Scientific paper

Synthesis and Anti-inflammatory Activity of New *N*-Acyl-2-pyrazolines Bearing Homologous Alkyloxy Side Chains

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Abstract

A series of new pyrazoline derivatives (**1a-2h**) equipped with *N*-acyl arms and homologous alkyloxy side chains were synthesized and characterized on the basis of spectroscopic data and microanalysis. All the synthesized compounds were screened for their *in-vitro* anti-inflammatory activity to examine the effect of alkyloxy side chain length on activity. Compounds with odd number of carbons in alkyloxy side chain showed better activity as compared to even ones. Compound **2c** (96% inhibition, IC_{50} = 173.06 ± 2.312 mM) was found to be the most active compound of the series with better activity than the standard (Indomethacine, 92% inhibition, IC_{50} = 273.12 ± 2.33 mM). Compound **1a** (86%, IC_{50} = 296.16 ± 2.091 mM) was the second best with comparable activity to the standard drug. However, the other compounds of series showed moderate to low activity. Interestingly, parallel cytotoxicity studies of compounds **1a-2h** against PC-3 cell line revealed either no or very low cytotoxicity. The study may contribute in developing useful alternatives to presently used NSAIDs with harmful gastric effects due to direct cytotoxicity.

Keywords: ***N*-**Acyl-2-pyrazolines, synthesis, anti-inflammatory, cytotoxicity

1. Introduction

Pyrazolines being a member of five memebered heterocycles family, represent a class of compounds having immense importance in heterocyclic chemistry. Pyrazoline is a dihydropyrazole having two nitrogen atoms in adjacent positions and possessing only one endocyclic double bond. Considerable interest on the pyrazoline structure has been focused in the field of medicinal chemistry. Among all the pyrazolines, 2-pyrazoline has gained much attention due to its broad spectrum biological activities[1–3] such as antiamoebic,[4–7] antimycobacterial,[5] antibacterial/antifungal,[6] anti-inflammatory,[8] anticancer,[9,10] antidepressant,[11,12] neuroprotector,[13,14] antiviral[15,16] and antiobesity[17] and its presence in a number of pharmacologically active molecules such as azolid/ tandearil (anti-inflammatory), phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), anturane (uricosuric) and indoxacarb (insecticidal). Although, a number of pyrazoline-based new compounds have been made and patented in recent years possessing diverse biological activities [1–3] but still it is an active area of research[18–23] and many new aspects need to be explored and worked on.

Inflammation occurs as a defensive biological response of vascular tissues to harmful stimuli resulting in some physiological adaptations to minimize tissue damage and initiate the healing process.[24–26] Non-steroidal anti-inflammatory drugs (NSAIDs) are usually used to treat inflammation. The delay in treatment may lead to vasomotor rhinnorrhoea, rheumatoid arthritis, and atherosclerosis.[27] NSAIDs inhibit the activity of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) which are the key enzymes involved in the biosynthesis of prostaglandin from arachidonic acid.[28,29] Such inhibition reduces the levels of protection resulting in harmful gastric effects.[30] Therefore, most of the presently used NSAIDs are not very useful in all inflammatory disorders.[31] However, it has recently been found that harmful gastric effects of NSAIDs are not related to PGE2 inhibition but are rather due to the direct cytotoxicity in the stomach to gastric cells.[32,33] Therefore, new anti-inflammatory agents with no/less such adverse gastric effects are needed. As a conti-

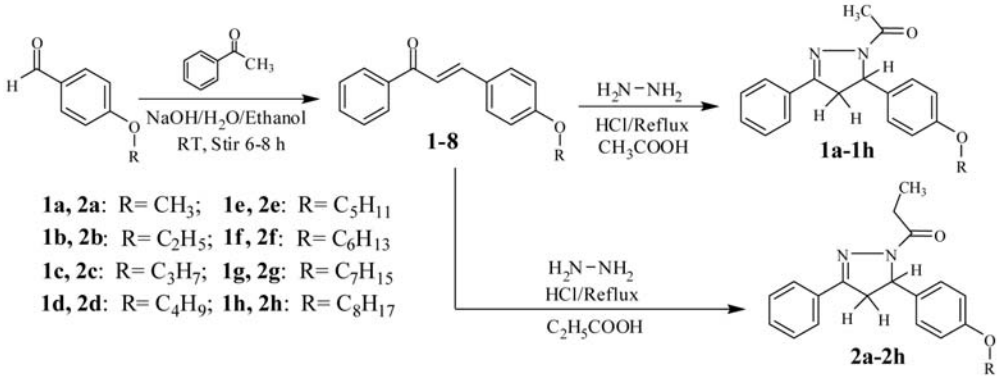
nuation of our ongoing project on synthesis and applications of pyrazolines,[34–37] herein, we report the synthesis of some new anti-inflammatory *N*-acyl pyrazolines bearing homologous alkyloxy side chains with almost negligible cytotoxicity.

2. Results and Discussion

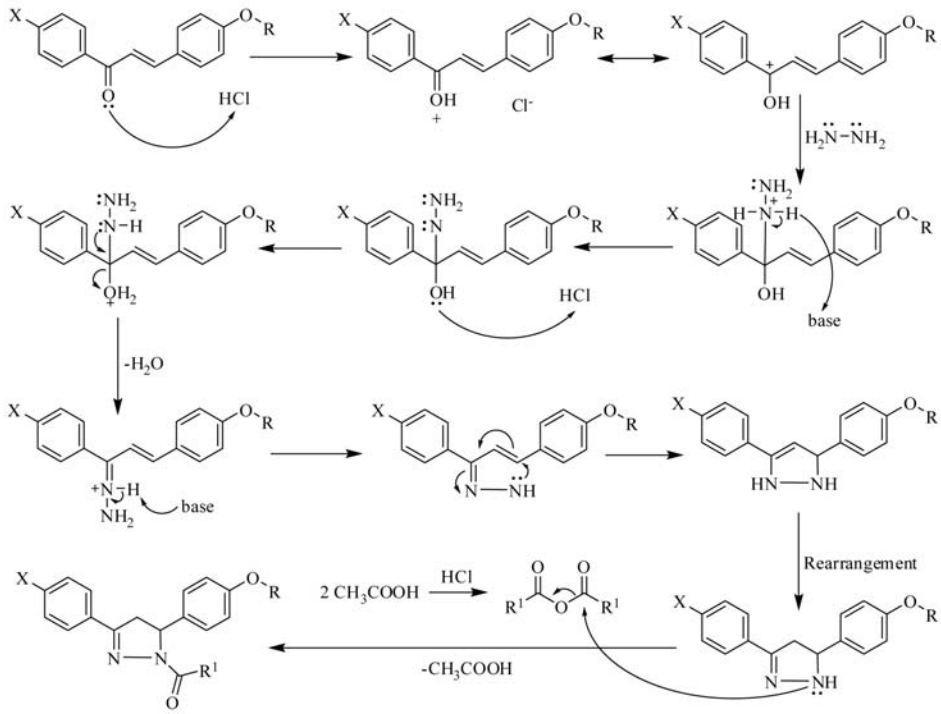
2. 1. Chemistry

The compounds **1a-2h** were synthesized by refluxing an equimolar mixture of (*E*)-3-(4-alkyloxyphenyl)-1-phenylprop-2-en-1-ones (**1-8**)[38] and hydrazine in the respective solvents such as glacial acetic acid and propionic acid containing catalytic amount of hydrochloric acid (Scheme 1 & 2) and purified by silica gel column chromatography using petroleum ether/ethyl acetate (4:1) as mobile phase. All the products were obtained as solids in 81–89% yield. The structures of all the synthesized compounds were deduced by their spectroscopic (IR, ^{1}H NMR & ^{13}C NMR) and elemental analyses data.

In the IR spectra of compounds (**1a-2h),** a sharp band at 1647–1633 cm^{-1} and 1688–1675 cm^{-1} was assigned to the stretching of ν(C=N) and ν(C=O), respectively.[34–37,39–41] The carbon-nitrogen single bond (C-N) stretching frequencies were observed at 1298–1290 cm^{-1}. The presence of these frequencies suggests the formation of cyclization product. Two strong bands at stretching frequencies in the range of 1259–1250 cm^{-1} and 1056–1042 cm^{-1} indicate the presence of Ar–O–R group. The formation of the five membered pyrazoline ring was further confirmed by the presence of three doublet of doublets due to



Scheme 1. Synthesis of 2-functionalised pyrazolines **1a-2h**.



Scheme 2. Proposed mechanism for the synthesis of 2-functionalised pyrazolines **1a-2h**

two methylene protons (H_a and H_b) and one methine proton (H_x) in ^{1}H NMR spectroscopy. The methyl protons of acetyl group (O=C–C***H***$_3$) were observed at 2.43 ppm as singlet for compounds **1a**-**1h**, whereas a triplet and quartet at 1.20–1.22 and 2.83–2.84 ppm was noticed for methyl protons (O=C–CH_2–C***H***$_3$) and the methylene protons (O=C–C***H***$_2$–CH_3), respectively for propionyl group of compounds **2a–2h**. A triplet was observed in the range of 3.79–4.00 ppm for the methylenic protons (Ar–O–C***H***$_2$–) of the alkoxy chain directly attached to the oxygen atom. All the other protons of alkoxy chain appeared in the range of 0.90–1.77 ppm. The ^{13}C NMR spectra of compounds (**1a**–**2h**) displayed peaks at 55–65 ppm, 59–70 ppm and 41–44 ppm for C_5, C_3 and C_4 carbons, respectively. All the aromatic carbons were observed in the range of 114–159 ppm. The signals for acyl carbons were noticed in the range of 167–173 ppm. Furthermore, a molecular ion peak ($M^{+\bullet}$) for each compound was also observed at their respective masses along with their typical pyrazoline fragmentation pattern.[42] In addition, the number of the protons and carbons were found in good agreement with elemental (CHN) analyses suggesting the formation of the target compounds. The structures of the two compounds **1a** [43] and **1f** [44] were unambiguously confirmed through single crystal X-Ray diffraction technique (Figure 1).

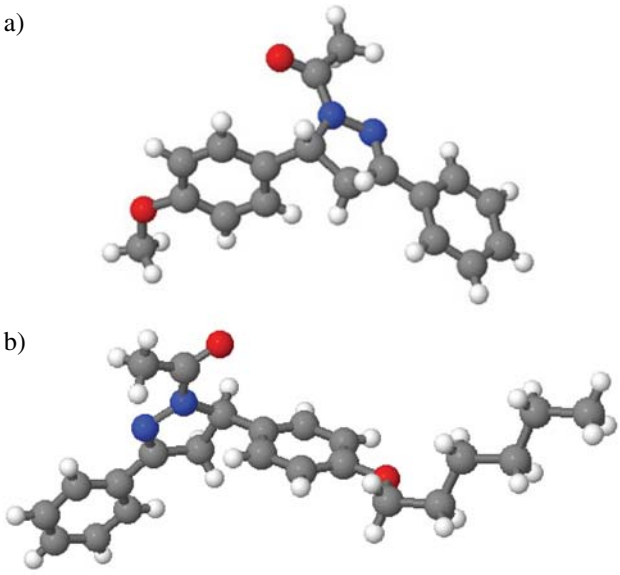


Figure 1. (a) Crystal Structure of **1a**.[43] (b) Crystal Structure of **1f.**[44]

2. 2. Antiinflammatory Activity (in vitro)

The defensive process of host in response to foreign challenge or tissue injury for restoration of normal tissue structure and function is initiated by the activation of phagocyte-specific enzyme, NADPH oxidase which generates superoxide anion (a reactive free radical) by transferring electrons from NADPH to molecular oxygen inside the cell across the membrane. The generated superoxide then kills bacteria and fungi by still unknown mechanisms. This is the key step of immune response and inflammatory cascade. However, this superoxide may lead to the formation of hydrogen peroxide which is capable of undergoing further reactions to produce highly toxic reactive oxygen species (ROS). In immune compromised patients, ROS are formed in large quantities. Therefore, their inhibition is one approach to treat chronic inflammation and to modulate immune response.

This study used the water-soluble tetrazolium salt (WST-1) to measure superoxide production by neutrophils activated by opsonized zymosan, which induces phagocytic activation of neutrophils. This technique is more sensitive and reliable to measure the superoxide scavenging properties as compared to other available techniques, a perfect protocol for indirect evaluation of anti-inflammatory potential.[45] Using this technique, the anti-inflammatory potential of the *N*-acyl-2-pyrazolines **1a–2h** bearing homologous alkyloxy side chains was determined in terms of percent inhibition. The compounds with ~50% inhibition were retested for their IC_{50} (inhibitory concentration 50%), the concentration of the compound which inhibits superoxide production by 50% of three independent experiments (Table 1, Figure 2). Indomethacine was used as the standard reference drug in this study. The compounds (**1a–2h**) showed a varying degree of anti-inflammatory activity, when compared to standard drug. Compound **2c** (96%**,** 173.06 ± 2.312) showed excellent anti-inflammatory activity even better than the standard (92%, 273.12 ± 2.33). Compound **1a** (86%, 296.16 ± 2.091) also exhibited good and comparable anti-inflammatory activity. Compound **1e** (55%, 465.23 ± 1.763), **1h** (52%, 492.20 ± 3.176), **2e** (76%, 346.13 ± 2.341) and **7c** (51%, 425.21 ± 2.732) showed moderate anti-inflammatory potential. However, compound **1b**, **1c**, **1d, 1f, 1g, 2a, 2b, 2d, 2f** and **2h** were considered to be least active compound among the series having less than 50% inhibition and were not further tested for their IC_{50} values.

This varying degree of anti-inflammatory activity of 16 tested compounds **(1a–2h)** can be attributed to alkyloxy side chain length because central nucleus *N*-acyl-2-pyrazolines is the same for all the compounds. Surprisingly, compounds with odd number of carbons in alkyloxy group showed maximum activity as compared to the compounds having even numbered alkyloxy side chain (Table 1, Figure 2). For example, compound **1a** (86%, 296.16 ± 2.091) and compound **2c** (96%**,** 173.06 ± 2.312) with methoxy and propyloxy substitutents, respectively showed maximum activity. This difference in activity with the change in alkyloxy side chain length in compound **(1a–2h)** may be credited to some specific conformational arrangements of alkoxy side chains due to different amount of non-covalent interactions in their packed state. The precise mechanism of inhibitory action of these compounds is now under investigation.

Table 1. Anti-inflammatory Activity of **1a-2h**.

Compd.	R^1	R^2	% Inhibition and IC_{50} % Inhibition (at 500 µM)	IC_{50} (µM)	Profile Activity
1a	CH_3	CH_3	**86**	296.16 ± 2.091	**Good**
1b	C_2H_5	CH_3	32	–	Weak
1c	C_3H_7	CH_3	21	–	Weak
1d	C_4H_9	CH_3	43	–	Weak
1e	C_5H_{11}	CH_3	55	465.23 ± 1.763	Moderate
1f	C_6H_{13}	CH_3	11	–	Weak
1g	C_7H_{15}	CH_3	17	–	Weak
1h	C_8H_{17}	CH_3	52	492.20 ± 3.176	Moderate
2a	CH_3	C_2H_5	15	–	Weak
2b	C_2H_5	C_2H_5	06	–	Weak
2c	C_3H_7	C_2H_5	**96**	173.06 ± 2.312	**Excellent**
2d	C_4H_9	C_2H_5	42	–	Weak
2e	C_5H_{11}	C_2H_5	76	346.13 ± 2.341	Moderate
2f	C_6H_{13}	C_2H_5	32	–	Weak
2g	C_7H_{15}	C_2H_5	51	425.21 ± 2.732	Moderate
2h	C_8H_{17}	C_2H_5	22	–	Weak
INDOM [a]	–	–	92	273.12 ± 2.33	Standard

[a] **INDOM** : Indomethacine (Standard Drug).

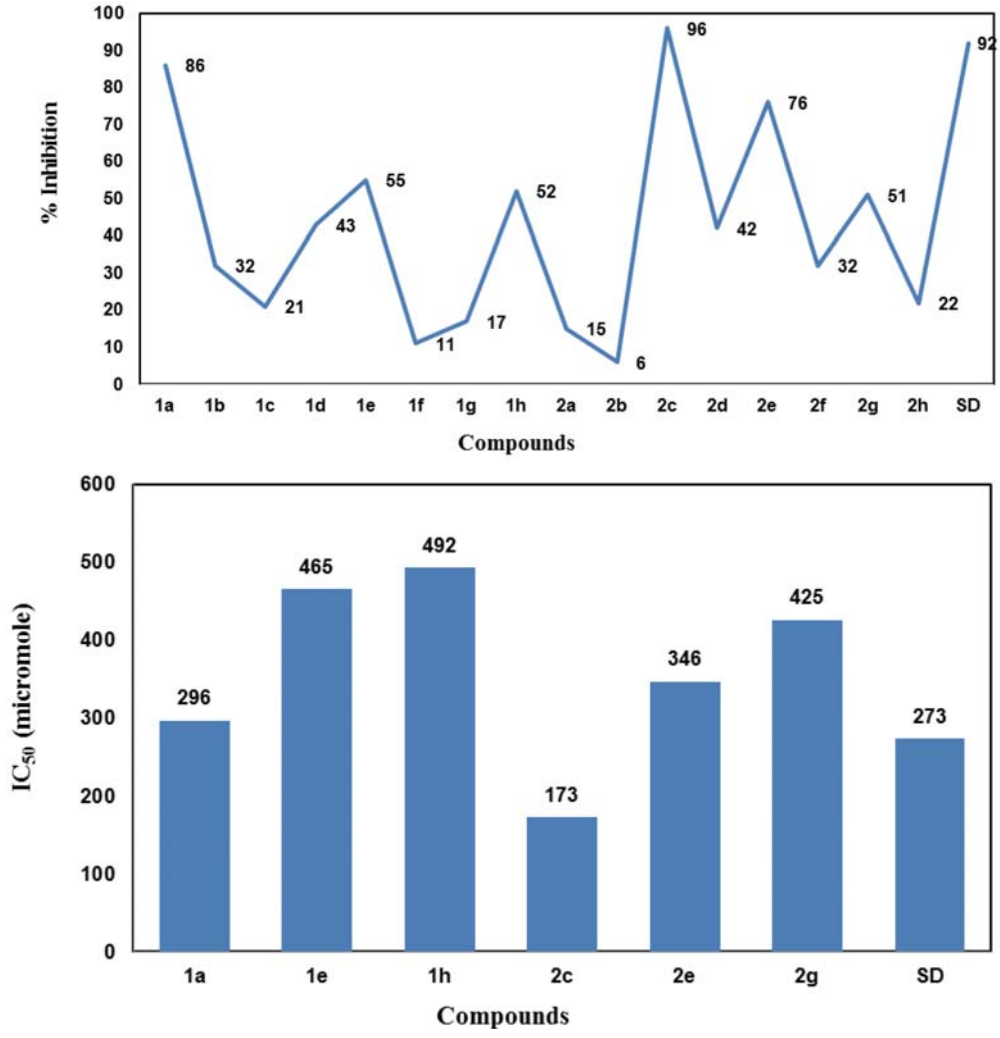


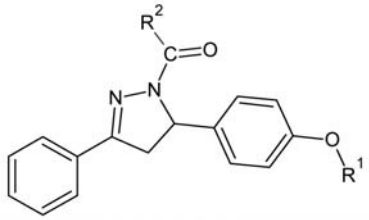
Figure 2: Anti-inflammatory activity of **1a–2h**, % inhibition (top) and IC_{50} (bottom) of compounds with more than 50% inhibition. SD = Indomethacine

2. 3. Cytotoxicity Assay Against Prostate Cancer (PC-3 Cell Line)

The newly synthesized compounds **1a–2h** were initially screened at the single concentration of 100 μM using the colorimetric MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to test their *in vitro* cytotoxicity,[46] against human prostate cancer cell line (PC3). Doxorubicin was used as the standard reference drug in this study. The cytotoxicity of tested compounds was estimated in terms of percent growth inhibition compared to untreated control cells. Then, the compounds effecting ~70% inhibition in one dose prescreening were retested by serial dilution from 100–20 μM. The results were expressed as IC_{50} (inhibitory concentration 50%), the concentration of the compound which inhibits the tumor cell growth by 50% and the data are presented in Table 2 & Figure 3.

Close inspection of the acquired cytotoxic data revealed that almost all of the tested compounds showed no/very low cyctotoxity against the PC-3 tested cell line. The compounds **1b**, **1h**, **2a**, **2b, 2c** and **2e** were found to be slightly toxic against the PC-3 tested cell line with IC_{50} values ranging from 27–67 **μM** compared to DOX, IC_{50} (0.912 **μM**) whereas the other compounds showed almost no cytotoxicity. The results of this study indicate that compounds **1a** and **2c** of this series having anti-inflamma-

Table 2. Cytotoxcity bioassay of compounds **1a–2h** against prostate cancer cell line (PC-3).



Compd.	R^1	R^2	IC_{50} (μM)	Compd.	R^1	R^2	IC_{50} (μM)
1a	CH_3	CH_3	>100	**2a**	CH_3	C_2H_5	41
1b	C_2H_5	CH_3	57	**2b**	C_2H_5	C_2H_5	29
1c	C_3H_7	CH_3	>100	**2c**	C_3H_7	C_2H_5	27
1d	C_4H_9	CH_3	>100	**2d**	C_4H_9	C_2H_5	>100
1e	C_5H_{11}	CH_3	>100	**2e**	C_5H_{11}	C_2H_5	67
1f	C_6H_{13}	CH_3	>100	**2f**	C_6H_{13}	C_2H_5	>100
1g	C_7H_{15}	CH_3	>100	**2g**	C_7H_{15}	C_2H_5	>100
1h	C_8H_{17}	CH_3	42	**2h**	C_8H_{17}	C_2H_5	>100
DOX [a]	–	–	0.912	**DOX**	–	–	0.912

[a] **DOX**: Doxorubinin (Standard Drug)

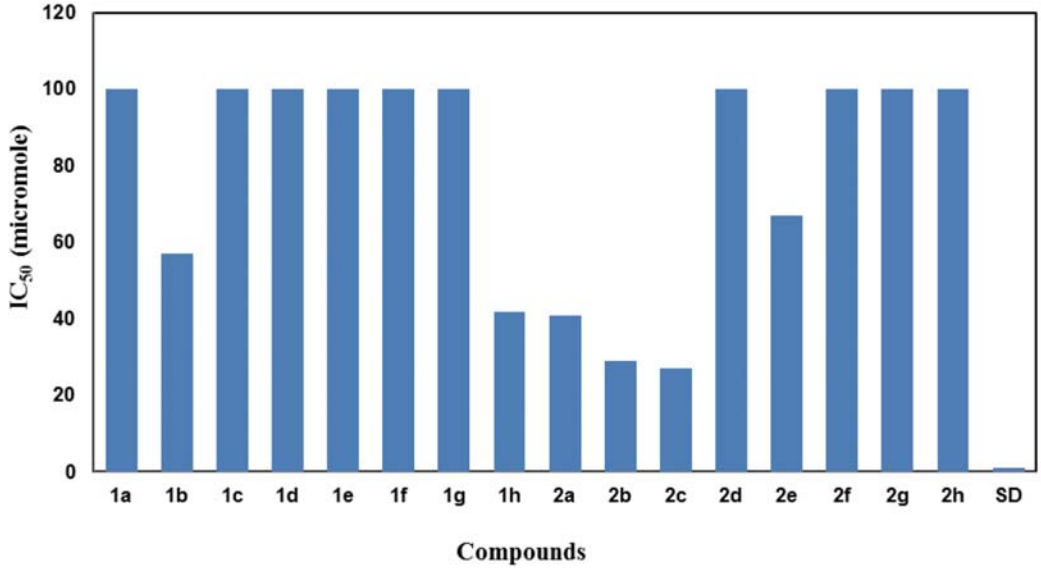


Figure 3. Cytotoxicity of **1a–2h** against PC-3 cell line, SD = Doxorubicin

tory activity better than and comparable to standard drug, and with no/little cytotoxicity are promising future candidates for further anti-inflammatory research to minimize harmful gastric effects, usually originate from direct cytotoxicity of NSAIDs.

3. Conclusions

In conclusion, we have presented the synthesis and anti-inflammatory activity of some new *N*-acyl arms & homologous alkyloxy side chains bearing pyrazoline derivatives (**1a–2h**). In general, compounds with odd carbon alkyloxy side chain showed better activity. Compound **2c** (96% inhibition, IC_{50} = 173.06 ± 2.312 μM) and **1a** (86%, IC_{50} = 296.16 ± 2.091 μM) showed maximum activity with **2c** even better than the standard drug, Indomethacine, (92% inhibition, IC_{50} = 273.12 ± 2.33 μM). Parrallel cytotoxicity studies on Prostate cancer (PC-3) cell line demonstrated no or very low activity for all the compounds. It has been shown recently that harmful gastric effects of NSAIDs are not related to PGE2 inhibition but are rather due to the direct cytotoxicity in the stomach to gastric cells.[32,33] The compounds of the present series may therefore be promising replacement anti-inflammatory agents to existing NSAIDs having harmful gastric effects due to direct cytotoxicity and merits further research. This study also insinuates constructive hints for the design of new effective anti-inflammatory agents having either no or very low cytotoxicity to gastric cells.

4. Experimental Protocols

4. 1. Materials and Methods

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as required. Thin layer chromatography was performed using aluminium sheets (Merck) coated with silica gel 60 F_{254}. Elemental analyses were carried out with a LECO-183 model. ^{1}H and ^{13}C NMR spectra of compounds were recorded with a Bruker 300 MHz spectrometer using deuterated solvents and TMS as internal standard. IR spectra of compounds were recorded on a Bio-Rad FTS 3000 MX spectrophotometer (400–4000 cm^{-1}). The melting points of compounds were determined using capillary tubes and an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo, Japan. In vitro anti-inflammatory, antifungal and cytotoxic properties were studied at HEJ research Institute of Chemistry, International Center for Chemical Sciences, university of Karachi, Pakistan.

4. 2. General procedure for the synthesis of compounds (1a–2h)

The carboxylic acid (25 mL) solution of the respective 4-alkoxychalcone (**1–8**)[38] (0.01 mole), hydrochloric acid (5–7 drops) was heated at 60–65 °C for 30 minutes with constant stirring. Hydrazine hydrate (80%) (1.0 g, 0.02 mole) was then added dropwise to the reaction flask and the reaction mixture was refluxed for about 4–5 hour before cooling it to room temperature and adding crushed ice into it to get the precipitates. The precipitates so obtained were filtered, washed with distilled water and dried, and further purified by column chromatography using silica gel and petroleum ether/ethyl acetate (4:1) as mobile phase to get pure **1a–2h** in 81–89% yields (Figure 4).

1-Acetyl-3-phenyl-5-(4-methoxyphenyl)-2-pyrazoline (1a)

Yellowish white crystals. Yield 85%. M. p. 123–125 °C; R_f = 0.68 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}): 1682, 1637, 1495, 1298, 1255, 1046, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.75 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.79 (s, 3H, –O–C***H***$_3$), 5.57 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.86 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.19 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.74–7.79 (m, 2H, Ar$H_{e=e'}$),^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 42.2, 55.2, 59.4, 114.2 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.3, 131.4, 134.1, 153.8, 159.0, 168.8, (EI) *m/z* ($M^{+\bullet}$ 294, Base Peak 251); Anal. calcd. For $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.49; H, 6.14; N, 9.59 %.

1-Acetyl-3-phenyl-5-(4-ethoxyphenyl)-2-pyrazoline (1b)

Yellowish white crystals. Yield 89%. M. p. 116–118 °C; R_f = 0.70 (petroleum ether:ethyl acetate, 4:1), FT-IR (KB-

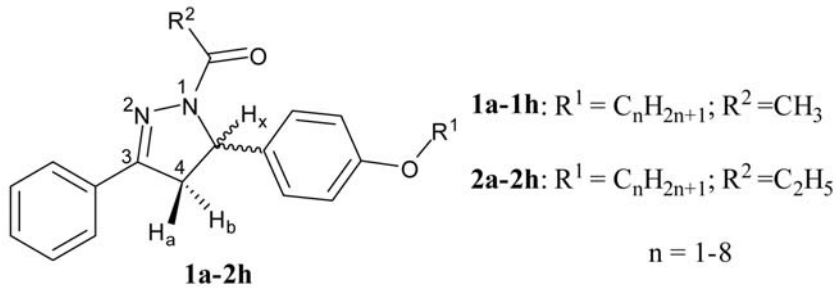


Figure 4. Labelling scheme of protons of compounds **1a-1h**.

r, cm^{-1}) 1678, 1632, 1499, 1295, 1257, 1042, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J* = 7.0 Hz, –O–CH_2–C***H***$_3$), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.75 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 4.0 (q, 3H, *J* = 6.9 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 12.0 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.43–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 22.0, 42.3, 59.4, 63.4, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.3, 131.4, 133.9, 153.8, 158.3, 168.8; (EI) *m/z* ($M^{+\bullet}$ 308, Base Peak 265). Anal. calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08; Found: C, 73.94; H, 6.49; N, 9.17 %.

1-Acetyl-3-phenyl-5-(4-propyloxyphenyl)-2-pyrazoline (1c)

Yellowish white crystals. Yield 83%. M. p. 114–116 °C; R_f = 0.72 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1679, 1644, 1489, 1297, 1252, 1043, , ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.5 Hz, –O–$(CH_2)_2$–C***H***$_3$), 1.80 (sextet 2H, *J* = 7.5 Hz, –O–CH_2–C***H***$_2$–CH_3), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.75 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.90 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.0, 22.5, 42.2, 59.4, 69.5, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.9, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 322, Base Peak 279). Anal. calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.48; H, 6.81; N, 8.78 %.

1-Acetyl-3-phenyl-5-(4-butyloxyphenyl)-2-pyrazoline (1d)

Yellowish white crystals. Yield 86%. M. p. 88–90 °C; R_f = 0.71 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1675, 1642, 1490, 1292, 1259, 1048, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.5 Hz, –O–$(CH_2)_3$–C***H***$_3$), 1.48 (sextet 2H, *J* = 7.8 Hz, –O–CH_2–CH_2–C***H***$_2$–CH_3), 1.76 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_2H_5), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.94 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 12.0 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.2, 22.0, 31.2, 42.2, 59.4, 67.6, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 336, Base Peak 293). Anal. calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33; Found: C, 74.92; H, 7.15; N, 8.41%.

1-Acetyl-3-phenyl-5-(4-pentyloxyphenyl)-2-pyrazoline (1e)

Yellowish white crystals. Yield 87%. M. p. 85–87 °C; R_f = 0.68 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1682, 1636, 1493, 1293, 1253, 1045, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_4$–C***H***$_3$), 1.35–1.46 (m 4H, *J* = 7.8 Hz, –O–CH_2–CH_2–$(CH_2)_2$ –CH_3), 1.77 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_3H_7), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 3.92 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 22.0, 22.4, 28.1, 28.9, 42.3, 59.4, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 350, Base Peak 307). Anal. calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99; Found: C, 75.36; H, 7.42; N, 8.07 %.

1-Acetyl-3-phenyl-5-(4-hexyloxyphenyl)-2-pyrazoline (1f)

Yellowish white crystals. Yield 83%. M.p. 82-85 °C; R_f = 0.69 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1676, 1634, 1497, 1295, 1250, 1049, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_5$–C***H***$_3$), 1.31–1.47 (m 6H, –O–CH_2–CH_2–$(CH_2)_3$– CH_3), 1.76 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_4H_9), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.2, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.0, 22.6, 25.7, 29.2, 31.5, 42.3, 59.4, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 364, Base Peak 321). Anal. calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69; Found: C, 75.74; H, 7.69; N, 7.78 %.

1-Acetyl-3-phenyl-5-(4-heptyloxyphenyl)-2-pyrazoline (1g)

Yellowish white crystals. Yield 89%. M.p. 89–91 °C; R_f = 0.71 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1678, 1639, 1487, 1291, 1256, 1052, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_6$–C***H***$_3$), 1.32–1.47 (m 8H, –O–CH_2–CH_2–$(CH_2)_4$– CH_3), 1.77 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_5H_{11}), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 12.0 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.6, 26.0, 29.0, 29.2, 31.7, 42.2, 59.4, 68.0, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 378, Base Peak 335). Anal. calcd. for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40; Found: C, 76.12; H, 7.91; N, 7.49%.

1-Acetyl-3-phenyl-5-(4-octyloxyphenyl)-2-pyrazoline (1h)

Yellowish white crystals. Yield 82%. M.p. 73-75 °C; R_f = 0.72 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1681, 1645, 1492, 1297, 1258, 1056, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_7$–C***H***$_3$), 1.29–1.49 (m 10H, –O–CH_2–CH_2–$(CH_2)_5$– CH_3), 1.76 (qn 2H, *J* = 7.8 Hz, –O–CH_2–C***H***$_2$–C_6H_{13}), 2.43 (s, 3H, O=C–C***H***$_3$), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 3.92 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.4, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 42.3, 59.4, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\bullet}$ 392, Base Peak 349). Anal. calcd. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; Found: C, 76.44; H, 8.18; N, 7.21%.

1- Propionyl-3-phenyl-5-(4-methoxyphenyl)-2-pyrazoline (2a)

Yellowish white crystals. Yield 81%. M.p. 100–103 °C; R_f = 0.73 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1685, 1635, 1493, 1294, 1254, 1049, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 2.84 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.17 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.73 (dd, 1H, *J* = 12.0, 17.7 Hz, ***H***$_b$), 3.79 (s, 3H, –O–C***H***$_3$), 5.56 (dd, 1H, *J* = 4.8, 11.7 Hz, ***H***$_x$), 6.86 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.19 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.46 (m, 3H, Ar$H_{f=f',g}$), 7.76–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 27.6, 42.0, 55.2, 59.6, 114.2 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.6, 134.3, 153.5, 158.9, 172.2, (EI) *m/z* ($M^{+\bullet}$ 308, Base Peak 252). Anal. calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08; Found: C, 73.93; H, 6.48; N, 9.19%

1- Propionyl-3-phenyl-5-(4-ethoxyphenyl)-2-pyrazoline (2b)

Yellowish white crystals. Yield 85%. M.p. 98-101 °C; R_f = 0.70 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1688, 1637, 1497, 1298, 1252, 1045, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.40 (t, 3H, *J* = 7.2 Hz, –O–CH_2–C***H***$_3$), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.16 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.72 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 4.00 (q, 2H, *J* = 7. Hz, –O–C***H***$_2$–CH_3), 5.55 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.84 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.43–7.45 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 14.8, 27.6, 42.0, 59.6, 63.4, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.6, 134.1, 153.6, 158.3, 172.3, (EI) *m/z* ($M^{+\bullet}$ 322, Base Peak 265). Anal. calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.46; H, 6.78; N, 8.79%.

1- Propionyl-3-phenyl-5-(4-propyloxyphenyl)-2-pyrazoline (2c)

Yellowish white crystals. Yield 88%. M.p. 107-109 °C; R_f = 0.71 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1683, 1641, 1490, 1296, 1255, 1047, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.5 Hz, –O–$(CH_2)_2$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.8 Hz, O=C–CH_2–C***H***$_3$), 1.80 (sextet, 2H, *J* = 7.2 Hz, –O–CH_2–C***H***$_2$–CH_3), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.17 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.73 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 3.90 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–CH_2–CH_3), 5.55 (dd, 1H, *J* = 4.8, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.46 (m, 3H, Ar$H_{f=f',g}$), 7.76–7.79 (m, 2H, Ar$H_{e=e'}$),^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 10.5, 22.5, 27.6, 42.0, 59.6, 69.4, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.6, 134.1, 153.5, 158.5, 172.2, (EI) *m/z* ($M^{+\bullet}$ 336, Base Peak 280). Anal. calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33; Found: C, 74.91; H, 7.16; N, 8.42%.

1- Propionyl-3-phenyl-5-(4-butyloxyphenyl)-2-pyrazoline (2d)

Yellowish white crystals. Yield 86%. M.p. 104-107 °C; R_f = 0.69 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1677, 1645, 1494, 1290, 1257, 1051, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_3$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.47 (sextet 2H, *J* = 7.8 Hz, –O–CH_2–CH_2–C***H***$_2$–CH_3), 1.76 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_2H_5), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.18 (dd, 1H, *J* = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.94 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.57 (dd, 1H, *J* = 4.5, 12.0 Hz, ***H***$_x$), 6.85 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 12.5, 22.5, 27.6, 28.1, 42.0, 59.6, 68.4, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 134.1, 153.5, 158.5, 172.4, (EI) *m/z* ($M^{+\bullet}$ 350, Base Peak 294). Anal. calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99; Found: C, 75.33; H, 7.45; N, 8.08%

1- Propionyl-3-phenyl-5-(4-pentyloxyphenyl)-2-pyrazoline (2e)

Yellowish white crystals. Yield 85%. M.p. 101-103 °C; R_f = 0.72 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1681, 1639, 1492, 1297, 1255, 1053, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_4$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.35–1.48 (m 4H, –O–CH_2–CH_2–$(CH_2)_2$–CH_3), 1.77 (qn 2H, *J* = 7.0 Hz, –O–CH_2–C***H***$_2$–C_3H_7), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.16 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.72 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.55 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.84 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.43–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.75–7.78 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 14.0, 22.4, 27.6, 28.1,

28.9, 42.0, 59.6, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.1, 131.6, 134.0, 153.5, 158.5, 172.2, (EI) *m/z* ($M^{+\bullet}$ 364, Base Peak 308). Anal. calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69; Found: C, 75.73; H, 7.71; N, 7.78%.

1- Propionyl-3-phenyl-5-(4-hexyloxyphenyl)-2-pyrazoline (2f)

Yellowish white crystals. Yield 82%. M.p. 95-98 °C; R_f = 0.68 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1679, 1638, 1498, 1293, 1253, 1045, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_5$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.31–1.47 (m 6H, –O–CH_2–CH_2–$(CH_2)_3$–CH_3), 1.77 (qn 2H, *J* = 7.5 Hz, –O–CH_2–C***H***$_2$–C_4H_9), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.17 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.73 (dd, 1H, *J* = 11.7, 17.7 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.55 (dd, 1H, *J* = 4.8, 12.0 Hz, ***H***$_x$), 6.84 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.43–7.47 (m, 3H, Ar$H_{f=f',g}$), 7.74–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 14.0, 22.6, 25.7, 27.6, 29.2, 31.5, 42.0, 59.6, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.1, 131.6, 134.0, 153.5, 158.5, 172.2, (EI) *m/z* ($M^{+\bullet}$ 378, Base Peak 322). Anal. calcd. for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40; Found: C, 76.09; H, 7.91; N, 7.51%.

1- Propionyl-3-phenyl-5-(4-heptyloxyphenyl)-2-pyrazoline (2g)

Yellowish white crystals. Yield 84%. M.p. 90–92 °C; R_f = 0.71 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1678, 1633, 1489, 1296, 1252, 1048, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_6$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.32–1.47 (m 8H, –O–CH_2–CH_2–$(CH_2)_4$–CH_3), 1.77 (qn 2H, *J* = 7.8 Hz, –O–CH_2–C***H***$_2$–C_5H_{11}), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.17 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.73 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.55 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.84 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.46 (m, 3H, Ar$H_{f=f',g}$), 7.76–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 14.1, 22.6, 26.0, 27.6, 29.0, 29.2, 31.8, 42.0, 59.6, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.6, 134.0, 153.5, 158.5, 172.2, (EI) *m/z* ($M^{+\bullet}$ 392, Base Peak 336). Anal. calcd. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; Found: C, 76.43; H, 8.18; N, 7.23%.

1- Propionyl-3-phenyl-5-(4-octyloxyphenyl)-2-pyrazoline (2h)

Yellowish white crystals. Yield 87%. M.p. 73-75 °C; R_f = 0.73 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1682, 1647, 1495, 1294, 1255, 1051, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz, –O–$(CH_2)_7$–C***H***$_3$), 1.21 (t, 3H, *J* = 7.5 Hz, O=C–CH_2–C***H***$_3$), 1.31–1.46 (m 10H, –O–CH_2–CH_2–$(CH_2)_5$–CH_3), 1.77 (qn 2H, *J* = 7.8 Hz, –O–CH_2–C***H***$_2$–C_6H_{13}), 2.83 (q, 2H, *J* = 7.5 Hz, O=C–C***H***$_2$–CH_3), 3.17 (dd, 1H, *J* = 4.8, 17.7 Hz, ***H***$_a$), 3.72 (dd, 1H, *J* = 11.7, 17.4 Hz, ***H***$_b$), 3.93 (t, 2H, *J* = 6.6 Hz, –O–C***H***$_2$–), 5.55 (dd, 1H, *J* = 4.5, 11.7 Hz, ***H***$_x$), 6.84 (d, 2H, *J* = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.46 (m, 3H, Ar$H_{f=f',g}$), 7.76–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 9.4, 14.1, 22.6, 26.0, 27.6, 29.2, 29.3, 31.8, 42.0, 59.6, 67.9, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.6, 134.0, 153.5, 158.5, 172.2, (EI) *m/z* ($M^{+\bullet}$ 406, Base Peak 350). Anal. calcd. for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89; Found: C, 76.77; H, 8.39; N, 6.96%.

4. 3. Anti-inflammatory Activity *(in vitro)*

Inflammation occurs as a defensive response, which induces physiological adaptations to limit tissue damage and removes the pathogenic infection. Reactive oxygen species (ROS) are formed subsequent to the assembly and activation of the phagocyte-specific enzyme, NADPH Oxidase. This process is initiated by the production of superoxide anion during a 'respiratory burst' of non-mitochondrial oxygen uptake by an NADPH oxidase system. This study used the water-soluble tetrazolium salt (WST-1) to measure superoxide production by neutrophils activated by opsonized zymosan, which induces phagocytic activation of neutrophils.[47] This techniqueis is more sensitive and reliable as compared to other available techniques.

4. 3. 1. Respiratory Burst Assay

Anti-inflammatory activity of the test compounds was determined by using a modified assay of Tan & Berridge.[45] This in vitro assay was based on the reduction of highly water-soluble tetrazolium salt (WST-1) in the presence of activated neutrophils. Anti-inflammatory activity was determined in a total volume of 200 µL MHS (pH 7.4) containing 1.0–104 neutrophils/mL, 250 µM WST-1 and various concentrations of test compounds. The control contained buffer, neutrophils and WST-1. All compounds were equilibrated at 37 °C and the reaction was initiated by adding opsonized zymosan A (15 mg/mL), which was prepared by mixing with human pooled serum, followed by centrifugation at 3000 rpm whereby the pellet was resuspended in PBS buffer. Absorbance was measured at 450 nm. Aspirin and indomethacin were used as positive controls which are widely used as non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of several inflammatory diseases. Values of IC_{50} were calculated by comparison with the DMSO as the blank and expressed as the percent inhibition of superoxide anions produced. The percent inhibitory activity by the samples was determined against a DMSO blank and calculated using the following formula: % Inhibition = 100 – [(OD test compound/OD control) × 100] IC_{50} of samples was determined by using EZ-FIT Windows-based software.

4. 4. Cytotoxicity Assay Against PC-3 Cell Line (Prostate Cancer)

Cytotoxic activity of the synthesized compounds was evaluated in 96-well flat-bottomed micro plates by using the standard MTT (3-[4, 5-dimethylthiazole-2-yl]-2,5-diphenyl-tetrazolium bromide) colorimetric assay.[46] For this purpose, PC-3 cells (Prostate Cancer) were cultured in Dulbecco's Modified Eagle's Medium, supplemented with 5% of fetal bovine serum (FBS), 100 IU/mL of penicillin and 100 μg/mL of streptomycin in 25 cm^3 flask, and kept in 5% CO_2 incubator at 37 ºC. Exponentially growing cells were harvested, counted with haemocytometer and diluted with a particular medium. Cell culture with the concentration of 1×10^5 cells/mL was prepared and introduced (100 μL/well) into 96-well plates. After overnight incubation, medium was removed and 200 μL of fresh medium was added with different concentrations of compounds (1-100 μM). After 48 h, 50 μL MTT (2 mg/mL) was added to each well and incubated further for 4 hrs. Subsequently, 100 μL of DMSO was added to each well. The extent of MTT reduction to formazan within cells was calculated by measuring the absorbance at 570 nm, using a micro plate reader (Spectra Max plus, Molecular Devices, CA, USA). The cytotoxicity was recorded as concentration causing 50% growth inhibition (IC_{50}) for PC3.

5. Acknowledgements

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Povzetek

Sintetizirali smo serijo novih pirazolinskih derivativov **1a**–**2h**, ki vsebujejo *N*-acilne skupine in homologne alkiloksi stranske verige. Karakterizacija novih spojin je temeljila na spektroskopskih in mikroanalitskih rezultatih. Vse pripravljene spojine smo *in vitro* testirali za njihovo proti vnetno učinkovanje; zanimal nas je predvsem vpliv dolžine alkiloksi stranske verige na aktivnost. Izkazalo se je, da spojine z lihim **številom** ogljikovih atomov v alkiloksi stranski verigi izkazujejo boljšo aktivnost kot spojine s sodim **številom** ogljikov. Spojina **2c** (96% inhibicija**,** IC_{50} = 173.06 ± 2.312 mM) se je izkazala kot najbolj aktivna izmed vseh spojin v seriji; bila je celo bolj aktivna kot standardna učinkovina (indometacin, 92% inhibicija, IC_{50} = 273.12 ± 2.33 mM). Spojina **1a** (86%, IC_{50} = 296.16 ± 2.091 mM) je bila druga najbolj učinkovita z aktivnostjo, primerljivo z aktivnostjo standardne učinkovine. Ostale spojine v seriji pa so pokazale le zmerno do nizko aktivnost. Zanimivo pa je, da so vzporedne študije citotoksičnosti spojin **1a**–**2h** proti celični liniji PC-3 pokazale zelo majhno ali celo ničelno aktivnost. Pričujoča študija bo morda lahko prispevala k razvoju novih alternativnih učinkovin trenutno uporabljanim nesteroidnim proti vnetnim učinkovinam (NSAID), ki zaradi neposredne citotoksičnosti kažejo škodljive vplive na prebavila.

