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Graphical Abstract

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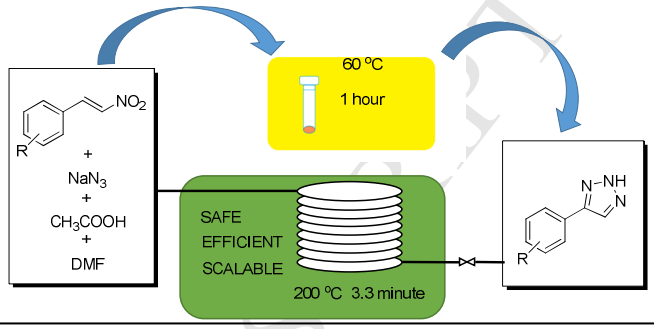

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A Flow Strategy for the Rapid, Safe and Scalable Synthesis of N-H 1, 2, 3-Triazoles via Acetic Acid Mediated Cycloaddition between Nitroalkene and NaN_3

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ABSTRACT

The N-unsubstituted 4-aryl-1H-1,2,3-triazoles were synthesized via the acetic acid promoted cycloaddition between β-nitrostyrenes with sodium azide under transition-metal-free conditions in a continuous flow microreactor. The continuous-flow microreactor provided a safe environment for the dangerous reagents NaN_3 and nitroalkene, and offered such a rapid procedure that the triazoles were formed in less than 4 minutes. In addition, the excess sodium azide was quenched by the by-product HNO_2 in the presence of acetic acid. The scale-up experiment proved again that the yield did not drop in the flow reaction. Moreover, the synthesis of N-unsubstituted 1,2,3-triazole was also explored via a one pot reaction with aldehyde, nitromethane and sodium azide, and this reaction was monitored with an "in-tube retention time gradient" (IT-RTG) technology, which may be a novel application of the continuous-flow microreactor.

Introduction

In the past decades, more and more research works have concentrated in the development of microreactors and continuous flow technology, because the continuous-flow microreactors possess a great many of benefits towards conventional batch-style reactor, such as easily controllable reaction parameters and excellent scalability to industrial level by simple number-amplification[1]. The continuous-flow microreactor have been applied in many kinds of organic reactions such as selective nitrification,[2] catalytic hydrogenation,[3] oxidation,[4] Grignard reaction,[5] synthesis of heterocycles,[6] C-C and C-N coupling.[7] Moreover, because of the enhanced heat- and mass-transfer ability, the flow reactor provides safe reaction environment to avoid the potential explosion caused by regional overheating or high active chemicals.[8] In addition, the high surface area-to-volume-ratio and low waste generation are also well-known advantages of continuous-flow reactor.[9]

The 1,2,3-triazoles are a class of vital heterocycle moieties that display many biological activities,[10] such as anti-HIV,[11] antifungal,[12] antiviral,[13] and antimicrobial aitivities.[14] So the synthesis of 1,2,3-triazoles was concerned greatly in recent years.[15] The conventional method of generating triazoles is the Huisgen 1,3-dipolar cycloaddition of alkynes with azides.[16] The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) was independently developed by the Sharpless' group and Meldal' s group to offer 1,4-disubstituted triazoles, and it was well-known as "click chemistry" due to its high chemo and regioselectivity.[17] Many works have revealed that the synthesis of triazole can greatly benefit from continuous-flow processing.[18] As the triazole are usually synthesized as the pharmaceutical, in-line metal scavenging, nontoxic metal catalyst and metal-free synthesis have to be developed.[19] In 2005, Quiclet-Sire and Amantini respectively reported that nitroalkenes were utilized to form the N-unsubstituted 4-aryl-1*H*-1,2,3-triazoles,[20] which have great potential in anticancer drugs.[21] That bright an alternative

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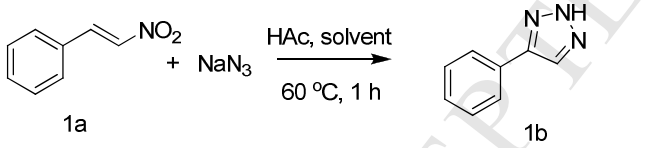
route to synthesize the triazole via the cyclization of nitroalkenes with azides.[22] However, hydrazoic acid may be generated in the reactions, which is toxic and explosive substance, and nitroalkenes are not as safe as the terminal alkynes. Conducting the reaction in a continues-flow microreactor will limit the contact of toxic intermediates, because they can be consumed in situ.[23] In 2010 and 2011, Bernhard Gutmann and Prakash B. Palde have independently reported the application of continuous-flow microreactor in the synthesis of tetrazoles, which was the acid-promoted cyclization of nitrile with the risky reagent NaN_3.[24] Therefore, we believe that the continuous-flow manner will be a good strategy for the cyclization of nitroalkenes with NaN_3. In this paper, we describe that acetic acid catalyzed to afford 4-aryl-1*H*-1,2,3-triazoles in a concise self-made continuous-flow microreactor.

Results and Discussion

The conditions optimization in Batch. The synthesis of 4-phenyl-N*H*-1,2,3-triazoles is selected as the model reaction, and it has been promoted by several acid catalyst, including pδ toluenesulfonic acid (TsOH) [22b] and Amberlyst-15.[22c] However, when the strong Bronst acids are employed as catalyst, the releasing of toxic HN_3 is inevitable. A weak acid such as acetic acid may reduce this risk. In the initial exploration, a mixture of β-nitrostyrene (**1a,** 0.3 mmol), sodium azide (0.6 mmol), 10 mol% acetic acid was dissolved in DMF then heated at 60 °C for 1 hour. The 4-phenyl-NH-1,2,3-triazole was obtained in 56% isolated yield. We optimized the reaction conditions carefully in a sealed tube, and we found that the amount of acetic acid was the key point (table 1). With the optimal amount of acetic acid (2.5 equiv. to β-nitrostyrene), the target product was obtained with >90% yield. Either more or less acetic acid gave unsatisfactory yield, especially when the dosage of acetic acid increased to 20 equivalents, the reaction did not occur and no desired product was obtained, whereas a catalyst-free reaction still afforded 40% yield of triazole.

Table 1. Conditions optimization for the cyclization of δ β-nitrostyrene with NaN_3 to afford 1,2,3-triazole in batch [a]



Entry	Amount of acetic acid (equiv.)	Yield (%)
1	0.1	56
2	0.5	77
3	1.0	85
4	2.0	84
5	2.5	93
6	5.0	77
7	10	71
8	20	0
9	-	40
10	2.5 (TsOH)	0
11	0.5 (TsOH)	93 ref. [22b]

[a] Reaction conditions: 1a (0.3 mmol), NaN_3 (2.0 equiv.), acid (indicated amount) and solvent (2 mL) were heated at 60 °C for 60 minutes.

The detailed exploration for the amounts of the acetic acid is presented in the table S2.

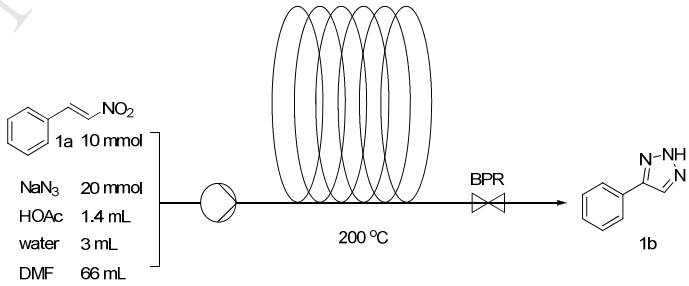
It seems that the acidity of the reaction solution was a key factor. The yield improved with the increasing amount of acid in low acidity range, but too much acid would protonate NaN_3 then the cyclization was restrained because the [3+2] cycloaddition of N_3^- to electro-deficient olefin is the critical step. So the optimal amount of weak acid (2.5 equiv. acetic acid) can play the equal role to a small amount of strong acid (0.5 equiv. TsOH [22b]), and the "lethal dose" of AcOH is several folds of TsOH (table 1, entry 8 and 10). It's interesting that the optimal dose for AcOH is the "lethal dose" for TsOH. Because one molecule of HNO_2 generates with the formation of triazole, the existence of sufficient HOAc is helpful to consume the excess NaN_3 due to the following reaction (eq. 1):

$$NaN_3 + HNO_2 + HOAc \longrightarrow NaOAc + N_2O + N_2 + H_2O \quad \text{eq.1}$$

We estimated the residual N_3^- in the reaction mixture with the Fe (III) colorimetry,[25] and we found that most of the excess NaN_3 had been destroyed along with the process of the reaction, especially in high temperature reaction (table S3). That highlights the safety of the acetic acid promoted synthetic method.

Additionally, Lewis acids are less active than acetic acid, and bases are ineffective. Various solvents were tested, such as methanol, water, dichloromethane, acetone and toluene. The polar non-protonic solvent gave the best result. That agreed with the known report [22b] (For full version of conditions optimization, see supporting information).

Table 2. The optimization for the synthesis of 4-phenyl-NH-1, 2, 3-triazoles in the continuous flow reactor and its schematic diagram [a]

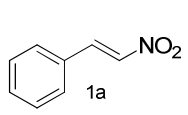
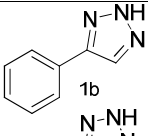
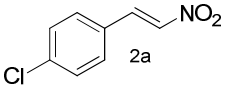
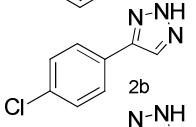
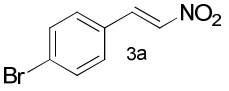
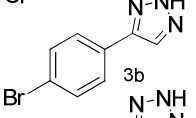
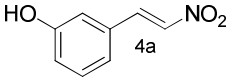
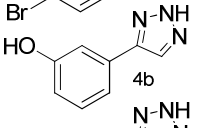
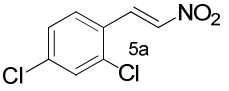
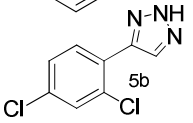
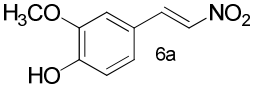
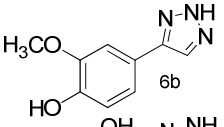
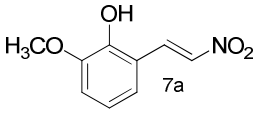
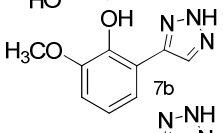
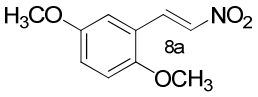
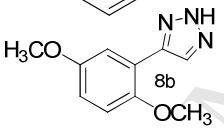
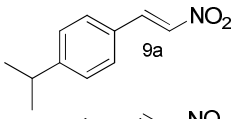
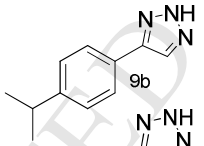
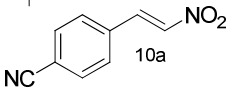
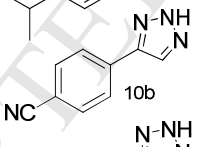
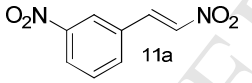
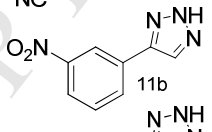
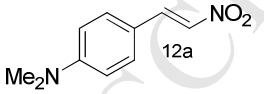
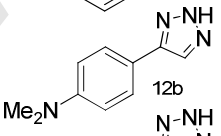
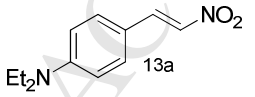
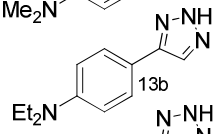
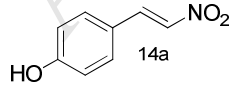
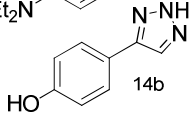


Entry	Flow rate (mL/min)	Retention time (min)	Temp (°C)	Yield (%)
1	1.0	1.65	120	75
2	1.0	1.65	150	81
3	1.0	1.65	200	85
4	0.5	3.3	200	93
5	0.33	5.0	200	93

[a] Reaction conditions: 1a (10 mmol), NaN_3 (2.0 equiv.), acetic acid (2.5 equiv.), DMF (66 mL), H_2O (3 mL) in continuous flow equipment with a 54 bar back pressure regulator (BPR).

The optimization in continuous-flow microreactor. When we replaced the batch reaction by a continuous-flow reactor, we found that the solubility of sodium azide was a problem.

Table 3. AcOH-mediated 1, 3-dipolar cycloaddition of nitroolefins with NaN_3 for the synthesis of 4-Aryl-NH-1,2,3-triazoles[a]

entry	substrate	product	Batch reaction[a] yield (%)	Continuous flow reaction[b] yield (%)
1			93	93
2			92	92
3			80	83
4			65	67
5			73	96
6			77	80
7			65	81
8			90	91
9			90	94
[d]10			50	62
11			65	83
12			73[c]	85
13			50[c]	71
14			75	86

[a] Reaction conditions in batch: nitroolefins (0.3 mmol), NaN_3 (2.0 equiv.), acetic acid (2.5 equiv.) and DMF (2 mL) were heated at 60 °C for 1 h in a sealed tube. [b] Reaction conditions in continuous flow: a mixture of nitroolefins (3.0 mmol), NaN_3 (2.0 equiv.), acetic acid (2.5 equiv.), DMF (20 mL) and H_2O (1 mL) was pumped to get through the microreactor at 200 °C with a retention time for 3.3 min. [c] The reaction was performed at 140 °C for 3 h in batch. [d] The corresponding tetrazoles (4-(1H-tetrazole-5-yl) -phenyl-NH-1,2,3-triazole) that was formed from the nitrile was detectable. The isolated yield of the tetrazole is 19% and 25% in the batch and continuous-flow reaction respectively.

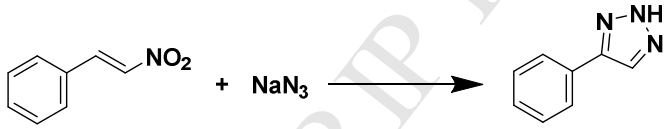
Therefore, minimized water was added into the solvent to resolve this problem, and more optimization were proceeded as listed in table 2. The synthesis of 4-phenyl-1,2,3-1*H*-triazole was still chosen as the model reaction, and the reaction could be performed at higher temperature in a microreactor to enhance the efficiency of synthesis by shortening the reaction time. These results showed that the reaction in the microreactor was more efficient than in the sealed tube. When the reaction was performed at 120 °C and a retention time of 1.65 min, 75% yield of 1b was obtained (table 2, entry1). Increasing the temperature from 120 °C to 200 °C, the yield improved by 10% at the same retention time. To extend the reaction time slightly gave the excellent yield of triazole, which was 93% at 200 °C for 3.3 min (table 2, entry 4). To our delight, the reaction in the continuous-flow microreactor have better chemoselectivity than in the sealed tube, which because the cycloaddition of nitroalkene with azide benefits from high temperature as mentioned in the literature.[20a] That may be deduced from the high cycloaddition' activation energy, so the higher reaction temperature provides the better selectivity.

The scope of functionalities. Under the optimized experimental conditions, a range of nitroolefins were used to investigate the scope of the methodology both in batch and the continuous flow equipment. As shown in table 3, the nitroolefins with electron-donating or electron-withdrawing group on aryl ring all reacted smoothly with sodium azide to afford the corresponding products in good to excellent yields. Especially, the nitroolefins bearing isopropyl, methoxyl and chloro atom gave excellent yields (table 3, entries 1, 2, 5, 8, 9). The strong electron-withdrawing substituents on the aryl ring are disadvantageous for the reaction, and the corresponding products were acquired in moderate yields (table 3, entries 10 and 11). As [3+2] cycloaddition was catalyzed by acid, the reaction of nitroolefin bearing basic amino group was so slow that only a small amount of **12b** and **13b** was formed at 60 °C for 1 hour. Raising the temperature to 140 °C and extending the reaction time to 3 h gave the satisfactory results. As expected, the reactions in continuous flow microreactor possessed better selectivity than in batch for most substrates. For example, TLC monitoring showed several by-products in the reactions of **7a** in batch, but only few of them were detectable in the continuous-flow protocol. Besides, both of **12b** and **13b** obtained good yields in such a short retention time.

The scaled-up study for the synthesis of triazoles. To investigate the scale-up capabilities of the continuous process beyond laboratory scale, a gramscale reaction was performed (Scheme 1). The flow process was run continuously at the flow rate of 0.5 mL/min, and 73 mL of reaction liquid contained 10 mmol of β-nitrostyrene was collected in 146 minutes and gave 1.35g of 1b. The yield was 93%. We compare our results with other reported methods on gram scale (scheme 1). When the reaction was catalyzed by p-toluenesulfonic, the yield of gramscale preparation (70 mmol) of 4-phenyl-NH-1,2,3-triazole dropped by 12% comparing with the 0.3 mmol-scale reaction, [22b] and yield decreased by 9% as well when the same reaction catalyzed by Amberlyst-15 was amplified to 10 mmol scale from 0.2 mmol-scale.[22c] From the reported results above, we can deduce that the amplification effect is very serious in this reaction, especially in batch. The continuous-flow manner can easily solve the problem because the chemical reaction has been in a steady state during the reaction. Without any losing of yield we amplified the reaction to 10 mmol scale from 0.3 mmol.

The synthesis of triazoles from a one-pot procedure. Because nitroolefins was artificially synthesized from aldehydes and nitromethane, the protocol that nitroalkenes as substrate seems to be arduous. Encouraged by the recent reports,[22g] we attempted to perform the condensation and the cycloaddition in "one pot" procedure to produce NH-1,2,3-triazoles from the simple and accessible materials. That meant a more step-economical method for the synthesis of N-unsubstituted 4-aryl-1*H*-1,2,3-triazoles, as the separation of the intermediates is avoidable. We conducted the three-component reaction of nitroalkane, aldehydes and sodium azide with acetic acid as the catalyst. The model reaction of benzaldehyde, nitromethane and sodium azide was carried out under different reaction conditions.

Scheme1. The scale-up capabilities of the continuous-flow process



0.3mmol	93%	Ref. 22b
70mmol	81%	TsOH as catalyst
0.2mmol	95%	Ref. 22c
10mmol	86%	Amberlyst as catalyst
0.3mmol	93%	This work
10mmol	93%	Acetic acid as catalyst

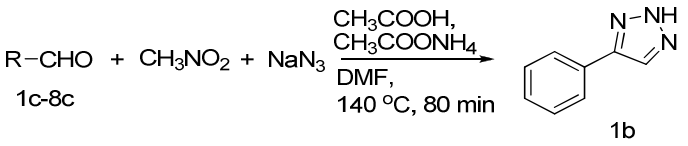
The best results was obtained when the reaction was carried out at 140 °C for 80 min in the presence of 8 equivalent acetic acid and 1 equivalent ammonium acetate, and the yield was up to 97% (table 4, entry 1). The lower reaction temperature did not give a desired yield of triazole (table 4, entry 2). Furthermore, the lack of either glacial acetic acid or ammonium acetate led to the decrease of the yield (Table 4, entry 3, 4).

Under the optimized reaction conditions, a range of aldehydes were used to investigate the tolerance of the reaction. For aromatic aldehydes, the desired triazoles were obtained in good to excellent yields after isolated by silica gel chromatography (Table 4, entries 1, 5~11). Obviously, the influence of the functional group for the reaction was matched with the stepwise synthesis. The aromatic aldehydes bearing halogen atom, methoxy and alkyl group had a positive impact on the reaction, but the substrates with strongly electron-withdrawing group, such as NO_2, gave relatively low yields (Table 4, entry 10). Besides, because some nitroolefins are not easy to acquire, one-pot procedure to directly obtain the 4-aryl-1*H*-1,2,3-triazoles is favorable.

For continuous flow microreactor, we developed an "in-tube retention time gradient" (IT-RTG) technology, which is used for obtaining more data with less experimental operations. When the reaction mixture was at steady-state, the instantaneous switch of flow rate may lead to a gradient distribution of the retention time when the reaction solution were retained in the reaction channel. In this study, when the solution steadily flew through a 3.0 mL reaction channel at 1 mL/min, the flow rate was switched instantaneously to 0.1 mL / min at a certain time. As a result, the reaction solution remained in the channel was time-gradient distributed. The retention time of the reaction liquid at the

channel exit was 3 min, while at the entrance was 30 min and in the channel was gradient-distributed from 3 to 30 min according to their distances to the exit. Every 0.1 mL solution were collected for detecting, and 30 samples with different reaction times were obtained in one experiment, while the reagent consumption was only several milliliters. We utilized the IT-RTG technology to monitor the one-pot synthesis of 1,2,3-triazole, the results were presented in Fig.1 ultimately.

