Electronic Supplementary Material (ESI) for Chemical Communications

Electrophile Induced Branching Cascade: A Powerful Approach to Access Various Molecular Scaffolds and Their Exploration as Novel Anti-mycobacterial Agent

Nitin T. Patil, Ashok Konala, Sudha Sravanti, Ashita Singh, Ramesh Ummanni and Balasubramanian Sridhar*

Contents

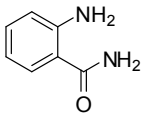
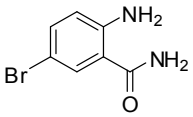
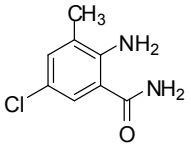
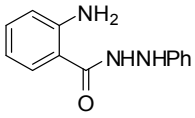
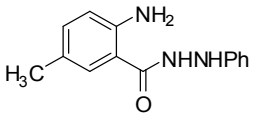
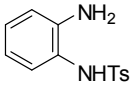
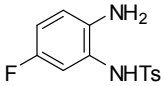
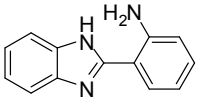
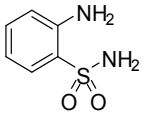
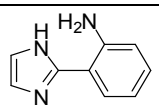
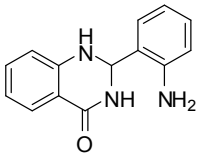
1. General Introduction

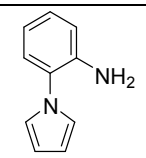
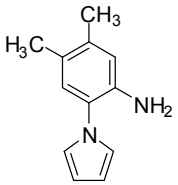
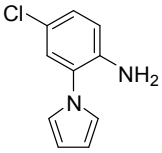
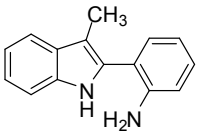
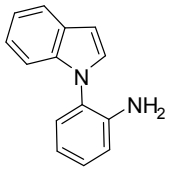
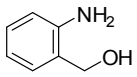
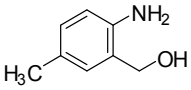
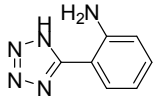
All cross coupling reactions were carried out in oven or flame dried vials with magnetic stirring under nitrogen atmosphere. Dried solvents and liquid reagents were transferred by oven-dried syringes or hypodermic syringe cooled to ambient temperature in a desiccators. All experiments were monitored by analytical thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining $KMnO_4$ and charring on a hot plate. Solvents were removed in vacuo and heated with a water bath at 35 °C. Silica gel finer than 200 mesh was used for flash column chromatography. Columns were packed as slurry of silica gel in hexane and equilibrated with the appropriate solvent mixture prior to use. The compounds were loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Melting points are uncorrected. IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1}. ^1H NMR spectra were recorded on 300 and 500, 600 MHz spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of ^1H NMR signals are designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet)… etc. ^{13}C NMR spectra were recorded on 75, 125, 150 MHz spectrometers. High-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry.

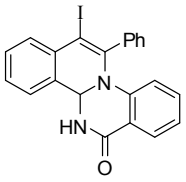
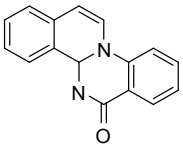
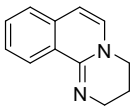
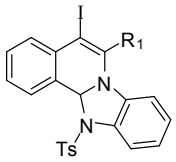
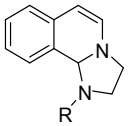
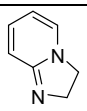
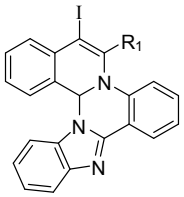
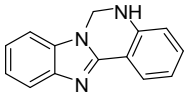
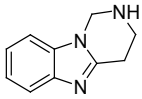
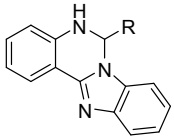
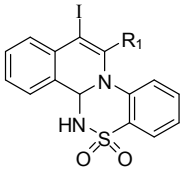
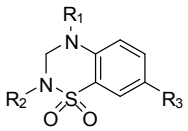
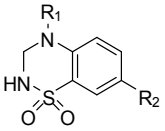
2. Synthesis of Scaffold Building Agents (SBAs)

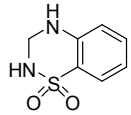
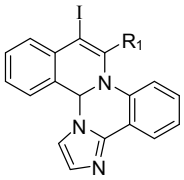
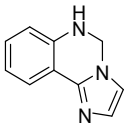
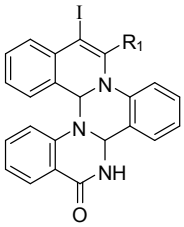
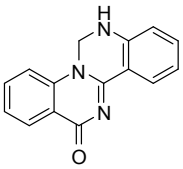
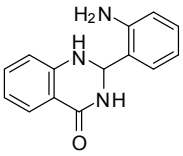
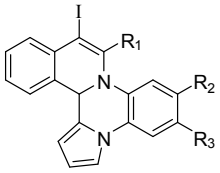
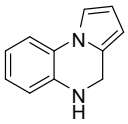
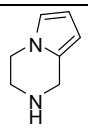
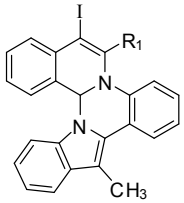
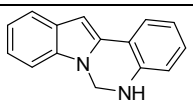
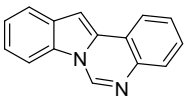
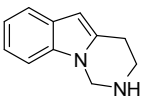
The scaffold building agents **1**, **3, 4** and **9** were commercially available while others prepared by literature known procedures. The details are given below in tabular form.

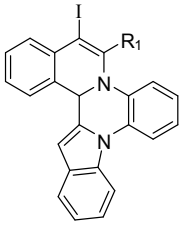
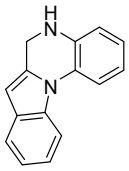
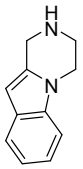
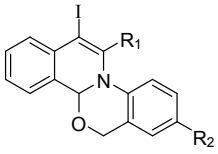
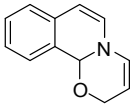
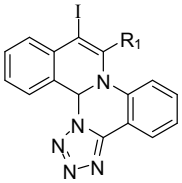
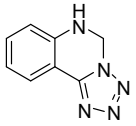
SBA No	Structures	References
1		Commercially available
1(I)		*Org. Biomol. Chem.*, **2003**, *11*, 383-392
1(II)		*J. Org. Chem.*, **2010**, *75*, 1277-1280
1(III)		*J. Indian Chem. Soc.*, **1980**, *57*, 887-889
1(VI)		*J. Indian Chem. Soc.*, **1980**, *57*, 887-889
2		*Angew. Chem. Int. Ed.*, **2007**, *46*, 7247-7250
2(I)		*Angew. Chem. Int. Ed.*, **2007**, *46*, 7247-7250
3		Commercially available
4		Commercially available
5		*Eur. J. Med. Chem.*, **1998**, *33*, 181-188
6		*J. Med. Chem.*, **1967**, *10*, 334-336

7		*J. Org. Chem.*, **2004**, *69*, 5578-5587
7(I)		*J. Med. Chem.*, **1999**, *42*, 4362-4379
7(II)		*J. Med. Chem.*, **2004**, *47*, 1997-2009
8		*Tetrahedron*, **1973**, *29*, 1429-1432
9		*J. Am. Chem. Soc.*, **2002**, *124*, 11684-11688
10		*Commercially available*
10(I)		*J. Org. Chem.*, **2008**, *73*, 4252-4255
11		*Chem. Comm.*, **2010**, *46*, 448-450

3. Polyheterocyclic Scaffolds Accessed Through EIBC– Literature Known Synthesis and Applications

Sl. No.	Scaffold	Sub-structures	Synthesis/Applications	References
1			Synthesis/TNF-α inhibition	*Chem. Commun.*, **2011**, *47*, 10263-10265
			Synthesis/Inhibition of FcεRI-mediated activation of mast Cells	*J. Med. Chem.*, **1998**, *41*, 1050-1059
2			Synthesis/DNA binding agent with cytotoxic properties	*J. Med. Chem*., **2005**, *48*, 4504-4506 *ChemBioChem*., **2006**, *7*, 1757-1763
			Synthesis/Hypoglycemic agent	US4097598 A1, **1978**
3			Synthesis/Lipid peroxidation inhibitory activity	*Eur. J. Med. Chem*., **1998**, *33*, 181-187
			Synthesis	*Ind. J. Chem*., **1970**, *8*, 126-129
			Used in an organic electronic device including OLED	WO200769847 A1, **2007**
4			Synthesis/Positive allosteric modulators of AMPA receptors	*J. Med. Chem.*, **2007**, *50*, 3153-3157
			Synthesis/Orally active potent cognitive enhancer	*J. Med. Chem.*, **2010**, *53*,1700-1711

			Synthesis/Antihypertensive agent	*J. Med. Chem.*, **1963**, *6*,122-127
5			Synthesis/Lipid peroxidation inhibitory activity	*Eur. J. Med. Chem.*, **1998**, *33*, 181-188
6			Synthesis	*Tetrahedron Lett.*, **2012**, *53*, 2643-2646
			Inhibitor of cell multiplication	*J. Med. Chem.*, **1967**, *10*, 334-336
7			Arginine vasopressin antagonists	*Bioorg. Med. Chem. Lett.*, **2003**, *13*, 2195-2198
			Hypotensive activity	*Pharmaceutical Chemistry Journal*, **1987**, *21*, 619-624
8			Synthesis	*Tetrahedron Lett.*, **2002**, *43*, 3347-3350
			Synthesis/Cataleptogenic activity	*J. Org. Chem.*, **1994**, *59*, 6777-6782 *Ger. Offen.*, **1971**, *961*, 2051
			Synthesis/Melatonin receptor ligands	*Org. Biomol. Chem.*, **2007**, *5*, 2129-2137

9			Synthesis/Antifungal activity	*Eur. J. Med. Chem.*, **2011**, 1919-1925
			Synthesis/5-HT_2 serotonin receptors	*Bioorg. Med. Chem. Lett.*, **2002**, *12*, 155-158
10			Synthesis	*Farmaco*, **1995**, *50*, 137-142
				Steroids, **1986**, *47*, 307-320
				Synthesis, **2012**, *44*, 2519-2526
				Eur. J. Org. Chem., **2010**, 1999-2007
11			Synthesis/Bronchodilator agents	US3835138, **1974**

4. General Procedures and Characterization Data of Compounds

Condition 1:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_1, N_2, N_4, N_6) (0.2205 mmoles) and 2-alkynylbenzaldehyde (0.2205 mmoles) in DCE (0.09 M) followed by the addition of iodine (3 eq). The reaction vial was fitted with a cap, evacuated and filled with nitrogen and stirred at rt for 3 hrs. The reaction mixture was quenched by the addition of aq. sodium thiosulphate solution, diluted with 5 mL water and extracted with DCM (10 mL x 3). Work up and purification by column chromatography using EtOAc/hexane or MeOH/DCM as an eluent afforded analytically pure compounds.

Condition 2:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_9) (0.1442 mmoles) and 2-alkynylbenzaldehyde (0.1442 mmoles) in CH_3CN (2.5 mL) followed by the addition of iodine (3 eq). The reaction vial was fitted with a cap and stirred at rt for 8 hrs. The reaction mixture was quenched by the addition of aq. sodium thiosulphate solution, diluted with 5 mL water

and extracted with EtOAc (10 mL x 3). Work up and purification by column chromatography using EtOAc/hexane as an eluent afforded analytically pure compound.

Condition 3:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_{10}) (0.2439 mmoles) and 2-alkynylbenzaldehyde (0.2439 mmoles) in CH_3CN (2.5 ml) followed by the addition of K_2CO_3 (2 eq), iodine (1.8 eq). The reaction vial was fitted with a cap, evacuated and filled with nitrogen and stirred at rt for 5 hrs. The reaction mixture was quenched by the addition of aq. sodium thiosulphate solution, diluted with 5 mL water, and extracted with EtOAc (10 mL x 3). Work up and purification by column chromatography using EtOAc/hexane as an eluent afforded analytically pure compound.

Condition 4:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_8) (0.1351 mmoles) and 2-alkynylbenzaldehyde (0.1351 mmoles) in DCE (2.5 mL) followed by the addition of K_2CO_3 (2 eq), iodine (1.8 eq). The reaction vial was fitted with a cap, evacuated and filled with nitrogen and stirred at 75^o C for 5 hrs. The reaction mixture was quenched by the addition of aq. sodium thiosulphate solution, diluted with 5 mL water, and extracted with EtOAc (10 mL x 3). Work up and purification by column chromatography using EtOAc/hexane as an eluent afforded analytically pure compounds.

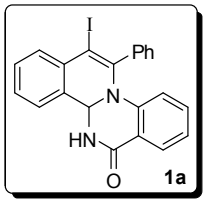
Condition 5:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_7) (0.1910 mmoles) and 2-alkynylbenzaldehyde (0.1910 mmoles) in DCE (2.5 mL) followed by the addition of 5 mol % *p*-TSA. The reaction vial was fitted with a cap, evacuated and filled with nitrogen and stirred at rt for 3 hrs. After specified time, K_2CO_3 (1.2 eq) and iodine (1.1eq) were added in a sequential manner and the reaction mixture was allowed to stir for 2 hrs. The reaction mixture was quenched by the addition of aq. sodium thiosulphate solution, diluted with 5 mL water, and extracted with EtOAc (10 mL x 3). Work up and purification by column chromatography using EtOAc/hexane as an eluent afforded analytically pure compounds.

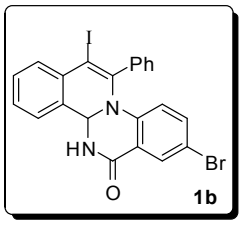
Condition 6:

To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent (N_3, N_5, N_{11}) (0.1442 mmoles) and 2-alkynylbenzaldehyde (0.1442 mmoles) in DCM (0.06 M) followed by the

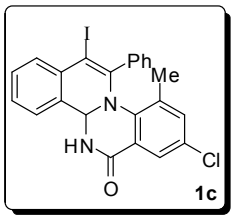
addition of 5 mol % *p*-TSA. The reaction vial was fitted with a cap, evacuated and filled with nitrogen and allowed to stirr at rt for 6 hrs. The reaction mixture was cooled to 0 ^{o}C and then ICl (1.1 eq) was added. The reaction mixture was stirred for 2 hrs and then subsquently quenched by the addition of aq. sodium bicarbonate solution followed by adition of water and EtOAc. Work up and purification by column chromatography using EtOAc/hexane as an eluent afforded analytically pure compounds.



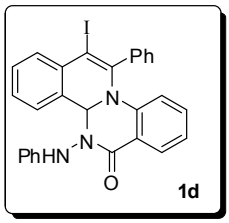
13-Iodo-12-phenyl-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1a): 92% yield; yellow solid (M.P. = 106-108 °C); R_f 0.30 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.48-7.33 (m, 9H), 7.09 (dd, *J* = 2.3 Hz, *J* = 8.7, 1H), 6.23 (t, *J* = 8.7 Hz, 1H), 6.11 (s, 1H); ^{13}C NMR (150 MHz, DMSO d_6): δ 165.7, 153.1, 143.9, 138.5, 136.7, 134.8, 132.9, 132.0, 130.7, 129.1, 128.4, 127.5, 127.2, 126.7, 125.6, 122.5, 117.6, 111.2, 103.1, 70.4, 67.1; IR (KBr): ν_{max} 3420, 3057, 2923, 1671, 1626, 1552, 1511, 1471, 1336, 1160, 1129, 1072, 1025, 816, 759, 696, 642, 543cm^{-1}; MS (ESI) *m/z* 451 (M^+ + H); HRMS calcd. for $C_{22}H_{16}IN_2O$ (M^+ + H) 451.0307, found 451.0315.



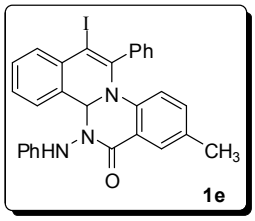
8-Bromo-13-iodo-12-phenyl-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1b): 89% yield; yellow solid (M.P. = 136-138 °C); R_f 0.32 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 3H), 7.38-7.33 (m, 5H), 7.10 (d, *J* = 9.1 Hz, 1H), 6.24 (d, *J* = 9.1 Hz, 1H), 6.13 (s, 1H); ^{13}C NMR (125 MHz, DMSO d_6+$CDCl_3$): δ 164.4, 159.9, 152.5, 141.6, 140.3, 136.8, 135.9, 134.9, 133.8, 133.0, 132.5, 131.9, 128.0, 127.8, 125.8, 124.5, 122.8, 118.8, 116.7, 110.5, 66.3, 65.3; IR (KBr): ν_{max} 3429, 3232, 2924, 1674, 1590, 1472, 1392, 1342, 1315, 1284, 1198, 1169, 1127, 1079, 1027, 905, 805, 762, 726, 698, 551, 468 cm^{-1}; MS (ESI) *m/z* 529 (M^+ + H); HRMS calcd. for $C_{22}H_{15}BrIN_2O$ (M^+ + H) 528.9412, found 528.9418.



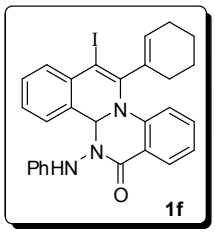
8-Chloro-13-iodo-10-methyl-12-phenyl-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1c): 84% yield; brown solid (M.P. = 108-110 °C); R_f 0.34 (hexane/EtOAc= 70/30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (t, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.51 (tt, *J* = 7.6, 1.4 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.34 (dt, *J* = 6.6, 0.9 Hz, 1H), 7.30 (dt, *J* = 6.6, 0.9 Hz, 1H), 7.22 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 6.9 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 153.5, 144.7, 141.6, 138.3, 135.3, 134.2, 133.7, 132.3, 130.9, 130.5, 129.1, 128.7, 127.8, 127.1, 126.3, 125.5, 124.6, 68.2, 60.3, 17.9; IR (KBr): ν_{max} 3381, 3056, 2922, 1725, 1666, 1613, 1584, 1451, 1375, 1264, 1214, 1186, 1136, 1035, 927, 879, 847, 961, 700, 634, 598, 565, 535, 477, 422cm^{-1}; MS (ESI) *m/z* 499 (M^+ + H); HRMS calcd. for $C_{23}H_{17}ClIN_2O$ (M^+ + H) 499.0074, found 499.0068.



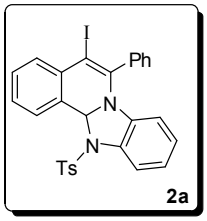
13-Iodo-12-phenyl-5-(phenylamino)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1d): 84% yield; solid (M.P. = 176-178 °C); R_f 0.30 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 3H), 7.40-7.32 (m, 3H), 7.22-7.14 (m, 3H), 7.07-7.00 (m, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 6.41 (d, *J* = 8.3 Hz, 1H), 6.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 145.9, 143.7, 143.1, 136.6, 135.8, 133.7, 131.8, 131.1, 130.2, 129.8, 129.5, 129.2, 128.7, 128.5, 128.4, 125.7, 125.2, 122.3, 121.9, 120.7, 116.5, 113.8, 69.4, 75.0; IR (KBr): ν_{max} 3255, 3025, 2922, 1663, 1597, 1491, 1467, 1403, 1300, 1272, 1154, 1109, 1029, 966, 876, 847, 817, 753, 694, 577, 546, 499 cm^{-1}; MS (ESI) *m/z* 542 (M^+ + H); HRMS calcd. for $C_{28}H_{21}IN_3O$ (M^+ + H) 542.0729, found 542.0723.



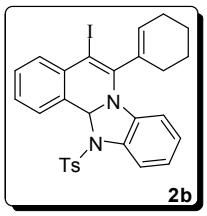
13-Iodo-12-phenyl-8-methyl-5-(phenylamino)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1e): 83% yield; solid (M.P. = 164-166 °C); R_f 0.31 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 2.3 Hz, 1H), 8.01 (d, *J* = 1.5 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.61 (dd, *J* = 1.5 Hz, *J* = 6.0, 1H), 7.33-7.28 (m, 2H), 7.20-7.16 (m, 5H), 7.02-6.96 (m, 2H), 6.84 (dt, *J* = 2.3 Hz, *J* = 6.0, 2H), 6.70-6.65 (m, 1H), 6.34 (d, *J* = 8.3 Hz, 1H), 6.30 (d, *J* = 9.0 Hz, 1H), 6.01 (s, 1H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $DMSOd_6$): δ 164.2, 160.8, 148.7, 147.1, 143.4, 140.4, 136.6, 135.7, 134.3, 132.5, 131.0, 130.7, 129.9, 129.8, 129.3, 128.4, 128.1, 127.7, 125.0, 122.7, 119.8, 116.1, 112.3, 75.8, 74.8, 19.7; IR (KBr): ν_{max} 3258, 3056, 3024, 2922, 2855, 1662, 1603, 1490, 1441, 1405, 1344, 1273, 1136, 1027, 966, 906, 822, 751, 727, 693, 534, 502 cm^{-1}; MS (ESI) *m/z* 556 (M^+ + H); HRMS calcd. for $C_{29}H_{23}N_3OI$ (M^+ + H) 556.0886, found 556.0880.



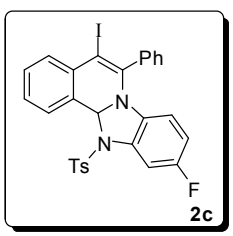
13-Iodo-12-cyclohexenyl-5-(phenylamino)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1f): 81% yield; solid (M.P. = 170-172 °C); R_f 0.32 (hexane/EtOAc= 70/30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.30-7.27 (m, 4H), 7.23-7.20 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.82 (t, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.73 (s, 1H), 1.88-1.69 (m, 8H); ^{13}C NMR (125 MHz, DMSO): δ 165.1, 161.2, 147.4, 145.0, 143.3, 133.5, 132.5, 130.9, 130.6, 129.2, 128.4, 127.3, 126.2, 123.5, 119.9, 117.4, 116.3, 115.3, 112.3, 75.6, 75.0, 25.6, 24.2, 22.1, 21.7; IR (KBr): ν_{max} 3251, 3052, 3029, 2921, 2850, 1668, 1607, 1491, 1446, 1408, 1341, 1275, 1132, 1022, 962, 904, 820, 759, 725, 698, 531 cm^{-1}; MS (ESI) *m/z* 546 (M^+ + H); HRMS calcd. for $C_{28}H_{25}IN_3O$ (M^+ + H) 546.1042, found546 .1048.



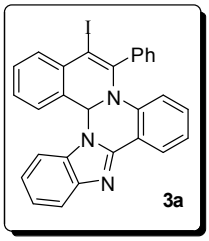
5-Iodo-6-phenyl-12-tosyl-12,12a-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (2a): 72% yield; thick liquid; R_f 0.52 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.68 (m, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.54-7.52 (m, 3H), 7.39-7.36 (m, 3H), 7.31-7.26 (m, 4H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.63 (t, *J* = 8.3 Hz, 1H), 6.55 (s, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 142.6, 139.7, 138.8, 133.7, 133.1, 131.1, 130.4, 129.9, 129.6, 128.7, 128.1, 127.6, 127.1, 126.4, 126.0, 123.9, 117.3, 114.7, 110.8, 82.7, 78.3, 21.3; IR : ν_{max} 3446, 2924, 2856, 1728, 1630, 1593, 1539, 1454, 1378, 1236, 1152, 1110, 1001, 912, 811, 741, 678, 562 cm^{-1}; MS (ESI) *m/z* 577 (M^+ + H); HRMS calcd. for $C_{28}H_{22}IN_2O_2S$(M^+ + H) 577.0447, found 577. 0452.



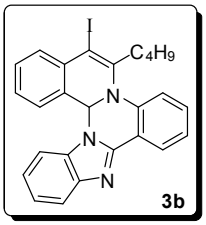
5-Iodo-6-cyclohexenyl-12-tosyl-12,12a-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (2b): 68% yield; yellow solid (M.P. = 78-80 °C); R_f 0.54 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.59 (m, 2H), 7.47-7.41 (m, 3H), 7.32-7.29 (m, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.89 (t, *J* = 6.0 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 6.8 Hz, 1H), 6.00-5.98 (m, 1H), 2.38 (s, 3H), 1.61-1.57 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 136.7, 134.8, 132.6, 131.8, 129.6, 128.9, 128.6, 127.5, 127.1, 126.1, 125.5, 123.3, 122.8, 120.4, 119.1, 114.6, 110.3, 86.7, 78.2, 27.3, 25.3, 22.2, 21.5, 21.3; IR (KBr): ν_{max} 3448, 2920, 2852, 1726, 1635, 1591, 1530, 1458, 1371, 1239, 1158, 1008, 914, 816, 742, 676, 560 cm^{-1}; MS (ESI) *m/z* 581 (M^+ + H); HRMS calcd. for $C_{28}H_{26}IN_2O_2S$ (M^+ + H)581.0760, found 581.0765.



10-Fluoro-5-iodo-6-phenyl-12-tosyl-12,12a-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (2c): 60% yield; thick liquid; R_f 0.50 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.67 (m, 1H), 7.56-7.52 (m, 4H), 7.42-7.39 (m, 2H), 7.38-7.35 (m, 2H), 7.32-7.28 (m, 3H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.57 (s, 1H), 6.43 (dt, *J* = 3.0, *J* = 6.0 Hz, 1H), 5.01 (dd, *J* = 2.3, *J* = 6.8 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 160.6 ($J_{13C\text{-}19F}$ = 243.4 Hz), 144.8, 140.3, 140.2, 138.4, 135.3, 133.6, 132.7, 130.8, 130.5, 130.0, 129.8, 129.1, 129.0, 128.3, 127.7, 126.9, 123.5, 120.1, 120.0 ($J_{13C\text{-}19F}$ = 9.9 Hz), 106.6, 106.4 ($J_{13C\text{-}19F}$ = 23.6 Hz), 99.4, 99.2 ($J_{13C\text{-}19F}$ = 29.9 Hz), 83.8, 79.1, 21.6; IR : ν_{max} 3441, 2929, 2853, 1722, 1637, 1537, 1455, 1372, 1239, 1150, 1114, 910, 817, 743, 675, 568 cm^{-1}; MS (ESI) *m/z* 595 (M^+ + H); HRMS calcd. for $C_{28}H_{21}FIN_2O_2S$ (M^+ + H) 595.0352, found 595.0356.

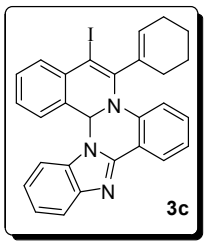


10-Iodo-9-phenyl-14bH-benzimidazo[1,2-c]isoquinolino[2,1-a]quinazoline (3a): 75% yield; yellow solid (M.P. = 198-200 °C); R_f 0.40 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 1.5 Hz, *J* = 6.0, 1H), 7.97-7.94 (m, 3H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.44-7.42 (m, 4H), 7.35 (t, *J* = 3.7 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.93 (dt, *J* = 1.5 Hz, *J* = 6.0, 2H), 6.88 (d, *J* = 6.8 Hz, 2H), 6.48 (d, *J* = 6.8 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 141.9, 138.8, 137.2, 134.9, 133.8, 132.4, 130.8, 130.5, 130.3, 129.4, 128.8, 128.3, 127.9, 127.7, 127.6, 126.6, 124.6, 122.4, 121.2, 119.6, 116.9, 70.4, 59.4; IR (KBr): ν_{max} 3062, 2954, 2924, 2860, 1728, 1614, 1582, 1530, 1471, 1378, 1306, 1242, 1156, 1120, 1072, 836, 751, 614 cm^{-1}; MS (ESI) *m/z* 524 (M^+ + H); HRMS calcd. for $C_{28}H_{19}IN_3$ (M^+ + H) 524.0624, found 524.0632.

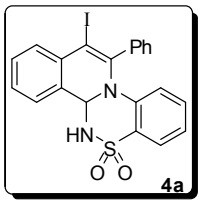


10-Iodo-9-^{n}butyl-14bH-benzimidazo[1,2-c]isoquinolino[2,1-a]quinazoline (3b): 71% yield; thick liquid; R_f 0.42 (hexane/EtOAc= 70/30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 1.5 Hz, *J* = 6.2, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 6.6 Hz, 1H), 7.34-7.29 (m,

3H), 7.22 (d, *J* = 5.9 Hz, 1H), 7.05 (t, *J* = 6.6 Hz, 1H), 6.99 (t, *J* = 6.7 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.59 (s, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 3.09-3.03 (m, 1H), 2.63-2.57 (m, 1H), 1.89-1.82 (m, 1H), 1.73-1.64 (m, 1H), 1.49-1.43 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 145.3, 141.1, 134.9, 133.8, 131.3, 129.6, 129.0, 128.4, 16.2, 125.4, 123.3, 122.9, 122.1, 121.6, 120.9, 119.9, 116.3, 111.1, 109.0, 73.7, 69.5, 36.7, 28.5, 22.1, 13.2; IR: ν_{max} 3062, 2958, 2928, 2864, 1729, 1616, 1585, 1534, 1473, 1377, 1303, 1240, 1158, 1122, 1072, 919, 838, 751, 618 cm^{-1}; MS (ESI) *m/z* 504 (M^+ + H); HRMS calcd. for $C_{26}H_{23}IN_3$ (M^+ + H) 504.0937, found 504.0931.

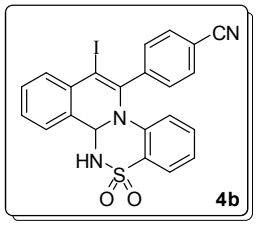


10-Iodo-9-cyclohexenyl-14bH-benzimidazo[1,2-c]isoquinolino[2,1-a]quinazoline (3c): 62% yield; yellow solid (M.P. = 188-190 °C); R_f 0.41 (hexane/EtOAc= 70/30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.41(t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 3H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.68-6.63 (m, 2H), 6.30 (d, *J* = 7.5 Hz, 1H), 7.42-7.35 (m, 4H), 7.28 (dd, *J* = 1.5 Hz, *J* = 6.0, 2H), 7.20-7.12 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 1H), 1.75-1.42 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 145.8, 139.3, 138.0, 136.6, 135.6, 134.6, 133.7, 131.8, 131.1, 128.9, 127.7, 127.2, 125.9, 123.7, 121.5, 119.4, 116.9, 111.6, 109.3, 69.4, 60.3, 28.9, 25.7, 22.8, 21.7; IR (KBr): ν_{max} 3064, 2956, 2925, 2860, 1728, 1614, 1582, 1530, 1471, 1378, 1306, 1242, 1156, 1120, 1072, 836, 751, 614 cm^{-1}; MS (ESI) *m/z* 528 (M^+ + H); HRMS calcd. for $C_{28}H_{23}IN_3$ (M^+ + H) 528.0937, found 528.0931.

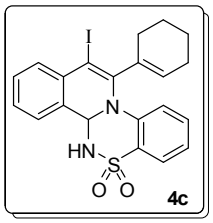


13-Iodo-12-phenyl-4b*H*-benzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline-6,6-dione (4a): 80% yield; yellow solid (M.P. = 124-126 °C); R_f 0.35 (hexane/EtOAc= 70/30); ^{1}H NMR (500 MHz, DMSO d_6): δ 9.19 (d, *J* = 11.1 Hz, 1H), 7.61 (t, *J* = 8.7 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.41-7.37 (m, 3H), 7.34-7.27 (m, 3H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 6.19 (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 139.7, 139.0, 137.6, 135.7,

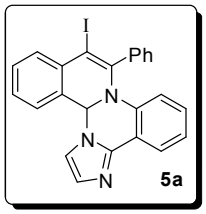
130.9, 129.6, 129.2, 128.9, 128.7, 128.6, 128.5, 128.1, 127.7, 127.5, 125.2, 124.0, 70.5, 60.4; IR (KBr): ν_{max} 3381, 3055, 1654, 1617, 1589, 1479, 1444, 1380, 1338, 1205, 1167, 1080, 1022, 916, 758, 700, 596, 544 cm^{-1}; MS (ESI) *m/z* 486 (M^+ + H); HRMS calcd. for $C_{21}H_{16}IN_2O_2S$ (M^+ + H) 486.9977, found 486.9972.



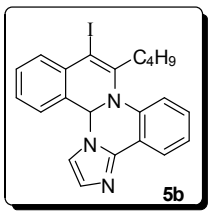
13-Iodo-12-(4-cyanophenyl)-4b*H*-benzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline-6,6dione (4b): 87% yield; yellow solid (M.P. = 150-152 °C); R_f 0.36 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.68-7.65 (m, 1H), 7.62-7.59 (m, 1H), 7.46-7.44 (m, 2H), 7.40-7.37 (m, 3H), 7.30-7.28 (m, 3H), 6.91 (t, *J* = 6.8 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.47 (d, *J* = 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2, 138.5, 137.8, 132.8, 132.5, 131.9, 131.6, 131.2, 129.7, 129.4, 127.9, 125.8, 124.2, 122.7, 118.4, 118.2, 112.5, 111.9, 70.8, 60.4; IR (KBr): ν_{max} 3388, 3050, 2252, 1650, 1612, 1582, 1478, 1442, 1382, 1335, 1202, 1168, 1084, 1028, 914, 752, 590, 541 cm^{-1}; MS (ESI) *m/z* 289 (M^+ + H); HRMS calcd. for $C_{23}H_{15}IN_3O_2S$ (M^+ + H) 511.9930, found 511.9938.



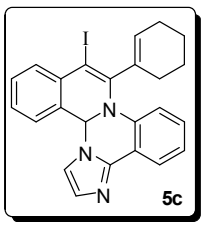
13-Iodo-12-cyclohexenyl-4b*H*-benzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline-6,6-dione (4c): 78% yield; yellow solid (M.P. = 140-142 °C); R_f 0.38 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 6.6 Hz, 1H), 7.24-7.22 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 12.3 Hz, 1H), 6.03 (s, 1H), 5.41 (d, *J* = 8.5 Hz, 1H), 1.68-1.41 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 144.3, 142.2, 139.3, 136.6, 135.7, 134.5, 131.7, 130.7, 129.2, 129.8, 128.5, 128.0, 126.9, 124.5, 123.6, 70.0, 53.4, 29.6, 25.1, 22.1, 21.4; IR (KBr): ν_{max} 3421, 3017, 1620, 1588, 1480, 1447, 1378, 1336, 1270, 1169, 1079, 906, 750, 689, 646, 593, 554, 494 cm^{-1}; MS (ESI) *m/z* 491 (M^+ + H); HRMS calcd. for $C_{21}H_{20}IN_2O_2S$ (M^+ + H) 491.0290, found 491.0294.



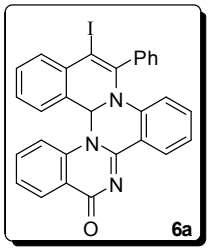
10-Iodo-9-phenyl-14bH-imidazo[1,2-c]isoquinolino[2,1-a]quinazoline (5a): 84% yield; solid (M.P. = 208-210 °C); R_f 0.33 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.44-7.38 (m, 4H), 7.42-7.35 (m, 4H), 7.30 (s, 1H), 7.11-7.04 (m, 2H), 7.01 (s, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.13 (d, *J* = 6.8 Hz, *J* , 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 143.7, 136.5, 135.2, 132.7, 131.5, 131.1, 130.9, 130.8, 128.4, 128.2, 127.9, 127.8, 127.6, 127.2, 127.0, 126.4, 124.8, 123.6, 115.3, 73.3, 70.3; IR (KBr): ν_{max} 3425, 3048, 2925, 2858, 1654, 1572, 1558, 1520, 1472, 1441, 1380, 1352, 1293, 1241, 1214, 1132, 1091, 1060, 978, 875, 804, 732, 693, 576, 462 cm^{-1}; MS (ESI) *m/z* 474 (M^+ + H); HRMS calcd. for $C_{24}H_{17}IN_3$ (M^+ + H) 474.0467, found 474 .0462.



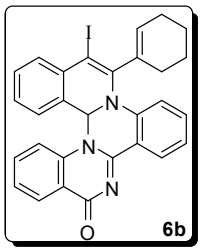
10-Iodo-9-^{n}butyl-14bH-imidazo[1,2-c]isoquinolino[2,1-a]quinazoline (5b): 62% yield; thick liquid; R_f 0.32 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (d, *J* = 6.0 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 2H), 7.65-7.63 (m, 2H), 7.46 (t, *J* = 8.3 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 2H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 1.79-1.66 (m, 2H), 0.84-0.74 (m, 2H), 0.69-0.56 (m, 2H), 0.41 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 145.5, 139.1, 134.2, 131.0, 130.1, 128.4, 128.2, 127.6, 126.5, 126.1, 124.3, 123.7, 125.6, 115.9, 115.6, 73.4, 71.3, 36.8, 28.5, 22.1, 13.2; IR : ν_{max} 3063, 2957, 2927, 2862, 2229, 1717, 1617, 1529, 1473, 1378, 1309, 1158, 1104, 940, 871, 760, 664 cm^{-1}; MS (ESI) *m/z* 454 (M^+ + H); HRMS calcd. for $C_{22}H_{21}IN_3$ (M^+ + H) 454.0780, found 454.0774.



10-Iodo-9-cyclohexenyl-14bH-imidazo[1,2-c]isoquinolino[2,1-a]quinazoline (5c): 75% yield; solid (M.P. = 168-170 °C); R_f 0.31 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.39-7.28 (m, 4H), 7.19-7.17 (m, 1H), 7.05-7.04 (m, 1H), 6.48-6.46 (m, 1H), 6.39-6.36 (m, 1H), 5.81 (s, 1H), 2.12-1.45 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 142.5, 138.9, 137.1, 133.9, 133.0, 131.9, 130.8, 130.5 128.8, 127.9, 127.7, 127.3, 127.2, 126.6, 124.7, 123.8, 123.3, 121.2, 116.5, 70.4, 69.9, 25.9, 24.9, 21.8, 21.3; IR (KBr): ν_{max} 3423, 3045, 2924, 2854, 1702, 1659, 1579, 1551, 1526, 1478, 1448, 1387, 1356, 1290, 1244, 1217, 1138, 1095, 1069, 1037, 976, 920, 872, 809, 758, 735, 695, 579, 532, 465 cm^{-1}; MS (ESI) *m/z* 478 (M^+ + H); HRMS calcd. for $C_{24}H_{21}IN_3$ (M^+ + H) 478.0780, found 478.0774.

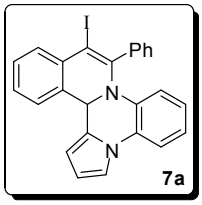


16-Iodo-17-phenyl-isoquinolino[2,1-a]quinazolino[1,2-c]quinazolin-6(11aH)-one (6a): 49% yield; thick liquid; R_f 0.40 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (d, *J* = 8.1 Hz, 1H), 8.36 (dd, *J* = 1.3 Hz, *J* = 6.4, 1H), 7.78 (d, *J* = 6.6 Hz, 1H), 7.67-7.64 (m, 3H), 7.41-7.37 (m, 8H), 7.22-7.19 (m, 2H), 7.11 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 151.5, 146.7, 142.1, 138.3, 133.1, 132.2, 131.5, 131.2, 130.5, 130.1, 129.3, 128.9, 128.7, 128.2, 128.0, 127.8, 127.2, 126.5, 125.3, 123.7, 121.4, 120.7, 116.7, 67.9, 66.7, 46.4 ; IR : ν_{max} 2925, 1670, 1628, 1550, 1510, 1476, 1338, 1156, 1122, 1078, 1024, 806, 548 cm^{-1}; MS (ESI) *m/z* 552 (M^+ + H); HRMS calcd. for $C_{29}H_{19}IN_3O$ (M^+ + H) 552.0573, found 552.0578.

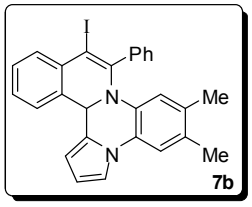


16-Iodo-17-cyclohexenyl-isoquinolino[2,1-a]quinazolino[1,2-c]quinazolin-6(11aH)-one (6b): 53% yield; thick liquid; R_f 0.42 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 4.5 Hz, 1H), 7.38-7.20 (m, 3H), 7.16 (s, 1H), 7.14-7.10 (m, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.54 (s, 1H), 6.47-6.43 (m, 2H), 5.64 (d, *J* = 4.5 Hz, 1H), 1.83-1.64 (m, 8H). ^{13}C NMR

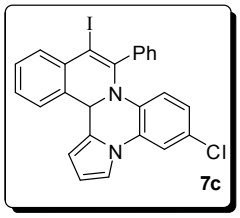
(125 MHz, $CDCl_3$): δ 160.6, 147.1, 145.1, 144.2, 138.4, 134.7, 133.2, 132.4, 130.1, 129.7, 128.2, 127.7, 127.2, 125.5, 123.5, 122.9, 120.6, 119.8, 116.8, 115.8, 115.3, 67.7, 60.3, 25.8, 24.9, 22.5, 22.1; IR : ν_{max} 2921, 1674, 1618, 1518, 1466, 1328, 1154, 1112, 1072, 1026, 807, 545 cm^{-1}; MS (ESI) *m/z* 556 (M^+ + H); HRMS calcd. for $C_{29}H_{23}IN_3O$ (M^+ + H) 556.0886, found 556.0892.



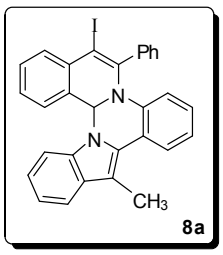
11-Iodo-10-phenyl-15bH-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline (**7a**): 55% yield; thick liquid; R_f 0.80 (hexane/EtOAc= 95/05); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.42-7.35 (m, 4H), 7.28 (dd, *J* = 1.5 Hz, *J* = 6.0, 2H), 7.20-7.12 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.73 (dt, *J* = 1.5 Hz, *J* = 6.0, 1H), 6.64 (dt, *J* = 1.5 Hz, *J* = 6.0, 1H), 6.52 (t, *J* = 3.0 Hz, 1H), 6.35-6.30 (m, 2H), 5.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 135.7, 133.6, 129.8, 128.9, 128.8, 127.9, 127.6, 126.2, 124.9, 124.6, 124.3, 123.4, 119.9, 118.9, 116.8, 114.6, 114.5, 110.4, 107.9, 68.2, 56.9; IR : ν_{max} 3058, 2924, 2853, 1695, 1607, 1560, 1473, 1453, 1343, 1282, 1240, 1200, 1106, 1049, 1024, 919, 889, 849, 760, 720, 696, 671, 608, 566, 534, 448 cm^{-1}; MS (ESI) *m/z* 473 (M^+ + H); HRMS calcd. for $C_{25}H_{18}IN_2$ (M^+ + H) 473.0515, found 473.0518.



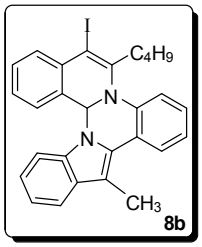
11-Iodo-6,7-dimethyl-10-phenyl-15bH-1soquinolino[2,1-c]quinoxaline (**7b**): 59% yield; thick liquid; R_f 0.81 (hexane/EtOAc= 95/05); ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 6.8 Hz, 2H), 7.28-7.39 (m, 4H), 7.21 (dt, *J* = 1.5 Hz, *J* = 6.0, 1H), 7.13 (dt, *J* = 1.5 Hz, *J* = 6.0, 2H), 7.05 (s, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 6.30 (d, *J* = 3.0 Hz, 1H), 6.08 (s, 1H), 5.59 (s, 1H), 2.08 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 141.7, 136.2, 135.1, 132.8, 129.7, 128.9, 128.4, 128.7, 127.7, 127.4, 126.2, 125.9, 124.6, 120.2, 116.4, 115.8, 114.3, 109.9, 107.6, 68.2, 57.0, 19.5, 19.0 ; IR : ν_{max} 2924, 2855, 1728, 1660, 1598, 1518, 1446, 1342, 1249, 1157, 1081, 1029, 858, 757, 667, 613 cm^{-1}; MS (ESI) *m/z* 501 (M^+ + H); HRMS calcd. for $C_{27}H_{22}IN_2$ (M^+ + H) 501.0828, found 501.0824.



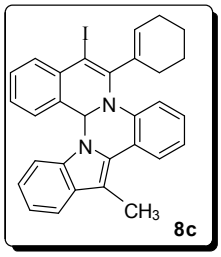
6-Chloro-11-iodo-10-phenyl-15bH-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline (7c): 50% yield; thick liquid; R_f 0.82 (hexane/EtOAc= 95/05); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.42-7.35 (m, 4H), 7.30-7.27 (m, 2H), 7.19-7.16 (m, 2H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.68 (dd, *J* = 2.1 Hz, *J* = 6.2 Hz, 1H), 6.52 (t, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 2.1 Hz, 1H), 5.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 134.9, 133.5, 132.5, 130.9, 129.1, 128.8, 128.3, 128.0, 127.8, 126.1, 124.5, 125.1, 119.9, 118.7, 117.3, 115.4, 114.6, 110.8, 108.2, 108.5, 57.2, 56.9; IR : ν_{max} 3054, 2922, 2855, 1698, 1600, 1568, 1475, 1459, 1341, 1280, 1244, 1104, 1047, 1022, 914, 885, 843, 762, 724, 692, 675 cm^{-1}; MS (ESI) *m/z* 507 (M^+ + H); HRMS calcd. for $C_{25}H_{17}ClIN_2$ (M^+ + H) 507.0125, found 507.0129.



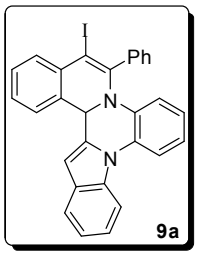
1-Iodo-8-methyl-2-phenyl-13aH-indolo[1,2-c]isoquinolino[2,1-a]quinazoline (8a): 64% yield; solid (M.P. = 96-98 °C); R_f 0.76 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.46-7.44 (m, 4H), 7.33 (t, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.01 (t, *J* = 6.8 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.88-6.78 (m, 2H), 6.61-6.56 (m, 2H), 6.10(d, *J* = 8.3 Hz, 1H), 5.6 (d, *J* = 1.5 Hz, *J* = 8.3 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 136.9, 135.9, 135.0, 133.4, 131.5, 130.8, 129.5, 129.0, 128.1, 127.4, 126.2, 125.1, 122.6, 122.2, 121.1, 120.0, 118.9, 117.9, 116.6, 69.0, 70.9, 10.7; IR (KBr): ν_{max} 3422, 3056, 2924, 2854, 1647, 1603, 1577, 1462, 1382, 1335, 1260, 1218, 1143, 1073, 1030, 939, 892, 756, 698, 665, 628 cm^{-1}; MS (ESI) *m/z* 537 (M^+ + H); HRMS calcd. for $C_{30}H_{22}IN_2$ (M^+ + H) 537.0828, found 537.0822.



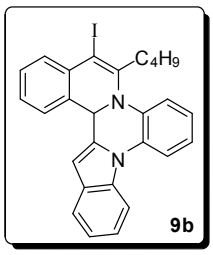
1-Iodo-8-methyl-2-^{n}butyl-13aH-indolo[1,2-c]isoquinolino[2,1-a]quinazoline (8b): 48% yield; thick liquid; R_f 0.78 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2H), 7.71-7.70 (m, 1H), 7.56 (d, *J* = 7.5 Hz,1H), 7.22-7.20 (m, 2H), 7.07-7.00 (m, 2H), 6.92-6.98 (m, 2H), 6.59 (d, *J* = 6.8 Hz, 1H), 6.47 (s, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 3.09-2.99 (m, 1H), 2.70 (s, 3H), 2.59-2.50 (m, 1H), 1.90-1.75 (m, 1H), 1.69-1.58 (m, 1H), 1.46-1.35 (m, 2H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 140.2, 134.1, 132.5, 130.8, 129.4, 128.8, 128.6, 127.7, 126.4, 125.4, 122.7, 121.2, 119.9, 119.0, 118.8, 116.6, 110.8, 108.6, 72.3, 71.1, 37.5, 29.7, 23.0, 13.9, 10.7; IR : ν_{max} 3371, 3054, 2955, 2924, 2856, 1692, 1601, 1462, 1380, 1358, 1334, 1260, 1214, 1160, 1129, 1076, 1016, 980, 899, 867, 814, 740, 631, 587, 542, 460 cm^{-1}; MS (ESI) *m/z* 517 (M^+ + H); HRMS calcd. for $C_{28}H_{26}IN_2$ (M^+ + H) 517.1141, found 517.1135.



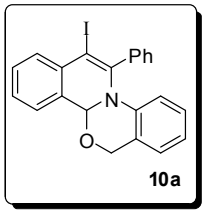
2-Cyclohexenyl-1-iodo-8-methyl-13aH-indolo[1,2-c]isoquinolino[2,1-a]quinazoline (8c): 62% yield; thick liquid; R_f 0.75 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.63-7.53 (m, 1H), 7.41-7.36 (m, 1H), 7.28-7.18 (m, 4H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.62-6.60 (m, 1H), 6.47 (s, 1H), 6.27 (d, *J* = 7.5 Hz, 1H), 5.29 (s, 1H), 2.69 (s, 3H), 1.66-1.56 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 137.1, 135.9, 134.9, 133.5, 130.6, 129.7, 128.5, 128.2, 127.4, 126.9, 125.0, 123.2, 122.4, 121.9, 120.8, 119.8, 118.8, 117.1, 108.6, 70.5, 68.6, 29.0, 25.9, 22.8, 21.8, 10.7; IR : ν_{max} 3428, 3052, 2928, 2850, 1646, 1605, 1572, 1468, 1380, 1332, 1261, 1219, 1142, 1076, 1039, 932, 898, 759, 695, 622 cm^{-1}; MS (ESI) *m/z* 541 (M^+ + H); HRMS calcd. for $C_{30}H_{26}IN_2$ (M^+ + H) 541.1141, found 541.1145.



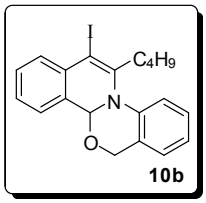
7-Iodo-6-phenyl-11bH-indolo[2,1-c]isoquinolino[2,1-a]quinoxaline (9a): 58% yield; thick liquid; R_f 0.81 (hexane/EtOAc= 95/05); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.85 (t, *J* = 8.3 Hz, 3H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.42-7.27 (m, 8H), 7.14 (t, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 6.0 Hz, 1H), 6.74-6.71 (m, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 5.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 133.5, 132.7, 132.5, 132.0, 131.1, 129.0, 128.5, 127.9, 127.8, 127.6, 127.1, 125.1, 124.7, 123.9, 122.7, 121.1, 121.3, 120.5, 119.2, 116.8, 116.4, 112.3, 110.8, 102.4, 60.4, 57.9; IR : ν_{max} 3382, 3057, 2924, 2854, 1668, 1596, 1498, 1454, 1395, 1361, 1279, 1220, 1111, 1061, 1024, 886, 848, 749, 694, 667, 614, 573, 527, 440 cm^{-1}; MS (ESI) *m/z* 523 (M^+ + H); HRMS calcd. for $C_{29}H_{20}IN_2$ (M^+ + H) 523.0671, found 523.0675.



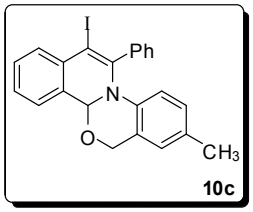
7-Iodo-6-^{n}butyl-11bH-indolo[2,1-c]isoquinolino[2,1-a]quinoxaline (9b): 52% yield; thick liquid; R_f 0.82 (hexane/EtOAc= 95/05); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (t, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.45-7.37 (m, 2H), 7.28-7.22 (m, 3H), 7.19-7.13 (m, 5H), 7.0 (d, *J* = 7.5 Hz, 2H), 5.92 (s, 1H), 5.56 (s, 1H), 2.01 (d, *J* = 6.8 Hz, 2H), 0.97-0.87 (m, 4H), 0.51 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ144.5, 139.4, 133.9, 133.3, 128.6, 126.7, 127.2, 124.7, 123.3, 122.4, 121.2, 120.9, 123.5, 117.7, 116.4, 114.7, 112.2, 110.6, 100.8, 99.5, 57.4, 58.1, 32.0, 29.1, 21.7, 13.5; IR : ν_{max} 3061, 2956, 2927, 2865, 1714, 1597, 1496, 1455, 1380, 1223, 1049, 936, 784, 610, 426 cm^{-1}; MS (ESI) *m/z* 503 (M^+ + H); HRMS calcd. for $C_{27}H_{24}IN_2$ (M^+ + H) 503.0984, found 503.0990.



13-Iodo-12-phenyl-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (10a): 74% yield; thick liquid; R_f 0.52 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.28-7.26 (m, 3H), 7.12-7.18 (m, 2H), 6.97 (d, *J* = 6.9 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 1H), 6.73 (t, *J* = 6.9 Hz, 1H), 6.28 (d, *J* = 8.9 Hz, 1H), 5.98 (s, 1H), 5.85 (d, *J* = 14.9 Hz, 1H), 5.24 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2, 140.6, 139.8, 133.3, 131.4, 130.5, 129.9, 129.6, 128.4, 128.2, 127.8, 126.9, 126.8, 126.1, 125.5, 125.0, 124.4, 123.8, 84.3, 74.4, 67.8; IR : ν_{max} 3379, 3060, 2931, 1695, 1652, 1619, 1598, 1498, 1450, 1377, 1337, 1268, 1216, 1156, 1028, 835, 756, 697, 664, 640 cm^{-1}; MS (ESI) *m/z* 438 (M^+ + H); HRMS calcd. for $C_{22}H_{17}INO$ (M^+ + H) 438.0355, found 438.0349.

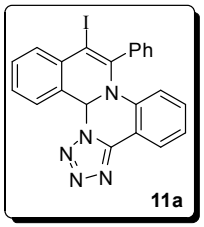


13-Iodo-12-^{n}butyl-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (10b): 63% yield; thick liquid; R_f 0.51 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 6.4 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.20 (s, 1H), 5.59 (s, 1H), 5.45 (d, *J* = 14.6 Hz, 1H), 4.97 (d, *J* = 14.6 Hz, 1H), 2.16 (t, *J* = 6.4 Hz, 1H), 2.10 (t, *J* = 7.0 Hz, 1H), 1.13-1.01 (m, 2H), 0.8-0.9 (m, 2H), 0.56 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 141.2, 133.5, 130.9, 129.5, 129.3, 126.8, 126.1, 125.2, 125.7, 84.2, 74.2, 67.5, 36.5, 29.7, 22.1, 13.6; IR : ν_{max} 3444, 2955, 2925, 2856, 1711, 1656, 1584, 1553, 1486, 1458, 1378, 1293, 1242, 1202, 1130, 1019, 916, 758 cm^{-1}; MS (ESI) *m/z* 418 (M^+ + H); HRMS calcd. for $C_{20}H_{21}INO$ (M^+ + H) 418.0668, found418.0662.



