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Identification of Benzochromen derivatives as a highly specific Nor A efflux pump inhibitor to mitigate drug resistant strains of *S.aureus*

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Experimental Section

General

All the chemicals were purchased from Sigma Aldrich, Loba chemicals, Merck, Avra synthesis, and SD Fine chemicals and all used without any other further purification. Melting points were taken in the microscopic melting point meter and were uncorrected. Subsequently ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) were recoreded by a Bruker Av-300MHz spectrometer. ^{13}C-NMR (100 MHz) for cyclic ketone derivatives were recorded by a Bruker 400MHz spectrometer. All the reactions were conducted to the 10 ML round bottom flask with a magnetic stirrer. Both PEI-Bz and PEI-Me are prepared by previously reported procedure.[1] Hyperbranched polyamine with number average molecular weight (M_n) 1200 was chosen for studies. The number of primary (1^o), secondary (2^o), tertiary (3^o) amine group present in the hyperbranched polyamine is calculate based on inverted-gate ^{13}C-NMR spectroscopy as shown below (Figure S1).

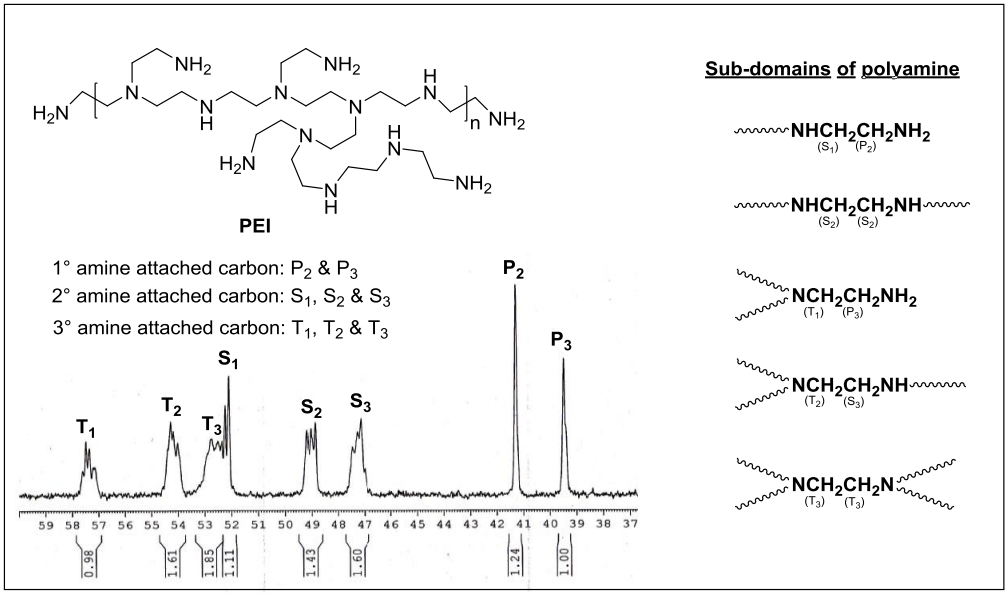


Figure S1: Sub-domains in Polyamine and the corresponding NMR signals

$1° : 2° : 3° = I_{(P_2+P_3)} : I_{(S_1+S_2+S_3)}/2 : I_{(T_1+T_2+T_3)}/3$

$= 2.24 : 2.07 : 1.48$

Polyamine = $\{[(CH_2)NH_2]_{2.24}[(CH_2)_2NH]_{2.07}[(CH_2)_3N)]_{1.48}\}_n$

Average Empirical Wt = mass of $[(CH_2)NH_2]$ x 2.24 +
mass of $[(CH_2)_2NH]$ x 2.07 +
mass of $[(CH_2)_3N]$ x 1.48

$= 30.03(2.24) + 43.04(2.07) + 56.05(1.48)$

$= 239.3$

Average Molecular Wt = 1200

Multiplication factor = 1200/239.3

$= 5.015$

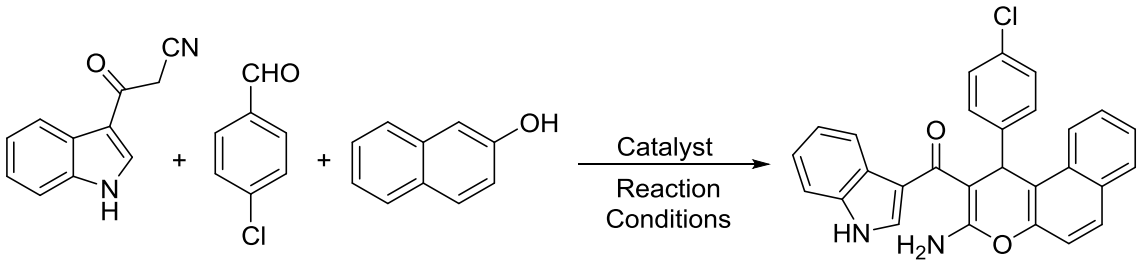
Average number of 1° amine = 2.24 x 5.015 = 11.23
Average number of 2° amine = 2.07 x 5.015 = 10.38
Average number of 3° amine = 1.48 x 5.015 = 7.42

Chart S1: Calculation of number of amine functionalities

The ratio of 1°, 2° and 3° amine functionalities in PEI is calculated from the peak intensities of inverted-gate ^{13}C NMR and the obtained value for the ratio of 1°, 2° and 3° amine is 2.24:2.07:1.48 (Chart S1).[2] Based on the ratio of three different amine functionalities, we have deduced the number of amine moieties present in the hyperbranched polyamines (Chart S1). The whole polyamine molecule can be sub-grouped to $(CH_2)NH_2$, $(CH_2)_2NH$ and $(CH_2)_3N)$ units. A molecular formula of $\{[(CH_2)NH_2]x[(CH_2)_2NH]y[(CH_2)_3N)]z\}n$ defines the whole polymer molecule. The values x, y and z are the ratio of 1°, 2° and 3° amine functionalities, respectively and n being an arbitrary value. Based on NMR peak intensities of inverted-gate ^{13}C NMR, an empirical formula of $[(CH_2)NH_2]_{2.24}[(CH_2)_2NH]_{2.07}[(CH_2)_3NH)]_{1.48}$ is deduced. The average empirical weight is 239.3 (calculated from the empirical formula). The average molecular weight of hyperbranched polyamine chosen is 1200, hence the multiplication factor value (n) is 5.015. Multiplying the ratio of 1°, 2° and 3° amine functionality with multiplication factor gives the number of three types of amine functionalities (1°, 2° and 3°) as 11.23, 10.38 and 7.42 respectively.

The screening of reaction conditions for the synthesis of benzochromenes was given in the following table. The PEI-Me exhibited excellent catalytic potential compared to other polyamine derivatives.

Table S1: Optimization of reaction condition for benzochromenes derivatives[a]

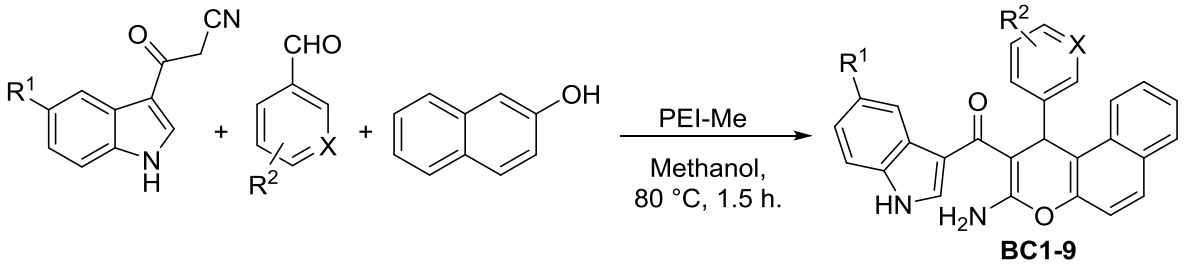


Entry	Catalyst	Solvent (ml)	Temp.(°C)	Time (h)	Yield (%)[b]
1[c]	PEI-Me	EtOH	80	3.0	46
2[c]	PEI-Me	MeOH	r.t.	24	No reaction
3[c]	PEI-Me	MeOH	60	7.0	67
4[c]	**PEI-Me**	**MeOH**	**80**	**1.5**	**90**
5[c]	PEI-Me	THF	80	1.5	30
6[c]	PEI-Me	CH_3CN	80	1.5	42
7[c]	PEI-Me	1,4-dioxane	80	1.5	Traces
8[c]	PEI-Me	1,2-DCE	80	1.5	35
9[c]	PEI-Me	DCM	80	1.5	28
10[c]	PEI-Me	DMF	80	1.5	53
11[c]	PEI-Bz	MeOH	80	1.5	76
12[c]	PEI	MeOH	80	1.5	Traces
13[d]	Piperidine	MeOH	80	1.5	53
14[d]	Pyridine	MeOH	80	1.5	49
15[d]	DBU	MeOH	80	1.5	68
15[d]	K_2CO_3	MeOH	80	1.5	Traces
16[d]	Cs_2CO_3	MeOH	80	1.5	Traces

[a]All the reaction were carried out 1 mmol 3-cyanoacetyl indole, 1 mmol naphthol and 1 mmol 4-chlorobenzaldehyde in 3 ml of various solvents and catalysts
[b]Isolated yield
[c]50 mg of catalyst was used

[d]0.5 mmol of catalyst was used
PEI = Polyamine

General procedure for the synthesis of benzochromenes (BC1-9): A mixture of substituted aldehyde (1 mmol), Substituted 3-cyanoacetyl indole (1 mmol) and 2-naphthol (1 mmol) containing PEI-Me catalyst (50 mg) were taken in the 5 ml of methanol and it was stirred at 80°C in appropriate time. The progress of the reaction was monitored through thin layer chromatography (TLC) using methanol and Chloroform (1:9) as eluent mixture. After completion, the reaction mixture was cooled to room temperature and the solid obtained was filtered through the Whatman filter paper and washed with cold ethanol. The product thus obtained was in essentially pure form.



1-(4-chlorophenyl)-2-(1*H*-indole-3-carbonyl)-1*H*-benzo[*f*]chromen-3-amine (BC1)

Yield: 89%; Appearance: white solid; mp = 220-222 °C (220–222 °C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.13 (s, 1H), 6.67 (d, 2H, *J* = 8.4 Hz), 6.96 (t, 1H, *J* = 7.8 Hz), 7.16–7.26 (m,3H), 7.44–7.60 (m, 5H), 7.71 (t, 1H, *J* = 5.7 Hz), 7.79 (d, 1H, *J* = 2.4 Hz), 7.98 (d, 2H, *J* = 9.0 Hz), 8.78 (s, 2H), 11.68 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 36.9, 88.9, 112.2, 116.8, 117.5, 119.1, 119.6, 120.2, 120.3, 121.9, 122.7, 124.9, 125.2, 127.2, 128.4, 128.6, 128.7, 129.0, 130.0, 130.8, 131.3, 135.9, 145.9, 147.1, 161.8, 187.5.

1-(4-bromophenyl)-2-(1*H*-indole-3-carbonyl)-1*H*-benzo[*f*]chromen-3-amine (BC2)

Yield: 86%; Appearance: white solid; mp = 221-223 °C (220–222 °C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.15 (s, 1H), 6.73 (d, 2H, *J* = 7.8 Hz), 6.96 (t,1H, *J* = 7.5 Hz), 7.10–7.21 (m,3H), 7.44–7.60 (m, 5H), 7.71 (t, 1H, *J* = 4.5 Hz), 7.78 (s, 1H), 7.97 (d, 2H, *J* = 8.4 Hz), 8.77 (s, 2H), 11.67 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 36.8, 88.9, 112.1, 116.7, 117.5, 119.6, 120.2, 120.3, 121.9, 122.7, 124.9, 125.2, 127.2, 128.1, 128.3, 128.7, 129.0, 130.0, 130.6, 130.8, 135.9, 145.5, 147.1, 161.8, 187.4.

2-(1*H*-indole-3-carbonyl)-1-(3-nitrophenyl)-1*H*-benzo[*f*]chromen-3-aminen (BC3)

Yield: 84%; Appearance: Yellow solid; mp = 212-214 °C (213–215°C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.27 (s, 1H), 6.96 (t, 1H, *J* = 7.8 Hz), 7.17 (q, 2H, *J* = 7.8 Hz), 7.35 (t, 1H, *J* = 8.1 Hz), 7.44–7.56 (m, 6H), 7.70 (t, 1H, *J* = 5.4 Hz), 7.81 (d, 1H, *J* = 2.4 Hz), 7.85 (d, 1H, *J* = 1.8 Hz), 7.88 (s,

1H, *J* = 2.1Hz), 7.97-8.04 (m, 2H), 8.82 (s, 2H),11.72 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, $CDCl_3$ δ ppm); 36.8, 89.0, 111.6, 116.1, 117.9, 118.1, 119.5, 120.2, 120.3, 120.9, 121.6, 122.1, 123.9,124.3, 126.5, 127.17, 127.9, 128.5, 128.6, 129.8, 130.5, 132.4, 135.6, 147.0, 147.3, 147.9, 161.4, 187.9.

1-(2,4-dichlorophenyl)-2-(1*H*-indole-3-carbonyl)-1*H*-benzo[*f*]chromen-3-amine (BC4)

Yield: 91%; Appearance: white solid; mp = 229-232 °C (229–230°C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.41 (s, 1H), 6.85-6.94 (m, 2H), 7.14 (t, 2H, *J* = 7.5 Hz), 7.23 (d, 1H, *J* = 1.8 Hz), 7.98 (t, 2H, *J* = 9 Hz), 8.55 (s, 2H), 11.63 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); ^{13}C-NMR (75 MHz, DMSO, -d6, δ ppm); 34.9, 88.6, 112.0, 116.9, 118.1, 119.3, 119.6, 120.2, 121.7, 122.4, 125.0, 125.4, 127.2, 127.9, 128.6, 128.7, 128.9, 129.3, 130.2, 130.7, 130.9, 131.3, 136.0, 143.7, 147.2, 160.9, 187.9.

2-(1*H*-indole-3-carbonyl)-1-(3-methoxyphenyl)-1*H*-benzo[*f*]chromen-3-amine (BC5)

Yield: 83%; Appearance: white solid; mp = 229-232°C (228–230°C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 3.43 (s, 3H), 6.13-6.31 (m, 3H,), 6.56 (s, 1H), 6.96-7.96 (m, 12H), 8.77 (s, 2H),7.44–7.56 (m, 6H), 11.66 (s, 1H). ^{13}C-NMR (75 MHz, DMSO, δ ppm); ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 37.2, 89.2, 110.9, 112.1, 112.4, 116.7, 117.6, 118.5, 120.0, 120.3, 121.9, 122.8, 124.8, 125.3, 127.0, 128.2, 128.6, 128.8, 129.5, 130.2, 130.8, 135.9, 147.2, 148.1, 159.0, 161.9, 187.5.

2-(5-bromo-1*H*-indole-3-carbonyl)-1-(naphthalen-2-yl)-1*H*-benzo[*f*]chromen-3-amine (BC6)

Yield: 78%; Appearance: pale brown solid; mp = 255-257°C (256–258°C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.27 (s, 1H), 7.06 (d, 1H, *J* = 9.9 Hz), 7.16 (s, 1H), 7.28-7.38 (m, 3H), 7.43–7.53 (m, 5H), 7.64 (d, 1H, *J* = 8.7 Hz), 7.68-7.74 (m, 2H), 7.97 (t, 4H, *J* = 9.0 Hz), 8.83 (s, 2H), 11.85 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 37.5, 88.9, 113.1, 114.0, 116.7, 116.9, 119.9, 122.6, 122.8, 124.2, 124.5, 124.9, 125.2, 125.6, 126.1, 127.2, 127.4, 127.5, 128.3, 128.6, 128.9, 129.6, 130.2, 130.8, 131.5, 132.6, 134.6, 143.8, 147. 1, 162.1, 186.8.

2-(5-bromo-1*H*-indole-3-carbonyl)-1-(4-chlorophenyl)-1*H*-benzo[*f*]chromen-3-amine (BC7)

Yield: 88%; Appearance: white solid; mp = 230-232 °C (231–233 °C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.10 (s, 1H), 6.82 (d, 2H, *J* = 8.4 Hz), 7.13(d, 2H, *J* = 8.4 Hz), 7.29 (dd,1H, *J* = 8.7 Hz, *J* = 1.8 Hz), 7.43–7.55 (m, 4H), 7.76 (d, 1H, *J* = 1.5 Hz), 7.87 (d, 1H, *J* = 8.1 Hz), 7.98 (t, 3H, *J* = 9.9 Hz), 8.82 (s, 2H), 11.87 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm);34.8, 88.5, 113.1, 113.9, 116.9, 117.3, 119.7, 121.8, 122.2, 124.2, 125.0, 127.4, 128.2, 128.7, 129.4, 130.1, 130.4, 130.7, 131.2, 131.4, 134.7, 143.5, 147.2, 161.2, 187.0.

2-**(5-bromo-1*H*-indole-3-carbonyl)-1-(2,4-dichlorophenyl)-*1H*-benzo[*f*]chromen-3-amine (BC8)**

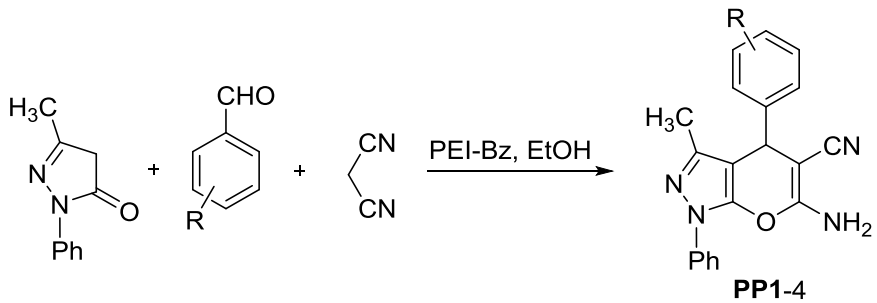
Yield: 86%; Appearance: white solid; mp = 229-232 °C (228–230 °C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.38 (s, 1H), 6.97 (d, 1H, *J* = 8.7 Hz), 7.16-7.28 (m, 3H), 7.44–7.52 (m,5H), 7.77 (d, 1H,

J = 6.0 Hz), 7.87 (s, 1H), 7.99-8.02 (m, 2H), 8.57 (s, 2H), 11.82 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 36.7, 88.7, 113. 2, 114.1, 116.6, 116.7, 119.7, 122.7, 124.4, 124.9, 127.4, 127.51, 128.2, 128.4, 128.7, 129.0, 129.7, 129.9, 130.7, 130.79, 134.6, 145.3, 147.0, 162.2, 186.6.

2-(5-bromo-1*H*-indole-3-carbonyl)-1-(pyridin-3-yl)-1*H*-benzo[*f*]chromen-3-amine (BC9)

Yield: 90%; Appearance: white solid; mp = 249–251°C (248–251°C)[3]; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 6.16 (s, 1H), 7.09- 7.13(m, 1H), 7.17-7.21 (m, 1H), 7.29 (dd, 1H, *J* = 8.4 Hz, 1.8 Hz), 7.44–7.56 (m, 4H), 7.75 (d, 1H, *J* = 1.8 Hz), 7.90 (d, 1H, *J* = 8.1Hz), 7.98-8.01 (m, 4H), 8.20 (dd, 1H, *J* = 4.8 Hz, 1.5 Hz), 8.85 (s, 2H), 11.85 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d6, δ ppm); 35.1, 88.3, 113.2, 114.0, 116.5, 116.7, 119.0, 122.6, 122.7, 123.8, 124.5, 124.9, 127.5, 127.6, 128.7, 129.2, 129.6, 129.9, 130.8, 133.9, 134.6, 141.8, 147.0, 147.3, 147.5, 162.1, 186.6.

General procedure for the synthesis of pyranopyrazoles (PP 1-4). A mixture of aromatic substituted aldehyde (1 mmol), 3-methyl-1-phenyl-2-pyrazoline-5-one (174.20 mg, 1mmol), malononitrile(66mg, 1 mmol) and PEI-Bz (50 mg) were taken in the 3 ml of ethanol and was stirred at 80 °C for 45 min to 1 h. The progress of the reaction was monitored through thin layer chromatography (TLC) using chloroform and methanol (9:1) as eluent mixture. After completion, the reaction mixture was cooled to room temperature and the reaction was quenched with distilled water (5 mL) followed by extracted with ethyl acetate (2×5 mL), washed with brine solution and dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated under reduced pressure. The crude reaction mass further purified through column chromatography (Chloroform: Methanol (9:1)).



PP1-4

6-amino-4-(4-chlorophenyl)-3-methyl-1-phenyl-1H,4*H*-pyrano[2,3-c]pyrazole-5-carbonitrile (PP1)

Yield:96%;Appearance: white solid; mp = 175-176 °C (175-176 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$): δH (ppm) 1.89 (s, 3H), 4.66 (s, 1H), 4.72 (s, 2H),7.20 (d, *J* = 4.8 Hz, 2H),7.30-7.35 (m, 3H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d6, $CDCl_3$ δ ppm);12.8, 36.7, 60.8, 97.9, 119.6, 120.9, 126.5, 128.7, 129.1, 129.2, 132.9, 137.6, 141.2, 144.0, 145.9, 159.1.

6-amino-3-methyl-4-(4-nitrophenyl)-1-phenyl-1*H*,4*H*-pyrano[2,3-c]pyrazole-5-carbonitrile (PP2)

Yield: 97%;Appearance: white Solid; mp= 195-196°C, (196-198 °C)[4];^{1}H NMR (300 MHz, $CDCl_3$): δH (ppm) 1.82 (s, 3H), 4.74 (s, 2H), 4.75 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.37-7.44 (m, 4H), 7.60 (d, *J* = 9.6 Hz, 2H), 8.17 (dd, *J* = 8.7, 1.8 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d6, $CDCl_3$ δ ppm); 12.3, 28.9, 58.5, 96.6, 119.0, 120.4, 123.4, 126.0, 128.3, 128.6, 136.9, 143.6, 145.1, 146..5, 149.6, 159.1.