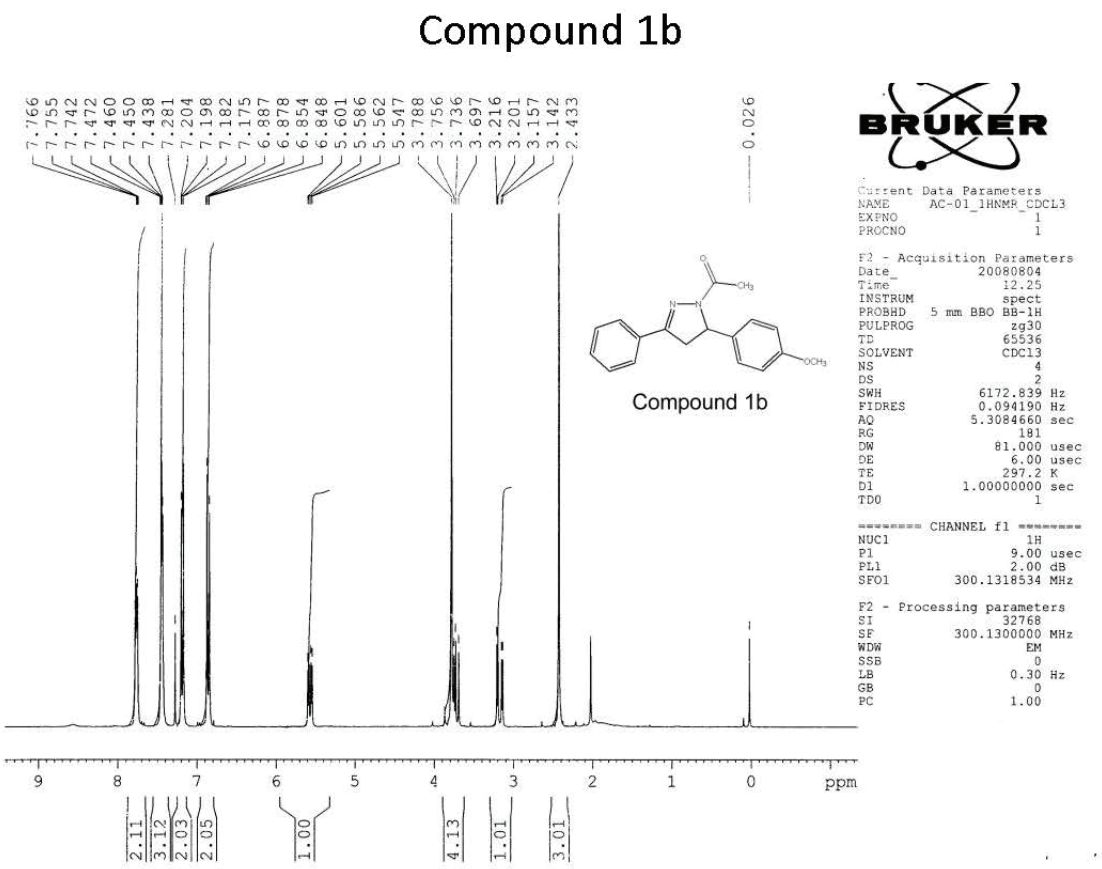
Supplementary material

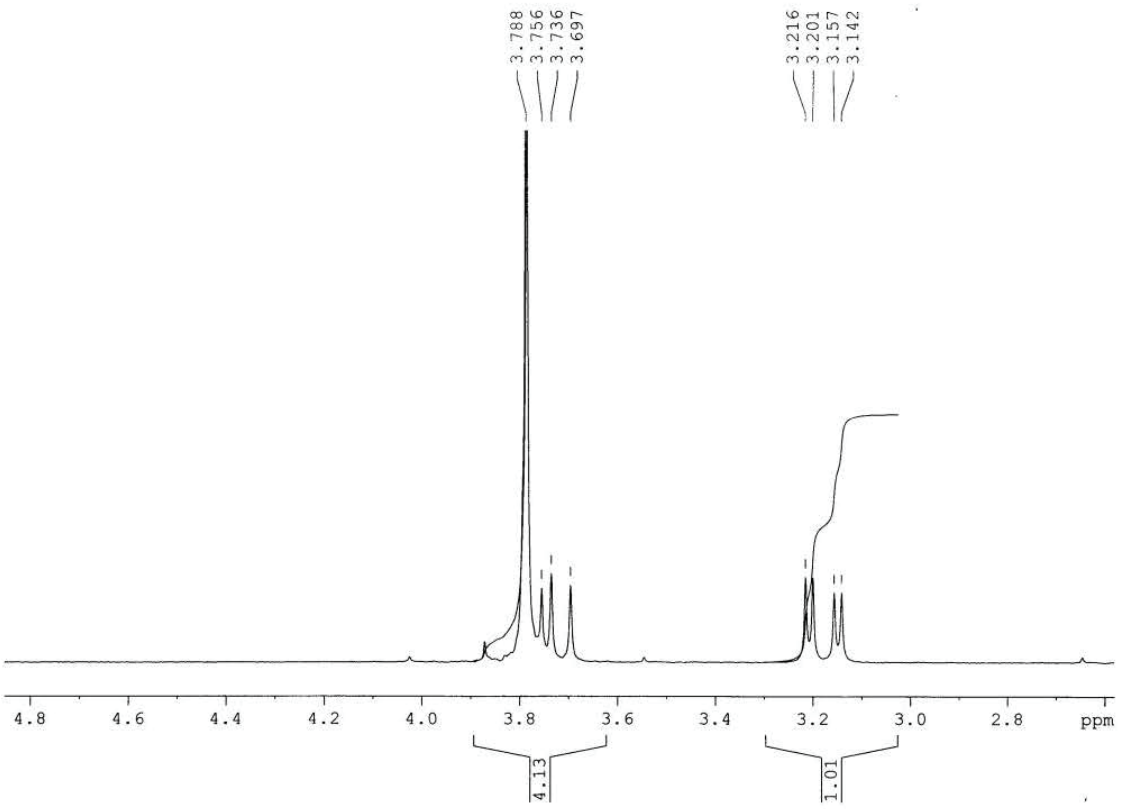
Synthesis and Anti-inflammatory Activity of New *N*-Acyl-2-pyrazolines Bearing Homologous Alkyloxy Side Chains

Asghar Abbas and Muhammad Moazzam Naseer

Received: 03-04-2014

Copies of ^{1}H and ^{13}C NMR of 1b-8c

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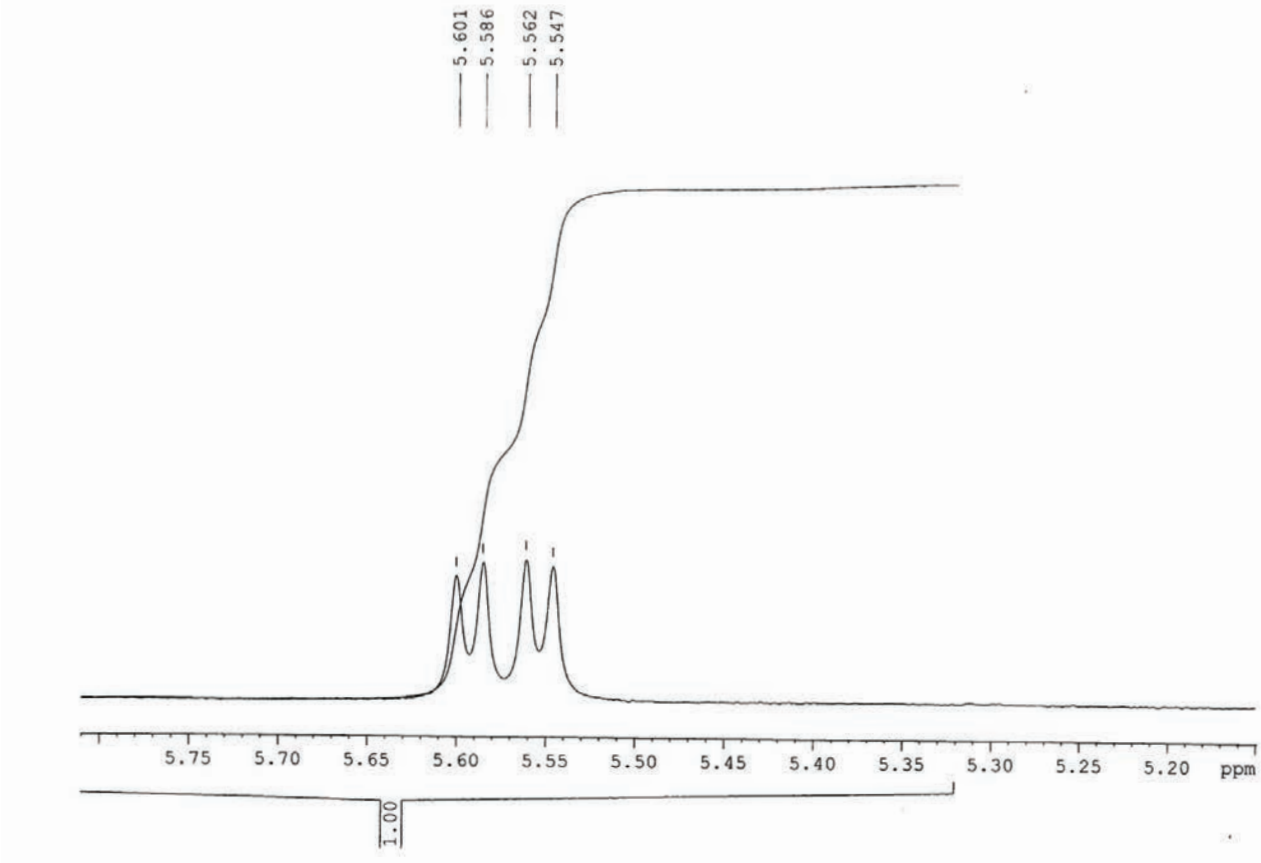
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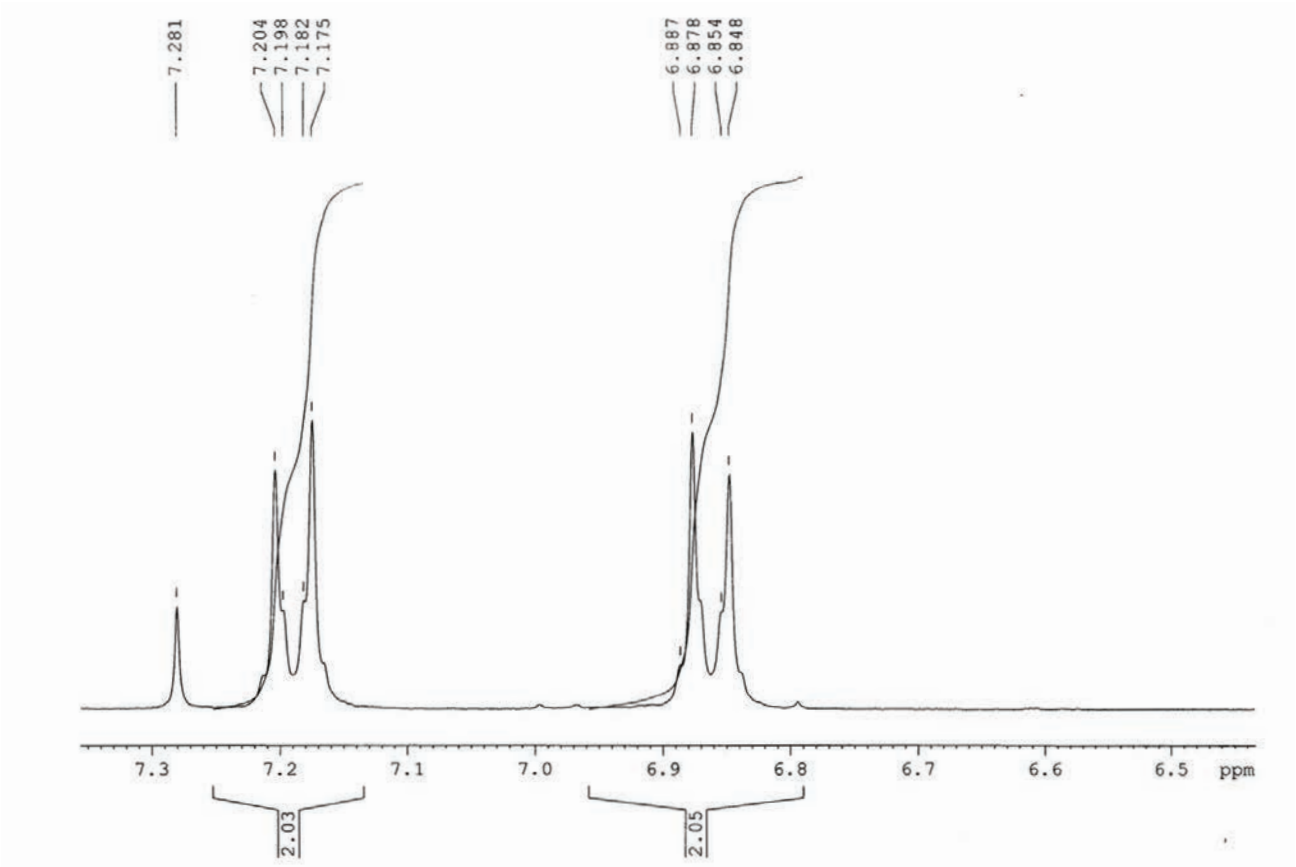
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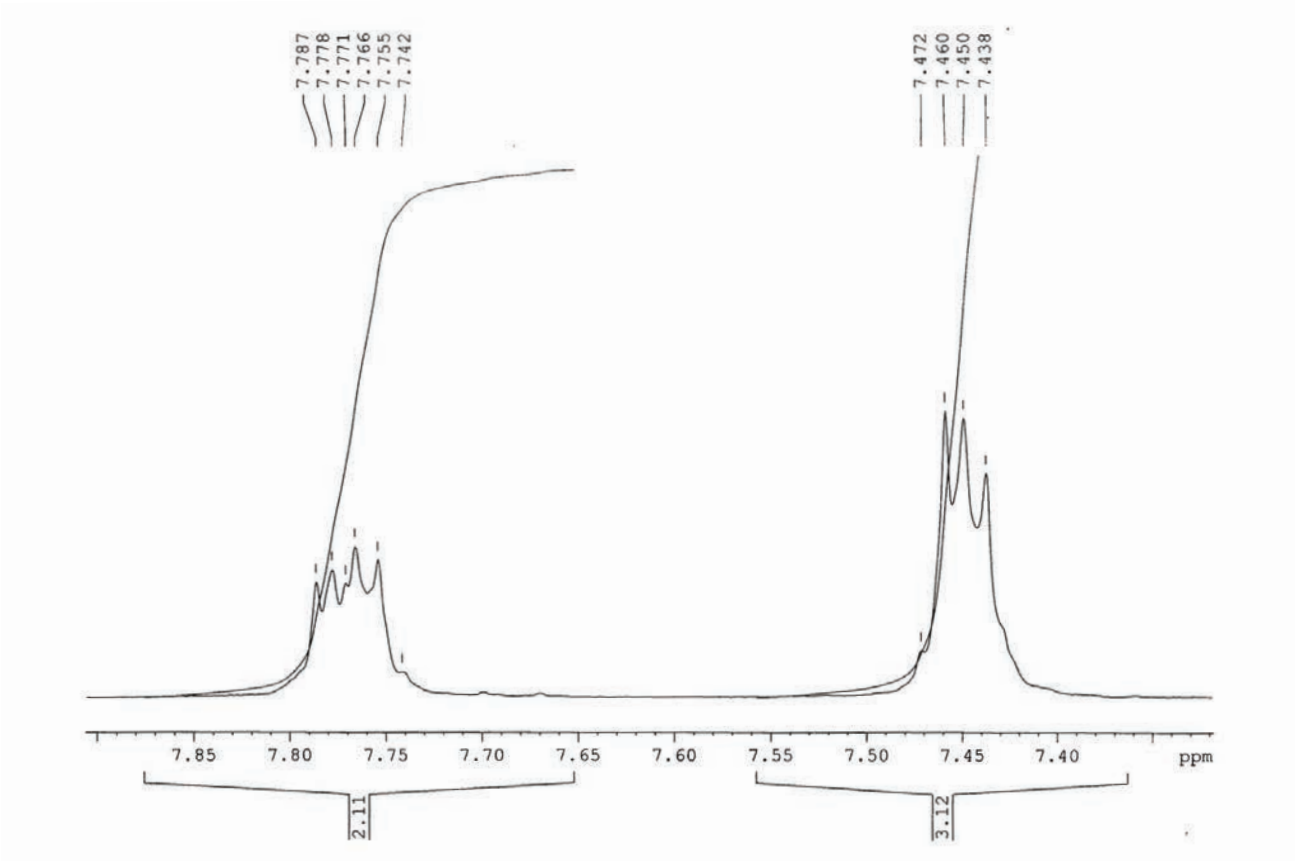
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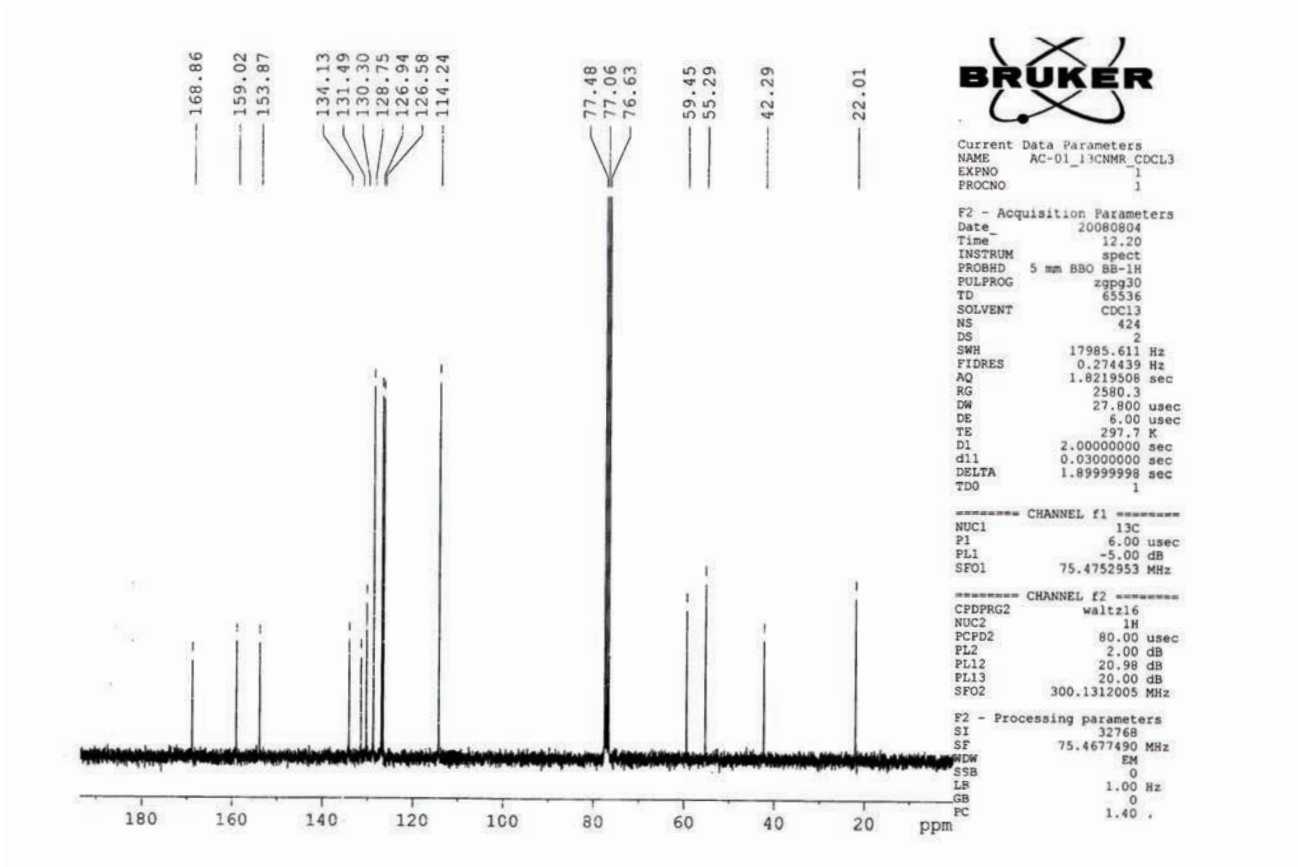
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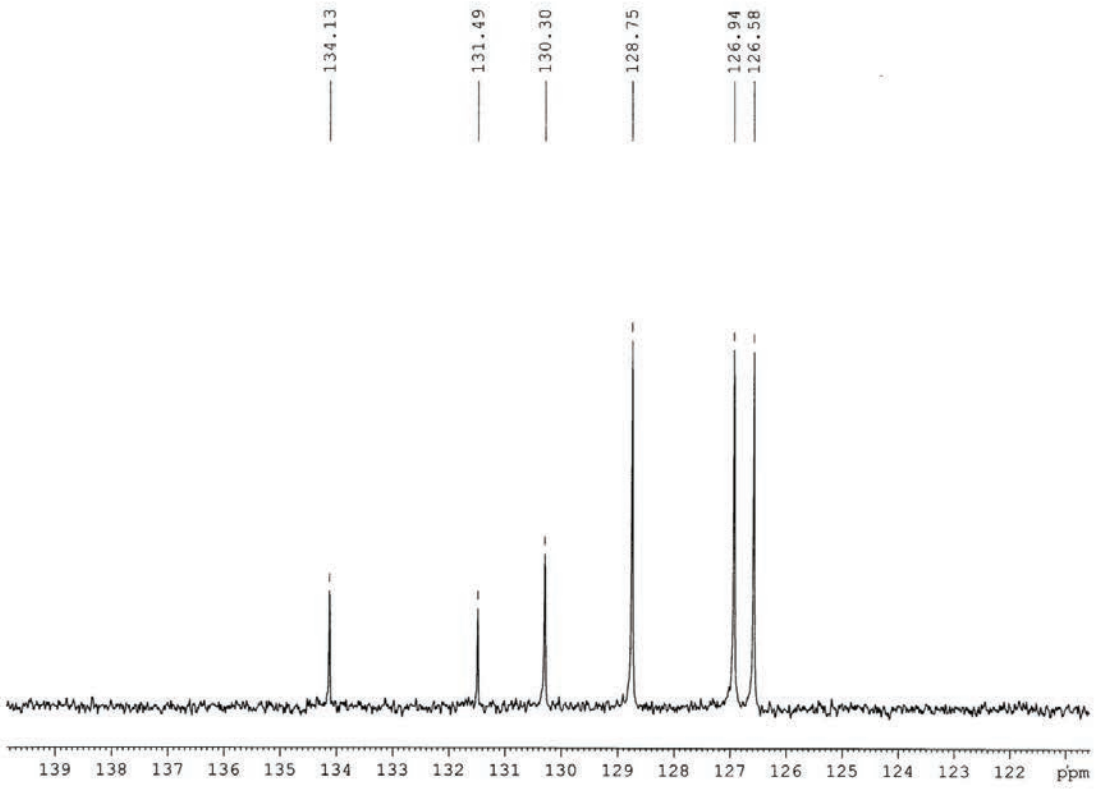
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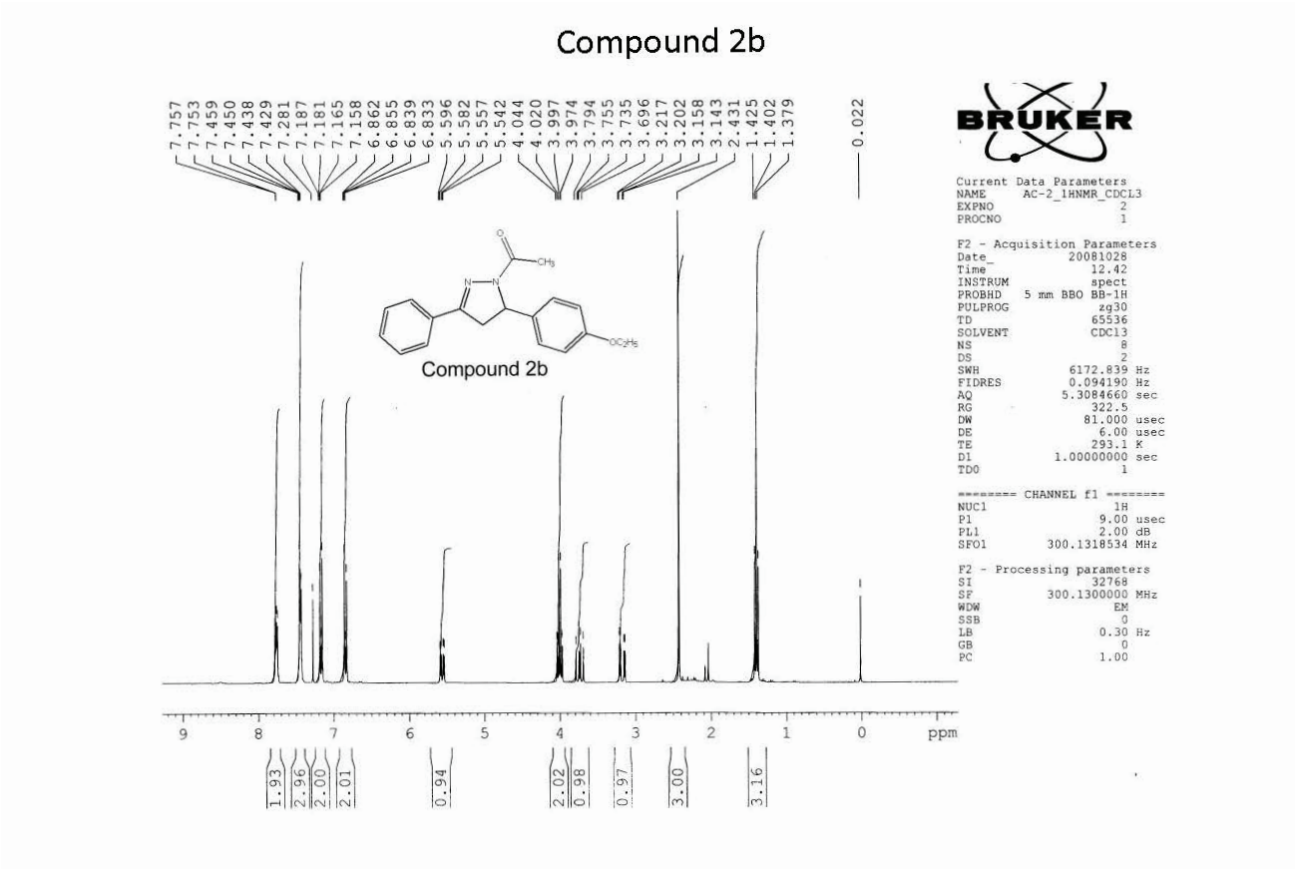
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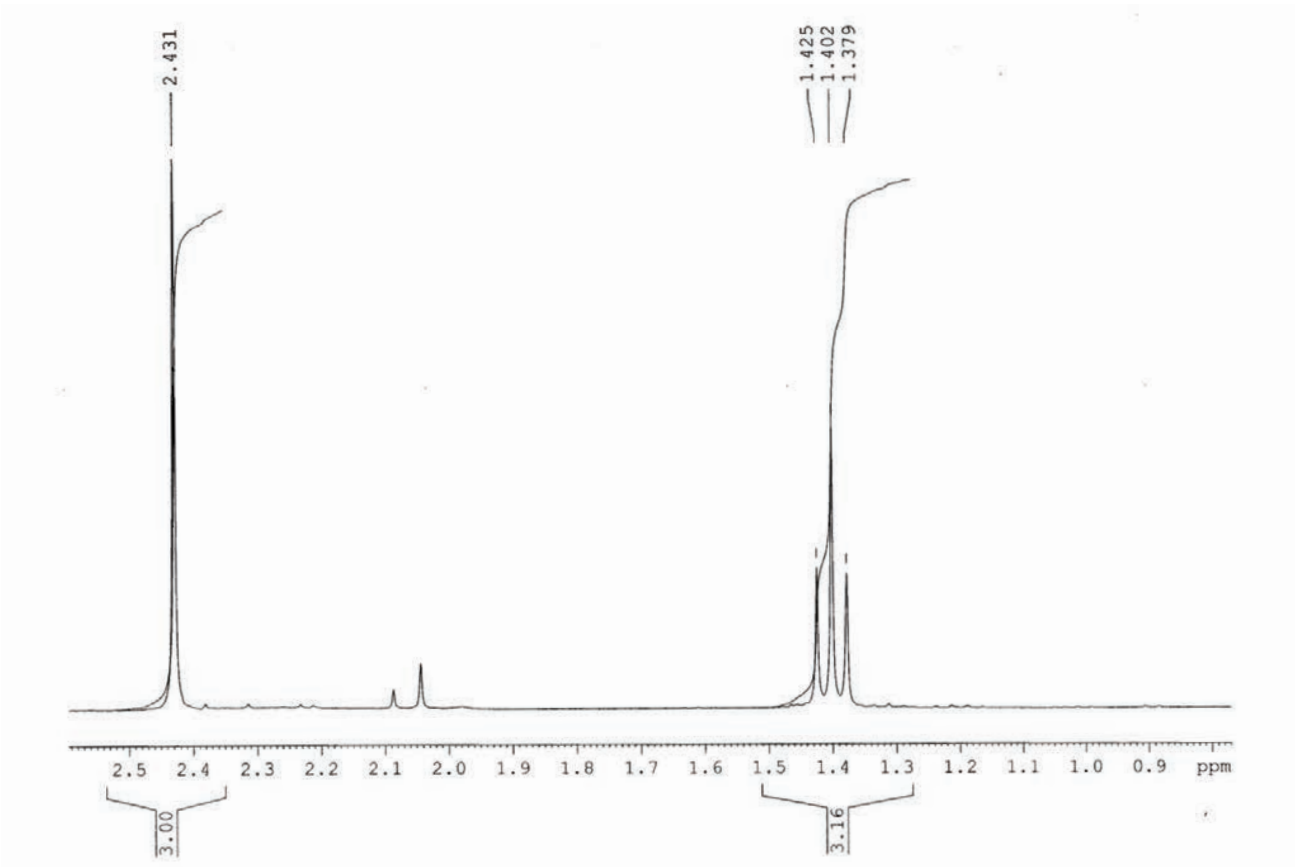
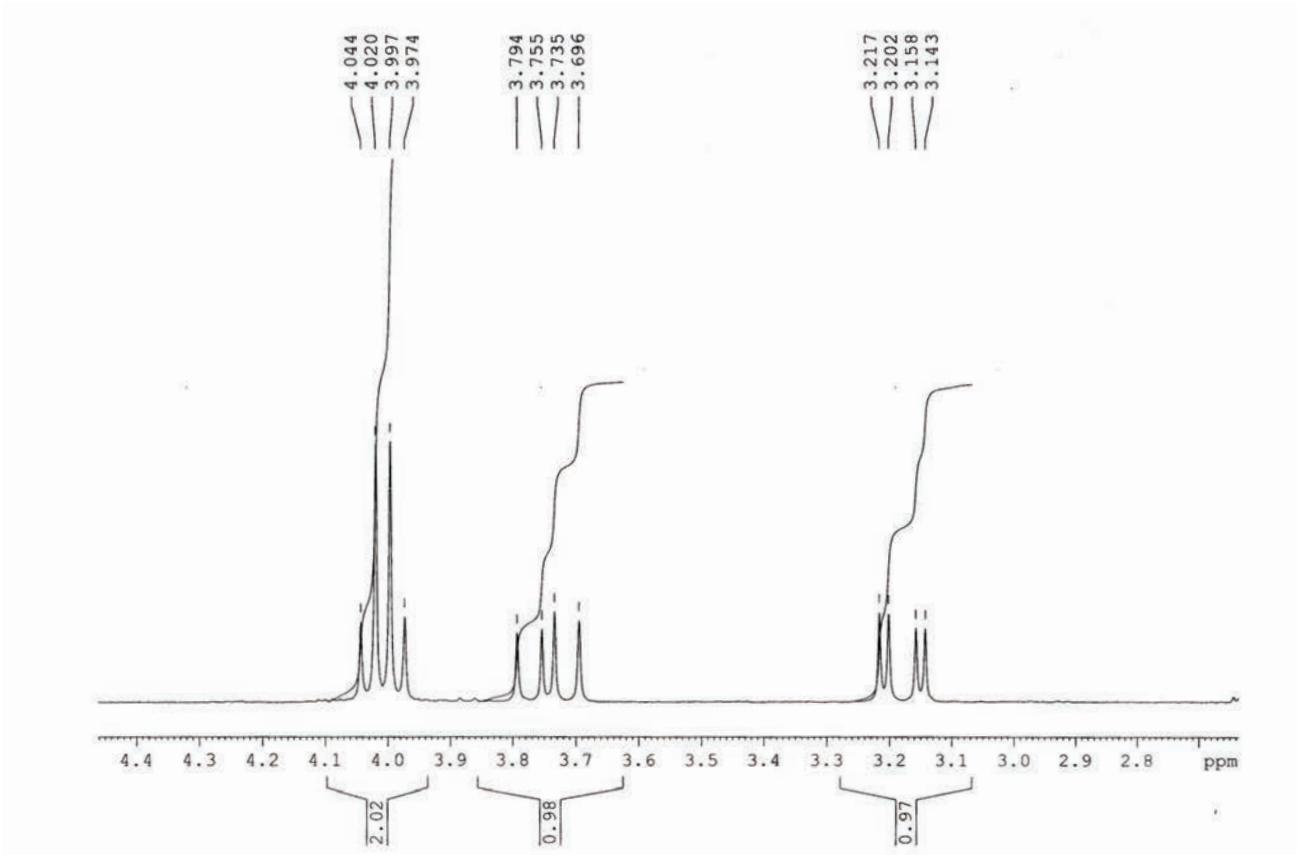
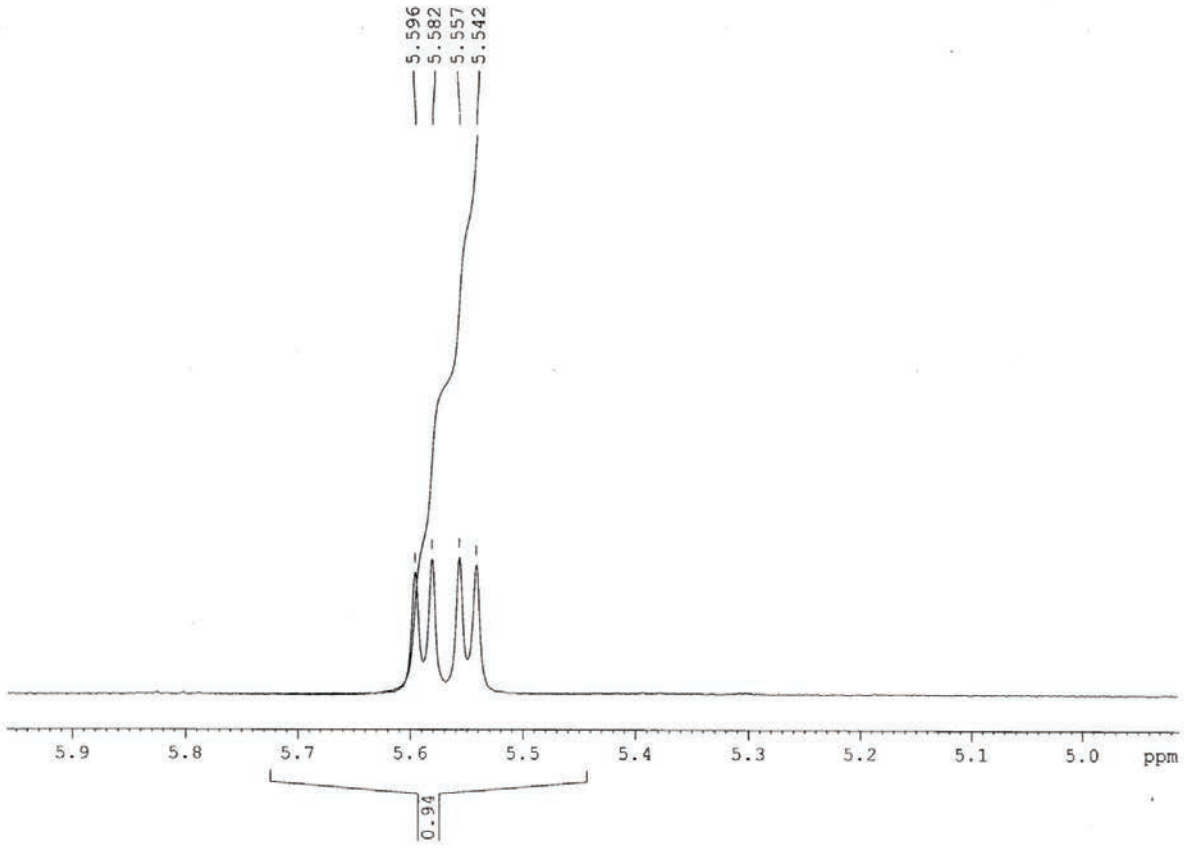
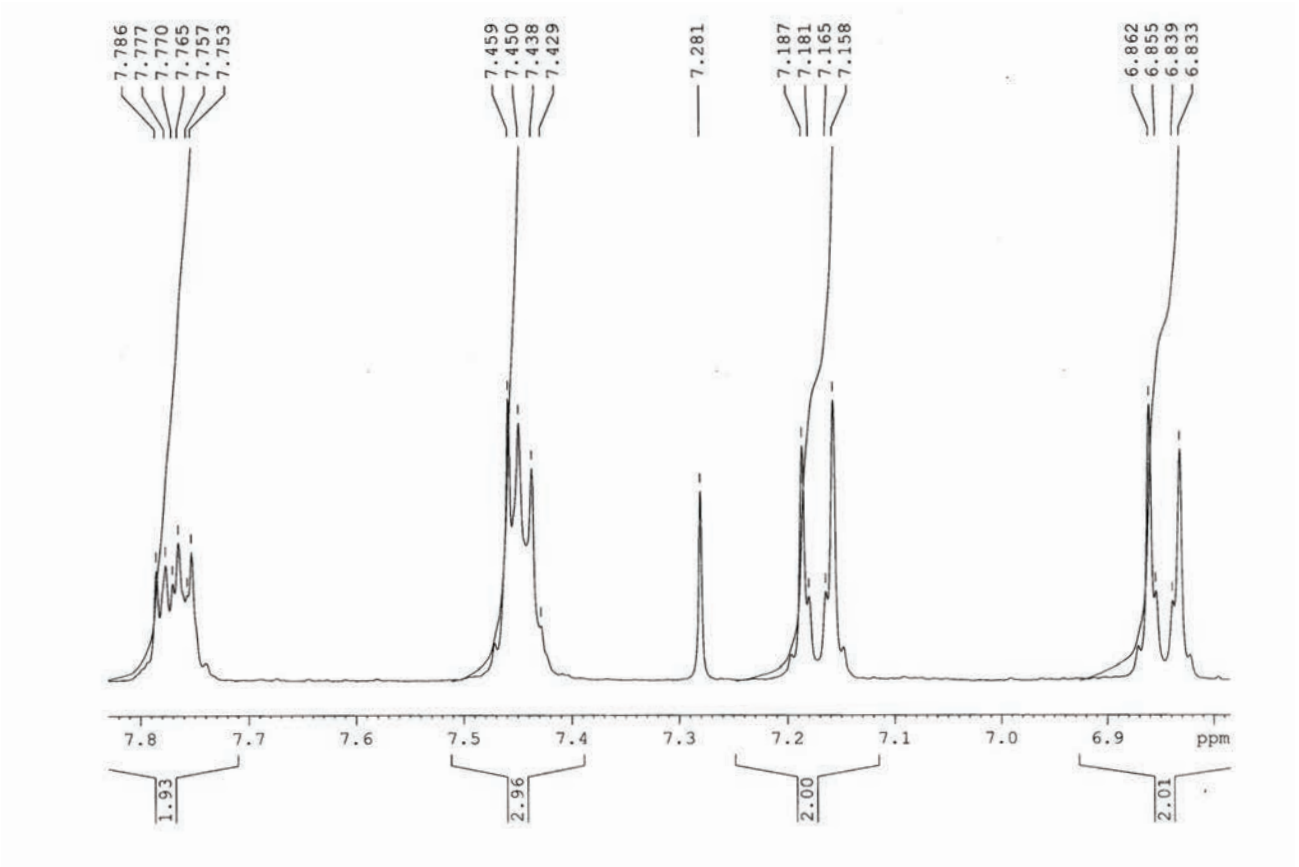
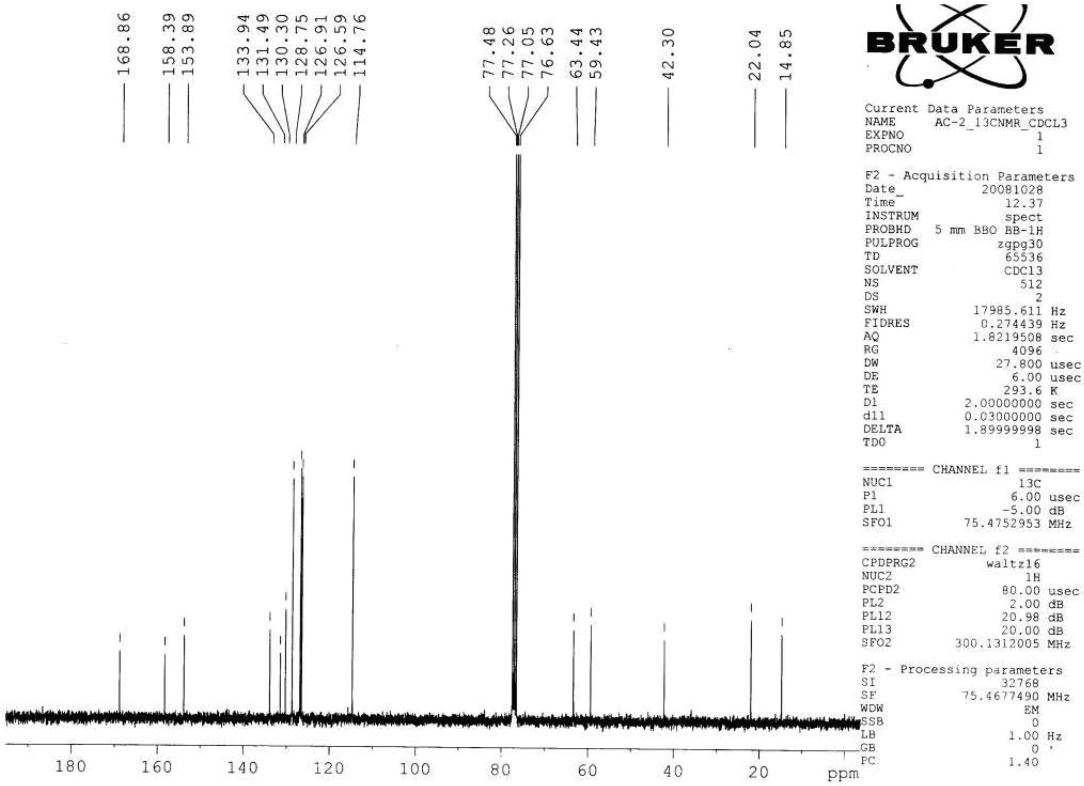
TE 293.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 0 ppm
1.93
2.96
2.00
2.01
0.94
2.02
0.98
0.97
3.00
3.16


2.431
1.425
1.402
1.379
2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 ppm
3.00
3.16


4.044
4.020
3.997
3.974
3.794
3.755
3.735
3.696
3.217
3.202
3.158
3.143
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 ppm
2.02
0.98
0.97

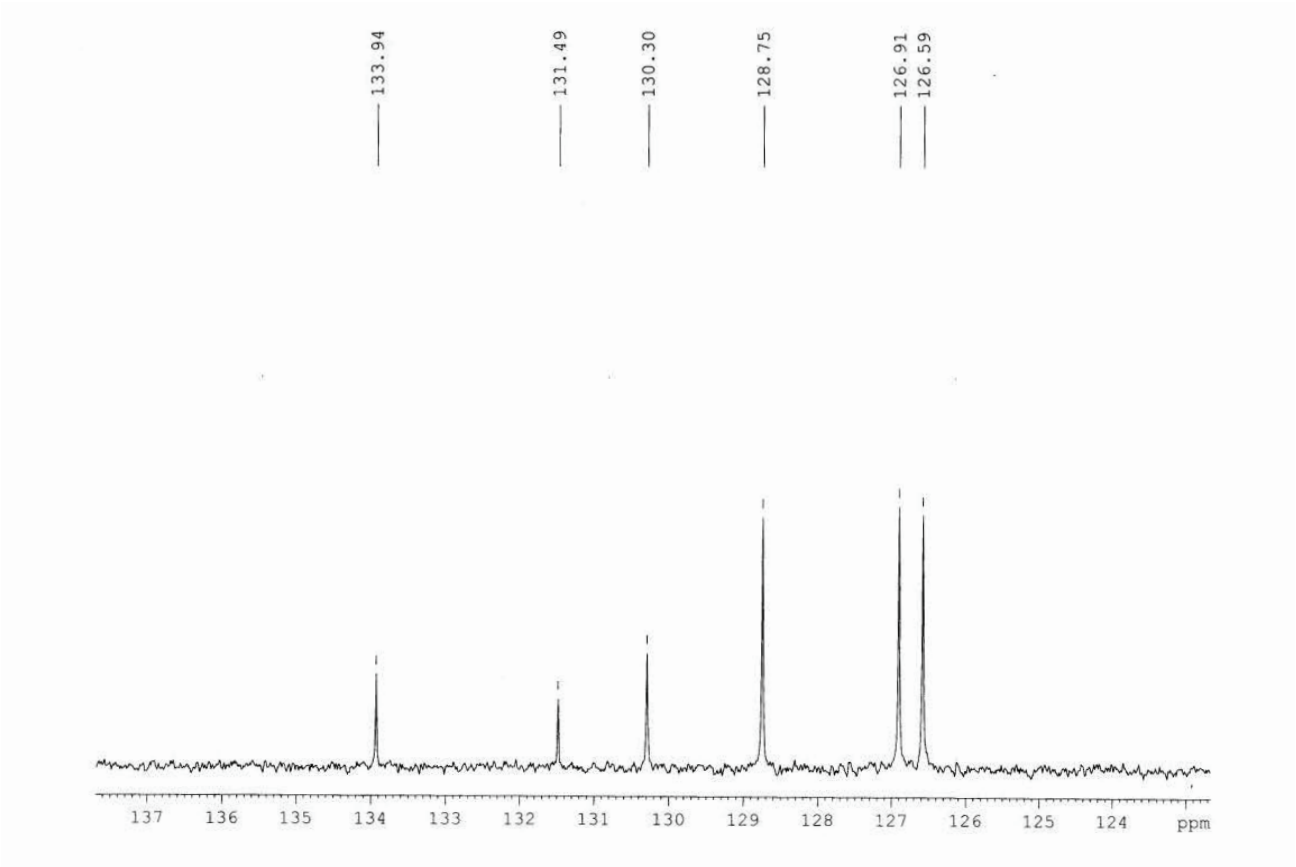

5.596
5.582
5.557
5.542
5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 ppm
0.94



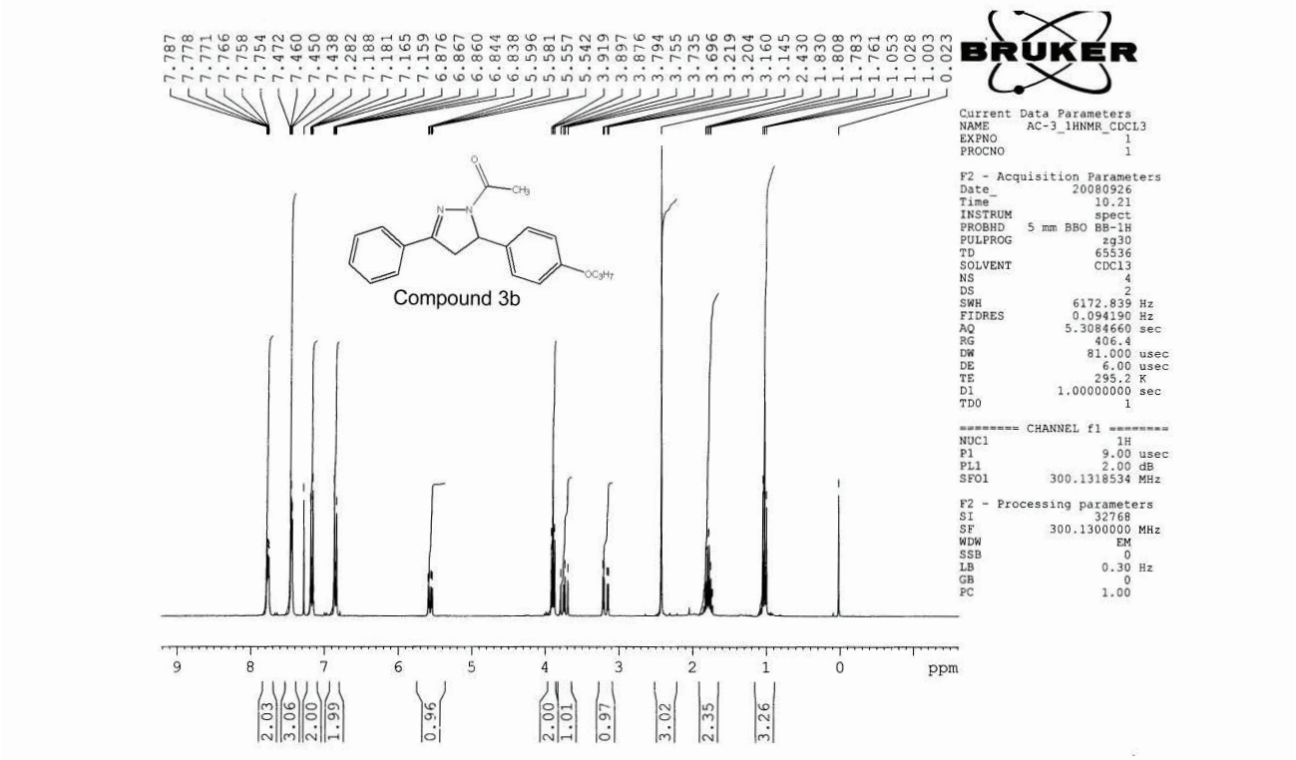


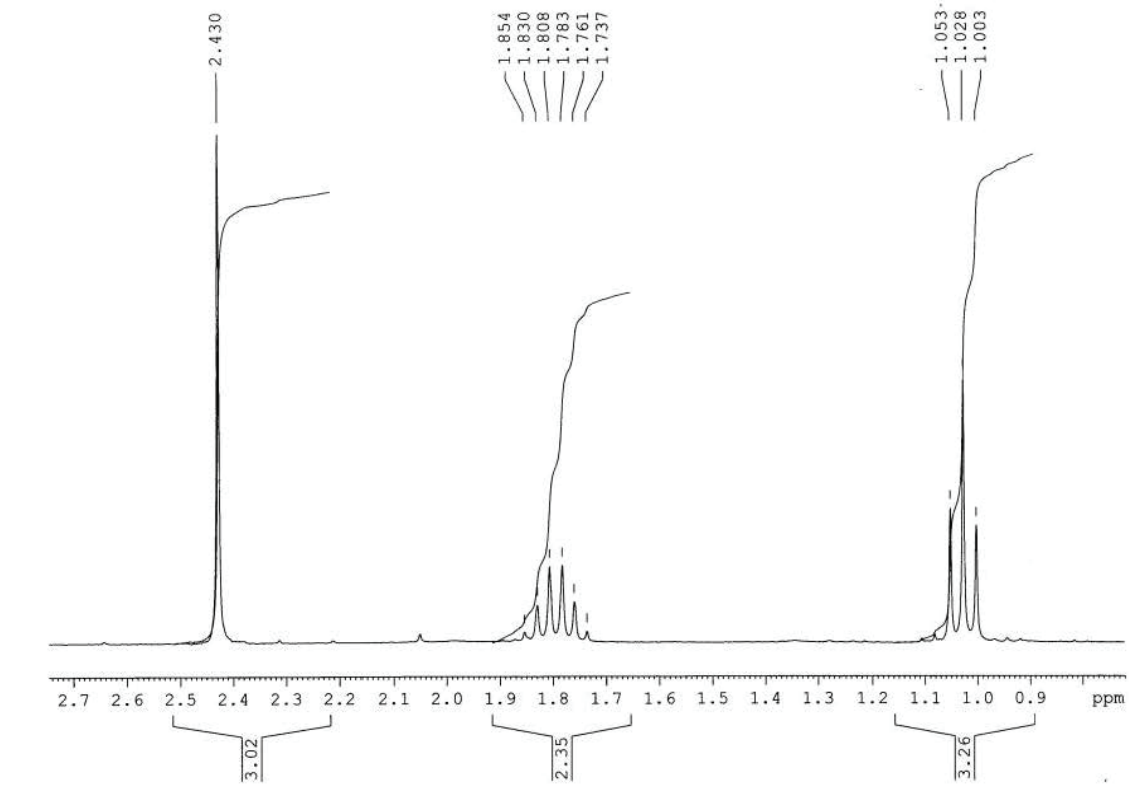
BRUKER

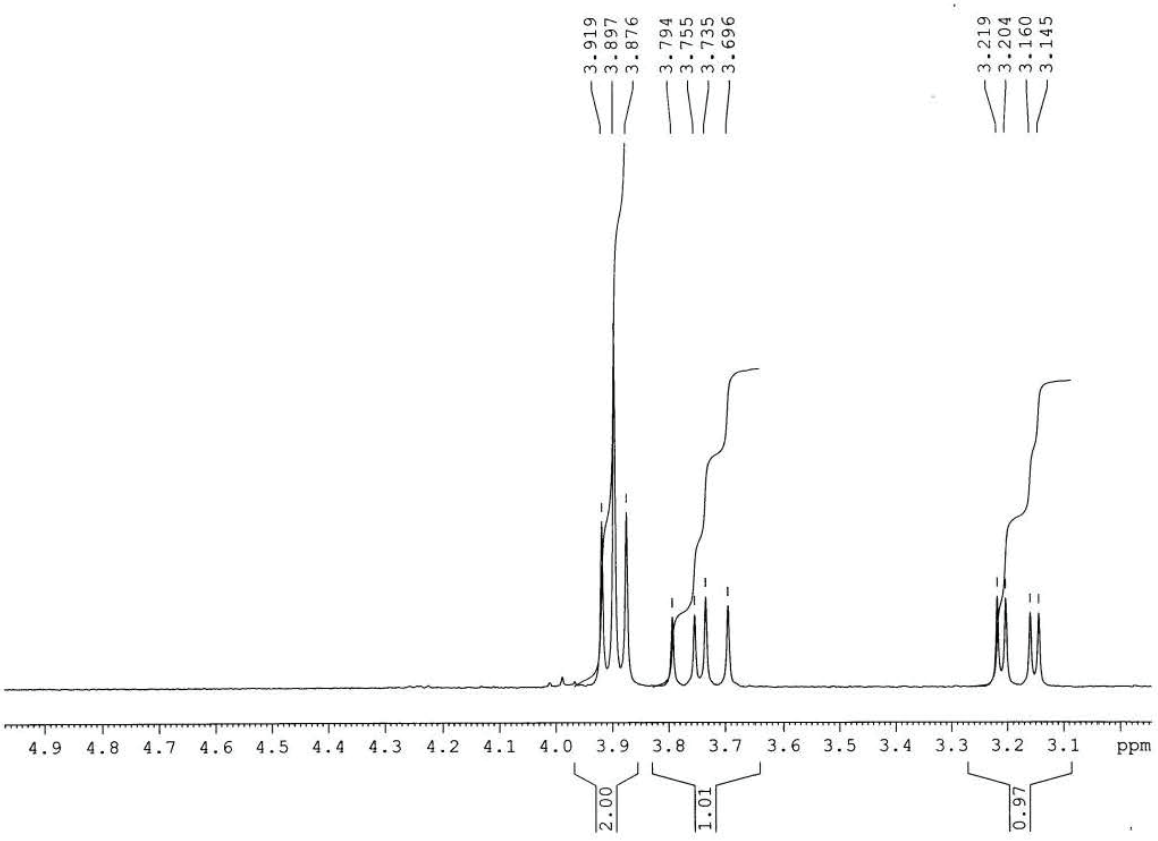
```
Current Data Parameters
NAME      AC-2_13CNMR_CDCL3
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20081028
Time                  12.37
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       2
SWH             17985.611 Hz
FIDRES          0.274439 Hz
AQ              1.8219508 sec
RG                    4096
DW                27.800 usec
DE                 6.00 usec
TE                 293.6 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  6.00 usec
PL1                -5.00 dB
SFO1          75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 2.00 dB
PL12               20.98 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
```

