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Advances in Transitional Metal Catalyzed Bond-Forming Reactions via Aqueous Micellar Catalysis

A dissertation submitted in partial satisfaction of the

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in Chemistry

by

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September 2020

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July 2020

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July 2020

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PUBLICATIONS

(1) Du, B.; Jin, B.; Sun, P. "The syntheses of α-ketoamides via $^{n}Bu_4NI$-catalyzed multiple sp^3 C–H bonds oxidation of ethylarenes and sequential coupling with dialkylformamides" *Org. Biomol. Chem.*, **2014**, *12*, 4586-4589.

(2) Du, B.; Jin, B.; Sun, P. "Syntheses of Sulfides and Selenides through Direct Oxidative Functionalization of $C(sp^3)$−H Bond " *Org. Lett.* **2014**, *16*, 3032-3035.

(3) Dong, J.; Jin, B.; Sun, P. "Palladium-Catalyzed Direct Ortho-Nitration of Azoarenes Using NO_2 as Nitro Source" *Org. Lett.* **2014**, *16*, 4540-4542.

(4) Pang, H.; Jin, B.; Lipshutz, B. H. "Pentafluorophenylboronic acid " *e-EROS* **2019**

(5) Jin, B.; Reilly, J.; Gallou, F.; Lipshutz, B. H. "ppm Pd-Catalyzed, Cu-free Sonogashira couplings in water using commercially available catalyst precursors" *Chem. Sci.*, **2019**, *10*, 3481-3485.

(6) Handa, S.; Jin, B.; Bora, P. P.; Wang, Y.; Zhang, X.; Gallou, F.; Reilly, J.; Lipshutz, B. H. "Sonogashira Couplings Catalyzed by Fe Nanoparticles Containing ppm Levels of Reusable Pd, under Mild Aqueous Micellar Conditions" *ACS Catal.* **2019**, *9*, 2423-2431.

(7) Wood, A. B.; Nandiwale, K.; Mo, Y.; Jin, B.; Schultz, V. L.; Pomberger, A.; Gallou, F.; Jensen, K. F.; Lipshutz, B. H. "Continuous Flow Suzuki-Miyaura Couplings Under Aqueous Micellar Conditions in a CSTR Cascade Catalyzed by Fe/ppm Pd Nanoparticles" , *Green Chem*. **2020**, *22*, 3441-3444.

ABSTRACT

Advances in Transitional Metal Catalyzed Bond-Forming Reactions via Aqueous Micellar Catalysis

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Traditional Sonogashira coupling reactions require high loadings of both palladium(II) and copper(I) catalysts. A copper-free, ppm palladium approach was discovered by using a combination of novel ligand and palladium pre-catalyst. A wide range of (hetero)aryl bromides and terminal alkynes can be tolerated under standard reaction condition in water at 45 ^{o}C without any organic solvent. In many cases solid crude products can be obtained by simple filtration, and the filtrate can be recycled. No more than 1 ppm of palladium residue was detected in ICP-MS analysis. A key internal alkyne precursor of commercially available tyrosine-kinase inhibitor ponatinib (Iclusig®) was prepared by using this methodology. This reaction is efficient, greener and cost-effective compared with currently used ones.

Fe/ppm Pd nanoparticles are highly useful catalysts used in Suzuki-Miyaura coupling reactions. However, the relatively long reaction time at 45 ^{o}C limits their applications in time-sensitive reactions. Modifications of the original nanoparticles were conducted by adding another earth abundant metal (Ni, Co, Mn) and screening different types of ligands. The original nanoparticles were used in a newly designed continuous

flow reactor to synthesize key pharmaceutical intermediates. The sartan precursor, JAK inhibitor precursor and BRAF inhibitor precursor were prepared in this continuous flow platform. This approach gives an idea of how to perform large scale Suzuki-Miyaura coupling reactions in water using Fe/ppm Pd nanoparticles.

Diaryl ethers are common structures in drugs. These compounds are usually prepared by copper catalyzed Ullmann-type reactions under harsh conditions in organic solvents. Different types of ligands were tested with copper(I) or palladium(II) salts in water. These reactions give a hint of ligands and co-solvents used under aqueous micellar condition.

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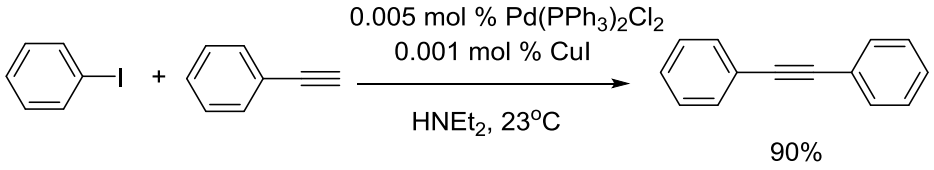
I. ppm Pd-catalyzed, Cu-free Sonogashira couplings in water using commercially available catalyst precursors

Introduction

Among all Pd-catalyzed cross-coupling name reactions, Sonogashira coupling is unique due to its formation new sp^2-sp C-C bonds from readily available starting materials: an aryl (vinyl) halide and a terminal alkyne. Since the discovery by Sonogashira in 1975[1] (Scheme 1), it has become the third most widely used cross-coupling reaction[2] applicable to many syntheses of drugs and natural products (Figure 1). As originally prescribed, a mix of palladium(II) and copper(I) catalysts is used as "standard" catalyst[3] for this reaction. Copper under these conditions aims to activate the terminal alkyne by forming a copper acetylide intermediate in order to facilitate transmetalation. However, homocoupling occurs between reactive copper acetylide and a terminal alkyne, which reduces the yield of desired coupling product, especially in the presence of adventitious oxygen.[4] Although this recipe works in many cases, improvements in reaction conditions are still very much of interest. Eliminating the use of copper, reducing the palladium loading, and performing this reaction under greener and milder conditions are major ways to refine and modernize this reaction.[5]



Scheme 1. The original Sonogashira coupling

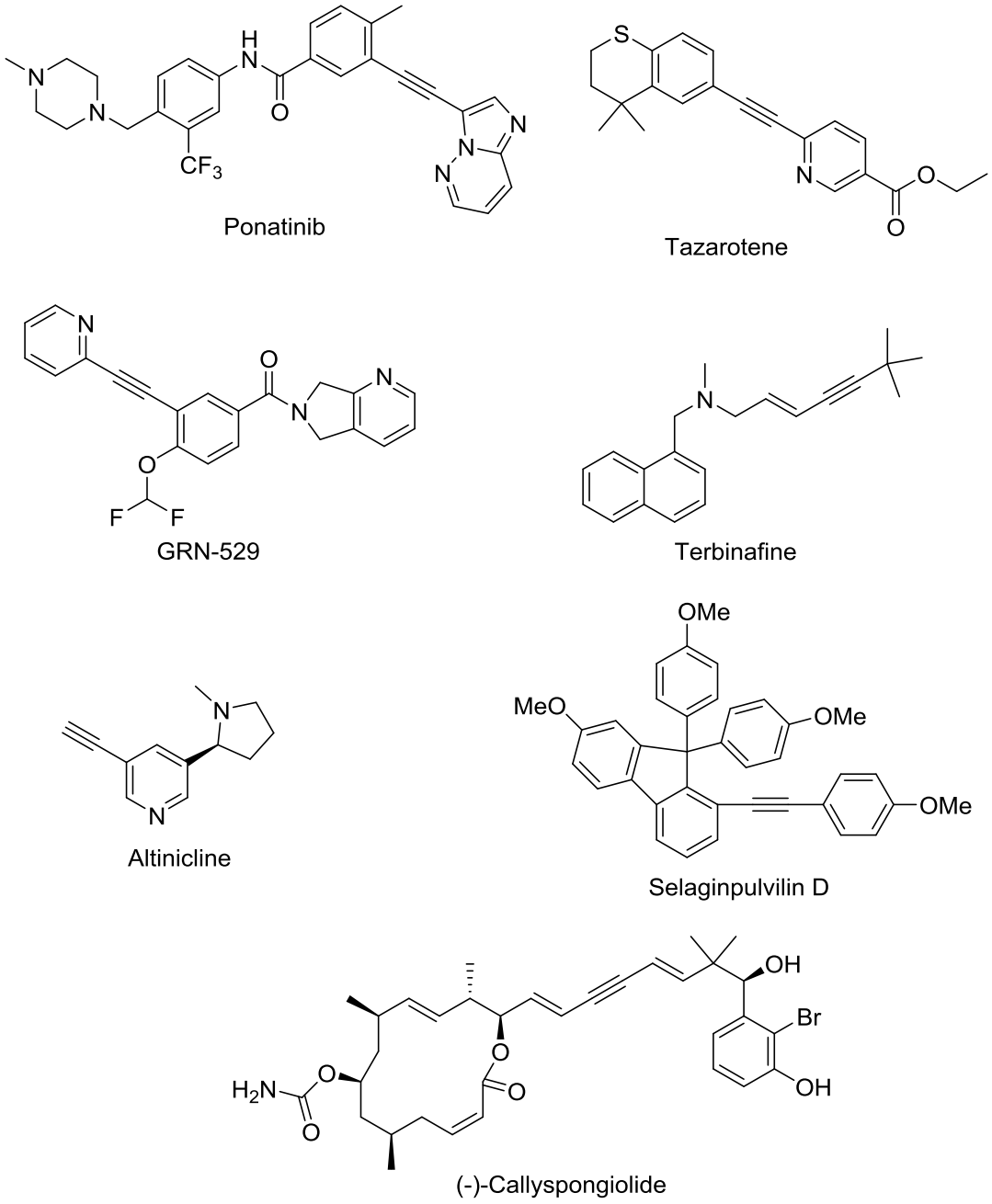
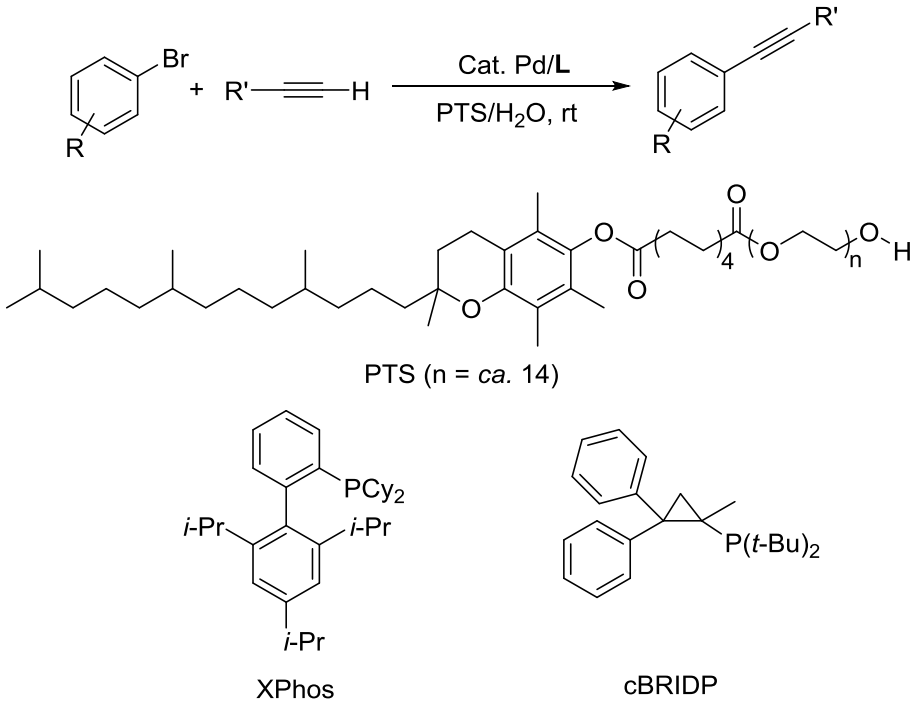


Figure 1. Examples of important drugs and natural products synthesized by Sonogashira coupling reactions.

Previous Work

Copper-free Sonogashira couplings can easily be achieved using expensive aryl (vinyl) iodides as starting materials.[6] However, the reactions involving aryl bromides are much more challenging. These types of substrates usually represent a trade-off between use of a high Pd loading[7] and harsh conditions reflecting the bromides lower reactivity.[8] To further optimize this reaction, a combination of a highly reactive palladium catalyst and optimal reaction conditions is required. In 2008, a graduate student, David Chung, from our group discovered a copper-free approach in water at room temperature.[9]

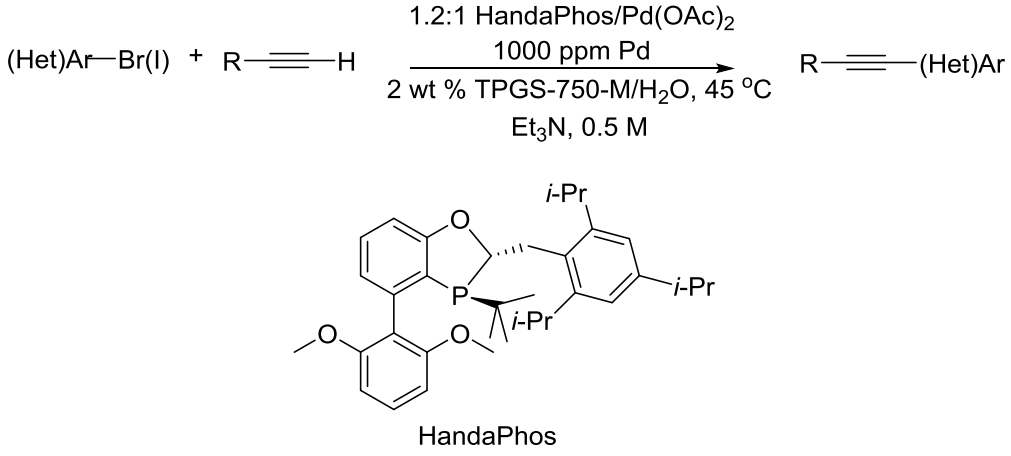


Scheme 2. David Chung's copper-free approach

In this project, reaction conditions were carefully optimized by screening different palladium pre-catalysts, ligands, bases, and other variables. The combination of $PdCl_2(CH_3CN)_2$ and XPhos was found to afford the most reactive catalyst for electron-rich aryl bromides. Cs_2CO_3 and Et_3N were the preferred bases based on

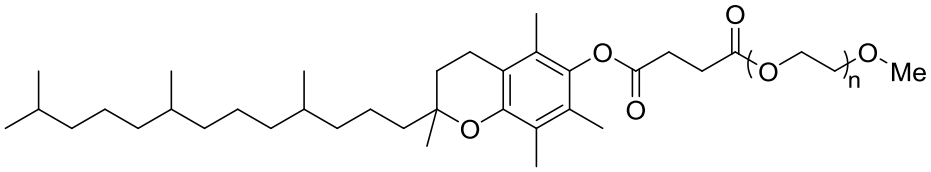
substrates examined. All reactions were carried out in an aqueous solution of PTS,[10] and 3 wt % was found to be the best concentration for this surfactant in water. This methodology enabled room temperature, copper-free Sonogashira couplings of election-rich aryl bromides using a relatively low palladium loading (1 mol %). Additional experiments revealed that a combination of $Pd(OAc)_2$ and Takasago's cBRIDP[11] ligand outperformed the original catalyst in the case of electron-rich aryl bromides (Scheme 2). However, the substrate scope was limited and higher palladium loading was required in challenging cases.

HandaPhos[12] is a novel phosphine ligand designed for palladium catalyzed cross coupling reactions under micellar catalysis conditions based on the BI-DIME[13] skeleton. Extra lipophilicity associated with this ligand comes from its greasy side chain which further encourages the catalyst to stay inside the micellar core.[14] A previous group member, Sachin Handa, developed a ppm-palladium technology[15] to perform copper-free Sonogashira couplings in water using this ligand.

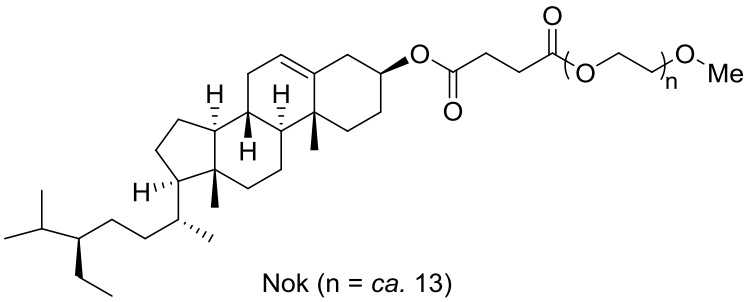


Scheme 3. HandaPhos enabled ppm-Pd catalyzed copper-free Sonogashira couplings in water under mild conditions.

In the ligand screening section, HandaPhos showed superior reactivity compared with commonly used dialkylbiaryl phosphine ligands (e.g., XPhos, SPhos). Only 1000 ppm of $Pd(OAc)_2$ together with 1200 ppm of HandaPhos was found to be sufficient to drive Sonogashira couplings of both iodides and bromides to completion at 45 ^oC (Scheme 3). Couplings using the second generation surfactant TPGS-750-M[16] and the third generation Nok (i.e., SPGS-550-M)[17] were equally reactive but the former was chosen because of its availability (Scheme 4).



TPGS-750-M (n = *ca.* 17)



Nok (n = *ca.* 13)

Scheme 4. Structures of TPGS-750-M and Nok.

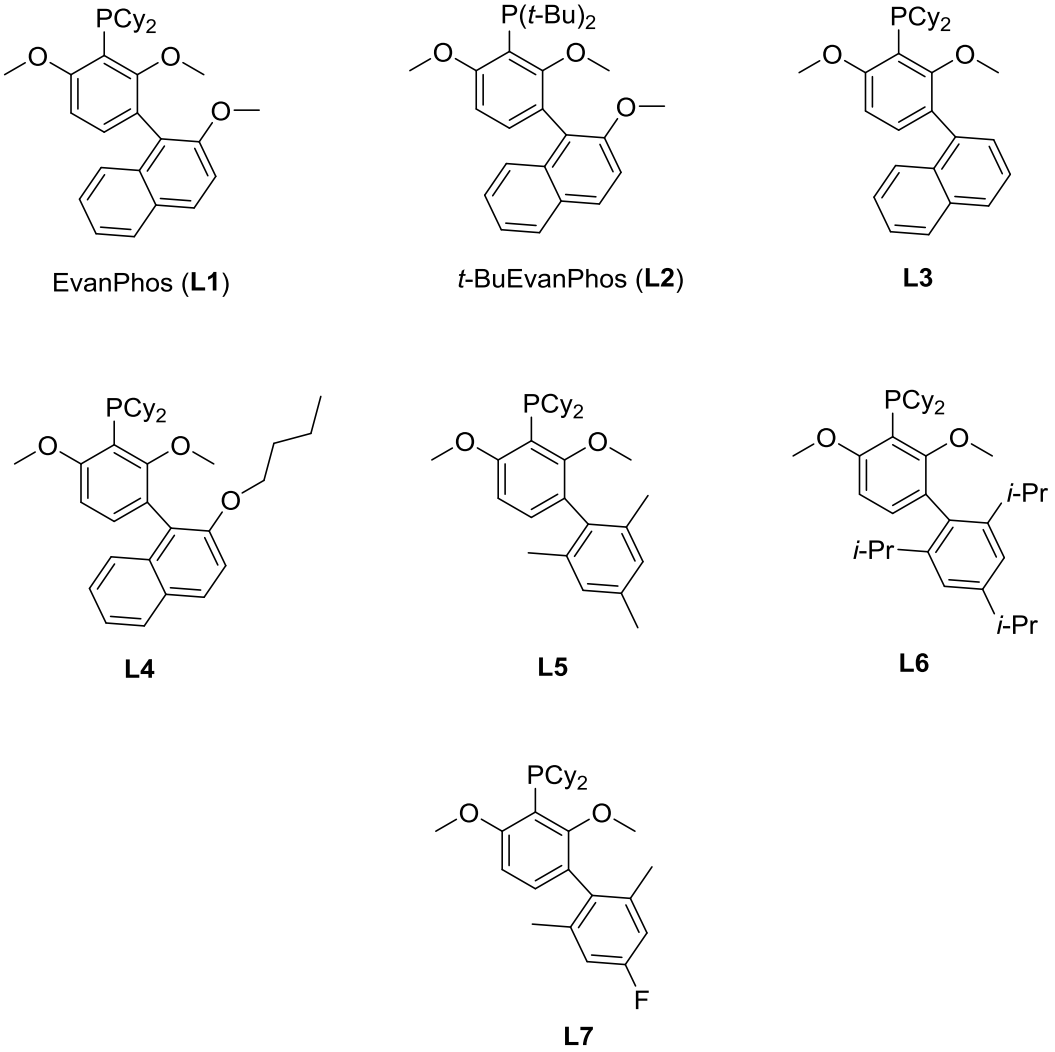
A wide range of functional groups could be tolerated under these mild reaction conditions. Use of low palladium loadings resulted to reduced levels of residual palladium found in the cross coupling products, which was beneficial to the synthesis of pharmaceutical intermediates. Using the "in-flask" extraction technique,[18] this catalyst could be recycled for four times without losing its reactivity. While this methodology is highly useful in organic synthesis, the main drawback is the synthesis of the ligand itself. Ten steps[12, 13, 19] are required to synthesize HandaPhos from commercially available

materials. Considering the usefulness of Sonogashira couplings, it is highly desirable to discover novel solutions that are more efficient, economical, and accessible.

Recently, Sparr reported a new approach[20] using commercially available CataCXium Pd G3 pre-catalyst at only 0.3 mol % palladium loading. However, the substrate scope was limited, and 15 mol % of THF was required as co-solvent.

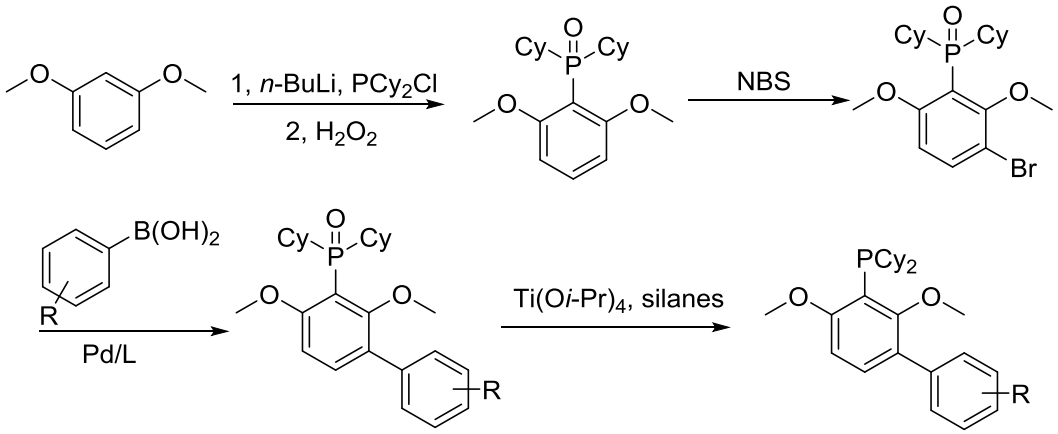
Results and Discussion

Ligands used in Sonogashira couplings play a vital role in the reactivity of the resulting catalytic species. EvanPhos[21] is a mono-phosphine ligand designed by previous group member Evan Landstrom that features a novel biaryldialkyl phosphine skeleton. This ligand was shown to be effective in Suzuki-Miyaura coupling reactions at low palladium loadings, and its synthesis in only two steps made its availability far greater as compared with HandaPhos. Following this idea, a series of EvanPhos analogs were proposed (Scheme 5).



Scheme 5. EvanPhos and its analogs.

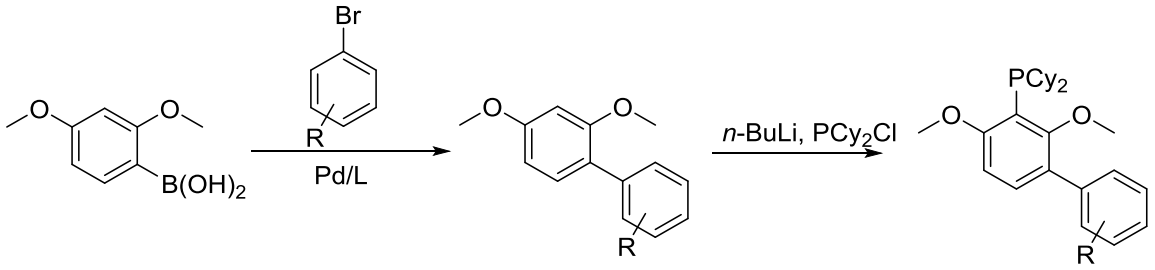
Ligand EvanPhos (**L1**) and *t*-BuEvanPhos (**L2**) were the original ligands synthesized by Evan. Their analogs **L3-L7** were modified mainly on the bottom, naphthalene ring by changing both its electron density and increasing steric bulk associated with the attached substituents. Their route towards their syntheses is shown in Scheme 6.



Scheme 6. First generation synthesis route of EvanPhos analogs.

This route to various analogs seemed reasonable. However, the bromination step was difficult to control. Double bromination and demethylation of methoxy groups were major side reactions. On the other hand, the last reduction reaction of phosphine oxide to phosphine using titanium isopropoxide and silanes was highly air sensitive.[22] Considering all of these disadvantages, this route needed to be improved. Eventually, it was found that the dialkylphosphine could be installed in the last step eliminating the extra redox step, if the initial product of Suzuki-Miyaura coupling could tolerate condition under which it would be then treated with *n*-BuLi. With the availability of the coupling partner 2,4-dimethoxyphenylboronic acid, the Suzuki-Miyaura coupling was carried out using the corresponding aryl bromides. In this way, the problems of bromination of

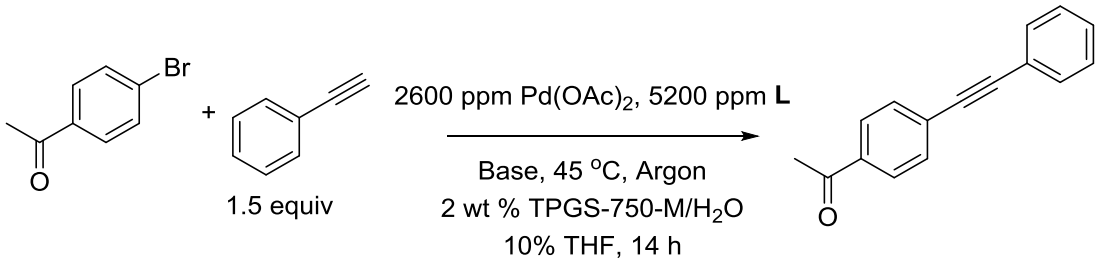
electron-rich 1,3-dimethoxybenzene, or preparation of the boronic acids of different bottom rings could be avoided. The revised synthesis could be as short as two steps.



Conditions: Step 1: aryl bromide (1.0 equiv), 2,4-dimethoxyphenylboronic acid (1.5 equiv), $Pd(OAc)_2$ (1 mol %), SPhos (1.5 mol %) in 2 wt% TPGS-750-M/H_2O (0.5 M) and THF (10 vol %) at 60 ^oC overnight. Step 2: 1-aryl-2,4-dimethoxybenzene (1.0 equiv), *n*-BuLi (0.97 equiv), PCy_2Cl (0.95 equiv) in THF, -78 ^oC to rt, 12 h.

Scheme 7. Revised synthesis of EvanPhos analogs.

Ligands **L3-L7** were synthesized using the revised route in Scheme 7. Aryl bromides for **L3**, **L5**, **L6** and **L7** were commercially available and the aryl bromide for **L4**, 1-bromo-2-butoxynaphthalene, was synthesized by alkylation of β-naphthol using 1-bromobutane followed by bromination at the ortho alpha position using NBS.

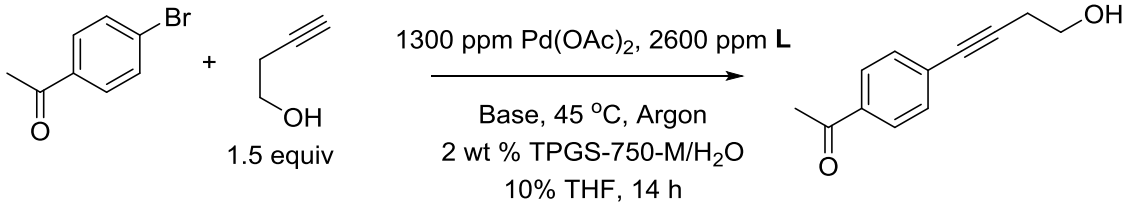


Entry	Ligand	Base	GC yield (%)[a]
1	**L3**	$K_3PO_4•H_2O$ (3 equiv)	trace
2	**L4**	$K_3PO_4•H_2O$ (3 equiv)	trace
3	XPhos	Et_3N (3 equiv)	98
4	**L4**	$K_3PO_4•H_2O$ (2 equiv)	31

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 1. Initial screening of ligands.

Initial screening using ligands **L3** and **L4** gave inferior results compared with XPhos used in the previous publication.[9] XPhos gave almost a stoichiometric yield of desired product, while in the best case, **L4** gave only a 31% yield (Table 1). The homocoupling product of the terminal alkyne was the major by-product of this reaction. A different terminal alkyne (1-butyn-4-ol) was used in further screenings.



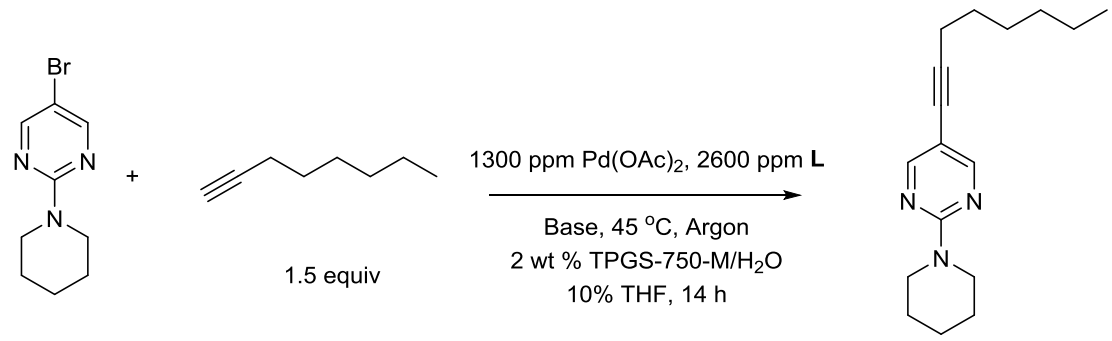
Entry	Ligand	Base (2 equiv)	GC yield (%)[a]
1	XPhos	Et_3N	trace
2	XPhos	Et_3N	trace[b]
3	**L1**	K_3PO_4•H_2O	0
4	**L3**	K_3PO_4•H_2O	0
5	**L4**	K_3PO_4•H_2O	0
6	**L4**	K_3PO_4•H_2O	0[a]

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O. **[b]:** Under air.

Table 2. Further screening of ligands.

Reducing the palladium loading to 1300 ppm with a polar terminal alkyne totally shut down these reactions. All ligands screened failed to give any conversion under the given conditions. Using this relatively polar terminal alkyne could be the

reason for low reactivity since micellar catalysis favors greasy substrates that react inside the lipophilic cores (Table 2). Thus, additional screenings of other ligands were conducted using relatively nonpolar substrates.



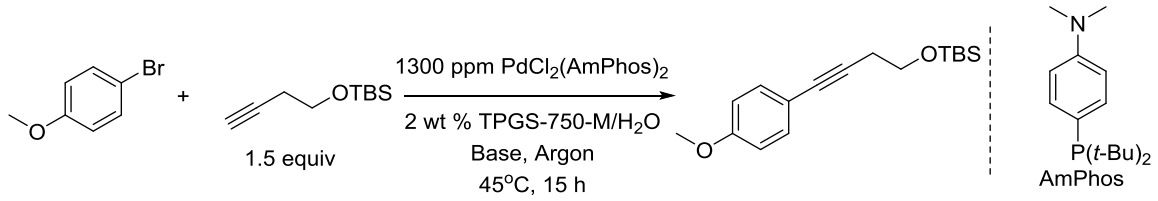
Entry	Ligand	Base (2 equiv)	GC yield (%)[a]
1	XPhos	Et_3N	0
2	**L2**	$K_3PO_4•H_2O$	0
3	**L2**	Et_3N	0
4	**L5**	$K_3PO_4•H_2O$	0
5	**L5**	Et_3N	0
6	**L6**	$K_3PO_4•H_2O$	0
7	**L6**	Et_3N	0
8	**L7**	$K_3PO_4•H_2O$	0
9	**L7**	Et_3N	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 3. Screening of other EvanPhos derivatives.

Other EvanPhos derivatives were also tested but none showed reactivity at 1300 ppm palladium loading (Table 3). Other activation methods like reducing with DIBAL-H were also tested but no reactivity was observed. In order to get reactivity a better hint of

catalysts is required. Colacot[23] reported copper-free Sonogashira couplings using the AmPhos as ligand. This catalyst is effective for both aryl bromides and chlorides at relatively low palladium loadings (0.5-1.5 mol %).



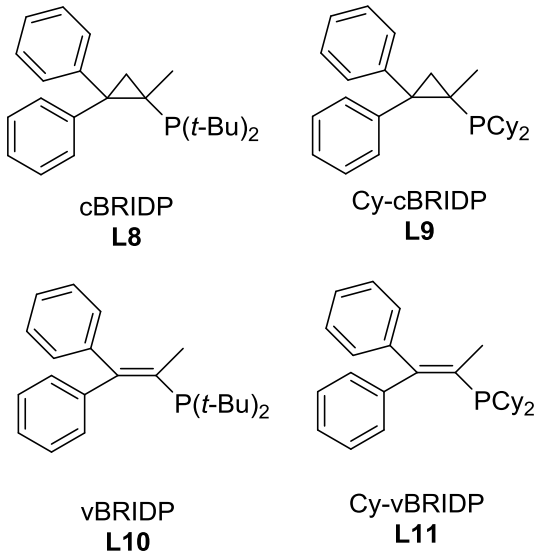
Entry	Base	Cosolvent	GC yield (%)[a]
1	$K_3PO_4•H_2O$ (2 equiv)	-	19
2	$K_3PO_4•H_2O$ (2 equiv)	THF (10 vol %)	30
3	$K_3PO_4•H_2O$ (2 equiv)	THF (5 vol %)	19
4	$K_3PO_4•H_2O$ (2 equiv)	THF (15 vol %)	27
5	$K_3PO_4•H_2O$ (1.5 equiv)	THF (10 vol %)	58

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 4. Reactions using $PdCl_2(AmPhos)_2$ as catalyst.

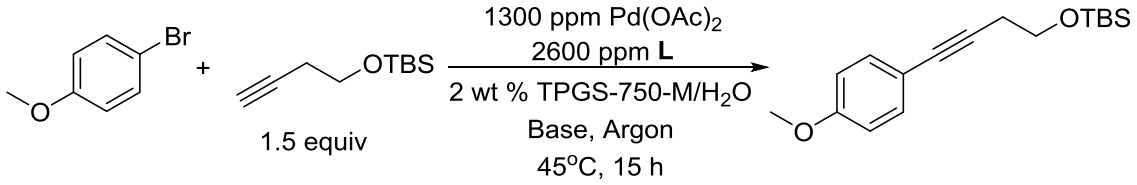
After some condition optimizations, $PdCl_2(AmPhos)_2$ showed some reactivity at 1300 ppm palladium loading (Table 4). However, this catalyst is still not efficient enough to drive reactions to completion. A more reactive catalyst system is crucial for this reaction.

Developed by Takasago, the BRIDP ligand family (Scheme 8) was a set of four different phosphine ligands. This array of ligands was found to be powerful in palladium catalyzed cross-coupling reactions, including Suzuki-Miyaura couplings,[24] aminations[11, 24, 25] and α-arylations.[24]



Scheme 8. BRIDP ligand family.

However, their applicability to Sonogashira coupling reactions was not discovered until David Chung's work. In his studies, Sonogashira couplings using BRIDP ligands were found to be faster and cleaner compared with the original ligand XPhos. Thus, these four ligands were tested again at 1300 ppm palladium loading.



Entry	Ligand	Base (2 equiv)	GC yield (%)[a]
1	**L8**	$K_3PO_4•H_2O$	85 (76)[b]
2	**L9**	$K_3PO_4•H_2O$	trace
3	**L10**	$K_3PO_4•H_2O$	19
4	**L11**	$K_3PO_4•H_2O$	trace

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O. [b]: Isolated yield.

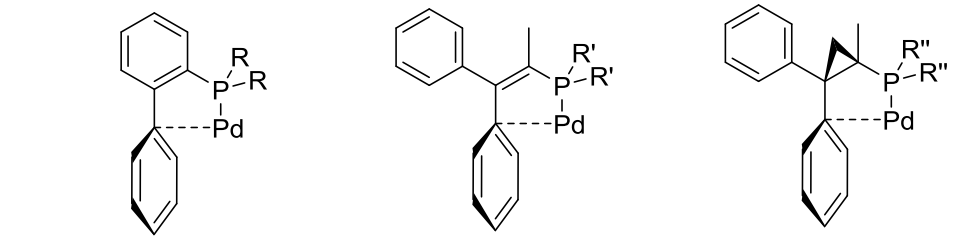
Table 5. Initial screenings of BRIDP family.

Remarkably, ligand cBRIDP (**L8**) showed good reactivity in this electron-rich aryl bromide substrate, giving an 85% GC yield and 76% isolated yield while the other three ligands showed low reactivity under identical conditions (Table 5). This result was in line with previous work that **L8** was also the best ligand, albeit at 1% palladium loading.

Electron density on the phosphine center determines the rate of oxidative addition. Attaching more electron-donating groups to phosphorus generally increases the electron density on the phosphine center. However, the increased electron density will labialize the ligand. For example, tricyclohexylphosphine will be readily oxidized by air[26] and more electron-rich tri-*t*-butylphosphine is pyrophoric in air.[27] Also, these electron donating groups must tolerate usually harsh conditions needed to install the phosphine onto the ligand backbone. Considering all these requirements, hydrocarbons like *t*-butyl, cyclohexyl, and adamantyl groups are most commonly used electron-donating groups in phosphine ligands. Tri-*t*-butylphosphine enabled some early examples of palladium catalyzed cross coupling reactions[28] including Sonogashira couplings[29] under mild conditions, although relatively high palladium loadings and extremely air-sensitive ligands were major drawbacks. Recently, Carrow reported the first practical synthesis of an air-stable electron-rich ligand tri(1-adamantyl)phosphine,[30] and Gessner reported ylide-functionalized phosphine ligands[31] used as strong donor ligands in palladium-catalyzed aminations and α-arylations. These two ligands are examples of developing novel electron-rich phosphine ligands but their usage in Sonogashira coupling reactions

have yet to be reported. On the other hand, steric effects can also play an important role in the catalytic cycle. Specifically, when a traditionally considered monodentate ligand can occupy a second bonding site of palladium, or known as *pseudo*-bidentate ligand, the reactivity will increase dramatically. This effect was first discovered in palladium complex of 2-dimethylamino-2'-diphenylphosphino-1,1'-binaphthyl[32] and developed into dialkylbiaryl phosphine ligands.[33] A recent publication[34] indicated that ylide-functionalized phosphine ligands or even tri-*t*-butylphosphine could work as *pseudo*-bidentate ligands via a weak sp^3 C-H---Pd interaction.

Given all the information above, we can now consider the design of the BRIDP ligand family. It is obvious that vBRIDP and Cy-vBRIDP are basically simplified dialkylbiaryl phosphine ligands.

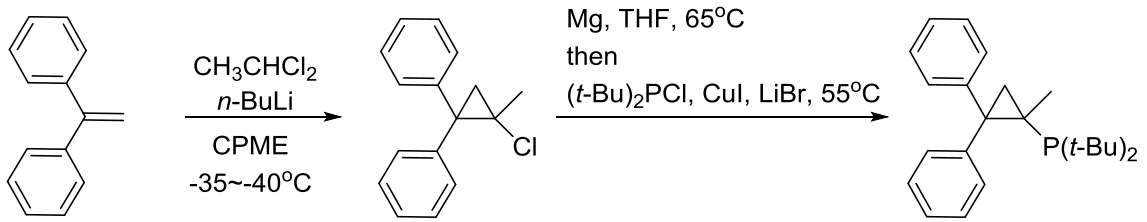


Dialkylbiaryl phosphine-Pd R'=*t*-Bu vBRIDP-Pd Cy Cy-vBRIDP-Pd R''=*t*-Bu cBRIDP-Pd Cy Cy-cBRIDP-Pd

Scheme 9. Structures of dialkylbiaryl phosphine-Pd and BRIDP-Pd complexes.

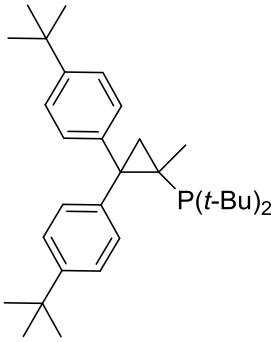
On the contrary, cyclopropane based cBRIDP and Cy-cBRIDP are designed after much deliberation. In the case of traditional dialkylbiaryl phosphines, the phosphorus atom is always connected to one aryl group and two alkyl groups, which limits the electron density at the phosphorus center. The use of the cyclopropyl group maintains relative configuration at the phosphorus center and the β-aryl ring increases the electron density on the phosphorus center and allows another substitution at the α-position. The

weak interaction between the Pd center and β-aryl ring was determined by ^{31}P-NMR[35] (Scheme 9).



Scheme 10. Original synthesis of cBRIDP (**L8**).

Ligand cBRIDP could be synthesized easily in two steps[24] (Scheme 10). 1,1-Diphenylethylene was treated with 1,1-dichloroethane and *n*-BuLi to form the core cyclopropane skeleton. The derived cyclopropyl Grignard reagent was formed by refluxing this chloride with magnesium metal and then transmetallated to the corresponding cuprate by adding copper(I) iodide and lithium bromide. Finally, the target ligand was synthesized by coupling the cuprate with di-*t*-butylchlorophosphine. Considering the relatively simple structure, structure modification of cBRIDP ligand would seem to be feasible.

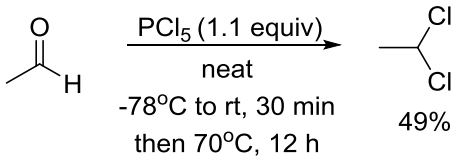


L12

Scheme 11. Structure of **L12**.

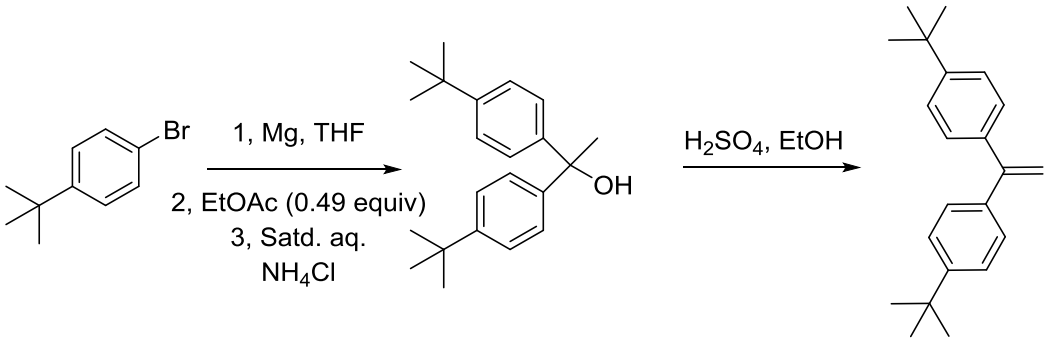
The nature of micellar catalysis requires greasy substrates and catalyst. We proposed a *para*-*t*-butyl cBRIDP derivative **L12**. Two extra *t*-butyl groups offer extra

hydrocarbon that should impart a greater binding constant, thereby encouraging the catalyst to stay in the hydrophobic pockets within the micellar array (Scheme 11). Based on the original synthesis of cBRIDP, we needed to synthesize 1,1-dichloroethane and 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene).



Scheme 12. Synthesis of 1,1-dichloroethane.

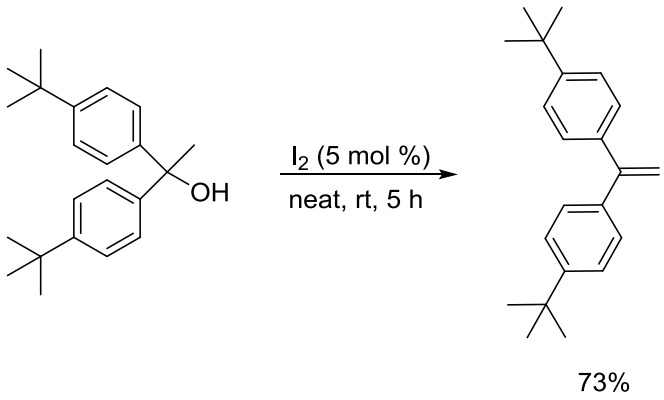
1,1-Dichloroethane was prepared by reacting PCl_5 with acetaldehyde in the absence of solvent (Scheme 12). Using DCM as solvent in this reaction did not give any desired product. The product was isolated by fractional distillation. Unlike the commercially available 1,1-diphenylethylene used in the synthesis of cBRIDP, its *t*-butyl derivative 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) needs to be synthesized from commercially available starting materials.



Scheme 13. Original synthesis plan towards 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene).

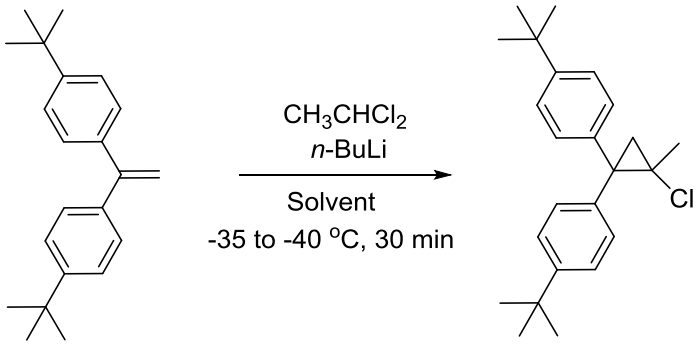
The 4-*t*-butylphenyl Grignard reagent was prepared from 1-bromo-4-*t*-butylbenzene in THF. The Grignard reagent was then quenched with 0.49 equivalents of readily available two-carbon source ethyl acetate to afford the desired

benzyl alcohol. Acidic dehydration of the alcohol affords the key 1,1-substituted ethylene intermediate (Scheme 13).



Scheme 14. Revised dehydration reaction.

However, an easier approach to dehydration[36] was applied using iodine as a catalyst under solvent-free conditions (Scheme 14).

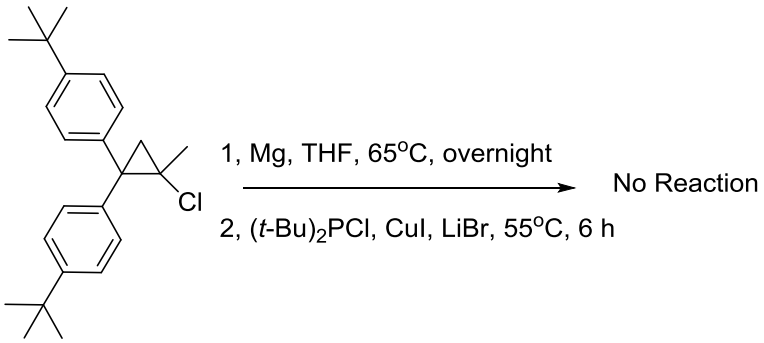


Entry	Solvent	Isolated yield (%)
1	THF	No reaction
2	ether	22
3	CPME	20

Conditions: 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) (5.05 mmol), CH_3CHCl_2 (2.0 equiv), solvent (6 mL), *n*-BuLi (2.0 equiv), -35 to -40 °C, 30 min.

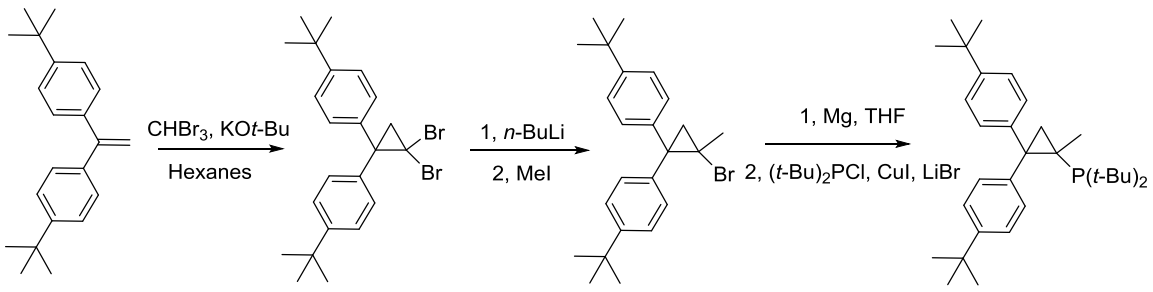
Table 6. Cyclopropylation using 1,1-dichloroethane in different organic solvents.

The cyclopropanation reaction between 1,1-dichloroethane and 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) was conducted based on a published procedure.[11] The solvent played an important role in this reaction. Ether and CPME gave around 20% isolated yields but THF gave no product at all (Table 6).



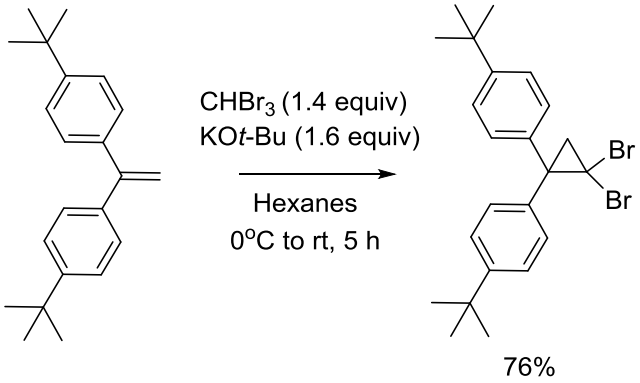
Scheme 15. First attempt to prepare **L12**.

Final coupling using a published procedure failed. No **L12** was obtained in this reaction and magnesium turnings were not consumed in the first step (Scheme 15). Considering the low yields in the cyclopropanation step and low reactivity in the coupling step, changing the route to find a more efficient way to synthesize **L12** was considered. The oxidative addition reaction of magnesium to an alkyl bromide should be faster than to an alkyl chloride. On the other hand, *gem*-dibromocyclopropane can be easily synthesized by addition of dibromocarbene to the 1,1-disubstituted ethylene.[37] A new synthesis was proposed.



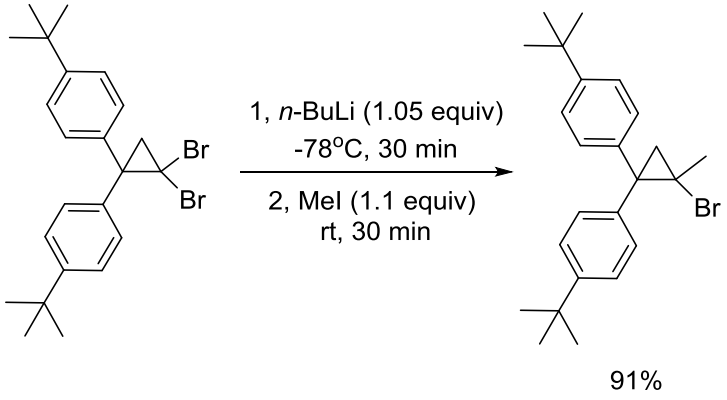
Scheme 16. Revised synthesis of **L12**.

The revised synthesis of **L12** is one step longer than the reported synthesis (Scheme 16). However, toxic PCl_5 is not required in this route and the low-yield cyclopropanation step can be avoided in this route.



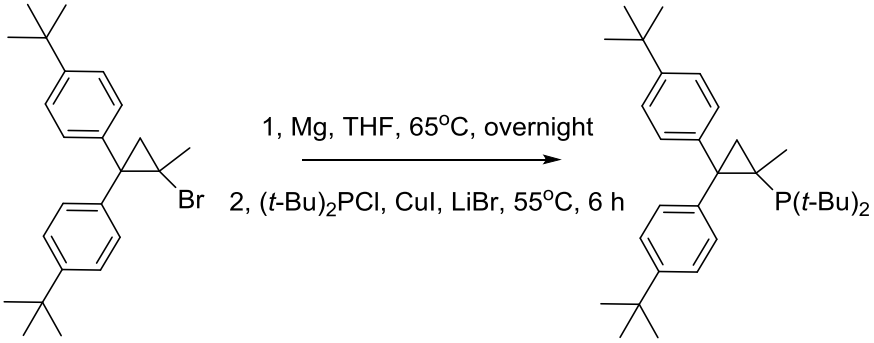
Scheme 17. Cyclopropanation using bromoform.

Generation of dibromocarbene and cyclopropanation could be carried out smoothly in hexanes without the use of phase transfer catalysis[38] (Scheme 17). This was probably because of the high solubility of ethylene as starting material in hexanes. Once the *gem*-dibromocyclopropane was obtained, the lithium-halogen exchange reaction could be used to transfer one of the two bromides into a methyl group[39] (Scheme 18).



Scheme 18. Lithium-halogen exchange and methylation.

The lithium-halogen exchange reaction gave relatively high yield because the lithiate was stabilized by another bromide. Thirty minutes was the minimum amount of time required to consume all starting materials at -78 ^{o}C. Reduced reaction time led to incomplete conversion. The desired cyclopropyl bromide was prepared in a relatively efficient fashion (69% over 2 steps) compared with the original synthesis of cyclopropyl chloride (22%).



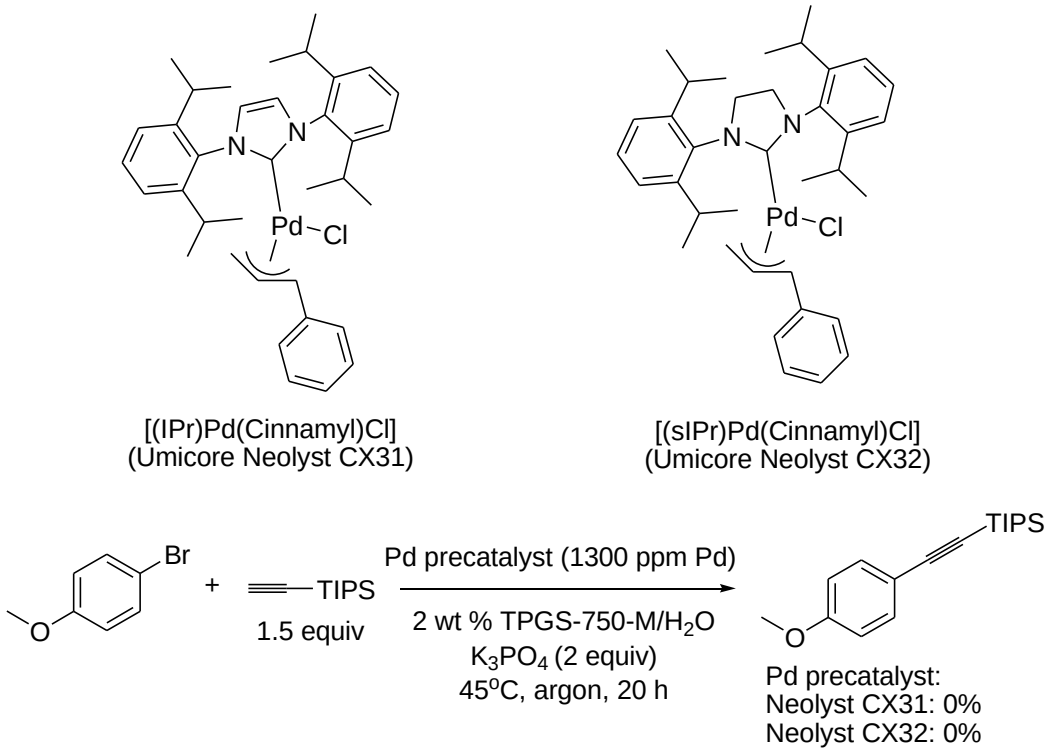
Entry	Mg source	Isolated yield (%)
1	Mg turnings	0
2	Mg powders	0
3	Mg turnings (pretreated with HNO_3 and HCl)	0

Conditions: 4,4'-(2-Bromo-2-methylcyclopropane-1,1-diyl)bis(*t*-butylbenzene) (0.5 mmol), Mg (1.05 equiv), THF (2 mL), I_2 (one crystal), 1,2-dibromoethane (one drop) and *t*-BuMgCl (one drop) at 65 ^{o}C overnight then (*t*-Bu)$_2$PCl (1.0 equiv), CuI (1.0 equiv), LiBr (1.3 equiv) at 55 ^{o}C for 6 h.

Table 7. Preparation of **L12** using different Mg sources.

Different forms of magnesium metal were used to prepare the cyclopropyl magnesium bromide including magnesium turnings, magnesium powders, and acid-washed magnesium turnings. Iodine, 1,2-dibromoethane and one drop of *t*-BuMgCl were used to initiate the reaction. However, no **L12** was detected in all reaction mixtures (Table 7). Other activation methods were tested as well including DIBAL-H[40] and the

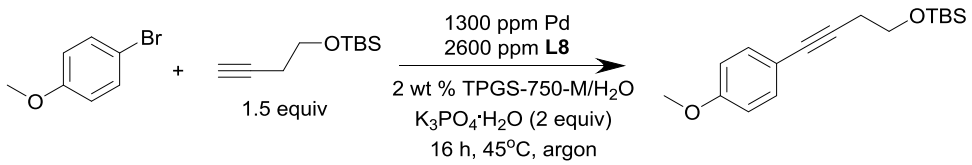
turbo Grignard reagent[41] but no product was obtained. Yitao Zhang eventually prepared the desired ligand **L12** by using *t*-BuLi. The ligand **L12** was found to be similar in reactivity compared with the original ligand cBRIDP (**L8**).



Scheme 19. Sonogashira couplings catalyzed by commercially available NHC-type catalysts.

NHC-type palladium pre-catalysts are also reactive catalysts used in the copper-free Sonogashira couplings.[42] Commercially available NHC-type palladium pre-catalysts Neolyst CX-31 and Neolyst CX-32 from Umicore were tested under aqueous micellar condition (Scheme 19). No reactivity was observed at 1300 ppm palladium loading.

At this point, cBRIDP (**L8**) showed the best reactivity among all ligands screened. Other variables were also screened.

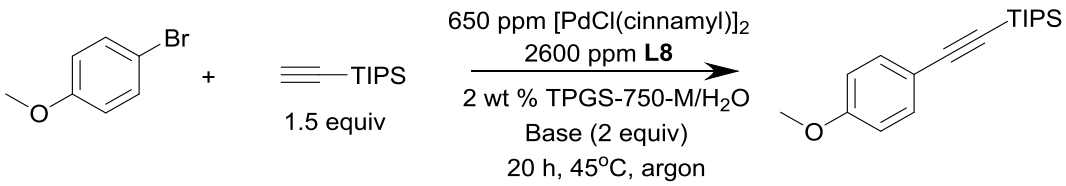


Entry	Palladium source	GC yield (%)[a]
1	$PdCl_2(CH_3CN)_2$	23
2	$Pd(OAc)_2$	85
3	$[PdCl(allyl)]_2$	67
4	$[PdCl(crotyl)]_2$	83
5	$[PdCl(cinnamyl)]_2$	95

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 8. Screening of different palladium sources.

Different palladium sources were screened with **L8** as shown in Table 8, including $PdCl_2(CH_3CN)_2$ used in the previous work,[9] commonly used $Pd(OAc)_2$, and three η^3-type palladium pre-catalysts. Interestingly, GC yield increased with the increase in size of substituents at the 1-position of the allyl groups in the pre-catalysts. Hazari[43] and Colacot[44] reported similar observations in the case of NHC and phosphine ligands, respectively. Unreactive Pd(I) dimer is formed via a comproportionation reaction between Pd(II) pre-catalyst and L-Pd^0 in the catalytic cycle. By increasing the bulkiness of palladium pre-catalyst, the comproportionation reaction can be retarded and more L-Pd^0 will stay in the catalytic cycle.

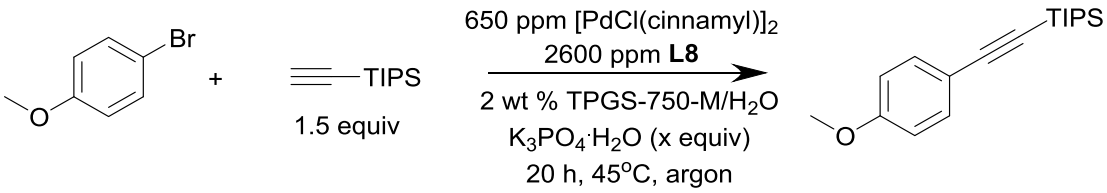


Entry	Base	GC yield (%)[a]
1	$K_3PO_4•H_2O$	75
2	Et_3N	60
3	DABCO	40
4	NaOH	39
5	K_2CO_3	28

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 9. Screening of base.

Commonly used bases were screened as shown in Table 9. Potassium phosphate tribasic monohydrate was the best base among all bases screened.

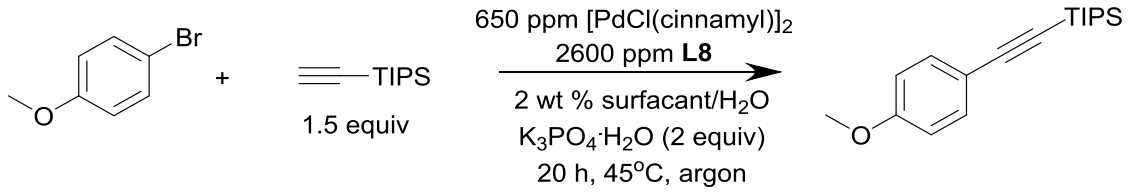


Entry	Base (equiv)	GC yield (%)[a]
1	$K_3PO_4•H_2O$ (1.5)	73
2	$K_3PO_4•H_2O$ (2.0)	75
3	$K_3PO_4•H_2O$ (2.5)	50

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 10. Screening of equivalents of base needed.

The amount of potassium phosphate tribasic monohydrate was screened as shown in Table 10. Two equivalents of base was found to be the best amount.

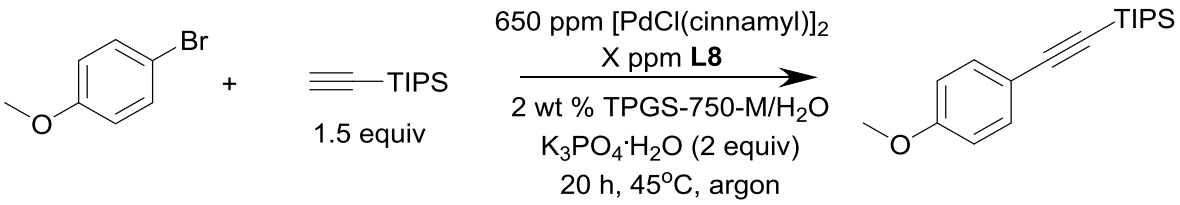


Entry	Surfacant (2 wt %)	GC yield (%)[a]
1	TPGS-750-M	75
2	PTS	72
3	Cremophor EL	33
4	Triton X-100	6
5	Brij 30	38
6	Pluronic	66

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 11. Screening of surfactants.

Different commercially available surfactants were screened as shown in Table 11; TPGS-750-M turned out to be the best in this reaction. The first-generation surfactant PTS showed slightly inferior results.

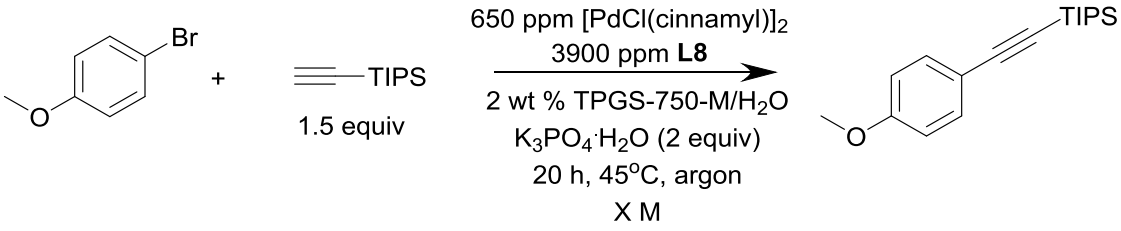


Entry	Ligand equivalence to Pd	GC yield (%)[a]
1	1.0	24
2	1.5	36
3	2.0	75
4	3.0	93
5	4.0	65

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 12. Screening of ligand equivalents.

The ligand to palladium ratio was also screened as shown in Table 12. Interestingly, the highest yield was obtained when the ratio was 3:1. Usually a 2:1 ratio is used in the case of dialkylbiaryl phosphine-Pd complexes,[45] but the oxidation of ligand by trace amounts of oxygen dissolved in the surfactant solution might be the reason.

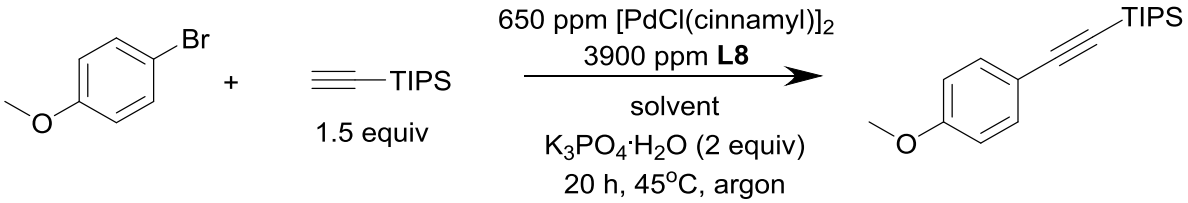


Entry	Global concentration (M)	GC yield (%)[a]
1	0.4	83
2	0.5	93
3	0.75	75
4	1.0	49

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 13. Screening of global concentration.

Global concentration can be crucial when using aqueous micellar catalysis. The yield peaked at 0.5 M global concentration, as shown in Table 13. Decreased concentration reduced the rate of micellar exchange, while increased concentration retarded stirring.



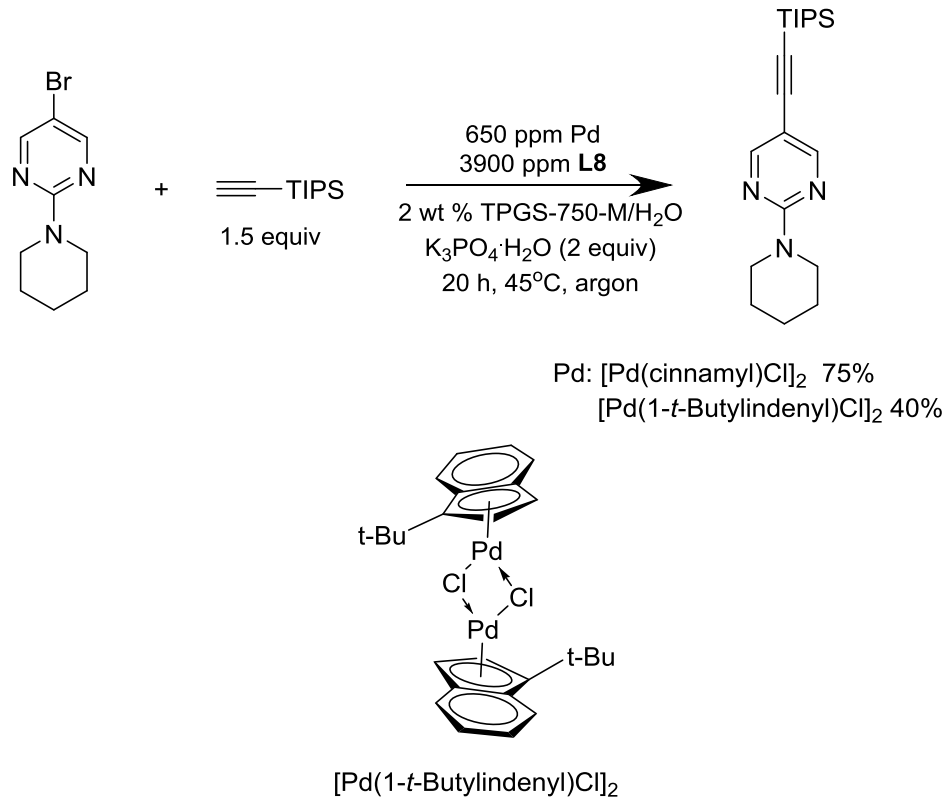
Entry	Solvent	GC yield (%)[a]
1	2 wt % TPGS-750-M	93
2	2 wt % TPGS-750-M/THF (9:1)	17
3	H_2O/THF (1:9)	trace

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of solvent.

Table 14. Co-solvent screening.

Co-solvent changes the size of micelles[46] and sometimes improves reactivity of micellar catalysis. In Table 14 different solvent mixtures were tested. Addition of 10 vol % THF led to poor reactivity compared with co-solvent-free conditions. A 1:9 ratio of water/THF mixture gave, literally, no conversion.

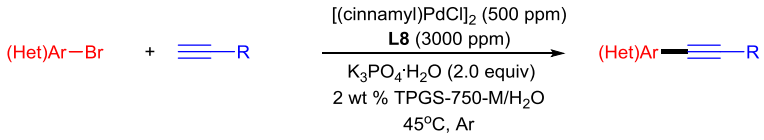
Hazari[47] reported that using (η^3-1-*t*-Bu-indenyl)$_2$(μ-Cl)$_2$Pd$_2$ as pre-catalyst could prevent formation of unreactive Pd(I) dimer. This new pre-catalyst was tested in a Sonogashira coupling reaction under our conditions, as shown in Scheme 20.

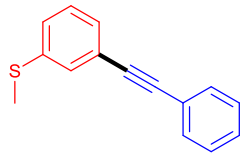


Scheme 20. Comparison of [Pd(cinnamyl)Cl]$_2$ and [Pd(1-*t*-butylindenyl)Cl]$_2$.

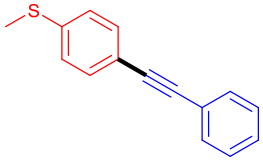
In this reaction the newly developed pre-catalyst led to inferior results compared with those using [Pd(cinnamyl)Cl]$_2$ under our original conditions.

With the reaction optimizations mentioned above, the best set of conditions were now in hand. Different (hetero)aryl bromides and terminal alkynes were tested under these newly developed conditions to determine the substrate scope for this reaction.

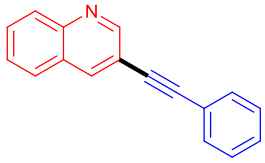




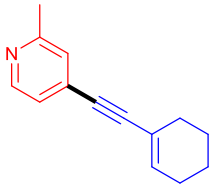
5 h, 96%



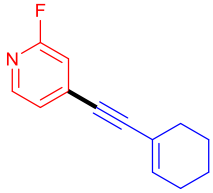
5 h, 99%[a]



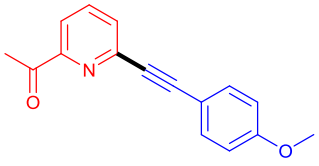
5 h, 95%



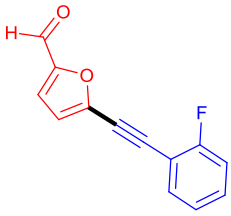
16 h, 94%



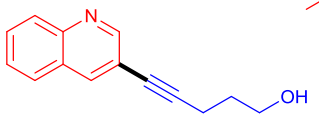
16 h, 87%



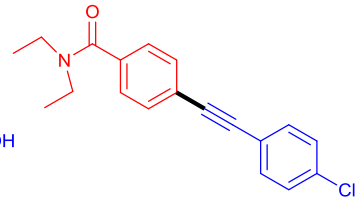
3 h, 88%



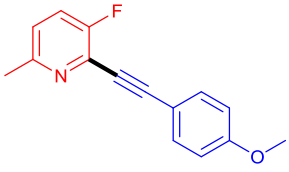
18 h, 82%



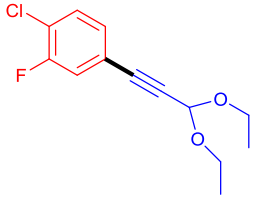
12 h, 74%[a]



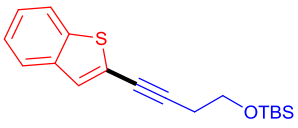
22 h, 98%[a, b]



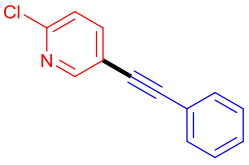
3 h, 97%[a]



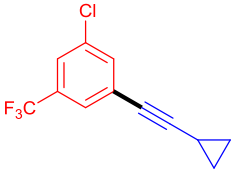
43 h, 70%[a, b]



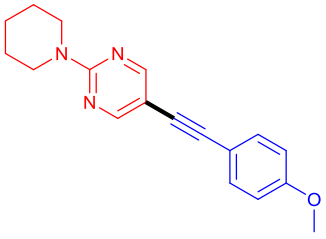
43 h, 96%[b]



5 h, 88%



13 h, 86%[a, c]



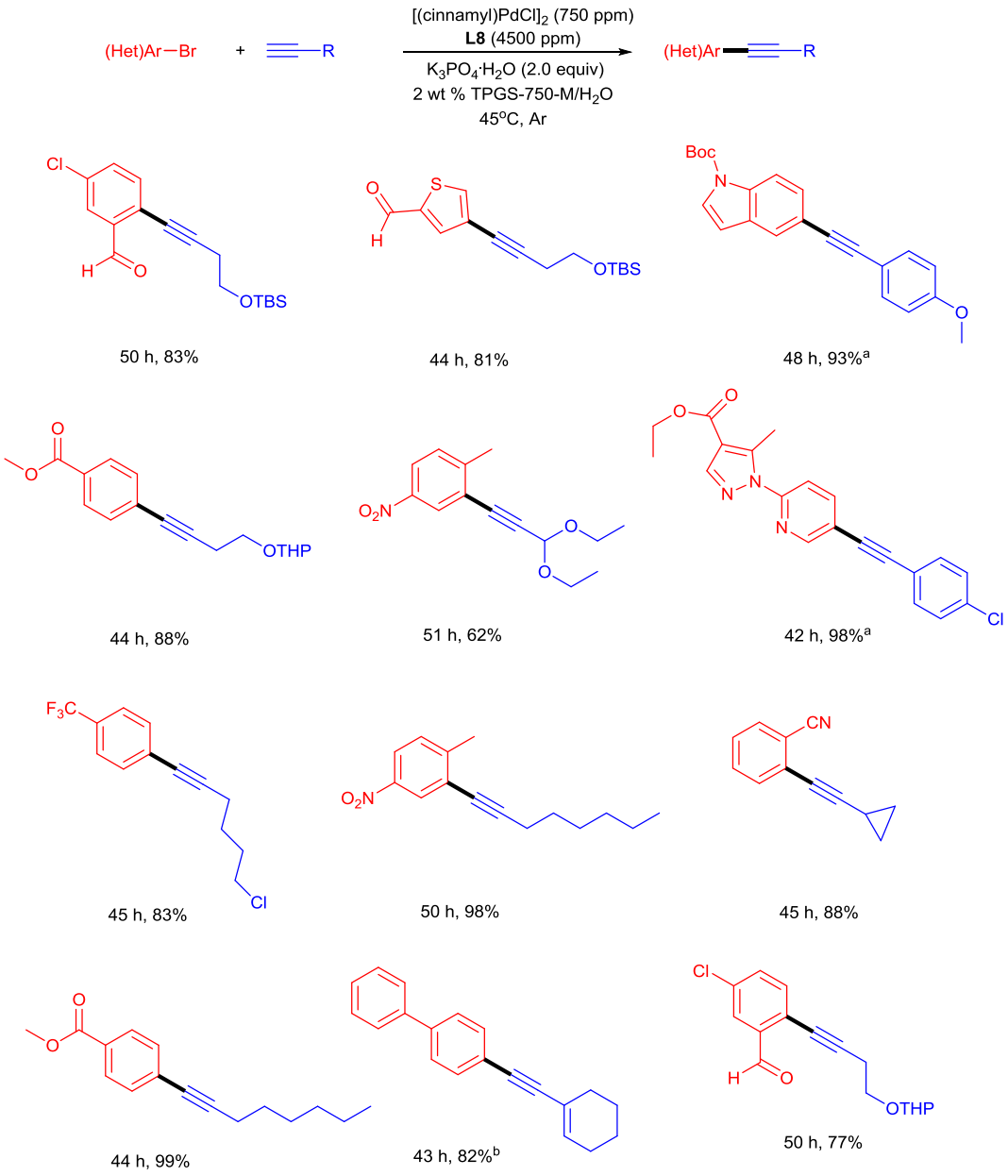
8 h, 95%[a]
8 h, 87% / 1.27 g[a]

Conditions: bromide (0.5 mmol), terminal alkyne (0.6 mmol), $[(cinnamyl)PdCl]_2$ (0.05 mol %), **L8** (0.30 mol %), $K_3PO_4 \bullet H_2O$ (2.0 equiv), TPGS-750-M/H_2O (2 wt %, 1 mL), 45 °C, Ar. Isolated yield. **[a]:** Et_3N

(2.0 equiv) as base. **[b]:** 1.5 equiv terminal alkyne used. **[c]:** Reaction run at 35 ^{o}C, 1.1 equiv terminal alkyne used.

Table 15. Substrate scope at 1000 ppm Pd loading.

Substrates synthesized using 1000 ppm Pd loading are shown in Table 15. In some cases, Et_3N was used as base instead of $K_3PO_4 \bullet H_2O$ due to the viscosity of the medium. All reactions were performed using a pre-mixed THF stock solution containing both palladium pre-catalyst and ligand. These results suggest that sensitive functional groups can be tolerated, including chloro, fluoro, -trifluoromethyl, aldehyde, ketone, thioether and amide. Different heterocycles can also be used as substrates, including 2-, 3-, and 4-substituted pyridines, quinoline, furan, benzothiophine, and pyrimidine. A gram-scale reaction was performed using a pyrimidine-containing substrate and comparable results were obtained. No stock solution is required if solid palladium pre-catalyst and ligand can be weighed out. In most cases only 1.2 equivalents of terminal alkyne is required. A palladium loading of 1500 ppm was utilized with more challenging substrates.



Conditions: bromide (0.5 mmol), terminal alkyne (0.75 mmol), [(cinnamyl)PdCl]$_2$ (0.075 mol %), **L8** (0.45 mol %), K_3PO_4•H_2O (2.0 equiv), TPGS-750-M/H_2O (2 wt %, 1 mL), 45 ^oC, Ar. Isolated yield. **[a]:** Et_3N (2.0 equiv) as base. **[b]:** 1.2 equiv terminal alkyne used.

Table 16. Substrate scope at 1500 ppm Pd loading.

Substrates synthesized using a 1500 ppm Pd loading are shown in Table 16. More functional groups can be tolerated including esters, nitro and nitrile. Thiophene, indole, and pyrazole can also be used in this reaction. Important protecting groups, such as -TBS,

-THP and -Boc remained intact under these reaction conditions. However, certain substrates gave little-to-no conversion under these reaction conditions (Table 17).

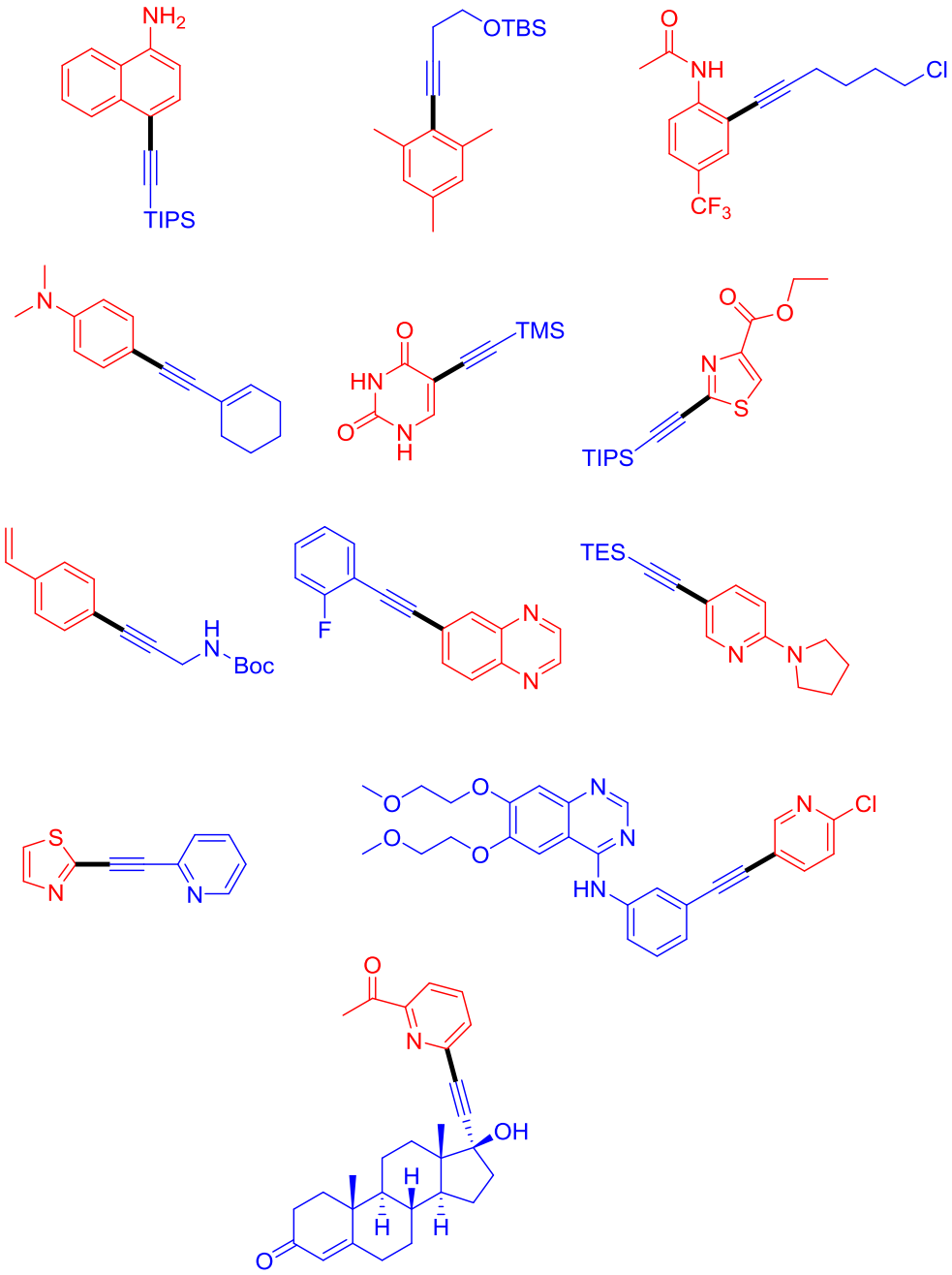
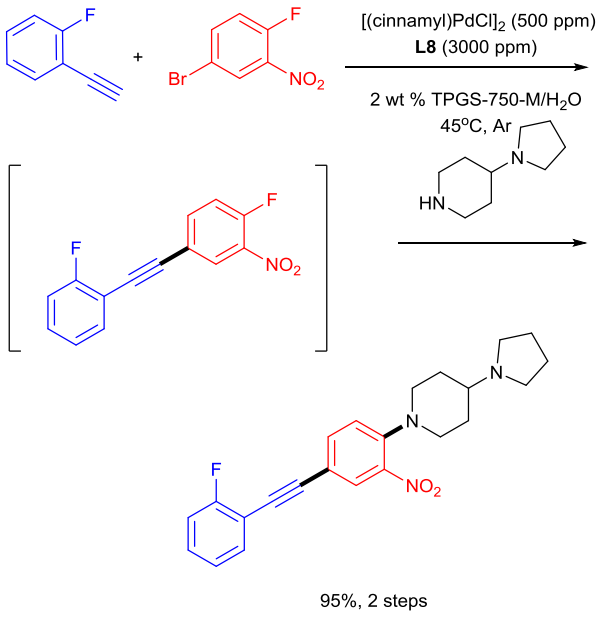


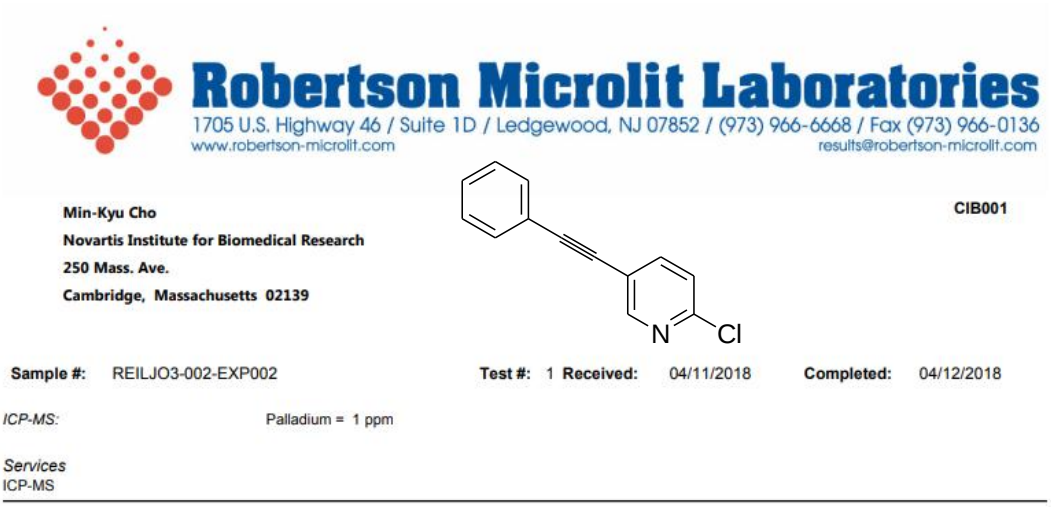
Table 17. Substrates that gave little-to-no conversion.

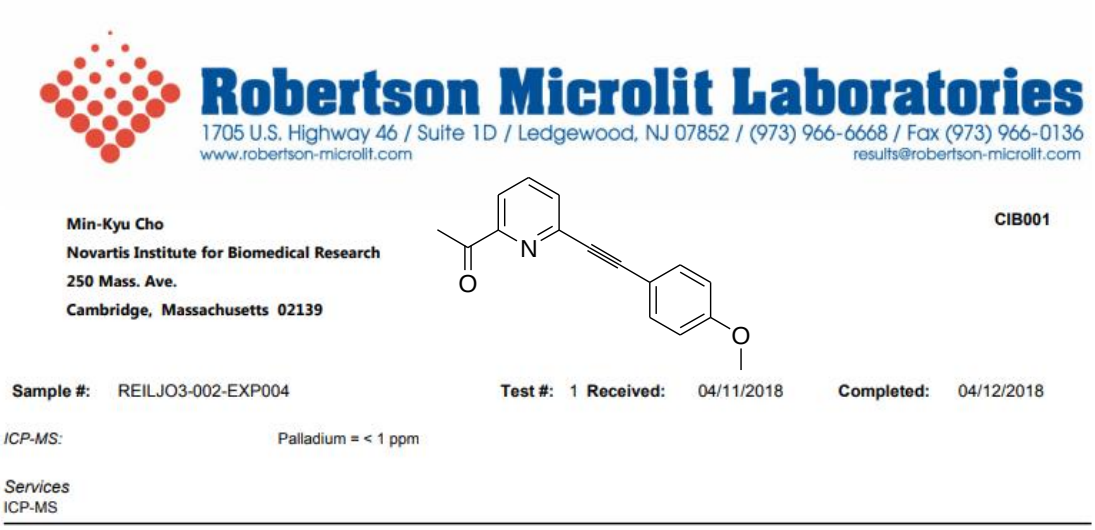


Conditions: Step 1: 4-Bromo-1-fluoro-2-nitrobenzene (0.5 mmol), (2-Fluorophenyl)acetylene (1.1 equiv), [(cinnamyl)PdCl]$_2$ (500 ppm), **L8** (3000 ppm), K_3PO_4•H_2O (2.0 equiv), 2 wt % TPGS-750-M/H_2O (1 mL), 45 ^oC, argon, 20 h. Step 2: 4-(1-Pyrrolidinyl)piperidine (1.0 equiv), THF (20 vol %), 45 ^oC, 5 h.

Scheme 21. 2-Step, 1-pot process.

