

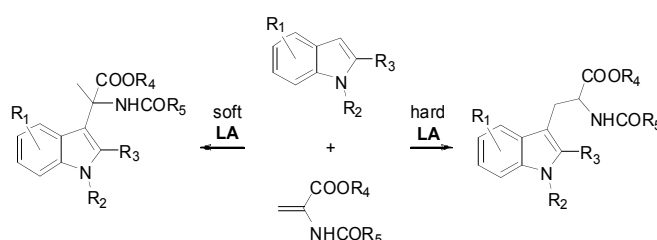
Supporting Information for

Switchable reactivity of acylated α,β -dehydro-amino ester in the Friedel-Crafts alkylation of indoles by changing Lewis acid

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Highly regioselective electrophilic substitution of indoles with *N*-acetylated α,β -dehydroalanine methyl ester, promoted by different transition metal salts was achieved. The orthogonal regioselectivity provides an efficient protocol toward highly functionalized 3-indolyl- α -amino acids. The mechanism of the reactions was explored by NMR studies.

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I. General Information

General Procedures: All reactions were performed in round-bottom flasks, under a positive pressure of nitrogen. Column chromatography purifications were performed under “flash” conditions using 230-400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F₂₅₄ plates, that were visualized by exposure to ultraviolet light and by exposure to an aqueous solution of ceric ammonium molibdate (CAM). The ¹H peak assignments were supported by 2D-COSY experiments.

Materials: All reagents and solvents were used as supplied by common companies.

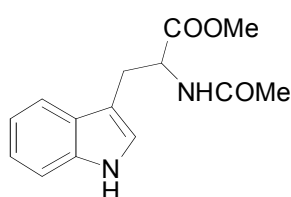
Instrumentation: Melting points are uncorrected. Proton nuclear magnetic resonance (¹H NMR) and Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded on a 200 MHz spectrometer, using CDCl₃ or DMSO-d₆ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (*J* values) are given in hertz (Hz). ESI-MS, only molecular ions (M+1) are given. Infrared spectra were obtained on FTIR spectrometer, absorbances are reported in cm⁻¹ (intensity of absorption, s = strong, m = medium, w = weak, br = broad).

II. Experimental Procedures and Characterization Data

General Procedure for the Michael addition of various indoles to methyl-2-acetamidoacrylate (**1**):

A 1 M solution of EtAlCl₂ in hexane (2 mmol, 2 mL) was added dropwise to a stirred and cooled (0°C) mixture of methyl 2-acetamidoacrylate **1** (143 mg, 1 mmol) and indole (**2a**) or substituted indoles **2b-j** (1,5 mmol) in dry CH₂Cl₂ (4 mL) under a nitrogen atmosphere. The mixture was stirred at 0°C for 2 h, then carefully poured into an ice-cold saturated aqueous sodium hydrogen carbonate solution (10 mL). The resulting suspension of Al(OH)₃ was filtered through Celite and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (column size: 15 x 1,5 cm) on silica gel to give the product **4a-j**.

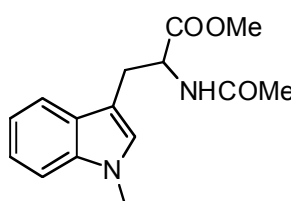
N-Acetyltryptophan methyl ester (4a): Prepared according to **General Procedure**. The



4a

compound **4a** was isolated as a white solid (75% yield) after flash chromatography on silica gel (ethyl acetate). Spectroscopic data obtained were in accordance with those reported in: Bucciarelli M., Forni A., Moretti I., Prati F., Torre G. *Tetrahedron: Asymmetry* **1995**, 8, 2073. ¹H NMR spectra of **4a** is reported at S-10.

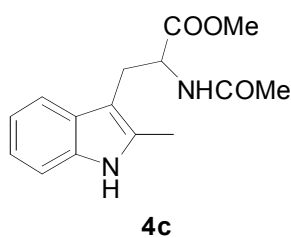
N_α-Acetyl-N-methyltryptophan methyl ester (4b): Prepared according to **General**



4b

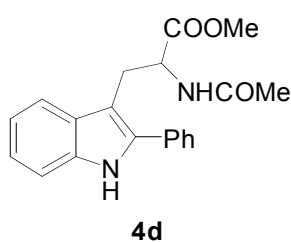
Procedure. The compound **4b** was isolated as a yellow oil (60% yield) after flash chromatography on silica gel (ethyl acetate). TLC (EtOAc 100%), R_f : 0.49 (UV, CAM); ¹H NMR (200 MHz, CDCl₃): δ 1.97 (s, 3H, NHCOCH₃), 3.30 (dd, 2H, J₁ = 5.3 Hz, J₂ = 1.1 Hz, CH₂), 3.71 (s, 3H, COOCH₃), 3.75 (s, 3H, NCH₃), 4.89 – 4.98 (m, 1H, CH), 5.98 (br d, 1H, J = 7.5 Hz, NHCOCH₃), 6.83 – 7.53 (m, 5H, ArH); ¹³C NMR (50 MHz, CDCl₃): δ 172.3, 169.6, 136.7, 128.1, 127.2, 121.6, 119.0, 118.4, 109.2, 108.3, 53.0, 52.1, 32.5, 27.3, 23.0; FTIR (CH₂Cl₂) ν_{max}/cm⁻¹ : 3293 (br), 2951 (m), 1743 (s), 1655 (s), 1545 (s); MS (ESI) : 275 (M+1); Anal. Calcd. for C₁₅H₁₈N₂O₃ % C, 65.68; H, 6.61; N, 10.21; Found % C, 65.69; H, 6.62; N, 10.22. ¹H and ¹³C NMR spectra of **4b** are reported at S-11.

N-Acetyl-2-methyltryptophan methyl ester (4c): Prepared according to **General**



Procedure. The compound **4c** was isolated as a pinkish solid (66% yield) after flash chromatography on silica gel (ethyl acetate). Spectroscopic data obtained were in accordance with those reported in: Ritchie R., Saxton J. E. *Tetrahedron* **1981**, *24*, 4295. ^1H NMR spectra of **4c** is reported at S-12.

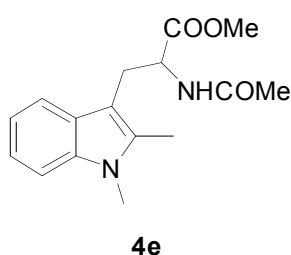
N-Acetyl-2-phenyltryptophan methyl ester (4d): Prepared according to **General**



Procedure. The compound **4d** was isolated as a white solid (52% yield) after flash chromatography on silica gel (cyclohexane / ethyl acetate 7 : 3). Mp: 85 – 86 °C; TLC (cyclohexane / ethyl acetate 3 : 2), R_f : 0.57 (UV, CAM); ^1H NMR (200 MHz, CDCl_3): δ 1.63 (s, 3H, NHCOCH_3), 3.26 (s, 3H, COOCH_3), 3.54 (d, 2H, $J = 5.4$ Hz, CH_2),

4.76 – 4.86 (m, 1H, CH), 5.77 (br d, 1H, $J = 8.2$ Hz, NHCOCH_3), 7.07 – 7.57 (m, 9H, ArH), 8.19 (br s, 1H, NH); ^{13}C NMR (50 MHz, CDCl_3): δ 172.1, 169.5, 135.9, 135.7, 133.2, 129.4, 129.1, 128.3, 128.0, 122.5, 120.0, 118.9, 110.9, 106.9, 52.8, 51.9, 26.6, 22.8; FTIR (CDCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$: 3391 (br), 2920 (m), 1731 (s), 1649 (s), 1567 (s); MS (ESI) : 337 (M+1); Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ % C, 71.41; H, 5.99; N, 8.33; Found % C, 71.32; H, 6.02; N, 8.27. ^1H and ^{13}C NMR spectra of **4d** are reported at S-13.

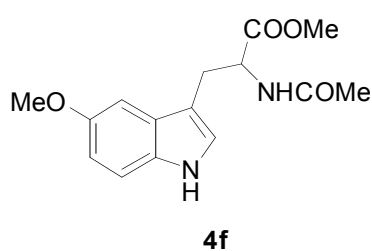
N $_{\alpha}$ -Acetyl-1,2-dimethyltryptophan methyl ester (4e): Prepared according to **General**



Procedure. The compound **4e** was isolated as a white solid (35% yield) after flash chromatography on silica gel (ethyl acetate). Mp: 134 – 135 °C; TLC (EtOAc 100%), R_f : 0.55 (UV, CAM); ^1H NMR (200 MHz, CDCl_3): δ 1.93 (s, 3H, NHCOCH_3), 2.31 (s, 3H, α -indole CH_3), 3.28 (dd, 2H, $J_1 = 5.0$ Hz, $J_2 = 1.1$ Hz, CH_2), 3.65 (s,

3H, COOCH_3), 3.68 (s, 3H, NCH_3), 4.85 – 4.95 (m, 1H, CH), 5.97 (br d, 1H, $J = 7.8$ Hz, NHCOCH_3), 7.00 – 7.41 (m, 4H, ArH); ^{13}C NMR (50 MHz, CDCl_3): δ 172.5, 169.5, 136.5, 134.5, 128.1, 120.8, 119.1, 117.6, 108.7, 104.7, 53.0, 52.3, 29.5, 26.9, 23.2, 10.2; FTIR (CH_2Cl_2) $\nu_{\text{max}}/\text{cm}^{-1}$: 3385 (br), 2950 (m), 1741 (s), 1653 (s), 1541 (s); MS (ESI): 289 (M+1); Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$ % C, 66.65; H, 6.99; N, 9.72; Found % C, 66.66; H, 6.94; N, 9.66. ^1H and ^{13}C NMR spectra of **4e** are reported at S-14.

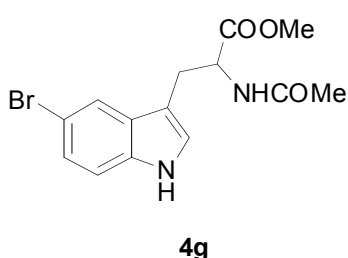
5-Methoxy-*N*-acetyltryptophan methyl ester (4f): Prepared according to **General**



Procedure. The compound **4f** was isolated as a white solid (77% yield) after flash chromatography on silica gel (ethyl acetate). Spectroscopic data obtained were in accordance with those reported in: Irie K., Ishida A., Nakamura T. *Chem. Pharm. Bull.* **1984**, 6; 2126. ^1H NMR spectra of **4f** is reported

at S-15.

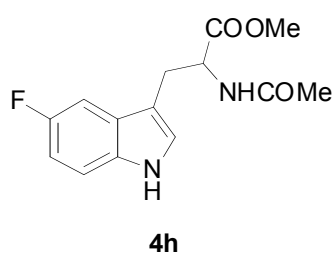
5-Bromo-*N*-acetyltryptophan methyl ester (4g): Prepared according to **General**



Procedure. The compound **4g** was isolated as a light pink solid (65% yield) after flash chromatography on silica gel (ethyl acetate). Mp: 152 – 153 °C; TLC (EtOAc 100%), R_f : 0.50 (UV, CAM); ^1H NMR (200 MHz, DMSO- d_6): δ 1.81 (s, 3H, NHCOCH₃), 2.99-3.10 (m, 2H, CH₂), 3.58 (s, 3H, COOCH₃),

4.40 – 4.54 (m, 1H, CH), 7.12 – 7.34 (m, 3H, ArH), 7.66 (s, 1H, ArH), 8.27 (br d, 1H, J = 7.3 Hz, NHCOCH₃), 11.05 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO- d_6): δ 172.2, 169.1, 134.7, 128.9, 125.3, 123.2, 120.4, 113.3, 111.0, 109.4, 53.0, 51.6, 26.8, 22.1; FTIR (Nujol) $\nu_{\text{max}}/\text{cm}^{-1}$: 3323 (br), 2923 (m), 1731 (s), 1661 (s), 1530 (s); MS (ESI): 340 (M+1); Anal. Calcd. for C₁₄H₁₅BrN₂O₃ % C, 49.57; H, 4.46; N, 8.26; Found % C, 49.67; H, 4.47; N, 8.22. ^1H and ^{13}C NMR spectra of **4g** are reported at S-16.