6-amino-3-methyl-4-(4-methylphenyl)-1-phenyl-1*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (PP3)

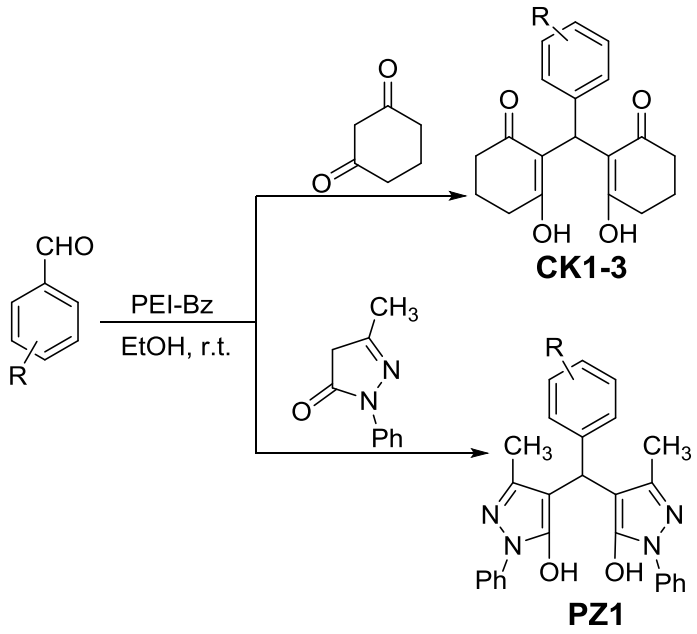
Yield:82%;Appearance: white Solid; mp= 177-178 °C(177-179 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$): δH (ppm) 1.18 (s, 3H), 1.82 (s, 3H), 4.75 (s, 1H), 4.77 (merged singlet, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 2H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 3H), 8.04 (s, 1H), 8.12 (d, *J* = 9 Hz,1H); ^{13}C-NMR (75 MHz, DMSO-d6, $CDCl_3$ δ ppm);12.6, 29.4, 37.2, 61.6, 98.2, 119.5, 120.7, 126.2, 127.1, 127.6, 128.4, 128.9, 137.4, 142.2, 143.8, 146.0, 158.7.

6-amino-3-methyl-1,4-diphenyl-1*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (PP4)

Yield: 97%; Appearance: white Solid; mp=170-171 °C (169-171 °C)[4];^{1}H NMR (300 MHz, $CDCl_3$): δ δH (ppm) 1.82 (s, 3H), 4.59 (s, 1H), 4.63 (s, 2H), 7.17-7.31 (m, 6H), 7.39-7.41 (m, 2H), 7.58 (dd, *J* = 9.6, 0.9 Hz, 2H). ^{13}C-NMR (75 MHz, DMSO-d6, $CDCl_3$ δ ppm);12.6, 37.1, 59.7, 96.9, 119.2, 120.8, 122.3, 122.4, 126.4, 128.9, 129.5, 133.9, 137.2, 143.8, 144.7, 145.5, 148.3, 159.2

General procedure for the synthesis of cyclic ketones (CK 1-3) or pyrazole (PZ1): A mixture of substituted aldehyde (1 mmol), 1,3 cyclohexadienone (or) 3-methyl-1-phenyl-2-pyrazoline-5-one (348.4 mg; 2 mmol) and PEI-Bz polyamine catalyst (100 mg) were taken in the 5 ml of ethanol and it was stirred at RT. The progress of the reaction was monitored through thin layer chromatography (TLC) using ethyl acetate and petroleum ether (3: 7) as eluent mixture. After completion, the reaction mixture was poured in to crushed ice and filtered through the Whatman filter paper. The solid mass was collected and further stirred in hexane (1 x 10 mL) for 10 minutes and filtered through whatman filter paper. The product thus obtained was essentially pure.

Cyclic ketone derivatives have limited solubility in $CDCl_3$. Hence, ^{13}C-NMR spectra's were run on DMSO-d6 solvent. The Cyclic ketone derivatives exhibited keto-enol tautomerism in polar DMSO-d6 solvent. Yu *et al*., already reported the presence of keto-enol tautomerism in cyclic ketone derivatives.[5a]



2-[(4-chlorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)methyl]-3-hydroxycyclohex-2-en-1-one. (**CK1**)

Yield: 97%; Appearance: white solid; mp = 202-204 °C (202-204 °C)[5b]; ^{1}H NMR (300 MHz, $CDCl_3$): δ δH (ppm) 1.94-2.07 (m, 4H), 2.33-2.68 (m, 8H), 5.40 (s, 1H), 7.02 (dd, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 6.9 Hz, 2H), 12.34 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d6, δ ppm);20.2, 20.4, 20.9, 21.0, 28.92, 29.1, 31.9, 32.6, 33.5, 35.3, 36.2, 37.1, 37.2, 59.4, 60.0.100.5, 101.5, 111.2, 115.8, 127..6, 127.7, 127.8, 128.2, 128.8, 129.8, 130.1, 130.2, 130.8, 143.9, 144.6, 198.3, 169.9, 189.7, 195.9, 196.4, 205.3, 206.3.

3-hydroxy-2-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(phenyl)methyl]cyclohex-2-en-1-one (CK2)

Yield: 98%; Appearance: white solid; mp = 190-191 °C (190-191 °C)[5b]; ^{1}H NMR (300 MHz, $CDCl_3$): δ δH (ppm) 1.94-2.00 (m, 4H), 2.26-2.60 (m, 8H), 5.40 (s, 1H), 7.02-7.12 (m, 3H),7.17-7.22 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 12.0 (br s, 1H), 12.30 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d6, δ ppm); 19.0, 20.2, 20.4, 20.5, 21.0, 29.0, 29.1, 32.7, 32.9, 33.7, 35.4, 36.1, 37.1, 37.2, 59.8, 60.5, 100.5, 101.4, 111.5, 116.0, 116.3, 125.3, 125.6, 126.9, 127.7, 127.8, 128.2, 128.9, 144.8, 145.7, 167.9, 169.6, 189.7, 198.9, 196.4, 205.3, 206.7.

3-hydroxy-2-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(4-methoxyphenyl)methyl]cyclohex-2-en-1-one (CK3)

Yield: 82%; Appearance: white solid; mp = 194-196 °C (195-197 °C)[5b]; ^{1}H NMR (300 MHz, $CDCl_3$): δ δH (ppm) 1.90-1.99 (m, 4H), 2.25-2.59 (m, 8H),3.71 (s, 3H), 5.35 (s, 1H), 6.73 (d, *J* = 9.0Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 12.30 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d6, δ ppm); 21.0, 29.0, 29.1, 32.0, 32.3,

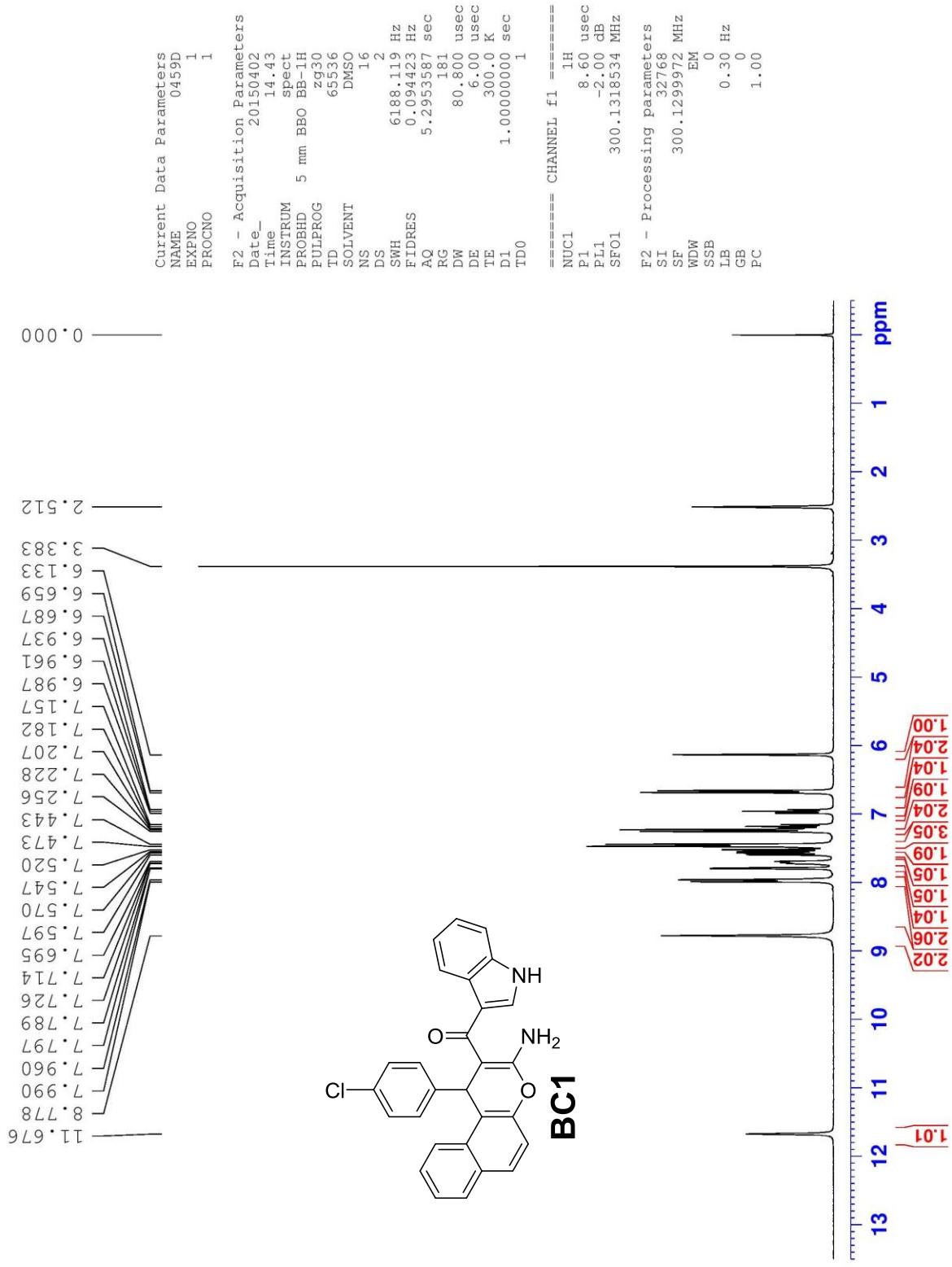
33.6, 35.4, 35.9, 37.1, 37.3, 55.3, 55.4, 60.6, 100.5, 101.4, 111.9, 113.2, 113.3, 113.7, 116.3, 116.5, 127.8, 129..1, 129.7, 136.6, 137.5, 157.2, 157.3, 167.6, 169.4, 189.9, 195.9, 196.3, 205.4, 206.8.

4-[(4-chlorophenyl)(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl]-3-methyl-1-phenyl-1*H*-pyrazol-5-ol (PZ1)

Yield: 89%; Appearance: white solid; mp = 208-210 °C (210-212 °C)[6]; ^{1}H NMR (300 MHz, DMSO-d_6): δH (ppm) 2.32 (s, 6H), 4.97 (s, 1H), 7.25 (t, *J* = 8.1 Hz, 4H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.70 (t, *J* = 8.1 Hz, 4H),12.51 (s, 1H), 13.89 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d6, δ ppm); 12.1, 331, 121.0, 126.1, 128.5, 129.4, 129.6, 131.1, 137.7, 141.6, 146.7.

Procedure for recyclability of PEI-Bz on CK1 synthesis

-the reaction mixture was poured in to crushed ice and filtered through the Whatman filter paper. The combined filtrate was concentrated under reduced pressure and extracted with chloroform (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The recycled catalyst was without further purification.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PROCNO 1
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 181
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299972 MHz
WDW EM
SSB 0
LB 0.30 Hz
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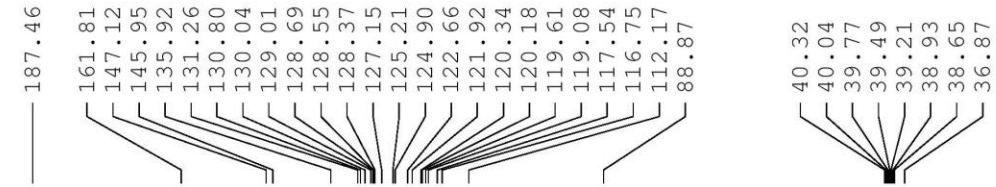
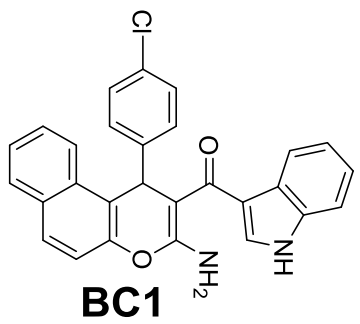
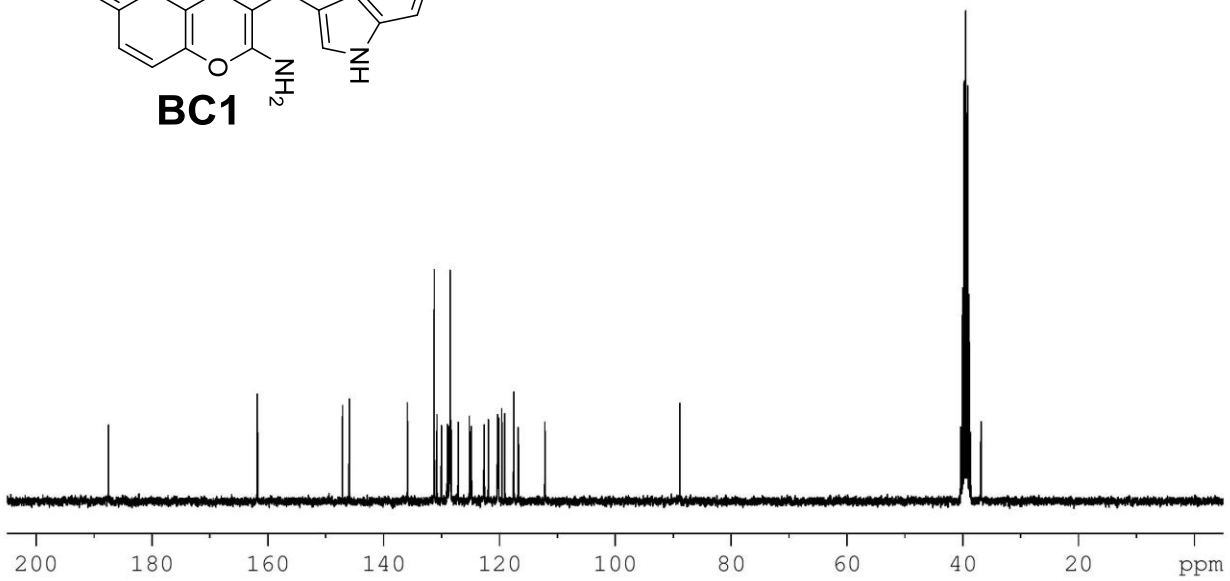




BC1

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EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160113
Time                  18.18
INSTRUM               spect
PROBHD    5 mm BBO BB-1H
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      225
DS                        4
SWH               18028.846 Hz
FIDRES             0.275098 Hz
AQ                 1.8175818 sec
RG                      256
DW                   27.733 usec
DE                    6.00 usec
TE                   300.0 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   10.00 usec
PL1                   0.00 dB
SFO1            75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 16.98 dB
PL13                 20.00 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
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SF              75.4677867 MHz
WDW                      EM
SSB                       0
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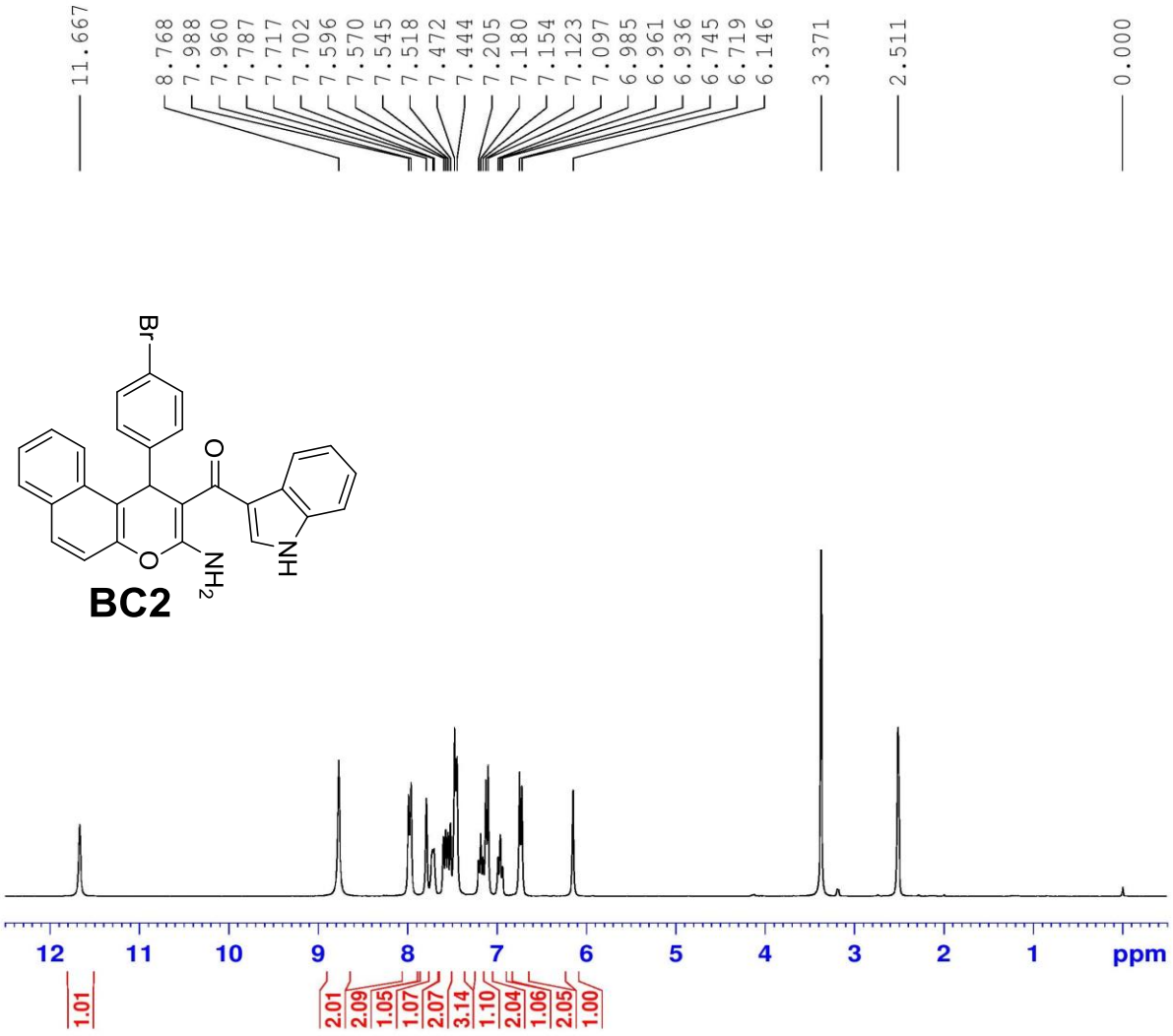


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Current Data Parameters
NAME                  0654H
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150525
Time                 14.47
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH               6188.119 Hz
FIDRES           0.094423 Hz
AQ               5.2953587 sec
RG                      203
DW                 80.800 usec
DE                  6.00 usec
TE                  300.0 K
D1             1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.60 usec
PL1                 -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1299977 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                    1.00
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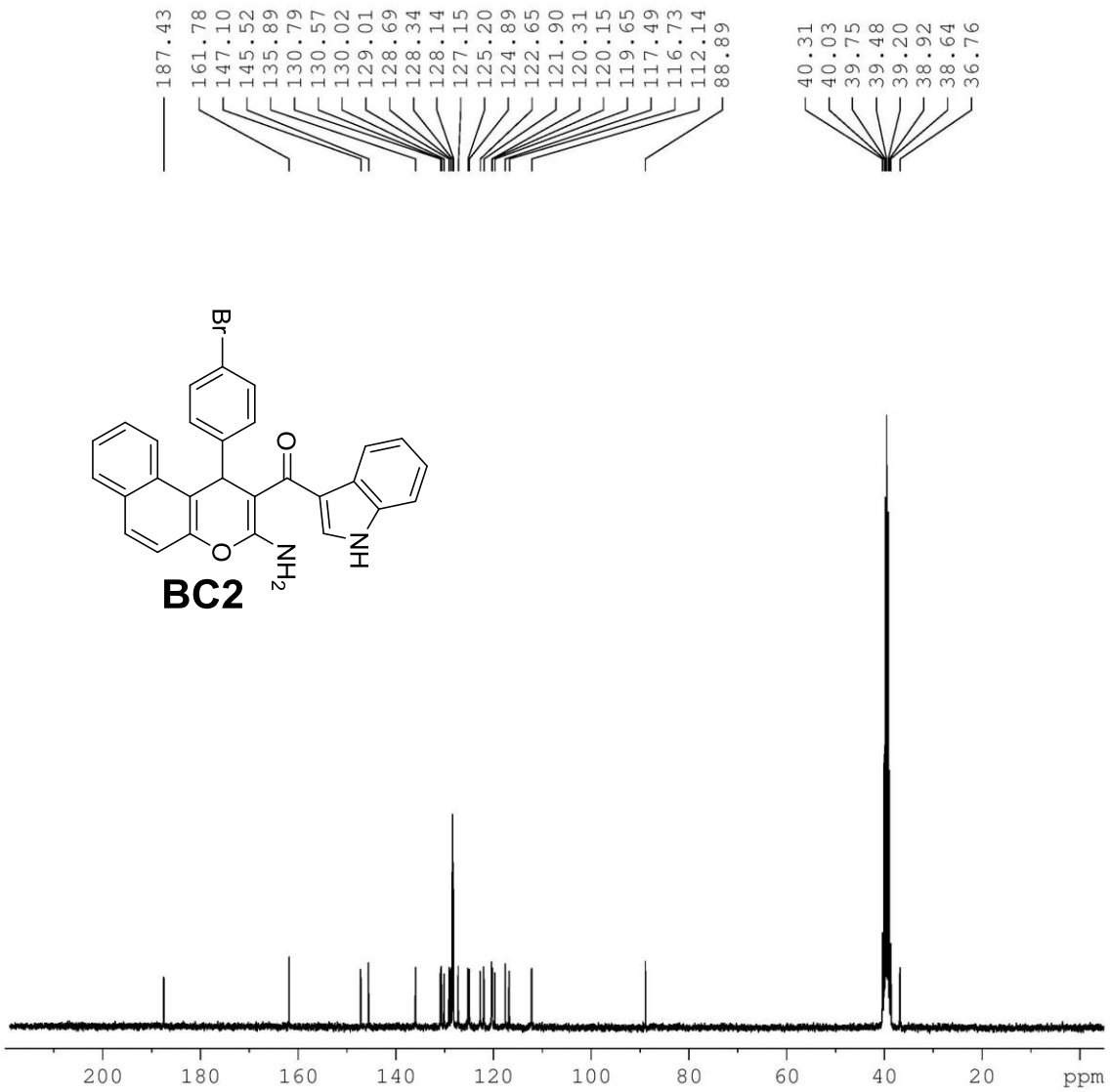