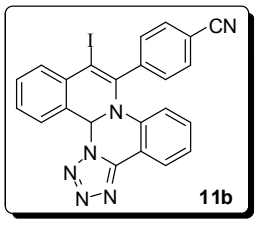
13-Iodo-8-methyl-12-phenyl-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (10c): 66% yield; yellow solid (M.P. = 136-138°C) thick liquid; R_f 0.50 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.38-7.46 (m, 2H), 7.29-7.26 (m, 4H), 7.19-7.13 (m, 2H), 6.77 (s, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 6.17 (d, *J* = 8.3 Hz, 1H), 5.93 (s, 1H), 5.21 (d, *J* = 15.1 Hz,

1H), 5.04 (d, *J* = 14.9 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 140.2, 138.4, 133.8, 132.4, 131.8, 130.6, 129.8, 129.1, 128.6, 128.3, 127.9, 126.8, 126.2, 125.2, 124.9, 123.5, 84.5, 73.8, 67.9, 14.2; IR (KBr): ν_{max} 3435, 3058, 2923, 1698, 1652, 1620, 1496, 1446, 1377, 1338, 1276, 1217, 1156, 1068, 1029, 880, 812, 759, 697, 666, 637, 528 cm^{-1}; MS (ESI) *m/z* 452 (M^+ + H); HRMS calcd. for $C_{23}H_{19}INO$ (M^+ + H) 452.0511, found 452.0516.



11a

10-Iodo-9-phenyl-14bH-isoquinolino[2,1-a]tetrazo[1,5-c]quinazoline (11a): 62% yield; solid (M.P. = 212-214 °C); R_f 0.28 (hexane/EtOAc= 60/40); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.6Hz, 1H), 7.92 (d, *J* = 3.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.46-7.44 (m, 4H), 7.36 (d, *J* = 3.8 Hz, 1H), 7.21 (s, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 7.46-7.44 (m, 4H), 7.36 (d, *J* = 3.8 Hz, 1H), 7.21 (s, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO d_6): δ 154.8, 147.6, 139.1, 137.1, 136.8, 131.6, 131.2, 130.6, 130.3, 129.8, 129.4, 128.6, 127.9, 127.7, 127.1, 124.9, 124.2, 120.9, 117.4, 70.5, 54.8; IR (KBr): ν_{max} 3044, 2920, 2852, 1648, 1575, 1518, 1482, 1431, 1382, 1349, 1290, 1248, 1234, 1138, 1090, 1062, 974, 885, 814, 698, 575 cm^{-1}; MS (ESI) *m/z* 476 (M^+ + H); HRMS calcd. for $C_{22}H_{15}IN_5$ (M^+ + H) 476.0372, found 476 .0378.

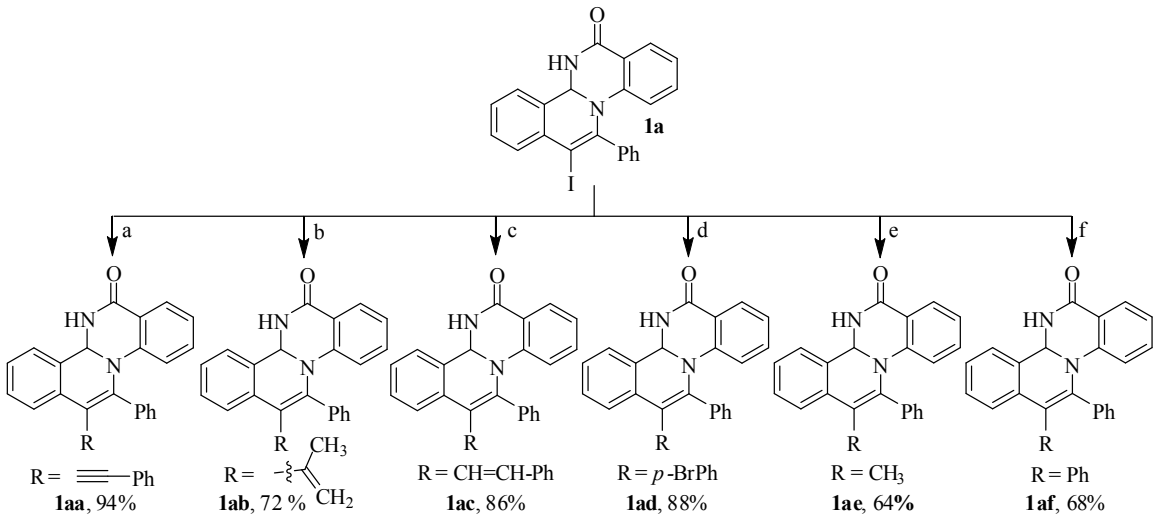


11b

4-(10-Iodo-14bH-isoquinolino[2,1-a]tetrazolo[1,5-c]quinazolin-9-yl)benzonitrile (11b): 72% yield; solid (M.P. = 172-174 °C); R_f 0.29 (hexane/EtOAc= 60/40); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.51-7.48 (m, 3H), 7.39-7.36 (m, 4H), 7.28 (d, *J* = 6.7 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 2H), 6.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 147.9, 139.2, 138.9, 138.1, 136.6, 131.9, 131.5, 130.8, 130.6, 130.3, 129.7, 129.1, 128.5, 128.1, 127.6, 124.6, 120.9, 117.4, 70.3, 59.8; IR (KBr): ν_{max} 3042, 2928, 2850, 2254, 1651, 1576, 1527, 1476, 1380, 1356, 1294, 1138, 1097, 1062, 974, 876, 732, 695, 468 cm^{-1}; MS (ESI) *m/z* 501 (M^+ + H); HRMS calcd. for $C_{23}H_{14}IN_6$ (M^+ + H) 501.0325, found 501.0329.

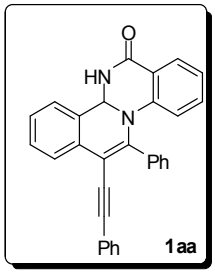
5. Diversification of Products

The scope and synthetic utility of this newly developed EIBC approach was enhanced by diversifying branch-1 via metal catalyzed cross- coupling reactions. For instance, compound **1a** was subjected to Sonogashira, Stille, Heck, Suzuki, Kumada and Negishi cross-coupling reaction conditions to afford products **1aa**, **1ab**, **1ac**, **1ad**, **1ae** and **1af**; respectively, in moderate to good yields.



a) Sonogashira coupling (1a → 1aa):

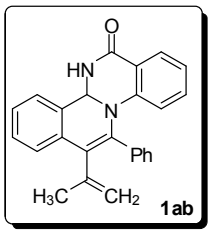
To a 25 mL round bottom flask a solution of **1a** (0.050 g, 1 eq) in DMF (2.5 mL) was added Et_3N (5 eq) and purged with dry nitrogen for 30 minutes. Catalysts $PdCl_2(PPh_3)_2$ (0.004 g, 0.05 eq) and CuI (0.001 g, 0.05 eq) were introduced into the flask under nitrogen atmosphere at room temperature. To the above flask phenyl acetylene (0.012 g, 1.1 eq) was added drop wise. The reaction mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad followed by addition of water to remove DMF and extracted with DCM (10 mL x 3). Work up and purification by column chromatography using hexane/ethyl acetate (70/30) as eluent to afford **1aa** (94%) as a pure product.



12-Phenyl-13-(phenylethynyl)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1aa): 94% yield; solid (M.P. = 106-108 °C); R_f 0.31 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03-7.99 (m, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.56-7.47 (m, 5H), 7.39-7.30 (m, 8H), 7.07-7.01 (m, 2H), 6.49 (s, 1H), 6.38-6.36 (m, 1H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 145.4, 142.8, 134.5, 133.2, 132.4, 132.2, 131.5, 130.8, 130.0, 129.4, 129.1, 128.9, 128.5, 128.3, 128.2, 128.0, 127.6, 124.8, 123.7, 123.2, 94.5, 86.4,67.3; IR (KBr): ν_{max} 3199, 3055, 2923, 2196, 1672, 1599, 1552, 1517, 1480, 1349, 1306, 1160, 1071, 1026, 908, 756, 727, 692, 641, 542, 430cm^{-1}; MS (ESI) *m/z* 375 (M^+ + H); HRMS calcd. for $C_{26}H_{19}N_2O$ (M^+ + H) 375.1497, found 375.1491.

b) Stille coupling (1a → 1ab):

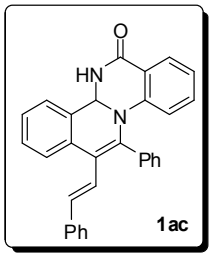
To a 25 mL round bottom flask a solution of **1a** (0.060 g, 1 eq) in DMF (2.5 mL) was added tri ^{n} butyl(prop-1-en-2-yl) stannane (54 mg, 1.2 eq), $Pd(PPh_3)_4$ (6mg, 0.04 eq), CuI (1.2 mg, 0.05 eq) , CsF (0.020 g, 2 eq) and purged with dry nitrogen for 30 minutes. The reaction mixture was heated to 100 °C and stirred for 8 hr. The reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad followed by addition of water to remove DMF and extracted with DCM (10 mL x 3). Work up and purification by column chromatography by using hexane/ethyl acetate (70/30) as eluent to afford **1ab** (72%) as a pure product.



12-Phenyl-13-(prop-1-en-2-yl)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1ab): 72% yield; thick liquid ; R_f 0.32 (hexane/EtOAc= 70/03); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.1 Hz, 1H), 7.46-7.30 (m, 9H), 7.04-6.93 (m, 2H), 6.42 (d, *J* = 8.3 Hz, 1H), 6.26 (s, 1H), 6.15 (s, 1H), 5.32 (s, 1H), 5.04 (s, 1H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 143.8, 140.4, 136.6, 133.5, 133.1, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 127.8, 126.6, 124.2, 123.8, 121.2, 119.6, 117.7, 67.6, 24.1; IR : ν_{max} 3192, 3054, 2928, 1674, 1594, 1559, 1502, 1480, 1348, 1306, 1164, 1072, 1024, 904, 751, 696, 646, 542, 434 cm^{-1}; MS (ESI) *m/z* 365 (M^+ + H); HRMS calcd. for $C_{25}H_{21}N_2O$ (M^+ + H) 365.1654, found 365.1661.

c) Heck coupling (1a → 1ac):

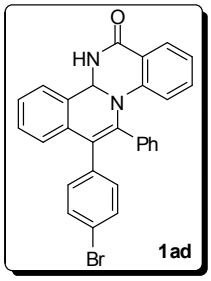
To a 25 mL round bottom flask a solution of **1a** (0.050 g, 1 eq) in DMF(2.5 mL) was added styrene (.0042 g, 3 eq), $Pd(OAc)_2$ (2 mg, 0.05 eq), PPh_3 (0.006 g, 0.1 eq), Bu_4NBr (0.036 g, 1 eq), Na_2CO_3 (0.035 g, 3 eq) and purged with dry nitrogen for 30 minutes. The reaction mixture was heated to 100 °C and stirred for 8 hr. The reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad followed by addition of water to remove DMF and extracted with DCM (10 mL x 3). Work up and purification by column chromatography by using hexane/ethyl acetate (70/30) as eluent to afford **1ac** (86%) as a pure product.



12-Phenyl-13-(styryl)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1ac): 86% yield; solid (M.P. = 208-206 °C); R_f 0.31 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-7.93 (m, 1H), 7.70-7.63 (m, 4H), 7.55-7.52 (m, 1H), 7.49-7.43 (m, 4H), 7.39-7.36 (m, 2H), 7.33-7.23 (m, 6H), 7.02-6.99 (m, 2H), 6.39-6.36 (m, 2H), 6.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 145.2, 142.6, 134.9, 134.3, 133.0, 132.2, 131.9, 131.7, 131.3, 130.6, 129.8, 129.2, 128.9, 128.7, 128.3, 128.1, 127.9, 127.8, 127.4, 126.5, 126.2, 125.9, 125.1, 124.6, 123.5, 123.0, 67.1 ; IR (KBr): ν_{max} 3190, 3052, 2928, 2198, 1678, 1590, 1558, 1512, 1484, 1345, 1307, 1162, 1074, 1025, 902, 758, 720, 696, 646, 543, 435 cm^{-1}; MS (ESI) *m/z* 427 (M^+ + H); HRMS calcd. for $C_{30}H_{23}N_2O$ (M^+ + H) 427.1810, found 427.1815.

d) Suzuki coupling (1a → 1ad):

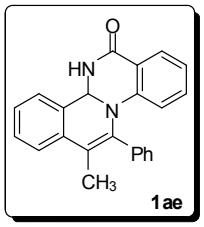
To a 25 mL round bottom flask a solution of **1a** (0.050 g, 1 eq) in DMF(2.5 mL) and H_2O (0.5 mL) was added K_2CO_3 (0.031 g, 2 eq) and purged with dry nitrogen for 30 minutes. To the above flask *p*-bromobenzene boronic acid (0.033 g, 1.5 eq) and $PdCl_2(PPh_3)_2$ (0.008 g, 0.1 eq) were introduced under nitrogen atmosphere at room temperature. The reaction mixture was heated to 100 °C and stirred for 8 hr. The reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad followed by addition of water to remove DMF and extracted with DCM (10 mL x 3). Work up and purification by column chromatography using hexane/ethyl acetate (70/30) as eluent to afford **1ad** (88%) as a pure product.



12-Phenyl-13-(4-bromophenyl)-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1ad): 88% yield; thick liquid; R_f 0.30 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.99 (m, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.55-7.44 (m, 5H), 7.39-7.30 (m, 7H), 7.06-7.02 (m, 2H), 6.49 (s, 1H), 6.38-6.35 (m, 1H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 143.7, 138.5, 136.6, 134.7, 133.5, 133.3, 132.1, 131.8, 131.7, 131.0, 130.1, 128.6, 128.3, 128.1, 127.9, 127.4, 126.9, 126.6, 124.5, 67.7 ; IR : 3182, 3055, 2927, 1679, 1600, 1519, 1480, 1356, 1317, 1254, 1163, 1123, 1020, 918, 800, 754, 720, 698, 597, 549ν_{max} cm^{-1}; MS (ESI) *m/z* 479 (M^+ + H); HRMS calcd. for $C_{28}H_{20}BrN_2O$ (M^+ + H) 479. 0759, found 479.0765.

e) Kumada coupling (1a → 1ae):

To a 25 mL round bottom flask a solution of **1a** (0.050 g, 1 eq) in THF (3 ml) was added $Ni(PPh_3)_2Cl_2$ (0.008 g, 0.1 eq) and purged with dry nitrogen for 30 minutes. To the above flask CH_3MgI (0.055 g, 3 eq) was introduced under nitrogen atmosphere at room temperature. The reaction mixture was warmed to 80 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad and the filtrate was concentrated. The residue was purified by column chromatography by using hexane/ethyl acetate (70/30) as eluent to afford **1ae** (64%) as a pure product.

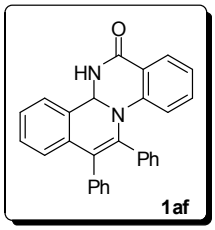


12-Phenyl-13-methyl-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1ae): 64% yield; solid (M.P. = 178-180 °C); R_f 0.30 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-7.94 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.35-7.29 (m, 5H), 7.25-7.23 (m, 1H), 7.00-7.01 (m, 2H), 6.39-6.37 (m, 1H), 6.18 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125MHz, DMSO d_6): δ 161.6, 144.1, 141.8, 143.8, 134.8, 132.8, 130.8, 130.0, 129.0, 128.1, 127.1, 125.7, 125.5, 123.3, 119.7,

116.4, 66.9, 30.6 ; IR (KBr): ν_{max} 3445, 3293, 3146, 2926, 2853, 1634, 1494, 1442, 748 cm^{-1}; MS (ESI) *m/z* 339 (M^+ + H); HRMS calcd. for $C_{23}H_{19}N_2O$ (M^+ + H) 339.1497, found 339.1452.

f) Negishi coupling (1a → 1af):

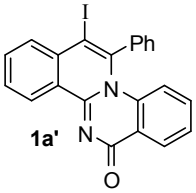
To a 25 mL round bottom flask a solution of **1a** (0.050 g, 1 eq) in DMF (2.5 ml) was added $Pd(OAc)_2$ (2 mg, 0.05 eq), Bu_4NBr (0.036 g, 1 eq) purged with dry nitrogen for 30 minutes. To the above flask benzene PhZnCl (0.023 g, 1.2 eq) was introduced under nitrogen atmosphere at room temperature. The reaction mixture was stirred at rt for 12 hrs then the reaction mixture was cooled to room temperature and filtered through a short SiO_2 pad followed by the addition of water to remove DMF and extracted with DCM (10 mL x 3). Work up and purification by column chromatography column chromatography by using hexane/ethyl acetate (70/30) as eluent to afford **1af** (68%) as a pure product.

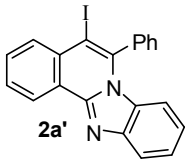


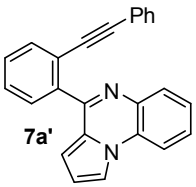
12,13-Diphenyl-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (1af): 68% yield; thick liquid; R_f 0.30 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 6.9 Hz, 2H), 7.31-7.19 (m, 7H), 7.14-7.08 (m, 3H), 7.05-6.97 (m, 4H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.4 Hz, 1H), 6.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 163.7, 143.9, 138.7, 136.9, 134.9, 133.5, 132.3, 132.0, 131.9, 131.2, 130.3, 130.9, 128.8, 128.5, 128.2, 128.0, 127.8, 127.6, 127.2, 126.8, 124.7, 122.0, 67.8; IR : ν_{max} 3180, 3053, 2923, 1673, 1602, 1516, 1480, 1403, 1358, 1310, 1255, 1161, 1122, 1023, 910, 801, 756, 727, 699, 644, 594, 541, 424cm^{-1}; MS (ESI) *m/z* 401 (M^+ + H); HRMS calcd. for $C_{28}H_{21}N_2O$ (M^+ + H) 401.1654, found 401.1662.

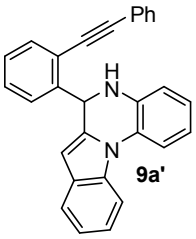
6. Undesired Products Obtained During Optimization Studies and Characterization Data:

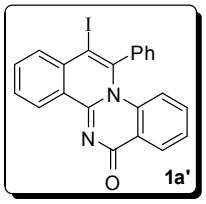
The following undesired products were observed in some cases during optimization studies. In case of SBA-1 prolonging the reaction for 8 hrs, **1a′** was observed as a major product. In case of SBA-2 under the reaction condition-4, **2a′** was the major product. In case of SBA-7 under the reaction condition-1, **7a′** was the major product. In case of SBA-9 under the reaction condition-1, intermediate dihydroindoloquinoxaline **9a′** was the major product.



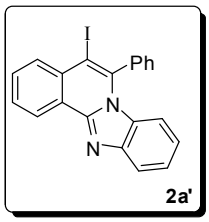




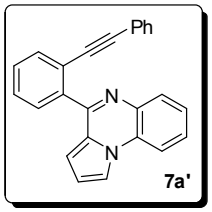




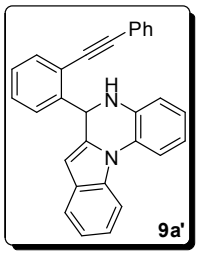
13-Iodo-12-phenyl-6H-isoquinolino[2,1-a]quinazolin-6-one (1a′): 76% yield; solid (M.P. = 94-96 °C); R_f 0.24 (hexane/EtOAc= 70/30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 1.5 Hz, *J* = 8.3, 1H), 7.70-7.65 (m, 2H), 7.44-7.37 (m, 5H), 7.31 (dd, *J* = 3.7 Hz, 2H), 7.02 (t, *J* = 9.0 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 154.1, 151.2, 138.3, 136.8, 133.5, 132.3, 131.5, 130.6, 130.1, 129.3, 128.7, 127.9, 127.5, 127.1, 126.8, 126.4, 122.1, 117.8, 67.9 ; IR (KBr): ν_{max} 2925, 1672, 1628, 1554, 1518, 1474, 1336, 1162, 1130, 1062, 1045, 806, 729, 686, 542 cm^{-1}; MS (ESI) *m/z* 449 (M^+ + H); HRMS calcd. for $C_{22}H_{14}IN_2O$ (M^+ + H) 449.0151, found 449 .0158.



5-Iodo-6-phenylbenzo[4, 5]imidazo[2, 1-a]isoquinoline (2a′): 71% yield; solid (M.P. = 194-196 °C); R_f 0.52 (hexane/EtOAc= 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91-8.88 (m, 1H), 8.20-8.17 (m, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.78-7.69 (m, 5H), 7.49-7.46 (m, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.83 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 143.6, 139.6, 138.4, 132.4, 130.9, 130.3, 129.8, 129.5, 128.6, 125.0, 124.5, 122.4, 121.6, 119.5, 113.9, 86.9; IR (KBr): ν_{max} 2928, 2854, 1726, 1631, 1593, 1452, 1372, 1232, 1150, 1118, 914, 740, 672, 568 cm^{-1}; MS (ESI) *m/z* 421 (M^+ + H); HRMS calcd. for $C_{21}H_{14}N_2I$ (M^+ + H) 421.0202, found 421.0212.



4-[(2-phenyl-1-ethynyl)phenyl]pyrrolo[1,2-*a*]quinoxaline (7a′): 58% yield; thick liquid; R_f 0.48 (hexane/EtOAc= 95/05); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 1.4 Hz, *J* = 6.7, 1H), 8.01-8.00 (m, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.73-7.70 (m, 2H), 7.56-7.53 (m, 1H), 7.50-7.46 (m, 3H), 7.19-7.12 (m, 3H), 7.05-7.04 (m, 2H), 6.88-6.87 (m, 1H), 6.79-6.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 140.1, 136.0, 132.9, 131.3, 130.2, 129.2, 128.9, 128.2, 127.9, 127.6, 127.3, 125.8, 125.2, 123.1, 122.5, 114.2, 113.7, 113.9, 109.0; IR (KBr): ν_{max} 3050, 2926, 2858, 1690, 1605, 1564, 1475, 1346, 1284, 1205, 1108, 1046, 768, 698, 618, 560, 445 cm^{-1}; MS (ESI) *m/z* 345 (M^+ + H); HRMS calcd. for $C_{25}H_{17}N_2$ (M^+ + H) 345.1392 found 345.1385.

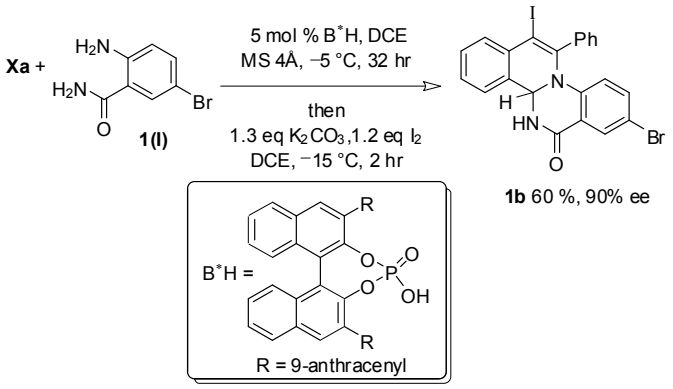


6-[(2-phenyl-1-ethynyl)phenyl]-5,6-dihydroindolo[1,2-*a*]quinoxaline (9a′): 65% yield; thick liquid; R_f 0.78 (hexane/EtOAc= 95/05); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 8.3 Hz, 2H), 7.23-7.13 (m, 3H), 7.07-7.02 (m, 1H), 6.93-6.84 (m, 4H), 6.77 (s, 1H), 6.66 (s, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 133.8, 133.4, 132.4, 131.9, 129.8, 128.9, 128.5, 128.1, 127.9, 127.7, 126.1, 125.0, 124.6, 123.8, 122.6, 121.1, 120.4,119.1, 118.5, 116.7, 116.3, 112.2, 102.3, 57.8; IR (KBr): ν_{max} 3384, 2924, 2852, 1596, 1490, 1451, 1392, 1274, 1224, 1066, 1022, 840, 698, 664, 615, 526 cm^{-1}; MS (ESI) *m/z* 397 (M^+ + H); HRMS calcd. for $C_{29}H_{21}N_2$ (M^+ + H) 397.1705, found 397.1712.

7. Enantioselective Experiment and HPLC Chromatograms

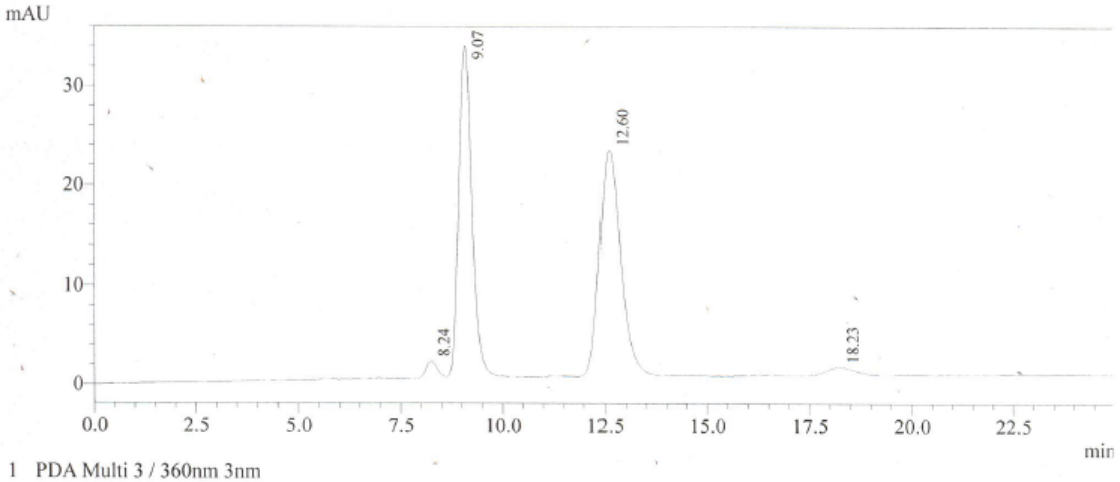
The EIBC approach could be made enantioselective under the catalysis of chiral Brønsted acid with the realm of iodine cyclization. To our satisfaction, when substrate 2-(phenylethynyl) benzaldehyde **Xa** treated with 2-amino-5-bromobenzamide **1(I)** in the presence of 5 mol% (*S*)-3,3′-

bis (9-anthracenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate in DCE followed by addition of 1.3 eq K_2CO_3 and 1.2 eq I_2, the product **1b** was obtained in 60% yield with 90% ee.



Experimental procedure:To a screw-cap 2.5 ml vial containing stir bar, were added scaffold building agent **1 (I)** (0.030 g, 1 eq) and 2-ethynylbenzaldehyde **Xa** (1 eq) in DCE (0.09 M) followed by the addition of 4A^{o} MS and 5-mol % (*S*)-3,3′-bis(9-anthracenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate[1]. The reaction vial was fitted with a cap, evacuated and filled with nitrogen and stirred at −5 ^{o}C for 32 hrs. After the prescribed time, the reaction mixture was cooled to −15 ^{o}C followed by the addition of K_2CO_3 (1.3 eq) and iodine (1.2 eq) in a sequential manner and allowed to stir for 2 hrs. The reaction mixture was quenched by the addition of aq.sodium thiosulphate solution, diluted with 5 mL water and extracted with DCM (10 mL x 3). Work up and purification by column chromatography using MeOH/DCM as an eluent to afford analytically pure compound in 60% yield with 90% ee. **HPLC conditions:** OD-H column, n-hexane/2-propanol = 80/20, flow rate 0.8 mL/min; λ = 360 nm; t_{minor} = 9.12, t_{major} = 12.64; $[\alpha]_D^{28.4}$ = – 156.8 (c = 0.25, $CHCl_3$)

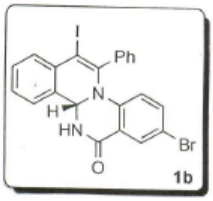
[1] J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem., Int. Ed.,* **2006**, *45*, 4796–4798.

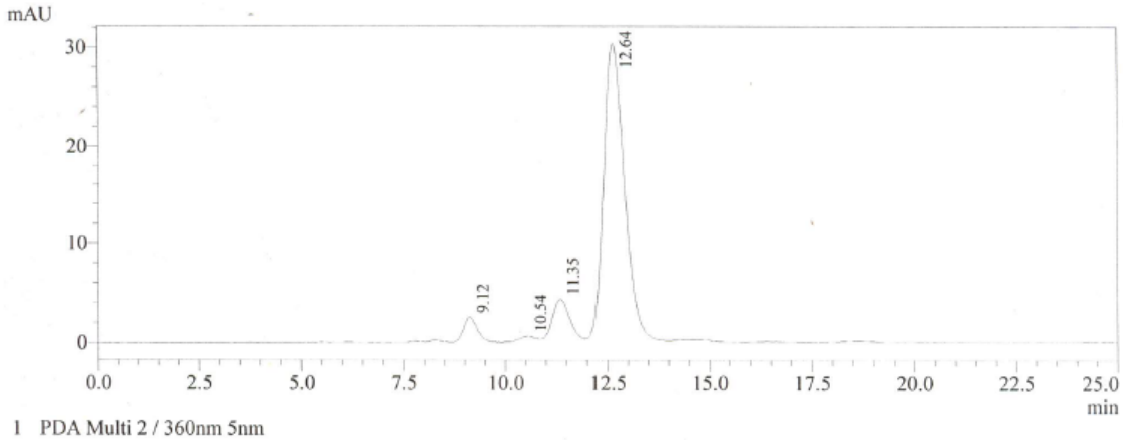


1 PDA Multi 3 / 360nm 3nm

PDA Ch3 360nm 3nm

Peak#	Ret. Time	Area	Area %
1	8.24	32362	2.00
2	9.07	752373	46.39
3	12.60	800289	49.35
4	18.23	36770	2.27
Total		1621795	100.00





1 PDA Multi 2 / 360nm 5nm

PDA Ch2 360nm 5nm

Peak#	Ret. Time	Area	Area %
1	9.12	56771	4.52
2	10.54	13880	1.11
3	11.35	124908	9.95
4	12.64	1060073	84.43
Total		1255632	100.00

8. Anti mycobacterial activity

Tuberculosis is a foremost destroyer worldwide causing an estimated 1.4 million deaths per year.[2] The re-emergence of TB as a public health threat emphasizes a need to develop novel antimycobacterial agents with lesser toxicity. Some of poly heterocyclic compounds resulted through EIBC resembles structures of reported anti-tubercular agents.[3] Therefore, compounds accessed through EIBC were evaluated for their anti-mycobacterial activities. The assay was performed with *Mycobacterium.smegmatis* (MC^2155) as surrogate model for screening drugs against mycobacterium[4] using growth inhibition assay by broth dilution method. The results were analyzed as the percentage of growth inhibition and from dose response curves MIC of all compounds are calculated and presented in Table 1. The screening results revealed that the compounds **7a**, **7b**, and **8a** show excellent anti-mycobacterial activities in a reference to isoniazid and rifampicin.

Table 1: Anti-mycobacterial activities of selected compounds

Sl. No.	product	MIC µg/mL	Sl. No.	product	MIC [a,b,c,d] µg/mL
1	**1a**	>50	11	**4c**	>50
2	**1b**	>50	12	**5a**	>50
3	**1c**	>50	13	**5c**	>50
4	**1d**	>50	14	**7a**	11.15 ± 0.24
5	**1f**	>50	15	**7b**	6.14±0.03
6	**2a**	>50	16	**8a**	7.70±0.58
7	**3a**	>50	17	**9a**	31.04±0.17
8	**3c**	30.49±2.06	18	**10a**	>50
9	**4a**	49.59±2.44	19	**10b**	23.47±0.72
10	**4b**	>50	20	**11a**	47.82±4.41
*	**Rifampicin**	1.87	*	**Isoniazid**	15.25

[a]*Mycobacterium.smegmatis* ATCC 14468 (MC^2155). [b]MIC is the concentration of compounds inhibiting growth by 90%. [c]50 µg/mL of compound concentration is considered as showing no significant activity. [d]All experiments were carried out in triplicates and results were reported as ± SD.

Next, we have evaluated cytotoxicity effect of the same compounds using cell-based assays to shed light on selectivity issues. The *in vitro* cell cytotoxicity assays were performed on four different human cancer cell lines such as A549 (human lung carcinoma epithelial), HeLa (human

2 WHO global health observatory data report. Geneva: GlobalTuberculosis Program; 2012

3 a) L. Ballell, R. H. Bates, R. J. Young, D. Alvarez-Gomez, E. Alvarez-Ruiz, V. Barroso, D. Blanco, B. Crespo, J. Escribano, R. González, S. Lozano, S. Huss, A. Santos-Villarejo, J. J. Martín-Plaza, A. Mendoza, M. J. Rebollo-Lopez, M. Remuiñan-Blanco, J. L. Lavandera, E. Pérez-Herran, F. J. Gamo-Benito, J. F. García-Bustos, D. Barros, J. P. Castro, N. Cammack, *ChemMedChem*, **2013**, *8*, 313-321; b) L. G. Dover, G. D. Coxon, *J. Med. Chem.* **2011**, *54*, 6157-6165.

4 a) M. Altaf, C. H. Miller, D. S. Bellows, R. Toole, *Tuberculosis* **2010**, *90*, 333-337; b) C. O. Esimone, C. S. Nworu, E. B. Onuigbo, J. U. Omeje, K. L. Nsirim, J. C. Ogbu, M. I. Ngwu, K. F. Chah, *International journal of Green Pharmacy* **2009**, *3*, 201-205; c) V. Chaturvedi, N. Dwivedi, R. P. Tripathi, S. Sinha, *J. Gen. Appl. Microbiol*., **2007**, *53*, 333-337.

epithelial cervical cancer), DU145 (prostate cancer) and MCF-7 (breast cancer). The selectivity index (SI, IC_{50}/MIC ratio) is summarized in the Table 2 which showed that the compounds **7a**, **7b** and **8a** displayed extraordinary selectivity towards *Mycobacterium.smegmatis*. The results are very promising as these compounds especially **7a**, **7b** and **8a** are active against mycobacterium with no cytotoxicity and therefore could have potential for further optimization as potential anti-TB drugs.

Table 2: Selectivity index (SI) is the ratio of IC_{50}/MIC

Sl. No	product	DU145	Hela	MCF-7	A549
1	**3c**	1.62	>13	2.85	2.31
2	**4a**	0.83	>13	>13	1.45
3	**7a**	**5.66**	**4.17**	**3.98**	**4.19**
4	**7b**	**6.94**	**13.37**	**14.25**	**10.54**
5	**8a**	**>13**	**>13**	**>13**	**11.15**
6	**9a**	1.28	2.71	63.12	1.99
7	**10b**	1.42	>13	>13	2.83
8	**11a**	1.11	1.66	>13	1.60

Methods:

In vitro anti-mycobacterial activity assay: Anti-mycobacterial activity of the synthesized compounds was performed with *Mycobacterium. smegmatis* strain using growth inhibition assay by turbidometry. Briefly, isolated single colonies of *M. smegmatis* MC^2 155 (ATCC 14468) from 7H10 agar plate were grown overnight in Middlebrook 7H9 medium (0.47% Middlebrook 7H9 broth base, 10% ADS, 0.2% glycerol, and 0.1% Tween-80) to mid exponential phase at 37 ^oC. Subsequently, 5 ml of Middlebrook 7H9 broth were inoculated with the overnight grown culture and allowed to grow at 37 ^oC to early log phase ($OD_{600} \approx 0.3$). For anti-microbial assay, 98 µl of 1:1000-folds dilution of secondary culture was dispensed into 96-well microtiter plate. To each well 2 µl of test compound was added to attain a final concentration of 6.25, 12.5, 25 and 50 µM, and allowed to grow at 37 ^oC for 32 hours. 240 µl of sterile water were added to each well of the peripheral rows of 96-well plate to minimize media evaporation during assay incubation. Bacterial growth was assessed after 32 hours of incubation by measuring turbidity at 600nm OD_{600} values using TECAN Infinite 200 PRO™ (Tecan Instruments, Switzerland). Positive controls were included in every assay plates using stock solutions of INH (10 mg/mL, HiMedia) and Rifampicin (10 mg/mL, HiMedia) to achieve the final concentration of 0.5, 1, 2, 4, 8 and 16 μg/mL for INH and 0.25, 0.5, 1, 2, 4 and 8 μg/mL for Rifampicin. Additional controls DMSO (solvent without compound) and medium without inoculums were included in all the assay plates avoiding intra assay variability. The results were analyzed as the

percentage of growth inhibition. All experiments were carried out in triplicates and results were reported as ± SD. From the percentage of the growth inhibition, the GI_{50} values are calculated.

Anti cell proliferative Assays: The synthesized compounds have been valuated for their *in vitro* cytotoxicity in four different human cancer cell lines. All cell lines used in this study were purchased from the American Type Culture Collection (ATCC, USA). A549 (human lung carcinoma epithelial), HeLa (human epithelial cervical cancer), DU145 (prostate cancer) and MCF-7 (breast cancer) were grown in standard Dulbecco's modified Eagles medium containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 ^oC. Cells were trypsinized when sub-confluent from T75 flasks/ 90mm dishes and seeded in 96 well plates at a density of 5000-10000 cells/well depending on the doubling time of individual cell lines further continued to grow in complete medium under standard conditions. After 18 hrs to treat cells with test molecules, aliquots of 2 µL of the compound dilutions were added to the appropriate microtiter wells already containing 198 µL of fresh medium with cells, resulting in the required final drug concentrations. As a standard reference drug we have used Doxorubicin in all assay plates served as internal control. For each, compound four concentrations (0.1, 1, 10 and 100 µM) were evaluated as per NCI cell line screening protocol and each was done in triplicate wells. Plates were incubated further for 48h and assay was terminated by the addition of 10 µL of 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide **(**MTT, 5mg/ml) and incubated for 60 min at 37 ^oC. The plates were air-dried and the dye bound to the cells was subsequently solubilized in 100 µl of DMSO, and the absorbance was red on a multimode reader (Tecan) at a wavelength of 560 nm is directly proportional to cell growth. Percent growth was calculated for test wells relative to control wells. The above determinations were repeated three times. The growth inhibitory effects of the compounds were analyzed by generating dose response curves as a plot of the percentage surviving cells versus drug concentration. Sensitivity of the cancer cells to the drug treatment was expressed in terms of the concentration of drug required for 50% inhibition of cell growth (IC_{50}) results were presented in table 03 supplementary materials.

Table 03: Selected compounds IC_{50} values for different cancer cell lines

		DU-145		**HeLa**		**MCF-7**		**A549**	
S. No.	Compound	IC-50 (µM)	Std Dev.	IC-50 (µM)	Std Dev.	IC-50 (µM)	Std Dev.	IC-50 (µM)	Std Dev.
1	**1a**	14.27	1.71	>200		113.27	5.69	138.08	12.74
2	**1b**	79.58	6.86	120.57	2.32	165.11	12.32	143.47	10.70
3	**1c**	27.95	3.65	127.66	24.93	126.62	6.26	125.68	1.20
4	**2a**	85.59	3.24	>200		>200		146.87	7.17

5	**3a**	131.71	14.05	>200		173.90	22.52	175.99	7.95
6	**3c**	93.74	7.45	>200		165.09	0.05	133.63	9.82
7	**4a**	84.26	12.29	>200		>200		148.29	21.44
8	**4b**	95.41	7.27	>200		>200		126.67	0.07
9	**4c**	88.58	5.12	165.28	14.27	155.34	9.82	168.59	7.87
10	**5a**	87.29	12.97	>200		185.73	29.64	125.71	16.52
11	**5c**	65.47	3.01	153.38	6.87	192.21	20.01	137.54	12.02
12	**7a**	133.72	3.28	98.41	14.02	94.06	6.10	99.02	3.30
13	**7b**	85.15	1.81	164.09	39.61	174.90	12.34	129.33	25.96
14	**8a**	>200		>200		>200		160.09	9.49
15	**9a**	76.37	1.42	161.10	12.11	185.61	11.69	118.21	4.98
16	**10a**	81.27	5.40	>200		>200		>200	
17	**10b**	79.91	5.38	>200		>200		159.30	33.25
18	**1d**	87.74	4.10	159.52	13.53	>200		138.68	20.71
19	**1f**	160.78	20.54	>200		>200		>200	
20	**11a**	111.88	6.08	166.70	26.00	>200		160.60	6.41
21	Doxorubucin	6.73	0.18	7.51	0.10	7.87	0.13	7.17	0.39

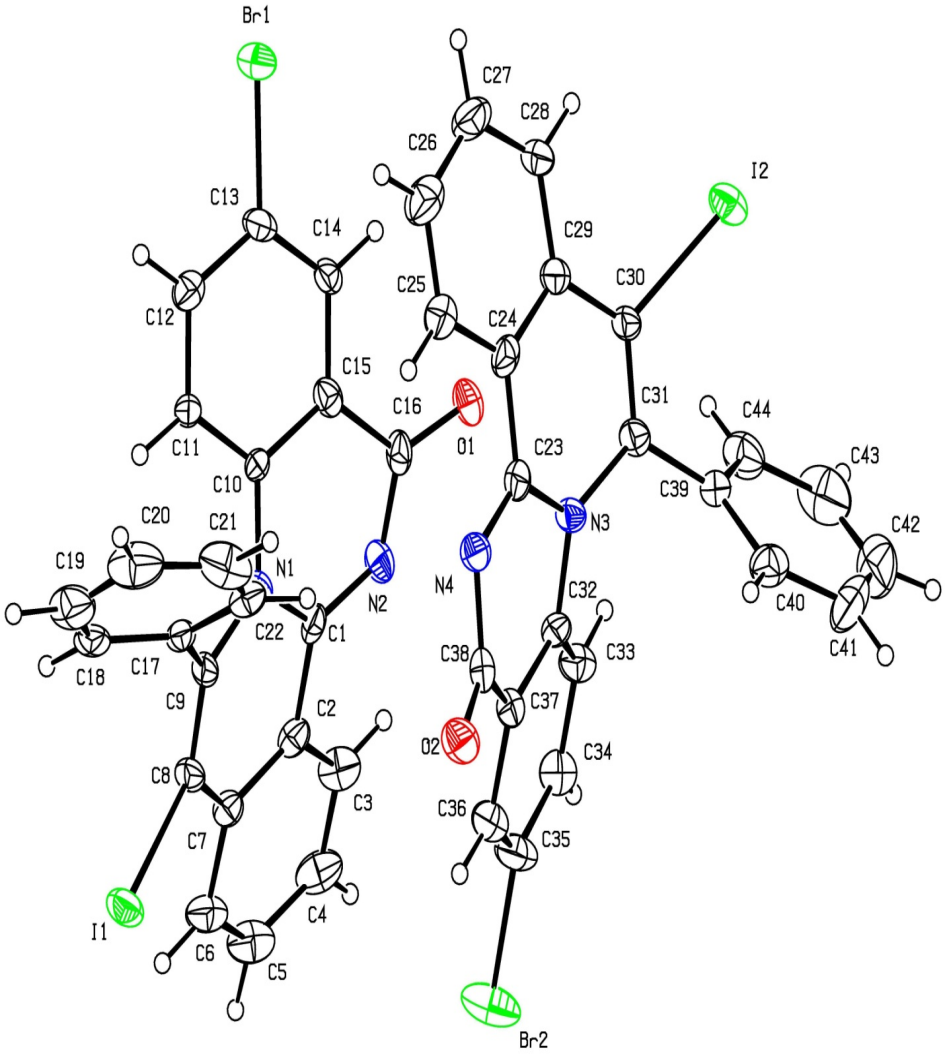
9. X- ray Crystallography Data:

X-ray data for the compounds were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method [Bruker (2001). SAINT (Version 6.28a) & SMART (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA.]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames.

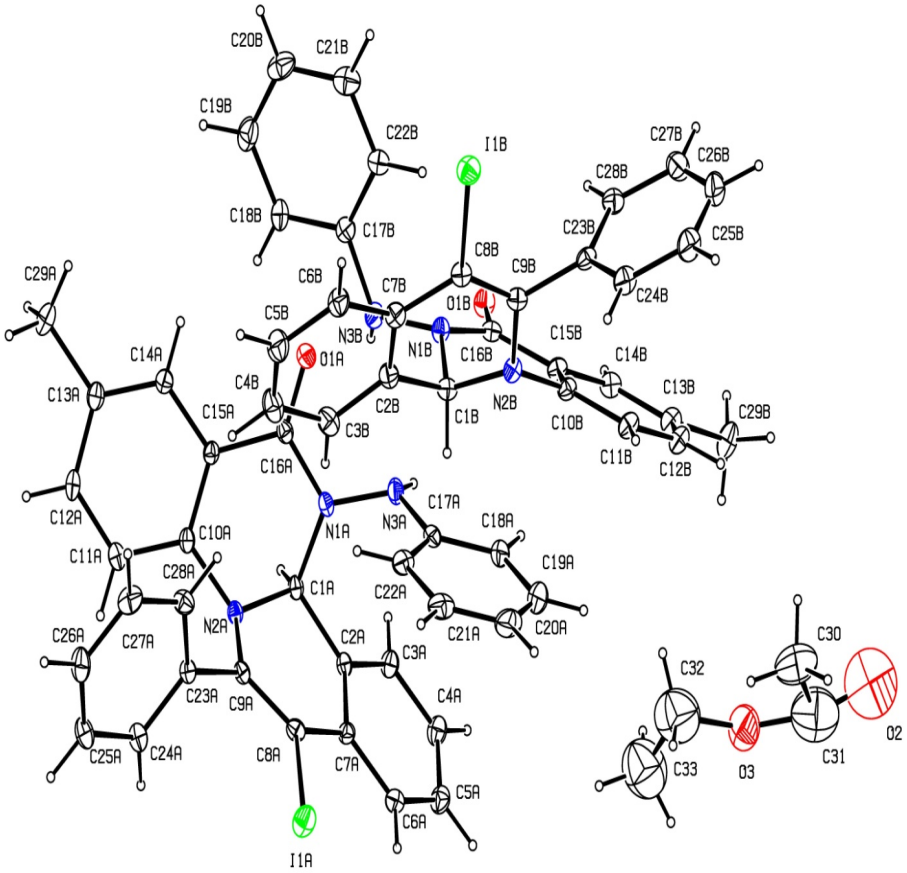
Integration and scaling of intensity data were accomplished using SAINT program [Bruker (2001). SAINT (Version 6.28a) & SMART (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA.]. The structure was solved by direct methods using SHELXS97 [Sheldrick GM. (2008**)** Acta Crystallogr A64: 112-122.] and refinement was carried out by full-matrix least-squares technique using SHELXL97 [Sheldrick GM. (2008**)** Acta Crystallogr A64: 112-122.]. Anisotropic displacement parameters were included for all non-hydrogen atoms. The hydrogen atoms attached to nitrogen atoms of **1e** were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms with C-H = 0.93 - 0.96 Å and U_{iso}(H) = 1.2 or 1.5U_{eq}(C). In **1e**, the ethyl acetate solvent shows high thermal vibrations, hence attempts were made to refine the solvent with disorder model was unsuccessful. The ethyl acetate atoms C30/C31/C32/C33/O2/O3 were constrained with distance and ISOR restrains. In **5c**,

the atoms C22 and C23 were disordered over two sites (C22/C22' & C23/C23') and the site-occupancy factors of the disordered atoms were refined to 0.63(2) and 0.37(2). The major and minor components of the disordered atoms were restrained to be similar using SIMU and DELU instructions. The C-C distances of the disordered atoms were constrained with 1.45(1)Å.