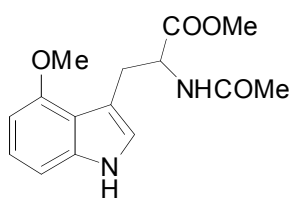
5-Fluoro-*N*-acetyltryptophan methyl ester (4h): Prepared according to **General**



Procedure. The compound **4h** was isolated as a light pink solid (80% yield) after flash chromatography on silica gel (ethyl acetate). Mp: 173 – 174 °C. TLC (EtOAc 100%), R_f : 0.49 (UV, CAM); ^1H NMR (200 MHz, DMSO- d_6): δ 1.81 (s, 3H, NHCOCH₃), 2.92 – 3.15 (m, 2H, CH₂), 3.57 (s, 3H, COOCH₃), 4.42 – 4.53 (m,

1H, CH), 6.91 (dt, 1H, J_1 = 9.3 Hz, J_2 = 2.5 Hz, ArH), 7.20 – 7.36 (m, 3H, ArH), 8.35 (br d, 1H, J = 7.6 Hz, NHCOCH₃), 10.99 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO- d_6): δ 172.5, 169.3, 156.7 (d, 1C, J = 230 Hz) 132.7, 127.3 (d, 1C, J = 10.0 Hz), 125.8, 112.3 (d, 1C, J = 10.0 Hz), 109.9 (d, 1C, J = 4.5 Hz), 109.1 (d, 1C, J = 26.0 Hz), 102.8 (d, 1C, J = 26.0 Hz), 53.0, 51.7, 27.0, 22.3; FTIR (Nujol) $\nu_{\text{max}}/\text{cm}^{-1}$: 3402 (br), 2916 (m), 1735 (s), 1718 (m), 1655 (s), 1530 (s); MS (ESI) : 279 (M+1); Anal. Calcd. for C₁₄H₁₅FN₂O₃ % C, 60.42; H, 5.43; N, 10.07; Found % C, 60.48; H, 5.39; N, 10.01. ^1H and ^{13}C NMR spectra of **4h** are reported at S-17.

4-Methoxy-*N*-acetyltryptophan methyl ester (4i): Prepared according to **General**



4i

Procedure except that 1 mmol of 4-methoxy-indole was employed.

The compound **4i** was isolated as a white solid (63% yield) after flash chromatography on silica gel (ethyl acetate). Mp: 170 – 171

°C; TLC (EtOAc 100%), R_f : 0.45 (UV, CAM); ^1H NMR (200 MHz, CDCl_3): δ 1.87 (s, 3H, NHCOCH_3), 3.25 (m, 2H, CH_2), 3.73 (s, 3H,

COOCH_3), 4.00 (s, 3H, OCH_3), 4.65 – 4.75 (m, 1H, CH), 6.54 (d, 1H, $J = 7.6$ Hz, ArH), 6.85

(br s, 1H, NHCOCH_3), 6.89 (s, 1H, ArH), 7.00 (d, 1H, $J = 8.0$ Hz, ArH), 7.11 (dd, 1H, $J_1 =$

8.0 Hz, $J_2 = 7.6$ Hz, ArH), 8.44 (br s, 1H, NH); ^{13}C NMR (50 MHz, CDCl_3) δ : 172.7, 170.0,

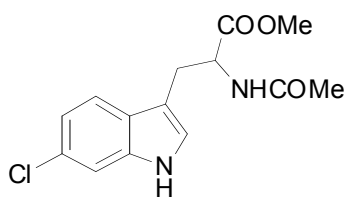
153.6, 137.8, 122.8, 122.0, 117.3, 110.4, 105.2, 99.6, 55.1, 54.9, 52.0, 28.3, 22.9; FTIR

(CH_2Cl_2) $\nu_{\text{max}}/\text{cm}^{-1}$: 3355 (br), 2926 (m), 1735 (s), 1654 (s), 1541 (s); MS (ESI) : 291

($\text{M}+1$); Anal. Calcd. % C, 62.06; H, 6.25; N, 9.65; Found for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$ % C, 62.12; H,

6.28; N, 9.70. ^1H and ^{13}C NMR spectra of **4i** are reported at S-18.

6-Chloro-*N*-acetyltryptophan methyl ester (4j): Prepared according to **General**



4j

Procedure. The compound **4j** was isolated as a light orange

solid (57% yield) after flash chromatography on silica gel (ethyl acetate). Mp: 149 – 150 °C; TLC (EtOAc 100%), R_f : 0.47 (UV,

CAM); ^1H NMR (200 MHz, CDCl_3): δ 1.97 (s, 3H, NHCOCH_3),

3.30 (dd, 2H, $J_1 = 5.3$ Hz, $J_2 = 3.0$ Hz, CH_2), 3.70 (s, 3H,

COOCH_3), 4.89 – 4.99 (m, 1H, CH), 5.98 (br d, 1H, $J = 7.6$ Hz, NHCOCH_3), 6.97 (s, 1H,

ArH), 7.09 (d, 1H, $J = 8.5$ Hz, ArH), 7.36 (s, 1H, ArH), 7.44 (d, 1H, $J = 8.5$ Hz, ArH), 8.24

(br s, 1H, NH); ^{13}C NMR (50 MHz, CDCl_3): δ 172.3, 169.6, 136.4, 128.2, 126.4, 123.2,

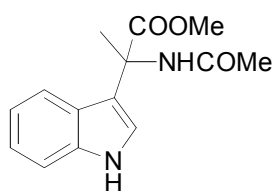
120.4, 119.4, 111.2, 110.5, 53.0, 52.3, 27.6, 23.1; FTIR (CH_2Cl_2) $\nu_{\text{max}}/\text{cm}^{-1}$: 3406 (br),

2924 (m), 1731 (s), 1654 (s); MS (ESI) : 295 ($\text{M}+1$); Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$ % C,

57.05; H, 5.13; N, 9.50; Found % C, 57.11; H, 5.12; N, 9.53. ^1H and ^{13}C NMR spectra of **4j**

are reported at S-19.

N-Acetyl- α -(3-indolyl)alanine methyl ester (3a): Prepared according to **General**

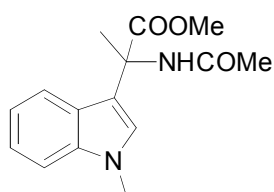


3a

Procedure. The compound **3a** was isolated as a white solid (yield depends of Lewis acid, see Table 1, S-7) after flash chromatography on silica gel (ethyl acetate). Spectroscopic data obtained were in accordance with those reported in: de la Hoz A., Díaz-Ortiz A., Gómez M. V., Mayoral J. A., Moreno A., Sánchez-Migallón A. M.,

Vázquez E. *Tetrahedron* **2001**, *25*, 5421. ^1H NMR spectra of **3a** is reported at S-20.

N-Acetyl- α -(1-methyl-3-indolyl)alanine methyl ester (3b): Prepared according to

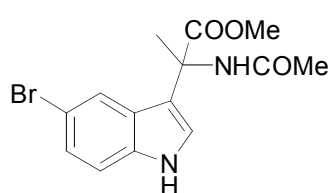


3b

General Procedure. The compound **3b** was isolated as a colorless oil (50% yield) after flash chromatography on silica gel (ethyl acetate). TLC (EtOAc 100%), R_f : 0.56 (UV, CAM); ^1H NMR (200 MHz, CDCl_3): δ 2.00 (s, 3H), 2.12 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 6.60 (br s, 1H), 7.11-7.27 (m, 4H, ArH), 7.77-7.82 (m, 1H, ArH); ^{13}C

NMR (50 MHz, CDCl_3) δ : 173.2, 169.1, 137.4, 127.5, 125.0, 121.9, 120.1, 119.7, 113.9, 109.7, 58.5, 52.8, 32.9, 23.6, 22.3; FTIR (CH_2Cl_2) $\nu_{\text{max}}/\text{cm}^{-1}$: 3289 (br), 2960 (m), 1745 (s), 1665 (s), 1541 (s); MS (ESI) : 275 (M+1); Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ % C, 65.68; H, 6.61; N, 10.21; Found % C, 65.61; H, 6.62; N, 10.31. ^1H and ^{13}C NMR spectra of **3b** are reported at 21.

N-Acetyl- α -(5-bromo-3-indolyl)alanine methyl ester (3c): Prepared according to

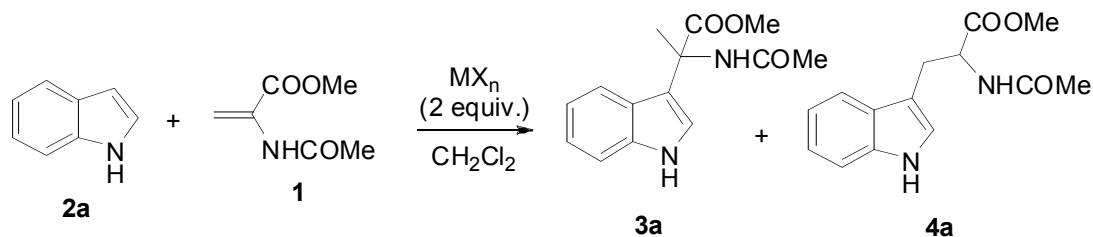


3c

General Procedure. The compound **3c** was isolated as a colorless oil (61% yield) after flash chromatography on silica gel (ethyl acetate). TLC (EtOAc 100%), R_f : 0.60 (UV, CAM); ^1H NMR (200 MHz, CDCl_3): δ 2.05 (s, 3H), 2.09 (s, 3H), 3.68 (s, 3H), 6.96-6.98 (br m, 2H), 7.11 (dd, 1H, $J_1 = 0.5$ Hz, $J_2 = 8.6$ Hz, ArH), 7.21

(dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 8.6$ Hz, ArH), 7.78 (d, 1H, $J = 1.8$ Hz, ArH), 8.98 (br s, 1H, NH); ^{13}C NMR (50 MHz, CDCl_3) δ : 173.7, 169.4, 135.3, 126.2, 124.9, 124.7, 121.9, 114.4, 113.2, 113.1, 58.4, 53.2, 24.0, 22.3; FTIR (Nujol) $\nu_{\text{max}}/\text{cm}^{-1}$: 3325 (br), 2926 (m), 1732 (s), 1660 (s), 1535 (s); MS (ESI): 340 (M+1); Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{BrN}_2\text{O}_3$ % C, 49.57; H, 4.46; N, 8.26; Found % C, 49.63; H, 4.48; N, 8.23. ^1H and ^{13}C NMR spectra of **3c** are reported at 22.

III. Effect of Lewis Acids in the Friedel-Crafts reaction

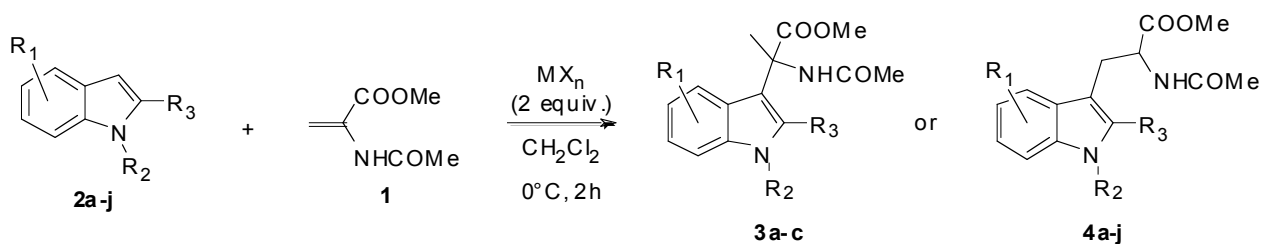


entry	MX _n	T (°C)	yield %	3a / 4a
1 ^a	EtAlCl ₂	0	10	0/100
2	EtAlCl ₂	0	75	0/100
3 ^{b,e}	EtAlCl ₂	0	58	0/100
4 ^b	EtAlCl ₂	83	50	0/100
5	BF ₃ •OEt ₂	0	NR ^c	-
6	GaCl ₃	rt	NR ^c	-
7 ^d	InCl ₃	rt	NR ^c	-
8	InCl ₃	0	NR ^c	-
9	LiClO ₄	rt	NR ^c	-
10	MgBr ₂	rt	NR ^c	-
11	Sc(OTf) ₃	rt	NR ^c	-
12 ^e	TiCl ₄	rt	30	0/100
13 ^f	ZrCl ₄	0	65	0/100
14 ^e	ReCl ₅	rt	55	100/0
15	IrCl ₄	rt	NR ^c	-
16 ^e	NaAuCl ₄ •2H ₂ O	rt	46	100/0
17	Cu(OTf) ₂	rt	NR ^c	-
18	Zn(OTf) ₂	rt	NR ^c	-
19 ^e	Bi(OTf) ₃	rt	62	100/0
20	CF ₃ SO ₃ H	0	NR ^c	-
21 ^g	HCl	0	NR ^c	-
22	Amberlyst [®]	0	NR ^c	-
23	Montmorillonite	0	NR ^c	-

^a 1 Equiv. of LA was used; ^b 1,2-dichloroethane was used as a solvent; ^c no reaction occurred; ^d H₂O/THF 9:1 mixture was used as a solvent; ^e the reaction was carried out for 4 h; ^f the reaction was carried out for 24 h; ^g HCl 4 M solution in dioxane was used.