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EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
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Time                  11.42
INSTRUM               spect
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PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      865
DS                        4
SWH               18028.846 Hz
FIDRES             0.275098 Hz
AQ                1.8175818 sec
RG                      228
DW                   27.733 usec
DE                    6.00 usec
TE                   300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                       1

========= CHANNEL f1 ========
NUC1                    13C
P1                    10.00 usec
PL1                    0.00 dB
SFO1             75.4752953 MHz

========= CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -2.00 dB
PL12                  16.98 dB
PL13                  20.00 dB
SFO2            300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF               75.4677867 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
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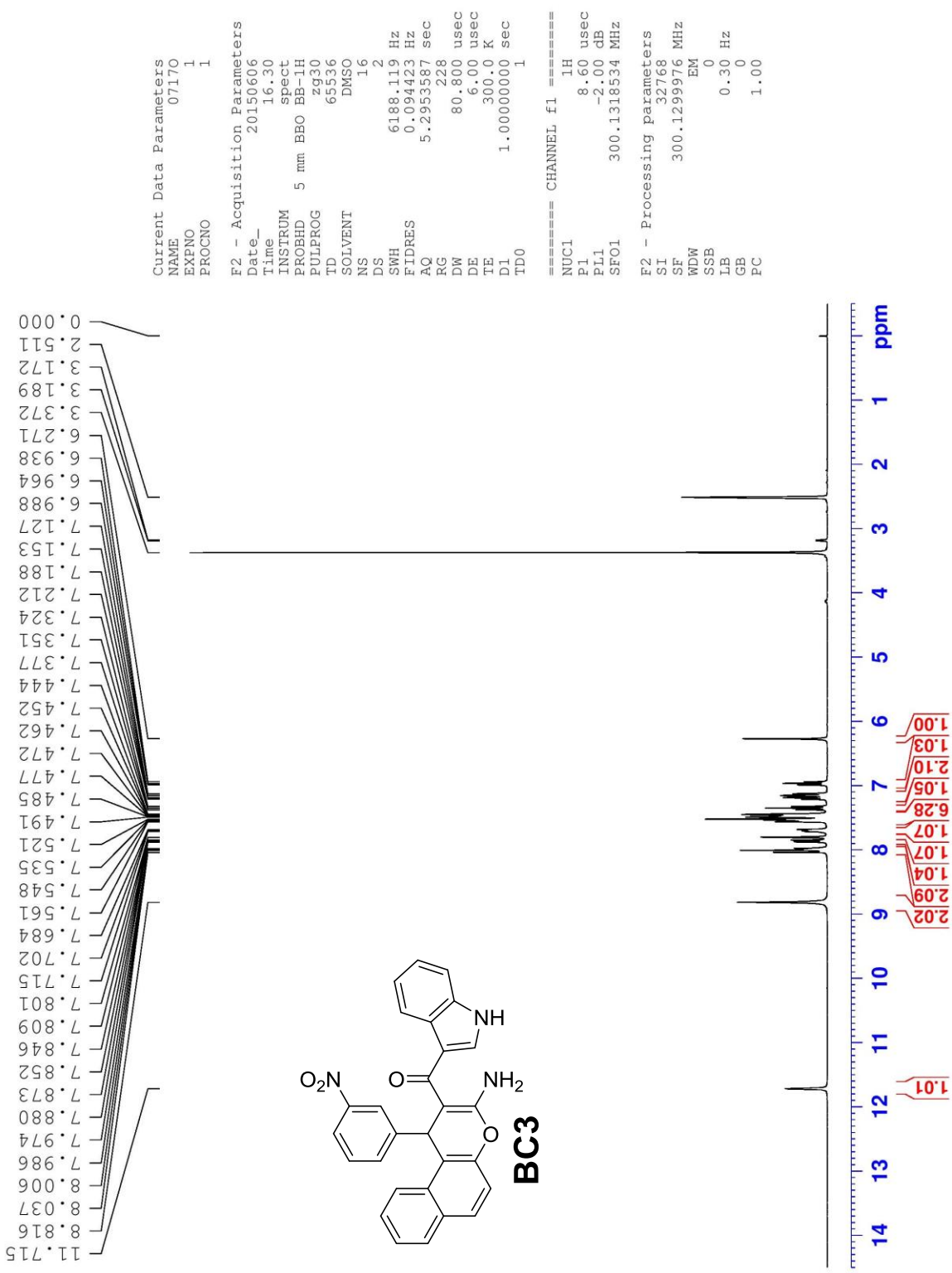
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EXPNO 1
PROCNO 1
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Time 16.30
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PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 228
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299976 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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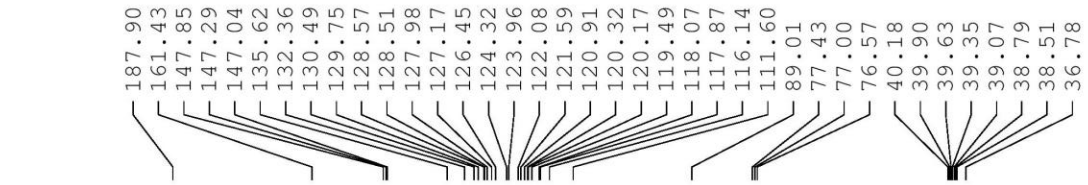

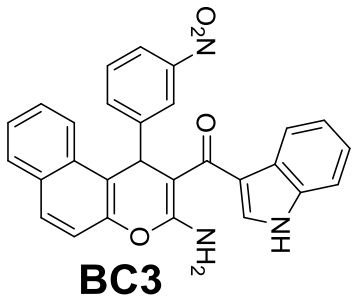

BC3


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Current Data Parameters
NAME                  1429D
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160222
Time                 16.39
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                     875
DS                       4
SWH              18028.846 Hz
FIDRES            0.275098 Hz
AQ                1.8175818 sec
RG                     228
DW                27.733 usec
DE                 6.00 usec
TE                 300.0 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                   13C
P1                  10.00 usec
PL1                  0.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -2.00 dB
PL12                16.98 dB
PL13                20.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF             75.4678042 MHz
WDW                      EM
SSB                       0
LB                   1.00 Hz
GB                        0
PC                     1.40
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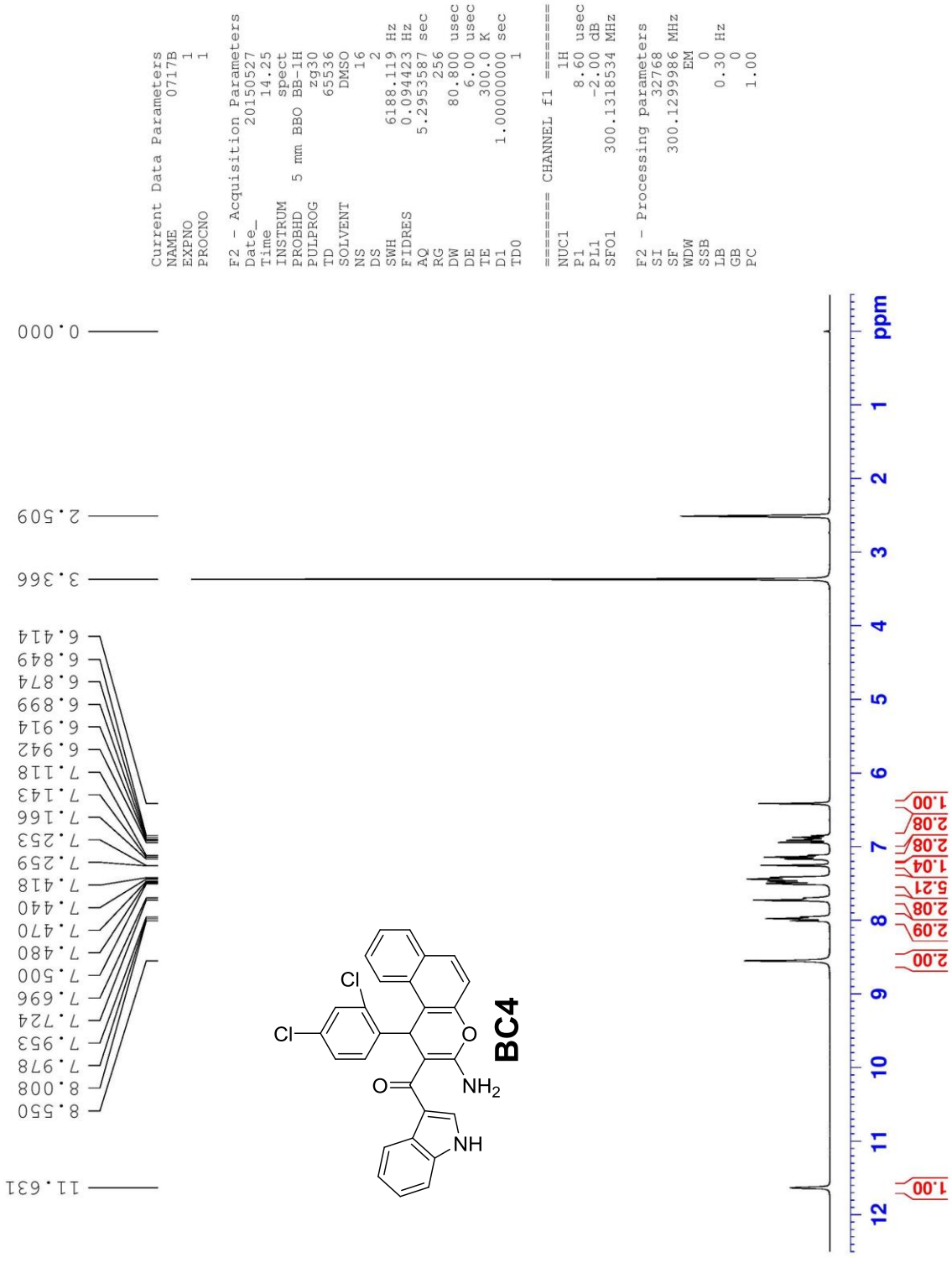
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NAME 0717B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 14.25
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.0944423 Hz
AQ 5.2953587 sec
RG 256
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299986 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
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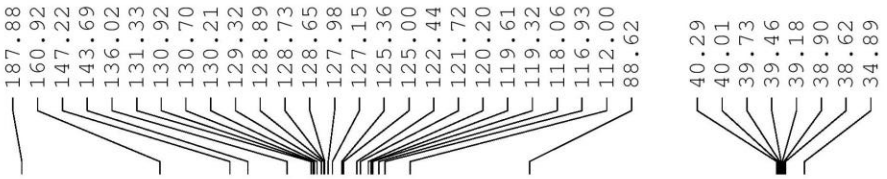
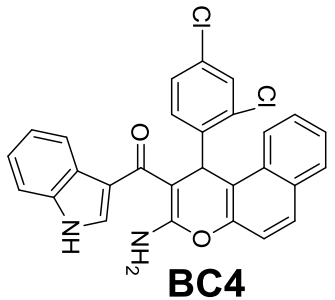
NH
BC4





BC4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Current Data Parameters
NAME                  1391M-R
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_                20160219
Time                    17.47
INSTRUM                 spect
PROBHD   5 mm BBO BB-1H
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       1024
DS                          4
SWH                18028.846 Hz
FIDRES              0.275098 Hz
AQ                  1.8175818 sec
RG                        228
DW                     27.733 usec
DE                      6.00 usec
TE                     300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
PL1                      0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    16.98 dB
PL13                    20.00 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF                 75.4677867 MHz
WDW                          EM
SSB                           0
LB                       1.00 Hz
GB                            0
PC                       1.40
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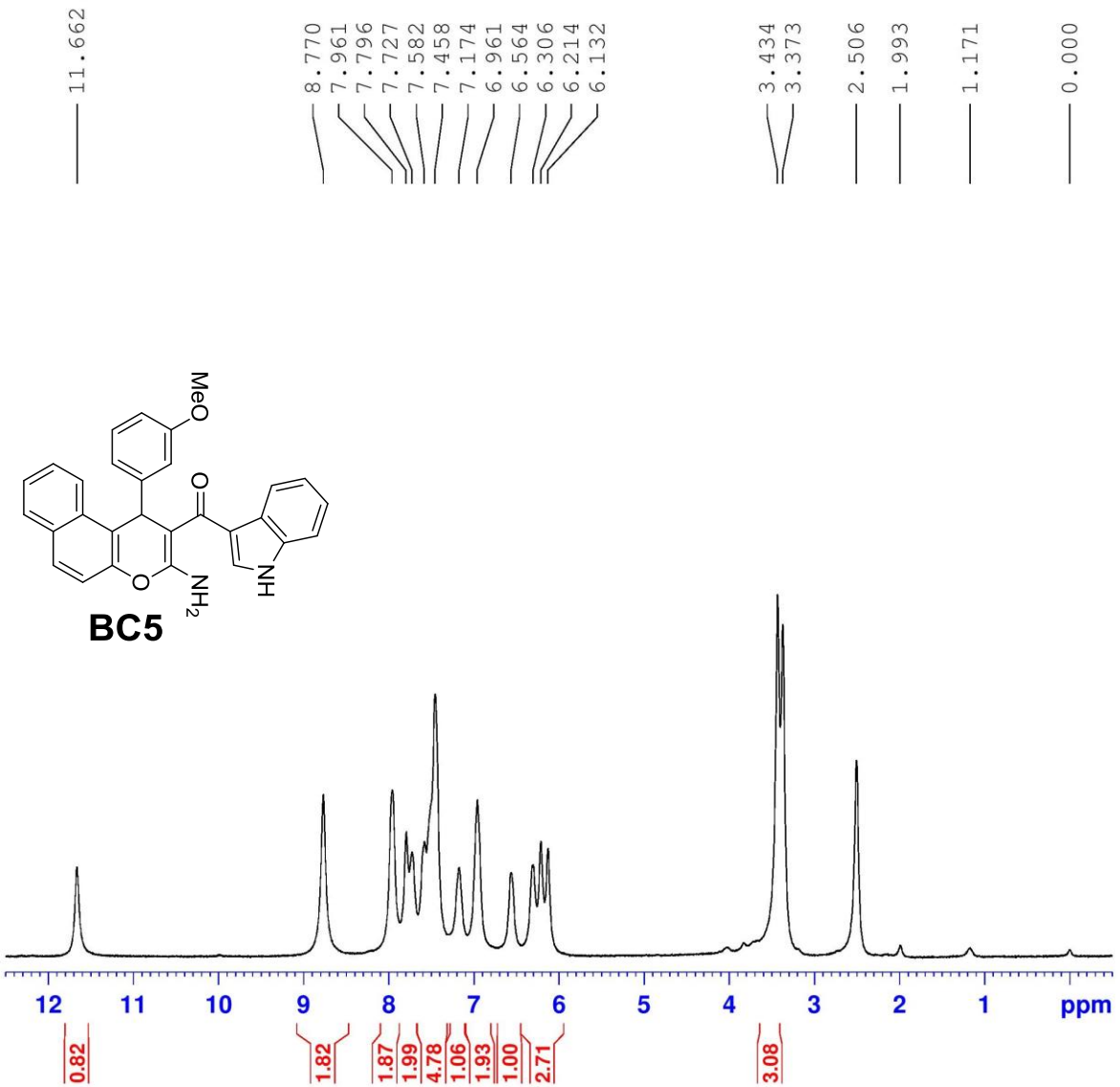


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Current Data Parameters
NAME                  0654I
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150525
Time                  14.56
INSTRUM               spect
PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH               6188.119 Hz
FIDRES            0.094423 Hz
AQ                5.2953587 sec
RG                      181
DW                  80.800 usec
DE                   6.00 usec
TE                   300.0 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    8.60 usec
PL1                  -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1299987 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
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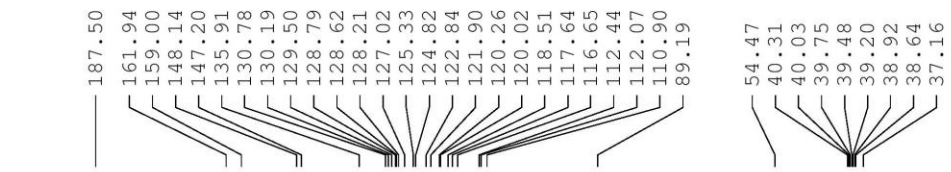

