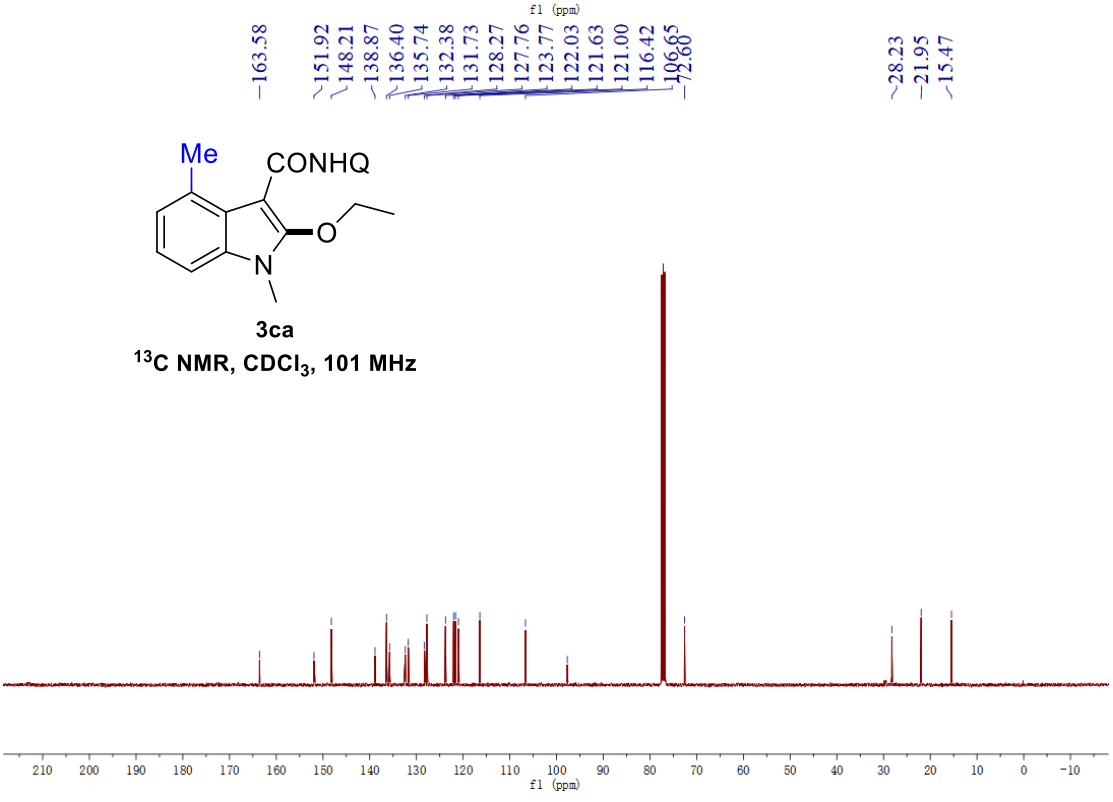
7

^{13}C NMR, $CDCl_3$, 101 MHz



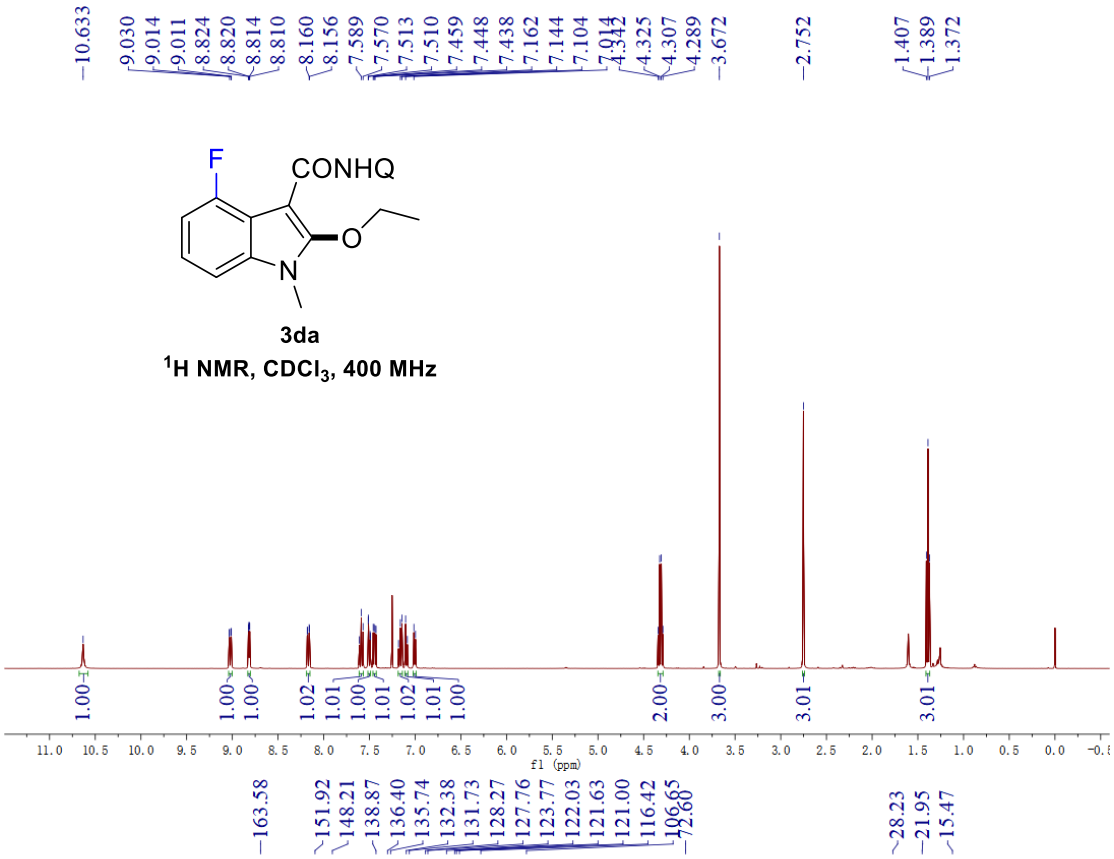
3ca

^{1}H NMR, $CDCl_3$, 400 MHz



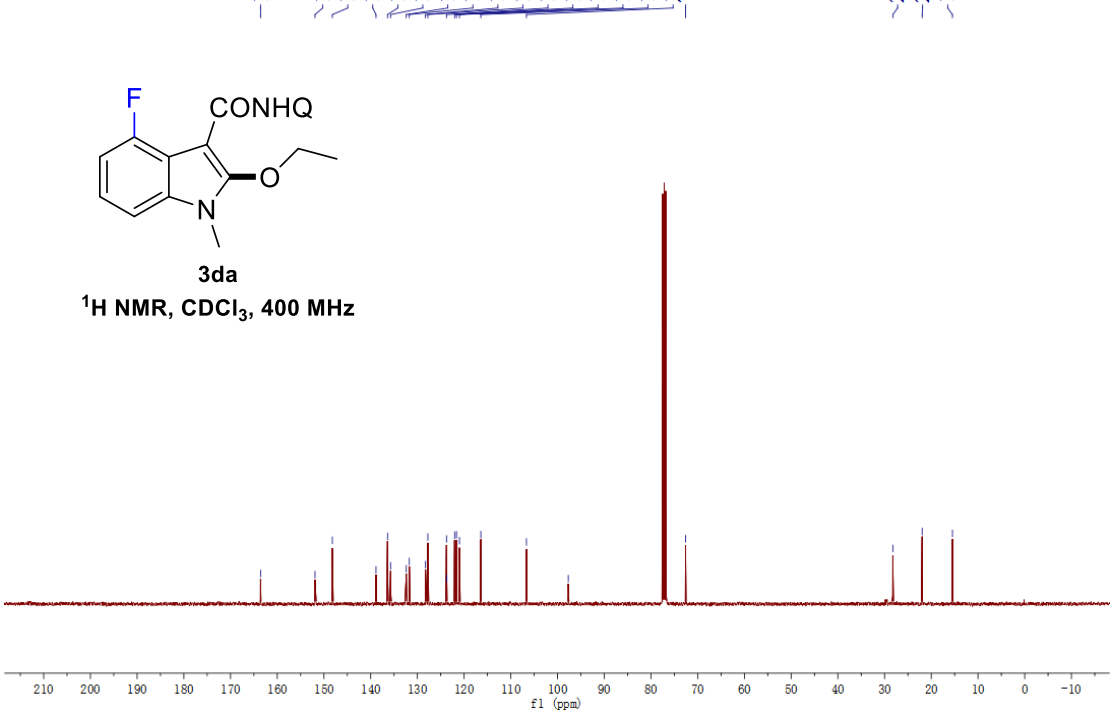
3ca

^{13}C NMR, $CDCl_3$, 101 MHz



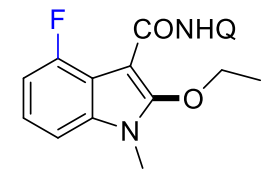
3da

^{1}H NMR, $CDCl_3$, 400 MHz



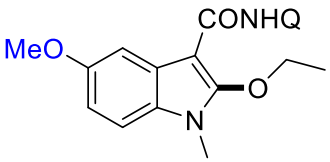
3da

^{1}H NMR, $CDCl_3$, 400 MHz



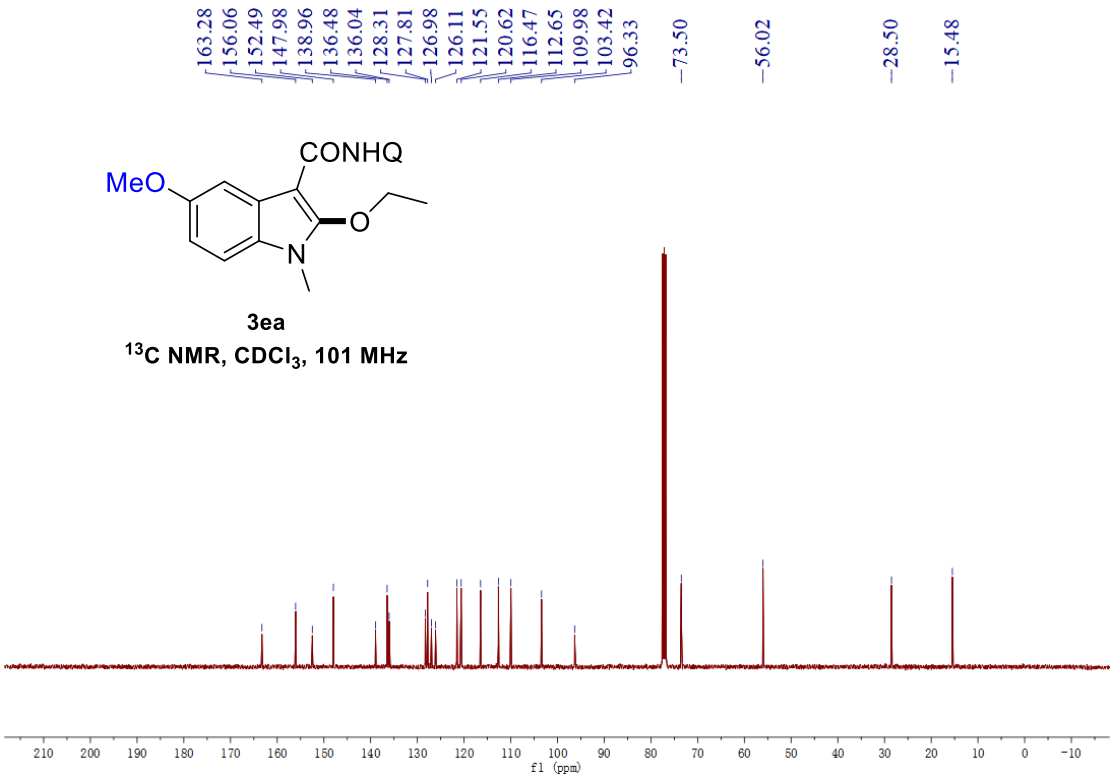