Table1.

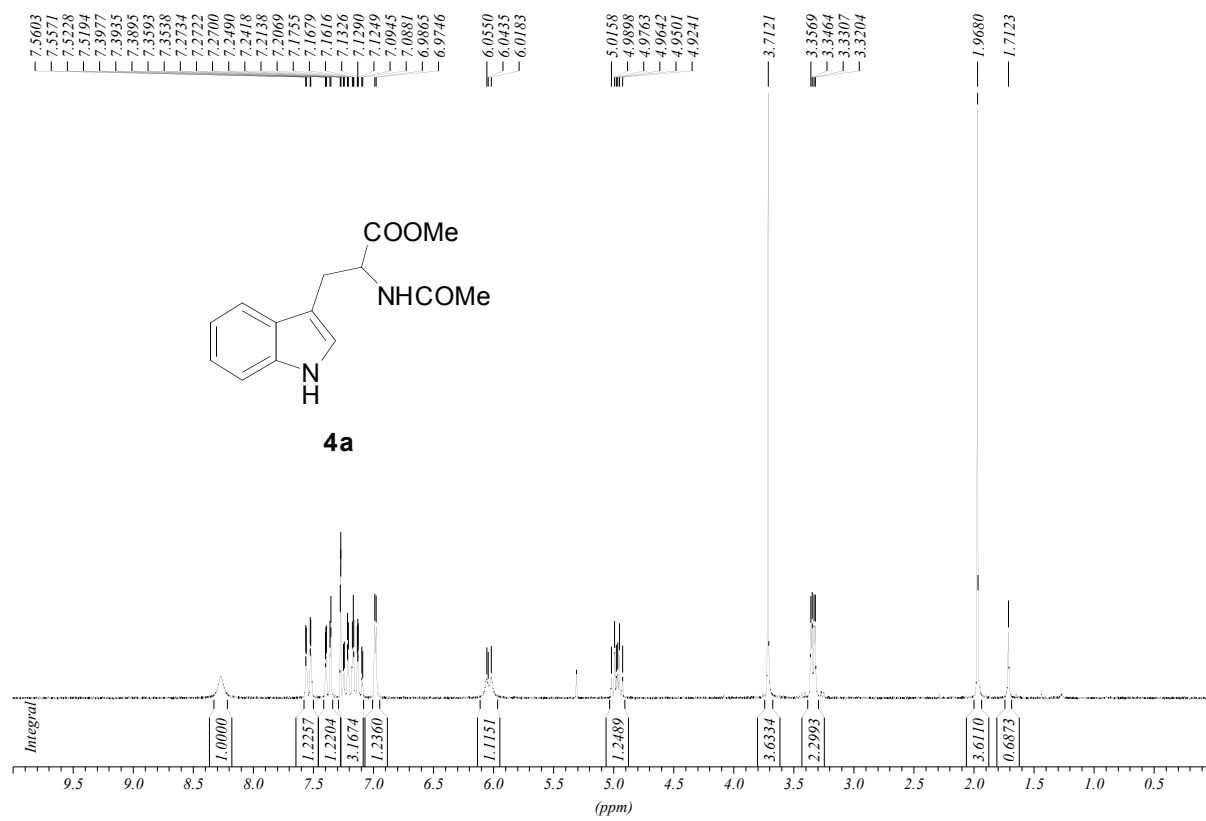
IV. Substrate scope for the Friedel-Crafts reaction

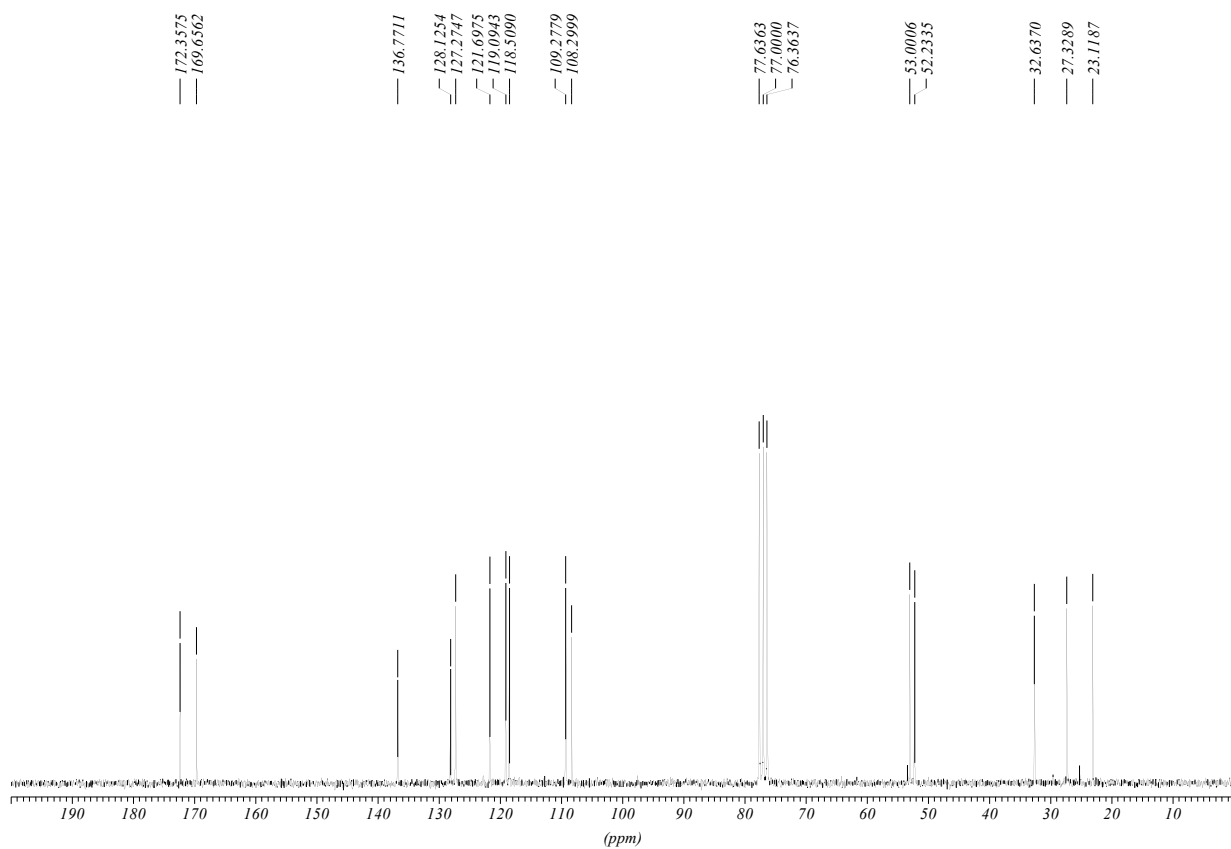
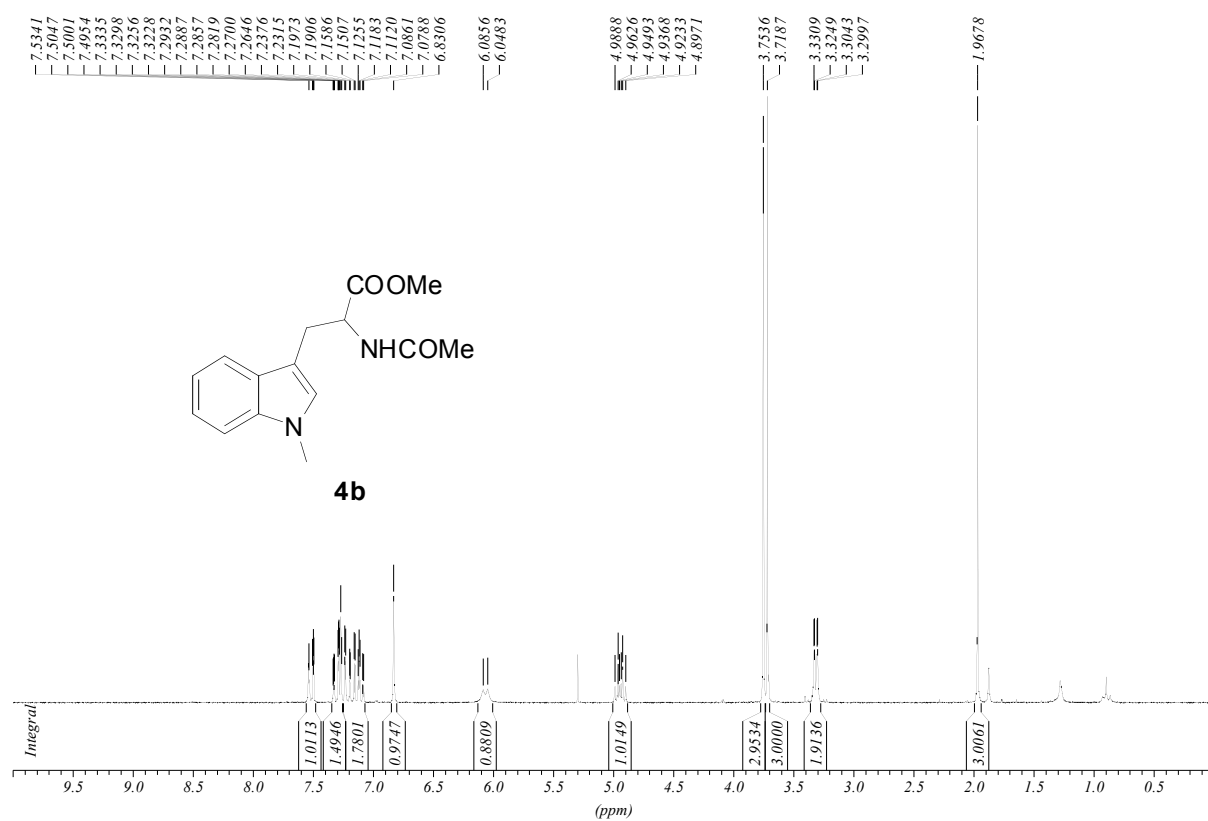


