Asymmetric direct α-alkylation of 2-oxindoles with Michlers Hydrol catalyzed by bis-cinchona alkaloid/Brønsted acid via S_N1-type pathway

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Supporting information

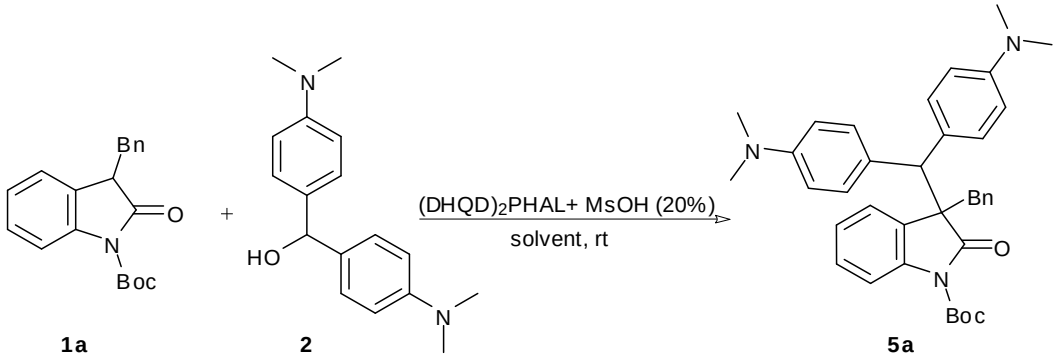
Contents

1. General methods

Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All reactions were carried out directly in air atmosphere, unless otherwise noted. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s= singlet, d= doublet, t= triplet, q= quartet, h= heptet, m= multiplet, br= broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). IR spectra were recorded on a Bruker tensor 27 infrared spectrometer. Melting points were measured on Beijing Tech X-4 apparatus without correction. Mass spectra were obtained using electrospray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length and are reported as follows: $[\alpha]_D^{rt}$ (c in g per 100 mL of solvent). HPLC analysis was performed using ChiralPak columns purchased. Column chromatography was performed using silica gel (200-300 mesh). TLC was performed on glass-backed silica plates.

2. Experimental section

2.1 Solvent screening

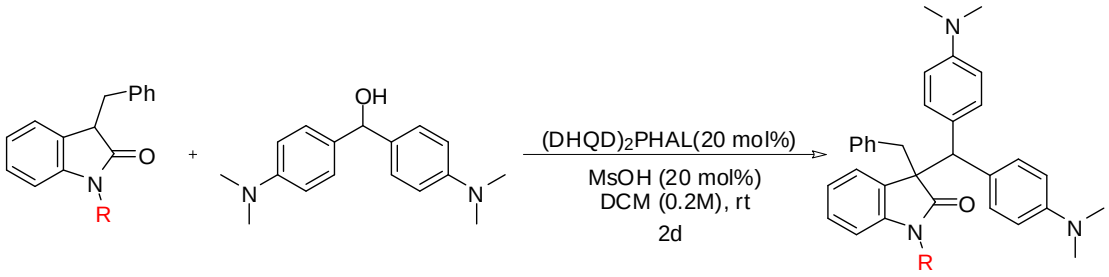


1a **2** **5a**

Entry[a]	Solvent	Ee (%)[b]
1	CCl_4	-14[c]
2	$CHCl_3$	73
3	EA	58
4	CH_3COCH_3	75
5	THF	69
6	CH_3CN	68
7	DMF	52
8	H_2O	37
9[d]	DCM	74
10[e]	DCM	75

[a] Reaction performed at a 0.11 mmol scale **1a** with 0.1 mmol of **2**, 20 mol % of **3b** in solvent (0.2M) for 2d. [b] Determined by chiral HPLC analysis. [c] The opposite enantiomer was obtained. [d] 0.1 mol/L, yield 76%. [e] 0.5 mol/L, yield 59%.

2.2 Effect of N-substituent of oxindoles



R = H, yield 65%, ee rac

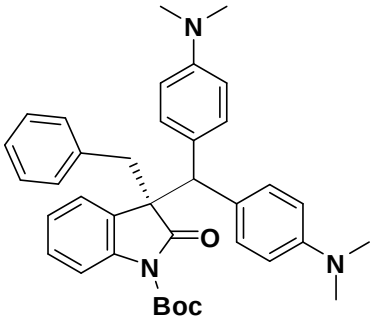
R = Me, no desired product

R = Boc, yield 85%, ee 76%

2.3 General procedure for direct α-alkylation of 2-oxindoles with Michlers Hydrol

To the mixture of 2-oxindoles (0.11mmol) and catalyst **3d** (0.02 mmol, 15.6 mg**)** in 0.5 mL DCM, MsOH (0.02 mmol, 1.3 μL**)** was added. After 5 minutes Michlers Hydrol **2** (0.1 mmol, 27 mg**)** was added to the mixture. Then, the reaction system was stirred for 1-2 days at room temperature. After silica gel was treated with Et_3N in petroleum ether (10%), FC (petroleum ether/ ethyl acetate, 8: 1 to 4: 1) afforded target products.

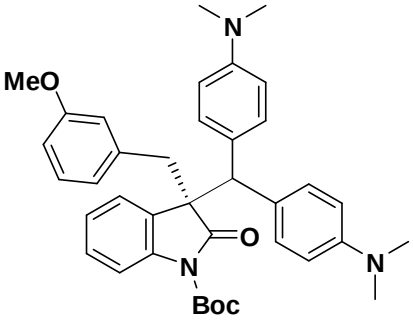
(*R*)-tert-butyl 3-benzyl-3-(bis(4-(dimethylamino)phenyl)methyl)-2-oxoindoline-1-carboxylate (5a):



white solid. yield 85%, ee 76%. $[\alpha]_D^{20}$ +56.3 (*c* 0.72, ethyl acetate). m.p. 60-62 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.47 (d, *J* = 7.8 Hz, 1H), δ 7.10-7.23 (m, 5H), δ 6.93 (s, 3H), δ 6.79-6.81 (d, *J* = 8.0 Hz, 2H), δ 6.65-6.73 (m, 4H), δ 6.44-6.49 (d, *J* = 8.0 Hz, 2H), δ 4.47 (s, 1H), δ 3.43-3.47(d, *J* = 12.8 Hz, 1H), δ 3.05-3.09 (d, *J* = 12.8 Hz, 1H), δ 2.92 (s, 6H), δ 2.81 (s, 6H), δ 1.40 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.5, 149.4, 149.2, 148.6, 140.7, 135.8, 131.3, 130.0, 129.8, 129.1, 128.5, 128.0, 127.5, 127.5, 126.2, 125.6, 123.1, 114.7, 112.4, 112.0, 83.1, 59.2, 58.3, 44.6, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1151, 1347, 1521, 1609, 1728, 1761. HRMS (ESI): calcd for $C_{37}H_{42}O_3N_3$ $[M+H]^+$ 576.3221; found: 576.3214. HPLC analysis [Chiralcel OD-H, n-hexane/ i-propanol (90:10), 15℃, 0.5 mL·min^{-1}, t_R = 20.2 min (major), 15.0 min (minor)].

(*R*)-tert-butyl

3-(bis(4-(dimethylamino)phenyl)methyl)-3-(3-methoxybenzyl)-2-oxoindoline-1-carboxylate (5b):

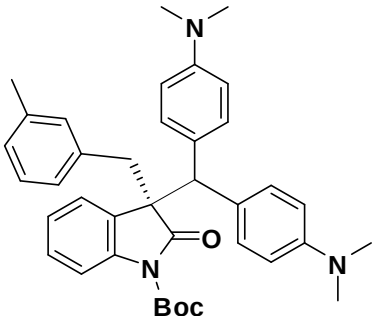


white solid. yield 63%, ee 82%. $[\alpha]_D^{20}$ +56.8 (*c* 0.76, DCM). m.p. 73-74 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.50 (d, *J* = 7.8 Hz, 1H), δ 7.19-7.23 (m, 3H), δ 7.07-7.12 (m, 1H), δ 6.78-6.87 (m, 3H), δ 6.65-6.68 (d, *J* = 8.7 Hz, 2H), δ 6.44-6.53 (m, 3H), δ 6.34-6.36 (d, *J* = 7.5 Hz, 1H), δ 6.20 (s, 1H), δ 4.47 (s, 1H), δ 3.50 (s, 3H), δ 3.40-3.44 (d, *J* = 12.9 Hz, 1H), δ 2.99-3.03 (d, *J* = 12.9 Hz, 1H), δ 2.93 (s, 6H), δ 2.81 (s, 6H), δ 1.41 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.4, 158.7, 149.4, 149.2, 148.7, 140.9, 137.2, 131.3, 129.8, 129.2, 128.5, 128.4, 128.1, 127.5, 125.5, 123.1, 122.5, 114.7, 114.5, 112.9, 112.4, 112.0, 83.2, 59.1, 58.2, 54.9, 44.8, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1151, 1347, 1521, 1609, 1728, 1763. HRMS (ESI): calcd for $C_{38}H_{44}O_4N_3$ $[M+H]^+$ 606.3326; found: 606.3316. HPLC analysis [Chiralcel OD-H, n-hexane/ i-propanol (90:10), 20℃, 0.5 mL·min^{-1}, t_R =

18.0 min (major), 16.2 min (minor)].

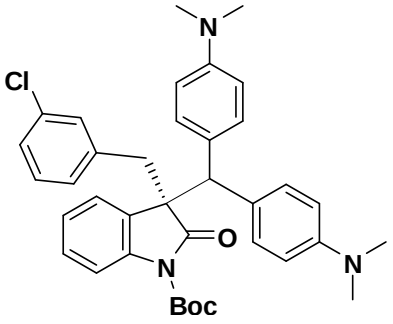
(*R*)-tert-butyl

3-(bis(4-(dimethylamino)phenyl)methyl)-3-(3-methylbenzyl)-2-oxoindoline-1-carboxylate (5c): white solid. yield 71%, ee 76%. $[\alpha]_D^{20}$ +54.5 (*c* 0.84, DCM). m.p. 145-147 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.49 (d, *J* = 8.1 Hz, 1H), δ 7.19-7.24 (m, 4H), δ 7.10-7.12 (m, 2H), δ 6.58-6.81 (m, 8H), δ 6.44-6.47 (d, *J* = 8.7 Hz, 2H), δ 4.46 (s, 1H), δ 3.38-3.42 (d, *J* = 12.9 Hz, 1H), δ 2.81-2.93 (d, *J* = 12.9 Hz, 1H), δ 2.93 (s, 6H), δ 2.81 (s, 6H), δ 2.11 (m, 3H), δ 1.26 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.6, 149.4, 149.2, 148.7, 140.8, 135.5, 132.7, 131.3, 129.8, 129.8, 129.3, 128.6, 128.2, 128.0, 127.6, 125.6, 123.1, 114.7, 112.4, 112.0, 83.1, 59.3, 58.3, 44.1, 40.6, 40.5, 27.9, 20.9. IR ν_{max} (KBr, film, cm^{-1}): 1153, 1339, 1519, 1609, 1726, 1762. HRMS (ESI): calcd for $C_{38}H_{44}O_3N_3$ $[M+H]^+$ 590.3377; found: 590.3369. HPLC analysis [Chiralcel OD-H, n-hexane/ i-propanol (90:10), 25℃, 0.5 mL·min^{-1}, t_R = 13.1 min (major), 11.6 min (minor)].



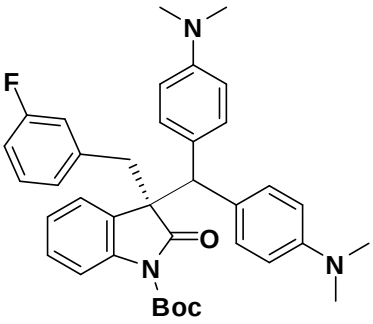
(*R*)-tert-butyl

3-(bis(4-(dimethylamino)phenyl)methyl)-3-(3-chlorobenzyl)-2-oxoindoline-1-carboxylate (5d): white solid. yield 62%, ee 76%. $[\alpha]_D^{20}$ +41.1 (*c* 0.76, DCM). m.p. 139-141 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.52 (d, *J* = 8.1 Hz, 1H), δ 7.08-7.24 (m, 5H), δ 6.92-6.95 (d, *J* = 8.1 Hz, 2H), δ 6.79-6.88 (m, 3H), δ 6.58-6.71 (m, 4H), δ 6.45-6.47 (d, *J* = 8.7 Hz, 2H), δ 4.44 (s, 1H), δ 3.38-3.42 (d, *J* = 12.9 Hz, 1H), δ 2.97-3.01 (d, *J* = 12.9 Hz, 1H), δ 2.93 (s, 6H), δ 2.82 (s, 6H), δ 1.43 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.2, 149.5, 149.2, 148.6, 140.7, 137.9, 133.2, 131.2, 130.1, 129.8, 128.7, 128.3, 128.1, 127.3, 126.5, 125.4, 123.3, 114.7, 112.4, 112.0, 83.4, 59.0, 58.2, 44.2, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1151, 1251, 1520, 1610, 1729, 1762. HRMS (ESI): calcd for $C_{37}H_{41}O_3N_3Cl$ $[M+H]^+$ 610.2831; found: 610.2824. HPLC analysis [Chiralcel IA, n-hexane/ i-propanol (90:10), 25℃, 0.5 mL·min^{-1}, t_R = 15.1 min (major), 16.7 min (minor)].



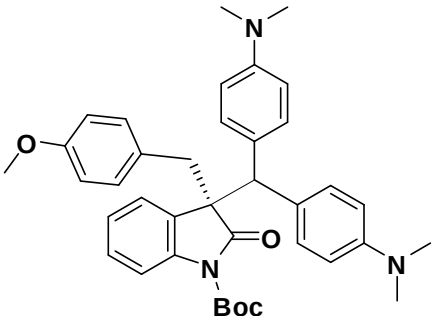
(*R*)-tert-butyl

3-(bis(4-(dimethylamino)phenyl)methyl)-3-(3-fluorobenzyl)-2-oxoindoline-1-carboxylate (5e): white solid. yield 64%, ee 80%. $[\alpha]_D^{20}$ +47.1 (*c* 0.76, DCM). m.p. 169-171 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.51 (d, *J* = 8.1 Hz, 1H), δ 7.08-7.22 (m, 5H), δ 6.78-6.92 (m, 3H), δ 6.63-6.68 (m, 3H), δ 6.44-6.51 (m, 3H), δ 4.45 (1, 1H), δ 3..41-3.45 (d, *J* = 12.9 Hz, 1H), δ 2.99-3.03 (d, *J* = 12.9 Hz, 1H), δ 2.93 (s, 6H), δ 2.82 (s, 6H), δ 1.42 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.3, 162.0 ($^1J_{CF}$ = 243.3 Hz), 149.5, 149.2, 148.6, 140.7, 138.4, 138.3, 131.2, 129.8, 128.9, 128.8, 128.3, 127.3, 125.7, 125.4, 123.3, 116.8 ($^2J_{CF}$ = 21.2 Hz), 114.7, 113.2 ($^2J_{CF}$ = 20.7 Hz), 112.4, 112.0, 83.4, 59.0, 58.3, 44.2, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1151, 1520, 1611, 1728, 1760. HRMS (ESI): calcd for $C_{37}H_{41}O_3N_3F$ $[M+H]^+$ 594.3127; found: 594.3116. HPLC analysis [Chiralcel IC, n-hexane/ i-propanol (90:10), 25℃, 0.5 mL·min^{-1}, t_R = 38.6 min (major), 32.2 min (minor)].



(*R*)-tert-butyl

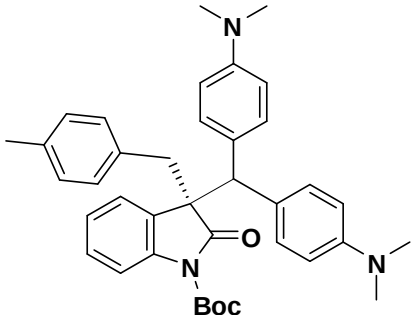
3-(bis(4-(dimethylamino)phenyl)methyl)-3-(4-methoxybenzyl)-2-oxoindoline-1-carboxylate (5f):



white solid. yield 71%, ee 73%. $[\alpha]_D^{20}$ +42.6 (*c* 0.86, DCM). m.p. 79-81 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.48 (d, *J* = 8.1 Hz, 1H), δ 7.17-7.24 (m, 3H), δ 7.07-7.15 (m, 2H), δ 6.78-6.86 (m, 2H), δ 6.61-6.69 (m, 4H), δ 6.44-6.47 (d, *J* = 8.7 Hz, 4H), δ 4.45 (s, 1H), δ 3.62 (s, 3H), δ 3.36-3.41 (d, *J* = 13.2 Hz, 1H), δ 2.95-2.99 (d, *J* = 13.2 Hz, 1H), δ 2.93 (s, 6H), δ 2.81 (s, 6H), δ 1.41 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.7, 157.9, 149.4, 149.2, 148.7, 140.8, 131.3, 130.9, 129.8, 129.3, 128.6, 128.0, 127.8, 127.6, 125.5, 123.1, 114.7, 112.9, 112.4, 112.1, 83.1, 59.3, 58.2, 54.9, 43.7, 40.6, 40.6, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1150, 1250, 1516, 1611, 1728, 1763. HRMS (ESI): calcd for $C_{38}H_{44}O_4N_3$ $[M+H]^+$ 606.3326; found: 606.3318. HPLC analysis [Chiralcel IA, n-hexane/ i-propanol (90:10), 20℃, 0.5 mL·min^{-1}, t_R = 20.2 min (major), 25.5 min (minor)].

(*R*)-tert-butyl

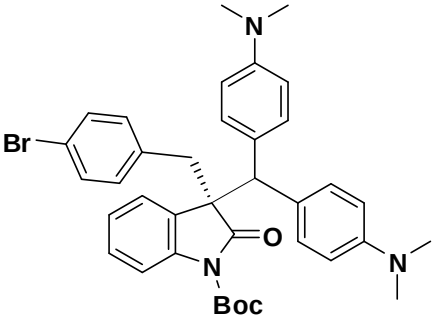
3-(bis(4-(dimethylamino)phenyl)methyl)-3-(4-methylbenzyl)-2-oxoindoline-1-carboxylate (5g):



white solid. yield 64%, ee 70%. $[\alpha]_D^{20}$ +48.7 (*c* 0.76, DCM). m.p. 69-71 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.42 (d, *J* = 7.8 Hz, 1H), δ 7.12-7.18 (m, 3H), δ 7.01-7.07 (m, 2H), δ 6.51-6.74 (m, 8H), δ 6.37-6.40 (d, *J* = 8.7 Hz, 2H), δ 4.38 (s, 1H), δ 3.31-3.35 (d, *J* = 12.9 Hz, 1H), δ 2.90-2.94 (d, *J* = 12.9 Hz, 1H), δ 2.85 (s, 6H), δ 2.74 (s, 6H), δ 2.04 (s, 3H), δ 1.33 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 176.6, 148.4, 148.1, 147.6, 139.8, 134.5, 131.6, 130.2, 128.8, 128.7, 128.2, 127.5, 127.2, 126.9, 126.5, 124.5, 122.1, 113.6, 111.3, 111.0, 82.0, 58.2, 57.3, 43.1, 39.5, 39.5, 26.8, 19.9. IR ν_{max} (KBr, film, cm^{-1}): 1151, 1251, 1520, 1610, 1728, 1763. HRMS (ESI): calcd for $C_{38}H_{44}O_3N_3$ $[M+H]^+$ 590.3377; found: 590.3369. HPLC analysis [Chiralcel AD-H, n-hexane/ i-propanol (90:10), 25℃, 0.5 mL·min^{-1}, t_R = 16.0 min (major), 18.8 min (minor)].