3da

^{19}F NMR, $CDCl_3$, 377 MHz



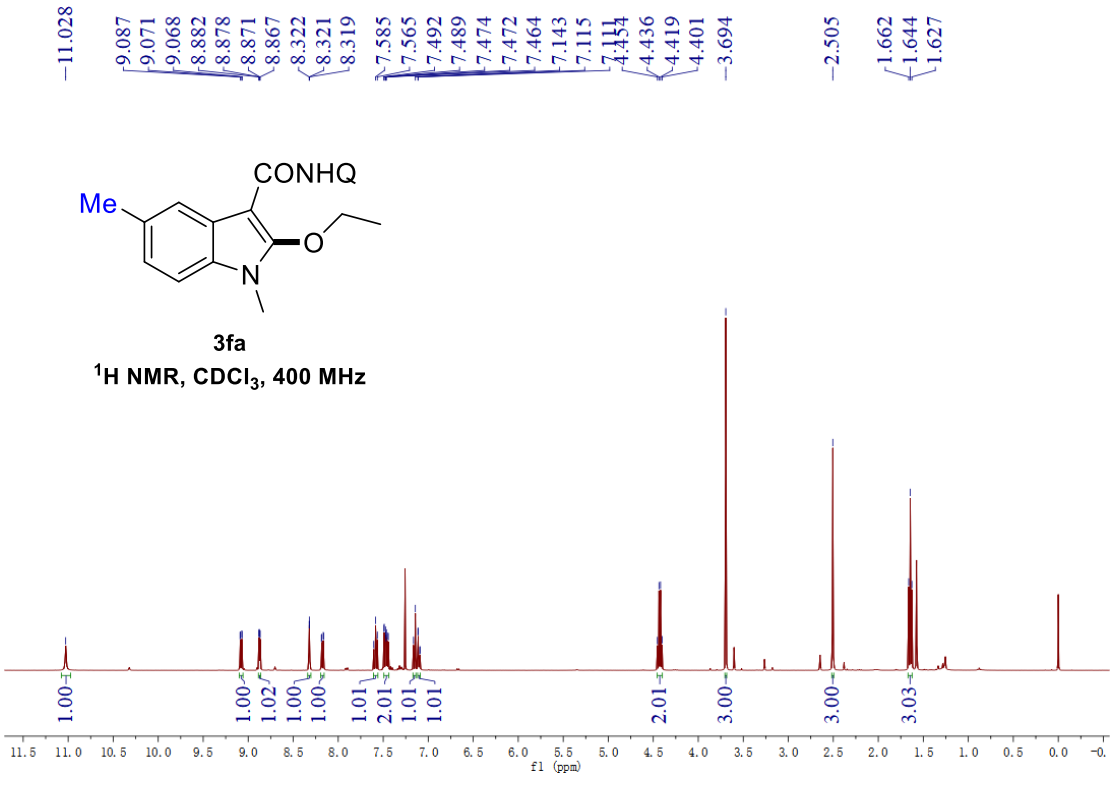
3ea

^{1}H NMR, $CDCl_3$, 400 MHz



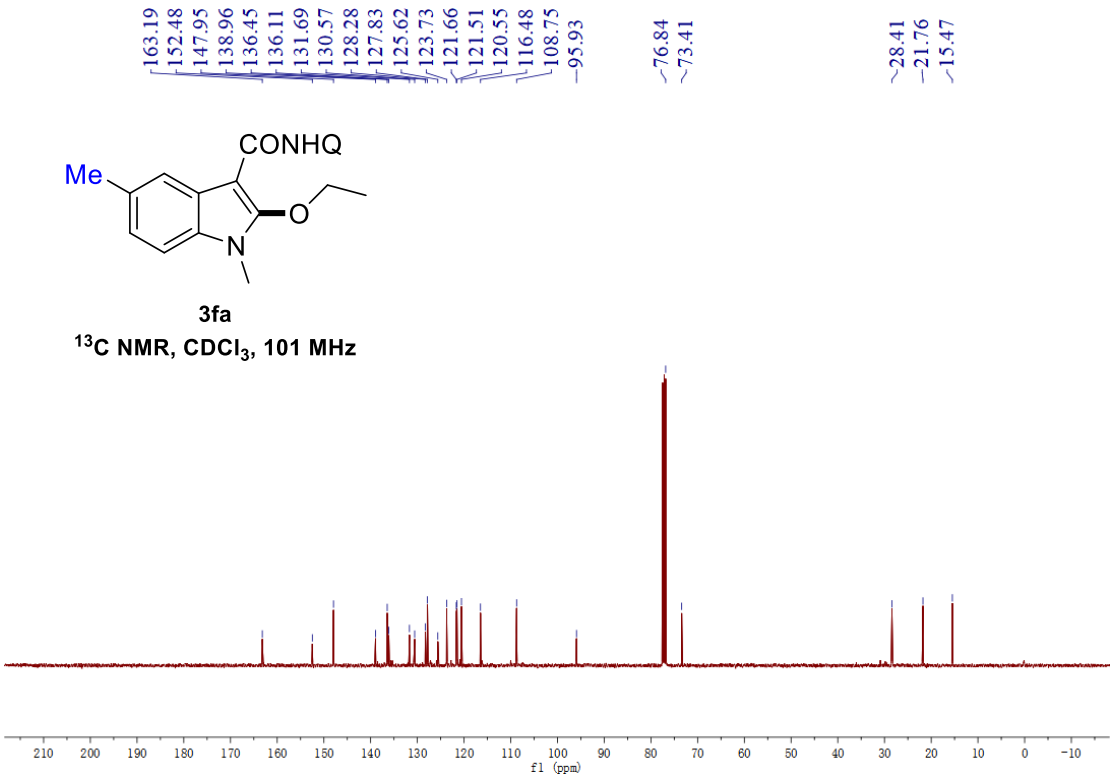
3ea

^{13}C NMR, $CDCl_3$, 101 MHz



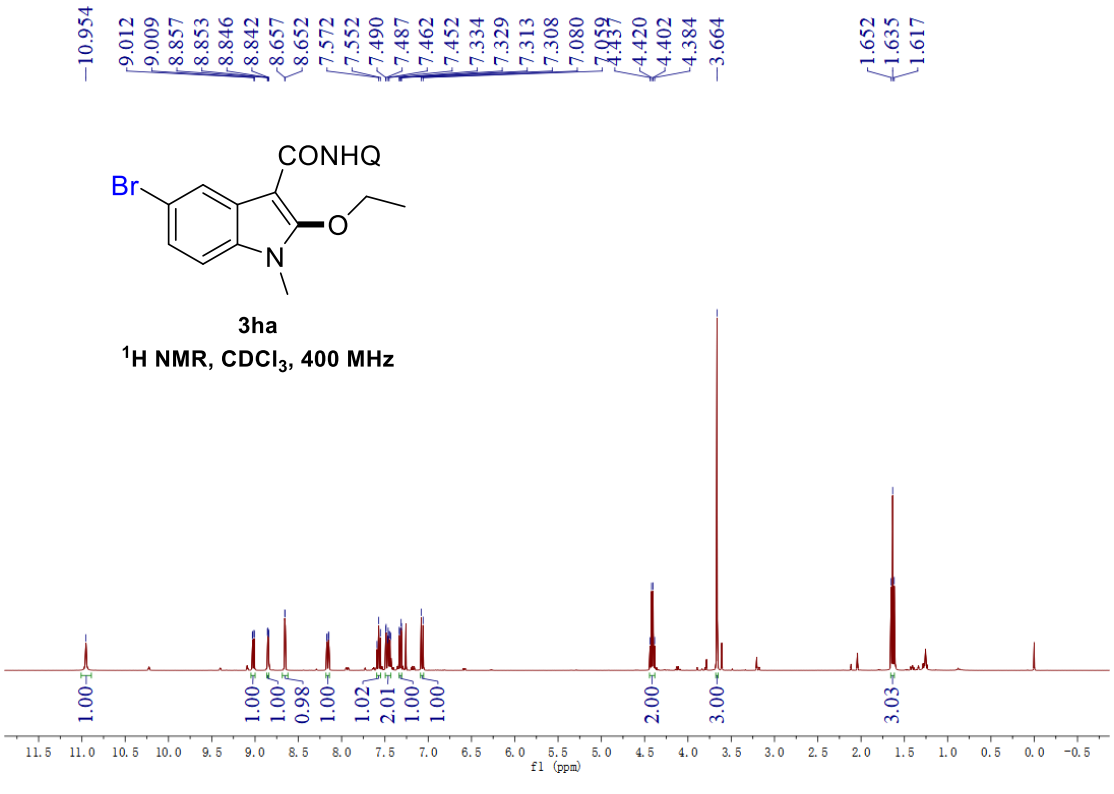
3fa

^{1}H NMR, $CDCl_3$, 400 MHz



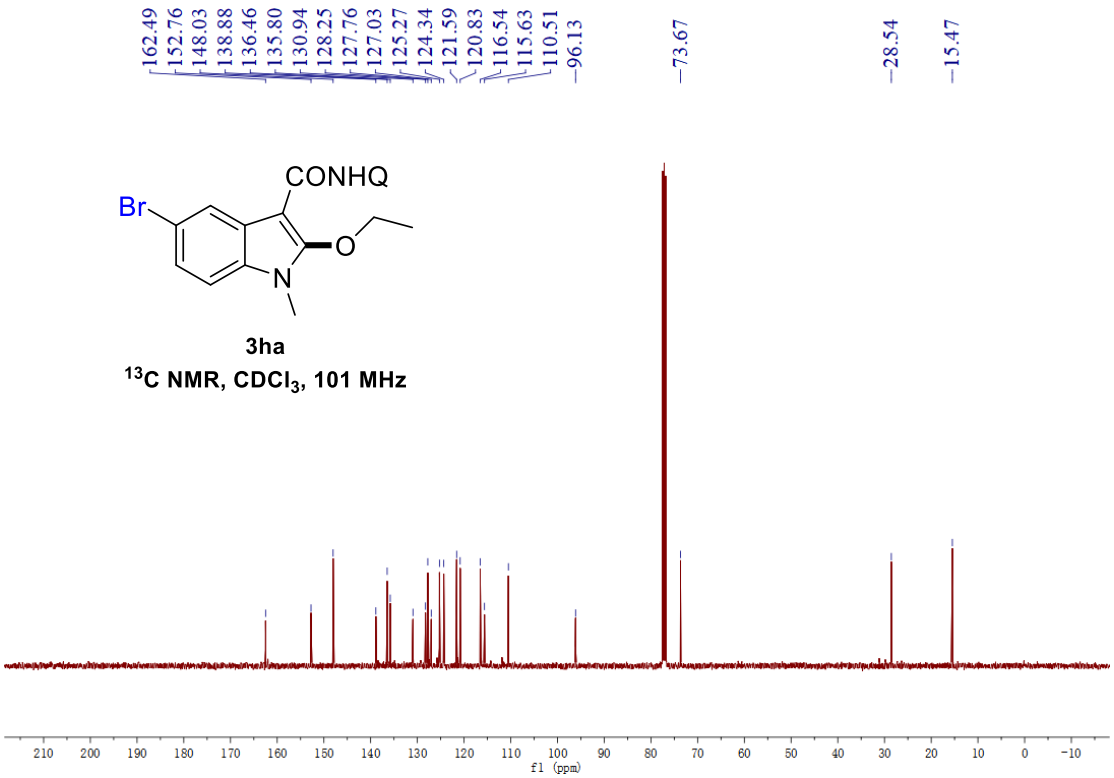
3fa

^{13}C NMR, $CDCl_3$, 101 MHz



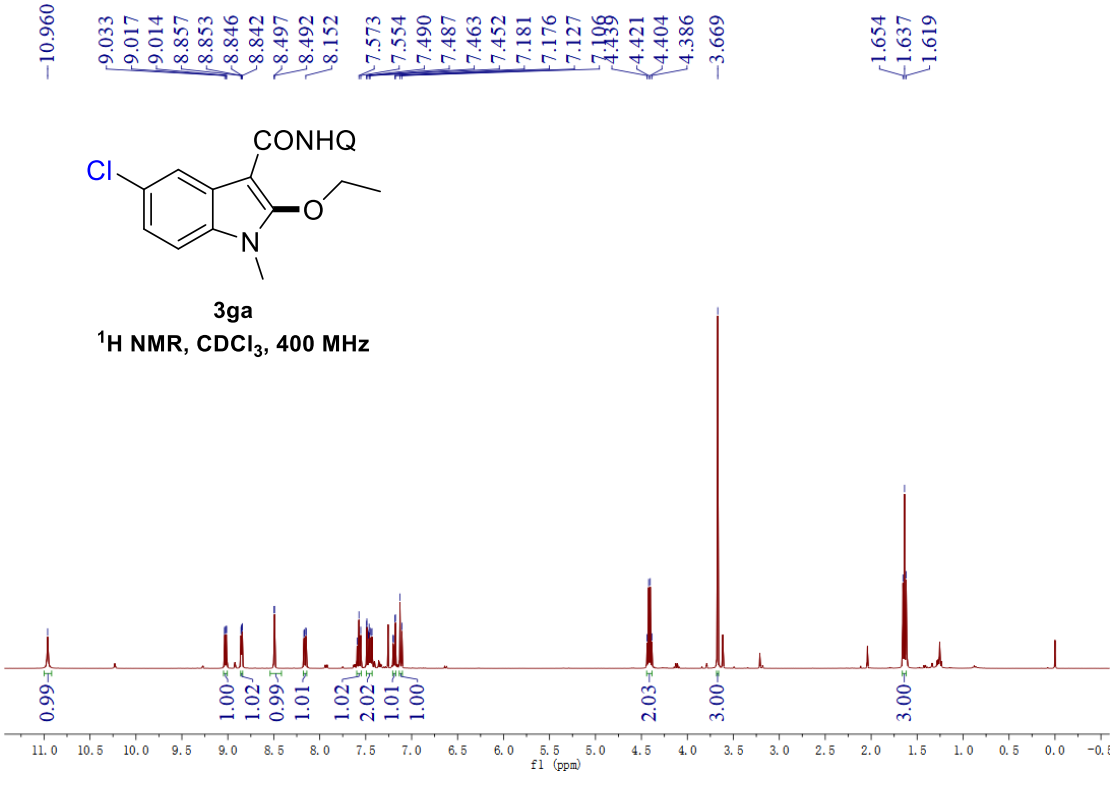
3ha

^{1}H NMR, $CDCl_3$, 400 MHz