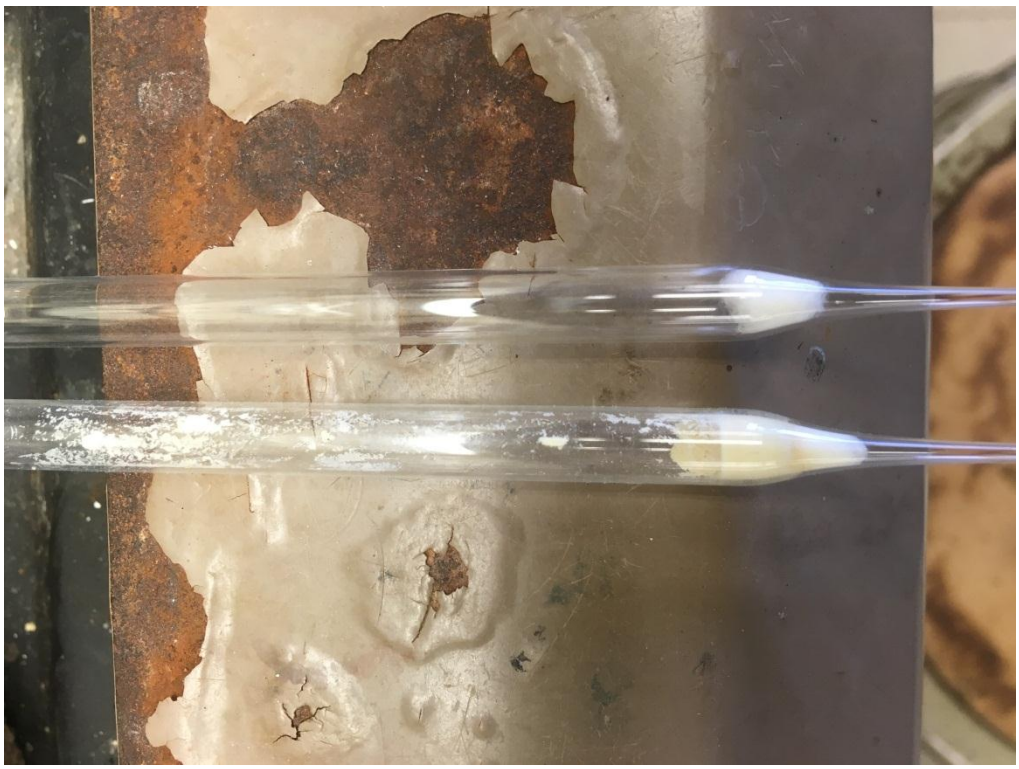
A 2-step, 1-pot sequence was performed as shown in Scheme 21. A Sonogashira coupling using standard conditions was followed by an S_NAr reaction facilitated by the internal alkyne installed in the first step as an activating group. The desired product was obtained in 95% isolated yield.





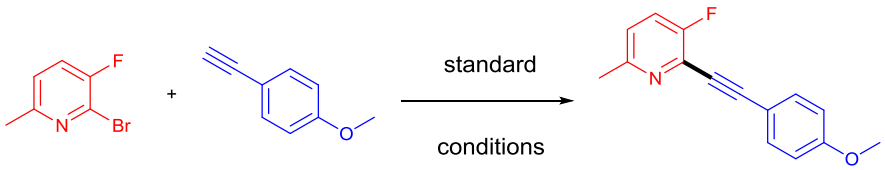
Scheme 22. ICP-MS analyses of residue palladium.

ICP-MS tests were performed using two products synthesized with 1000 ppm palladium loadings (Scheme 22). Not more than 1 ppm of palladium residue was detected, which is well under the 10 ppm level per dose set by FDA regulations.[48]



Scheme 23. Isolating crude products by filtration.

Instead of in-flask extraction techniques[18] used in previous publications, filtration was applied when the solid product precipitated out from the aqueous reaction mixture (Scheme 23).



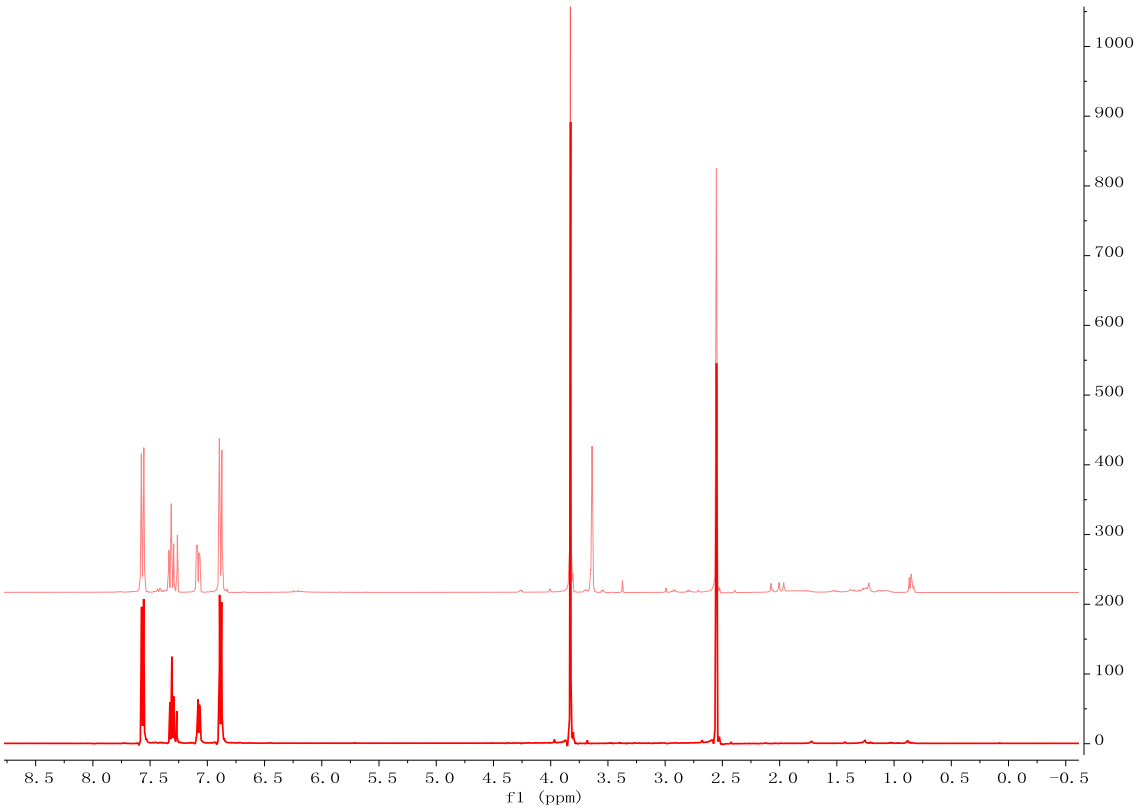
cycle	0	1	2	3
yield (%)	95	89	92	92

E Factor = 0.78

Conditions: 2-Bromo-3-fluoro-6-methylpyridine (0.5 mmol), 4-methoxyphenylacetylene (1.05 equiv), $[(cinnamyl)PdCl]_2$ (500 ppm), **L8** (3000 ppm), $K_3PO_4 \bullet H_2O$ (2.0 equiv), 2 wt % TPGS-750-M/H_2O (1 mL), 45 ^oC, argon, 4 h. 2-Bromo-3-fluoro-6-methylpyridine (0.5 mmol), 4-methoxyphenylacetylene (1.05 equiv), $[(cinnamyl)PdCl]_2$ (500 ppm), **L8** (3000 ppm) and $K_3PO_4 \bullet H_2O$ (2.0 equiv) were added after every recycle.

Scheme 24. Recycling study and E Factor determination.

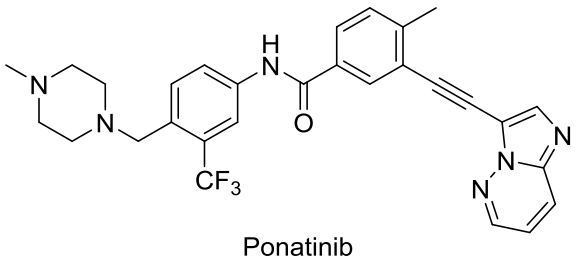
Using the filtration techniques mentioned above, the recycling study was performed and an E Factor[49] was determined, as shown in Scheme 24. No organic solvent is required except the small amount of THF used to prepare the stock solution of catalyst. Thus, the E Factor based on use of organic solvent was calculated to be 0.78. Nonetheless, solid palladium pre-catalyst and ligand can be used directly if the reaction scale is large enough. In this case, the E Factor will be zero. The aqueous TPGS-750-M solution was recycled three times without losing its enabling qualities. Palladium pre-catalyst(500 ppm), 3000 ppm of **L8**, and two equivalents of base were added after each recycle. The proton NMRs of the crude product obtained via filtration, and the pure product from column chromatography, were used to determine the purity of the crude product.



Scheme 25. ^{1}H NMRs of crude and pure product.

TPGS-750-M is a major impurity in the crude product as shown in Scheme 25, which can be removed easily by recrystallization.

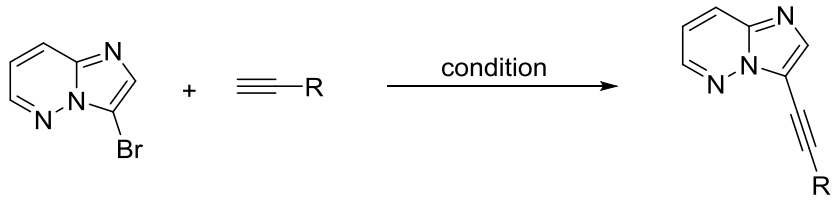
A stoichiometric amount of $[Pd(cinnamyl)Cl]_2$, three equivalents of **L8**, one equivalent of phenylacetylene, and two equivalents of $K_3PO_4 \bullet H_2O$ were added to 2 wt % TPGS-750-M aqueous solution and the mixture was heated at 45 ^{o}C under standard reaction conditions for one hour without the presence of aryl bromides. GC-MS analysis of this reaction mixture indicated that no cinnamyl alcohol was detected. Instead, only a phenylacetylene-substituted cinnamyl intermediate was found. This indicates that the pre-catalyst is activated by the terminal alkyne rather than by water. On the other hand, this suggests that the Sonogashira coupling occurs inside the micellar core.



Ponatinib

Scheme 26. Structure of Ponatinib.

Ponatinib (Iclusig®) is a tyrosine-kinase inhibitor developed by Takeda.[50] for the treatment of leukemia. The key internal alkyne can be synthesized by two Sonogashira couplings. However, a large amount of both palladium and copper were consumed in these couplings. The synthesis of this drug seemed like a good use of this new technology for constructing such internal alkynes.



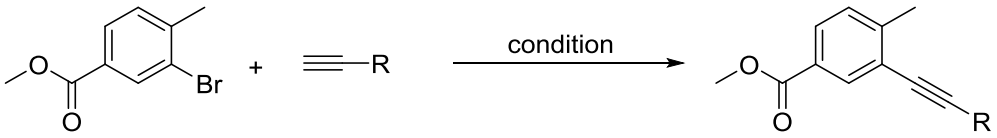
Entry	Terminal alkyne	GC yield (%)[a]
1	phenylacetylene	0
2	trimethylsilylacetylene	0
3	(triisopropylsilyl)acetylene	0

[a]: Conditions: 3-Bromoimidazo[1,2-*b*]pyridazine (0.5 mmol), terminal alkyne (0.75 mmol), $[Pd(cinnamyl)Cl]_2$ (2500 ppm), **L8** (1.5 mol %), $K_3PO_4 \bullet H_2O$ (2 equiv), 2 wt % TPGS-750-M (0.8 mL), DMF (0.2 mL), argon, 45 ^oC, 17 h.

Table 18. Initial couplings using 3-bromoimidazo[1,2-*b*]pyridazine.

The screening started from commercially available 3-bromoimidazo[1,2-*b*]pyridazine (Table 18). This bromide is only soluble in DMF, so

20 vol % of DMF was used as co-solvent in this reaction. Coupling partners included phenylacetylene (model of actual substituted phenylacetylene), trimethylsilylacetylene and (triisopropylsilyl)acetylene, but none gave any conversion at 5000 ppm palladium loading. Since this internal alkyne could be synthesized from either side, another aryl bromide, methyl 3-bromo-4-methylbenzoate was tested (Table 19).

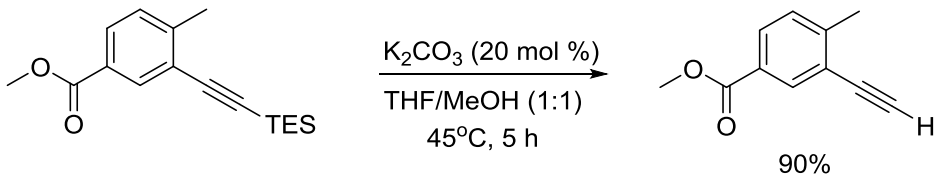


Entry	Terminal alkyne	GC yield (%)[a]
1	trimethylsilylacetylene	trace
2	triethylsilylacetylene	100 (94)[b]
3	(triisopropylsilyl)acetylene	17

[a]: Conditions: ethyl 3-bromo-4-methylbenzoate (0.5 mmol), terminal alkyne (1.0 mmol), $[Pd(cinnamyl)Cl]_2$ (750 ppm), **L8** (4500 ppm), Et_3N (2 equiv), 2 wt % TPGS-750-M (1.0 mL), argon, 45 ^oC, 47 h. **[b]:** Isolated yield.

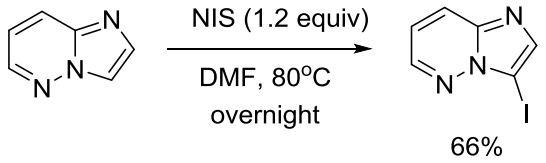
Table 19. Sonogashira couplings using methyl 3-bromo-4-methylbenzoate.

Among three protected acetylenes tested, triethylsilylacetylene showed superior reactivity, and a 94% isolated yield was obtained. The triethylsilyl protecting group was removed in the next step to generate the substituted phenylacetylene used in the second Sonogashira coupling reaction. Instead of using toxic and corrosive fluorides to do the deprotection, a new approach based on TMS deprotections[51] was used in this reaction.



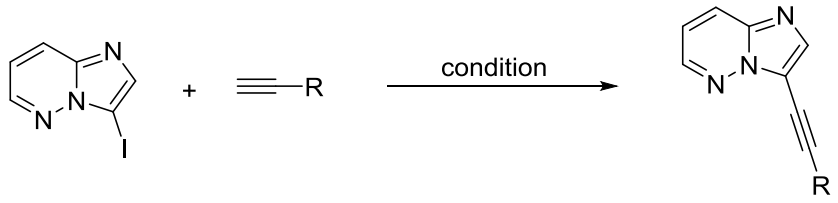
Scheme 27. Deprotection of the TES group.

The product from the first step was mixed with 20 mol % of potassium carbonate in a 1:1 mixture of THF and methanol. Methoxide is the nucleophile in this reaction that removes the protecting group. The usage of methanol also avoids the possible transesterification of the methyl ester in the starting material. A 90% isolated yield was obtained in this reaction at 45 ^{o}C for over five hours (Scheme 27). With the key substituted phenylacetylene in hand, attention next focused on how to synthesize the internal alkyne via a second Sonogashira coupling.



Scheme 28. Synthesis of 3-iodoimidazo[1,2-*b*]pyridazine.

3-Iodoimidazo[1,2-*b*]pyridazine was prepared by reacting the imidazo[1,2-*b*]pyridazine core with *N*-iodosuccinimide in DMF at 80 ^{o}C (Scheme 28). This iodide was used in a model reaction to determine the reactivity with different types of terminal alkynes.

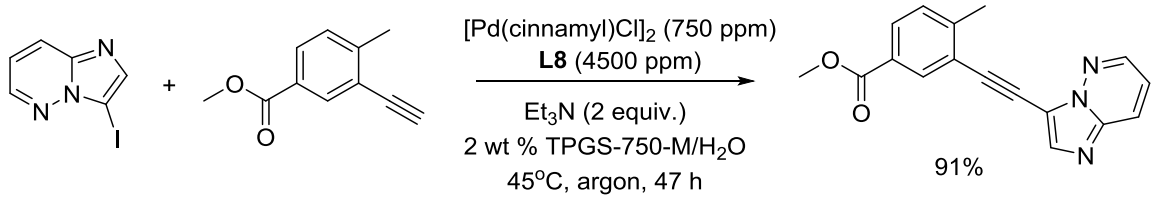


Entry	Terminal alkyne	GC yield (%)[a]
1	trimethylacetylene	0
2	triethylacetylene	0
3	(triisopropyl)acetylene	10
4	phenylacetylene	51
5	2-methyl-3-butyn-2-ol	0
6	1-ethynyl-1-cyclohexanol	0

[a]: Conditions: 3-iodoimidazo[1,2-*b*]pyridazine (0.5 mmol), terminal alkyne (0.75 mmol), $[Pd(cinnamyl)Cl]_2$ (750 ppm), **L8** (4500 ppm), Et_3N (2 equiv), 2 wt % TPGS-750-M (1 mL), argon, 45 ^oC, 12 h.

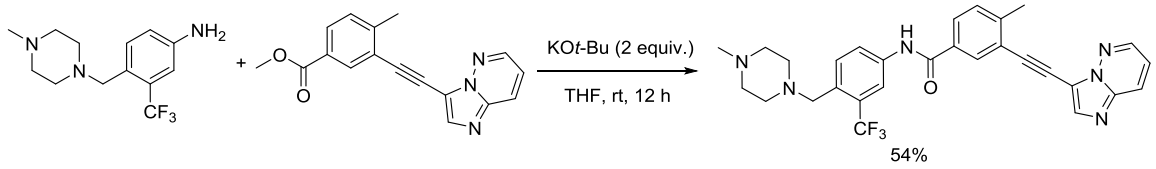
Table 20. Sonogashira couplings using 3-iodoimidazo[1,2-*b*]pyridazine.

Different types of terminal alkynes were tested in the coupling reactions with 3-iodoimidazo[1,2-*b*]pyridazine under standard reaction conditions (Table 20). 2-Methyl-3-butyn-2-ol and 1-ethynyl-1-cyclohexanol are acetone and cyclohexanone protected acetylenes. Unlike silyl protecting groups, their deprotection reactions require harsh, basic conditions.[52] The imidazo[1,2-*b*]pyridazine core can tolerate basic deprotection conditions, so these two protected terminal alkynes were also tested. Only phenylacetylene gave acceptable conversion under standard conditions after 12 h. However, the terminal alkyne prepared in the first two steps is essentially a substituted phenylacetylene, so the second Sonogashira coupling reaction was performed between 3-iodoimidazo[1,2-*b*]pyridazine and methyl 3-ethynyl-4-methylbenzoate (Scheme 29).



Scheme 29. The second Sonogashira coupling.

Finally, a 91% isolated yield of the key internal alkyne was obtained using standard conditions over 47 hours. At this point, the target drug ponatinib required only one additional step. The last amide bond forming reaction was conducted between this internal alkyne and commercially available 4-(4-methylpiperazin-1-ylmethyl)-3-trifluoromethylaniline (Scheme 30).



Scheme 30. Completion of synthesis.

KO*t*-Bu was used in the amide bond-forming reaction,[53] as suggested by the original route used towards this patented drug.[50] However, in our hands, the reaction worked only when both starting materials were present in THF before the addition of KO*t*-Bu. Only a moderate isolated yield (54%) was obtained because of the transesterification side reaction. Ultimately, ponatinib was successfully synthesized using this new Sonogashira coupling approach.

Conclusions and Outlook

A new approach to Cu-free, ppm palladium-catalyzed Sonogashira coupling reactions has been developed. Both palladium pre-catalyst and ligand are commercially available and bench stable. High efficiency is obtained by premixing the pre-catalyst and the ligand at a certain ratio. Only 1000 to 1500 ppm of palladium is required to catalyze these couplings between a wide range of (hetero)aryl bromides and terminal alkynes in water at 45 ^{o}C without any organic solvent. In many cases the crude product can be isolated by simple filtration. An application to the commercialized API ponatinib proves its practicality for us on "real world" cases. However, this methodology is still far from perfect. A better designed pre-catalyst or ligand will further improve the conditions of this reaction.

Experimental Section

All reactions were performed under an atmosphere of argon. A solution of 2 wt % TPGS-750-M/H_2O was prepared by dissolving TPGS-750-M solid in degassed HPLC grade water and was stored under argon. TPGS-750-M was made as previously described and is available from Sigma Aldrich® (catalog numbers 733857 and 763918). All commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25mm thick). Flash column chromatography was conducted in glass columns using Silica Gel 60 (EMD, 40-63 μm). Tetrahydrofuran (THF), taken from an Innovative Technologies Solvent Purification System (SPS), was further degassed by sparging with argon for 2 h while stirring. Diethyl ether, ethyl acetate, methylene chloride and hexanes were purchased from Fisher Scientific. *N*,*N*-dimethylformamide (DMF) and triethylamine were purchased from Merck. K_3PO_4•H_2O was purchased from Acros Organics. Palladium catalysts were purchased from Sigma Aldrich or generously donated by Johnson Matthey. BRIDP ligands were supplied by Takasago, Neolyst™ CX31 and Neolyst™ CX32 from Umicore AG & Co. KG. Reagents were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aesar, or Acros Organics. NMR solvents were purchased from Cambridge Isotope Laboratories. GC-MS data were recorded on an Agilent Technologies 7890A GC system coupled with Agilent Technologies 5975C mass spectrometer using HP-5MS column (30 m x 0.250 mm, 0.25 micron) purchased from Agilent Technologies. ^1H and ^{13}C NMR were recorded at 25 ℃ on a Varian Unity Inova 400 MHz or a Varian Unity Inova 500MHz spectrometers in $CDCl_3$ with residual $CHCl_3$ (^1H = 7.26 ppm, ^{13}C= 77.16 ppm) as internal standards. ^{19}F NMR was recorded at 25 ℃ on a Varian Unity Inova 400 MHz

spectrometer. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, p = pentet, m = multiplet), coupling constant (if applicable) and integration.

Preparation of a stock solution of catalyst.

In a 4 mL reaction vial containing a PTFE coated magnetic stir bar, cBRIDP (10.6 mg, 0.030 mmol) and $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol) were added in a glove box. The reaction vial was sealed with a rubber septum and degassed, after which anhydrous THF (2 mL) was added via syringe. The mixture was stirred for 5 min at rt. A yellow stock solution was obtained for subsequent Sonogashira reactions (**Always use fresh stock solution because it is unstable at rt as indicated by the color change from yellow to orange to black within one week**).

Procedure for Sonogashira reactions.

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, 100 μL of stock solution (1000 ppm palladium) or 150 μL of stock solution (1500 ppm palladium) was added and the THF was removed *in vacuo*, after which the reaction vial was backfilled with dry argon. All solid starting materials (bromide, terminal alkyne) and (or) base were added under an argon flow. The reaction vial was then evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and liquid starting

material (bromide, terminal alkyne) and/or base were added via syringe. The reaction mixture was then stirred vigorously at 45 ^{o}C (or at a different temperature as indicated) for a given time. After complete consumption of bromide, as monitored by TLC and/or GCMS, the reaction mixture was then extracted with EtOAc (1.0 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography over silica gel to afford pure product.

Gram Scale Reaction

In an oven-dried 50 mL round bottom flask charged with a PTFE coated magnetic stir bar, 5-bromo-2-(1-piperidinyl)pyrimidine (1210.5 mg, 5.0 mmol), $[Pd(cinnamyl)Cl]_2$ (1.3 mg, 0.0025 mmol, 500 ppm) and cBRIDP (5.3 mg, 0.015 mmol, 3000 ppm) were added. The flask was evacuated and refilled with argon three times. 4-Ethynylanisole (780 μL, 6.0 mmol, 1.2 equiv), Et_3N (1.4 mL, 10.0 mmol, 2.0 equiv) and 2 wt % TPGS-750-M/H_2O (10 mL) were added via syringe. The reaction mixture was heated at 45 ℃ for 8 h with vigorous stirring then allowed to cool to rt. The mixture was then extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed *in vacuo*. Crude product was purified with flash column chromatography to give 1272.1 mg (87%) of 5-(2-(4-methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine as a pale yellow solid (hexane/ether : 90/10).

2-Step, 1-pot reaction

Step 1:

In a 4 mL reaction vial, 4-bromo-1-fluoro-2-nitrobenzene (62 μL, 0.5 mmol), 1-ethynyl-2-fluorobenzene (62 μL, 0.55 mmol, 1.1 equiv), 100 μL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 20 h following the general procedure above.

Step 2:

4-(1-Pyrrolidinyl)piperidine (77 mg, 0.5 mmol, 1.0 equiv) and THF (0.2 mL) were added and the reaction mixture was heated at 45 ^oC for another 5 h. EtOAc (1 mL x 5) was used to extract the aqueous layer and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and crude product was purified by flash column chromatography to afford 186.7 mg (95%) of 1-(4-(2-(2-fluorophenyl)ethynyl)-2-nitrophenyl)-4-pyrrolidin-1-yl)piperidine as an orange solid (hexane/EtOAc : 50/50).

E Factor determination and recycling study

Initial Reaction:

Following the standard procedure, 2-bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (68 μL, 0.525 mmol, 1.05 equiv), 100 μL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 4 h then allowed to cool to rt. The reaction mixture was then transferred to a short pipette loaded with cotton. Liquid was collected and saved for recycle and the solid in the pipette was washed with 1 mL DI water and

air-dry to dryness to give 114.3 mg (95%) of the crude 3-fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine as a yellow solid.

E Factor calculation:

Density of THF = 0.889 g/mL

$$\text{E Factor} = \frac{Waste\ (mg)}{Product\ (mg)}$$

$$\frac{(0.10\ mL\ THF)(0.889\ \frac{g}{mL})}{0.1143\ g} = 0.78$$

1st Recycle:

A solution of TPGS-750-M was obtained from the initial reaction and was briefly degassed and then used as the reaction medium (about 0.8-0.9 mL). To this was added fresh 2 wt % TPGS-750-M/H_2O solution to maintain the original volume. Following the standard procedure, to a new 4 mL reaction vial containing a PTFE magnetic stir bar 2-bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (68 μL, 0.525 mmol, 1.05 equiv), 100 μL stock solution (1000 ppm Pd), K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) and 1 mL recycled TPGS-750-M/H_2O solution were heated at 45 ^oC for 4 h then allowed to cool to rt. The reaction mixture was then transferred to a short pipette loaded with cotton. Liquid was collected and saved for the next recycle while the solid in the pipette was washed with 1 mL DI water and air-dried to dryness to give the crude product.

2nd and 3rd Recycle: Repeat 1st recycle.

1st recycle: 89% yield

2nd recycle: 92% yield

3rd recycle: 92% yield

Synthesis of ponatinib

Step A (Table 19):

Following the standard procedure, methyl 3-bromo-4-methylbenzoate (78 μL, 0.5 mmol), (triethylsilyl)acetylene (179 μL, 1.0 mmol, 2.0 equiv) , 150 μL stock solution (1500 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 45 h yielding 135.7 mg (94%) of methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate as a yellow oil (hexane/ether : 97/3).

Step B (Scheme 27):

In a 50 mL oven-dried round bottom flask containing a PTFE coated magnetic stir bar, methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (1.344 g, 4.67 mmol), K_2CO_3 (129 mg, 0.934 mmol, 0.2 equiv) and 1:1 MeOH/THF (5 mL + 5 mL) were added and reaction mixture was heated at 45 ^oC for 5 h. Upon completion of the reaction as monitored by TLC, the mixture was allowed to cool to rt. Ether (10 mL) and satd. aqueous NH_4Cl solution (10 mL) were added. The organic layer was then extracted, washed with satd. aqueous NH_4Cl solution (5 mL x 2) and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* and the crude product was purified over flash column chromatography to yield 731.2 mg (90%) of methyl 3-ethynyl-4-methylbenzoate as a white solid (hexane/ether : 95/5).

Step C (Scheme 28):

A 50 mL oven-dried round bottom flask containing a PTFE magnetic stir bar was evacuated and refilled with argon three times. Imidazo[1,2-b]pyridazine (952.8 mg, 8.0

mmol) and *N*-iodosuccinimide (2.16 g, 9.6 mmol, 1.2 equiv) were added under an argon flow and DMF (15 mL) was added via syringe. The reaction mixture was heated at 80 ^{o}C overnight. The flask was cooled to rt and the reaction mixture was poured into a 125 mL separatory funnel. Water (30 mL) and DCM (30 mL) were added. The organic layer was then extracted and washed with water (20 mL x 5) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified over flash column chromatography to yield 1.29 g (66%) of 3-iodoimidazo[1,2-b]pyridazine as a brown solid (hexane/EtOAc : 50/50).

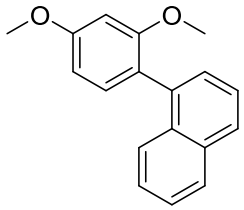
Step D (Scheme 29):

Following the standard procedure, 3-iodoimidazo[1,2-*b*]pyridazine (245 mg, 1.0 mmol) and methyl 3-ethynyl-4-methylbenzoate (209 mg, 1.2 mmol, 1.2 equiv), 300 μL stock solution (1500 ppm Pd) and Et_3N (280 μL, 2.0 mmol, 2.0 equiv) in 2.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ℃ for 47 h yielding 264.8 mg (91%) of methyl 3-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-4-methylbenzoate as a yellow solid (hexane/DCM : 65/35).

Step E (Scheme 30):

A 25 mL oven-dried round bottom flask containing a PTFE magnetic stir bar was evacuated and refilled with argon three times. Methyl 3-(2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl)-4-methylbenzoate (145.7 mg, 0.5 mmol, 1.0 equiv) and 4-(4-methylpiperazinomethyl)-3-(trifluoromethyl)aniline (136.7 mg, 0.5 mmol, 1.0 equiv) were charged under argon flow. Anhydrous THF (3.0 mL) was added via

syringe and the reaction mixture was stirred at rt for 5 min until a yellow homogeneous solution was obtained. KO*t*-Bu (112.2 mg, 1.0 mmol, 2.0 equiv) was then charged under argon flow and the reaction mixture was stirred at rt for 12 h. Upon complete consumption of methyl ester monitored by TLC the solvent was removed *in vacuo*. H_2O (5 mL) was added and the aqueous layer was then extracted with DCM (5 mL x 3). Organic layers were combined and solvent was removed *in vacuo*. Crude product was purified by flash column chromatography to afford 143.9 mg (54%) of ponatinib as a yellow solid. (EtOAc/DCM/MeOH : 8/2/1)

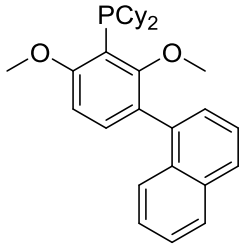


1-(2,4-Dimethoxyphenyl)naphthalene (BJ-1-256)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 2,4-dimethoxyphenylboronic acid (874 mg, 4.8 mmol, 1.2 eqiuv), $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.01 equiv), SPhos (33 mg, 0.08 mmol, 0.02 equiv) and K_3PO_4 (1700 mg, 8.0 mmol, 2.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. 1-Bromonaphthalene (828 mg, 560 μL, 4.0 mmol, 1.0 equiv), TPGS-750-M/H_2O (2 wt %, 8 mL) and THF (0.8 mL) were charged into the flask and covered with a rubber septum. The reaction mixture was heated at 60 ^oC for 24 h. The reaction mixture was then extracted with EtOAc (5 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The

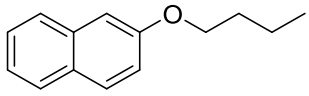
crude product was purified by flash column chromatography to afford 650 mg (62%) of 1-(2,4-dimethoxyphenyl)naphthalene as a white solid (hexane/ether : 95/5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (ddt, *J* = 14.1, 8.2, 1.0 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.52 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.46 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.38 (ddd, *J* = 8.0, 6.9, 1.4 Hz, 2H), 7.23 – 7.17 (m, 1H), 6.62 (d, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.68 (s, 3H).



Dicyclohexyl(2,6-dimethoxy-3-(naphthalen-1-yl)phenyl)phosphine (L3) (Prepared by Sachin Handa)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 14.1, 8.0 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.36 (m, 5H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.18 (s, 3H), 2.49 – 1.01 (m, 22H).

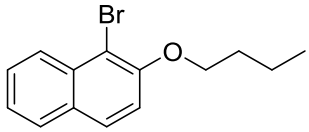


2-Butoxynaphthalene (BJ-1-66)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with β-naphthol (10.0 g, 69.4 mmol, 1.0 equiv), 1-bromobutane (11.4 g, 9.0 mL, 83.2 mmol, 1.2 equiv), KOH (7.8 g, 139.3 mmol, 2.0 equiv) and DMF (20 mL). The reaction mixture was heated at 60 ^oC for 12 h. Water (40 mL) was added to the reaction mixture. The mixture was then extracted with EtOAc (20 mL x 3). The combined organic layer was

dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 11.44 g (82.4%) of 2-butoxynaphthalene as a colorless oil (hexane/ether : 95/5).

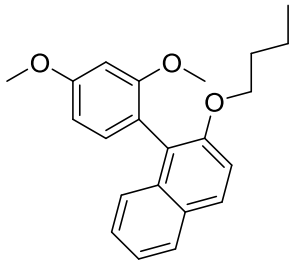
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 3H), 7.45 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.35 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.21 – 7.14 (m, 2H), 4.11 (t, *J* = 6.5 Hz, 2H), 1.86 (dq, *J* = 8.5, 6.6 Hz, 2H), 1.65 – 1.51 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).



1-Bromo-2-butoxynaphthalene (BJ-1-67)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 2-butoxynaphthalene (11.44 g, 57.2 mmol, 1.0 equiv), NBS (11.2 g, 62.9 mmol, 1.1 equiv) and chloroform (30 mL). The reaction mixture was stirred at rt for 12 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography to afford 16.0 g (quant.) of 1-bromo-2-butoxynaphthalene as a brown solid (hexane/ether : 95/5).

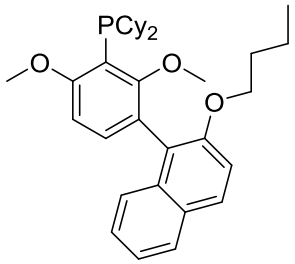
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.57 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 1.88 (ddt, *J* = 9.0, 7.8, 6.4 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).



2-Butoxy-1-(2,4-dimethoxyphenyl)naphthalene (BJ-1-208)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 1-bromo-2-butoxynaphthalene (1379 mg, 4.96 mmol, 1.0 equiv), 2,4-dimethoxyphenylboronic acid (1354.7 mg, 7.44 mmol, 1.5 equiv), $Pd(OAc)_2$ (11.1 mg, 0.049 mmol, 0.01 equiv), SPhos (30.5 mg, 0.074 mmol, 0.015 equiv) and $K_3PO_4 \bullet H_2O$ (2282 mg, 9.92 mmol, 2.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. TPGS-750-M/H_2O (2 wt %, 10 mL) and THF (1.0 mL) were charged into the flask and covered with a rubber septum. The reaction mixture was heated at 60 ^oC overnight. The reaction mixture was then extracted with EtOAc (5 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.54 g (92.7%) of 2-butoxy-1-(2,4-dimethoxyphenyl)-naphthalene as a white solid. (hexane/ether : 90/10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.0 Hz, 1H), 7.79 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.43 (dd, *J* = 6.2, 3.5 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.31 (dd, *J* = 6.4, 3.3 Hz, 2H), 7.13 – 7.08 (m, 1H), 6.62 (dd, *J* = 6.3, 2.5 Hz, 2H), 4.00 (td, *J* = 6.5, 2.1 Hz, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 1.63 – 1.55 (m, 2H), 1.28 (h, *J* = 7.4 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H).



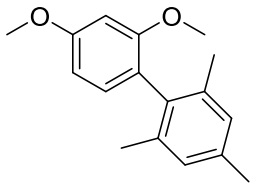
(3-(2-Butoxynaphthalen-1-yl)-2,6-dimethoxyphenyl)dicyclohexylphosphine (L4)

(BJ-1-210)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 2-butoxy-1-(2,4-dimethoxyphenyl)naphthalene (1.54 g, 4.58 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. Anhydrous THF (30 mL) was charged into the flask. The mixture was stirred at rt for 5 min to get a homogeneous solution. The flask was submerged in an acetone/Dry Ice bath for 5 min. *n*-BuLi (2.0 M in hexanes, 2.2 mL, 4.4 mmol, 0.96 equiv) was added dropwise via syringe. The mixture was stirred for another 30 min at rt. The flask was submerged in the acetone/Dry Ice bath again and chlorodicyclohexylphosphine (922 μL, 4.17 mmol, 0.91 equiv) was added dropwise via syringe. The flask was removed from acetone/Dry Ice bath. Stirring was continued for 12 h at rt. Water (50 mL) was added to the reaction mixture and the resulting mixture was then extracted with ether (20 mL x 3). The combined organic layer was washed with 10% sulfuric acid (20 mL x 3). The combined acidic aqueous layer was mixed with ether (50 mL) and satd. sodium carbonate solution was added slowly until no gas evolution. The layers were separated and the aqueous layer was then extracted with ether (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo* to afford 1.31g (54%)

of (3-(2-butoxynaphthalen-1-yl)-2,6-dimethoxyphenyl)dicyclohexylphosphine as a white foam.

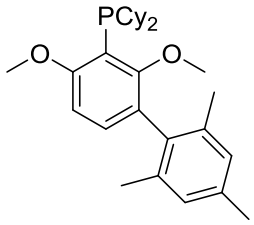
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.0 Hz, 1H), 7.81 – 7.78 (m, 1H), 7.48 – 7.43 (m, 1H), 7.32 (td, *J* = 6.8, 3.2 Hz, 3H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.03 (qt, *J* = 9.2, 6.6 Hz, 2H), 3.88 (s, 3H), 3.22 (s, 3H), 2.01 – 1.17 (m, 26H), 0.83 (t, *J* = 7.4 Hz, 3H).



2',4'-Dimethoxy-2,4,6-trimethyl-1,1'-biphenyl (BJ-1-209)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 2,4-dimethoxyphenylboronic acid (1.214 g, 6.67 mmol, 1.5 equiv), $Pd(OAc)_2$ (10.0 mg, 0.045 mmol, 0.01 equiv.), SPhos (27.4 mg, 0.067 mmol, 0.015 equiv) and K_3PO_4•H_2O (2047 mg, 8.9 mmol, 2.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. 2-Bromomesitylene (885 mg, 681 μL, 4.45 mmol, 1.0 equiv), TPGS-750-M/H_2O (2 wt %, 10 mL) and THF (1.0 mL) were charged into the flask and covered with a rubber septum. The reaction mixture was heated at 60 ^oC overnight. The reaction mixture was then extracted with EtOAc (5 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.18 g (quant.) of 2',4'-dimethoxy-2,4,6-trimethyl-1,1'-biphenyl as a white solid (hexane/ether : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 7.6, 0.9 Hz, 3H), 6.55 (d, *J* = 7.7 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.32 (s, 3H), 1.99 (s, 6H).

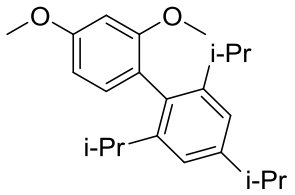


Dicyclohexyl(2,4-dimethoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)phosphane (L5) (BJ-1-212)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 2',4'-dimethoxy-2,4,6-trimethyl-1,1'-biphenyl (1.23 g, 4.8 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. Anhydrous THF (30 mL) was added via syringe. The mixture was stirred at rt for 5 min to get a homogeneous solution. The flask was submerged in an acetone/Dry Ice bath for 5 min. *n*-BuLi (2.0 M in hexanes, 2.33 mL, 4.66 mmol, 0.97 equiv) was added dropwise via syringe. The mixture was stirred for another 30 min at rt. The flask was submerged in the acetone/Dry Ice bath again and chlorodicyclohexylphosphine (1.0 mL, 4.56 mmol, 0.95 equiv) was added dropwise via syringe. The flask was removed from acetone/Dry Ice bath. Stirring was continued for 12 h at rt. Water (50 mL) was added to the reaction mixture and the resulting mixture was then extracted with ether (20 mL x 3). The combined organic layer was washed with 10% sulfuric acid (20 mL x 3). The combined acidic aqueous layer was mixed with ether (50 mL) and satd. sodium carbonate solution was added slowly until no gas evolution. Layers were separated and the aqueous

layer was then extracted with ether (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo* to afford 1.76 g (81%) of dicyclohexyl(2,4-dimethoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)phosphane as a white foam.

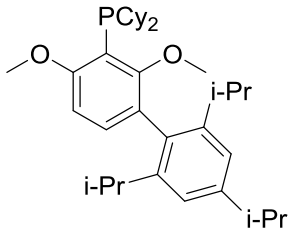
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.3 Hz, 1H), 6.92 (s, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.31 (d, *J* = 13.1 Hz, 3H), 2.32 (s, 3H), 2.04 (s, 6H), 1.97 – 0.98 (m, 22H).



2,4,6-Triisopropyl-2',4'-dimethoxy-1,1'-biphenyl (BJ-1-236)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 2,4-dimethoxyphenylboronic acid (965 mg, 5.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (7.9 mg, 0.035 mmol, 0.01 equiv), SPhos (29 mg, 0.07 mmol, 0.02 equiv) and K_3PO_4 (2245 mg, 10.59 mmol, 3.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. 1-Bromo-2,4,6-triisopropylbenzene (1.0 g, 894 μL, 3.53 mmol, 1.0 equiv) and toluene (7 mL) were charged into the flask and covered with a rubber septum. The reaction mixture was heated at 90 ^oC for 12 h. The solvent was evaporated *in vacuo* and the crude product was purified by flash column chromatography to afford 480 mg (40%) of 2,4,6-triisopropyl-2',4'-dimethoxy-1,1'-biphenyl as a white solid (hexane/ether : 97/3).

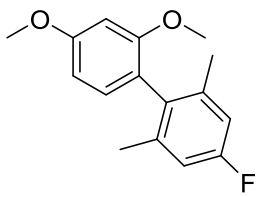
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.56 – 6.50 (m, 2H), 3.87 (s, 3H), 3.69 (s, 3H), 2.93 (p, *J* = 7.0 Hz, 1H), 2.58 (p, *J* = 6.9 Hz, 2H), 1.30 (dd, *J* = 7.0, 0.6 Hz, 6H), 1.06 (dd, *J* = 6.9, 5.7 Hz, 12H).



Dicyclohexyl(2',4',6'-triisopropyl-2,4-dimethoxy-[1,1'-biphenyl]-3-yl)phosphane (L6) (BJ-1-243)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 2,4,6-triisopropyl-2',4'-dimethoxy-1,1'-biphenyl (480 mg, 1.41 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. Anhydrous THF (30 mL) was added via syringe. The mixture was stirred at rt for 5 min to get a homogeneous solution. The flask was submerged in an acetone/Dry Ice bath for 5 min. *n*-BuLi (2.0 M in hexanes, 700 μL, 1.40 mmol, 0.99 equiv) was added dropwise via syringe. The mixture was stirred for another 30 min at rt. The flask was submerged in the acetone/Dry Ice bath again and chlorodicyclohexylphosphine (300 μL, 1.36 mmol, 0.96 equiv) was added dropwise via syringe. The flask was removed from acetone/Dry Ice bath. Stirring was continued for 12 h at rt. One drop of water was added to quench the reaction and the solvent was removed *in vacuo.* The crude product was purified by flash column chromatography to afford 412 mg (54%) of dicyclohexyl(2',4',6'-triisopropyl-2,4-dimethoxy-[1,1'-biphenyl]-3-yl)phosphane as a white foam.

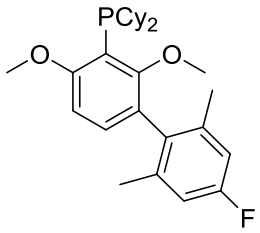
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.56 – 6.50 (m, 1H), 3.85 (s, 3H), 3.29 (s, 3H), 2.96 – 2.90 (m, 1H), 2.66 (p, *J* = 6.9 Hz, 2H), 1.84 – 0.99 (m, 40H).



4-Fluoro-2',4'-dimethoxy-2,6-dimethyl-1,1'-biphenyl (BJ-1-216)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 2,6-dimethyl-4-fluorobromobenzene (591 mg, 2.91 mmol, 1.0 equiv), 2,4-dimethoxyphenylboronic acid (795 mg, 4.37 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 0.01 equiv), SPhos (17.9 mg, 0.044 mmol, 0.015 equiv) and $K_3PO_4 \bullet H_2O$ (1338.6 mg, 5.82 mmol, 2.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. TPGS-750-M/H_2O (2 wt%, 10 mL) and THF (1.0 mL) were charged into the flask and covered with a rubber septum. The reaction mixture was heated at 60 ^oC overnight. The reaction mixture was then extracted with EtOAc (5 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 760 mg (quant.) of 4-fluoro-2',4'-dimethoxy-2,6-dimethyl-1,1'-biphenyl as a white solid.

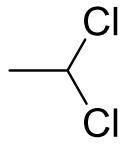
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 – 6.88 (m, 1H), 6.80 (dt, *J* = 9.6, 0.6 Hz, 2H), 6.58 – 6.54 (m, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.00 (s, 6H).



Dicyclohexyl(4'-fluoro-2,4-dimethoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)phosphane (L7) (BJ-1-222)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 4-fluoro-2',4'-dimethoxy-2,6-dimethyl-1,1'-biphenyl (760 mg, 2.92 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. Anhydrous THF (30 mL) was added via syringe. The mixture was stirred at rt for 5 min to get a homogeneous solution. The flask was submerged in an acetone/Dry Ice bath for 5 min. *n*-BuLi (2.0 M in hexanes, 1.4 mL, 2.8 mmol, 0.96 equiv) was added dropwise via syringe. The mixture was stirred for another 30 min at rt. The flask was submerged in the acetone/Dry Ice bath again and chlorodicyclohexylphosphine (600 μL, 2.66 mmol, 0.91 equiv) was added dropwise via syringe. The flask was removed from acetone/Dry Ice bath. Stirring was continued for 12 h at rt. Water (50 mL) was added to the reaction mixture and the resulting mixture was then extracted with ether (20 mL x 3). The combined organic layer was washed with 10% sulfuric acid (20 mL x 3). The combined acidic aqueous layer was mixed with ether (50 mL) and satd. Sodium carbonate solution was added slowly until no gas evolution. Layers were separated and the aqueous layer was then extracted with ether (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo* to afford 400 mg (30%) of dicyclohexyl(4'-fluoro-2,4-dimethoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)phosphane as a white foam.

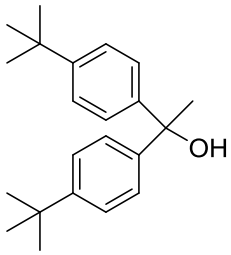
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 9.6 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.30 (s, 3H), 2.36 (s, 2H), 2.07 (s, 6H), 1.96 – 0.99 (m, 20H).



1,1-Dichloroethane (BJ-2-1)

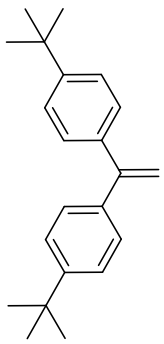
Phosphorus pentachloride (22.62 g, 108.8 mmol, 1.1 equiv) was added to a 100 mL oven-dried round bottom flask with a magnetic stir bar. A water condenser was attached to the flask and the flask was submerged in an acetone/Dry Ice bath for 10 min. Acetaldehyde (4.35 g, 5.52 mL, 98.9 mmol, 1.0 equiv) was added to the flask cautiously all at one time. The reaction mixture was stirred for 10 min and then the low temperature bath was removed.

The reaction mixture was then allowed to warm up to rt with stirring for 30 min. The reaction mixture was heated to 70 ^oC using an oil bath with stirring for 12 h. The reaction mixture was then allowed to cool to rt. The product was isolated by fractional distillation (b.p. 57 ^oC) to give 4.81 g (49%) of 1,1-dichloroethane was obtained as a colorless liquid.



1,1-Bis(4-(*t*-butyl)phenyl)ethan-1-ol (BJ-1-297)

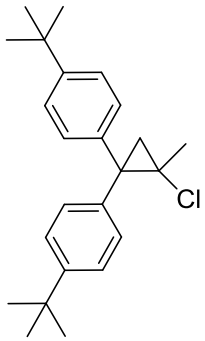
In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with magnesium turnings (729 mg, 30.0 mmol, 1.0 equiv) and a tiny iodine crystal. The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times and submerged to an ice bath for 5 min. 1-Bromo-4-*t*-butylbenzene (6.39 g, 5.2 mL, 30.0 mmol, 1.0 equiv) was added to 20 mL of dry THF. This THF solution was slowly added to the flask *via* syringe. One drop of 1,2-dibromoethane was added to the flask *via* syringe. The reaction mixture was stirred for half an hour and then the ice bath was removed. Stirring was continued at rt until the amount of magnesium turnings remained constant. The flask was submerged to the ice bath again for 5 min. EtOAc (1.294 g, 1.44 mL, 14.7 mmol, 0.49 equiv) was added to the reaction mixture dropwise *via* syringe. After the addition of EtOAc the ice bath was removed and the reaction mixture was allowed to stir at rt for 1 h. Saturated ammonium chloride solution (5 mL) was added to the reaction mixture slowly. Water (50 mL) was added to the mixture and the mixture was then extracted with ether (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography to afford 2.806 g (61.5%) of 1,1-bis(4-(*t*-butyl)phenyl)ethan-1-ol as a white solid (hexanes/ether : 92/8).



4,4'-(Ethene-1,1-diyl)bis(*t*-butylbenzene) (BJ-1-291)

In an oven-dried 50 mL round bottom flask with a magnetic stir bar was charged with 1,1-bis(4-(*t*-butyl)phenyl)ethan-1-ol (950 mg, 3.06 mmol, 1.0 equiv) and iodine (38.9 mg, 0.153 mmol, 0.05 equiv). The reaction mixture was stirred neat at rt for 5 h. Saturated sodium thiosulfate solution (10 mL) was added to the reaction mixture and the mixture was stirred at rt until the color of iodine disappeared. The mixture was then extracted with ether (10 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo.* The crude product was purified by column chromatography to afford 650 mg (73%) of 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) as a white solid (hexanes/ether : 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 4H), 7.31 – 7.27 (m, 4H), 5.41 (s, 2H), 1.34 (s, 18H).

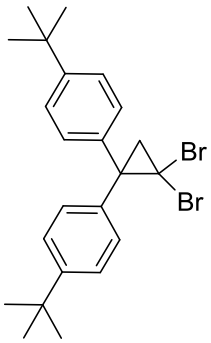


4,4'-(2-Chloro-2-methylcyclopropane-1,1-diyl)bis(*t*-butylbenzene) (BJ-2-5)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) (1.477 g, 5.05 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times and submerged to a Dry Ice/acetonitrile bath for 5 min. Dry ether (6 mL) was added *via*

syringe. 1,1-Dichloroethane (1.0 g, 833 μL, 10.1 mmol, 2.0 equiv) was added *via* syringe. The reaction mixture was stirred for 5 min and *n*-BuLi (2.0 M in hexanes, 5.05 mL, 10.1 mmol, 2.0 equiv) was added dropwise *via* syringe. The cold bath was removed and the reaction mixture was stirred at rt for 30 min. Water (10 mL) was added to the mixture and layers were separated. Aqueous layer was then extracted with ether (6 mL x 2) and the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo.* The crude product was purified by column chromatography to afford 400 mg (22%) of 4,4'-(2-chloro-2-methylcyclopropane-1,1-diyl)bis(*t*-butylbenzene) as a white solid (hexanes/ether : 95/5). (No reaction occurred in THF and only 20% in CPME)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.34 – 7.31 (m, 2H), 7.30 – 7.25 (m, 4H), 1.83 (d, *J* = 6.1 Hz, 1H), 1.63 (d, *J* = 6.1 Hz, 1H), 1.56 (s, 3H), 1.26 (d, *J* = 5.2 Hz, 18H).

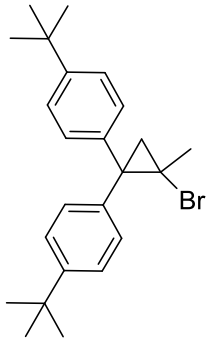


4,4'-(2,2-Dibromocyclopropane-1,1-diyl)bis(*t*-butylbenzene) (BJ-2-14)

In an oven-dried 100 mL round bottom flask with a magnetic stir bar was charged with 4,4'-(ethene-1,1-diyl)bis(*t*-butylbenzene) (1.0 g, 3.42 mmol, 1.0 equiv), KO*t*-Bu (617.1 mg, 5.51 mmol, 1.6 equiv) and hexanes (10 mL). The flask was submerged in an ice bath. The reaction mixture was stirred for 5 min. $CHBr_3$ (1.2119 g, 420 μL, 4.79 mmol, 1.4

equiv) was added dropwise to the reaction mixture *via* syringe. After completion, the ice bath was removed and the reaction mixture was stirred at rt for 5 h. Water (20 mL) was added slowly to quench the reaction. The mixture was then extracted with DCM (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to afford 1.21 g (76.6%) of 4,4'-(2,2-dibromocyclopropane-1,1-diyl)bis(*t*-butylbenzene) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 4H), 7.31 (d, *J* = 8.5 Hz, 4H), 2.43 (s, 2H), 1.27 (s, 18H).

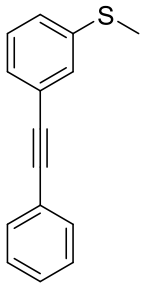


4,4'-(2-Bromo-2-methylcyclopropane-1,1-diyl)bis(*t*-butylbenzene) (BJ-2-23)

In an oven-dried 25 mL round bottom flask with a magnetic stir bar was charged with 4,4'-(2,2-dibromocyclopropane-1,1-diyl)bis(*t*-butylbenzene) (520 mg, 1.13 mmol, 1.0 equiv). The flask was sealed with a rubber septum. The flask was evacuated and refilled with argon three times. Anhydrous THF (6 mL) was added via syringe. The mixture was stirred at rt for 5 min to get a homogeneous solution. The flask was submerged in an acetone/Dry Ice bath for 5 min. *n*-BuLi (2.5 M in hexanes, 476 μL, 1.19 mmol, 1.05 equiv) was added dropwise via syringe. The reaction mixture was stirred for 30 min at -78 ^oC (Less reaction time will lead to incomplete reaction). Methyl iodide (176 mg, 77

μL, 1.24 mmol, 1.1 equiv) was added dropwise *via* syringe. The cold bath was removed and the reaction mixture was allowed to warm to rt. Water (10 mL) was added slowly to quench the reaction. The reaction mixture was then extracted with ether (5 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to afford 410.3 mg (91.3%) of 4,4'-(2-bromo-2-methylcyclopropane-1,1-diyl)bis(*t*-butylbenzene) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.36 – 7.32 (m, 2H), 7.30 (q, *J* = 2.2 Hz, 1H), 7.28 (q, *J* = 2.0 Hz, 2H), 7.26 (d, *J* = 3.2 Hz, 1H), 1.93 (d, *J* = 6.3 Hz, 1H), 1.73 (s, 3H), 1.68 (d, *J* = 6.3 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 18H).



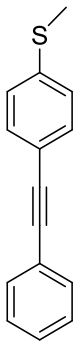
Methyl(3-(2-phenylethynyl)phenyl)sulfane (BJ-3-14)

3-Bromothioanisole (67 μL, 0.5 mmol), phenylacetylene (66 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 5 h yielding 107.7 mg (96%) of methyl(3-(2-phenylethynyl)phenyl)sulfane as a brown oil (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.36 (dd, *J* = 5.1, 2.1 Hz, 3H), 7.32 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.23 (dt, *J* = 7.9, 1.7 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.02, 131.77, 129.15, 128.78, 128.52, 128.50, 128.32, 126.61, 124.08, 123.19, 89.88, 89.07, 15.79.

HRMS: (EI, [$C_{15}H_{12}S$]) calcd, 224.0660; found *m/z*: 224.0661.



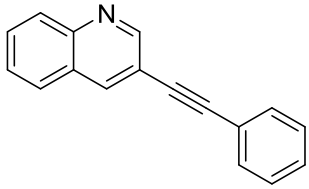
Methyl(4-(2-phenylethynyl)phenyl)sulfane (BJ-3-15)

4-Bromothioanisole (101.5 mg, 0.5 mmol), phenylacetylene (66 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 5 h yielding 111.4 mg (99%) of methyl(4-(2-phenylethynyl)phenyl)sulfane as a pale yellow soild (hexane/ether: 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.47 – 7.42 (m, 2H), 7.38 – 7.30 (m, 3H), 7.24 – 7.19 (m, 2H), 2.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.44, 132.01, 131.67, 128.48, 128.32, 126.02, 123.43, 119.69, 89.60, 89.33, 15.53.

Huang, H.; Liu, H.; Jiang, H.; Chen, K. *J. Org. Chem.* **2008**, *73*, 6037-6040.



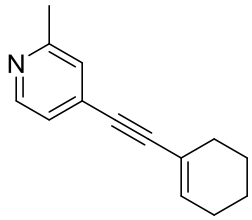
3-(2-Phenylethynyl)quinolone (BJ-3-13)

3-Bromoquinoline (68 μL, 0.5 mmol), phenylacetylene (66 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 5 h yielding 109.5 mg (95%) of 3-(2-phenylethynyl)quinoline as a brown oil (hexane/ether : 92/8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.1 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.60 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.56 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.38 (dd, *J* = 5.0, 2.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.23, 146.94, 138.33, 131.85, 130.16, 129.53, 128.92, 128.59, 127.71, 127.39, 127.37, 122.71, 117.56, 92.74, 86.75.

Handa, S.; Smith, J. D.; Zhang, Y.; Takale, B. S.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2018**, *20*, 542-545.



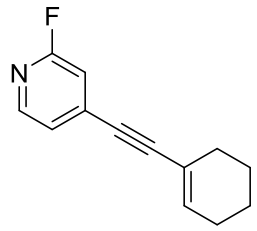
4-(2-Cyclohexenylethynyl)-2-methylpyridine (BJ-2-129)

4-Bromo-2-methylpyridine (59 μL, 0.5 mmol), 1-ethynylcyclohexene (71 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 16 h yielding 92.8 mg (94%) of 4-(2-cyclohexenylethynyl)-2-methylpyridine as an orange oil (hexane/ether : 85/15).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.13 (dt, *J* = 1.3, 0.6 Hz, 1H), 7.05 (dt, *J* = 5.1, 1.1 Hz, 1H), 6.26 (tt, *J* = 3.9, 1.8 Hz, 1H), 2.50 (s, 3H), 2.17 – 2.22 (m, 2H), 2.12 – 2.16 (m, 2H), 1.69 – 1.63 (m, 2H), 1.63 – 1.56 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.42, 149.09, 137.31, 132.25, 125.05, 122.62, 120.33, 95.56, 84.66, 29.04, 25.95, 24.41, 22.31, 21.49.

HRMS: (EI, [$C_{14}H_{15}N$]) calcd, 197.1205; found *m/z*: 197.1198.



4-(2-Cyclohexenylethynyl)-2-fluoropyridine (BJ-2-129)

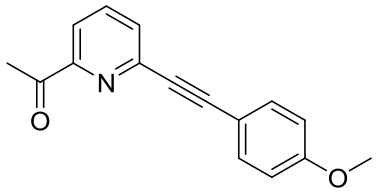
4-Bromo-2-fluoropyridine (51 μL, 0.5 mmol), 1-ethynylcyclohexene (71 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 16 h yielding 87.4 mg (87%) of 4-(2-cyclohexenylethynyl)-2-fluoropyridine as a yellow oil (hexane/ether : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 5.2 Hz, 1H), 7.13 (dt, *J* = 5.2, 1.6 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.31 (tt, *J* = 3.8, 1.7 Hz, 1H), 2.22 – 2.18 (m, 2H), 2.18 – 2.13 (m, 2H), 1.73 – 1.64 (m, 2H), 1.64 – 1.59 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.83, 162.94, 147.66, 147.53, 138.46, 137.16, 137.09, 123.43, 123.40, 120.03, 111.51, 111.20, 97.51, 83.55, 83.51, 28.88, 26.00, 22.25, 21.42.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.15.

HRMS: (EI, [$C_{13}H_{12}FN$]) calcd, 201.0954; found *m/z*: 201.0949.



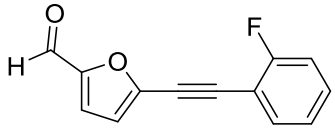
1-(6-(2-(4-Methoxyphenyl)ethynyl)pyridin-2-yl)ethanone (BJ-2-217)

2-Acetyl-6-bromopyridine (100 mg, 0.5 mmol), 4-ethynylanisole (78 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 3 h yielding 110.4 mg (88%) of 1-(6-(2-(4-methoxyphenyl)ethynyl)pyridin-2-yl)ethanone as a white solid (hexane/ether : 80/20).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.59 – 7.54 (m, 2H), 6.94 – 6.87 (m, 2H), 3.84 (s, 3H), 2.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.02, 160.51, 153.94, 143.36, 137.08, 133.84, 130.46, 120.40, 114.25, 114.08, 90.28, 87.37, 55.47, 25.98.

HRMS: (ESI, [$C_{16}H_{13}NO_2$ + Na]) calcd, 274.0844; found *m/z*: 274.0853.



5-(2-(2-Fluorophenyl)ethynyl)furan-2-carbaldehyde (BJ-2-192)

5-Bromo-2-furaldehyde (87.5 mg, 0.5 mmol), 1-ethynyl-2-fluorobenzene (68 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 18 h

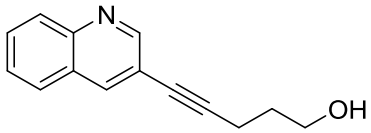
yielding 87.6 mg (82%) of 5-(2-(2-fluorophenyl)ethynyl)furan-2-carbaldehyde as a yellow solid (hexane/ether : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.52 (td, *J* = 7.3, 1.8 Hz, 1H), 7.39 (dddd, *J* = 8.4, 7.3, 5.3, 1.8 Hz, 1H), 7.25 (d, *J* = 3.7 Hz, 1H), 7.18 – 7.08 (m, 2H), 6.82 (d, *J* = 3.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.41, 163.87, 161.85, 152.76, 141.61, 133.61, 133.60, 131.69, 131.62, 124.38, 124.35, 121.28, 117.67, 115.98, 115.82, 110.18, 110.06, 89.96, 83.24, 83.21.

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.47, -108.49, -108.50, -108.51, -108.51, -108.53.

HRMS: (ESI, [$C_{13}H_7FO_2$ + Na]) calcd, 237.0328; found *m/z*: 237.0337.



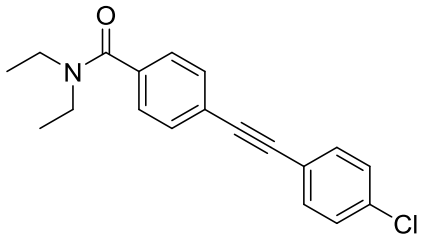
5-(Quinolin-3-yl)pent-4-yn-1-ol (BJ-3-37)

3-Bromoquinoline (68 μL, 0.5 mmol), 4-pentyn-1-ol (56 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 12 h yielding 78.3 mg (74%) of 5-(quinolin-3-yl)pent-4-yn-1-ol as a yellow oil (hexane/EtOAc : 60/40).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.85 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.57(br s, 1H), 1.91 (p, *J* = 6.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.48, 146.60, 138.25, 129.90, 129.31, 127.55, 127.44, 127.29, 118.10, 93.32, 78.42, 61.54, 31.47, 16.21.

Jean, A.; Blanchet, J.; Rouden, J.; Maddaluno, J.; De Paolis, M. *Chem. Commun.* **2013**, *49*, 1651-1653.



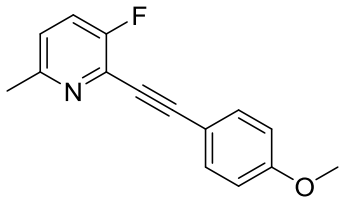
4-(2-(4-Chlorophenyl)ethynyl)-*N*,*N*-diethylbenzamide (BJ-2-260)

4-Bromo-*N*,*N*-diethylbenzamide (128 mg, 0.5 mmol), 1-chloro-4-ethynylbenzene (102.5 mg, 0.75 mmol, 1.5 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 22 h yielding 153.5 mg (98%) of 4-(2-(4-chlorophenyl)ethynyl)-N,N-diethylbenzamide as a white solid (hexane/EtOAc : 70/30).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 17.1, 8.4 Hz, 4H), 3.54 (s, 2H), 3.25 (s, 2H), 1.24 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.67, 137.23, 134.66, 132.97, 131.73, 128.87, 126.60, 123.96, 121.58, 89.76, 89.49, 43.41, 39.46, 14.35, 13.01.

HRMS: (ESI, [$C_{19}H_{18}ClNO$ + Na]) calcd, 334.0975; found *m/z*: 334.0970.



3-Fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine (BJ-3-17)

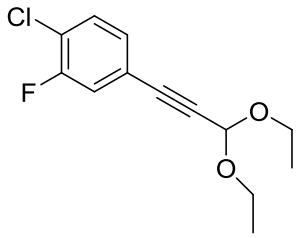
2-Bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (78 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 3 h yielding 117.1 mg (97%) of 3-fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine as a yellow solid (hexane/ether : 75/25).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.54 (m, 2H), 7.30 (t, *J* = 8.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 3.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 3.82 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.47, 159.63, 157.58, 154.67, 154.63, 133.84, 131.76, 131.64, 123.57, 123.54, 123.38, 123.23, 114.24, 114.16, 95.38, 95.34, 81.99, 81.95, 55.43, 23.94, 23.93.

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.59, -123.60, -123.61, -123.62.

HRMS: (ESI, [$C_{15}H_{12}FNO$ + H]) calcd, 242.0981; found *m/z*: 242.0984.



1-Chloro-4-(3,3-diethoxyprop-1-ynyl)-2-fluorobenzene (BJ-3-5)

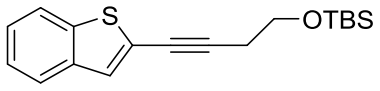
4-Bromo-1-chloro-2-fluorobenzene (61 μL, 0.5 mmol), 3,3-diethoxy-1-propyne (108 μL, 0.75 mmol, 1.5 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 43 h yielding 89.6 mg (70%) of 1-chloro-4-(3,3-diethoxyprop-1-ynyl)-2-fluorobenzene as a colorless liquid (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 1H), 7.24 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.19 (ddd, *J* = 8.3, 1.8, 0.9 Hz, 1H), 5.46 (s, 1H), 3.79 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.65 (dq, *J* = 9.4, 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.73, 156.74, 130.74, 128.61, 128.58, 122.34, 122.26, 122.20, 120.09, 119.91, 91.76, 91.74, 86.31, 83.08, 83.06, 61.23, 15.21.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.71, -114.73, -114.75.

HRMS: (CI, [$C_{13}H_{14}ClFO_2$ + H]) calcd, 257.0745; found *m/z*: 257.0739.



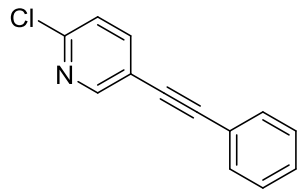
(4-(Benzo[b]thiophen-2-yl)but-3-ynyloxy)(*t*-butyl)dimethylsilane (BJ-2-250)

2-Bromobenzothiophene (106.5 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 μL, 0.75 mmol, 1.5 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 43 h yielding 152.3 mg (96%) of (4-(benzo[b]thiophen-2-yl)but-3-ynyloxy) (*t*-butyl)dimethylsilane as a yellow oil (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H), 7.39 – 7.31 (m, 3H), 3.86 (t, *J* = 6.9 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 0.95 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.97, 139.26, 128.02, 125.22, 124.69, 124.07, 123.69, 122.07, 93.80, 75.31, 61.75, 26.06, 24.35, 18.51, -5.07.

HRMS: (EI, [$C_{18}H_{24}OSSi$]) calcd, 316.1317; found *m/z*: 316.1319.



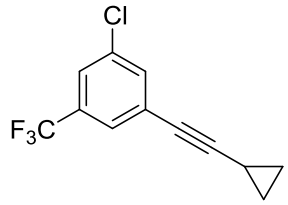
2-Chloro-5-(2-phenylethynyl)pyridine (BJ-2-216)

5-Bromo-2-chloropyridine (96.2 mg, 0.5 mmol), phenylacetylene (66 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 5 h yielding 93.3 mg (88%) of 2-chloro-5-(2-phenylethynyl)pyridine as a white solid (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.54 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.38 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.32 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.19, 150.57, 141.02, 131.84, 129.18, 128.64, 124.04, 122.33, 119.53, 93.88, 84.83.

HRMS: (EI, [$C_{13}H_8ClN$]) calcd, 213.0345; found *m/z*: 213.0347.



1-Chloro-3-(2-cyclopropylethynyl)-5-(trifluoromethyl)benzene (BJ-3-28)

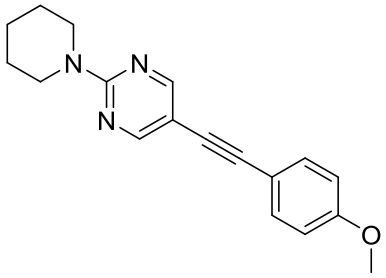
3-Bromo-5-chlorobenzotrifluoride (76 μL, 0.5 mmol), cyclopropylacetylene (46 μL, 0.55 mmol, 1.1 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 35 ^oC for 13 h yielding 104.9 mg (86%) of 1-chloro-3-(2-cyclopropylethynyl)-5-(trifluoromethyl)benzene as a colorless oil (hexane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.47 (d, *J* = 1.9 Hz, 1H), 1.45 (tt, *J* = 8.3, 5.0 Hz, 1H), 0.95 – 0.89 (m, 2H), 0.85 – 0.80 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.84, 134.68 (q, *J* = 1.2 Hz), 132.32 (q, *J* = 33.1 Hz), 126.86, 126.77 (q, *J* = 3.8 Hz), 124.51 (q, *J* = 3.8 Hz), 123.17 (q, *J* = 272.9 Hz), 97.15, 73.51, 8.94, 0.23.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.18.

HRMS: (EI, [$C_{12}H_8ClF_3$]) calcd, 244.0267; found *m/z*: 244.0259.



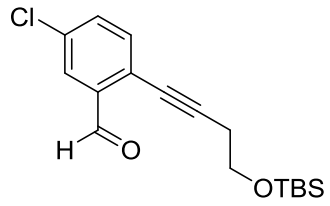
5-(2-(4-Methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine (BJ-3-16)

5-Bromo-2-(1-piperidinyl)pyrimidine (121 mg, 0.5 mmol), 4-ethynylanisole (78 μL, 0.6 mmol, 1.2 equiv), 100 μL stock solution (1000 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 8 h yielding 140.1 mg (95%) of 5-(2-(4-methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine as a pale yellow solid (hexane/ether : 85/15).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.45 – 7.41 (m, 2H), 6.88 – 6.84 (m, 2H), 3.81 (d, *J* = 2.3 Hz, 7H), 1.72 – 1.65 (m, 2H), 1.64 – 1.57 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.88, 159.65, 159.61, 132.92, 115.48, 114.13, 106.32, 91.87, 83.34, 55.42, 45.04, 25.88, 24.92.

HRMS: (ESI, [$C_{18}H_{19}N_3O$ + H]) calcd, 294.1606; found *m/z*: 294.1603.



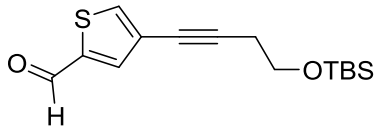
2-(4-(*t*-Butyldimethylsilyloxy)but-1-ynyl)-5-chlorobenzaldehyde (BJ-2-150)

2-Bromo-5-chlorobenzaldehyde (110 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 50 h yielding 134.2 mg (83%) of 2-(4-(*t*-butyldimethylsilyloxy)but-1-ynyl)- 5-chlorobenzaldehyde as a yellow oil (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 3.84 (t, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.90, 137.26, 134.69, 134.64, 133.82, 127.06, 125.97, 96.34, 76.49, 61.59, 25.99, 24.20, 18.46, -5.15.

HRMS: (ESI, [$C_{17}H_{23}ClO_2Si$ + Na]) calcd, 345.1053; found *m/z*: 345.1057.



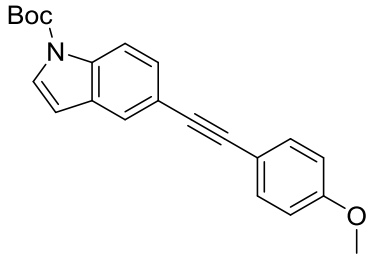
4-(4-(*t*-Butyldimethylsilyloxy)but-1-ynyl)thiophene-2-carbaldehyde (BJ-2-155)

4-Bromo-2-thiophenecarboxaldehyde (95.5 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 44 h yielding 119.3 mg (81%) of 4-(4-(*t*-butyldimethylsilyloxy)but-1-ynyl)thiophene- 2-carbaldehyde as a pale yellow oil (hexane/ether : 95/5).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 2H), 3.81 (t, *J* = 6.9 Hz, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.68, 143.40, 138.66, 136.69, 124.54, 88.52, 75.29, 61.78, 26.02, 23.86, 18.50, -5.10.

HRMS: (CI, [$C_{15}H_{22}O_2SSi$ + H]) calcd, 295.1188; found *m/z*: 295.1177.



***t*-Butyl 5-(2-(4-methoxyphenyl)ethynyl)-1H-indole-1-carboxylate (BJ-2-256)**

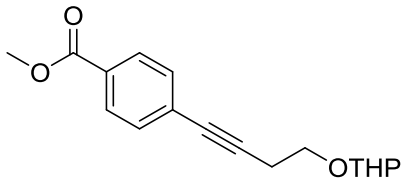
N-Boc-5-Bromoindole (148 mg, 0.5 mmol), 4-ethynylanisole (98 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 48 h yielding 151.0 mg (93%)

of *t*-butyl 5-(2-(4-methoxyphenyl)ethynyl)-1H-indole-1-carboxylate as a white solid (hexane/ether : 95/5).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 3.7 Hz, 1H), 7.51 – 7.46 (m, 3H), 6.91 – 6.87 (m, 2H), 6.56 (d, *J* = 3.7 Hz, 1H), 3.83 (s, 3H), 1.68 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.58, 149.65, 134.75, 133.09, 130.66, 127.80, 126.84, 124.34, 117.87, 115.85, 115.26, 114.12, 107.24, 88.84, 88.12, 84.11, 55.42, 28.31.

HRMS: (EI, [$C_{22}H_{21}NO_3$ –Boc + H]) calcd, 247.0997; found *m/z*: 247.1001.



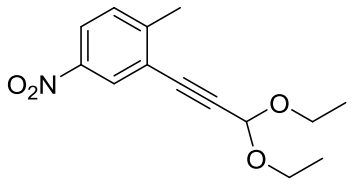
Methyl 4-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzoate (BJ-2-155)

Methyl 4-bromobenzoate (107.5 mg, 0.5 mmol), 2-(3-butynyloxy)tetrahydro-2H-pyran (118 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 44 h yielding 126.7 mg (88%) of methyl 4-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzoate as a pale yellow oil (hexane/ether : 75/25).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.68 (t, *J* = 3.6 Hz, 1H), 3.95 – 3.84 (m, 5H), 3.65 (dt, *J* = 9.7, 7.0 Hz, 1H), 3.52 (dddd, *J* = 10.7, 6.4, 4.3, 2.6 Hz, 1H), 2.73 (t, *J* = 7.1 Hz, 2H), 1.83 (ddd, *J* = 9.8, 7.8, 4.8 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.66 – 1.47 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.71, 131.62, 129.51, 129.17, 128.64, 98.90, 90.60, 81.02, 65.62, 62.32, 52.26, 30.68, 25.54, 21.15, 19.49.

HRMS: (ESI, [$C_{17}H_{20}O_4$ + Na]) calcd, 311.1259; found *m/z*: 311.1249.



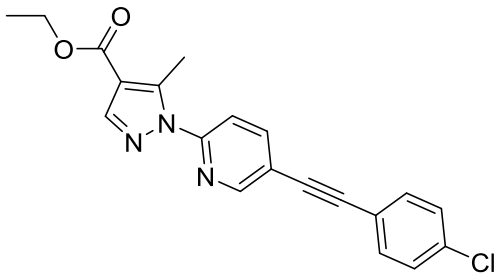
2-(3,3-Diethoxyprop-1-ynyl)-1-methyl-4-nitrobenzene (BJ-2-143)

2-Bromo-4-nitrotoluene (108 mg, 0.5 mmol), 3,3-diethoxy-1-propyne (108 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 51 h yielding 81.2 mg (62%) of 2-(3,3-diethoxyprop-1-ynyl)-1-methyl-4-nitrobenzene as a yellow oil (hexane/ether : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.53 (s, 1H), 3.83 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.69 (dq, *J* = 9.5, 7.1 Hz, 2H), 2.54 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.08, 146.14, 130.46, 127.35, 123.59, 123.44, 91.80, 90.84, 81.78, 61.32, 21.16, 15.26.

HRMS: (CI, [$C_{14}H_{17}NO_4$ + H]) calcd, 264.1236; found *m/z*: 264.1235.



Ethyl

1-(5-(2-(4-chlorophenyl)ethynyl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylate

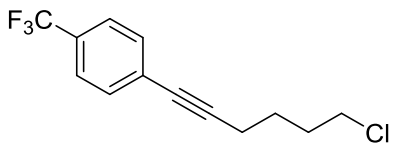
(BJ-2-282)

Ethyl 1-(5-bromopyridin-2-yl)-5-methylpyrazole-4-carboxylate (155 mg, 0.5 mmol), 1-chloro-4-ethynylbenzene (102.5 mg, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and Et_3N (140 μL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 42 h yielding 179.5 mg (98%) of ethyl 1-(5-(2-(4-chlorophenyl)ethynyl)pyridin- 2-yl)-5-methyl-1H-pyrazole-4-carboxylate as a yellow solid (hexane/EtOAc : 90/10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.6 Hz, 1H), 8.03 (s, 1H), 7.94 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.95 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.72, 151.92, 150.30, 145.79, 142.84, 141.01, 135.17, 133.02, 129.00, 120.99, 118.75, 116.86, 114.60, 92.31, 86.42, 60.23, 14.53, 13.39.

HRMS: (EI, [$C_{20}H_{16}ClN_3O_2$]) calcd, 365.0931; found *m/z*: 365.0915.



1-(6-Chlorohex-1-ynyl)-4-(trifluoromethyl)benzene (BJ-2-144)

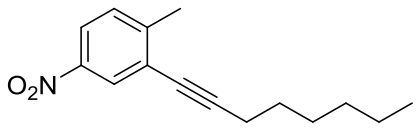
4-Bromobenzotrifluoride (70 μL, 0.5 mmol), 6-chloro-1-hexyne (91 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and $K_3PO_4 \cdot H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 45 h yielding 107.5 mg (83%) of 1-(6-chlorohex-1-ynyl)-4-(trifluoromethyl)benzene as a colorless oil (hexane/ether : 99/1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.97 (ddt, *J* = 9.4, 8.1, 6.4 Hz, 2H), 1.84 – 1.73 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.92, 129.96, 129.70, 129.44, 129.19, 127.81, 127.79, 127.39, 125.33, 125.30, 125.27, 125.23, 125.22, 123.06, 120.90, 92.27, 80.25, 80.24, 44.59, 44.58, 31.76, 25.86, 18.89.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.77.

Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu,L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, 135, 8436-8439.



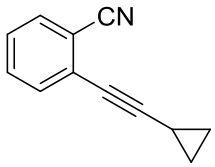
1-Methyl-4-nitro-2-(oct-1-ynyl)benzene (BJ-2-149)

2-Bromo-4-nitrotoluene (108 mg, 0.5 mmol), 1-octyne (110 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and $K_3PO_4 \cdot H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 50 h yielding 121.0 mg (98%) of 1-methyl-4-nitro-2-(oct-1-ynyl)benzene as a yellow solid (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.5 Hz, 1H), 7.98 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 3H), 2.46 (t, *J* = 7.1 Hz, 2H), 1.63 (dt, *J* = 14.9, 7.1 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.40 – 1.27 (m, 4H), 0.94 – 0.85 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.64, 146.09, 130.17, 130.02, 126.76, 126.67, 125.54, 122.21, 122.17, 97.51, 77.69, 31.44, 28.69, 22.67, 21.18, 21.08, 19.61, 14.15.

HRMS: (EI, [$C_{15}H_{19}NO_2$]) calcd, 245.1416; found *m/z*: 245.1405.



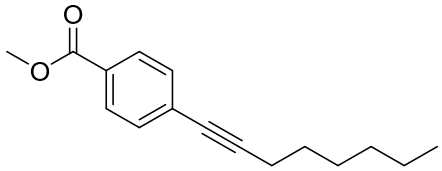
2-(2-Cyclopropylethynyl)benzonitrile (BJ-2-143)

2-Bromobenzonitrile (91 mg, 0.5 mmol), cyclopropylacetylene (51 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 45 h yielding 73.5 mg (88%) of 2-(2-cyclopropylethynyl)benzonitrile as a pale yellow oil (hexane/ether : 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.31 (td, *J* = 7.4, 1.9 Hz, 1H), 1.51 (tt, *J* = 8.1, 5.2 Hz, 1H), 0.99 – 0.86 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.53, 132.32, 132.21, 128.10, 127.50, 117.84, 115.38, 101.33, 72.42, 9.29, 0.45.

HRMS: (EI, [$C_{12}H_9N$]) calcd, 167.0735; found *m/z*: 167.0729.



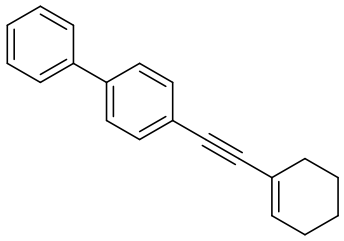
Methyl 4-(oct-1-ynyl)benzoate (BJ-2-155)

Methyl 4-bromobenzoate (107.5 mg, 0.5 mmol), 1-octyne (110 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 44 h yielding 121.5 mg (99%) of methyl 4-(oct-1-ynyl)benzoate as a yellow oil (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.46 – 7.40 (m, 2H), 3.90 (s, 3H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.64 – 1.56 (m, 2H), 1.49 – 1.41 (m, 2H), 1.38 – 1.26 (m, 4H), 0.94 – 0.86 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.78, 131.57, 129.50, 129.09, 128.92, 94.14, 80.23, 52.23, 31.47, 28.73, 28.68, 22.67, 19.63, 14.17.

HRMS: (EI, [$C_{16}H_{20}O_2$]) calcd, 244.1463; found *m/z*: 244.1456.



4-(Cyclohex-1-en-1-ylethynyl)-1,1'-biphenyl (BJ-2-142)

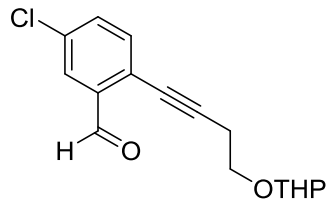
4-Bromobiphenyl (116.5 mg, 0.5 mmol), 1-ethynylcyclohexene (71 μL, 0.6 mmol, 1.2 equiv), 150 μL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^oC for 43 h yielding 105.9

mg (82%) of 4-(cyclohex-1-en-1-ylethynyl)-1,1'-biphenyl as a yellow solid (hexane/ether : 98/2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.25 (dt, *J* = 4.1, 2.2 Hz, 1H), 2.31 – 2.23 (m, 2H), 2.23 – 2.14 (m, 2H), 1.76 – 1.68 (m, 2H), 1.68 – 1.61 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.58, 140.53, 135.38, 131.98, 128.95, 127.63, 127.10, 127.02, 122.86, 120.92, 92.12, 86.83, 29.39, 25.94, 22.50, 21.67.

HRMS: (EI, [$C_{20}H_{18}$]) calcd, 258.1408; found *m/z*: 258.1396.



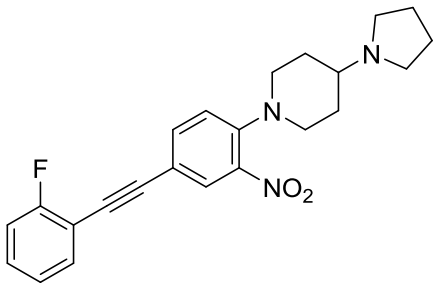
5-Chloro-2-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzaldehyde (BJ-2-150)

2-Bromo-5-chlorobenzaldehyde (110 mg, 0.5 mmol), 2-(3-butynyloxy)tetrahydro-2H-pyran (118 μL, 0.75 mmol, 1.5 equiv), 150 μL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 45 ^{o}C for 50 h yielding 112.8 mg (77%) of 5-chloro-2-(4-(tetrahydro-2H-pyran-2-yloxy) but-1-ynyl)benzaldehyde as a pale yellow oil (hexane/ether : 80/20).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 4.67 (t, *J* = 3.7 Hz, 1H), 3.93 (dt, *J* = 9.7, 6.8 Hz, 1H), 3.88 (td, *J* = 8.4, 4.3 Hz, 1H), 3.65 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.55 – 3.49 (m, 1H), 2.78 (t, *J* = 6.8 Hz, 2H), 1.89 – 1.78 (m, 1H), 1.77 – 1.69 (m, 1H), 1.65 – 1.47 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.91, 137.31, 134.70, 134.59, 133.78, 127.02, 125.87, 99.02, 96.12, 76.39, 65.40, 62.43, 30.67, 25.50, 21.30, 19.52.

HRMS: (ESI, [$C_{16}H_{17}ClO_3$ + Na]) calcd, 315.0764; found *m/z*: 315.0760.



1-(4-(2-(2-Fluorophenyl)ethynyl)-2-nitrophenyl)-4-(pyrrolidin-1-yl)piperidine (BJ-2-227)

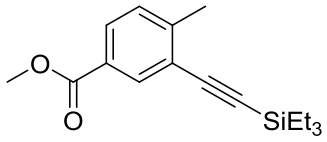
For details, see 2-step, 1-pot section.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.93 (m, 1H), 7.54 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.31 (q, *J* = 6.8 Hz, 1H), 7.10 (dt, *J* = 14.6, 8.2 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 2H), 2.93 (t, *J* = 11.3 Hz, 2H), 2.65 – 2.51 (m, 4H), 2.18 (ddd, *J* = 14.2, 10.0, 3.6 Hz, 1H), 1.96 (dd, *J* = 13.5, 3.8 Hz, 2H), 1.87 – 1.65 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.72, 161.71, 145.99, 141.02, 136.31, 133.47, 133.46, 130.29, 130.23, 129.79, 124.16, 124.13, 120.45, 115.77, 115.61, 114.44, 111.75, 111.63, 92.56, 92.53, 83.22, 61.17, 51.54, 50.22, 31.42, 23.40.

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.78, -109.80, -109.80, -109.81, -109.81, -109.82, -109.83, -109.84.

HRMS: (ESI, [$C_{23}H_{24}FN_3O_2$ + H]) calcd, 394.1931; found *m/z*: 394.1940.

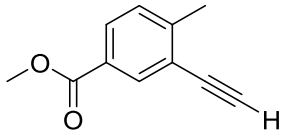


Methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (BJ-2-262)

For details, see section on synthesis of ponatinib.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 1.9 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.28 – 7.25 (m, 1H), 3.90 (s, 3H), 2.49 (s, 3H), 1.06 (t, *J* = 7.9 Hz, 9H), 0.69 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.67, 145.95, 133.57, 129.64, 129.43, 127.86, 123.72, 104.09, 96.99, 52.23, 21.16, 7.67, 4.59.

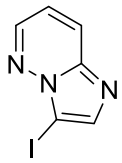


Methyl 3-ethynyl-4-methylbenzoate (BJ-2-290)

For details, see section on synthesis of ponatinib.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.9 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 3.31 (s, 1H), 2.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.54, 146.14, 133.88, 129.84, 129.77, 127.99, 122.48, 81.95, 81.62, 52.28, 20.99.

