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Iodine and palladium approaches to medicinally interesting heterocycles and carbocycles

by

Jesse Page Waldo

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock, Major Professor
George A. Kraus
Klaus Schmidt-Rohr
Walter S. Trahanovsky
Yan Zhao

Iowa State University

Ames, Iowa

2008

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To my wife, Samantha
To my family

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LIST OF ABBREVATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br s	broad singlet
Bu	butyl
t-Bu	*tert*-butyl
BuLi	butyl lithium
^{o}C	degree Celsius
calcd	calculated
cat.	catalytic
concd	concentrated
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DMF	*N*,*N*-dimethylformamide
DPPF	1,1'-bis(diphenylphosphino)ferrocenediphenylphosphine
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl

h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
m	multiplet
m	meta
Me	methyl
mg	milligram
mL	milliliter(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
ppm	parts per million
q	quartet
s	singlet
satd	saturated
t	triplet
TBAC	tetra-*n*-butylammonium chloride

tert	tertiary
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
Ts	*para*-toluenesulfonyl

GENERAL INTRODUCTION

Low molecular weight heterocycles and carbocycles are among the most highly valued targets in modern synthetic chemistry for use as biological probes. However, many routes to these important classes of molecules require harsh reaction conditions or have poor selectivity. Recent research in the Larock group has investigated the electrophilic cylization of functionalized alkynes to form various heterocycles and carbocycles. Over the last 25 years, the Larock group has also been heavily involved in examining palladium-catalyzed transformations. This thesis describes several novel and useful methodologies that target important biological scaffolds through the use of electrophilic iodine reactions and palladium-catalyzed chemistry.

Dissertation organization

This dissertation is divided into five chapters. Each chapter is written in American Chemical Society format as required by the *Journal of Organic Chemistry* and the *Journal of Combinatorial Chemistry* and is composed of an abstract, introduction, results and discussion, conclusions, experimental, acknowledgments, and references.

Chapter 1 describes an efficient, simple method for the synthesis of highly substituted isoxazoles. *O*-Methyl oximes of 2-alkyn-1-ones react in the presence of ICl to afford the corresponding 3,5-disubstituted-4-iodoisoxazoles in good yields. The resulting 4-iodoisoxazoles undergo various palladium-catalyzed reactions. An efficient synthesis of the potent COX-II inhibitor, valdecoxib, using this methodology is reported. Many functional groups are tolerated using mild reaction conditions.

The isoxazole skeleton is an important heteroaromatic pharmacophore, which is known to possess a variety of biological activities. A library of highly substituted isoxazoles have been prepared in high purities starting from the corresponding 3,5-disubstituted 4-iodoisoxazoles through various palladium-catalyzed reactions. By using this methodology a 51-member library of highly substituted isoxazoles has been generated.

Dehydration/iodination of *N*-acyldihydropryazoles could be a potentially useful way to selectively synthesize substituted *N*-acyl-1*H*-pyrazoles from readily available starting materials. A variety of substituted *N*-acyl-4-iodopyrazoles have been synthesized in good yields by the dehydration/iodination of 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles under mild reaction conditions.

The electrophilic cyclization of alkynamides has led to the formation of oxazolium salts in good yields. The resulting oxazolium salts are extremely stable and efforts towards conversion to the corresponding free bases have been met with only limited success.

The fluoren-9-one core is present in a variety of substrates exhibiting interesting biological activities and has been recently discovered in natural products. Fluoren-9-ones and analogues have been readily synthesized by the palladium-catalyzed reactions of *o*-haloarenecarboxaldehydes with *o*-silylaryl triflates in the presence of CsF.

Finally, all of the ^{1}H and ^{13}C NMR spectra for the previously unknown starting materials and products are compiled in appendices A-E.

CHAPTER 1. The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization. An Efficient Synthesis of Valdecoxib

Based on a paper published in the *Journal of Organic Chemistry*[1]

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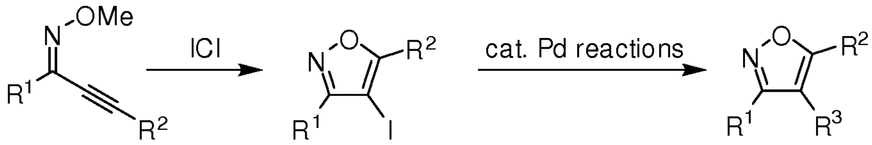
Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

Abstract



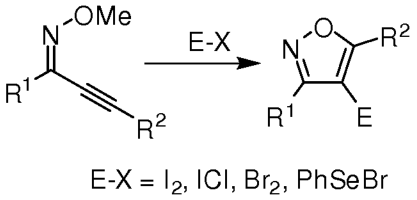
R^1 = H, Me, Ar, n-C_6H_{13}, t-Bu, etc.
R^2 = Me, Ar, t-Bu, etc.
R^3 = aryl, alkynyl, vinylic, CO_2R, CO_2NHR

A large number of functionally-substituted 2-alkyn-1-one *O*-methyl oximes have been cyclized under mild reaction conditions in the presence of ICl to give the corresponding 4-iodoisoxazoles in moderate to excellent yields. The resulting 4-iodoisoxazoles undergo various palladium-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles, including valdecoxib.

Introduction

The isoxazole skeleton has been the focus of many biological studies in recent years.[2] Our group and others have reported that the electrophilic cyclization of functionally-substituted acetylenes is a powerful synthetic tool for constructing a diverse assortment of ring systems, including benzo[*b*]thiophenes,[3] isoquinolines and naphthyridines,[4] isocoumarins and α-pyrones,[5] benzofurans,[6] furans,[7] indoles,[8] furopyridines,[9] cyclic carbonates,[10] 2,3-dihydropyrroles and pyrroles,[11] pyrilium salts and isochromenes,[12] bicyclic β-lactams,[13] 2*H*-benzopyrans,[14] naphthalenes and 2-naphthols,[15] chromones,[16] isoindolin-1-ones[17] and benzo[*b*]selenophenes.[18]

We recently reported the synthesis of numerous highly substituted isoxazoles through the cyclization of various 2-alkyn-1-one *O*-methyl oximes (eq 1)[19] by a variety of electrophiles. The yields of the desired Z-*O*-methyl oximes from the ynones are generally good, and these compounds are easily isolated by column chromatography on silica gel. We now report the full details of our work on the ICl-induced cyclization of 2-alkyn-1-one *O*-methyl oximes, which provides a very efficient synthesis of 4-iodoisoxazoles. Numerous examples are reported. The resulting 4-iodoisoxazoles are readily elaborated by conventional palladium-catalyzed processes to afford highly substituted isoxazoles, including valdecoxib.

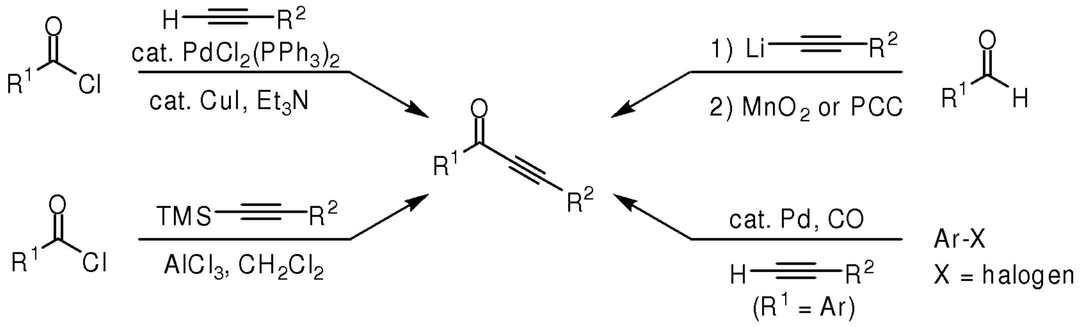


(1)

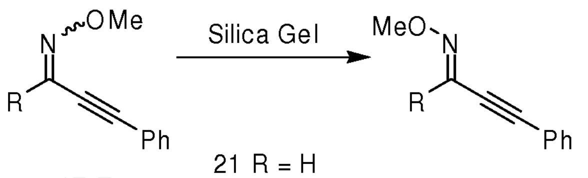
Results and Discussion

The requisite ynones can be easily prepared (Scheme 1) by the palladium/copper-catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene[20] or by Pd-catalyzed carbonylative coupling of terminal acetylenes with aryl iodides.[21] The ynones can also be prepared by allowing a lithium acetylide to react with an aldehyde, followed by oxidation of the resulting secondary alcohol.[22] In addition, ynones can be conveniently prepared by the treatment of silyl acetylenes with an acid chloride in the presence of aluminum chloride.[23]

Scheme 1



The *O*-methyl oximes required in our isoxazole synthesis are readily prepared by stirring the ynone in the presence of methoxylamine hydrochloride, pyridine, and Na_2SO_4 or $MgSO_4$ at room temperature using methanol as the solvent.[24] Heating is sometimes required, especially when R^1 is an aromatic ring bearing electron-donating groups. When R^1 is a bulky group relative to the alkyne moiety, the desired Z isomer is the predominant product. However, if R^1 is significantly less bulky, a mixture of isomers often results and the desired isomer must be separated by column chromatography. Upon preparation of the 2-alkyn-1-one *O*-methyl oximes 21 and 23, a 1:1 mixture of *E*:*Z* *O*-methyl oximes, observable by ^{1}H NMR spectroscopy, was obtained. Our attempts at separating these isomers on a silica gel column led to the unwanted *E* isomer exclusively (eq 2). The 1:1 mixture of *E*:*Z* *O*-methyl oximes 21 and 23 isomerized exclusively to their *E* isomers. This isomerization only occurred when R was either a proton or a methyl group, but was not observed in any other cases. Nevertheless, in the cases when R is equal to a proton (21) or methyl (23), the desired *Z*-*O*-methyl oxime could be isolated by utilizing a basic alumina column, although the yields were only modest. It was discovered that only the *Z* isomer cyclized when subjected to our usual ICl cyclization conditions. Our attempts at simultaneous isomerization and cyclization of the *E* isomer were unsuccessful. Consequently, it is essential that the *Z*-*O*-methyl oxime isomer be employed in the cyclization process.



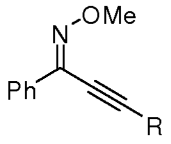
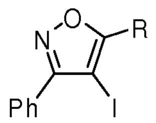
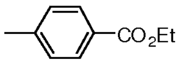
1:1/*E*:*Z*

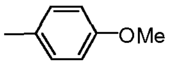
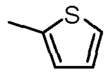
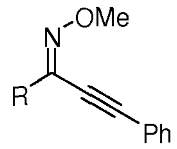
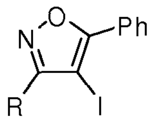
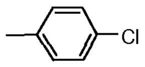
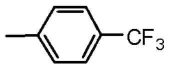
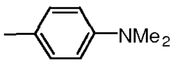
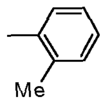
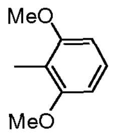
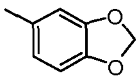
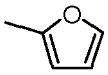
21 R = H
23 R = Me

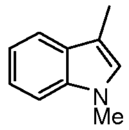
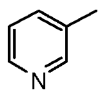
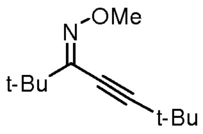
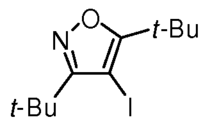
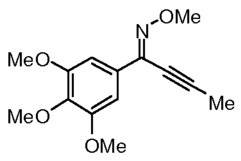
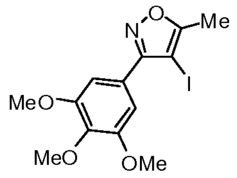
(2)

With the desired *Z*-*O*-methyl oximes in hand, we studied the scope of the cyclization methodology (Table 1). In our earlier studies, we discovered that using ICl as the source of electrophilic iodine provided the best results for the formation of isoxazoles. I_2 may also be used to induce the cyclization of compound 1. However, the reactions are slower and higher molar equivalents of I_2 are required to achieve yields comparable to those of ICl (Table 1, compare entries 1 and 2).

Table 1. The Synthesis of 4-Iodoisoxazoles by Electrophilic Cyclization[a]

entry	*O*-methyl oxime	electrophile	time (h)	product	yield (%)[b]
					
1	R = Ph (1)	3.0 I_2[c]	1.0	(2)	77
2		1.2 ICl	0.5		86
3	R = Me (3)	1.2 ICl	0.75	(4)	99
4	R = *n*-Bu (5)	1.2 ICl	0.75	(6)	91
5	R = *t*-Bu (7)	1.2 ICl	0.75	(8)	90
6	R =  (9)	1.2 ICl	0.5	(10)	87

7	R = 	(11)	1.2 ICl	0.5	(12)	89
8	R = 	(13)	1.2 ICl	0.5	(14)	82
						
9	R = 	(15)	1.2 ICl	1.0	(16)	94
10	R = 	(17)	1.2 ICl	1.0	(18)	93
11	R = 	(19)	2.2 ICl	6.0	(20)	98
12	R = H	(21)	1.2 ICl	0.5	(22)	83
13	R = Me	(23)	1.2 ICl	0.75	(24)	79
14	R = n-C_6H_{13}	(25)	1.2 ICl	0.75	(26)	94
15	R = t-Bu	(27)	1.2 ICl	0.75	(28)	100
16	R = 	(29)	1.2 ICl	0.5	(30)	93
17	R = 	(31)	1.2 ICl	1.0	(32)	89
18	R = 	(33)	1.2 ICl	1.0	(34)	82
19	R = 	(35)	1.2 ICl	0.5	(36)	86

20	R = 	(37)	1.2 ICl	0.5		(38)	55
21	R = 	(39)	3.0 ICl	3.0		(40)	68
22		(41)	1.2 ICl	2.0		(42)	87
23		(43)	1.2 ICl	1.0		(44)	96

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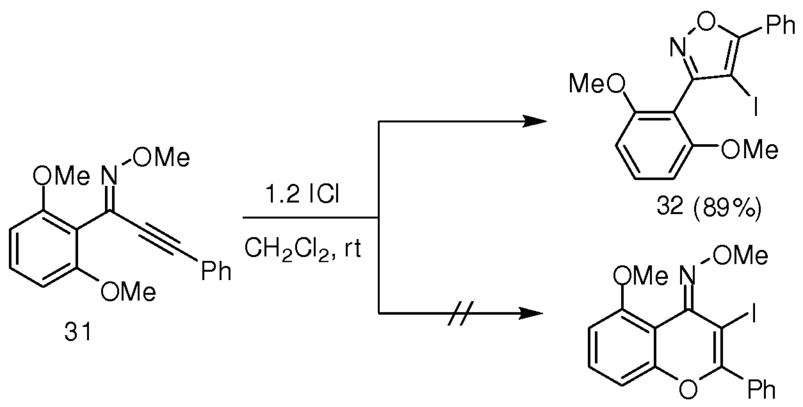
[a] All reactions were carried out in CH_2Cl_2 (10 mL/mmol) at room temperature using 0.25 mmol of starting material unless otherwise specified. [b] Isolated yields after column chromatography. [c] The reaction was carried out in CH_3CN.

When the terminus of the alkynyl moiety was substituted with aliphatic substituents ranging from compact to bulky, the yields were excellent (entries 3-5). Furthermore, the introduction of substituents on the aryl group, has little effect on the yield of the reaction. The electron-withdrawing group CO_2Et (9) and the electron-donating group OMe (11), both in the *para* position of the phenyl ring, did not significantly change the reaction yields compared to the parent system (entries 6 and 7). Furthermore, substituting the alkynyl unit with a thiophene heterocycle (13) lowered the yield only slightly (entry 8).

The effect of changing the substituents in the 1 position of the 2-alkyn-1-one *O*-methyl oxime was also studied. The *para* electron-withdrawing groups in compounds 15 and 17 provided the corresponding isoxazoles 16 and 18 in excellent yields (entries 9 and 10). The electron-donating group NMe_2 in the *para* position of compound 19 required a dramatic increase in reaction time and 2.2 mole equivalents of ICl had to be used to achieve an excellent yield of 20. 1.2 Mole equivalents of ICl provided only a trace of 20 and the reaction suffered from low conversion. No further iodinated products were observed in the reaction.

Other substituents in the 1 position of the 1-alkynone were generally quite successful. For example, compounds 21 and 23, as the pure *Z*-isomers, afforded the expected product with only a slight decrease in yields (entries 12 and 13) using our standard procedure, while compound 25 provided an excellent yield of 26 (entry 14). Introducing a bulky *t*-Bu group (27) into the alkynone provided a quantitative yield of the desired isoxazole 28 (entry 15). Compounds 29 and 31 introduce steric bulk at the *ortho* positions of the parent phenyl rings. This did not hinder the reaction and high yields of the isoxazole products 30 and 32 were obtained using short reaction times (entries 16 and 17). Thus, steric effects appear to be minimal in this process. It is noteworthy that compound 31 cyclized exclusively to the desired 5-*endo dig* isoxazole product 32 and the possible 6-*exo dig* chromone oxime product was not observed, even though we have successfully cyclized closely related ketones to the corresponding chromones (Scheme 2).

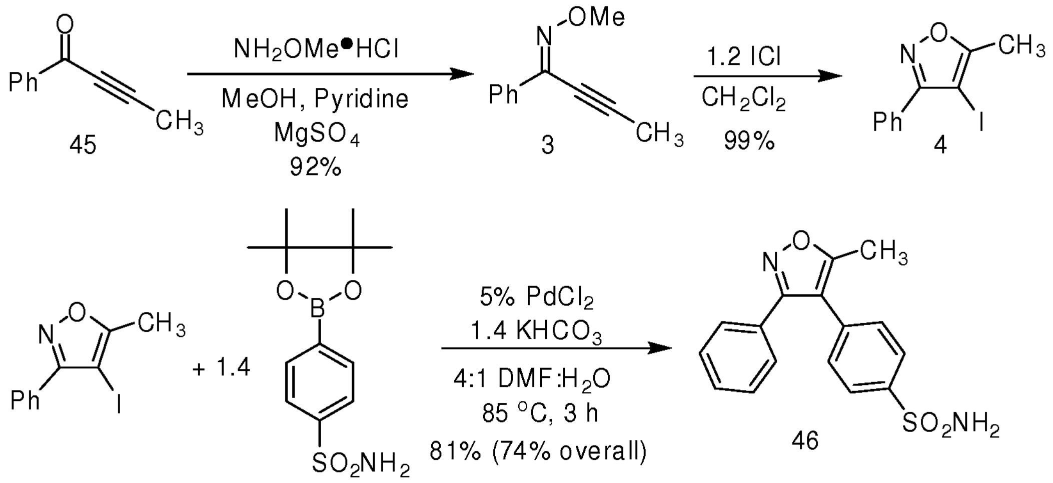
Scheme 2



Introduction of the oxygen-containing heterocycles 33 and 35 into the alkynone also provided isoxazoles in good yields (entries 18 and 19). The nitrogen-containing heterocycles 37 and 39 also afforded the desired isoxazoles, although the yields were only modest (entries 20 and 21). The cyclization of compound 39 required the use of 3 equivalents of ICl, as well as an increased reaction time. Compound 41 was synthesized to study the effect of having two sterically bulky *t*-Bu substituents present in the same substrate. The reaction required a slight increase in time. Nevertheless, isoxazole 42 was obtained in a very good yield (entry 22). The highly substituted aryl group of *O*-methyl oxime 43 also provided an excellent yield of isoxazole 44 (entry 23). Scaled up reactions, including multi-gram preparations of compounds 2, 4, and 44, did not affect the yield or outcome of the methodology. This is important to note in cases where one wishes to produce a large quantity of product for use in total synthesis or library generation.

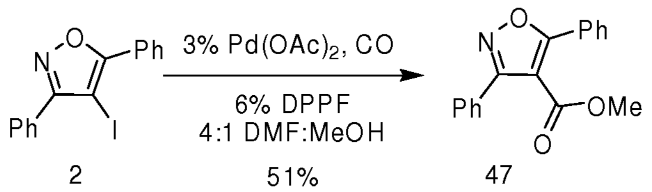
To demonstrate the value of the 4-iodoisoxazole products generated in this methodology, a number of reactions were carried out utilizing the iodine handle. We reasoned that we could approach the highly potent COX-2 inhibitor 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib) (46)[25,1g] by a Suzuki-Miyaura cross-coupling of isoxazole 4 with the appropriate boronic acid ester.[26] Using our isoxazole methodology to prepare 4 and a Suzuki-Miyaura coupling with the commercially available benzenesulfonamide-4-boronic acid pinacol ester, we were able to develop a very efficient route to valdecoxib (Scheme 3). Starting with ynone 45, *O*-methyl oxime 3 was obtained in a 92% yield. Compound 3 was subjected to our ICl cyclization conditions to afford isoxazole 4 in nearly a quantitative yield. After several protocols were screened, Suzuki cross-coupling was best accomplished using 5 mol % $PdCl_2$ catalyst, 1.4 equiv of $KHCO_3$ in 4:1 DMF:H_2O at 85 °C for 3 h to provide valdecoxib (46) in an 81% isolated yield, which constitutes a 74% overall yield from ynone 45.

Scheme 3

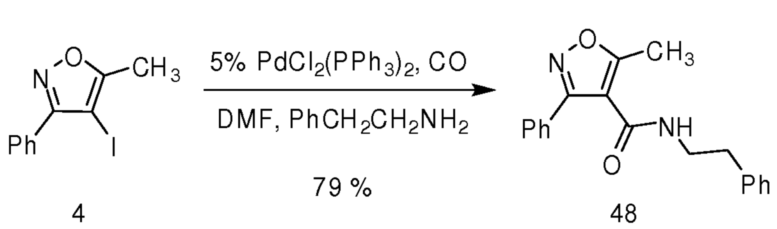

Ph
CH3
45
NH2OMe•HCl
MeOH, Pyridine
MgSO4
92%
N
OMe
Ph
3
CH3
1.2 ICl
CH2Cl2
99%
N
O
CH3
Ph
I
4
+ 1.4
O
B
O
SO2NH2
5% PdCl2
1.4 KHCO3
4:1 DMF:H2O
85 °C, 3 h
81% (74% overall)
46
SO2NH2

This synthetic route to valdecoxib provides a high overall yield and utilizes very mild reaction conditions compared to those previously reported. Earlier reports on the synthesis of valdecoxib required the use of strong bases, such as *n*-BuLi,[1g,25,27] or the preparation of boronic acids *in situ* using air and water sensitive triisopropyl borate $(i\text{-PrO})_3B$. These previous processes also suffer from poor overall yields. In addition to the aforementioned advantages of this synthesis, one may construct many analogues of valdecoxib by choosing from the wide array of commercially available starting materials that are appropriate for this methodology.

Other palladium-catalyzed methodology has also proven useful for further elaboration of these iodoisoxazoles. For example, we were able to convert 4-iodo-3,5-diphenylisoxazole (2) to the corresponding methyl ester by allowing 2 to react in the presence of catalytic amounts of $Pd(OAc)_2$ plus a ferrocene ligand, carbon monoxide and methanol to afford methyl ester 47 in a 51% yield (eq 3).[28] Reduction of compound 2 to 3,5-diphenylisoxazole was an observed minor side product. In addition, we were able to convert 4-iodo-5-methyl-3-phenylisoxazole (4) to the corresponding phenethylamide by a similar approach using a modified literature procedure.[29] By allowing compound 4 to react in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$, carbon monoxide and 2-phenethyl amine, we were able to obtain 48 cleanly in good yield (eq 4).


Ph
Ph
I
N
O
2
3% Pd(OAc)2, CO
6% DPPF
4:1 DMF:MeOH
51%
Ph
Ph
OMe
O
47

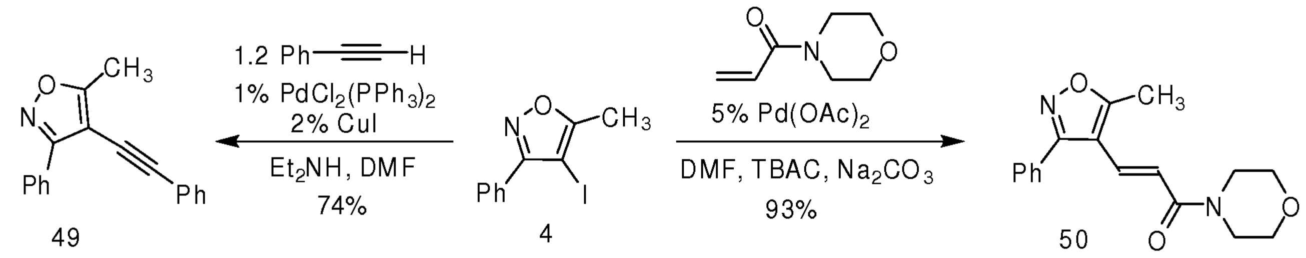
(3)


CH3
Ph
I
N
O
4
5% PdCl2(PPh3)2, CO
DMF, PhCH2CH2NH2
79 %
CH3
Ph
NH
O
Ph
48

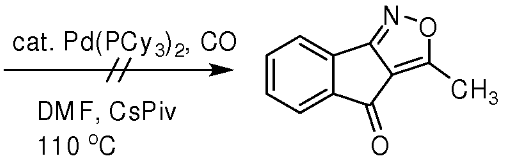
(4)

Additionally, we were able to affect Heck and Sonogashira cross-couplings on 4-iodo-5-methyl-3-phenylisoxazole (4) (Scheme 4). By allowing compound 4 to react under standard Sonogashira[30] conditions in the presence of 1.2 equiv of phenyl acetylene, alkyne 49 was obtained in a good yield. Also, allowing compound 4 to react under Heck[31] reaction conditions in the presence of *N*-acryloylmorpholine, provided the desired α,β-unsaturated amide 50 in excellent yield.

Scheme 4


CH3
Ph
Ph
49
1.2 Ph—≡—H
1% PdCl2(PPh3)2
2% CuI
Et2NH, DMF
74%
CH3
Ph
I
4
5% Pd(OAc)2
DMF, TBAC, Na2CO3
93%
CH3
Ph
N
O
50

Unfortunately, the palladium-catalyzed carbonylative cyclization[32] of isoxazole 4 failed and reduction of the starting material was the only observed product (eq 5).

4  (5)

Conclusions

3,4,5-Trisubstituted isoxazoles have been generated in high yields under mild reaction conditions by the electrophilic cyclization of *Z*-*O*-methyl oximes of 2-alkyn-1-ones. Our methodology tolerates a wide variety of functional groups, including heterocycles and sterically cumbersome substrates. This process can be scaled up to provide multi-gram quantities of the desired product without sacrificing the yield or outcome of the methodology. One can construct libraries of highly substituted isoxazoles by invoking the appropriate starting materials in an orderly fashion. Furthermore, the iodine handle of the products provides an opportunity for further functionalization, as demonstrated by the ester and amide products 47 and 48, the Sonogashira product 49 and the Heck product 50.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. The following starting materials were made according to literature procedures: 1,3-diphenylprop-2-yn-1-one, 1-phenyl-2-butyn-1-one,[33] 4,4-dimethyl-1-phenylpent-1-yn-3-one, *N*-methyl-3-indolecarboxaldehyde,[34] 1-phenylnon-1-yn-3-one,[35] 2,2,6,6-tetramethylhept-4-yn-3-one,[36] 1-(furan-2-yl)-3-phenylprop-2-yn-1-one[37] and 1-(4-chlorophenyl)-3-phenylprop-

2-yn-1-one. Compounds 1-4, 7, 8, 21, 22, 25-28, 37 and 38 have been reported in our previous communication.

General procedure for the preparation of alkynones from acyl chlorides. To a 25 mL flask were added CuI (0.05 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of benzoyl chloride (3.25 mmol, 1.3 equiv). If the acid chloride is a solid, it was added as a THF solution. The resulting mixture was allowed to stir at room temperature overnight, water (5 mL) was added, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkynone.

1-Phenylhept-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 381 mg (82%) of the product as a yellow oil with spectral properties identical to those previously reported.[38]

Ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 570 mg (86%) of the product as a pale yellow solid: mp 54-56 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.42 (t, J = 7.2 Hz, 3H), 4.39-4.44 (q, J = 7.0 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.74-7.76 (d, J = 8.4 Hz, 2H), 8.1 (t, J = 8.2 Hz, 2H), 8.22-8.23 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ 14.5, 61.7, 88.7, 91.5, 124.6, 128.9, 129.8 (2 carbons), 132.3, 133.0, 134.6, 136.8, 165.8, 177.9; HRMS Calcd for $C_{18}H_{14}O_3$: 278.0943. Found: 278.0947.

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded 470 mg (84%) of the product as a colorless solid: mp 121-122 °C (lit. 81-85 °C)[39] with spectral properties identical to those previously reported.[40]

1-Phenyl-3-(thiophen-2-yl)prop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 413 mg (78%) of the product as a yellow oil with spectral properties identical to those previously reported.[41]

3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 413 mg (79%) of the product as a colorless solid: mp 75-77 °C (lit. 70-72 °C) with spectral properties identical to those previously reported.[42]

3-Phenyl-1-*o*-tolylprop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 440 mg (80%) of the product as a pale yellow liquid with spectral properties identical to those previously reported.[43]

4,4-Dimethyl-1-phenyl-2-pentyn-1-one. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 428 mg (92%) of the product as a pale yellow oil with spectral properties identical to those previously reported.[44]

1-(3,4,5-Trimethoxyphenyl)but-2-yn-1-one. A modified procedure was used. To a 25 mL flask were added CuI (0.05 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and 3,4,5-trimethoxybenzoyl chloride (3.25 mmol) in THF (5 mL) was added to the flask. The flask was flushed with propyne and a balloon of propyne gas was placed on the reaction flask. The resulting suspension was allowed to stir overnight. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 550 mg (94%) of the product as a pale yellow solid: mp 99-100 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.17 (s, 3H), 3.94 (s, 9H), 7.41 (s, 2H); ^{13}C NMR δ 4.6, 56.5, 61.2, 79.1, 92.4, 107.1, 132.2, 143.6, 153.2, 177.2; HRMS Calcd for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0895.

General procedure for the preparation of alkynones by the reaction of aldehydes with lithium acetylides, followed by oxidation with MnO_2. To a three-neck flask was added phenyl acetylene (11.2 mmol, 1.14 g) and anhydrous THF (7 mL). The stirred solution was cooled to 0 °C and flushed with argon. To the stirred solution, *n*-BuLi (2.5 M in hexanes, 4.5 mL, 11.2 mmol) was added dropwise. The resulting mixture was allowed to stir for 30 min at 0 °C. The aldehyde (9.3 mmol) in anhydrous THF (5 mL) was added dropwise and allowed to stir for 1 h at 0 °C. The solution was quenched with a satd aq NH_4Cl solution and extracted with ether. The organic layers were combined, dried and concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL) and MnO_2 (27.9 mmol, 2.43 g) was added to the solution. The suspension was refluxed for 1 h, the solution was cooled and filtered through a pad of celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford the product. When the product was a solid, it was recrystallized from hexanes/EtOAc or hexanes/CH_2Cl_2 to afford spectroscopically pure product.

1-(2,6-Dimethoxyphenyl)-3-phenylprop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 2.37 g (96%) of the product as an orange oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.83 (s, 6H), 6.57-6.59 (d, *J* = 8.4 Hz, 2H), 7.30-7.35 (m, 3H), 7.38-7.42 (m, 1H), 7.52-7.55 (td, *J* = 6.8, 1.6 Hz, 2H); ^{13}C NMR δ 56.1, 90.1, 90.5, 104.3, 119.0, 120.6, 128.6, 130.5, 132.2, 133.0, 158.1, 178.5; HRMS Calcd for $C_{17}H_{14}O_3$: 266.0943. Found 266.0947.

3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 1.19 g (62%) of the product as a brown solid: mp 73-75 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.42-7.54 (m, 4H), 7.69-7.71 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.42-8.45 (m, 1H), 8.84-8.86 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.45 (t, *J* = 0.8 Hz, 1H); ^{13}C NMR δ 86.4, 94.8, 119.6, 123.7, 128.9, 131.4, 132.3, 133.4, 136.3, 151.5, 154.3, 176.5; HRMS Calcd for $C_{14}H_9NO$: 207.0684. Found: 207.0689.

1-[4(Dimethylamino)phenyl]-3-phenylprop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 2.13 g (92%) of the product as a bright yellow solid: mp 155-156 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.09 (s, 6H), 6.67-6.69 (d, *J* = 9.2 Hz, 2H), 7.40-7.45 (m, 3H), 7.65-7.67 (m, 2H), 8.10-8.12 (dd, *J* = 7.2, 2.0 Hz, 2H); ^{13}C NMR δ 40.3, 87.6, 91.3, 110.8, 121.0, 125.7, 128.7. 130.3, 132.2, 133.0, 154.3, 176.2; HRMS Calcd for $C_{17}H_{15}NO$: 249.1154. Found: 249.1160.

1-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-one. The residue was purified by flash chromatography on silica gel (1:1 hexanes:$CHCl_3$) to afford 1.72 g (74%) of the product as a yellow oil with spectral properties identical to those previously reported.[45]

General procedure for preparation of the *O*-methyl oximes. The alkynone (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), Na_2SO_4 (7.0 mmol, 994 mg) and pyridine (1 mL) in methanol (10 mL) were stirred at room temperature. The addition of the co-solvent benzene was used in cases where the ynone showed poor solubility in methanol. In some cases the reaction required refluxing conditions to go to completion. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine, dried and evaporated. The residue was then purified by column chromatography on silica gel, unless otherwise stated, to afford the desired *O*-methyl oxime.

(*Z*)-1-Phenylhept-2-yn-1-one *O*-methyl oxime (5). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 617 mg (82%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.93-0.98 (t, *J* = 7.3 Hz, 3H), 1.46-1.56 (m, 2H), 1.63-1.68 (m, 2H), 2.52-2.57 (t, *J* = 8.2 Hz, 2H), 4.08 (s, 3H), 7.35-7.37 (m, 3H), 7.82-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.7, 22.3, 30.6, 71.7, 104.2, 126.7, 128.5, 129.7, 134.1, 140.5; HRMS Calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1314.

(*Z*)-Ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate *O*-methyl oxime (9). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 904 mg (82%) of the product as a colorless oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.15 (s, 21H), 4.07 (s, 3H), 7.34-7.37 (m, 3H), 7.84-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.4, 18.9, 63.2, 96.1, 105.6, 126.6, 128.6, 129.7, 133.8, 140.1; HRMS Calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1212.

(*Z*)-3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (11). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 677 mg (73%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.83 (s, 3H), 4.13 (s, 3H), 6.88-6.91 (d, J = 8.9 Hz, 2H), 7.38-7.40 (m, 3H), 7.54-7.57 (d, J = 8.9 Hz, 2H) 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 63.3, 78.8, 101.9, 114.0, 114.3, 126.7, 128.6, 129.8, 134.0, 134.1, 140.4, 160.9; HRMS Calcd for $C_{17}H_{15}NO_2$: 265.1103. Found: 265.1107.

(*Z*)-1-Phenyl-3-(thiophen-2-yl)prop-2-yn-1-one *O*-methyl oxime (13). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 523 mg (62%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.13 (s, 3H), 7.02-7.05 (m, 1H), 7.38-7.41 (m, 5H), 7.86-7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.4, 83.7, 94.7, 121.7, 126.7, 127.6, 128.7, 129.6, 130.0, 133.6, 134.3, 140.0; HRMS Calcd for $C_{14}H_{11}NOS$: 241.0561. Found: 241.0566.

(*Z*)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (15). Purification by flash chromatography (6:1 hexanes/$CHCl_3$) afforded 621 mg (69%) of the product as a colorless solid: mp 52-54 °C: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.13 (s, 3H), 7.34-7.41 (m, 5H), 7.59-7.62 (m, 2H), 7.83-7.86 (dt, J = 8.8, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 63.4, 79.2, 101.7, 121.7, 127.9, 128.7, 128.8, 129.9, 132.2, 132.3, 135.8, 139; HRMS Calcd for $C_{16}H_{12}ClNO$: 269.0607. Found: 269.0611.

(*Z*)-3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-one *O*-methyl oxime (17). Purification by flash chromatography (3:1 hexanes/ $CHCl_3$) afforded 530 mg (50%) of the product as a tan solid: mp 41-43 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.17 (s, 3H), 7.36-7.43 (m, 3H), 7.61-7.66 (m, 4H), 8.02-8.04 (dd, J = 8.0, 0.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 63.69, 79.10, 102.20, 121.65, 125.53, 125.57, 125.61, 125.65, 125.95, 126.95, 126.96, 126.99, 128.75, 128.76, 128.77, 130.03, 132.39, 132.41, 132.42, 132.43, 137.15, 138.92 (extra peaks due to C-F coupling); HRMS Calcd for $C_{17}H_{12}F_3NO$: 303.0871. Found: 303.0875.

(*Z*)-1-[4(Dimethylamino)phenyl]-3-phenylprop-2-yn-1-one *O*-methyl oxime (19). Purification by flash chromatography ($CHCl_3$) afforded 710 mg (73%) of the product as a yellow solid: mp 81-83 °C: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.99 (s, 6H), 4.10 (s, 3H), 6.69-

6.71 (m, 2H), 7.35-7.39 (m, 3H), 7.60-7.62 (m, 2H), 7.76-7.80 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 40.6, 63.0, 80.2, 100.5, 111.9, 122.3, 127.8, 128.6, 129.5, 132.4, 140.3, 151.6; HRMS Calcd for $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1424.

(*Z*)-4-Phenylbut-3-yn-2-one *O*-methyl oxime (23). Purification by flash chromatography on basic alumina (hexanes) afforded 291 mg (48%) of the product as a colorless liquid: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.13 (s, 3H), 3.97 (s, 3H), 7.34-7.36 (m, 3H), 7.51-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 62.5, 81.2, 99.3, 121.9, 128.6, 129.6, 132.3, 137.8; HRMS Calcd for $C_{11}H_{11}NO$: 173.0841. Found: 173.0845.

(*Z*)-3-Phenyl-1-*o*-tolylprop-2-yn-1-one *O*-methyl oxime (29). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 488 mg (56%) of the product as a yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.54 (s, 3H), 4.12 (s, 3H), 7.22-7.35 (m, 6H), 7.52-7.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.1, 63.3, 80.9, 101.5, 122.0, 126.2, 128.7, 129.4, 129.7, 129.8, 131.3, 132.3, 133.6, 137.1, 141.1; HRMS Calcd for $C_{17}H_{15}NO$: 249.1154. Found: 249.1158.

(*Z*)-1-(2,6-Dimethoxyphenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (31). Purification by flash chromatography ($CHCl_3$) afforded 630 mg (61%) of the product as a yellow solid: mp 144-146 °C: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.83 (s, 6H), 4.11 (s, 3H), 6.58-6.60 (d, *J* = 8.4 Hz, 2H), 7.27-7.33 (m, 4H), 7.49-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4, 63.1, 81.4, 98.6, 104.4, 112.2, 122.4, 128.5, 129.3, 131.0, 132.4, 135.0, 159.0; HRMS Calcd for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1212.

(*Z*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (33). Purification by flash chromatography (1:1 hexanes/$CHCl_3$) afforded 322 mg (53%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.11 (s, 3H), 5.99 (s, 2H), 6.82-6.84 (d, *J* = 8.0, 0.8 Hz, 1H), 7.36-7.45 (m, 5H), 7.59-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.1, 79.6, 101.1, 101.7, 106.4, 108.3, 121.8, 121.9, 128.1, 128.8, 132.4, 139.6, 148.1, 149.3; HRMS Calcd for $C_{17}H_{13}INO_3$: 279.0895. Found: 279.0900.

(*Z*)-1-(Furan-2-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (35). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 575 mg (73%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.14 (s, 3H), 6.47-6.48 (m, 1H), 6.82-6.83 (d, *J* = 3.8 Hz, 1H), 7.34-7.40 (m, 3H), 7.49 (t, *J* = 0.8 Hz, 1H), 7.58-7.6 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.6, 78.2, 99.6, 111.8, 112.7, 121.6, 128.7, 130.0, 132.2, 132.4, 144.4, 148.3; HRMS Calcd for $C_{14}H_{11}NO_2$: 225.0789. Found: 225.0793.

(*Z*)-3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one *O*-methyl oxime (39) Purification by flash chromatography (2:1 hexanes/EtOAc) afforded 471 mg (57%) of the product as an orange oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 4.16 (s, 3H), 7.29-7.40 (m, 4H), 7.60-7.63 (m, 2H) 8.16-8.20 (m, 1H), 8.62-8.64 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.14-9.15 (dd, *J* = 2.3, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 63.6, 78.7, 102.3, 121.6, 123.4, 128.7, 129.7, 130.1, 132.4, 133.6, 137.7, 148.3, 150.7; HRMS Calcd for $C_{15}H_{12}N_2O$: 236.0950. Found: 236.0953.

(*Z*)-2,2,6,6-Tetramethylhept-4-yn-3-one *O*-methyl oxime (41). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 566 mg (83%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.17 (s, 9H), 1.31 (s, 9H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 28.35, 28.36, 30.9, 37.1, 62.3, 69.9, 110.9, 149.7; HRMS Calcd for $C_{12}H_{21}NO$: 195.1623. Found: 195.1626.

(*Z*)-1-(3,4,5-Trimethoxyphenyl)but-2-yn-1-one *O*-methyl oxime (43). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 838 mg (91%) of the product as a pale yellow solid: mp 99-100 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.21 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 4.09 (s, 3H), 7.09 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 5.1, 56.3, 61.0, 63.1, 70.8, 99.5, 103.9, 129.4, 139.6, 140.0, 153.1; HRMS Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1162.

General procedure for iodocyclization using ICl. To a stirred solution of the appropriate *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added ICl (1M in CH_2Cl_2, 1.2 equiv) dropwise and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a satd aq soln of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/EtOAc or hexanes/$CHCl_3$ as the eluent.

5-Butyl-4-iodo-3-phenylisoxazole (6). The product was obtained as a pale yellow oil; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.3 Hz, 3H), 1.37-1.49 (m, 2H), 1.72-1.80 (m, 2H), 2.88 (t, J = 7.6 Hz, 2H), 7.47-7.49 (m, 3H), 7.76-7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 27.1, 29.5, 57.5, 128.7 (2 carbons), 129.0, 130.1, 162.9, 175.0; HRMS Calcd for $C_{13}H_{14}INO$: 327.0120. Found: 327.0126.

Ethyl 4-(4-iodo-3-phenylisoxazol-5-yl)benzoate (10). The product was obtained as a colorless solid: mp 151-153 °C; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.43 (t, J = 7.2 Hz, 3H), 4.39-4.46 (q, J = 7.1 Hz, 2H), 7.51-7.54 (m, 3H) 7.76-7.80 (m, 2H), 8.16-8.22 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.6, 57.8, 61.6, 127.8, 128.7, 128.8, 129.2, 130.1, 130.4, 131.2, 132.4, 165.2, 166.0, 168.0; HRMS Calcd for $C_{18}H_{14}INO_3$: 419.0019. Found: 419.0026.

4-Iodo-5-(4-methoxyphenyl)-3-phenylisoxazole (12). The product was obtained as a colorless solid: mp 153-155 °C; ^1H NMR ($CDCl_3$ 300 MHz) δ 3.88 (s, 3H), 7.02-7.05 (m, 2H), 7.47-7.52 (m, 3H), 7.76-7.80 (m, 2H), 8.03-8.06 (dd, J = 9.1, 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.9, 55.7, 114.4, 120.0, 128.7, 129.1, 129.2, 129.6, 130.2, 161.6, 164.9, 169.1; HRMS Calcd for $C_{16}H_{12}INO_2$: 376.9913. Found: 376.9918.

4-Iodo-3-phenyl-5-(thiophen-2-yl)isoxazole (14). The product was obtained as a yellow solid: mp 118-120 °C; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.20-7.23 (dt, J = 3.8, 1.2 Hz, 1H), 7.49-7.54 (m, 3H), 7.56-7.81 (dd, J = 6.8, 1.2 Hz, 1H), 7.76-7.81 (m, 2H), 7.98-8.00 (dd, J = 3.8, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.9, 55.7, 114.4, 120.0, 128.7, 129.1, 129.2, 129.6, 130.2, 161.6, 164.9, 169.1; HRMS Calcd for $C_{13}H_8INOS$: 352.9371. Found: 352.9376.

3-(4-Chlorophenyl)-4-iodo-5-phenylisoxazole (16). The product was obtained as a colorless solid: mp 165-167 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 7.48-7.53 (m, 5H), 7.72-7.76 (td, J = 8.8, 2.2 Hz, 2H), 8.04-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 127.3, 127.4, 128.0, 129.0, 129.1, 130.5, 131.1, 136.6, 164.0; HRMS Calcd for $C_{15}H_9ClINO$: 380.9417. Found: 380.9425.

4-Iodo-5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole (18). The product was obtained as a pale yellow solid: mp 174-175 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 7.52-7.55 (m, 3H), 7.77-7.79 (d, *J* = 8.0 Hz, 2H), 7.92-7.94 (d, *J* = 8.4 Hz, 2H), 8.06-8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.72, 125.74, 125.78, 125.81, 125.85, 127.18, 128.01, 128.02, 128.03, 129.05, 129.06, 129.65, 129.67, 131.19, 163.87, 169.73 (extra peaks due to C-F coupling); HRMS Calcd for $C_{16}H_9F_3INO$: 416.9681. Found: 414.9686.

4-Iodo-3-[4(dimethylamino)phenyl]-5-phenylisoxazole (20). The product was obtained as a pale yellow solid: mp 148-149 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 3.04 (s, 6H), 6.80-6.82 (d, *J* = 8.8 Hz, 2H), 7.49-7.53 (m, 3H), 7.72-7.74 (td, *J* = 7.0, 2.1 Hz, 2H), 8.05-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 40.5, 56.6, 111.9, 127.7, 128.0, 128.8, 128.9, 130.0, 130.7, 151.5, 164.6, 168.7; HRMS for $C_{17}H_{15}IN_2O$: 390.0229. Found: 390.0234.

4-Iodo-3-methyl-5-phenylisoxazole (24). The product was isolated as a pale yellow oily solid: mp 31-34 °C; ^1H NMR ($CDCl_3$ 300 MHz) δ 2.35 (s, 3H), 7.48-7.50 (m, 3H), 8.01-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 58.0, 127.4, 127.5, 128.9, 130.7, 163.2, 167.5; HRMS for $C_{10}H_8INO$: 284.9651. Found: 284.9654.

4-Iodo-5-phenyl-3-*o*-tolylisoxazole (30). The product was obtained as a pale yellow solid: mp 84-86 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 2.31 (s, 3H), 7.28-7.34 (m, 4H), 7.38-7.41 (m, 1H), 7.50-7.54 (m, 3H), 8.12-8.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.3, 58.8, 126.0, 127.4, 127.7, 128.7, 129.0, 130.2, 130.4, 130.7, 131.0, 137.7, 166.9, 168.2; HRMS Calcd for $C_{16}H_{12}INO$: 360.9964. Found: 360.9968.

3-(2,6-Dimethoxyphenyl)-4-iodo-5-phenylisoxazole (32). The product was obtained as a yellow solid: mp 141-143 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 3.78 (s, 6H), 6.65-6.67 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.47-7.52 (m, 2H), 8.12-8.15 (m, 2H); ^{13}C NMR

($CDCl_3$) δ 56.3, 60.7, 104.7, 106.7, 127.6, 127.8, 128.9, 130.6, 132.1, 159.1, 162.6, 167.5; HRMS Calcd for $C_{17}H_{14}INO_3$: 407.0019. Found: 407.0026.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-iodo-5-phenylisoxazole (34). The product was obtained as a colorless solid: mp 126-128 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 6.05 (s, 2H), 6.93-6.95 (dd *J* = 8.0, 0.4 Hz, 1H), 7.25-7.26 (m, 1H), 7.30-7.33 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.51-7.54 (m, 3H), 8.04-8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4, 101.8, 108.7, 109.5, 122.5, 123.6, 127.5, 128.0, 129.0, 130.9, 148.0, 149.4, 164.5, 169.2; HRMS Calcd for $C_{16}H_{10}INO_3$: 390.9705. Found: 390.9712.

3-(Furan-2-yl)-4-iodo-5-phenylisoxazole (36). The product was obtained as an orange solid: mp 50-53 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 6.37-6.38 (d, *J* = 3.6 Hz, 1H), 7.34-7.35 (d, *J* = 3.6 Hz, 1H), 7.52-7.54 (m, 4H), 8.02-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.3, 108.4, 114.9, 126.9, 128.1, 129.0, 131.2, 139.5, 142.9, 155.7, 169.6; HRMS Calcd for $C_{13}H_8INO_2$: 336.9600. Found: 3363.9606.

3-(4-Iodo-5-phenylisoxazol-3-yl)pyridine (40). The product was obtained as a pale yellow solid: mp 144-146 °C; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.44-7.49 (m, 1H), 7.54-7.56 (m, 3H), 8.06-8.15 (m, 3H), 8.76-8.77 (dd, *J* = 4.9, 1.6 Hz, 1H), 9.07 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 123.5, 125.3, 127.1, 128.0, 129.1, 131.2, 136.6, 149.8, 151.3, 162.7, 169.7; HRMS Calcd for $C_{14}H_9IN_2O$: 347.9760. Found: 347.9765.

3,5-Di-*tert*-butyl-4-iodoisoxazole (42). The product was obtained as a colorless solid: mp 106-108 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 1.47 (s, 9H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 28.4, 28.5, 33.8, 34.6, 50.6, 169.4, 177.6; HRMS Calcd for $C_{11}H_{18}INO$: 307.0433. Found: 307.0437.

4-Iodo-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole (44). The product was obtained as a colorless solid: mp 148-150 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 2.56 (s, 3H), 3.91 (s, 3H), 3.93 (s, 6H), 7.06 (s, 2H) ; ^{13}C NMR ($CDCl_3$) δ 13.2, 56.4, 57.9, 61.1, 105.8, 124.0, 139.6, 153.4, 162.4, 171.7; HRMS Calcd for $C_{13}H_{14}INO_4$: 374.9968. Found: 374.9971.

Procedure for the Suzuki-Miyaura cross-coupling to form 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib) (46). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.25 mmol, 71 mg), benzenesulfonamide-4-boronic acid pinacol ester (0.35 mmol, 99 mg), $KHCO_3$ (0.35 mmol, 35 mg) and $PdCl_2$ (0.0125 mmol, 2.2 mg) in 4:1 DMF:H_2O (2.5 mL). The solution was stirred for 5 min at room temperature and flushed with argon and then heated to 80 °C for 2 h. The product was concentrated under reduced pressure and isolated by column chromatography on silica gel (2:3 hexanes/EtOAc) to afford 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib) (46) as a colorless solid: mp 160-162 °C (lit.[25a] 155-157 °C, lit.[46] 172-173 °C) with spectral properties identical to those previously reported.[25a,46]

Procedure for the palladium-catalyzed carbonylative esterification to form methyl 3,5-diphenylisoxazole-4-carboxylate (47). To a 4-dram vial was added 4-iodo-3,5-diphenylisoxazole (0.44 mmol, 152 mg), $Pd(OAc)_2$ (0.0132 mmol, 2.8 mg), DPPF (0.028 mmol, 14.8 mg) in 4:1 DMF:H_2O (1.25 mL). The reaction mixture was evacuated and back-filled with carbon monoxide three times. A balloon of carbon monoxide was attached to the vial, which was heated to 55 °C for 18 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 10:1 hexanes/EtOAc to afford the compound as a colorless solid: mp 94-96 °C; ^1H NMR ($CDCl_3$ 400 MHz) δ 3.72 (s, 3H), 7.48-7.54 (m, 6H), 7.65-7.67 (m, 2H), 7.67-7.93 (dd, *J* = 7.8, 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.2, 108.2, 127.0, 128.5 (2 peaks), 128.7, 128.8, 128.9, 129.1, 130.1, 131.5, 163.1, 163.2, 172.7; HRMS Calcd for $C_{17}H_{13}NO_3$: 279.0895. Found: 279.0899.

Procedure for the palladium-catalyzed carbonylative amidation to form *N*-phenethyl-5-methyl-3-phenylisoxazole-4-carboxamide (48). A modified literature procedure was used. To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.17 mmol, 48 mg), $PdCl_2(PPh_3)_2$ (0.0085 mmol, 6 mg), 2-phenethyl amine (0.25 mL) in DMF (1 mL). The reaction mixture was evacuated and back-filled with carbon monoxide three times. A balloon of carbon monoxide was placed on the vial, which was heated to 80 °C for 18 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 4:1 hexanes/EtOAc to afford the compound as a colorless solid: mp 145-146 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.51 (s, 3H), 2.71 (t, *J* = 6.8 Hz, 2H), 3.51-3.56 (q, *J* = 6.8 Hz, 2H), 5.41 (br s, 1H), 6.96-6.98 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.20-7.26 (m, 3H), 7.39-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.2, 35.2, 40.7, 111.2, 126.8, 128.3, 128.7, 128.9, 129.1, 129.3, 130.6, 138.5, 160.3, 161.7, 174.3; HRMS Calcd for $C_{19}H_{18}N_2O_2$: 306.1368. Found: 306.1374.

Procedure for the Sonogashira coupling to form 5-methyl-3-phenyl-4-(phenylethynyl)isoxazole (49). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.5 mmol, 142 mg), phenyl acetylene (0.6 mmol, 61.2 mg), $PdCl_2(PPh_3)_2$ (0.005 mmol, 3.5 mg), CuI (0.01 mmol, 1.9 mg), DMF (1.5 mL) and Et_2NH (1.85 mL). The solution was stirred for 5 minutes at room temperature and flushed with argon and then heated to 50 °C for 6 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 10:1 hexanes/EtOAc to afford the compound as a brown solid: mp 98-100 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.58 (s, 3H), 7.35 (t, *J* = 4.2 Hz, 3H), 7.46-7.51 (m, 5 H), 8.09-8.12 (dd, *J* = 7.2, 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.3, 78.4, 95.1, 99.5, 122.9, 127.7, 128.6, 128.7, 128.8, 130.3, 131.6, 161.3, 173.1; HRMS Calcd for $C_{18}H_{13}NO$: 259.0997. Found: 259.1001.

Procedure for the Heck coupling to form (*E*)-3-(5-methyl-3-phenylisoxazol-4-yl)-1-morpholinoprop-2-en-1-one (50). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.25 mmol, 71 mg), *N*-acryloylmorpholine (1.0 mmol, 141 mg), $PdOAc_2$ (0.0132 mmol, 2.8 mg), TBAC (0.25 mmol, 69 mg), Na_2CO_3 (0.625 mmol, 66 mg) and DMF (1 mL), which was then heated to 85 °C for 24 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 1:1 hexanes/EtOAc to afford the compound as a yellow oil; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.59 (s, 3H), 3.27 (br s, 2H), 3.60 (br s, 2H), 3.68 (br s, 4H), 6.28-6.33 (d, *J* = 15.3 Hz, 1H), 7.46-7.51 (m, 4H), 7.53-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.3, 42.5, 46.0, 66.8, 111.7, 118.5, 128.9, 129.0, 129.2, 130.0, 130.8, 161.8, 165.1, 169.3; HRMS Calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1321.

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CHAPTER 2. Solution Phase Synthesis of a Diverse Library of Highly Substituted Isoxazoles

Based on a paper submitted to the *Journal of Combinatorial Chemistry*

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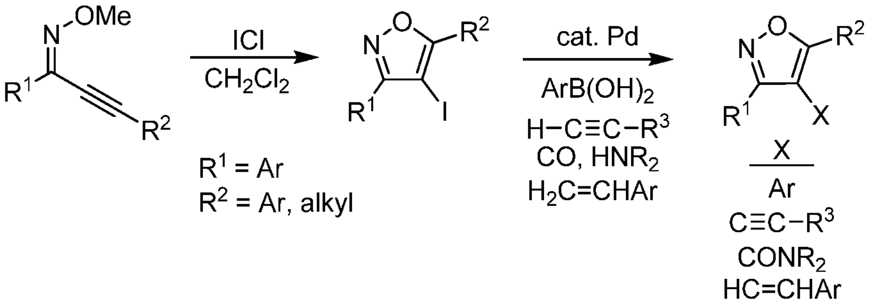
Abstract



The iodocyclization of *O*-methyloximes of 2-alkyn-1-ones affords 4-iodoisoxazoles, which undergo various palladium-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles. The palladium-catalyzed processes have been adapted to parallel synthesis utilizing commercially available boronic acid, acetylene, styrene and amine sublibraries. Accordingly, a diverse 51-member library of 3,4,5-trisubstituted isoxazoles has been generated.

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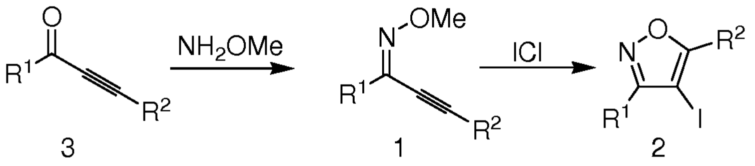
[†] Iowa State University.
[‡] University of Kansas.

Introduction

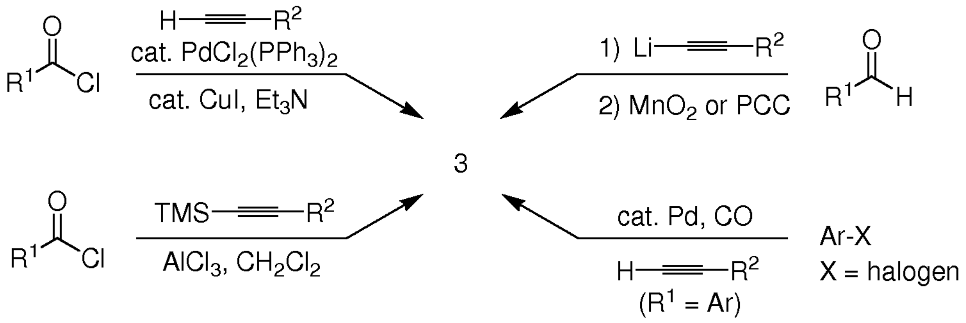
Low molecular weight nitrogen-containing heterocycles are securing their place among the most highly recognized pharmacophores.[1] Among them, the isoxazole scaffold is of particular interest, since it is known to exhibit a broad range of biological activity.[2] Isoxazoles have also had a significant impact as intermediates in the synthesis of various natural products.[3] Consequently, isoxazoles are prized as potential drug candidates and biological probes. There have been several reports relating to the synthesis of functionalized isoxazoles by combinatorial techniques,[4] although the use of 4-iodoisoxazoles as the key intermediate for library generation is thus far unreported. Many of the reported libraries have been limited to the preparation of disubstituted isoxazoles. Additionally, functionalization at the C4 position of the isoxazole core, with respect to library generation, has previously met with limited success. Until recently, restricted access to 4-haloisoxazoles by a route involving mild reaction conditions, has prevented them from being an important intermediate for library generation. The halogenation of isoxazoles at the C4 position generally requires the use of high temperatures and harsh acids.[5]

Previous work in our laboratory has demonstrated that the electrophilic cyclization of *Z*-2-alkyn-1-one *O*-methyl oximes (1), using ICl, provides a mild and selective route to 3,5-disubstituted-4-iodoisoxazoles (2) (Scheme 1).[6] The requisite 2-alkyn-1-ones (3) required for this methodology can be readily synthesized by established chemistry utilizing commercially available starting materials (Scheme 2).[7]

Scheme 1

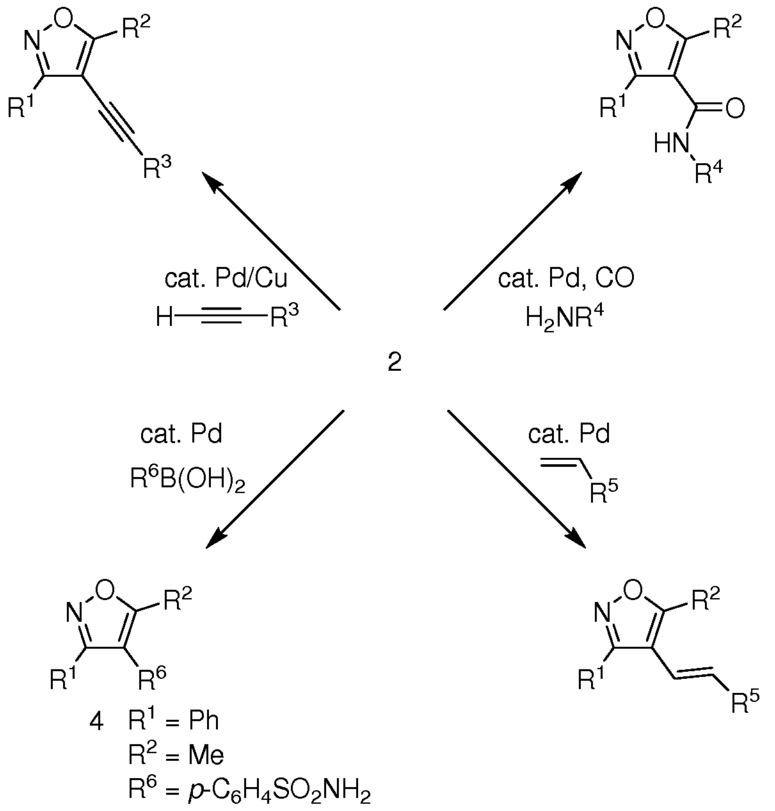

NH$_2$OMe
ICl
3
1
2

Scheme 2


H—≡—R^2
cat. PdCl$_2$(PPh$_3$)$_2$
cat. CuI, Et$_3$N
1) Li—≡—R^2
2) MnO$_2$ or PCC
3
TMS—≡—R^2
AlCl$_3$, CH$_2$Cl$_2$
cat. Pd, CO
H—≡—R^2
(R^1 = Ar)
Ar-X
X = halogen

We have previously demonstrated the significance of this methodology by reporting individual examples of Sonogashira,[8] Suzuki-Miyaura,[9] Heck,[10] and carbonylative amidation cross-coupling reactions,[11] which provide the corresponding 3,4,5-trisubstituted isoxazoles in good yields, including the highly potent COX-2 inhibitor valdecoxib (4) (Scheme 3).[12] With optimized conditions in hand for each of these processes, we wished to adapt these reactions to library generation. Herein, we report the success of this objective.

Scheme 3



Results and Discussion

Our 4-iodoisoxazole synthesis has previously been demonstrated to tolerate, but not be limited to, alkyl and aryl groups at the R^1 or R^2 positions of the isoxazole core. During our initial study, we found that employing of *Z*-*O*-methyloximes was essential to the success of our methodology, since the corresponding *E*-*O*-methyloximes proved ineffective in the electrophilic cyclization process. Since bulky groups at the R^1 position provided the highest yields of the necessary *Z*-*O*-methyloximes required for our 4-iodoisoxazole synthesis, R^1 was restricted to aryl groups for library generation. Since R^2 substituents had less of an effect on the outcome of our methodology, there was no need to adhere to strict guidelines when choosing R^2. Accordingly, we chose a subset of various 4-iodoisoxazoles which could be synthesized from readily available starting materials (Figure 1).

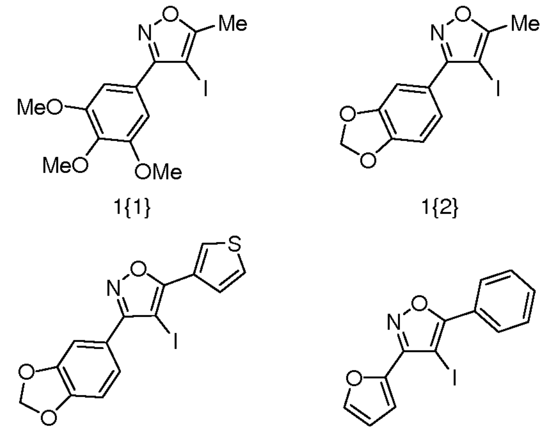


Figure 1. 4-Iodoisoxazole sublibrary.

Isoxazoles 1{1-4} were selected because their synthesis is straightforward and the oxygen heteroatoms provide desired polarity in the resulting library.

The alkyne sublibrary, used for Sonogashira cross-coupling, was chosen based on commercially available, heteroatom-containing acetylenes that could provide hydrogen bond donors and/or acceptors (Figure 2).

A small styrene sublibrary for Heck cross-coupling was chosen to demonstrate vinylic functionalization. However, only a few functionally diverse styrenes were available from commercial sources (Figure 3). We avoided the use of better Michael acceptors, such as acrylates or acrylonitriles, since the resulting Heck products would also be excellent Michael acceptors and thus undesirable for subsequent pharmaceutical applications.

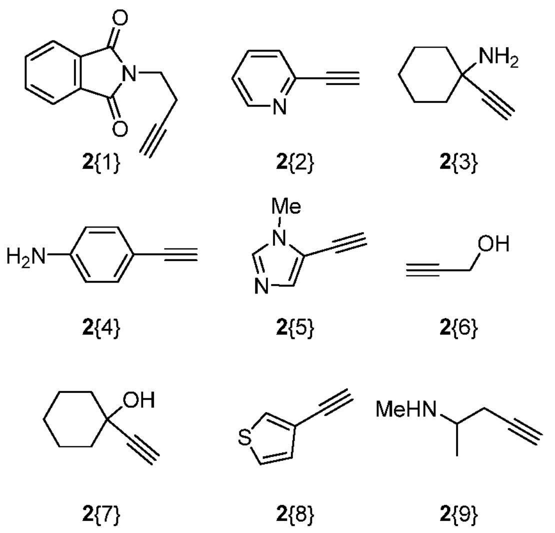

2{1}
2{2}
2{3}
H2N
NH2
Me
N
OH
2{4}
2{5}
2{6}
S
MeHN
2{7}
2{8}
2{9}

Figure 2. Terminal acetylene sublibrary.

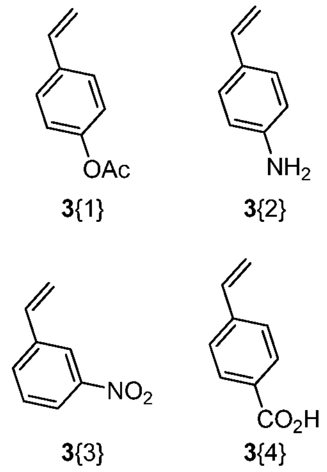

OAc
NH2
3{1}
3{2}
NO2
CO2H
3{3}
3{4}

Figure 3. Styrene sublibrary.

Commercially available boronic acids, for Suzuki-Miyaura cross-coupling, were chosen based on their diverse functionality (Figure 4). 5-Indoleboronic acid 4{1} was chosen because the resulting cross-coupling products could generate druglike scaffolds with potentially positive physiochemical properties. Arylboronic acids 4{3} and 4{6} were chosen because the resulting cross-coupling products would contain fluorine atoms. Organofluorine compounds are of considerable interest because of their versatile applications in industry and medicine.[13] Other boronic acids within the sublibrary were chosen because they contain heterocycles and polar functionality that would incorporate druglike moieties in the resulting cross-coupling products.

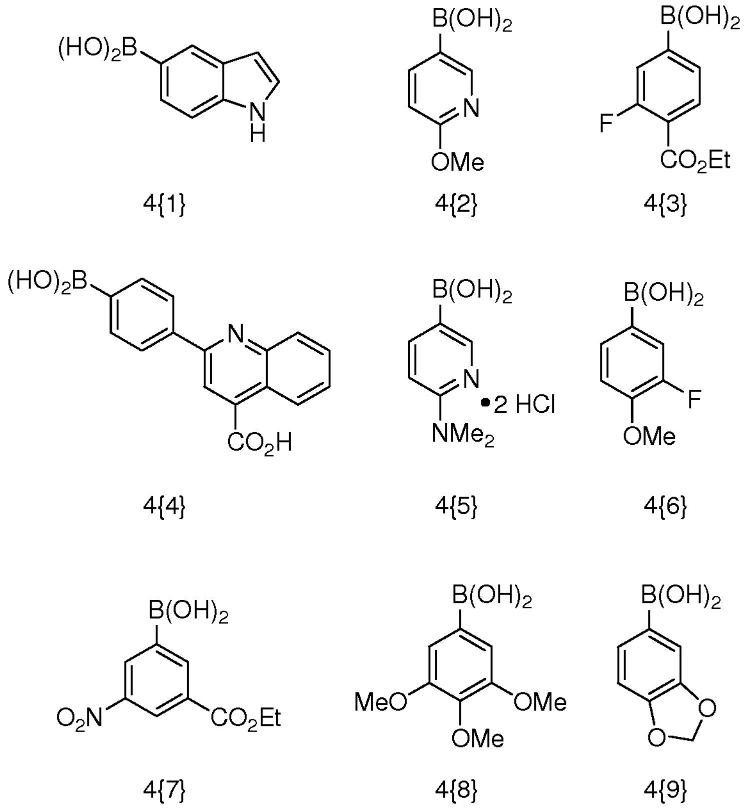

(HO)2B
N
H
4{1}
B(OH)2
N
OMe
4{2}
B(OH)2
F
CO2Et
4{3}
(HO)2B
N
CO2H
4{4}
B(OH)2
N
•2 HCl
NMe2
4{5}
B(OH)2
F
OMe
4{6}
B(OH)2
O2N
CO2Et
4{7}
B(OH)2
MeO
OMe
OMe
4{8}
B(OH)2
O
O
4{9}

Figure 4. Boronic acid sublibrary.

Primary amines were chosen as a sublibrary for palladium-catalyzed amide formation, because the resulting nitrogen-containing products would enable us to make compounds with potentially attractive druglike features, including molecular weight, solubility and molecular polarizability. Amines 5{1-11} were chosen to represent compounds found in natural products and derivatives of substances known to possess biological activity (Figure 5).

To ease the transition from our isoxazole methodology to library generation, we wished to preserve the protocols we had originally employed for the cross-coupling of 4-

iodoisoxazoles with terminal acetylenes, styrenes, boronic acids and amines.[6b] With these preliminary findings, we proceeded to prepare a diverse library of 3,4,5-trisubstituted isoxazoles as outlined in Scheme 3. The crude products were analyzed by LC/MS, followed by purification by preparative HPLC.

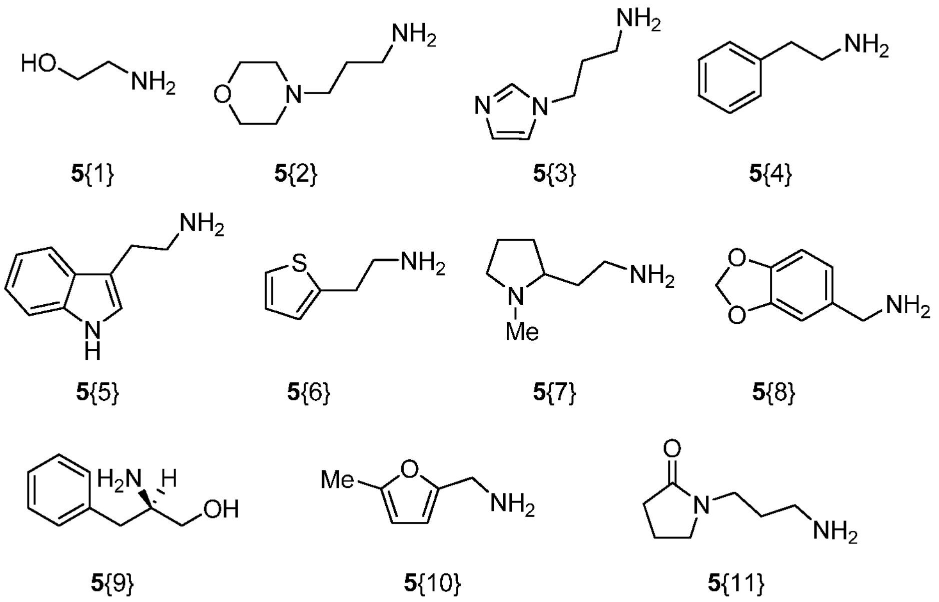
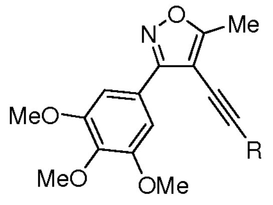
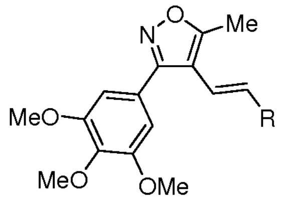


Figure 5. Primary amine sublibrary.

Table 1. Library Data for Compounds 6{1-13}


6{1-9}


6{10-13}

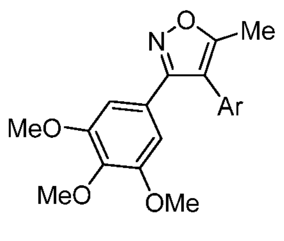
compound	R	yield[a] (%)	purity[b] (%)
6{1}	2-ethylphthalimide	40	94
6{2}	2-pyridinyl	30	97
6{3}	1-amino-1-cyclohexyl	42	95
6{4}	4-$H_2NC_6H_4$	62	99
6{5}	1-methyl-1*H*-imidazo-5-yl	83	95

6{6}	CH_2OH	67	97
6{7}	1-hydroxy-1-cyclohexyl	59	99
6{8}	3-thiophenyl	75	97
6{9}	2-(*N*-methyl)propyl	50	97
6{10}	4-$AcOC_6H_4$	60	94
6{11}	4-$H_2NC_6H_4$	67	93
6{12}	3-$O_2NC_6H_4$	73	95
6{13}	4-$HO_2CC_6H_4$	8	87

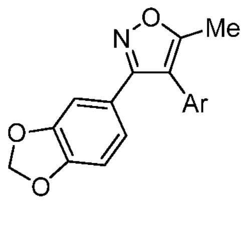
[a] Isolated yield after preparative HPLC.
[b] UV purities determined at 214 nm after preparative HPLC.

The results of the library synthesis are summarized in Tables 1-3. The crude products were subjected to preparative HPLC and purities in the range of 87-100% were achieved after purification. Most of the reactions proceeded well, with the exception of the Heck reaction of 4-vinylbenzoic acid. In the Suzuki-Miyaura reaction of boronic acids 4{5} and 4{7}, poor or no yield of the desired product was observed. Palladium-catalyzed amide formation using carbon monoxide and primary amines proceeded smoothly and provided the corresponding amides in satisfactory yields with high purities. Out of a total of 54 palladium-catalyzed processes attempted, only three failed completely.

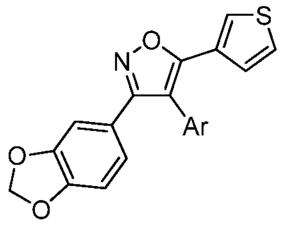
Table 2. Library Data for Compounds 6{14-45}



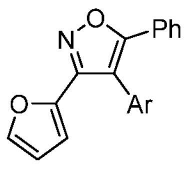
6{14-20}



6{21-27}

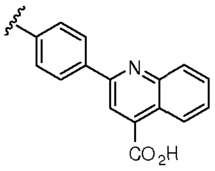
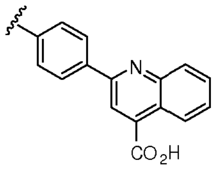
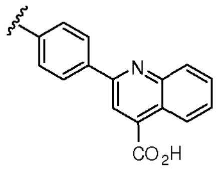


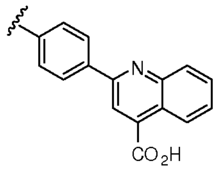
6{28-35}



6{36-43}

compound	Ar	yield[a] (%)	purity[b] (%)

6{14}	5-indolyl	24	92
6{15}	6-methoxy-3-pyridinyl	29	95
6{16}	4-EtO$_2$C-3-FC$_6$H$_4$	53	96
6{17}		5	87
6{18}	6-(*N*,*N*-dimethyl)-3-pyridinyl	22	94
6{19}	4-MeO-3-FC$_6$H$_4$	58	97
6{20}	3-MeO$_2$C-5-O$_2$NC$_6$H$_4$	44	97
6{21}	5-indolyl	51	92
6{22}	6-methoxy-3-pyridinyl	26	95
6{23}	4-EtO$_2$C-3-FC$_6$H$_4$	26	97
6{24}		0	
6{25}	6-(*N*,*N*-dimethyl)-3-pyridinyl	7	100
6{26}	4-MeO-3-FC$_6$H$_4$	46	88
6{27}	3-MeO$_2$C-5-O$_2$NC$_6$H$_4$	0	
6{28}	5-indolyl	79	97
6{29}	6-methoxy-3-pyridinyl	81	95
5{30}	4-EtO$_2$C-3-FC$_6$H$_4$	73	99
6{31}		57	94
6{32}	6-(*N*,*N*-dimethyl)-3-pyridinyl	85	96
6{33}	4-MeO-3-FC$_6$H$_4$	73	99
6{34}	3,4,5-(MeO)$_3$C$_6$H$_4$	44	91
6{35}	5-indolyl	75	96
6{36}	6-methoxy-3-pyridinyl	16	91

6{37}	4-EtO_2C-3-FC_6H_4	64	98
6{38}		7	100
6{39}	6-(*N*,*N*-dimethyl)-3-pyridinyl	20	92
6{40}	4-MeO-3-FC_6H_4	60	99
6{41}	3-EtO_2C-5-$O_2NC_6H_4$	0	
6{42}	3,4,5-$(MeO)_3C_6H_4$	53	99
6{43}	3,4-$(OCH_2CH_2O)C_6H_3$	44	99

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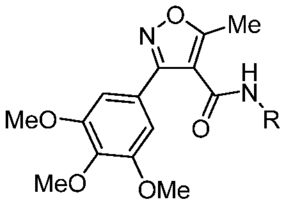
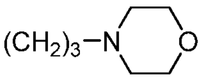
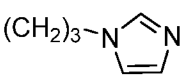
[a] Isolated yield after preparative HPLC.

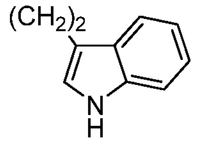
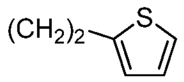
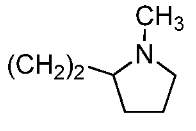
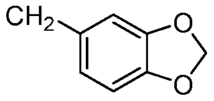
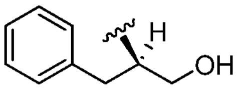
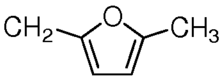
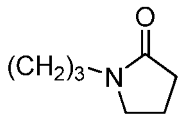
[b] UV purities determined at 214 nm after preparative HPLC.

Table 2. Library Data for Compounds 6{44-54}



6{44-54}

compound	R	yield[a] (%)	purity[b] (%)
6{44}	$(CH_2)_2OH$	24	99
6{45}		44	99
6{46}		50	100
6{47}	$(CH_2)_2Ph$	58	96

6{48}		39	97
6{49}		79	99
6{50}		65	96
6{51}		40	99
6{52}		27	99
6{53}		80	99
6{54}		69	99

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[a] Isolated yield after preparative HPLC.

[b] UV purities determined at 214 nm after preparative HPLC.

Because of our interest in synthesizing heterocycles for use in high-throughput screening projects, an *in silico* evaluation of library members was carried out to determine their agreement with Lipinski's[14] "rule of five" and Veber's rules.[15] Molecular weight, clog P, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were either specified or calculated for each of the library members using the SYBYL[16] program (Table 4). Most of the isoxazole library members were highly Lipinski compliant. In fact, 96% of the library members are entirely compliant with

Lipinski rules and only compound 6{31} had multiple violations, including molecular weight and clog P.

Table 4. *In silico* parameters for gauging oral availability / drug-likeness

	Mean	St. Dev.	Range
Clog P	3.13	1.40	-0.01 - 6.87
Mol. Weight	380.8	46.4	292.3 - 518.5
H-Bond Acceptors	6.00	1.13	3 - 9
H-Bond Donors	0.92	0.73	0 - 2
Rotatable Bonds	5.14	1.67	2 - 8

Conclusion

In conclusion, the preparation and subsequent palladium-catalyzed reactions of 4-iodoisoxazoles with various cross-coupling partners has allowed for simple construction of a 51-member library of 3,4,5-trisubstituted isoxazoles. The average yield of the library was 49% and the average purity after preparative HPLC was 96%.

Experimental

General. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All reagents were used directly as obtained commercially unless otherwise noted. THF and CH_2Cl_2 were distilled from sodium/benzophenone or CaH_2 respectively, under an atmosphere of argon prior to use. All glassware and stirring bars were oven dried prior to use.

HPLC analysis was carried out using an XBridge MS C-18 column (5 μM, 4.6 × 150 mm) with gradient elution (5% CH_3CN to 100% CH_3CN) on a Waters Alliance 2795 Separation Module with a Waters 2996 Photodiode Array UV detector and a Waters/Micromass LCT Premier (TOF) detector. Purification was carried out using an XBridge MS C-18 column (5 μM, 19 × 150 mm) with gradient elution (a narrow CH_3CN gradient was chosen based on the targets retention time from LCMS analysis of the crude sample) on a Mass Directed Fractionation instrument with a Waters 2767 sample manager, a Waters 2525 HPLC pump, a Waters 2487 dual λ absorbance detector, and a Waters/Micromass ZQ (quadrupole) detector. Fractions were triggered using an MS and/or UV threshold determined by an LCMS analysis of the crude sample. One of three aqueous mobile phases were chosen for both analysis and purification to promote the targets neutral state (water, 0.05% formic acid or pH 9.8 1mM HCO_2NH_4). High resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Premier (TOF instrument).

Iodoisoxazoles 1{1} and 1{4} were prepared by procedures described earlier.[6b]

Procedure for the preparation of 1-(benzo[*d*][1,3]dioxol-5-yl)-3-(thiophen-3-yl)prop-2-yn-1-one. To a 100 mL flask were added CuI (0.22 mmol, 41.9 mg), $PdCl_2(PPh_3)_2$ (0.12 mmol, 84.2 mg) and triethylamine (40 mL). The flask was flushed with argon and 3-ethynylthiophene (11.0 mmol, 1.19 g, 1.08 mL) was added to the stirred suspension, followed by immediate dropwise addition of piperonyloyl chloride (10.8 mmol, 3.0 g) as a solution in THF (8 mL). The resulting mixture was allowed to stir at room temperature overnight, filtered through a plug of silica gel, and concentrated under reduced pressure. Purification by column chromatography on silica gel using (4:1 hexanes/EtOAc) afforded 2.49 g (90%) of the product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.07 (s, 2H), 6.88-6.90 (d, *J* = 8.2 Hz, 1H), 7.28-7.30 (td, *J* = 0.6, 5.0 Hz, 1H), 7.35-7.37 (dd, *J* = 2.9, 5.0 Hz, 1H), 7.57-7.58 (d, *J* = 1.7 Hz, 1H), 7.81-7.87 (m, 2H); ^{13}C NMR δ 87.12, 87.88, 102.26, 108.11, 108.34, 119.52, 126.36, 127.28, 130.32, 132.11, 133.77, 148.32, 152.96, 176.18; HRMS Calcd for $C_{14}H_8O_3S$: 256.0194. Found: 256.0195.

Procedure for the preparation of 1-(benzo[*d*][1,3]dioxol-5-yl)but-2-yn-1-one. A modified procedure was used. To a 100 mL flask were added CuI (0.43 mmol, 81.9 mg), $PdCl_2(PPh_3)_2$ (0.22 mmol, 154.4 mg) and triethylamine (50 mL). The flask was flushed with argon and piperonyloyl chloride (21.7 mmol, 4.0 g) as a solution in THF (10 mL) was added to the flask. The flask was flushed with propyne and a balloon of propyne gas was placed on the reaction flask. The resulting suspension was allowed to stir overnight, filtered through a plug of silica gel, and concentrated under reduced pressure. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 3.72 g (91%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14 (s, 3H), 6.06 (s, 2H), 6.85-6.87 (d, *J* = 8.1 Hz, 1H), 7.53-7.54 (d, *J* = 1.7 Hz, 1H), 7.79-7.81 (dd, *J* = 1.7, 8.2 Hz, 1H); ^{13}C NMR δ 4.50, 78.97, 91.86, 102.22, 108.04, 108.48, 127.33, 132.12, 148.23, 152.84, 176.52; HRMS Calcd for $C_{11}H_8O_3$: 188.0473. Found: 188.0476.

General procedure for preparation of the *O*-methyl oximes. The alkynone (7.0 mmol), methoxylamine hydrochloride (14.0 mmol, 1.16 g), Na_2SO_4 (14.0 mmol, 1.99 g) and pyridine (2 mL) in methanol (20 mL) were stirred at room temperature. Benzene was added as a co-solvent in cases where the alkynone showed poor solubility in methanol. In some cases, the reaction required refluxing conditions to reach completion. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine, dried and evaporated. The residue was then purified by column chromatography on silica gel to afford the desired *O*-methyl oxime.

Z-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(thiophen-3-yl)prop-2-yn-1-one *O*-methyl oxime. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 1.64 g (82%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (s, 3H), 5.98 (s, 2H), 6.81-6.83 (d, *J* = 8.5 Hz, 1H), 7.24-7.25 (t, *J* = 2.0 Hz, 1H), 7.30-7.32 (m, 1H), 7.40-7.42 (m, 2H), 7.66-7.67 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 63.20, 79.33, 96.23, 101.57, 106.32, 108.19, 120.92, 121.67, 125.88, 127.94, 130.08, 131.04, 139.52, 148.01, 149.17; HRMS Calcd for $C_{15}H_{11}NO_3S$: 285.0460. Found: 285.0463.

Z-1-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-yn-1-one *O*-methyl oxime. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 1.32 g (87%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 4.05 (s, 3H), 5.96 (s, 2H), 6.77-6.70 (d, *J* = 8.5 Hz, 1H), 7.34-7.36 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR δ 5.08, 63.11, 70.96, 99.32, 101.59, 106.38, 108.11, 121.71, 128.29, 139.88, 147.97, 149.13; HRMS Calcd for $C_{12}H_{11}NO_3$: 217.0739. Found: 217.0744.

General procedure for iodocyclization using ICl. To a stirred solution of the appropriate *O*-methyl oxime (2.5 mmol) in CH_2Cl_2 (25 mL) was added ICl (1M in CH_2Cl_2, 1.2 equiv) dropwise and the solution was allowed to stir at room temperature.

The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a satd aq soln of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-iodo-5-(thiophen-3-yl)isoxazole. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 804 mg (81%) of the product: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.05 (s, 2H), 6.93-6.95 (d, J = 8.1 Hz, 1H), 7.25-7.26 (apparent doublet merged with $CDCl_3$, 1H), 7.29-7.32 (dd, J = 1.6, 8.0 Hz, 1H), 7.46-7.48 (dd, J = 3.0, 5.1 Hz, 1H), 7.81-7.82 (m, 1H), 8.28-8.29 (m, 1H); ^{13}C NMR δ 55.59, 101.71, 108.66, 109.41, 122.28, 123.48, 126.33, 126.68, 126.84, 128.24, 147.93, 149.33, 164.13, 165.96; HRMS Calcd for $C_{14}H_8INO_3S$: 396.9270. Found: 396.9278.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-iodo-5-methylisoxazole. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 732 mg (89%) of the product: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.53 (s, 3H), 6.03 (s, 2H), 6.92-6.90 (d, J = 8.1 Hz, 1H), 7.25-7.26 (apparent doublet merged with $CDCl_3$, J = 1.6 Hz, 1H), 7.30-7.33 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR δ 13.22, 58.12, 101.71, 108.67, 108.99, 122.57, 123.04, 148.00, 149.32, 162.49, 171.60; HRMS Calcd for $C_{11}H_8INO_3$: 328.9549. Found: 329.9555.

General procedure for Sonogashira coupling. To a 4-dram vial was added the appropriate 4-iodoisoxazole (0.25 mmol), the acetylene (0.30 mmol), $PdCl_2(PPh_3)_2$ (0.0025 mmol, 1.8 mg), CuI (0.005 mmol, 1.0 mg), DMF (1.5 mL) and Et_2NH (1.85 mL).

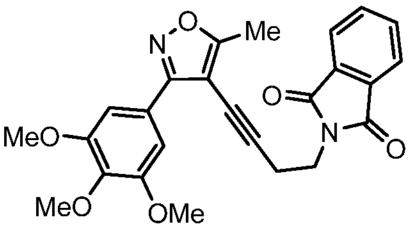
If the acetylene is a solid, it was added as a solution in THF. The solution was stirred for 5 minutes at room temperature and flushed with argon and then heated to 50 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by preparative HPLC.

General procedure for Heck coupling. To a 4-dram vial was added the appropriate 4-iodoisoxazole (0.25 mmol, 71 mg), the styrene (1.0 mmol), $Pd(OAc)_2$ (0.0132 mmol, 2.8 mg), *n*-Bu_4NCl (0.25 mmol, 69 mg), Na_2CO_3 (0.625 mmol, 66 mg) and DMF (1 mL), which was then heated to 85 °C for 24 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by preparative HPLC.

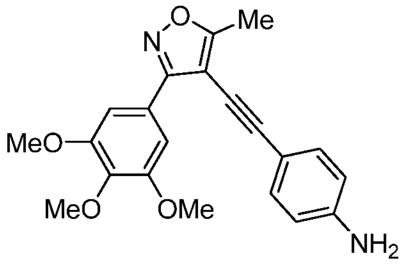
General procedure for Suzuki-Miyaura cross-coupling. To a 4-dram vial was added the appropriate 4-iodoisoxazole (0.25 mmol), the boronic acid (0.35 mmol), $KHCO_3$ (0.35 mmol, 35 mg) and $PdCl_2$ (0.0125 mmol, 2.2 mg) in 4:1 DMF:H_2O (2.5 mL). The solution was stirred for 5 min at room temperature and flushed with argon and then heated to 80 °C until TLC revealed complete conversion of the starting material. The residue was concentrated under reduced pressure and isolated preparative HPLC.

General procedure for the palladium-catalyzed carbonylative amidation. A modified literature procedure was used. To a 2-dram vial was added the appropriate 4-iodoisoxazole (0.17 mmol, 48 mg), $PdCl_2(PPh_3)_2$ (0.0085 mmol, 6.0 mg), DMF (1 mL) and the amine (0.25 mL) if liquid or (0.5 mmol) if solid. The reaction mixture was stirred for 2 minutes at room temperature and flushed with carbon monoxide. A balloon of carbon monoxide was placed on the vial, which was heated to 80 °C for 18 h. The solution was allowed to cool and the solvent was removed by a stream of nitrogen. The residue was purified by preparative HPLC.

Characterization data for a representative 20 compounds

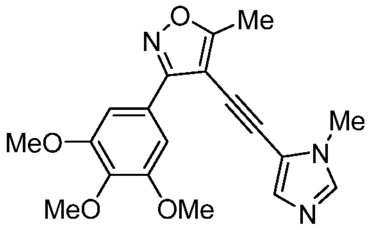


4-(4-Phthalimidoylbut-1-ynyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole 6{1}. Yield = 40%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.43 (s, 3H), 2.84-2.88 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.87 (s, 6H), 3.92-3.96 (t, *J* = 7.0 Hz, 2H), 7.25 (s merged with CDCl$_3$, 2H), 7.70-7.72 (dd, *J* = 2.6, 5.4 Hz, 2H), 7.81-7.83 (dd, *J* = 2.8, 5.6 Hz, 2H); ^{13}C NMR δ 11.85, 19.5, 36.63, 56.13, 60.93, 71.67, 91.69, 98.80, 104.53, 123.36, 123.80, 131.86, 134.20, 153.26, 160.85, 168.00, 173.42 (1 peak missing due to overlap); HRMS Calcd for $C_{25}H_{26}N_3O_6$: 464.1821 $[M + NH_4]^+$. Found: 464.1844.

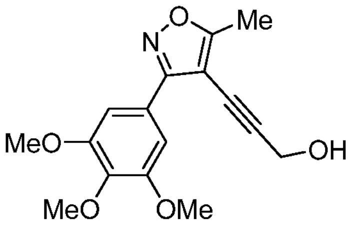


4-(4-Aminophenylethynyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole 6{4}. Yield = 62%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.58 (s, 2H), 3.87 (s, 6H), 3.90 (s, 3H), 6.61-6.65

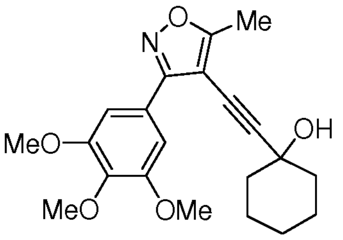
(td, *J* = 2.2, 8.8 Hz, 2H), 7.27-7.31 (td, *J* = 2.2, 8.4 Hz, 2H), 7.44 (s, 2H); ^{13}C NMR δ 12.11, 56.14, 60.94, 76.06, 95.82, 99.59, 104.60, 111.77, 114.76, 124.06, 132.81, 139.44, 147.12, 153.31, 160.63, 172.59; HRMS Calcd for $C_{21}H_{21}N_2O_4$: 365.1501 [M + H]$^+$. Found: 365.1510.



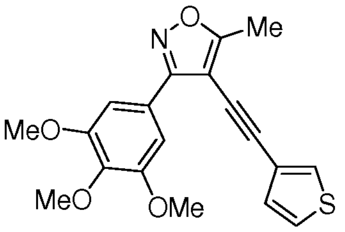
5-Methyl-4-(1-methyl-1*H*-imidazol-5-ylethynyl)-3-(3,4,5-trimethoxyphenyl)-isoxazole 6{5}. Yield = 83%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.60 (s, 3H), 3.70 (s, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 7.35 (s, 2H), 7.44-4.70 (m, 2H); ^{13}C NMR δ 12.36, 32.28, 56.35, 61.09, 76.87, 85.54, 98.87, 104.93, 123.67, 128.57, 128.69, 132.28, 139.96, 153.55, 160.86, 173.74; HRMS Calcd for $C_{19}H_{20}N_3O_4$: 354.1554 [M + H]$^+$. Found: 354.1559.



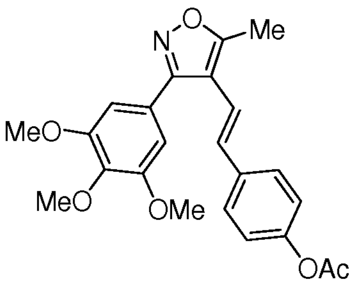
4-(3-Hydroxyprop-1-ynyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole 6{6}. Yield = 67%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.94 (br s, 1H), 2.53 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 4.52 (s, 2H), 7.33 (s, 2H); ^{13}C NMR δ 12.04, 51.59, 56.18, 60.95, 75.08, 93.48, 98.44, 104.64, 123.61, 139.59, 153.35, 160.90, 173.67; HRMS Calcd for $C_{16}H_{18}NO_5$: 304.1185 [M + H]$^+$. Found: 304.1204.



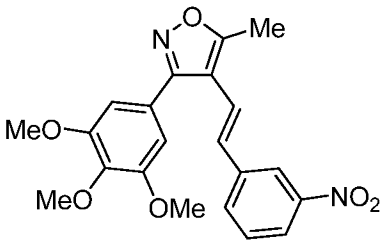
1-((5-Methyl-3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)ethynyl)cyclohexanol 6{7}. Yield = 59%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.25-1.34 (m, 1H), 1.53-1.77 (m, 8H), 1.96-2.00 (m, 2H), 2.11 (br s, 1H), 2.53 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 7.31 (s, 2H); ^{13}C NMR δ 12.03, 23.36, 25.10, 40.08, 40.96, 56.30, 60.94, 69.26, 73.37, 98.65, 99.16, 104.81, 123.81, 139.70, 153.38, 160.68, 173.57 (1 peak missing due to overlap); HRMS Calcd for $C_{21}H_{26}NO_5$: 372.1811 [M + H]$^+$. Found: 372.1832.



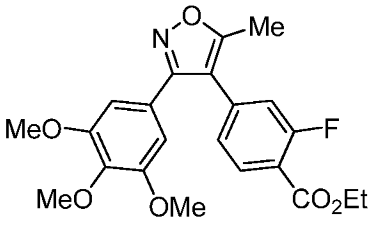
5-Methyl-4-(thiophen-3-ylethynyl)-3-(3,4,5-trimethoxyphenyl)isoxazole 6{8}. Yield = 75%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.59 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 7.15-7.17 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.32-7.34 (dd, *J* = 3.0, 5.0 Hz, 1H), 7.41 (s, 2H), 7.50-7.51 (dd, *J* = 1.2, 2.8 Hz, 1H); ^{13}C NMR δ 12.17, 56.13, 60.95, 77.95, 90.20, 99.08, 104.64, 121.59, 123.83, 125.93, 129.01, 129.53, 139.59, 153.36, 160.71, 173.19; HRMS Calcd for $C_{19}H_{18}NO_4S$: 356.0957 [M + H]$^+$. Found: 356.0961.



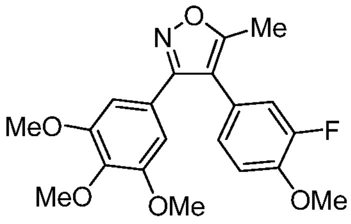
4-(*E*-2-(4-Acetoxyphenyl)ethenyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)-isoxazole 6{10}. Yield = 60%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.31 (s, 3H), 2.60 (s, 3H), 3.85 (s, 6H), 3.91 (s, 3H), 6.68-6.72 (d, *J* = 16.4 Hz, 1H), 6.76-6.80 (d, *J* = 16.4 Hz, 1H), 6.89 (s, 2H), 7.07-7.09 (d, *J* = 8.8 Hz, 2H), 7.41-7.43 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 12.41, 21.14, 56.26, 60.98, 105.76, 112.46, 116.65, 122.02, 124.60, 127.04, 131.30, 134.66, 139.21, 150.32, 153.51, 161.44, 166.43, 169.46; HRMS Calcd for $C_{23}H_{24}NO_6$: 410.1604 $[M + H]^+$. Found: 410.1628.



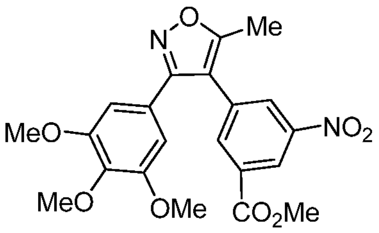
5-Methyl-4-(*E*-2-(3-nitrophenyl)ethenyl)-3-(3,4,5-trimethoxyphenyl)isoxazole 6{12}. Yield = 73%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.64 (s, 3H), 3.86 (s, 6H), 3.92 (s, 3H), 6.75-6.79 (d, *J* = 16.4 Hz, 2H), 6.87 (s, 2H), 6.96-7.00 (d, *J* = 16.4 Hz, 2H), 7.50-7.54 (t, *J* = 8.0 Hz, 1H), 7.67-7.69 (d, *J* = 8.0 Hz, 1H), 8.10-8.12 (m, 1H), 8.27-8.28 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 12.53, 56.28, 61.00, 105.86, 111.92, 119.71, 120.52, 122.40, 124.30, 129.41, 129.80, 131.84, 138.70, 139.43, 148.78, 153.62, 161.50, 167.14; HRMS Calcd for $C_{42}H_{44}N_5O_{12}$: 810.2987 $[2M + NH_4]^+$. Found: 810.2996.



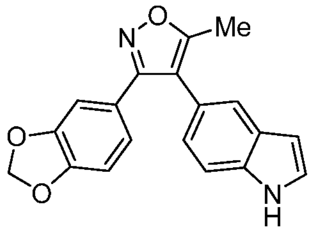
4-(4-Ethoxycarbonyl-3-fluorophenyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)-isoxazole 6{16}. Yield = 53%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.39-1.43 (t, *J* = 7.2 Hz, 3H), 2.48 (s, 3H), 3.69 (s, 6H), 3.87 (s, 3H), 4.39-4.44 (q, *J* = 7.2 Hz, 2H), 6.63 (s, 2H), 7.02-7.08 (m, 2H), 7.95-7.98 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 11.90, 14.42, 56.18, 61.09, 61.73, 76.89, 105.80, 114.21, 118.24, 118.30, 118.40, 118.47, 123.69, 125.67, 125.70, 132.55, 132.56, 137.38, 137.47, 139.47, 153.49, 160.65, 160.83, 163.24, 164.07, 164.11, 167.57 (extra peaks due to C-F splitting); HRMS Calcd for $C_{22}H_{23}FNO_6$: 416.1509 [M + H]$^+$. Found: 416.1533.



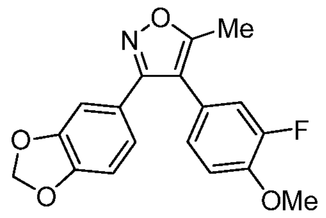
4-(3-Fluoro-4-methoxyphenyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole 6{19}. Yield = 58%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.43 (s, 3H), 3.68 (s, 6H), 3.86 (s, 3H), 3.92 (s, 3H), 6.69 (s, 2H), 6.92-7.02 (m, 3H); ^{13}C NMR δ 11.52, 55.94, 60.91, 105.49, 113.54, 113.56, 114.46, 114.47, 117.65, 117.84, 123.23, 123.31, 124.11, 126.17, 126.20, 139.03, 147.27, 147.38, 150.98, 153.17, 160.60, 166.82 (extra peaks due to C-F splitting); HRMS Calcd for $C_{20}H_{21}FNO_5$: 374.1404 [M + H]$^+$. Found: 374.1424.



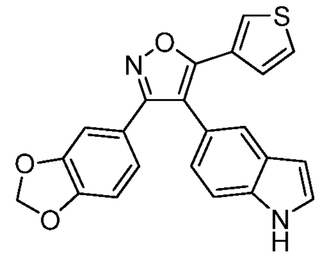
4-(3-Methoxycarbonyl-5-nitrophenyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)-isoxazole 6{20}. Yield = 44%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.51 (s, 3H), 3.67 (s, 6H), 3.86 (s, 3H), 3.98 (s, 3H), 6.60 (s, 2H) 8.23-8.24 (t, *J* = 1.4 Hz, 1H), 8.26-8.27 (t, *J* = 2.0 Hz, 1H), 8.83-8.84 (m, 1H); ^{13}C NMR δ 11.89, 53.17, 56.19, 61.05, 105.85, 113.34, 123.31, 123.68, 128.45, 132.55, 133.25, 136.43, 139.69, 148.62, 153.58, 160.78, 164.54, 167.92; HRMS Calcd for $C_{42}H_{44}N_5O_{16}$: 874.2783 [2M + NH$_4$]$^+$. Found: 874.2822.



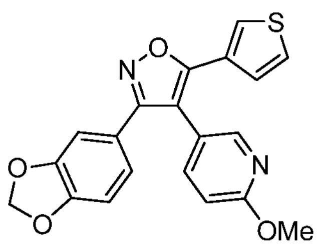
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(1*H*-indol-5-yl)-5-methylisoxazole 6{21}. Yield = 24%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.42 (s, 3H), 5.92 (s, 3H), 6.55-6.56 (m, 1H), 6.67-6.69 (d, *J* = 8.0 Hz, 1H), 6.93-7.00 (m, 3H), 7.25-7.27 (apparent doublet merged with CDCl$_3$, *J* = 2.0 Hz, 1H), 7.38-7.40 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 0.6 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR δ 11.72, 101.31, 102.95, 108.47, 108.87, 111.56, 116.64, 122.26, 122.88, 123.49, 124.32, 125.08, 128.32, 135.40, 147.73, 148.55, 161.01, 166.63; HRMS Calcd for $C_{19}H_{15}N_2O_3$: 319.1083 [M + H]$^+$. Found: 319.1100.



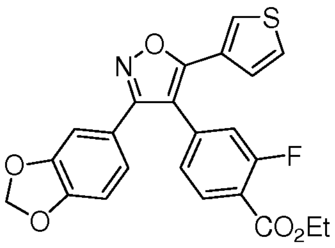
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazole 6{26}. Yield = 46%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.41 (s, 3H), 3.93 (s, 3H), 5.93 (s, 2H), 6.75-6.77 (d, *J* = 8.0 Hz, 1H), 6.88-7.03 (m, 4H), 7.22-7.28 (m, 1H); ^{13}C NMR δ 11.54, 56.22, 101.30, 108.47, 108.62, 113.54, 113.56, 113.69, 114.51, 117.45, 117.64, 122.19, 122.23, 122.64, 122.67, 125.83, 125.87, 147.75, 148.66, 151.00. 153.45, 160.64, 166.63 (extra peaks due to C-F splitting); HRMS Calcd for $C_{18}H_{15}FNO_4$: 328.0985 [M + H]$^+$. Found: 328.1004.



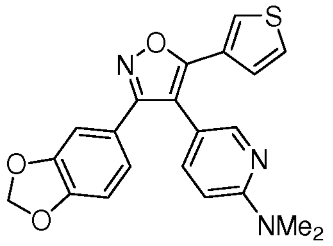
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(1*H*-indol-5-yl)-5-(thiophen-3-yl)isoxazole 6{28}. Yield = 79%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.91 (s, 2H), 6.56-6.57 (m, 1H), 6.65-6.67 (d, *J* = 8.4 Hz, 1H), 6.95-6.98 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.03-7.04 (d, *J* = 1.6 Hz, 1H), 7.08-7.11 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.15-7.16 (dd, *J* = 1.4, 5.0 Hz, 1H), 7.20-7.22 (dd, *J* = 3.0, 5.0 Hz, 1H), 7.28-7.30 (t, *J* = 2.8 Hz, 1H), 7.44-7.48 (m, 2H), 7.59-7.60 (t, *J* = 0.8 Hz, 1H), 8.35 (br s, 1H); ^{13}C NMR δ 101.34, 103.26, 108.50, 108.79, 112.14, 115.36, 121.84, 122.86, 123.09, 123.33, 124.63, 124.73, 125.18, 125.88, 126.11, 128.67, 129.36, 135.86, 147.75, 148.65, 161.76, 162.75; HRMS Calcd for $C_{22}H_{15}N_2O_3S$: 387.0803 $[M + H]^+$. Found: 387.0816.



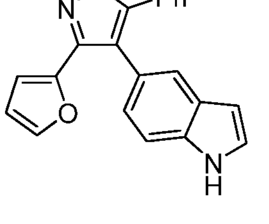
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(6-methoxypyridin-3-yl)-5-(thiophen-3-yl)isoxazole 6{29}. Yield = 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 5.96 (s, 2H), 6.73-6.75 (d, *J* = 7.6 Hz, 1H), 6.80-6.82 (dd, *J* = 0.8, 8.4 Hz, 1H), 6.87-6.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.93-6.94 (d, *J* = 1.6 Hz, 1H), 7.16-7.17 (dd, *J* = 1.2, 5.2 Hz, 1H), 7.29-7.31 (dd, *J* = 2.8, 8.4 Hz, 1H), 7.52-7.53 (dd, *J* = 1.2, 3.2 Hz, 1H), 8.08-8.09 (dd, *J* = 0.6, 1.4 Hz, 1H); ^{13}C NMR δ 53.65, 101.36, 108.54, 108.63, 110.64, 111.44, 119.29, 122.33, 122.75, 125.12, 125.46, 126.59, 128.49, 140.67, 147.84, 148.30, 148.79, 161.74, 163.06, 164.06; HRMS Calcd for $C_{20}H_{15}N_2O_4S$: 379.0753 $[M + H]^+$. Found: 379.0761.



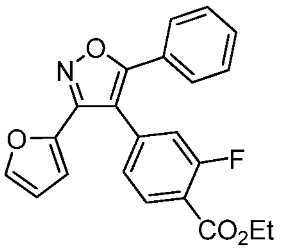
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(4-ethoxycarbonyl-3-fluorophenyl)-5-(thiophen-3-yl)isoxazole 6{30}. Yield = 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.45 (t, *J* = 7.0 Hz, 3H), 4.41-4.47 (q, *J* = 7.1 Hz, 2H), 5.99 (s, 2H), 6.74-7.76 (d, *J* = 8.0 Hz, 1H), 6.83-6.85 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.92-6.93 (d, *J* = 1.6 Hz, 1H), 7.08-7.18 (m, 3H), 7.32-7.34 (dd, *J* = 3.0, 5.0 Hz, 1H), 7.55-7.56 (dd, *J* = 1.2, 3.2 Hz, 1H), 7.98-8.02 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 14.53, 61.88, 101.66, 108.80, 108.81, 119.19, 119.42, 122.12, 122.99, 125.70, 125.85, 126.49, 126.52, 127.01, 128.28, 133.10, 137.55, 148.15, 149.20, 161.50, 163.13, 163.53 (extra peaks due to C-F splitting); HRMS Calcd for $C_{23}H_{17}FNO_5S$: 438.0812 $[M + H]^+$. Found: 438.0840.



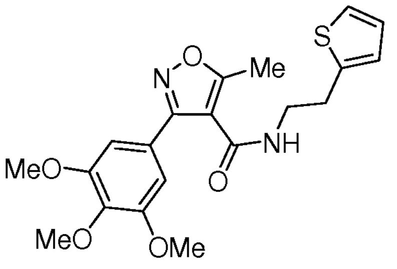
3-(Benzo[*d*][1,3]dioxol-5-yl)-4-(6-(dimethylamino)pyridin-3-yl)-5-(thiophen-3-yl)isoxazole 6{32}. Yield = 85%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.15 (s, 3H), 5.97 (s, 2H), 6.55-6.57 (dd, *J* = 0.4, 8.8 Hz, 1H), 6.75-6.77 (d, *J* = 8.4 Hz, 1H), 6.97-6.99 (dd, 1.8, 8.2 Hz, 1H), 7.01-7.02 (d, *J* = 1.6 Hz, 1H), 7.24-7.26 (dd, *J* = 1.2, 5.2 Hz, 1H), 7.29-7.34 (m, 2H), 7.56-7.57 (dd, *J* = 1.2, 2.8 Hz, 1H), 8.08-8.09 (dd, *J* = 0.8, 2.4 Hz, 1H); ^{13}C NMR δ 38.25, 101.47, 106.00, 108.70, 108.89, 111.71, 113.29, 122.97, 124.98, 125.80, 126.51, 129.07, 139.30, 147.94, 148.83, 149.44, 159.01, 162.08, 163.04 (1 peak missing due to overlap); HRMS Calcd for $C_{21}H_{18}N_3O_3S$: 329.1069 $[M + H]^+$. Found: 329.1089.



3-(Furan-2-yl)-4-(1*H*-indol-5-yl)-5-phenylisoxazole 6{35}. Yield = 75%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98-5.99 (dd, *J* = 0.8, 3.6 Hz, 1H), 6.25-6.27 (dd, *J* = 1.8, 3.4 Hz, 1H), 6.58-6.60 (m, 1H), 7.14-7.17 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.28-7.33 (m, 4H), 7.46-7.58 (m, 4H), 7.65 (t, *J* = 0.8 Hz, 1H), 8.42 (br s, 1H); ^{13}C NMR δ 103.07, 111.09, 111.97, 112.00, 115.02, 121.23, 122.80, 124.26, 125.05, 126.74, 127.82, 128.50, 128.57, 129.63, 135.81, 143.49, 144.24, 154.89, 165.07; HRMS Calcd for $C_{21}H_{15}N_2O_2$: 327.1136 $[M + H]^+$. Found: 327.1156.



4-(4-Ethoxycarbonyl-3-fluorophenyl)-3-(furan-2-yl)-5-phenylisoxazole 6{37}. Yield = 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.46 (t, *J* = 7.2 Hz, 3H), 4.44-4.48 (q, *J* = 7.2 Hz, 2H), 6.36-6.37 (dd, *J* = 0.6, 3.4 Hz, 1H), 6.40-6.41 (dd, *J* = 1.8, 3.4 Hz, 1H), 7.17-7.20 (dd, *J* = 1.4, 11.0 Hz, 1H), 7.22-7.24 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.33-7.7.45 (m, 3H), 7.48-7.51 (m, 3H), 8.02-8.05 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 14.30, 61.67, 111.35, 111.92, 119.07, 119.30, 126.31, 126.34, 126.76, 127.02, 128.93, 130.47, 132.77, 137.06, 143.26, 144.15, 153.88, 160.67, 163.27, 164.06, 166.17 (extra peaks due to C-F splitting); HRMS Calcd for $C_{44}H_{36}F_2N_3O_8$: 772.2465 $[2M + NH_4]^+$. Found: 772.2476.



N-(2-(Thiophen-2-yl)ethyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole-4-carboxamide 6{49}. Yield = 79%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.69 (s, 3H), 2.94-2.97 (t, *J* = 6.6 Hz, 2H), 3.55-3.60 (q, *J* = 6.8 Hz, 2H), 3.84 (s, 6H), 3.90 (s, 3H), 5.74 (br s, 1H), 6.59-6.60 (m, 1H), 6.73 (s, 2H), 6.83-6.96 (dd, *J* = 3.6, 5.2 Hz, 1H), 7.10-7.11 (dd, *J* = 1.2, 5.2 Hz, 1H); ^{13}C NMR δ 12.97, 29.58, 40.68, 56.25, 60.96, 105.92, 110.99, 123.21, 124.11, 125.24, 126.97, 139.64, 140.47, 153.68, 160.04, 161.54, 174.03; HRMS Calcd for $C_{20}H_{23}N_2O_5S$: 403.1328 $[M + H]^+$. Found: 403.1343.

Acknowledgment

We would like to thank Frank Schoenen for his useful discussions and David Hill at the University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development for obtaining the library NMR spectra. We thank the National Institute of General Medical Sciences (R01 GM070620 and R01 GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (P50 GM069663) for support of this research; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts; and Frontier Scientific and Synthonix for donations of boronic acids.

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CHAPTER 3. Room Temperature ICl-Induced Dehydration/Iodination of 1-Acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles. A Selective Route to Substituted 1-Acyl-4-iodo-1*H*-pyrazoles

A paper submitted to the *Journal of Organic Chemistry*

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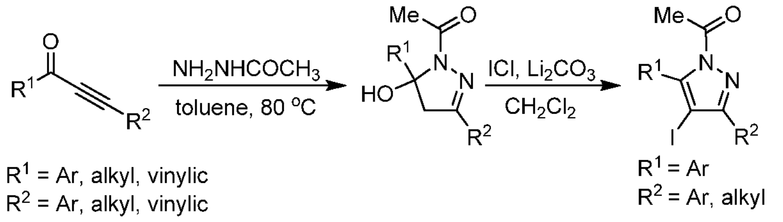
Abstract



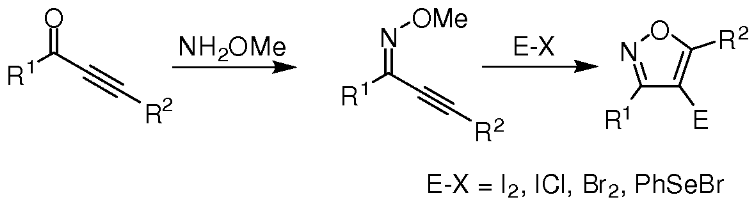
A number of new functionally-substituted 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been prepared in moderate to excellent yields from the corresponding 2-alkyn-1-ones. The resulting dihydropyrazoles undergo dehydration and iodination in the presence of ICl and Li_2CO_3 at room temperature to provide 1-acyl-4-iodo-1*H*-pyrazoles.