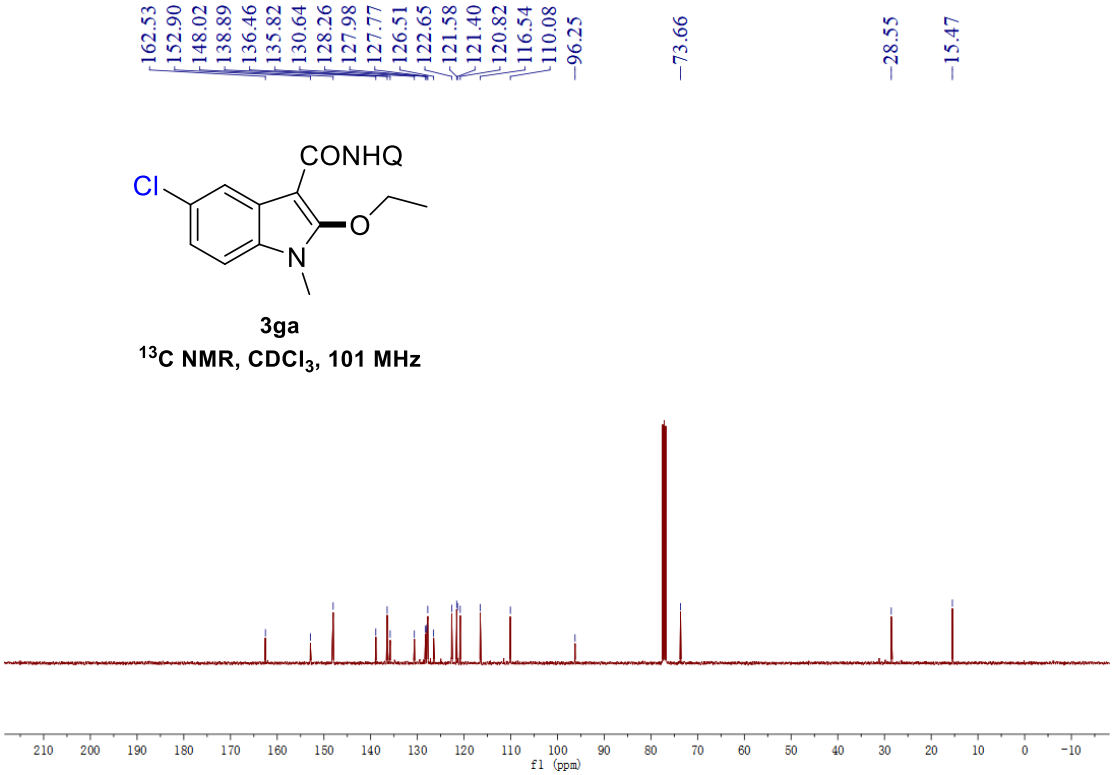
3ha

^{13}C NMR, $CDCl_3$, 101 MHz



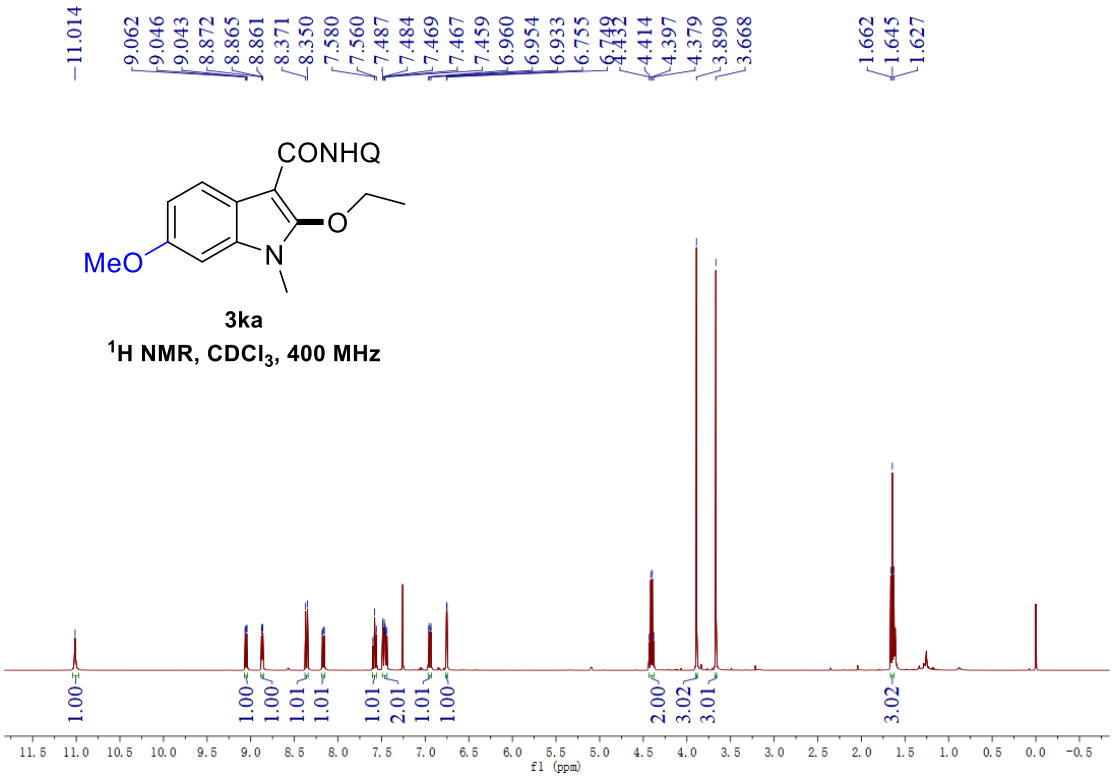
3ga

^{1}H NMR, $CDCl_3$, 400 MHz



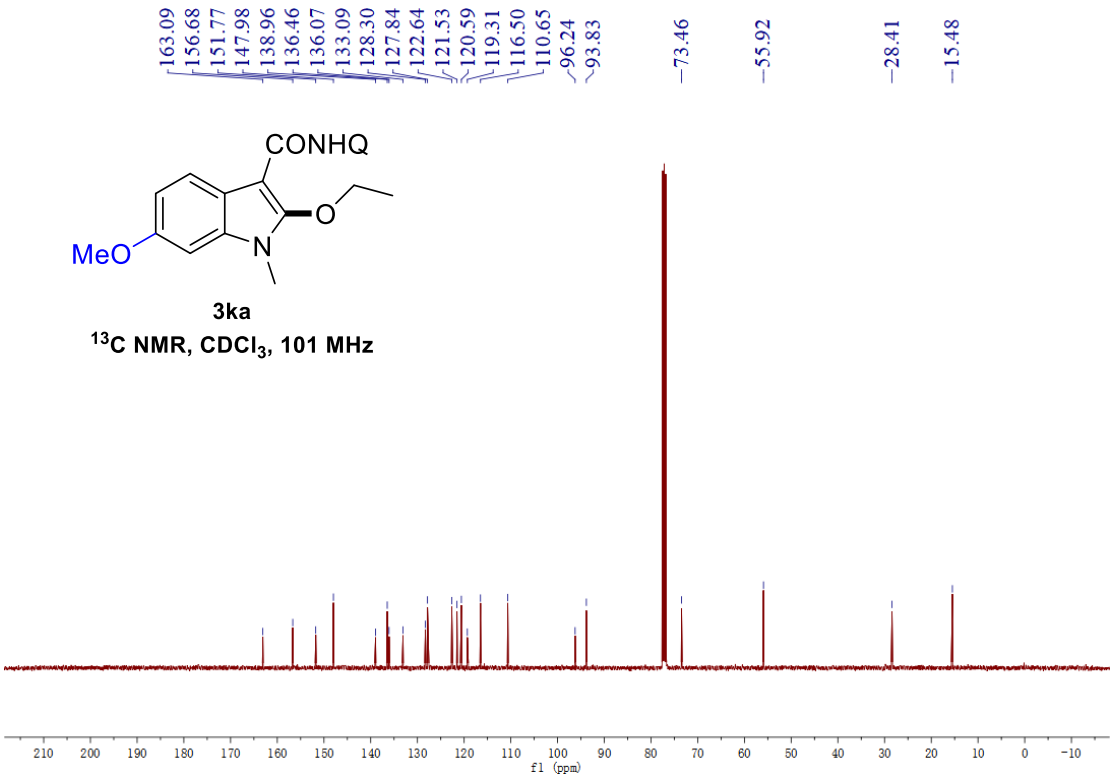
3ga

^{13}C NMR, $CDCl_3$, 101 MHz



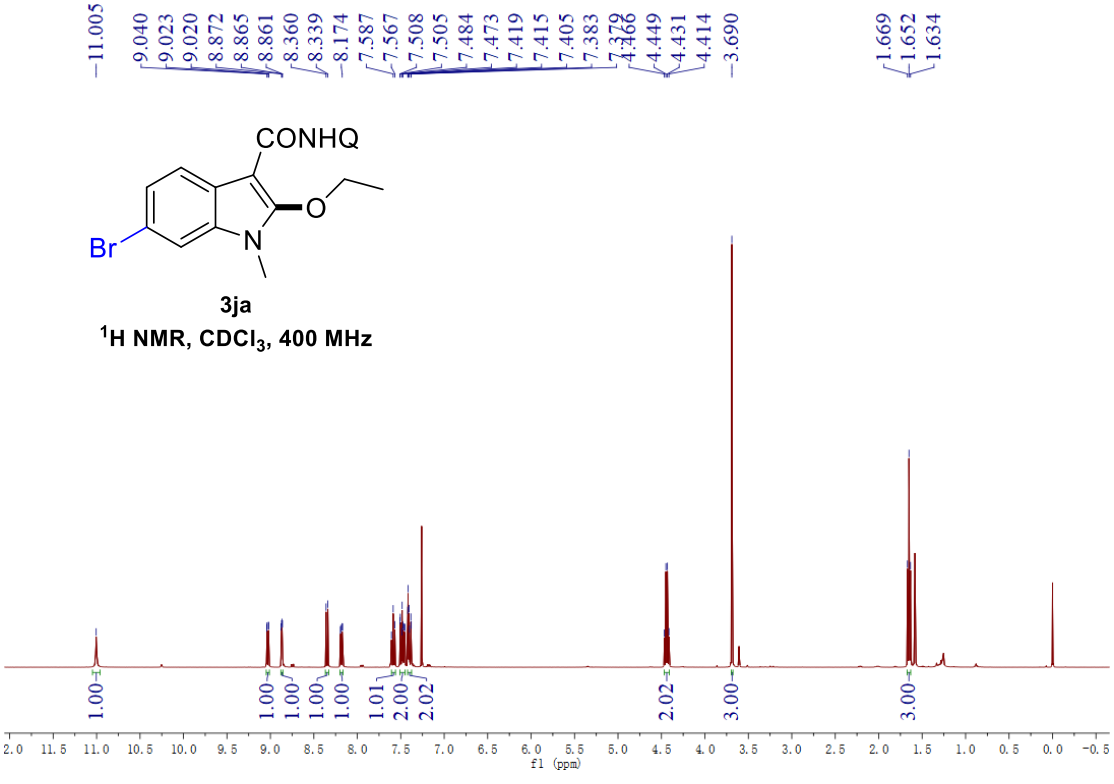
3ka

^{1}H NMR, $CDCl_3$, 400 MHz



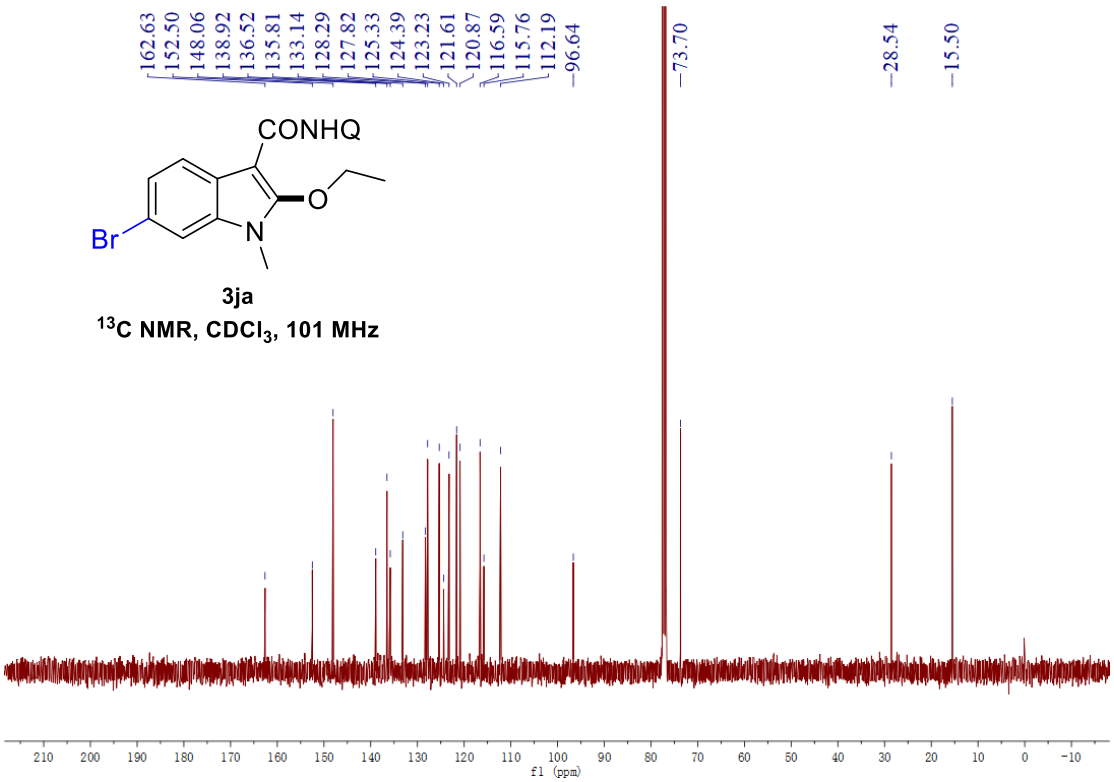
3ka

^{13}C NMR, $CDCl_3$, 101 MHz



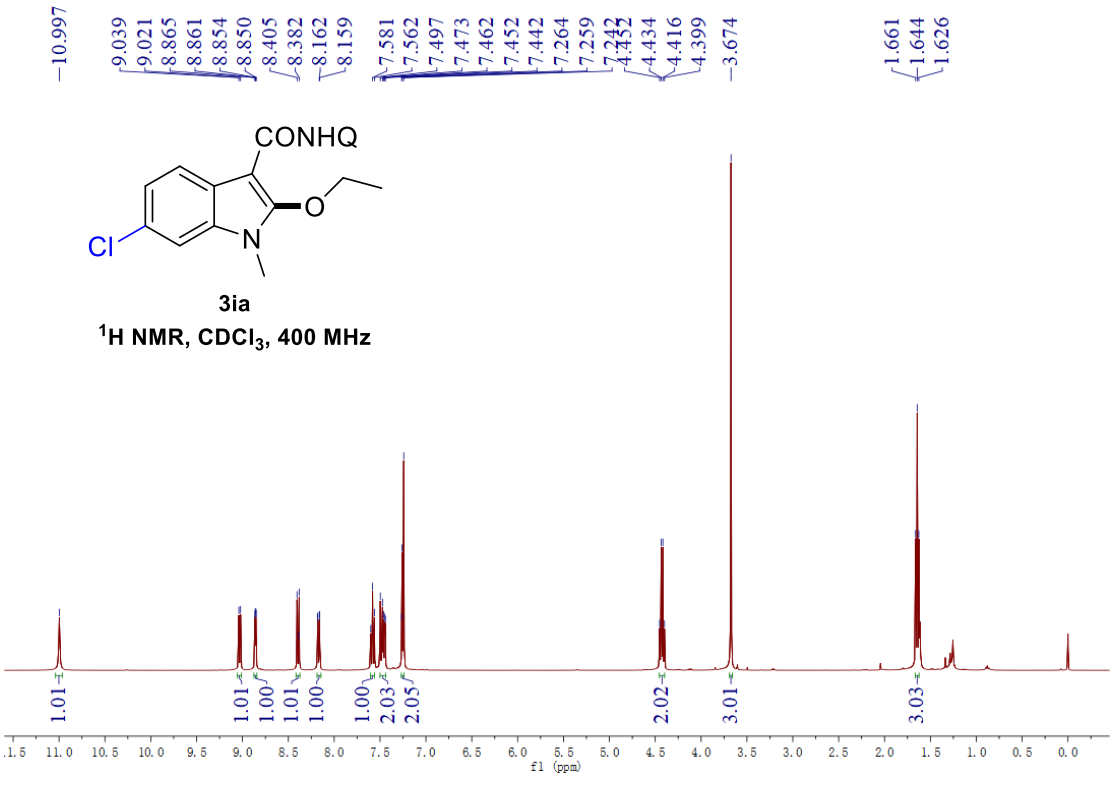
3ja