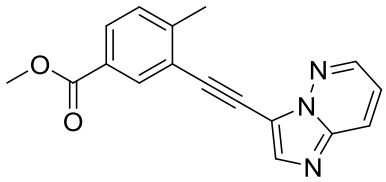


3-Iodoimidazo[1,2-b]pyridazine (BJ-2-228)

For details, see section on synthesis of ponatinib.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.9 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 3.31 (s, 1H), 2.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.54, 146.14, 133.88, 129.84, 129.77, 127.99, 122.48, 81.95, 81.62, 52.28, 20.99.



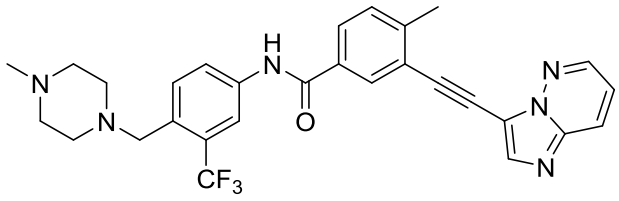
Methyl 3-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methylbenzoate (BJ-3-21)

For details, see section on synthesis of ponatinib.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.05 (s, 1H), 8.00 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.7 Hz, 1H), 7.13 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.92 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.51, 145.54, 143.96, 139.79, 138.42, 133.16, 129.83, 129.82, 128.05, 126.00, 122.84, 117.77, 113.28, 96.84, 80.57, 52.26, 21.18.

HRMS: (ESI, [$C_{17}H_{13}N_3O_2$ + H]) calcd, 292.1086; found *m/z*: 292.1077.



Ponatinib (BJ-3-168)

For details, see section on synthesis of ponatinib.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.42 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.07 (s, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 2H), 7.82 (ddd, *J* = 9.6, 8.5, 1.8 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.06 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.60 (s, 2H), 2.55 (s, 3H), 2.49 (s, 8H), 2.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.53, 144.45, 144.03, 139.75, 138.23, 137.22, 133.48, 132.28, 131.40, 130.29, 130.18, 129.58, 129.34, 129.09, 128.86, 128.24, 125.82, 125.28, 123.60, 123.10, 122.60, 117.98, 113.23, 96.77, 80.62, 57.87, 55.22, 52.97, 45.97, 20.94.

^{19}F NMR (376 MHz, $CDCl_3$) δ -59.40.

HRMS: (ESI, [$C_{29}H_{27}F_3N_6O$ + H]) calcd, 533.2277; found *m/z*: 533.2266.

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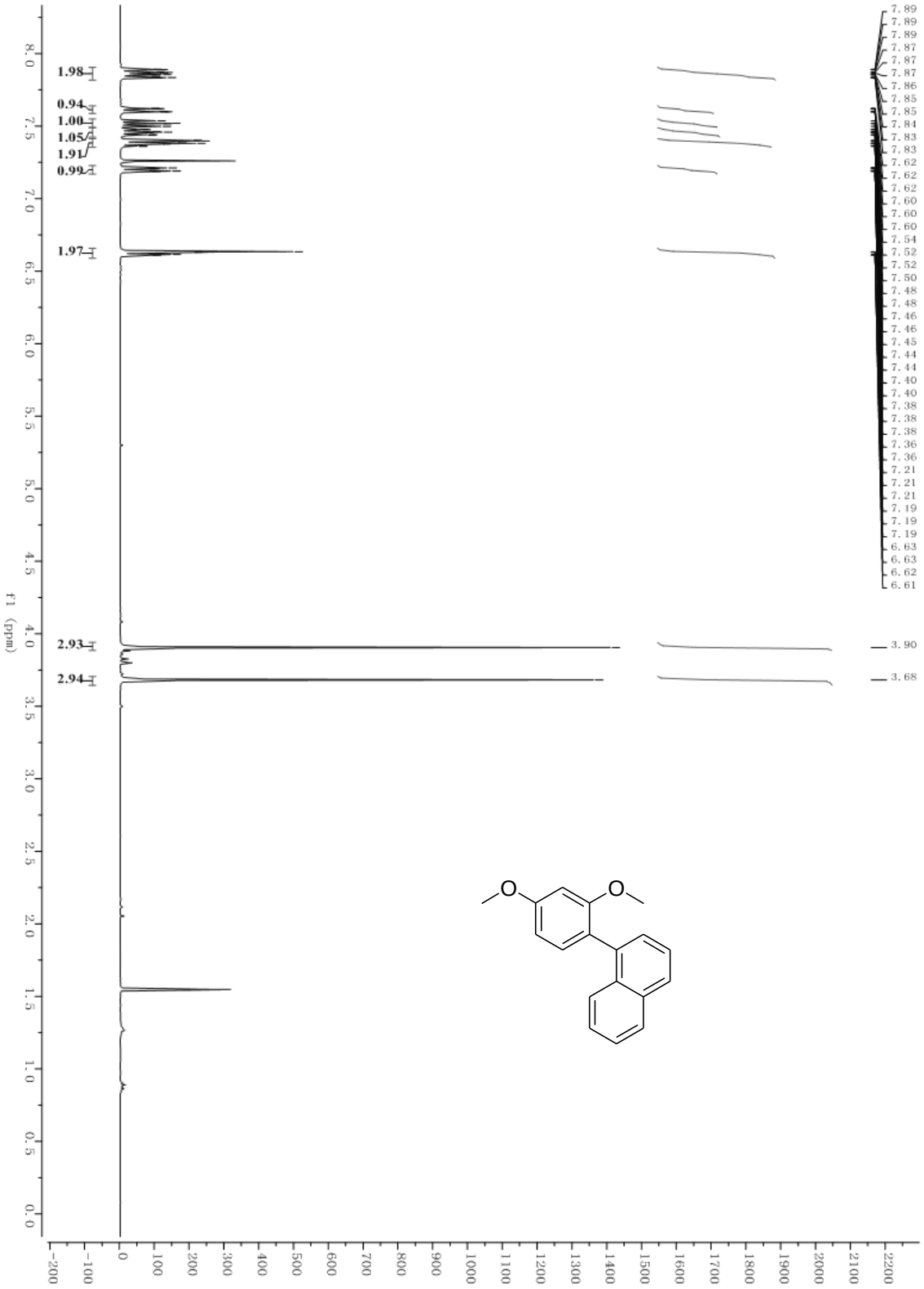
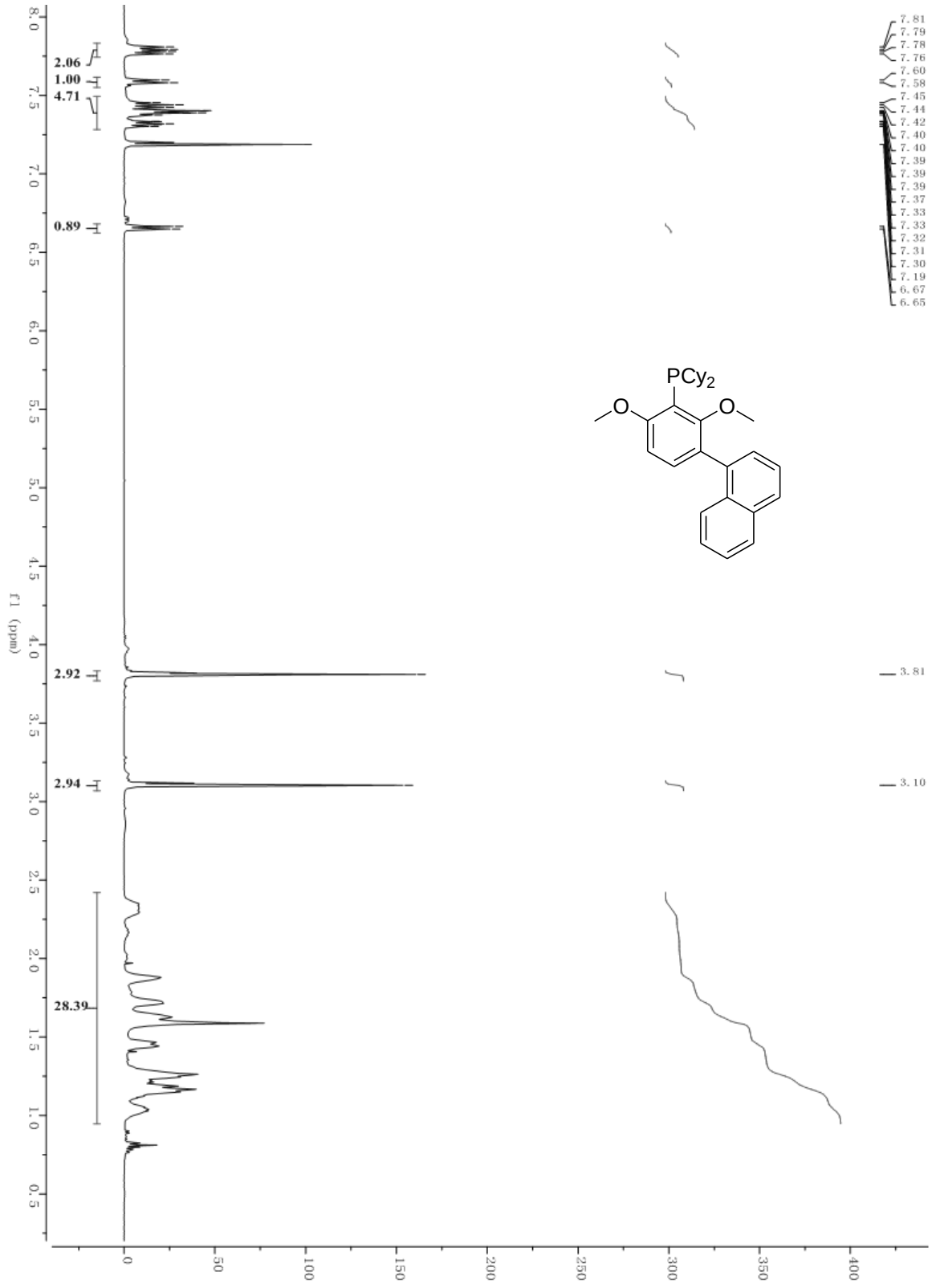
Selected Spectra

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2.94
28.39
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O
O
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7.78
7.76
7.60
7.58
7.45
7.44
7.42
7.40
7.40
7.39
7.39
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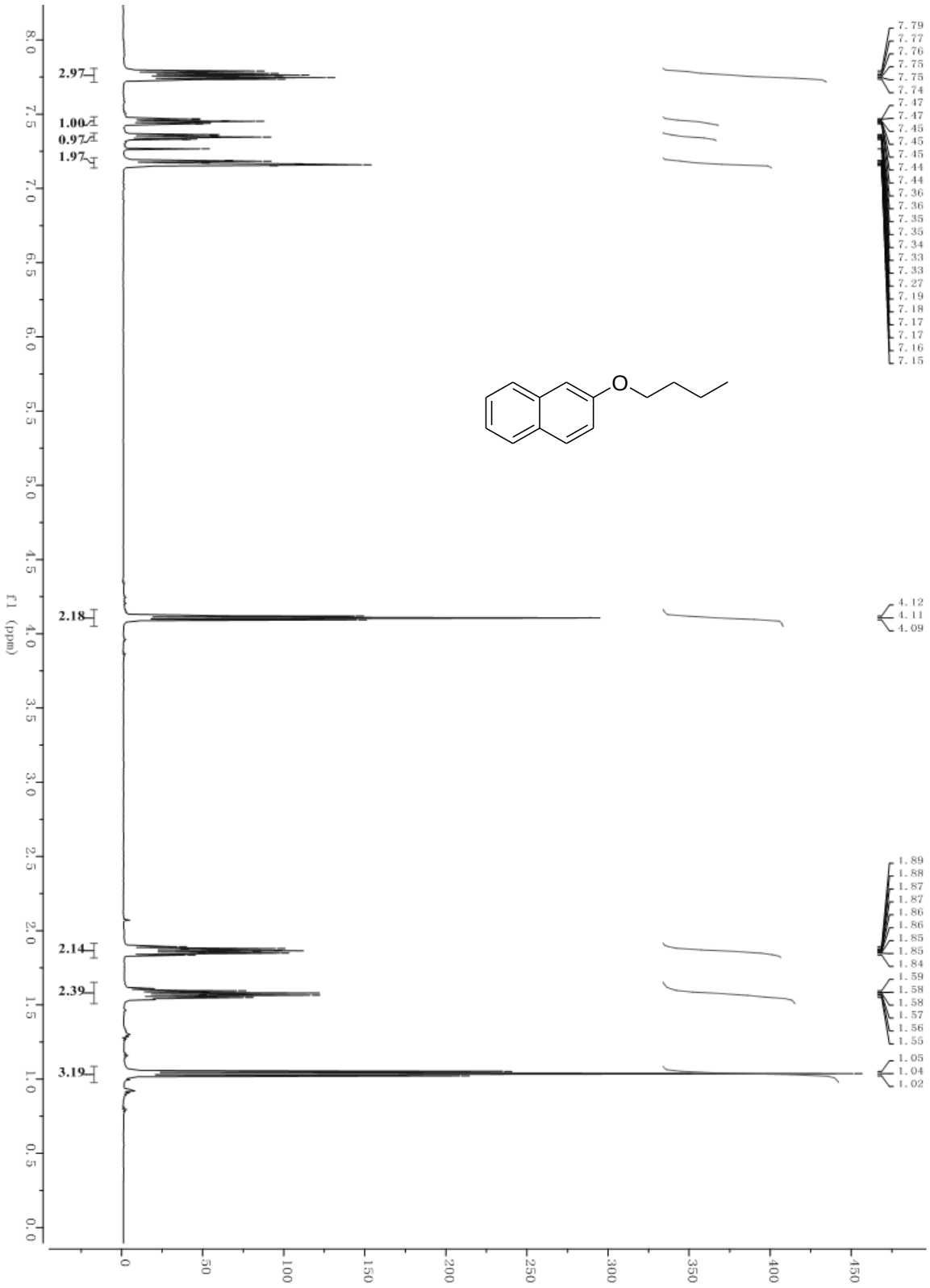
7.30
7.19
6.67
6.65
3.81
3.10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7.77
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7.75
7.74
7.47
7.47
7.45
7.45
7.45
7.44
7.44
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.27
7.19
7.18
7.17
7.17
7.16
7.15
4.12
4.11
4.09
1.89
1.88
1.87
1.87
1.86
1.86
1.85
1.85
1.84
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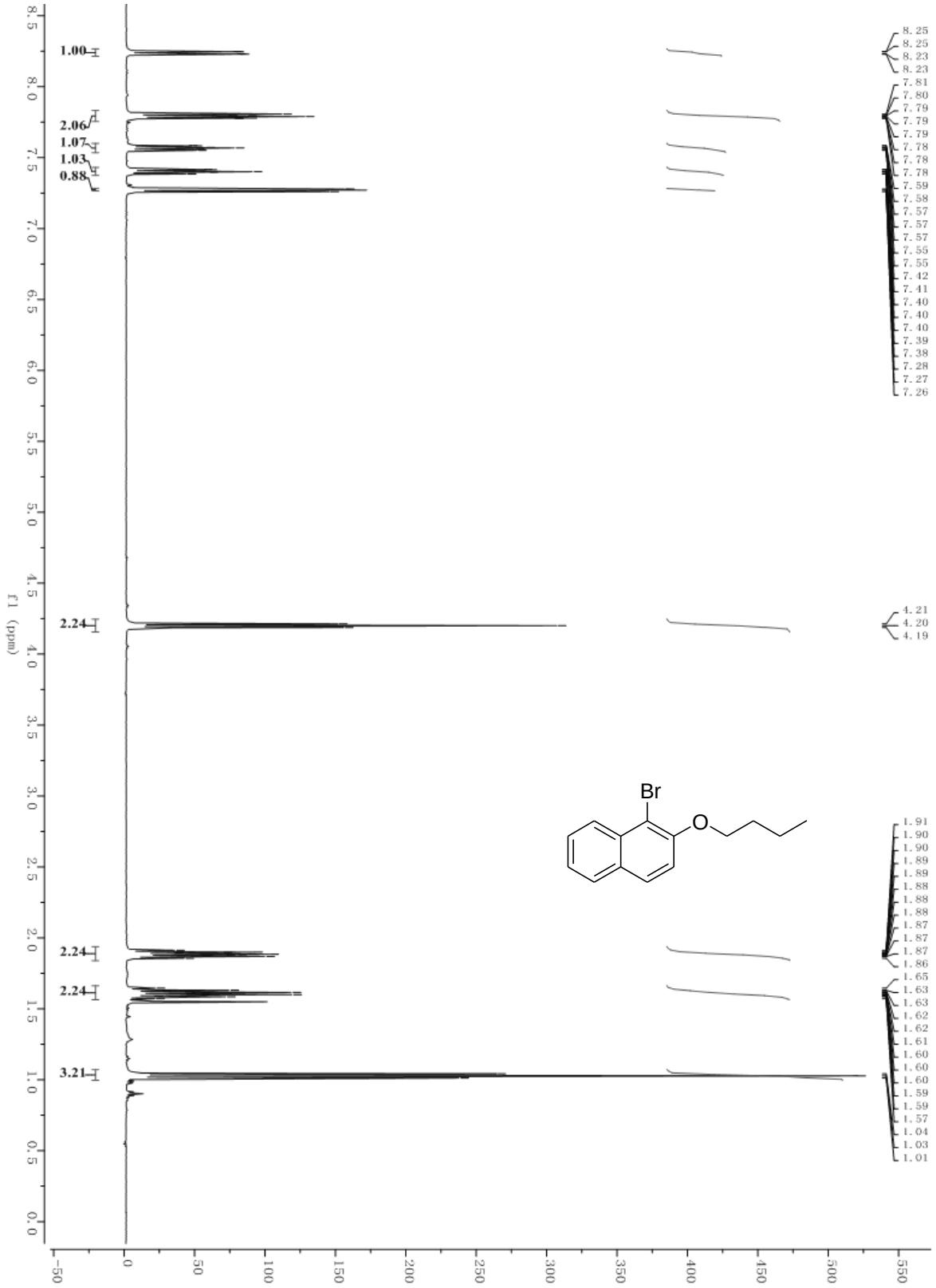
1.58
1.58
1.57
1.56
1.55
1.05
1.04
1.02
f1 (ppm)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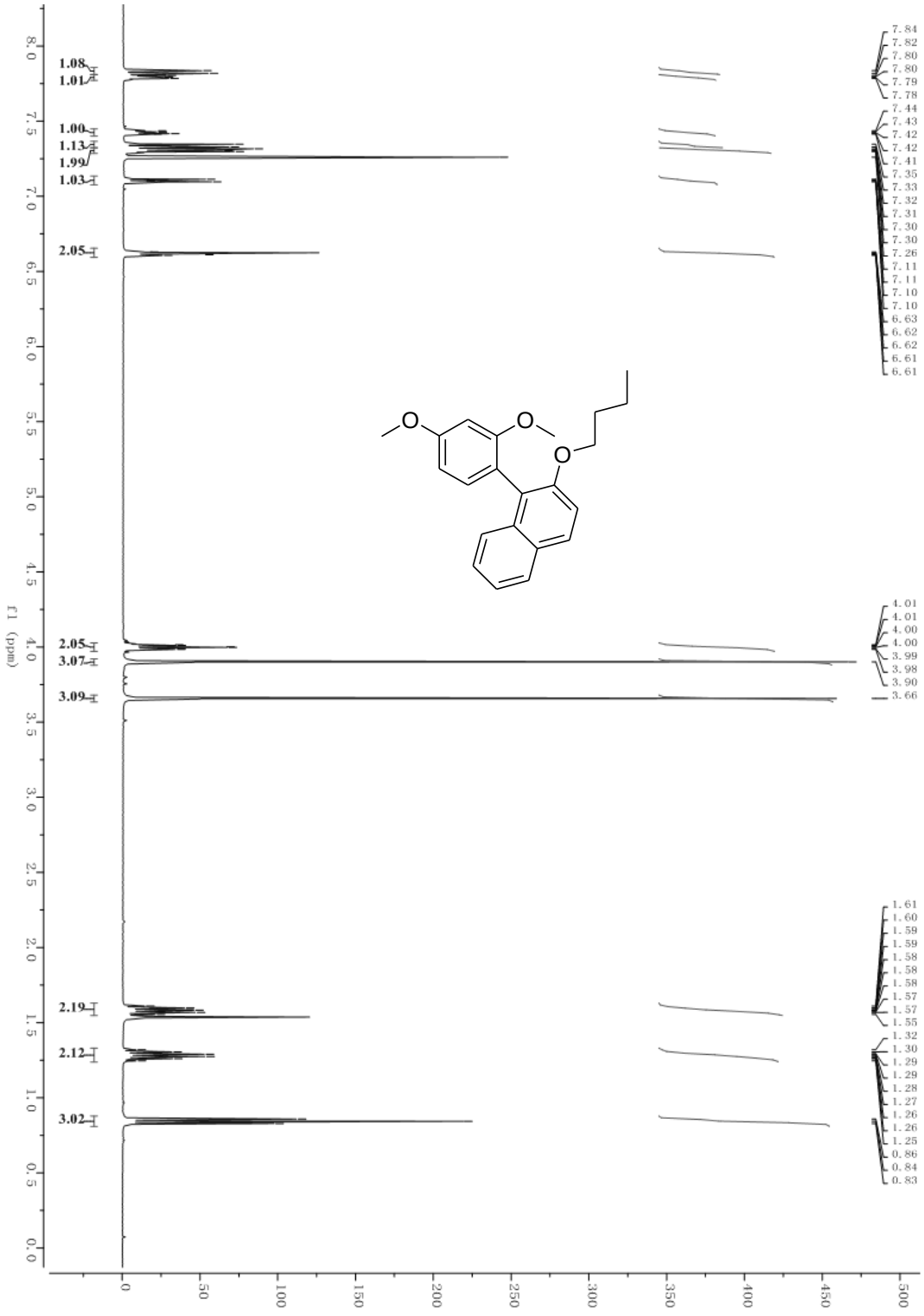
3.21
f1 (ppm)
Br
O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1.99
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3.07
3.09
2.19
2.12
3.02
O
O
O
7.84
7.82
7.80
7.80
7.79
7.78
7.44
7.43
7.42
7.42
7.41
7.35
7.33
7.32
7.31
7.30
7.30
7.26
7.11
7.11
7.10
7.10
6.63
6.62
6.62
6.61
6.61
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4.01
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1.55
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1.26
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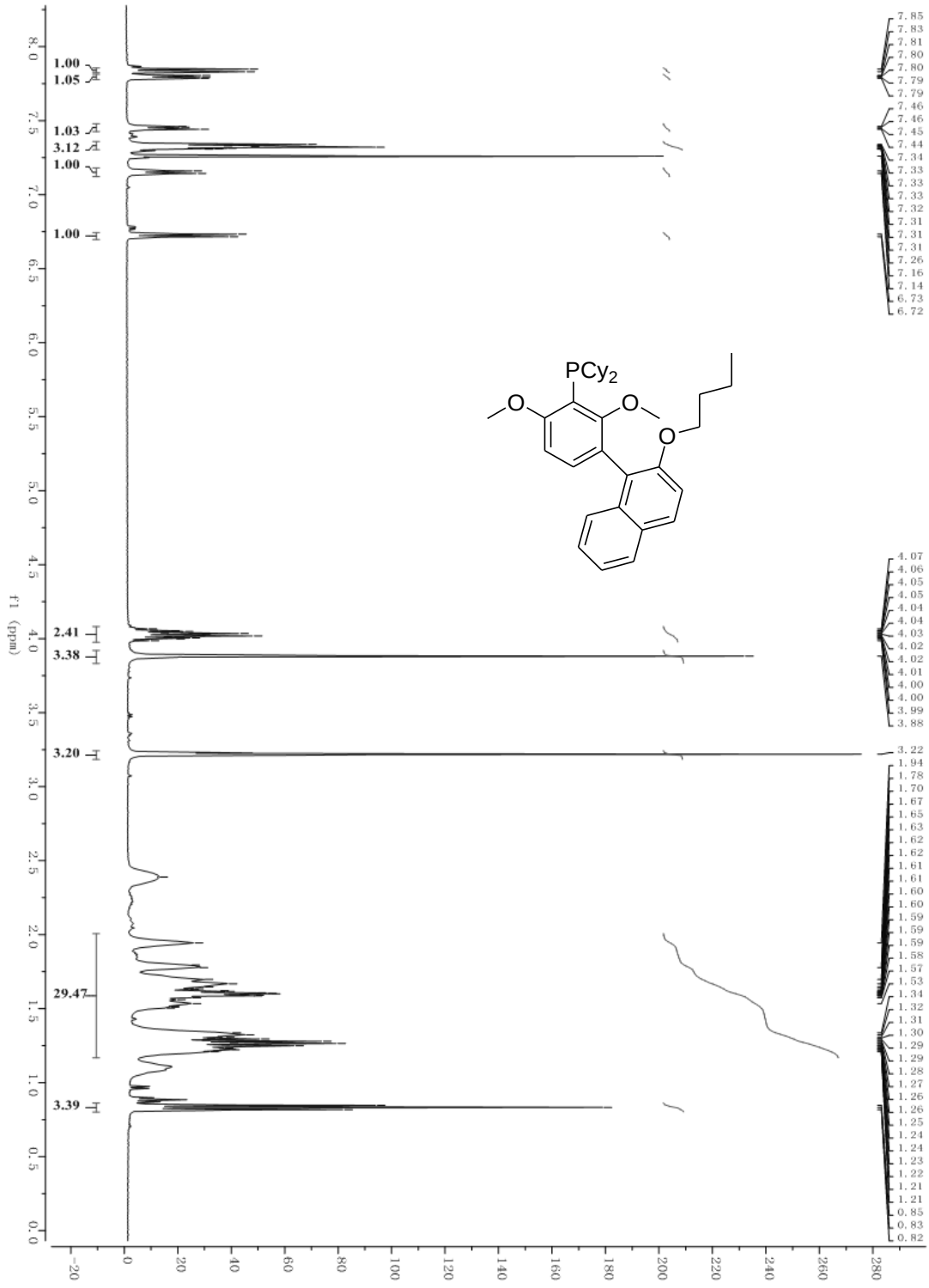
0.83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O
O
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1.03
3.12
1.00
1.00
2.41
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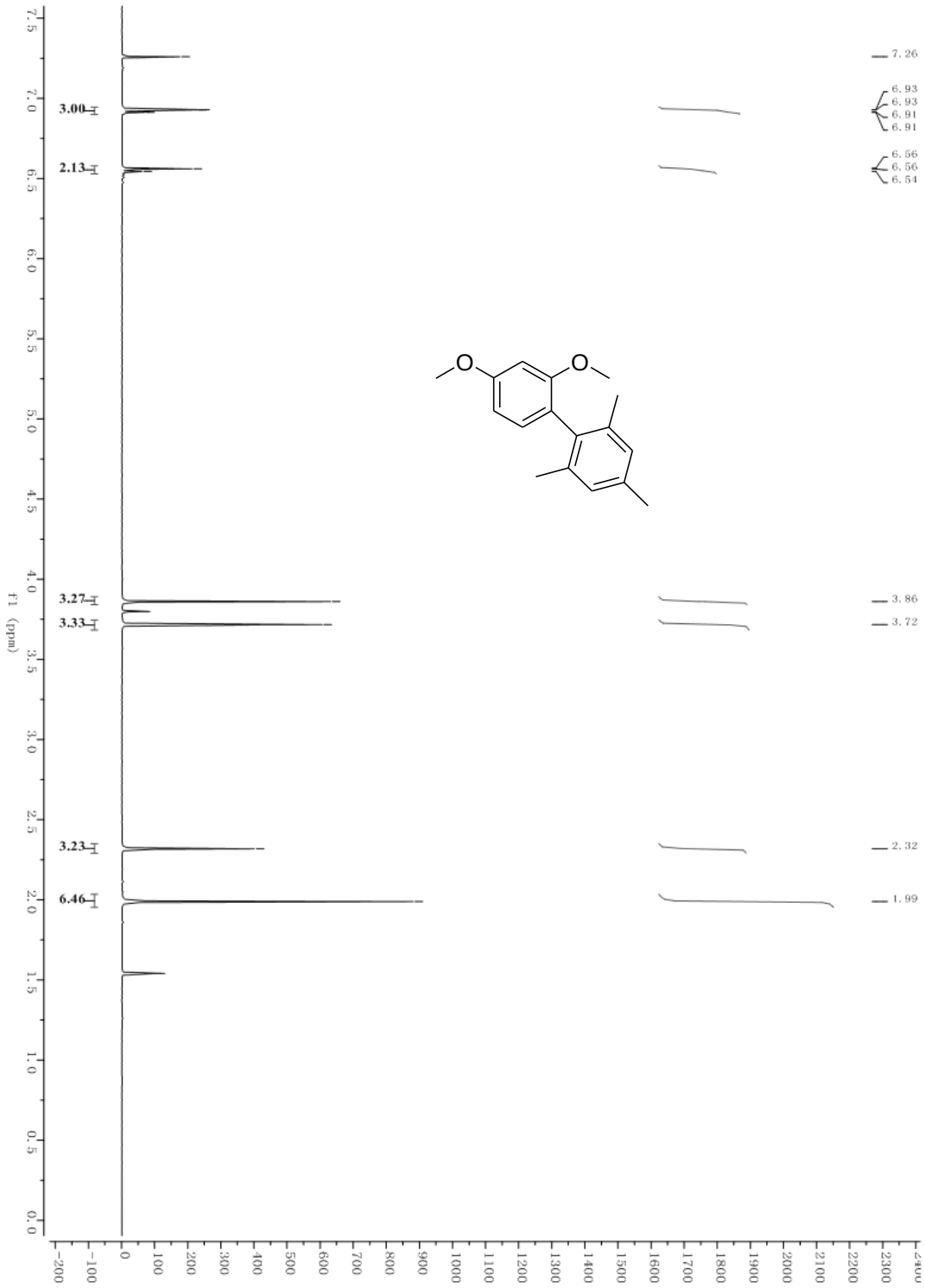
3.20
29.47
3.39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3.00
2.13
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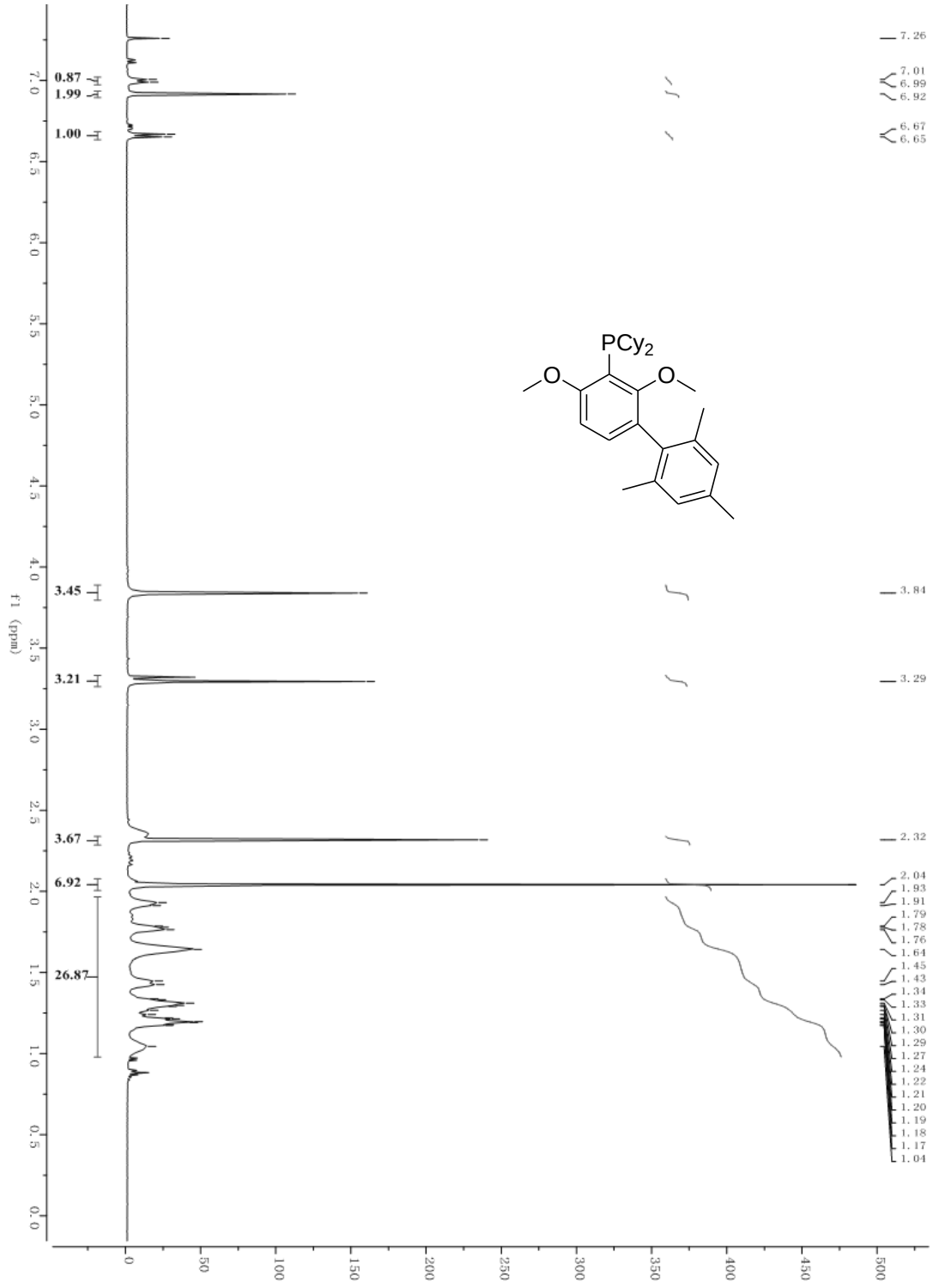
3.23
6.46
O
O
f1 (ppm)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O
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26.87
7.26
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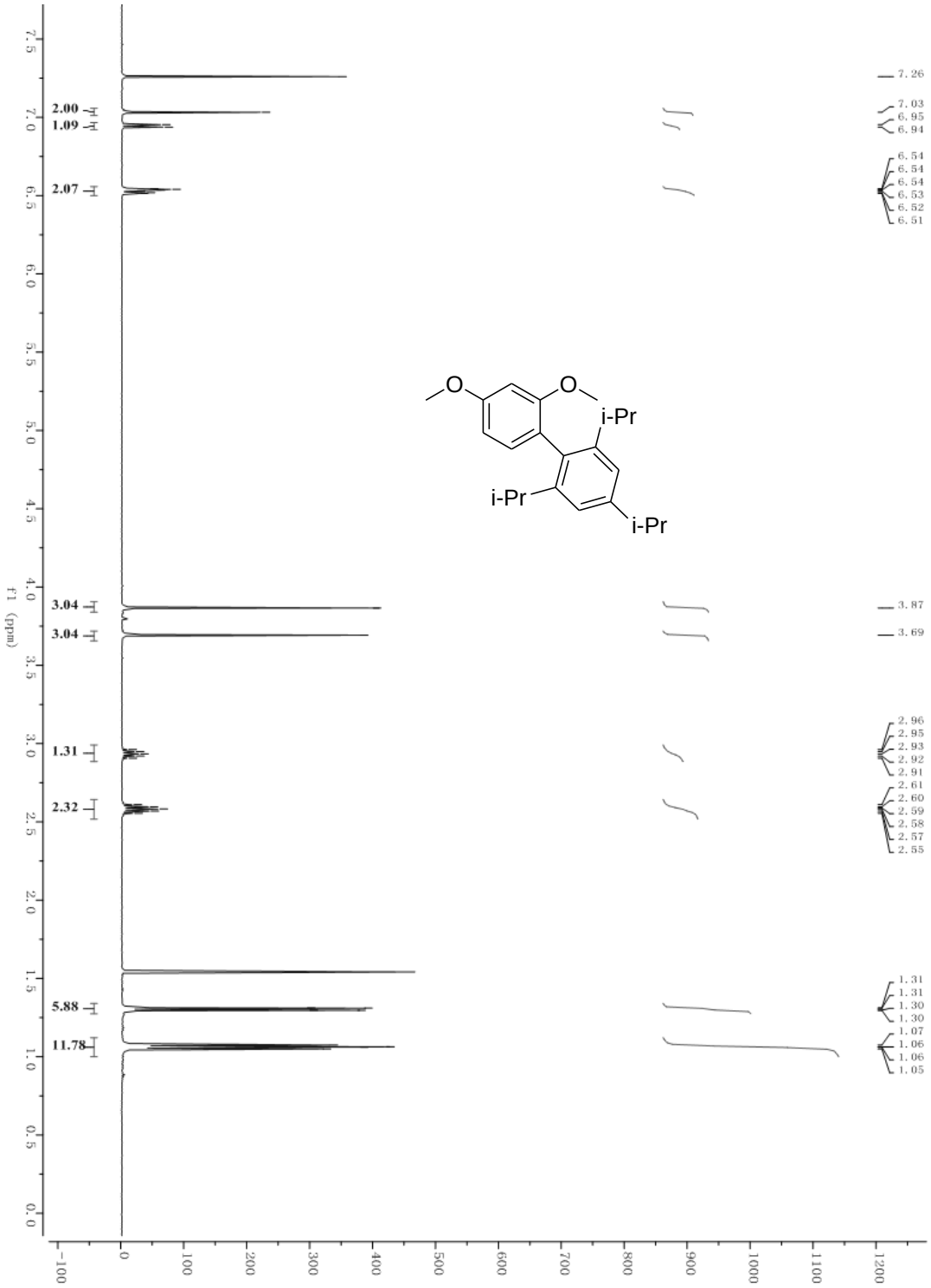
6.99
6.92
6.67
6.65
3.84
3.29
2.32
2.04
1.93
1.91
1.79
1.78
1.76
1.64
1.45
1.43
1.34
1.33
1.31
1.30
1.29
1.27
1.24
1.22
1.21
1.20
1.19
1.18
1.17
1.04
f1 (ppm)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O
i-Pr
i-Pr
i-Pr
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3.04
3.04
1.31
2.32
5.88
11.78
7.26
7.03
6.95
6.94
6.54
6.54
6.54
6.53
6.52
6.51
3.87
3.69
2.96
2.95
2.93
2.92
2.91
2.61
2.60
2.59
2.58
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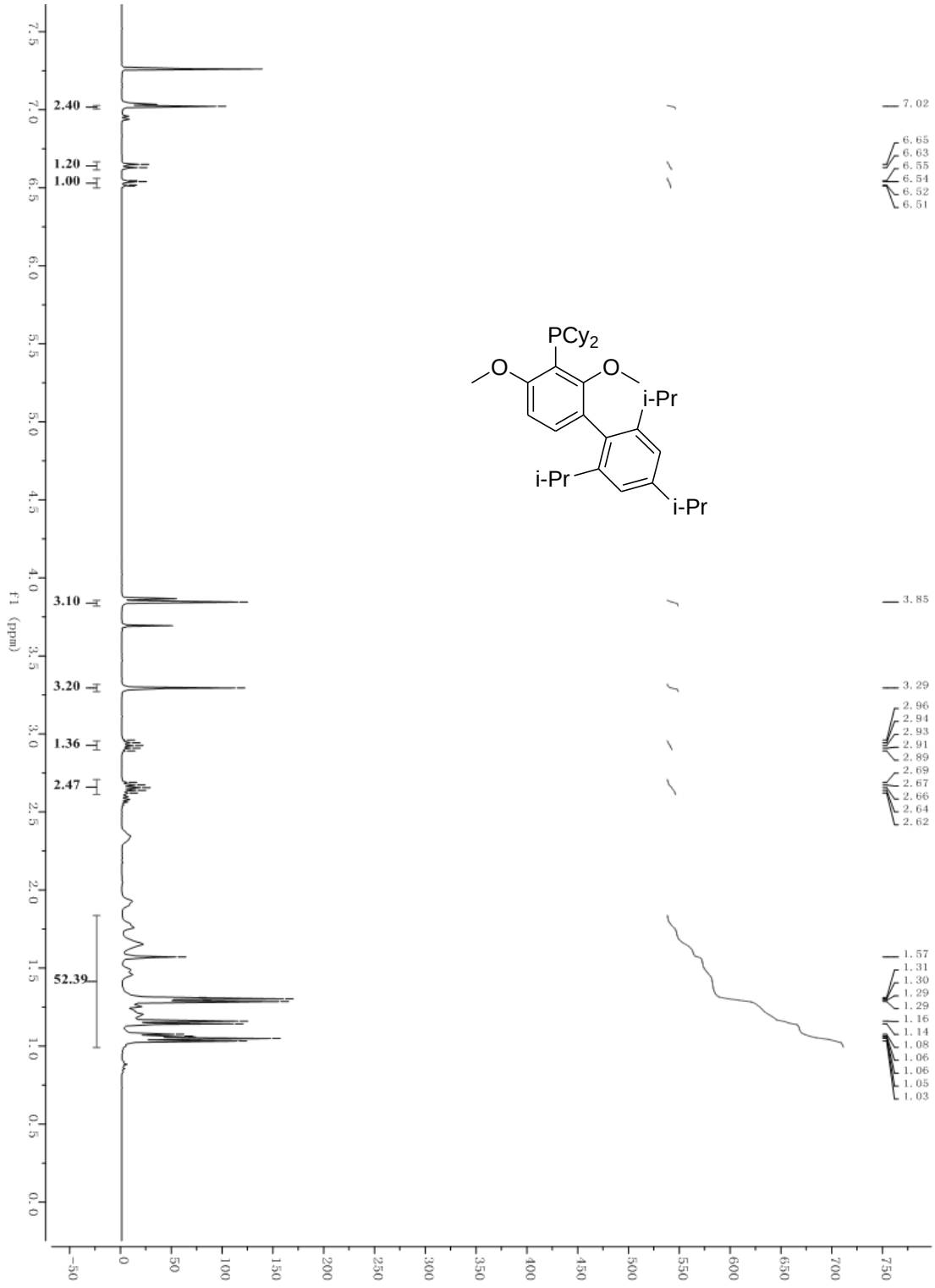
1.07
1.06
1.06
1.05
f1 (ppm)


PCy2
O
O
i-Pr
i-Pr
i-Pr
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52.39
7.02
6.65
6.63
6.55
6.54
6.52
6.51
3.85
3.29
2.96
2.94
2.93
2.91
2.89
2.69
2.67
2.66
2.64
2.62
1.57
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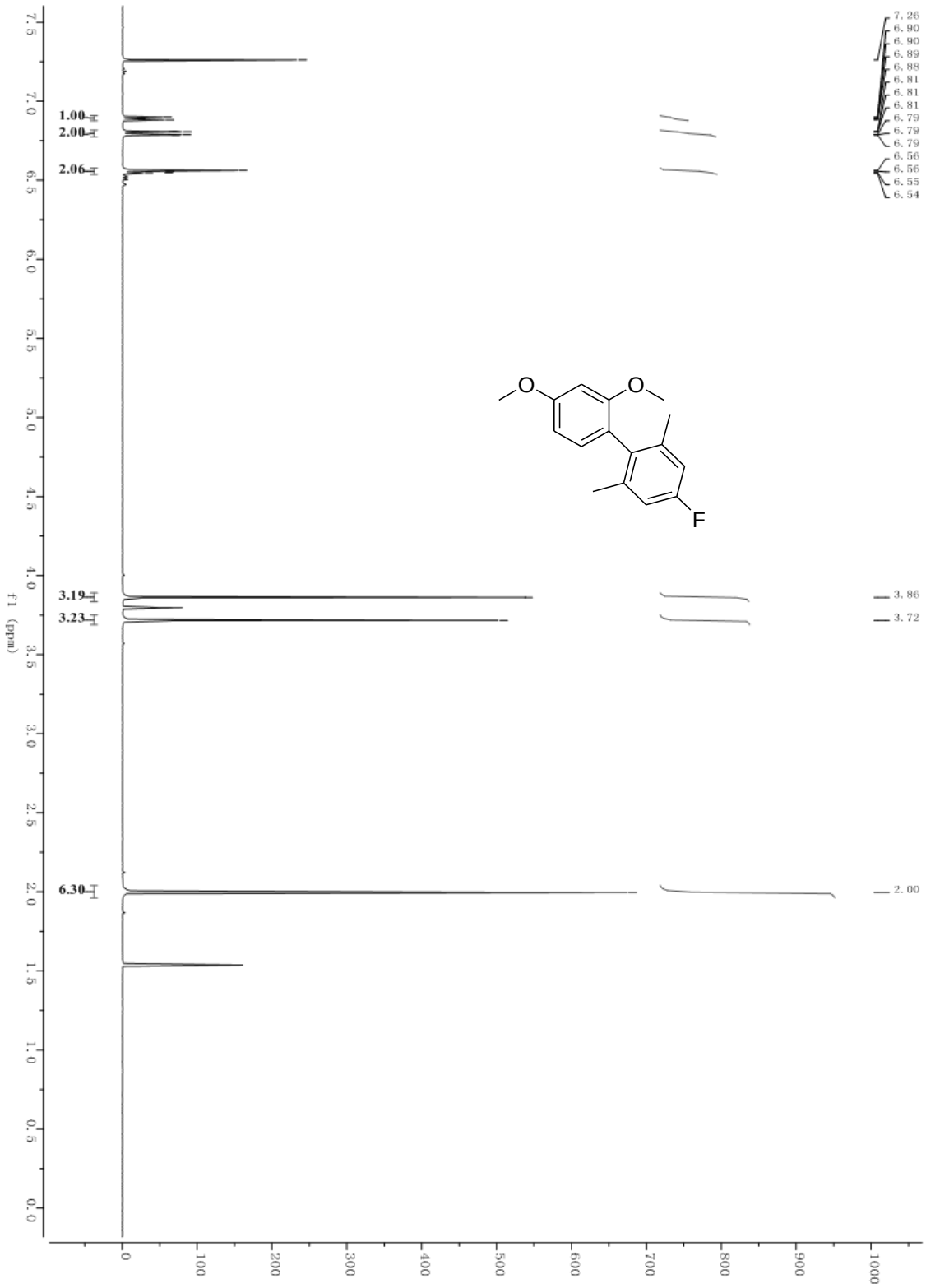
1.30
1.29
1.29
1.16
1.14
1.08
1.06
1.06
1.05
1.03
f1 (ppm)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6.55
6.54
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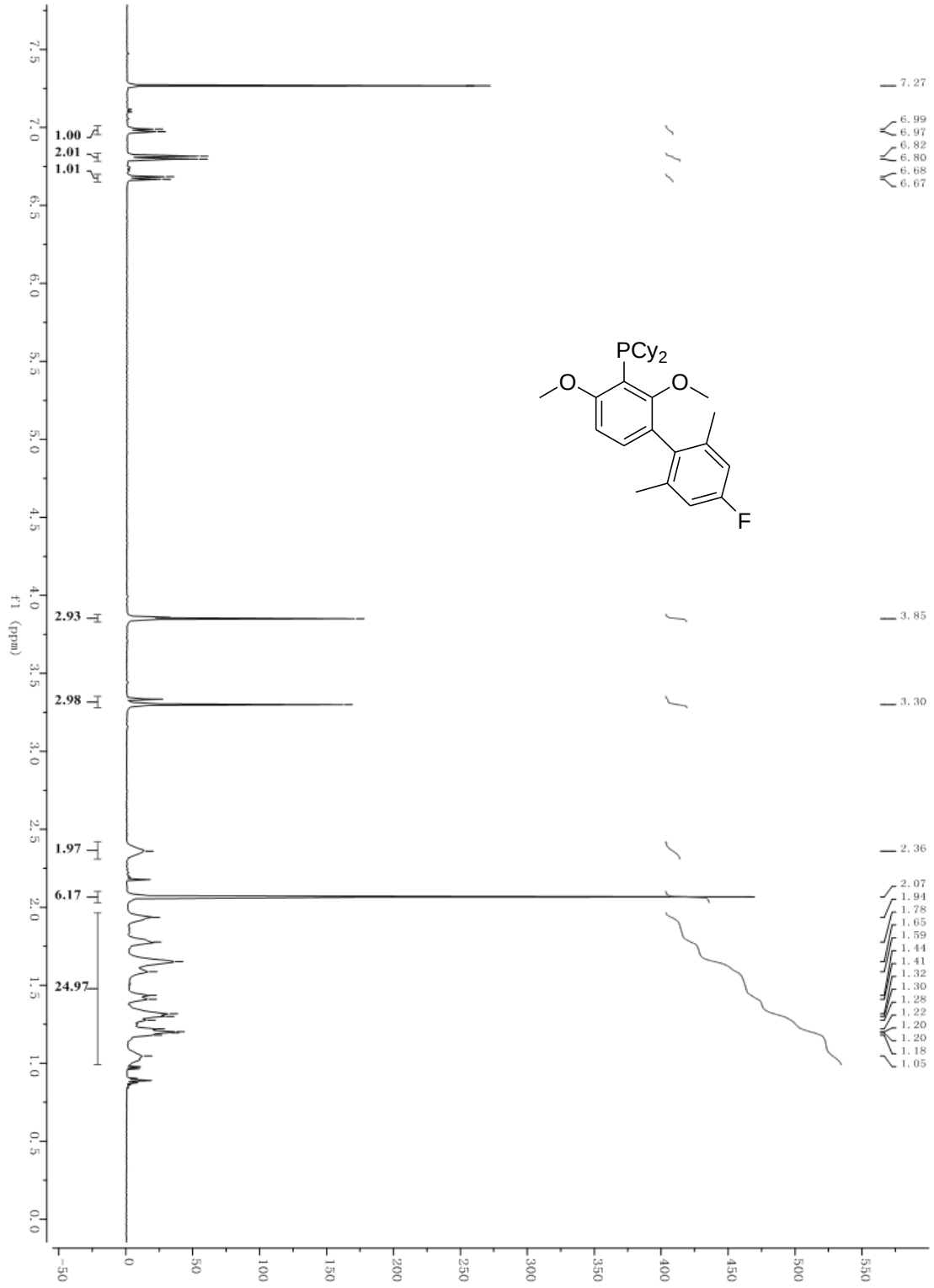
2.00
2.06
3.19
3.23
6.30
3.86
3.72
2.00
O
O
F
f1 (ppm)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O
F
f1 (ppm)
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1.01
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24.97
7.27
6.99
6.97
6.82
6.80
6.68
6.67
3.85
3.30
2.36
2.07
1.94
1.78
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1.28
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1.20
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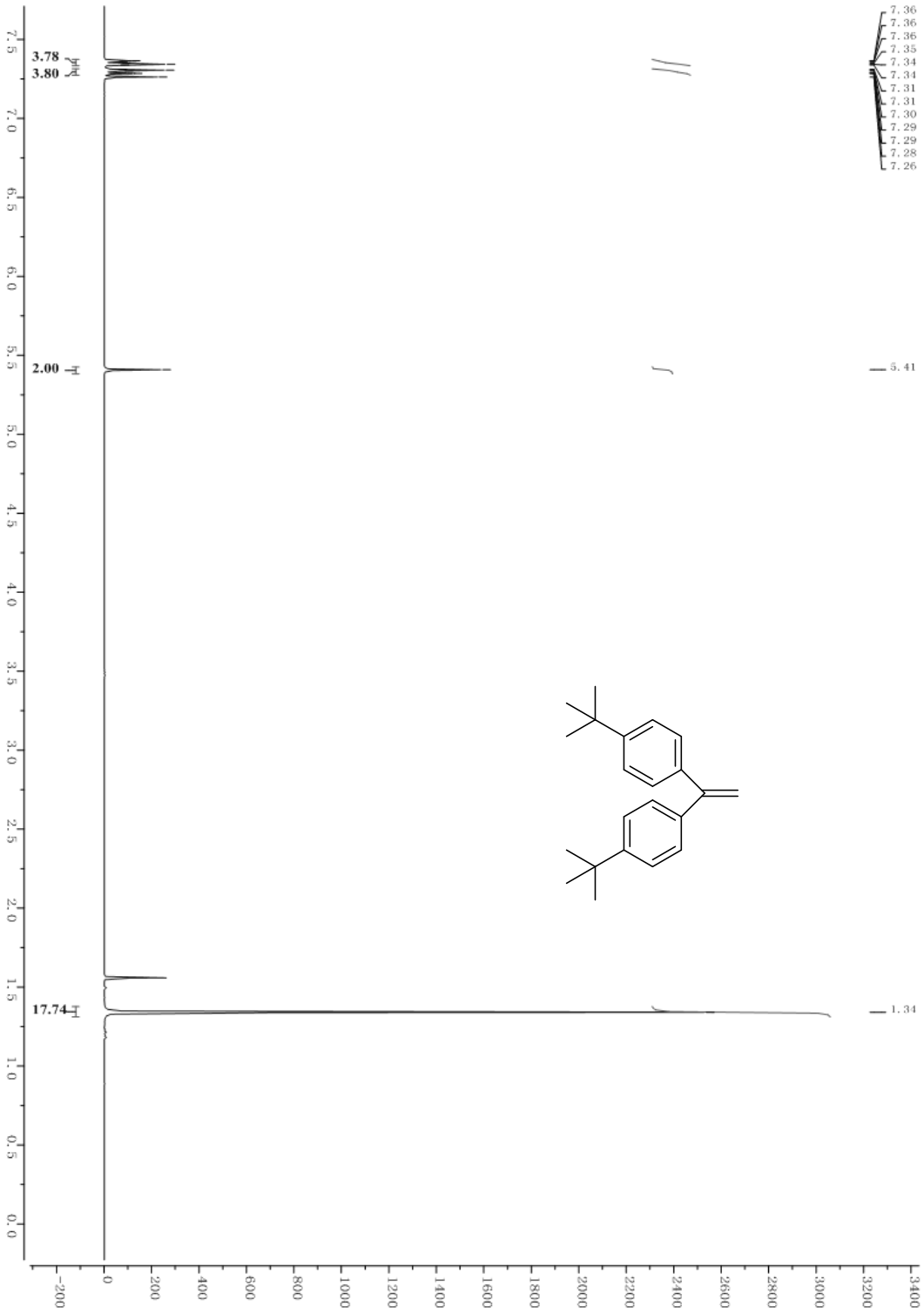
1.18
1.05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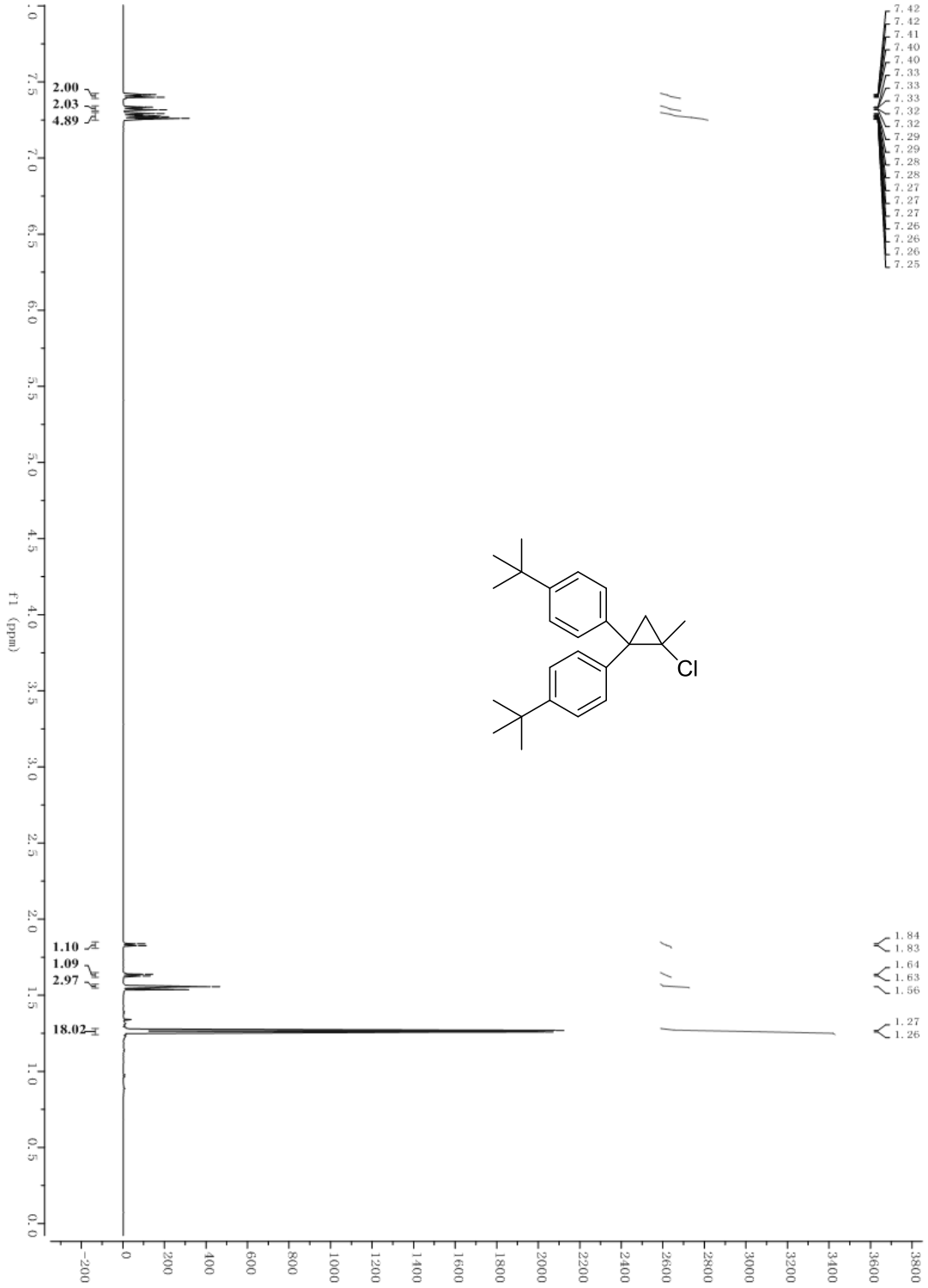
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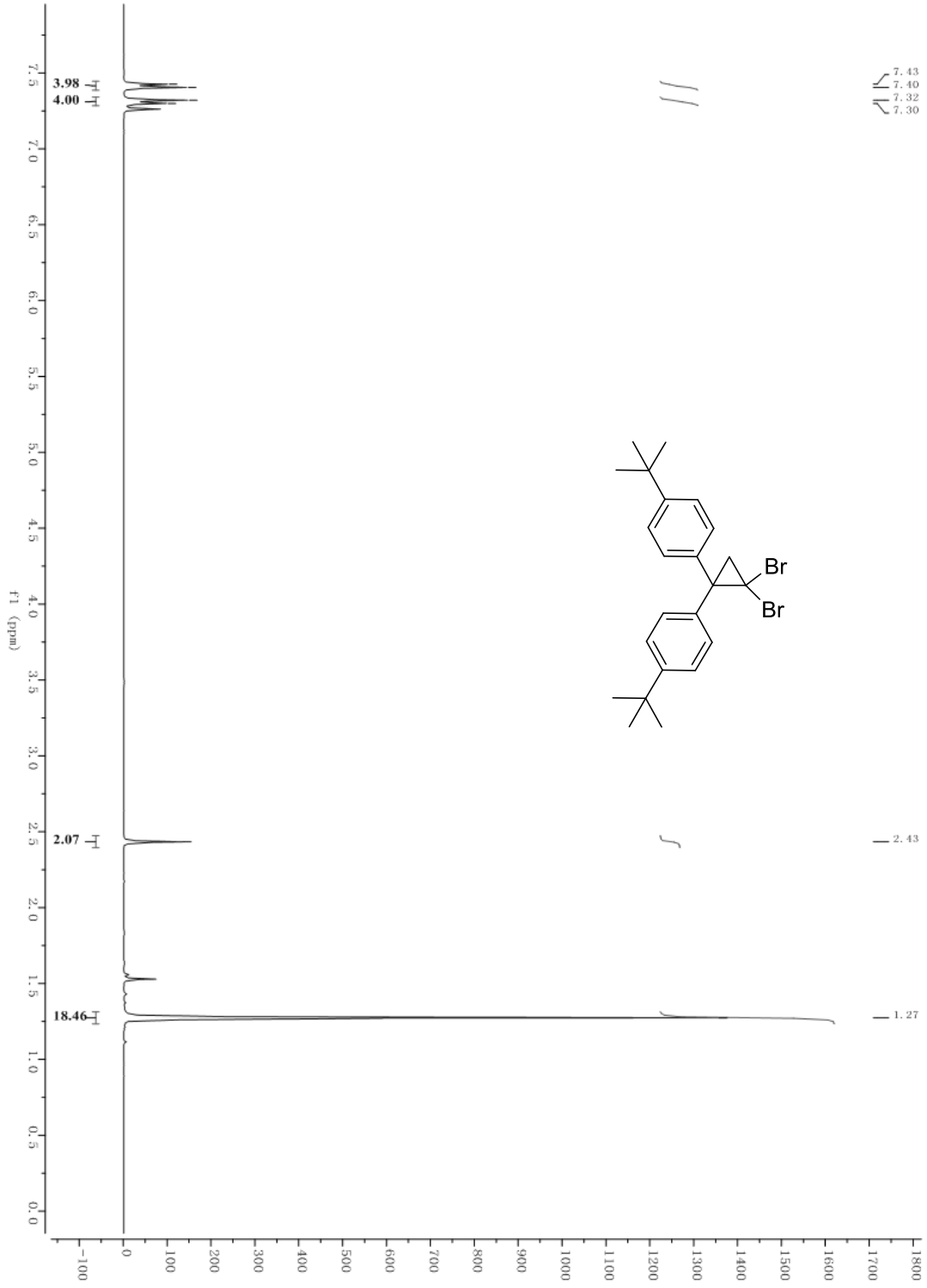
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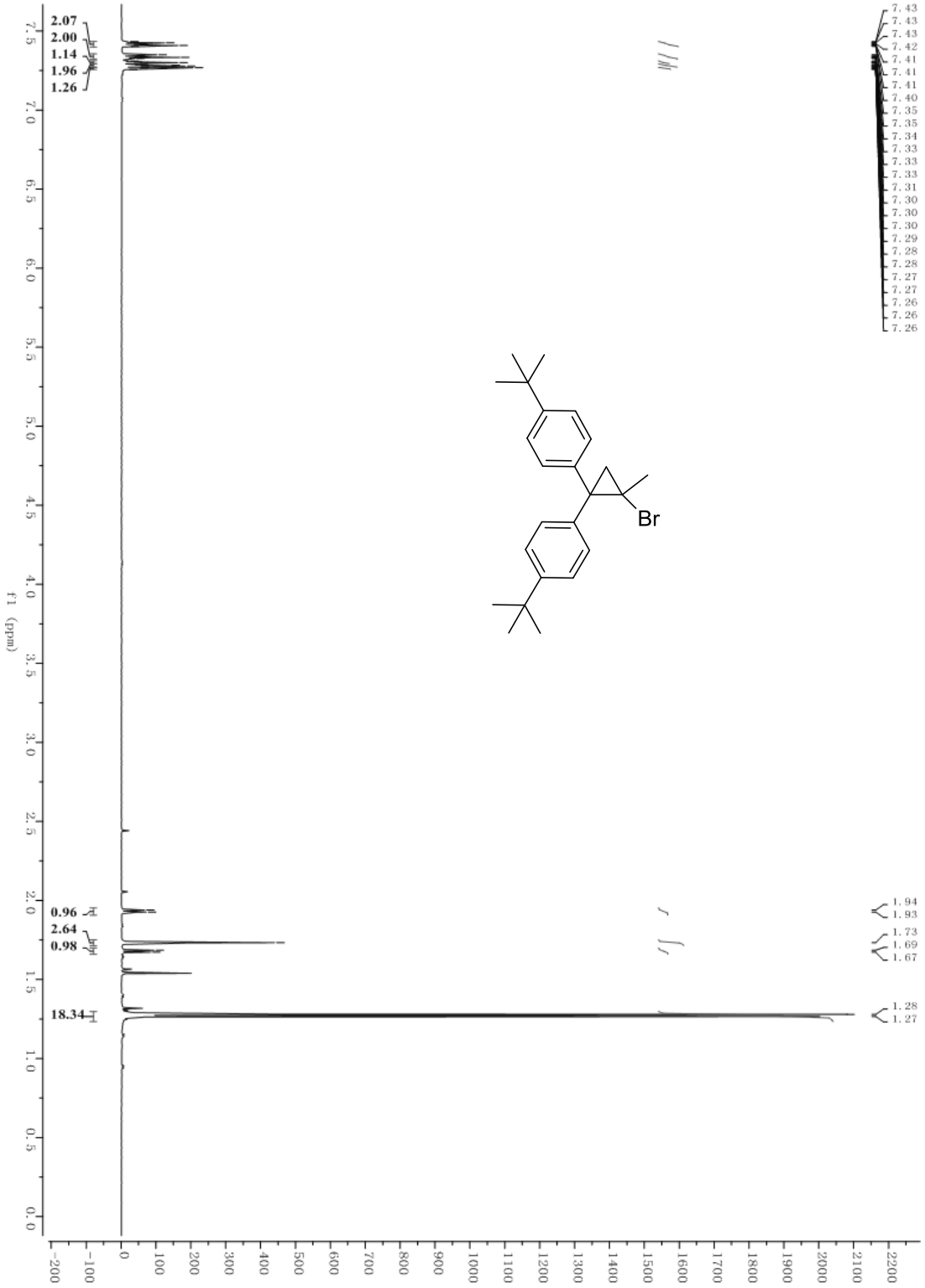
Br
f1 (ppm)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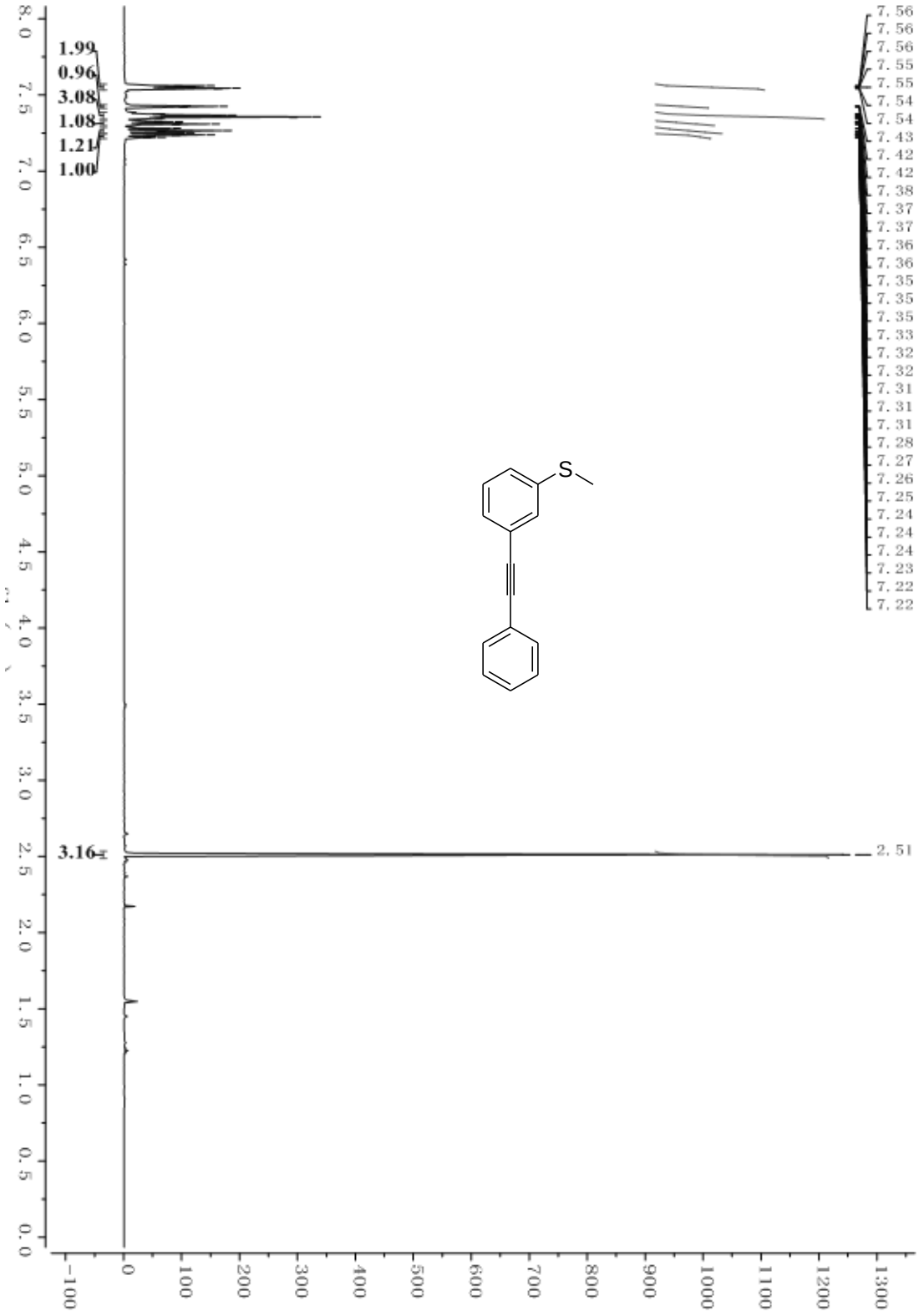
Br
f1 (ppm)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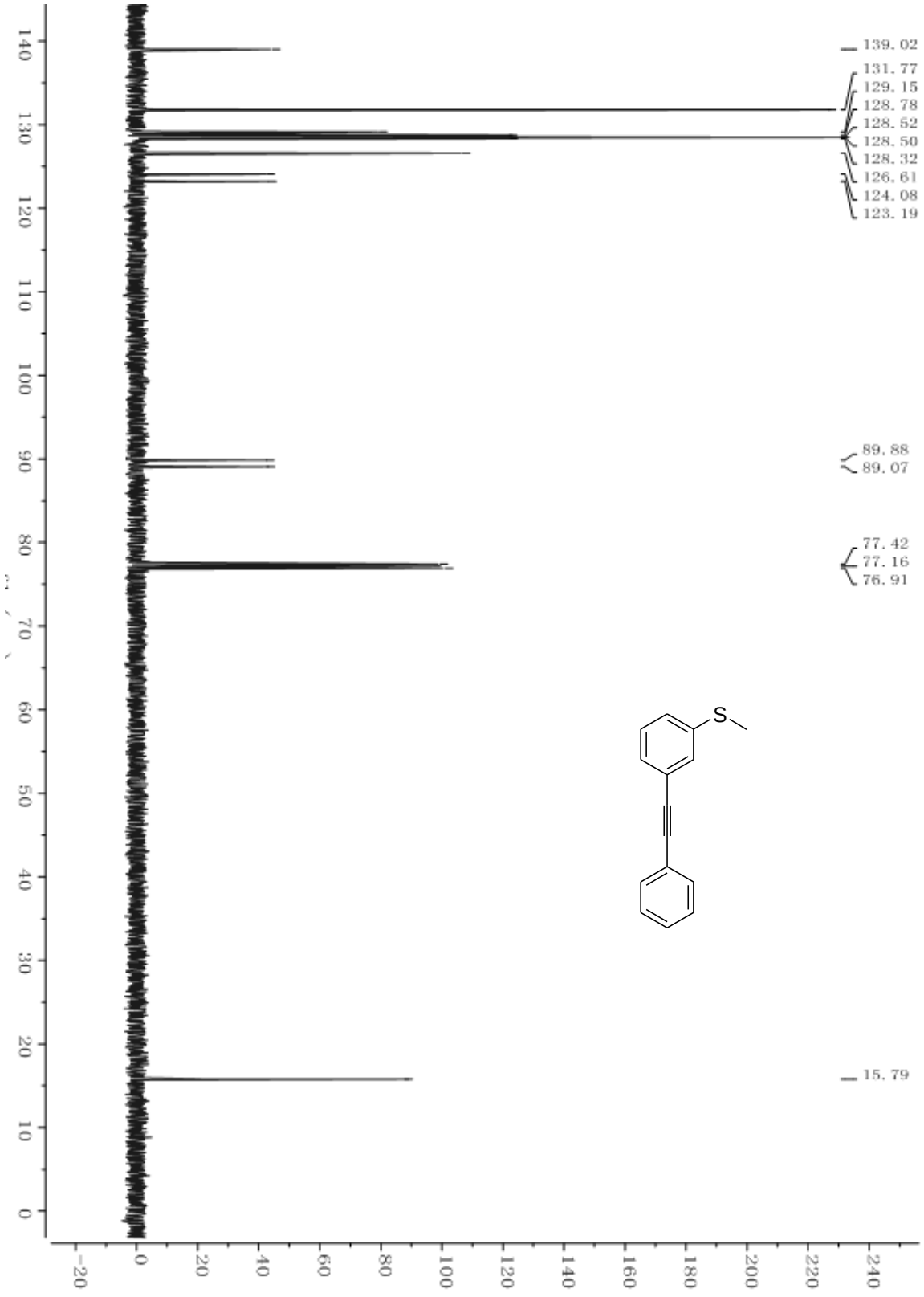
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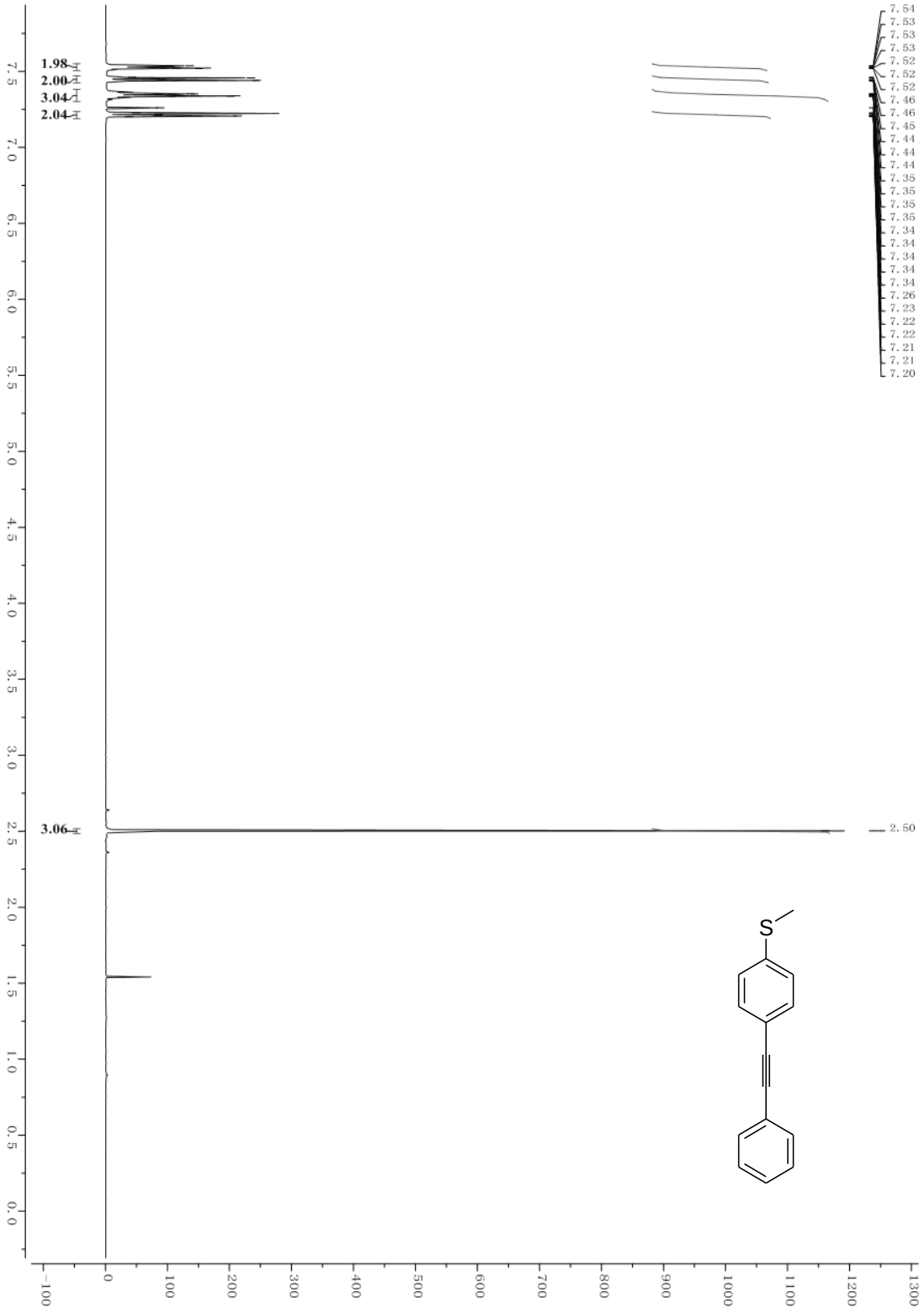
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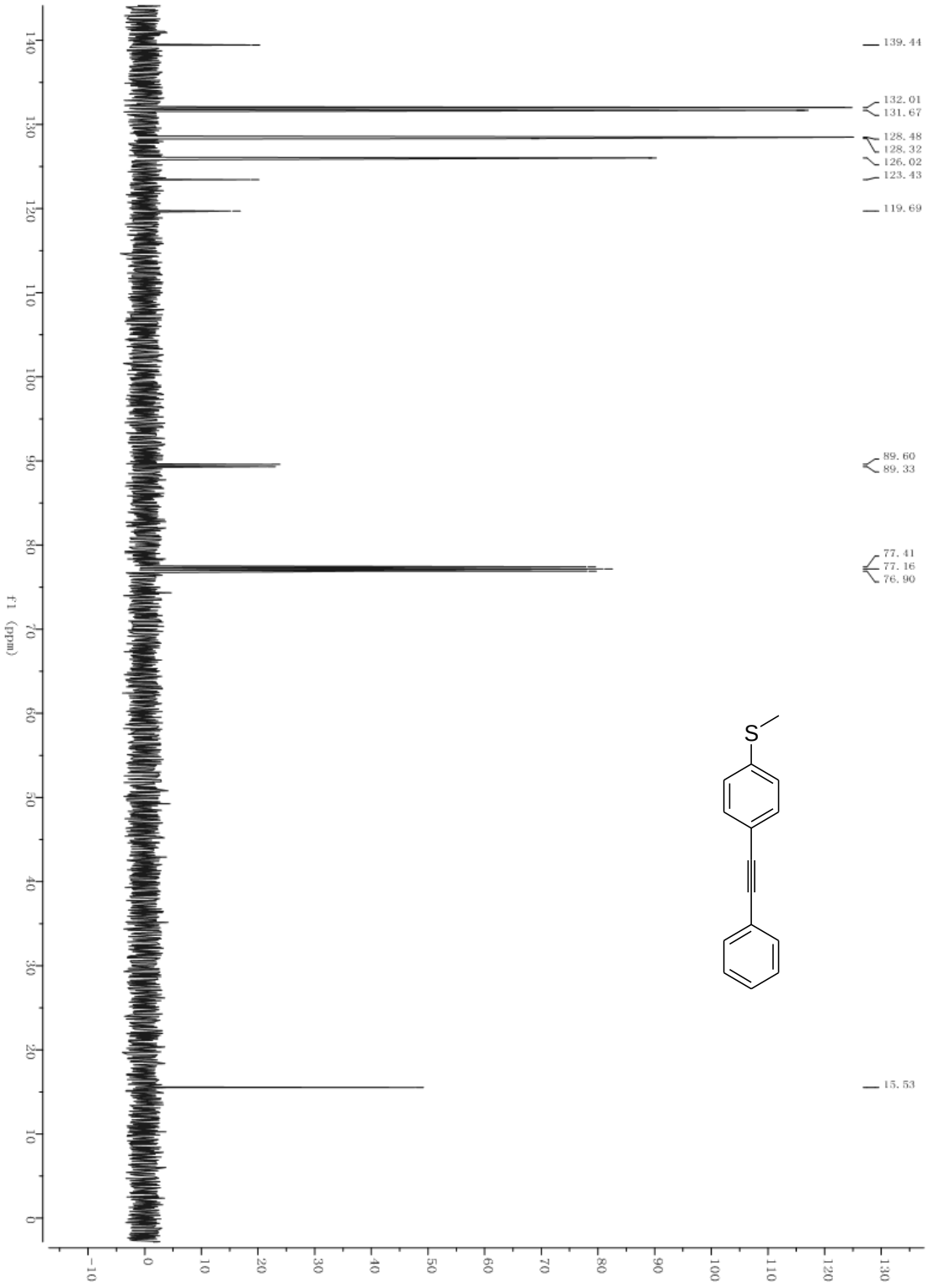
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76.90
15.53
S
f1 (ppm)


0.87
1.01
0.93
1.06
1.02
1.93
1.05
3.00
9.01
9.01
8.30
8.29
8.11
8.10
7.80
7.79
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7.78
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7.38
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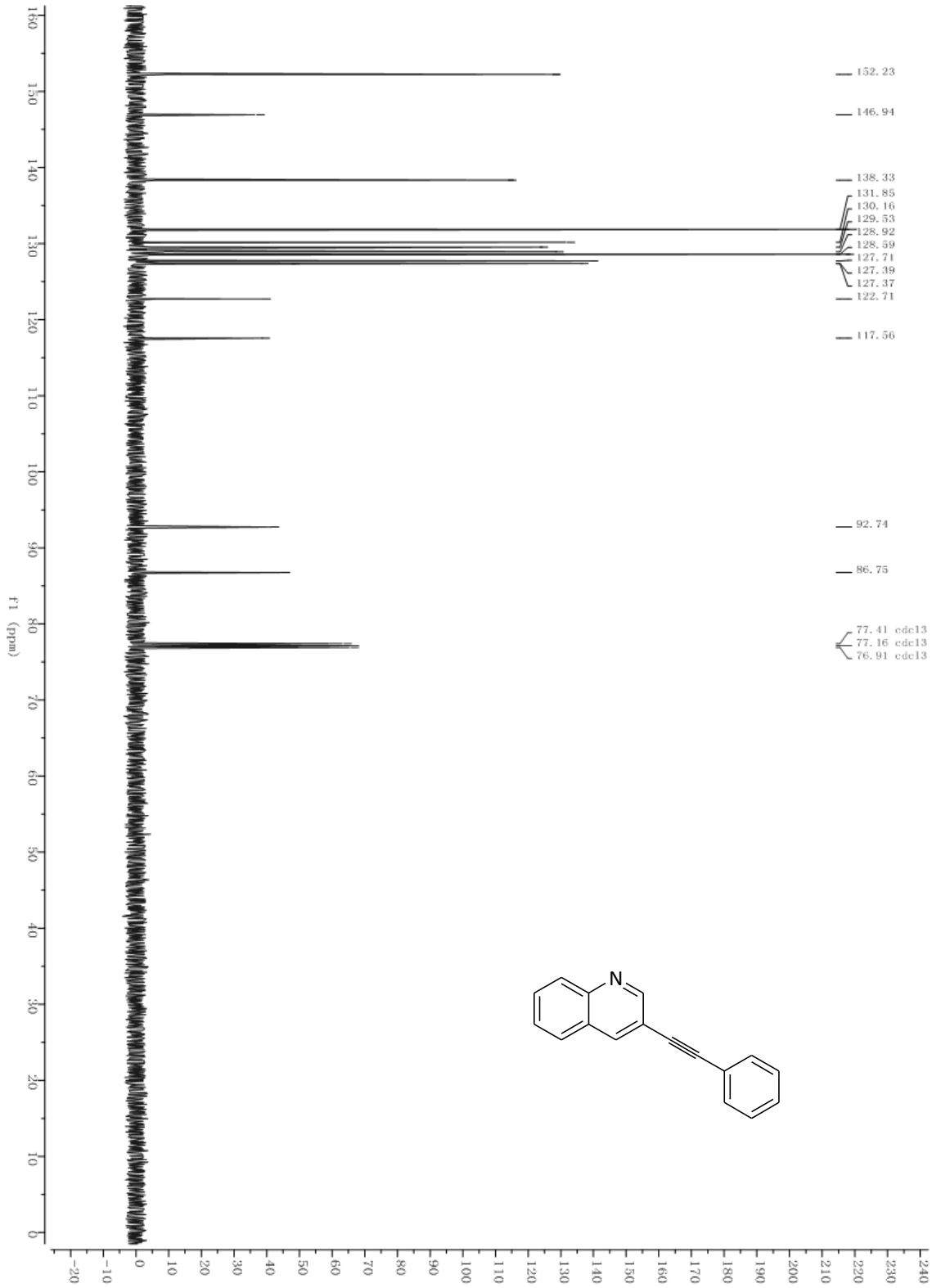
f1 (ppm)
N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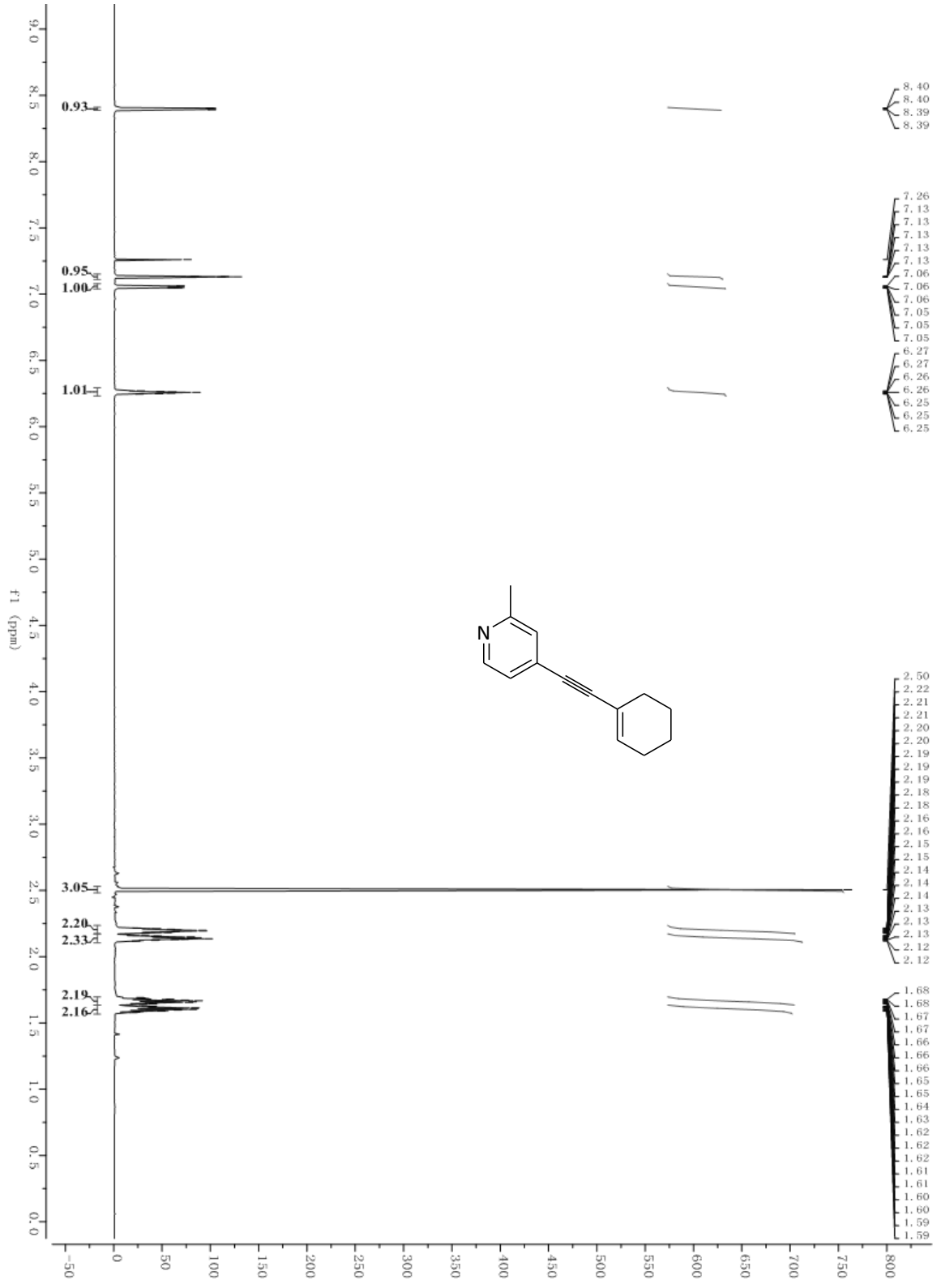
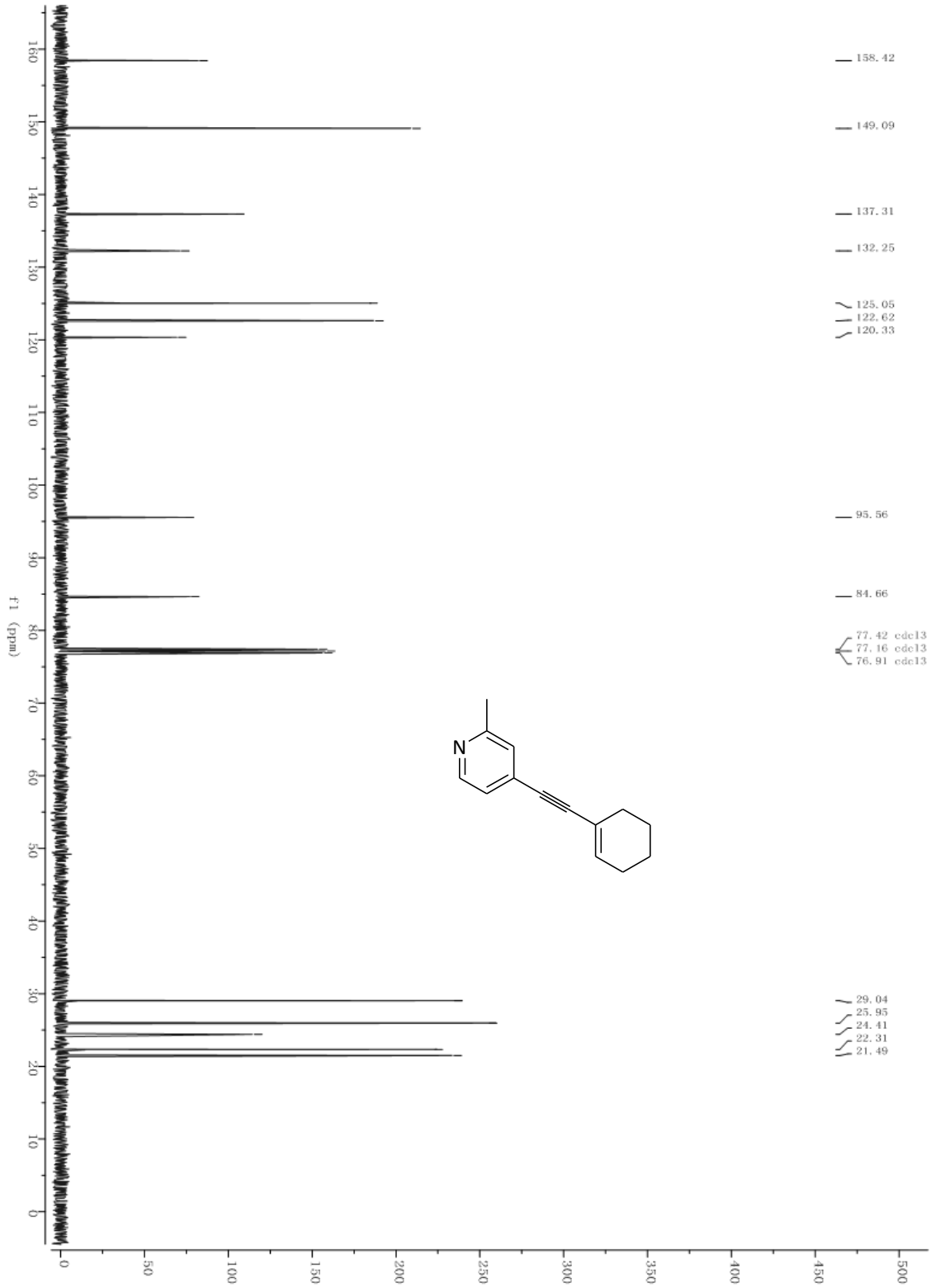
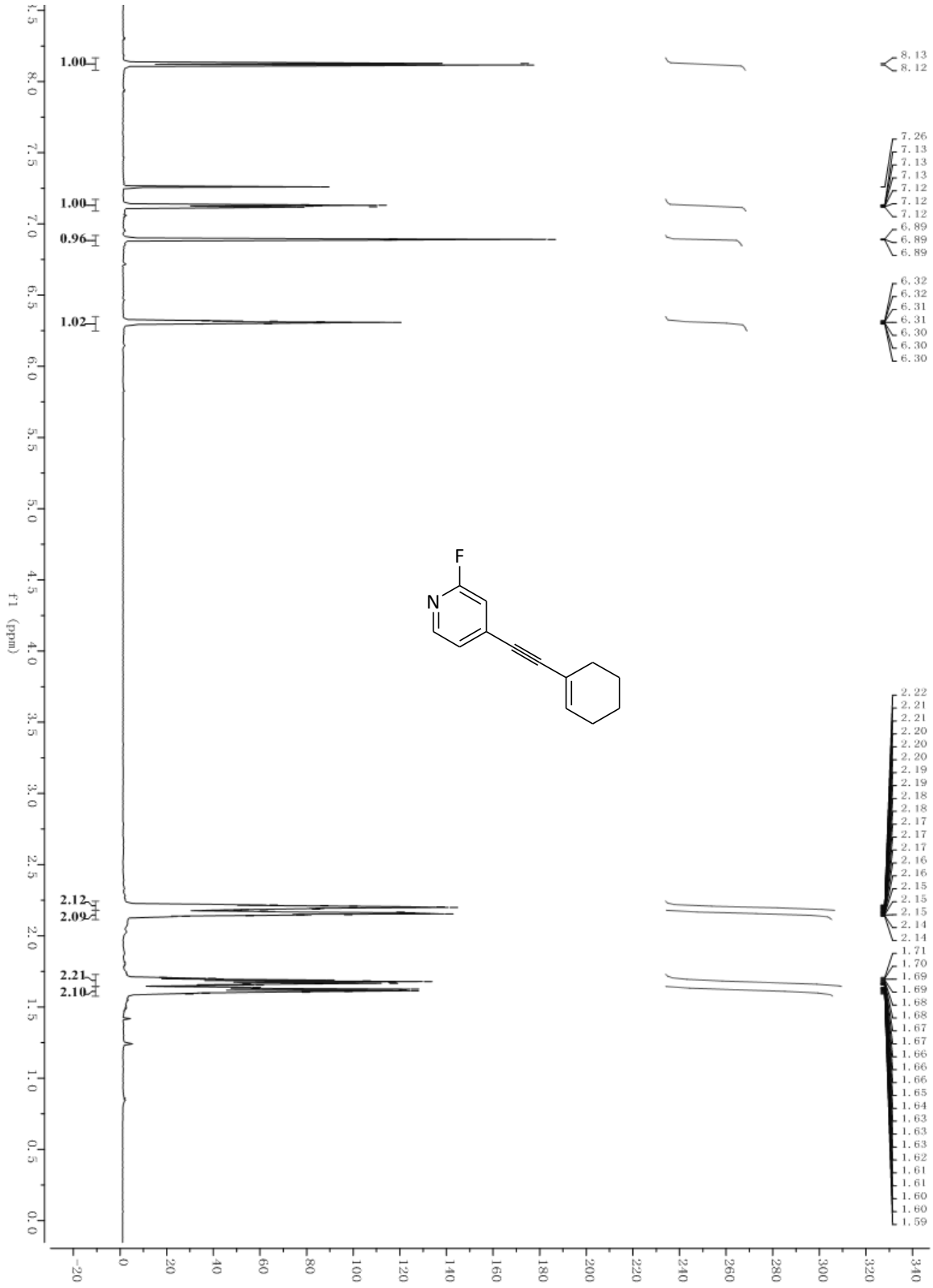
92.74
86.75
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
N
f1 (ppm)