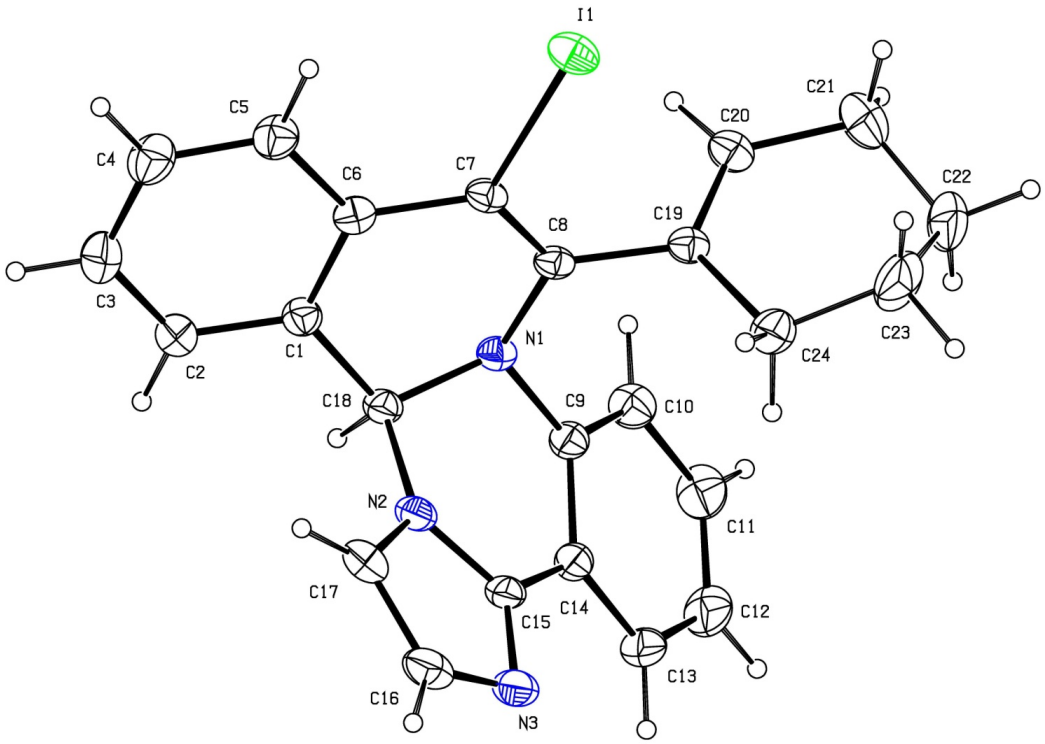
ORTEP diagram of **1b (CCDC 928899**)



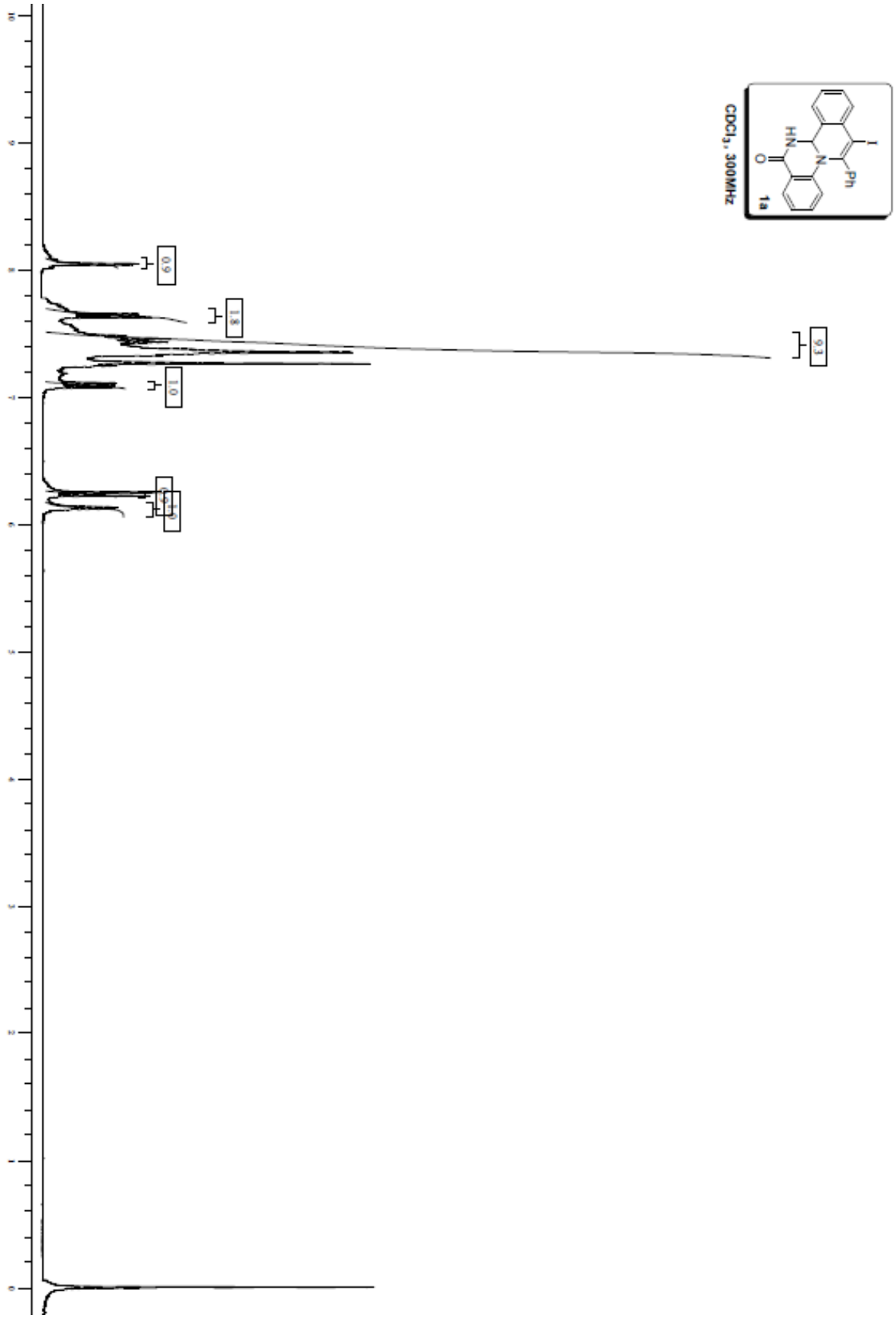
ORTEP diagram of **1e** (**CCDC 929085**)

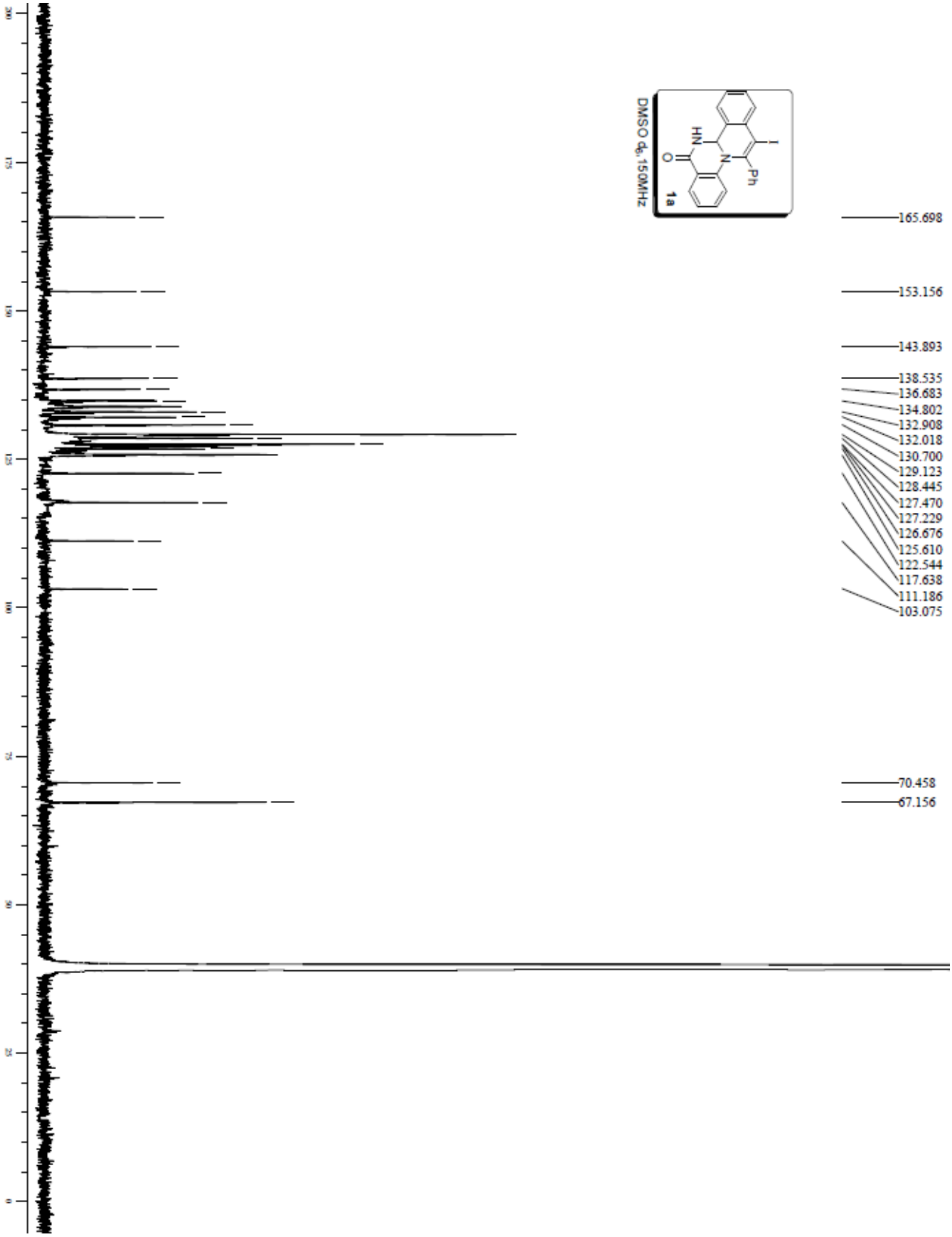


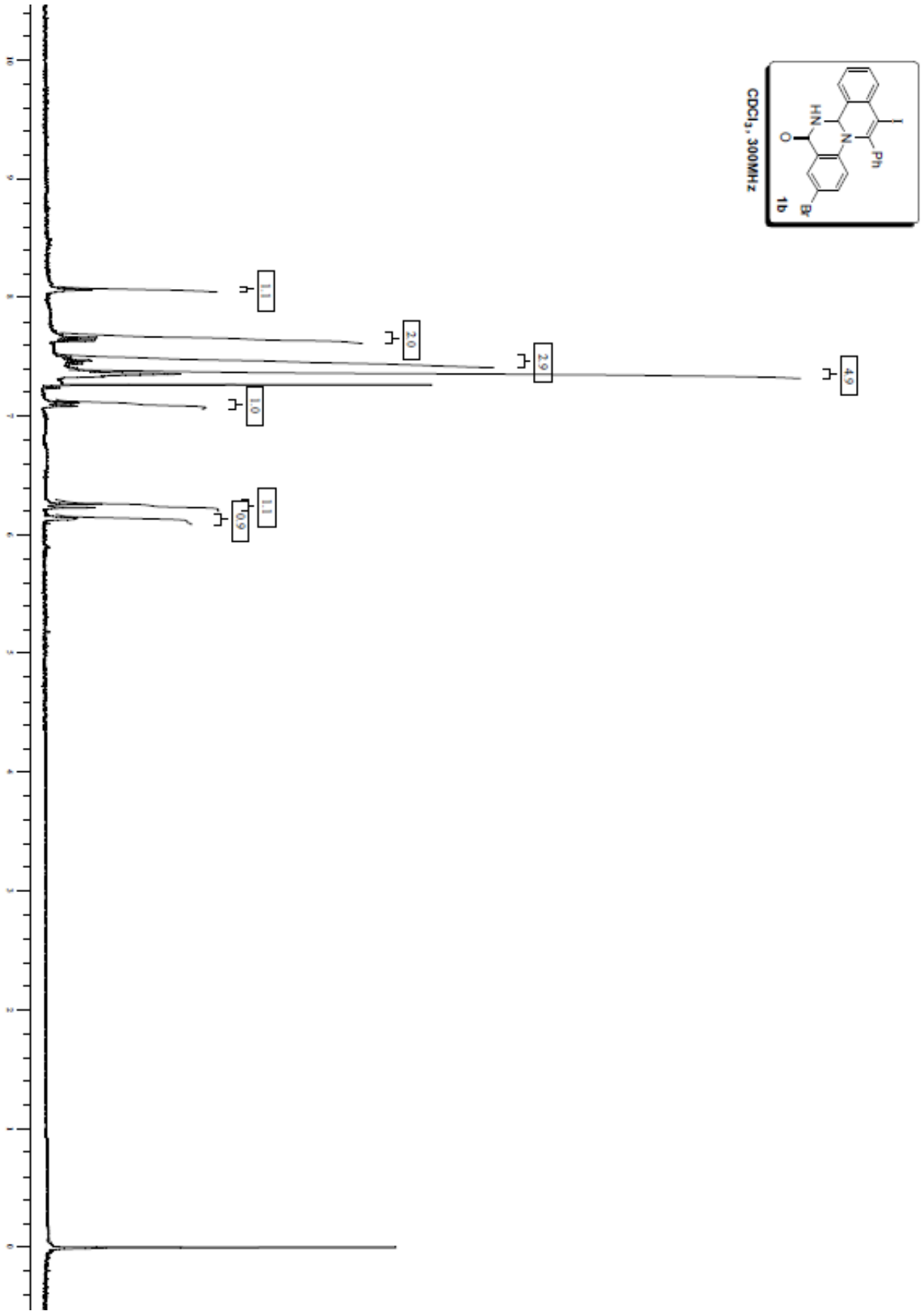
ORTEP diagram of **5c (CCDC928900**)

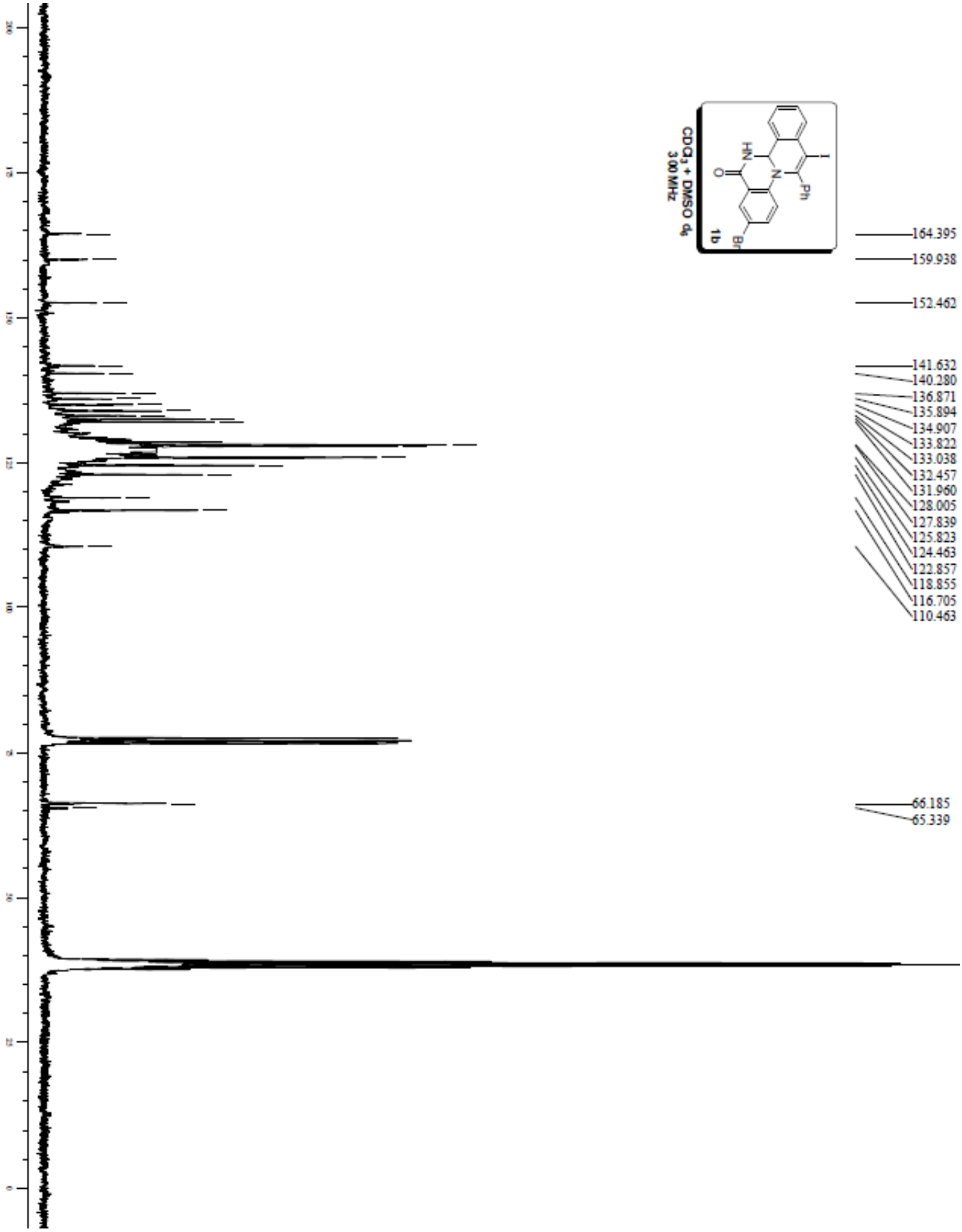


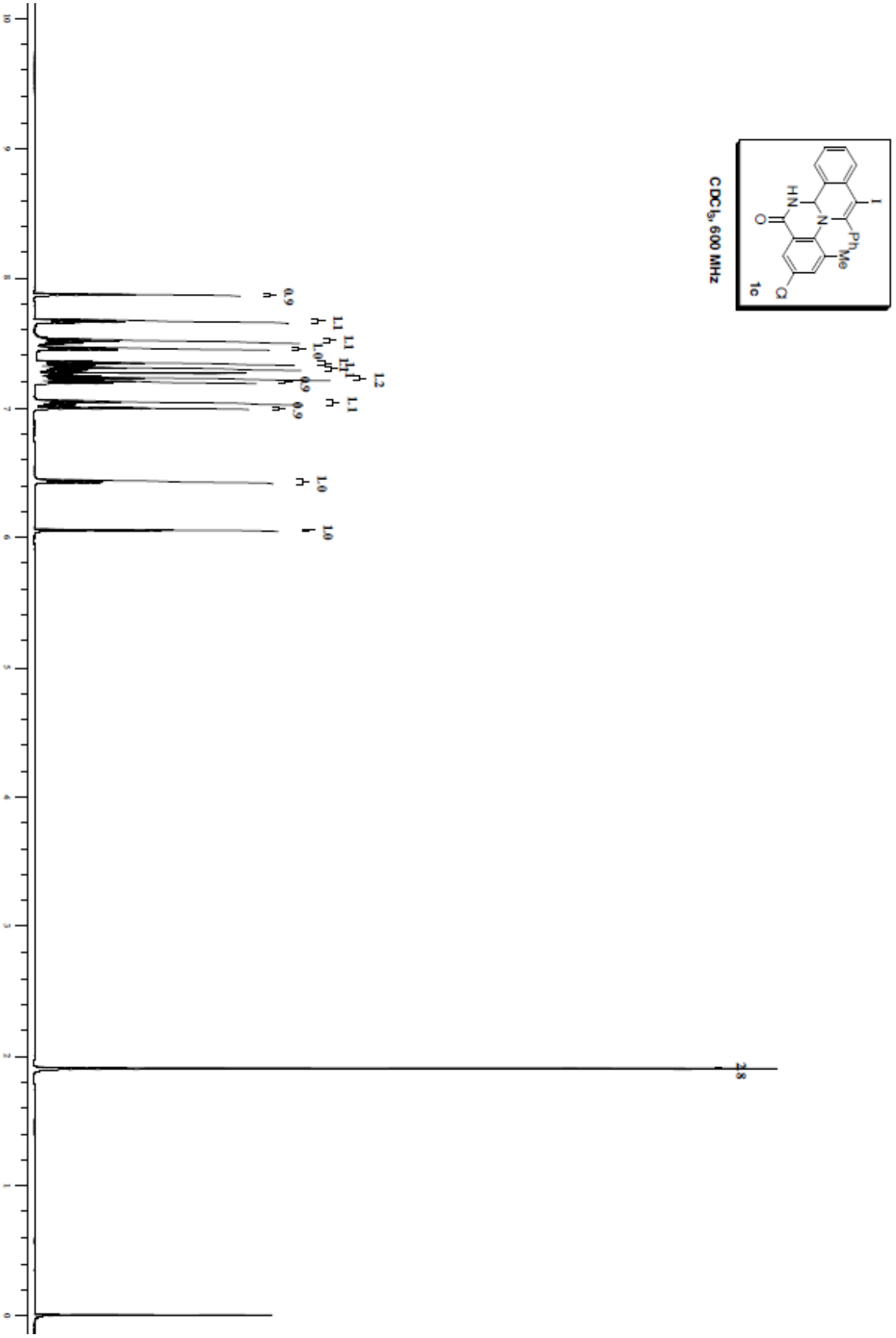
10. ^{1}H NMR and ^{13}C NMR Spectra of Compounds







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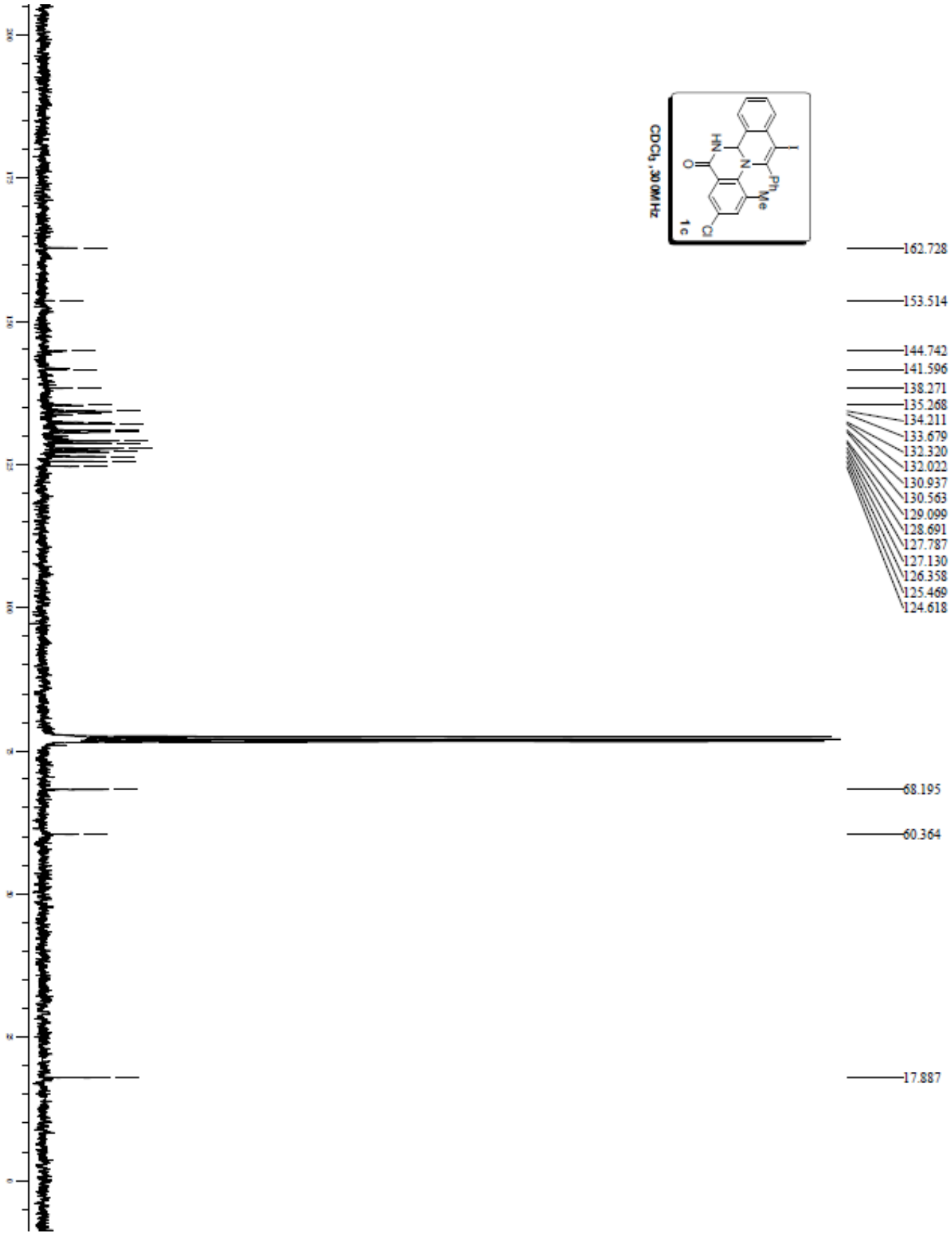
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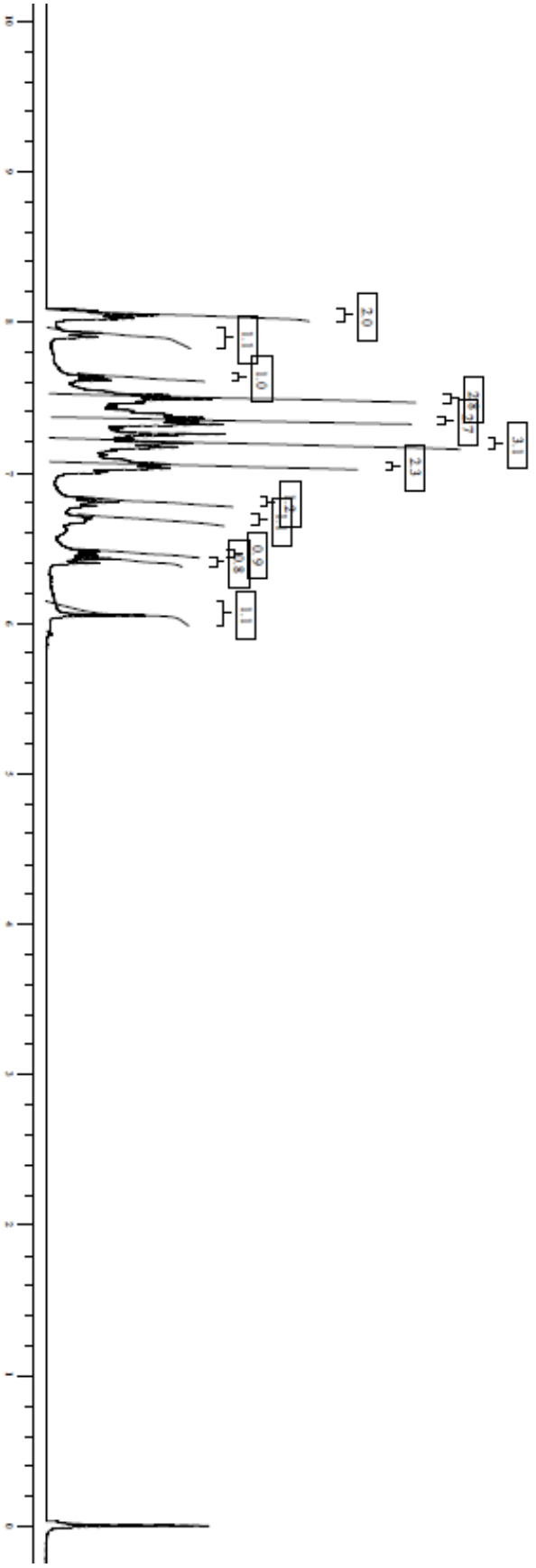

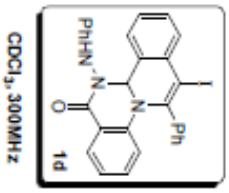
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O
N
I
Ph
1d
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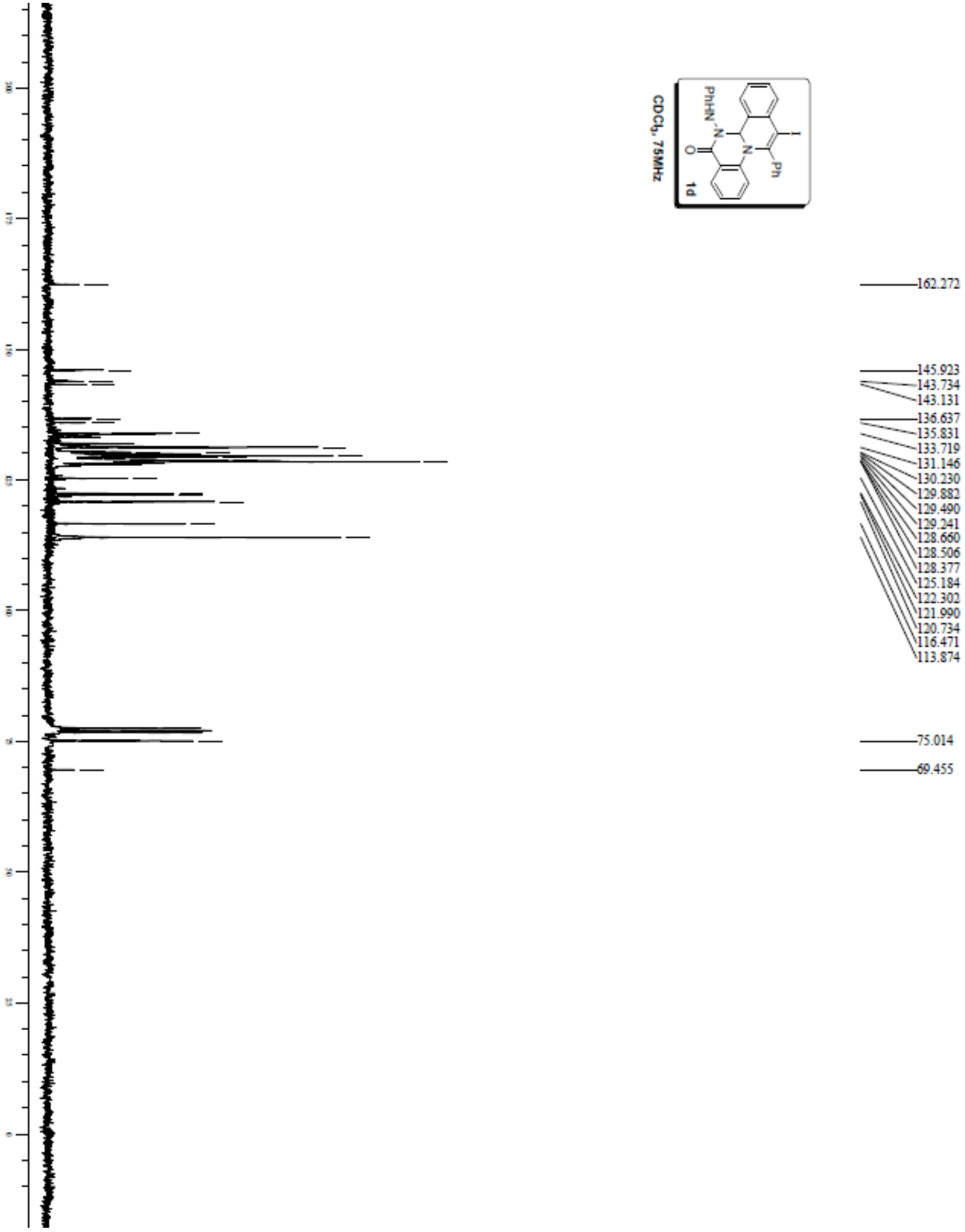

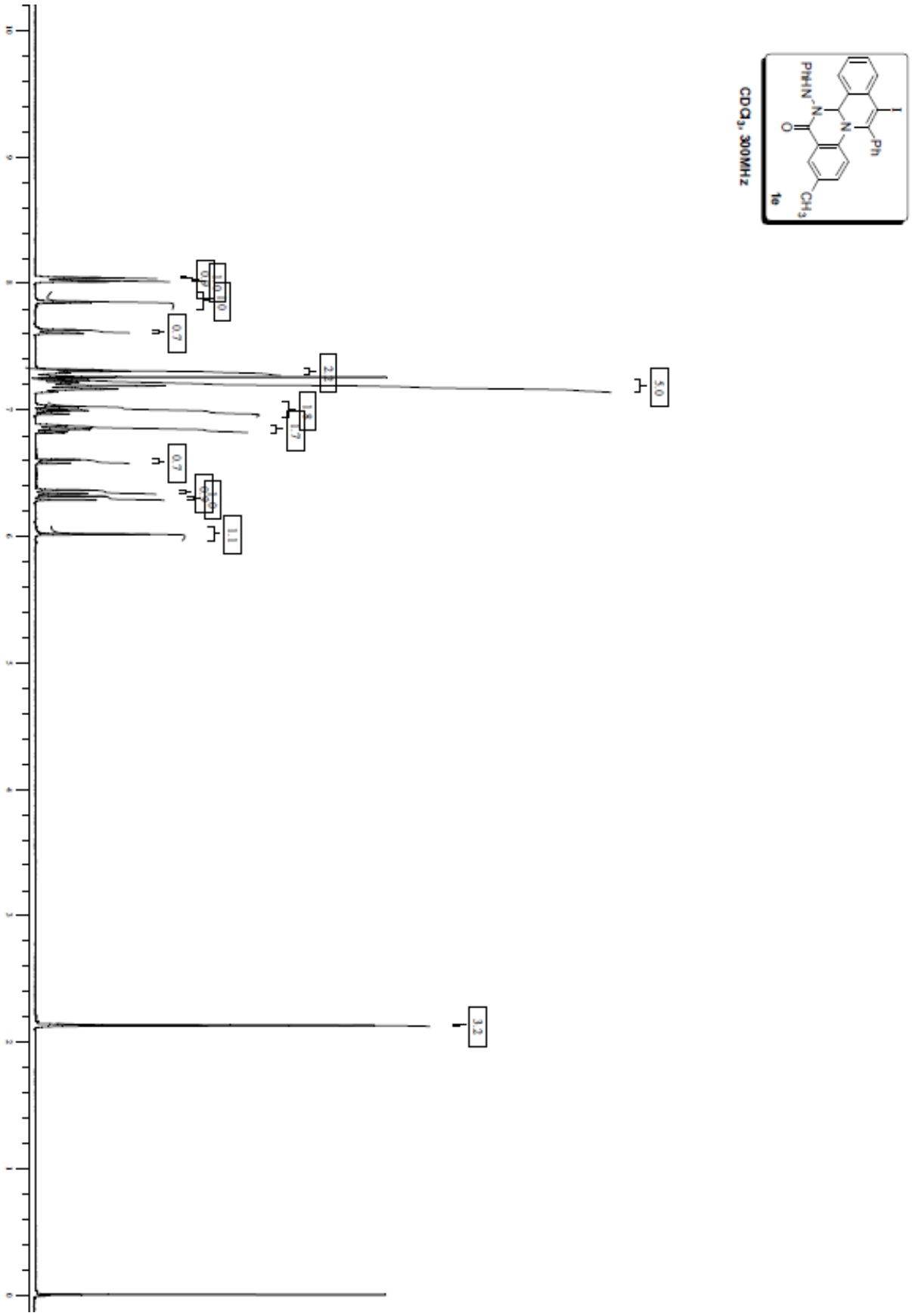
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O
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I
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2.3
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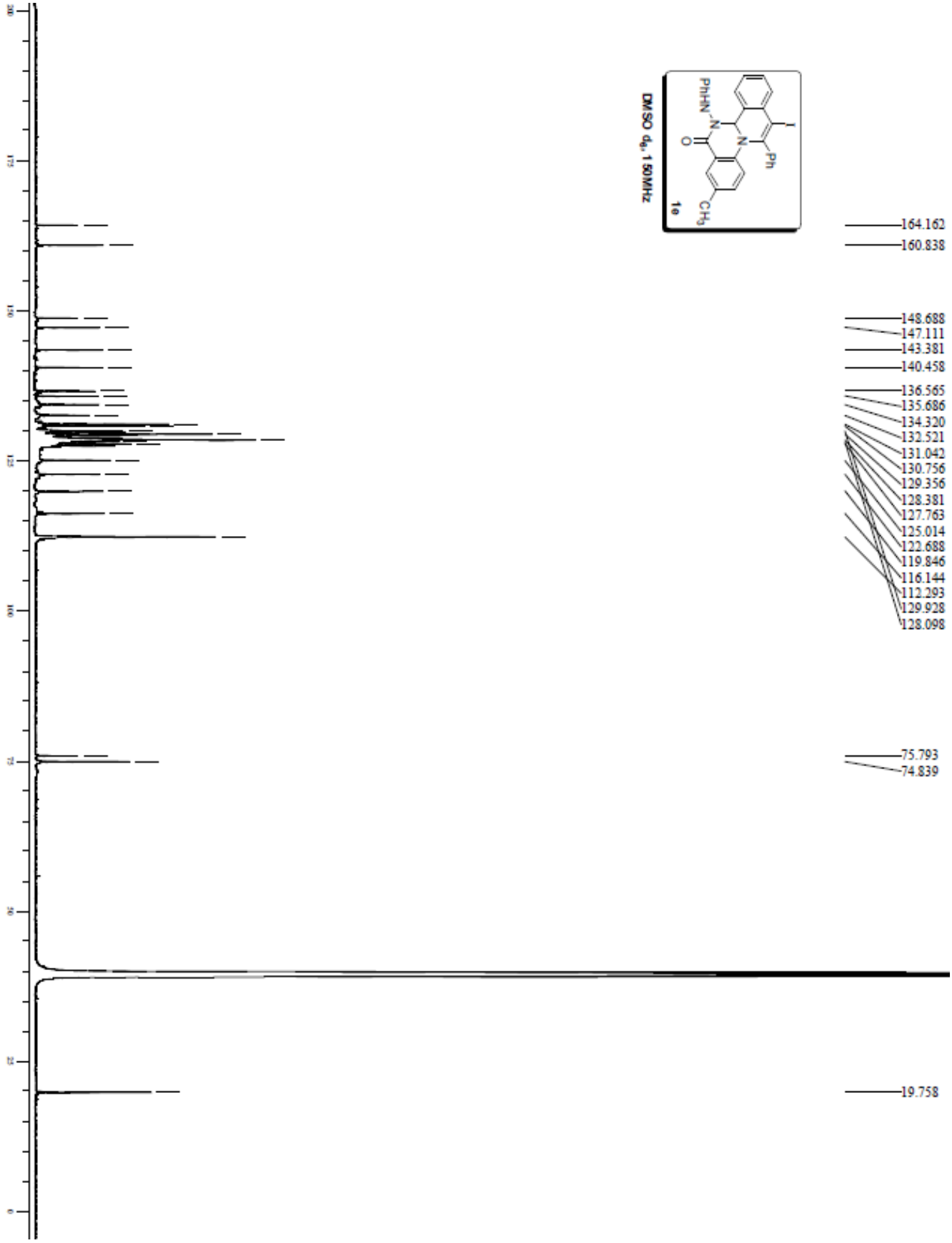
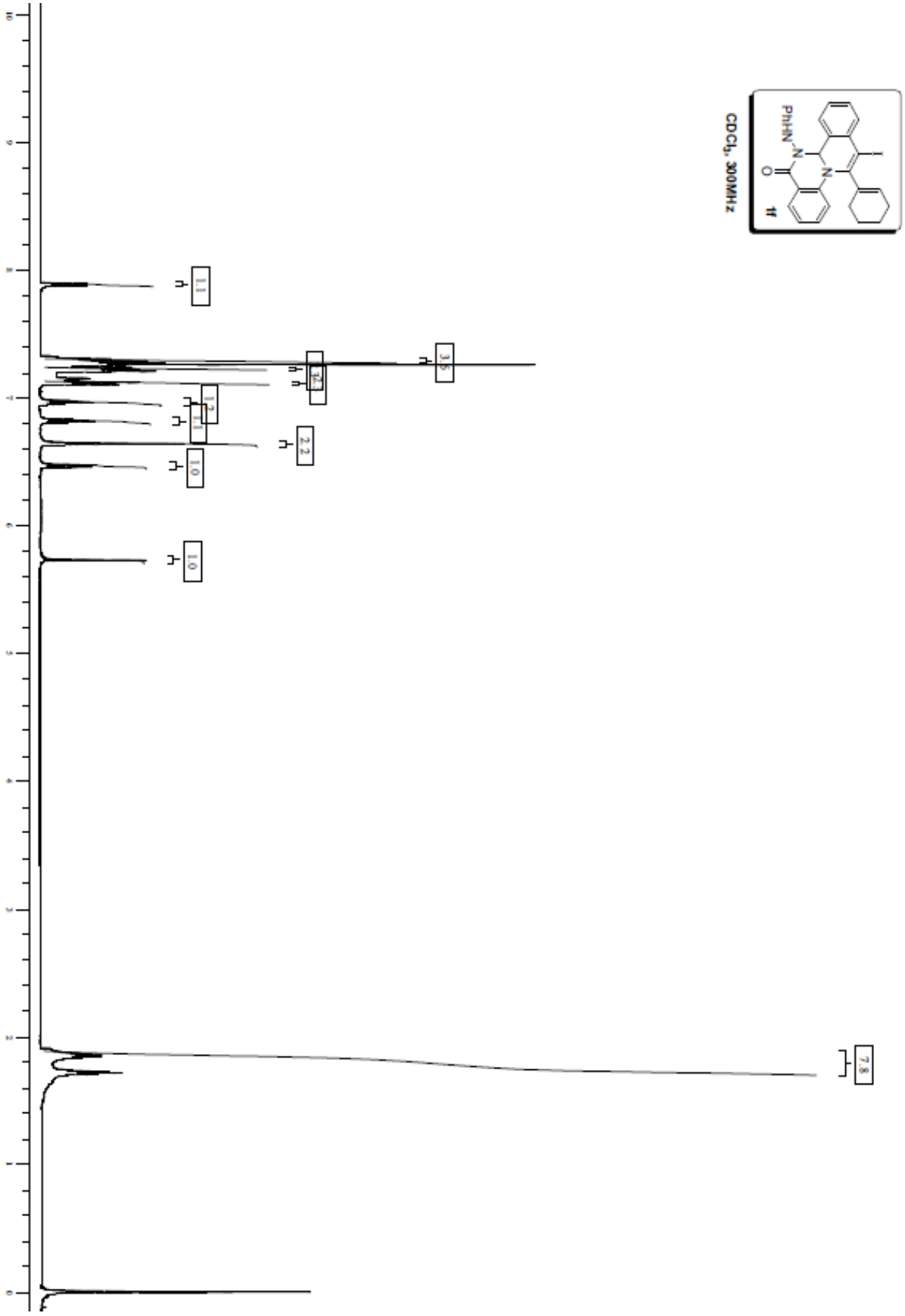
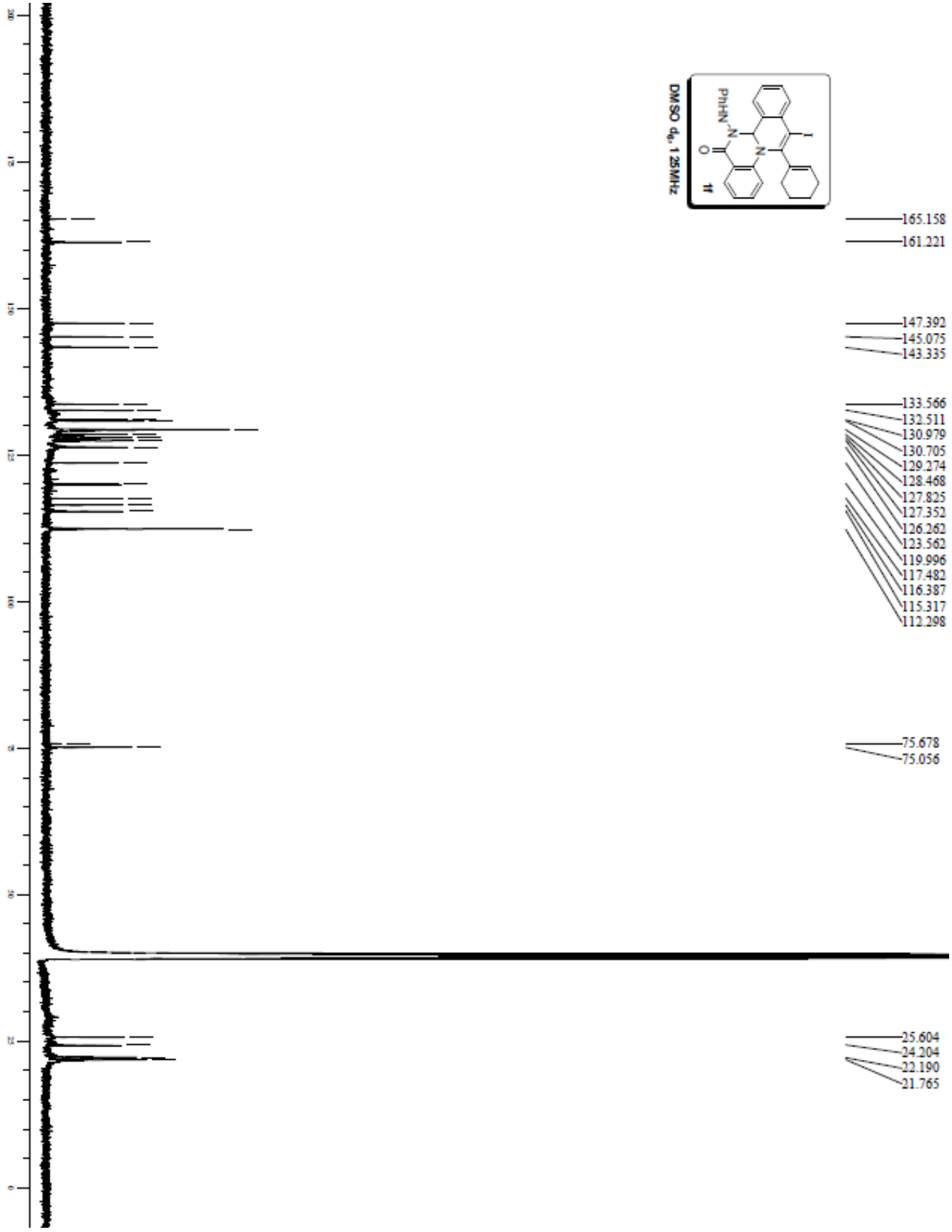
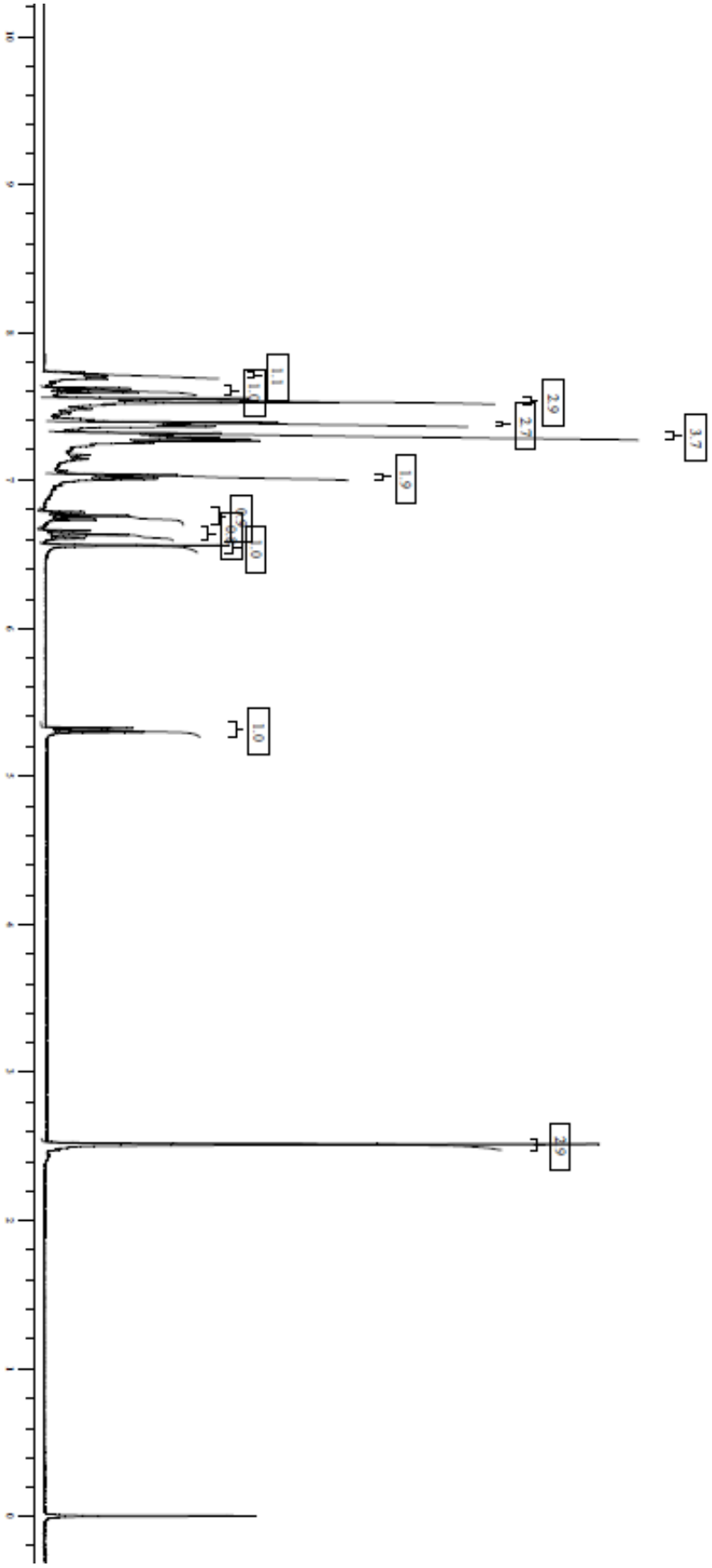
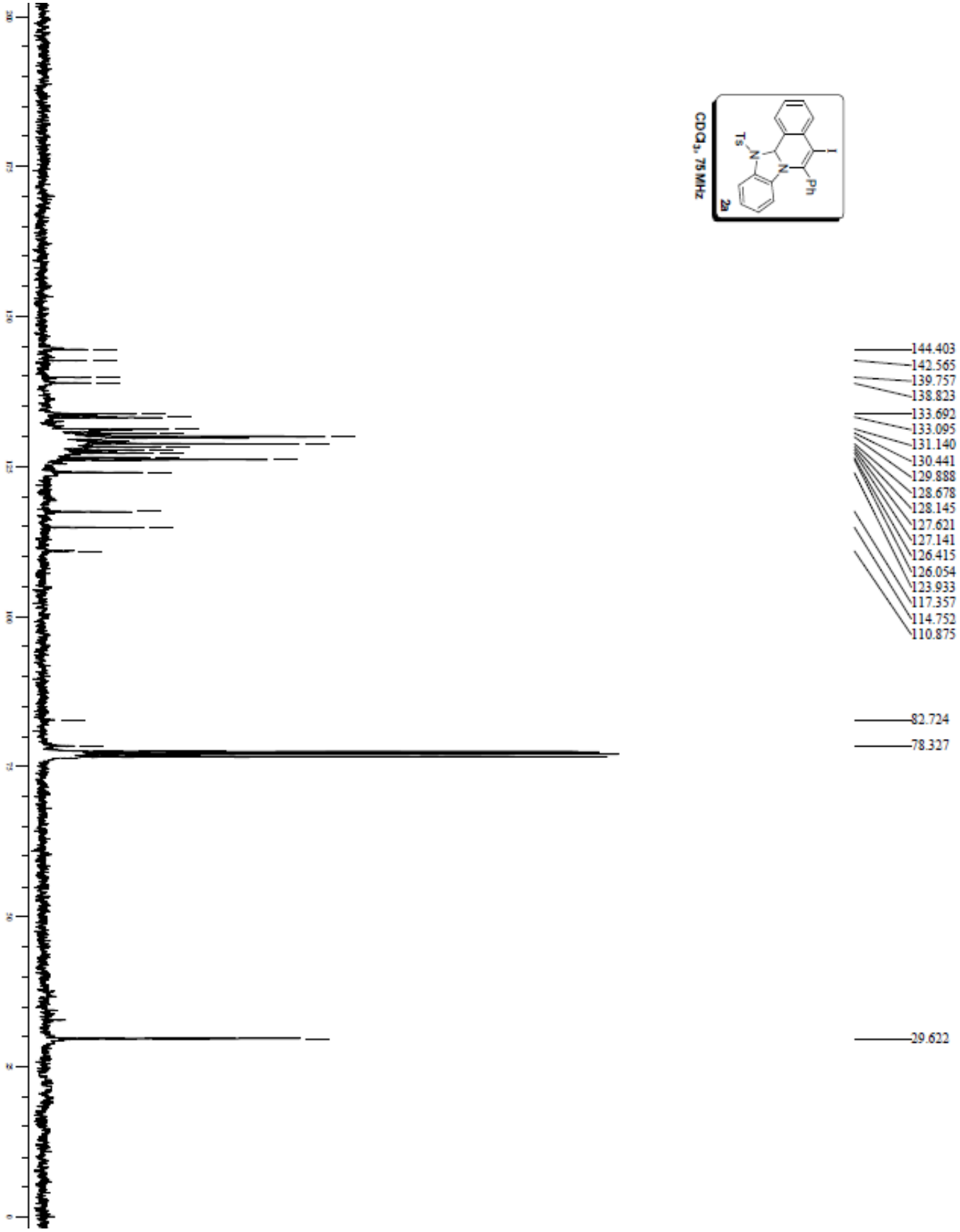
0.6
1.0
1.1
3.2

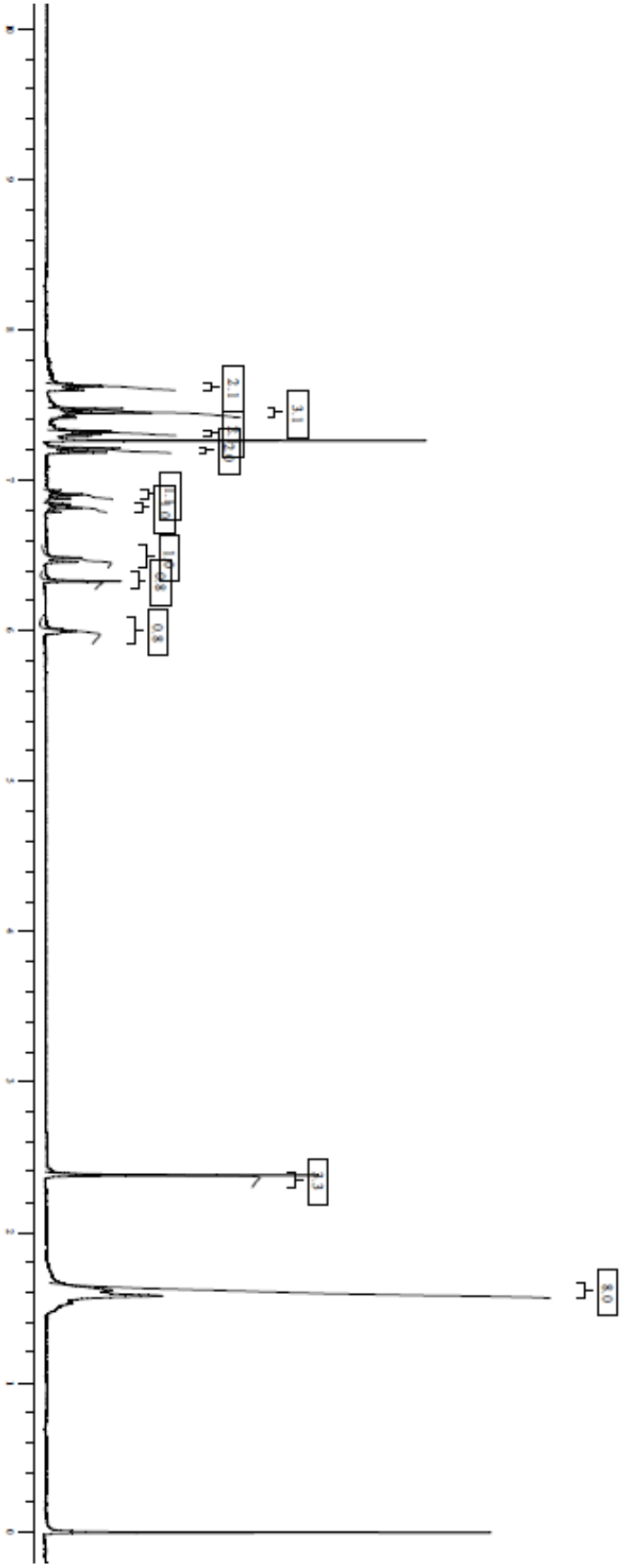

DMSO d_6, 150MHz
PhHN
N
O
N
Ph
I
CH_3
1e
164.162
160.838
148.688
147.111
143.381
140.458
136.565
135.686
134.320
132.521
131.042
130.756
129.356
128.381
127.763
125.014
122.688
119.846
116.144
112.293
129.928
128.098
75.793
74.839
19.758

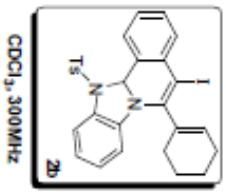

CDCl3, 300MHz
PhHN
N
N
O
I
1f
1.11
3.15
2.24
2.12
2.11
2.22
1.10
1.10
7.38

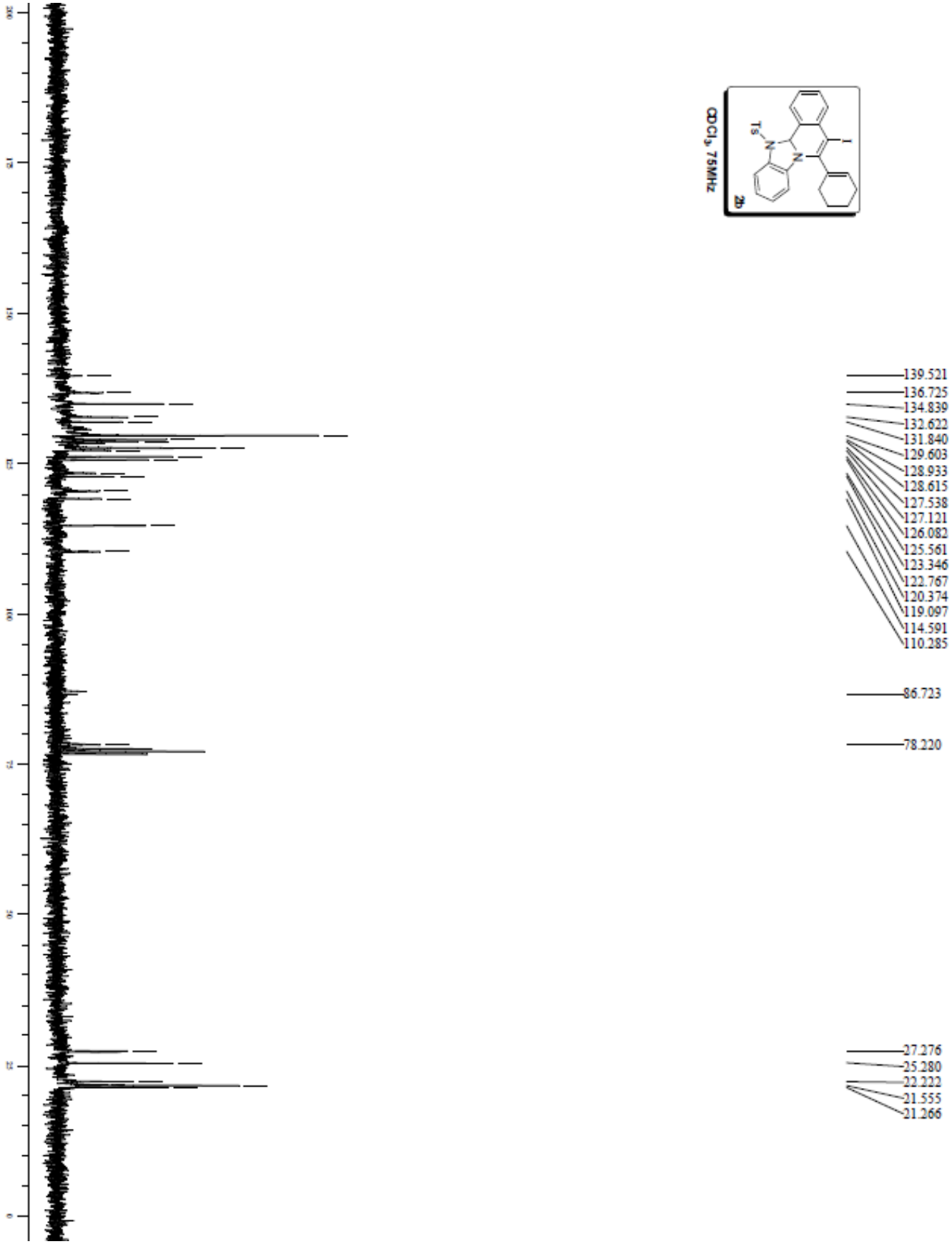

DMSO d_6, 125MHz
1f
165.158
161.221
147.392
145.075
143.335
133.566
132.511
130.979
130.705
129.274
128.468
127.825
127.352
126.262
123.562
119.996
117.482
116.387
115.317
112.298
75.678
75.056
25.604
24.204
22.190
21.765