Table 4. The synthesis of 4-aryl-NH-1,2,3-triazole through a three-component reaction [a]



Entry	R	Product	Yield (%) [b]
1	phenyl (1c)	1b	97
2	phenyl (1c)	1b	72[c]
3	phenyl (1c)	1b	73[d]
4	phenyl (1c)	1b	84[e]
5	4-chlorophenyl（2c）	2b	89
6	4-bromophenyl（3c）	3b	90
7	3-hydroxphenyl (4c)	4b	68
8	2,5-dimethoxyphenyl (5c)	8b	88
9	4-isopropylphenyl（6c）	9b	92
10	3-nitrophenyl (7c)	11b	70
11	4-(dimethylamino)phenyl(8c)	12b	84

[a] Reaction conditions: aldehydes (1 mmol), nitroalkanes (2 mmol), sodium azide (2 mmol), CH_3COOH (8 equiv.), CH_3COONH_4 (1 equiv.), DMF (6 ml) at 140 °C for 80 min. [b] Isolated yield. [c] the reaction was performed at 60 °C for 80 min; [d] in the absence of CH_3COONH_4; [e] in the absence of CH_3COOH

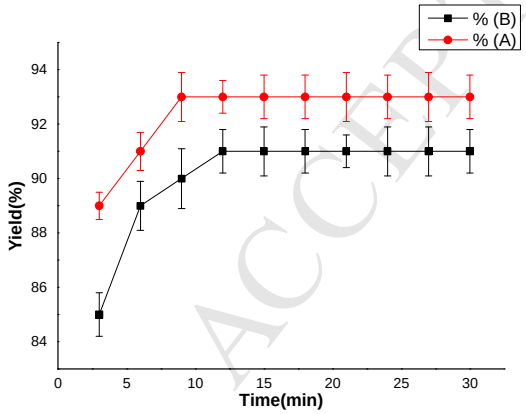


Fig.1 Monitoring of the synthesis of 1,2,3-triazole with IT-RTG technology. A: the reaction of benzaldehyde (1c) B: the reaction of 4-isopropylbenzaldehyde (4c)

Both benzaldehyde (A) and 4-isopropylbenzaldehyde (B) were carried out in the continuous flow microreactor at 190 °C with the IT-RTG operation. In a short time (3 min), the reactions reached high yield (according to HPLC detection), which were 89% for 1c and 85% for 4c. With the extension of reaction time, the yields increased and reached steady-state after 12 min.

DSC experiments. The cyclization of β-nitrostyrene with NaN_3 is usually an exothermic reaction. As these two kinds of reagents are dangerous under heating, the differential scanning calorimetry (DSC) measurements were carried out for the reactions of 2,5-dimethoxy-nitro-styrene and 2,5-dimethoxybenzaldehyde (one pot reaction). The samples were heated in a sealed crucible from 25 °C to 200 °C at a ramp of 10 °C/min. The results are shown in Figure 2.

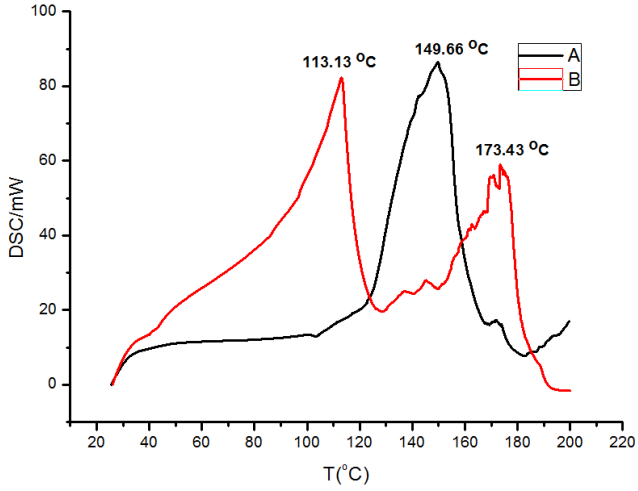


Fig.2 DSC results for the reactions. A: 2,5-dimethoxy-β-nitrostyrene reacts with NaN_3 to afford 1,2,3-triazole. B: 2,5-dimethoxybenzaldehyde reacts with NaN_3 and CH_3NO_2 to afford 1,2,3-triazole.

In the cyclization of 2,5-dimethoxyδ β-nitrostyrene with NaN_3, the reaction rate is quite slow when the temperature is below 100 °C. The reaction dramatically speeds up from about 120 °C, and the exothermic peak appears at 149.66 °C (A). In the one-pot reaction that forms the same product, there are two exothermic peaks, one is at 113.13 and the other is at 173.43 °C (B). We suspect that the two peaks indicate the two steps of the reaction, and there are complex side reactions.[20a]

Conclusion

We demonstrated that acetic acid was an effective catalyst for the synthesis of 4-aryl-N*H*-1,2,3-triazoles from nitroalkenes and sodium azide, and continuous-flow technology offered outstanding safety and efficiency. When the reaction was conducted in a high-temperature/high-pressure system, most target products were obtained in a very short period of time with excellent yield. Moreover, the continuous-flow reaction could be directly amplified without any loss of yield. On the other hand, the one-pot three-component reaction of aldehydes, nitromethane and NaN_3 was proved to be a convenient protocol for the same synthesis. The scalable synthesis in the manner of continuous-flow appears to be well appropriate to produce safely industrial-scale 4-aryl-NH-1,2,3-triazoles.

Experimental Section

Typical procedure for the synthesis of 1,2,3-triazole in batch: formation of 4-phenyl-NH-1,2,3-triazoles (1a): A mixture of 0.3 mmol δ β-nitrostyrene, 0.6 mmol NaN_3 , 0.75 mmol HOAc and 2 mL DMF was stirred in a sealed tube at 60 °C for 1h. On completion of the reaction (detected by TLC), the reaction liquid was cooled to room temperature, quenched with

H_2O (10 mL) and extracted with EtOAc (3×10 mL). The organic phase was dried with hydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (SiO_2, hexanes/EtOAc) to afford the 4-phenyl-N*H*-1,2,3-triazole **1a** as a white solid in 93% yield.

Description of the continuous-flow microreactor. The reaction channel was a stainless steel tube with inner diameter of 0.03 inches and the effective length of 3.6 meters, so the inner volume of the reactor was 1.65 mL. The channel was enwound to the aluminum block that was electrically heated to the desired reaction temperatures and wrapped with asbestos cloth on the outside. The reaction mixture was pumped to get through the reactor pipe by a LC-9A pump, and a 54 bar back-pressure regulator was equipped at the end of the reaction tube. The retention time was controlled by the flow rate. All joints are standard HPLC components which can endure 50 MPa pressure, so the self-made continuous-flow microreactor possesses outstanding safety performance in operation.

Typical procedure for the synthesis of 1,2,3-triazole in continuous-flow microreactor: formation of 4-phenyl-NH-1,2,3-triazoles (1a): A mixture of 1a (3.0 mmol), NaN_3 (2.0 equiv., cation! The sodium azide is dangerous and it must be operated in a hood), acetic acid (2.5 equiv.) with DMF (20 mL) and H_2O (1 mL) was pumped into the reactor with the temperature of 200°C under the flow rate of 0.5 mL/min, then was collected steadily. The yield was calculated from a sample that was collected in 5 minutes and was handled with a general work-up procedure described above. 93% of 1b was obtained as a white solid.

5-phenyl-1*H*-1,2,3-triazole (**1b**) White solid. m.p. 140-143 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.28 (s, 1H), 7.91-7.80 (m, 2H), 7.51-7.39 (m, 2H), 7.37-7.23 (m, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 145.41, 131.30, 129.38, 128.25, 127.66, 125.97. MS (ESI) m/z for $C_8H_8N_3$: 146 ([M+H]$^+$)

5-(4-chlorophenyl)-1*H*-1,2,3-triazole (**2b**), White solid. m.p. 155-157 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 15.22 (s, 1H), 8.40 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 133.06, 129.49, 127.76. MS (ESI) m/z for $C_8H_7ClN_3$: 180 ([M+H]$^+$)

5-(4-bromophenyl)-1*H*-1,2,3-triazole (**3b**), White solid. m.p. 170-171°C; ^{1}H NMR (600 MHz, DMSO-D6) δ 15.23 (s, 1H), 8.41 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-D6) δ 143.90, 132.26, 132.10, 127.65, 120.00. HRMS Calcd (ESI) m/z for $C_8H_7BrN_3$: [M+H]$^+$ 223.9823, found: 223.9818

3-(1*H*-1,2,3-triazol-5-yl)phenol (**4b**), White solid. m.p. 205-208 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.30 (s, 1H), 7.37-7.26 (m, 3H), 6.82 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 158.31, 131.97, 130.51, 117.01, 115.73, 112.85. MS (ESI) m/z for $C_8H_8N_3O$: 162 ([M+H]$^+$)

5-(2,4-dichlorophenyl)-1*H*-1,2,3-triazole (**5b**), White solid. m.p. 178-179 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 16.03-14.47 (s, 1H), 8.73-8.15 (m, 1H), 8.13-7.80 (m, 1H), 7.75 (s, 1H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-D6) δ 133.78, 132.21, 131.79, 130.20, 128.89, 128.32. MS (ESI) m/z for $C_8H_6N_2Cl_2$: 214 ([M+H]$^+$)

2-methoxy-4-(1*H*-1,2,3-triazol-5-yl)phenol (**6b**), White solid. m.p. 165-171 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 9.64 (s, 1H), 7.33 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-D6) δ 190.33, 158.71, 149.67, 127.89, 126.20, 116.31, 110.37, 55.80. HRMS Calcd. (ESI) m/z for $C_9H_{10}N_3O_2$: [M+H]$^+$ 192.0768, found 192.0773

2-methoxy-6-(1*H*-1,2,3-triazol-5-yl)phenol (**7b**), Yellow solid. m.p. 173-174 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.17 (s, 1H), 7.42 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, DMSO-D6) δ 148.60, 144.47, 142.53, 128.28, 119.51, 119.21, 117.46, 111.46, 56.38. HRMS Calcd. (ESI) m/z for $C_9H_{10}N_3O_2$: [M+H]$^+$ 192.0768, found 192.0765

5-(2,5-dimethoxyphenyl)-1*H*-1,2,3-triazole (**8b**), Yellow solid. m.p. 118-119 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 8.19 (s, 1H), 7.58 (s, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (151 MHz, DMSO-D6) δ 153.77, 150.59, 140.90, 129.37, 120.21, 114.53, 113.50, 112.83, 56.46, 55.95. HRMS Calcd. (ESI) m/z for $C_{10}H_{12}N_3O_2$: [M+H]$^+$ 206.0924, found 206.0920

5-(4-isopropylphenyl)-1*H*-1,2,3-triazole (**9b**), White solid. m.p. 145-150 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.20 (s, 1H), 7.92 – 7.43 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-D6) δ 148.58, 145.27, 128.83, 127.27, 126.05, 33.74, 24.32. MS (ESI) m/z for $C_{11}H_{14}N_3$: 188 ([M+H]$^+$)

4-(1*H*-1,2,3-triazol-5-yl)benzonitrile (**10b**), Yellow solid. m.p. 170-172 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 15.41 (s, 1H), 8.59 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 133.21, 125.87, 119.83. MS (ESI) m/z for $C_9H_7N_4$: 171 ([M+H]$^+$)

4-(3-nitrophenyl)-1*H*-1,2,3-triazole (**11b**), Yellow solid. m.p. 201-204 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.28 (s, 1H), 7.76-7.07 (m, 3H), 6.79 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 158.31, 130.49, 116.99, 115.70, 112.84. MS (ESI) m/z for $C_8H_7N_4O_2$: 191 ([M+H]$^+$)

N,N-dimethyl-4-(1*H*-1,2,3-triazol-5-yl)aniline (**12b**) Yellow solid. m.p. 162-164 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 8.02 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 2.89 (s, 6H). ^{13}C NMR (151 MHz, DMSO-D6) δ 150.63, 126.95, 118.56, 112.88. MS (ESI) m/z for $C_{10}H_{12}N_4Na$: 221 ([M+Na]$^+$)

N,N-diethyl-4-(1*H*-1,2,3-triazol-5-yl)aniline (**13b**), Yellow solid. m.p. 105-113 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.01 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 4H), 1.10 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-D6) δ 147.70, 145.10, 127.29, 126.86, 117.37, 112.05, 44.17, 12.96. MS (ESI) m/z for $C_{12}H_{17}N_4$: 217 ([M+H]$^+$)

4-(1*H*-1,2,3-triazol-5-yl)phenol (**14b**), White solid. m.p. 213-214 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 10.61 (s, 1H), 9.80 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 191.46, 163.85, 132.62, 128.95, 116.37. MS (ESI) m/z for $C_8H_8N_3O$: 162 ([M+H]$^+$)

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Supporting Information for:

A Flow Strategy for the Rapid, Safe and Scalable Synthesis of N-H 1,2,3-Triazoles via Acetic Acid Mediated Cycloaddition Between Nitroalkene and NaN_3

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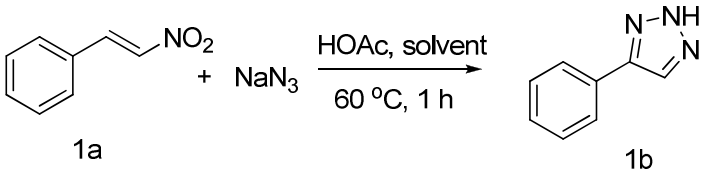
Table of Content

Table S1. Conditions optimization of the cyclization of nitrostyrene with NaN_3 to afford 1,2,3-triazole in batch[a]



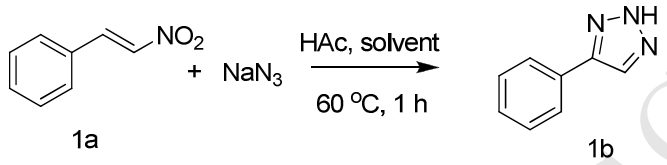
Entry	catalyst	solvent	yield（%）
1	HCOOH	DMF	78
2	TsOH	DMF	0
3	$CuCl_2$	DMF	76
4	$FeCl_3$	DMF	75
5	$BiCl_3$	DMF	70
6	CH_3COOH	DMF	93
7	CH_3COOH	CH_3OH	30
8	CH_3COOH	H_2O	trace
9	CH_3COOH	CH_2Cl_2	trace
10	CH_3COOH	CH_3COCH_3	trace
11	CH_3COOH	toluene	trace
12	CH_3COOH	CH_3OH	90[b]
13	CH_3COOH	DMF	78[c]
14	CH_3COOH	DMF	86[d]
15	Urotropine	DMF	42
16	Tri-n-butylamine	DMF	39
17	-	DMF	40
18	Tri-n-butylamine +TsOH	DMF	72[e]

[a]Reaction conditions: 1a (0.3 mmol), NaN_3 (2.0 equiv), catalyst (2.5 equiv.) and solvent (2 mL) were heated at 60 °C for 60 minutes. [b] 6.0 eqive. NaN_3 and 120 °C; [c]1.6 eq. NaN_3 was used. [d] 1.8 eq. NaN3 was used. [e] 2.5 equiv. TsOH and 1 equiv. Tri-n-butylamine.

We can find that less NaN_3 lead to decrease of yield (entry 13, 14), and pure bases

have no catalytic activity (entry 15, 16). However, the co-existence of acid and base may promote the cyclization (entry 18). Of the tested solvent, only methanol can afford separable product, and by modifying the reaction conditions, the reaction in methanol can provide acceptable yield of triazole. Unfortunately, the required dosage of NaN_3 is too much. (entry 12)

Table S2. The detailed exploration for the amounts of acetic acid (equiv.) between 2.0 and 5.0



Entry	Amount of acetic acid (equiv.)	Yield (%)
1	2.3	90
2	2.4	92
3	2.5	93
4	2.6	92
5	2.7	89
6	3.0	85
7	4.0	80
8	5.0	77

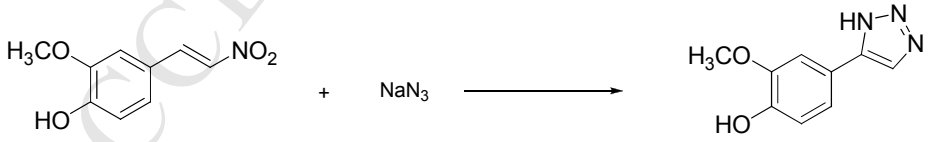
With the increase of amount of acetic acid, the yield of product rise in the first stage, and then decrease. And the optimal dosage of acetic acid was determined for 2.5 equiv.

The estimation of residual NaN_3

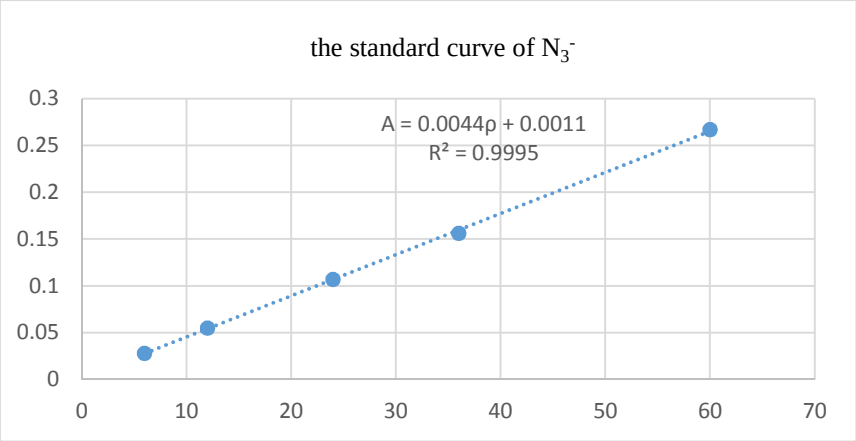
Generally, the residual sodium azide has to be destroyed in the reactions that excess sodium azide is used. However, we do not worry about this question in our protocol. The nitrous acid that generates from the cascade elimination of the cyclization of nitroalkene and NaN_3 can destroy the excess sodium azide in the present of excess acetic acid. We estimated the azide ion in two reactions (the formation of 1b and 6b).

We took an internationally recognized method to detect azide, namely Fe(III) colorimetry at 465 nm wavenumber. As the composition of the reaction liquid is complicated and we can't contain all influence factors in the blank solution, the data we get can only reflect the general trend. Firstly, we confirmed that DMF and tiny amount of ethyl acetate have no effect on the detection method by preparing the same concentration of aqueous solution of sodium azide. Then, we made a series of standard solution of sodium azide containing a certain amount of chromogenic agent and established the standard calibration of azide concentration and absorbance. Finally, we diluted the aqueous phase of the reaction extract to a certain volume and detected the azide concentration to calculate the consumption and the remaining amount of azide.

Detailed process for 6b



m	0.7g		0.45g
M	195		65
n	0.0036 mol		0.0069 mol
	1	:	1.92



Firstly，we diluted the aqueous phase of the reaction extract to 46.8g. Then, we took 500 mg of diluent out and diluted to 0.025L containing a certain amount of chromogenic agent. Later, we conducted the UV-VIS detection at 465 nm wavenumber.

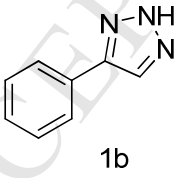
M(N3-)/500mg = ρ * V = ρ * 0.02500

M(N3-)total = M(N3-)/500mg *46.8g / 0.5g

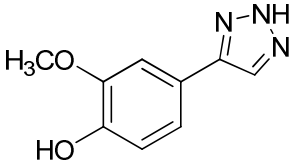
Consumption (%) = (0.45-M(N3-)total)/0.45

T(° C)	140	160	170	190	200
A	0.7024	0.6211	0.5076	0.2961	0.1939
ρ (mg/L)	159.39	140.91	115.11	67.05	43.82
Volume(L)	0.02500	0.02500	0.02500	0.02500	0.02500
M(N_3^-)/500mg	3.98mg	3.52mg	2.88mg	1.68mg	1.10mg
M(N_3^-)total	0.373g	0.330g	0.270g	0.157g	0.103g
Consumption(%)	17	27	40	65	77

Table S3. The estimation of residual NaN_3 in the synthesis of 1b and 6b



1b



6b

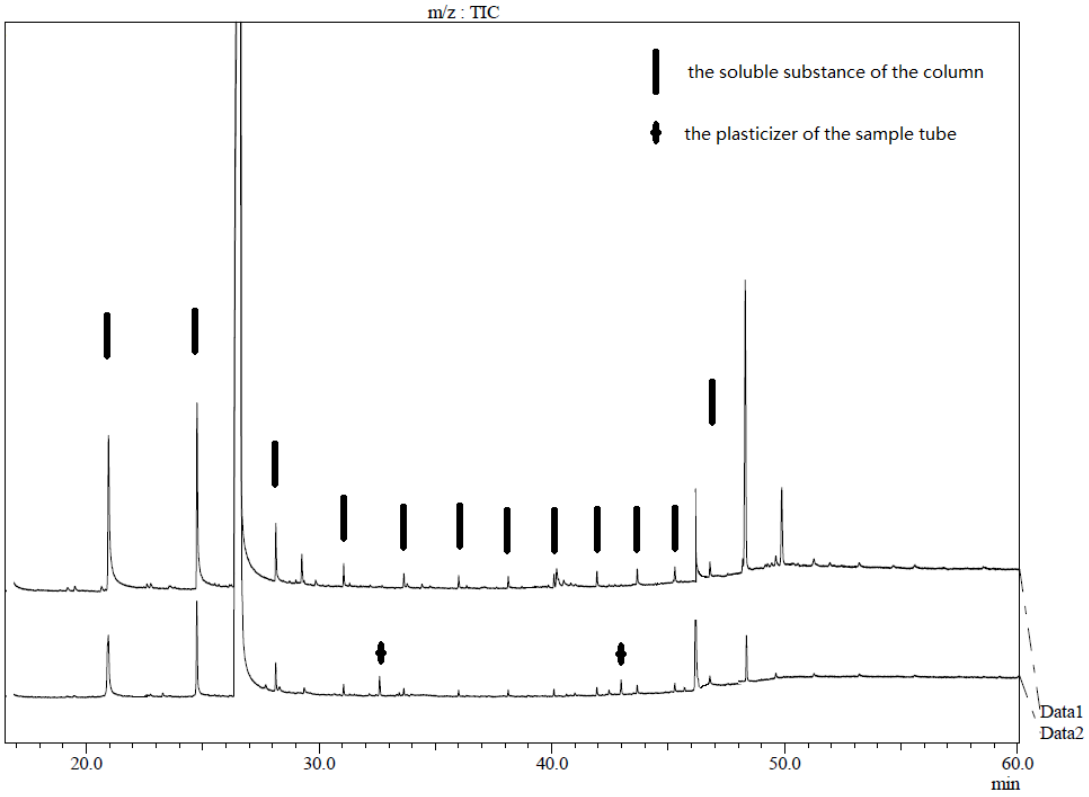
	Removal of excess NaN_3 (%)	
T（℃）	For **1b**	For **6b**
140	87	17
160	86	27
170	86	40
190	86	65
200	87	77

In the reaction that formats **1b**, the removal of NaN_3 is nearly 90% under various reaction temperature. This is close to the yield of **1b.** There is one mole of nitrous acid generates accompany with triazole, and according to eq. (1) that indicates the consumption of NaN_3 requires one equivalence of HNO_2, the results of NaN_3 determination is reliable to the yield of triazole.. As this reaction that forms **1b** is fast, there is no difference in various temperature. To further confirm the results, we checked a slow reaction that was the synthesis of **6b**, and we found that as the temperature raised, the consumption of azide gradually increased. When the temperature rises to 210 ^{o}C, the consumption of N_3^- achieved to 77%. In our reactions, when the temperature was 200 ^{o}C, there was 80% of **6b** was obtained. It is obvious that the produced HNO_2 destroyed the excess sodiun azide.