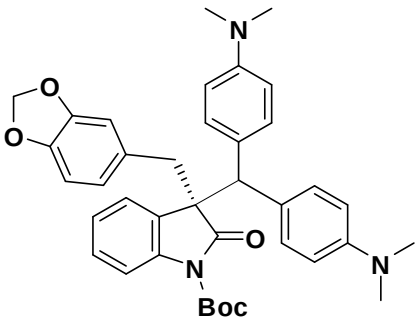
(*R*)-tert-butyl

3-(bis(4-(dimethylamino)phenyl)methyl)-3-(4-bromobenzyl)-2-oxoindoline-1-carboxylate (5h):

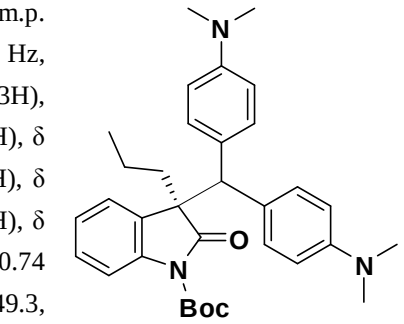


white solid. yield 63%, ee 72%. $[\alpha]_D^{20}$ +43.3 (*c* 0.82, DCM). m.p. 94-96 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.49 (d, *J* = 8.1 Hz, 1H), δ 7.03-7.24 (m, 7H), δ 6.78-6.81 (d, *J* = 8.4 Hz, 2H), δ 6.64-6.67 (d, *J* = 8.7 Hz, 2H), δ 6.58-6.60 (d, *J* = 8.1 Hz, 2H), δ 6.44-6.47 (d, *J* = 8.7 Hz, 2H), δ 4.44 (s, 1H), 3.36-3.41 (d, *J* = 12.9 Hz, 1H), δ 2.93-2.99 (overlap: s, 6H; d, *J* = 12.9 Hz, 1H), δ 2.81 (s, 6H), δ 1.42 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.4, 149.5, 149.3, 148.5, 140.7, 134.9, 131.7, 131.2, 130.6, 129.8, 128.7, 128.3, 128.1, 127.2, 125.4, 123.3, 120.4, 114.9, 112.3, 112.0, 83.4, 59.1, 58.4, 43.7, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1150, 1520, 1610, 1729, 1762. HRMS (ESI): calcd for $C_{37}H_{41}O_3N_3Br$ $[M+H]^+$ 654.2326; found: 654.2318. HPLC analysis [Chiralcel IA, n-hexane/ i-propanol (90:10), 20℃, 0.5 mL·min^{-1}, t_R = 19.8 min (major), 26.3 min (minor)].

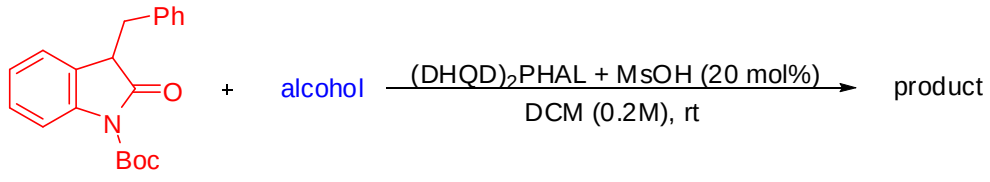
(*R*)-tert-butyl 3-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(bis(4-(dimethylamino)phenyl)methyl)-2-oxoindoline-1-carboxylate (5i): white solid. yield 73%, ee 70%. $[\alpha]_D^{20}$ +51.3 (*c* 0.8, ethyl acetate). m.p. 83-85 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.54 (d, *J* = 8.1 Hz, 1H), δ 7.06-7.23 (m, 5H), δ 6.77-6.80 (d, *J* = 8.7 Hz, 2H), δ 6.64-6.67 (d, *J* = 8.7 Hz, 2H), δ 6.44-6.47 (d, *J* = 8.7 Hz, 2H), δ 6.37-6.39 (d, *J* = 7.8 Hz, 1H), δ 6.17-6.23 (td, *J* = 8.1 Hz, *J* = 1.2 Hz, 2H), δ 5.74 (t, *J* = 1.2 Hz, 2H), δ 4.42 (s, 1H), δ 3.34-3.38 (d, *J* = 13.2 Hz, 1H), δ 2.92-2.97 (overlap: d, *J* = 13.2 Hz, 1H; s, 6H), δ 2.81 (s, 6H), δ 1.43 (s, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 177.5, 149.4, 149.2, 148.7, 146.7, 145.8, 140.8, 131.2, 129.8, 129.5, 129.1, 128.4, 128.1, 127.5, 125.5, 123.3, 123.2, 114.7, 112.4, 112.0, 110.3, 107.4, 100.5, 83.2, 59.3, 58.3, 44.1, 40.6, 40.5, 27.9. IR ν_{max} (KBr, film, cm^{-1}): 1150, 1250, 1520, 1610, 1728, 1762. HRMS (ESI): calcd for $C_{38}H_{42}O_3N_5$ $[M+H]^+$ 620.3119; found: 620.3109. HPLC analysis [Chiralcel IA, n-hexane/ i-propanol (90:10), 25℃, 0.5 mL·min^{-1}, t_R = 22.8 min (major), 28.0 min (minor)].

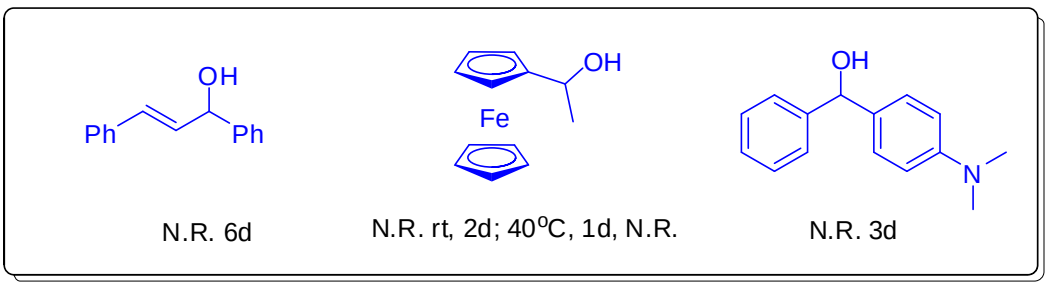


(*R*)-tert-butyl 3-(bis(4-(dimethylamino)phenyl)methyl)-2-oxo-3-propylindoline-1-carboxylate (5j): white solid. yield 58%, ee 76%. $[\alpha]_D^{20}$ +32.1 (*c* 0.61, DCM). m.p. 49-51 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.72 (d, *J* = 8.4 Hz, 1H), δ 7.29-7.34 (t, *J* = 7.8 Hz, 1H), δ 7.11-7.14 (d, *J* = 8.4 Hz, 3H), δ 6.88-6.91 (d, *J* = 7.2 Hz, 1H), δ 6.76-6.78 (d, *J* = 8.7 Hz, 2H), δ 6.61-6.63 (d, *J* = 8.4 Hz, 2H), δ 6.44-6.47 (d, *J* = 8.7 Hz, 2H), δ 4.19 (s, 1H), δ 2.90 (s, 6H), δ 2.81 (s, 6H), δ 2.04-2.13 (m, 1H), δ 1.68-1.77 (m, 1H), δ 1.46 (s, 9H), δ 0.91-0.99 (m, 2H), δ 0.69-0.74 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 178.6, 149.3, 149.3, 148.9, 140.9, 131.0, 130.0, 129.7, 128.3, 127.9, 127.6, 124.9, 123.5, 114.7, 112.2, 112.0, 83.3, 59.1, 58.2, 40.6, 40.6, 39.7, 27.9, 18.0, 14.2. IR ν_{max} (KBr, film, cm^{-1}): 1154, 1291, 1521, 1727, 1763. HRMS (ESI): calcd for $C_{33}H_{42}O_3N_3$ $[M+H]^+$ 528.3221; found: 528.3218. HPLC analysis [Chiralcel IB, n-hexane/ i-propanol (90:10), 15℃, 0.3 mL·min^{-1}, t_R = 15.0 min (major), 16.1 min (minor)].

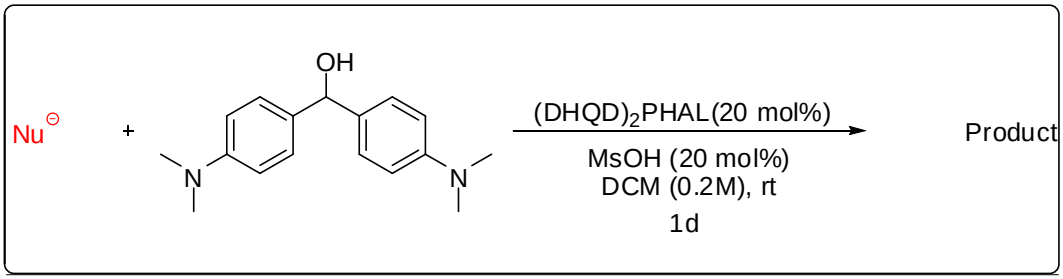


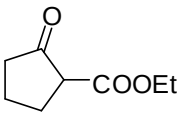
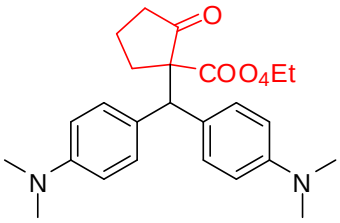
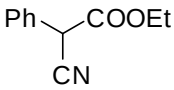
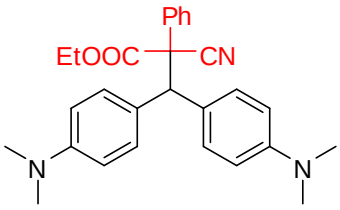
2.4 Other attempts of alcohols



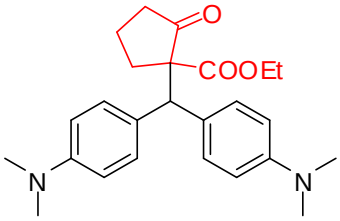


2.5 Other attempts of nucleophiles

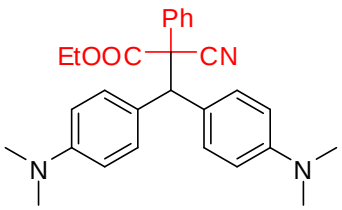


Nu⊖	Product	yield	ee
		90%	15%
		92%	6%

ethyl 1-(bis(4-(dimethylamino)phenyl)methyl)-2-oxocyclopentanecarboxylate: pale solid. yield 90%, ee 15%. $[\alpha]_D^{20}$ +30.7 (*c* 0.98, EA). m.p. 113-115 ℃. ^{1}H NMR (3 00 MHz, $CDCl_3$): δ 7.10-7.13 (d, *J* = 8.5 Hz, 1H), δ 6.94-6.96 (d, *J* = 8.5 Hz, 2H), δ 6.62-6.65 (d, *J* = 8.5 Hz, 2H), δ 6.55-6.57 (d, *J* = 8.5 Hz, 2H), δ 5.07 (s, 1H), δ 3.84-4.02 (m, 2H), δ 2.98-3.03 (m, 1H), δ 2.87-2.89 (s, 6H; s, 6H), δ 2.19-2.32 (m, 2H), δ 1.67-1.87 (m, 2H), δ 1.51-1.54 (m, 1H), δ 0.89-0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 214.8, 169.0, 149.0, 149.0, 130.7, 129.8, 129.5, 129.0, 112.6, 112.2, 66.7, 61.5, 53.6, 40.7, 40.5, 38.8, 29.2, 19.9, 13.7. IR ν_{max} (KBr, film, cm^{-1}): 1221，1356，1521，1614，1715. HRMS (ESI): calcd for $C_{25}H_{33}O_2N_3$ $[M+H]^+$ 409.24857; found: 409.24947. HPLC analysis [Chiralcel AD, n-hexane/ i-propanol (90:10), 15℃, 0.5 mL·min^{-1}, t_R = 28.5 min (major), 20.5 min (minor)].



ethyl 2-cyano-3,3-bis(4-(dimethylamino)phenyl)-2-phenylpropanoate: colorless oil. yield 92%, ee 6%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.64 (m, 2H), δ 7.41-7.44 (d, *J* = 8.7 Hz, 2H), δ 7.28-7.33 (m, 3H), δ 6.89-6.92 (d, *J* = 8.7 Hz, 2H), δ 6.66-6.69 (d, *J* = 8.8 Hz, 2H), δ 6.41-6.44 (d, *J* = 8.8 Hz, 2H), δ4.92 (s, 1H), δ 4.01-4.21 (m, 2H), δ 2.91 (s, 6H), δ 2.81 (s, 6H), δ 1.08-1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 167.5, 149.6, 149.2, 134.1, 130.1, 129.5, 128.6, 128.5, 128.2, 127.3, 126.2, 118.8, 112.5, 111.9, 63.0, 60.1, 56.6, 40.6, 40.4, 13.7. IR ν_{max} (KBr, film, cm^{-1}): 1229，1353，1522，1612，1741. HRMS (ESI): calcd for $C_{28}H_{32}O_3N_2$ $[M+H]^+$ 442.24890; found: 442.24804. HPLC analysis [Chiralcel AD, n-hexane/ i-propanol (90:10), 15℃, 0.5 mL·min^{-1}, t_R = 36.3 min (major), 28.0 min (minor)].



3. Determination of absolute configuration of 5a

Experimental:

The sample (**5a**) was dissolved in $CDCl_3$ (5.2 mg/0.15mL) and placed in a 100 μm pathlength cell with BaF_2 windows. IR and VCD spectra were recorded on a Chiral*IR*-2*X*TM VCD spectrometer (BioTools, Inc.) equipped with dual-*PEM* accessory, with 4 cm^{-1} resolution, 23h collection for both the sample and CDCl3, and instrument optimized at 1400 cm^{-1}. The solvent-subtracted IR&VCD spectra are shown in ***Figure 1***.

Theoretical Calculations:

Since there is only one chiral center in the molecule, the R configuration was built with ComputeVOA (BioTools Inc.). A conformational search was carried out with ComputeVOA for R configuration at the molecular mechanics level to give 1373 low energy conformers. Geometry, frequency, and IR and VCD intensity calculations of the 107 lowest-energy conformers resulted from the conformational search were carried out at the DFT level (B3LYP functional/ 6-31G(d) basis set) with Gaussian 09 (Gaussian Inc., Wallingford, CT). The calculated frequencies were scaled by 0.97 and the IR and VCD intensities were converted to Lorentzian bands with 6-cm^{-1} half-width for comparison to experiment.

For the *R* configuration Gaussian calculations resulted in two low energy conformers, and all the other conformers are more than 2.2 kcal/mol higher than the lowest energy conformer. The optimized geometries, the relative energies of the two lowest-energy conformers of the *R* configuration are shown in **Figure 2**. The IR and VCD spectrum of the two conformers are plotted against the observed spectra of **5a** in **Figure 3**. The comparison of the observed VCD and IR spectra with those of the Boltzmann-weighted sum of the two calculated lowest-energy conformers of the R configuration is shown in **Figure 4**. Therefore the absolute configuration of **5a** is assigned as (*R*). The assignment was also evaluated by Compare*VOA* program (**Figure 5** and **6**). The confidence level of the assignment of *R* is 100% based on current database that includes 106 previous correct assignments for different chiral structures, which confirms the assignment of the absolute configuration of **5a** is *R*.

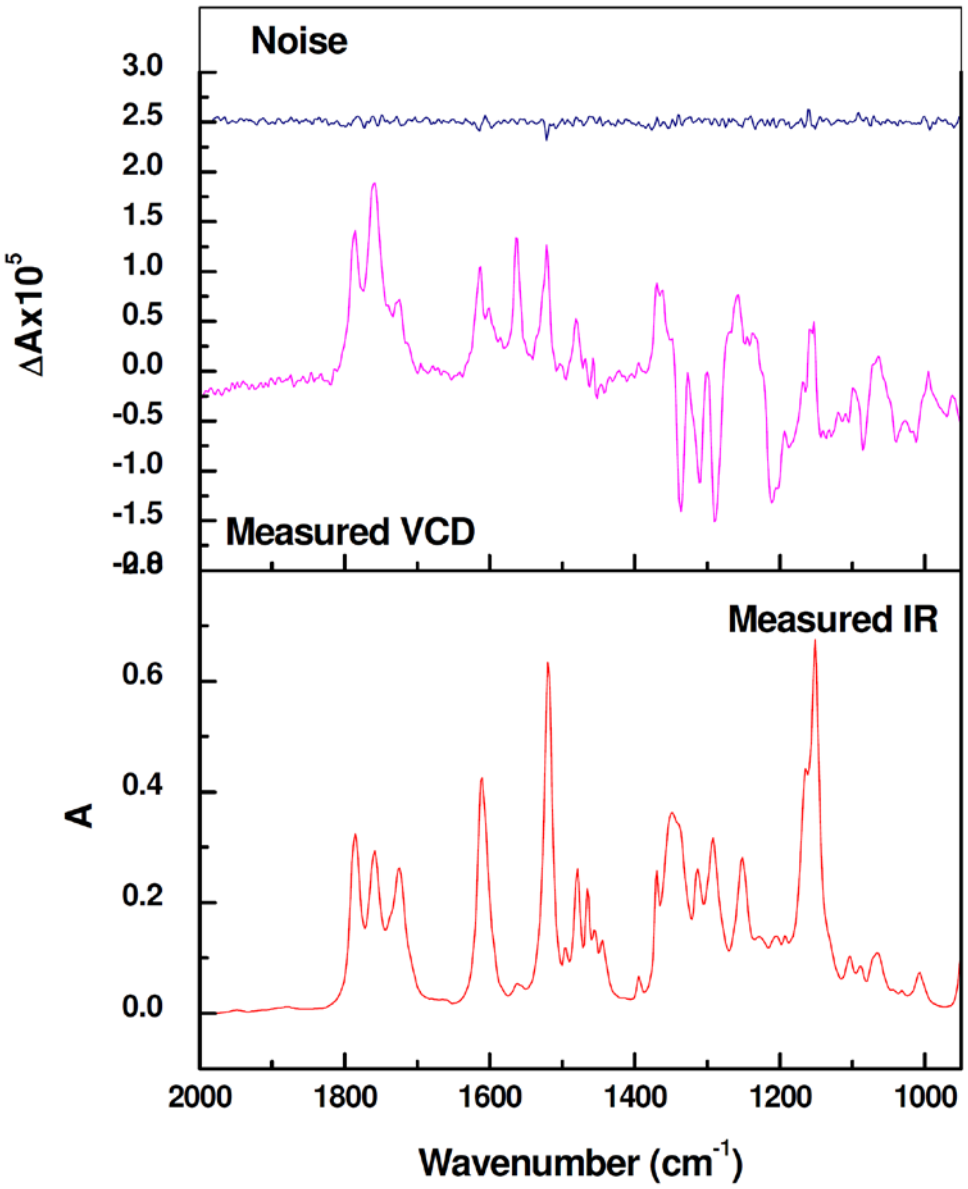


Figure 1. IR (lower frame) and VCD (upper frame) spectra of **5a** in $CDCl_3$ (5.2 mg/0.15 mL); 100-μm path-length cell with BaF_2 windows; 23 h collection for sample and solvent; instrument optimized at 1400 cm^{-1}. Solvent-subtracted spectra are shown. Uppermost trace is the VCD noise.

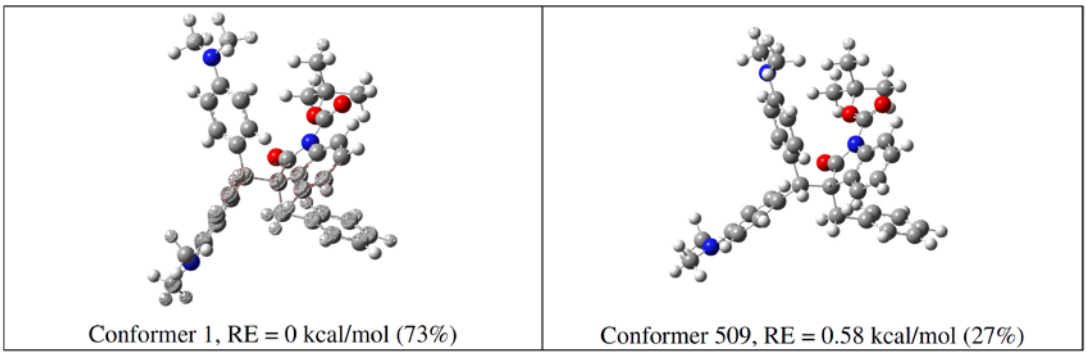


Figure 2. Optimized geometry, relative energies and Boltzmann population of the two calculated lowest-energy *R* conformer of **5a**.

