Electronic Supplementary Material (ESI) for ChemComm.

Accelerated hydration reaction of an unsymmetrical tolan evidenced by a Hg(II)-trapped macrocycle and its application as a Hg(II)-selective indicator

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Contents

General Experiments

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields of synthesized compounds were measured after chromatographic purification. Stock solutions of all of the compounds studied were made up in CH_3CN with the final concentrations being between 2×10^{-5} M and 2×10^{-6} M. ACS grade solvents were purchased and used without purification. The stock solutions were appropriately diluted with HPLC water (or HEPES buffer) for the ensuing studies.

Structural supporting data for 2b

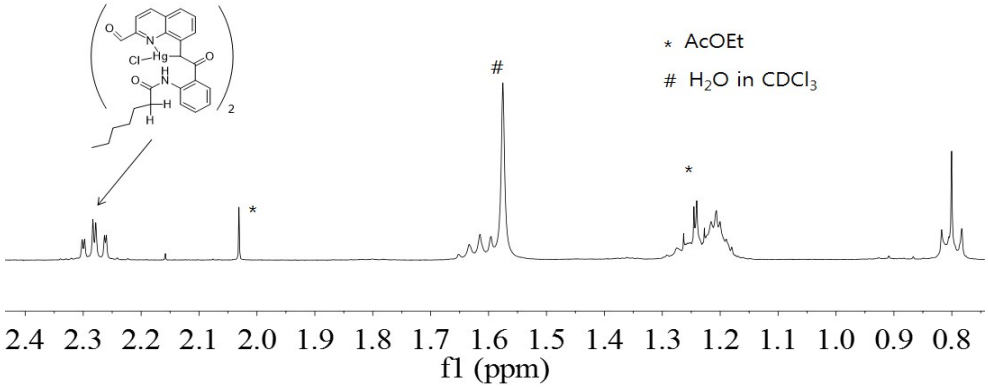


Figure S1. Partial ^{1}H NMR spectrum (400 MHz) of **2b** recorded in $CDCl_3$.

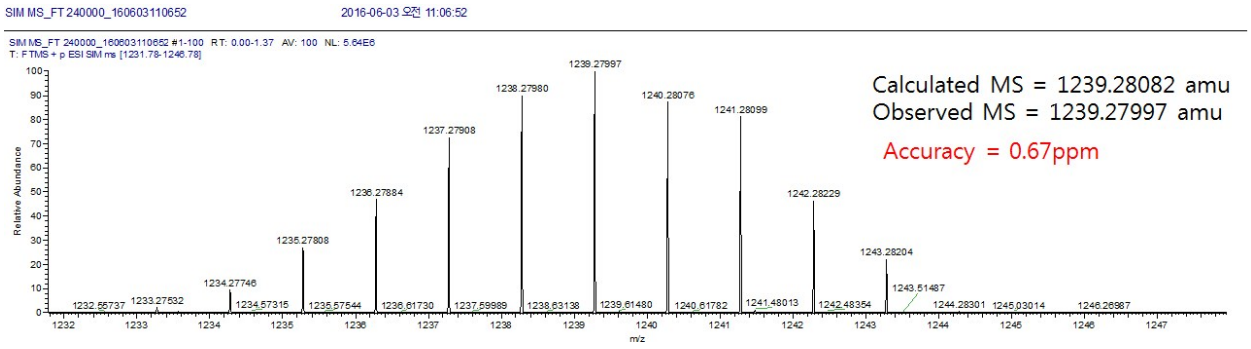


Figure S2. Observed high mass spectrum of **2b** (m/z, [**2b** – Cl^-]$^+$ = 1239.2800**)**. The value was obtained by high-resolution ESI mass spectrometry.

Stacked ^{1}H NMR spectra of unreactive 1

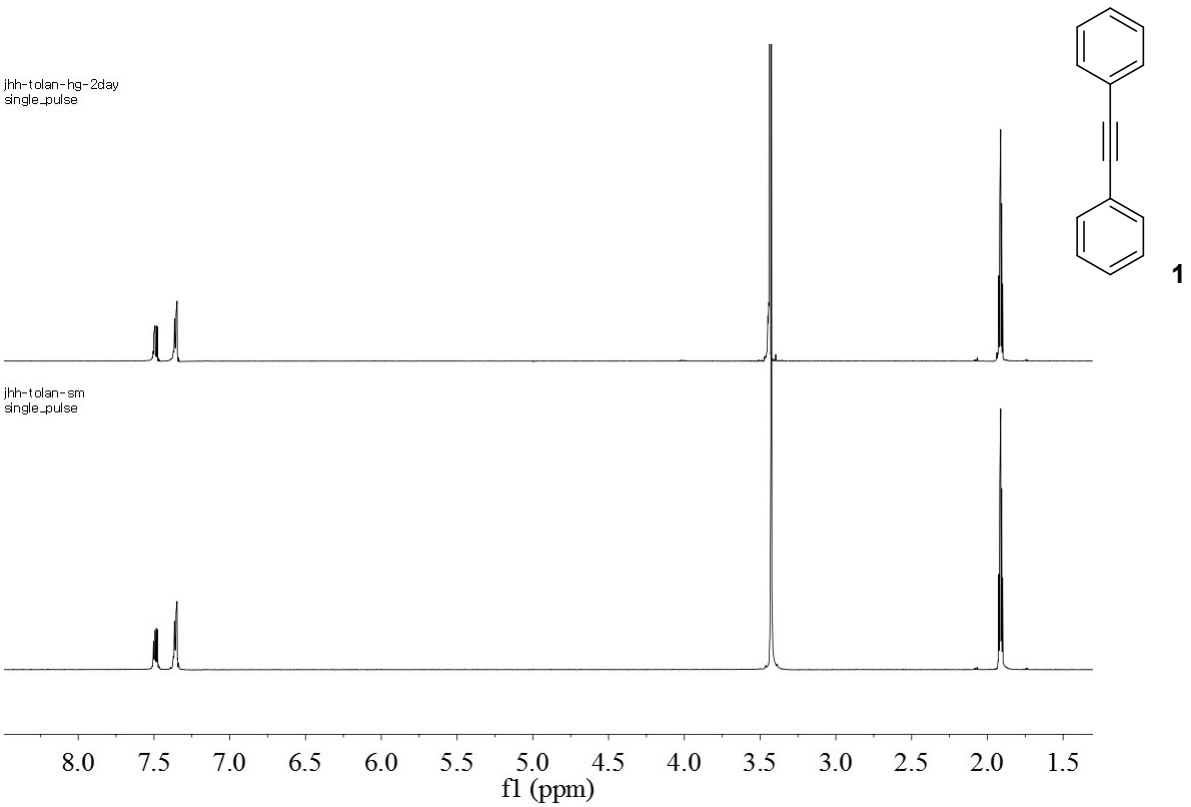


Figure S3. ^{1}H NMR spectra of **1** (2 mM in 20% D_2O containing CH_3CN-d3) recorded before and 48 h after the addition of 2 equiv of Hg(II).

Fluorescence studies of tolans

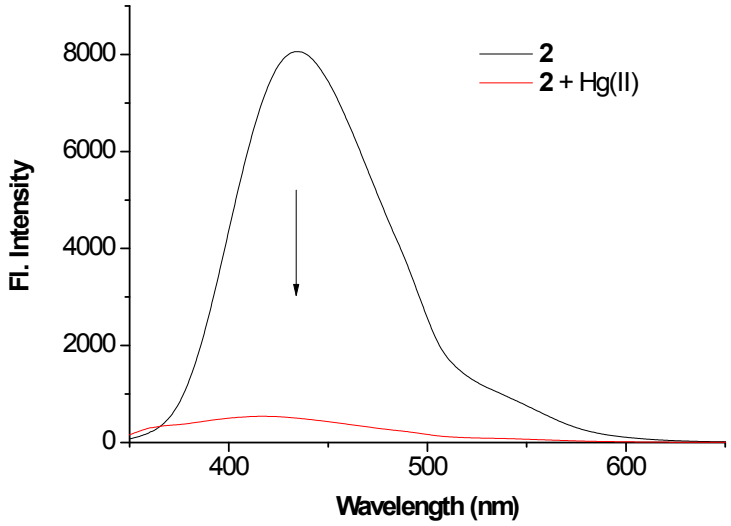


Figure S4. Fluorescence spectra of **2** (2 μM) and final diluted solution obtained from reaction depicted in Figure 1, excited at 323 nm at 25 °C.