Introduction

Pyrazoles and derivatives have attracted considerable attention due to the wide variety of biological activities they exhibit, including hypoglycemic, antimicrobial, amoebicidal, anti-bacterial, anti-inflammatory, antipyretic and analgesic activities.[1] Specifically, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles are known to possess anti-inflammatory and analgesic activity.[2] Pyrazoles exhibit analgesic,[3] antimicrobial,[4] anti-inflammatory,[5] anti-hypertensive,[6] and hypoglycemic[7] activities, and appear promising as potential antiprotozoal and cytotoxic agents,[8] and CB1 cannabinoid receptor antagonists as appetite suppressants for the treatment of obesity.[9]

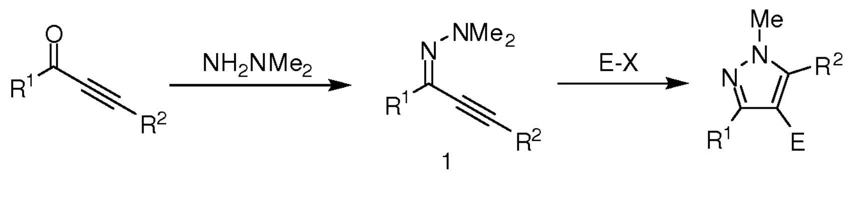
We recently reported the synthesis of highly substituted isoxazoles by the electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes (Scheme 1).[10] The requisite ynone *O*-methyl oximes were prepared by stirring the ynone in the presence of methoxylamine hydrochloride, pyridine and Na_2SO_4 or $MgSO_4$ at room temperature using methanol as the solvent.[11]

Scheme 1



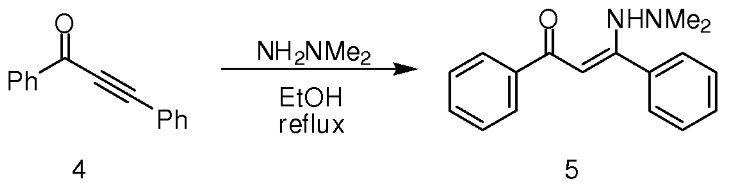
We reasoned that an analogous synthetic strategy could be applied towards the synthesis of highly substituted pyrazoles. We envisioned that 2-alkyn-1-one *N*,*N*-dimethylhydrazones (1) would react in the presence of an electrophile to afford substituted 1-methylpyrazoles (Scheme 2). However, this synthetic strategy was unsuccessful, because we were unable to prepare the requisite hydrazones, and thus an alternative route to 4-halopyrazoles was ultimately developed. We wish herein to report our results on that project.

Scheme 2



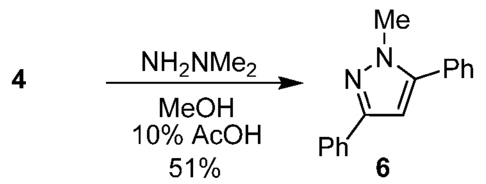
Results and Discussion

The preparation of dimethylhydrazones, such as 1, is not as straightforward as was first anticipated. The reaction of 1,1-dimethylhydrazine with 1,3-diphenylprop-2-yn-1-one (4) in ethanol at reflux has been reported to afford 3-(2,2-dimethylhydrazinyl)-1,3-diphenylprop-2-en-1-one (5) (eq 1).[12]



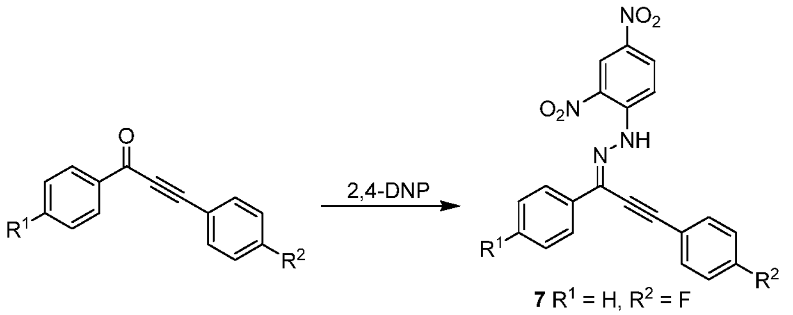
(1)

We have found that when 4 was allowed to react with 1,1-dimethylhydrazine and a catalytic amount of acetic acid in methanol at reflux, 1-methyl-3,5-diphenylpyrazole (6) was the major product isolated in a 51% yield (eq 2). None of the desired hydrazone product was observed. To our surprise, reactions at room temperature still afforded pyrazole 6 in modest yields. A similar result has been reported when compound 5 was heated in the presence of acetic anhydride. Once again, one of the two methyl groups of the hydrazine was also eliminated to afford 6.[13]



(2)

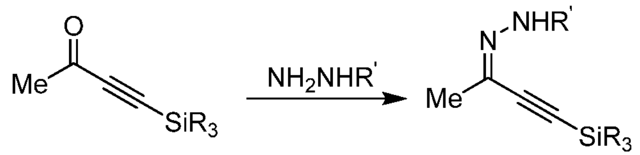
These results do not provide a particularly useful route to 1-substituted pyrazoles, since it has been reported that mono-substituted hydrazines react with 2-alkyn-1-ones to afford pyrazoles regioselectively in good yields.[14] The latter reaction occurs by 1,4-addition of the mono-substituted hydrazine to the alkynone, followed by dehydration to form the substituted pyrazole. In the same study, when 2,4-dinitrophenylhydrazine was employed, 1,2-addition dominated, resulting in the formation of 2-alkyn-1-one hydrazones 7 and 8 (eq 3).



7 $R^1 = H$, $R^2 = F$
8 $R^1 = F$, $R^2 = H$

(3)

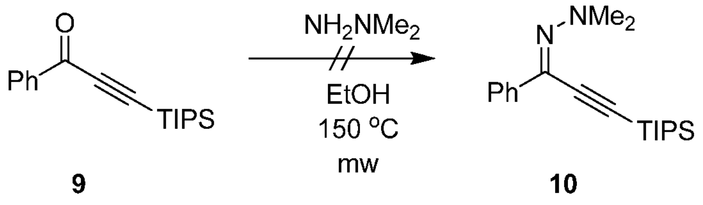
Hydrazones of 2-alkyn-1-ones have also been reported when mono-substituted hydrazines are allowed to react with alkynones bearing sterically bulky silanes on the alkyne terminus and a proton or methyl group on the carbonyl moiety (eq 4).[15]



$R_3 = Me_3$, *t*-$BuPh_2$
$R' = H, Me, Ph$

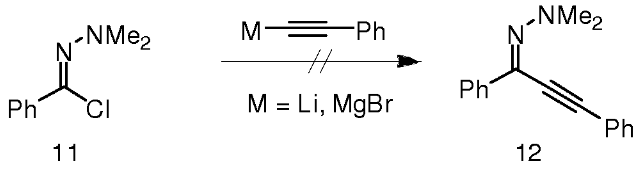
(4)

This prompted us to employ a bulky triisopropylsilyl group on the alkyne terminus to form the desired alkynone hydrazones. When alkynone 9 was subjected to 1,1-dimethylhydrazine in ethanol at reflux, no reaction was observed. Only when the solution was heated to 150 °C by microwave irradiation did conversion of 9 occur slowly, but dimethylhydrazone 10 was not observed (eq 5). Presumably, the diminished reactivity of 1-phenyl-3-(triisopropylsilyl)prop-2-yn-1-one (9) towards 1,2-addition of the 1,1-dimethylhydrazine, as compared to 3-silylalkynones bearing a proton or methyl at the 1-position, is due to the ketone bearing an aromatic ring.



(6)

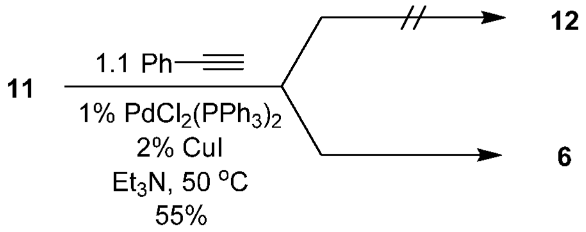
Given that the preparation of *N*,*N*-dimethylhydrazones by the addition of 1,1-dimethylhydrazine to alkynones is not at this stage apparently a very general reaction, we explored indirect routes towards their synthesis. Hydrazonyl chloride 11, prepared in two steps from benzoyl chloride,[16] failed to react with Li and Mg acetylides to provide the desired dimethylhydrazone (12) (eq 6). The analogous coupling of alkynyl Grignard reagents with imidoyl chlorides has been reported.[17] Surprisingly, refluxing 11 in the presence of lithium phenylacetylide in THF provided no reaction.



(6)

The palladium-catalyzed cross-coupling of terminal acetylenes with imidoyl chlorides has been reported.[18] When compound 11 was subjected to Sonogashira cross-coupling conditions in the presence of phenyl acetylene at room temperature, no reaction occurred. However, when the temperature was increased to 50 °C, pyrazole 6 was isolated in a 55% yield (Scheme 3). A similar result has been reported when copper and silver acetylides are allowed to react with *N*-substituted hydrazonyl bromides to give 1,3,5-trisubstituted pyrazoles.[19] Our attempts at copper-free cross-coupling conditions resulted in no reaction of 11.[20]

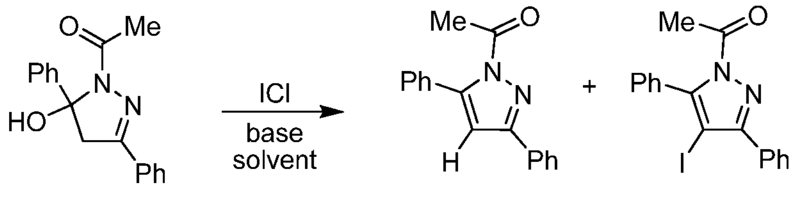
Scheme 3



When acyl and aroyl hydrazine derivatives were first allowed to react with alkynones, the products were originally assigned an open chain form. Since then, their structures have been reassigned and a small number of 5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been reported by the reaction of hydrazine derivatives with alkynones.[21] To the best of our knowledge, the analogous reaction using acetylhydrazine has not been reported. 5-Hydroxy-4,5-dihydro-1*H*-pyrazoles have also been prepared by the reaction of hydrazine derivatives with 3-alkoxyalk-2-en-1-ones.[22] The synthesis of 5-hydroxy-4,5-dihydro-1*H*-pyrazoles from alkynones is attractive due to the many ways one can selectively synthesize alkynones from commercially available starting materials.[23]

A literature search revealed that iodine has been used as a Lewis acid for the facile dehydration of aldoximes to nitriles.[24] We envisioned that the dehydration of *N*-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles, followed by iodination, could provide a selective route to substituted 1-acyl-4-pyrazoles. Thus, we synthesized 1-acetyl-5-hydroxy-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (13) as the model system for optimization of this process. The use of I_2 and carbonate bases, such as K_2CO_3, Li_2CO_3 and Na_2CO_3, in CH_2Cl_2 or CH_3CN provided no reaction of 13. We then shifted our attention to the use of ICl. ICl has been established as the most Lewis acidic of the halogens.[25] We were pleased to find that 1.2 equiv of ICl in the presence of 2 equiv of Na_2CO_3 in CH_2Cl_2 provided complete conversion of 13 to the corresponding 1-acetyl-3,5-diphenyl-1*H*-

pyrazole (14) (60% yield) and 1-acetyl-4-iodo-3,5-diphenyl-1*H*-pyrazole (15) (30% yield) (eq 7).



13 **14** **15** (7)

In order to increase the solubility of the inorganic base, CH_3CN and $MeNO_2$ were screened as solvents under the same reaction conditions. However, this provided messy reaction mixtures and provided none of the desired product. Among carbonate bases screened, using CH_2Cl_2 as the solvent in the presence of ICl, Li_2CO_3 provided the best results. The use of Li_2CO_3 nearly reversed the product ratio, compared with Na_2CO_3, providing a 13% yield of 14 and a 52% yield of 15, although the reaction took two days to reach completion. Omitting Li_2CO_3 from the reaction, led to the formation of deacylated pyrazole products, presumably due to the formation of HCl. The optimal reaction conditions thus far developed involve stirring 0.25 mmol of the dihydropyrazole 13, 3 equiv of ICl and 2 equiv of Li_2CO_3 in 2.5 mL of CH_2Cl_2 at room temperature, which affords a 95% yield of 15.

With optimized conditions in hand, we synthesized a number of 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles from the corresponding 2-alkyn-1-ones (Table 1). In most cases, preparation of the 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles proceeded smoothly in good yield by simply heating the appropriate alkynone in the presence of 2 equiv of acetylhydrazine in toluene at 80 °C. When R^1 is a phenyl group, the reaction proceeds satisfactorily in most cases. Both the parent system and one containing an electron-deficient aryl group gave the desired dihydropyrazoles 16 and 17 in good yields (Table 1, entries 1 and 2). Substituting an *n*-butyl group on the terminus of the alkyne moiety was also tolerated well and provided 18 in a good yield (Table 1, entry 3). Only when R^2 = 1-cyclohexenyl did the reaction afford only a modest yield of compound 19 (Table 1, entry 4).

When the 1 position of the 2-alkyn-1-one was substituted with a 2-naphthyl group, the reaction gave a yield of 20 comparable to that of the parent system (Table 1, compare entries 1 and 5). Halogens in the *para* position of the aromatic ring, including F, Cl, Br and trifluoromethyl, provided good yields of the desired 5-hydroxy-4,5-dihydro-1*H*-pyrazoles 21, 22, 23 and 24 respectively (Table 1, entries 6-9). The presence of an electron-withdrawing cyano group in the *para* position also gave a good yield of 25 (Table 1, entry 10). Electron-rich aryl groups, including *p*-*t*-Bu, 3,4-OCH_2CH_2O-, and 3,4,5-trimethoxy phenyl groups also worked well and provided good yields of 26, 27, and 28 respectively (Table 1, entries 11-13). The highly electron-rich benzene ring containing a *p*-Me_2N group provided only a modest yield of 29 and the reaction required a four fold increase in reaction time (Table 1, entry 14). A methyl group in the *ortho* position of the benzene ring provided a slightly lower yield of 30 and required a longer reaction time compared to that of the parent system (Table 1, compare entries 1 and 15). A 3-pyridyl substituent provided an excellent yield of 31 (Table 1, entry 16). The reaction also tolerated a vinylic group in the R^1 position, affording cinnamyl derivative 32 (Table 1, entry 17). Thus, this approach to 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles appears to be quite general.

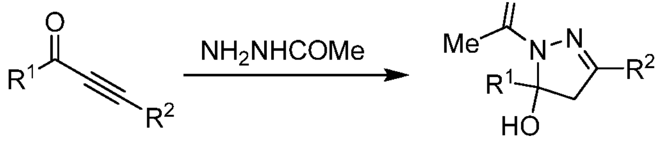
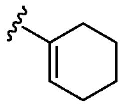
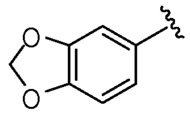
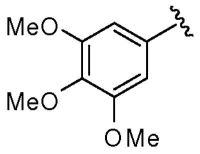
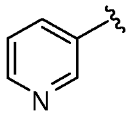
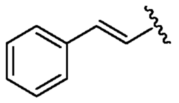

R1
O
R2
NH2NHCOMe
Me
O
N
N
R2
R1
HO

Table 1. Synthesis of 1-Acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles.[a]

entry	R^1	R^2	product	yield (%)[b]
1	Ph	Ph	16	77
2	Ph	p-$EtO_2CC_6H_4$	17	86
3	Ph	n-Bu	18	60
4	Ph		19	47
5	2-naphthyl	Ph	20	79
6	p-FC_6H_4	Ph	21	95
7	p-ClC_6H_4	Ph	22	78[c]
8	p-BrC_6H_4	Ph	23	72
9	p-$CF_3C_6H_4$	Ph	24	96
10	p-NCC_6H_4	Ph	25	71

11	*p*-*t*-BuC_6H_4	Ph	26	65
12		Ph	27	71
13		CH_3	28	78
14	*p*-$Me_2NC_6H_4$	Ph	29	53[d]
15	*o*-MeC_6H_4	Ph	30	64[d]
16		Ph	31	93
17		Ph	32	68

a) All reactions were carried out using 1.0 mmol of alkynone, 2.0 mmol of acetylhydrazine in toluene (5 mL) at 80 °C for 6 h unless otherwise specified. b) Isolated yields after column chromatography. c) X-ray crystallographic data are available for this compound in the supporting information. d) The reaction required 24 h to reach completion.

With the desired 1-acetyl-5-hydroxy-4,5-dihydropyrazole derivatives in hand, we studied the scope of the ICl-induced dehydration/iodination process (Table 2). Under our optimized conditions, pyrazole 33 was obtained in an excellent yield (Table 2, entry 1). Substitution of the phenyl ring in the R^2 group by an electron-withdrawing CO_2Et group afforded a slightly lower yield of 34 as compared to the parent system (Table 2, compare entries 1 and 2). Replacing the aryl moiety with an alkyl group also led to the desired pyrazole 35 in an excellent yield (Table 2, entry 3). Unfortunately, introducing a vinylic group in the R^2 position led to only a low yield of the desired pyrazole 36 (Table 2, entry

4). Pyrazole 36 was observed by ^{1}H NMR spectroscopy. However, inseparable impurities alongside the product could not be removed by column chromatography. The lower yield may be attributed to the generation of HCl in the reaction mixture, which may cause unwanted side reactions with the 1-cyclohexenyl group or perhaps the ICl is reacting directly with the carbon-carbon double bond.

We have also studied the effect of varying the nature of the R^1 group, while retaining R^2 as a phenyl group. When R^1 is a 2-naphthyl group, the reaction proceeded smoothly and gave an excellent yield of the pyrazole 37, which is comparable to the yield of the parent system (Table 2, compare entries 1 and 5). Phenyl groups bearing an F, Cl or Br in the 4-position all provided the corresponding 4-iodopyrazoles 38, 39 and 40 respectively in good yields (Table 2, entries 6-8). The structure of compound 39 has been confirmed by X-ray analysis. The presence of a CF_3 group in the 4-position of the aromatic ring also provided the desired 4-iodopyrazole 41 in a good yield (Table 2, entry 9). Introducing an electron-withdrawing CN group into the 4-position of the phenyl group of R^1 provided only a modest yield of 4-iodopyrazole 42 and a dramatic increase in the required reaction time was noted (Table 2, entry 10). Increasing the amount of ICl only provided a modest increase in yield and the results were within experimental error. Electron-rich aromatic rings, including 4-t-BuC_6H_4 and 3,4-methylenedioxyphenyl, provided good yields of 43 and 44 respectively (Table 2, entries 11 and 12). To examine the effect of steric bulk on the benzene ring, we employed compound 30 under our optimized reaction conditions. The reaction proceeded, although an increased reaction time was required and only a moderate yield of 45 was obtained. Unfortunately, 45 could not be separated from its non-halogenated counterpart (Table 2, entry 13). When R^1 was a p-$Me_2NC_6H_4$ or 3-

pyridyl group, the reaction provided none of the desired 4-iodopyrazoles (Table 2, entries 14 and 15). Despite employing 10 equiv of ICl, 31 failed to react. This observation may be a result of the basic nitrogen atoms tying up the Lewis acidic ICl, preventing it from effecting the desired dehydration reaction. Additional equivalents of ICl were not attempted in the case of compound 29 because of the likelihood of an unwanted side reaction caused by iodination of the *p*-$Me_2NC_6H_4$ moiety through electrophilic aromatic substitution. Compound 28 was subjected to our dehydration conditions in order to study the effect of an electron-rich ring in the R^1 position and a sterically compact group in the R^2 position. This reaction suffered from extended reaction times and the corresponding pyrazole, minus an iodine moiety, was detected as the major side product by ^1H NMR spectroscopy, along with 4-iodopyrazole 46 (Table 2, entry 16).

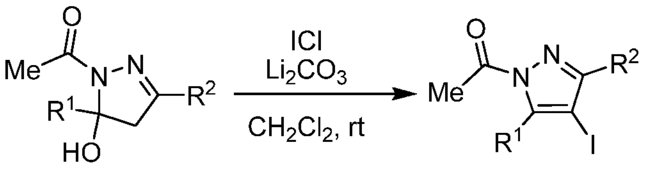
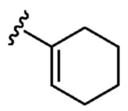
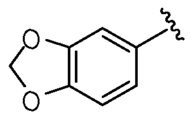
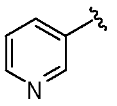
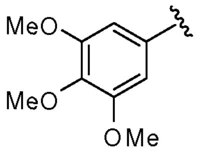


Table 2. Synthesis of 1-Acetyl-4-iodopyrazoles.[a]

entry	R^1	R^2	time (h)	product	yield (%)[b]
1	Ph	Ph	0.75	33	95
2	Ph	*p*-$EtO_2CC_6H_4$	1	34	75
3	Ph	*n*-Bu	0.75	35	97
4	Ph		0.75	36	37[c]

5	2-naphthyl	Ph	0.75	37	96
6	*p*-FC_6H_4	Ph	1	38	84
7	*p*-ClC_6H_4	Ph	1	39	87[d]
8	*p*-BrC_6H_4	Ph	1	40	82
9	*p*-$CF_3C_6H_4$	Ph	1	41	71
10	*p*-NCC_6H_4	Ph	12	42	56[e]
11	*p*-*t*-BuC_6H_4	Ph	1	43	90
12		Ph	1	44	93
13	*o*-MeC_6H_4	Ph	12	45	60[f]
14	*p*- $Me_2NC_6H_4$	Ph	24		0
15		Ph	24		0
16		CH_3	12	46	41[f]

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a) Unless otherwise stated, all reactions were carried out in CH_2Cl_2 (10 mL/mmol) at room temperature using 2.0 equiv of Li_2CO_3 and 3.0 equiv of ICl. b) Isolated yields after column chromatography. c) Yield determined by NMR spectroscopy. d) X-ray crystallographic data are available for this compound in the supporting information. e) Four equiv of ICl were used. f) Yield determined by NMR spectroscopy. Non-halogenated pyrazole is the major side product.

The advantage of this methodology is that 1-acyl-4-iodo-3,5-disubstituted-1*H*-pyrazoles can be synthesized selectively from the corresponding alkynones under mild reaction conditions. To the best of our knowledge, the iodination of 1-acylpyrazoles has not been reported, although bromination has.[26] Aryl iodides generally react more readily than their bromine counterparts in the presence of palladium catalysts due to more facile oxidative addition. 1-Acyl-4-halopyrazoles have demonstrated their importance as intermediates for palladium-catalyzed Sonogashira cross-coupling reactions leading to compounds of pharmacological interest. [27] Also, the palladium-catalyzed Heck[28] cross-coupling of 1-acyl-4-halopyrazoles has been demonstrated. In addition, another advantage of this methodology is the fact that the acylation of pyrazoles often gives a mixture of *N*-acylated products,[13,29] leading to unwanted and often inseparable product mixtures, where our process eliminates this problem. We believe that this approach to substituted pyrazoles should be quite useful in synthesis, considering the many ways one can transform the resulting iodine functional group by catalytic methods other than those described above.

Conclusions

A number of new 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been synthesized in good to excellent yields from 2-alkyn-1-ones. 3,5-Disubstituted-1-acyl-4-iodo-1*H*-pyrazoles have been synthesized in moderate to excellent yields by a novel dehydration/iodination of 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles under mild reaction conditions. Our methodology is fairly general and provides a selective route to

1-acyl-4-iodopyrazoles. To the best of our knowledge, this is the first report of an ICl-induced dehydration of a heterocyclic derivative that provides iodinated pyrazoles.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. THF and CH_2Cl_2 were distilled from sodium/benzophenone or CaH_2 respectively, under an atmosphere of argon prior to use. All glassware and stirring bars were oven dried prior to use. The high-resolution mass spectra were recorded using EI at 70 eV. The following starting materials were made according to literature procedures: 1,3-diphenylprop-2-yn-1-one,[23a] 1-phenyl-2-butyn-1-one,[30] 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one,[31] ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate,[10a] 3-phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-one,[10a] 3-phenyl-1-*o*-tolylprop-2-yn-1-one,[10a] 1-(3,4,5-trimethoxyphenyl)but-2-yn-1-one,[10a] 3-phenyl-1-(pyridin-3-yl)prop-2-yn-1-one,[10a] 1-[4-(dimethylamino)phenyl]-3-phenylprop-2-yn-1-one,[10a] 1-(benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-one,[10a] 3-(cyclohex-1-enyl)-1-phenylprop-2-yn-1-one,[10b] 4-(3-phenylpropynoyl)benzonitrile,[32] 1-(4-bromophenyl)-3-phenylprop-2-yn-1-one[33] and 1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-one.[34]

General procedure for the preparation of alkynones from acetyl chlorides. To a 25 mL flask were added CuI (0.05 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of benzoyl chloride (3.25 mmol, 1.3 equiv). If the acid chloride is a solid, it was added as a THF solution. The resulting mixture was allowed to stir at room temperature overnight, filtered through a plug of silica gel, and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkynone.

3-[(4-*tert*-Butyl)phenyl]-1-phenylpropynone. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 538 mg (82%) of the product with spectral properties identical to those previously reported.

1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 488 mg (87%) of the product with spectral properties identical to those previously reported.[35]

General procedure for preparation of the 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles. The alkynone (1.0 mmol), acetyl hydrazide (2.0 mmol, 148.2 mg) in toluene (5 mL) were heated to 80 °C with stirring. The reaction was monitored by TLC until the reaction was complete. The solution was concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using CH_2Cl_2/EtOAc as the eluent.

1-Acetyl-3,5-diphenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (16). The product was obtained as a colorless solid: mp 139-141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 1H), 3.33-3.39 (d, *J* = 18.3 Hz, 1H), 3.67-3.73 (d, *J* = 18.2 Hz, 1H), 5.12 (s, 1H), 7.29-7.43 (m, 8H), 7.69-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.52, 50.74, 94.04, 124.11, 126.76, 128.37, 129.01, 130.74, 131.36, 143.98, 152.84, 171.08 (1 peak missing due to overlap); HRMS Calcd for $C_{17}H_{16}N_2O_2$: 280.1212. Found: 280.1221.

Ethyl-4-(1-acetyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)benzoate (17). The product was obtained as a pale yellow solid: mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 3.35-3.40 (d, *J* = 18.3 Hz, 1H), 3.69-3.73 (d, *J* = 18.3 Hz, 1H), 4.37-4.42 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 7.29-7.43 (m, 5H), 7.75-7.77 (d, *J* = 8.4 Hz, 2H), 8.07-8.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.49, 22.50, 61.44, 94.15, 123.98, 126.48, 128.94, 130.04, 131.99, 135.26, 143.58, 151.65, 166.04, 171.09; HRMS Calcd for $C_{20}H_{20}N_2O_4$: 352.1423. Found: 352.1411.

1-Acetyl-3-butyl-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazole (18). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.35-1.42 (m, 2H), 1.53-1.62 (m, 2H), 2.32 (s, 3H), 2.35 (t, *J* = 7.7 Hz, 2H), 2.88-2.94 (d, *J* = 18.6 Hz, 1H), 3.23-3.30 (d, *J* = 18.5 Hz, 1H), 7.25-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.37, 22.55, 28.53, 30.12, 52.87, 93.31, 123.97, 128.11, 128.84, 144.12, 157.98, 170.58; HRMS Calcd for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1526.

1-Acetyl-3-(1-cyclohexenyl)-5-hydroxy-5-phenyl-4,5-dihydro-1*H*-pyrazole (19). The product was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63-1.71 (m, 4H), 2.18 (br s, 2H), 2.34 (s, 3H), 2.43 (br s, 2H), 3.07-3.13 (d, *J* = 17.8 Hz, 1H), 3.39-3.45 (d, *J* = 17.9 Hz, 1H), 5.09 (s, 1H), 5.98-6.01 (m, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.13, 22.19, 22.28, 24.37, 26.15, 49.97, 93.49, 123.99, 128.06, 128.78, 131.80, 134.08, 144.14, 154.86, 170.80; HRMS Calcd for $C_{17}H_{20}N_2O_2$: 284.1525. Found: 284.1528.

1-Acetyl-5-hydroxy-5-(2-naphthyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (20). The product was obtained as a pale yellow oily solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 3.38-3.42 (d, *J* = 18.3 Hz, 1H), 3.71-3.76 (d, *J* = 18.2 Hz, 1H), 5.31 (s, 1H), 7.36-7.47 (m, 6H), 7.69-7.71 (m, 2H), 7.77-7.83 (m, 3H), 7.93-7.94 (d, *J* = 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.49, 50.61, 93.99, 122.06, 122.95, 126.42, 126.56, 126.66, 127.72, 128.49, 128.88, 129.03, 130.64, 131.20, 133.11, 133.18, 141.07, 152.81, 171.01; HRMS Calcd for $C_{21}H_{16}N_2O$ (M^+ - H_2O): 312.1263. Found: 312.1263.

1-Acetyl-5-(4-fluorophenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (21). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H), 3.29-3.34 (d, *J* = 18.2 Hz, 1H), 3.67-3.71 (d, *J* = 18.2 Hz, 1H), 5.34 (br s, 1H), 6.99-7.04 (m, 2H), 7.36-7.42 (m, 5H), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.49, 50.73, 93.54, 115.56, 115.78, 125.91, 125.99, 126.64, 128.89, 130.70, 131.09, 139.73, 139.76, 152.76, 161.26, 163.72, 170.99 (extra peaks due to C-F splitting); HRMS Calcd for $C_{17}H_{15}FN_2O_2$: 298.1118. Found: 298.1108.

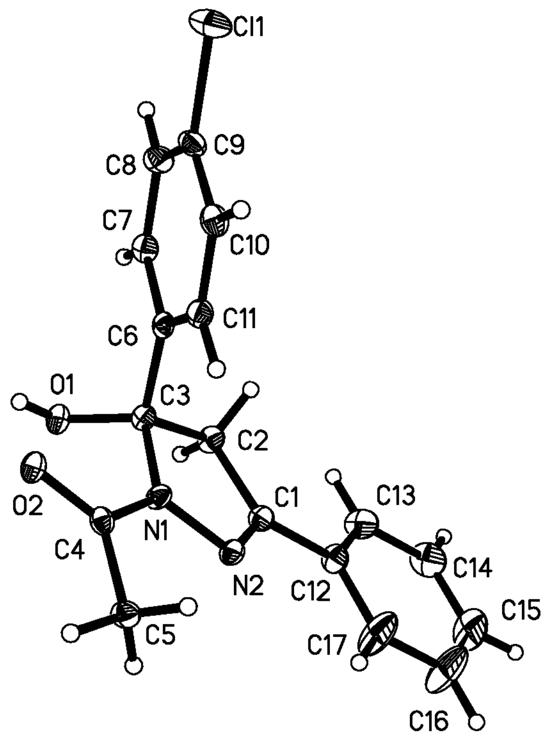

FIGURE 1: X-Ray Crystal Structure of Product 22.

1-Acetyl-5-(4-chlorophenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (22). The product was obtained as a pale yellow solid: mp 138-140 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.41 (s, 3H), 3.24-3.30 (d, J = 18.3 Hz, 1H), 3.62-3.68 (d, J = 18.3 Hz, 1H), 5.40 (br s, 1H), 7.20-7.41 (m, 8H), 7.65-7.69 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 22.36, 50.57, 93.22, 125.55, 126.54, 128.79, 130.59, 130.94, 133.82, 142.36, 152.61, 170.71 (1 peak missing due to overlap); HRMS Calcd for $C_{17}H_{15}ClN_2O_2$: 314.0822. Found: 314.0826.

1-Acetyl-5-(4-bromophenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (23). The product was obtained as a pale yellow solid: mp 168-169 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.43 (s, 3H), 3.29-3.36 (d, J = 18.3 Hz, 1H), 3.67-3.73 (d, J = 18.3 Hz, 1H), 5.13 (br s, 1H), 7.27-7.32 (m, 2H), 7.40-7.51 (m, 5H), 7.68-7.72 (m, 2H); ^{13}C NMR (CDCl$_3$) δ

22.43, 50.56, 93.53, 122.39, 126.00, 126.73, 129.00, 130.85, 131.06, 132.08, 143.04, 152.83, 171.14; HRMS Calcd for $C_{17}H_{13}BrN_2O$ (M^+ - H_2O): 340.0211. Found: 340.0200.

1-Acetyl-5-hydroxy-3-phenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (24). The product was obtained as a colorless solid: mp 169-171 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 3.32-3.37 (d, *J* = 18.3 Hz, 1H), 3.71-3.75 (d, *J* = 18.4 Hz, 1H), 5.24 (s, 1H), 7.40-7.45 (m, 3H), 7.54-7.56 (d, *J* = 8.1 Hz, 2H), 7.61-7.64 (d, *J* = 8.3 Hz, 2H), 7.70-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.46, 50.62, 93.41, 115.51, 124.66, 125.58, 125.85, 125.99, 126.02, 126.06, 126.10, 126.72, 126.74, 126.76, 126.77, 129.01, 129.03, 129.04, 129.19, 130.37, 130.69, 130.92, 130.95, 147.68, 147.70,152.87, 171.20 (extra peaks due to C-F splitting); HRMS Calcd for $C_{18}H_{13}F_3N_2O$ (M^+ - H_2O): 330.0988. Found: 330.0980.

1-Acetyl-5-(4-cyanophenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (25). The product was obtained as a colorless solid: mp 179-180 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 3.30-3.35 (d, *J* = 18.4 Hz, 1H), 3.70-3.75 (d, *J* = 18.3, 1H), 5.19 (s, 1H), 7.40-7.48 (m, 3H), 7.53-7.55 (d, *J* = 8.4 Hz, 2H), 7.65-7.67 (d, *J* = 8.3 Hz, 2H), 7.70-7.72 (dd, *J* = 1.7, 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.35, 50.47, 93.10, 112.18, 118.61, 125.09, 126.70, 128.98, 130.72, 130.96, 132.80, 148.80, 152.81, 171.09; HRMS Calcd for $C_{18}H_{15}N_3O_2$: 305.1164. Found: 305.1165.

1-Acetyl-5-(4-*tert*-butylphenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (26). The product was obtained as a pale yellow solid: mp 199-201 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 2.44 (s, 3H), 3.33-3.37 (d, *J* = 18.2 Hz, 1H), 3.65-3.70 (d, *J* = 18.2 Hz, 1H), 5.13 (s, 1H), 7.31-7.40 (m, 7H), 7.68-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.51, 31.48, 34.66, 50.62, 93.99, 123.70, 125.78, 126.62, 128.84, 130.56, 131.29, 140.81, 150.99, 152.78, 170.93; HRMS Calcd for $C_{21}H_{24}N_2O_2$: 336.1838. Found: 336.1831.

1-Acetyl-5-hydroxy-5-(3,4-methylenedioxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (27). The product was obtained as a light brown solid: mp 138-140 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.30-3.36 (d, *J* = 18.3 Hz, 1H), 3.64-3.70 (d, *J* = 18.3 Hz, 1H), 5.10 (br s, 1H), 5.93 (s, 2H), 6.75-6.78 (d, *J* = 8.1 Hz, 1H), 6.86-6.93 (m, 2H), 7.39-7.42 (m, 3H), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.47, 50.67, 93.87, 101.46, 105.04, 108.44, 117.38, 126.66, 128.91, 130.67, 131.24, 138.12, 147.55, 148.25, 152.81, 11.06; HRMS Calcd for $C_{18}H_{16}N_2O_4$: 324.1110. Found: 324.1120.

1-Acetyl-5-hydroxy-3-methyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole (28). The product was obtained as a yellow solid: mp 108-111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06, (s, 3H), 2.34 (s, 3H), 2.90-2.95 (d, *J* = 18.8 Hz, 1H), 3.23-3.27 (d, *J* = 18.8 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 6H), 5.16 (s, 1H), 6.57 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 16.08, 22.29, 54.31, 56.10, 60.72, 93.41, 100.92, 137.42, 139.65, 153.38, 154.52, 170.44; HRMS Calcd for $C_{15}H_{20}N_2O_5$: 308.1372. Found: 308.1364.

1-Acetyl-5-(4-(*N,N*-dimethylamino)phenyl)-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (29). The product was obtained as an orange solid: mp 123-125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 2.91 (s, 6H), 3.32-3.38 (d, *J* = 18.3 Hz, 1H), 3.64-3.70 (d, *J* = 18.3, 1H), 5.08 (s, 1H), 6.67-6.70 (d, *J* = 9.0 Hz, 2H), 7.24-7.27 (d, *J* = 9.0 Hz, 2H), 7.38-7.40 (m, 3H), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.47, 40.59, 50.59, 94.17, 112.48, 124.86, 126.58, 128.82, 130.45, 131.47, 131.55, 150.36, 152.76, 170.86; HRMS Calcd for $C_{19}H_{21}N_3O_2$: 323.1634. Found: 323.1622.

1-Acetyl-5-hydroxy-5-(2-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (30). The product was obtained as a pale yellow solid: mp 135-137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (br s, 3H), 2.46 (s, 3H), 3.36-3.40 (d, *J* = 18.4 Hz, 1H), 3.70-3.74 (d, *J* = 18.4 Hz, 1H), 5.21 (br s, 1H), 7.16-7.23 (m, 3H), 7.38-7.40 (m, 4H), 7.69-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.87, 22.45, 49.08, 94.26, 125.20, 126.05, 126.62, 128.42, 128.83, 130.59, 131.13, 132.59, 134.57, 140.35, 153.41, 171.13; HRMS Calcd for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1367.

1-Acetyl-5-hydroxy-3-phenyl-5-(3-pyridinyl)-4,5-dihydro-1*H*-pyrazole (31). The product was obtained as a pale orange solid: mp 154-157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.52-3.38 (d, *J* = 18.3 Hz, 1H), 3.70-3.76 (d, *J* = 18.3 Hz, 1H), 5.79 (br s, 1H), 7.24-7.28 (m, 1H), 7.39-7.43 (m, 3H), 7.67-7.75 (m, 3H), 8.51-8.52 (d, *J* = 3.6 Hz, 1H), 8.67-8.68 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.37, 50.69, 92.33, 123.42, 126.61, 128.86, 130.73, 130.88, 132.12, 139.32, 146.15, 149.27, 152.58, 170.86; HRMS Calcd for $C_{16}H_{15}N_3O_2$: 281.1164. Found: 281.1173.

1-Acetyl-5-hydroxy-3-phenyl-5-styryl-4,5-dihydro-1*H*-pyrazole (32). The product was obtained as an orange oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 3.39-3.43 (d, *J* = 18.4 Hz, 1H), 3.52-3.57 (d, *J* = 18.4 Hz, 1H), 5.05 (br s, 1H), 6.54-6.58 (d, *J* = 16.0 Hz, 1H), 6.71-6.75 (d, *J* = 16.0 Hz, 1H), 7.23-7.31 (m, 2H), 7.37-7.42 (m, 6H), 7.69-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.57, 47.77, 92.56, 126.59, 127.01, 128.23, 128.70, 128.88, 129.71, 130.33, 130.59, 131.27, 135.81, 152.99, 171.09; HRMS Calcd for $C_{19}H_{18}N_2O_2$: 306.1368. Found: 306.1374.

General procedure for dehydration/iodination of 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles using ICl. The appropriate 1-acetyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (0.25 mmol) and finely powdered Li_2CO_3 (0.5 mmol) in CH_2Cl_2 (2.5 mL) were allowed to stir vigorously for 5 min. at room temperature. To the vigorously stirred slurry, in the absence of light, was added a freshly prepared solution of ICl (1M in CH_2Cl_2, 3.0 equiv) slowly and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a satd aq soln of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

1-Acetyl-4-iodo-3,5-diphenyl-1*H*-pyrazole (33). The product was obtained as an off white solid: mp 86-88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.75 (s, 3H), 7.34-7.38 (dd, *J* = 3.8, 7.4 Hz, 2H), 7.44-7.53 (m, 6H), 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.08, 71.67, 128.39, 128.59, 128.91, 129.36, 129.54, 129.82, 131.37, 131.88, 148.09, 154.28, 169.37; HRMS Calcd for $C_{17}H_{13}IN_2O$: 388.0073. Found: 388.0073.

1-Acetyl-3-(4-(ethoxycarbonyl)phenyl)-4-iodo-5-phenyl-1*H*-pyrazole (34). The product was obtained as an off white solid: mp 105-107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41-1.45 (t, *J* = 7.2 Hz, 3H), 2.76 (s, 3H), 4.39-4.46 (q, *J* = 7.2 Hz, 2H), 7.35-7.38 (m, 2H), 7.48-7.50 (m, 3H), 8.02-8.05 (dd, *J* = 1.8, 6.6 Hz, 2H), 8.16-8.19 (td, *J* = 1.8, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.53, 23.06, 61.37, 71.30, 128.44, 128.79, 129.48, 129.78, 131.11, 131.23, 136.11, 148.38, 153.19, 166.39, 169.28 (1 peak missing due to overlap); HRMS Calcd for $C_{20}H_{17}IN_2O_3$: 460.0284. Found: 460.0292.

1-Acetyl-3-butyl-4-iodo-5-phenyl-1*H*-pyrazole (35). The product was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97-1.02 (t, *J* = 7.3 Hz, 3H), 1.41-1.53 (m, 2H), 1.68-1.78 (m, 2H), 2.64-2.69 [(m (a singlet merged with a triplet) 5H)], 7.30-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.71, 23.10, 28.58, 30.43, 74.14, 128.26, 129.18, 129.72, 131.37, 146.84, 157.05, 169.28; HRMS Calcd for $C_{15}H_{17}IN_2O$: 368.0386. Found: 368.0382.

1-Acetyl-4-iodo-5-(naphthalen-2-yl)-3-phenyl-1H-pyrazole (37). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (s, 3H), 7.41-7.56 (m, 6H), 7.88-7.95 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 23.09, 72.03, 126.56, 127.07, 127.08, 127.96, 128.06, 128.53, 128.59, 128.68, 128.91, 129.49, 129.55, 131.86, 132.98, 133.51, 147.95, 154.40, 169.34; HRMS Calcd for $C_{21}H_{15}IN_2O$: 438.0229. Found: 438.0237.

1-Acetyl-3-(4-fluorophenyl)-4-iodo-5-phenyl-1*H*-pyrazole (38). The product was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (s, 3H), 7.15-7.19 (t, *J* = 8.7 Hz, 2H), 7.34-7.37 (m, 2H), 7.46-7.52 (m, 3H), 7.90-7.92 (dd, *J* = 1.8, 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.16, 72.13, 115.56, 115.78, 127.24, 127.27, 128.15, 128.66, 128.91, 129.65, 131.77, 131.88, 131.96, 147.13, 154.36, 162.07, 164.54, 169.55 (extra peaks due to C-F splitting); HRMS Calcd for $C_{17}H_{12}FIN_2O$: 405.9978. Found: 405.9973.

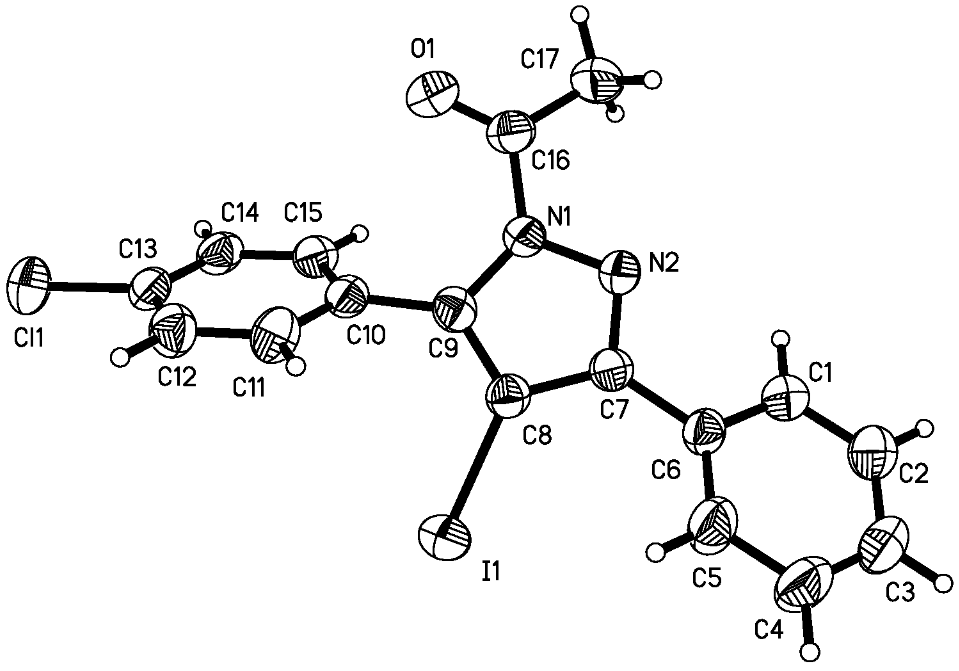

FIGURE 2: X-Ray Crystal Structure of Product 39.

1-Acetyl-3-(4-chlorophenyl)-4-iodo-5-phenyl-1*H*-pyrazole (39). The product was obtained as a pale yellow solid: mp 128-130 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.74 (s, 3H), 7.28-7.32 (td, *J* = 2.1. 8.7 Hz, 2H), 7.43-7.50 (m, 5H), 7.89-7.92 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 23.04, 71.97, 128.63, 128.76, 128.88, 129.64, 129.71, 131.29, 131.67, 135.49, 146.87, 154.41, 169.46; HRMS Calcd for $C_{17}H_{12}ClIN_2O$: 421.9683. Found: 421.9691.

1-Acetyl-3-(4-bromophenyl)-4-iodo-5-phenyl-1*H*-pyrazole (40). The product was obtained as a pale yellow solid: mp 134-137 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.74 (s, 3H), 7.23-7.25 (d, *J* = 8.5 Hz, 2H), 7.47-7.49 (m, 3H), 7.50-7.62 (m, 2H), 7.89-7.91 (dd, *J* = 1.9, 7.7 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 23.07, 71.93, 126.82, 128.62, 128.86, 129.63, 130.19, 131.50, 131.64, 131.69, 146.86, 154.42, 169.43; HRMS Calcd for $C_{17}H_{12}BrIN_2O$: 465.9178. Found: 465.9186.

1-Acetyl-4-iodo-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (41). The product was obtained as a colorless solid: mp 98-101 ºC; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.76 (s, 3H), 7.49-7.53 (m, 5H), 7.73-7.75 (d, *J* = 8.2 Hz, 2H), 7.90-7.92 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 22.97, 72.00, 125.37, 125.40, 125.44, 125.48, 128.12, 128.66, 128.85, 128.89, 129.73, 130.31, 130.39, 131.08, 131.53, 135.07, 146.52, 154.59, 169.44 (extra peaks due to C-F splitting); HRMS Calcd for $C_{18}H_{12}F_3IN_2O$: 455.9946. Found: 455.9956.

1-Acetyl-3-(4-cyanophenyl)-4-iodo-5-phenyl-1*H*-pyrazole (42). The product was obtained as a pale yellow solid: mp 170-172 ºC; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.76 (s, 3H), 7.48-7.52 (m, 5H), 7.76-7.79 (m, 2H), 7.89-7.91 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 22.90, 72.04, 113.18, 118.66, 128.70, 128.87, 129.81, 130.80, 131.36, 132.19, 136.12, 145.94, 154.72, 169.43; HRMS Calcd for $C_{18}H_{12}IN_3O$: 413.0025. Found: 413.0026.

1-Acetyl-3-(4-*tert*-butylphenyl)-4-iodo-5-phenyl-1*H*-pyrazole (43). The product was obtained as a pale yellow oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.37 (s, 9H), 2.74 (s, 3H), 7.29-7.31 (dd, *J* = 2.0, 6.6 Hz, 2H), 7.46-7.51 (m, 5H), 7.90-7.93 (dd, *J* = 1.6, 7.9 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 23.20, 31.52, 35.02, 71.71, 125.26, 128.10, 128.13, 128.55, 128.91, 129.47, 131.94, 148.21, 152.22, 154.30, 169.49; HRMS Calcd for $C_{21}H_{21}IN_2O$: 444.0699. Found: 444.0707.

1-Acetyl-4-iodo-3-(3,4-methylenedioxyphenyl)-5-phenyl-1*H*-pyrazole (44). The product was obtained as a pale yellow solid: mp 101-103 ºC; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.76 (s, 3H), 6.03 (s, 2H), 6.81-6.92 (m, 3H), 7.47-7.49 (m, 3H), 7.88-7.92 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 23.15, 72.07, 101.61, 108.39, 110.26, 110.33, 123.90, 124.55, 128.56, 128.85, 129.52, 131.84, 147.66, 148.51, 154.17, 169.39; HRMS Calcd for $C_{18}H_{13}IN_2O_3$: 431.9971. Found: 431.9980.

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Chapter 4. The Synthesis of Oxazolium Salts by Iodocyclization of Alkynamides. Efforts Towards Dequaternization

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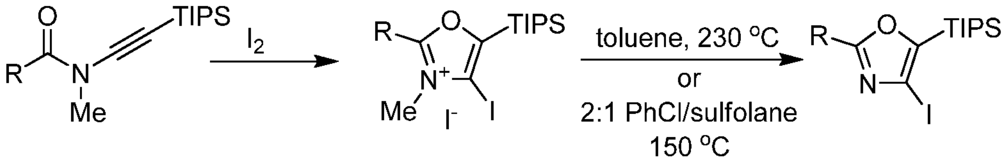
Abstract



Oxazolium salts are readily prepared by the iodine-induced cyclization of alkynamides. These oxazolium iodide salts are highly stable and attempts at their dequaternization have been met with limited success.

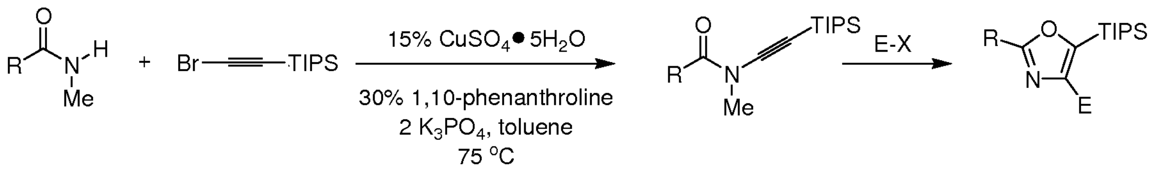
Introduction

Oxazoles have become the focus of many synthetic efforts due to their wide occurrence in natural products.[1] A number of compounds with the oxazole core have been examined as antitumor agents, antileukemia agents, antiviral agents, antifungal agents, ichthyotoxic agents, herpes simplex virus type 1 (HSV-1) inhibitors, serine-threonine phosphatase inhibitors, antibacterial agents, antialgicidal agents, and peripheral analgesics.[2] Oxazoles have also proven to be useful intermediates in the synthesis of a variety of biologically interesting scaffolds.[3,4] Though an assortment of synthetic methods for the construction of the oxazole core exist in the literature,[5] the demand for facile syntheses of this important class of heterocycle still remain.

The Larock group and others have studied electrophile-induced annulations of functionally substituted alkynes to form various heterocycles and carbocycles over the years, including benzo[*b*]thiophenes,[6] isoquinolines and naphthyridines,[7] isocoumarins and α-pyrones,[8] benzofurans,[9] furans,[10] indoles,[11] furopyridines,[12] cyclic carbonates,[13] 2,3-dihydropyrroles and pyrroles,[14] pyrilium salts and isochromenes,[15] bicyclic β-lactams,[16] 2*H*-benzopyrans,[17] naphthalenes and 2-naphthols,[18] chromones,[19] isoindolin-1-ones,[20] benzo[*b*]selenophenes[21] and isoxazoles.[22]

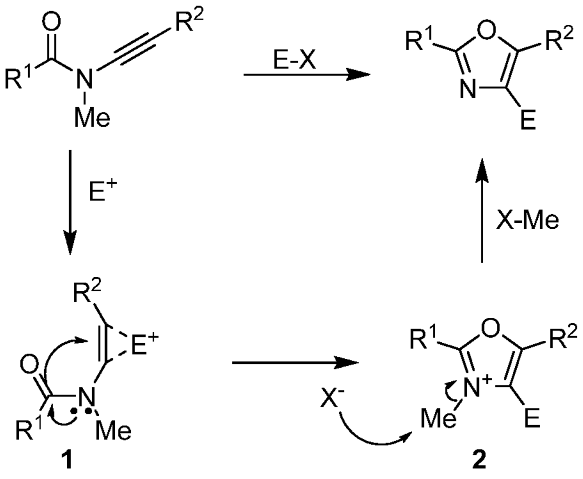
With convenient copper-catalyzed approaches to alkynamides presently available,[23] we reasoned that their electrophilic cyclization should afford oxazoles (Scheme 1).

Scheme 1



The proposed mechanism for the formation of an oxazole from an alkynamide is outlined in Scheme 2. This involves coordination of the electrophile to the triple bond, which leads to cation 1, followed by intramolecular nucleophilic attack by the oxygen of the amide to provide intermediate 2, and subsequent demethylation by the counterion to afford the oxazole.

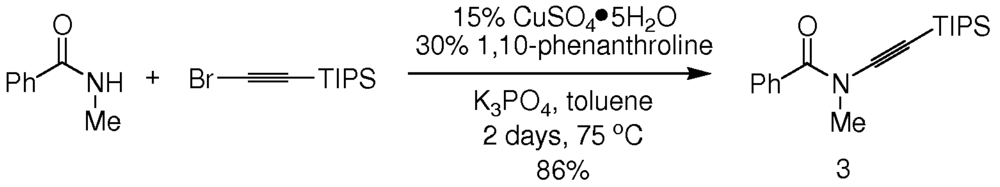
Scheme 2



This chapter describes our efforts to synthesize new oxazolium iodides and oxazoles by the electrophilic cyclization of alkynamides.

Results and Discussion

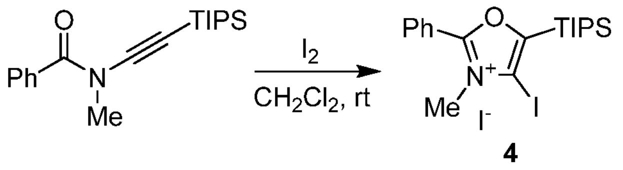
To examine the electrophilic cyclization process, we prepared the alkynamide 3 by the copper-catalyzed cross-coupling of *N*-methylbenzamide with 1-bromo-2-(triisopropylsilyl)acetylene (eq 1).



(1)

With alkynamide 3 in hand, we employed iodine electrophiles in the electrophilic cyclization process using CH_2Cl_2 as the solvent. ICl proved unsuccessful as an electrophile, providing only adducts arising from ICl addition across the triple bond. However, I_2 showed promise as an electrophile. Complete conversion of the alkynamide was observed when stirring at room temperature for 12 h in CH_2Cl_2. The resulting product was extremely polar and could not be isolated by column chromatography on silica gel. The compound was finally isolated pure by crystallization from methanol.

Unfortunately, ^{1}H NMR spectroscopic analysis revealed that the *N*-methyl group was still present in the product. As expected the *N*-methyloxazolium iodide salt 4 is apparently formed, but fails to undergo demethylation to the desired oxazole under our reaction conditions (eq 2). This assumption is based on four pieces of information: (i) the formation of a highly polar molecule as judged by silica gel TLC, (ii) the mass of the isolated compound was higher than the theoretical mass of the parent oxazole, (iii) a downfield shift of the *N*-Me protons[24] in the ^{1}H NMR spectrum relative to the *N*-methyl alkynamide, and (iv) mass spectroscopic analysis indicating a loss of methyl iodide in addition to a peak at m/z = 427. The proposed structure of oxazolium salt 4 was ultimately proven by x-ray crystallography (Figure 1).


O
TIPS
Ph
N
Me
I2
CH2Cl2, rt
Ph
O
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N+
Me
I-
I
4

(2)

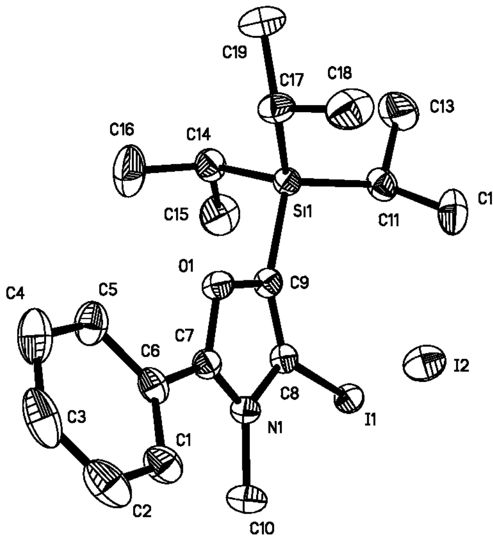

C19
C17
C18
C13
C16
C14
C15
Si1
C11
C12
O1
C9
C4
C5
C7
C6
C8
I2
C3
C1
N1
I1
C2
C10

Figure 1. ORTEP diagram of 4

With success in the electrophilic cyclization process, we focused our attention on demethylation of the oxazolium salt 4 (Table 1). Our initial efforts at demethylating 4 focused on increasing the amount of iodide ion in the reaction mixture. We reasoned that an increase in the concentration of the nucleophilic counter ion could promote demethylation of 4 and lead to oxazole 5. Thus, LiI was employed under various reaction conditions using CH_2Cl_2, CH_3CN and DMF as solvents at various temperatures (Table 1, entries 1-6). Unfortunately, these reactions did not provide any significant amount of 5. Organic bases, such as pyridine and DABCO, were also employed in attempts to dequaternize 4 (Table 1, entries 7 and 8). However, these experiments did not produce any oxazole 5, although oxazolium bromides, tosylates and perchlorates have been dequaternized in the presence of refluxing pyridine.[25] Sodium sulfide and sodium thiophenoxide[26] were examined as nucleophiles in the dequaternization process, which led to 100% conversion of 4, but the only products isolated from these reactions appeared to be ring-opened products (Table 1, entries 9 and 10). Similar results have been reported in the literature when sodium hydrosulfide was allowed to react with *N*-methyl oxazolium salts.[27]

It has been reported in the literature that heating oxazolium salts to temperatures of 230 ^{o}C in toluene leads to oxazole products. Our attempts at thermal demethylation of 4 led to the desired 4-iodo-2-phenyl-5-(triisopropylsilyl)oxazole (5), but in only a modest yield (Table 1, entry 11). Adding pyridine to remove the dissociated methyl iodide did not improve the outcome of the demethylation (Table 1, entry 12). Use of the inorganic silver bases Ag_2CO_3 and AgOAc in ethanol led to complete conversion of 4, but the products were inseparable mixtures of 5, its desilylated counterpart, and another unidentifiable compound (Table 1, entries 13 and 14).

Triphenylphosphine has been reported to act as an alkyl halide scavenger in dequaternization reactions.[28] It has been suggested that dequaternization occurs by nucleophilic attack of the counterion and that the PPh_3 serves to absorb the alkyl halide, thus preventing the reverse reaction from taking place. When compound 4 was heated to 150 °C in DMF in the presence of PPh_3, no conversion of 4 was observed (Table 1, entry 15). When the solvent was changed to 2:1 PhCl/sulfolane under similar reaction conditions, 5 was isolated in a 68% yield (Table 1, entry 16). Unfortunately, this procedure was not reproducible as high yields could not be achieved when the experiment was repeated.

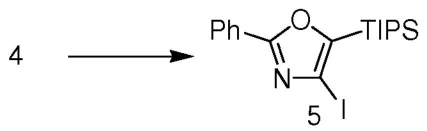


Table 1. Demethylation of 4-iodo-3-methyl-2-phenyl-5-(triisopropylsilyl)oxazolium iodide.[a]

entry	additive	temp. (°C)	solvent	time (h)	5 % yield[b]
1	LiI	r.t.	CH_2Cl_2	24	--[c]
2	LiI	reflux	CH_2Cl_2	24	--[c]
3	LiI	r.t.	CH_3CN	24	--[c]
4	LiI	reflux	CH_3CN	24	--[c]
5	LiI	reflux	CH_3CN	24	--[c]

6	LiI	150 °C	DMF	12	--[c]
7	--	reflux	pyridine	12	--[c]
8	DABCO	r.t.	CH_3CN	24	--[c]
9	Na_2S	r.t.	CH_3CN	6	0[d]
10	NaSPh	r.t.	CH_3CN	6	0[d]
11	--	230	toluene	0.15	48[e]
12	pyridine	230	toluene	0.15	44[e]
13	Ag_2CO_3	80	EtOH	6	22[f]
14	AgOAc	80	EtOH	6	27[f]
15	PPh_3	150	DMF	0.15	--[c]
16	PPh_3	150	PhCl:sulfolane 2:1	0.15	68

a) Unless otherwise stated, all reactions were carried out using 0.25 mmol of the crude product 4 from the iodine-induced cyclization of 3. b) Isolated yield after column chromatography. c) No reaction. d) Ring-opened products. e) The reaction was performed in a microwave reactor. f) Yield determined by ^{1}H NMR spectroscopy.

Since the demethylation of 4 proved difficult, other alkynamides were synthesized in order to test different leaving groups on the nitrogen atom (Table 2). For reasons of atom economy and the ready availability of substituted primary benzamides from commercial sources, benzamide was examined as a model alkynamide precursor. However, benzamide did not prove to be a good cross-coupling partner here, and none of the desired alkynamide was detected after 2 days of reaction (Table 2, entry 1). We felt that a *t*-Bu group might be promising, given that the Larock group has previously reported that acetylenic *t*-butylimines cyclize readily in the presence of electrophiles to provide isoquinolines in excellent yields under mild reaction conditions.[7] When *N*-*t*-butylbenzamide was subjected to the alkyne cross-coupling conditions, none of the desired alkynamide product was observed (Table 2, entry 2). This result might be due to the steric bulk of the *t*-Bu group hindering the cross-coupling reaction. *N*-(Trimethylsilyl)benzamide was also examined as a cross-coupling partner with alkynes, since it was felt that the longer C-Si bond length of a TMS group, compared with a *t*-Bu group, might allow for a successful cross-coupling. When R = TMS, the reaction proceeded to give complex mixtures with no sign of the desired alkynamide 8 (Table 2, entry 3). An *N*-MOM benzamide did not undergo cross-coupling either and none of the desired alkynamide 9 was observed (Table 2, entry 4). This reaction may not have proceeded, because of unfavorable chelation of the copper with the MOM-protected amide. *N*-Benzylbenzamide proved highly successful in the cross-coupling reaction and provided the corresponding alkynamide 10 in high yield (Table 2, entry 5). *N*-(4-Methoxybenzyl)benzamide reacted to form the desired ynamide 11, although the yield was poor (Table 2, entry 6). *N*-Allylbenzamide proved to be an average coupling partner with the bromosilylacetylene and a moderate yield of alkynamide 12 was achieved (Table 2, entry 7).

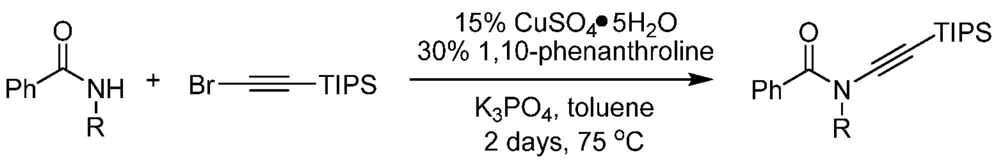


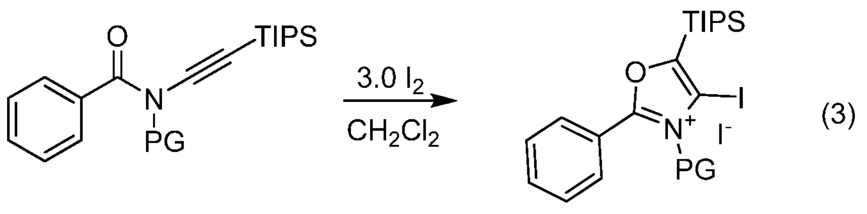
Table 2. Synthesis of alkynamides.[a]

entry	R	alkynamide	yield (%)[b]
1[c]	H	6	0
2	*t*-Bu	7	0
3	TMS	8	0
4	MOM	9	0
5	Bn	10	87
6	4-$MeOC_6H_4CH_2$	11	43
7	allyl	12	48

a) Unless otherwise specified, the reaction was carried out using 7.33 mmol of the amide, 1.0 equiv of 1-bromo-2-(triisopropylsilyl)acetylene, 15 mol % $CuSO_4{\bullet}5H_2O$, 30 mol % 1,10-phenanthroline, 1 equiv of K_3PO_4 in toluene (8 mL) at 75 °C for 2 days. b) Isolated yield after column chromatography. c) 3 Equiv of benzamide were used.

Attempts at deprotecting alkynamides 10 and 11 using HBr or CAN[29] (ceric ammonium nitrate) respectively to give alkynamide 6 did not provide any of the corresponding unprotected alkynamides.

N-Protected alkynamides 10, 11, and 12 were subjected to our I_2 cyclization conditions to form the corresponding oxazolium iodide salts 13, 14 and 15 respectively (eq 3). These iodocyclization reactions provided the expected oxazolium salts in good yields.

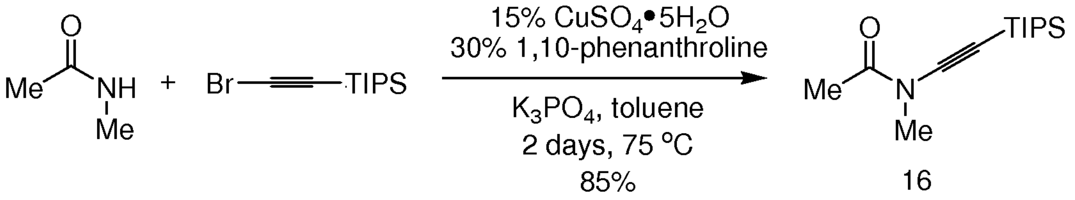


(3)

PG
13 Bn (94%)
14 4-$MeOC_6H_4CH_2$ (80%)
15 allyl (64%)

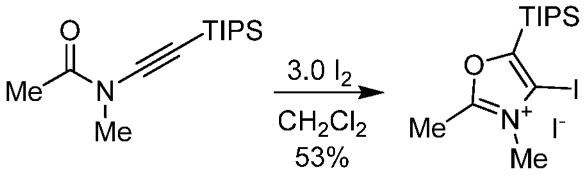
Oxazolium iodide 13 did not undergo deprotection in the presence of HBr, nor did oxazolium 14 undergo deprotection using CAN. Quaternary *N*-allyl ammonium salts have been deprotected in the presence of water or an amine base.[25] Our attempts at treating *N*-allyl oxazolium iodide 15 with H_2O, Et_2NH or Et_3N at room temperature or reflux, did not provide any of the desired oxazole product.

We speculate that these salts are extremely stable due to their conjugation with the lone pair of electrons on the oxygen atoms of the oxazolium ring, as well as the aromatic ring in the 2-position. To examine this hypothesis, we prepared alkynamide 16 by using the copper-catalyzed cross-coupling conditions (eq 4). We hoped that the diminished conjugation would destabilize the corresponding oxazolium salt.



(4)

When alkynamide 16 was subject to the iodine cyclization conditions, the reaction reached completion after 12 h. During the work-up, a soapy emulsion formed that could not be resolved. Presumably the emulsion is due to a less hydrophobic oxazolium salt, as compared with oxazolium iodides 4, 13, 14 and 15. Regardless, oxazolium iodide 17 could be isolated in a moderate yield by filtering the precipitate from the organic layer after the excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$ (eq 5).



17

(5)

To our surprise, oxazolium iodide 17 did not undergo demethylation in the presence of PPh_3 using a 2:1 PhCl/sulfolane solvent system at 150 °C. Increasing the temperature to 230 °C still did not provide any of the desired oxazole.

Conclusions

To date, the preparation of a variety of simple alkynamides has met with limited success.[30] Most reports of alkynamide syntheses have focused on amide derivatives, such as sulfonamides, ureas, carbamates, cyclic carbamates and lactams.[31] Thus, a wide variety of alkynamide starting materials are not available for our proposed oxazole synthesis.

Our experience with synthesizing simple alkynamides has been limited to alkynes bearing bulky silyl groups. Our attempts at synthesizing alkynamides bearing aromatic rings on the alkyne terminus led primarily to homo-coupling products. The synthesis of alkynamides bearing non-silyl groups on the alkyne terminus, such as those derived from lactams and cyclic carbamates, have provided only modest yields of alkynamides.[32] This includes efforts to employ Sonogashira cross-coupling reactions of terminal alkynamides with aryl halides.[33] Efforts to generalize this synthesis of oxazoles by the eletrophilic cyclization of alkynamides will have to wait until a more general alkynamide synthesis has been developed. The synthesis of alkynamides with a labile leaving group should be the focus of this research in the future, since the electrophilic cyclization of alkynamides leads to oxazolium salts. To the best of our knowledge, alkynamides bearing an N-H group have not been reported. Alternatively, allenamides[34] might be examined as possible candidates for electrophilic cyclization to oxazoles.

The electrophilic cyclization of alkynamides provides a convenient synthesis of oxazolium salts, rather than the desired oxazoles. Thus far, dequaternization has met with limited success and the conditions required are not mild.

It should be noted that *N*-alkyloxazolium salts have been shown to react with anhydrides, ammonia, and tris(trimethylsilyl)phosphine in the presence of KF, to generate pyroles,[35] imidazoles,[36] and 3-azaphospholes[37] respectively. Thus, our approach to these oxazolium salts could prove useful for the synthesis of these other heterocyclic ring systems if we can make it more general.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F) and visualization was effected with short wavelength UV light (254 nm). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Toluene and CH_2Cl_2 were distilled from CaH_2. All reagents were used directly as obtained commercially unless otherwise noted.

General Procedure for the Preparation of Alkynamides. To a mixture of the appropriate amide (7.33 mmol), anhydrous K_3PO_4 (7.33 mmol, 1.56 g), $CuSO_4$•$5H_2O$ (0.55 mmol, 137 mg), and 1,10-phenanthroline (1.09 mmol, 138 mg) in a 4 dram reaction vial was added 1-bromo-2-(triisopropylsilyl)acetylene (3.67 mmol, 956 mg) in toluene (8 mL). The reaction mixture was capped and heated in an oil bath at 75 °C for 48 h. The reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through Celite, and concentrated under vacuum. The crude products were purified by flash column chromatography on silica gel using hexanes/EtOAc to afford the desired alkynamide.

N-Methyl-*N*-[(triisopropylsilyl)ethynyl)]benzamide (3). The compound was isolated in an 86 % yield: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.94 (s, 21H), 3.36 (s, 3H), 7.35-7.45 (m, 3H), 7.78-7.80 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.46, 18.74, 37.96, 70.07, 100.35, 127.99, 128.79, 131.33, 133.78, 171.53; HRMS Calcd for $C_{19}H_{29}NOSi$: 315.2018. Found 315.2024.

N-Benzyl-*N*-[(triisopropylsilyl)ethynyl]benzamide (10). The compound was isolated in an 87 % yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 21H), 4.87 (s, 2H), 7.30-7.46 (m, 8H), 7.78-7.80 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.43, 18.69, 53.13, 72.32, 99.07, 128.01, 128.21, 128.72, 128.89, 129.19, 131.41, 133.83, 136.12, 171.02; HRMS Calcd for $C_{25}H_{33}NOSi$: 391.2331. Found 391.2338.

N-(4-Methoxybenzyl)-*N*-[(triisopropylsilyl)ethynyl]benzamide (11). The compound was isolated in a 43 % yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (s, 21H), 3.80 (s, 3H), 4.80 (s, 2H), 6.86-6.89 (dd, *J* = 2.6, 8.9 Hz, 2H), 7.32-7.44 (m, 5H), 7.76-7.79 (d, *J* = 8.0

Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.40, 18.66, 52.62, 55.50, 72.30, 99.10, 114.07, 127.96, 128.35, 128.84, 130.70, 131.32, 133.40, 159.70, 171.00; HRMS Calcd for $C_{26}H_{35}NO_2Si$: 421.2437. Found 421.2443.

N-Allyl-*N*-[(triisopropylsilyl)ethynyl]benzamide (12). The compound was isolated in a 48 % yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (s, 21H), 4.30-4.31 (d, *J* = 5.7 Hz, 2H), 5.28-5.38 (m, 2H), 5.94-5.98 (m, 1H), 7.34-7.45 (m, 3H), 7.79-7.81 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.45, 18.74, 52.01, 71.61, 98.88, 119.38, 127.99, 18.86, 131.40, 131.55, 133.82, 170.90; HRMS Calcd for $C_{21}H_{31}NOSi$: 341.2177. Found 341.2182.

N-Methyl-*N*-[(triisopropylsilyl)ethynyl]acetamide (16). The compound was isolated in an 85 % yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 21H), 2.34 (s, 3H), 3.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 11.53, 18.82, 22.44, 36.15, 70.06, 99.90, 172.53; HRMS Calcd for $C_{14}H_{27}NOSi$: 253.1862. Found 253.1865.

General Procedure for the Preparation of Oxazolium Salts. To a stirred solution of the appropriate alkynamide (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added finely divided I_2 (0.75 mmol, 191 mg) and the solution was allowed to stir at room temperature for 12 h. The reaction was monitored by TLC to establish completion. The excess I_2 was removed by washing with a satd aq soln of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by recrystallization from MeOH or CH_2Cl_2/hexanes.

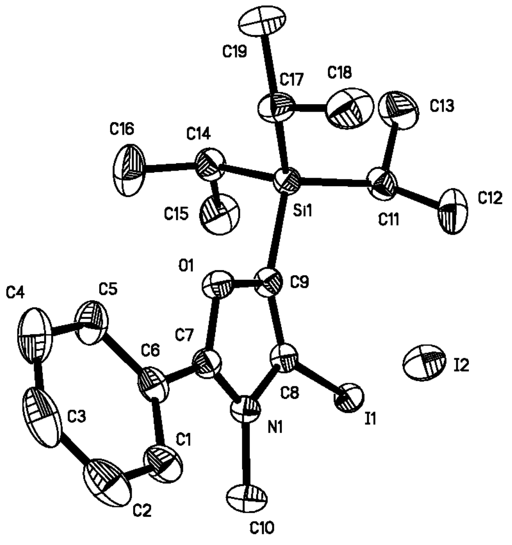


FIGURE 1: X-Ray Crystal Structure of Product 4.

4-Iodo-3-methyl-2-phenyl-5-(triisopropylsilyl)oxazolium iodide (4). The compound was isolated in a 91 % yield: ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 1.15-1.16 (d, *J* = 7.3 Hz, 18H), 1.59-1.63 (m, 3H), 3.95 (s, 3H), 7.73-7.79 (m, 2H), 7.84-7.86 (s, 1H), 7.96-7.97 (m, 2H); ^{13}C NMR (DMSO-d$_6$) δ 10.64, 18.13, 38.24, 99.83, 120.78, 129.49, 129.91, 134.42, 157.42, 164.73; HRMS Calcd for $C_{18}H_{26}INOSi$: 427.0828 (M – MeI)$^+$. Found 427.0835.

3-Benzyl-4-iodo-2-phenyl-5-(triisopropylsilyl)oxazolium iodide (13). The compound was isolated in a 94 % yield: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.20-1.22 (d, *J* = 7.5 Hz, 18H), 1.64-1.75 (m, 3H), 5.90 (s, 2H), 7.10-7.12 (m, 2H), 7.35-7.38 (m, 3 H), 7.50-7.54 (t, *J* = 7.9 Hz, 2H), 7.65-7.68 (t, *J* = 7.6 Hz, 1H), 7.80-7.82 (dd, *J* = 1.3, 8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 11.40, 18.82, 54.32, 107.09, 120.73, 126.40, 128.98, 129.67, 129.97, 132.70, 134.83, 160.33, 165.83; HRMS Calcd for $C_{18}H_{26}INOSi$: 427.0828 (M – $PhCH_2I)^+$. Found 427.0836.

3-Allyl-4-iodo-2-phenyl-5-(triisopropylsilyl)oxazolium iodide (15). The compound was isolated in a 64 % yield: ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 1.16-1.18 (d, *J* = 7.4 Hz, 18H), 1.59-1.67 (m, 3H), 4.67 (br s, 2H), 5.38-5.42 (br d, *J* = 17.1 Hz, 1H), 5.52-5.55 (br d, *J* = 10.7 Hz, 1H), 6.13-6.21 (m, 1H), 7.76-7.80 (t, *J* = 7.7 Hz, 2H), 7.86-7.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d$_6$) δ 10.71, 18.17, 52.65, 96.02, 119.81, 120.57, 129.49, 129.71, 129.95, 134.78, 158.68, 165.99; HRMS Calcd for $C_{18}H_{26}INOSi$ (M – $CH_2CHCH_2I)^+$: 427.0828. Found 427.0835.

Procedure for the Demethylation of Oxazolium Iodide 10 to form 4-Iodo-2-phenyl-5-(triisopropylsilyl)oxazole (5). To a microwave vial was added the crude oxazole salt 10 (0.25 mmol), PPh_3 (1 equiv) and 2:1 PhCl/sulfolane (2 mL). The microwave vial was capped and heated to 150 °C for 20 min. The solution was diluted with ethyl acetate (25 mL) and the organic layer washed with water, brine and dried with magnesium sulfate. The organic layer was concentrated under vacuum and the residue purified by column chromatography (20:1 hexanes/EtOAc) to afford the product as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15-1.17 (d, *J* = 7.5 Hz, 18H), 1.54-1.65 (m, 3H) 7.45-7.47 (m, 3H), 8.02-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.63, 18.86, 96.61, 126.69, 126.84, 129.00, 130.93, 155.26, 166.50; HRMS Calcd for $C_{18}H_{26}INOSi$: 427.0828. Found 427.0835.

Acknowledgements

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Chapter 5. An Efficient Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Annulation of Arynes by 2-Haloarenecarboxaldehydes

A paper submitted to the *Journal of Organic Chemistry*

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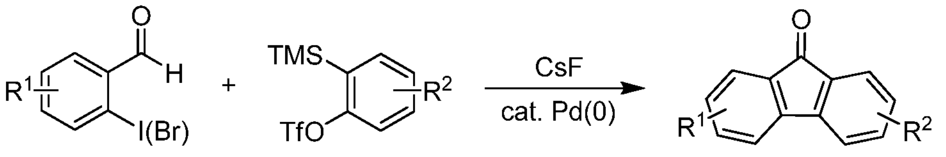
Abstract

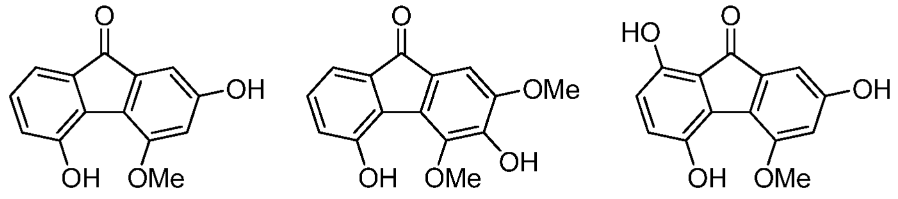


Fluoren-9-ones and derivatives are readily prepared in good yields by the annulation of *in situ* generated arynes by 2-haloarenecarboxaldehydes in the presence of a palladium catalyst.

Introduction

Recent groundbreaking work in the area of metal-catalyzed transformations of arynes, including the palladium-catalyzed cyclotrimerization of benzynes to form triphenylenes,[1] has provided novel new ways to rapidly construct fused aromatic polycycles. The metal-catalyzed cocyclization of arynes with alkynes has also been investigated.[2] Additionally, metal-catalyzed carbonylative cycloadditions of arynes[3] and the cocyclotrimerization of arynes with bicyclic alkenes[4] and allenes[5] have been reported. More recently, our group and others have synthesized fused polycyclic aromatics by palladium-catalyzed annulations of arynes with aryl halides.[6] We have also reported a palladium-catalyzed, three-component, sequential intermolecular coupling of aryl halides, alkynes, and arynes.[7]

The construction of heterocycles and carbocycles by the palladium-catalyzed annulation of alkynes by functionally-substituted aryl halides has proven a powerful synthetic tool.[8] Specifically, we have reported that 2-halobenzaldehydes can react with internal alkynes in the presence of a palladium catalyst to form substituted indenones in good yields.[9] Analogous to that work, we recently reported the synthesis of fluoren-9-ones by the palladium-catalyzed annulation of *in situ* generated benzynes by 2-haloarenecarboxaldehydes.[10] This provides a convenient synthesis of fluoren-9-ones, which are an important class of carbocycle, because of their important role in pharmaceutical applications,[11] as photosensitizers,[12] and their use as key intermediates in organic synthesis.[13] A number of fluoren-9-one natural products, including dengibsin, dengibsinin and dendroflorin, have recently been reported to occur in the Asiatic orchid *Dendrobium gibsonii* Lindley (Figure 1).[14] We now wish to report the full details of our work on the palladium-catalyzed annulation of arynes by 2-haloarenecarboxaldehydes.

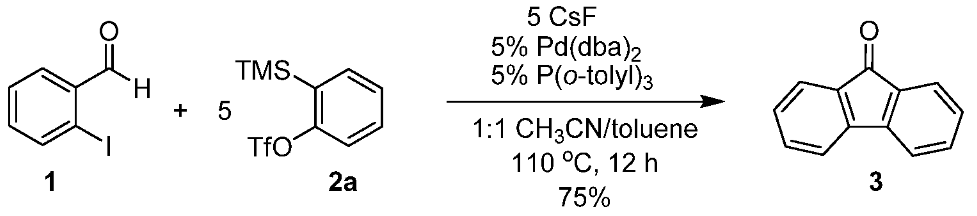


Dengibsin Dengibsinin Dendroflorin

Figure 1

Results and Discussion

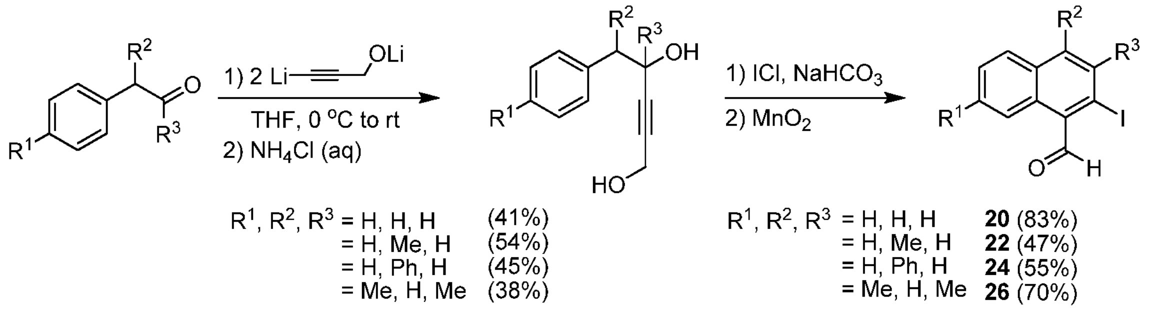
In our earlier study, it was found that the "optimal" conditions for our palladium-catalyzed annulation of arynes by 2-haloarenecarboxaldehydes involves stirring 0.3 mmol of the 2-iodobenzaldehyde (1), 1.5 mmol of the benzyne precursor 2-(trimethylsilyl)phenyl triflate (2a), 1.5 mmol of CsF, 5 mol % Pd(dba)$_2$ and 5 mol % P(*o*-tolyl)$_3$ ligand in 4 mL of 1:1 MeCN:toluene at 110 °C for 12 h. This affords the desired fluoren-9-one (3) in a 75% yield (eq 1).



(1)

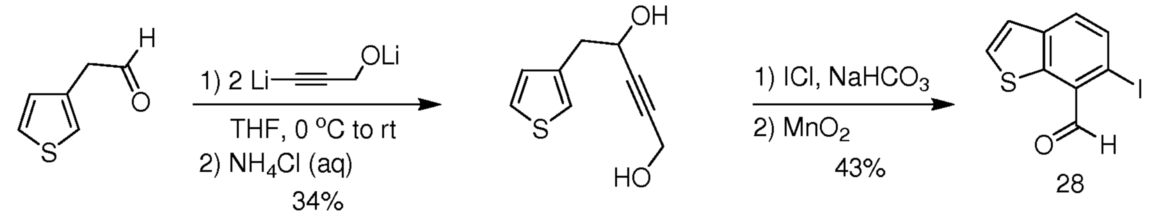
To determine the scope and limitations of this chemistry, a number of new *ortho*-haloarenecarboxaldehydes were required. However, many of the necessary starting materials were not readily accessible from commercial sources. The synthesis of *ortho*-iodonaphthalenecarboxaldehyde starting materials was achieved by employing a useful variant of some of our earlier reported[15] iodocyclization chemistry using appropriate benzylic-substituted propargylic diols, followed by oxidation of the resulting naphthalen-1-ylmethanols by MnO$_2$ (Scheme 1). The requisite diols are easily prepared by the reaction of the lithium acetylide dianion of propargyl alcohol with the corresponding 2-arylacetaldehyde or 2-arylacetone in THF at 0 °C, followed by quenching with a saturated solution of aqueous NH$_4$Cl.

Scheme 1

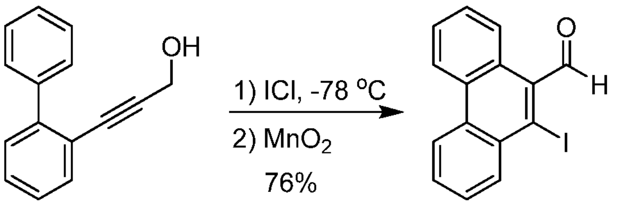

1) 2 Li—≡—OLi
THF, 0 °C to rt
2) NH4Cl (aq)
1) ICl, NaHCO3
2) MnO2
R1, R2, R3 = H, H, H (41%)
= H, Me, H (54%)
= H, Ph, H (45%)
= Me, H, Me (38%)
R1, R2, R3 = H, H, H 20 (83%)
= H, Me, H 22 (47%)
= H, Ph, H 24 (55%)
= Me, H, Me 26 (70%)

In addition to the *ortho*-halonaphthalenecarboxaldehydes described above, we prepared 6-iodobenzothiophene-7-carboxaldehyde (28) by an analogous route starting from 2-(thiophen-3-yl)acetaldehyde (Scheme 2). The iodocyclization of the thiophene-containing diol occurred selectively at the 2-position of the thiophene. The major side product appeared to arise by simple dehydration to an enynol product that did not cyclize.

Scheme 2


1) 2 Li—≡—OLi
THF, 0 °C to rt
2) NH4Cl (aq)
34%
1) ICl, NaHCO3
2) MnO2
43%
28

The synthesis of 10-iodophenanthrene-9-carbaldehyde (30) was achieved by the iodocyclization of 3-(biphen-2-yl)prop-2-yn-1-ol, followed by oxidation with MnO_2 (eq 2).[16]



30

(2)

With a number of new *ortho*-iodoarenecarboxaldehydes in hand, we examined the scope of the fluoren-9-one synthesis (Table 1). When 2-iodobenzaldehyde (1) and 2-bromobenzaldehyde (4) were allowed to react with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2a) under our optimized conditions, fluoren-9-one (3) was isolated in good yields, although a two fold increase in reaction time was required for the reaction of 4 to reach completion (Table 1, compare entries 1 and 2). 5-Bromo-2-iodobenzaldehyde (5) reacted selectively to afford the desired 2-bromofluoren-9-one (6) in good yield (Table 1, entry 3). 6-Fluoro-2-iodobenzaldehyde (7) reacted cleanly to provide 1-fluorofluoren-9-one (8) in an 82% yield (Table 1, entry 4). The increased yield of 8 compared to the parent system is presumably due to the electron-withdrawing nature of the fluorine atom on the aromatic ring, which presumably facilitates the oxidative addition of Pd(0) to the carbon-iodine bond of 7. In addition, the fluorine atom may increase the electrophilicity of the aldehyde moiety, promoting the final cyclization step (see the later mechanistic discussion). On the contrary, the reaction of 2-iodo-4,5-methylenedioxybenzaldehyde (9) with triflate 2a provided only a 50% yield of the desired fluoren-9-one 10 (Table 1, entry 5). This marked decrease in yield, as compared to the parent system, may be due to the electron-rich aromatic ring. Both 2-iodo-5,6-methylenedioxybenzaldehyde (11) and 2-bromo-5,6-methylenedioxybenzaldehyde (13) provided the corresponding fluoren-9-one 12. However, the aryl bromide gave a significantly reduced yield (Table 1, compare entries 6 and 7). The higher yield of 12 from 11, as opposed to that of 10 from 9, might be explained by the electron-withdrawing inductive effect of the oxygen atoms of 11 being greater due to their proximity to the aldehyde group, thus making the aldehyde more electrophilic (Table 1, compare entries 5 and 6). When 2-iodo-4,5-dimethoxybenzaldehde (14) was reacted with triflate 2, the desired fluoren-9-one 15 was obtained in a 53% yield (Table 1, entry 8). This result is in line with the reaction of triflate 2a with aldehyde 9. 2-Iodo-3,4,5-trimethoxybenzaldehyde (16) provided 2,3,4-trimethoxyfluoren-9-one (17) in only a modest yield of 41% (Table 1, entry 9). The decrease in yield, compared with other aryl ethers is presumably due to a steric effect of the MeO group *ortho* to the iodine atom. Steric congestion around the carbon-iodine bond may hinder oxidative addition of palladium to the C-I bond.

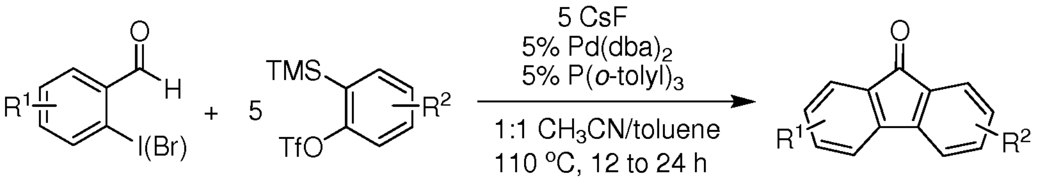
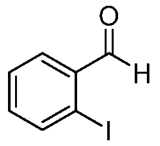
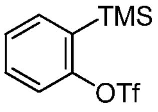
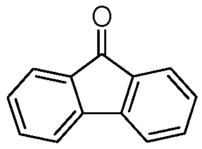
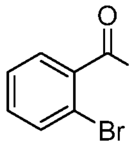
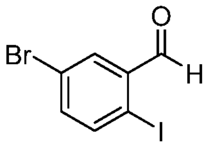
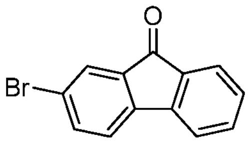
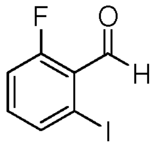
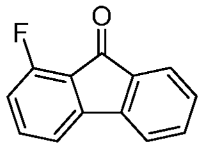
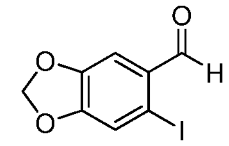
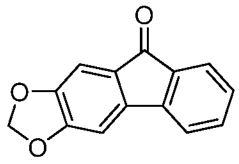
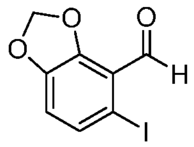
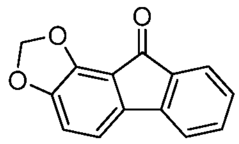
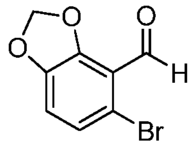
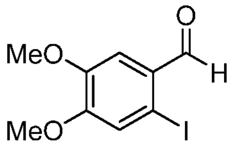
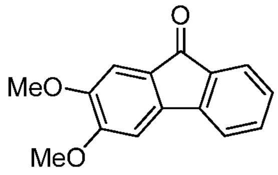
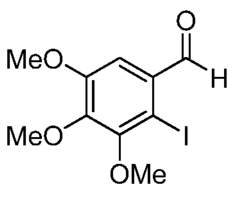
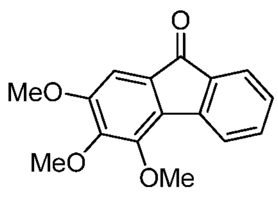
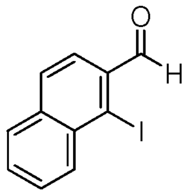
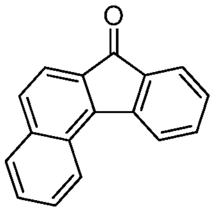
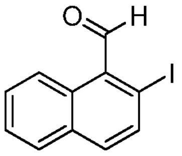
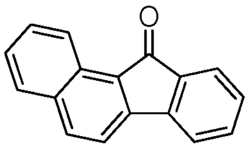
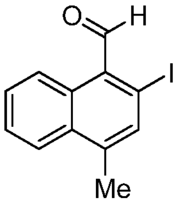
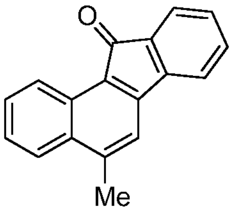
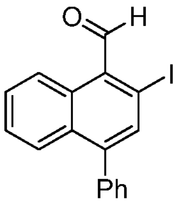
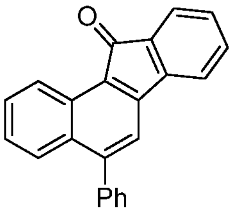
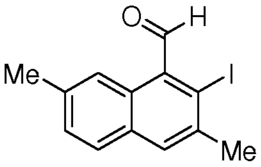
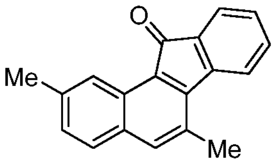
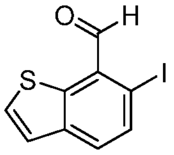
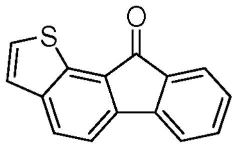
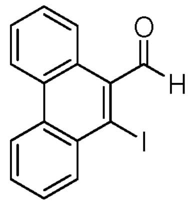
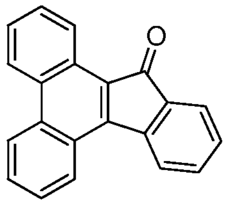
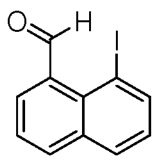
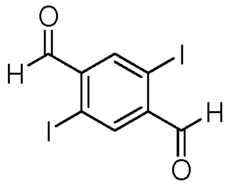
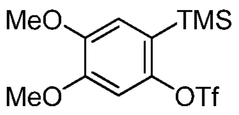
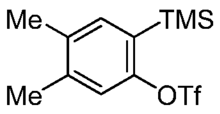
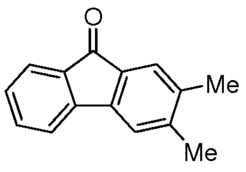
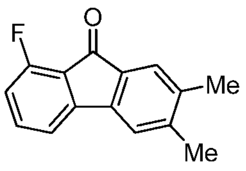
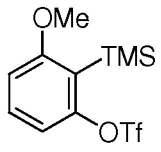
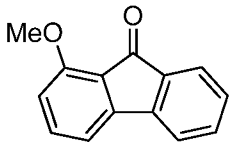
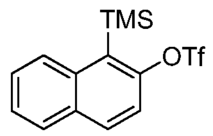


Table 1. Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Annulation of Arynes by *o*-Haloarenecarboxaldehydes.[a]

entry	*o*-haloaldehyde	aryne precursor	product(s)	% yield[b]
1	 1	 2a	 3	75

2		4	2a		3	73[c]
3		5	2a		6	61
4		7	2a		8	82
5		9	2a		10	50
6		11	2a		12	72
7		13	2a		12	56
8		14	2a		15	53
9		16	2a		17	41

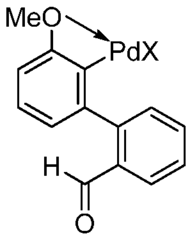
10		18	2a		19	48
11		20	2a		21	59
12		22	2a		23	61
13		24	2a		25	78
14		26	2a		27	48
15		28	2a		29	52

16		30		2a		31	61
17		32		2a	--		0
18		33		2a	--		messy
19		1		2b		15	33[d]
20		1		2c		34	71
21		7		2c		35	73
22		1		2d		36	61[e]
23		1		2e		19 + 21	trace 50

a) Unless otherwise specified, all reactions were carried out using 0.3 mmol of the aldehyde, 1.5 mmol of the aryne precursor, 1.5 mmol of CsF, 5 mol % of $Pd(dba)_2$ and 5 mol % of P(*o*-tol)$_3$ in 4 mL of 1:1 CH_3CN/toluene at 110 °C for 12 h. b) Isolated yield after column chromatography on silica gel. c) The reaction required 24 h to reach completion and the yield was determined by GC-MS. d) The yield was determined by ^1H NMR spectroscopy. (e) The yield of the other isomer was 7% according to gas chromatographic analysis.

In addition to benzaldehyde substrates, the annulation reaction has also been applied to 2-iodonaphthalene-1-carboxaldehydes. The annulation of triflate 2a by 1-iodonaphthalene-2-carboxaldehyde (18) provided fluorenone derivative 19 in a 48% yield (Table 1, entry 10). A marked increase in the yield of fluorenone was observed when 2-iodonaphthalene-1-carboxaldehyde (20) was allowed to react with triflate 2a (Table 1, compare entries 10 and 11). The increase in yield of 21, compared to regioisomer 19, is apparently due to decreased steric crowding around the carbon-iodine bond, resulting in a more facile oxidative addition of the palladium moiety. Reactions of 2-iodo-4-methylnaphthalene-1-carboxaldehyde (22) and 2-iodo-4-phenylnaphthalene-1-carboxaldehyde (24) with triflate 2a proceeded smoothly, and provided the corresponding fluorenones 23 and 25 respectively in good yields (Table 1, entries 12 and 13). 2-Iodo-3,7-dimethylnaphthalene-1-carboxaldehyde (26) afforded the desired compound 27 (Table 1, entry 14). However, the yield suffered, presumably due to steric hinderance in the vicinity of the carbon-iodine bond of 26. 6-Iodobenzothiophene-7-carboxaldehyde (28) gave the corresponding thiophene-containing fluorenone 29 in a 52% yield (Table 1, entry 15). When phenanthrene 30 was allowed to react with triflate 2a, the desired fluoren-9-one derivative 31 was obtained in a 61% yield (Table 1, entry 16). Naphthalene 32 was employed to see if this methodology could be extended to 6-membered rings, but, unfortunately, triphenylene was observed as the major product of this reaction, along with the reduced starting material naphthalene-1-carboxaldehyde (Table 1, entry 17). A double annulation was attempted by using diiododialdehyde 33. Unfortunately, the latter reaction provided a complex reaction mixture and none of the desired product was observed (Table 1, entry 18). A similar result was obtained when the reaction was performed using 0.3 mmol of diiododialdehyde 33, 3.0 mmol of 2-(trimethylsilyl)phenyl triflate (2a), 3.0 mmol of CsF, 10 mol % $Pd(dba)_2$ and 10 mol % $P(o\text{-tolyl})_3$ ligand in 8 mL of 1:1 CH_3CN/toluene.

In addition to the above reactions, which examined only the use of the benzyne precursor triflate 2a as an annulation partner, other aryne precursors have been examined in our methodology. 4,5-Dimethoxybenzyne precursor 2b was examined under our annulation conditions and gave the expected 2,3-dimethoxyfluoren-9-one (15), although the yield was poor (Table 1, entry 19). The low yield in this latter reaction may be attributed to the slower rate of generation of 4,5-dimethoxybenzyne from 2b, compared with the generation of benzyne from 2a, as has been suggested by earlier work in our group.[6a,c] However, when dimethylbenzyne precursor 2c was allowed to react with 2-iodobenzaldehydes 1 and 7 under our optimized conditions, it provided the corresponding fluoren-9-one products 34 and 35 respectively in good yields (Table 1, entries 20 and 21). The reaction of 3-methoxybenzyne, generated from triflate 2d, exhibited good regioselectivity (Table 1, entry 22). The reaction gave rise to both isomeric methoxyfluoren-9-ones in approximately a 9:1 ratio as determined by gas chromatographic analysis. 1-Methoxyfluoren-9-one (36) was the major product as determined by comparison of its ^1H and ^{13}C NMR spectra with those of the known compound.[17] The preference for regioisomer 36 over the other regioisomer can be attributed to coordination of the methoxy group to the palladium in the biarylpalladium intermediate 37 (Figure 2).[18] This regiochemistry also places the palladium on the inductively more thermodynamically stable carbanionic carbon. Intermediate 37 is also the product one would expect from the aryl moiety of the initial ArPdX adding to the most sterically accessible carbon of the aryne. As observed in the carbopalladation of alkynes,[8] Pd presumably prefers to add to the more hindered end of the aryne, which is *ortho* to the methoxy group.



37

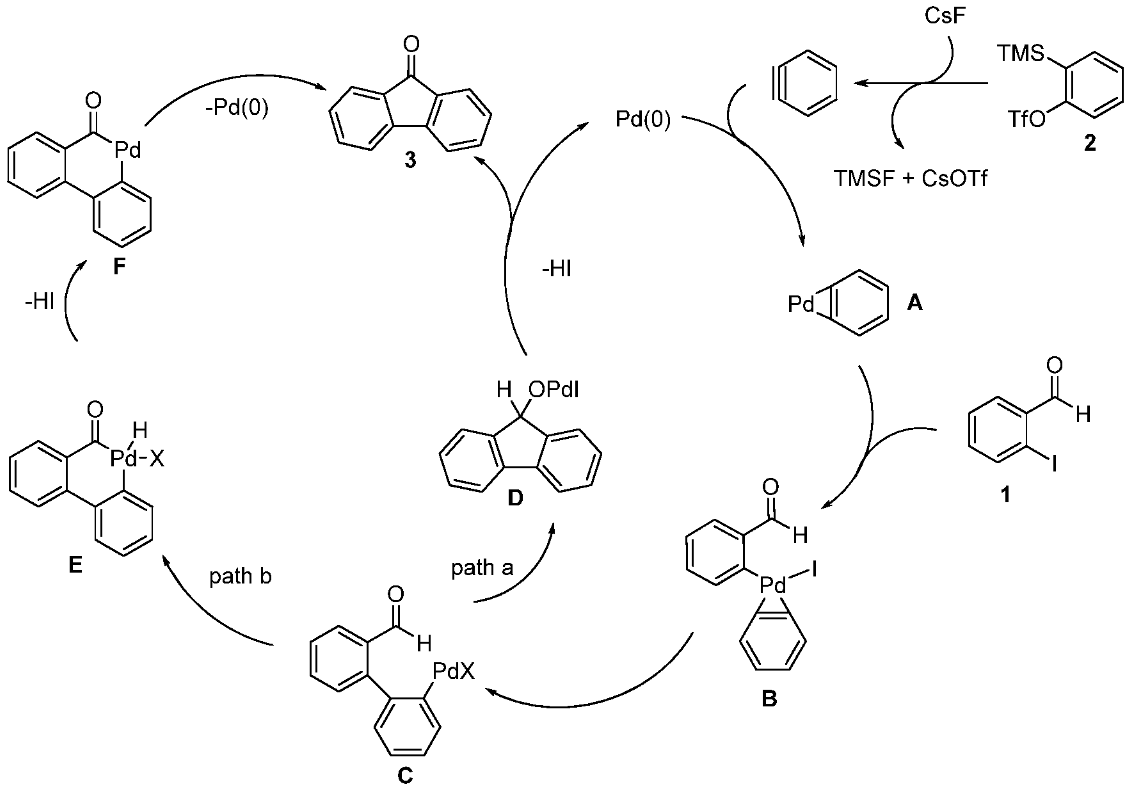
Figure 2

In addition to benzyne precursors, we have also examined the effect of naphthyne[2c] precursor 2e on the annulation process. We were pleased to find that one major regioisomer was formed in a 50% yield from the reaction of naphthyne precursor 2e with aldehyde 1 (Table 1, entry 23). This result is in agreement with the suggestion that the aryl moiety of the initial ArPdX adds to the more sterically exposed carbon of the aryne and that Pd prefers to add to the more hindered C1 of naphthyne.

In addition to the substrates illustrated in Table 1, we have also attempted to employ substituted 2-haloacrylaldehydes in this palladium-catalyzed annulation reaction to synthesize indenones.[9] Unfortunately, reactions with 2-iodocyclohex-1-enecarboxaldehyde and *Z*-3-iodo-3-phenylacrylaldehyde produced complex mixtures and only poor yields of indenones were achieved. Also, our attempts employing pyridine substrates, such as 2-bromopyridine-3-carboxaldehyde, 4-bromopyridine-3-carboxaldehyde and 2-fluoro-4-iodopyridine-3-carboxaldehyde, as starting materials did not lead to any formation of the desired fluoren-9-ones. This result is not surprising, since pyridine itself is known to react with benzynes to give novel polymers with *o*-phenylene and 2,3-dihydropyridine units in the main chain.[19]

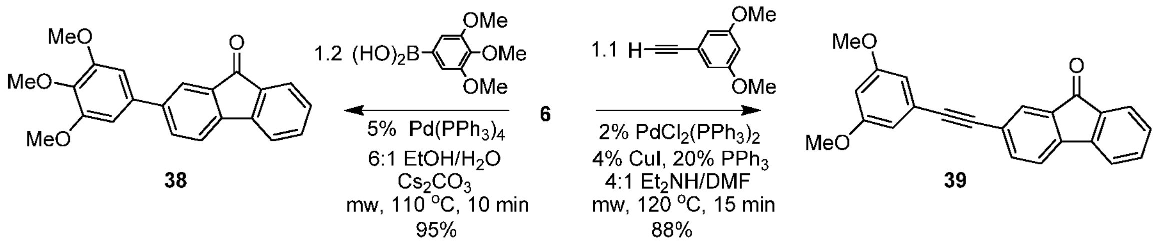
Based on previously reported palladium-catalyzed annulations of alkynes,[8] particularly the synthesis of indenones by the palladium-catalyzed coupling of internal alkynes with 2-haloarenecarboxaldehydes,[9] we propose that this fluorenone synthesis proceeds as shown in Scheme 3. First, oxidative cyclization of Pd(0) occurs with the aryne generated from the silyl triflate to form palladacycle A.[20] Oxidative addition of 1 to this palladacycle forms Pd(IV) intermediate B. Reductive elimination gives rise to arylPd(II) intermediate C. Arylpalladium intermediate C can add across the aldehyde to produce a palladium(II) alkoxide D,[21] which can undergo β-hydride elimination to produce the fluorenone product (path a). Alternatively, intermediate C can undergo oxidative addition of the aldehyde C-H bond to form palladium(IV) intermediate E,[22] followed by elimination of HI, and regeneration of the Pd(0) catalyst by further reductive elimination to the fluoren-9-one (path b). A similar mechanism involving the oxidative addition of an aldehyde to an organopalladium(II) intermediate has been proposed for the palladium-catalyzed reactions of *o*-bromobenzaldehyde with methyl acrylate.[23] However, there does not appear to be any particular precedent favoring either of these paths. In addition, we cannot rule out the possibility that Pd(0) inserts directly into the C-I bond of 1, followed by carbopalladation of the aryne, to give rise to intermediate C directly. This pathway has been suggested by experiments in our earlier work on the synthesis of fused polycyclic aromatics by the palladium-catalyzed annulation of arynes by aryl halides.[6a,c]

Scheme 3


CsF
TMS
TfO
2
TMSF + CsOTf
Pd(0)
Pd
A
1
B
C
D
E
F
3
-Pd(0)
-HI
-HI
path a
path b
H OPdI
PdX
Pd-X
Pd-I

In order to demonstrate the utility of 2-bromofluoren-9-one (6) generated by our methodology, we have elaborated the carbon-bromine bond by palladium-catalyzed, microwave-assisted Sonogashira[24] and Suzuki-Miyaura[25] cross-coupling reactions (Scheme 4). These reactions proceeded cleanly to give acetylenic fluoren-9-one 39 and 2-(3,4,5-trimethoxyphenyl)fluoren-9-one (38) in high yields.

Scheme 4


MeO
MeO
MeO
O
38
1.2 (HO)2B
OMe
OMe
OMe
5% Pd(PPh3)4
6:1 EtOH/H2O
Cs2CO3
mw, 110 °C, 10 min
95%
6
1.1 H
OMe
OMe
2% PdCl2(PPh3)2
4% CuI, 20% PPh3
4:1 Et2NH/DMF
mw, 120 °C, 15 min
88%
MeO
MeO
O
39

Conclusions

In summary, we have developed a novel synthesis of fluoren-9-ones, which involves the palladium-catalyzed annulation reaction of arynes by 2-haloarenecarboxaldehydes. This method provides an efficient synthesis of substituted fluoren-9-ones from readily available starting materials. Additionally, this methodology provides a route to fluoren-9-ones that avoids the use of harsh oxidizing agents and strong mineral acids.[26] Our process has been shown to be tolerant of benzaldehydes containing multiple halogens. The resulting halogenated 2-bromofluoren-9-one may be further elaborated by palladium-catalyzed processes, such as Sonogashira and Suzuki-Miyaura cross-coupling reactions. Furthermore, this methodology has been extended to naphthalene derivatives of fluoren-9-ones and has also been shown to work in the presence of a heterocycle.

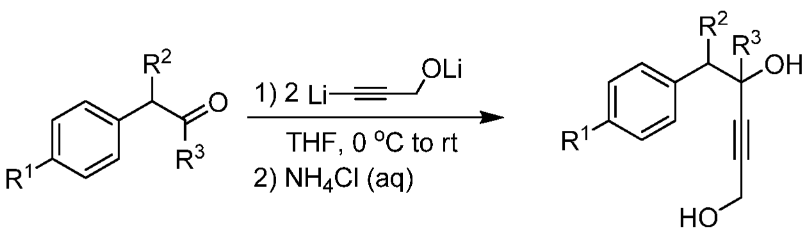
Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and/or a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Toluene, CH_2Cl_2 and MeCN were distilled from CaH_2 under an atmosphere of argon prior to use and stored over 4Å molecular sieves. Anhydrous CsF and $Pd(dba)_2$ were stored in a glove box under an atmosphere of N_2. All glassware and stirring bars were oven dried prior to use. All reagents were used directly as obtained commercially unless otherwise noted. Compounds 3, 7-12, 18, 19, and 34-36 have been reported in our previous communication.[10]

Synthesis of Starting Materials. Compounds 14,[27] 16[28] and benzyne precursors 2a-e[29] were prepared according to literature procedures.

Procedure for the Synthesis of 2-(Thiophen-3-yl)acetaldehyde. 2-(Thiophen-3-yl)ethanol (20 mmol, 2.56 g) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. PCC (26 mmol, 5.59 g) was added slowly. The solution was allowed to slowly warm to room temperature and stirred for 18 h. The resulting brown suspension was filtered through a plug of silica gel and the solvent concentrated to give the product as an orange oil. The resulting product was taken on to the next step immediately. The resulting aldehyde was unstable and should be used immediately.

General Procedure for the Synthesis of Alkynediols.



Propargyl alcohol (16.6 mmol, 930 mg, 0.98 mL) was dissolved in THF (100 mL) and cooled to 0 °C. Under an atmosphere of argon, *n*-BuLi (2.5 M in hexanes, 33.2 mmol, 13.3 mL) was added slowly and the resulting solution allowed to stir at 0 °C for 1 h. A solution of the appropriate arylacetaldehyde or arylacetone (8.3 mmol) in THF (10 mL) was added slowly, and the solution was allowed to warm to room temperature over a period of 12 h. The solution was quenched with a satd aq NH_4Cl solution and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude products were isolated by flash column chromatography on silica gel (2:1 hexanes:EtOAc).

5-Phenylpent-2-yne-1,4-diol. This compound was isolated as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94-2.95 (d, *J* = 6.6 Hz, 2H), 3.66 (br s, 2H), 4.16 (s, 2H), 4.52-4.55 (t, *J* = 6.5 Hz, 1H), 7.21-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 44.0, 50.7, 63.2, 84.0, 86.1, 127.0, 128.5, 129.8, 136.8; HRMS Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0840.

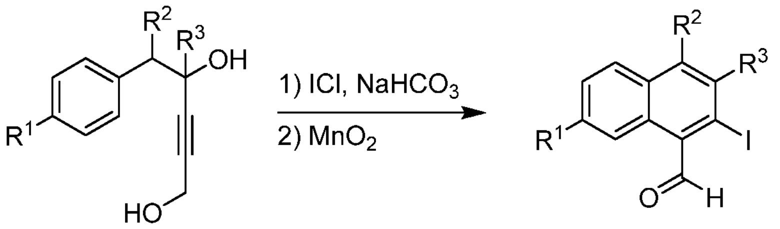
5-Phenylhex-2-yne-1,4-diol. This compound was isolated as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39-1.38 (d, *J* = 7.1 Hz, 3H), 2.96-3.04 (m, 1H), 3.38-3.39 (d, *J* = 5.3 Hz, 1H), 3.56 (br s, 1H), 4.12 (s, 2H), 4.45 (br s, 1H), 7.22-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.5, 45.9, 50.8, 67.2, 84.7, 85.5, 127.2, 128.5, 128.7, 142.3; HRMS Calcd for $C_{12}H_{14}O_2$: 190.0994. Found: 190.0997.

5,5-Diphenylpent-2-yne-1,4-diol. This compound was isolated as a colorless oil that solidified upon standing: mp 106-108 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.97-3.99 (d, *J* = 5.8 Hz, 2H), 4.12-4.14 (d, *J* = 9.0 Hz, 1H), 5.03-5.07 (m, 1H), 5.09-5.12 (t, *J* = 5.7

Hz, 1H), 5.61-5.63 (d, $J = 6.1$ Hz, 1H), 7.14-7.18 (m, 2H), 7.24-7.28 (t, $J = 7.4$ Hz, 4H), 7.37-7.40 (t, $J = 6.6$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 49.0, 57.9, 63.5, 84.7, 85.8, 126.0, 126.3, 128.0, 128.1, 128.6, 128.7, 142.2, 142.3; HRMS Calcd for $C_{17}H_{16}O_2$: 252.1150. Found: 252.1154.

4-Methyl-5-*p*-tolylpent-2-yne-1,4-diol. This compound was isolated as a pale yellow oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.48 (s, 3H), 2.31 (s, 3H), 2.86-2.93 (m, 2H), 3.03 (br s, 1H), 3.13 (br s, 1H), 7.09-7.11 (d, $J = 7.8$ Hz, 2H), 7.17-7.19 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 21.2, 29.3, 49.1, 50.8, 68.2, 82.8, 89.2, 128.9, 130.7, 133.2, 136.6; HRMS Calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1174.