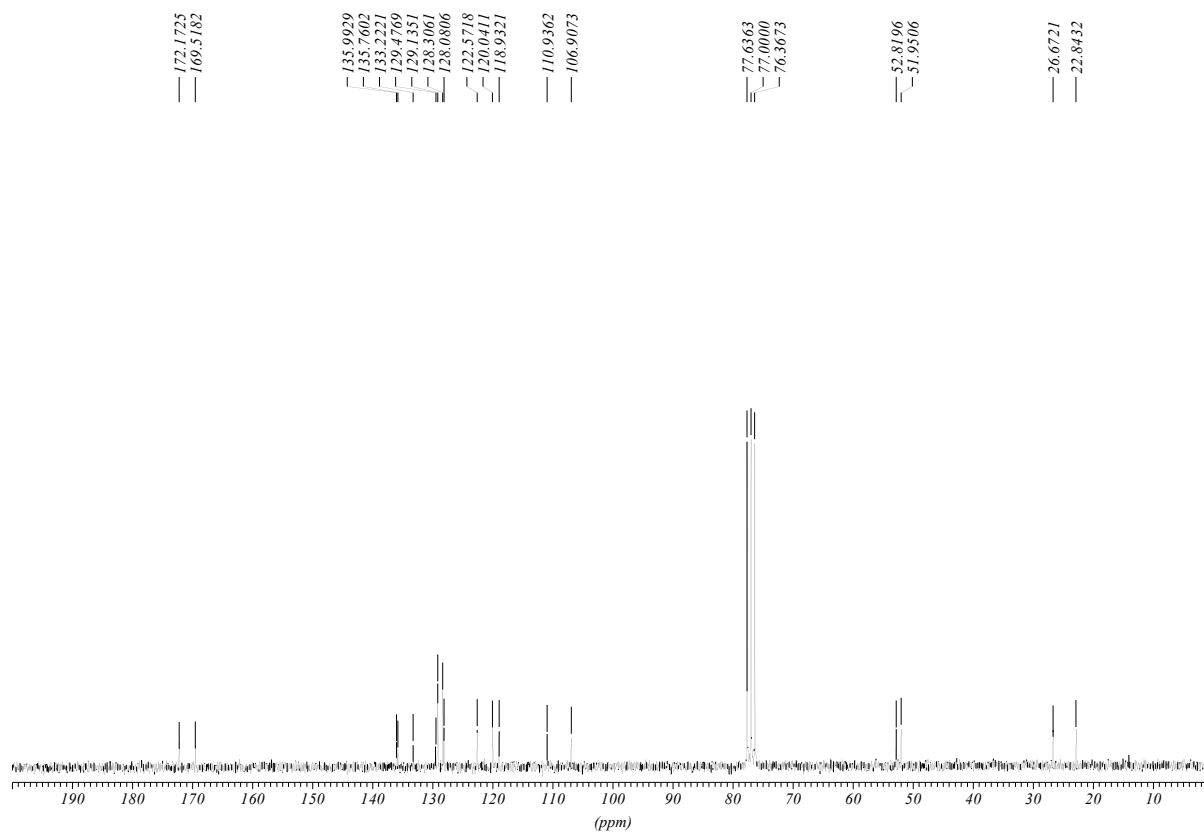
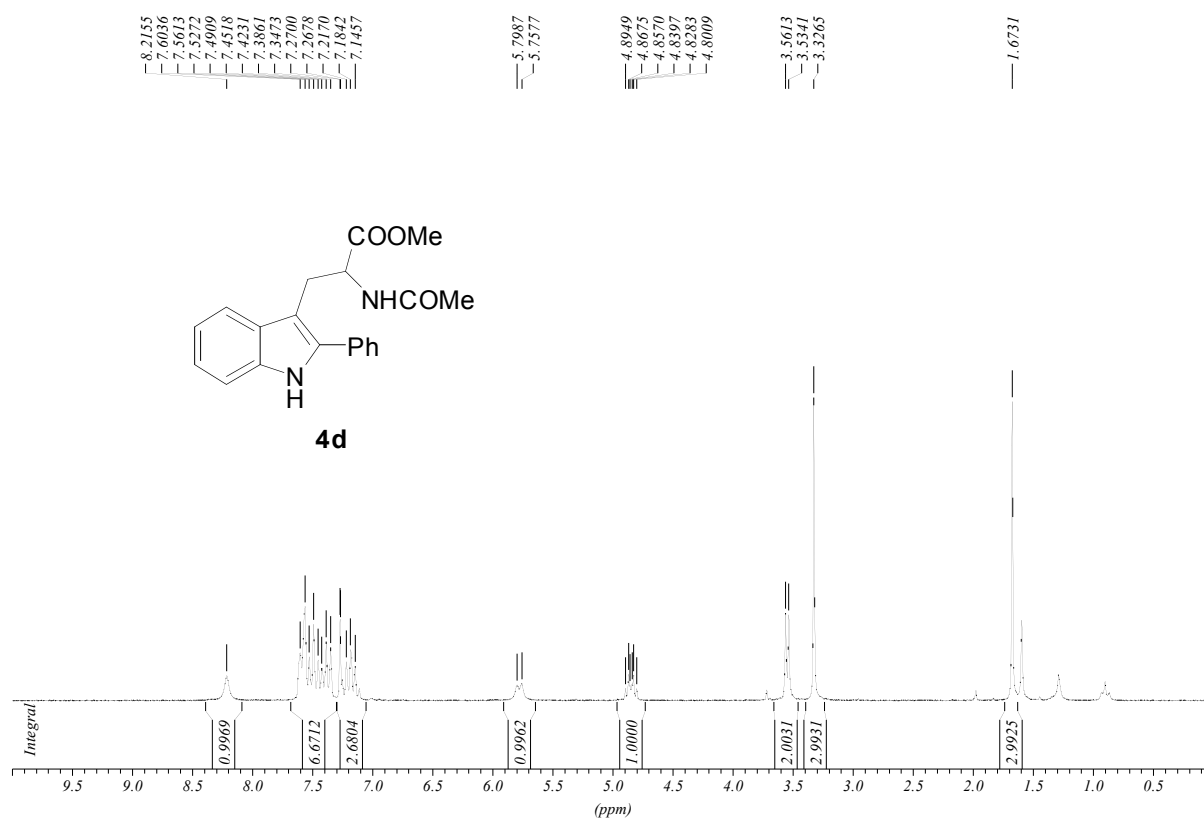
entry	Indole	MX_n	Product	yield %
1	Indole (2a)	EtAlCl_2	4a	75
2	<i>N</i> -Methylindole (2b)	EtAlCl_2	4b	60
3	2-Methylindole (2c)	EtAlCl_2	4c	66
4	2-Phenylindole (2d)	EtAlCl_2	4d	52
5	<i>N</i> -Methyl-2-methylindole (2e)	EtAlCl_2	4e	35
6	5-Methoxyindole (2f)	EtAlCl_2	4f	77
7	5-Bromoindole (2g)	EtAlCl_2	4g	65
8	5-Fluoroindole (2h)	EtAlCl_2	4h	80
9	4-Methoxyindole (2i)	EtAlCl_2	4i	63
10	6-Chloroindole (2j)	EtAlCl_2	4j	57
11	Indole (2a)	EtAlCl_2	3a	62
12	<i>N</i> -Methylindole (2b)	EtAlCl_2	3b	50
13	5-Bromoindole (2g)	EtAlCl_2	3c	61

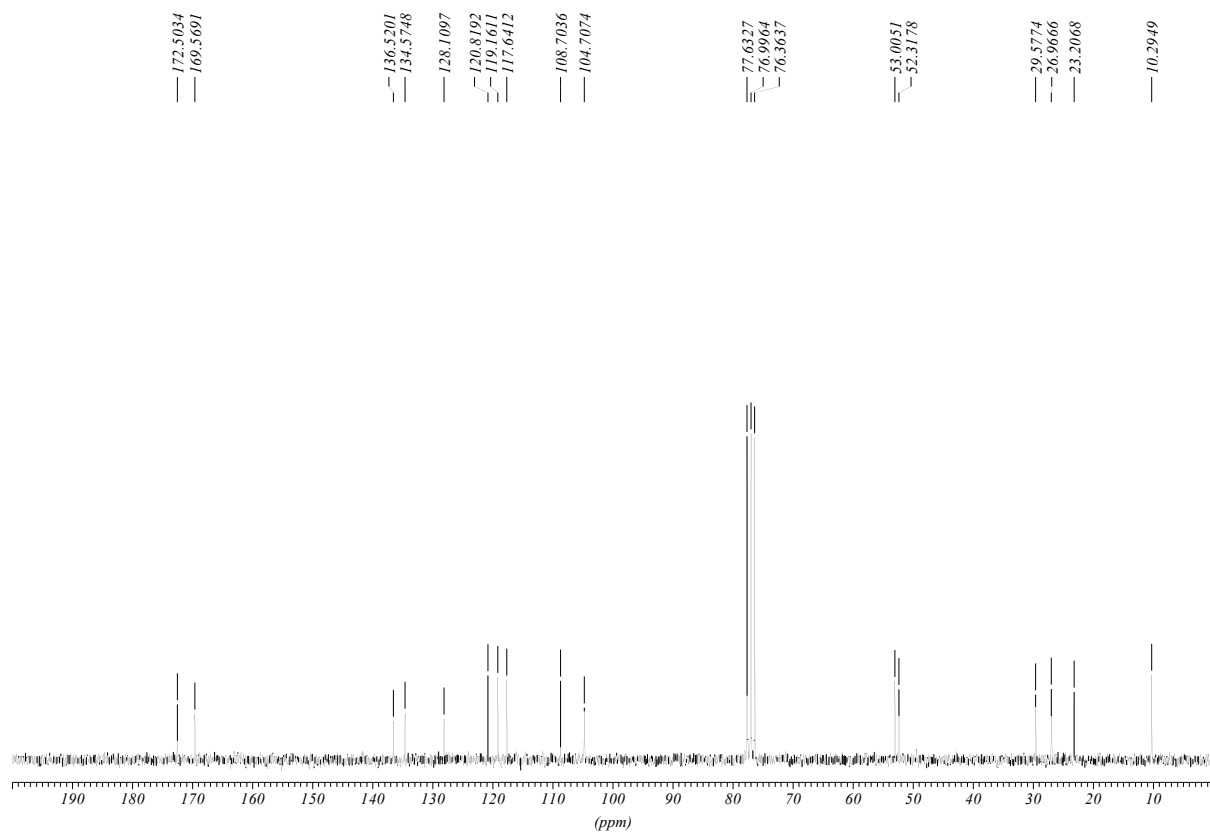
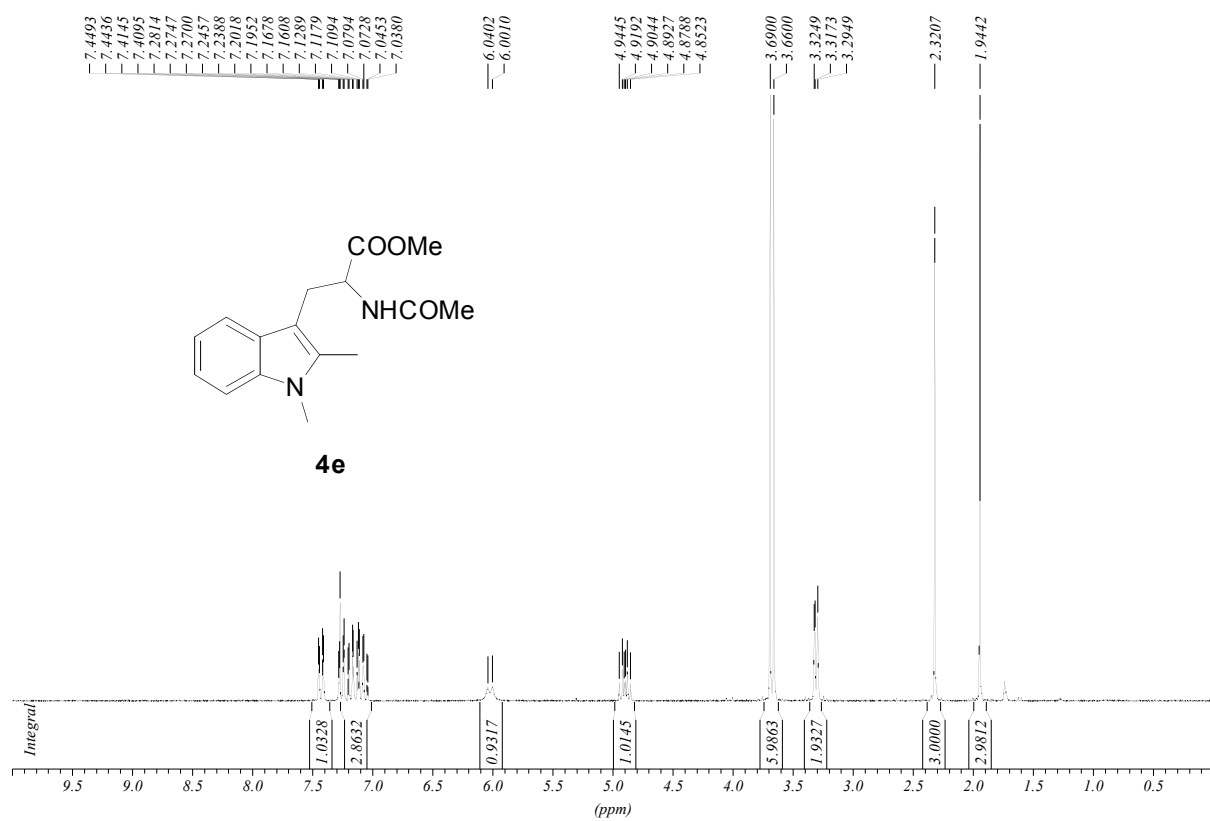
Table 2.