0.93
0.95
1.00
1.01
3.05
2.20
2.33
2.19
2.16
N
f1 (ppm)


158.42
149.09
137.31
132.25
125.05
122.62
120.33
95.56
84.66
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
29.04
25.95
24.41
22.31
21.49
N
f1 (ppm)


F
N
1.00
1.00
0.96
1.02
2.12
2.09
2.21
2.10
8.13
8.12
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7.13
7.13
7.13
7.12
7.12
7.12
6.89
6.89
6.89
6.32
6.32
6.31
6.31
6.30
6.30
6.30
2.22
2.21
2.21
2.20
2.20
2.20
2.19
2.19
2.18
2.18
2.17
2.17
2.17
2.16
2.16
2.15
2.15
2.15
2.14
2.14
1.71
1.70
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.66
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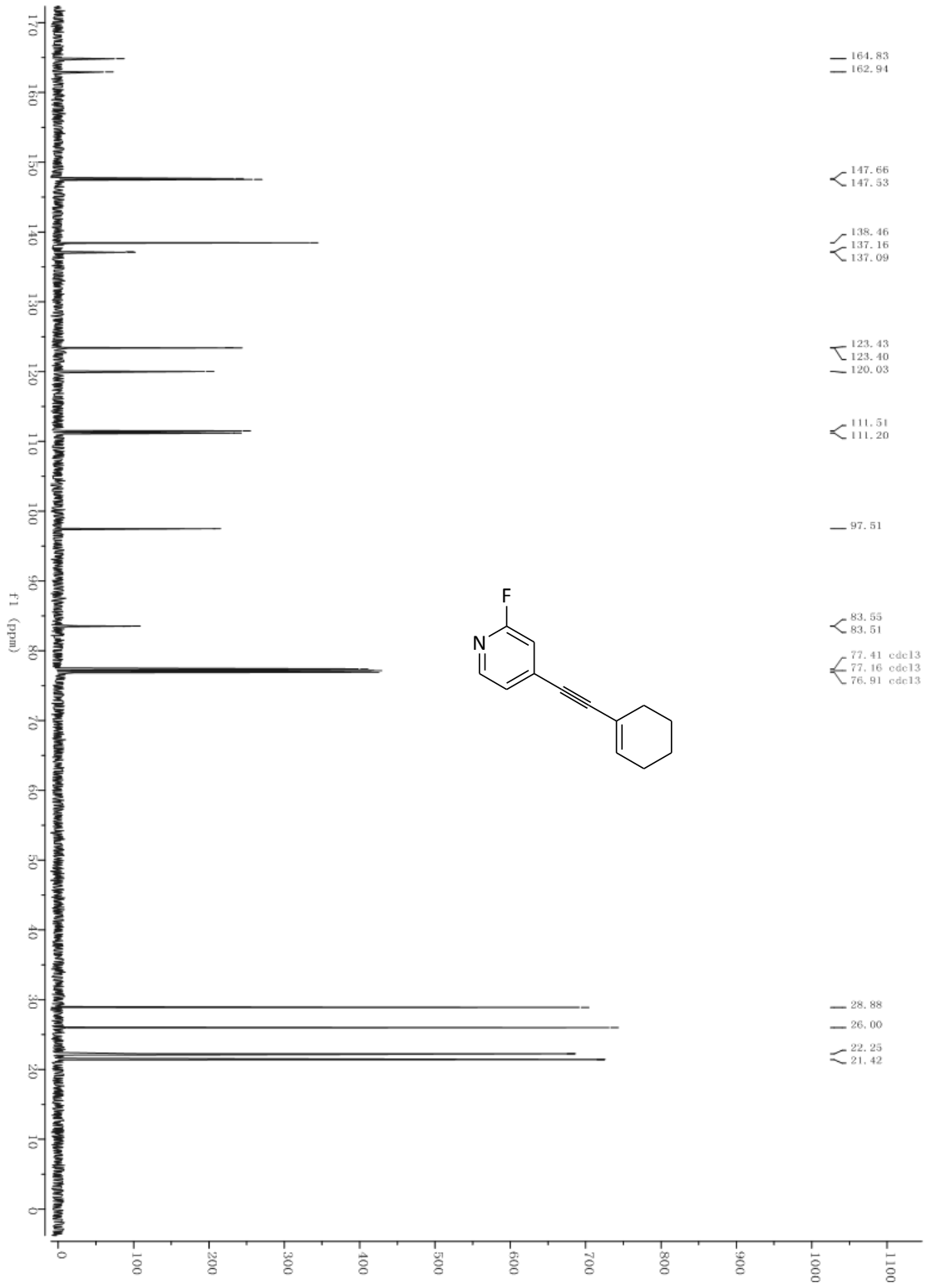
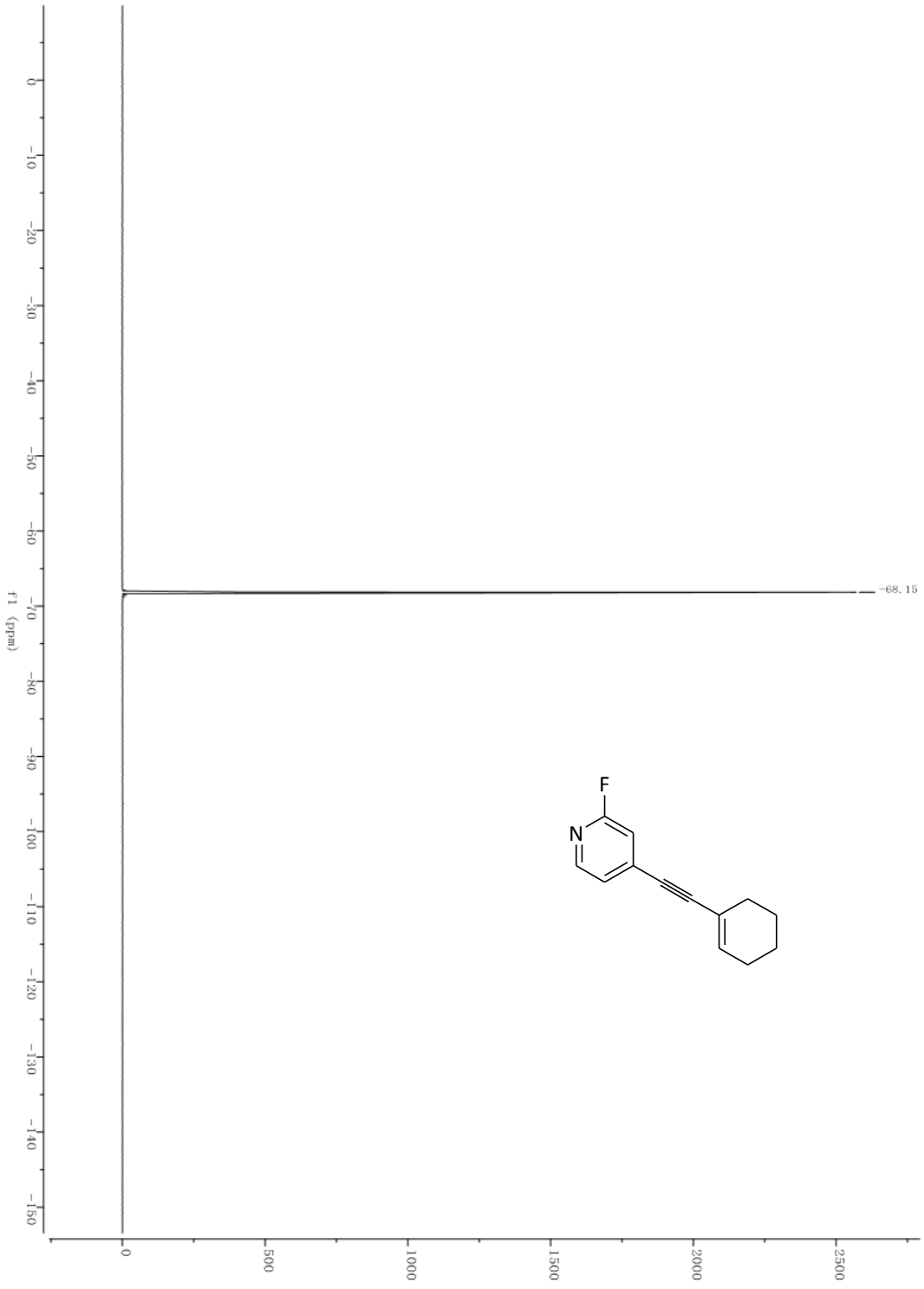
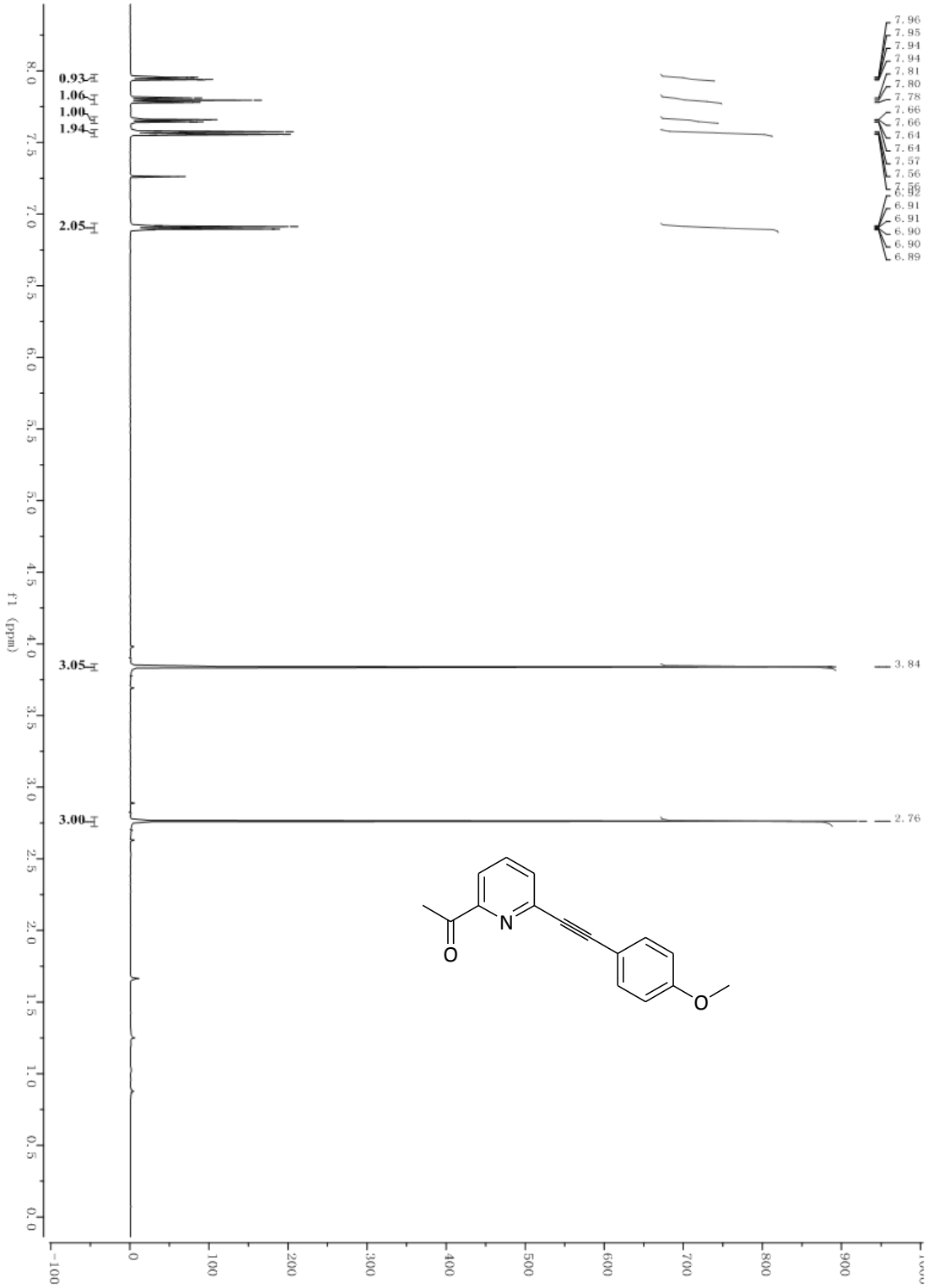
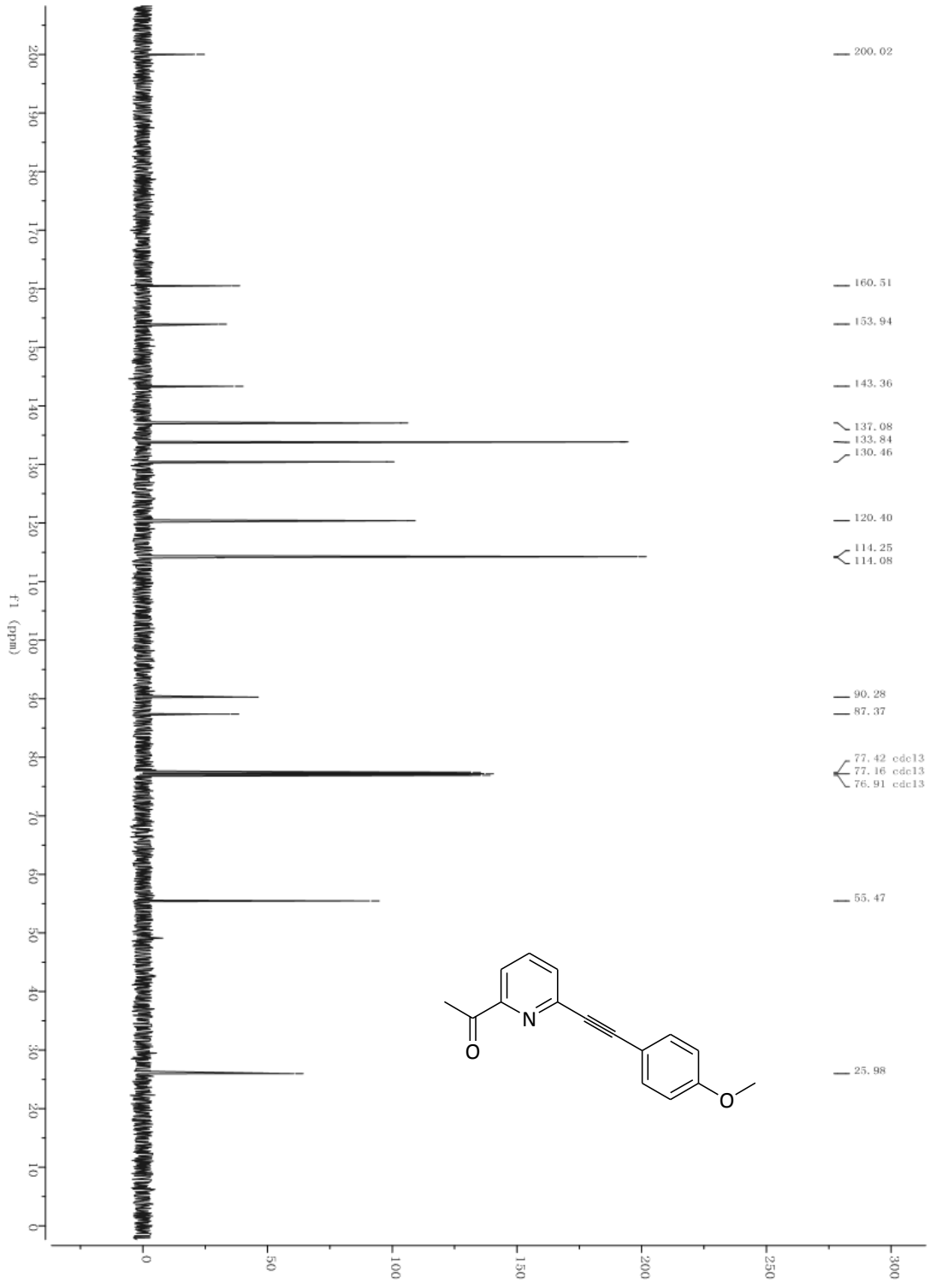
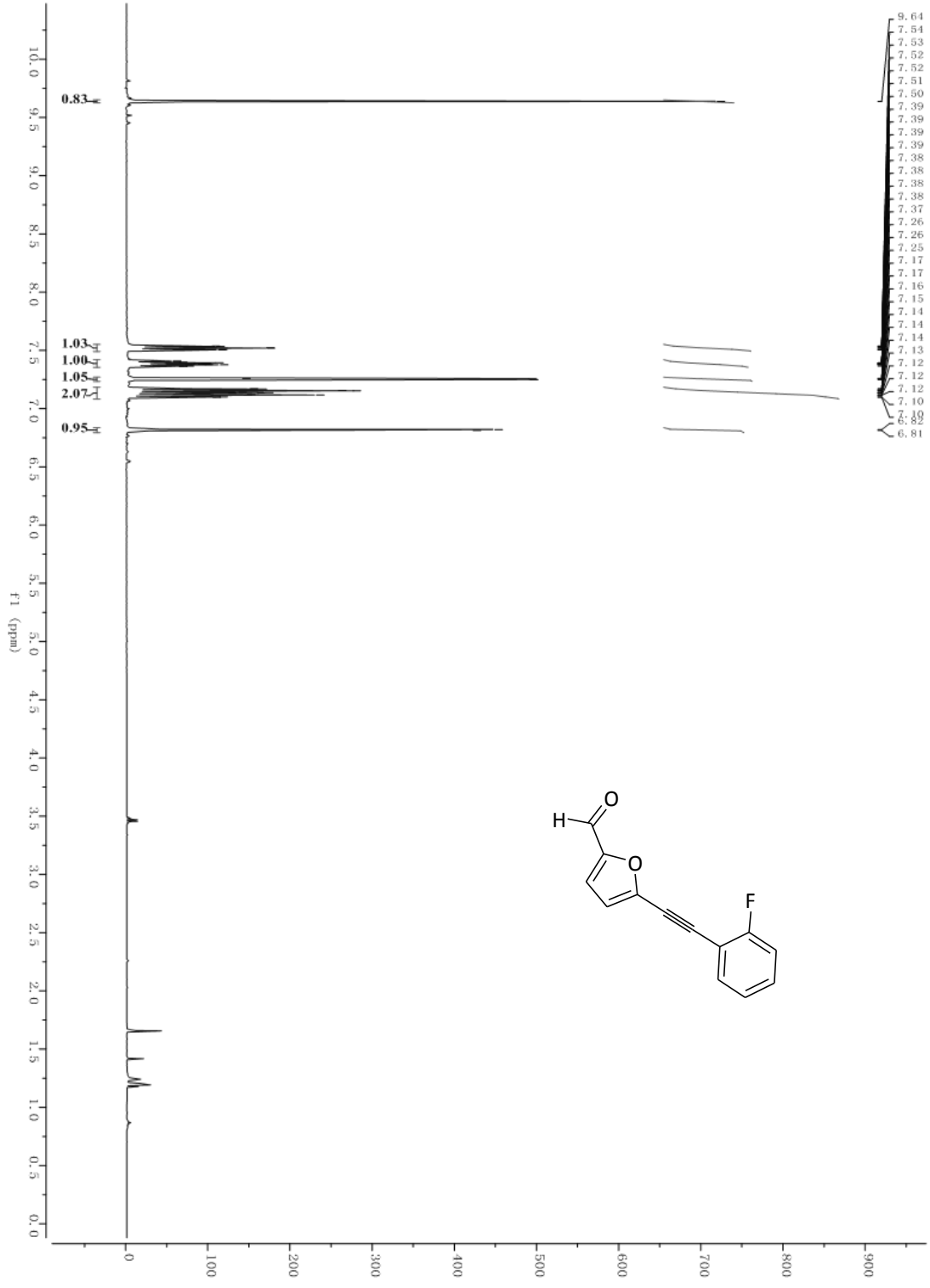
1.61
1.61
1.60
1.60
1.59
f1 (ppm)

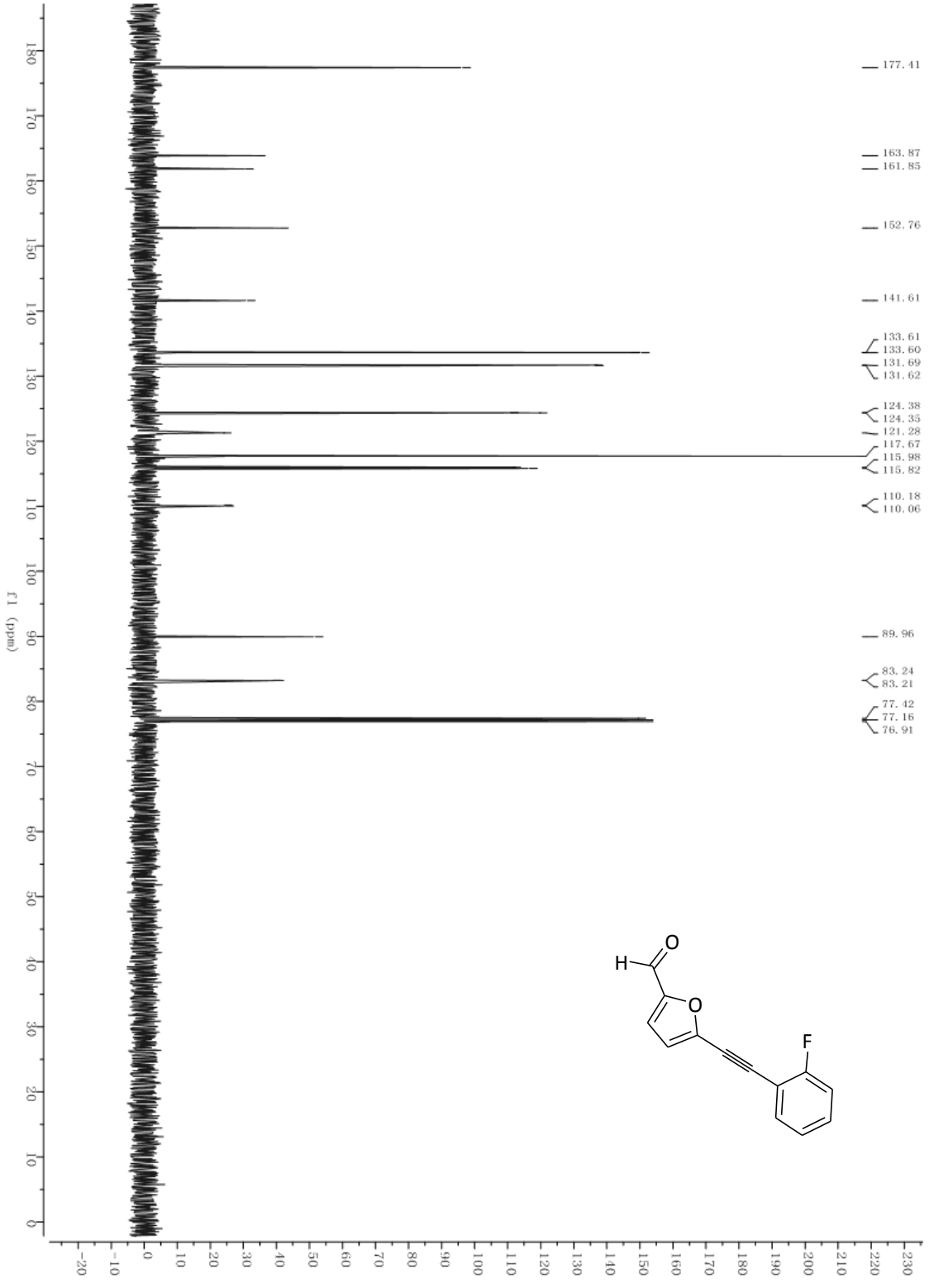

164.83
162.94
147.66
147.53
138.46
137.16
137.09
123.43
123.40
120.03
111.51
111.20
97.51
83.55
83.51
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
28.88
26.00
22.25
21.42
F
N
f1 (ppm)

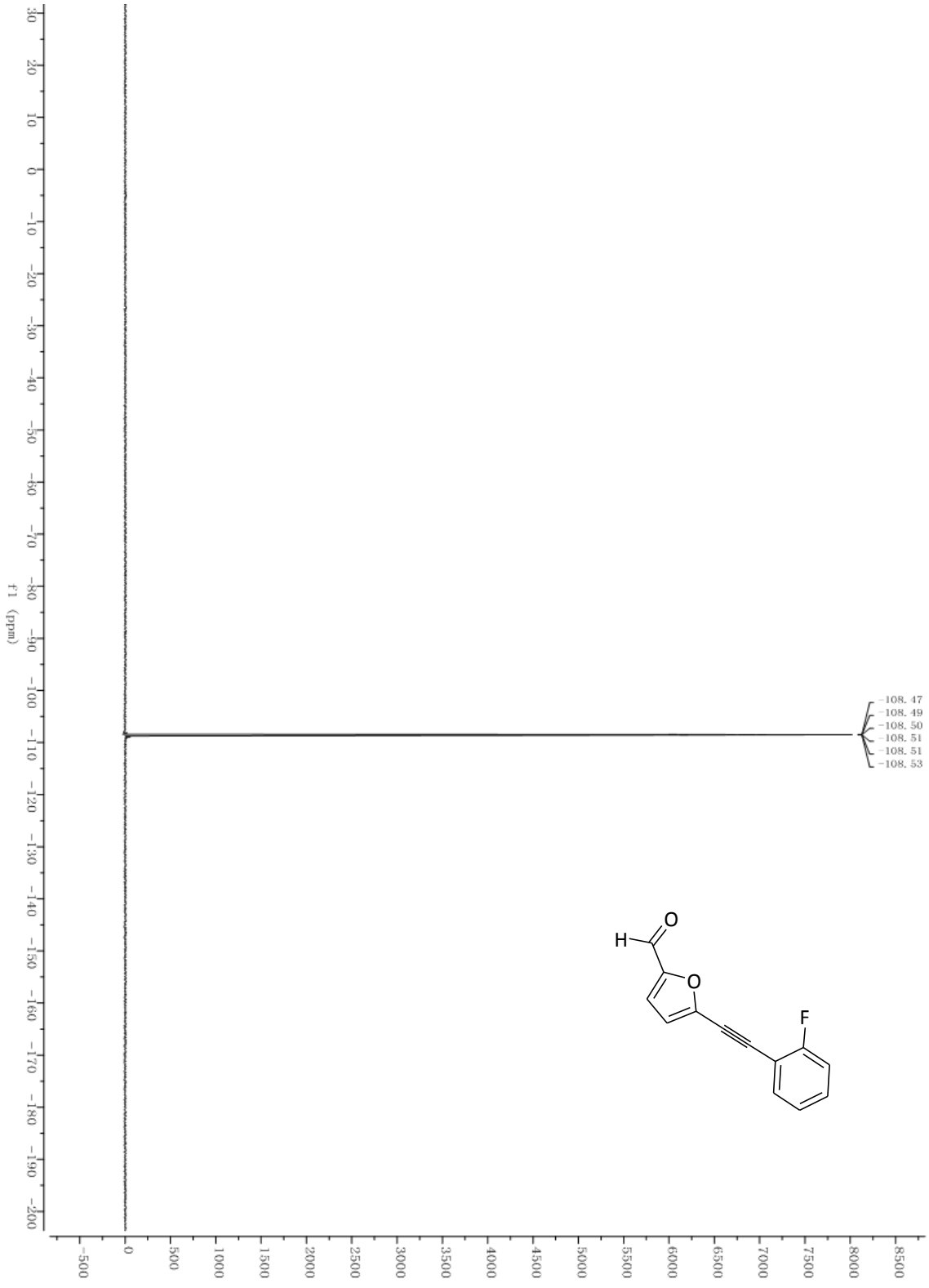

-68.15
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
0
500
1000
1500
2000
2500
F
N

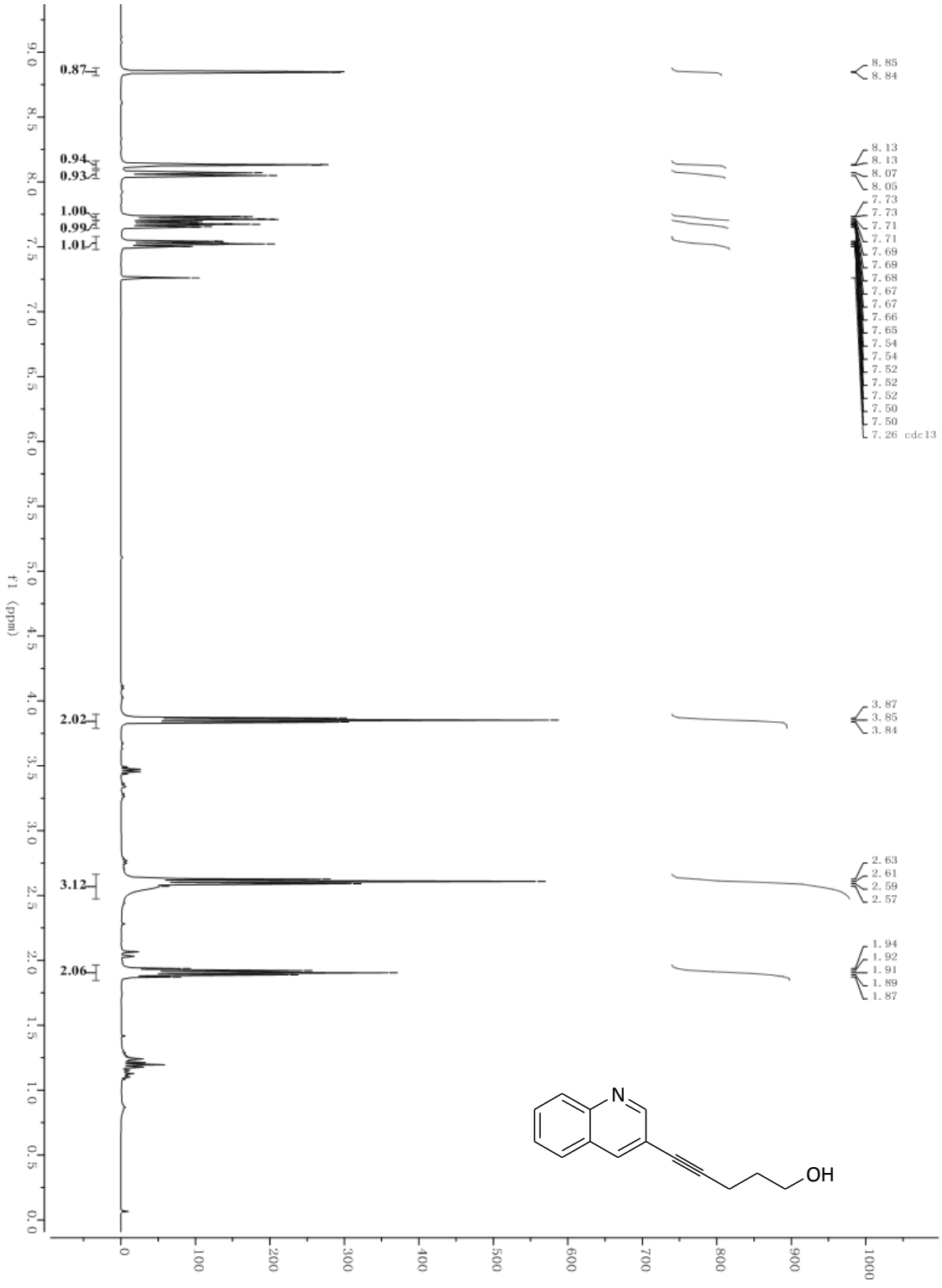

7.96
7.95
7.94
7.94
7.81
7.80
7.78
7.66
7.66
7.64
7.64
7.57
7.56
6.91
6.91
6.90
6.90
6.89
0.93
1.06
1.00
1.94
2.05
3.05
3.00
3.84
2.76
N
O
O
f1 (ppm)

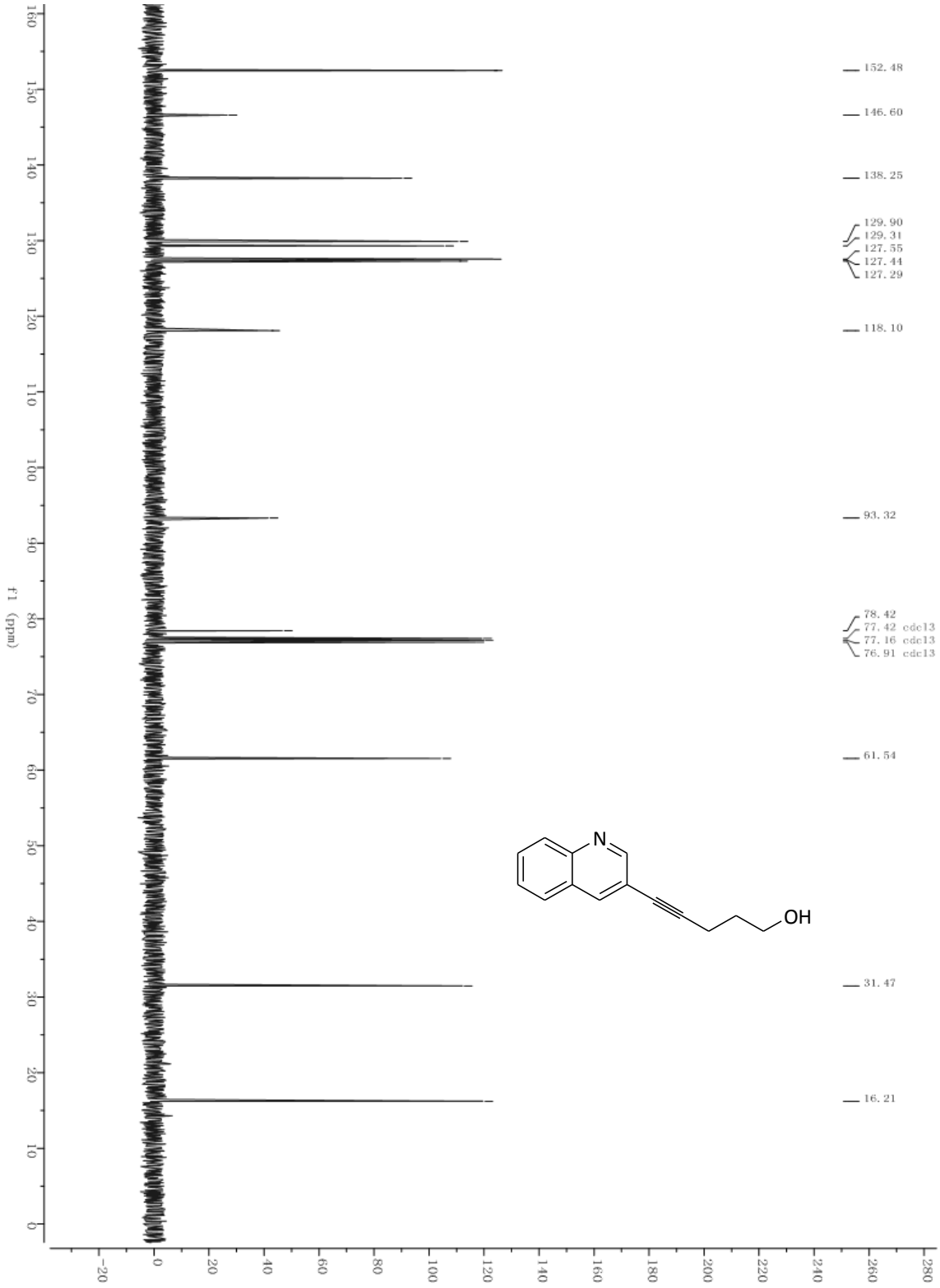

200.02
160.51
153.94
143.36
137.08
133.84
130.46
120.40
114.25
114.08
90.28
87.37
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
55.47
25.98
f1 (ppm)
N
O
O

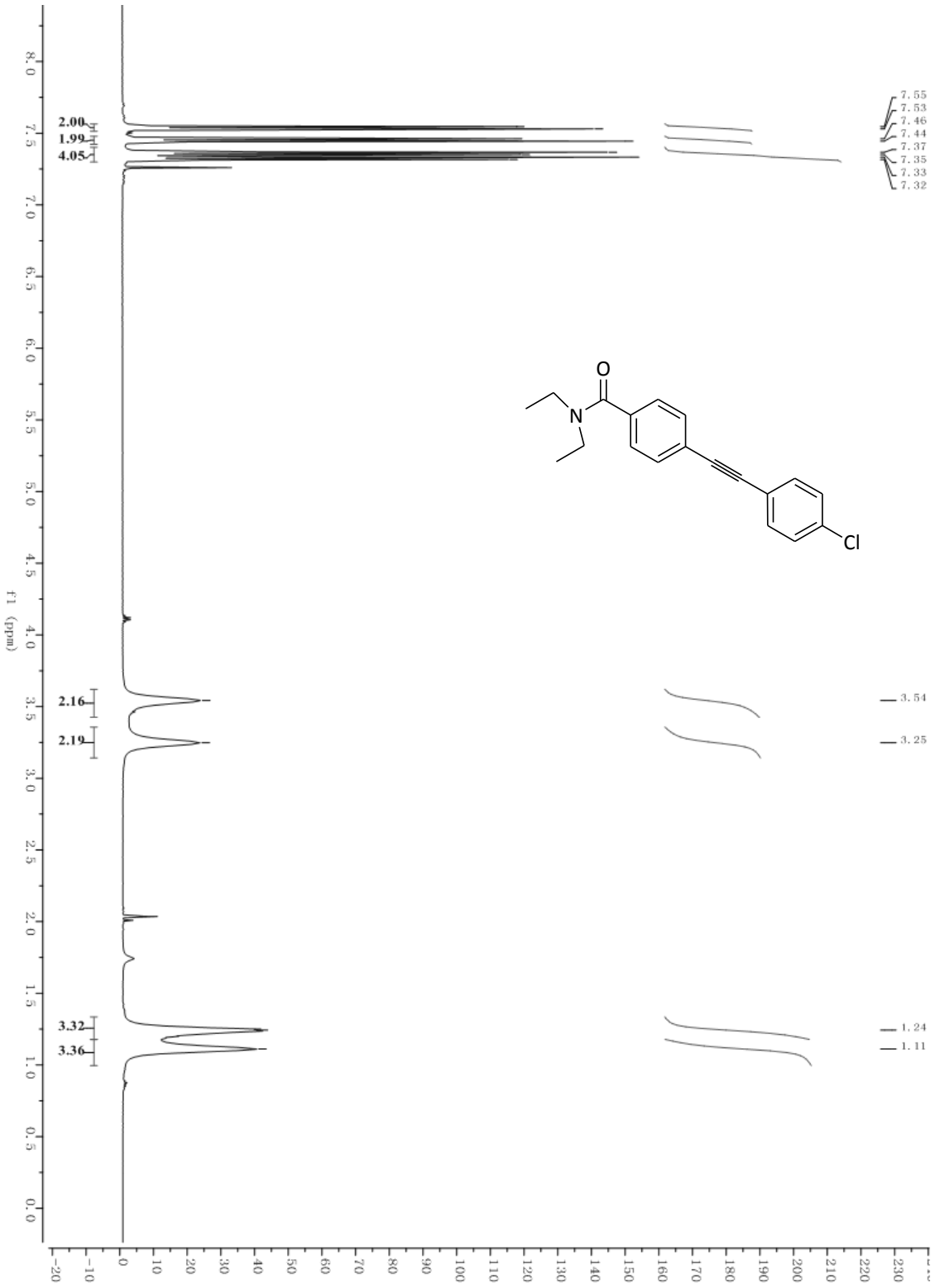

9.64
7.54
7.53
7.52
7.52
7.51
7.50
7.39
7.39
7.39
7.39
7.38
7.38
7.38
7.38
7.37
7.26
7.26
7.25
7.17
7.17
7.16
7.15
7.14
7.14
7.14
7.13
7.12
7.12
7.12
7.10
6.82
6.81
0.83
1.03
1.00
1.05
2.07
0.95
f1 (ppm)
O
H
O
F

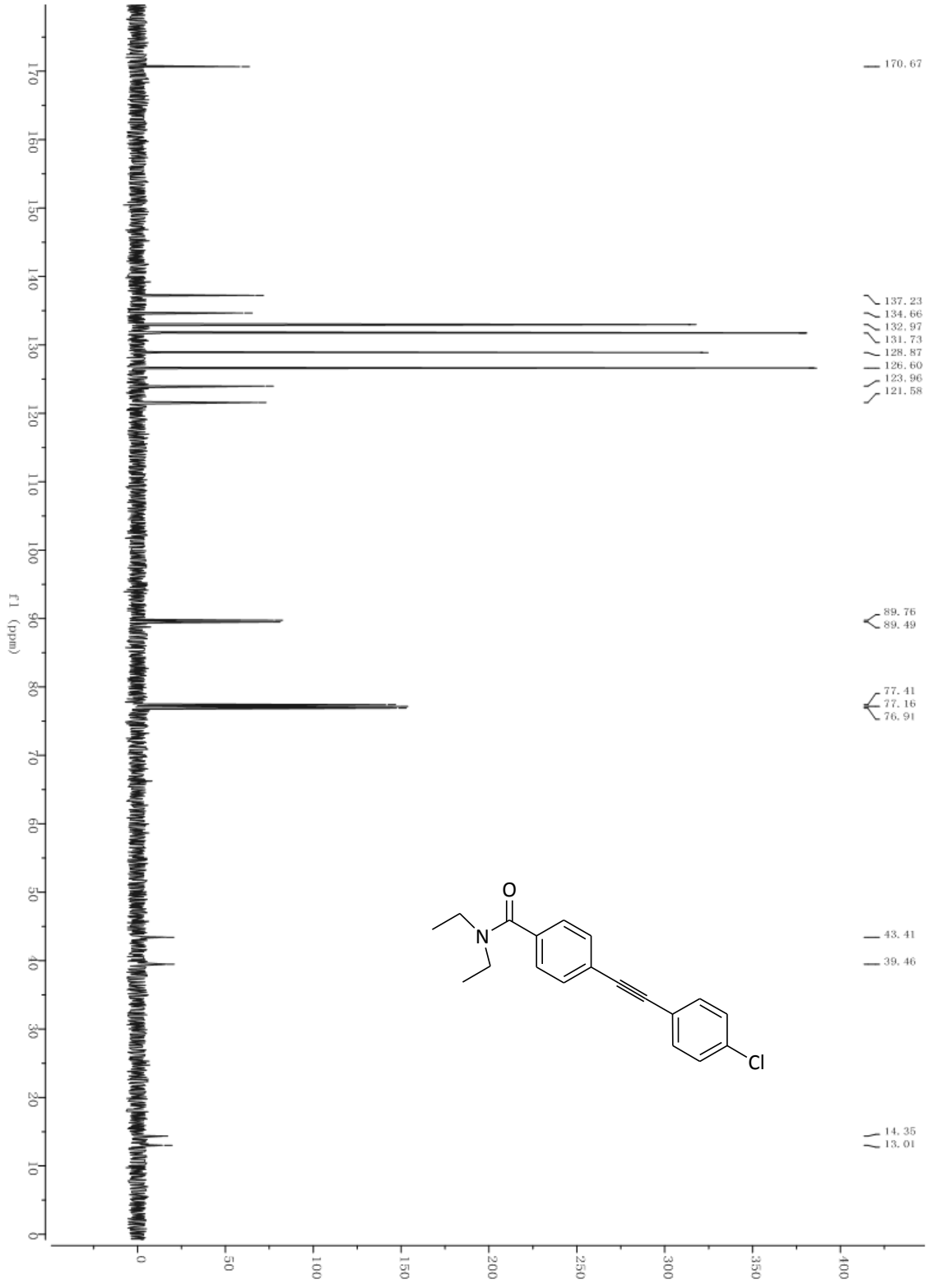

177.41
163.87
161.85
152.76
141.61
133.61
133.60
131.69
131.62
124.38
124.35
121.28
117.67
115.98
115.82
110.18
110.06
89.96
83.24
83.21
77.42
77.16
76.91
O
H
O
F
f1 (ppm)

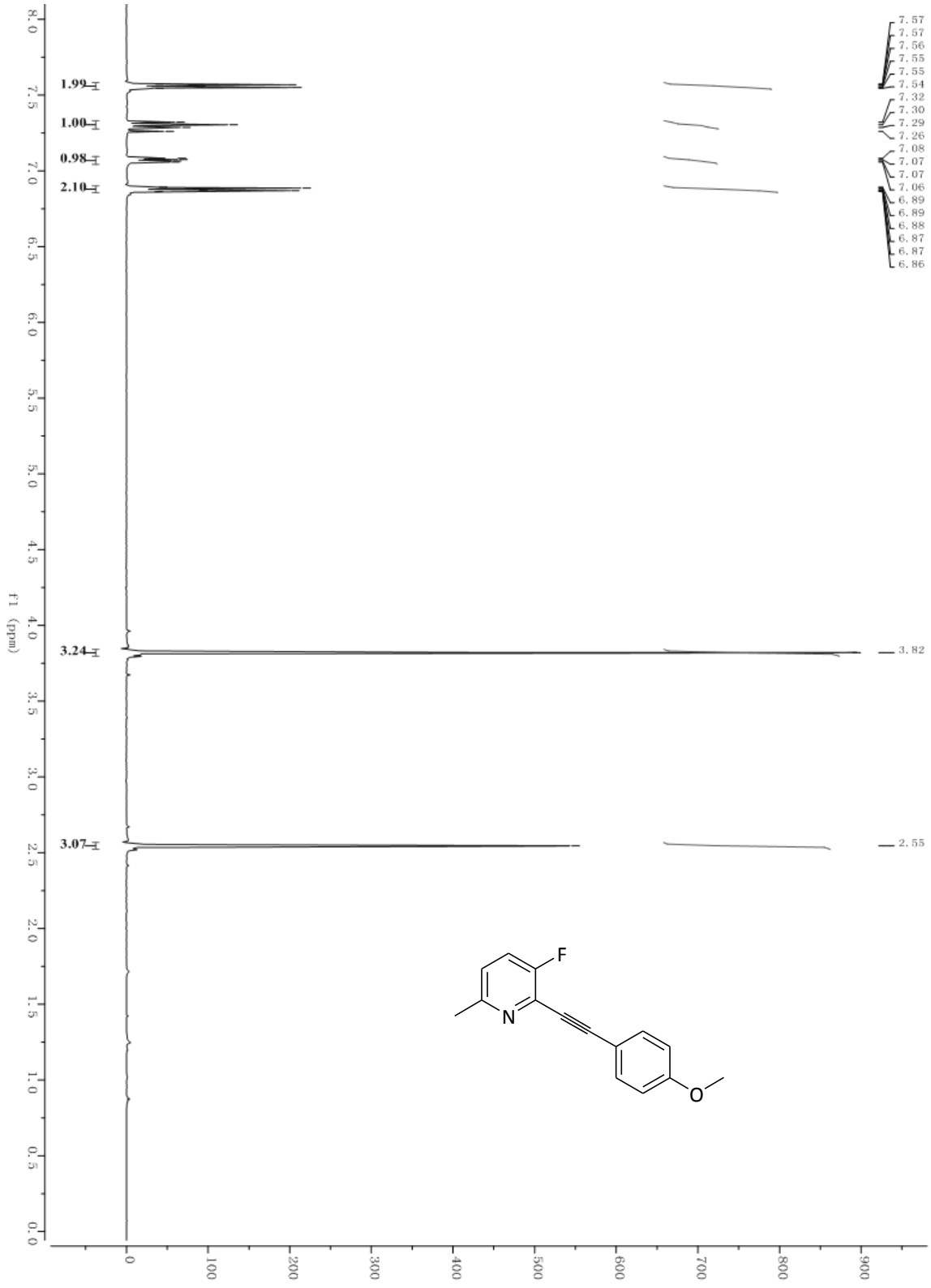

-108.47
-108.49
-108.50
-108.51
-108.51
-108.53
f1 (ppm)
O
H
O
F

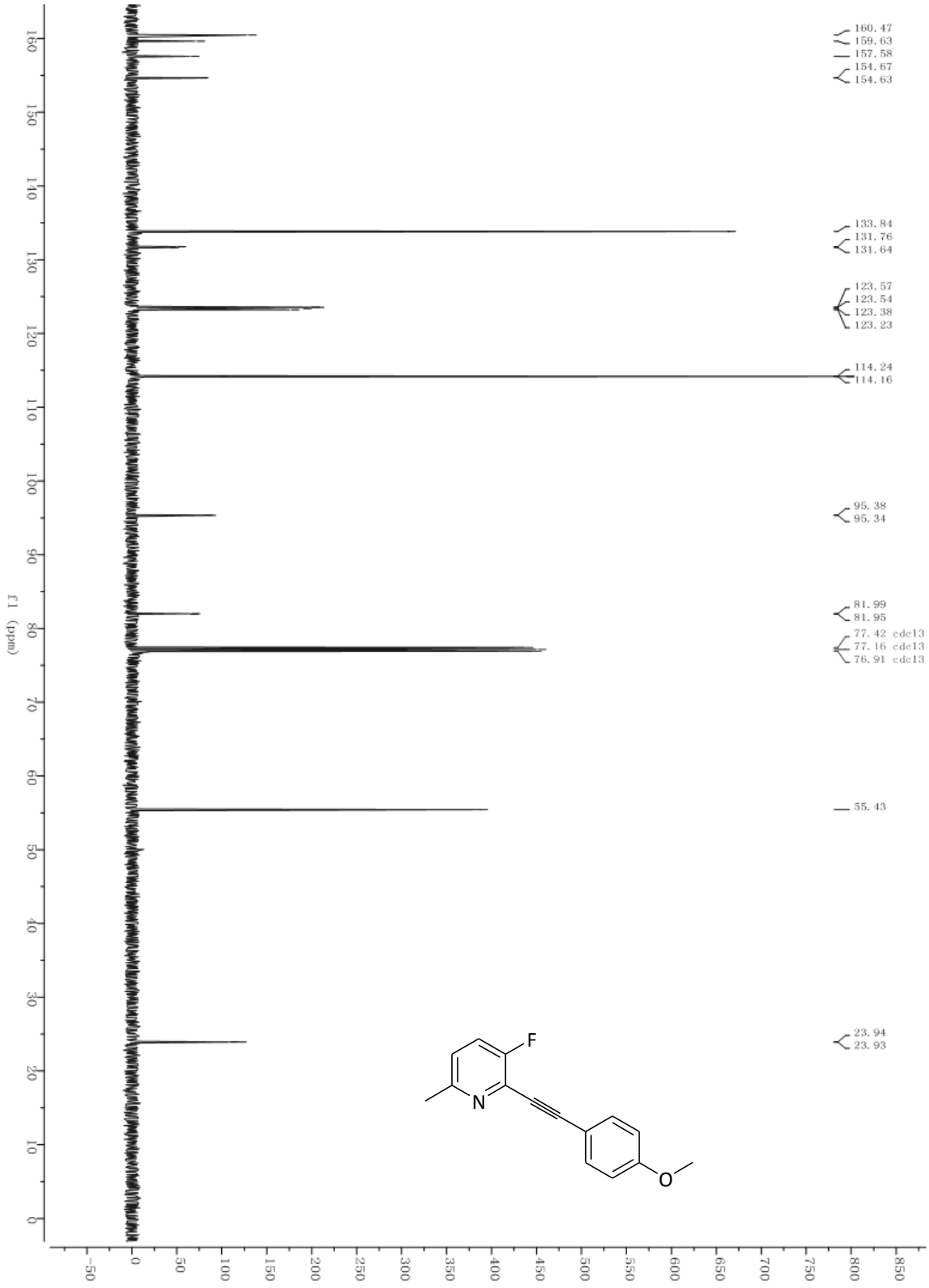

0.87
0.94
0.93
1.00
0.99
1.01
2.02
3.12
2.06
f1 (ppm)
8.85
8.84
8.13
8.13
8.07
8.05
7.73
7.73
7.71
7.71
7.69
7.69
7.68
7.67
7.67
7.66
7.65
7.54
7.54
7.52
7.52
7.52
7.50
7.50
7.26 cdcl3
3.87
3.85
3.84
2.63
2.61
2.59
2.57
1.94
1.92
1.91
1.89
1.87
N
OH


152.48
146.60
138.25
129.90
129.31
127.55
127.44
127.29
118.10
93.32
78.42
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
61.54
31.47
16.21
N
OH
f1 (ppm)


2.00
1.99
4.05
2.16
2.19
3.32
3.36
7.55
7.53
7.46
7.44
7.37
7.35
7.33
7.32
3.54
3.25
1.24
1.11
O
N
Cl
f1 (ppm)


170.67
137.23
134.66
132.97
131.73
128.87
126.60
123.96
121.58
89.76
89.49
77.41
77.16
76.91
43.41
39.46
14.35
13.01
f1 (ppm)
O
N
Cl


7.57
7.57
7.56
7.55
7.55
7.54
7.32
7.30
7.29
7.26
7.08
7.07
7.07
7.06
6.89
6.89
6.88
6.87
6.87
6.86
1.99
1.00
0.98
2.10
3.24
3.07
3.82
2.55
f1 (ppm)
F
N
O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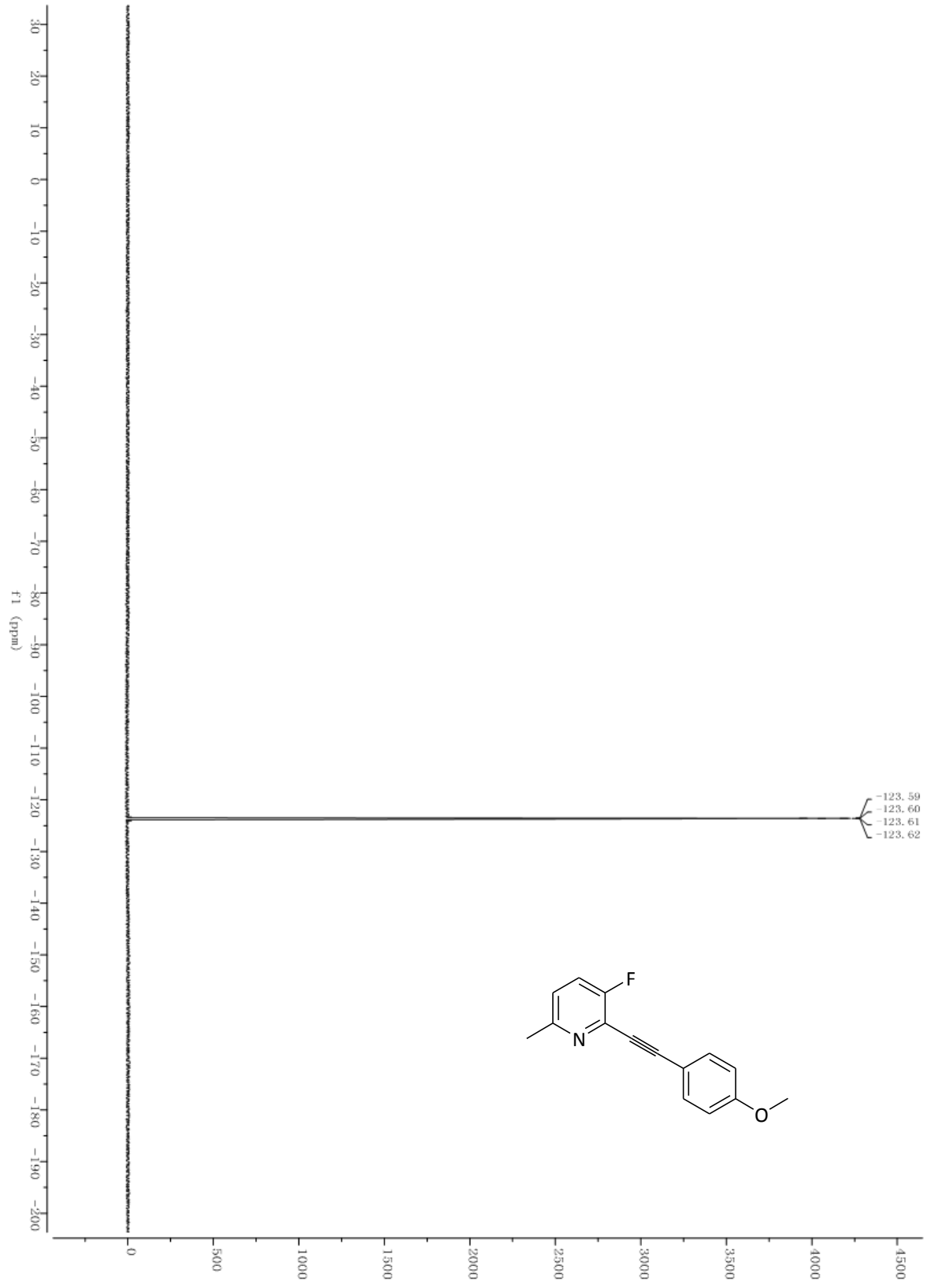
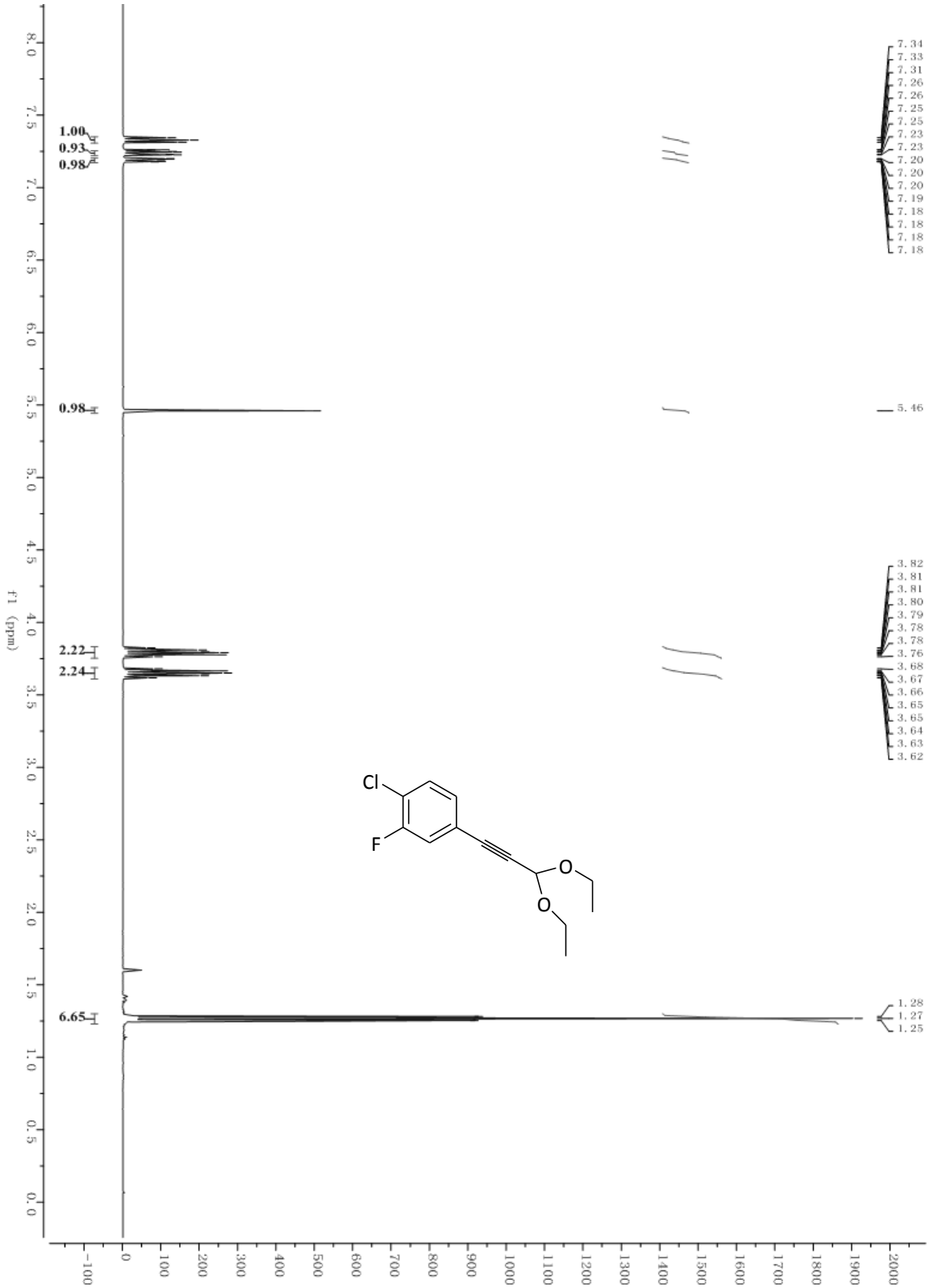
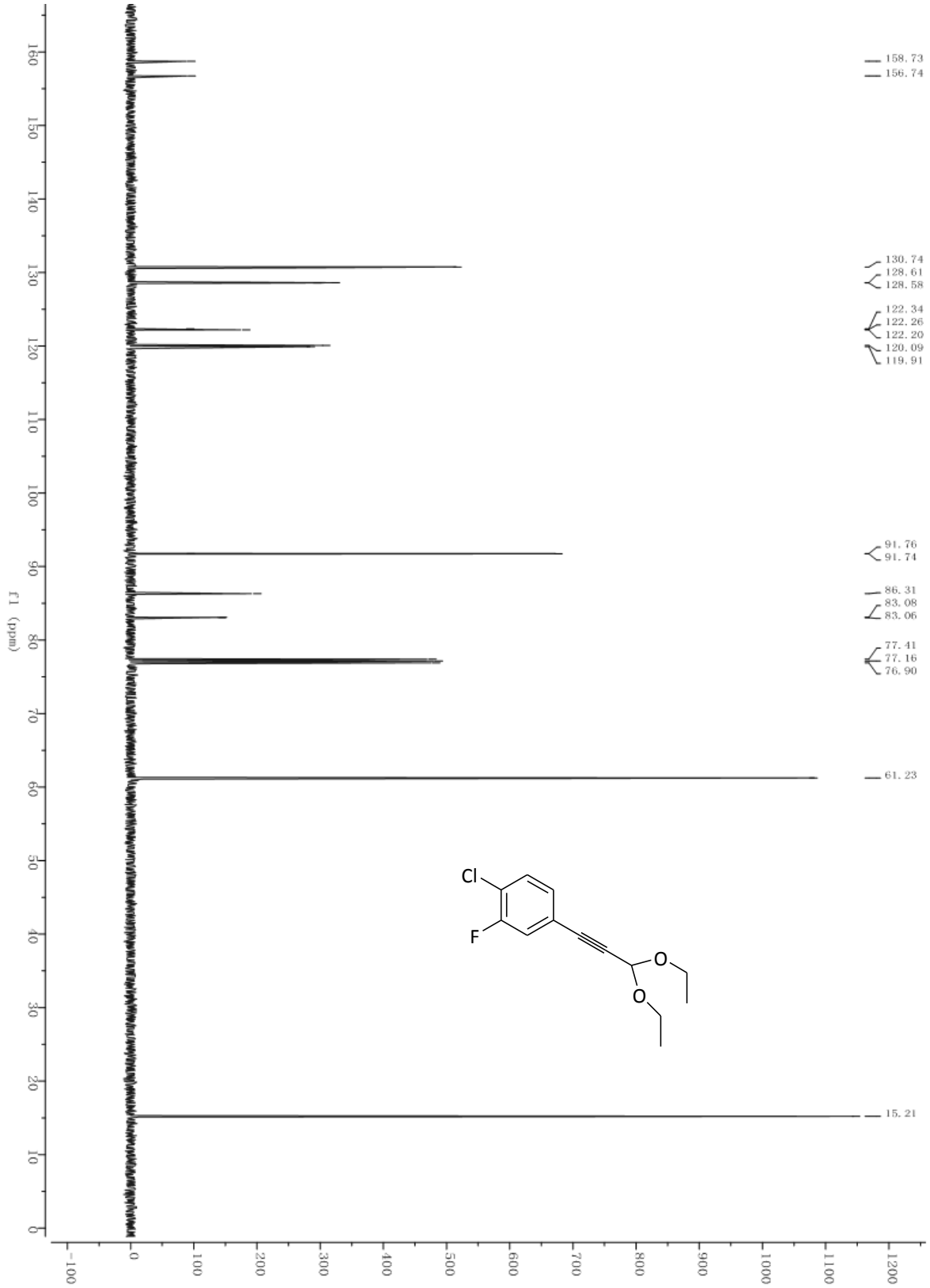
159.63
157.58
154.67
154.63
133.84
131.76
131.64
123.57
123.54
123.38
123.23
114.24
114.16
95.38
95.34
81.99
81.95
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
55.43
23.94
23.93
F
N
O
f1 (ppm)


-123.59
-123.60
-123.61
-123.62
F
N
O
f1 (ppm)


7.34
7.33
7.31
7.26
7.26
7.25
7.25
7.23
7.23
7.20
7.20
7.20
7.19
7.18
7.18
7.18
7.18
5.46
3.82
3.81
3.81
3.80
3.79
3.78
3.78
3.76
3.68
3.67
3.66
3.65
3.65
3.64
3.63
3.62
1.28
1.27
1.25
1.00
0.93
0.98
0.98
2.22
2.24
6.65
Cl
F
O
O
f1 (ppm)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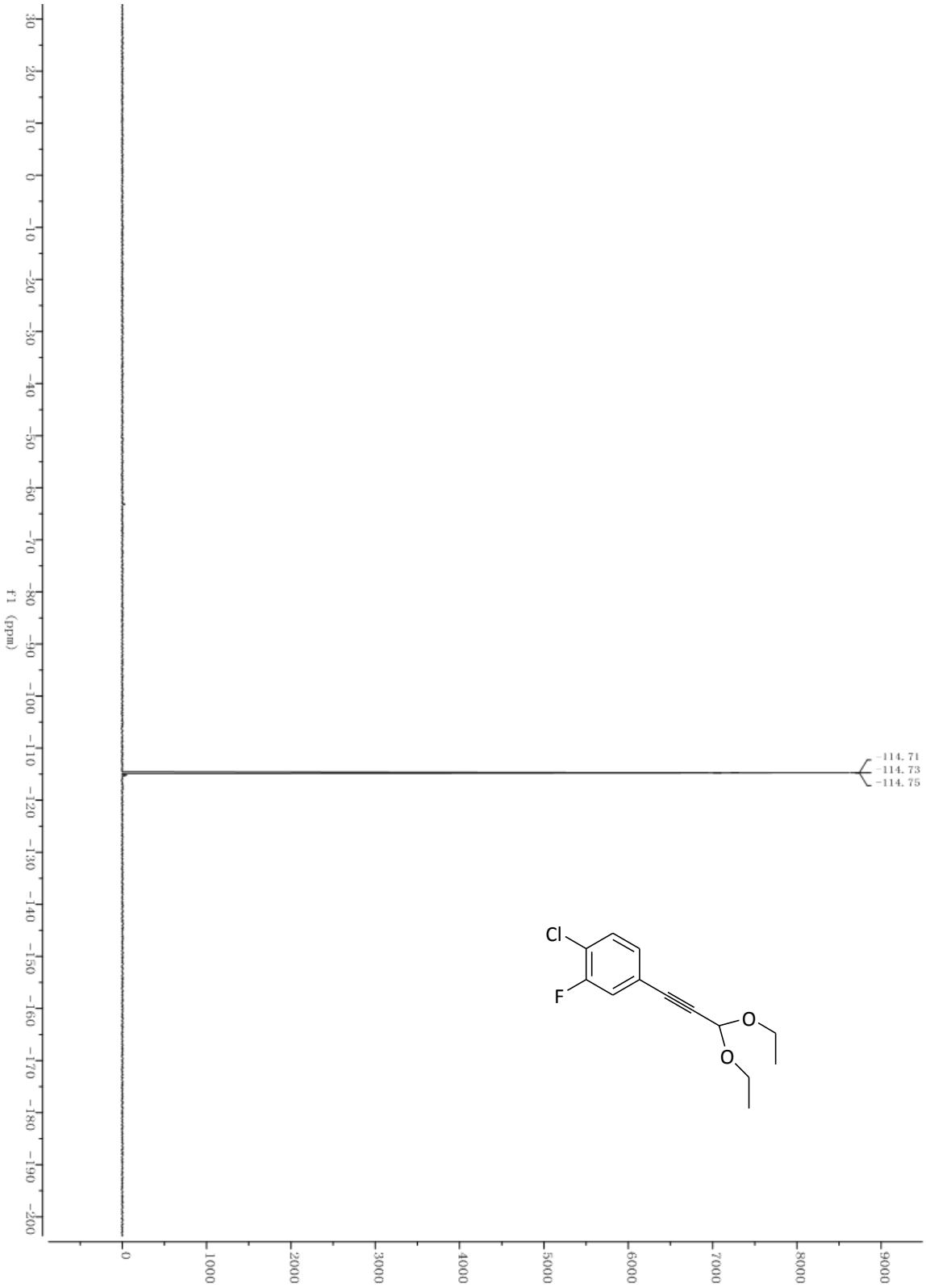
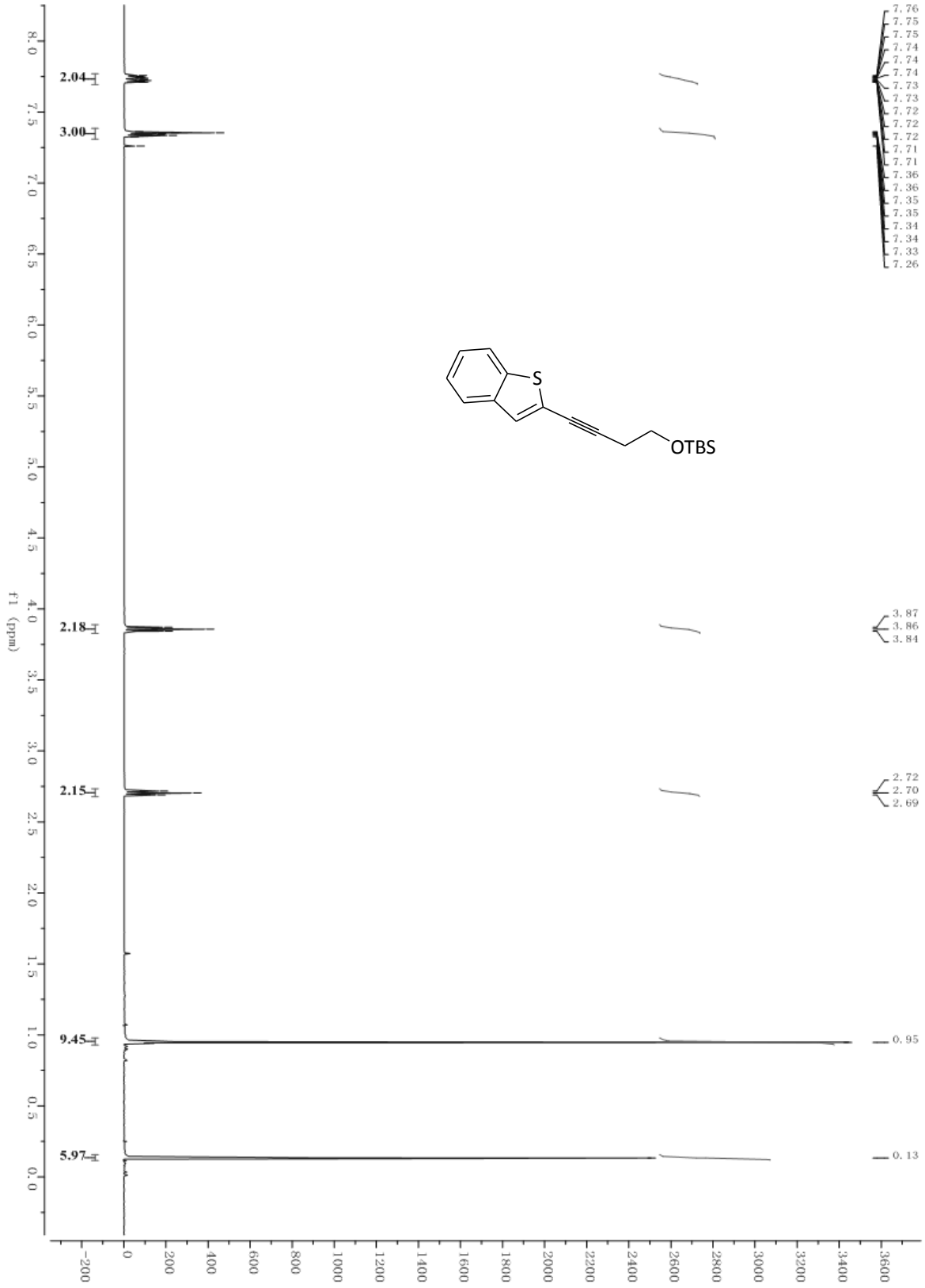
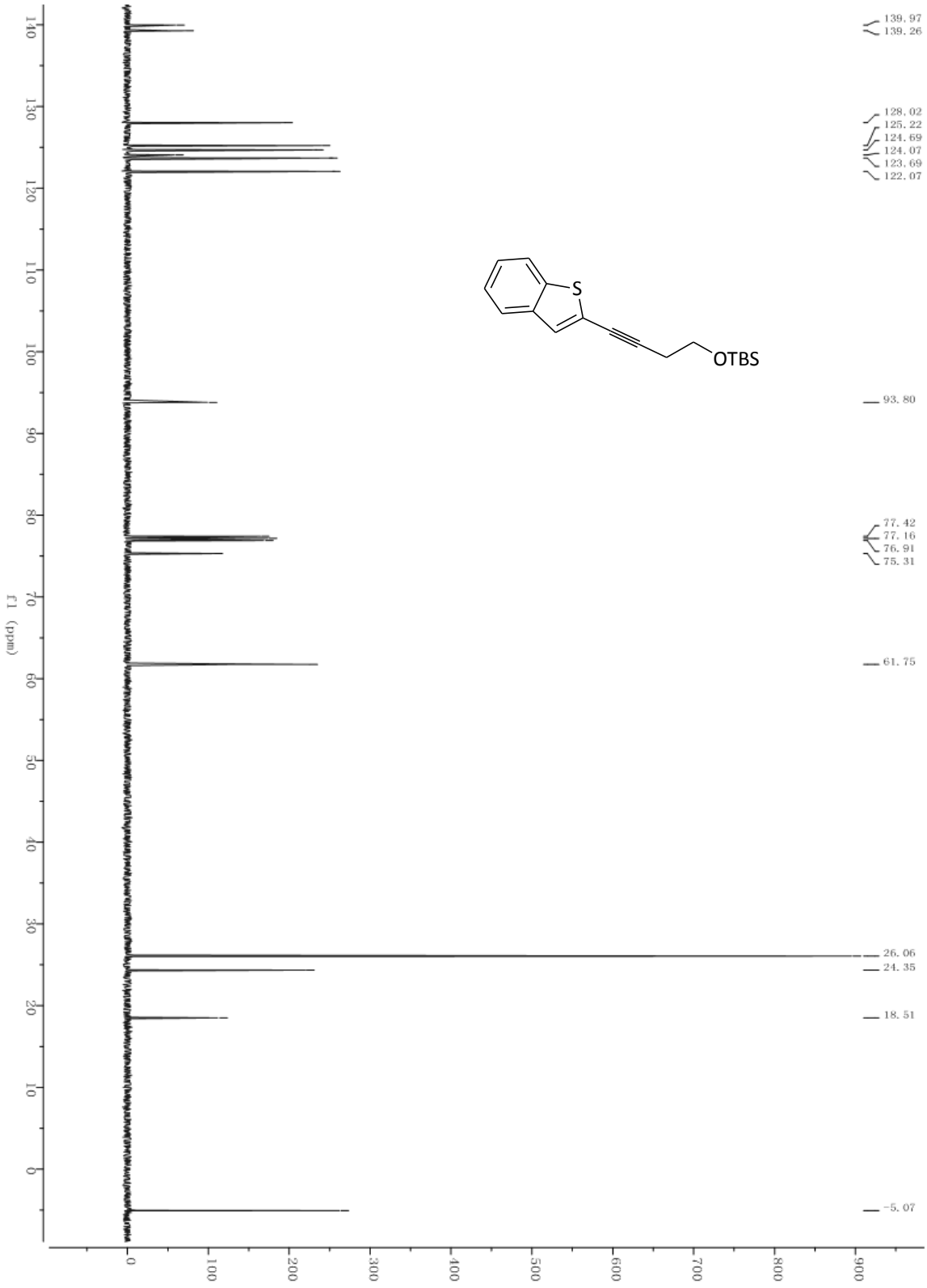
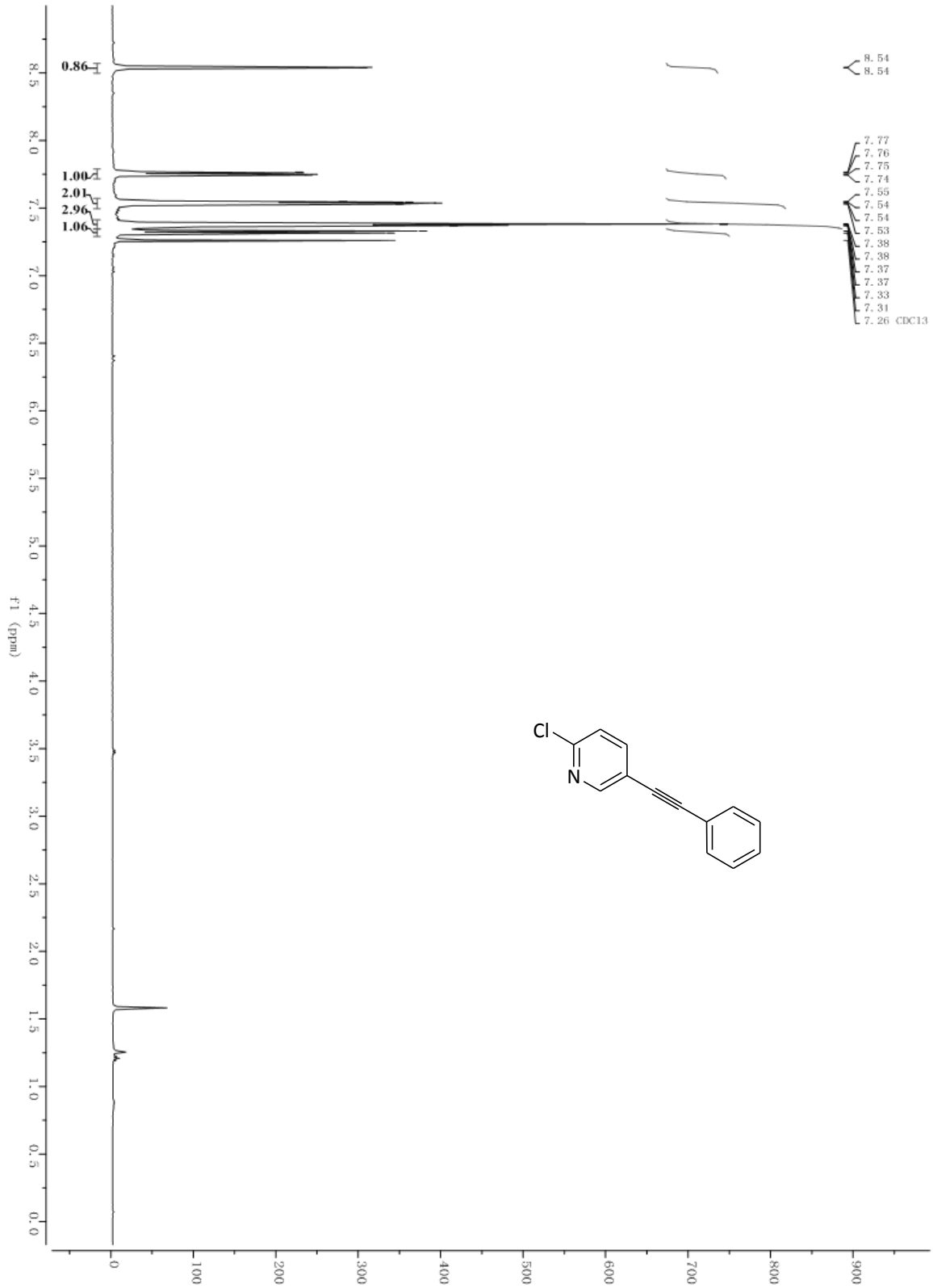
156.74
130.74
128.61
128.58
122.34
122.26
122.20
120.09
119.91
91.76
91.74
86.31
83.08
83.06
77.41
77.16
76.90
61.23
15.21
Cl
F
O
O
f1 (ppm)


30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
-114.71
-114.73
-114.75
Cl
F
O
O


7.76
7.75
7.75
7.74
7.74
7.74
7.73
7.73
7.72
7.72
7.72
7.71
7.71
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.26
S
OTBS
2.04
3.00
2.18
2.15
9.45
5.97
3.87
3.86
3.84
2.72
2.70
2.69
0.95
0.13
f1 (ppm)


139.97
139.26
128.02
125.22
124.69
124.07
123.69
122.07
93.80
77.42
77.16
76.91
75.31
61.75
26.06
24.35
18.51
-5.07
S
OTBS
f1 (ppm)