The GC-MS results for batch and continuous-flow reaction with benzaldehyde as a substrate

Oven Temp. Program

Rate	Temperature(°C)	Hold Time(min)
-	40.0	5.00
6.00	300.0	20.00

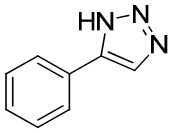


No.1 and No.2 are the result of the batch and the continuous-flow reaction, respectively. Due to the hot fluid was collected with plastic tube, some plasticizer dissolved in the reaction liquid. Some oligomer are undetectable in the GC-MS. The peak at 26.617 is assigned to the triazole. The peak at 29.269 represents for unknown by-product. The substance appeared at 46.521 min is the product of Michael addition that nitroolefin with acetic acid. The peak at 48.313 is assigned to the triphenylbenzene. The peak at 49.423 represents for triphenylbenzene contains one nitro.

The typical procedure for the synthesis of triazole via the three-component reaction

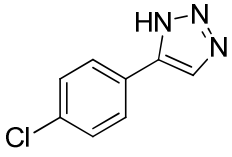
The mixed of aldehydes (1mmol), nitroalkanes (2 mmol), sodium azide (2 mmol), CH_3COOH (8 equiv.) and CH_3COONH_4 (1 equiv.) were stirred in DMF (6 mL) at 140 ^oC for 80 min. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, then quenched with H_2O (30 mL) and extracted with EtOAc (3×30 mL). The organic layers was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (SiO_2, hexane/EtOAc) to afford the 4-phenyl-N*H*-1,2,3-triazole **1a** as a white solid in 97% yield. Other of 4-aryl-N*H*-1,2,3-triazoles were prepared by the similar procedure.

Characterization data of products



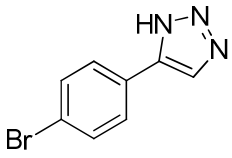
1b

5-phenyl-1*H*-1,2,3-triazole (**1b**)[1] White solid. m.p. 140-143 ^oC; ^1H NMR (400 MHz, DMSO-D6) δ 8.28 (s, 1H), 7.91-7.80 (m, 2H), 7.51-7.39 (m, 2H), 7.37-7.23 (m, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 145.41, 131.30, 129.38, 128.25, 127.66, 125.97. MS (ESI) m/z for $C_8H_8N_3$: 146 ($[M+H]^+$)



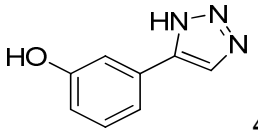
2b

5-(4-chlorophenyl)-1*H*-1,2,3-triazole (**2b**),[1] White solid. m.p. 155-157 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 15.22 (s, 1H), 8.40 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 133.06, 129.49, 127.76. MS (ESI) m/z for $C_8H_7ClN_3$: 180 ($[M+H]^+$)



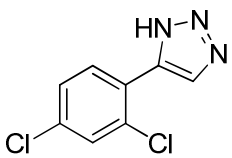
3b

5-(4-bromophenyl)-1*H*-1,2,3-triazole (**3b**),[1] White solid. m.p. 170-171°C; ^{1}H NMR (600 MHz, DMSO-D6) δ 15.23 (s, 1H), 8.41 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-D6) δ 143.90, 132.26, 132.10, 127.65, 120.00. HRMS Calcd (ESI) m/z for $C_8H_7BrN_3$: $[M+H]^+$ 223.9823, found: 223.9818



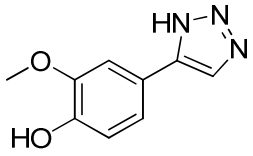
4b

3-(1*H*-1,2,3-triazol-5-yl)phenol (**4b**),[2] White solid. m.p. 205-208 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.30 (s, 1H), 7.37-7.26 (m, 3H), 6.82 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 158.31, 131.97, 130.51, 117.01, 115.73, 112.85. MS (ESI) m/z for $C_8H_8N_3O$: 162 ($[M+H]^+$)



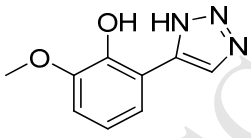
5b

5-(2,4-dichlorophenyl)-1*H*-1,2,3-triazole (**5b**),[1] White solid. m.p. 178-179 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 16.03-14.47 (s, 1H), 8.73-8.15 (m, 1H), 8.13-7.80 (m, 1H), 7.75 (s, 1H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-D6) δ 133.78, 132.21, 131.79, 130.20, 128.89, 128.32. MS (ESI) m/z for $C_8H_6N_2Cl_2$: 214 ($[M+H]^+$)



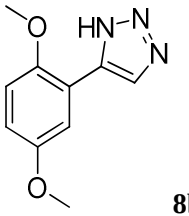
6b

2-methoxy-4-(1*H*-1,2,3-triazol-5-yl)phenol (**6b**), White solid. m.p. 165-171 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 9.64 (s, 1H), 7.33 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-D6) δ 190.33, 158.71, 149.67, 127.89, 126.20, 116.31, 110.37, 55.80. HRMS Calcd. (ESI) m/z for $C_9H_{10}N_3O_2$: $[M+H]^+$ 192.0768, found 192.0773



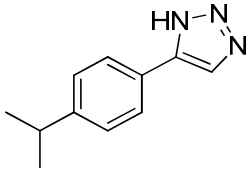
7b

2-methoxy-6-(1*H*-1,2,3-triazol-5-yl)phenol (**7b**), Yellow solid. m.p. 173-174 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.17 (s, 1H), 7.42 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, DMSO-D6) δ 148.60, 144.47, 142.53, 128.28, 119.51, 119.21, 117.46, 111.46, 56.38. HRMS Calcd. (ESI) m/z for $C_9H_{10}N_3O_2$: $[M+H]^+$ 192.0768, found 192.0765



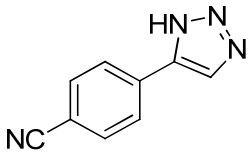
8b

5-(2,5-dimethoxyphenyl)-1*H*-1,2,3-triazole (**8b**), Yellow solid. m.p. 118-119 °C; ^{1}H NMR (600 MHz, DMSO-D6) δ 8.19 (s, 1H), 7.58 (s, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (151 MHz, DMSO-D6) δ 153.77, 150.59, 140.90, 129.37, 120.21, 114.53, 113.50, 112.83, 56.46, 55.95. HRMS Calcd. (ESI) m/z for $C_{10}H_{12}N_3O_2$: $[M+H]^+$ 206.0924, found 206.0920



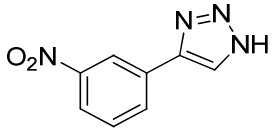
9b

5-(4-isopropylphenyl)-1*H*-1,2,3-triazole (**9b**),[3] White solid. m.p. 145-150 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.20 (s, 1H), 7.92 – 7.43 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-D6) δ 148.58, 145.27, 128.83, 127.27, 126.05, 33.74, 24.32. MS (ESI) m/z for $C_{11}H_{14}N_3$: 188 ($[M+H]^+$)



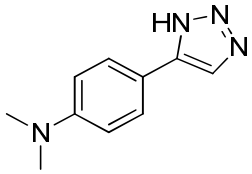
10b

4-(1*H*-1,2,3-triazol-5-yl)benzonitrile (**10b**),[1] Yellow solid. m.p. 170-172 ^{o}C; ^{1}H NMR (600 MHz, DMSO-D6) δ 15.41 (s, 1H), 8.59 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 133.21, 125.87, 119.83. MS (ESI) m/z for $C_9H_7N_4$: 171 ($[M+H]^+$)



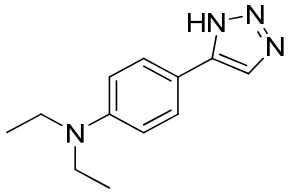
11b

4-(3-nitrophenyl)-1*H*-1,2,3-triazole (**11b**),[1] Yellow solid. m.p. 201-204 ^{o}C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.28 (s, 1H), 7.76-7.07 (m, 3H), 6.79 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D6) δ 158.31, 130.49, 116.99, 115.70, 112.84. MS (ESI) m/z for $C_8H_7N_4O_2$: 191 ($[M+H]^+$)



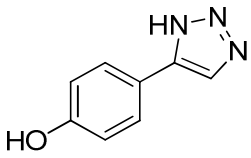
12b

N,N-dimethyl-4-(1*H*-1,2,3-triazol-5-yl)aniline (**12b**)[4] Yellow solid. m.p. 162-164 ^{o}C; ^{1}H NMR (600 MHz, DMSO-D6) δ 8.02 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 2.89 (s, 6H). ^{13}C NMR (151 MHz, DMSO-D6) δ 150.63, 126.95, 118.56, 112.88. MS (ESI) m/z for $C_{10}H_{12}N_4Na$: 221 ($[M+Na]^+$)



13b

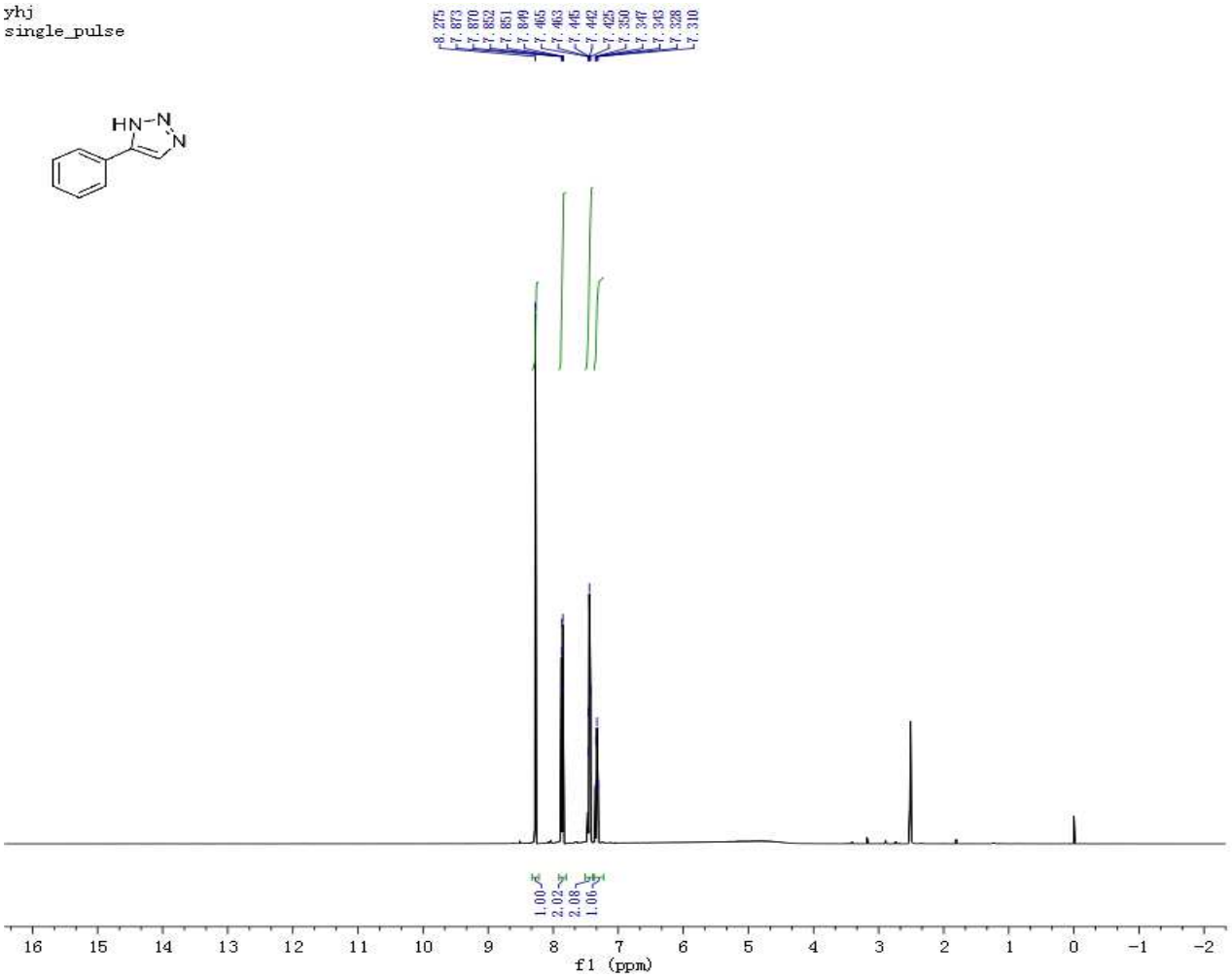
N,N-diethyl-4-(1*H*-1,2,3-triazol-5-yl)aniline (**13b**), Yellow solid. m.p. 105-113 ^{o}C; ^{1}H NMR (400 MHz, DMSO-D6) δ 8.01 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 4H), 1.10 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-D6) δ 147.70, 145.10, 127.29, 126.86, 117.37, 112.05, 44.17, 12.96. MS (ESI) m/z for $C_{12}H_{17}N_4$: 217 ($[M+H]^+$)



14b

4-(1*H*-1,2,3-triazol-5-yl)phenol (**14b**),[2] White solid. m.p. 213-214 ^{o}C; ^{1}H NMR (400 MHz, DMSO-D6) δ 10.61 (s, 1H), 9.80 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-D6) δ 191.46, 163.85, 132.62, 128.95, 116.37. MS (ESI) m/z for $C_8H_8N_3O$: 162 ($[M+H^+$)

Copies of 1H and 13C NMR spectrums



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5	Owner	
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8	Author	HappyNMR
9	Solvent	DMSO-D6
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24	Acquired Size	16384
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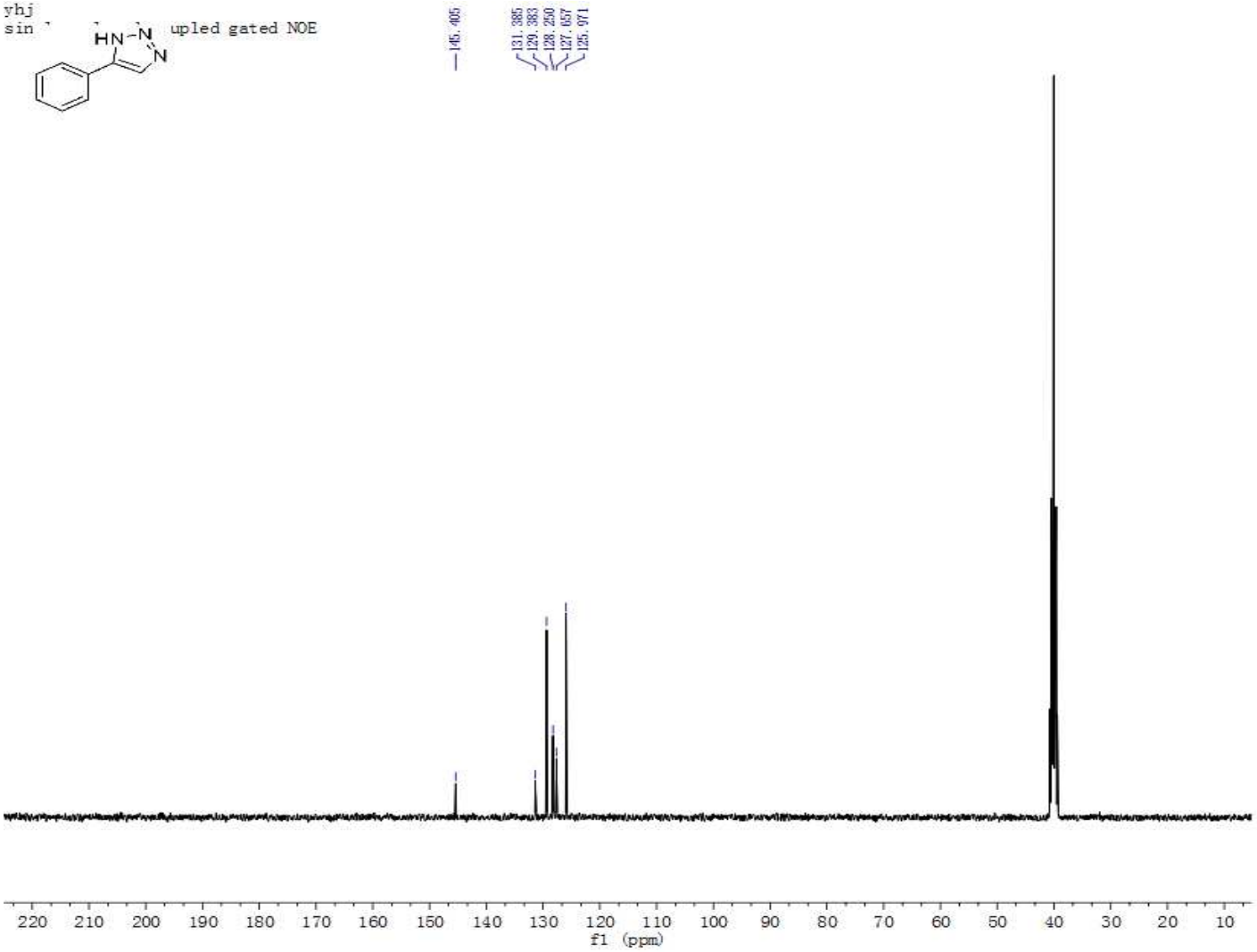