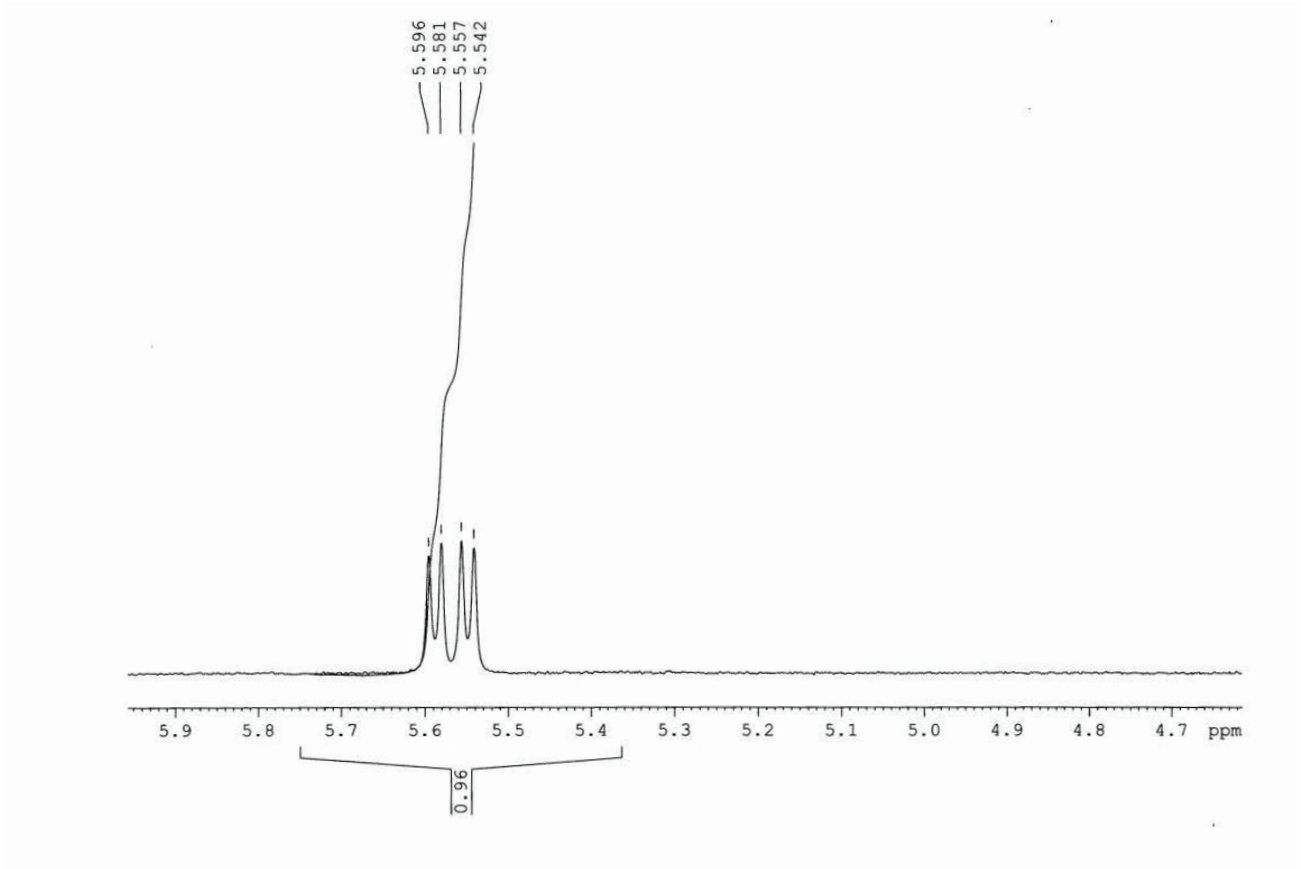

133.94
131.49
130.30
128.75
126.91
126.59
137 136 135 134 133 132 131 130 129 128 127 126 125 124 ppm

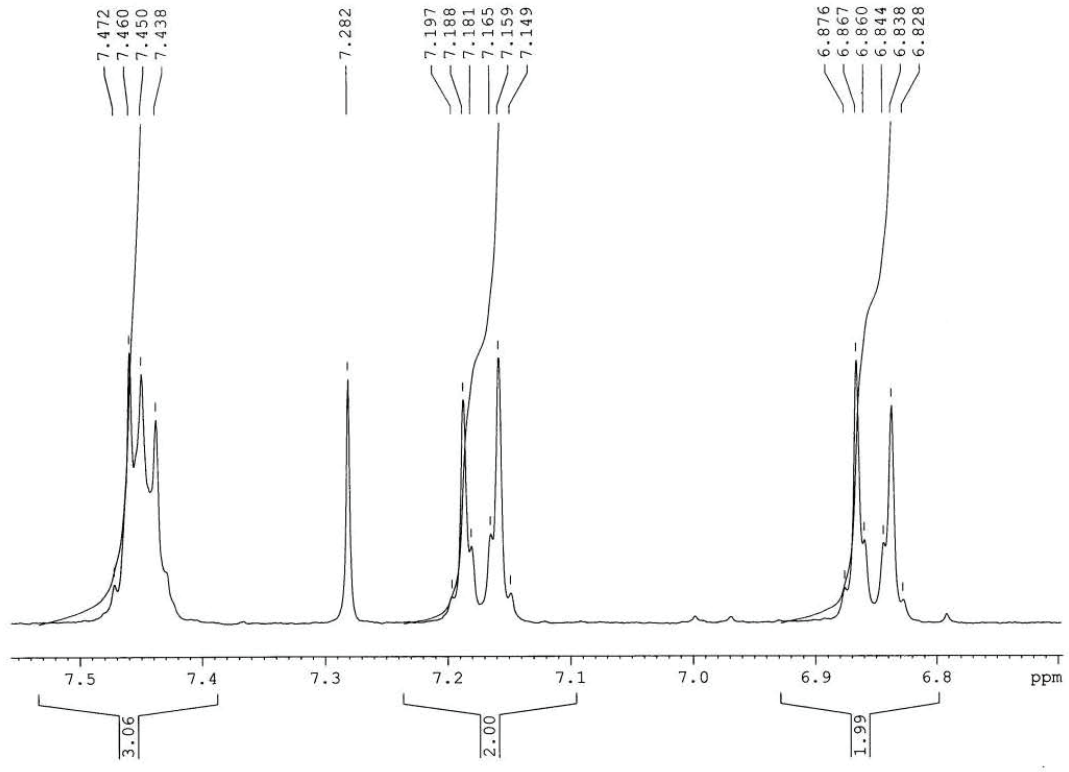
Compound 3b

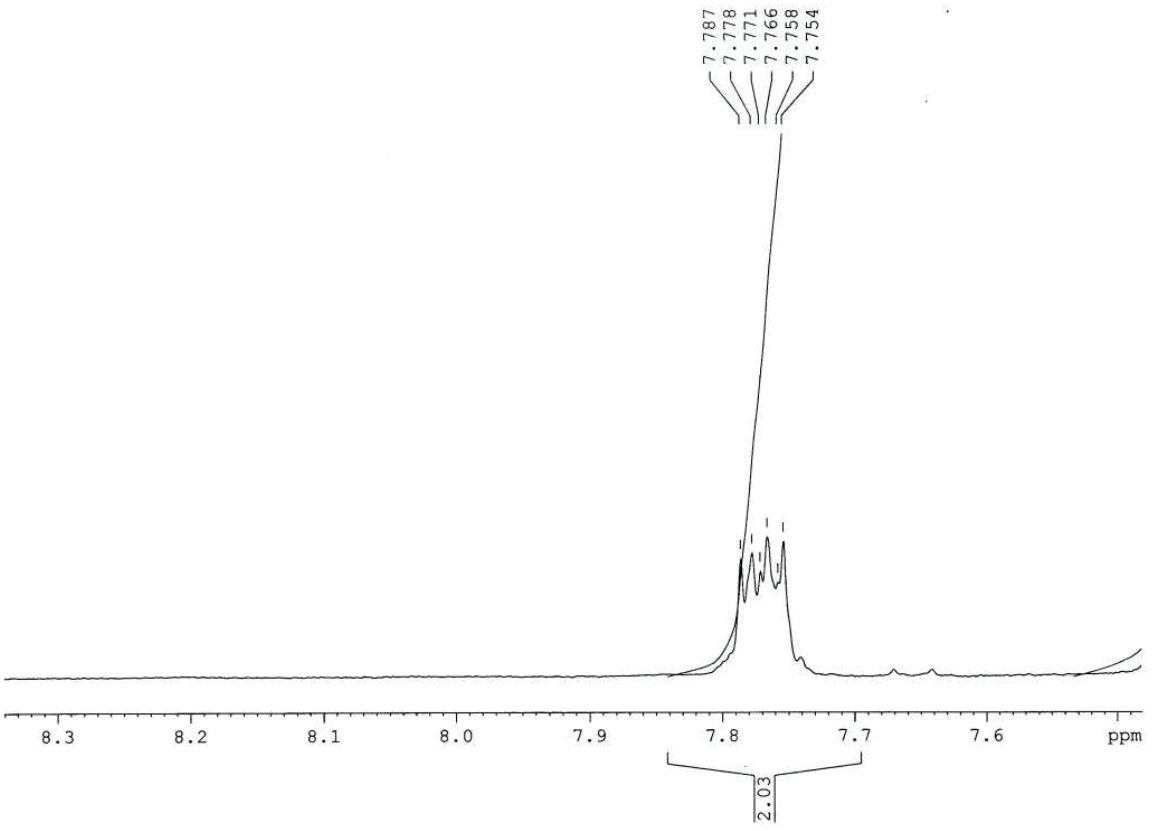

7.787 7.778 7.771 7.766 7.758 7.754 7.472 7.460 7.450 7.438 7.282 7.188 7.181 7.165 7.159 6.876 6.867 6.860 6.844 6.838 5.596 5.581 5.557 5.542 3.919 3.897 3.876 3.794 3.755 3.735 3.696 3.219 3.204 3.160 3.145 2.430 1.830 1.808 1.783 1.761 1.053 1.028 1.003 0.023
BRUKER
Current Data Parameters
NAME AC-3_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080926
Time 10.21
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 406.4
DW 81.000 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Compound 3b
9 8 7 6 5 4 3 2 1 0 ppm
2.03 3.06 2.00 1.99 0.96 2.00 1.01 0.97 3.02 2.35 3.26

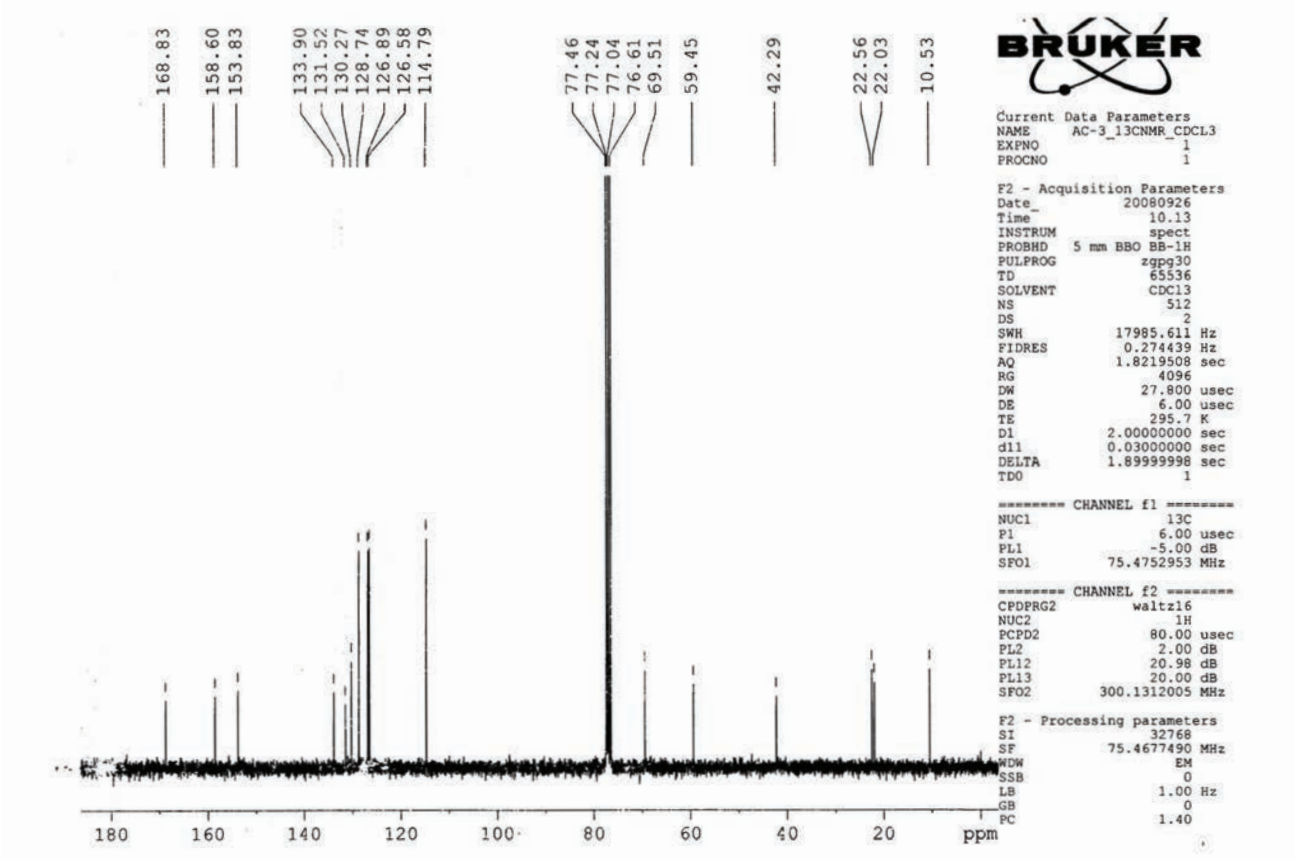

2.430
1.854
1.830
1.808
1.783
1.761
1.737
1.053
1.028
1.003
2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 ppm
3.02
2.35
3.26

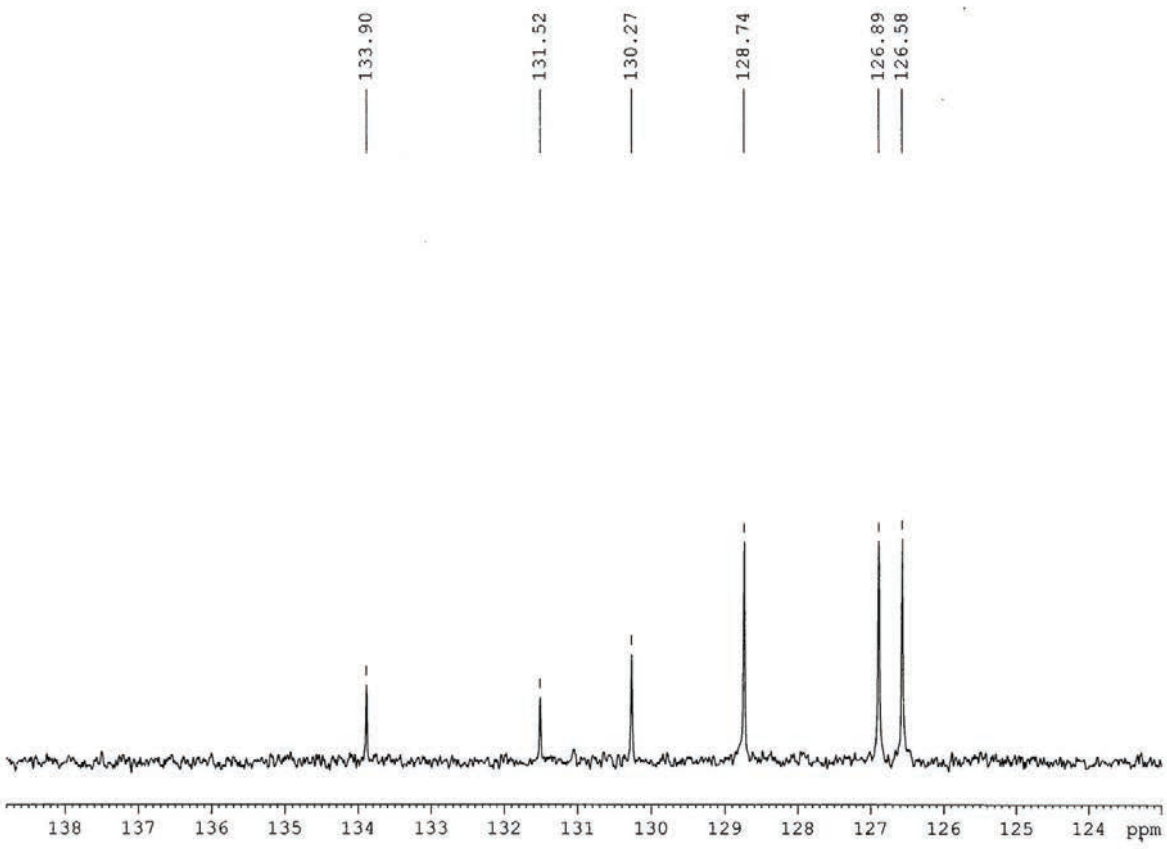

3.919
3.897
3.876
3.794
3.755
3.735
3.696
3.219
3.204
3.160
3.145
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 ppm
2.00
1.01
0.97

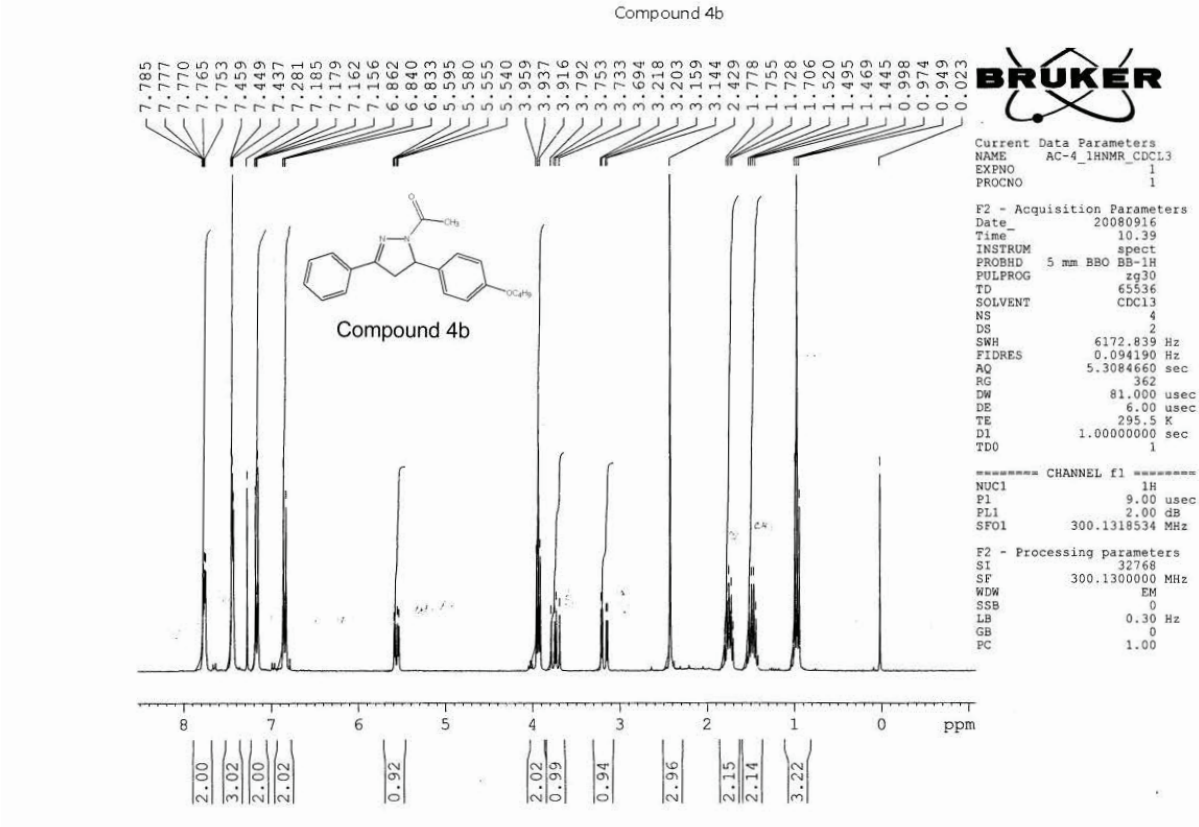

5.596
5.581
5.557
5.542
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
ppm
0.96

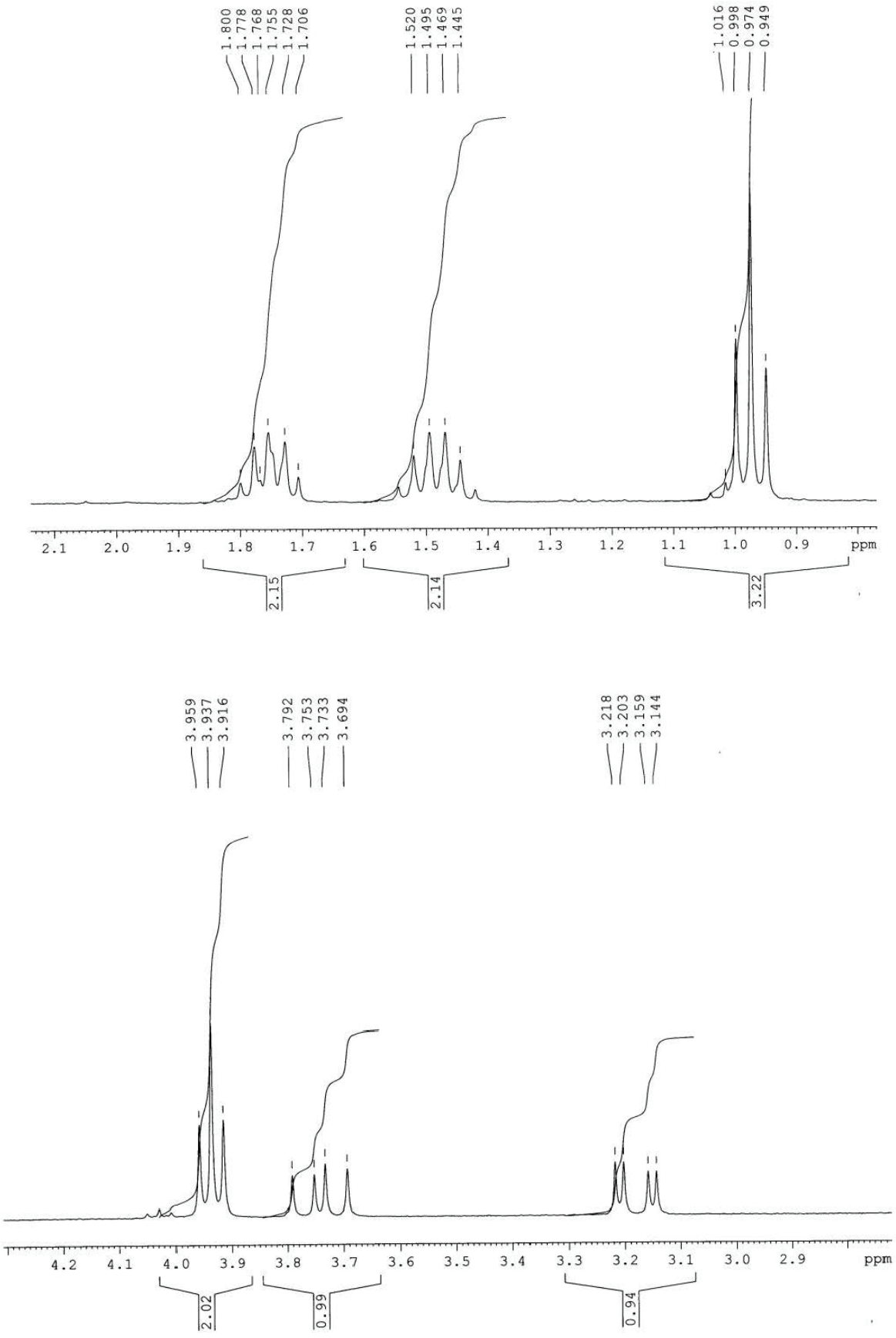

7.472
7.460
7.450
7.438
7.282
7.197
7.188
7.181
7.165
7.159
7.149
6.876
6.867
6.860
6.844
6.838
6.828
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
3.06
2.00
1.99

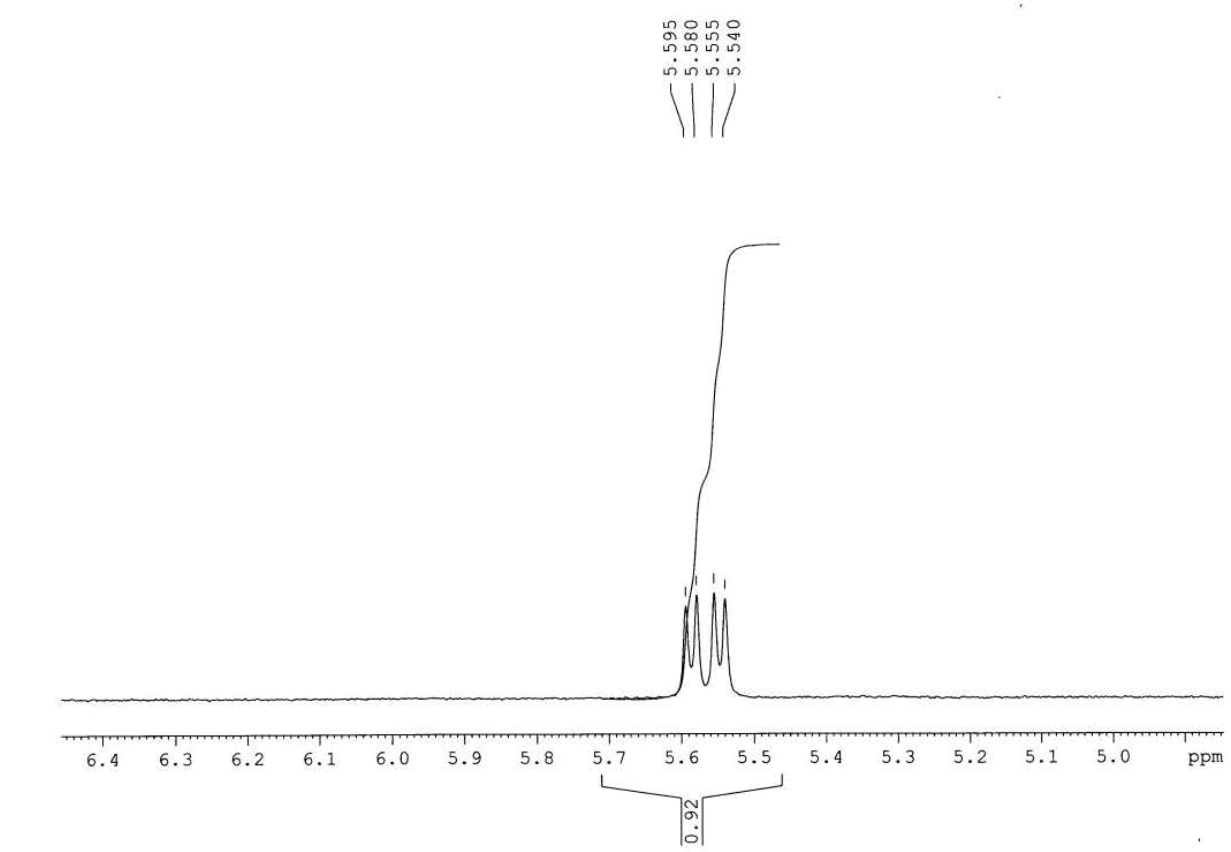

7.787
7.778
7.771
7.766
7.758
7.754
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
ppm
2.03

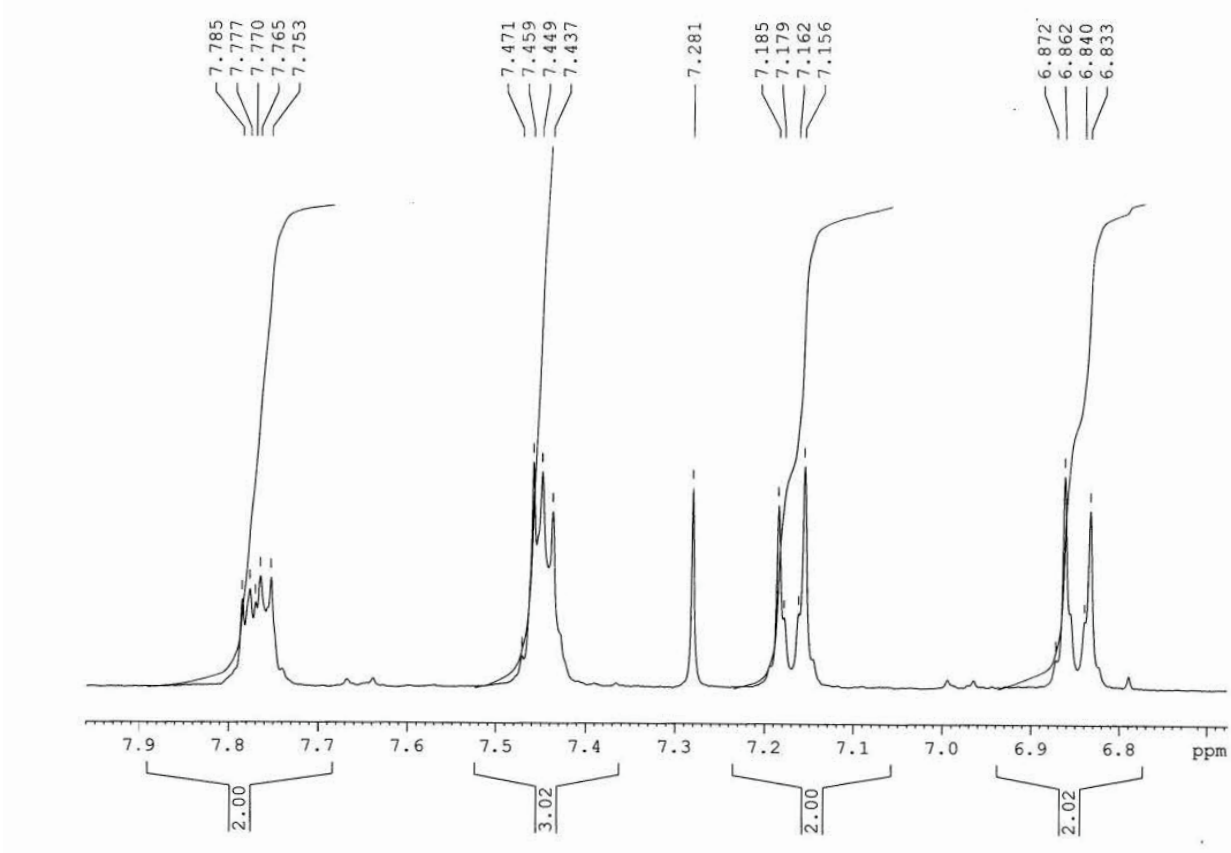

168.83
158.60
153.83
133.90
131.52
130.27
128.74
126.89
126.58
114.79
77.46
77.24
77.04
76.61
69.51
59.45
42.29
22.56
22.03
10.53
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME AC-3_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080926
Time 10.13
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 4096
DW 27.800 usec
DE 6.00 usec
TE 295.7 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

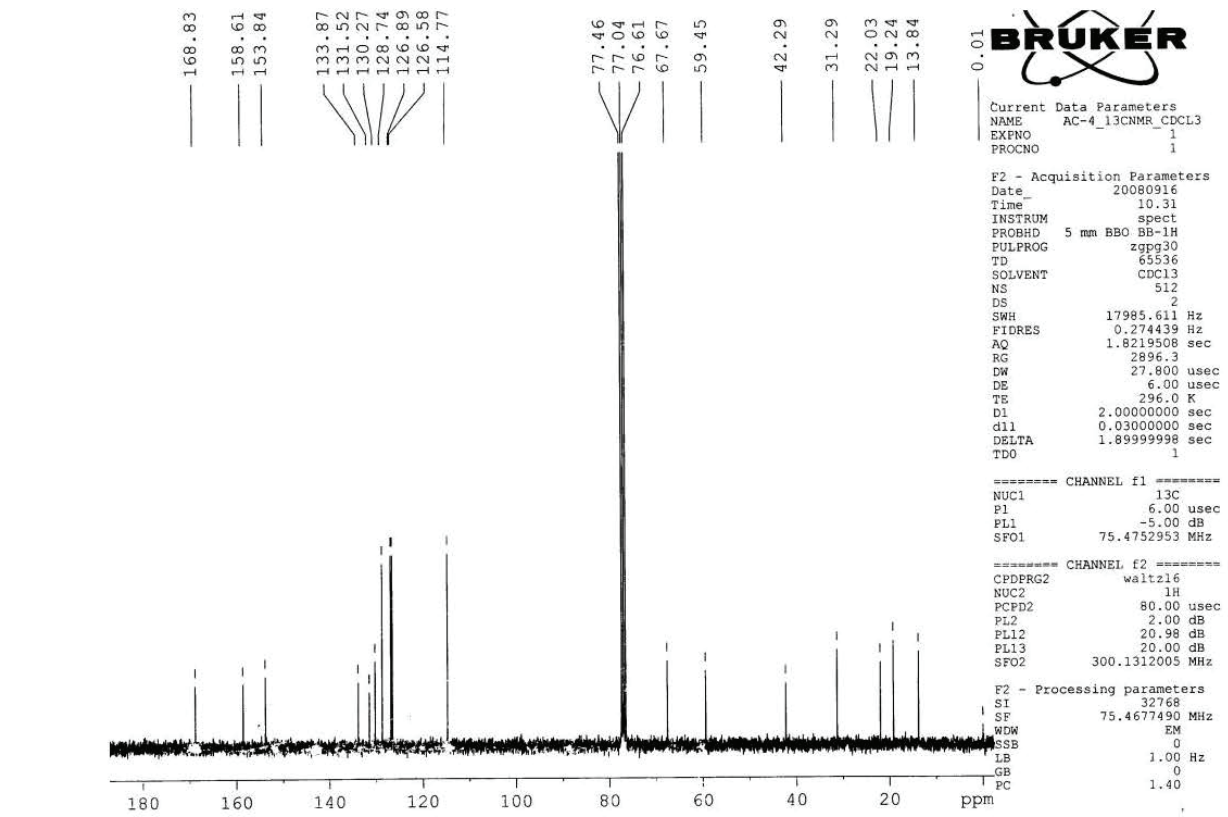

133.90
131.52
130.27
128.74
126.89
126.58
138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 ppm

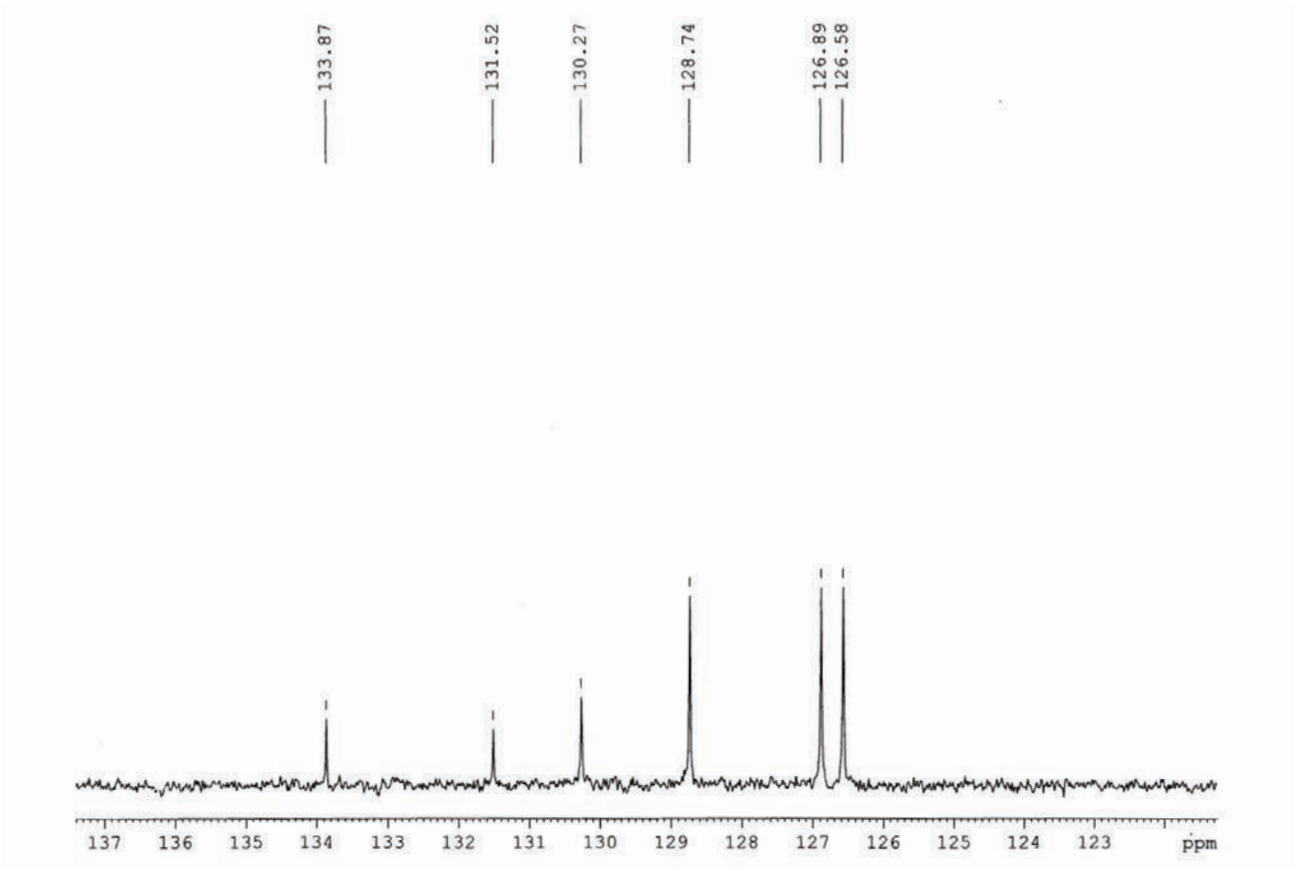

Compound 4b
7.785 7.777 7.770 7.765 7.753 7.459 7.449 7.437 7.281 7.185 7.179 7.162 7.156 6.862 6.840 6.833 5.595 5.580 5.555 5.540 3.959 3.937 3.916 3.792 3.753 3.733 3.694 3.218 3.203 3.159 3.144 2.429 1.778 1.755 1.728 1.706 1.520 1.495 1.469 1.445 0.998 0.974 0.949 0.023
Compound 4b
BRUKER
Current Data Parameters
NAME AC-4_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080916
Time 10.39
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 362
DW 81.000 usec
DE 6.00 usec
TE 295.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8 7 6 5 4 3 2 1 0 ppm
2.00 3.02 2.00 2.02 0.92 2.02 0.99 0.94 2.96 2.15 2.14 3.22

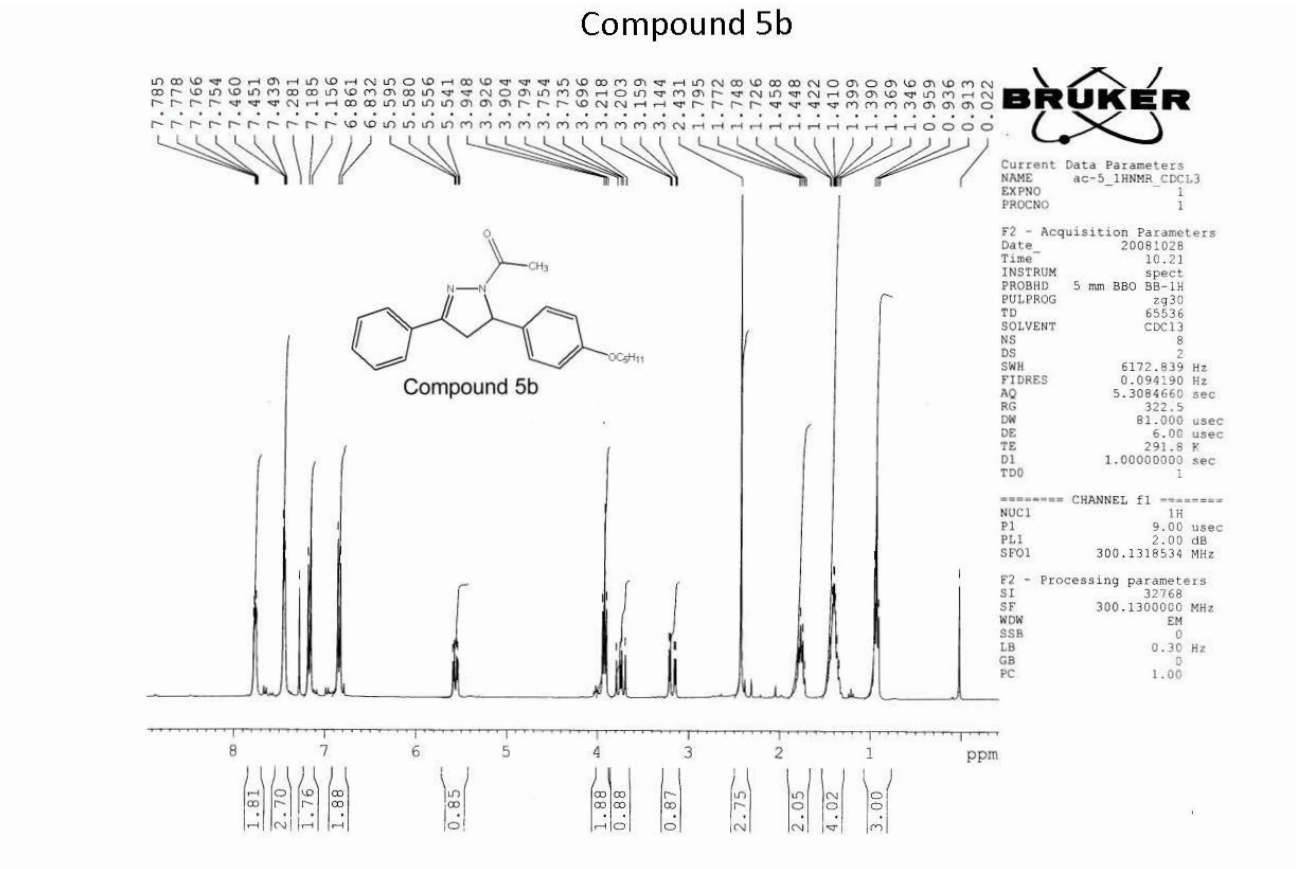

1.800
1.778
1.768
1.755
1.728
1.706
1.520
1.495
1.469
1.445
1.016
0.998
0.974
0.949
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
ppm
2.15
2.14
3.22
3.959
3.937
3.916
3.792
3.753
3.733
3.694
3.218
3.203
3.159
3.144
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
ppm
2.02
0.99
0.94

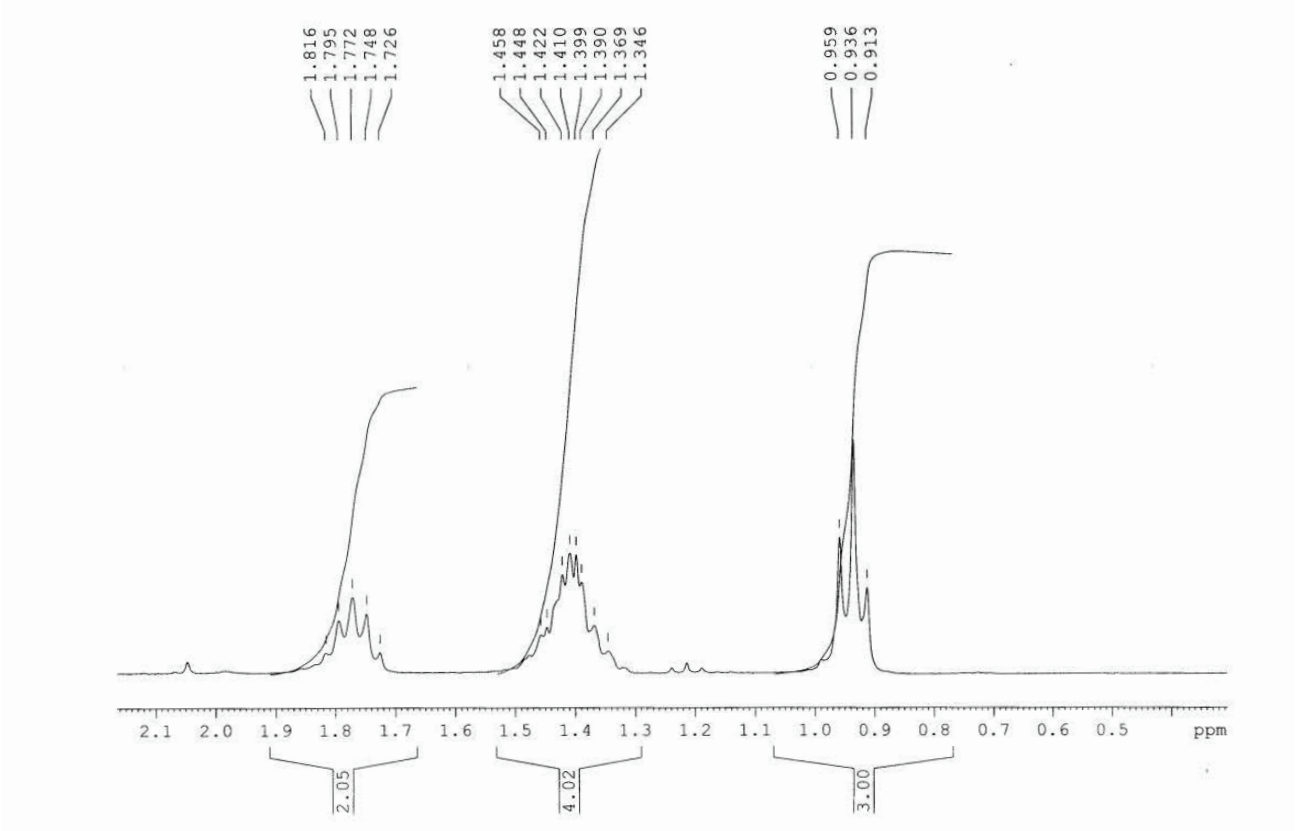

5.595
5.580
5.555
5.540
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 ppm
0.92

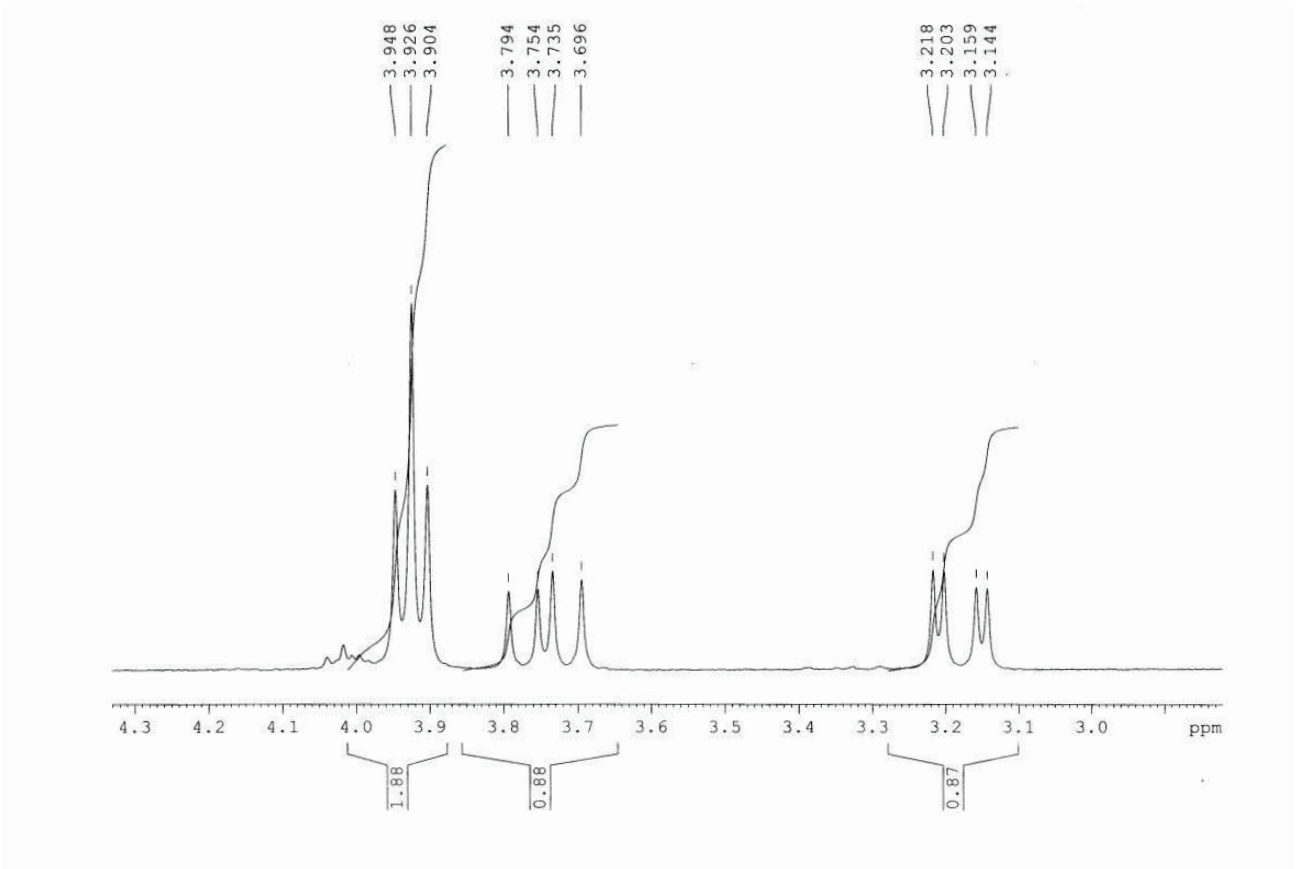

7.785
7.777
7.770
7.765
7.753
7.471
7.459
7.449
7.437
7.281
7.185
7.179
7.162
7.156
6.872
6.862
6.840
6.833
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
2.00
3.02
2.00
2.02

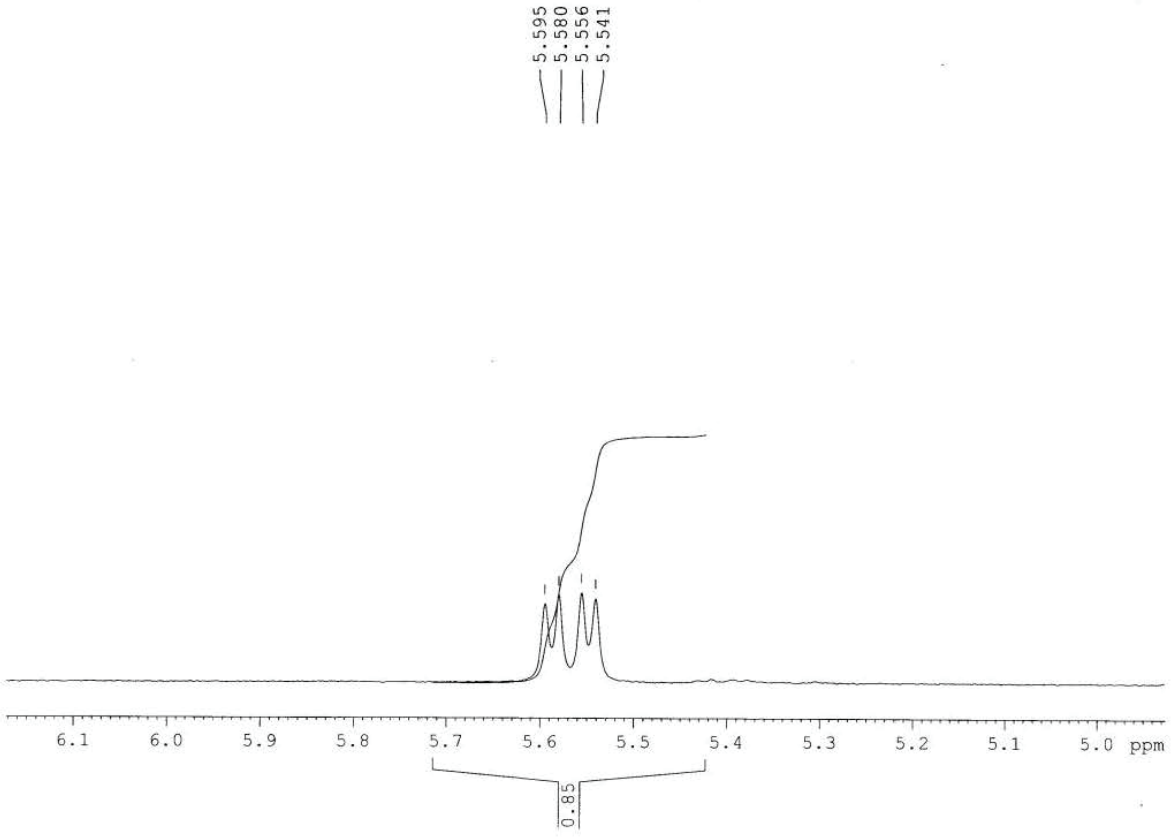

168.83
158.61
153.84
133.87
131.52
130.27
128.74
126.89
126.58
114.77
77.46
77.04
76.61
67.67
59.45
42.29
31.29
22.03
19.24
13.84
0.01
BRUKER
Current Data Parameters
NAME AC-4_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080916
Time 10.31
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 2896.3
DW 27.800 usec
DE 6.00 usec
TE 296.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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
180 160 140 120 100 80 60 40 20 ppm