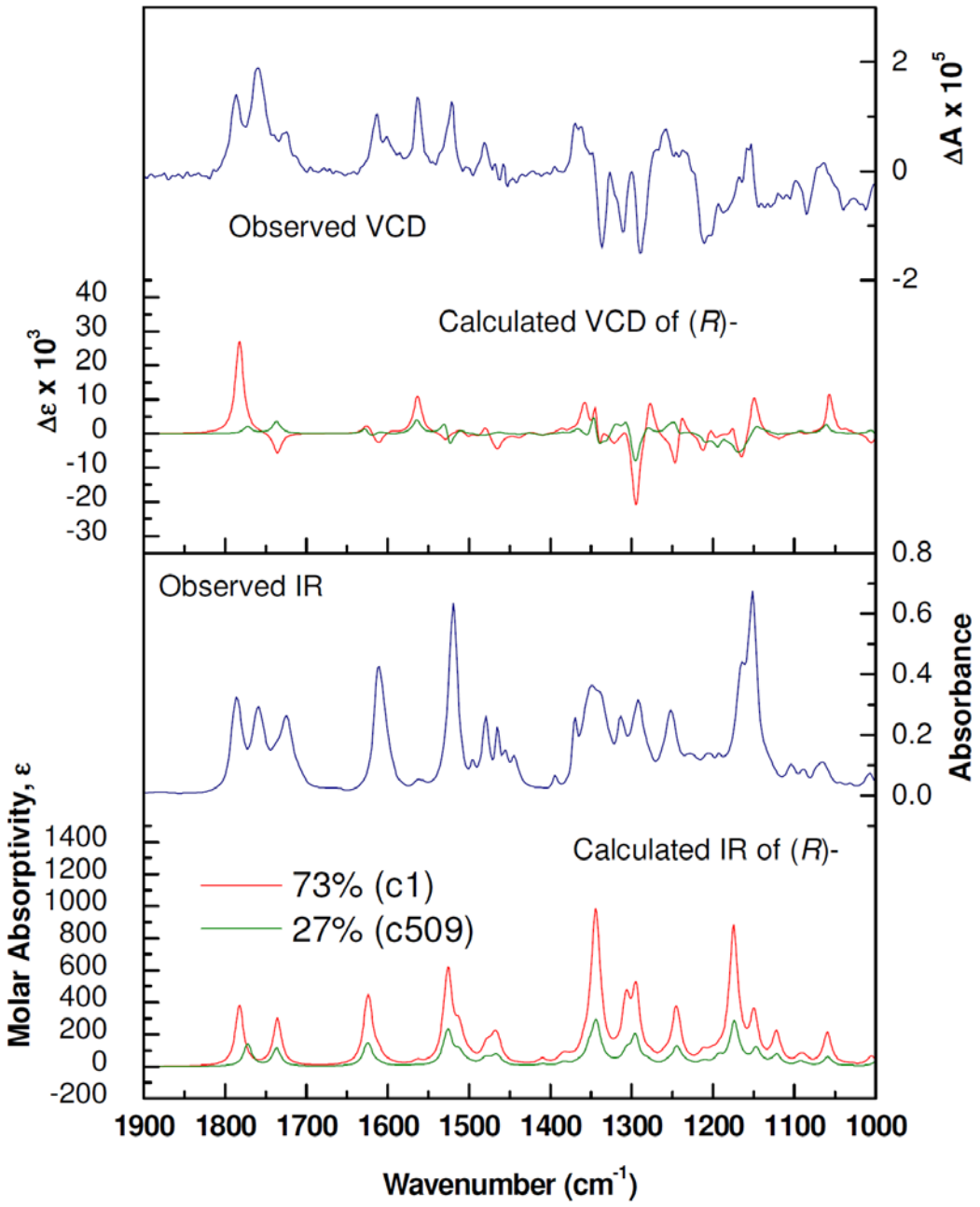


Figure 3. IR (lower frame) and VCD (upper frame) spectra observed for **5a** (right axes) compared with calculated spectra of the two calculated lowest-energy conformations for the *R*- configuration (left axes).

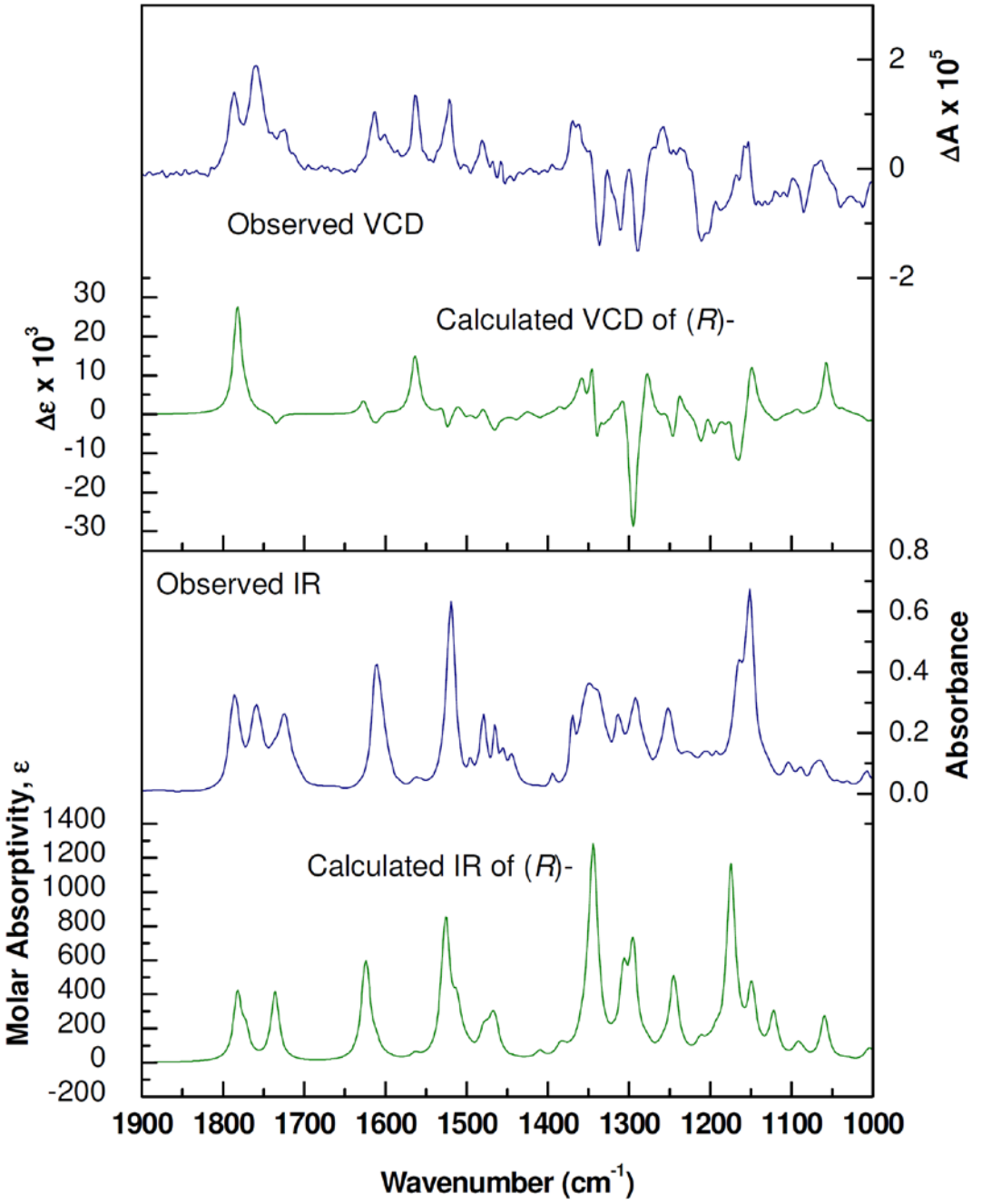


Figure 4. IR (lower frame) and VCD (upper frame) spectra observed for **5a** (right axes) compared with the Boltzmann-population-weighted calculated spectra for the two lowest-energy conformations of the *R* configurations (left axes).

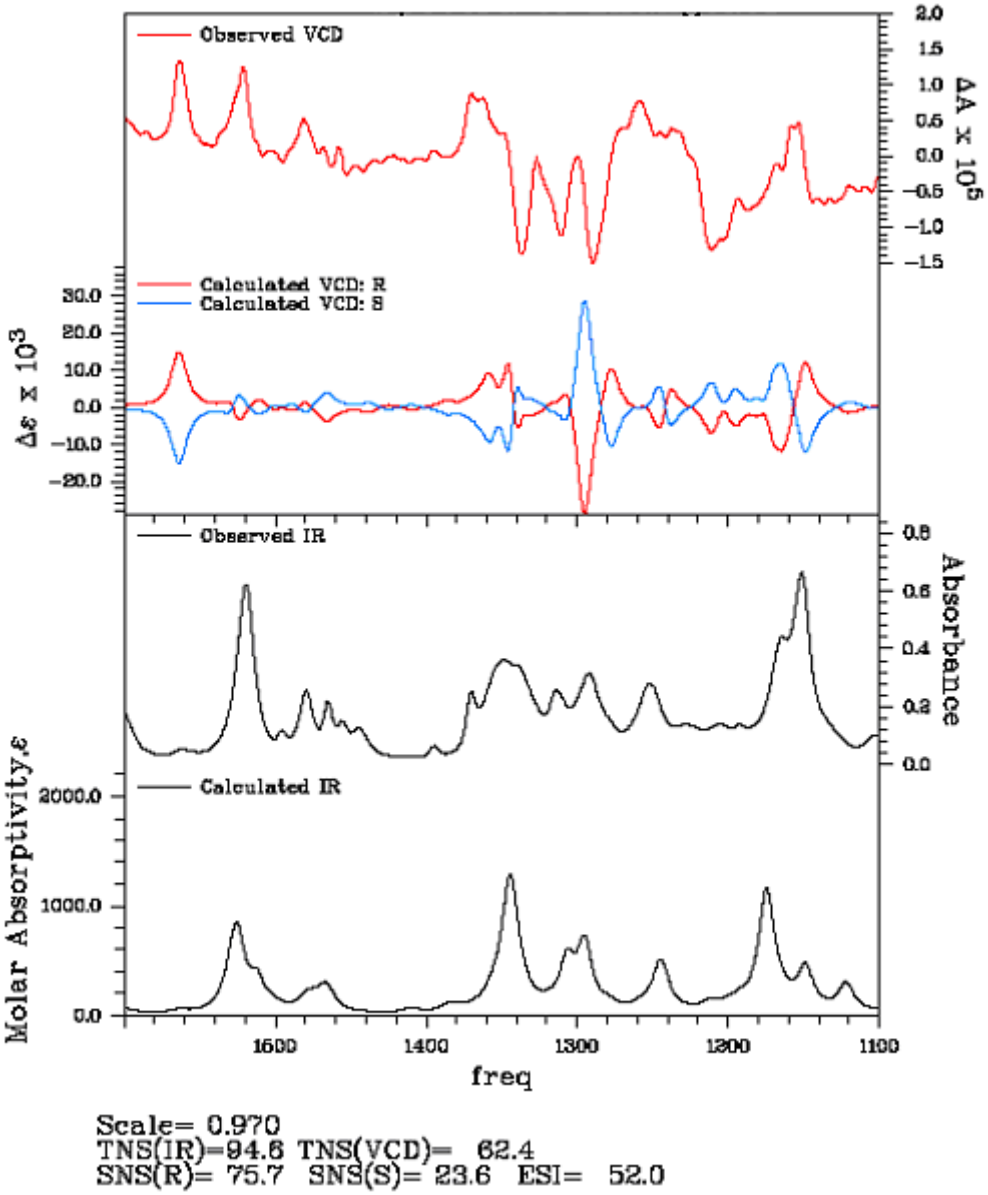


Figure 5. Compare VOA result for comparing the observed IR and VCD spectra with the calculated spectra of the *R* configuration.

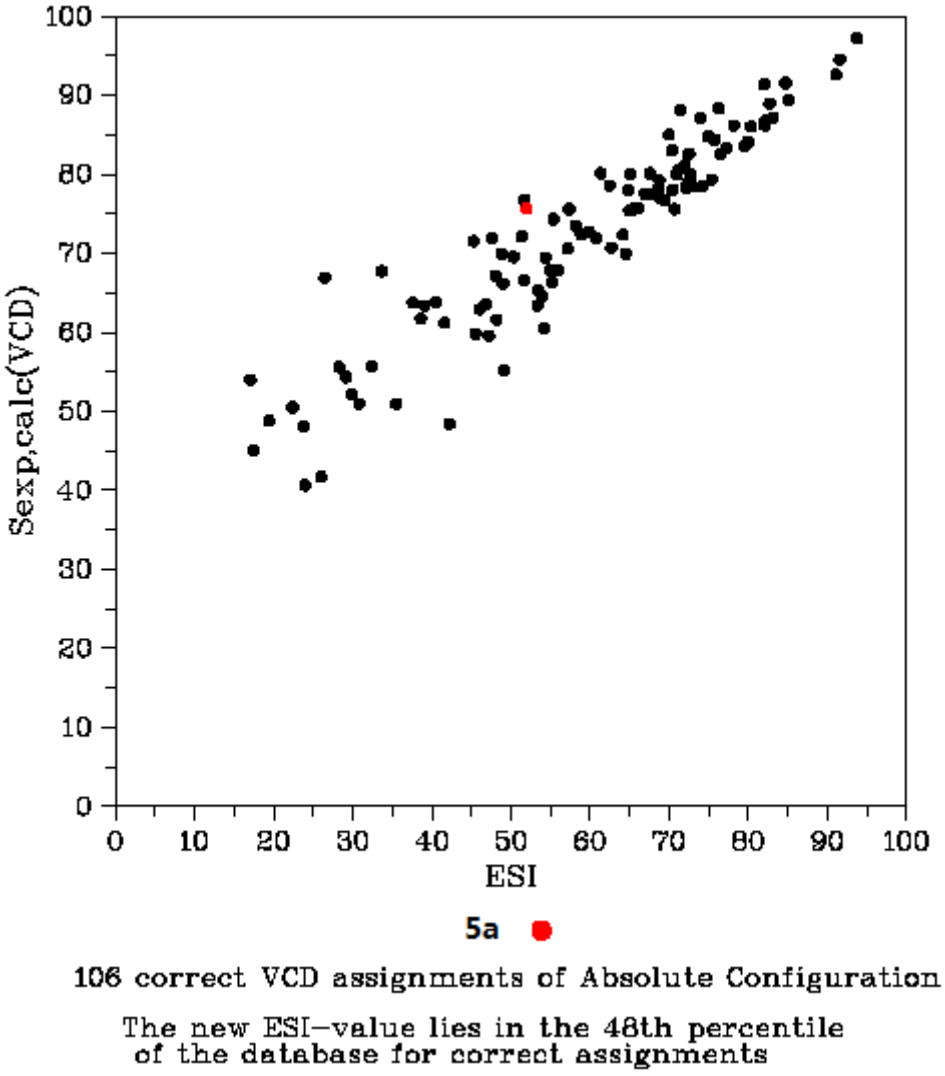
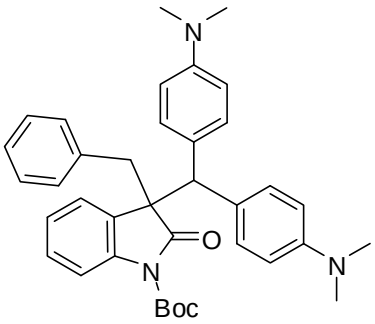
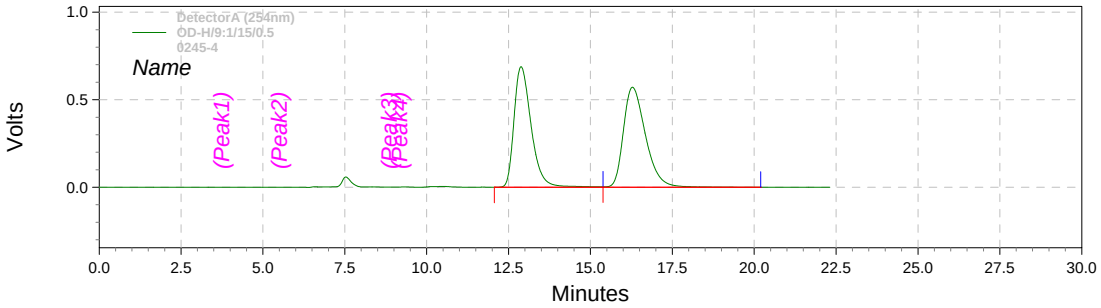


Figure 6. Compare VOA result for comparing the observed IR and VCD spectra with the calculated spectra of the *R* configuration.





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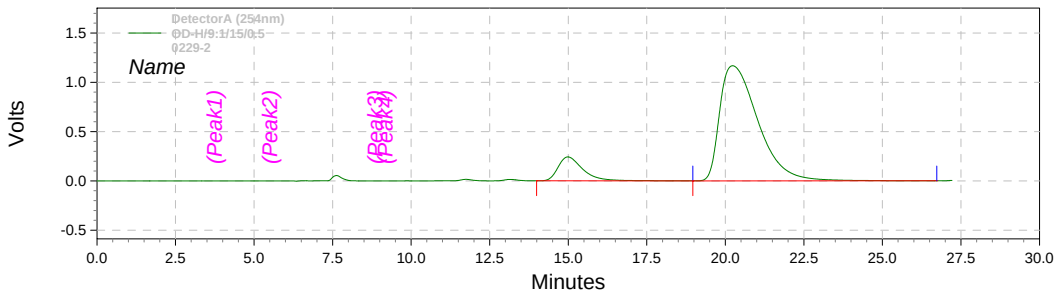

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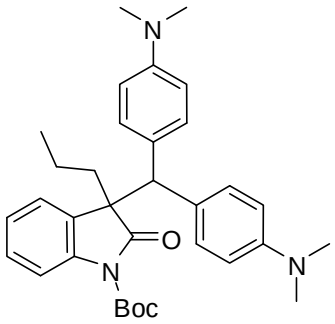

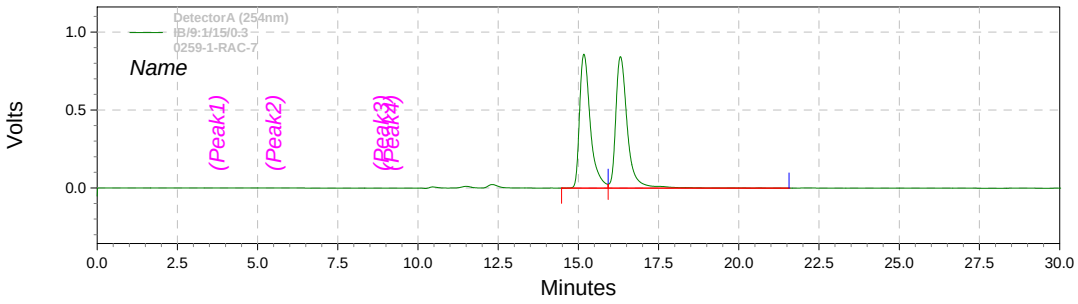

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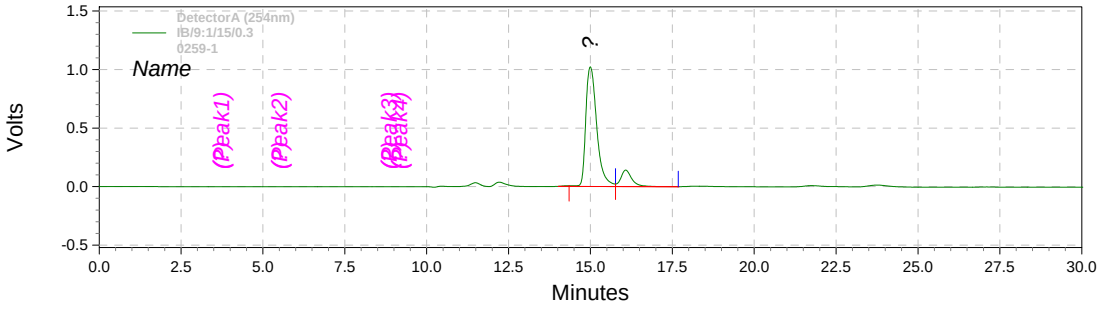

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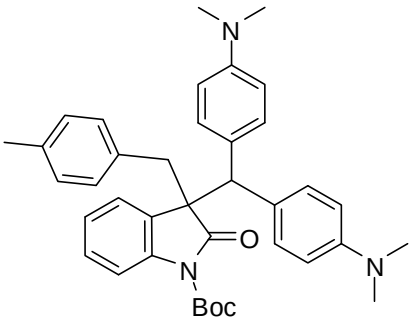