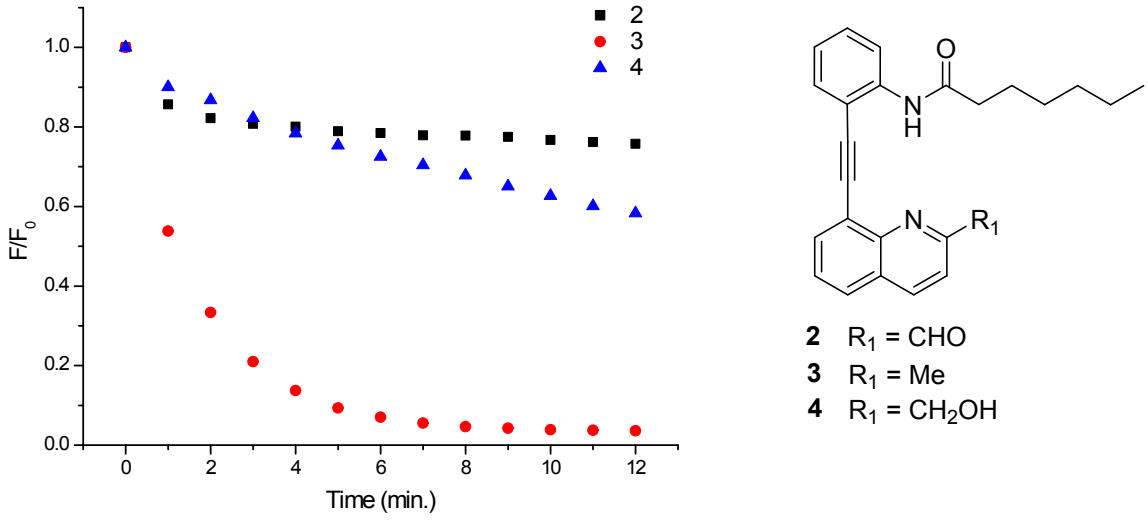


Figure S5. Plot of observed fluorescence ratio (F/F_0) of each tolan (2 μM) in CH_3CN/water (1:1, v/v) at 428 nm as a function of time (F_0: the emission intensity of each tolan, F: the emission intensity of each tolan in the presence of 2 equiv of Hg(II)).

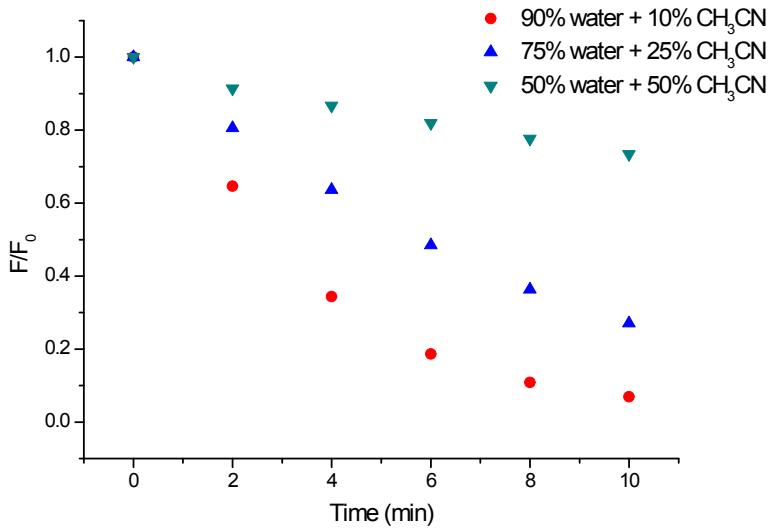


Figure S6. Plots of observed fluorescence ratio (F/F_0) of **3** (0.2 μM) at 428 nm as a function of time in various percentages of water and CH_3CN (v/v) (F_0: the emission intensity of each tolan, F: the emission intensity of **3** in the presence of 2 equiv of Hg(II)).

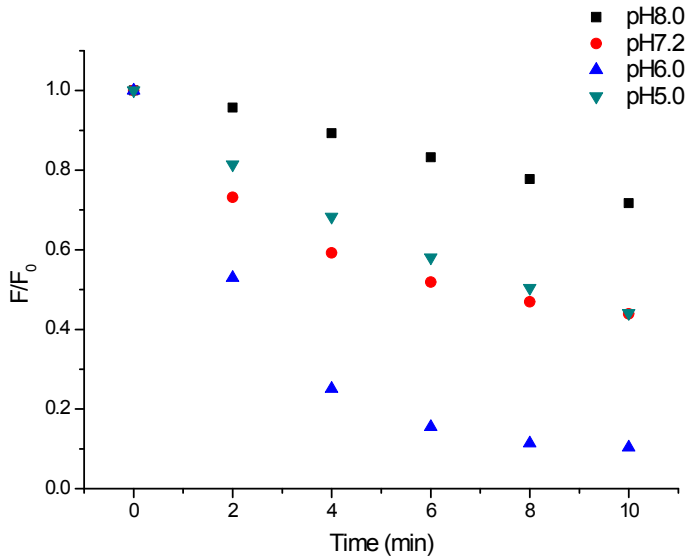
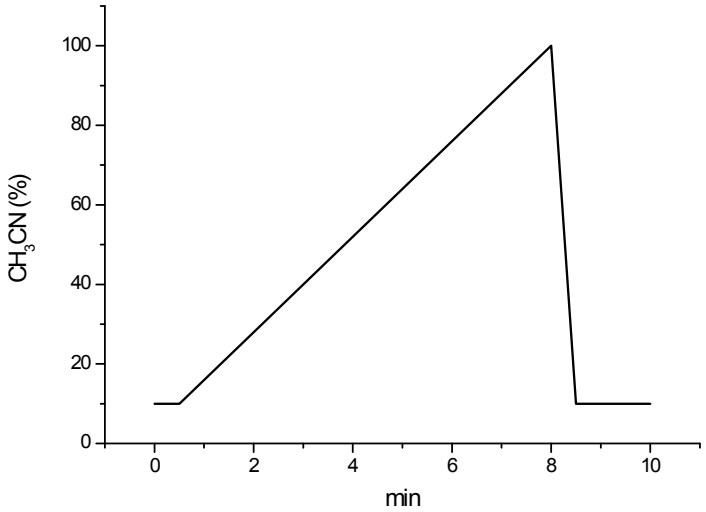


Figure S7. Plots of observed fluorescence ratio of **3** (0.2 μM) at 423nm as a function of time in various pH in 10 mM 90% HEPES buffer congaing CH_3CN (F_0: the emission intensity of each tolan, F: the emission intensity of **3** in the presence of 2 equiv of Hg(II)).

LC-MS Spectroscopy



All LC-MS spectra were generated by Shimadzu LCMS-2020 (column; Sim-pack GIS C18, CN (100 × 3.0 mm, 3 μm); mobile phase flow; 0.8000 mL/min; mobile phase conditions (gradient A:B = water (0.1%TFA):acetonitrile) as shown above).

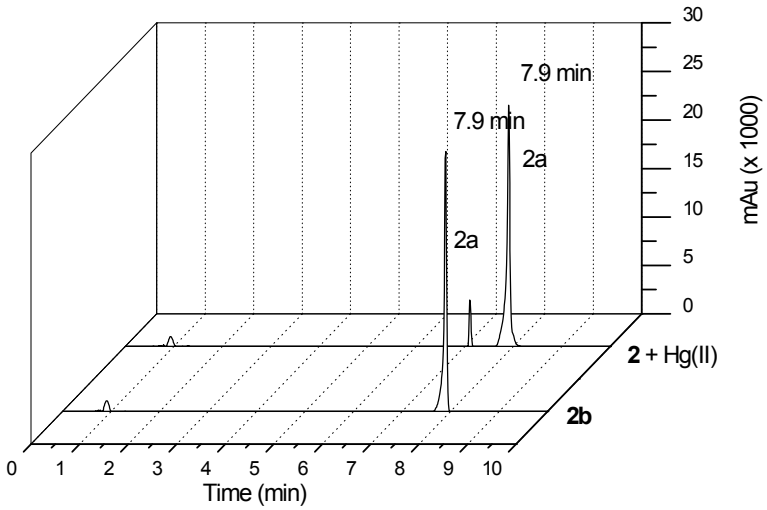


Figure S8. Obtained peak in the liquid chromatograms that undergo change upon the addition of Hg(II) (2 equiv) to a solution of indicator **2** (20 μM in CH_3CN-water (80:20, v/v) and resulted peak from pure **2b** (20 μM in CH_3CN-water (80:20, v/v) without Hg(II).