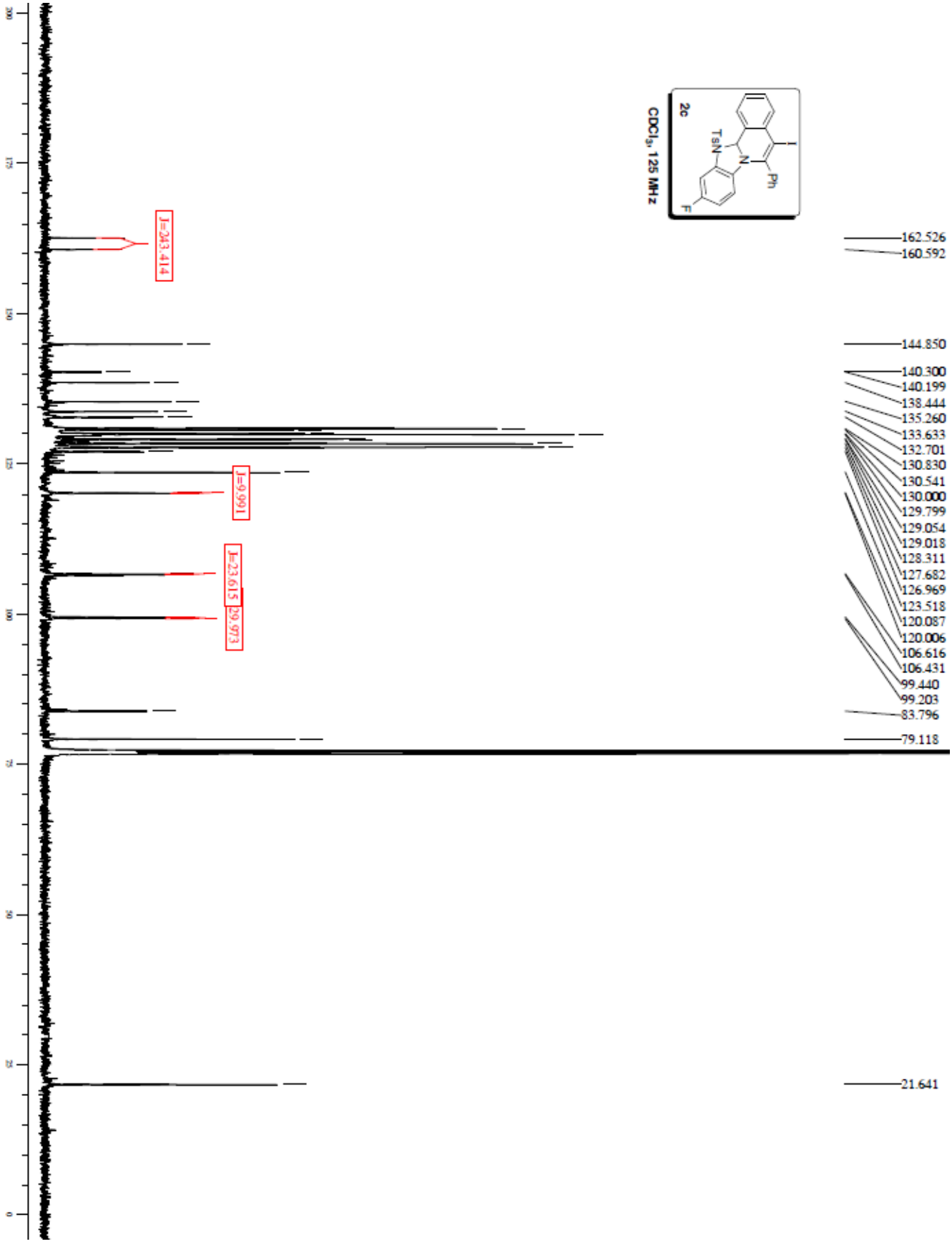

CDCl3, 300MHz
Ts
N
N
I
Ph
2a
11
1.1
2.9
2.7
3.7
1.9
2.0
1.0
1.0
2.9

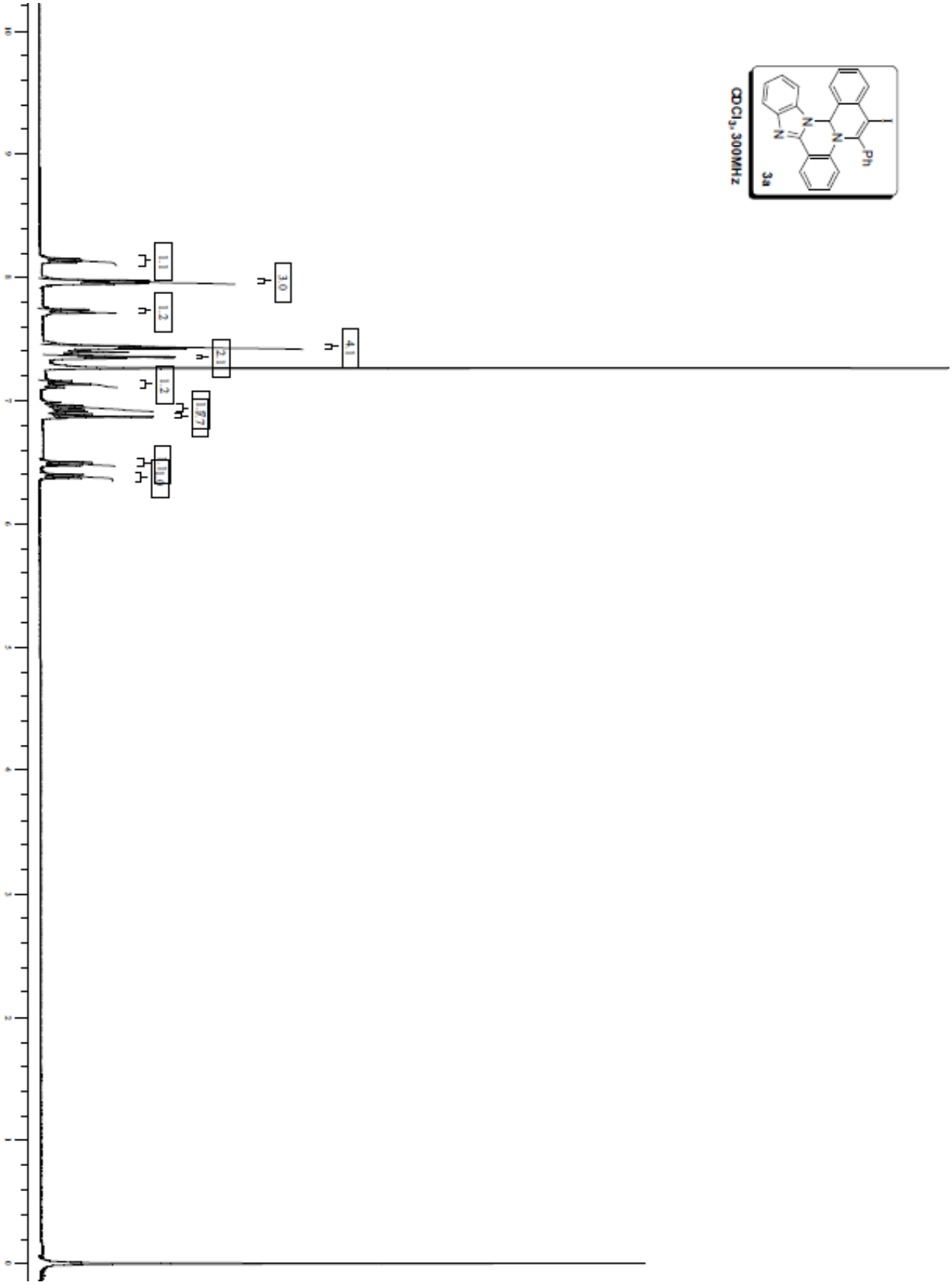


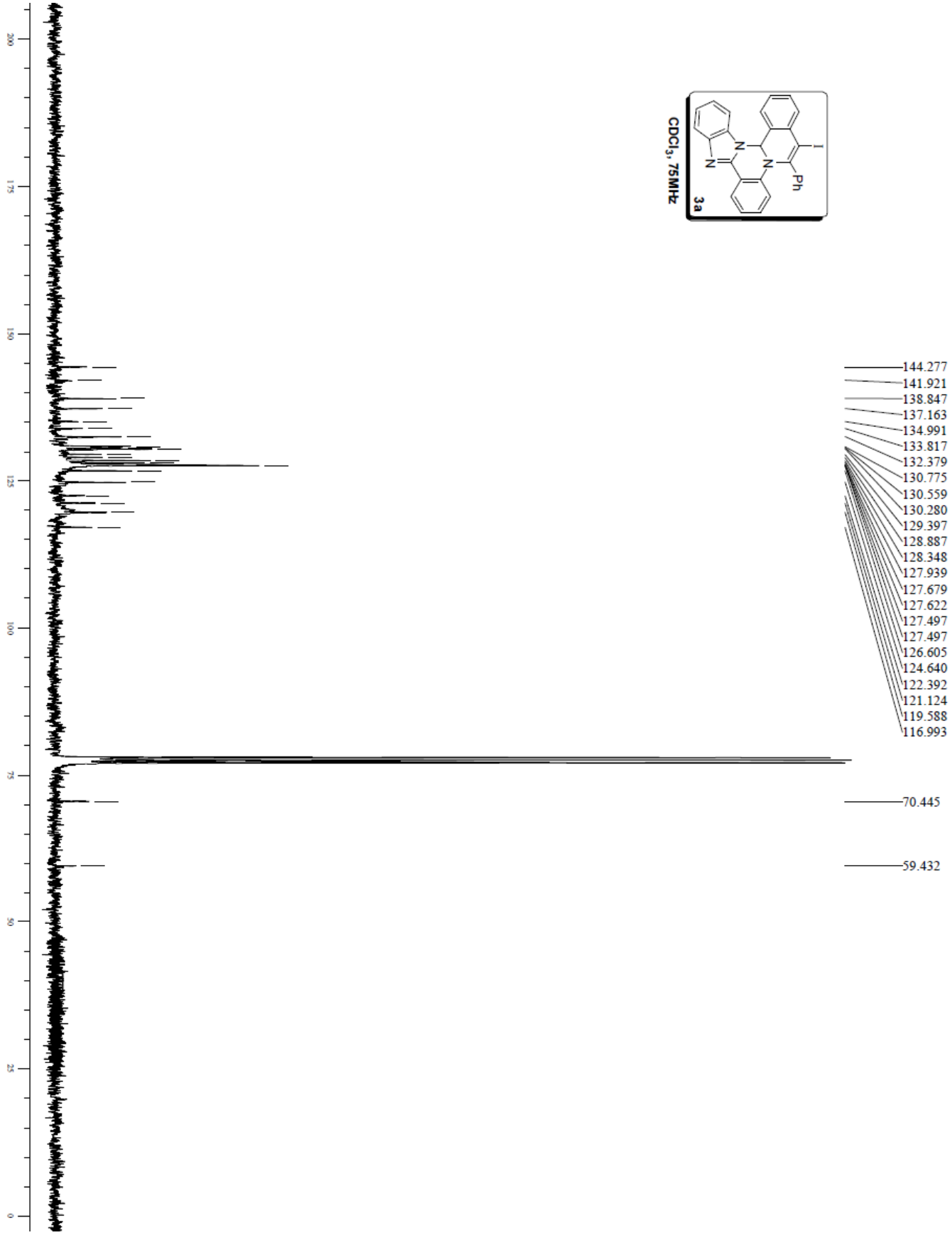

2.11
3.11
2.01
1.97
1.00
0.98
0.96
2.13
8.00

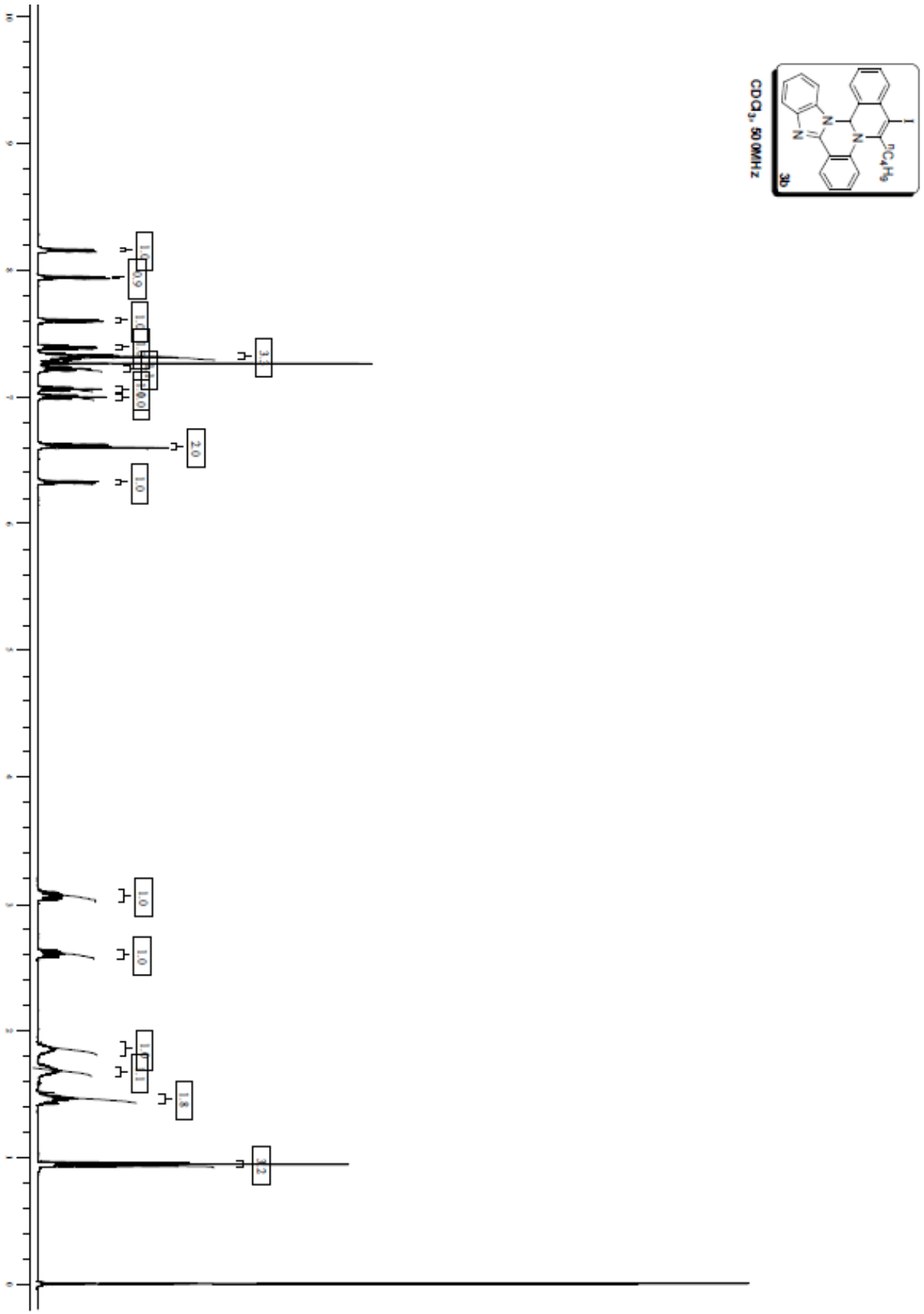

CDCl3, 300MHz
Ts
N
N
I
2b

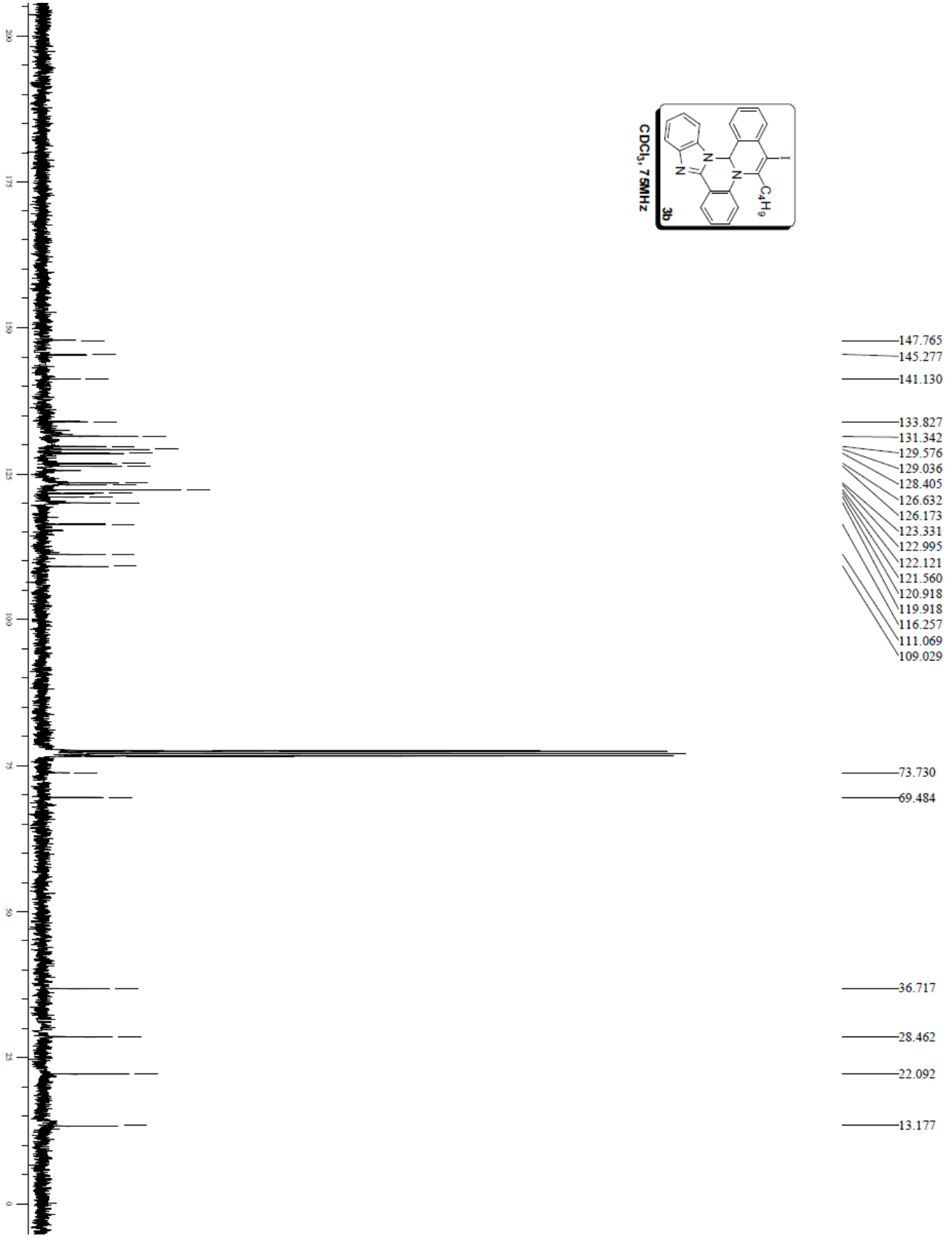


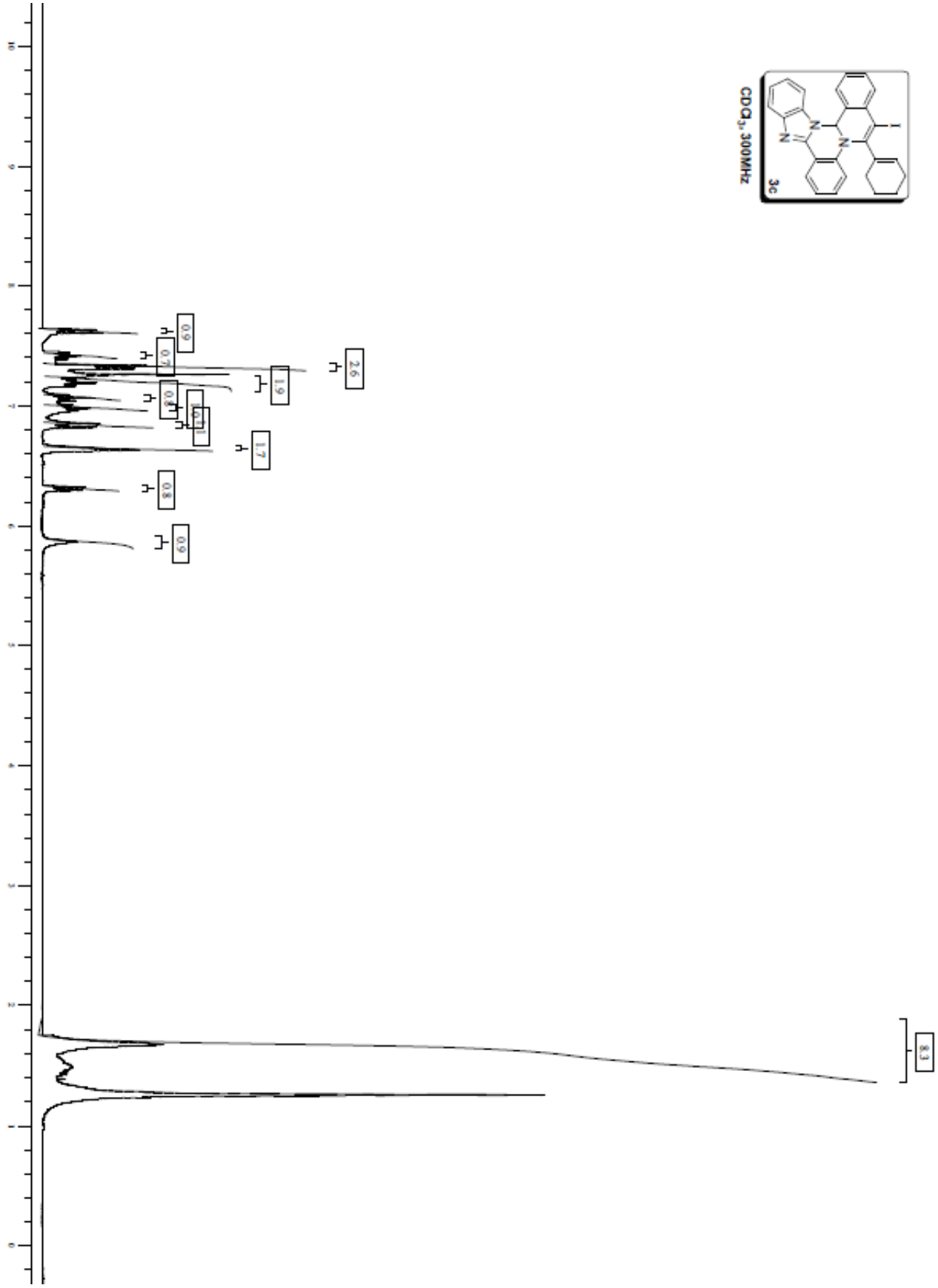


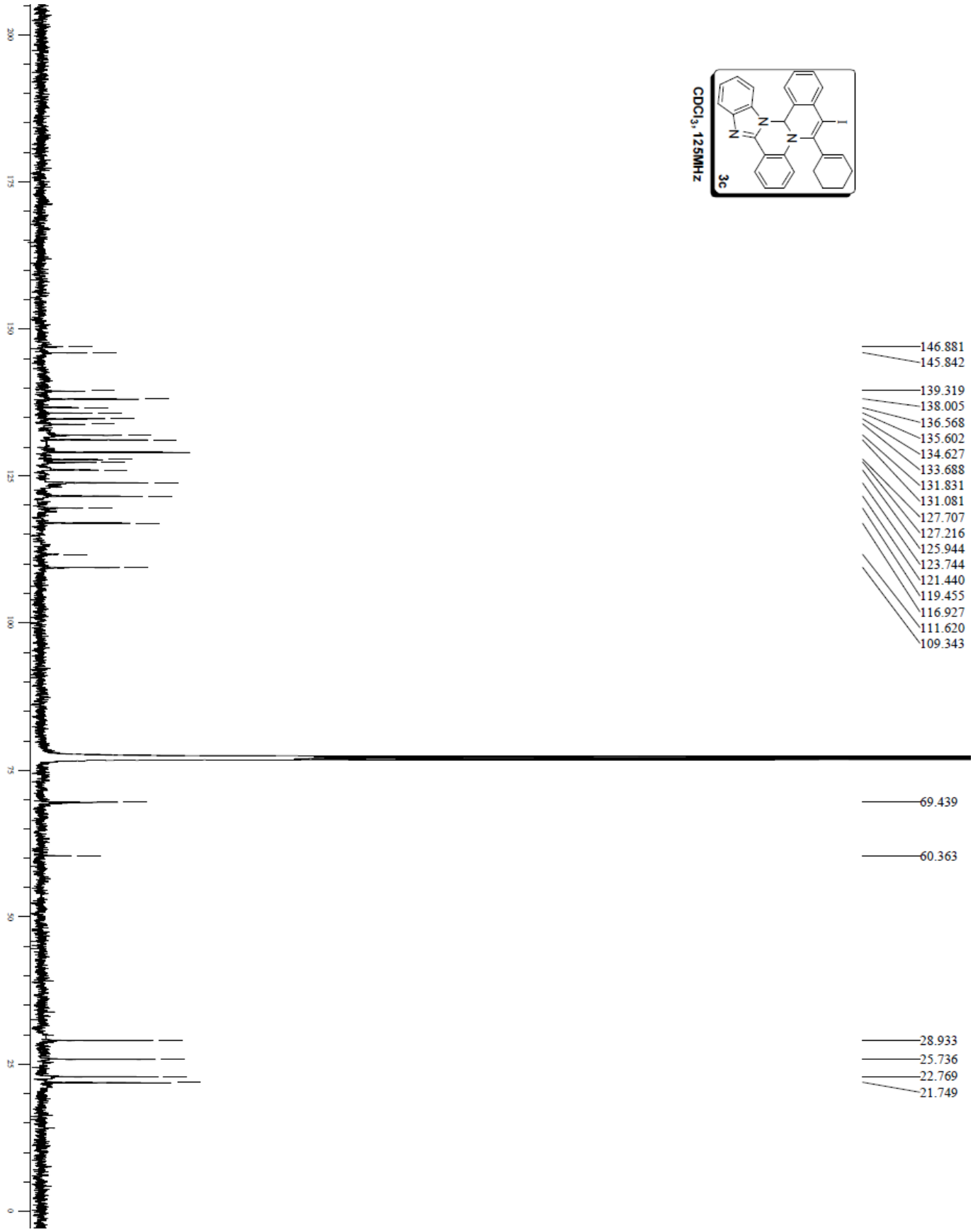


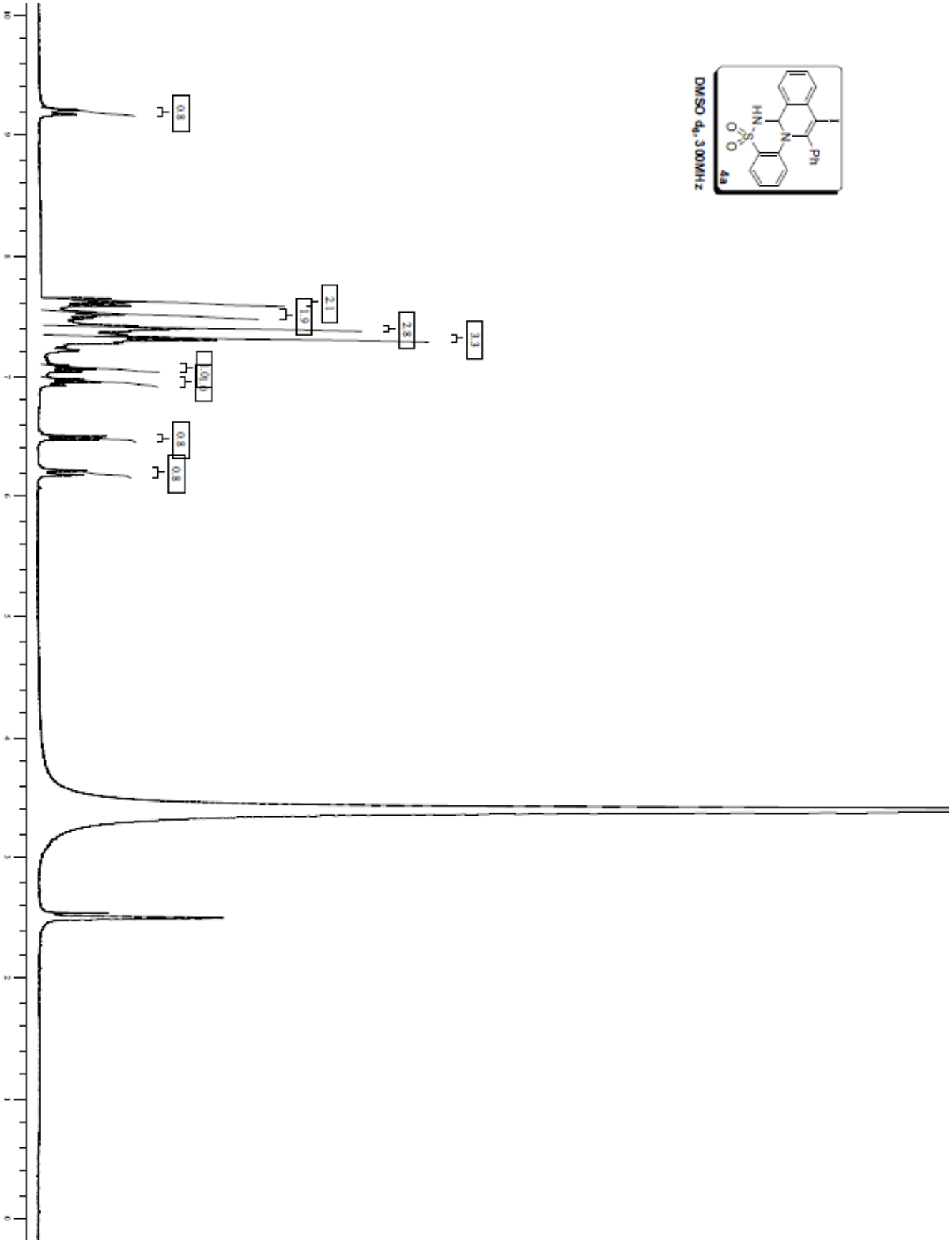


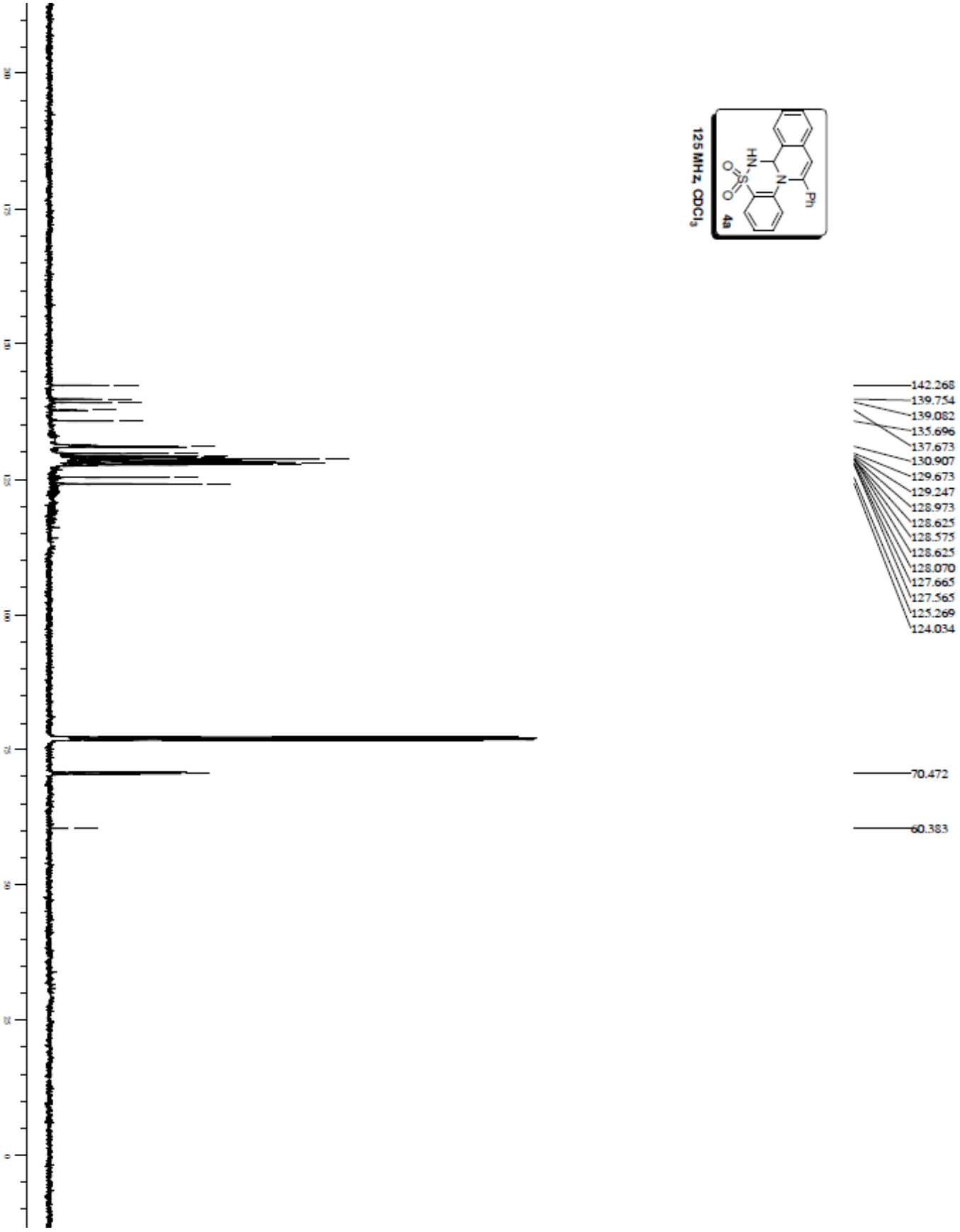


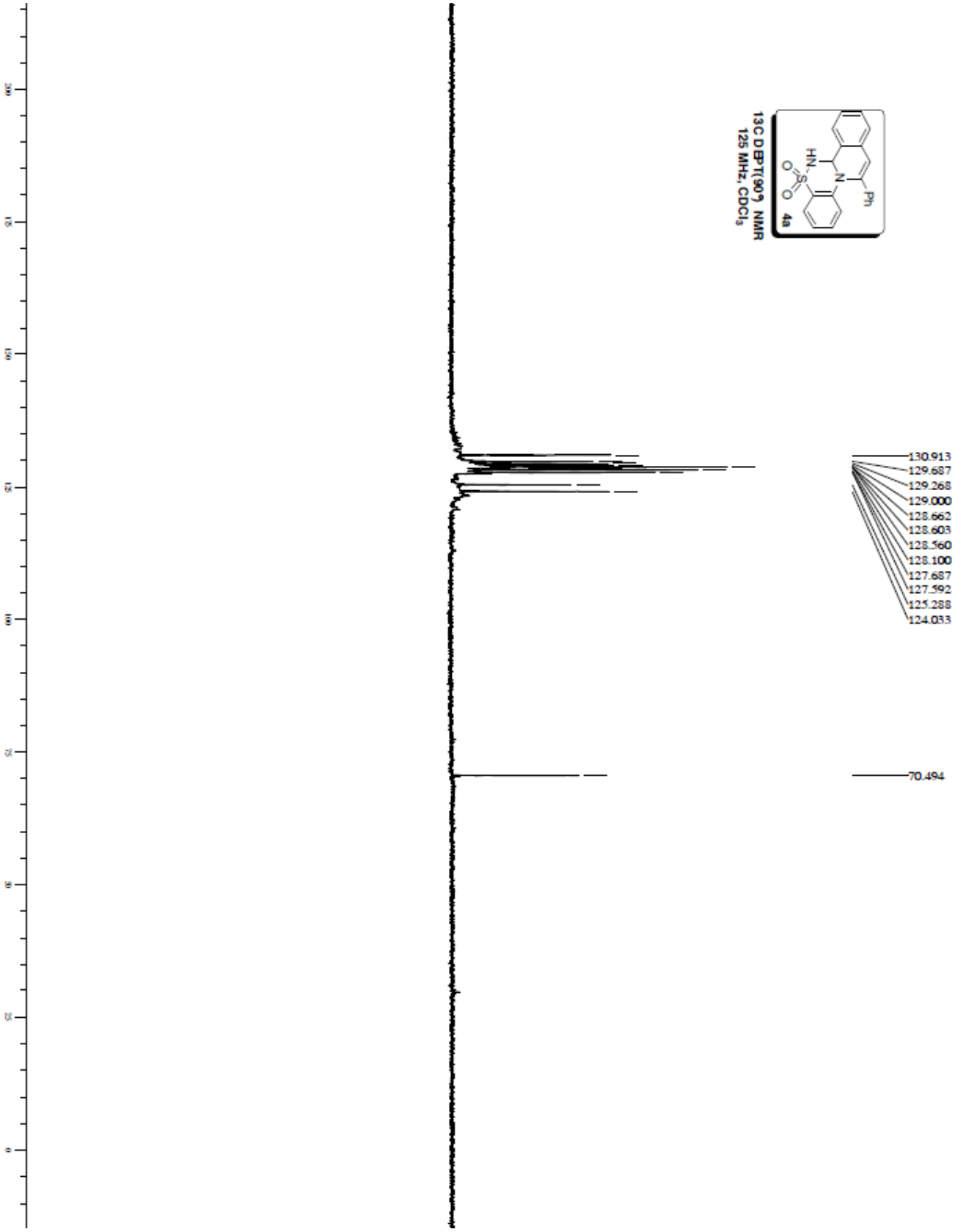


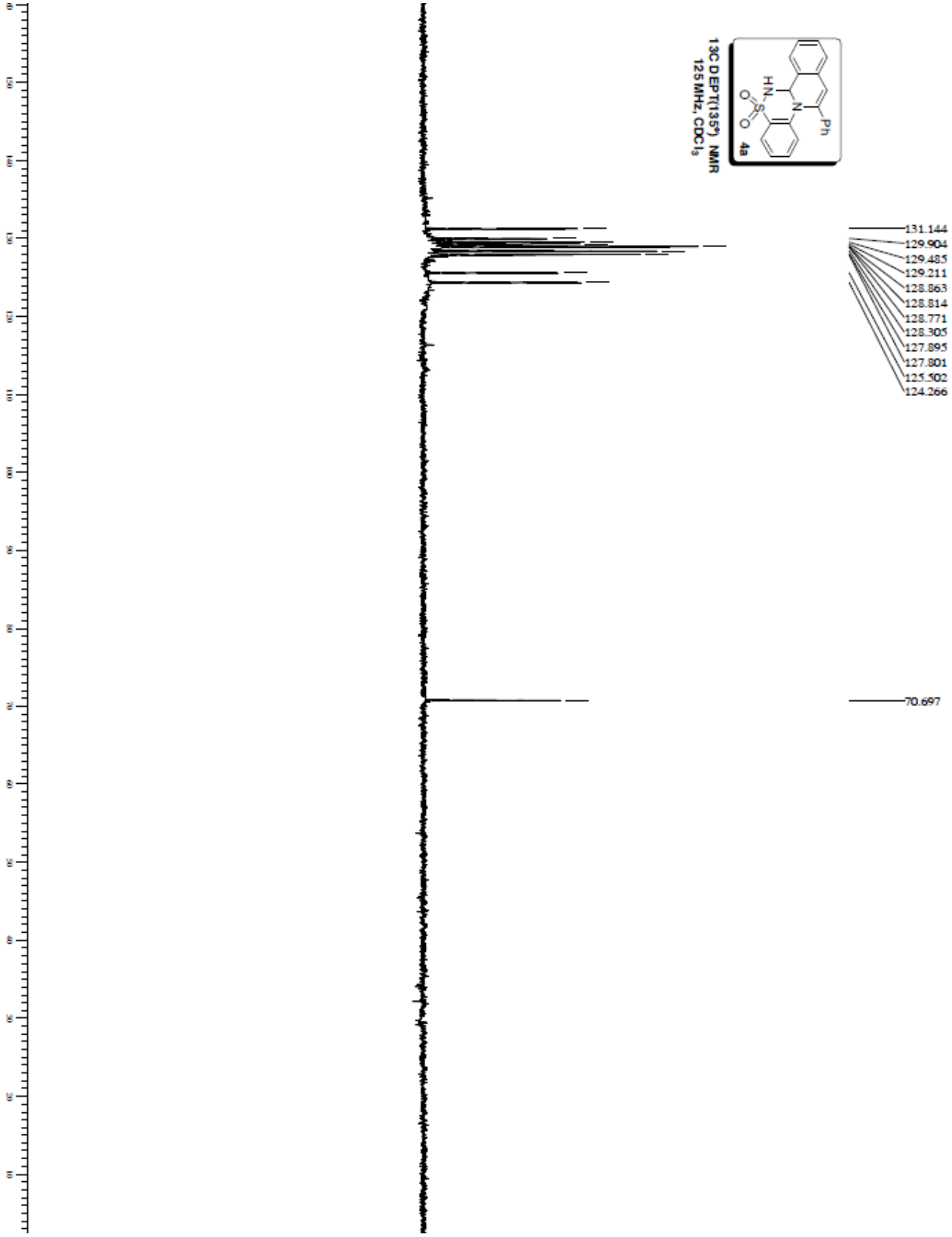

CDCl3, 300MHz
3c
I
N
N
N
0.9
0.7
0.8
0.8
0.8
1.9
2.6
1.7
0.8
0.9
8.3

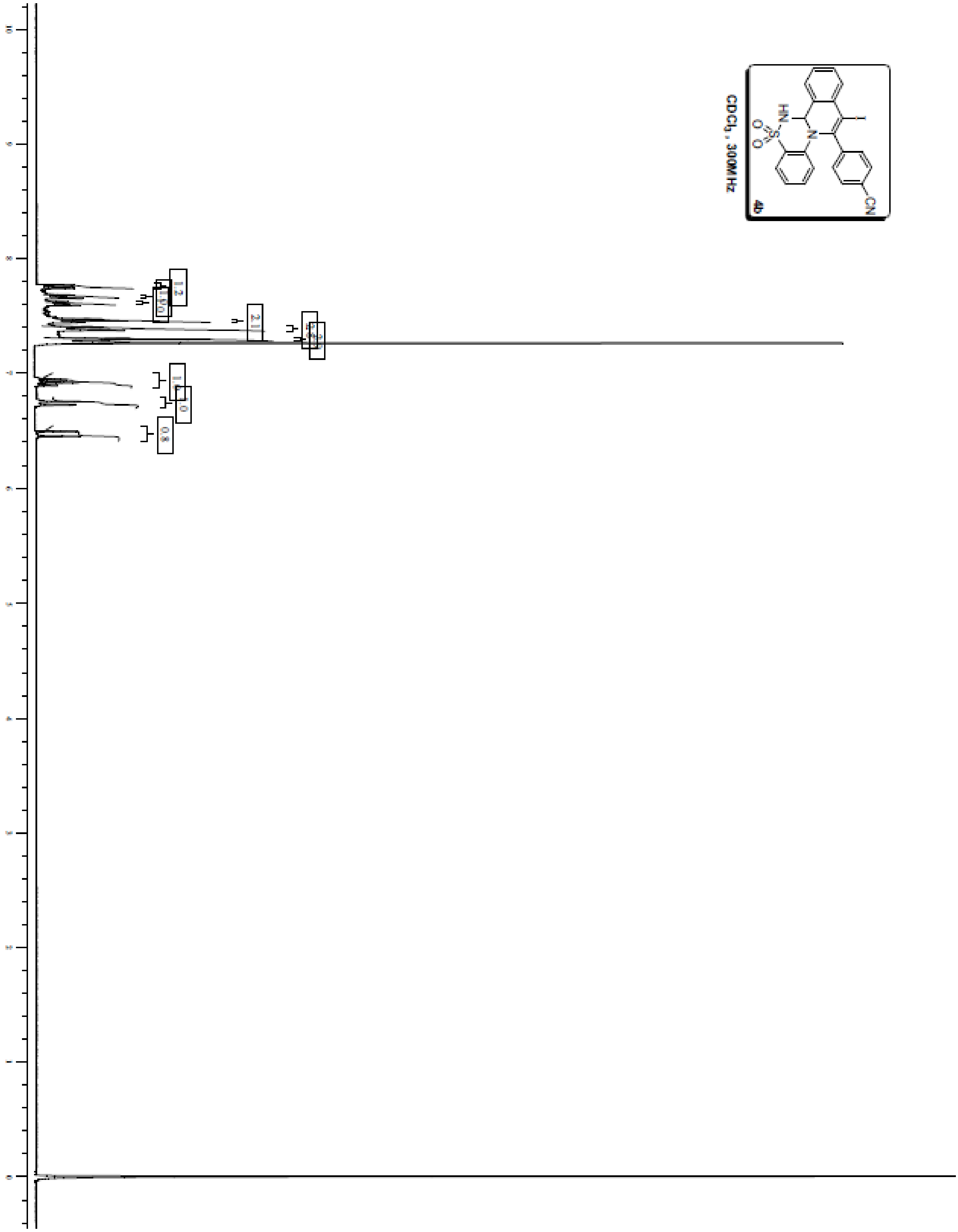

CDCl3, 125MHz
3c
146.881
145.842
139.319
138.005
136.568
135.602
134.627
133.688
131.831
131.081
127.707
127.216
125.944
123.744
121.440
119.455
116.927
111.620
109.343
69.439
60.363
28.933
25.736
22.769
21.749

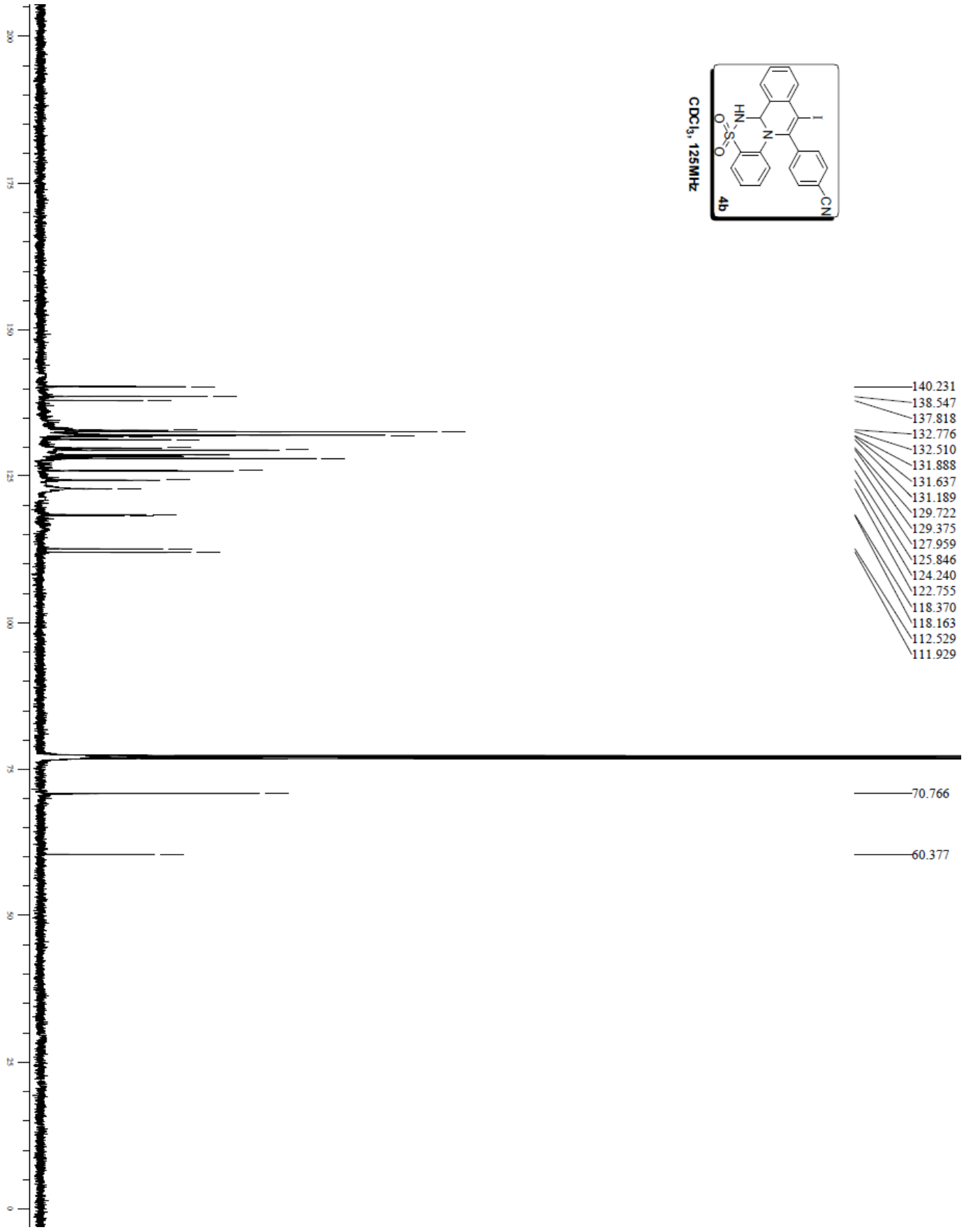

DMSO d_6, 300MHz
4a
0.8
2.1
11.9
2.8
3.3
1.9
0.8
0.8

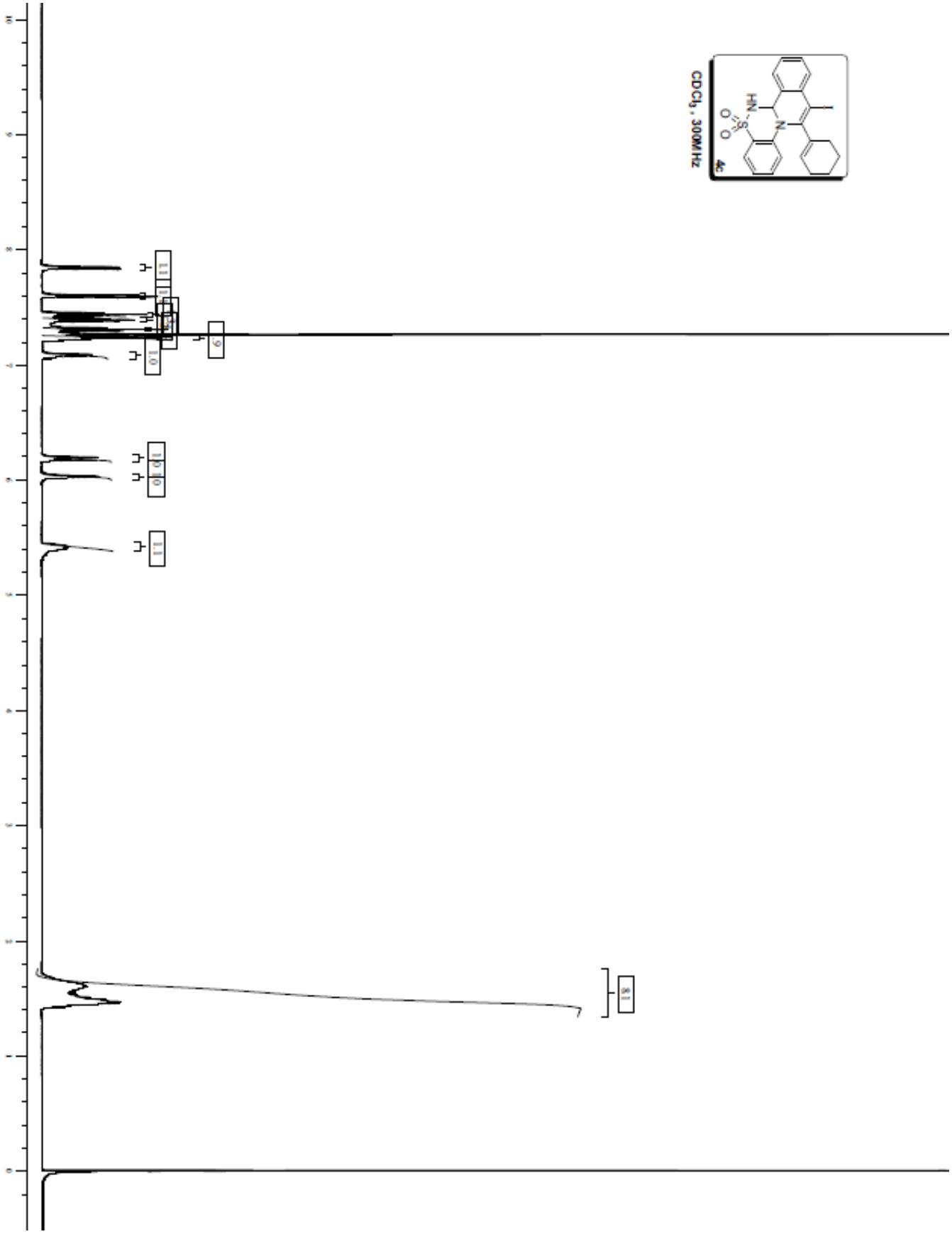


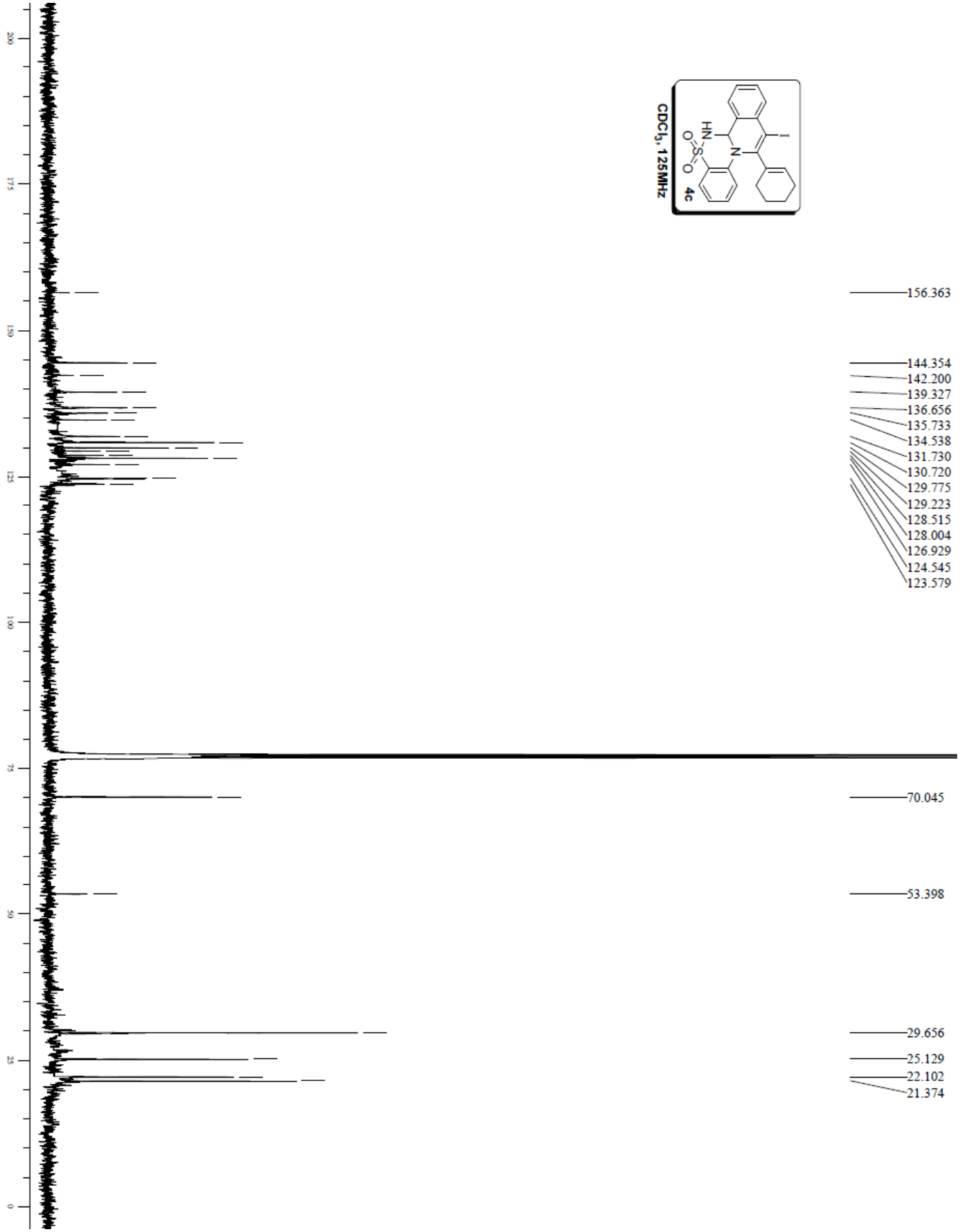

13C DEPT(90°) NMR
125 MHz, CDCl3
4a
HN
N
Ph
130.913
129.687
129.268
129.000
128.662
128.603
128.560
128.100
127.687
127.592
125.288
124.033
70.494