0.86
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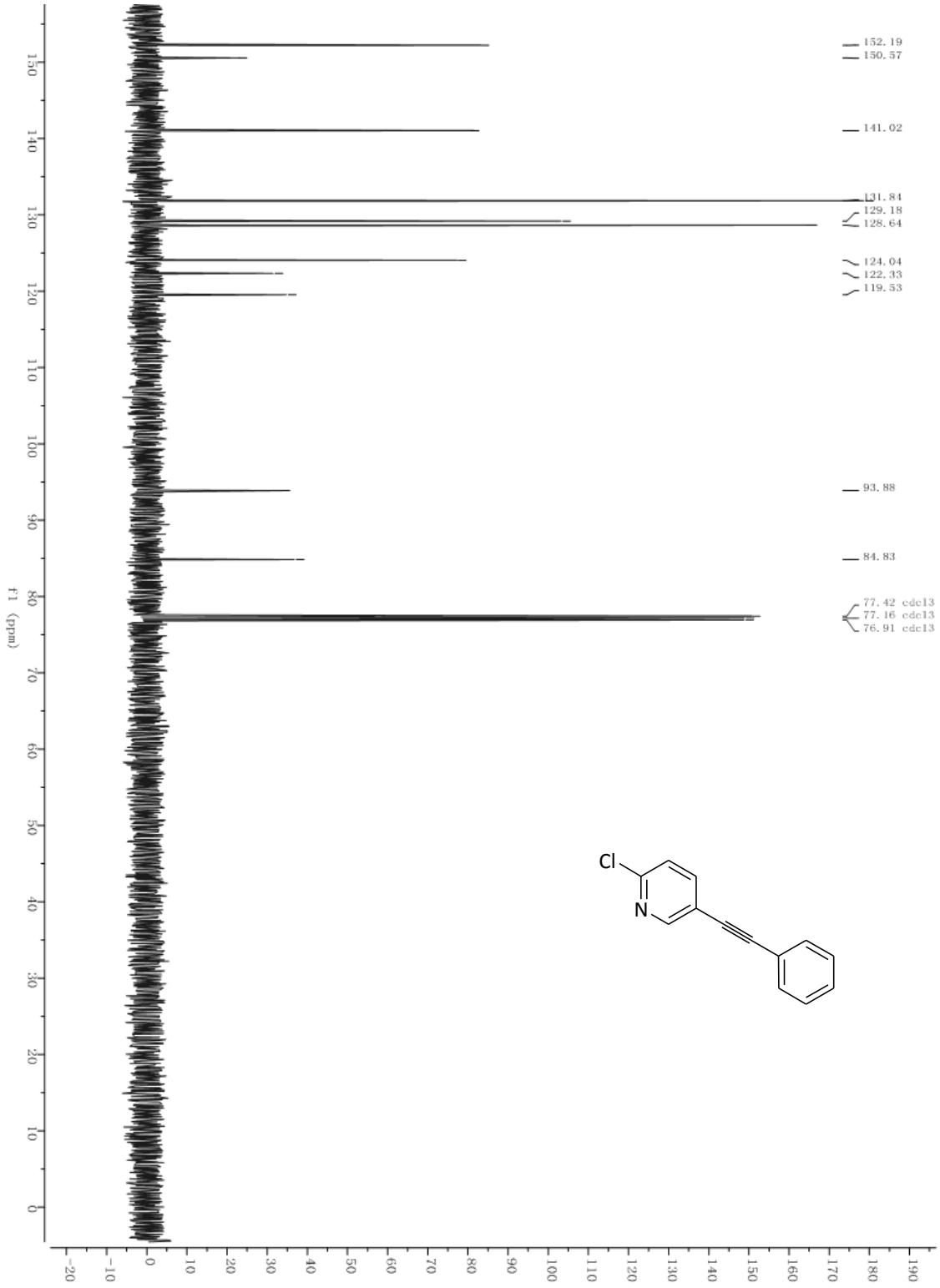
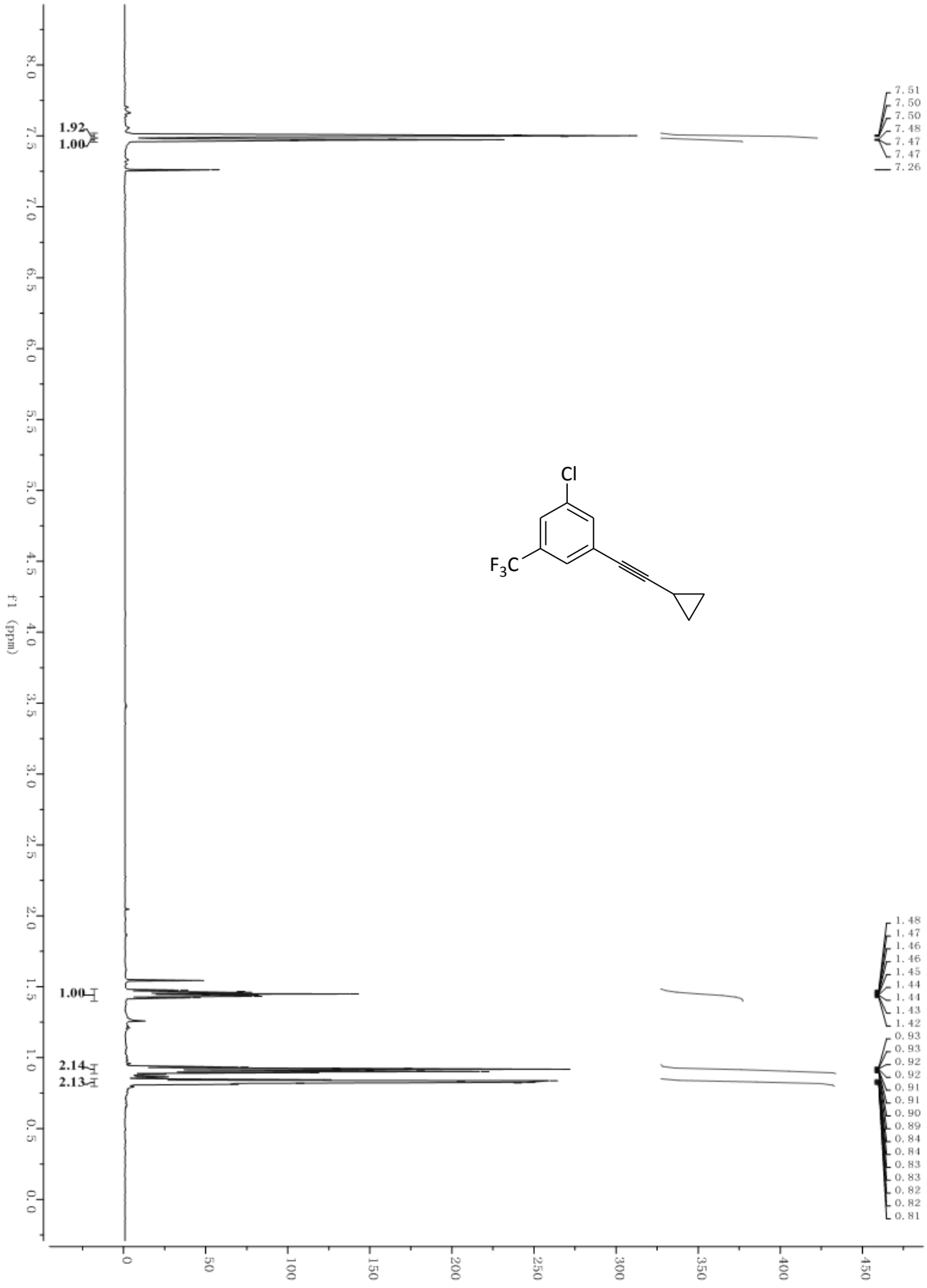
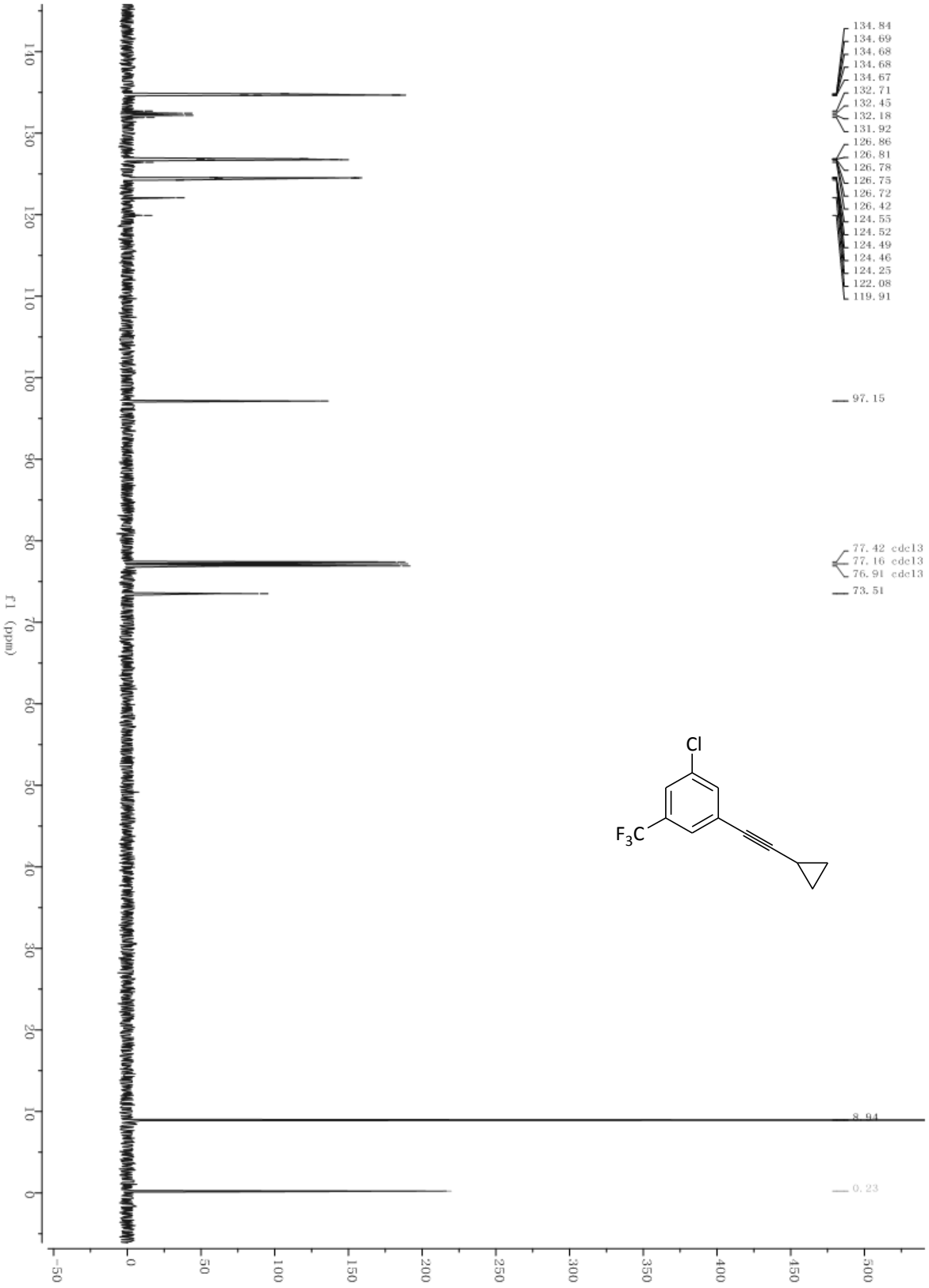
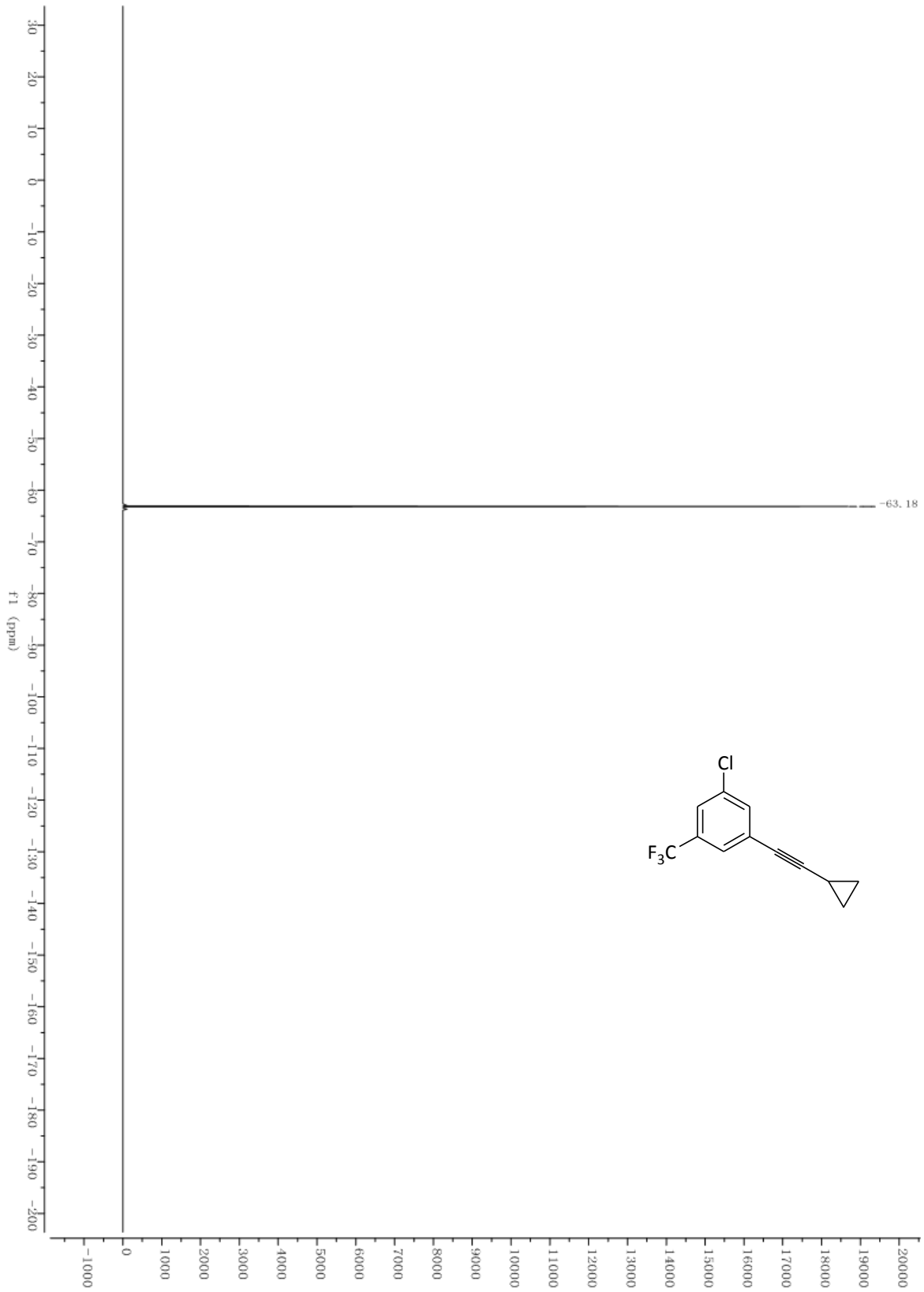
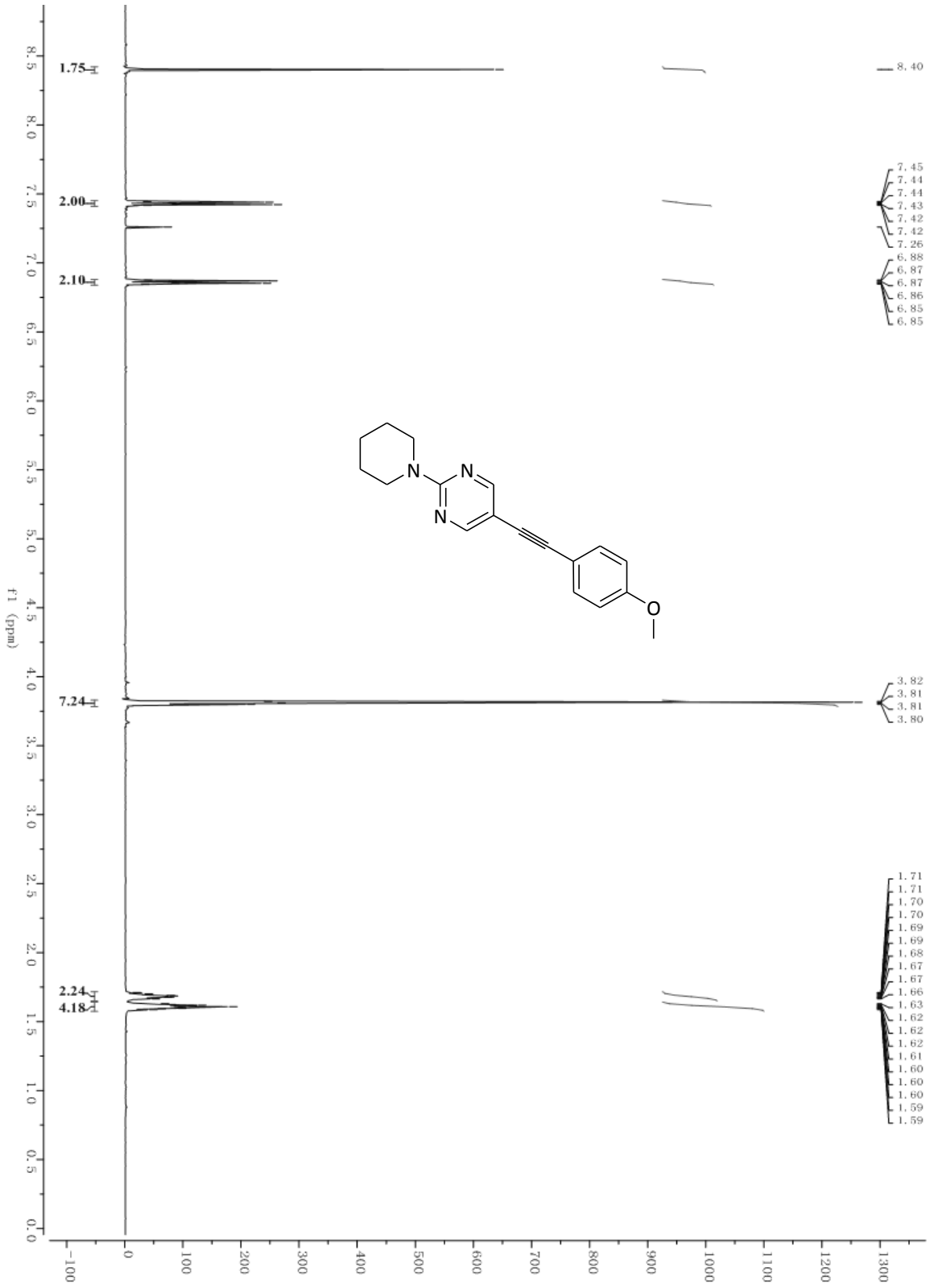
2.01
2.96
1.06
8.54
8.54
7.77
7.76
7.75
7.74
7.55
7.54
7.54
7.53
7.38
7.38
7.37
7.37
7.33
7.31
7.26 CDCl3
f1 (ppm)
Cl
N


152.19
150.57
141.02
131.84
129.18
128.64
124.04
122.33
119.53
93.88
84.83
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
f1 (ppm)
Cl
N


1.92
1.00
1.00
2.14
2.13
7.51
7.50
7.50
7.48
7.47
7.47
7.26
1.48
1.47
1.46
1.46
1.45
1.44
1.44
1.43
1.42
0.93
0.93
0.92
0.92
0.91
0.91
0.90
0.89
0.84
0.84
0.83
0.83
0.82
0.82
0.81
Cl
F3C
f1 (ppm)


134.84
134.69
134.68
134.68
134.67
132.71
132.45
132.18
131.92
126.86
126.81
126.78
126.75
126.72
126.42
124.55
124.52
124.49
124.46
124.25
122.08
119.91
97.15
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
73.51
8.94
0.23
f1 (ppm)
Cl
F3C


-63.18
Cl
F3C
f1 (ppm)


1.75
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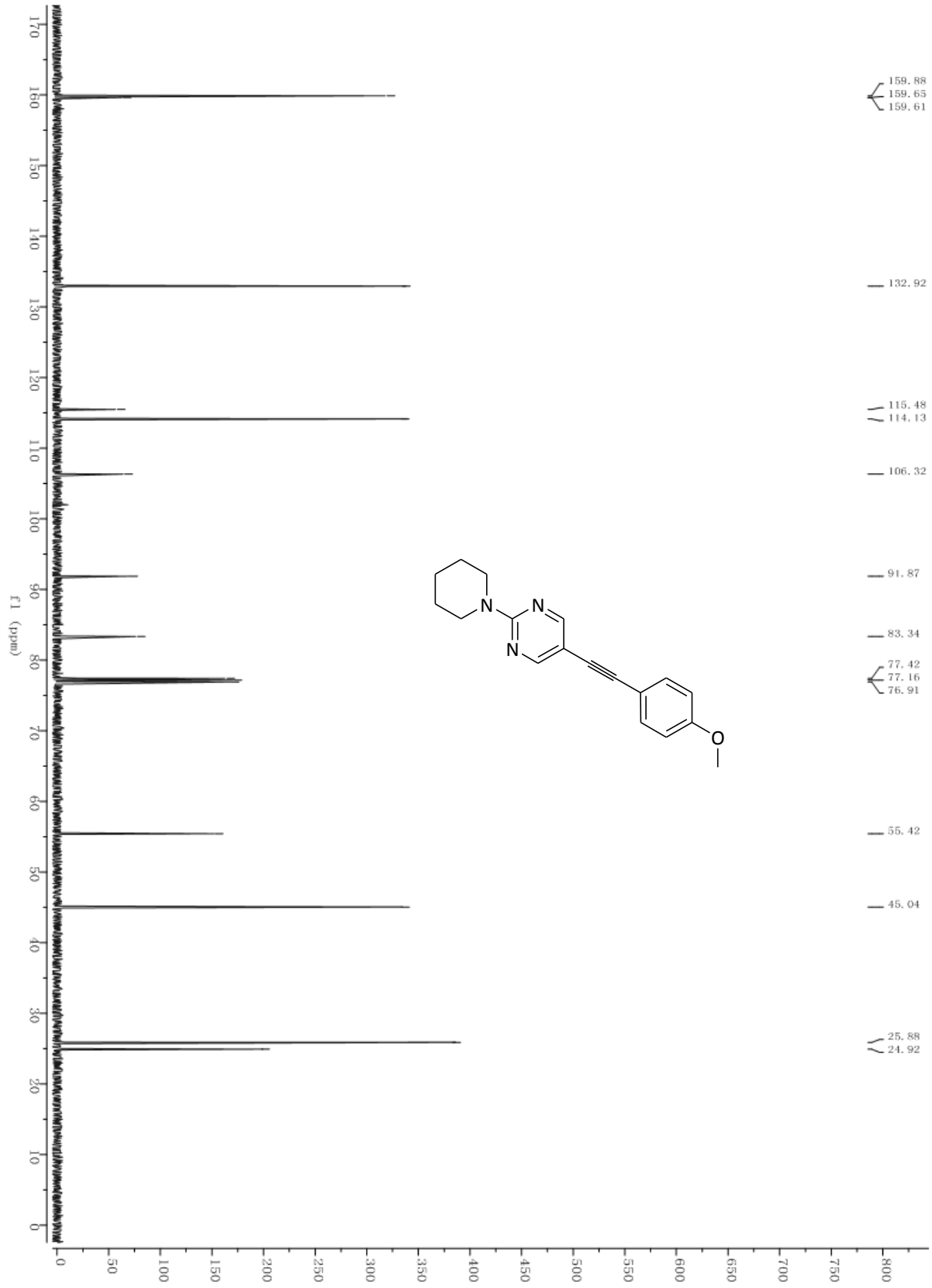
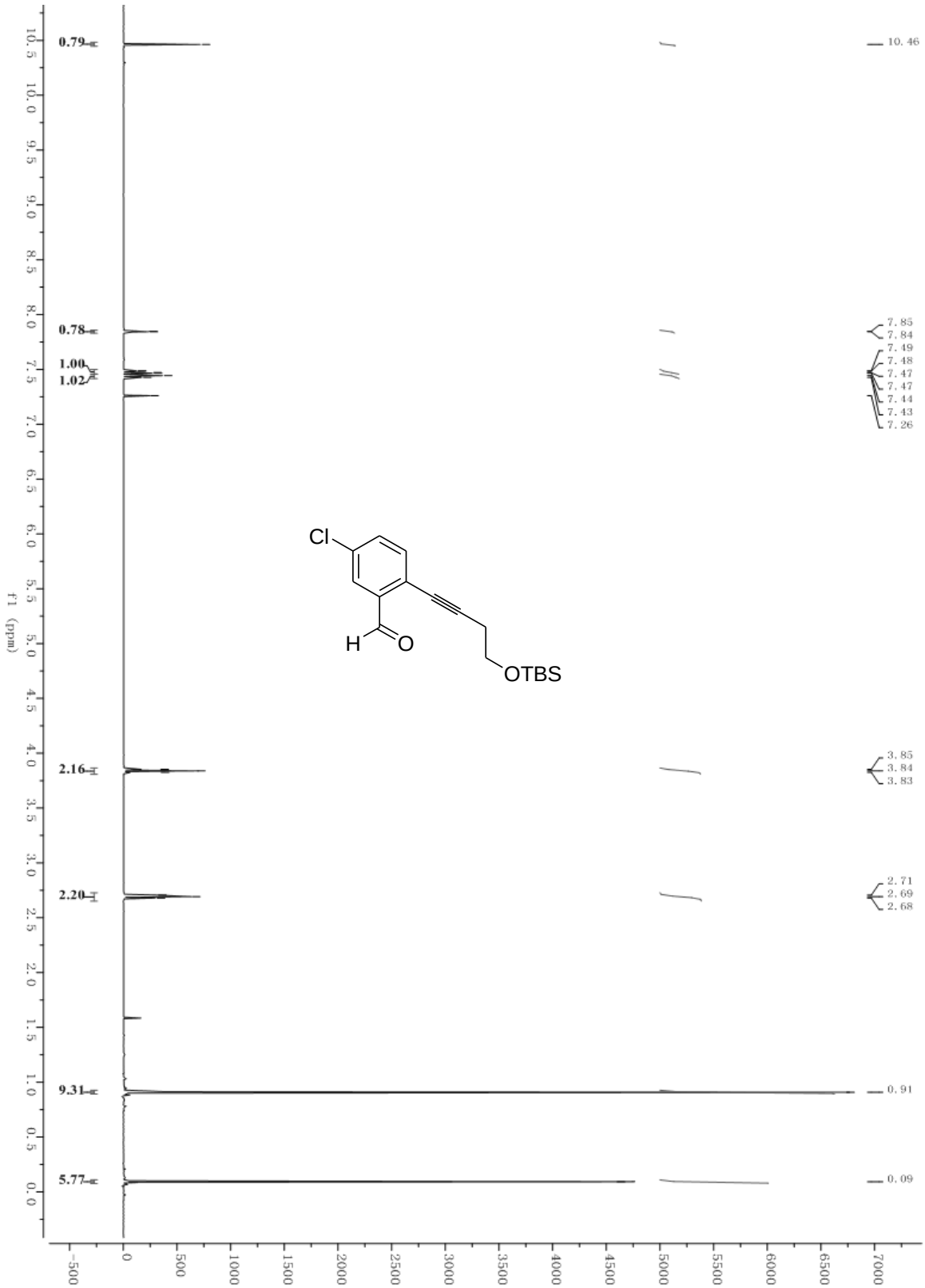
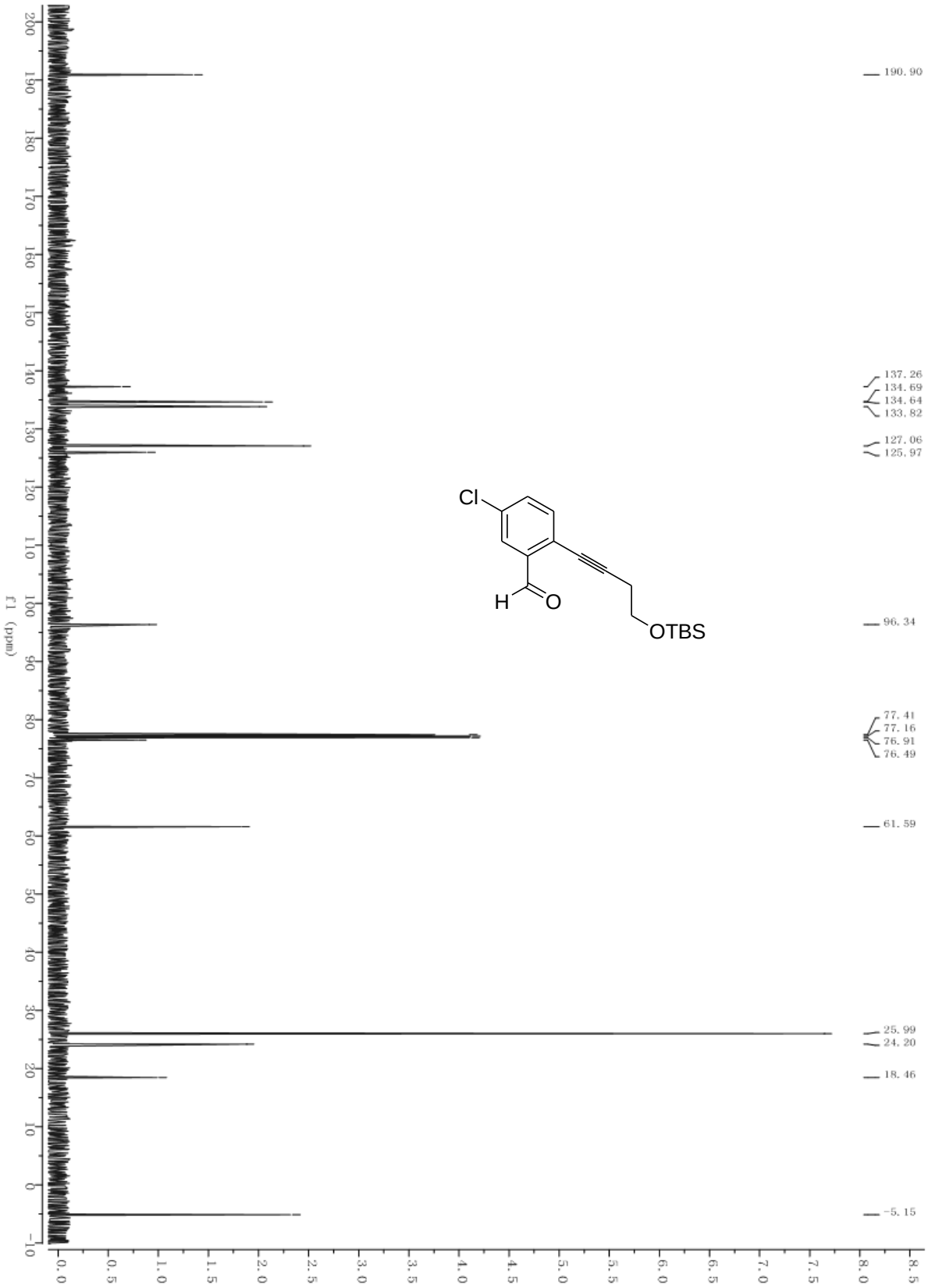
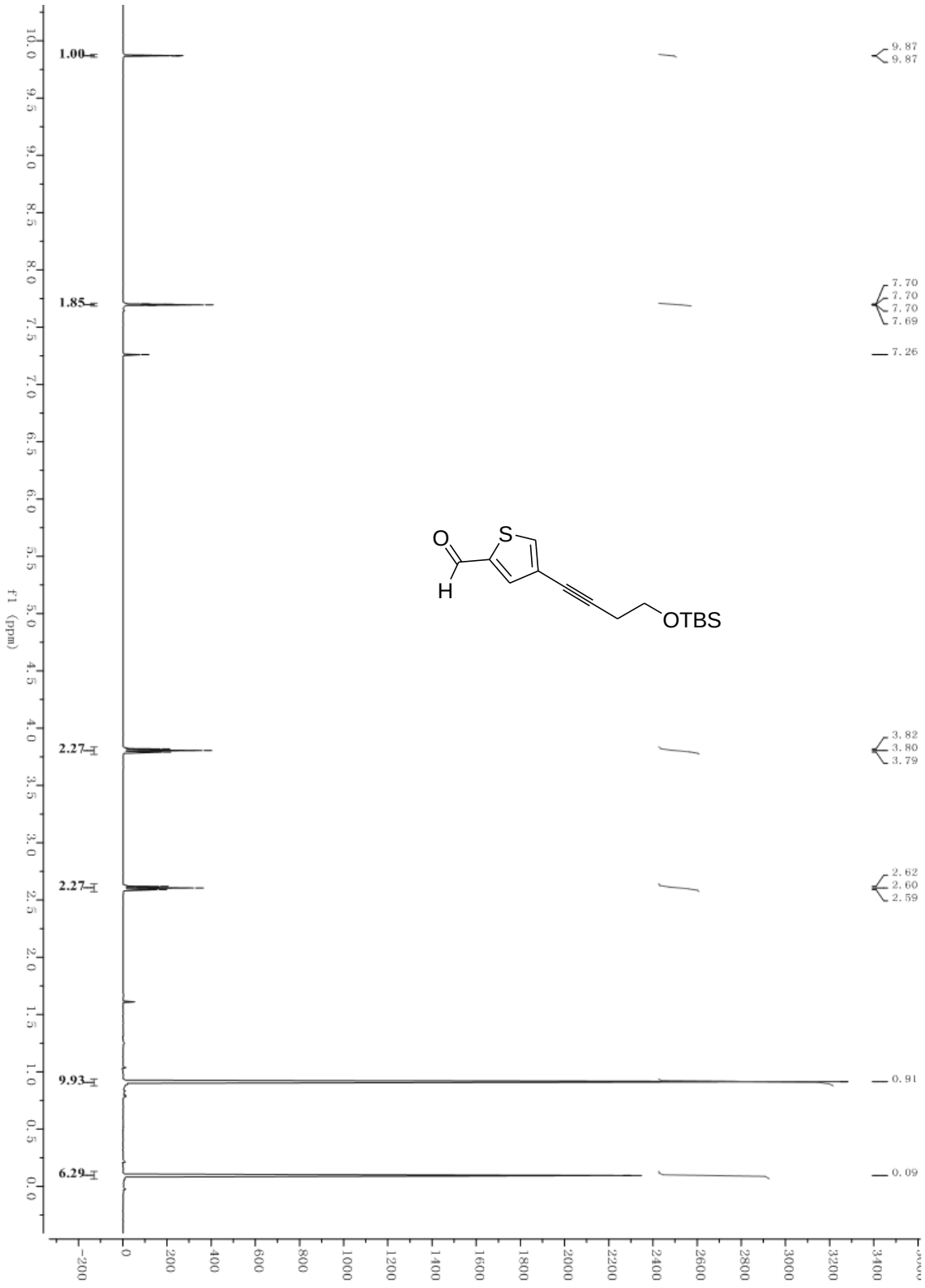
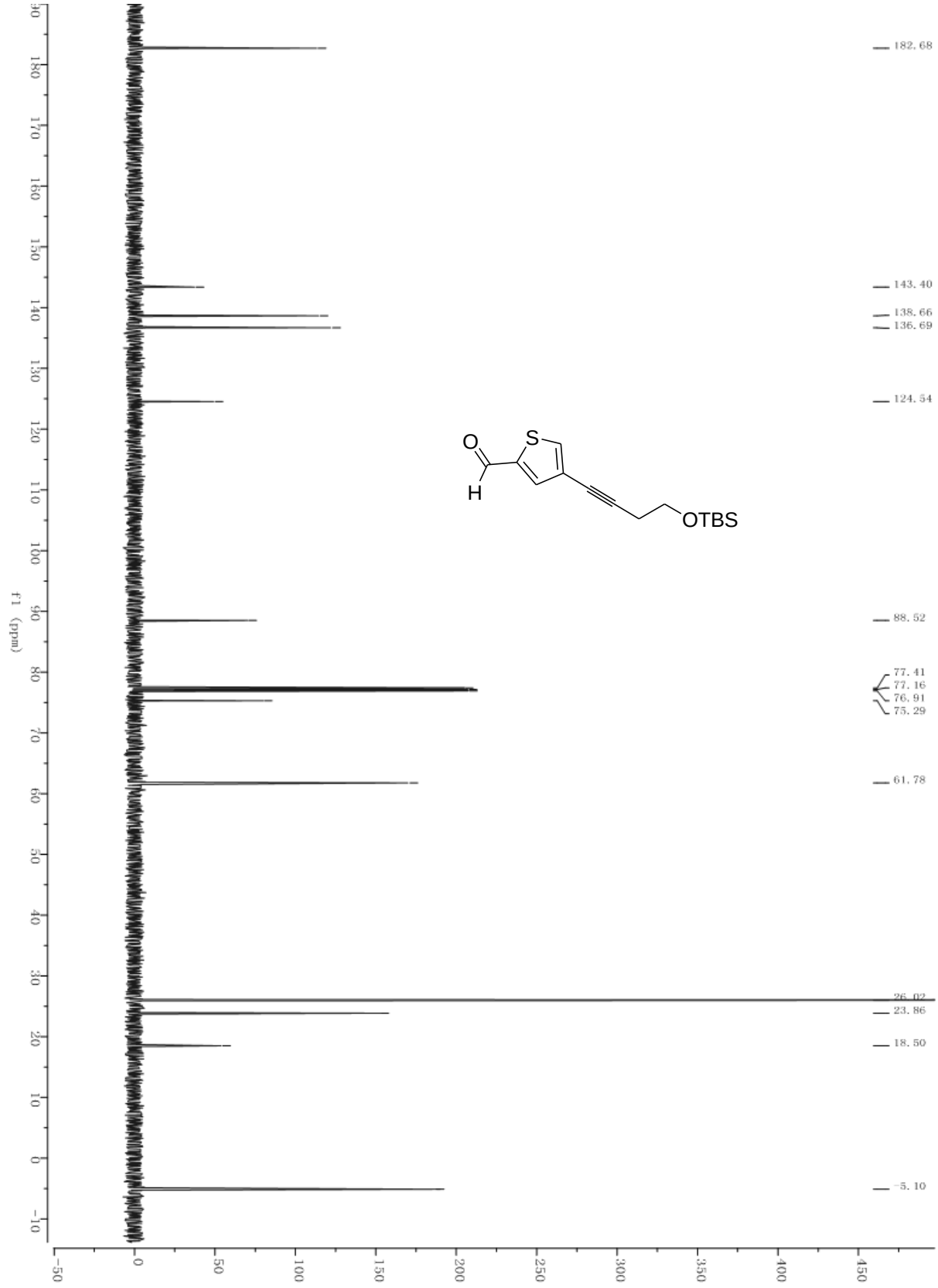
2.10
7.24
2.24
4.18
8.40
7.45
7.44
7.44
7.43
7.42
7.42
7.26
6.88
6.87
6.87
6.86
6.85
6.85
3.82
3.81
3.81
3.80
1.71
1.71
1.70
1.70
1.69
1.69
1.68
1.67
1.67
1.66
1.63
1.62
1.62
1.62
1.61
1.60
1.60
1.60
1.59
1.59
N
N
N
O
f1 (ppm)

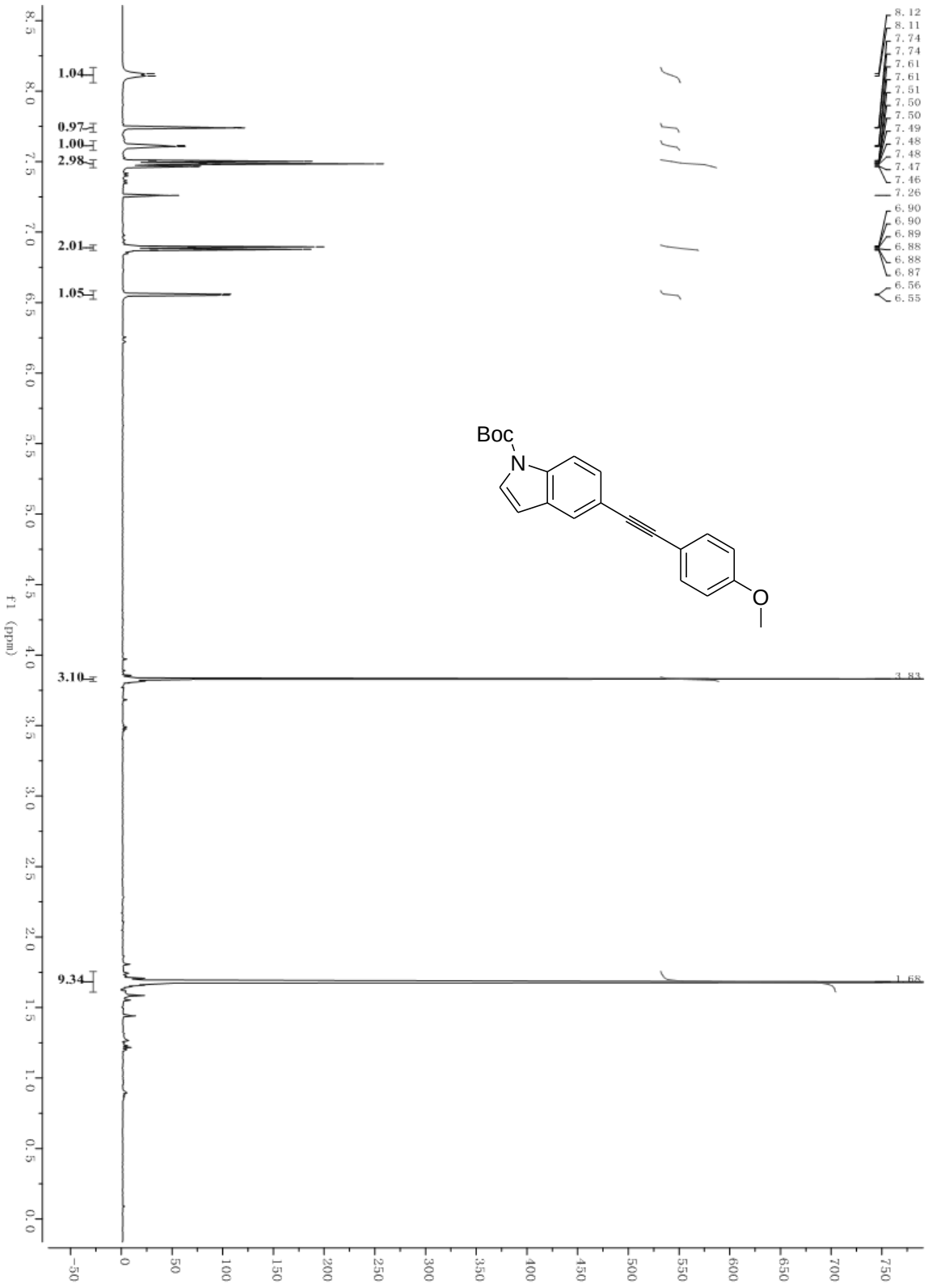

159.88
159.65
159.61
132.92
115.48
114.13
106.32
91.87
83.34
77.42
77.16
76.91
55.42
45.04
25.88
24.92
f1 (ppm)

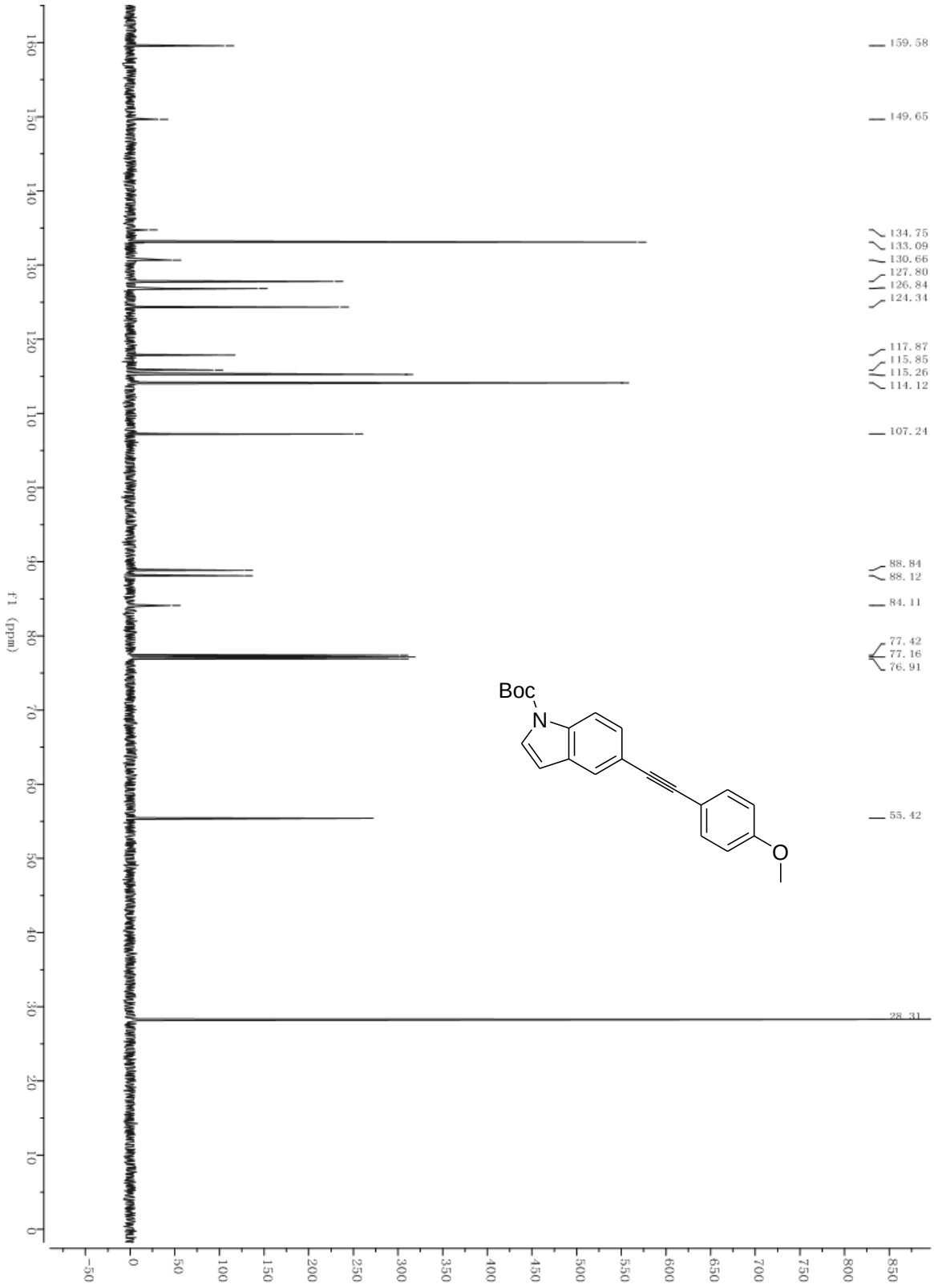

0.79
0.78
1.00
1.02
2.16
2.20
9.31
5.77
10.46
7.85
7.84
7.49
7.48
7.47
7.47
7.44
7.43
7.26
3.85
3.84
3.83
2.71
2.69
2.68
0.91
0.09
Cl
H
O
OTBS
f1 (ppm)

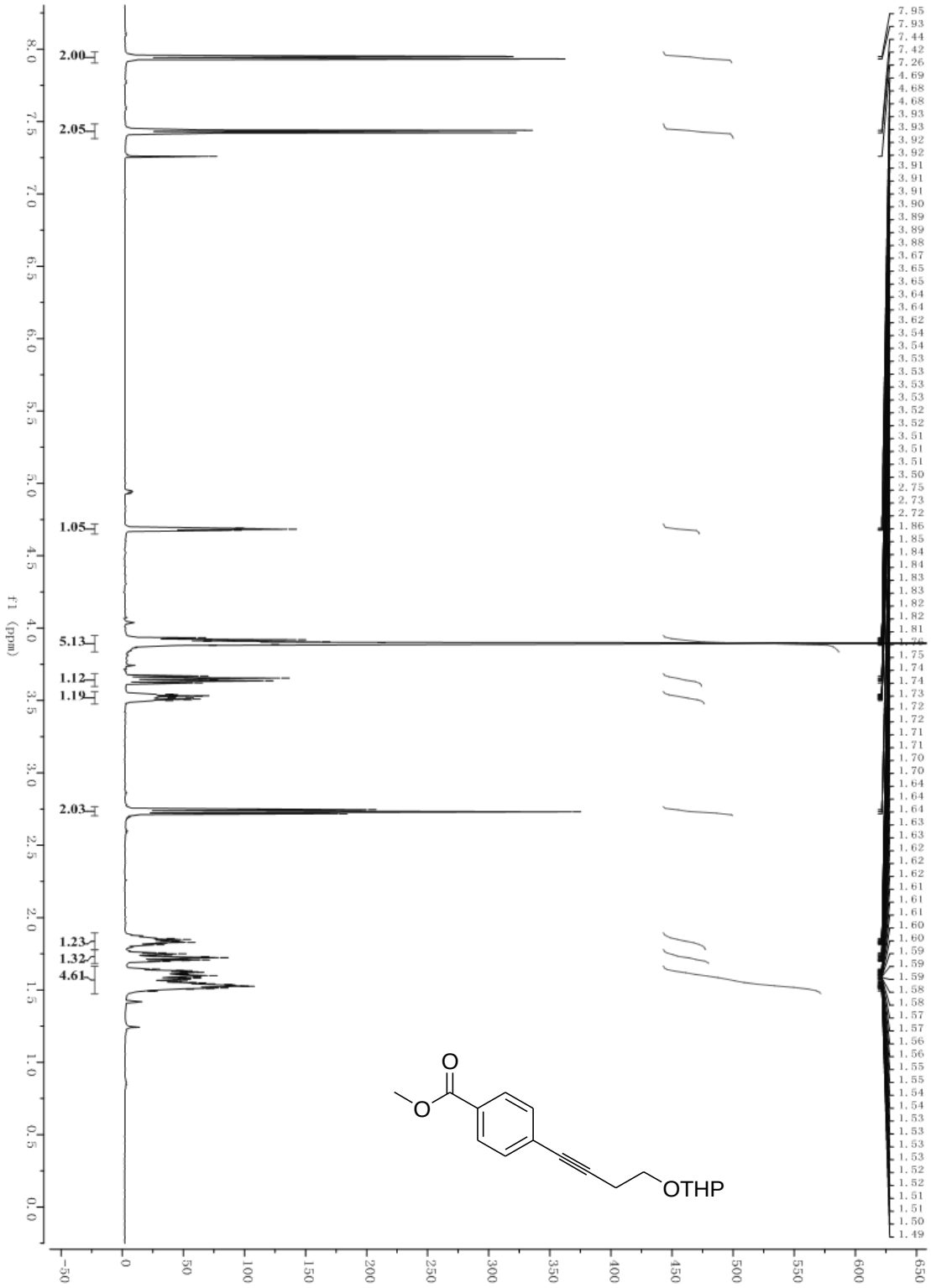

190.90
137.26
134.69
134.64
133.82
127.06
125.97
96.34
77.41
77.16
76.91
76.49
61.59
25.99
24.20
18.46
-5.15
Cl
H
O
OTBS
f1 (ppm)

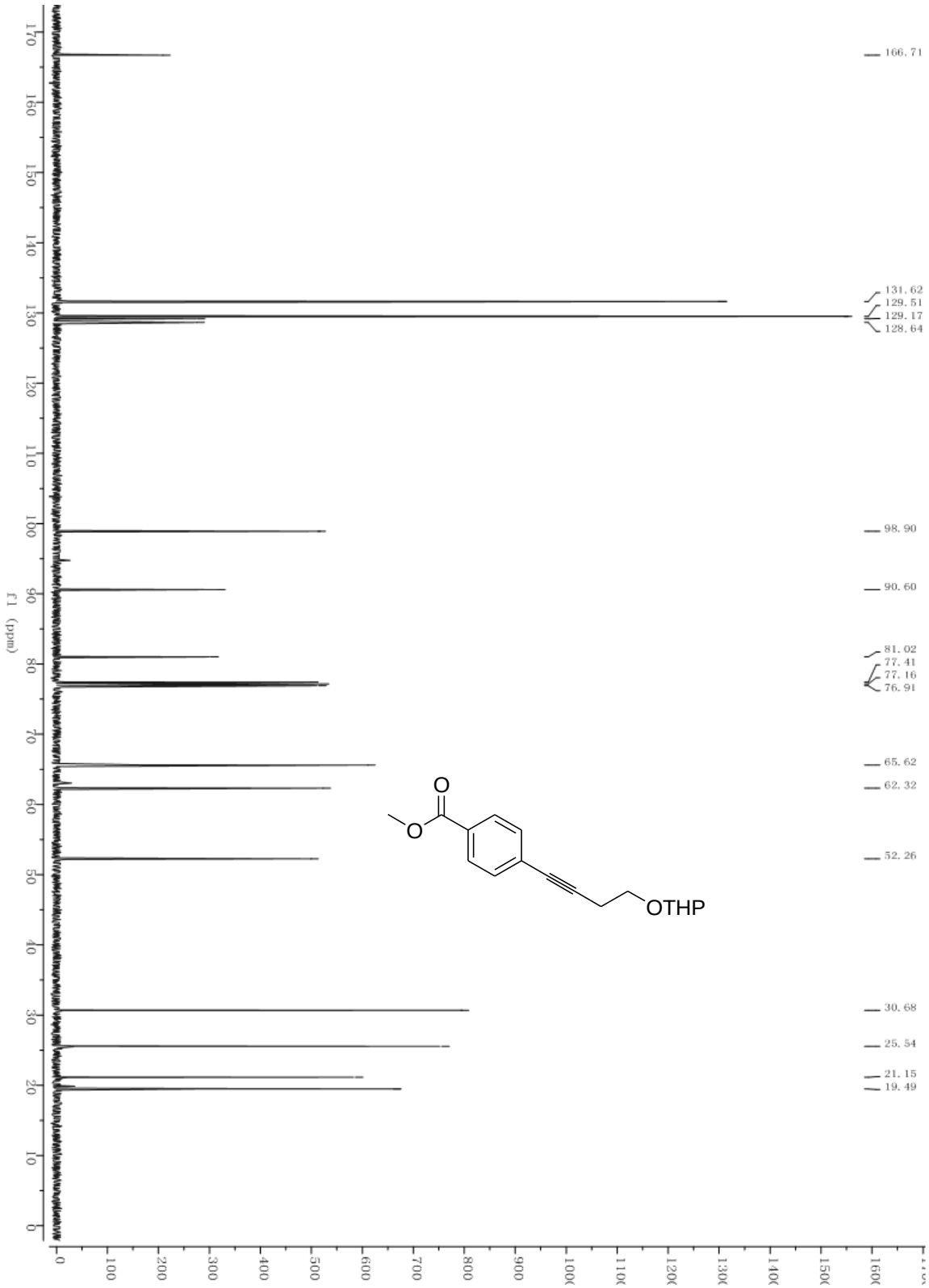

1.00
1.85
2.27
2.27
9.93
6.29
9.87
9.87
7.70
7.70
7.70
7.69
7.26
3.82
3.80
3.79
2.62
2.60
2.59
0.91
0.09
O
H
S
OTBS
f1 (ppm)

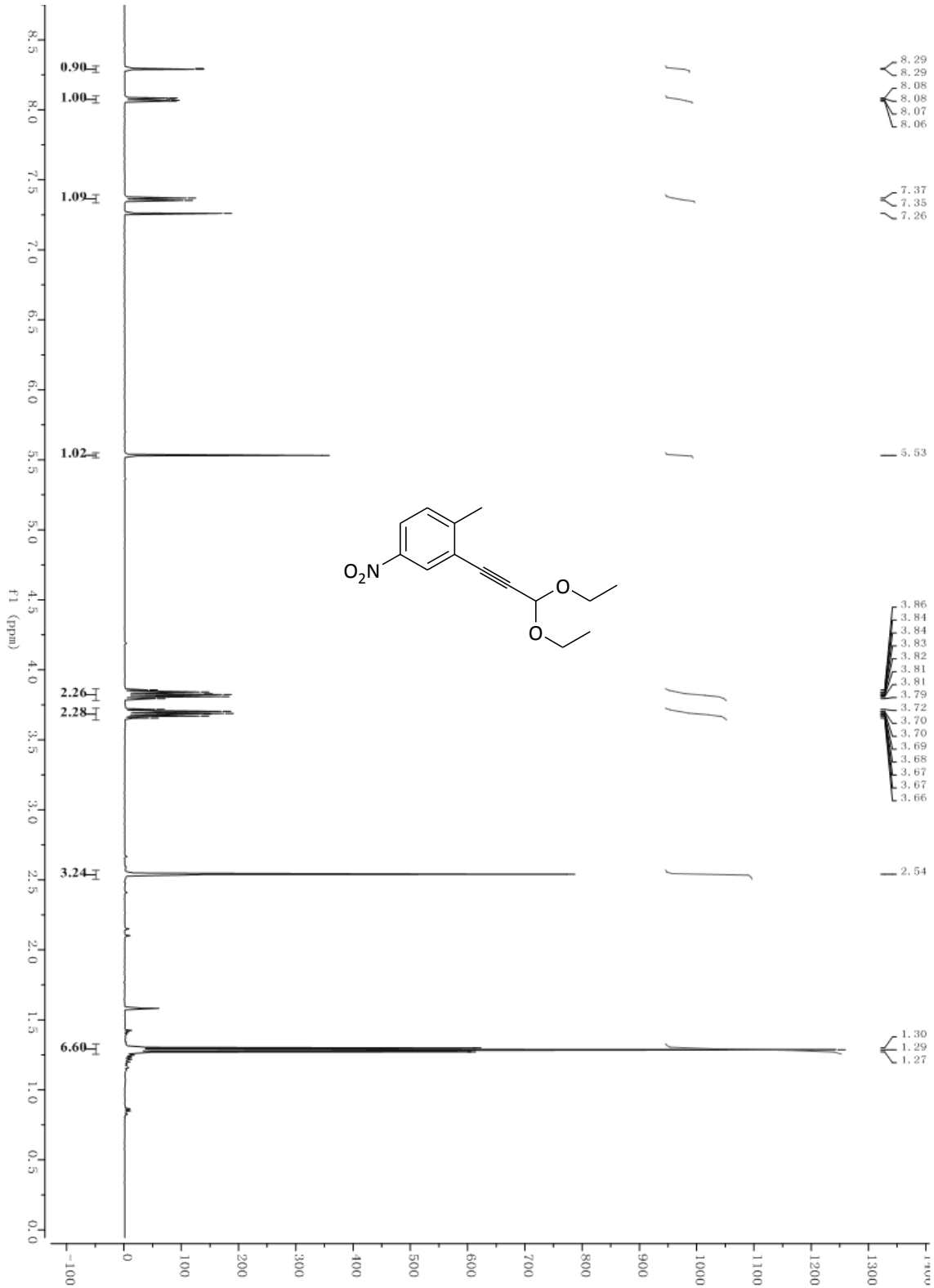

182.68
143.40
138.66
136.69
124.54
88.52
77.41
77.16
76.91
75.29
61.78
26.02
23.86
18.50
-5.10
O
S
H
OTBS
f1 (ppm)

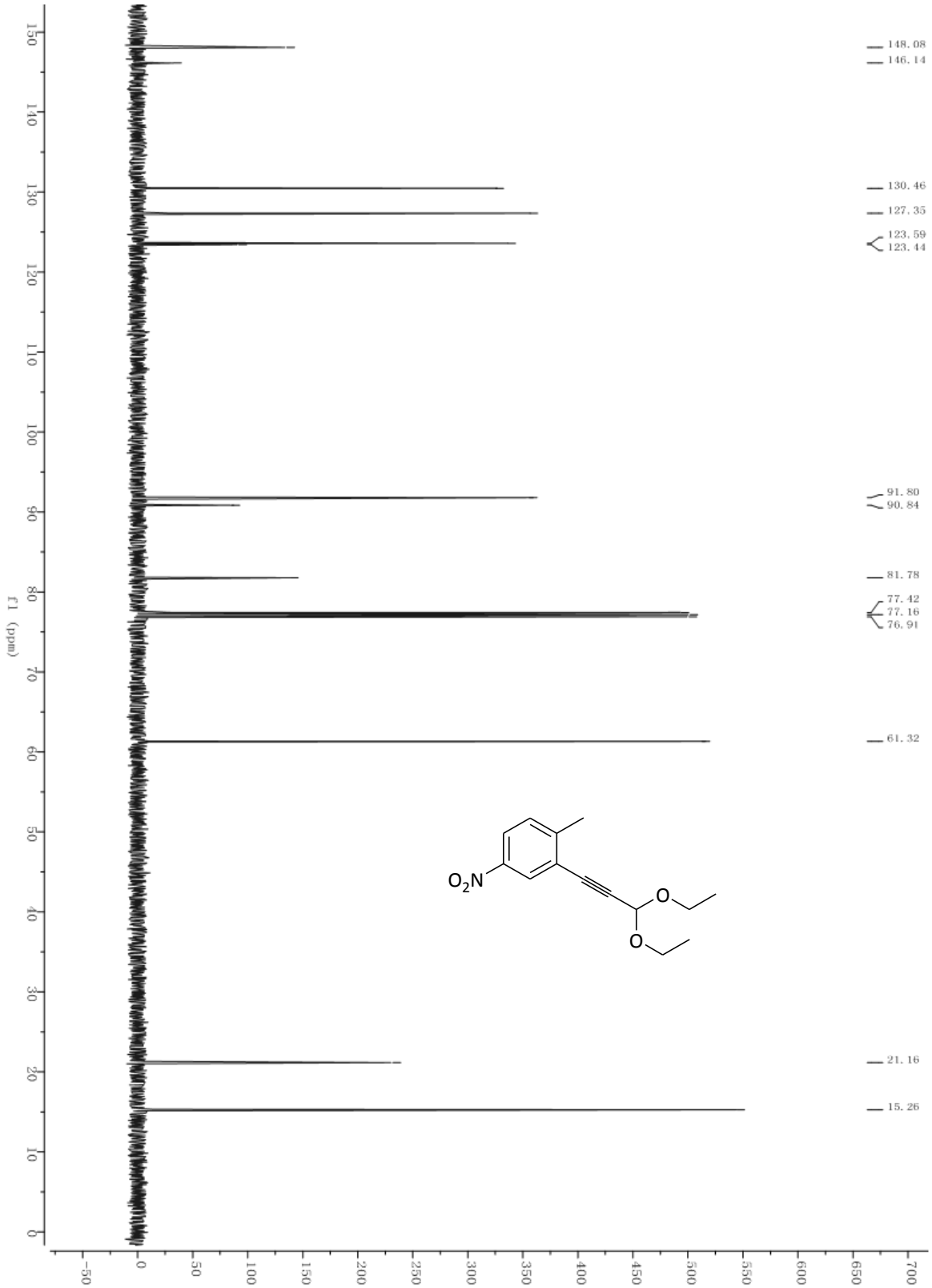

8.12
8.11
7.74
7.74
7.61
7.61
7.51
7.50
7.50
7.49
7.48
7.48
7.47
7.46
7.26
6.90
6.90
6.89
6.88
6.88
6.87
6.56
6.55
1.04
0.97
1.00
2.98
2.01
1.05
3.10
9.34
3.83
1.68
Boc
N
O
f1 (ppm)

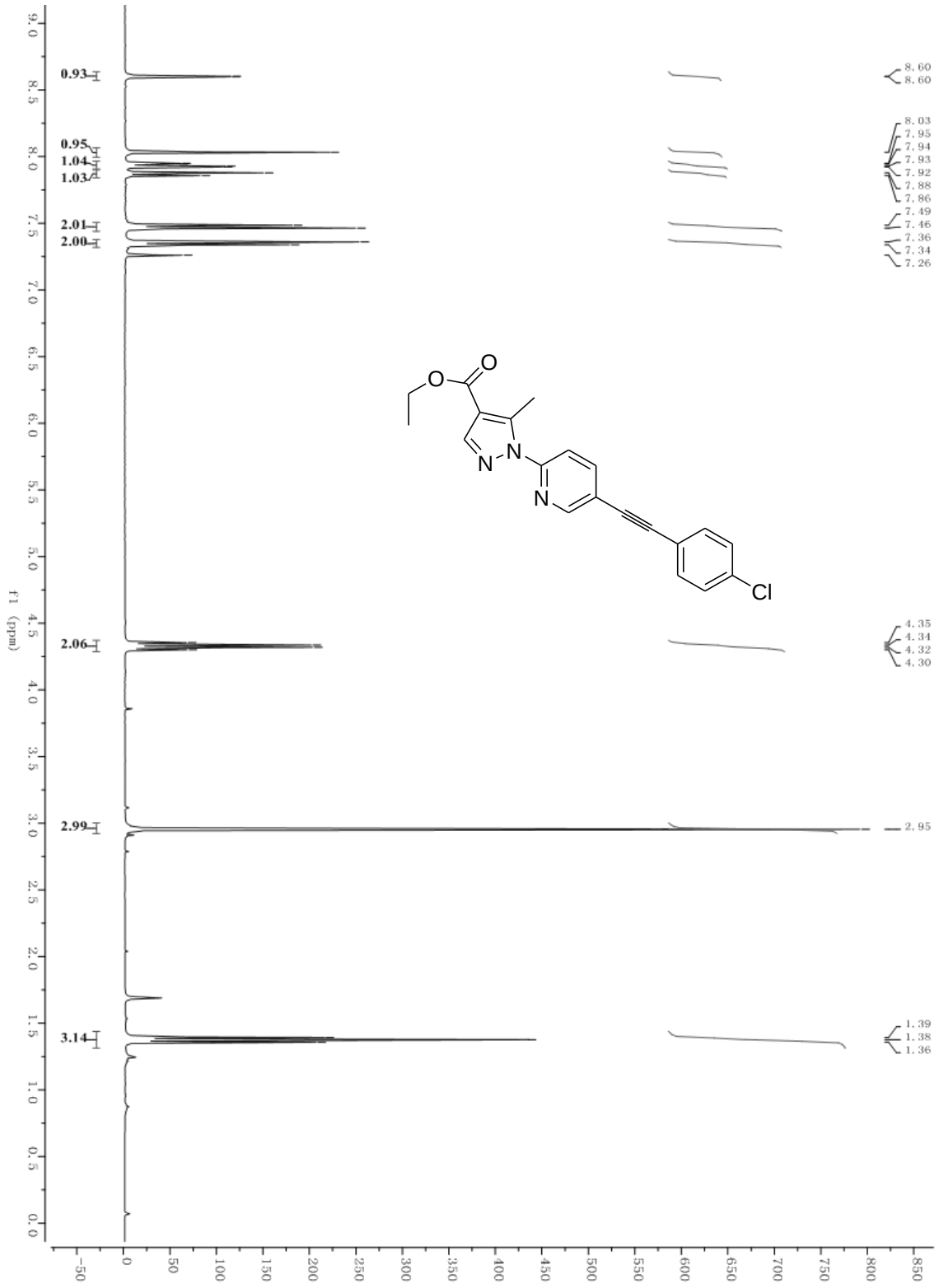

159.58
149.65
134.75
133.09
130.66
127.80
126.84
124.34
117.87
115.85
115.26
114.12
107.24
88.84
88.12
84.11
77.42
77.16
76.91
55.42
28.31
Boc
N
O
f1 (ppm)

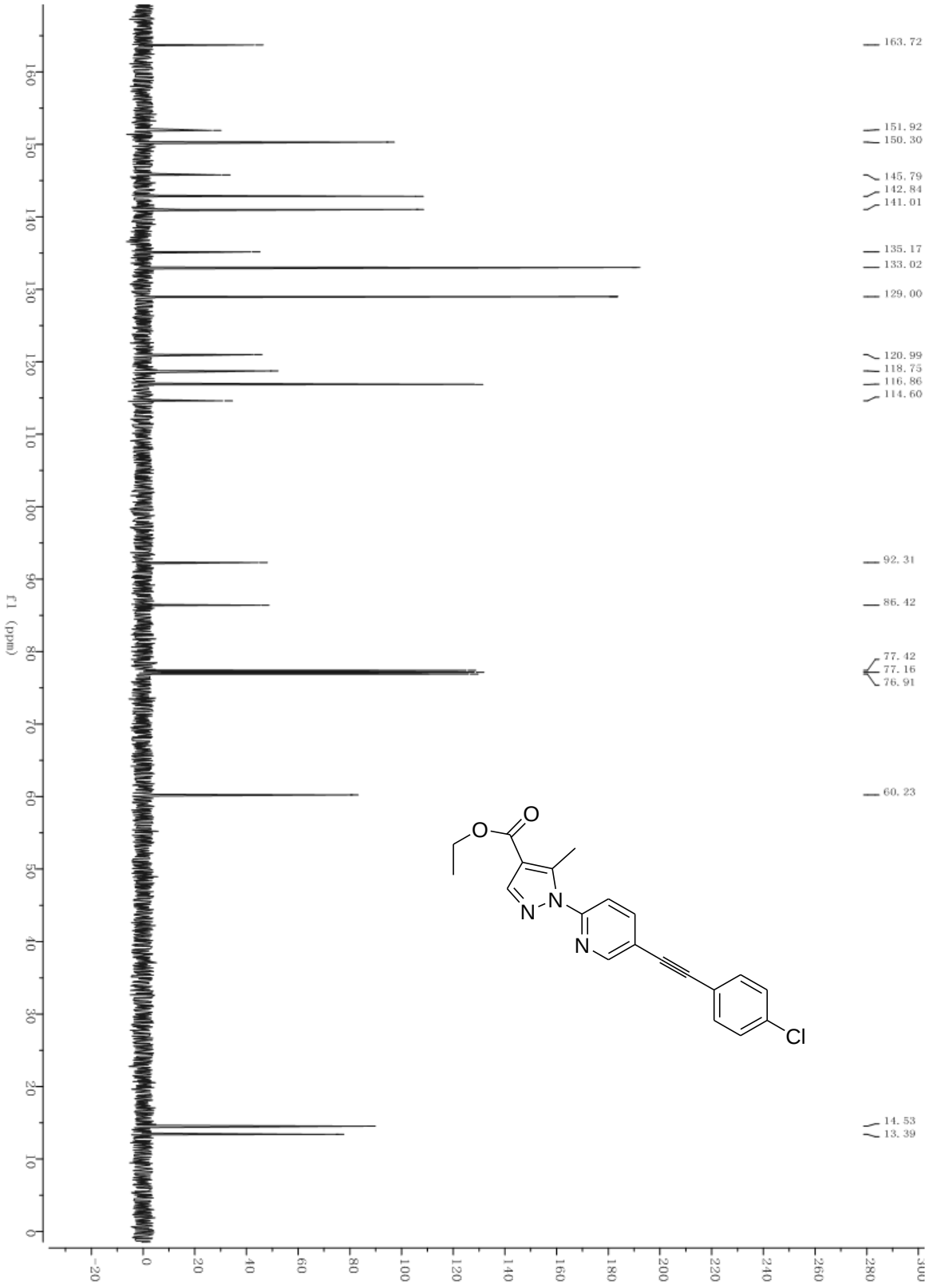

2.00
2.05
1.05
5.13
1.12
1.19
2.03
1.23
1.32
4.61
f1 (ppm)
O
O
OTHP

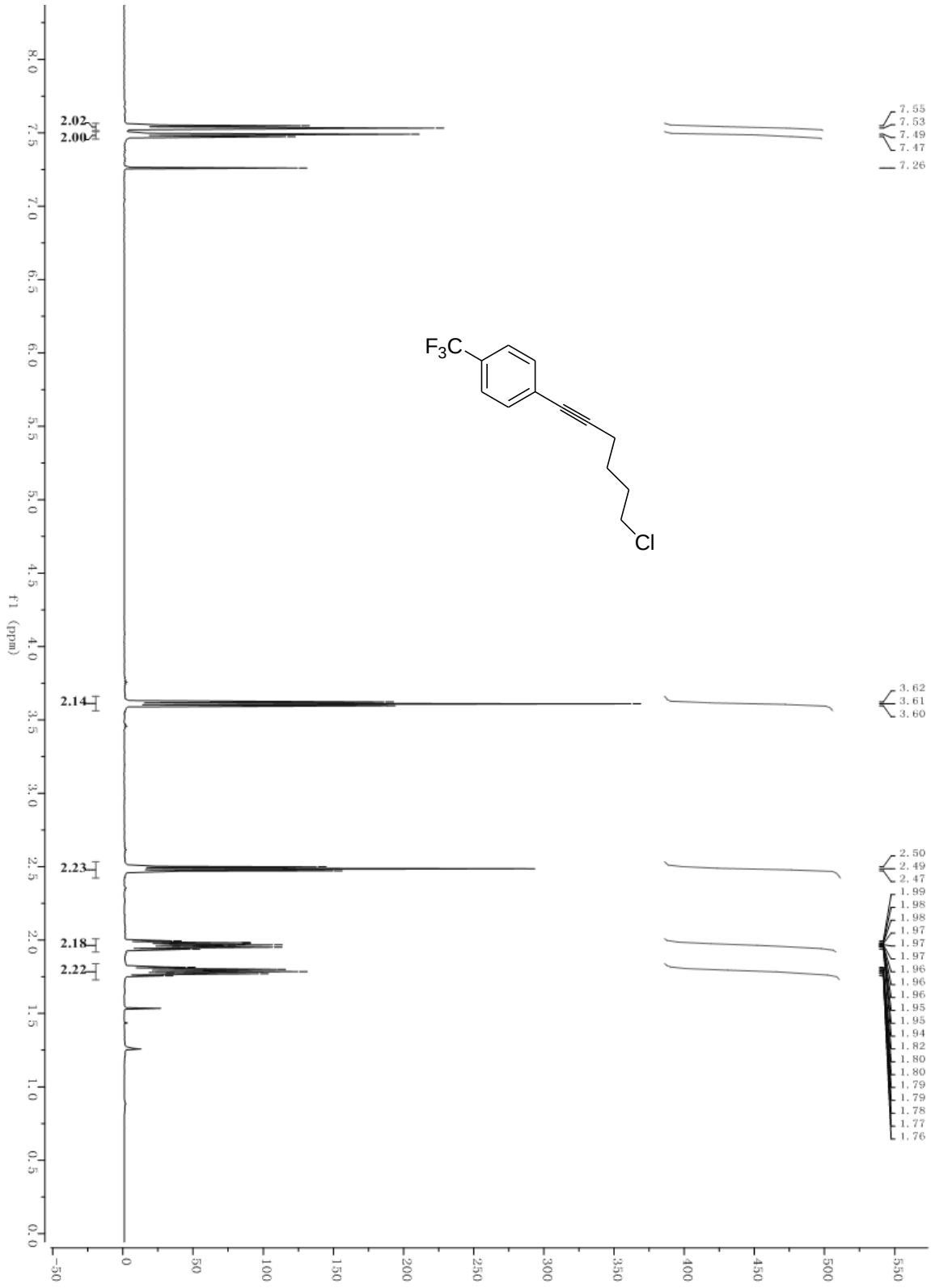

166.71
131.62
129.51
129.17
128.64
98.90
90.60
81.02
77.41
77.16
76.91
65.62
62.32
52.26
30.68
25.54
21.15
19.49
O
O
OTHP
f1 (ppm)


0.90
1.00
1.09
1.02
2.26
2.28
3.24
6.60
8.29
8.29
8.08
8.08
8.07
8.06
7.37
7.35
7.26
5.53
3.86
3.84
3.84
3.83
3.82
3.81
3.81
3.79
3.72
3.70
3.70
3.69
3.68
3.67
3.67
3.66
2.54
1.30
1.29
1.27
O2N
O
O
f1 (ppm)


148.08
146.14
130.46
127.35
123.59
123.44
91.80
90.84
81.78
77.42
77.16
76.91
61.32
21.16
15.26
f1 (ppm)
O2N
O
O


0.93
0.95
1.04
1.03
2.01
2.00
2.06
2.99
3.14
8.60
8.60
8.03
7.95
7.94
7.93
7.92
7.88
7.86
7.49
7.46
7.36
7.34
7.26
4.35
4.34
4.32
4.30
2.95
1.39
1.38
1.36
O
O
N
N
N
Cl
f1 (ppm)


163.72
151.92
150.30
145.79
142.84
141.01
135.17
133.02
129.00
120.99
118.75
116.86
114.60
92.31
86.42
77.42
77.16
76.91
60.23
14.53
13.39
f1 (ppm)
O
O
N
N
N
Cl


F3C
Cl
2.02
2.00
2.14
2.23
2.18
2.22
7.55
7.53
7.49
7.47
7.26
3.62
3.61
3.60
2.50
2.49
2.47
1.99
1.98
1.98
1.97
1.97
1.97
1.96
1.96
1.96
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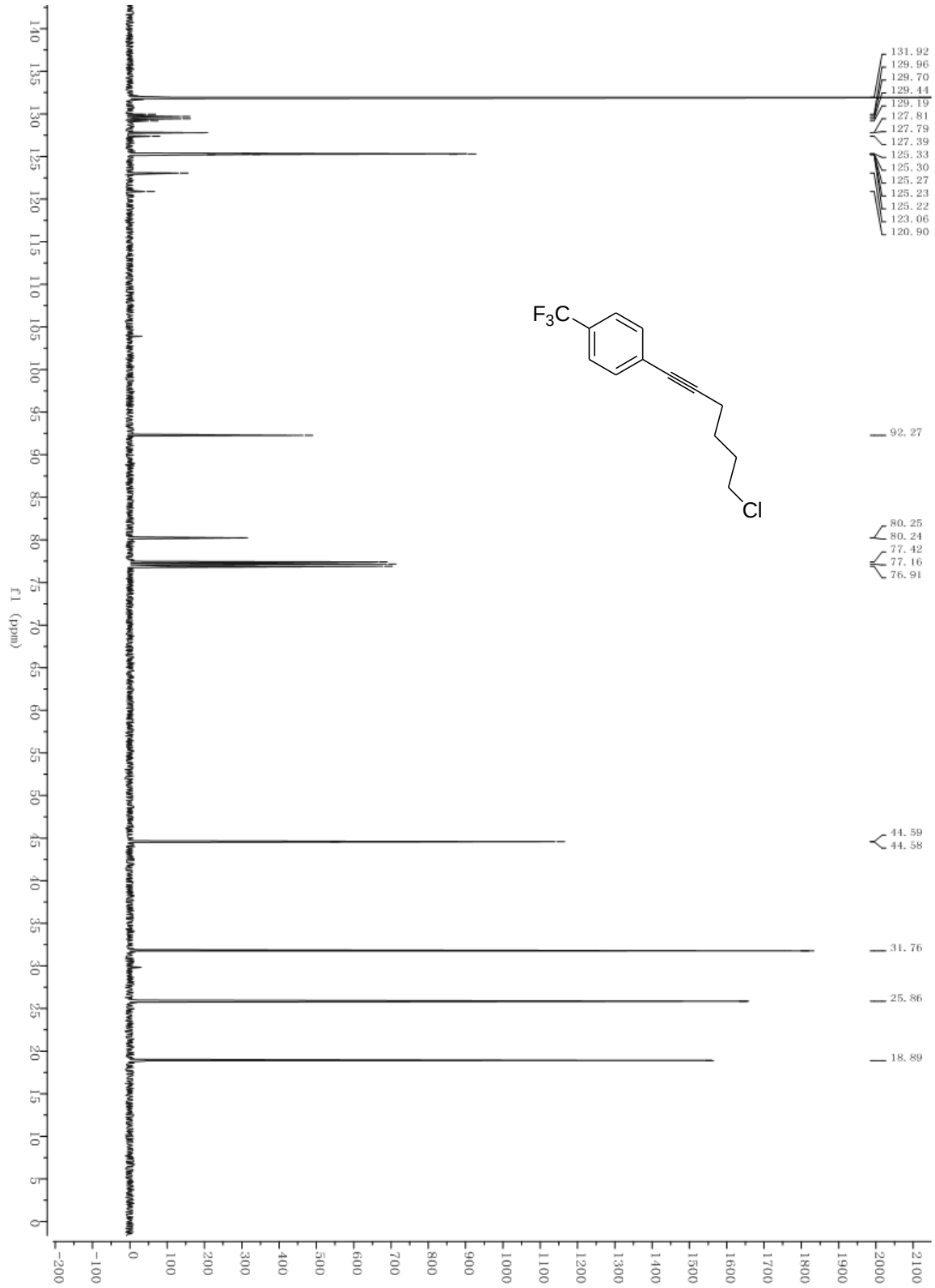
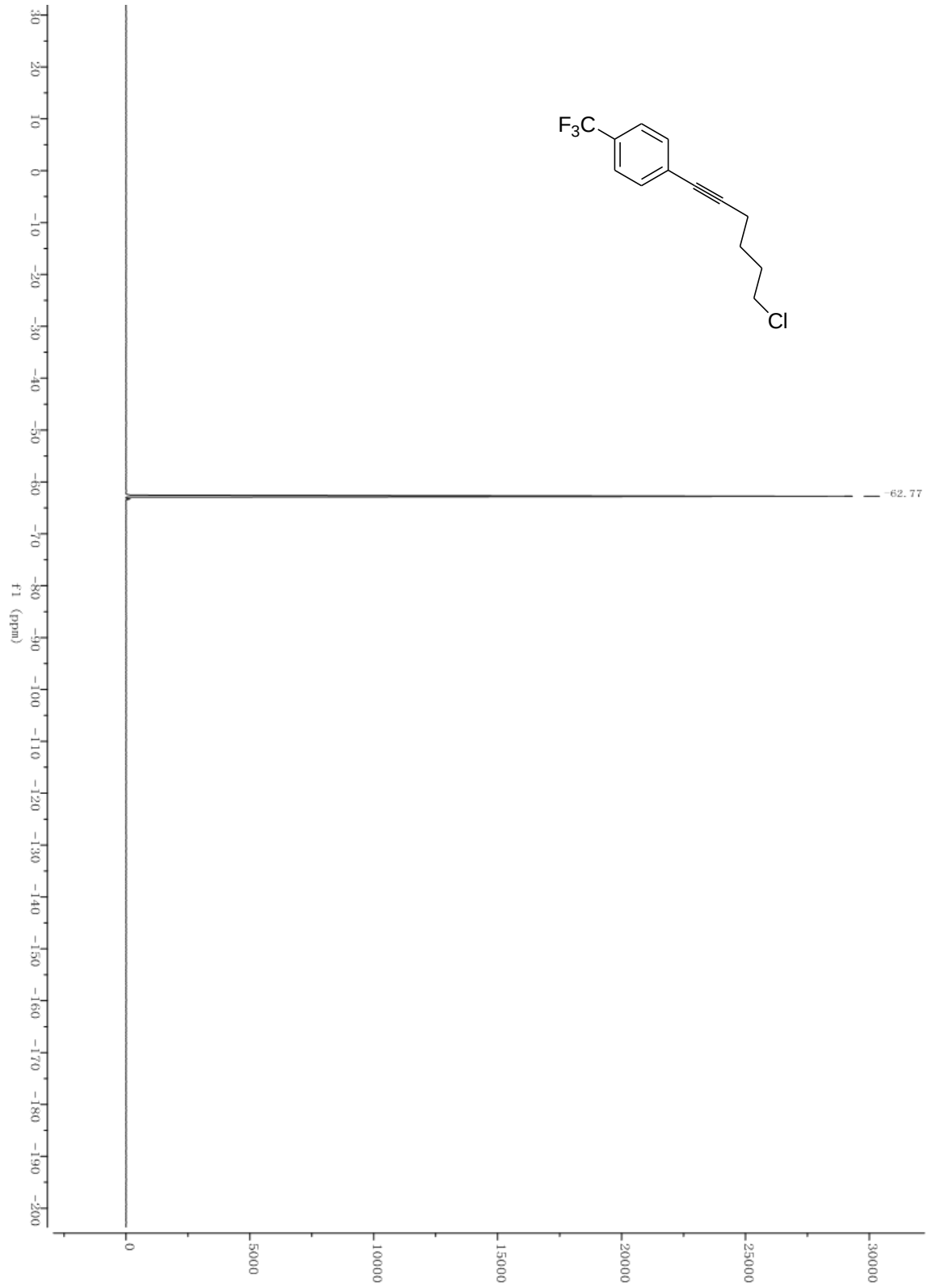
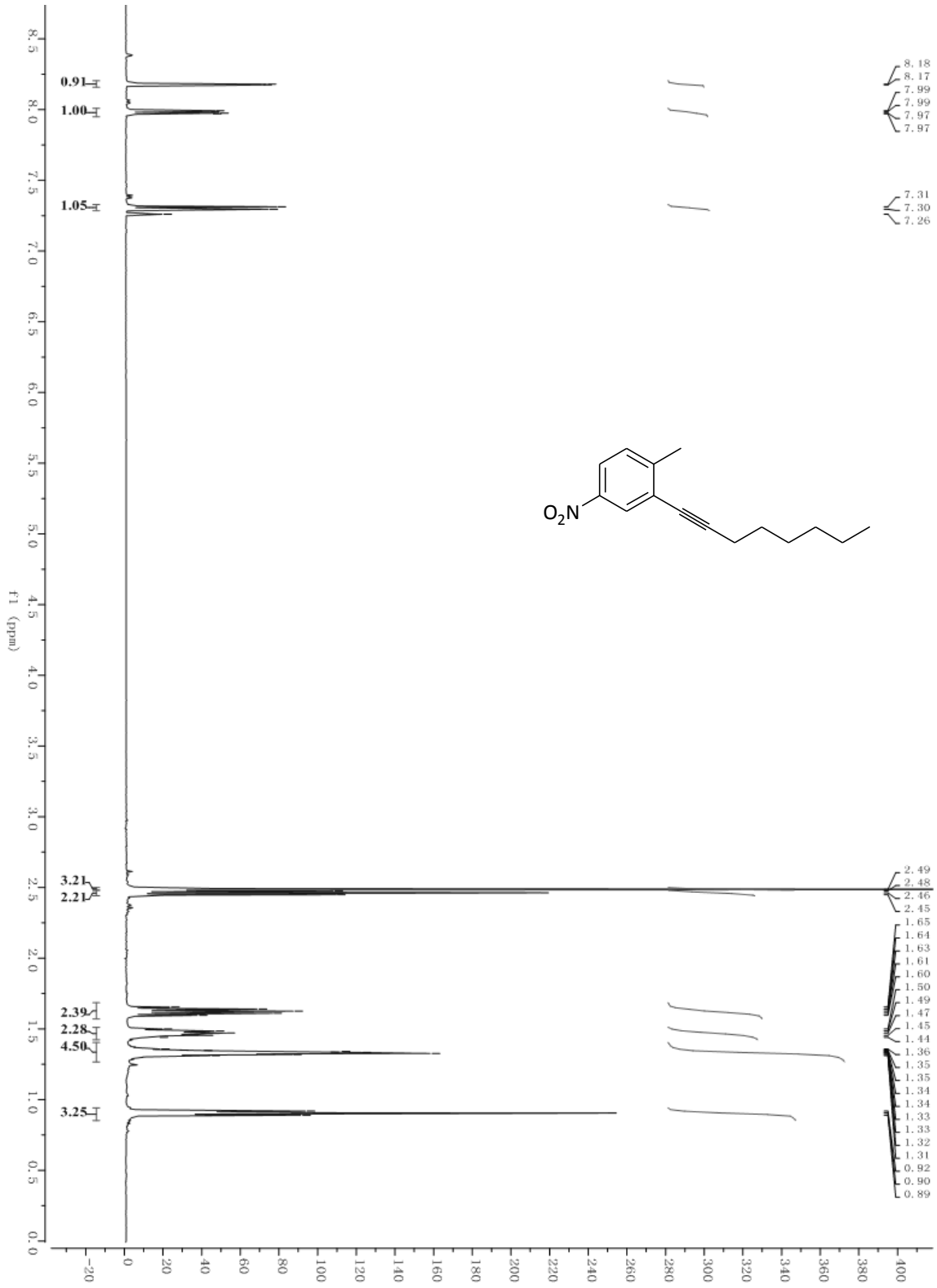
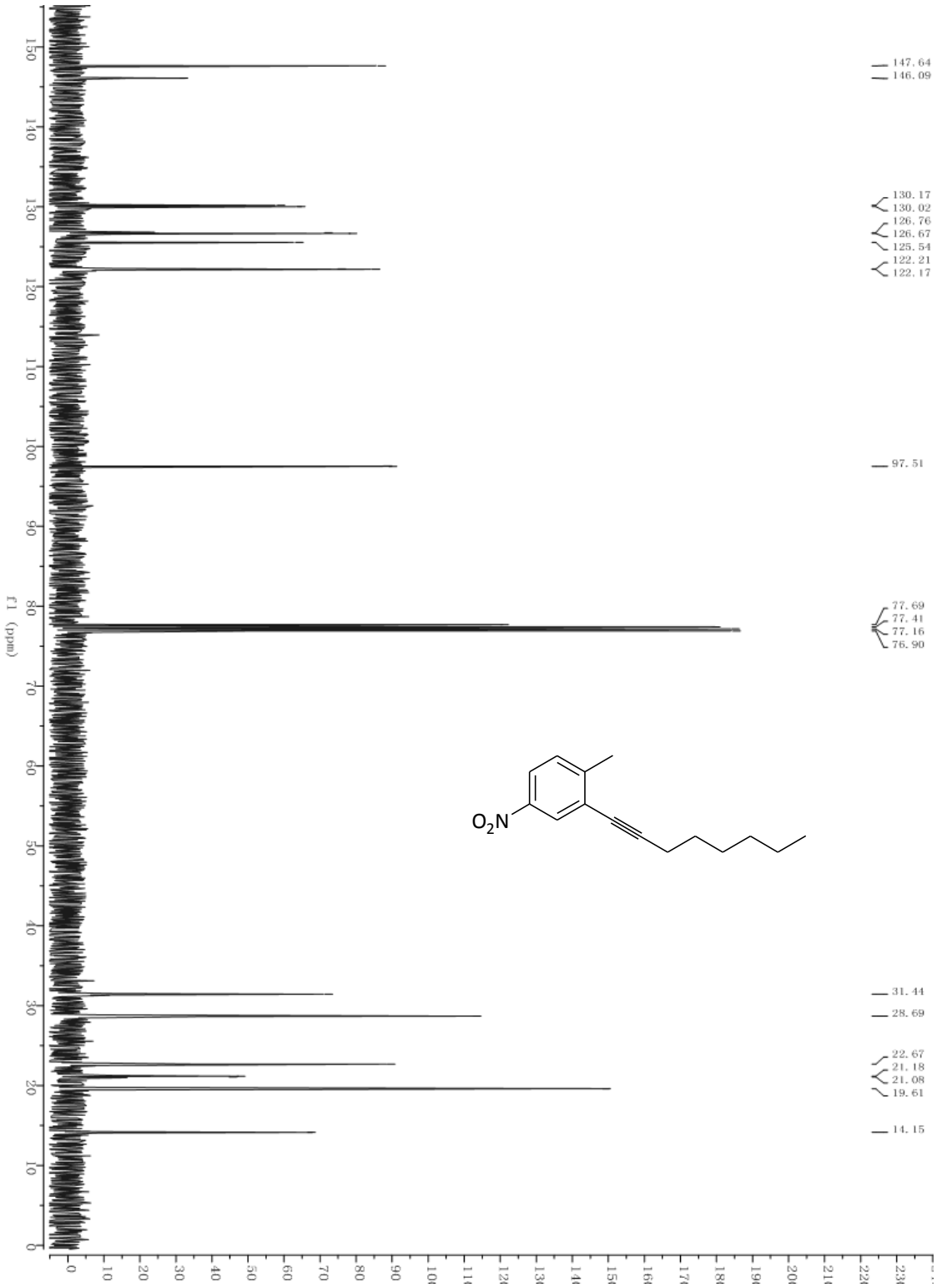
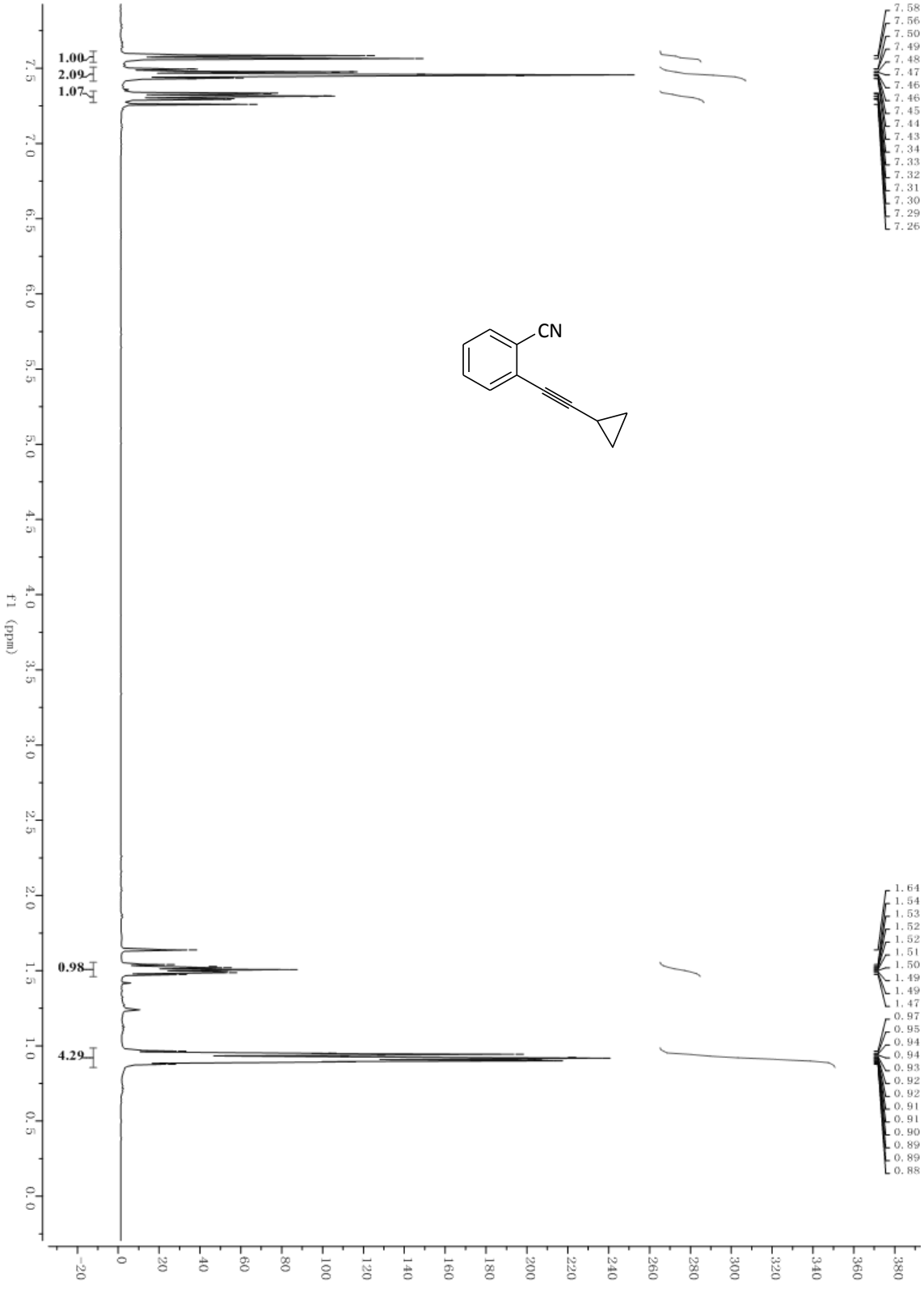
1.79
1.78
1.77
1.76
f1 (ppm)

