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Controllable Synthesis of Bis(1,2,3-triazole)s and 5-Alkynyl-triazoles via Temperature Effect on Copper-catalyzed Huisgen Cycloaddition

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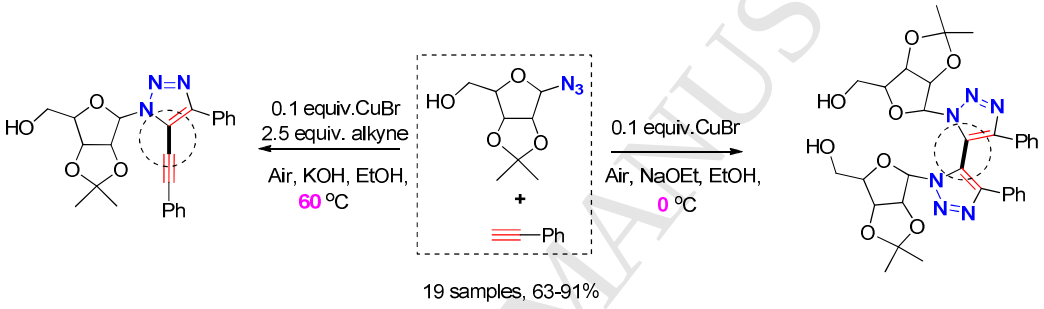


Abstract: A facile synthetic protocol has been developed for the controllable preparation of bis(1,2,3-triazole)s and 5-alkynyl-1,2,3-triazoles from alkyne and azide under different temperatures. Various azides and alkynes were used as substrates for the reactions and the successful applications in nucleoside analogues manifested the values of this method in syntheses of bioactive molecules. Besides, a possible temperature-guided triazolyl-copper intermediate aerobic oxidative coupling mechanism was proposed for this controllable reaction procedure.

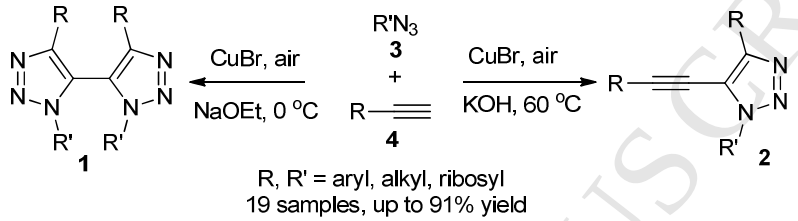
Keywords: bis(1,2,3-triazole)s, 5-alkynyl-triazoles, nucleoside analogues

1. Introduction

Since the concept of "click chemistry" was presented in 2001, [1] the preparation and application of 1,2,3-triazoles have attracted wide interest in organic chemistry [2], medicinal chemistry [3] and material sciences [4]. Besides being applied as a simple linkage to connect different building blocks, 1,2,3-triazole itself has been also explored as bioisoster of peptide bonds [5], multi-functional ligands [6], and supermolecular binding groups [7]. Several synthetic protocols for the preparation of 1,2,3-triazoles derivatives have been developed: (1) cycoloaddition between substituted-alkyne and organic azide; [8] (2) electrophilic trapping of triazolyl-copper intermediate; [9] (3) C-H activation on 5-H of 1,2,3-triazole. [10]

Bis(1,2,3-triazole)s (**1**) and 5-alkynyl-1,2,3-triazoles (**2**) were initially found as trace by-products of the copper-catalyzed Huisgen cycloaddition reaction (CuAAC reaction). [11] Recent researches showed functional perspectives of these two 1,2,3-triazole derivatives in ligand design or as synthetic intermediates of fused rings.[12] Angell *et al.* developed the first preparative method for bis(1,2,3-triazole)s in the presence of Na_2CO_3, [13] in which only propargyl ethers could lead to desirable yields due to the sensitive steric effect. [13.14] Very recently, Xu *et al.* reported their ligand-controlled synthesis of bis(1,2,3-triazole)s. Moderate to good yields of bis(1,2,3-triazole)s could be achieved by using polysiloxane-supported secondary amine as ligand. [15] As for 5-alkynyl-1,2,3-triazoles, the preparative method was reported by Porco Jr *et al* in 2006, in which moderate yields were obtained through additional co-oxidant together with ligand control. In this paper, based on temperature

effect, a facile protocol for controllable syntheses of **1** and **2** has been developed under ligand-free reaction conditions with CuBr as catalyst (Scheme 1). A wide scope of substrates and tolerance of sensitive building blocks illustrate the potential applications of this method in the design and synthesis of bioactive molecules.

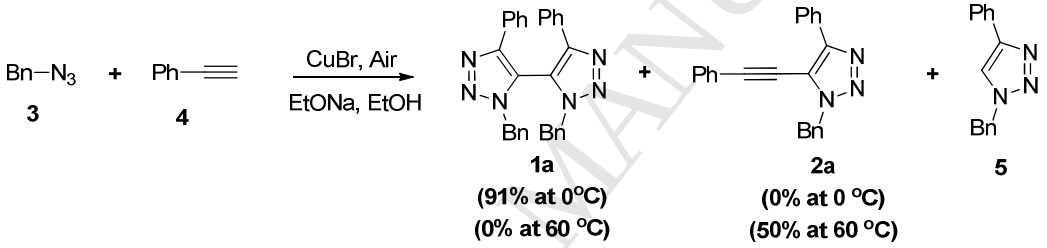


Scheme 1. Temperature-regulated approaches for the preparation of bis(1,2,3-triazole)s **1** and 5-alkynyl-1,2,3-triazoles **2** from alkynes and azides.

2. Results and discussion

Temperature effect was accidently found during working on derivatization of 1,2,3-triazole in drug design.[3d, 9b,c] Under dry air, benzyl azide (**3a**, 0.16mmol) and phenylacetylene (**4a**, 0.17 mmol) were added to a mixture of CuBr (0.016 mmol) and NaOEt (0.32 mmol) in EtOH to immediately generate a yellow suspension. The mixture was stirred at 0 ^{o}C for 20 hours, all of the insoluble materials disappeared to produce a light brown solution, and the staring material was completely comsumed by TLC detection. The structure of product was determined by ^{1}HNMR and LC-MS. Unexpectedly, instead of click product **5**, bis(1,2,3-triazole)s **1a** was obtained in 91% yield, which is much higher than 34% that was reported by Angell *et al* in 2009. More interestingly, when the reaction temperature increased to 60 ^{o}C, no **1a** could be

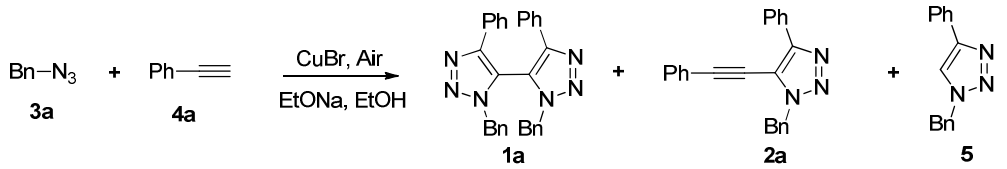
detected. Instead, 5-alkynyl-1,2,3-triazole **2a** became the major product with 50% yield slightly higher than click product **5a** (41%) (Scheme 2). When the amount of alkyne was increased to 2.5 equiv. of azide, 65% yield of **2a** can be obtained. Considering the same catalytic system and reactants, the reaction temperature might play a role in regulation of the distributions of 1,2,3-triazole derivatives in oxidative CuAAC reaction. Thus, we considered to develop a convenient synthetic protocol for the controllable preparation of **1a** and **2a** from alkyne and azide through optimization of the reaction temperature and other reaction conditions.



Scheme 2. CuAAC reaction products under different temperature conditions.

Initially, the temperature effect on the three products **1a**, **2a** and **5** was investigated systemically under 0°C, 10 °C, 20 °C, 30°C, 40 °C, 50 °C, 60 °C and 70 °C with 10 mol% CuBr as catalyst, NaOEt as base, and EtOH as solvent. From the reaults in Table 1, it could be concluded that **1a** increased with the decrease of reaction temperature, at the same time, **2a** gradually increased with the increase of reaction temperature. An exception was Entry 9, in which 55% yield of **2a** was obtained at 70 °C less than 65% at 60 °C. Thus, 60 °C was chosen as the best temperature in the following optimization of reaction conditons for the preparation of **2a**.

Table 1. Effect of temperature on the products of oxidative CuAAC reaction.

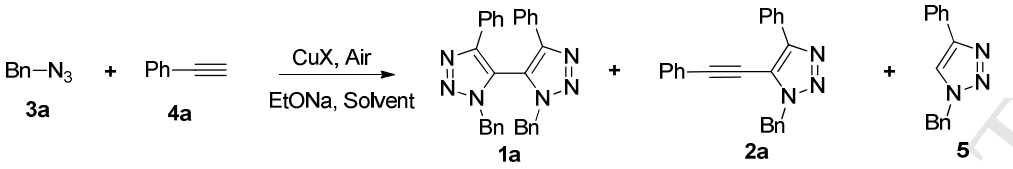


Entry [a]	Temperature (°C)	Isolated yield (%)		
		1a	**2a**	**5**
1	**0**	**91**	**0**	5
2	10	85	0	10
3	20	70	7	18
4	30	50	10	32
5	40	21	18	55
6	50	10	35	50
7	60	0	50	41
8 [b]	**60**	**0**	**65**	31
9 [b]	70	0	55	42

[a] Reaction conditions: azide **3a** (0.16 mmol), alkyne **4a** (0.17mmol), CuBr (0.016 mmol), NaOEt (0.32 mmol) in 1.5 mL EtOH under dry air atmosphere for 20 h. [b] 0.40 mmol alkyne **4a** was used.

The effect of copper salts on the products of CuAAC reaction was then investigated (Entry 1-3 in Table 2) by taking the reaction of **3a** and **4a** as an example. Among three copper (I) salts, CuBr was the most effective catalyst for the preparation of bis(1,2,3-triazole)s **1a** and alkynyl-1,2,3-triazole **2a**. CuI showed the best catalytic activation for the preparation of 1,2,3-triazole **5**. The solvent effect on the prodcuts of CuAAC reaction was also investigated in the presence of 10 mol% CuBr as catalyst (Entry 4-11 in Table 2) at 0°C and 60°C respectively. For **1a**, protic solvents such as ethanol and methanol showed better results (91% and 83%) than aprotic solvents CH_3CN and THF (42% and 38%) at 0 °C. In pure water, none of the three products could be obtained with total recovery of starting materials. The investigation of solvent effect on **2a** was carried out under 60 °C. In CH_3CN, 61% yield of **2a** was obtained with 33% **5**. In EtOH, 68% yield of **2a** were obtained with 31% **5**.

Table 2 Effect of copper salt and solvent on the products of oxidative CuAAC reaction.



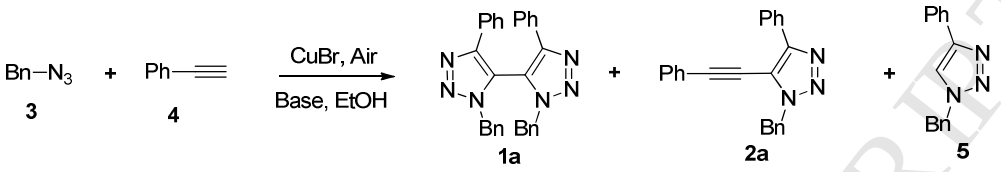
Entry [a]	Temperature (^{o}C)	Solvent	Catalyst	Isolated yield		
				1a	**2a**	**5**
1	25	THF	CuI	18	0	75
2	25	THF	CuBr	38	10	30
3	25	THF	CuCl	5	5	5
4	0	CH_2Cl_2	CuBr	35	5	15
5	0	CH_3CN	CuBr	42	5	22
6	0	EtOH	CuBr	91	0	5
7	0	MeOH [b]	CuBr	83	0	14
8	0	H_2O [c]	CuBr	NR	NR	NR
9 [d]	60	EtOH	CuBr	0	65	31
10 [d]	60	THF [c]	CuBr	0	58	35
11 [d]	60	CH_3CN [c]	CuBr	0	61	33

[a] Reaction conditions: azide **3a** (0.16 mmol), alkyne **4a** (0.17mmol), catalyst (0.016 mmol), NaOEt (0.32 mmol) in 1.5 mL solvent under dry air atmosphere for 20 h. [b] NaOMe (0.32 mmol) was used as base. [c] NaOH (0.32 mmol) was used as base. [d] 0.40 mmol alkyne **4a** was used.

The effect of base on the product of CuAAC reaction was studied by taking the reaction of **1a** and **2a** as a model in the presence of 10 mol% CuBr in EtOH at 0 ^{o}C and 60 ^{o}C respectively (Table 3). Angell *et al.* reported the effect of bases on the yield of bis(1,2,3-triazole)s [13]. Here we found that the strong base showed an effective promotion on the yield of **1a** at 0 ^{o}C, but the effect of base was negligible at higher reaction temperature. Using strong base NaOEt, 91% yield of **1a** was obtained at 0 ^{o}C. However, for the same reaction, if the reaction temperature increased to 60 ^{o}C, no **1a** could be detected, and in this case, **2a** became major product. Thus, the reaction temperature should take a more prominent role in the regulation of product

distribution of oxidative CuAAC reaction. Additionally, NaOH was found as the best base for the preparation of **5a** at 60 ^{o}C with 77% yield.

Table 3 Effect of base on the products of oxidative CuAAC reaction.

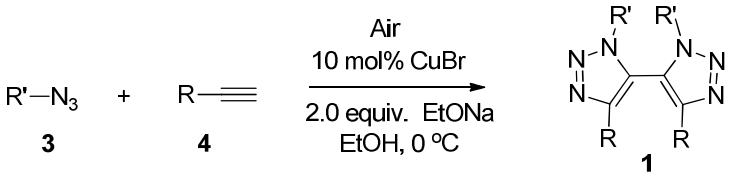


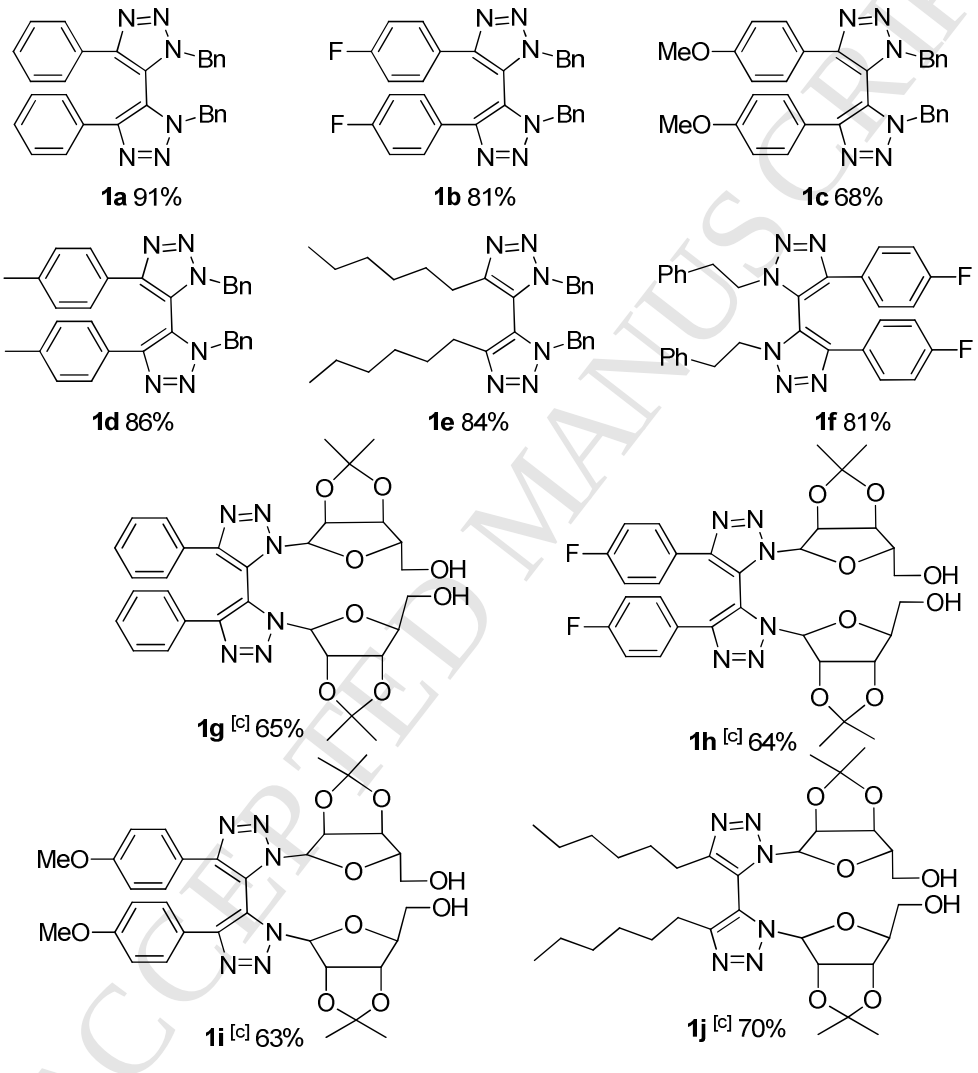
Entry [a]	Temprature (^{o}C)	Base	Isolated yield		
			1a	**2a**	**5**
1	0	K_2CO_3	62	15	17
2	0	Cs_2CO_3	55	30	10
3	0	KOH	35	10	35
4	0	NaOEt	91	0	5
5[b]	60	K_2CO_3	7	40	41
6[b]	60	Cs_2CO_3	0	44	43
7[b]	60	KOH	0	77	21
10[b]	60	NaOEt	0	65	31

[a] Reaction conditions: azide **3a** (0.16 mmol), alkyne **4a** (0.17 mmol), CuBr (0.016 mmol), Base (0.32 mmol) in 1.5 mL EtOH under dry air atmosphere for 20 h. [b] 0.40 mmol alkyne **4a** was used.

The scope of the reaction of terminal alkynes with azides for the preparation of **1** was investigated in the presence of 10 mol% CuBr, 0.2 equiv. NaOEt in EtOH under 0 ^{o}C (Table 4). Aromatic alkynes with both of electron-withdrawing and electron-donating groups reacted smoothly with azide **3a** to produce **1a-1d** with yields of 68%-91%. Aliphatic alkyne reacted with **3a** to produce compound **1e** with 84% yield. Phenethyl azide also reacted well with terminal alkyne to produce **1f** with 81% yield. Moreover, this method was applied for the syntheses of bis(1,2,3-triazole)s nucleoside derivatives. The ribosyl azide reacted with aromatic and aliphatic alkynes to give nucleoside analogues **1g-1j** with 61-70% yields.

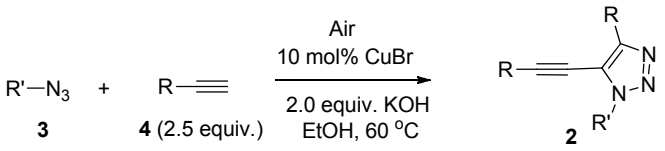
Table 4. The scope of the preparation of bis(1,2,3-triazole)s [a,b].

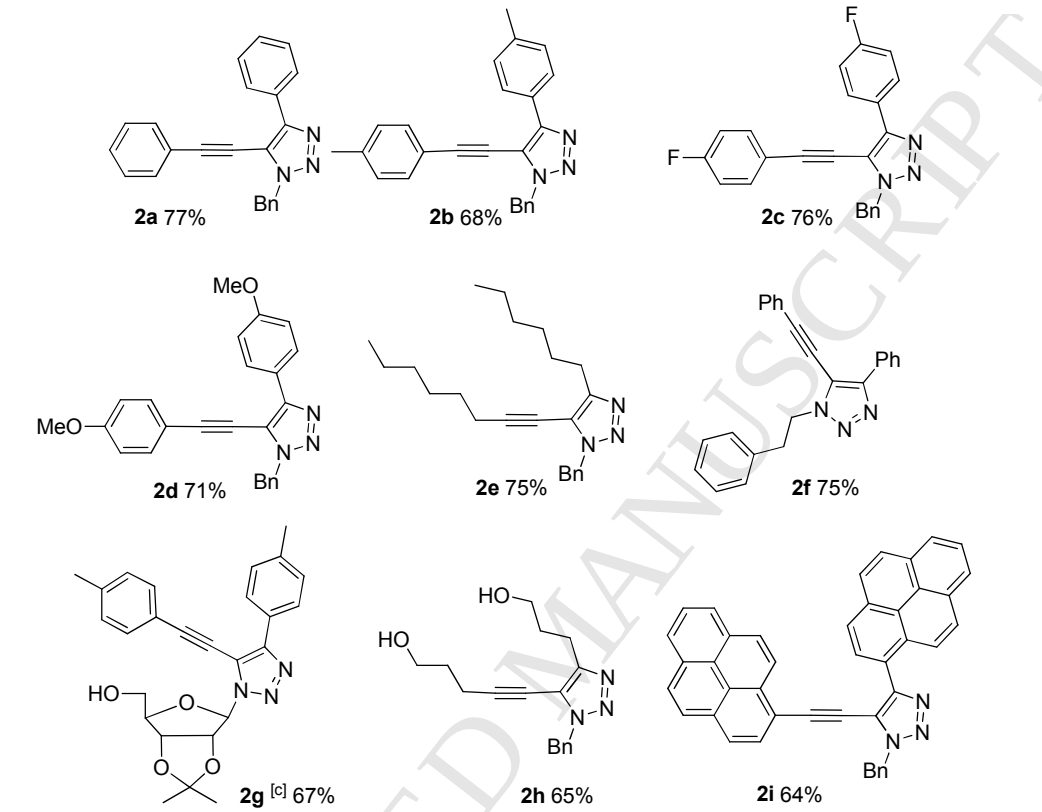




[a] Reaction conditions: azide **3** (0.16 mmol), alkyne **4** (0.17mmol), CuBr (0.016 mmol), NaOEt (0.32 mmol) in 1.5 mL EtOH under dry air atmosphere at 0 °C for 20 h.[b] Isolated yields.[c] Reaction time was 48 h.

Table 5. The scope of the preparation of 5-alkynyl-1,2,3-triazoles [a,b].

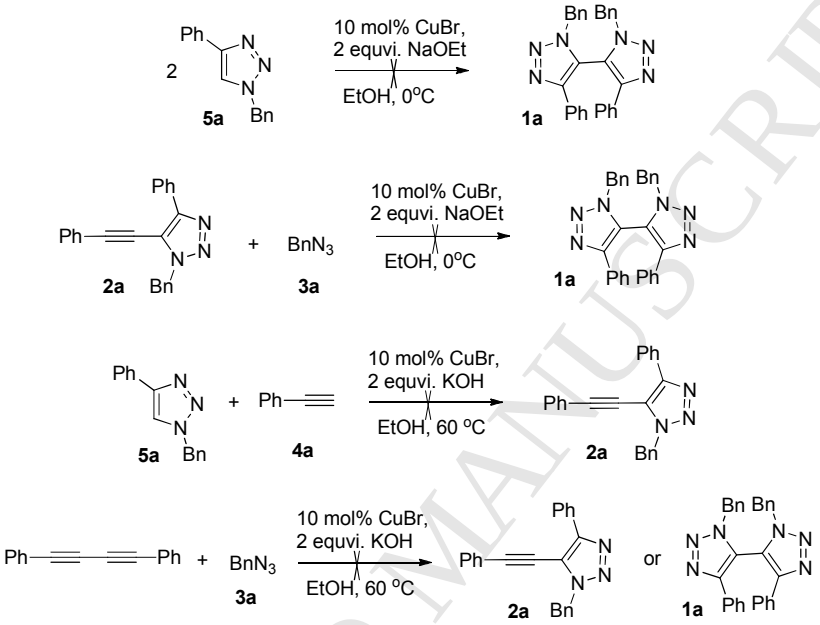




[a] Reaction conditions: azide **3** (0.16 mmol), alkyne **4** (0.4 mmol), CuBr (0.016 mmol), KOH (0.32 mmol) in 1.5 mL EtOH under dry air atmosphere at 60 °C for 20 h.[b] Isolated yields. [c] Reaction time was 20 h with NaOEt as base.

The scope of our method for the preparation of 5-alkynyl-1,2,3-triazole **2** was investigatd in the presence of 10 mol% CuBr, 0.2 equiv. KOH in EtOH under 60 °C as shown in Table 5. Aromatic alkynes with electron-withdrawing and electron-donating substituent groups both reacted smoothly with **1a** to produce **2a-2d** with high yields (68%-77%). Reactions of aliphatic alkynes 1-octyne and pent-4-yn-1-ol with **3a** produced compounds **2e, 2h** with yields of 75%, and 65%, respectively. Phenethyl azide reacted smoothly with terminal alkyne **4a** to produc **2f**

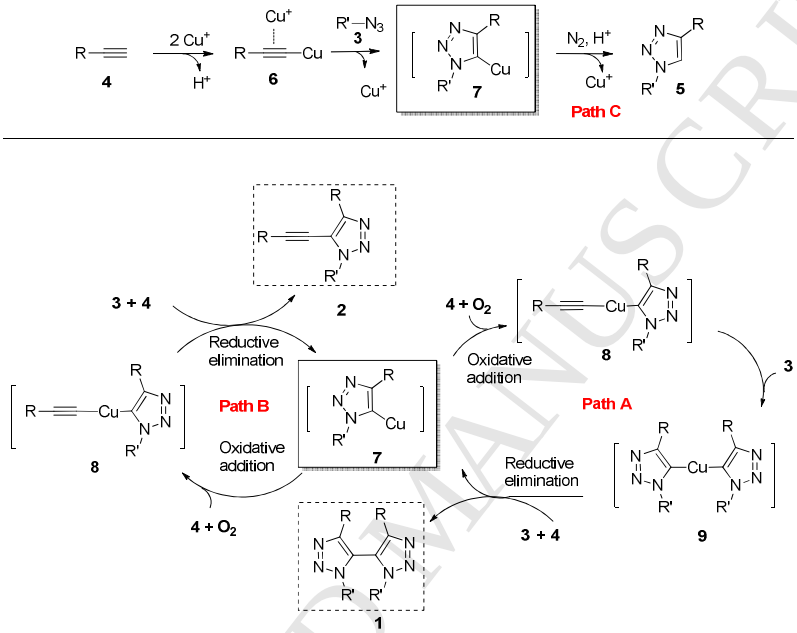
with 75% yield. Ribosyl azide donor was also used for the preparation of **2**, and a triazole nucleoside **2g** was obtained with 61% yield under the present condition. For the more bulky 1-ethynylpyrene, the 64% yield of **2i** was obtained.