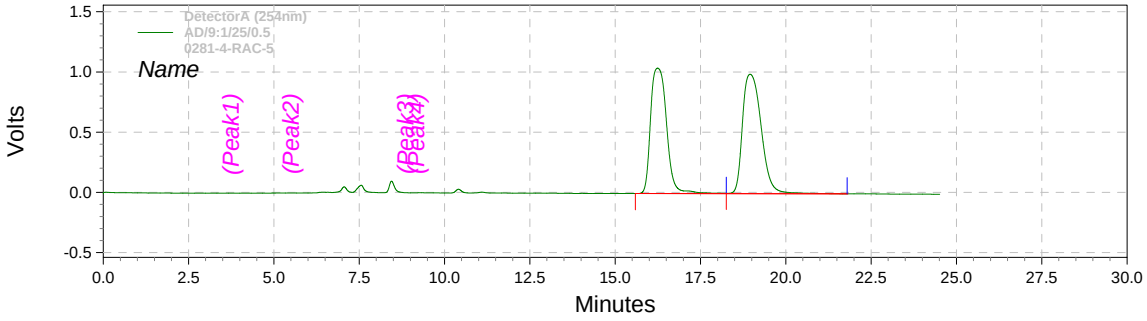

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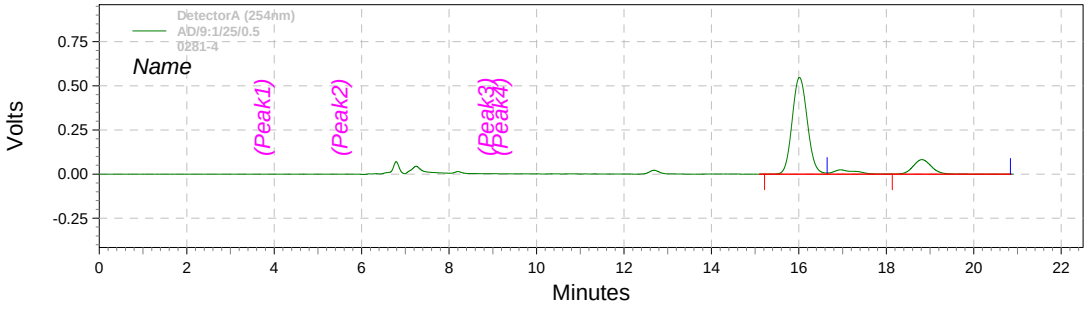

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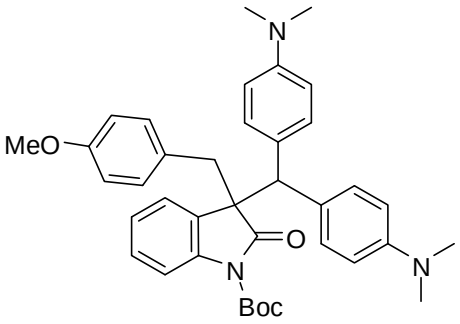

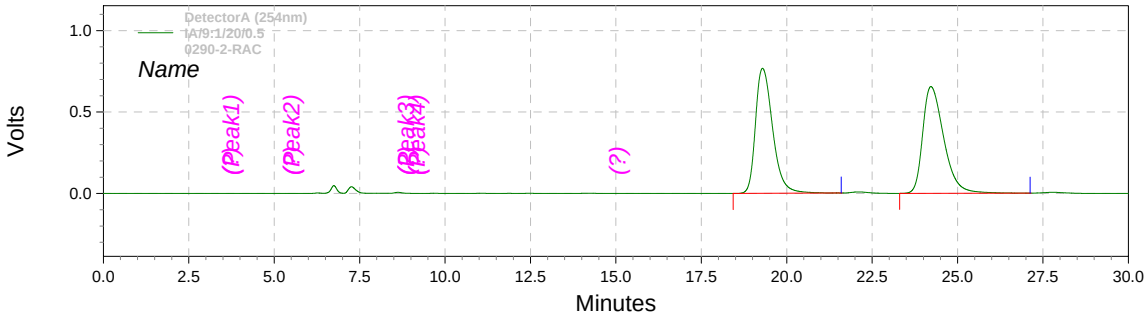

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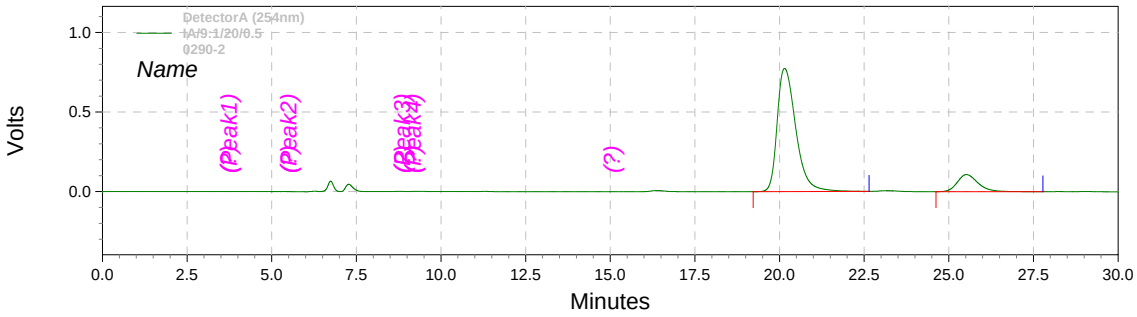

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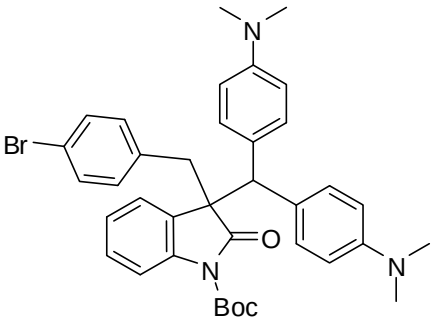

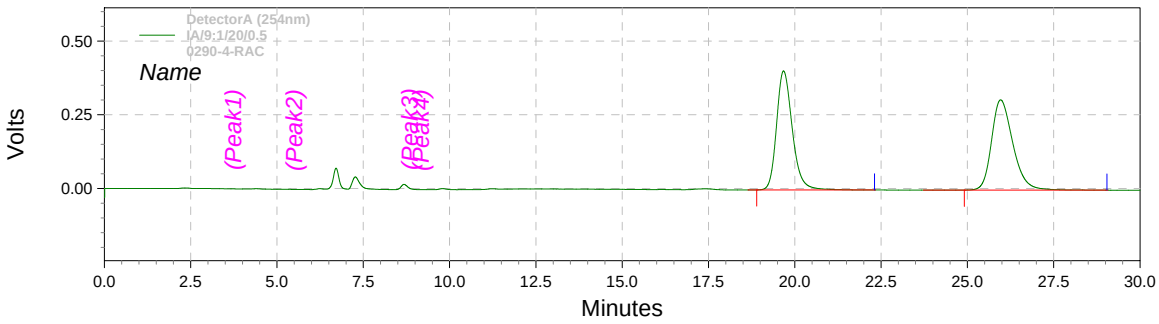

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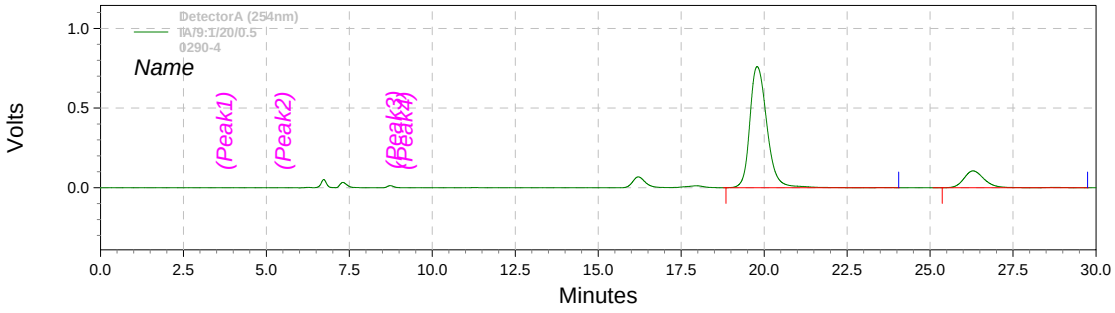

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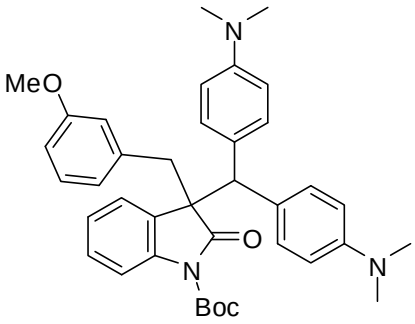

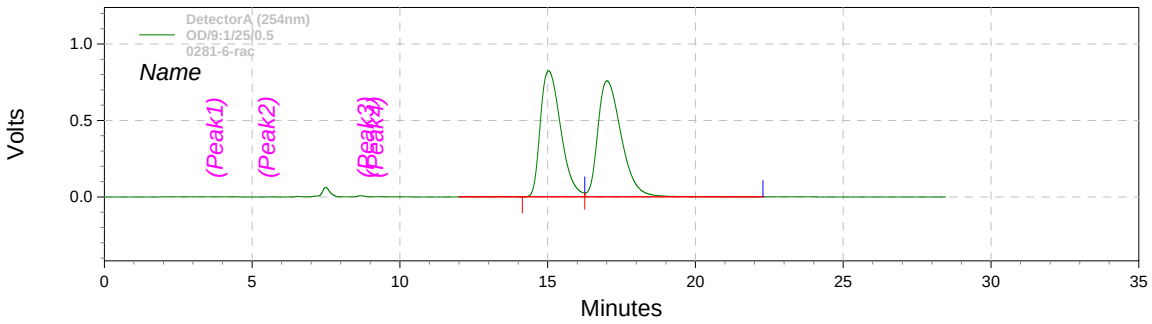

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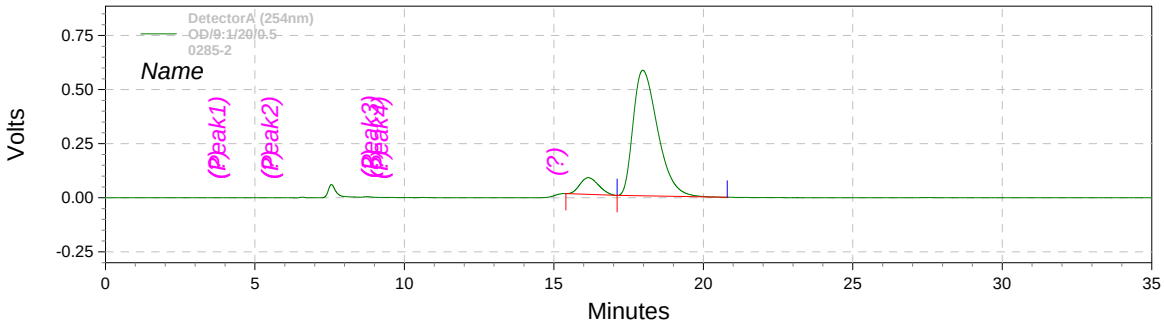

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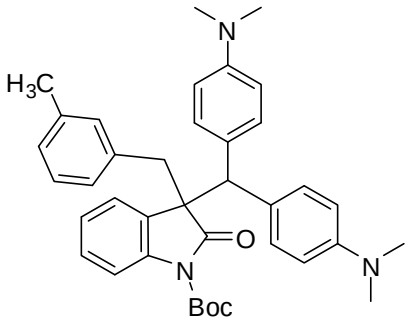

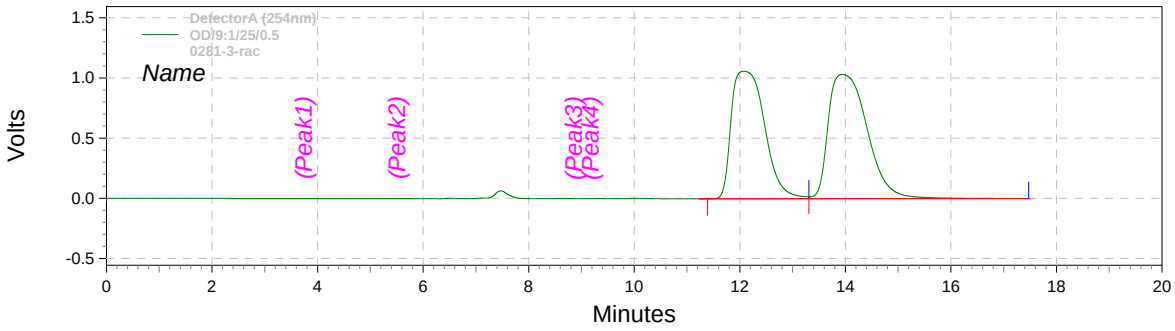

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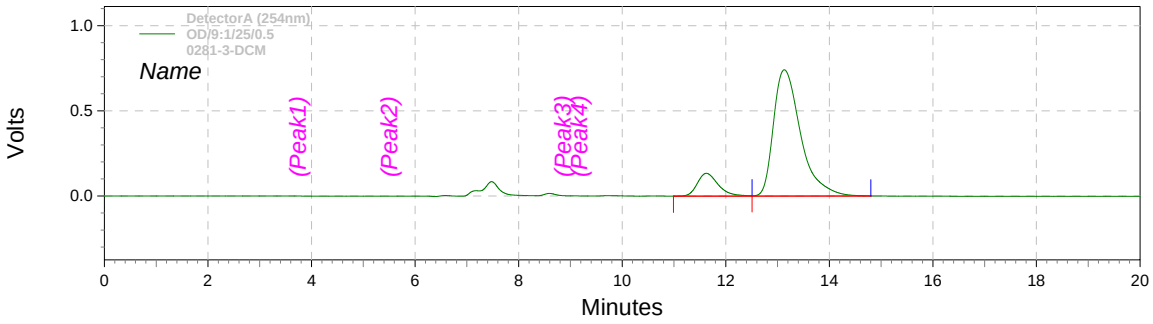

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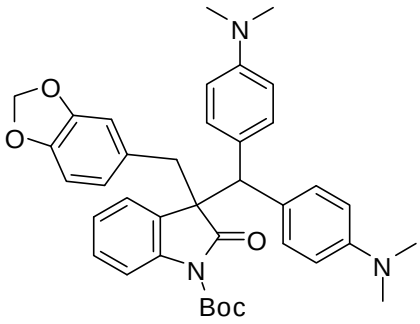
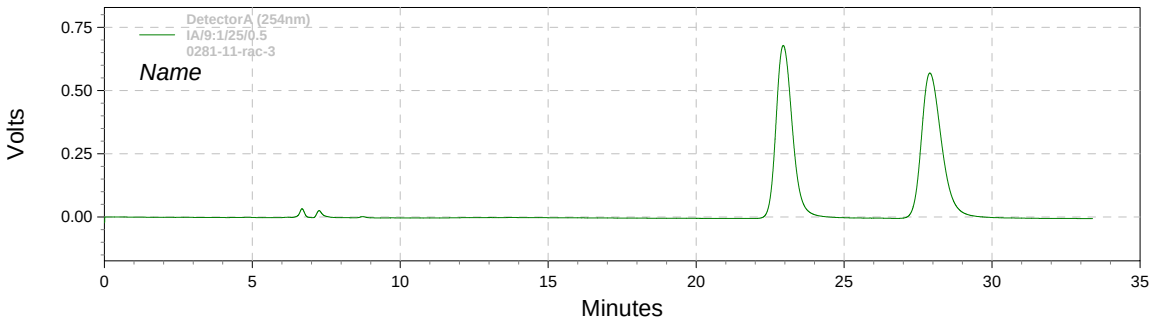
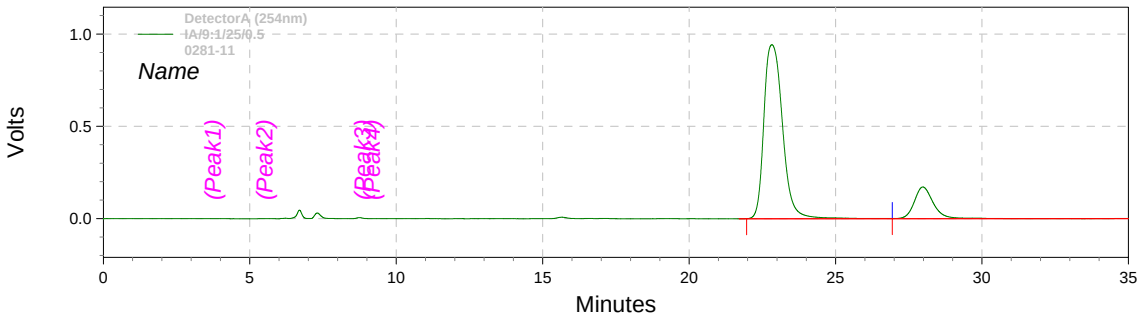
2	13.129	26935843	87.793
Totals		30680961	100.000

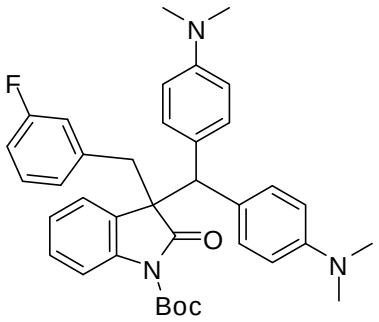


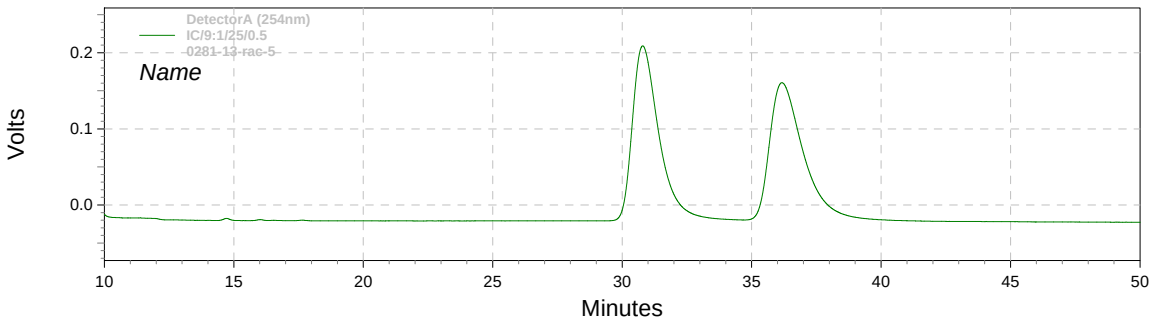


Pk #	Retention Time	Area	Area %
1	22.944	26759053	49.096
2	27.898	27744031	50.904
Totals		54503084	100.000

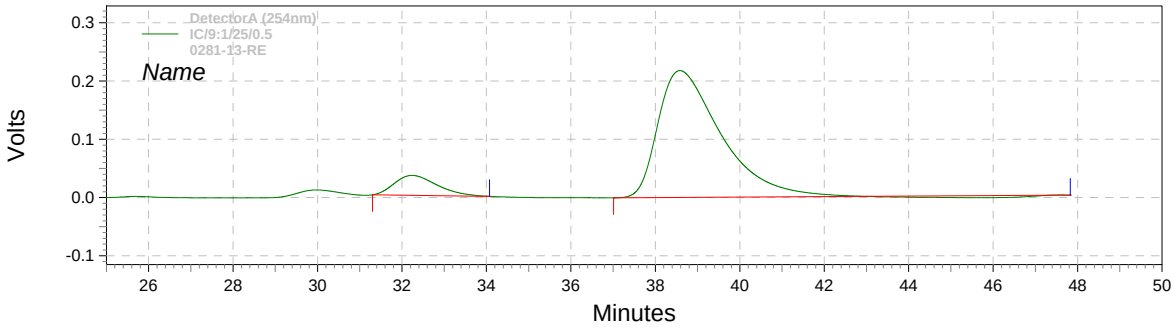


Pk #	Retention Time	Area	Area %
1	22.825	41673910	85.050
2	27.980	7325456	14.950
Totals		48999367	100.000

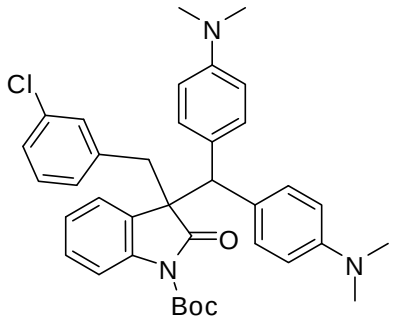


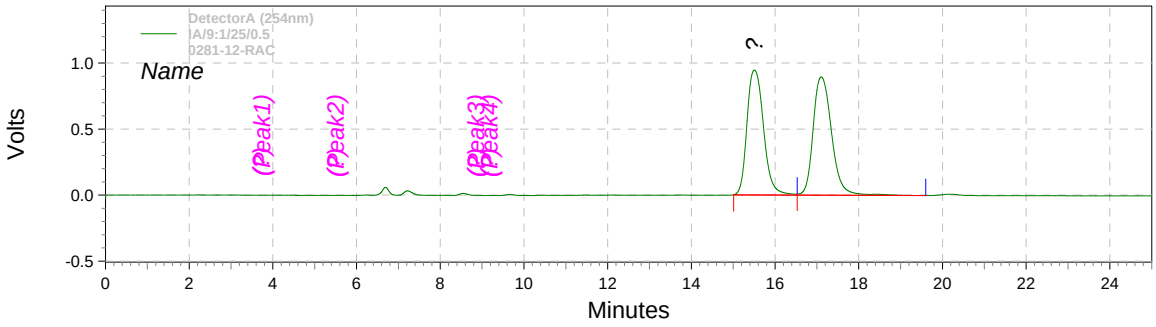


Pk #	Retention Time	Area	Area %
1	30.786	16656765	49.967
2	36.167	16678712	50.033
Totals		33335476	100.000