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24	Acquired Size	32768
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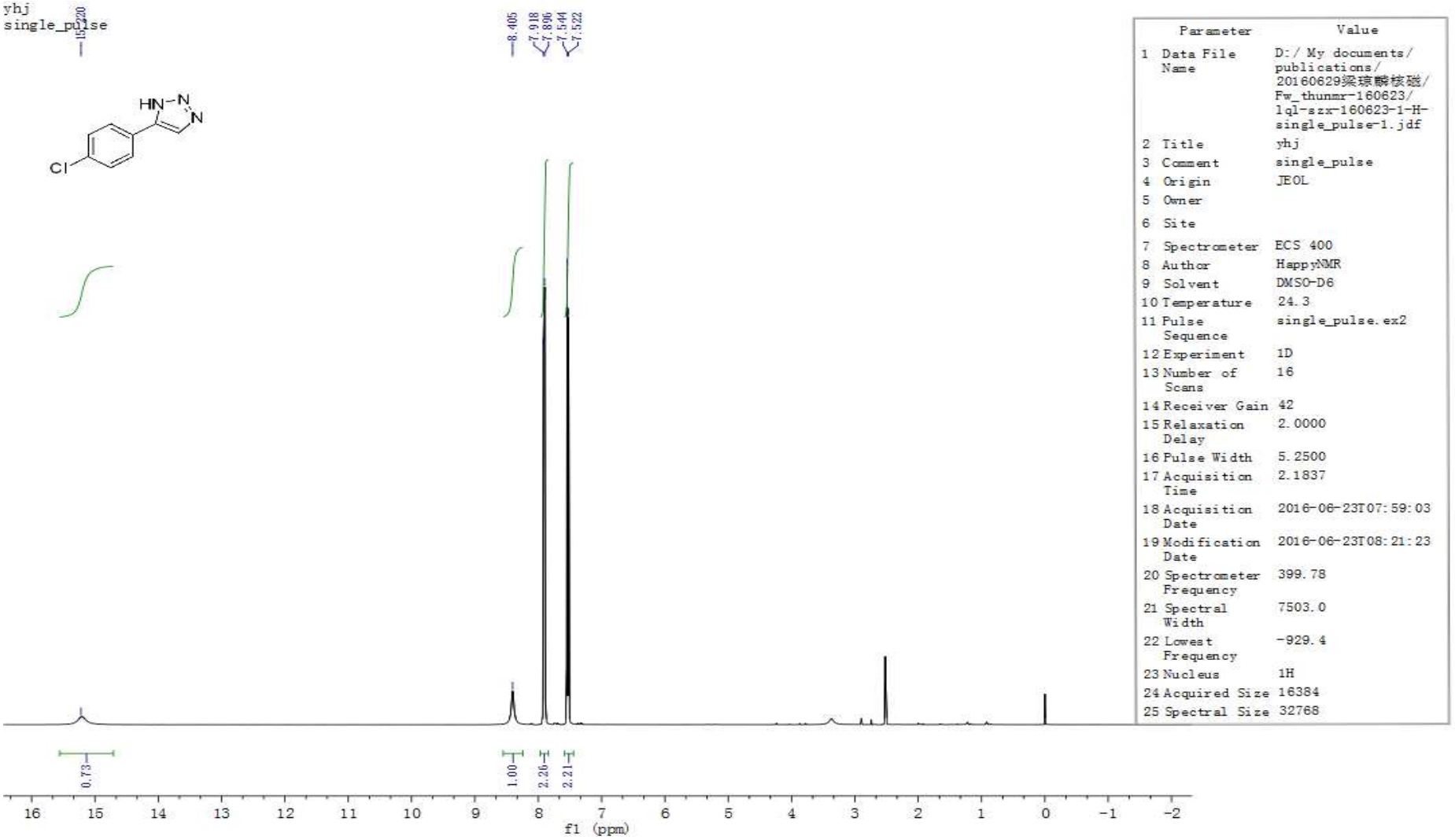

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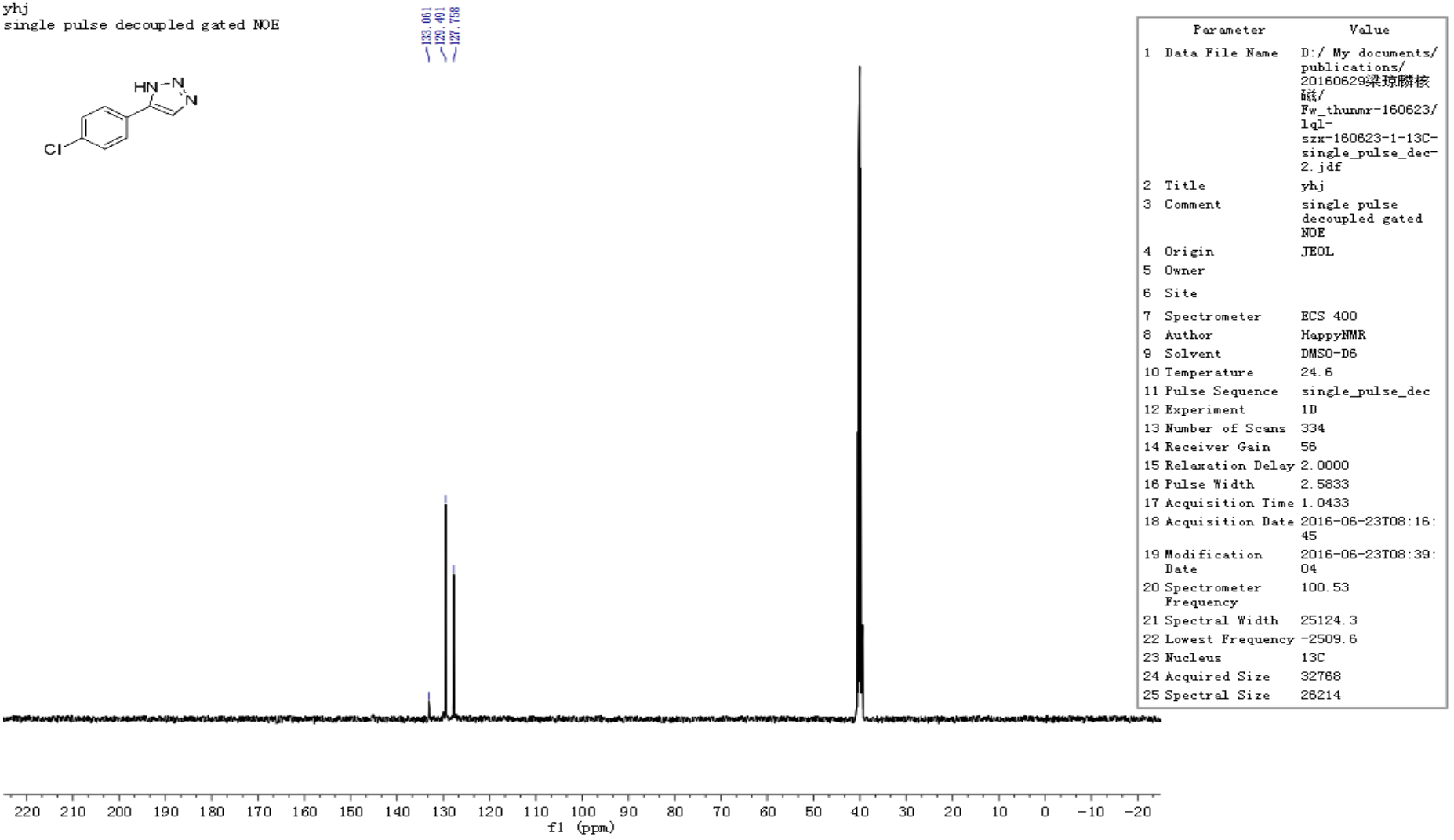
yhj
single pulse decoupled gated NOE



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8	Author	HappyNMR
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23	Nucleus	13C
24	Acquired Size	32768
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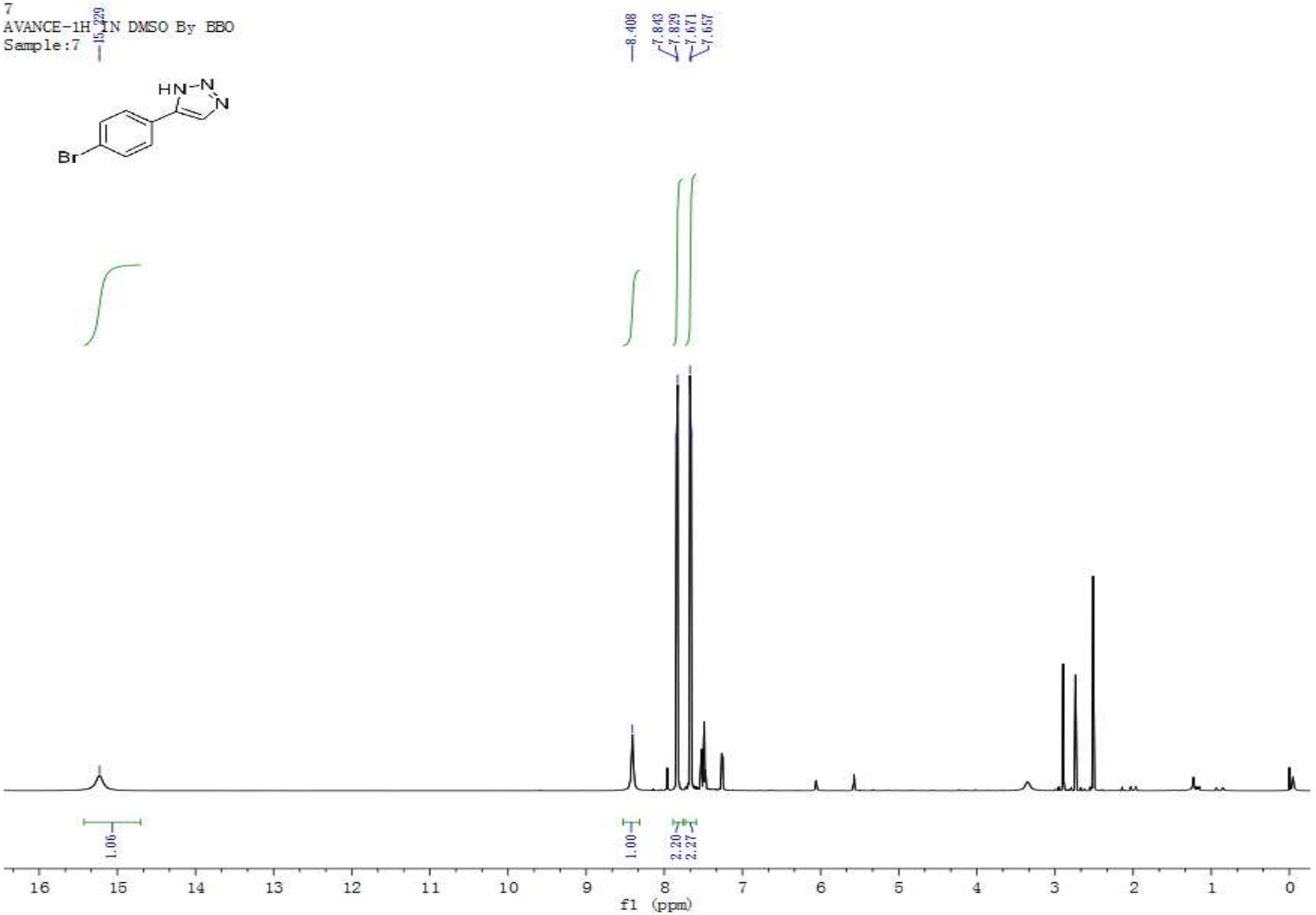

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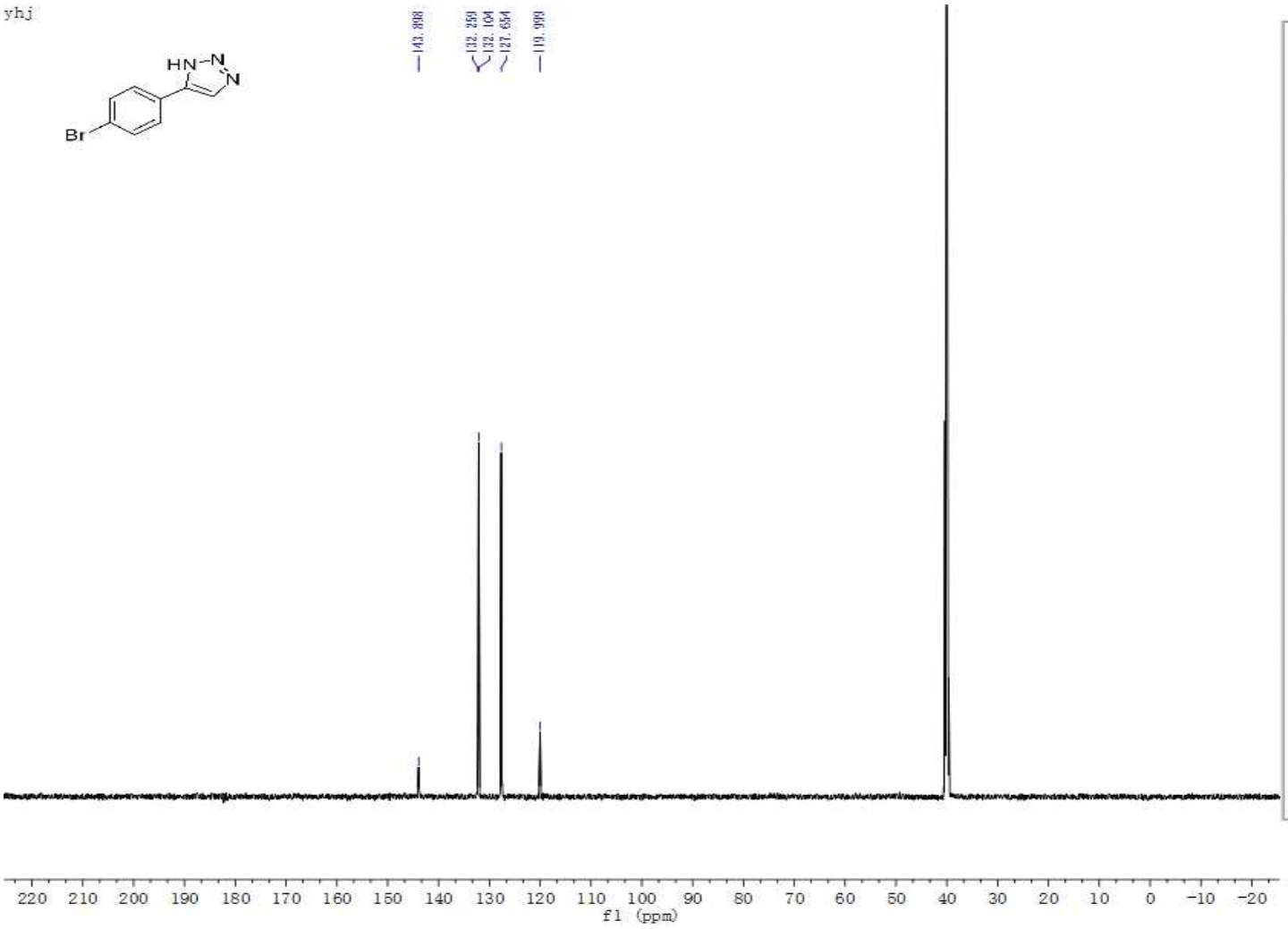

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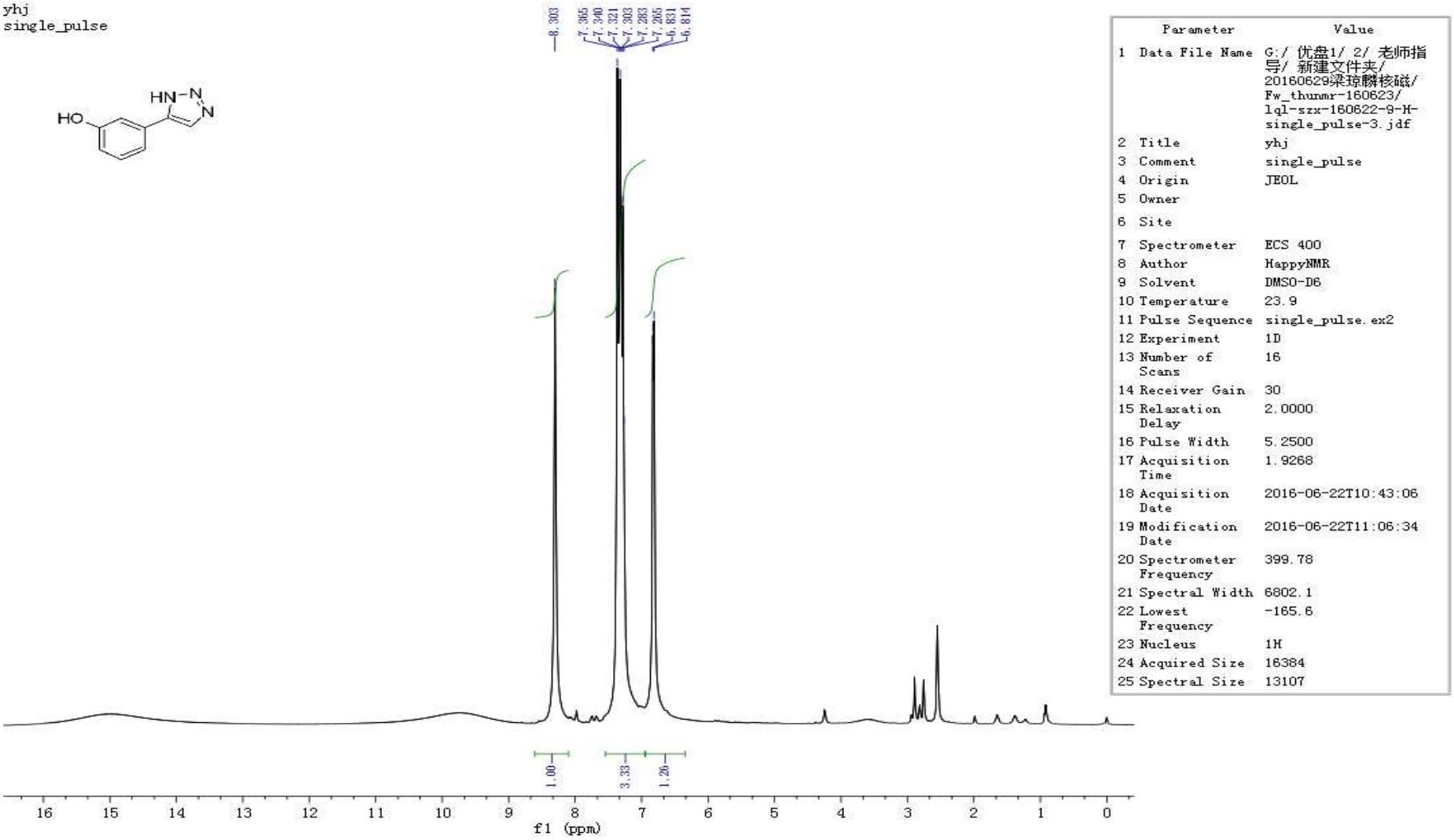

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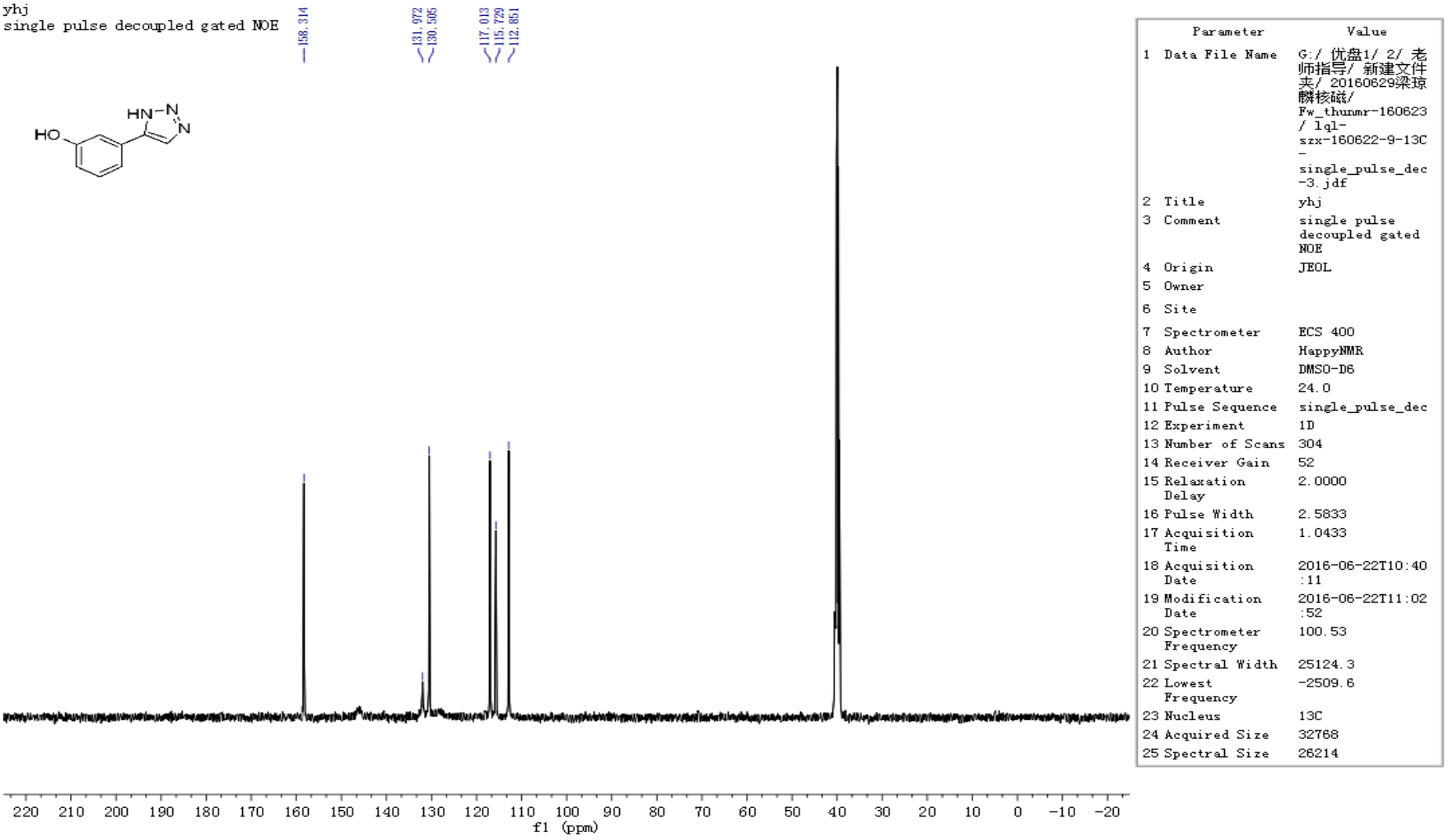