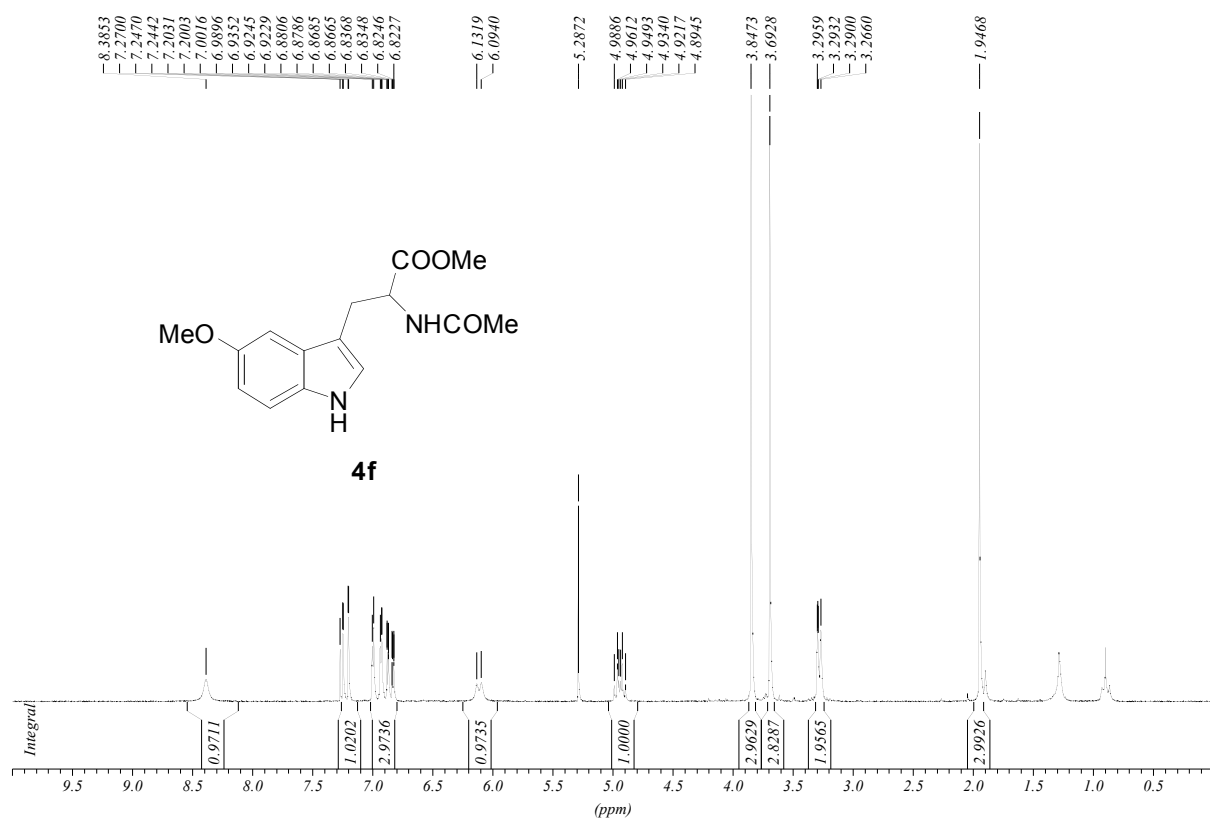
V. NMR spectra of the compounds

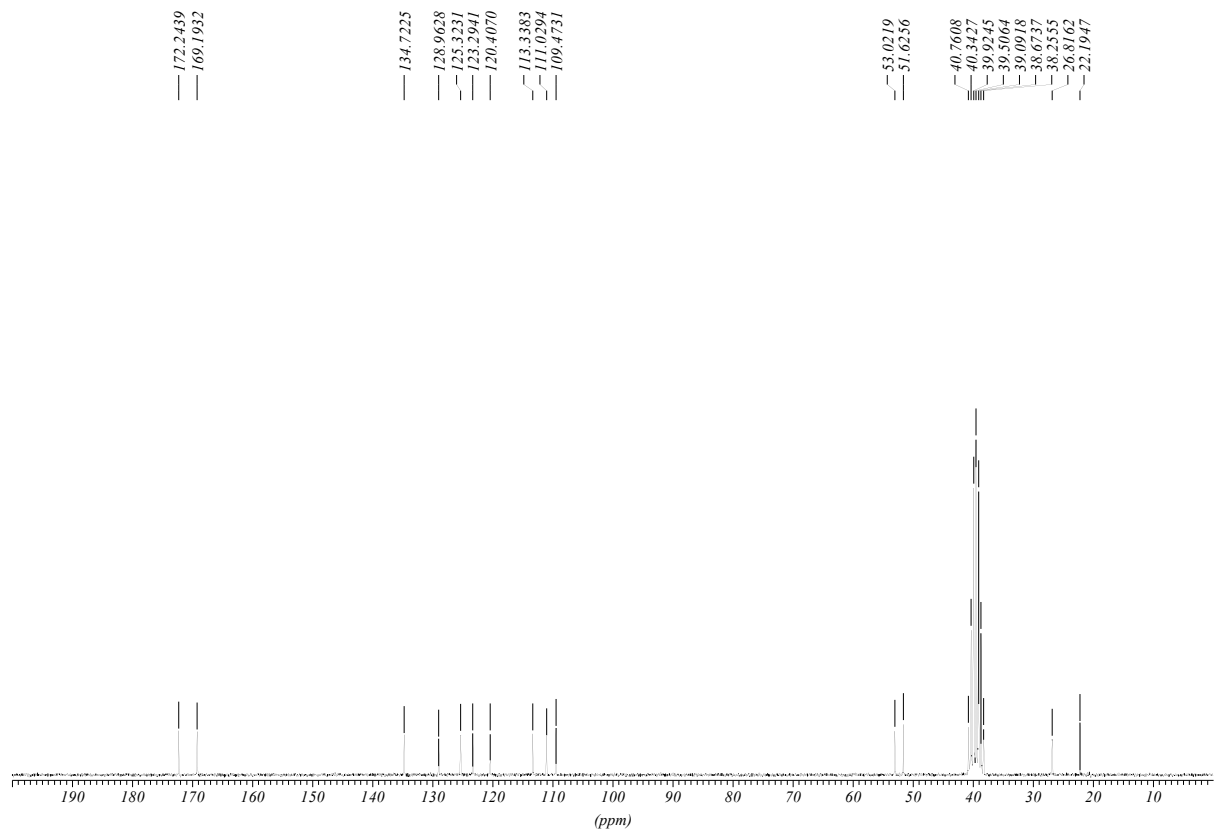
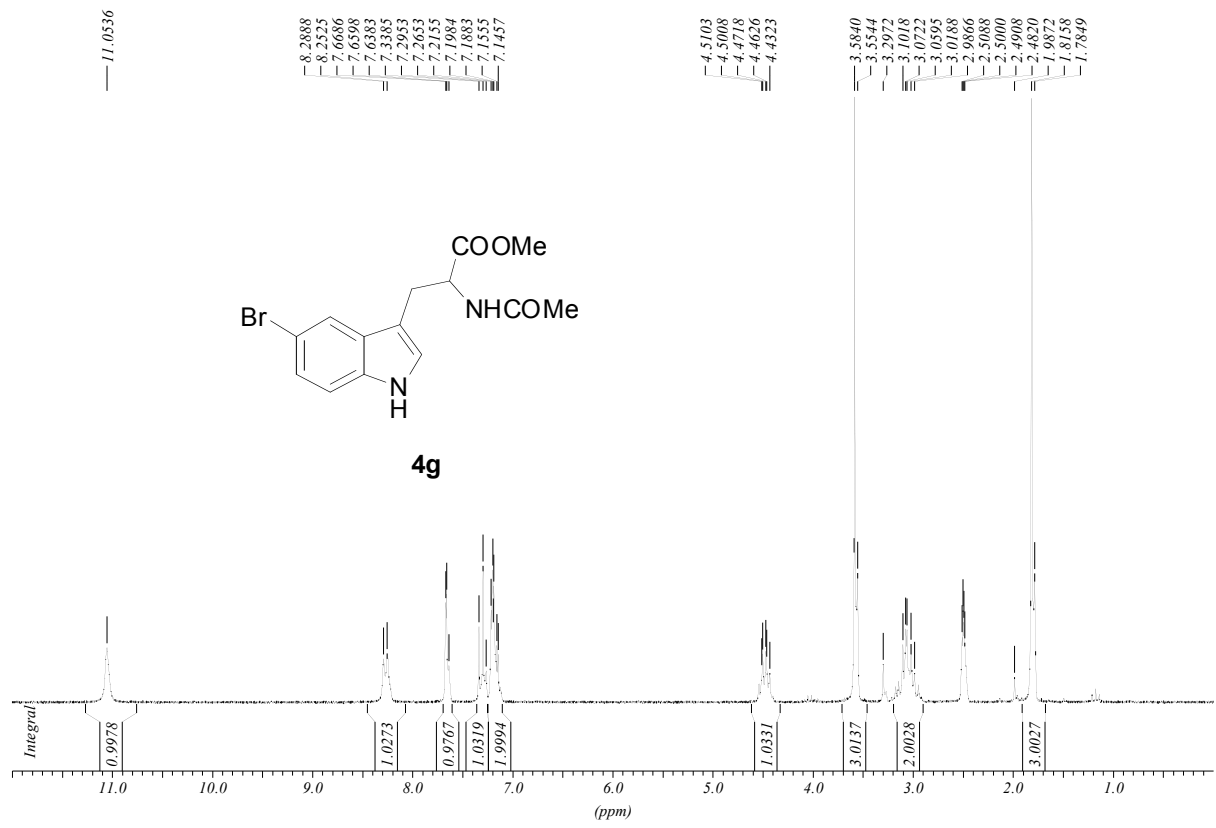


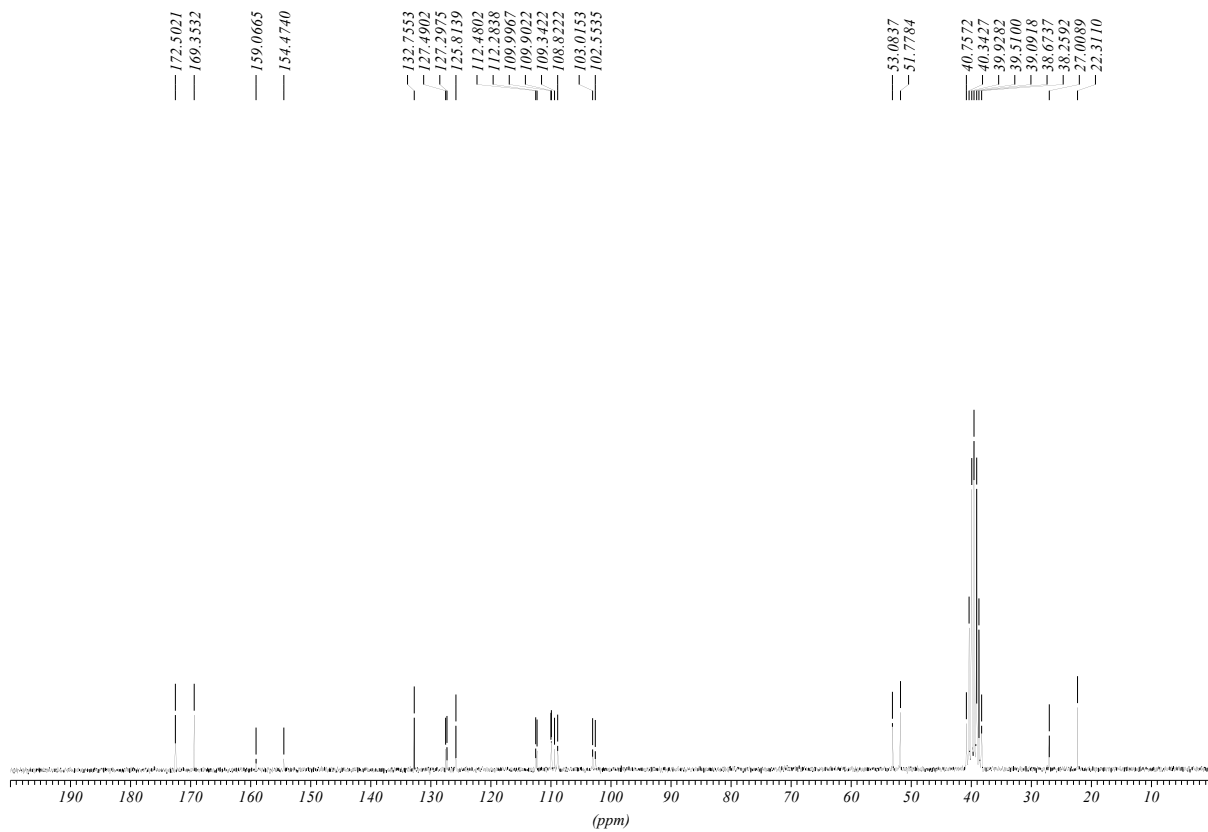
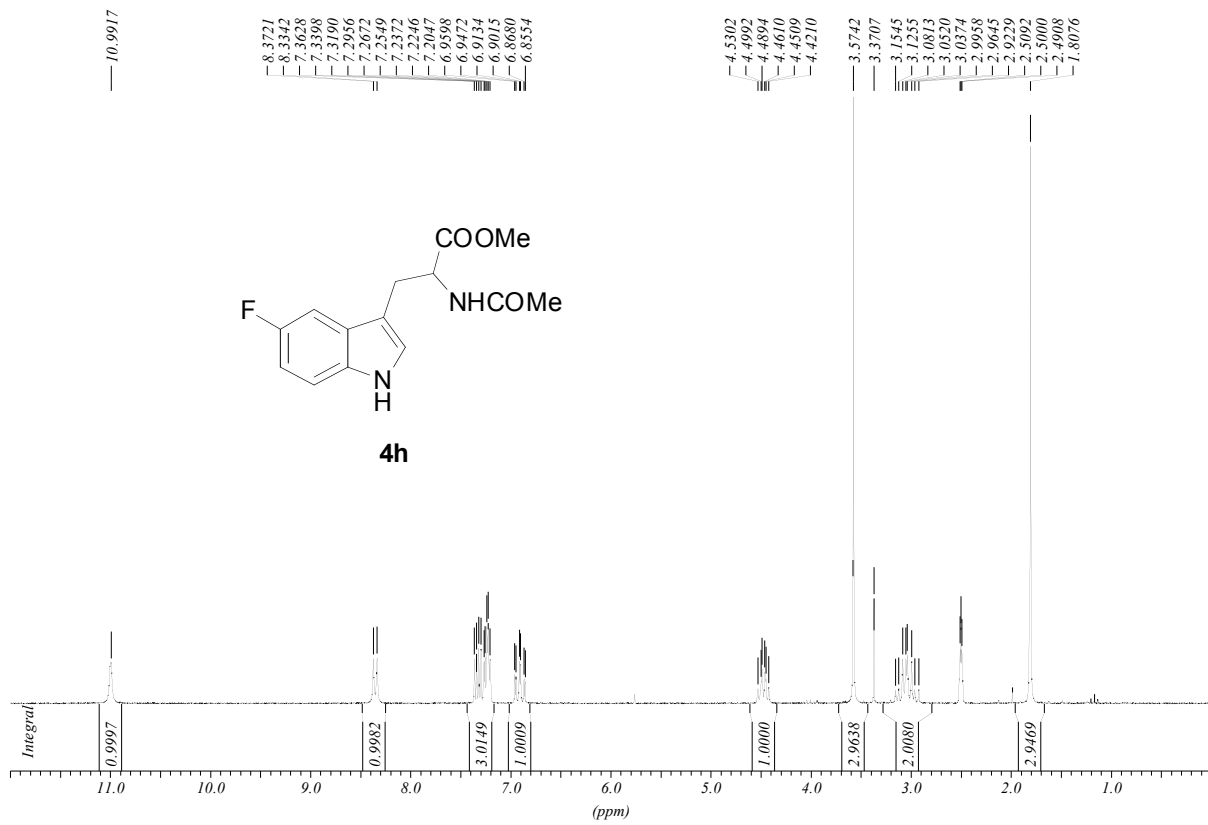