Scheme 3. The control experiments.

To elucidate the mechanism, some control experiments were carried out (Scheme 3). Under the current reaction conditions, **5a** could not react by self-coupling to **1a**, and **2a** could not react with azide **3a** to form **1a**, which ruled out the possibilities of the formation of **1a** via **5a** or **2a** as intermediates. **5a** could not react with alkyne **4a** to form **1a**, which ruled out the possibility of the formation of **2a** via **5a** as intermediate. Moreover, the 1,4-diphenyl-diyne could not react with azide **3a** to form either **2a** or **1a**, which ruled out the possibility of formation of **2a** and **1a** via cycloaddition of Glaser coupling product 1,3-diyne. These control experiments indicated that the cycloaddition step should take place before the oxidative coupling step. Additionally,

when air was replaced by nitrogen atomsphere in the reaction of **3a** and **4a** , product **1a** and **2a** could not be detected, instead, **5a** was obtained in 92% yield. Thus the formtion of 1,2,3-triazolyl-copper intermediate during this reaction proceedure should be resonable.



Scheme 4. The possible reaction mechanism.

On the basis of these preliminary results, a possible mechanism of the temperature-regulated oxidative CuAAC reaction was proposed (Scheme 4). The current reaction might proceed through a tandem aerobic oxidative coupling reaction of the triazolyl-copper complex intermediate **7** that was produced by CuAAC reaction[19]. At 0 ^{o}C, the aerobic oxidative coupling reaction could take place preferentially by Path A to produce **1**. While at 60 ^{o}C, the aerobic oxidative coupling reaction could take place preferentially by Path B to produce **2**. When the nitrogen atomphere was used for this reaction, the oxidative coupling reaction was supressed, and then the trapping proton on the intermediate **7** was prevailing to give **5** by Path C.

A possible reason for this temperature-guided product distribution could be the effect of temperature on the reactivity of triazolyl-copper complex **7** and **8**. However, the details of aerobic oxidative coupling machanism on complex **7** such as triazolyl Cu-O_2 intermediates are not clear at present. [20]

3. Conclusion

In conclusion, an effective controllable synthetic protocol has been developed for the preparation of bis(1,2,3-triazole)s and 5-alkynyl-1,2,3-triazole at 0 ^{o}C and 60 ^{o}C respectively. Various azides and alkynes can be used as the substrates for these reactions, and the successful applications in syntheses of nucleoside analogues manifest the values of this method in the design and synthesis of bioactive molecules. Besides, a possible temperature-guided copper-catalyzed aerobic oxidative coupling reaction mechanism is proposed, which provides an interesting example for the development of temperature-guided synthetic protocol for other copper-catalyzed coupling reactions. Further investigations to the reaction mechanism and application of this oxidative CuAAC coupling reaction in functionalized 1,2,3-triazole derivatives are still ongoing in our lab.

4. Experimental section

General

Solvents were dried by refluxing for at least 12 h over CaH_2 (CH_2Cl_2 and CH_3CN), sodium/benzophenone (THF), and freshly distilled prior to use. All reactions were carried out under anhydrous conditions with freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) on

silica gel GF254 precoated on plates. Spots were detected under UV light and/or by charring with phosphomolybdic acid in ethanol solution. Solvents were evaporated under reduced pressure and below 50 °C (water bath). High-resolution mass spectra (HRMS) analyses were carried out using electrospray ionization time-of-flight mass spectrometry (ESI-TOF/MS). ^{1}H NMR and ^{13}C NMR data were recorded with a Avance 400/DPX (Bruker) spectrometer from $CDCl_3$ solutions using the residual solvent signal or TMS as reference. Chemical shifts are reported in parts per million. All chemical shift values are quoted in ppm and coupling constants quoted in Hz.

Representative Procedure for the Preparation of compound 1a-j

Azide (0.16 mmol), alkyne (0.17mmol), and CuBr (2.3mg, 0.016mmol) were added into 1.5 ml fresh ethanol solution of NaOEt (14.5mg, 0.64 mmol) under dry air atmosphere at 0 ^{o}C. The reaction mixture was stirred for 20 hours at 0 ^{o}C, then the solvent was evaporated, and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NH_4Cl solution and H_2O, then dried over anhydrous Na_2SO_4 and evaporated. The residue was further purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give compound **1**.

Compound 1a Isolated yield 33 mg (91%) as white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 4 H, J = 8 Hz), 7.24-7.07 (m, 12 H), 6.79 (d, 4 H, J = 7 Hz), 4.68 (d, 2 H, J = 15 Hz), 4.62 (d, 2 H, J = 15 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 132.0, 128.4, 128.1, 127.92, 127.87, 127.82, 127.3, 124.9, 119.0, 51.8. HRMS (ESI-TOF) *m/z* calculate for ($M+H^+$) $C_{30}H_{25}N_6^+$ 469.2135, Found: 469.2196.

Compound 1b Isolated yield 32.5 mg (81%) as white amorphous solid; ^{1}H NMR ($CDCl_3$) δ 7.35-7.31 (m, 4 H), 7.17-7.07 (m, 6 H), 6.87-6.80 (m, 8 H), 4.75 (d, 2 H, J = 15 Hz) ,4.62 (d, 2 H, J = 15 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 160.8, 146.2, 131.9, 127.9, 127.2, 126.7, 126.6, 124.42, 124.39, 118.4, 115.2, 115.0, 51.9. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{30}H_{23}F_2N_6^+$ 505.1947, Found: 505.1903.

Compound 1c Isolated yield 28 mg (68%) as white amorphous solid; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 4 H, J =8 Hz), 7.15-7.05 (m, 6 H), 6.80 (d, 4 H, J = 8 Hz), 6.71 (d, 4 H, J = 8 Hz), 4.67 (d, 2 H, J = 15 Hz), 4.61 (d, 2 H, J = 15 Hz), 3.74 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 146.8, 132.2, 127.8, 127.7, 127.3, 126.3, 121.0 , 118.2, 113.5, 54.3, 51.7. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{32}H_{29}N_6O_2^+$ 529.2347, Found: 529.2373.

Compound 1d Isolated yield 34 mg (86%) as white amorphous solid; ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.32 (d, 4 H, J = 8 Hz), 7.13-6.99 (m, 10 H), 6.77 (d, 4 H, J = 8 Hz), 4.68 (d, 2 H, J = 15 Hz), 4.57 (d, 2 H, J = 15 Hz), 2.29 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147. 0, 137.9, 132.2, 128.8, 127.8, 127.6, 127.3, 125.6, 124.9, 118.7, 51.7, 20.3. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{32}H_{29}N_6^+$ 497.2448, Found: 497.2481.

Compound 1e Isolated yield 33 mg (84%) as white amorphous solid; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.26-7.25 (m, 6 H), 6.88-6.86 (m, 4 H), 4.89 (d, 2 H, J = 15 Hz), 5.56 (d, 2 H, J = 15 Hz), 2.11-2.03 (m, 2 H), 1.95-1.87 (m, 2 H), 1.43-1.33 (m, 4 H), 1.21-1.11 (m, 12 H), 084-0.80 (t, 6 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

149.4, 133.2, 128.1, 127.8, 126.8, 119.3, 51.5, 30.5, 28.2, 27.7, 24.0, 21.6, 13.1. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{30}H_{41}N_6^+$ 485.3387, Found: 485.3401.

Compound 1f Isolated yield 43 mg (81%) as white amorphous solid; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.52-7.48 (m, 4 H), 7.15-7.01 (m, 10 H), 6.81 (d, 4 H, J = 6.8 Hz), 3.76-3.72 (m, 4 H), 3.09-3.01 (m, 2 H), 2.75-2.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 161.0, 145.3, 135.4, 127.9, 127.6, 127.0, 126.9, 126.2, 124.6, 119.0, 115.6, 115.4, 48.7, 34.5. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{32}H_{27}F_2N_6^+$ 533.2260, Found: 533.2252.

Compound 1g Isolated yield 32 mg (65%) as white gum; The product as a mixture of two isomers(the ratio is 2:1)^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.60-7.53 (m, 6 H), 7.38-7.33 (m, 9 H), 5.71 (d, 1 H, J = 2 Hz), 5.52 (d, 2 H, J = 1 Hz), 5.41-5.39 (m, 2 H), 5.18-5.16 (m, 1 H), 4.88-4.87 (m, 2 H), 4.71-4.68 (m, 1 H), 4.38-4.37 (m, 2 H), 4.25-4.24 (m, 1 H), 3.72-3.63 (m, 3 H), 3.50-3.43 (m, 3 H), 3.21 (t, 2 H, J = 6 Hz), 2.84 (t, 1 H, J = 7 Hz), 1.30-1.22 (m, 18 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.2, 128.7, 128.6, 128.4, 128.3, 127.8, 127.5, 125.41, 125.35, 119.1, 118.6, 113.5, 112.7, 92.5, 91.2, 89.2, 87.5, 83.9, 83.3, 80.3, 62.4, 62.2, 25.9, 25.8, 24.1, 23.9. HRMS (ESI) *m/z* calculate for ($M+Na^+$) $C_{32}H_{36}N_6NaO_8^+$ 655.2487, Found: 655.2499.

Compound 1h Isolated yield 34 mg (64%) as white gum; The product as a mixture of two isomers (the ratio is 1:3) ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.53-7.47 (m, 5 H), 7.05-6.98 (m, 5 H), 5.65 (d, 0.7 H, J = 2 Hz), 5.46 (s, 2 H), 5.34 (d, 2 H, J = 6 Hz), 5.18-5.17 (m, 0.7 H), 4.85 (d, 2 H, J = 6 Hz), 4.76-4.75 (m, 0.7 H), 4.36-4.34 (m, 2 H), 4.27 (d, 0.7 H, J = 2 Hz), 3.71-3.67 (m, 2.7 H), 3.50-3.49 (m, 2.7 H), 3.11(s, 2 H),

2.85 (s, 0.7 H), 1.29-1.21 (m, 16 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 163.6, 161.3, 146.4, 127.34, 127.26, 123.7, 118.7, 115.8, 115.5, 115.3, 113.4, 112.8, 92.7, 91.5, 89.1, 87.7, 83.9, 83.4, 80.5, 80.4, 62.3, 62.2, 26.0, 25.8, 24.1. HRMS (ESI) *m/z* calculate for ($M+Na^+$) $C_{32}H_{34}F_2N_6NaO_8^+$ 691.2298, Found: 691.2277.

Compound 1i Isolated yield 35 mg (63%) as white gum; The product as a mixture of two isomers (the ratio is 1:2) ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.52-7.45 (m, 6 H), 6.89-6.84 (m, 6 H), 5.69 (s, 1 H), 5.53 (s, 2 H), 5.39 (d, 2 H, J = 4 Hz), 5.16 (d, 1 H, J = 4 Hz), 4.88 (d, 2 H, 8Hz), 4.72 (d, 1 H, J = 4 Hz), 4.37-4.36 (m, 2 H), 4.27-4.26 (m, 1 H), 3.78 (d, 9 H, J =12 Hz), 3.71-3.68 (m, 3 H), 3.48-3.46 (m, 3 H), 3.20 (m, 2 H), 2.95-2.91 (m, 1 H), 1.38-1.19 (m, 18 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7, 159.6, 147.3, 147.1, 126.7, 120.3, 120.0, 118.2, 117.7, 113.9, 113.7, 113.4, 112.7, 92.6, 91.0, 89.3, 87.6, 84.0, 83.3, 80.4, 80.3, 62.4, 62.3, 54.4, 26.0, 25.8, 24.2, 24.0. HRMS (ESI) *m/z* calculate for ($M+Na^+$) $C_{34}H_{40}N_6NaO10^+$ 715.2698, Found: 715.2711.

Compound 1j Isolated yield 36 mg (70%) as white gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.57 (s, 2 H), 5.48-5.46 (m, 2 H), 4.95 (d, 2 H, J = 4 Hz), 4.44 (m, 2 H), 3.76-3.74 (m, 2 H), 3.52-3.50 (m, 4 H), 2.63-2.55 (m, 2 H), 2.49-2.41 (m, 2 H), 1.62-1.57 (m, 4 H), 1.46 (s, 6H), 1.34 (s, 6 H), 1.24 (s, 12 H), 0.86-0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 119.8, 112.9, 91.5, 88.8, 83.9, 80.8, 62.5, 30.5, 28.1, 27.7, 26.0, 24.2, 24.1, 21.5, 13.1. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{32}H_{53}N_6O_8^+$ 649.3919, Found: 649.3935.

Representative Procedure for the Preparation of compound 2a-i

Azide (0.16 mmol), alkyne (0.4 mmol), CuBr (2.3 mg, 0.016 mmol), and KOH (17.7 mg, 0.32 mmol) were added to 1.5 ml ethanol at dry air atmosphere. The reaction

mixture was stirred at 60 ºC for 20 h, and then cooled to room temperature. The mixture was evaporated, and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NH_4Cl solution and H_2O, then dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by silica gel column chromatography (petroleum ether /ethyl acetate) to give compound **2**.

Compound 2a Isolated yield 37.5 mg (71%) as yellow amorphous solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, 2 H, J = 8 Hz), 7.42-7.34 (m, 7 H), 7.27-7.21 (m, 4 H), 5.66 (s, 2 H), 2.40 (d, 6H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.2, 139.2, 137.5, 133.9, 130.5, 128.52, 128.45, 127.9, 127.5, 127.2, 126.7, 125.2, 117.6, 116.2, 101.6, 74.3, 52.0. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{18}N_3^+$ 336.1495, Found: 336.1511.

Compound 2b Isolated yield 39 mg (68%) as yellow amorphous solid; ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 2 H, J = 8 Hz), 7.51-7.33 (m, 13 H), 5.68 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.2, 133.9, 130.7, 129.5, 128.9, 128.0, 127.84, 127.75, 127.6, 127.2, 125.3, 120.5, 116.4, 101.6, 74.8, 52.1. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{25}H_{22}N_3^+$ 364.1808, Found: 364.1811.

Compound 2c Isolated yield 45 mg (76%) as white amorphous solid; ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.15-8.13 (m, 2 H), 7.48-7.45 (m, 2 H), 7.37-7.34 (m, 5 H), 7.16-7.09 (m, 4 H), 5.66 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 161.2, 146.5, 133.7, 132.8, 128.0, 127.7, 127.1, 125.6, 116.5, 116.0, 115.4, 115.2, 114.9, 114.7, 100.4, 74.2, 52.2. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{16}F_2N_3^+$ 372.1307, Found: 372.1299.

Compound 2d Isolated yield 45 mg (71%) as yellow amorphous solid; ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.12 (d, 2 H, J = 8 Hz), 7.44-7.30 (m, 7 H), 6.99-6.91 (m, 4 H),5.64 (s, 2 H), 3.84 (d, 6H, J = 4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7, 158.9, 146.8, 134.0, 132.2, 127.9, 127.5, 127.2, 126.6, 122.2, 115.8, 113.4, 113.1, 112.6, 101.4, 73.7, 54.5, 54.4, 52.0. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{25}H_{22}N_3O_2^+$ 396.1707, Found: 396.1713.

Compound 2e Isolated yield 42 mg (75%) as white amorphous solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.28 (m, 5 H), 5.49 (s, 2 H), 2.68 (t, 2 H, J = 8 Hz), 2.44 (t, 2 H, J = 7 Hz), 1.73-1.66 (m, 2 H), 1.58-1.53 (m, 2 H), 1.30 (s, 12 H), 0.91-0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.3, 127.8, 127.3, 126.9, 118.3, 102.3, 65.4, 51.6, 30.6, 30.4, 28.0, 27.9, 27.6, 27.3, 24.7, 21.6, 18.7, 13.1. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{34}N_3^+$ 352.2747, Found: 352.2745.

Compound 2f Isolated yield 42 mg (75%) as white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14-8.10 (m, 2 H), 7.53-7.50 (m, 2 H), 7.30-7.22 (m, 3 H), 7.18-7.11 (m, 6 H), 4.70 (t, 2 H, J = 7 Hz), 3.32 (t, 2 H, J = 16Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.1, 136.1, 132.8, 127.9, 127.2, 127.1, 126.2, 125.6, 116.5, 116.1, 115.4, 115.2, 114.9, 114.7, 99.8, 74.0, 49.6, 35.5. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{24}H_{20}N_3^+$ 350.1652, Found: 350.1655.

Compound 2g Isolated yield 50 mg (67%) as white gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, 2 H, J = 8 Hz), 7.48 (d, 2 H, J = 8 Hz), 7.29-7.22 (m, 4 H), 6.42 (d, 1 H, J = 2 Hz), 5.36-5.34 (m, 1 H), 5.11-5.10 (m, 1 H), 4.58 (s, 1 H), 3.92-3.88 (m, 1 H), 3.77-3.68 (m, 1 H), 3.57-3.53 (m, 1H), 3.41(d, 6 H, J = 4 Hz), 1.64(s, 3 H), 1.40 (s, 3

H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 139.5, 138.0, 130.7, 128.5, 126.0, 125.3, 117.2, 116.7, 112.7, 102.6, 92.4, 88.4, 84.9, 81.2, 72.9, 62.7, 26.2, 24.3, 20.8, 20.4. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{26}H_{27}N_3NaO_4^+$ 468.1894, Found: 468.1879.

Compound 2h Isolated yield 31 mg (65%) as white gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.23 (m, 5 H), 5.49 (s, 2 H), 3.73-3.66 (m, 4 H), 2.84-2.78 (m, 2 H), 2.61-2.58 (m, 2 H), 1.98-1.89 (m, 2 H), 1.84-1.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.0, 128.2, 127.9, 127.4, 127.1, 126.9, 102.0, 65.5, 60.9, 60.0, 51.8, 30.4, 29.8, 21.0, 15.3. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{17}H_{22}N_3O_2^+$ 300.1707, Found: 300.1721.

Compound 2i Isolated yield 60 mg (64%) as yellow amorphous solid; ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.76 (d, 1 H, J = 8 Hz), 8.53 (d, 1 H, J = 8 Hz), 8.32 (d, 1 H, J = 8 Hz), 8.26 (d, 1 H, J = 8 Hz), 8.20-8.15 (m, 5 H), 8.08-7.97 (m, 7 H), 7.83 (d, 1 H, J = 8 Hz), 7.62 (d, 2 H, J = 8 Hz), 7.49-7.40 (m, 4 H),5.97 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ141.9, 134.0, 131.2, 131.1, 131.0, 130.5, 130.2, 129.8, 128.5, 128.3, 128.2, 128.0, 127.7, 127.2, 127.0, 126.5, 126.1, 125.5, 125.2, 125.1, 124.7, 124.5, 124.4, 124.3, 123.8, 123.5, 114.4, 52.6. HRMS (ESI) m/z calculate for ($M+H^+$) $C_{43}H_{26}N_3^+$ 584.2121, Found: 584.2137.

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Supporting Information

Controllable Synthesis of Bis(1,2,3-triazole)s and 5-Alkynyl-triazoles via Temperature Effect on Copper-catalyzed Huisgen Cycloaddition

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Structures of azide donors used in the experiment:

Compound **3c** were prepared with our previously reported methods.[1] Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification.

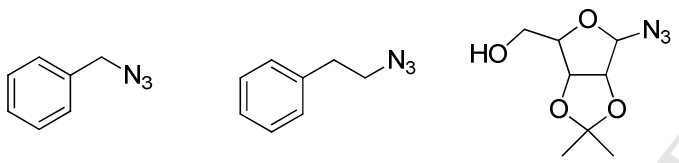

Figure 1. Organic azide compounds used in the preparation of 2,2'-bis(1,2,3-triazole)s and 2-alkynyl-1,2,3-triazoles.

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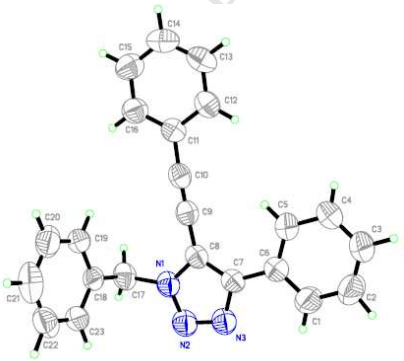
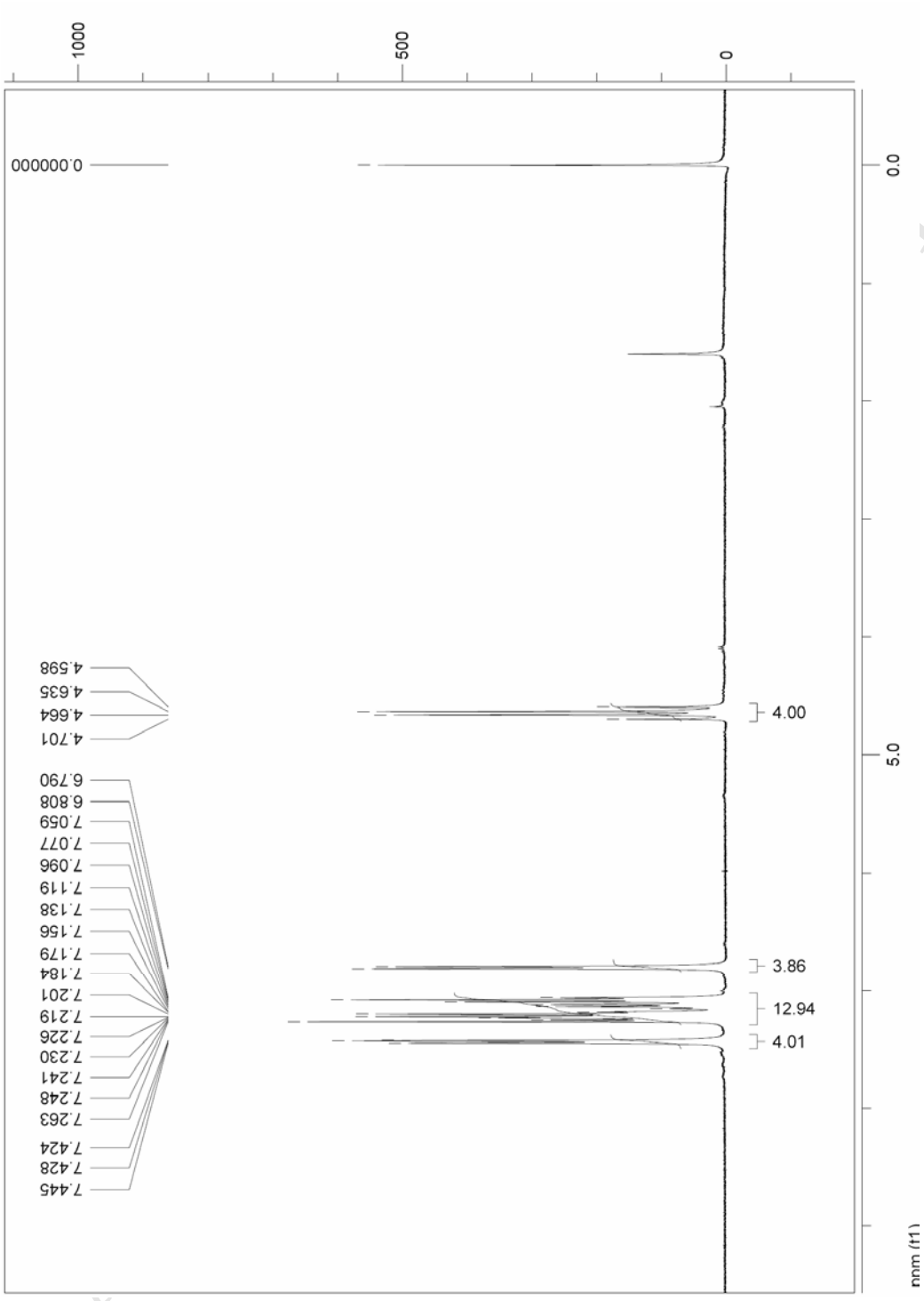