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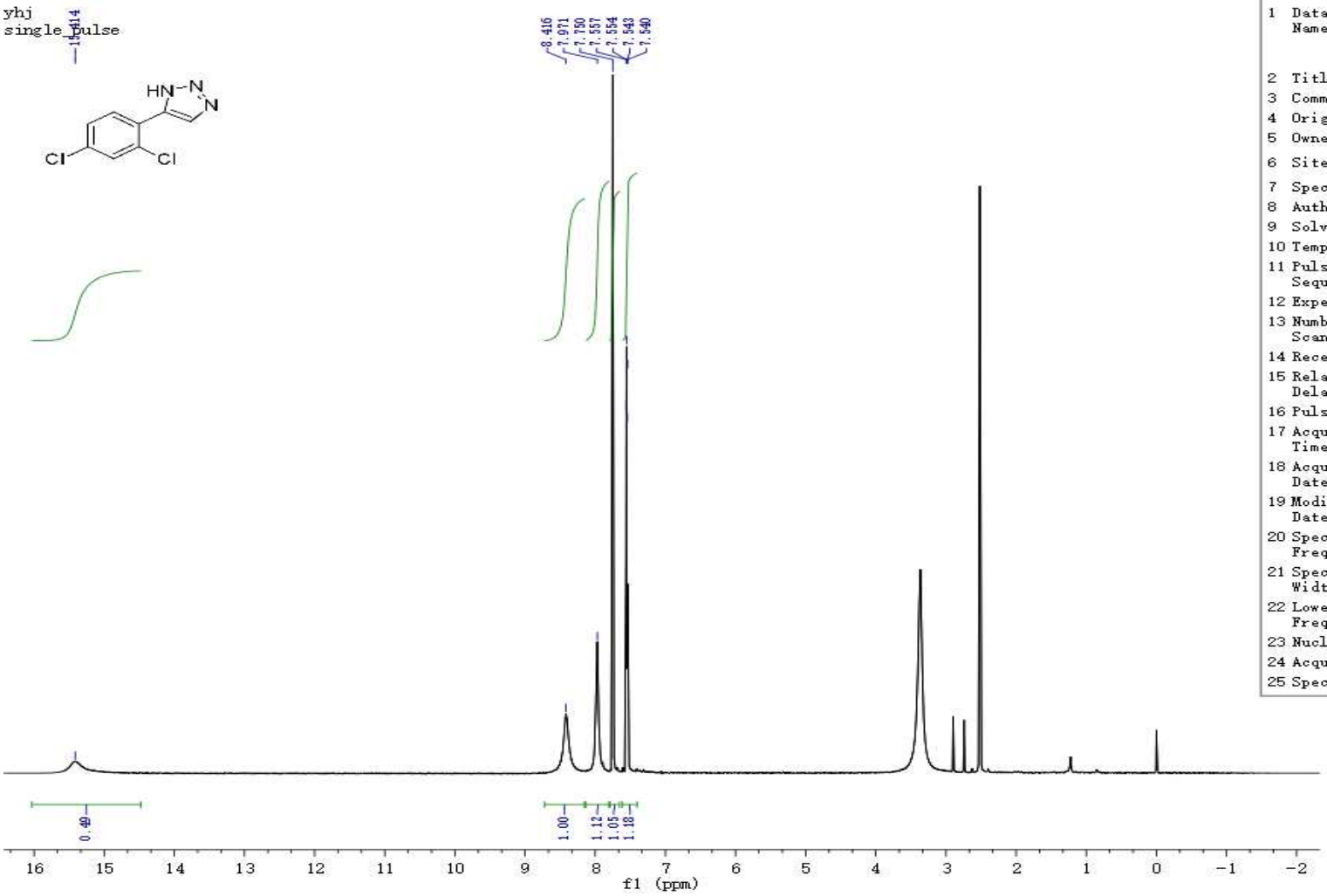
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	26214



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23	Nucleus	1H
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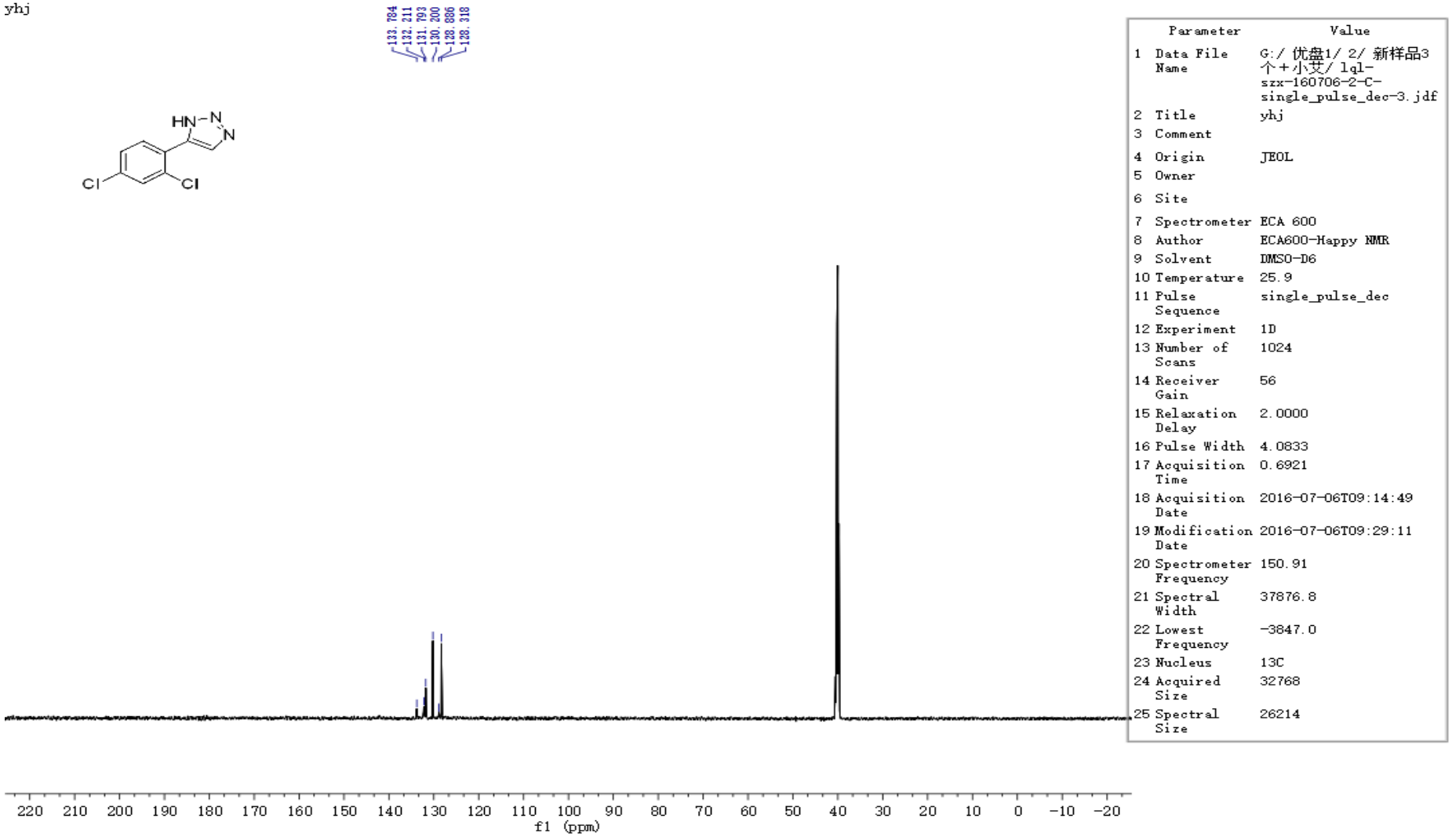
yhj



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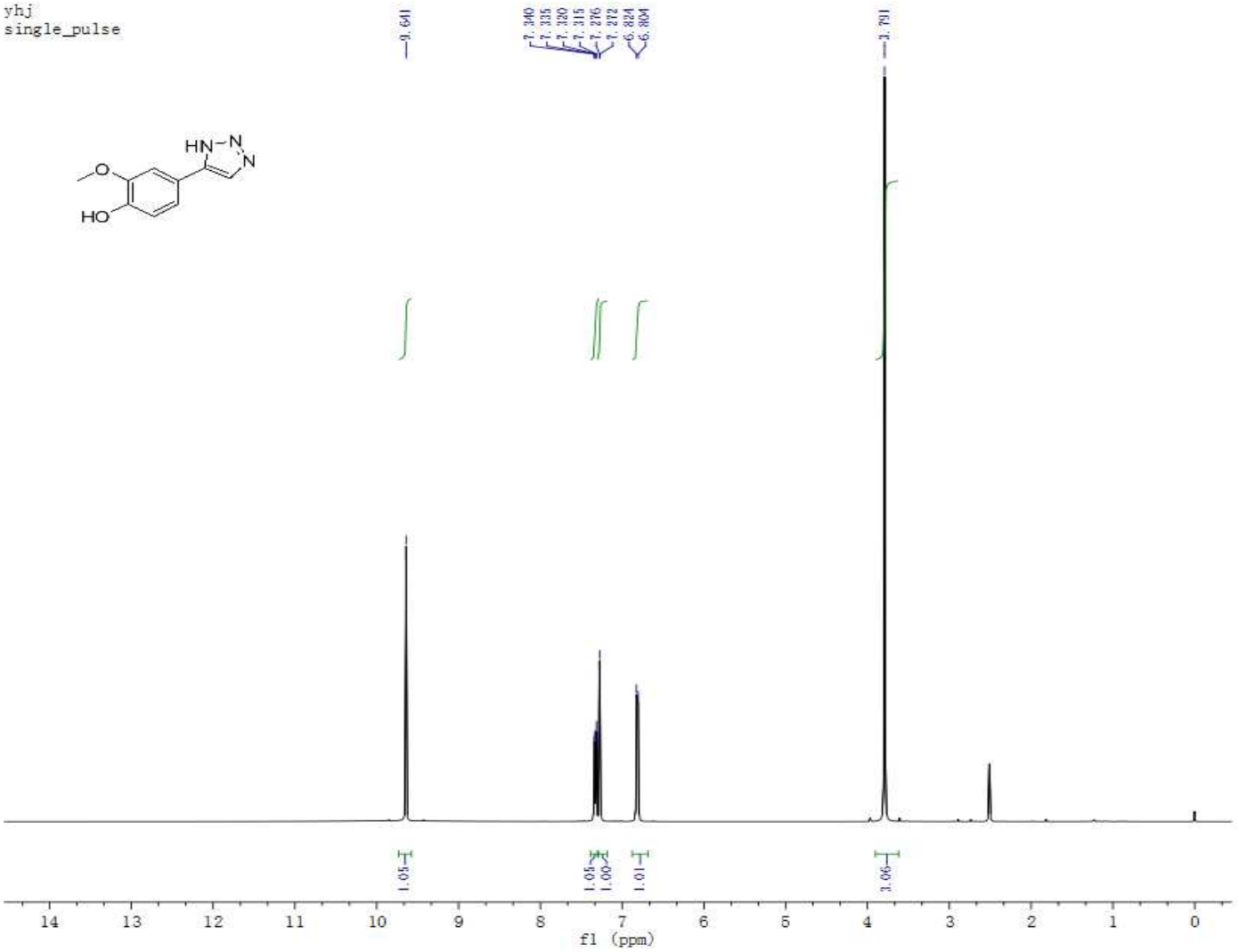

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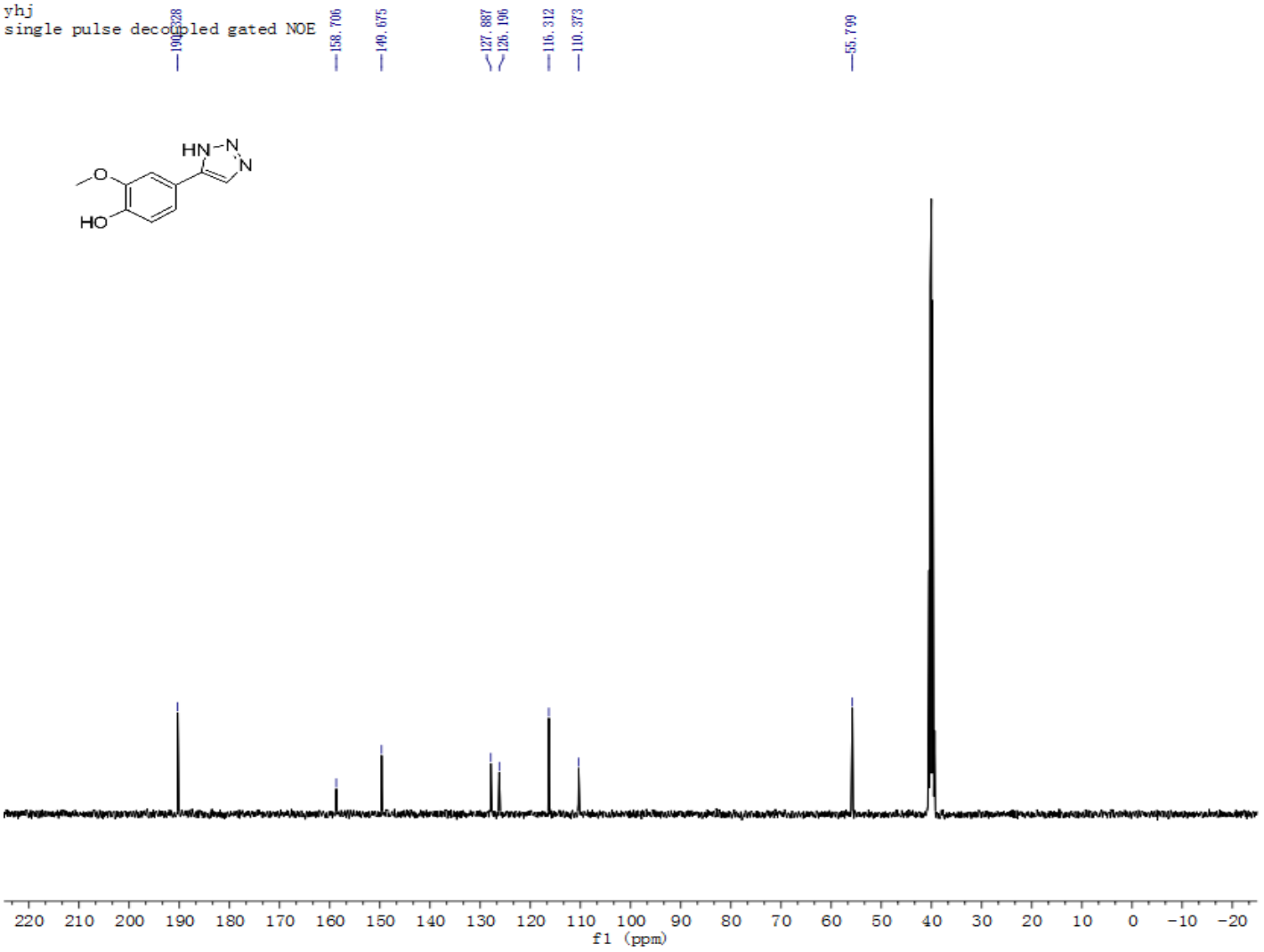

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24	Acquired Size	32768
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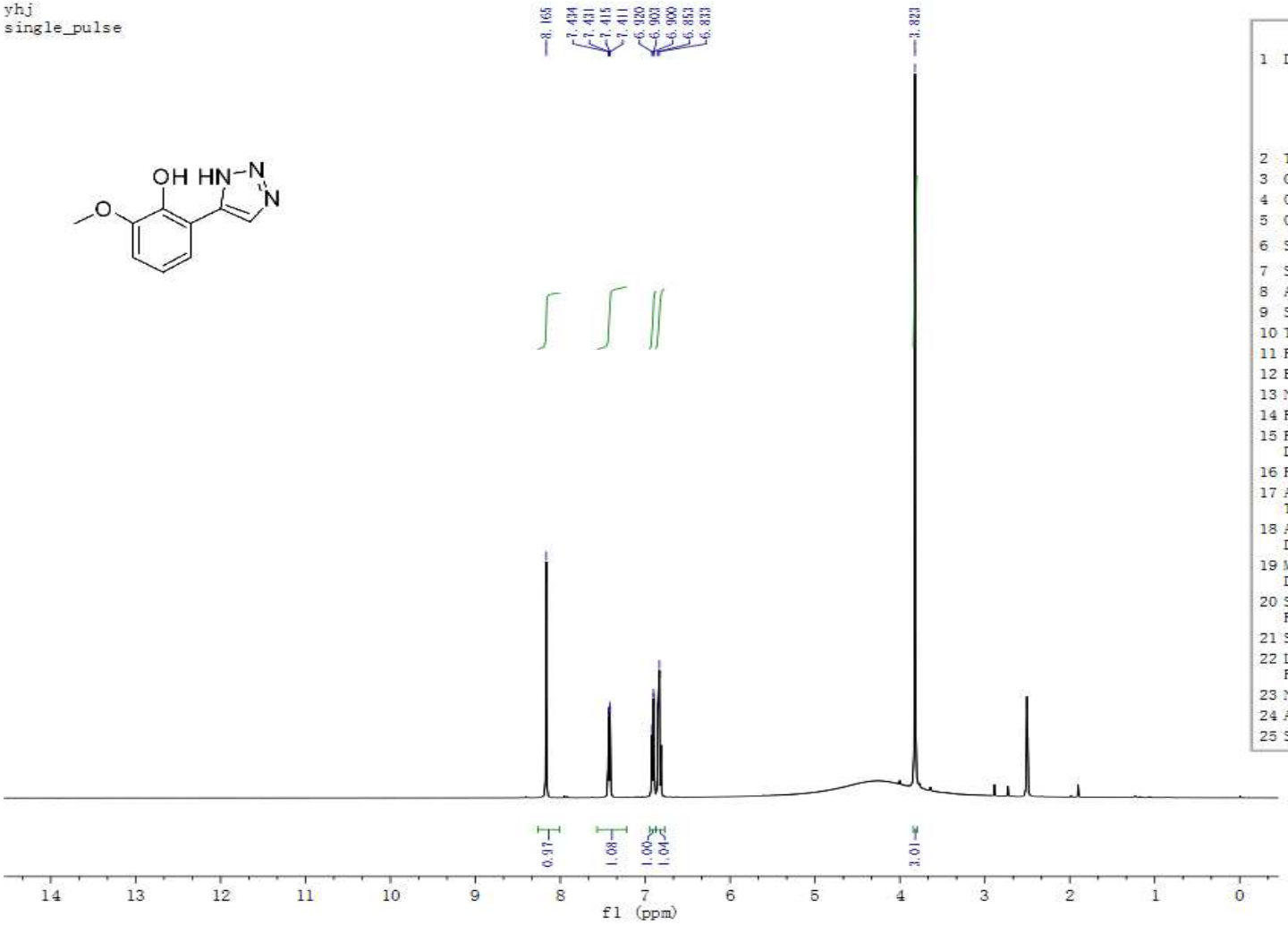