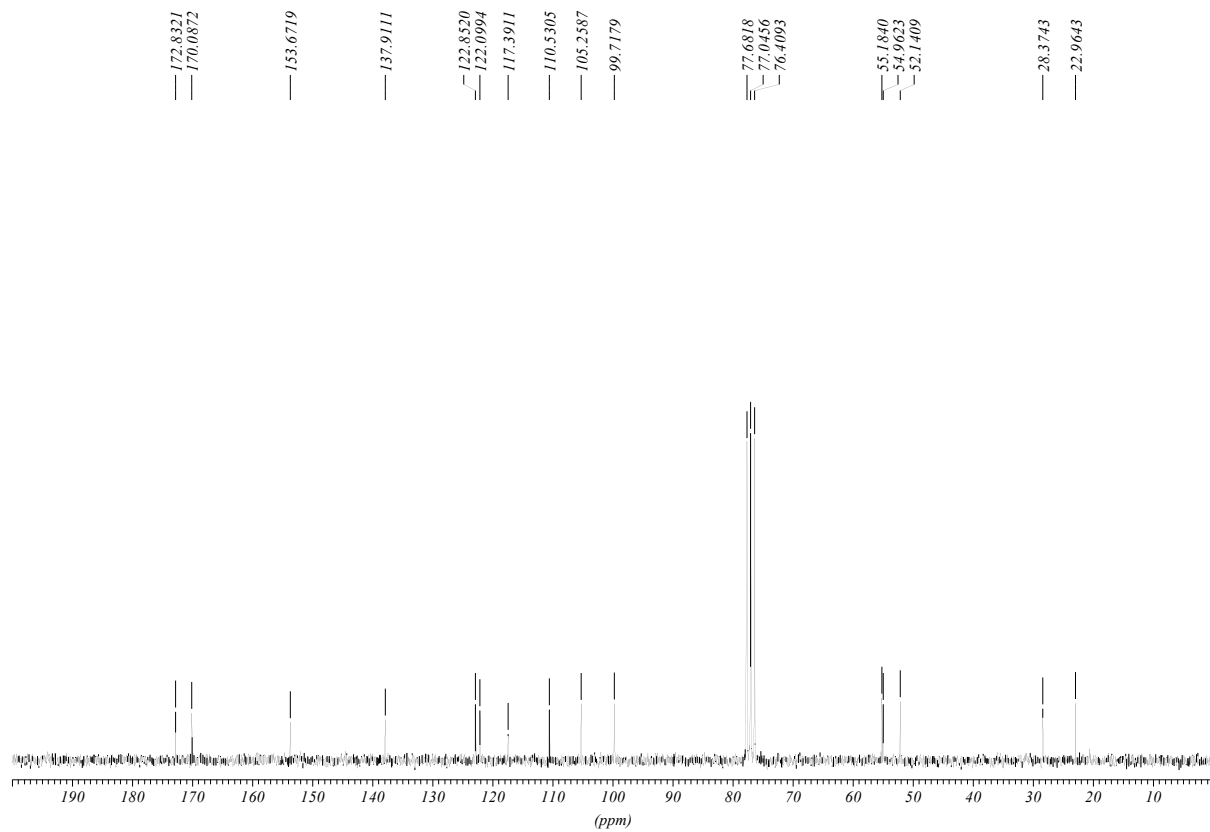
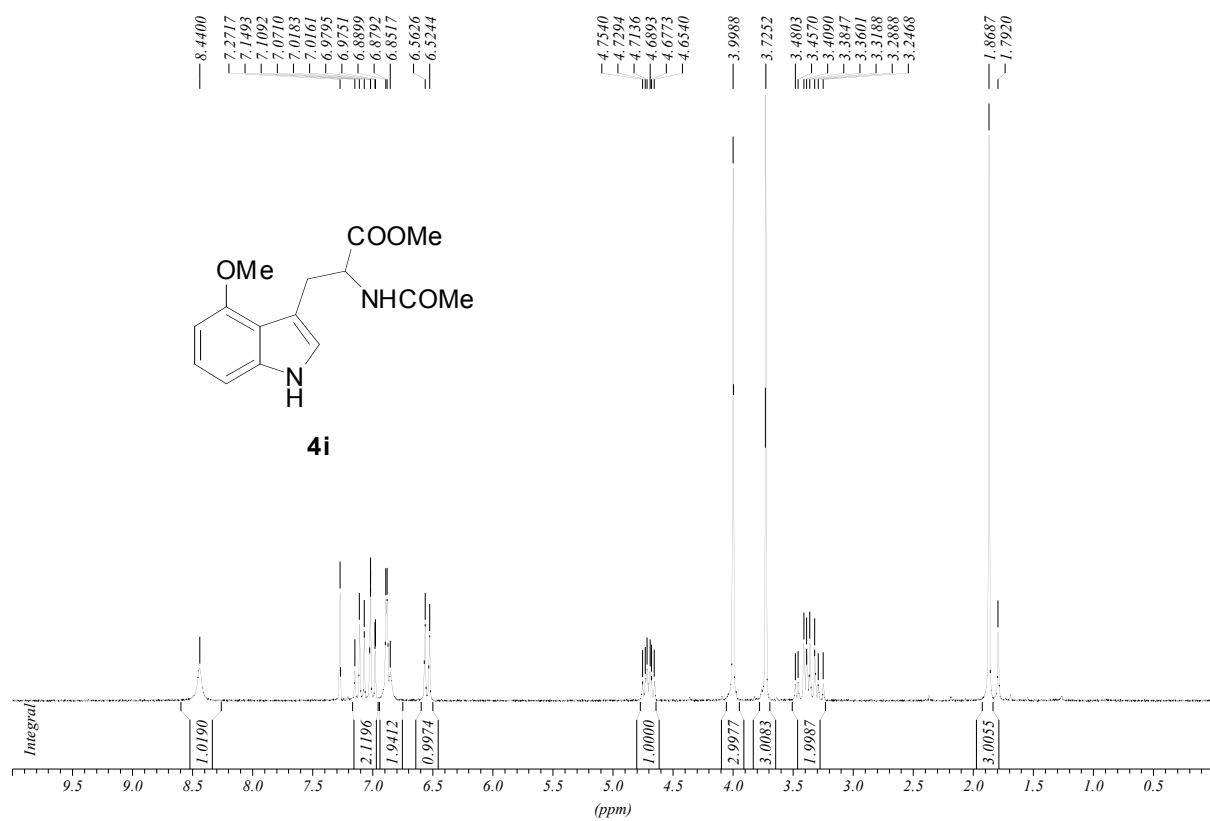