^{1}H NMR, $CDCl_3$, 400 MHz



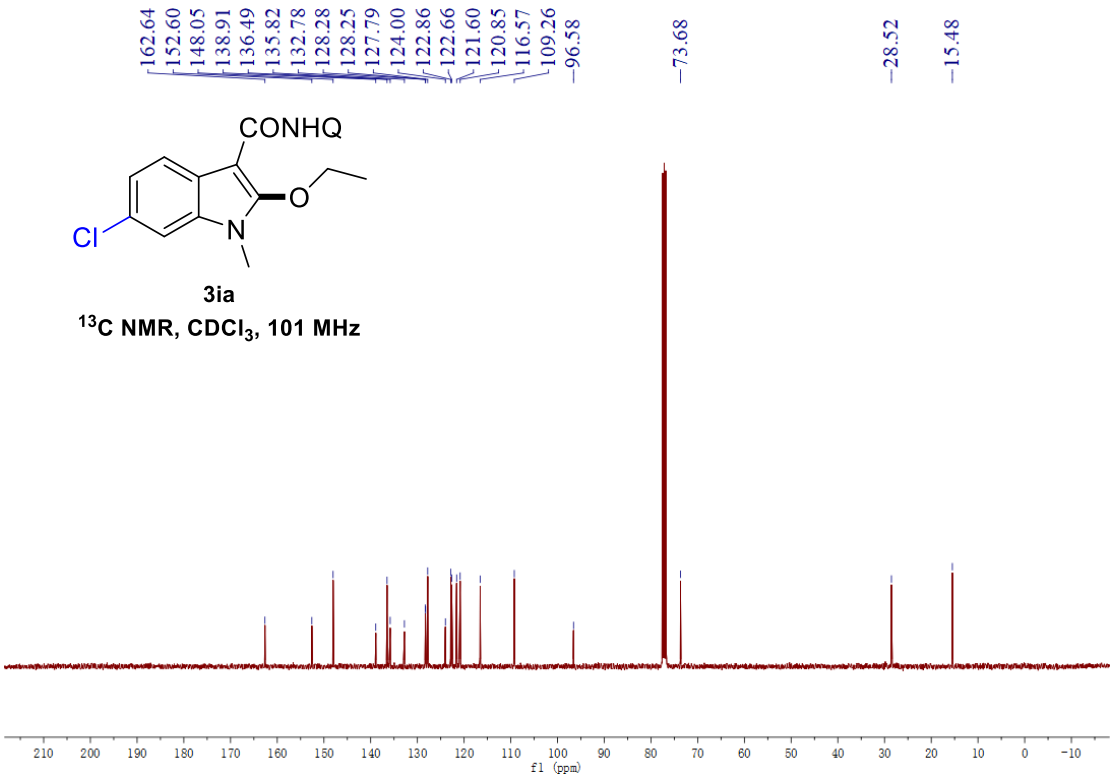
3ja

^{13}C NMR, $CDCl_3$, 101 MHz



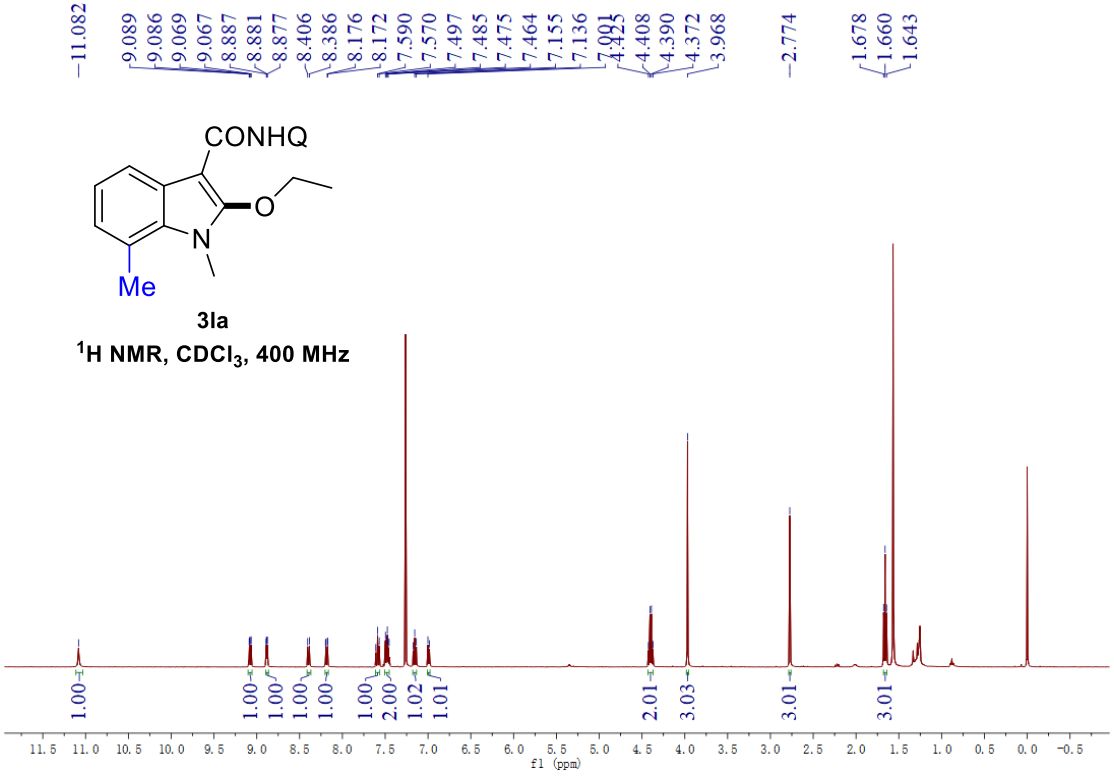
3ia

^{1}H NMR, $CDCl_3$, 400 MHz



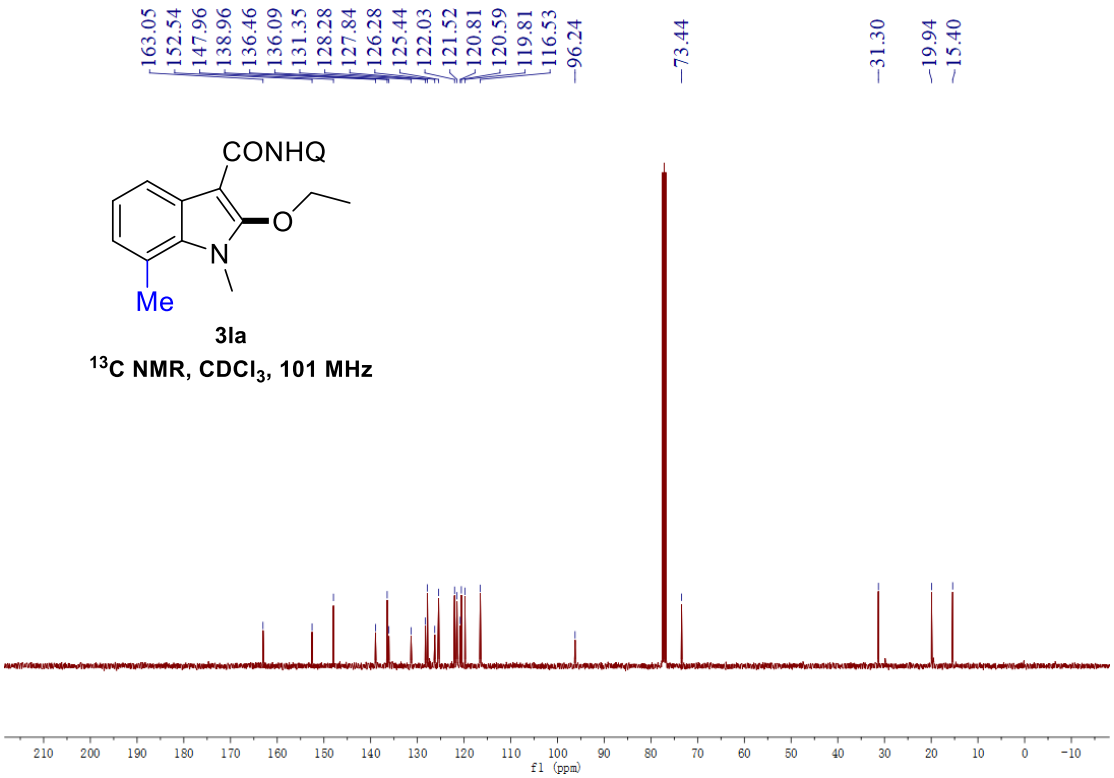
3ia

^{13}C NMR, $CDCl_3$, 101 MHz



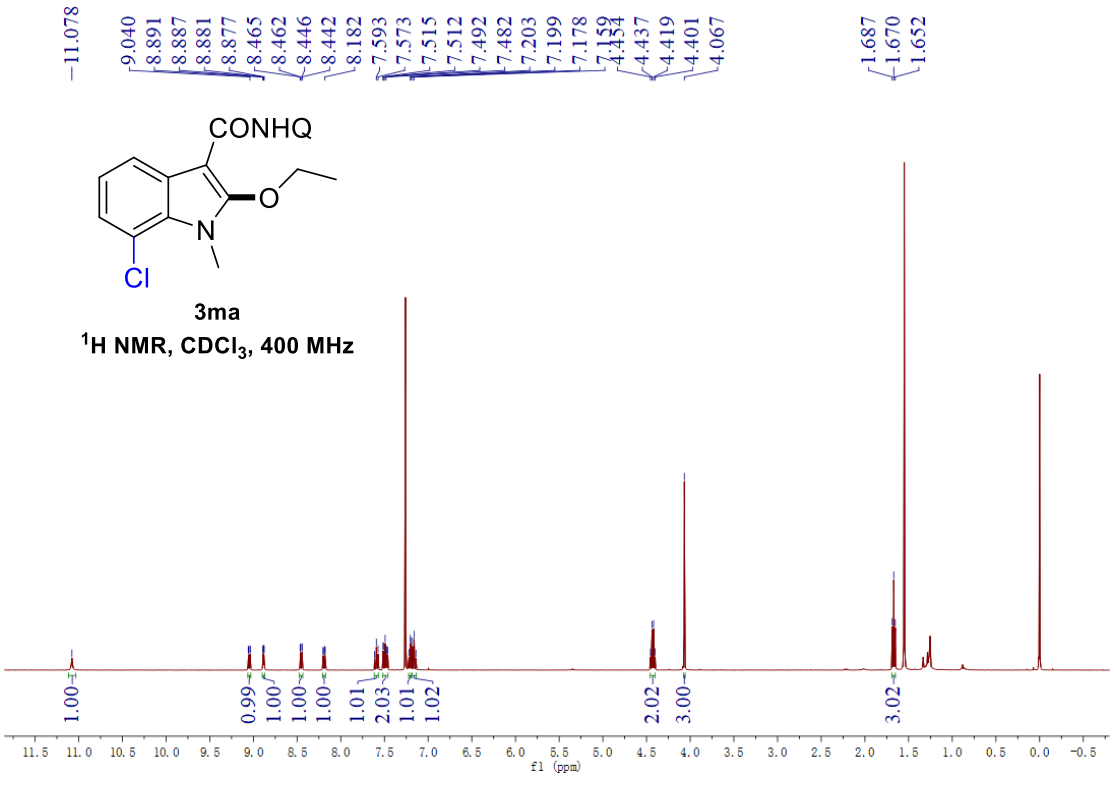
3ia

^{1}H NMR, $CDCl_3$, 400 MHz



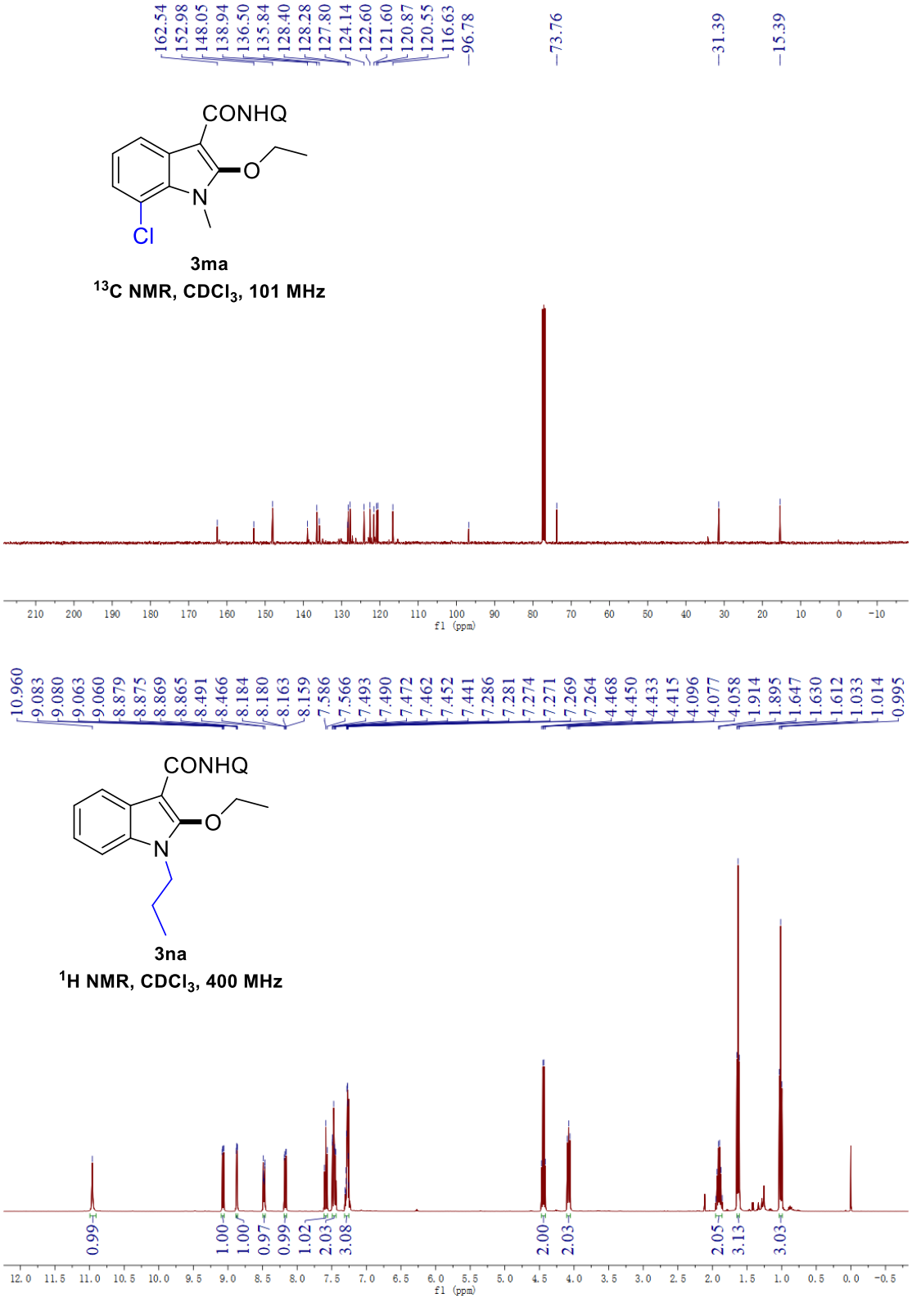
3la

^{13}C NMR, $CDCl_3$, 101 MHz



3ma