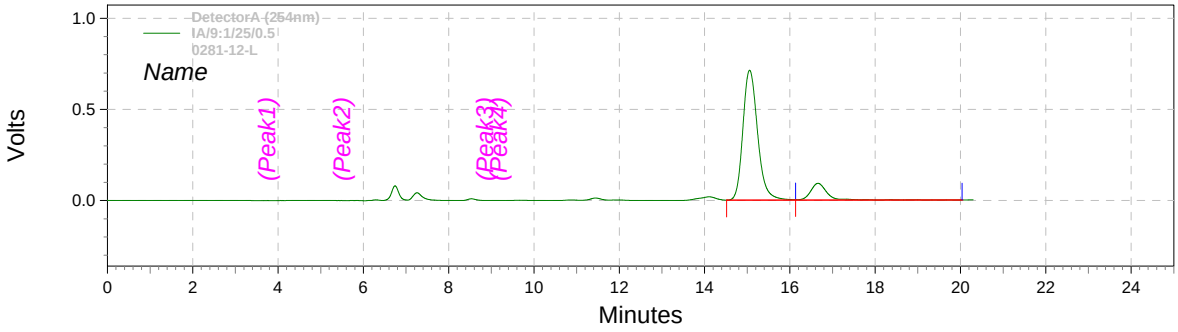


Pk #	Retention Time	Area	Area %
1	32.229	2409294	9.887
2	38.584	21958922	90.113
Totals		24368216	100.000

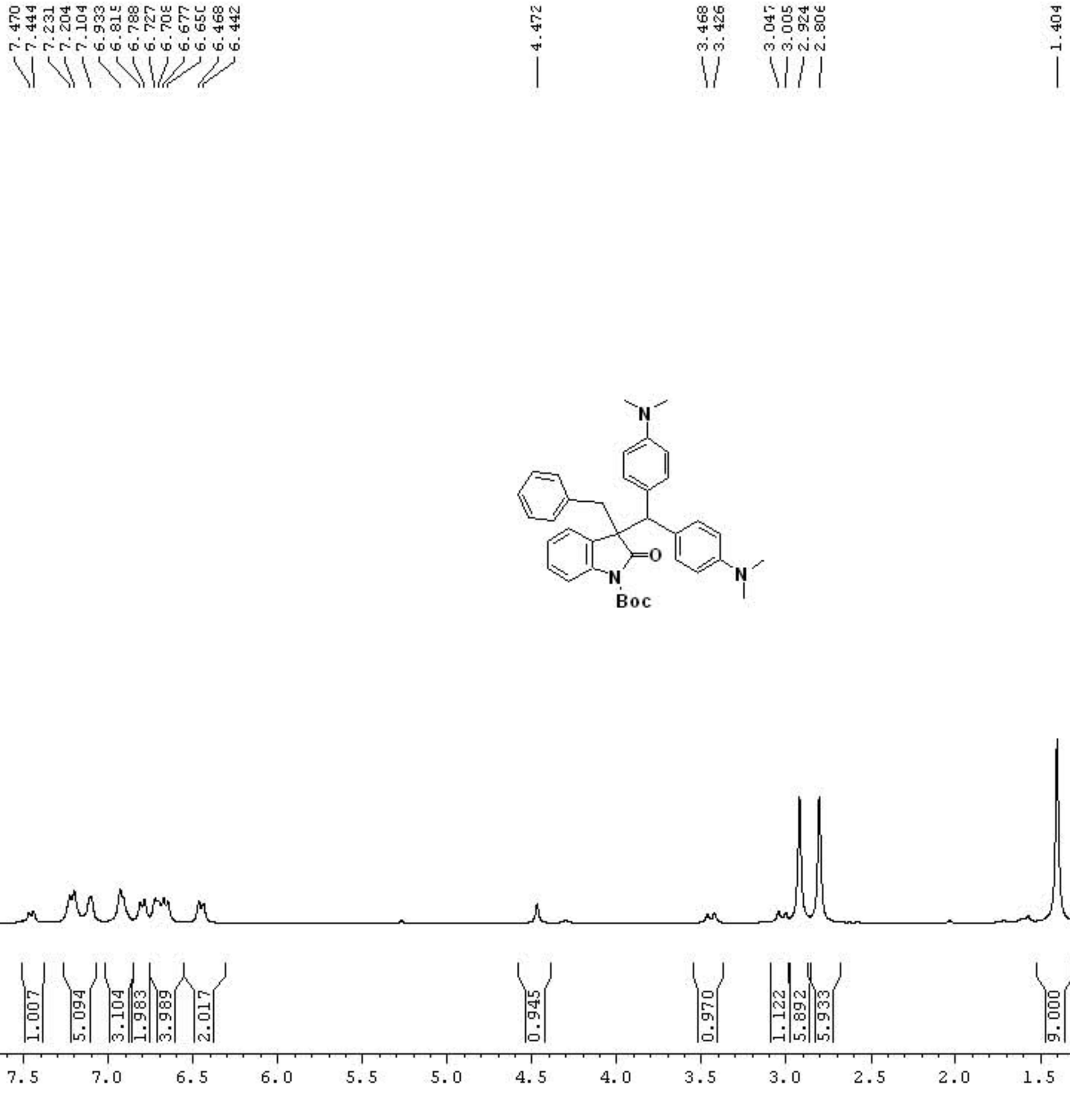




Pk #	Retention Time	Area	Area %
1	15.507	26029004	48.689
2	17.103	27430271	51.311
Totals		53459275	100.000



Pk #	Retention Time	Area	Area %
1	15.055	17081619	87.917
2	16.657	2347724	12.083
Totals		19429343	100.000



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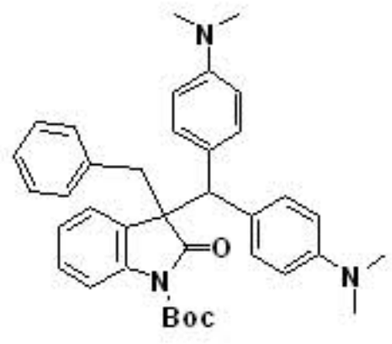

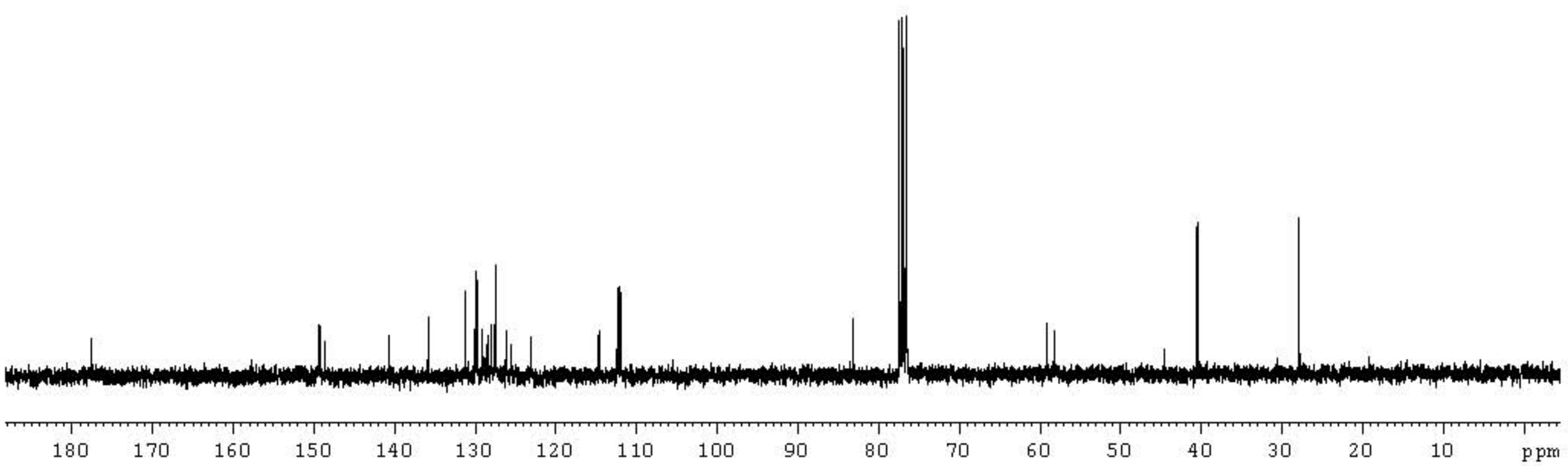

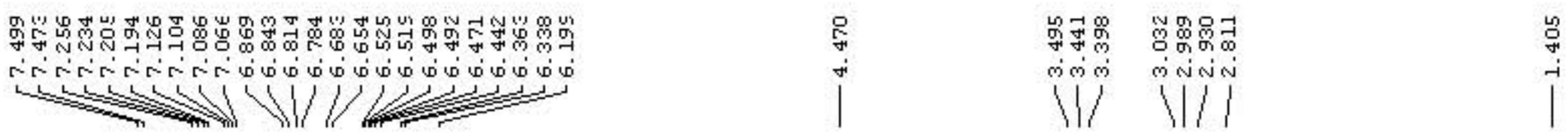

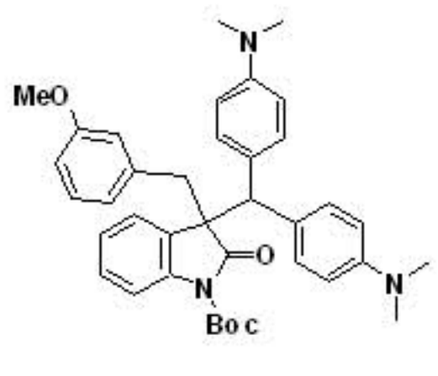

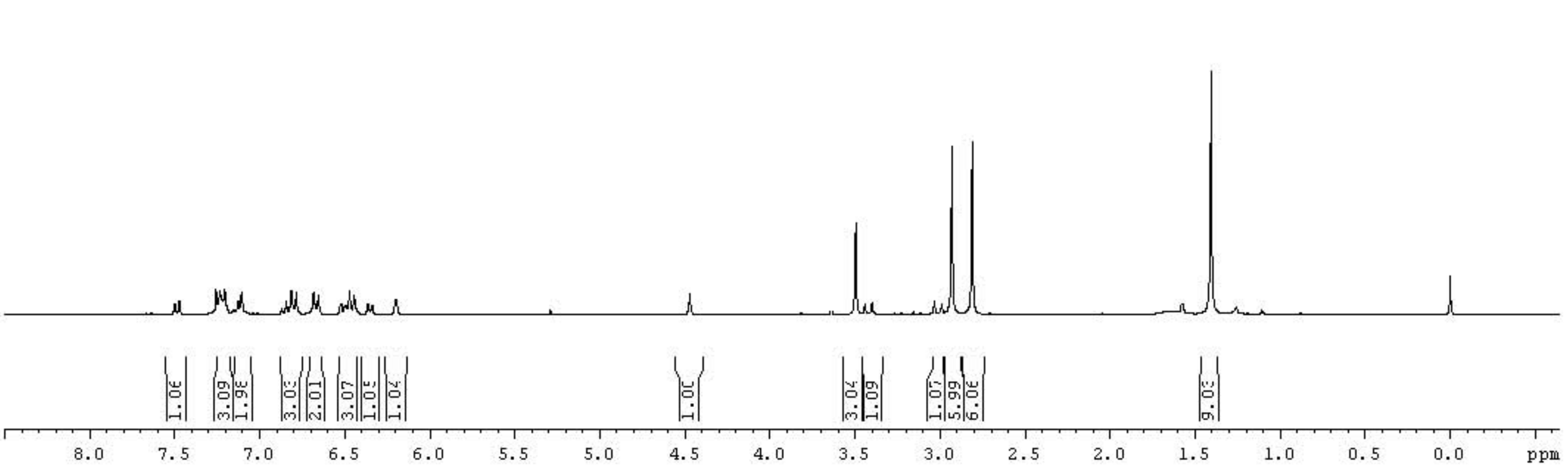

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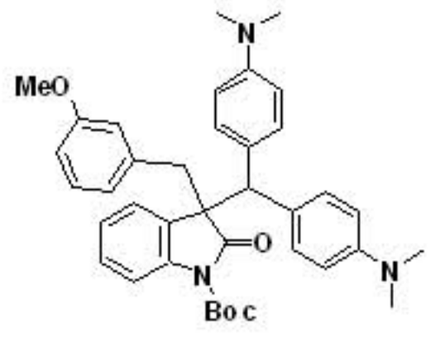

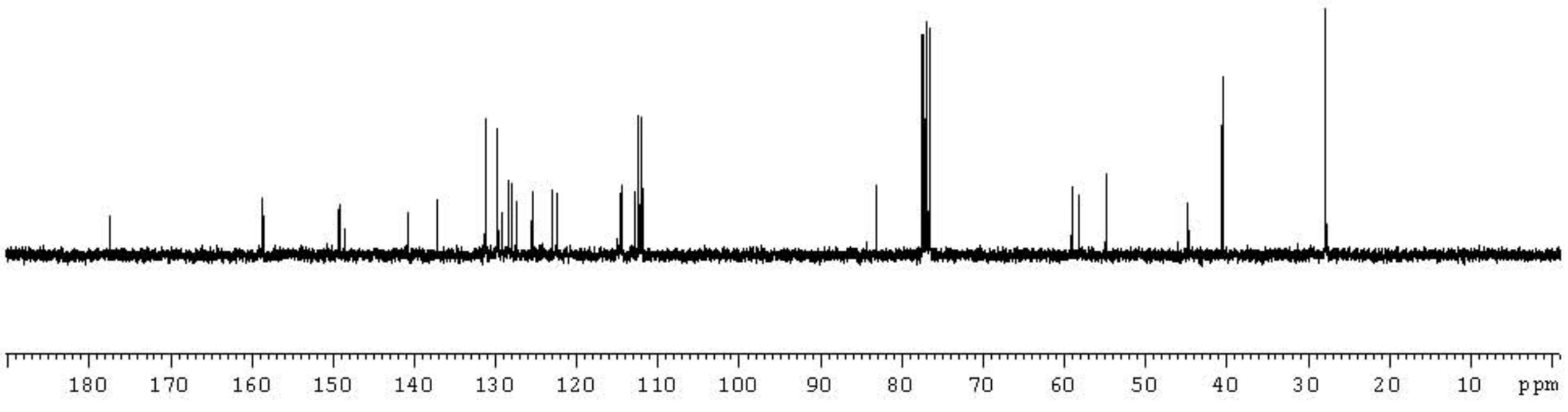

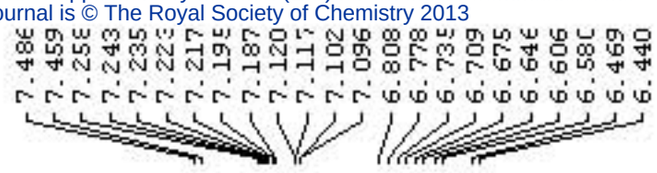

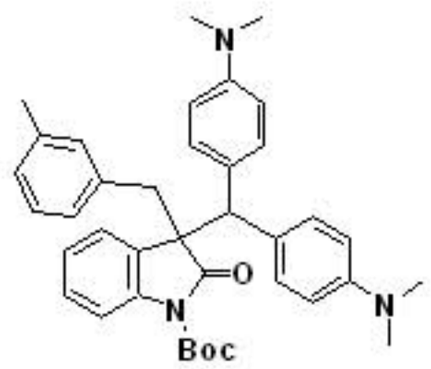

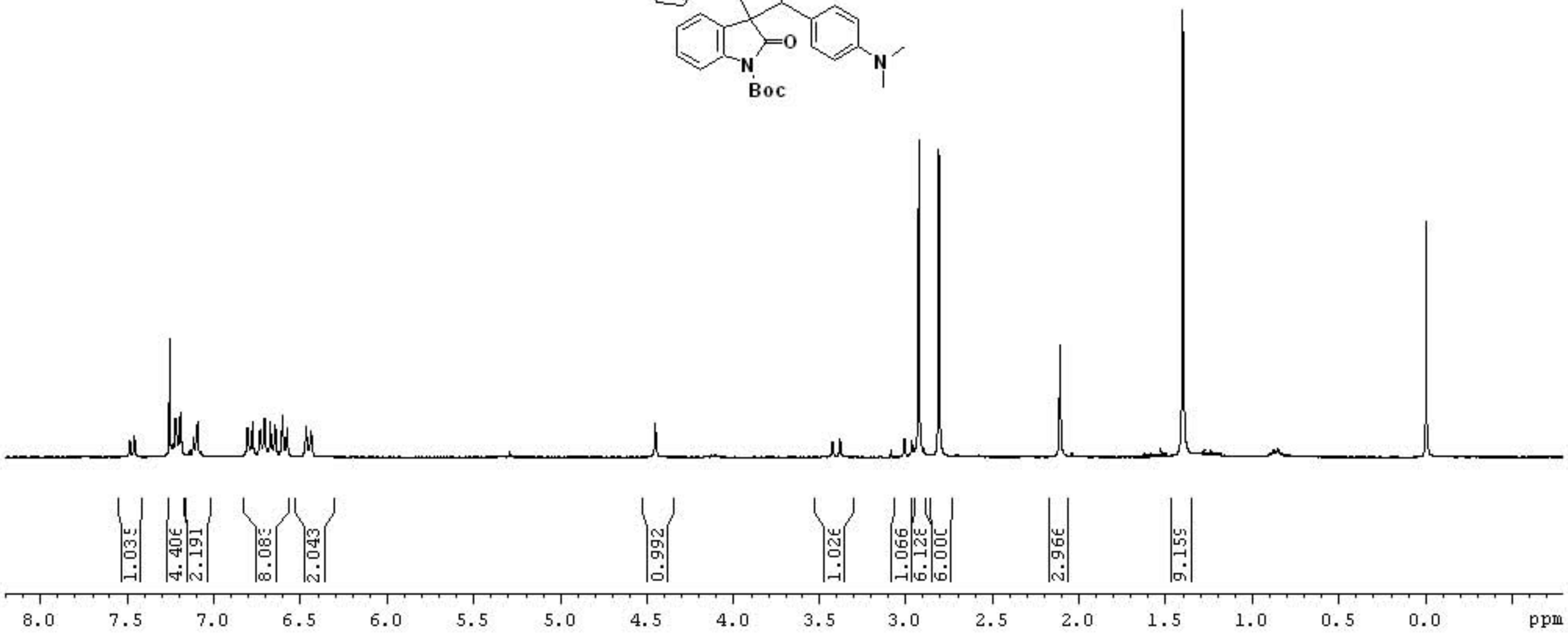

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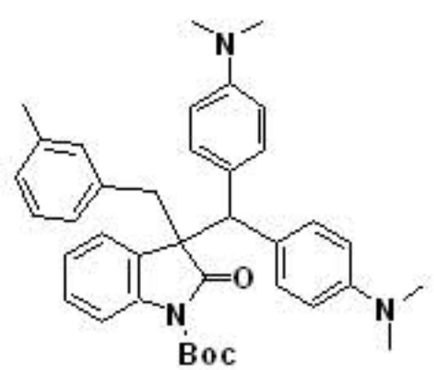