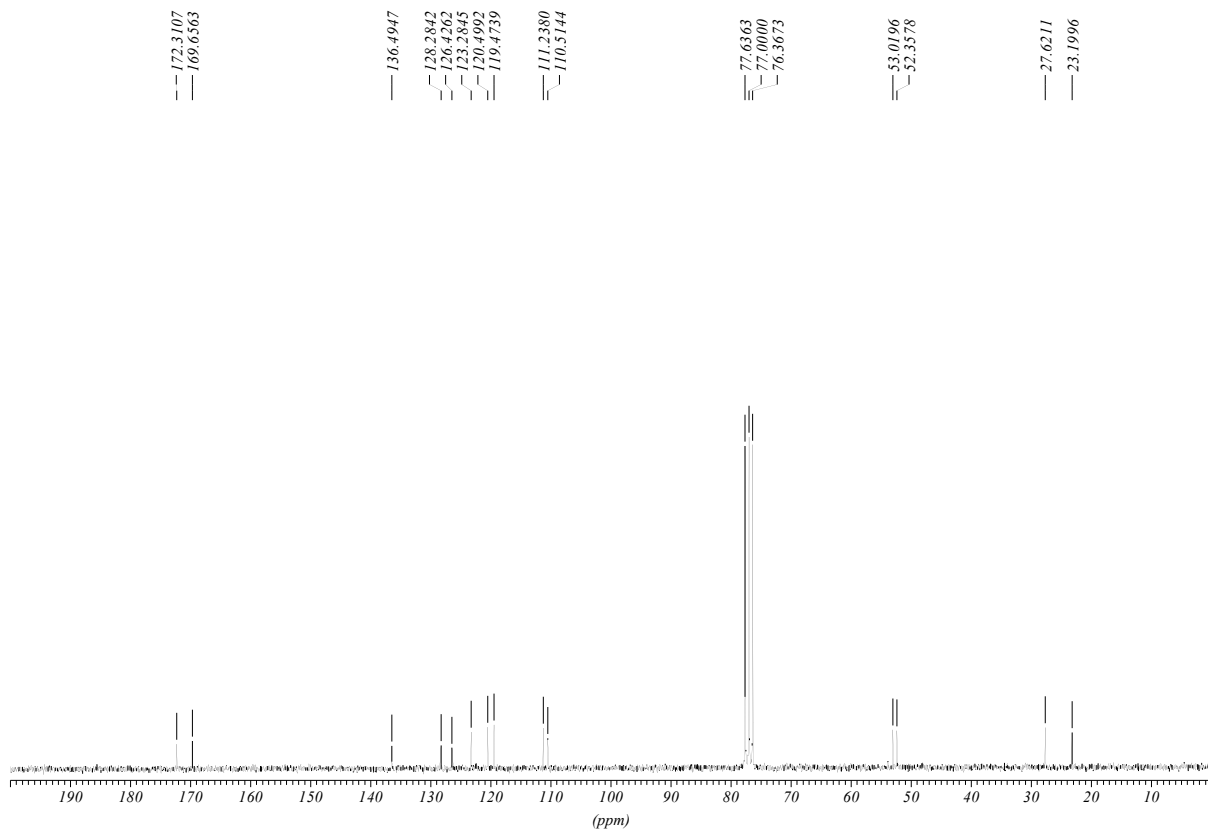
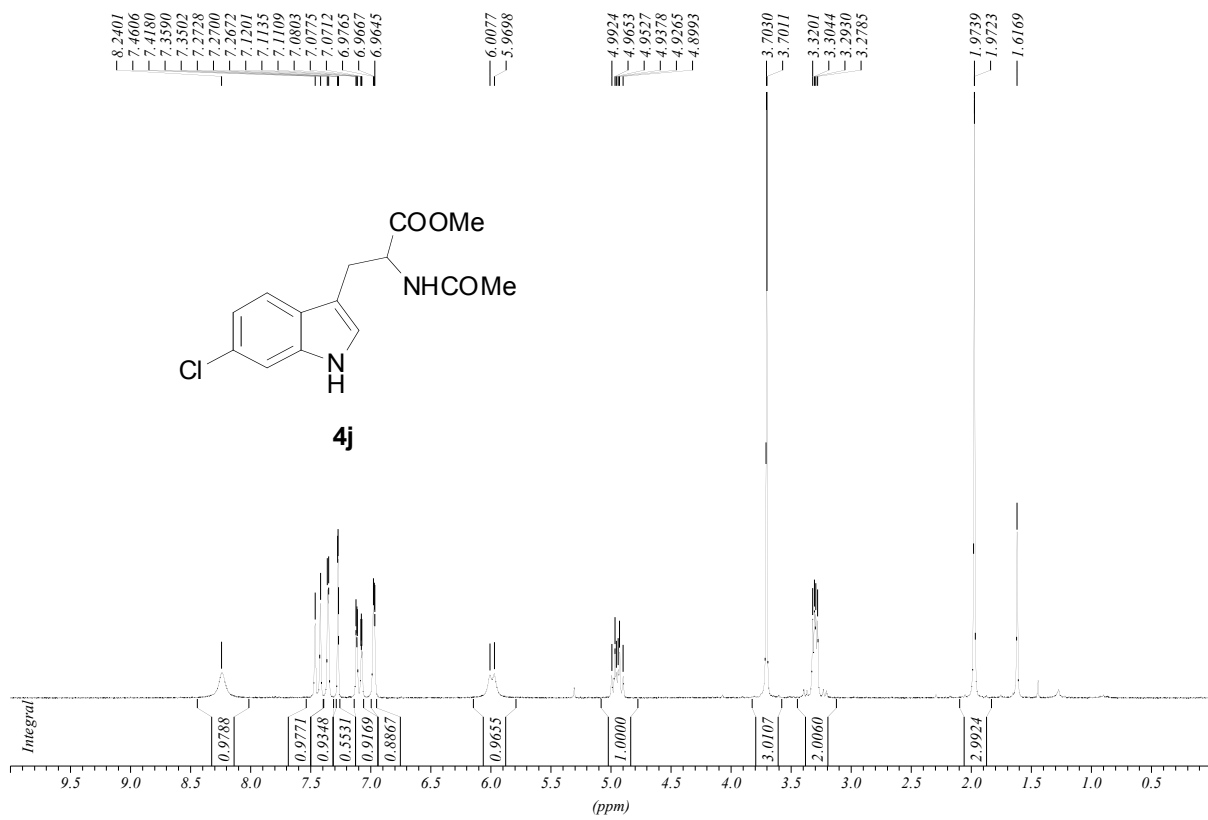


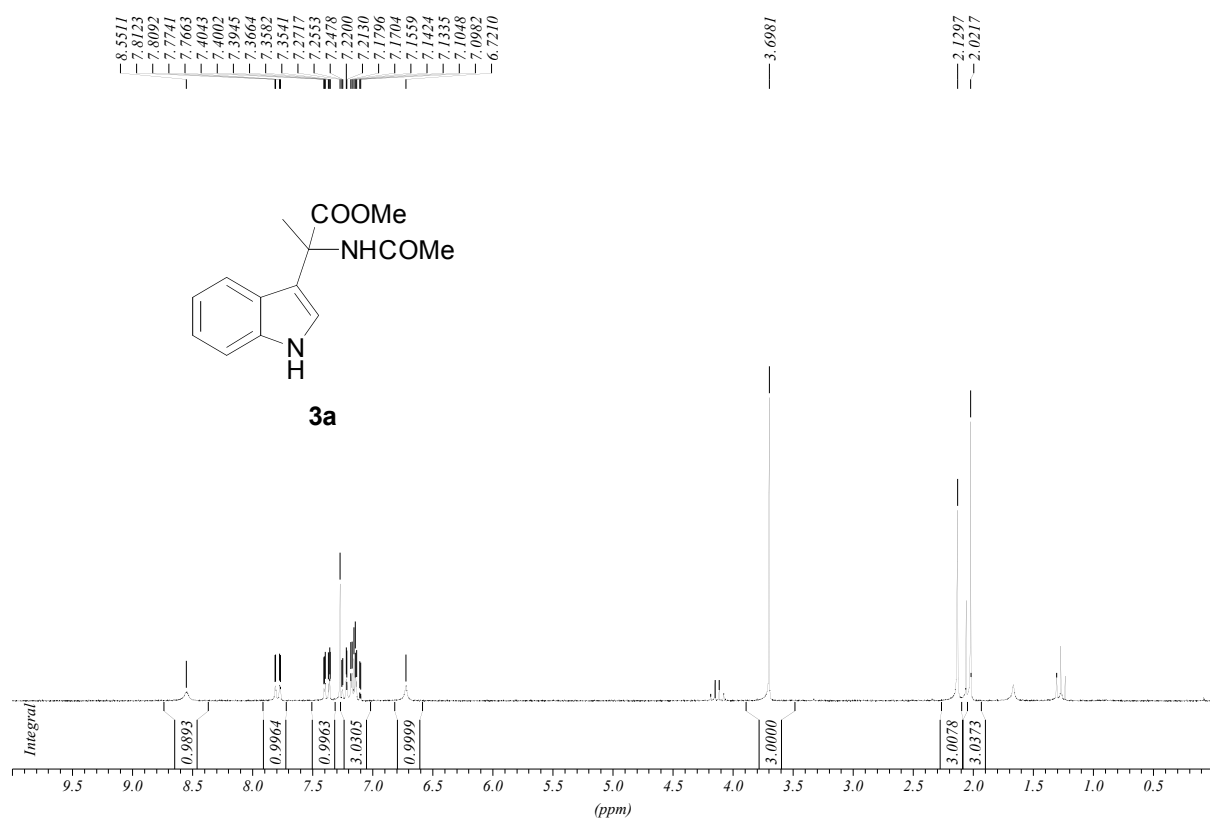


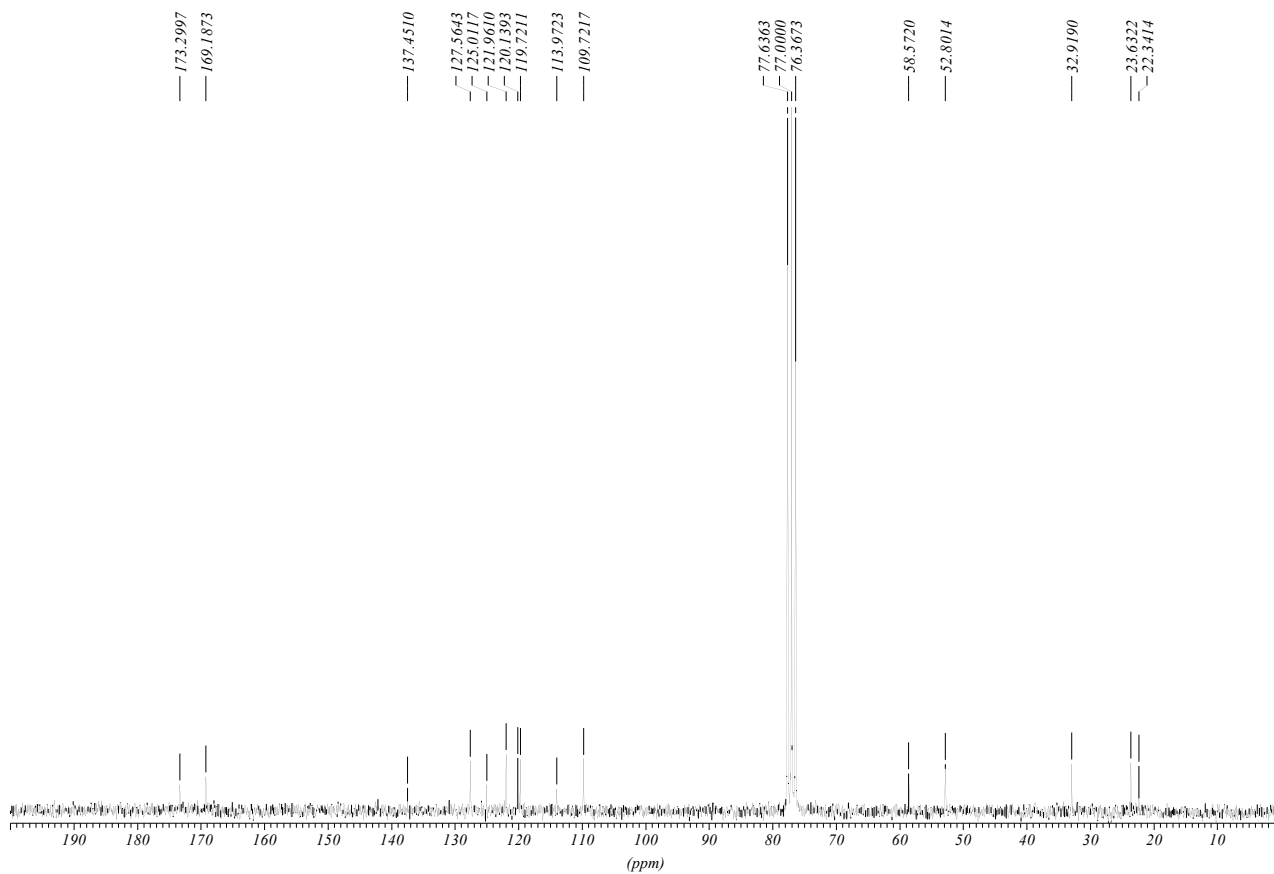
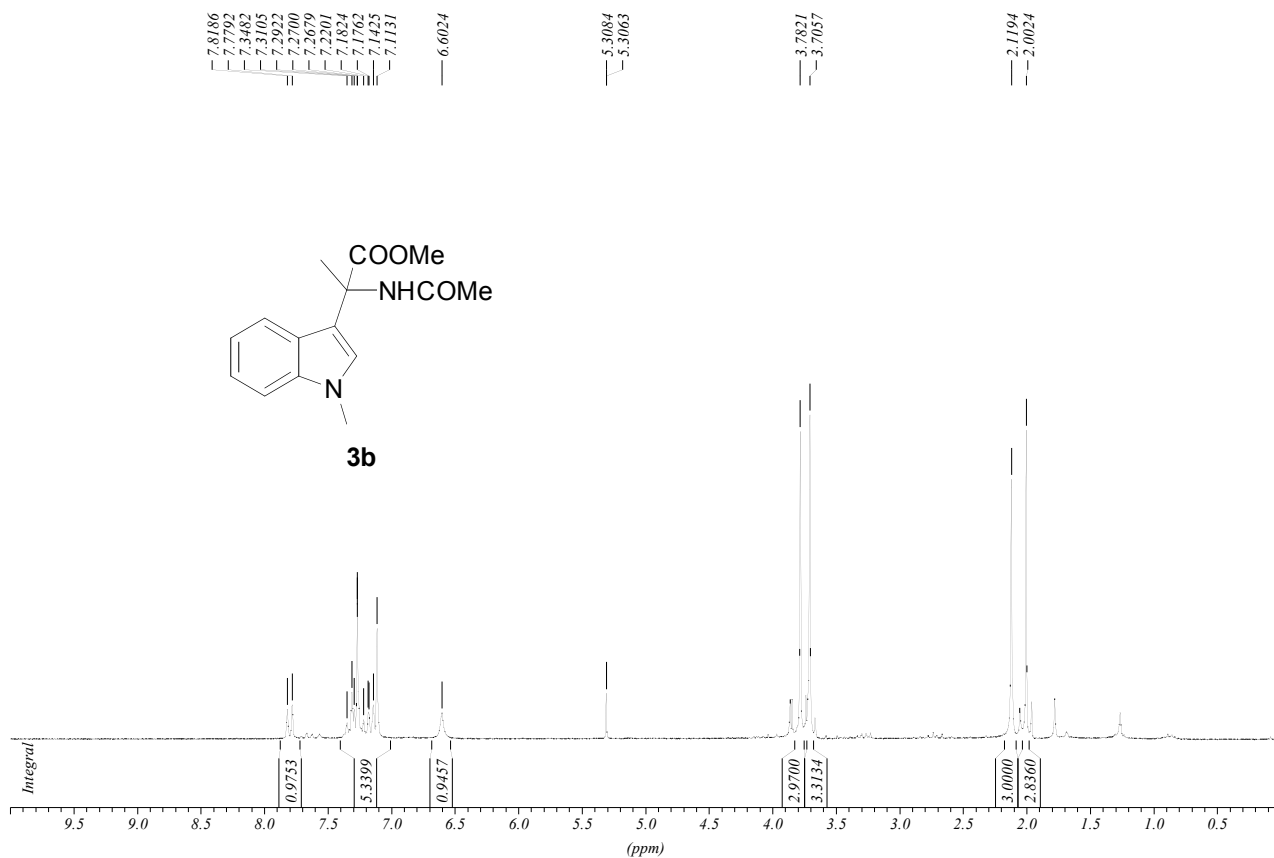