5-(Thiophen-3-yl)pent-2-yne-1,4-diol. This compound was isolated as an orange oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.98-3.00 (d, $J = 6.2$ Hz, 2H), 3.73 (br s, 2H), 4.19 (s, 2H), 5.49 (br s, 1H), 7.00-7.01 (d, $J = 4.2$ Hz, 1H), 7.09 (s, 1H), 7.23-7.28 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 38.4, 50.7, 62.6, 83.9, 86.3, 123.0, 125.6, 129.0, 137.0; HRMS Calcd for $C_9H_{10}O_2S$: 182.0402. Found: 182.0404.



General Procedure for the Electrophilic Cyclization of Alkynediols by ICl, Followed by Oxidation with MnO$_2$. A 1.2 mmol portion of the alkynediol, 2 equiv of NaHCO$_3$, and 8 mL of CH$_3$CN were placed in a vial and stirred for 1 min at room temperature. Two equiv of ICl in 2 mL of CH$_3$CN was added dropwise to the vial. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was then diluted with 25 mL of EtOAc and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated, and the aqueous layer was extracted with another 25 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the crude residue was filtered through a plug of silica gel rinsed with 25% EtOAc in hexanes. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (50 mL). The solution was cooled to 0 ^{o}C and MnO_2 (6.0 equiv based on the alkynediol) was added. The solution was warmed to room temperature and stirred for 18 h. The suspension was filtered through a plug of celite and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using a gradient solvent system (40:1 hexanes:EtOAc to 9:1 hexanes:EtOAc).

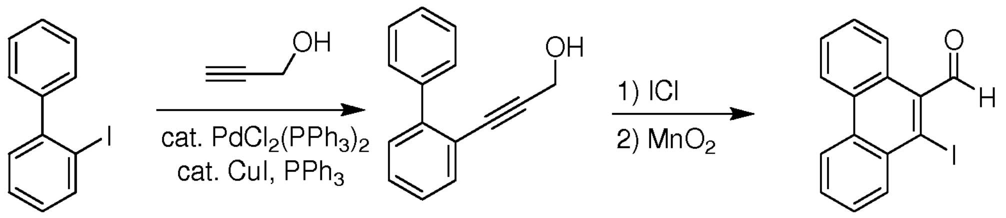
2-Iodonaphthalene-1-carboxaldehyde (20). This product was isolated as a yellow solid: mp 77-79 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55-7.59 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.62-7.67 (m, 2H), 7.80-7.82 (d, *J* = 8.1 Hz, 1H), 7.94-7.96 (d, *J* = 8.7 Hz, 1H), 9.01-9.03 (d, *J* = 8.7 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 105.6, 124.2, 127.5, 128.5, 129.4, 130.6, 131.7, 133.8, 135.1, 137.1, 199.0; HRMS Calcd for $C_{11}H_7IO$: 281.9542. Found: 281.9546.

2-Iodo-4-methylnaphthalene-1-carboxaldehyde (22). This product was isolated as a yellow solid: mp 100-102 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (s, 3H), 7.53-7.61 (m, 2H), 7.79 (s, 1H), 7.88-7.90 (d, *J* = 8.0 Hz, 1H), 9.06-9.08 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 106.8, 125.5, 124.6, 127.3, 128.9, 129.0, 131.5, 132.9, 137.9, 142.9, 198.9; HRMS Calcd for $C_{12}H_9IO$: 295.9698. Found: 295.9704.

2-Iodo-4-phenylnaphthalene-1-carboxaldehyde (24). This product was isolated as a yellow solid: mp 123-125 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.38-7.49 (m, 6H), 7.60-7.64 (t, *J* = 7.8 Hz, 1H), 7.83-7.85 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 9.13-9.15 (d, *J* = 8.7 Hz, 1H), 10.40 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 105.8, 124.5, 127.1, 127.6, 128.7, 128.8, 129.3, 129.8, 130.0, 132.3, 132.4, 138.1, 138.4, 147.5, 199.0 (one carbon missing due to overlap); HRMS Calcd for $C_{17}H_{11}IO$: 357.9855. Found: 357.9561.

2-Iodo-3,7-dimethylnaphthalene-1-carboxaldehyde (26). This product was isolated as a yellow solid: mp 63-65 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.51 (s, 3H), 2.60 (s, 3H), 7.32-7.34 (d, *J* = 8.3 Hz, 1H), 7.58-7.60 (d, *J* = 8.3 Hz, 1H), 7.70 (s, 1H), 8.54 (s, 1H), 10.39 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 22.5, 29.2, 111.9, 122.8, 127.5, 129.5, 130.1, 131.6, 132.0, 132.6, 137.2, 138.5, 199.4; HRMS Calcd for $C_{13}H_{11}IO$: 309.9855. Found: 309.9859.

6-Iodothiophene-7-carboxaldehyde (28). This product was isolated as a brown solid: mp 102-105 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34-7.35 (d, *J* = 5.5 Hz, 1H), 7.54-7.56 (d, *J* = 5.5 Hz, 1H), 7.70-7.72 (d, *J* = 8.2 Hz, 1H), 7.89-7.91 (d, *J* = 8.2 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 99.6, 122.8, 128.6, 130.5, 131.0, 136.3, 140.1, 141.3, 196.4; HRMS Calcd for C_9H_5IOS: 287.9106. Found: 287.9110.



Procedure for the Cross-Coupling of 2-Iodobiphenyl and Propargyl Alcohol to form 3-(Biphenyl-2-yl)prop-2-yn-1-ol. To a microwave vial were added 2-iodobiphenyl (1.79 mmol, 0.5 g), propargyl alcohol (1.96 mmol, 110 mg), $PdCl_2(PPh_3)_2$ (35.7 μmol, 25.1 mg), CuI (71.6 μmol, 13.6 mg), PPh_3 (0.36 mmol, 94.0 mg), DMF (0.5 mL) and Et_2NH (1.5 mL). The vial was capped and the solution was heated in a microwave reactor for 10 min at 100 °C. The solution was diluted with EtOAc (25 mL) and the organic layer washed with water and brine, and dried. The solvent was evaporated under reduced pressure and the product was purified by chromatography on a silica gel column to afford 240 mg (64%) of the product as a yellow-orange oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (br s, 1H), 4.28 (s, 2H), 7.24-7.28 (m, 1H), 7.33-7.41 (m, 5H), 7.52-7.57 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 51.7, 85.4, 90.2, 121.0, 127.2, 127.7, 128.1, 128.8, 129.7, 133.3, 140.5, 144.0; HRMS Calcd for $C_{15}H_{12}O$: 208.0888. Found: 208.0891.

Procedure for the Cyclization of 3-(Biphenyl-2-yl)prop-2-yn-1-ol by ICl and Oxidation by MnO_2 to form 10-Iodophenanthrene-9-carbaldehyde (30). To a solution of 3-(biphenyl-2-yl)prop-2-yn-1-ol (0.96 mmol) in CH_2Cl_2 (10 mL) under N_2 was added ICl (1.2 equiv) in CH_2Cl_2 (2 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 0.5 h. The reaction mixture was then diluted with 25 mL of EtOAc and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated, and the aqueous layer was extracted with another 25 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the crude residue was filtered through a plug of silica gel and rinsed with 25% EtOAc in hexanes. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (50 mL). The solution was cooled to 0 °C and MnO_2 (6.0 equiv) was added. The solution was warmed to room temperature and stirred for 18 h. The suspension was filtered through a plug of celite and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a gradient solvent system (40:1 hexanes:EtOAc to 9:1 hexanes:EtOAc) to afford 243 mg (76%) of the product as a yellow oil that solidified upon standing: mp 80-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.41 (m, 5H) 7.43-7.47 (m, 2H) 7.50-7.54 (dt, J = 1.5, 7.5 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 106.5, 127.8, 128.1, 128.6, 128.8, 128.9, 130.7, 130.8, 139.6, 140.2, 150.4, 185.9; HRMS Calcd for $C_{15}H_9IO$: 331.9698. Found: 331.9700.

General Procedure for the Palladium-Catalyzed Synthesis of Fluoren-9-ones. The 2-iodoarenecarboxaldehyde (0.30 mmol), the 2-(trimethylsilyl)aryl triflate (1.50 mmol), CsF (1.50 mmol), $Pd(dba)_2$ (0.015 mmol), P(*o*-tolyl)$_3$ (0.015 mmol), 2 mL of toluene, and 2 mL of MeCN were placed in a 4 dram vial and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 °C for 12 h. The mixture was allowed to cool to room temperature (CAUTION: OPENING THE VIAL AT HIGH TEMPERATURE CAN BE DANGEROUS!), diluted with diethyl ether, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel. Compounds 6,[30] 15,[31] 17[32] and 31[33] were obtained after flash chromatography, and their spectral properties are identical with these previously reported. In some cases, the product was recrystallized from hexanes/CH_2Cl_2 to afford a spectroscopically pure product.

11*H*-Benzo[*a*]fluoren-11-one (21). This product was obtained as an orange solid: mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.28 (apparent triplet merged with

$CDCl_3$, *J* = 7.3 Hz, 1H), 7.41-7.48 (m, 3H), 7.56-7.63 (m, 3H), 7.76-7.78 (d, *J* = 8.2 Hz, 1H), 7.96-7.98 (d, *J* = 8.2 Hz, 1H), 8.93-8.95 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 118.3, 120.1, 124.0, 124.4, 126.6, 127.0, 128.7, 129.4, 129.6, 130.3, 134.4, 134.6, 134.7, 136.1, 144.0, 146.3, 195.6; HRMS Calcd for $C_{17}H_{10}O$: 230.0732. Found: 230.0734.

5-Methyl-11*H*-benzo[*a*]fluoren-11-one (23). This product was obtained as an orange solid: mp 141-143 ºC; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.77 (s, 3H), 7.24-7.27 (apparent unresolved triplet merged with $CDCl_3$, 1H), 7.40-7.48 (m, 3H), 7.50 (s, 1H), 7.57-7.60 (t, *J* = 6.5 Hz, 2H), 7.92-7.95 (d, *J* = 8.5 Hz, 1H), 8.98-9.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 119.5, 119.9, 123.8, 124.8, 125.0, 125.5, 126.4, 129.2, 129.4, 130.5, 133.4, 134.1, 135.0, 143.9, 144.0, 146.1, 195.4; HRMS Calcd for $C_{18}H_{12}O$: 244.0888. Found: 244.0893.

5-Phenyl-11*H*-benzo[*a*]fluoren-11-one (25). This product was obtained as an orange solid: mp 205-207 ºC; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.28 (apparent doublet of triplets merged with $CDCl_3$, *J* = 1.1, 7.2 Hz, 1H), 7.33-7.45 (m, 3H), 7.49-7.61 (m, 8H), 7.78-7.79 (d, *J* = 8.4 Hz, 1H), 9.03-9.05 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 119.7, 120.1, 124.0, 124.7, 126.2, 126.6, 127.2, 128.3, 128.7, 129.4, 129.5, 129.9, 131.0, 132.8, 134.4, 135.0, 140.4, 143.8, 145.7, 148.6, 195.4 (one carbon missing due to overlap); HRMS Calcd for $C_{23}H_{14}O$: 306.1045. Found: 306.1051.

2,6-Dimethyl-11*H*-benzo[*a*]fluoren-11-one (27). This product was obtained as an orange solid: mp 203-205 ºC; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.51 (s, 3H), 2.69 (s, 3H), 7.21-7.24 (m, 2H), 7.39-7.42 (t, *J* = 7.4 Hz, 1H), 7.55-7.57 (d, *J* = 8.2 Hz, 2H), 7.59-7.61 (d, *J* = 7.5 Hz, 1H), 7.65 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.4, 123.2, 123.3, 123.9, 126.8, 127.5, 128.8, 129.2, 130.5, 133.0, 134.3, 135.3, 136.7, 139.0, 144.8, 145.5, 196.0; HRMS Calcd for $C_{19}H_{14}O$: 258.1045. Found: 258.1050.

10*H*-Fluoreno[1,2-*b*]thiophen-10-one (29). The product was obtained as an orange solid: mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.24 (dd, *J* = 1.0, 7.3 Hz, 1H), 7.28-7.30 (d, *J* = 5.4 Hz, 1H), 7.42-7.51 (m, 4H), 7.61-7.63 (d, *J* = 7.3 Hz, 1H), 7.88-7.90 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ116.9, 120.5, 123.3, 124.4, 127.8, 129.1, 129.5, 129.8, 134.4, 134.8, 136.0, 142.5, 144.9, 193.5; HRMS Calcd for $C_{15}H_8OS$: 236.0296. Found: 236.0299.

Procedure for the Synthesis of Fluoren-9-one 38 from 2-Bromofluoren-9-one. To a microwave vial was added 2-bromoflouren-9-one (0.20 mmol, 51.8 mg), $Pd(PPh_3)_4$ (10.0 µmol, 11.6 mg), 3,4,5-trimethoxyphenylboronic acid (0.24 mmol, 50.8 mg), Cs_2CO_3 (1M in H_2O, 0.24 mL), and EtOH (1.5 mL). The microwave vial was capped and heated to 110 °C for 10 min by microwave irradiation. Water (20 mL) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (4:1 hexanes:EtOAc) to afford 66 mg (95%) of the product as a yellow solid: mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 3.95 (s, 6H), 6.80 (s, 2H), 7.28-7.32 (m, 1H), 7.48-7.56 (m, 3H), 7.67-7.69 (m, 2H), 7.85-7.86 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 61.2, 91.2, 104.1, 120.6, 120.8, 123.0, 124.6, 129.2, 133.2, 134.6, 135.1, 135.9, 138.2, 142.4, 143.4, 144.4, 153.7, 194.1; HRMS Calcd for $C_{22}H_{18}O_4$: 346.1205. Found: 346.1210.

Procedure for the Synthesis of Alkyne 39 from 2-Bromofluoren-9-one. To a microwave vial was added 2-bromoflouren-9-one (0.20 mmol, 51.8 mg), PdCl$_2$(PPh$_3$)$_2$ (4.0 μmol, 2.8 mg), CuI (8.0 μmol, 1.5 mg), PPh$_3$ (0.04 mmol, 10.5 mg), DMF (0.5 mL) and Et$_2$NH (1.5 mL). The microwave vial was capped and heated to 120 °C for 15 min by microwave irradiation. Water (20 mL) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (MgSO$_4$). The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (4:1 hexanes:EtOAc) to afford 60 mg (88%) of the product as a yellow solid: mp 145-147 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.81 (s, 3H), 6.47-6.48 (t, J = 2.0 Hz, 1H), 6.68-6.69 (d, J = 2.4 Hz, 2H), 7.29-7.33 (dt, J = 1.8, 7.8 Hz, 1H), 7.49-7.51 (m, 3H), 7.63-7.68 (m, 2H), 7.79 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 55.7, 88.4, 91.3, 102.3, 109.5, 120.5, 120.8, 124.2, 124.3, 124.7 127.5, 129.6, 134.4, 134.5, 135.1, 137.8, 143.9, 144.1, 160.7, 193.2; HRMS Calcd for C$_{23}$H$_{16}$O$_3$: 340.1099. Found: 340.1105.

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GENERAL CONCLUSIONS

In this dissertation, new efficient approaches to various medicinally interesting heterocycles and carbocycles are described. These organic transformations occur by the electrophilic cyclization of functionalized acetylenes, ICl-induced dehydrations and by the palladium-catalyzed annulation of arynes by *o*-haloarencarboxaldehydes. The developed methodologies are quite general and can be utilized for the synthesis of various substituted isoxazoles, pyrazoles, oxazolium salts and fluoren-9-ones.

Chapter 1 is a publication that describes the electrophilic cylization of 2-alkyn-1-one *O*-methyl oximes to afford oxazoles. The methodology is selective, mild and tolerant of many functional groups. The presence of steric bulk at the 1- or 3-position of the 2-alkyn-1-one *O*-methyl oximes does not hinder the reaction. The resulting 4-iodoisoxazoles readily undergo palladium-catalyzed transformations to afford 3,4,5-trisubstituted isoxazoles in high yields. To date, this methodology has led to the most efficient synthesis of the potent, selective COX-II inhibitor valdecoxib from readily available starting materials.

Chapter 2 describes our efforts to adapt our methodology for the iodocylization of 2-alkyn-1-one *O*-methyl oximes to isoxazoles to library generation of a wide variety of highly substituted isoxazoles. The generation of a diverse library of isoxazoles has been accomplished by utilizing various palldium-catalyzed reactions to affect substitution of the C-I bond. These transformations allow for the construction of isoxazoles bearing functionally-substituted vinylic, alkynyl, amido and aryl groups. The products were isolated in high purity and are being evaluated for their biological potential. A 51 member library of substituted isoxazoles has been generated.

Chapter 3 is focused on the synthesis of 1-acyl-4-iodopyrazoles by a novel dehydration/iodination of 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pryazoles. Pyrazoles and derivatives are very important, because of their pronounced biological properties. A general method to construct 1-acyl-3,4,5-substituted pyrazoles has been examined. Our dehydration/iodination methodology provides a convenient and efficient approach to functionalized pyrazoles. The dehydration/iodination of 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles occurs at room temperature to afford 1-acyl-4-iodopyrazoles.

Chapter 4 outlines an approach to oxazolium iodide salts by the electrophilic cyclization of alkynamides. This methodology affords the expected oxazolium salts from the corresponding alkynamides. However, the oxazolium salts did not undergo dealkylation as expected and efforts towards their dealkylation have been met with limited success.

Chapter 5 illustrates arynes generated *in situ* from 2-(trimethylsilyl)aryl triflates and CsF undergo annulation by *o*-haloarenecarboxaldehydes in the presence of a palladium catalyst, providing a useful new method for the synthesis of fluoren-9-ones in good yields. The reaction tolerates both electron-rich and electron-deficient *o*-halocarboxaldehydes. Annulation even occurs in the presence of steric congestion around the carbon-halogen bond. This methodology can also be used to generate larger benzofluoren-9-ones and heterocycles containing fluorenone derivatives. In addition to the various 2-(trimethylsilyl)phenyl triflate benzyne precursors examined, a naphthyne precursor has been employed successfully as well.

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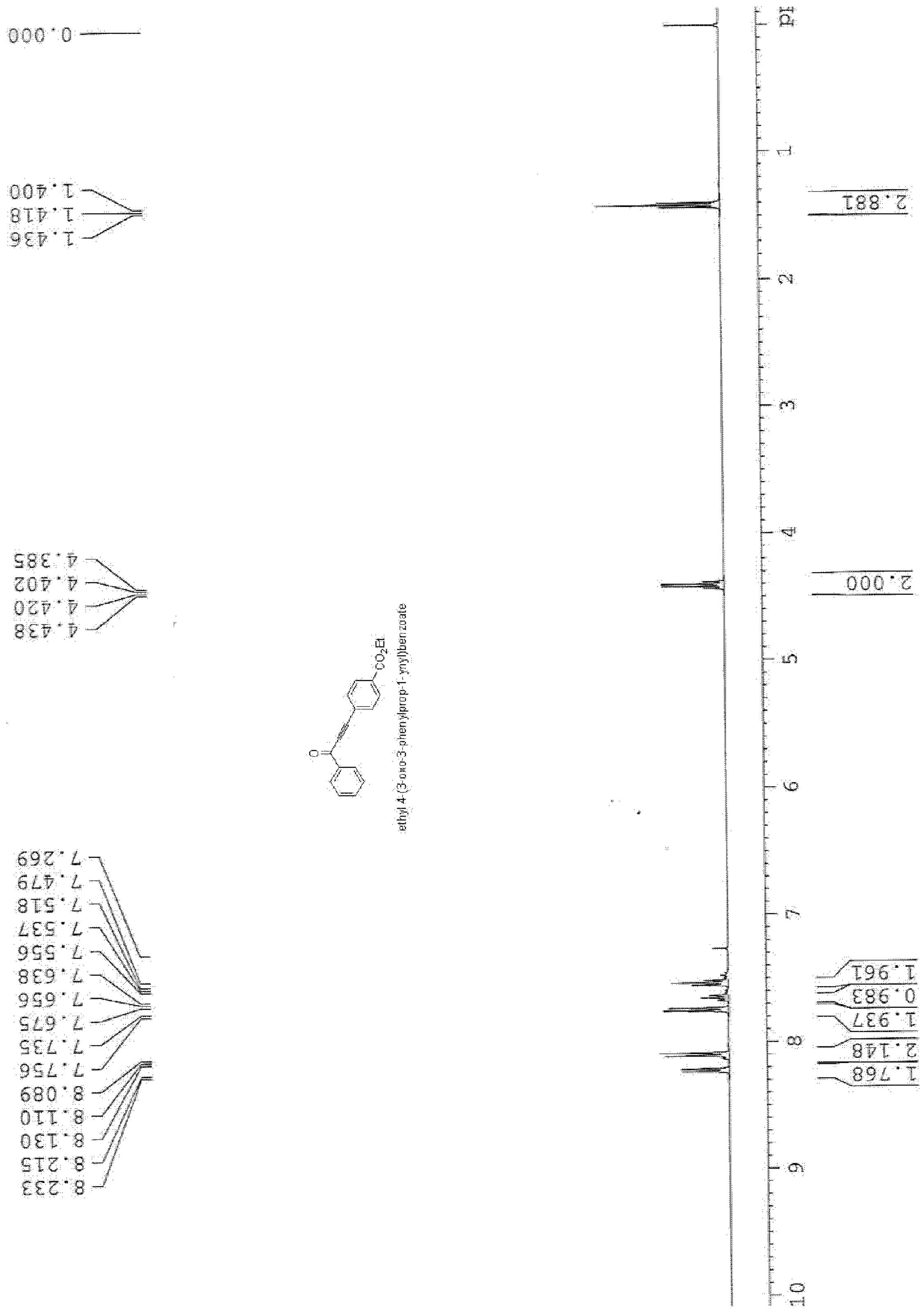
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA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1.436
4.385
4.402
4.420
4.438
7.269
7.479
7.518
7.537
7.556
7.638
7.656
7.675
7.735
7.756
8.089
8.110
8.130
8.215
8.233
2.881
2.000
1.961
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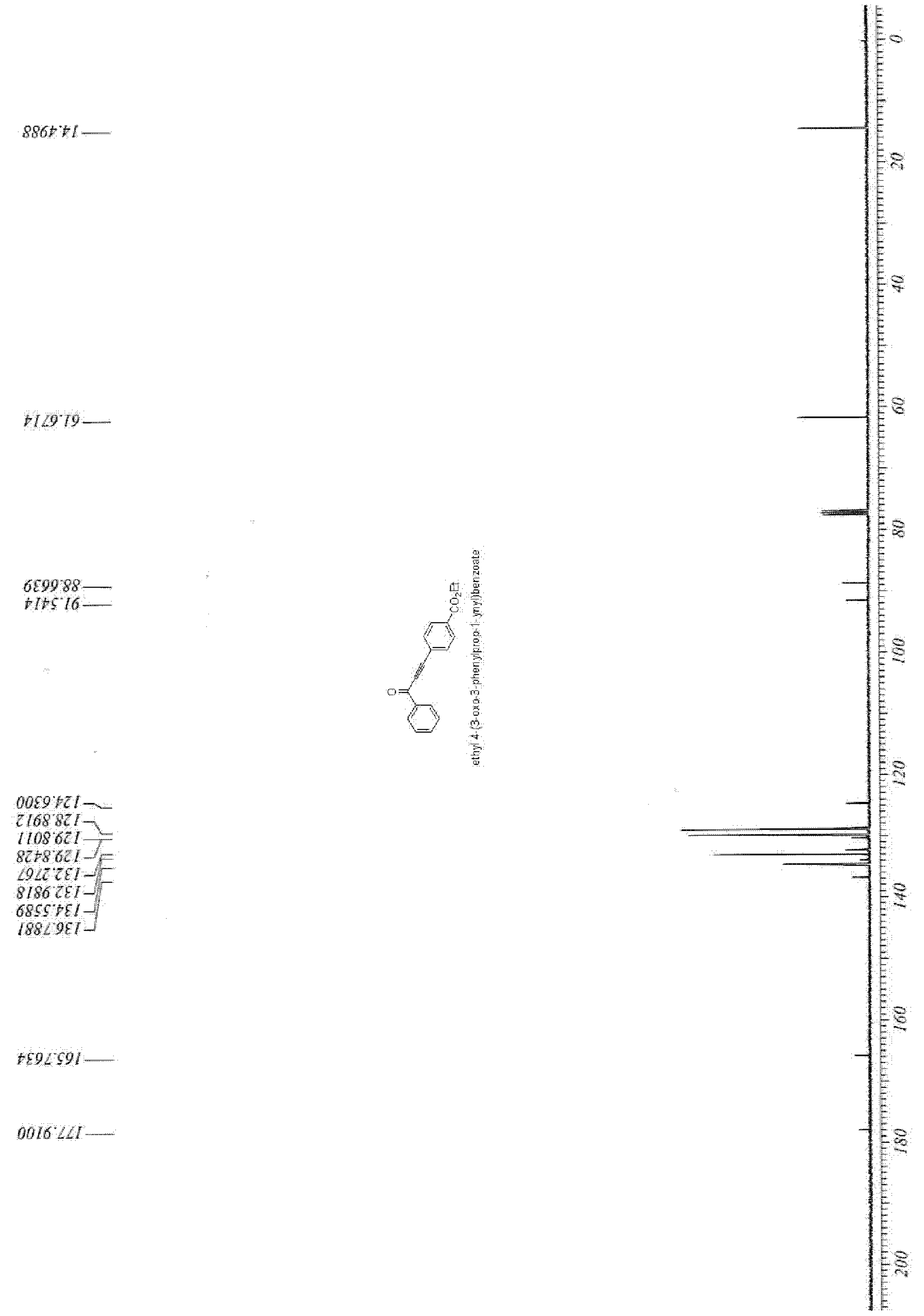
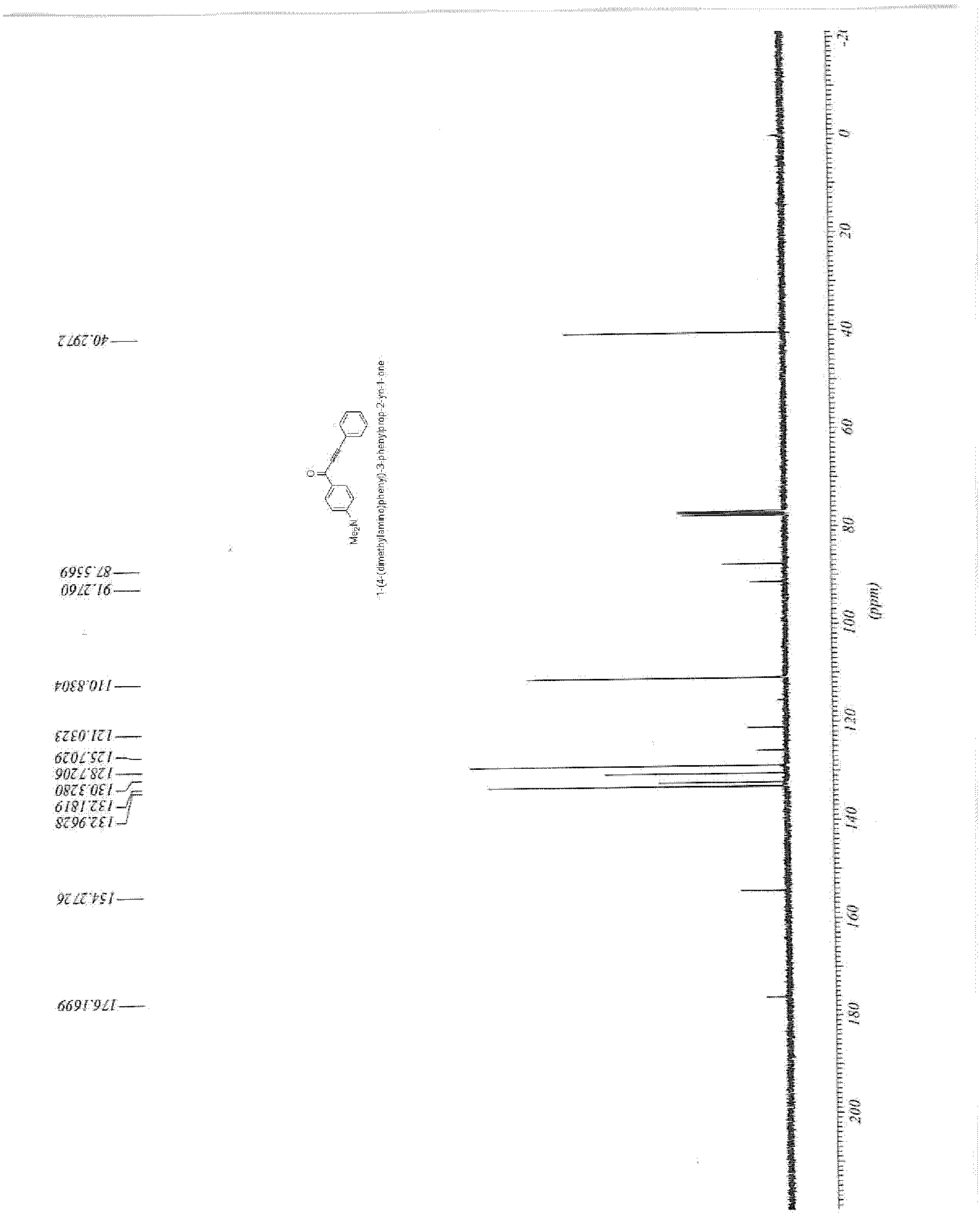
1.937
2.148
1.768
ppm
1
2
3
4
5
6
7
8
9
10



ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate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121.0323
125.7029
128.7206
130.3280
132.1819
132.9628
154.2726
176.1699
Me2N
O
1-(4-(dimethylamino)phenyl)-3-phenylprop-2-yn-1-one
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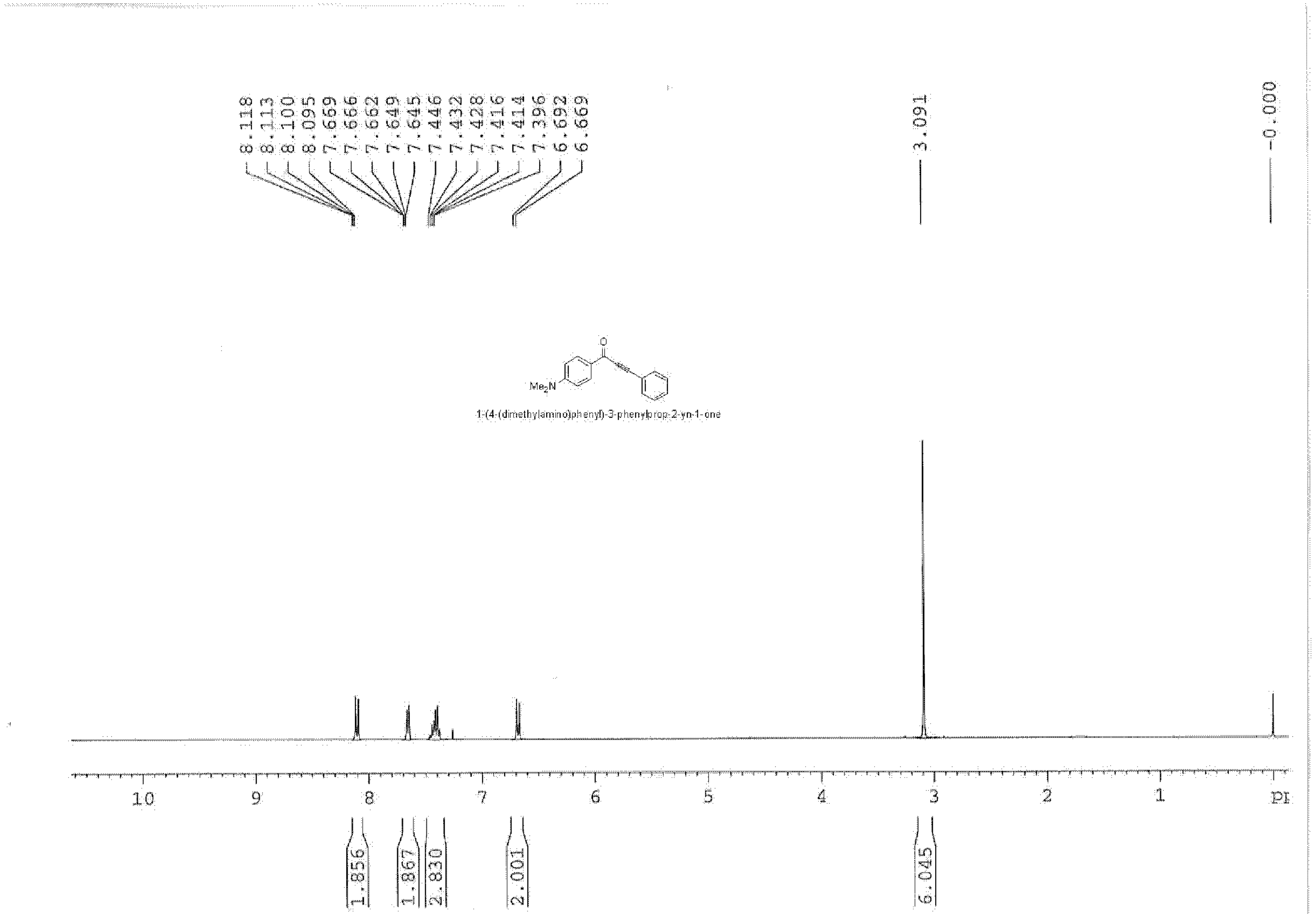
0
20
40
60
80
100
120
140
160
180
200
(ppm)



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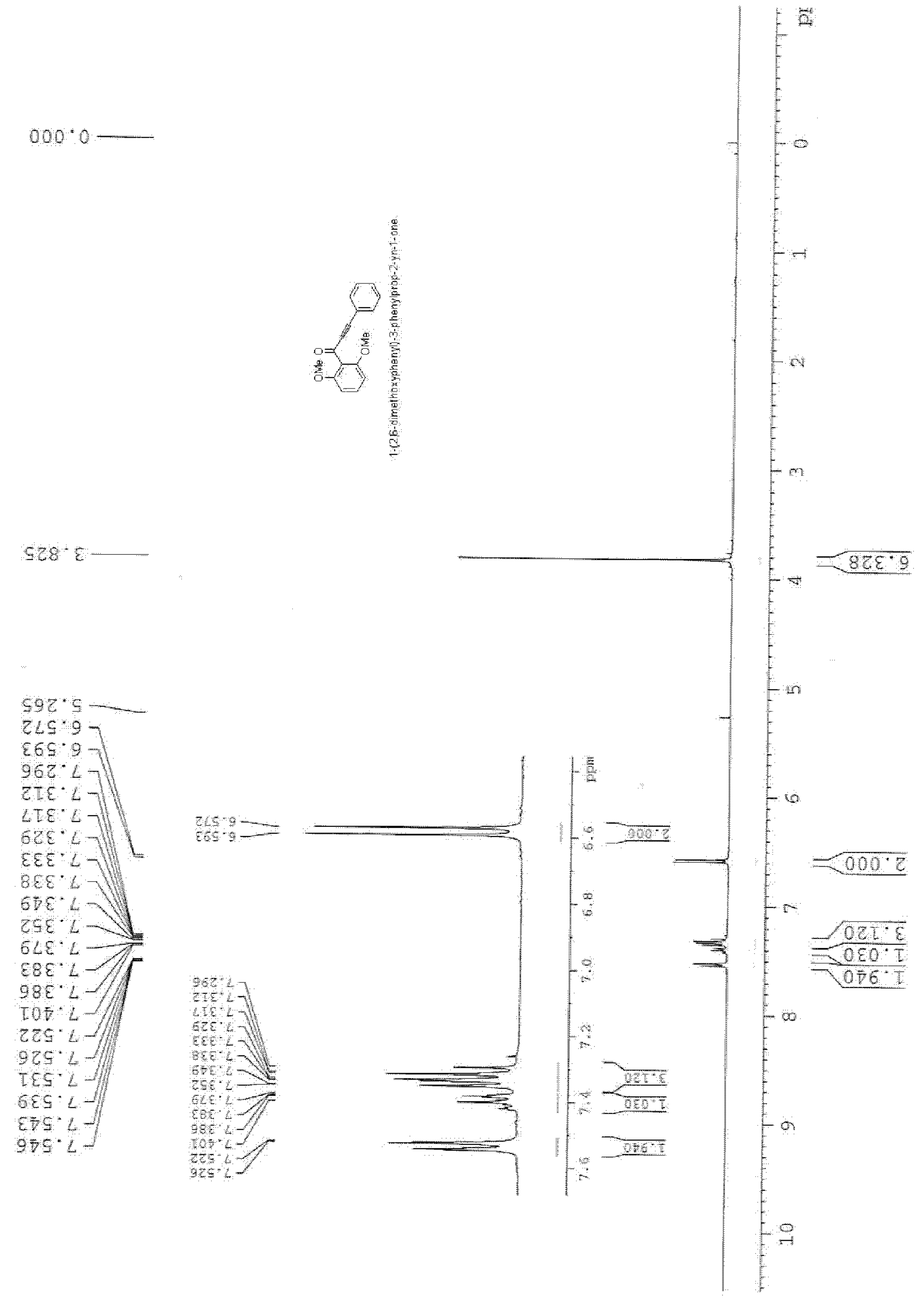
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OMe
O
OMe
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5.265
6.572
6.593
7.296
7.312
7.317
7.329
7.333
7.338
7.349
7.352
7.379
7.383
7.386
7.401
7.522
7.526
7.531
7.539
7.543
7.546
6.328
2.000
3.120
1.030
1.940
ppm
6.6
6.8
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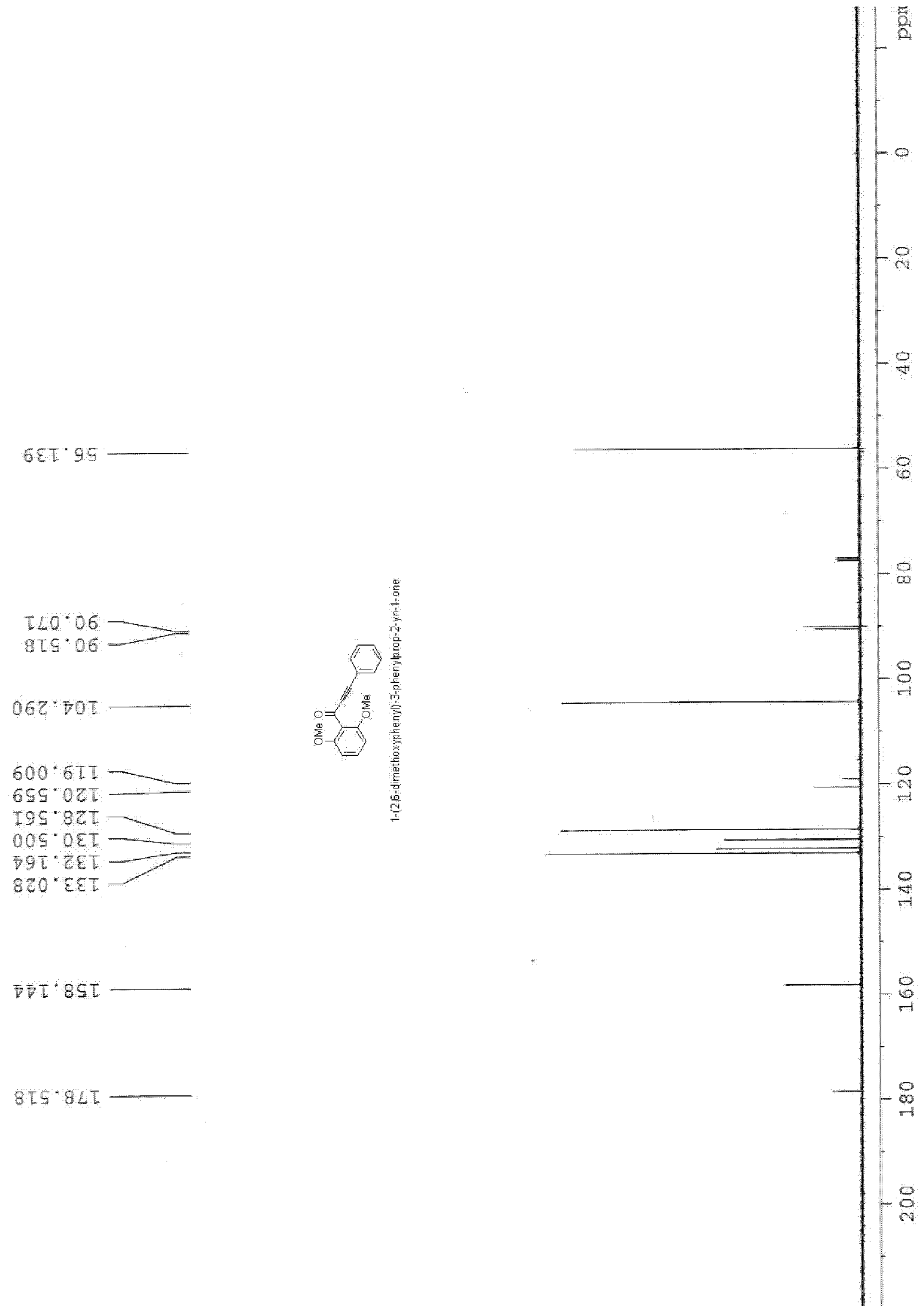
8
9
10
ppm



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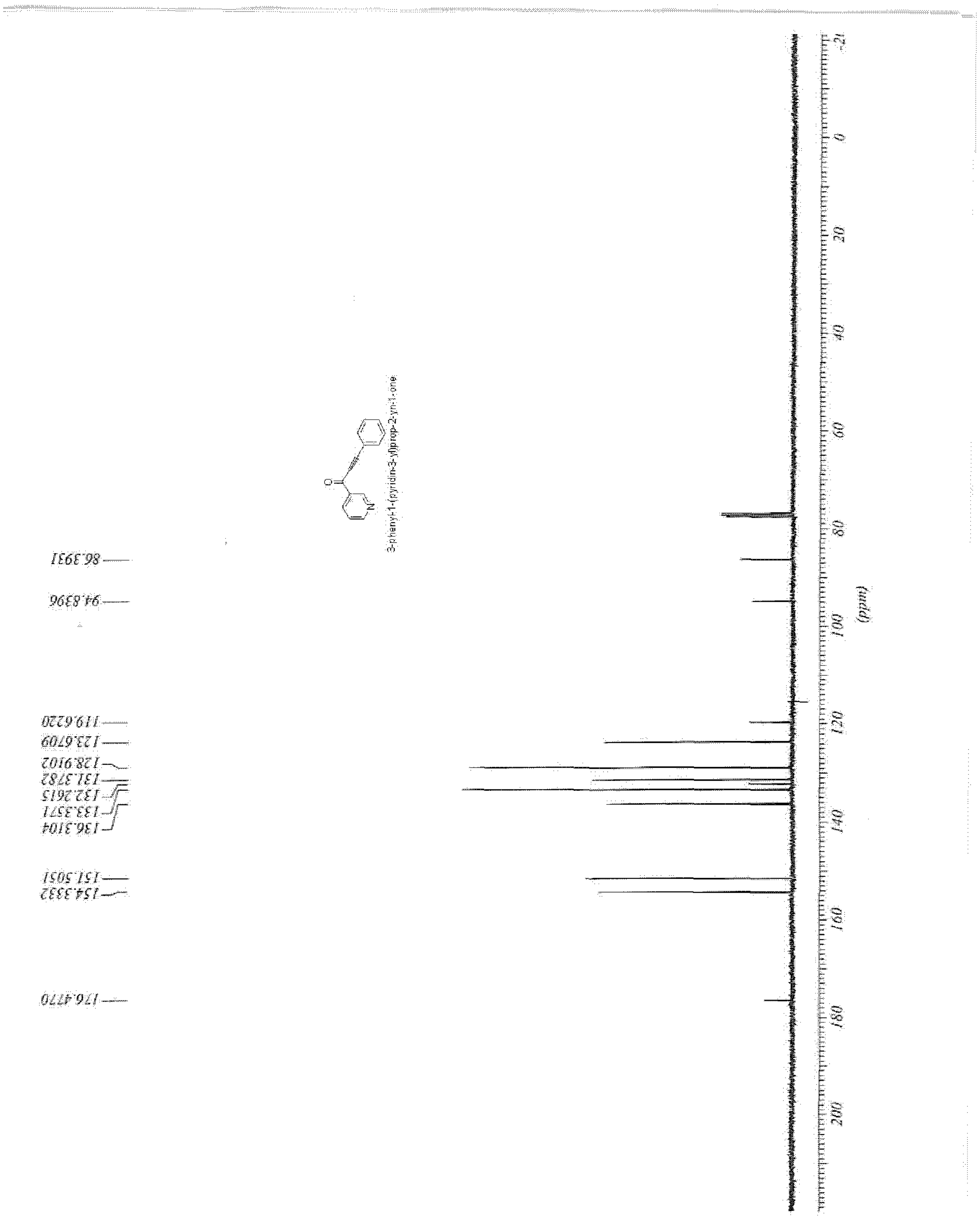
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N
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131.3782
132.2615
133.3571
136.3104
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176.4770
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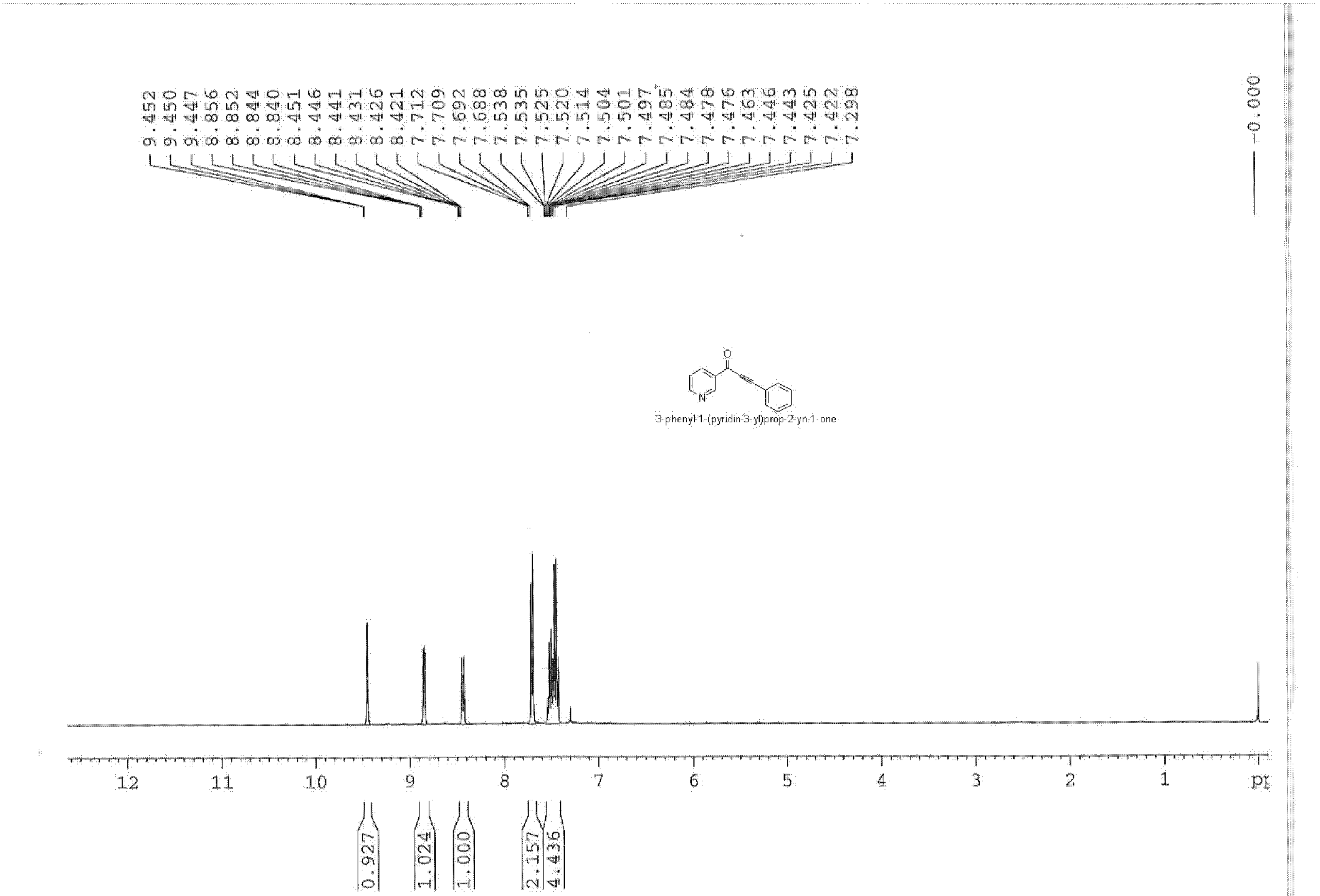
20
40
60
80
100
120
140
160
180
200
(ppm)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7.712
7.709
7.692
7.688
7.538
7.535
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7.514
7.504
7.501
7.497
7.485
7.484
7.478
7.476
7.463
7.446
7.443
7.425
7.422
7.298
-0.000
O
N
3-phenyl-1-(pyridin-3-yl)prop-2-yn-1-one
12
11
10
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8
7
6
5
4
3
2
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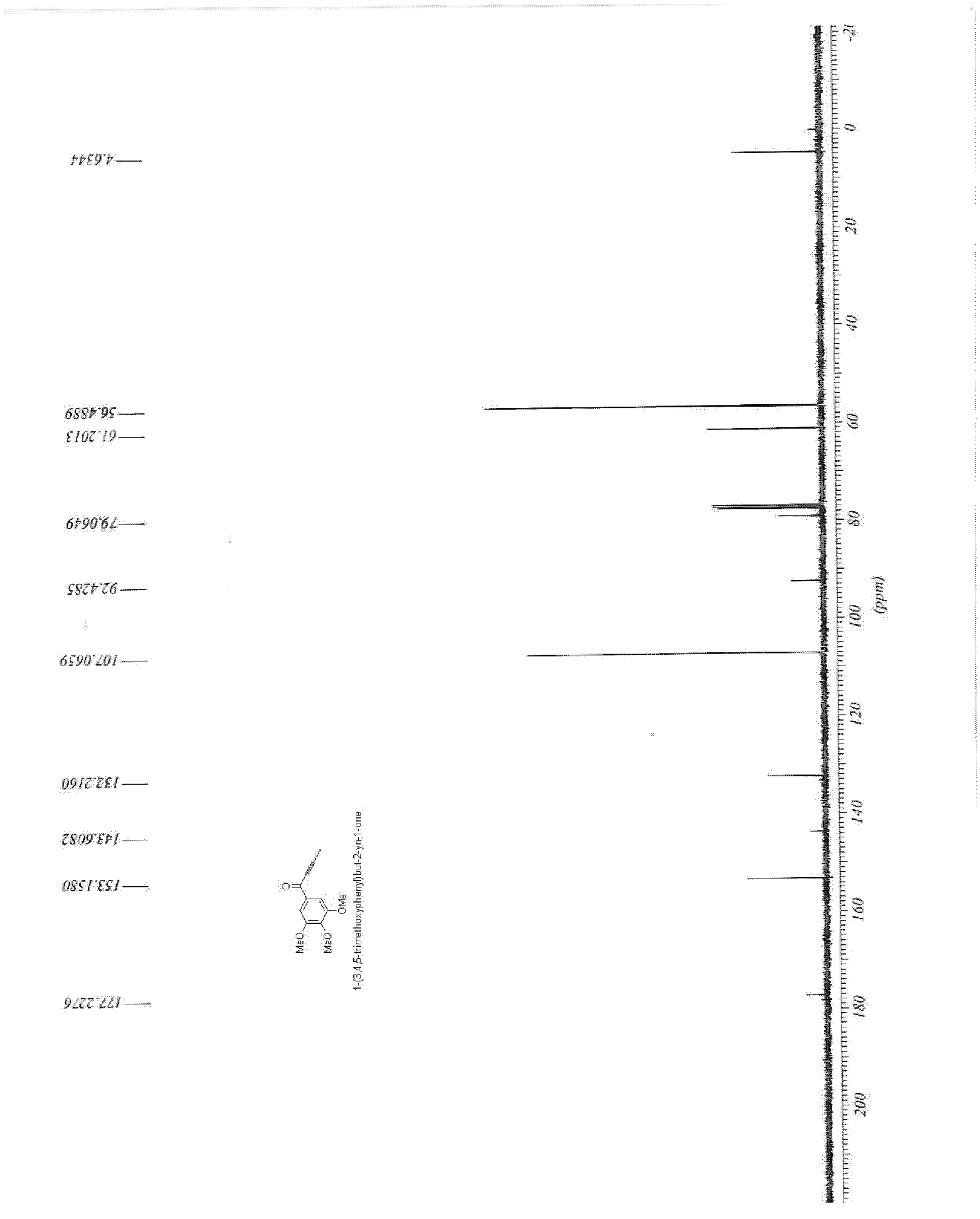
1.000
2.157
4.436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MeO
MeO
OMe
O
1-(3,4,5-trimethoxyphenyl)but-2-yn-1-one
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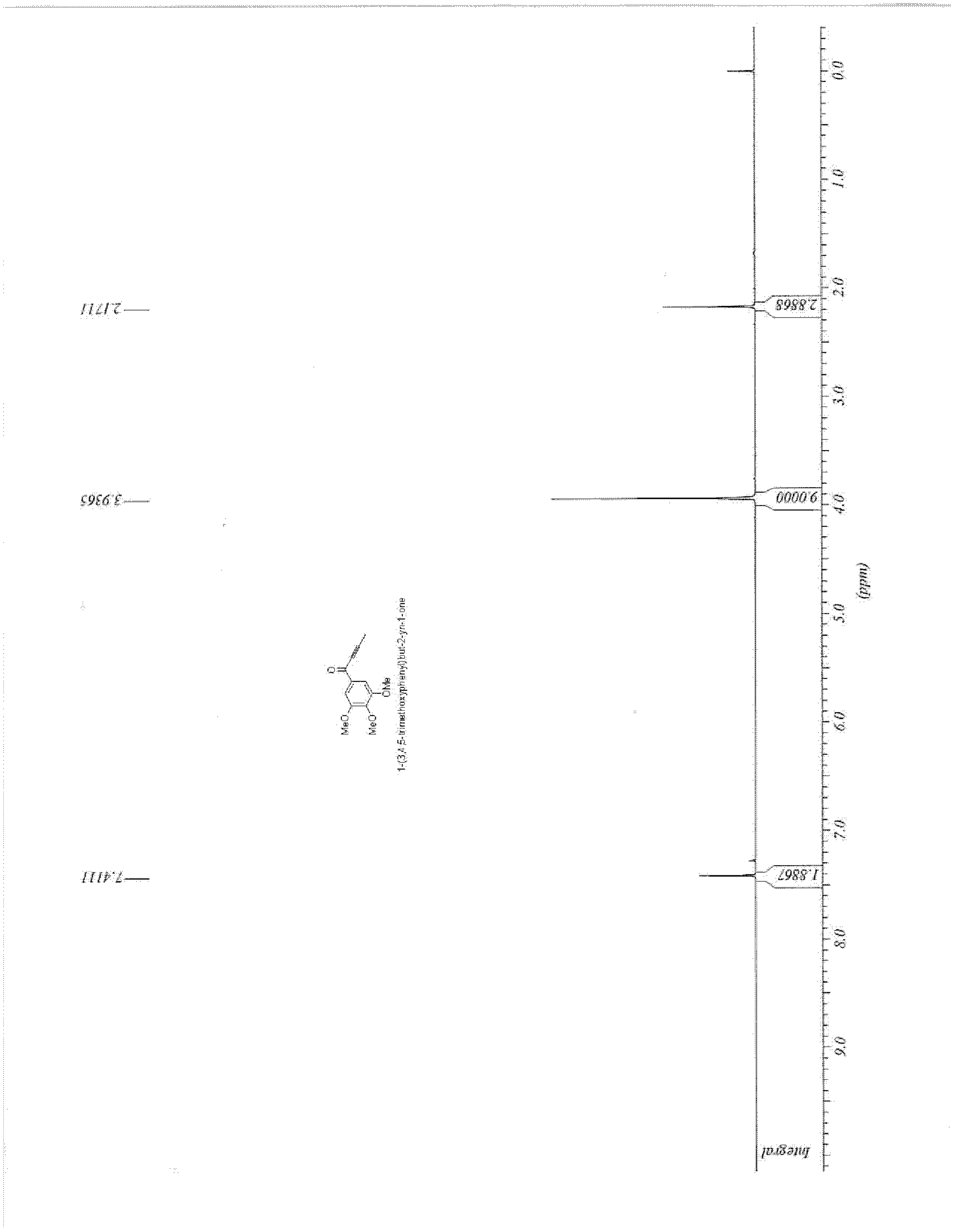
20
40
60
80
100
120
140
160
180
200
(ppm)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5.0
6.0
7.0
8.0
9.0
(ppm)
Integral
MeO
MeO
OMe
O
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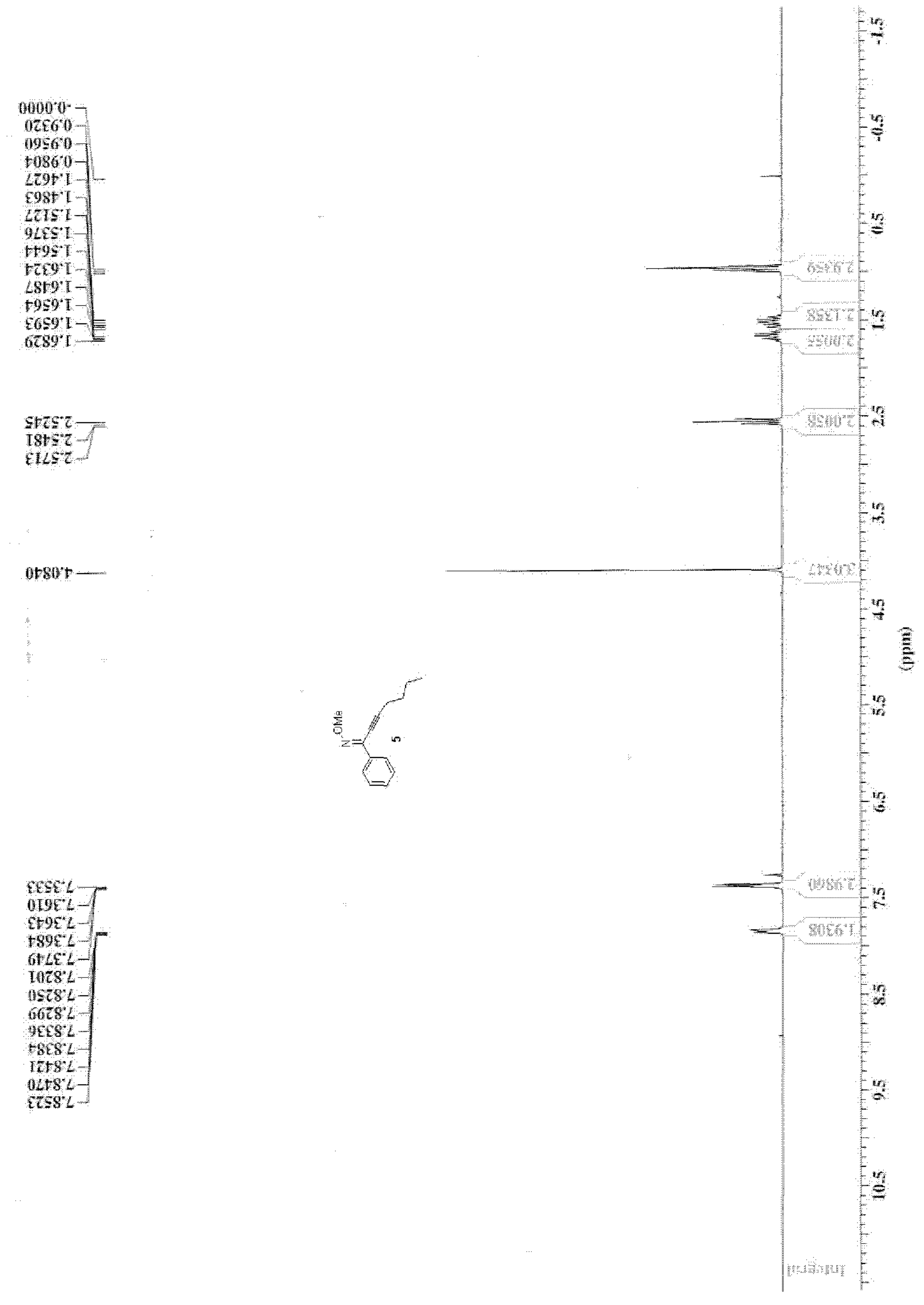
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7.3749
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7.8470
7.8523
N
OMe
5
2.9359
2.1358
2.0055
2.0038
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1.9308
Integral
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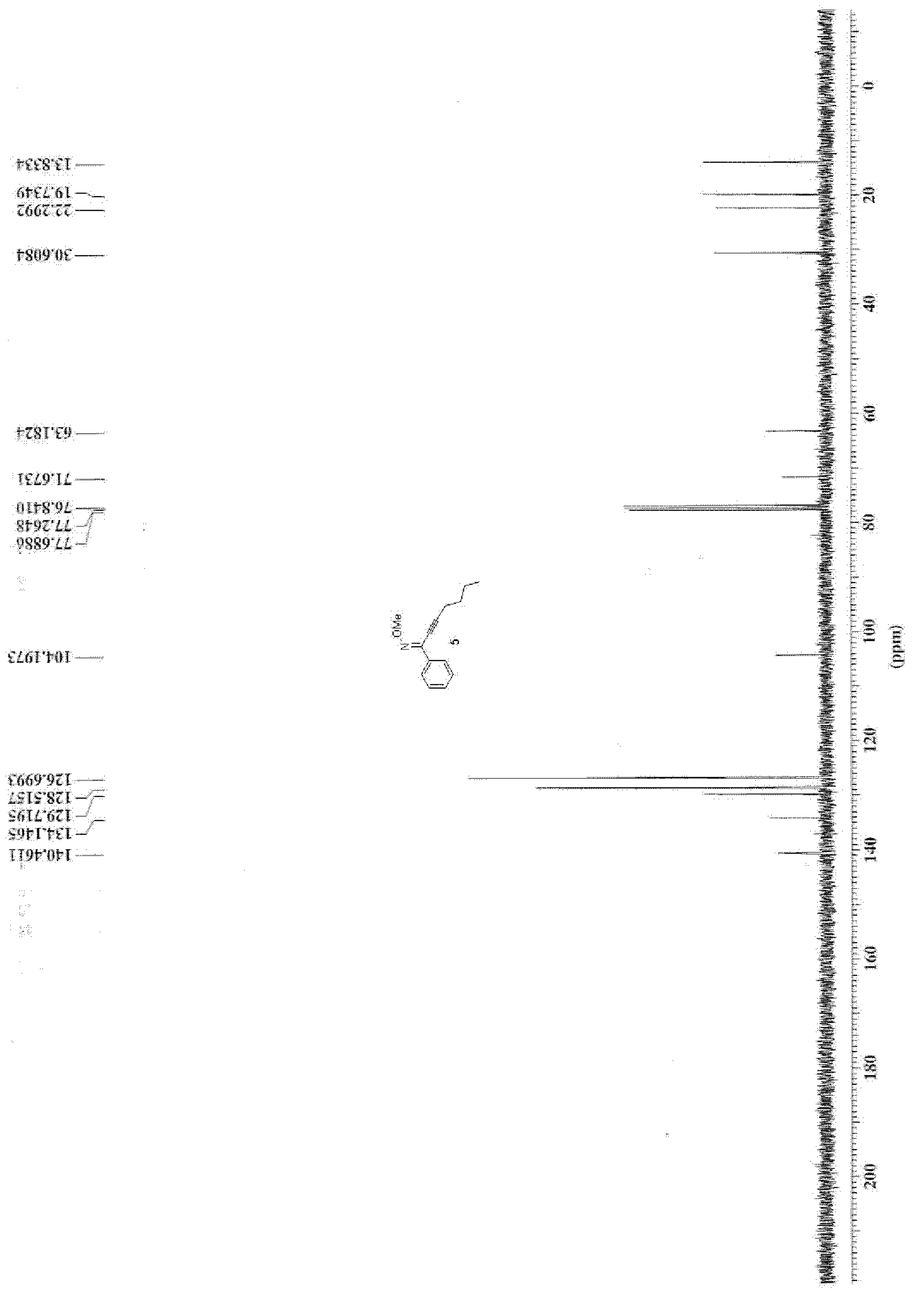
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128.5157
129.7195
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N
OMe
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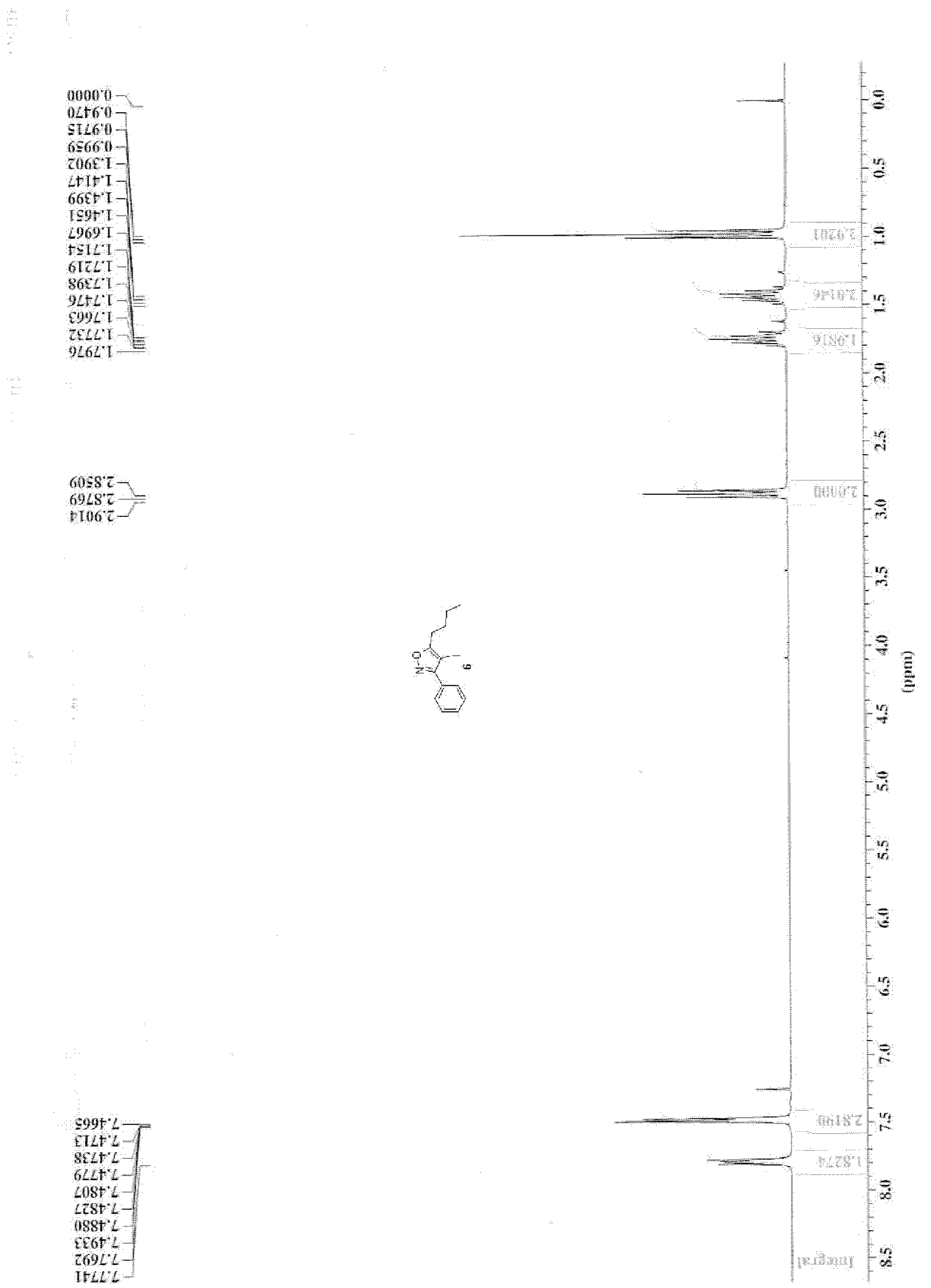
40
60
80
100
120
140
160
180
200
(ppm)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1.7219
1.7398
1.7476
1.7663
1.7732
1.7976
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2.8769
2.9014
7.4665
7.4713
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7.4807
7.4827
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7.4933
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N-O
9
2.9201
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1.9816
2.0000
2.8190
1.8274
Integral
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1.5
2.0
2.5
3.0
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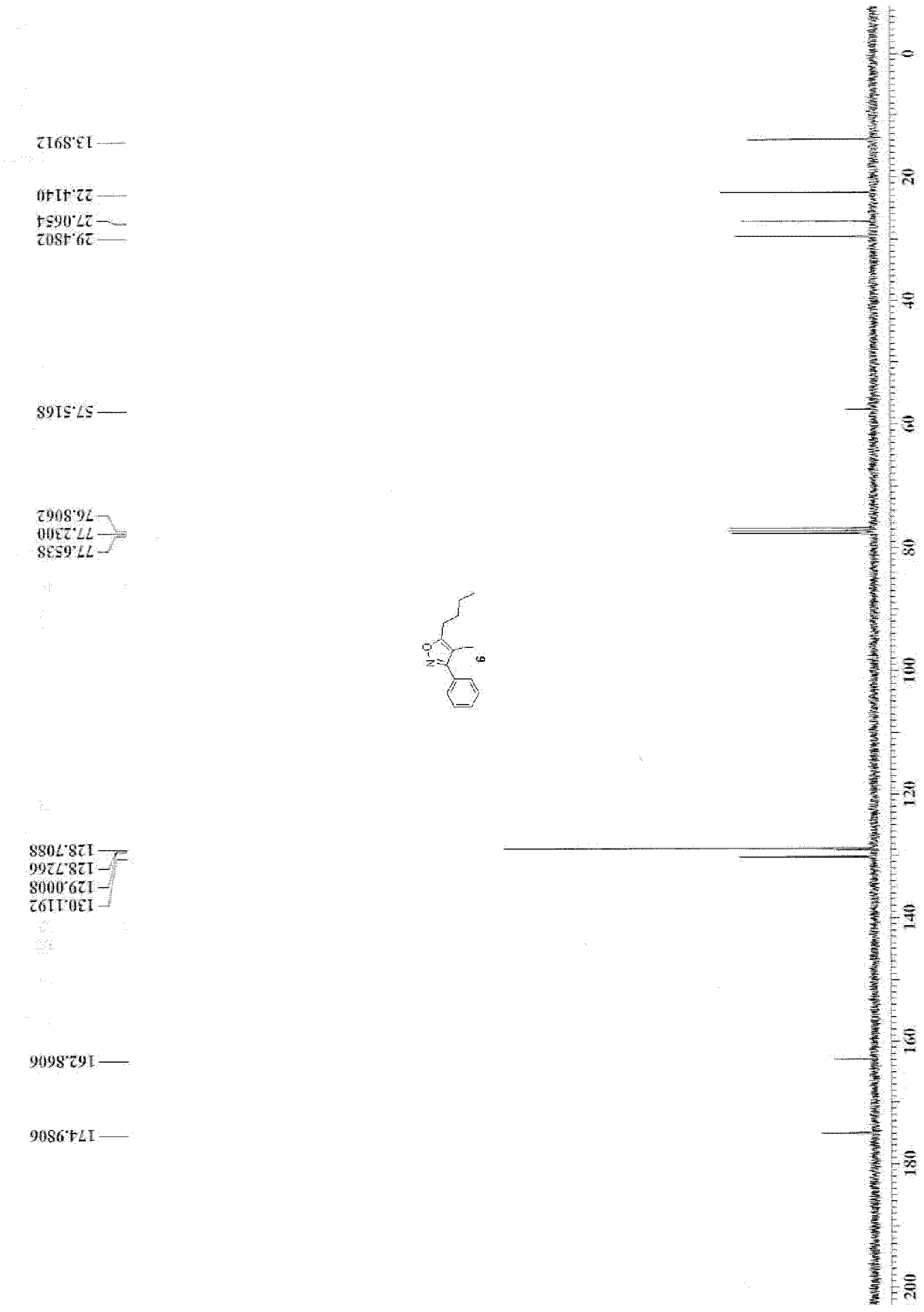
(ppm)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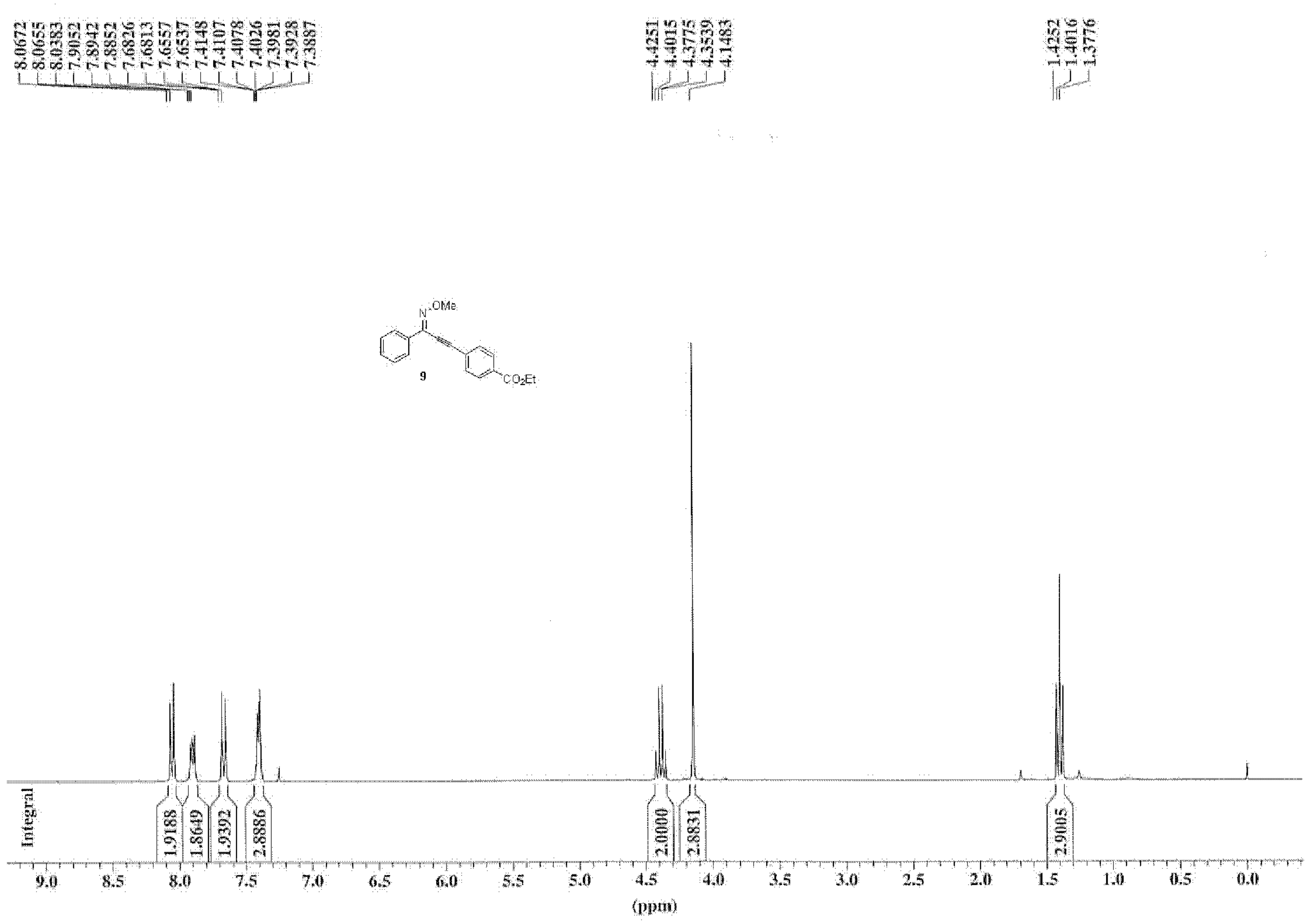

9

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7.3981
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7.3887
4.4251
4.4015
4.3775
4.3539
4.1483
1.4252
1.4016
1.3776
N
OMe
CO$_2$Et
Integral
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1.8649
1.9392
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2.0000
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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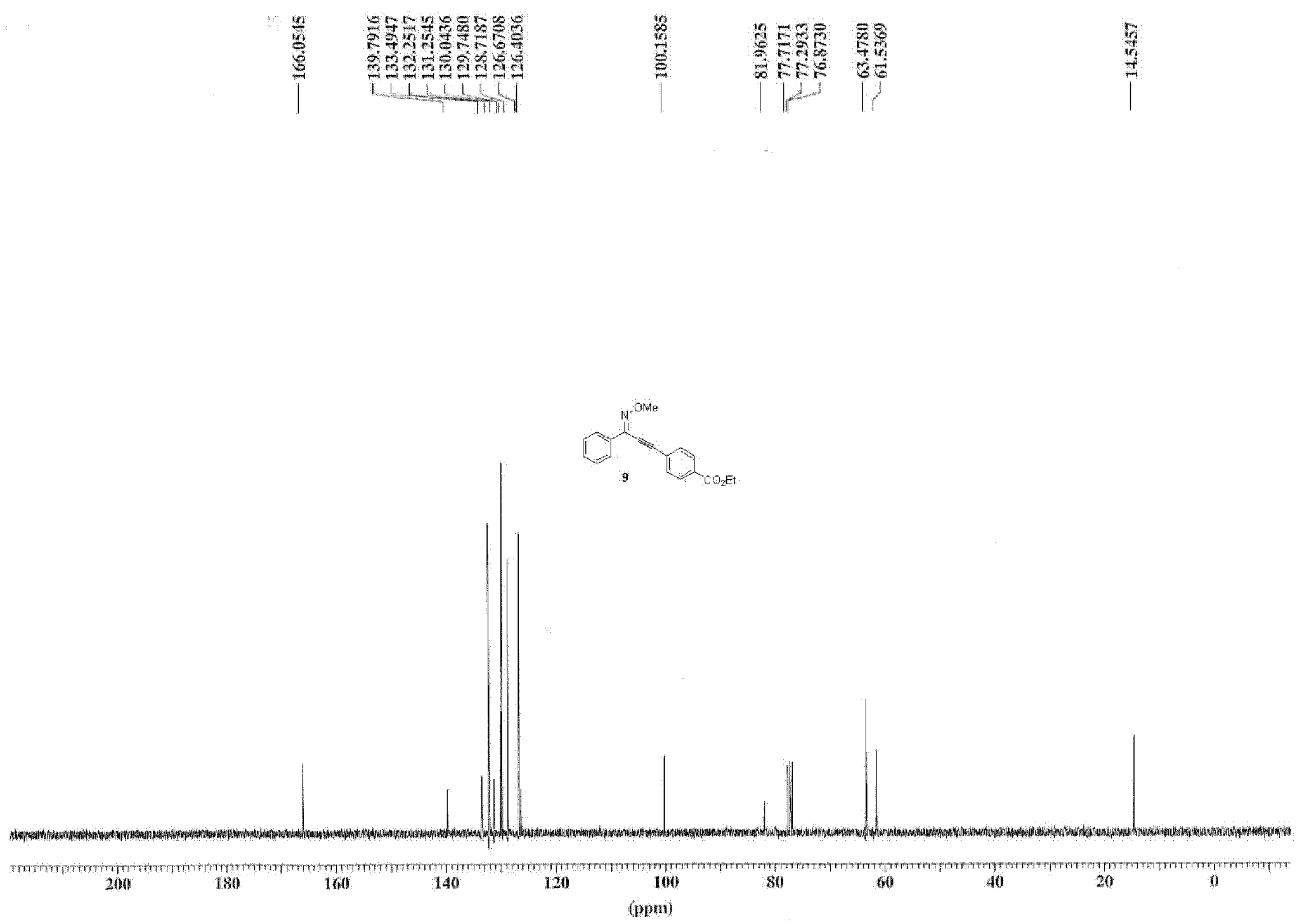
(ppm)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81.9625
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77.2933
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61.5369
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120
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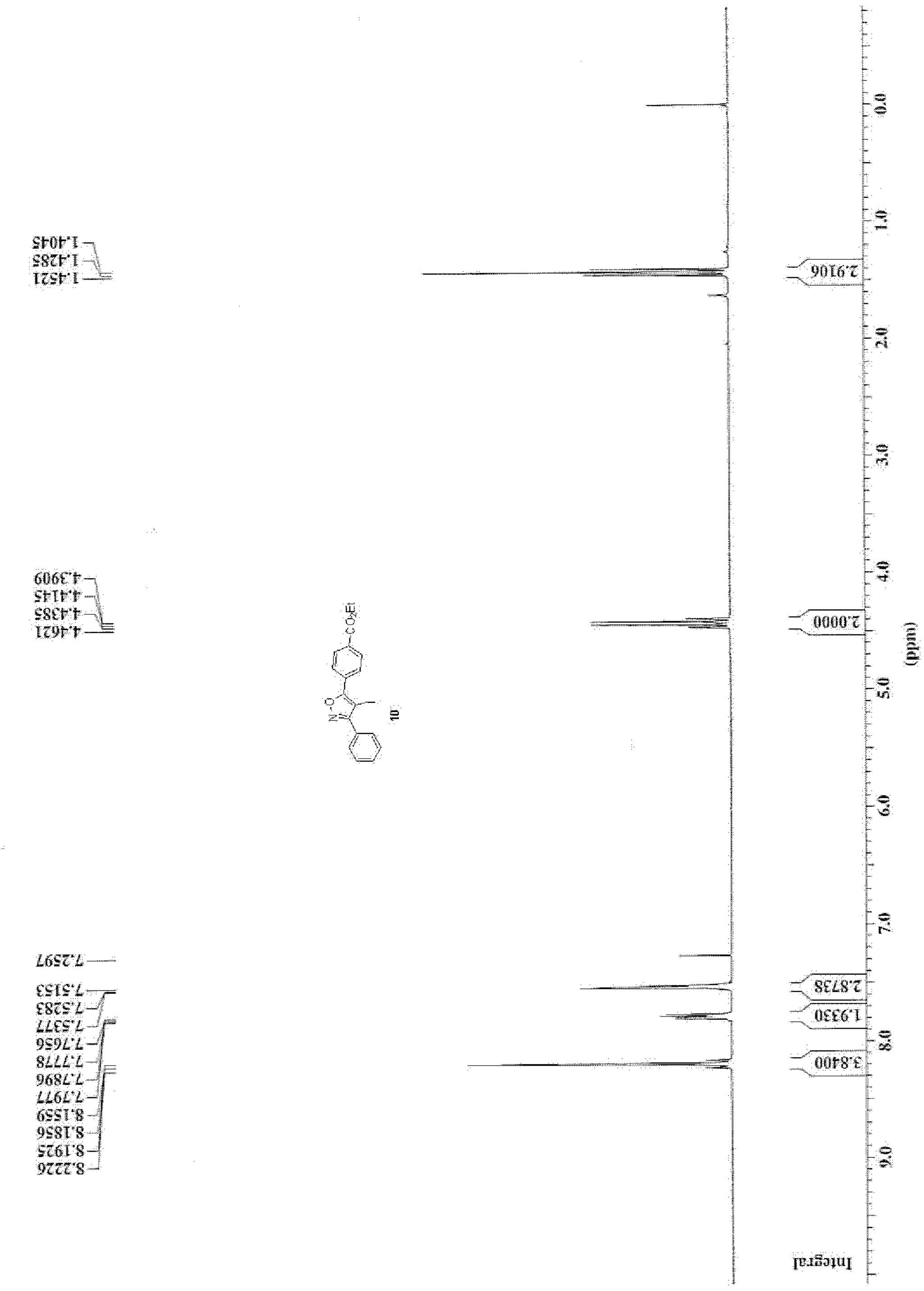
40
20
0
(ppm)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8.1925
8.2226
CO2Et
N-O
10
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2.8738
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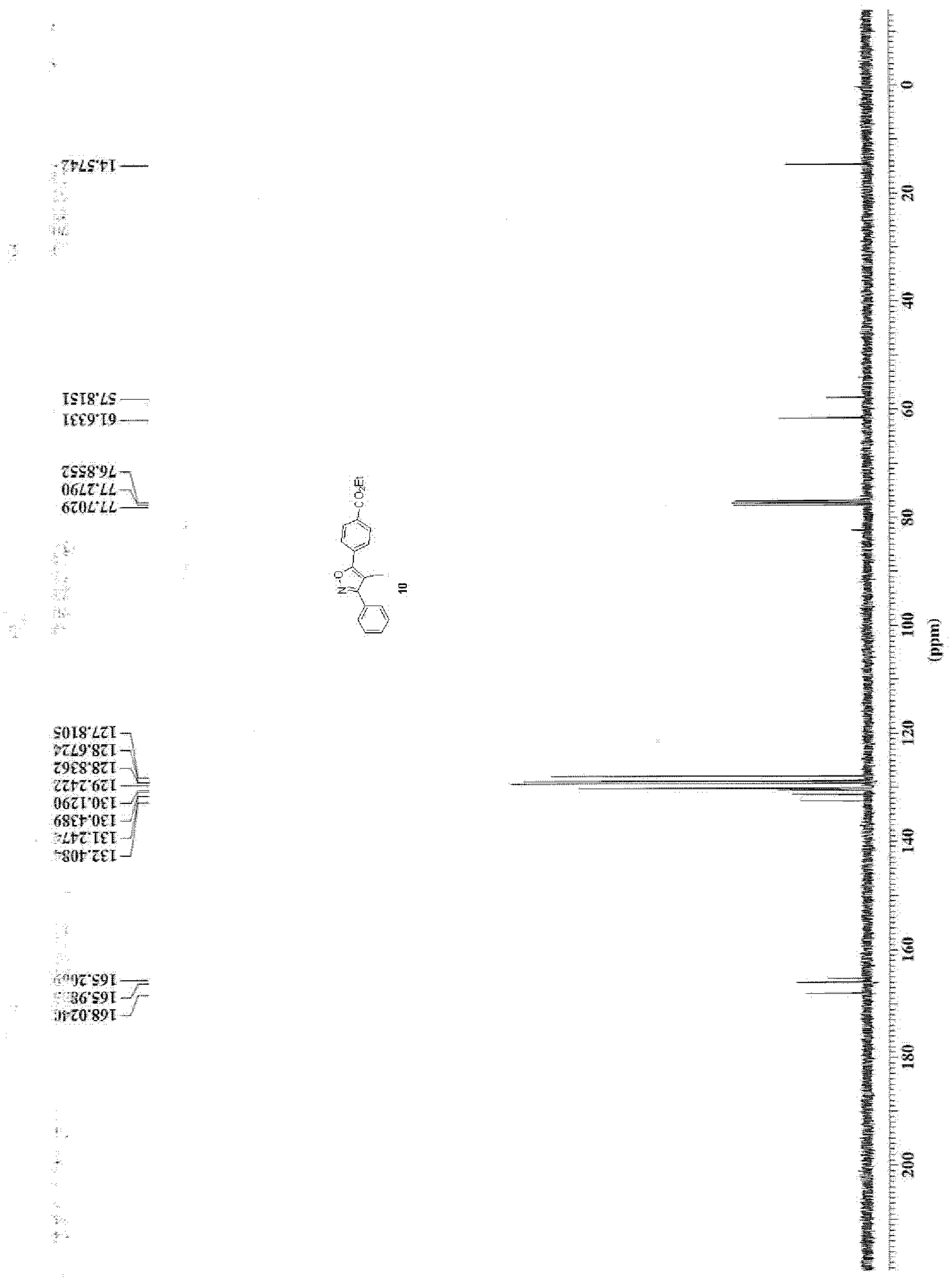
3.8400
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
(ppm)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130.1290
130.4389
131.247
132.408
165.26
165.98
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CO₂Et
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0
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80
100
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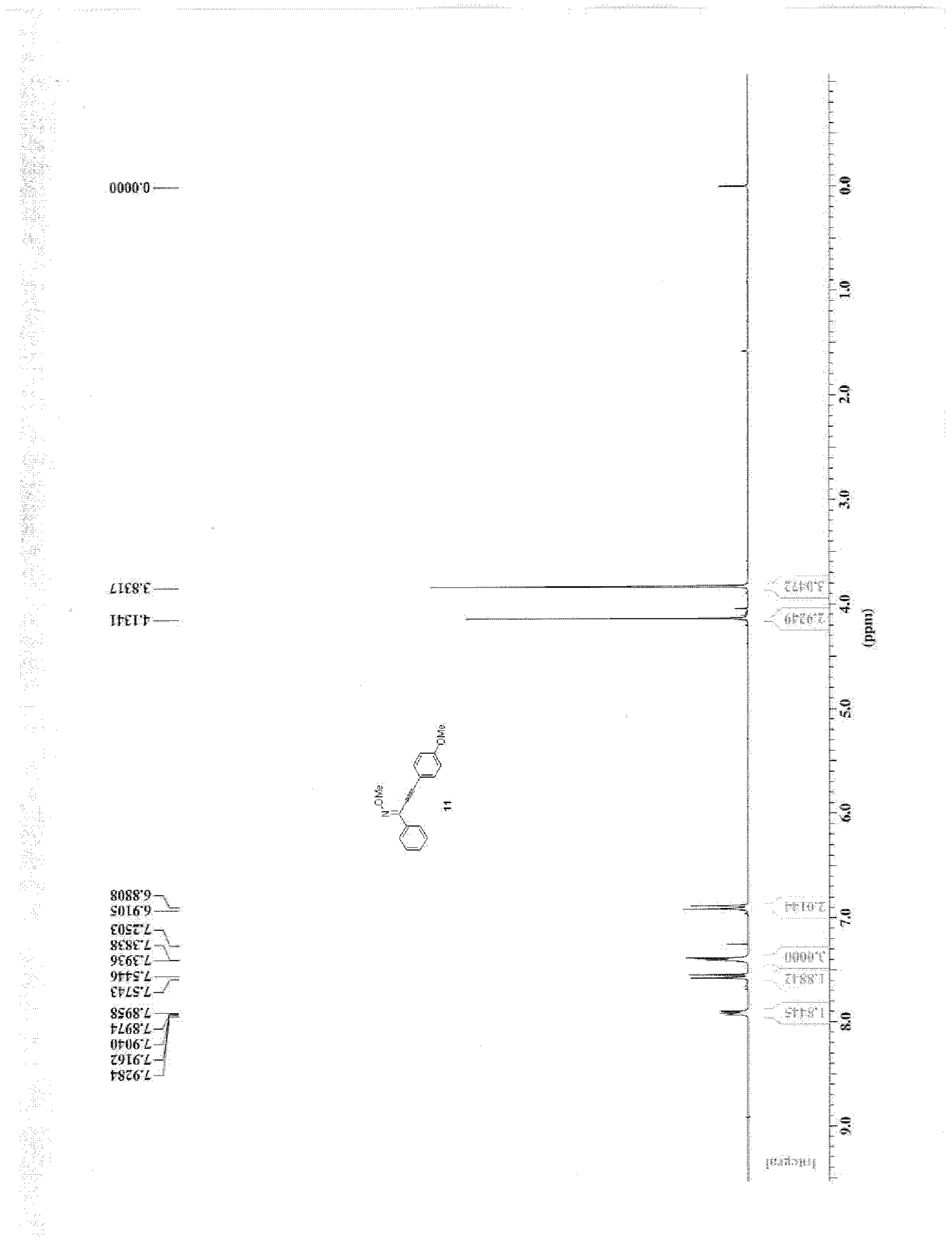
200
(ppm)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7.8958
7.8974
7.9040
7.9162
7.9284
N
OMe
OMe
11
3.0472
2.9249
2.0144
3.0000
1.8812
1.8445
Integral
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7.0
6.0
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4.0
3.0
2.0
1.0
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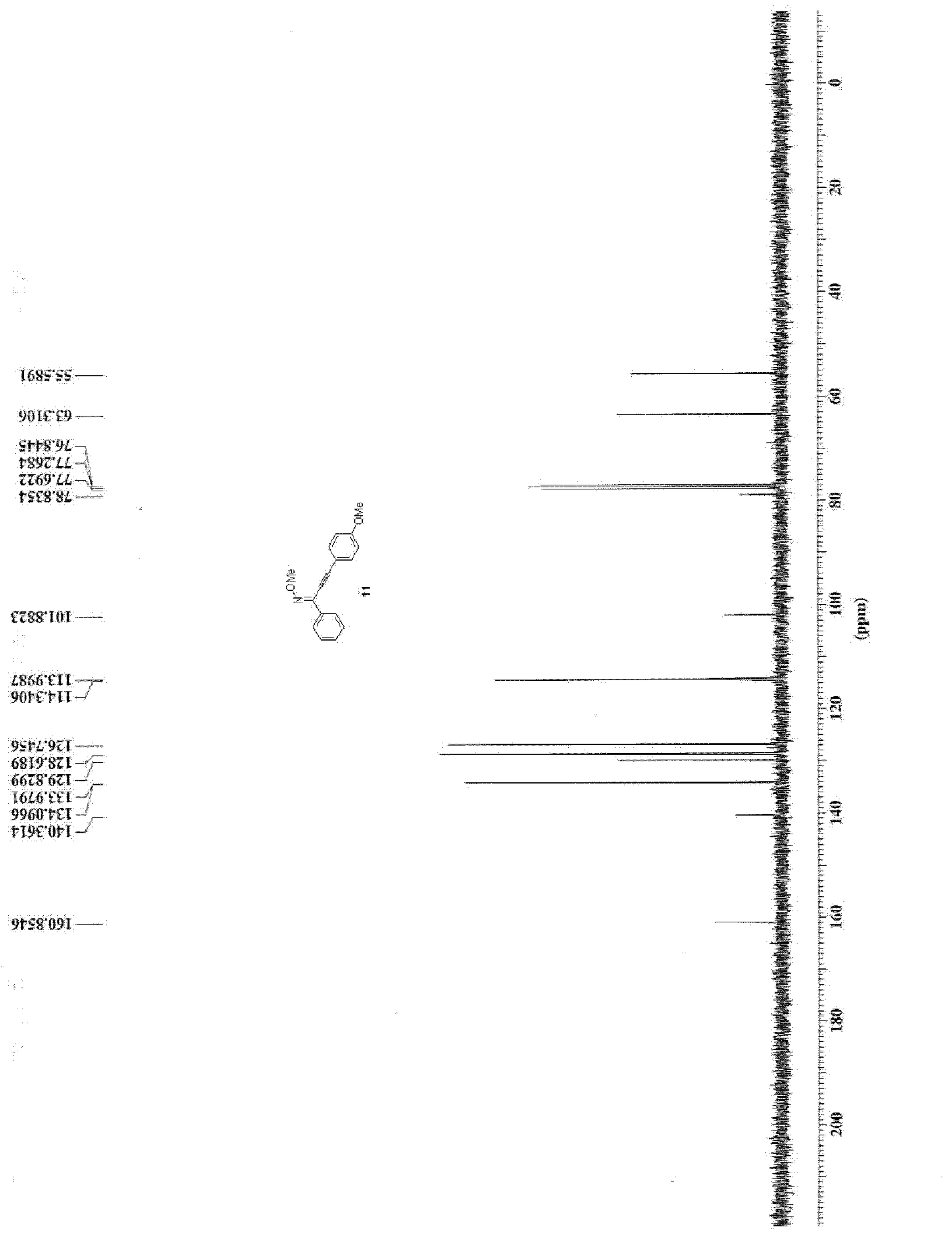
(ppm)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101.8823
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114.3406
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128.6189
129.8299
133.9791
134.0966
140.3614
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OMe
OMe
11
0
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180
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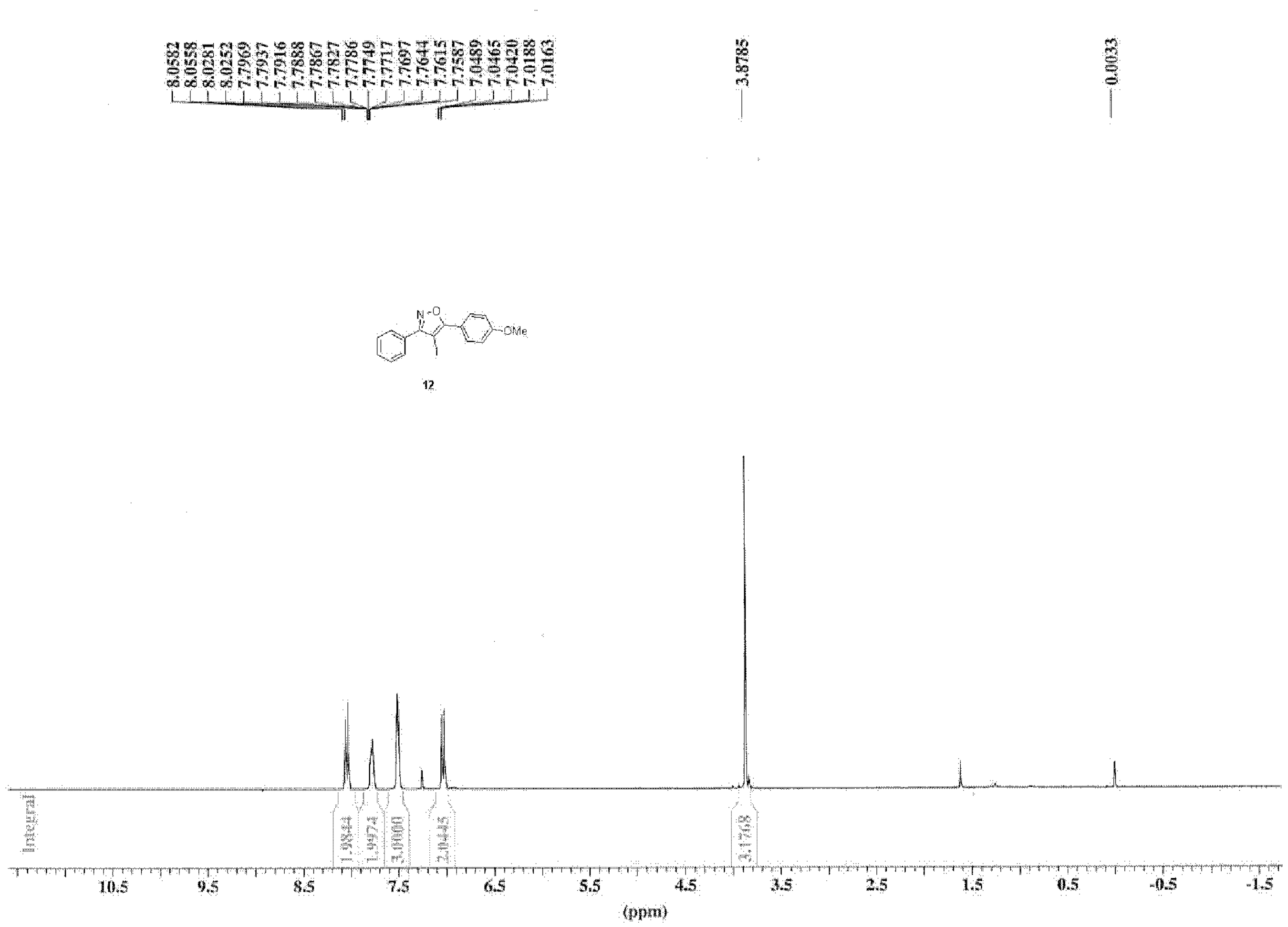
(ppm)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7.7916
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7.7867
7.7827
7.7786
7.7749
7.7717
7.7697
7.7644
7.7615
7.7587
7.0489
7.0465
7.0420
7.0188
7.0163
3.8785
0.0033
N-O
I
OMe
12
Integral
1.9844
1.9974
3.0000
2.0445
3.1768
10.5
9.5
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5.5
4.5
3.5
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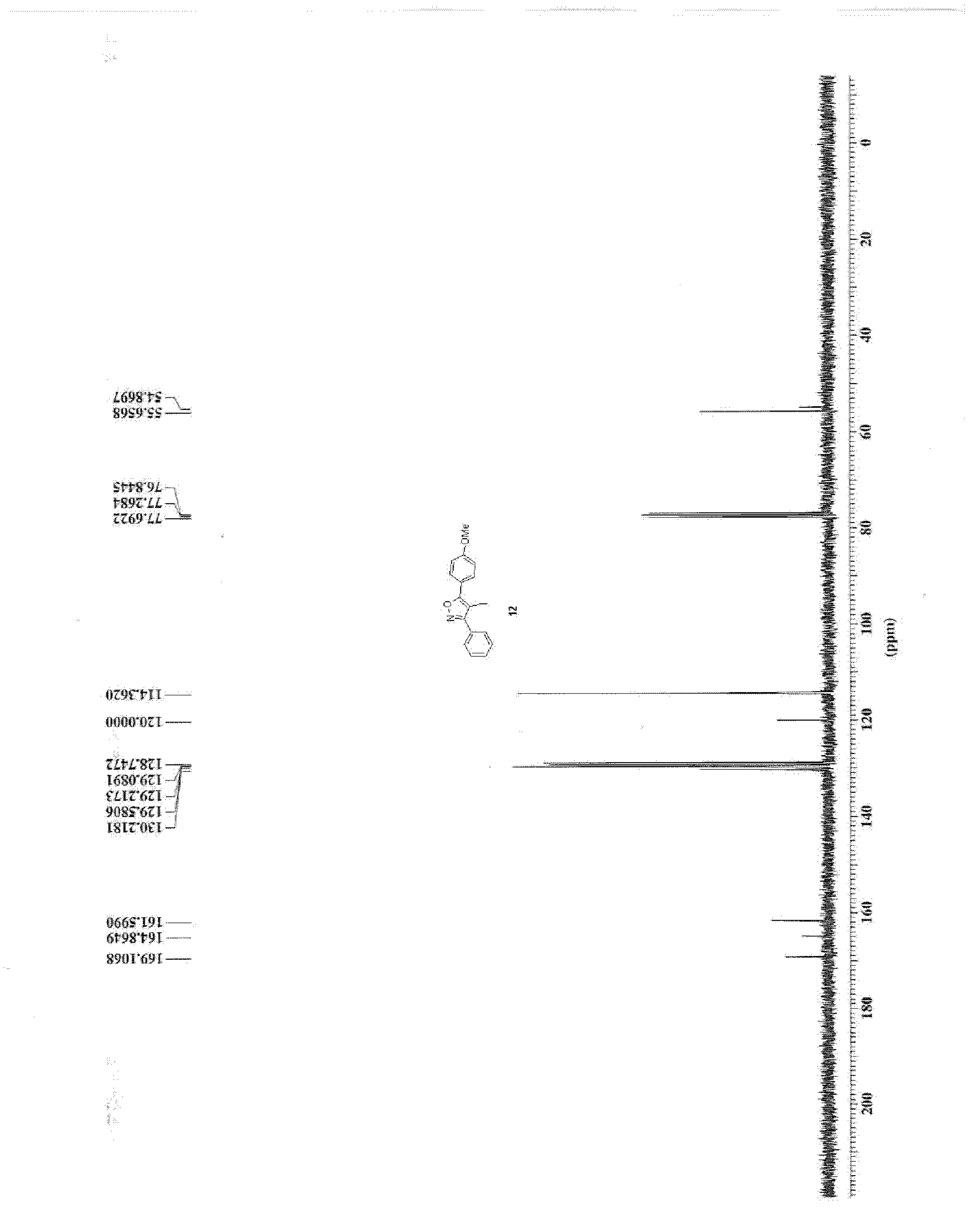
(ppm)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77.6922
114.3620
120.0000
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129.5806
130.2181
161.5990
164.8649
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N-O
OMe
12
0
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40
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80
100
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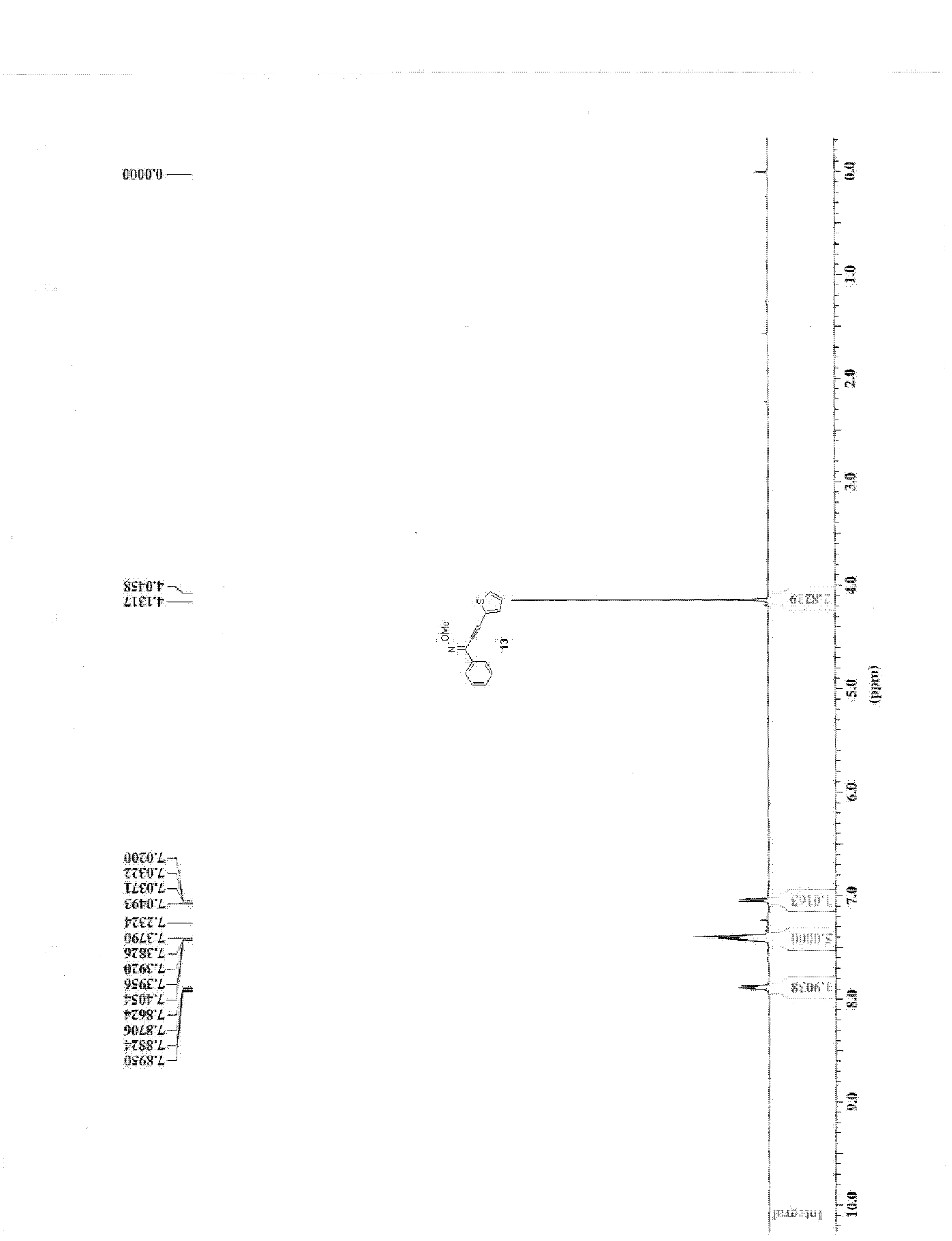
140
160
180
200
(ppm)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7.3920
7.3956
7.4054
7.8624
7.8706
7.8824
7.8950
S
N
OMe
13
2.8229
1.0163
5.0000
1.9038
Integral
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3.0
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6.0
7.0
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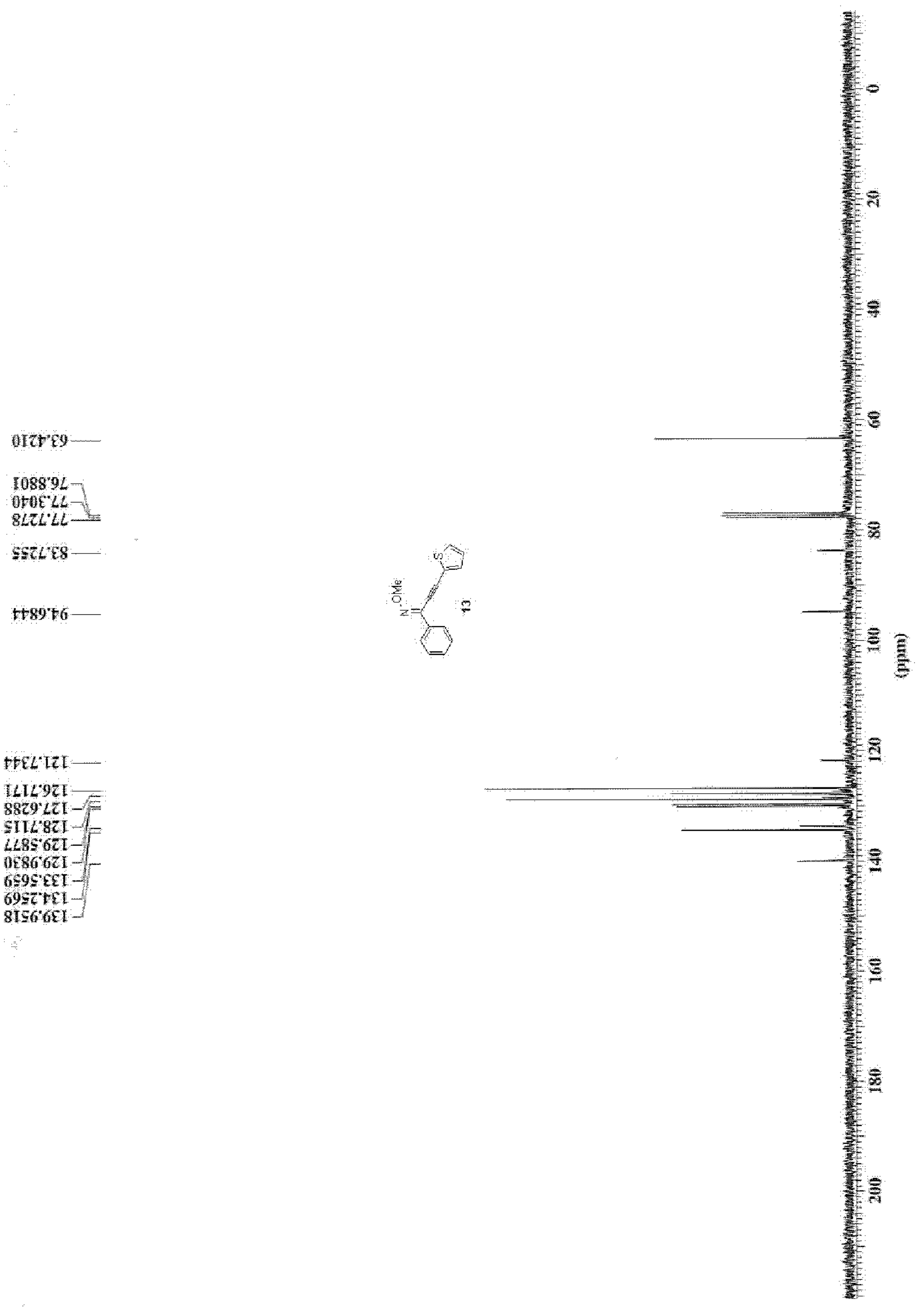
(ppm)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94.6844
121.7344
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127.6288
128.7115
129.5877
129.9830
133.5659
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OMe
S
13
0
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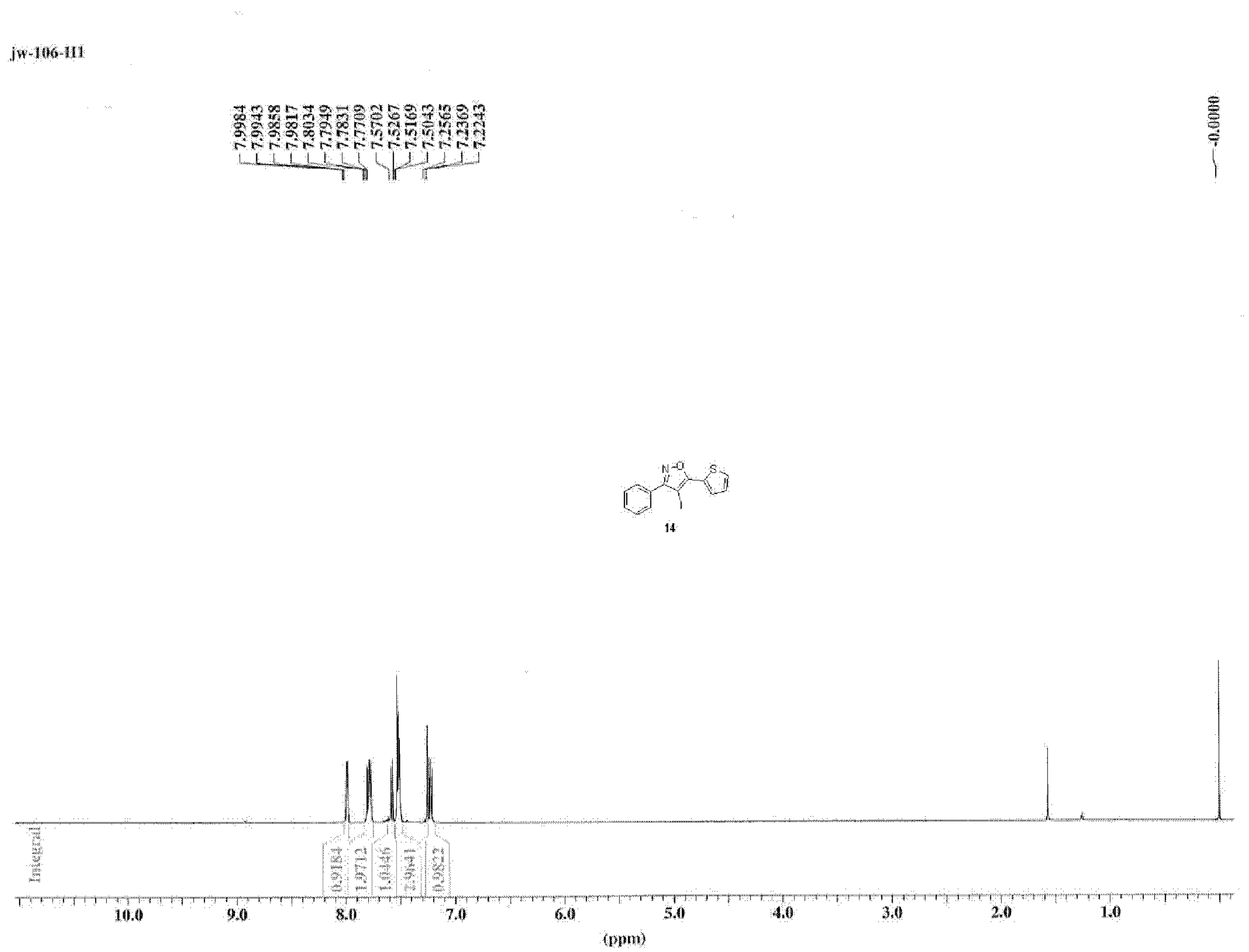
40
60
80
100
120
140
160
180
200
(ppm)