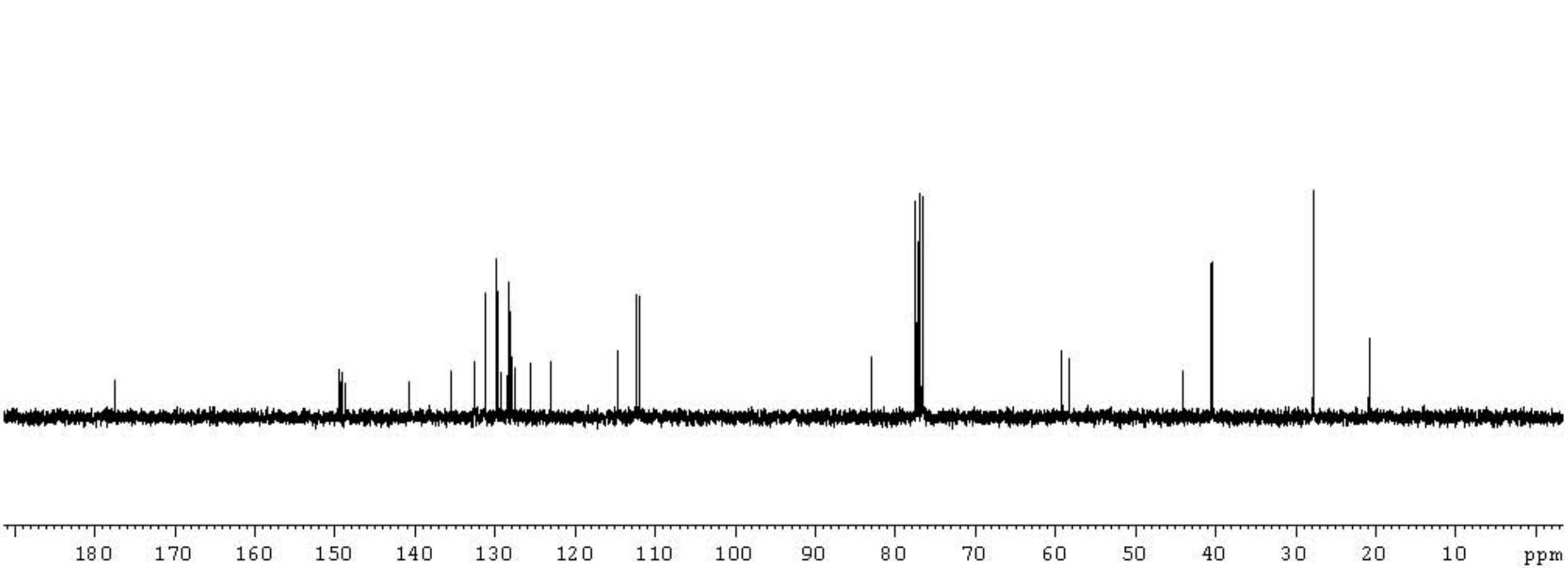

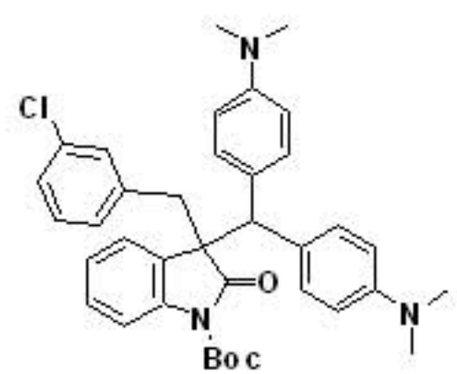

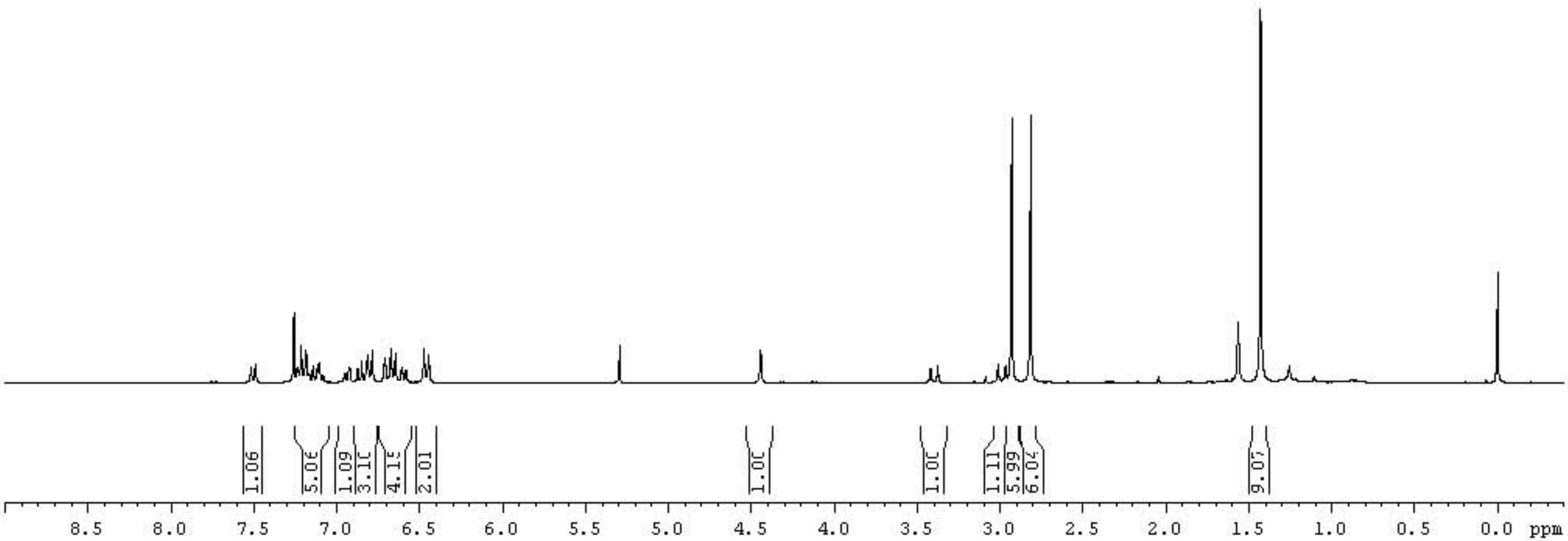

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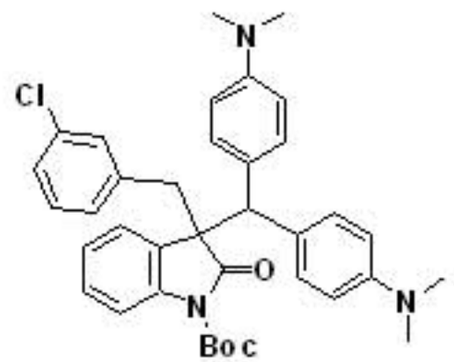

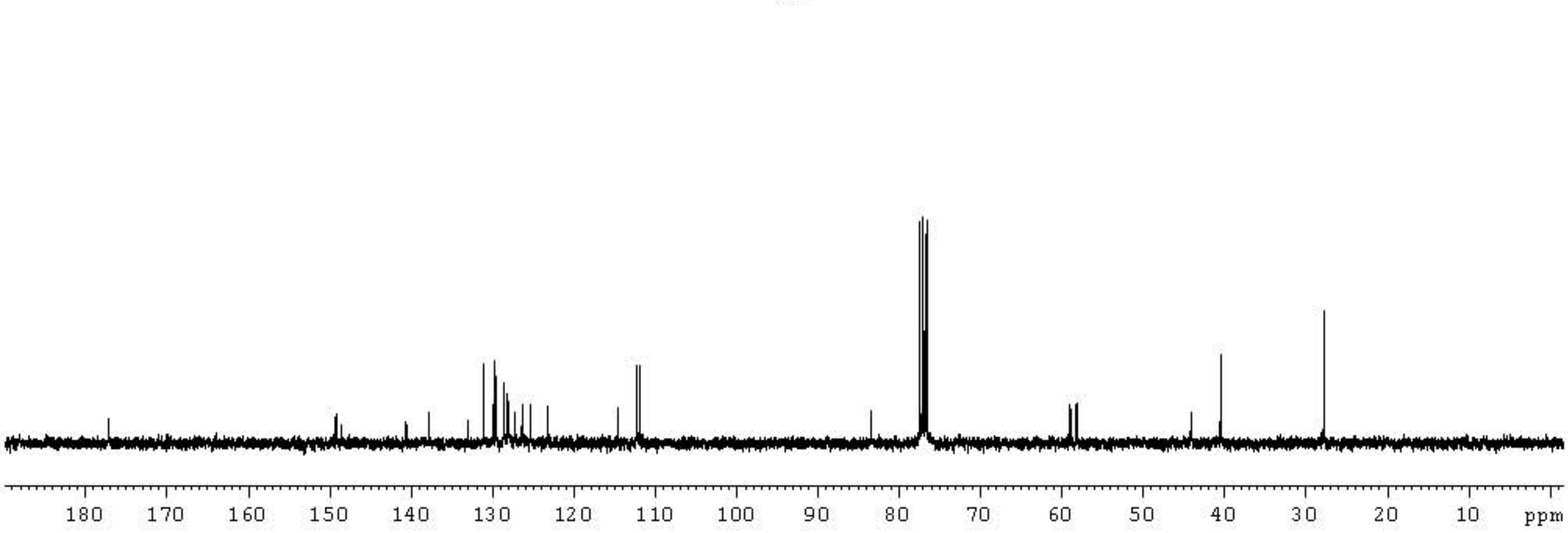

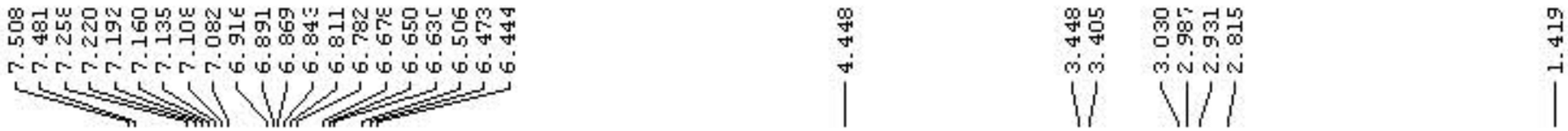

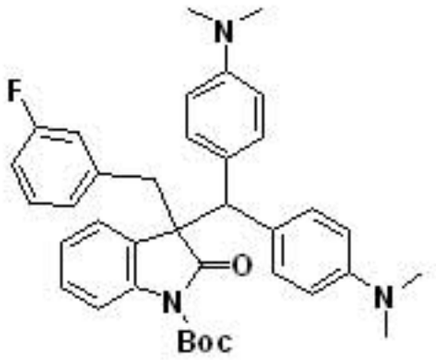

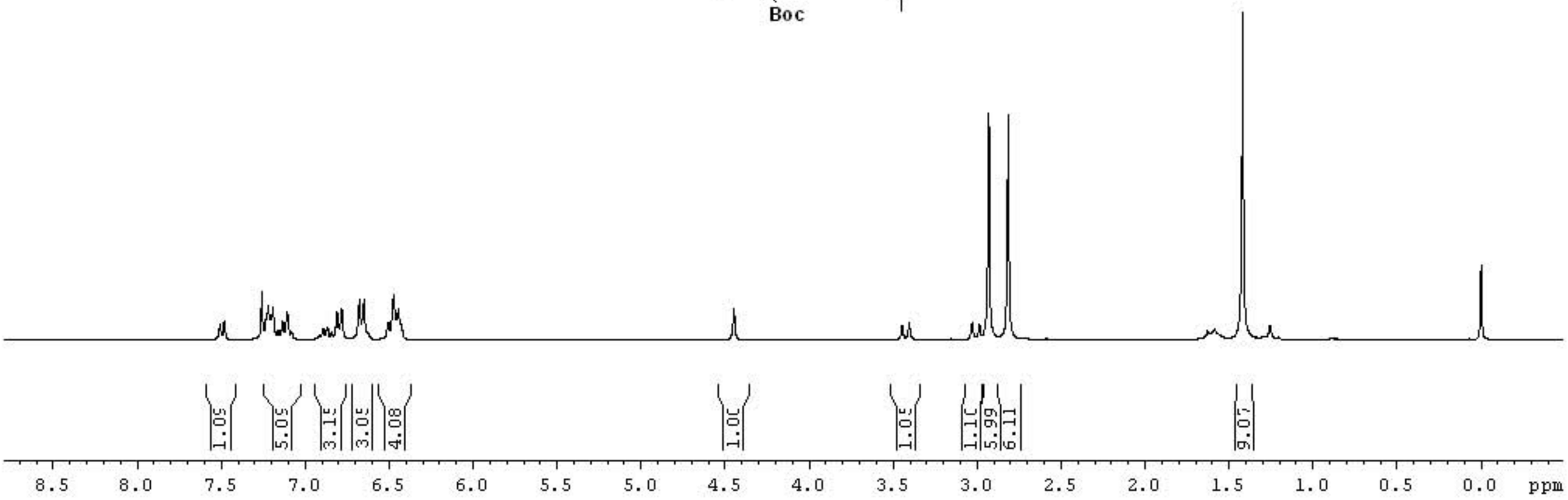

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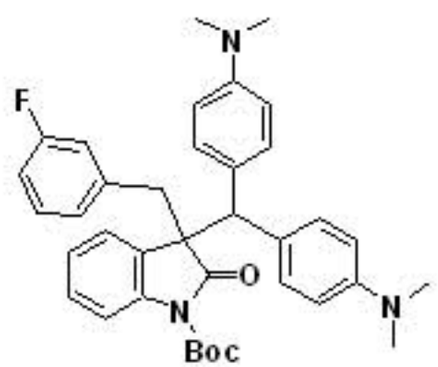

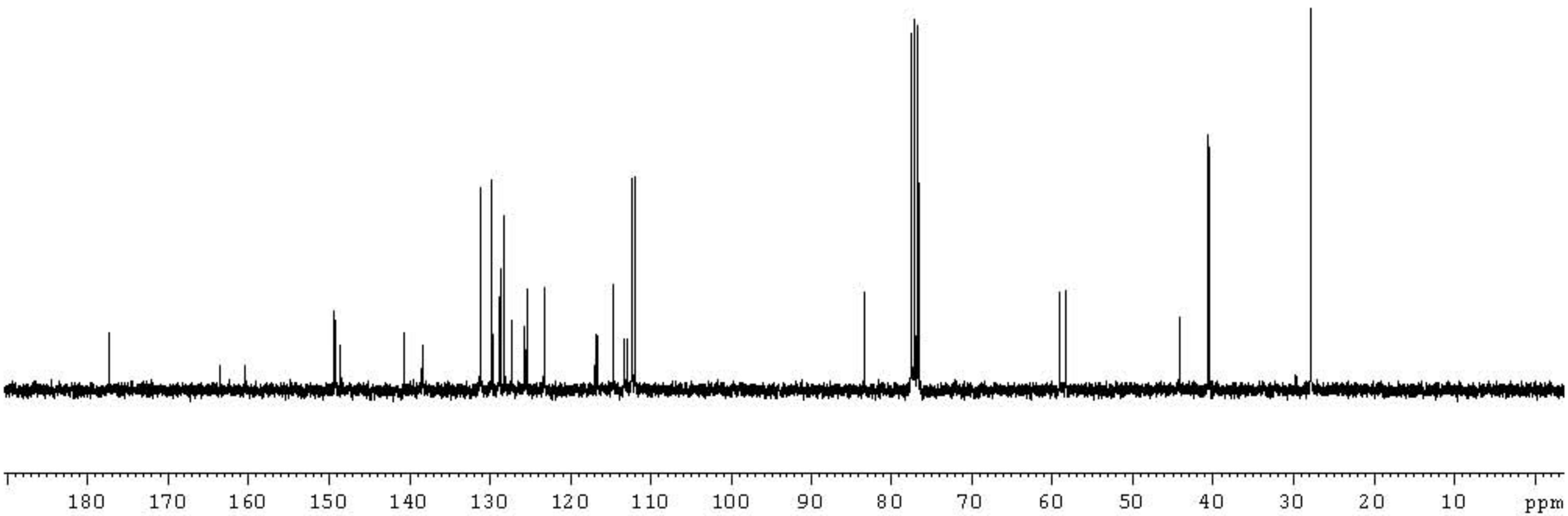

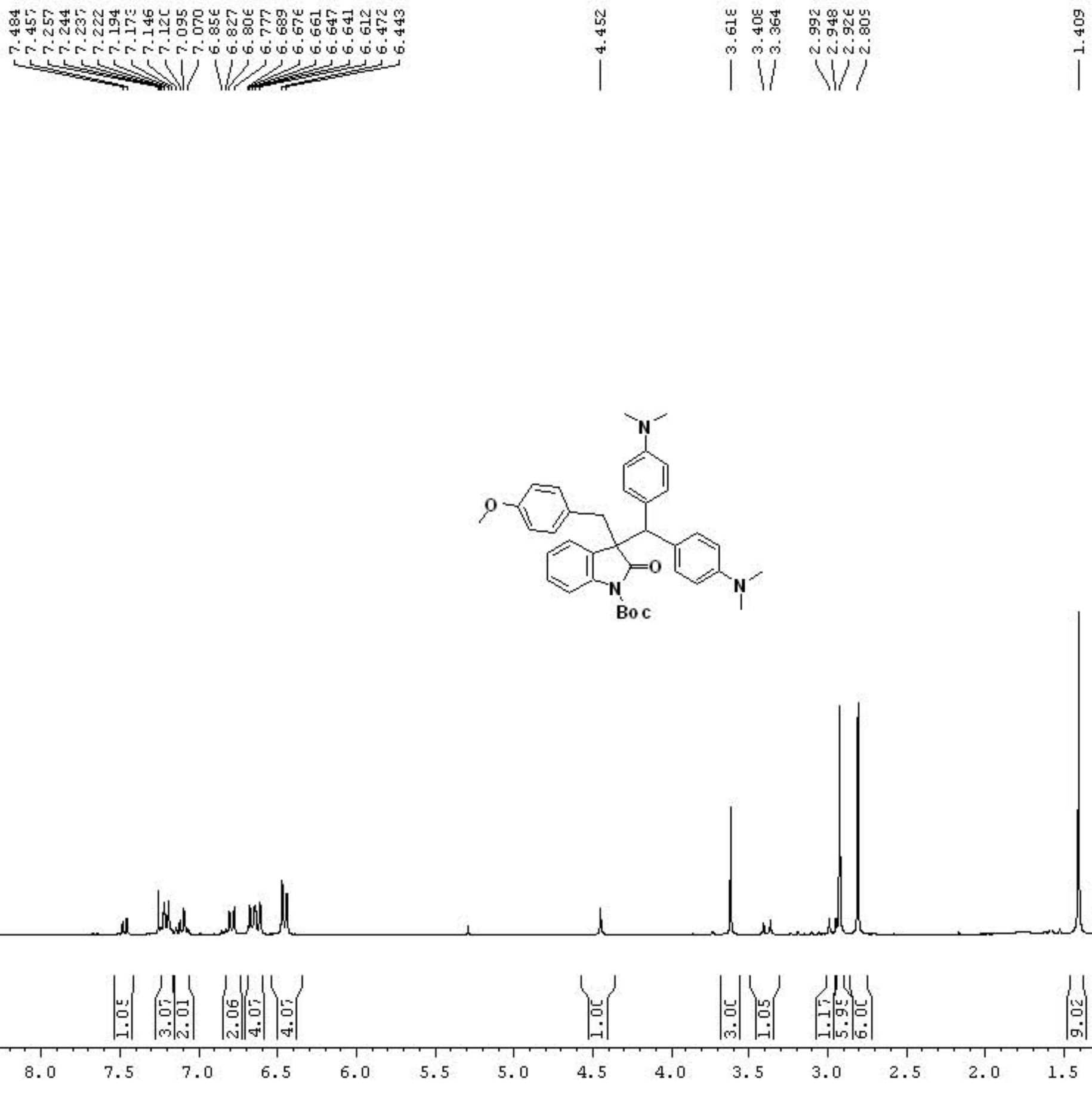

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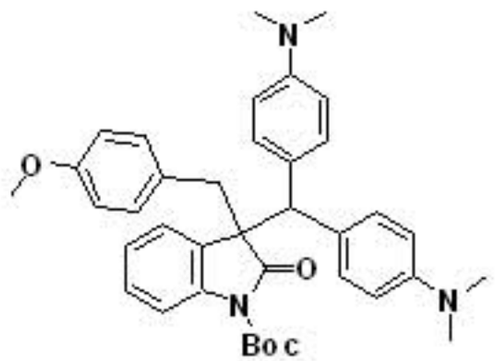