Figure 1. X-ray structure of compound **2a**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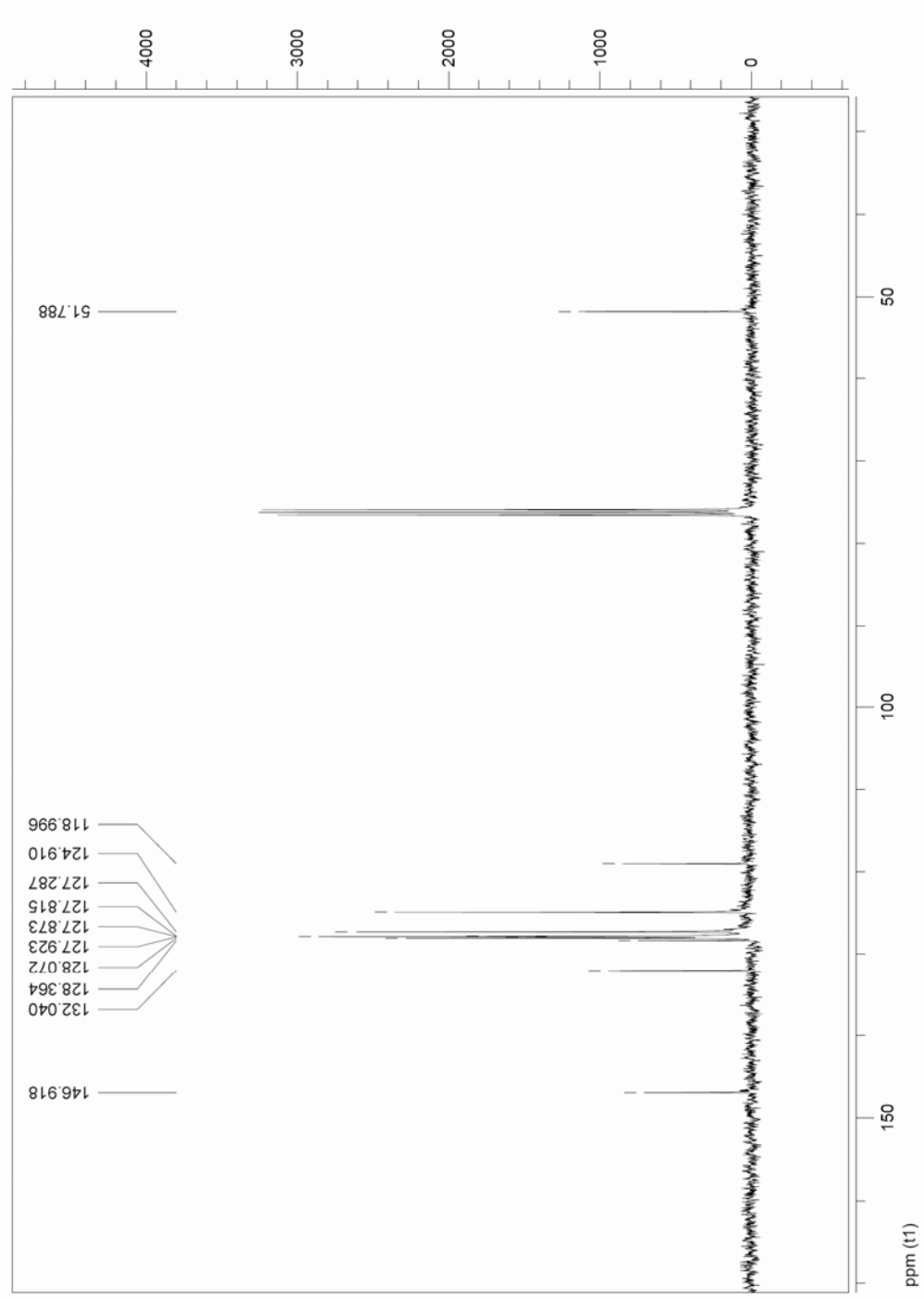
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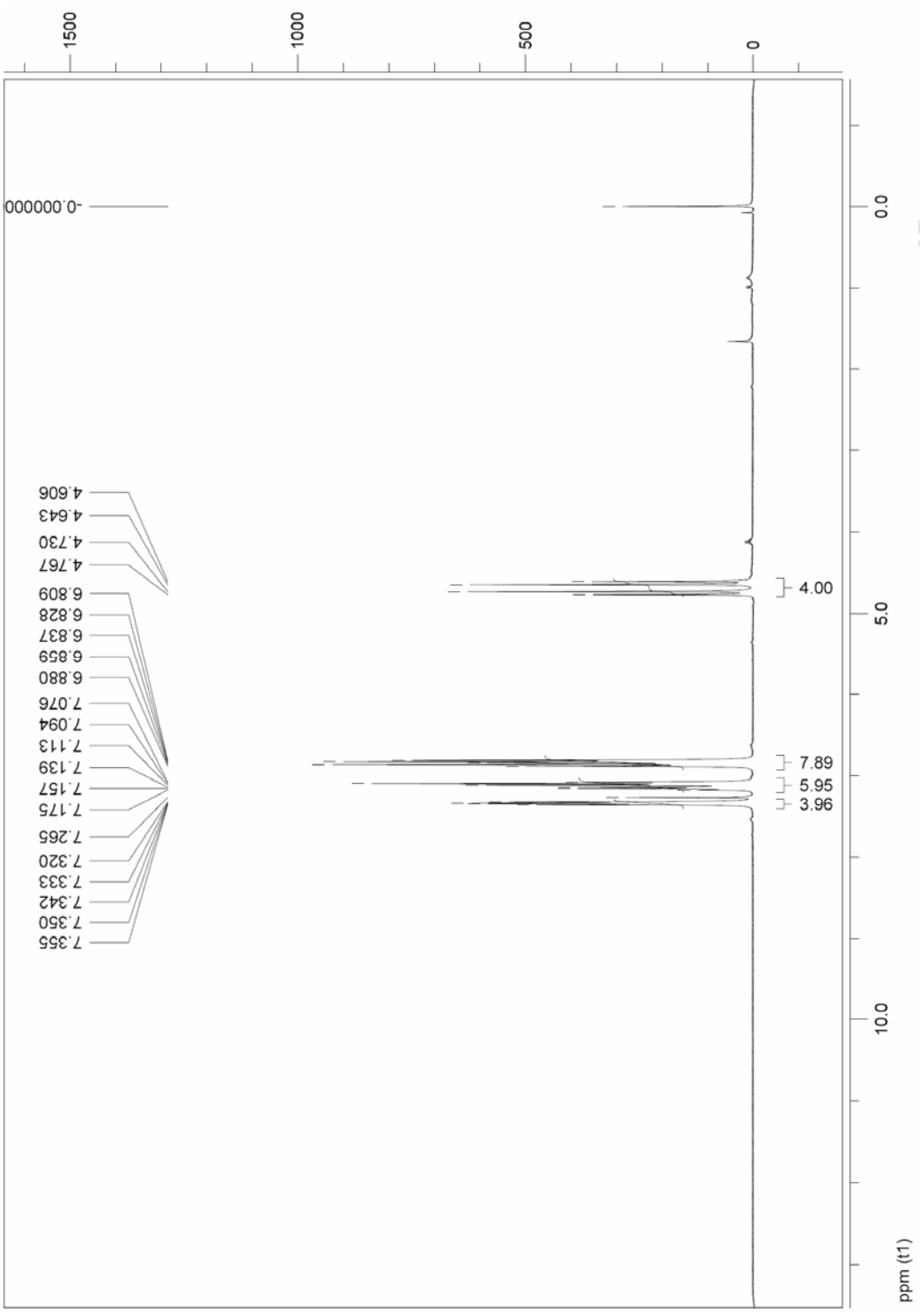
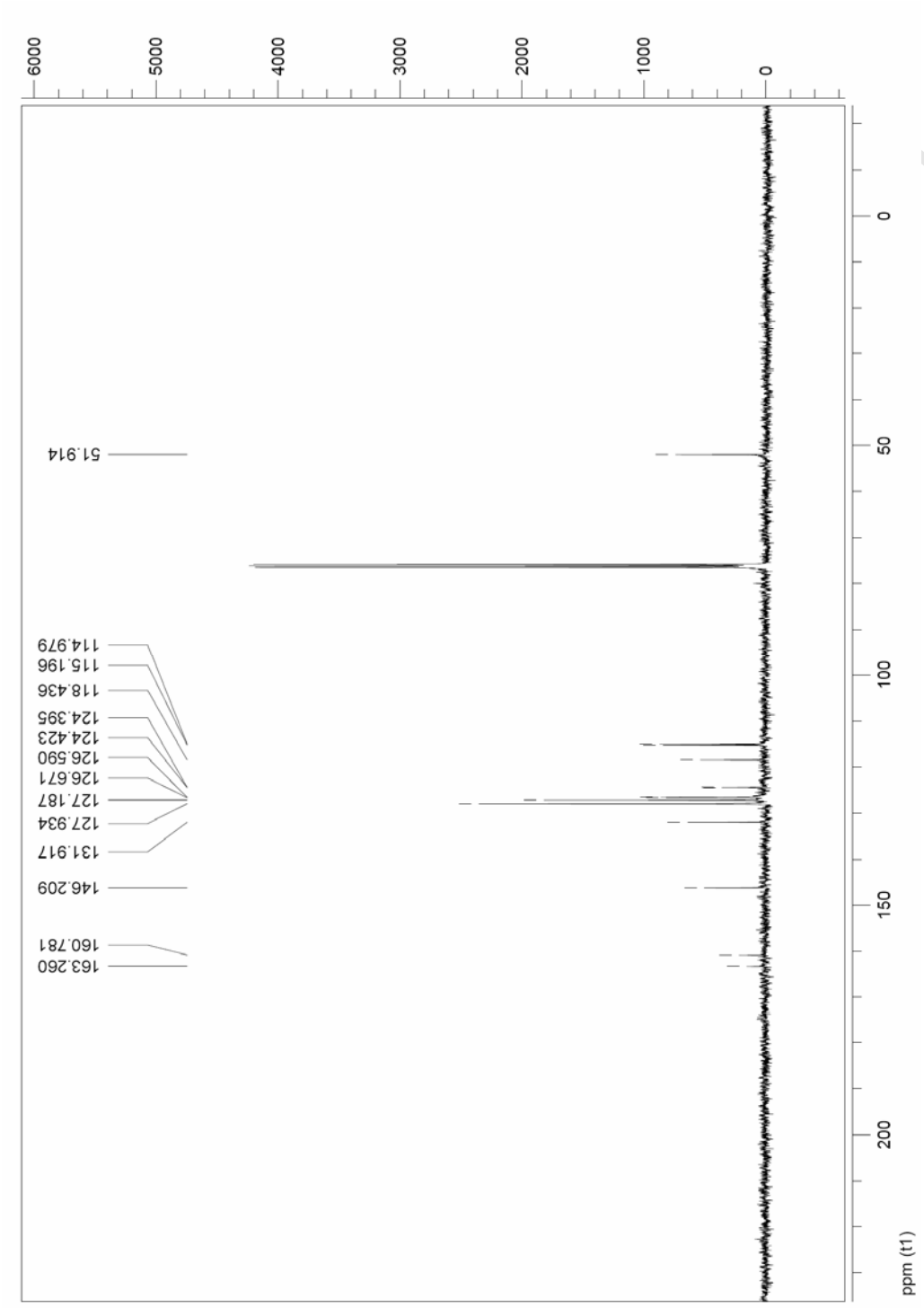
ppm (t1)

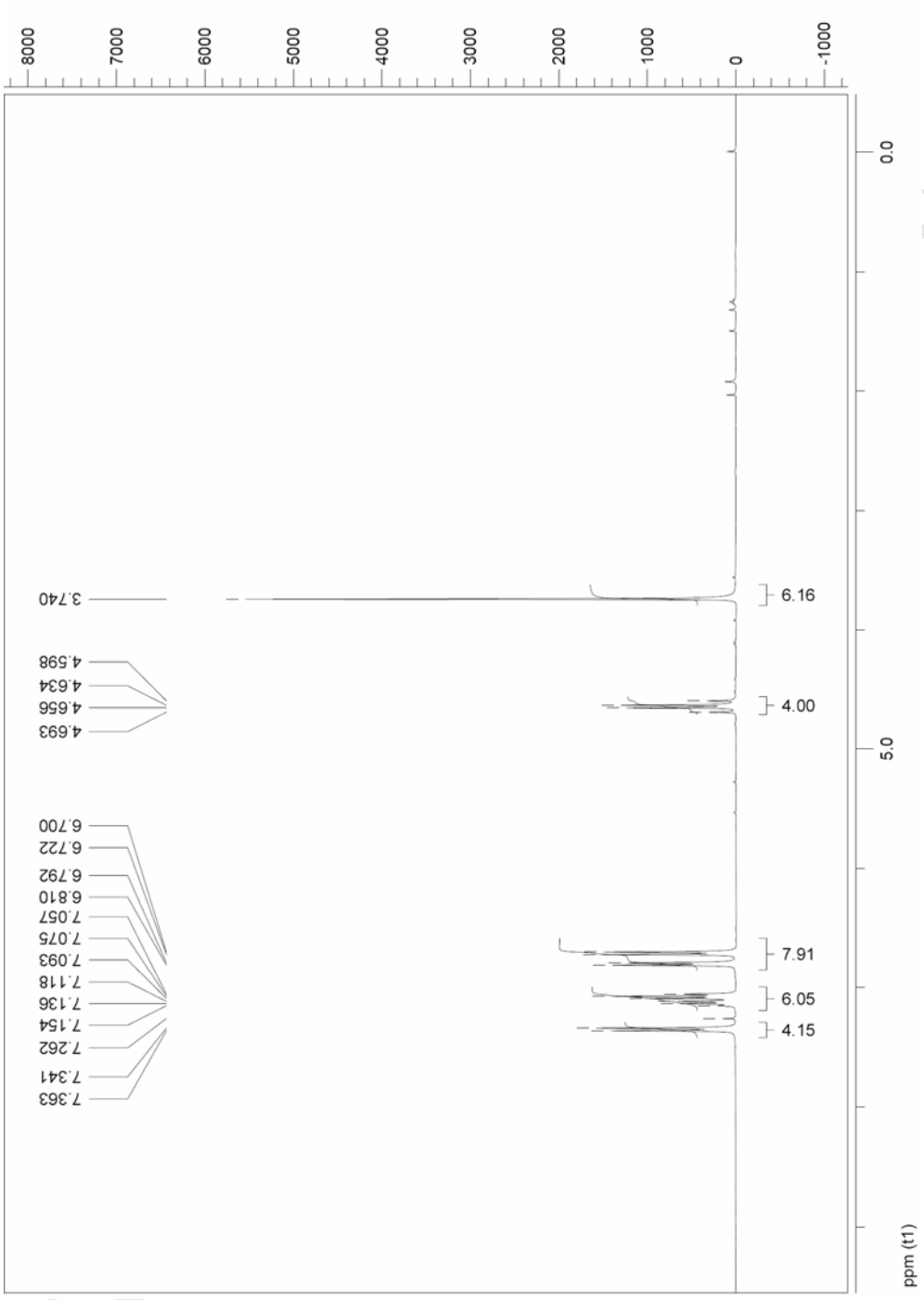
1a


1500
1000
500
0
0.000000
4.606
4.643
4.730
4.767
6.809
6.828
6.837
6.859
6.880
7.076
7.094
7.113
7.139
7.157
7.175
7.265
7.320
7.333
7.342
7.350
7.355
4.00
7.89
5.95
3.96
0.0
5.0
10.0
ppm (t1)

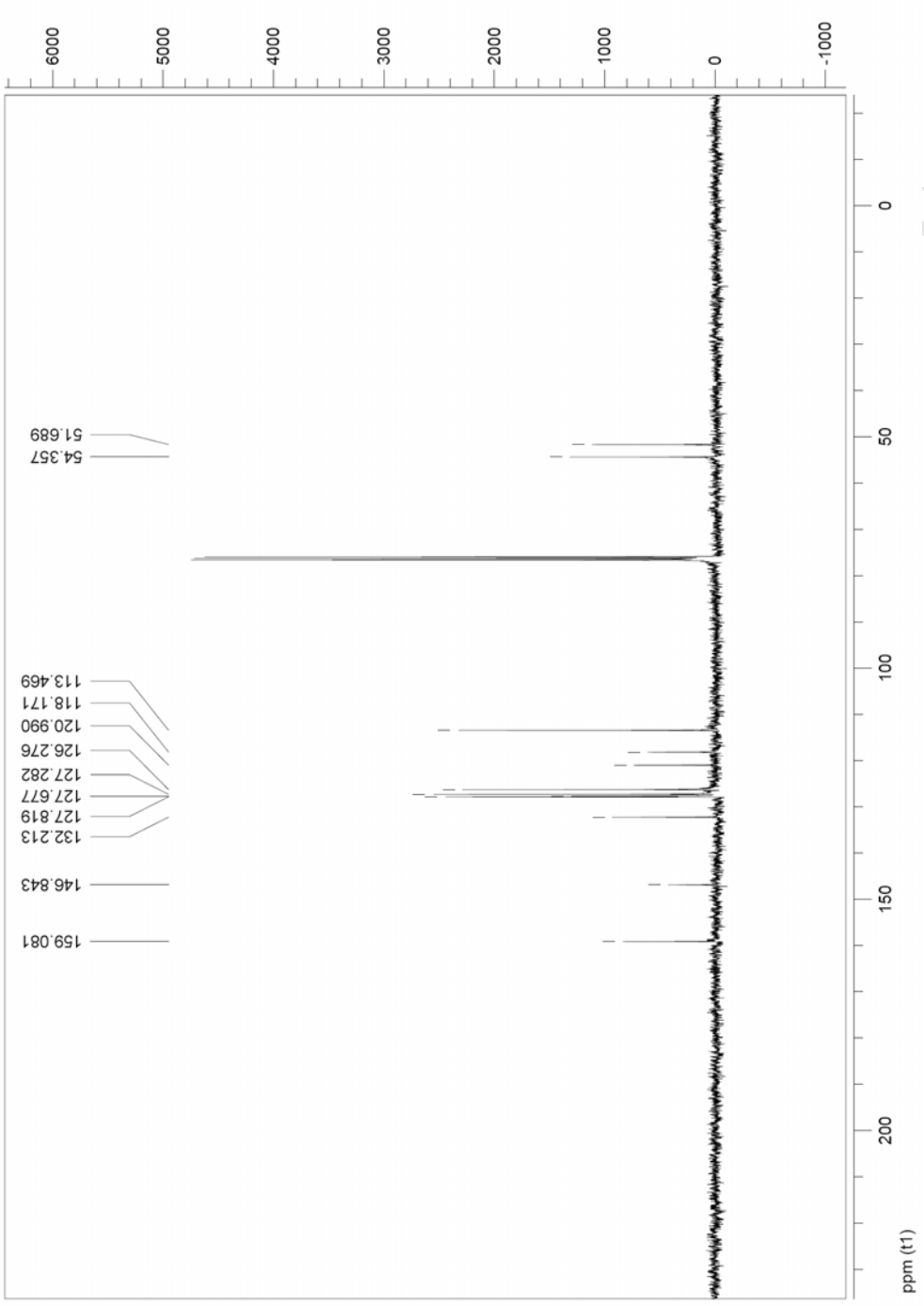
1b


6000
5000
4000
3000
2000
1000
0
51.914
114.979
115.196
118.436
124.395
124.423
126.590
126.671
127.187
127.934
131.917
146.209
160.781
163.260
0
50
100
150
200
ppm (t1)

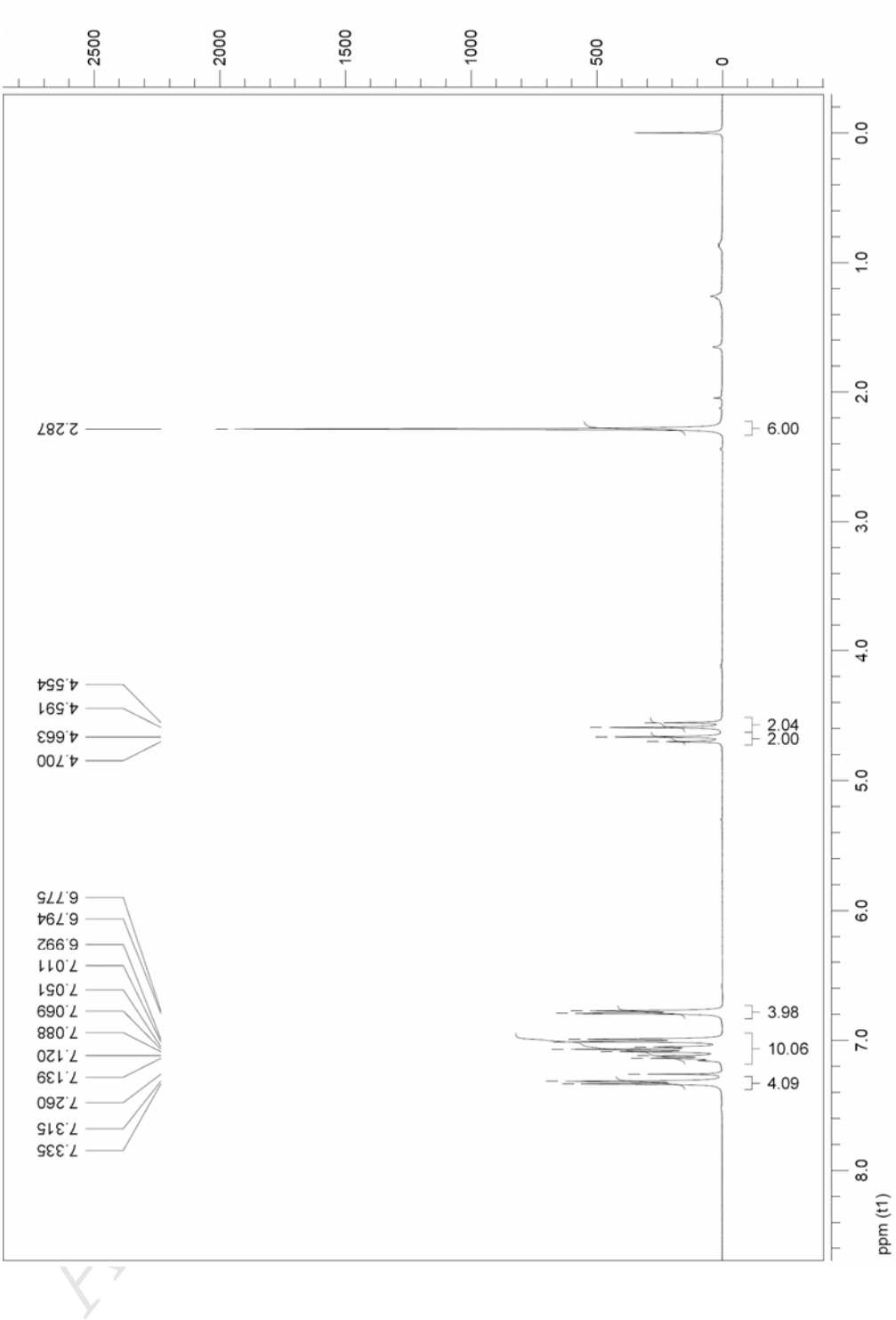
1b


8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.0
5.0
ppm (t1)
3.740
4.598
4.634
4.656
4.693
6.700
6.722
6.792
6.810
7.057
7.075
7.093
7.118
7.136
7.154
7.262
7.341
7.363
6.16
4.00
7.91
6.05
4.15

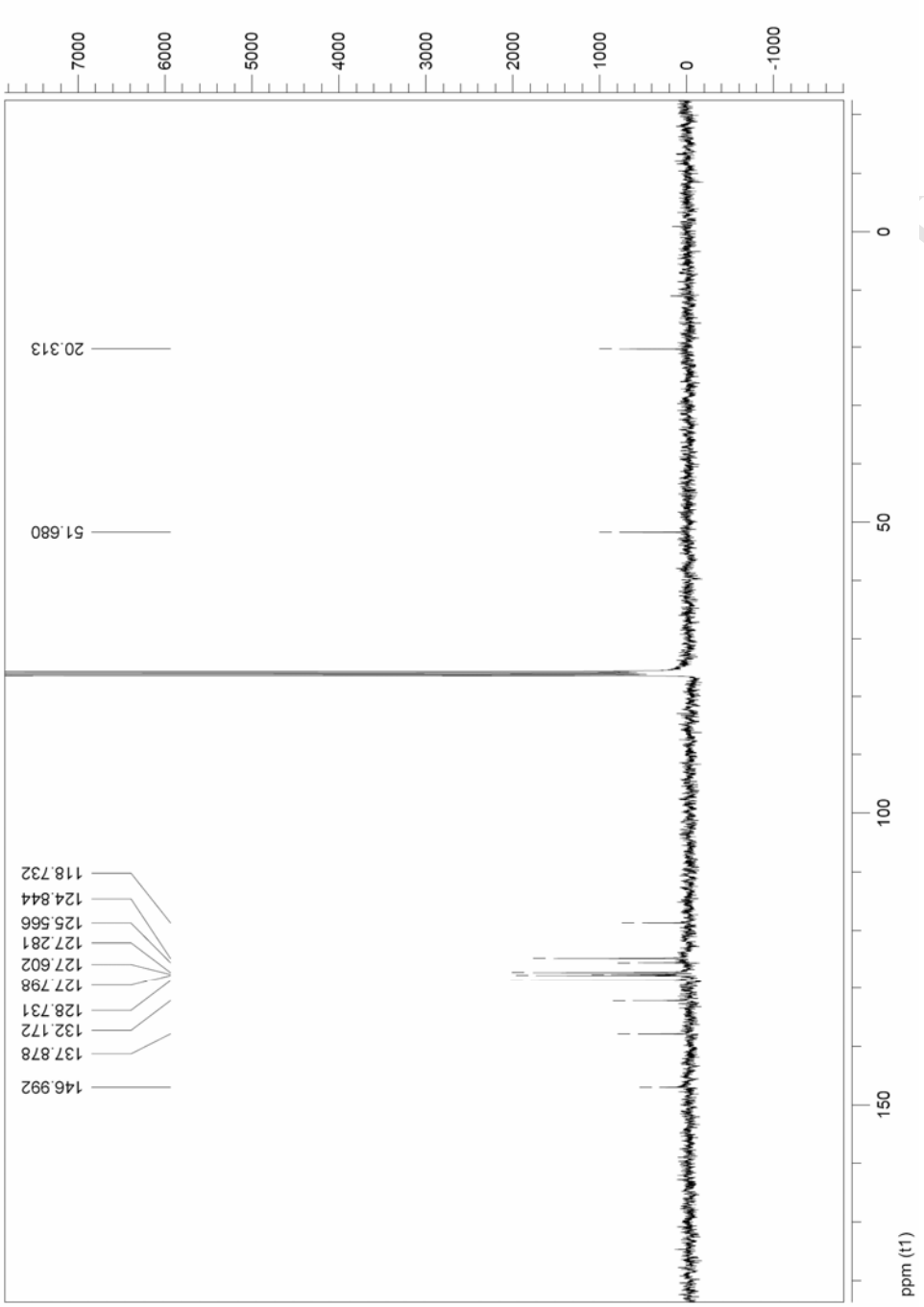
1c


6000
5000
4000
3000
2000
1000
0
-1000
0
50
100
150
200
ppm (t1)
51.689
54.357
113.469
118.171
120.990
126.276
127.282
127.677
127.819
132.213
146.843
159.081