jw-106-H1
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7.9817
7.8034
7.7949
7.7831
7.7709
7.5702
7.5267
7.5169
7.5043
7.2565
7.2369
7.2243
-0.0000
N-O
S
14
Integral
0.9184
1.9712
1.0446
2.9641
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9.0
8.0
7.0
6.0
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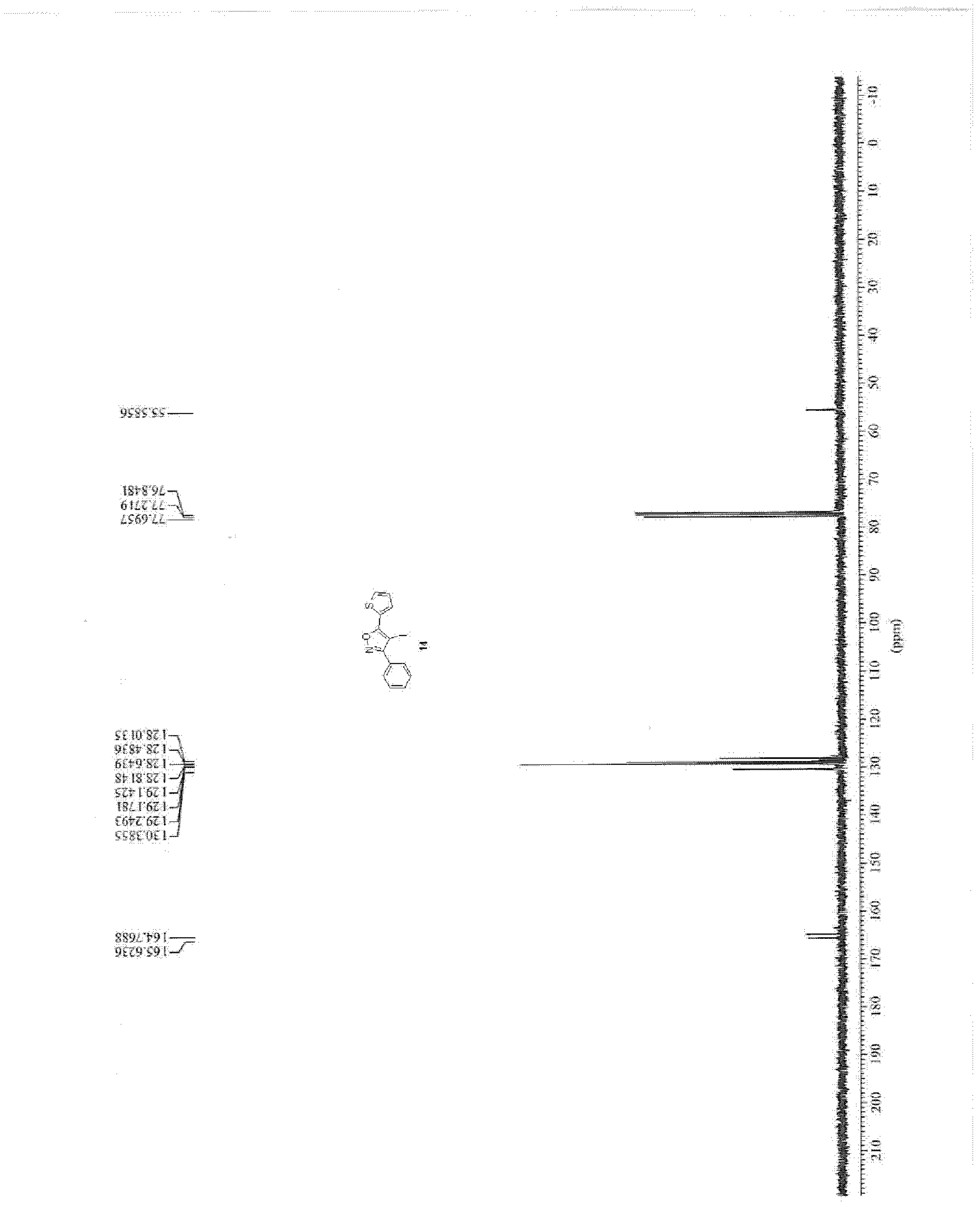
4.0
3.0
2.0
1.0
(ppm)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77.6957
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128.4836
128.6439
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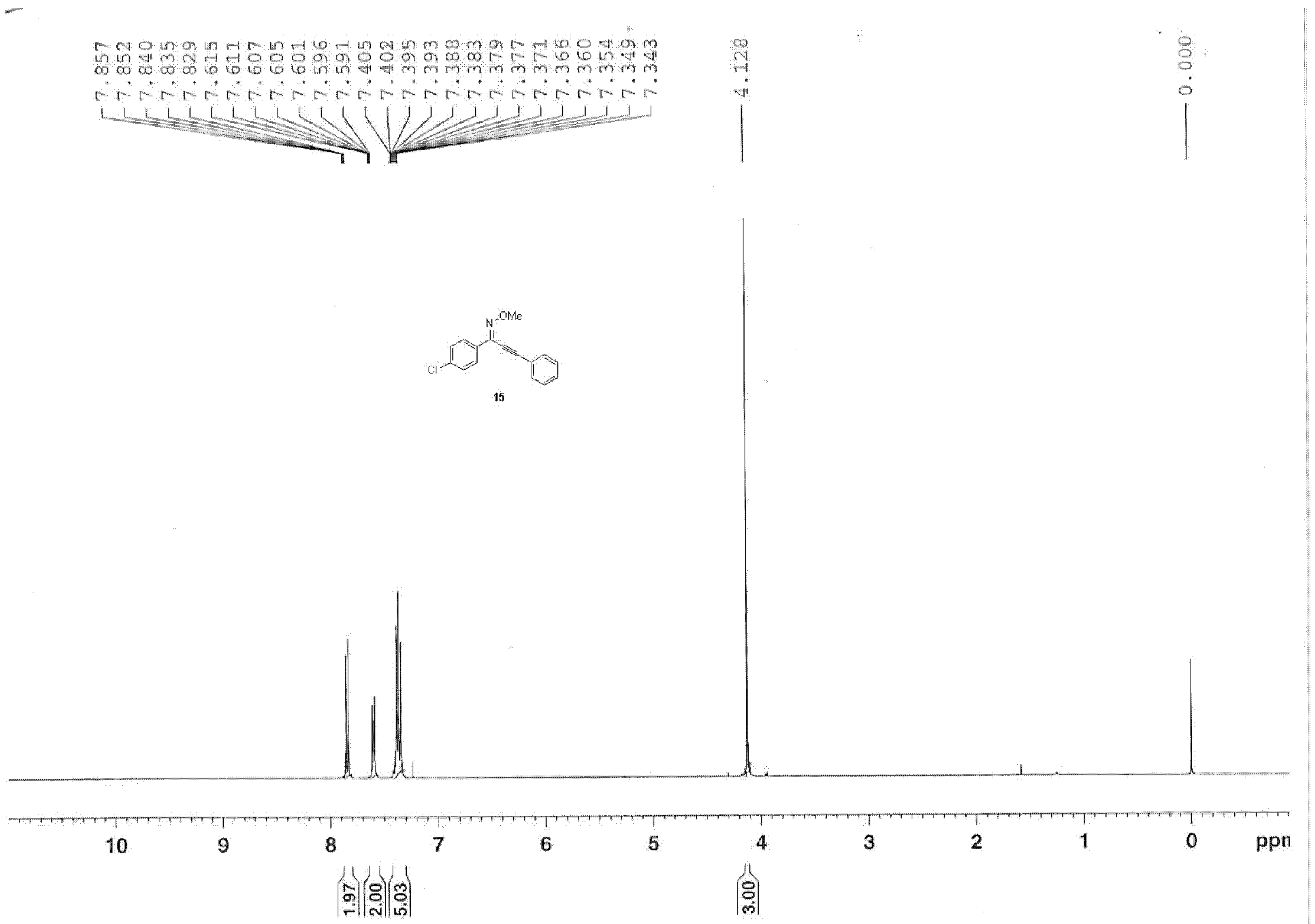
129.1425
129.1781
129.2493
130.3855
164.7688
165.6236
14
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
(ppm)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7.840
7.835
7.829
7.615
7.611
7.607
7.605
7.601
7.596
7.591
7.405
7.402
7.395
7.393
7.388
7.383
7.379
7.377
7.371
7.366
7.360
7.354
7.349
7.343
4.128
0.000
N
OMe
Cl
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10
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8
7
6
5
4
3
2
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0
ppm
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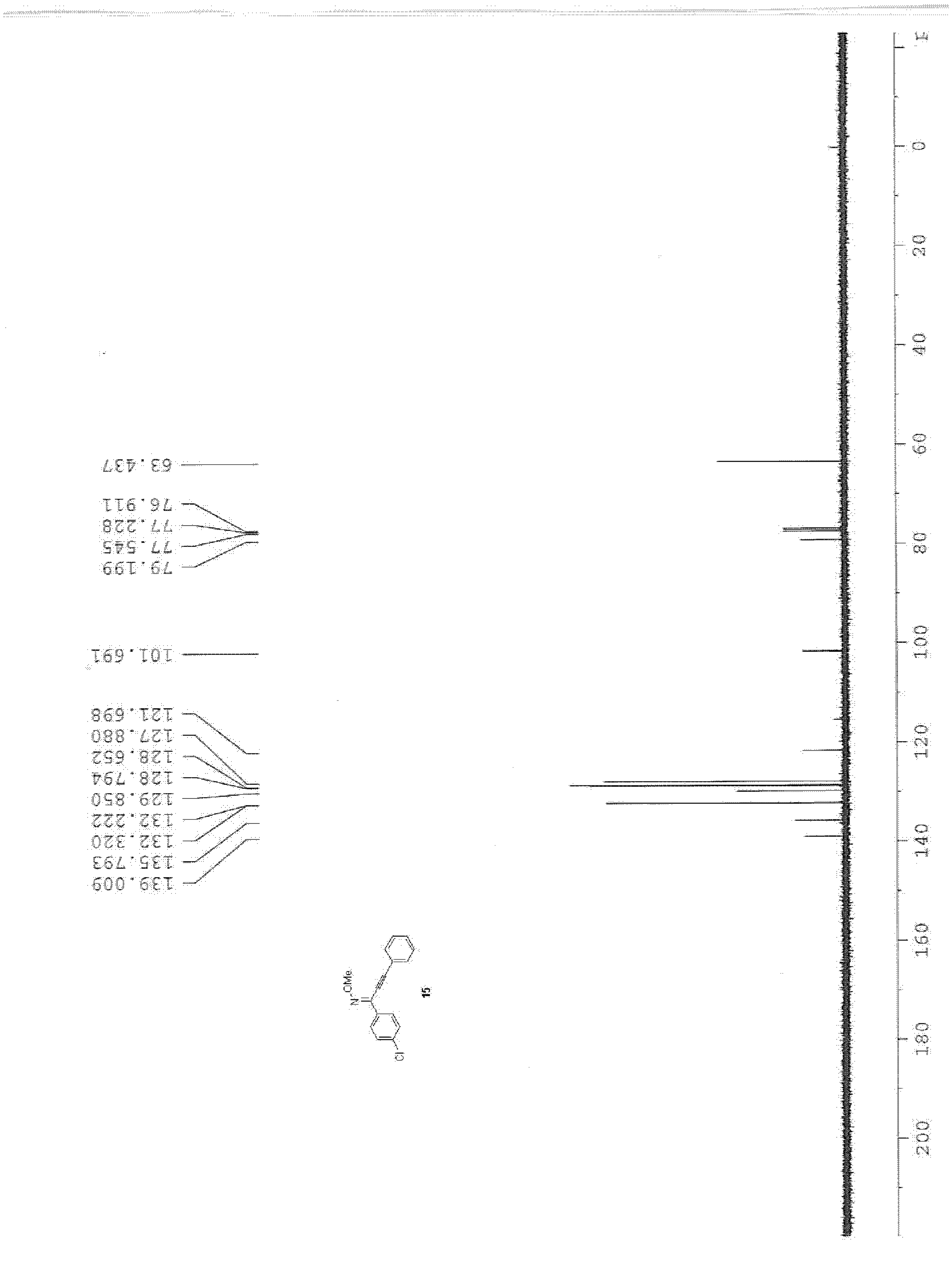
2.00
5.03
3.00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77.228
77.545
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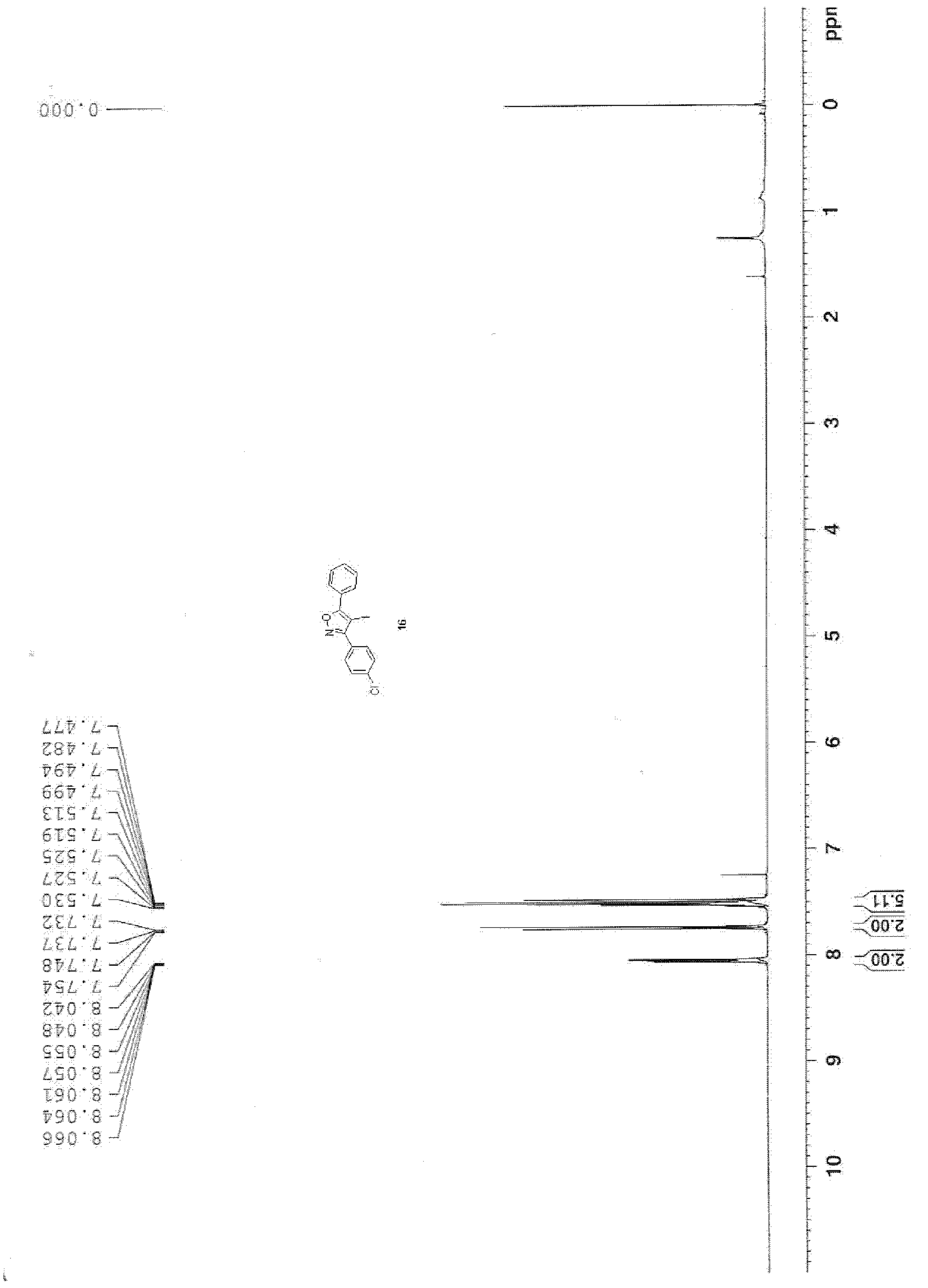
121.698
127.880
128.652
128.794
129.850
132.222
132.320
135.793
139.009
N
OMe
Cl
15
0
20
40
60
80
100
120
140
160
180
200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7.513
7.519
7.525
7.527
7.530
7.732
7.737
7.748
7.754
8.042
8.048
8.055
8.057
8.061
8.064
8.066
16
Cl
N–O
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2.00
2.00
ppm
0
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3
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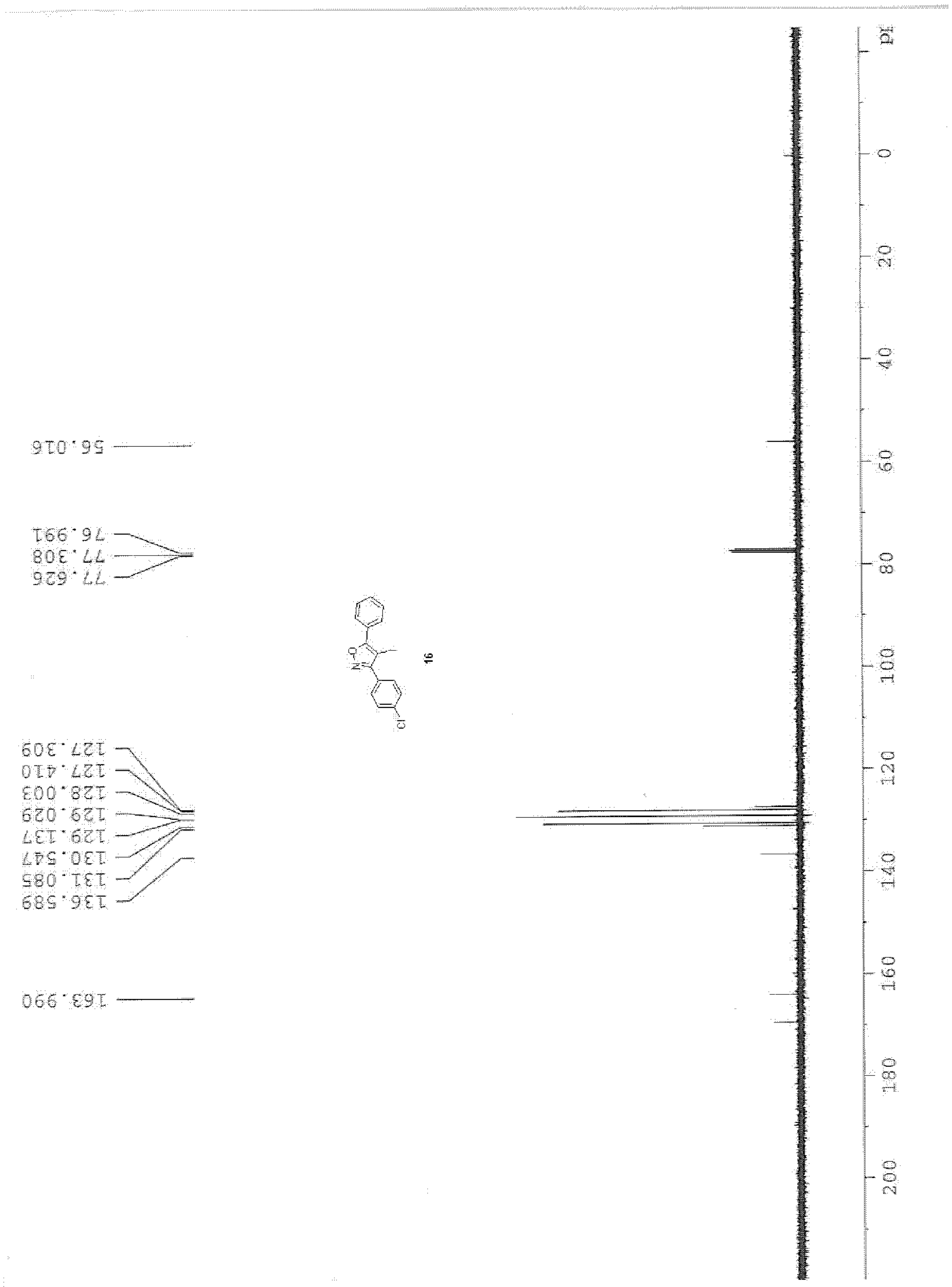
6
7
8
9
10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129.029
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130.547
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16
Cl
O
N
ppm
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60
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100
120
140
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180
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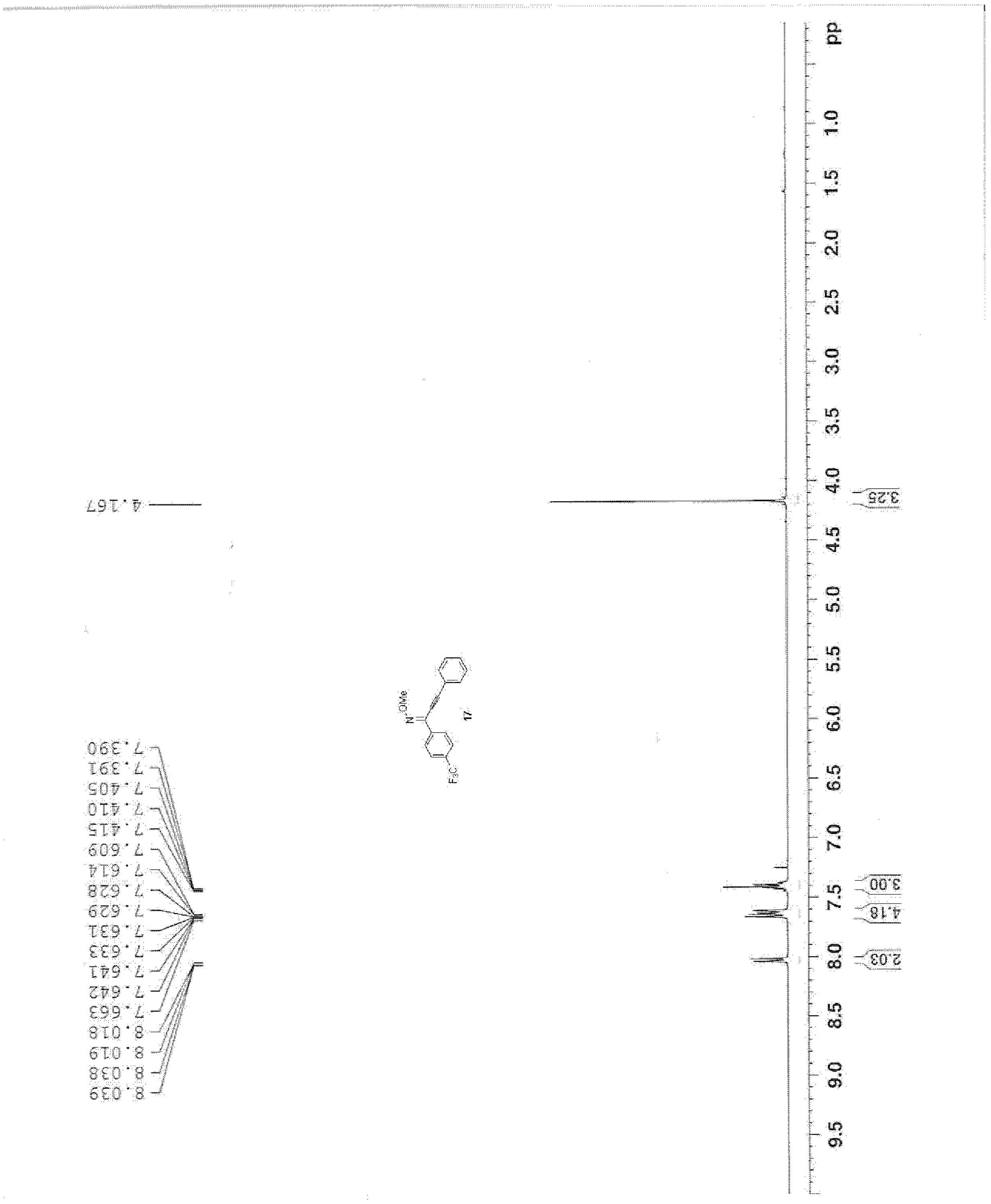
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7.641
7.642
7.663
8.018
8.019
8.038
8.039
F3C
N
OMe
1v
3.25
3.00
4.18
2.03
ppm
1.0
1.5
2.0
2.5
3.0
3.5
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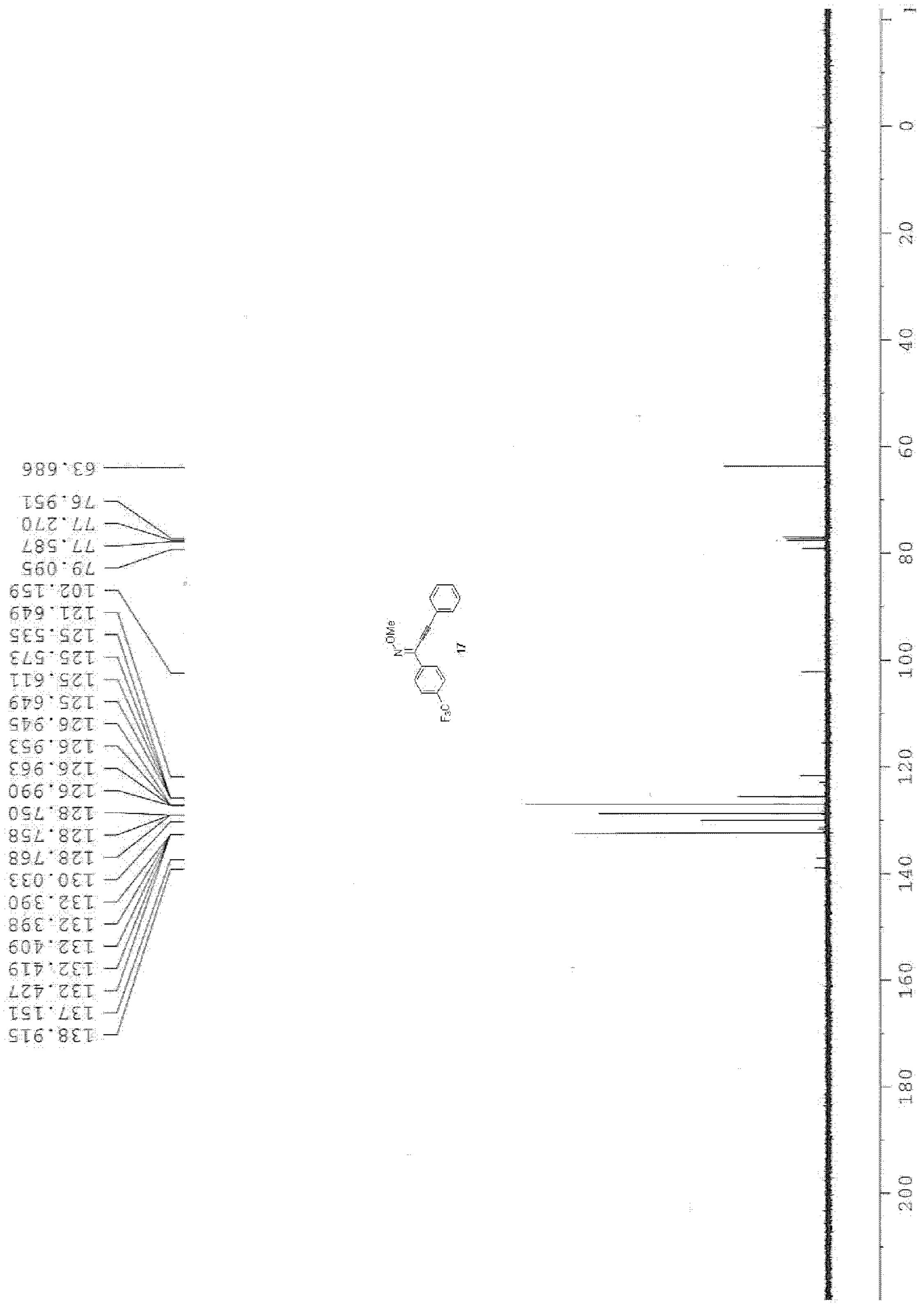
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126.953
126.963
126.990
128.750
128.758
128.768
130.033
132.390
132.398
132.409
132.419
132.427
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F₃C
N
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120
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80
60
40
20
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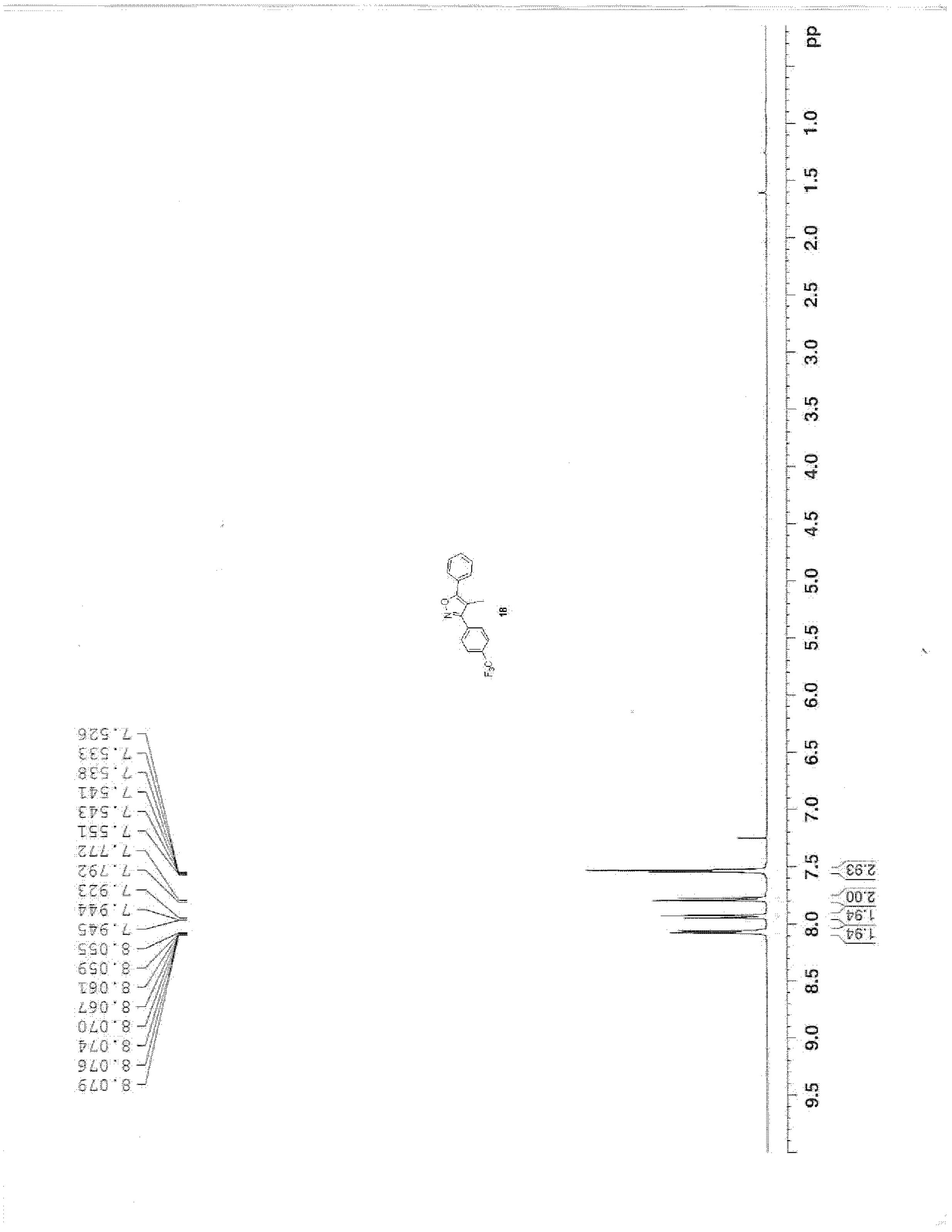
17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7.551
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7.792
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7.944
7.945
8.055
8.059
8.061
8.067
8.070
8.074
8.076
8.079
F3C
N-O
18
2.93
2.00
1.94
1.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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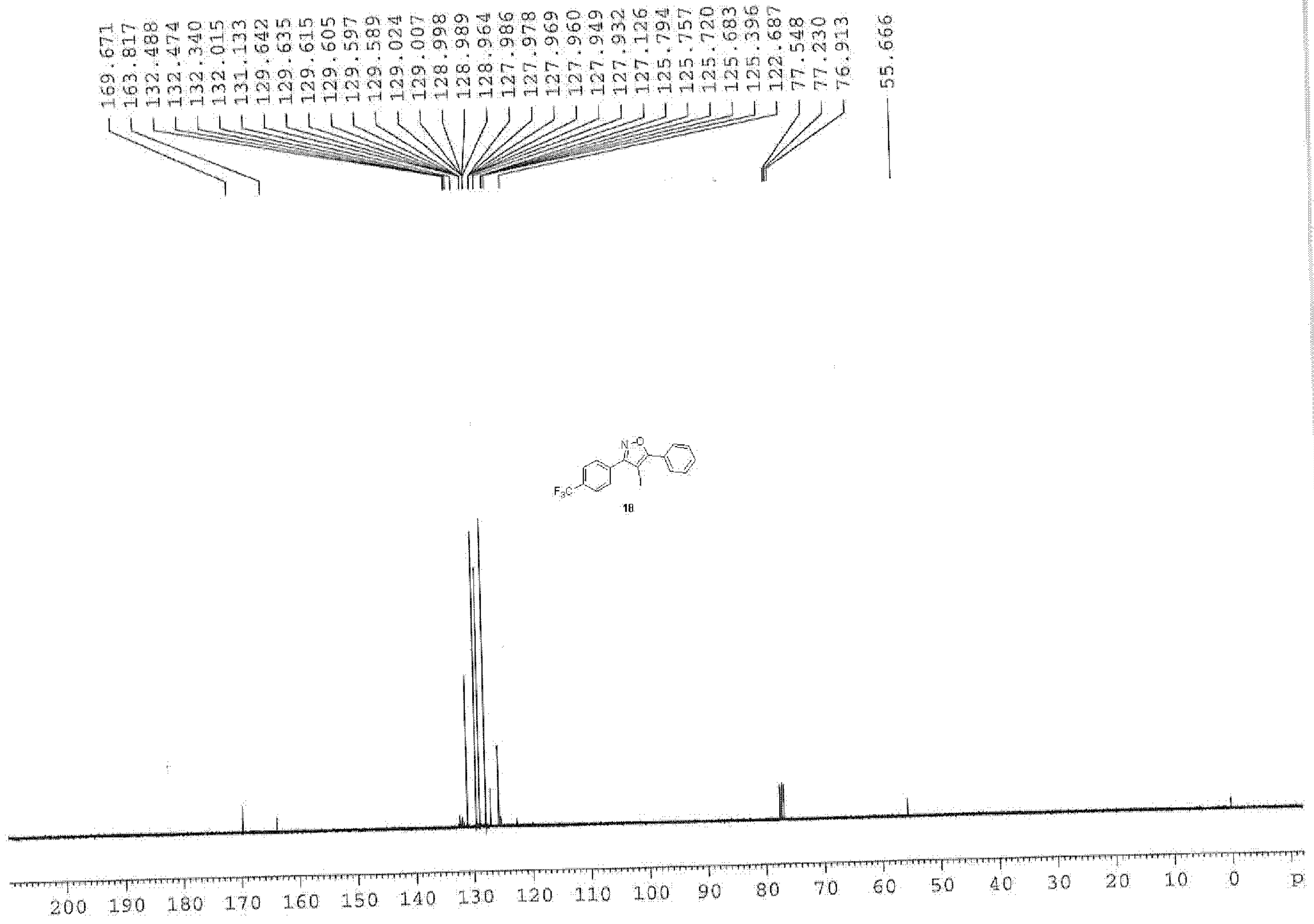
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
pp



18

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132.340
132.015
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129.642
129.635
129.615
129.605
129.597
129.589
129.024
129.007
128.998
128.989
128.964
127.986
127.978
127.969
127.960
127.949
127.932
127.126
125.794
125.757
125.720
125.683
125.396
122.687
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76.913
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F3C
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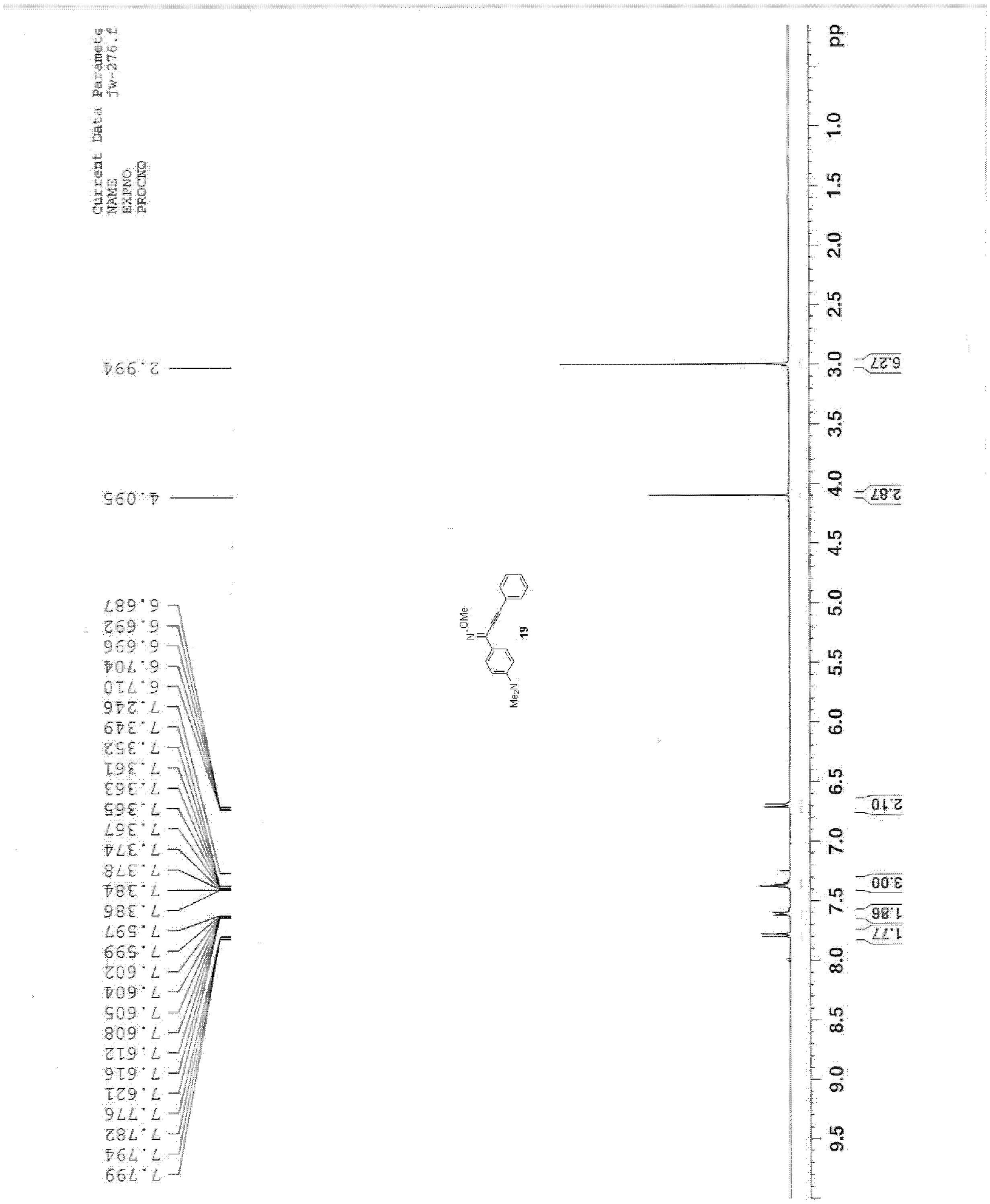
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PROCNO
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6.704
6.710
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7.349
7.352
7.361
7.363
7.365
7.367
7.374
7.378
7.384
7.386
7.597
7.599
7.602
7.604
7.605
7.608
7.612
7.616
7.621
7.776
7.782
7.794
7.799
Me2N
N
OMe
19
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2.87
2.10
3.00
1.86
1.77
pp
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2.5
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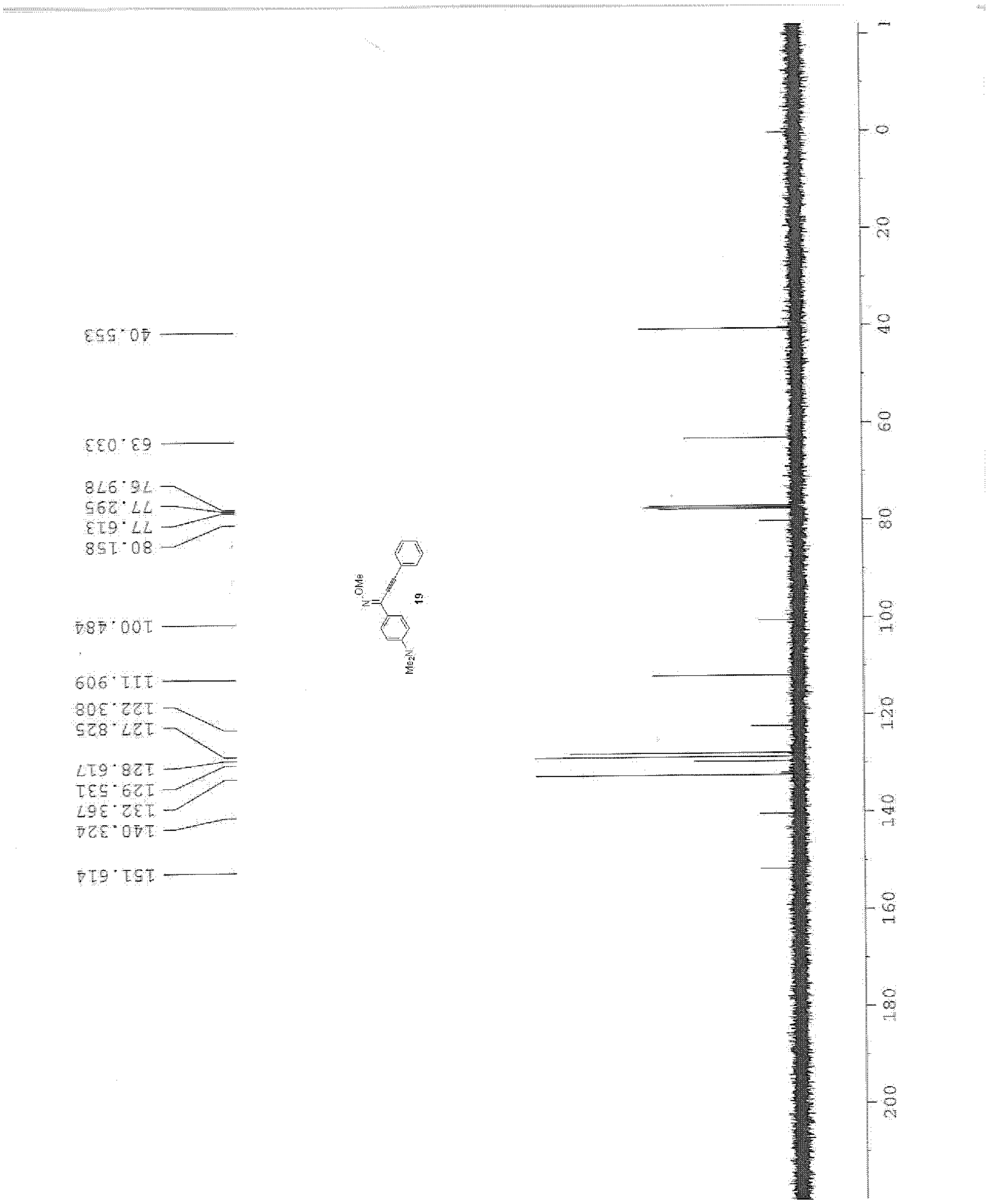
9.5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132.367
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151.614
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OMe
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60
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140
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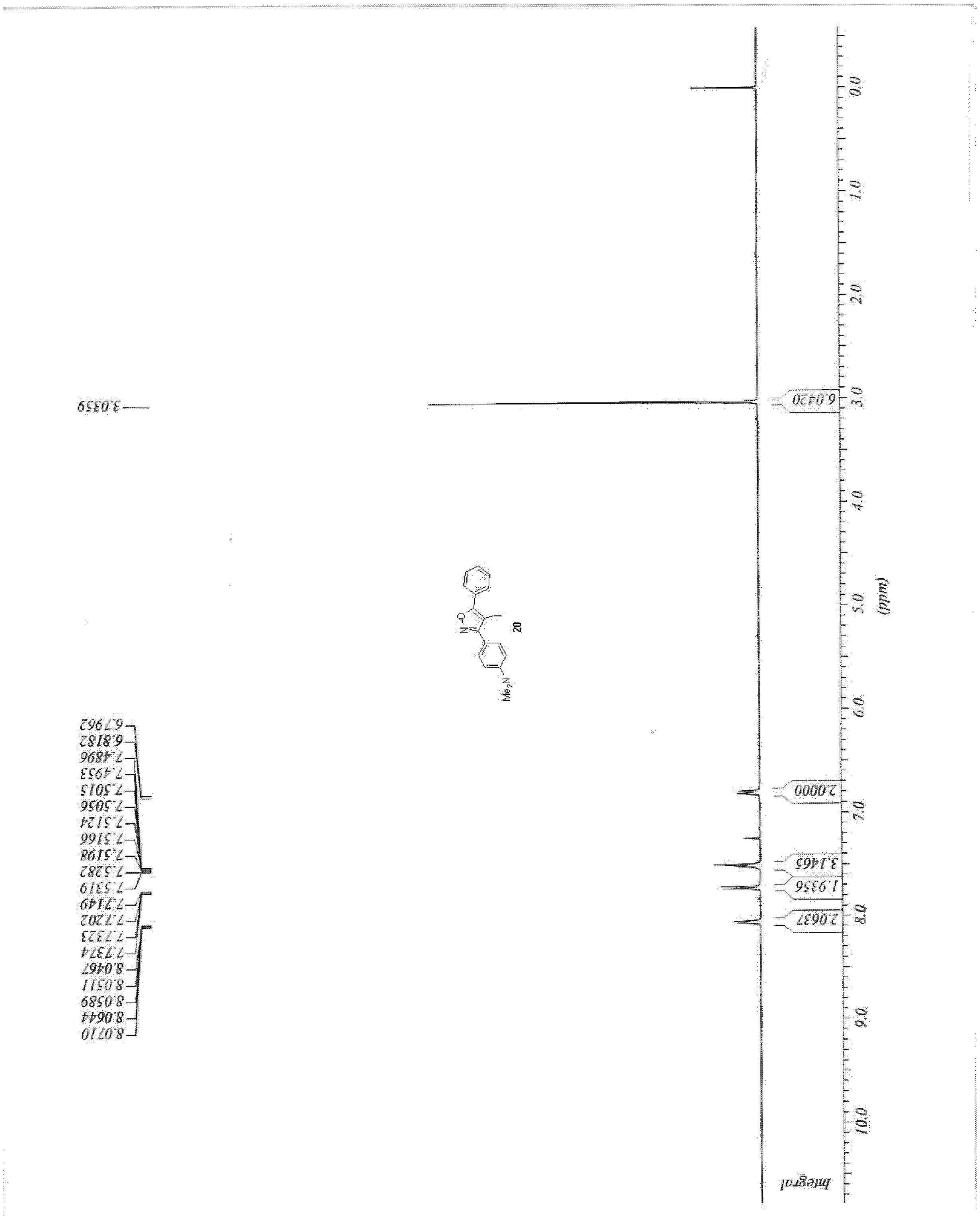
180
200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7.5166
7.5198
7.5282
7.5319
7.7149
7.7202
7.7323
7.7374
8.0467
8.0511
8.0589
8.0644
8.0710
Me2N
N
O
20
6.0420
2.0000
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1.9336
2.0637
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8.0
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10.0
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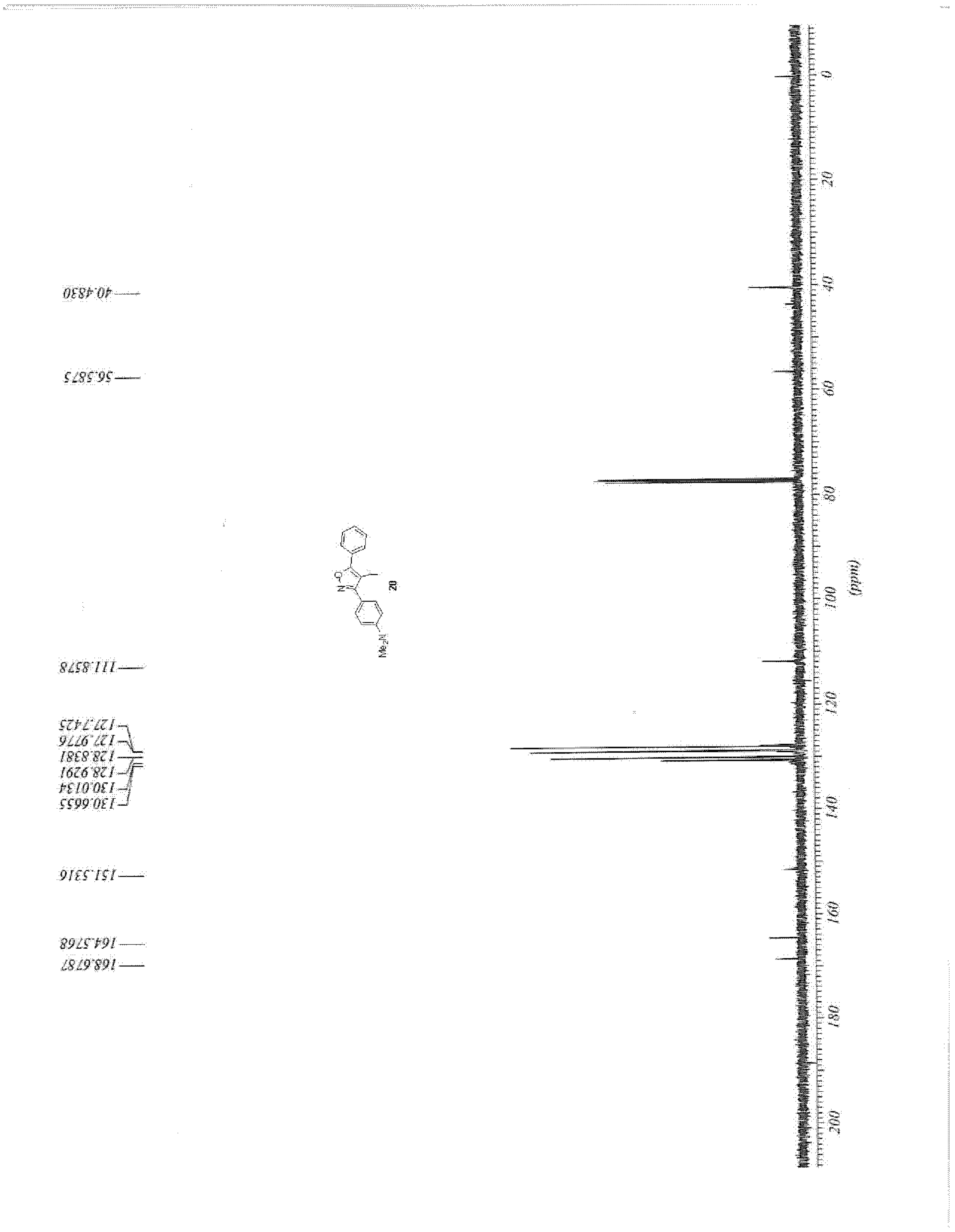
Integral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130.6655
151.5316
164.5768
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Me2N
N
O
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40
60
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100
120
140
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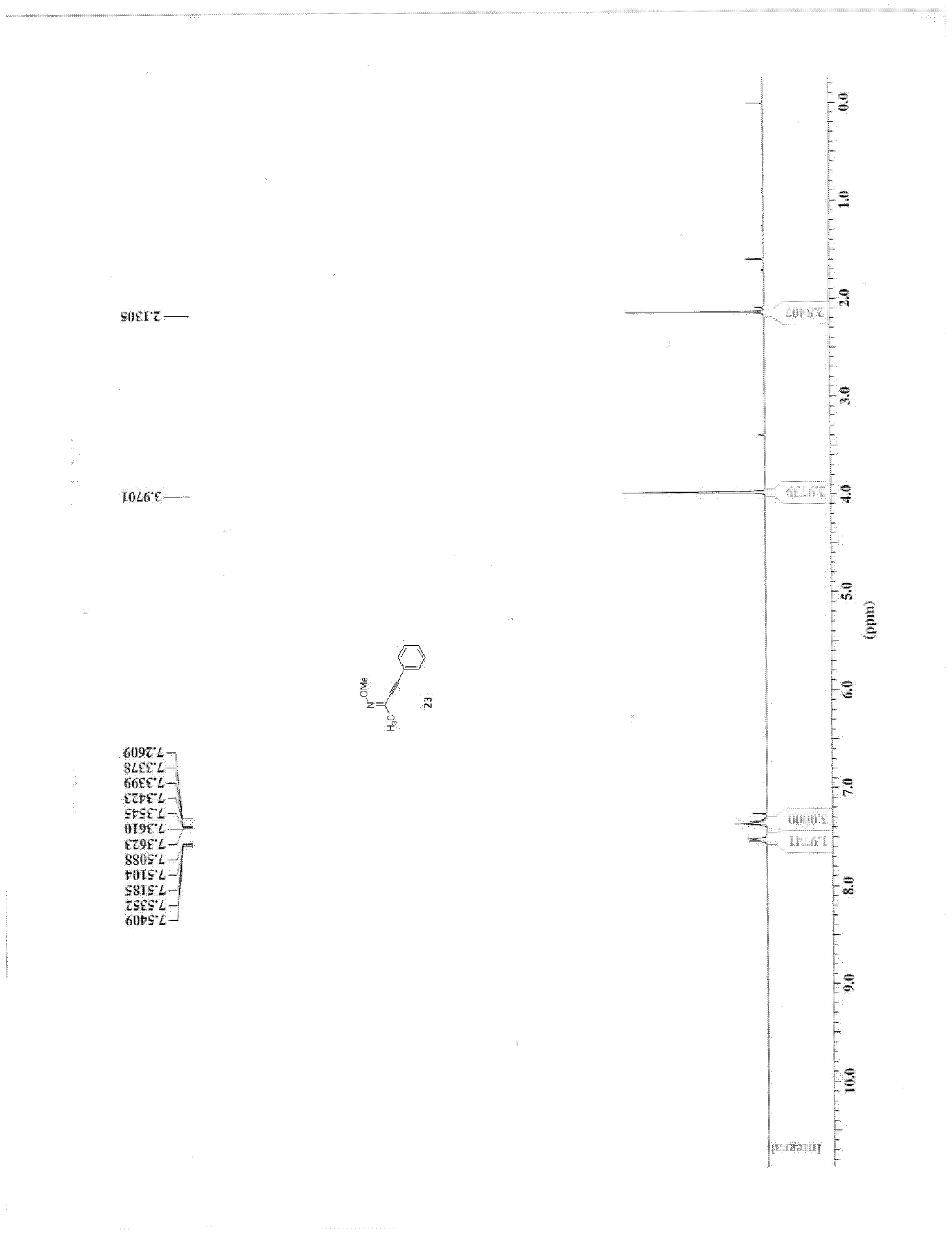
180
200
(ppm)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7.2609
7.3378
7.3399
7.3423
7.3545
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7.3623
7.5088
7.5104
7.5185
7.5352
7.5409
N
OMe
H3C
23
2.8407
2.9739
3.0000
1.9741
Integral
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1.0
2.0
3.0
4.0
5.0
6.0
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8.0
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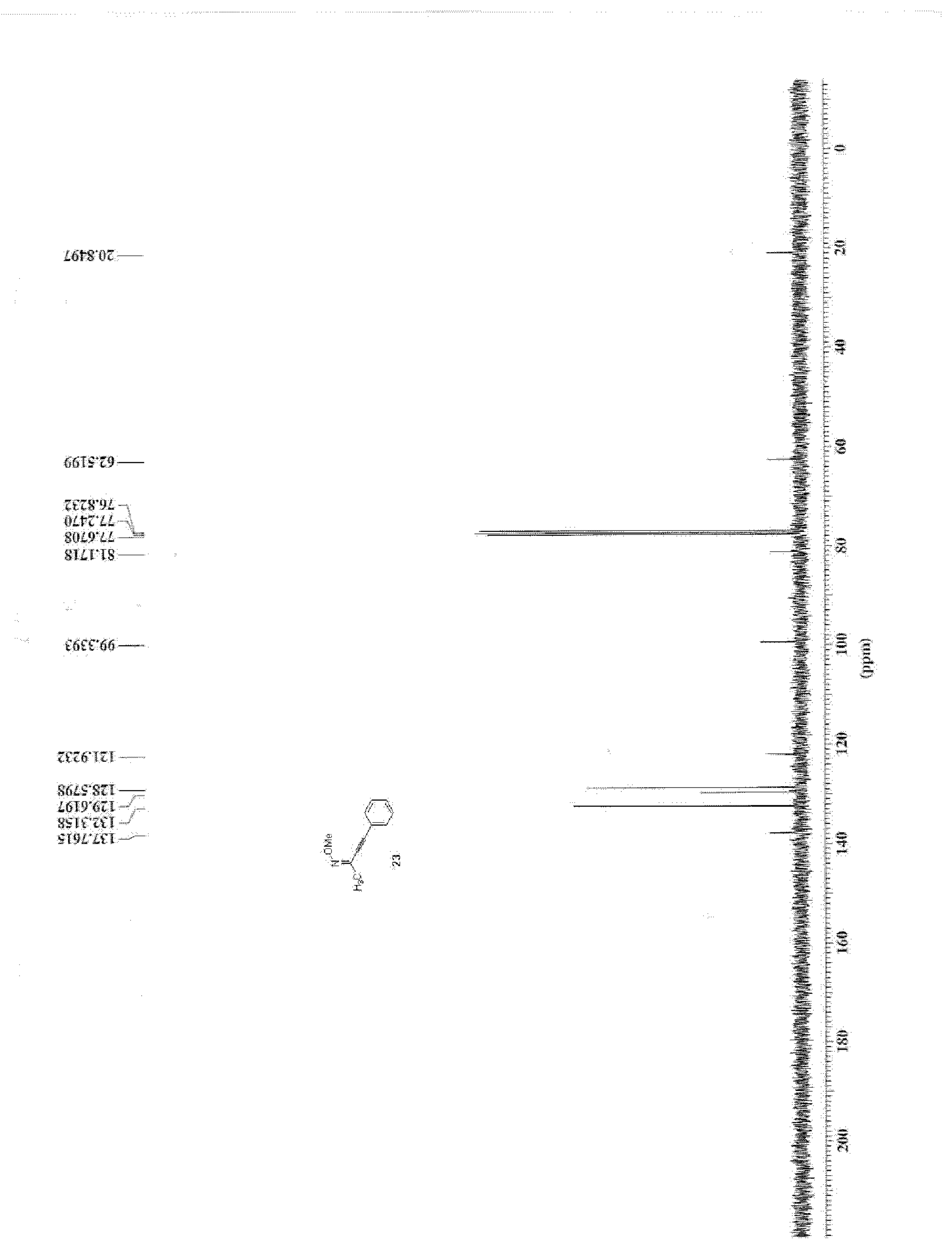
10.0
(ppm)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128.5798
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132.3158
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OMe
H3C
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0
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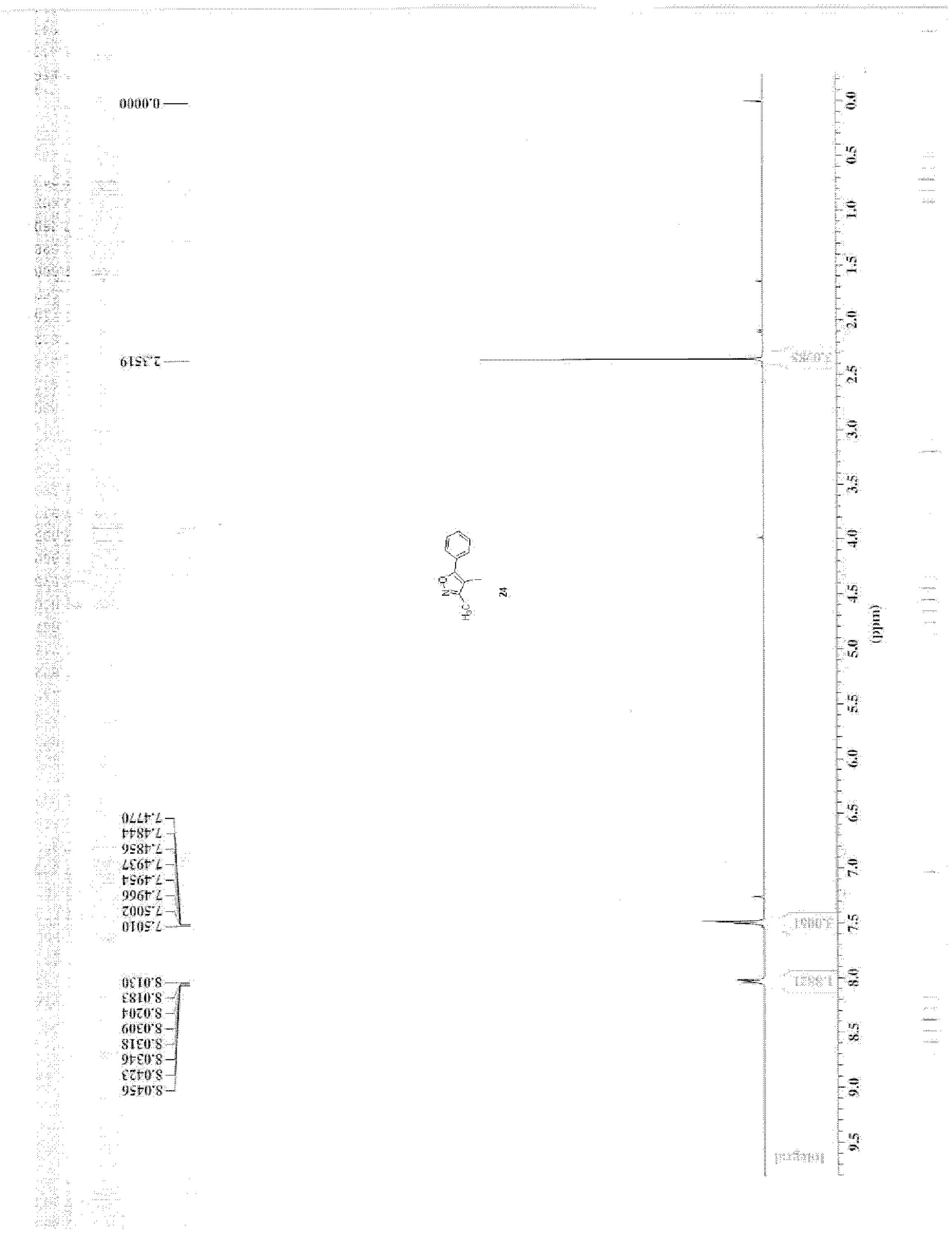
40
60
80
100
120
140
160
180
200
(ppm)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7.4937
7.4954
7.4966
7.5002
7.5010
8.0130
8.0183
8.0204
8.0309
8.0318
8.0346
8.0423
8.0456
N–O
H3C
24
1.8821
Integral
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
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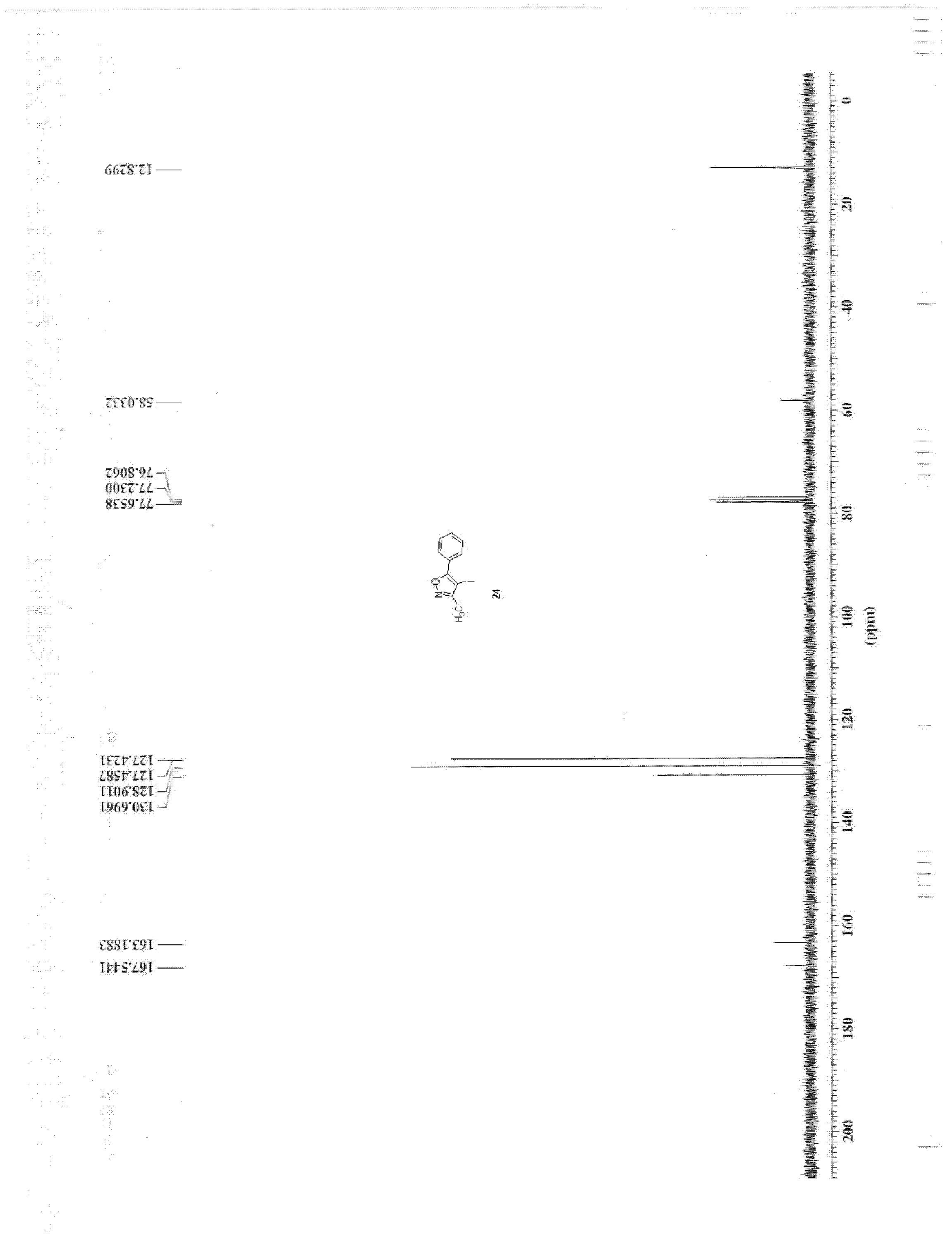
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
(ppm)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77.6538
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127.4587
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20
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80
100
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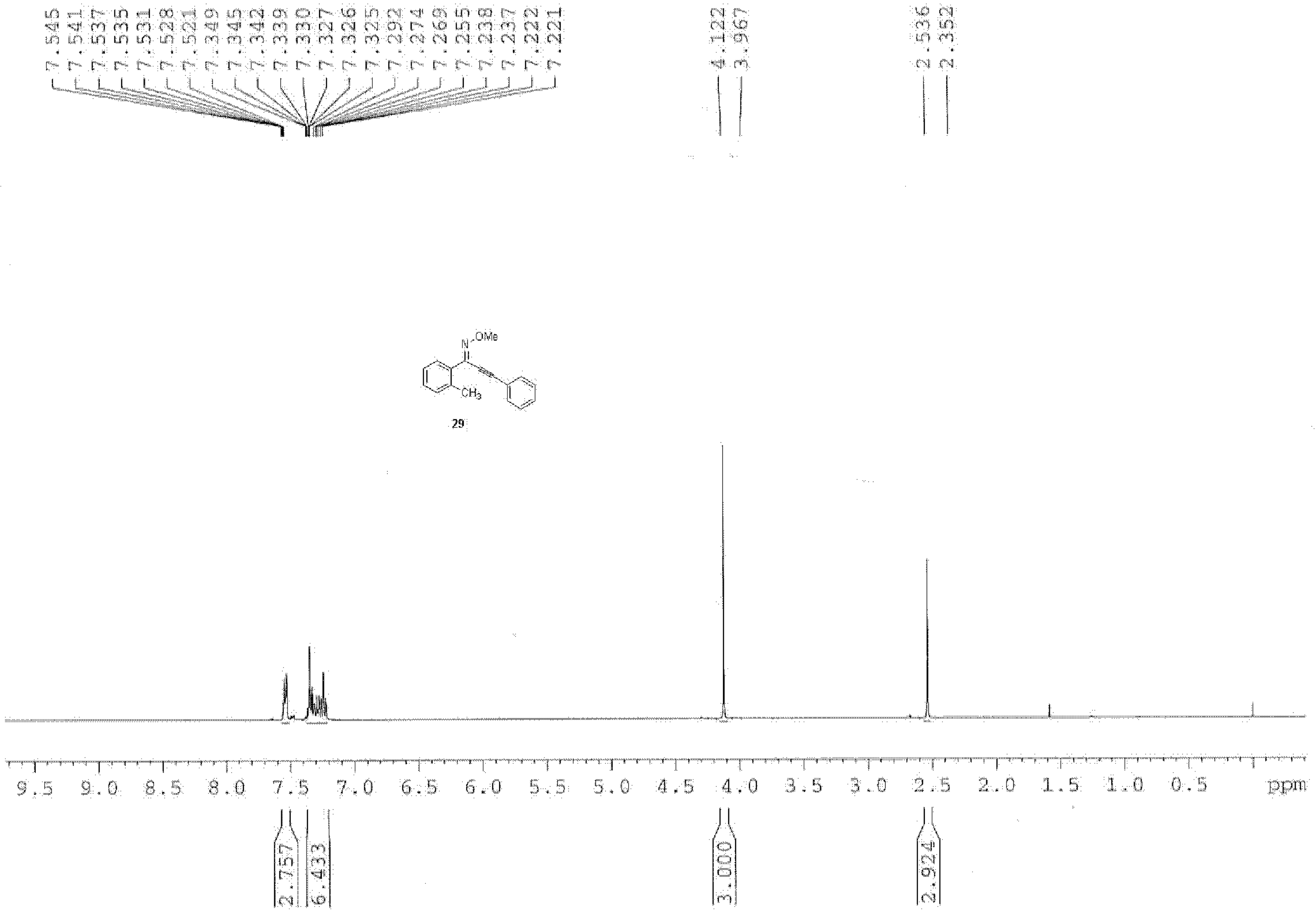
140
160
180
200
(ppm)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7.349
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7.342
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7.330
7.327
7.326
7.325
7.292
7.274
7.269
7.255
7.238
7.237
7.222
7.221
4.122
3.967
2.536
2.352
OMe
N
CH3
29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
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ppm
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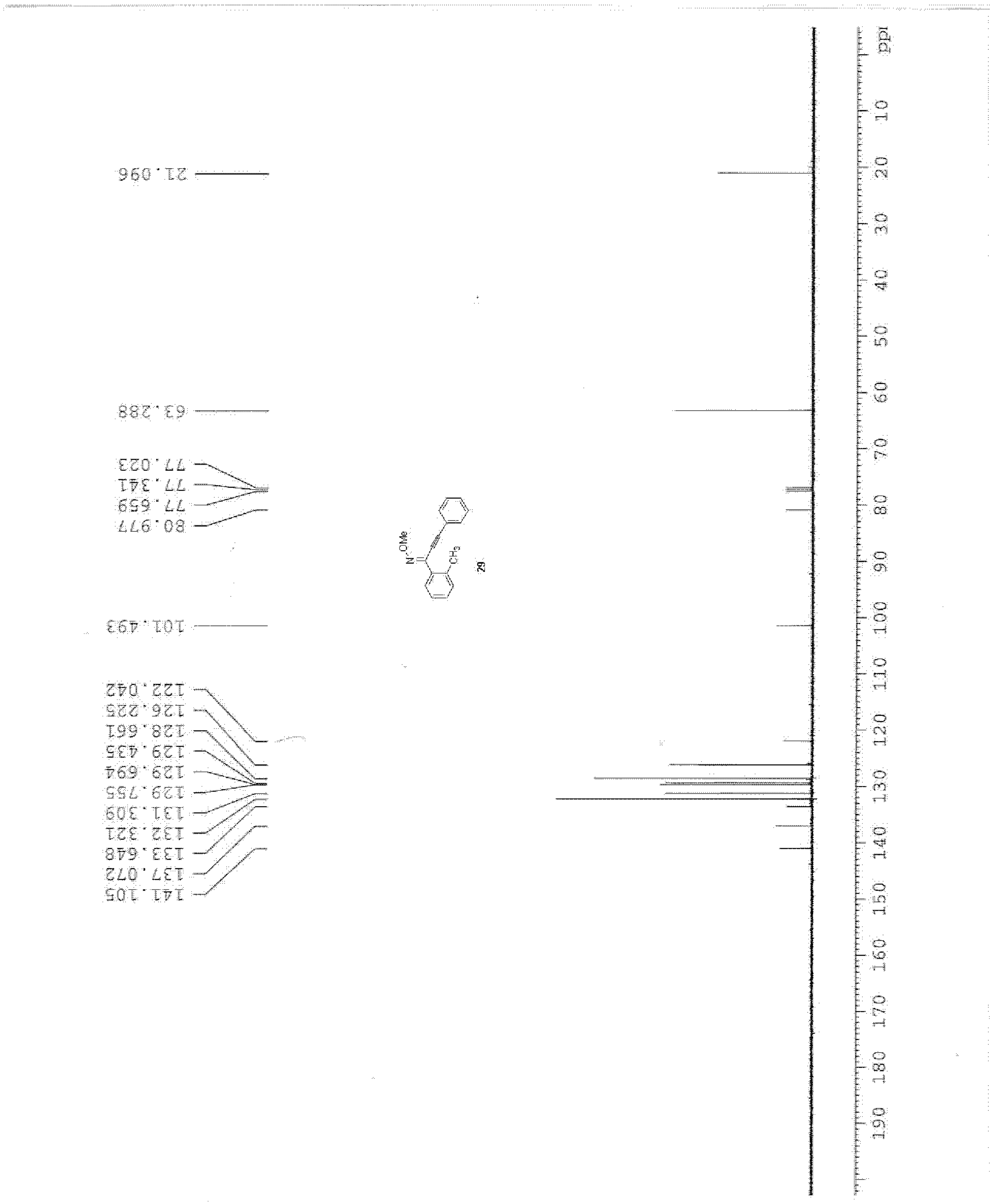
2.924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129.755
131.309
132.321
133.648
137.072
141.105
N
OMe
CH3
29
ppm
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60
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120
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150
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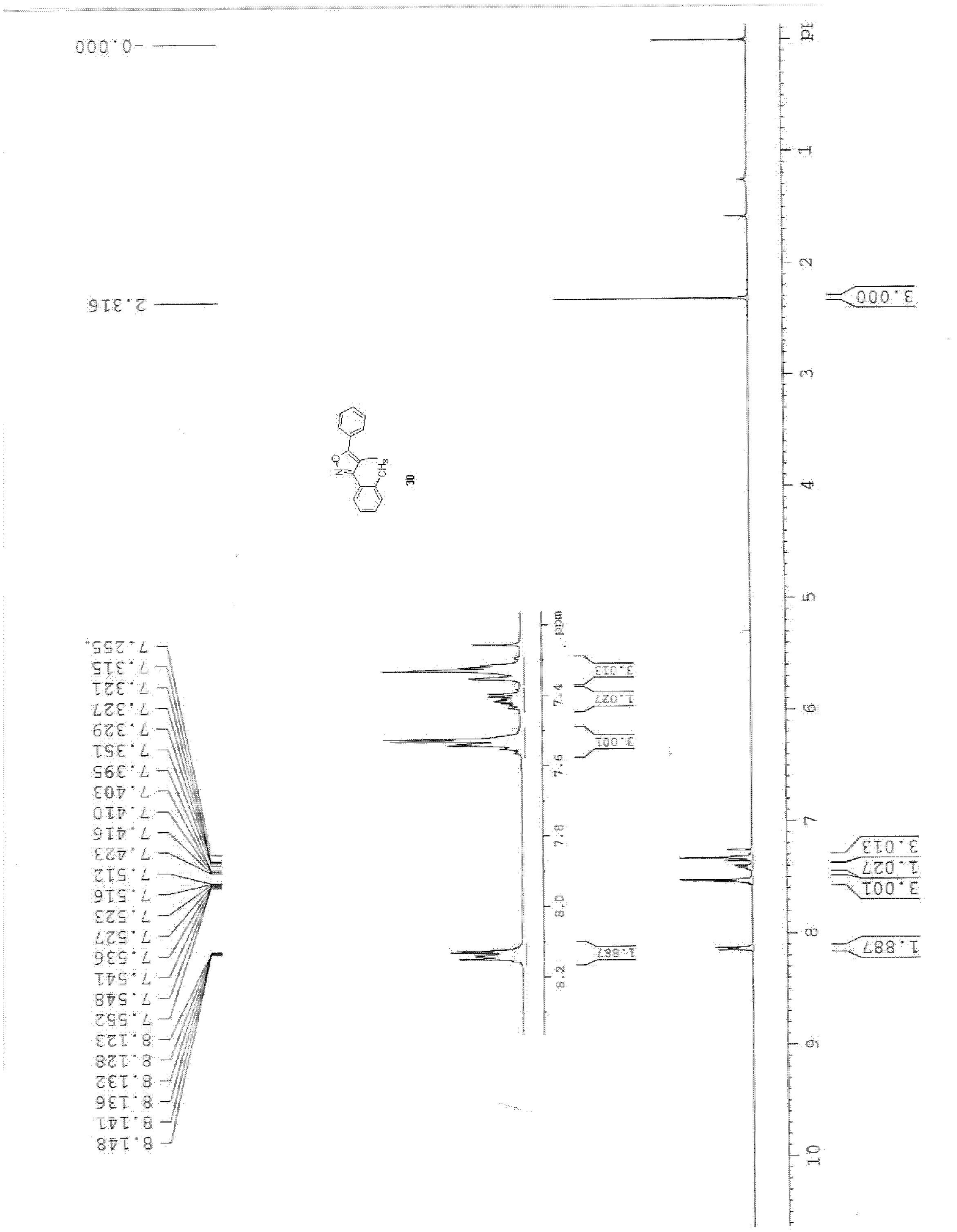
170
180
190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7.329
7.351
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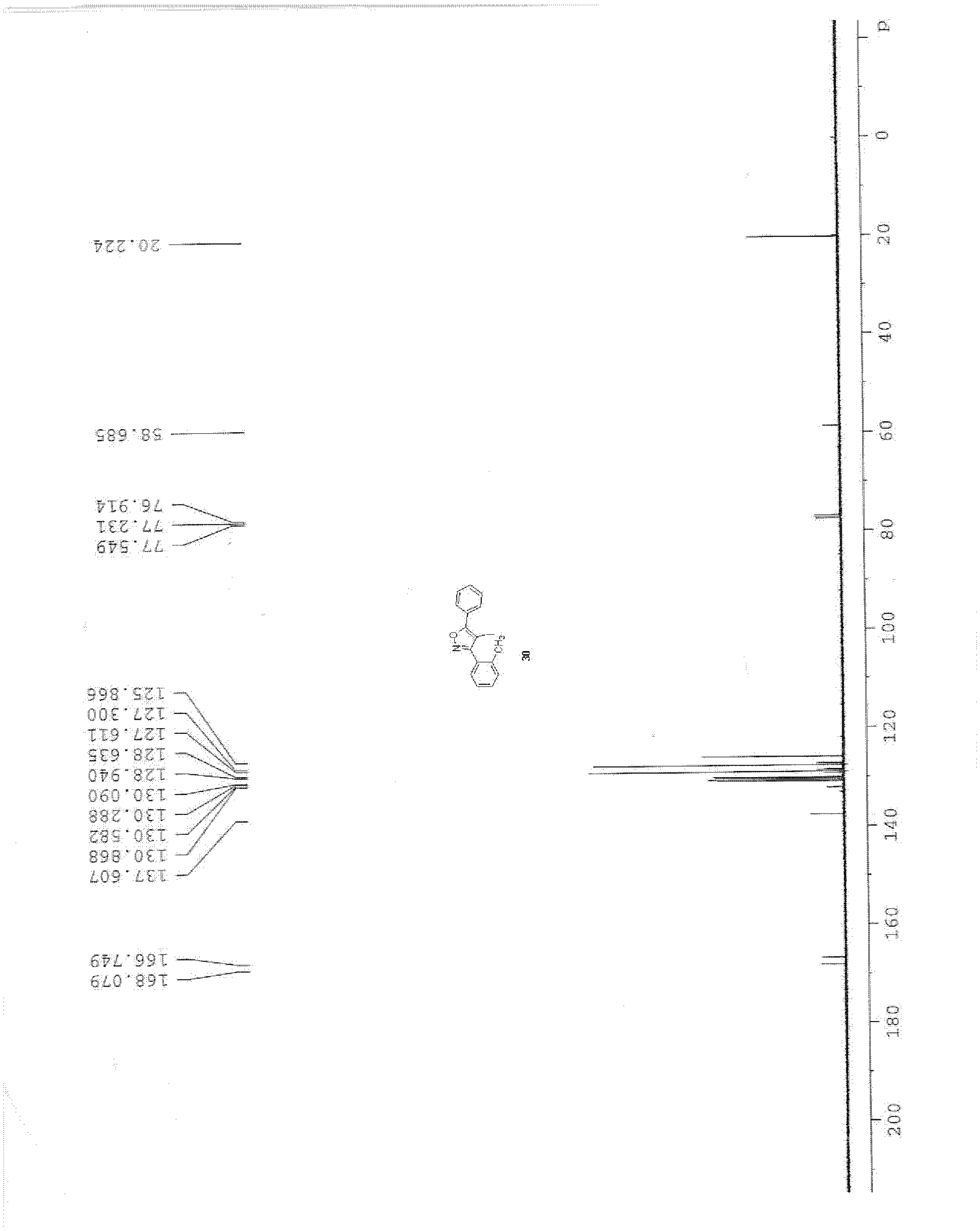
7.403
7.410
7.416
7.423
7.512
7.516
7.523
7.527
7.536
7.541
7.548
7.552
8.123
8.128
8.132
8.136
8.141
8.148
N-O
CH3
30
3.000
3.013
1.027
3.001
1.887
ppm
0
1
2
3
4
5
6
7
8
9
10
7.4
7.6
7.8
8.0
8.2
ppm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130.582
130.868
137.607
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CH3
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p
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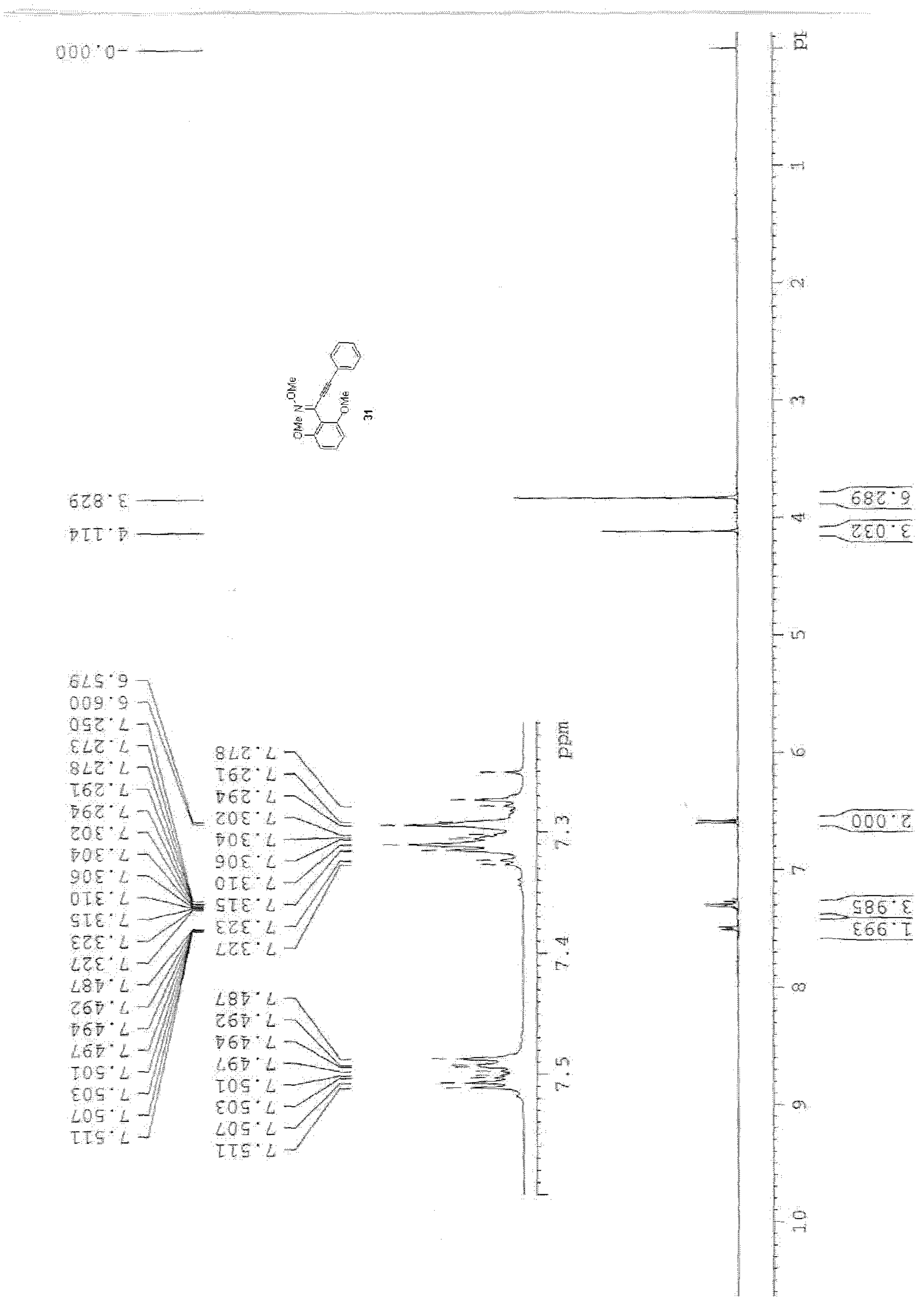
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7.304
7.306
7.310
7.315
7.323
7.327
7.487
7.492
7.494
7.497
7.501
7.503
7.507
7.511
OMe
N
OMe
OMe
31
ppm
7.3
7.4
7.5
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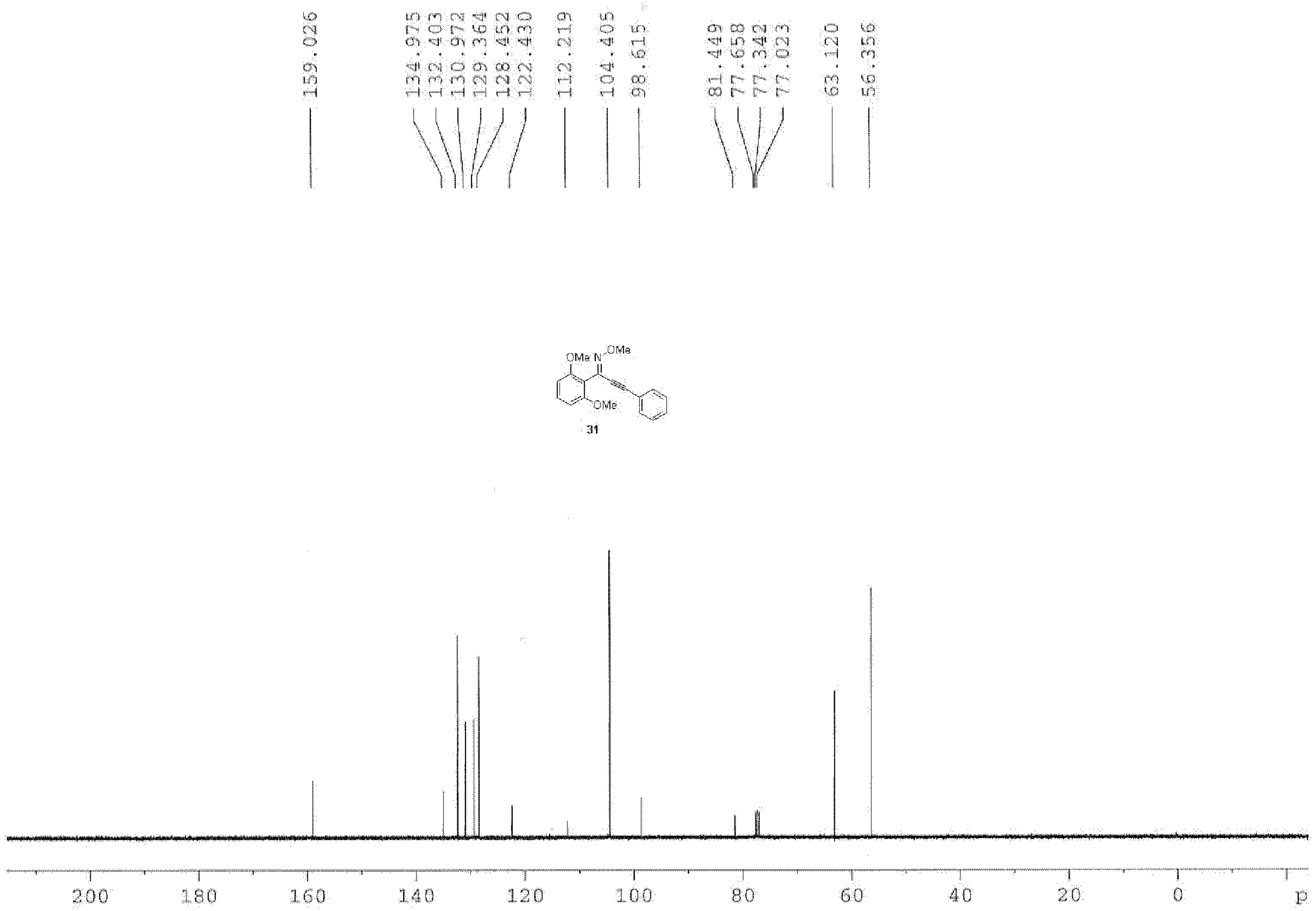
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77.342
77.023
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OMe
OMe
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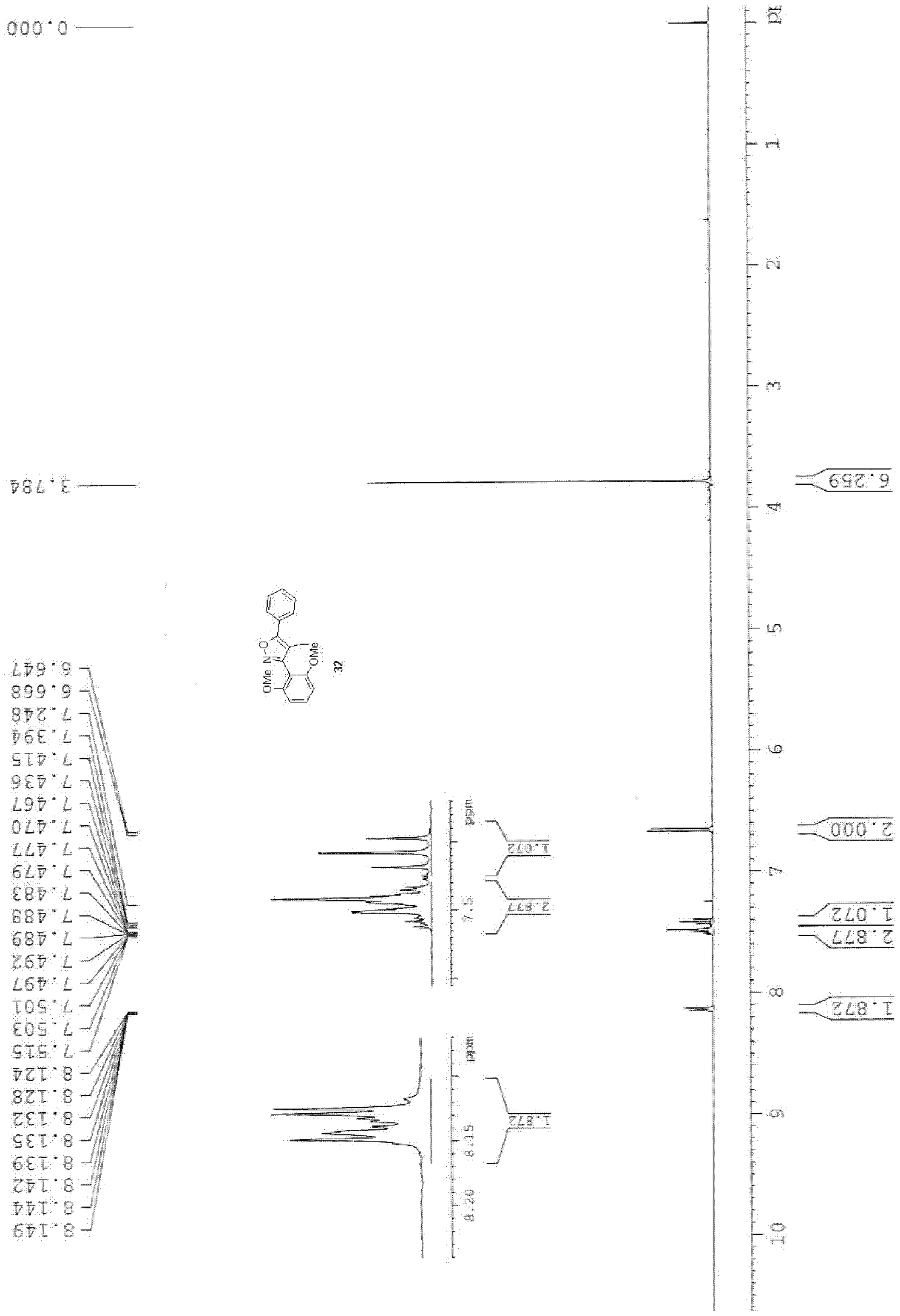
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7.479
7.483
7.488
7.489
7.492
7.497
7.501
7.503
7.515
8.124
8.128
8.132
8.135
8.139
8.142
8.144
8.149
OMe
N
O
OMe
32
ppm
7.5
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8.15
8.20
1.872
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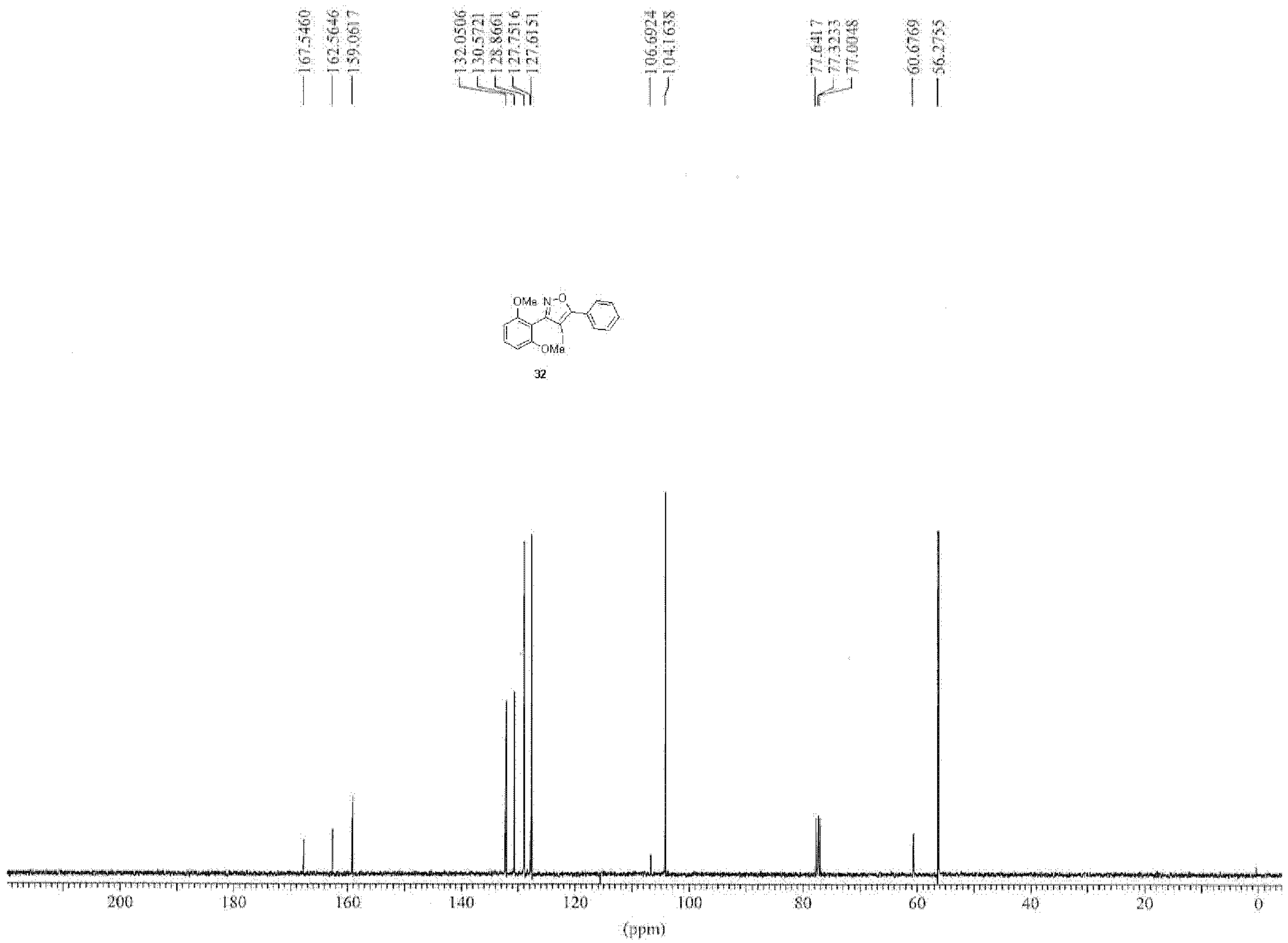
10
pl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130.5721
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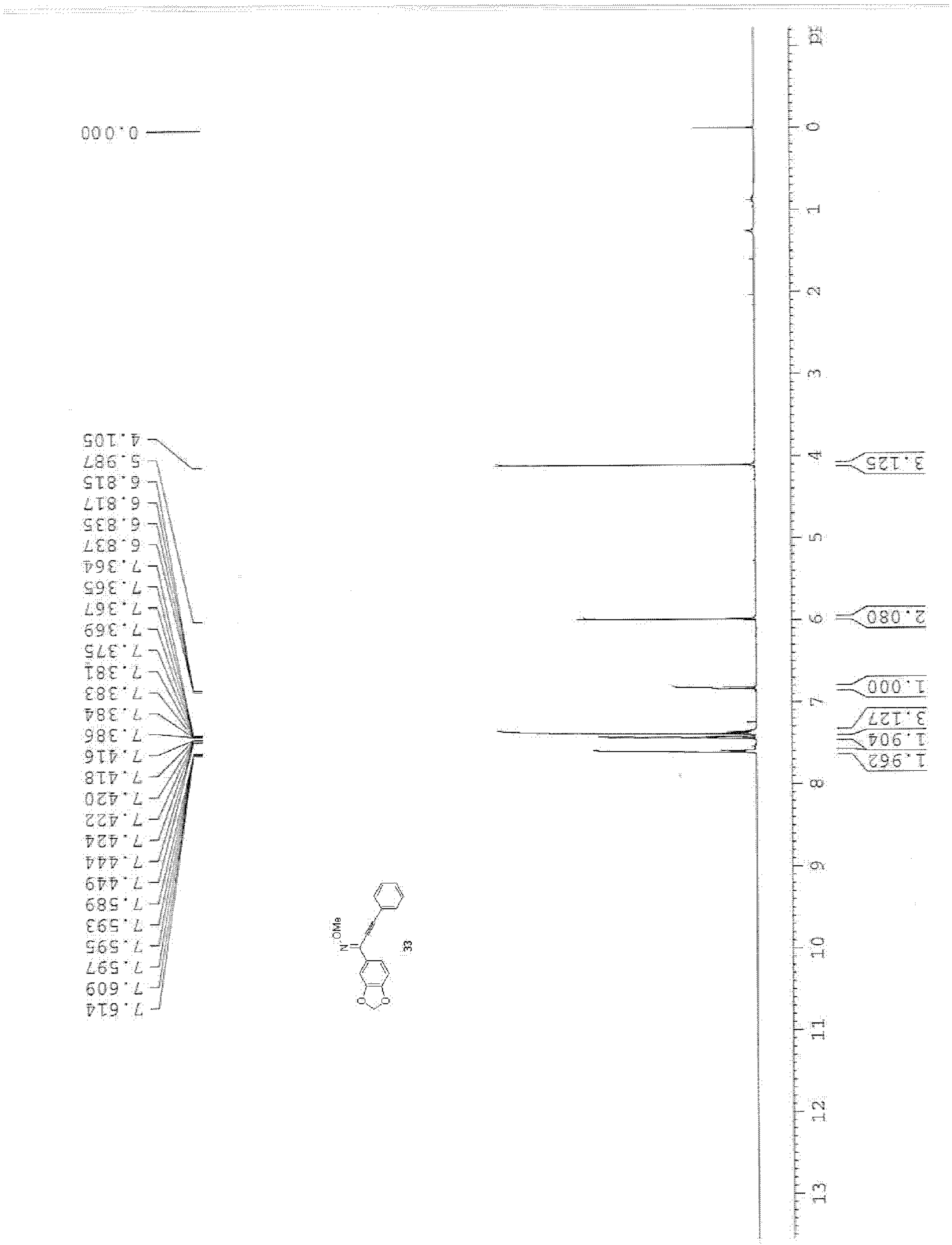
127.7516
127.6151
106.6924
104.1638
77.6417
77.3233
77.0048
60.6769
56.2755
OMe
N-O
OMe
32
200
180
160
140
120
100
80
60
40
20
0
(ppm)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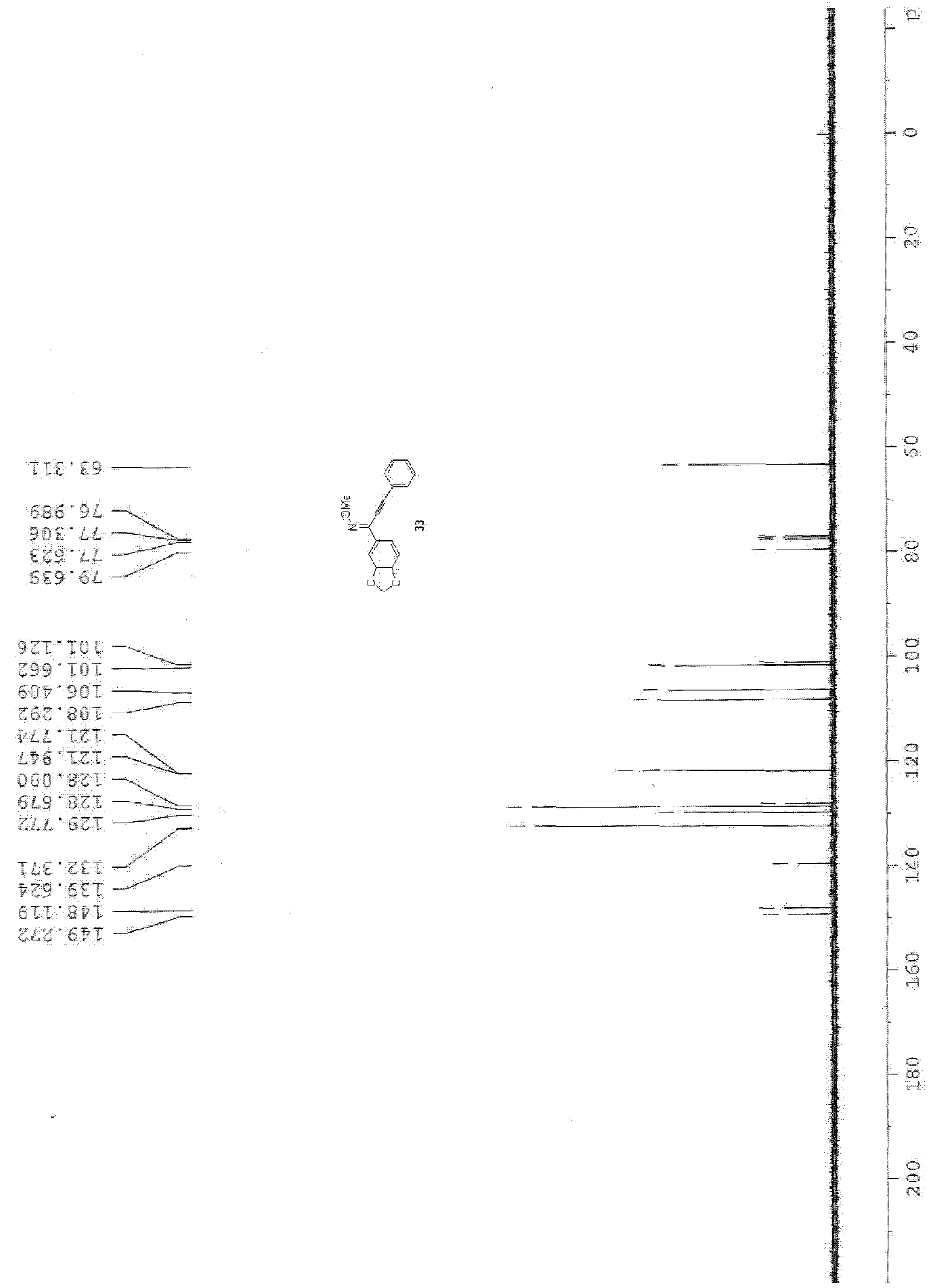
6.817
6.835
6.837
7.364
7.365
7.367
7.369
7.375
7.381
7.383
7.384
7.386
7.416
7.418
7.420
7.422
7.424
7.444
7.449
7.589
7.593
7.595
7.597
7.609
7.614
N
OMe
33
3.125
2.080
1.000
3.127
1.904
1.962
0
1
2
3
4
5
6
7
8
9
10
11
12
13
pp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106.409
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128.679
129.772
132.371
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148.119
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N
OMe
33
p
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60
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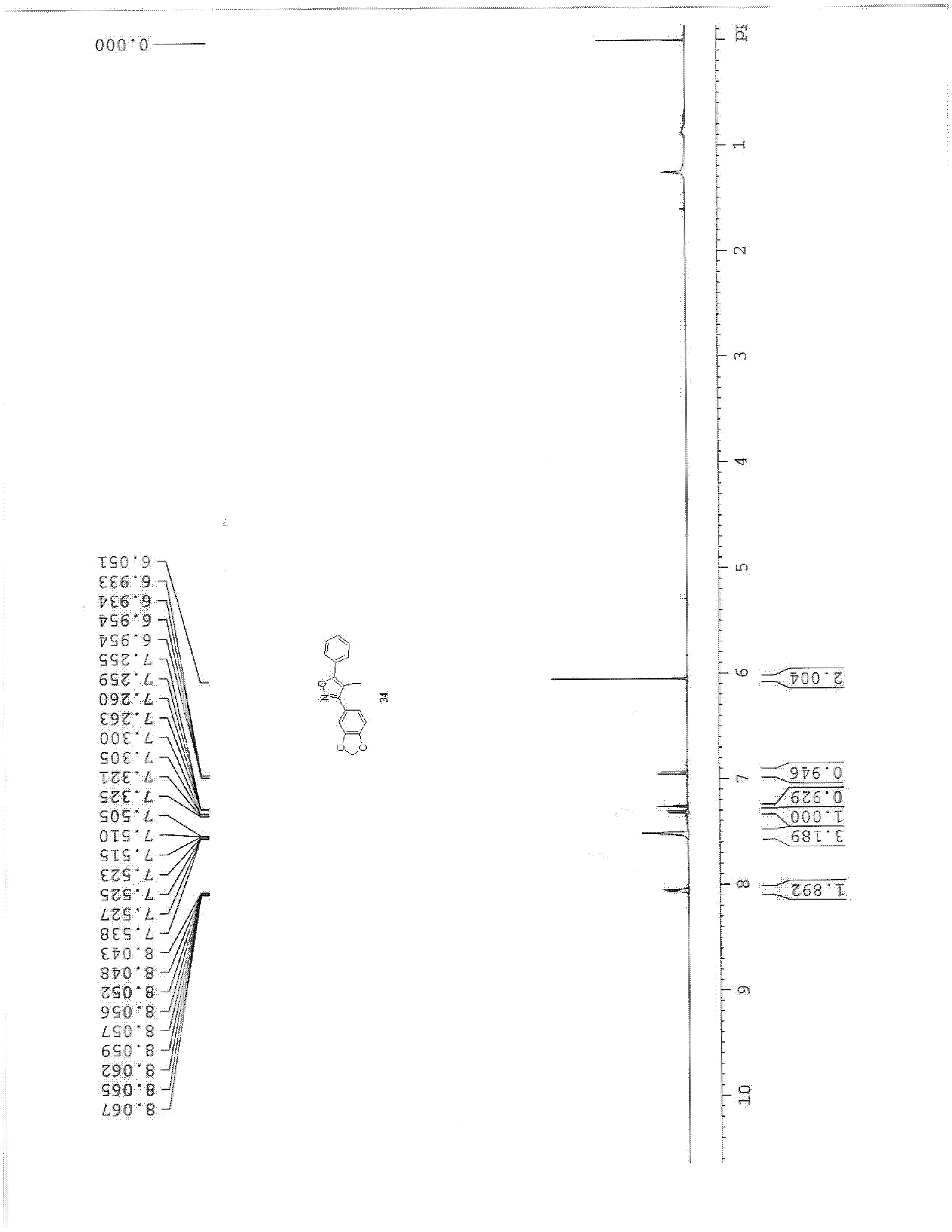
100
120
140
160
180
200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6.954
7.255
7.259
7.260
7.263
7.300
7.305
7.321
7.325
7.505
7.510
7.515
7.523
7.525
7.527
7.538
8.043
8.048
8.052
8.056
8.057
8.059
8.062
8.065
8.067
34
2.004
0.946
0.929
1.000
3.189
1.892
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2
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4
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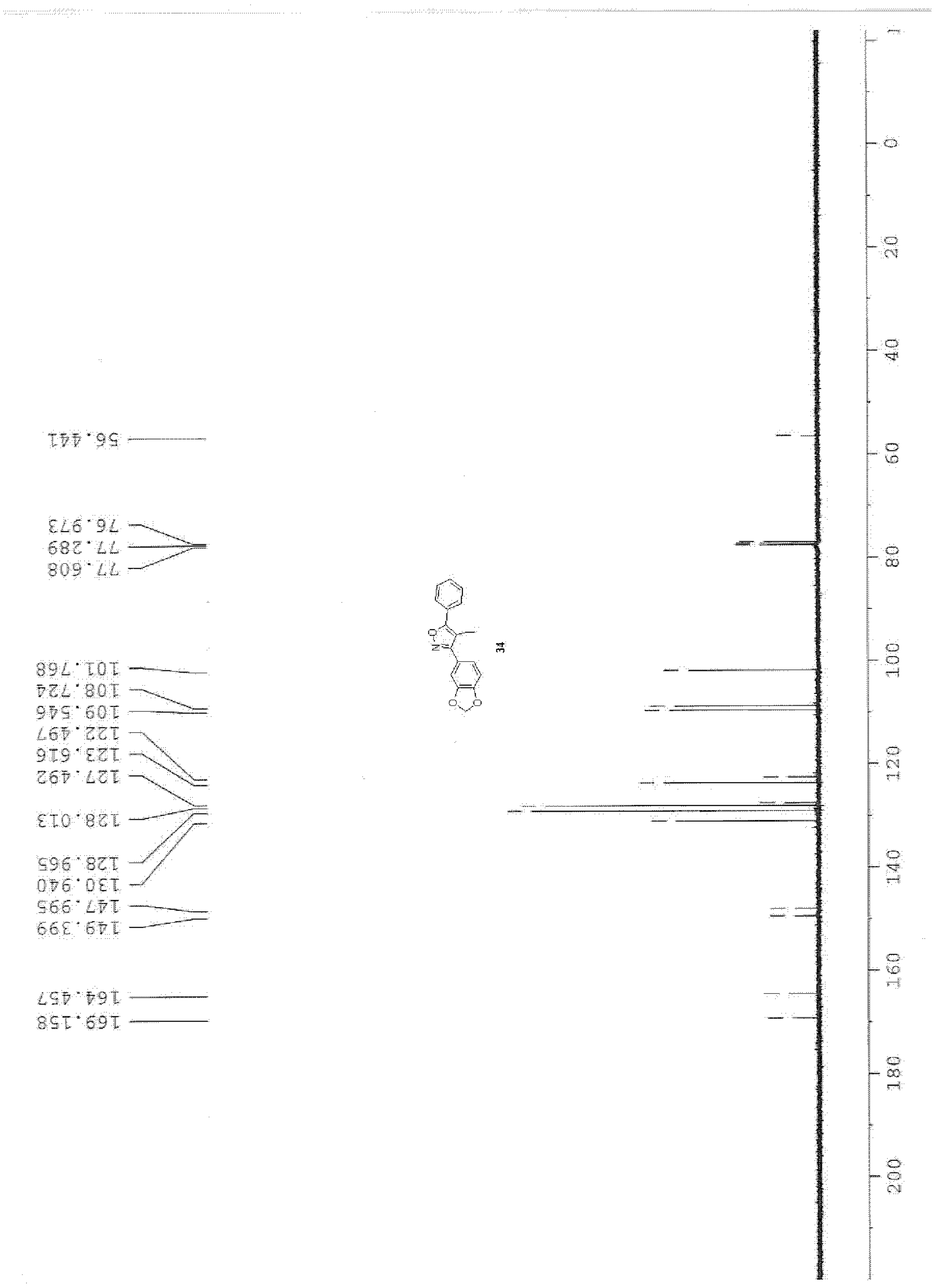
6
7
8
9
10
pp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122.497
123.616
127.492
128.013
128.965
130.940
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164.457
169.158
N–O
34
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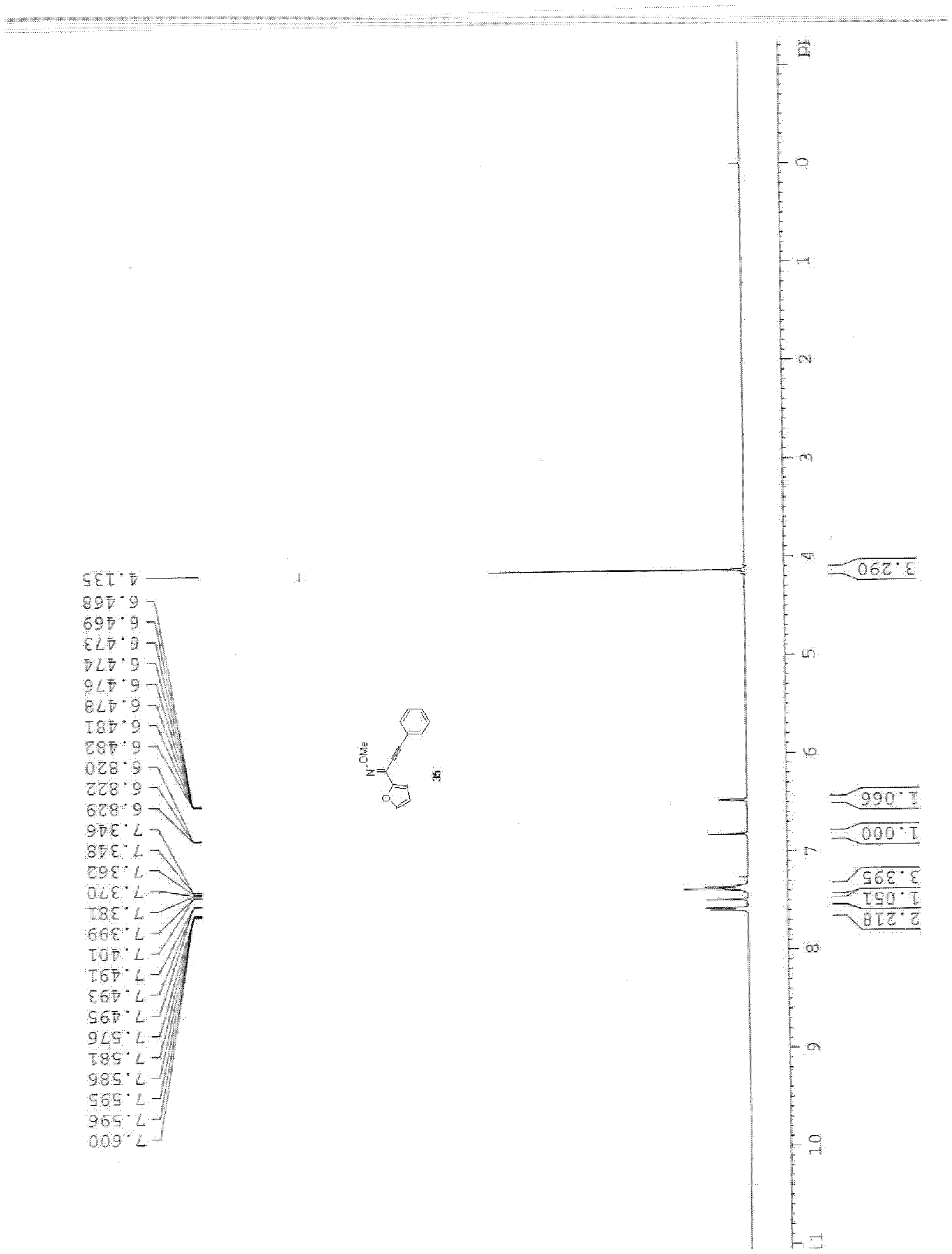
60
80
100
120
140
160
180
200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6.468
6.469
6.473
6.474
6.476
6.478
6.481
6.482
6.820
6.822
6.829
7.346
7.348
7.362
7.370
7.381
7.399
7.401
7.491
7.493
7.495
7.576
7.581
7.586
7.595
7.596
7.600
OMe
N
O
35
3.290
1.066
1.000
3.395
1.051
2.218
ppm
0
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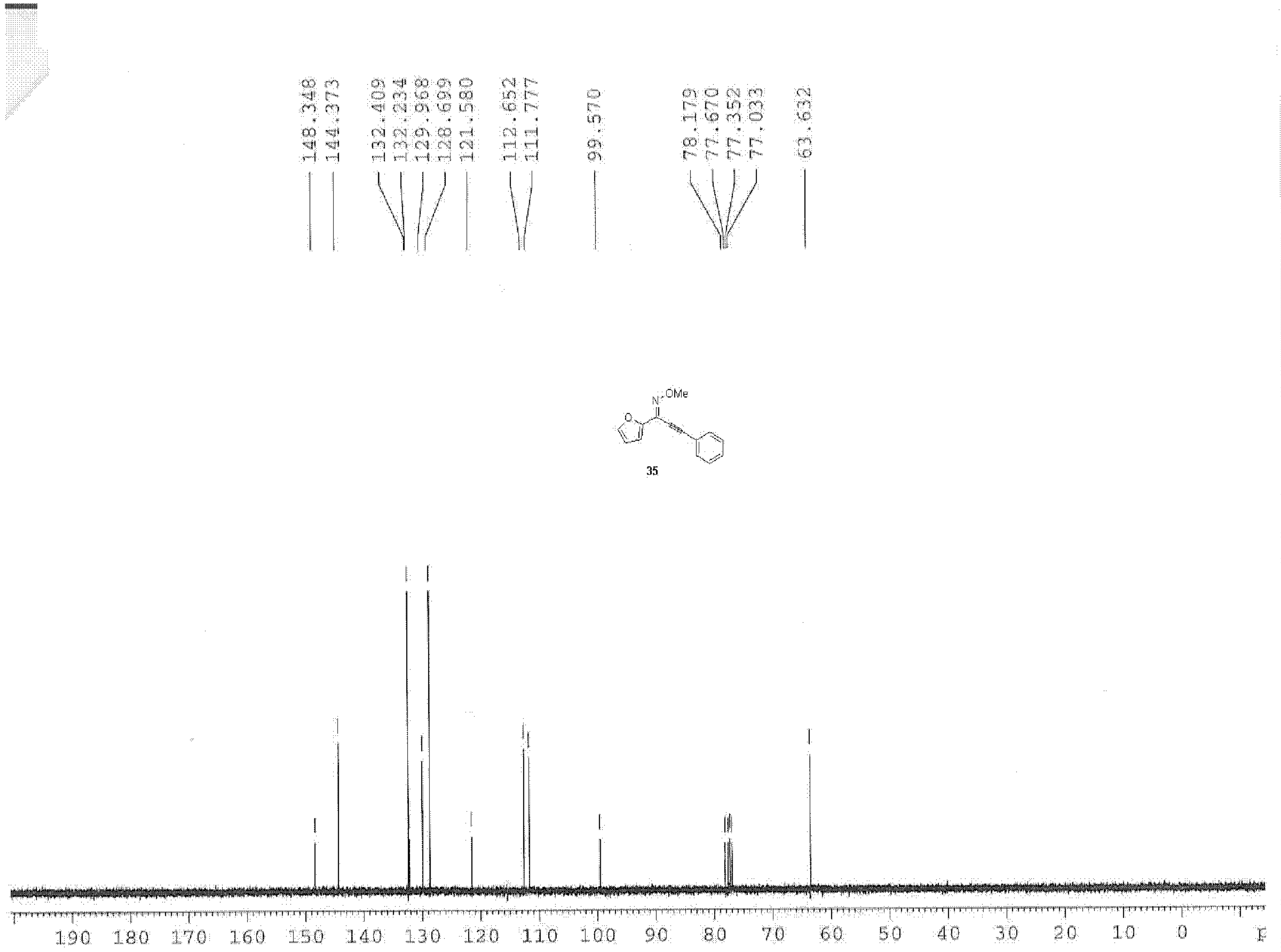
2
3
4
5
6
7
8
9
10
11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132.409
132.234
129.968
128.699
121.580
112.652
111.777
99.570
78.179
77.670
77.352
77.033
63.632
N
OMe
O
35
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140
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110
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50
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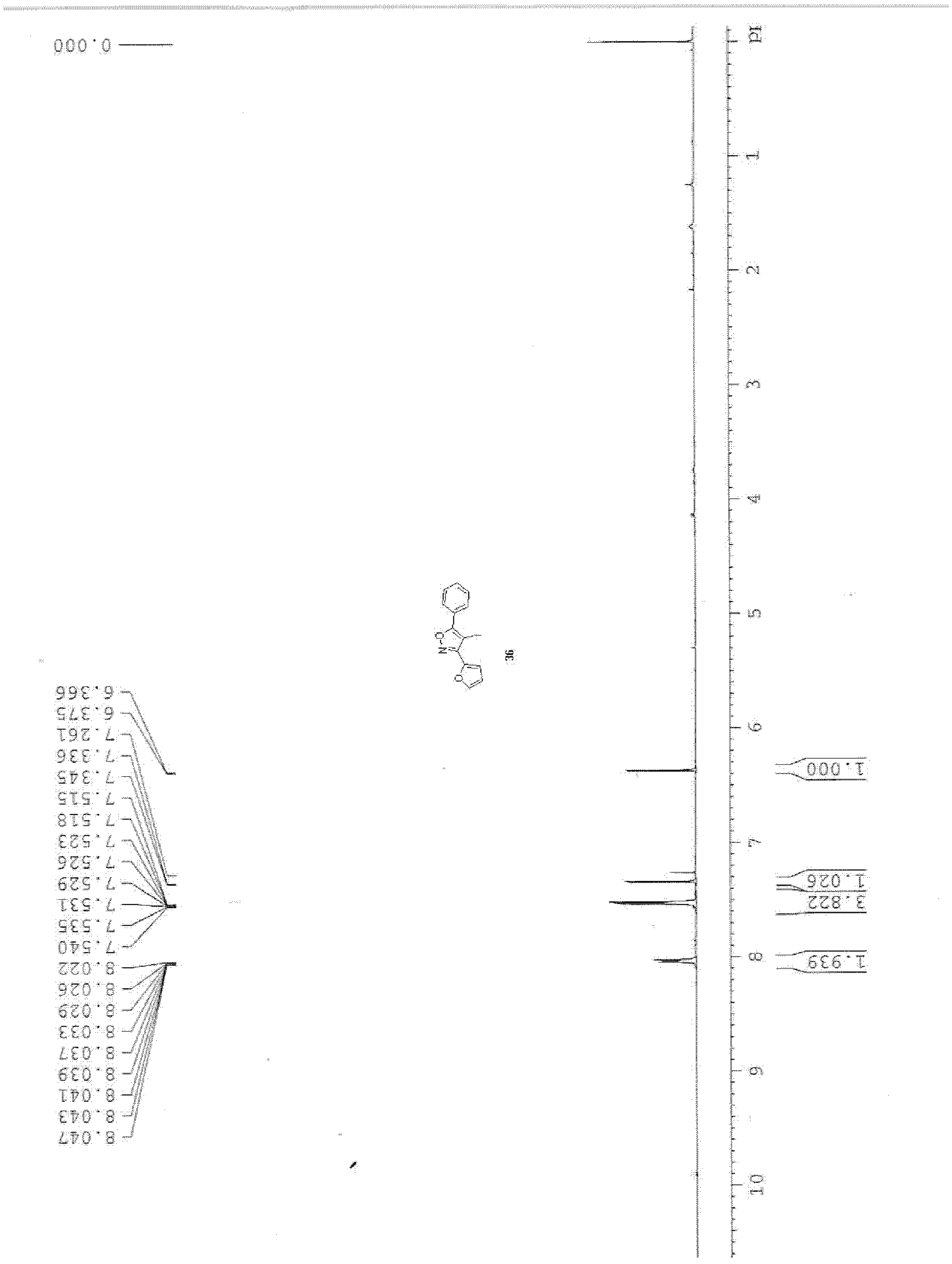
30
20
10
0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6.375
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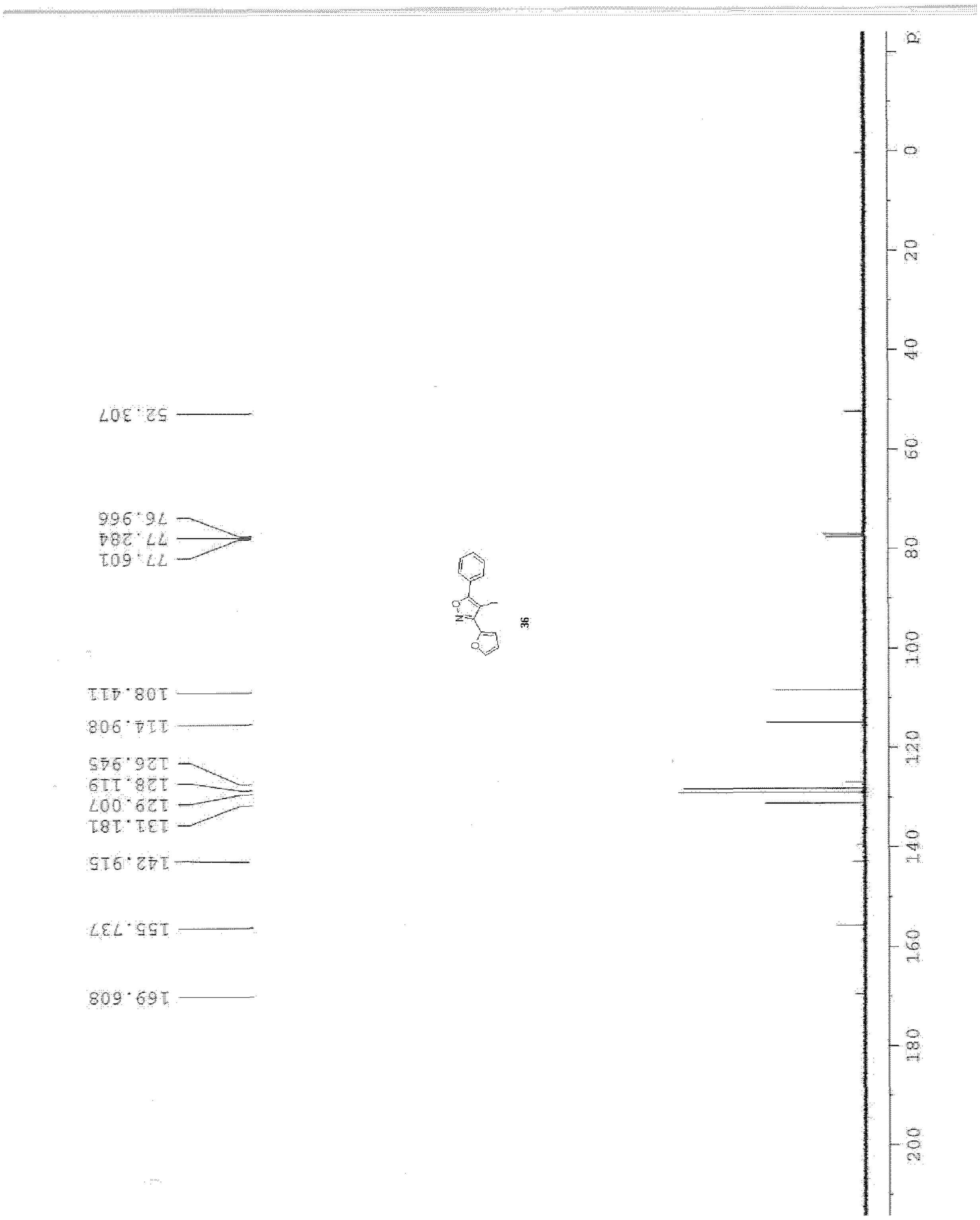
7.336
7.345
7.515
7.518
7.523
7.526
7.529
7.531
7.535
7.540
8.022
8.026
8.029
8.033
8.037
8.039
8.041
8.043
8.047
N
O
1.000
1.026
3.822
1.939
0
1
2
3
4
5
6
7
8
9
10
ppm