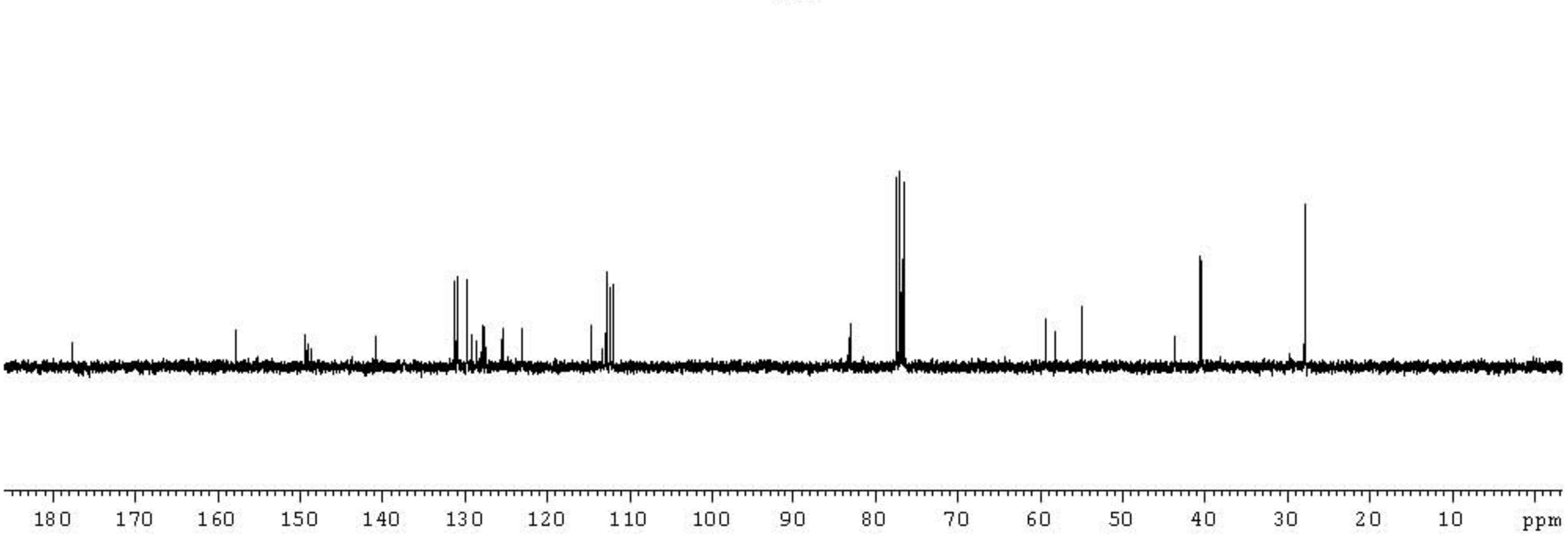

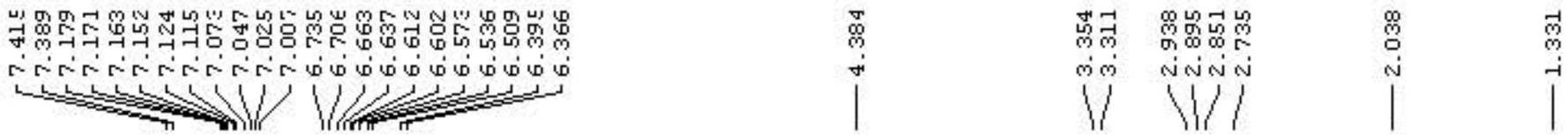

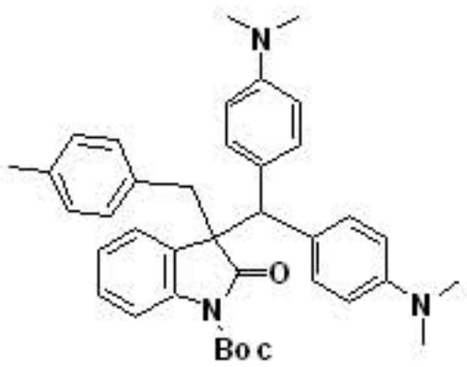

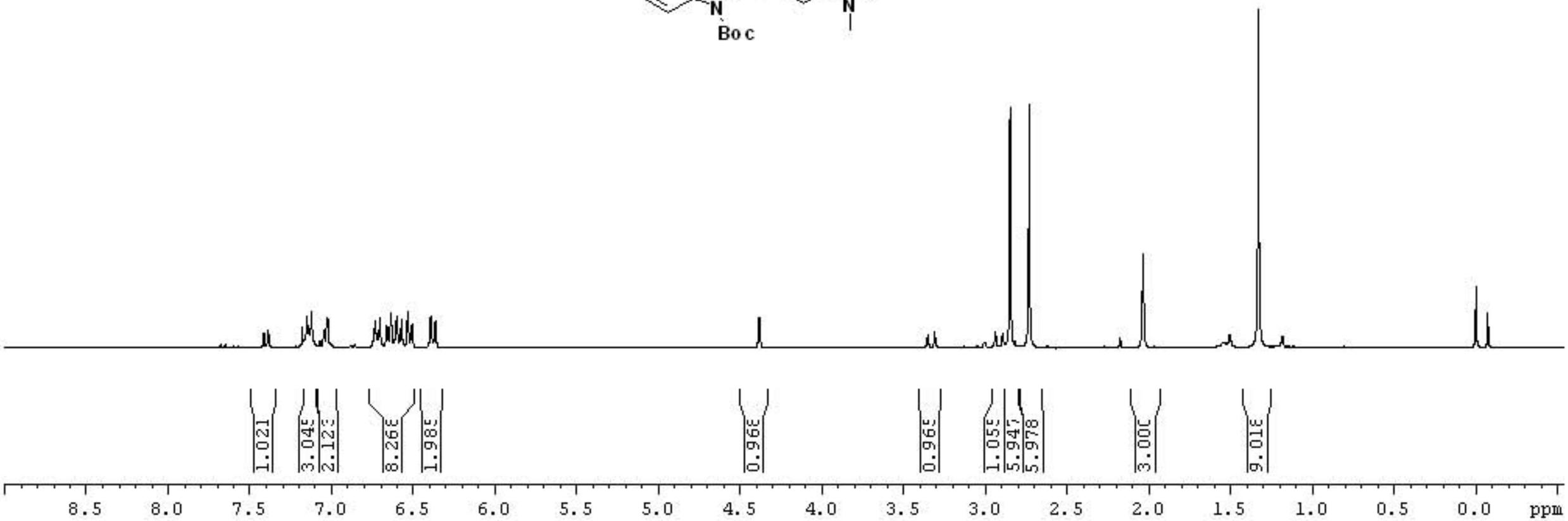

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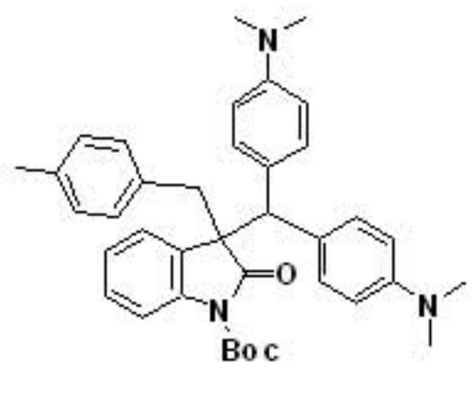

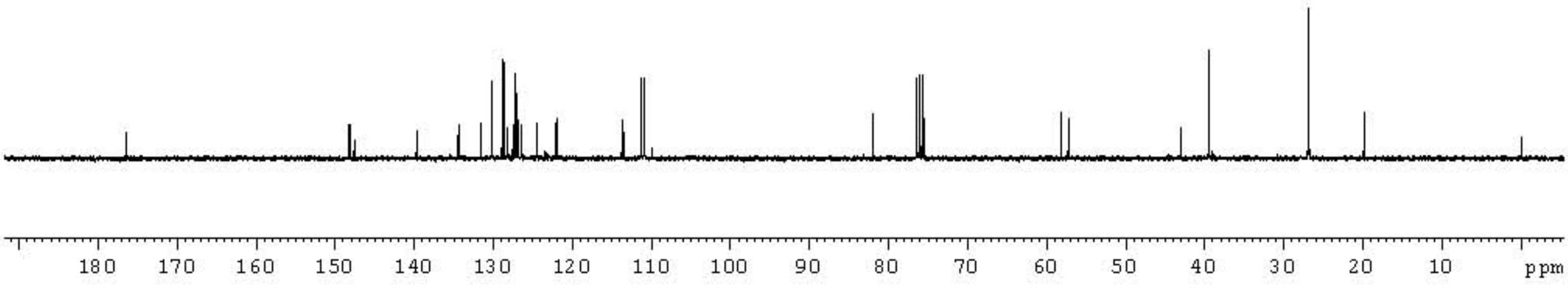

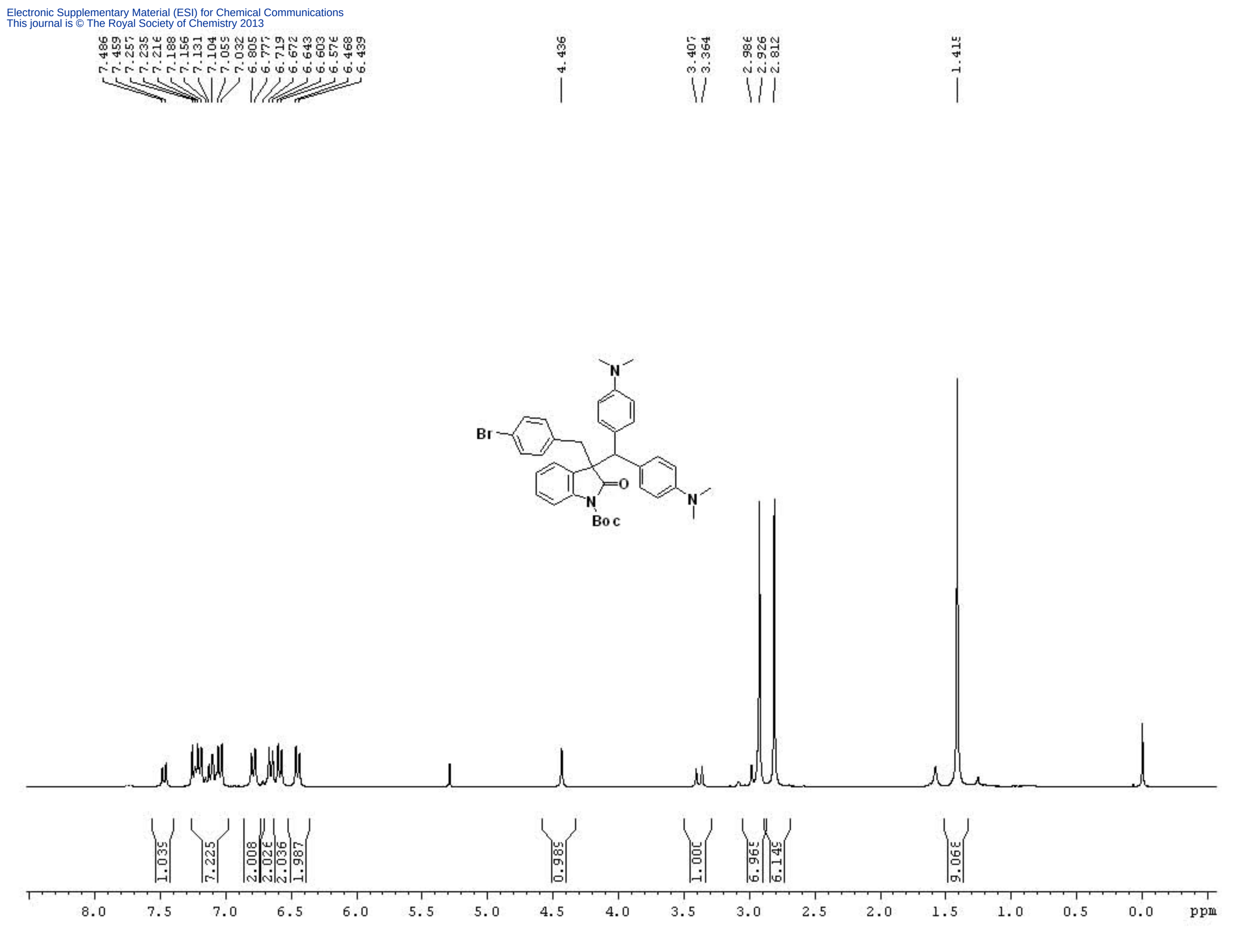

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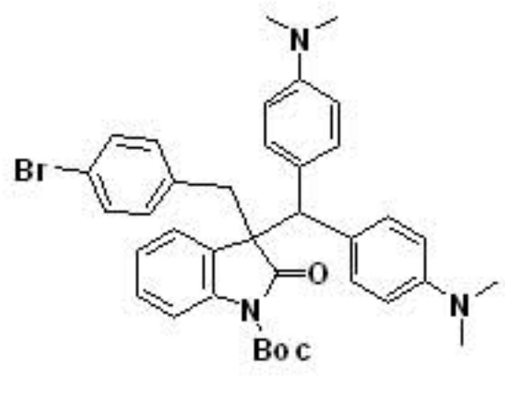

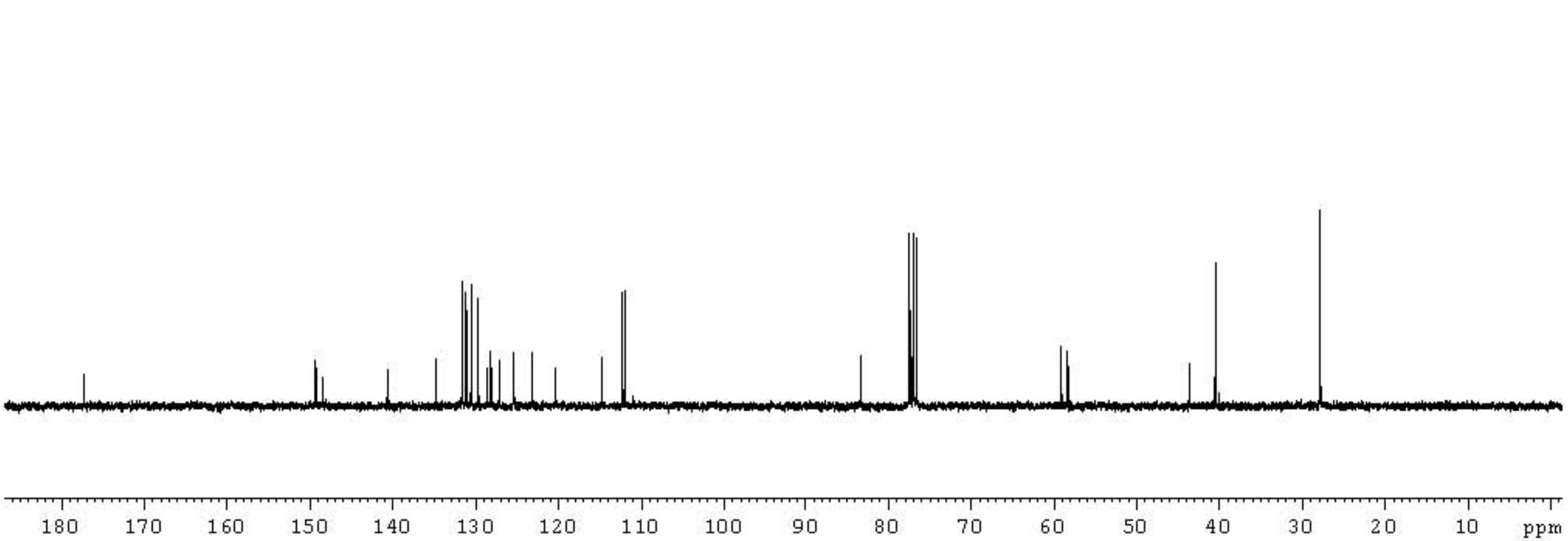

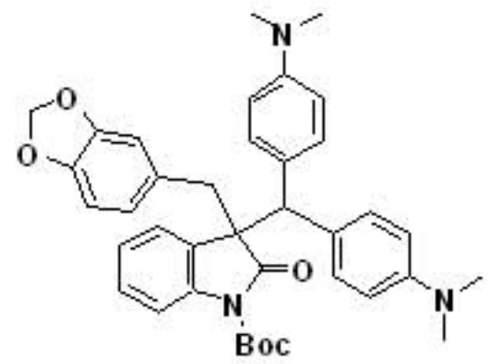

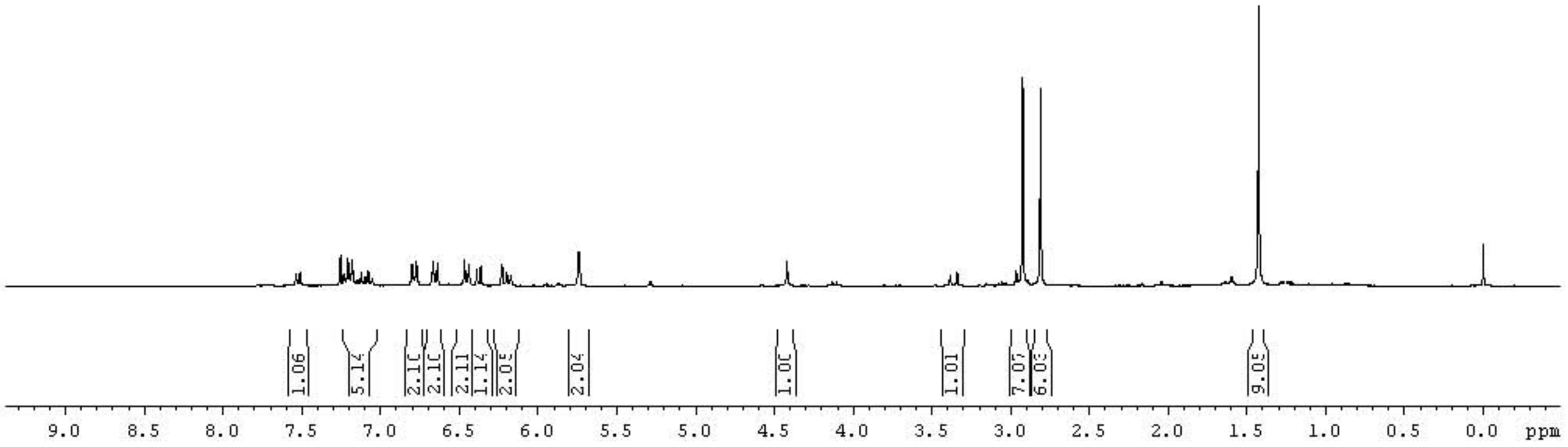

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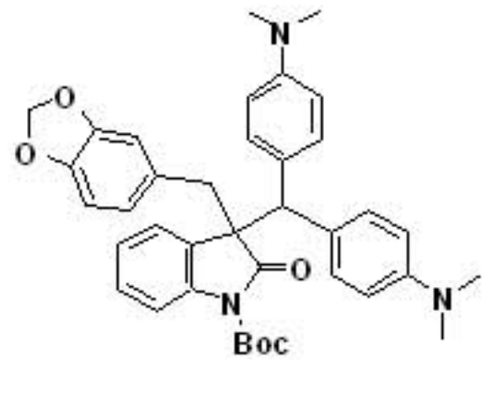