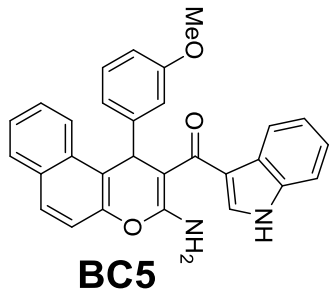

BC5


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Current Data Parameters
NAME                  1273T
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160118
Time                  13.02
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                      666
DS                        4
SWH              18028.846 Hz
FIDRES            0.275098 Hz
AQ                1.8175818 sec
RG                      228
DW                  27.733 usec
DE                   6.00 usec
TE                  300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   10.00 usec
PL1                   0.00 dB
SFO1            75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 16.98 dB
PL13                 20.00 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
SI                     32768
SF              75.4677867 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
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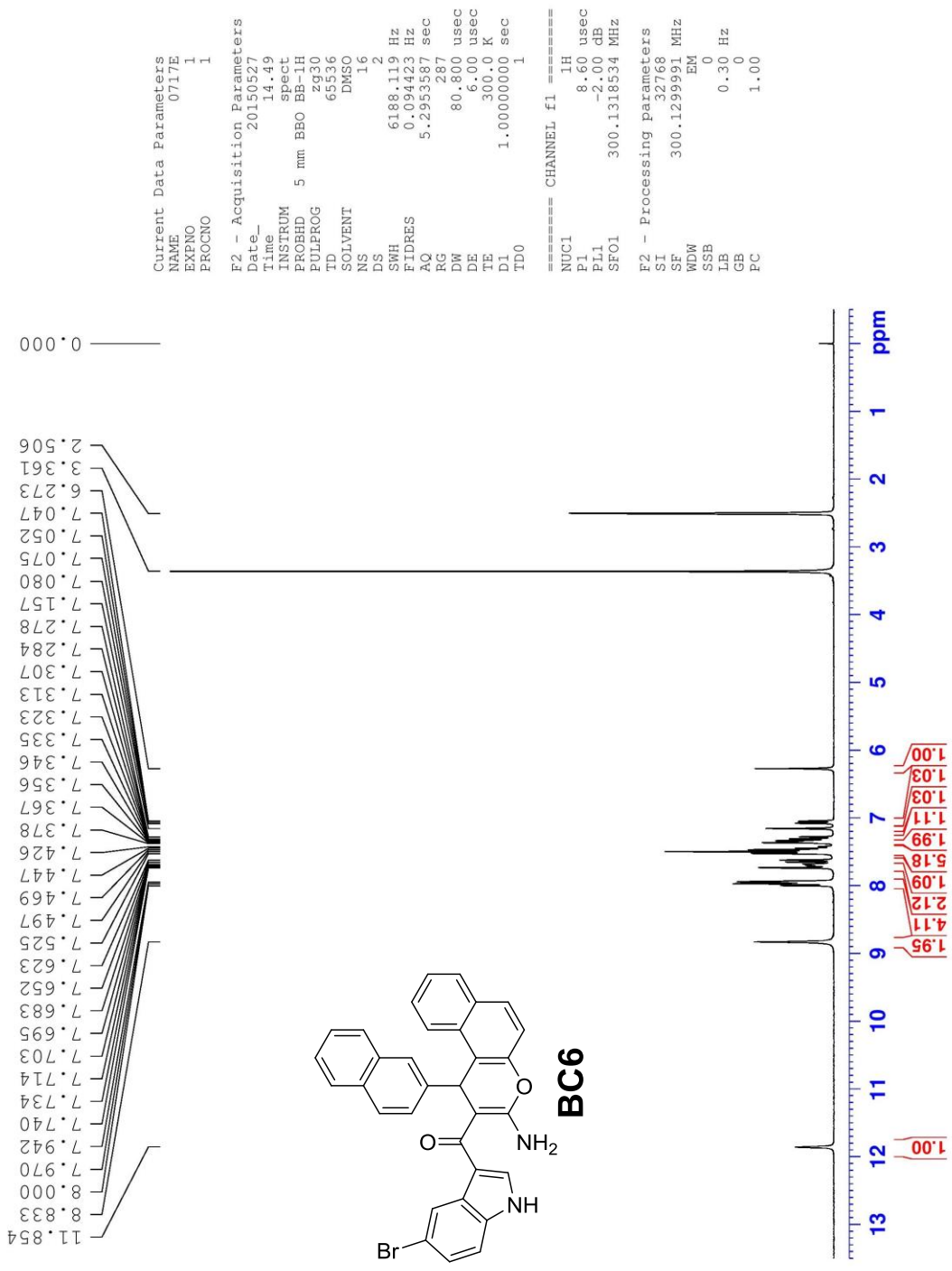
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NAME 0717E
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 14.49
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 287
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299991 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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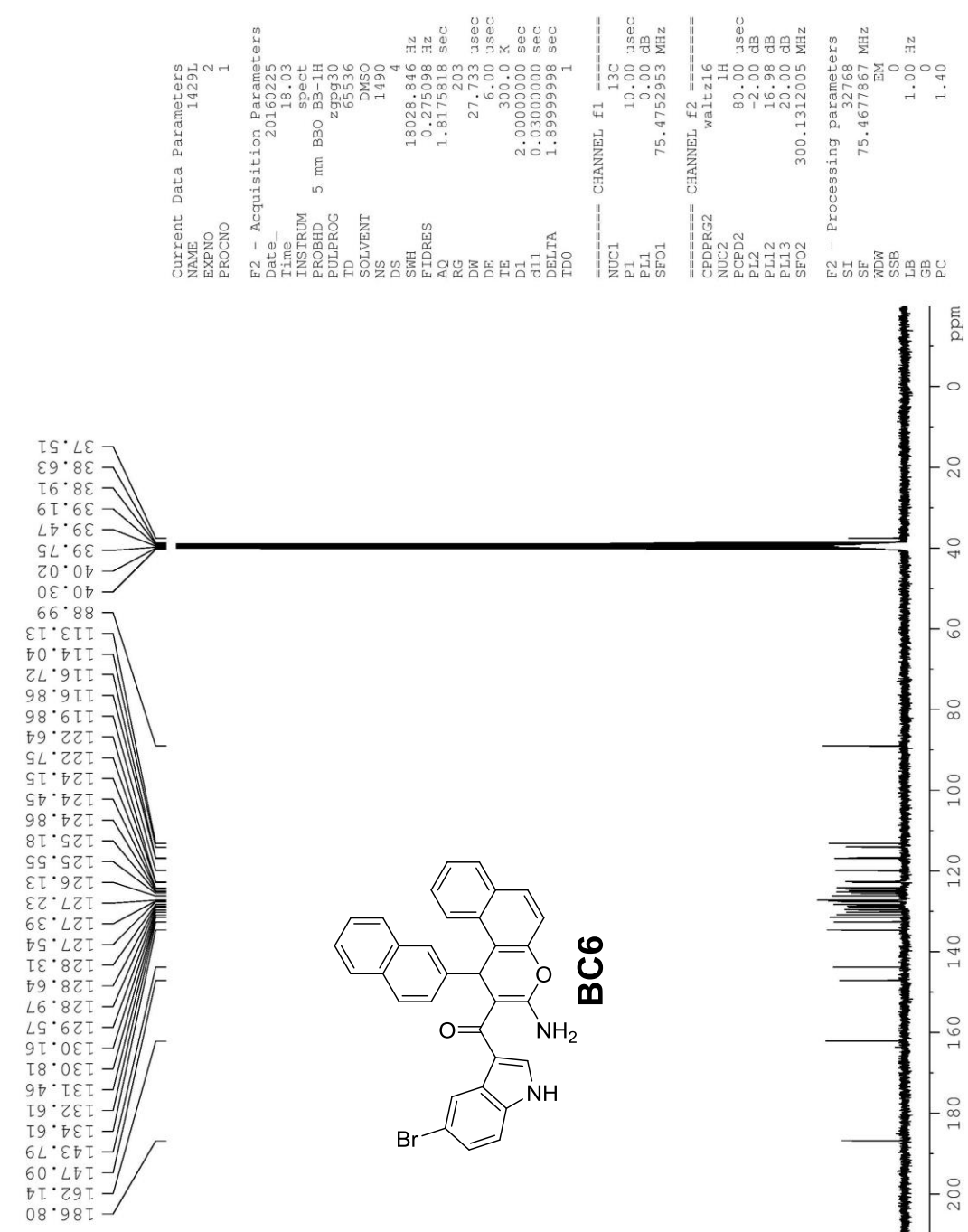
BC6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EXPNO 2
PROCNO 1
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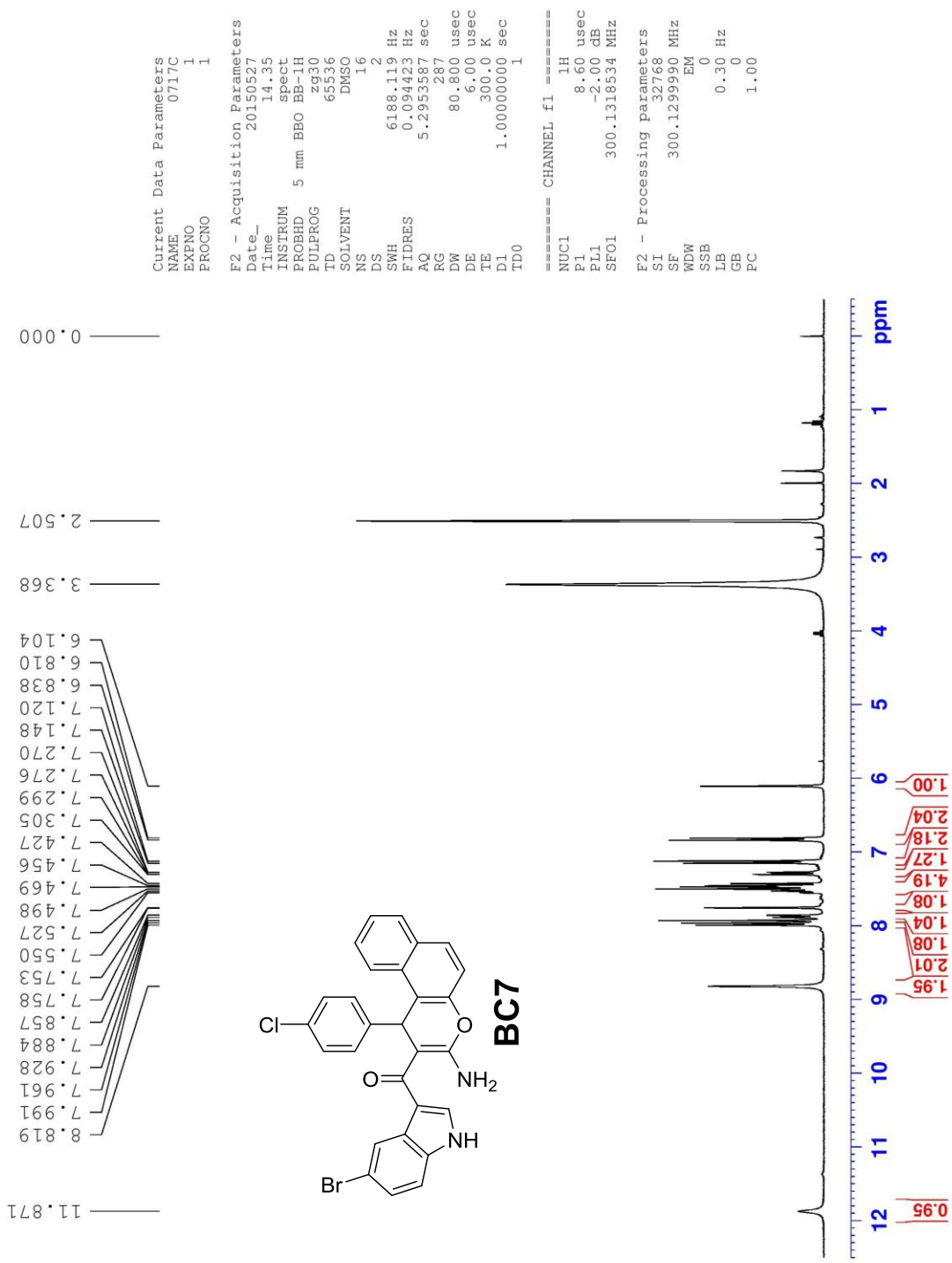
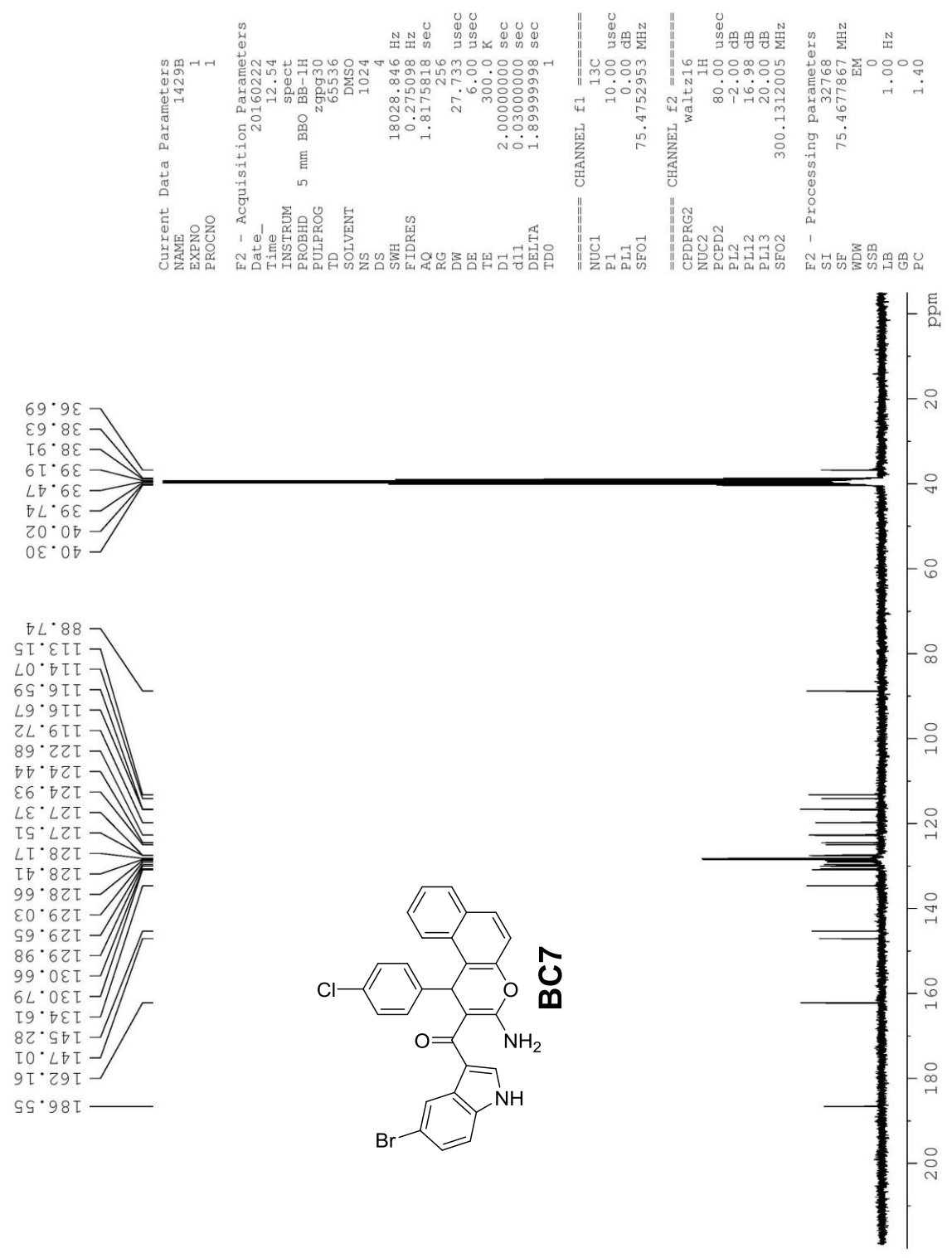
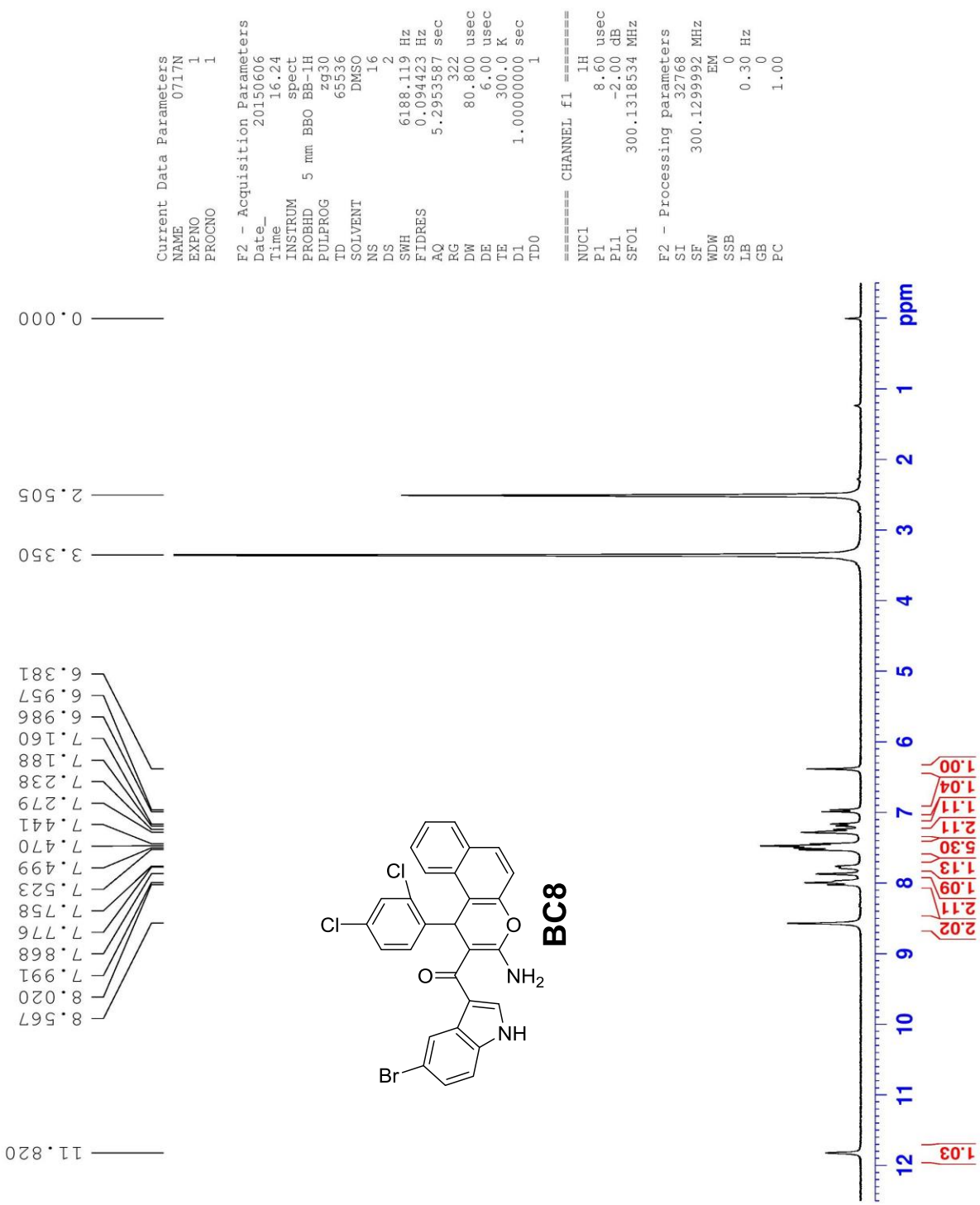
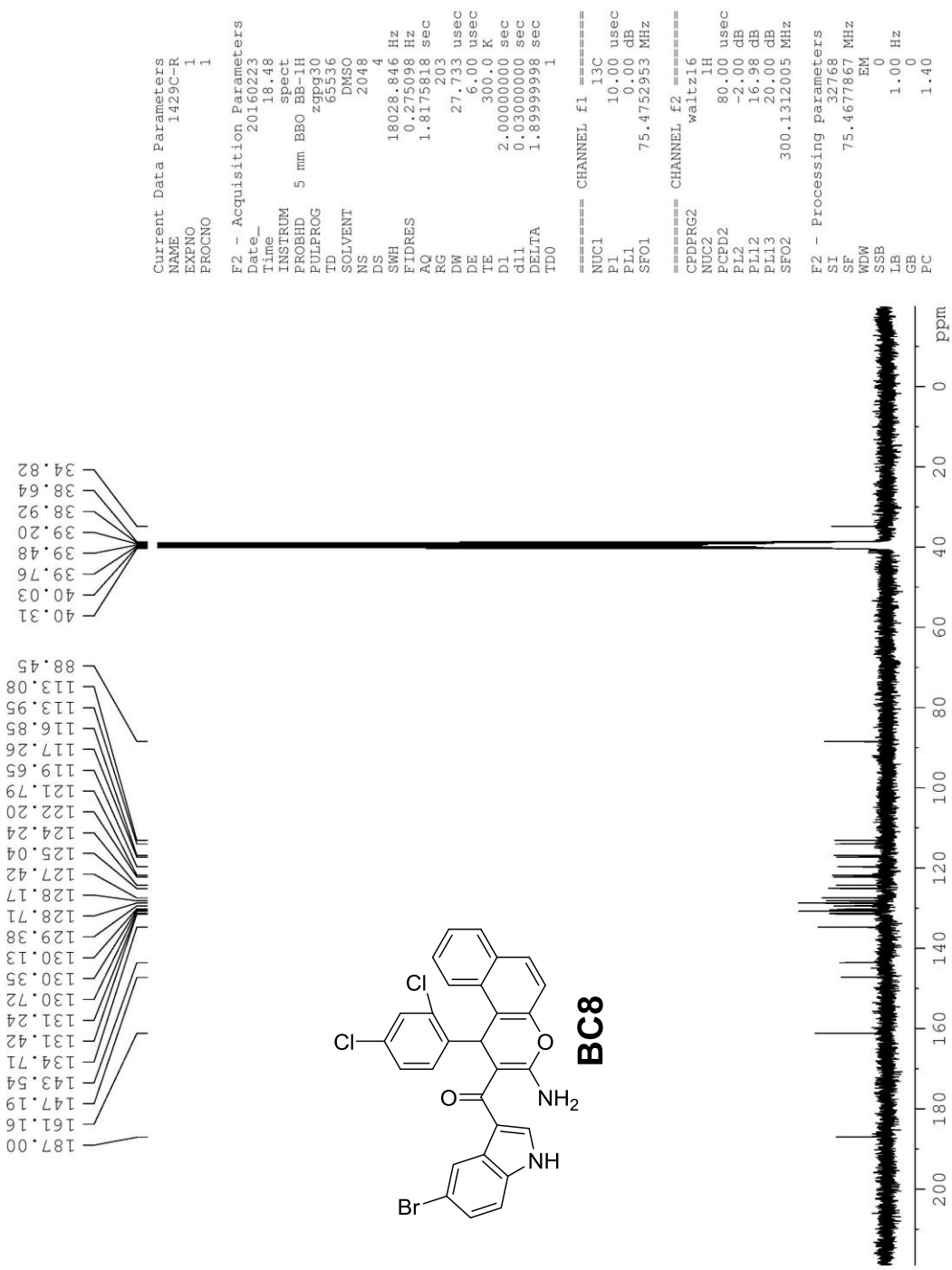
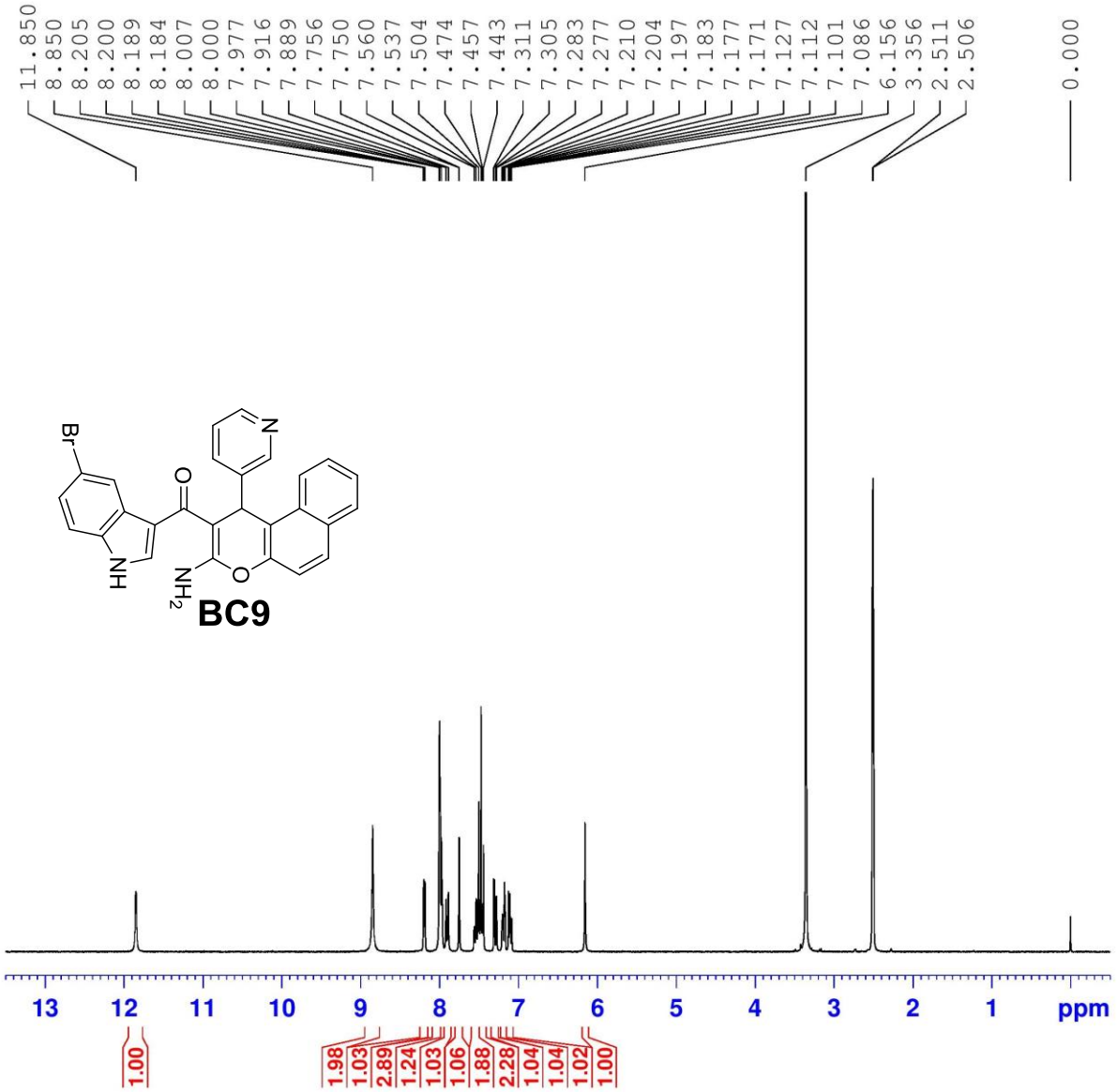
Time 18.03
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1490
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 203
DW 27.733 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
37.51
38.63
38.91
39.19
39.47
39.75
40.02
40.30
88.99
113.13
114.04
116.72
116.86
119.86
122.64
122.75
124.15
124.45
124.86
125.18
125.55
126.13
127.23
127.39
127.54
128.31
128.64
128.97
129.57
130.16
130.81
131.46
132.61
134.61
143.79
147.09
162.14
186.80
O
NH2
NH
Br
BC6
200
180
160
140
120
100
80
60
40
20
0
ppm


Current Data Parameters
NAME 0717C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 14.35
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 287
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299990 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.000
2.507
3.368
6.104
6.810
6.838
7.120
7.148
7.270
7.276
7.299
7.305
7.427
7.456
7.469
7.498
7.527
7.550
7.753
7.758
7.857
7.884
7.928
7.961
7.991
8.819
11.871
Cl
O
O
NH2
NH
Br
BC7
ppm
1.00
2.04
2.18
1.27
4.19
1.08
1.04
1.08
2.01
1.95
0.95