36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114.908
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52.307
36
200
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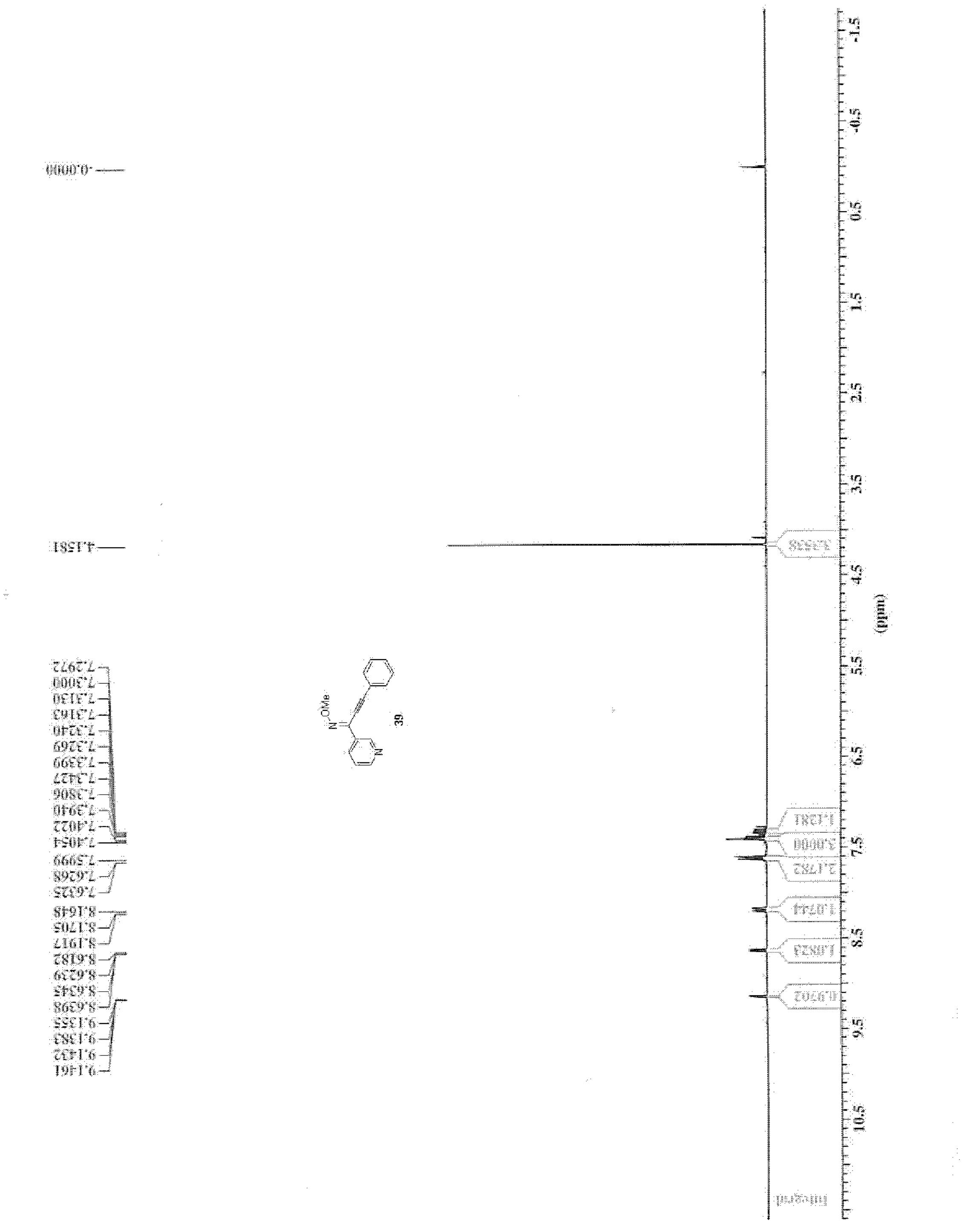
140
120
100
80
60
40
20
0
p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7.3000
7.3130
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7.3399
7.3427
7.3906
7.3940
7.4022
7.4054
7.5999
7.6268
7.6325
8.1648
8.1705
8.1917
8.6182
8.6239
8.6345
8.6398
9.1355
9.1383
9.1432
9.1461
N
OMe
N
3.3538
1.1281
3.0000
2.1782
1.0744
1.0823
0.9702
Integral
-1.5
-0.5
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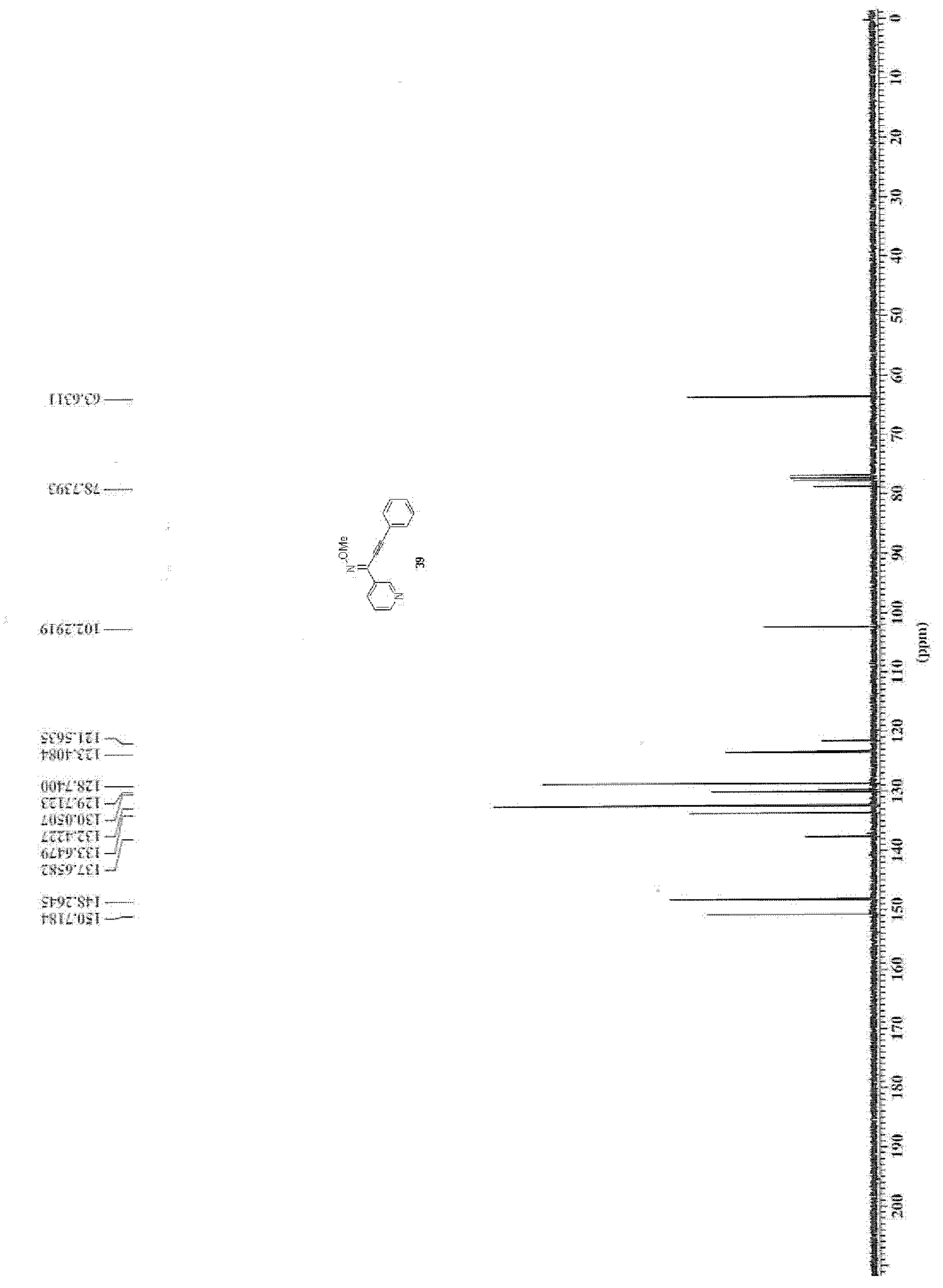
2.5
3.5
4.5
5.5
6.5
7.5
8.5
9.5
10.5
(ppm)

39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102.2919
121.5635
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132.4227
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137.6582
148.2645
150.7184
N
OMe
N
39
0
10
20
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70
80
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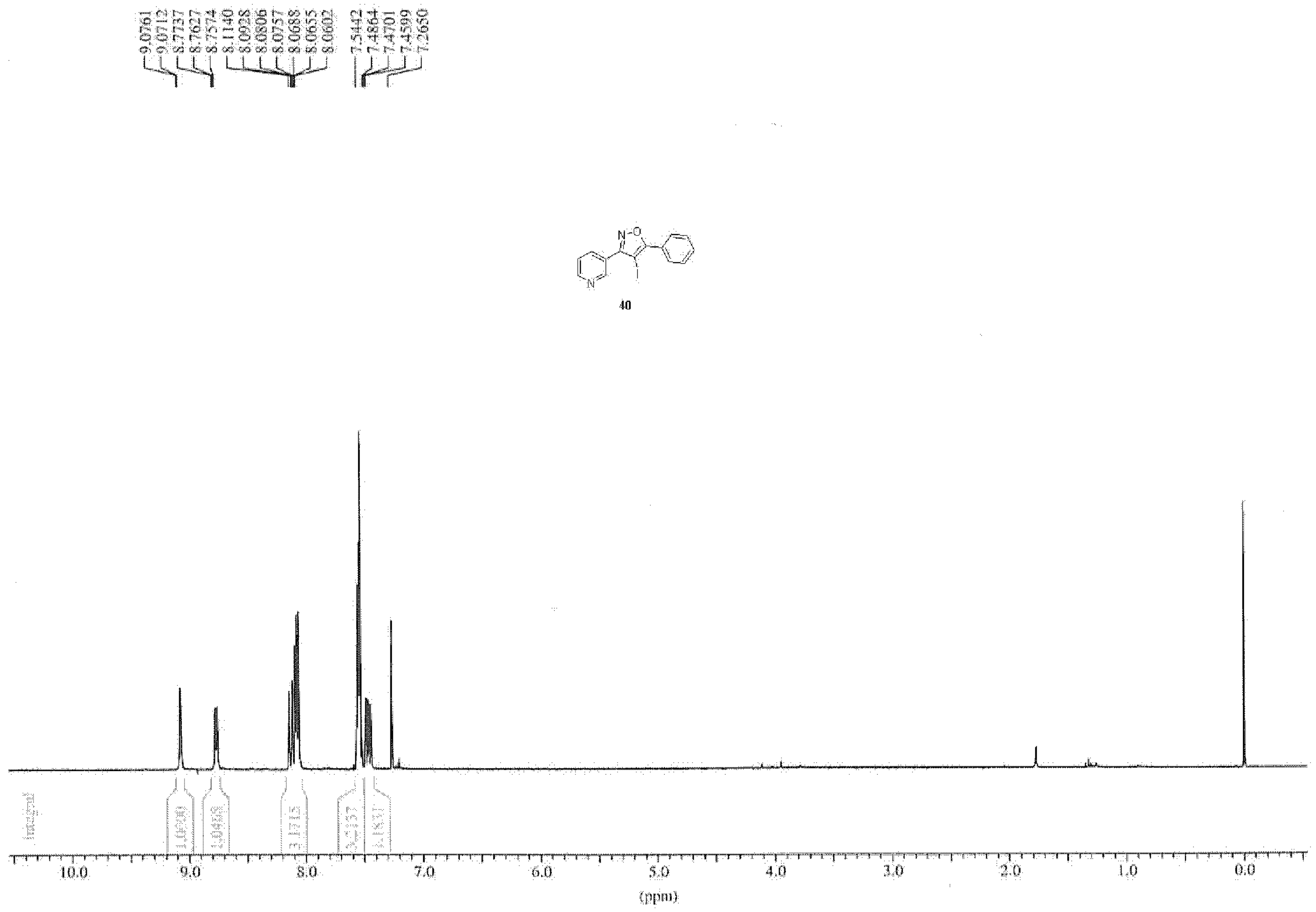
100
110
120
130
140
150
160
170
180
190
200
(ppm)



40

9.0761
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8.0928
8.0806
8.0757
8.0688
8.0655
8.0602
7.5442
7.4864
7.4701
7.4599
7.2650
N-O
N
Integral
1.0000
1.0468
3.1715
3.2157
1.1831
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7.0
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5.0
4.0
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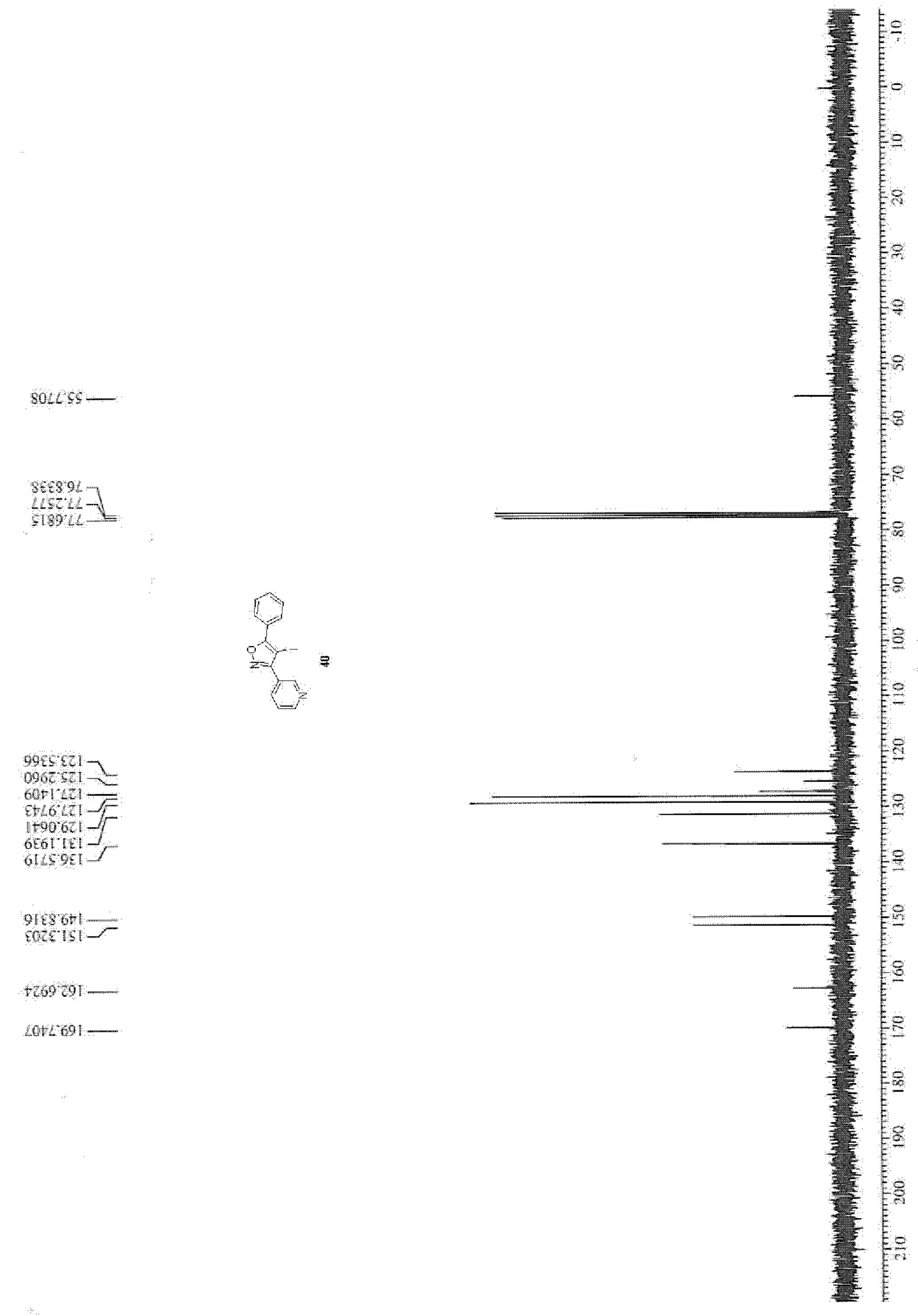
(ppm)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129.0641
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136.5719
149.8316
151.3203
162.6924
169.7407
40
-10
0
10
20
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90
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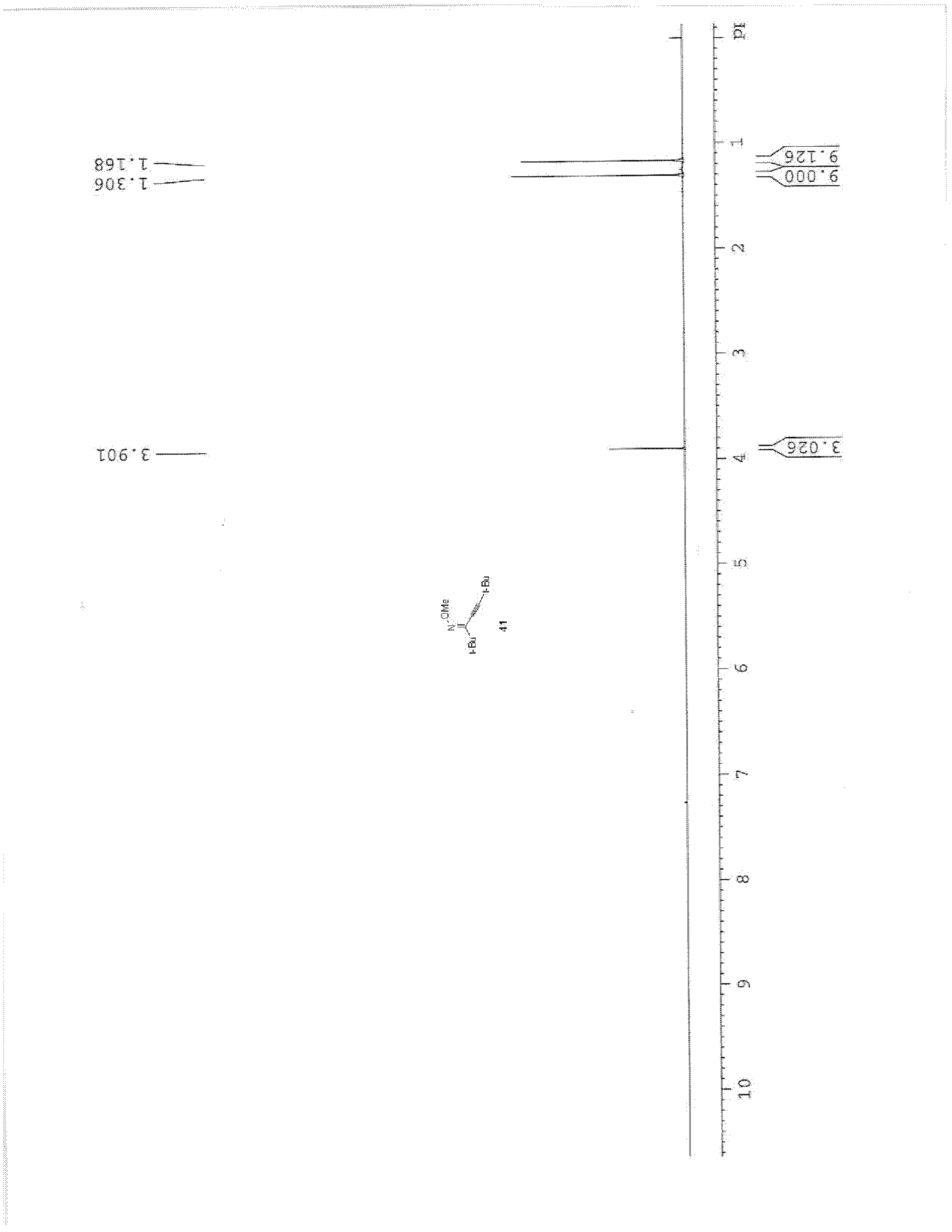
110
120
130
140
150
160
170
180
190
200
210
(ppm)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2
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6
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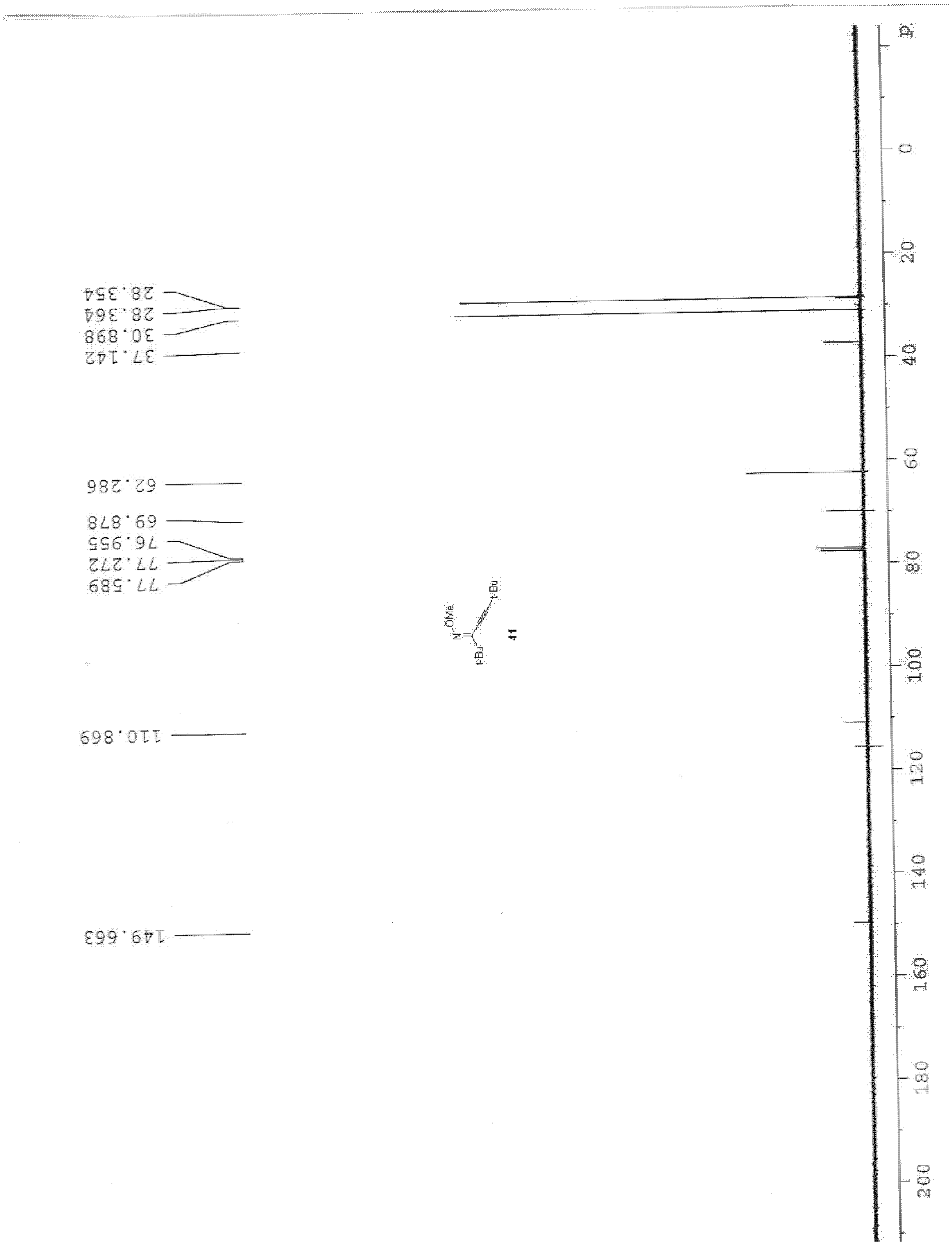
OMe
t-Bu
t-Bu
41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77.272
77.589
110.869
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t-Bu
t-Bu
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80
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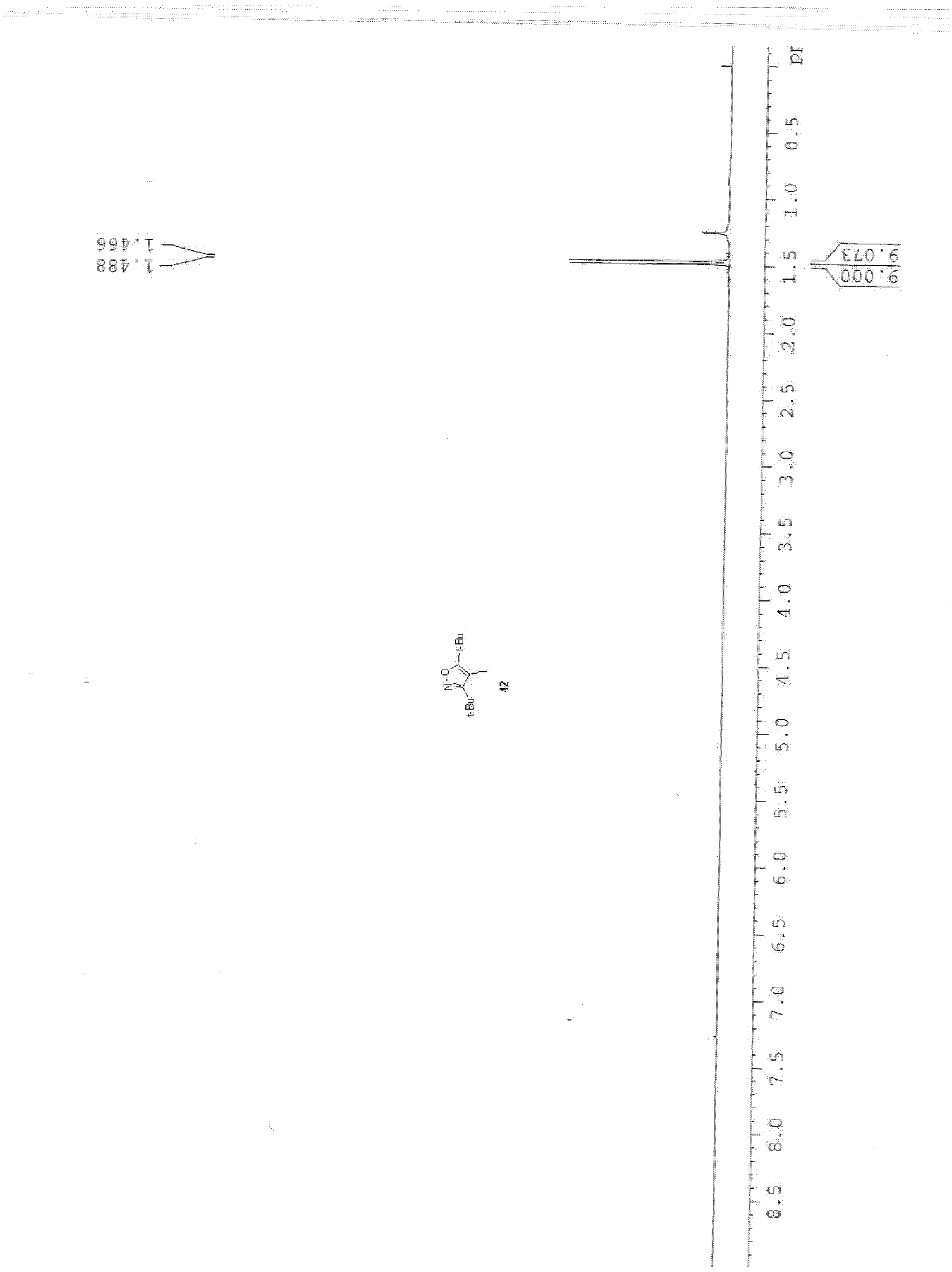
200
p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2.0
2.5
3.0
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4.0
4.5
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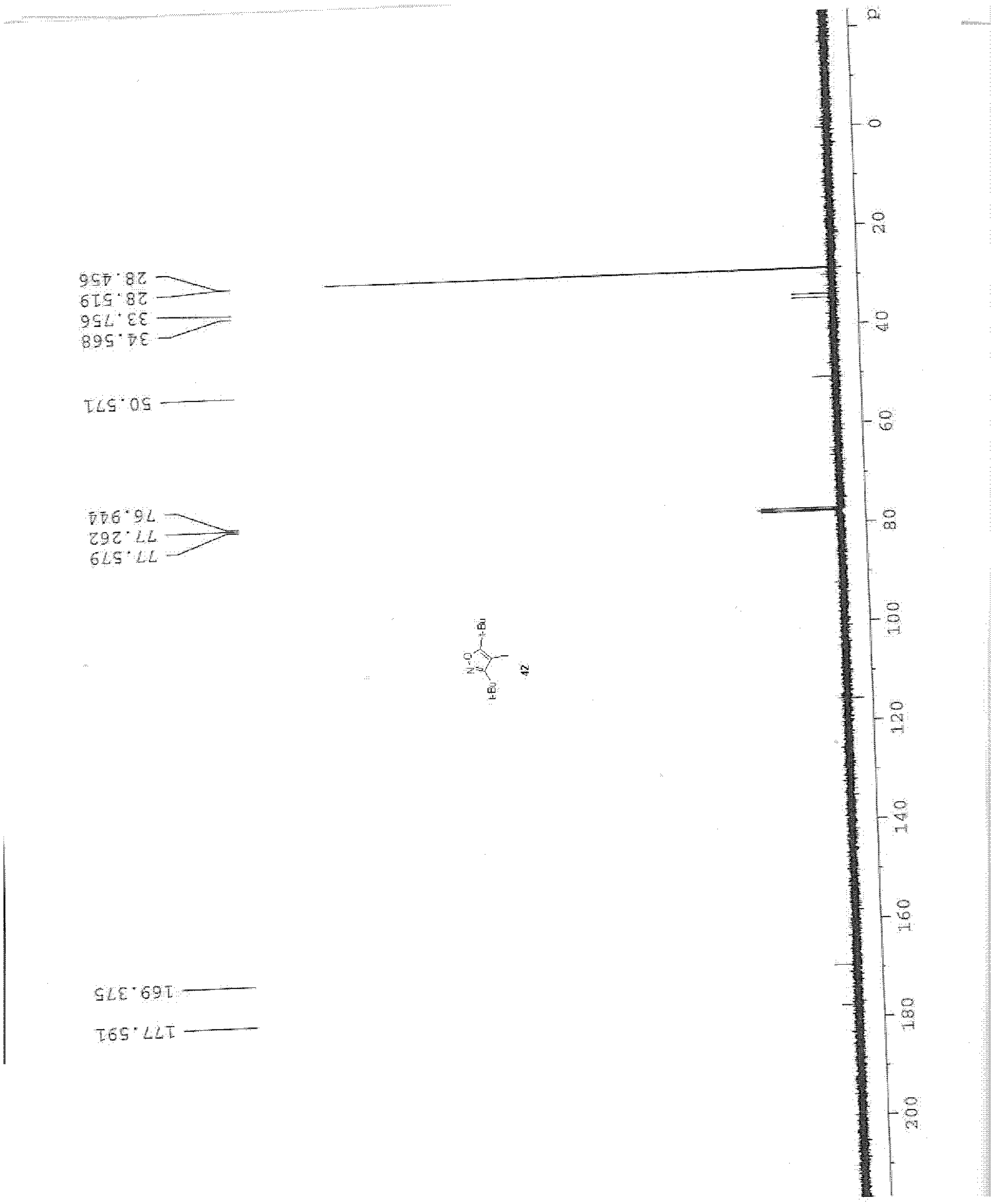
5.5
6.0
6.5
7.0
7.5
8.0
8.5
N-O
t-Bu
t-Bu
42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33.756
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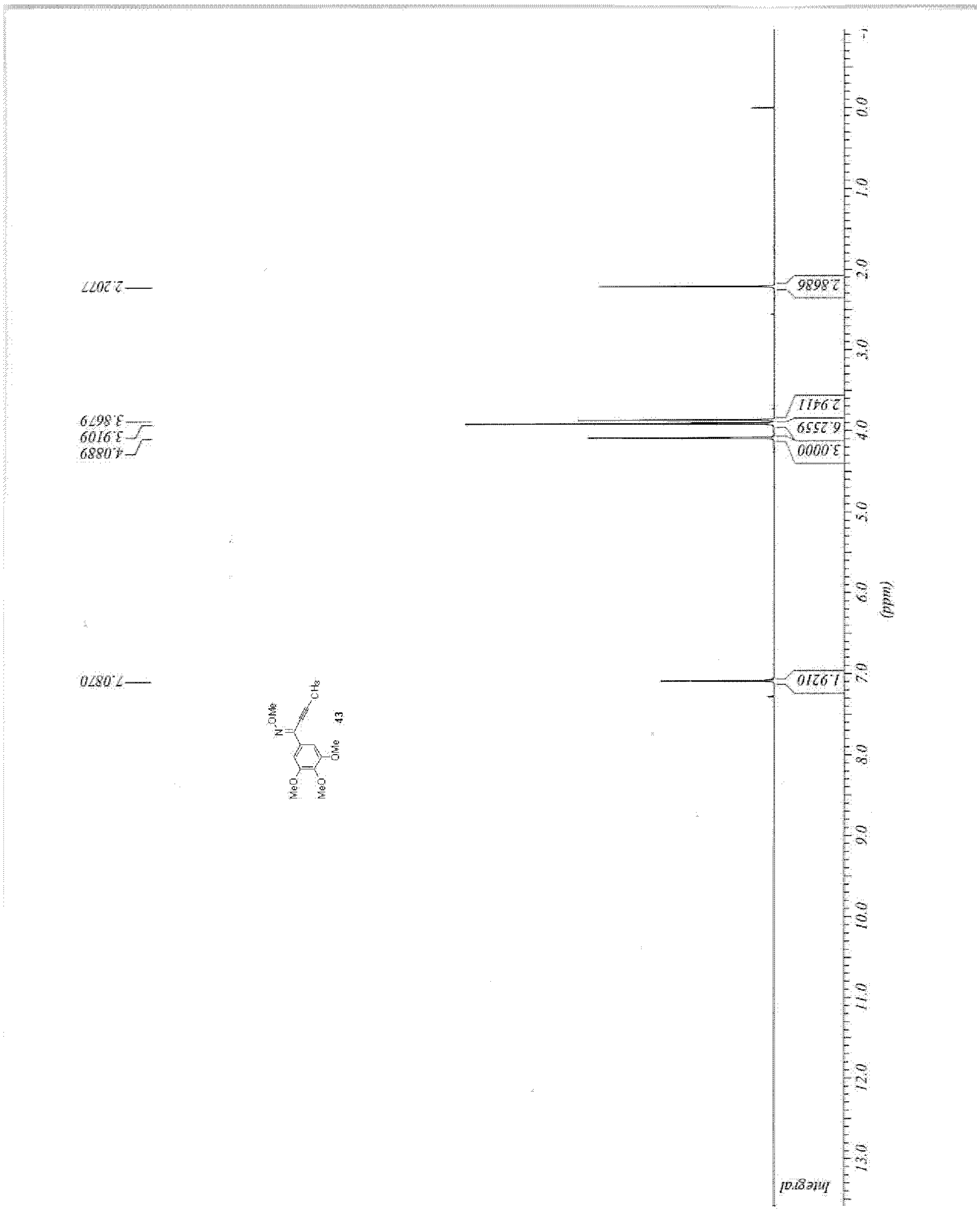
76.944
77.262
77.579
169.375
177.591
t-Bu
N–O
t-Bu
42
p
0
20
40
60
80
100
120
140
160
180
200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2.9411
6.2559
3.0000
1.9210
MeO
MeO
OMe
N
OMe
CH3
43
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
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10.0
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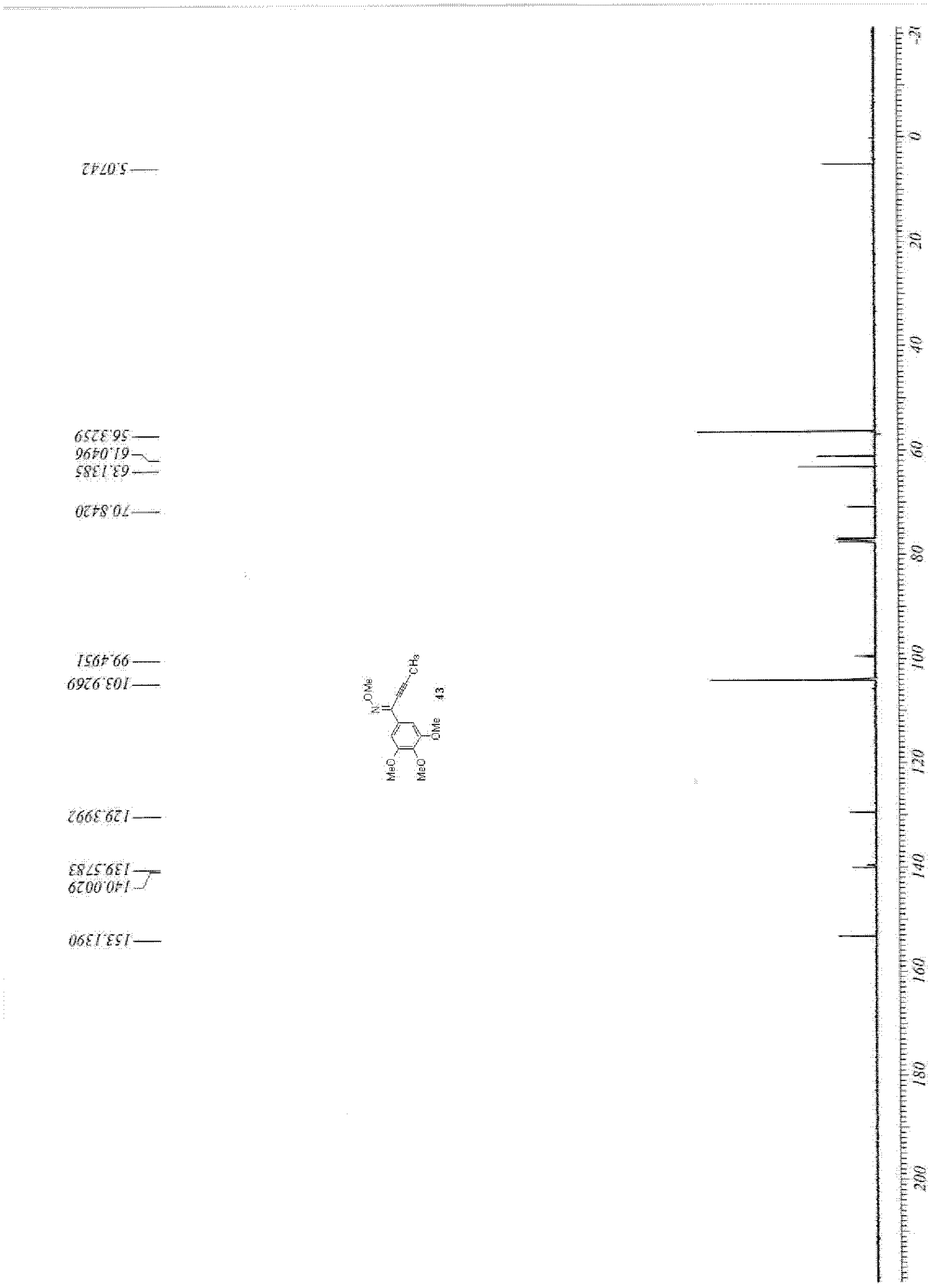
13.0
(ppm)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103.9269
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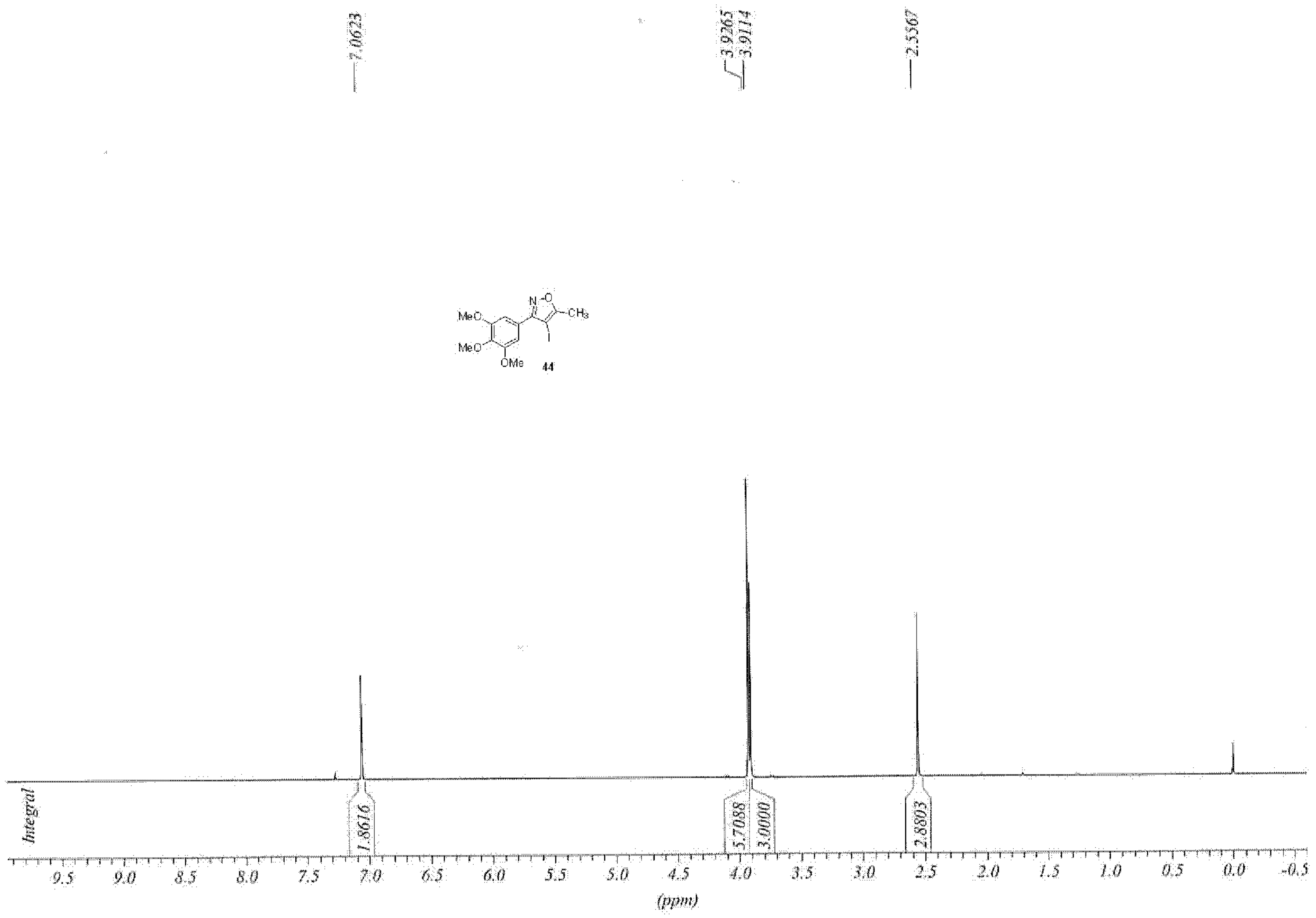
139.5783
140.0029
153.1390
MeO
MeO
OMe
N
OMe
CH3
43
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)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3.9114
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MeO
OMe
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O
CH3
I
44
Integral
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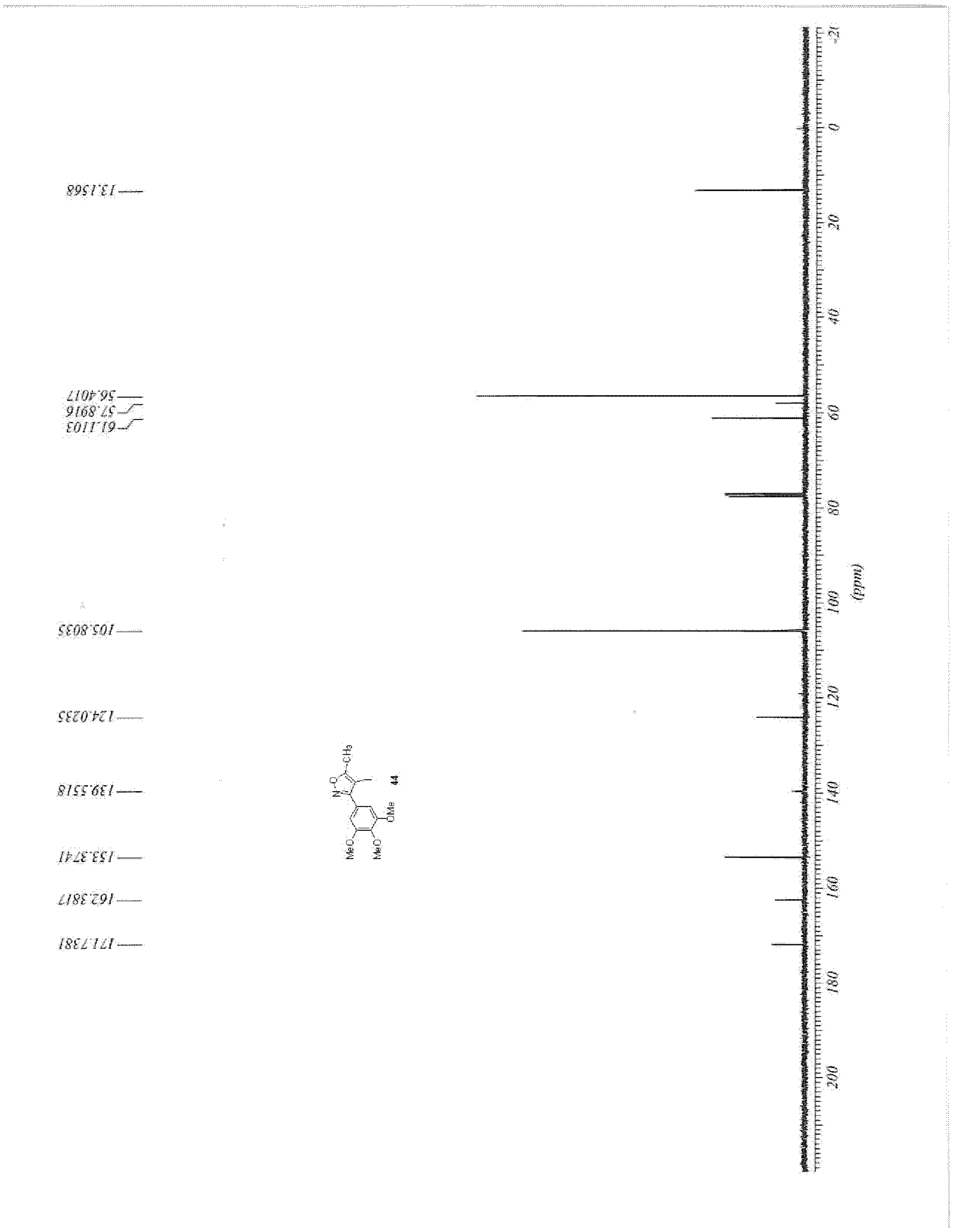
2.8803
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)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139.5518
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162.3817
171.7381
N-O
CH3
MeO
MeO
OMe
44
-20
0
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40
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100
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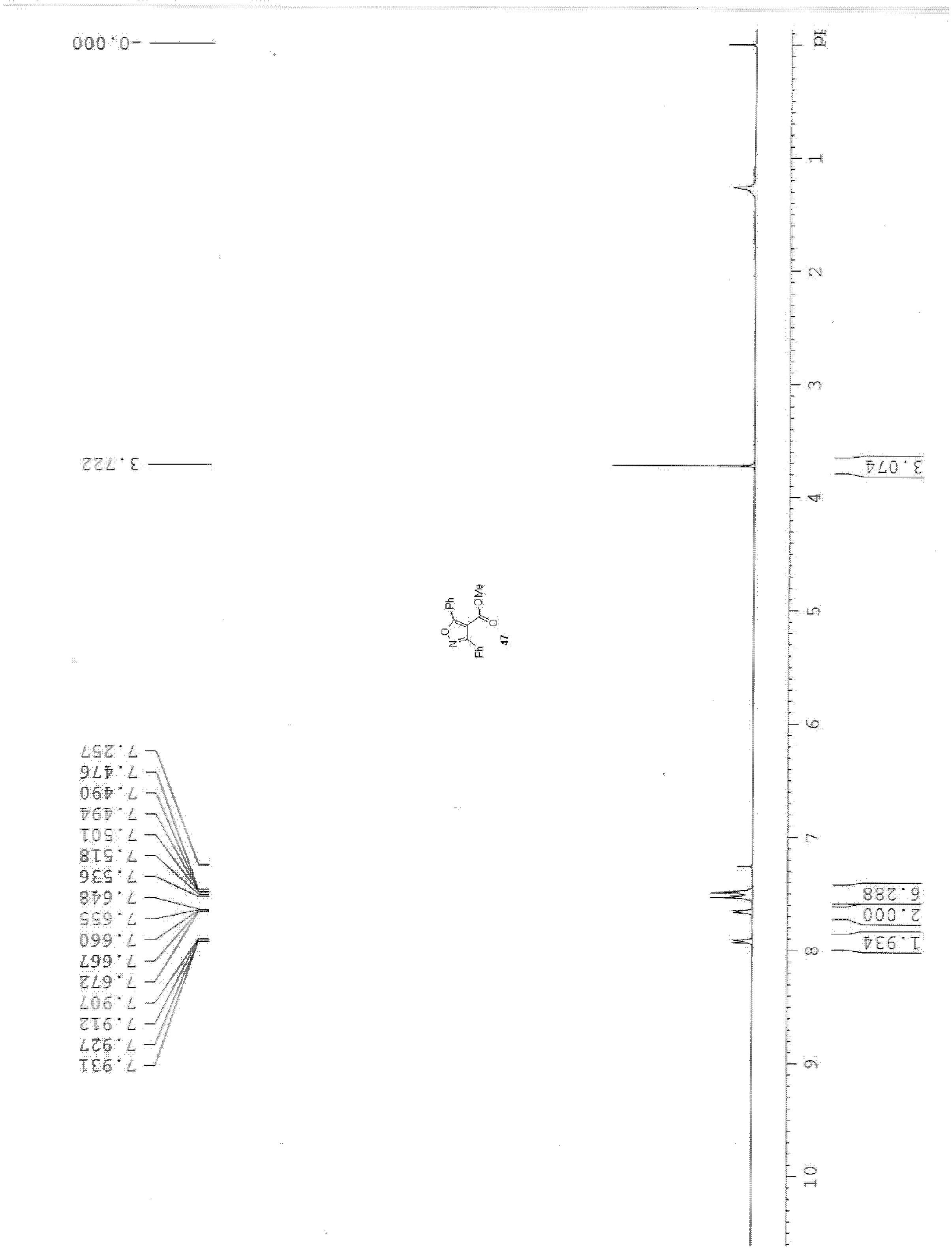
160
180
200
(ppm)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7.494
7.501
7.518
7.536
7.648
7.655
7.660
7.667
7.672
7.907
7.912
7.927
7.931
3.074
6.288
2.000
1.934
ppm
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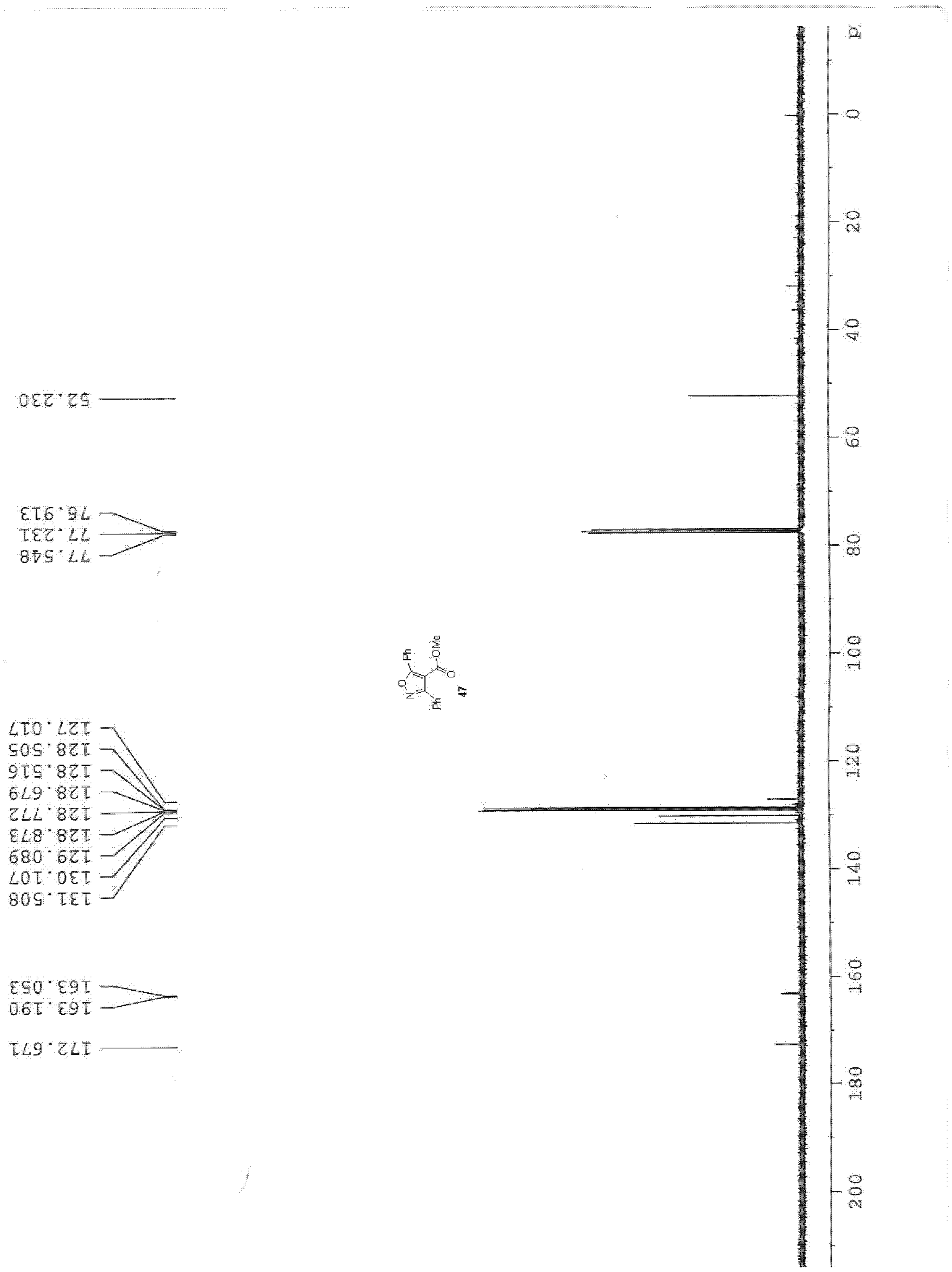
2
3
4
5
6
7
8
9
10
Ph
N
O
Ph
OMe
O
47


52.230
76.913
77.231
77.548
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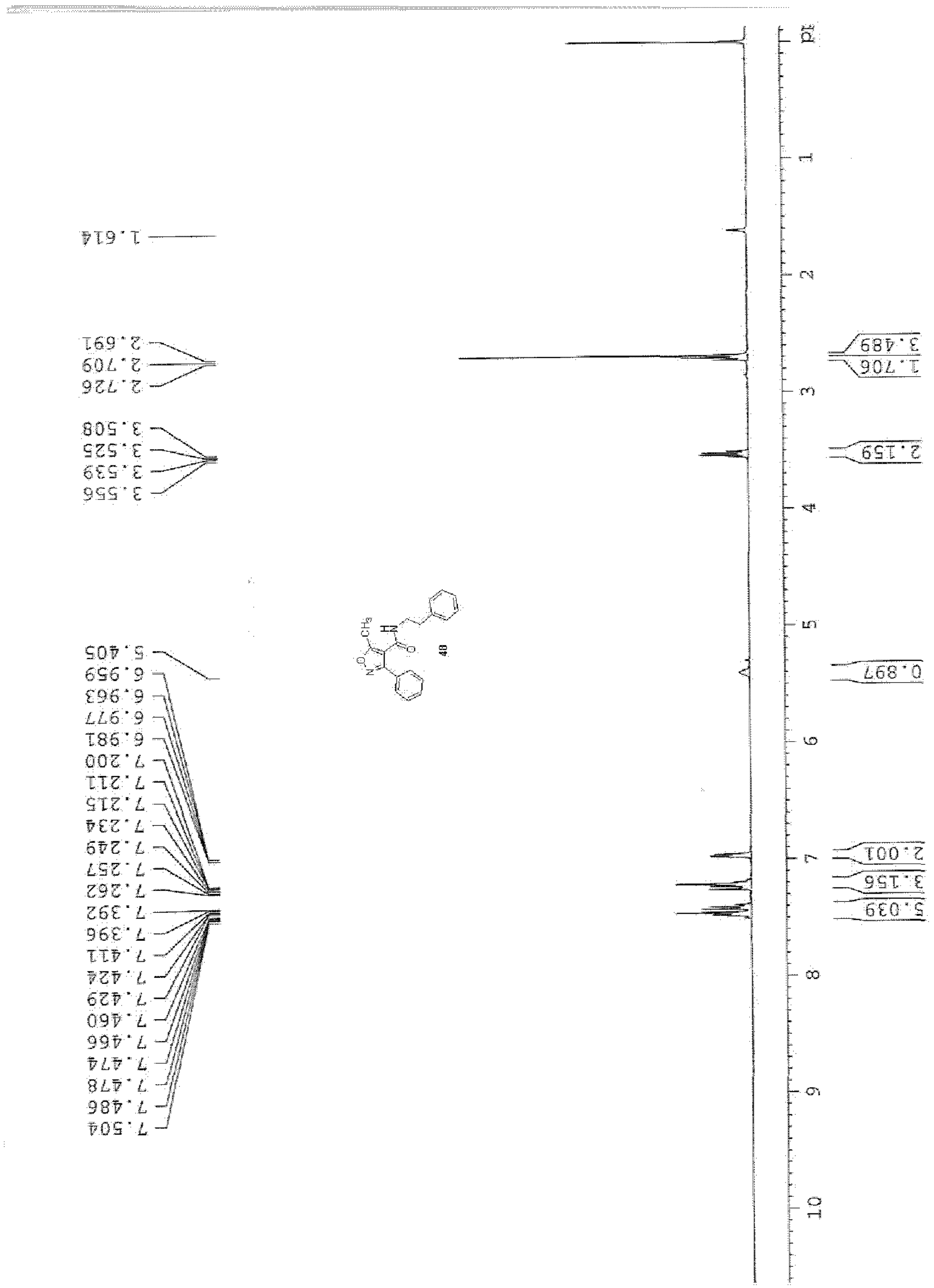
128.505
128.516
128.679
128.772
128.873
129.089
130.107
131.508
163.053
163.190
172.671
Ph
N
O
Ph
OMe
O
47
0
20
40
60
80
100
120
140
160
180
200
p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2.726
3.508
3.525
3.539
3.556
5.405
6.959
6.963
6.977
6.981
7.200
7.211
7.215
7.234
7.249
7.257
7.262
7.392
7.396
7.411
7.424
7.429
7.460
7.466
7.474
7.478
7.486
7.504
CH3
N
O
H
N
O
48
3.489
1.706
2.159
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2.001
3.156
5.039
ppm
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2
3
4
5
6
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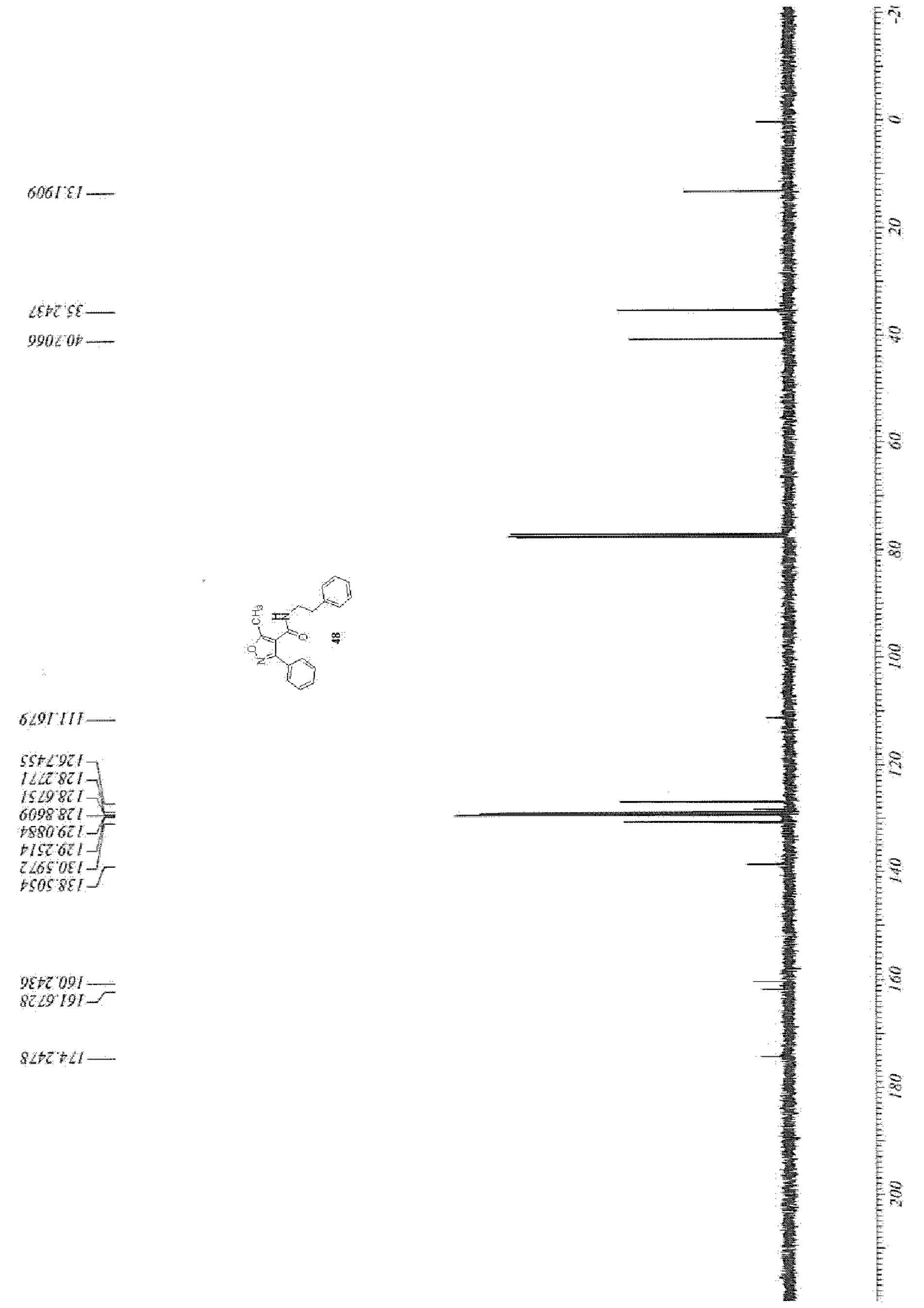
8
9
10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130.5972
138.5054
160.2436
161.6728
174.2478
CH3
N
O
H
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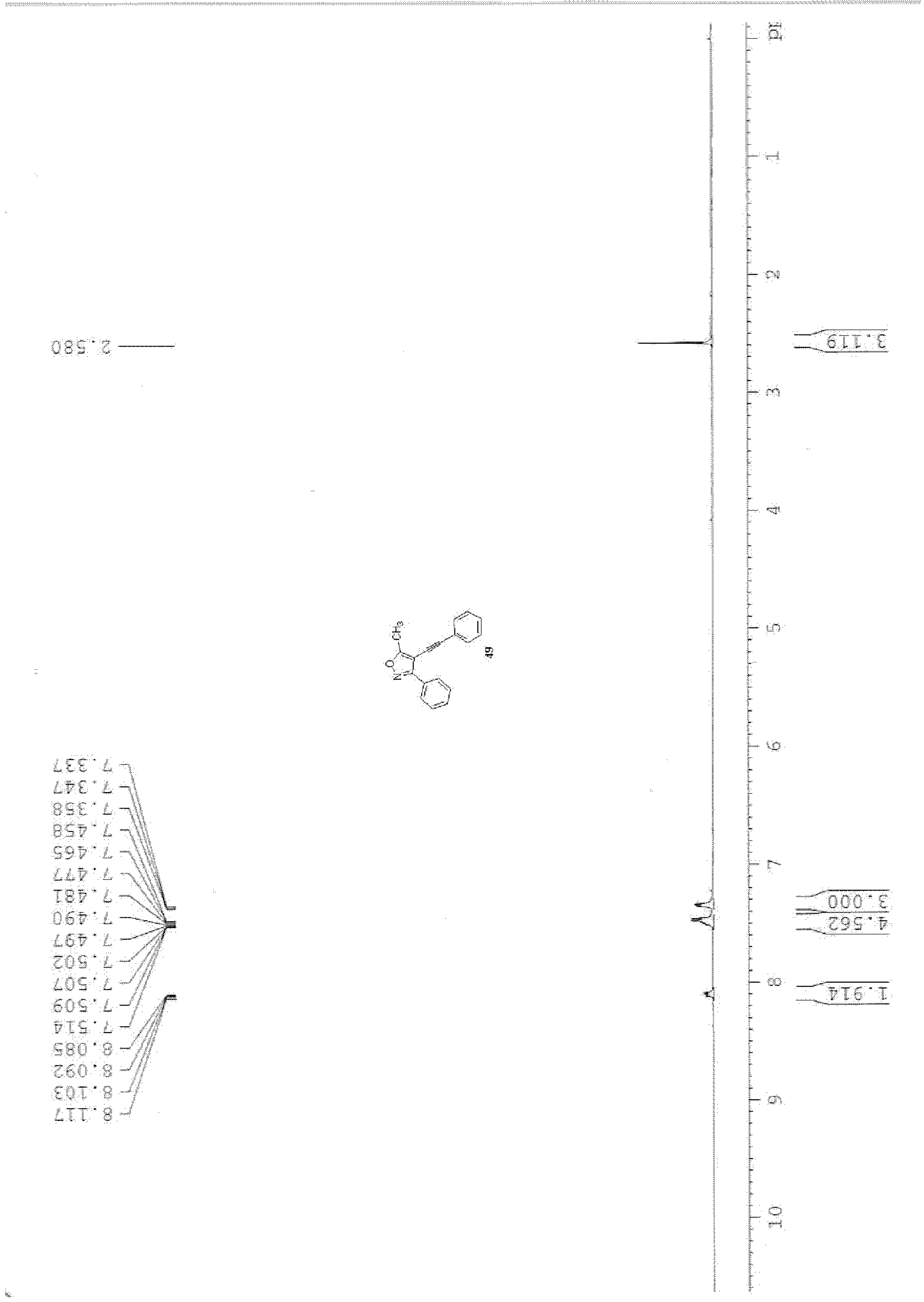
-20
0
20
40
60
80
100
120
140
160
180
200


2.580
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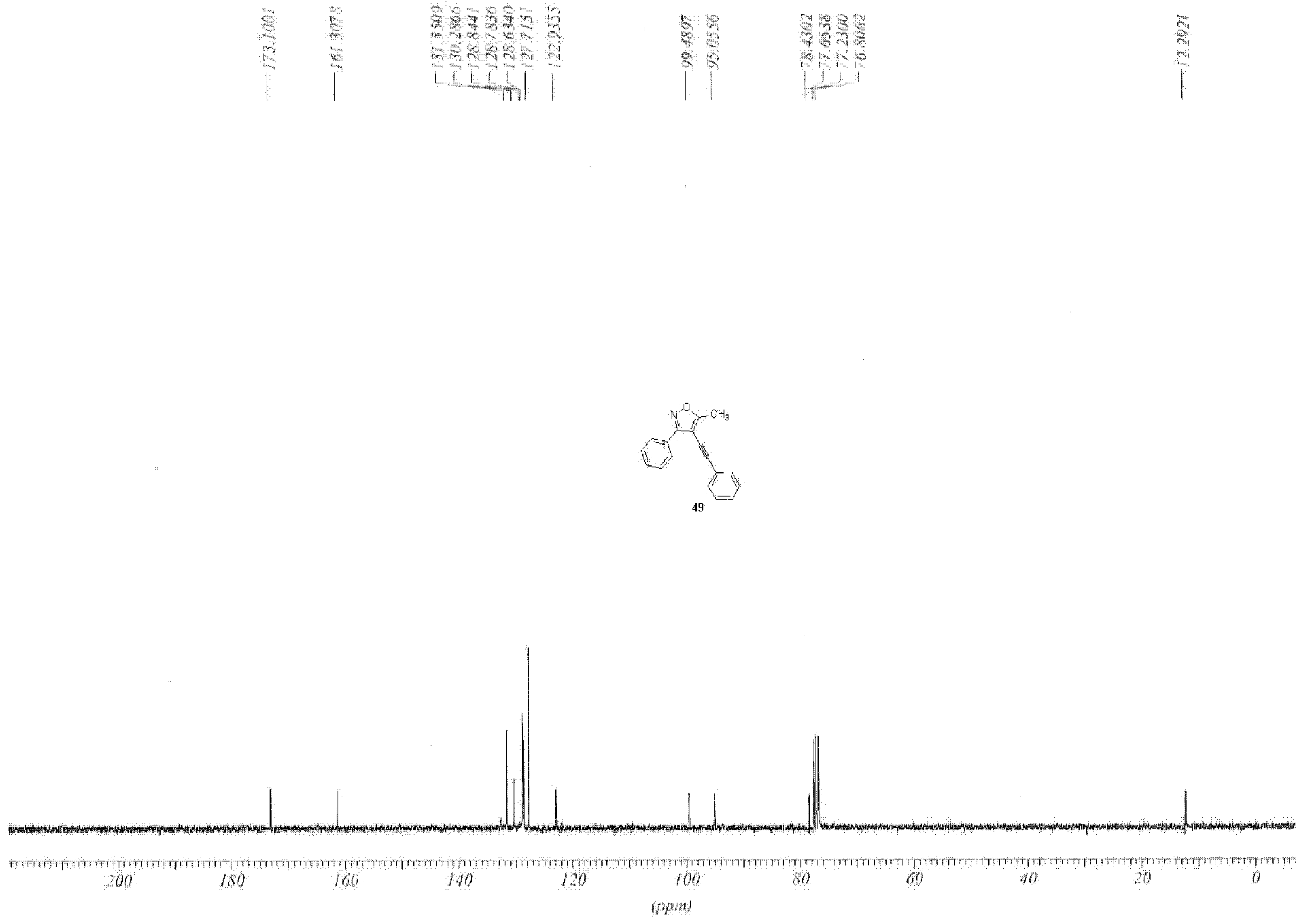
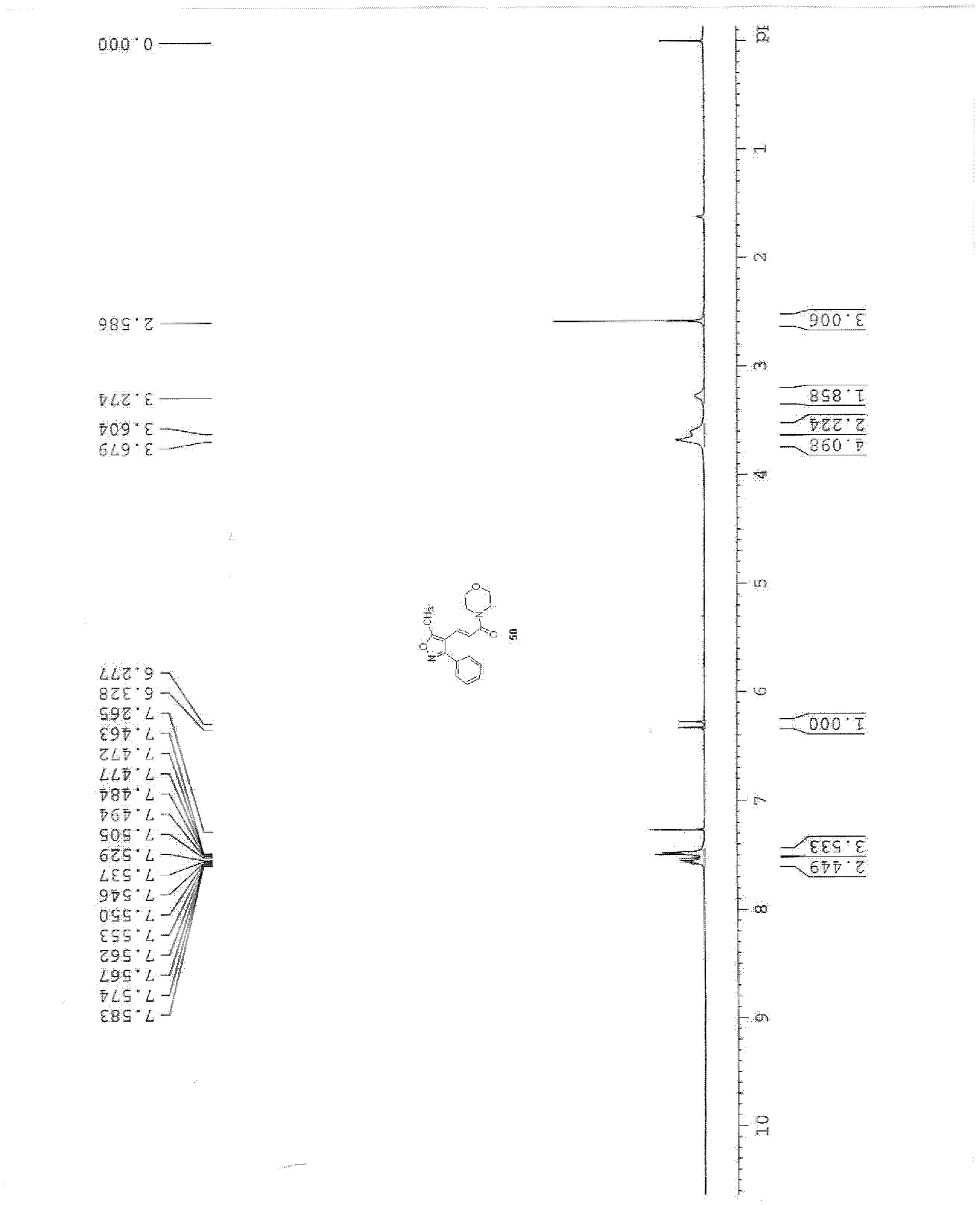
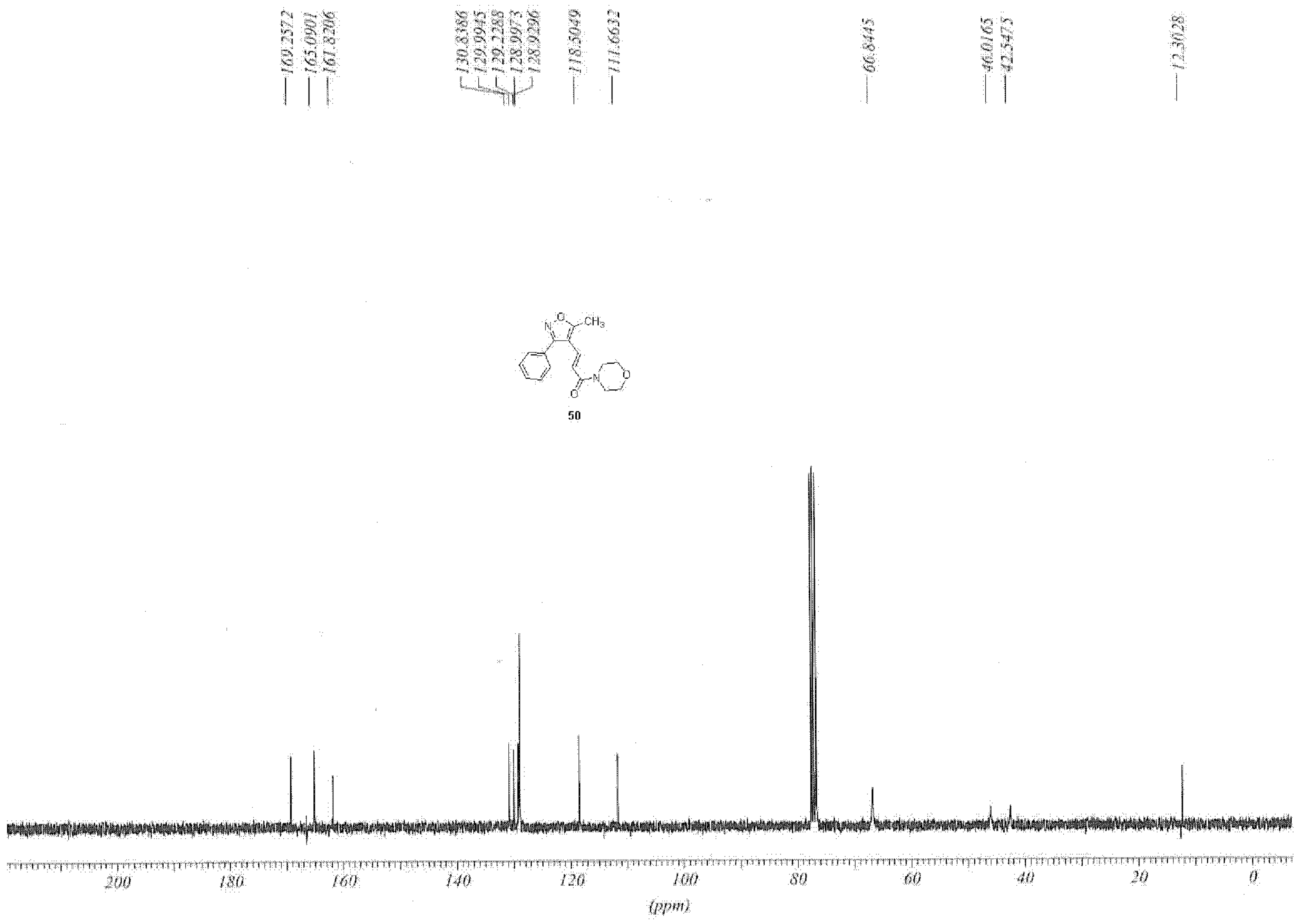
7.347
7.358
7.458
7.465
7.477
7.481
7.490
7.497
7.502
7.507
7.509
7.514
8.085
8.092
8.103
8.117
N
O
CH3
49
3.119
3.000
4.562
1.914
1
2
3
4
5
6
7
8
9
10
pp


49
173.1001
161.3078
131.5509
130.2866
128.8441
128.7836
128.6340
127.7151
122.9355
99.4897
95.0556
78.4302
77.6538
77.2300
76.8062
12.2921
CH3
N
O
200
180
160
140
120
100
80
60
40
20
0
(ppm)

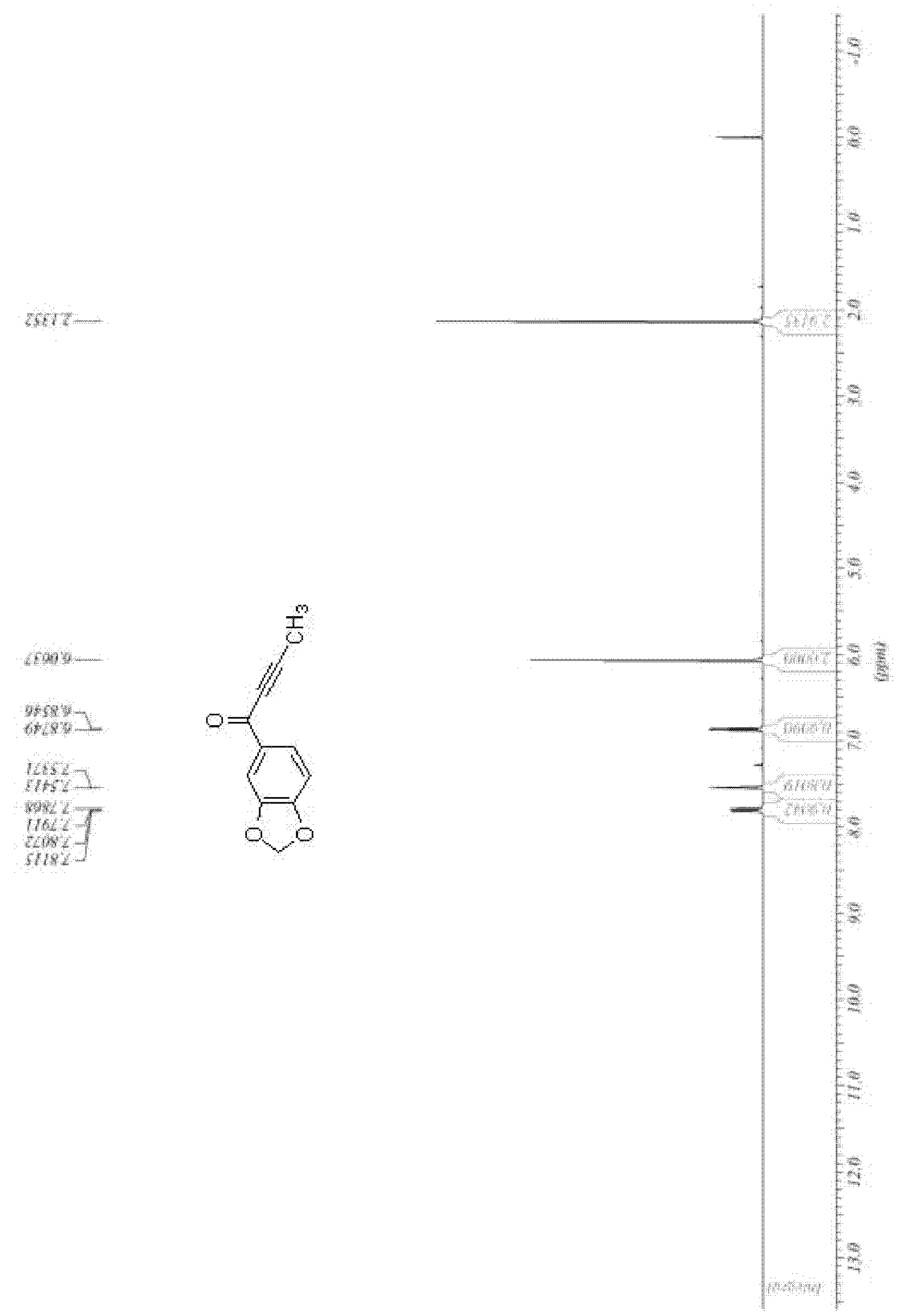


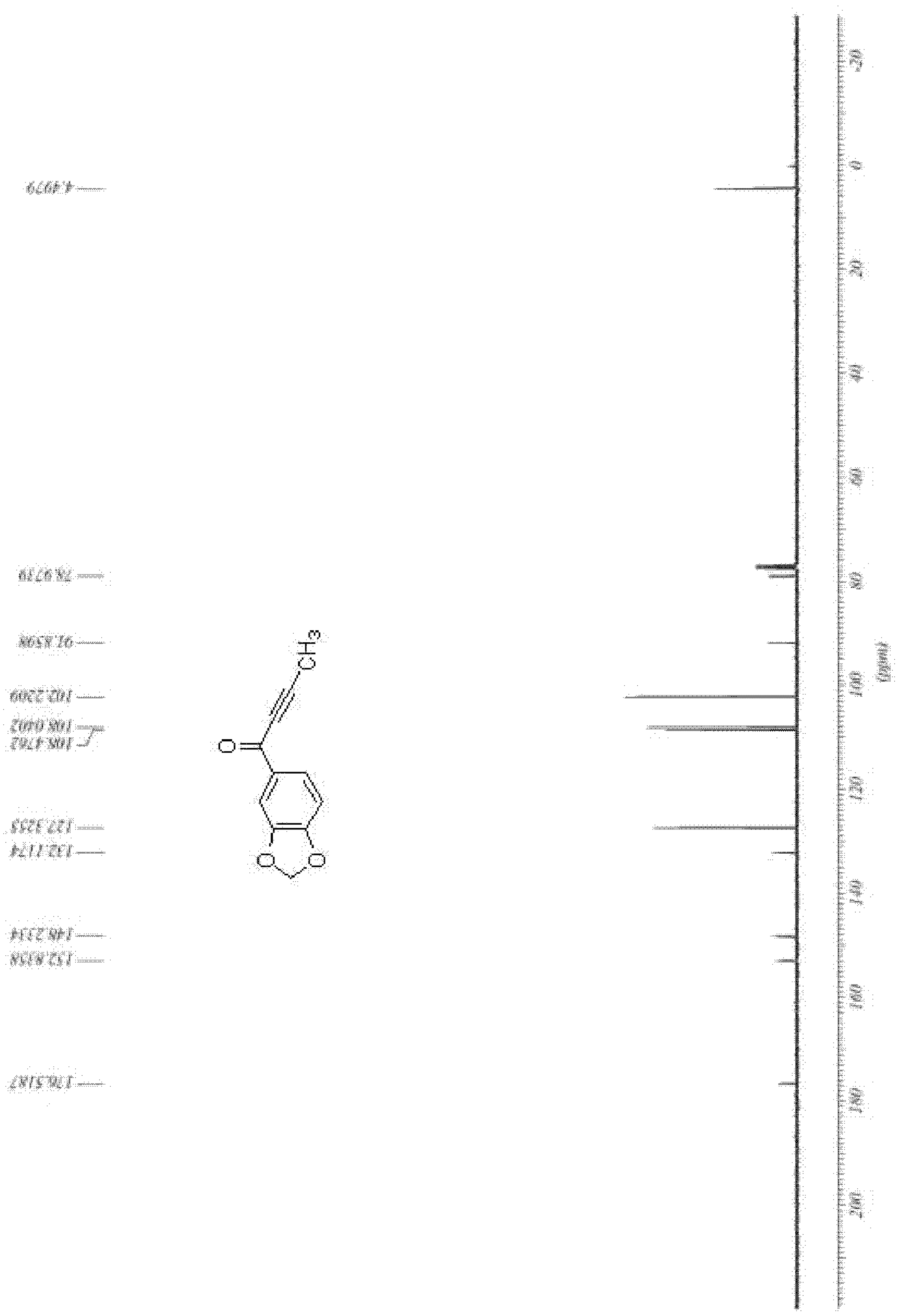
50

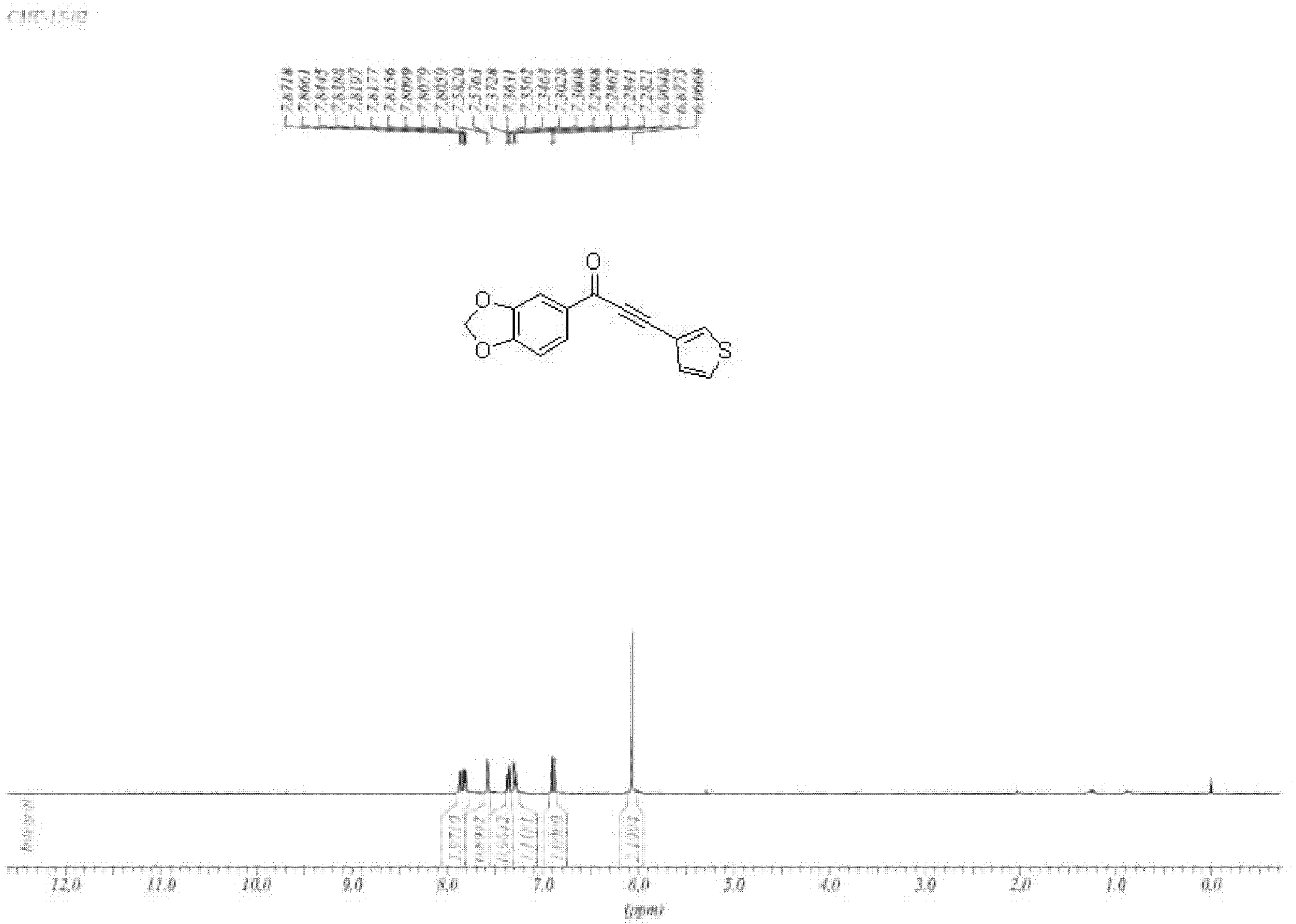
0.000
2.586
3.274
3.604
3.679
6.277
6.328
7.265
7.463
7.472
7.477
7.484
7.494
7.505
7.529
7.537
7.546
7.550
7.553
7.562
7.567
7.574
7.583
3.006
1.858
2.224
4.098
1.000
3.533
2.449
ppm
1
2
3
4
5
6
7
8
9
10
N
O
CH3
O
N
O

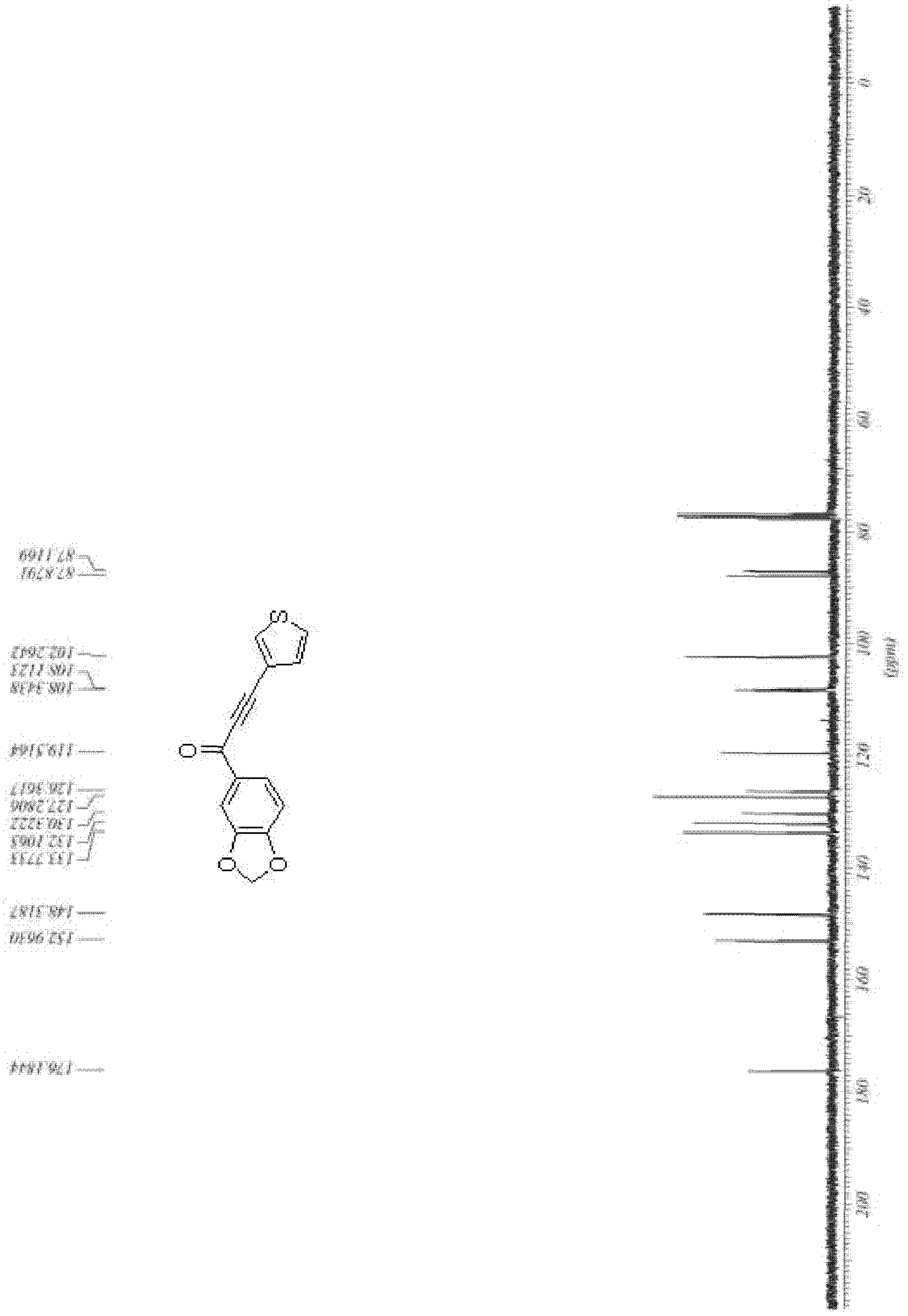

169.2572
165.0901
161.8206
130.8386
129.9945
129.2288
128.9973
128.9296
118.5049
111.6632
66.8445
46.0165
42.5475
12.3028
N
O
CH3
O
N
O
50
200
180
160
140
120
100
80
60
40
20
0
(ppm)

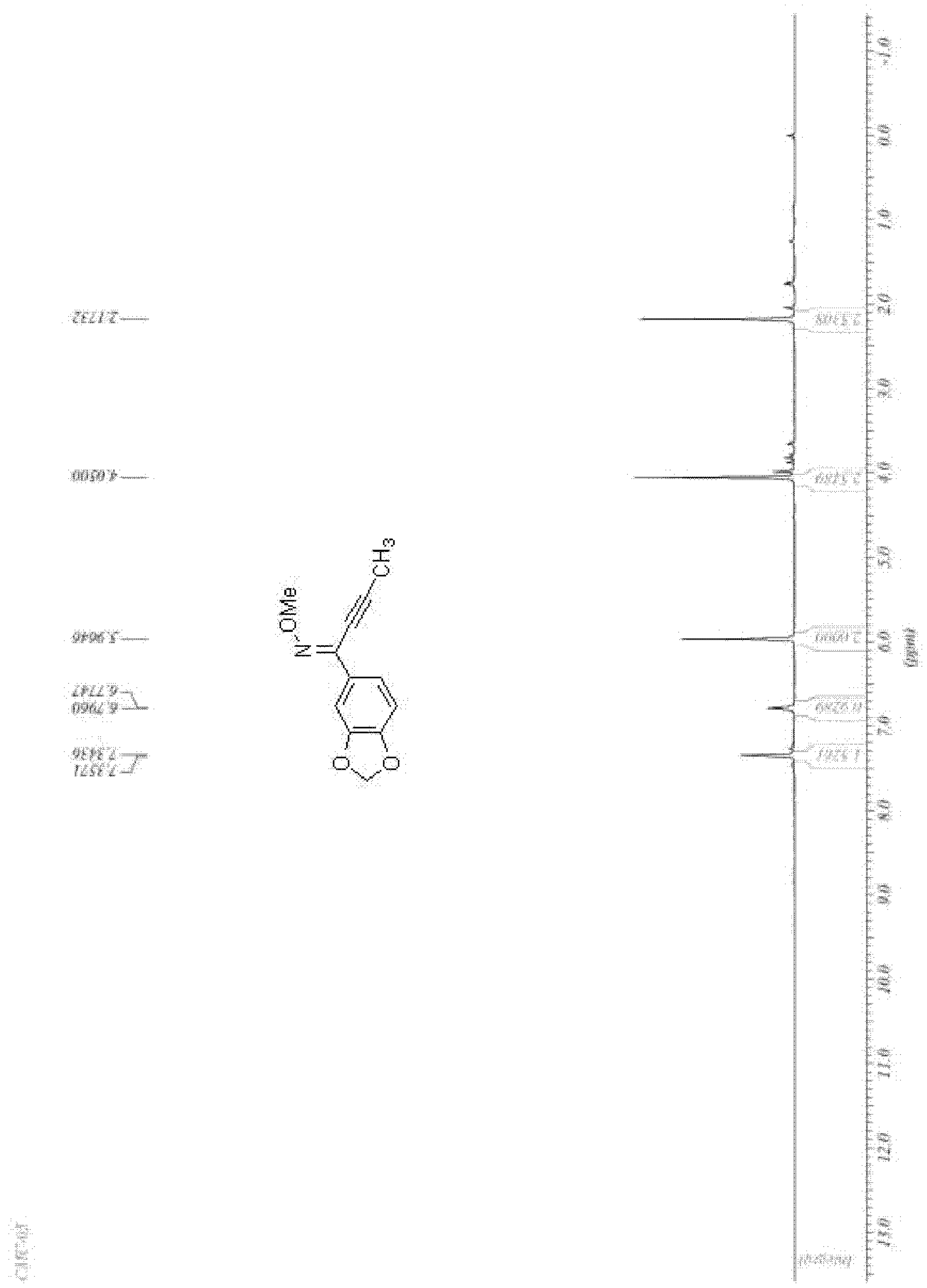
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