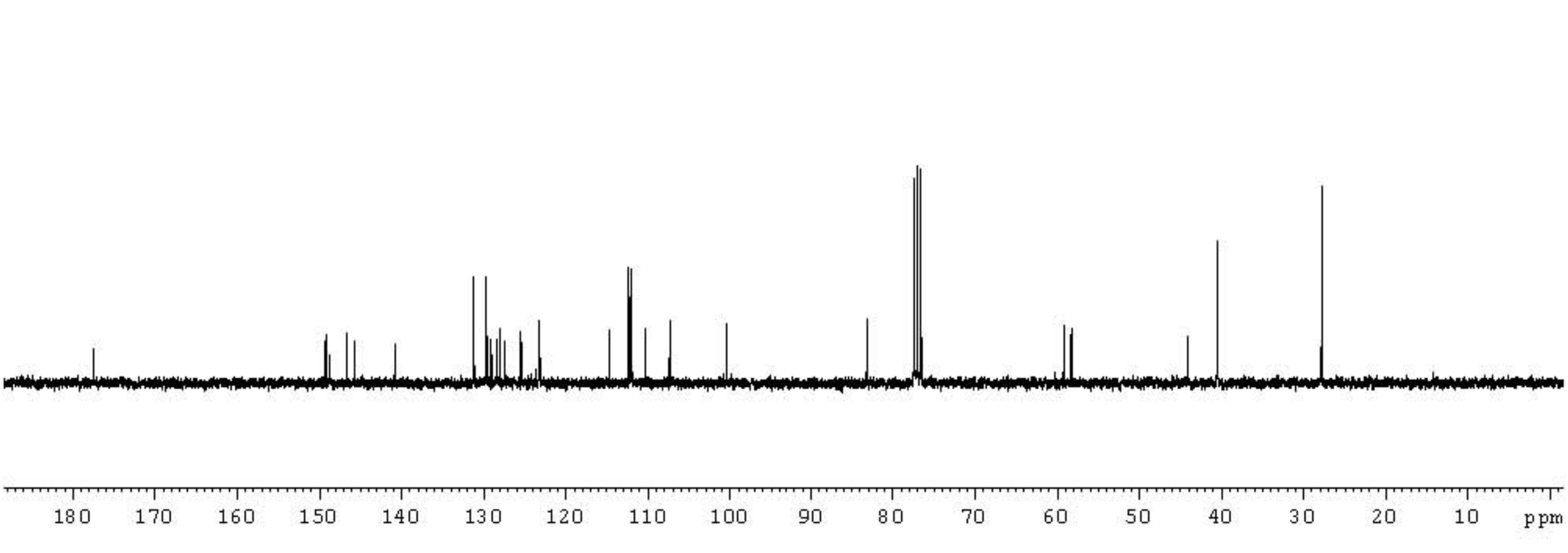

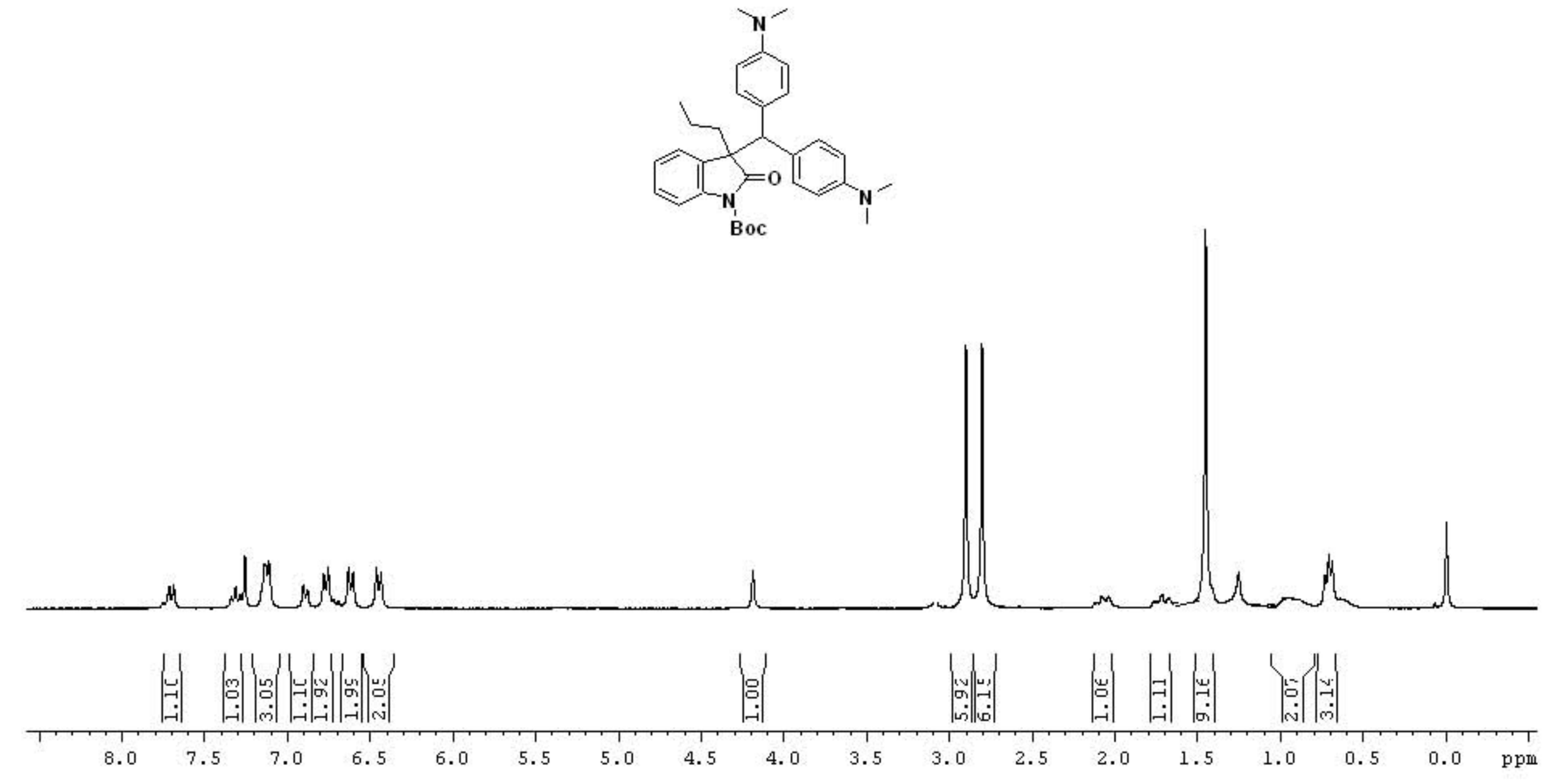

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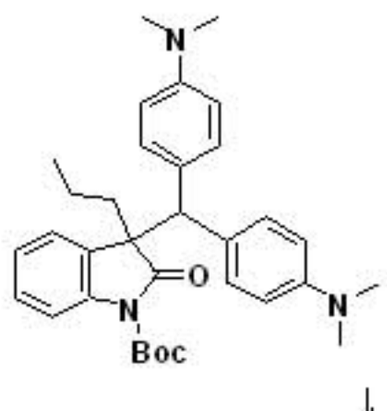

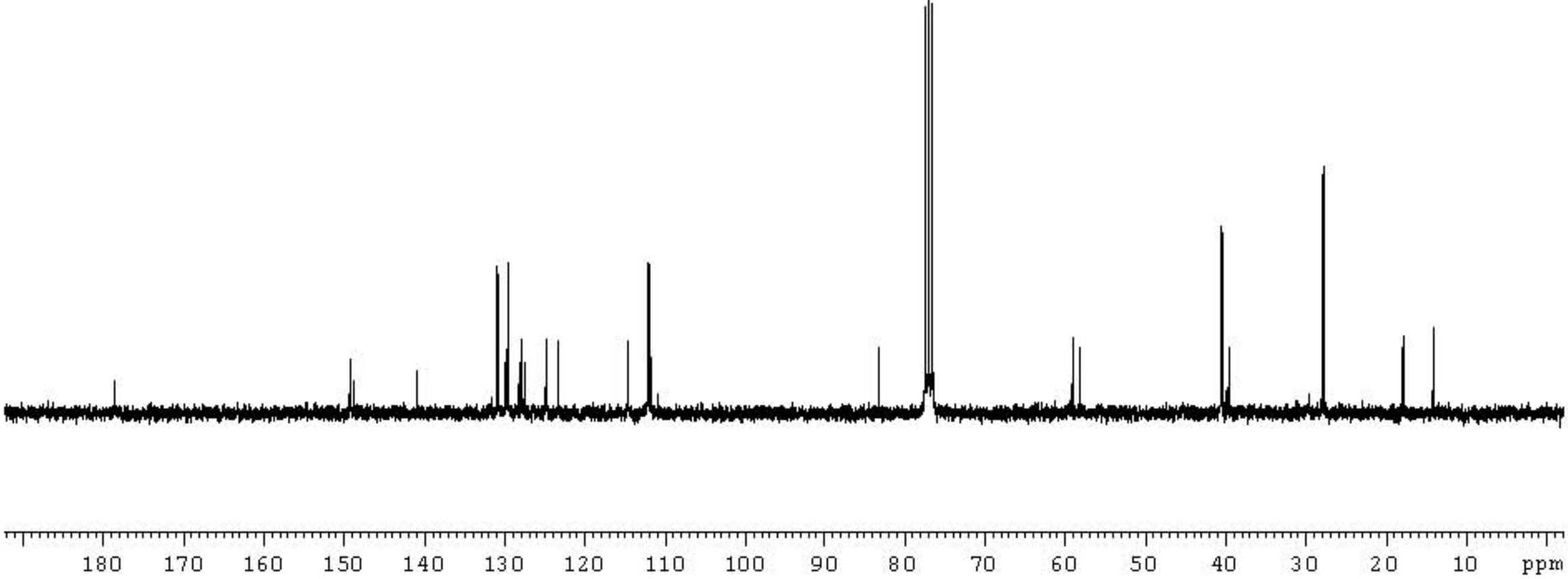

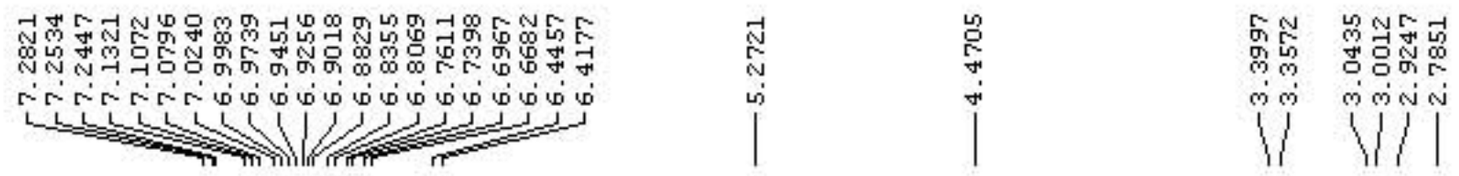

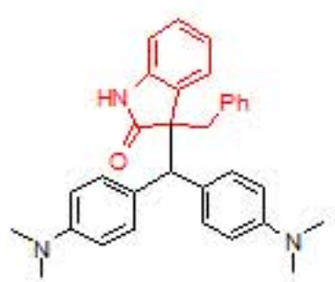

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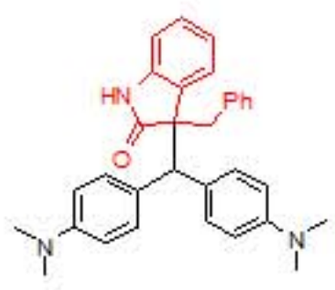

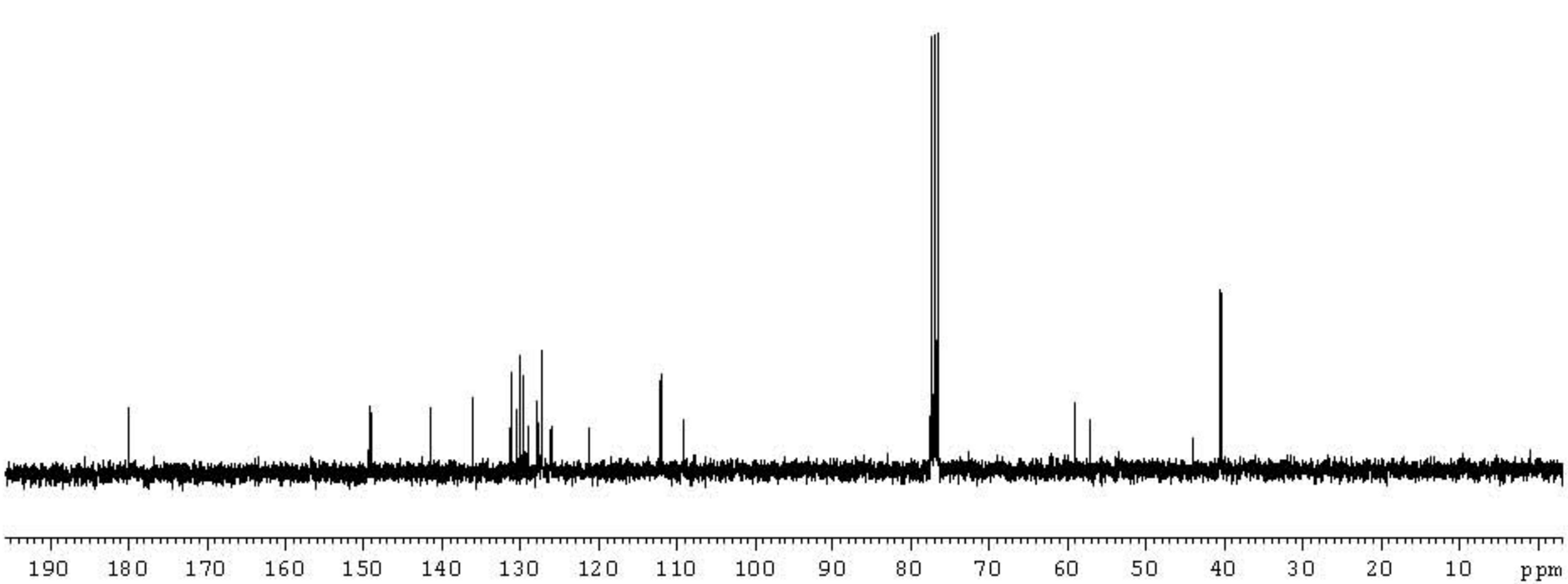

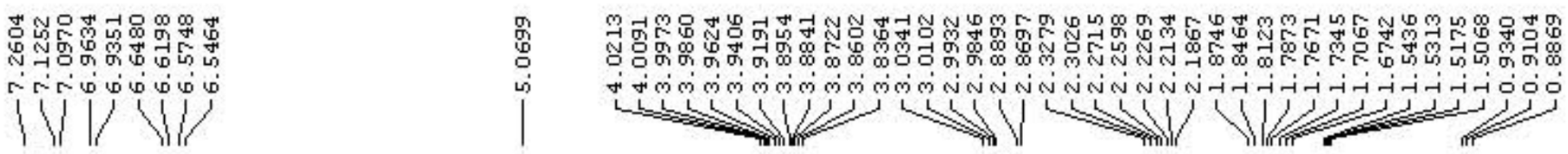

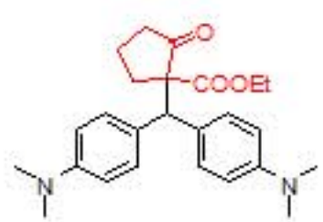

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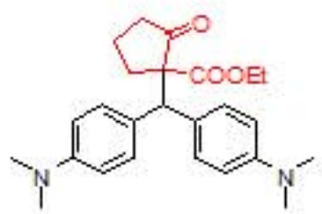

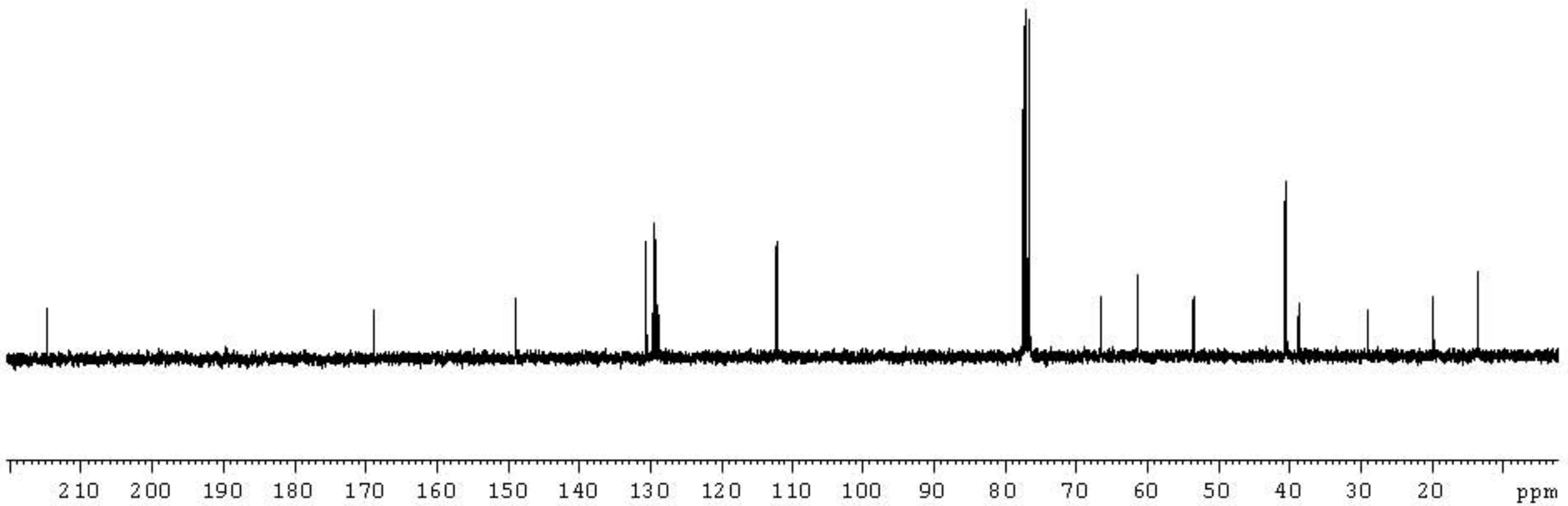

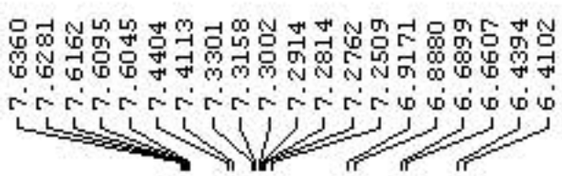

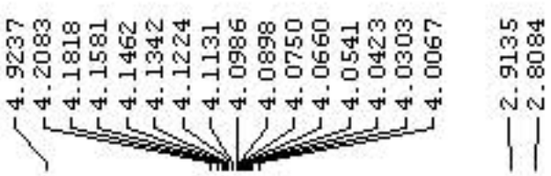

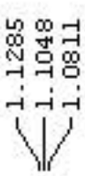

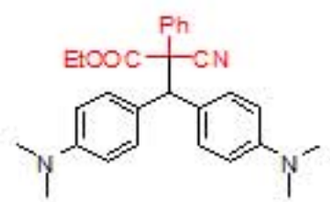

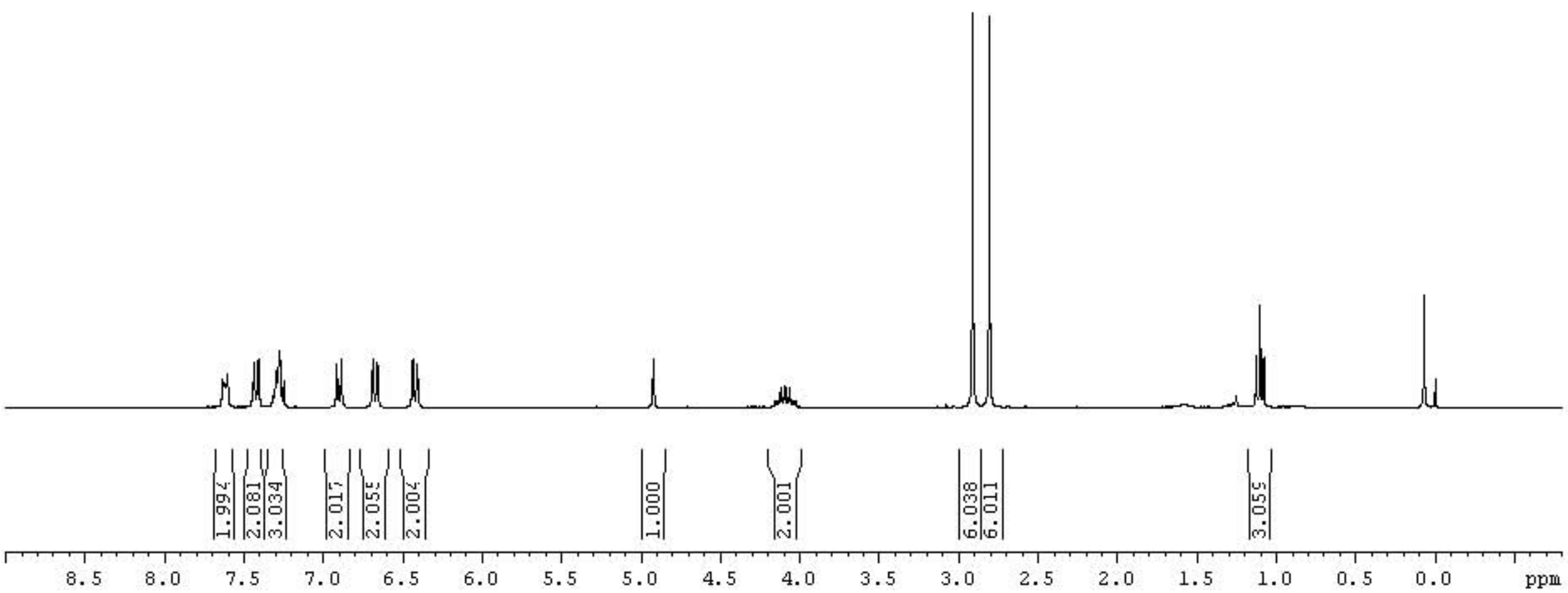

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