Stacked ^{1}H NMR spectra of 2, 2a, 2b, and crude sample (**2** + Hg(II))

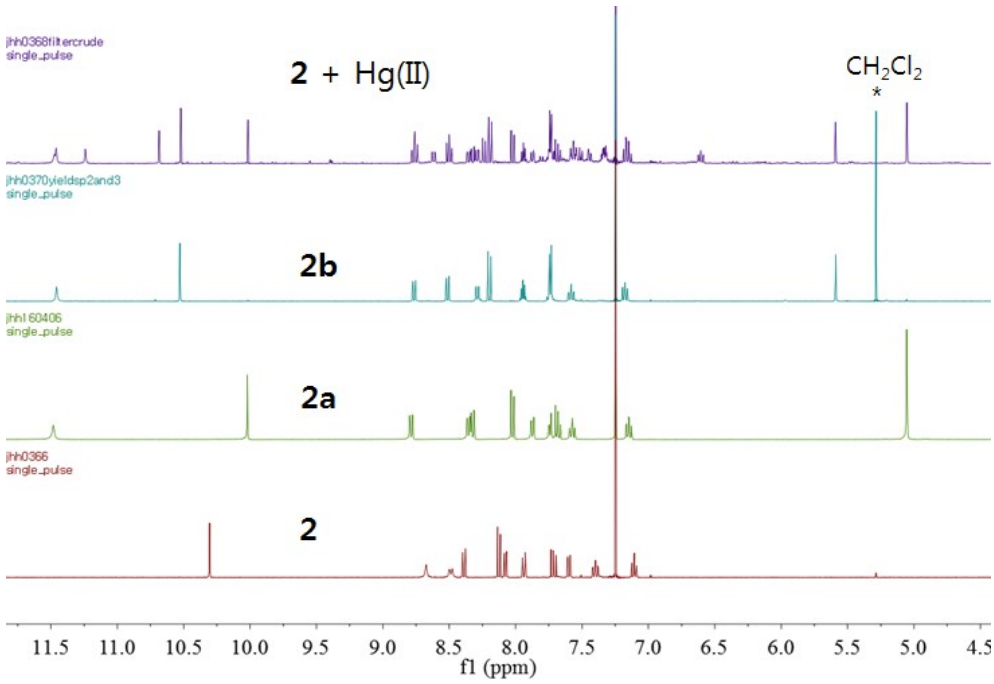


Figure S9. Stacked ^{1}H NMR spectra of **2**, **2a**, **2b**, and crude sample (**2** + Hg(II)) obtained after the hydration reaction for 10 min and extraction with CH_2Cl_2 in $CDCl_3$

X-ray structural data of 2b

Table S1. Crystal data and structure refinement for **2b**.

Identification code	**2b**
Empirical formula	$C_{25}H_{25}ClHgN_2O_3$
Formula weight	637.51
Temperature/K	296.15
Crystal system	triclinic
Space group	P-1
a/Å	9.4629(2)
b/Å	11.3500(2)
c/Å	12.3473(3)
α/°	103.8430(10)
β/°	109.6160(10)
γ/°	99.7450(10)
Volume/Å^3	1166.86(4)
Z	2
ρ_{calc}g/cm^3	1.814
μ/mm^{-1}	6.739
F(000)	620.0
Crystal size/mm^3	0.435 × 0.283 × 0.22
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.7 to 56.54
Index ranges	-12 ≤ h ≤ 12, -15 ≤ k ≤ 15, -16 ≤ l ≤ 16
Reflections collected	21104
Independent reflections	5748 [R_{int} = 0.0418, R_{sigma} = 0.0363]
Data/restraints/parameters	5748/0/291
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0250, wR_2 = 0.0589
Final R indexes [all data]	R_1 = 0.0259, wR_2 = 0.0593
Largest diff. peak/hole / e Å^{-3}	2.25/-1.39

Table S2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for y2. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Hg1	1149.55(12)	1721.74(9)	6479.58(9)	13.04(5)
Cl1	2120.4(10)	515.7(8)	5225.4(8)	23.80(17)
O3	801(3)	4798(2)	7761(2)	18.2(4)
O1	6961(3)	2476(3)	8154(2)	34.4(7)
O2	-1503(3)	6517(2)	4577(2)	22.9(5)
N2	-729(3)	5657(3)	6097(2)	17.5(5)
N1	3560(3)	2890(3)	8534(2)	14.5(5)
C21	1004(6)	8350(5)	7551(4)	50.4(14)
C19	-576(4)	6573(3)	5574(3)	17.9(6)
C1	5644(4)	2553(4)	7941(3)	23.4(7)
C14	-2823(4)	2438(3)	5733(3)	15.5(6)
C7	1322(4)	3125(3)	8982(3)	14.2(6)
C12	-147(3)	3748(3)	7233(3)	12.6(5)
C5	3931(4)	3754(3)	10635(3)	16.1(6)
C6	2958(4)	3257(3)	9376(3)	14.0(6)
C8	732(4)	3462(3)	9850(3)	19.4(6)
C22	2489(5)	9396(4)	8297(3)	31.4(8)
C17	-3371(4)	4351(3)	4751(3)	22.1(7)
C23	2617(9)	10171(6)	9502(5)	83(2)
C15	-4252(4)	2265(3)	4821(3)	21.4(7)
C3	6122(4)	3494(3)	10129(3)	19.9(6)
C13	-1636(3)	3562(3)	6189(3)	12.5(5)
C9	1692(4)	3954(3)	11095(3)	22.3(7)
C10	3267(4)	4115(3)	11488(3)	20.3(7)
C11	210(4)	2667(3)	7658(3)	13.1(6)
C16	-4525(4)	3230(3)	4345(3)	25.4(7)
C20	879(5)	7650(4)	6331(3)	30.7(9)
C4	5545(4)	3886(3)	10988(3)	19.5(6)
C18	-1916(4)	4529(3)	5661(3)	14.5(6)
C2	5077(4)	2999(3)	8908(3)	17.4(6)
C25	-2596(9)	-490(5)	8421(5)	67.0(18)
C24	-2305(10)	355(7)	-332(5)	81(2)

Synthetic experimental

Synthetic procedures for Unsymmetrical tolans

N-(2-((2-formylquinolin-8-yl)ethynyl)phenyl)heptanamide (2)

N-(2-ethynylphenyl)heptanamide (81 mg, 0.35 mmol), PPh_3(4.6 mg, 0.175 mmol), $Pd(PPh_3)_2Cl$ (12.4 mg, 0.018 mmol), and $Cu(OAc)_2$ (7 mg, 0.035 mmol) were added to a well-stirred solution of 8-iodoquinoline-2-carbaldehyde (100 mg, 0.35 mmol) in dry DMF (4 mL) and DIEA (0.24 mL, 1.40 mmol). The resulting mixture was heated at 65 °C for 3 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc/water. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue. The residue was purified over silica gel to afford **2** (68 mg, 53%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.52 (d, *J* = 0.9 Hz, 1H), 8.89 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.30 (dd, *J* = 7.2, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.93 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.82 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.62 (ddd, *J* = 8.8, 7.6, 1.5 Hz, 1H), 7.33 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.89 (tt, *J* = 7.7, 7,7 Hz, 2H), 1.50 – 1.39 (m, 2H), 1.39 – 1.24 (m, 4H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 193.03, 171.68, 152.89, 147.59, 139.79, 138.31, 134.30, 131.47, 130.40, 130.28, 128.96, 128.71, 124.01, 123.38, 119.83, 118.32, 112.05, 93.57, 92.18, 38.33, 31.49, 28.85, 25.56, 22.43, 13.99. HRMS–EI: m/z $[M]^+$ calcd for $C_{25}H_{24}N_2O_2$: 384.1838; found: 384.1837.