^{1}H NMR, $CDCl_3$, 400 MHz

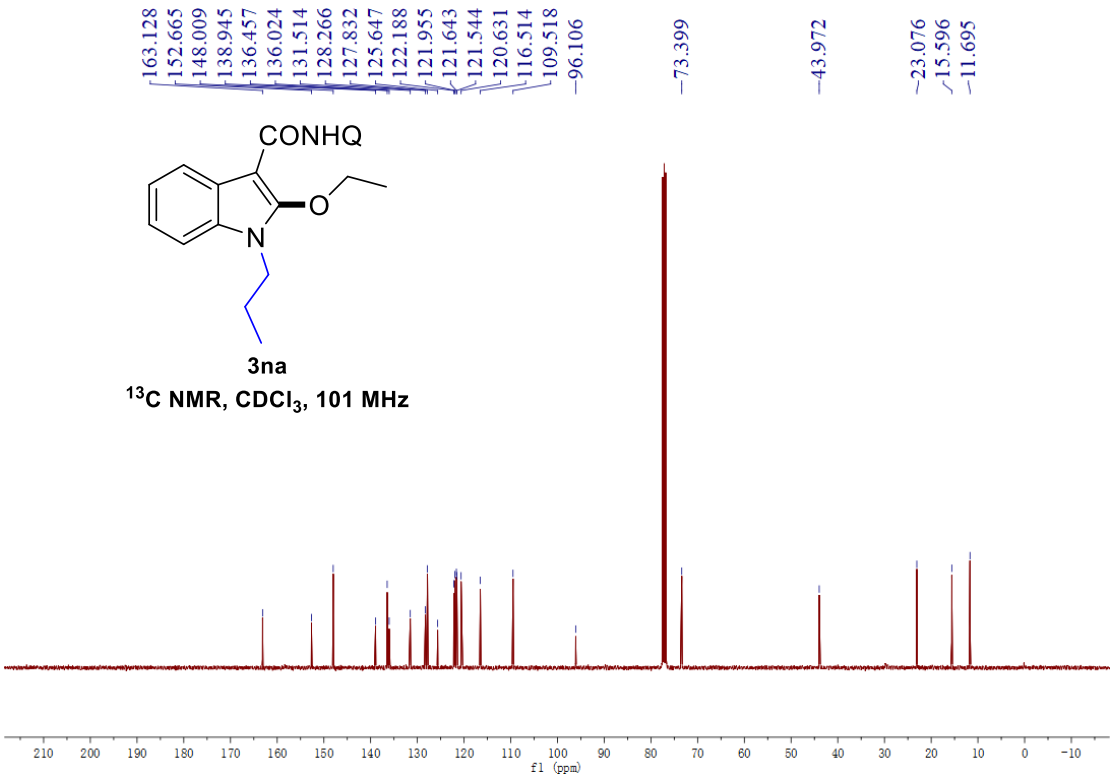


3ma

^{13}C NMR, $CDCl_3$, 101 MHz

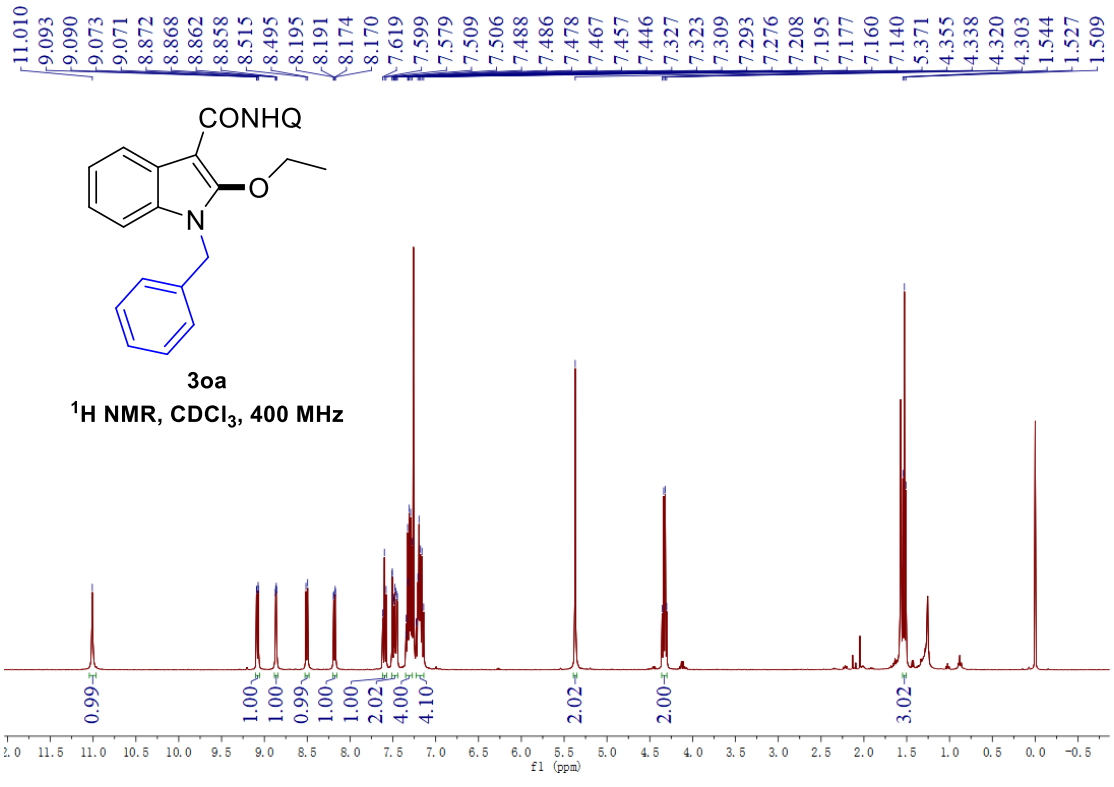
3na

^{1}H NMR, $CDCl_3$, 400 MHz



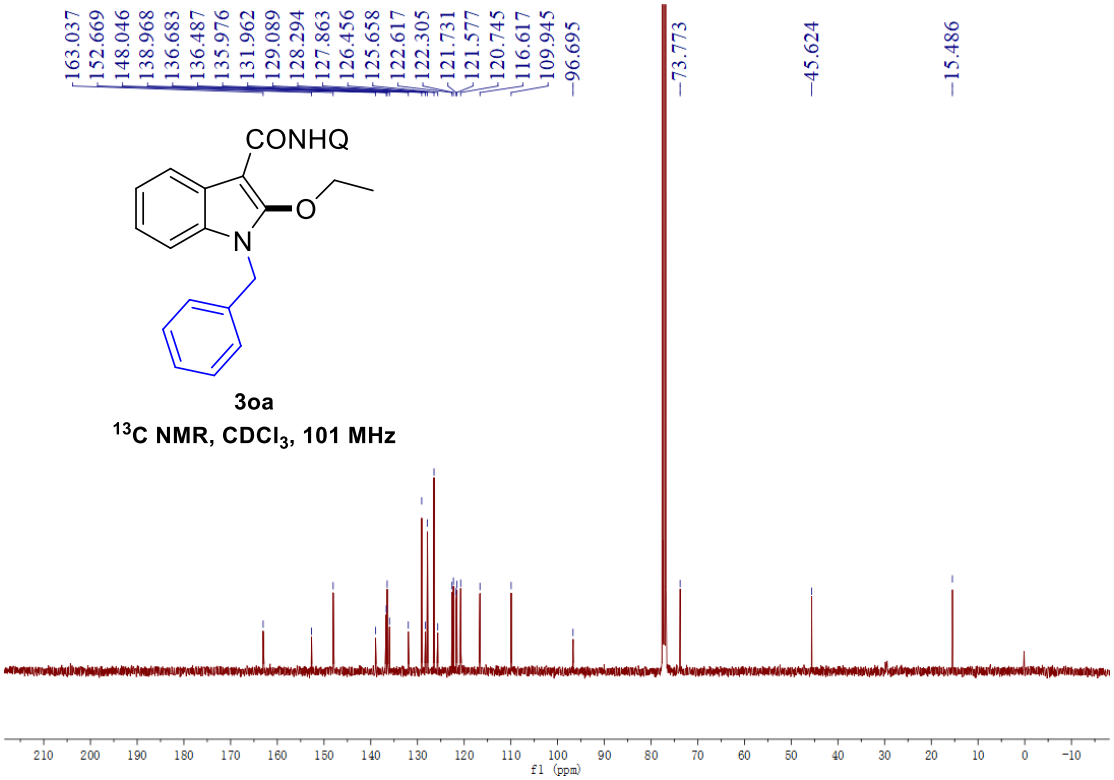
3na

^{13}C NMR, $CDCl_3$, 101 MHz



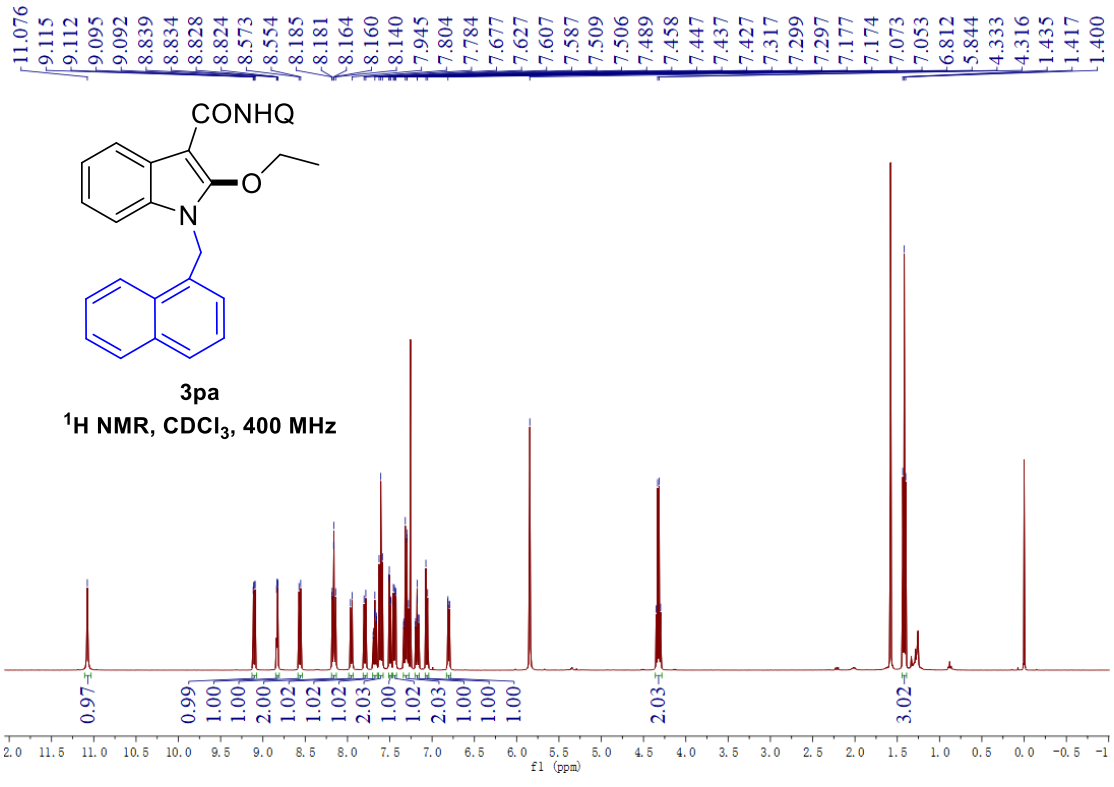
3oa

^{1}H NMR, $CDCl_3$, 400 MHz



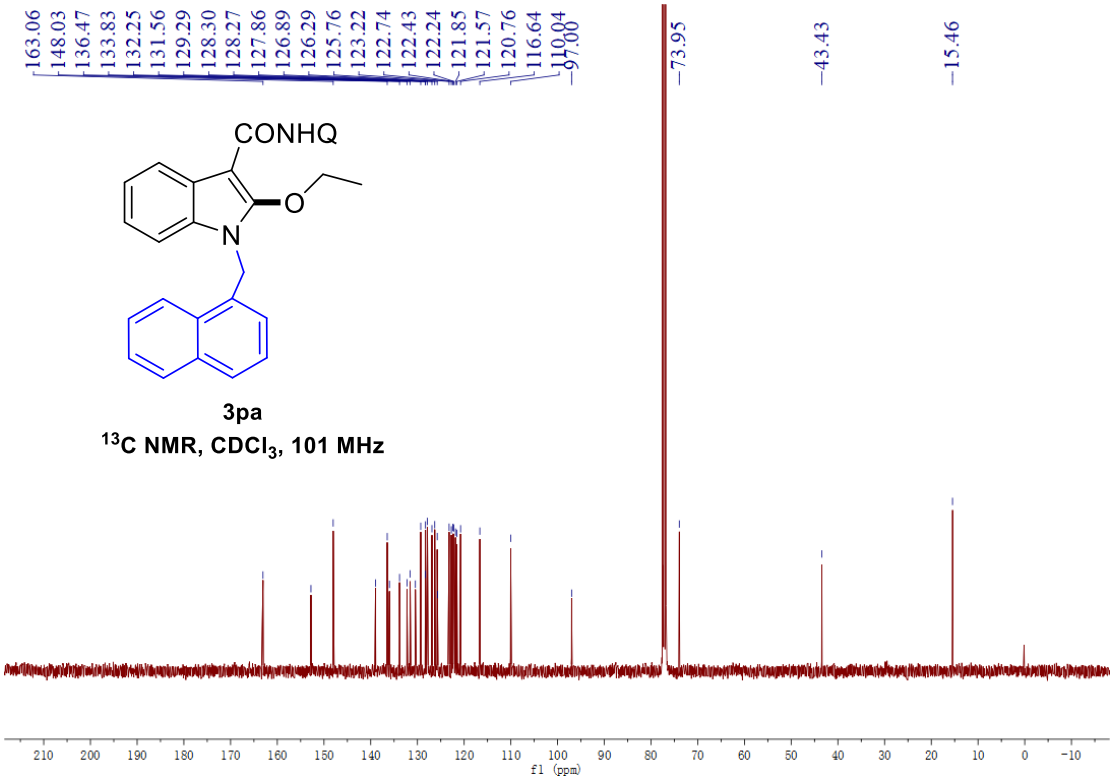
3oa

^{13}C NMR, $CDCl_3$, 101 MHz