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24	Acquired Size	16384
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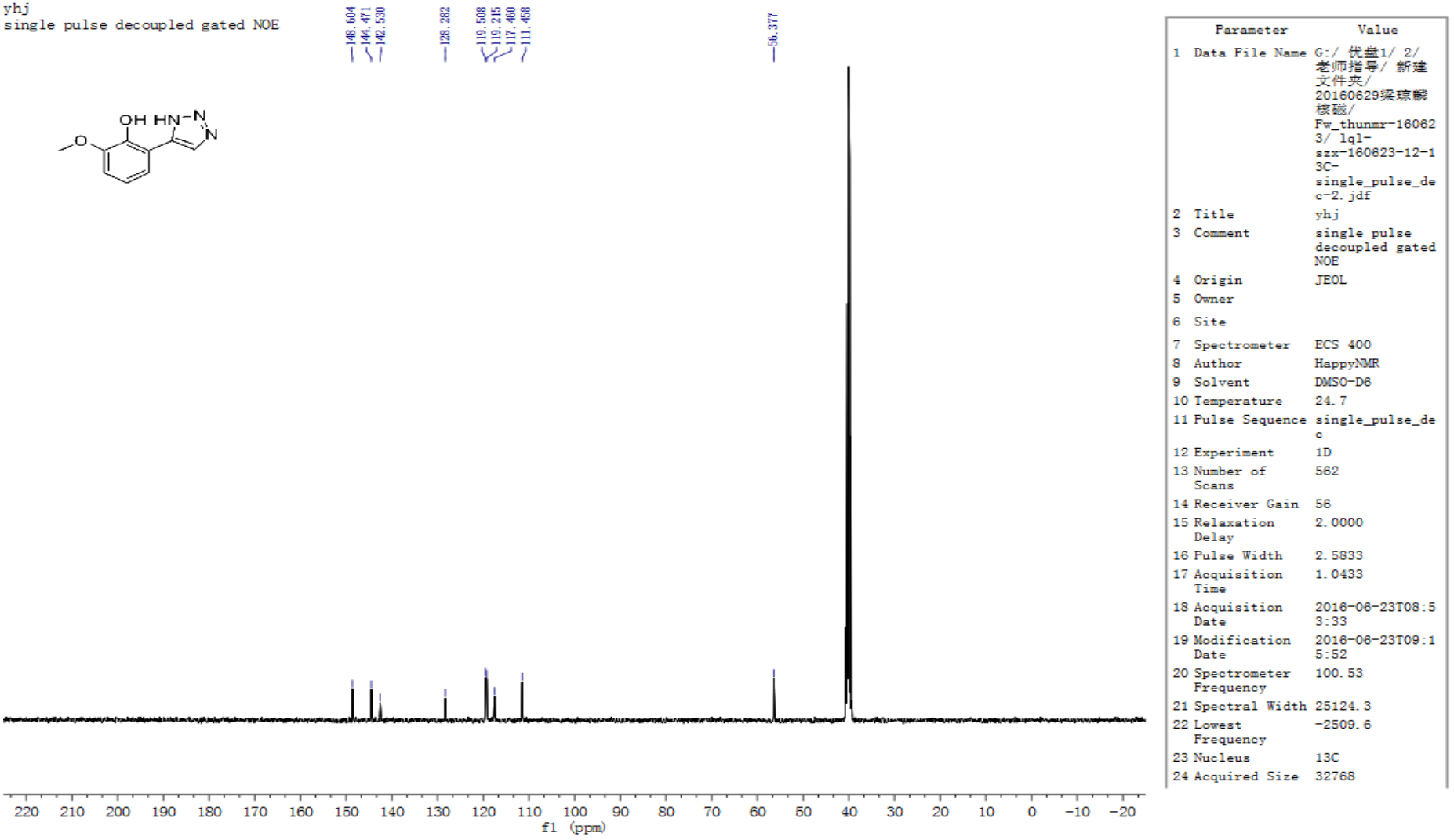
yhj
single pulse decoupled gated NOE



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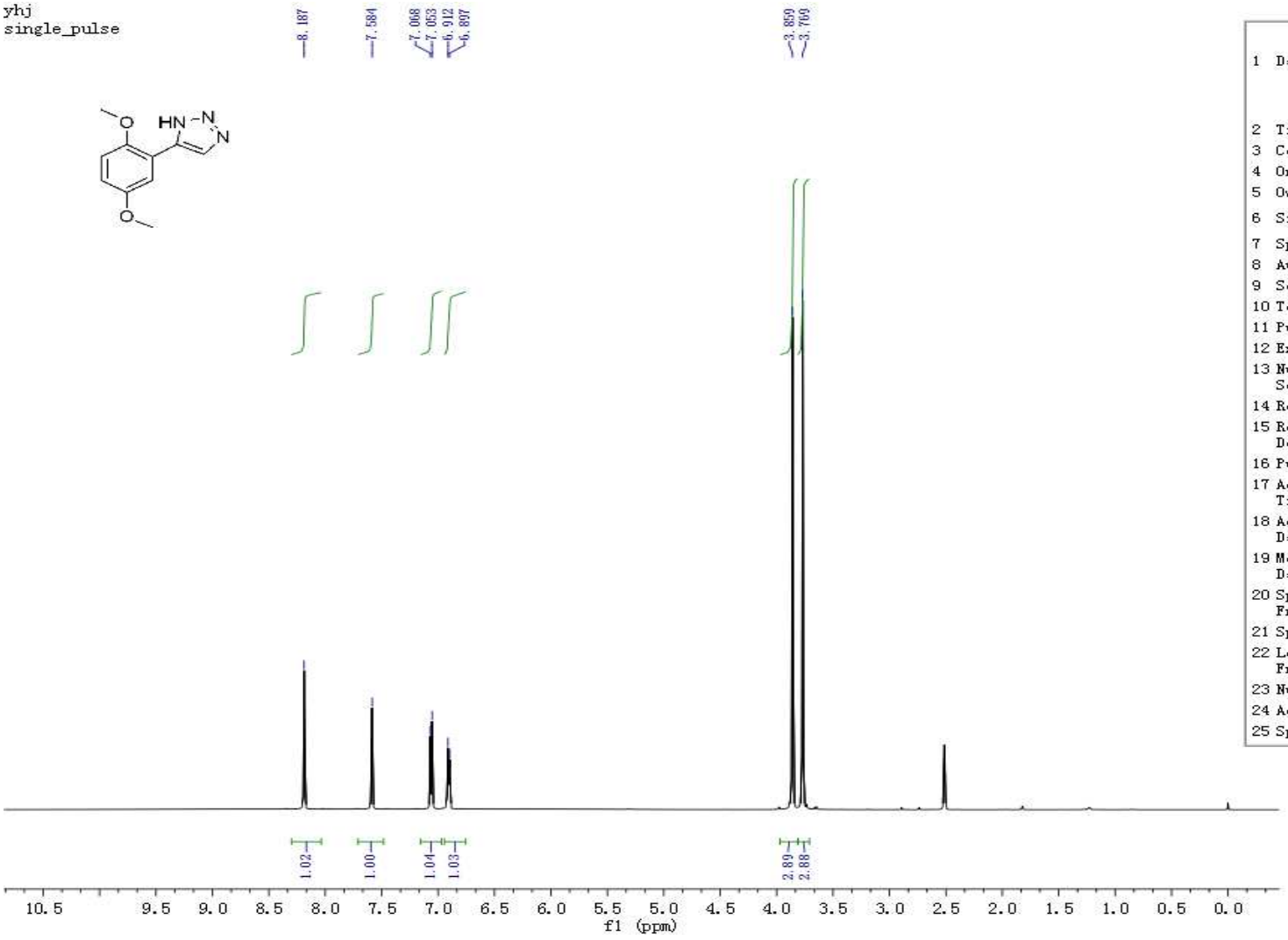
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768



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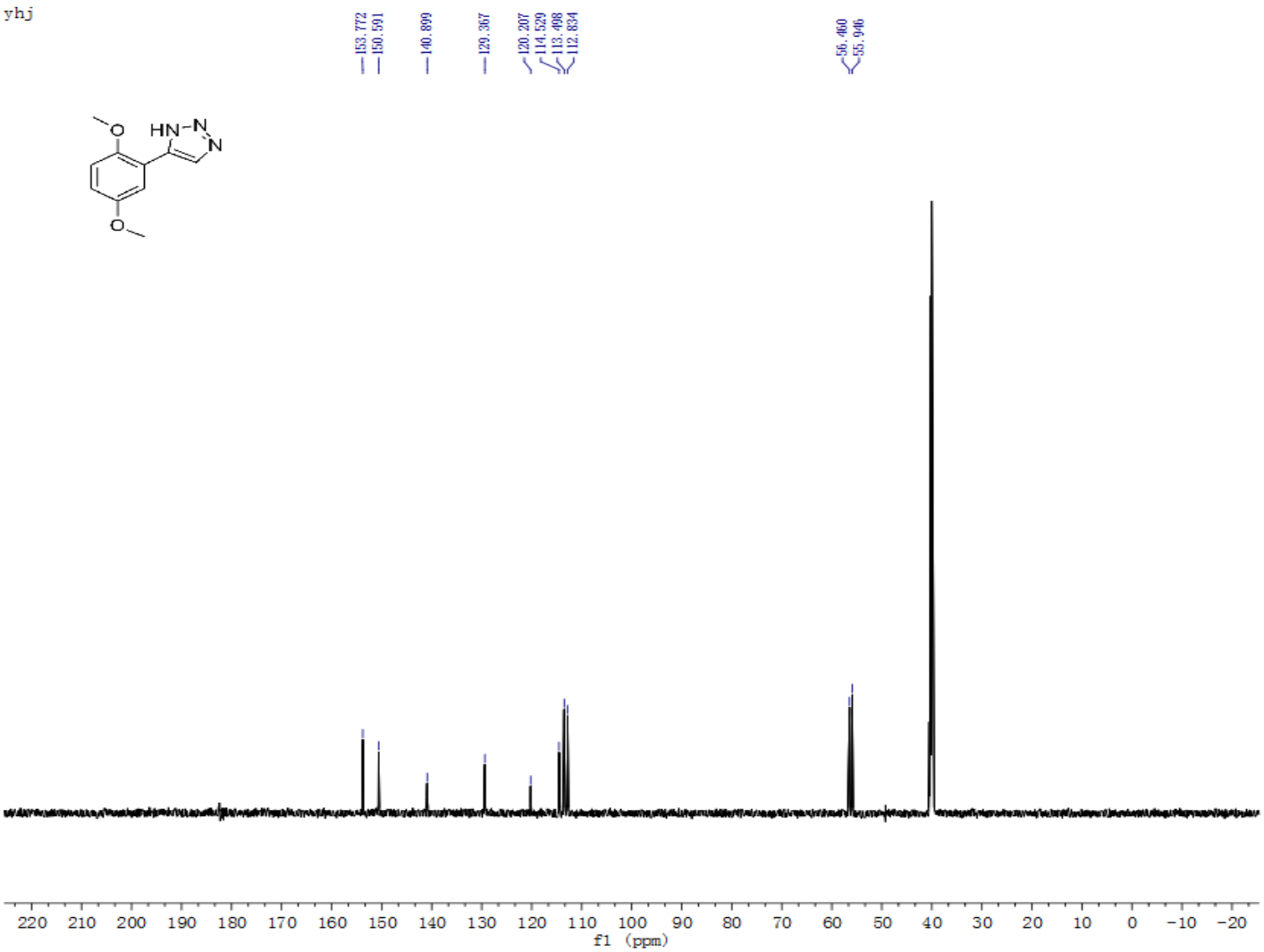

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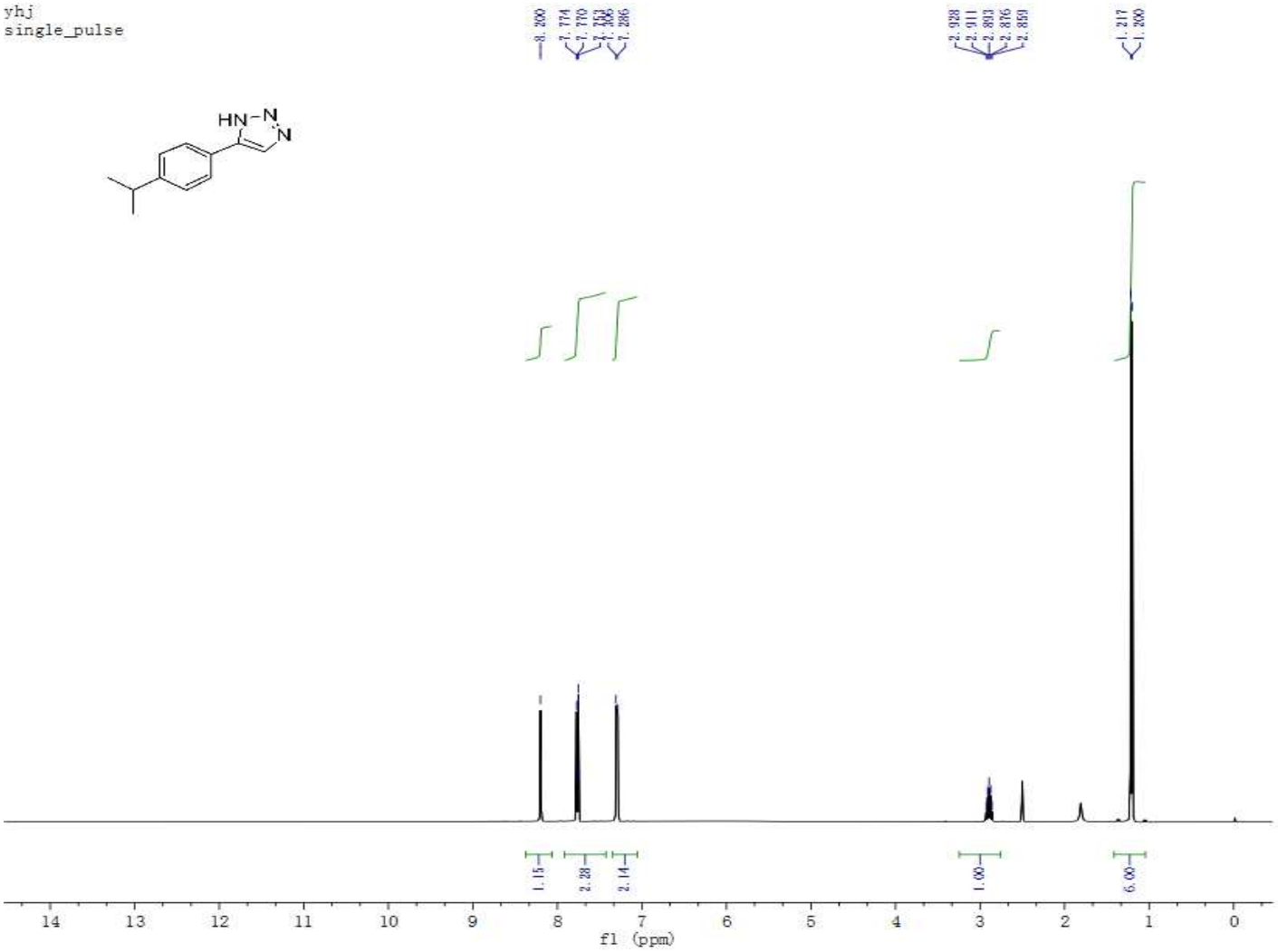

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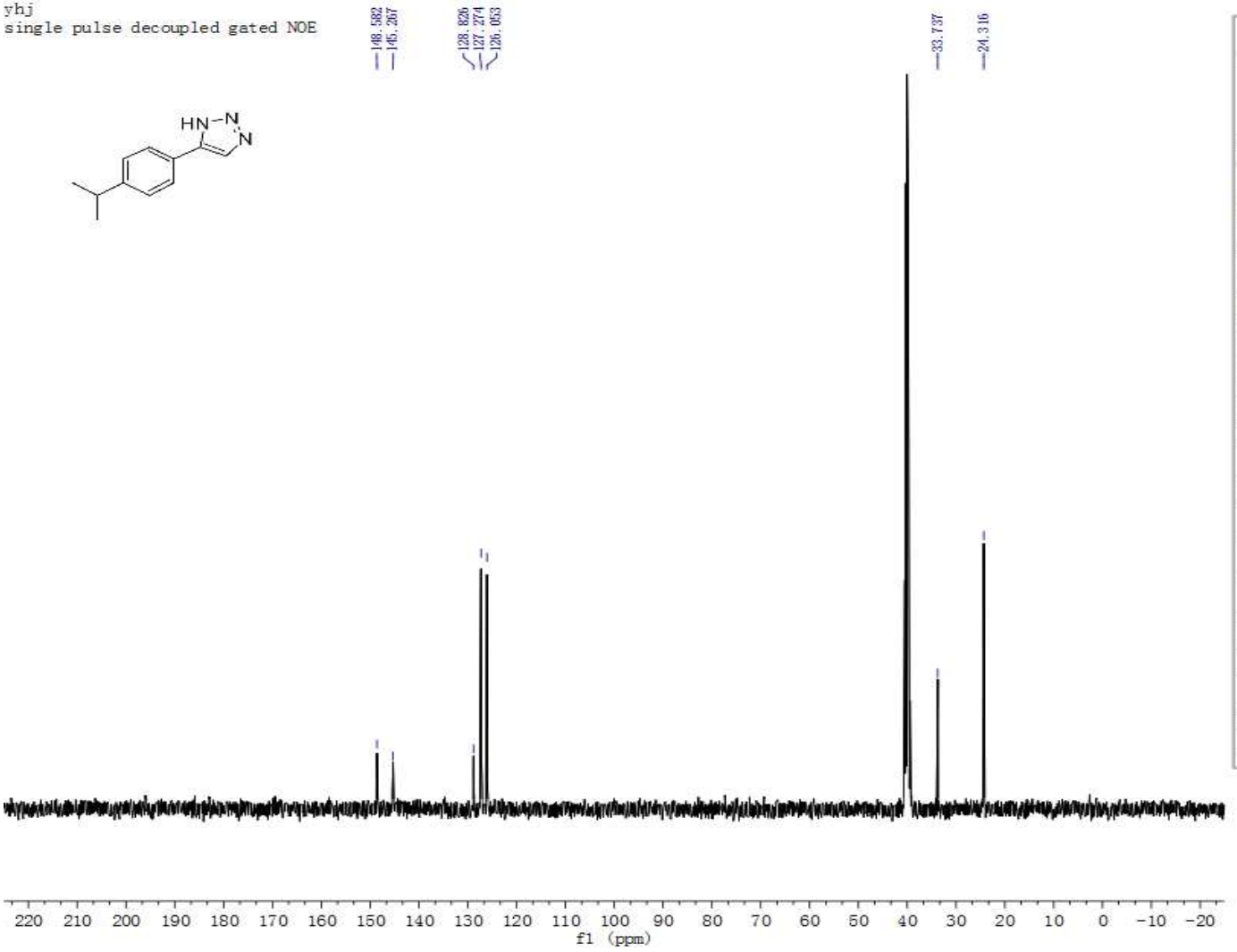
1	Data File Name	G:/ 优盘1/ 2/ 老师指导/ 新建文件夹/ 20160629梁琼麟核磁/ Fw_thunmr-160629/ lql-szx-160627-1S-H-single_pulse-2.jdf
2	Title	yhj
3	Comment	single_pulse
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	24.6
11	Pulse Sequence	single_pulse.ex2
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	34
15	Relaxation Delay	2.0000
16	Pulse Width	5.2500
17	Acquisition Time	2.1837
18	Acquisition Date	2016-06-28T08:51:01
19	Modification Date	2016-06-28T09:12:49
20	Spectrometer Frequency	399.78
21	Spectral Width	6001.9
22	Lowest Frequency	-186.9
23	Nucleus	1H
24	Acquired Size	16384
25	Spectral Size	13107



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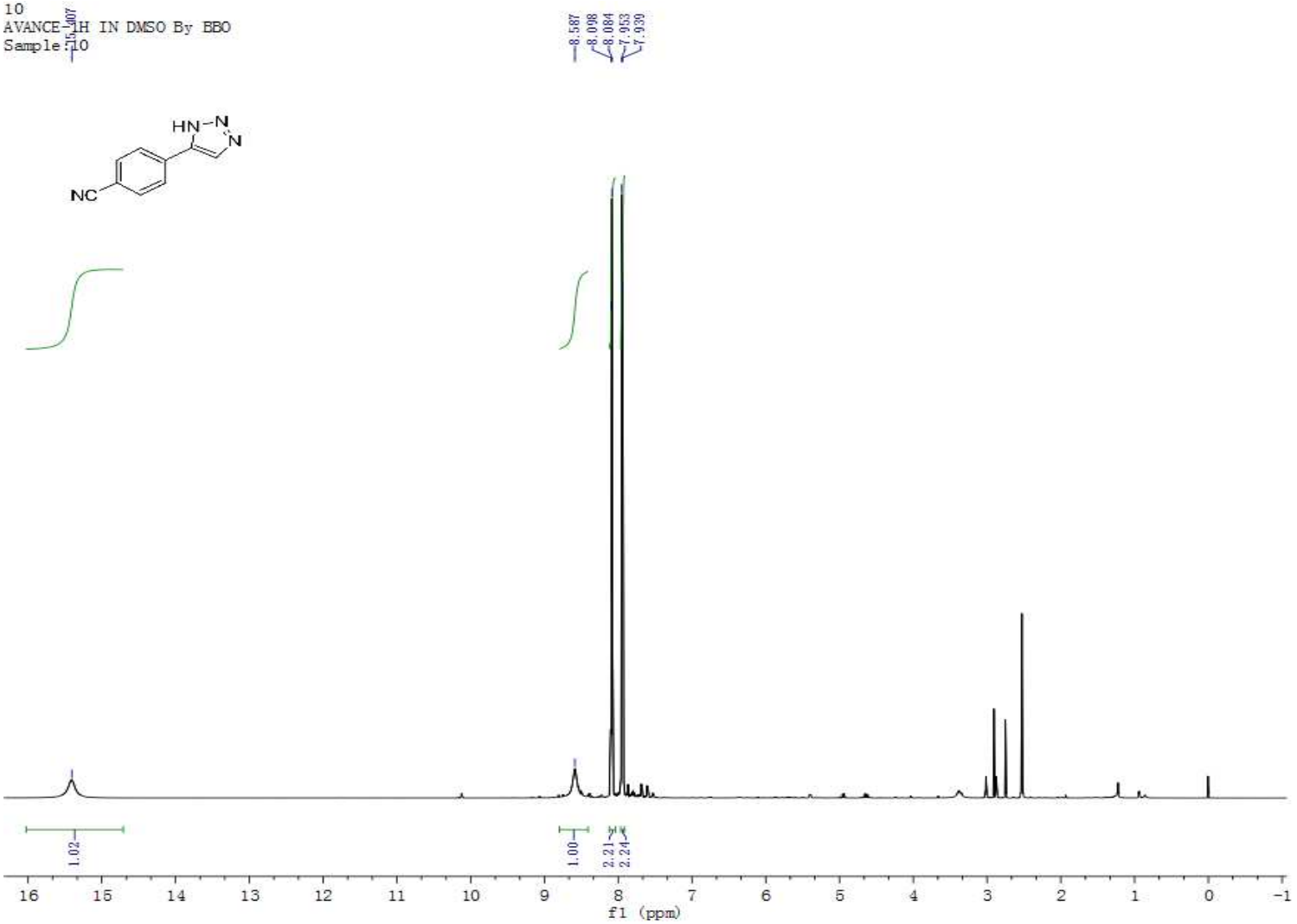
2	Title	yhj
3	Comment	single pulse decoupled gated NOE
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	24.8
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	56
14	Receiver Gain	54
15	Relaxation Delay	2.0000
16	Pulse Width	2.5833
17	Acquisition Time	1.0433
18	Acquisition Date	2016-06-28T08:54:30
19	Modification Date	2016-06-28T09:16:19
20	Spectrometer Frequency	100.53
21	Spectral Width	25124.3
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	26214