N-(2-((2-methylquinolin-8-yl)ethynyl)phenyl)heptanamide (3)

By following the general procedure, the reaction of 8-iodo-2-methylquinoline (100 mg, 0.37 mmol) yielded **3** (37 mg, 27%). To obtain the product, CuI was used instead of $Cu(OAc)_2$ due to Glazer reaction.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 9.25 (d, *J* = 8.3 Hz, 1H), 8.88 (d, *J* = 8.8 Hz, 1H), 8.73 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.28 (dd, *J* = 7.6, 7.6 Hz, 1H), 8.19 – 8.11 (m, 2H), 8.05 (d, *J* = 1.0 Hz, 1H), 7.87 (dd, *J* = 7.8 Hz, 1H), 3.60 (s, 3H), 3.25 (t, *J* = 7.6 Hz, 2H), 2.47 (tt, *J* = 7.6, 7.6 Hz, 2H), 2.16 – 1.98 (m, 2H), 1.98 – 1.84 (m, 4H), 1.54 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.83, 160.88, 148.56, 140.64, 137.55, 133.98, 131.90, 130.50, 129.42, 127.54, 126.21, 124.04, 123.64, 122.78, 120.74, 113.62, 95.56, 91.55, 38.91, 32.30, 29.69, 26.89, 26.43, 23.24, 14.79. HRMS–EI: m/z $[M]^+$ calcd for $C_{25}H_{26}N_2O$: 370.2045; found: 370.2042.

N-(2-((2-(hydroxymethyl)quinolin-8-yl)ethynyl)phenyl) heptanamide (4)

To a well-stirred solution of **3** (52 mg, 0.135 mmol) in MeOH (3.5 mL) was added $NaBH_4$(7.7 mg, 0.20 mmol). The reaction mixture was stirred at 0 °C for 0.5 h. After the reaction mixture was quenched by adding one drop of water, MeOH was removed. The residue was extracted with Et_2O/EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue. The residue was purified over silica gel to afford **4** (45 mg, 87%).

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.61 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 7.1, 1.5 Hz, 1H), 7.95 (dd, J = 8.2, 1.4 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.39 (ddd, J = 8.6, 7.7, 1.3 Hz, 1H), 7.13 (ddd, J = 7.7, 7,7, 0.9 Hz, 1H), 4.88 (d, J = 5.3 Hz, 2H), 4.07 (t, J = 5.4 Hz, 1H), 2.39 (t, J = 7.5 Hz, 2H), 1.59 (tt, J = 7.6 Hz, 2H), 1.25 – 1.77(m, 2H), 1.17 – 1.01 (m, 4H), 0.72 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 172.89, 163.28, 147.59, 140.74, 138.47, 134.60, 132.43, 130.63, 130.22, 128.73, 126.96, 124.60, 122.63, 121.40, 120.81, 114.17, 95.25, 91.16, 65.96, 38.38, 32.26, 29.55, 26.34, 23.18, 14.31. HRMS–EI: m/z [M]$^+$ calcd for $C_{25}H_{26}N_2O_2$: 386.1994; found: 386,1997.

Synthetic procedures for ketones with Hg(II)

N-(2-(2-(2-formylquinolin-8-yl)acetyl)phenyl)heptanamide (2a)

To a well-stirred solution of **2** (20 mg, 0.052 mmol) in CH_3CN/water (20 mL/4 mL) was added $HgCl_2$ (28 mg, 0.104 mmol). The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was poured into H_2O, and the product was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue. To obtain **2a** without **2b**, the same crude was dissolved in DCM (4 mL) and then 0.42 mL of HCl (1.25 M in MeOH, 0.52 mmol) was added to the solution. The reaction was stirred for 10 min. The residue was purified over preparative TLC to afford **2a** (17 mg, 82%).

^{1}H NMR (400 MHz, Chloroform-d) δ 11.48 (s, 1H), 10.02 (d, J = 0.9 Hz, 1H), 8.79 (dd, J = 8.5, 1.2 Hz, 1H), 8.35 (dd, J = 8.1, 1.6 Hz, 1H), 8.32 (dd, J = 8.4, 0.9 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.87 (dd, J = 8.1, 1.6 Hz, 1H), 7.74 (dd, J = 7.1, 1.6 Hz, 1H), 7.68 (dd, J = 8.1, 7.1 Hz, 1H), 7.57 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.15 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 5.05 (s, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.64 (tt, J = 7.6, 7.6 Hz, 2H), 1.35 – 1.15 (m, 4H), 0.82 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 202.71, 193.68, 172.82, 151.96, 146.16, 141.41, 137.91, 135.76, 135.22, 131.82, 131.39, 130.41, 129.13, 127.54, 122.35, 121.84, 121.07, 117.49, 42.31, 38.74, 31.54, 28.89, 25.51, 22.53, 14.07. HRMS–FAB: m/z [M + H]$^+$ calcd for $C_{25}H_{27}N_2O_3$: 403.2022; found: 403.2024.

(1-(2-formylquinolin-8-yl)-2-(2-heptanamidophenyl)-2-oxoethyl)mercury(II) chloride (2b)

The residue obtained from the reaction of **2** with $HgCl_2$ was directly purified by preparative TLC, which afforded **2a** (2.7 mg, 13%) and **2b** (21.8 mg 66%).

^{1}H NMR (400 MHz, Chloroform-d) δ 11.46 (s, 1H), 10.53 (d, J = 0.9 Hz, 1H), 8.76 (dd, J = 8.5, 1.2 Hz, 1H), 8.51 (dd, J = 8.4, 0.9 Hz, 1H), 8.29 (dd, J = 8.2, 1.6 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 5.3, 4.4 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.58 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 7.18 (ddd, J = 8.1, 7.3, 1.3 Hz, 1H), 5.59 (d, J = 0.5 Hz, 1H), 2.28 (td, J = 7.5, 1.5 Hz, 2H), 1.63 (tt, J = 7.5, 7.5 Hz, 2H), 1.32 – 1.13 (m, 6H), 0.80 (t, J = 6.8 Hz, 3H). HRMS–ESI: m/z [M – Cl$^-$]$^+$ calcd for $C_{50}H_{50}ClHg_2N4O_6$: 1239.2808; found: 1239.2800.

N-(2-(2-(2-methylquinolin-8-yl)acetyl)phenyl)heptanamide (**3a**)

By following the procedure of **2a**, the reaction of **3** (20 mg, 0.054 mmol) yielded **3a** (11.1 mg, 53%).