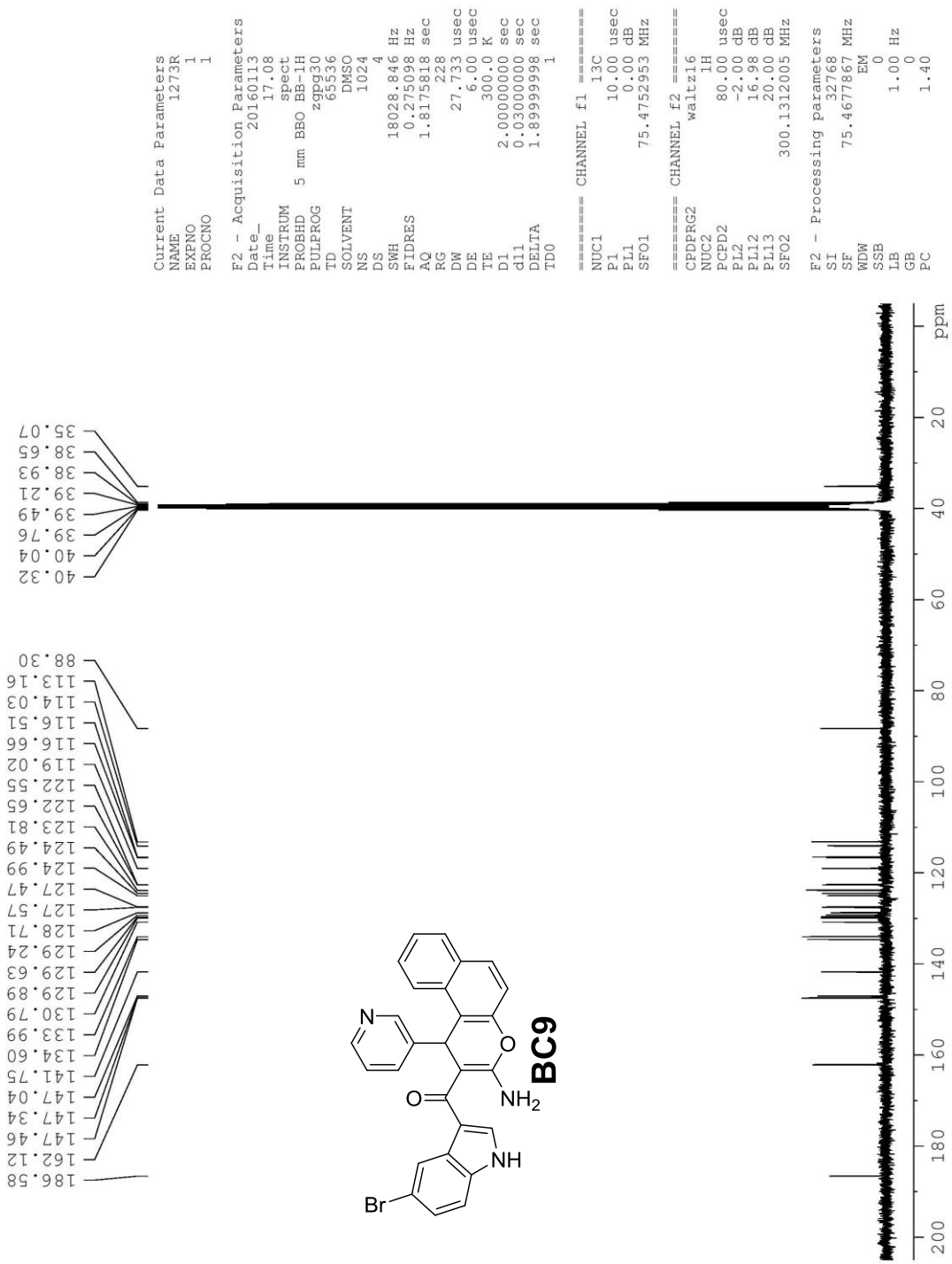

Current Data Parameters
NAME 1429B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160222
Time 12.54
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 256
DW 27.733 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
40.30
40.02
39.74
39.47
39.19
38.91
38.63
36.69
186.55
162.16
147.01
145.28
134.61
130.79
130.66
129.98
129.65
129.03
128.66
128.41
128.17
127.51
127.37
124.93
124.44
122.68
119.72
116.67
116.59
114.07
113.15
88.74
Cl
O
O
NH2
NH
Br
BC7
ppm

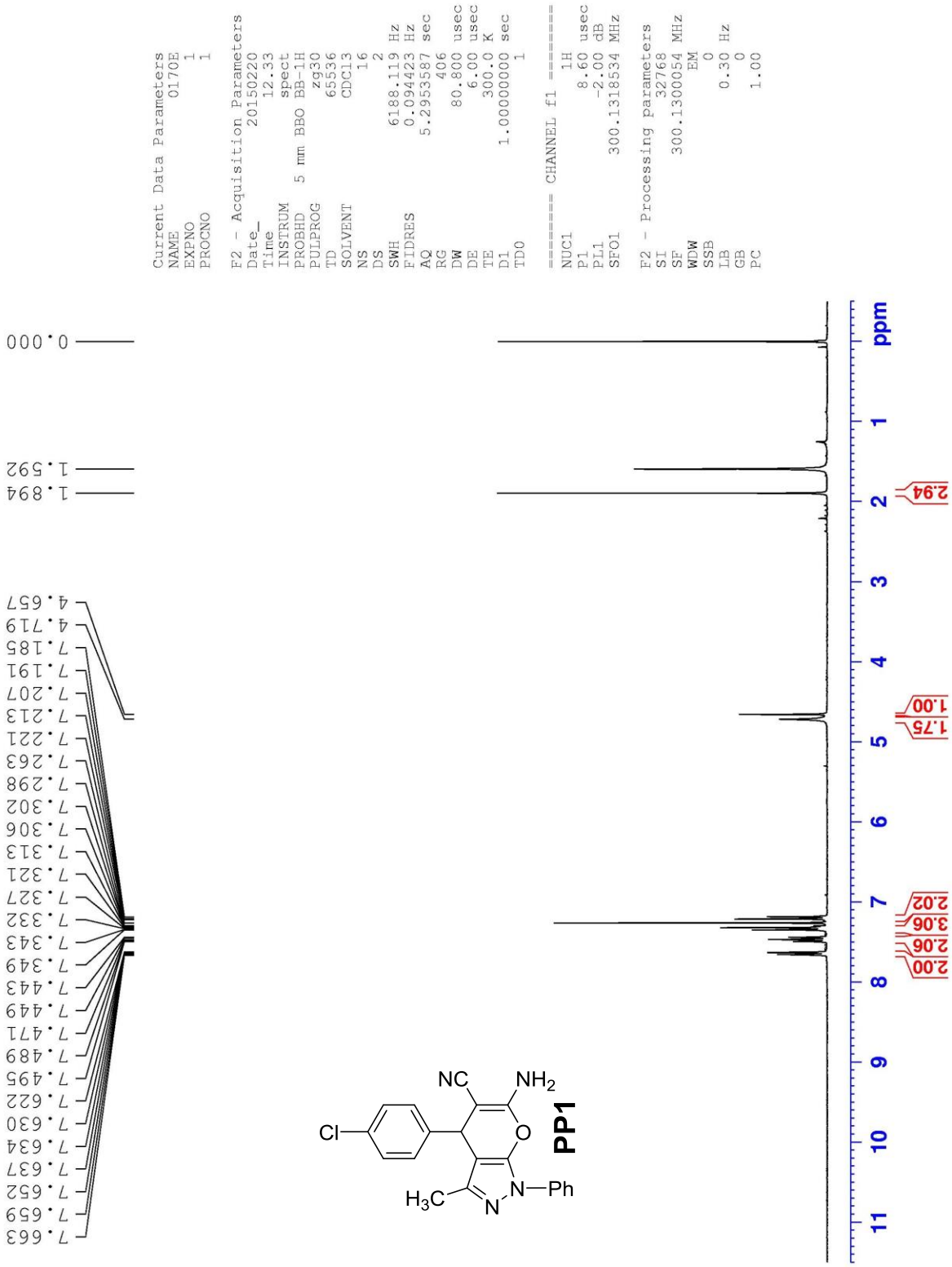

Current Data Parameters
NAME 0717N
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150606
Time 16.24
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 322
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1299992 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.000
2.505
3.350
6.381
6.957
6.986
7.160
7.188
7.238
7.279
7.441
7.470
7.499
7.523
7.758
7.776
7.868
7.991
8.020
8.567
11.820
ppm
1 2 3 4 5 6 7 8 9 10 11 12
1.00
1.04
1.11
2.11
5.30
1.13
1.09
2.11
2.02
1.03
Cl
Cl
O
O
NH2
NH
Br
BC8

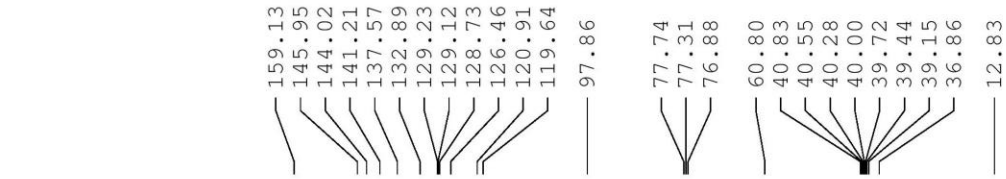

Current Data Parameters
NAME 1429C-R
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160223
Time 18.48
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 203
DW 27.733 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
34.82
38.64
38.92
39.20
39.48
39.76
40.03
40.31
88.45
113.08
113.95
116.85
117.26
119.65
121.79
122.20
124.24
125.04
127.42
128.17
128.71
129.38
130.13
130.35
130.72
131.24
131.42
134.71
143.54
147.19
161.16
187.00
Cl
Cl
O
O
NH2
NH
Br
BC8
ppm
200
180
160
140
120
100
80
60
40
20
0

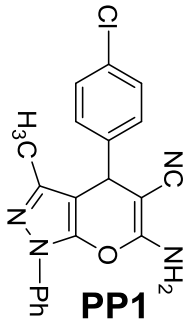



```
Current Data Parameters
NAME                  0717A
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150527
Time                 14.16
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               6188.119 Hz
FIDRES            0.094423 Hz
AQ                5.2953587 sec
RG                     287
DW                  80.800 usec
DE                   6.00 usec
TE                  300.0 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    8.60 usec
PL1                  -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1299991 MHz
WDW                      EM
SSB                       0
LB                    0.30 Hz
GB                        0
PC                    1.00
```


Current Data Parameters
NAME 1273R
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160113
Time_ 17.08
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 228
DW 27.733 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
35.07
38.65
38.93
39.21
39.49
39.76
40.04
40.32
88.30
113.16
114.03
116.51
116.66
119.02
122.55
122.65
123.81
124.49
124.99
127.47
127.57
128.71
129.24
129.63
129.89
130.79
133.99
134.60
141.75
147.04
147.34
147.46
162.12
186.58
N
O
O
NH2
NH
Br
BC9
ppm
200
180
160
140
120
100
80
60
40
20

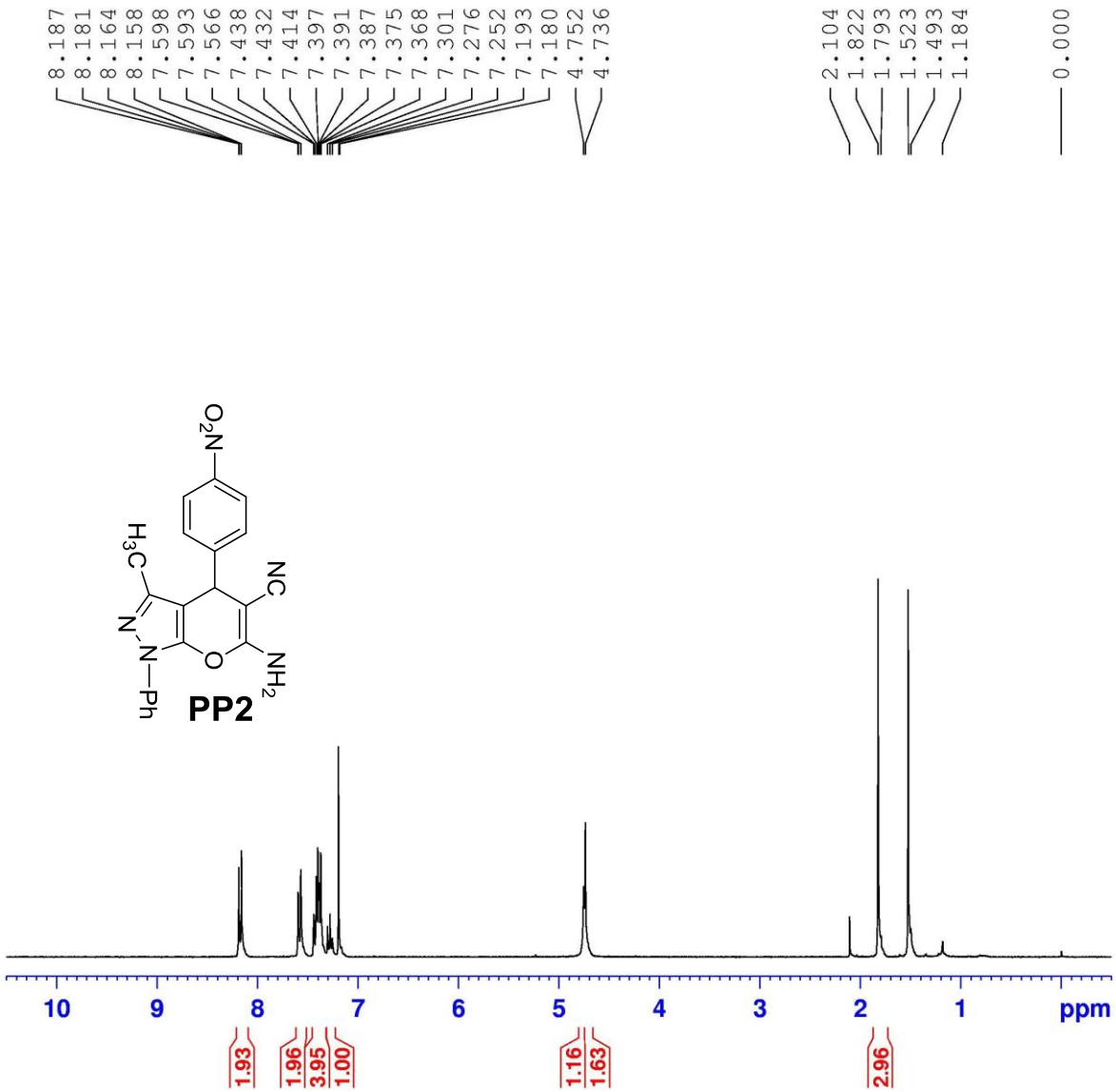

Current Data Parameters
NAME 0170E
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150220
Time 12.33
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 406
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.000
1.592
1.894
4.657
4.719
7.185
7.191
7.207
7.213
7.221
7.263
7.298
7.302
7.306
7.313
7.321
7.327
7.332
7.343
7.349
7.443
7.449
7.471
7.489
7.495
7.622
7.630
7.634
7.637
7.652
7.659
7.663
ppm
1
2
3
4
5
6
7
8
9
10
11
2.94
1.00
1.75
2.00
2.06
3.06
2.02
NC
NH2
Cl
O
N
Ph
H3C
PP1



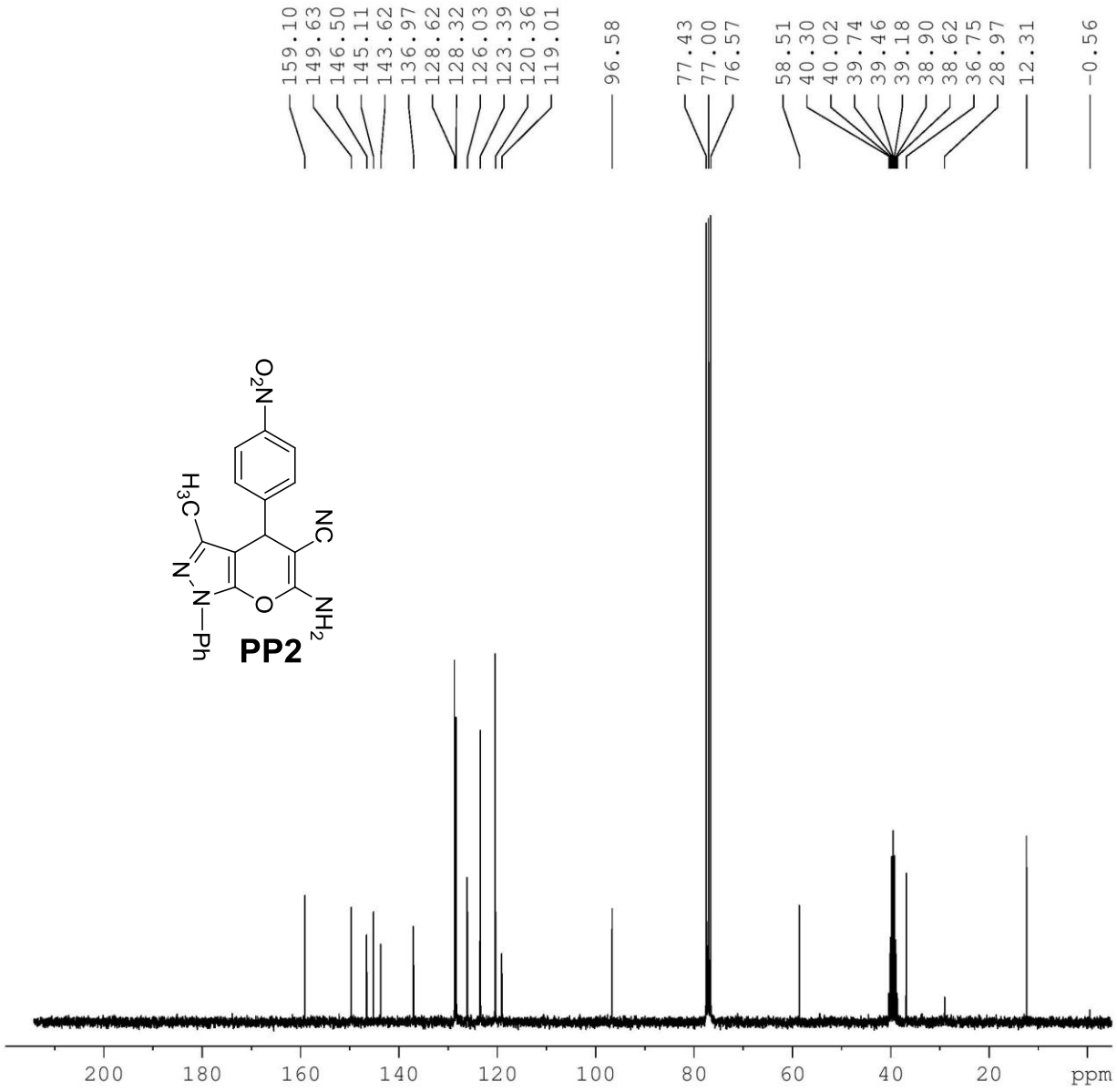


PP1

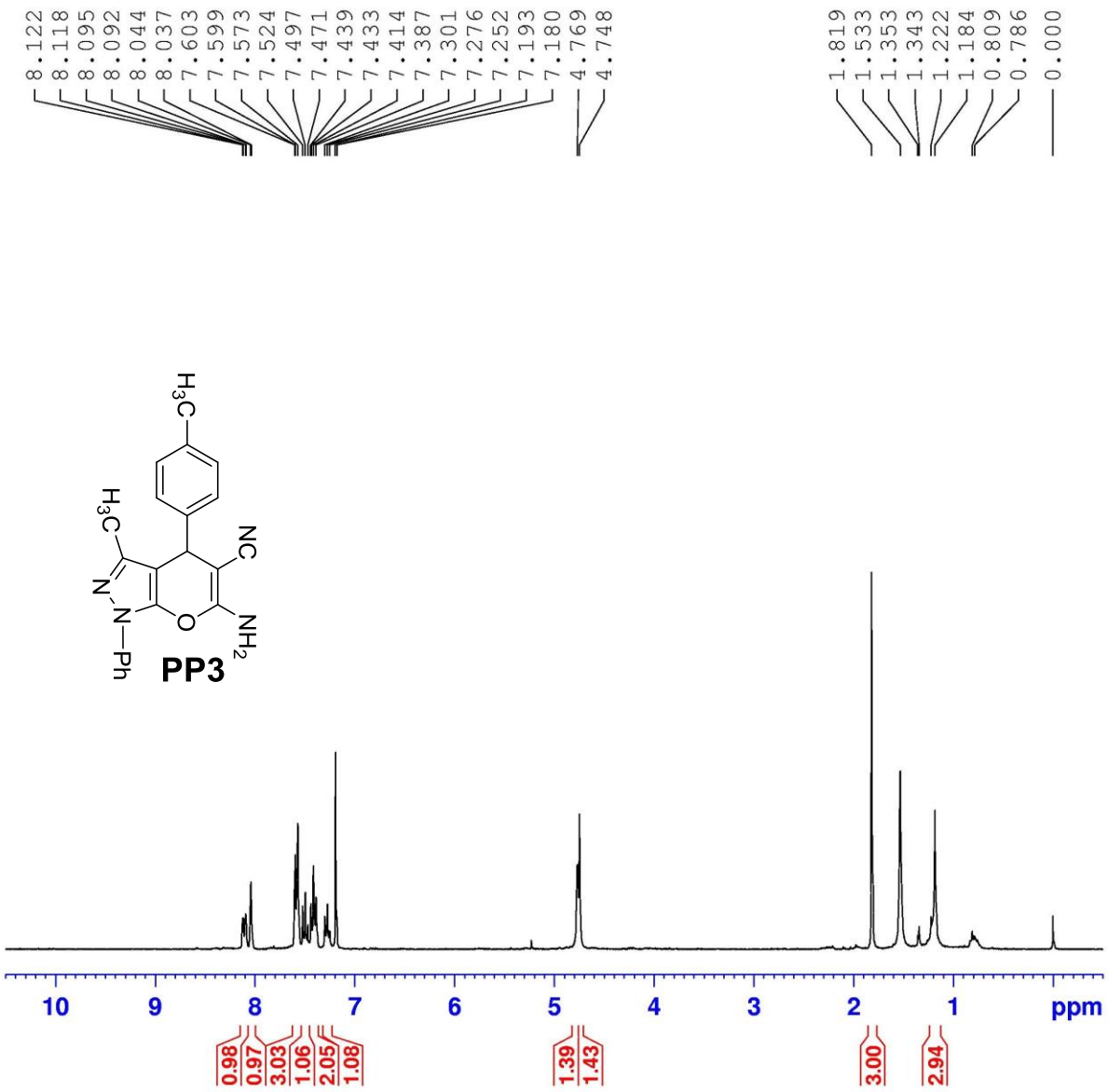

```
Current Data Parameters
NAME                  1429H
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160224
Time                  15.27
INSTRUM               spect
PROBHD    5 mm BBO BB-1H
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH              18028.846 Hz
FIDRES            0.275098 Hz
AQ                1.8175818 sec
RG                      256
DW                   27.733 usec
DE                    6.00 usec
TE                   300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                    10.00 usec
PL1                    0.00 dB
SFO1            75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -2.00 dB
PL12                  16.98 dB
PL13                  20.00 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF              75.4677490 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
```