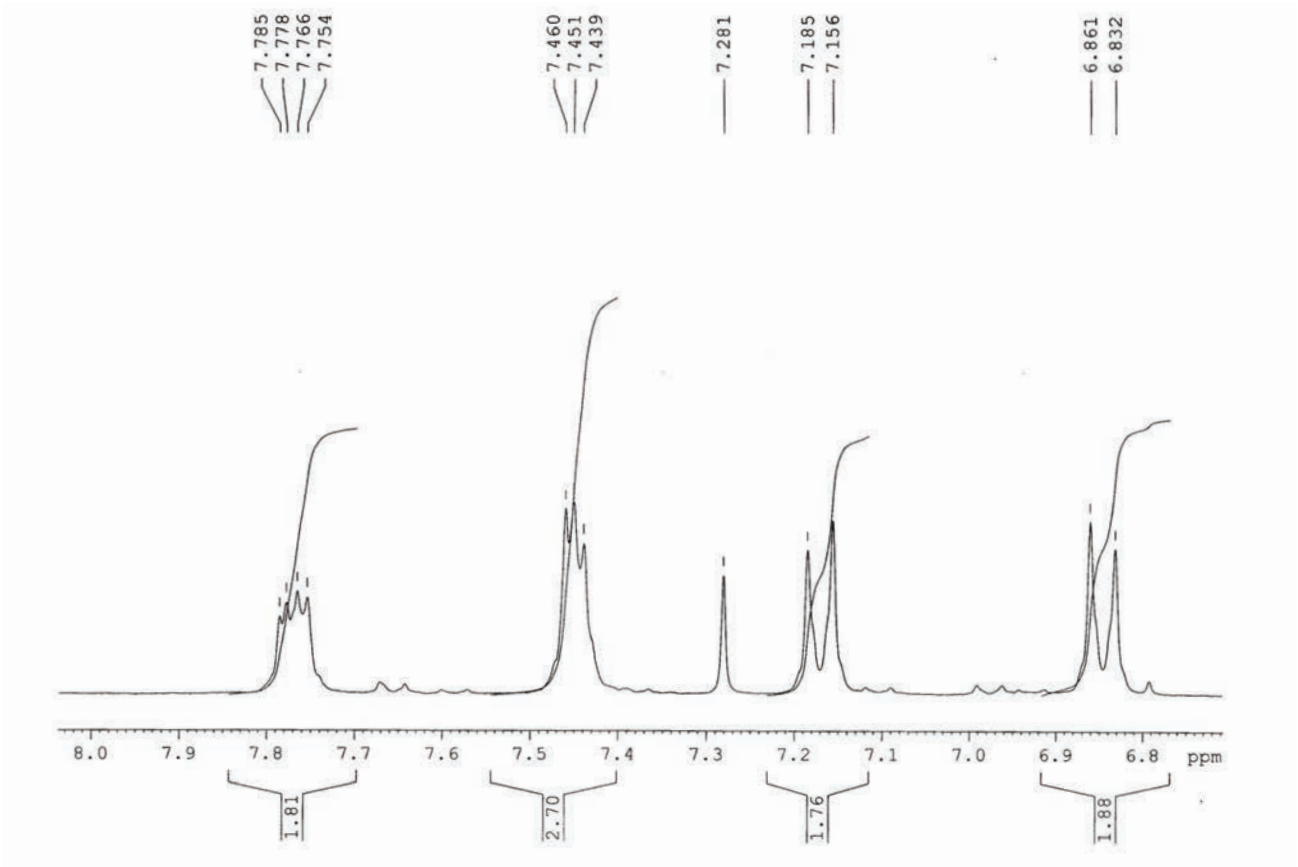

133.87
131.52
130.27
128.74
126.89
126.58
137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 ppm

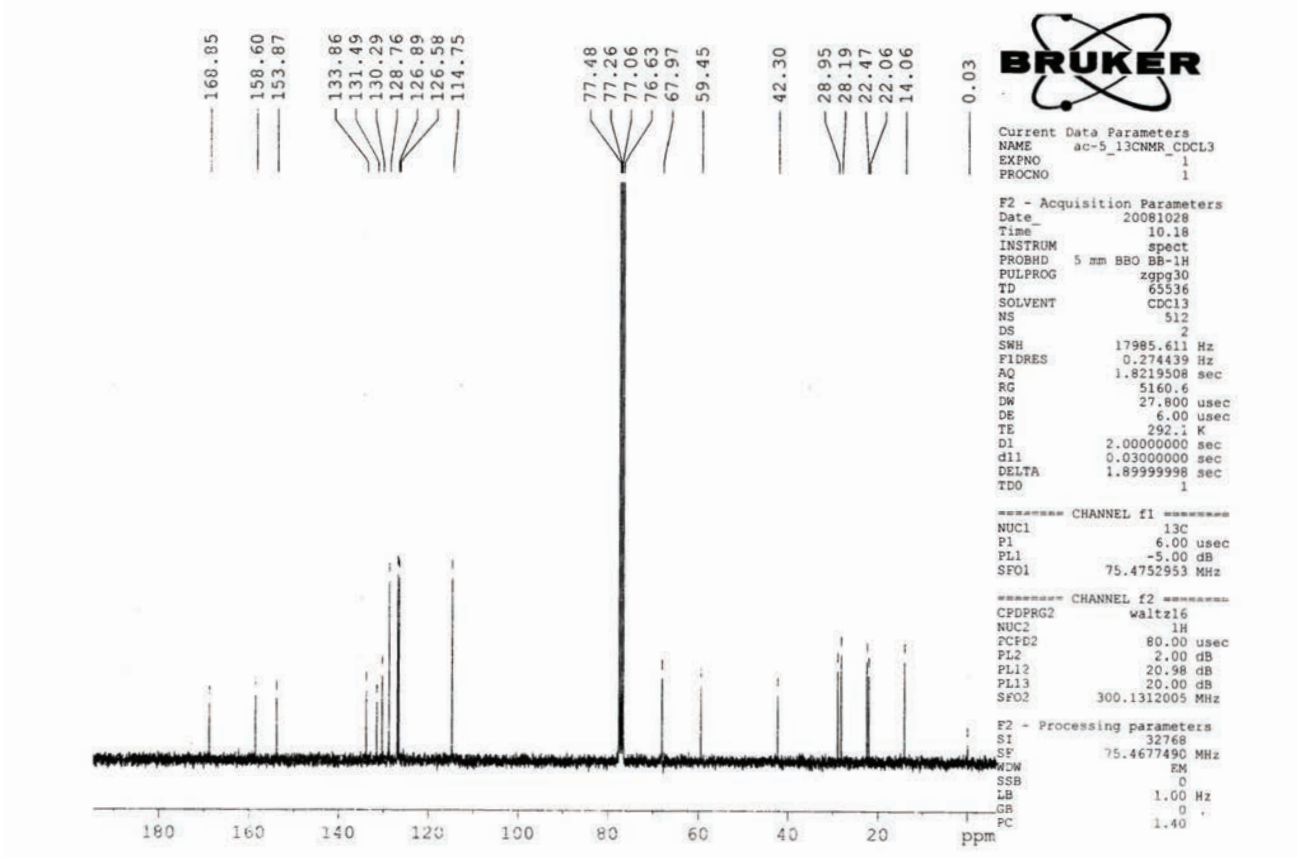

Compound 5b
7.785
7.778
7.766
7.754
7.460
7.451
7.439
7.281
7.185
7.156
6.861
6.832
5.595
5.580
5.556
5.541
3.948
3.926
3.904
3.794
3.754
3.735
3.696
3.218
3.203
3.159
3.144
2.431
1.795
1.772
1.748
1.726
1.458
1.448
1.422
1.410
1.399
1.390
1.369
1.346
0.959
0.936
0.913
0.022
BRUKER
Current Data Parameters
NAME ac-5_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081028
Time 10.21
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 322.5
DW 81.000 usec
DE 6.00 usec
TE 291.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Compound 5b
ppm
1.81
2.70
1.76
1.88
0.85
1.88
0.88
0.87
2.75
2.05
4.02
3.00

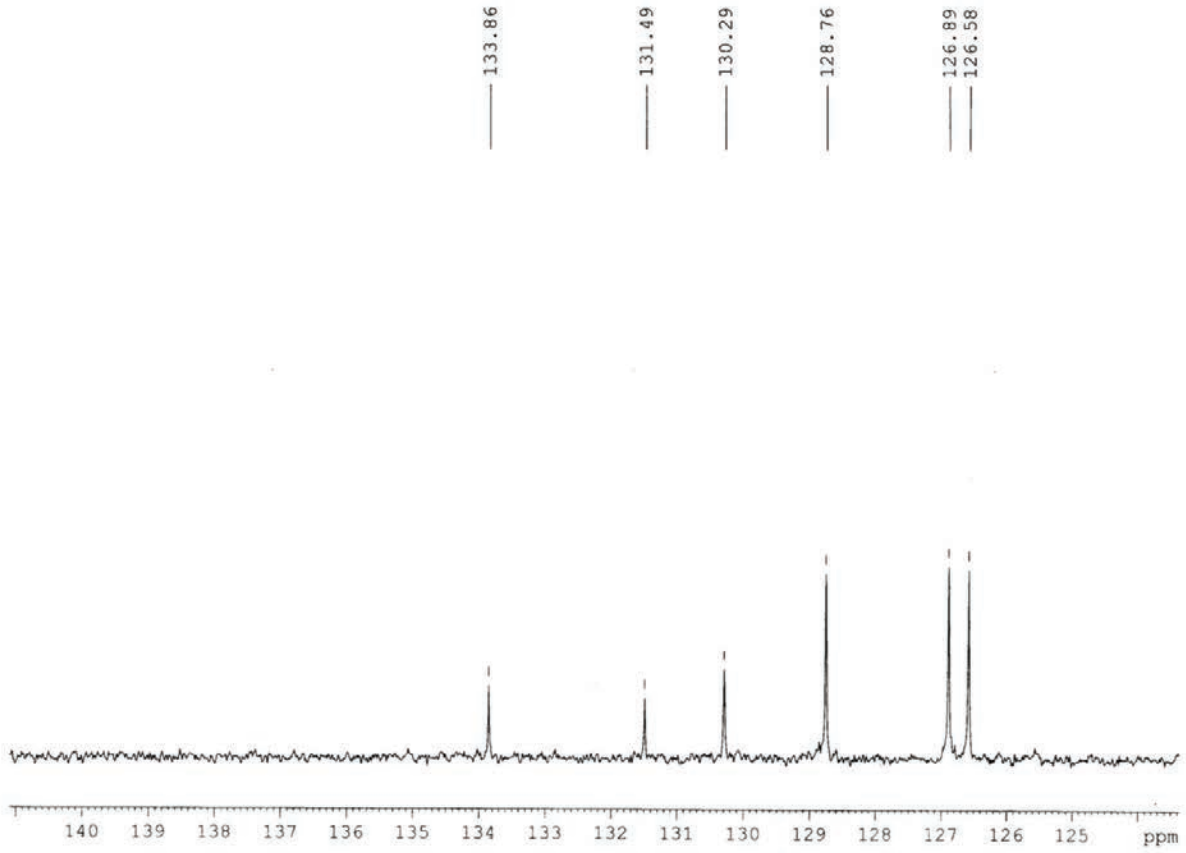

1.816
1.795
1.772
1.748
1.726
1.458
1.448
1.422
1.410
1.399
1.390
1.369
1.346
0.959
0.936
0.913
ppm
2.05
4.02
3.00


3.948
3.926
3.904
3.794
3.754
3.735
3.696
3.218
3.203
3.159
3.144
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
1.88
0.88
0.87

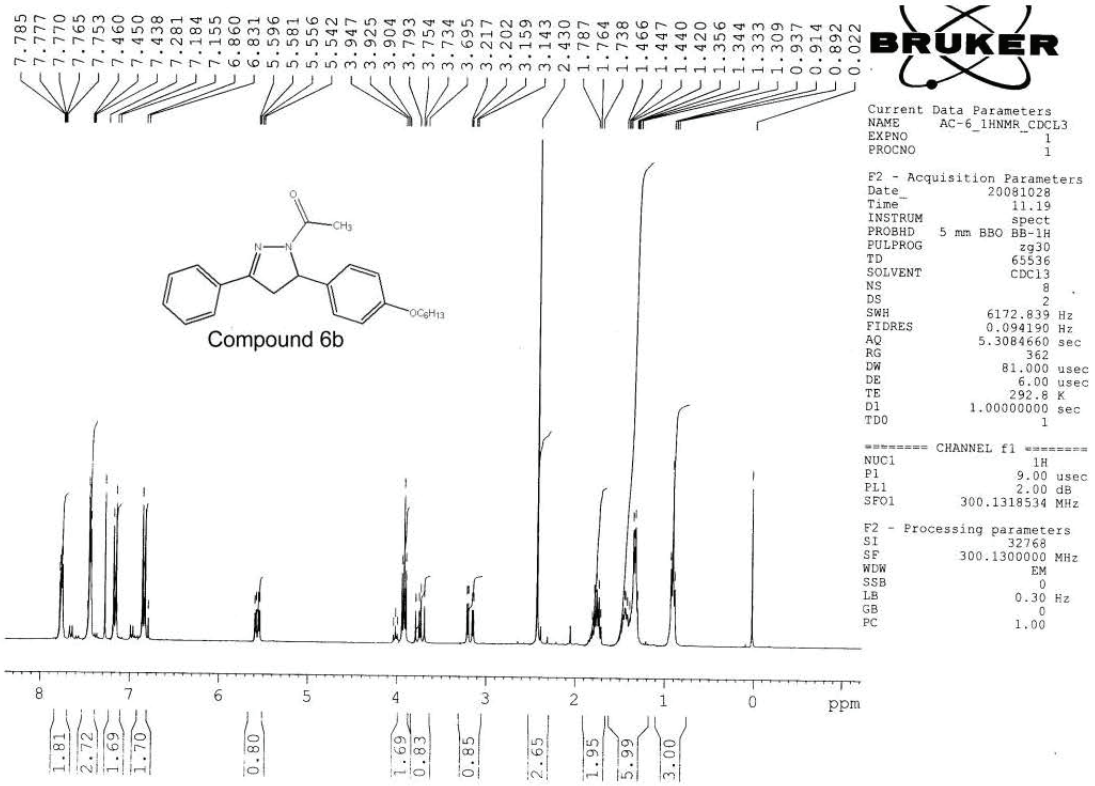

5.595
5.580
5.556
5.541
6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 ppm
0.85


7.785
7.778
7.766
7.754
7.460
7.451
7.439
7.281
7.185
7.156
6.861
6.832
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
1.81
2.70
1.76
1.88


168.85
158.60
153.87
133.86
131.49
130.29
128.76
126.89
126.58
114.75
77.48
77.26
77.06
76.63
67.97
59.45
42.30
28.95
28.19
22.47
22.06
14.06
0.03
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME ac-5_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081028
Time 10.18
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 5160.6
DW 27.800 usec
DE 6.00 usec
TE 292.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

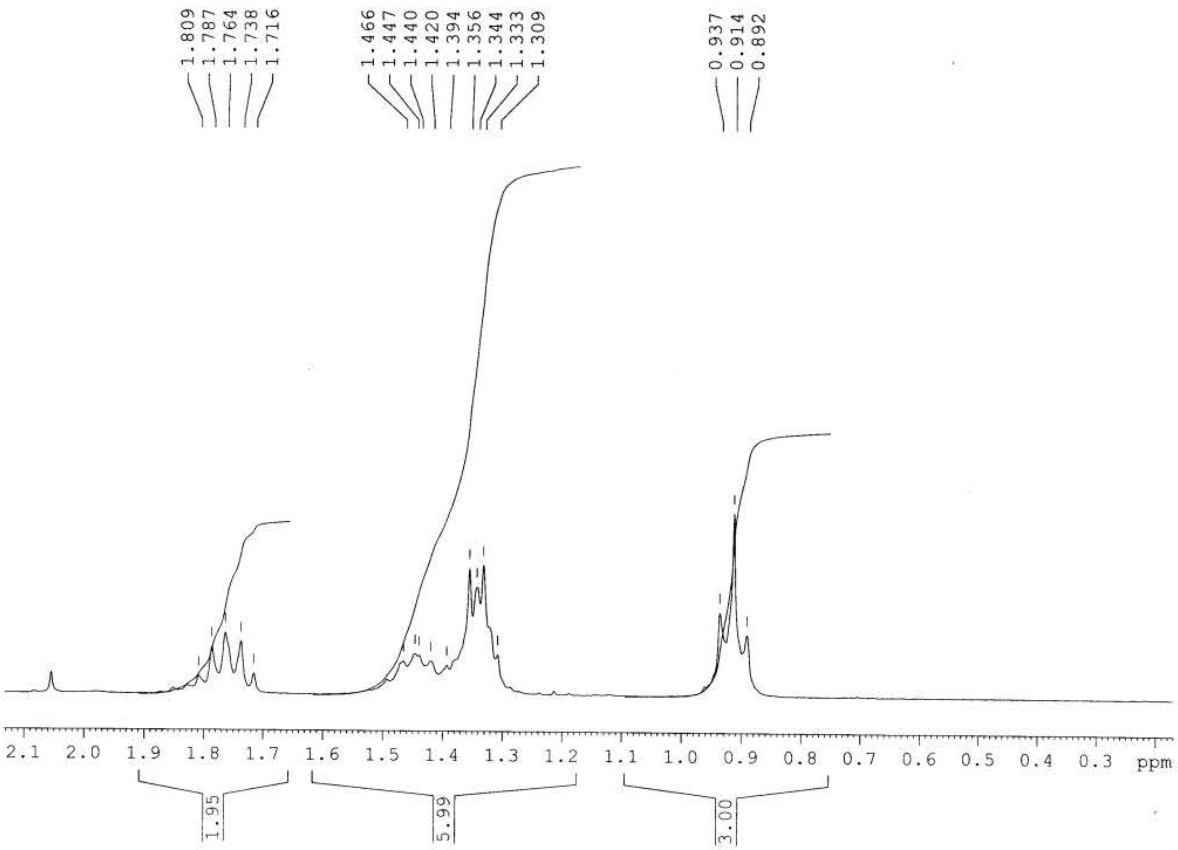


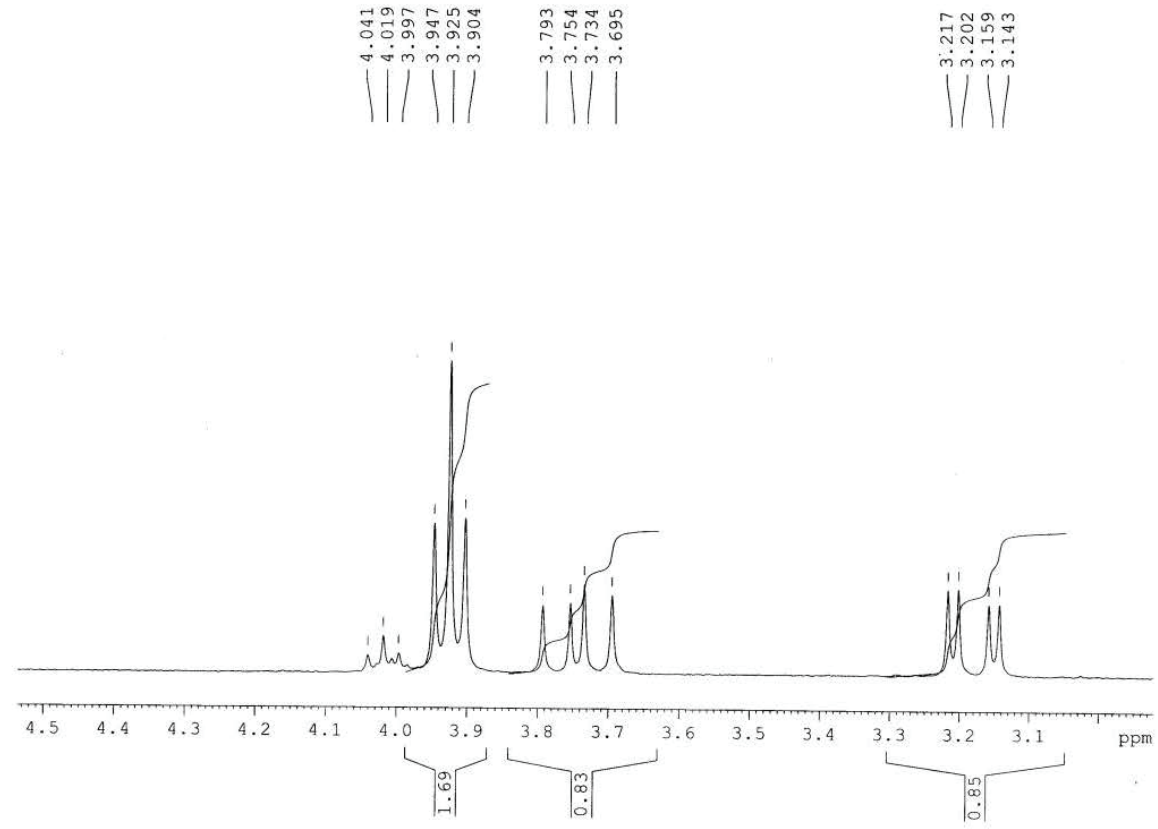
Compound 6b

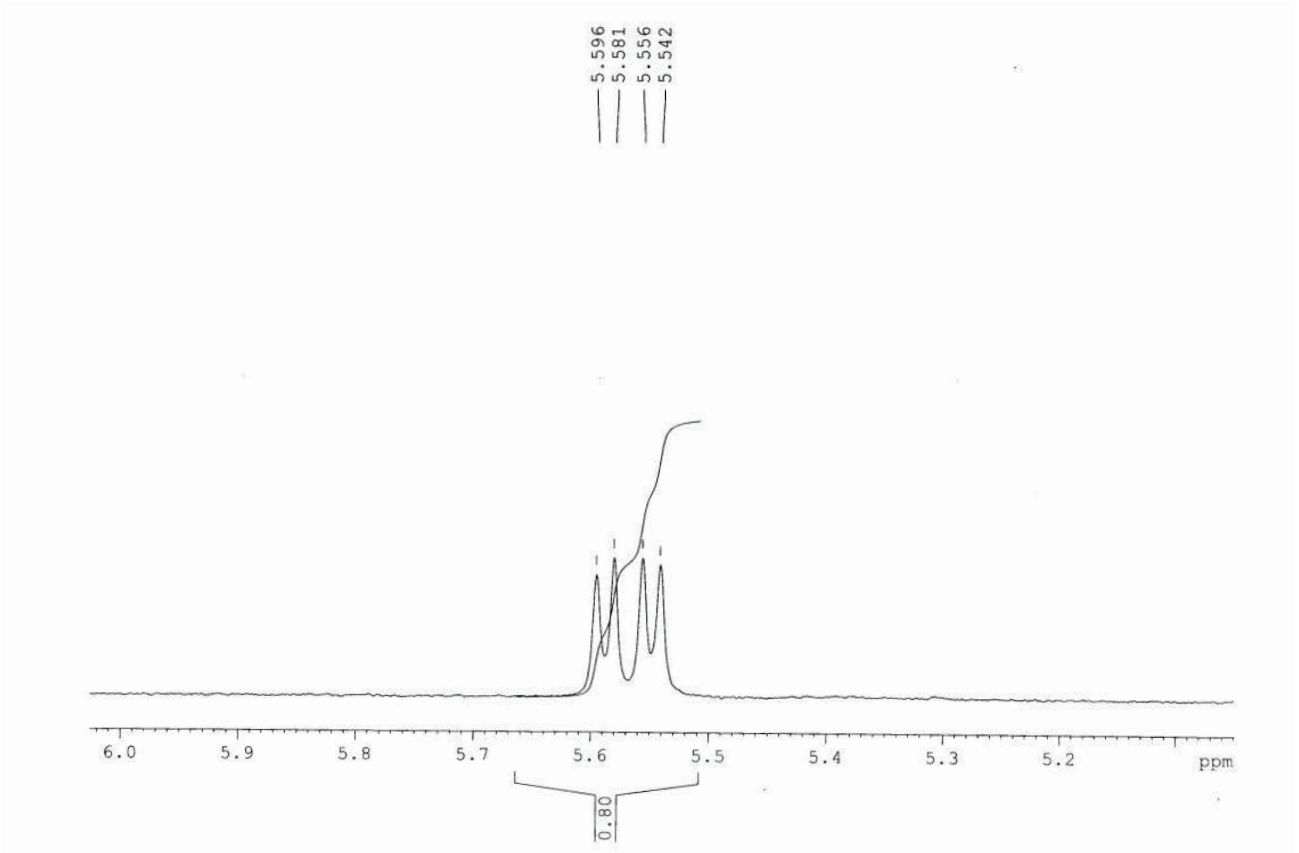


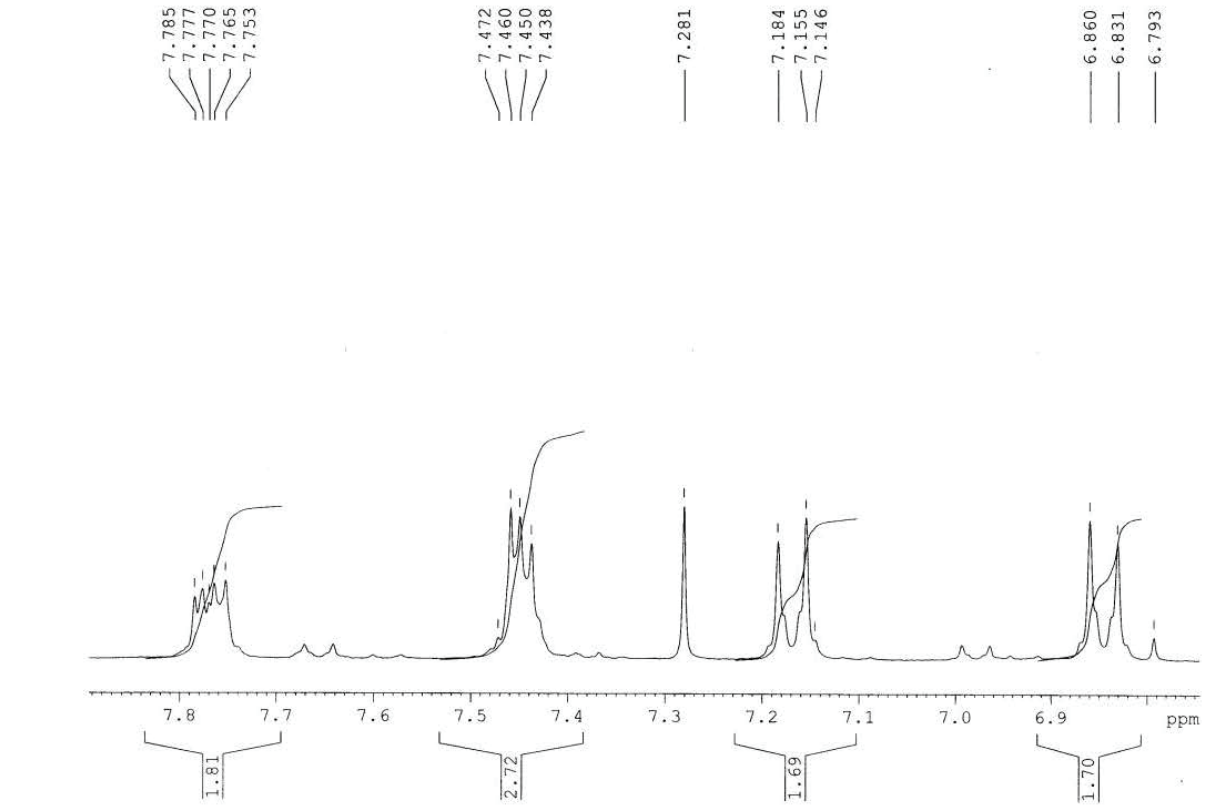
BRUKER

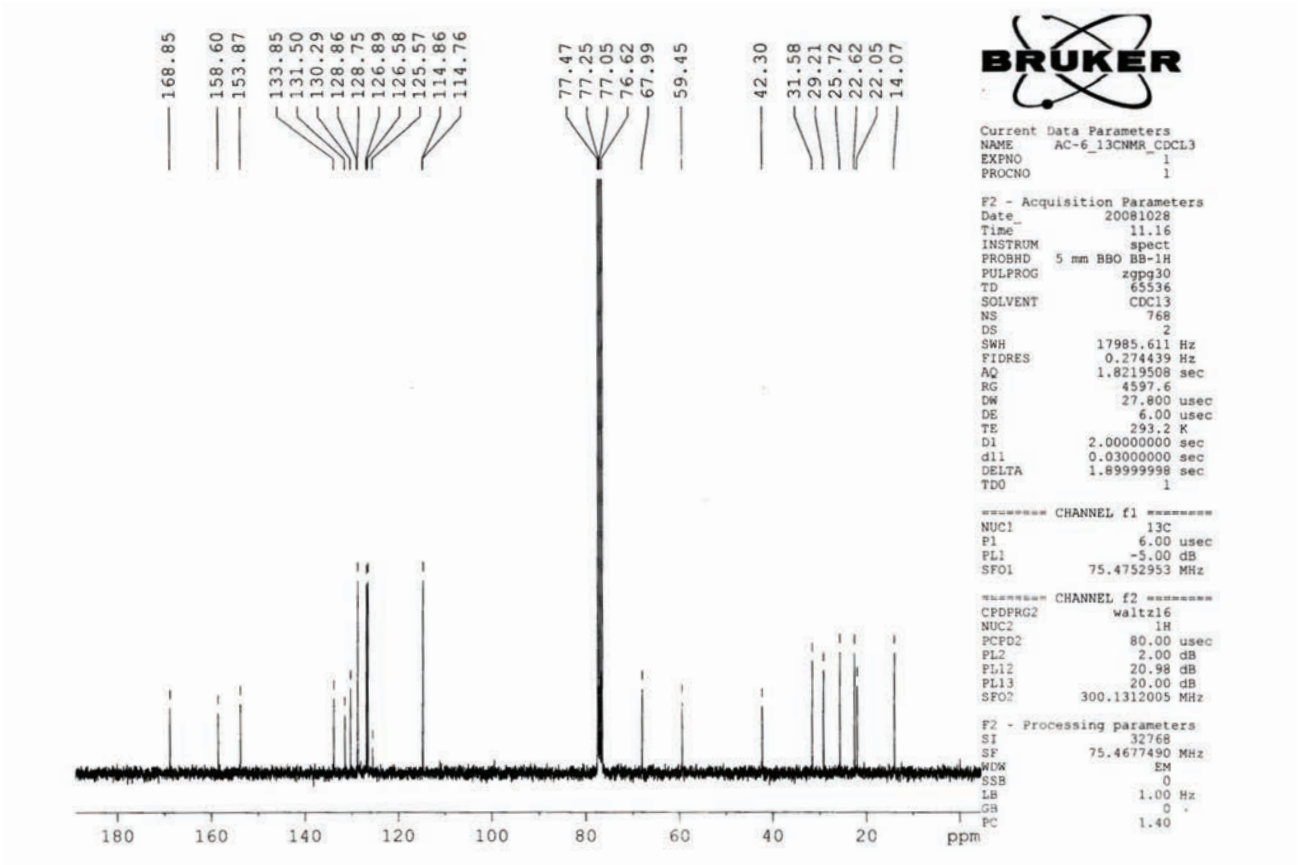
```
Current Data Parameters
NAME        AC-6_1HNMR_CDCL3
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20081028
Time                   11.19
INSTRUM                spect
PROBHD   5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        8
DS                        2
SWH                6172.839 Hz
FIDRES            0.094190 Hz
AQ                5.3084660 sec
RG                      362
DW                 81.000 usec
DE                  6.00 usec
TE                  292.8 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                  9.00 usec
PL1                 2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF            300.1300000 MHz
WDW                      EM
SSB                       0
LB                 0.30 Hz
GB                        0
PC                     1.00
```

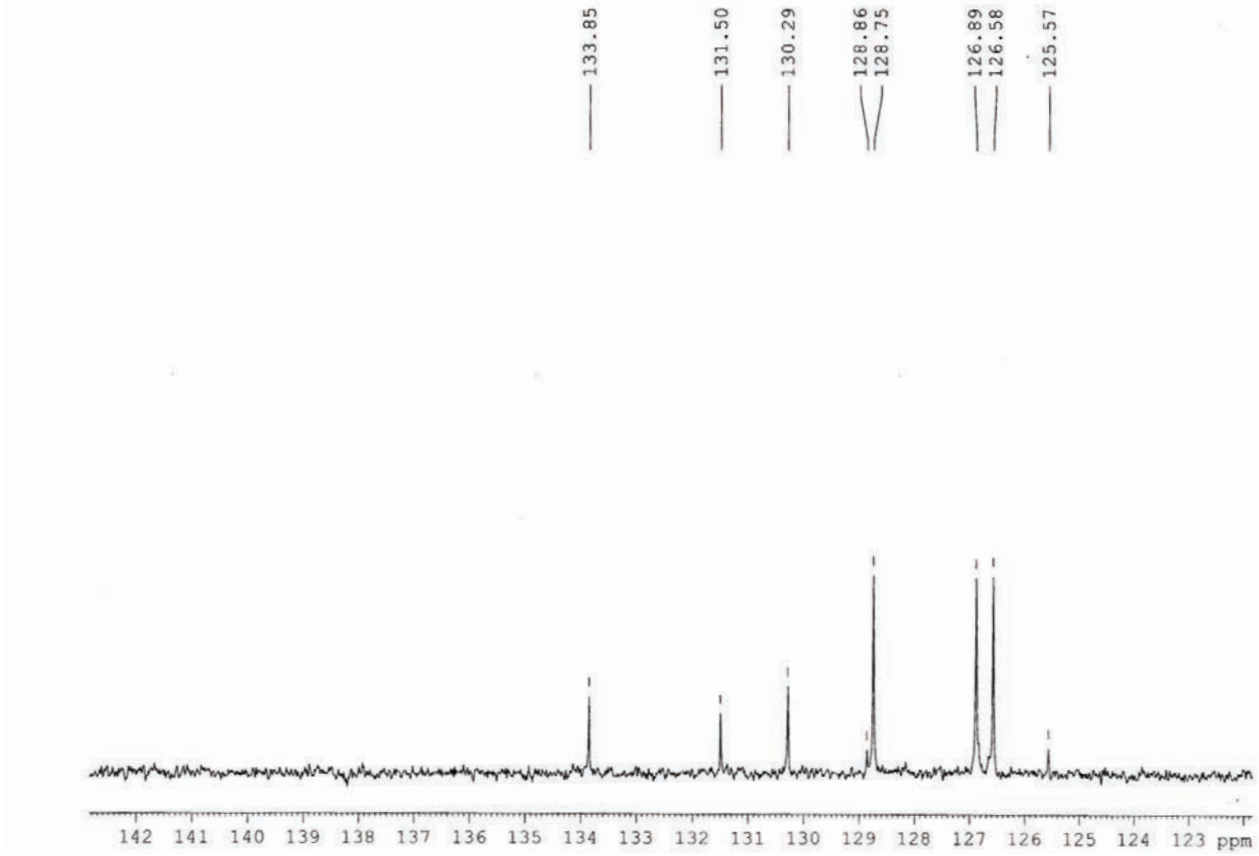

1.809
1.787
1.764
1.738
1.716
1.466
1.447
1.440
1.420
1.394
1.356
1.344
1.333
1.309
0.937
0.914
0.892
2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 ppm
1.95
5.99
3.00

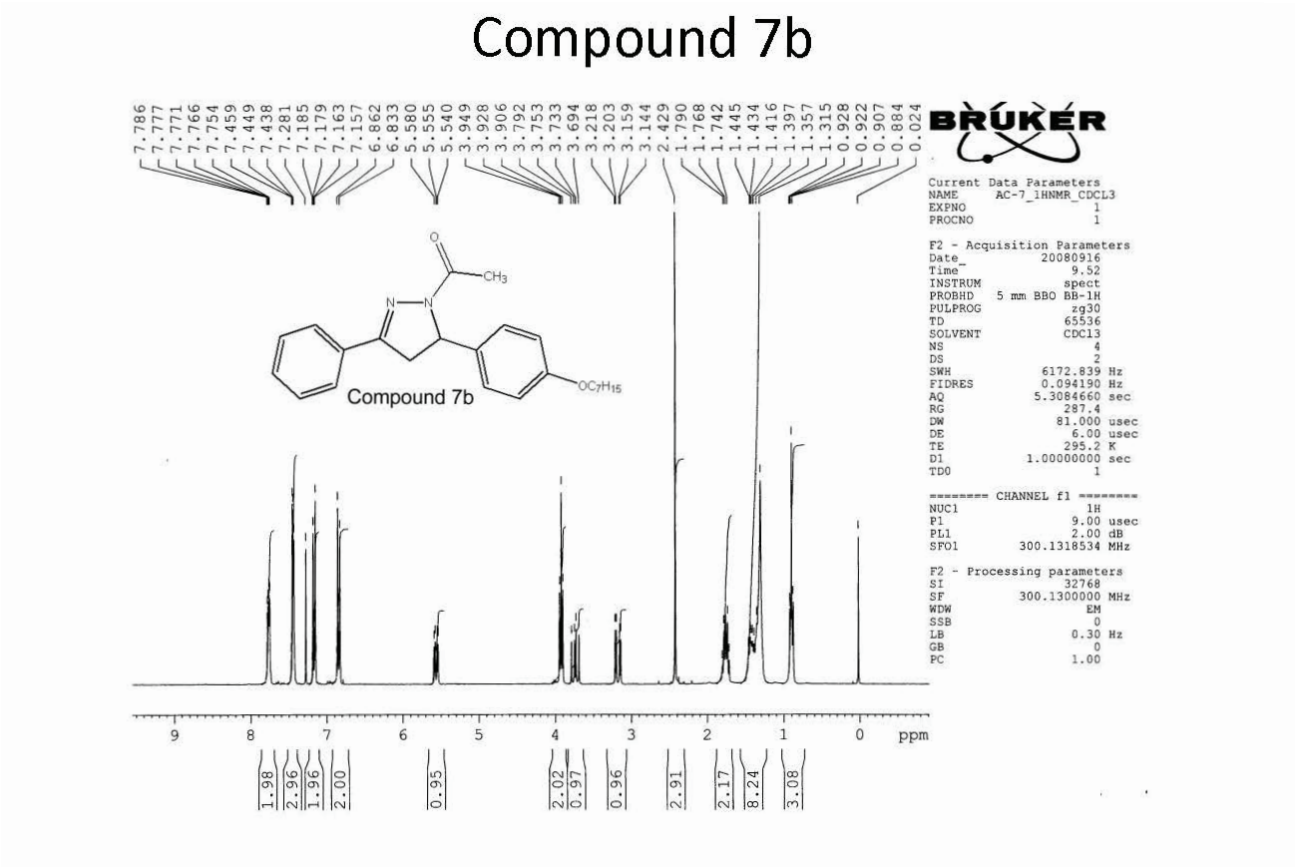

4.041
4.019
3.997
3.947
3.925
3.904
3.793
3.754
3.734
3.695
3.217
3.202
3.159
3.143
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 ppm
1.69
0.83
0.85

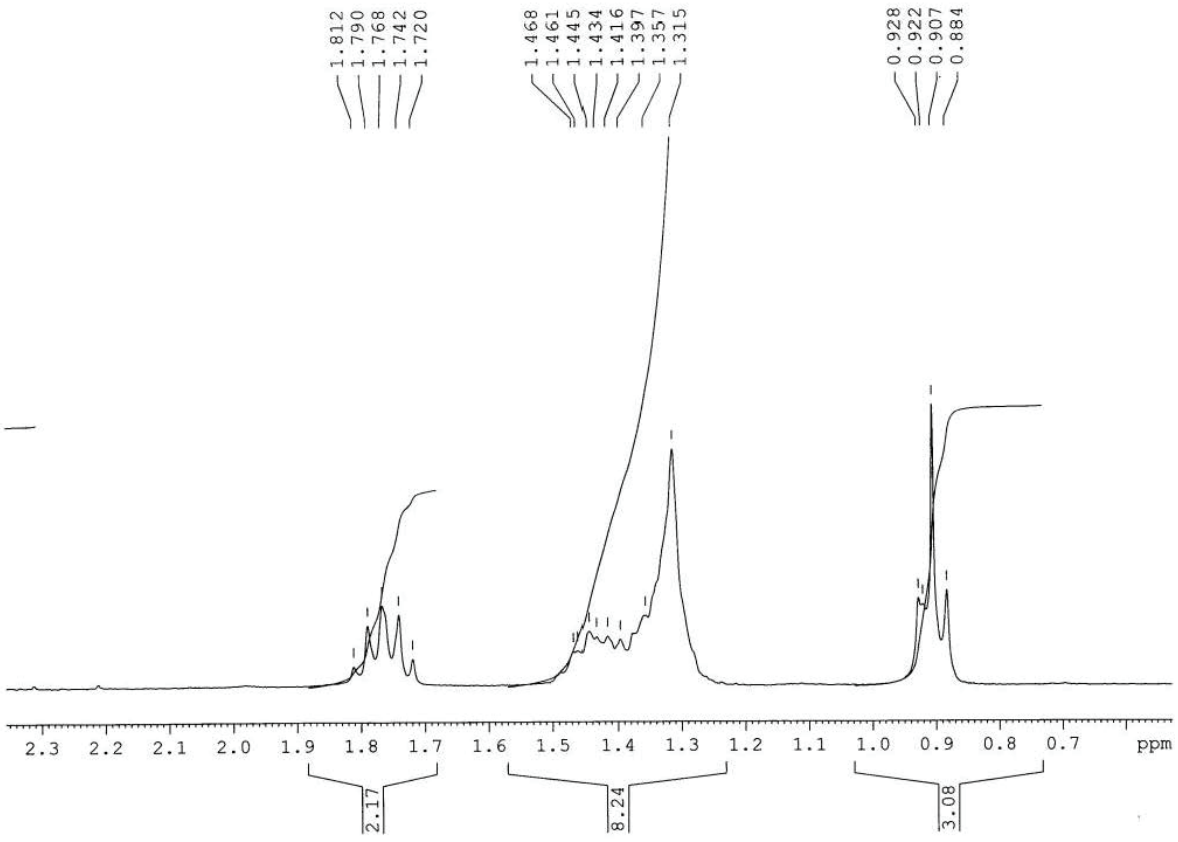

5.596
5.581
5.556
5.542
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
ppm
0.80

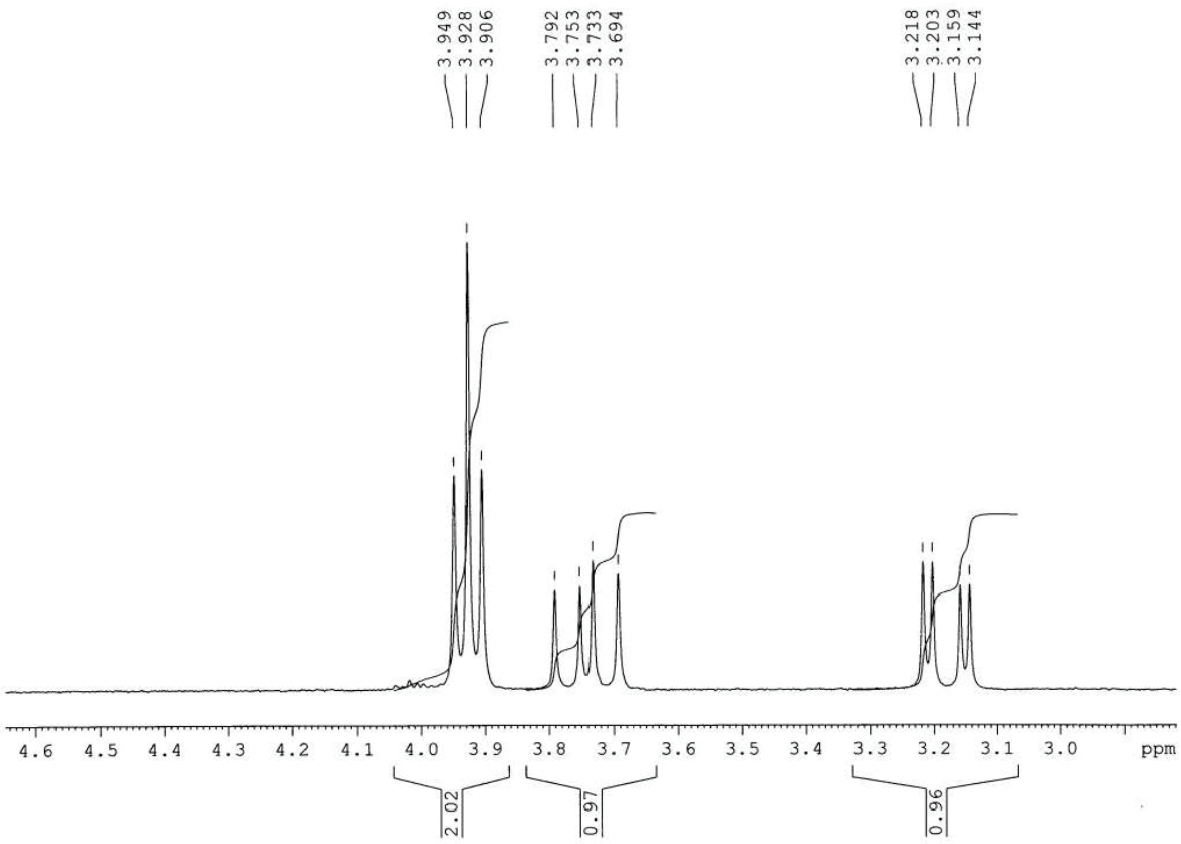

7.785
7.777
7.770
7.765
7.753
7.472
7.460
7.450
7.438
7.281
7.184
7.155
7.146
6.860
6.831
6.793
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
1.81
2.72
1.69
1.70

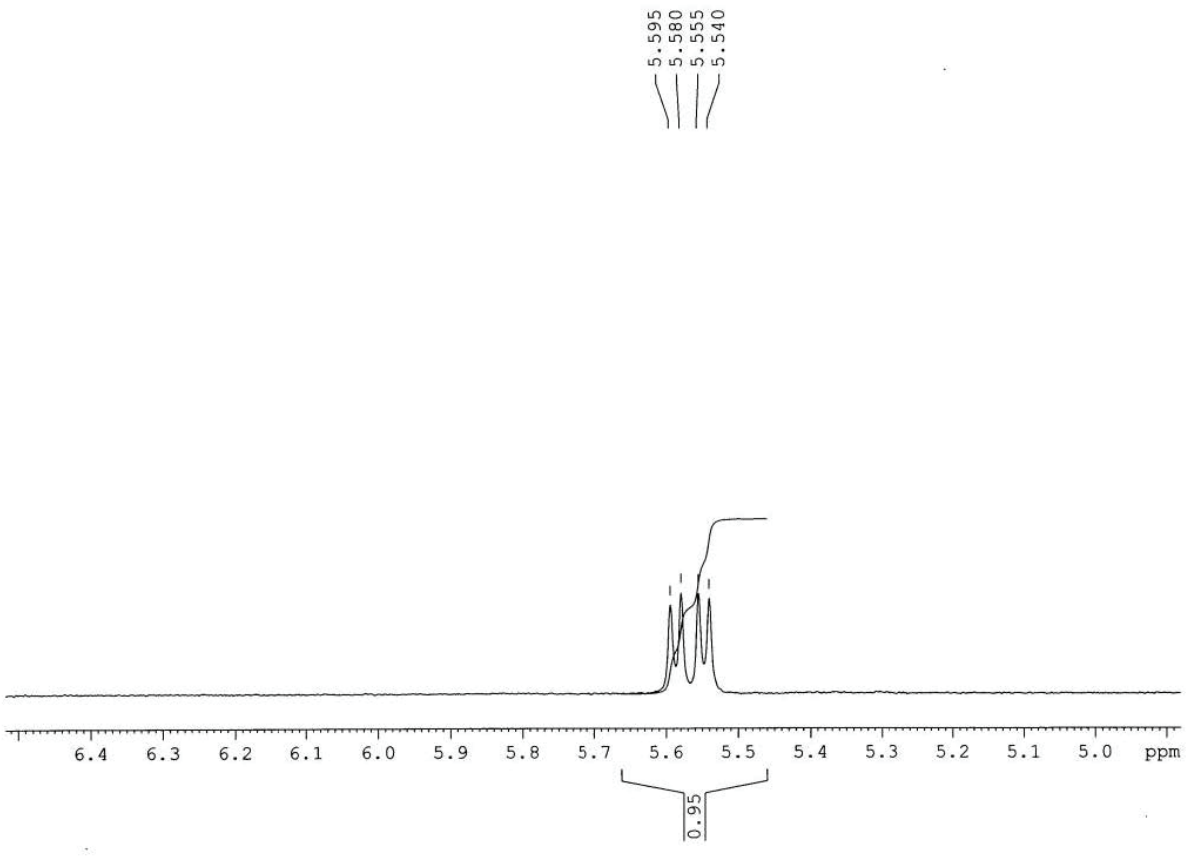

168.85
158.60
153.87
133.85
131.50
130.29
128.86
128.75
126.89
126.58
125.57
114.86
114.76
77.47
77.25
77.05
76.62
67.99
59.45
42.30
31.58
29.21
25.72
22.62
22.05
14.07
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME AC-6_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081028
Time 11.16
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 768
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 4597.6
DW 27.800 usec
DE 6.00 usec
TE 293.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