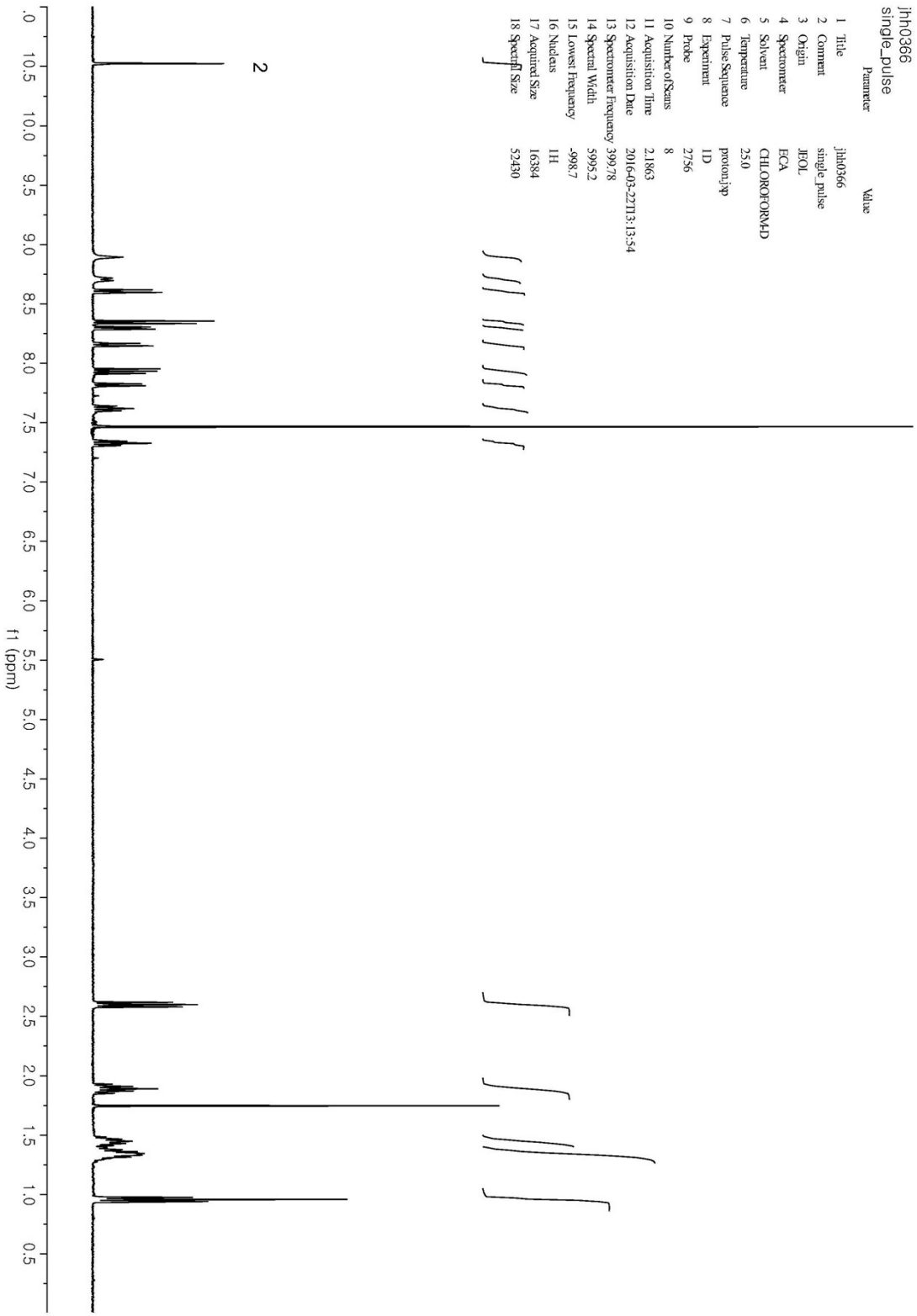
^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.55 (s, 1H), 8.74 (d, *J* = 8.7 Hz, 1H), 8.35 (d, *J* = 9.6 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.52 (ddd, *J* = 8.6, 7.8, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.09 (ddd, *J* = 8.3, 7.4, 1.3 Hz, 1H), 4.91 (s, 2H), 2.60 (s, 3H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.65 (tt, *J* = 7.6 Hz, 2H), 1.33 – 1.16 (m, 6H), 0.84 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 203.86, 172.92, 158.55, 145.89, 141.22, 136.54, 134.78, 134.02, 131.80, 130.60, 127.32, 126.84, 125.58, 122.68, 122.36, 122.24, 120.99, 42.70, 38.88, 31.71, 29.07, 25.71, 25.52, 22.69, 14.23. HRMS–EI: m/z $[M]^+$ calcd for $C_{25}H_{28}N_2O_2$: 388.2151; found: 388.2153.

N-(2-(2-(2-(hydroxymethyl)quinolin-8-yl)acetyl)phenyl)heptanamid (**4a**)

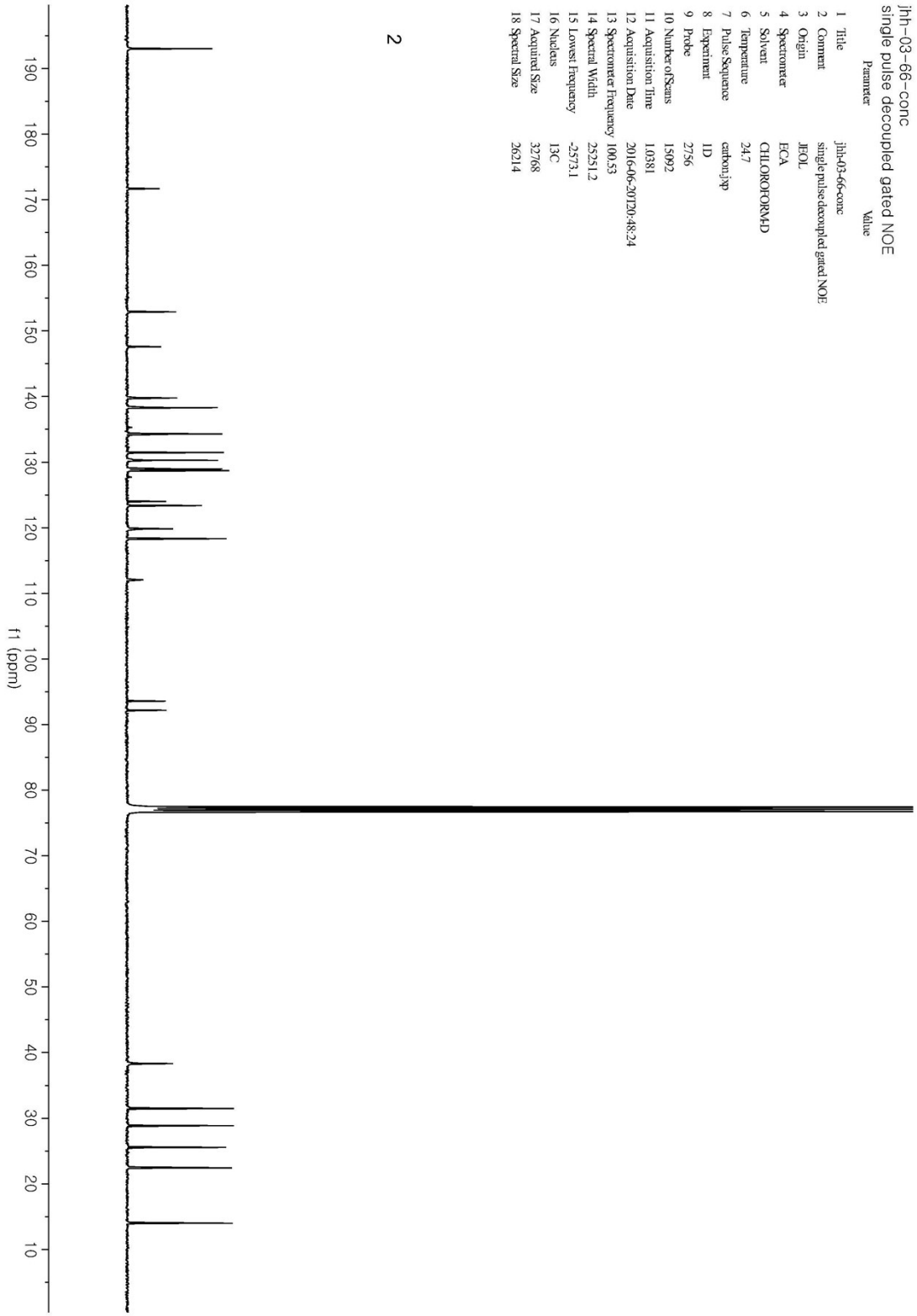
By following the procedure of **2a**, the reaction of **4** (20 mg, 0.052 mmol) yielded **4a** (9.8 mg, 47%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.50 (s, 1H), 8.76 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.6, 1.1 Hz, 1H), 4.92 (s, 2H), 4.82 (s, 2H), 3.98 (s, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.65 (tt, *J* = 7.6 Hz, 2H), 1.36 – 1.17 (m, 6H), 0.83 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 203.04, 172.90, 158.62, 144.81, 141.43, 137.41, 135.18, 133.74, 131.34, 131.04, 127.86, 127.53, 126.32, 122.37, 121.71, 121.17, 118.58, 64.29, 42.97, 38.71, 31.58, 28.92, 25.50, 22.55, 14.09. HRMS–EI: m/z $[M]^+$ calcd for $C_{25}H_{28}N_2O_3$: 404.2100; found: 404.2098.