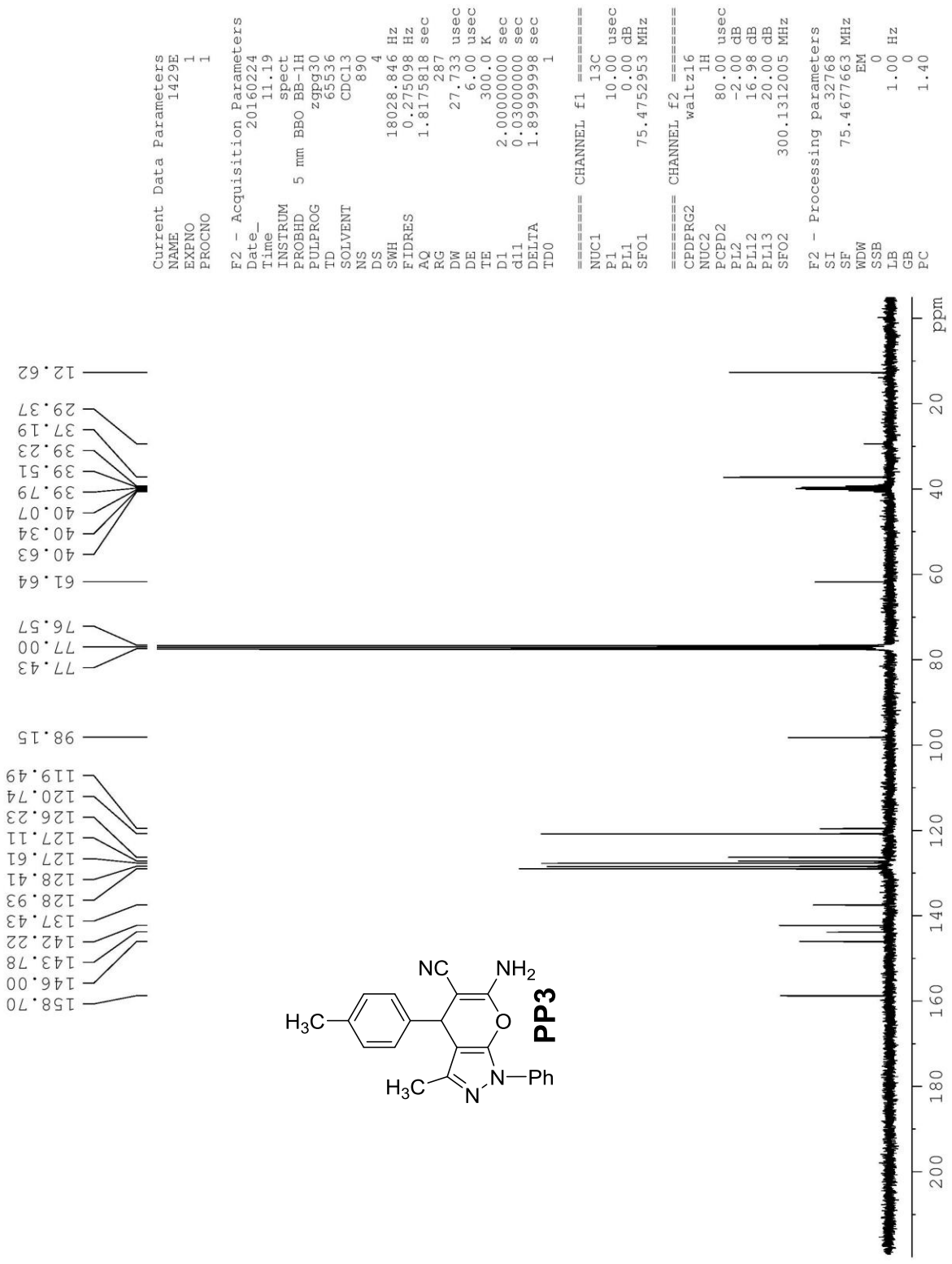

```
Current Data Parameters
NAME                  0368C
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150323
Time                  15.42
INSTRUM               spect
PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               6188.119 Hz
FIDRES            0.094423 Hz
AQ                5.2953587 sec
RG                      406
DW                  80.800 usec
DE                   6.00 usec
TE                  300.0 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    8.60 usec
PL1                  -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1300266 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

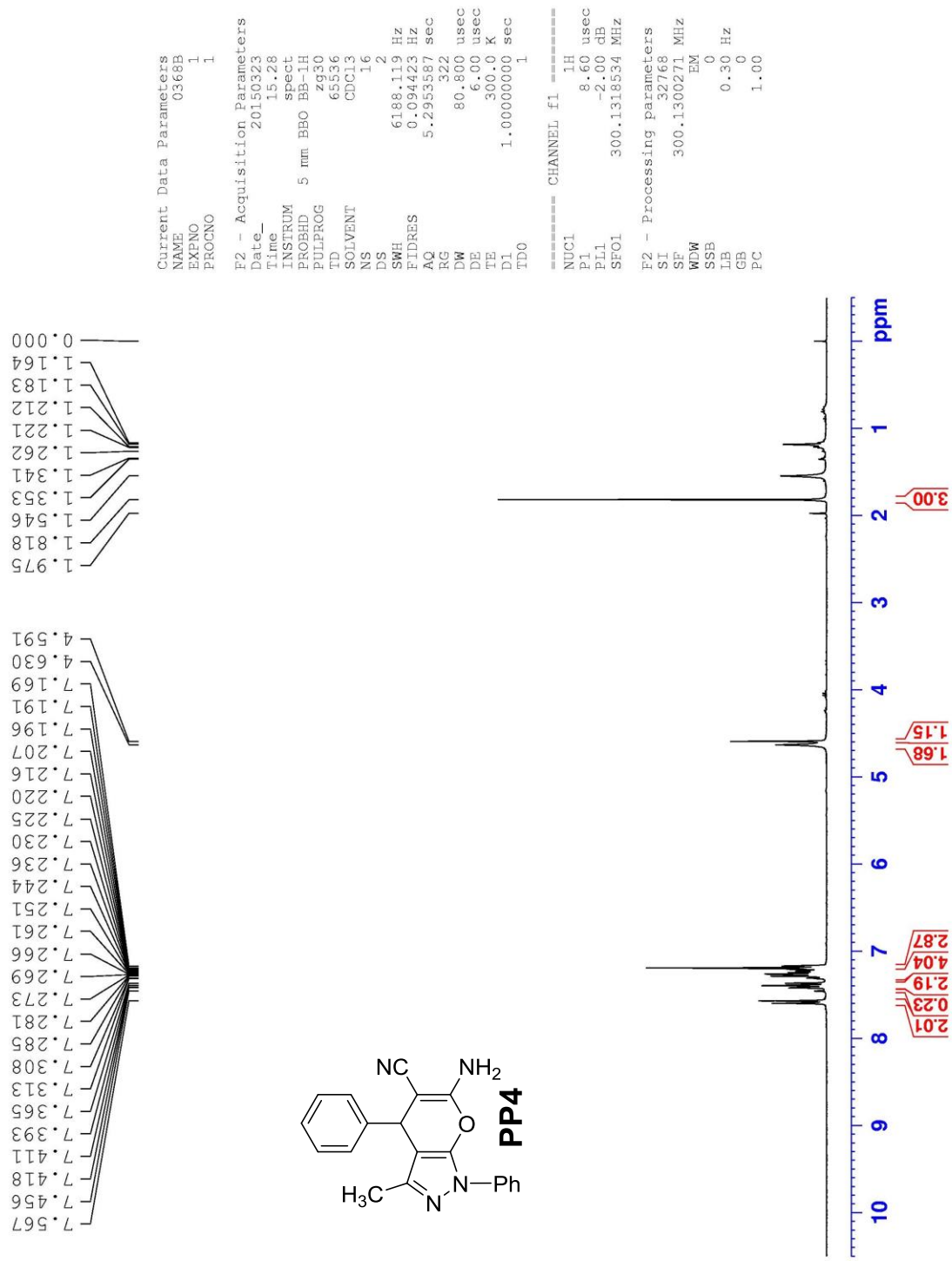


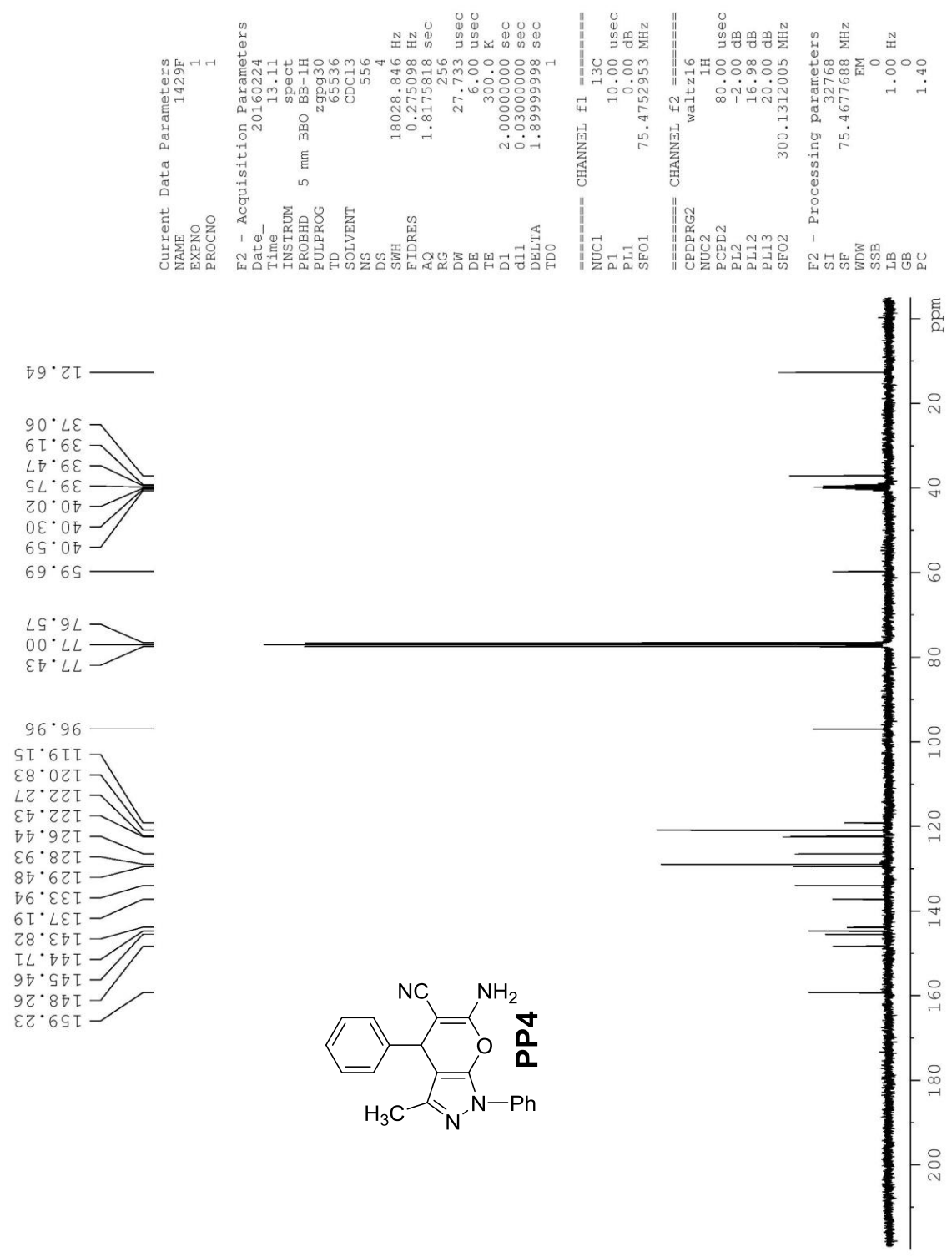

```
Current Data Parameters
NAME                 1429G
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160224
Time                 14.14
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     886
DS                       4
SWH              18028.846 Hz
FIDRES           0.275098 Hz
AQ               1.8175818 sec
RG                     256
DW                27.733 usec
DE                 6.00 usec
TE                 300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  10.00 usec
PL1                  0.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -2.00 dB
PL12                16.98 dB
PL13                20.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                   32768
SF             75.4681536 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                   1.40
```