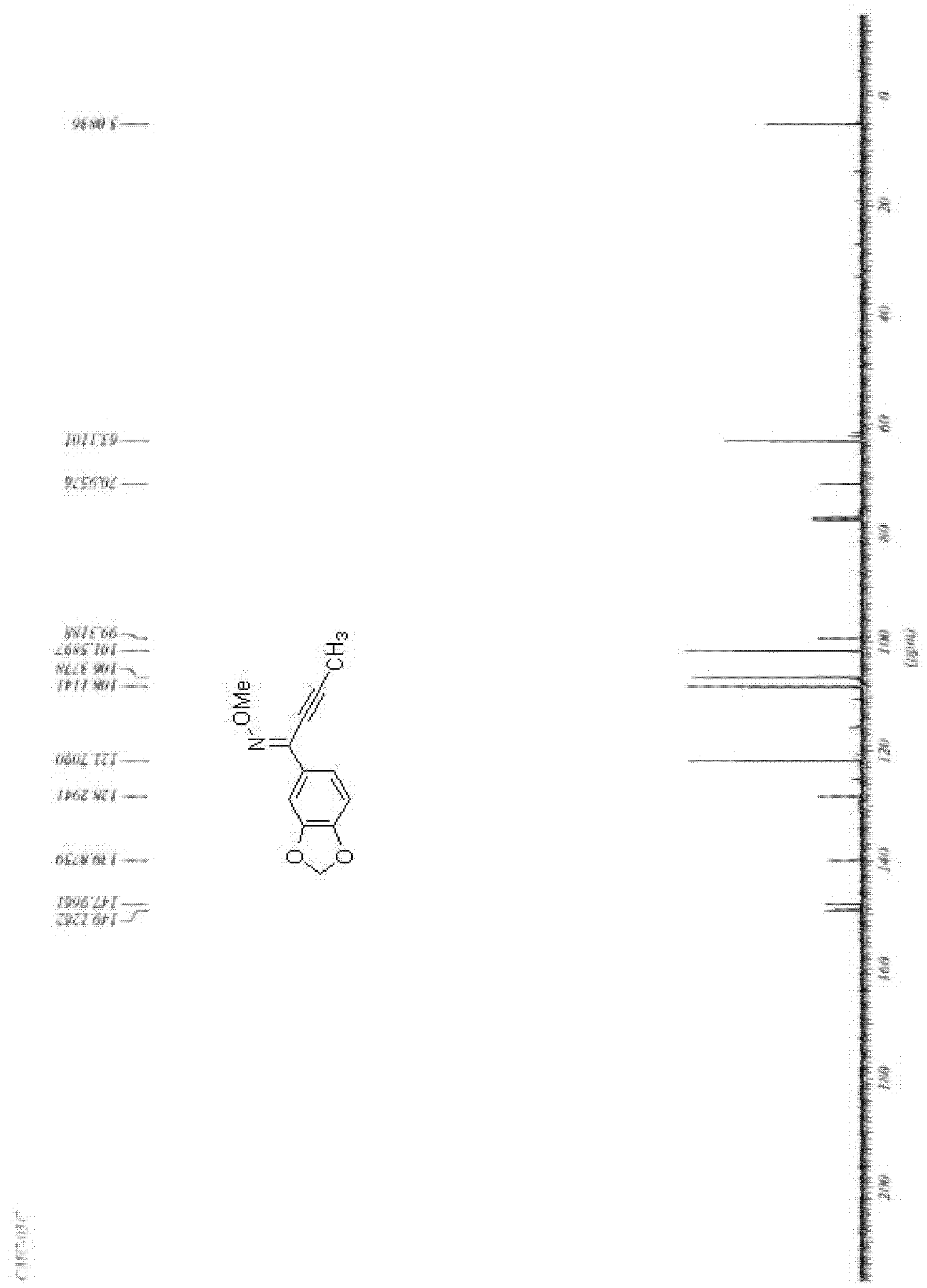

2.1352
6.0637
6.8546
6.8749
7.5371
7.5413
7.7868
7.7911
7.8072
7.8115
O
CH3
O
O
3.0145
2.0000
0.9990
0.9819
0.9642
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

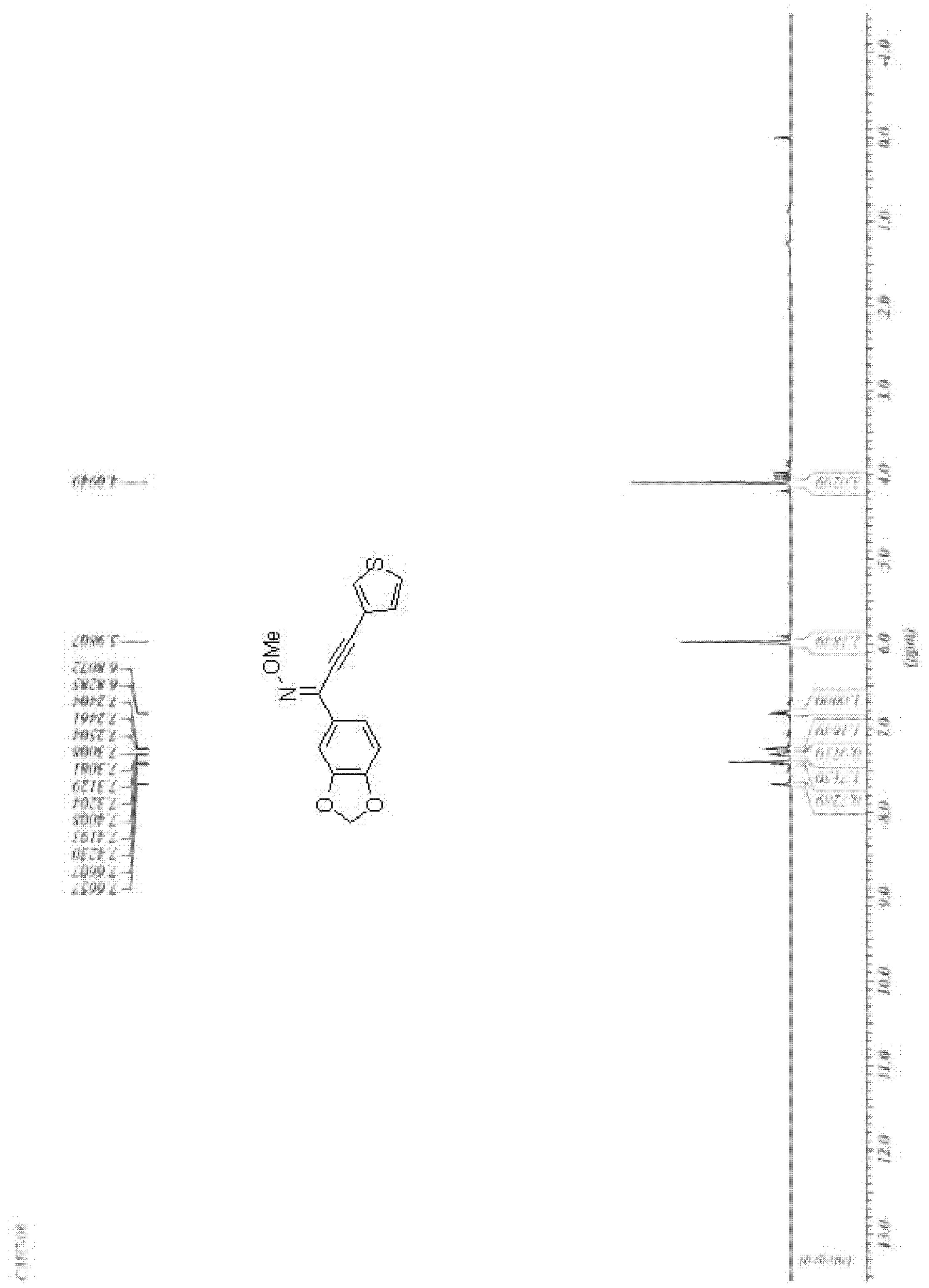

4.4079
78.9719
91.8598
102.2209
108.0402
108.4762
127.3255
132.1174
148.2334
152.8358
176.5187
CH3
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

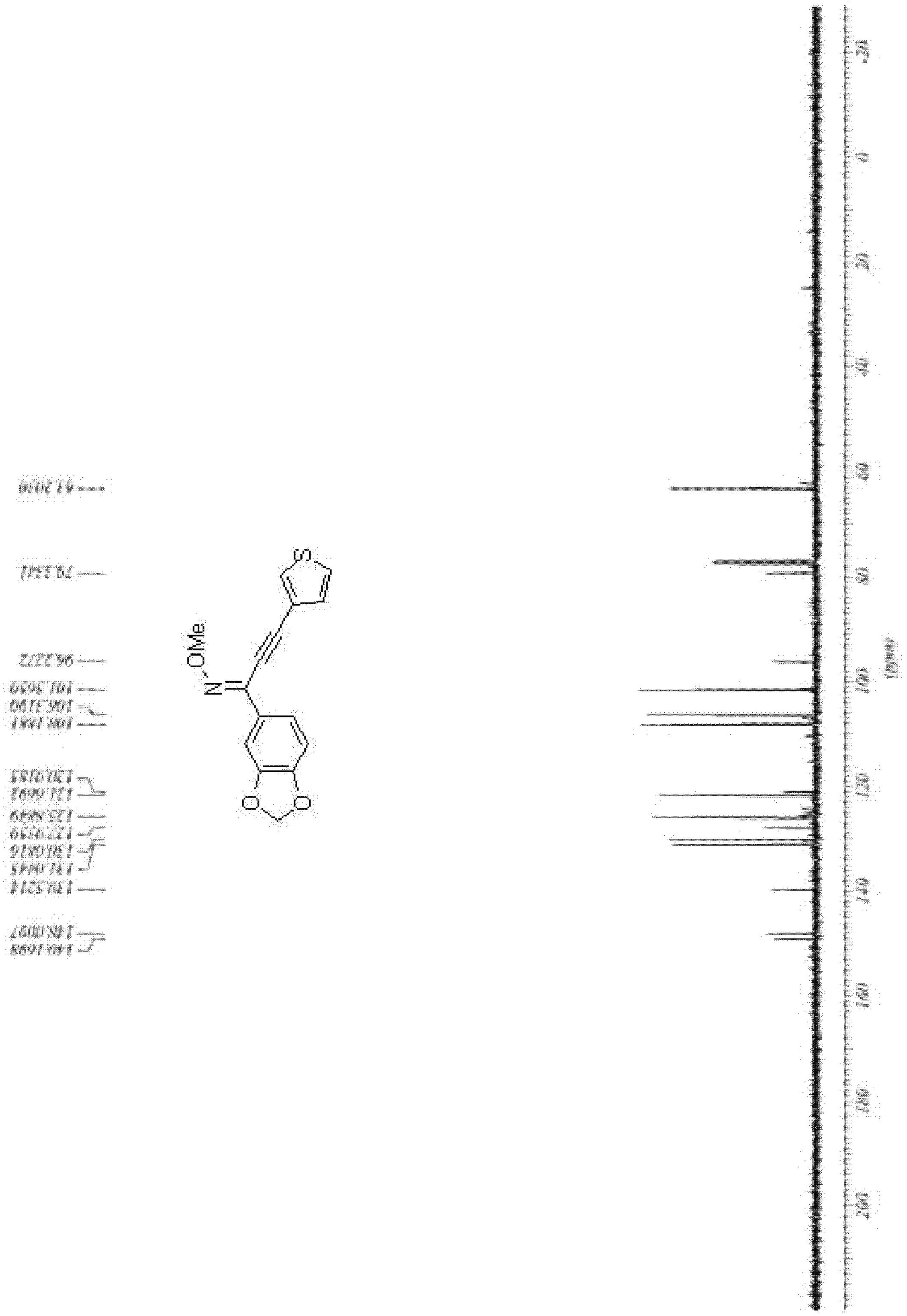

CHY-15-02
7.8718
7.8661
7.8445
7.8388
7.8197
7.8177
7.8156
7.8099
7.8079
7.8059
7.5820
7.5763
7.3728
7.3631
7.3562
7.3464
7.3028
7.3008
7.2988
7.2862
7.2841
7.2821
6.9048
6.8773
6.0668
O
O
O
S
1.9710
0.8932
0.9642
1.1181
1.0000
2.1994
Integral
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

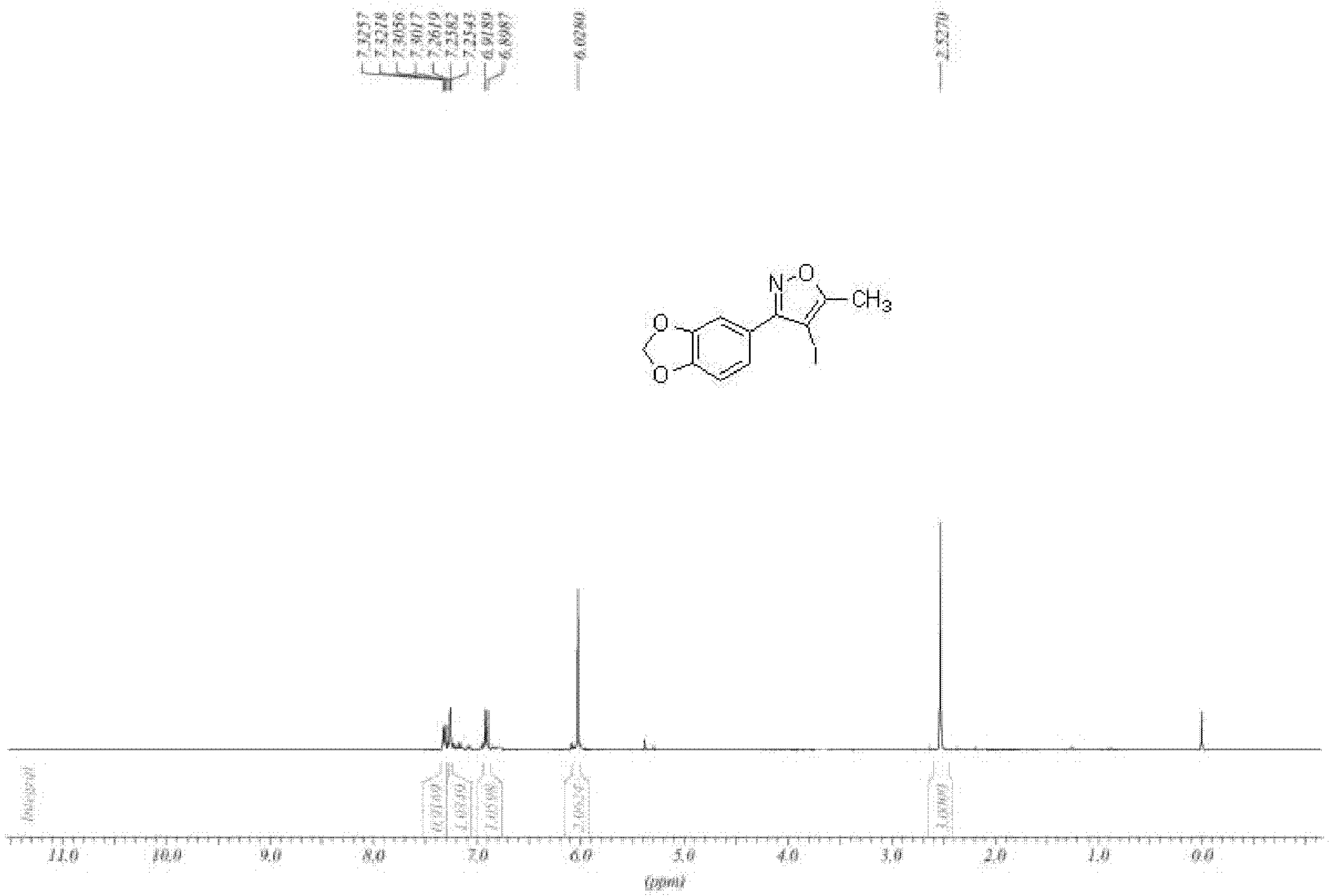

87.1169
87.8791
102.2642
106.1123
108.3438
119.5164
126.3617
127.2806
130.3222
132.1065
133.7753
148.3187
152.9610
176.1844
0
20
40
60
80
100
120
140
160
180
200
(ppm)

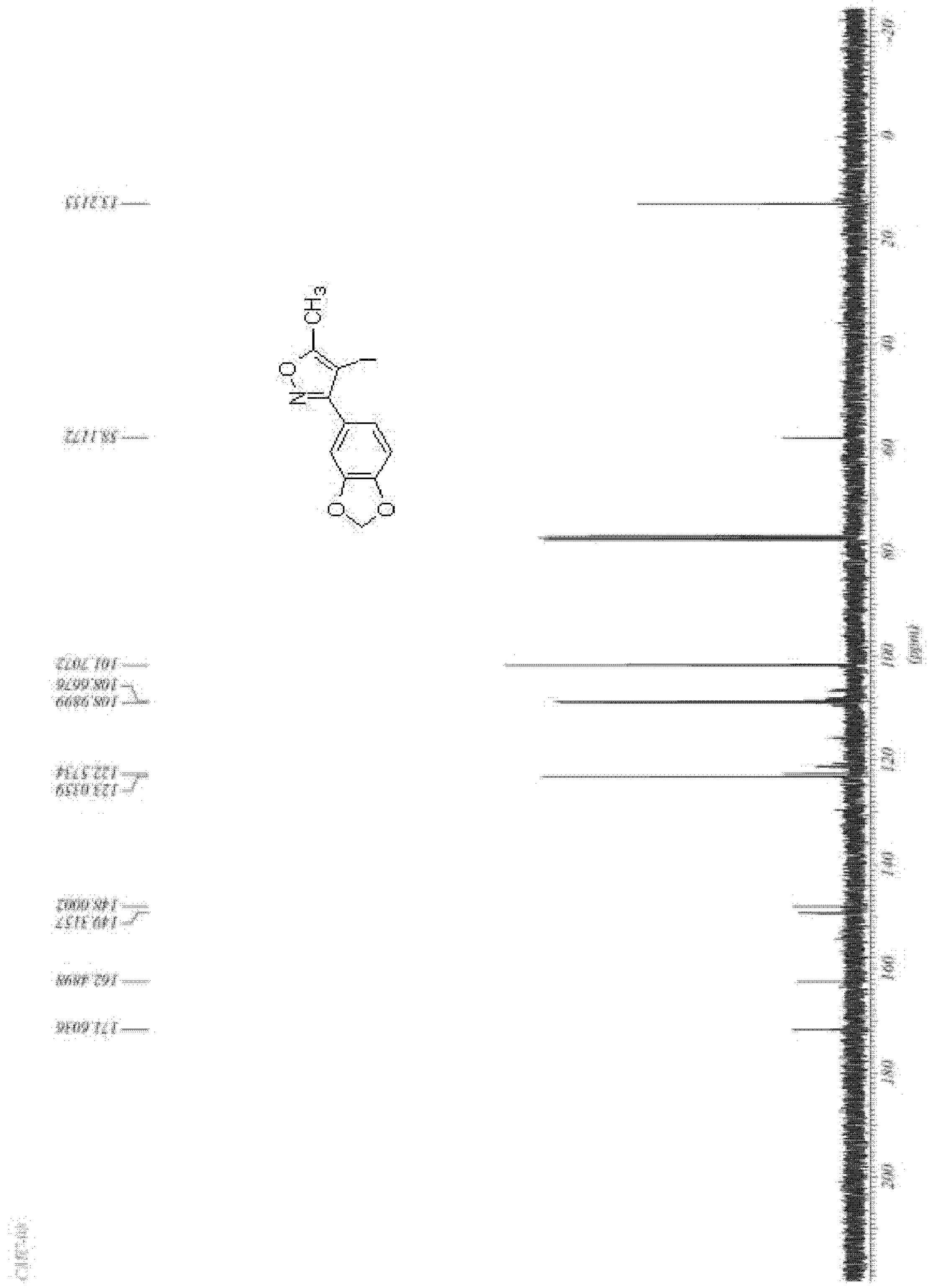

2.1732
4.0500
5.9646
6.7747
6.7960
7.3436
7.3571
OMe
N
CH3
O
O
2.5308
2.5189
2.0000
0.9269
1.5261
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
CDCl3

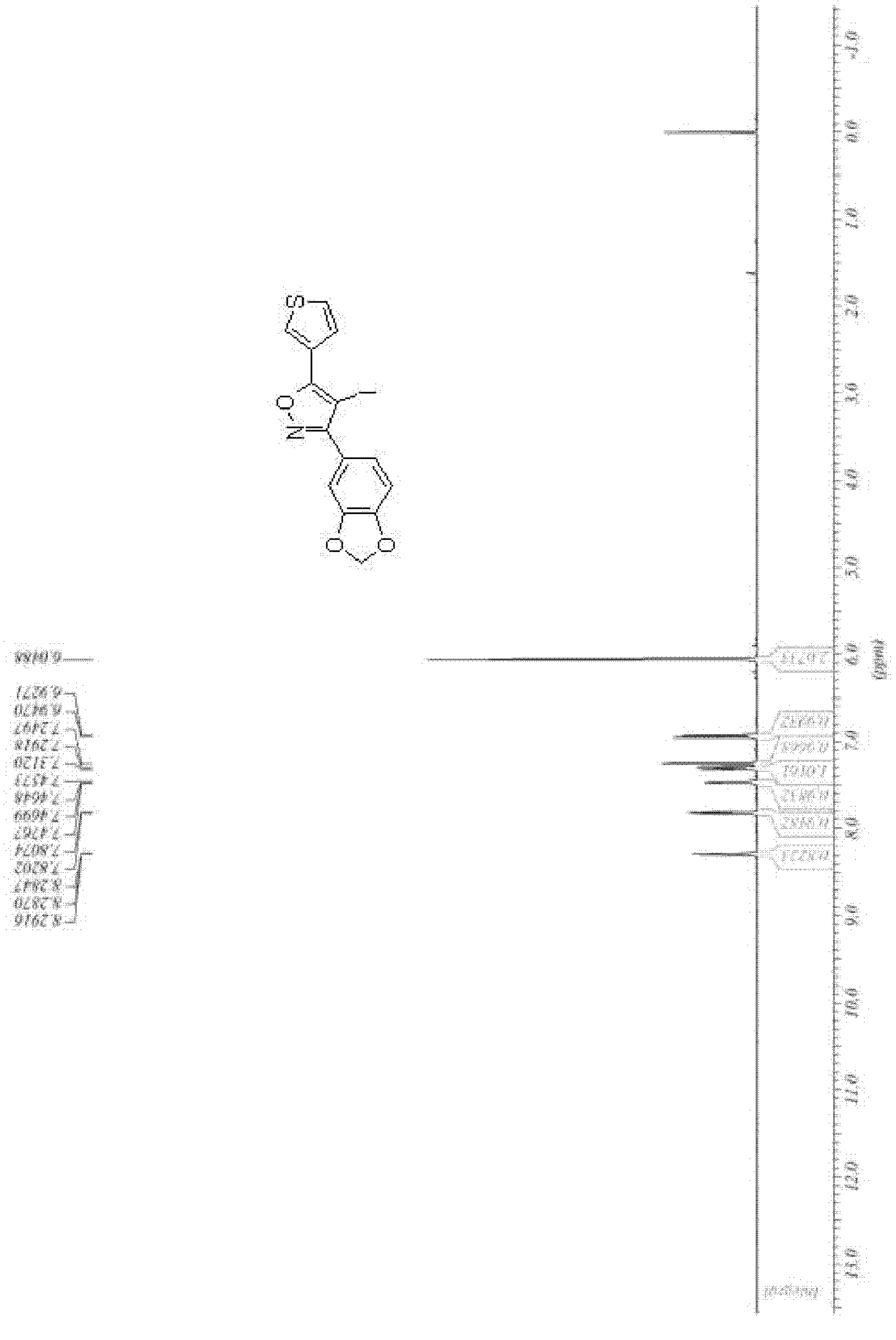

5.0836
63.1101
70.9576
99.3188
101.5897
106.3778
108.1141
121.7090
128.2941
139.8759
147.9661
149.1262
N
OMe
CH3
O
O
0
20
40
60
80
100
120
140
160
180
200
(ppm)

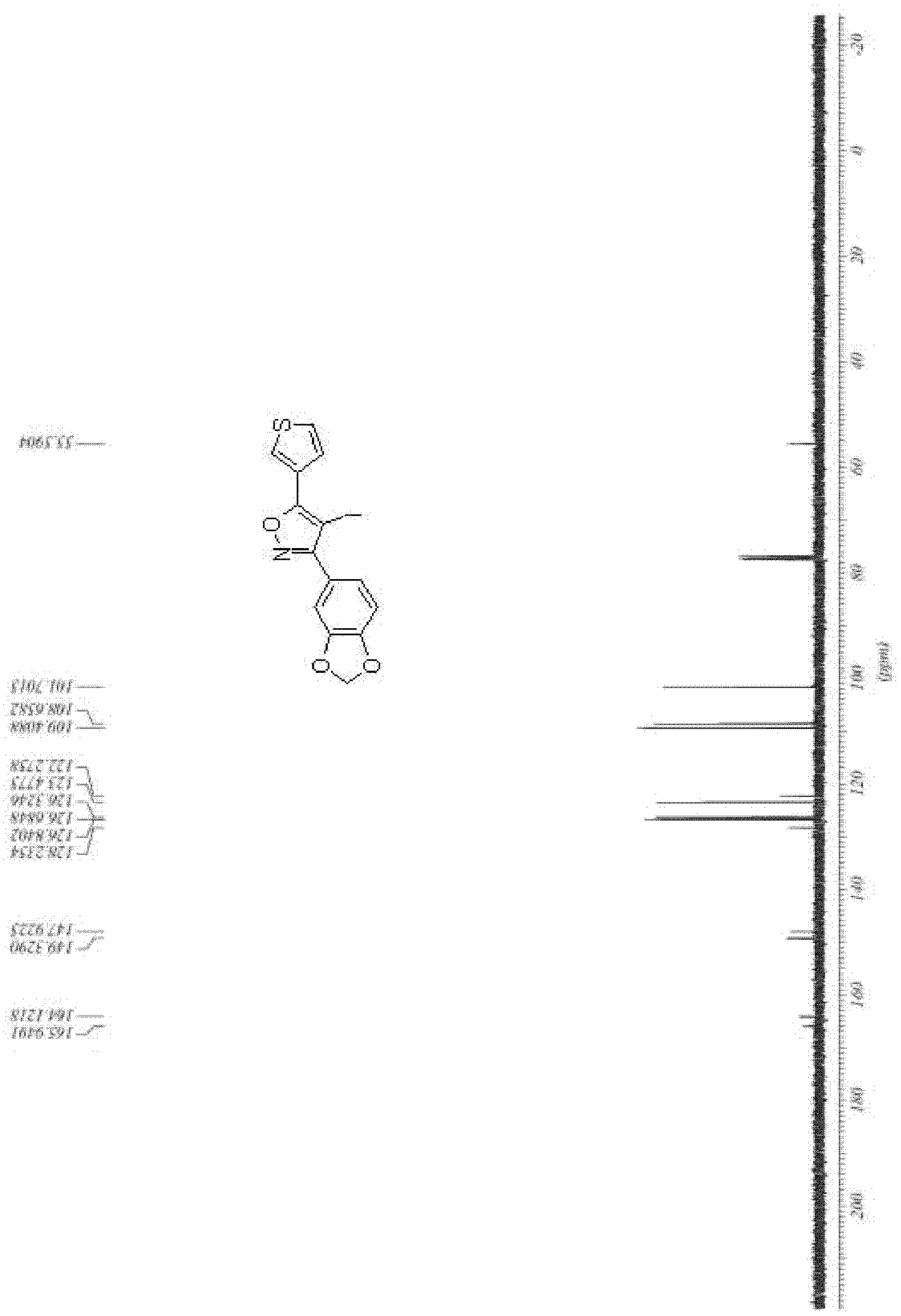

4.0949
5.9807
6.8072
6.8285
7.2404
7.2461
7.2504
7.3008
7.3081
7.3129
7.3204
7.4008
7.4195
7.4230
7.6607
7.6657
N
OMe
S
O
O
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

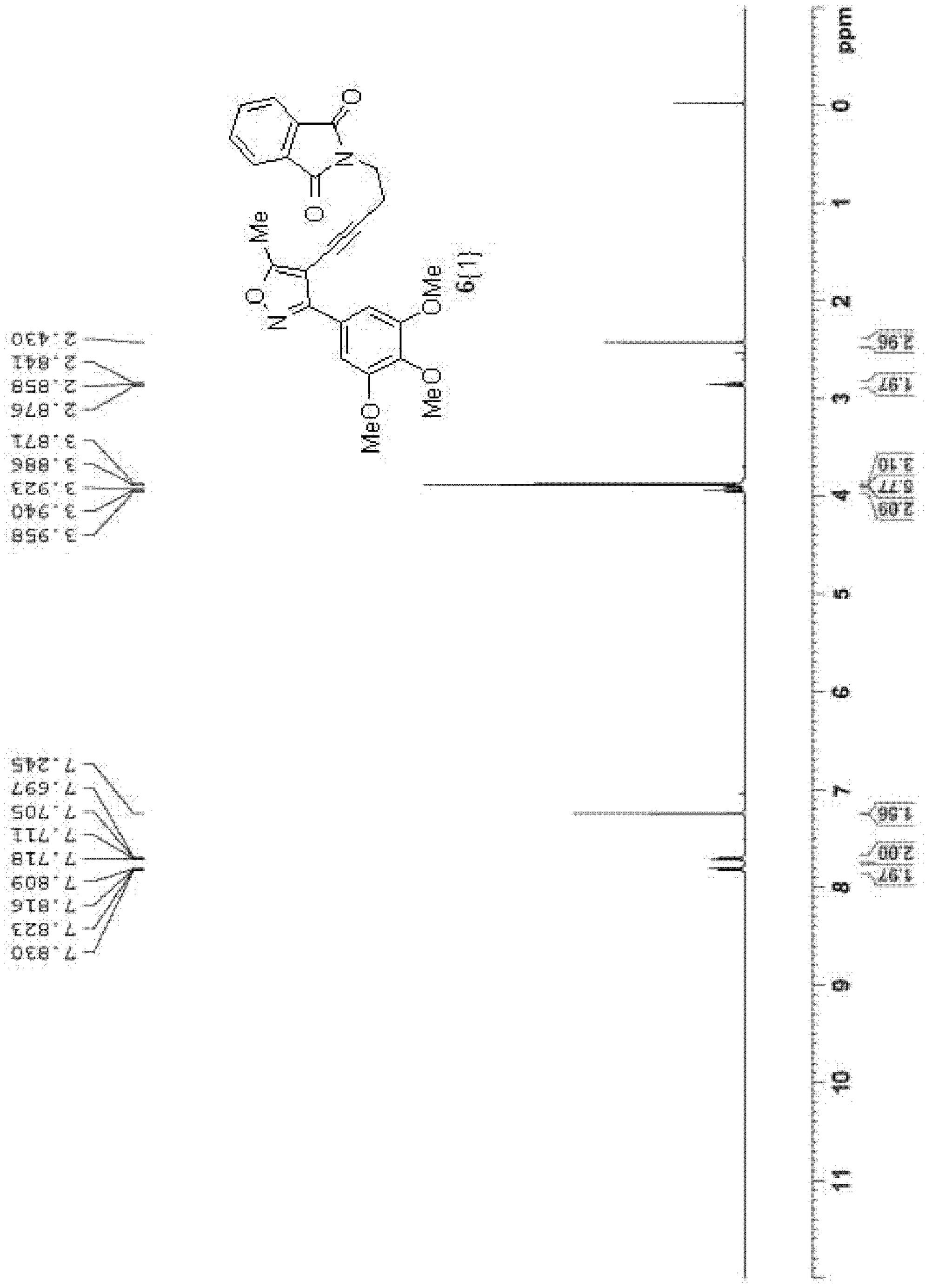

63.2030
79.3341
96.2272
101.5650
106.3190
108.1881
120.9185
121.6692
125.8849
127.9359
130.0816
131.0445
139.5214
148.0097
149.1698
OMe
N
S
O
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


7.3257
7.3218
7.3056
7.3017
7.2619
7.2582
7.2543
6.9189
6.8987
6.0280
2.5270
N
O
CH3
O
O
I
Integral
0.9169
1.0249
1.0598
2.0624
3.0000
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

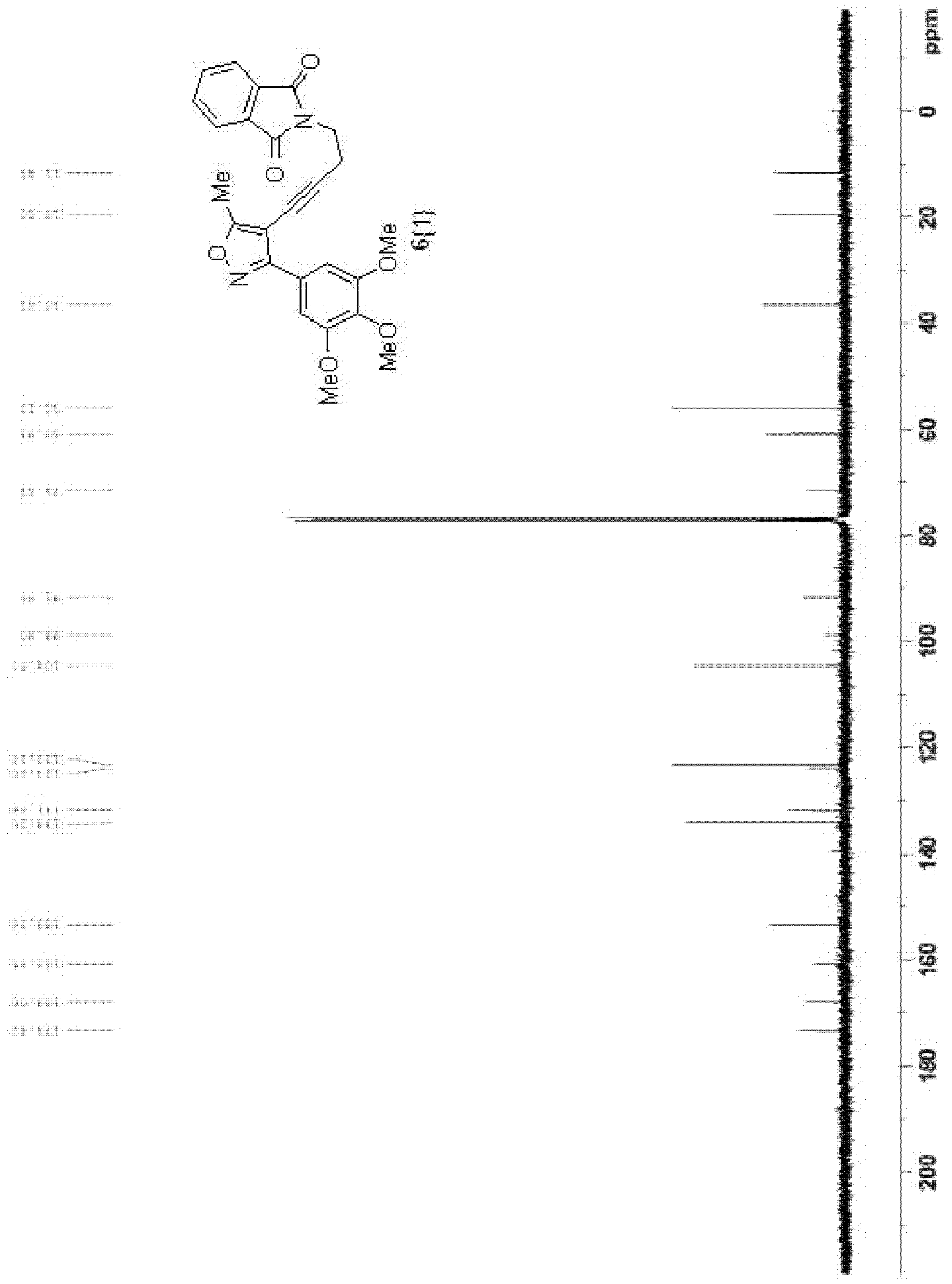

13.2153
58.1172
101.7072
108.6676
108.9899
122.5734
123.0359
148.0002
149.3157
162.4898
171.6036
CH3
N-O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


6.0188
6.9271
6.9470
7.2497
7.2918
7.3120
7.4573
7.4648
7.4699
7.4757
7.8074
7.8202
8.2847
8.2870
8.2916
2.0713
0.9932
0.9648
1.0161
0.9812
0.9882
0.8231
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral
S
O
N

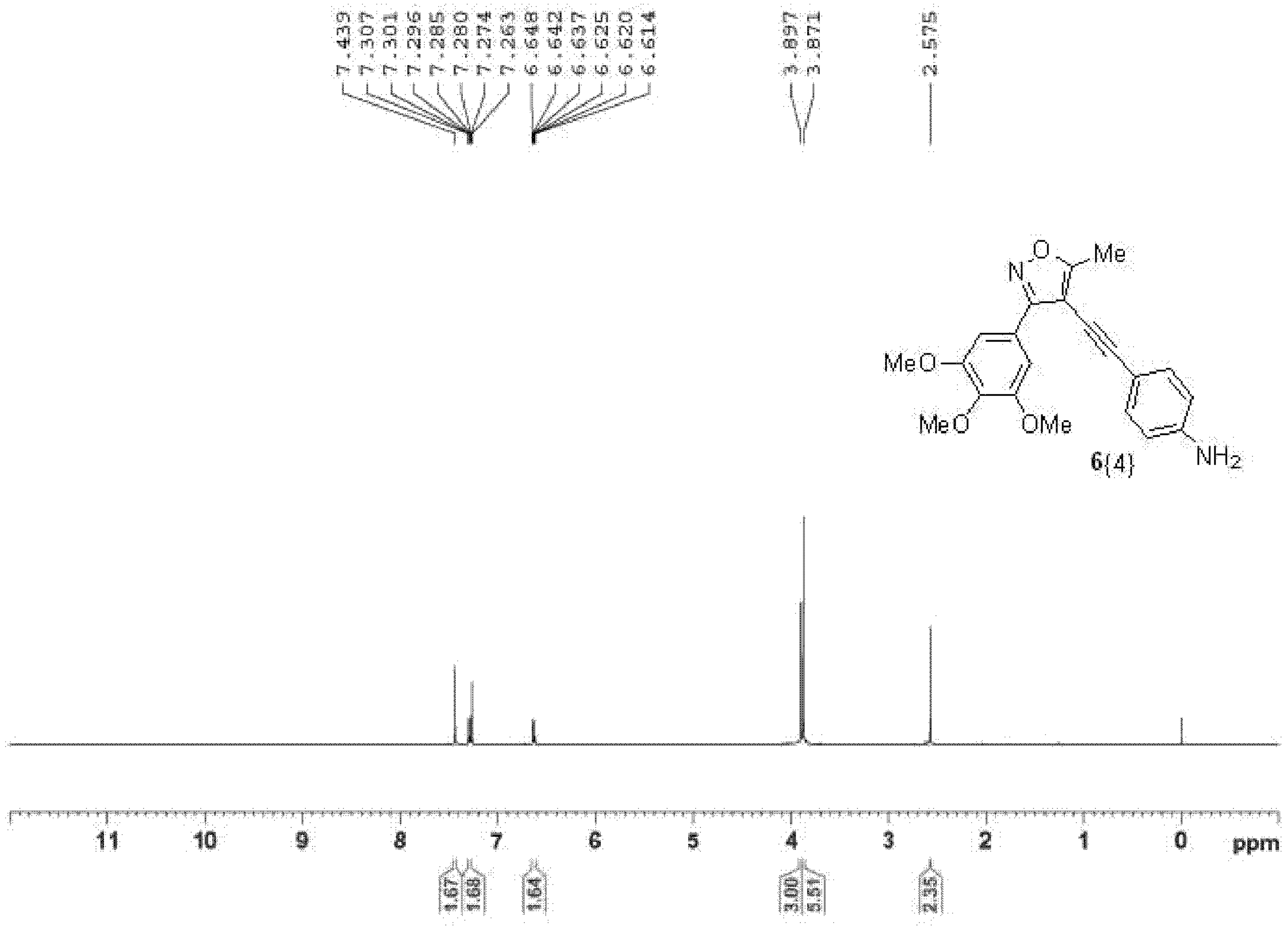

55.5904
101.7015
108.6582
109.4089
122.2758
123.4775
126.3246
126.6848
126.8402
128.2154
147.9225
149.3290
164.1218
165.9491
S
O
N
O
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


2.430
2.841
2.858
2.876
3.871
3.886
3.923
3.940
3.958
7.245
7.697
7.705
7.711
7.718
7.809
7.816
7.823
7.830
Me
O
N
MeO
MeO
OMe
O
N
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.96
1.97
3.10
5.77
2.09
1.56
2.00
1.97

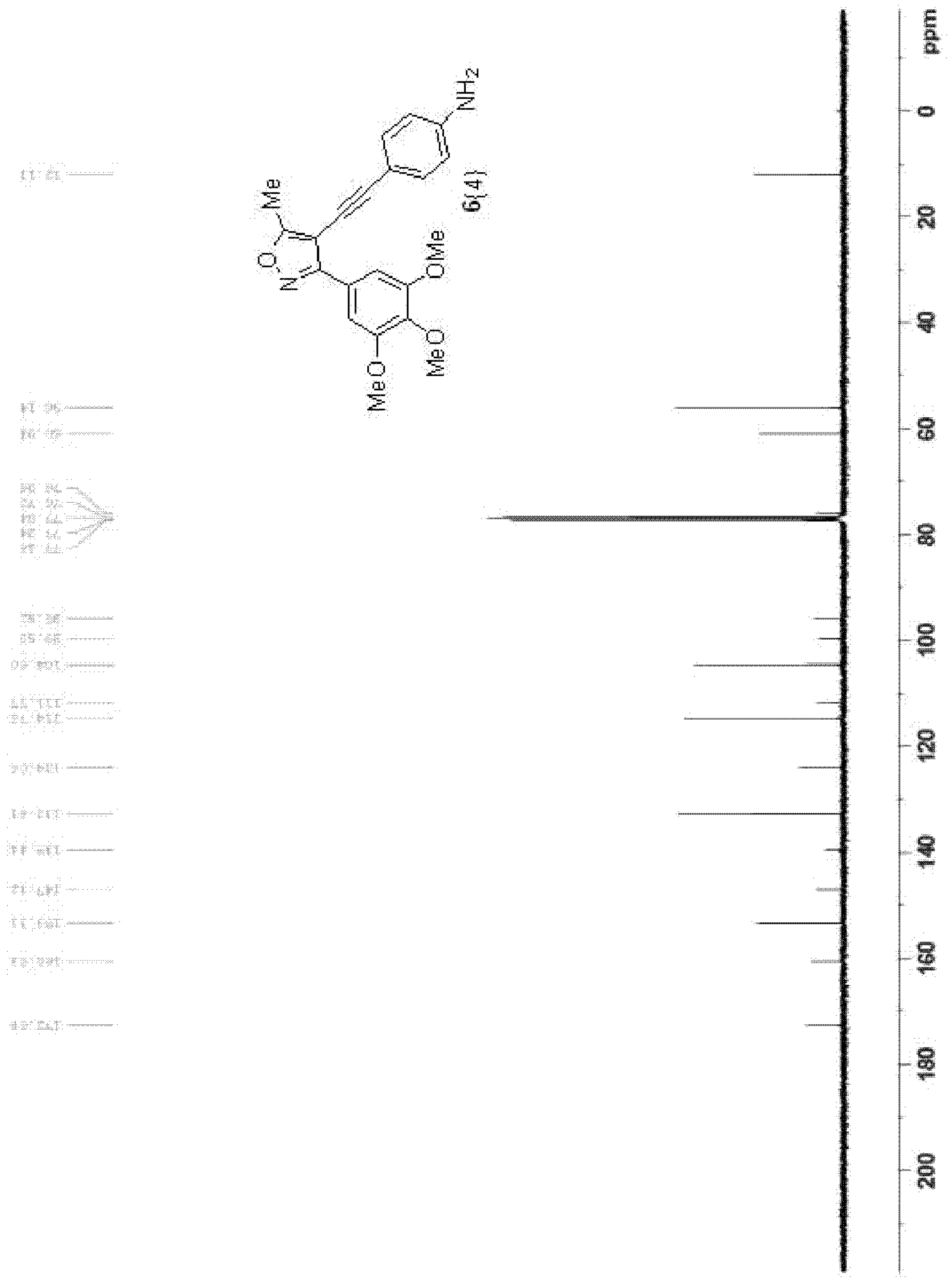
6(1)



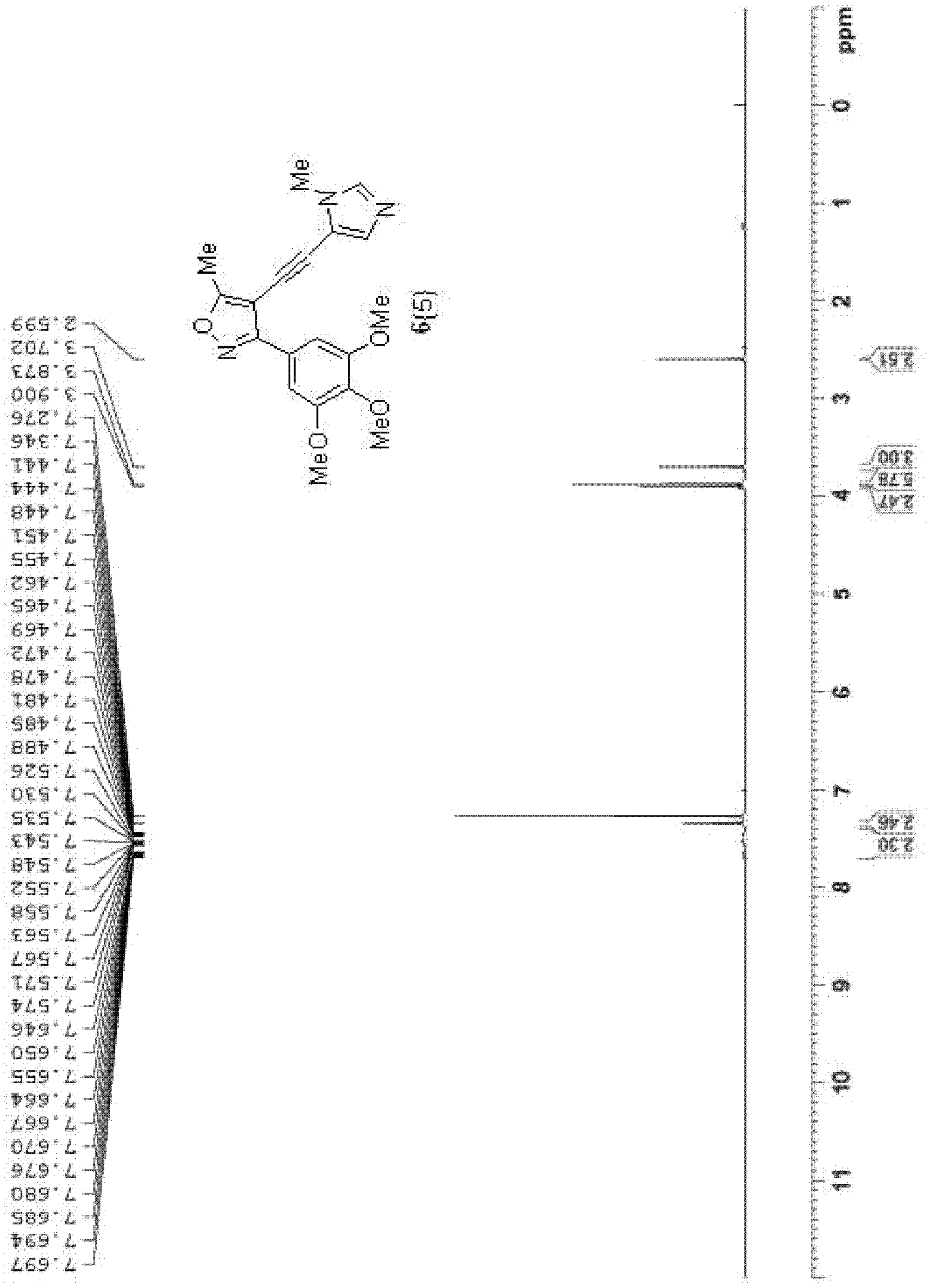
6{1}


7.439
7.307
7.301
7.296
7.285
7.280
7.274
7.263
6.648
6.642
6.637
6.625
6.620
6.614
3.897
3.871
2.575
MeO
MeO
OMe
N
O
Me
NH2
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.67
1.68
1.64
3.00
5.51
2.35

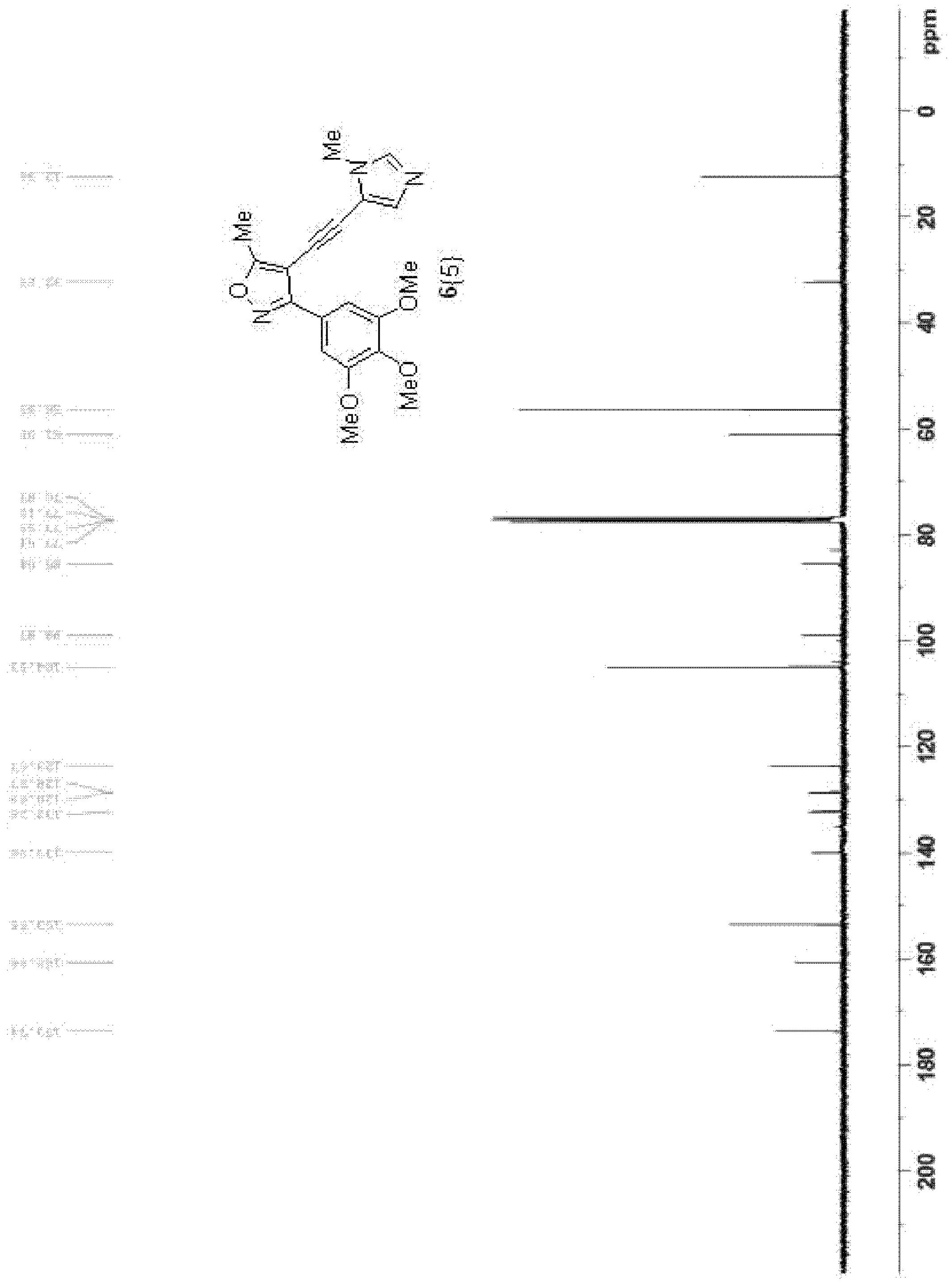
6{4}



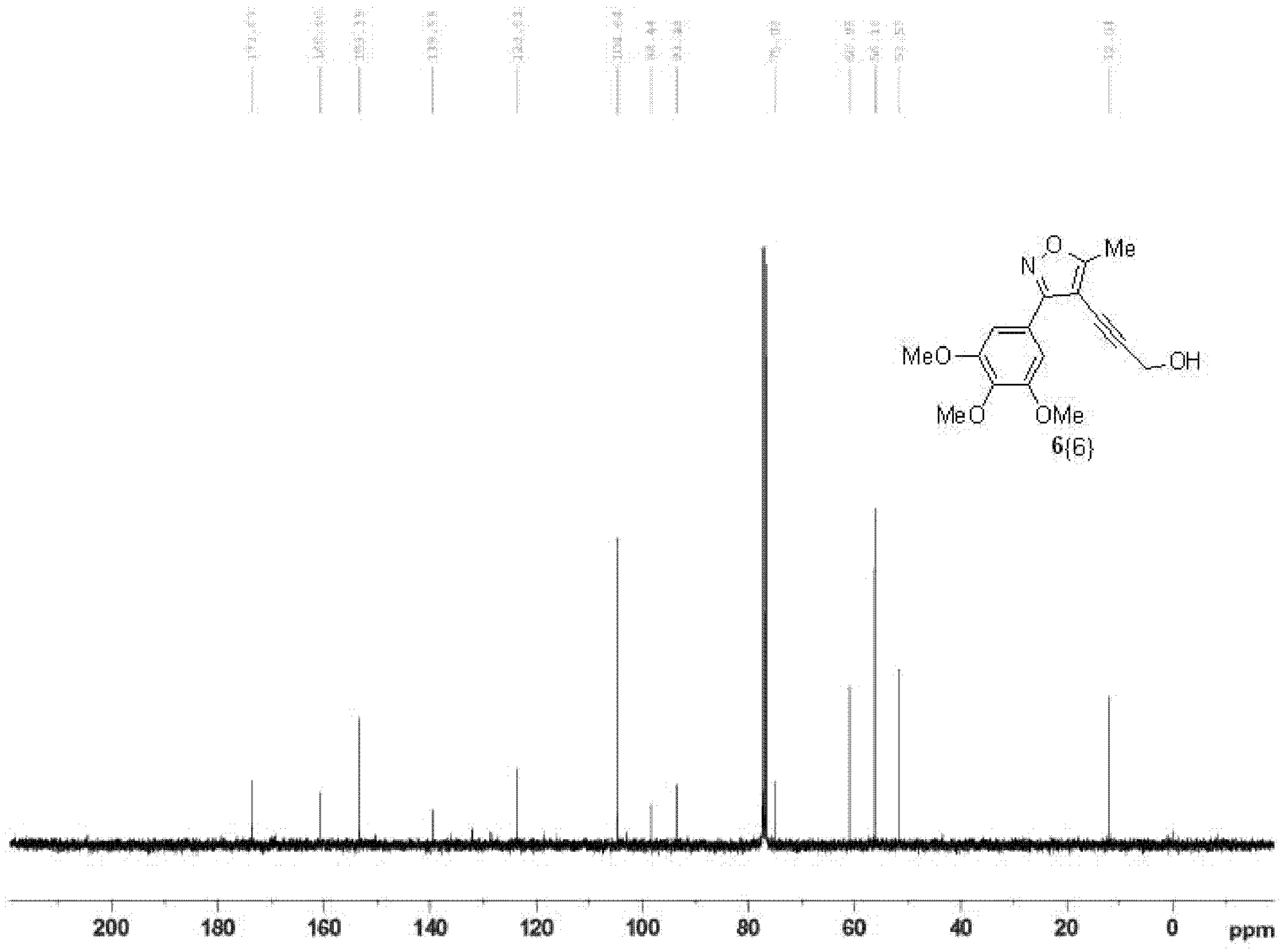
6(4)


2.599
3.702
3.873
3.900
7.276
7.346
7.441
7.444
7.448
7.451
7.455
7.462
7.465
7.469
7.472
7.478
7.481
7.485
7.488
7.526
7.530
7.535
7.543
7.548
7.552
7.558
7.563
7.567
7.571
7.574
7.646
7.650
7.655
7.664
7.667
7.670
7.676
7.680
7.685
7.694
7.697
Me
O
N
Me
N
N
MeO
MeO
OMe
2.51
3.00
5.78
2.47
2.46
2.30
ppm
0
1
2
3
4
5
6
7
8
9
10
11

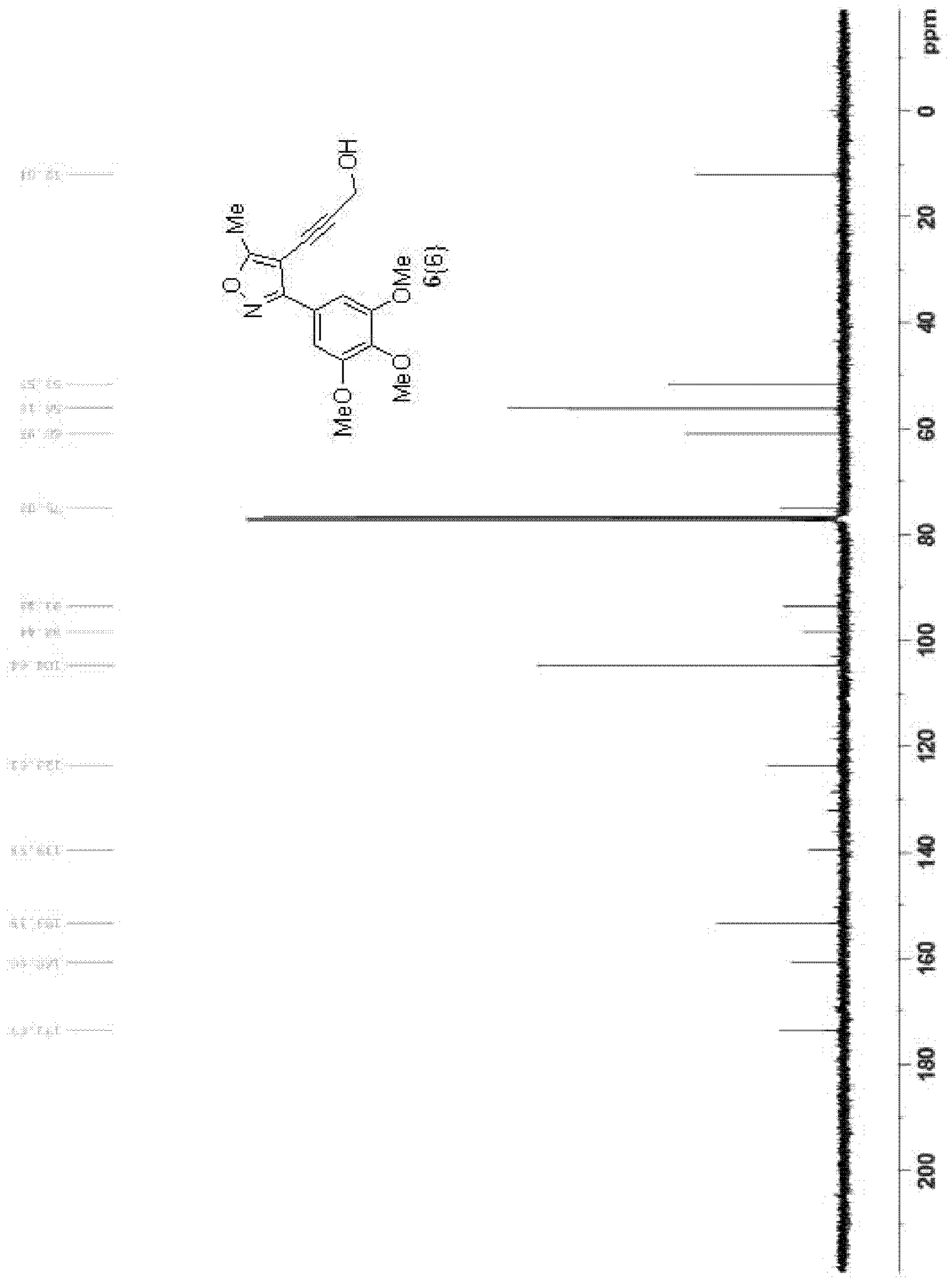
6(5)



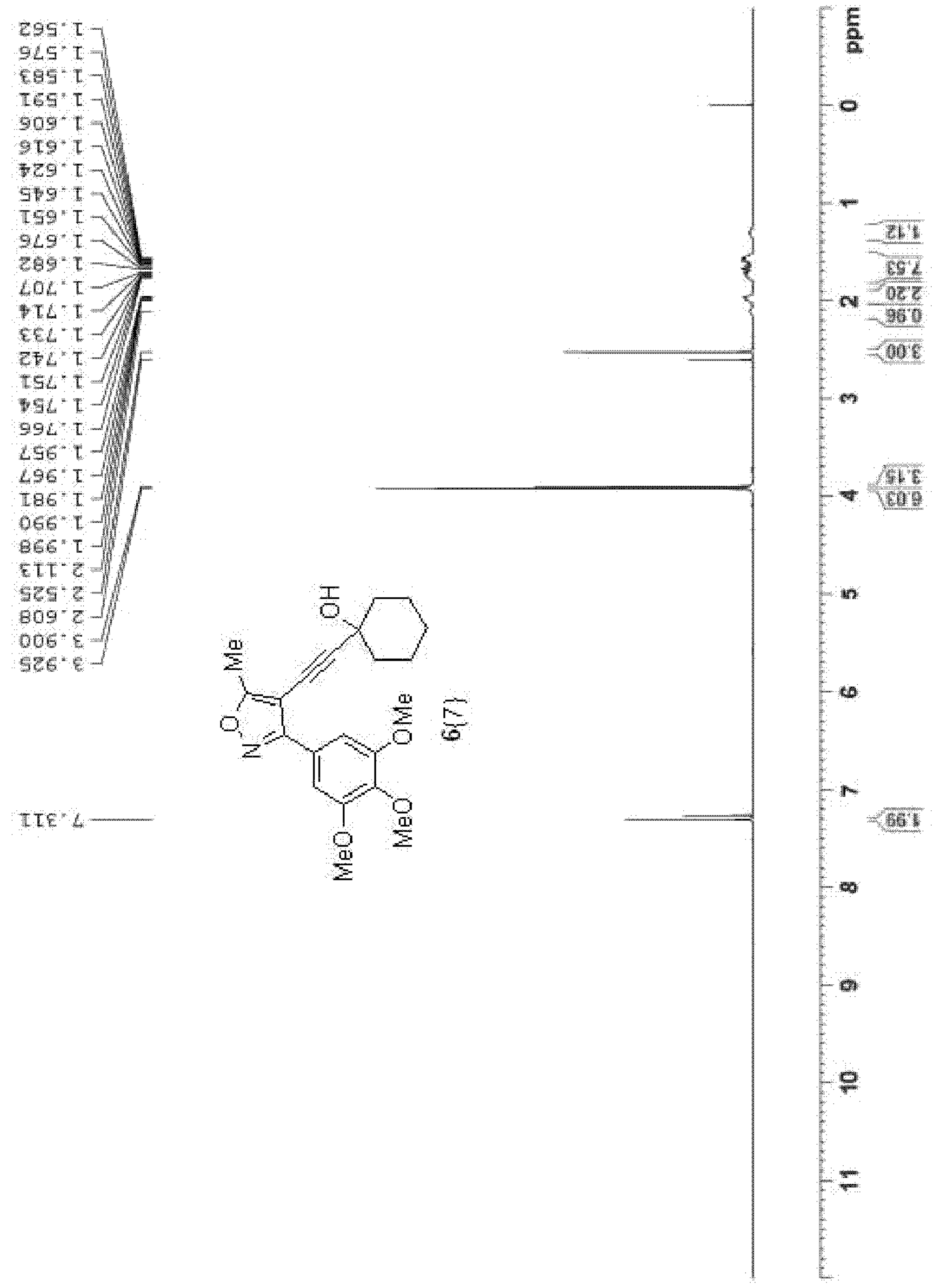
6(5)



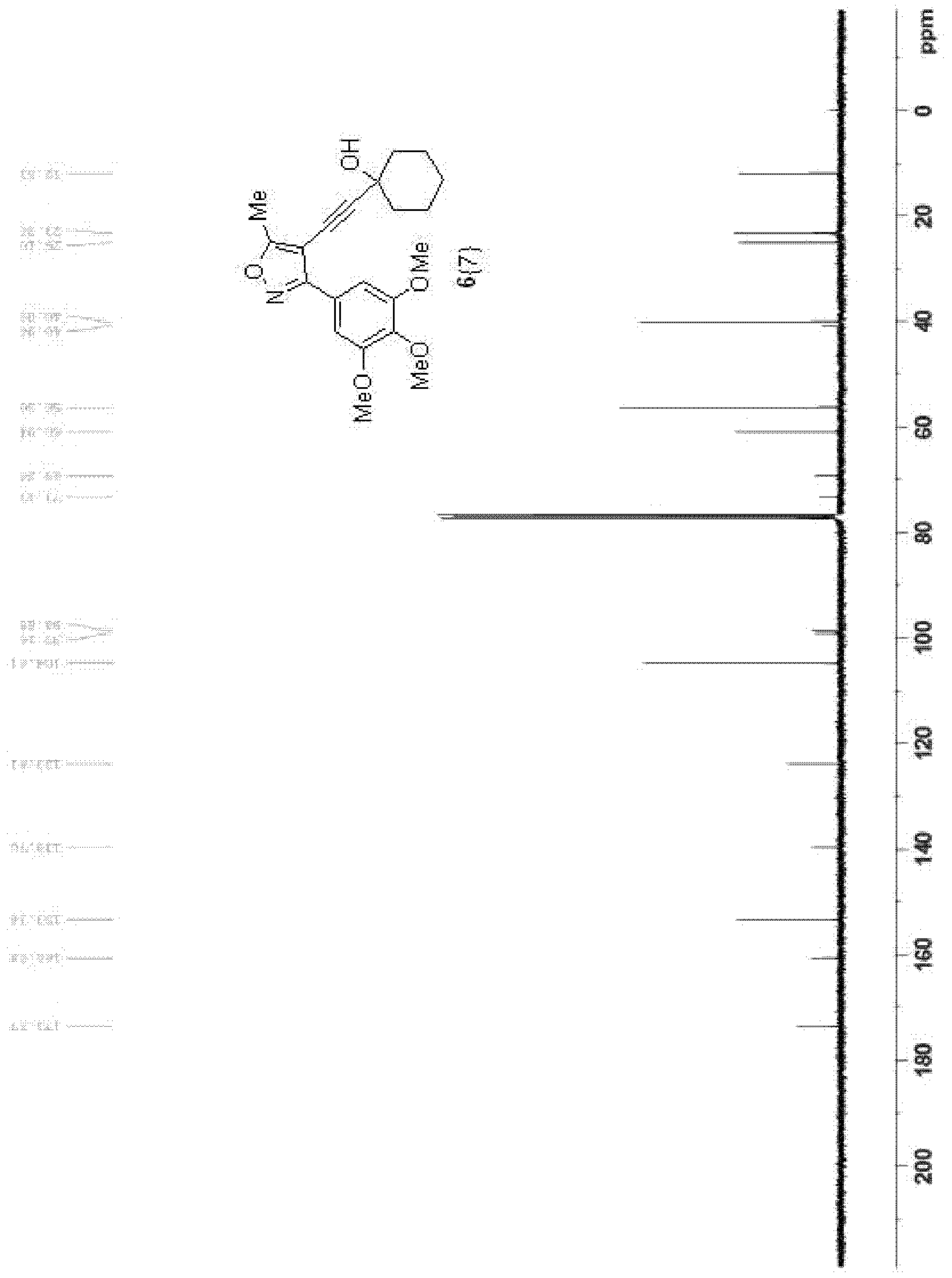
6{6}



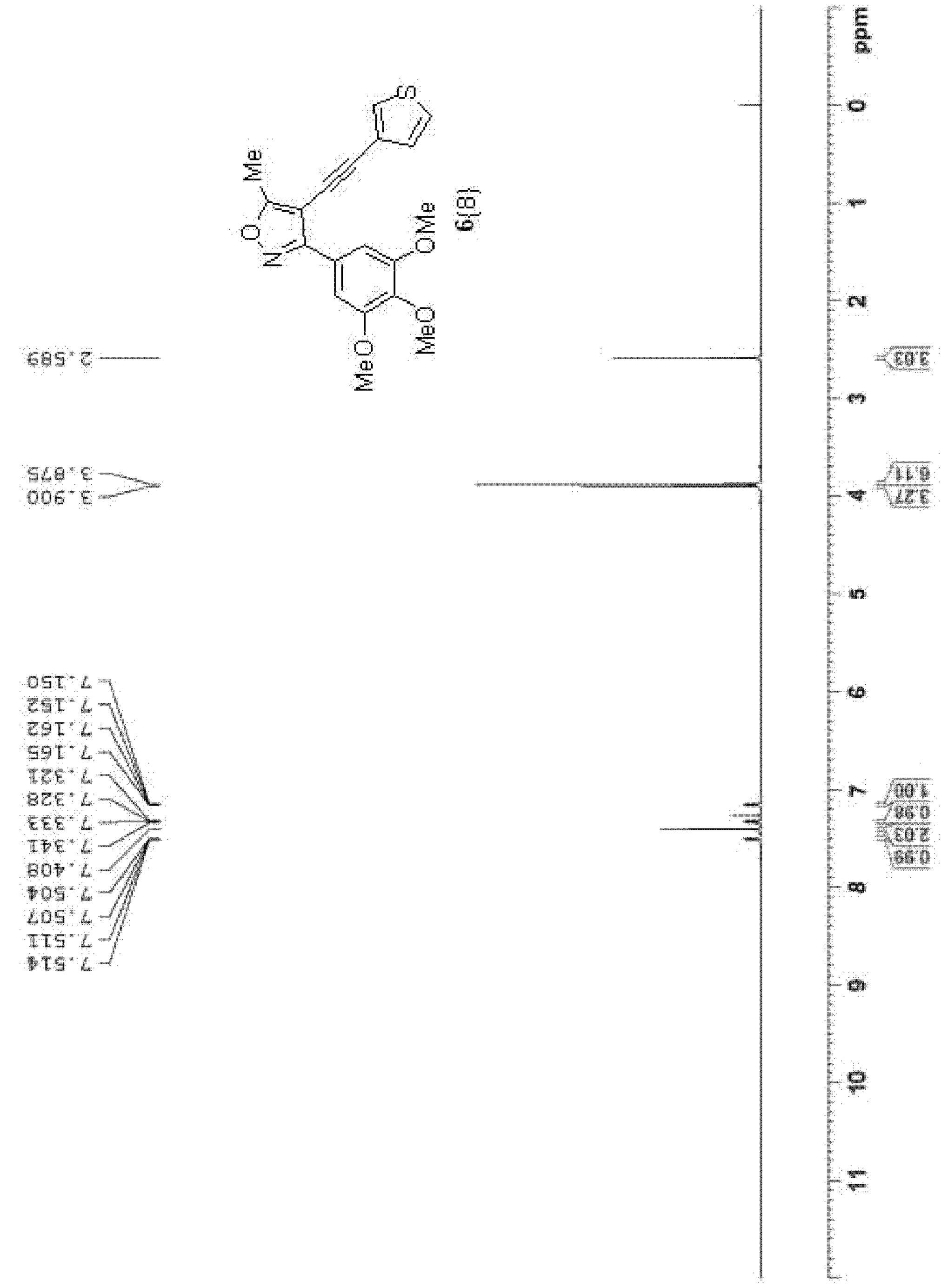
6(6)


1.562
1.576
1.583
1.591
1.606
1.616
1.624
1.645
1.651
1.676
1.682
1.707
1.714
1.733
1.742
1.751
1.754
1.766
1.957
1.967
1.981
1.990
1.998
2.113
2.525
2.608
3.900
3.925
7.311
Me
O
N
OH
MeO
MeO
OMe
1.12
7.53
2.20
0.96
3.00
3.15
6.03
1.99
ppm
0
1
2
3
4
5
6
7
8
9
10
11

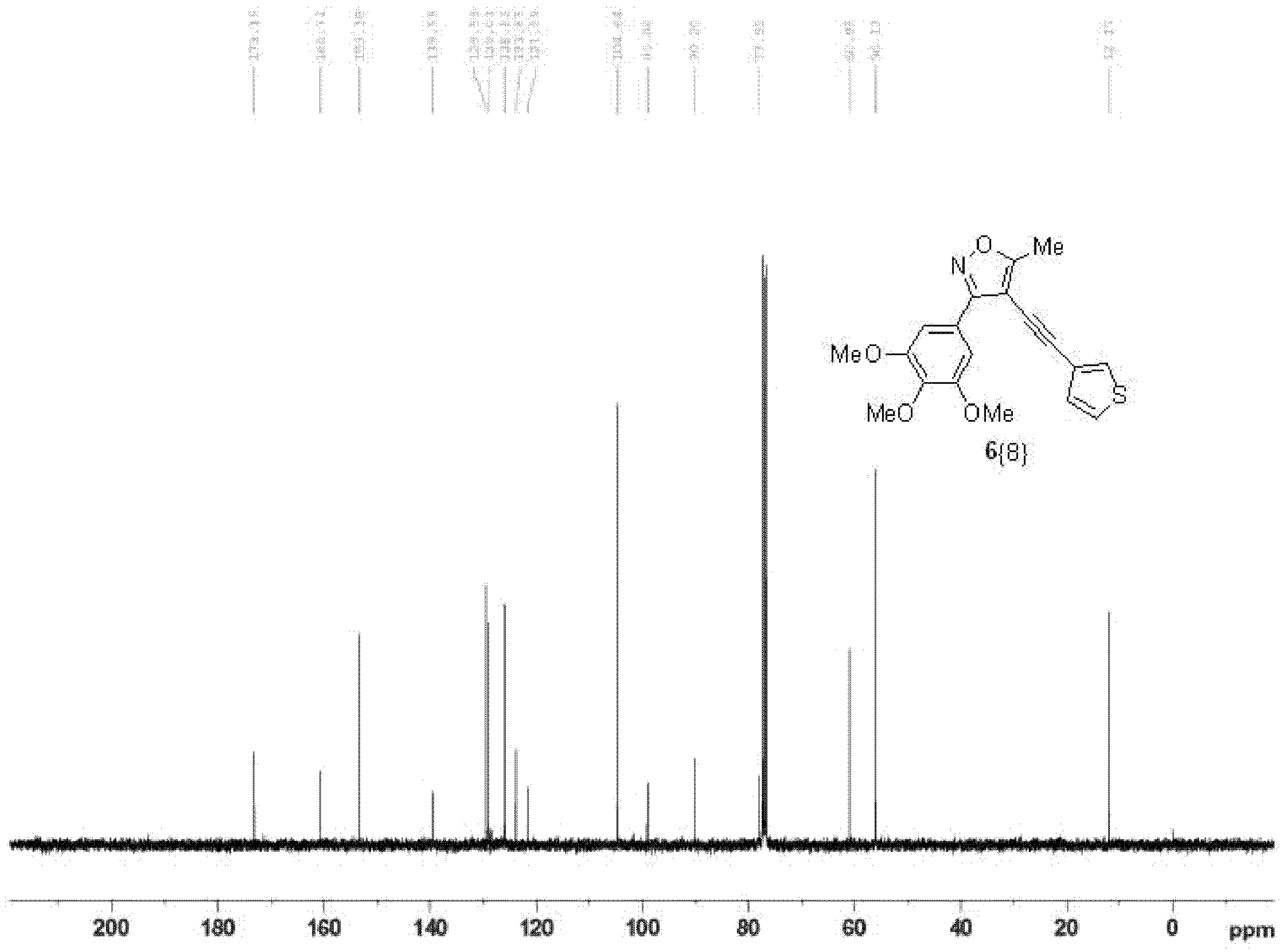
6{7}



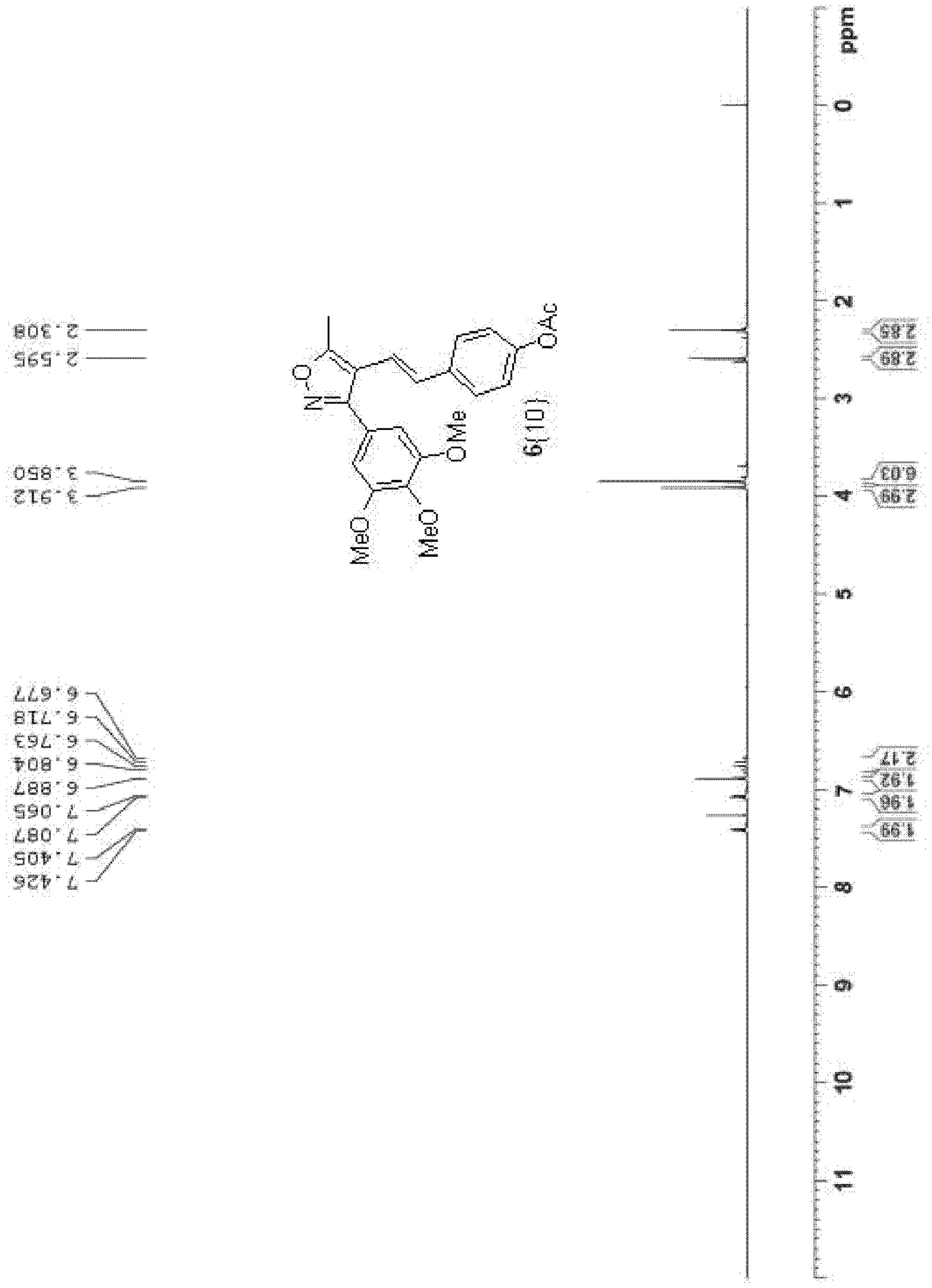
6(7)


2.589
3.875
3.900
7.150
7.152
7.162
7.165
7.321
7.328
7.333
7.341
7.408
7.504
7.507
7.511
7.514
Me
O
N
S
MeO
MeO
OMe
3.03
6.11
3.27
1.00
0.98
2.03
0.99
ppm
0
1
2
3
4
5
6
7
8
9
10
11

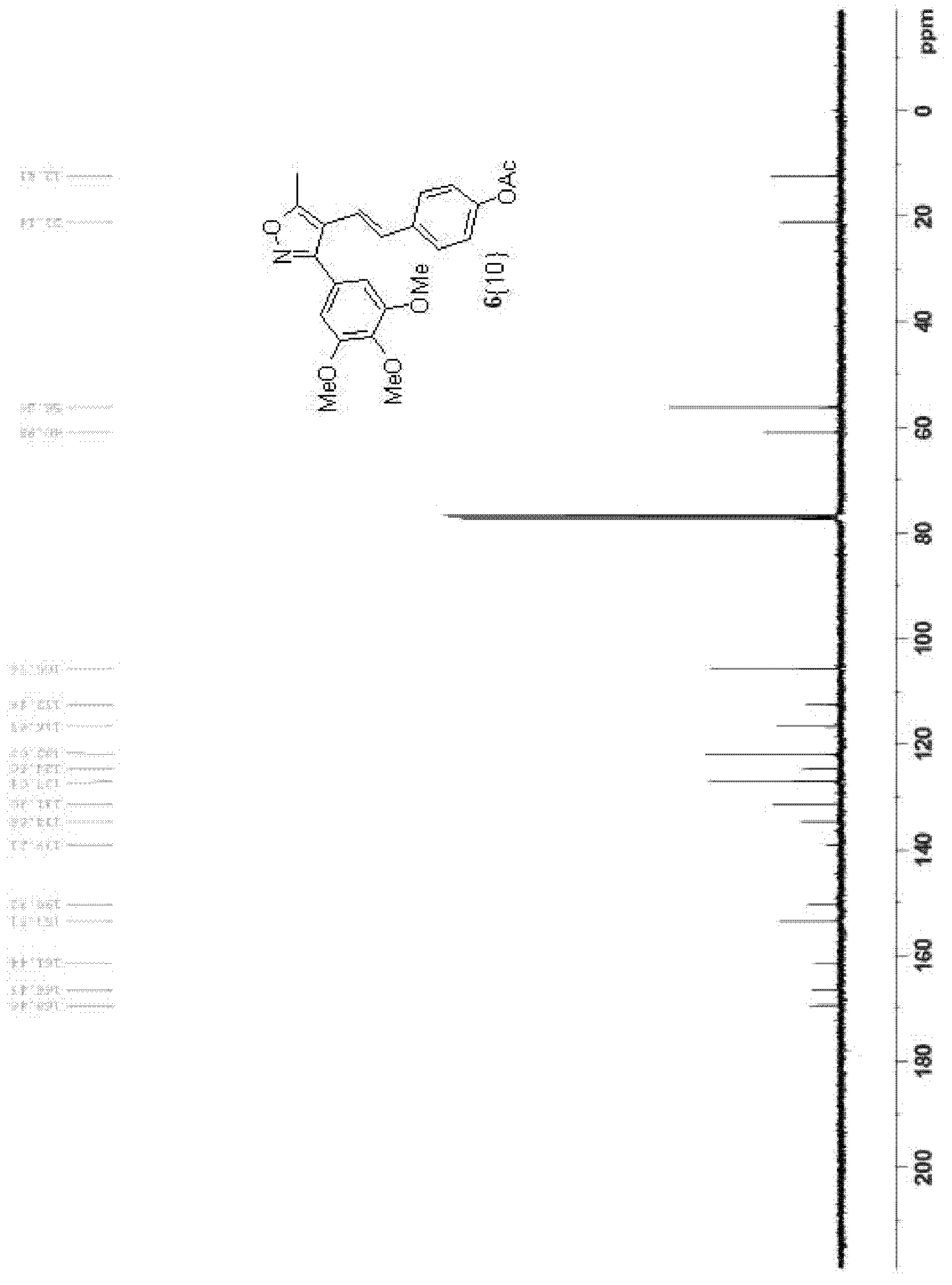
6{8}


173.15
160.71
153.38
139.53
129.59
129.03
126.15
123.85
121.95
104.64
99.08
90.26
77.55
60.95
56.13
12.17
N
O
Me
MeO
MeO
OMe
S
200
180
160
140
120
100
80
60
40
20
0
ppm

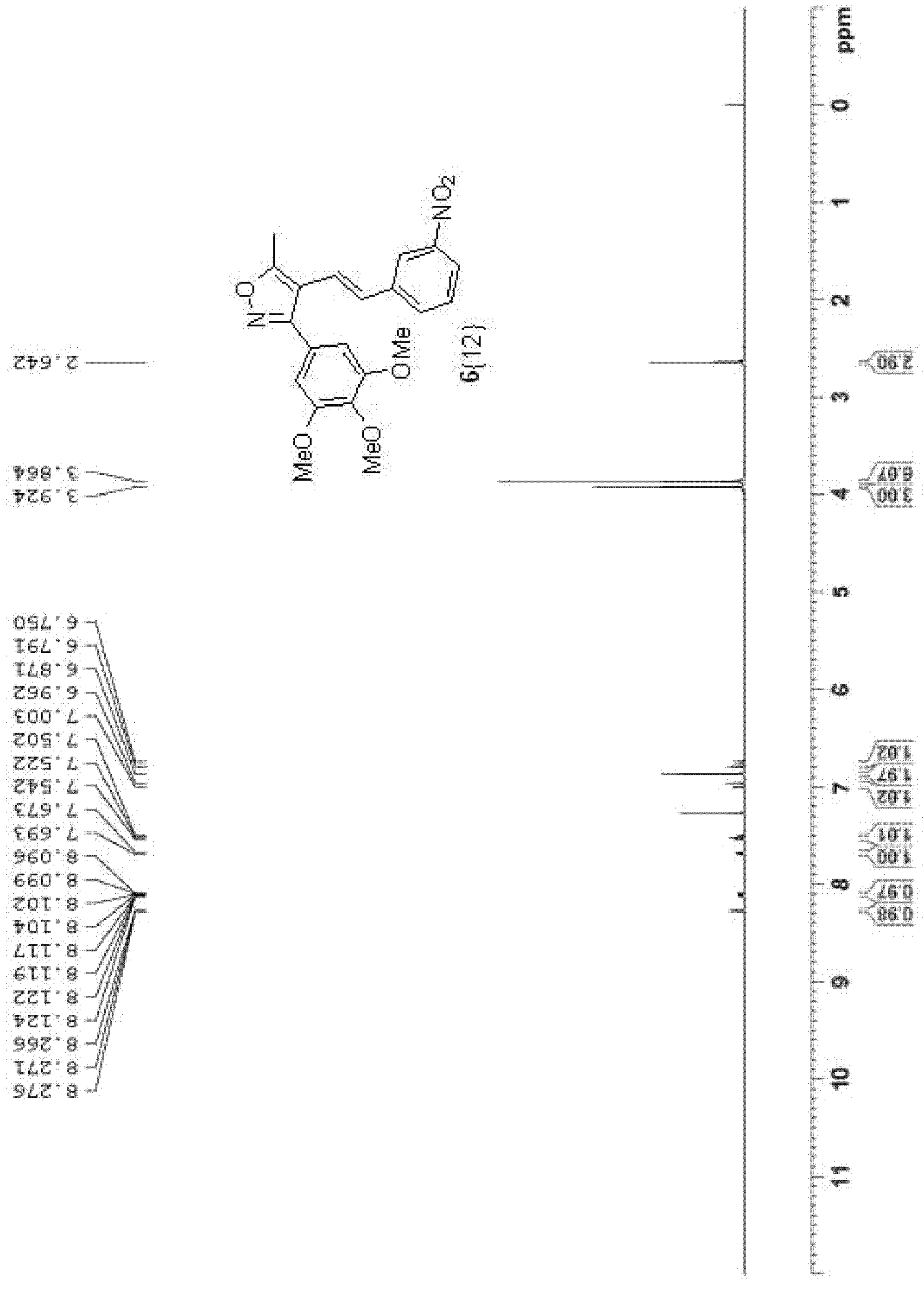
6{8}

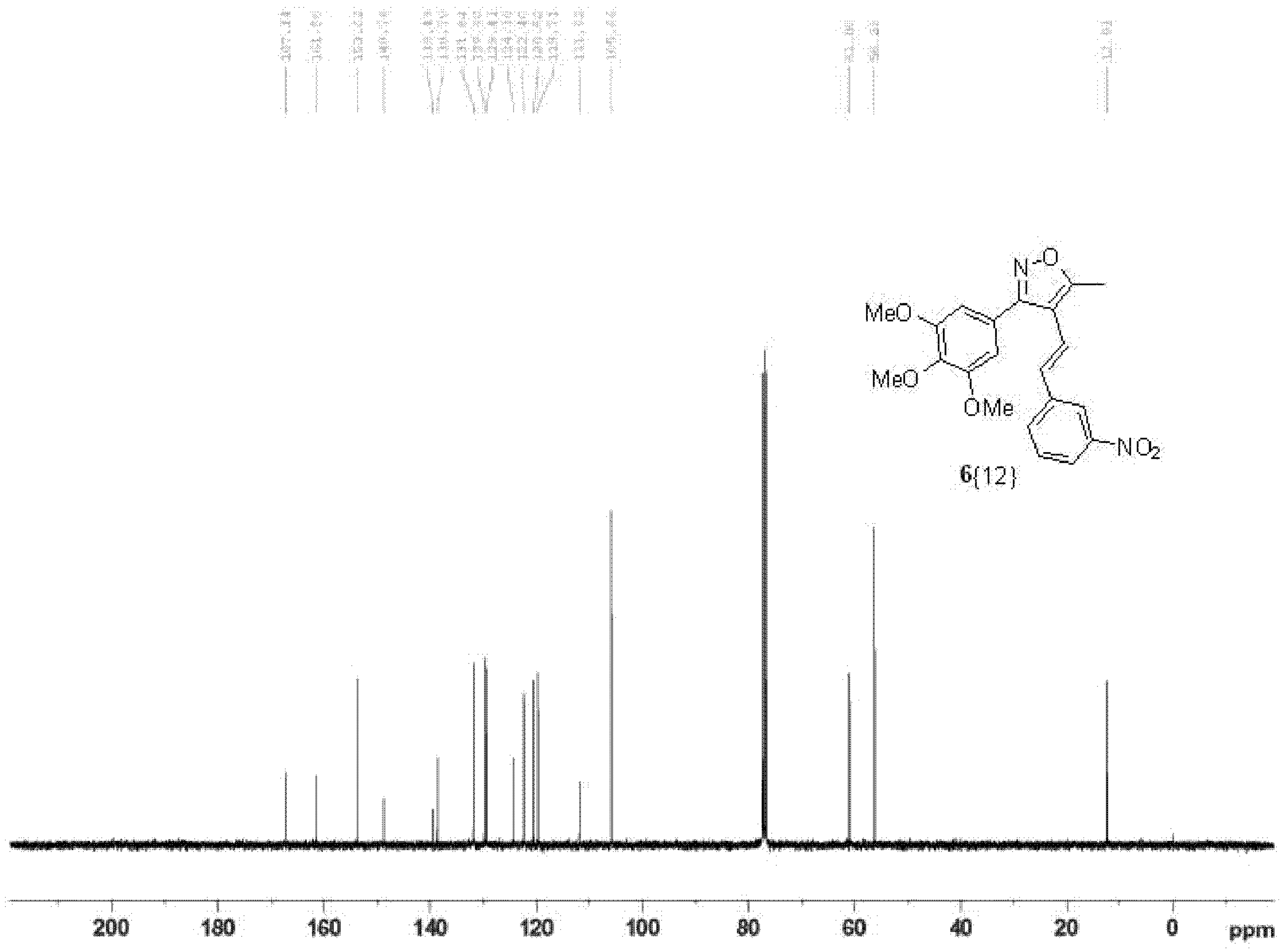

2.308
2.595
3.850
3.912
6.677
6.718
6.763
6.804
6.887
7.065
7.087
7.405
7.426
N
O
MeO
MeO
OMe
OAc
2.85
2.89
6.03
2.99
2.17
1.92
1.96
1.99
ppm
0
1
2
3
4
5
6
7
8
9
10
11

6(10)

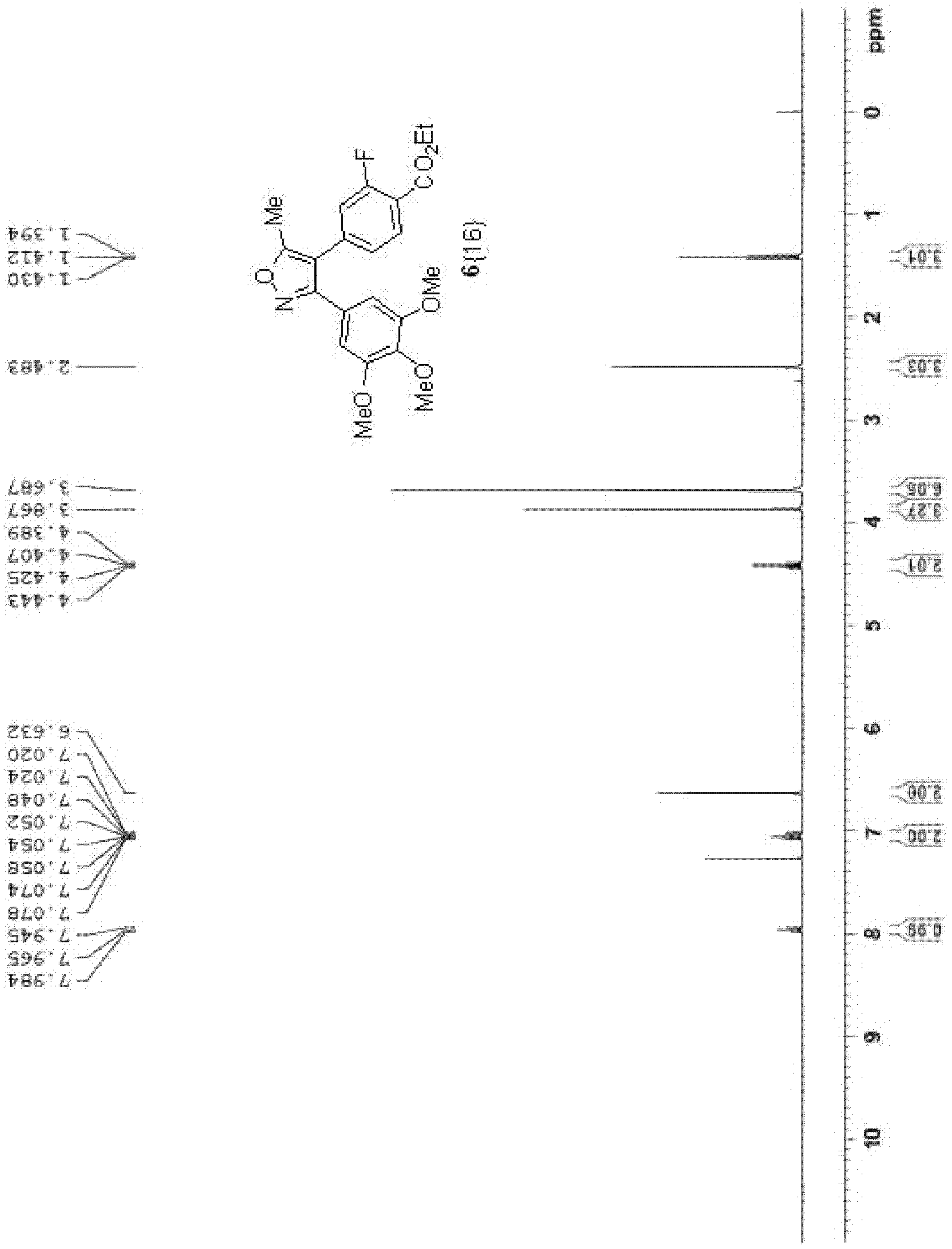


6{10}


2.642
3.864
3.924
6.750
6.791
6.871
6.962
7.003
7.502
7.522
7.542
7.673
7.693
8.096
8.099
8.102
8.104
8.117
8.119
8.122
8.124
8.266
8.271
8.276
MeO
MeO
OMe
N
O
NO$_2$
6(12)
2.90
6.07
3.00
1.02
1.97
1.02
1.01
1.00
0.97
0.98
ppm
0
1
2
3
4
5
6
7
8
9
10
11

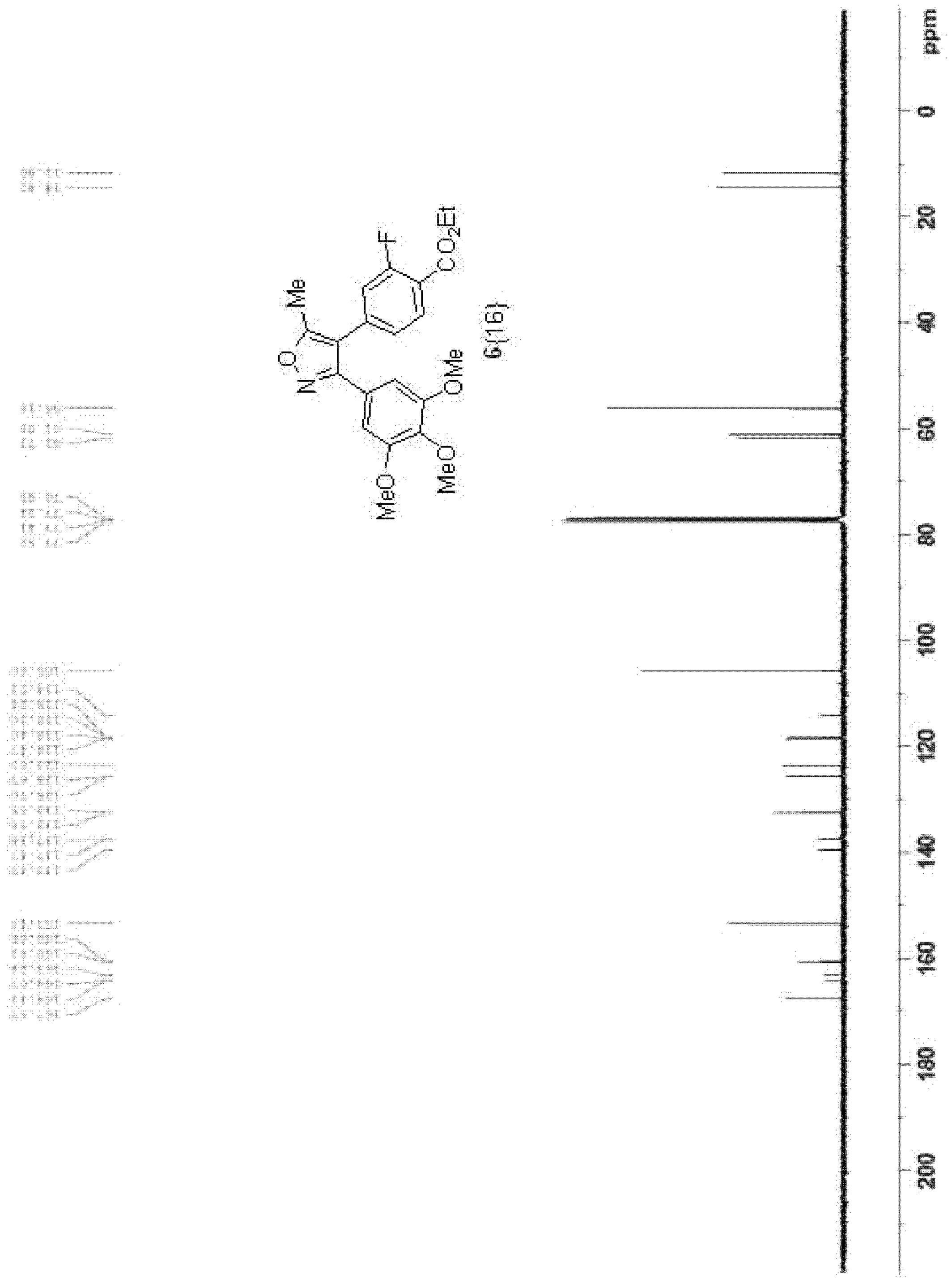


6{12}

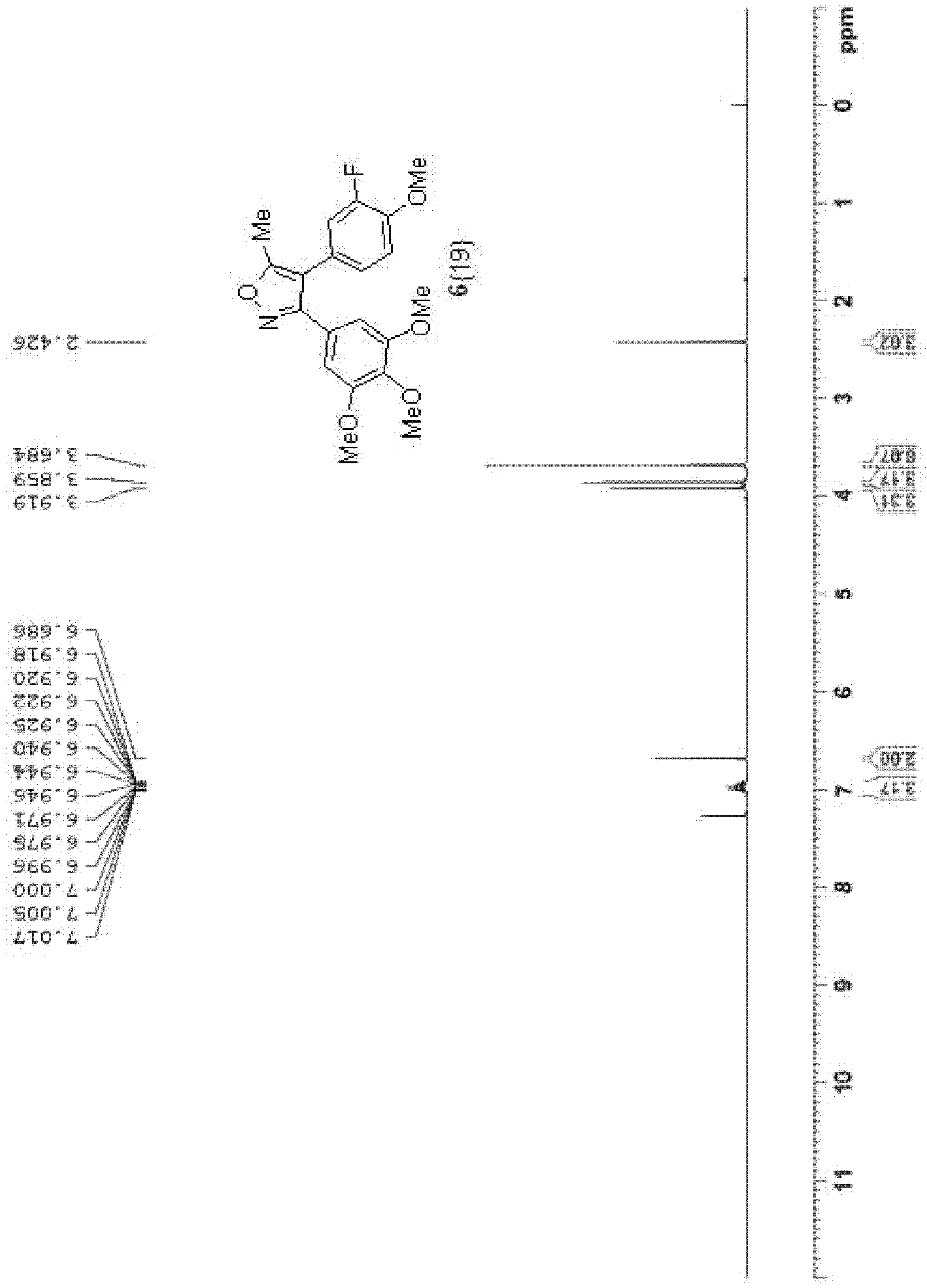


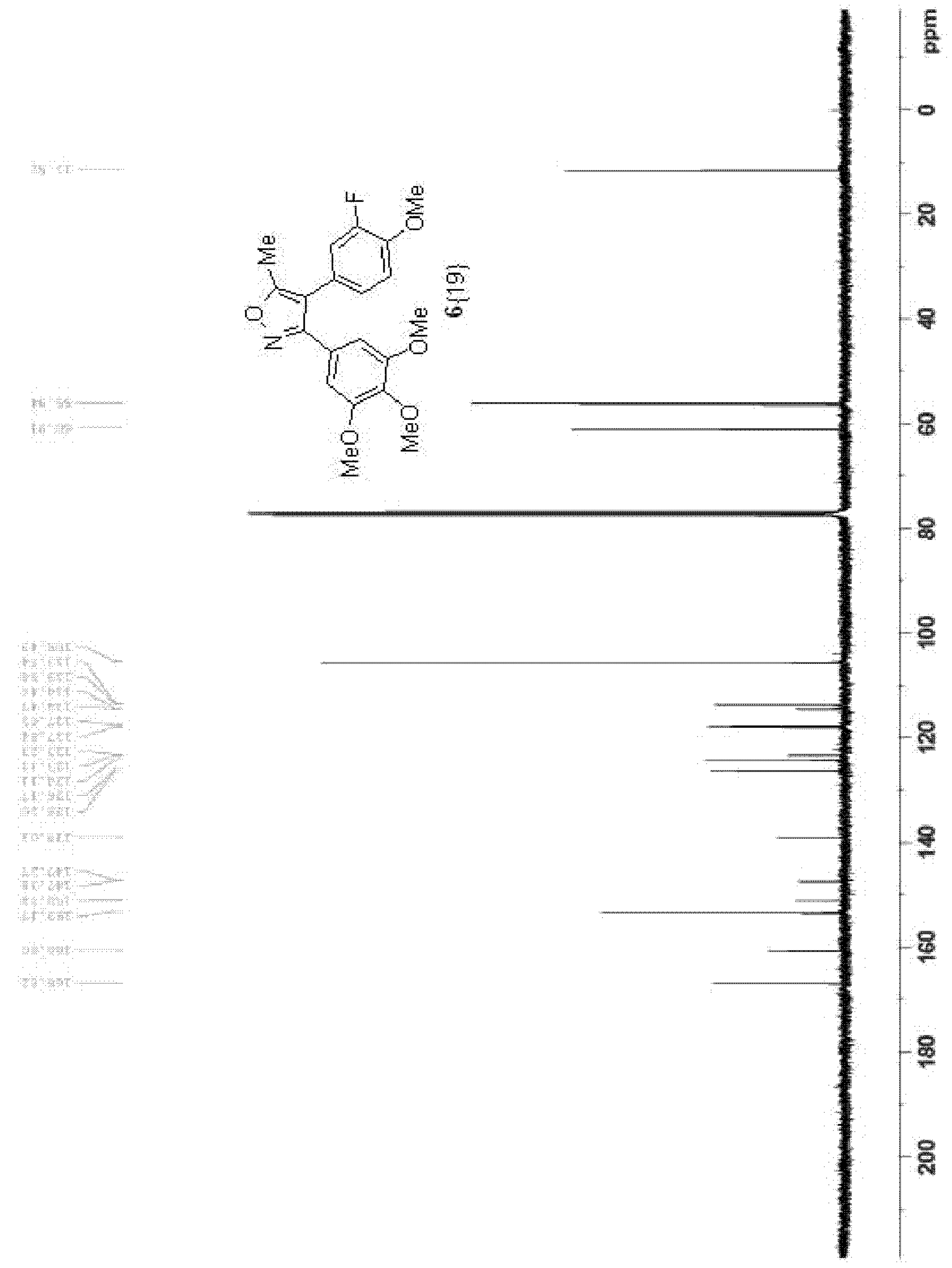
6{16}

1.394
1.412
1.430
2.483
3.687
3.867
4.389
4.407
4.425
4.443
6.632
7.020
7.024
7.048
7.052
7.054
7.058
7.074
7.078
7.945
7.965
7.984
Me
F
CO$_2$Et
N
O
MeO
MeO
OMe
3.01
3.03
6.05
3.27
2.01
2.00
2.00
0.99
ppm
0
1
2
3
4
5
6
7
8
9
10

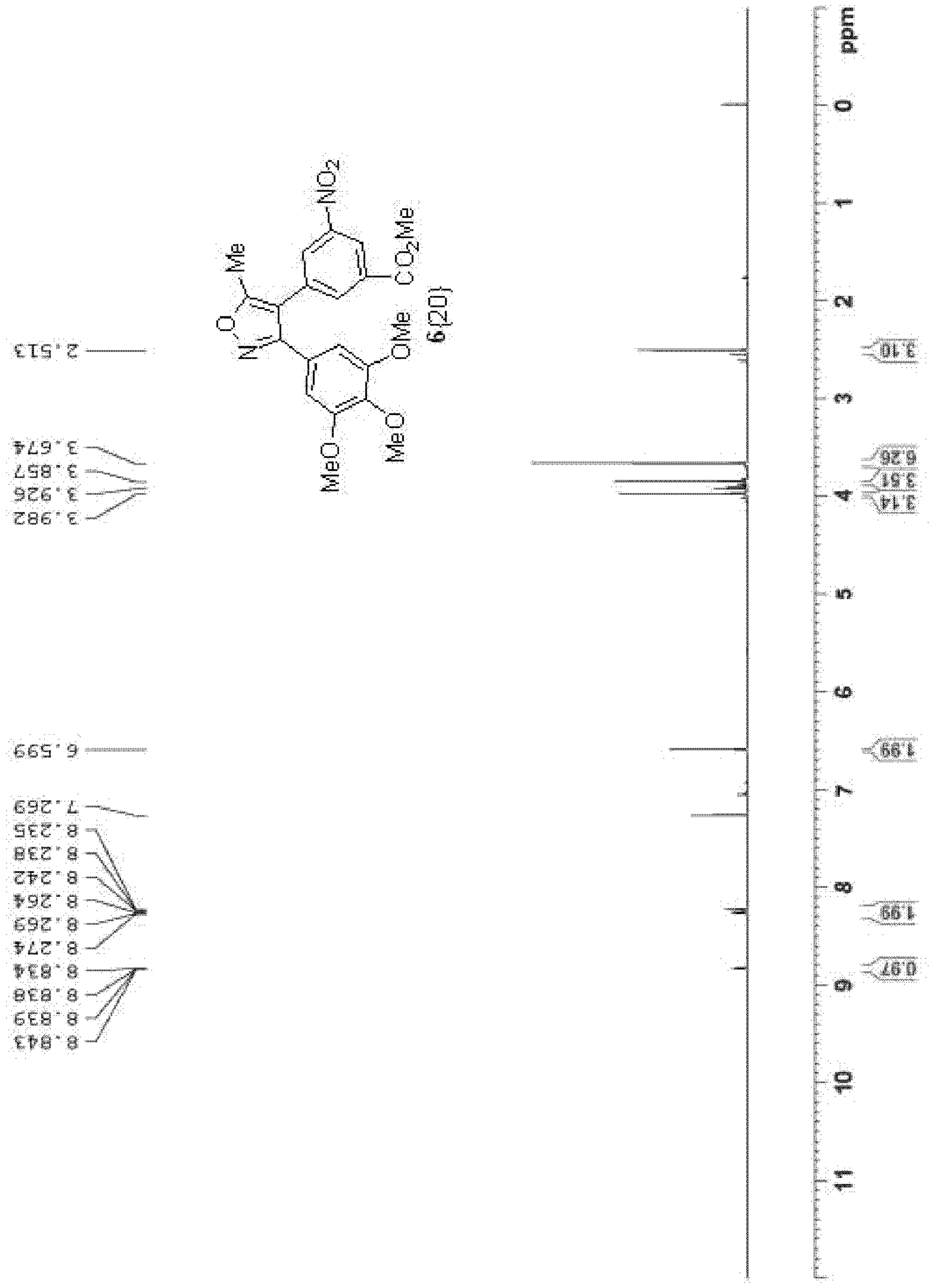


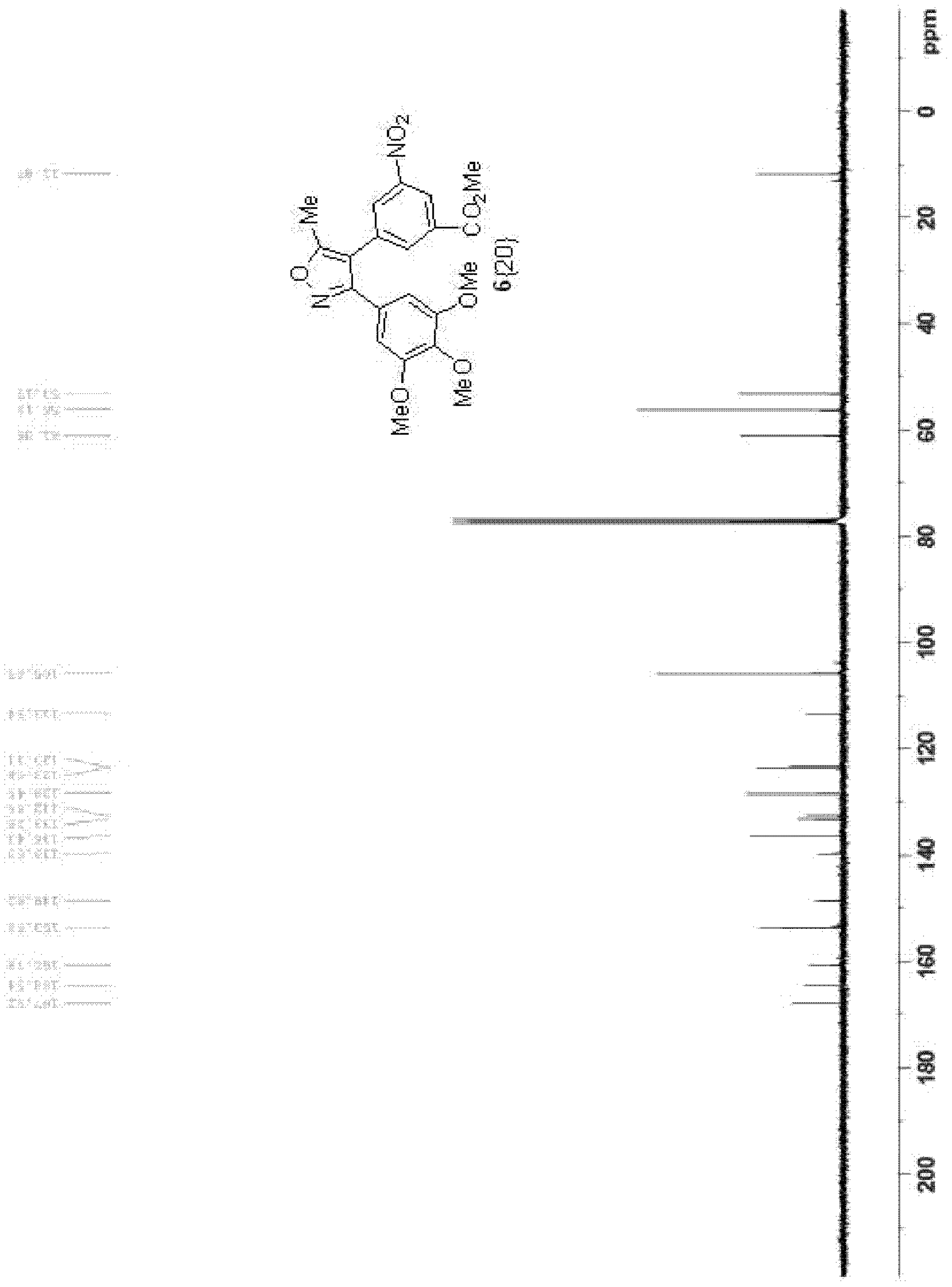
6{16}


2.426
3.684
3.859
3.919
6.686
6.918
6.920
6.922
6.925
6.940
6.944
6.946
6.971
6.975
6.996
7.000
7.005
7.017
Me
O
N
F
OMe
MeO
MeO
OMe
6{19}
3.02
6.07
3.17
3.31
2.00
3.17
ppm
0
1
2
3
4
5
6
7
8
9
10
11