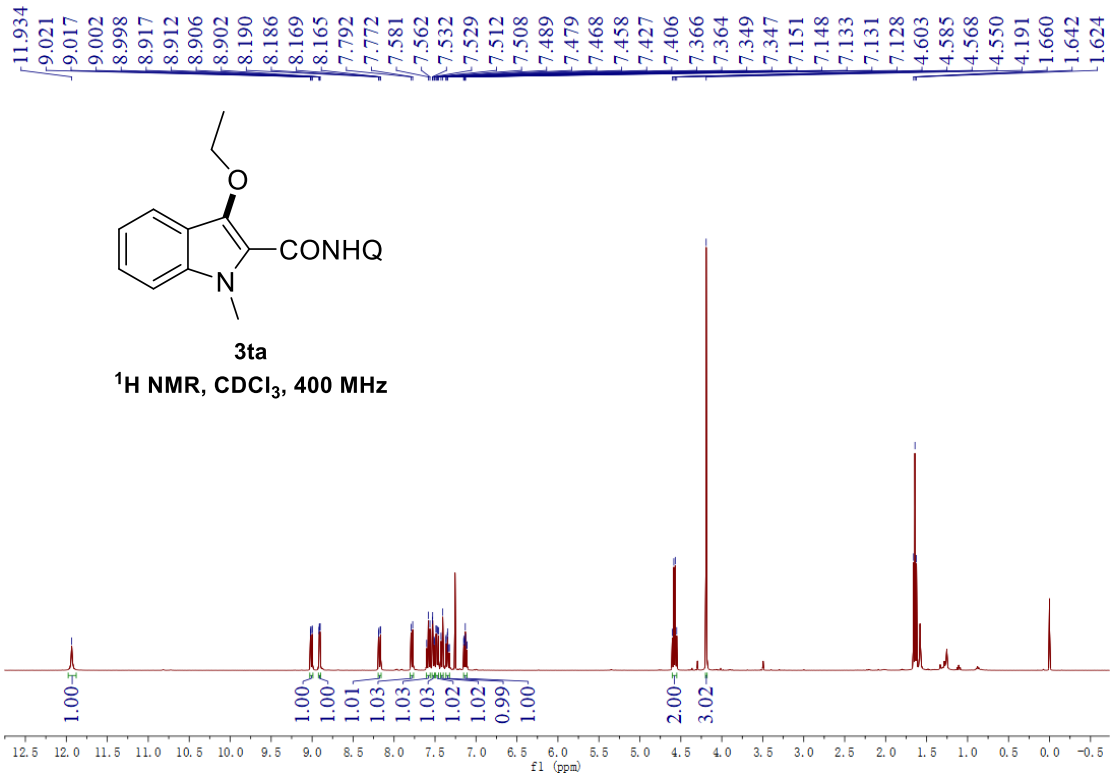
3pa

^{1}H NMR, $CDCl_3$, 400 MHz



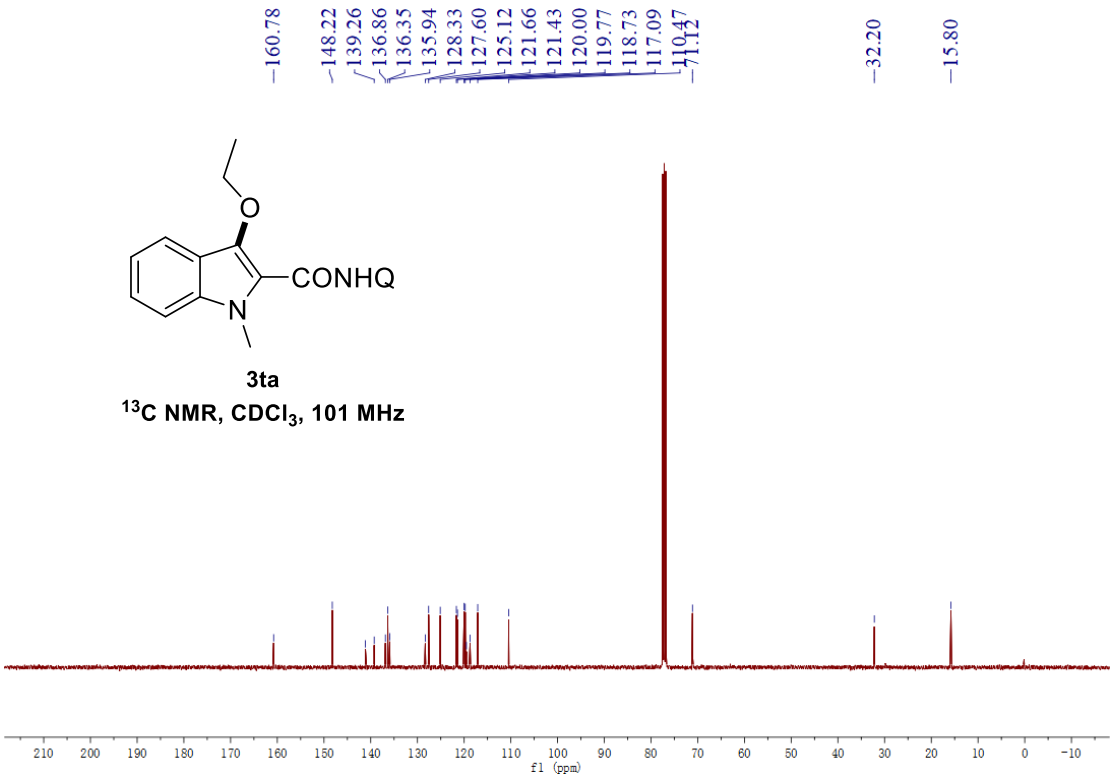
3pa

^{13}C NMR, $CDCl_3$, 101 MHz



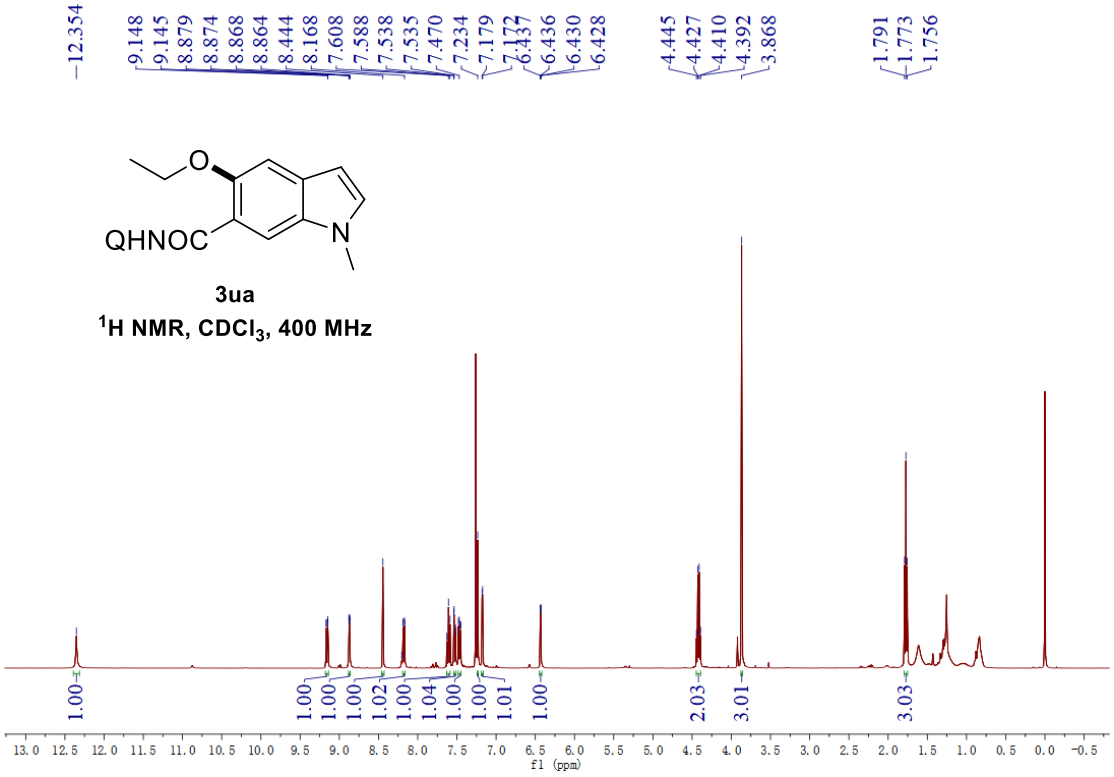
3ta

^{1}H NMR, $CDCl_3$, 400 MHz



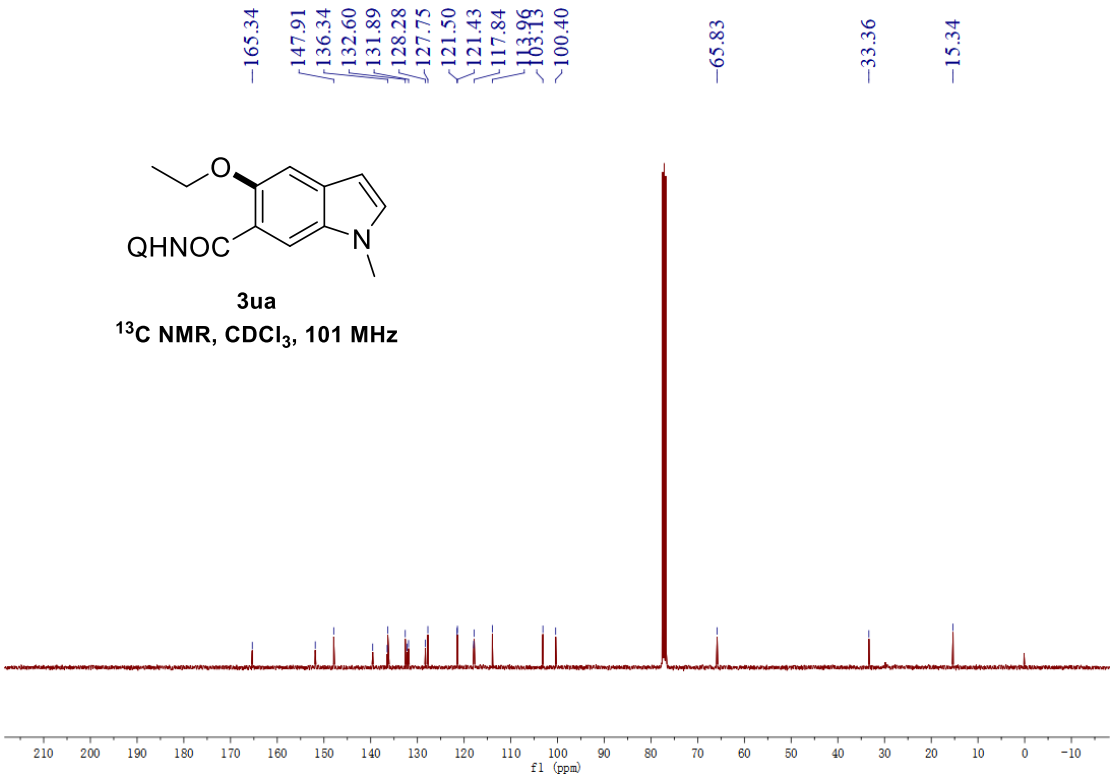
3ta

^{13}C NMR, $CDCl_3$, 101 MHz



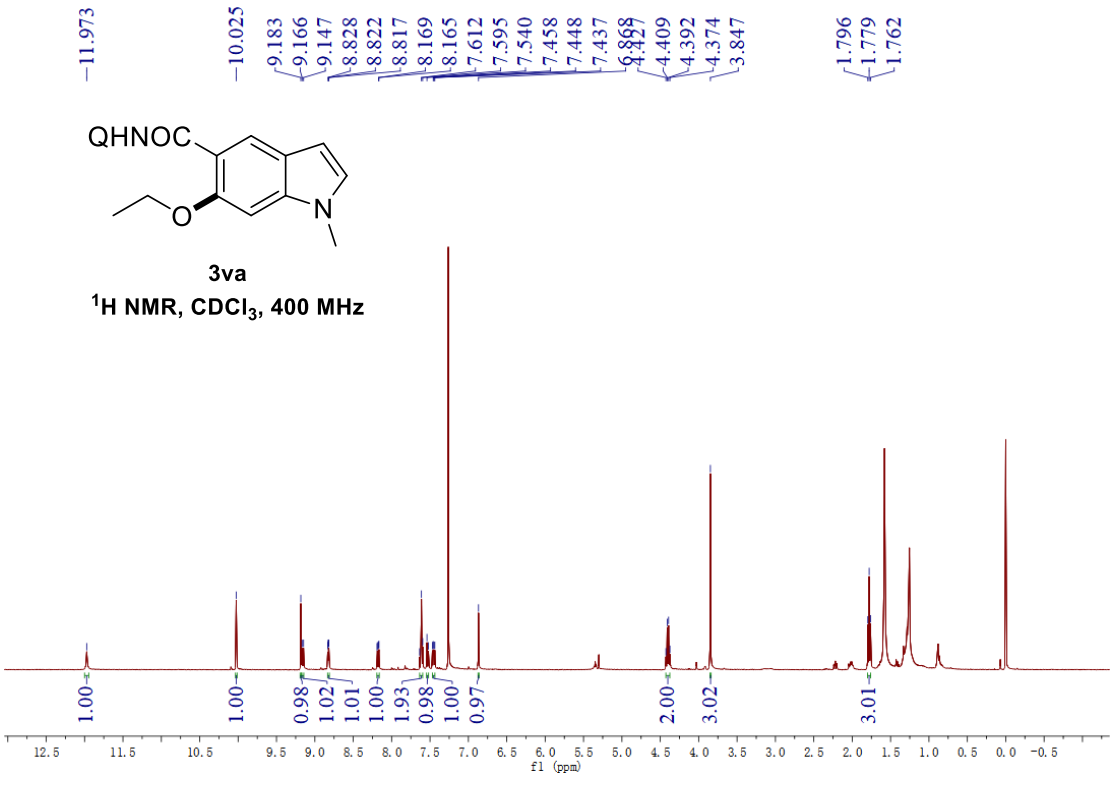
3ua

^{1}H NMR, $CDCl_3$, 400 MHz



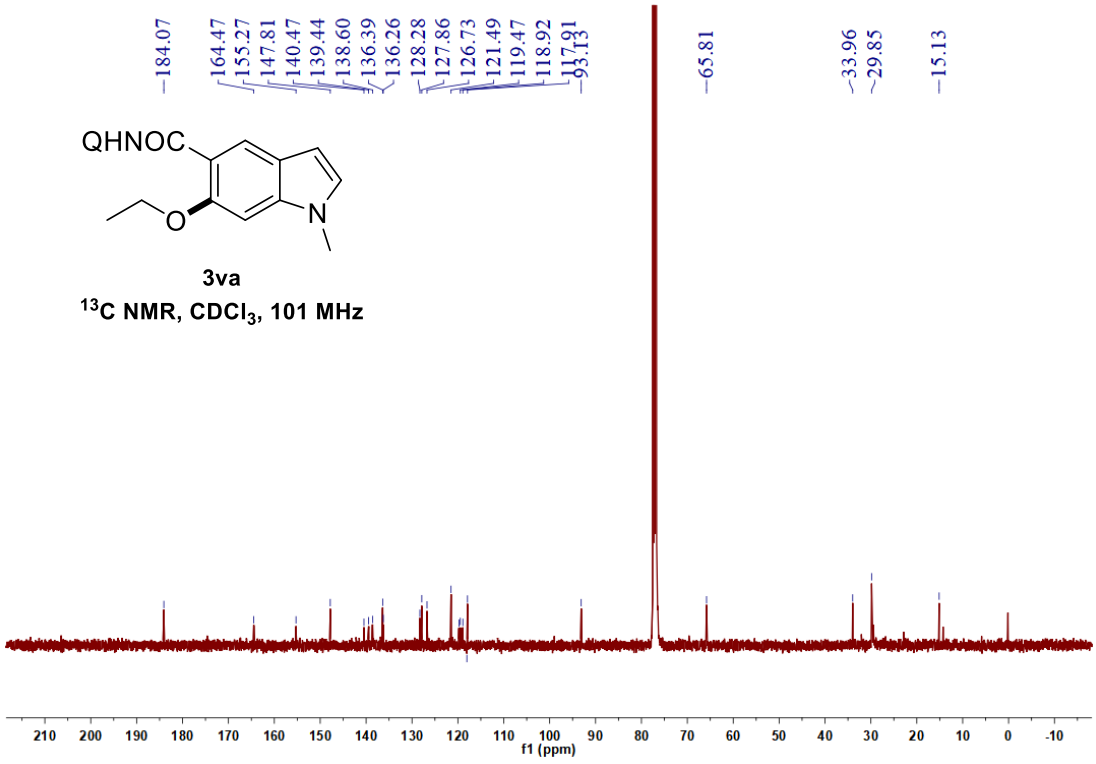
3ua