```
Current Data Parameters
NAME                  0368E
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150324
Time                 14.34
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               6188.119 Hz
FIDRES               0.094423 Hz
AQ                5.2953587 sec
RG                     362
DW                   80.800 usec
DE                    6.00 usec
TE                   300.0 K
D1             1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    8.60 usec
PL1                  -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1300265 MHz
WDW                      EM
SSB                       0
LB                    0.30 Hz
GB                        0
PC                    1.00
```


Current Data Parameters
NAME 1429E
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160224
Time 11.19
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 890
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 287
DW 27.733 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677663 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
12.62
29.37
37.19
39.23
39.51
39.79
40.07
40.34
40.63
61.64
76.57
77.00
77.43
98.15
119.49
120.74
126.23
127.11
127.61
128.41
128.93
137.43
142.22
143.78
146.00
158.70
ppm
NC
NH2
H3C
O
N
Ph
H3C
PP3


Current Data Parameters
NAME 0368B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150323
Time 15.28
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 322
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300271 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.975
1.818
1.546
1.353
1.341
1.262
1.221
1.212
1.183
1.164
0.000
7.567
7.456
7.418
7.411
7.393
7.365
7.313
7.308
7.285
7.281
7.273
7.269
7.266
7.261
7.251
7.244
7.236
7.230
7.225
7.220
7.216
7.207
7.196
7.191
7.169
4.630
4.591
NC
NH2
O
N
N—Ph
H3C
PP4
ppm
1
2
3
4
5
6
7
8
9
10
3.00
1.68
1.15
2.87
4.04
2.19
0.23
2.01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SOLVENT CDCl3
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d11 0.03000000 sec
DELTA 1.89999998 sec
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PL1 0.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 80.00 usec
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SFO2 300.1312005 MHz
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39.19
39.47
39.75
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76.57
77.00
77.43
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129.48
133.94
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143.82
144.71
145.46
148.26
159.23
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H3C
PP4
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60
80
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120
140
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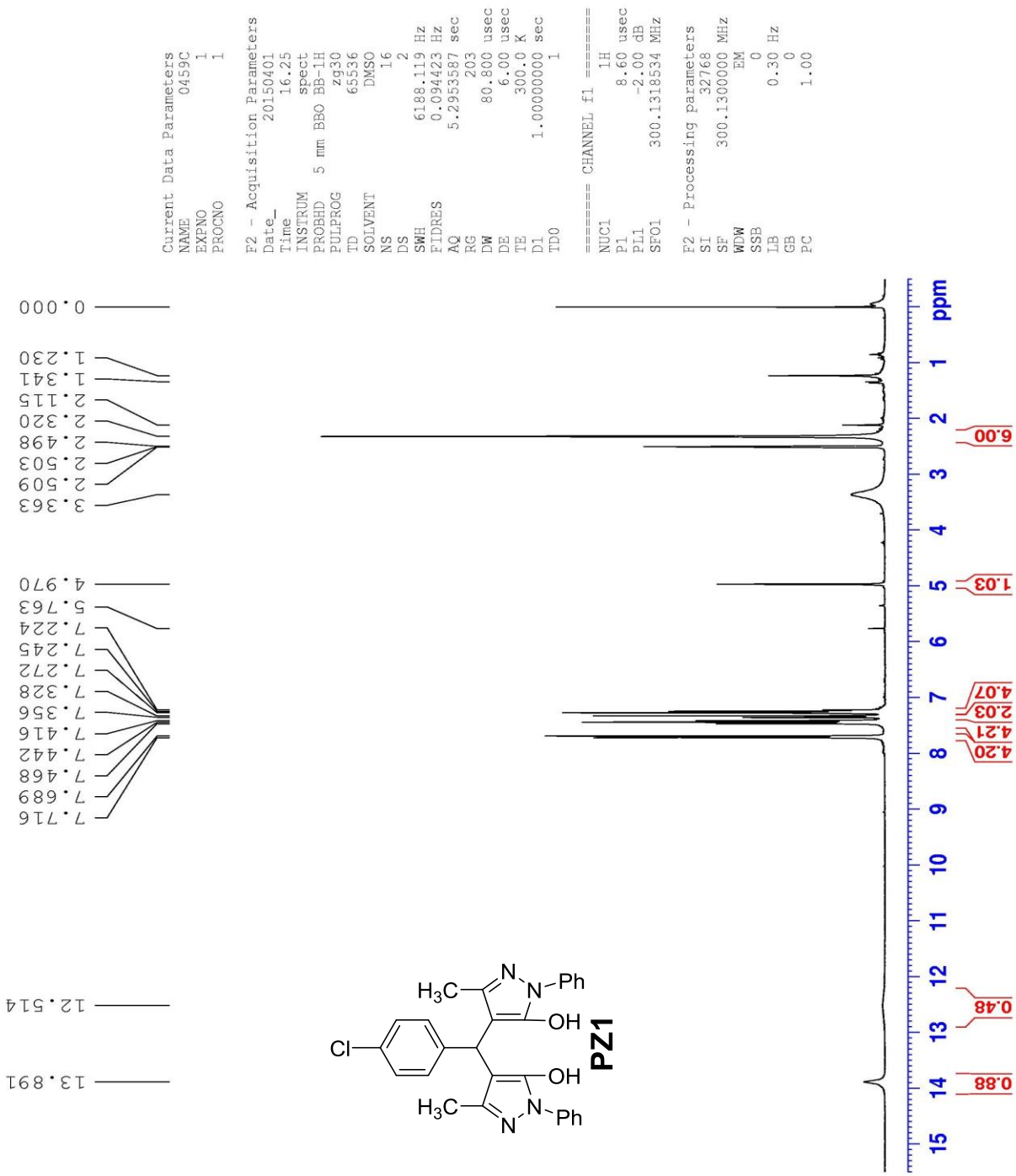
180
200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PULPROG zg30
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SOLVENT DMSO
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 203
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
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SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
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PC 1.00
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1.341
2.115
2.320
2.498
2.503
2.509
3.363
4.970
5.763
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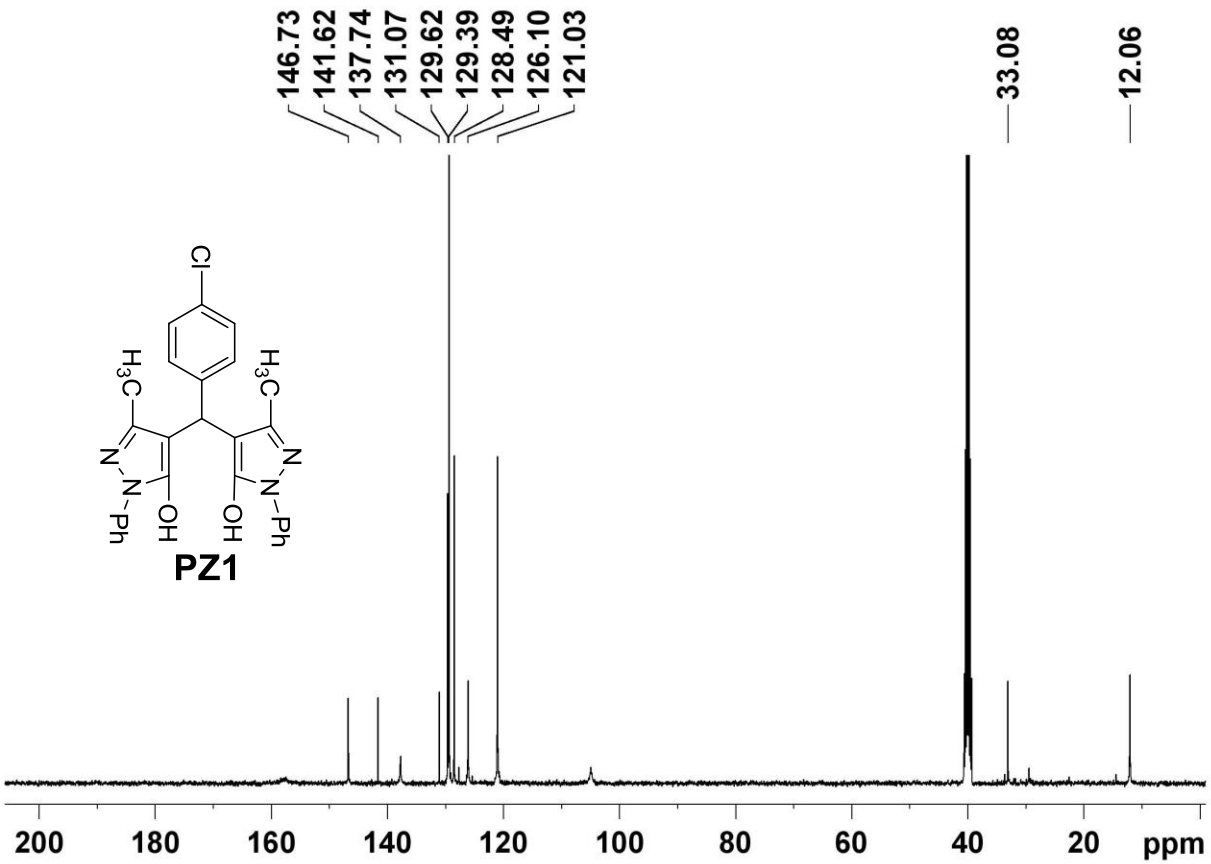
S4 13C NMR



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PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 204.46
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

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NUC1 13C
P1 10.62 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
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NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.24083000 W
PLW13 0.19508000 W

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LB 2.00 Hz
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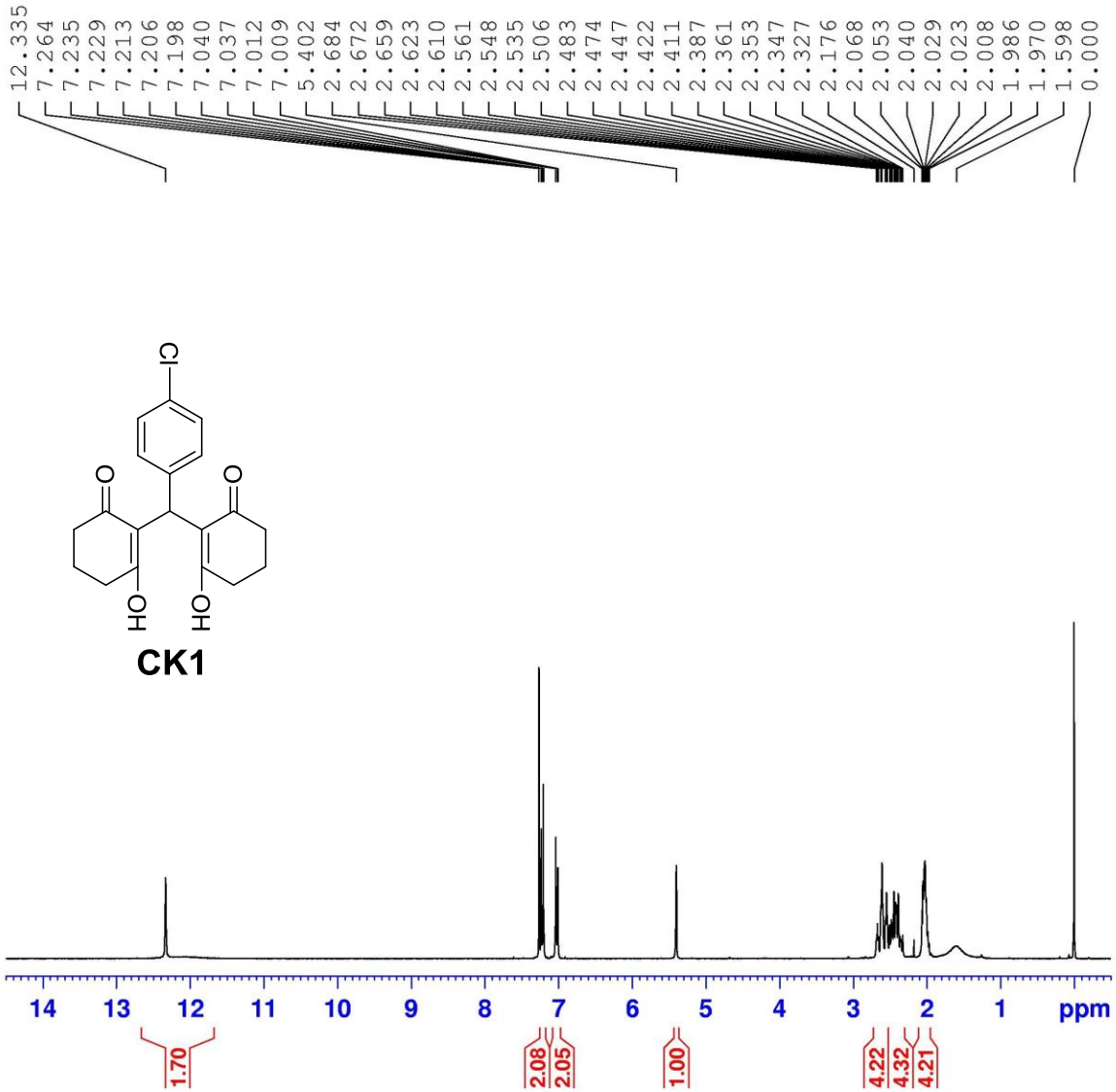
PC 1.40

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TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                6188.119 Hz
FIDRES            0.094423 Hz
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DE                    6.00 usec
TE                   300.0 K
D1              1.00000000 sec
TD0                       1

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PL1                  -2.00 dB
SFO1           300.1318534 MHz

F2 - Processing parameters
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WDW                      EM
SSB                       0
LB                     0.30 Hz
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PC                     1.00
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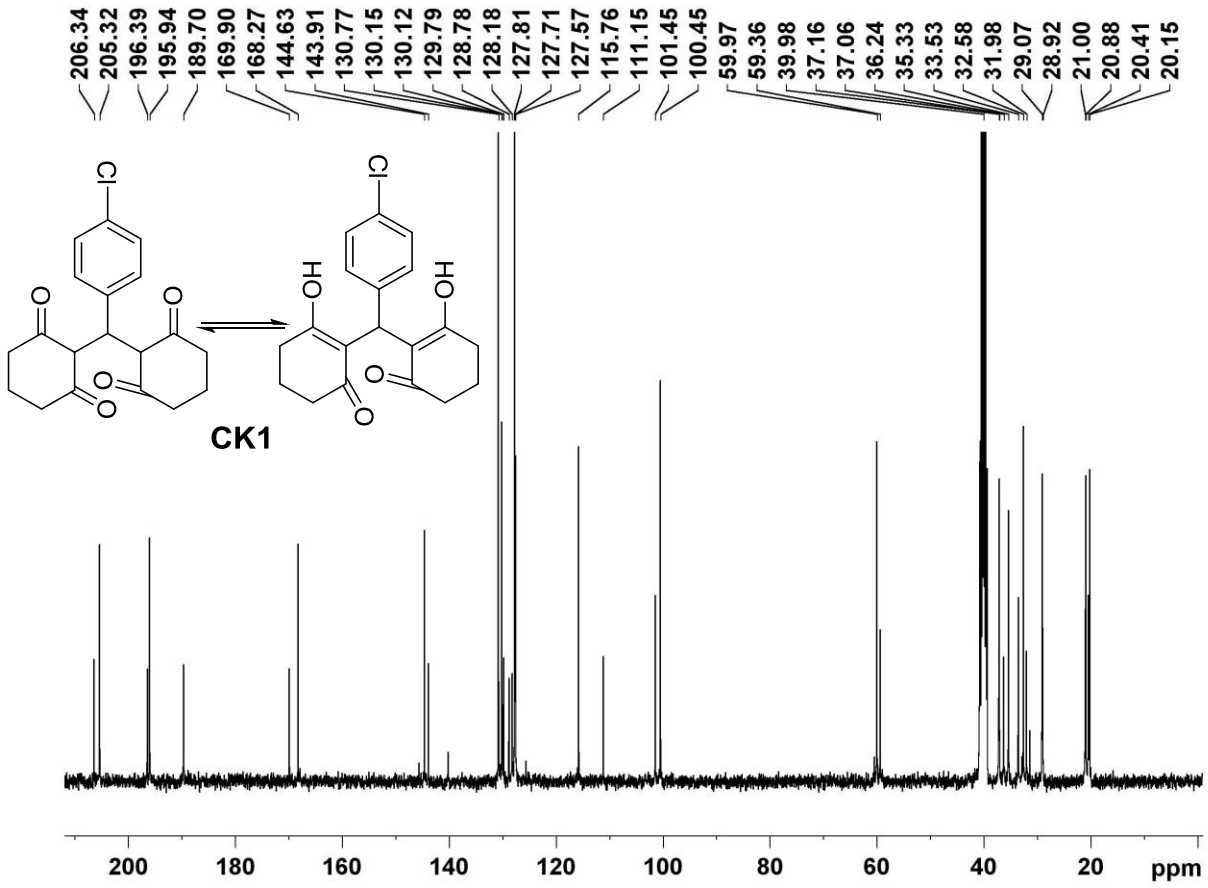
S1 13C NMR



BRUKER

Current Data Parameters
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EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 9.54
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 204.46
DW 20.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6479769 MHz
NUC1 13C
P1 10.62 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
SFO2 400.2316009 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.24083000 W
PLW13 0.19508000 W

F2 - Processing parameters
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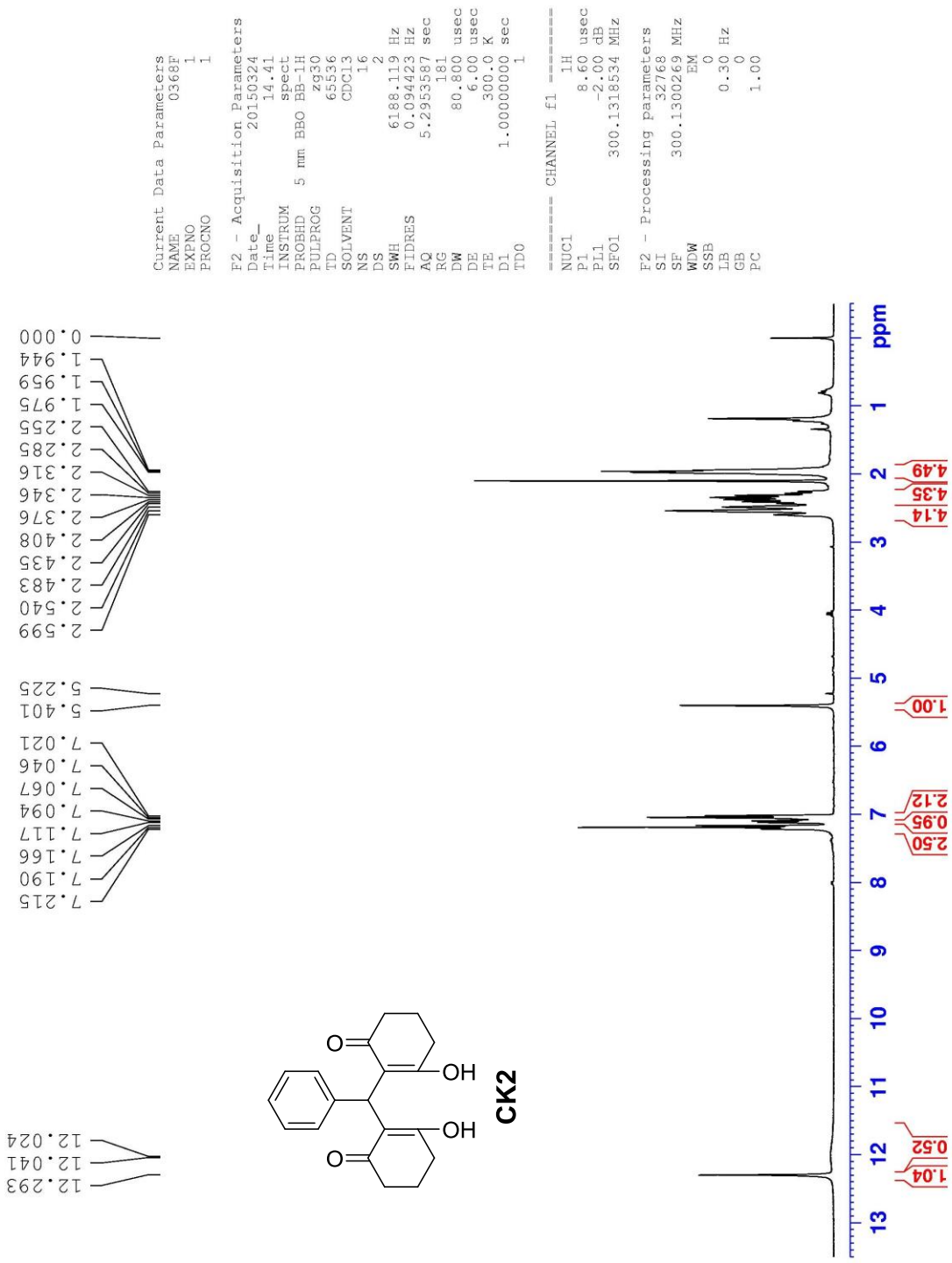
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40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TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
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WDW EM
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LB 0.30 Hz
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7.215
7.190
7.166
7.117
7.094
7.067
7.046
7.021
5.401
5.225
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2.540
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2.255
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1.959
1.944
0.000
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O
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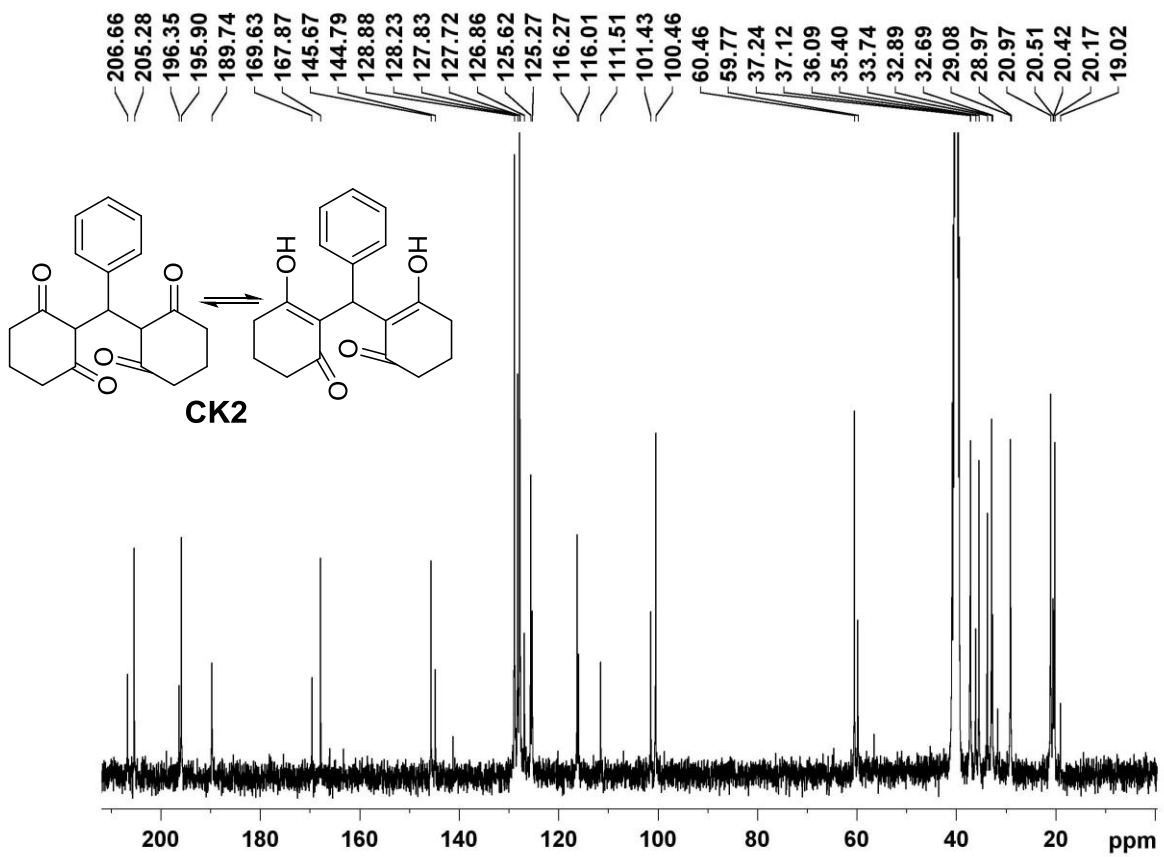
S2 13C NMR



BRUKER

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EXPNO 2
PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 204.46
DW 20.800 usec
DE 6.50 usec
TE 297.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6479769 MHz