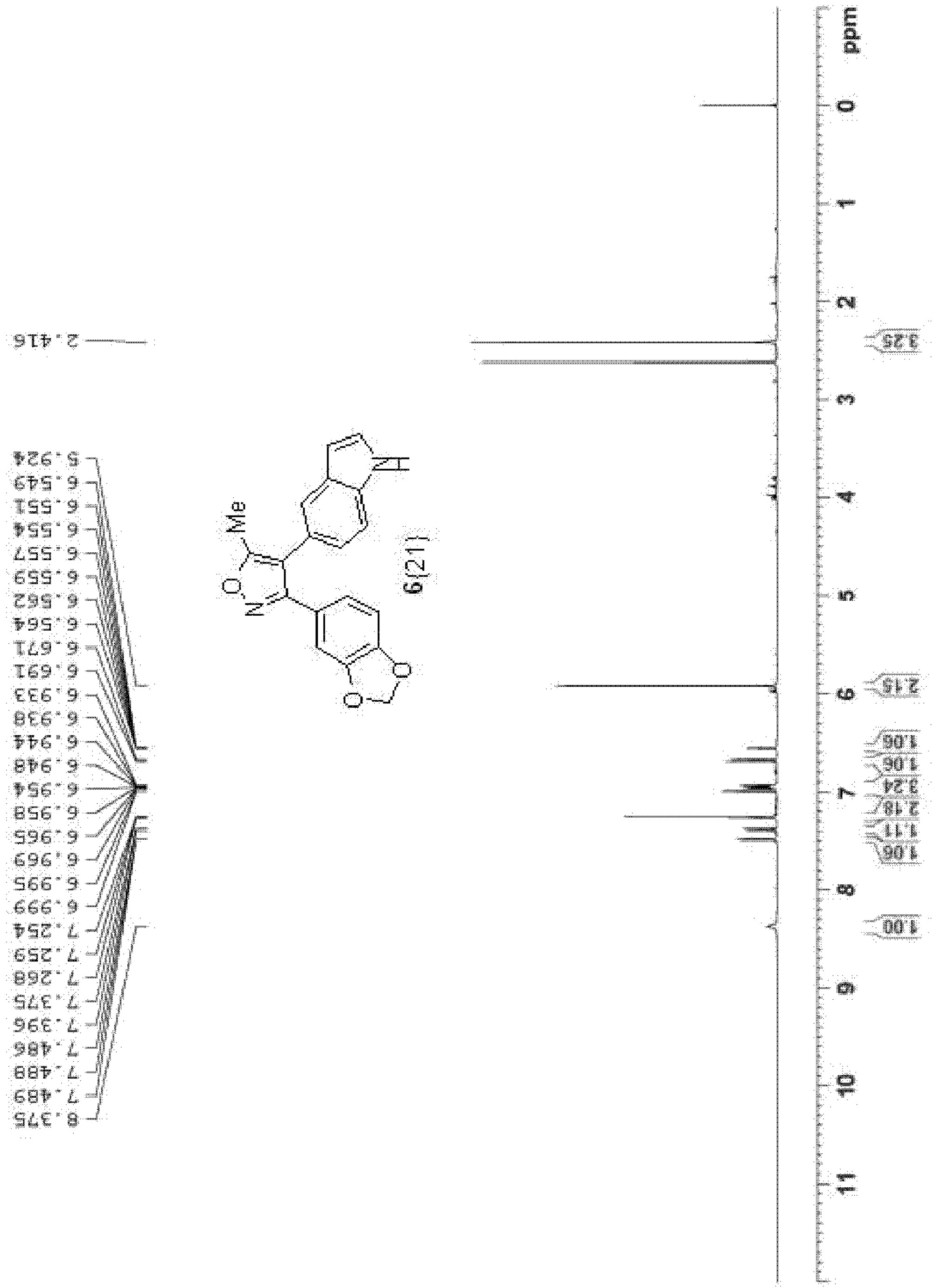

166.62
160.60
153.17
150.73
147.38
147.27
139.03
126.10
126.17
124.11
123.13
122.93
117.84
117.63
114.47
114.44
113.56
113.54
105.43
60.91
55.94
11.52
N
O
Me
F
OMe
MeO
MeO
OMe
ppm
0
20
40
60
80
100
120
140
160
180
200

6{19}

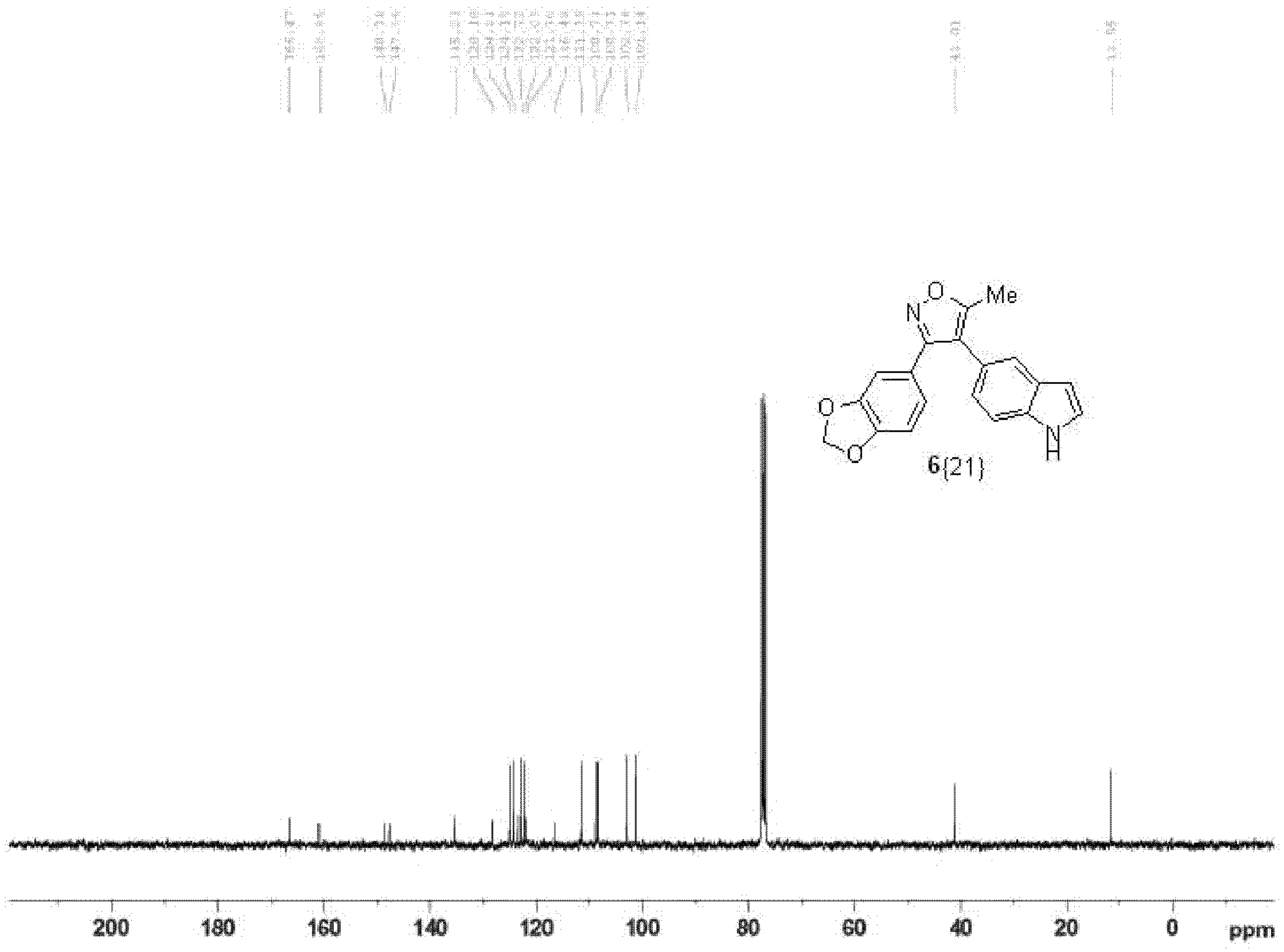

6{20}
Me
NO2
CO2Me
OMe
MeO
MeO
N
O
2.513
3.674
3.857
3.926
3.982
6.599
7.269
8.235
8.238
8.242
8.264
8.269
8.274
8.834
8.838
8.839
8.843
3.10
6.26
3.51
3.14
1.99
1.99
0.97
ppm
0
1
2
3
4
5
6
7
8
9
10
11


NO2
Me
N
O
CO2Me
OMe
MeO
MeO
ppm
0
20
40
60
80
100
120
140
160
180
200

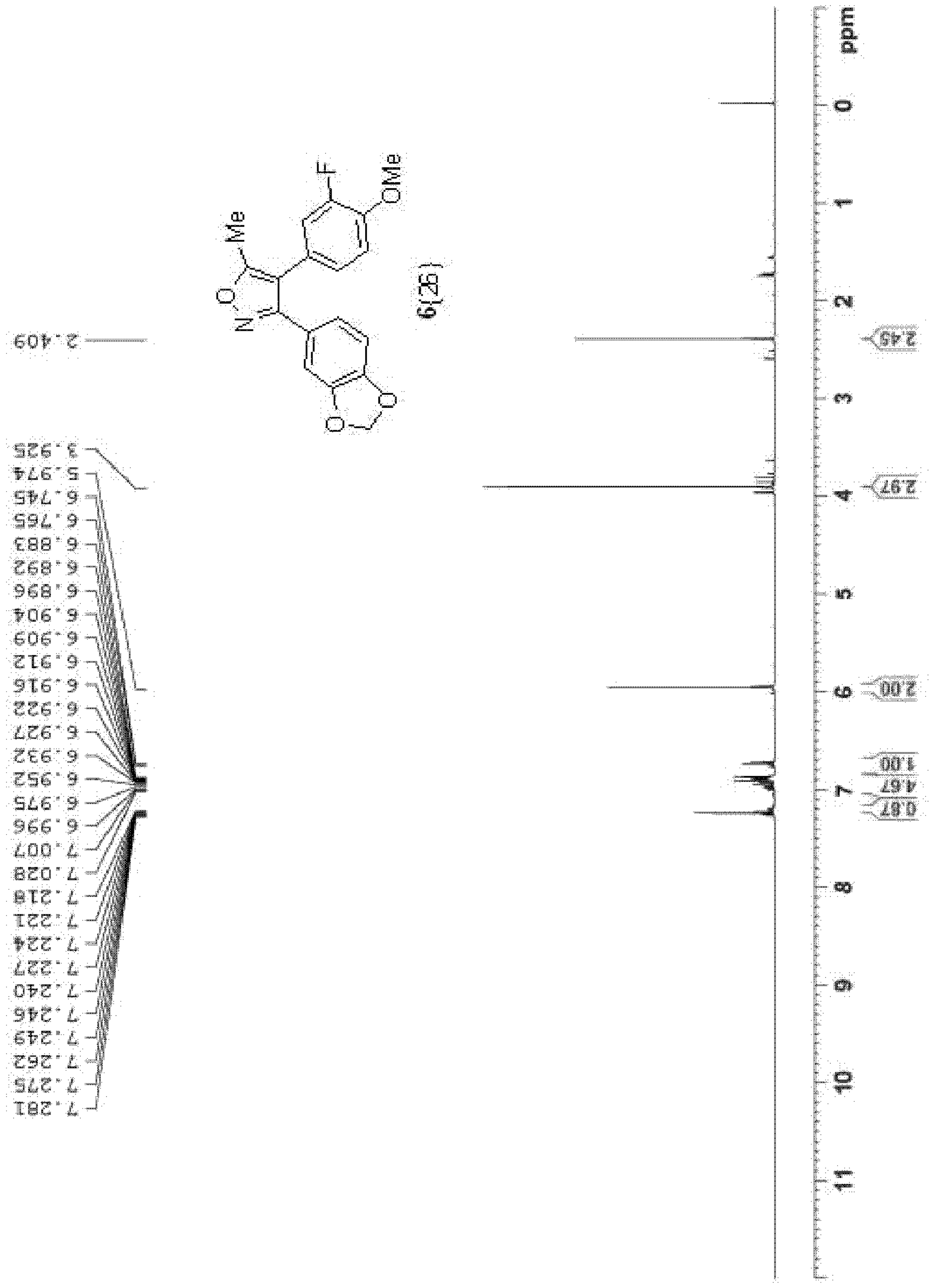
6(20)


6(21)

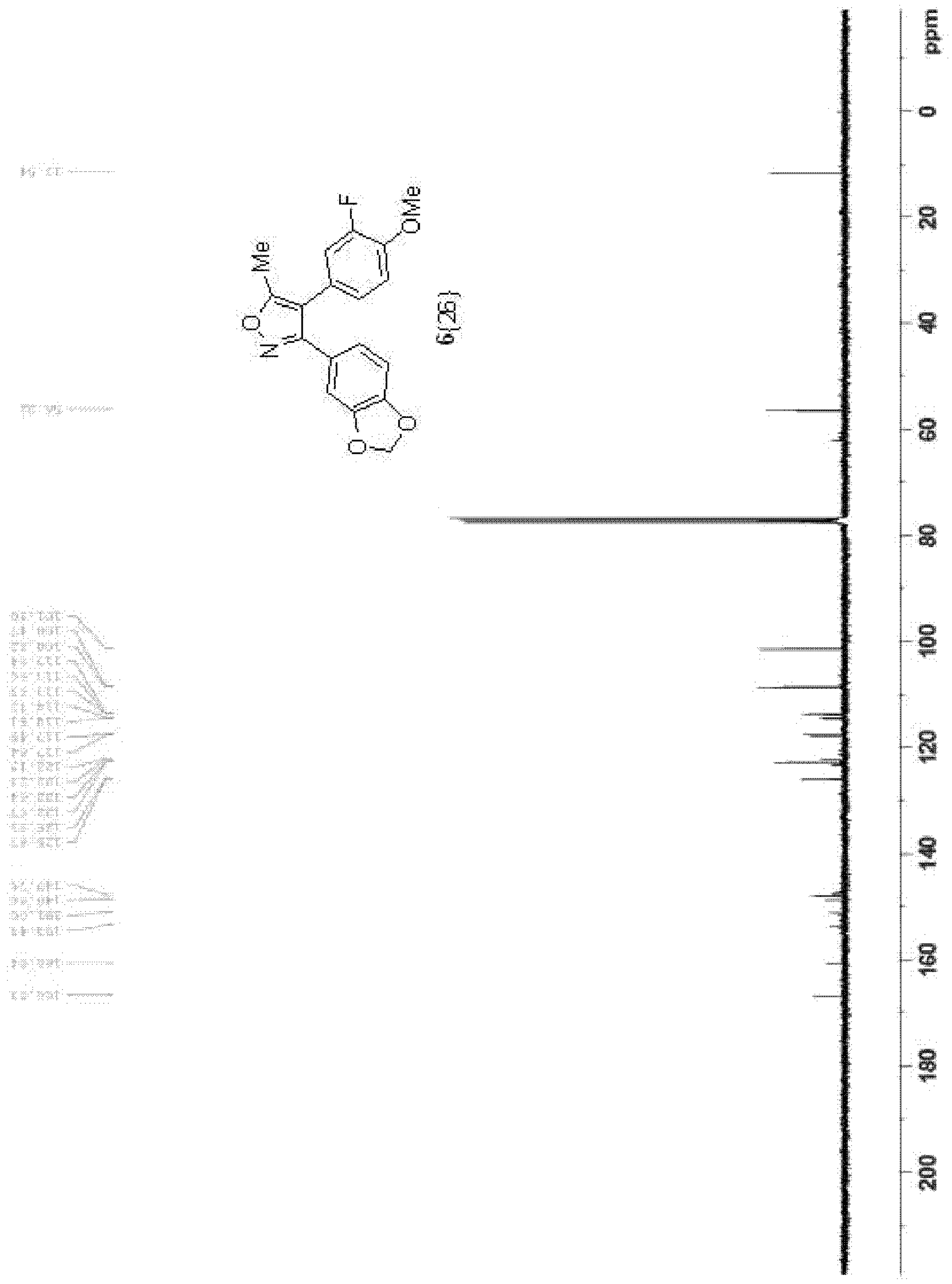
2.416
5.924
6.549
6.551
6.554
6.557
6.559
6.562
6.564
6.671
6.691
6.933
6.938
6.944
6.948
6.954
6.958
6.965
6.969
6.995
6.999
7.254
7.259
7.268
7.375
7.396
7.486
7.488
7.489
8.375
Me
O
N
O
O
N
H
3.25
2.15
1.06
1.06
3.24
2.18
1.11
1.06
1.00
ppm
0
1
2
3
4
5
6
7
8
9
10
11


165.47
160.66
148.31
147.56
135.03
128.10
124.41
124.15
122.75
122.03
121.90
116.48
111.15
108.73
108.71
102.76
101.14
41.01
11.56
N
O
Me
O
O
NH
200
180
160
140
120
100
80
60
40
20
0
ppm

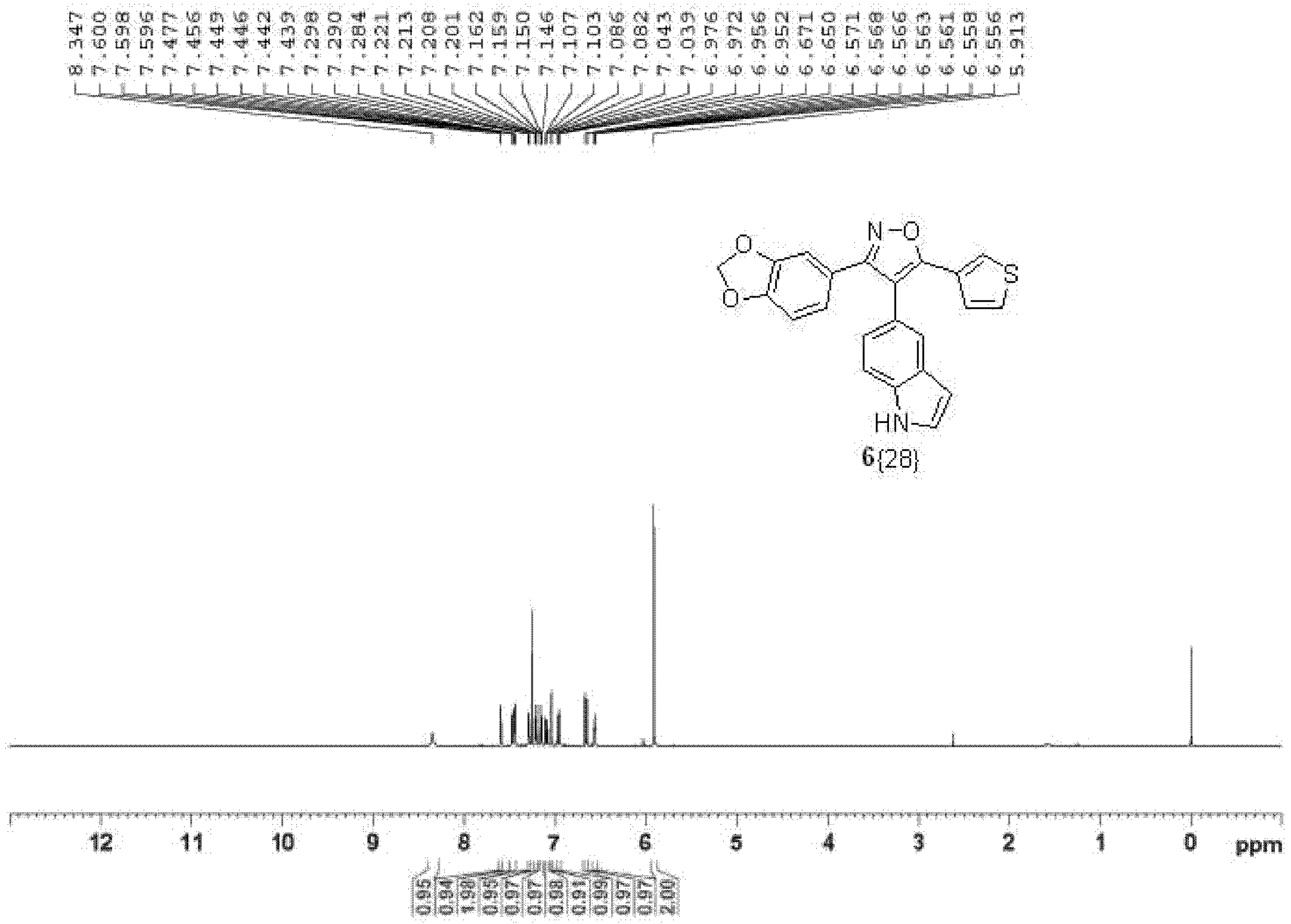
6{21}


6(26)

2.409
3.925
5.974
6.745
6.765
6.883
6.892
6.896
6.904
6.909
6.912
6.916
6.922
6.927
6.932
6.952
6.975
6.996
7.007
7.028
7.218
7.221
7.224
7.227
7.240
7.246
7.249
7.262
7.275
7.281
Me
N
O
F
OMe
2.45
2.97
2.00
1.00
4.67
0.87
ppm
0
1
2
3
4
5
6
7
8
9
10
11

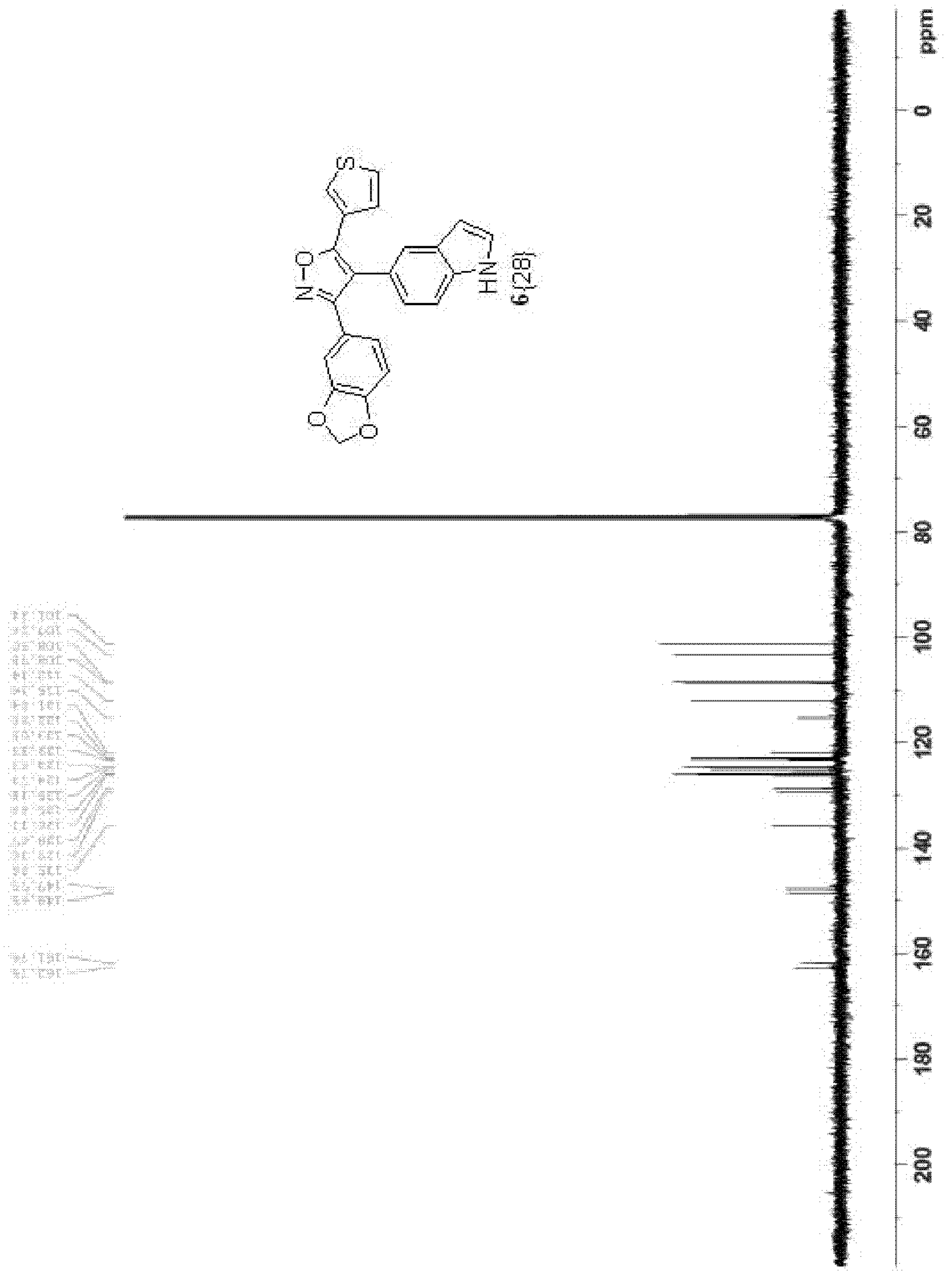


6{26}

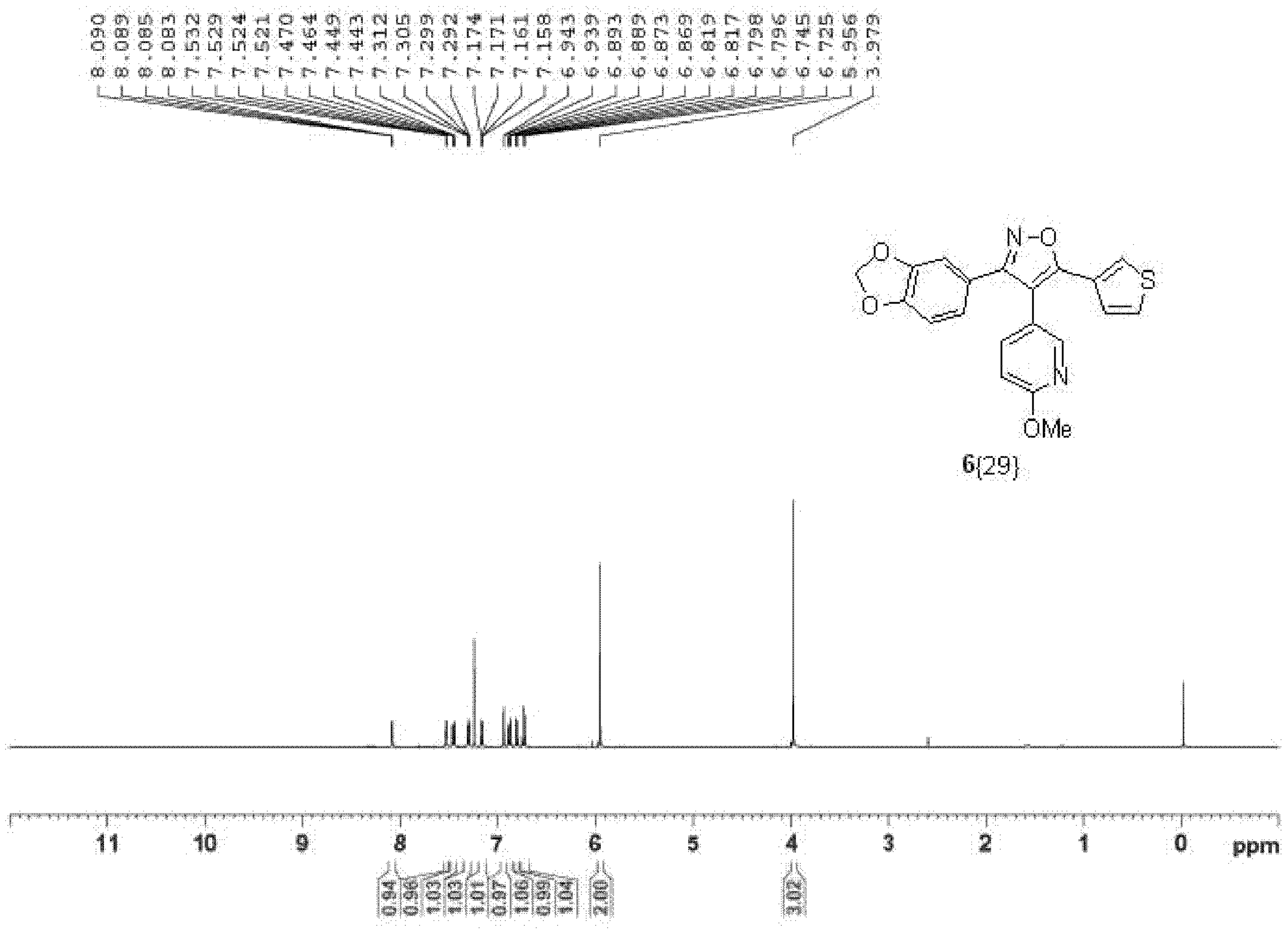


6{28}

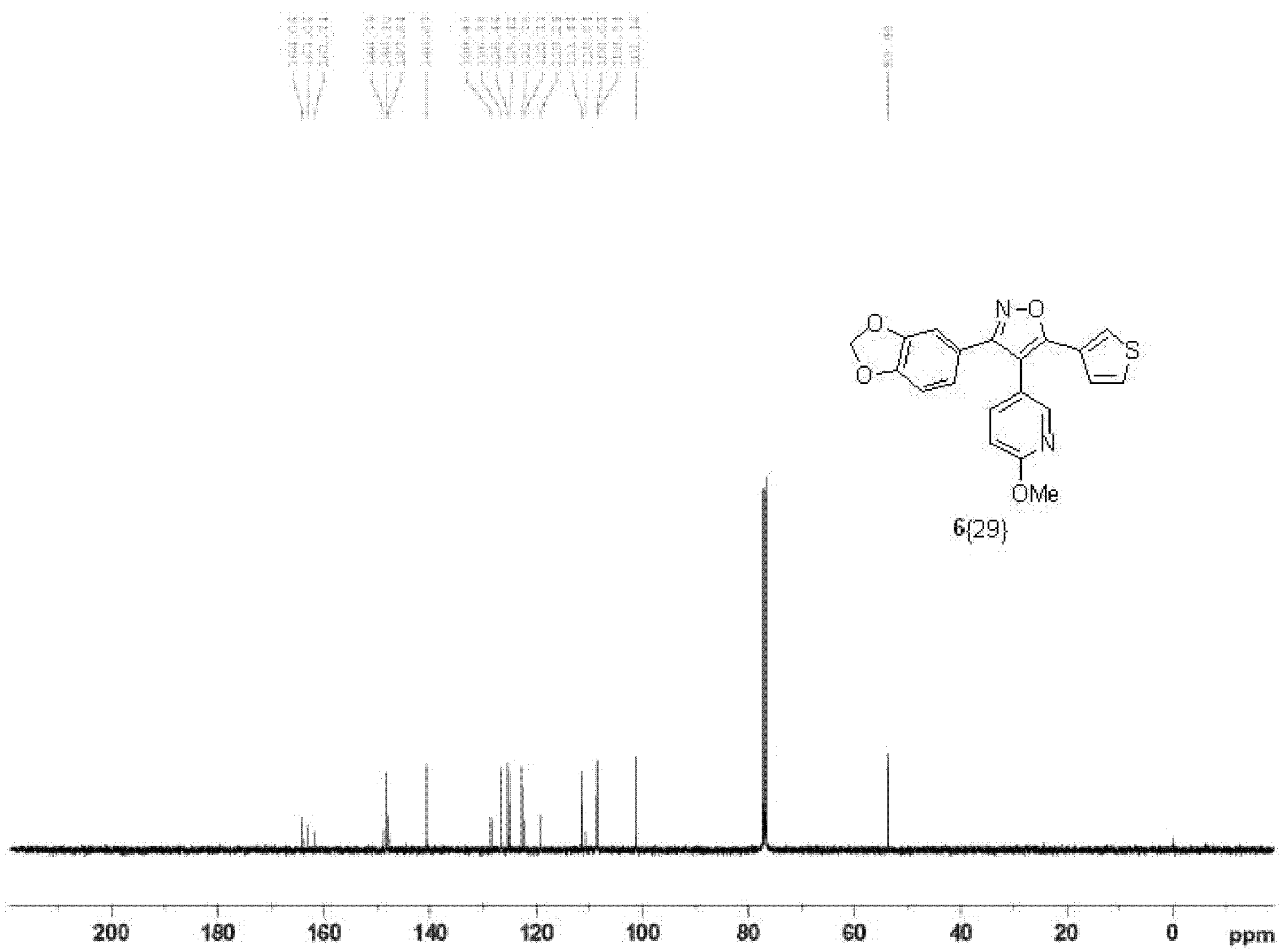
8.347
7.600
7.598
7.596
7.477
7.456
7.449
7.446
7.442
7.439
7.298
7.290
7.284
7.221
7.213
7.208
7.201
7.162
7.159
7.150
7.146
7.107
7.103
7.086
7.082
7.043
7.039
6.976
6.972
6.956
6.952
6.671
6.650
6.571
6.568
6.566
6.563
6.561
6.558
6.556
5.913
N
O
S
O
O
HN
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
0.94
1.98
0.95
0.97
0.97
0.98
0.91
0.99
0.97
0.97
2.00

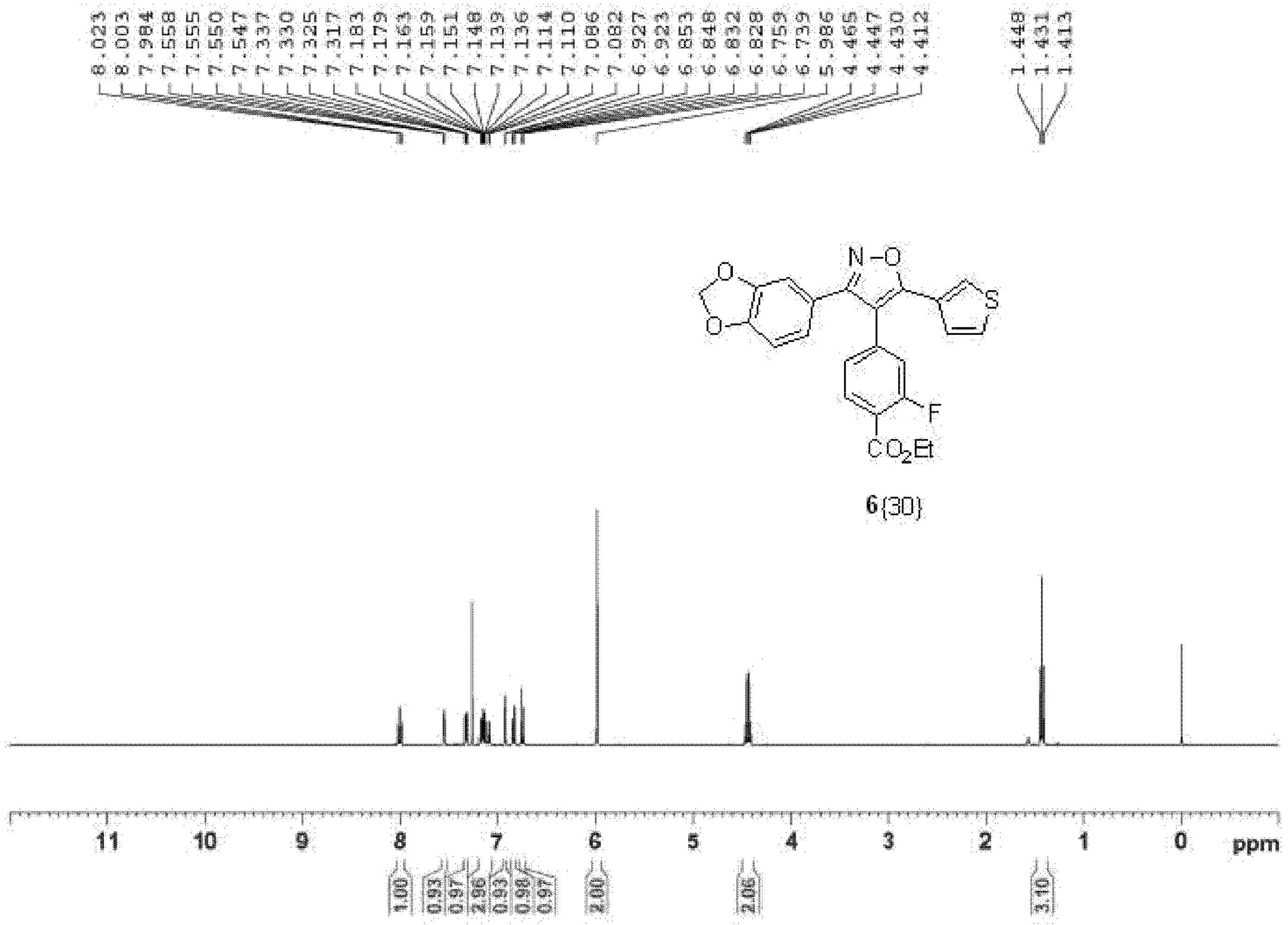


6{28}


8.090
8.089
8.085
8.083
7.532
7.529
7.524
7.521
7.470
7.464
7.449
7.443
7.312
7.305
7.299
7.292
7.174
7.171
7.161
7.158
6.943
6.939
6.893
6.889
6.873
6.869
6.819
6.817
6.798
6.796
6.745
6.725
5.956
3.979
N-O
S
N
OMe
O
O
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.94
0.96
1.03
1.03
1.01
0.97
1.06
0.99
1.04
2.00
3.02

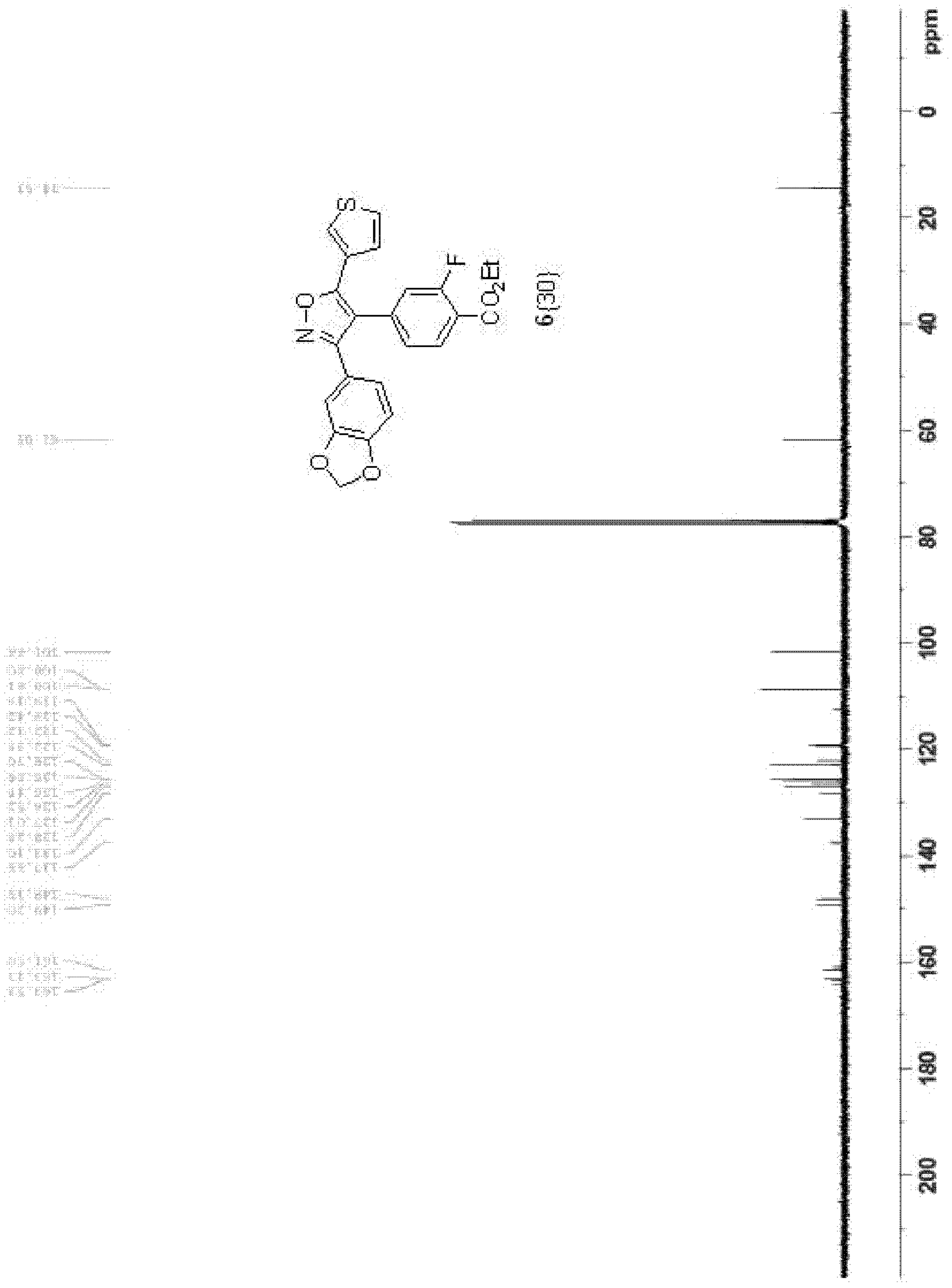
6{29}


N-O
O
O
S
N
OMe
6{29}
200
180
160
140
120
100
80
60
40
20
0
ppm

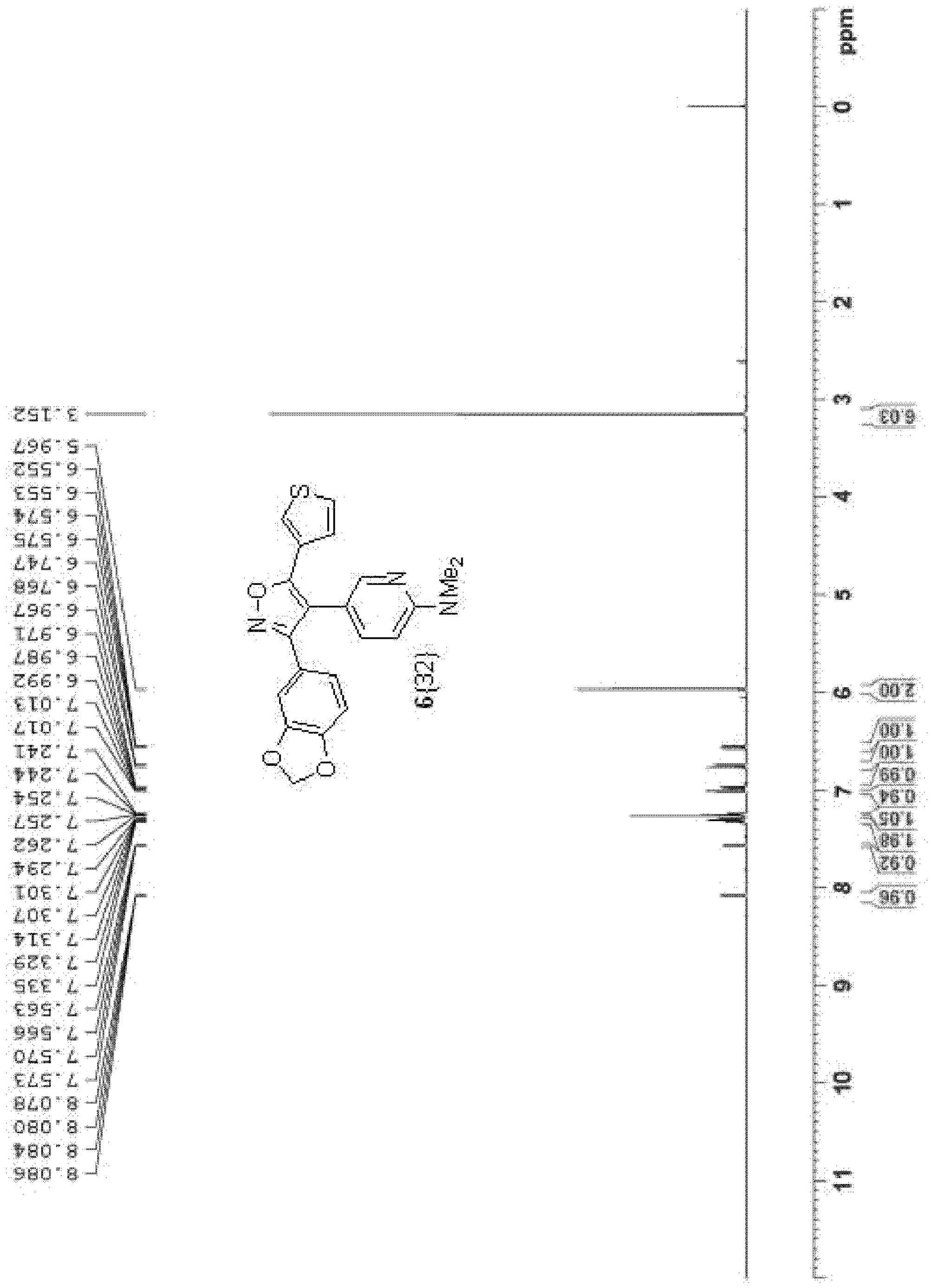


6{30}

8.023
8.003
7.984
7.558
7.555
7.550
7.547
7.337
7.330
7.325
7.317
7.183
7.179
7.163
7.159
7.151
7.148
7.139
7.136
7.114
7.110
7.086
7.082
6.927
6.923
6.853
6.848
6.832
6.828
6.759
6.739
5.986
4.465
4.447
4.430
4.412
1.448
1.431
1.413
N-O
O
O
S
F
CO2Et
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.93
0.97
2.96
0.93
0.98
0.97
2.00
2.06
3.10

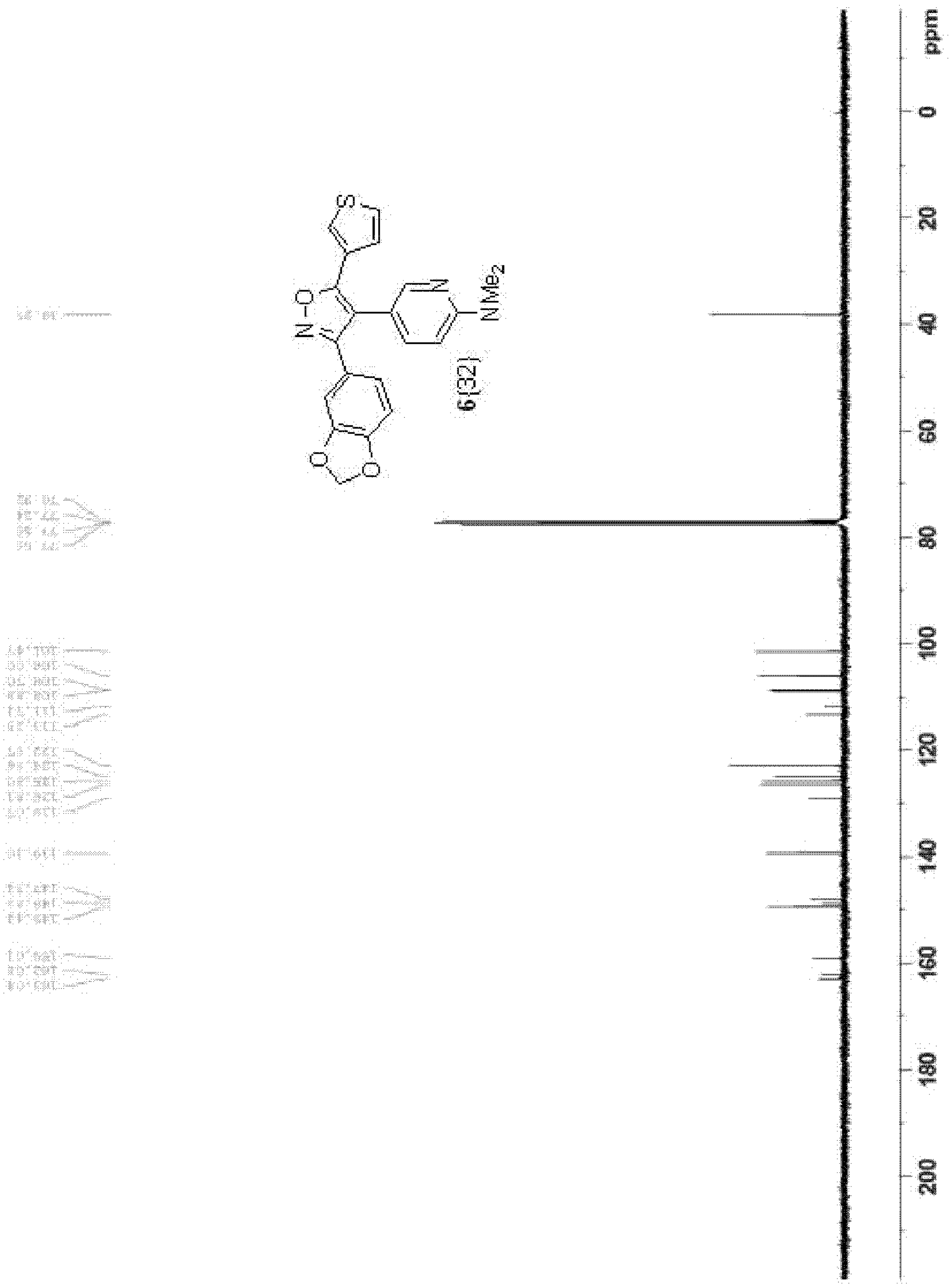


6(30)

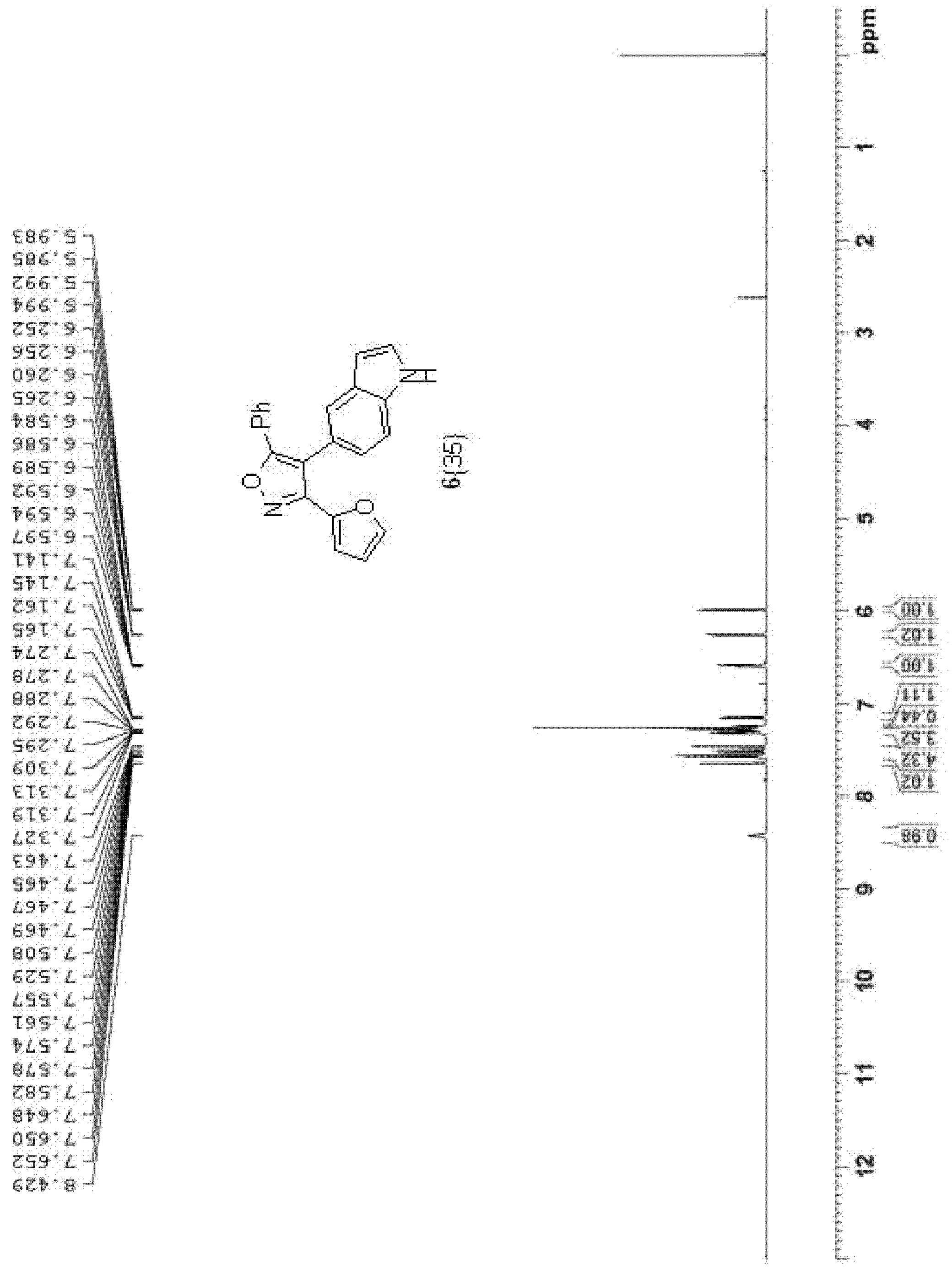


6{32}

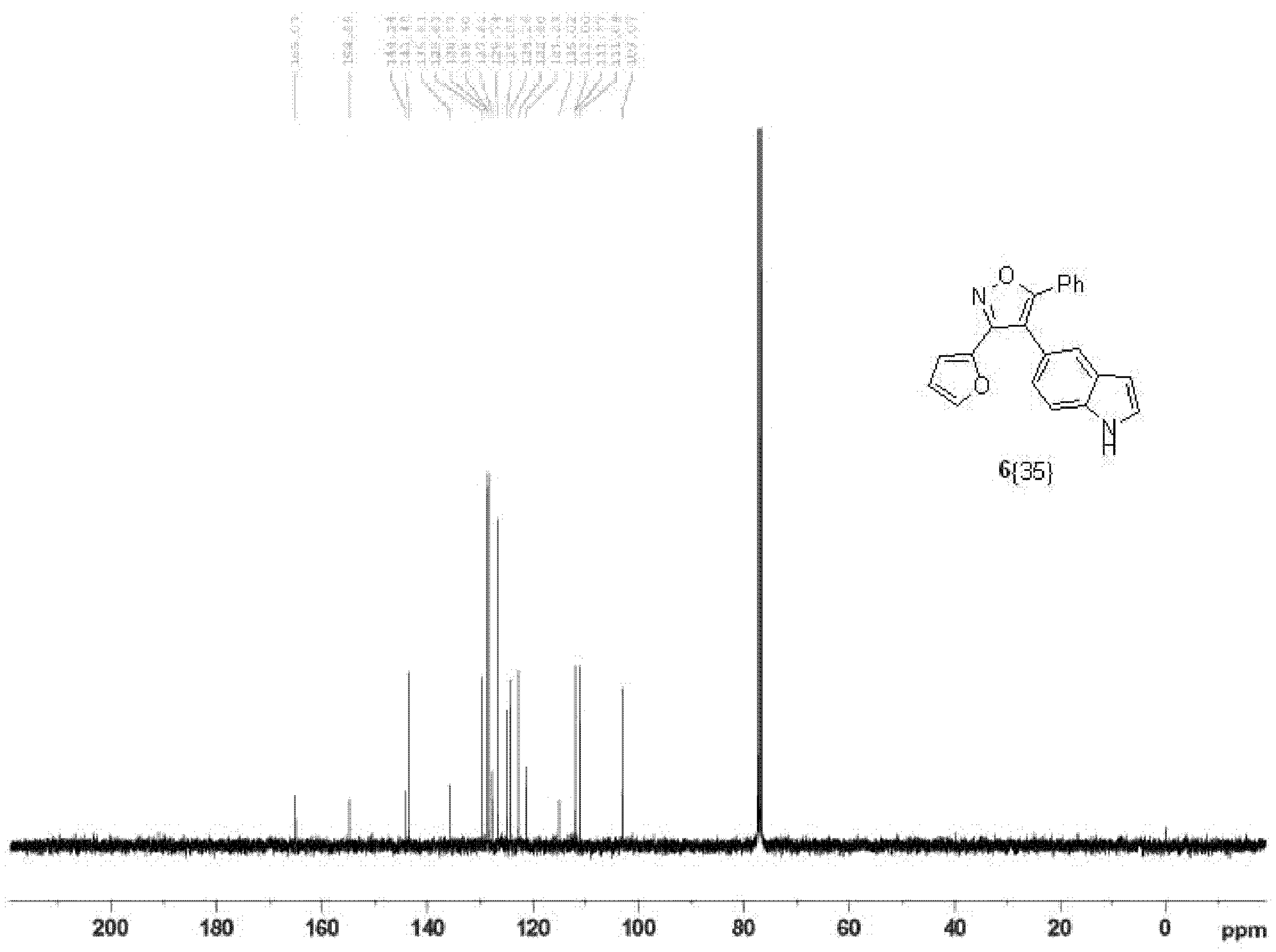
3.152
5.967
6.552
6.553
6.574
6.575
6.747
6.768
6.967
6.971
6.987
6.992
7.013
7.017
7.241
7.244
7.254
7.257
7.262
7.294
7.301
7.307
7.314
7.329
7.335
7.563
7.566
7.570
7.573
8.078
8.080
8.084
8.086
S
N–O
N
NMe$_2$
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.03
2.00
1.00
1.00
0.99
0.94
1.05
1.98
0.92
0.96



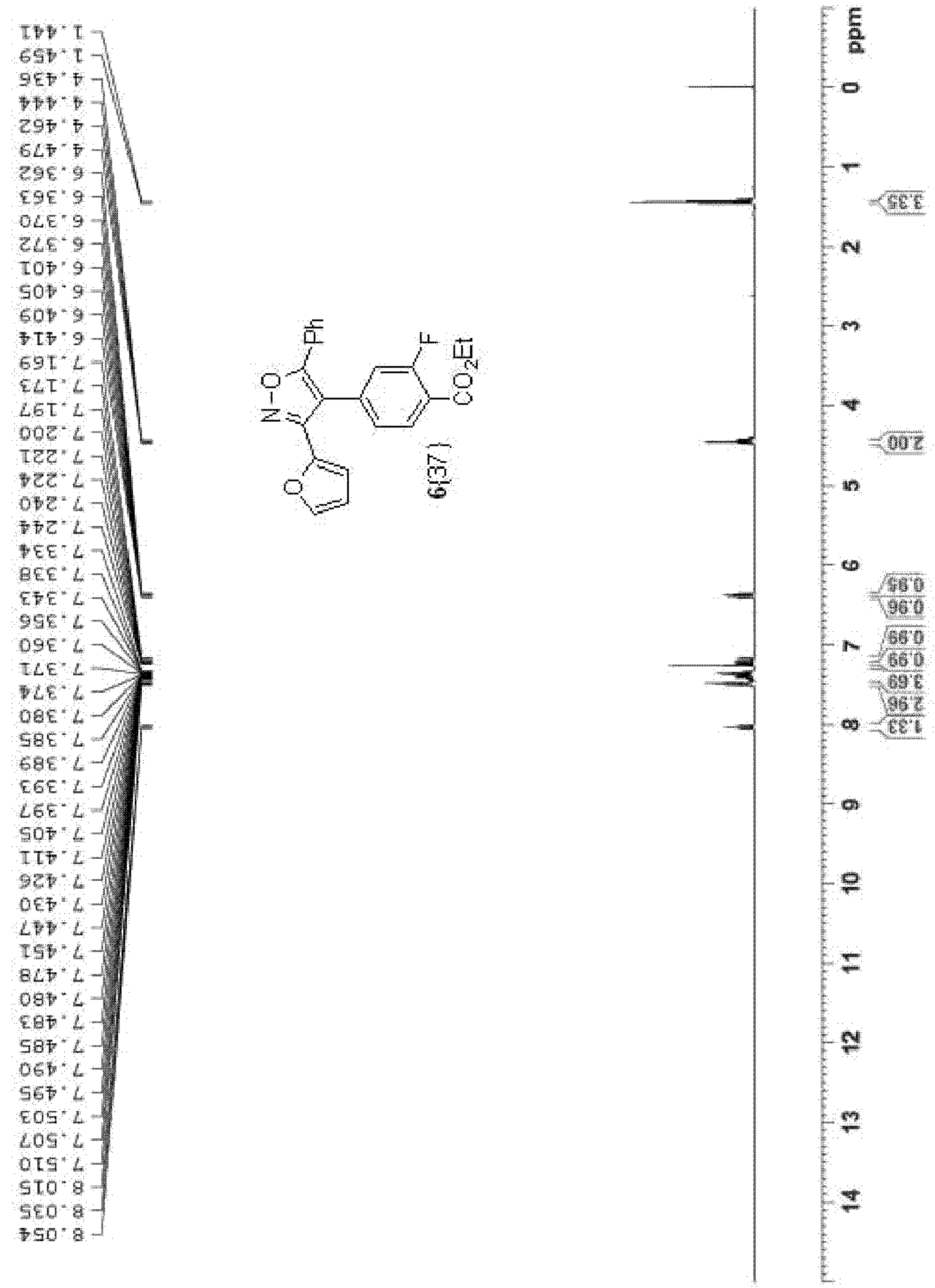
6(32)


6(35)

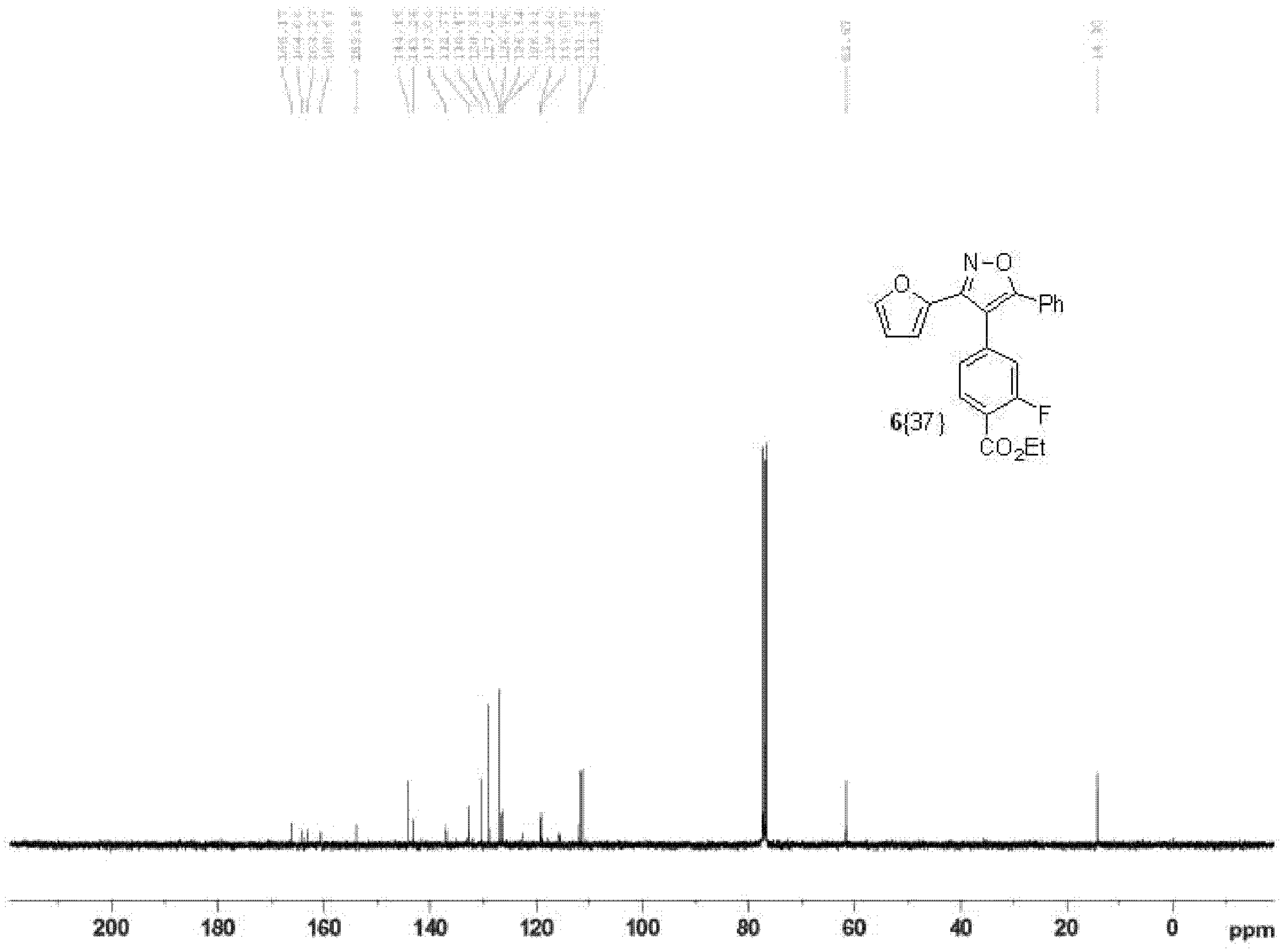
Ph
O
N
H
5.983
5.985
5.992
5.994
6.252
6.256
6.260
6.265
6.584
6.586
6.589
6.592
6.594
6.597
7.141
7.145
7.162
7.165
7.274
7.278
7.288
7.292
7.295
7.309
7.313
7.319
7.327
7.463
7.465
7.467
7.469
7.508
7.529
7.557
7.561
7.574
7.578
7.582
7.648
7.650
7.652
8.429
1.00
1.02
1.00
1.11
0.44
3.52
4.32
1.02
0.98
ppm
1
2
3
4
5
6
7
8
9
10
11
12



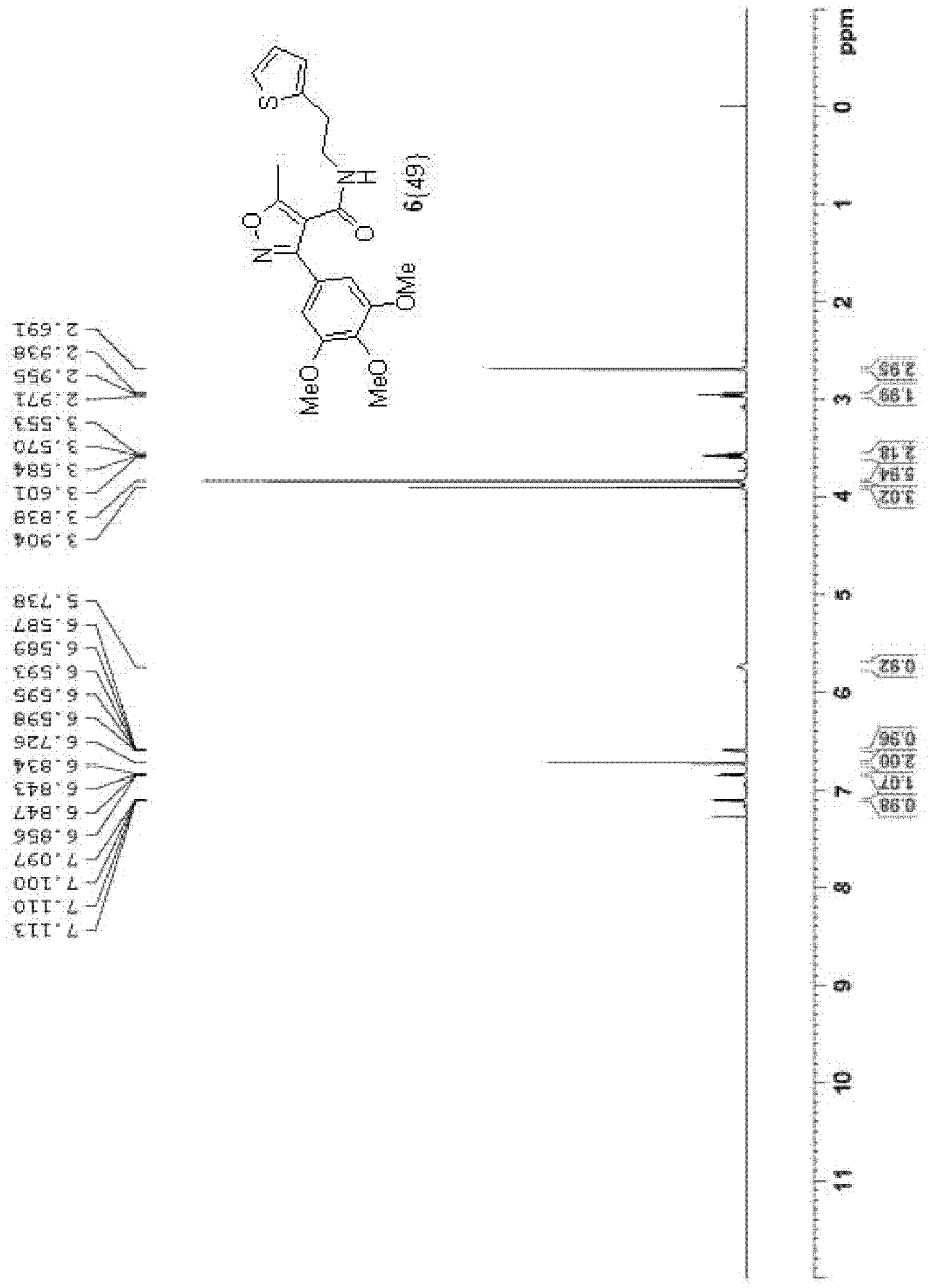
6{35}


1.441
1.459
4.436
4.444
4.462
4.479
6.362
6.363
6.370
6.372
6.401
6.405
6.409
6.414
7.169
7.173
7.197
7.200
7.221
7.224
7.240
7.244
7.334
7.338
7.343
7.356
7.360
7.371
7.374
7.380
7.385
7.389
7.393
7.397
7.405
7.411
7.426
7.430
7.447
7.451
7.478
7.480
7.483
7.485
7.490
7.495
7.503
7.507
7.510
8.015
8.035
8.054
N–O
Ph
F
CO2Et
3.35
2.00
0.95
0.96
0.99
0.99
3.69
2.96
1.33
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14

6(37)

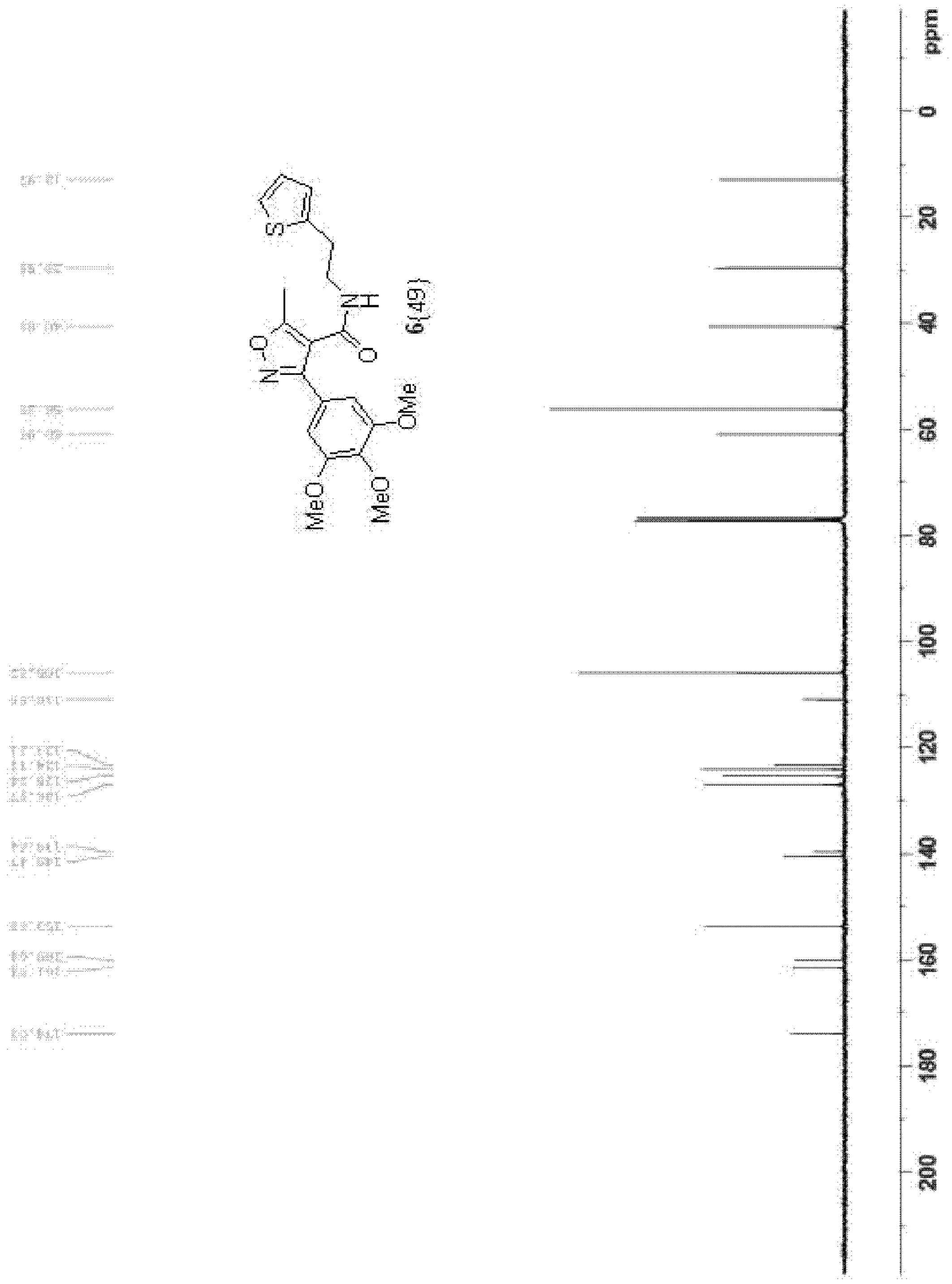


6{37}

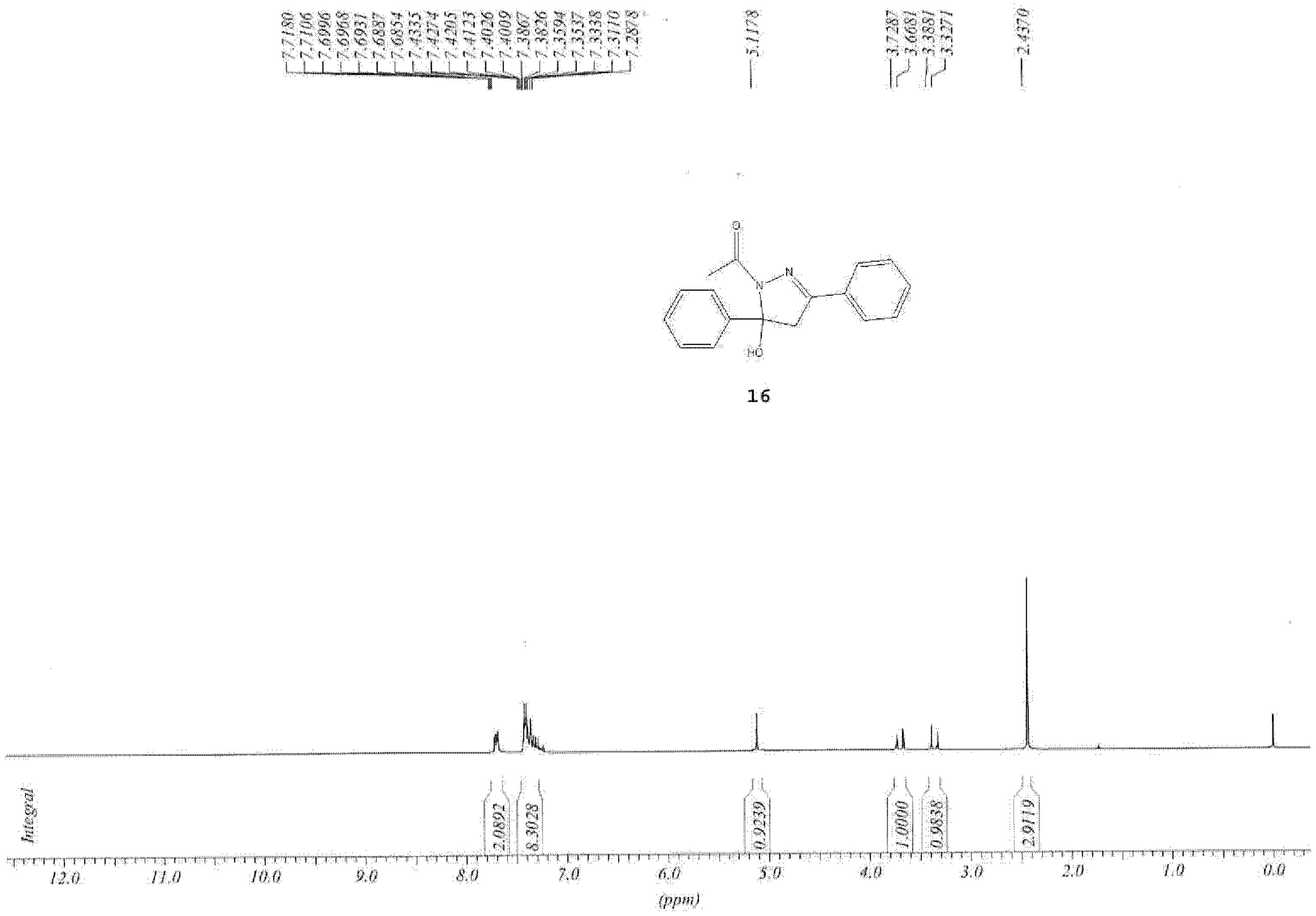


6(49)

MeO
MeO
OMe
N-O
O
N
H
S
2.691
2.938
2.955
2.971
3.553
3.570
3.584
3.601
3.838
3.904
5.738
6.587
6.589
6.593
6.595
6.598
6.726
6.834
6.843
6.847
6.856
7.097
7.100
7.110
7.113
2.95
1.99
2.18
5.94
3.02
0.92
0.96
2.00
1.07
0.98
ppm
0
1
2
3
4
5
6
7
8
9
10
11

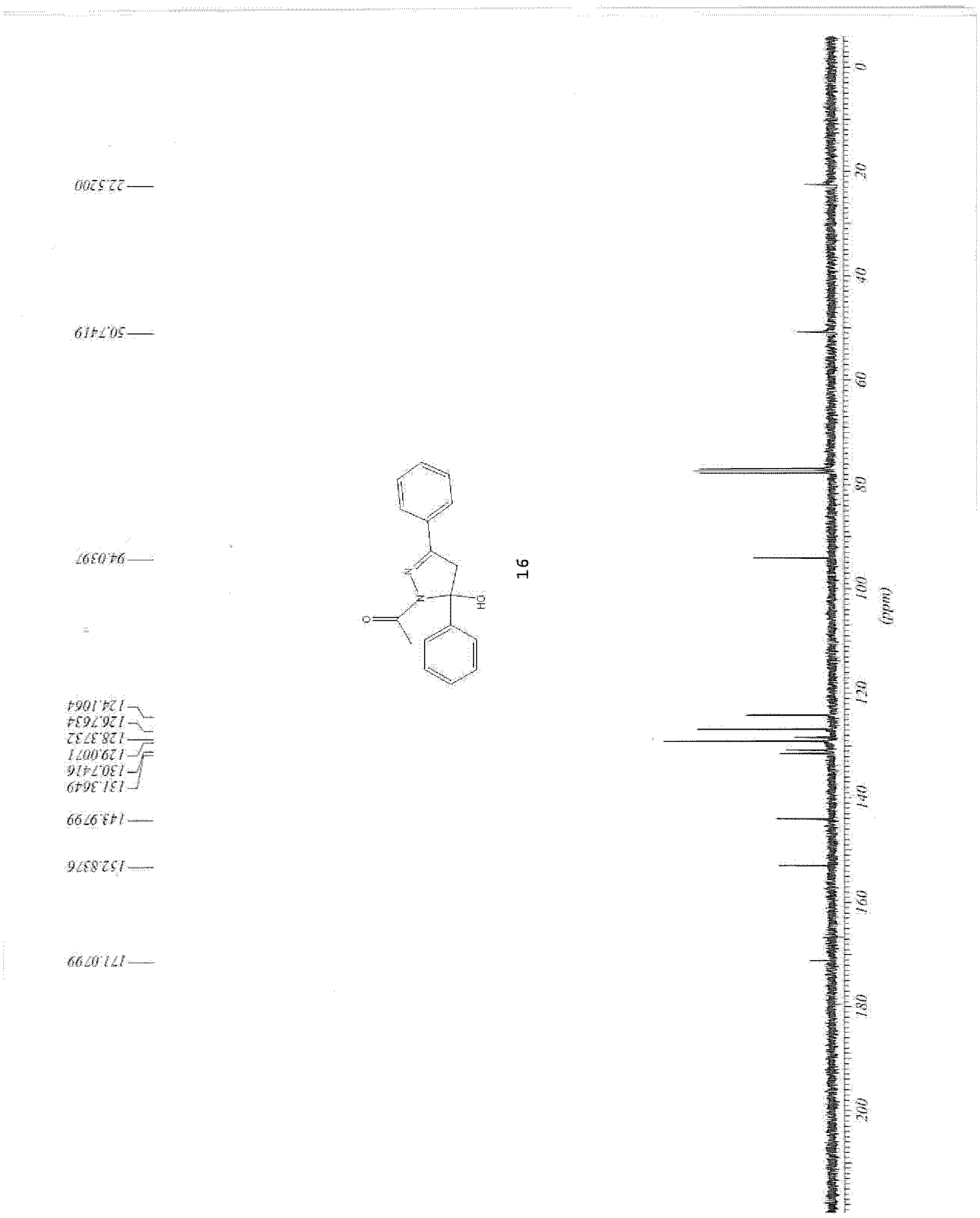

6(49)

APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA

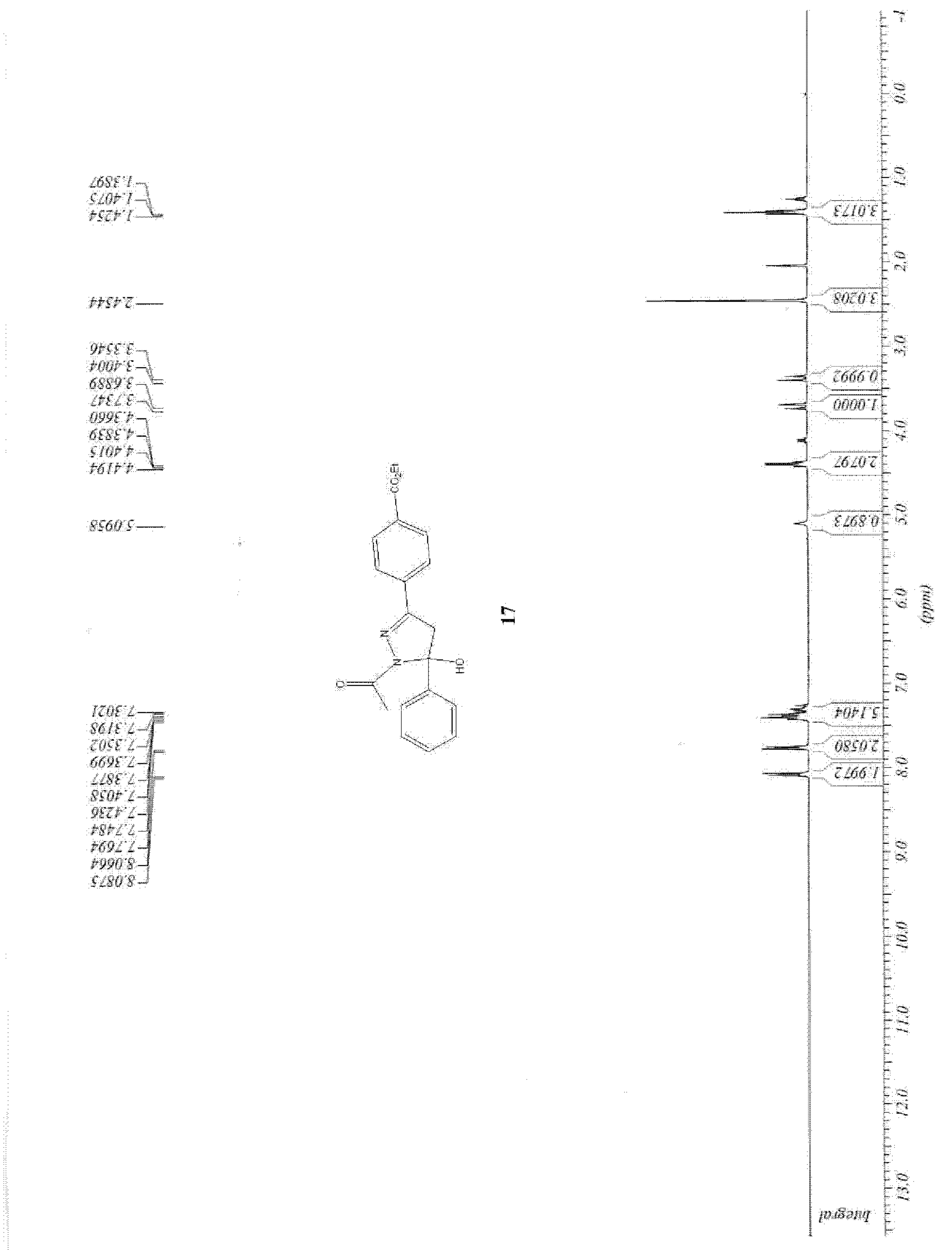


16

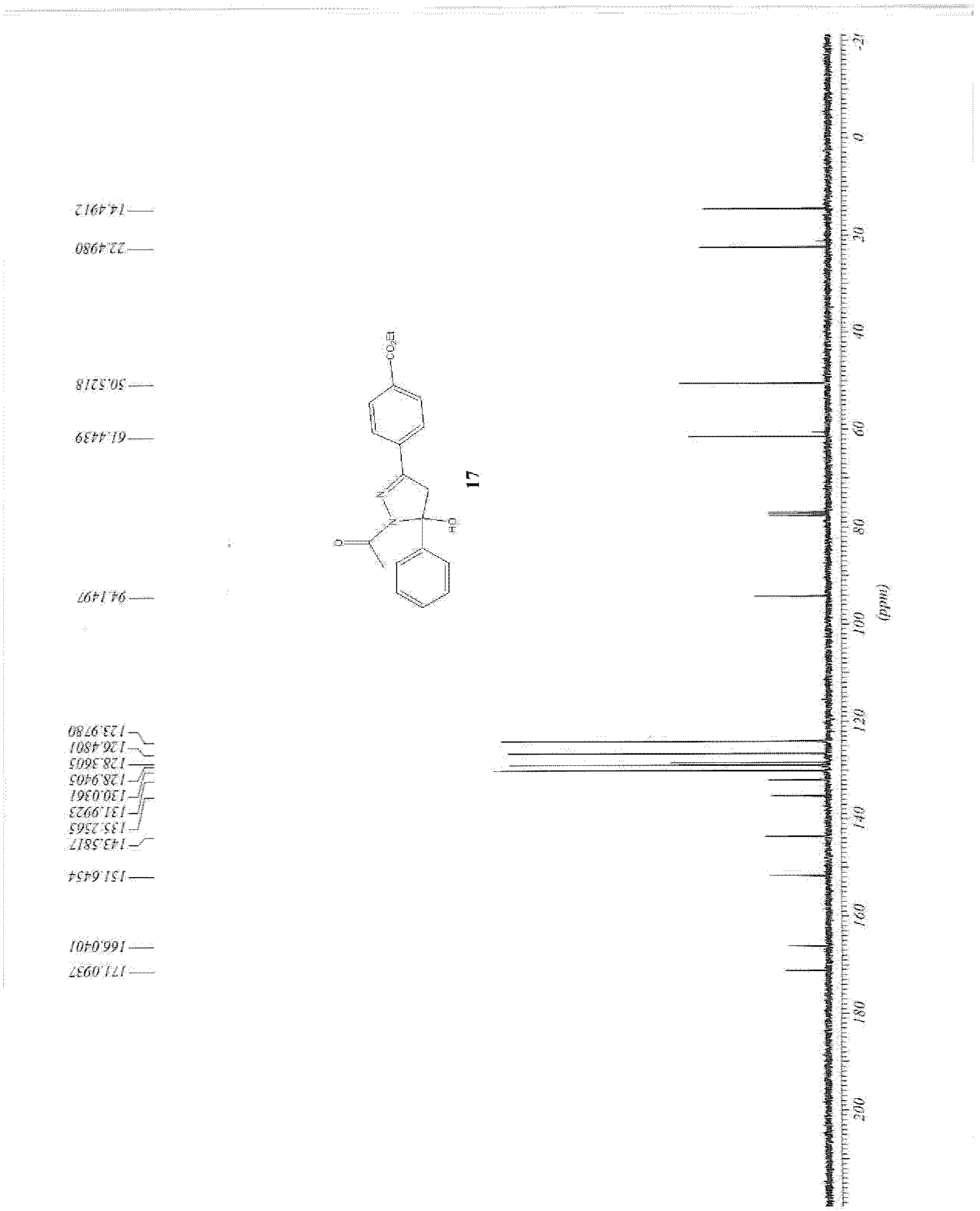
7.7180
7.7106
7.6996
7.6968
7.6931
7.6887
7.6854
7.4335
7.4274
7.4205
7.4123
7.4026
7.4009
7.3867
7.3826
7.3594
7.3557
7.3338
7.3110
7.2878
5.1178
3.7287
3.6681
3.3881
3.3271
2.4370
N
O
HO
Integral
2.0892
8.3028
0.9239
1.0000
0.9838
2.9119
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


22.5200
50.7419
94.0397
124.1064
126.7634
128.3732
129.0071
130.7416
131.3649
143.9799
152.8376
171.0799
O
N
N
HO
0
20
40
60
80
100
120
140
160
180
200
(ppm)

16

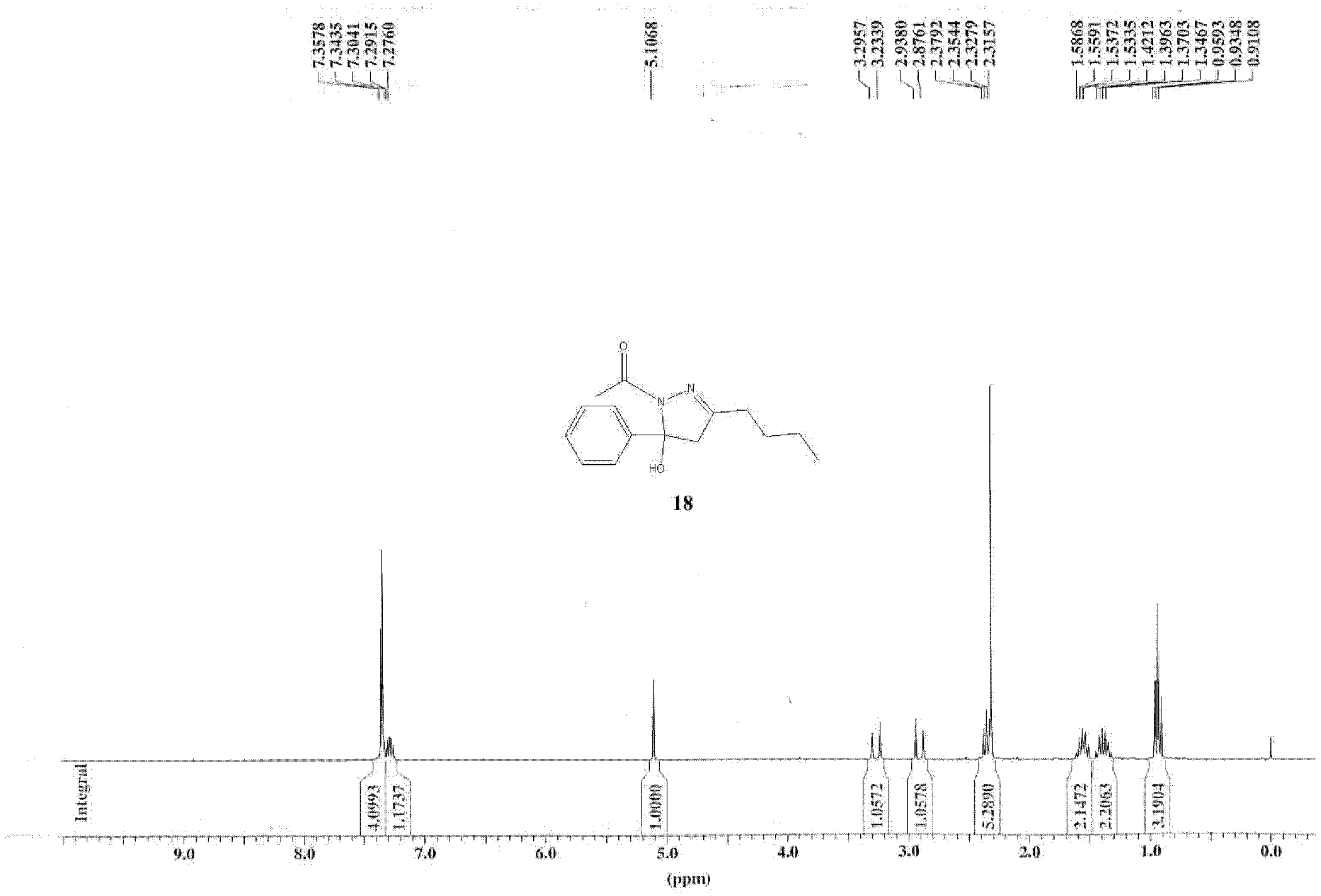

1.3897
1.4075
1.4254
2.4544
3.3546
3.4004
3.6889
3.7347
4.3660
4.3839
4.4015
4.4194
5.0958
7.3021
7.3198
7.3502
7.3699
7.3877
7.4058
7.4236
7.7484
7.7694
8.0664
8.0873
CO2Et
N
N
O
HO
3.0173
3.0208
0.9992
1.0000
2.0797
0.8973
5.1404
2.0580
1.9972
Integral
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

17



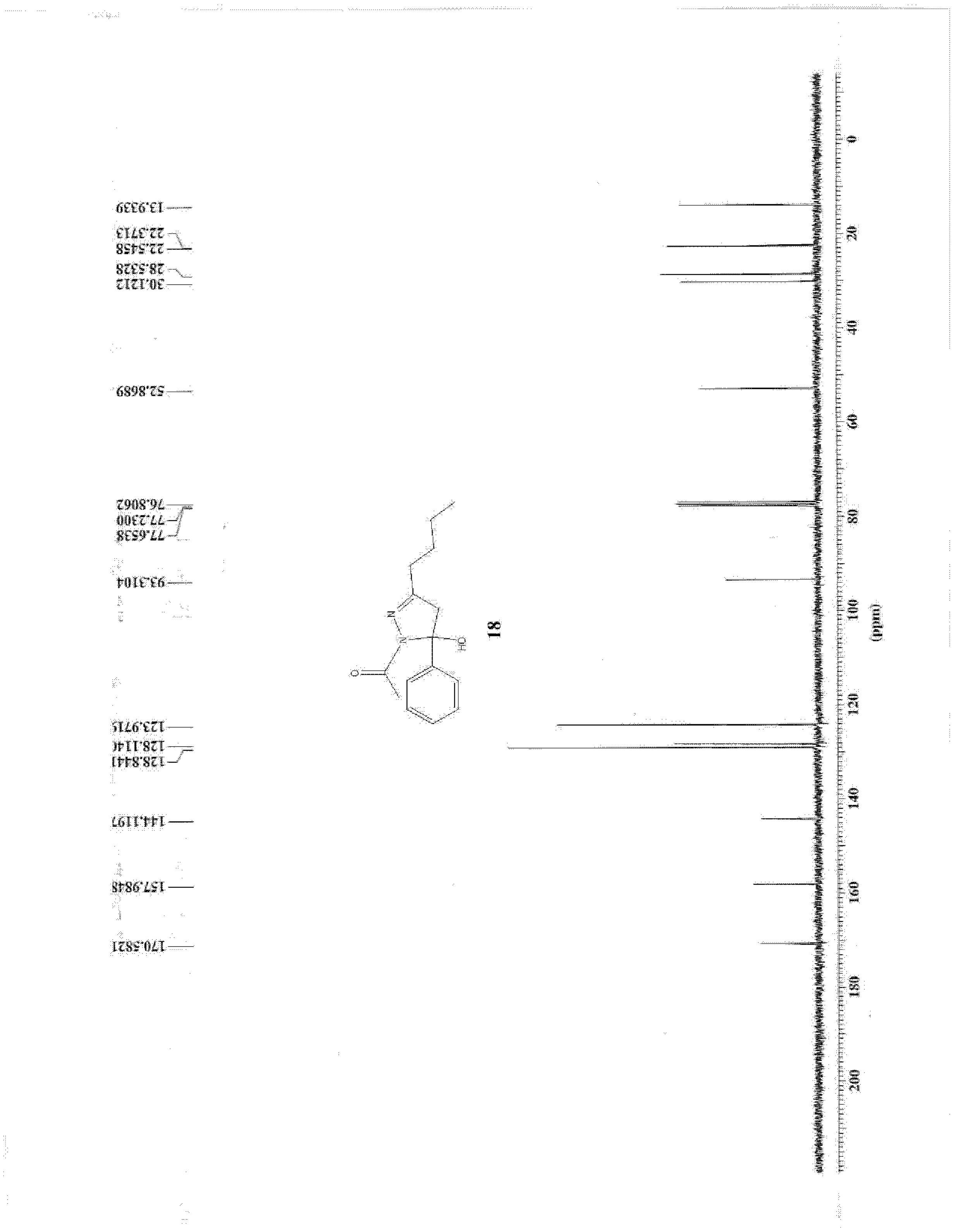
14.4912
22.4980
50.5218
61.4439
94.1497
123.9780
126.4801
128.3605
128.9405
130.0361
131.9923
135.2565
143.5817
151.6454
166.0401
171.0937
CO2Et
N
N
OH
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

17

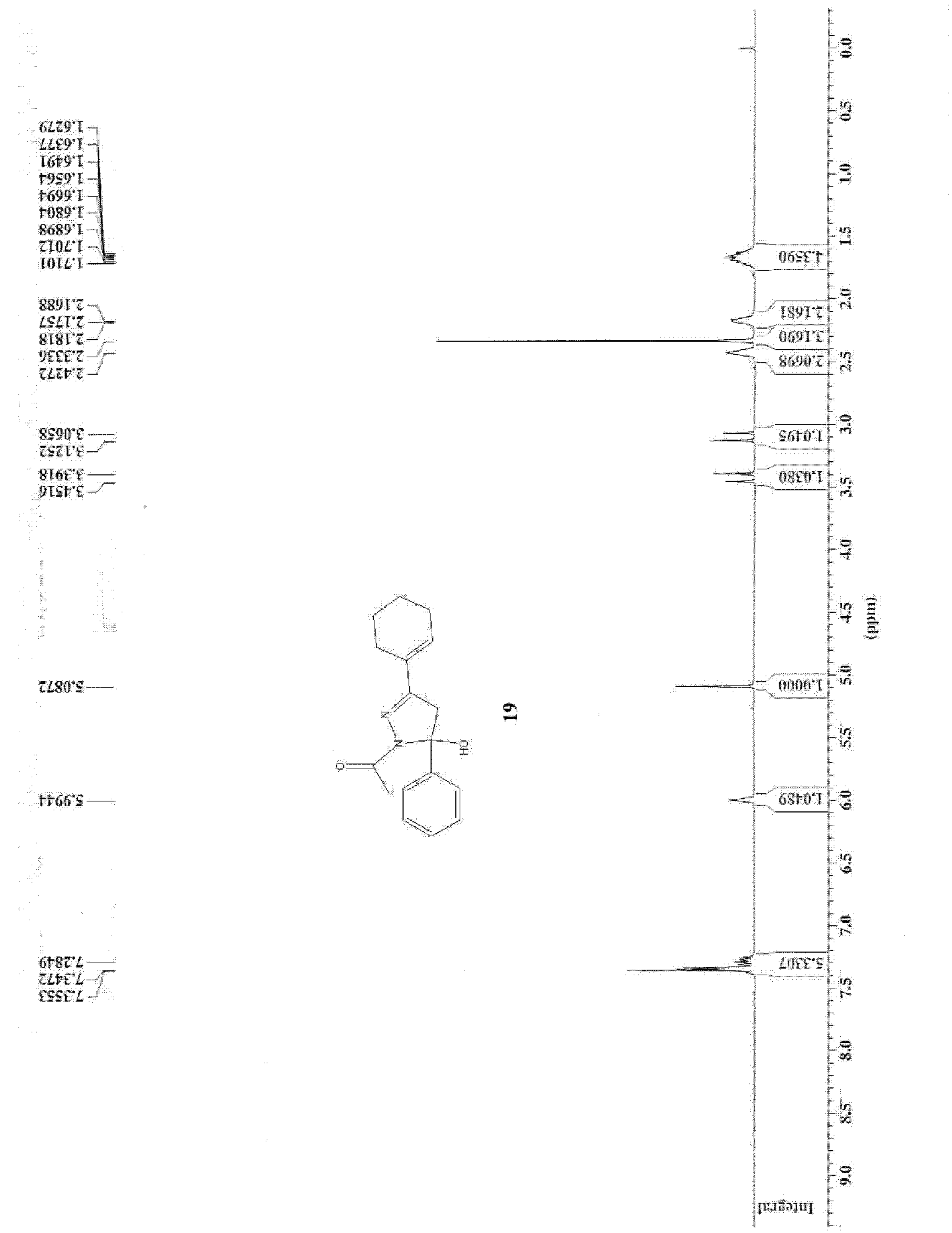


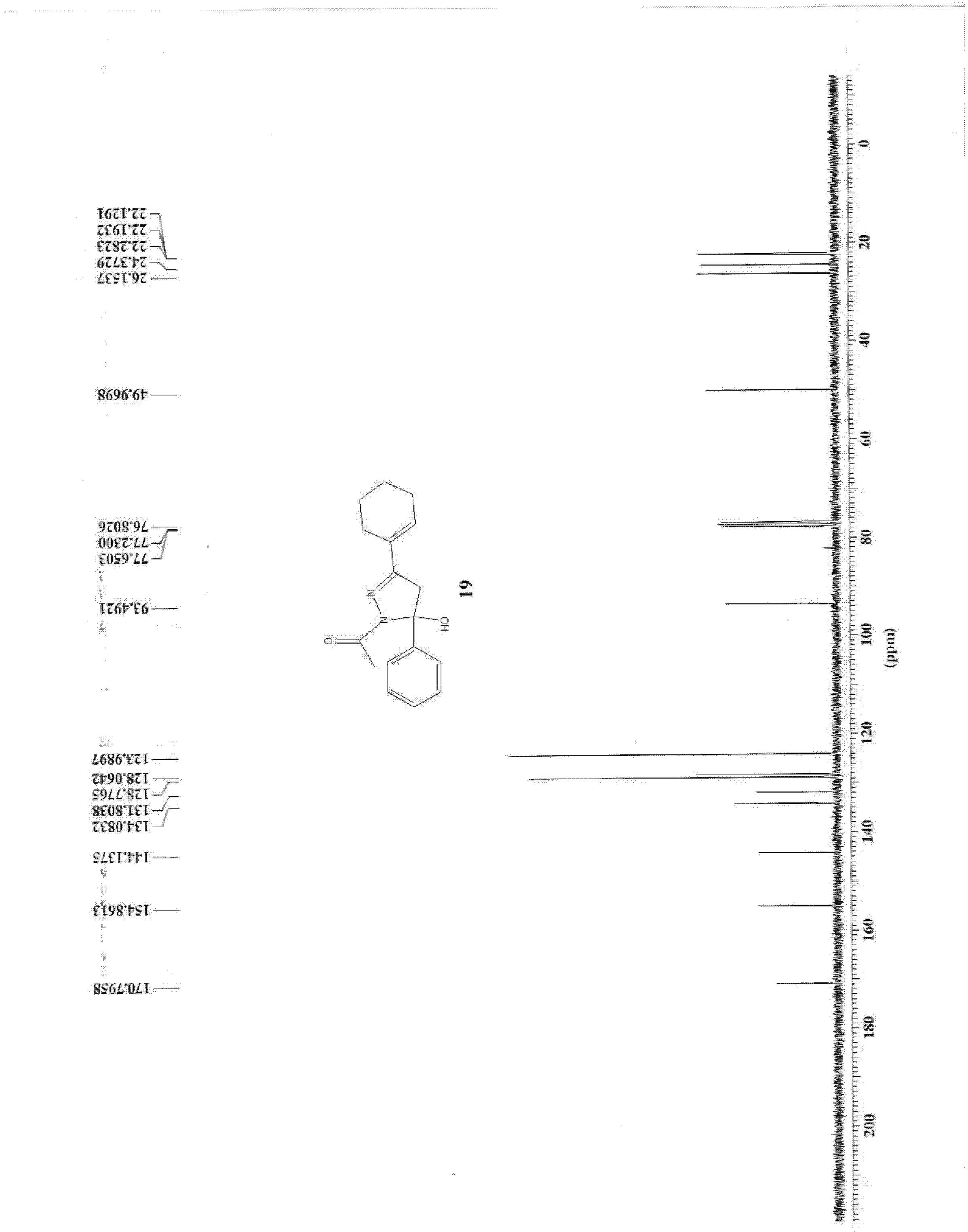
18

7.3578
7.3435
7.3041
7.2915
7.2760
5.1068
3.2957
3.2339
2.9380
2.8761
2.3792
2.3544
2.3279
2.3157
1.5868
1.5591
1.5372
1.5335
1.4212
1.3963
1.3703
1.3467
0.9593
0.9348
0.9108
HO
N
N
O
Integral
4.0993
1.1737
1.0000
1.0572
1.0578
5.2890
2.1472
2.2063
3.1904
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

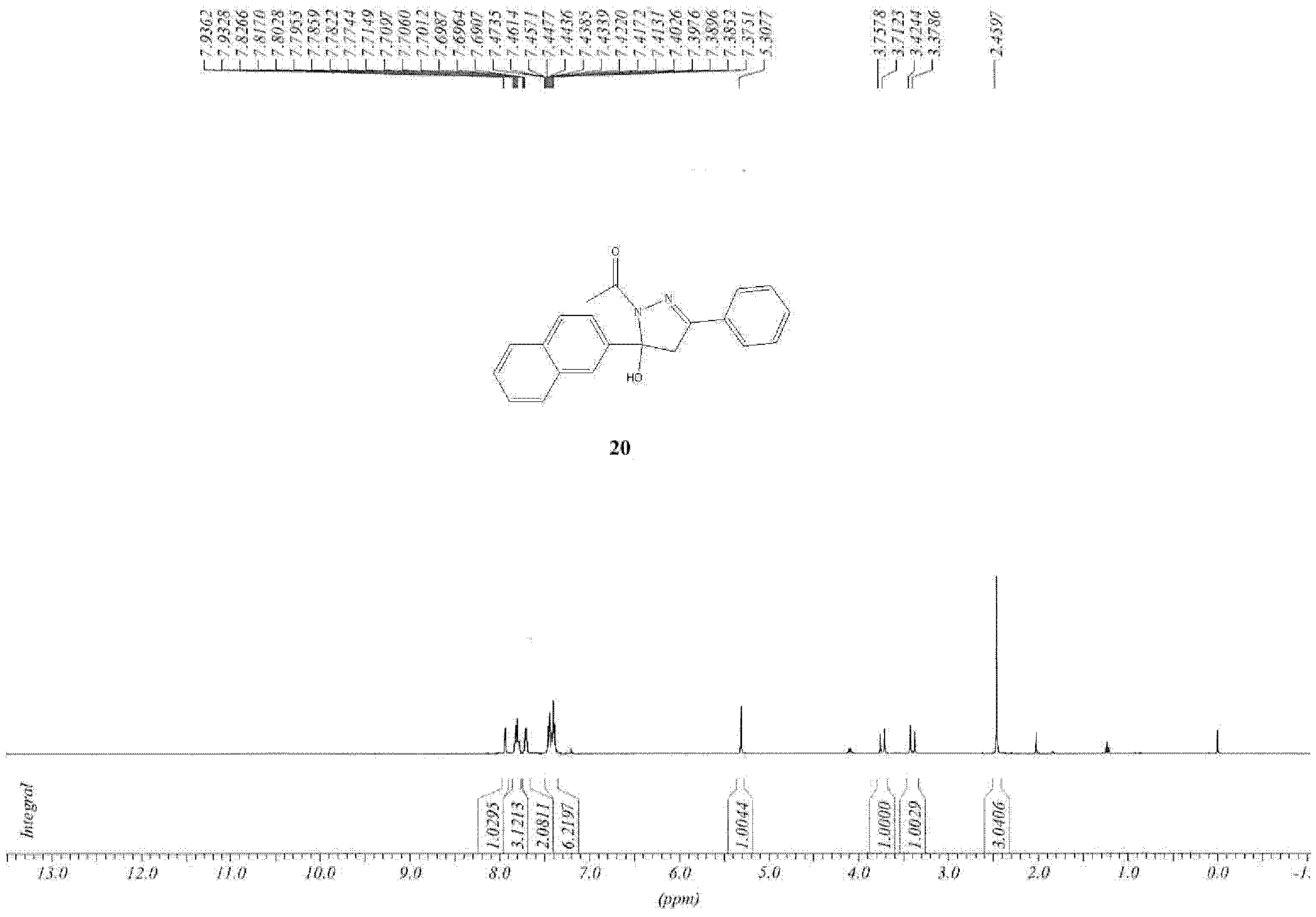

13.9339
22.3713
22.5458
28.5328
30.1212
52.8689
76.8062
77.2300
77.6538
93.3104
123.9715
128.1140
128.8441
144.1197
157.9848
170.5821
0
20
40
60
80
100
120
140
160
180
200
(ppm)
N
N
O
HO

18


7.3553
7.3472
7.2849
5.9944
5.0872
3.4516
3.3918
3.1252
3.0658
2.4372
2.3336
2.1818
2.1757
2.1688
1.7101
1.7012
1.6898
1.6804
1.6694
1.6564
1.6491
1.6377
1.6279
19
OH
N
N
O
5.3307
1.0489
1.0000
1.0380
1.0495
2.0698
3.1690
2.1681
4.3590
Integral
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


22.1291
22.1932
22.2823
24.3729
26.1537
49.9698
76.8026
77.2300
77.6503
93.4921
123.9897
128.0642
128.7765
131.8038
134.0832
144.1375
154.8613
170.7958
O
N
N
OH
0
20
40
60
80
100
120
140
160
180
200
(ppm)

19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7.8266
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7.8028
7.7955
7.7859
7.7822
7.7744
7.7149
7.7097
7.7060
7.7012
7.6987
7.6964
7.6907
7.4735
7.4614
7.4571
7.4477
7.4436
7.4385
7.4339
7.4220
7.4172
7.4131
7.4026
7.3976
7.3896
7.3852
7.3751
5.3077
3.7578
3.7123
3.4244
3.3786
2.4597
HO
N
N
O
Integral
1.0295
3.1213
2.0811
6.2197
1.0044
1.0000
1.0029
3.0406
13.0
12.0
11.0
10.0
9.0
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7.0
6.0
5.0
4.0
3.0
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1.0
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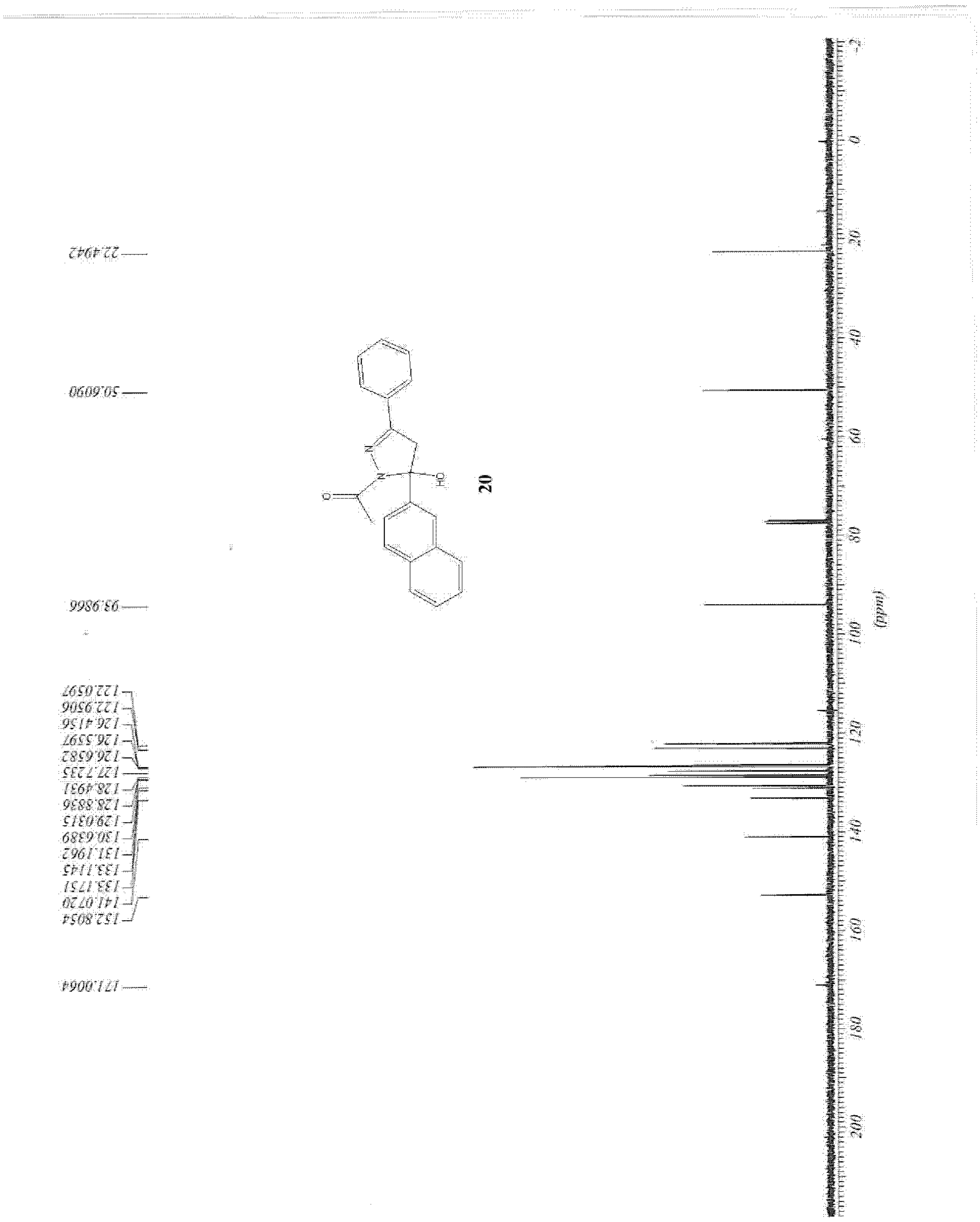
-1.
(ppm)