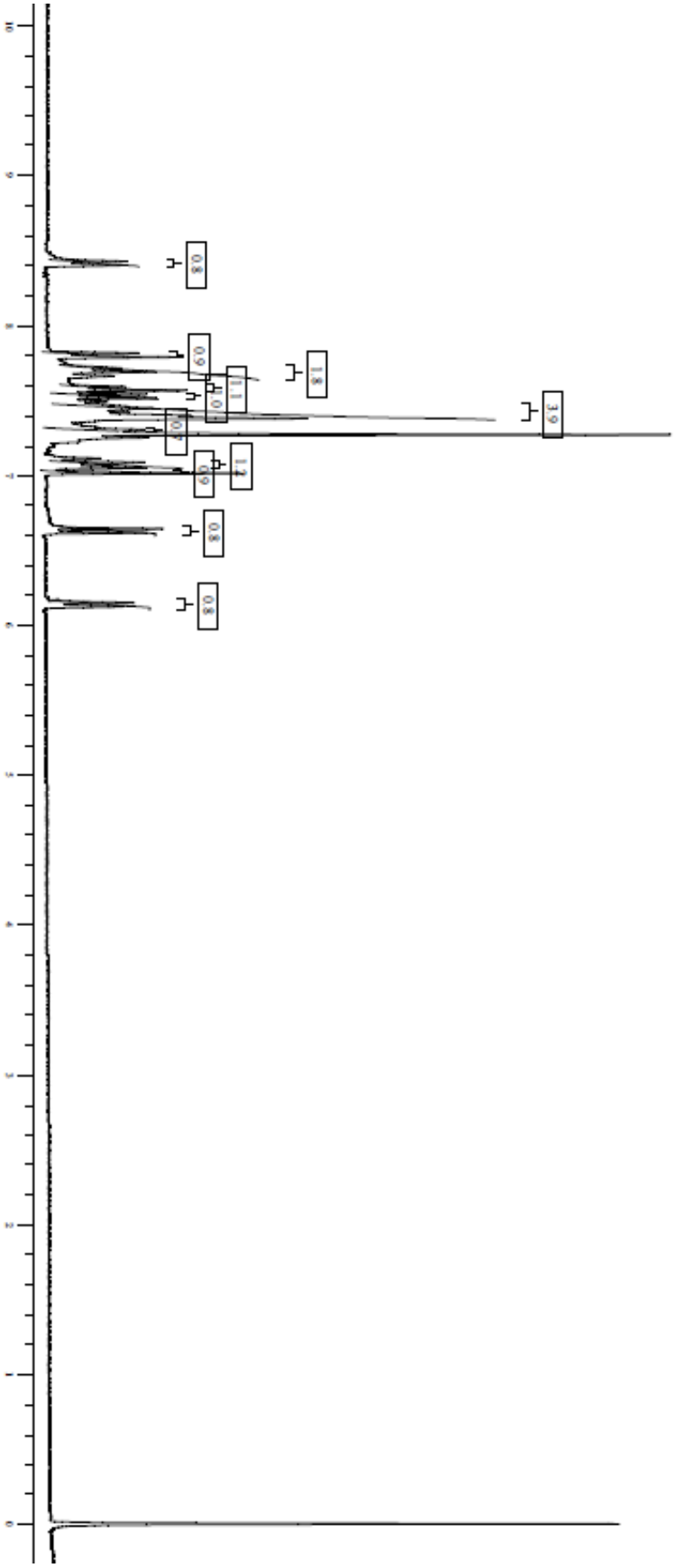

13C DEPT(135°) NMR
125 MHz, CDCl3
HN
S
O
O
N
Ph
4a
131.144
129.904
129.485
129.211
128.863
128.814
128.771
128.305
127.895
127.801
125.502
124.266
70.697

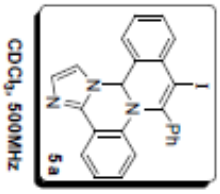

CDCl$_3$, 300MHz
4b

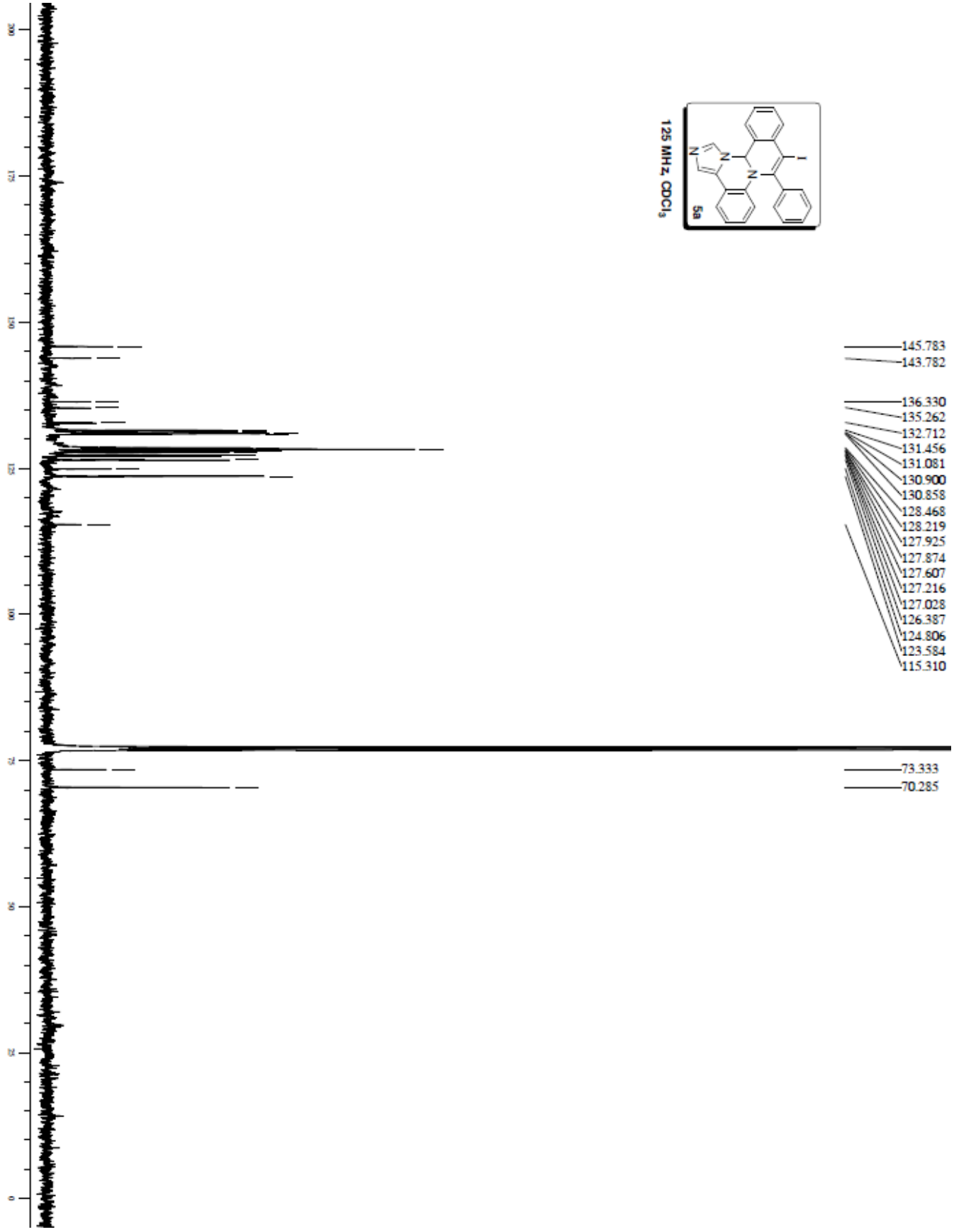


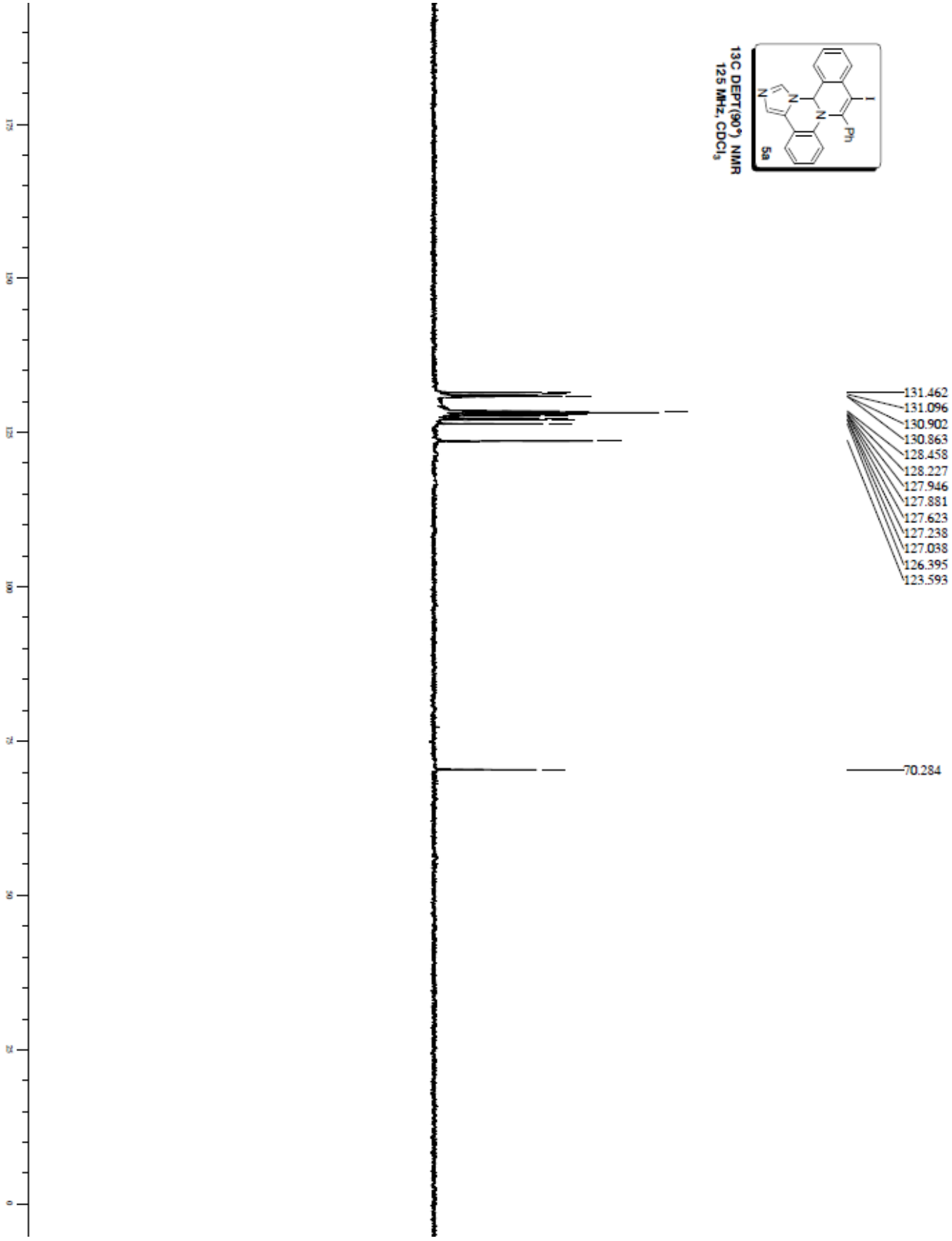

CDCl3 , 300MHz
4c

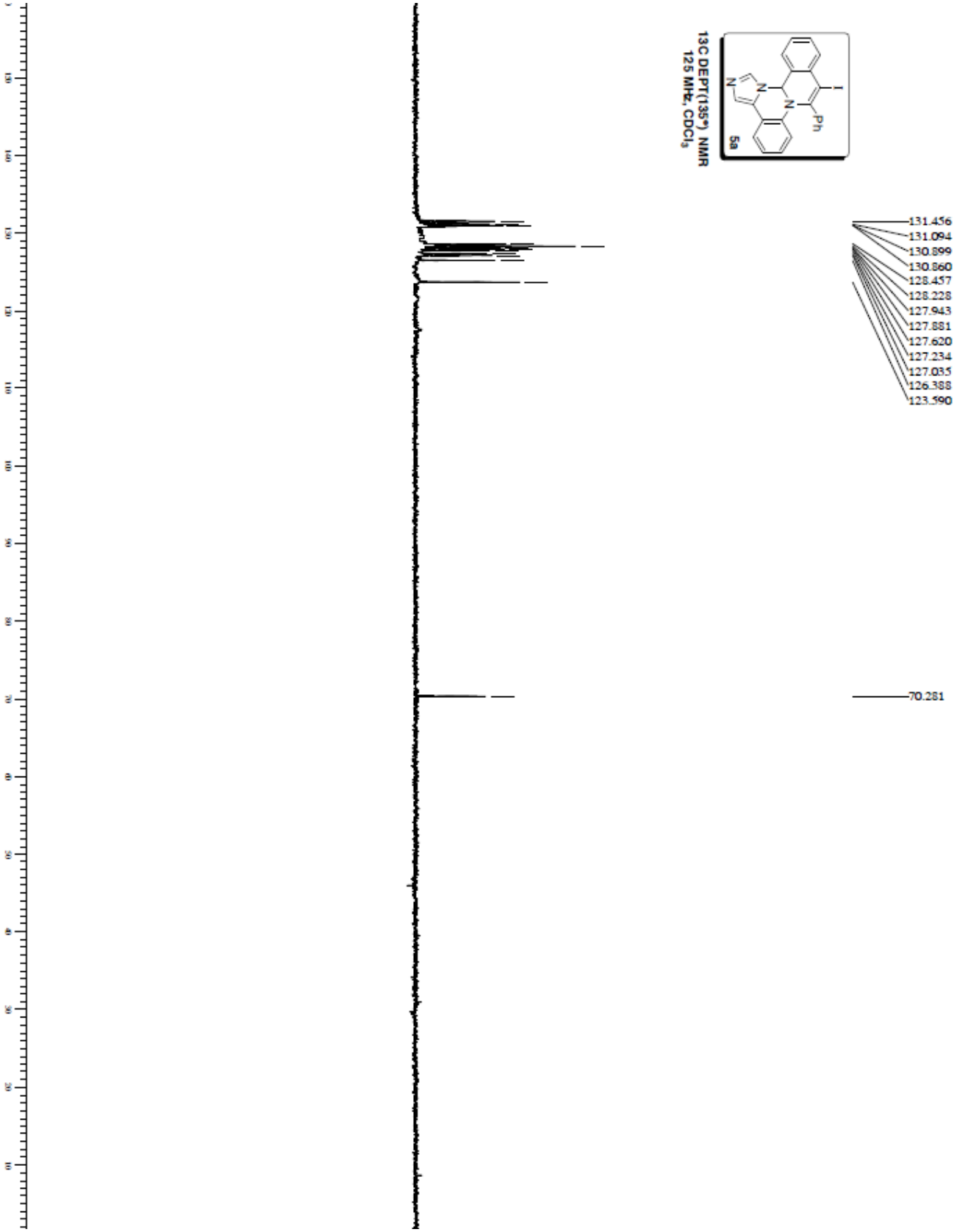


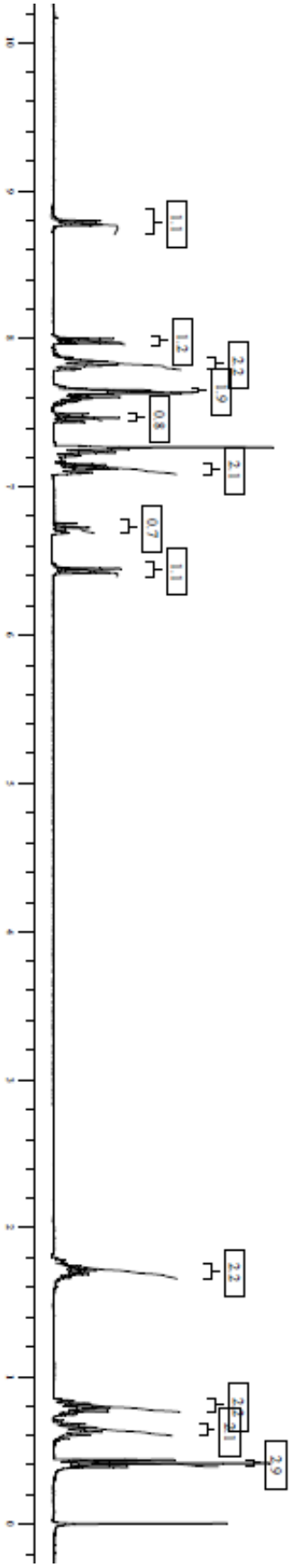

0.98
1.00
1.11
1.18
3.00
1.04
1.00
1.27
1.00
0.98

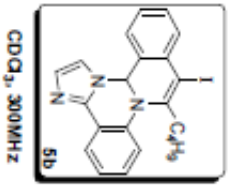

CDCl3, 500MHz
5a
I
Ph
N
N
N

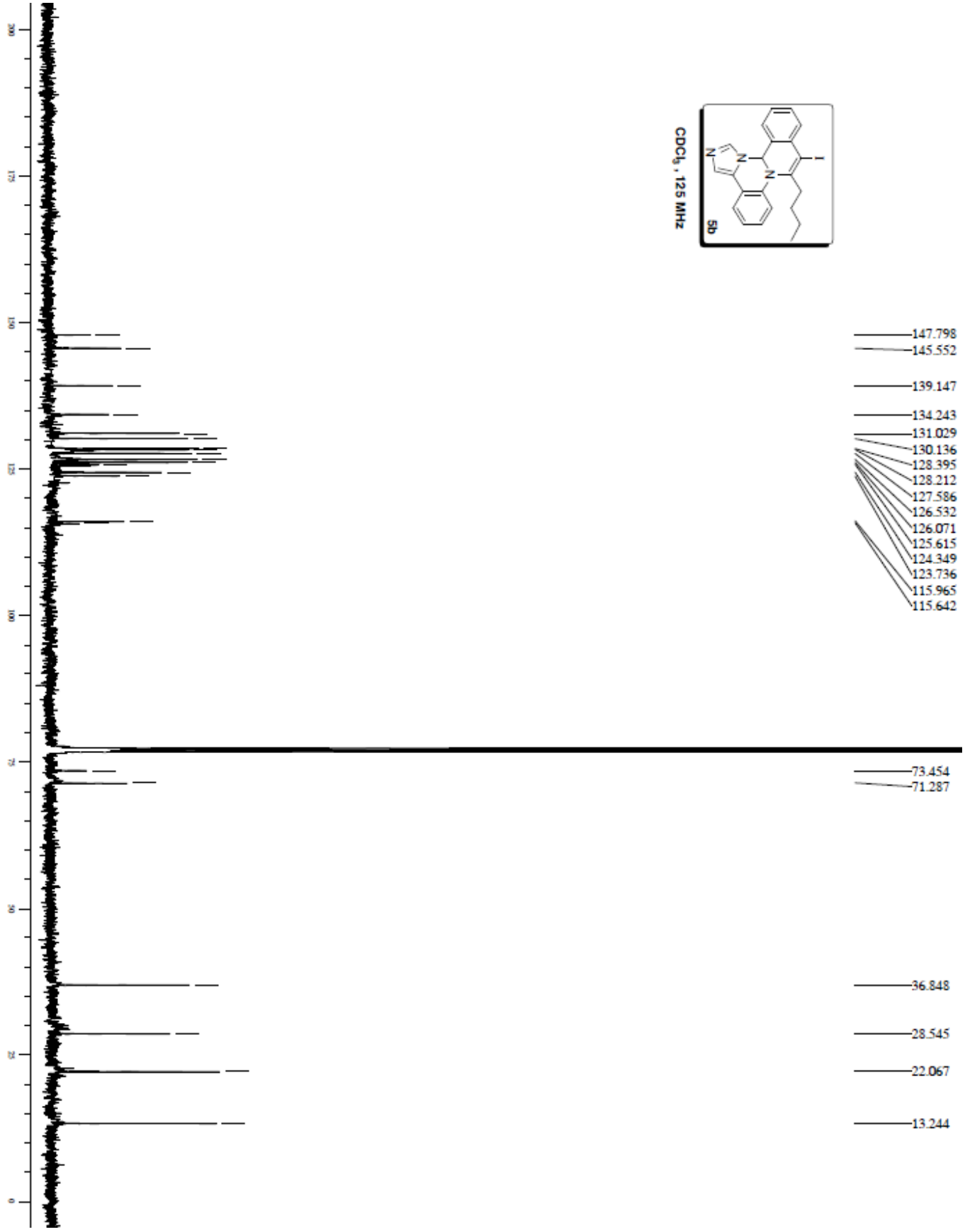

125 MHz, CDCl3
5a
145.783
143.782
136.330
135.262
132.712
131.456
131.081
130.900
130.858
128.468
128.219
127.925
127.874
127.607
127.216
127.028
126.387
124.806
123.584
115.310
73.333
70.285

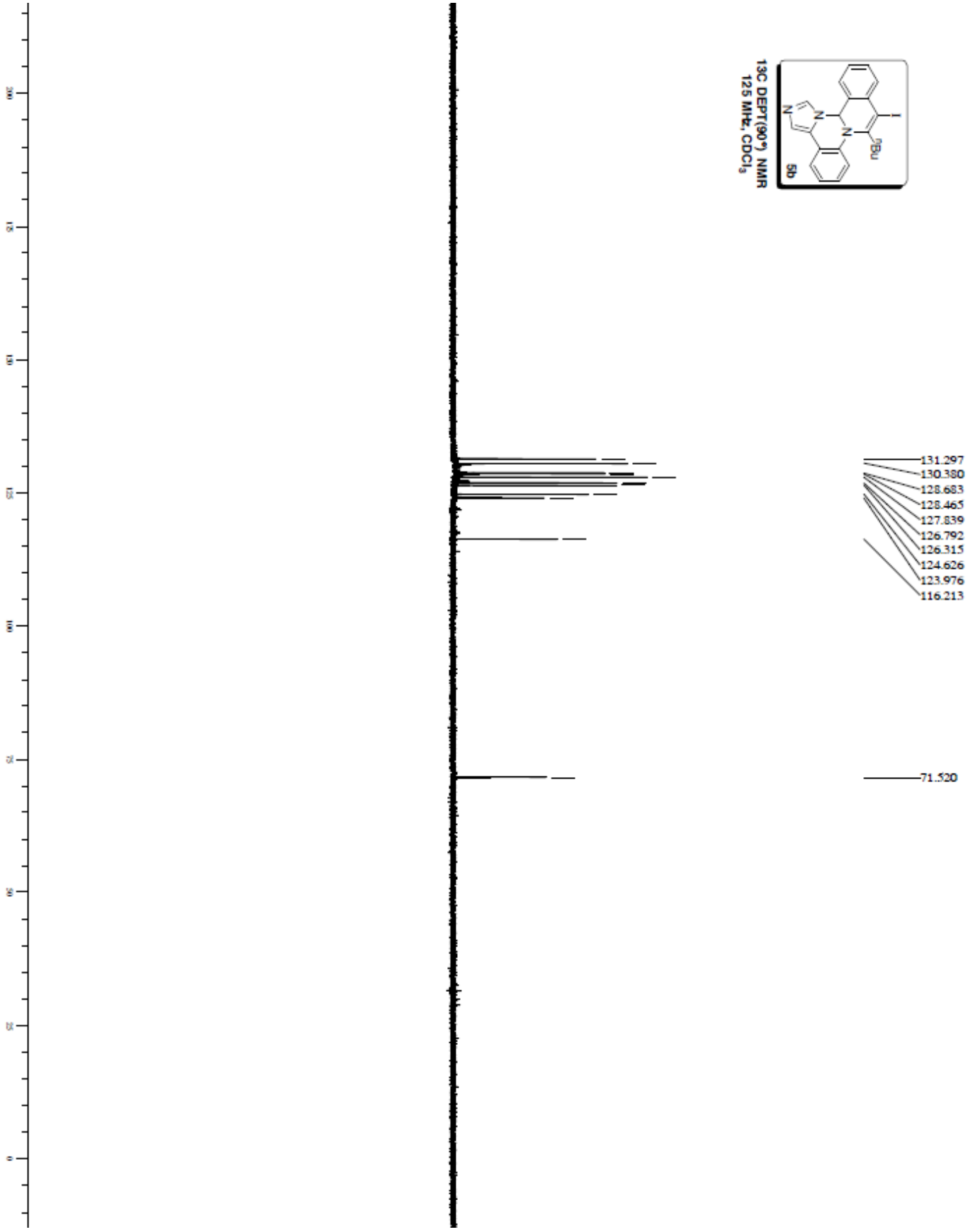

13C DEPT(90°) NMR
125 MHz, CDCl3
5a
I
Ph
N
N
N
131.462
131.096
130.902
130.863
128.458
128.227
127.946
127.881
127.623
127.238
127.038
126.395
123.593
70.284
175
150
125
100
75
50
25
0

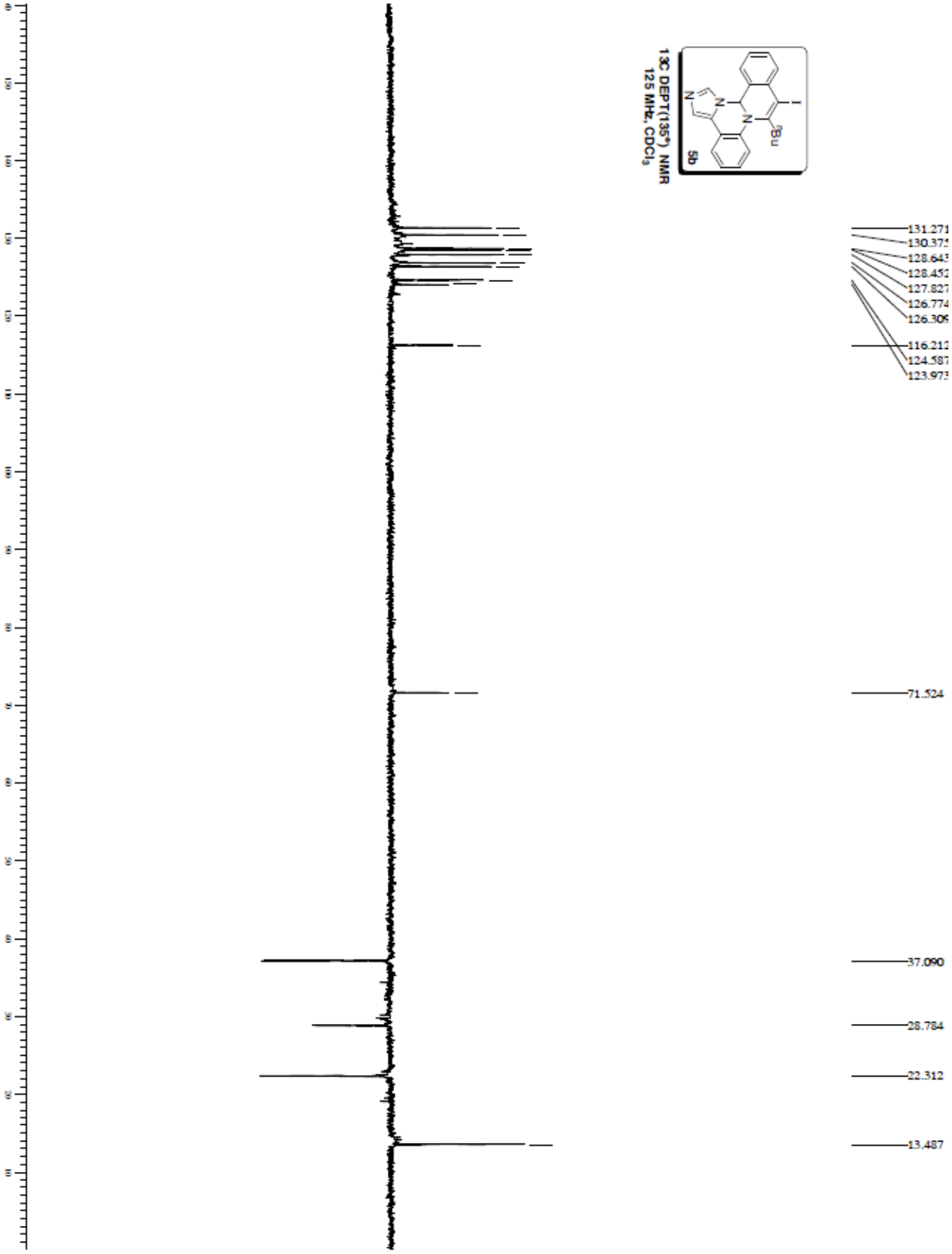

13C DEPT(135°) NMR
125 MHz, CDCl3
5a
131.456
131.094
130.899
130.860
128.457
128.228
127.943
127.881
127.620
127.234
127.035
126.388
123.590
70.281

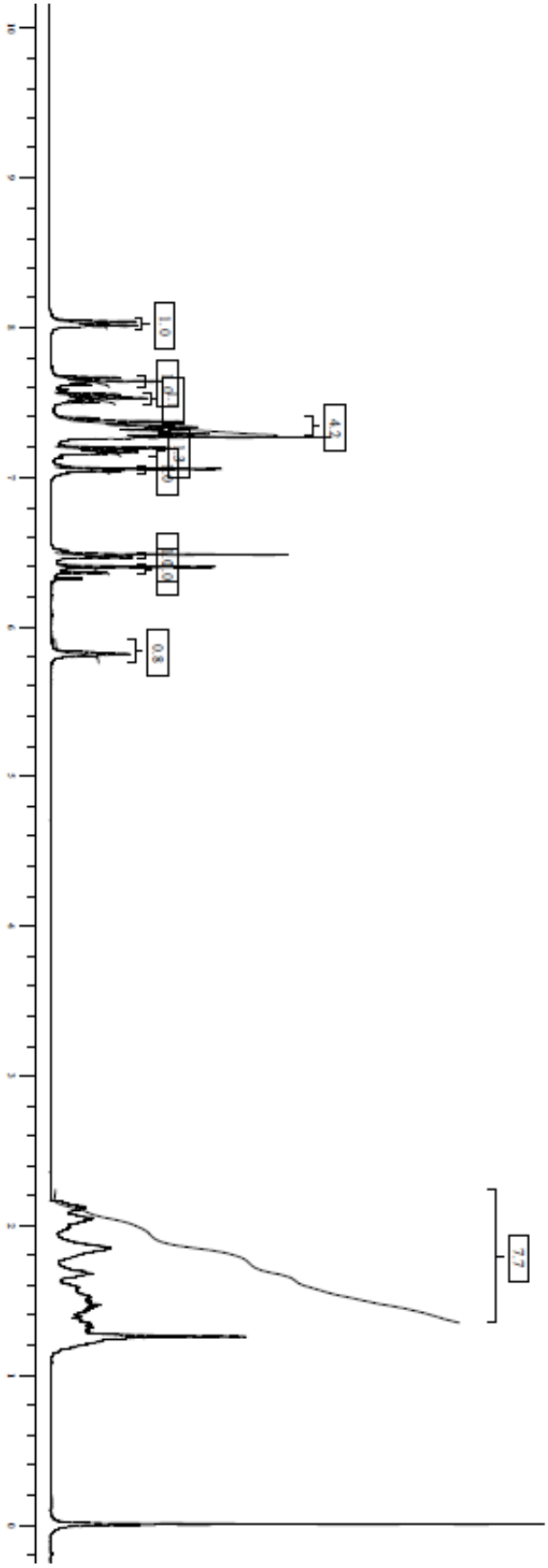

1.11
1.12
2.23
1.9
0.8
2.11
0.7
1.11
2.22
2.29
1.11
2.9

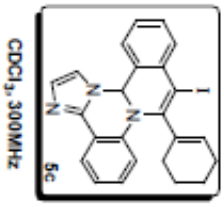

CDCl3, 300MHz
5b

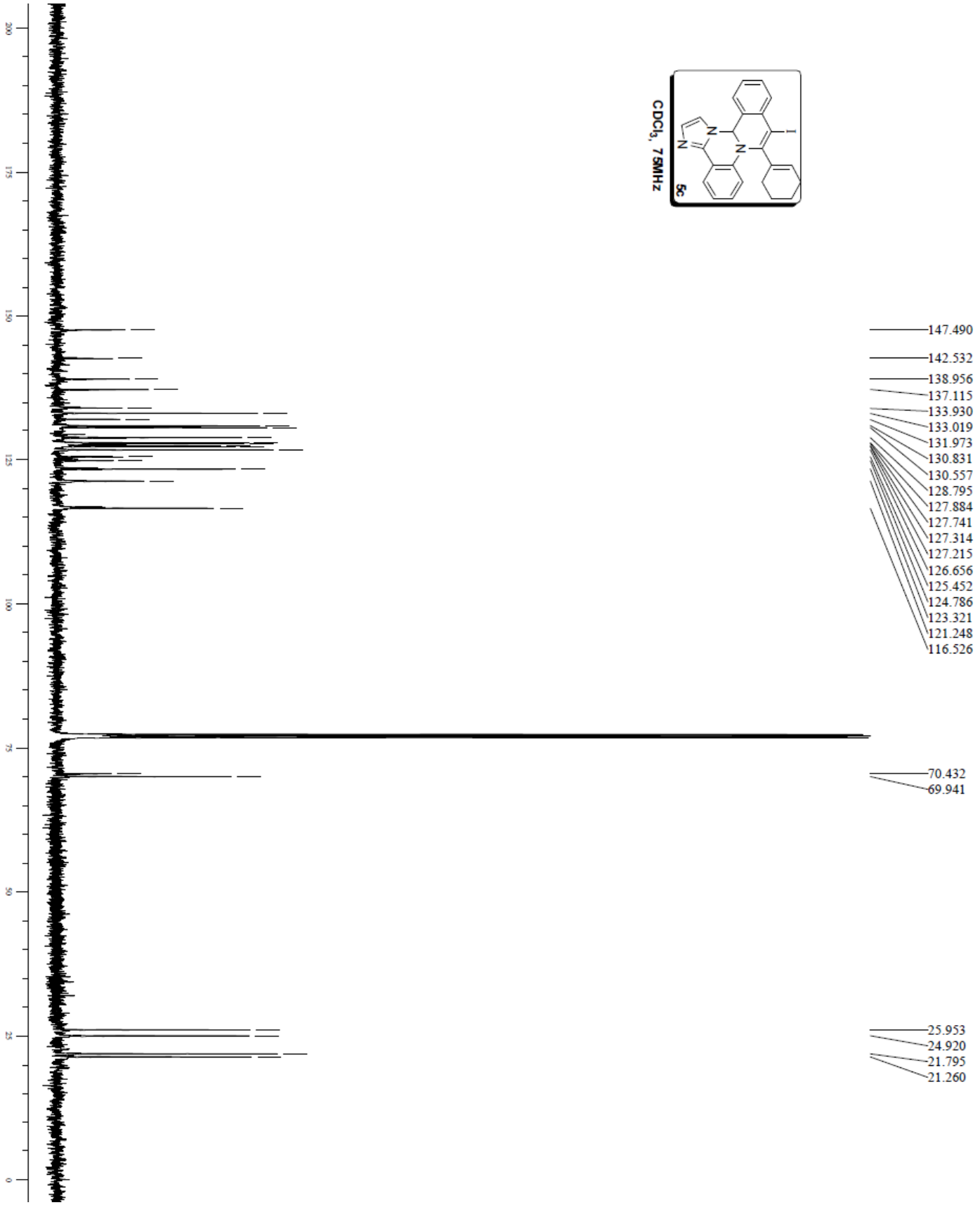

CDCl3 , 125 MHz
5b
147.798
145.552
139.147
134.243
131.029
130.136
128.395
128.212
127.586
126.532
126.071
125.615
124.349
123.736
115.965
115.642
73.454
71.287
36.848
28.545
22.067
13.244

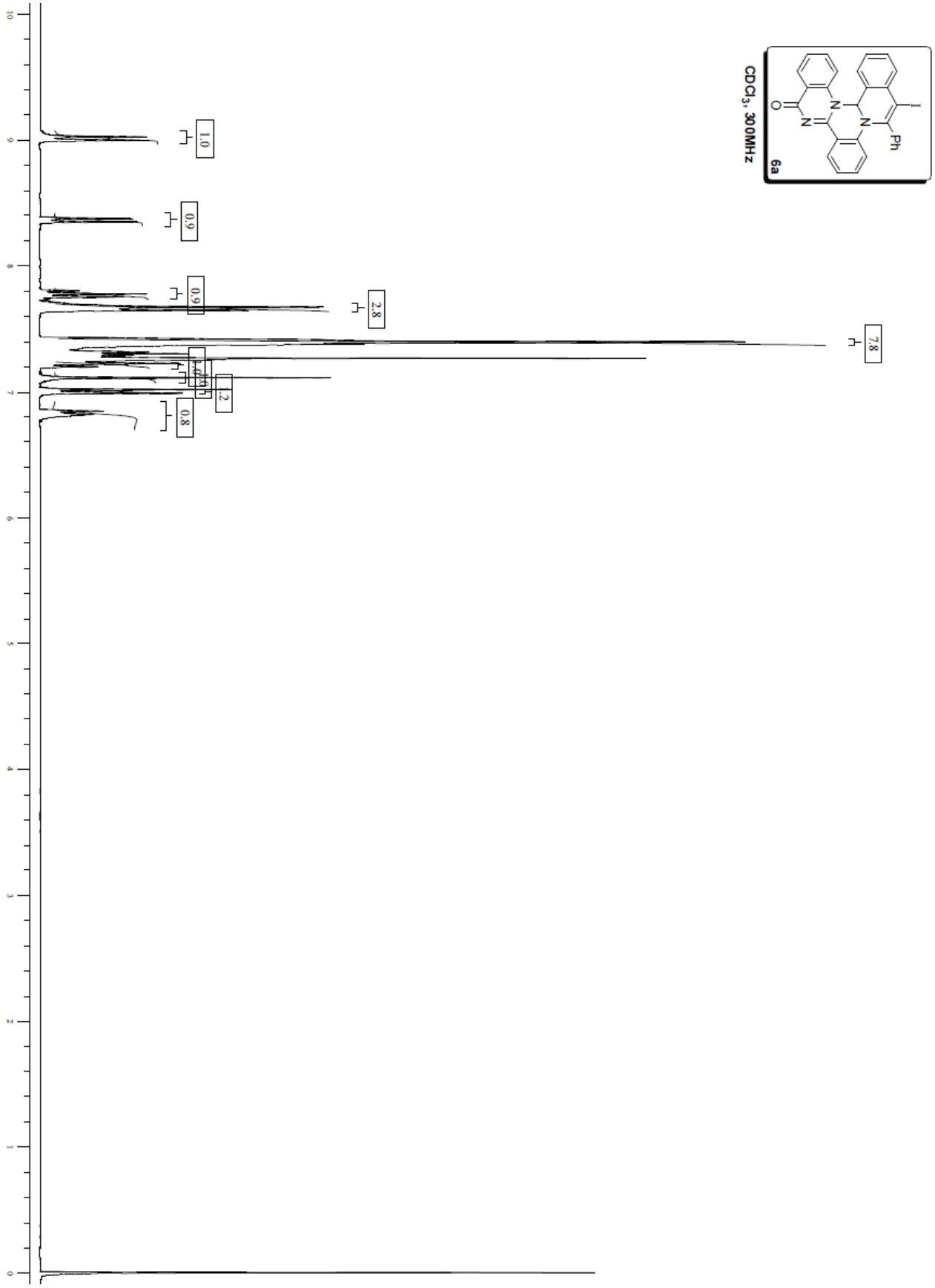

13C DEPT(90°) NMR
125 MHz, CDCl3
5b
131.297
130.380
128.683
128.465
127.839
126.792
126.315
124.626
123.976
116.213
71.520

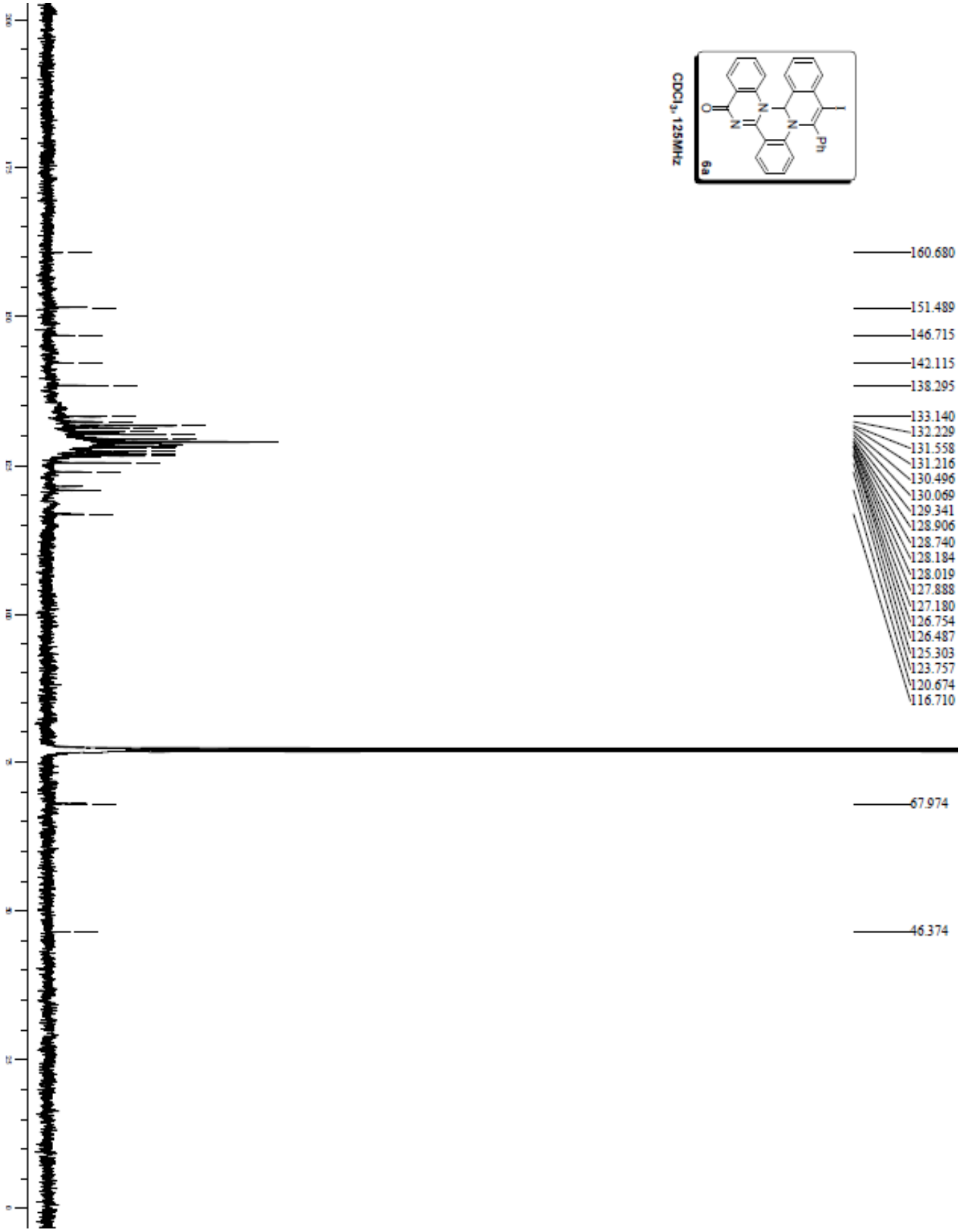

13C DEPT(135°) NMR
125 MHz, CDCl3
5b
131.271
130.375
128.643
128.452
127.827
126.774
126.309
116.212
124.587
123.973
71.524
37.090
28.784
22.312
13.487