NUC1 13C
P1 10.62 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
SFO2 400.2316009 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.24083000 W
PLW13 0.19508000 W

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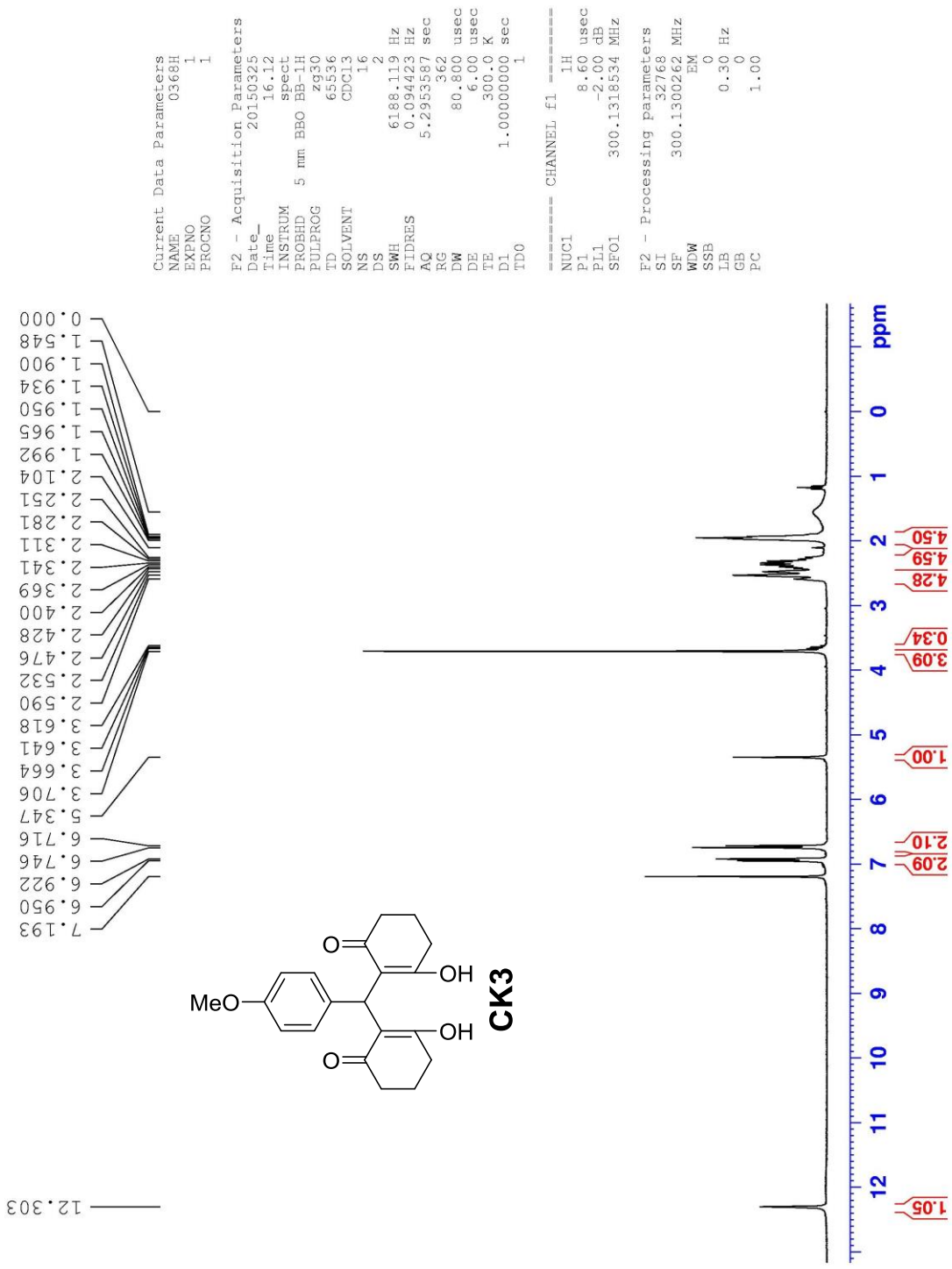
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PROCNO 1
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PULPROG zg30
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SOLVENT CDCl3
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 362
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
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F2 - Processing parameters
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2.400
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2.251
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OH
OH
O
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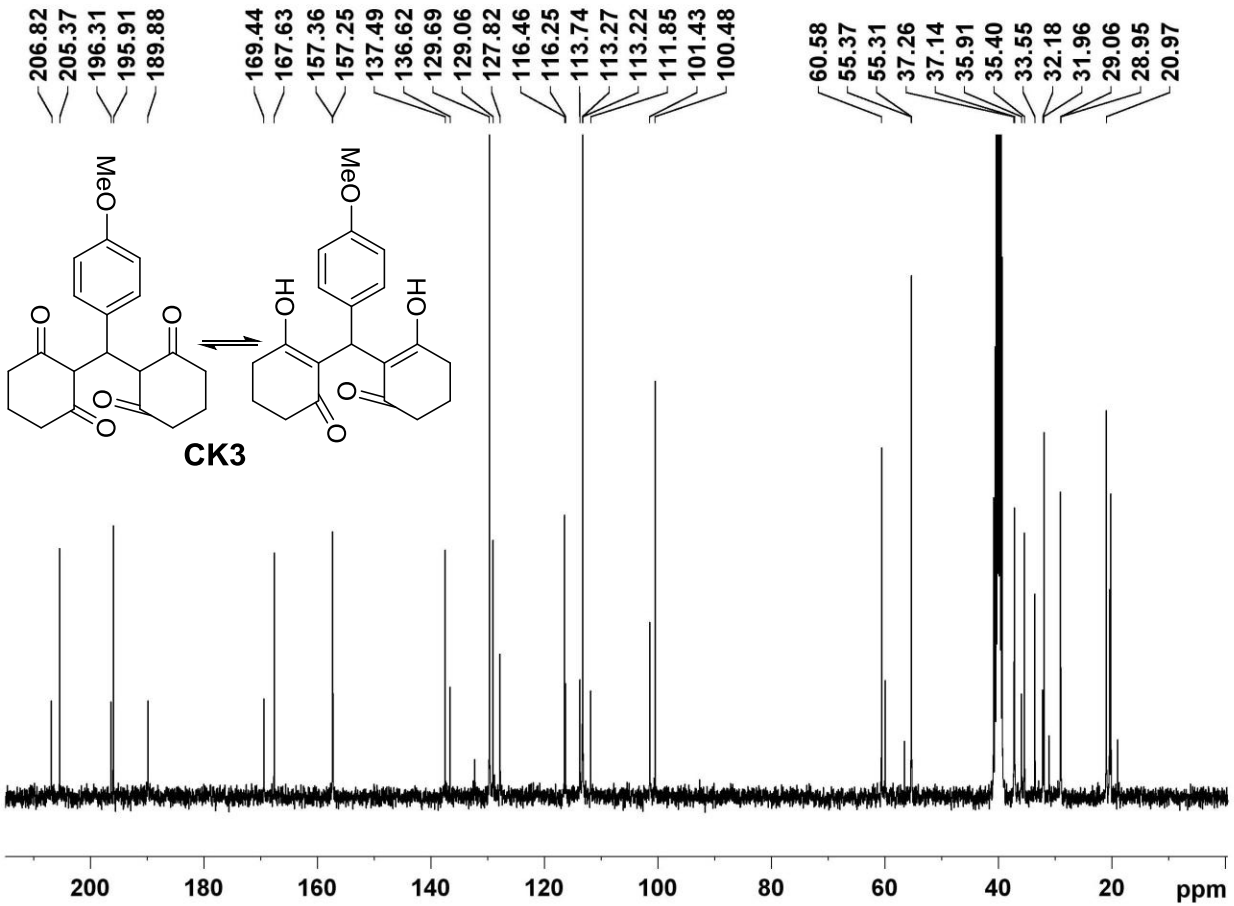
4.50

S3 13C NMR



BRUKER

Current Data Parameters
NAME S3
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 15.57
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 204.46
DW 20.800 usec
DE 6.50 usec
TE 297.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6479769 MHz
NUC1 13C
P1 10.62 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
SFO2 400.2316009 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.24083000 W
PLW13 0.19508000 W

F2 - Processing parameters
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WDW EM
SSB 0
LB 2.00 Hz
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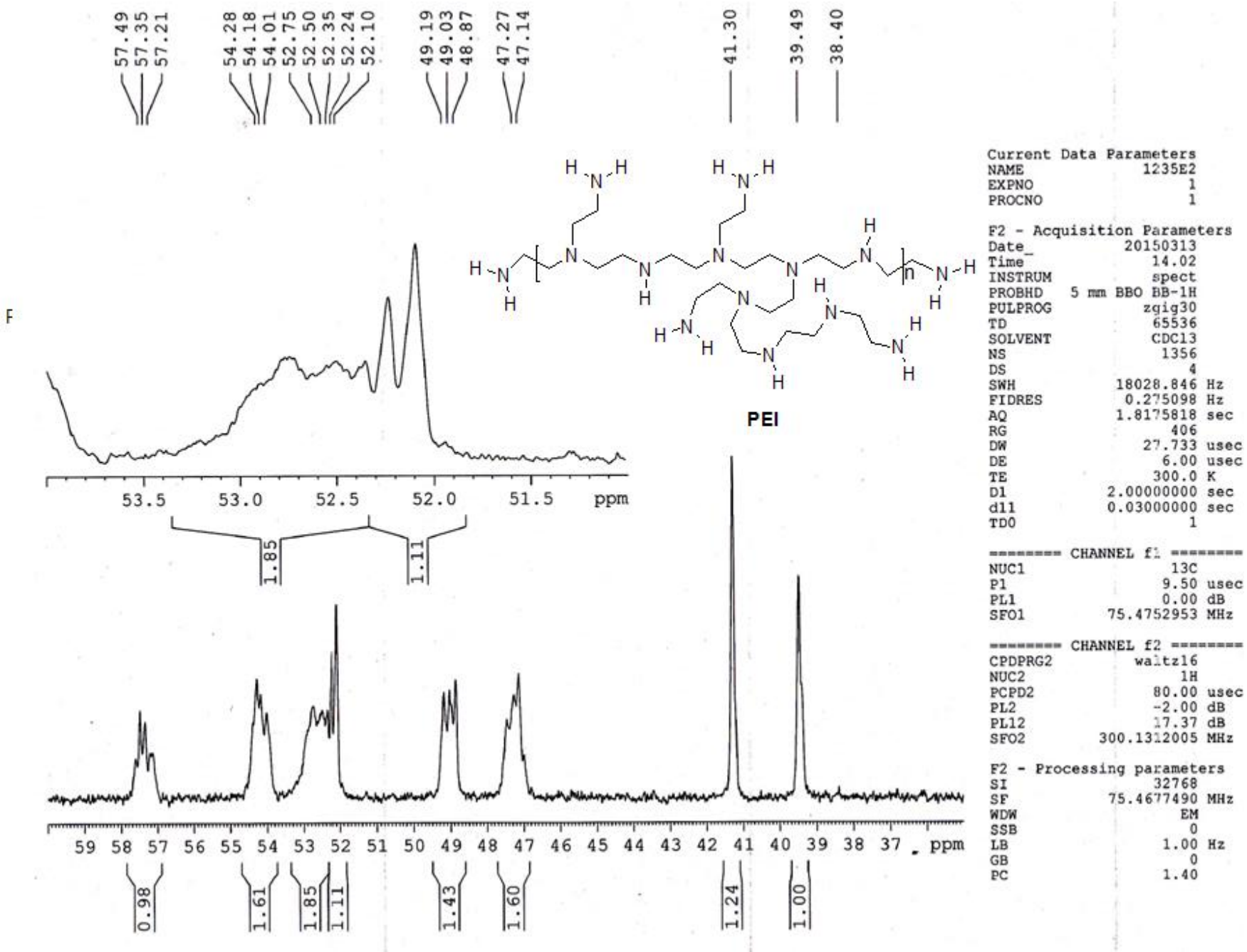
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52.50
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52.24
52.10
49.19
49.03
48.87
47.27
47.14
41.30
39.49
38.40
PEI
53.5
53.0
52.5
52.0
51.5
ppm
1.85
1.11
59 58 57 56 55 54 53 52 51 50 49 48 47 46 45 44 43 42 41 40 39 38 37 ppm
0.98
1.61
1.85
1.11
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1.60
1.24
1.00
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PROCNO 1
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TD 65536
SOLVENT CDC13
NS 1356
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SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.8175818 sec
RG 406
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DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 9.50 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 17.37 dB
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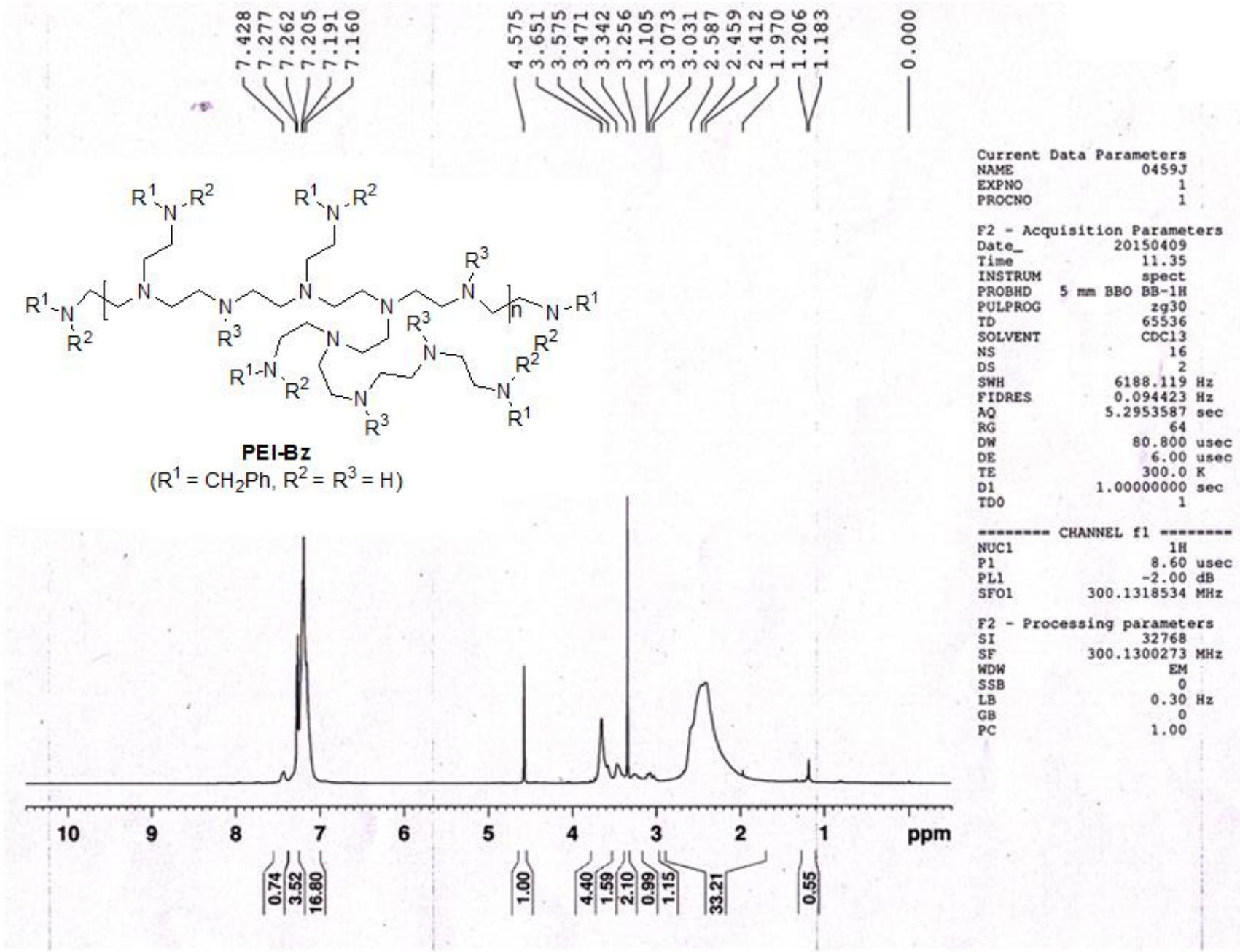
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3.073
3.031
2.587
2.459
2.412
1.970
1.206
1.183
0.000
PEI-Bz
(R1 = CH2Ph, R2 = R3 = H)
10
9
8
7
6
5
4
3
2
1
ppm
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3.52
16.80
1.00
4.40
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0.99
1.15
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PROCNO 1
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Time 11.35
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
AQ 5.2953587 sec
RG 64
DW 80.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -2.00 dB
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F2 - Processing parameters
SI 32768
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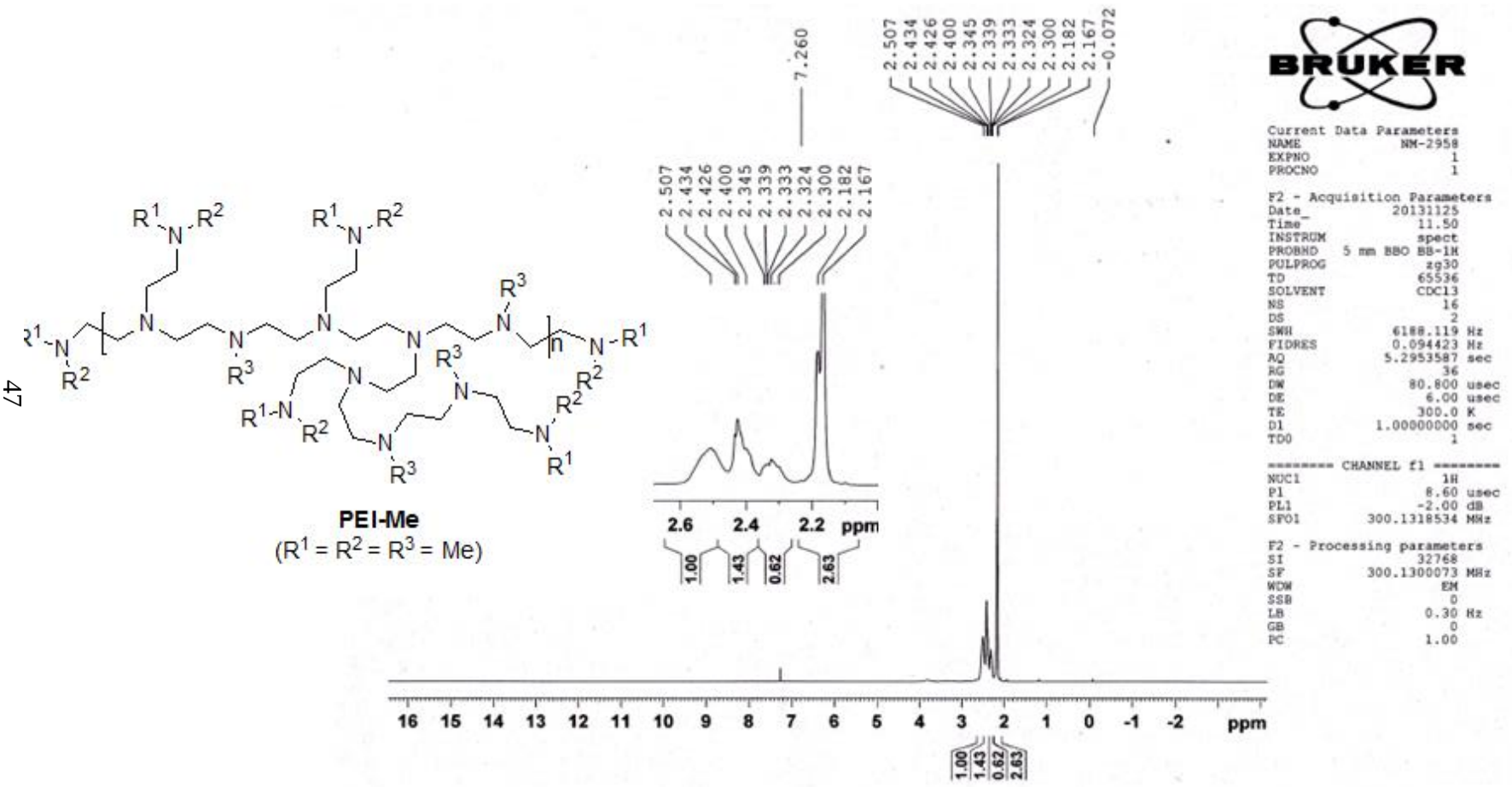
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(R1 = R2 = R3 = Me)
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2.324
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2.167
-0.072
7.260
2.6
2.4
2.2
ppm
1.00
1.43
0.62
2.63
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
BRUKER
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PROCNO 1
F2 - Acquisition Parameters
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PULPROG zg30
TD 65536
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NS 16
DS 2
SWH 6188.119 Hz
FIDRES 0.094423 Hz
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RG 36
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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P1 8.60 usec
PL1 -2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300073 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Table S2: Heterocyclic ring derivatives identified by docking with NorA homologue MFS

S. No.	Compound ID	Binding Energy (kcal/mol)
1	BC6	-11.59
2	BC1	-11.23
3	BC9	-11.22
4	BC2	-10.56
5	BC3	-10.18
6	CK1	-9.56
7	CK3	-9.29
8	BC4	-9.22
9	BC7	-9.12
10	BC8	-9.1
11	PP3	-8.88
12	PP2	-8.79
13	PP1	-8.76
14	PP4	-8.72
15	PZ1	-8.69
16	CK2	-8.2
17	BC5	-8.01

Table S3: Anti staphylococcal effect of Heterocyclic ring derivatives against *S.aureus* (SA-1199B)

Compounds	MIC (µg/ml)
CK1	> 64
BC1	> 64
BC9	> 64
BC2	> 64
BC3	64
BC6	64
CK2	> 64
BC5	> 64
PZ1	> 64

Table S4: Mortality based toxicity assessment of Zebra Fish exposed to chosen putative EPIs

Compound	Conc.* µg/ml	No. of fishes alive after 24hrs	% survival
BC1[#]	16	3	100
BC2	16	1	33.33
BC3	16	1	33.33
BC6[#]	16	3	100
BC9	16	3	100

***indicates double dose;**
 # indicates the compound was sparingly soluble

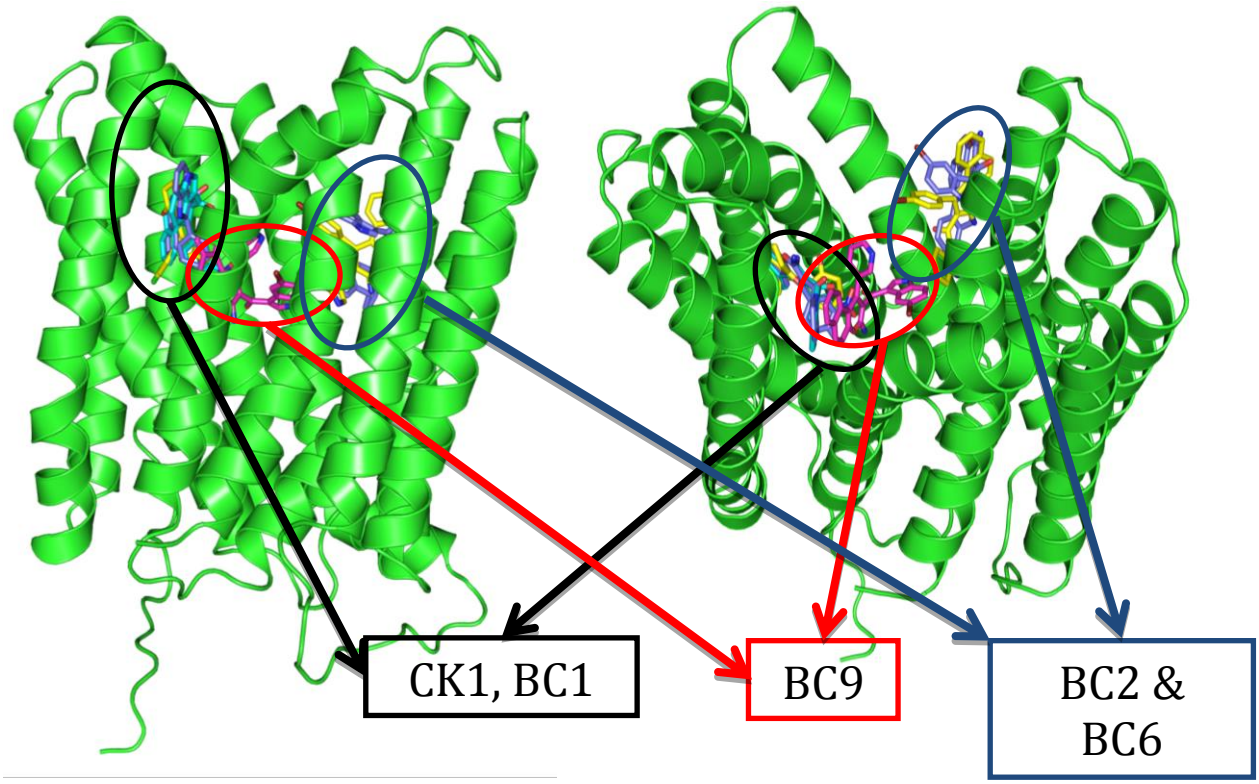

Figure S1: Figure showing the three different binding sites and with the ligands bound in the respective binding sites.

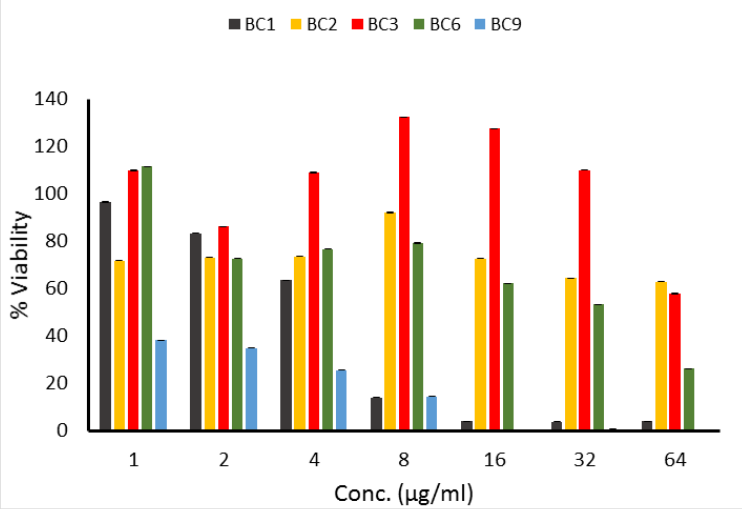

Figure S2: Effect of BC series of compounds on Cell Viability

Pancreatic cell line was treated with BC series compounds at varying concentration (1-64µg/ml) for 24h and cell viability was measured by MTT assay

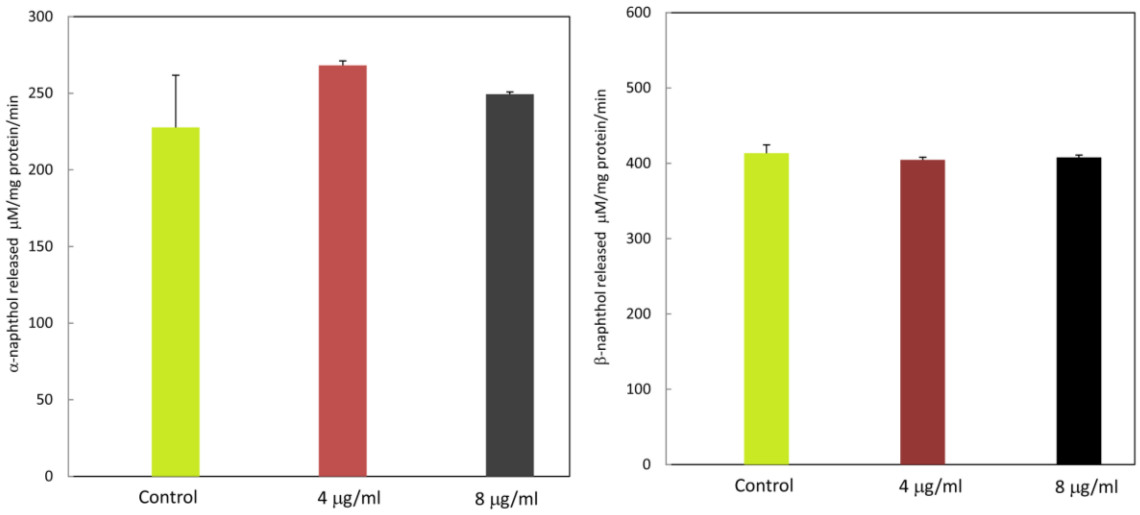

Figure S3.1: Effect of compound BC9 on the activity of liver carboxylesterase in zebra fish. Each bar represents mean ± SD of 5 determinations in duplicates using liver samples pooled from two fishes. The difference between the exposed and control fish were not observed to be significant.

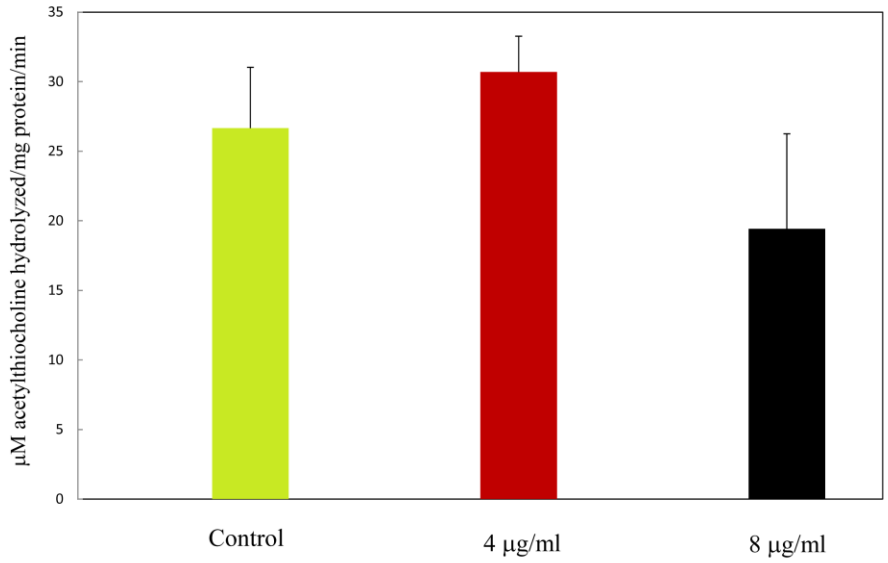

Figure S3.2: Effect of compound BC9 on the activity of brain acetylcholinesterase in zebrafish. Each bar represents mean±SD of 5 determinations in duplicates using liver samples pooled from two fishes. Though there was a decrease in acetylcholinesterase activity in zebrafish exposed to 8mg/ml, this was not statistically significant ($p<0.05$).

References

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3 R. H. nia, M. Mamaghani, K. Tabatabaeian, F. Shirini and M Rassa. *Bioorg. Med. Chem. Lett*. 2012, **22**, 5956–5960.
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