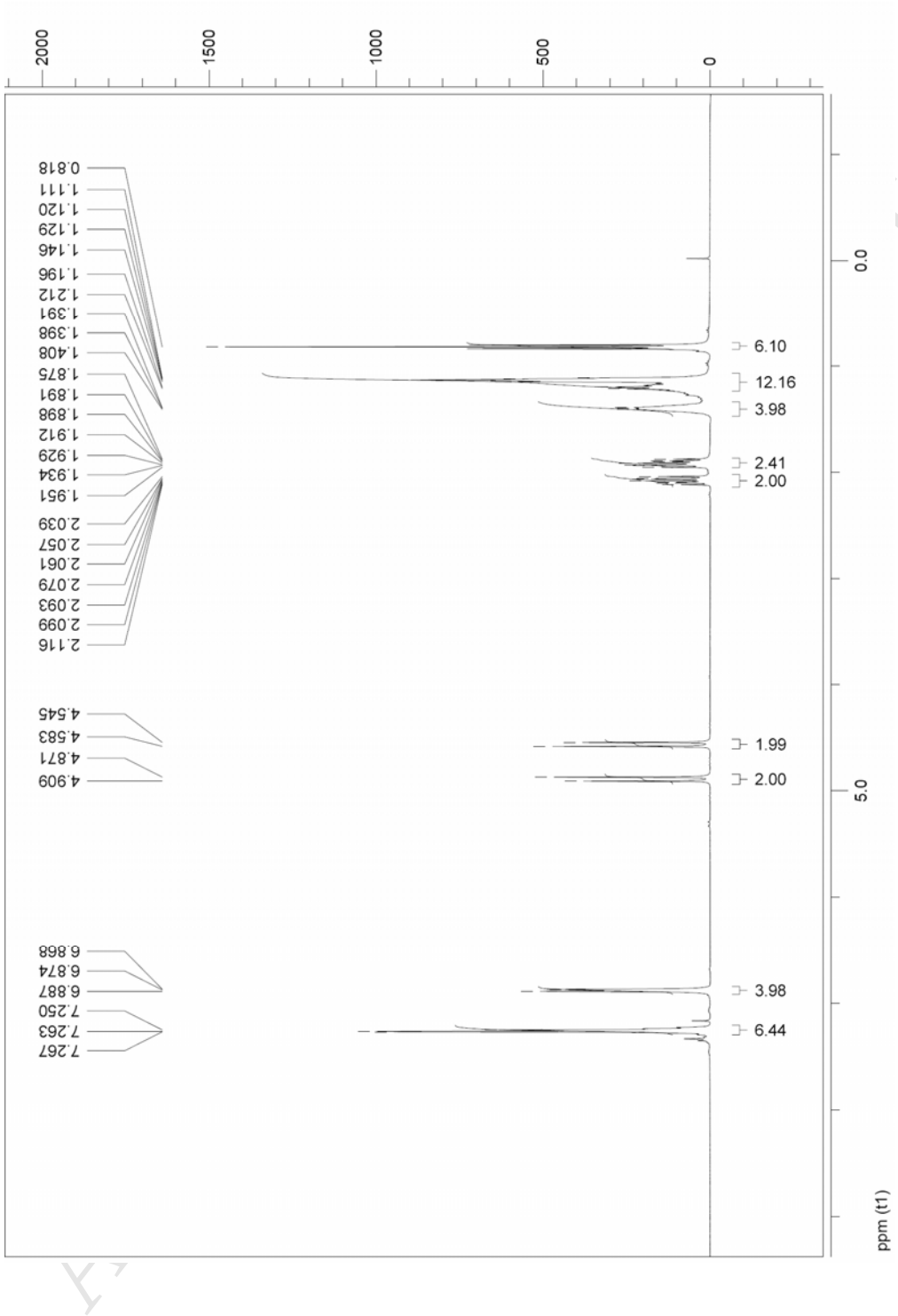
1c


2500
2000
1500
1000
500
0
2.287
4.554
4.591
4.663
4.700
6.775
6.794
6.992
7.011
7.051
7.069
7.088
7.120
7.139
7.260
7.315
7.335
6.00
2.04
2.00
3.98
10.06
4.09
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

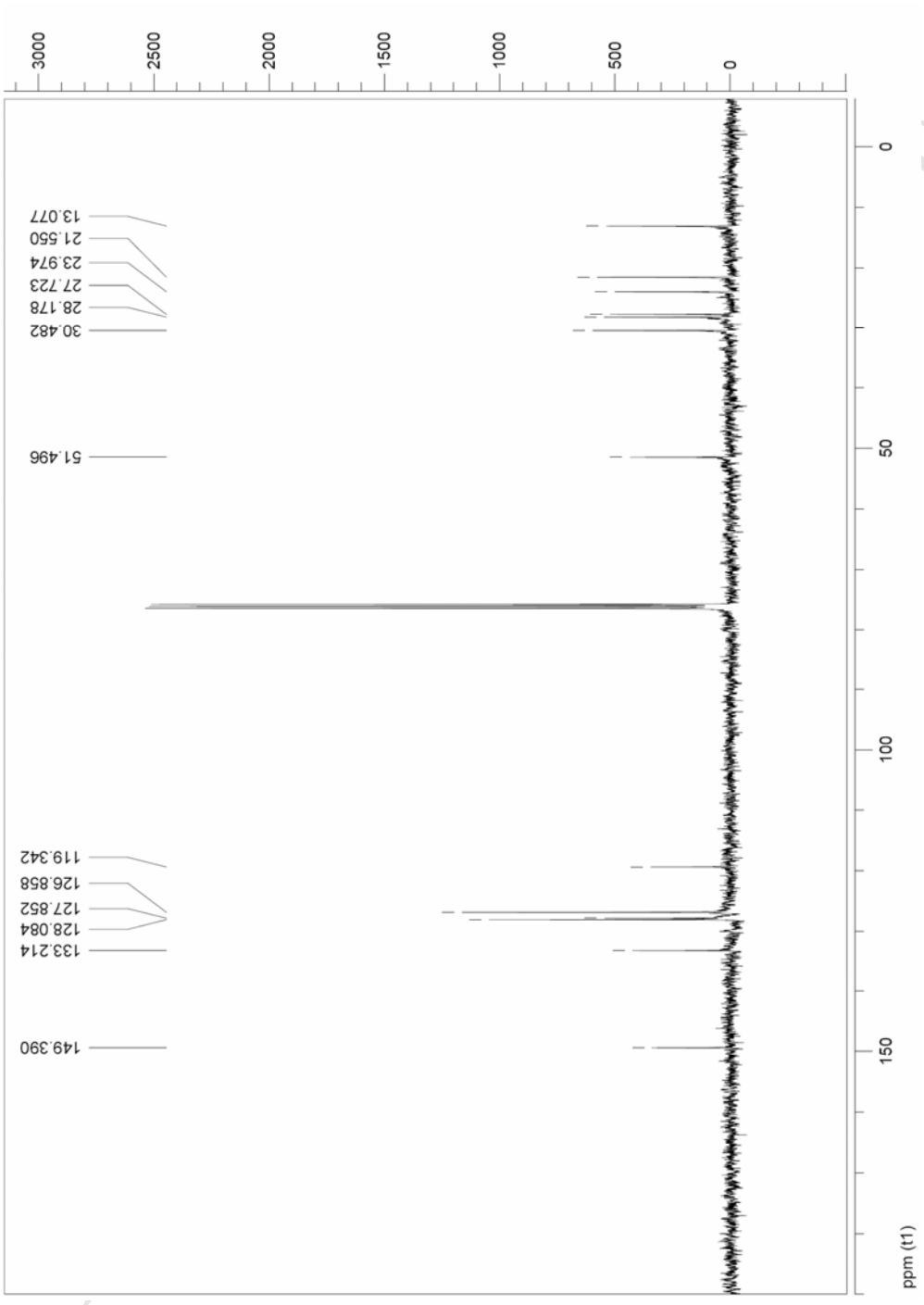
1d


7000
6000
5000
4000
3000
2000
1000
0
-1000
20.313
51.680
118.732
124.844
125.566
127.281
127.602
127.798
128.731
132.172
137.878
146.992
0
50
100
150
ppm (t1)

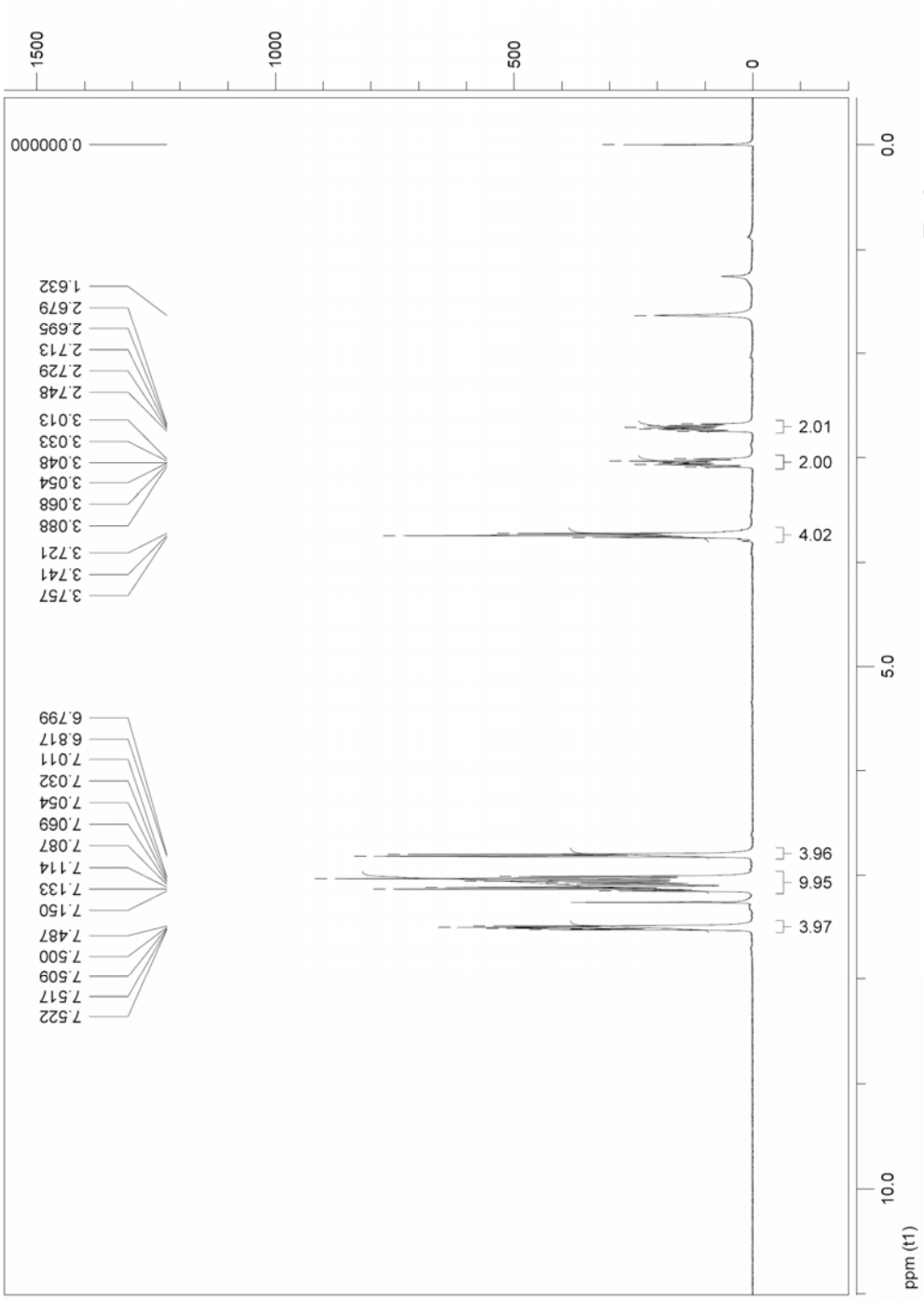
1d


2000
1500
1000
500
0
0.818
1.111
1.120
1.129
1.146
1.196
1.212
1.391
1.398
1.408
1.875
1.891
1.898
1.912
1.929
1.934
1.951
2.039
2.057
2.061
2.079
2.093
2.099
2.116
4.545
4.583
4.871
4.909
6.868
6.874
6.887
7.250
7.263
7.267
6.10
12.16
3.98
2.41
2.00
1.99
2.00
3.98
6.44
0.0
5.0
ppm (t1)

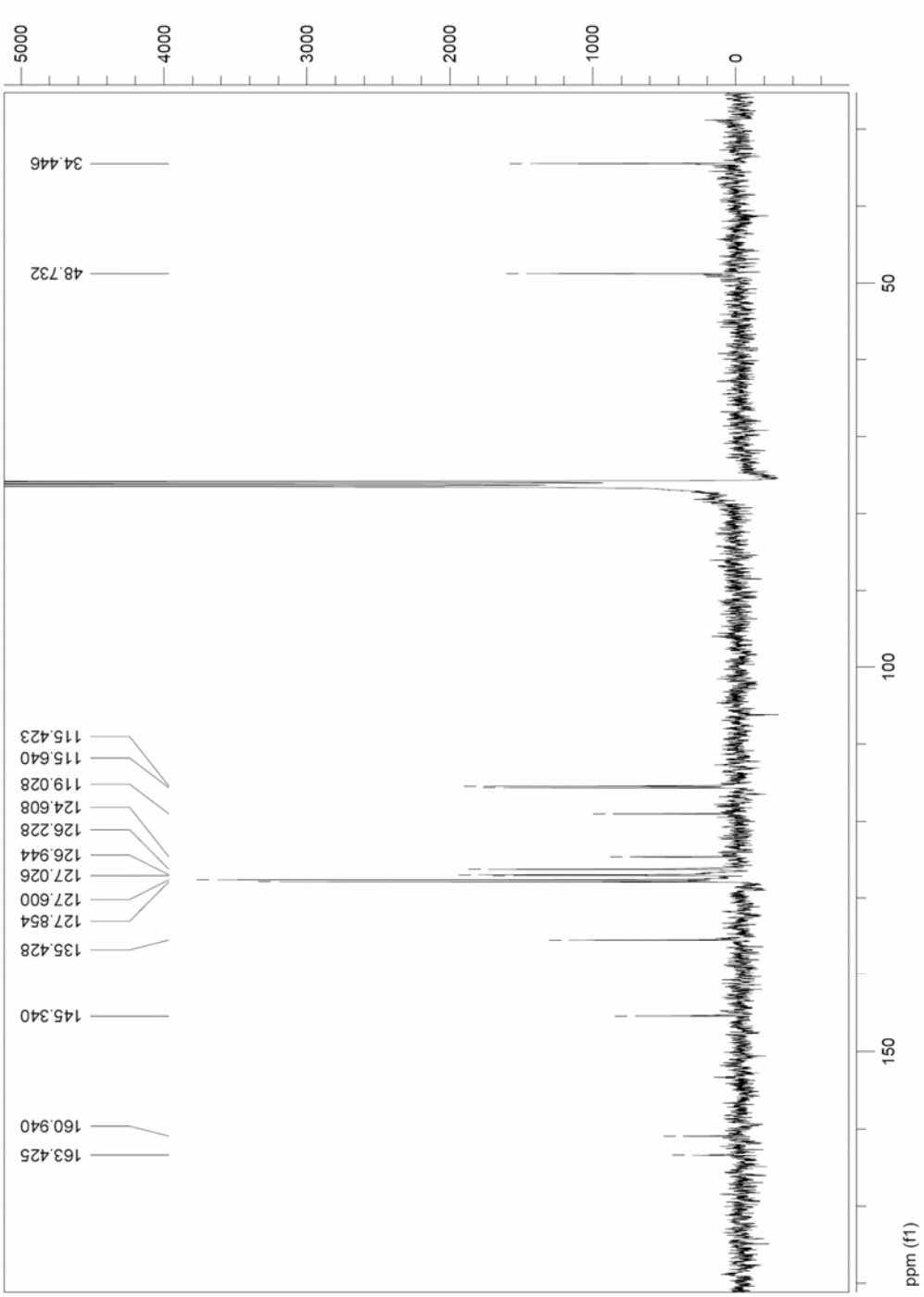
1e


3000
2500
2000
1500
1000
500
0
13.077
21.550
23.974
27.723
28.178
30.482
51.496
119.342
126.858
127.852
128.084
133.214
149.390
0
50
100
150
ppm (t1)

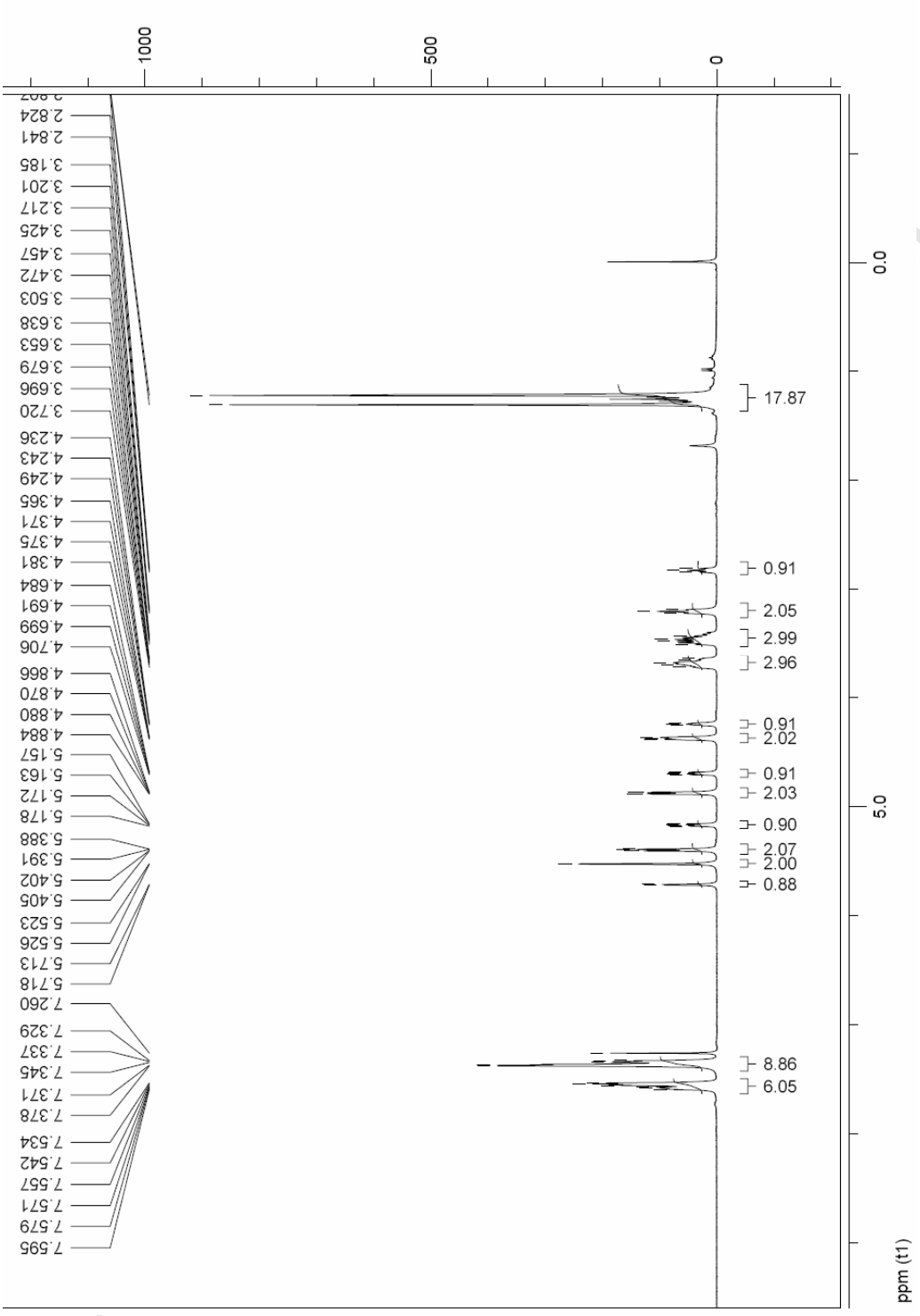
1e


1500
1000
500
0
0.000000
1.632
2.679
2.695
2.713
2.729
2.748
3.013
3.033
3.048
3.054
3.068
3.088
3.721
3.741
3.757
6.799
6.817
7.011
7.032
7.054
7.069
7.087
7.114
7.133
7.150
7.487
7.500
7.509
7.517
7.522
2.01
2.00
4.02
3.96
9.95
3.97
0.0
5.0
10.0
ppm (t1)

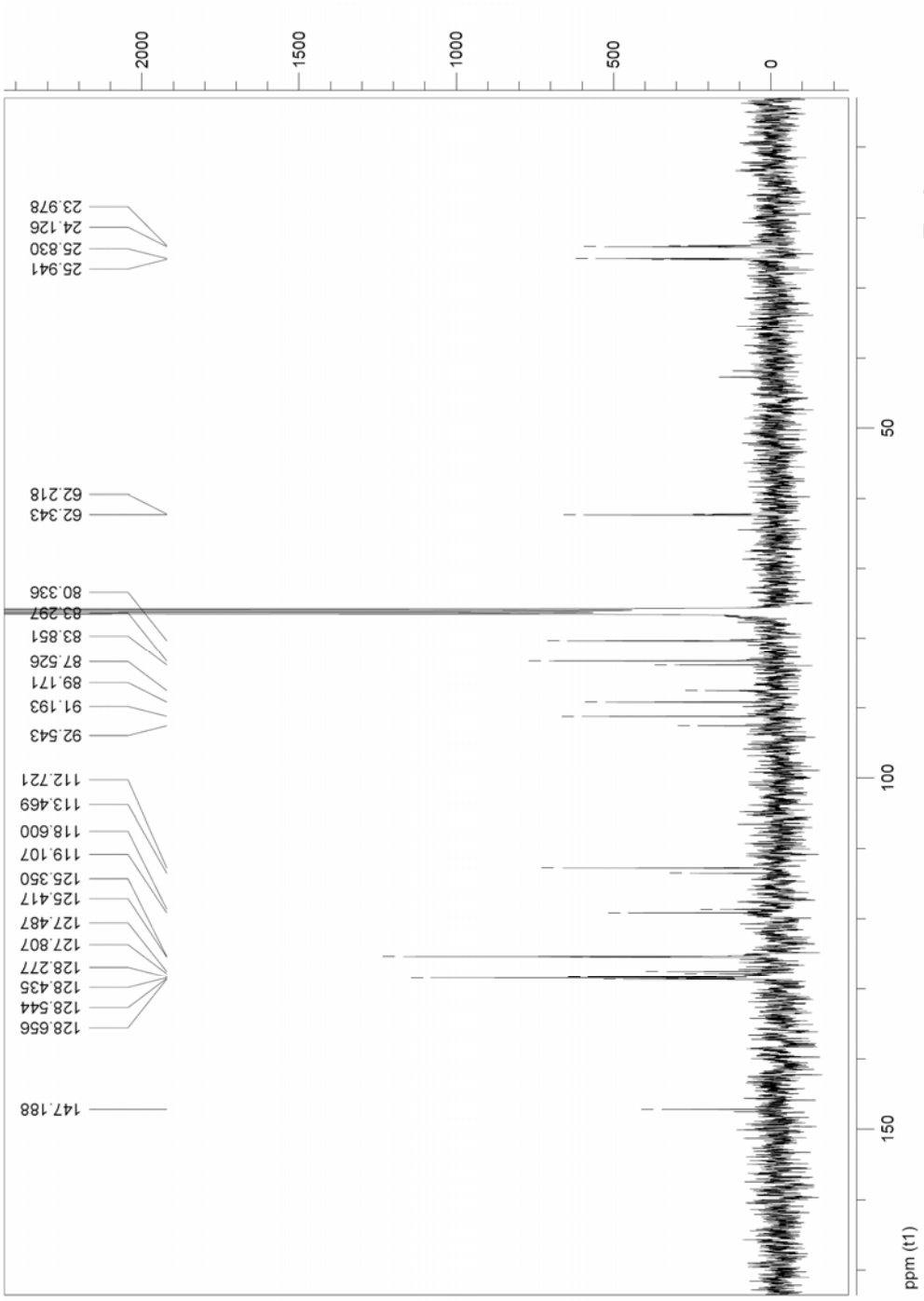
1f


5000
4000
3000
2000
1000
0
34.446
48.732
115.423
115.640
119.028
124.608
126.228
126.944
127.026
127.600
127.854
135.428
145.340
160.940
163.425
50
100
150
ppm (f1)