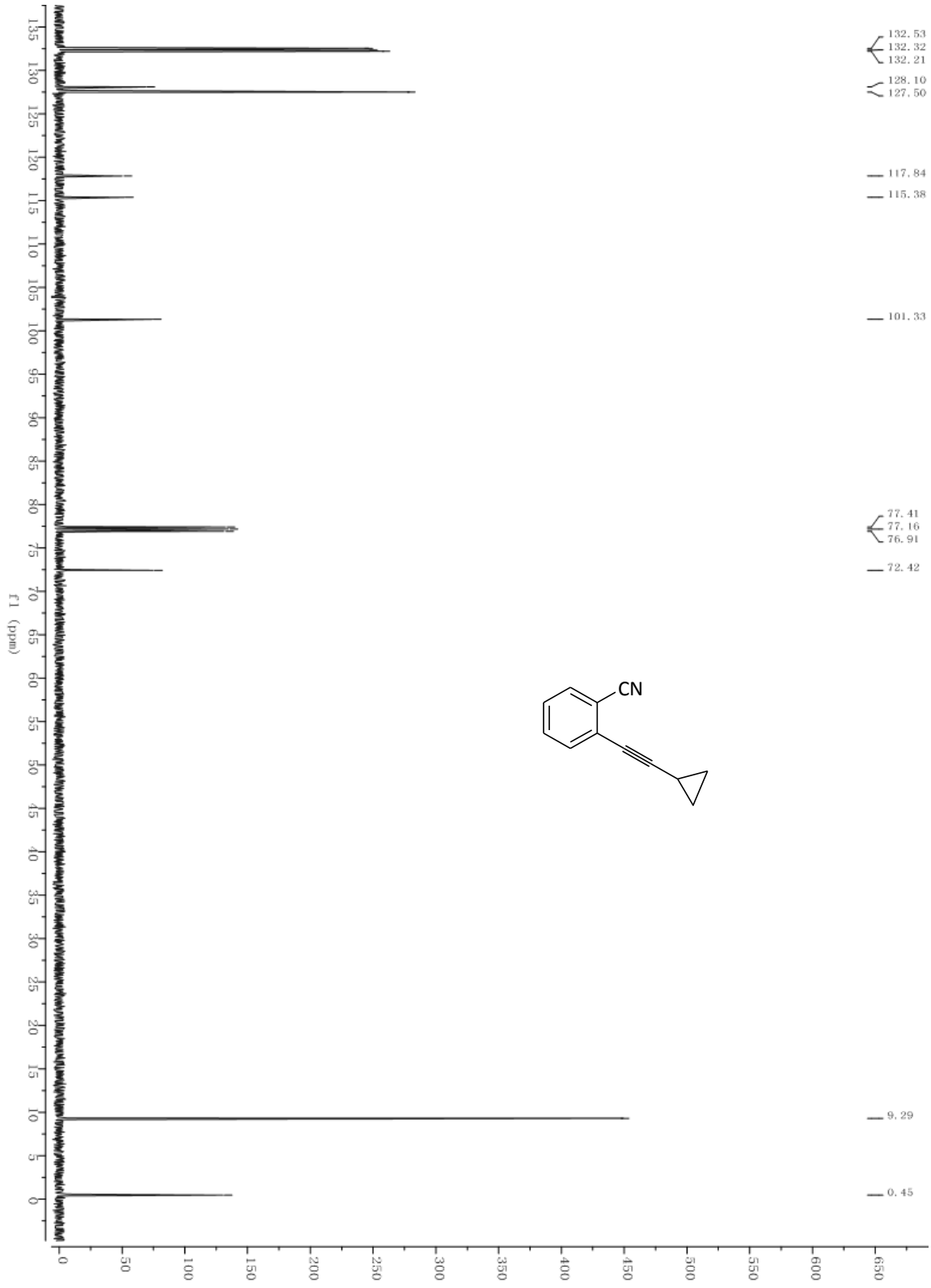

131.92
129.96
129.70
129.44
129.19
127.81
127.79
127.39
125.33
125.30
125.27
125.23
125.22
123.06
120.90
92.27
80.25
80.24
77.42
77.16
76.91
44.59
44.58
31.76
25.86
18.89
F3C
Cl
f1 (ppm)

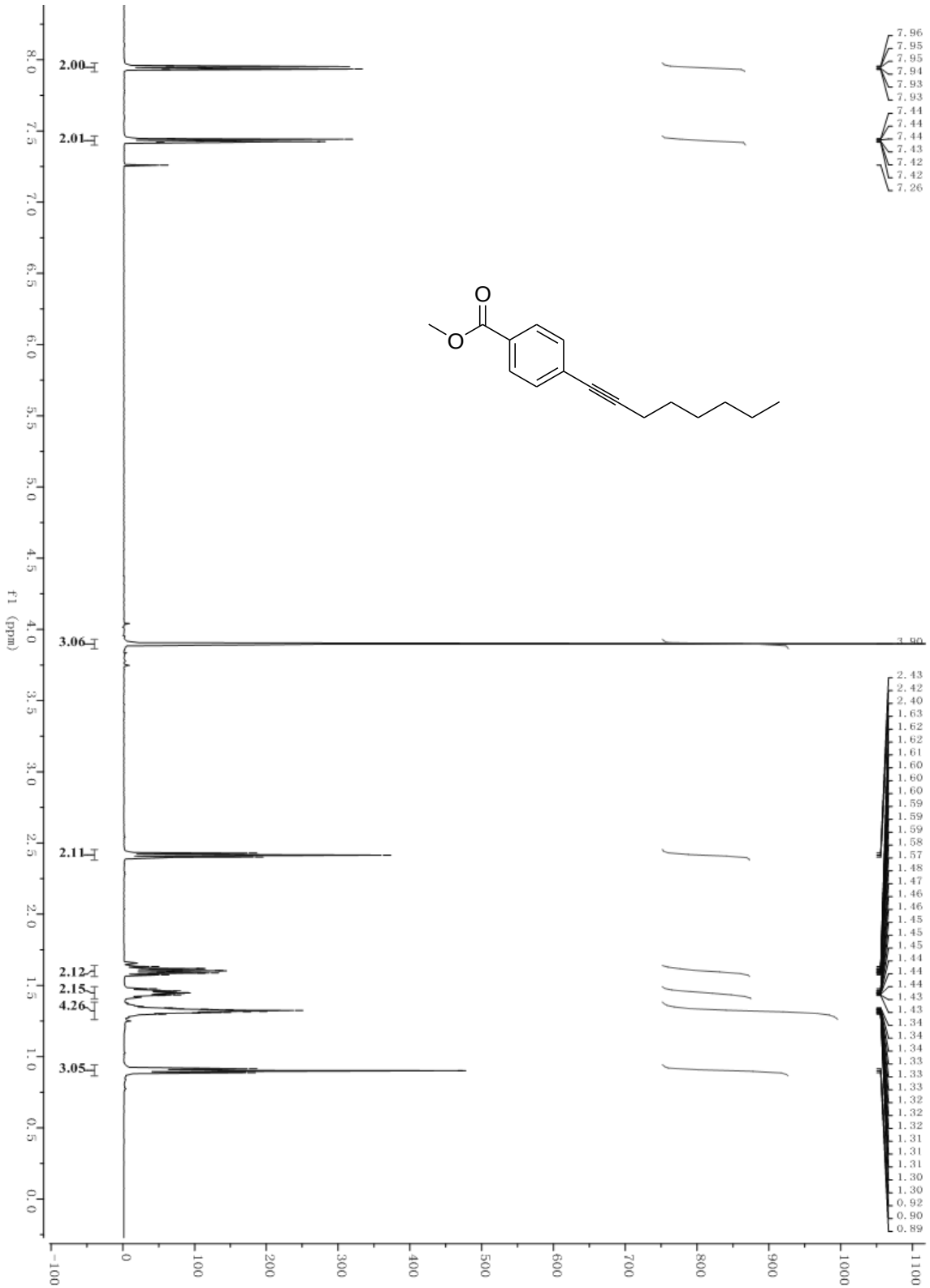

F3C
Cl
-62.77
f1 (ppm)

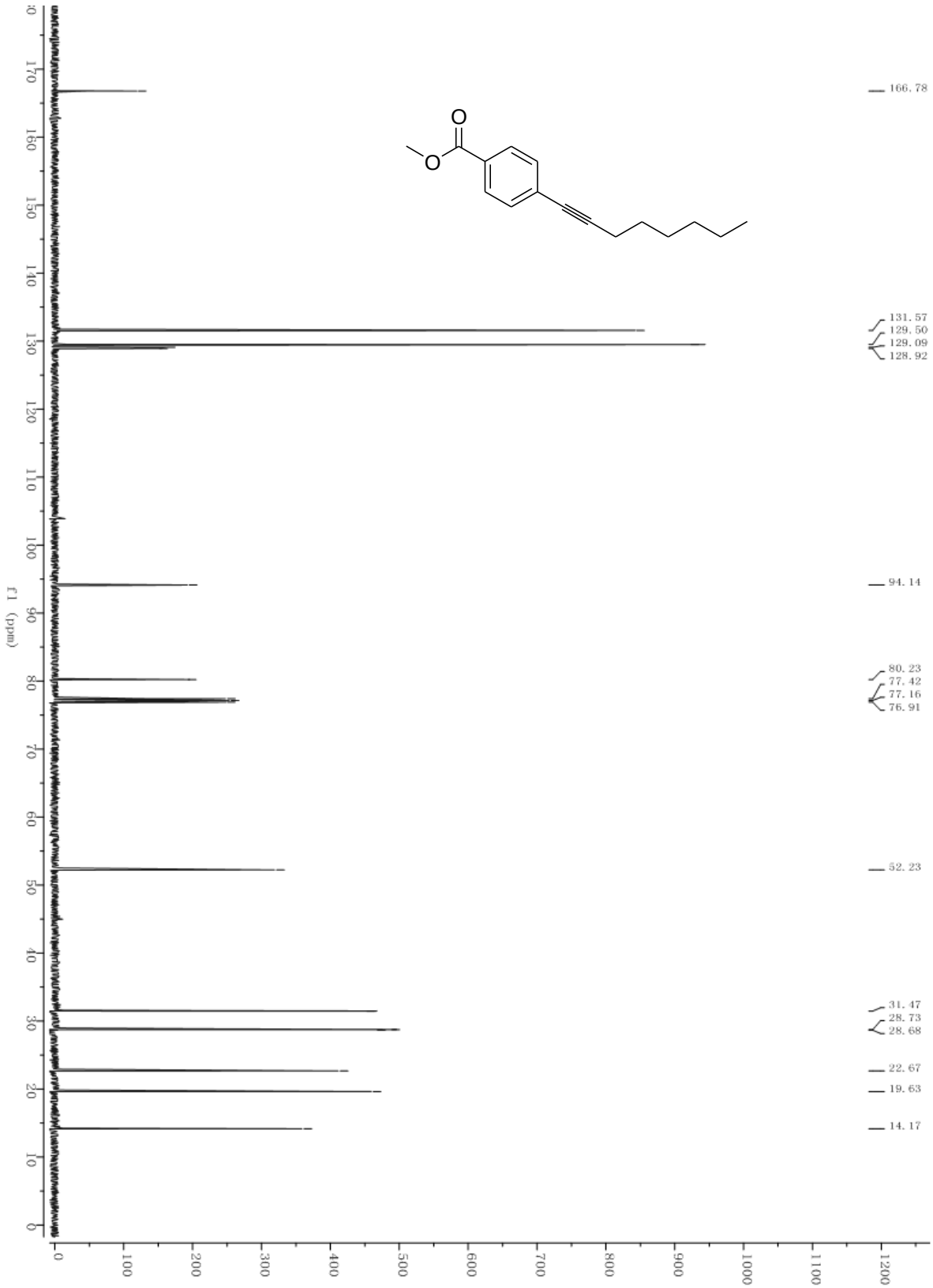

0.91
1.00
1.05
3.21
2.21
2.39
2.28
4.50
3.25
8.18
8.17
7.99
7.99
7.97
7.97
7.31
7.30
7.26
2.49
2.48
2.46
2.45
1.65
1.64
1.63
1.61
1.60
1.50
1.49
1.47
1.45
1.44
1.36
1.35
1.35
1.34
1.34
1.33
1.33
1.32
1.31
0.92
0.90
0.89
O2N
f1 (ppm)

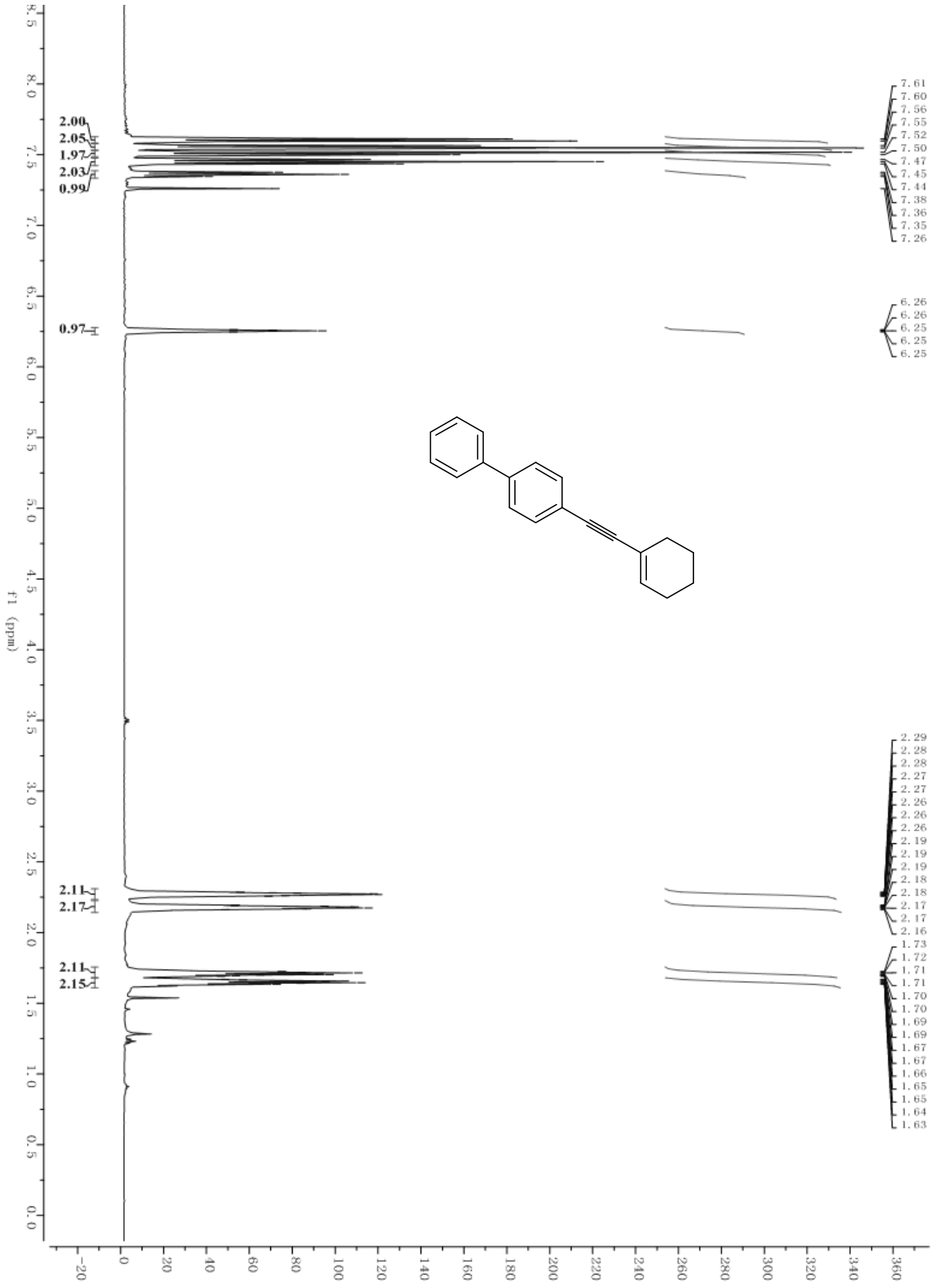

147.64
146.09
130.17
130.02
126.76
126.67
125.54
122.21
122.17
97.51
77.69
77.41
77.16
76.90
31.44
28.69
22.67
21.18
21.08
19.61
14.15
f1 (ppm)
O2N

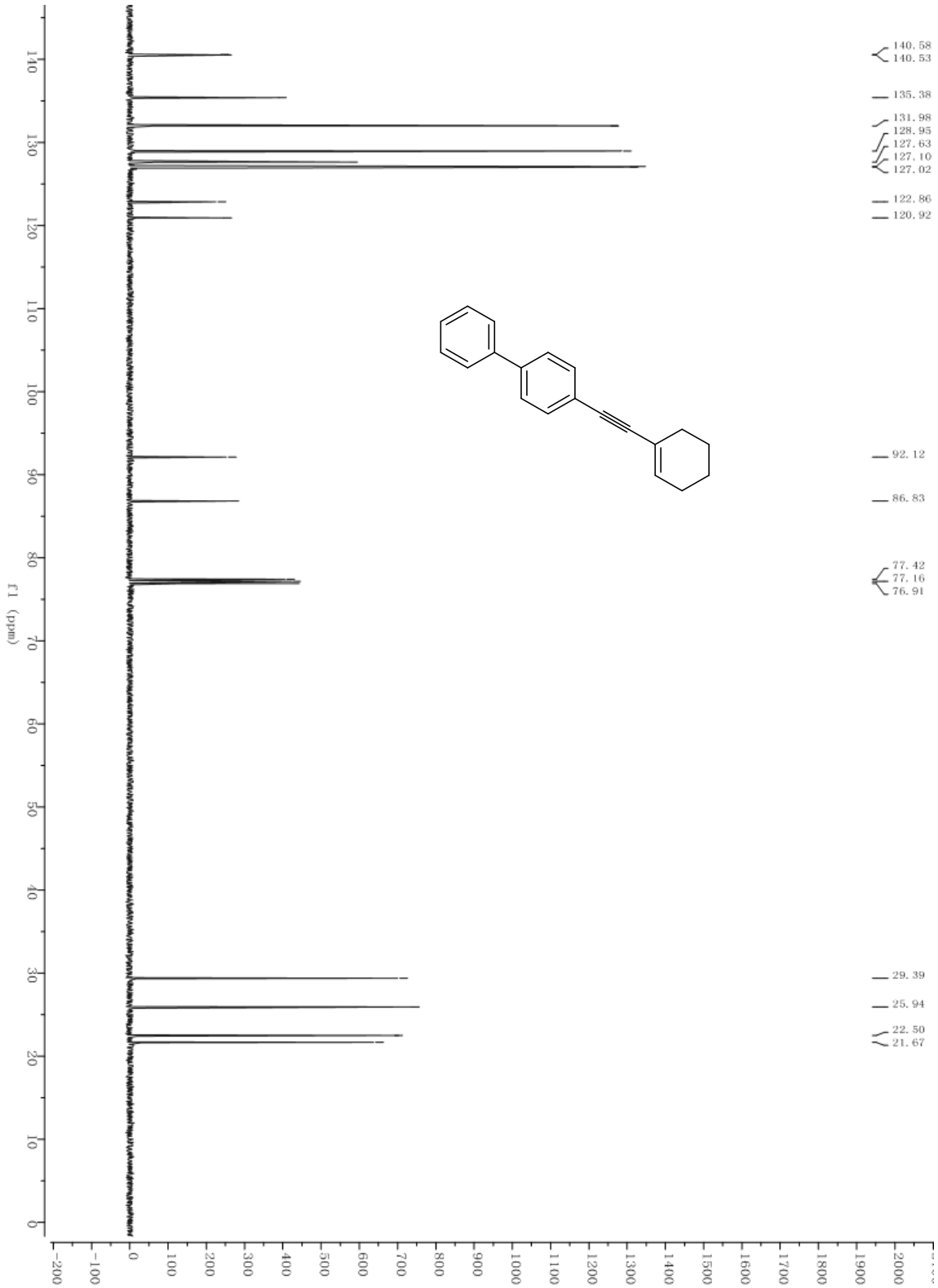

1.00
2.09
1.07
0.98
4.29
CN
7.58
7.56
7.50
7.49
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.34
7.33
7.32
7.31
7.30
7.29
7.26
1.64
1.54
1.53
1.52
1.52
1.51
1.50
1.49
1.49
1.47
0.97
0.95
0.94
0.94
0.93
0.92
0.92
0.91
0.91
0.90
0.89
0.89
0.88
f1 (ppm)

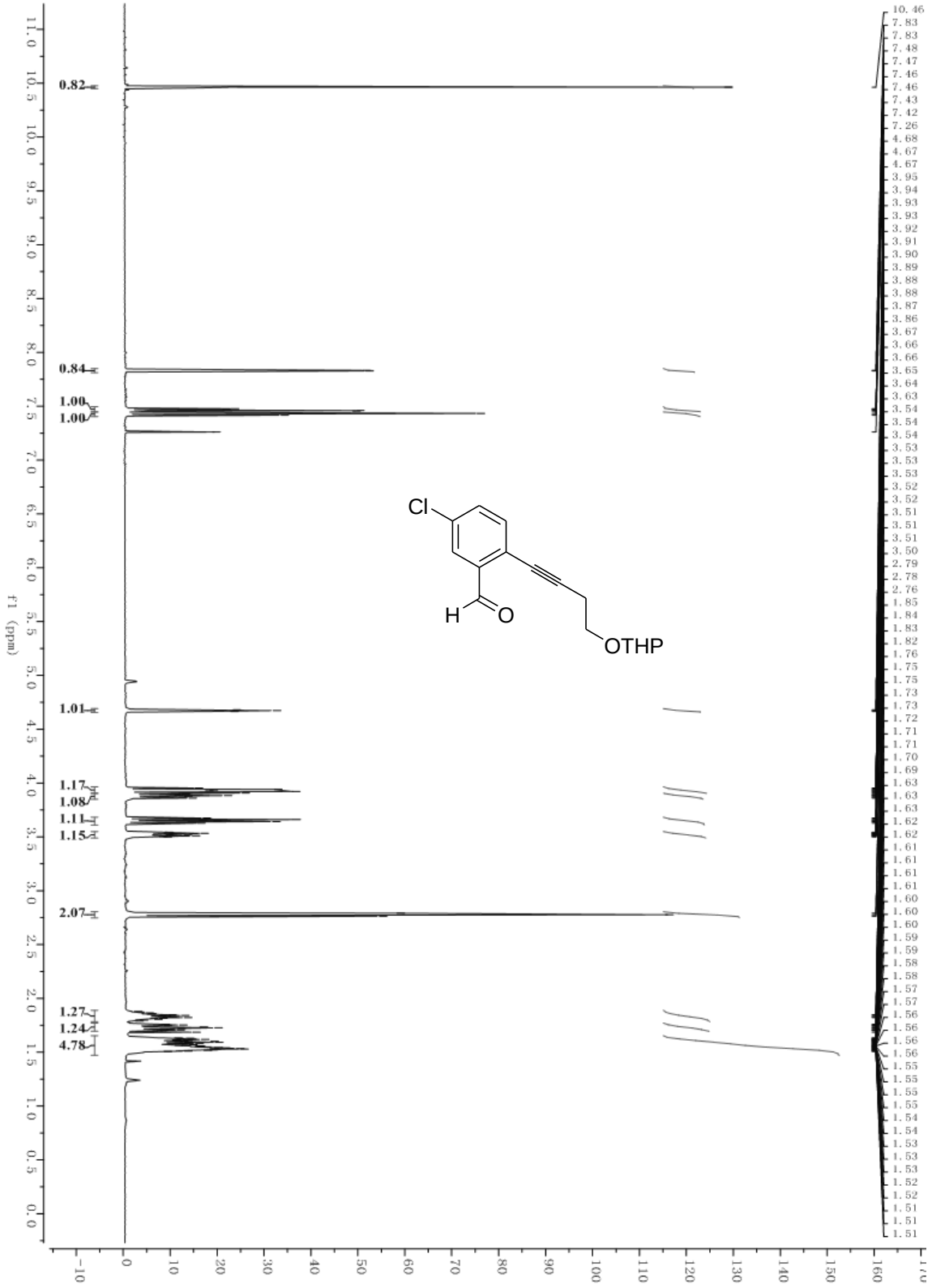

132.53
132.32
132.21
128.10
127.50
117.84
115.38
101.33
77.41
77.16
76.91
72.42
9.29
0.45
f1 (ppm)
CN

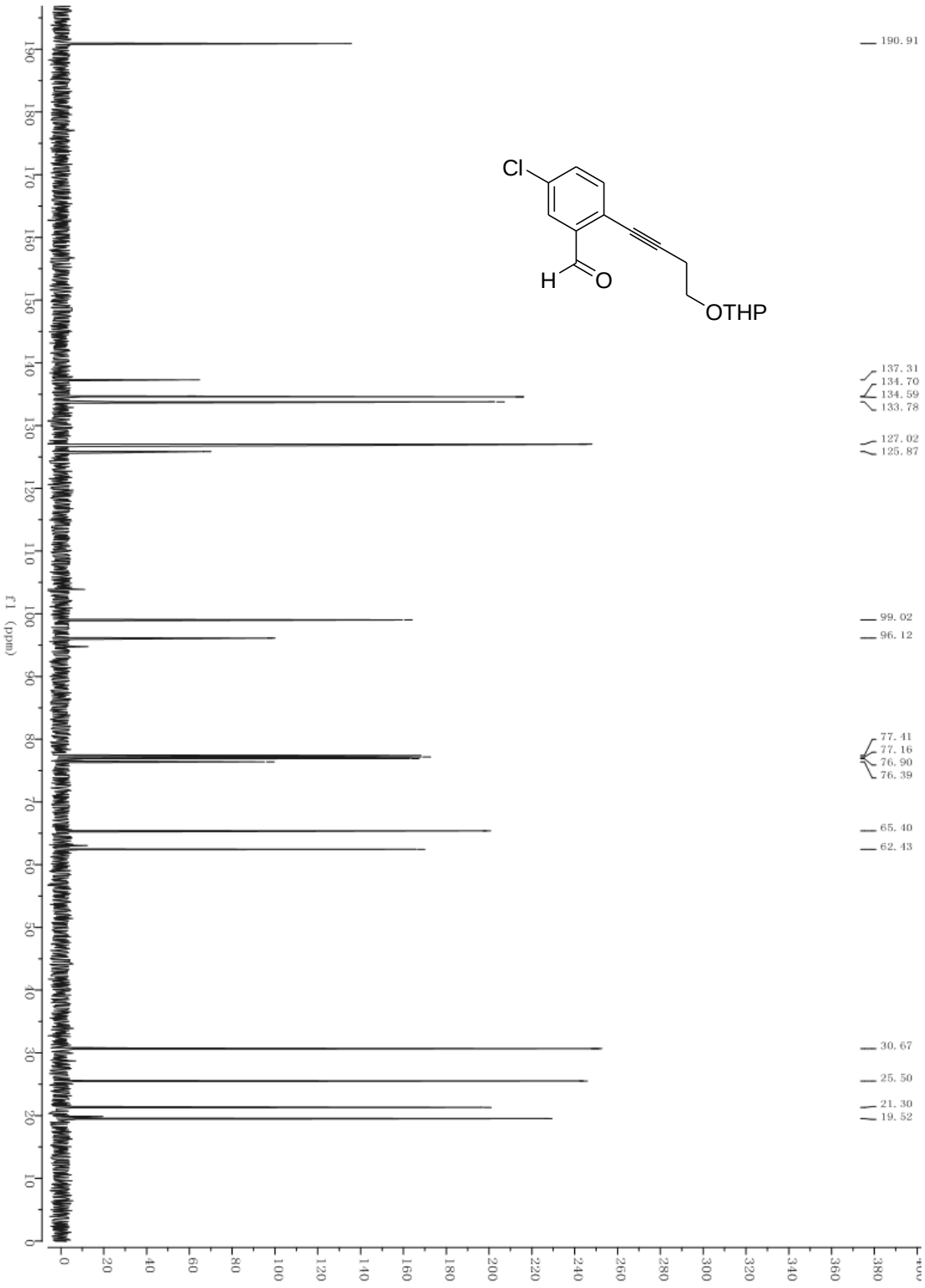

2.00
2.01
3.06
2.11
2.12
2.15
4.26
3.05
f1 (ppm)
O
O

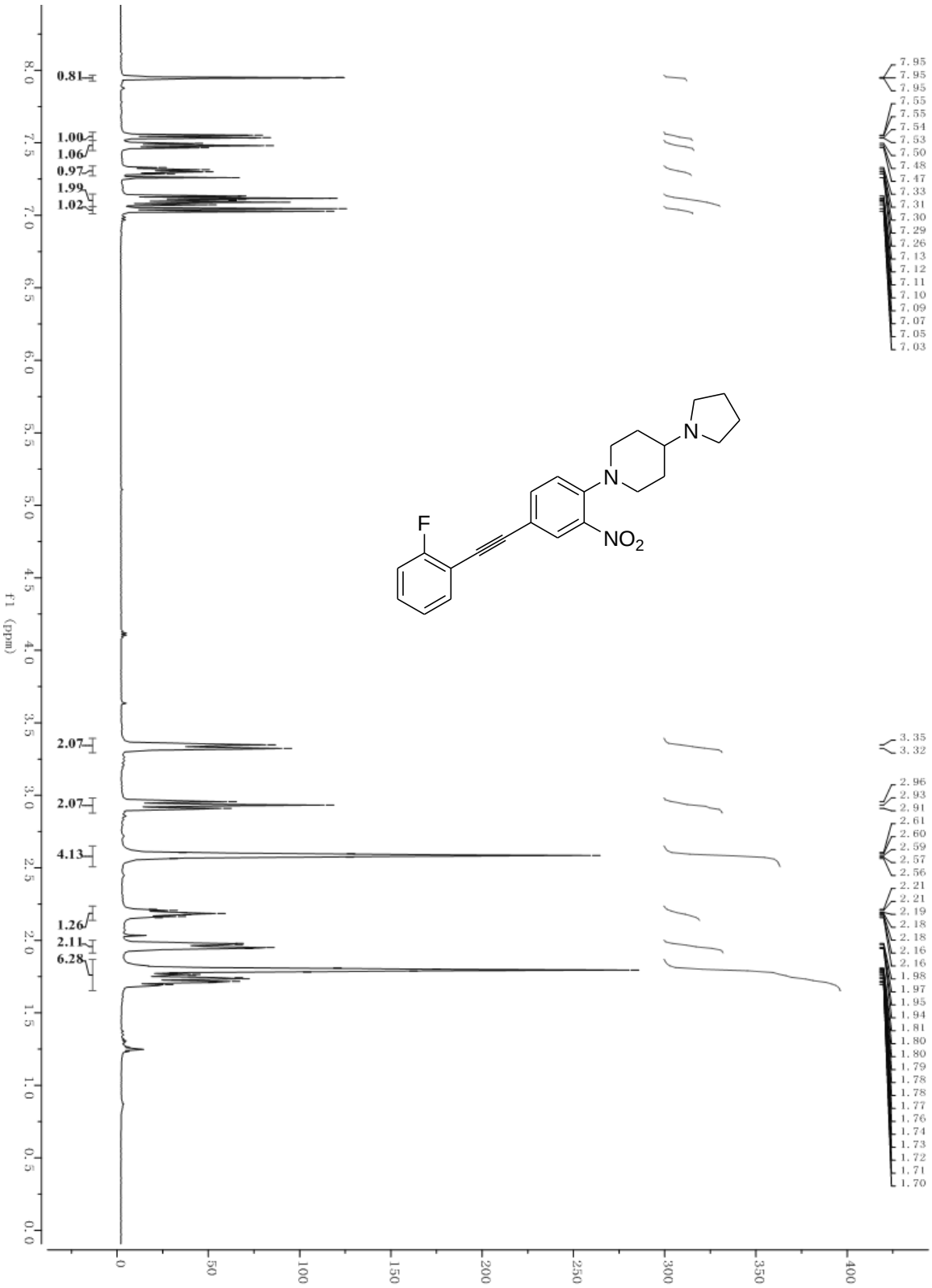

166.78
131.57
129.50
129.09
128.92
94.14
80.23
77.42
77.16
76.91
52.23
31.47
28.73
28.68
22.67
19.63
14.17
f1 (ppm)

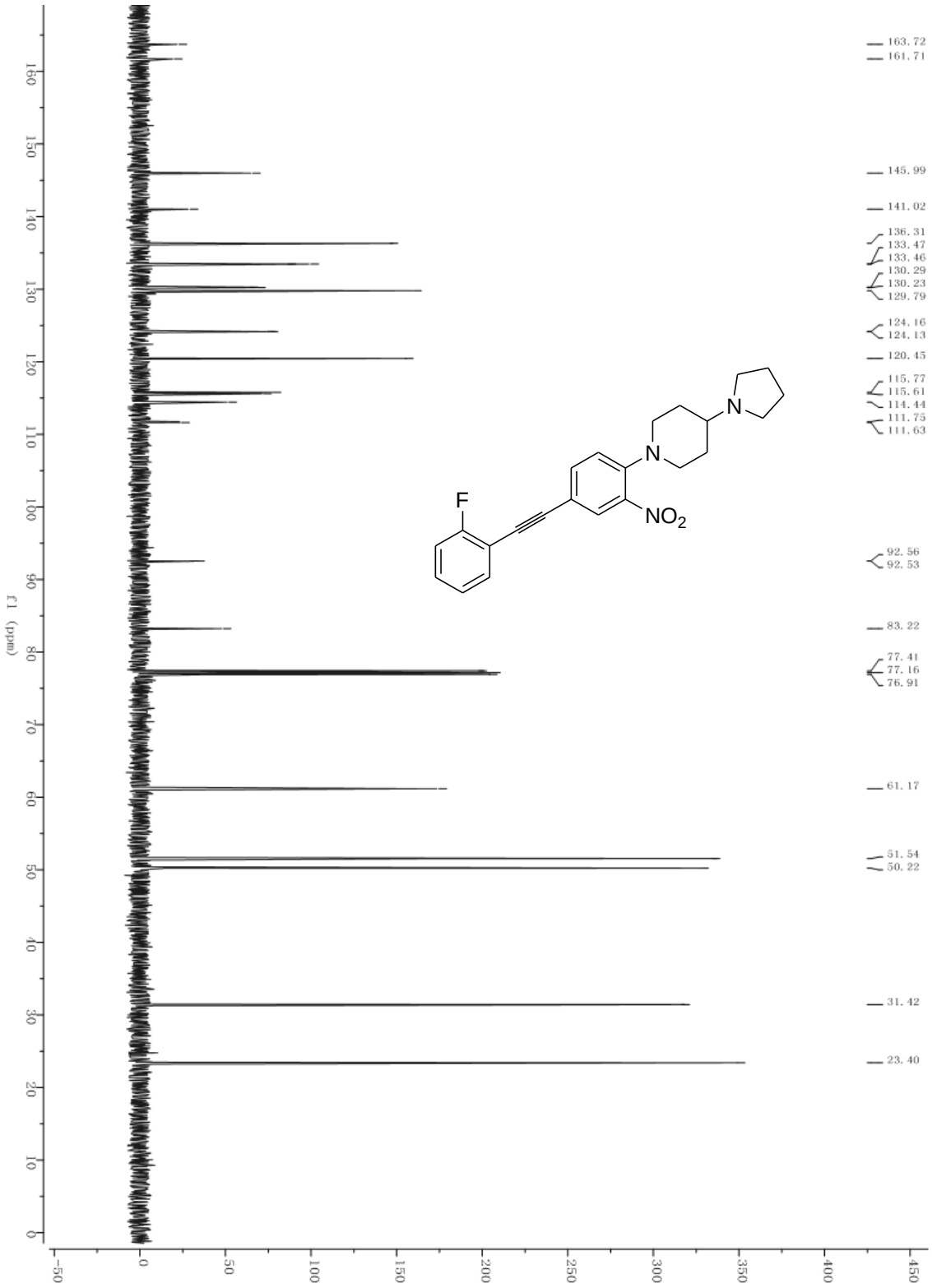

2.00
2.05
1.97
2.03
0.99
0.97
2.11
2.17
2.11
2.15
7.61
7.60
7.56
7.55
7.52
7.50
7.47
7.45
7.44
7.38
7.36
7.35
7.26
6.26
6.26
6.25
6.25
6.25
2.29
2.28
2.28
2.27
2.27
2.26
2.26
2.26
2.19
2.19
2.19
2.18
2.18
2.17
2.17
2.16
1.73
1.72
1.71
1.71
1.70
1.70
1.69
1.69
1.67
1.67
1.66
1.65
1.65
1.64
1.63
f1 (ppm)

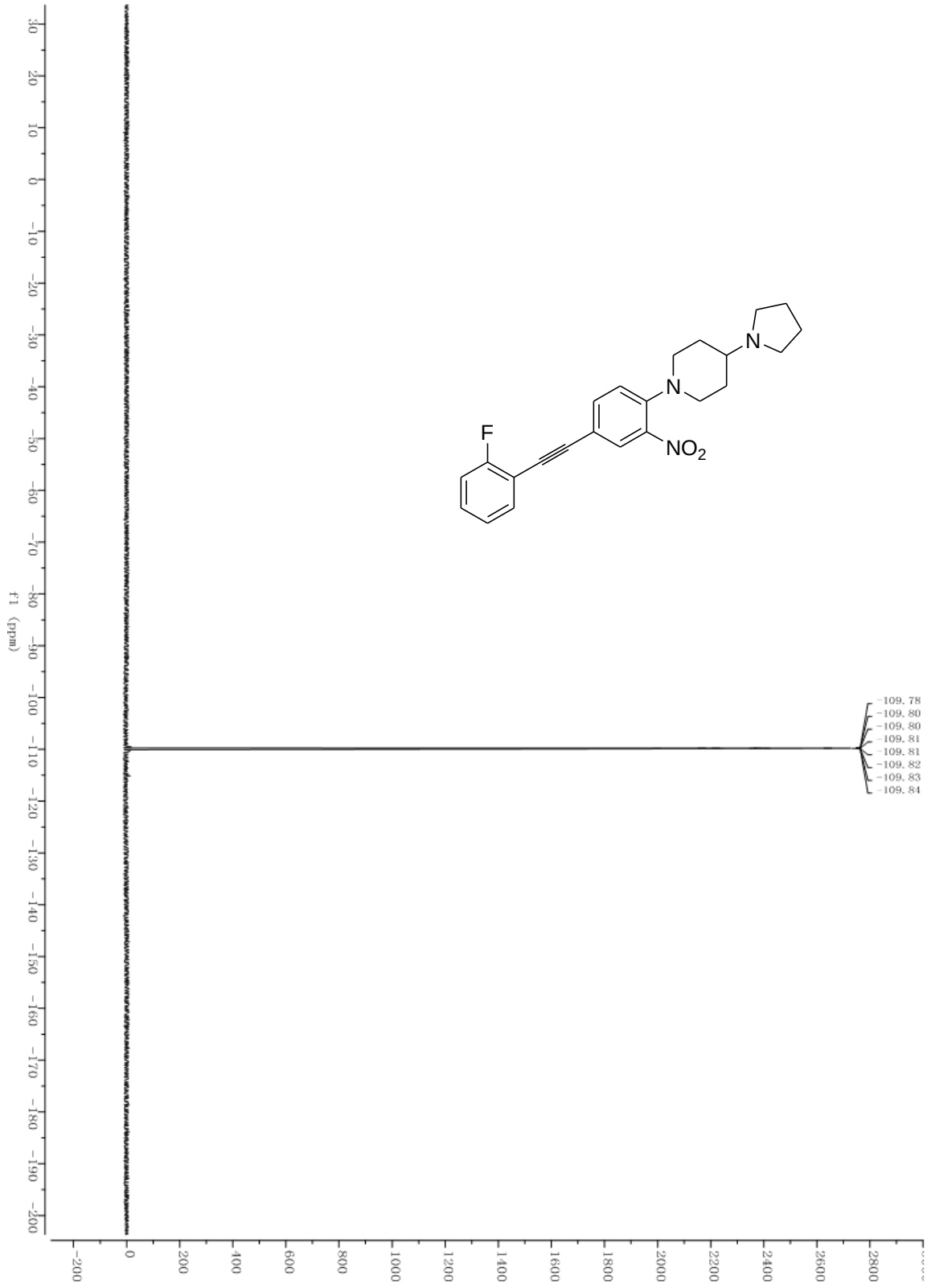

140.58
140.53
135.38
131.98
128.95
127.63
127.10
127.02
122.86
120.92
92.12
86.83
77.42
77.16
76.91
29.39
25.94
22.50
21.67
f1 (ppm)

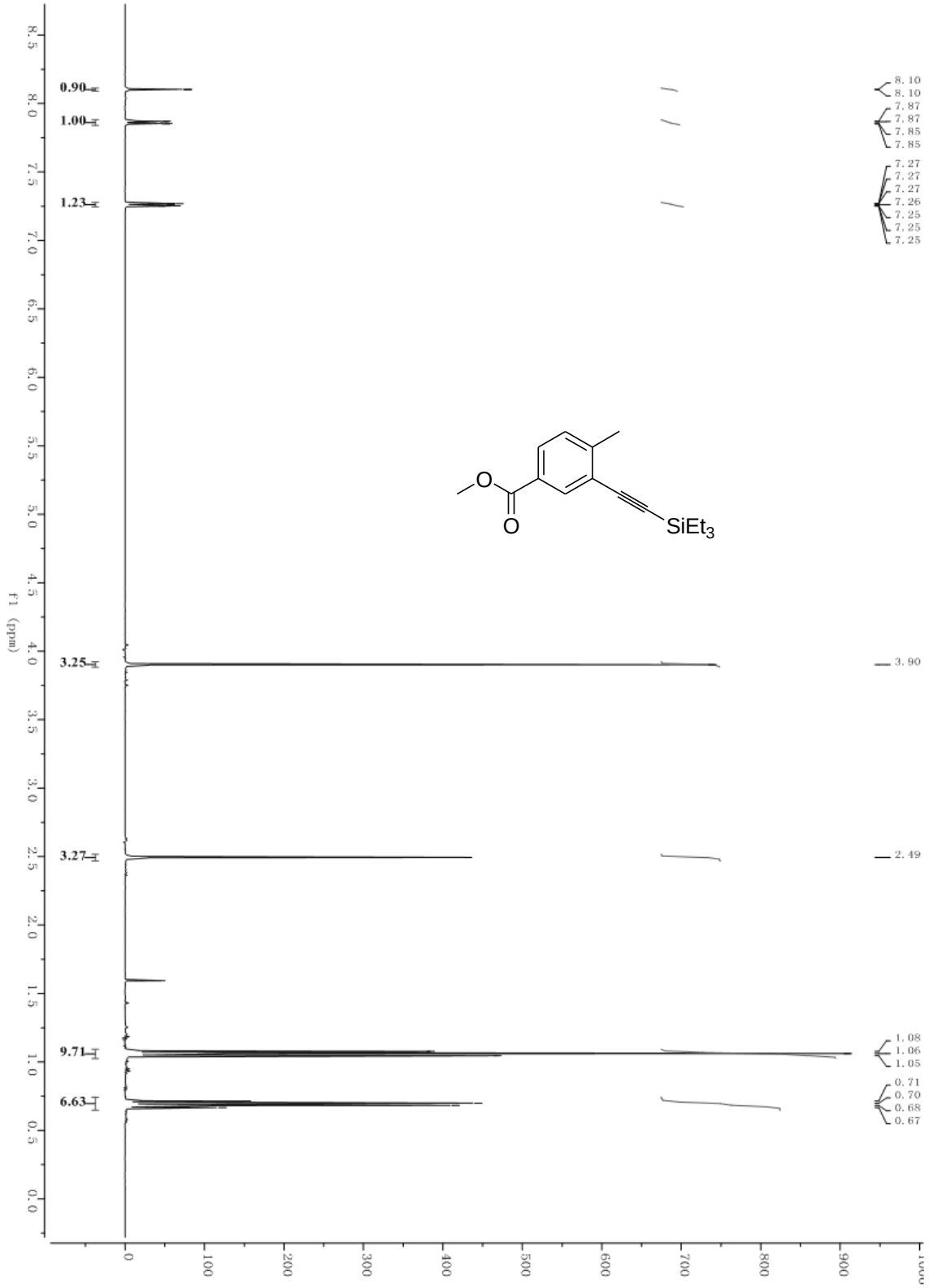

Cl
H
O
OTHP
0.82
0.84
1.00
1.00
1.01
1.17
1.08
1.11
1.15
2.07
1.27
1.24
4.78
f1 (ppm)

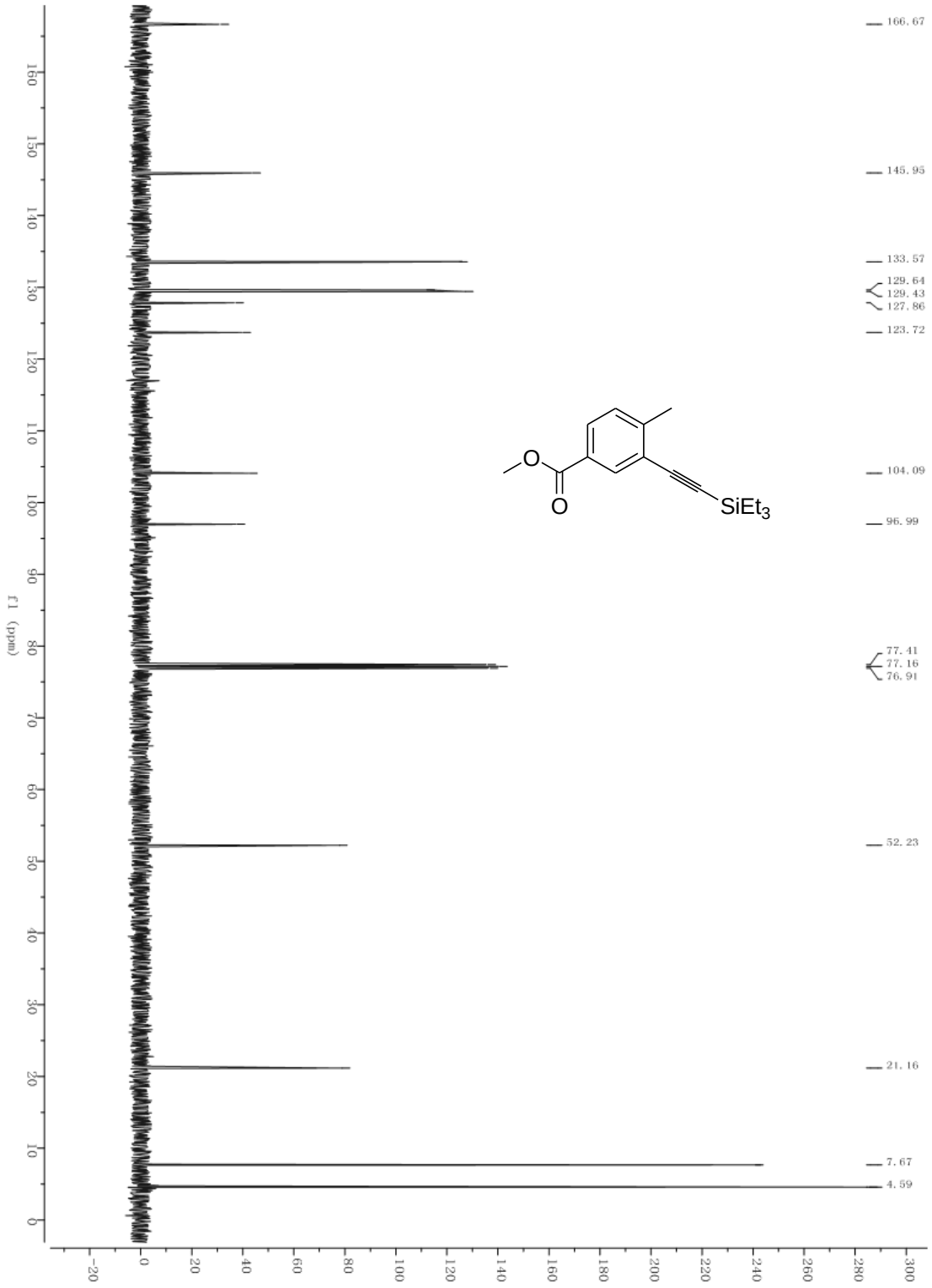

Cl
H
O
OTHP
190.91
137.31
134.70
134.59
133.78
127.02
125.87
99.02
96.12
77.41
77.16
76.90
76.39
65.40
62.43
30.67
25.50
21.30
19.52
f1 (ppm)

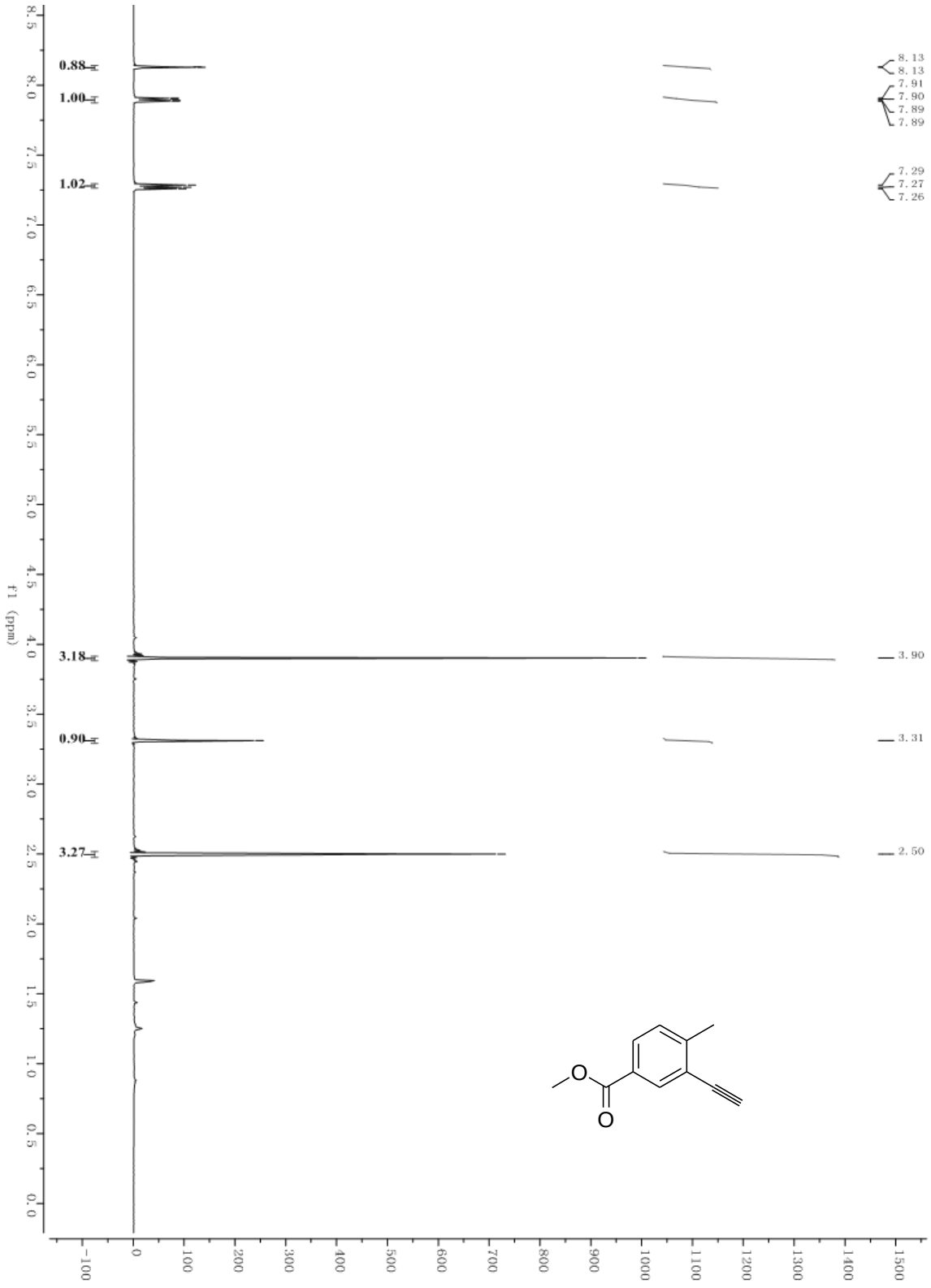

0.81
1.00
1.06
0.97
1.99
1.02
2.07
2.07
4.13
1.26
2.11
6.28
F
N
N
NO2
f1 (ppm)

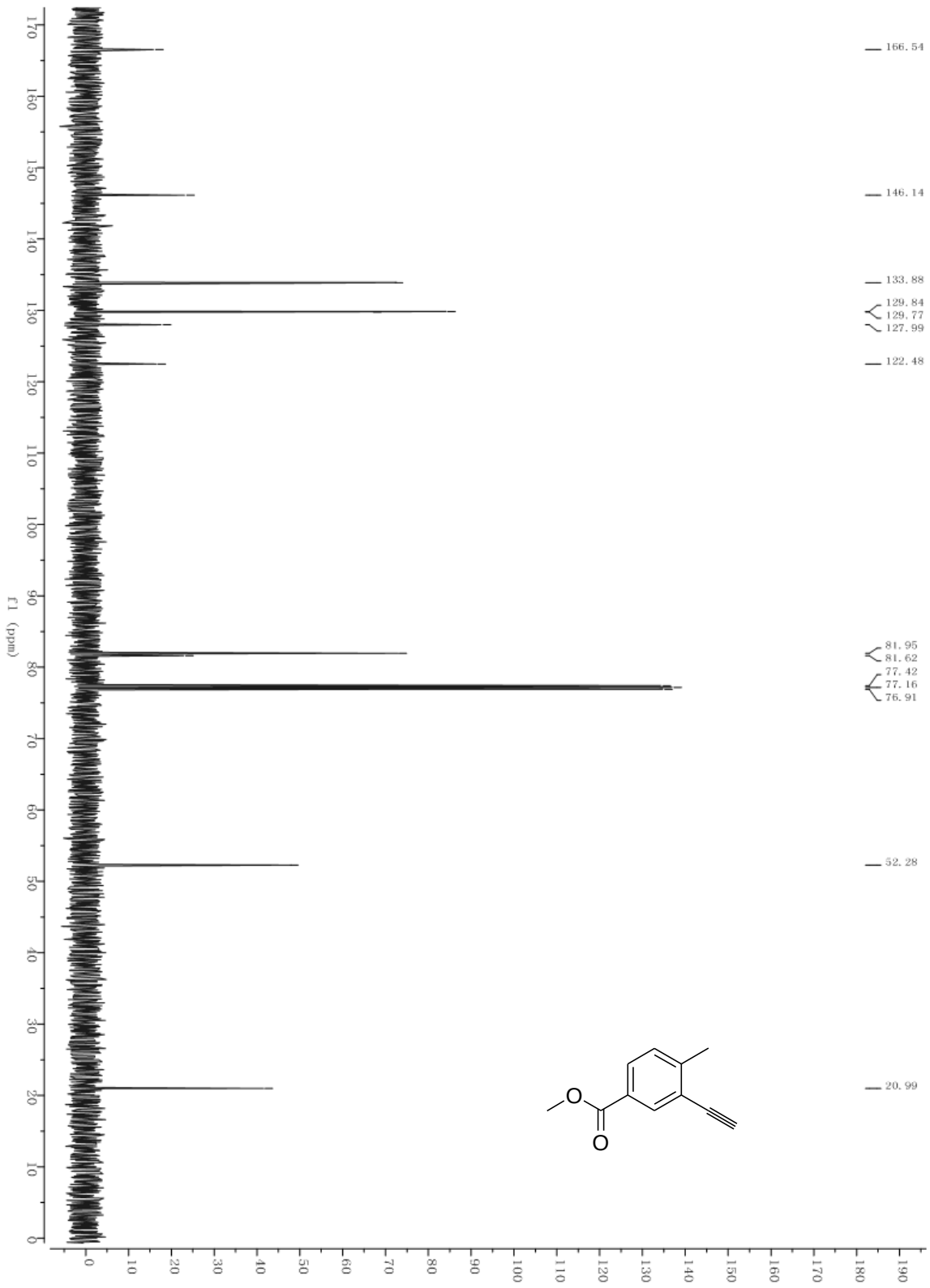

163.72
161.71
145.99
141.02
136.31
133.47
133.46
130.29
130.23
129.79
124.16
124.13
120.45
115.77
115.61
114.44
111.75
111.63
92.56
92.53
83.22
77.41
77.16
76.91
61.17
51.54
50.22
31.42
23.40
F
N
N
NO2
f1 (ppm)

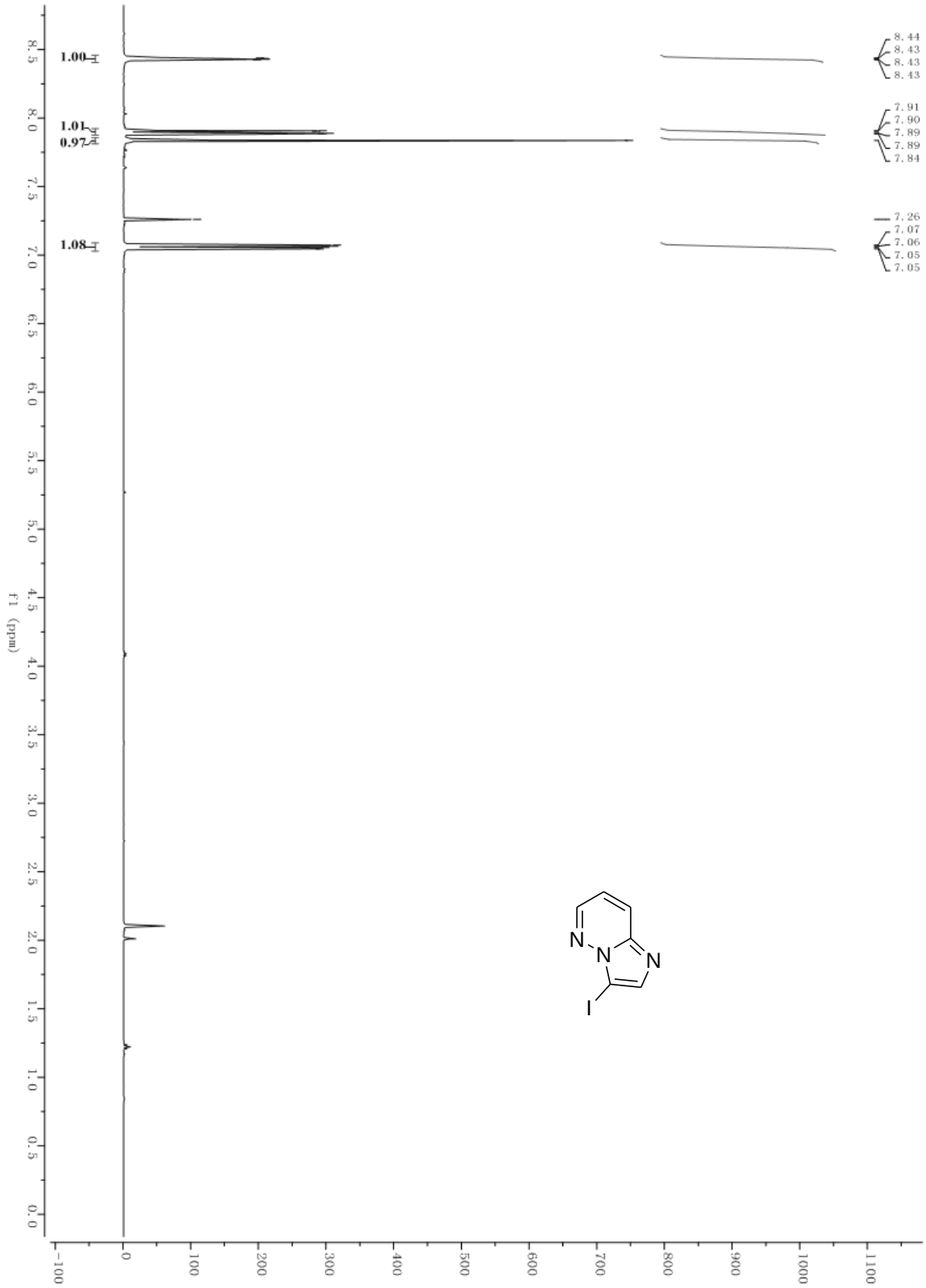

F
N
N
NO2
-109.78
-109.80
-109.80
-109.81
-109.81
-109.82
-109.83
-109.84
f1 (ppm)


0.90
1.00
1.23
3.25
3.27
9.71
6.63
8.10
8.10
7.87
7.87
7.85
7.85
7.27
7.27
7.27
7.26
7.25
7.25
7.25
3.90
2.49
1.08
1.06
1.05
0.71
0.70
0.68
0.67
O
O
SiEt3
f1 (ppm)


166.67
145.95
133.57
129.64
129.43
127.86
123.72
104.09
96.99
77.41
77.16
76.91
52.23
21.16
7.67
4.59
O
O
SiEt3
f1 (ppm)


0.88
1.00
1.02
3.18
0.90
3.27
8.13
8.13
7.91
7.90
7.89
7.89
7.29
7.27
7.26
3.90
3.31
2.50
f1 (ppm)


166.54
146.14
133.88
129.84
129.77
127.99
122.48
81.95
81.62
77.42
77.16
76.91
52.28
20.99
f1 (ppm)
O
O


1.00
1.01
0.97
1.08
8.44
8.43
8.43
8.43
7.91
7.90
7.89
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7.84
7.26
7.07
7.06
7.05
7.05
f1 (ppm)
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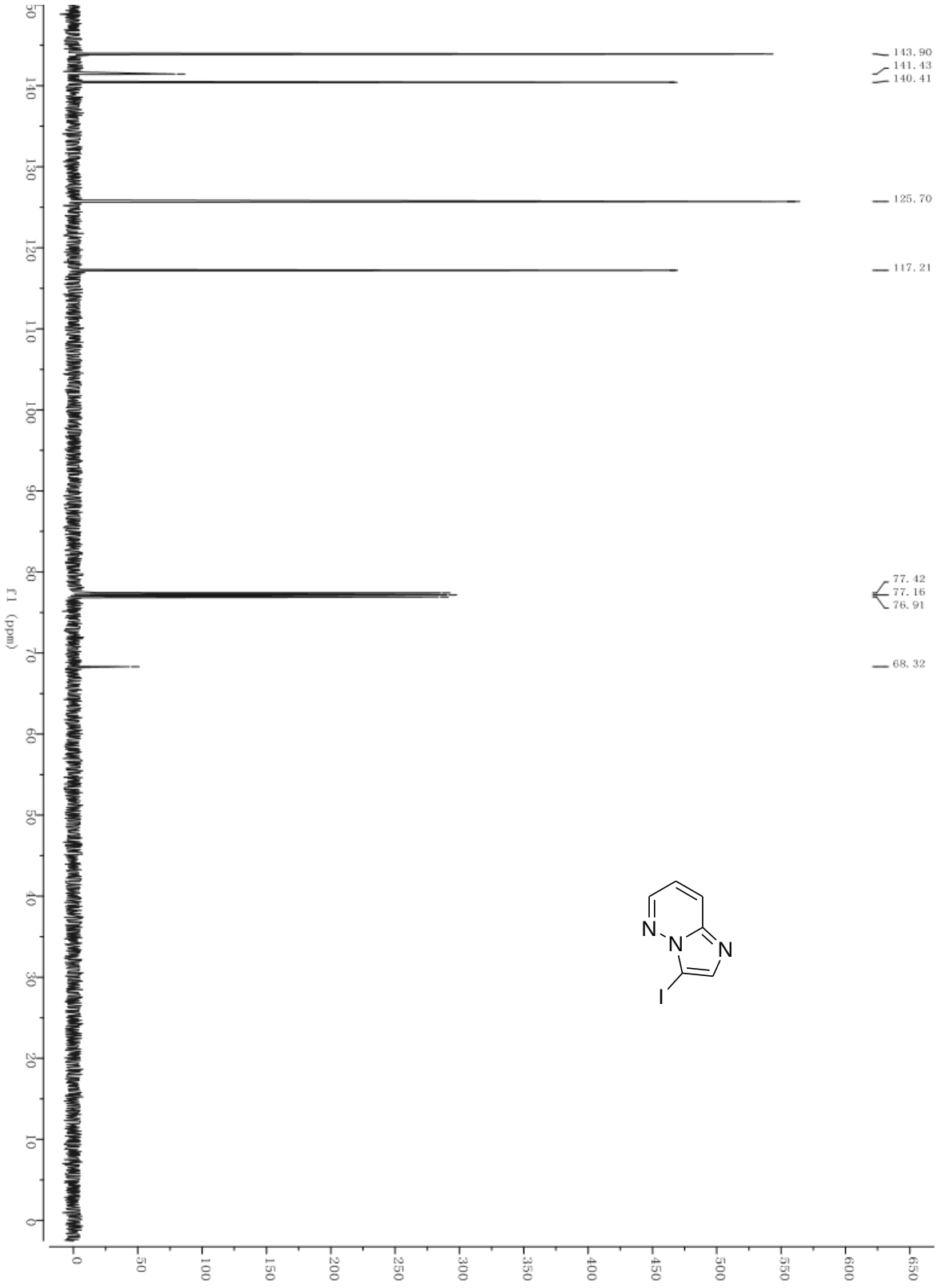
N
N
I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N
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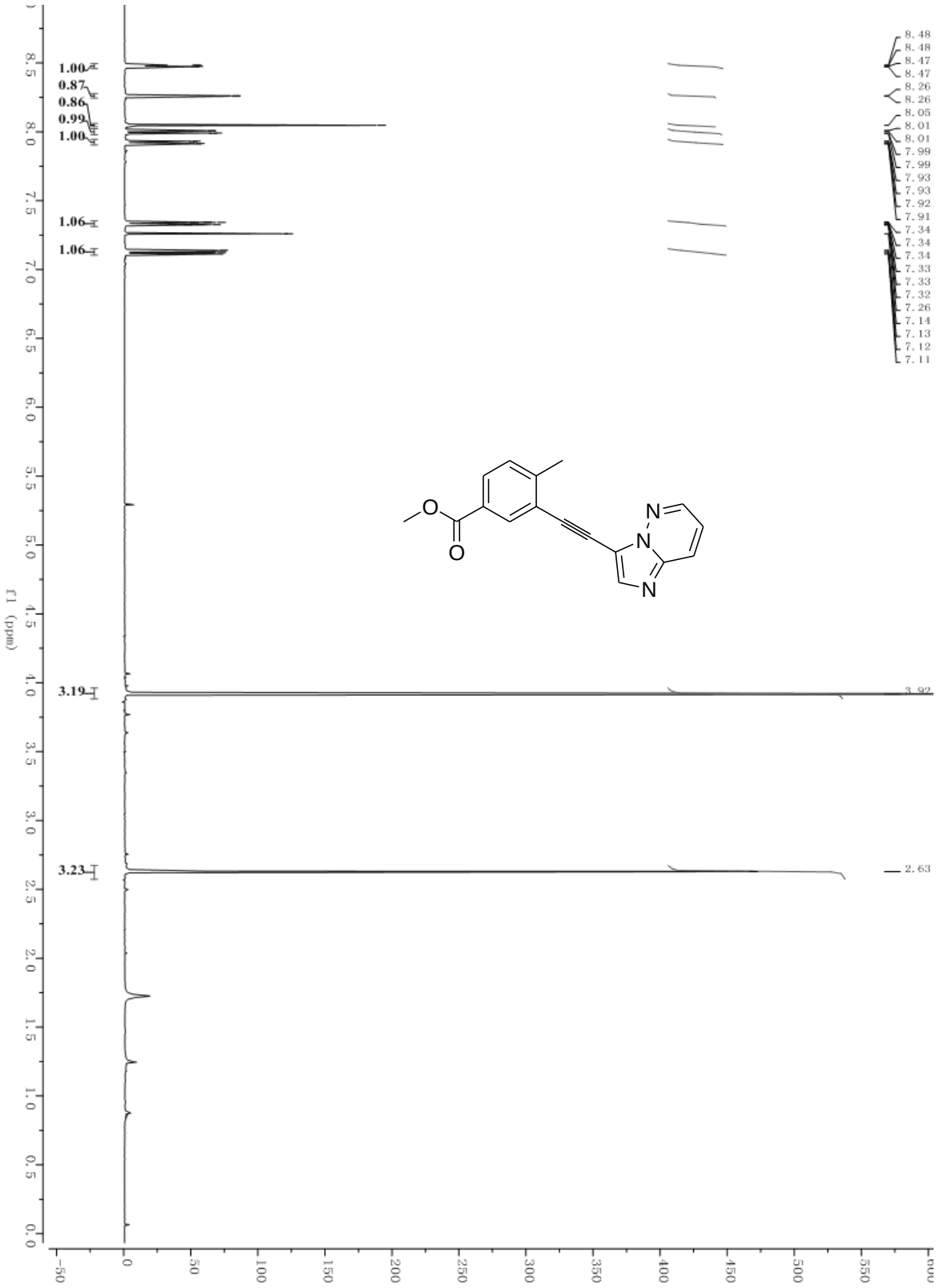
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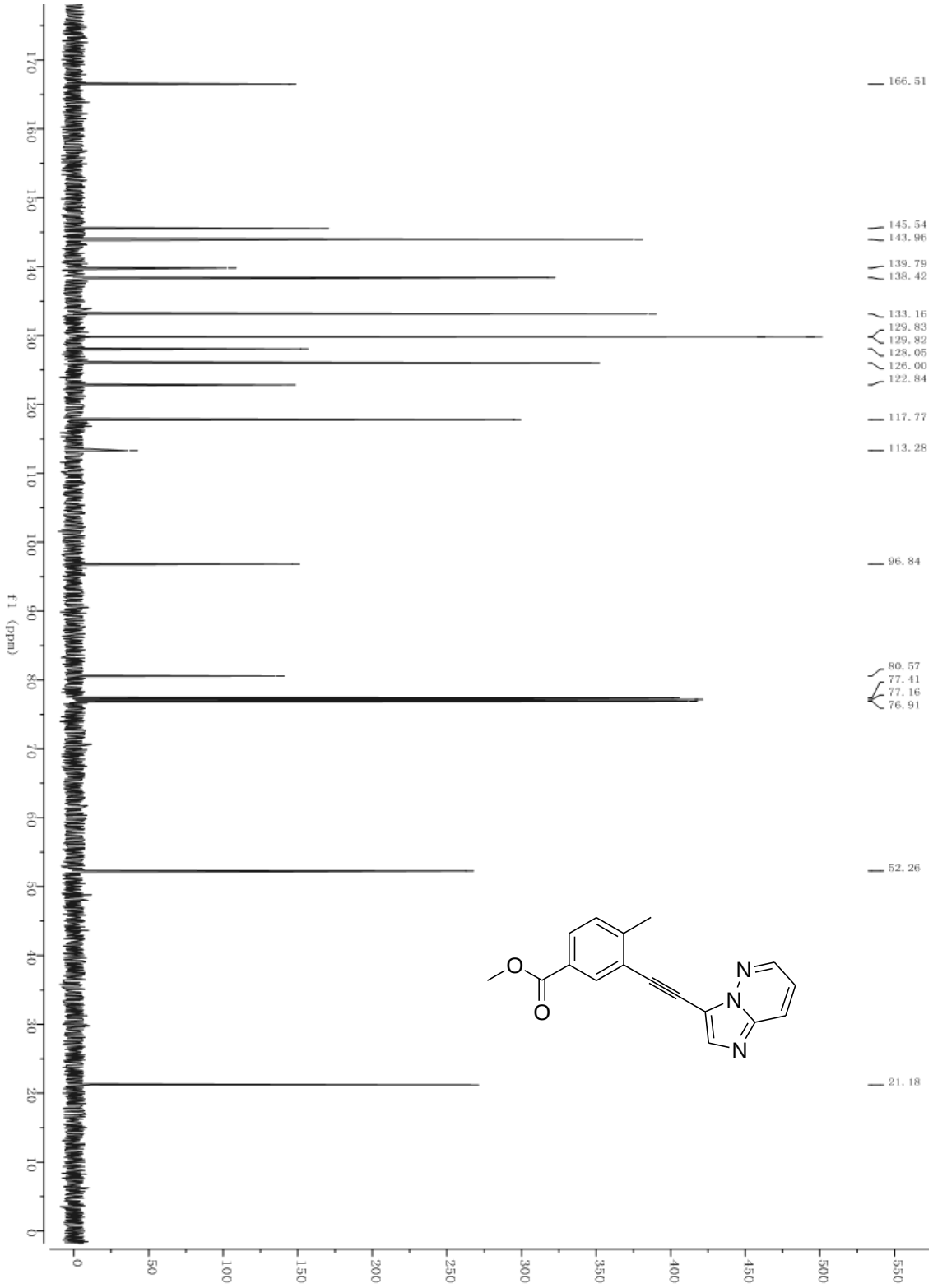
f1 (ppm)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129.82
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126.00
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77.41
77.16
76.91
52.26
21.18
f1 (ppm)
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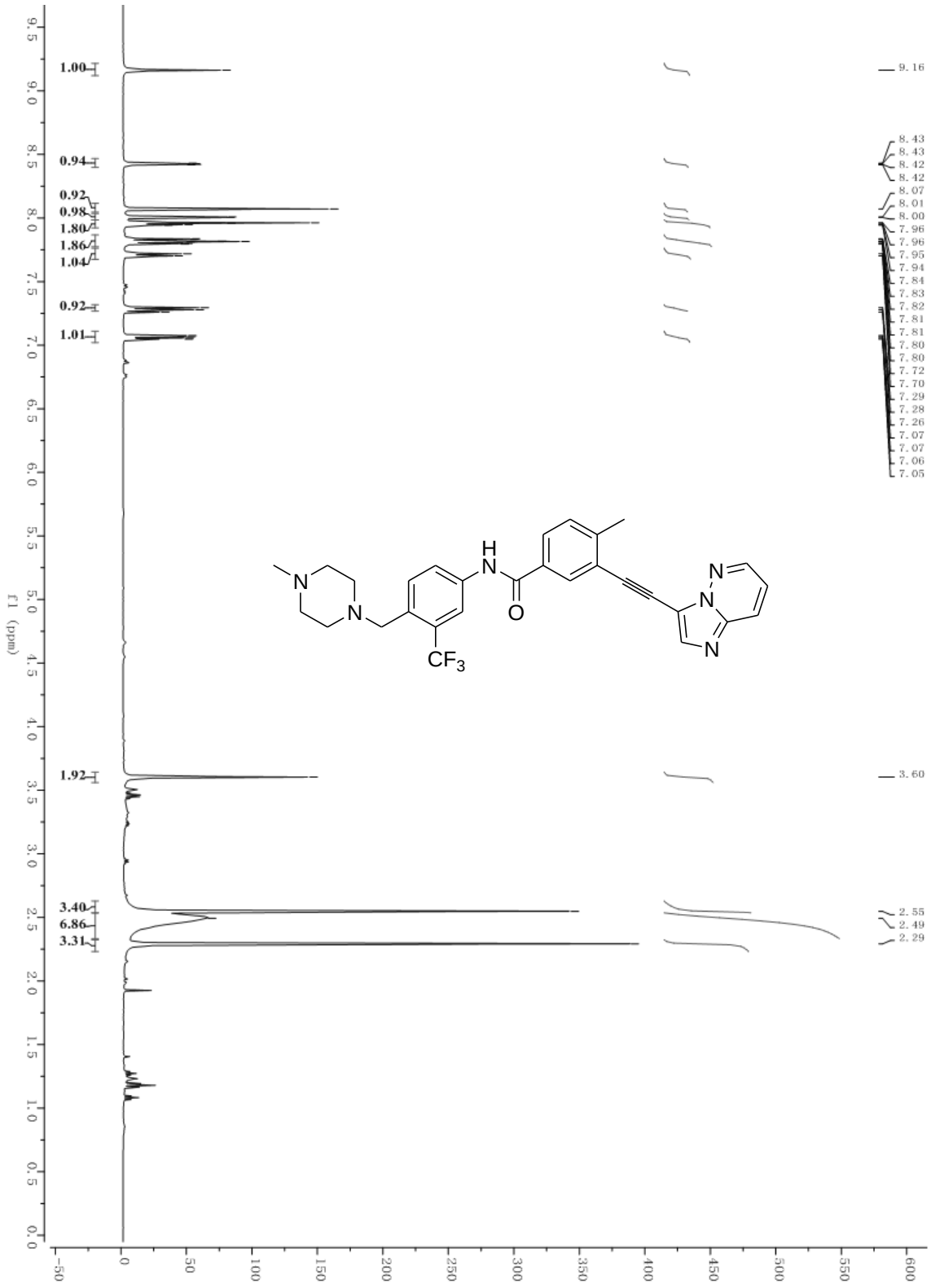
O
N
N
N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3.31
9.16
8.43
8.43
8.42
8.42
8.07
8.01
8.00
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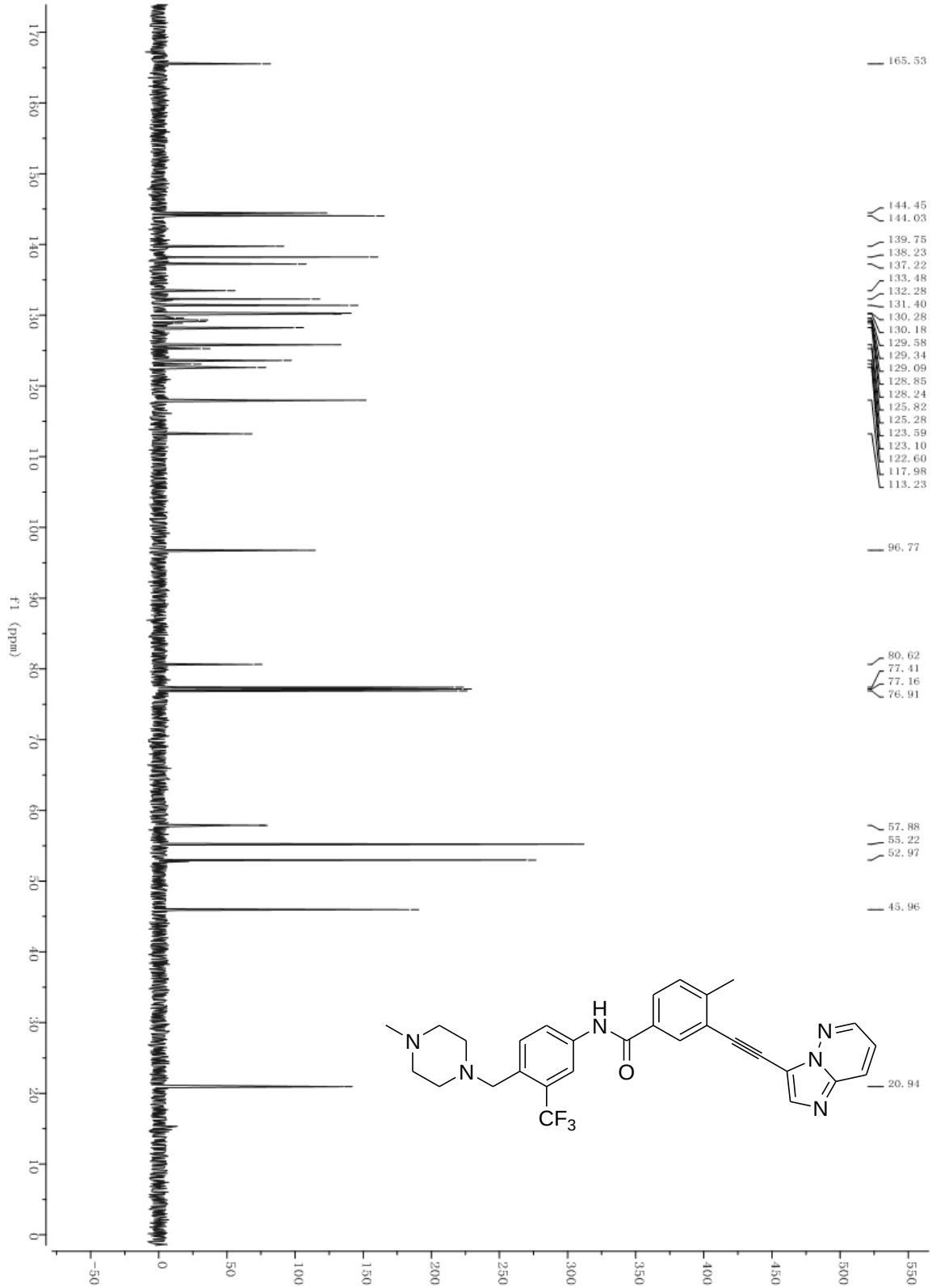
CF3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129.09
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128.24
125.82
125.28
123.59
123.10
122.60
117.98
113.23
96.77
80.62
77.41
77.16
76.91
57.88
55.22
52.97
45.96
20.94
f1 (ppm)
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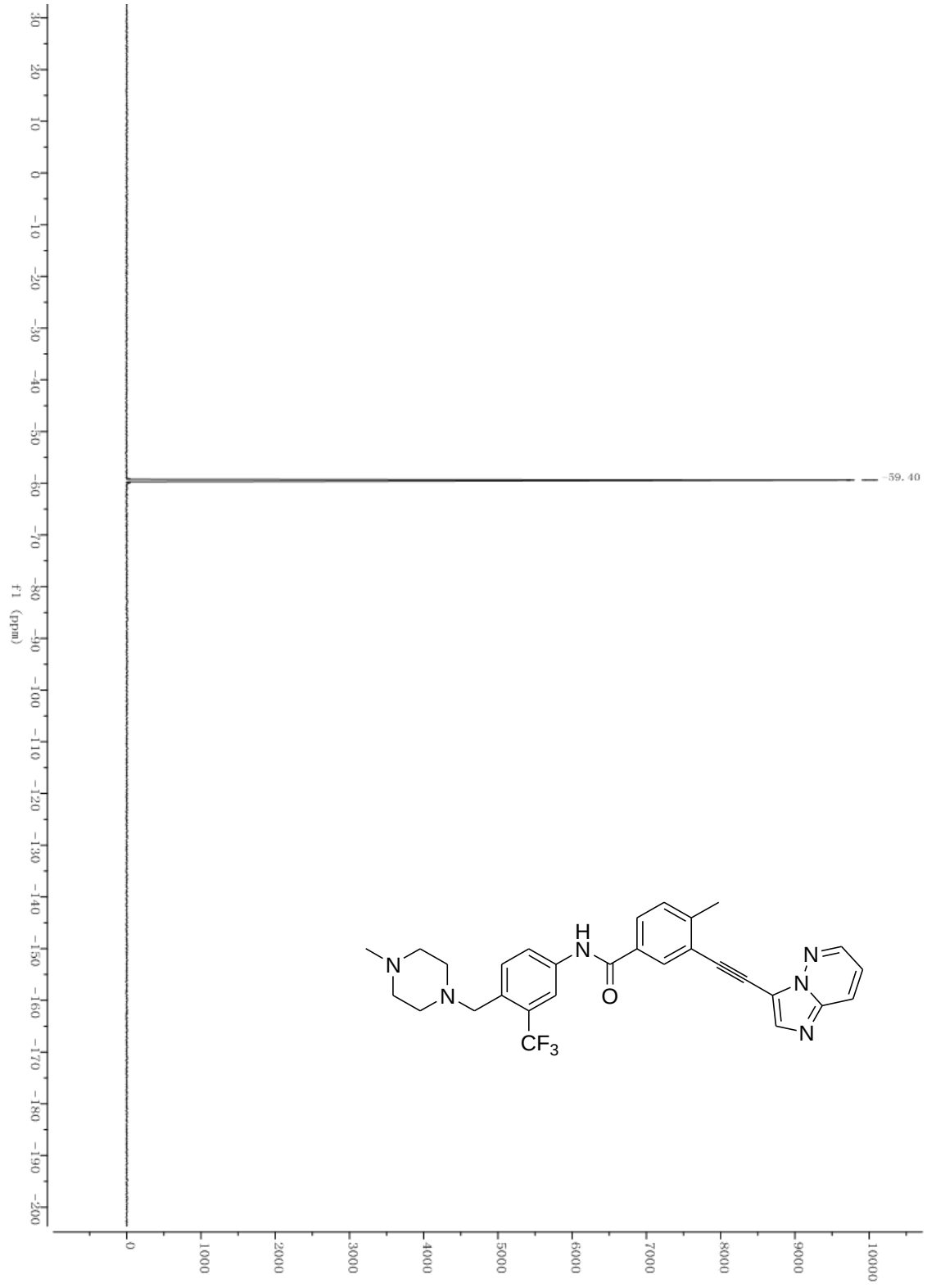
N
O
N
N
N
N
CF3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f1 (ppm)
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O
N
N
N
N
N
CF3

II. Modifications of Fe/ppm Pd nanoparticles used in Suzuki-Miyaura couplings and their applications to flow chemistry

Introduction

The Suzuki-Miyaura reaction is one of three palladium-catalyzed cross coupling reactions recognized by the Nobel Prize committee on Chemistry for 2010.[1] Interestingly, this reaction is the most widely used palladium-catalyzed coupling reaction in the pharmaceutical industry.[2] The reaction conditions can be modified in many different ways. Developing novel ligands for palladium,[3] replacing expensive palladium with earth abundant metals,[4] and using environmentally friendly solvents[5] are major approaches to improve the conditions associated with this reaction. Other than the modifications mentioned above, preparing heterogeneous palladium catalysts has been a hot topic, as this method dramatically increases the surface area of an active catalyst while adopting all modifications used in homogeneous catalysis. An ideal heterogeneous catalyst for the Suzuki-Miyaura reaction should be low-cost, easy to prepare, relatively stable, be sufficiently active to catalyze the couplings under mild conditions, and be applicable to industrial needs, especially at scale.