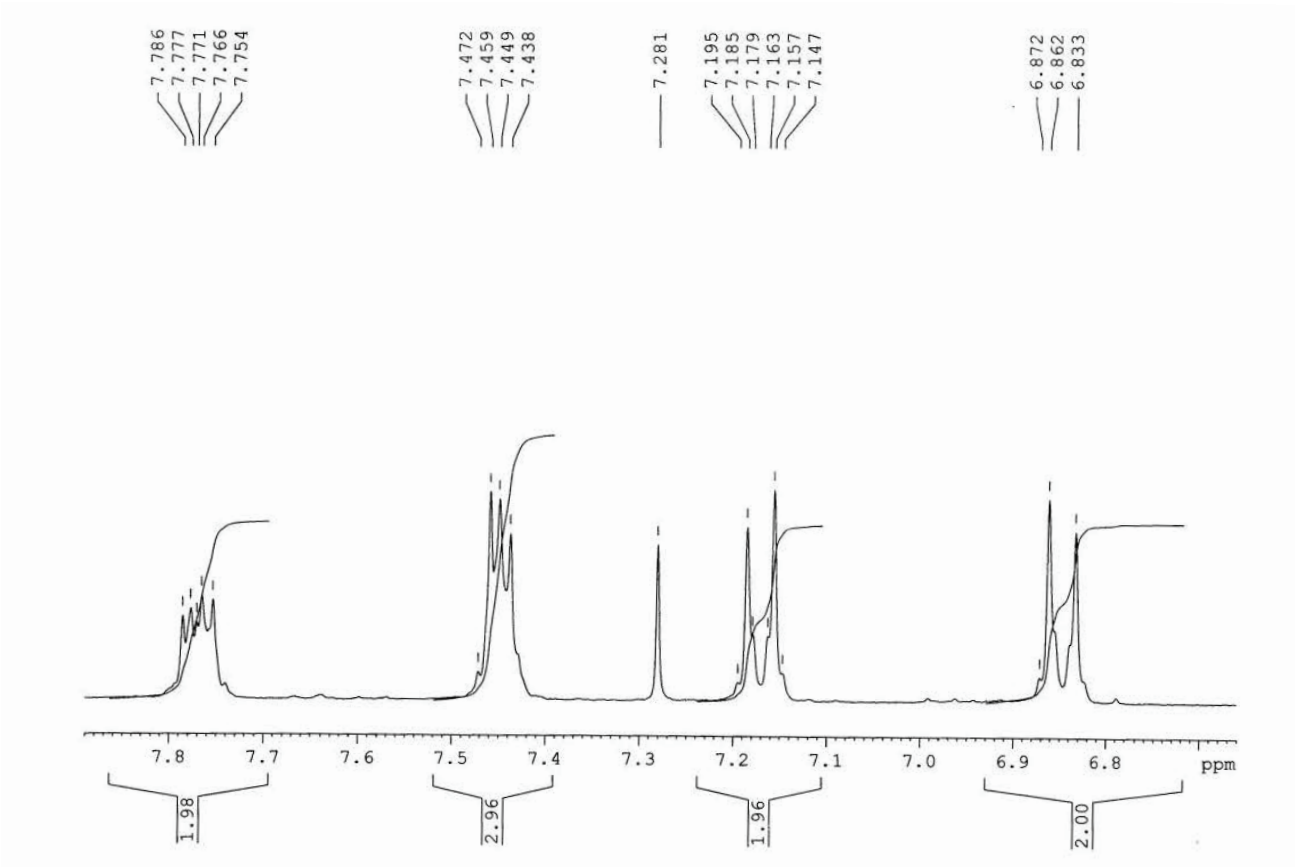

133.85
131.50
130.29
128.86
128.75
126.89
126.58
125.57
142
141
140
139
138
137
136
135
134
133
132
131
130
129
128
127
126
125
124
123
ppm

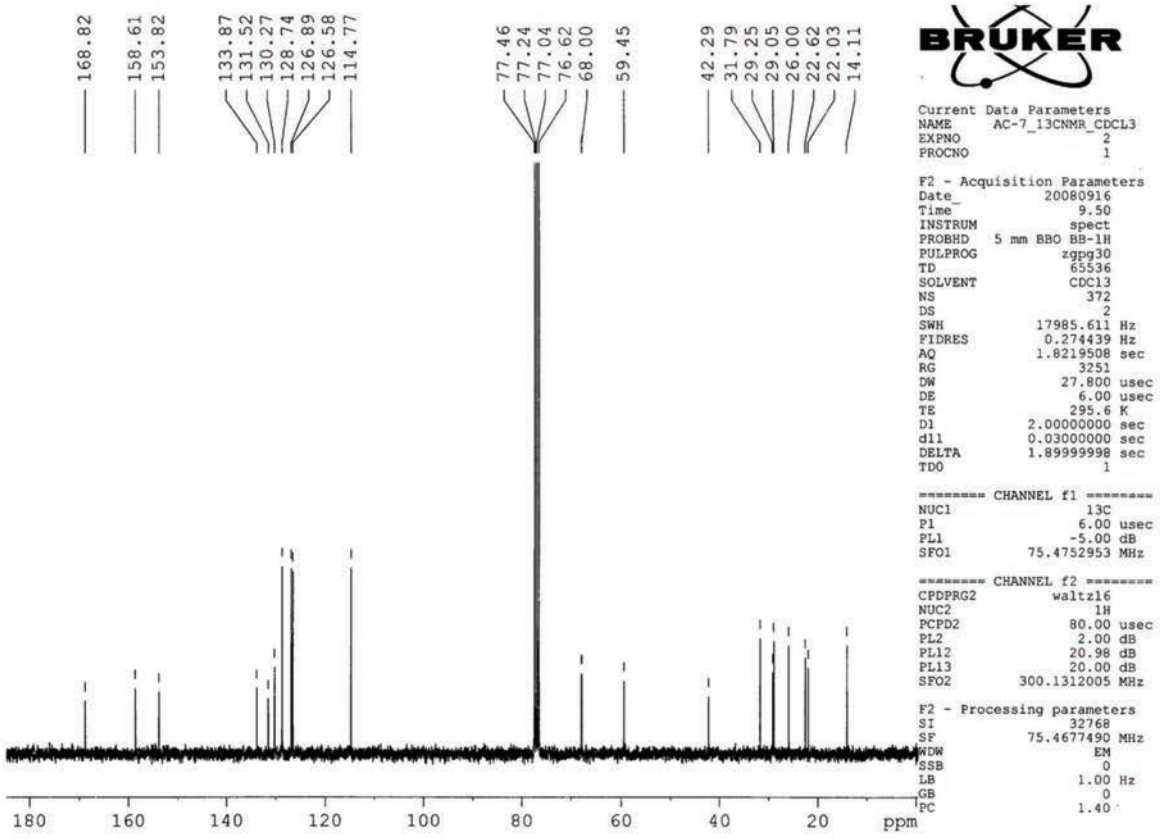

Compound 7b
7.786
7.777
7.771
7.766
7.754
7.459
7.449
7.438
7.281
7.185
7.179
7.163
7.157
6.862
6.833
5.580
5.555
5.540
3.949
3.928
3.906
3.792
3.753
3.733
3.694
3.218
3.203
3.159
3.144
2.429
1.790
1.768
1.742
1.445
1.434
1.416
1.397
1.357
1.315
0.928
0.922
0.907
0.884
0.024
BRUKER
Current Data Parameters
NAME AC-7_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080916
Time 9.52
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 287.4
DW 81.000 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Compound 7b
ppm
1.98
2.96
1.96
2.00
0.95
2.02
0.97
0.96
2.91
2.17
8.24
3.08


1.812
1.790
1.768
1.742
1.720
1.468
1.461
1.445
1.434
1.416
1.397
1.357
1.315
0.928
0.922
0.907
0.884
ppm
2.17
8.24
3.08


3.949
3.928
3.906
3.792
3.753
3.733
3.694
3.218
3.203
3.159
3.144
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
2.02
0.97
0.96

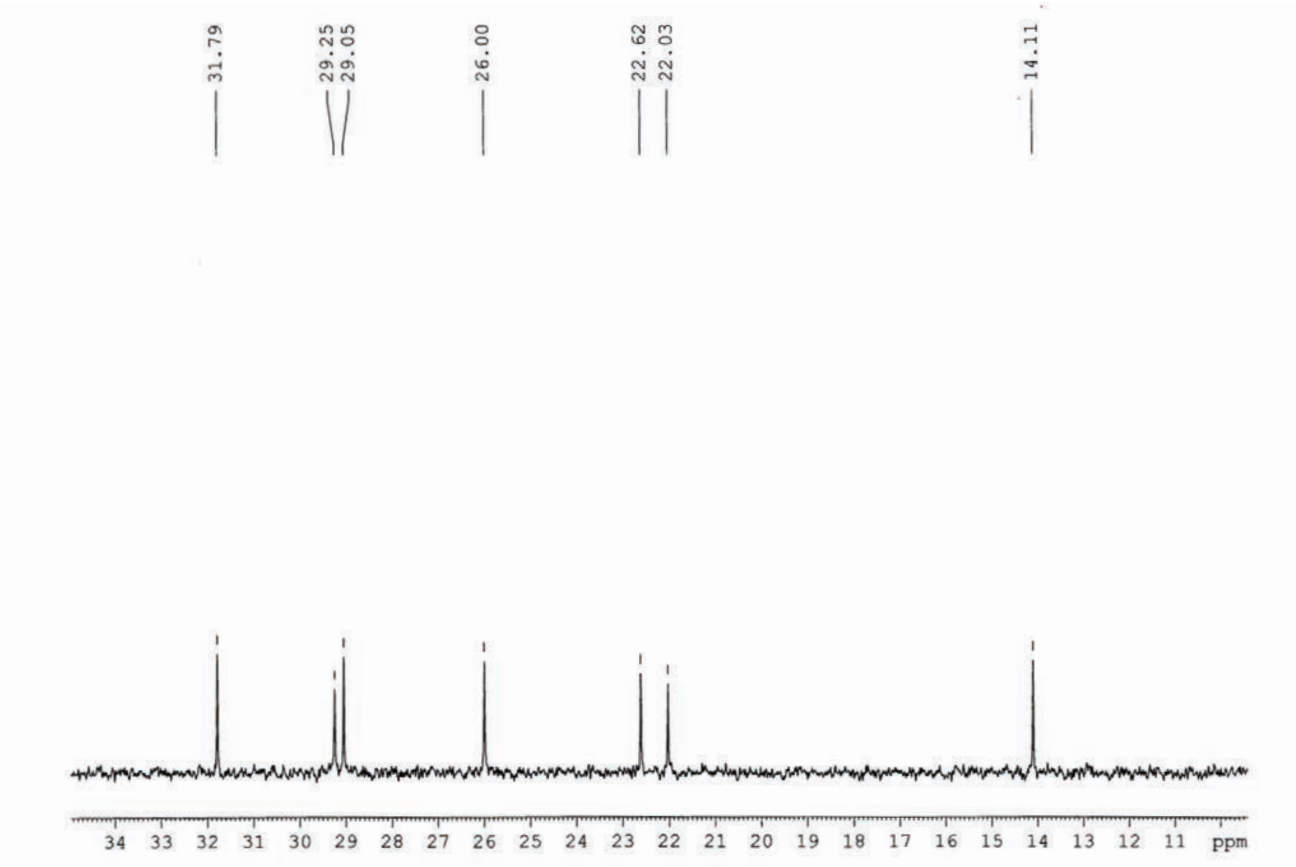

5.595
5.580
5.555
5.540
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 ppm
0.95

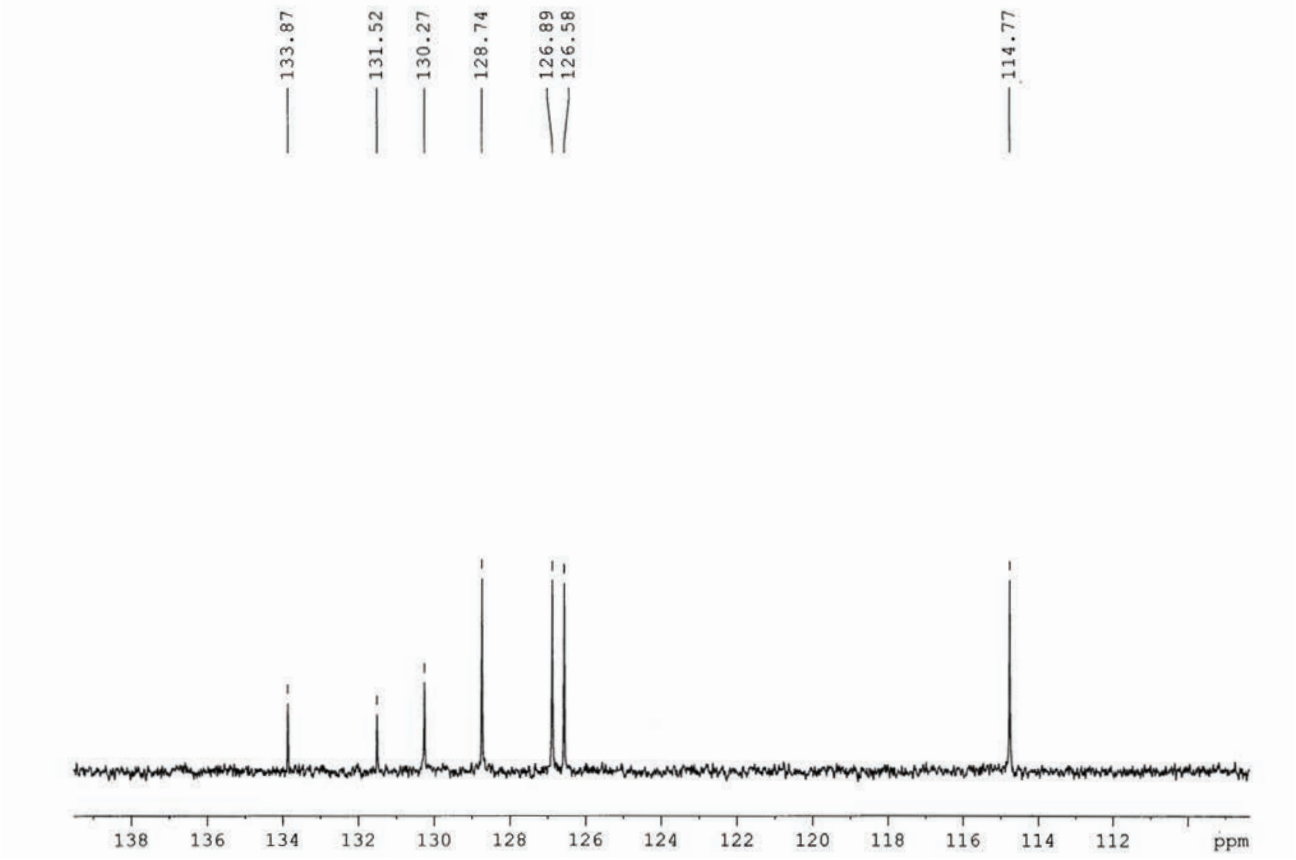


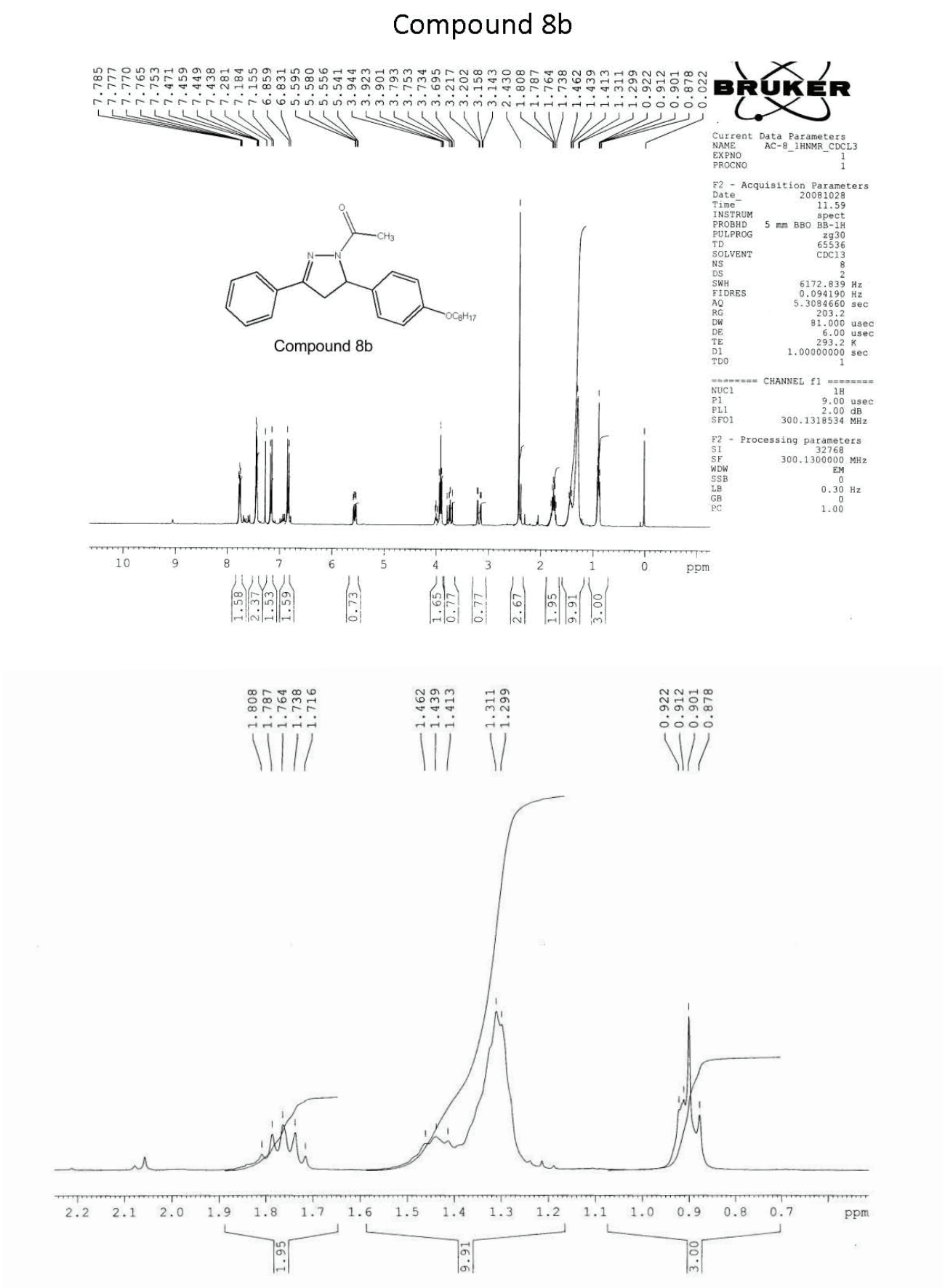


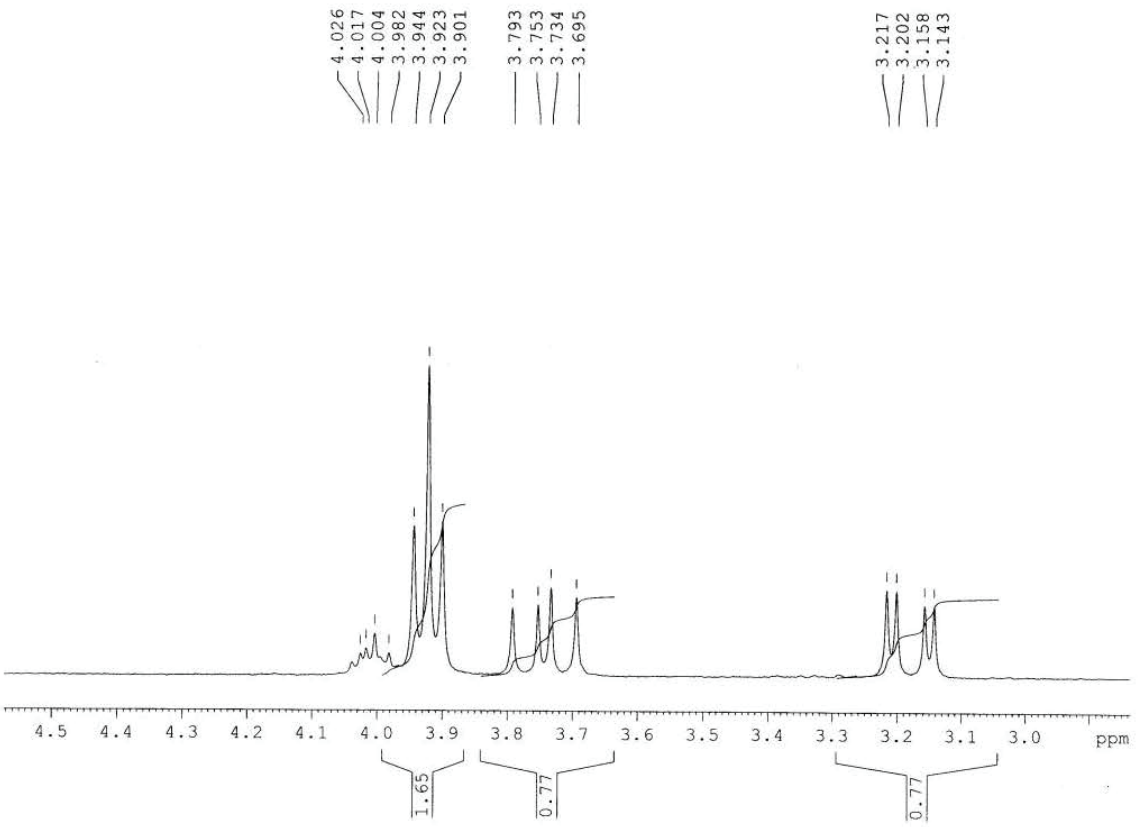
BRUKER

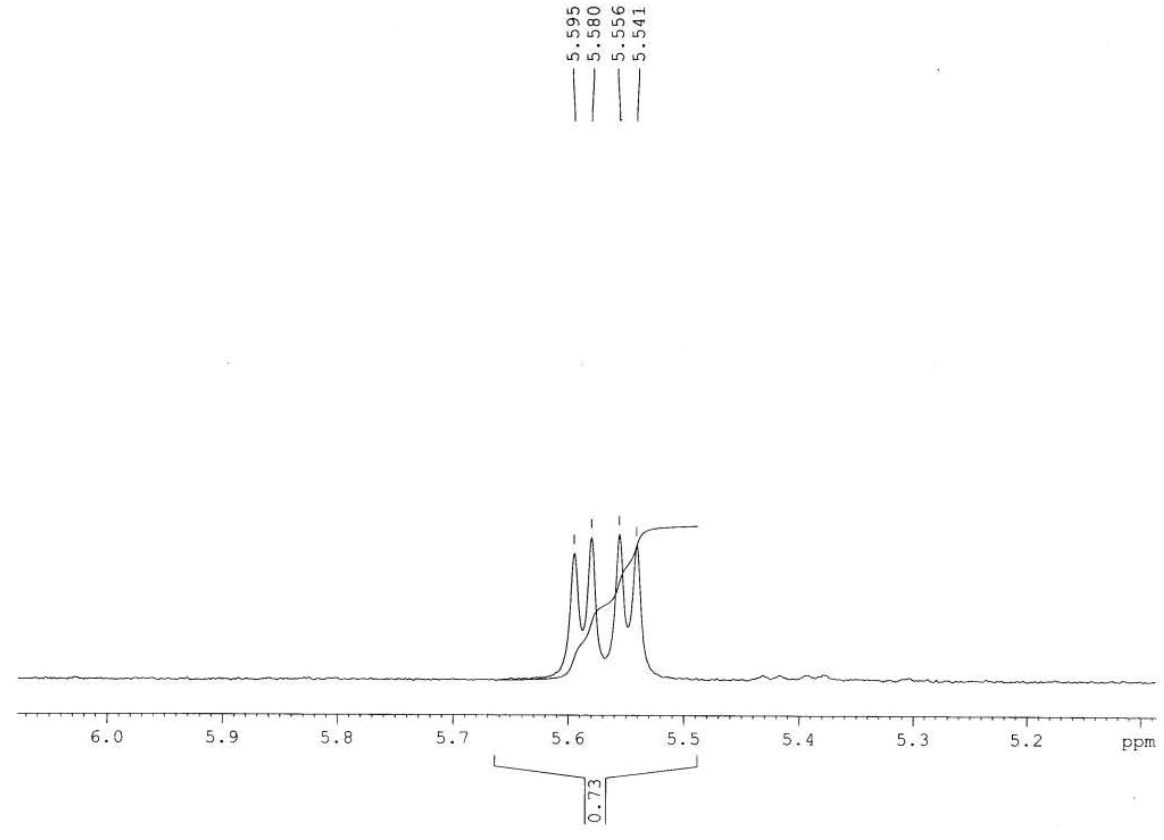
```
Current Data Parameters
NAME      AC-7_13CNMR_CDCL3
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20080916
Time                  9.50
INSTRUM              spect
PROBHD   5 mm BBO BB-1H
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     372
DS                       2
SWH           17985.611 Hz
FIDRES         0.274439 Hz
AQ             1.8219508 sec
RG                    3251
DW                27.800 usec
DE                 6.00 usec
TE                295.6 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  6.00 usec
PL1                -5.00 dB
SFO1          75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 2.00 dB
PL12               20.98 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
```

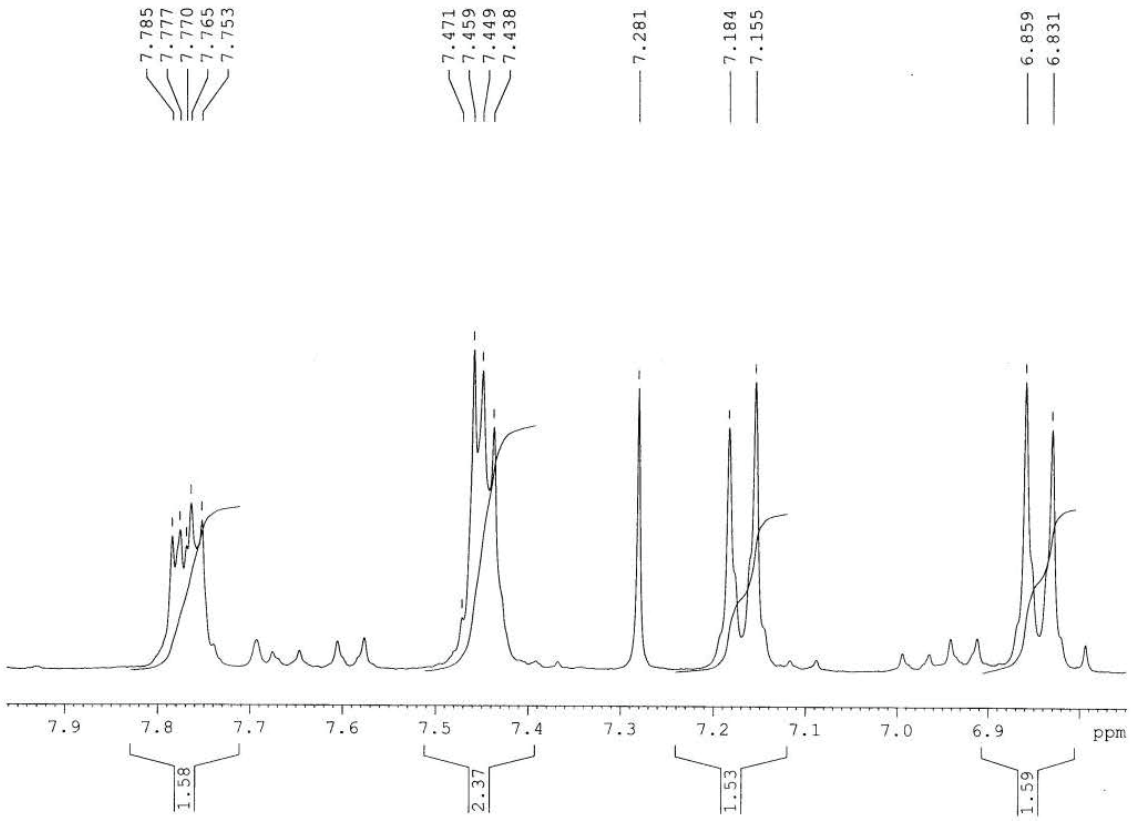

31.79
29.25
29.05
26.00
22.62
22.03
14.11
34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 ppm

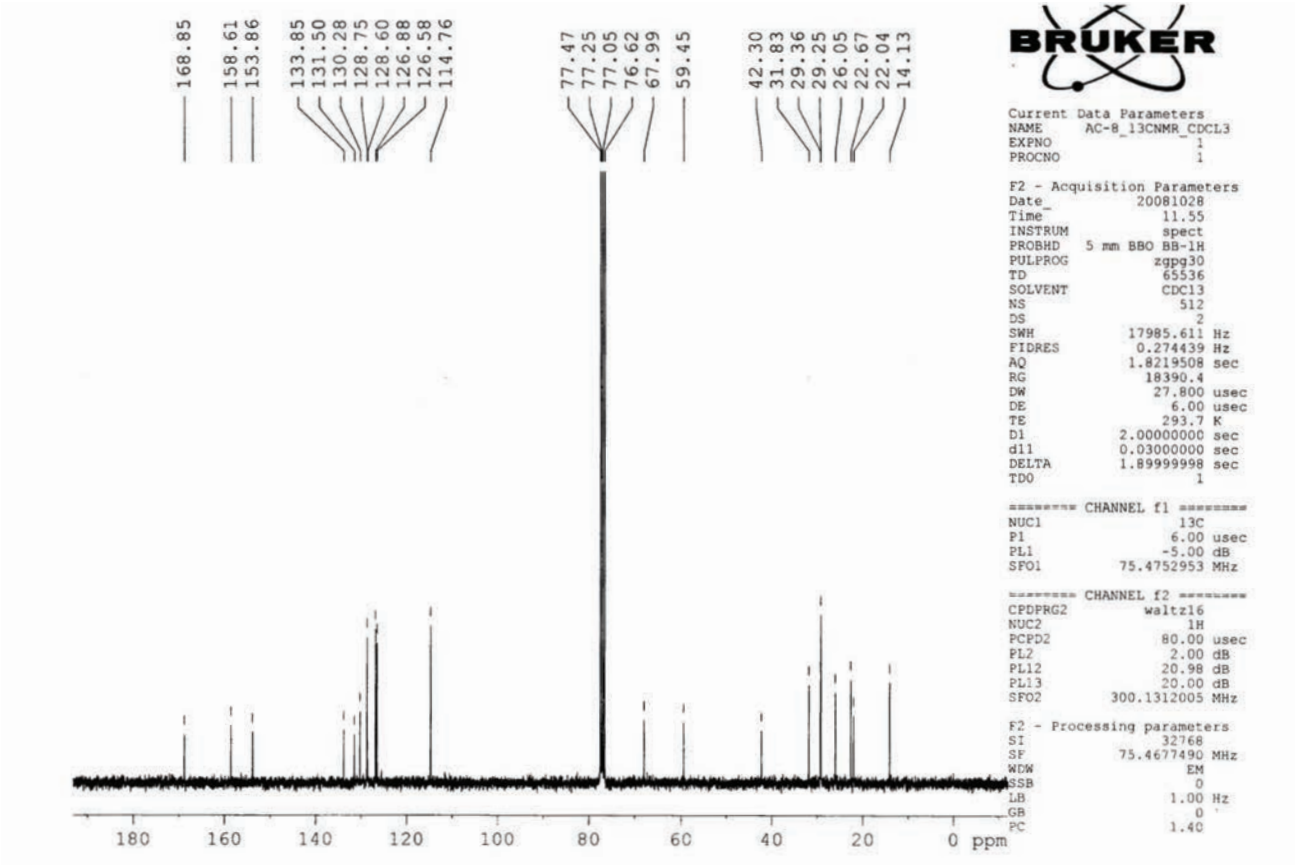

133.87
131.52
130.27
128.74
126.89
126.58
114.77
138 136 134 132 130 128 126 124 122 120 118 116 114 112 ppm

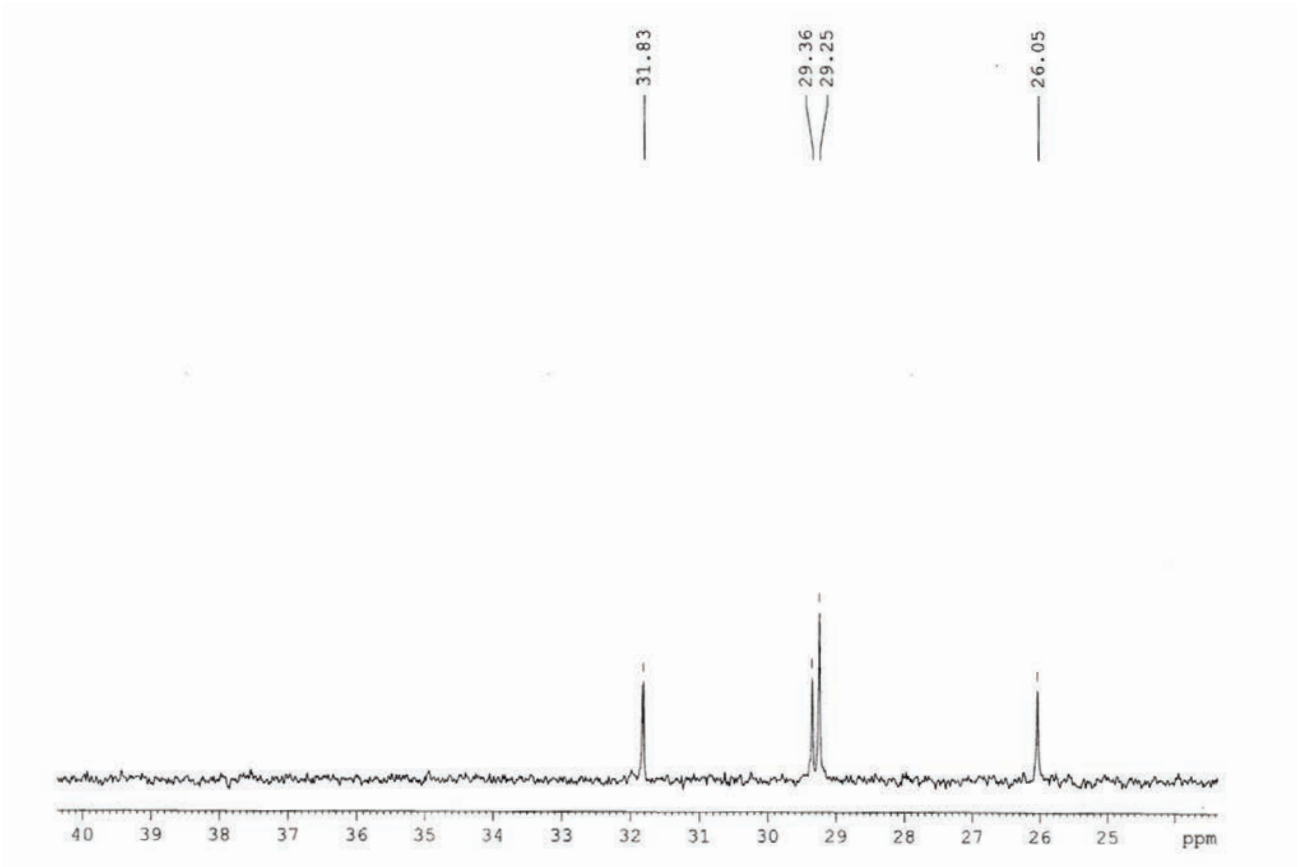

Compound 8b
7.785
7.777
7.770
7.765
7.753
7.471
7.459
7.449
7.438
7.281
7.184
7.155
6.859
6.831
5.595
5.580
5.556
5.541
3.944
3.923
3.901
3.793
3.753
3.734
3.695
3.217
3.202
3.158
3.143
2.430
1.808
1.787
1.764
1.738
1.462
1.439
1.413
1.311
1.299
0.922
0.912
0.901
0.878
0.022
BRUKER
Current Data Parameters
NAME AC-8_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081028
Time 11.59
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 203.2
DW 81.000 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Compound 8b
ppm
1.58
2.37
1.53
1.59
0.73
1.65
0.77
0.77
2.67
1.95
9.91
3.00
1.808
1.787
1.764
1.738
1.716
1.462
1.439
1.413
1.311
1.299
0.922
0.912
0.901
0.878
ppm
1.95
9.91
3.00

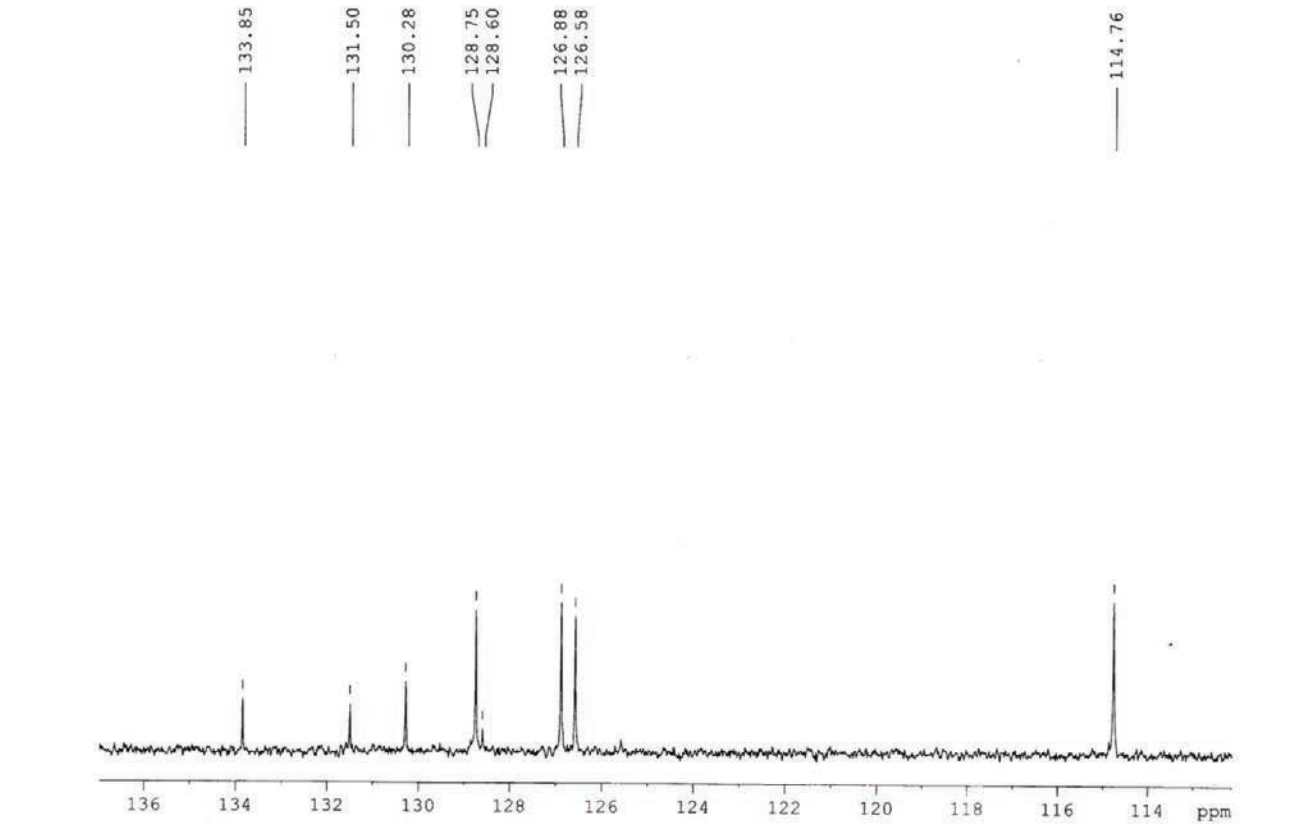

4.026
4.017
4.004
3.982
3.944
3.923
3.901
3.793
3.753
3.734
3.695
3.217
3.202
3.158
3.143
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm
1.65
0.77
0.77


5.595
5.580
5.556
5.541
6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 ppm
0.73

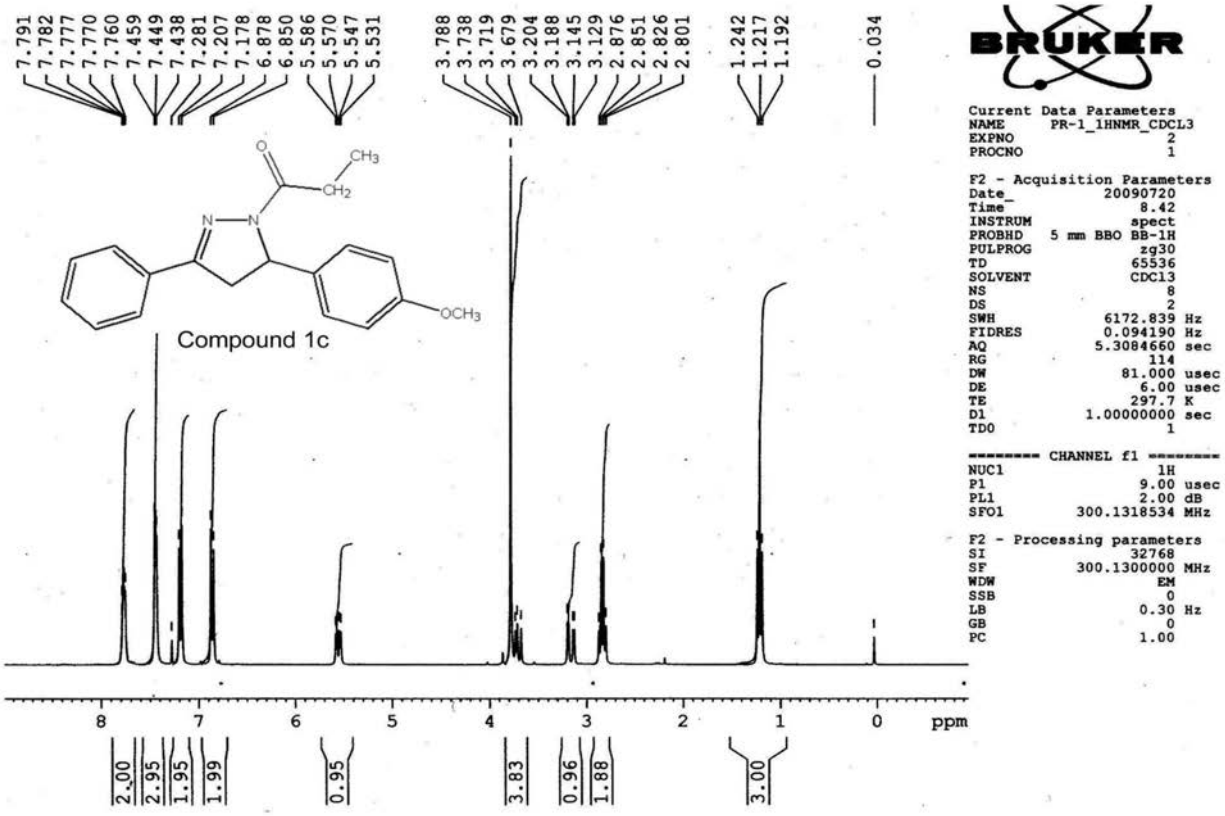

7.785
7.777
7.770
7.765
7.753
7.471
7.459
7.449
7.438
7.281
7.184
7.155
6.859
6.831
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
1.58
2.37
1.53
1.59

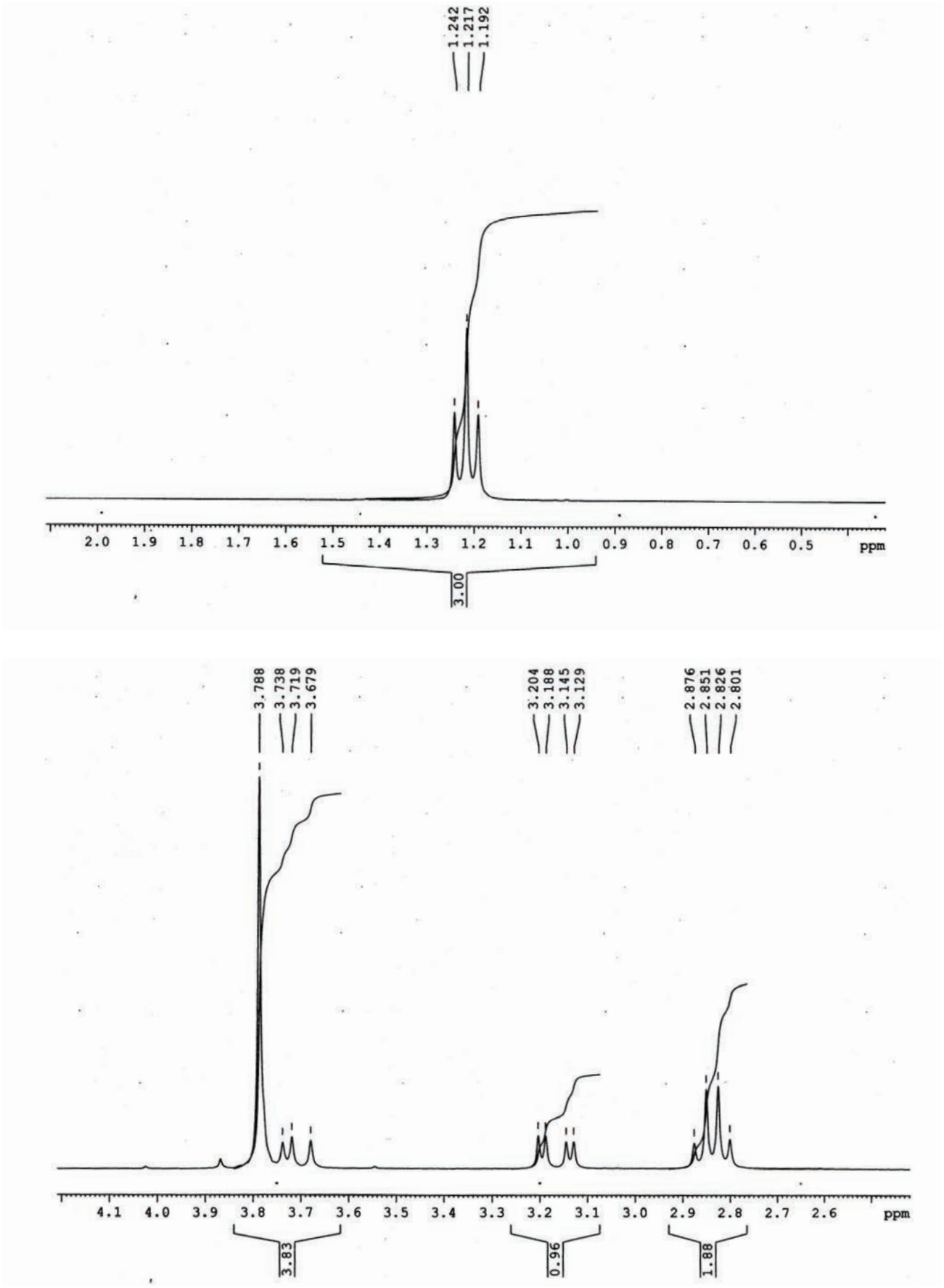

168.85
158.61
153.86
133.85
131.50
130.28
128.75
128.60
126.88
126.58
114.76
77.47
77.25
77.05
76.62
67.99
59.45
42.30
31.83
29.36
29.25
26.05
22.67
22.04
14.13
180
160
140
120
100
80
60
40
20
0 ppm
BRUKER
Current Data Parameters
NAME AC-8_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081028
Time 11.55
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 18390.4
DW 27.800 usec
DE 6.00 usec
TE 293.7 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

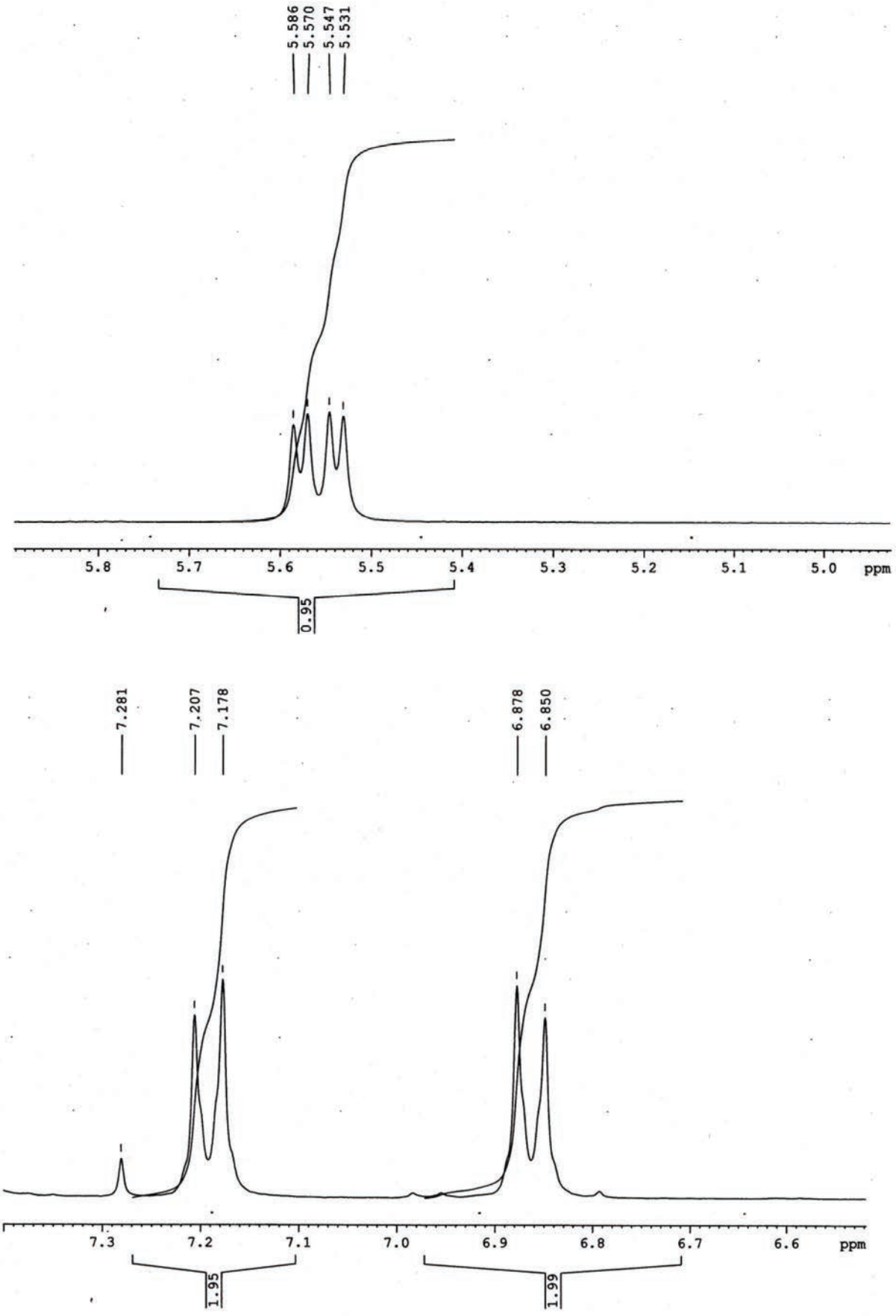

31.83
29.36
29.25
26.05
40 39 38 37 36 35 34 33 32 31 30 29 28 27 26 25 ppm

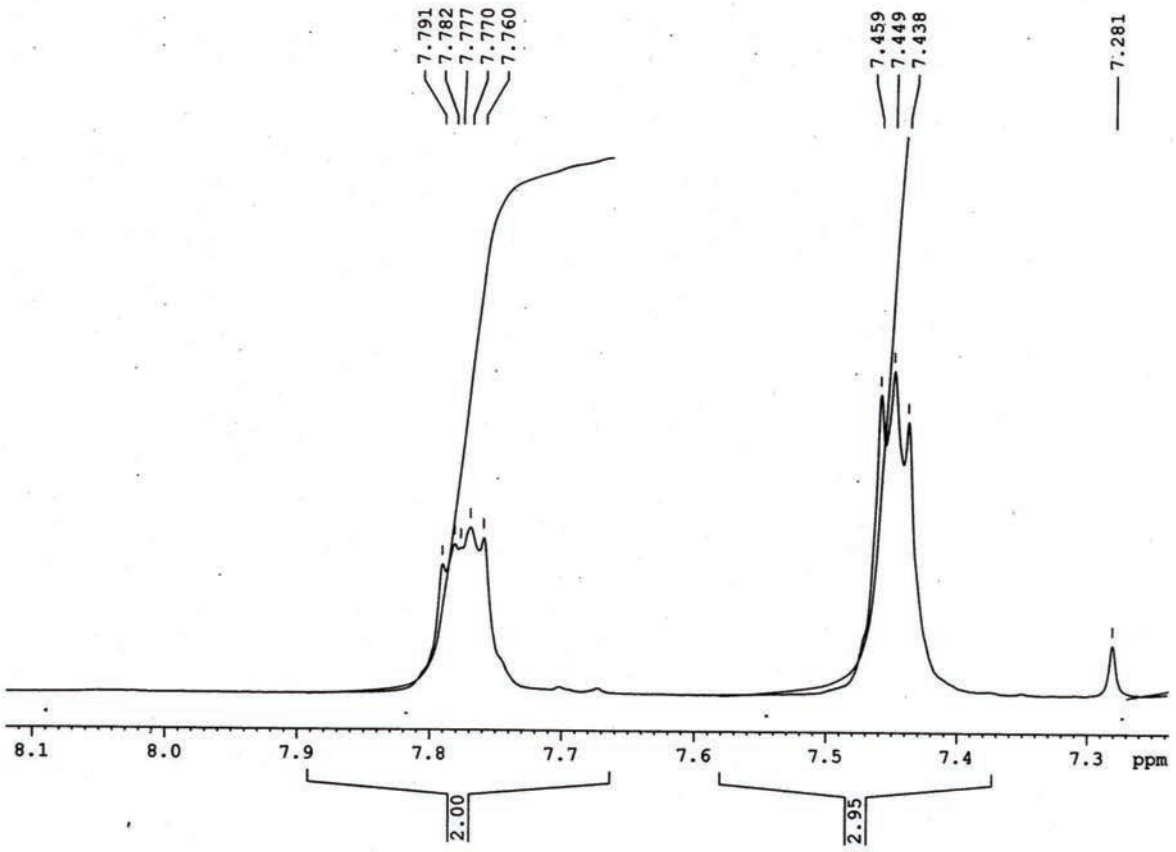

133.85
131.50
130.28
128.75
128.60
126.88
126.58
114.76
136 134 132 130 128 126 124 122 120 118 116 114 ppm