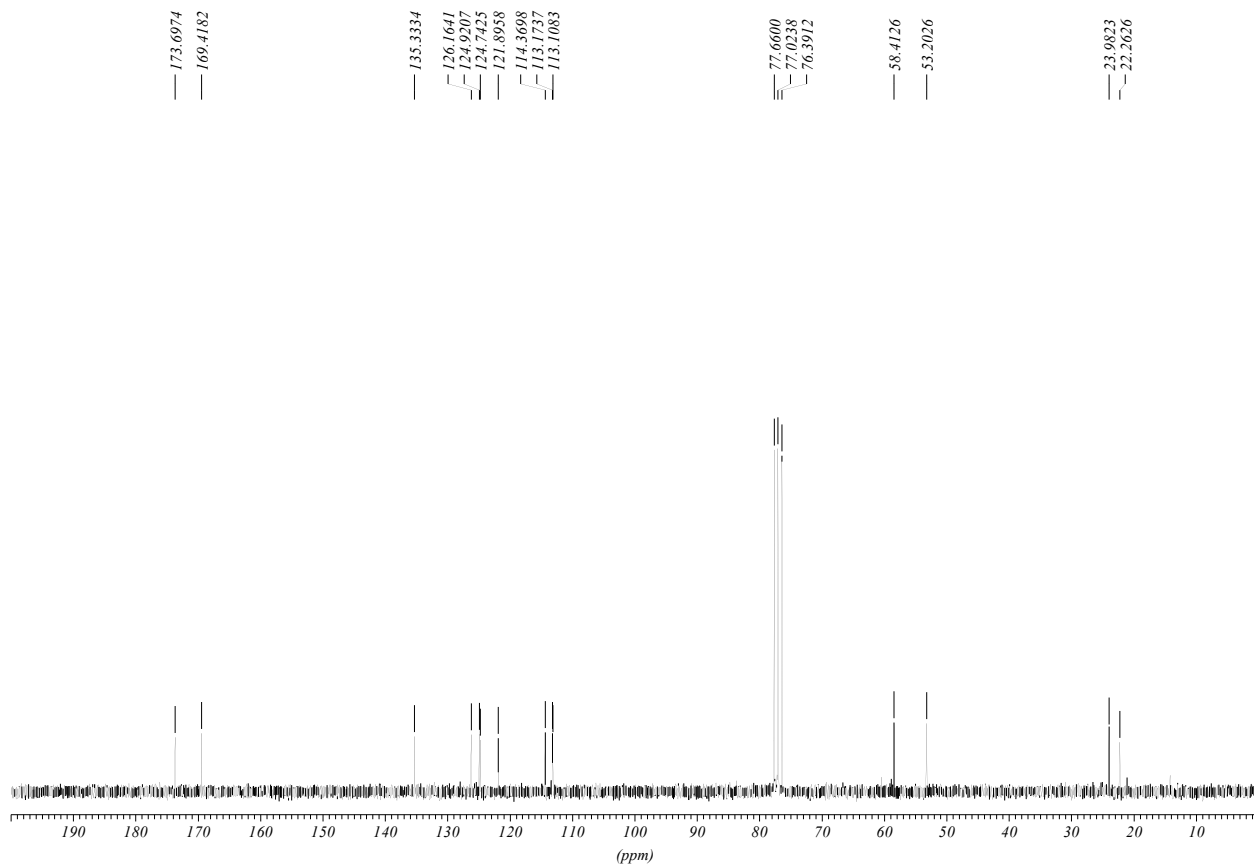
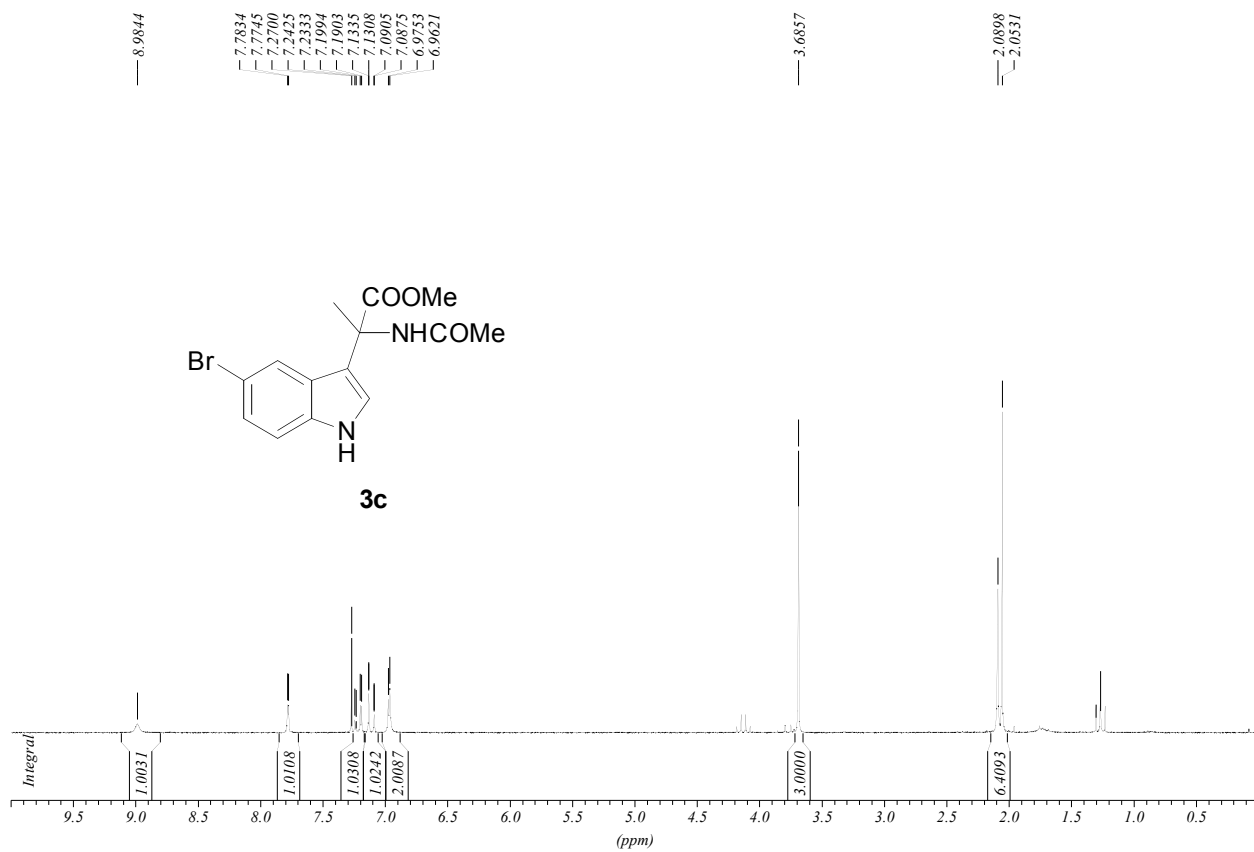




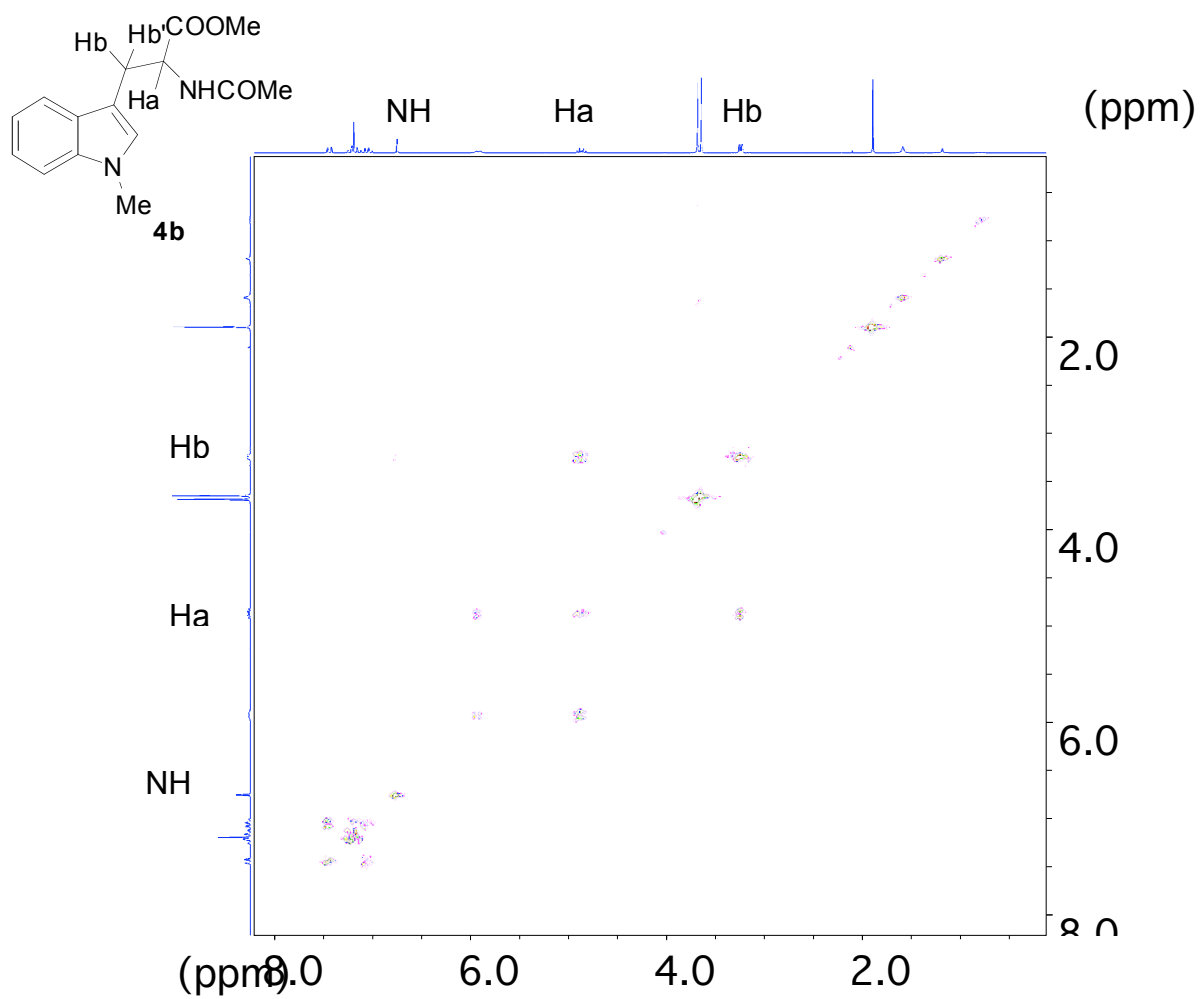








VI. COSY NMR spectra of the compound 4b in CDCl₃



All the other proton signals assignment were done based on this 2D-NMR spectra.

VIII. ^1H NMR titration of **1** with $\text{Bi}(\text{OTf})_3$ in CD_3CN