NMR Spectra



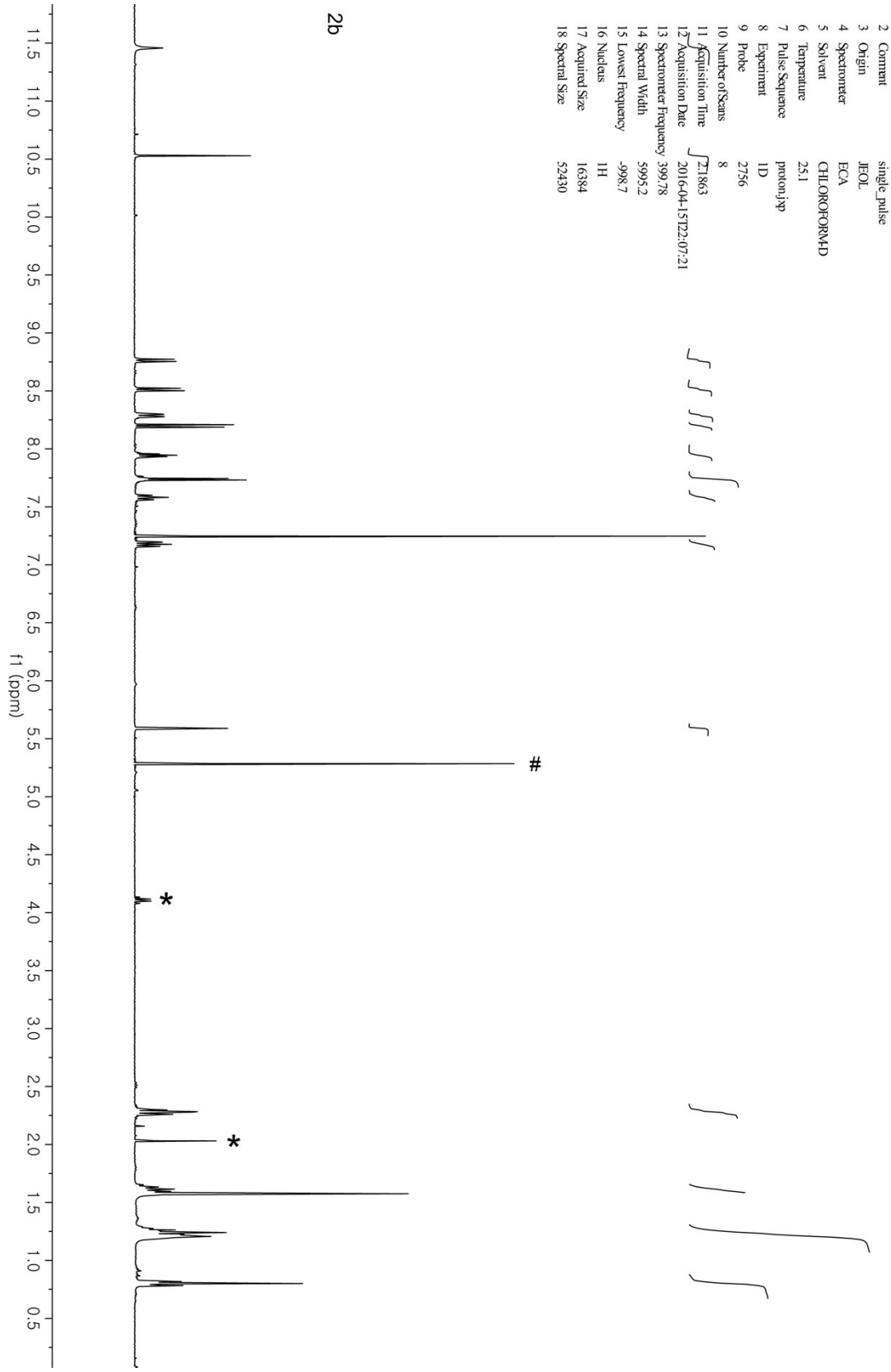
^{1}H NMR spectrum of **2** recorded in $CDCl_3$



^{13}C NMR spectrum of **2** recorded in $CDCl_3$

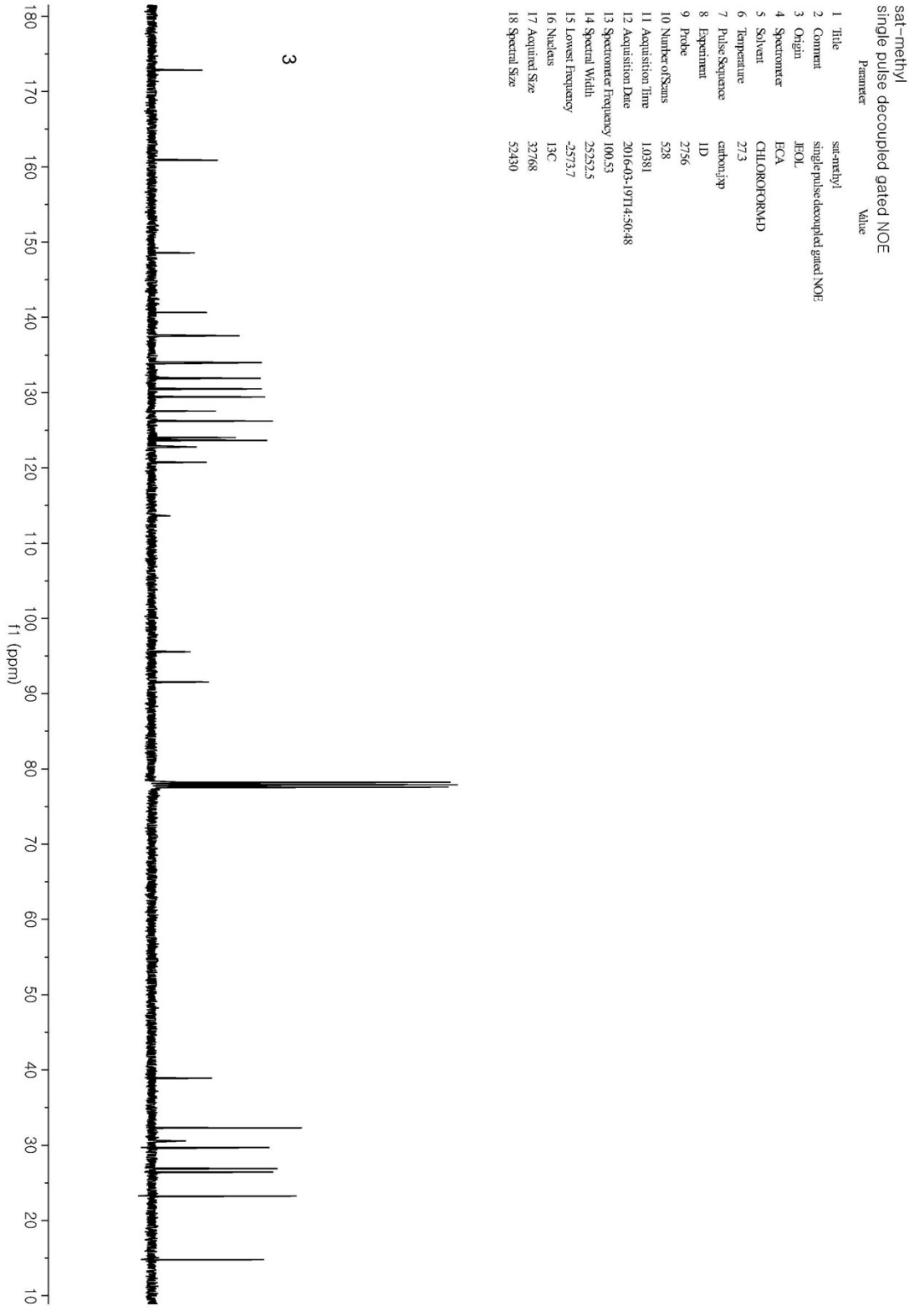
^{1}H NMR spectrum of **2a** recorded in $CDCl_3$