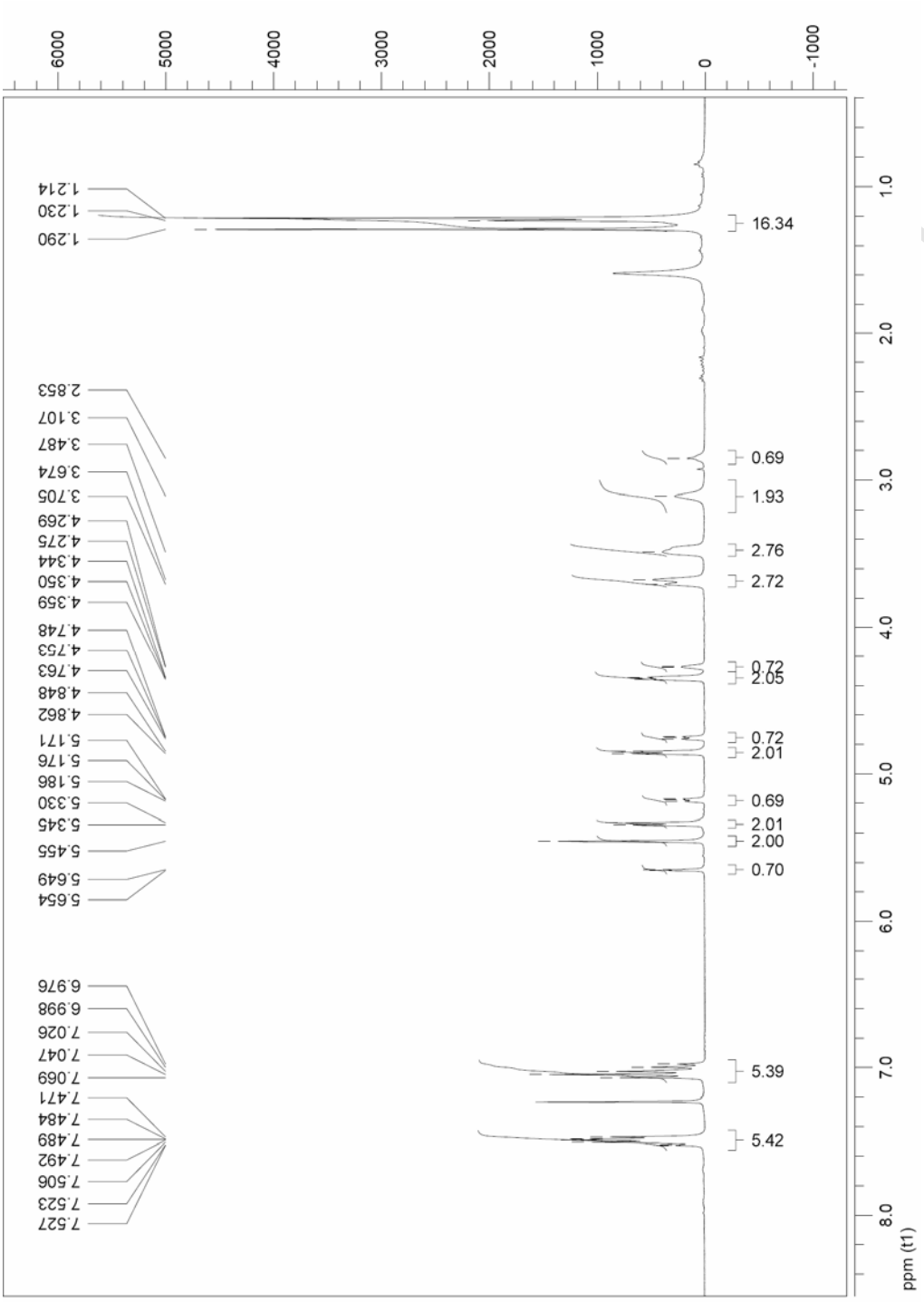
1f


1000
500
0
2.824
2.841
3.185
3.201
3.217
3.425
3.457
3.472
3.503
3.638
3.653
3.679
3.696
3.720
4.236
4.243
4.249
4.365
4.371
4.375
4.381
4.684
4.691
4.699
4.706
4.866
4.870
4.880
4.884
5.157
5.163
5.172
5.178
5.388
5.391
5.402
5.405
5.523
5.526
5.713
5.718
7.260
7.329
7.337
7.345
7.371
7.378
7.534
7.542
7.557
7.571
7.579
7.595
17.87
0.91
2.05
2.99
2.96
0.91
2.02
0.91
2.03
0.90
2.07
2.00
0.88
8.86
6.05
0.0
5.0
ppm (t1)

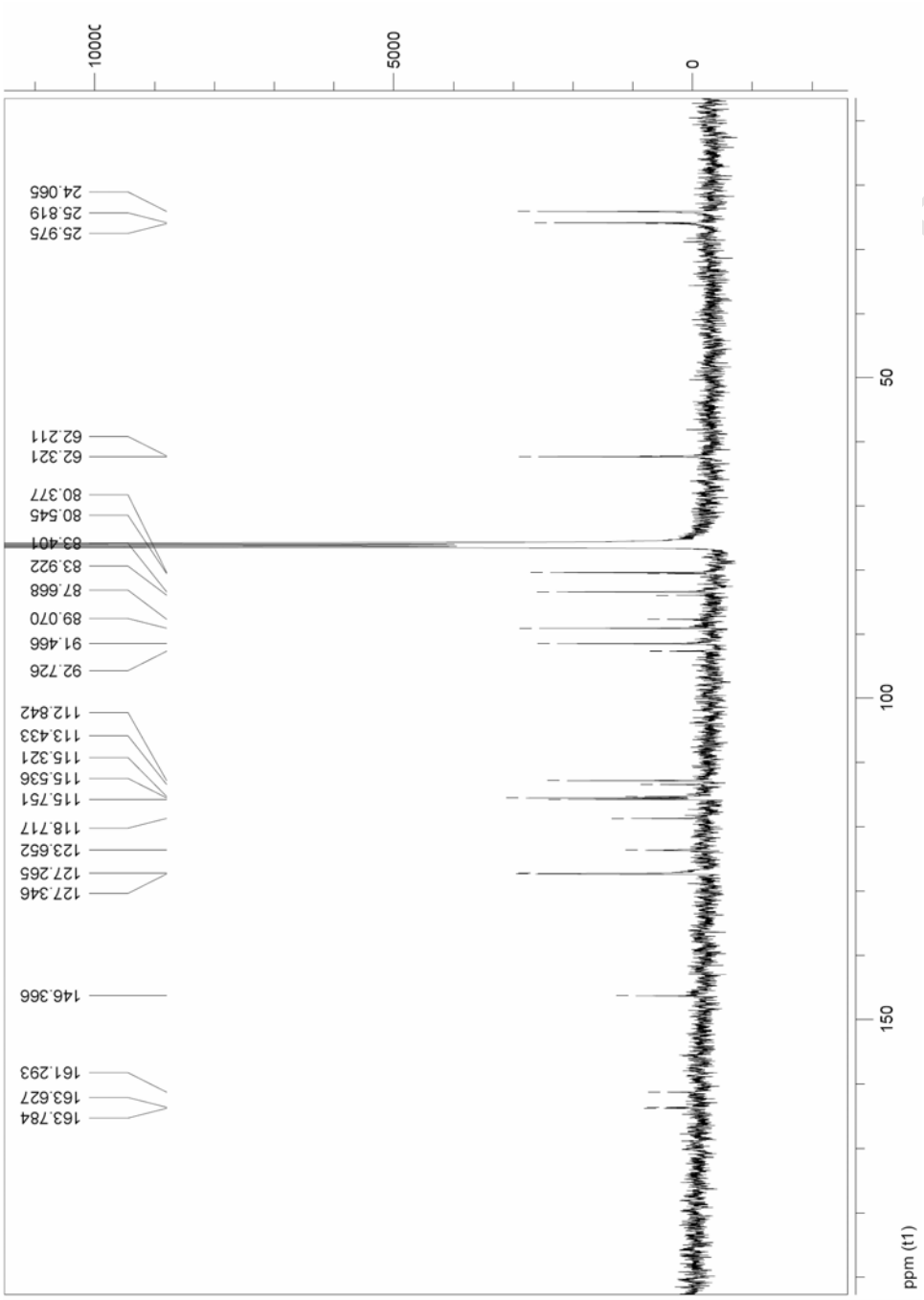
1g


2000
1500
1000
500
0
23.978
24.126
25.830
25.941
62.218
62.343
80.336
83.297
83.851
87.526
89.171
91.193
92.543
112.721
113.469
118.600
119.107
125.350
125.417
127.487
127.807
128.277
128.435
128.544
128.656
147.188
50
100
150
ppm (t1)

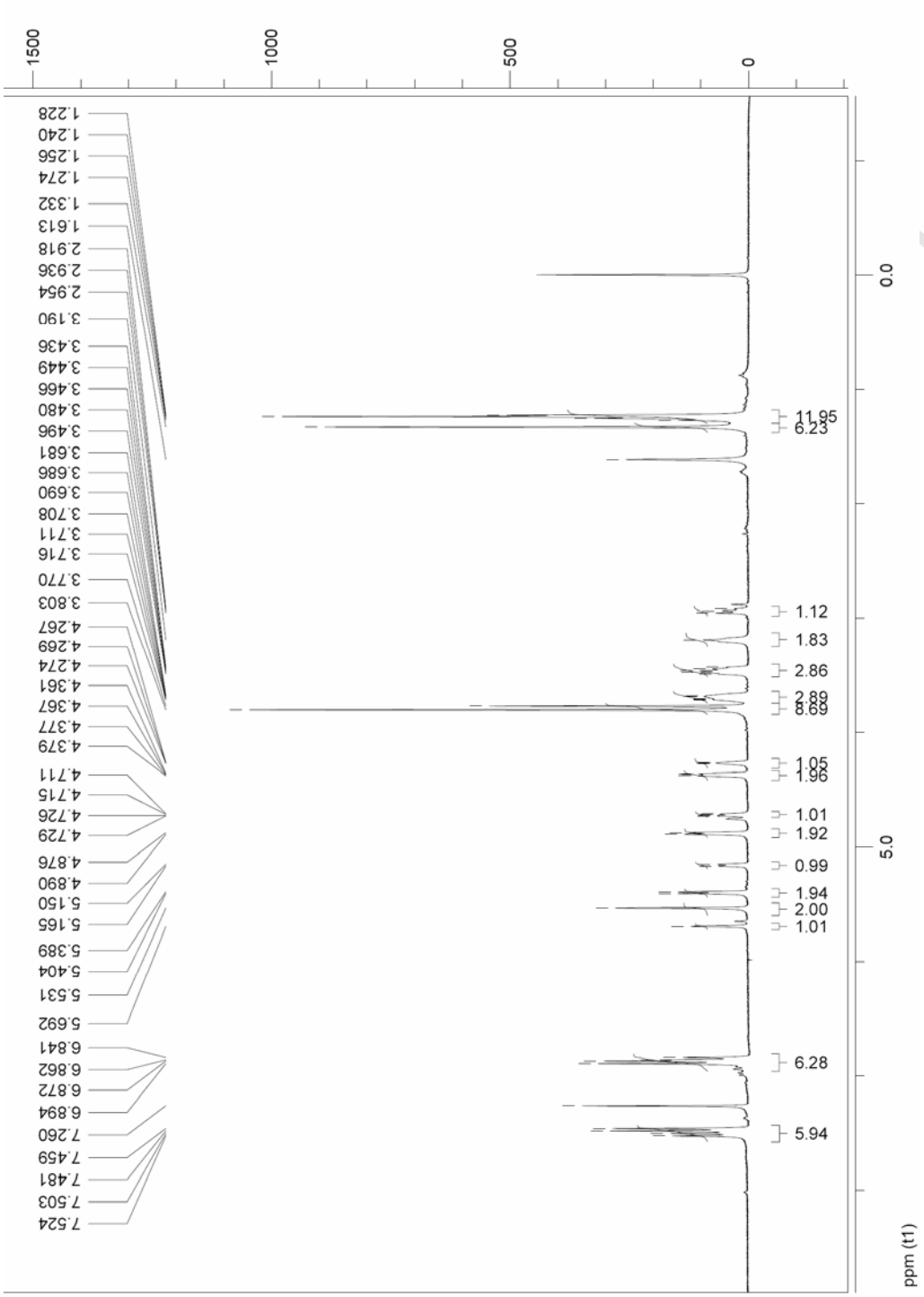
1g


6000
5000
4000
3000
2000
1000
0
-1000
1.214
1.230
1.290
2.853
3.107
3.487
3.674
3.705
4.269
4.275
4.344
4.350
4.359
4.748
4.753
4.763
4.848
4.862
5.171
5.176
5.186
5.330
5.345
5.455
5.649
5.654
6.976
6.998
7.026
7.047
7.069
7.471
7.484
7.489
7.492
7.506
7.523
7.527
16.34
0.69
1.93
2.76
2.72
0.72
2.05
0.72
2.01
0.69
2.01
2.00
0.70
5.39
5.42
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

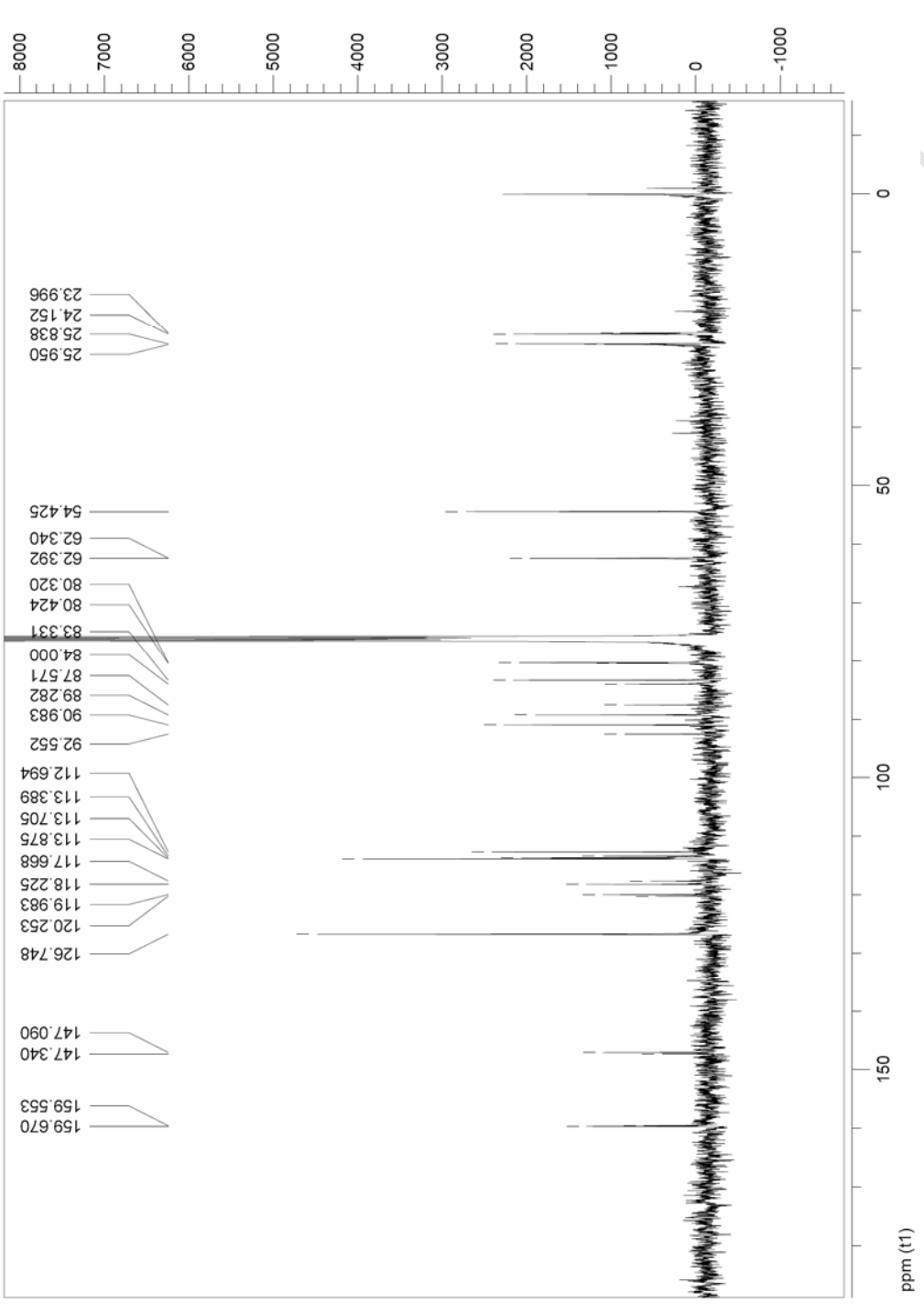
1h


10000
5000
0
24.065
25.819
25.975
62.211
62.321
80.377
80.545
83.401
83.922
87.668
89.070
91.466
92.726
112.842
113.433
115.321
115.536
115.751
118.717
123.652
127.265
127.346
146.366
161.293
163.627
163.784
50
100
150
ppm (t1)

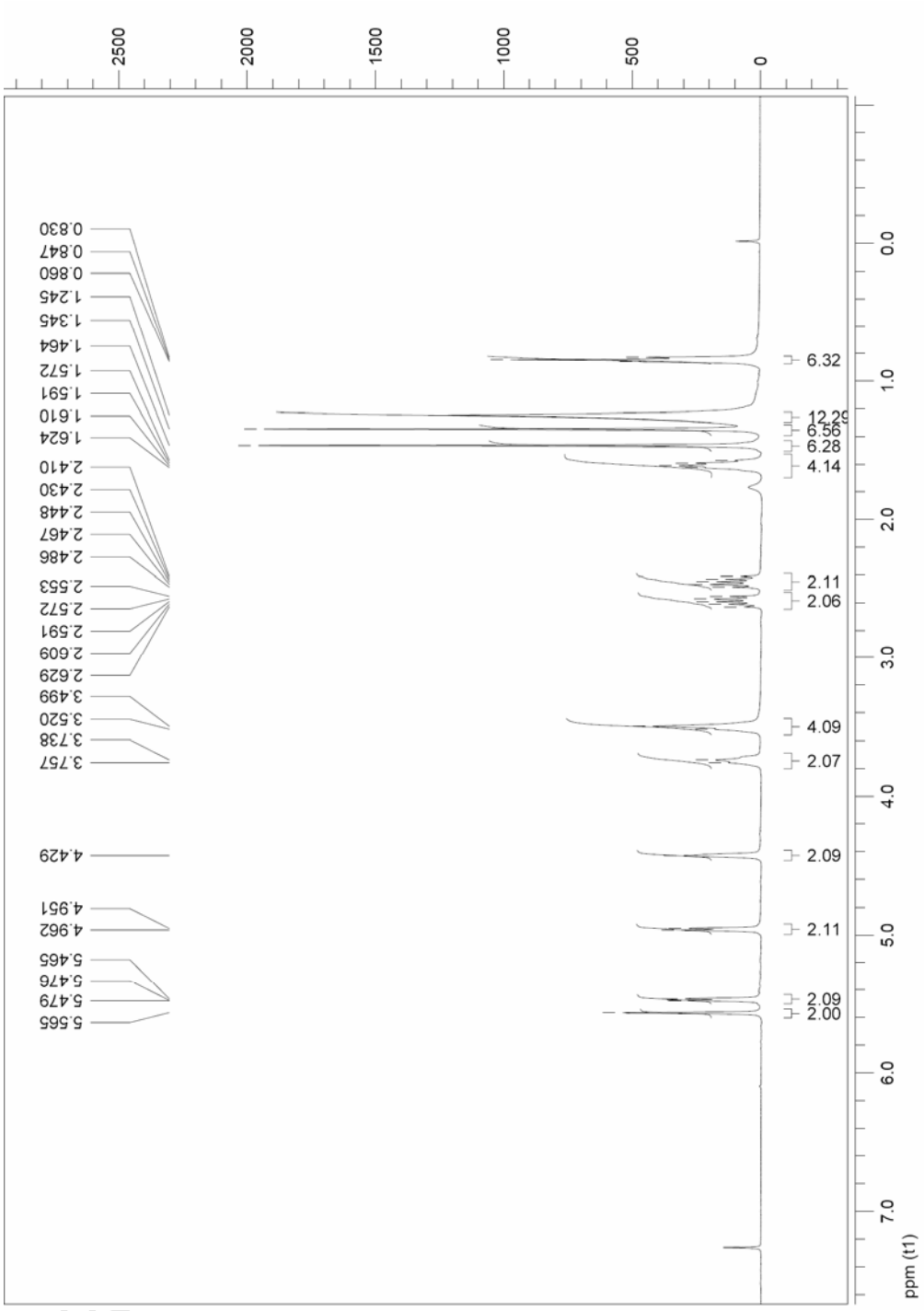
1h


1500
1000
500
0
1.228
1.240
1.256
1.274
1.332
1.613
2.918
2.936
2.954
3.190
3.436
3.449
3.466
3.480
3.496
3.681
3.686
3.690
3.708
3.711
3.716
3.770
3.803
4.267
4.269
4.274
4.361
4.367
4.377
4.379
4.711
4.715
4.726
4.729
4.876
4.890
5.150
5.165
5.389
5.404
5.531
5.692
6.841
6.862
6.872
6.894
7.260
7.459
7.481
7.503
7.524
11.95
6.23
1.12
1.83
2.86
2.89
8.69
1.05
1.96
1.01
1.92
0.99
1.94
2.00
1.01
6.28
5.94
0.0
5.0
ppm (t1)

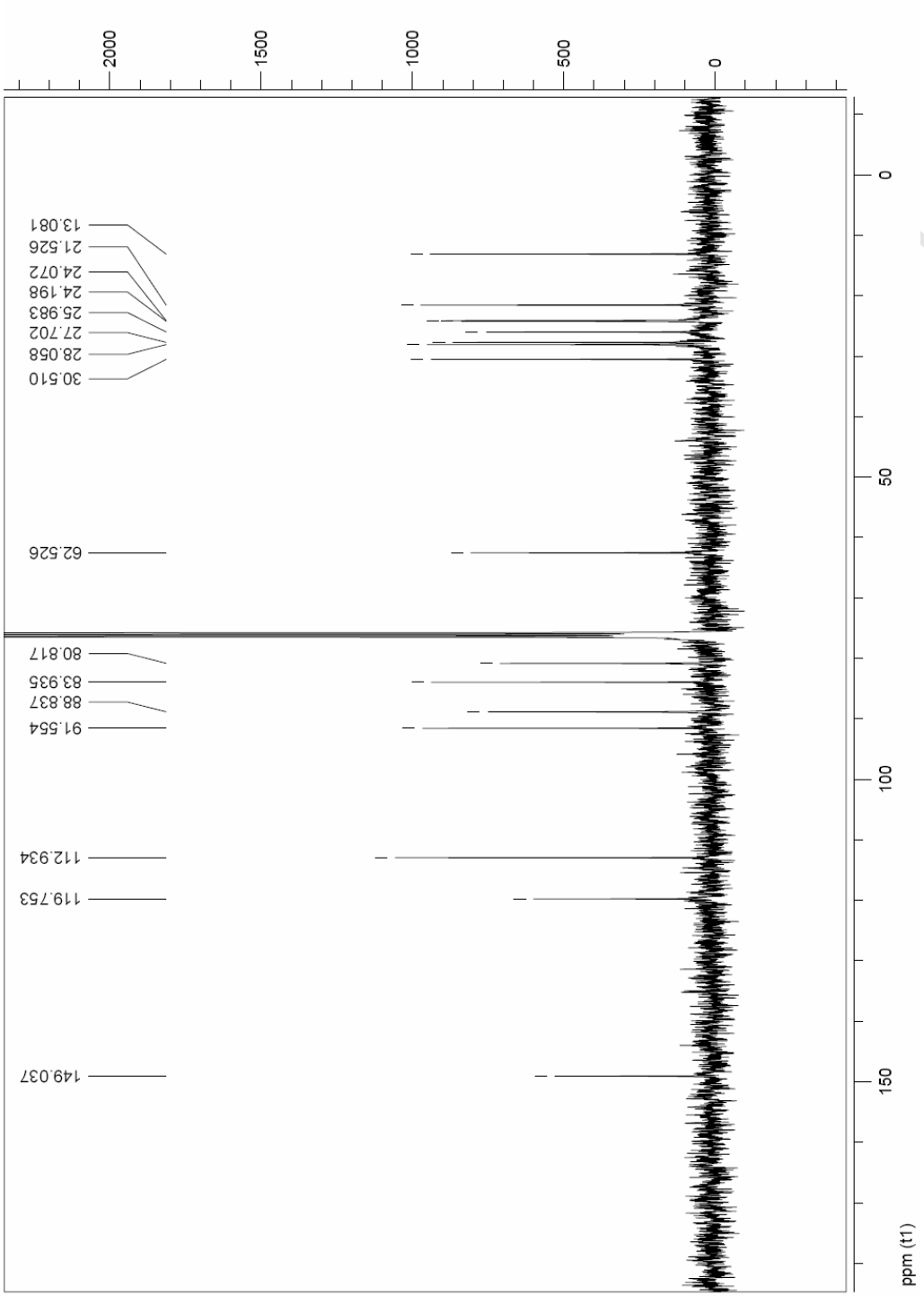
1i


8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0
50
100
150
ppm (t1)
23.996
24.152
25.838
25.950
54.425
62.340
62.392
80.320
80.424
83.331
84.000
87.571
89.282
90.983
92.552
112.694
113.389
113.705
113.875
117.668
118.225
119.983
120.253
126.748
147.090
147.340
159.553
159.670