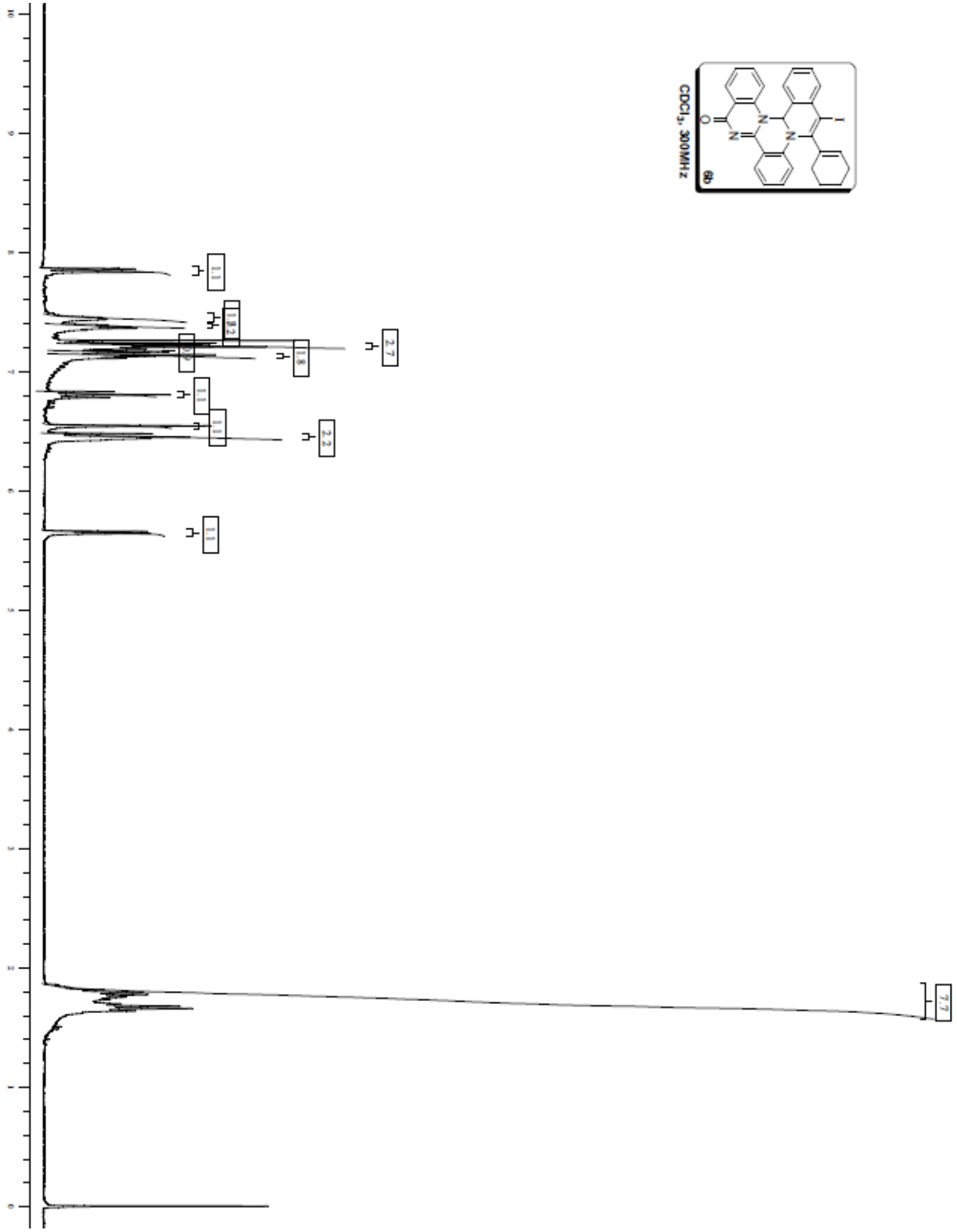

1.0
4.2
0.8
7.7

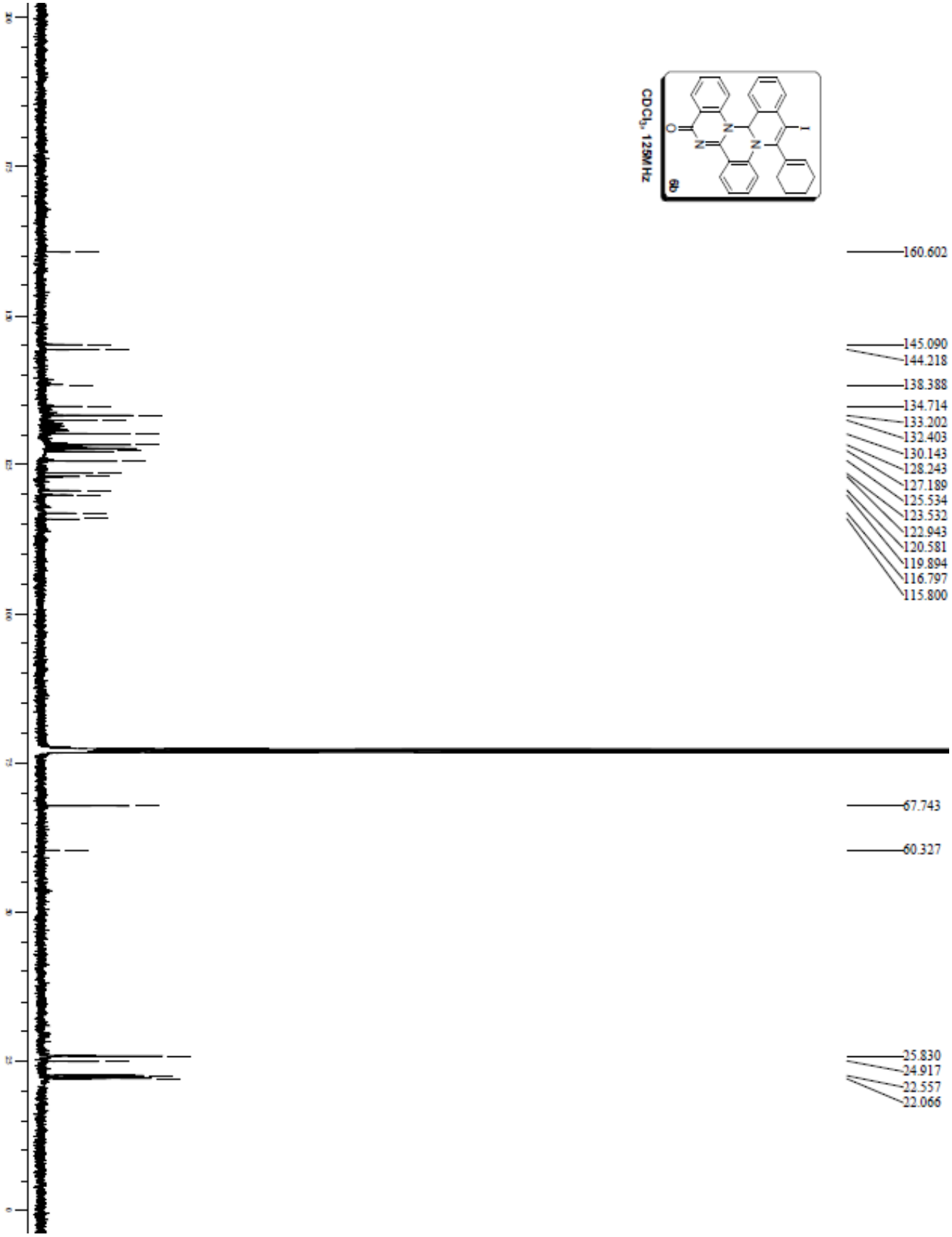

CDCl3, 300MHz
5c

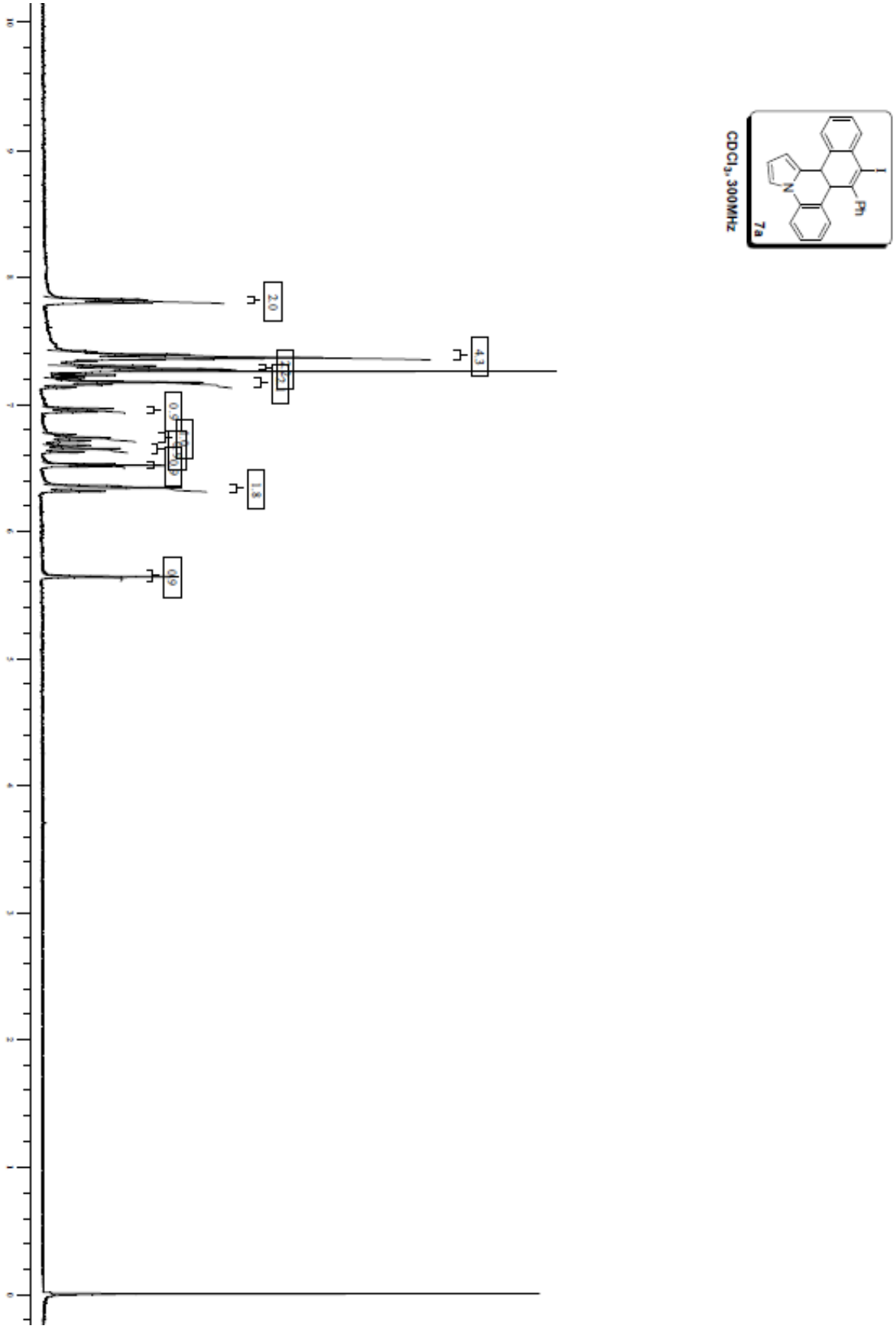


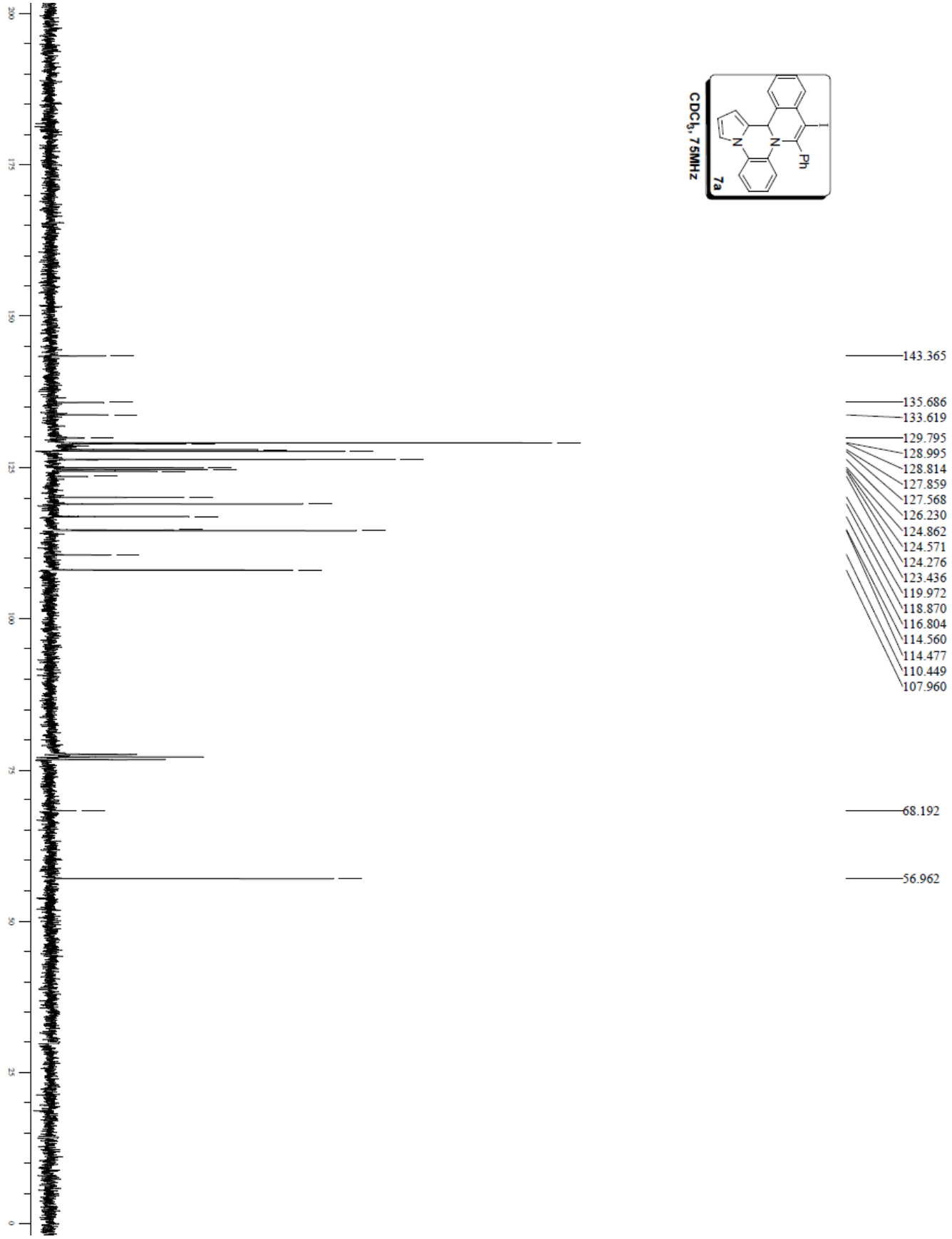

CDCl3, 300MHz
6a
1.0
0.9
0.9
2.8
7.8
2
0.8

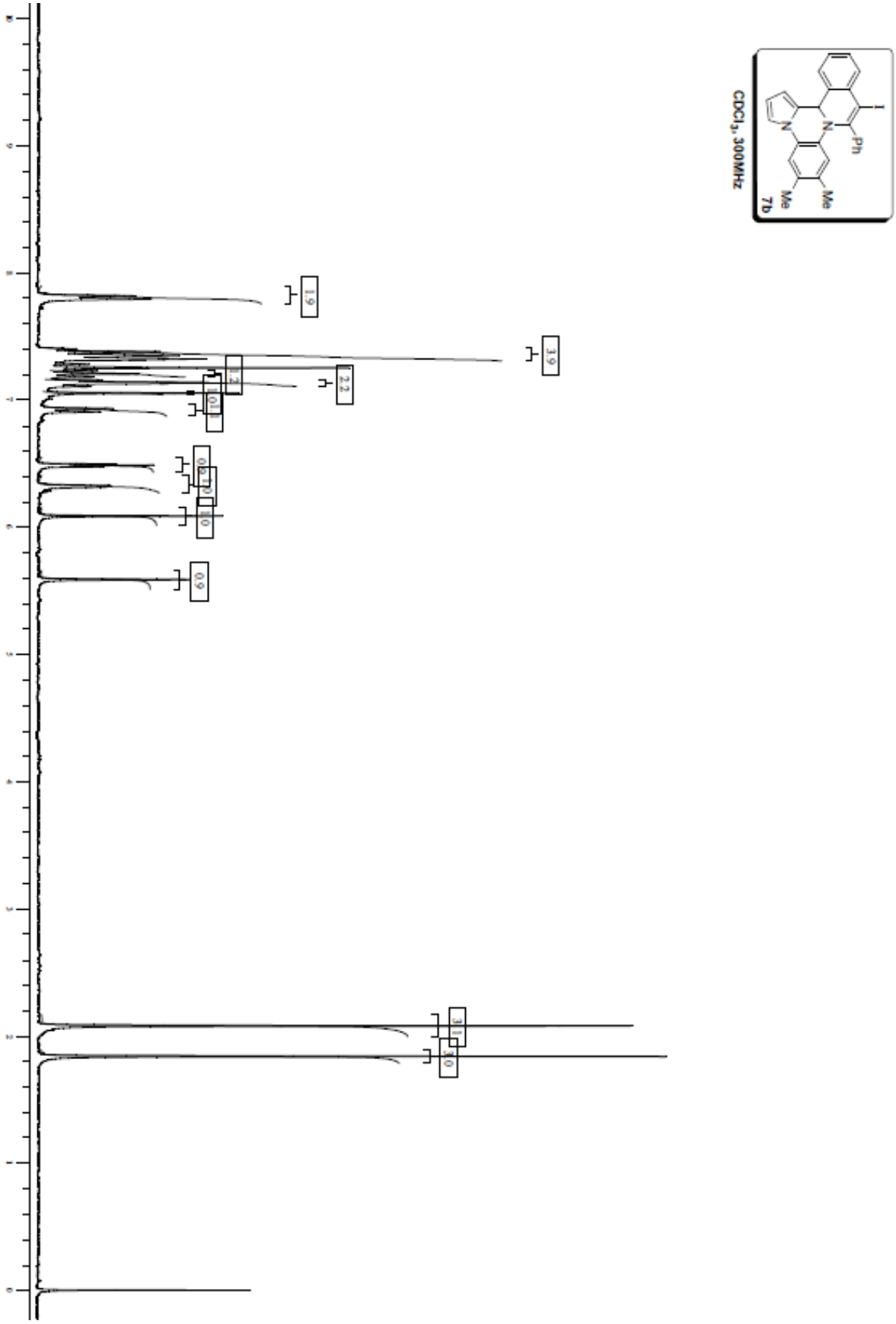


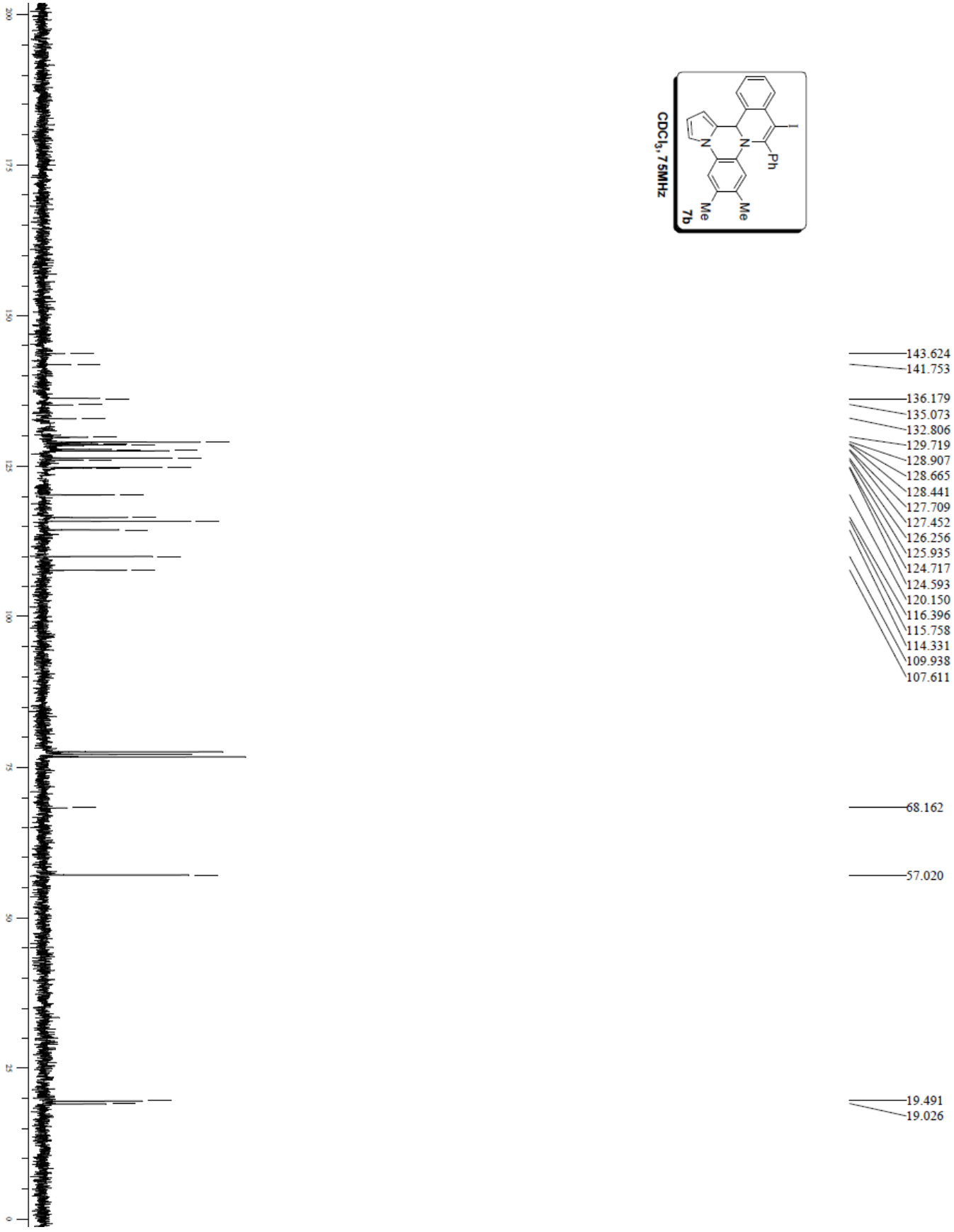

CDCl3, 300MHz
4b
1.11
1.32
1.16
2.77
1.11
1.11
2.22
1.11
7.77

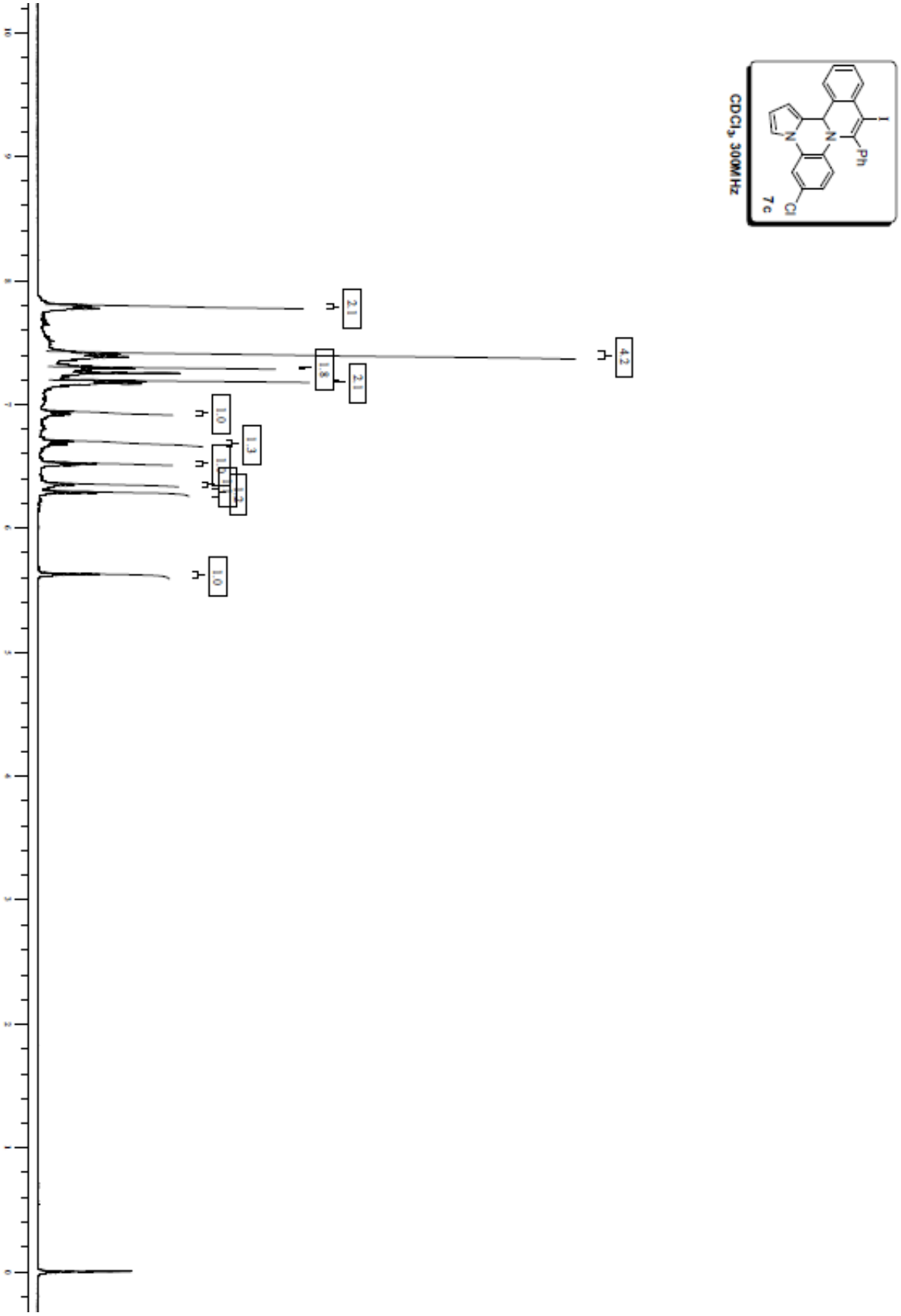


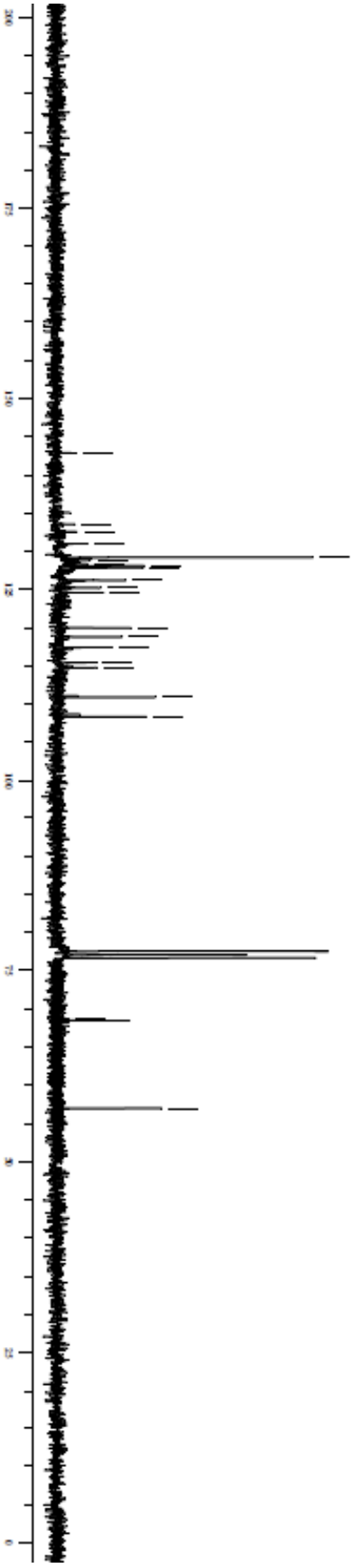

CDCl3, 300MHz
7a
I
Ph
N
2.0
4.3
1.8
1.0

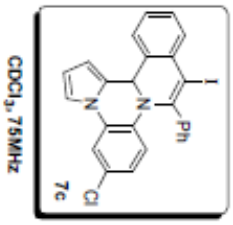

CDCl3, 75MHz
7a
Ph
I
N
N
143.365
135.686
133.619
129.795
128.995
128.814
127.859
127.568
126.230
124.862
124.571
124.276
123.436
119.972
118.870
116.804
114.560
114.477
110.449
107.960
68.192
56.962


CDCl3, 300MHz
7b
Me
Me
Ph
I
N
N
1.9
3.9
2.3
2.2
1.1
0.9
1.0
3.1
3.0

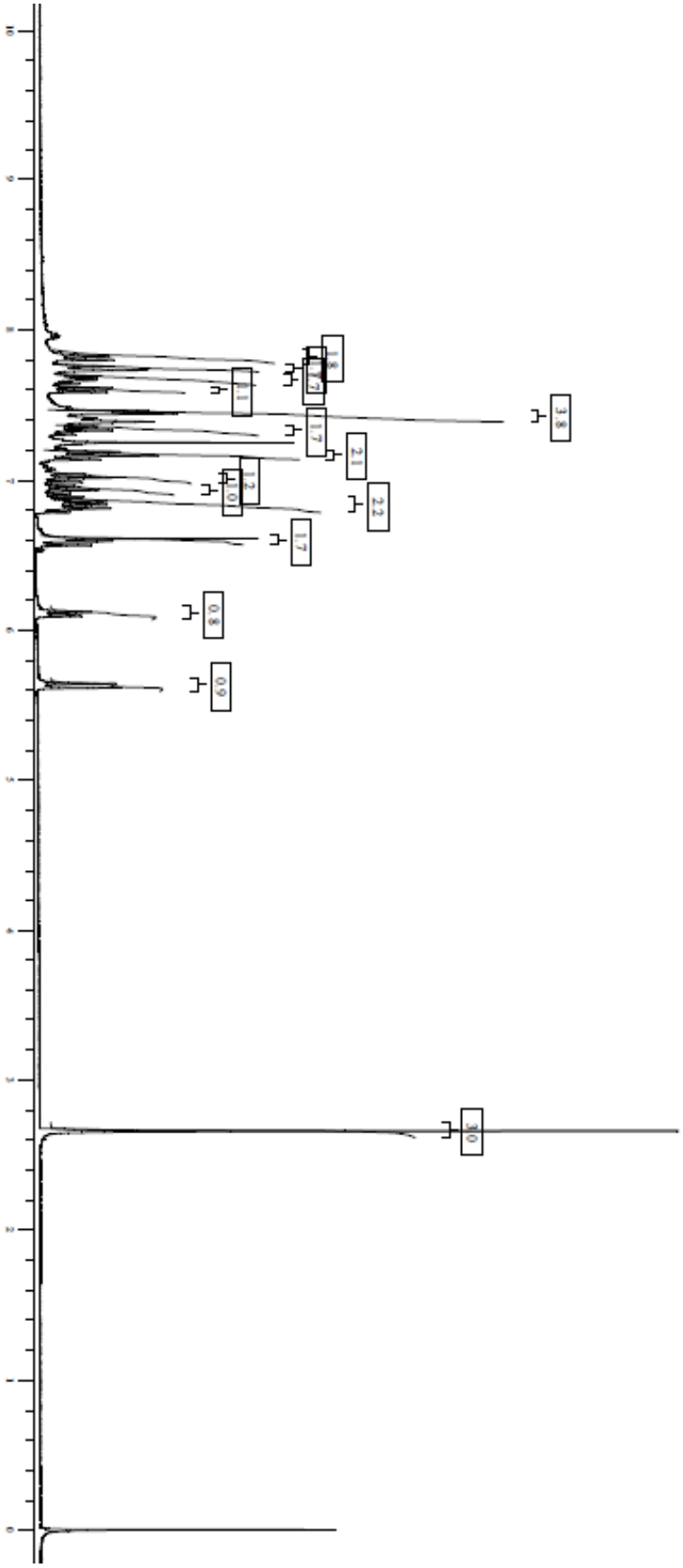

CDCl3, 75MHz
7b
Ph
Me
Me
143.624
141.753
136.179
135.073
132.806
129.719
128.907
128.665
128.441
127.709
127.452
126.256
125.935
124.717
124.593
120.150
116.396
115.758
114.331
109.938
107.611
68.162
57.020
19.491
19.026

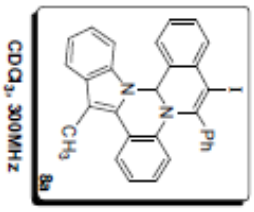

CDCl3, 300MHz
7c
Cl
N
N
Ph
I
2.1
4.2
1.8
2.1
1.0
1.3
1.0

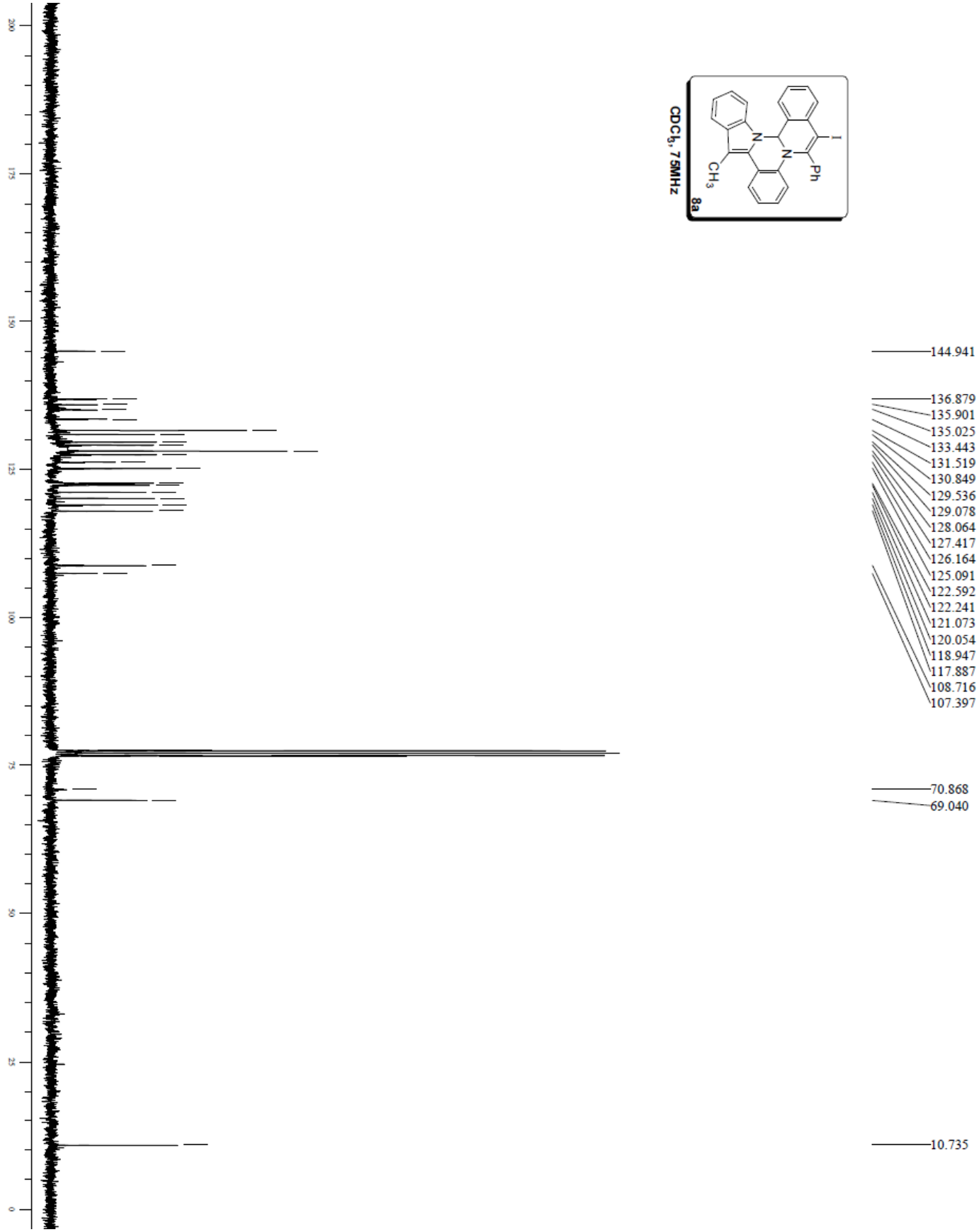


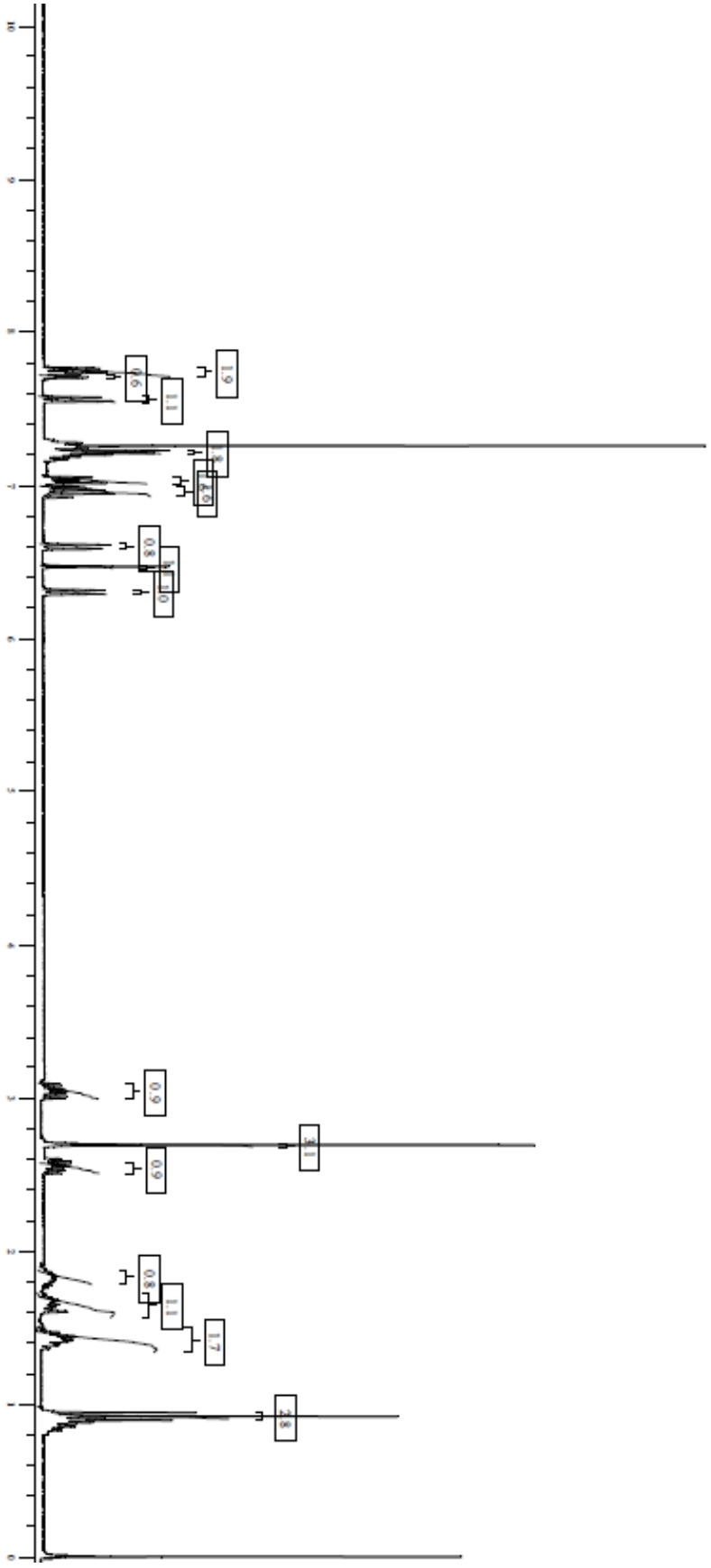


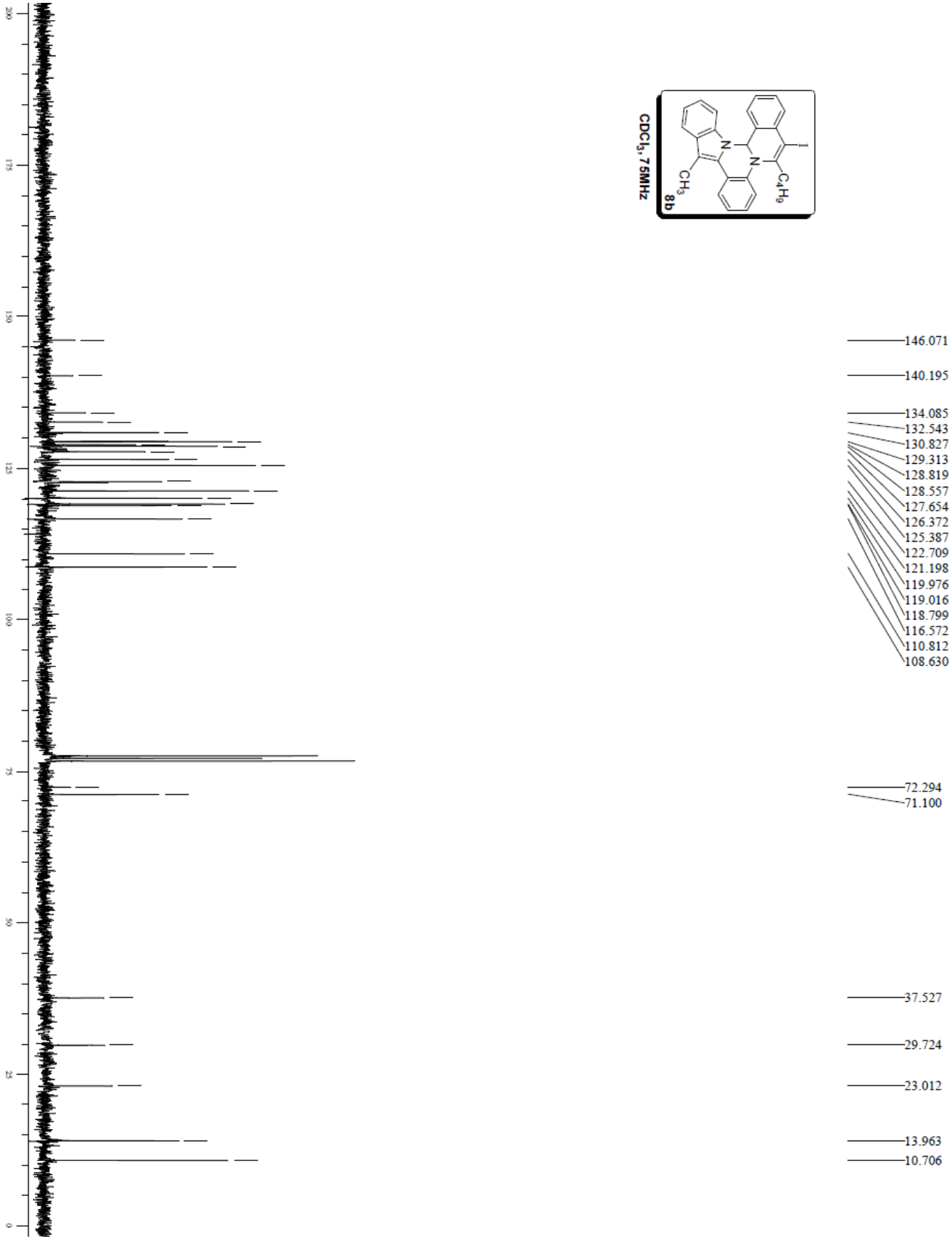
142.812
133.474
132.482
130.913
129.138
128.818
128.293
128.032
127.770
126.110
125.154
124.513
119.888
118.696
117.327
115.367
114.651
110.783
108.221
68.628
56.904


3.16
2.11
2.22
1.17
0.80
0.60
3.00


CDCl3, 300MHz
8a
CH3
N
N
Ph
I




CDCl3, 300MHz
8b
CH3
C4H9
I
N
N


CDCl3, 75MHz
8b
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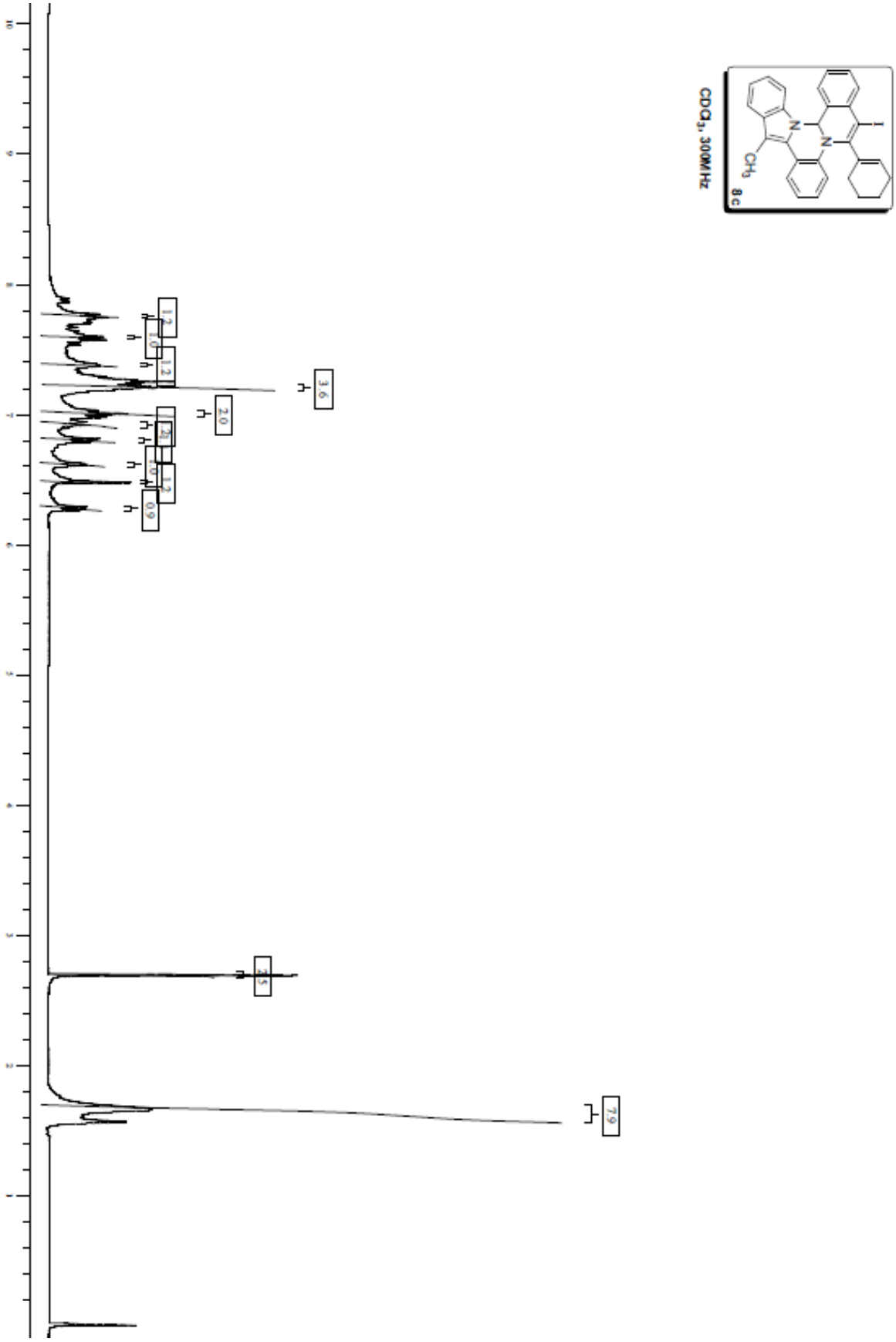
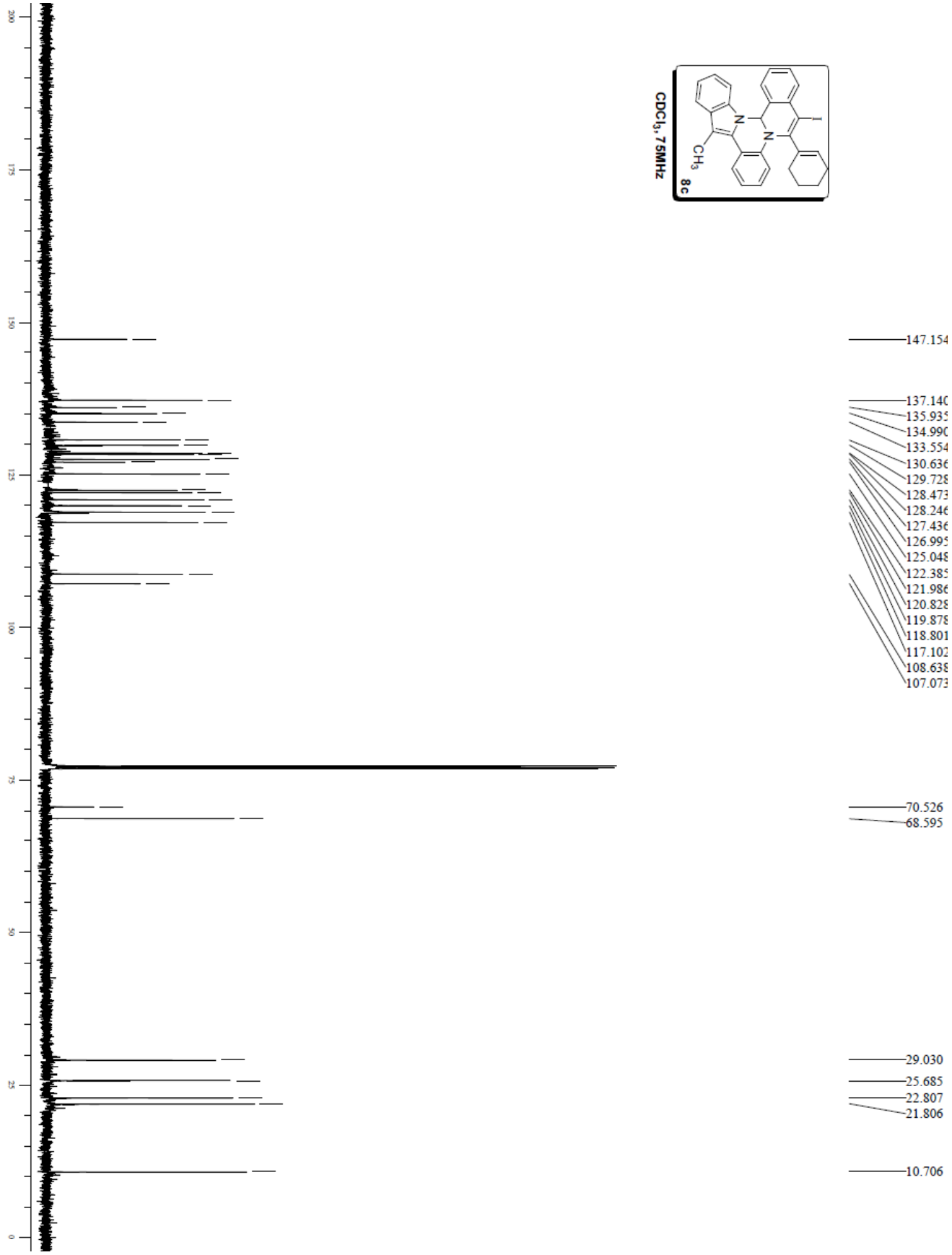
134.085
132.543
130.827
129.313
128.819
128.557
127.654
126.372
125.387
122.709
121.198
119.976
119.016
118.799
116.572
110.812
108.630
72.294
71.100
37.527
29.724
23.012
13.963
10.706


CDCl3, 300MHz
8c
CH3
N
N
I
1.2
1.0
1.2
3.6
2.0
2.3
1.2
1.0
0.9
3.3
7.9


CDCl3, 75MHz
8c
147.154
137.140
135.935
134.990
133.554
130.636
129.728
128.473
128.246
127.436
126.995
125.048
122.385
121.986
120.828
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118.801
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108.638
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68.595
29.030
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22.807
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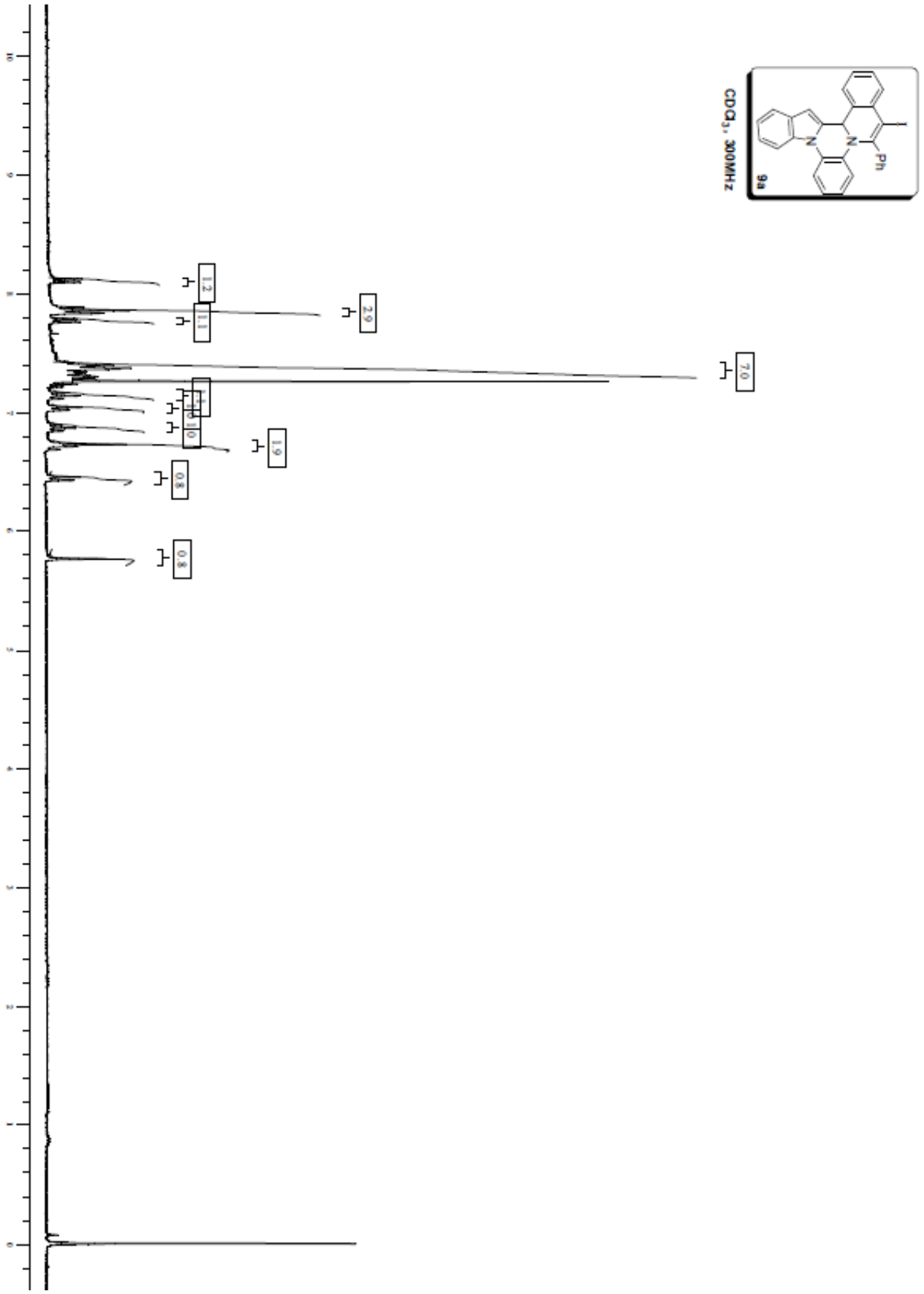
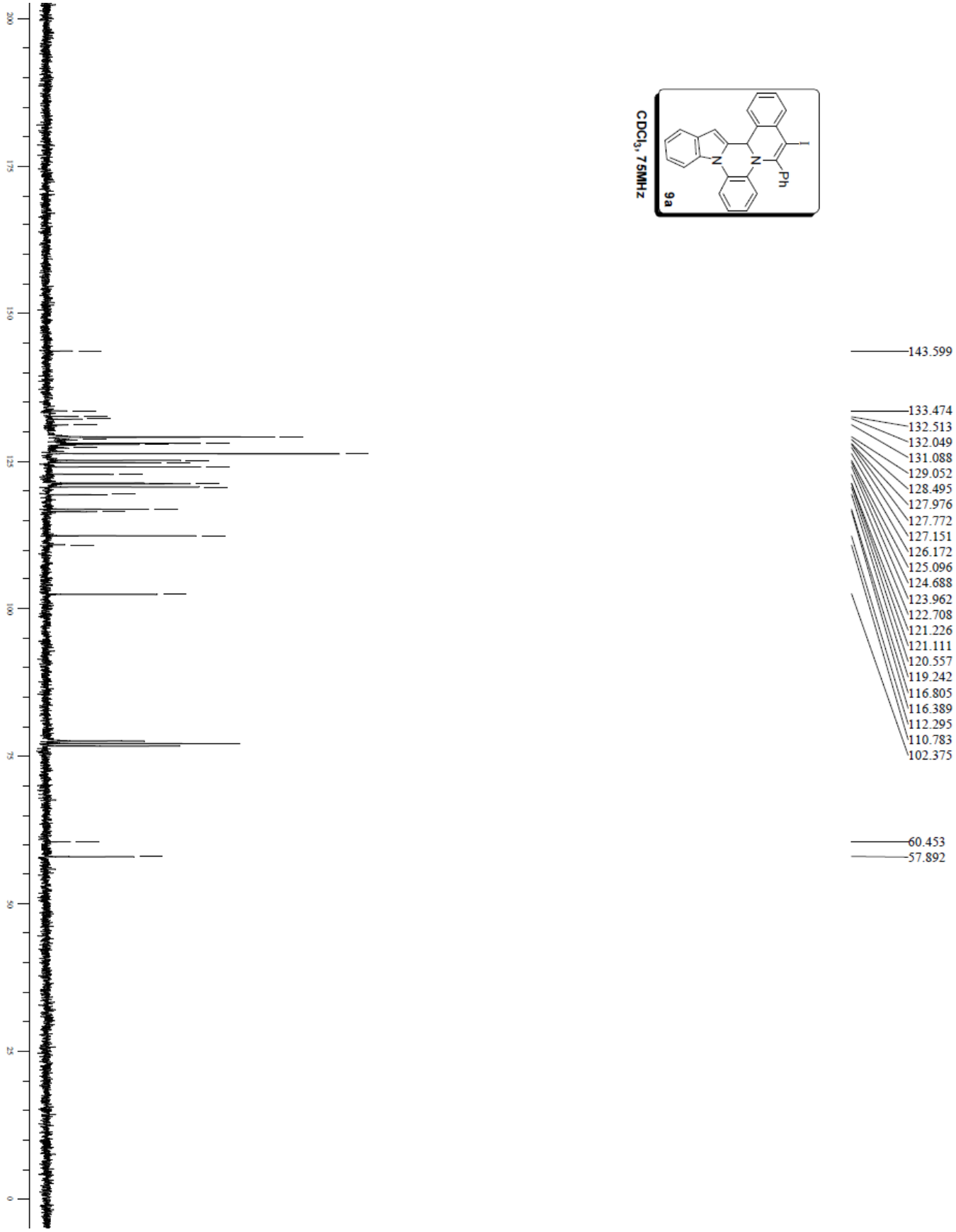
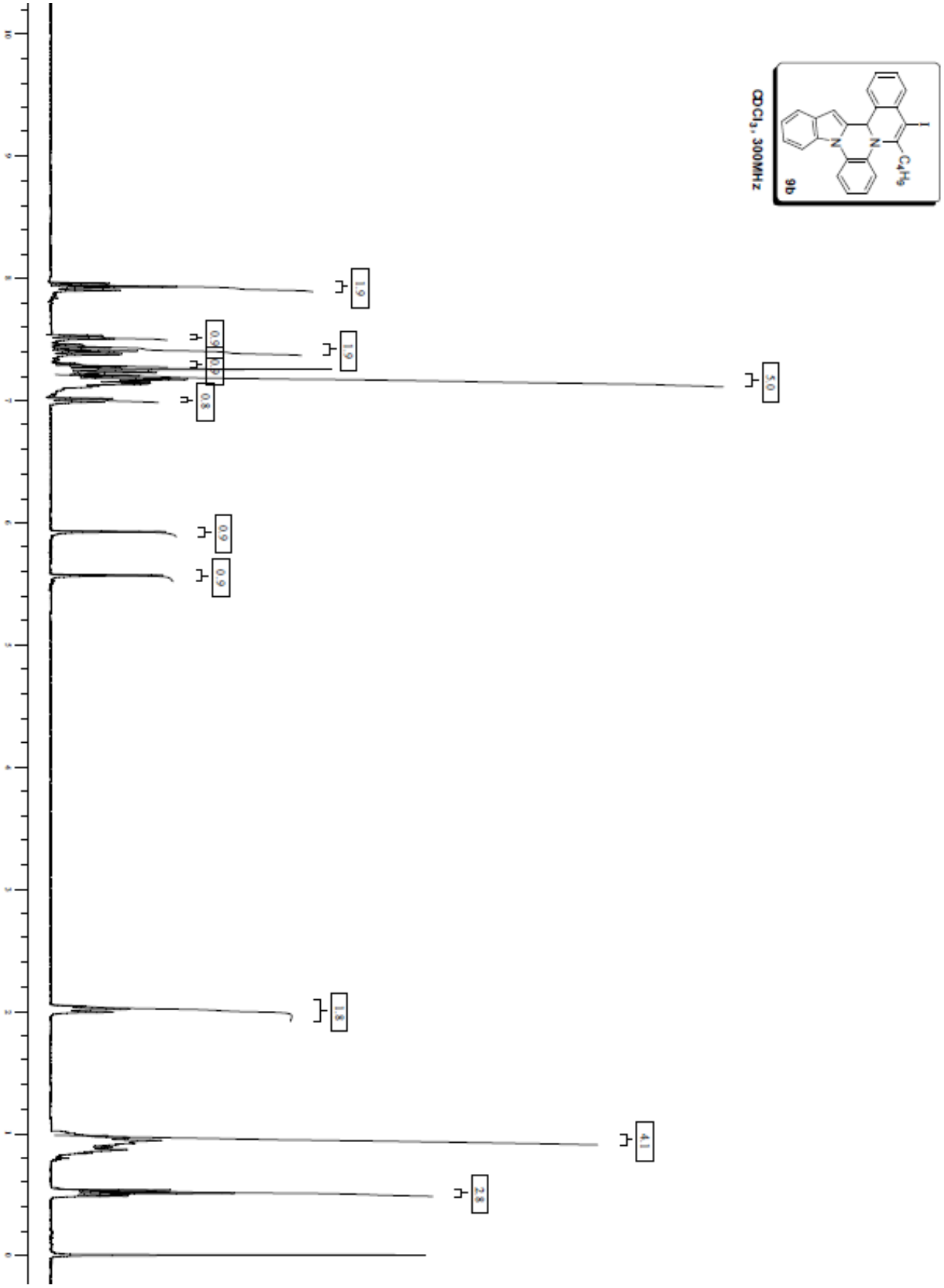
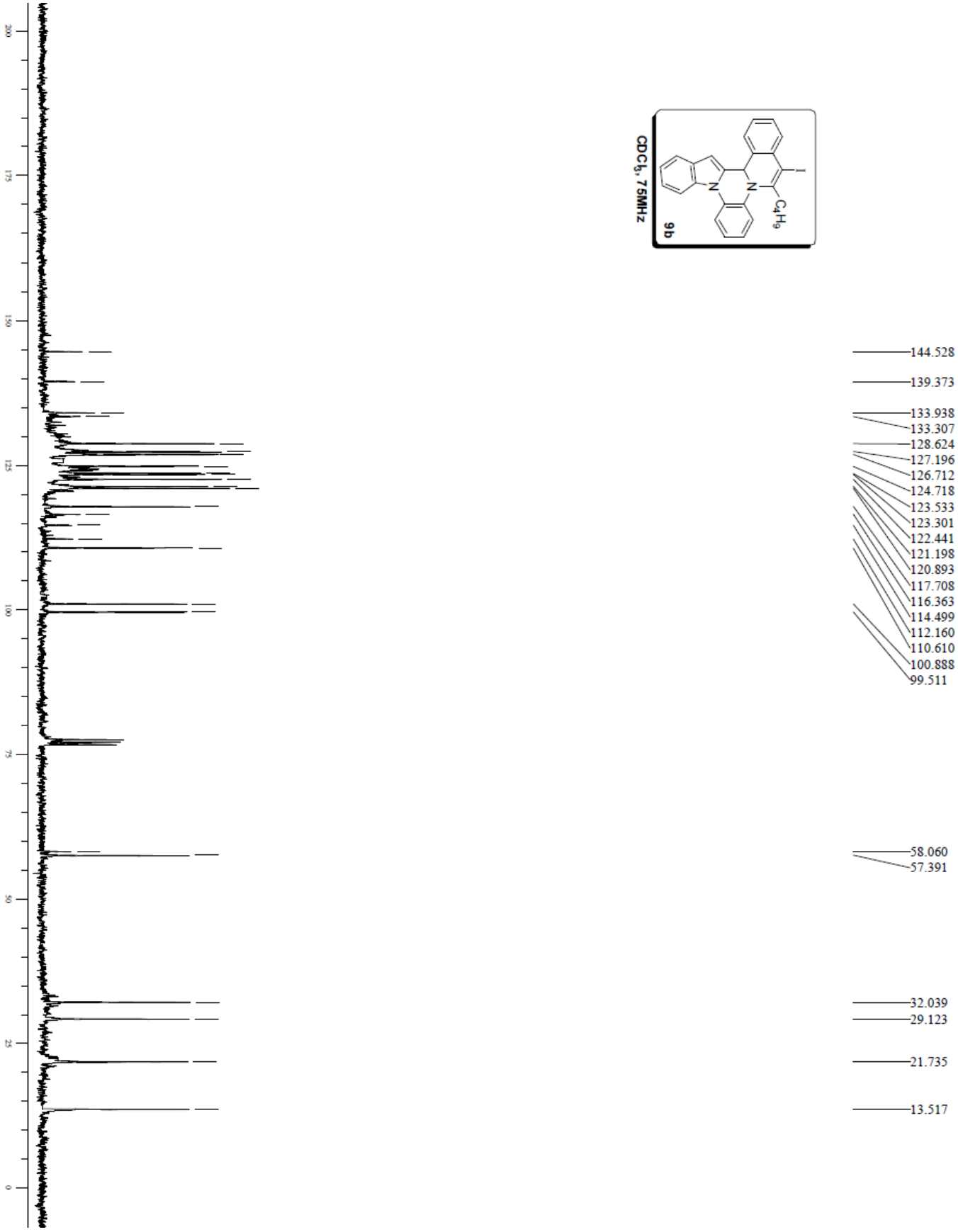
10.706