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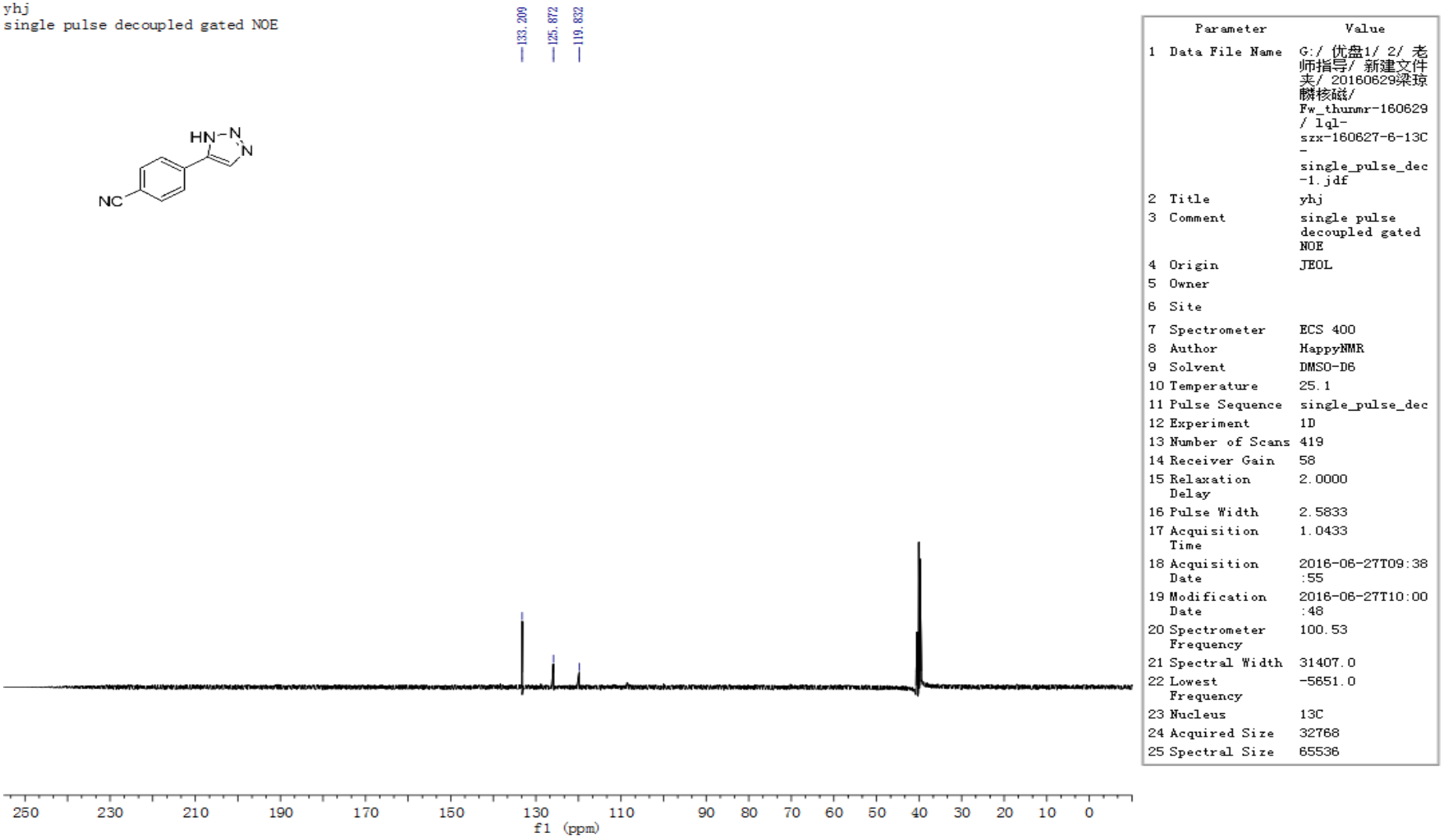
1	Origin	Bruker BioSpin GmbH
2	Spectrometer	spect
3	Solvent	DMSO
4	Temperature	297.9
5	Pulse Sequence	zg30
6	Experiment	1D
7	Number of Scans	16
8	Receiver Gain	175
9	Relaxation Delay	1.0000
10	Pulse Width	12.8500
11	Acquisition Time	2.6564
12	Acquisition Date	2015-10-23T 15:06:03
13	Modification Date	2015-10-23T 15:06:06
14	Spectrometer Frequency	600.13
15	Spectral Width	12335.5
16	Lowest Frequency	-2452.4
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

yhj
single pulse decoupled gated NOE



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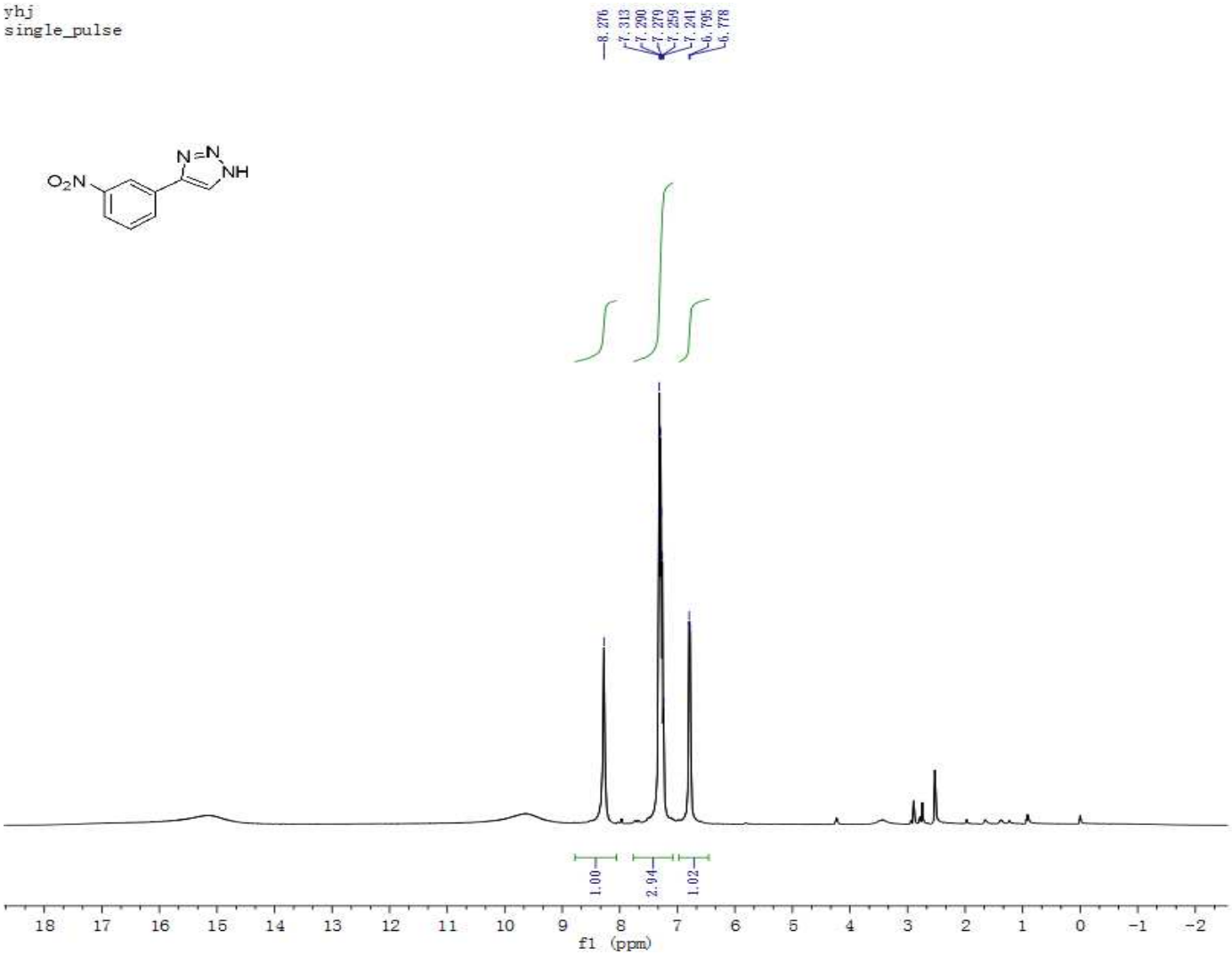
2	Title	yhj
3	Comment	single pulse decoupled gated NOE
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	25.1
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	419
14	Receiver Gain	58
15	Relaxation Delay	2.0000
16	Pulse Width	2.5833
17	Acquisition Time	1.0433
18	Acquisition Date	2016-06-27T09:38 :55
19	Modification Date	2016-06-27T10:00 :48
20	Spectrometer Frequency	100.53
21	Spectral Width	31407.0
22	Lowest Frequency	-5851.0
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536



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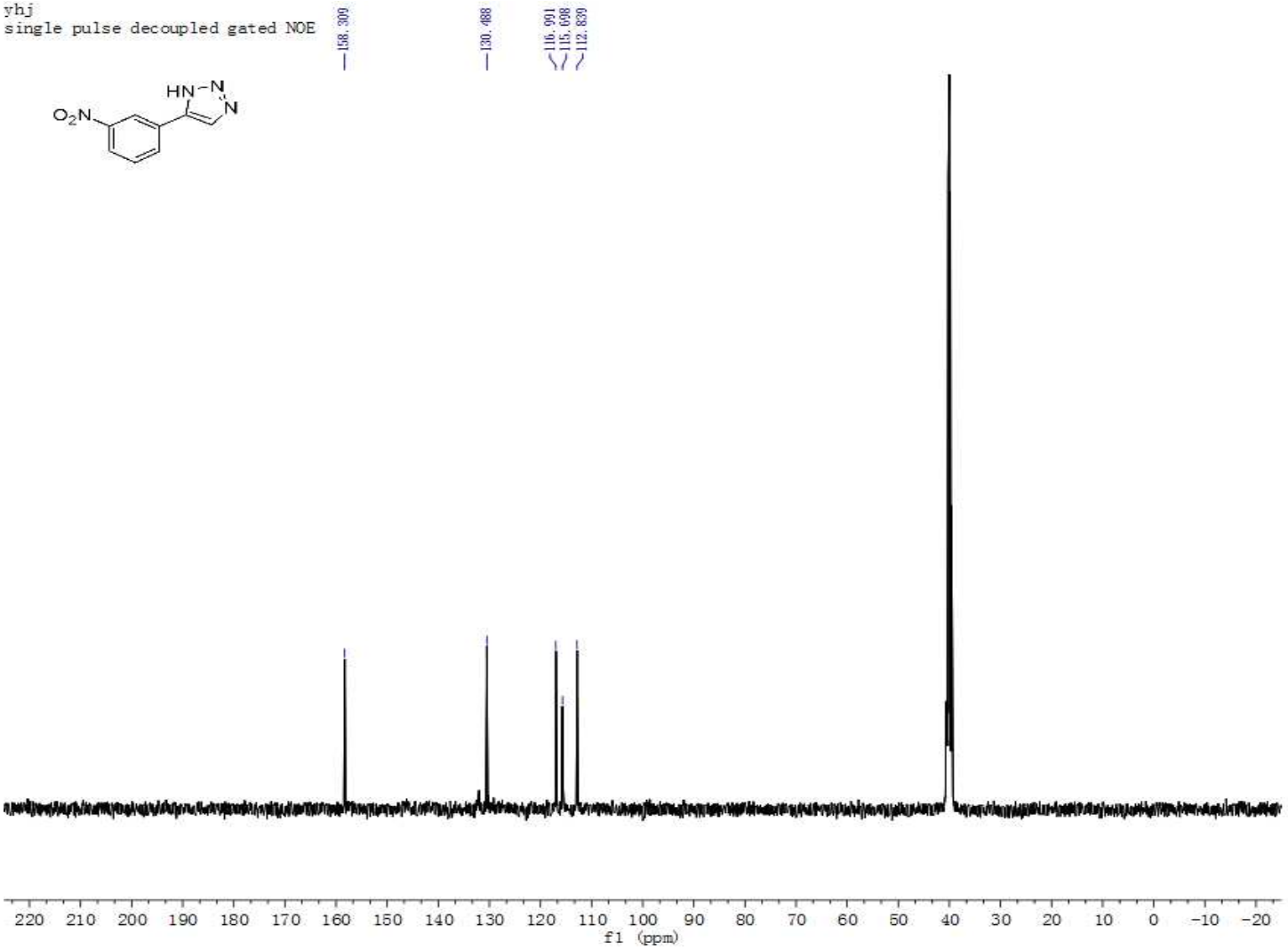
2	Title	yhj
3	Comment	single_pulse
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	25.3
11	Pulse Sequence	single_pulse.ex2
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	36
15	Relaxation Delay	2.0000
16	Pulse Width	5.2500
17	Acquisition Time	1.9268
18	Acquisition Date	2016-06-23T14:32:26
19	Modification Date	2016-06-23T14:54:43
20	Spectrometer Frequency	399.78
21	Spectral Width	8503.4
22	Lowest Frequency	-1027.5
23	Nucleus	1H
24	Acquired Size	16384
25	Spectral Size	32768



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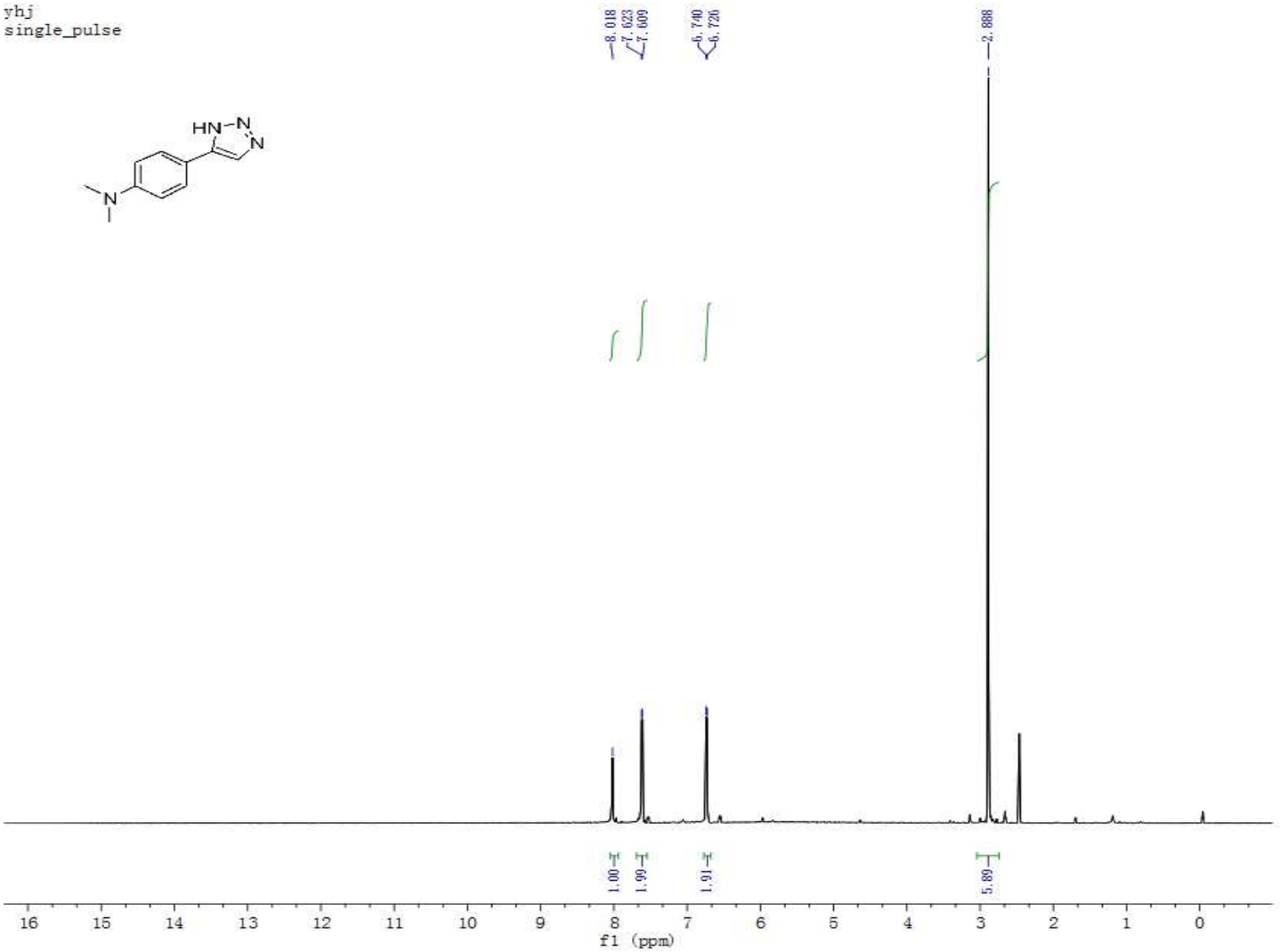
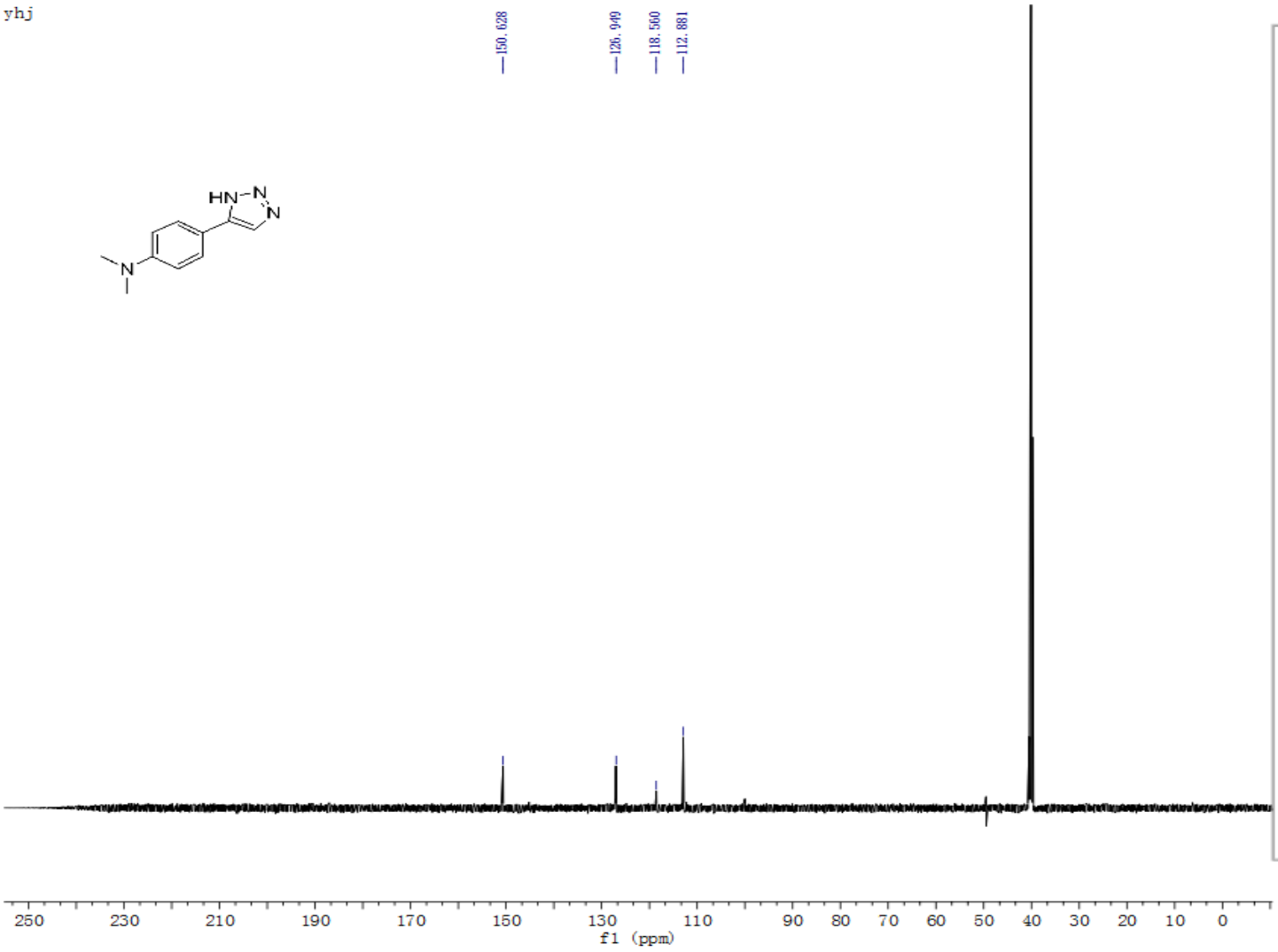
2	Title	yhj
3	Comment	single pulse decoupled gated NOE
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	25.4
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	131
14	Receiver Gain	52
15	Relaxation Delay	2.0000
16	Pulse Width	2.5833
17	Acquisition Time	1.0433
18	Acquisition Date	2016-06-23T14:30:51
19	Modification Date	2016-06-23T14:53:09
20	Spectrometer Frequency	100.53
21	Spectral Width	25124.3
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	26214