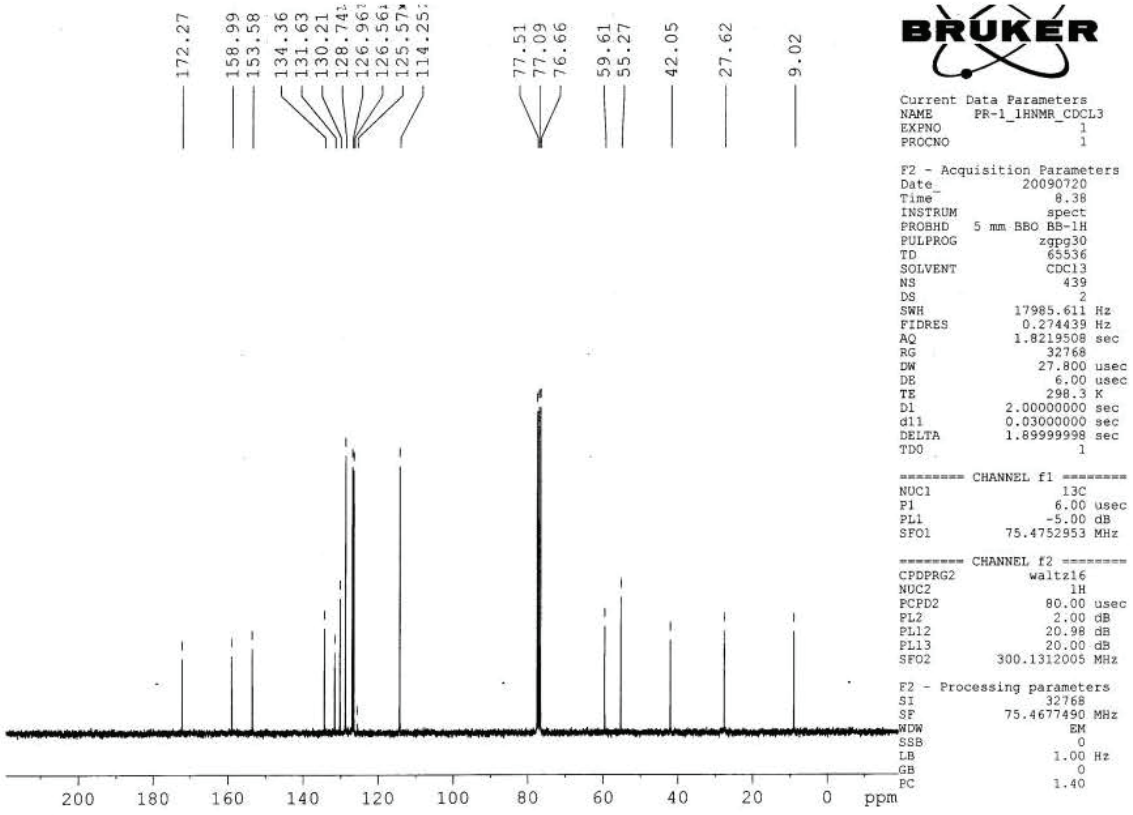
Compound 1c


7.791
7.782
7.777
7.770
7.760
7.459
7.449
7.438
7.281
7.207
7.178
6.878
6.850
5.586
5.570
5.547
5.531
3.788
3.738
3.719
3.679
3.204
3.188
3.145
3.129
2.876
2.851
2.826
2.801
1.242
1.217
1.192
0.034
Compound 1c
8
7
6
5
4
3
2
1
0
ppm
2.00
2.95
1.95
1.99
0.95
3.83
0.96
1.88
3.00
BRUKER
Current Data Parameters
NAME PR-1_1HNMR_CDCL3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090720
Time 8.42
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


1.242
1.217
1.192
2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 ppm
3.00
3.788
3.738
3.719
3.679
3.204
3.188
3.145
3.129
2.876
2.851
2.826
2.801
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 ppm
3.83
0.96
1.88

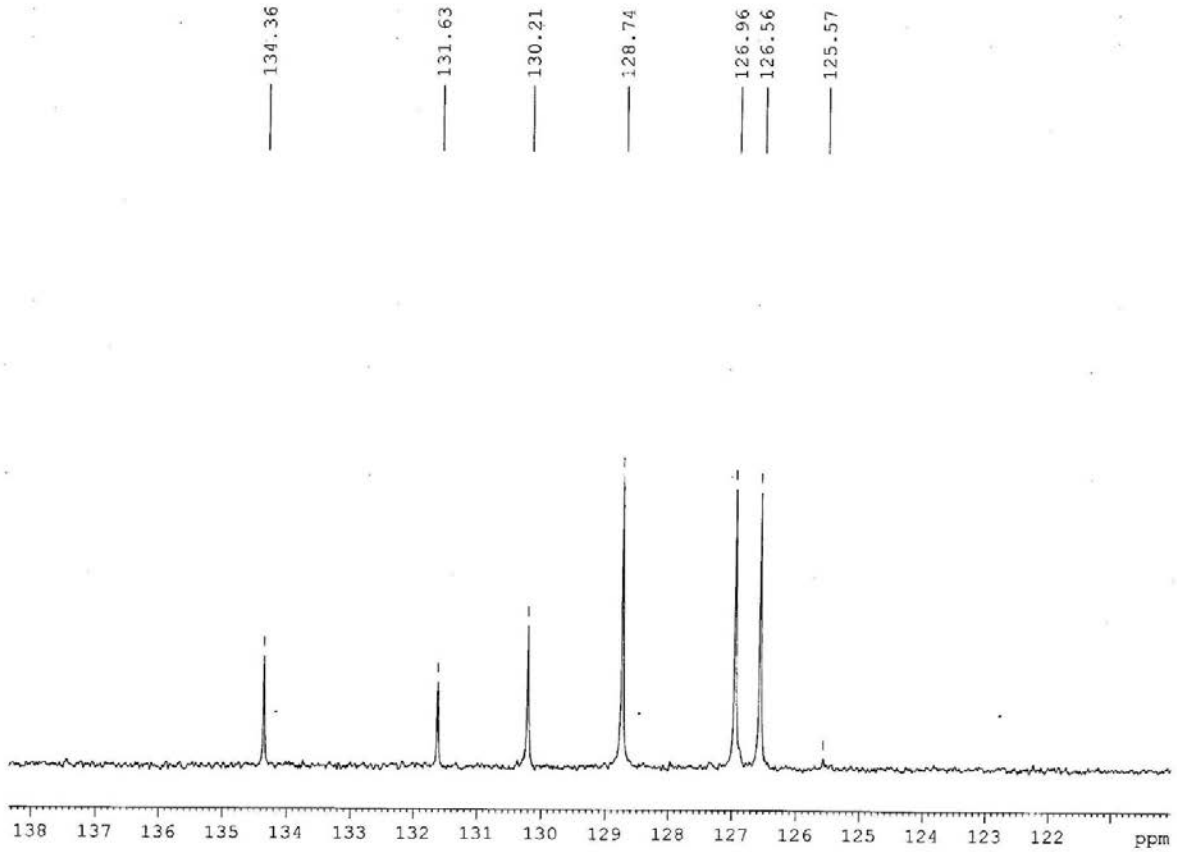

5.586
5.570
5.547
5.531
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
ppm
0.95
7.281
7.207
7.178
6.878
6.850
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm
1.95
1.99



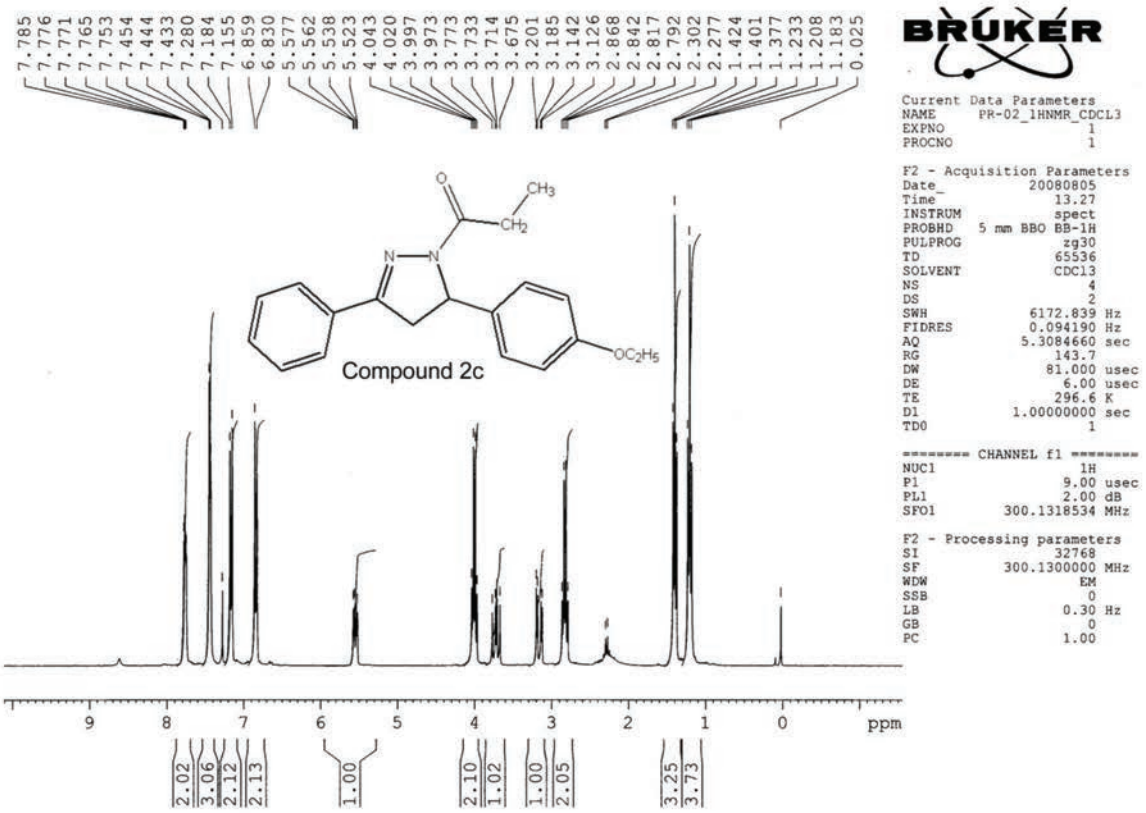


BRUKER

```
Current Data Parameters
NAME      PR-1_1HNMR_CDCL3
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20090720
Time                  8.38
INSTRUM              spect
PROBHD   5 mm BBO BB-1H
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   439
DS                     2
SWH           17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8219508 sec
RG                 32768
DW               27.800 usec
DE                6.00 usec
TE                298.3 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                 6.00 usec
PL1               -5.00 dB
SFO1         75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                2.00 dB
PL12              20.98 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
```

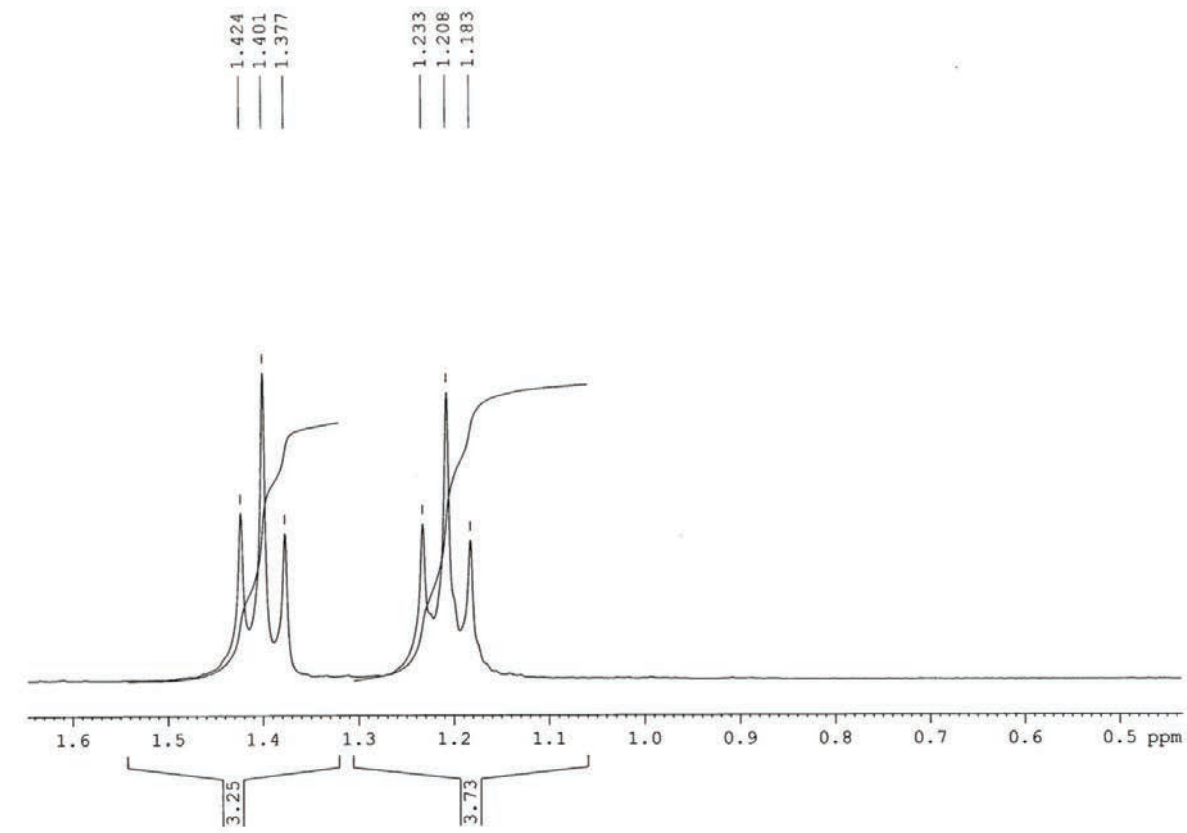


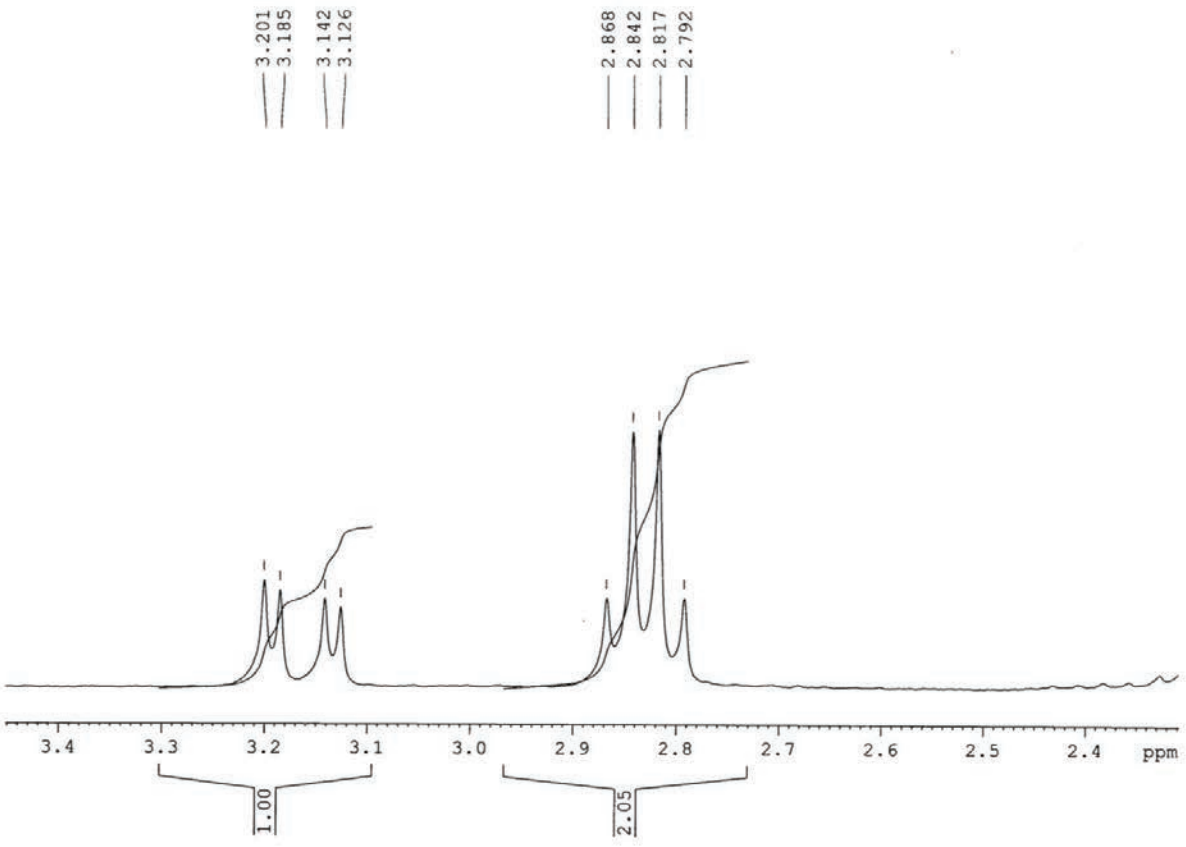
Compound 2c

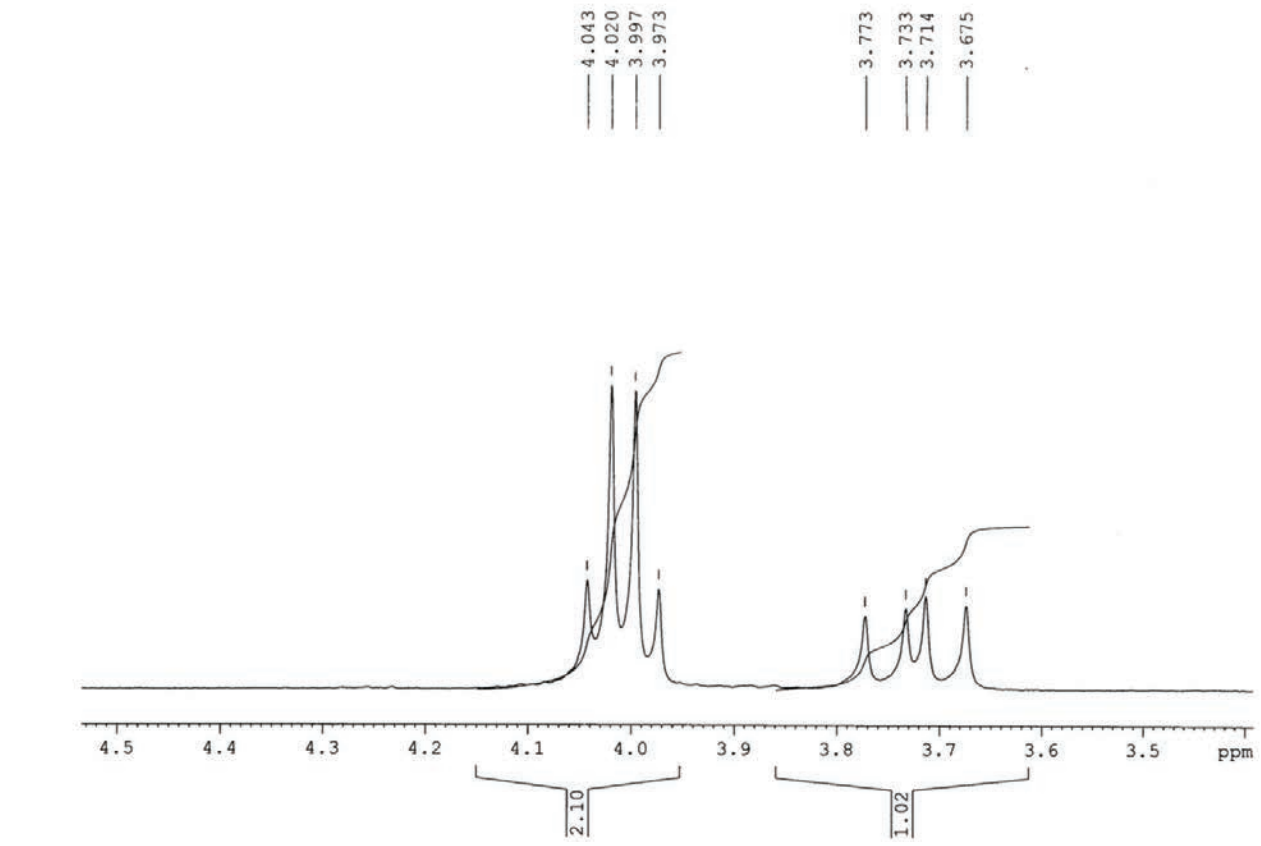


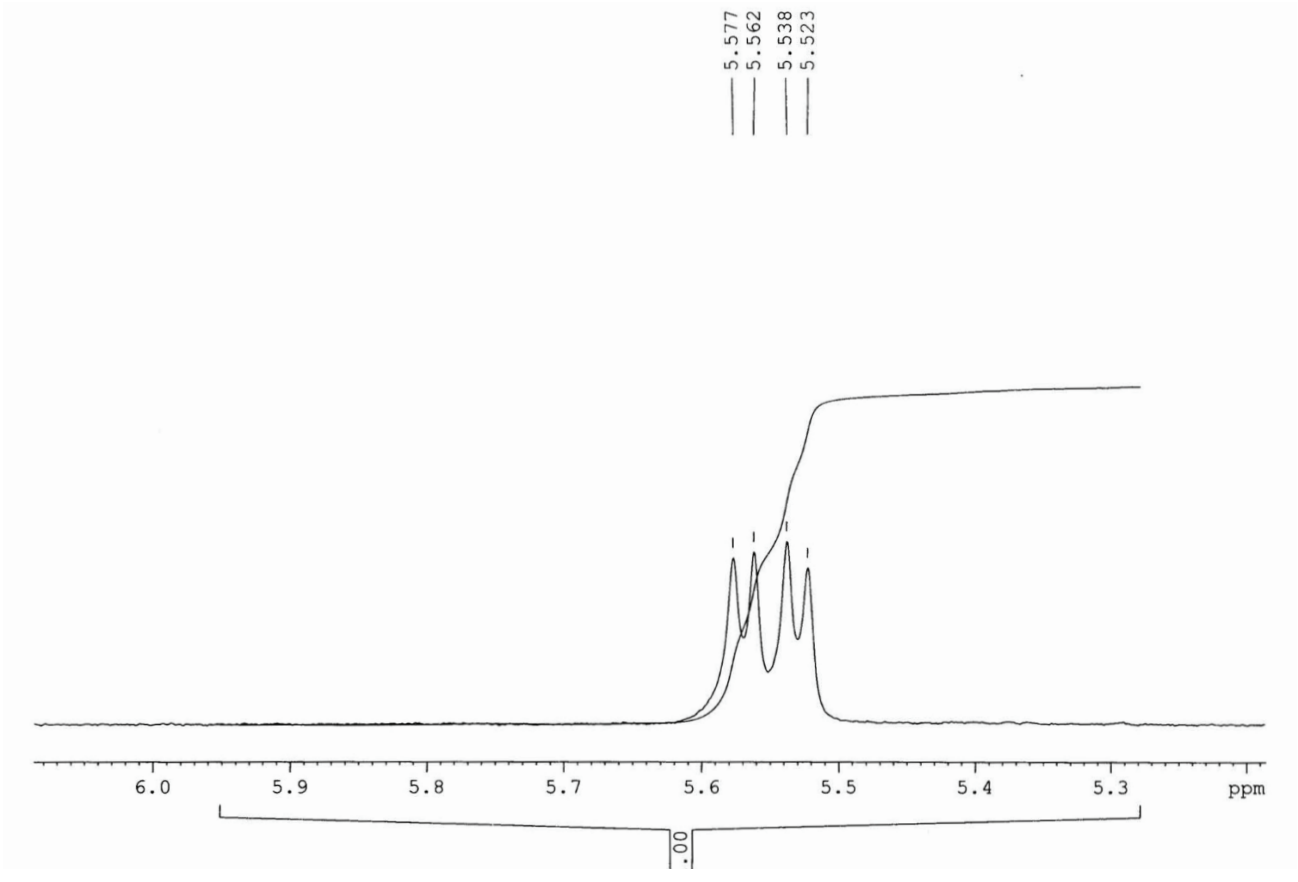
BRUKER

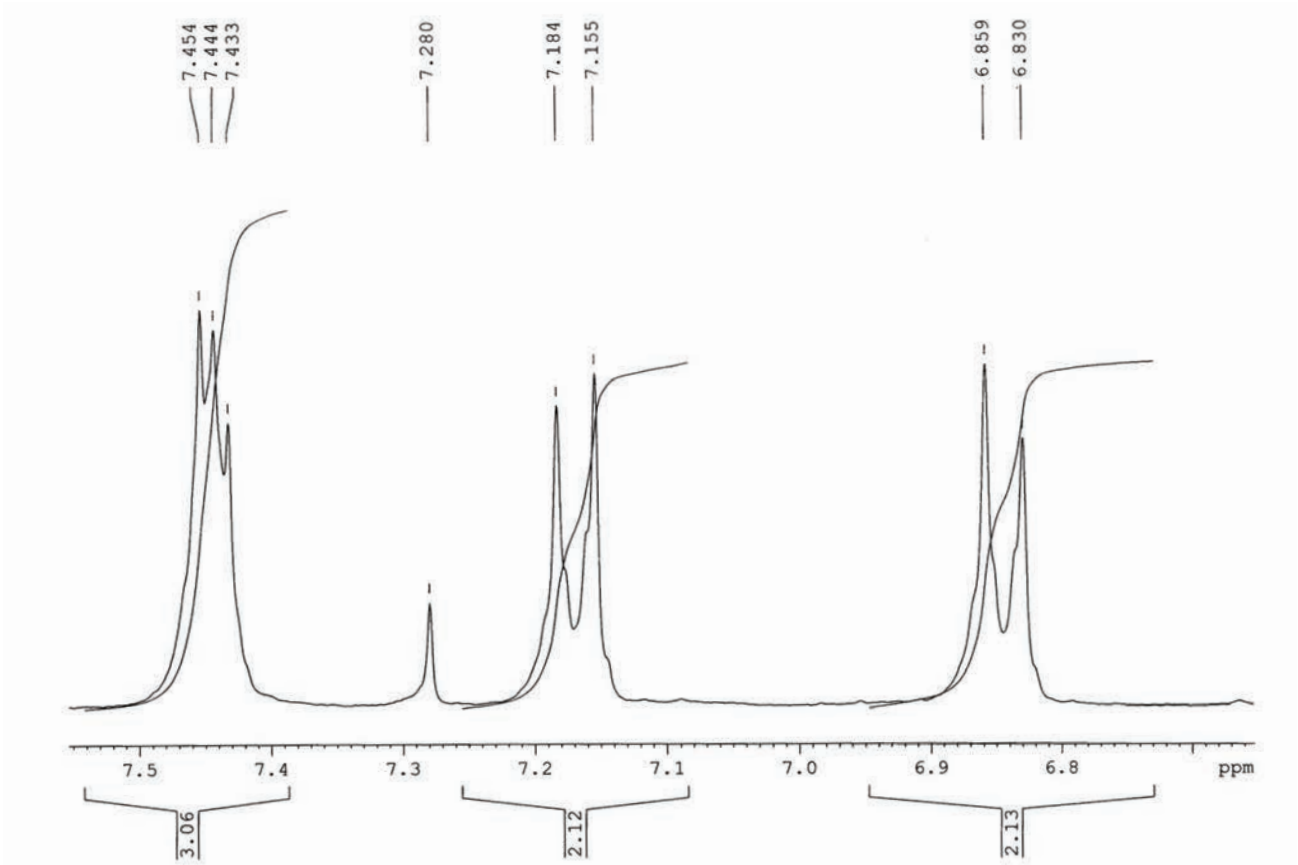
```
Current Data Parameters
NAME      PR-02_1HNMR_CDCL3
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20080805
Time                  13.27
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        4
DS                        2
SWH                6172.839 Hz
FIDRES            0.094190 Hz
AQ                5.3084660 sec
RG                    143.7
DW                   81.000 usec
DE                    6.00 usec
TE                   296.6 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                    9.00 usec
PL1                   2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF          300.1300000 MHz
WDW                      EM
SSB                       0
LB                    0.30 Hz
GB                        0
PC                    1.00
```

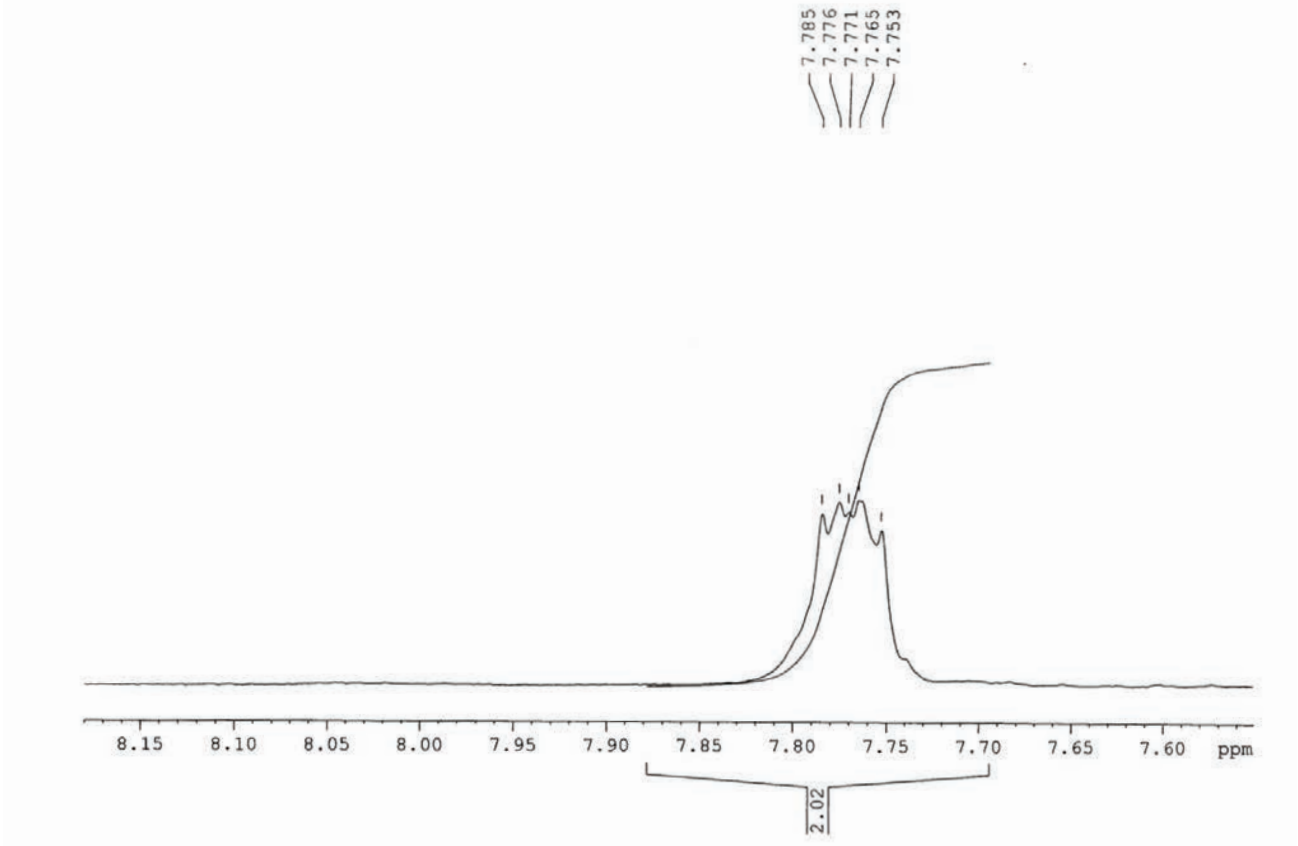

1.424
1.401
1.377
1.233
1.208
1.183
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5 ppm
3.25
3.73

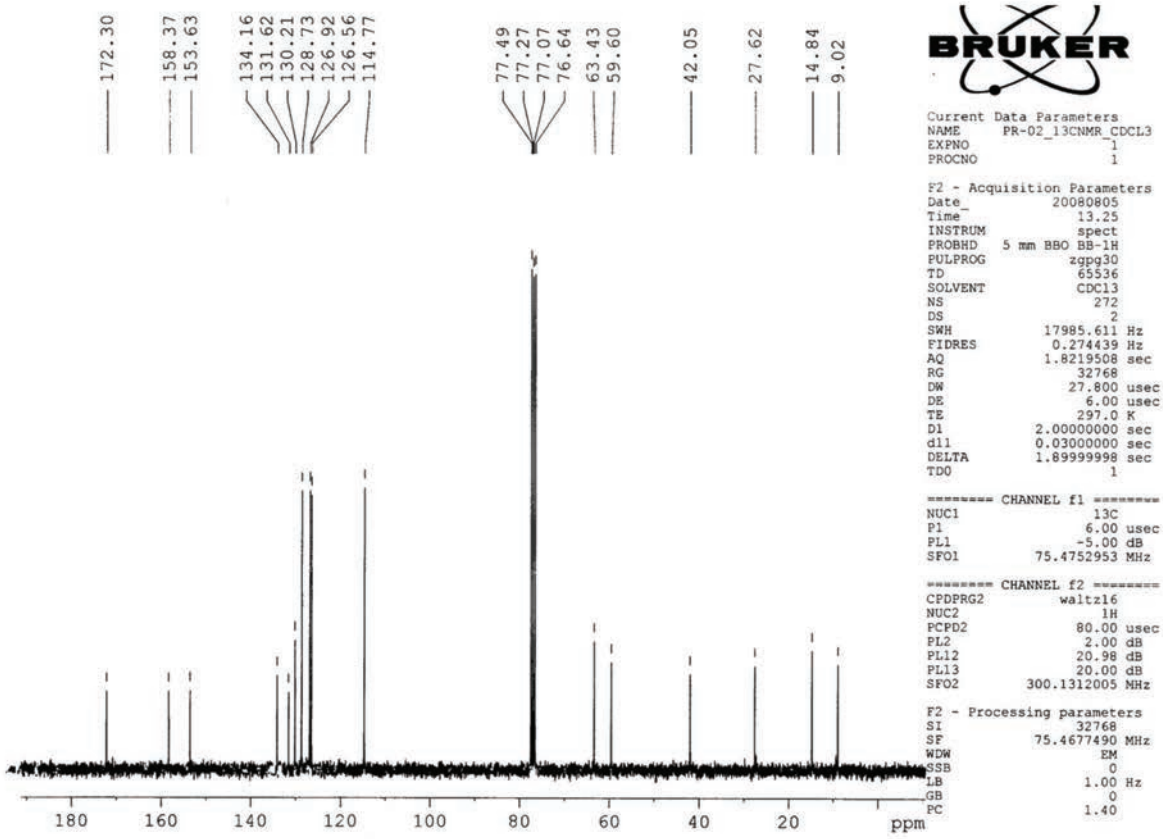

3.201
3.185
3.142
3.126
2.868
2.842
2.817
2.792
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
ppm
1.00
2.05

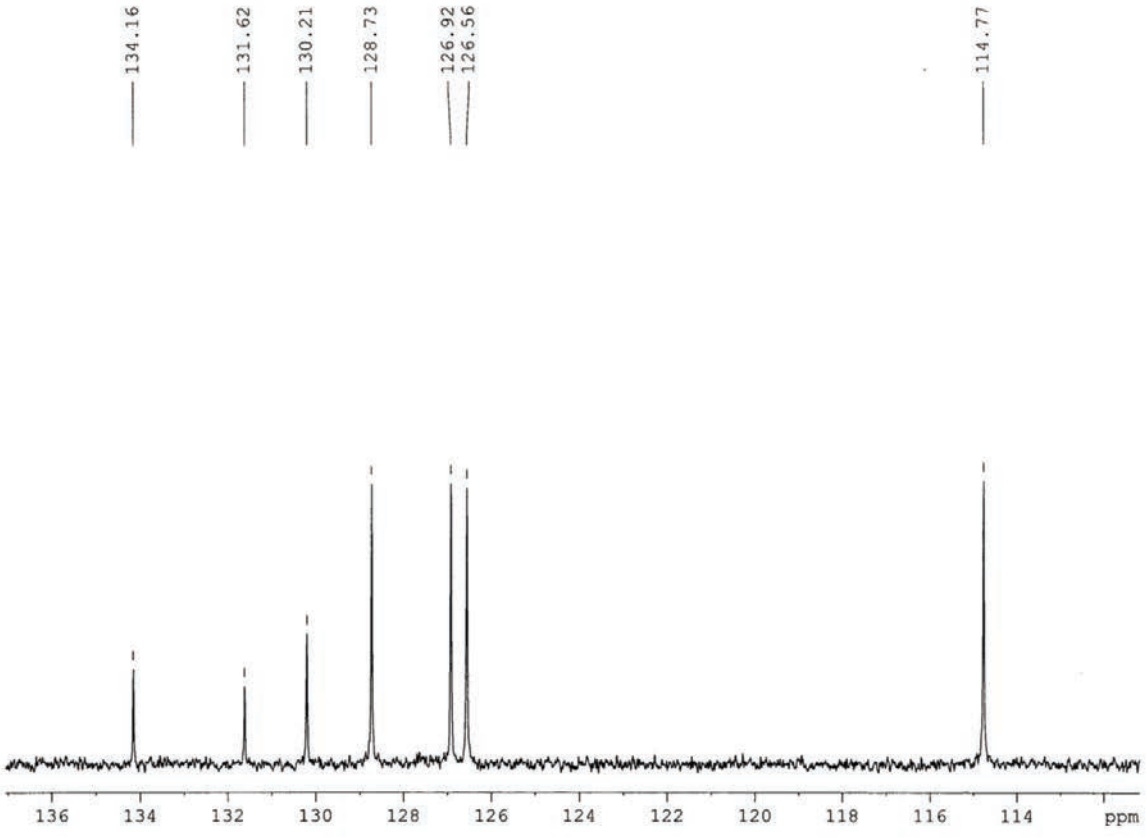

4.043
4.020
3.997
3.973
3.773
3.733
3.714
3.675
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
ppm
2.10
1.02

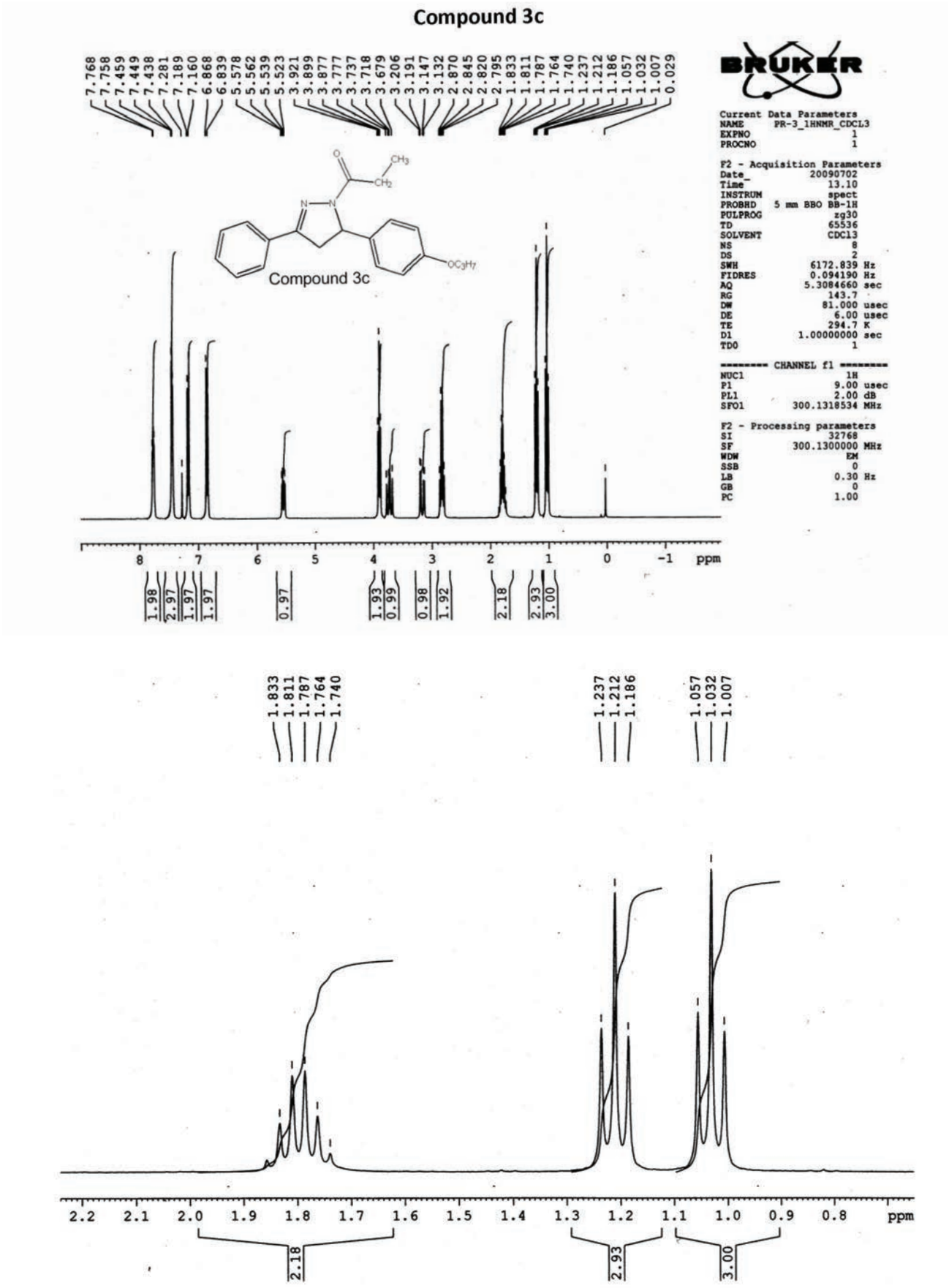

5.577
5.562
5.538
5.523
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
ppm
.00


7.454
7.444
7.433
7.280
7.184
7.155
6.859
6.830
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ppm
3.06
2.12
2.13

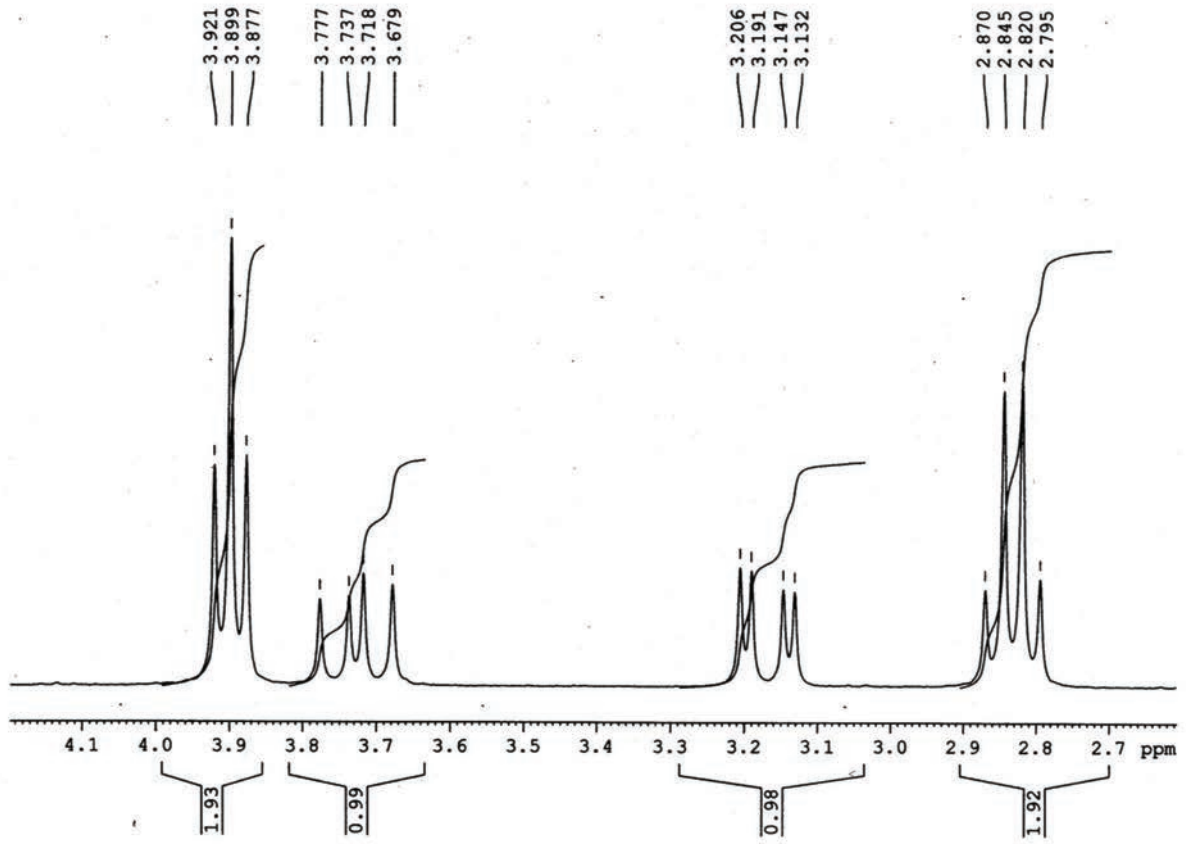

7.785
7.776
7.771
7.765
7.753
8.15
8.10
8.05
8.00
7.95
7.90
7.85
7.80
7.75
7.70
7.65
7.60
ppm
2.02

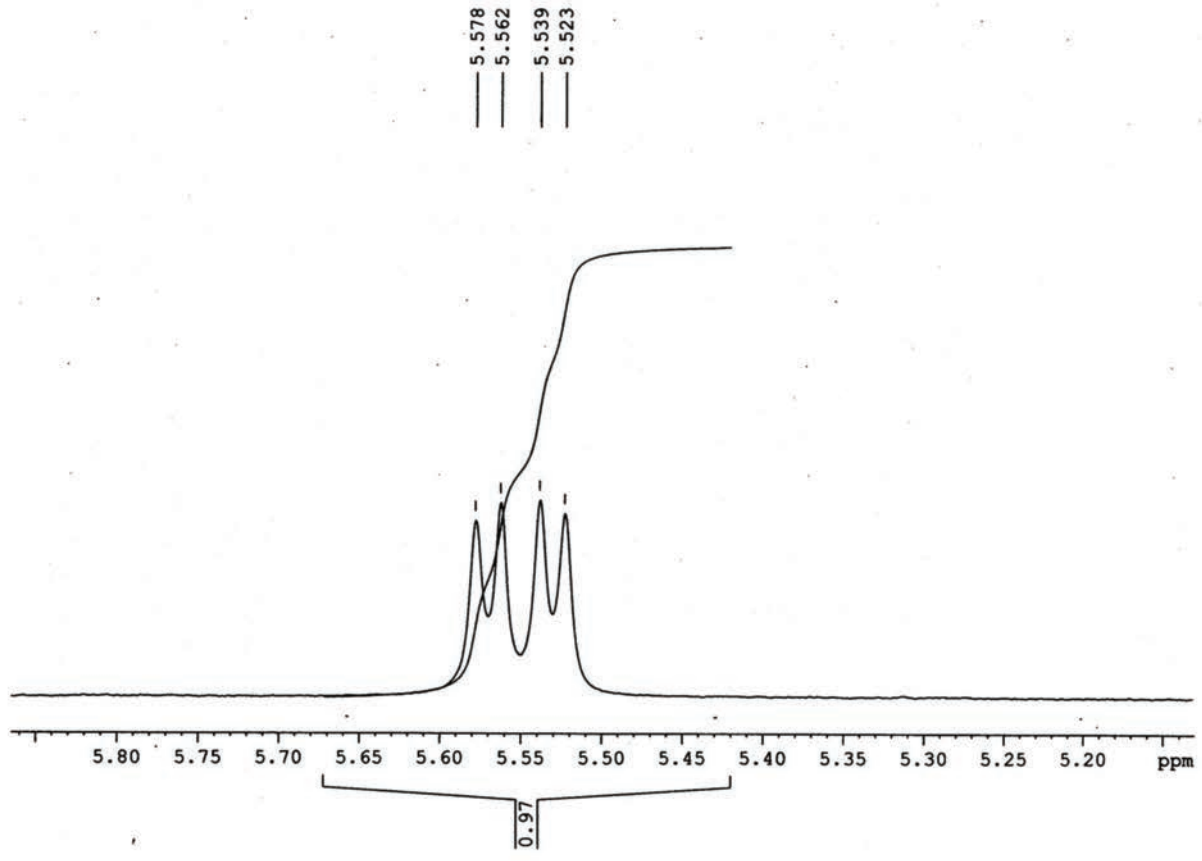

172.30
158.37
153.63
134.16
131.62
130.21
128.73
126.92
126.56
114.77
77.49
77.27
77.07
76.64
63.43
59.60
42.05
27.62
14.84
9.02
BRUKER
Current Data Parameters
NAME PR-02_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080805
Time 13.25
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 272
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 297.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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
180
160
140
120
100
80
60
40
20
ppm