^{13}C NMR spectrum of **2a** recorded in $CDCl_3$

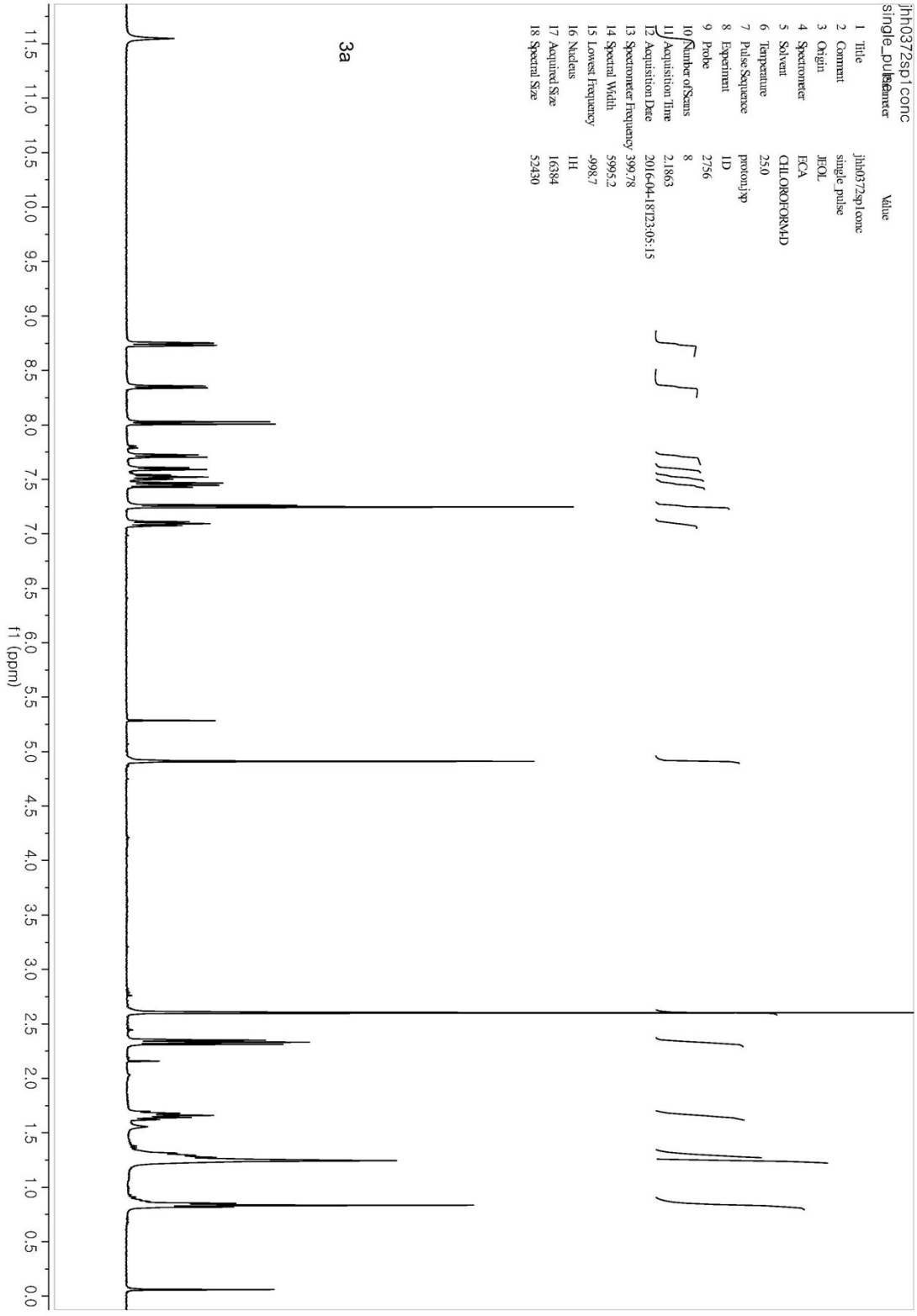


^{1}H NMR spectrum of **2b** recorded in $CDCl_3$ (#:CH2Cl2, *:EtOAc)

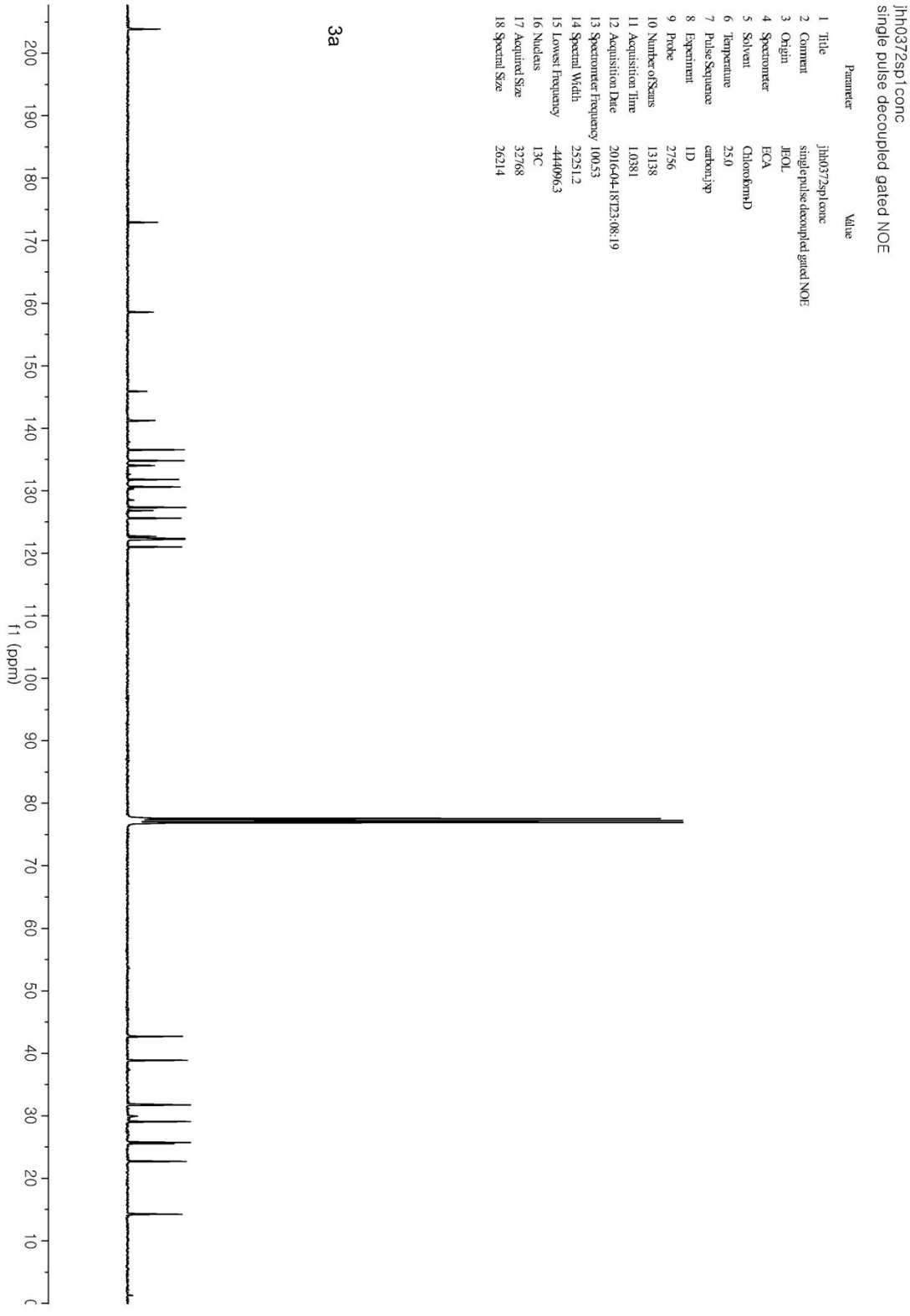
^{1}H NMR spectrum of **3** recorded in $CDCl_3$