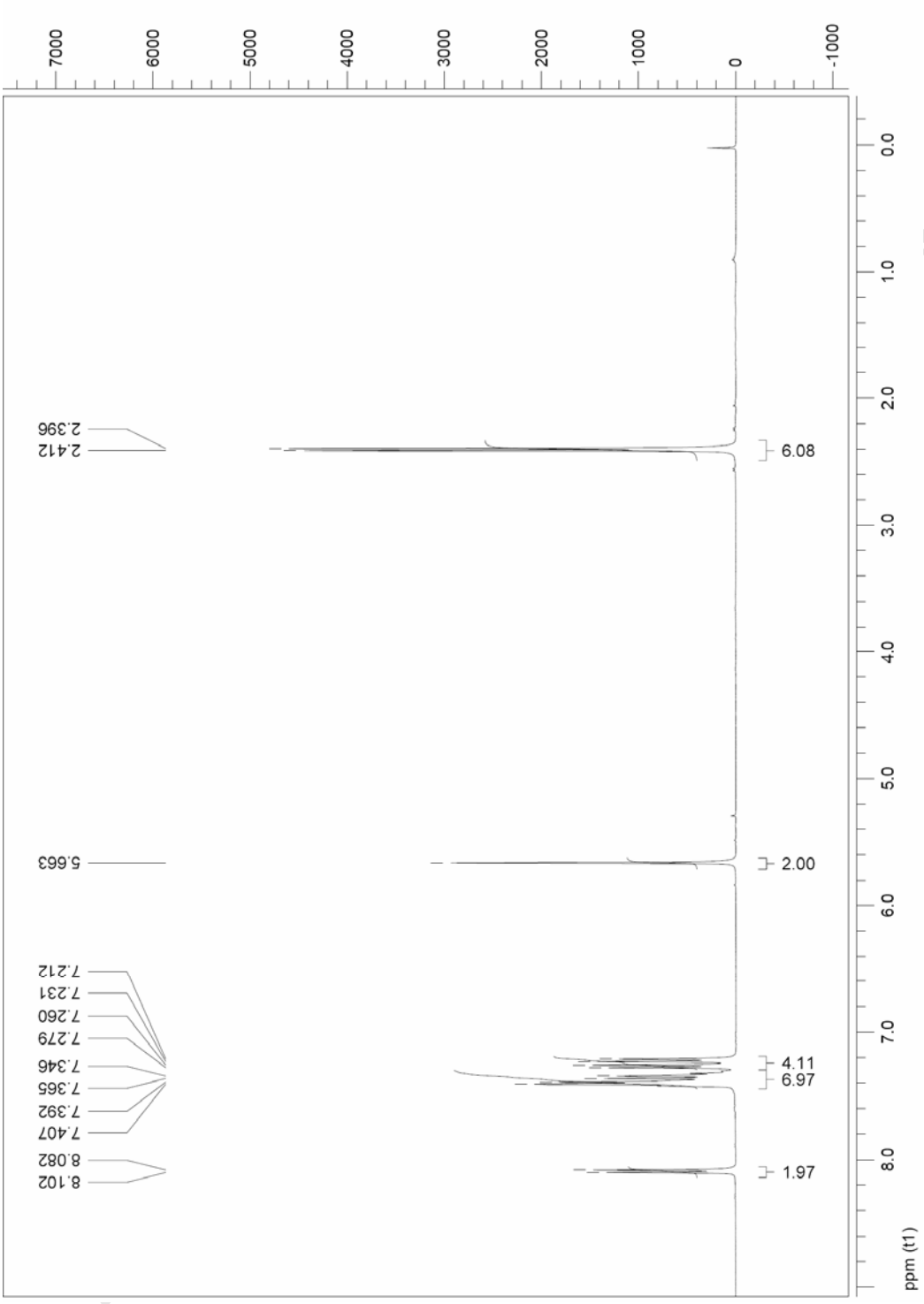
1i


2500
2000
1500
1000
500
0
0.830
0.847
0.860
1.245
1.345
1.464
1.572
1.591
1.610
1.624
2.410
2.430
2.448
2.467
2.486
2.553
2.572
2.591
2.609
2.629
3.499
3.520
3.738
3.757
4.429
4.951
4.962
5.465
5.476
5.479
5.565
6.32
12.29
6.56
6.28
4.14
2.11
2.06
4.09
2.07
2.09
2.11
2.09
2.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

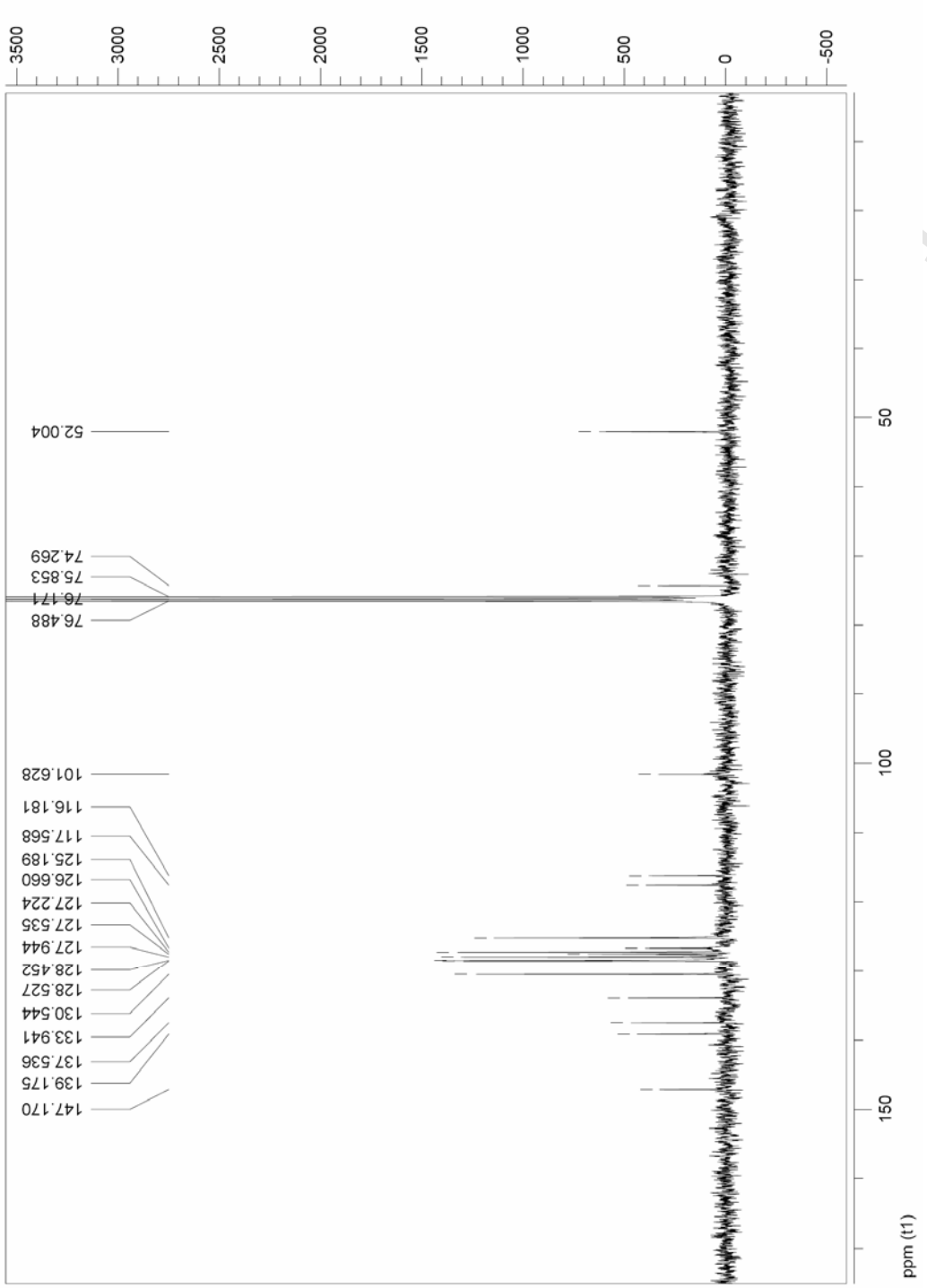
1j


2000
1500
1000
500
0
13.081
21.526
24.072
24.198
25.983
27.702
28.058
30.510
62.526
80.817
83.935
88.837
91.554
112.934
119.753
149.037
0
50
100
150
ppm (t1)

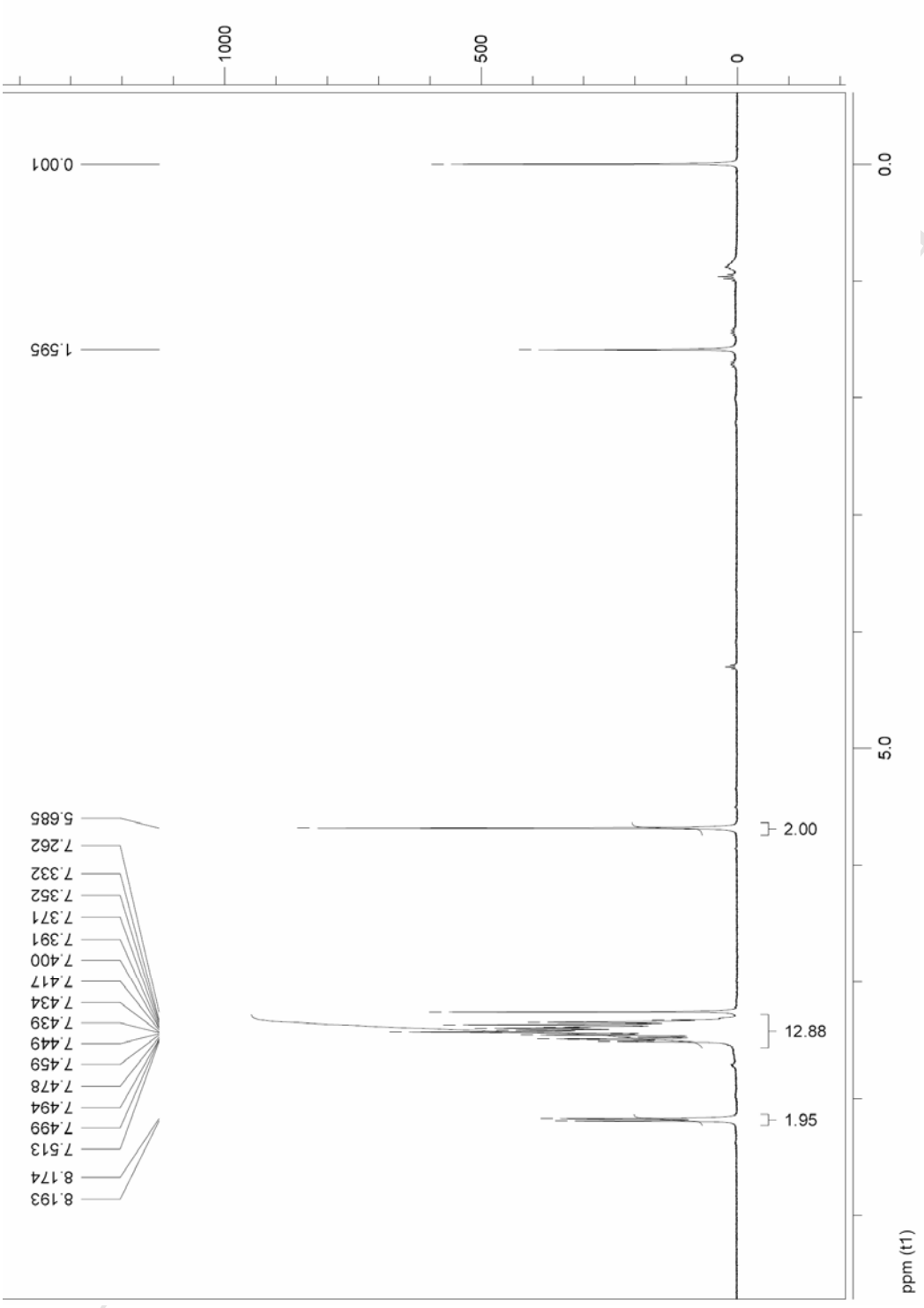
1j


7000
6000
5000
4000
3000
2000
1000
0
-1000
2.396
2.412
5.663
7.212
7.231
7.260
7.279
7.346
7.365
7.392
7.407
8.082
8.102
6.08
2.00
4.11
6.97
1.97
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

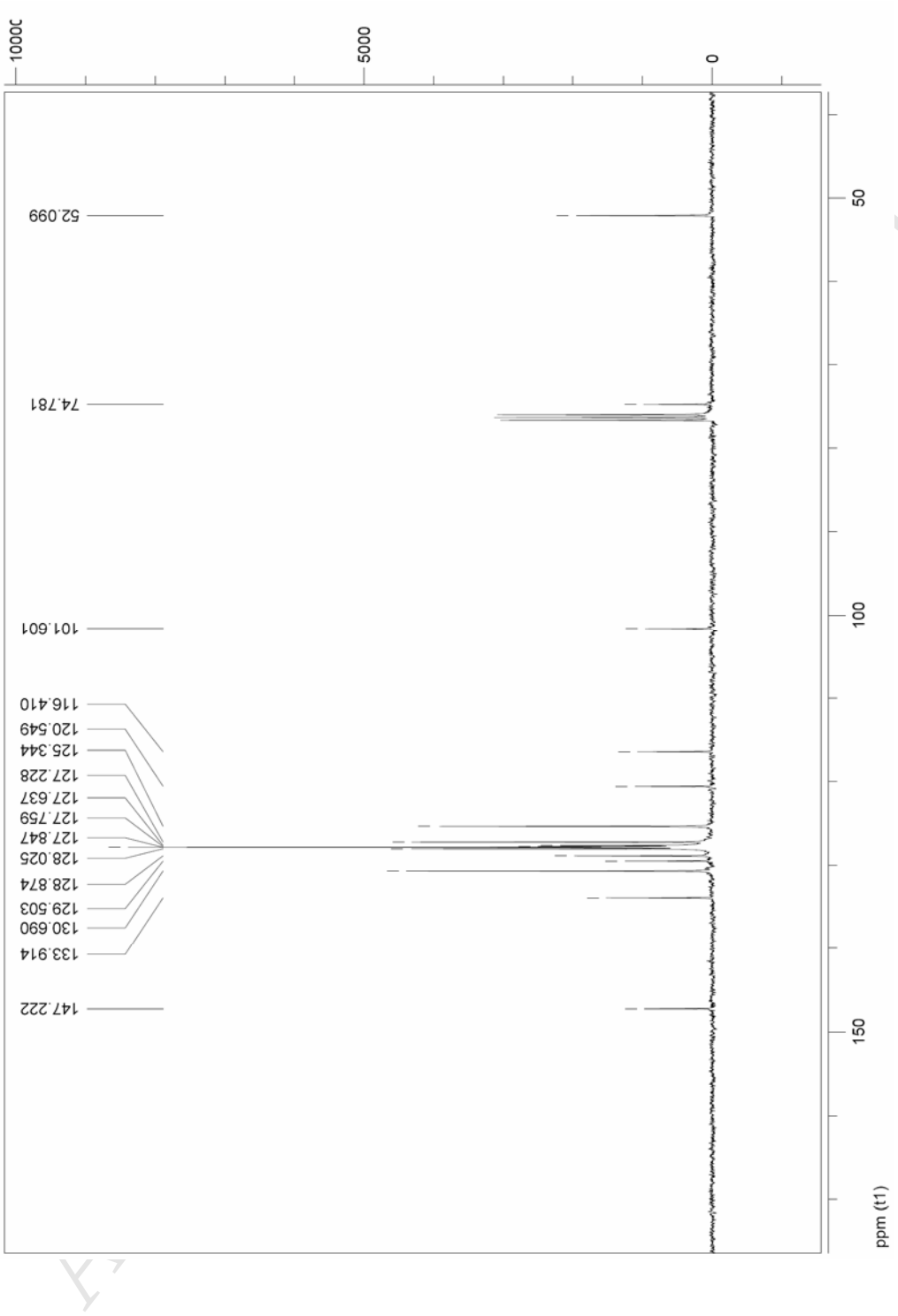
2a


3500
3000
2500
2000
1500
1000
500
0
-500
52.004
74.269
75.853
76.171
76.488
101.628
116.181
117.568
125.189
126.660
127.224
127.535
127.944
128.452
128.527
130.544
133.941
137.536
139.175
147.170
50
100
150
ppm (t1)

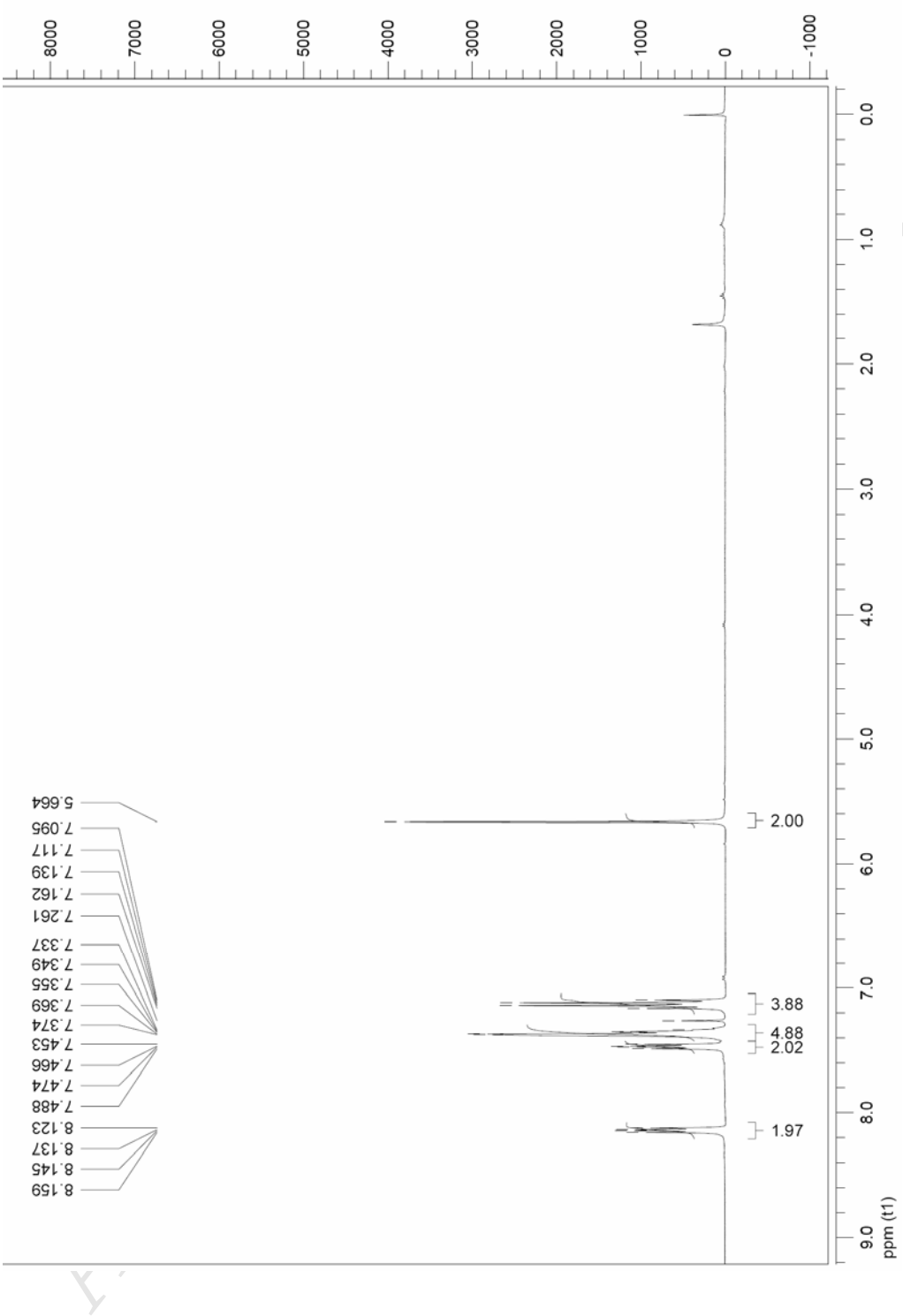
2a


1000
500
0
0.001
1.595
5.685
7.262
7.332
7.352
7.371
7.391
7.400
7.417
7.434
7.439
7.449
7.459
7.478
7.494
7.499
7.513
8.174
8.193
2.00
12.88
1.95
0.0
5.0
ppm (t1)

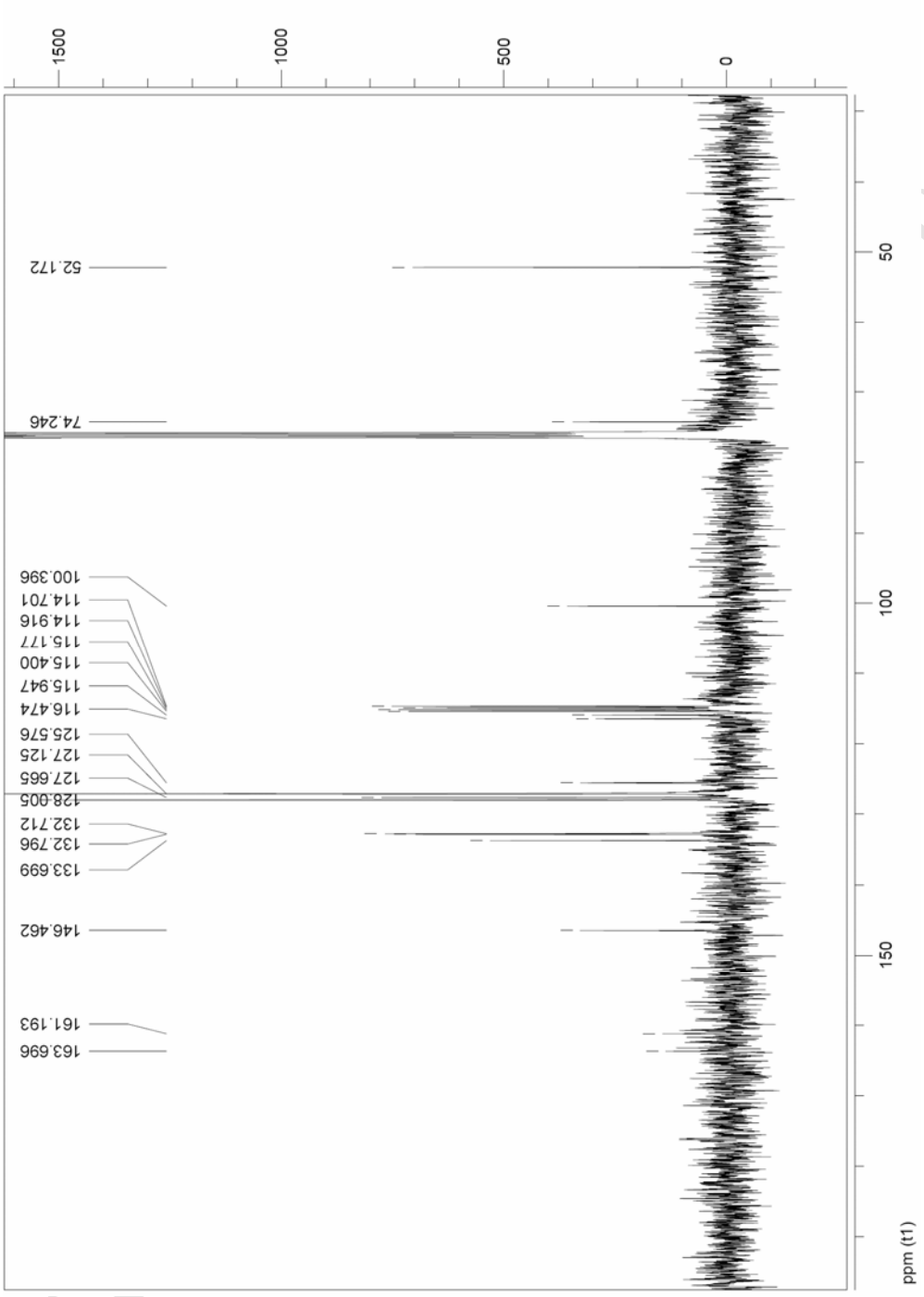
2b


10000
5000
0
52.099
74.781
101.601
116.410
120.549
125.344
127.228
127.637
127.759
127.847
128.025
128.874
129.503
130.690
133.914
147.222
50
100
150
ppm (t1)