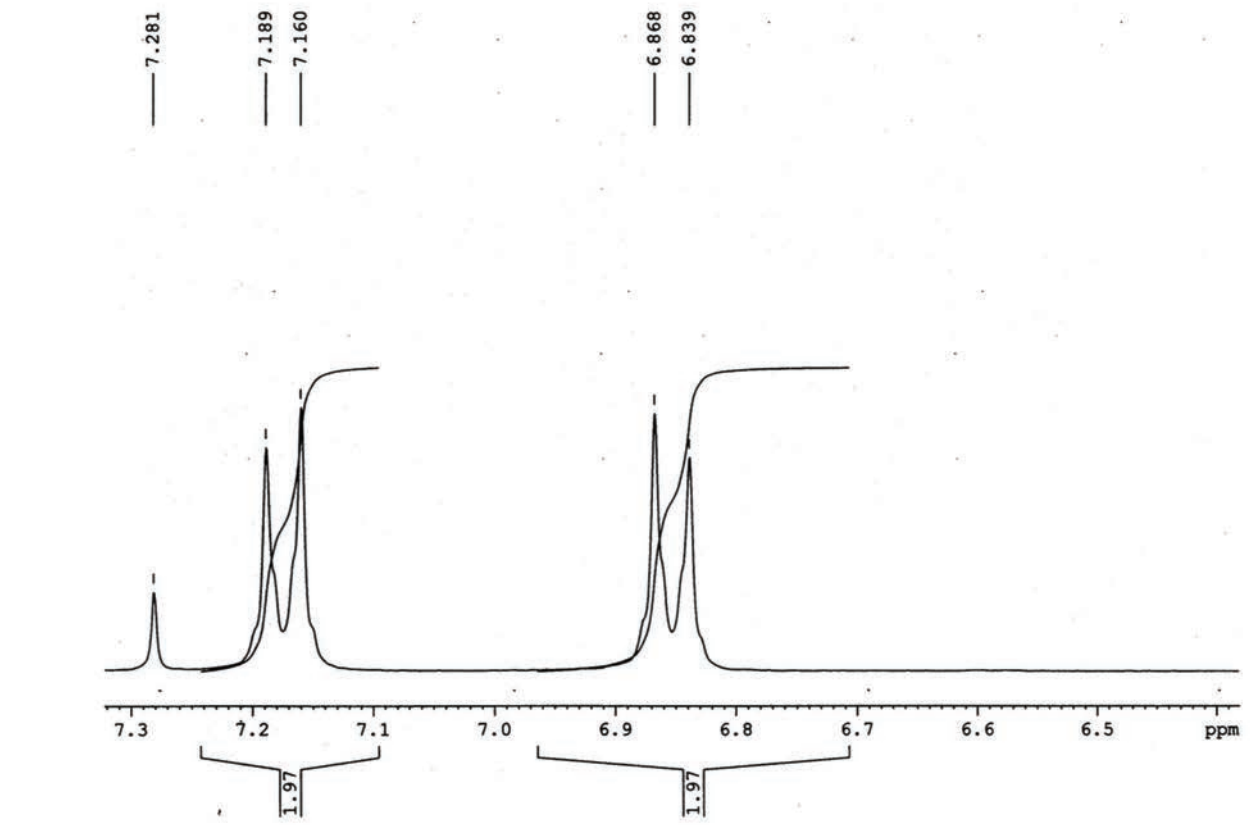

134.16
131.62
130.21
128.73
126.92
126.56
114.77
136
134
132
130
128
126
124
122
120
118
116
114
ppm

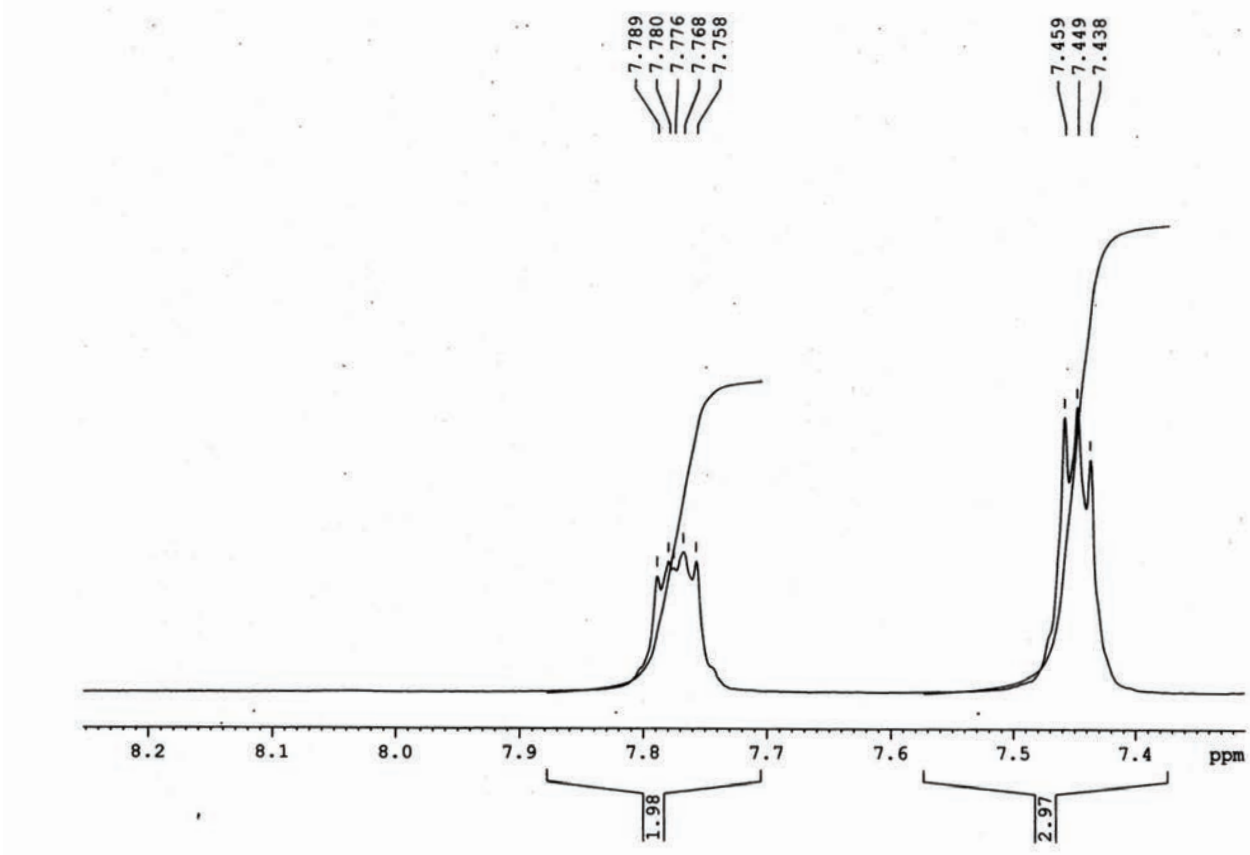

Compound 3c
7.768
7.758
7.459
7.449
7.438
7.281
7.189
7.160
6.868
6.839
5.578
5.562
5.539
5.523
3.921
3.899
3.877
3.777
3.737
3.718
3.679
3.206
3.191
3.147
3.132
2.870
2.845
2.820
2.795
1.833
1.811
1.787
1.764
1.740
1.237
1.212
1.186
1.057
1.032
1.007
0.029
Compound 3c
BRUKER
Current Data Parameters
NAME PR-3_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090702
Time 13.10
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 143.7
DW 81.000 usec
DE 6.00 usec
TE 294.7 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
1.98
2.97
1.97
1.97
0.97
1.93
0.99
0.98
1.92
2.18
2.93
3.00

1.833
1.811
1.787
1.764
1.740
1.237
1.212
1.186
1.057
1.032
1.007
ppm
2.18
2.93
3.00

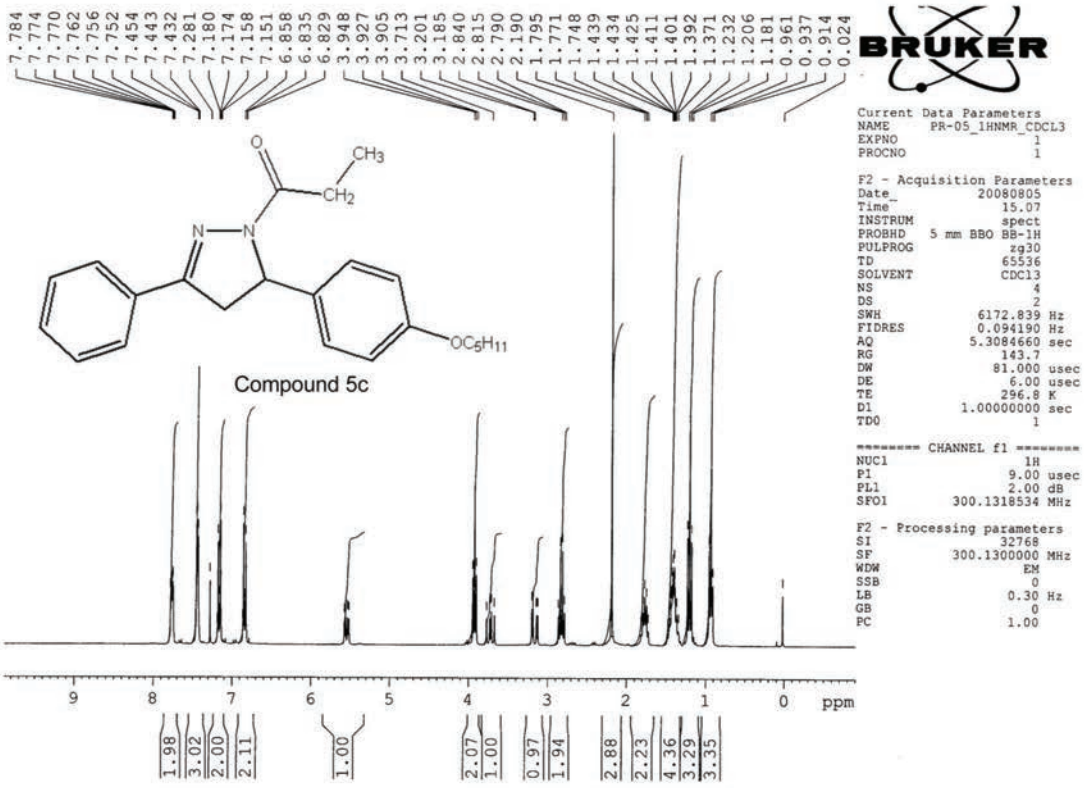

3.921
3.899
3.877
3.777
3.737
3.718
3.679
3.206
3.191
3.147
3.132
2.870
2.845
2.820
2.795
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 ppm
1.93
0.99
0.98
1.92

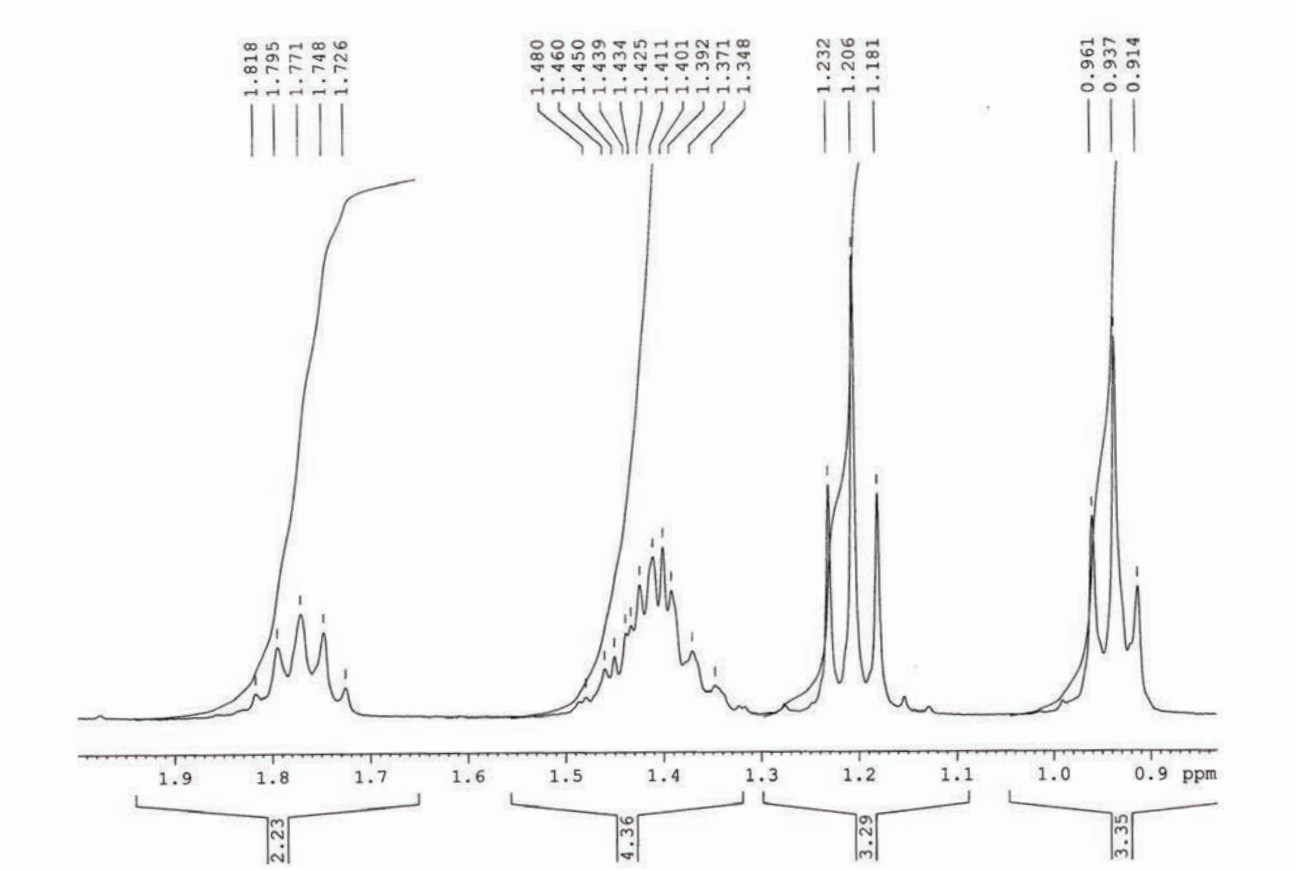

5.578
5.562
5.539
5.523
5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20 ppm
0.97


7.281
7.189
7.160
6.868
6.839
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
ppm
1.97
1.97


7.789
7.780
7.776
7.768
7.758
7.459
7.449
7.438
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
ppm
1.98
2.97

Compound 5c


7.784
7.774
7.770
7.762
7.756
7.752
7.454
7.443
7.432
7.281
7.180
7.174
7.158
7.151
6.858
6.835
6.829
3.948
3.927
3.905
3.713
3.201
3.185
2.840
2.815
2.790
2.190
1.795
1.771
1.748
1.439
1.434
1.425
1.411
1.401
1.392
1.371
1.232
1.206
1.181
0.961
0.937
0.914
0.024
BRUKER
Current Data Parameters
NAME PR-05_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080805
Time 15.07
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 143.7
DW 81.000 usec
DE 6.00 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
CH3
CH2
N
N
OC5H11
Compound 5c
9
8
7
6
5
4
3
2
1
0
ppm
1.98
3.02
2.00
2.11
1.00
2.07
1.00
0.97
1.94
2.88
2.23
4.36
3.29
3.35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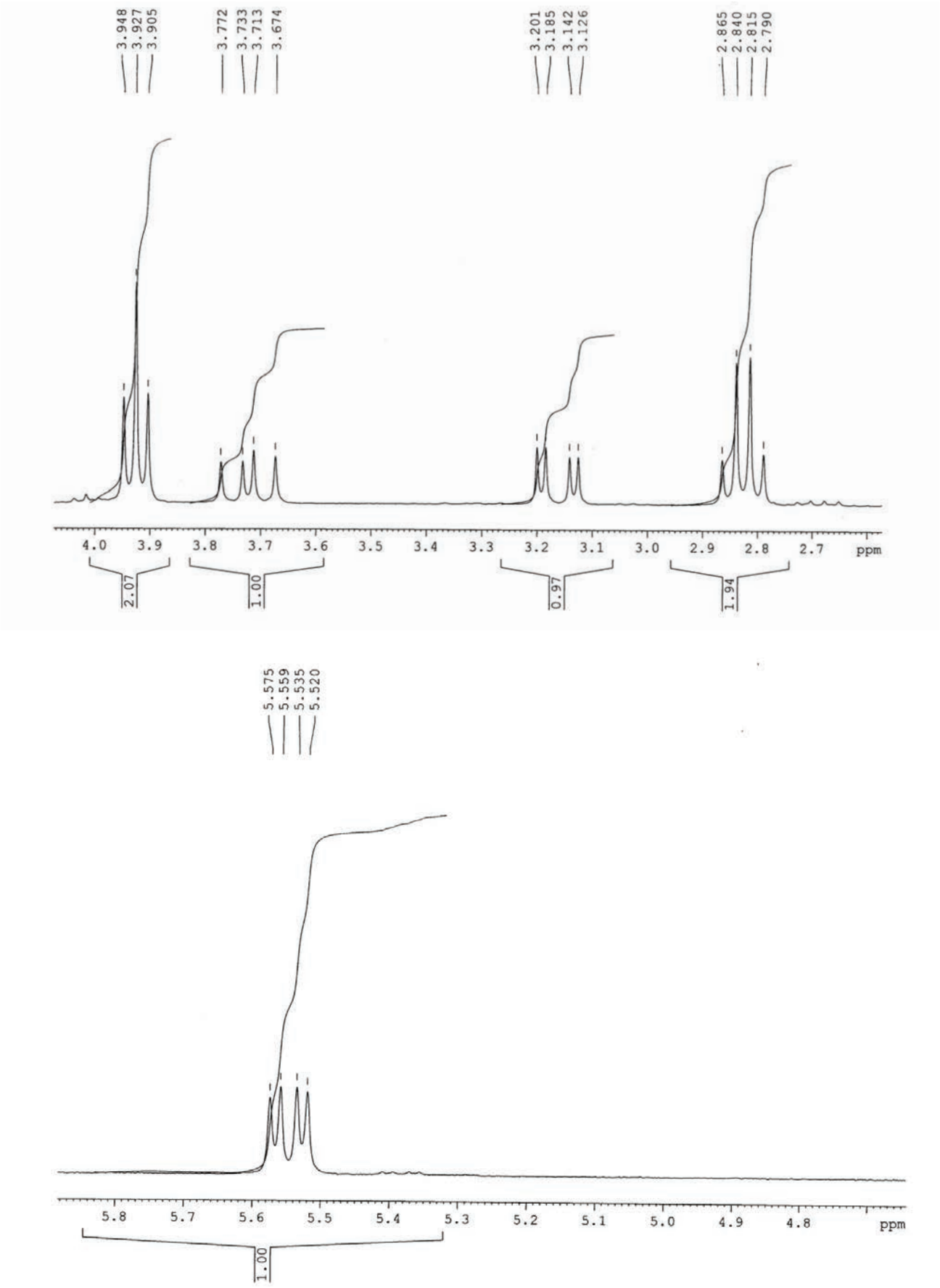
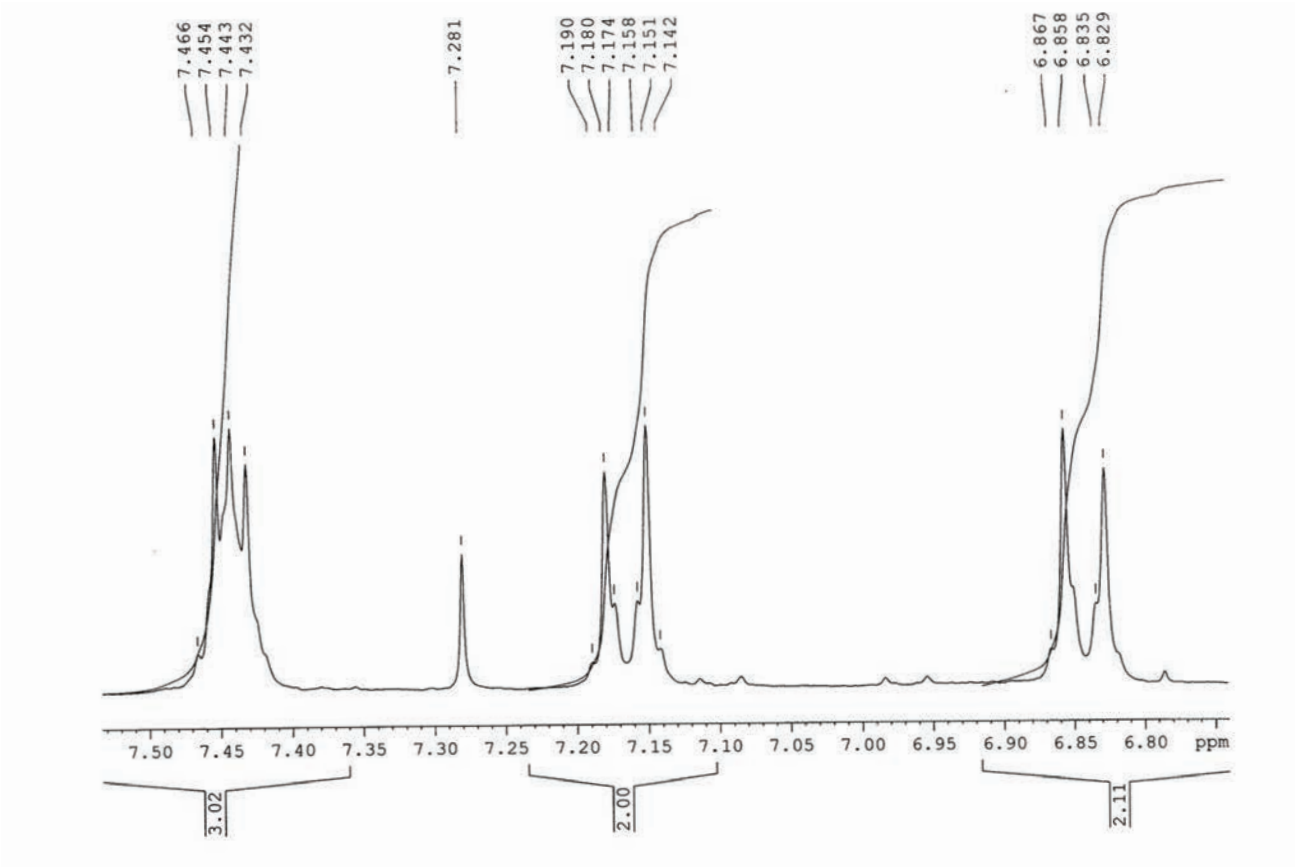
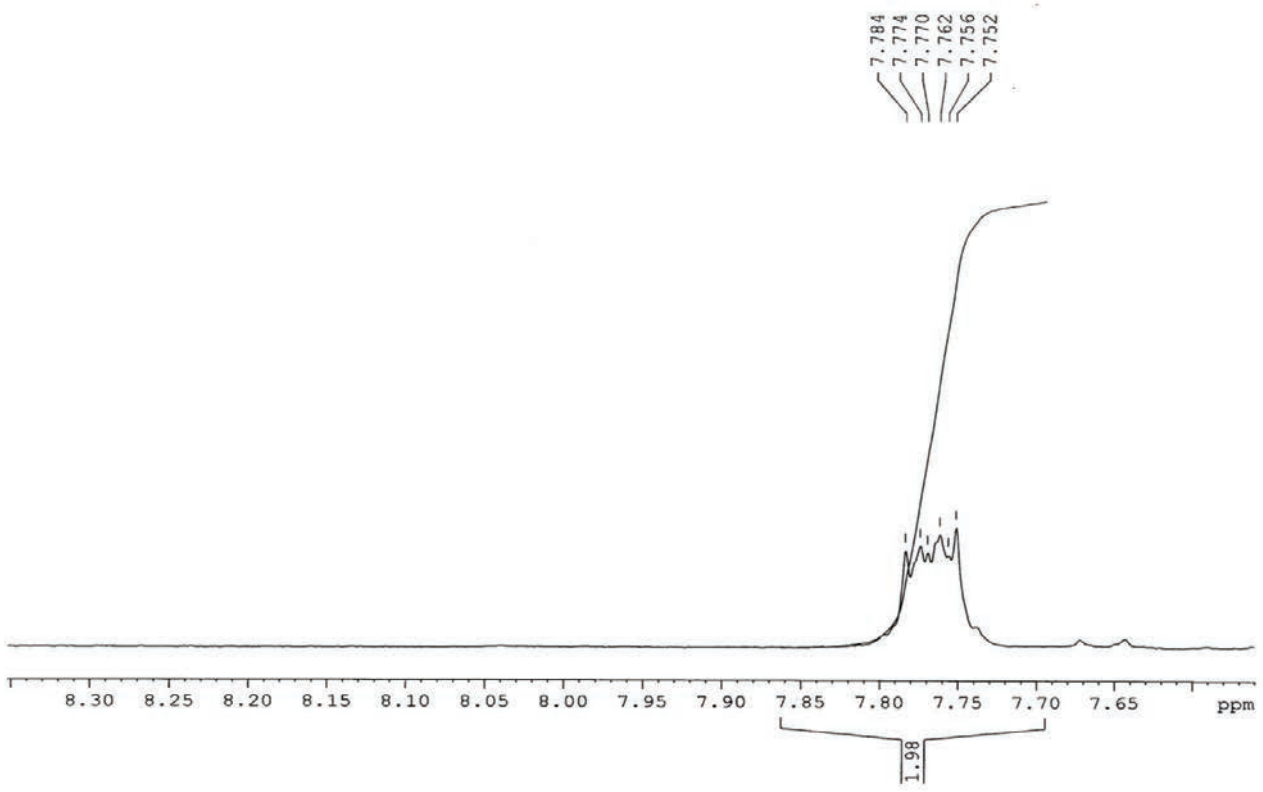
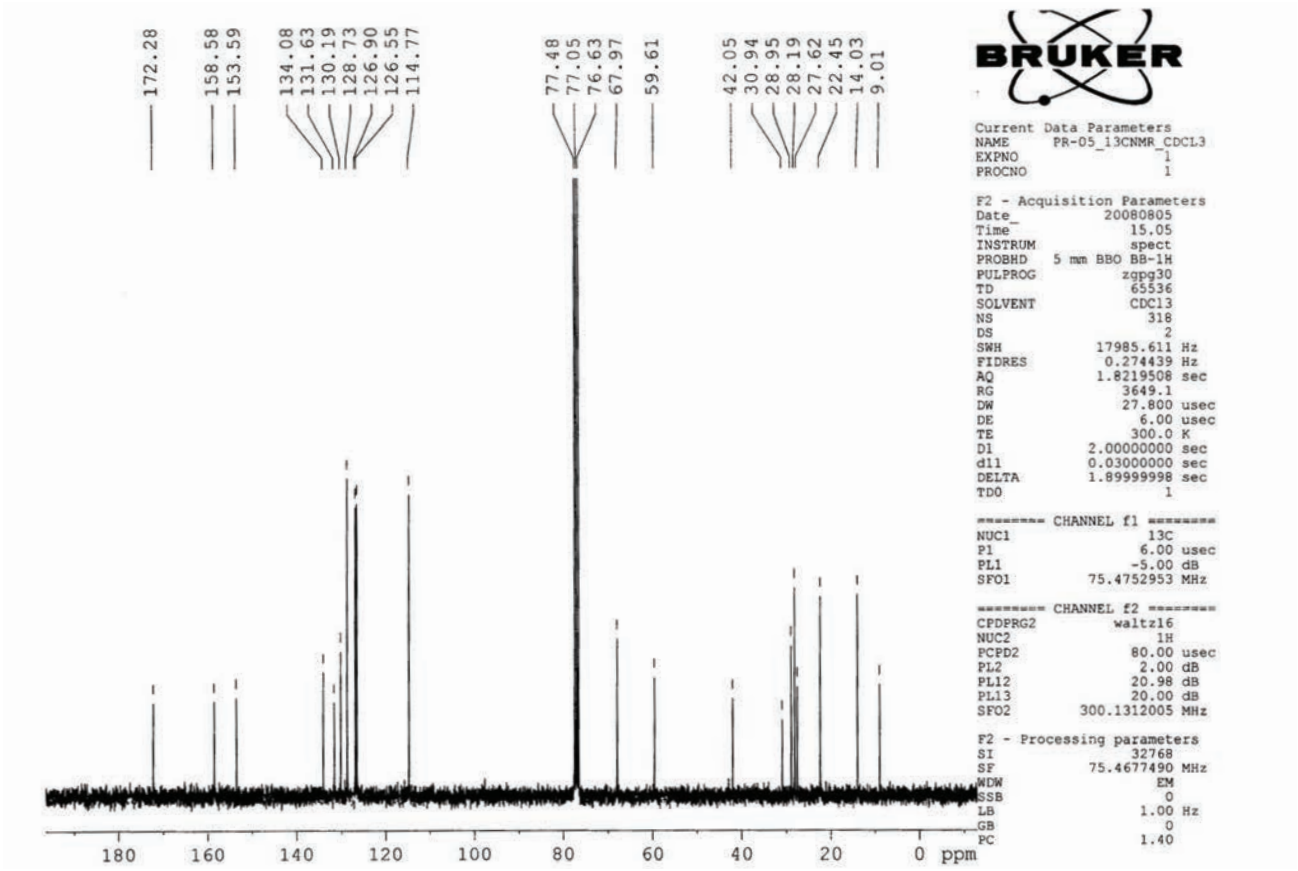
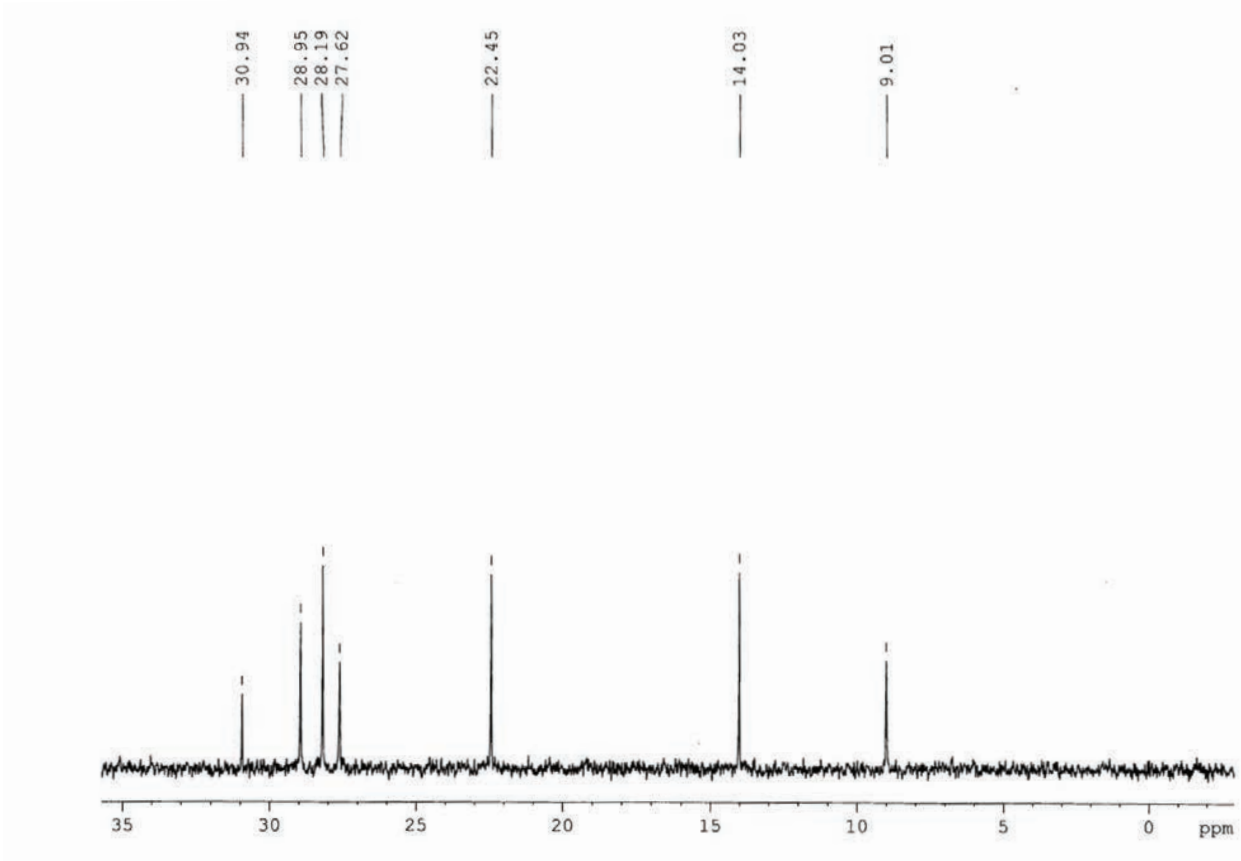
1.795
1.771
1.748
1.726
1.480
1.460
1.450
1.439
1.434
1.425
1.411
1.401
1.392
1.371
1.348
1.232
1.206
1.181
0.961
0.937
0.914
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
ppm
2.23
4.36
3.29
3.35

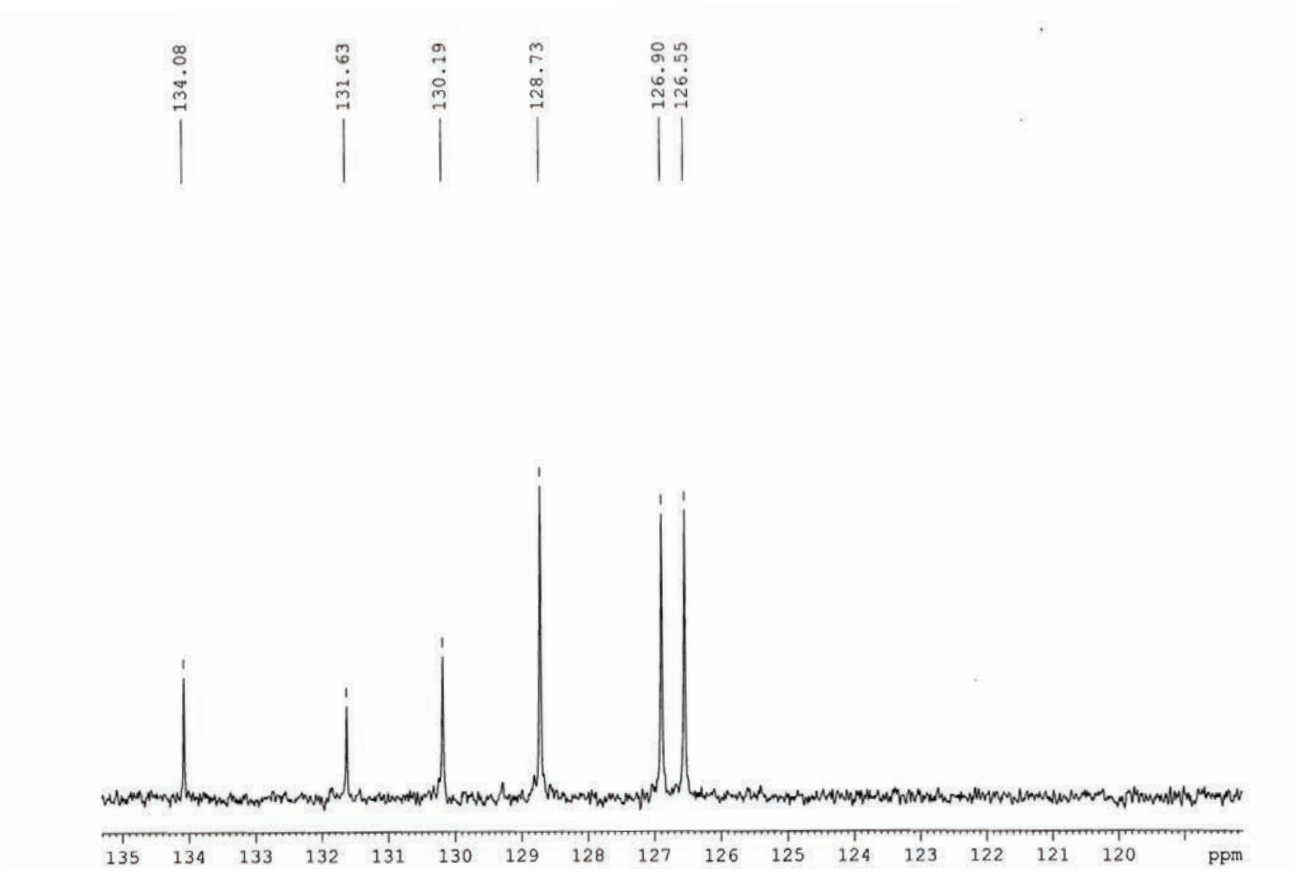

3.948
3.927
3.905
3.772
3.733
3.713
3.674
3.201
3.185
3.142
3.126
2.865
2.840
2.815
2.790
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
ppm
2.07
1.00
0.97
1.94
5.575
5.559
5.535
5.520
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
ppm
1.00

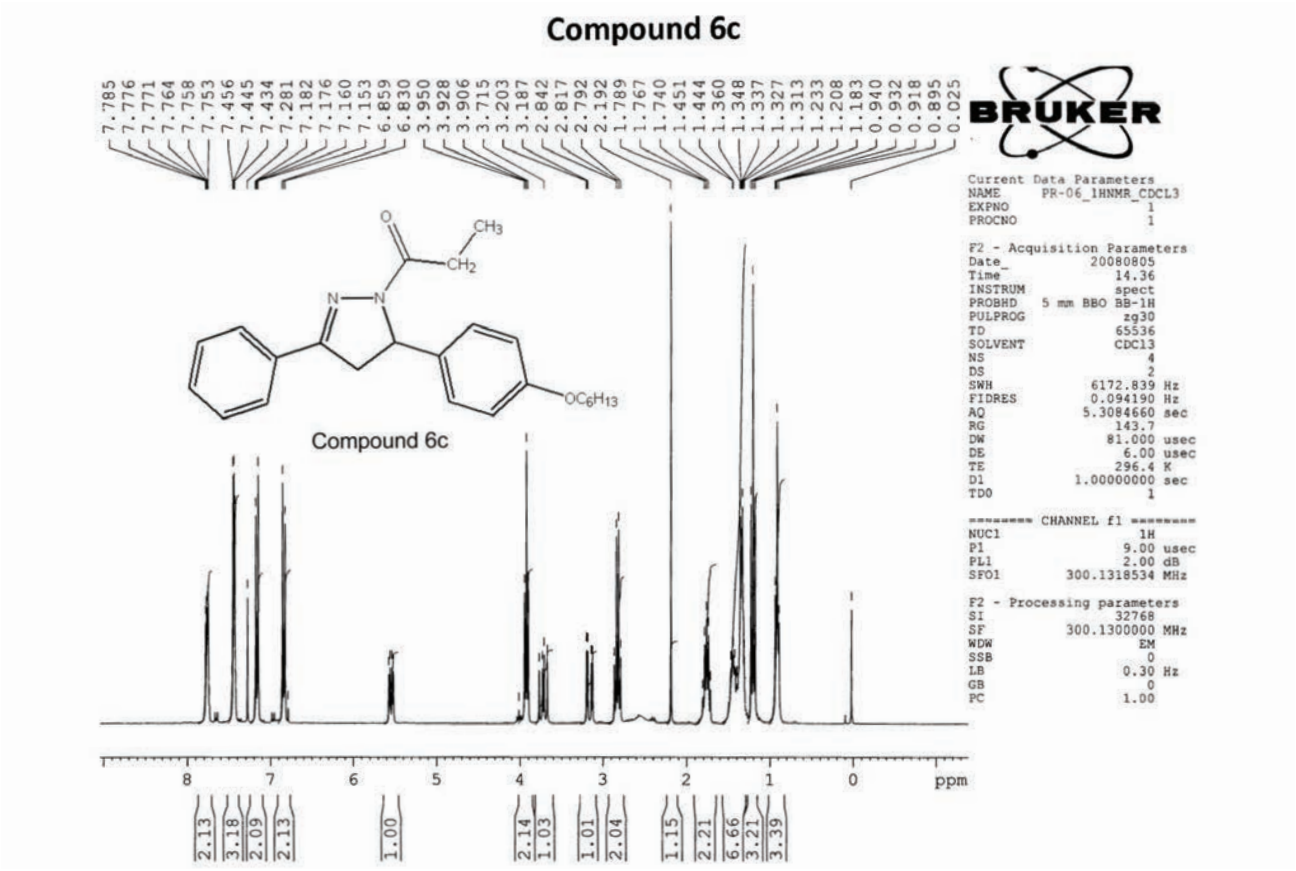

7.466
7.454
7.443
7.432
7.281
7.190
7.180
7.174
7.158
7.151
7.142
6.867
6.858
6.835
6.829
7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 ppm
3.02
2.00
2.11

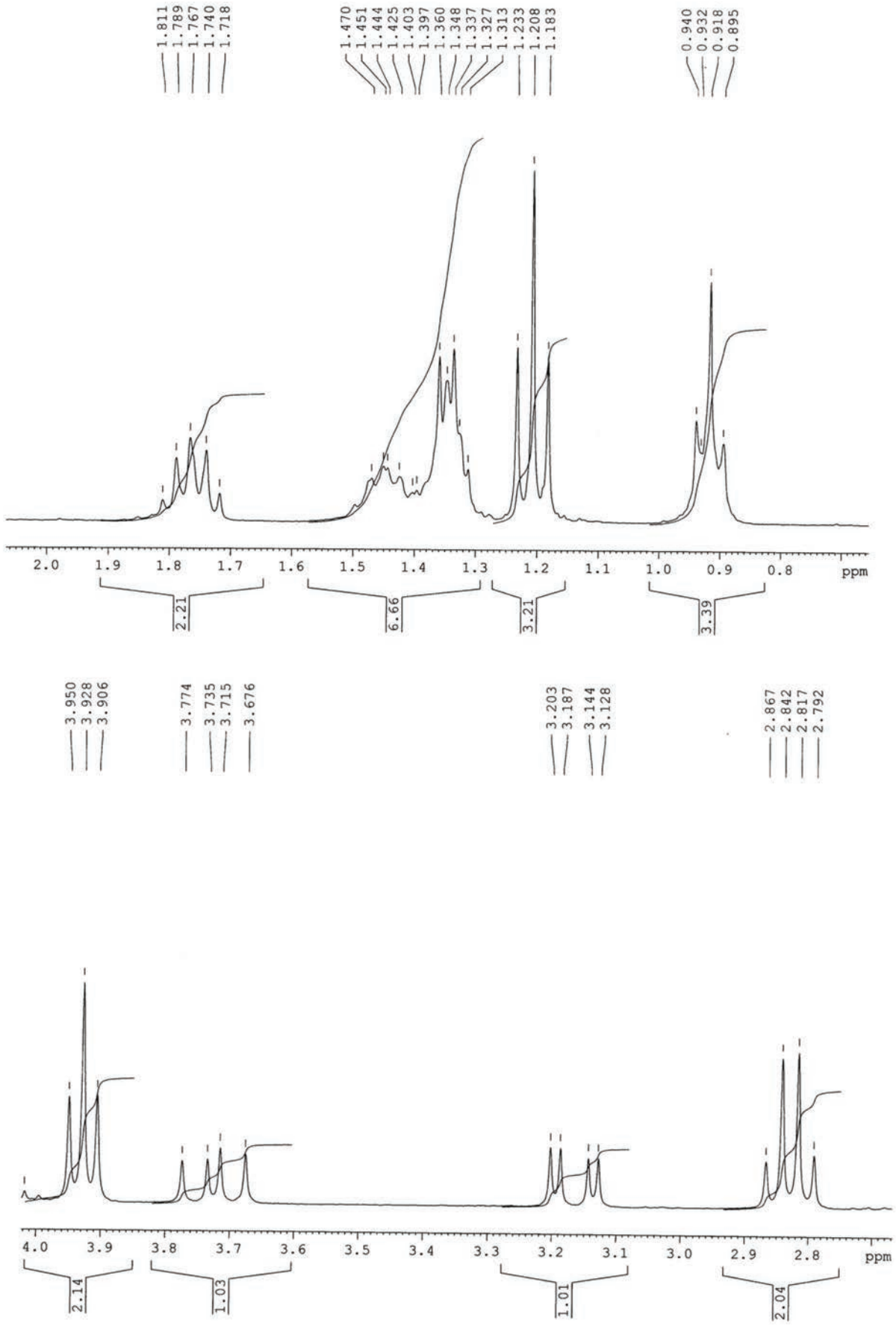

7.784
7.774
7.770
7.762
7.756
7.752
8.30 8.25 8.20 8.15 8.10 8.05 8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65 ppm
1.98

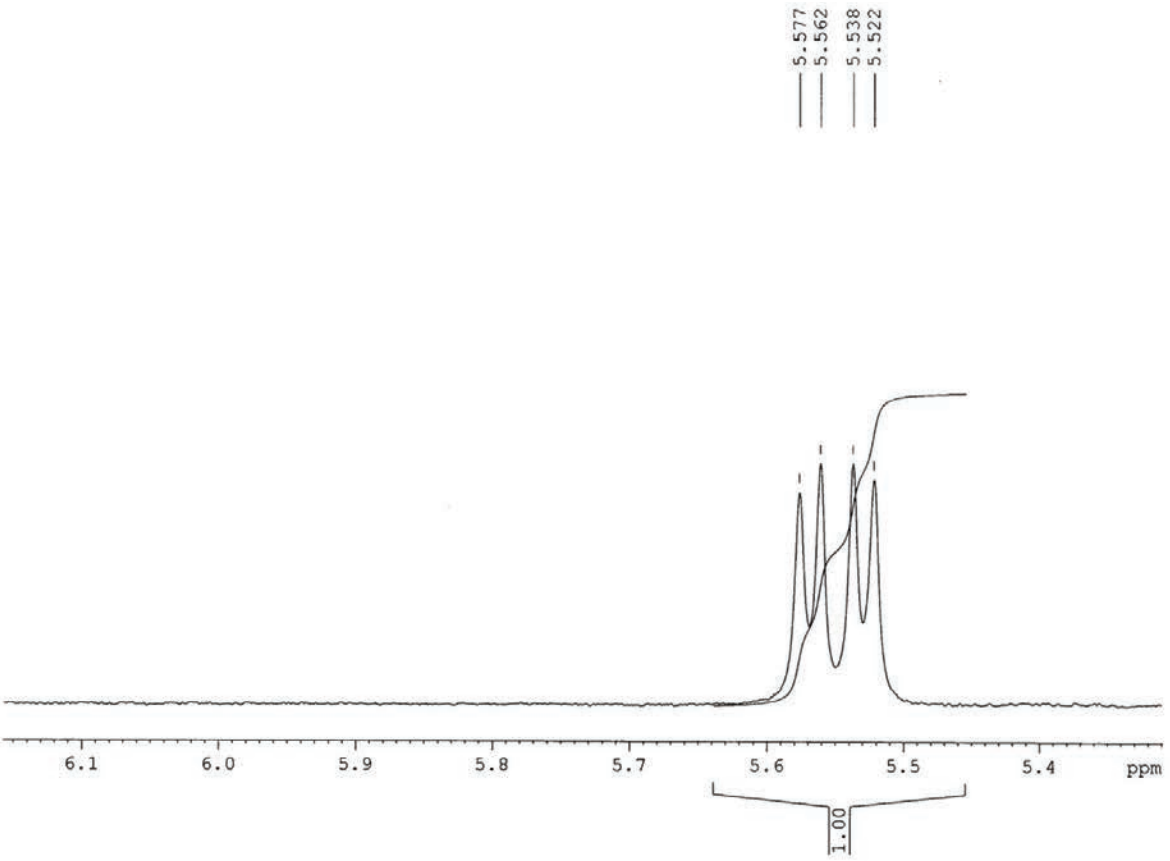

172.28
158.58
153.59
134.08
131.63
130.19
128.73
126.90
126.55
114.77
77.48
77.05
76.63
67.97
59.61
42.05
30.94
28.95
28.19
27.62
22.45
14.03
9.01
180
160
140
120
100
80
60
40
20
0 ppm
BRUKER
Current Data Parameters
NAME PR-05_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080805
Time 15.05
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 316
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 3649.1
DW 27.800 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 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

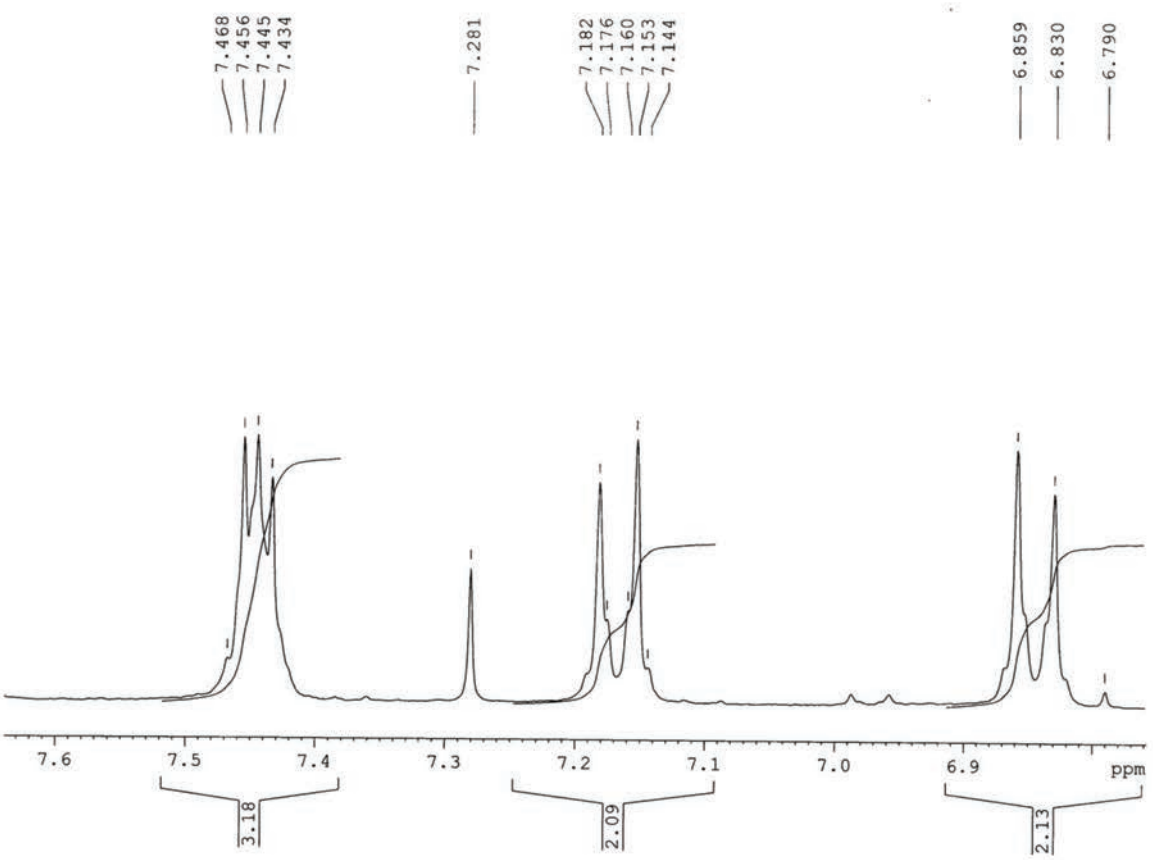

30.94
28.95
28.19
27.62
22.45
14.03
9.01
35
30
25
20
15
10
5
0 ppm

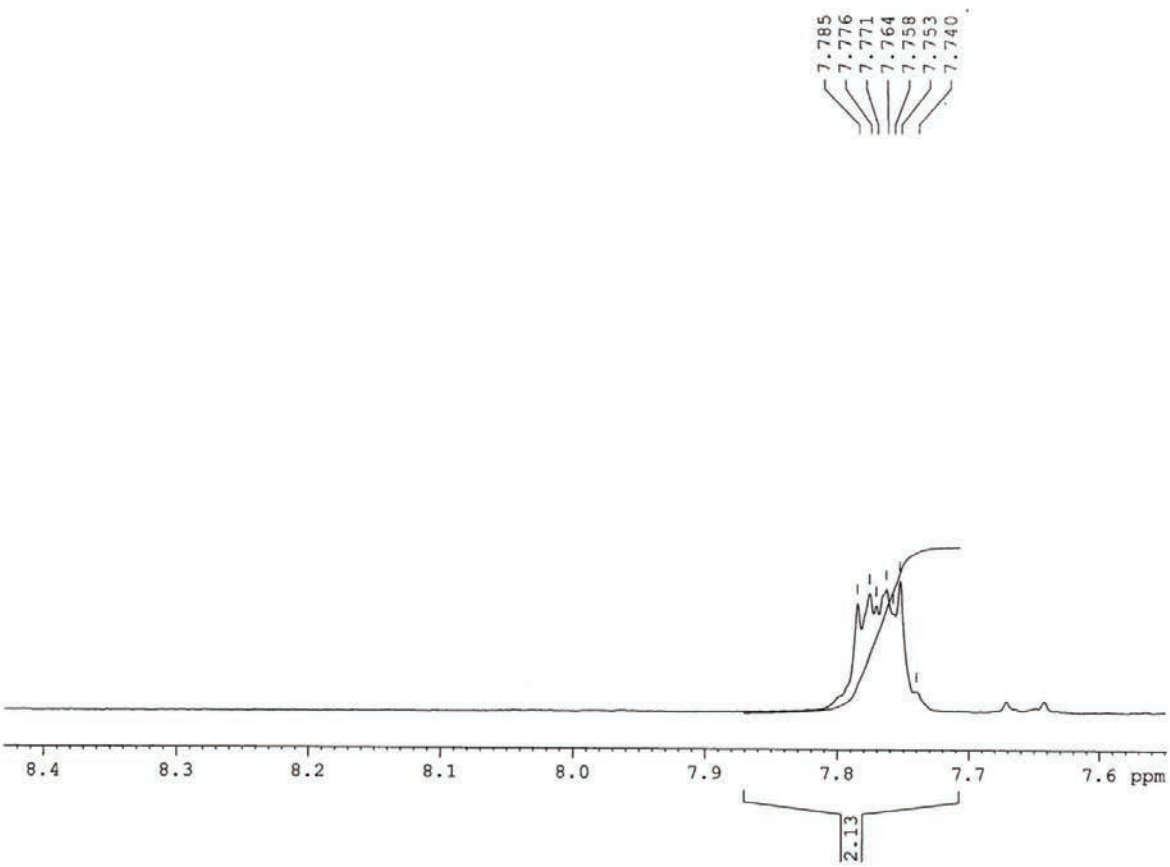

134.08
131.63
130.19
128.73
126.90
126.55
135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120 ppm