CDCl3, 300MHz
9a
Ph
1.2
1.1
2.9
7.0
1.0
1.0
1.0
1.9
0.8
0.8


CDCl3, 75MHz
9a
I
Ph
N
N
143.599
133.474
132.513
132.049
131.088
129.052
128.495
127.976
127.772
127.151
126.172
125.096
124.688
123.962
122.708
121.226
121.111
120.557
119.242
116.805
116.389
112.295
110.783
102.375
60.453
57.892
200
175
150
125
100
75
50
25
0


CDCl3, 300MHz
9b
I
N
N
C4H9
1.0
1.9
0.60
0.60
0.80
0.9
0.9
1.18
4.11
2.26


CDCl3, 75MHz
9b
I
N
N
C4H9
144.528
139.373
133.938
133.307
128.624
127.196
126.712
124.718
123.533
123.301
122.441
121.198
120.893
117.708
116.363
114.499
112.160
110.610
100.888
99.511
58.060
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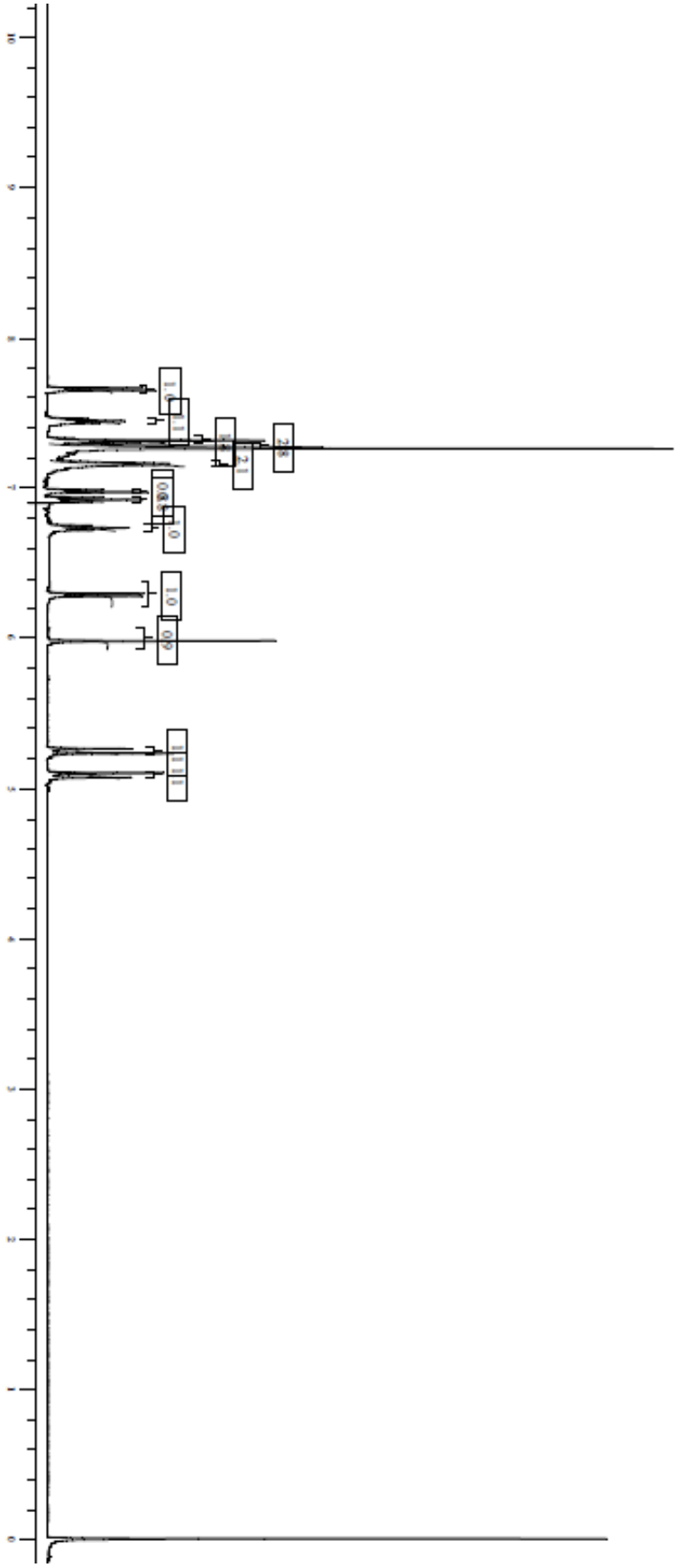
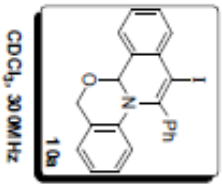
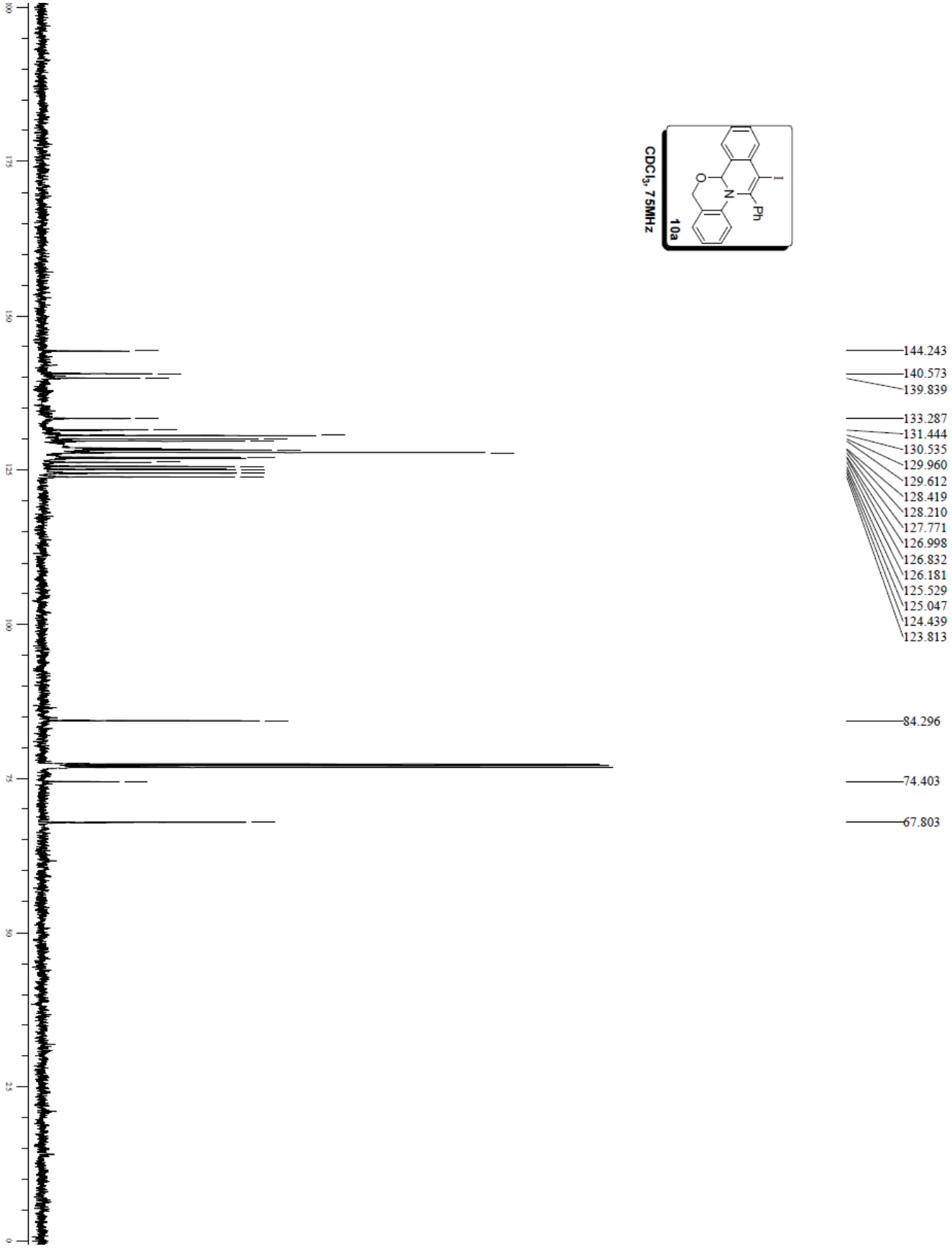
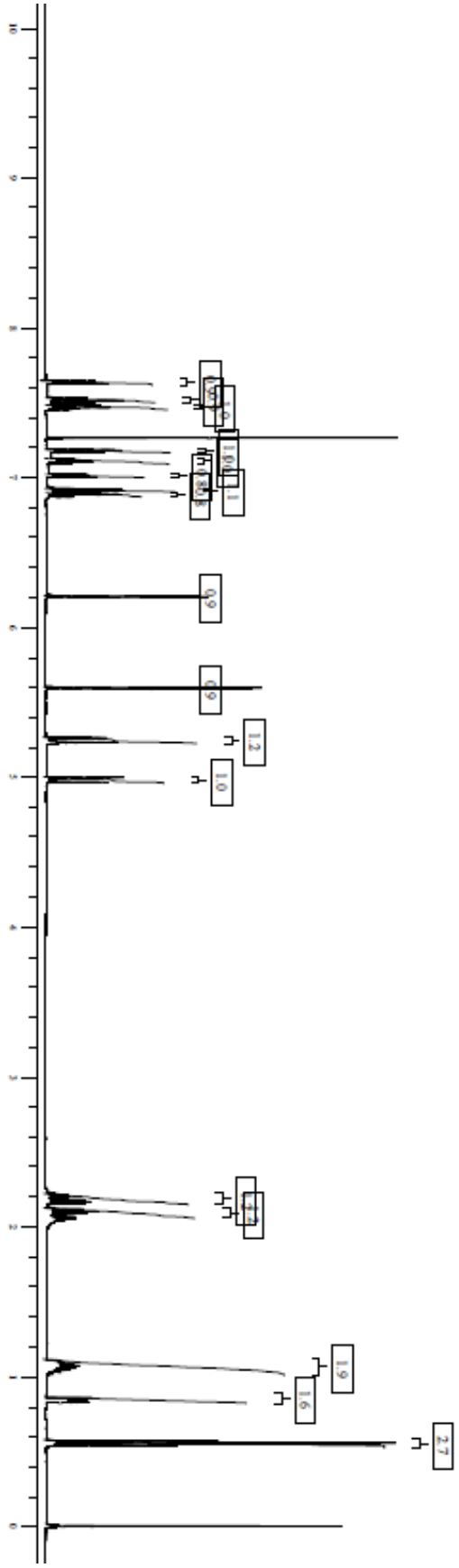
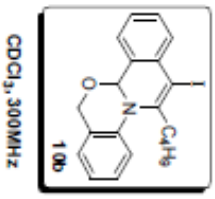
32.039
29.123
21.735
13.517
200
175
150
125
100
75
50
25
0

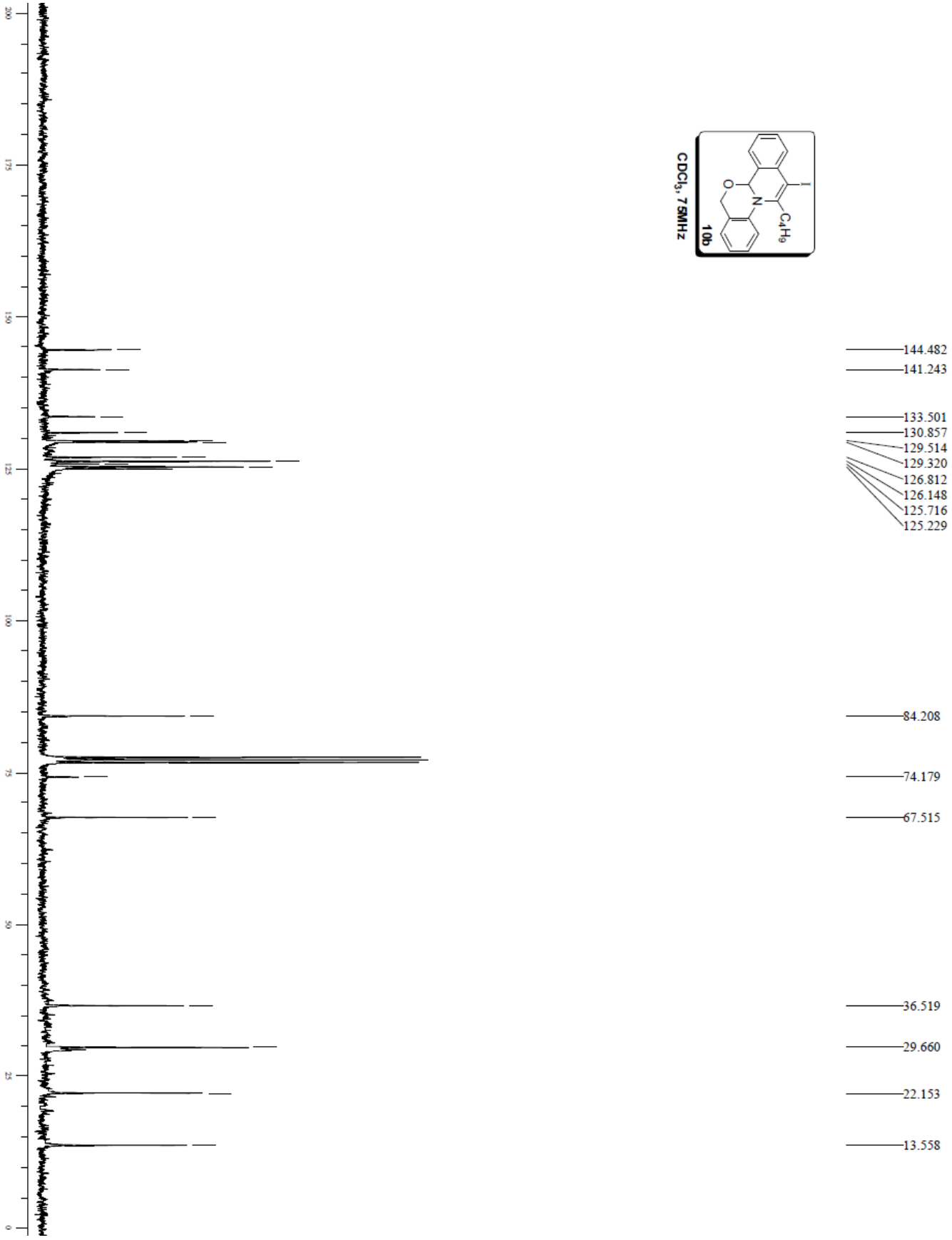


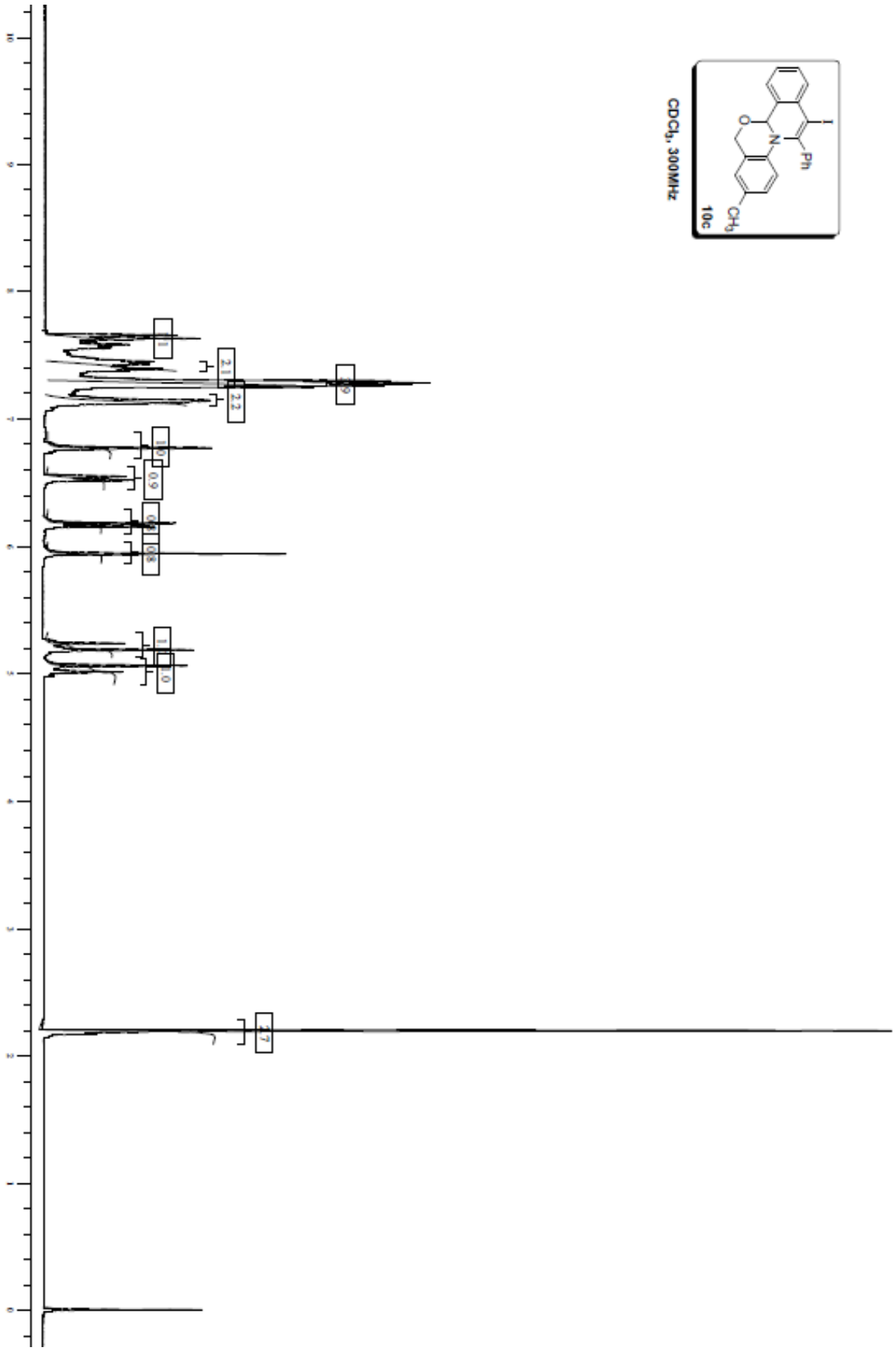

CDCl3, 300MHz
10a
I
Ph
O
N

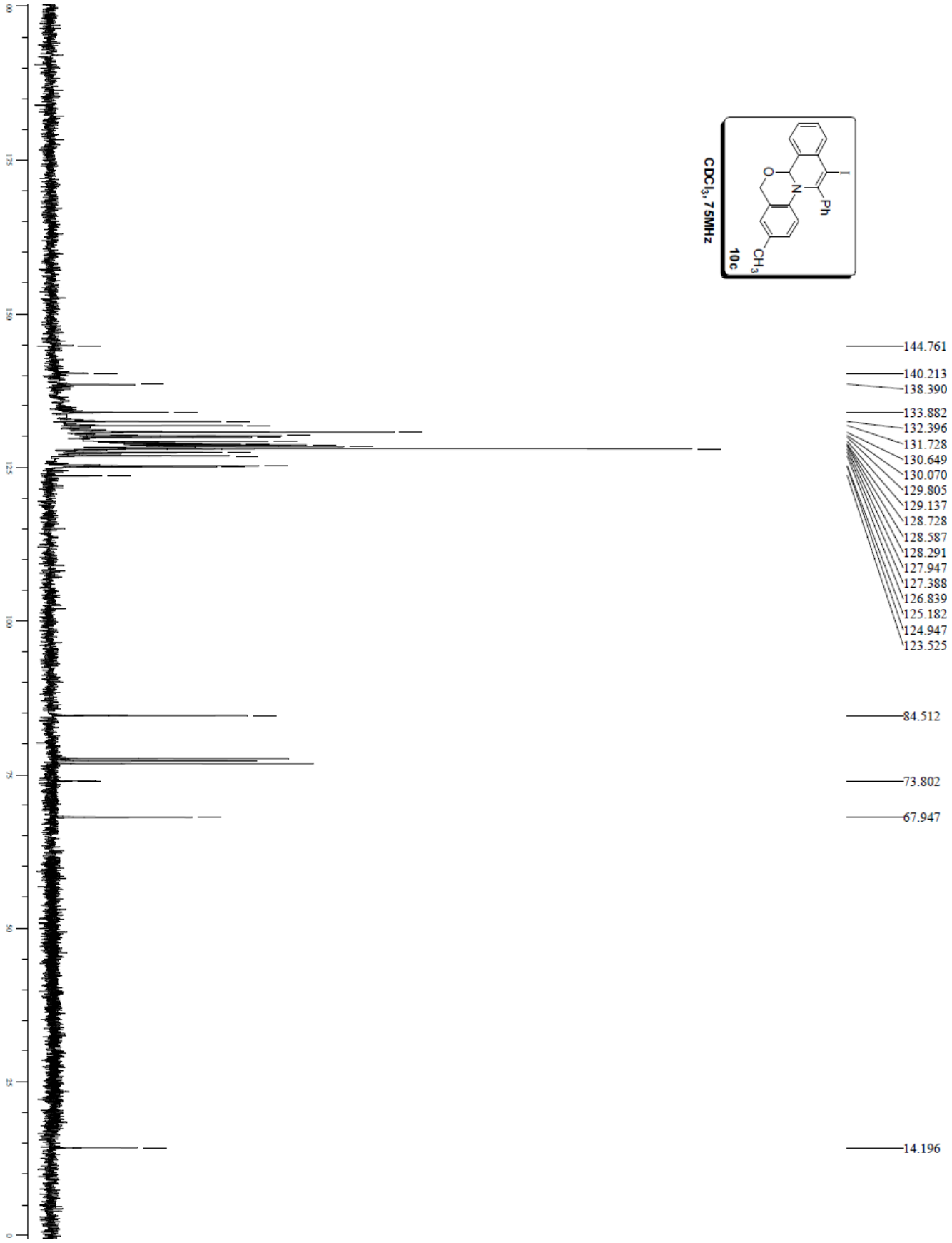


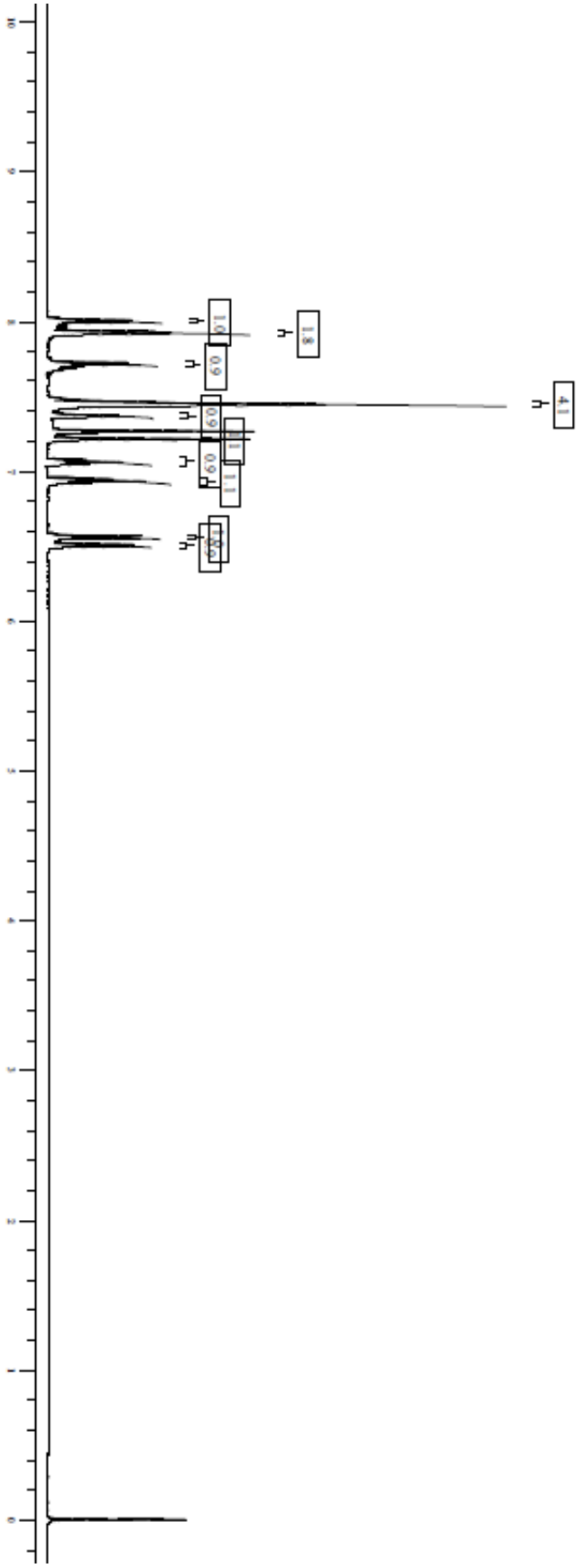

0.9
0.9
1.2
1.0
1.9
1.6
2.7

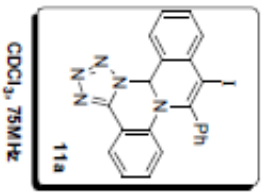

CDCl3, 300MHz
10b
C4H9
I
O
N

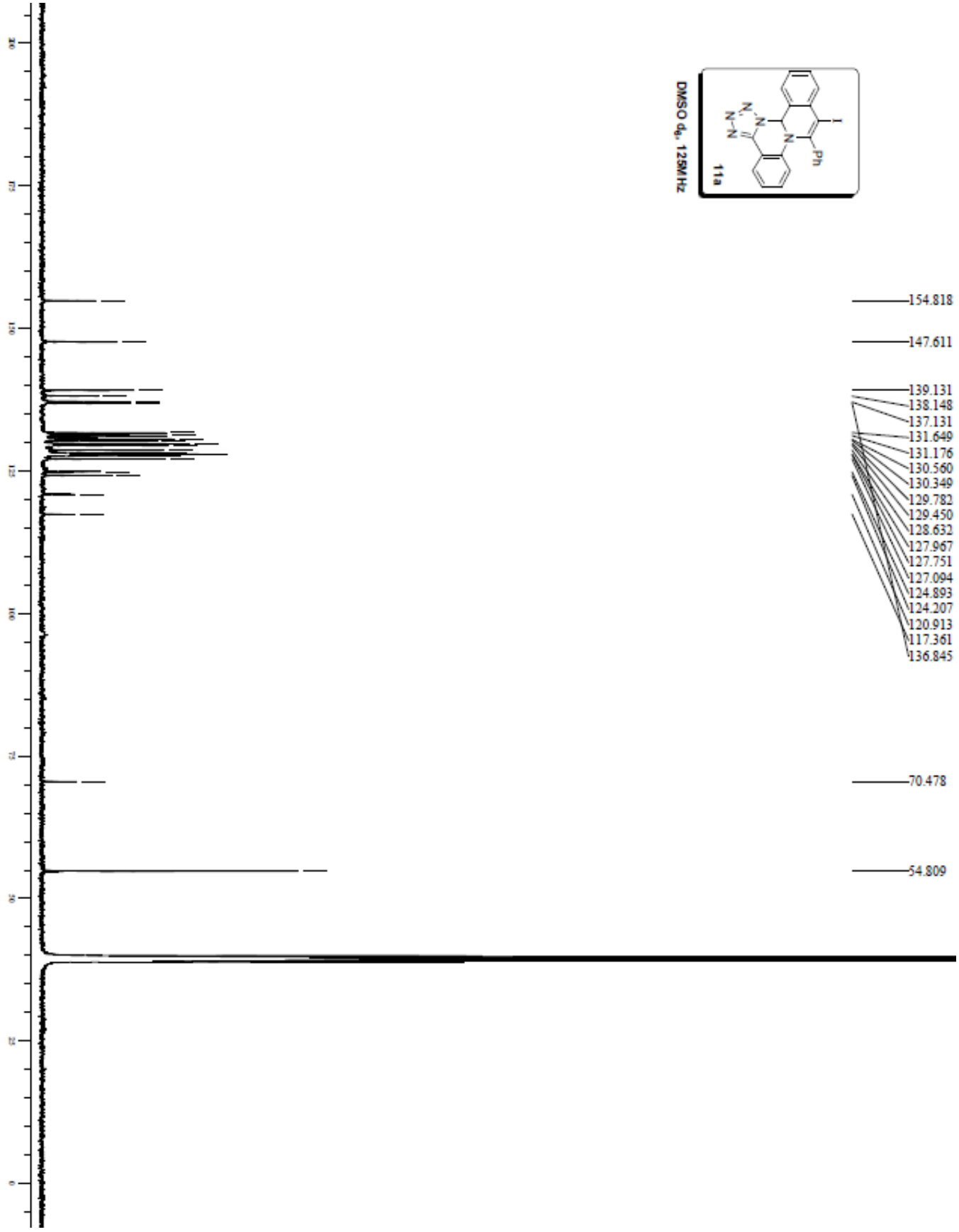


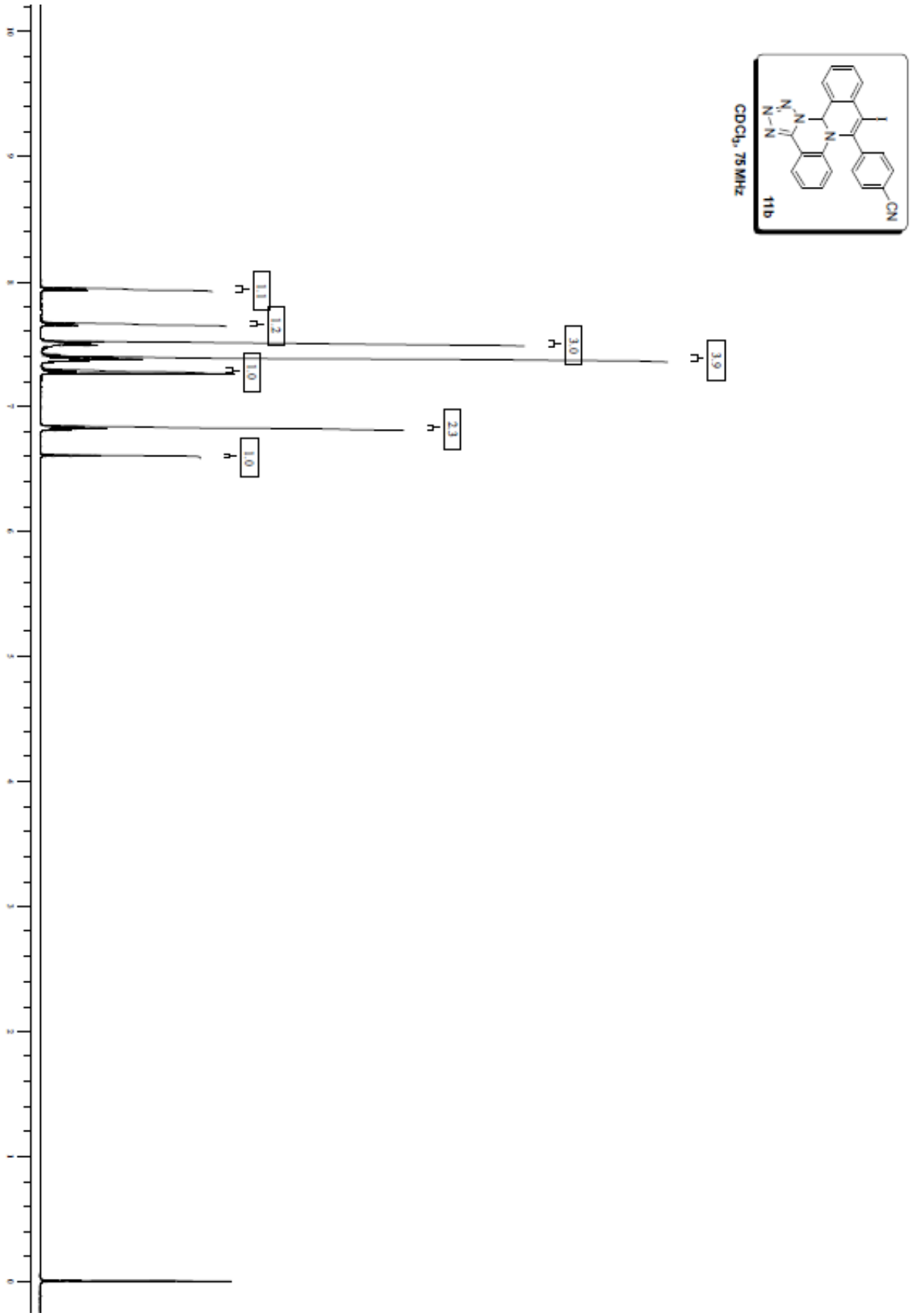

CDCl3, 300MHz
10c
Ph
CH3
1.1
2.1
2.2
1.9
0.6
0.6
0.8
1.1
1.0
2.7

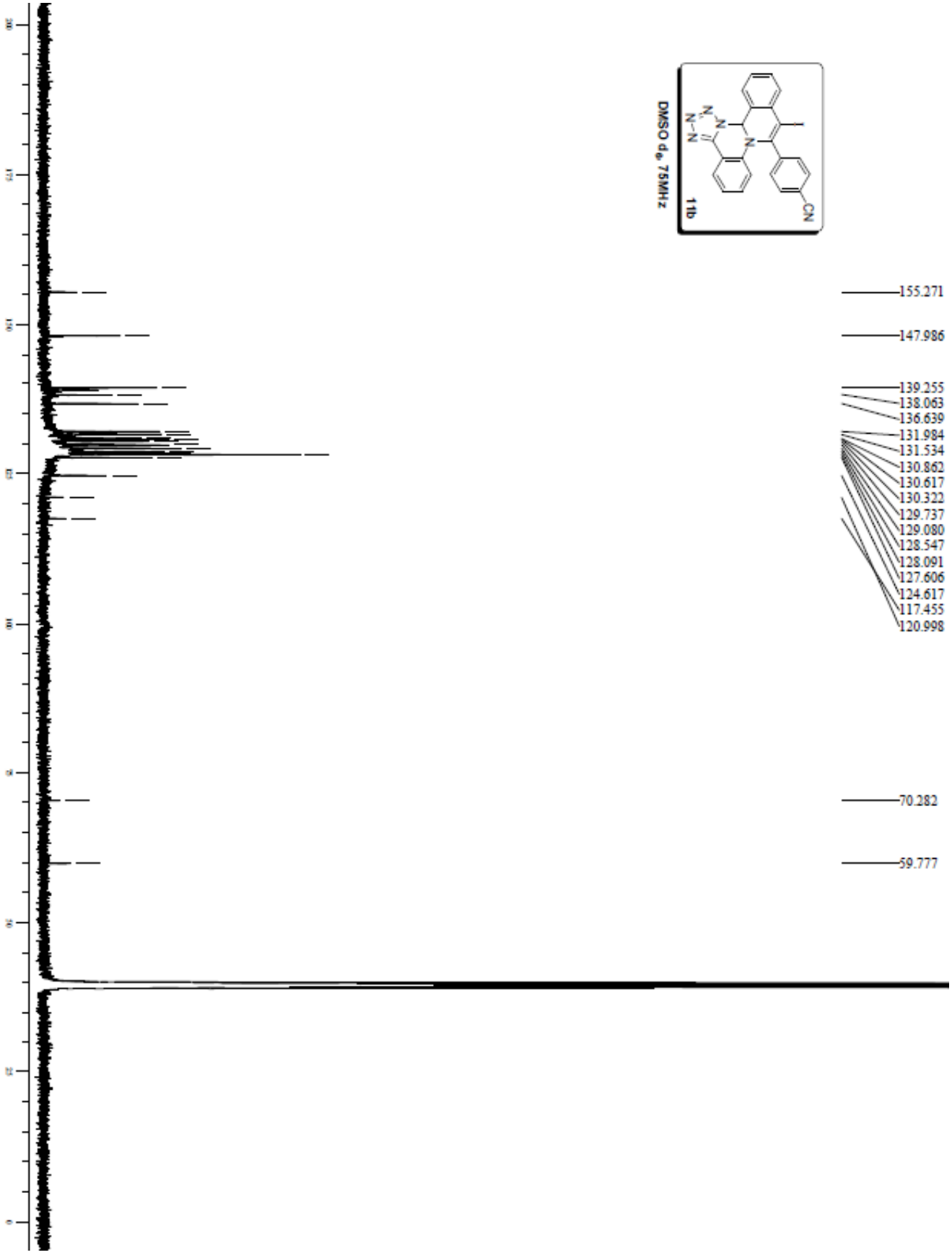


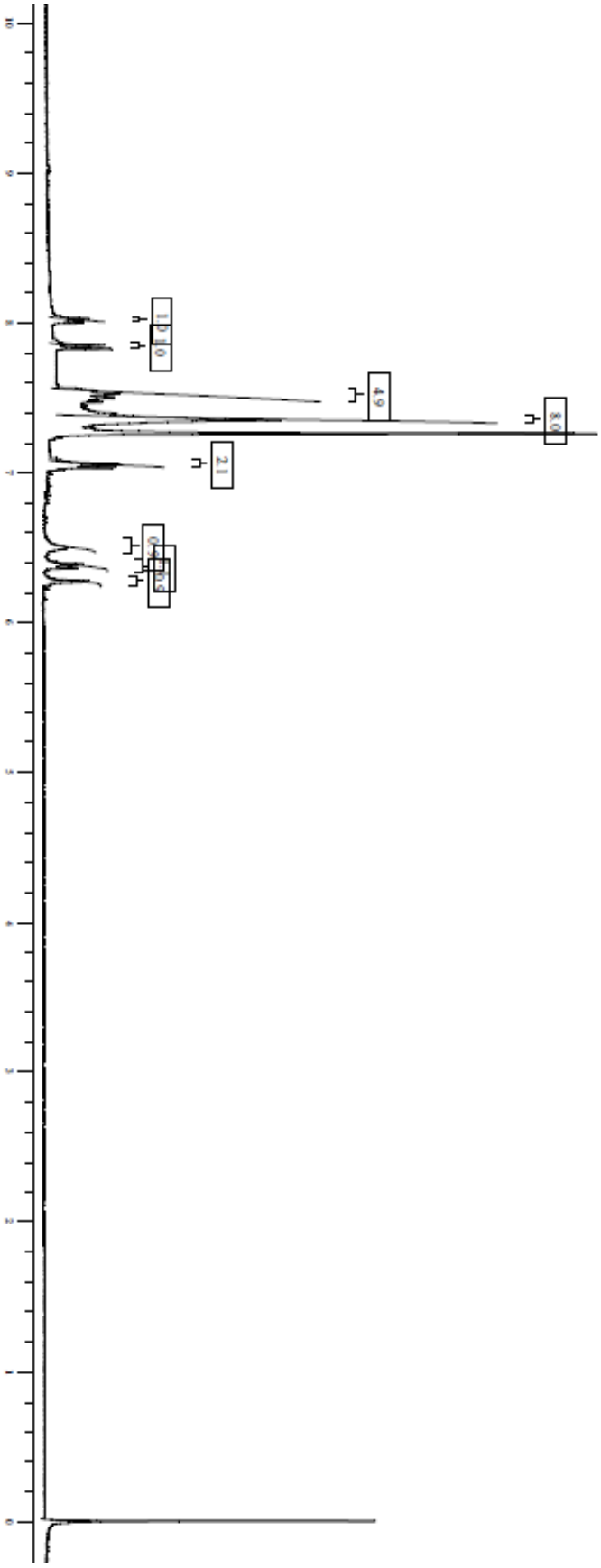


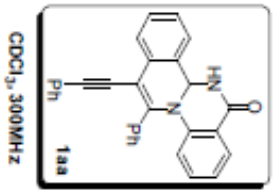

CDCl3, 75MHz
11a
I
Ph

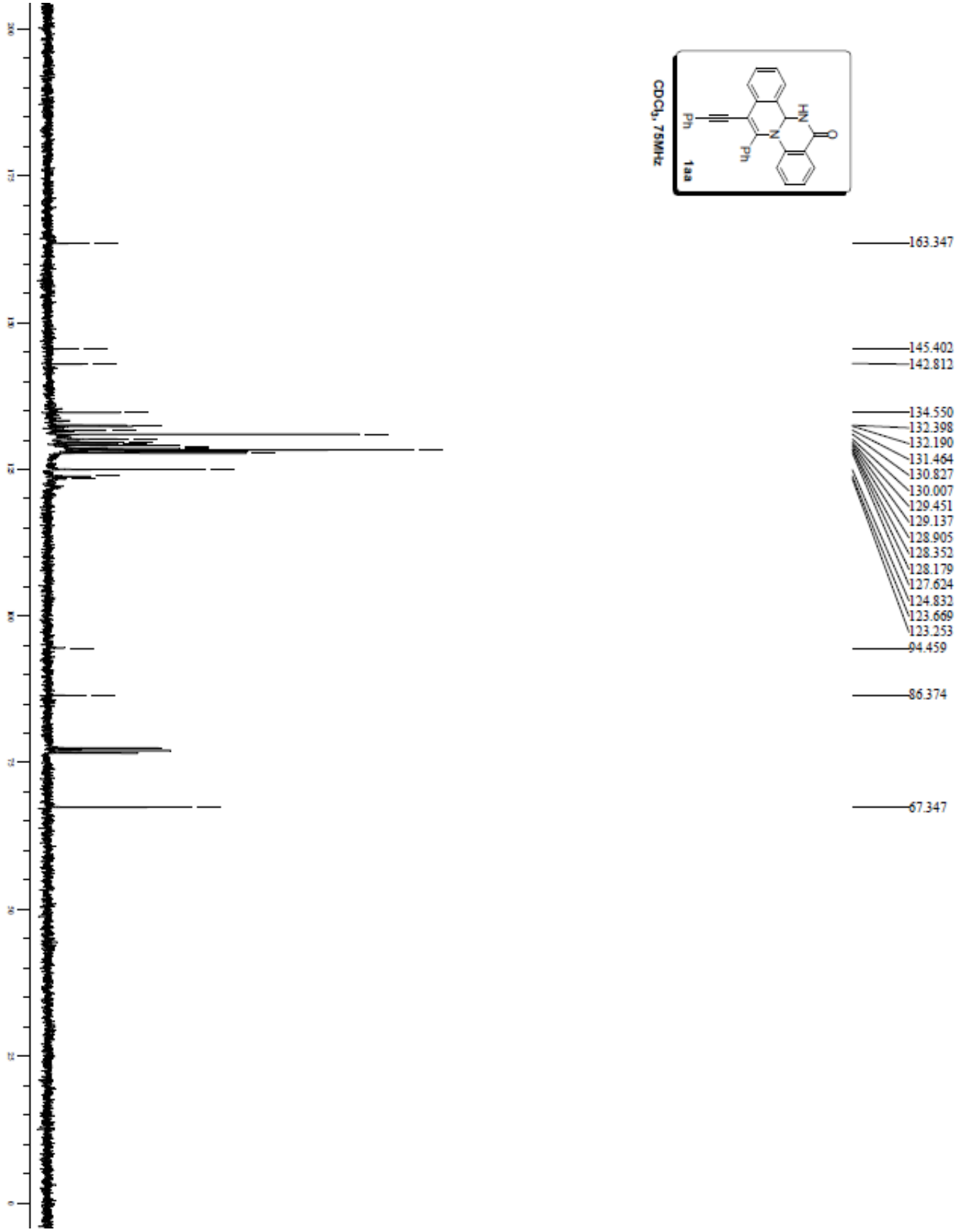


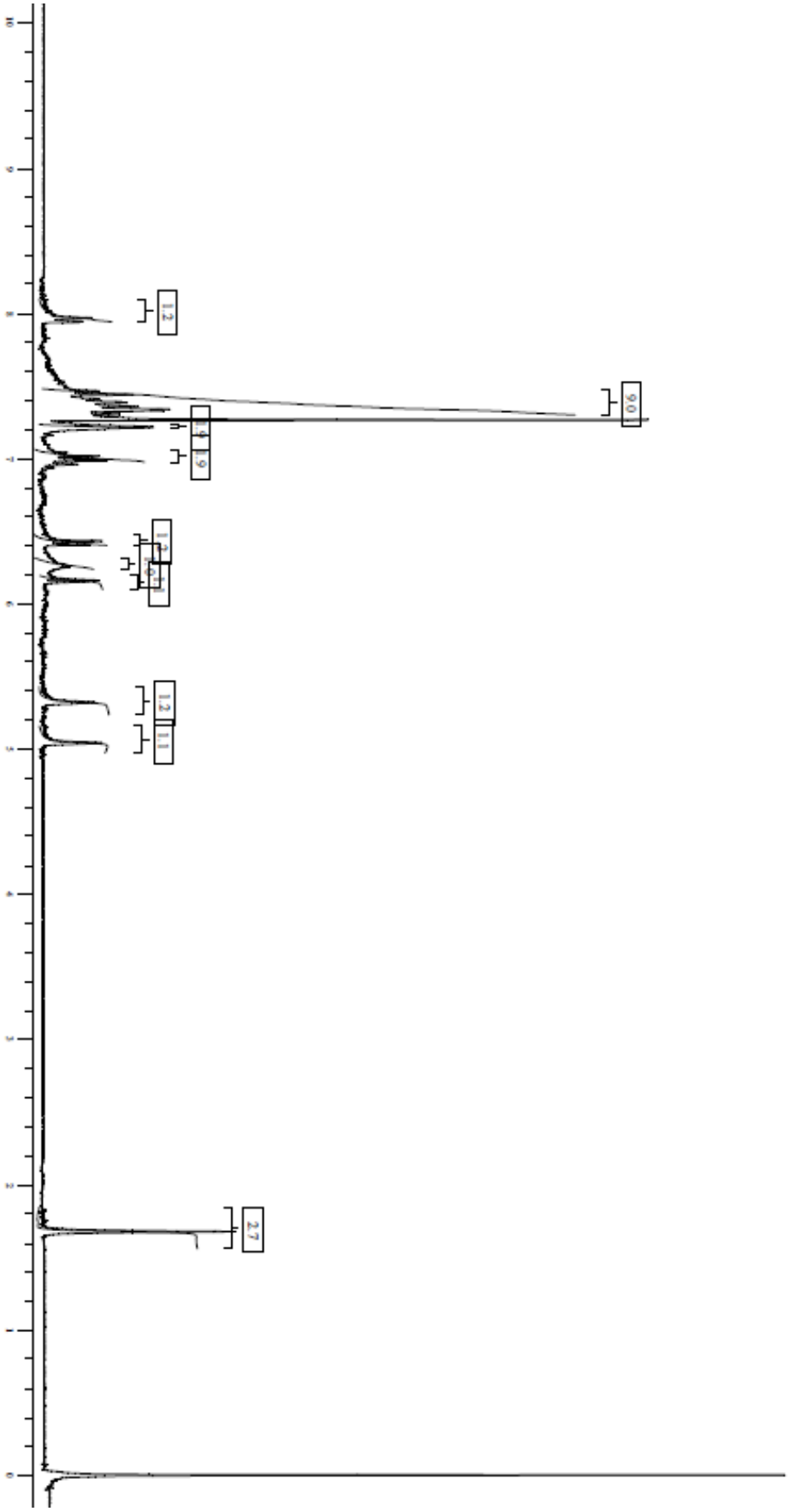

CDCl3, 75 MHz
11b
CN
I
1.11
1.12
3.01
3.9
1.10
2.23
1.10

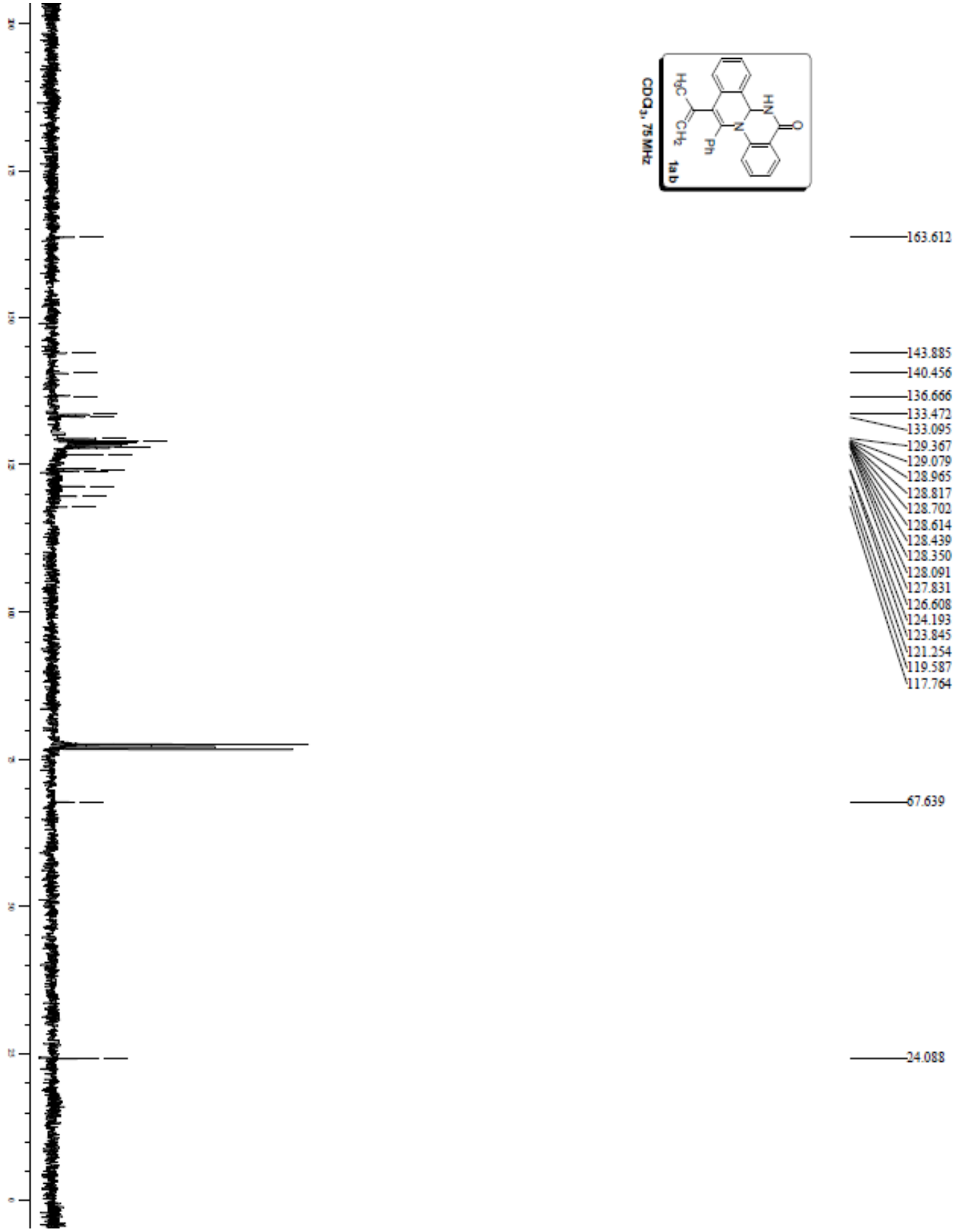


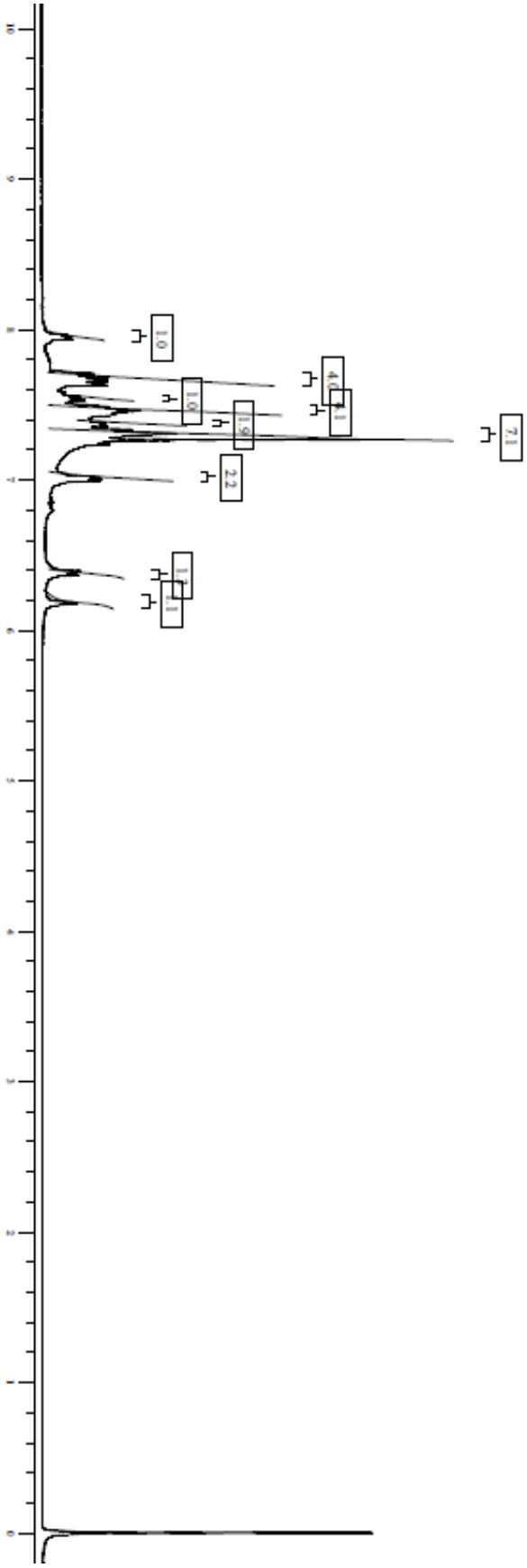

11.10
4.9
8.0
2.1
1.0
1.0

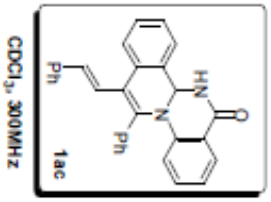

CDCl3, 300MHz
Ph
HN
O
N
Ph
1aa

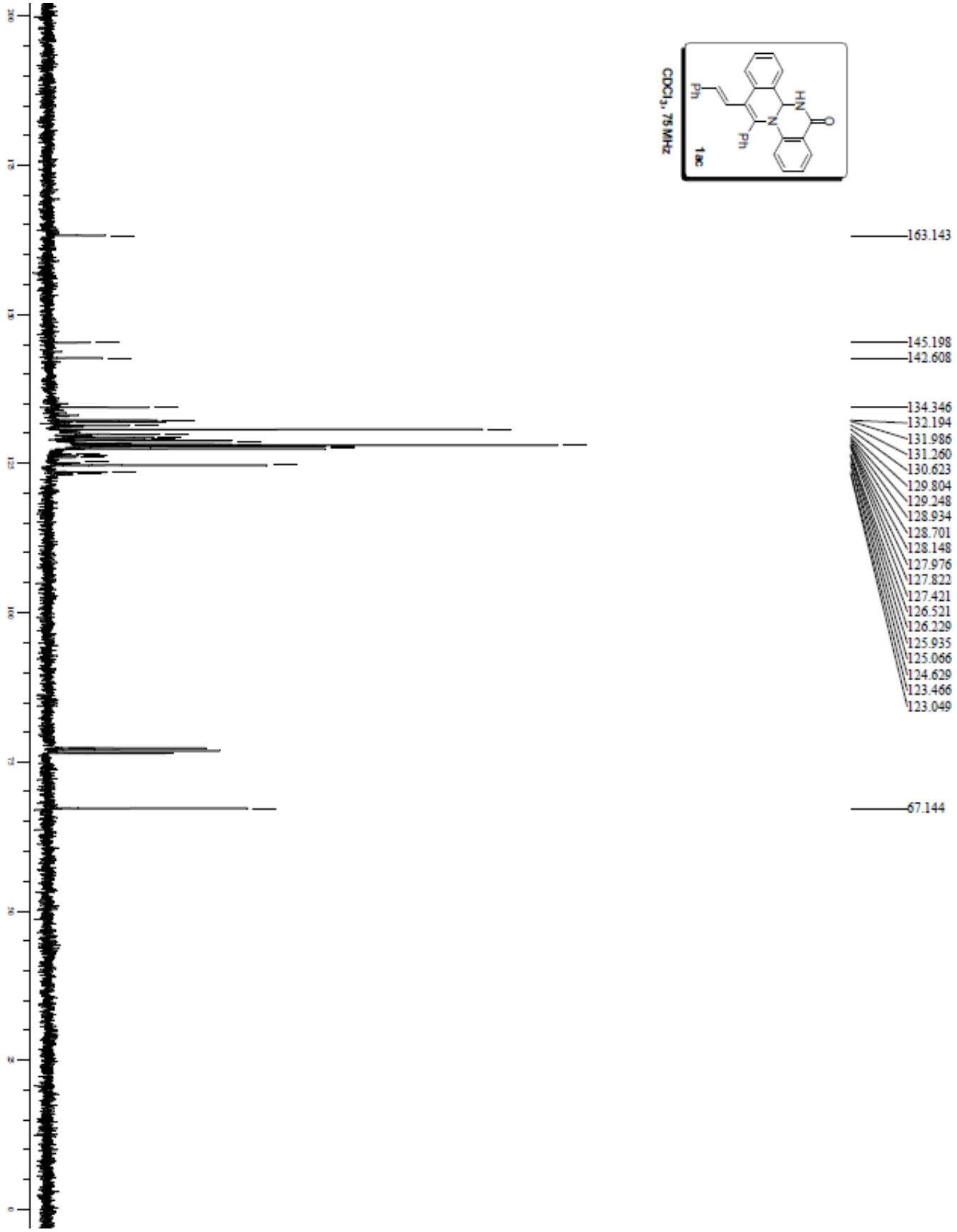

CDCl3, 75MHz
Ph
HN
N
O
Ph
1aa
163.347
145.402
142.812
134.550
132.398
132.190
131.464
130.827
130.007
129.451
129.137
128.905
128.352
128.179
127.624
124.832
123.669
123.253
94.459
86.374
67.347