Previous Work

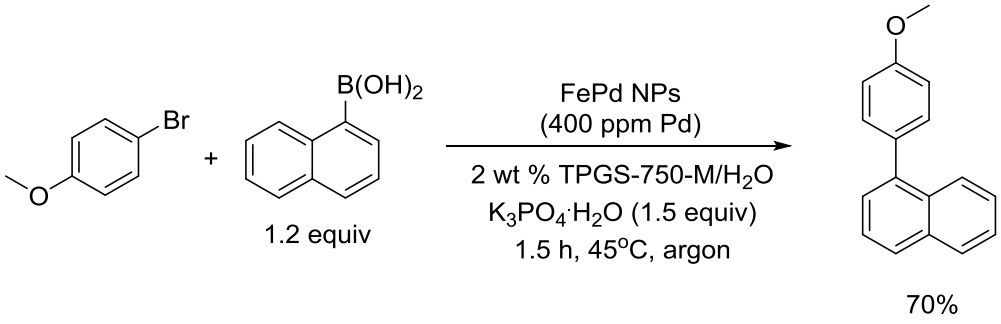
A previous group member, Sachin Handa, developed a method to prepare iron-based nanoparticles containing ppm levels of palladium as an impurity that is in sufficient quantity to catalyze Suzuki-Miyaura reactions.[6] The preparation of these Fe/ppm Pd nanoparticles is quite straightforward. MeMgCl was added to a THF solution of Pd-containing $FeCl_3$, $Pd(OAc)_2$, and SPhos. This heterogeneous catalyst, used at only 320 ppm Pd loading, allows for reactions that involve substrates that contain a wide range of functional groups. Very low residual palladium (<10 ppm) was found in the products of these reactions. The idea of reducing a pre-catalyst with a Grignard reagent comes from the preparation of a nanonickel pre-catalyst used in Suzuki-Miyaura reactions.[7] Associated with this nanoparticle, the Pd-L complex is the catalyst that mediates Suzuki-Miyaura reactions, the role played by iron is still not known. The structures of iron complexes after the addition of a Grignard reagent to iron salts have drawn lots of attention.[8] The interactions between organoferrate and palladium complexes are yet to be determined. However, most reactions take a long time to go to completion.

A similar procedure was used to prepare Fe/ppm Pd nanoparticles for nitro group reductions in the absence of phosphine ligands.[9] Haobo Pang, a graduate student in the group, discovered that adding a third metal, nickel, during preparation of these nanoparticles could significantly increase reaction rates.[10] We wondered if this modification could be applied to nanoparticles catalyzing Suzuki-Miyaura coupling reactions.

Clogging is the major problem encountered in reactions run under heterogeneous continuous flow conditions. Different types of reactors have been designed to alleviate this problem.[11] However, a more reliable solution is required to handle these type of reactions.

Results and Discussion

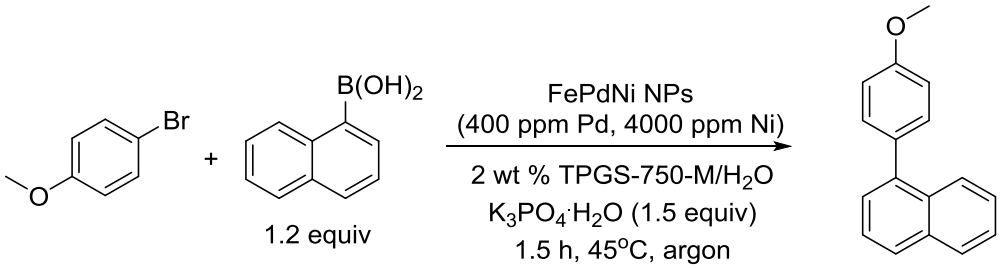
Three different earth abundant metals (Ni, Co, Mn) were used in the preparation of Fe/ppm Pd nanoparticles (for details, see Experimental Section). These nanoparticles were tested in the Suzuki-Miyaura reactions using otherwise standard conditions.



Scheme 1. Control reaction catalyzed by Fe/ppm Pd NPs.

A 70% GC yield was obtained in the Suzuki-Miyaura reaction used as a control, catalyzed by the original Fe/ppm Pd nanoparticles.

Nickel itself is able to catalyze Suzuki-Miyaura coupling reactions.[12] Among five different nickel(II) salts ($NiSO_4$•$6H_2O$, $NiCl_2$, $NiBr_2$, $Ni(OAc)_2$•$4H_2O$, and $Ni(NO_3)_2$•$6H_2O$), only $Ni(NO_3)_2$•$6H_2O$ is soluble in THF. Various Fe/Pd/Ni nanoparticles were prepared using $Ni(NO_3)_2$•$6H_2O$ as nickel source in situ with different types of ligands to test their reactivity in Suzuki-Miyaura coupling reactions.



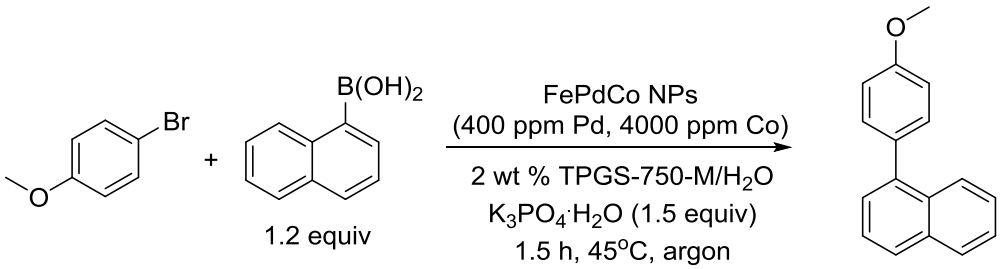
Entry	Ligand	GC yield (%)[a]
1	XPhos	0
2	*t*-BuXPhos	3
3	PCy_3	0
4	Dtbpf	0
5	Cy-cBRIDP	0
6	Cy-vBRIDP	0
7	vBRIDP	0
8	cBRIDP	0
9	XantPhos	0
10	IPr	10
11	*rac*-BINAP	0
12	Dppf	0
13	$P(Ad)_3$	0
14	2,2'-bipyridyl	0
15	1,10-phenanthroline	0
16	3,4,7,8-tetramethyl-1,10-phenanthroline	0
17	SPhos	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 1. Screening of ligands used in Fe/Pd/Ni nanoparticles.

All Fe/Pd/Ni nanoparticles prepared showed little-to-no reactivity in Suzuki-Miyaura coupling reactions.

Cobalt(II) salts were found to be efficient in catalyzing certain types of Suzuki-Miyaura coupling reactions.[13] Six different cobalt(II) salts were tested to determine solubility in THF. $Co(OAc)_2 \cdot 4H_2O$ and $CoSO_4 \cdot 7H_2O$ were found to be insoluble in THF. Four other cobalt(II) salts ($CoBr_2$, $Co(acac)_2$, $CoCl_2 \cdot 6H_2O$ and $Co(NO_3)_2 \cdot 6H_2O$) were used in the preparation of Fe/Pd/Co nanoparticles.

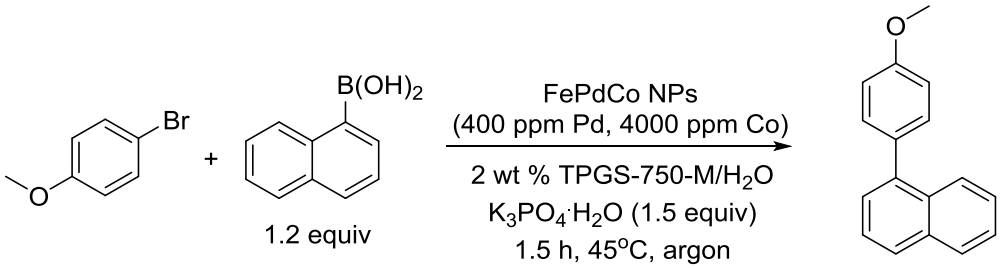


Entry	cobalt(II) source	GC yield (%)[a]
1	$CoBr_2$	12
2	$Co(acac)_2$	51
3	$CoCl_2 \cdot 6H_2O$	44
4	$Co(NO_3)_2 \cdot 6H_2O$	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 2. Screening of cobalt(II) sources used in Fe/Pd/Co nanoparticles.

Among the four different cobalt(II) salts tested, $Co(acac)_2$ gave the best reactivity. Different Fe/Pd/Co nanoparticles were prepared using this cobalt(II) source along with a variety of different ligands.



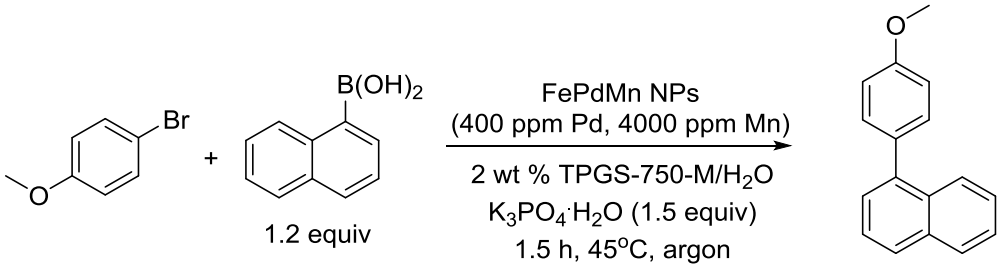
Entry	Ligand	GC yield (%)[a]
1	SPhos	51
2	$P(Cy)_3$	0
3	Dtbpf	0
4	cBRIDP	9
5	salen	0
6	IPr	9
7	*rac*-BINAP	0
8	P(Ad)3	0
9	XantPhos	0
10	XPhos	9
11	*t*-BuXPhos	0
12	2,2'-bipyridyl	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 3. Screening of ligands used in Fe/Pd/Co nanoparticles.

Different types of ligands were screened in the preparation of Fe/Pd/Co nanoparticles, with SPhos found to be the best ligand for this reaction. However, comparing the results with those using Fe/Pd nanoparticles, the addition of cobalt(II) salts offered no advantages.

A supported Mn catalyst was able to catalyze Suzuki-Miyaura coupling reactions.[14] Five different manganese(II) salts ($Mn(OAc)_2$, $Mn(acac)_2$, $MnCl_2•4H_2O$, $MnBr_2•4H_2O$ and $MnSO_4•H_2O$) were tested to determine solubility in THF. Only $MnBr_2•4H_2O$ was found to be soluble in THF.

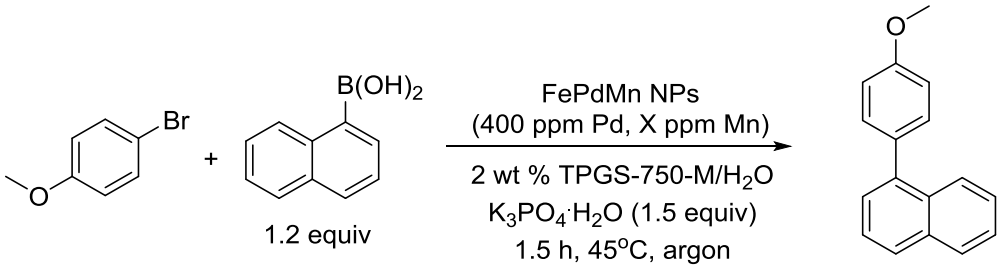


Entry	Ligand	GC yield (%)[a]
1	SPhos	67
2	IPr	0
3	XPhos	10
4	XantPhos	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 4. Screening of ligands used in Fe/Pd/Mn nanoparticles.

Fe/Pd/Mn nanoparticles prepared using SPhos as ligand gave comparable yields as compared with those obtained using the original Fe/Pd nanoparticles. The amount of $MnBr_2•4H_2O$ added to the nanoparticles was further screened.



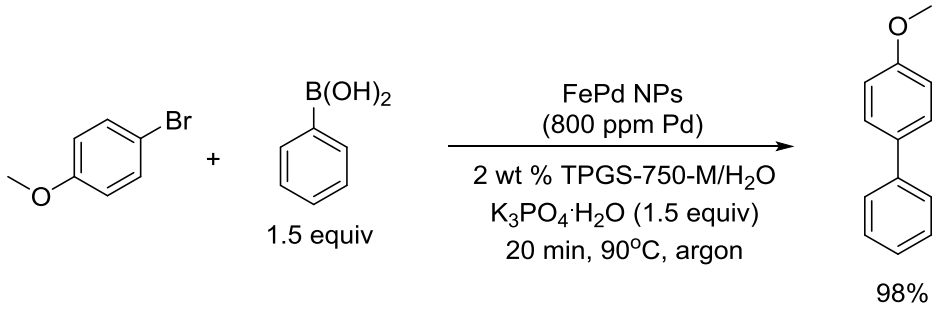
Entry	Amount of $MnBr_2$•$4H_2O$ (ppm)	GC yield (%)[a]
1	1000	39
2	2000	47
3	4000	67
4	10000	23
5	20000	42
6	40000	25

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 5. Screening of $MnBr_2$•$4H_2O$ amounts in Fe/Pd/Mn nanoparticles.

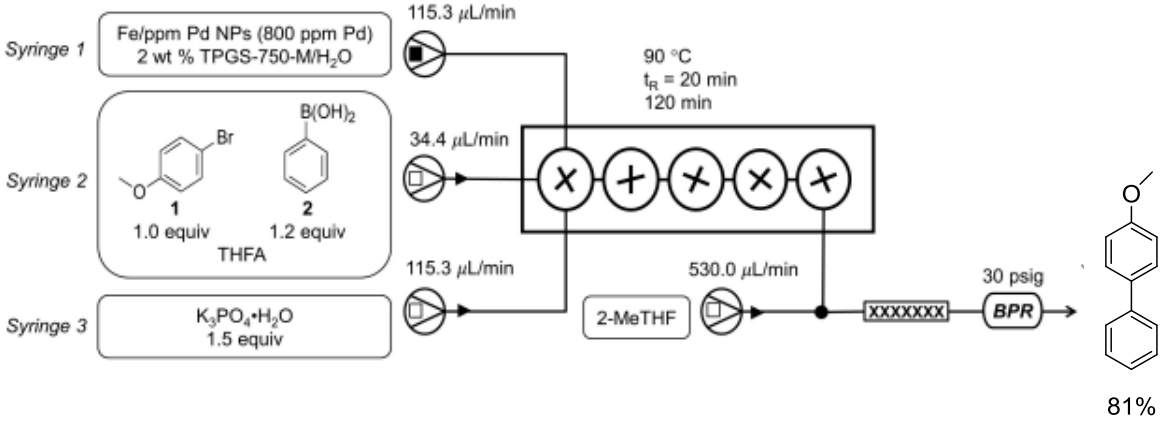
No better reactivity was found from variations in the $MnBr_2$•$4H_2O$ loading in the Fe/Pd/Mn nanoparticles.

Continuous flow chemistry is the new trend in pharmaceutical manufacturing. However, use of heterogeneous catalysts in traditional plug-flow systems is limited due to the clogging of the thin tubes.[15] Jensen *et al.* developed a new continuous stirred-tank reactor (CSTR)[16] that can handle solid-containing reactions much better than traditional systems. Suzuki-Miyaura couplings were performed using the original Fe/Pd nanoparticles in a CSTR system.



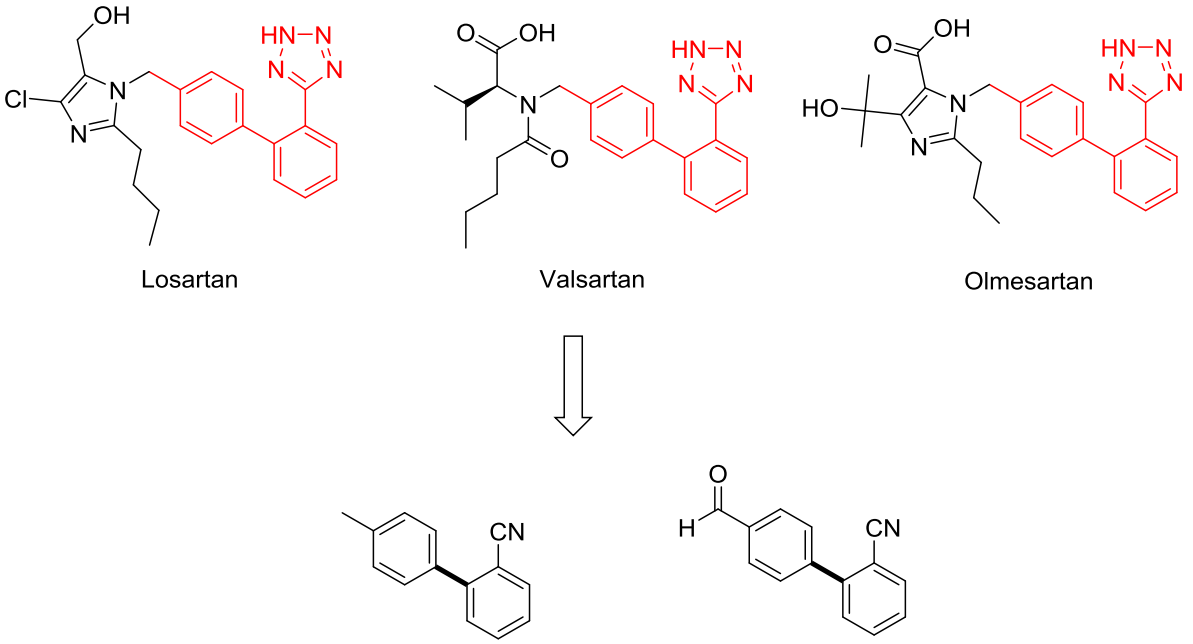
Scheme 2. Model Suzuki-Miyaura coupling in batch mode.

4-Bromoanisole and phenylboronic acid were used as substrates in the model reaction. A 98% isolated yield was obtained in twenty minutes at 90 ^{o}C in batch mode. This reaction was then transferred to the CSTR reactor.



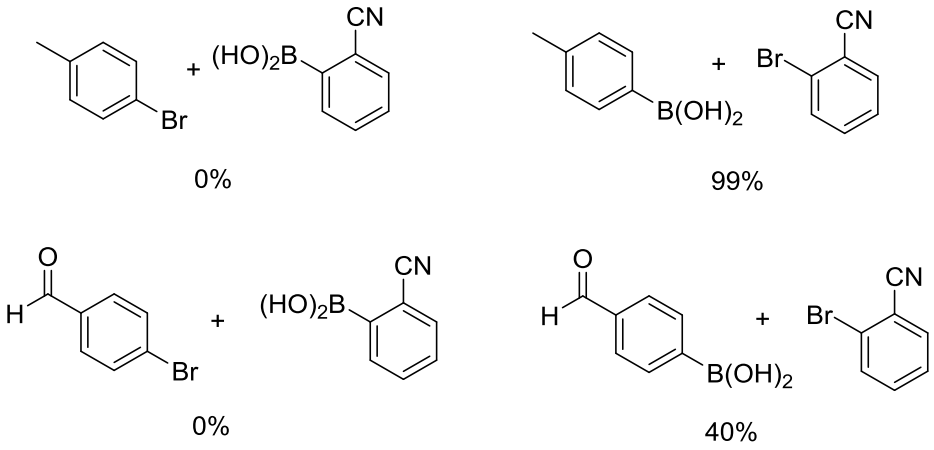
Scheme 3. Model Suzuki-Miyaura coupling under flow conditions.

Unlike batch conditions, two coupling partners were first dissolved in degassed tetrahydrofurfuryl alcohol in Syringe 2. This modification led to lower isolated yield compared with batch conditions.



Scheme 4. Sartans and their precursors.

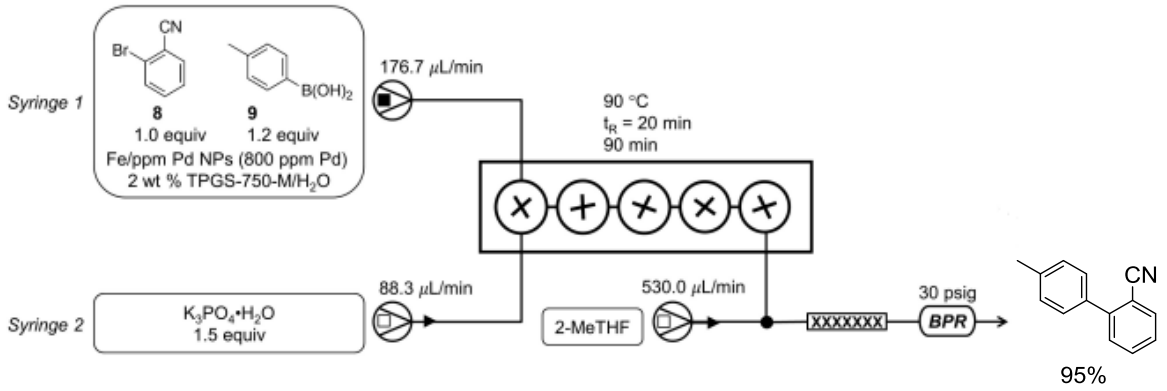
Sartans are commonly used drugs to treat high blood pressure. Four sartan-containing drugs were listed in the top 200 pharmaceuticals by retail sales in 2019.[17] All sartans share a common biaryl tetrazole structure, which can be synthesized by two biaryl intermediates, as shown in Scheme 4. These two intermediates can be prepared by Suzuki-Miyaura couplings.



Scheme 5. Four possible Suzuki-Miyaura couplings.

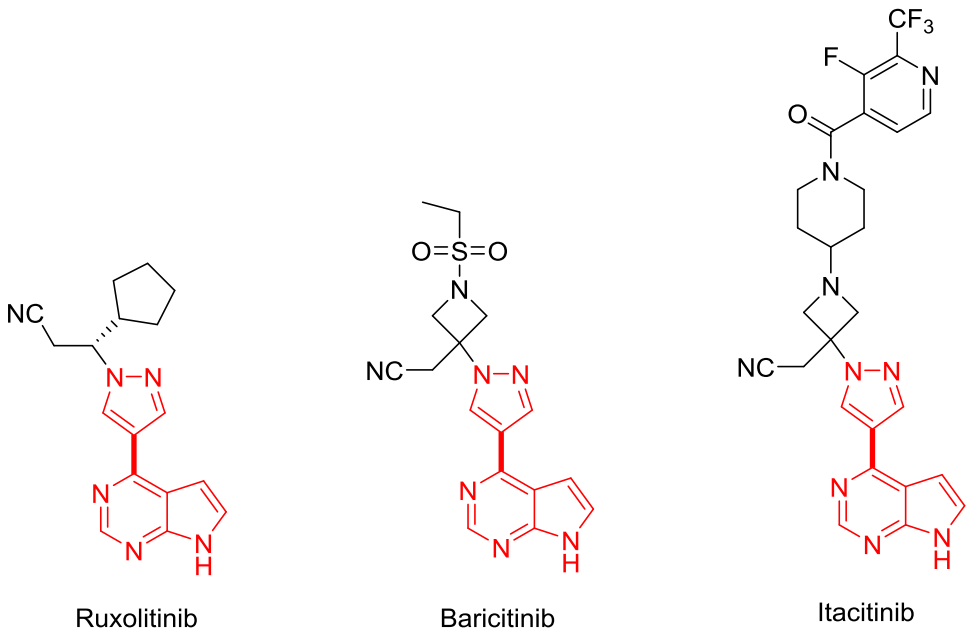
Four possible Suzuki-Miyaura coupling reactions were performed for twenty minutes at 90 ^{o}C using NPs containing 800 ppm palladium loading. A high yield was only

obtained by using 2-bromobenzonitrile and *p*-tolylboronic acid as coupling partners. This reaction was then performed in the CSTR system.



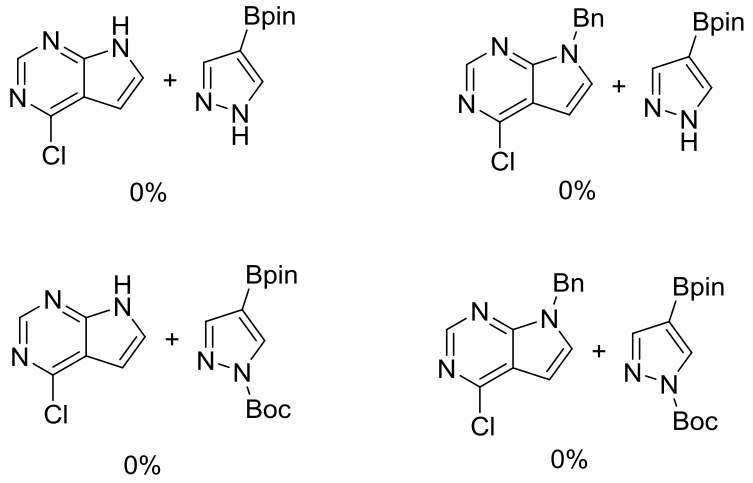
Scheme 6. Synthesis of sartan precursor in CSTR.

In the flow system, the substrate and nanoparticle slurry was injected into the reactor using a slurry pump. The reaction proceeded smoothly as indicated by a 95% isolated yield.



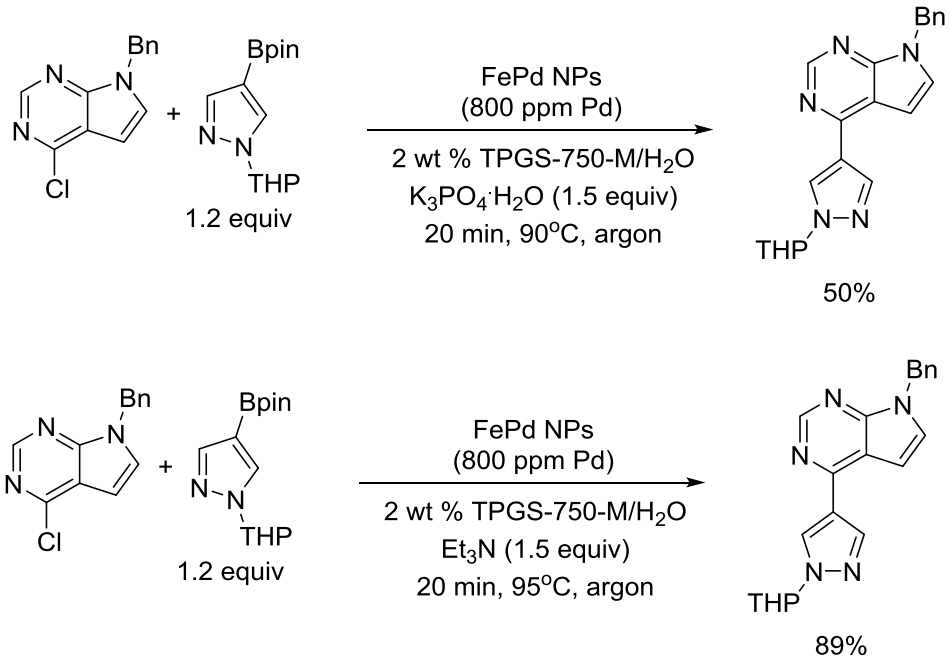
Scheme 7. JAK inhibitors that share the same fragment.

Ruxolitinib(Jakafi®) is the first marketed Janus kinase inhibitor developed by Incyte Corp. It shares the same precursor with two other Incyte inhibitors. The key C-C bond was originally made by a Suzuki-Miyaura coupling reaction using relatively high palladium loading (4 mol %).[18]



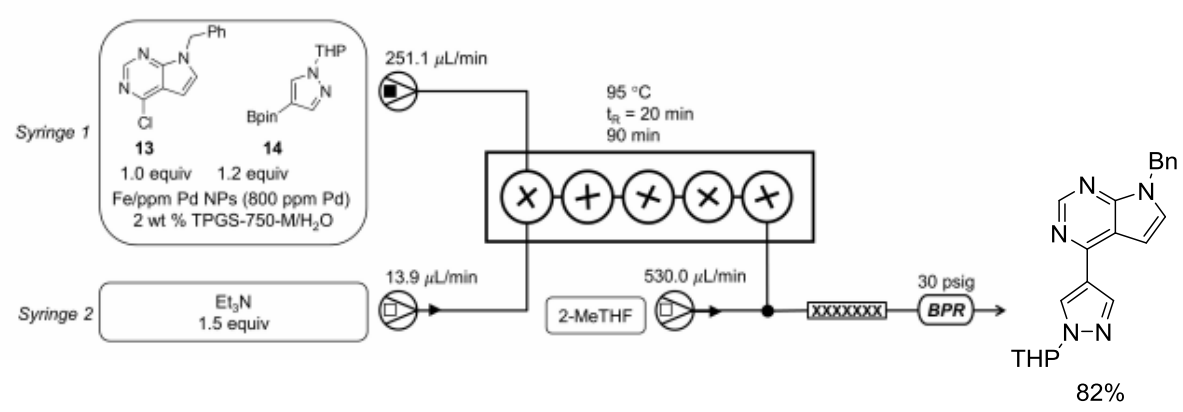
Scheme 8. Initial screenings.

Different coupling partners were screened, as illustrated in Scheme 8, under standard reaction conditions using NPs containing 800 ppm palladium loading; no conversion was observed in any of these reactions.



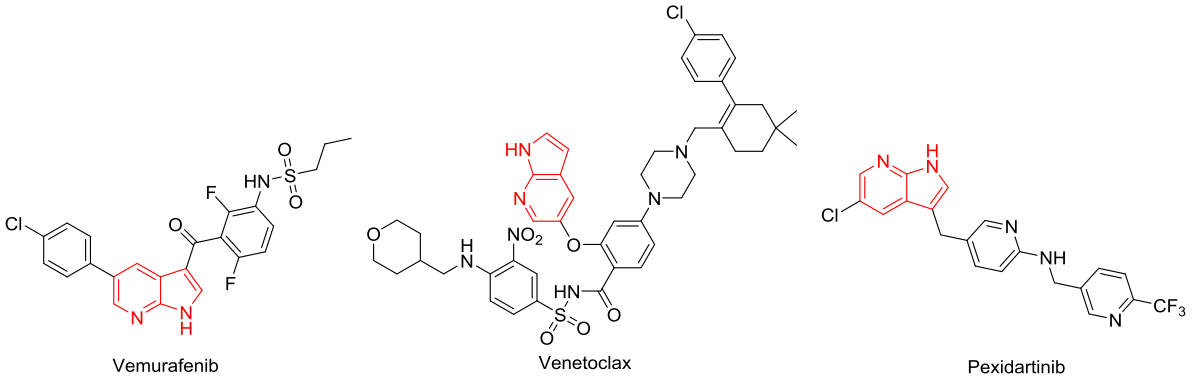
Scheme 9. Optimized conditions for the preparation of a JAK inhibitor precursor.

Instead of using ethyl vinyl ether to protect the pyrazole coupling partner as indicated by the original procedure, a commercially available THP-protected pyrazole boronic acid pinacol ester was used in this reaction. A fifty percent isolated yield was obtained under standard conditions. Switching base to triethylamine and increasing the reaction temperature to 95 °C improve the isolated yield to 89%.



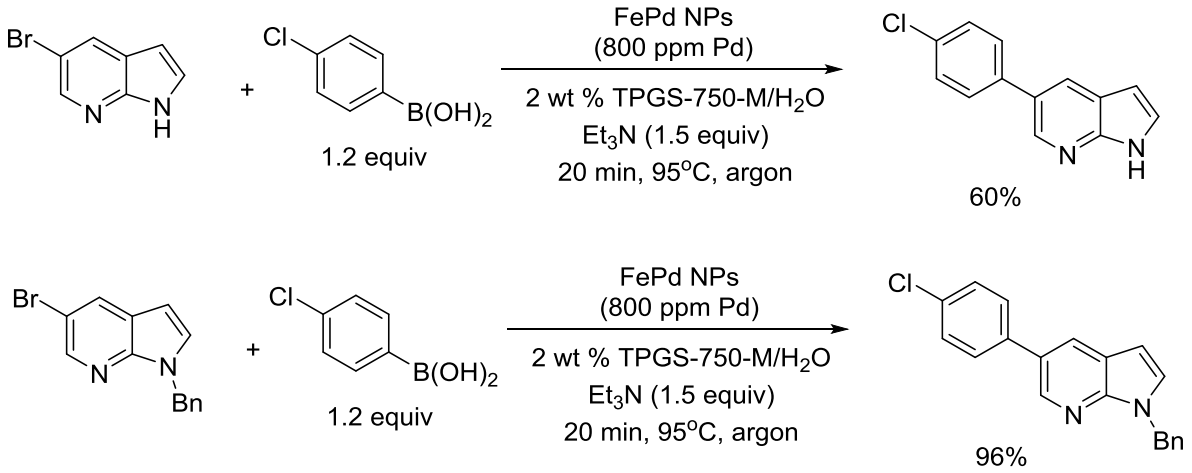
Scheme 10. Synthesis of JAK inhibitor precursor in CSTR.

All modifications of these conditions were then transferred to the flow reactor. The desired intermediate was obtained in 82% isolated yield.



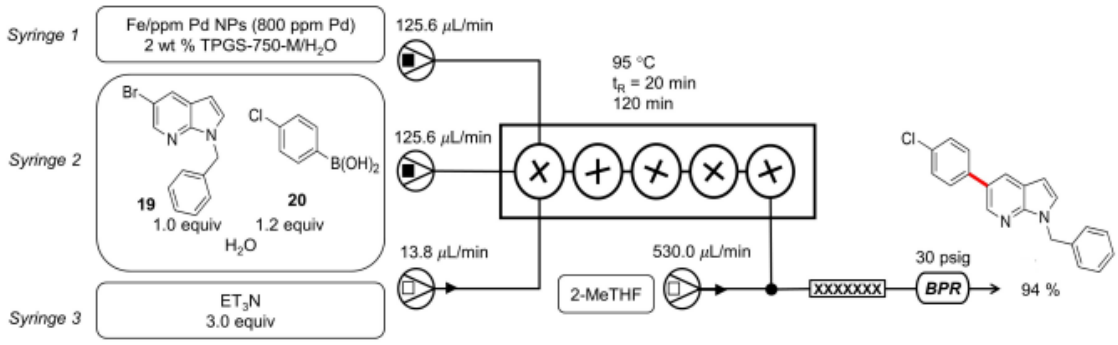
Scheme 11. Examples of 7-azaindole containing drugs.

Vemurafenib (Zelboraf®) is a BRAF inhibitor developed by Roche. It has a 7-azaindole core that is shared by other recently approved drugs (Scheme 11). The 5-aryl group can be installed by Suzuki-Miyaura coupling reactions.



Scheme 12. Vemurafenib precursor synthesis screening.

Using 5-bromo-7-azaindole directly in the Suzuki-Miyaura reaction only gave a 60% isolated yield. Installing a benzyl group dramatically increased the yield to 96%.



Scheme 13. Synthesis of vemurafenib precursor in CSTR.

In the CSTR system the target precursor was obtained in 94% isolated yield in 20 minutes using NPs containing 800 ppm palladium loading.

Conclusions and Outlook

The heterogeneous reagent containing Fe/Pd embedded within nanoparticles is a highly reactive catalyst for Suzuki-Miyaura coupling reactions. Modifications using other earth abundant metals as additives did not give better results. More attention to the catalytic mechanisms involved with these nanoparticles is required to determine ways of improving their efficiency. Nonetheless, they can be used as a very effective heterogeneous catalyst in a newly developed continuous flow system. Different drug precursors can be synthesized using this methodology.

Experimental Section

Preparation of Fe/ppm Pd nanoparticles

A 100 mL flame-dried round bottom flask containing a PTFE coated magnetic stir bar was charged with anhydrous $FeCl_3$ (100 mg, 0.617 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.2 mg, 0.0053 mmol, 0.0087 equiv), ligand (0.8 equiv) and a third metal salt (0.087 equiv, if applicable) in a glovebox, sealed with a rubber septum, and then charged with 30 mL dry THF. The mixture was allowed to stir at rt for 5 min before the dropwise addition of freshly titrated MeMgCl (2.0 equiv). The mixture continued to stir for 10 min before removal of the stir bar and the solvent was removed *in vacuo*. Pentane (20 mL) was used to wash the solid residue and was removed *in vacuo*. The product catalyst was obtained as a light grey powder. The palladium concentration was determined by calculation based on the total weight of nanoparticles.

Example:

Total Pd in batch: 0.0053 mmol $Pd(OAc)_2$ x 224.5 mg/mmol $Pd(OAc)_2$ = 1.2 mg $Pd(OAc)_2$

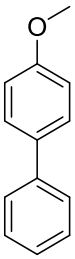
Total Ni in batch: 0.053 mmol $Ni(NO_3)_2 \cdot 6H_2O$ x 290.8 mg/mmol $Ni(NO_3)_2 \cdot 6H_2O$ = 15.4 mg $Ni(NO_3)_2 \cdot 6H_2O$

Total yield of batch: 625.2 mg

400 ppm Pd loading at 0.5 mmol scale: 0.5 mmol Ar-X x 400 ppm x 10^{-6} x 224.5 mg/mmol / 1.2 mg $Pd(OAc)_2$ x 625.2 mg = 23.4 mg NP

Procedure for Suzuki-Miyaura reactions

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, all solid starting materials (halide, boronic acid) and Fe/ppm Pd nanoparticles were charged under an argon flow. The reaction vial was then sealed with a rubber septum, evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and liquid starting materials and/or base were added via syringe. The reaction mixture was then stirred vigorously at 45 ^{o}C (or at a different temperature as indicated) for a given time. After complete consumption of bromide, as monitored by TLC and/or GCMS, the reaction mixture was then extracted with EtOAc (1.0 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography over silica gel to afford pure product.



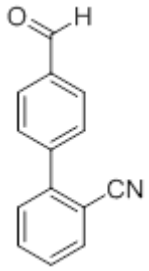
4-Methoxylbiphenyl (BJ-4-26)

4-Bromoanisole (63 μL, 0.5 mmol, 1.0 equiv), phenylboronic acid (91.5 mg, 0.75 mmol, 1.5 equiv), Fe/ppm Pd NP (20 mg, 800 ppm Pd) and K_3PO_4•H_2O (172.5 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 90 ^{o}C for 20 min yielding 90.6 mg (98%) of 4-methoxybiphenyl as a white solid (hexane/ether : 96/4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.50 (m, 4H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.31 (td, *J* = 7.3, 1.2 Hz, 1H), 7.03 – 6.94 (m, 2H), 3.86 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.31, 140.99, 133.95, 128.86, 128.30, 126.89, 126.80, 114.36, 55.50.

Guo, W.-J.; Wang, Z.-X. *J. Org. Chem.* **2013**, *78*, 1054-1061.

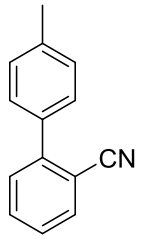


4'-Formyl-[1,1'-biphenyl]-2-carbonitrile (BJ-3-189)

2-Bromobenzonitrile (91 mg, 0.5 mmol, 1.0 equiv), (4-formylphenyl)boronic acid (90 mg, 0.6 mmol, 1.2 equiv), Fe/ppm Pd NP (19.6 mg, 800 ppm Pd) and K_3PO_4•H_2O (172.5 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 90 ^oC for 20 min yielding 36.1 mg (35%) of 4'-formyl-[1,1'-biphenyl]-2-carbonitrile as a white solid (hexane/ether : 70/30).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.81 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.70 (td, *J* = 7.7, 1.4 Hz, 1H), 7.57 – 7.50 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.82, 144.15, 144.06, 136.34, 134.06, 133.18, 130.18, 130.14, 129.69, 128.65, 118.35, 111.46.



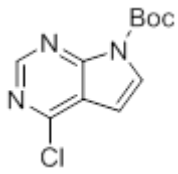
4'-Methyl-[1,1'-biphenyl]-2-carbonitrile (BJ-3-200)

2-Bromobenzonitrile (91 mg, 0.5 mmol, 1.0 equiv), *p*-tolylboronic acid (81.6 mg, 0.6 mmol, 1.2 equiv), Fe/ppm Pd NP (19.6 mg, 800 ppm Pd) and $K_3PO_4 \bullet H_2O$ (172.5 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 90 ^oC for 20 min yielding 95.9 mg (99%) of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile as a white solid (hexane/ether : 94/6).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.65, 138.81, 135.39, 133.83, 132.88, 130.09, 129.56, 128.73, 127.39, 118.99, 111.32, 21.37.

Liang, Q.; Xing, P.; Huang, Z.; Dong, J.; Sharpless, K. B.; Li, X.; Jiang, B. *Org. Lett.* **2015**, *17*, 1942-1945.

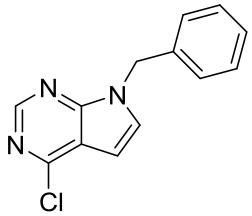


***t*-Butyl 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (BJ-3-202)**

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (1.0 g, 6.54 mmol, 1.0 equiv), di-*t*-butyl dicarbonate (1.5 g, 6.87 mmol, 1.05 equiv) and Et_3N (1.2 mL, 870.6 mg, 8.6 mmol, 1.3 equiv) were dissolved in DCM (10 mL). The reaction mixture was stirred at rt overnight. 1-Methylpiperazine (0.3 mL, 270.9 mg, 2.7 mmol, 0.41 equiv) was added to the reaction mixture. The mixture was then stirred at rt for 30 min and washed with 10% H_2SO_4 (10mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The

crude product was purified by flash column chromatography to afford 1.22 g (74%) of *t*-butyl 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate as a white solid (hexane/DCM : 60/40).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.70 (d, *J* = 4.1 Hz, 1H), 6.65 (d, *J* = 4.1 Hz, 1H), 1.68 (s, 9H).

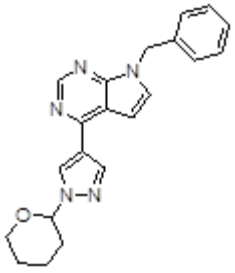


7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (BJ-3-201)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (1.075 g, 7.0 mmol, 1.0 equiv), benzyl chloride (1.2 mL, 1.32 g, 10.42 mmol, 1.49 equiv) and K_2CO_3 (2.9 g, 21.0 mmol, 3.0 equiv) were dissolved in DMF (50 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was poured into water (100 mL). The mixture was then extracted with EtOAc (30 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.4435 g (85%) of 7-benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine as a white solid (hexane/EtOAc : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.35 – 7.27 (m, 3H), 7.21 (dd, *J* = 6.0, 2.7 Hz, 3H), 6.61 (d, *J* = 3.5 Hz, 1H), 5.45 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.33, 151.29, 151.00, 136.37, 129.18, 129.07, 128.32, 127.74, 117.60, 100.10, 48.59.



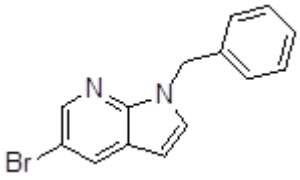
7-Benzyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine (BJ-3-219)

7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (121.5 mg, 0.5 mmol, 1.0 equiv), 1-(2-tetrahydropyranyl)-1H-pyrazole-4-boronic acid, pinacol ester (167 mg, 0.6 mmol, 1.2 equiv), Fe/ppm Pd NP (19.9 mg, 800 ppm Pd) and Et_3N (158 μL, 1.13 mmol, 2.26 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 95 ^oC for 20 min yielding 160.2 mg (89%) of 7-benzyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine as a white solid (hexane/EtOAc : 50/50).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.42 (s, 1H), 8.29 (s, 1H), 7.31 (tt, *J* = 7.0, 6.1 Hz, 3H), 7.25 – 7.21 (m, 2H), 7.20 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 5.48 (s, 3H), 4.13 – 4.06 (m, 1H), 3.80 – 3.71 (m, 1H), 2.17 (dt, *J* = 6.2, 1.8 Hz, 2H), 2.10 – 2.01 (m, 1H), 1.78 – 1.57 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.85, 151.68, 151.18, 139.56, 136.99, 129.00, 128.60, 128.47, 128.09, 127.70, 122.12, 114.32, 100.34, 88.01, 67.88, 48.04, 30.71, 25.07, 22.32.

HRMS: (ESI, [$C_{21}H_{21}N_5O$ + H]) calcd, 360.1824; found *m/z*: 360.1825.



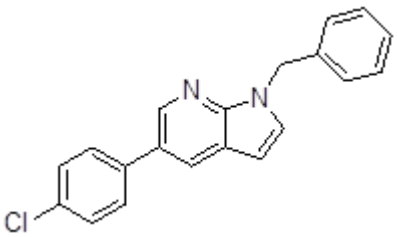
1-Benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine (BJ-3-249)

5-Bromo-7-azaindole (1.576 g, 8.0 mmol, 1.0 equiv), benzyl bromide (1.05 mL, 8.8 mmol, 1.1 equiv) and KO*t*-Bu (987.4 mg, 8.8 mmol, 1.1 equiv) were dissolved in DMF (10 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was poured into water (100 mL). The mixture was then extracted with EtOAc (30 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.9 g (83%) of 1-benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine as a white solid (hexane/EtOAc : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.2 Hz, 1H), 8.04 (d, *J* = 2.2 Hz, 1H), 7.30 (dddd, *J* = 12.3, 7.0, 4.6, 2.3 Hz, 3H), 7.23 – 7.15 (m, 3H), 6.43 (d, *J* = 3.5 Hz, 1H), 5.46 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.20, 143.66, 137.46, 130.91, 129.47, 128.88, 127.89, 127.57, 122.12, 111.86, 99.80, 48.16.

Laha, J. K.; Bhimpuria, R. A.; Prajapati, D. V.; Dayal, N.; Sharma, S. *Chem. Commun.* **2016**, *52*, 4329-4332.



1-Benzyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine (BJ-3-255)

1-Benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine (143.5 mg, 0.5 mmol, 1.0 equiv), 4-chlorophenylboronic acid (93.6 mg, 0.6 mmol, 1.2 equiv), Fe/ppm Pd NP (19.9 mg, 800 ppm Pd) and Et_3N (158 μL, 1.13 mmol, 2.26 equiv) in 1.0 mL 2 wt % TPGS-750-M/H_2O were heated at 95 ^oC for 20 min yielding 153.4 mg (96%) of

1-benzyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine as a white solid (hexane/DCM : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.27 (m, 3H), 7.24 (dd, *J* = 7.5, 2.4 Hz, 3H), 6.54 (d, *J* = 3.5 Hz, 1H), 5.53 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.52, 142.33, 138.33, 137.76, 133.19, 129.17, 129.02, 128.87, 128.72, 128.61, 127.80, 127.57, 127.24, 120.56, 100.54, 48.11.

HRMS: (ESI, [$C_{20}H_{15}ClN_2$ + H]) calcd, 319.1002; found *m/z*: 319.1003.

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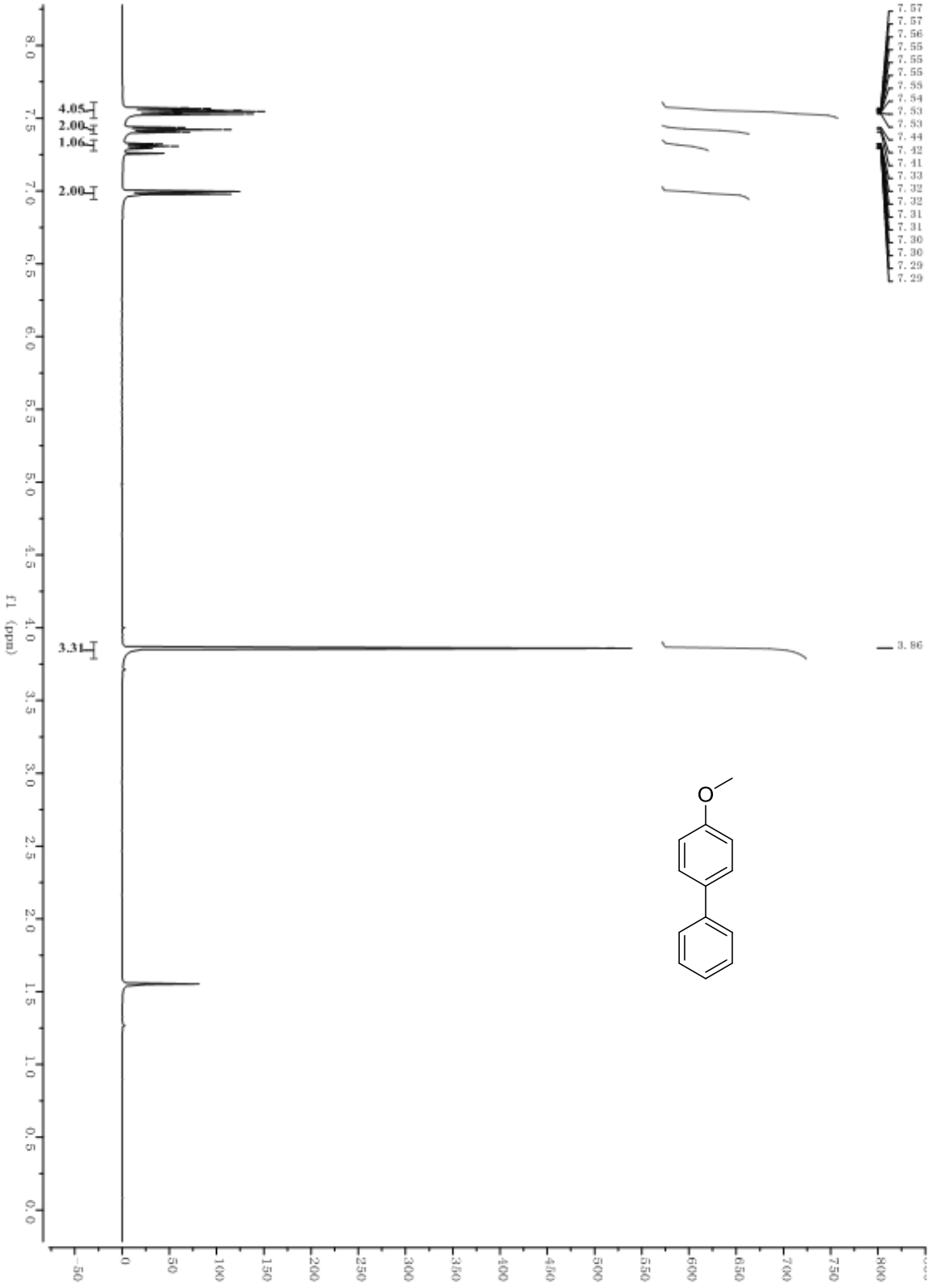
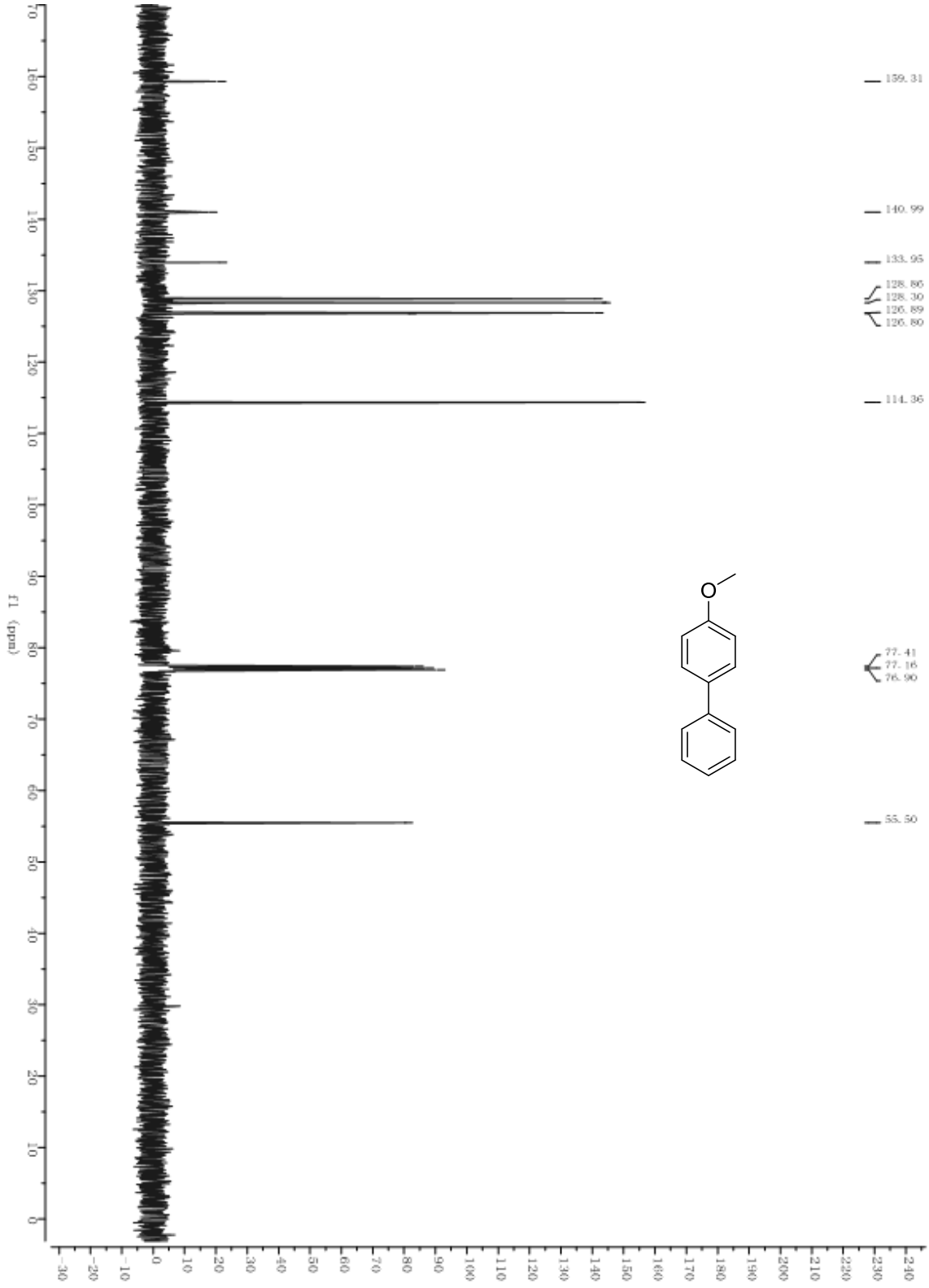
Selected Spectra

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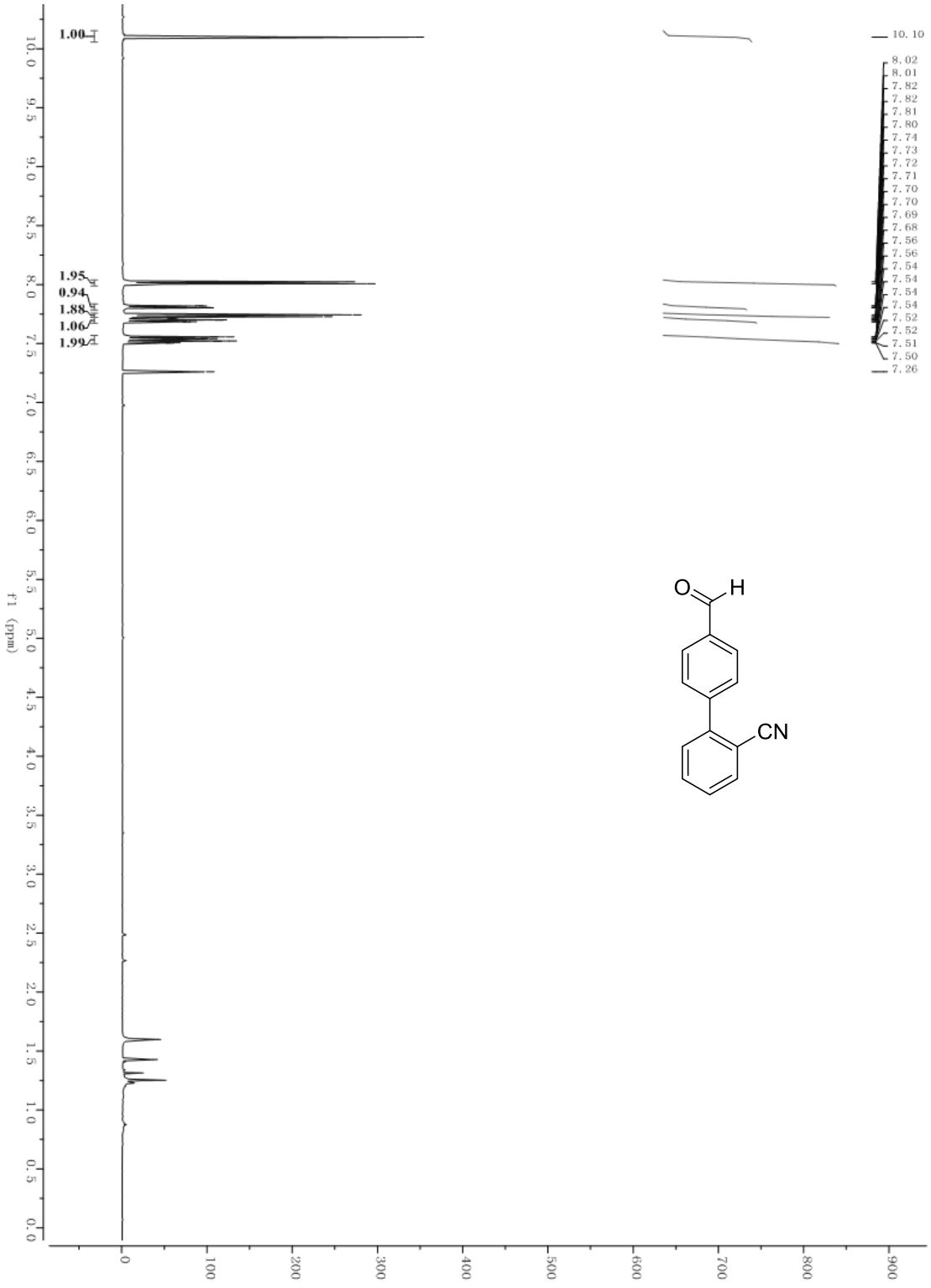
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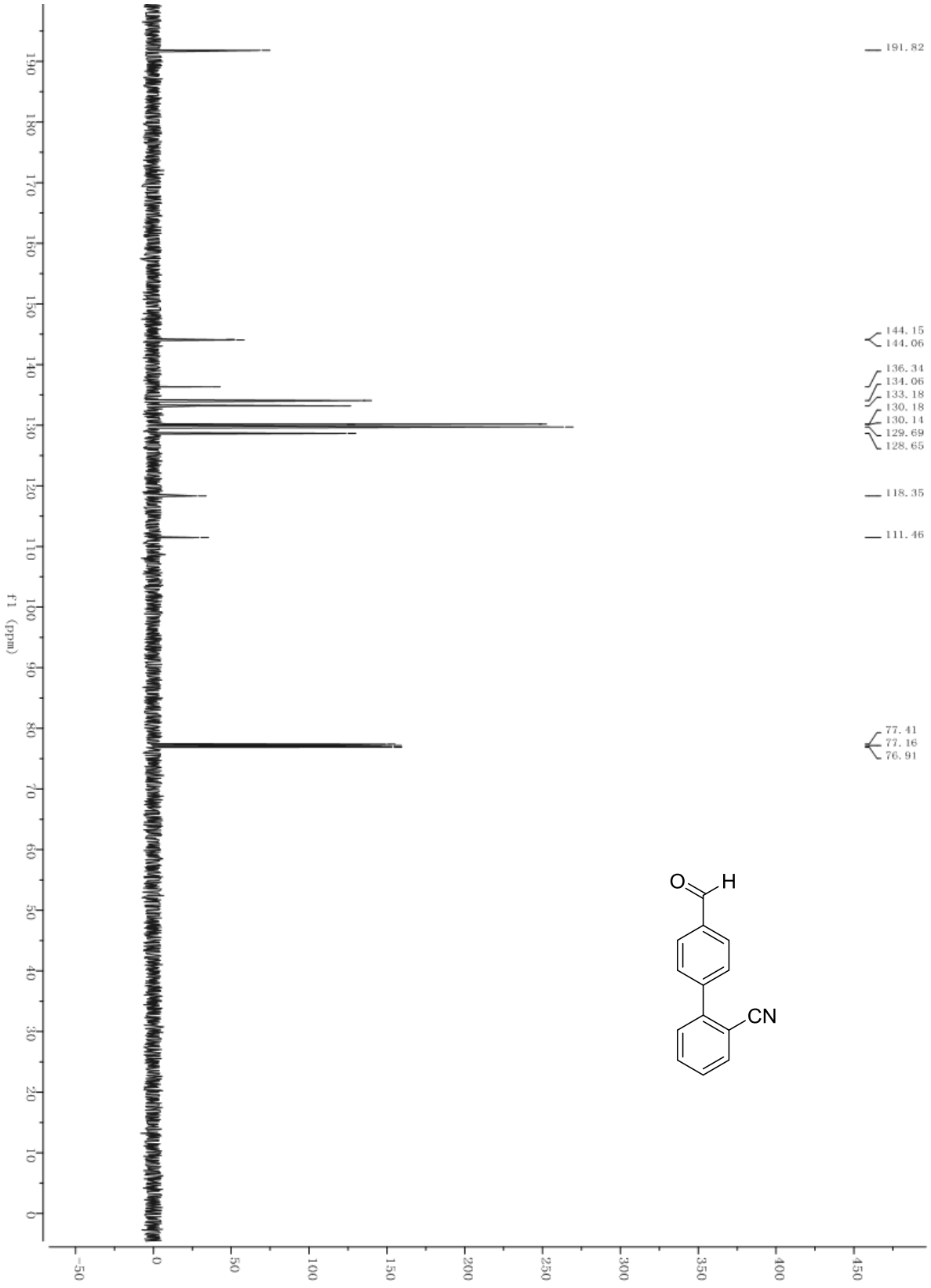
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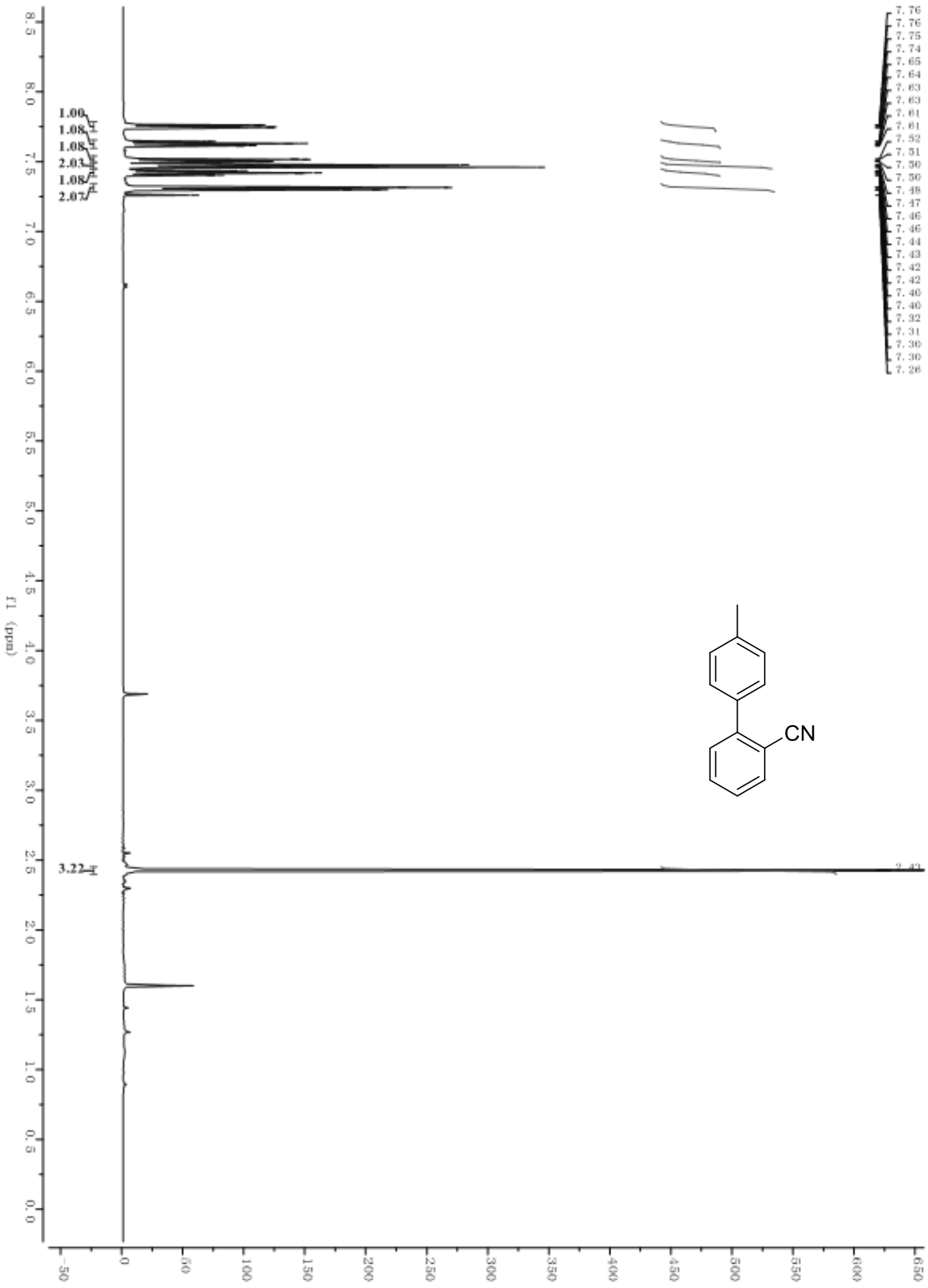
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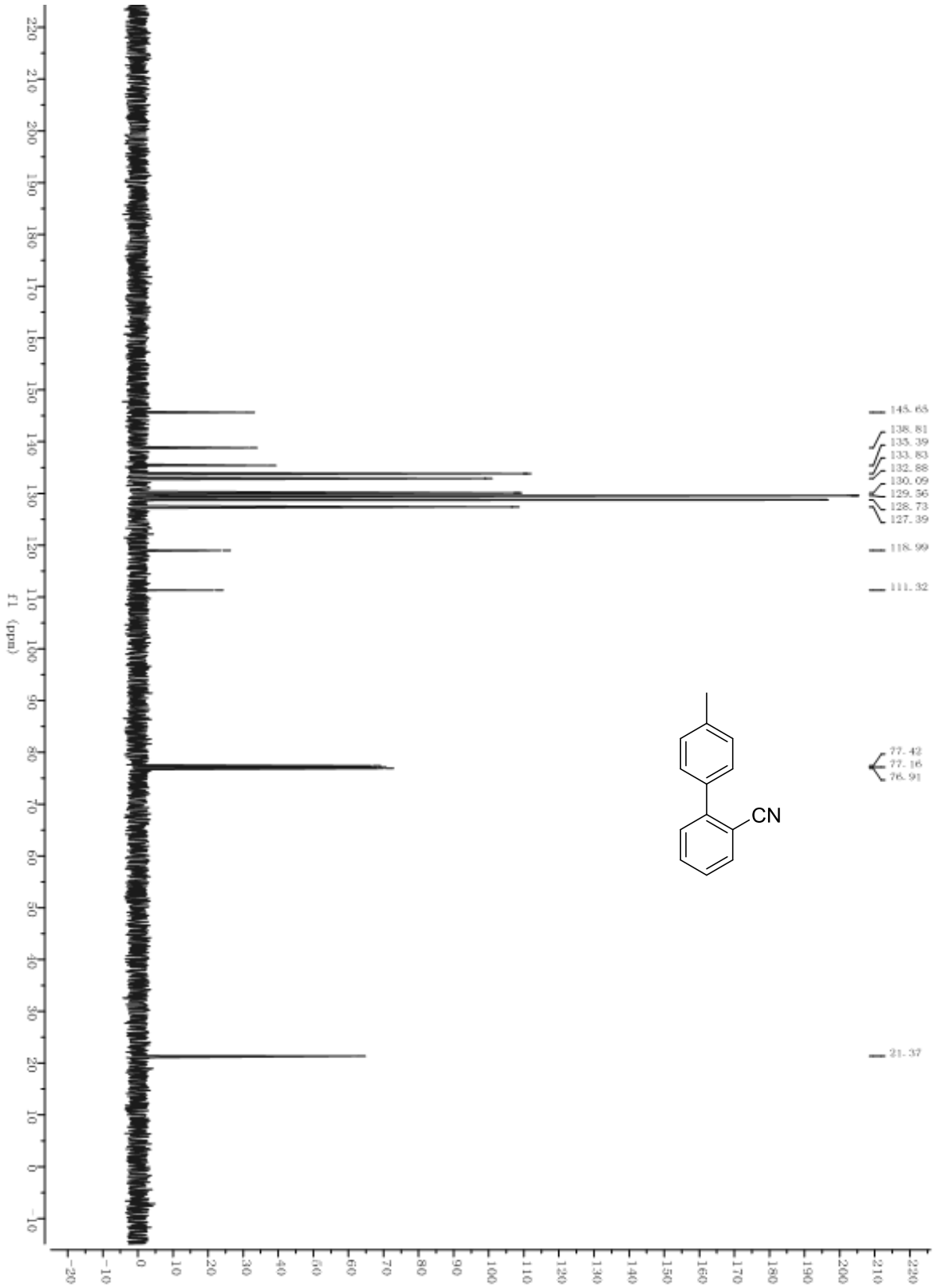
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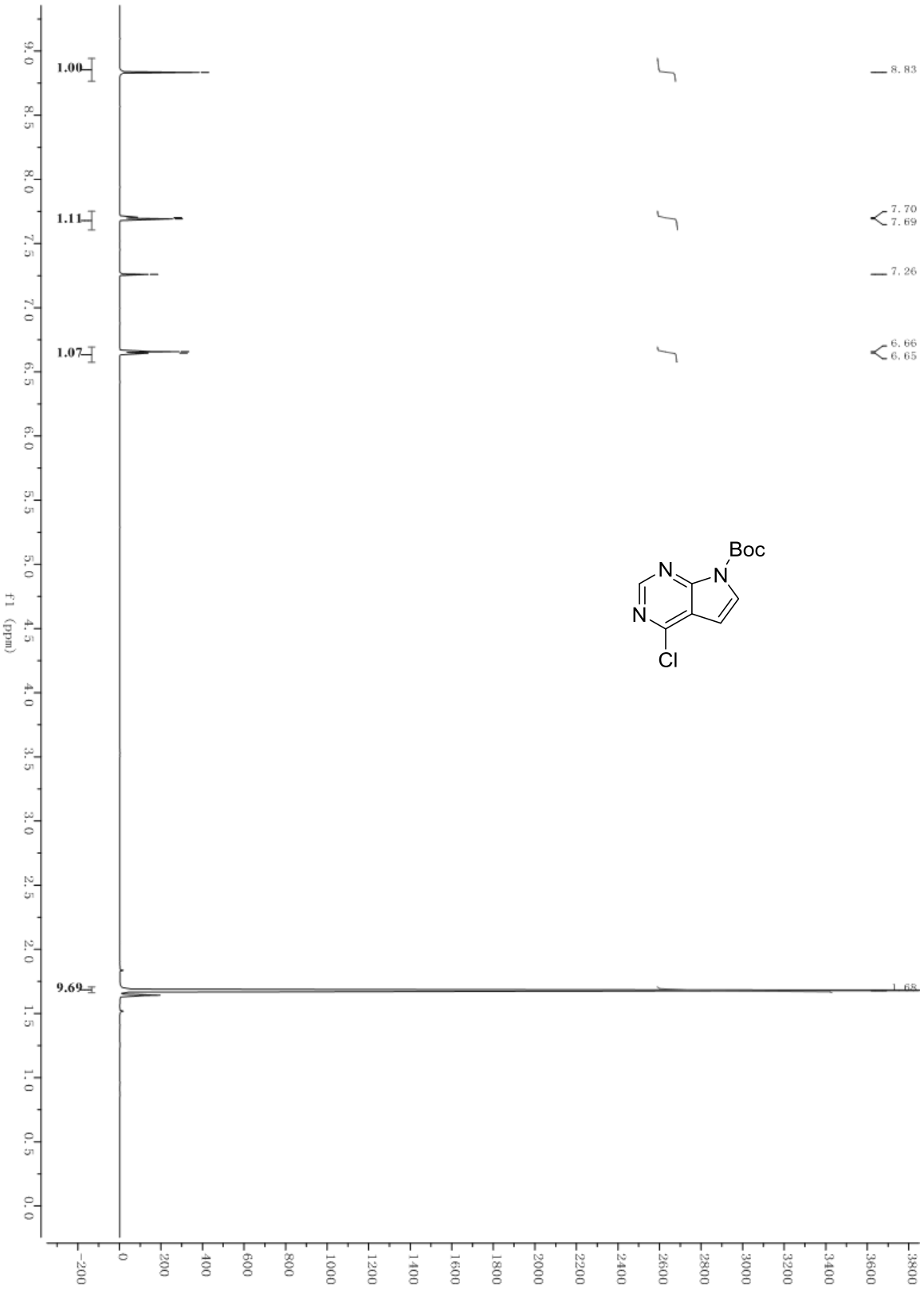
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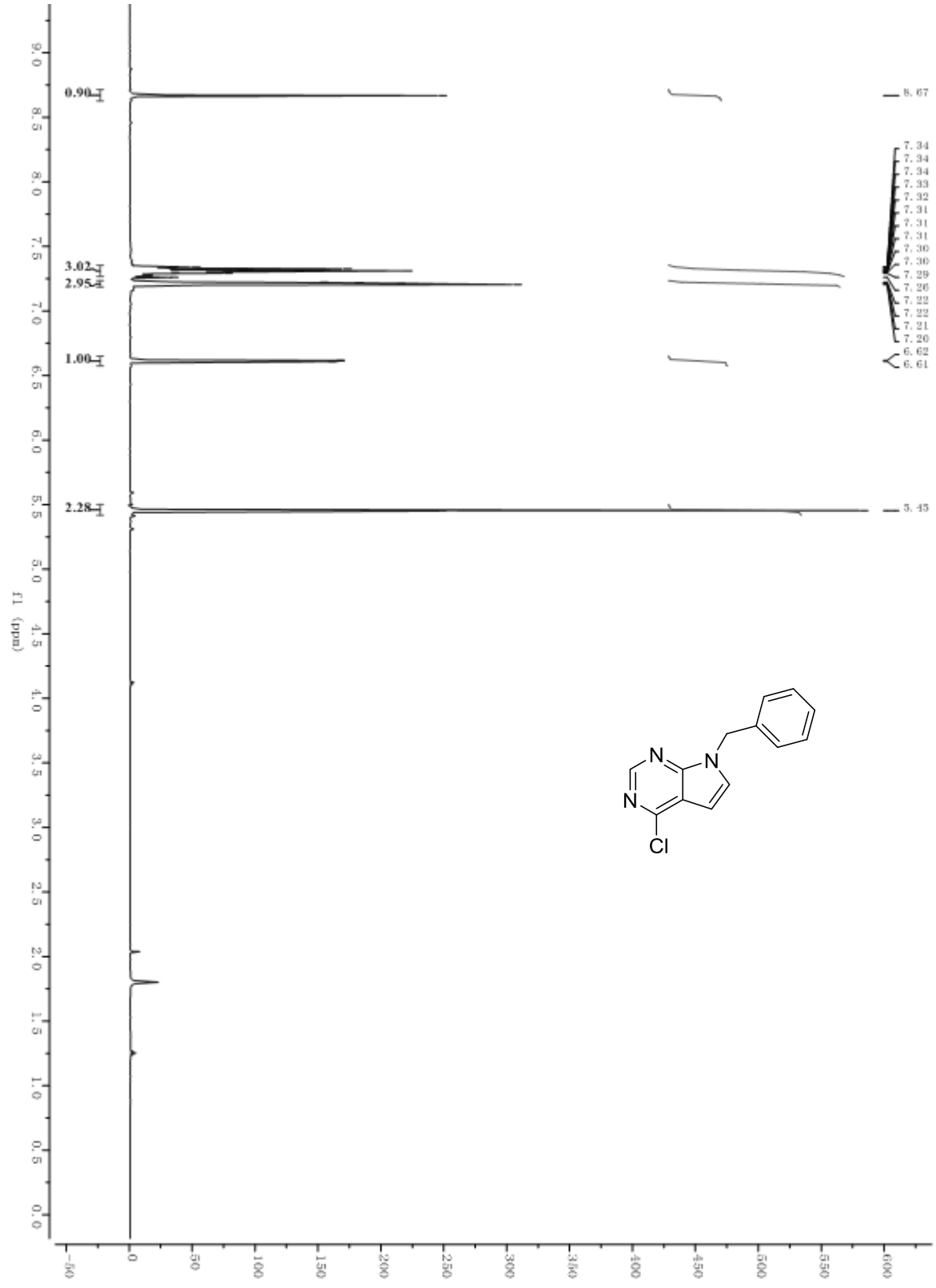
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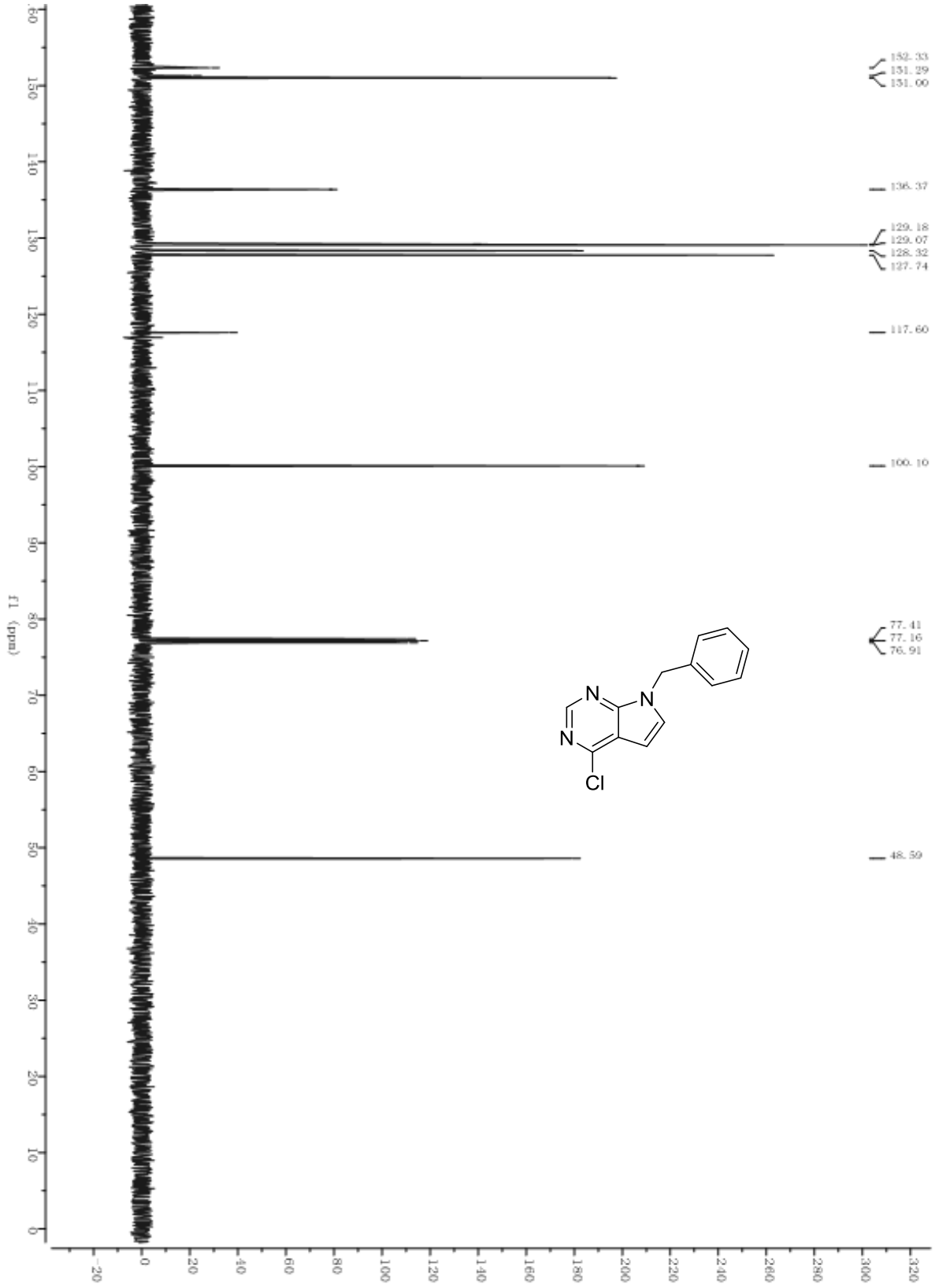
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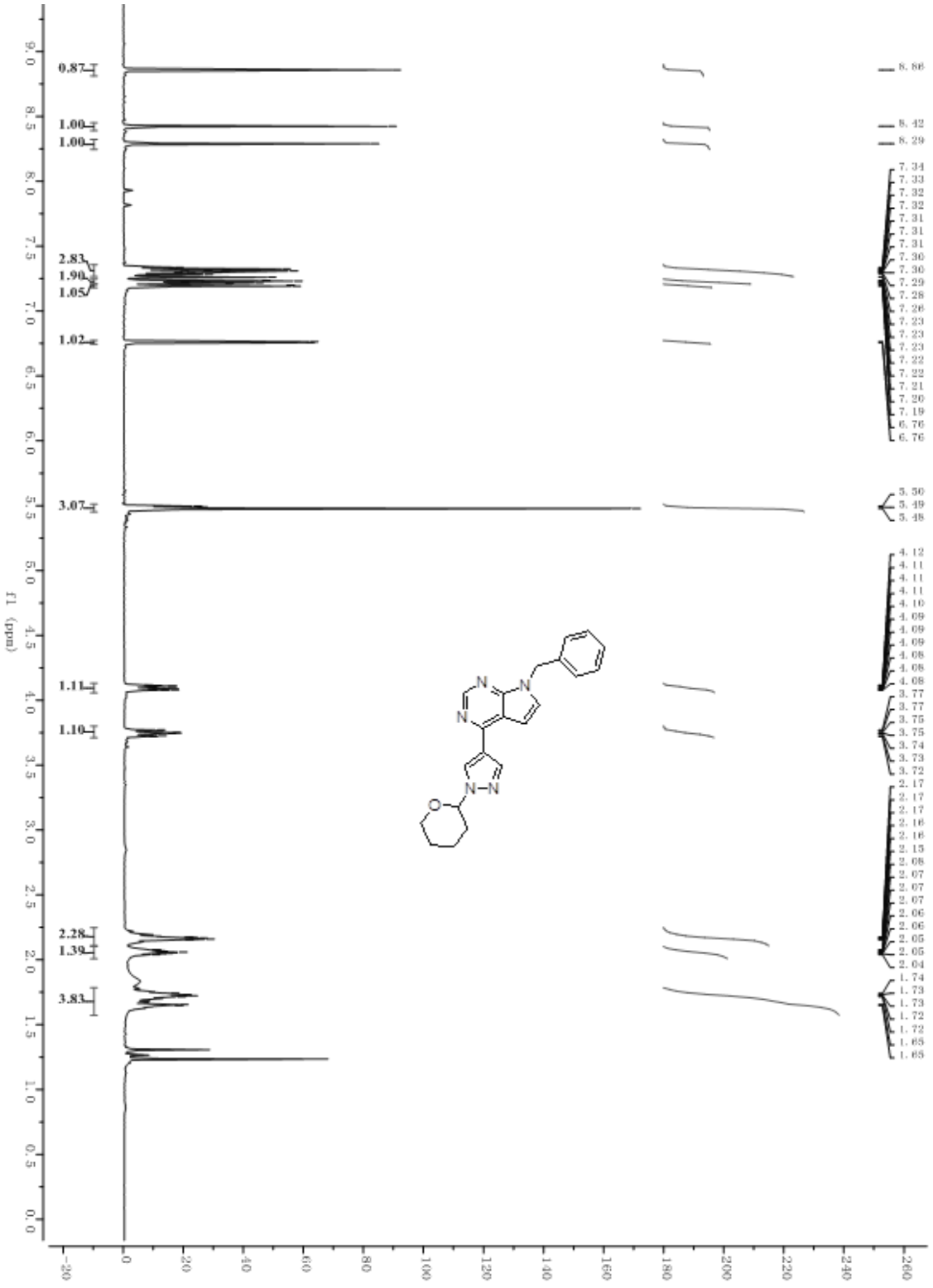
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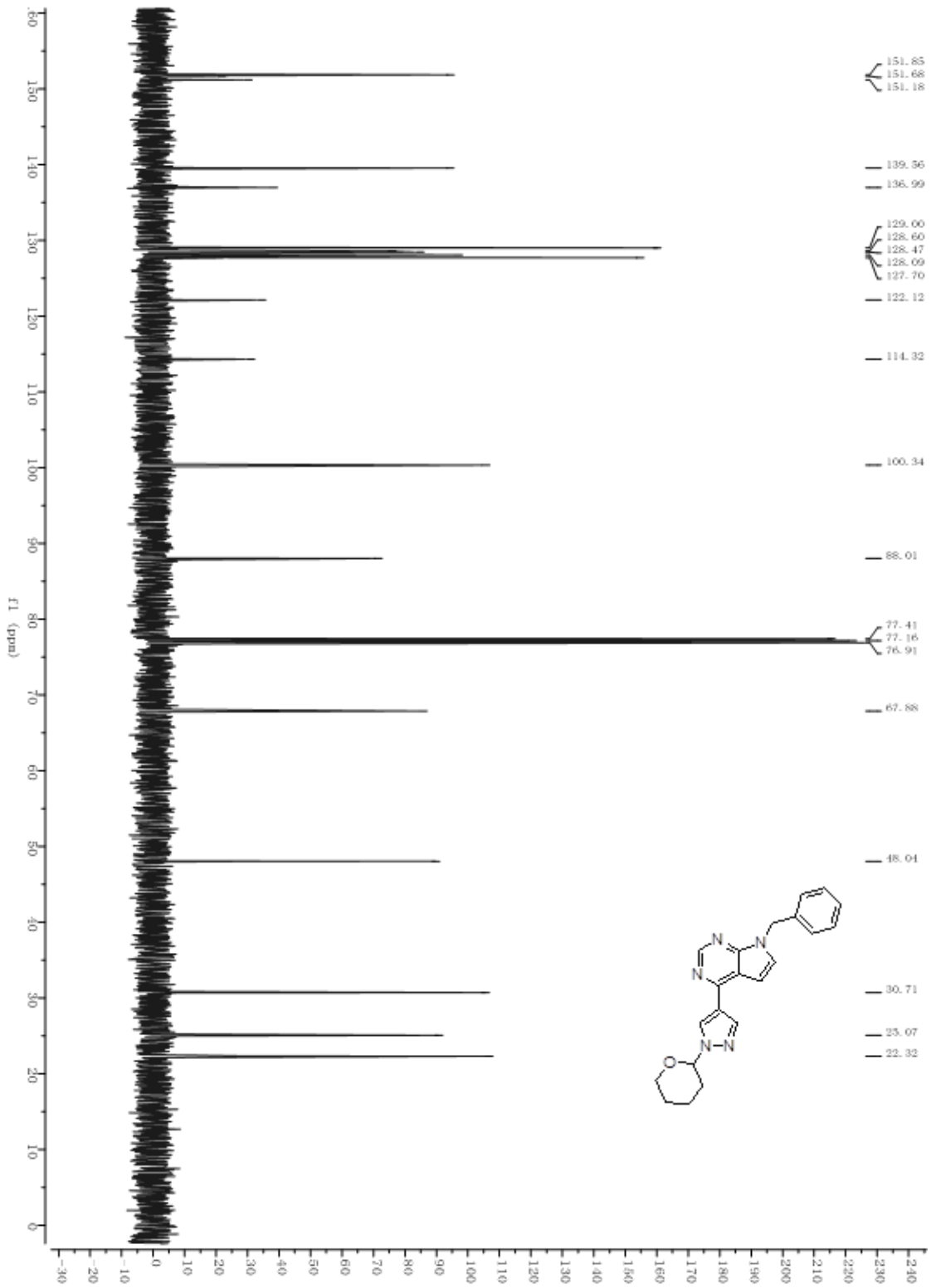
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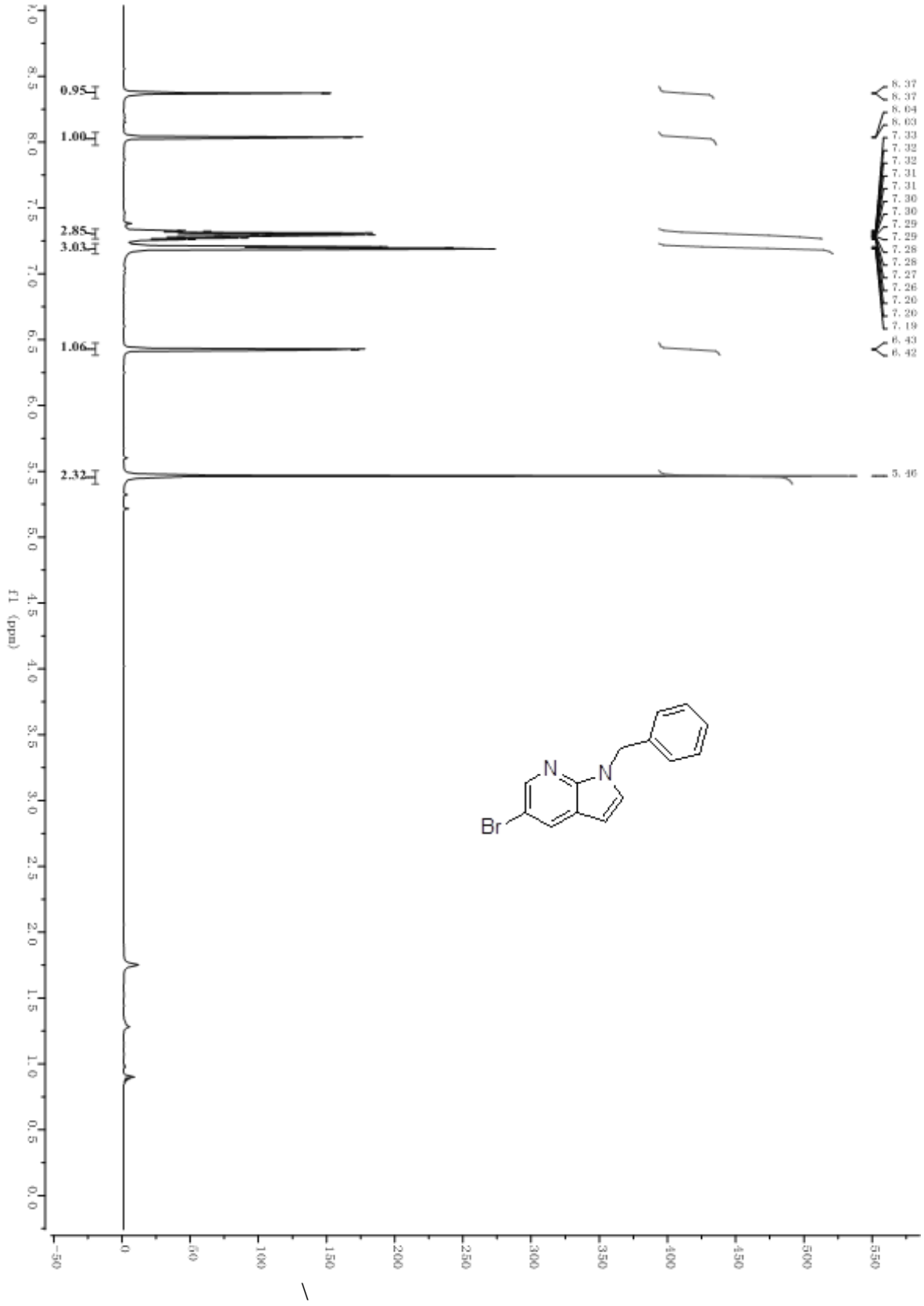
f1 (ppm)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8.03
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7.31
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7.30
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7.28
7.28
7.27
7.26
7.26
7.26
7.19
6.43
6.42
5.46
f1 (ppm)
N
N
Br