	Parameter	Value
1	Data File Name	G:/ 优盘1/ 2/ 老师指导/ 新建文件夹/ 最后三个/ lql-szx-160829-1-H-single_pulse-1.jdf
2	Title	yhj
3	Comment	single_pulse
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECA 600
8	Author	ECA600-Happy NMR
9	Solvent	DMSO-D6
10	Temperature	24.6
11	Pulse Sequence	single_pulse.ex2
12	Experiment	1D
13	Number of Scans	8
14	Receiver Gain	50
15	Relaxation Delay	2.0000
16	Pulse Width	7.1000
17	Acquisition Time	2.9098
18	Acquisition Date	2016-08-30T08:01:15
19	Modification Date	2016-08-30T08:15:54
20	Spectrometer Frequency	600.17
21	Spectral Width	11261.3
22	Lowest Frequency	-1429.4
23	Nucleus	1H
24	Acquired Size	32768
25	Spectral Size	65536



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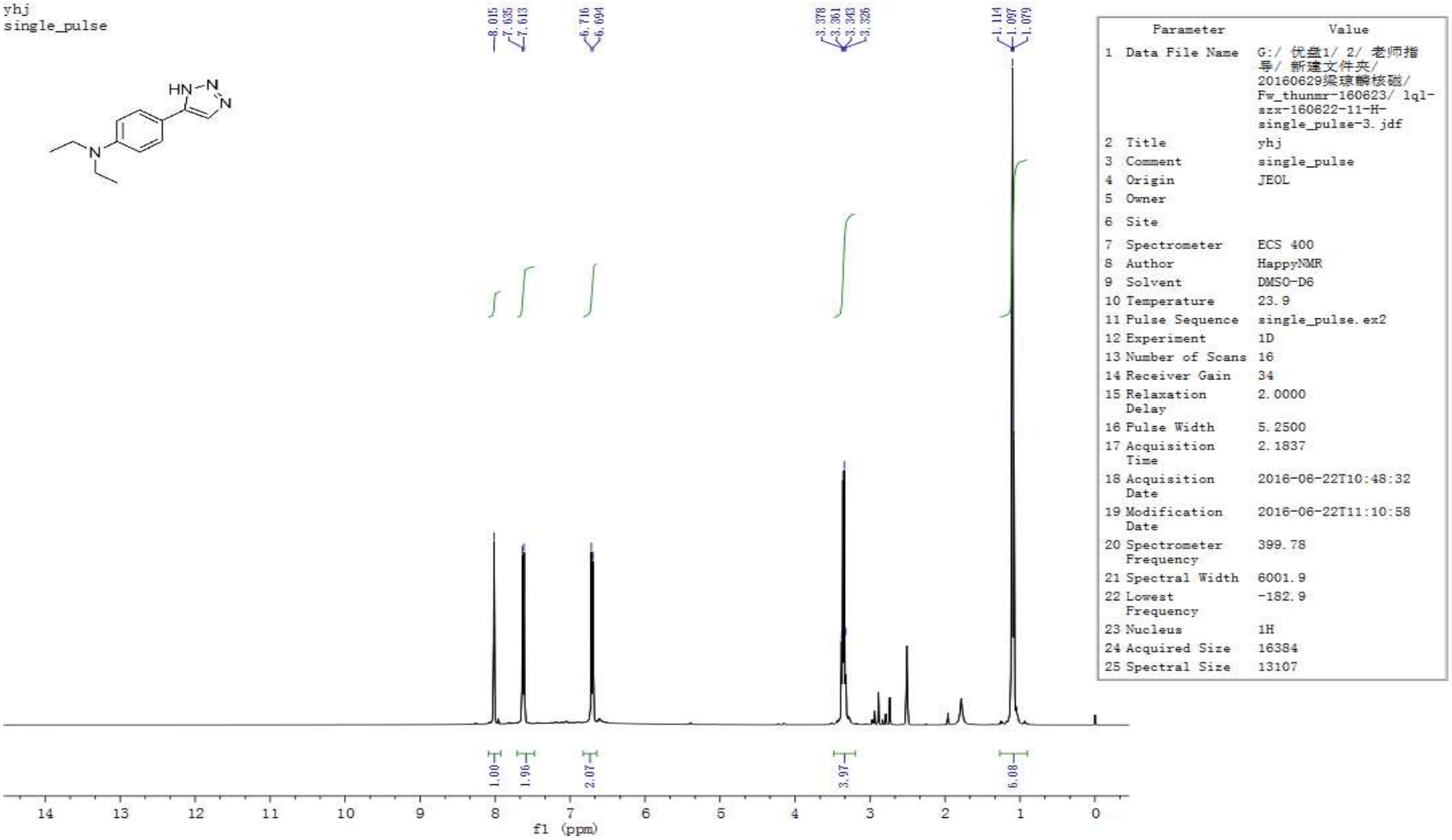
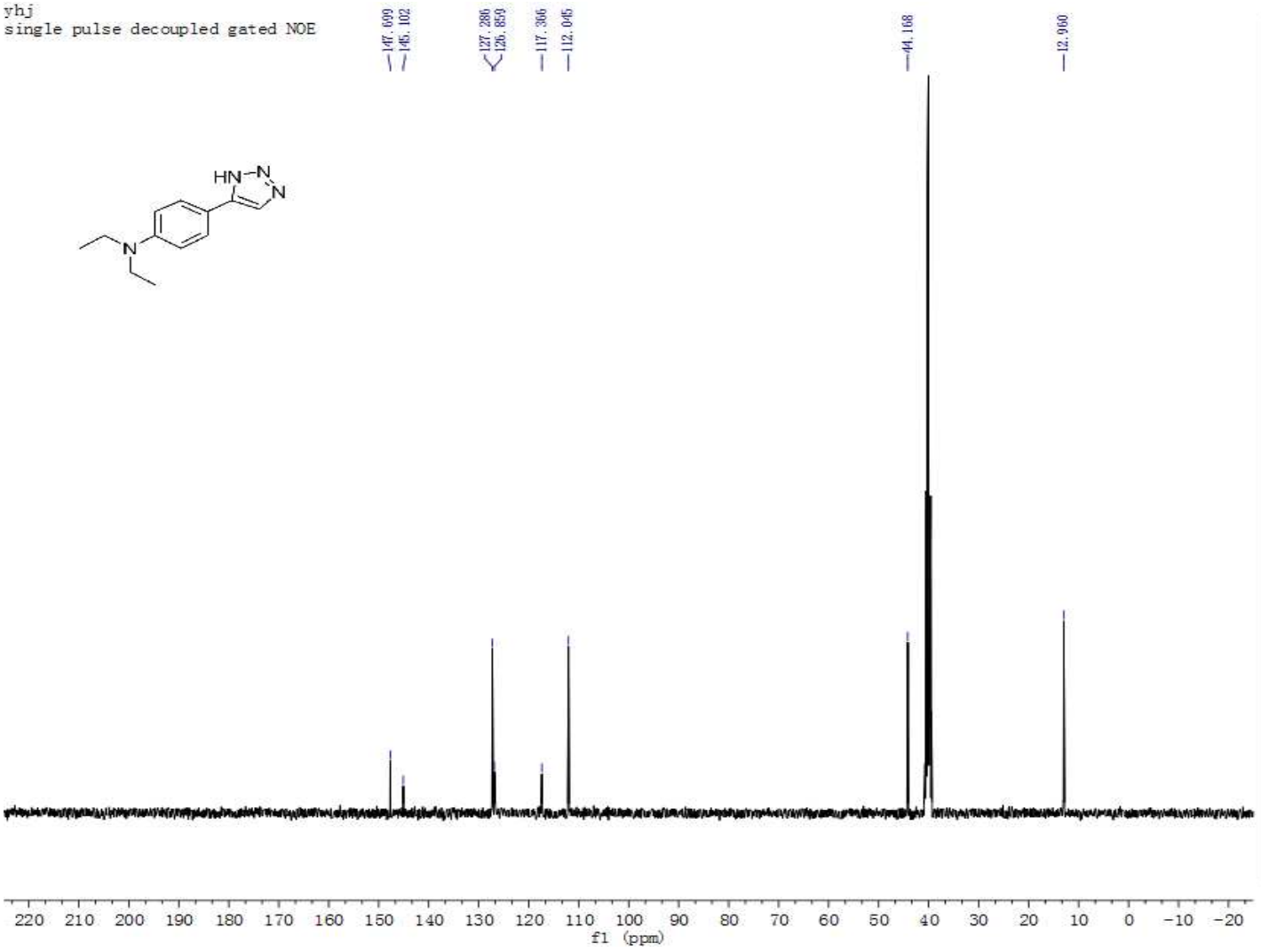
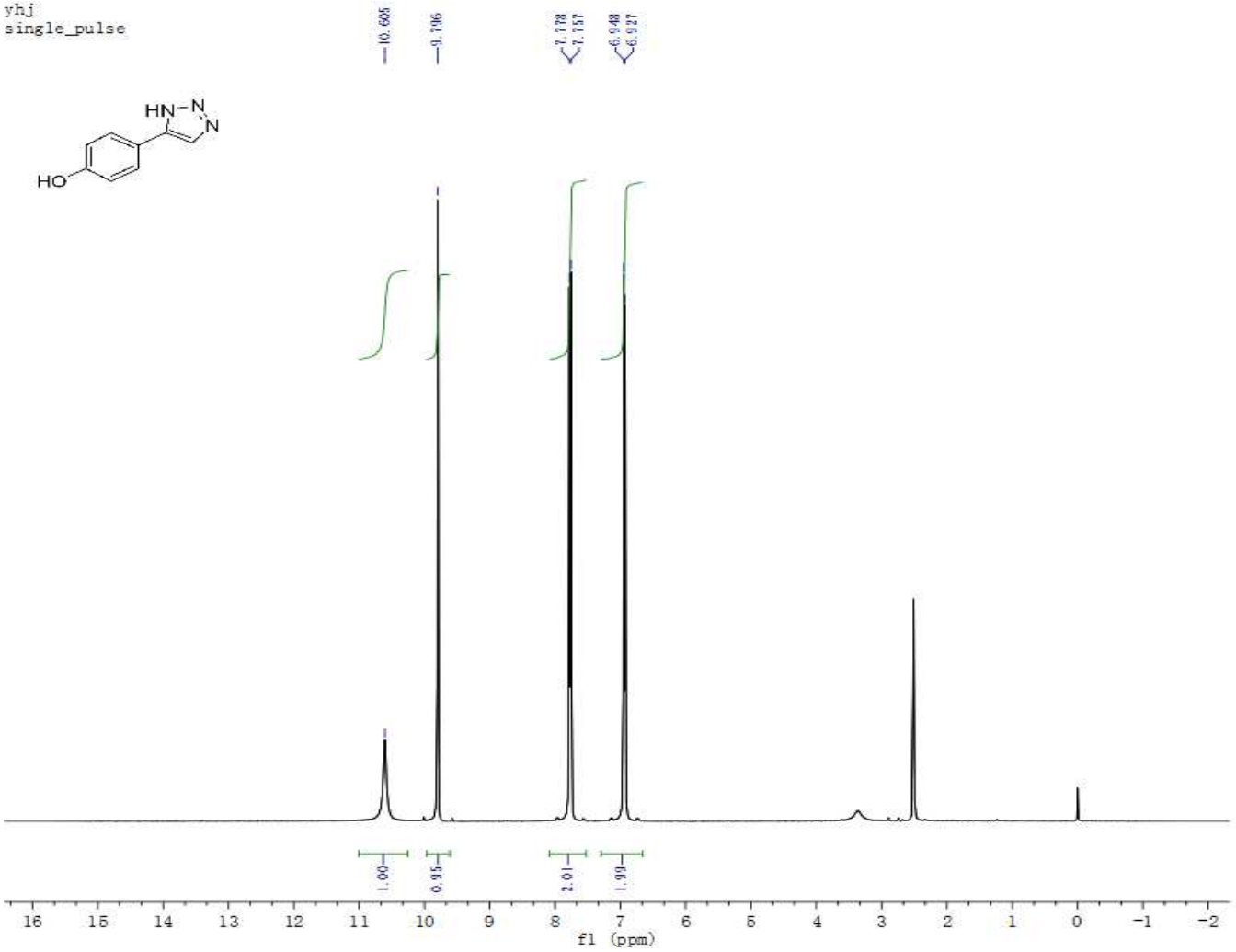
2	Title	yhj
3	Comment	
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECA 600
8	Author	ECA600-Happy NMR
9	Solvent	DMSO-D6
10	Temperature	25.1
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	1024
14	Receiver Gain	58
15	Relaxation Delay	2.0000
16	Pulse Width	4.0833
17	Acquisition Time	0.6921
18	Acquisition Date	2016-08-30T08:47:59
19	Modification Date	2016-08-30T09:02:39
20	Spectrometer Frequency	150.91
21	Spectral Width	47348.5
22	Lowest Frequency	-8582.9
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536



Parameter	Value
1 Data File Name	G:/ 优盘1/ 2/ 老师指导/ 新建文件夹/ 20160629梁琼麟核磁/ Fw_thunmr-160623/ lql-szx-160622-11-H-single_pulse-3.jdf
2 Title	yhj
3 Comment	single_pulse
4 Origin	JEOL
5 Owner	
6 Site	
7 Spectrometer	ECS 400
8 Author	HappyNMR
9 Solvent	DMSO-D6
10 Temperature	23.9
11 Pulse Sequence	single_pulse.ex2
12 Experiment	1D
13 Number of Scans	16
14 Receiver Gain	34
15 Relaxation Delay	2.0000
16 Pulse Width	5.2500
17 Acquisition Time	2.1837
18 Acquisition Date	2016-06-22T10:48:32
19 Modification Date	2016-06-22T11:10:58
20 Spectrometer Frequency	399.78
21 Spectral Width	6001.9
22 Lowest Frequency	-182.9
23 Nucleus	1H
24 Acquired Size	16384
25 Spectral Size	13107



	Parameter	Value
1	Data File Name	G:/ 优盘1/ 2/ 老师指导/ 新建文件夹/ 20160629梁琼麟核磁/ Fw_thunmr-160623/ lql-szx-160622-11-13C-single_pulse_dec-2.jdf
2	Title	yhj
3	Comment	single pulse decoupled gated NOE
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	24.1
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	143
14	Receiver Gain	54
15	Relaxation Delay	2.0000
16	Pulse Width	2.5833
17	Acquisition Time	1.0433
18	Acquisition Date	2016-06-22T10:56:25
19	Modification Date	2016-06-22T11:18:51
20	Spectrometer Frequency	100.53
21	Spectral Width	25124.3
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	26214



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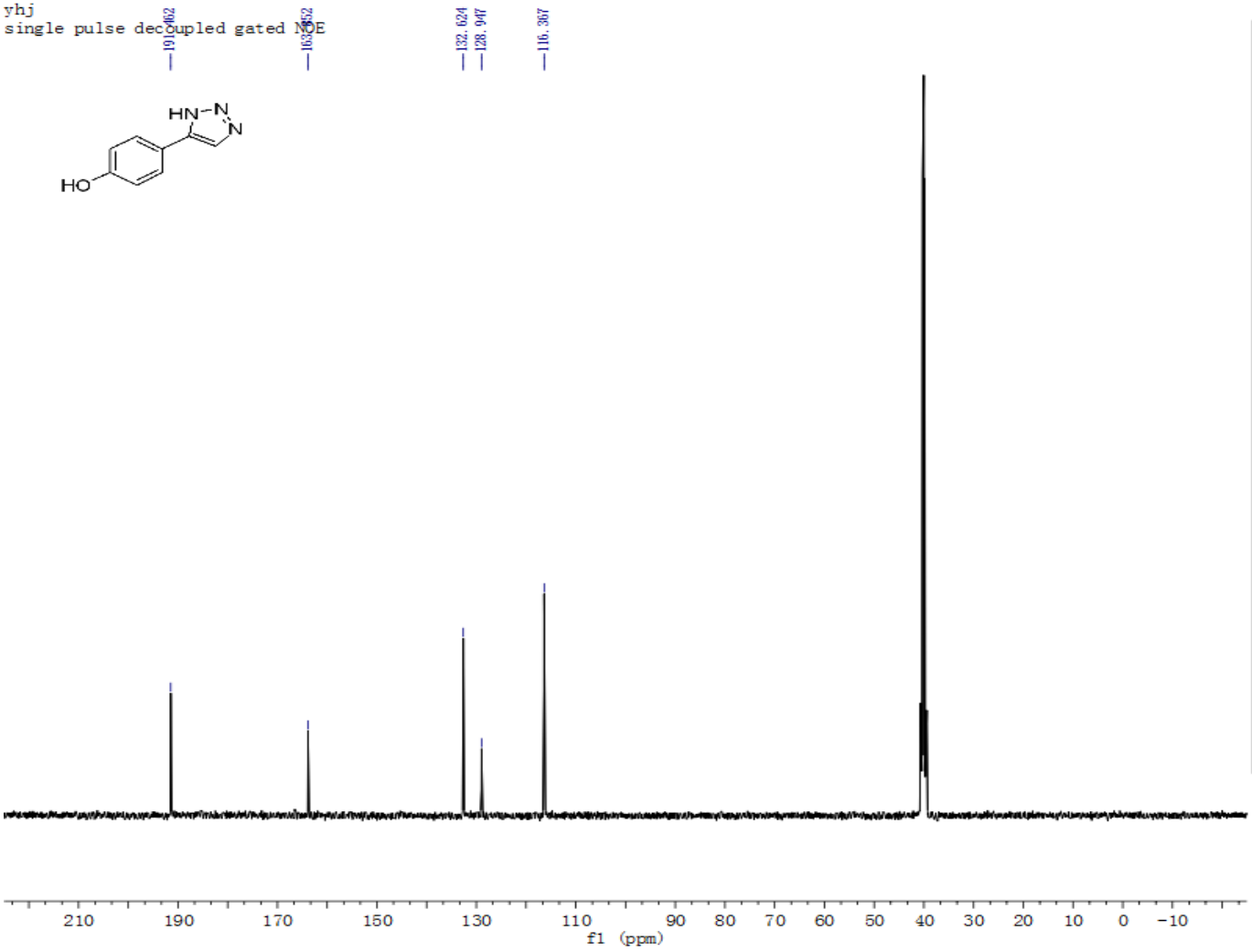
2	Title	yhj
3	Comment	single_pulse
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	23.9
11	Pulse Sequence	single_pulse.ex2
12	Experiment	1D
13	Number of Scans	16
14	Receiver Gain	42
15	Relaxation Delay	2.0000
16	Pulse Width	5.2500
17	Acquisition Time	2.1837
18	Acquisition Date	2016-06-22T11:04:13
19	Modification Date	2016-06-22T11:26:38
20	Spectrometer Frequency	399.78
21	Spectral Width	7503.0
22	Lowest Frequency	-932.6
23	Nucleus	1H
24	Acquired Size	16384
25	Spectral Size	32768



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2	Title	yhj
3	Comment	single pulse decoupled gated NOE
4	Origin	JEOL
5	Owner	
6	Site	
7	Spectrometer	ECS 400
8	Author	HappyNMR
9	Solvent	DMSO-D6
10	Temperature	24.1
11	Pulse Sequence	single_pulse_dec
12	Experiment	1D
13	Number of Scans	321
14	Receiver Gain	50
15	Relaxation Delay	2.0000
16	Pulse Width	2.5833
17	Acquisition Time	1.0433
18	Acquisition Date	2016-06-22T11:21:02
19	Modification Date	2016-06-22T11:43:28
20	Spectrometer Frequency	100.53
21	Spectral Width	25124.3
22	Lowest Frequency	-2509.6
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	26214

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(2) Kallander, L. S.; Lu, Q.; Chen, W. F.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G. F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. W.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**; *48*: 5644.

(3) Wang, X.; Kuang, C.; Yang, Q. *Eur. J. Org. Chem.* **2012**; *2012*: 424.

(4) Jarowski, P. D., Wu, Y. L., Schweizer, W. B., & Diederich, F. . *Org. lett*. 2008; *10*: 3347.