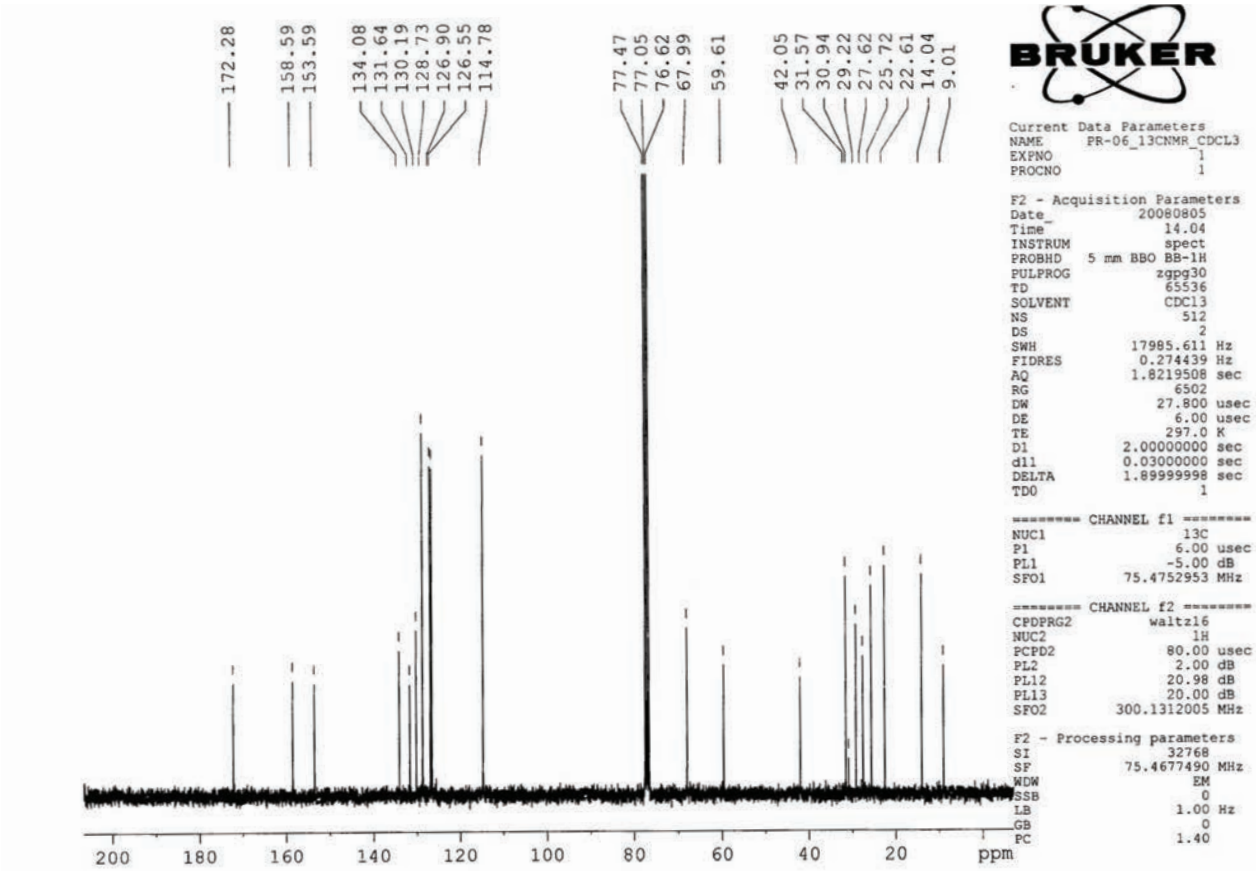

Compound 6c
7.785 7.776 7.771 7.764 7.758 7.753 7.456 7.445 7.434 7.281 7.182 7.176 7.160 7.153 6.859 6.830 3.950 3.928 3.906 3.715 3.203 3.187 2.842 2.817 2.792 2.192 1.789 1.767 1.740 1.451 1.444 1.360 1.348 1.337 1.327 1.313 1.233 1.208 1.183 0.940 0.932 0.918 0.895 0.025
BRUKER
Current Data Parameters
NAME PR-06_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080805
Time 14.36
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 143.7
DW 81.000 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Compound 6c
8 7 6 5 4 3 2 1 0 ppm
2.13 3.18 2.09 2.13 1.00 2.14 1.03 1.01 2.04 1.15 2.21 6.66 3.21 3.39

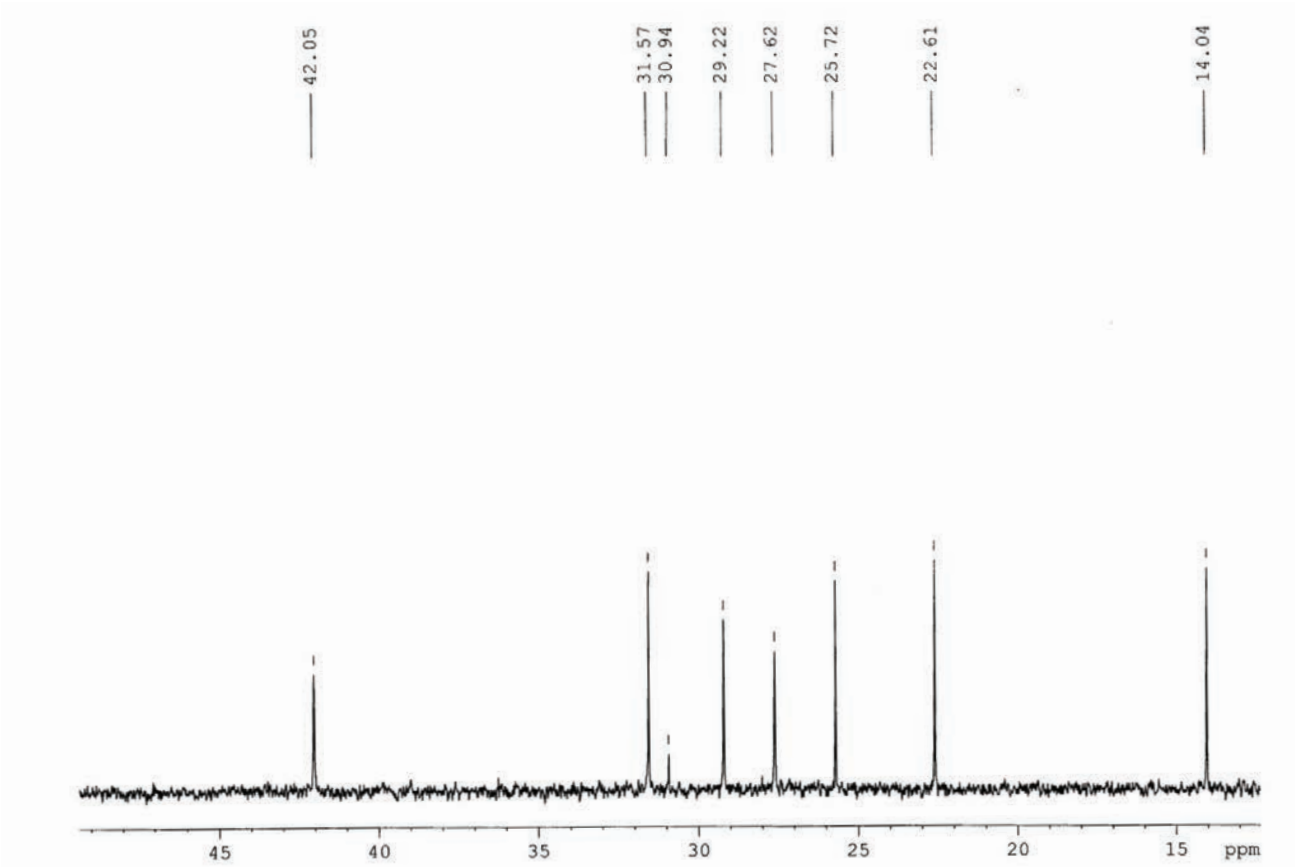

1.811
1.789
1.767
1.740
1.718
1.470
1.451
1.444
1.425
1.403
1.397
1.360
1.348
1.337
1.327
1.313
1.233
1.208
1.183
0.940
0.932
0.918
0.895
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
ppm
2.21
6.66
3.21
3.39
3.950
3.928
3.906
3.774
3.735
3.715
3.676
3.203
3.187
3.144
3.128
2.867
2.842
2.817
2.792
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
ppm
2.14
1.03
1.01
2.04

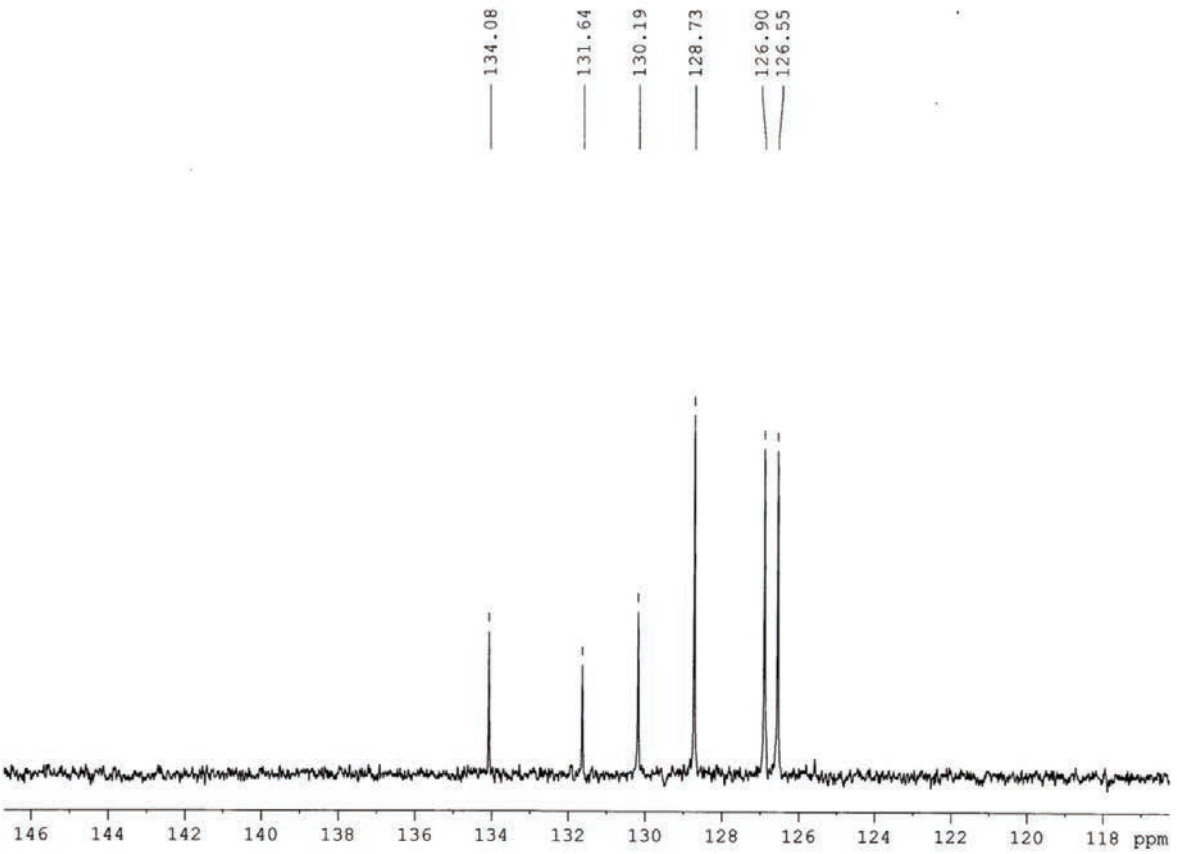

5.577
5.562
5.538
5.522
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
ppm
1.00

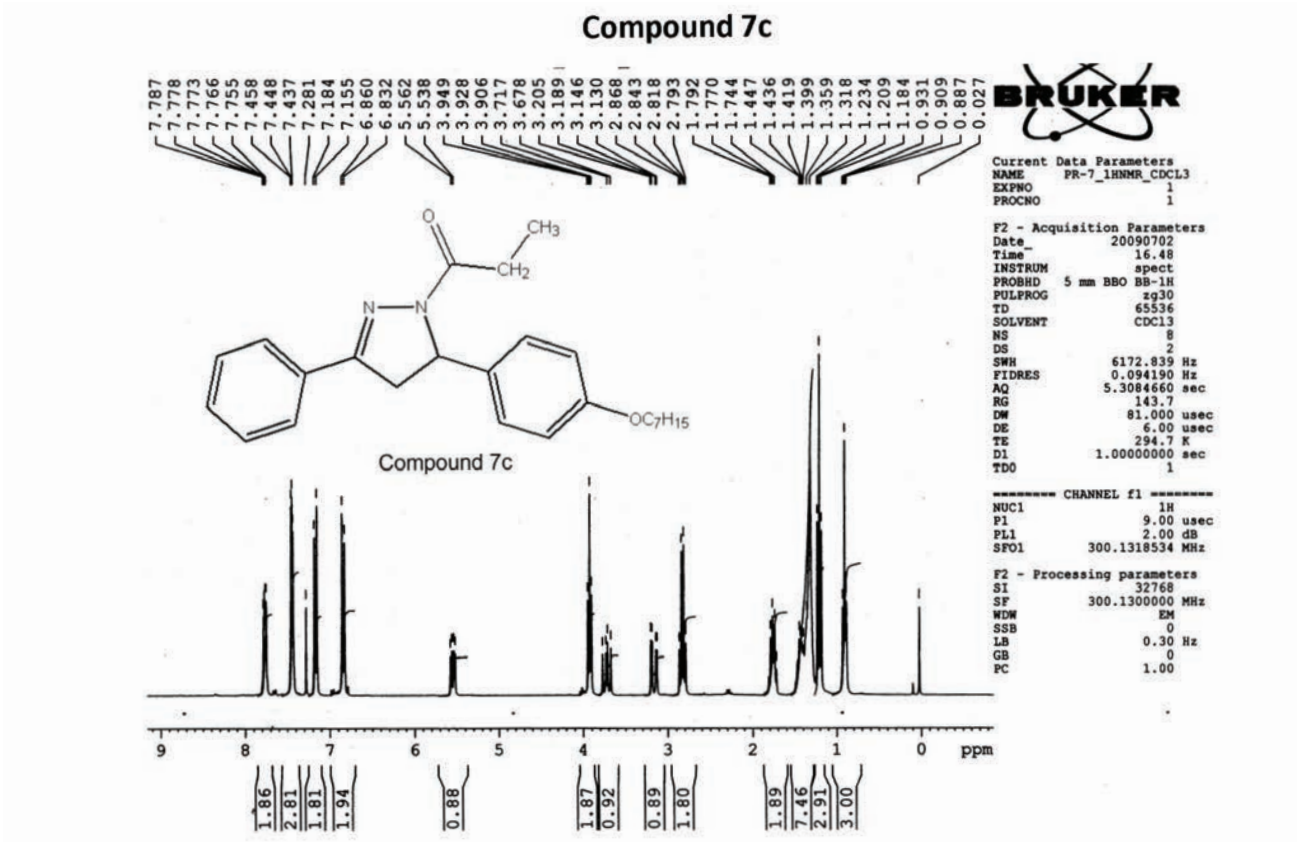

7.468
7.456
7.445
7.434
7.281
7.182
7.176
7.160
7.153
7.144
6.859
6.830
6.790
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
3.18
2.09
2.13

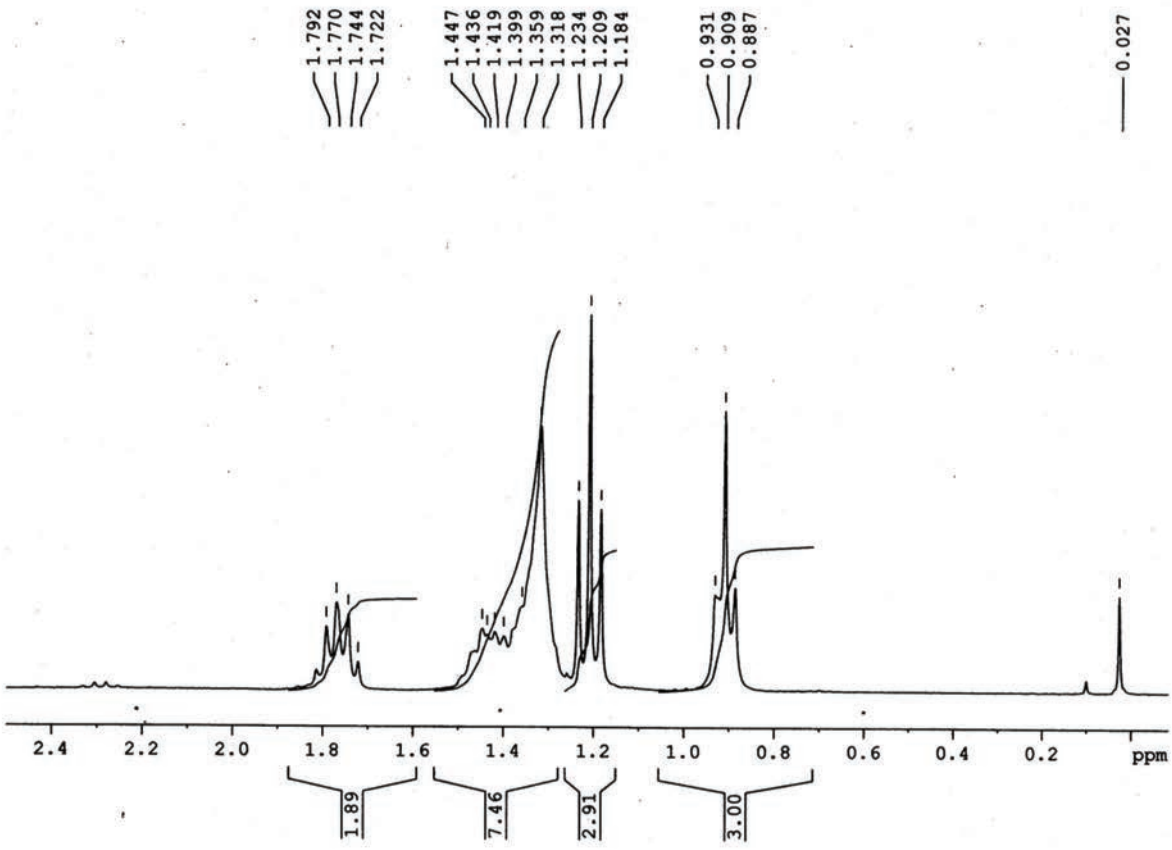

7.785
7.776
7.771
7.764
7.758
7.753
7.740
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6 ppm
2.13

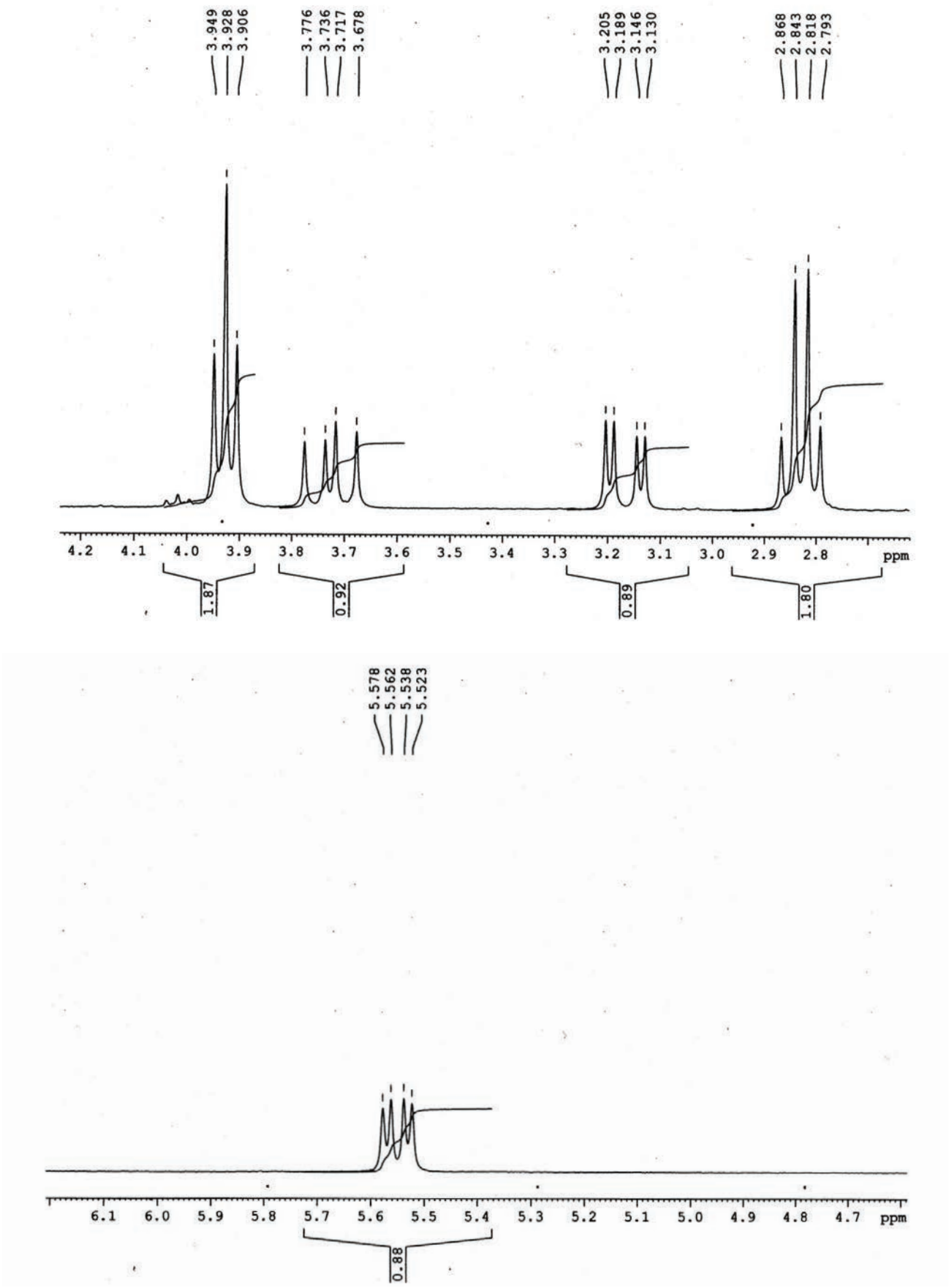

172.28
158.59
153.59
134.08
131.64
130.19
128.73
126.90
126.55
114.78
77.47
77.05
76.62
67.99
59.61
42.05
31.57
30.94
29.22
27.62
25.72
22.61
14.04
9.01
200
180
160
140
120
100
80
60
40
20
ppm
BRUKER
Current Data Parameters
NAME PR-06_13CNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080805
Time 14.04
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 6502
DW 27.800 usec
DE 6.00 usec
TE 297.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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

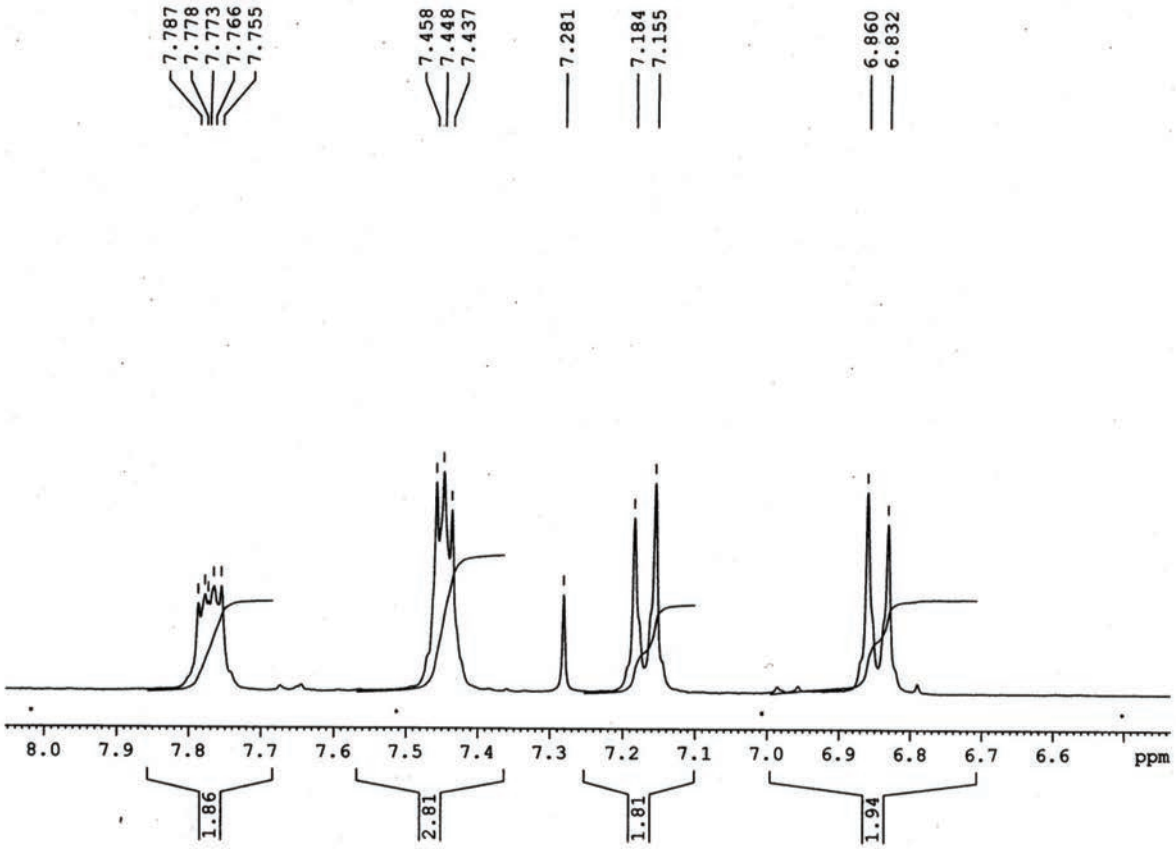

42.05
31.57
30.94
29.22
27.62
25.72
22.61
14.04
45
40
35
30
25
20
15
ppm


134.08
131.64
130.19
128.73
126.90
126.55
146
144
142
140
138
136
134
132
130
128
126
124
122
120
118
ppm

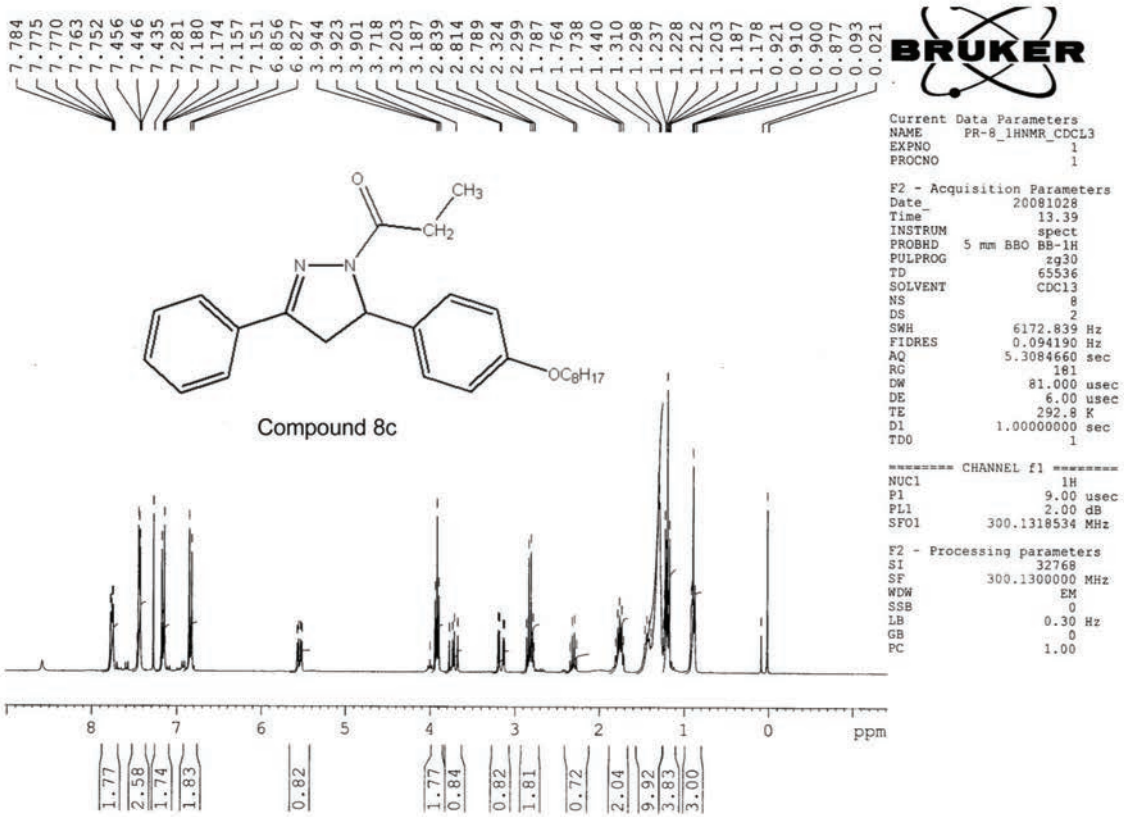

Compound 7c
7.787
7.778
7.773
7.766
7.755
7.458
7.448
7.437
7.281
7.184
7.155
6.860
6.832
5.562
5.538
3.949
3.928
3.906
3.717
3.678
3.205
3.189
3.146
3.130
2.868
2.843
2.818
2.793
1.792
1.770
1.744
1.447
1.436
1.419
1.399
1.359
1.318
1.234
1.209
1.184
0.931
0.909
0.887
0.027
BRUKER
Current Data Parameters
NAME PR-7_1HNMR_CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090702
Time 16.48
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 143.7
DW 81.000 usec
DE 6.00 usec
TE 294.7 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
CH3
CH2
N
N
OC7H15
Compound 7c
ppm
1.86
2.81
1.81
1.94
0.88
1.87
0.92
0.89
1.80
1.89
7.46
2.91
3.00


1.792
1.770
1.744
1.722
1.447
1.436
1.419
1.399
1.359
1.318
1.234
1.209
1.184
0.931
0.909
0.887
0.027
ppm
1.89
7.46
2.91
3.00


3.949
3.928
3.906
3.776
3.736
3.717
3.678
3.205
3.189
3.146
3.130
2.868
2.843
2.818
2.793
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 ppm
1.87
0.92
0.89
1.80
5.578
5.562
5.538
5.523
6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 ppm
0.88



Compound 8c



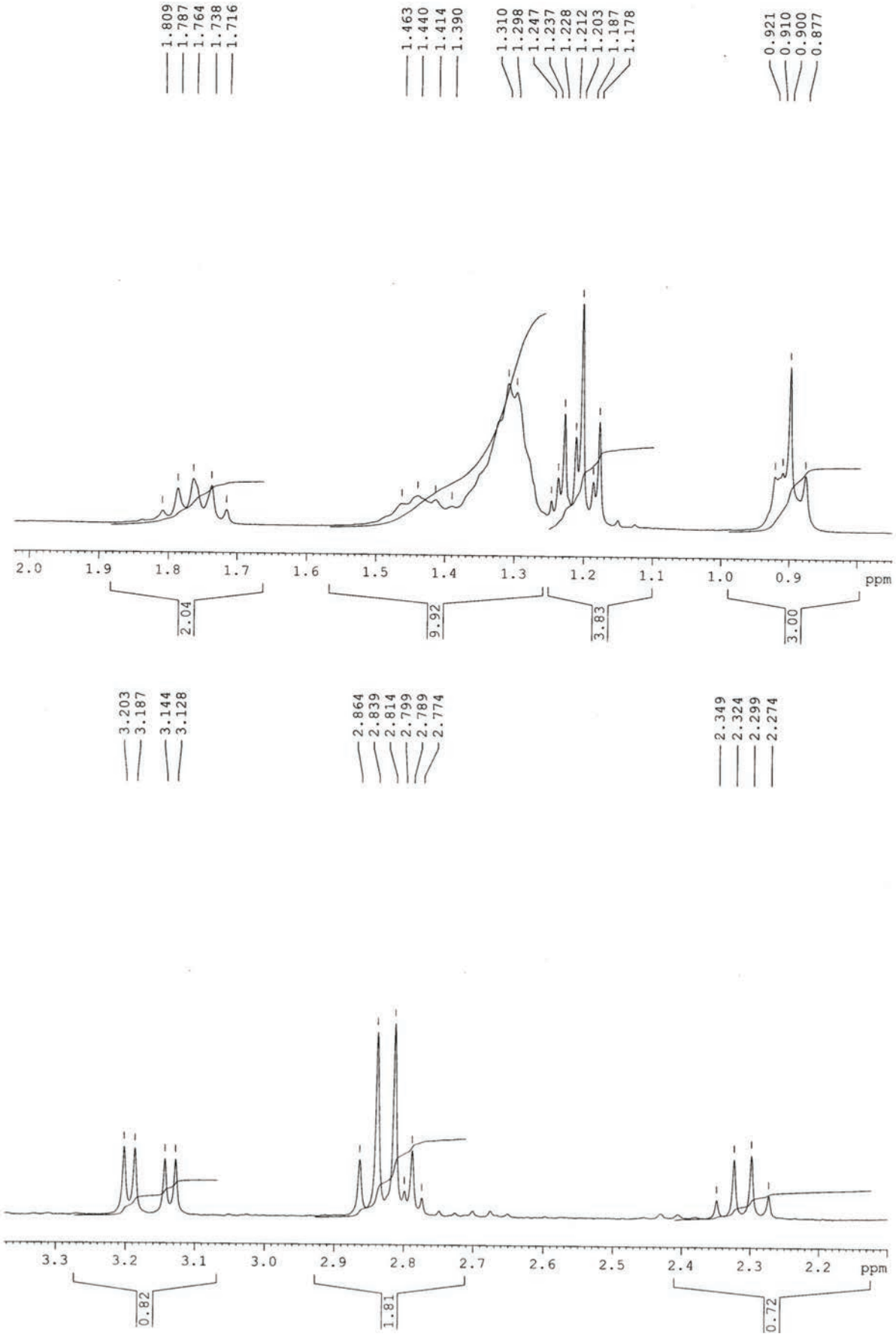
BRUKER

```
Current Data Parameters
NAME      PR-8_1HNMR_CDCL3
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20081028
Time                 13.39
INSTRUM              spect
PROBHD   5 mm BBO BB-1H
PULPROG              zg30
TD                  65536
SOLVENT             CDC13
NS                      8
DS                      2
SWH              6172.839 Hz
FIDRES           0.094190 Hz
AQ               5.3084660 sec
RG                    181
DW                 81.000 usec
DE                  6.00 usec
TE                 292.8 K
D1              1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                  32768
SF            300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```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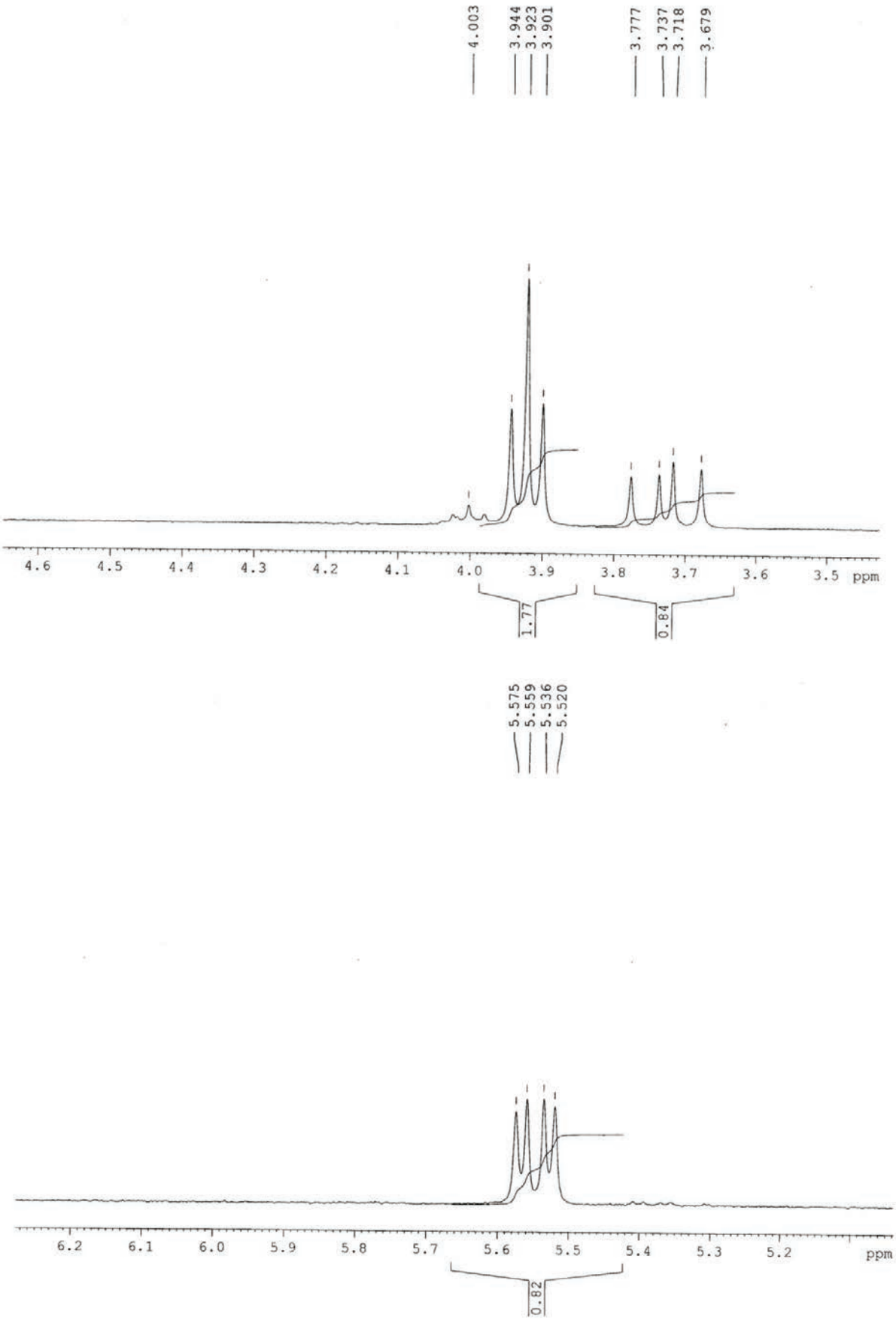
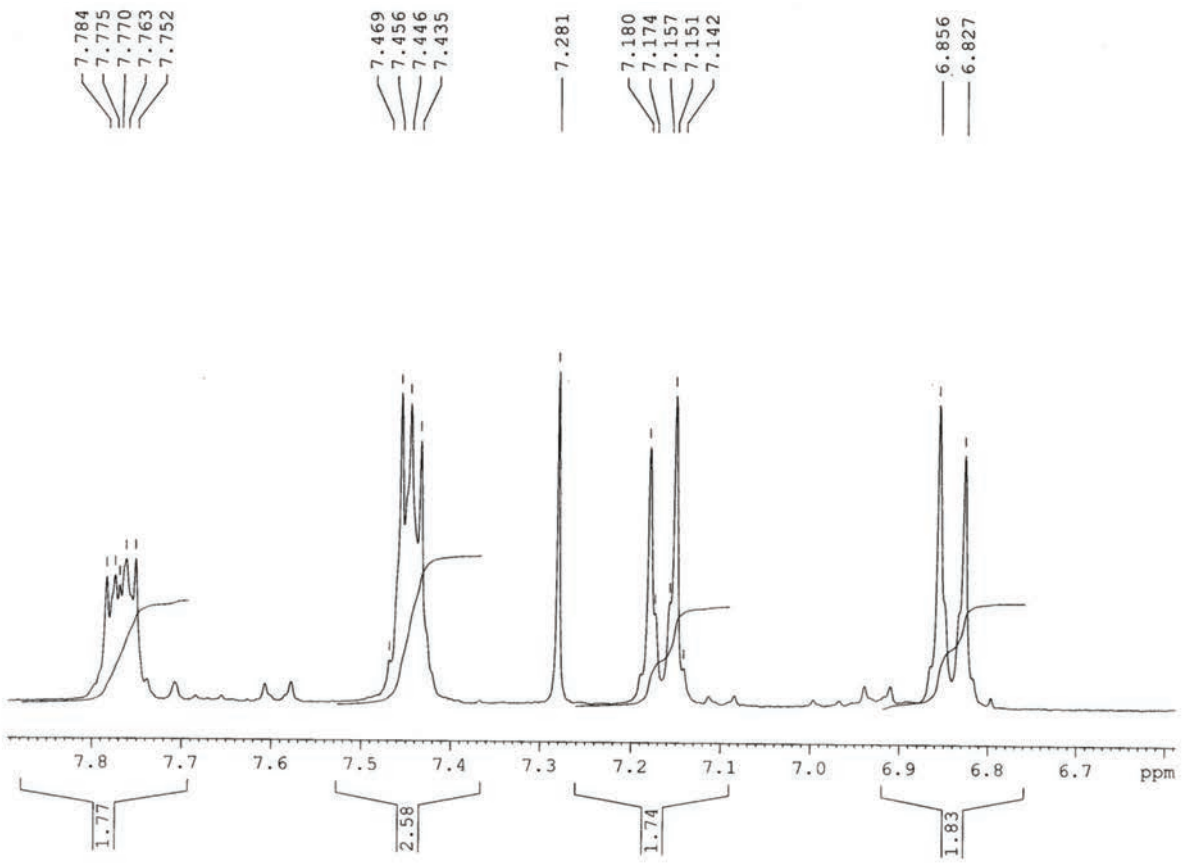
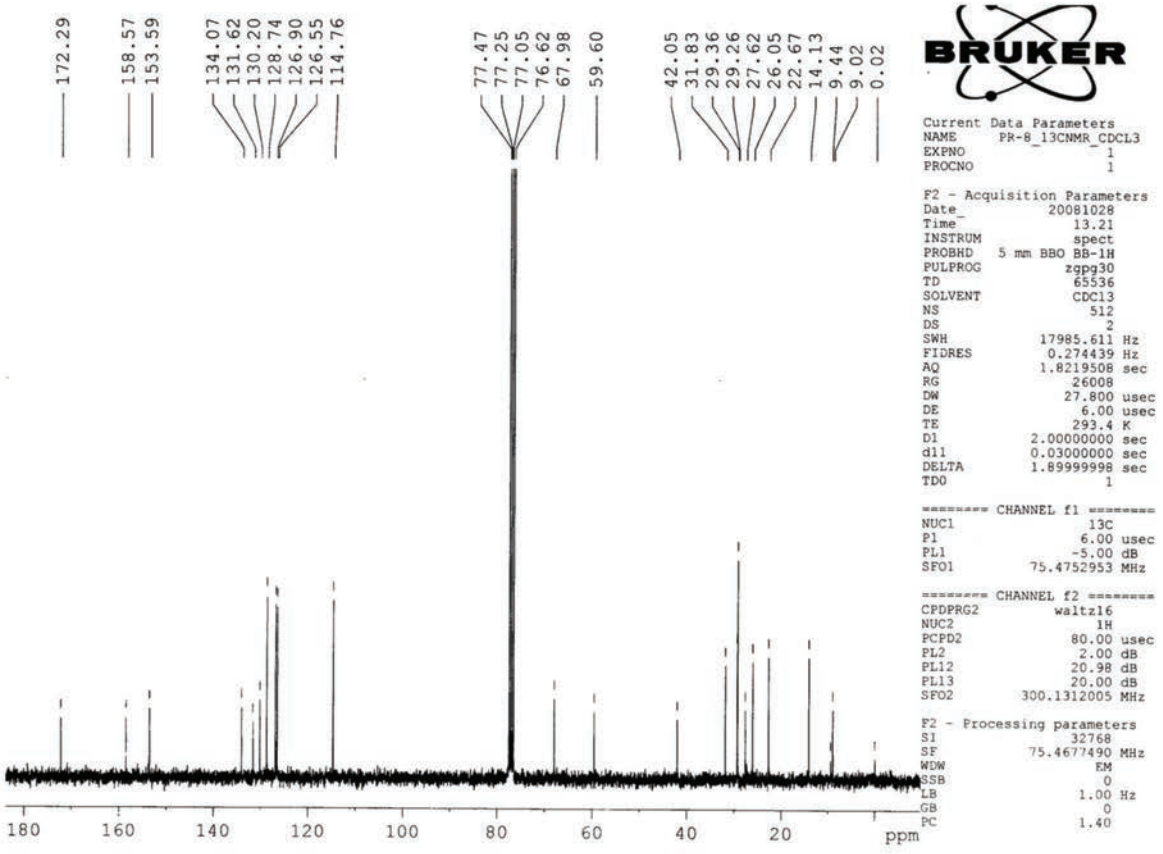
1.764
1.738
1.716
1.463
1.440
1.414
1.390
1.310
1.298
1.247
1.237
1.228
1.212
1.203
1.187
1.178
0.921
0.910
0.900
0.877
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
ppm
2.04
9.92
3.83
3.00
3.203
3.187
3.144
3.128
2.864
2.839
2.814
2.799
2.789
2.774
2.349
2.324
2.299
2.274
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
ppm
0.82
1.81
0.72


4.003
3.944
3.923
3.901
3.777
3.737
3.718
3.679
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5 ppm
1.77
0.84
5.575
5.559
5.536
5.520
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
ppm
0.82





BRUKER

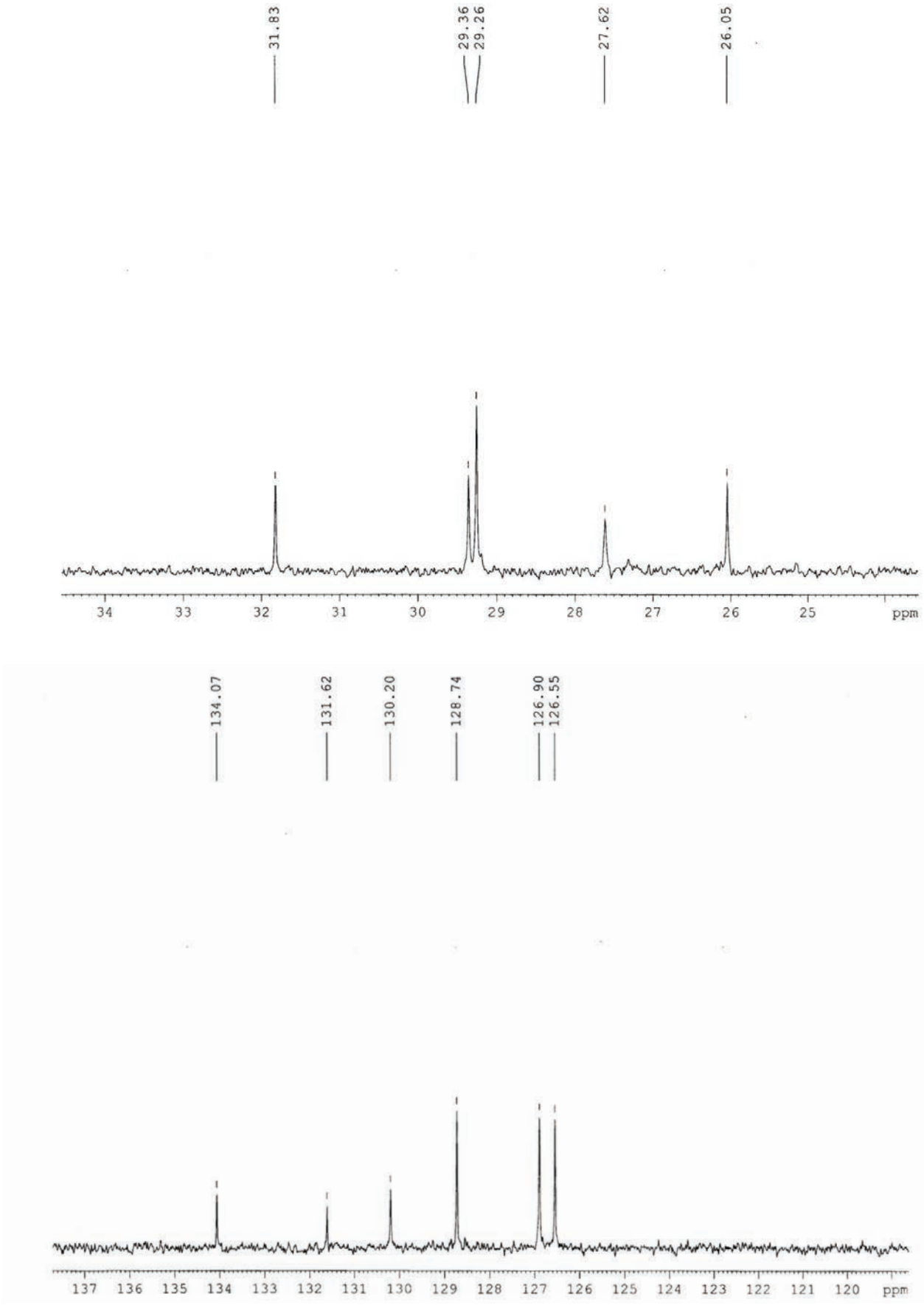
Current Data Parameters
NAME PR-8_13CNMR_CDCL3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20081028
Time 13.21
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 26008
DW 27.800 usec
DE 6.00 usec
TE 293.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 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


31.83
29.36
29.26
27.62
26.05
34
33
32
31
30
29
28
27
26
25
ppm
134.07
131.62
130.20
128.74
126.90
126.55
137
136
135
134
133
132
131
130
129
128
127
126
125
124
123
122
121
120
ppm