^{13}C NMR spectrum of **3** recorded in $CDCl_3$

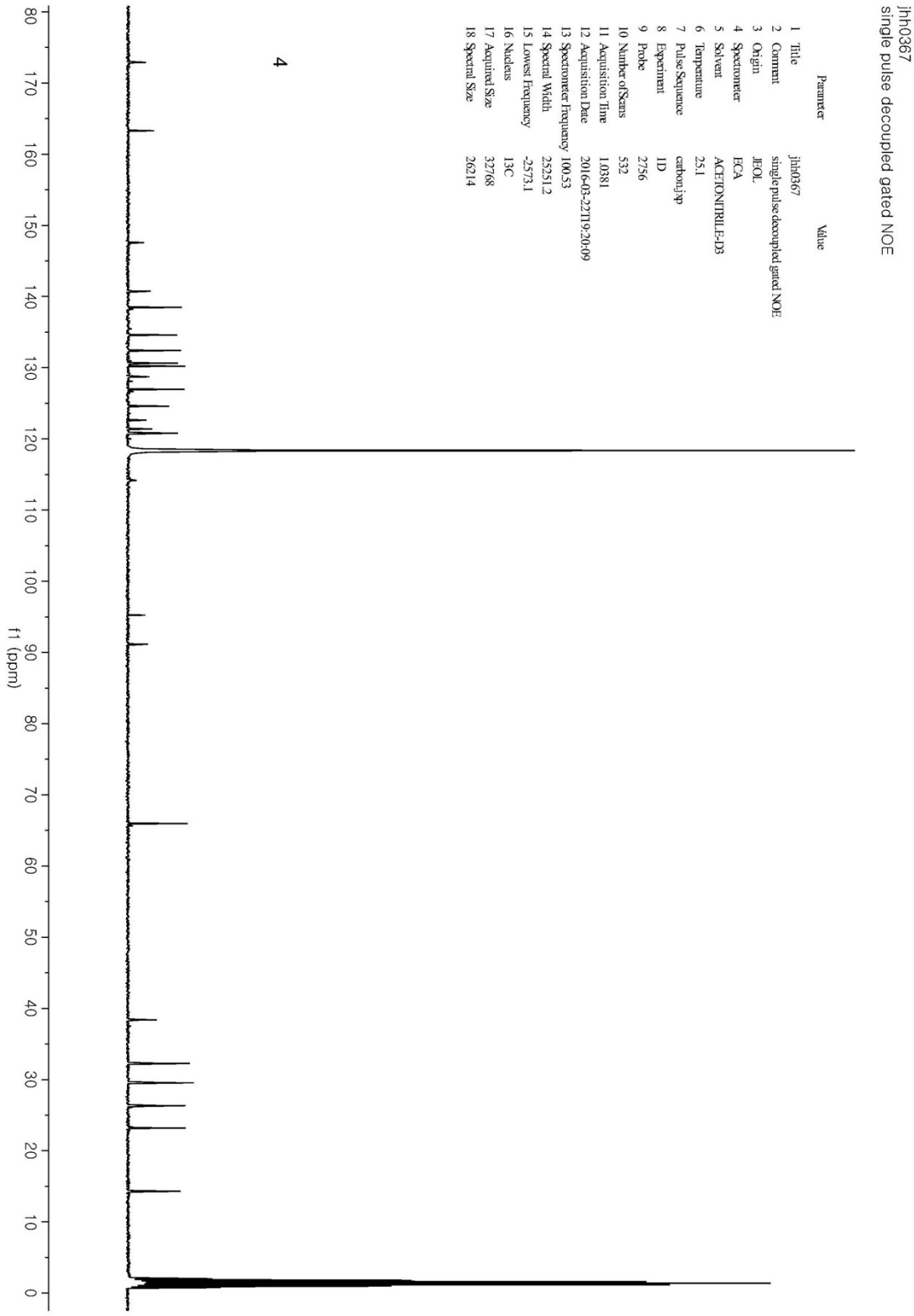


^{1}H NMR spectrum of **3a** recorded in $CDCl_3$

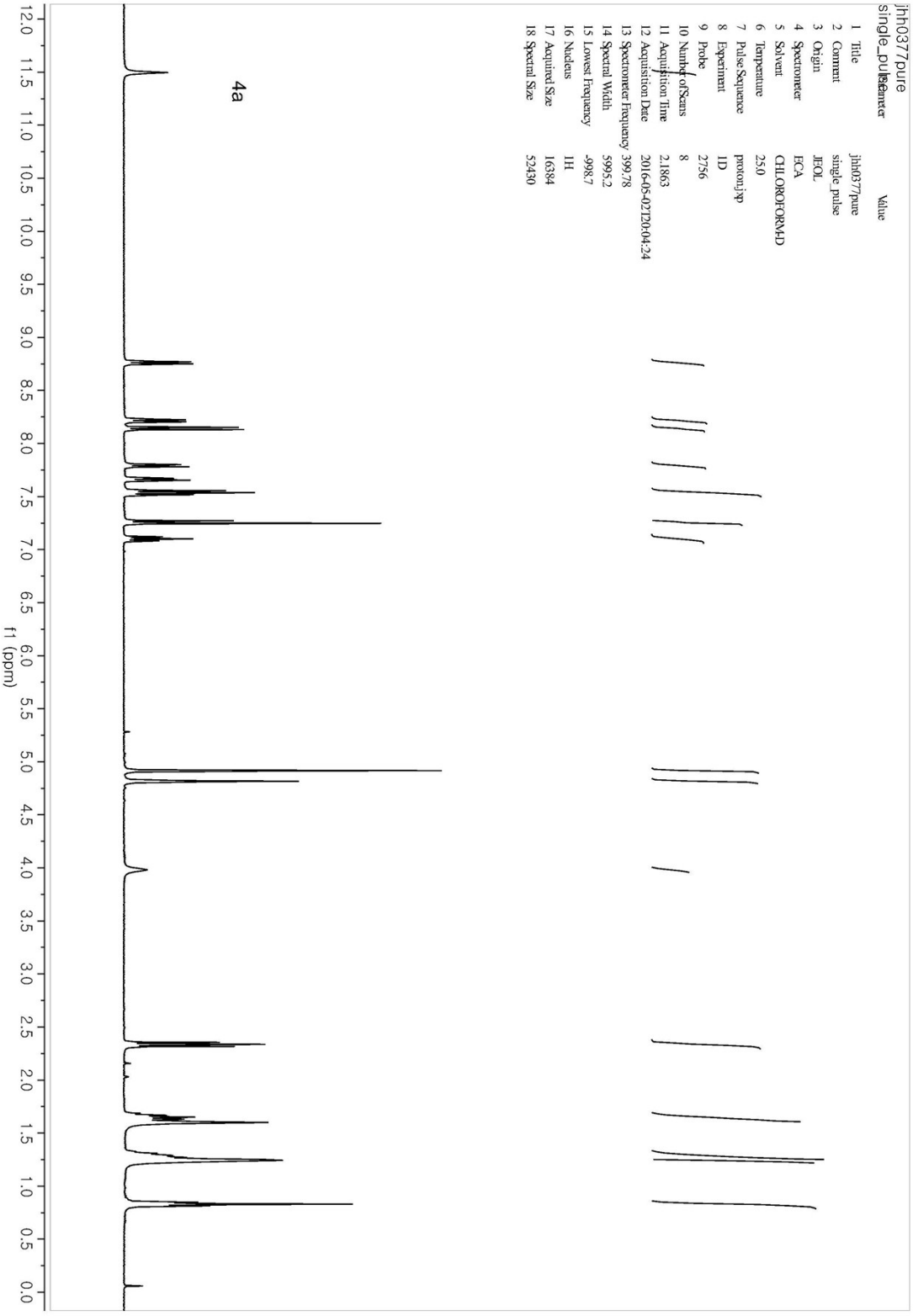


^{13}C NMR spectrum of **3a** recorded in $CDCl_3$

^{1}H NMR spectrum of **4** recorded in CD_3CN



^{13}C NMR spectrum of **4** recorded in CD_3CN



^{1}H NMR spectrum of **4a** recorded in $CDCl_3$

^{13}C NMR spectrum of **4a** recorded in $CDCl_3$