^{13}C NMR, $CDCl_3$, 101 MHz



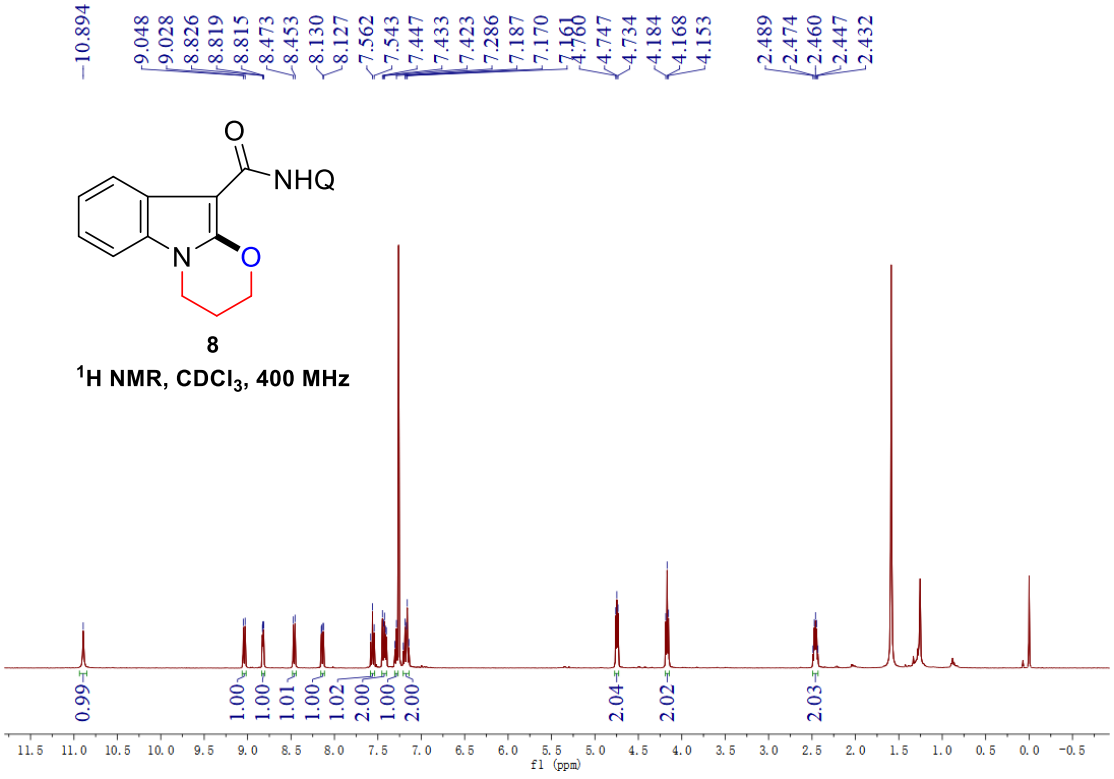
3va

^{1}H NMR, $CDCl_3$, 400 MHz



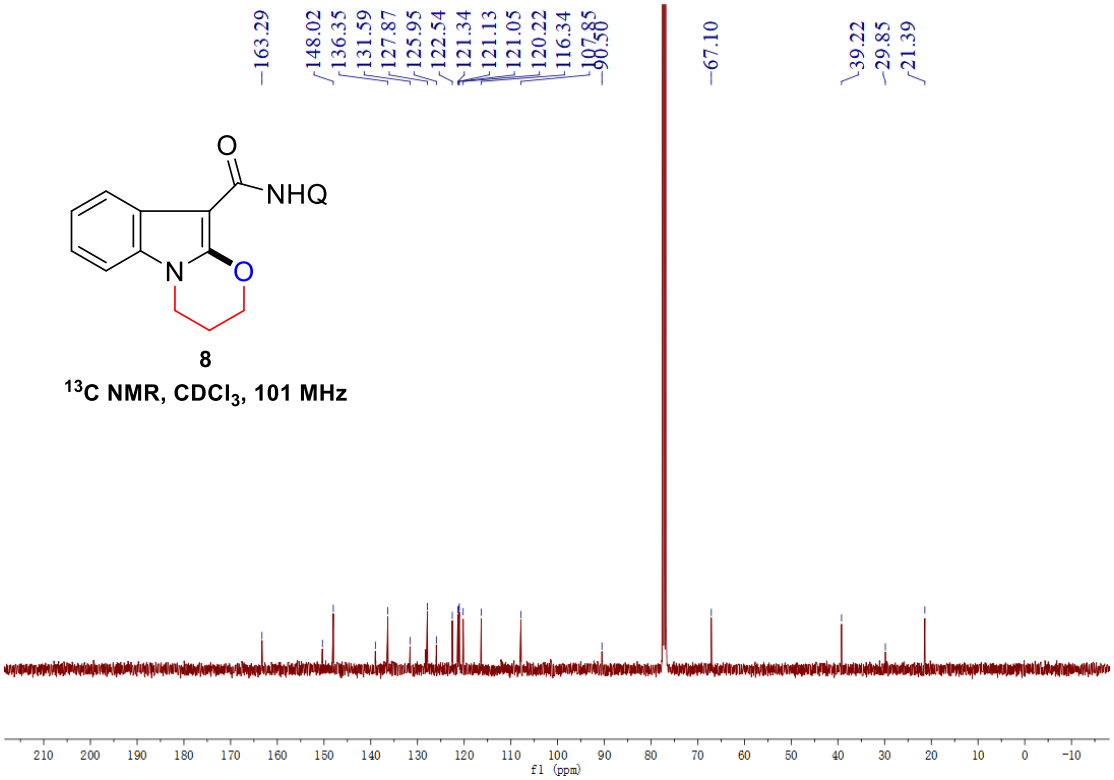
3va

^{13}C NMR, $CDCl_3$, 101 MHz



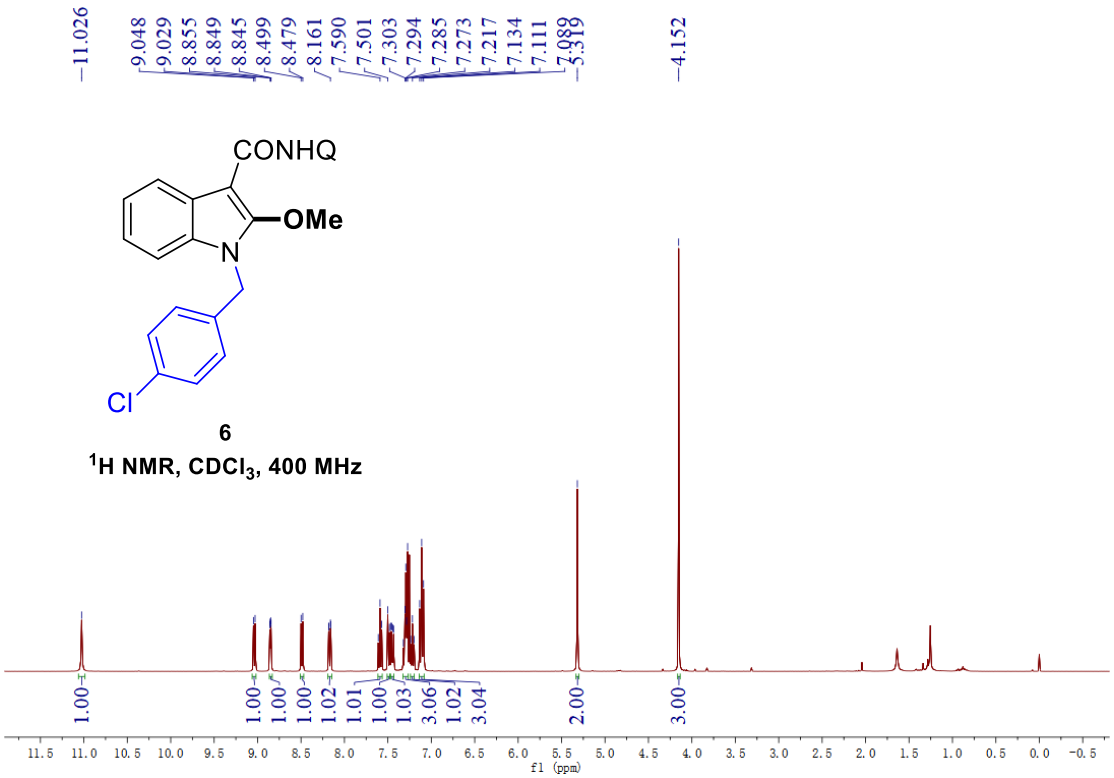
8

^{1}H NMR, $CDCl_3$, 400 MHz



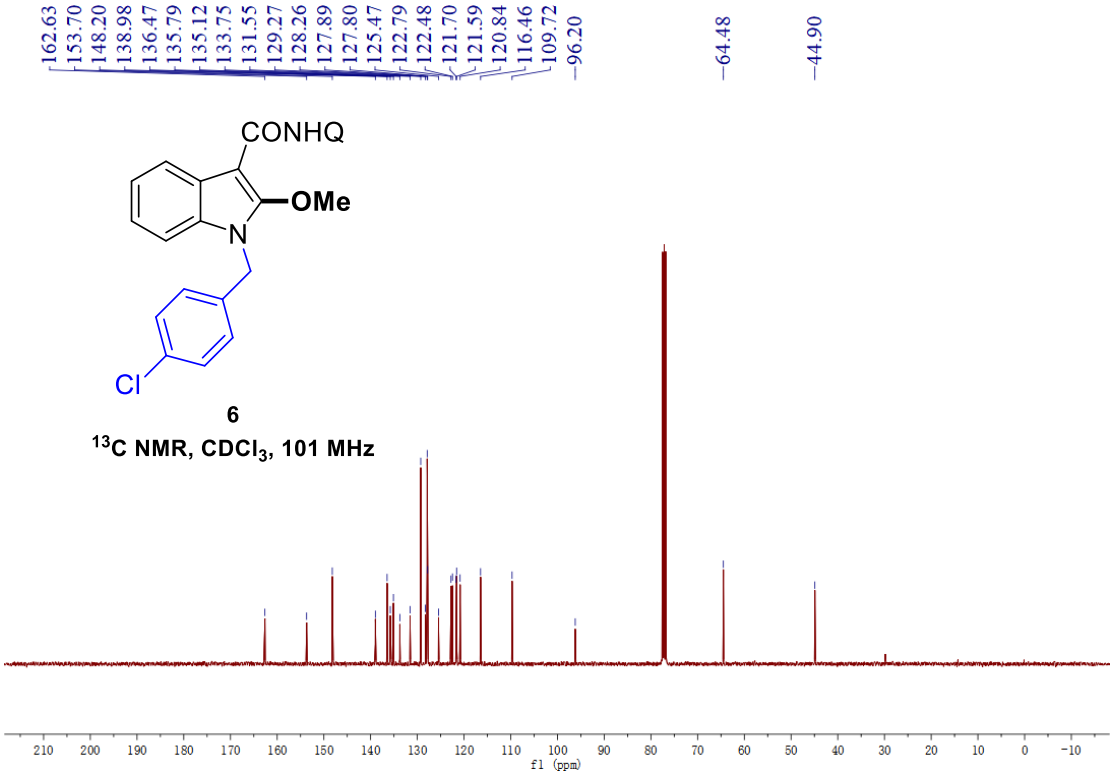
8

^{13}C NMR, $CDCl_3$, 101 MHz



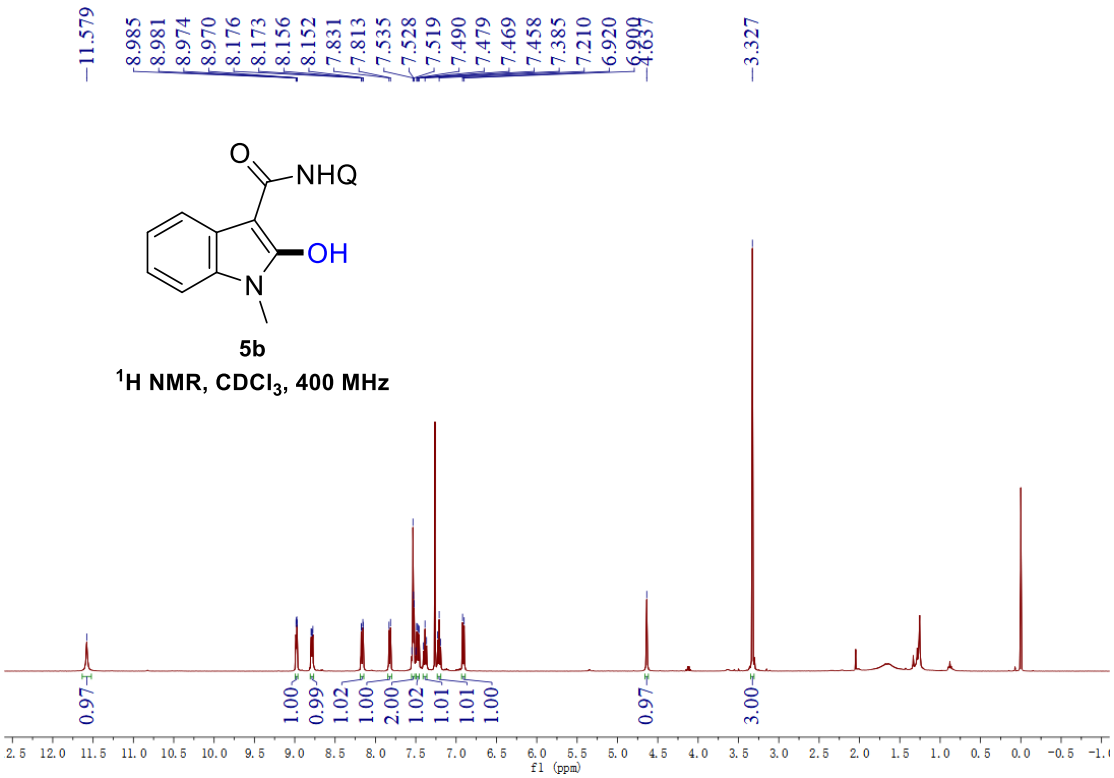
6

^{1}H NMR, $CDCl_3$, 400 MHz



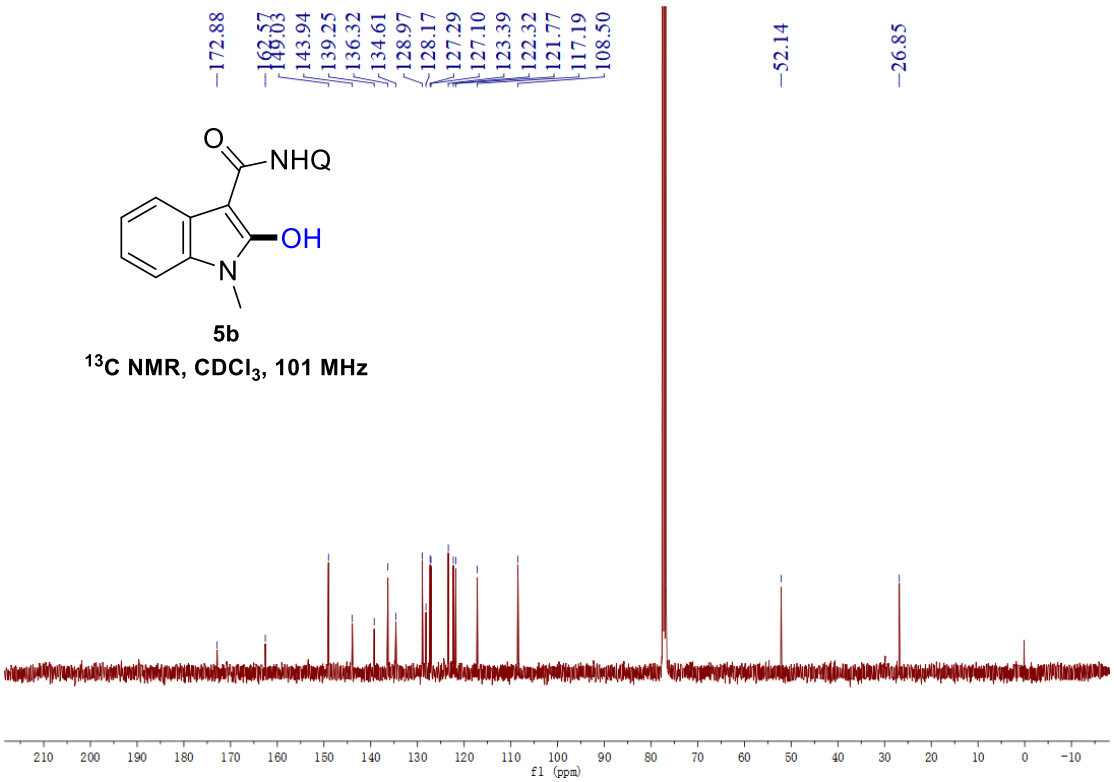