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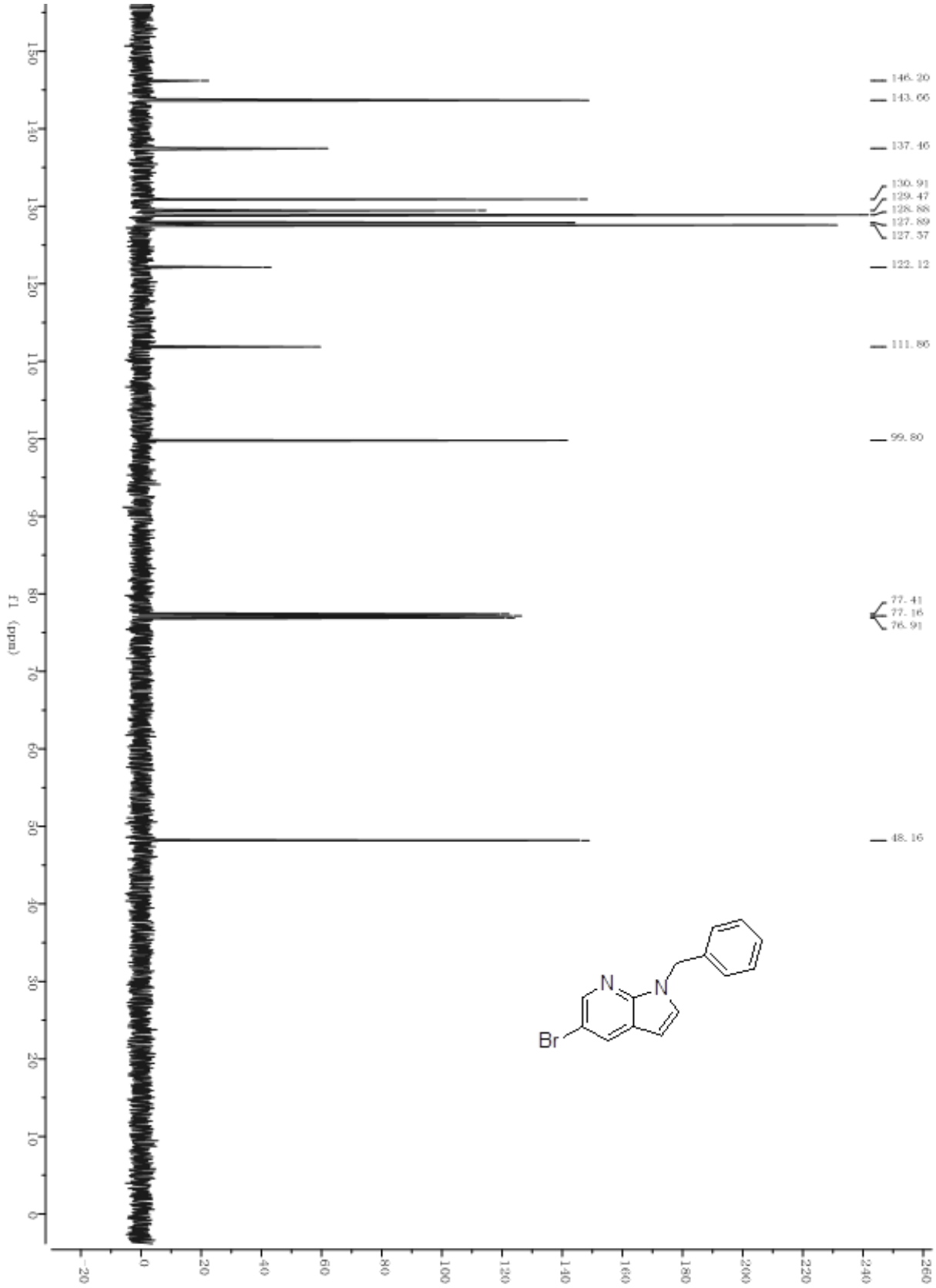
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f1 (ppm)
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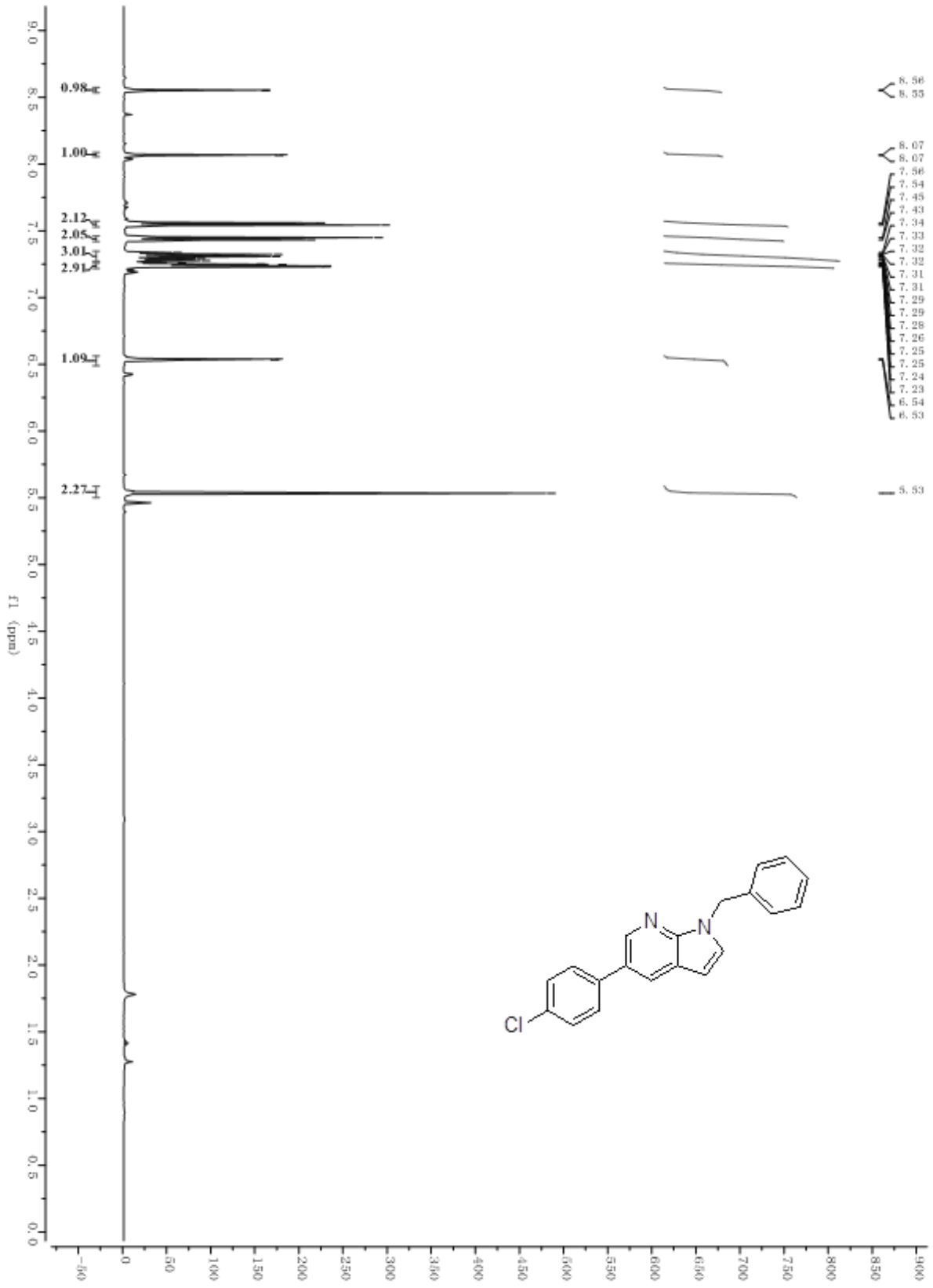
Br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7.29
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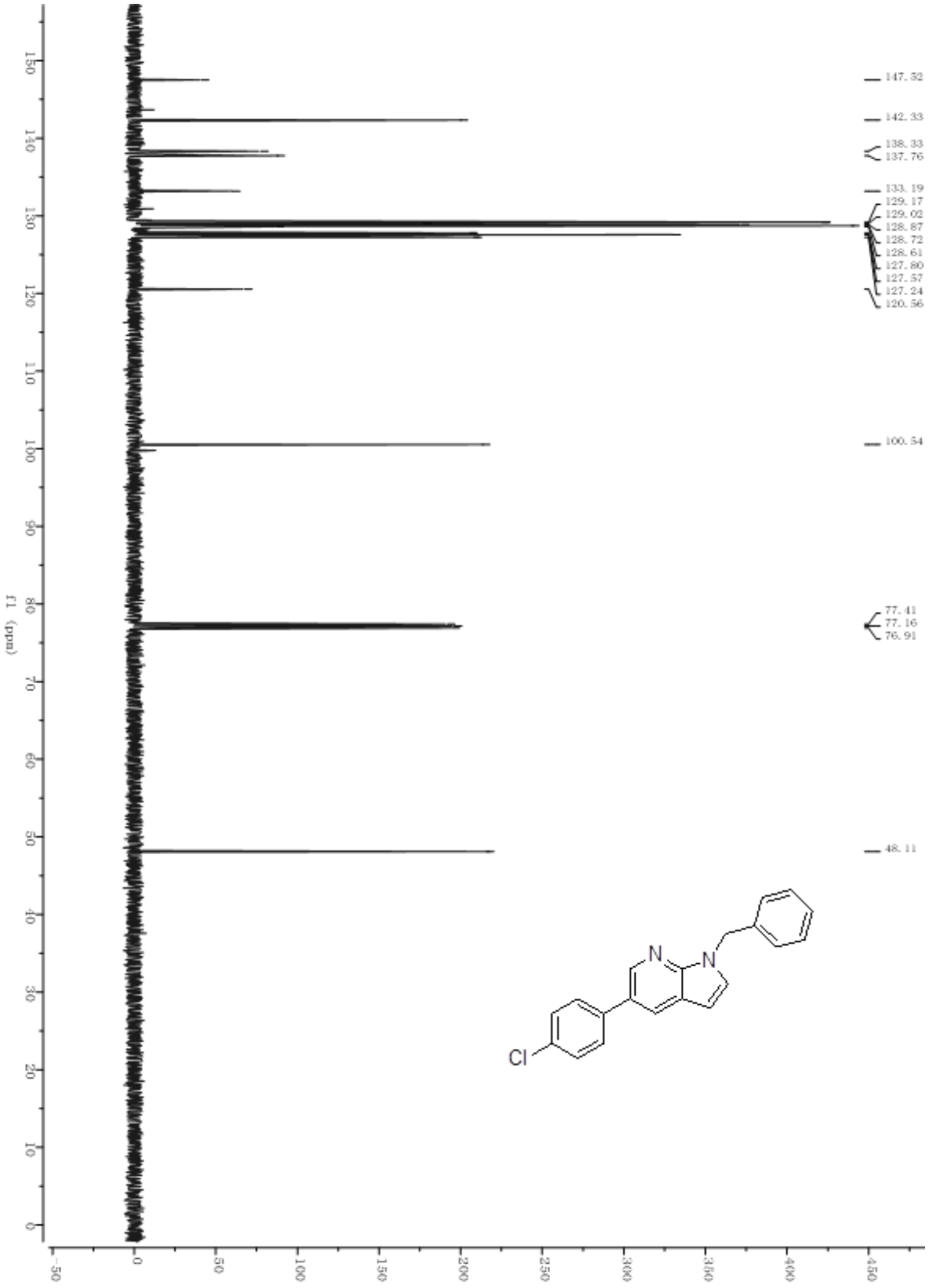
N
Cl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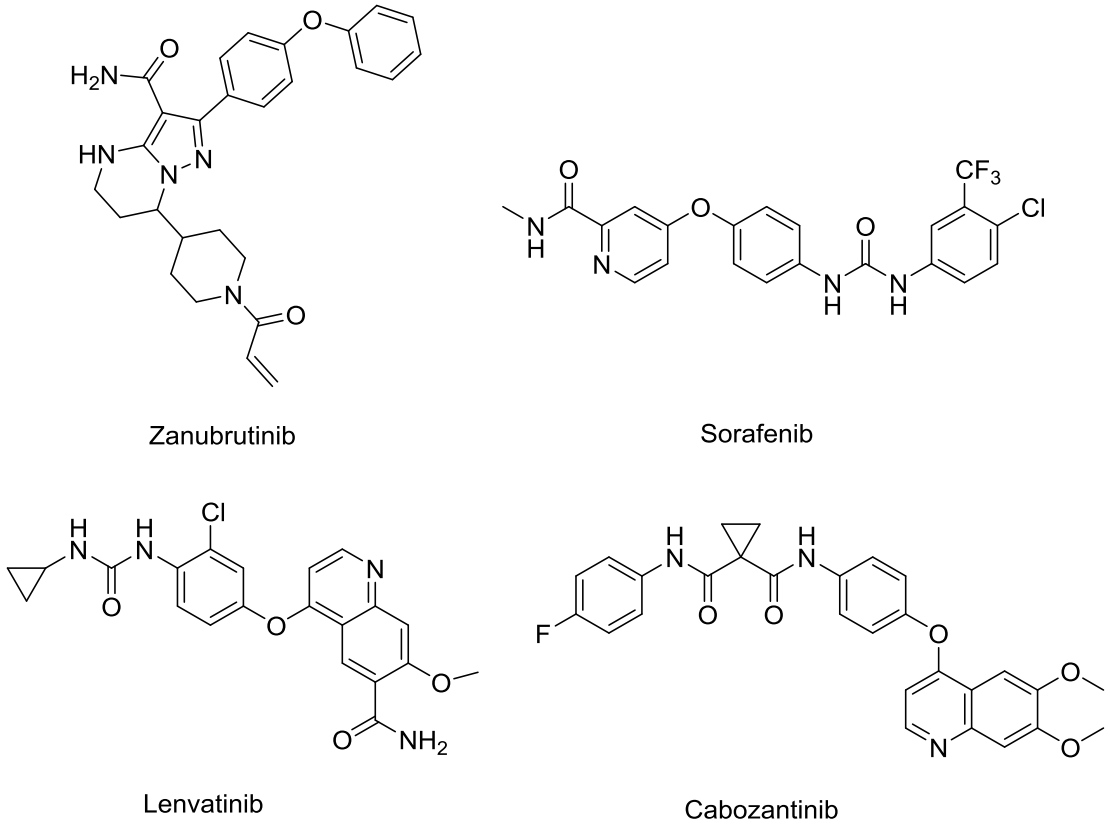
100.54
77.41
77.16
76.91
48.11
f1 (ppm)
N
N
Cl

III. Advances in diaryl ether forming reactions in water

Introduction

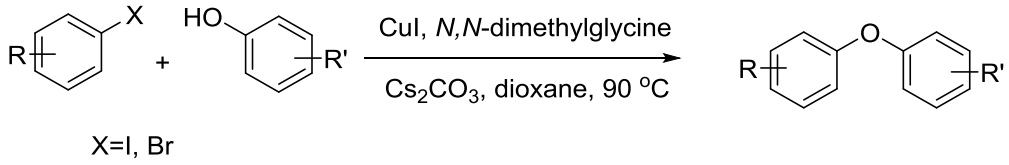
Diaryl ethers are highly useful structures in organic chemistry. Numerous commercially available drugs contain this functional group (Scheme 1). Traditionally, copper was used to catalyze this type of transformation under harsh Ullmann conditions. These reactions are usually performed in organic solvents like DMF and dioxane. Green chemistry calls for milder reaction conditions and environmentally friendly solvents. Different metals, ligands, and reaction conditions were tested in an aqueous micellar environment in efforts to improve these approaches.



Scheme 1. Examples of drugs containing diaryl ether fragments.

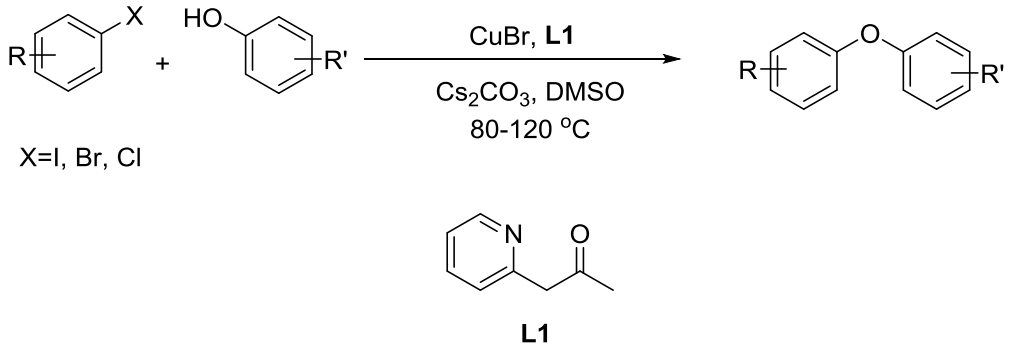
Previous Work

Ma *et al.* discovered that amino acids could work as ligands to facilitate diaryl ether forming reactions (Scheme 2).[1]



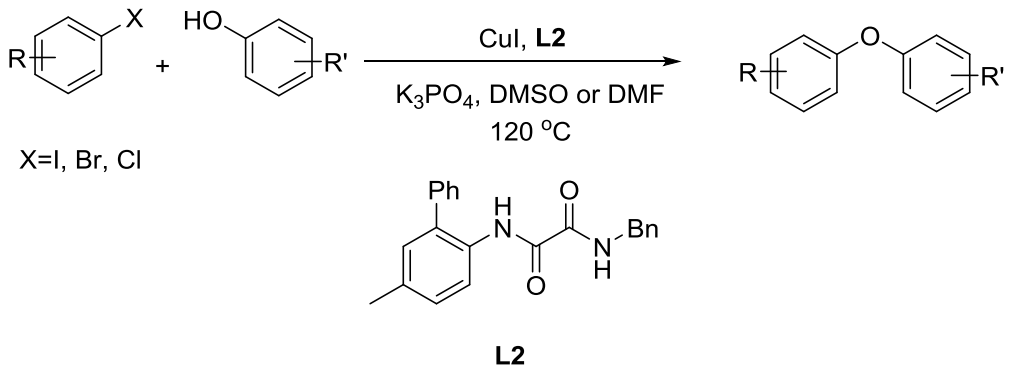
Scheme 2. Amino acids facilitated diaryl ether forming reactions.

These reactions require long reaction times and relatively high temperatures with a narrow substrate scope. Ding found that using a 2-pyridyl *β*-ketone ligand the substrate scope could be extended to aryl chlorides.[2]



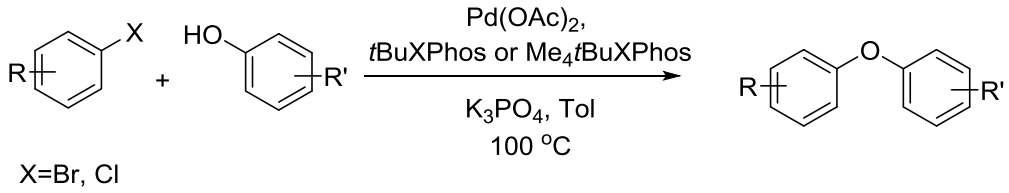
Scheme 3. Diaryl ether forming reactions using a 2-pyridyl *β*-ketone ligand.

However, high catalyst loadings (5-10 mol %) and harsh conditions limit applications of these reactions. Similar to **L1**, reactions that use other ligands like 8-hydroxyquinoline and its esters,[3] 1,3-diketones,[4] 1,10-phenanthrolines[5] and picolinic acid[6] suffer from similar drawbacks. Ma developed a series of oxalamide ligands[7] that could be used in different copper-catalyzed cross-coupling reactions. A 4-methyl-2-phenylaniline-derived oxalamide ligand was found to be the best ligand in the diaryl ether forming reactions.[8]



Scheme 4. Diaryl ether forming reactions using an oxalamide ligand.

Aryl chlorides can be used in this reaction, and different functional groups can be tolerated. However, the inherited problems like harsh conditions and hazardous solvents show the limitations of Ullmann-type reactions. On the other hand, palladium catalyzed cross-coupling reactions are widely used reactions. Buchwald developed palladium catalyzed diaryl ether forming reactions using biaryl dialkyl ligands.[9]

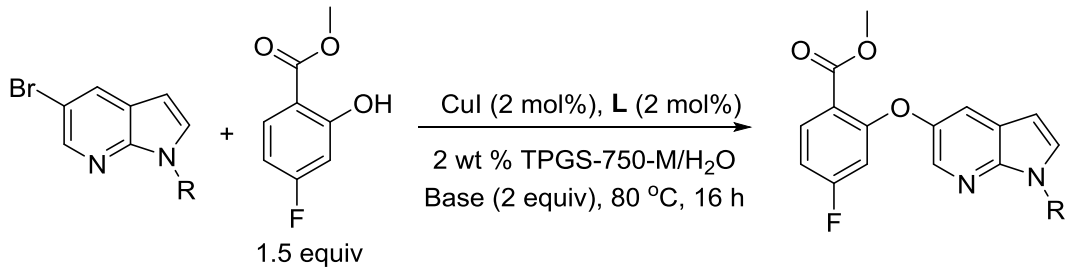


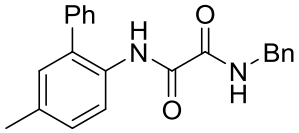
Scheme 5. Palladium catalyzed diaryl ether forming reactions.

In this case, harsh conditions were still required to achieve high reactivity. A modified ligand was discovered to enable room temperature couplings of activated substrates.[10] To further improve reaction conditions of this type of reactions, different parameters will need to be optimized under aqueous micellar conditions.

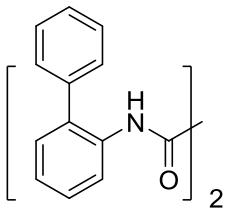
Results and Discussion

The synthesis of a BCL-2 inhibitor venetoclax[11] precursor was used as a model reaction. Different oxalamide ligands were prepared based on previous reports.[8, 12]





L2



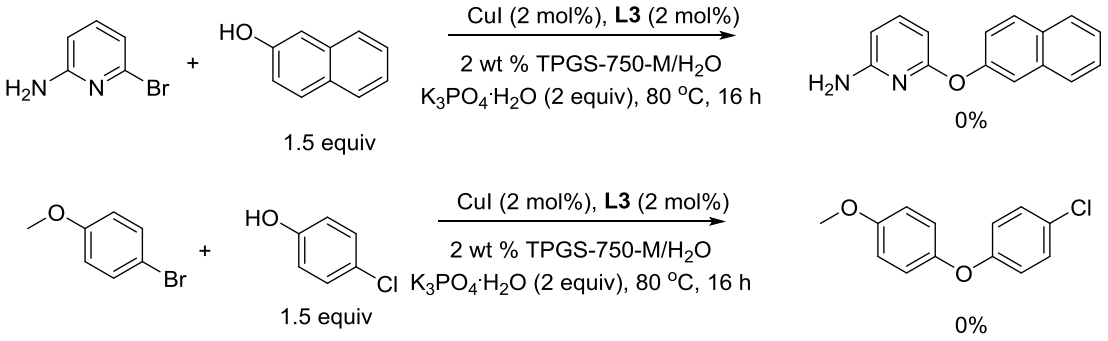
L3

Entry	Ligand	Base	R	GC yield (%)[a]
1	**L2**	Et_3N	H	0
2	**L2**	Et_3N	Boc	0
3	**L2**	Et_3N	Bn	0
4	**L3**	$K_3PO_4•H_2O$	H	0
5	**L3**	$K_3PO_4•H_2O$	Boc	0
6	**L3**	$K_3PO_4•H_2O$	Bn	0
7	**L3**	Et_3N	H	0
8	**L3**	Et_3N	Boc	0
9	**L3**	Et_3N	Bn	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

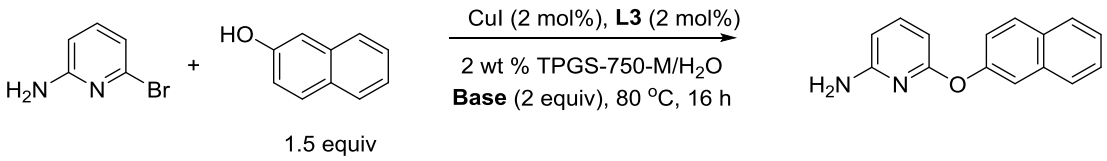
Table 1. Initial screenings of oxalamide ligands in water.

Initial screenings gave no desired product under all conditions examined. However, the methyl ester coupling partner was all consumed in this reaction. The methyl ester may not be able to tolerate these reaction conditions. Two sets of coupling partners selected from a previous publication[12] were tested.



Scheme 6. Testing two pairs of coupling partners from a previous publication.

No reactivity was observed in previously reported coupling partners. Other variables were further tested to determine the best conditions

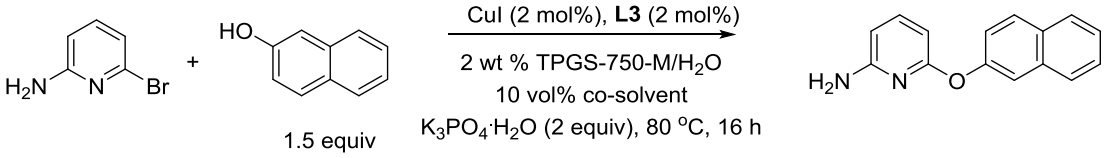


Entry	Base	GC yield (%)[a]
1	K_2CO_3	0
2	Et_3N	0
3	DBU	0
4	DABCO	0
5	Cs_2CO_3	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 2. Screenings of bases in water.

All bases screened in Table 2 showed no product formation. Both polar starting materials might be difficult to get into the micelles. Different types of co-solvents were tested in this reaction.

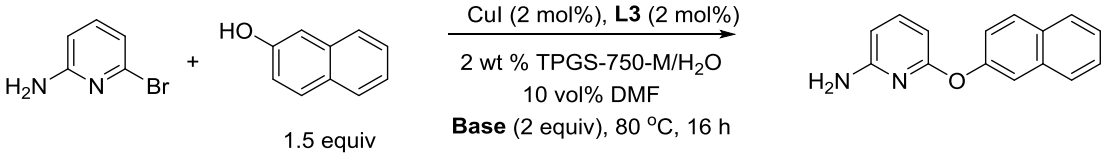


Entry	Co-solvent	GC yield (%)[a]
1	EtOAc	0
2	EtOH	0
3	acetone	0
4	DMF	55
5	DMSO	0
6	MeCN	0
7	THF	0
8	toluene	0

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 3. Screenings of co-solvents.

Among all co-solvents tested in Table 3, only DMF showed reactivity. All other co-solvents gave no conversion. Using DMF as a co-solvent, different bases were screened again.

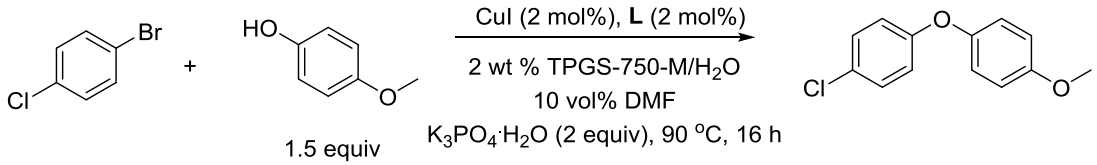


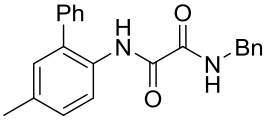
Entry	Base	GC yield (%)[a]
1	$K_3PO_4•H_2O$	55
2	K_2CO_3	<5
3	Et_3N	<5
4	DBU	40
5	DABCO	<5
6	Cs_2CO_3	<5

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

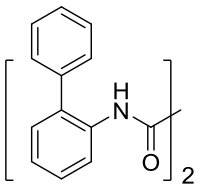
Table 4. Screenings of bases in a water/DMF mixture.

Compared with $K_3PO_4•H_2O$ used in the original conditions, all other bases tested gave inferior results. The reactivity of oxalamide ligands in water/DMF mixture was not as good as that in just DMF. Other types of ligands were also screened to find a lead in this reaction.





L2



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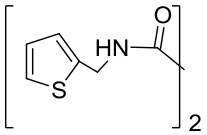

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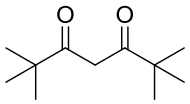

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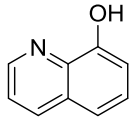

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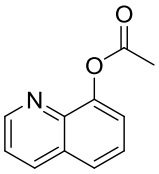

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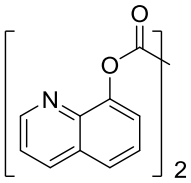

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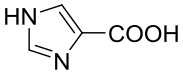

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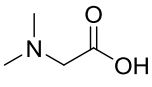

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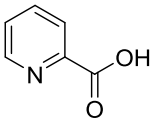

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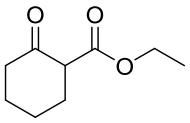

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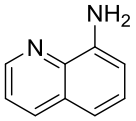

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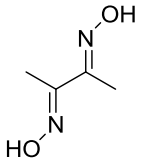

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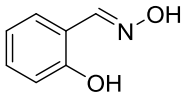


L15

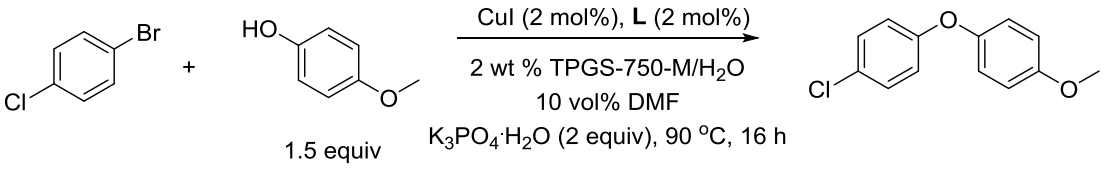
Entry	Ligand	GC yield (%)[a]
1	**L2**	<20
2	**L3**	<20
3	**L4**	<20
4	**L5**	57
5	**L6**	22
6	**L7**	35

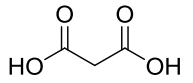
7	**L8**	45
8	**L9**	23
9	**L10**	<20
10	**L11**	<20
11	**L12**	<20
12	**L13**	<20
13	**L14**	<20
14	**L15**	<20

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

Table 5. Screening of different types of ligands.

Different types of ligands were tested, as shown in Table 5. Oxalamides were found to be much less reactive compared with the substrate screened previously. 1,3-Diketone ligand such as **L5** gave the best yield among all ligands, while β-keto ester like **L12** gave inferior results. 8-Hydroxyquinolines and its esters gave moderate yields. Other traditional ligands all failed to give more than 20% yield. Readily available 1,3-dicarbonyl compounds were screened again to find a better ligand hit.





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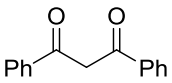

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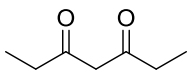

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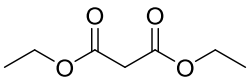

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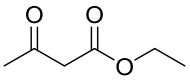

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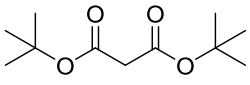

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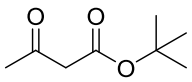

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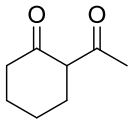

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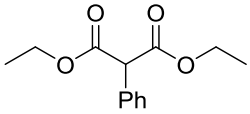

L24

Entry	Ligand	GC yield (%)[a]
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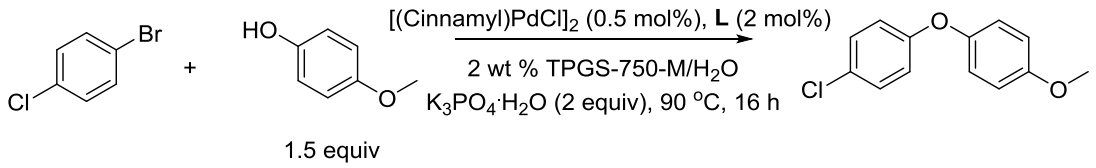
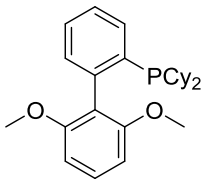
2	**L17**	<20
3	**L18**	<20
4	**L19**	<20
5	**L20**	<20
6	**L21**	<20
7	**L22**	<20
8	**L23**	<20
9	**L24**	<20

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O.

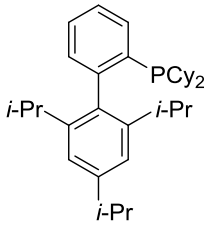
Table 6. Screening of different types of 1,3-dicarbonyl compounds.

All 1,3-dicarbonyl ligands screened in Table 6 were found to be unreactive. Palladium can also catalyze this type of reaction. Some reactions were performed using a palladium catalyst in water without participation of a co-solvent.

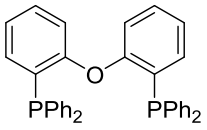




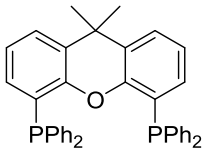
L25



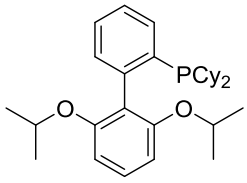
L26



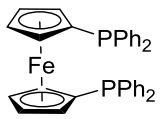
L27



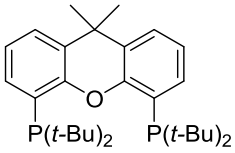
L28



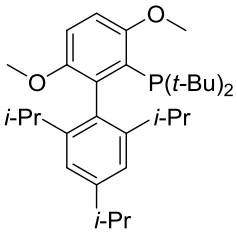
L29



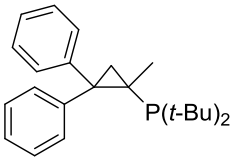
L30



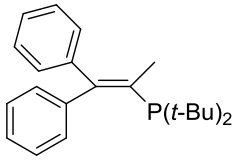
L31



L32



L33



L34

Entry	Ligand	GC yield (%)[a]
1	**L25**	0
2	**L26**	0
3	**L27**	0
4	**L28**	0

5	**L29**	0
6	**L30**	0
7	**L31**	<10
8	**L32**	<10
9	**L33**	100(<10)[b]
10	**L34**	100(<10)[b]

[a]: Reactions were carried out on a 0.5 mmol scale in 1 mL of 2 wt % TPGS-750-M/H_2O. **[b]:** 60^oC

Table 7. Screenings of ligands used in palladium catalyzed diaryl ether forming reactions.

Only **L33** and **L34** gave full conversion under harsh condition (90 ^oC). Reducing the temperature to 60 ^oC shut down the reaction. The identical diaryl ether product can be synthesized by a copper catalyst at a fraction of the cost compared with the palladium catalyst so this reaction was not further pursued.

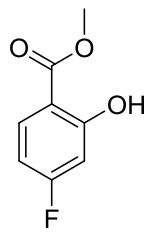
Conclusions and Outlook

Both copper and palladium catalysts were screened in diaryl ether forming reactions under micellar conditions. DMF is required as a co-solvent in copper-catalyzed reactions. However, the efficiency was not comparable to those using just organic solvents when oxalamides were used as ligands. Palladium catalysts are potential alternatives but their high cost limits applications in larger scale reactions.

Experimental Section

Procedure for C-O coupling reactions.

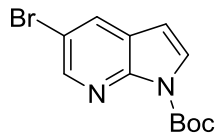
To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, all solid starting materials (halide, phenol), metal salt and ligand were charged under an argon flow. The reaction vial was then sealed with a rubber septum, evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and liquid starting materials, co-solvent and/or base were added via syringe. The reaction mixture was then stirred vigorously at a given temperature for a given time. The reaction vial was then allowed to cool down to rt, and the reaction progress was monitored by TLC and/or GCMS.



Methyl 4-fluoro-2-hydroxybenzoate (BJ-3-292)

4-Fluoro-2-hydroxybenzoic acid (2341 mg, 15.0 mmol, 1.0 equiv), MeOH (5 mL) and concentrated sulfuric acid (0.5 mL) were charged to an oven-dried 25 mL round bottom flask with a magnetic stir bar. A water condenser and a drying tube were attached to the flask. The reaction mixture was heated to 70 ^{o}C overnight. The reaction mixture was then allowed to cool to rt. EtOAc (10 mL) was added to the reaction mixture. The mixture was washed with 5 % $NaHCO_3$ solution (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo* to afford 1.74 g (68%) of methyl 4-fluoro-2-hydroxybenzoate as a colorless solid.

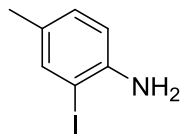
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 8.9, 6.6 Hz, 1H), 6.66 (dd, *J* = 10.3, 2.5 Hz, 1H), 6.62 – 6.55 (m, 1H), 3.94 (s, 3H).



***t*-Butyl 5-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (BJ-3-225)**

5-Bromo-7-azaindole (1970 mg, 10.0 mmol, 1.0 equiv), di-*t*-butyl dicarbonate (2292 mg, 10.5 mmol, 1.05 equiv) and Et_3N (4.2 mL, 30.0 mmol, 3.0 equiv) were dissolved in DCM (30 mL). The reaction mixture was stirred at rt overnight. 1-Methylpiperazine (0.3 mL, 270.9 mg, 2.7 mmol, 0.27 equiv) was added to the reaction mixture. The mixture was then stirred at rt for 30 min and washed with 10% H_2SO_4 (10mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.845 g (62%) of *t*-butyl 5-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate as a yellow solid (hexane/EtOAc : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.2 Hz, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 4.0 Hz, 1H), 6.44 (d, *J* = 4.1 Hz, 1H), 1.65 (s, 9H).

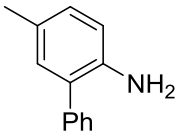


2-Iodo-4-methylaniline (BJ-3-295)

p-Toluidine (2.65 g), 24.8 mmol, 1.0 equiv), iodine (6.07 g, 23.9 mmol, 0.96 equiv) and $NaHCO_3$ (1.83 g, 21.8 mmol, 0.88 equiv) were dissolved in a mixture of DCM (50 mL) and

water (25 mL). The reaction mixture was stirred at rt overnight. The organic layer was separated, washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 4.67 g (81%) of 2-iodo-4-methylaniline as a yellow oil (hexane/EtOAc : 95/5).

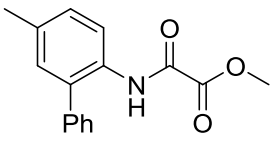
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 1H), 6.95 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.62 (br, s, 2H), 2.21 (s, 3H).



5-Methyl-[1,1'-biphenyl]-2-amine (BJ-3-298)

2-Iodo-4-methylaniline (1.56 g, 6.7 mmol, 1.0 equiv), phenylboronic acid (978.8 mg, 8.0 mmol, 1.2 equiv), Pd(dtbpf)Cl_2 (30.5 mg, 0.0468 mmol, 0.007 equiv) and Et_3N (1.86 mL, 13.38 mmol, 2.0 equiv) were dissolved in 2 wt% TPGS-750-M/H_2O (10 mL). The reaction mixture was stirred at 55^{o}C for 24 h. The mixture was then extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 then concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 979 mg (80%) of 5-methyl-[1,1'-biphenyl]-2-amine as a brown oil (hexane/ether : 80/20).

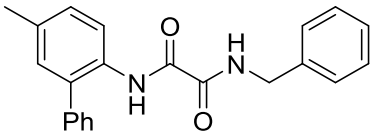
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 4H), 7.35 (ddd, *J* = 8.6, 4.7, 2.6 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.71 (d, *J* = 7.9 Hz, 1H), 3.37 (s, 2H), 2.29 (s, 3H).



Methyl 2-((5-methyl-[1,1'-biphenyl]-2-yl)amino)-2-oxoacetate (BJ-3-302)

5-Methyl-[1,1'-biphenyl]-2-amine (488 mg, 2.66 mmol, 1.0 equiv) and Et_3N (444 μL, 3.19 mmol, 1.2 equiv) were dissolved in anhydrous THF (5 mL). The reaction mixture was cooled to 0^oC using an ice bath. Methyl oxalyl chloride (270 μL, 2.93 mmol, 1.1 equiv) was added dropwise. The ice bath was removed after the completion of addition. The reaction mixture was then allowed to stir at rt overnight. Water (5 mL) was added to the reaction mixture, and the crude product was obtained by vacuum filtration. 674 mg (94%) of methyl 2-((5-methyl-[1,1'-biphenyl]-2-yl)amino)-2-oxoacetate was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.41 – 7.34 (m, 2H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 3.87 (s, 3H), 2.38 (s, 3H).

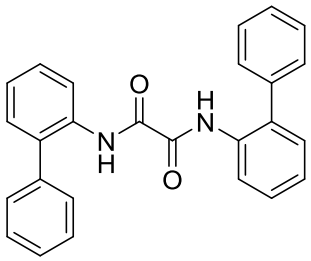


N^1-Benzyl-N^2-(5-methyl-[1,1'-biphenyl]-2-yl)oxalamide (L2) (BJ-4-1)

Methyl 2-((5-methyl-[1,1'-biphenyl]-2-yl)amino)-2-oxoacetate (609 mg, 2.26 mmol, 1.0 equiv) and benzylamine (296 μL, 2.71 mmol, 1.2 equiv) were dissolved in anhydrous THF (2.5 mL). The reaction mixture was heated at 70^oC for 8 h. The reaction mixture was allowed to cool to rt and the crude product was obtained by vacuum filtration. 723.7 mg (93%) of N^1-benzyl-N^2-(5-methyl-[1,1'-biphenyl]-2-yl)oxalamide was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.83 (t, *J* = 6.3 Hz, 1H), 7.52 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.47 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H), 7.37 – 7.30 (m,

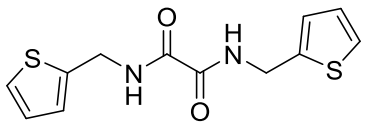
3H), 7.30 – 7.27 (m, 2H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 4.48 (d, *J* = 6.2 Hz, 2H), 2.38 (s, 3H).



***N*^{1},*N*^{2}-Di([1,1'-biphenyl]-2-yl)oxalamide (L3) (BJ-3-301)**

2-Phenylaniline (338.4 mg, 2.0 mmol, 1.0 equiv) and Et_3N (293 μL, 2.1 mmol, 1.05 equiv) were dissolved in anhydrous THF (6 mL). The reaction mixture was cooled to 0^{o}C using an ice bath. Oxalyl chloride (85 μL, 1.0 mmol, 0.5 equiv) was added dropwise. The ice bath was removed after the completion of addition. The reaction mixture was allowed to stir at rt overnight. Water (6 mL) was added to the reaction mixture, and the crude product was obtained by vacuum filtration. 526.4 mg (67%) of *N*^{1},*N*^{2}-di([1,1'-biphenyl]-2-yl)oxalamide was obtained as a white solid.

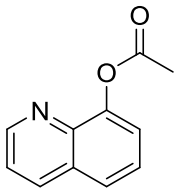
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.49 – 7.43 (m, 1H), 7.43 – 7.34 (m, 3H), 7.31 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.23 (dd, *J* = 8.3, 7.1 Hz, 1H).



***N*^{1},*N*^{2}-bis(Thiophen-2-ylmethyl)oxalamide (L4) (BJ-4-64)**

2-Aminomethylthiophene (412 μL, 4.0 mmol, 1.0 equiv) and Et_3N (585 μL, 4.2 mmol, 1.05 equiv) were dissolved in anhydrous THF (8 mL). The reaction mixture was cooled to 0°C using an ice bath. Oxalyl chloride (172 μL, 2.0 mmol, 0.5 equiv) was added dropwise. The ice bath was removed after the completion of addition. The reaction mixture was allowed to stir at rt overnight. Water (8 mL) was added to the reaction mixture, and the crude product was obtained by vacuum filtration. 340 mg (30%) of *N*[1],*N*[2]-bis(thiophen-2-ylmethyl)oxalamide was obtained as a white solid.

[1]H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.27 (d, *J* = 3.0 Hz, 1H), 7.06 – 6.93 (m, 2H), 4.68 (d, *J* = 6.1 Hz, 2H).



Quinolin-8-yl acetate (L7) (BJ-4-80)

8-Hydroxyquinoline (1161.6 mg, 8.0 mmol, 1.0 equiv) and concentrated sulfuric acid (0.5 mL) were dissolved in acetic anhydride (10 mL). The reaction mixture was allowed to stir at rt overnight. Water (10 mL) and EtOAc (10 mL) were added to the reaction mixture. The organic layer was separated and dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford 1.092 g (73%) of quinolin-8-yl acetate as a yellow solid (hexane/ether : 90/10).

[1]H NMR (500 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.50 (s, 3H).

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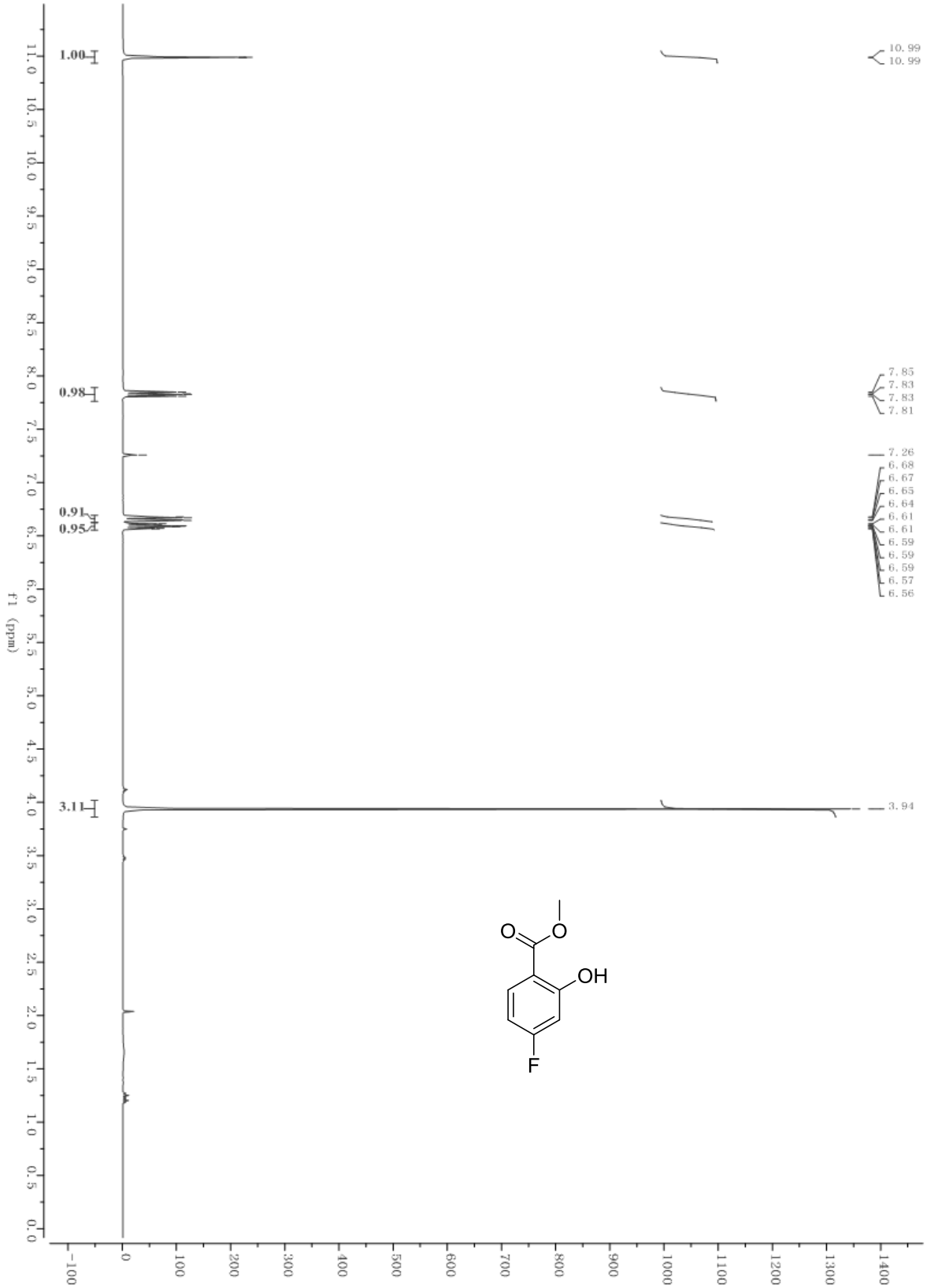
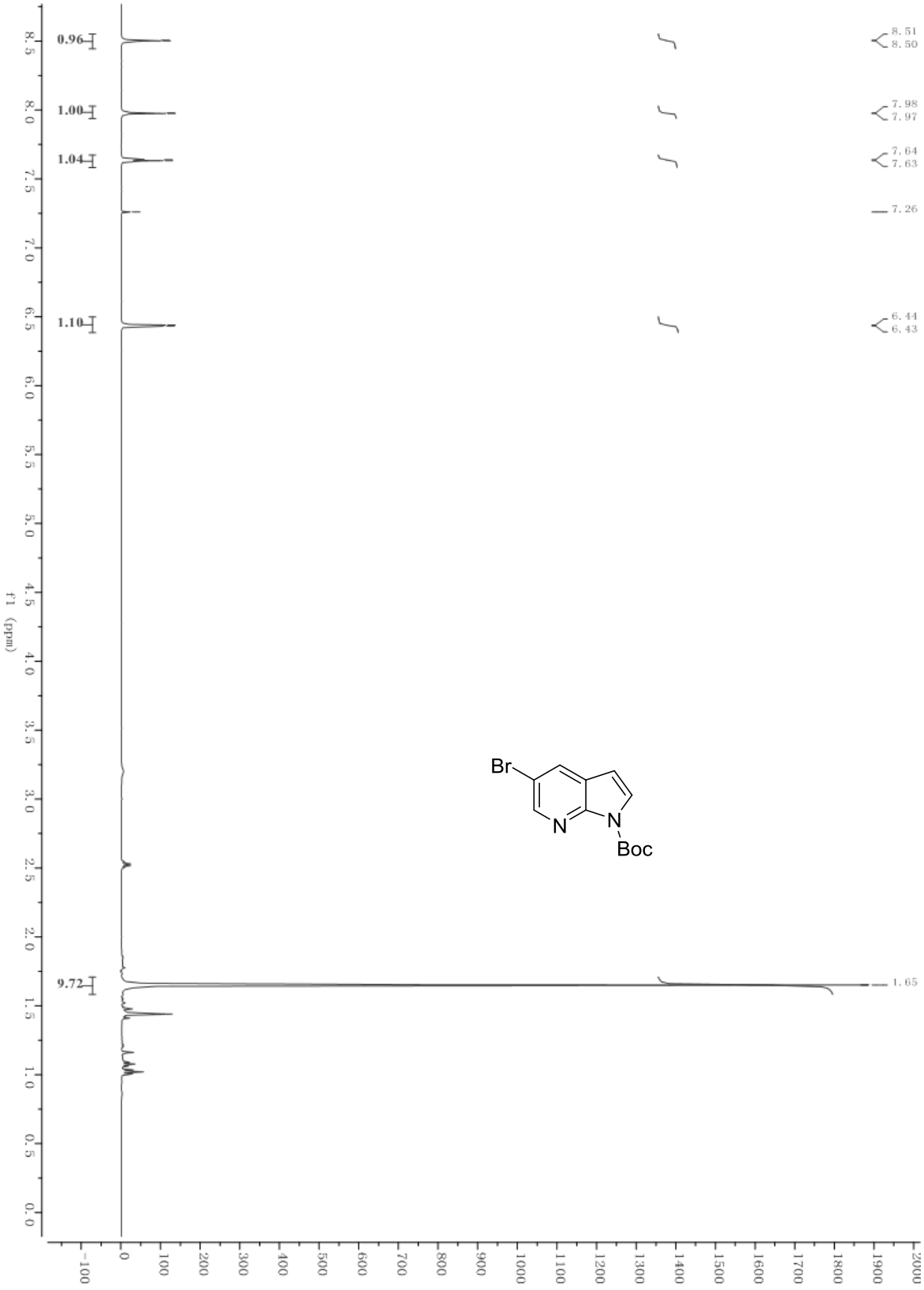
Selected Spectra

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7.64
7.63
7.26
6.44
6.43
1.65
0.96
1.00
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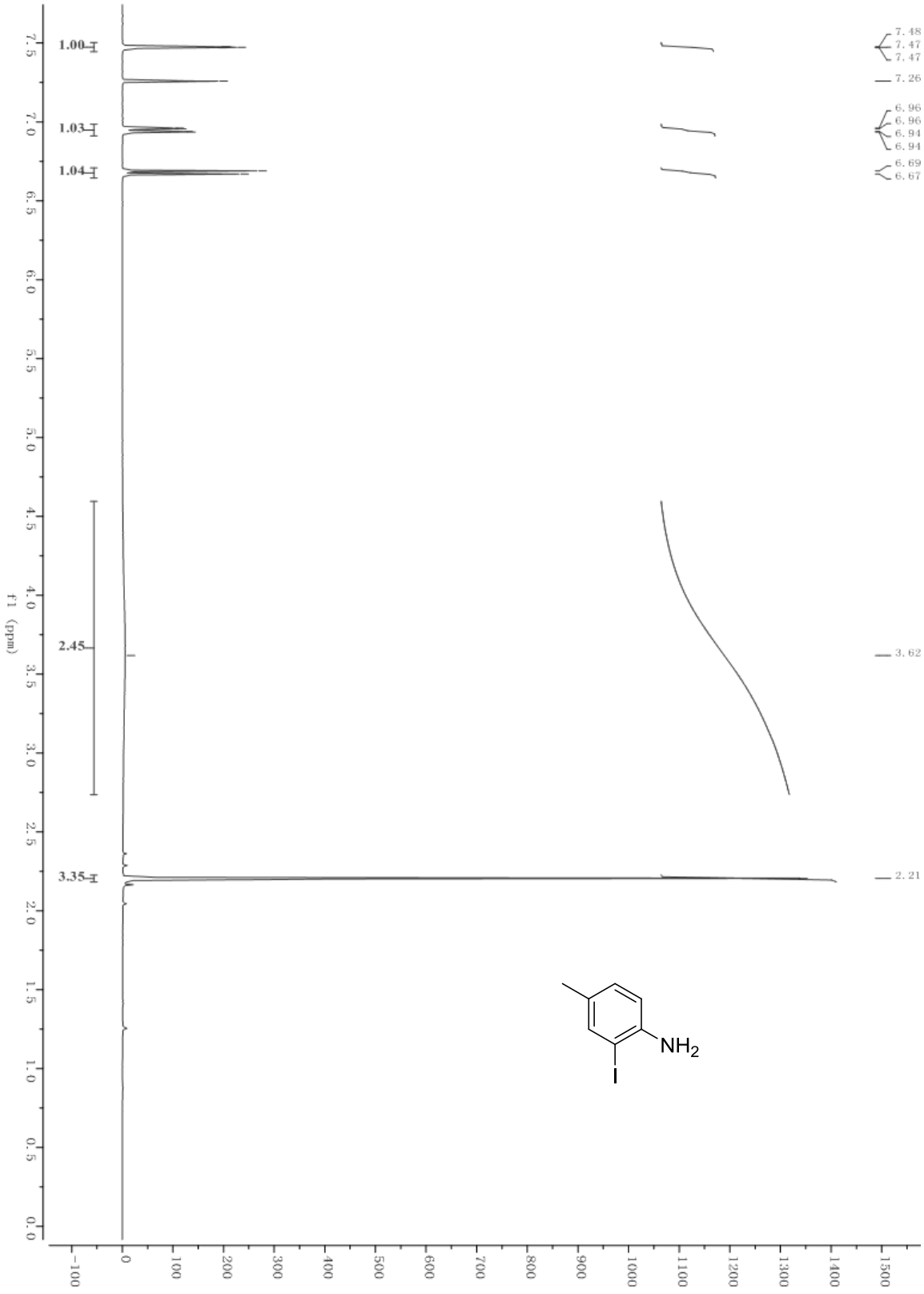
1.10
9.72
Br
N
N
Boc
f1 (ppm)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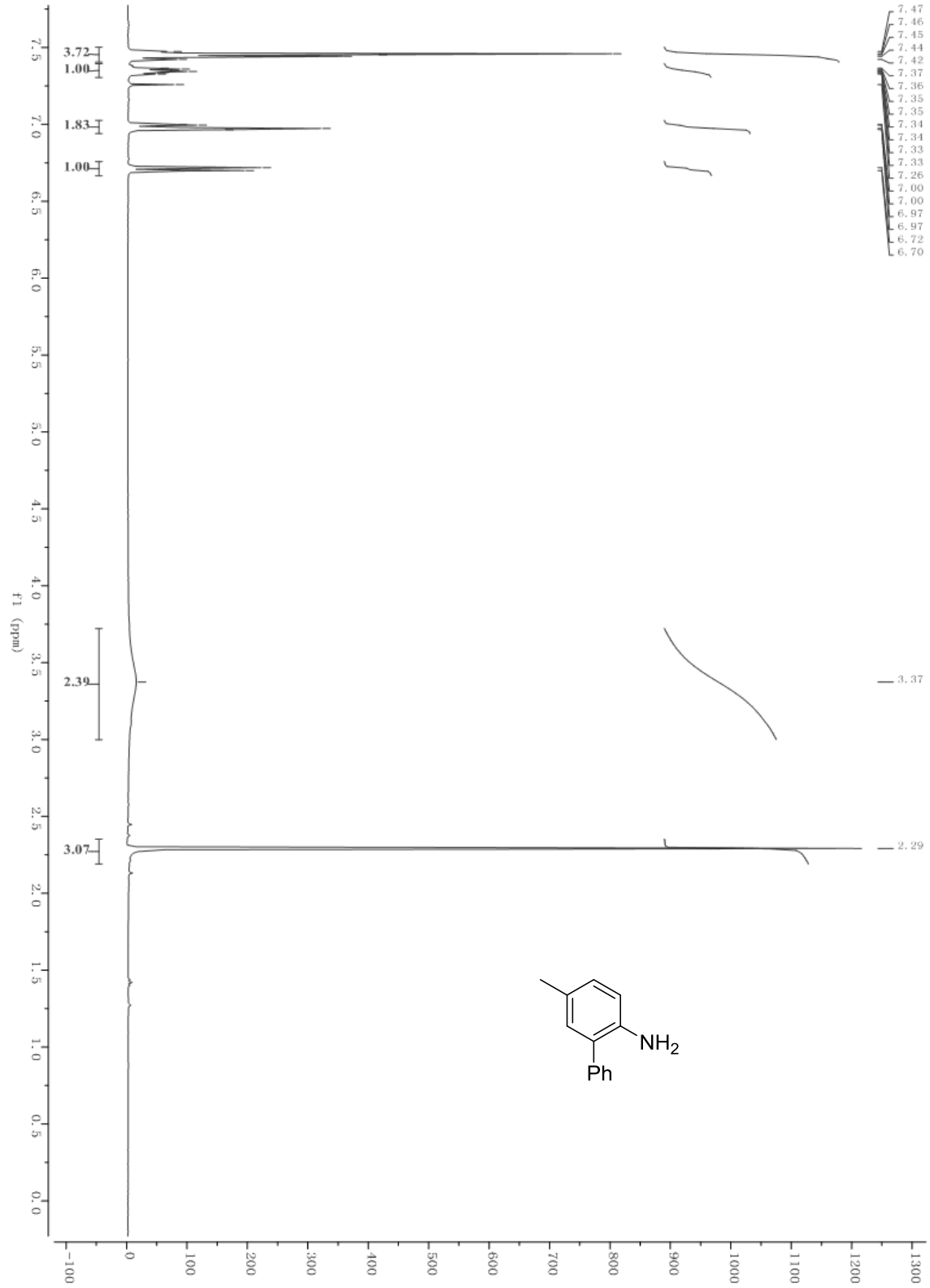
NH2
I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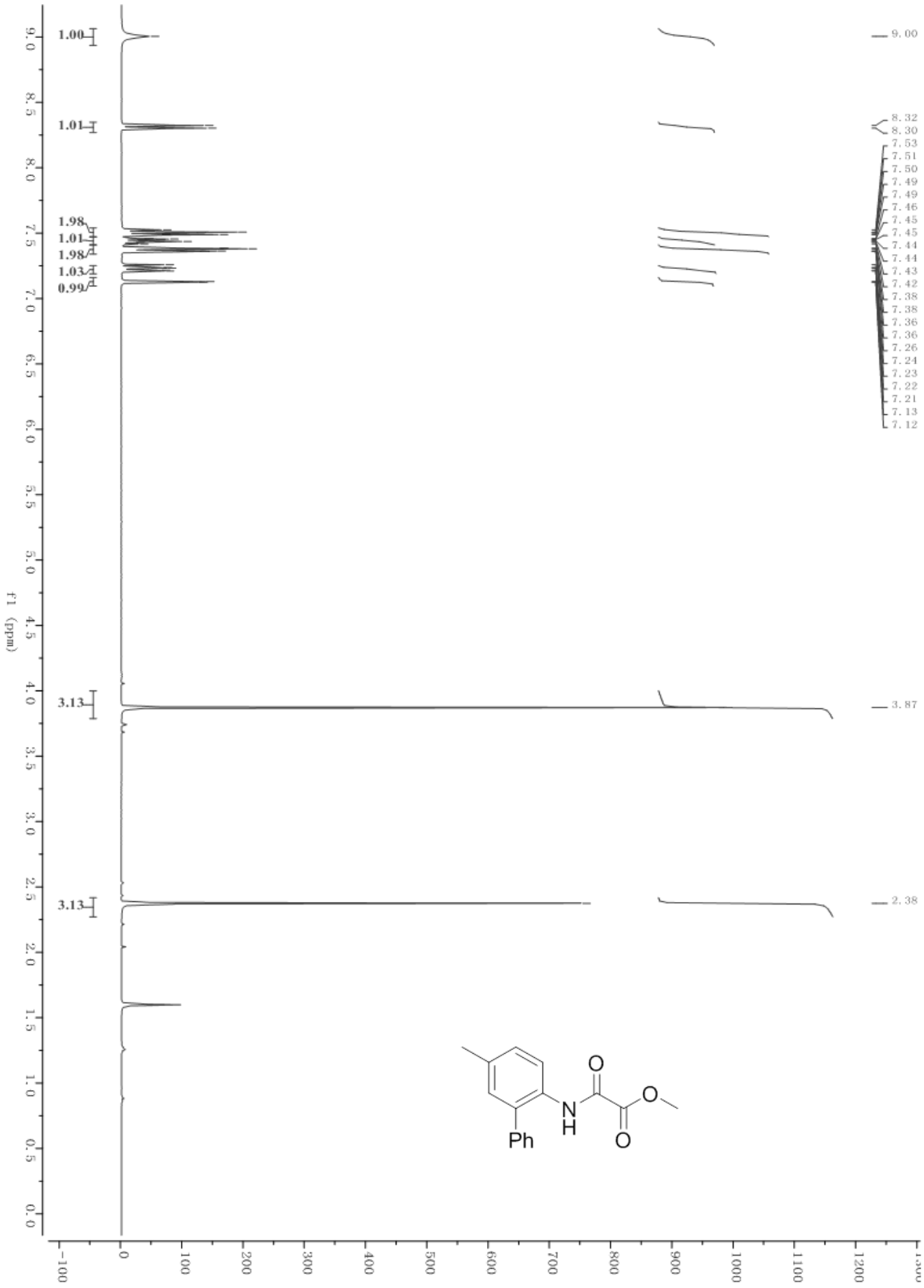
3.37
2.29
f1 (ppm)
NH2
Ph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7.44
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7.43
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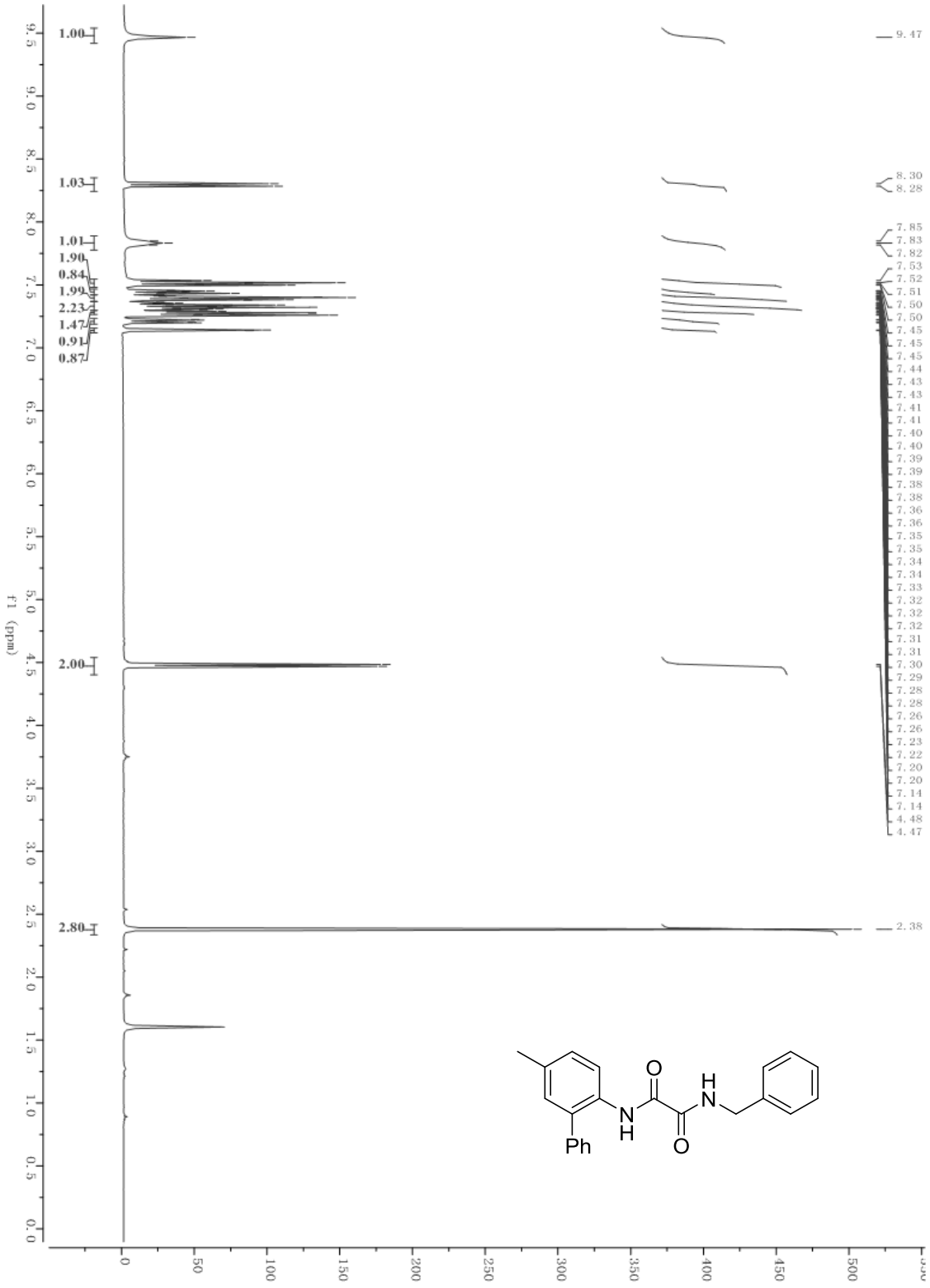
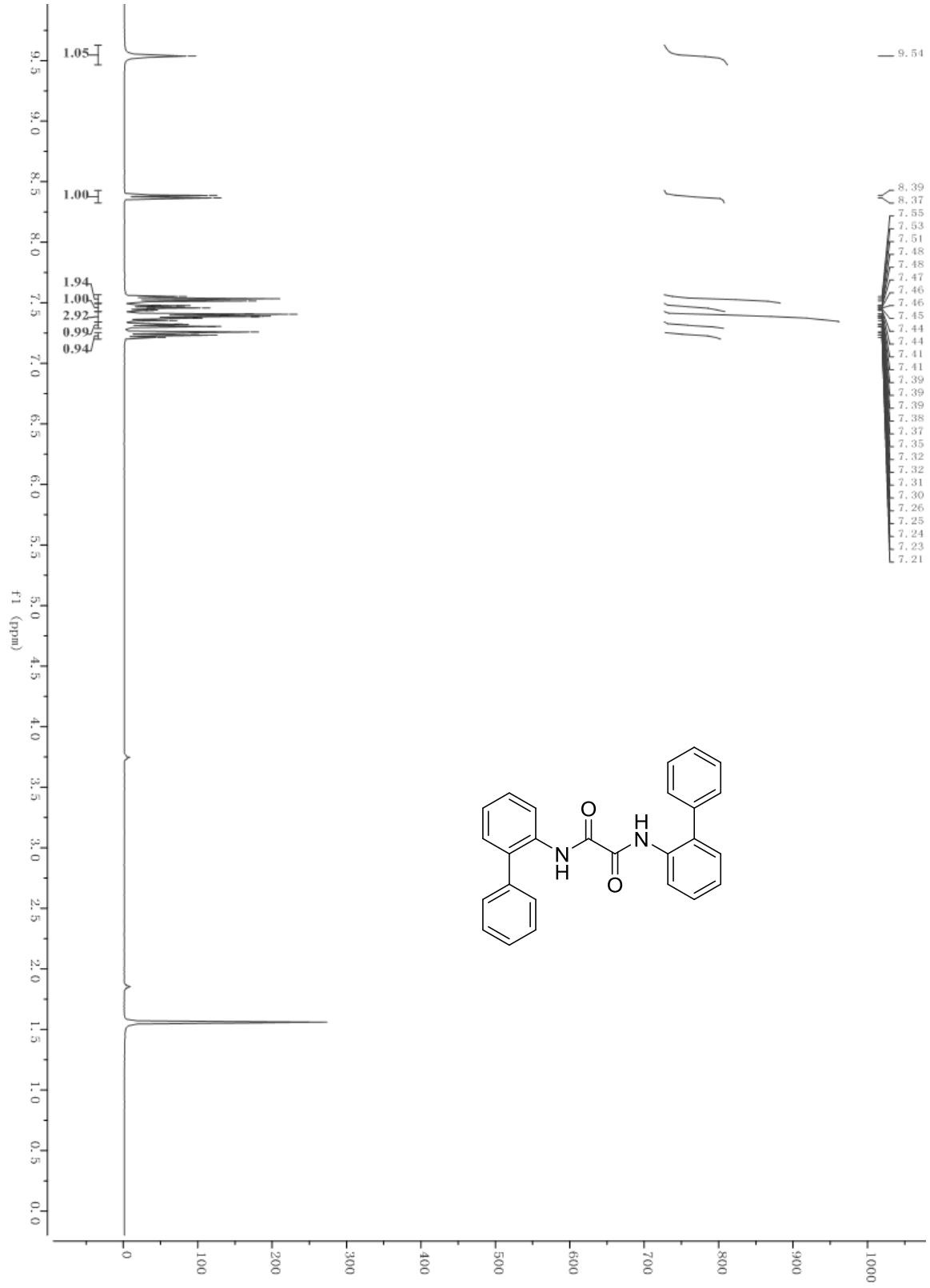
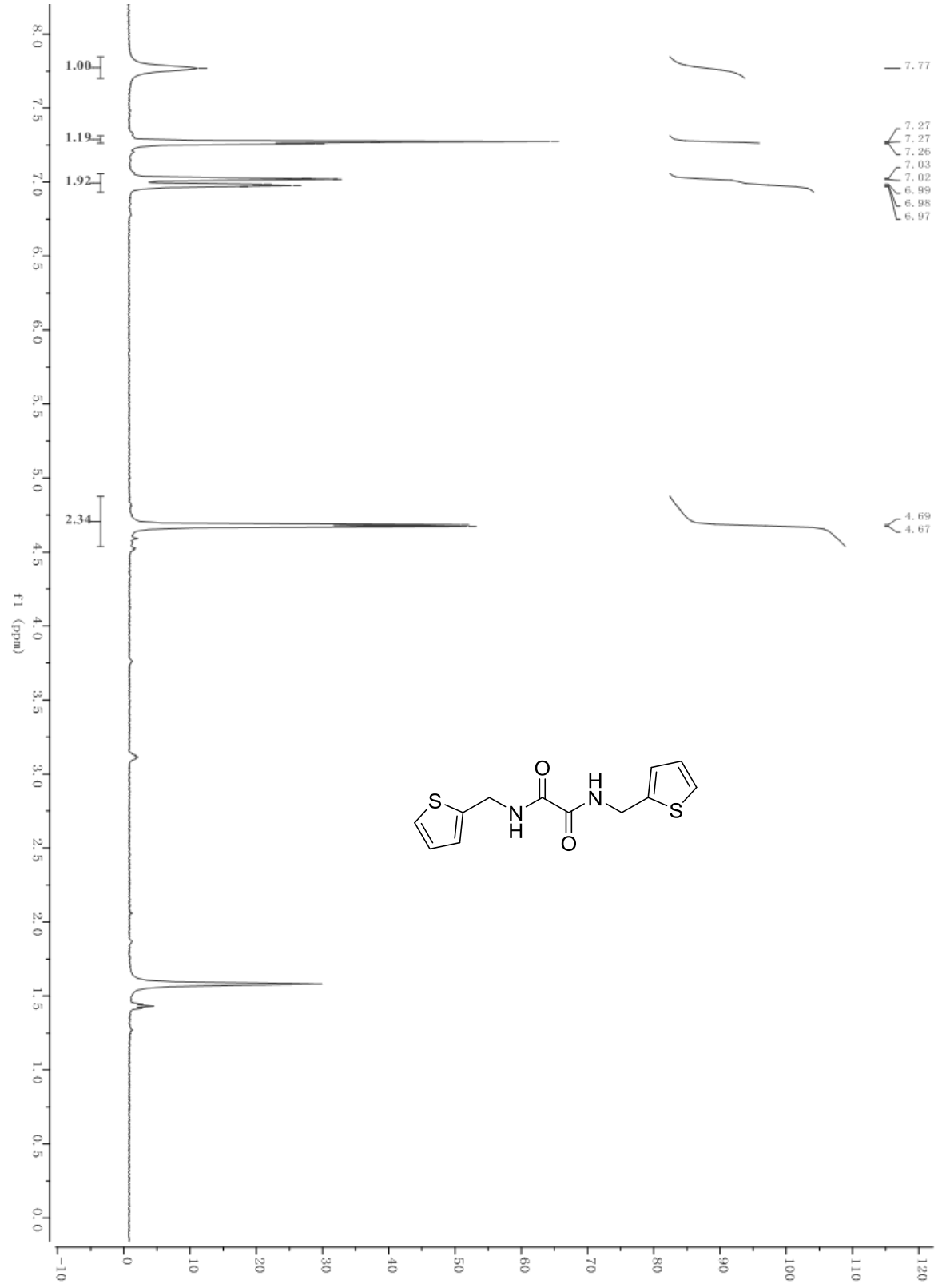
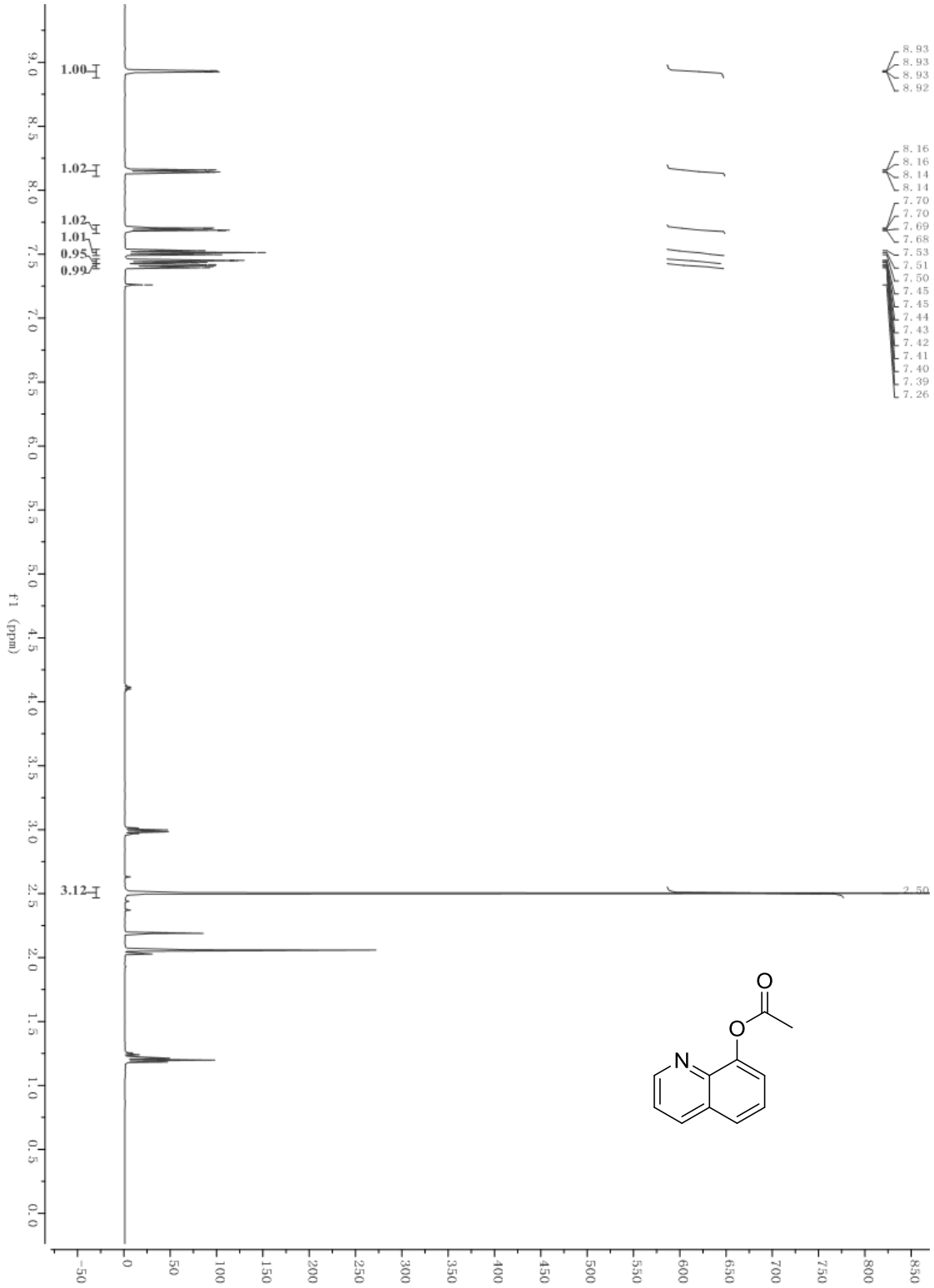
7.36
7.36
7.26
7.24
7.23
7.22
7.21
7.13
7.12
3.87
2.38
f1 (ppm)
O
O
O
N
H
Ph


1.00
1.03
1.01
1.90
0.84
1.99
2.23
1.47
0.91
0.87
2.00
2.80
f1 (ppm)
9.47
8.30
8.28
7.85
7.83
7.82
7.53
7.52
7.51
7.50
7.50
7.45
7.45
7.45
7.44
7.43
7.43
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.29
7.28
7.28
7.26
7.26
7.23
7.22
7.20
7.20
7.14
7.14
4.48
4.47
2.38
O
H
N
N
H
O
Ph


1.05
1.00
1.94
1.00
2.92
0.99
0.94
9.54
8.39
8.37
7.55
7.53
7.51
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.41
7.41
7.39
7.39
7.39
7.38
7.37
7.35
7.32
7.32
7.31
7.30
7.26
7.25
7.24
7.23
7.21
f1 (ppm)
O
H
N
N
H
O


1.00
1.19
1.92
2.34
7.77
7.27
7.27
7.26
7.03
7.02
6.99
6.98
6.97
4.69
4.67
f1 (ppm)
O
H
N
S
N
H
O
S


1.00
1.02
1.02
1.01
0.95
0.99
3.12
8.93
8.93
8.93
8.92
8.16
8.16
8.14
8.14
7.70
7.70
7.69
7.68
7.53
7.51
7.50
7.45
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.26
2.50
O
O
N
f1 (ppm)