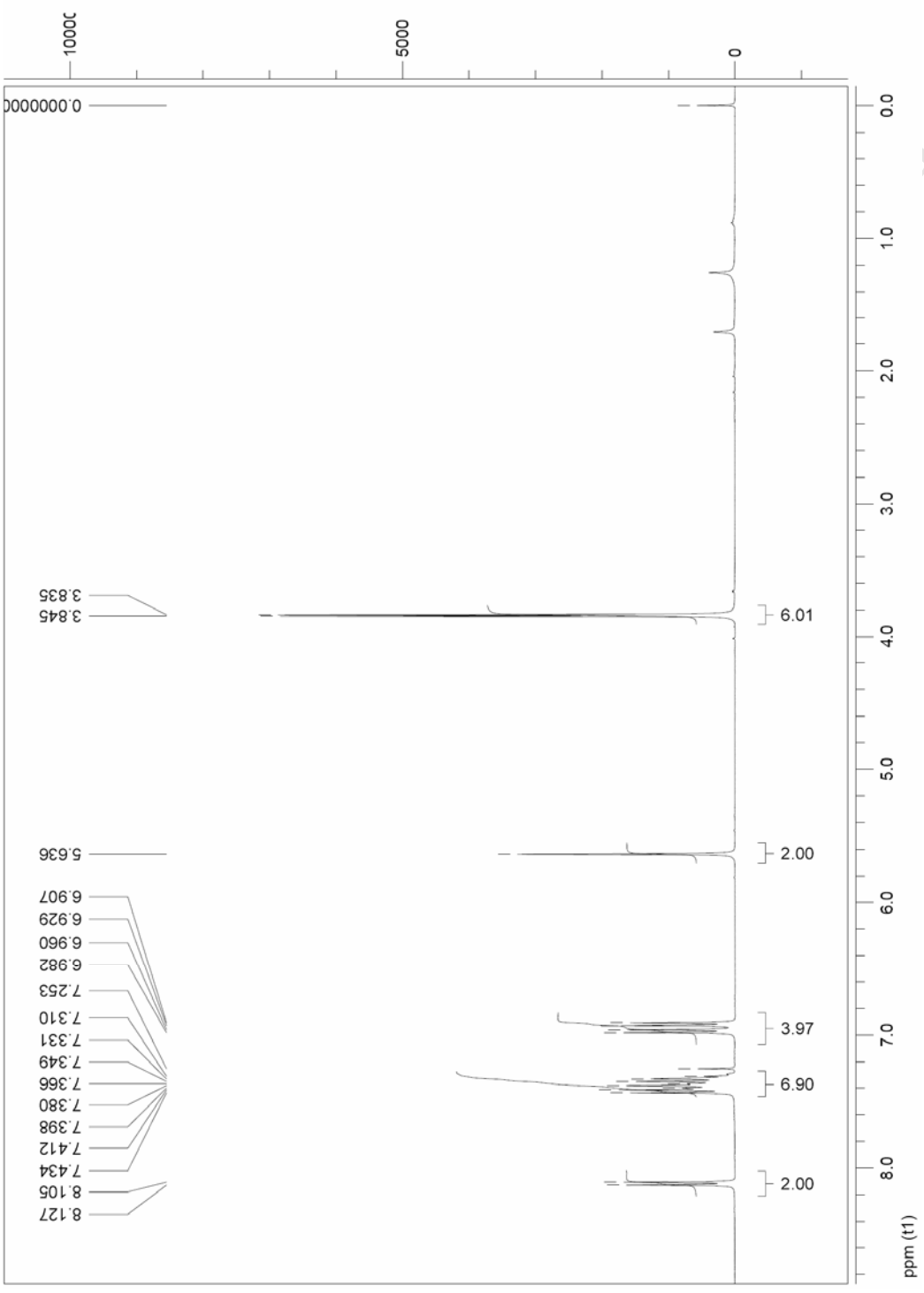
2b


8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
2.00
3.88
4.88
2.02
1.97
5.664
7.095
7.117
7.139
7.162
7.261
7.337
7.349
7.355
7.369
7.374
7.453
7.466
7.474
7.488
8.123
8.137
8.145
8.159

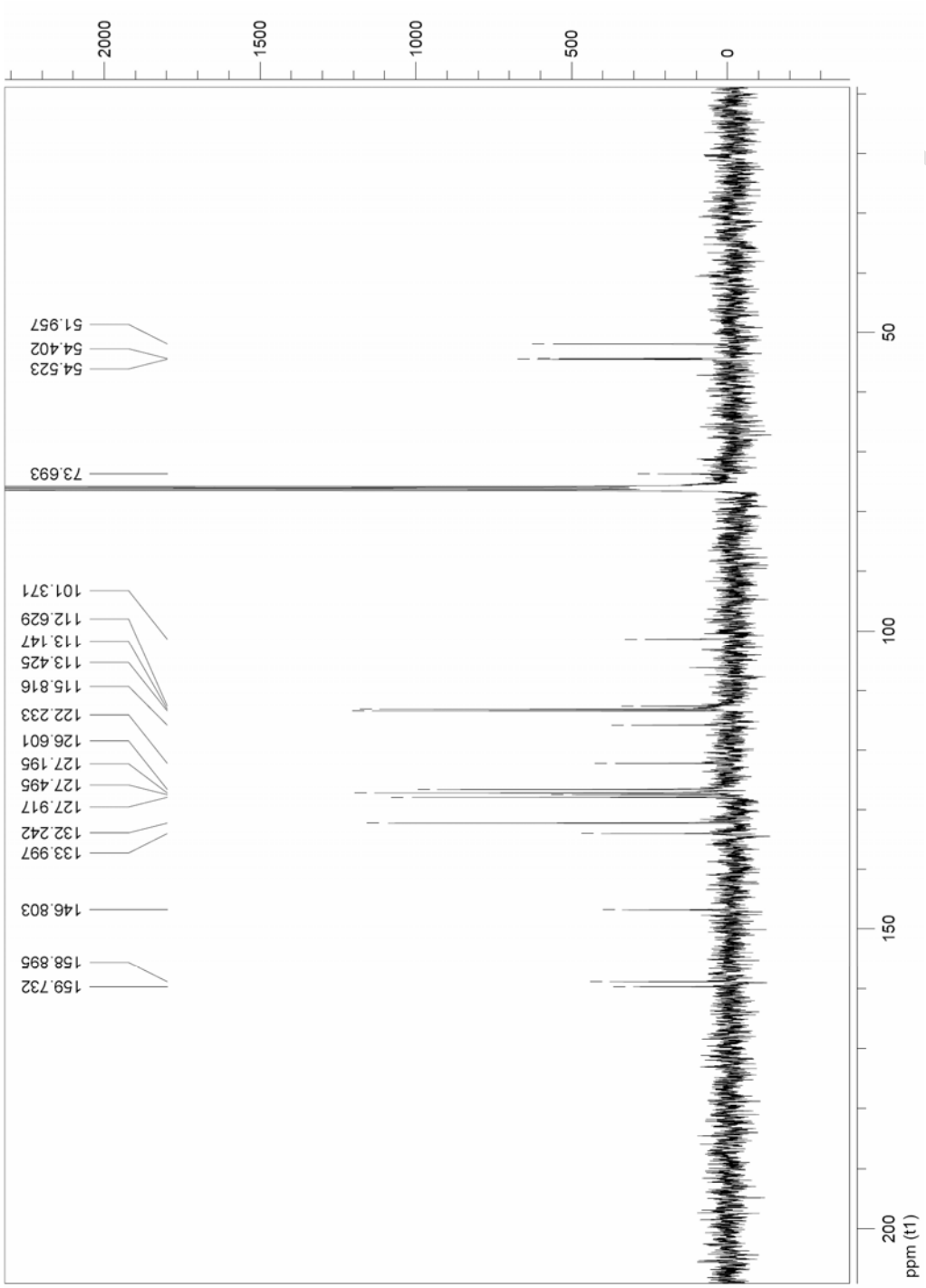
2c


1500
1000
500
0
52.172
74.246
100.396
114.701
114.916
115.177
115.400
115.947
116.474
125.576
127.125
127.665
128.005
132.712
132.796
133.699
146.462
161.193
163.696
50
100
150
ppm (t1)

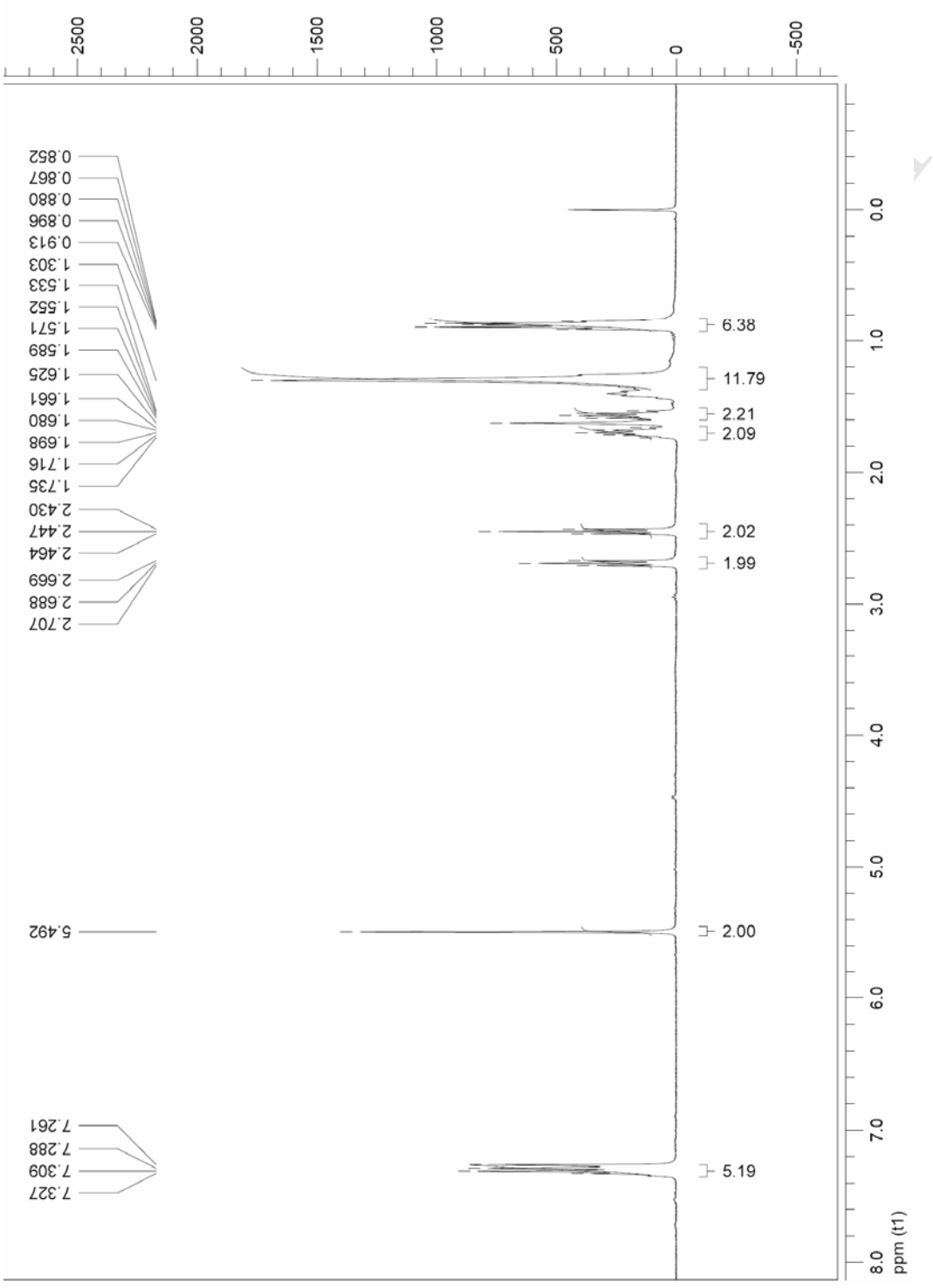
2c


10000
5000
0
0.000000
3.835
3.845
5.636
6.907
6.929
6.960
6.982
7.253
7.310
7.331
7.349
7.366
7.380
7.398
7.412
7.434
8.105
8.127
6.01
2.00
3.97
6.90
2.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

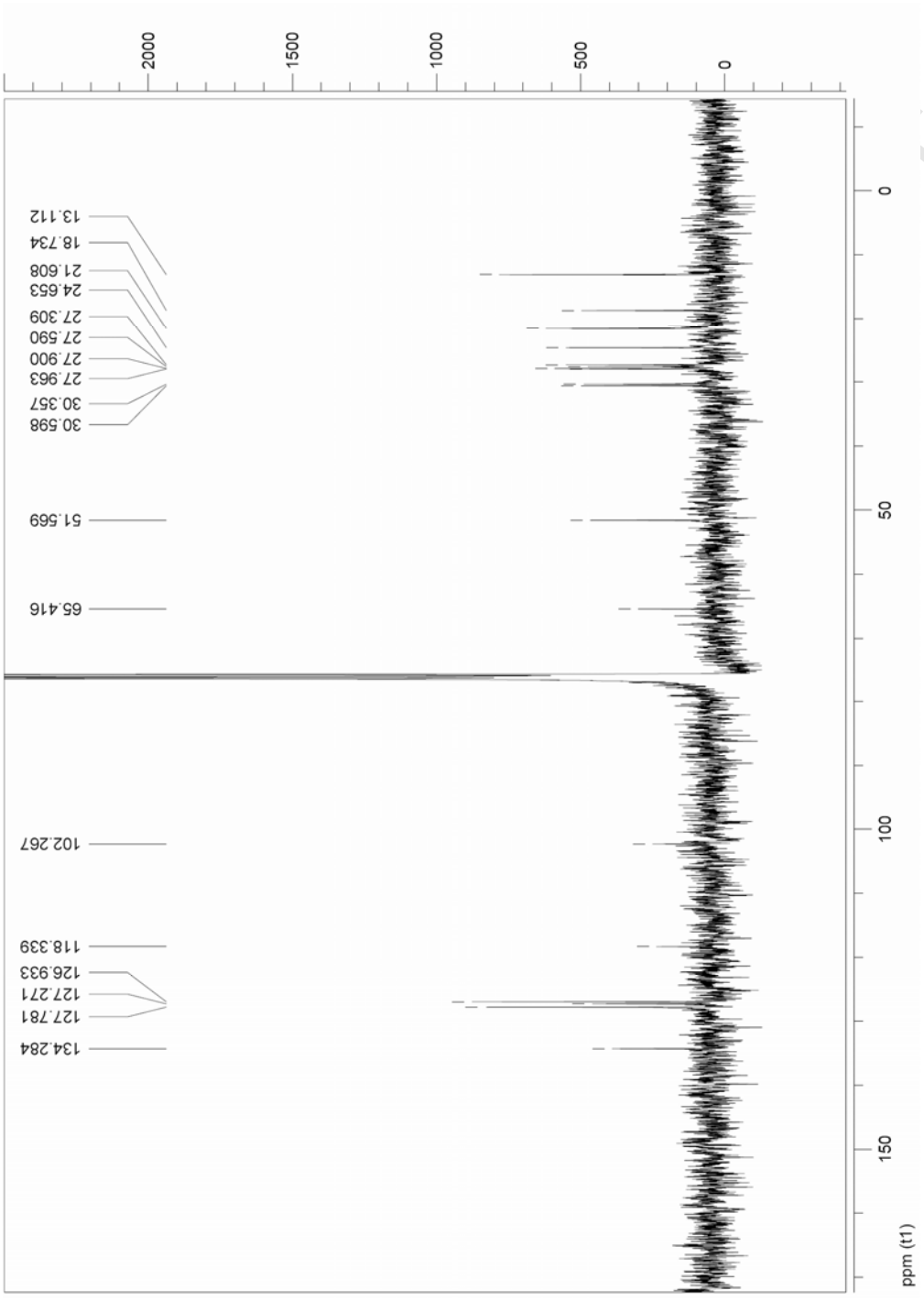
2d


2000
1500
1000
500
0
51.957
54.402
54.523
73.693
101.371
112.629
113.147
113.425
115.816
122.233
126.601
127.195
127.495
127.917
132.242
133.997
146.803
158.895
159.732
50
100
150
200
ppm (t1)

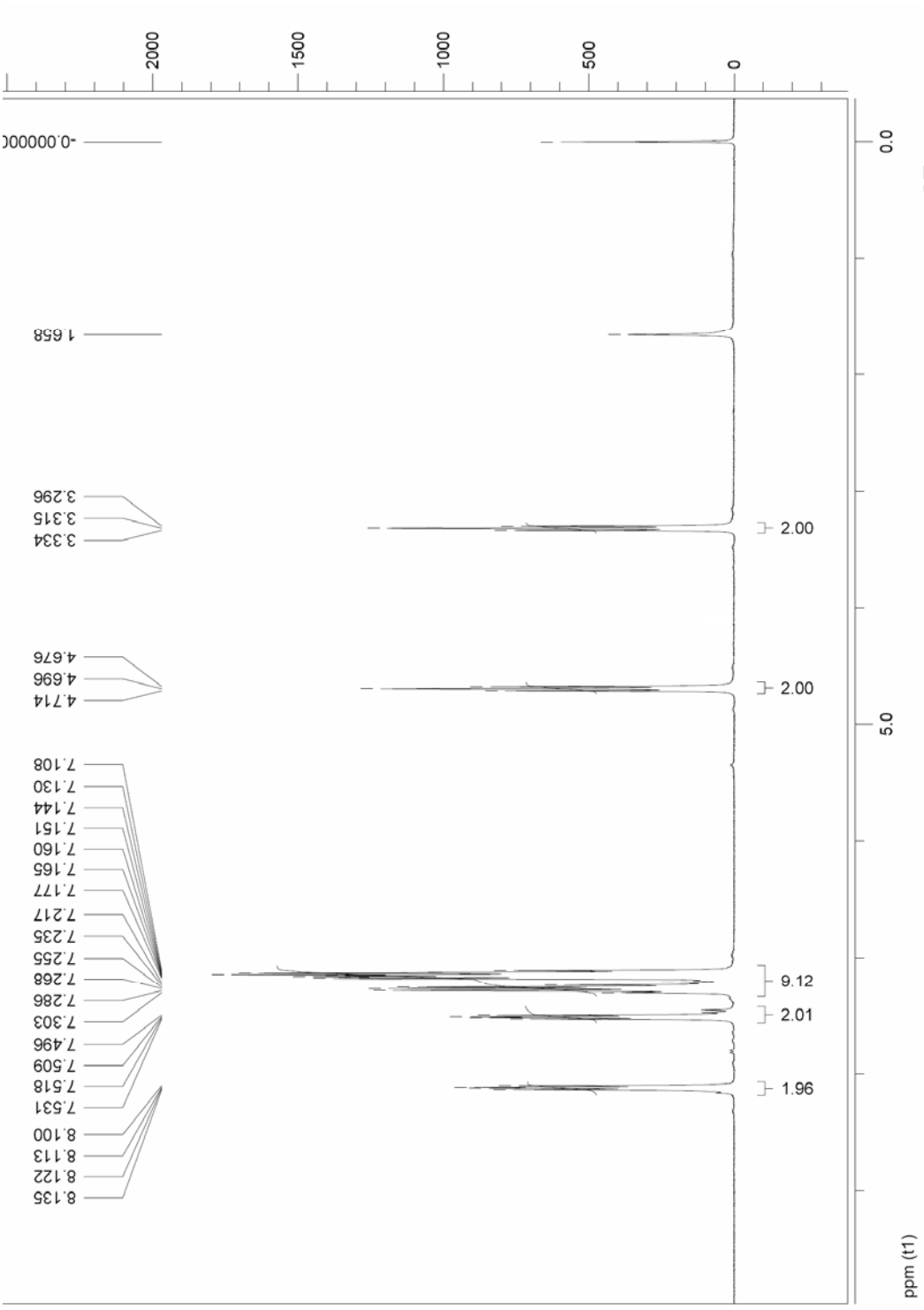
2d


2500
2000
1500
1000
500
0
-500
0.852
0.867
0.880
0.896
0.913
1.303
1.533
1.552
1.571
1.589
1.625
1.661
1.680
1.698
1.716
1.735
2.430
2.447
2.464
2.669
2.688
2.707
5.492
7.261
7.288
7.309
7.327
6.38
11.79
2.21
2.09
2.02
1.99
2.00
5.19
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

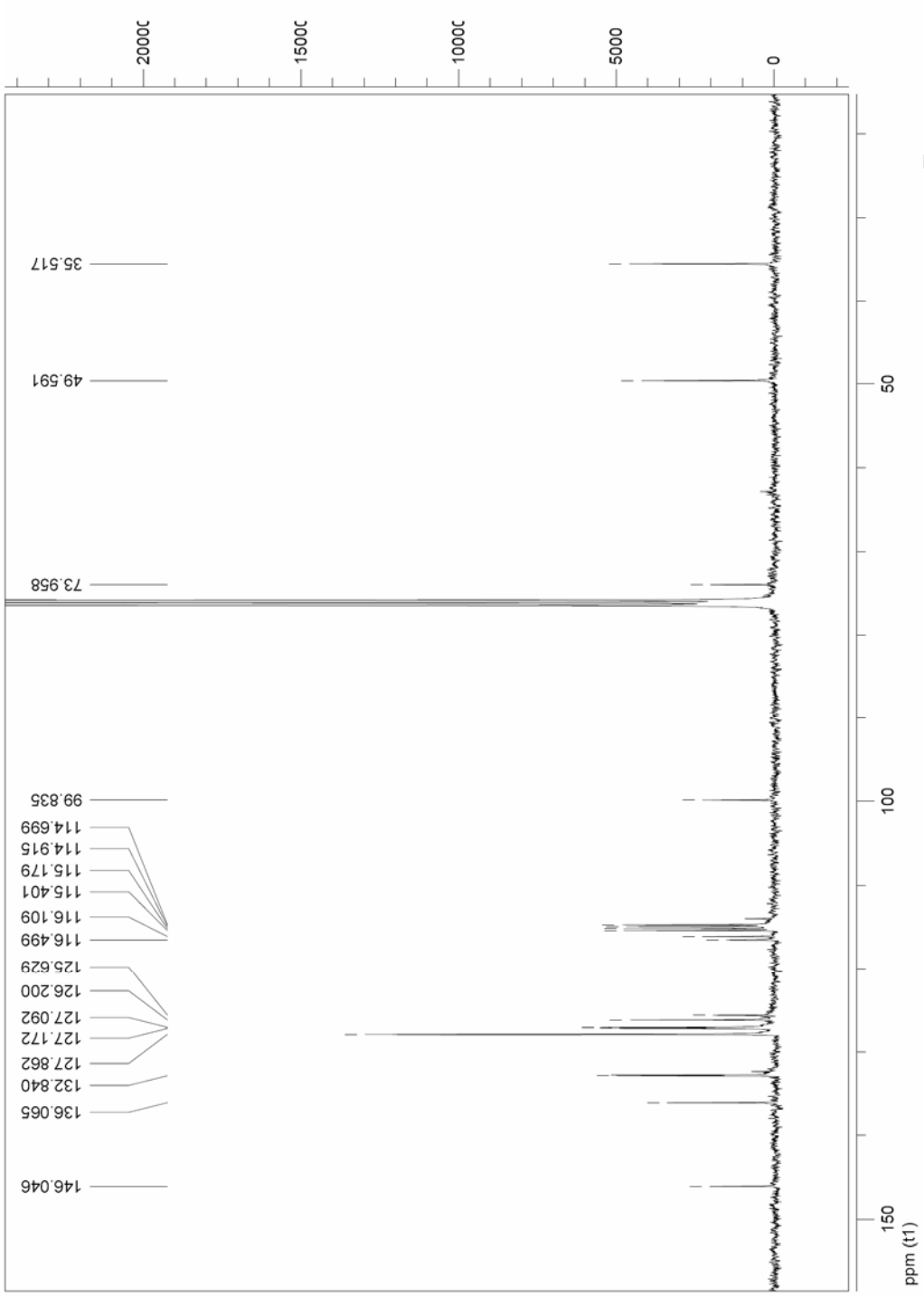
2fe


2000
1500
1000
500
0
13.112
18.734
21.608
24.653
27.309
27.590
27.900
27.963
30.357
30.598
51.569
65.416
102.267
118.339
126.933
127.271
127.781
134.284
0
50
100
150
ppm (t1)

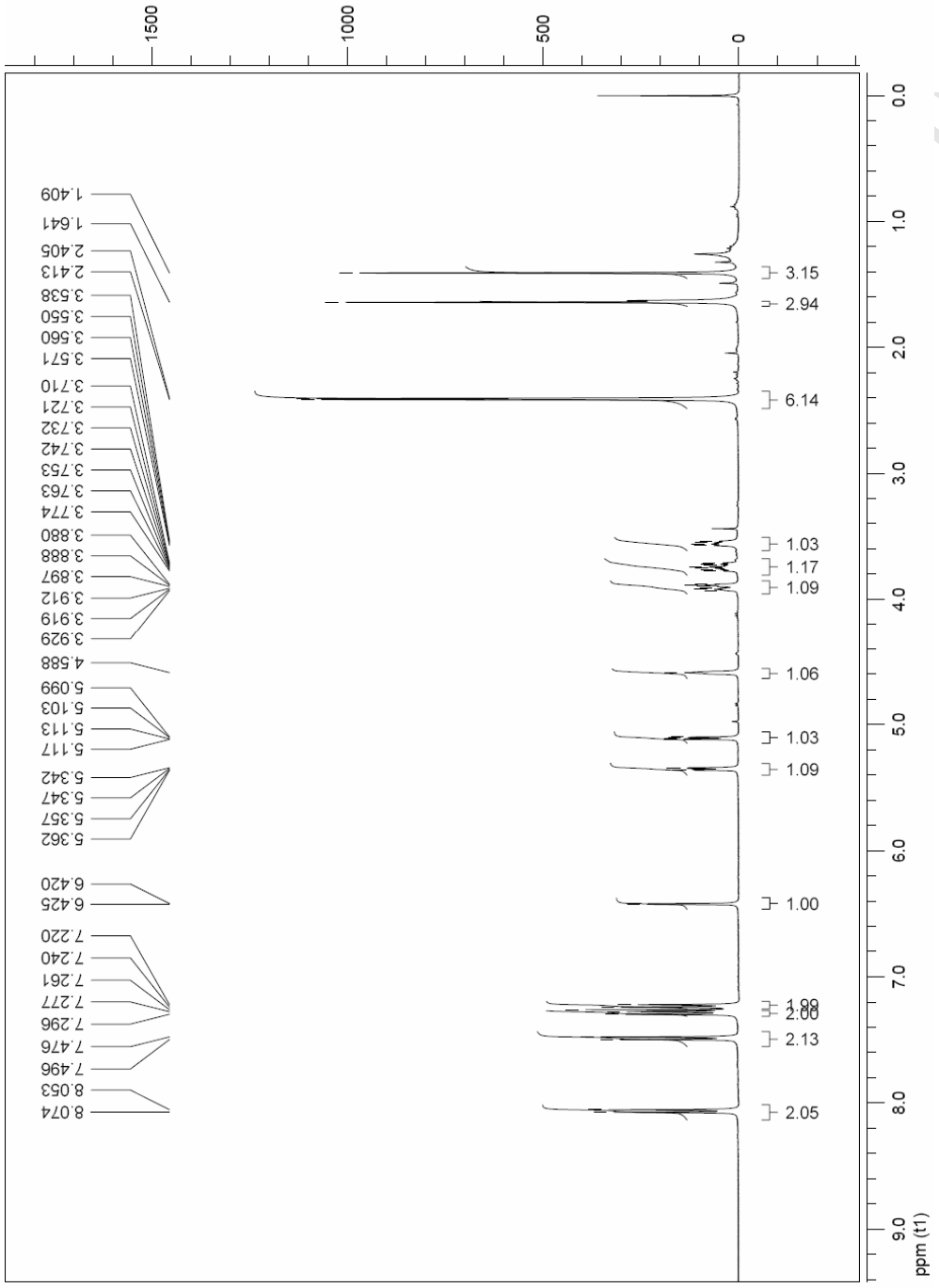
2fe


2000
1500
1000
500
0
0.000000
1.658
3.296
3.315
3.334
4.676
4.696
4.714
7.108
7.130
7.144
7.151
7.160
7.165
7.177
7.217
7.235
7.255
7.266
7.286
7.303
7.496
7.509
7.518
7.531
8.100
8.113
8.122
8.135
2.00
2.00
9.12
2.01
1.96
0.0
5.0
ppm (t1)