6

^{13}C NMR, $CDCl_3$, 101 MHz



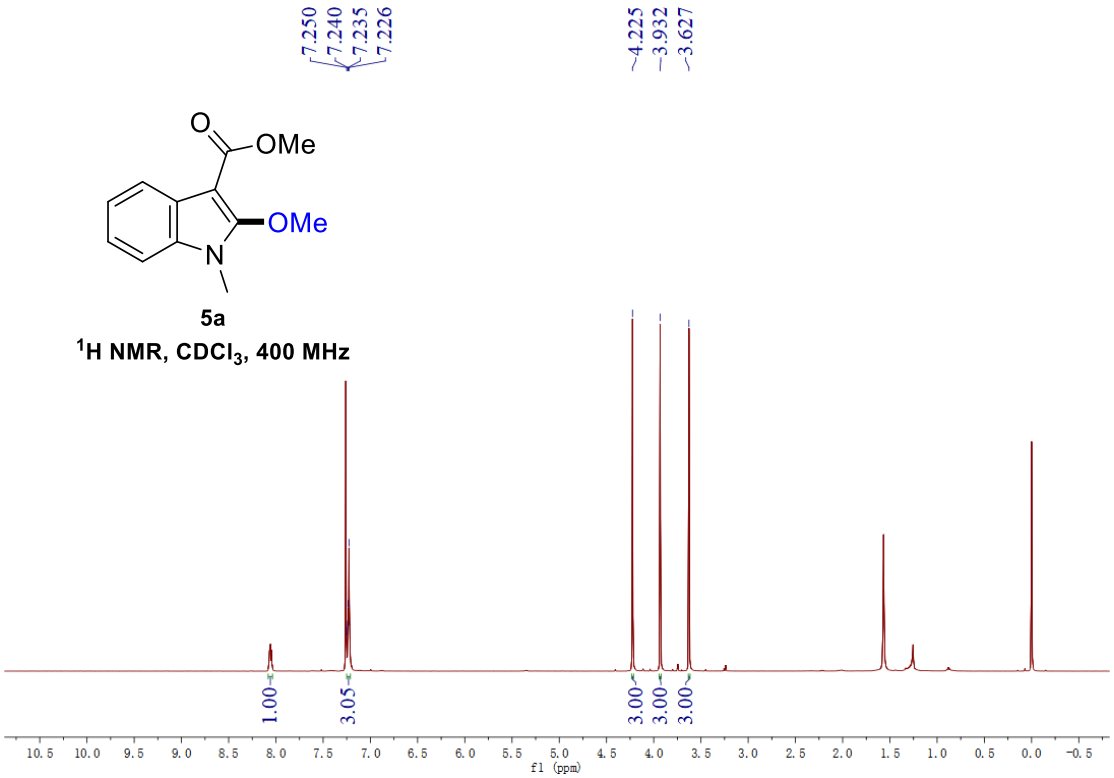
5b

^{1}H NMR, $CDCl_3$, 400 MHz



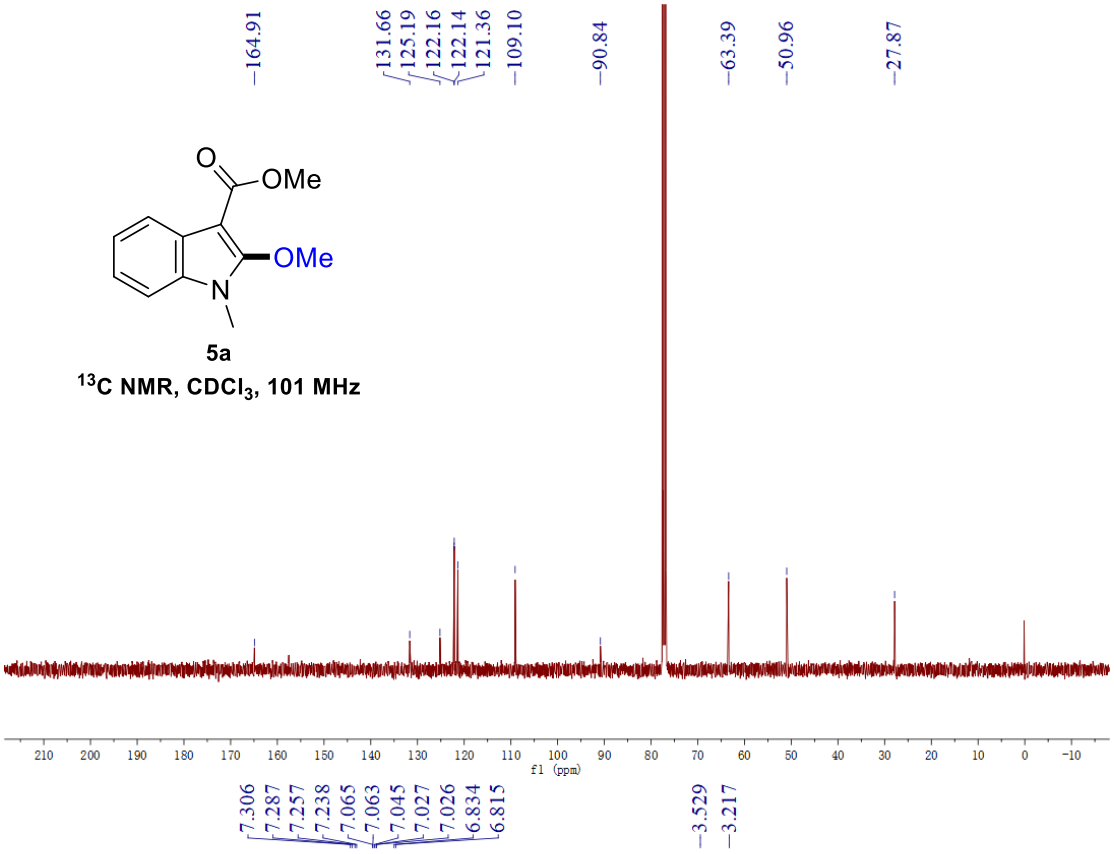
5b

^{13}C NMR, $CDCl_3$, 101 MHz



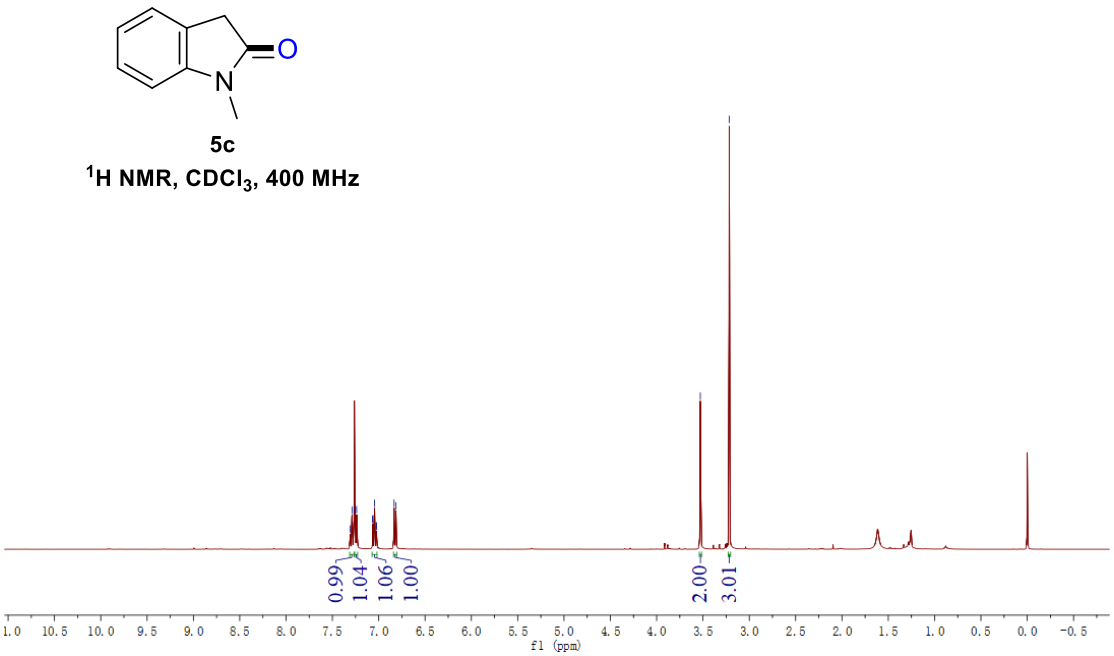
5a

^{1}H NMR, $CDCl_3$, 400 MHz



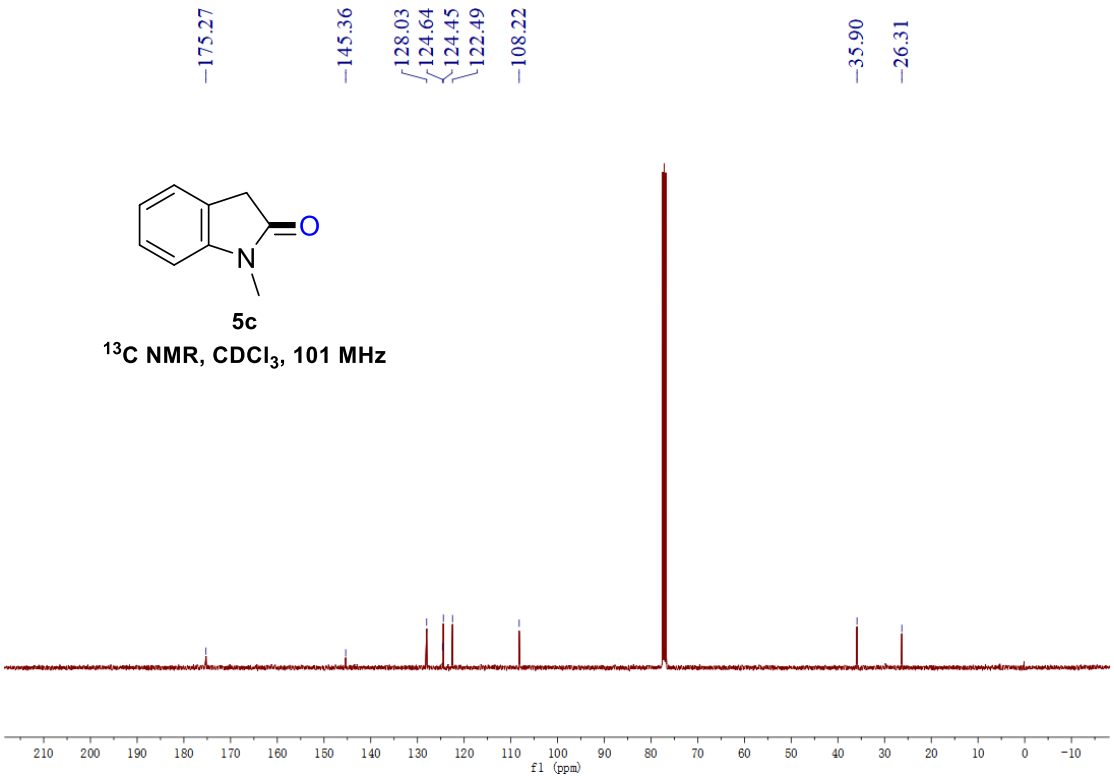
5a

^{13}C NMR, $CDCl_3$, 101 MHz



5c

^{1}H NMR, $CDCl_3$, 400 MHz



5c

^{13}C NMR, $CDCl_3$, 101 MHz