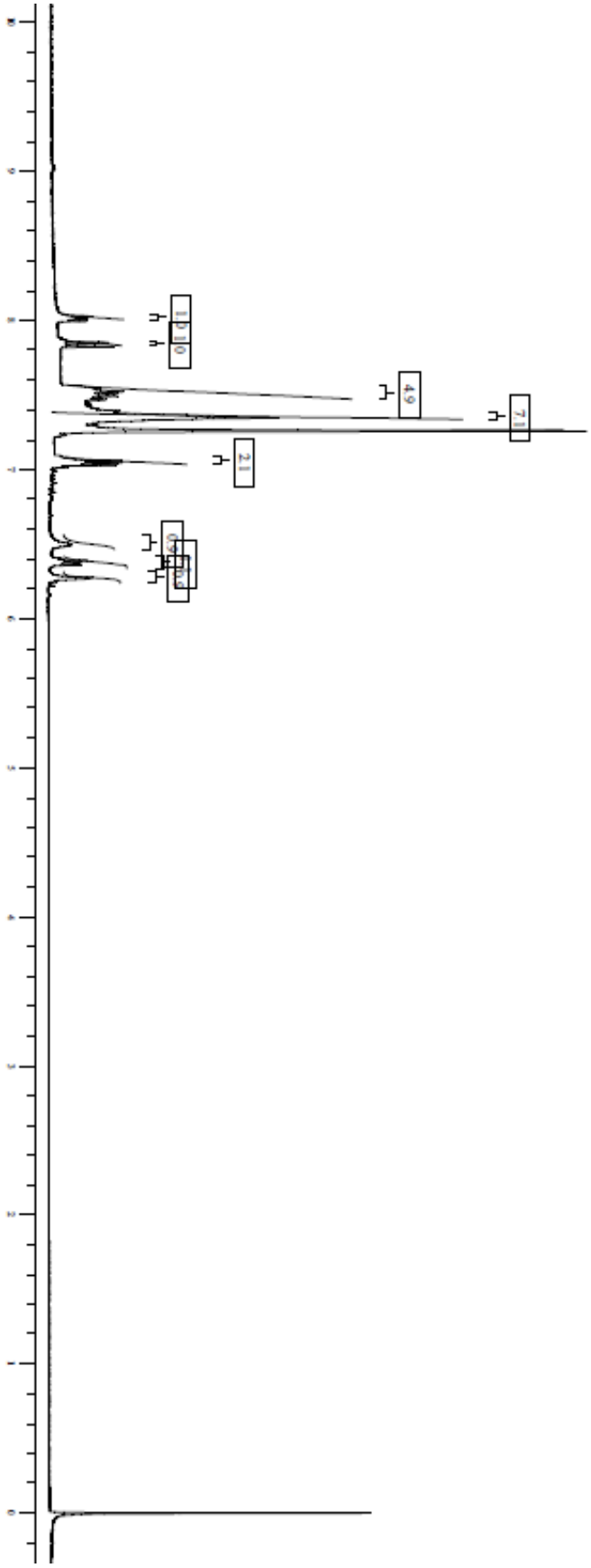

CDCl3, 300MHz
1ab
H3C
CH2
Ph
HN
O
N
12
9.0
1.9
1.2
0.9
1.2
1.1
2.7

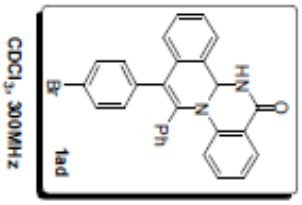

CDCl3, 75 MHz
1a,b
163.612
143.885
140.456
136.666
133.472
133.095
129.367
129.079
128.965
128.817
128.702
128.614
128.439
128.350
128.091
127.831
126.608
124.193
123.845
121.254
119.587
117.764
67.639
24.088

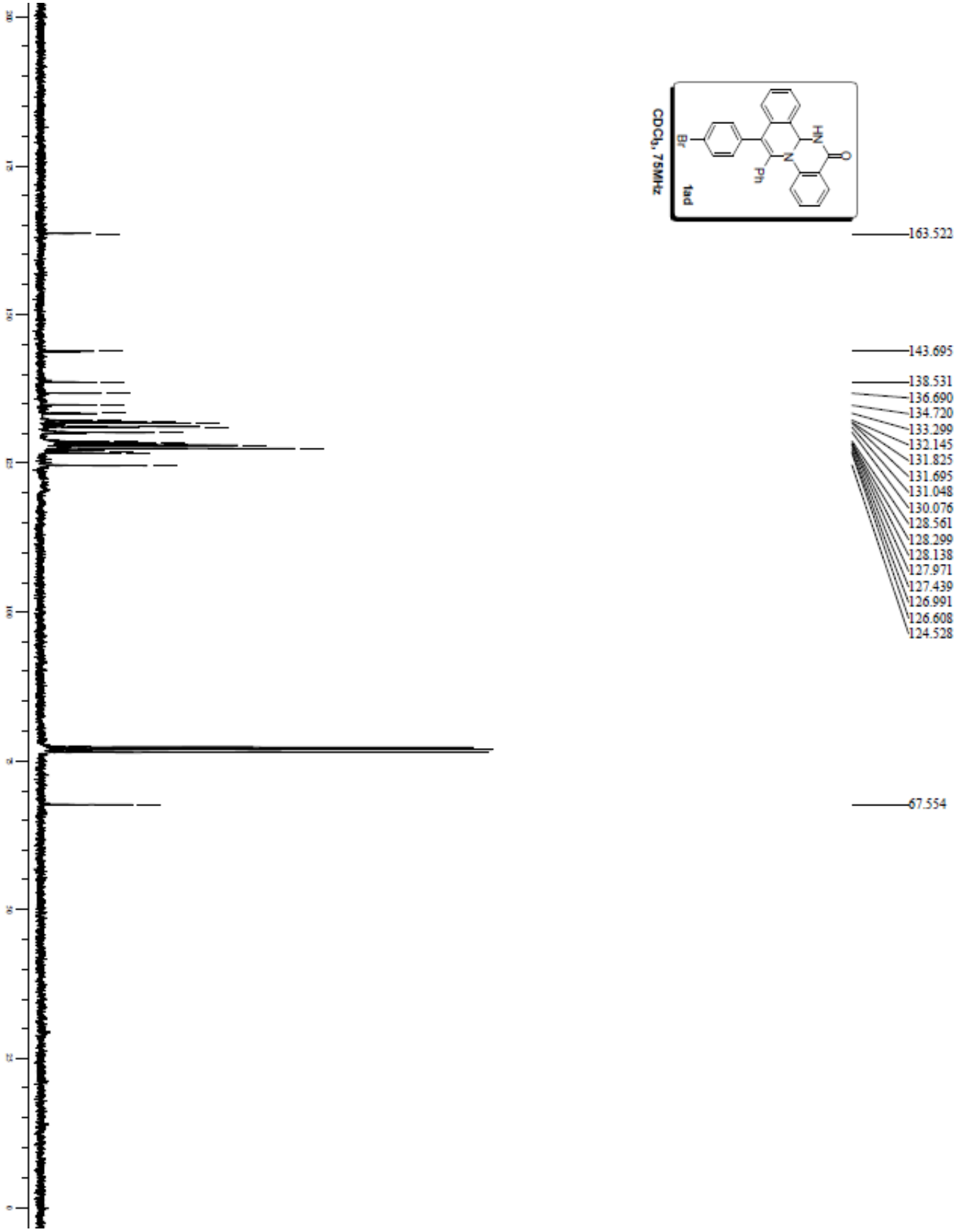


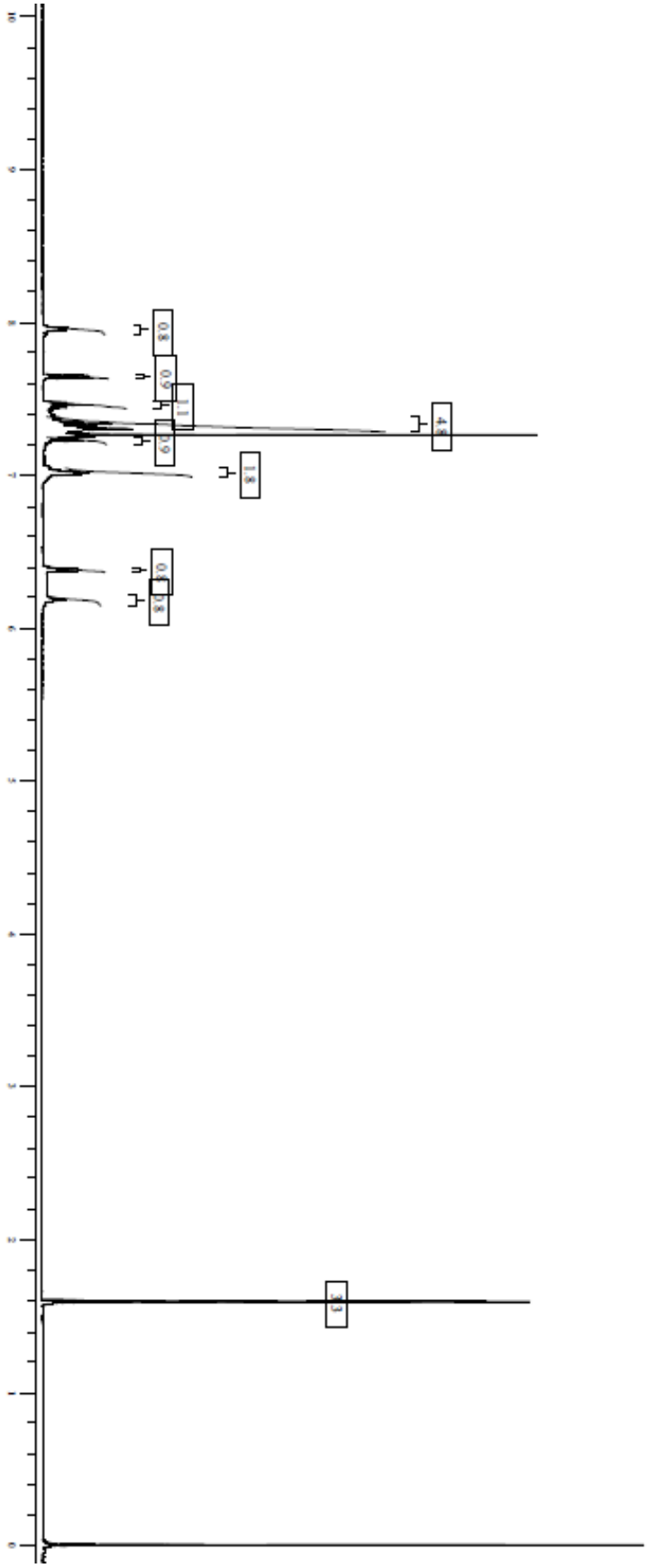


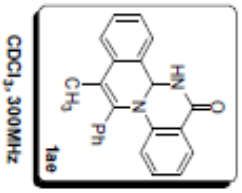


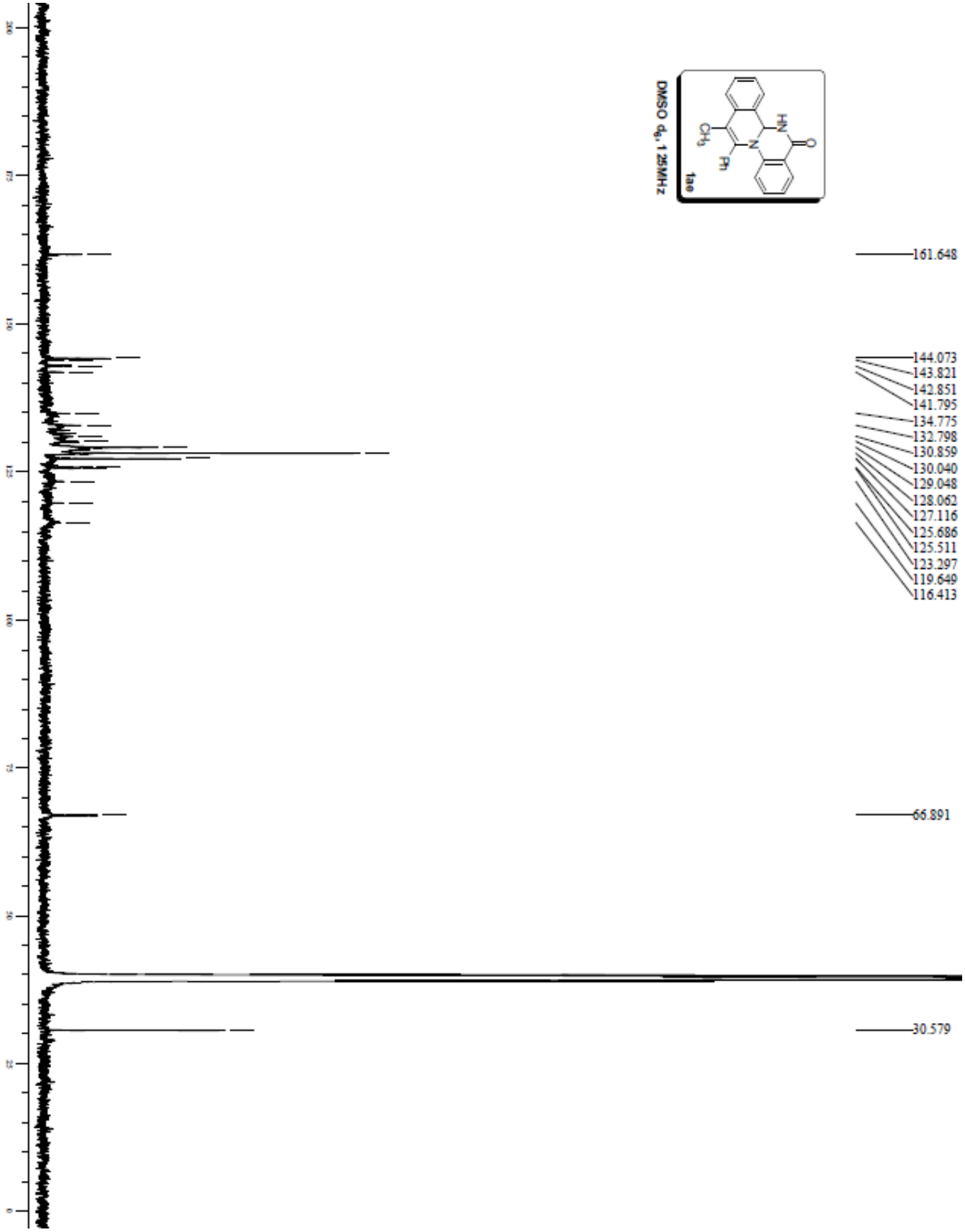


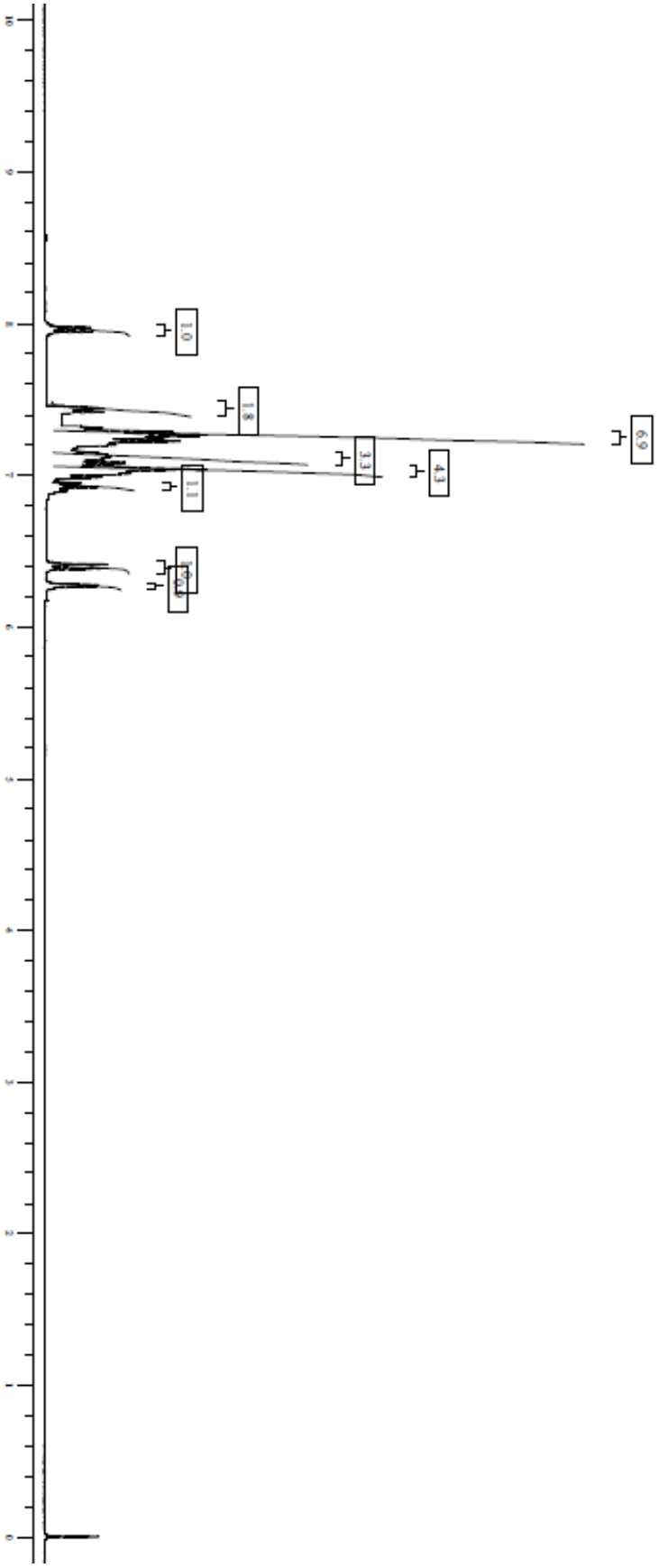

CDCl3, 300MHz
1ad
Br
Ph
N
HN
O

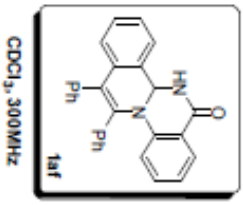

CDCl3, 75MHz
1ad
Br
Ph
HN
O
N
163.522
143.695
138.531
136.690
134.720
133.299
132.145
131.825
131.695
131.048
130.076
128.561
128.299
128.138
127.971
127.439
126.991
126.608
124.528
67.554

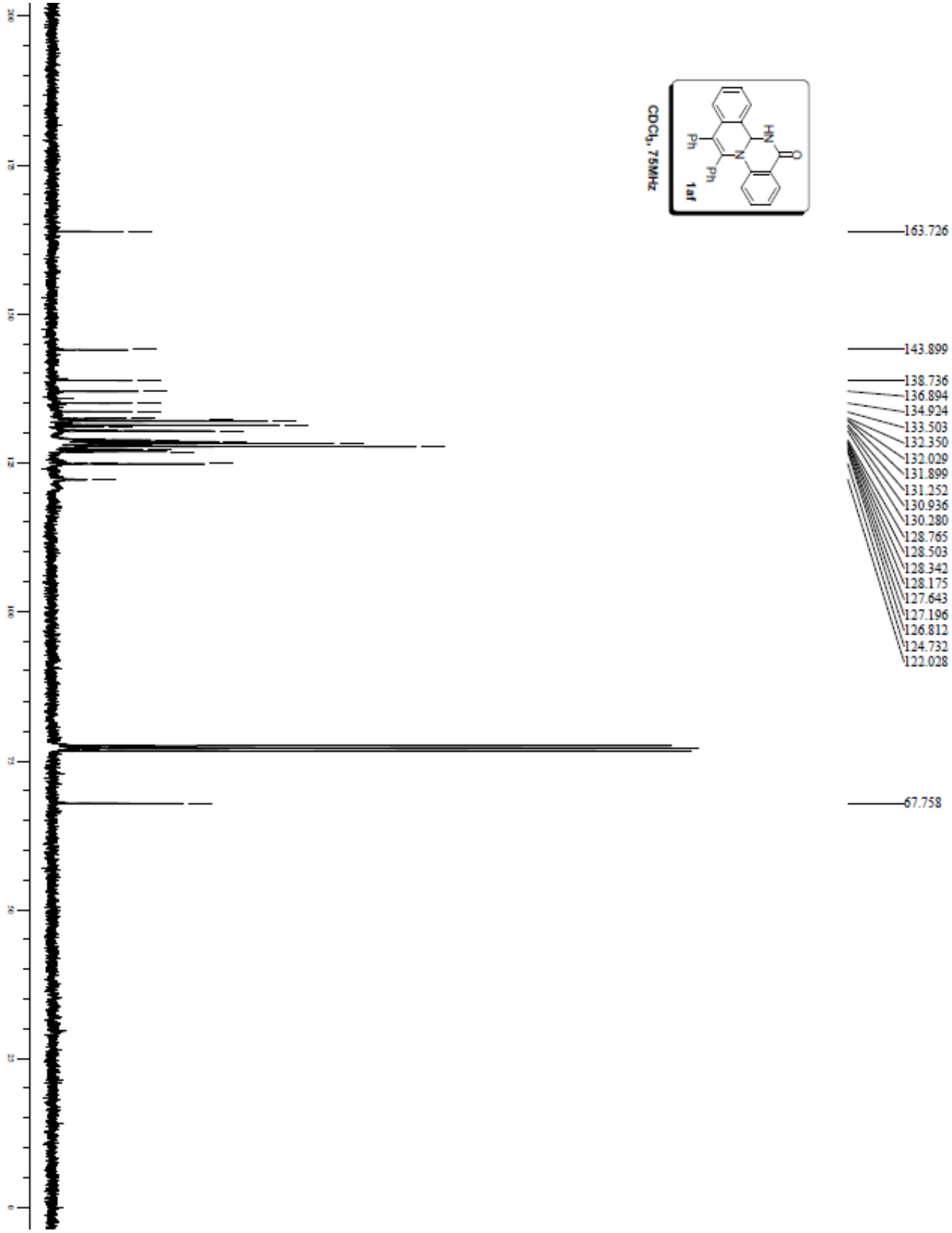

0.8
0.5
1.1
0.6
4.8
1.8
0.8
0.8
3.3

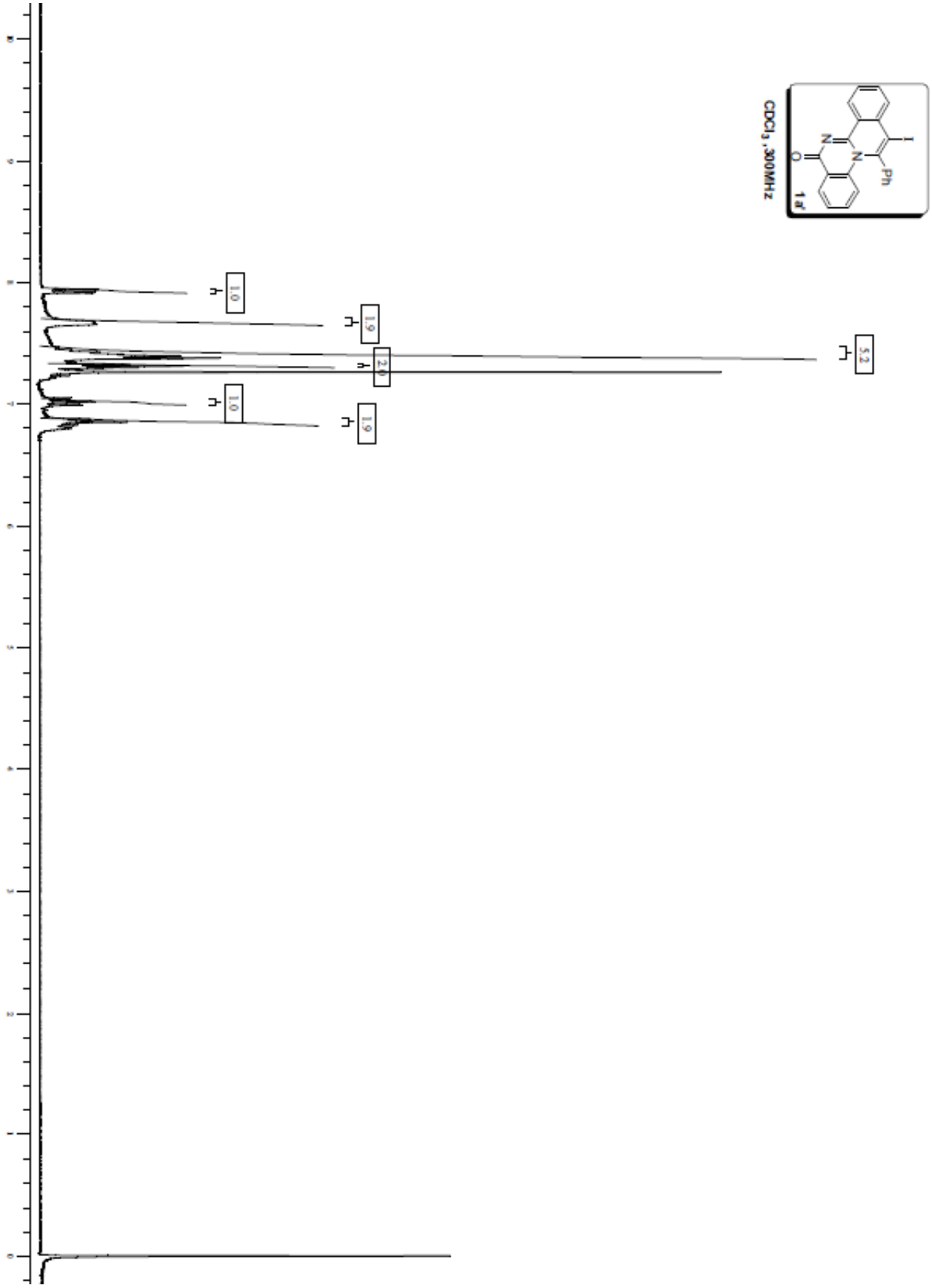

CDCl3, 300MHz
1ae
HN
O
CH3
Ph
N

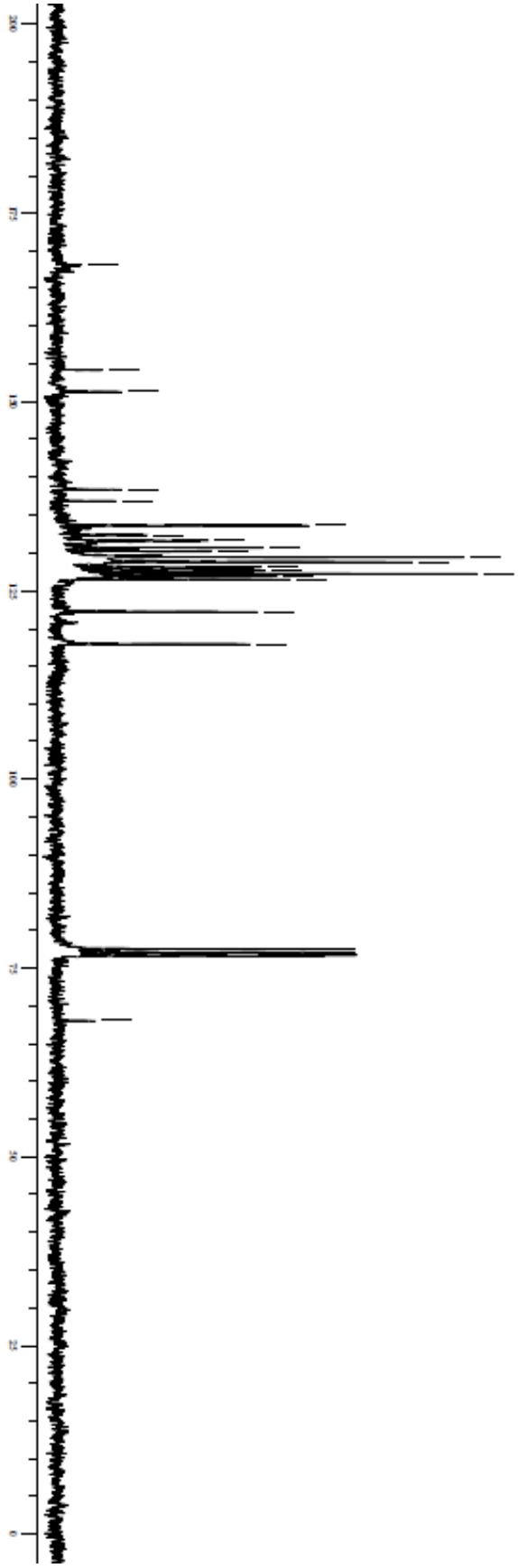

DMSO d_6, 125MHz
1ae
161.648
144.073
143.821
142.851
141.795
134.775
132.798
130.859
130.040
129.048
128.062
127.116
125.686
125.511
123.297
119.649
116.413
66.891
30.579

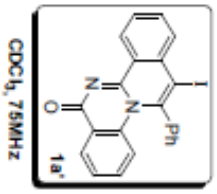

1.01
1.98
6.9
3.33
4.13
1.11
1.03
1.00


CDCl3, 300MHz
1af
Ph
Ph
N
HN
O

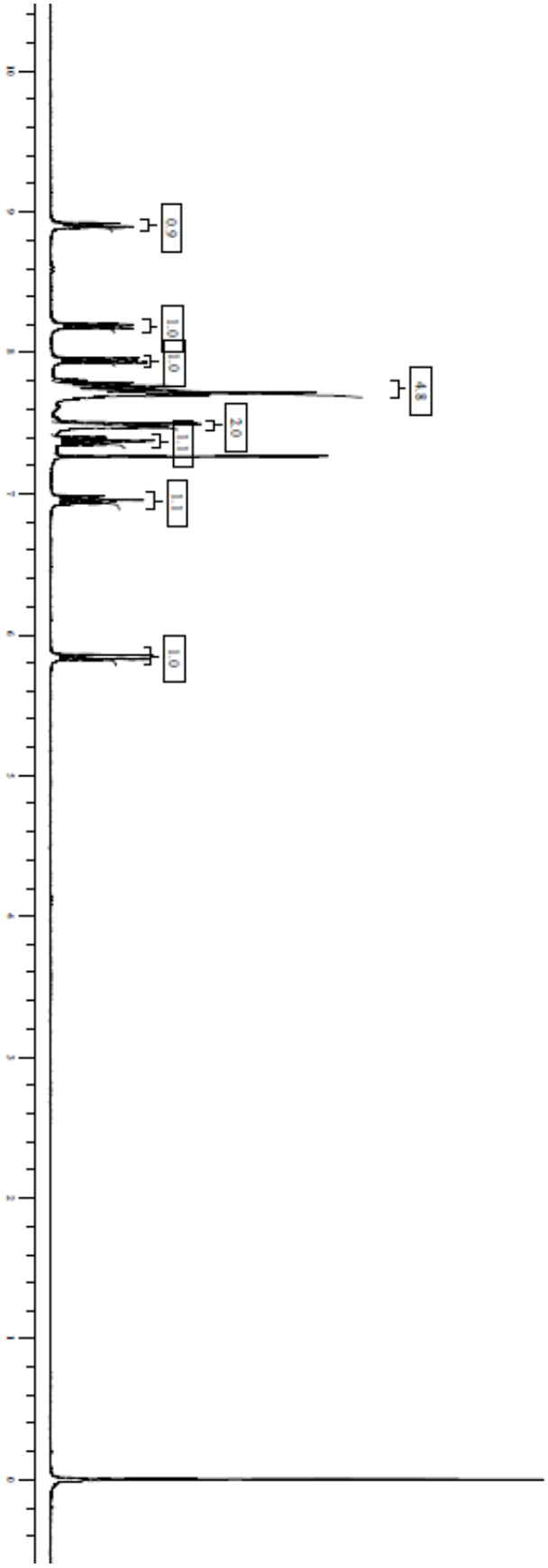


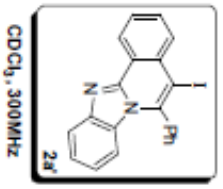


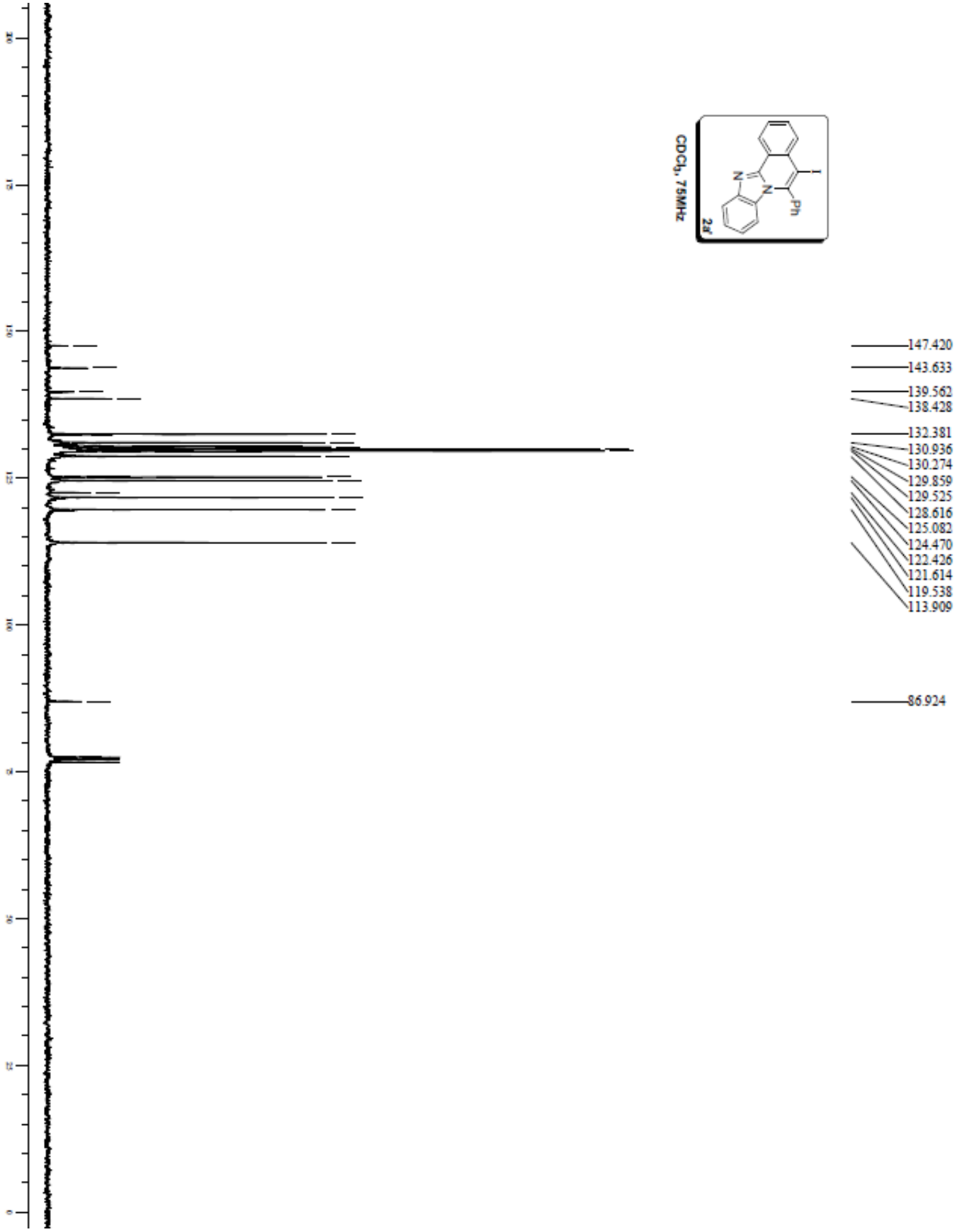


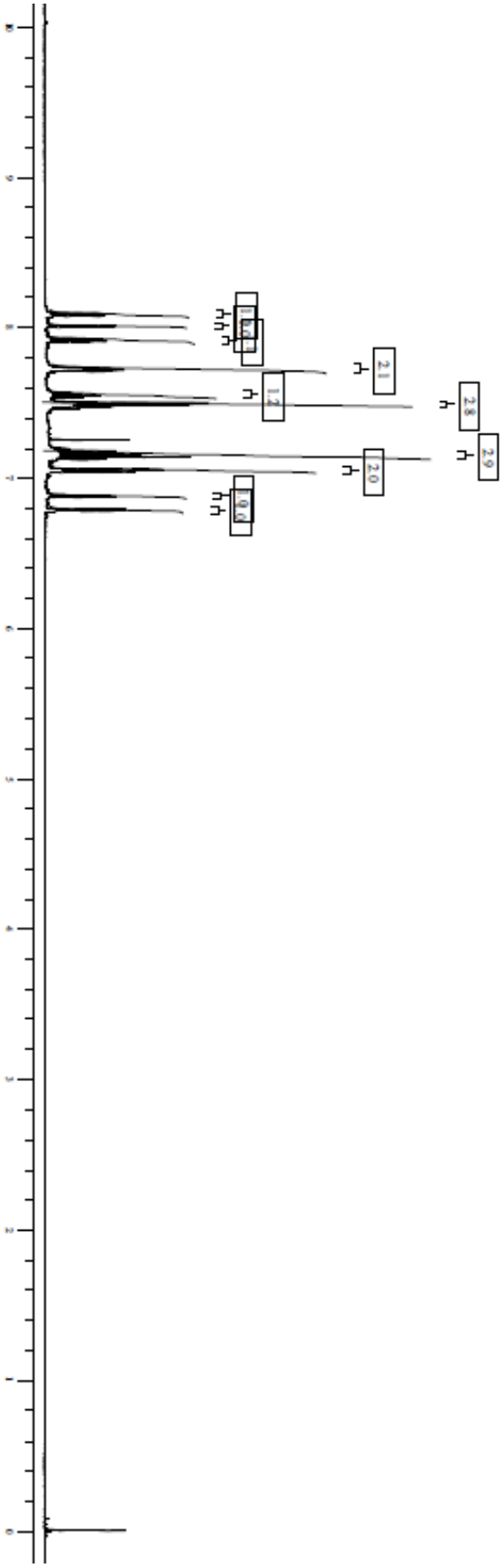


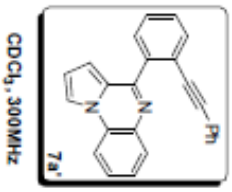
167.989
154.120
151.249
138.272
136.768
133.532
132.289
131.532
130.579
130.076
129.320
128.710
127.991
127.483
127.125
126.805
126.413
122.101
117.832
67.934

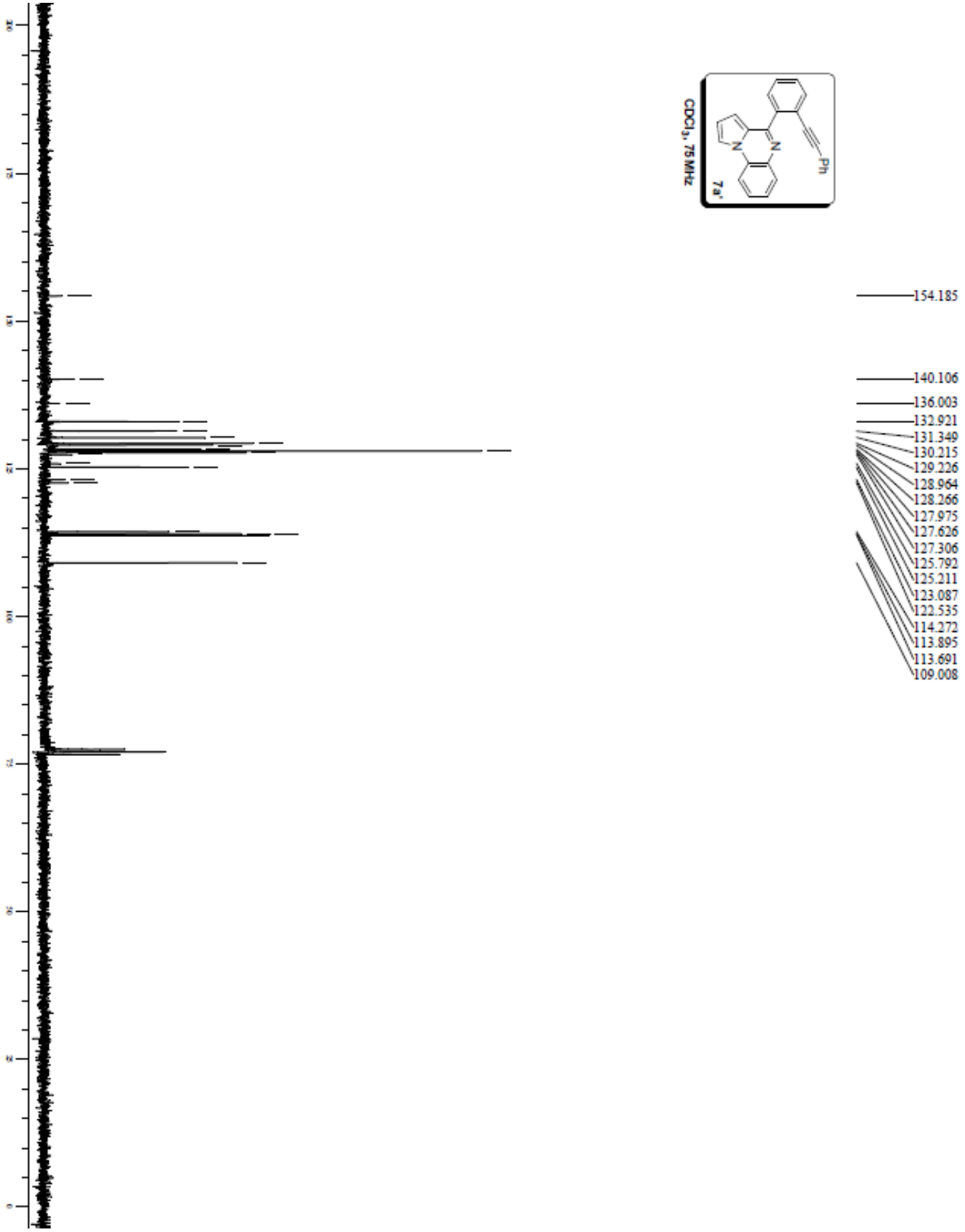

0.6
1.0
1.0
4.6
2.0
1.1
1.1
1.0


CDCl3, 300MHz
2af
N
N
I
Ph


CDCl3, 75MHz
2a'
I
Ph
147.420
143.633
139.562
138.428
132.381
130.936
130.274
129.859
129.525
128.616
125.082
124.470
122.426
121.614
119.538
113.909
86.924






CDCl3, 75 MHz
7a'
Ph
154.185
140.106
136.003
132.921
131.349
130.215
129.226
128.964
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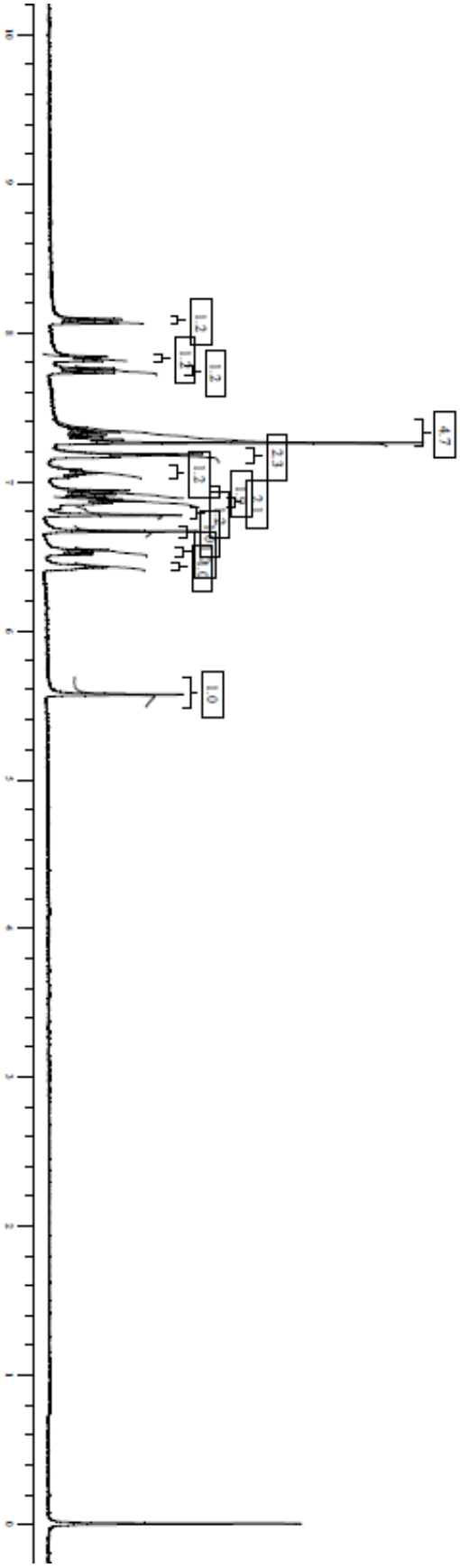
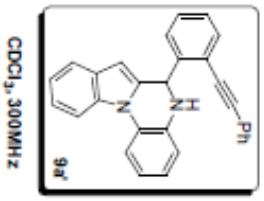
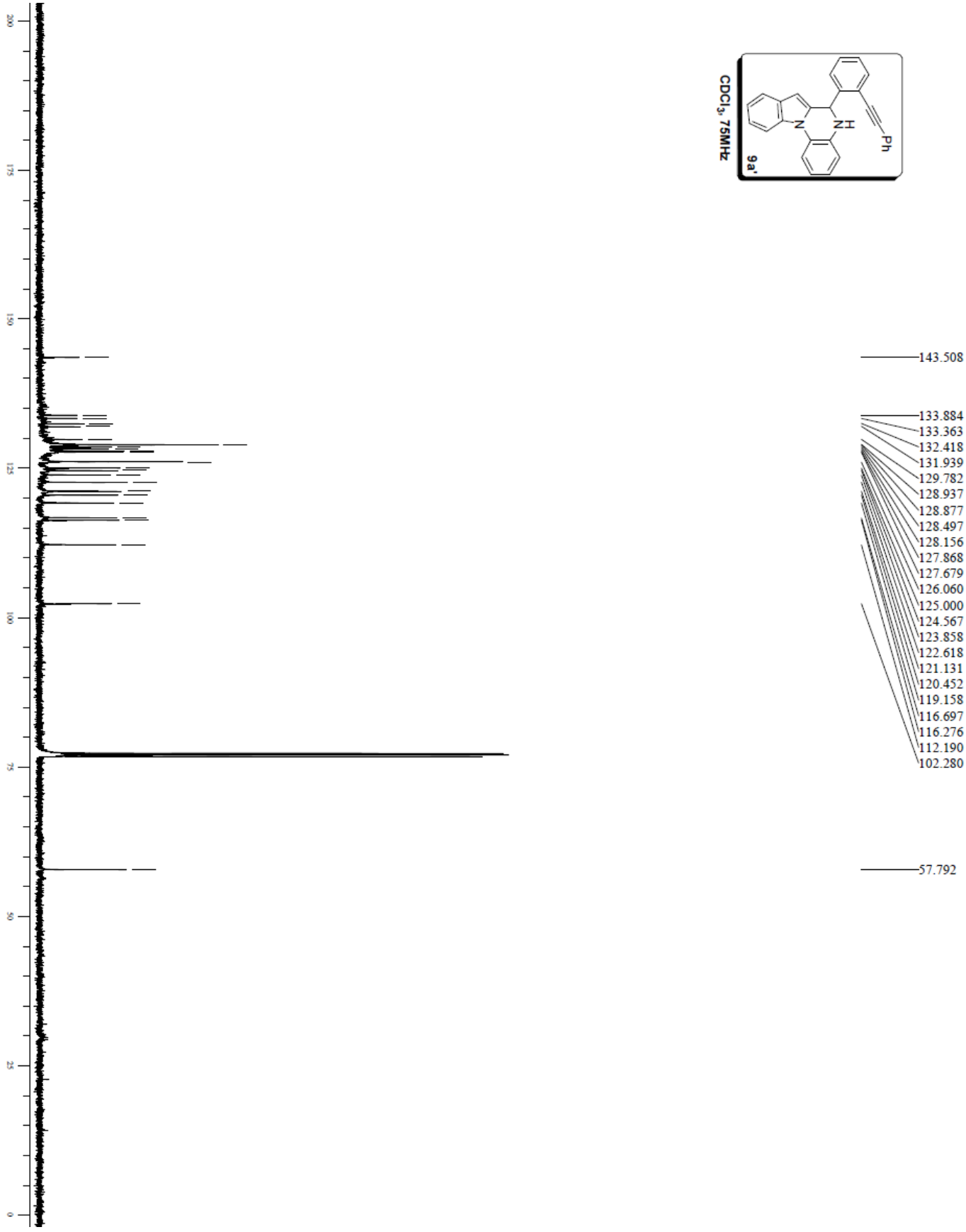
122.535
114.272
113.895
113.691
109.008


1.2
1.2
1.2
4.7
2.3
1.2
2.1
1.0


CDCl3, 300MHz
9a'
N
H
N
Ph


CDCl3, 75MHz
9a'
Ph
143.508
133.884
133.363
132.418
131.939
129.782
128.937
128.877
128.497
128.156
127.868
127.679
126.060
125.000
124.567
123.858
122.618
121.131
120.452
119.158
116.697
116.276
112.190
102.280
57.792