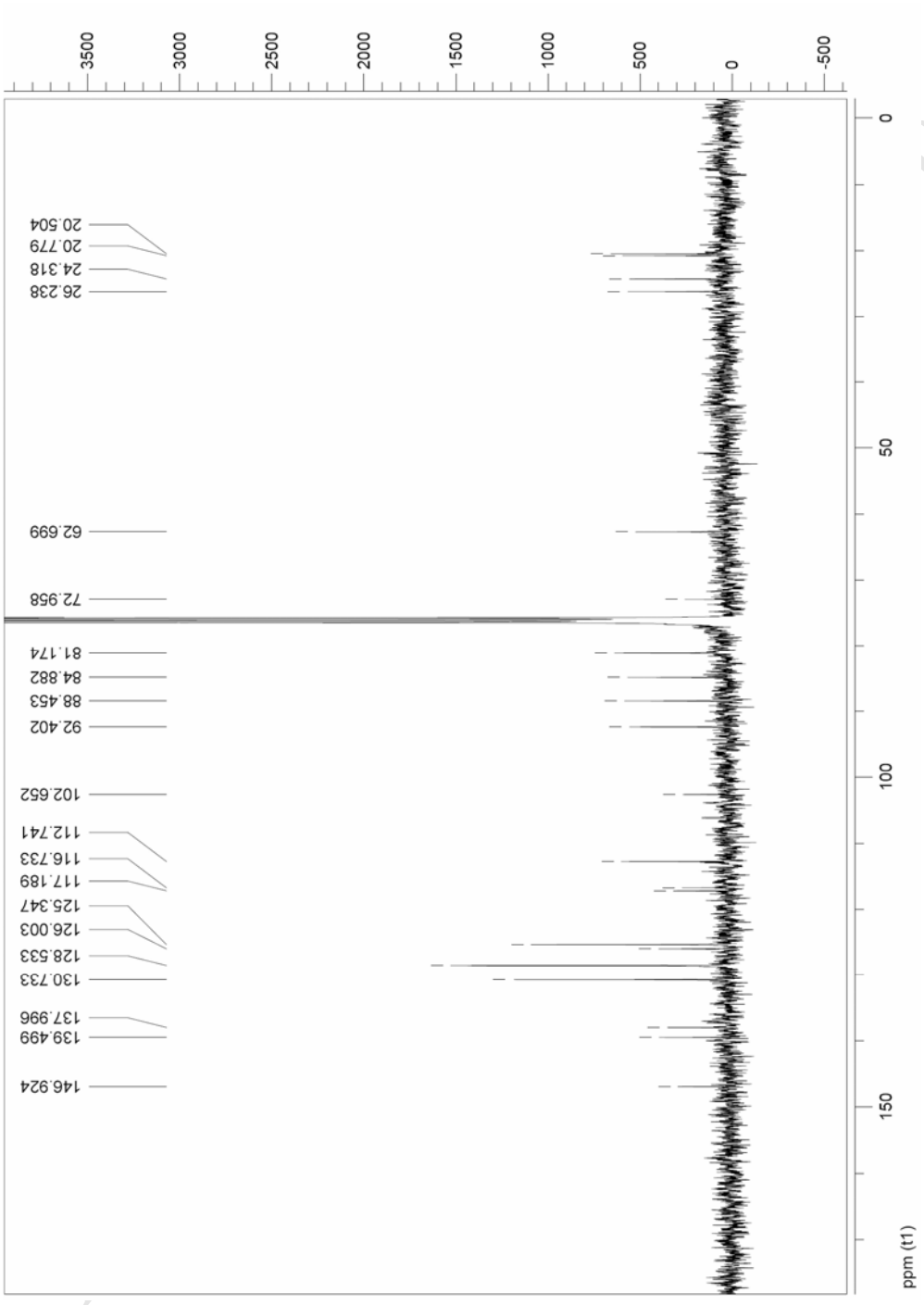
2hf


35.517
49.591
73.958
99.835
114.699
114.915
115.179
115.401
116.109
116.499
125.629
126.200
127.092
127.172
127.862
132.840
136.065
146.046
ppm (t1)

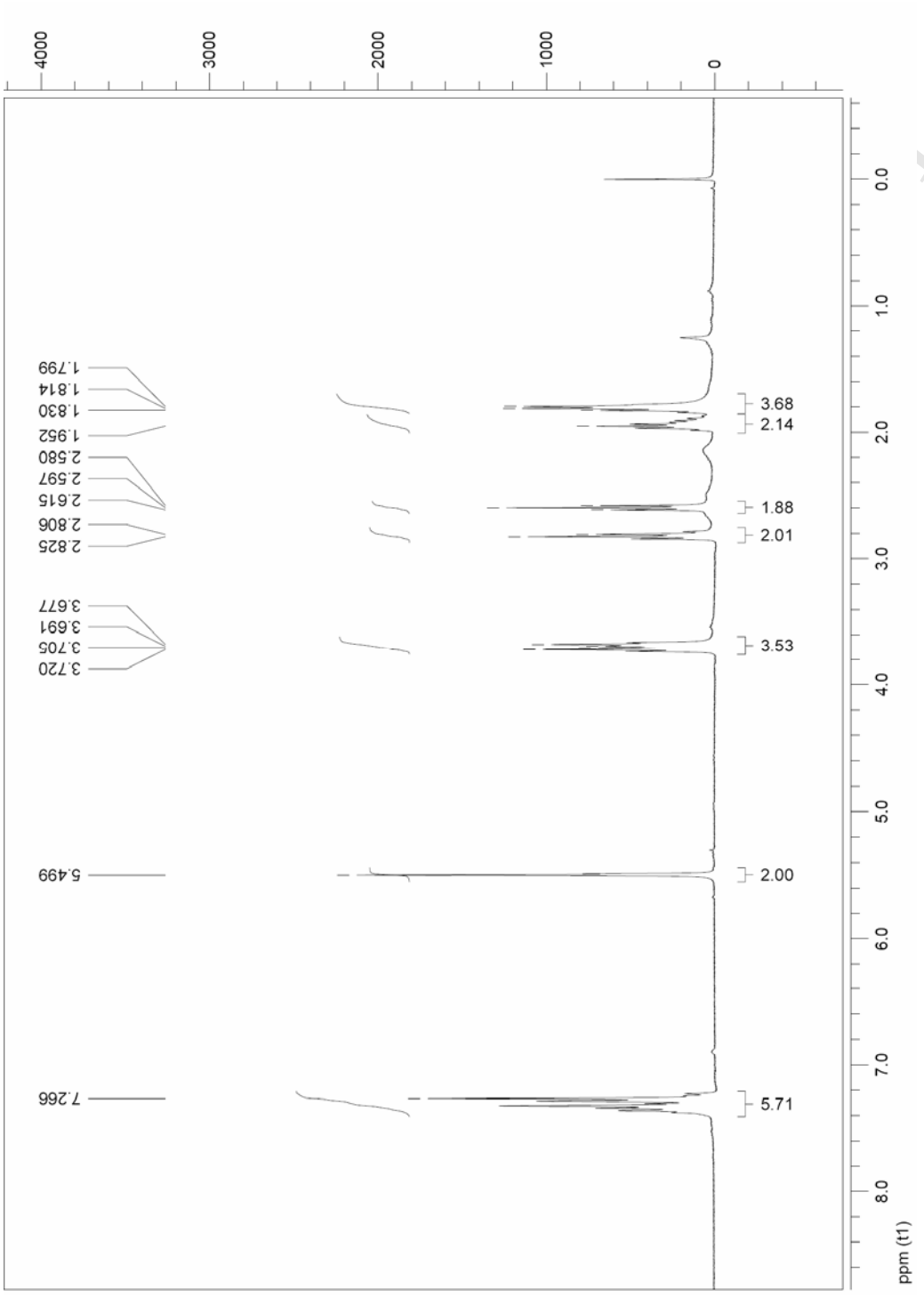
2hf


1500
1000
500
0
1.409
1.641
2.405
2.413
3.538
3.550
3.560
3.571
3.710
3.721
3.732
3.742
3.753
3.763
3.774
3.880
3.888
3.897
3.912
3.919
3.929
4.588
5.099
5.103
5.113
5.117
5.342
5.347
5.357
5.362
6.420
6.425
7.220
7.240
7.261
7.277
7.296
7.476
7.496
8.053
8.074
3.15
2.94
6.14
1.03
1.17
1.09
1.06
1.03
1.09
1.00
1.99
2.00
2.13
2.05
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)

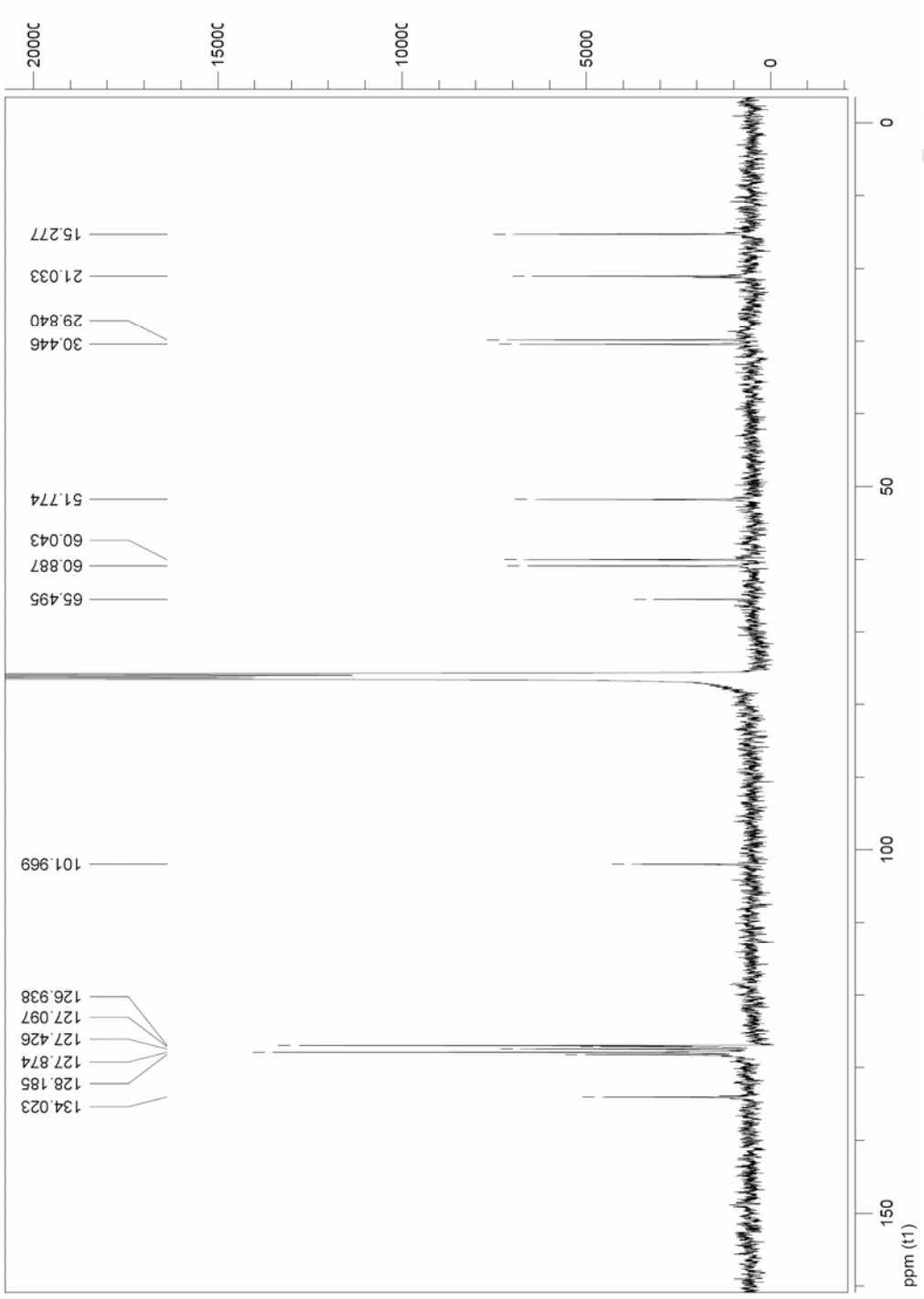
2ig


3500
3000
2500
2000
1500
1000
500
0
-500
0
50
100
150
ppm (t1)
20.504
20.779
24.318
26.238
62.699
72.958
81.174
84.882
88.453
92.402
102.652
112.741
116.733
117.189
125.347
126.003
128.533
130.733
137.996
139.499
146.924

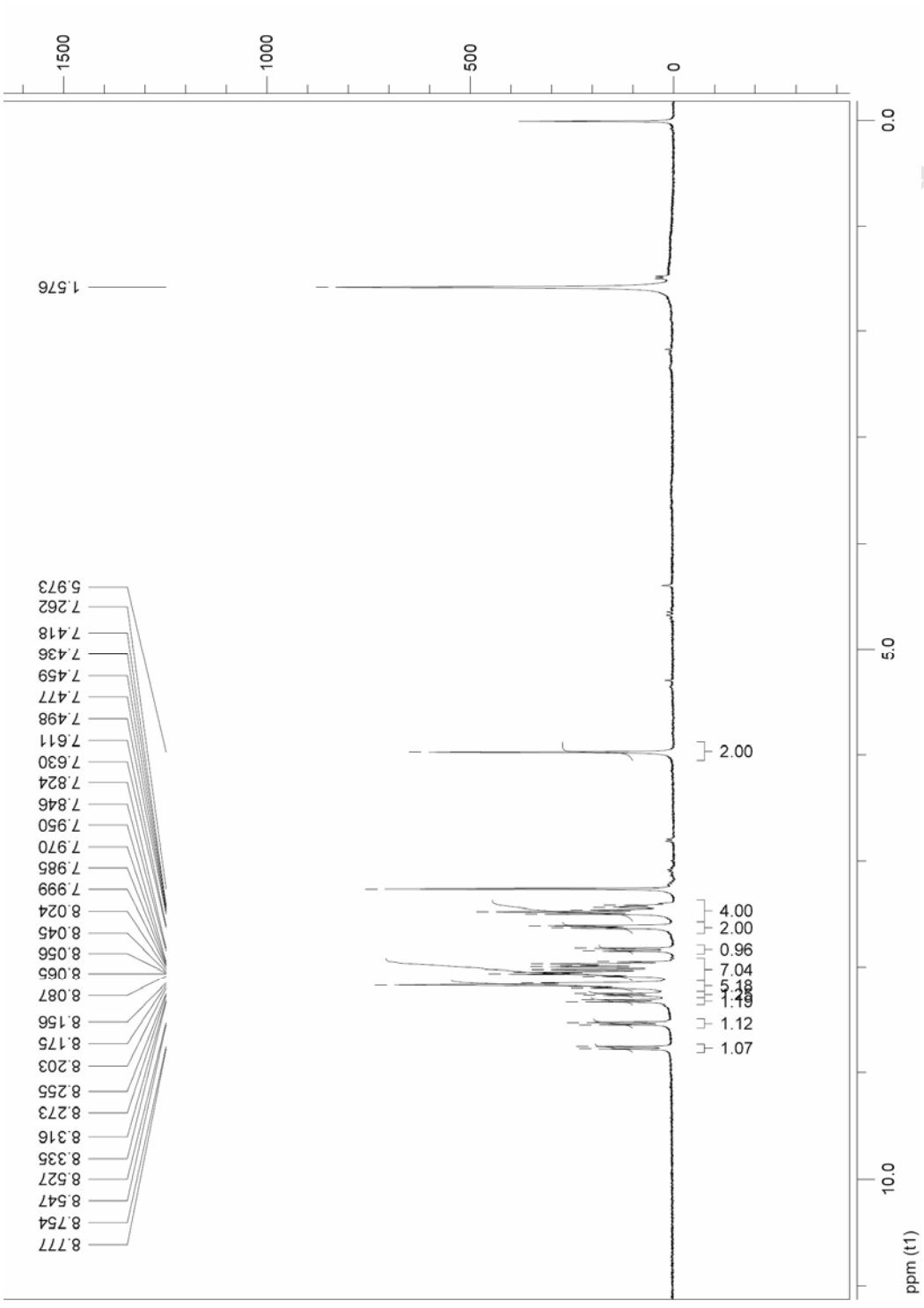
2ig


4000
3000
2000
1000
0
1.799
1.814
1.830
1.952
2.580
2.597
2.615
2.806
2.825
3.677
3.691
3.705
3.720
5.499
7.266
3.68
2.14
1.88
2.01
3.53
2.00
5.71
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

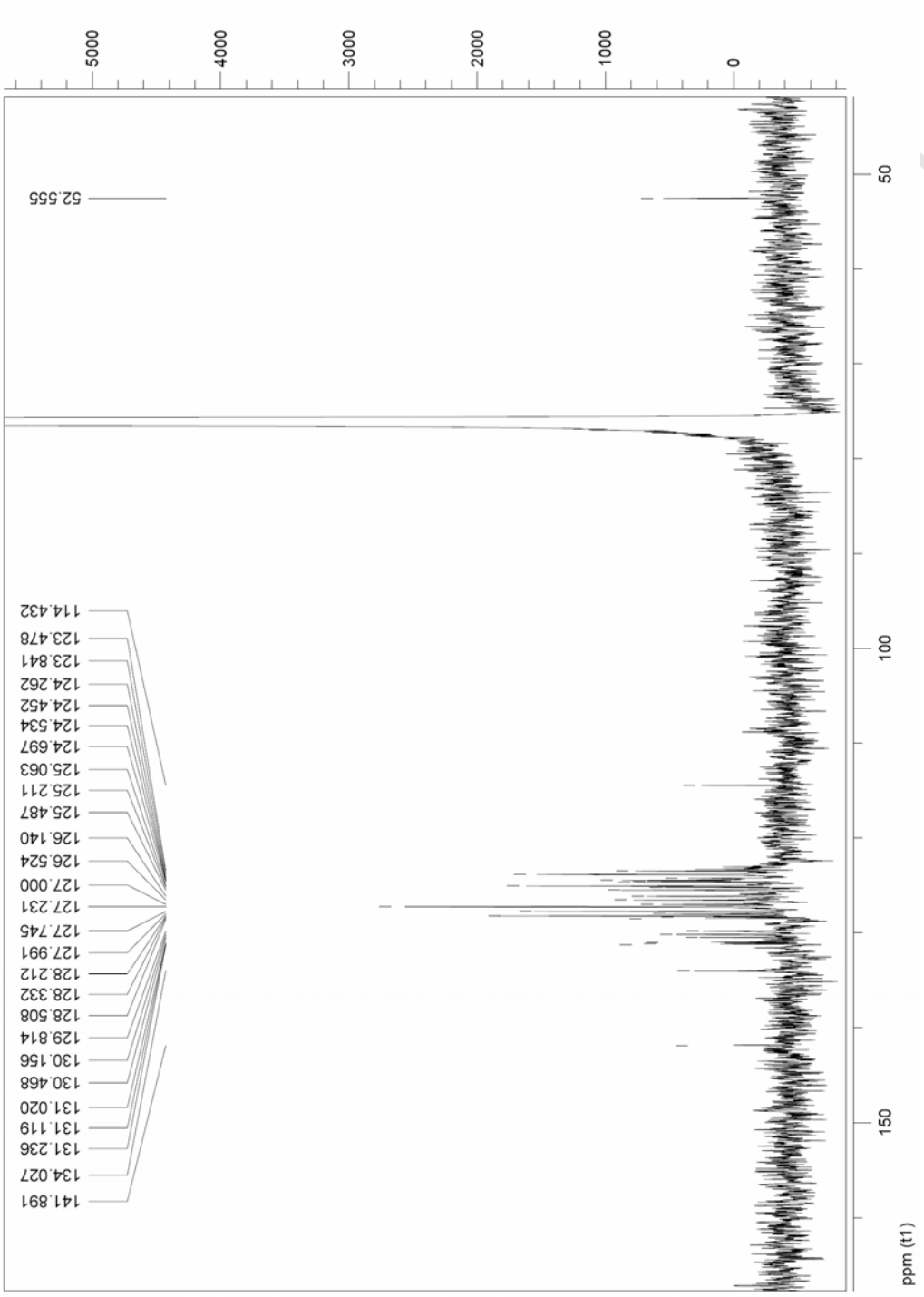
2gh


15.277
21.033
29.840
30.446
51.774
60.043
60.887
65.495
101.969
126.938
127.097
127.426
127.874
128.185
134.023
ppm (t1)

2gh


1500
1000
500
0
0.0
5.0
10.0
ppm (t1)
1.576
5.973
7.262
7.418
7.436
7.459
7.477
7.498
7.611
7.630
7.824
7.846
7.950
7.970
7.985
7.999
8.024
8.045
8.056
8.065
8.087
8.156
8.175
8.203
8.255
8.273
8.316
8.335
8.527
8.547
8.754
8.777
2.00
4.00
2.00
0.96
7.04
5.18
1.19
1.12
1.07

2ei


5000
4000
3000
2000
1000
0
52.555
114.432
123.478
123.841
124.262
124.452
124.534
124.697
125.063
125.211
125.487
126.140
126.524
127.000
127.231
127.745
127.991
128.212
128.332
128.508
129.814
130.156
130.468
131.020
131.119
131.236
134.027
141.891
50
100
150
ppm (t1)

2ei

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 1

```
Bond precision:  C-C = 0.0032 A          Wavelength=0.71073

Cell:            a=19.067(4)     b=5.5586(11)       c=17.969(4)
                 alpha=90        beta=109.77(3)     gamma=90
Temperature:     293 K
```

	Calculated	Reported
Volume	1792.2(7)	1792.2(6)
Space group	P 21/c	P2(1)/c
Hall group	-P 2ybc	?
Moiety formula	C23 H17 N3	?
Sum formula	C23 H17 N3	C23 H17 N3 O0
Mr	335.40	335.40
Dx,g cm-3	1.243	1.243
Z	4	4
Mu (mm-1)	0.075	0.075
F000	704.0	704.0
F000’	704.23	
h,k,lmax	25,7,24	25,7,24
Nref	4535	4482
Tmin,Tmax	0.985,0.985	
Tmin’	0.985	

```
Correction method= Not given

Data completeness= 0.988          Theta(max)= 28.440

R(reflections)= 0.0527( 2189)     wR2(reflections)= 0.1602( 4482)

S = 0.985                 Npar= 236
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT026_ALERT_3_C Ratio Observed / Unique Reflections too Low ....         49 %
PLAT241_ALERT_2_C Check High      Ueq as Compared to Neighbors for         C2
PLAT242_ALERT_2_C Check Low       Ueq as Compared to Neighbors for         C6
PLAT331_ALERT_2_C Small Average Phenyl   C-C Dist. C1     -C6           1.37 Ang.
```

Alert level G

```
CELLZ01_ALERT_1_G Difference between formula and atom_site contents detected.
CELLZ01_ALERT_1_G ALERT: Large difference may be due to a
           symmetry error - see SYMMG tests
          From the CIF: _cell_formula_units_Z    4
          From the CIF: _chemical_formula_sum  C23 H17 N3 O0
          TEST: Compare cell contents of formula and atom_site data

          atom    Z*formula  cif sites diff
          C         92.00     92.00    0.00
          H         68.00     68.00    0.00
          N         12.00     12.00    0.00
          O          4.00      0.00    4.00
PLAT005_ALERT_5_G No _iucr_refine_instructions_details  in the CIF          ? Do !
PLAT199_ALERT_1_G Check the Reported _cell_measurement_temperature        293 K
PLAT200_ALERT_1_G Check the Reported   _diffrn_ambient_temperature        293 K
PLAT371_ALERT_2_G Long   C(sp2)-C(sp1) Bond  C10    -   C11    ...       1.44 Ang.
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         26
           N3  -C8  -C9  -C10  -140.00  4.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         27
           C7  -C8  -C9  -C10    39.00  4.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         28
           C8  -C9  -C10 -C11   -37.00  7.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         29
           C9  -C10 -C11 -C16    18.00  0.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         30
           C9  -C10 -C11 -C12    -3.00  4.00   1.555   1.555   1.555   1.555
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   4 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  11 ALERT level G = General information/check it is not something unexpected

   4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   4 ALERT type 2 Indicator that the structure model may be wrong or deficient
   1 ALERT type 3 Indicator that the structure quality may be low
   5 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 01/06/2013; check.def file version of 24/05/2013

Datablock 1 - ellipsoid plot