20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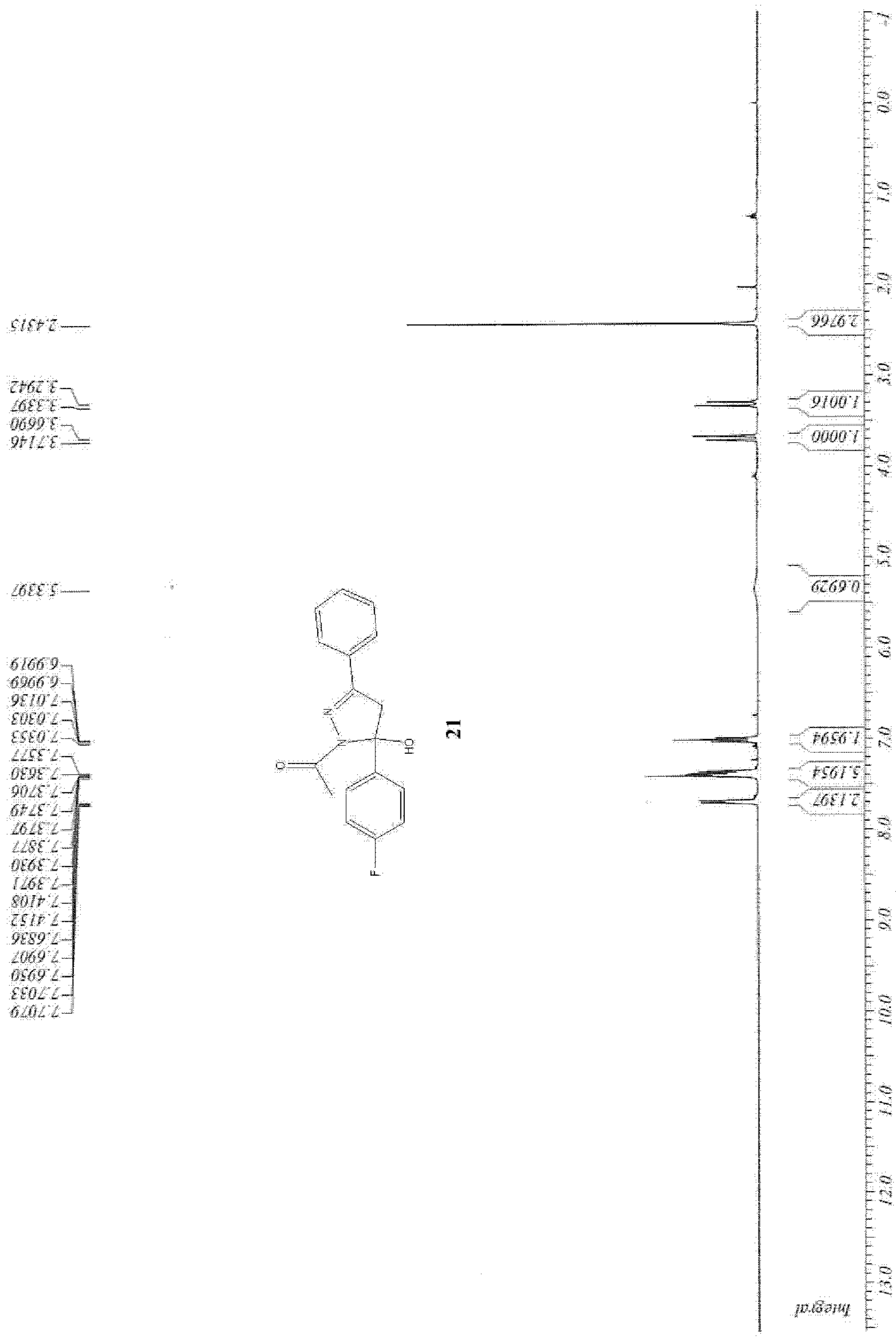
50.6090
93.9866
122.0597
122.9506
126.4156
126.5597
126.6582
127.7235
128.4931
128.8836
129.0315
130.6389
131.1962
133.1145
133.1751
141.0720
152.8054
171.0064
N
N
OH
O
-2
0
20
40
60
80
100
120
140
160
180
200
(ppm)

20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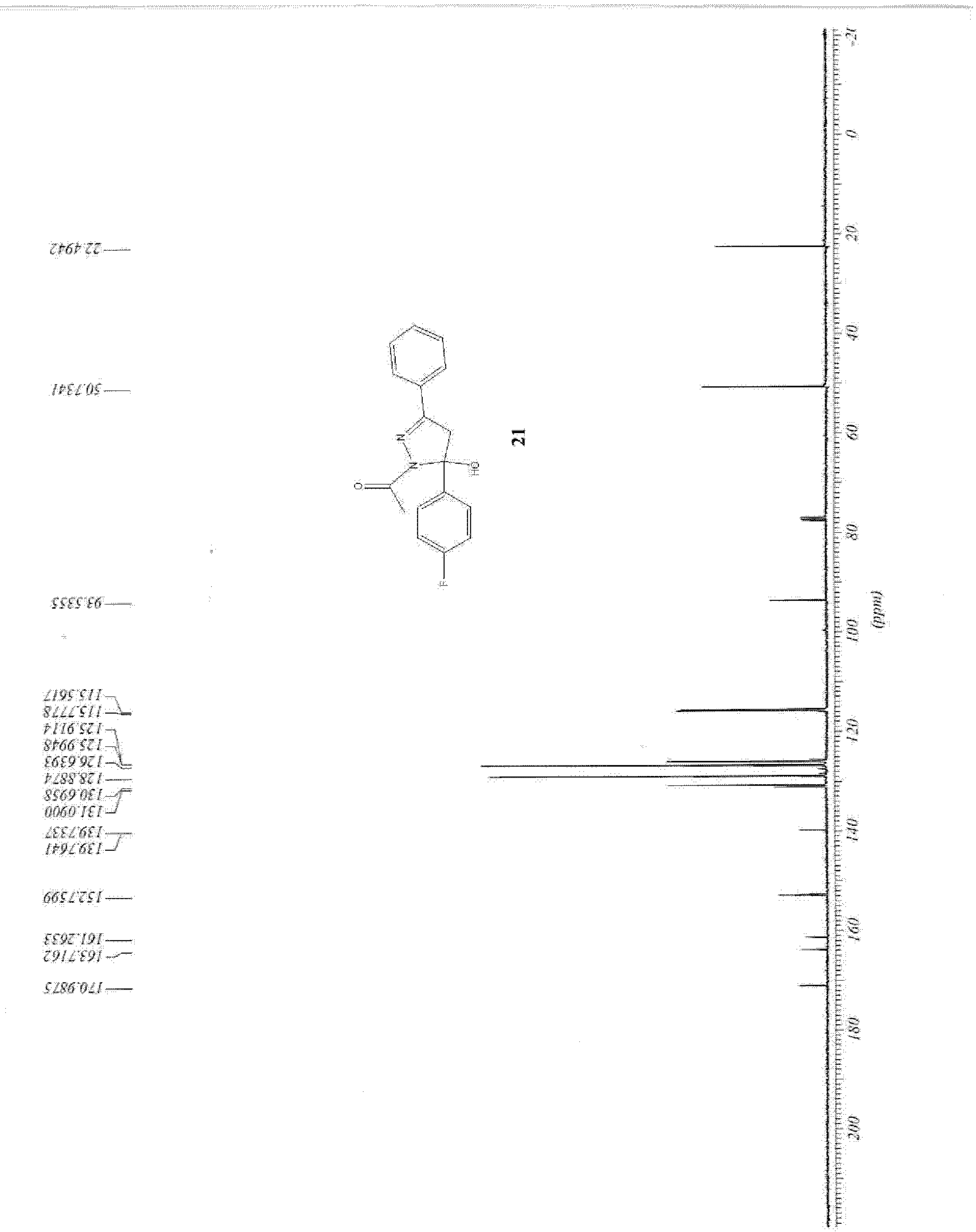
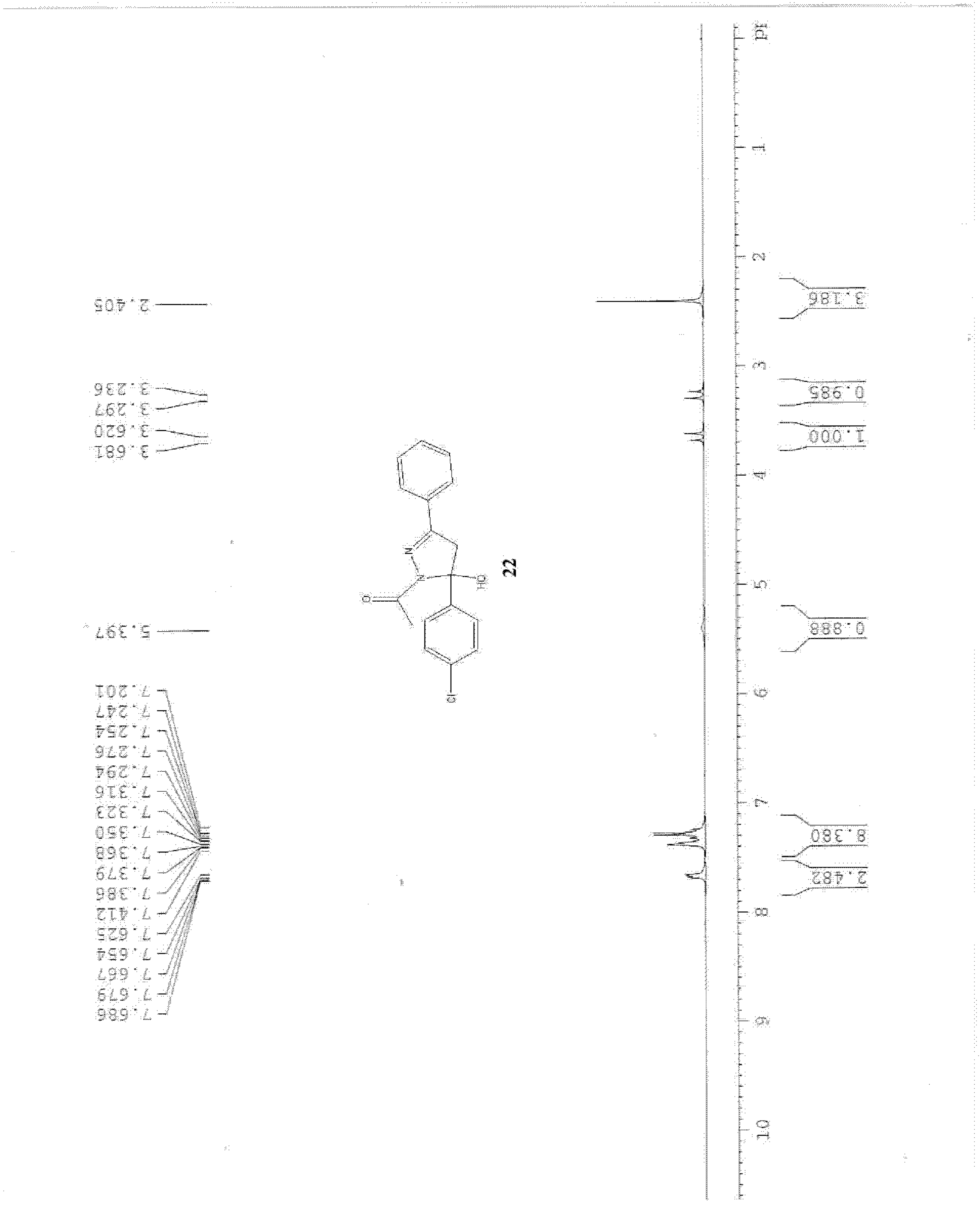
3.2942
3.3397
3.6690
3.7146
5.3397
6.9919
6.9969
7.0136
7.0303
7.0353
7.3577
7.3630
7.3706
7.3749
7.3797
7.3877
7.3930
7.3971
7.4108
7.4152
7.6836
7.6907
7.6950
7.7033
7.7079
N
O
HO
F
2.9766
1.0016
1.0000
0.6929
1.9594
5.1954
2.1397
Integral
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

21



21

22.4942
50.7341
93.5355
115.5617
115.7778
125.9114
125.9948
126.6393
128.8874
130.6958
131.0900
139.7337
139.7641
152.7599
161.2633
163.7162
170.9875
N
N
O
OH
F
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)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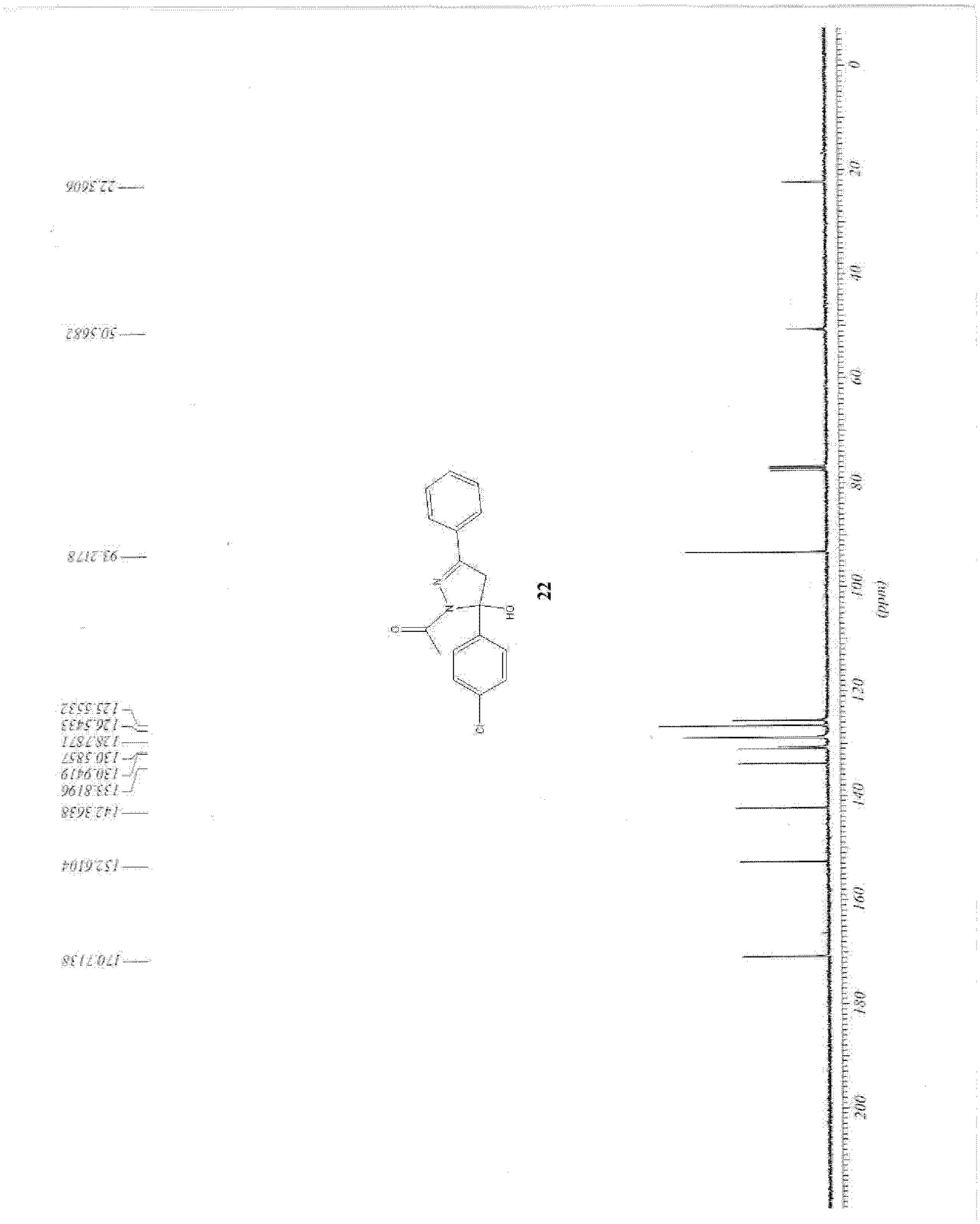
3.236
3.297
3.620
3.681
5.397
7.201
7.247
7.254
7.276
7.294
7.316
7.323
7.350
7.368
7.379
7.386
7.412
7.625
7.654
7.667
7.679
7.686
Cl
N
N
O
HO
3.186
0.985
1.000
0.888
8.380
2.482
1
2
3
4
5
6
7
8
9
10
ppm

22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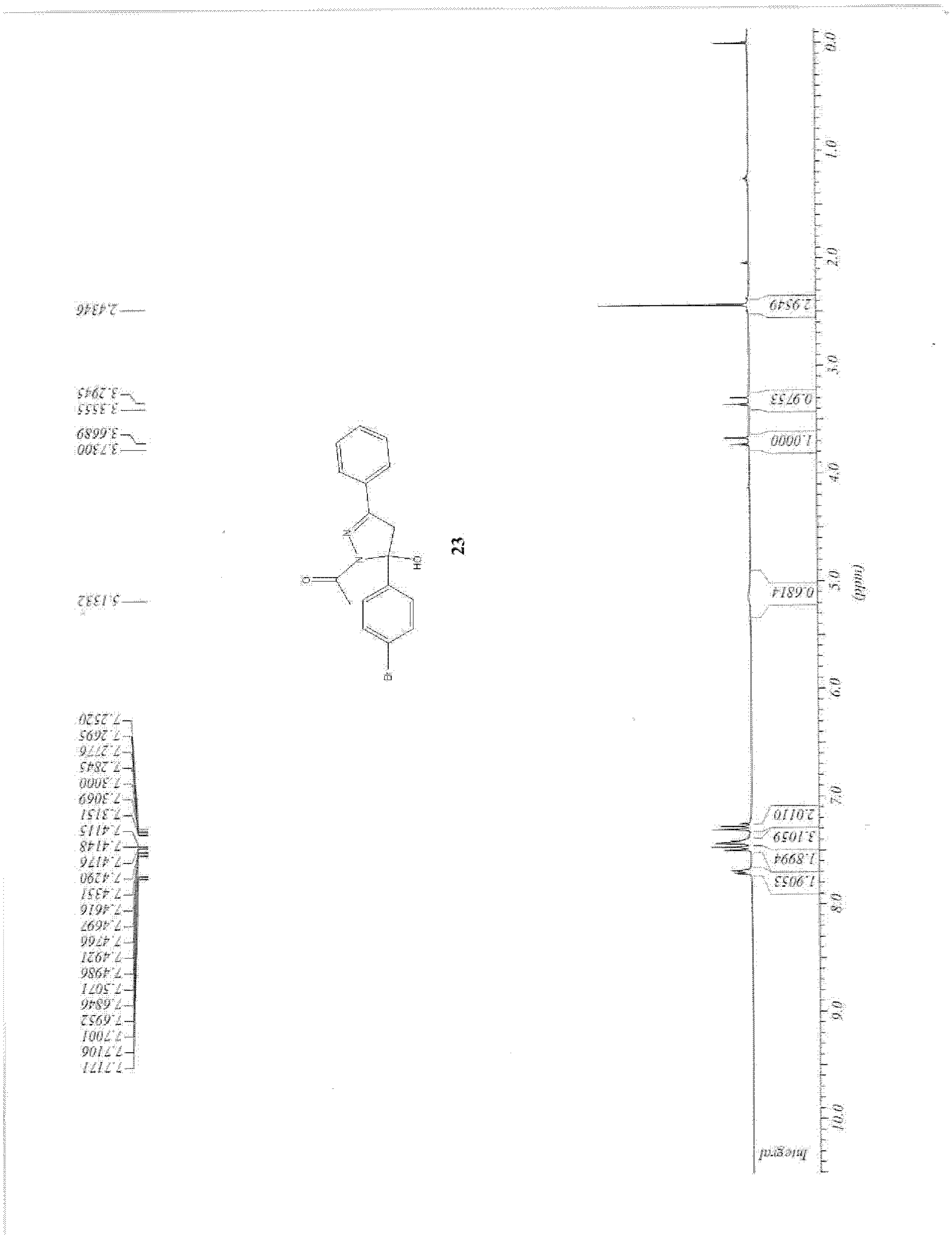
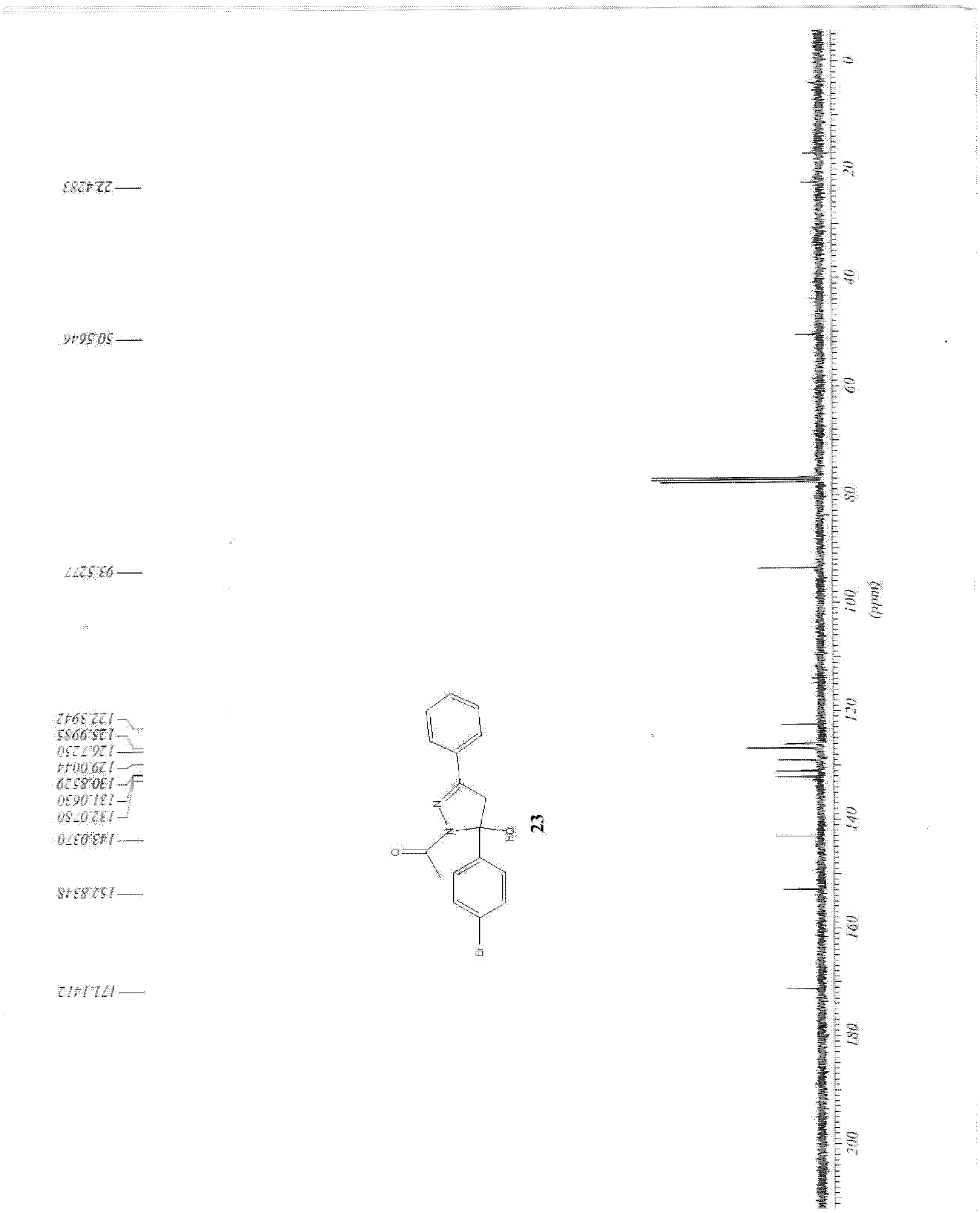
50.5682
93.2178
125.5532
126.5433
128.7871
130.5857
130.9419
133.8196
142.3638
152.6104
170.7138
Cl
N
N
O
HO
0
20
40
60
80
100
120
140
160
180
200
(ppm)

22


23
2.4346
3.2945
3.3555
3.6689
3.7300
5.1332
7.2520
7.2695
7.2776
7.2845
7.3000
7.3069
7.3151
7.4115
7.4148
7.4176
7.4290
7.4351
7.4616
7.4697
7.4766
7.4921
7.4986
7.5071
7.6846
7.6952
7.7001
7.7106
7.7171
2.9549
0.9753
1.0000
0.6814
2.0110
3.1059
1.8994
1.9053
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
(ppm)
O
N
N
OH
Br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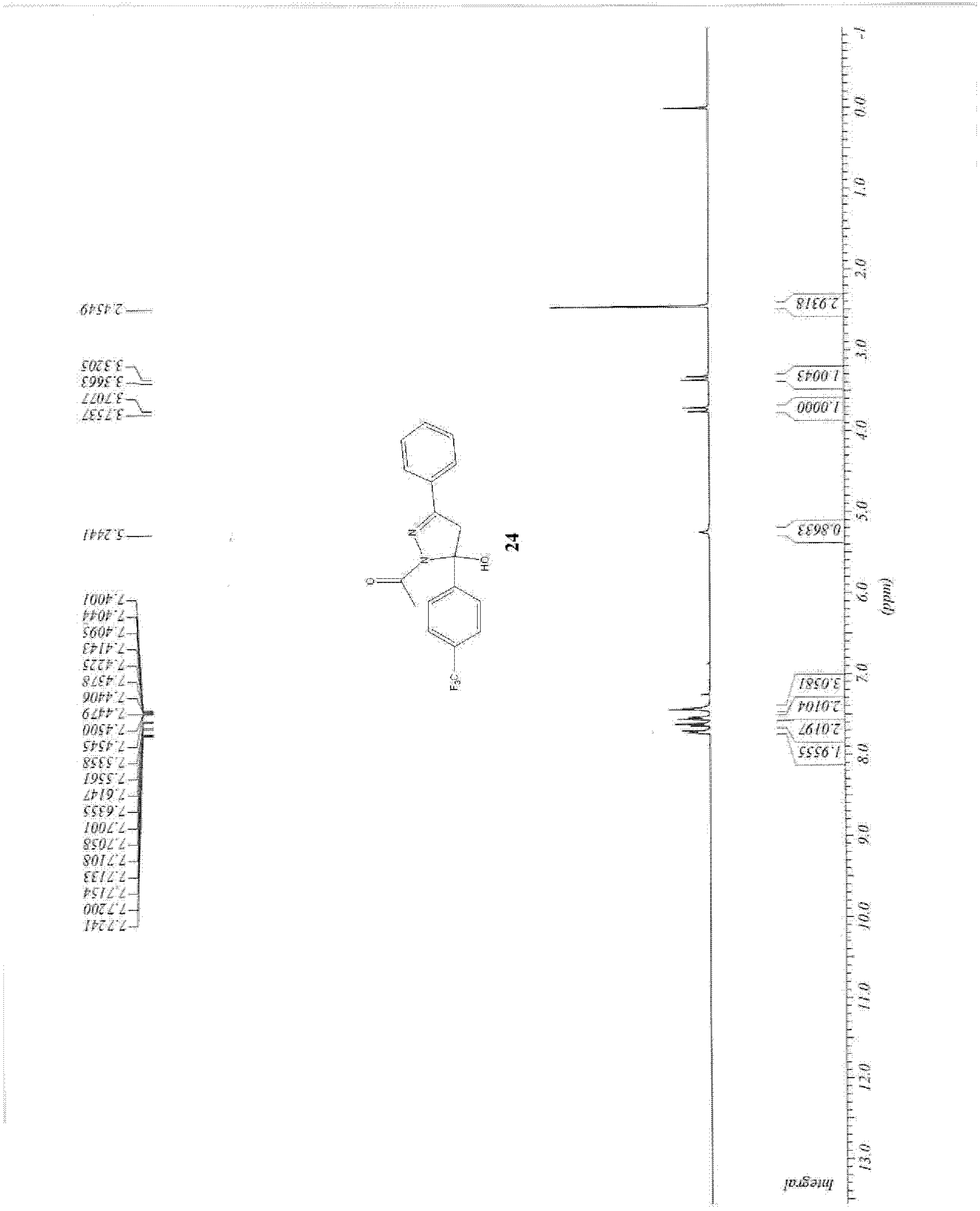
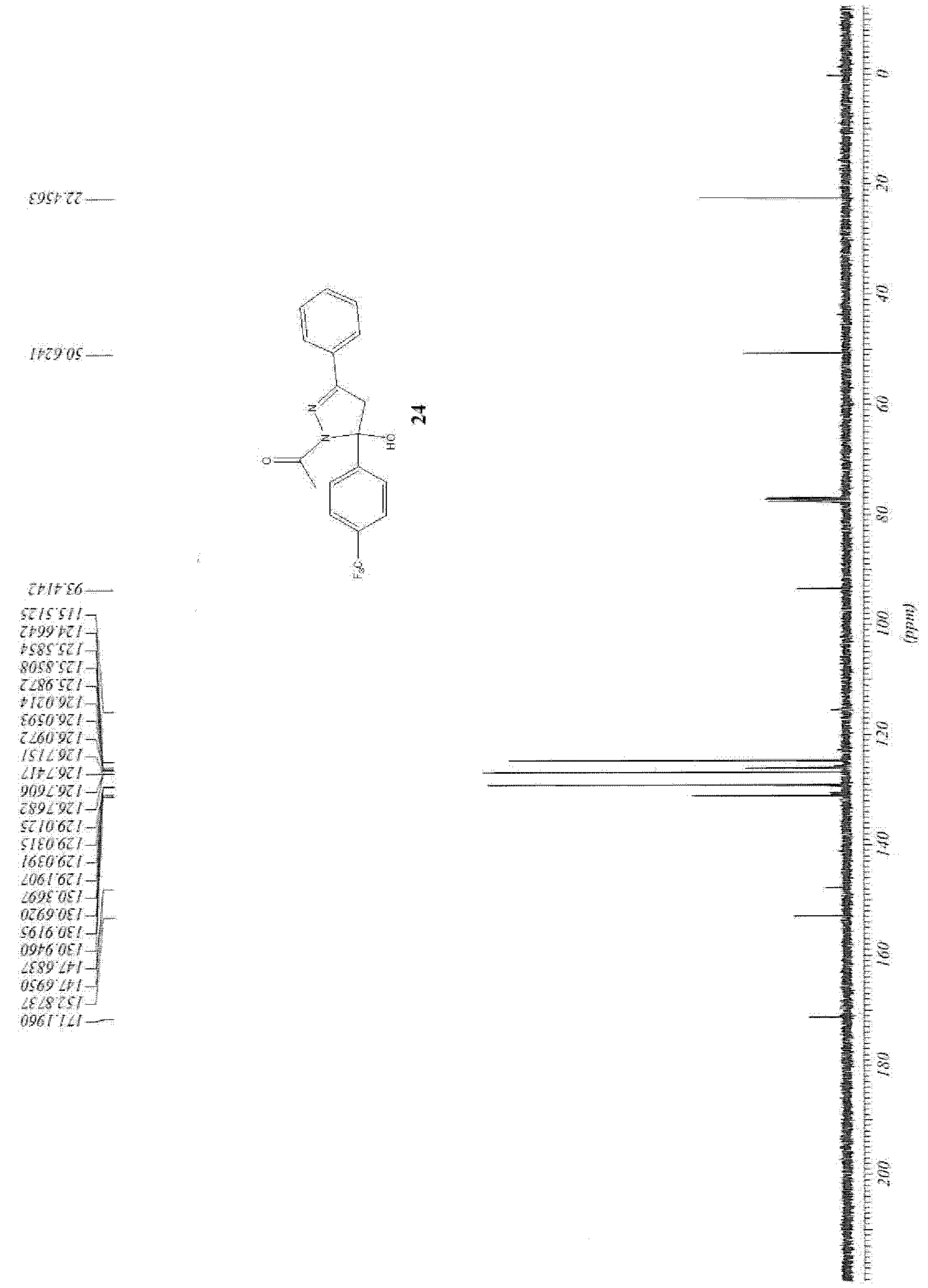
50.5646
93.5277
122.3942
125.9985
126.7250
129.0044
130.8529
131.0630
132.0780
143.0370
152.8348
171.1412
N
N
O
HO
Br
0
20
40
60
80
100
120
140
160
180
200
(ppm)

23


2.4549
3.3205
3.3663
3.7077
3.7537
5.2441
7.4001
7.4044
7.4095
7.4143
7.4225
7.4378
7.4406
7.4479
7.4500
7.4545
7.5358
7.5561
7.6147
7.6355
7.7001
7.7058
7.7108
7.7133
7.7154
7.7200
7.7241
N
N
O
HO
F3C
2.9318
1.0043
1.0000
0.8633
3.0581
2.0104
2.0197
1.9555
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral

24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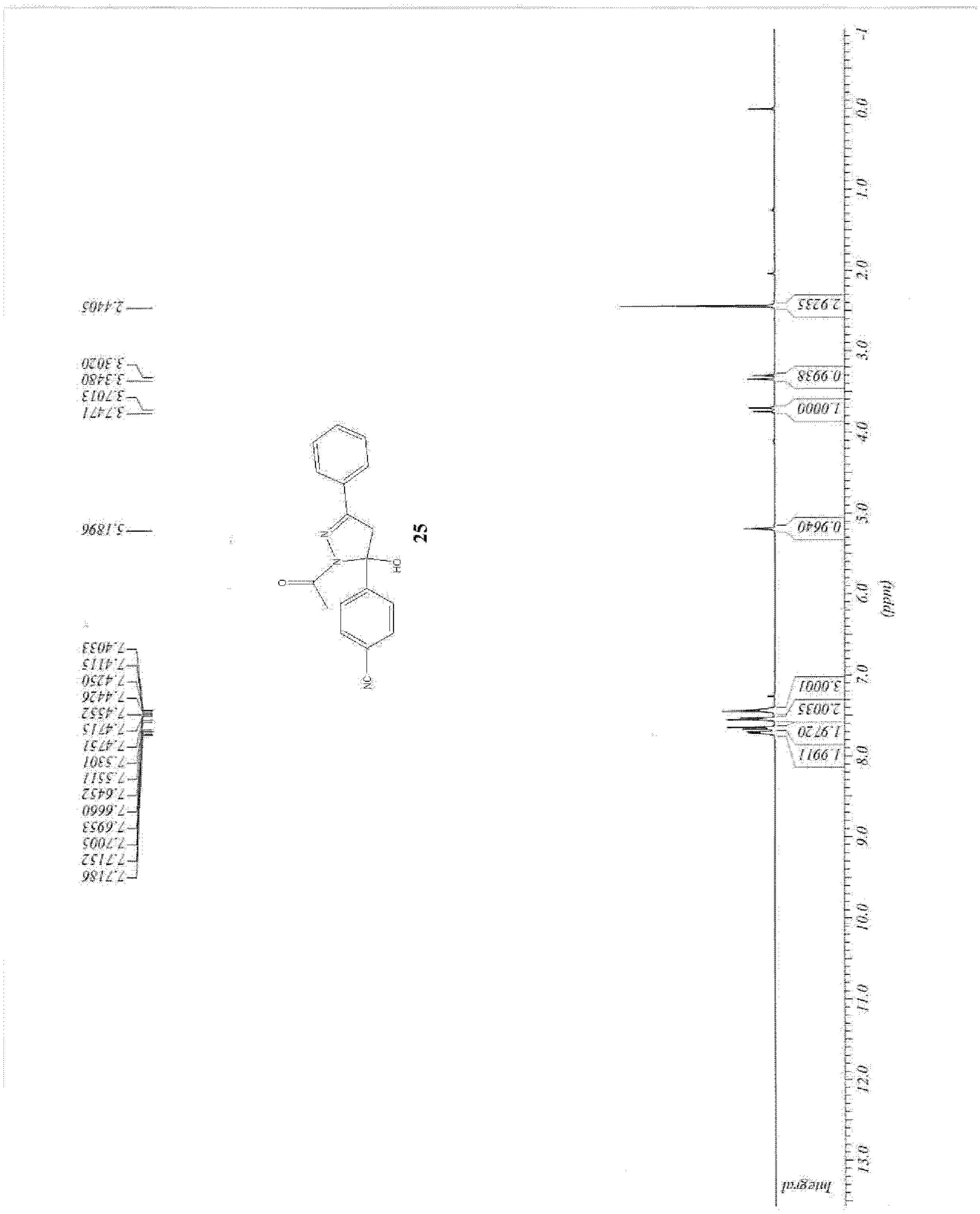
93.4142
115.5125
124.6642
125.5854
125.8508
125.9872
126.0214
126.0593
126.0972
126.7151
126.7417
126.7606
126.7682
129.0125
129.0315
129.0391
129.1907
130.3697
130.6920
130.9195
130.9460
147.6837
147.6950
152.8737
171.1960
N
N
O
HO
F3C
24
0
20
40
60
80
100
120
140
160
180
200
(ppm)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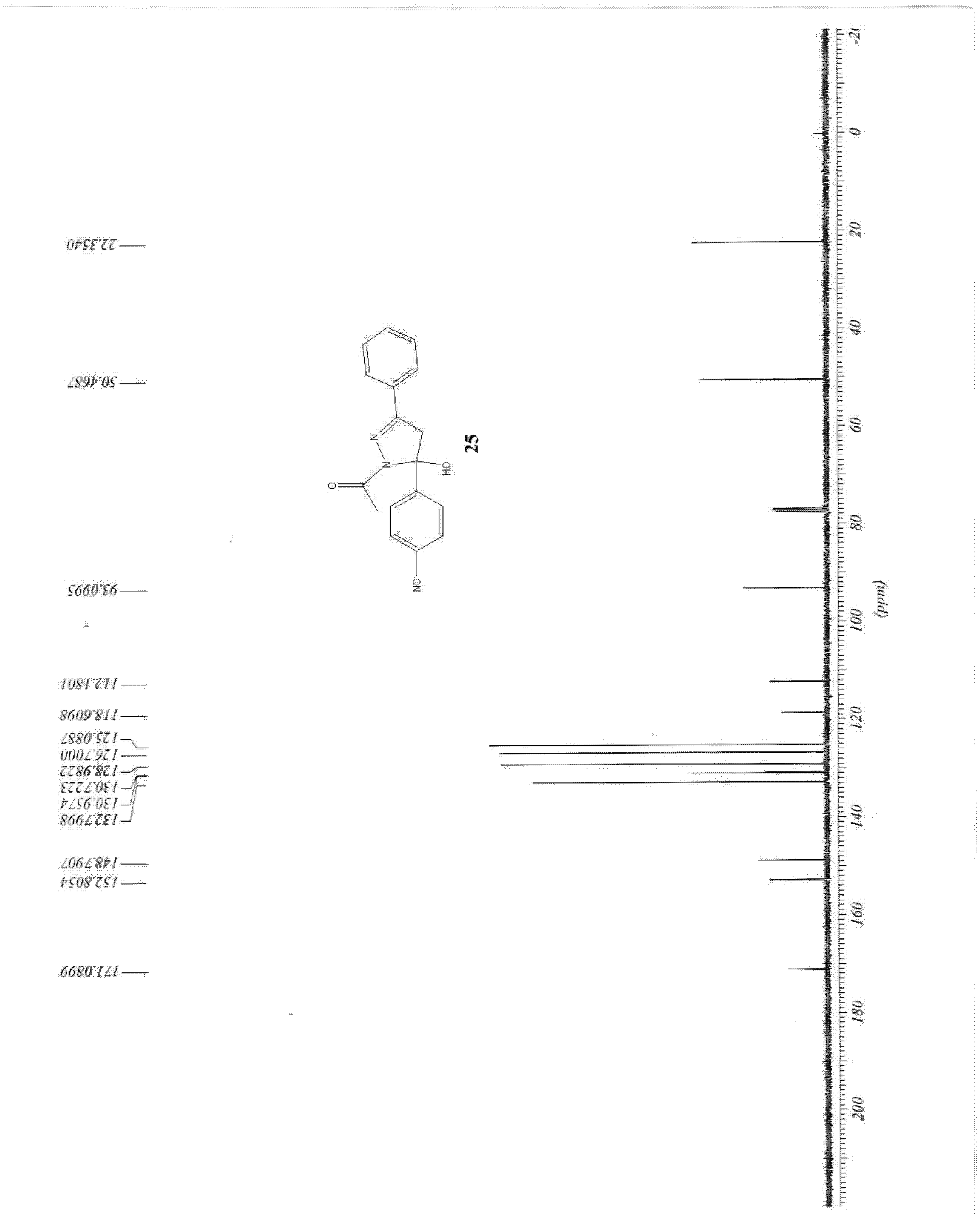
3.3020
3.3480
3.7013
3.7471
5.1896
7.4033
7.4115
7.4250
7.4426
7.4552
7.4715
7.4751
7.5301
7.5511
7.6452
7.6660
7.6953
7.7005
7.7152
7.7186
NC
N
N
OH
O
2.9235
0.9938
1.0000
0.9640
3.0001
2.0035
1.9720
1.9911
Integral
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

25



25

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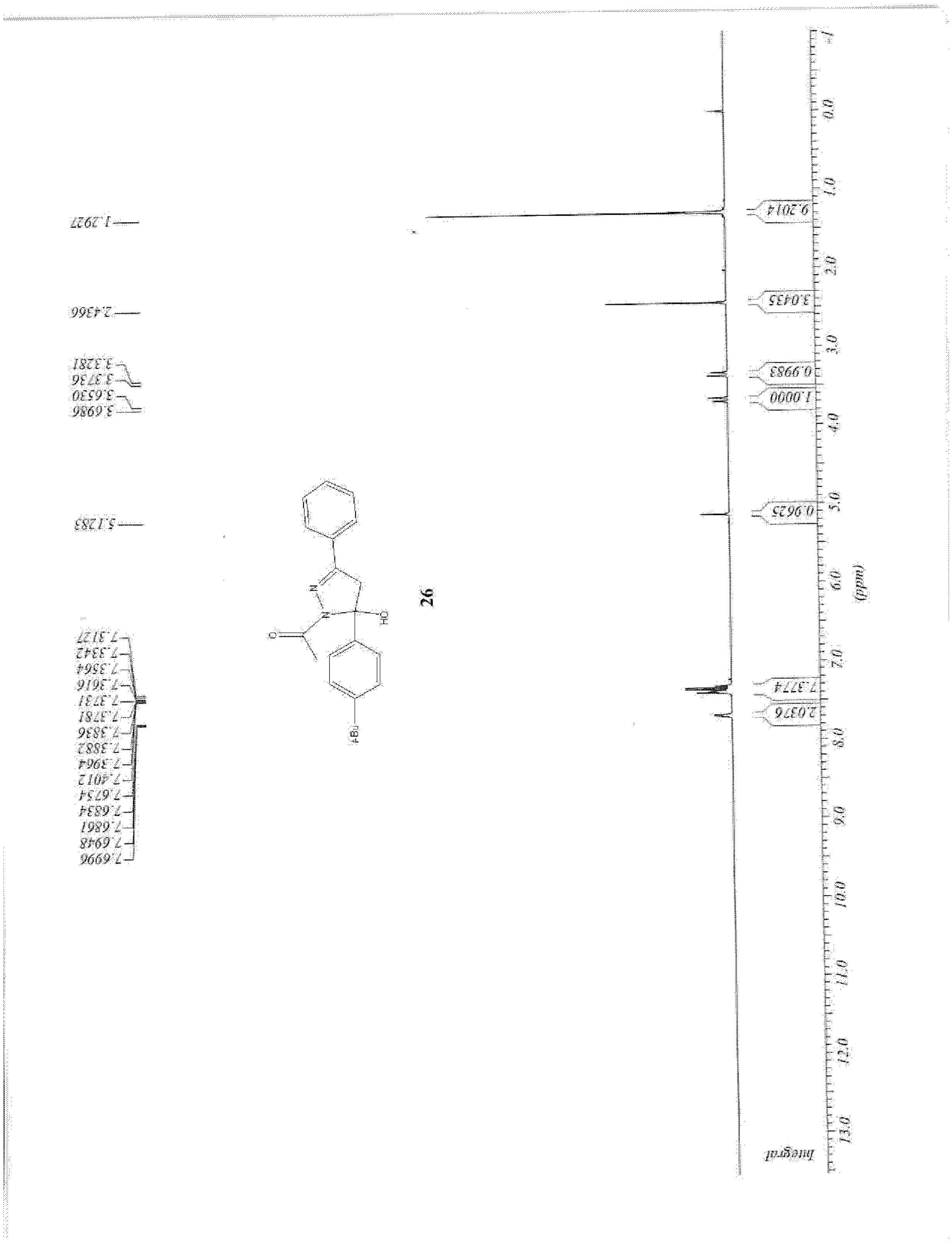
93.0995
112.1801
118.6098
125.0887
126.7000
128.9822
130.7223
130.9574
132.7998
148.7907
152.8054
171.0899
NC
HO
N
N
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)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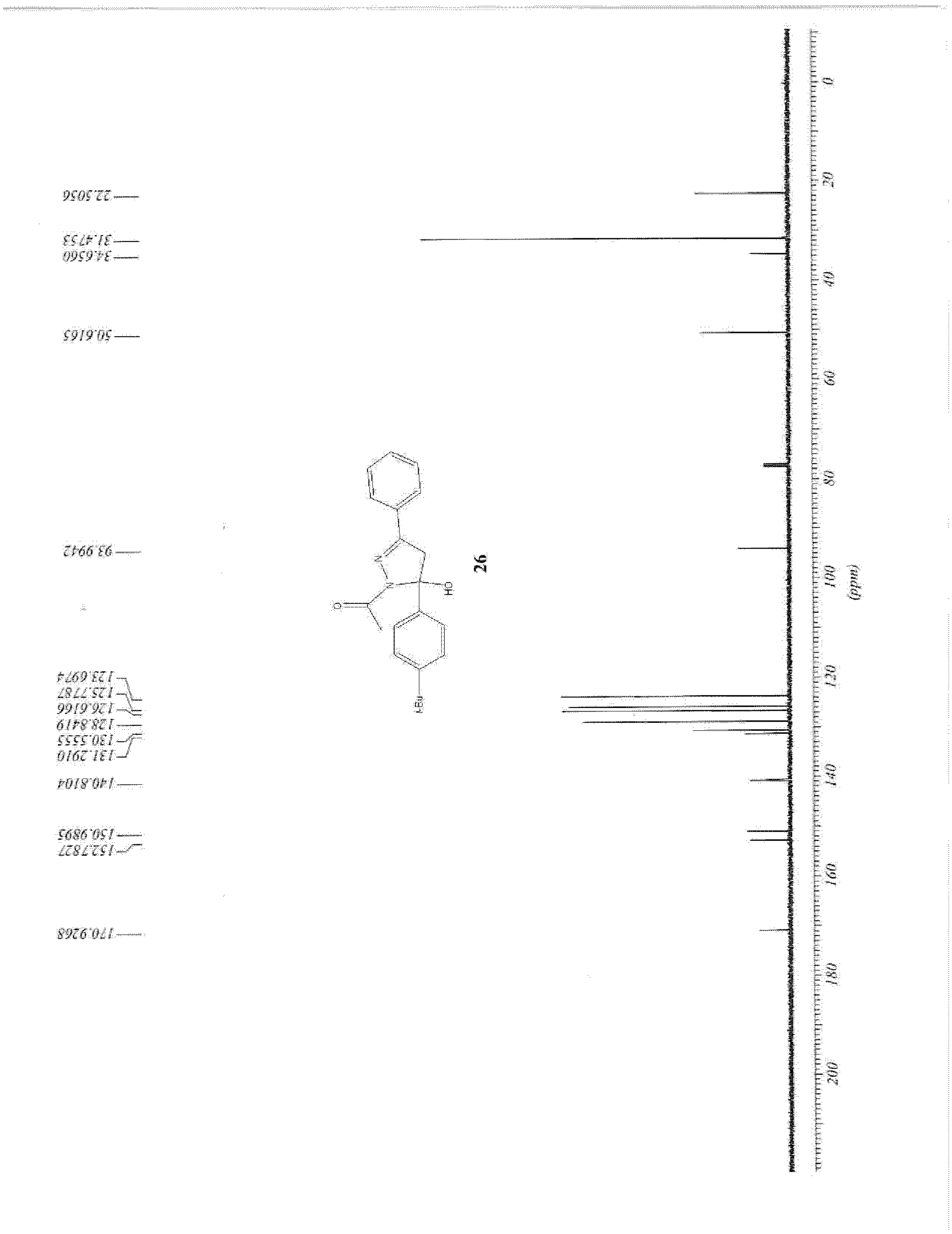
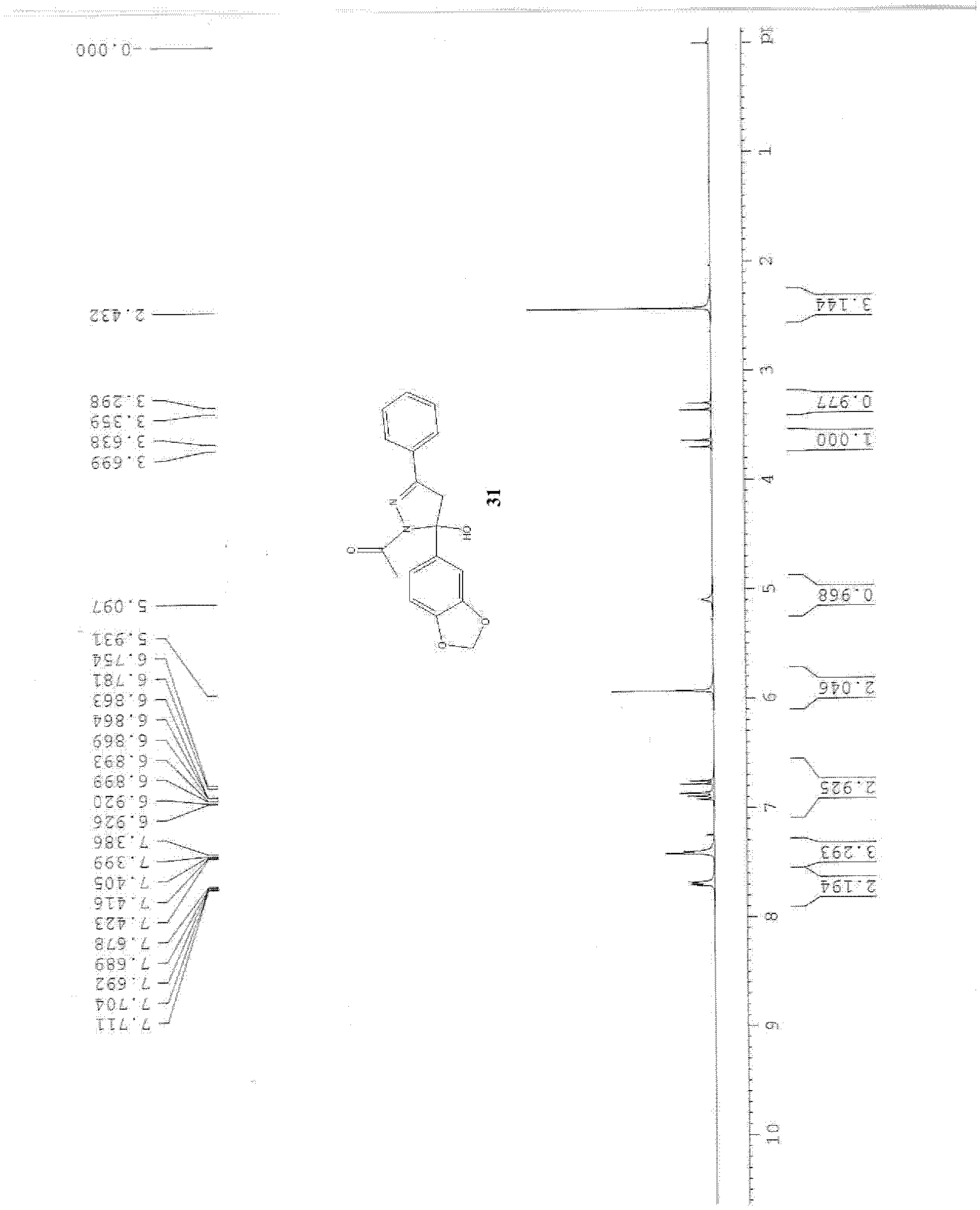
3.3281
3.3736
3.6530
3.6986
5.1283
7.3127
7.3342
7.3564
7.3616
7.3731
7.3781
7.3836
7.3882
7.3964
7.4012
7.6734
7.6834
7.6881
7.6948
7.6996
O
N
N
HO
t-Bu
26
9.2014
3.0435
0.9983
1.0000
0.9625
7.3774
2.0376
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral



26

22.5056
31.4753
34.6560
50.6165
93.9942
123.6974
125.7787
126.6166
128.8419
130.5555
131.2910
140.8104
150.9895
152.7827
170.9268
O
N
N
HO
t-Bu
0
20
40
60
80
100
120
140
160
180
200
(ppm)


31

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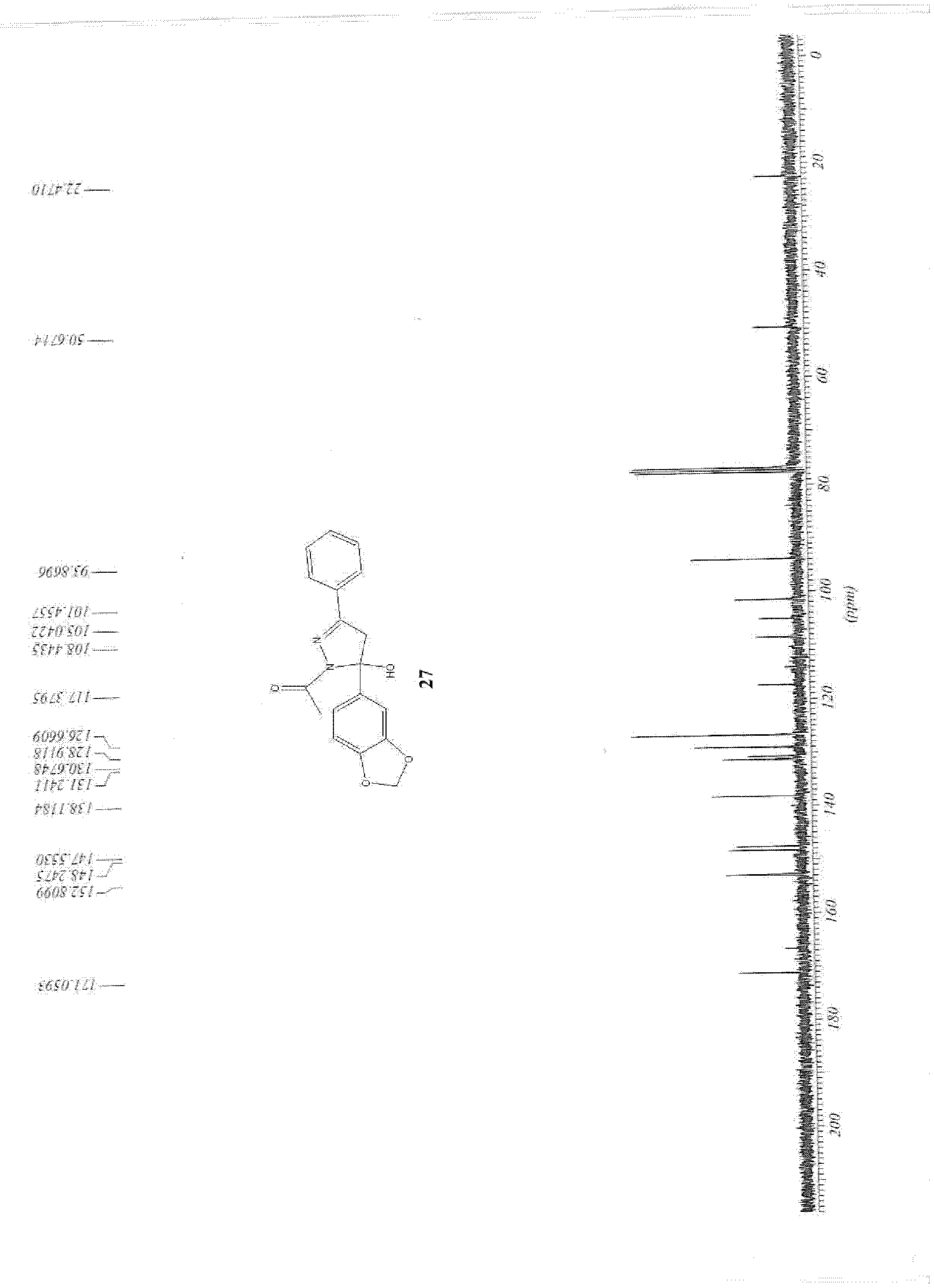
2.432
3.298
3.359
3.638
3.699
5.097
5.931
6.754
6.781
6.863
6.864
6.869
6.893
6.899
6.920
6.926
7.386
7.399
7.405
7.416
7.423
7.678
7.689
7.692
7.704
7.711
3.144
0.977
1.000
0.968
2.046
2.925
3.293
2.194
ppm
1
2
3
4
5
6
7
8
9
10
O
N
N
HO
O
O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117.3795
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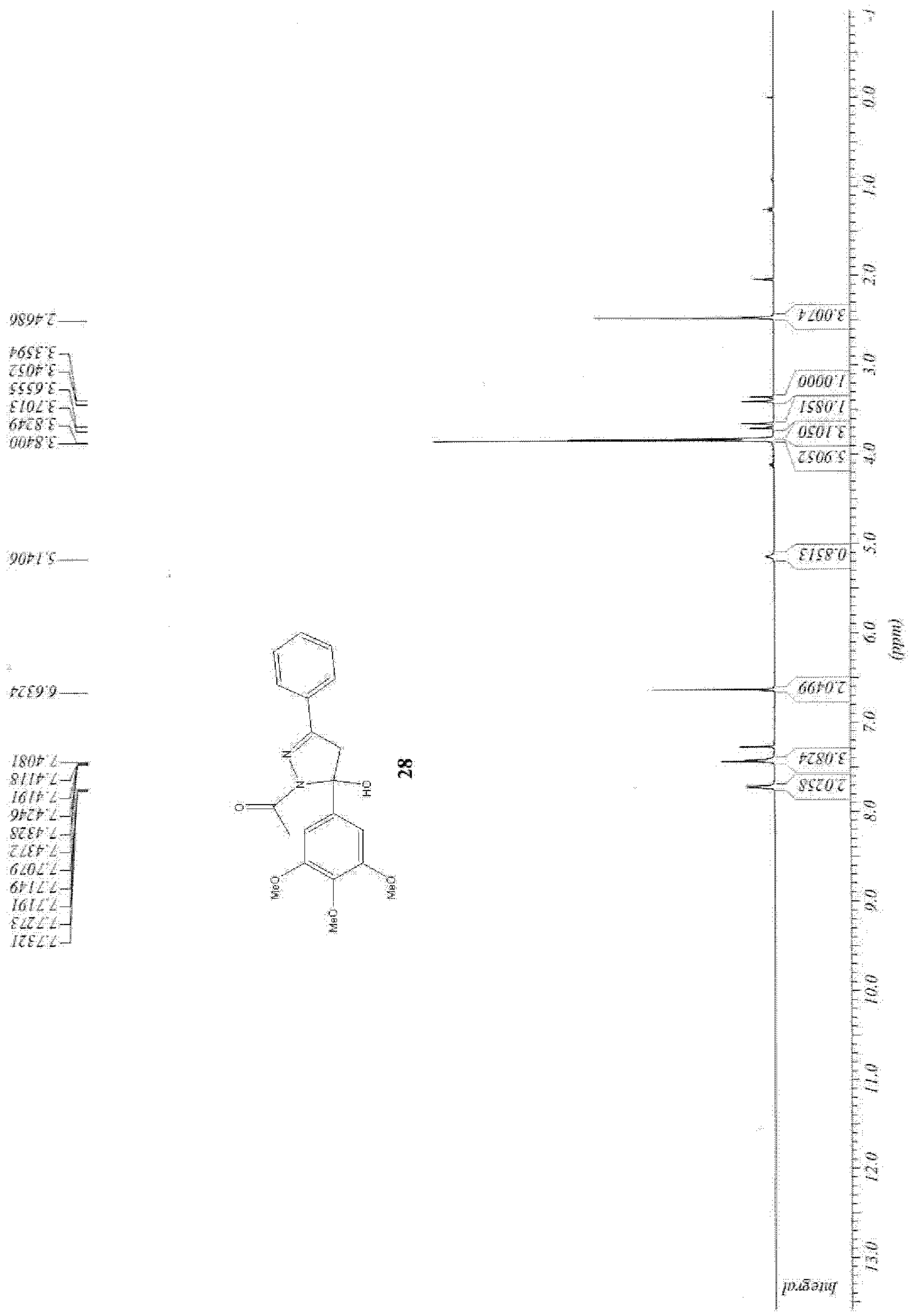
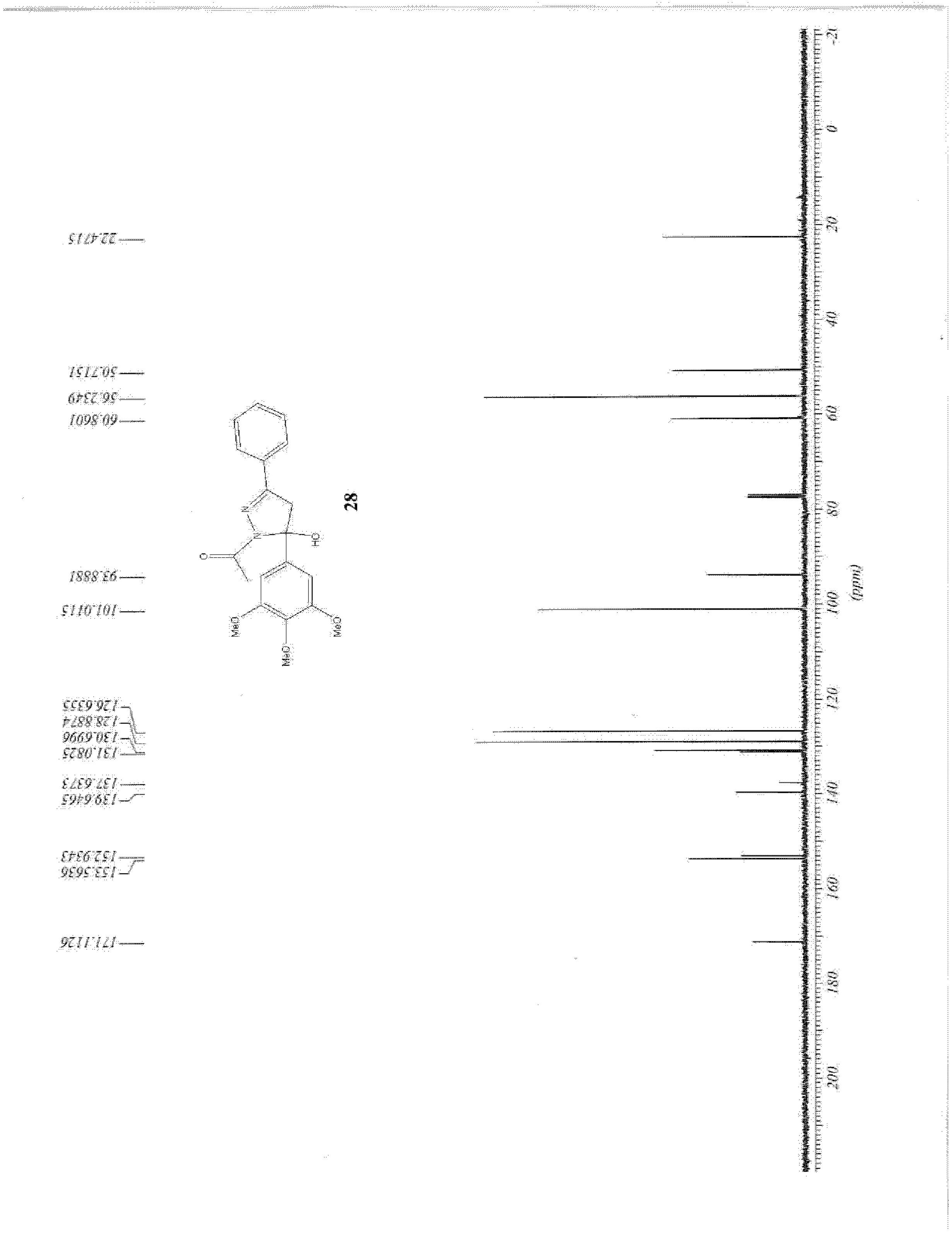
128.9118
130.6748
131.2411
138.1184
147.5530
148.2475
152.8099
171.0593
N
N
O
OH
O
O
0
20
40
60
80
100
120
140
160
180
200
(ppm)

27



28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56.2349
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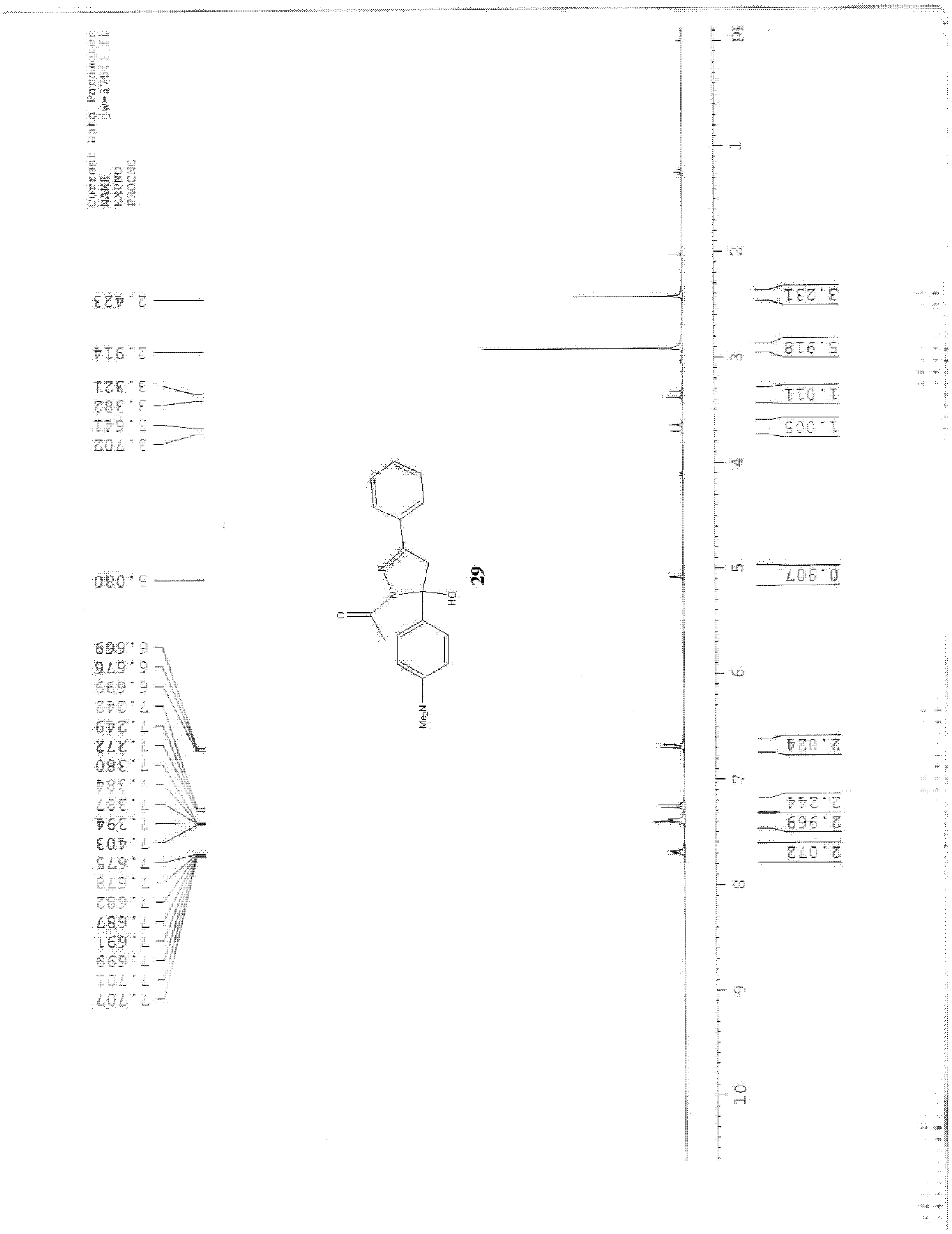
93.8881
101.0115
126.6355
128.8874
130.6996
131.0825
137.6373
139.6465
152.9343
153.5636
171.1126
MeO
MeO
MeO
OH
N
N
O
28
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


Current Data Parameters
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PROCNO
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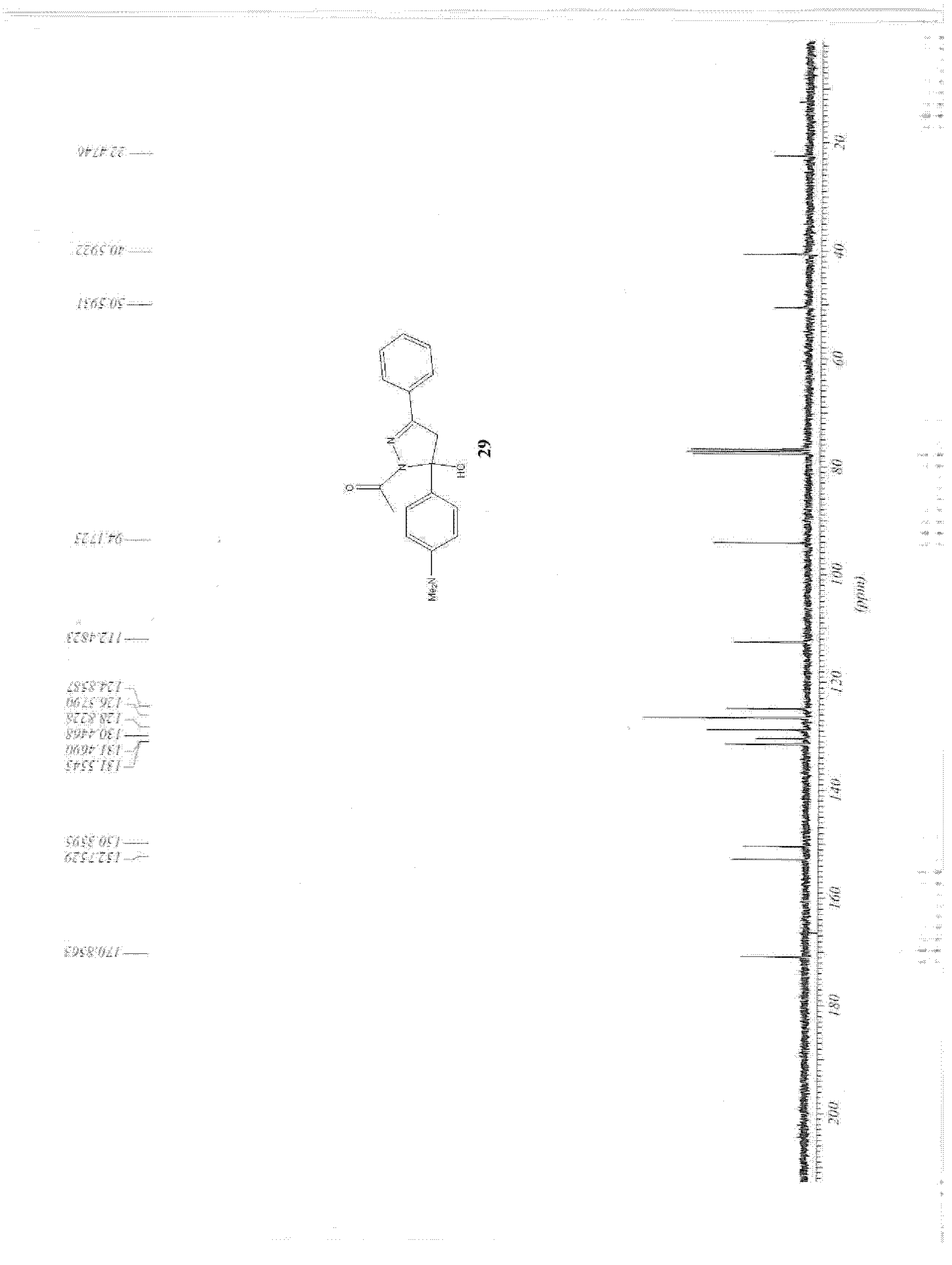
3.321
3.382
3.641
3.702
5.080
6.669
6.676
6.699
7.242
7.249
7.272
7.380
7.384
7.387
7.394
7.403
7.675
7.678
7.682
7.687
7.691
7.699
7.701
7.707
O
N
N
HO
Me2N
3.231
5.918
1.011
1.005
0.907
2.024
2.244
2.969
2.072
1
2
3
4
5
6
7
8
9
10
ppm

29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126.5790
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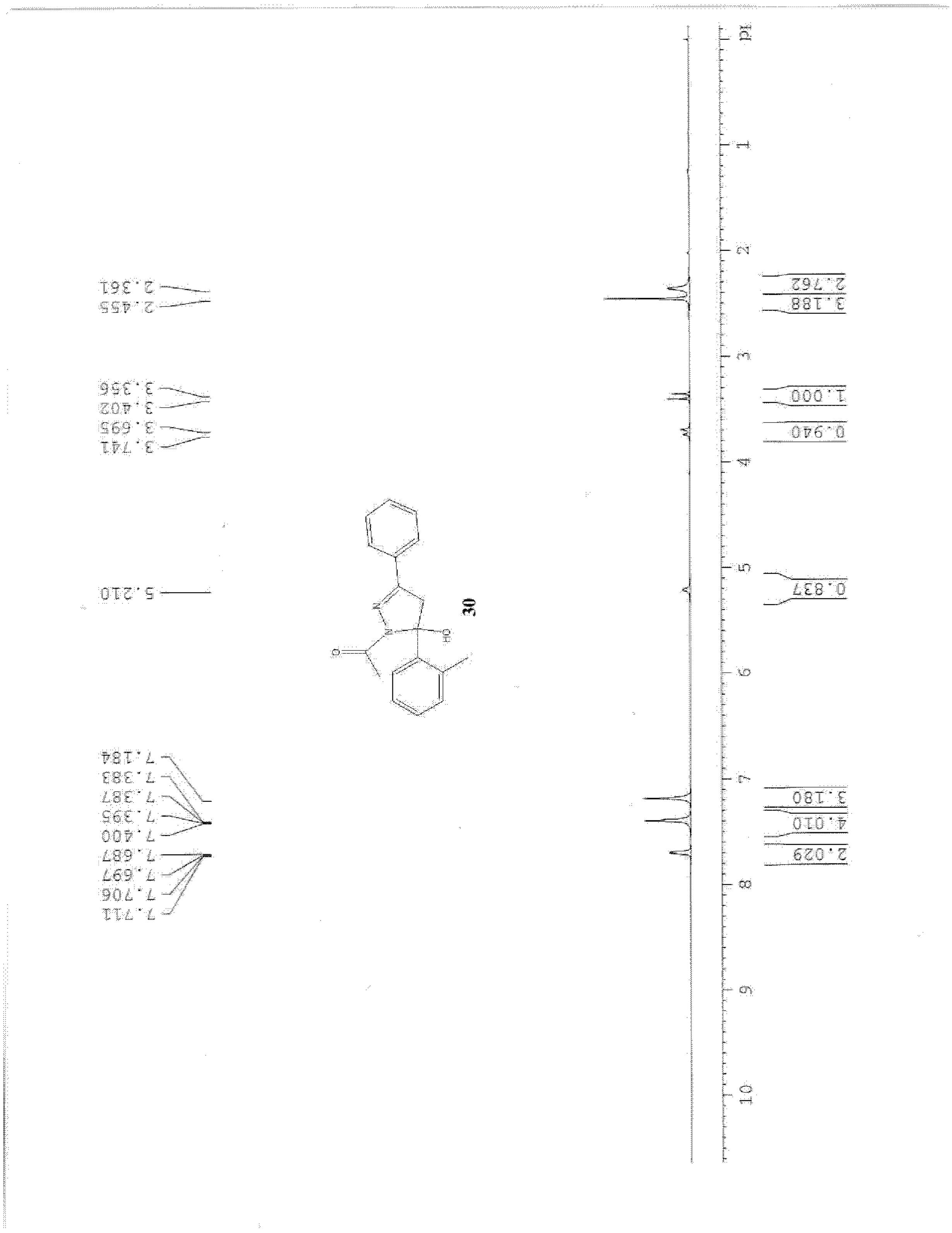
130.4468
131.4690
131.5545
150.3395
152.7529
170.8503
Me2N
HO
N
N
O
20
40
60
80
100
120
140
160
180
200
(ppm)

29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7.184
7.383
7.387
7.395
7.400
7.687
7.697
7.706
7.711
30
2.762
3.188
1.000
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4.010
2.029
0
1
2
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4
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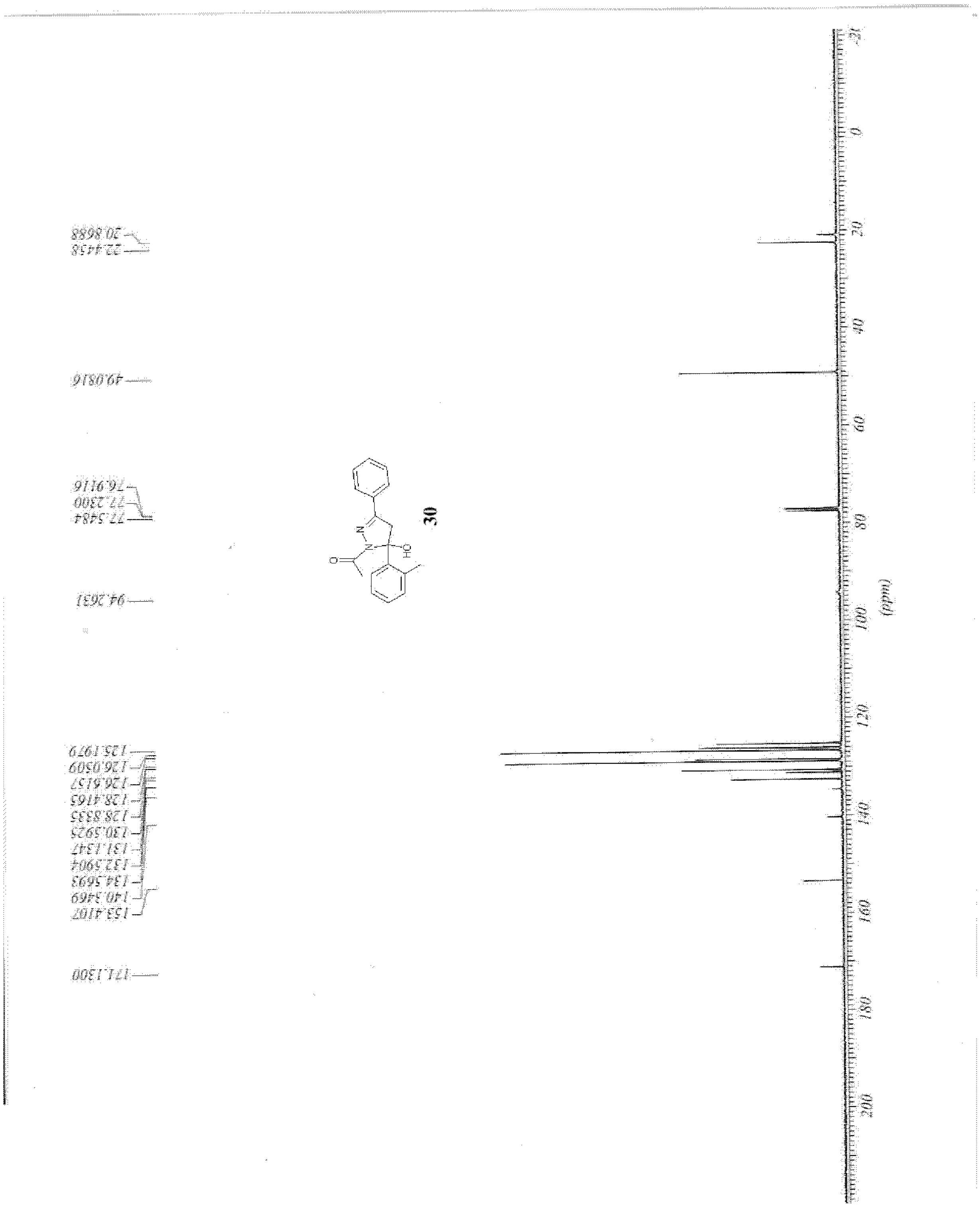
6
7
8
9
10
pl



30

20.8688
22.4458
49.0816
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77.2300
77.5484
94.2631
125.1979
126.0509
126.6157
128.4165
128.8335
130.5925
131.1347
132.5904
134.5693
140.5469
153.4107
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N
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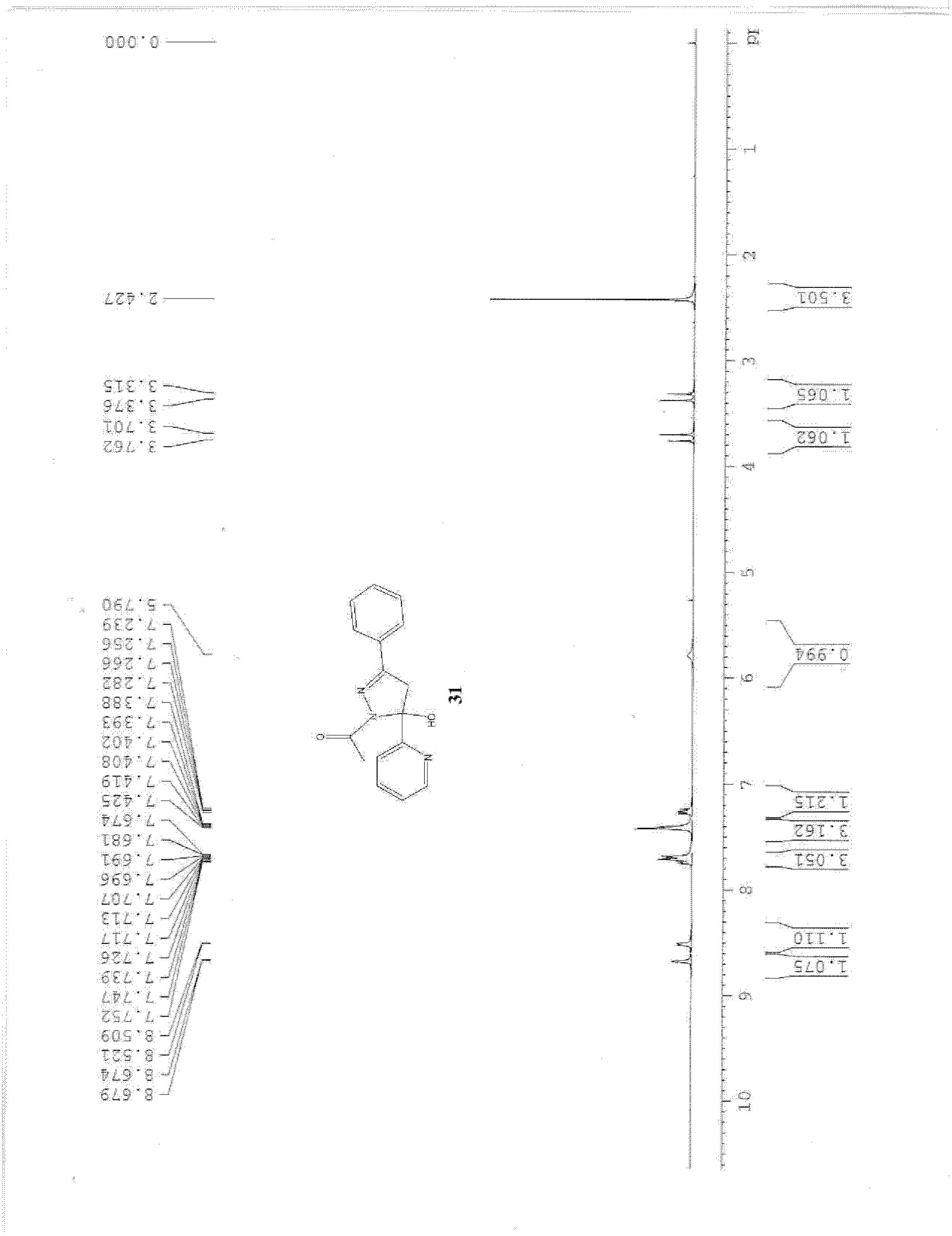
O
HO
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)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3.701
3.762
5.790
7.239
7.256
7.266
7.282
7.388
7.393
7.402
7.408
7.419
7.425
7.674
7.681
7.691
7.696
7.707
7.713
7.717
7.726
7.739
7.747
7.752
8.509
8.521
8.674
8.679
3.501
1.065
1.062
0.994
1.215
3.162
3.051
1.110
1.075
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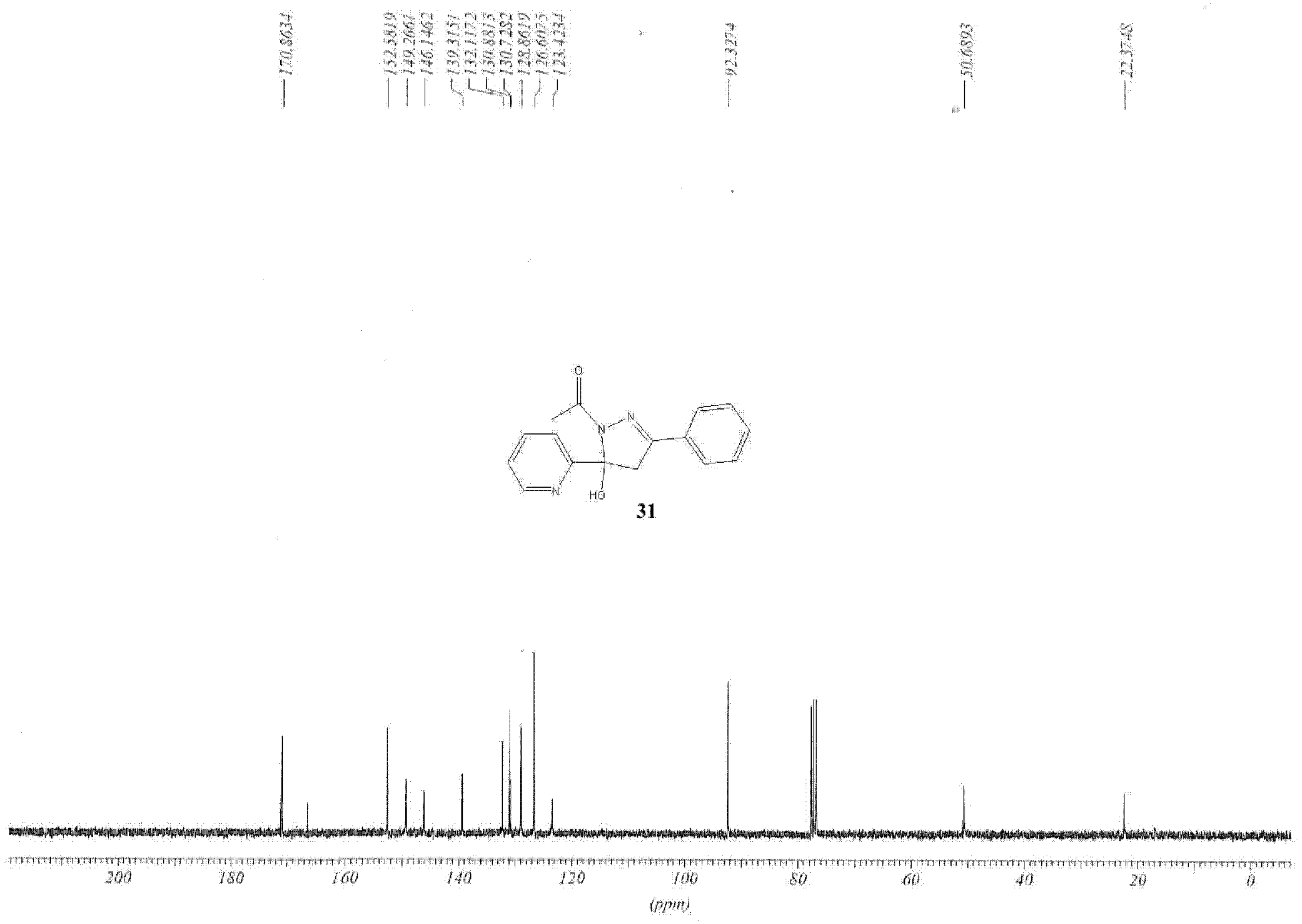
1
2
3
4
5
6
7
8
9
10
N
N
O
HO
N

31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128.8619
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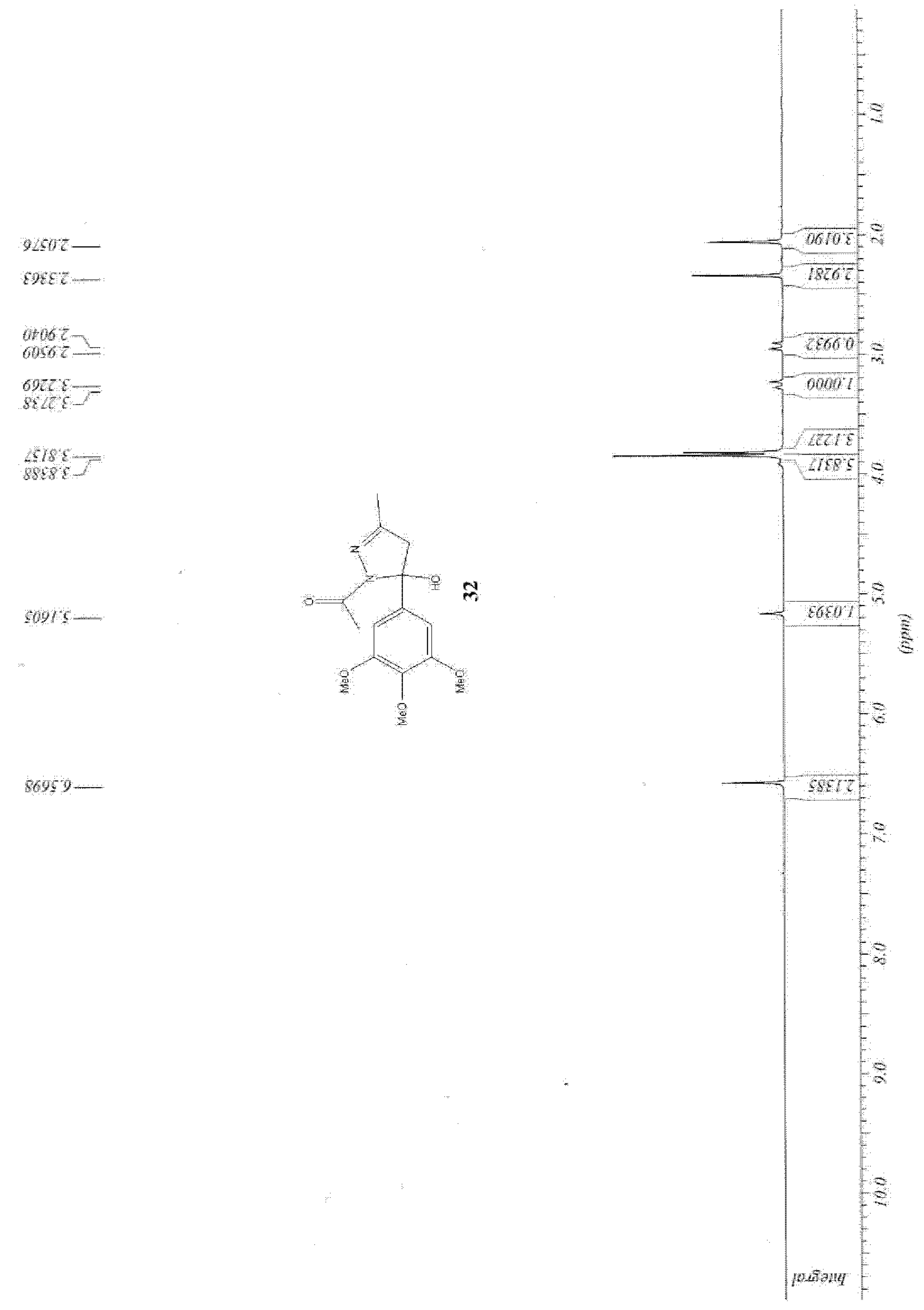
123.4234
92.3274
50.6893
22.3748
200
180
160
140
120
100
80
60
40
20
0
(ppm)
O
N
N
HO
N

31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2.9040
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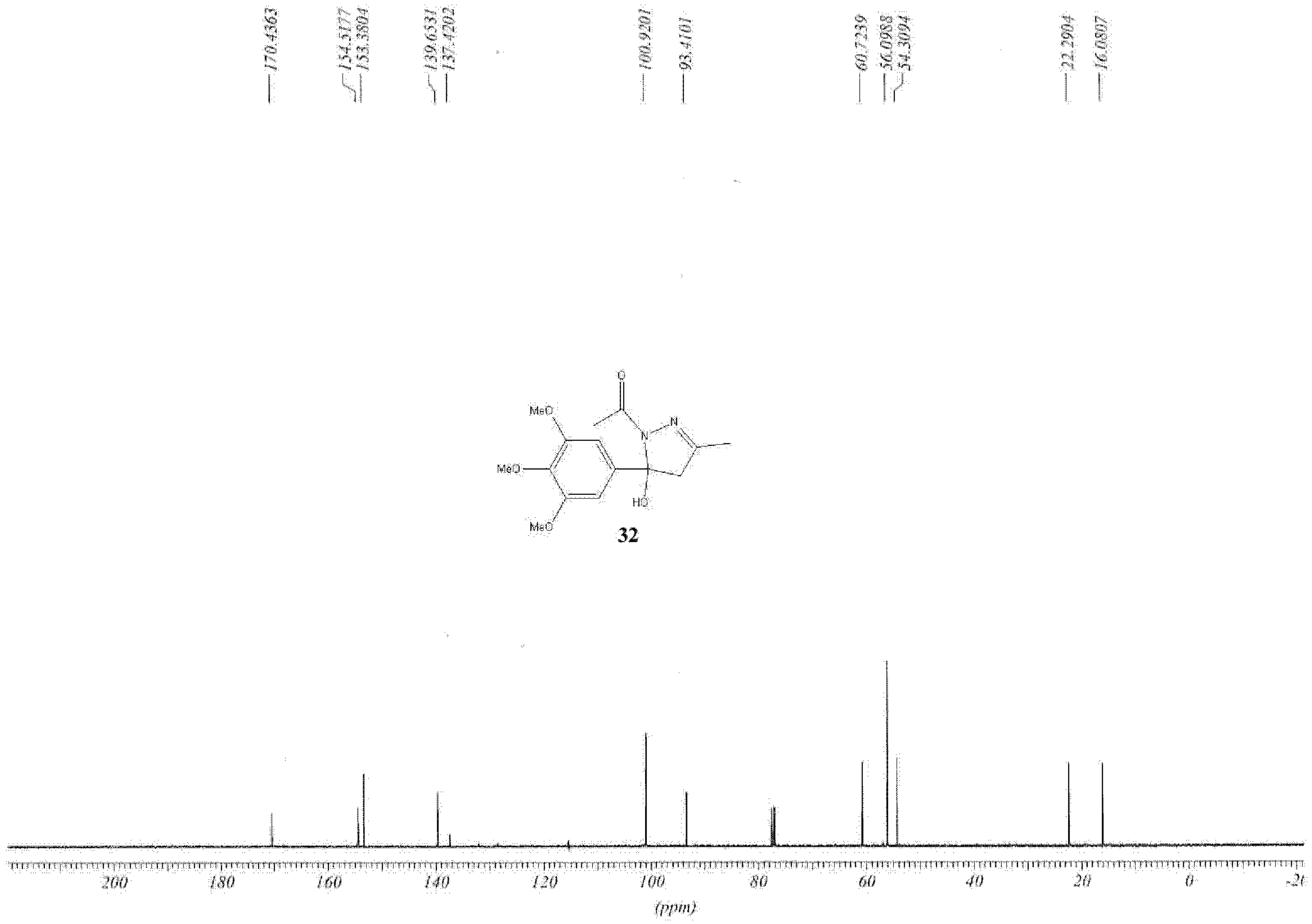
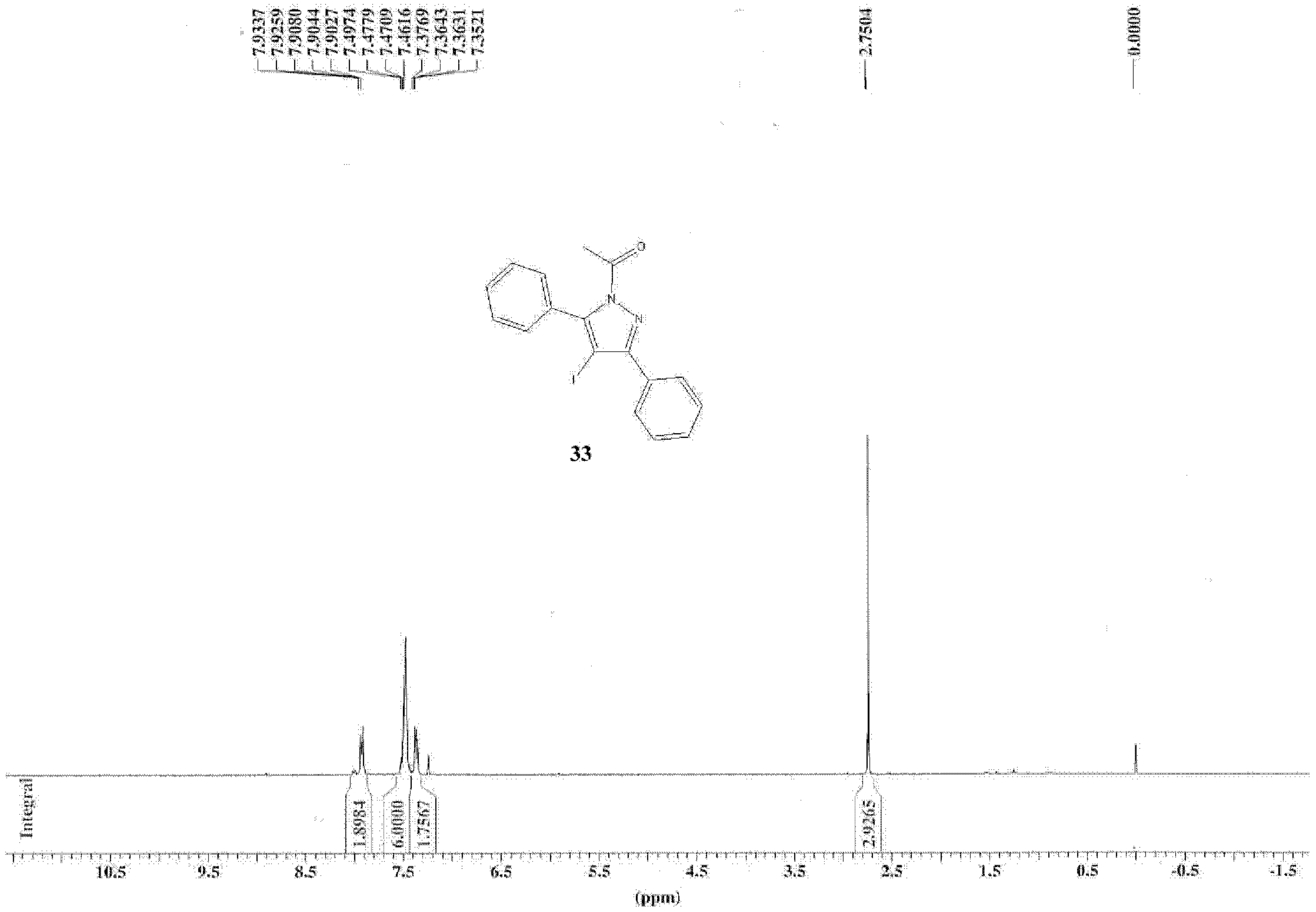
3.2269
3.2738
3.8137
3.8388
5.1603
6.5698
MeO
MeO
MeO
HO
N
32
3.0190
2.9281
0.9932
1.0000
3.1227
5.8317
1.0393
2.1385
Integral
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
(ppm)


32

170.4363
154.5177
153.3804
139.6531
137.4202
100.9201
93.4101
60.7239
56.0988
54.3094
22.2904
16.0807
MeO
MeO
MeO
O
N
N
HO
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)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7.4616
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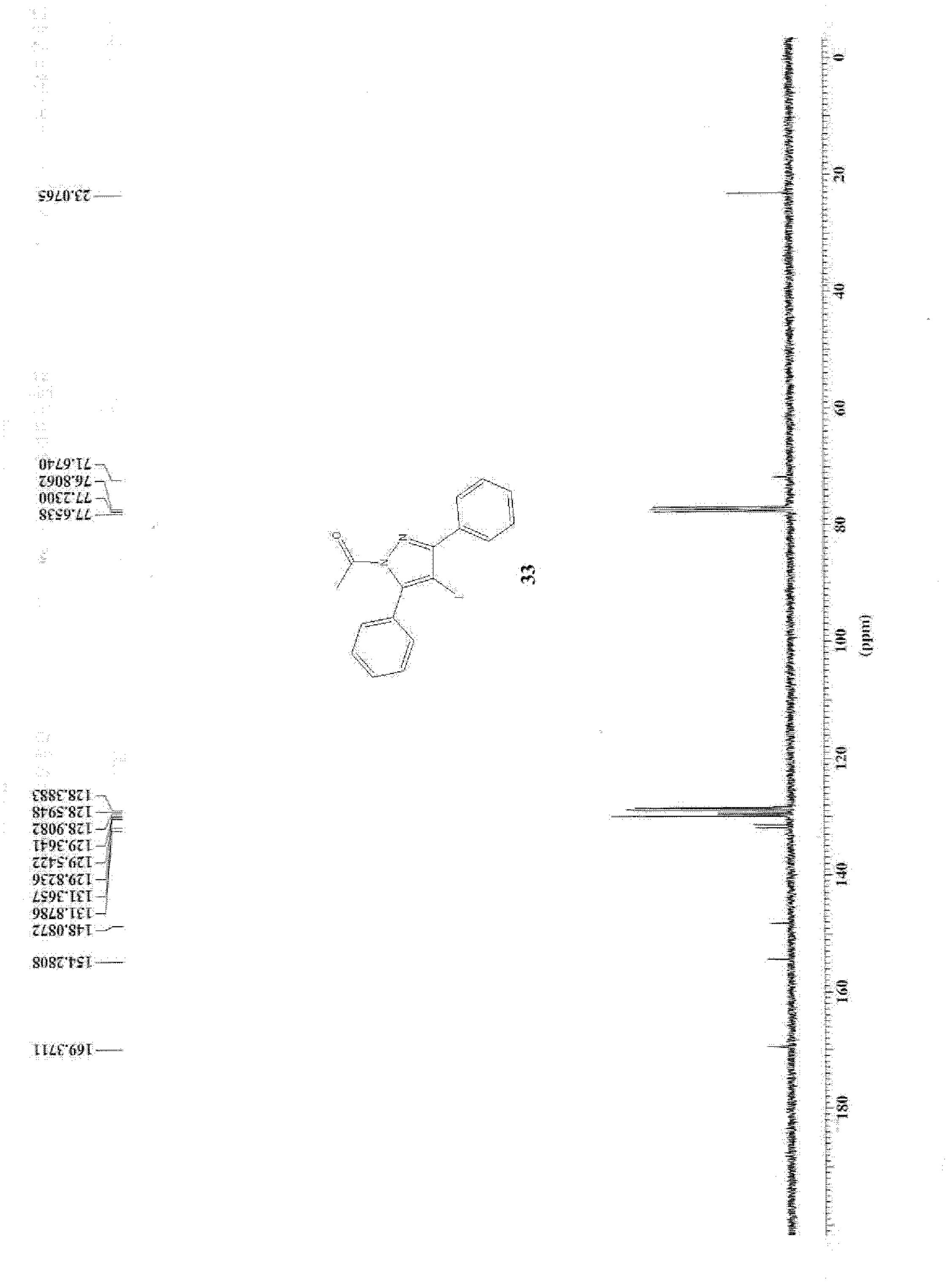
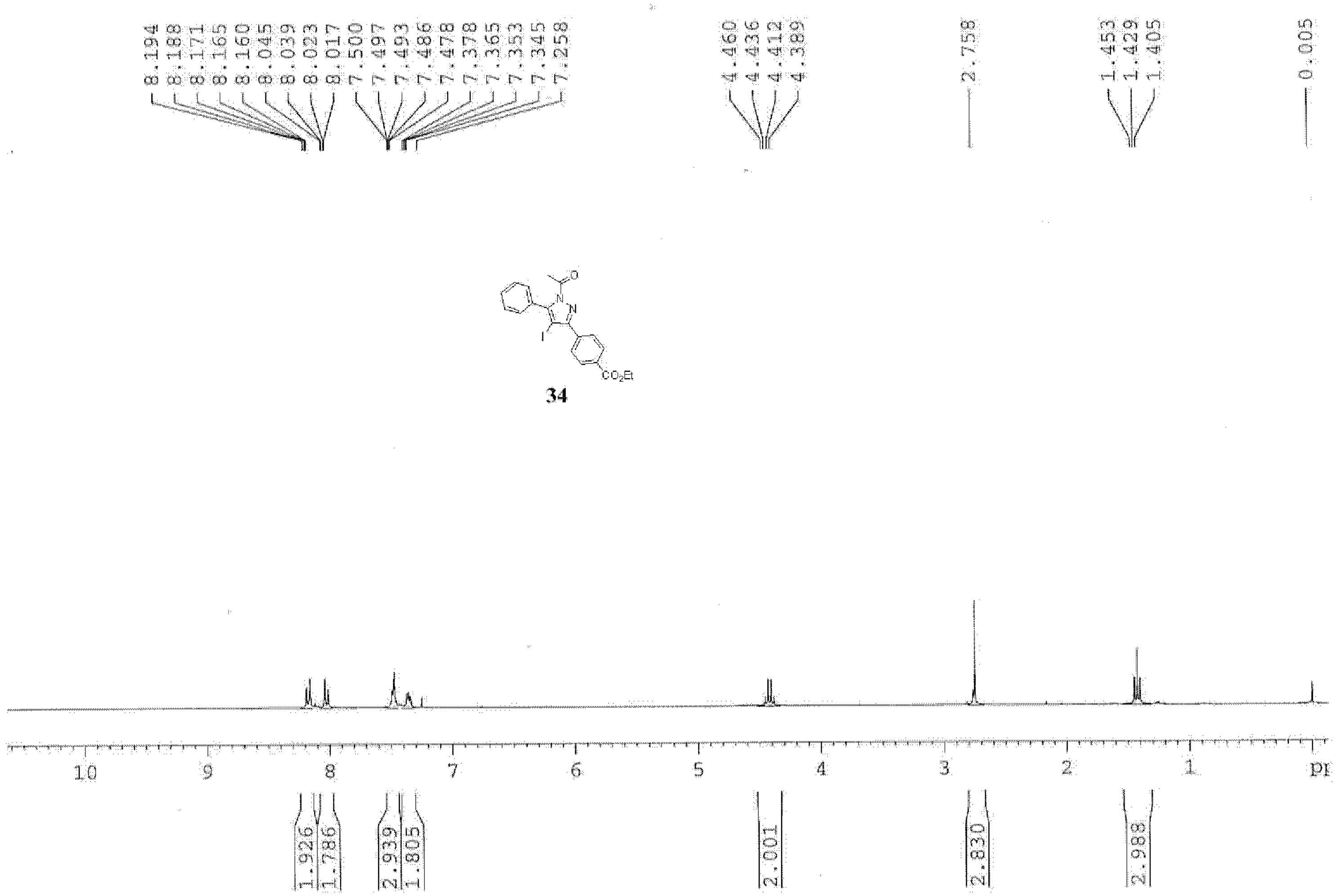
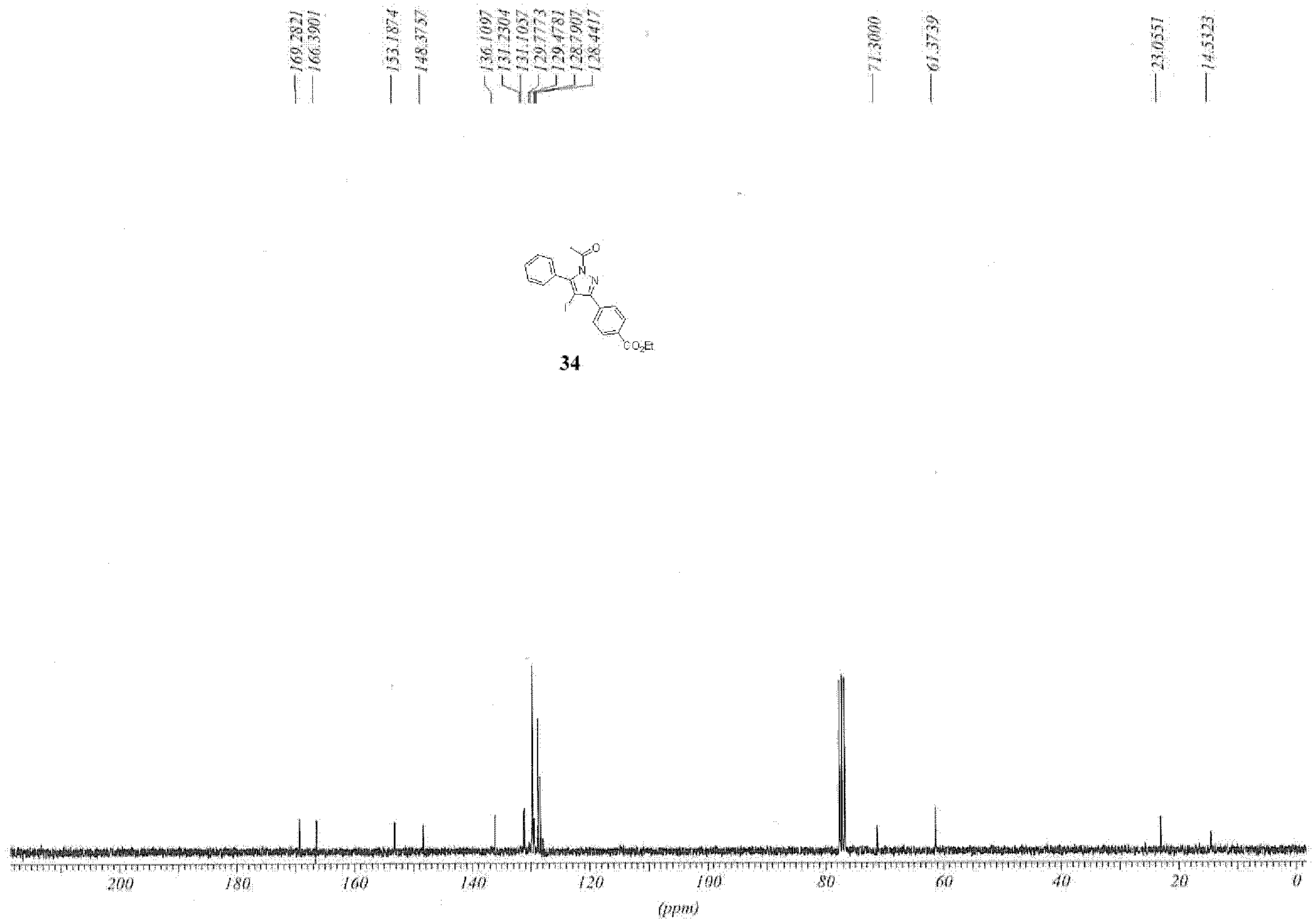
7.3643
7.3631
7.3521
2.7504
0.0000
N
N
O
I
Integral
1.8984
6.0000
1.7567
2.9265
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

33

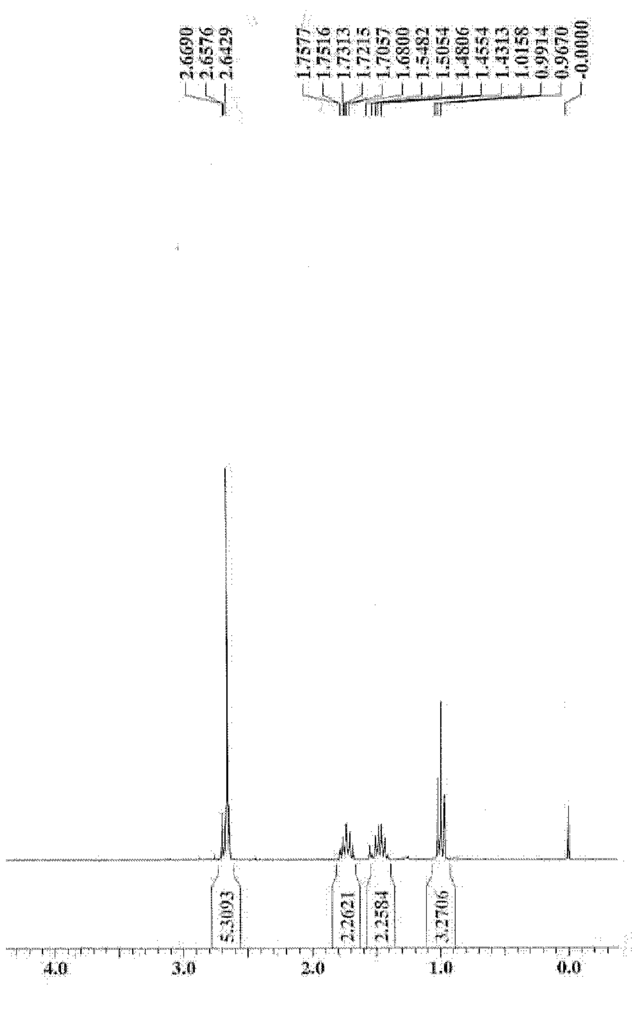

23.0765
71.6740
76.8062
77.2300
77.6538
128.3883
128.5948
128.9082
129.3641
129.5422
129.8236
131.3657
131.8786
148.0872
154.2808
169.3711
33
0
20
40
60
80
100
120
140
160
180
(ppm)

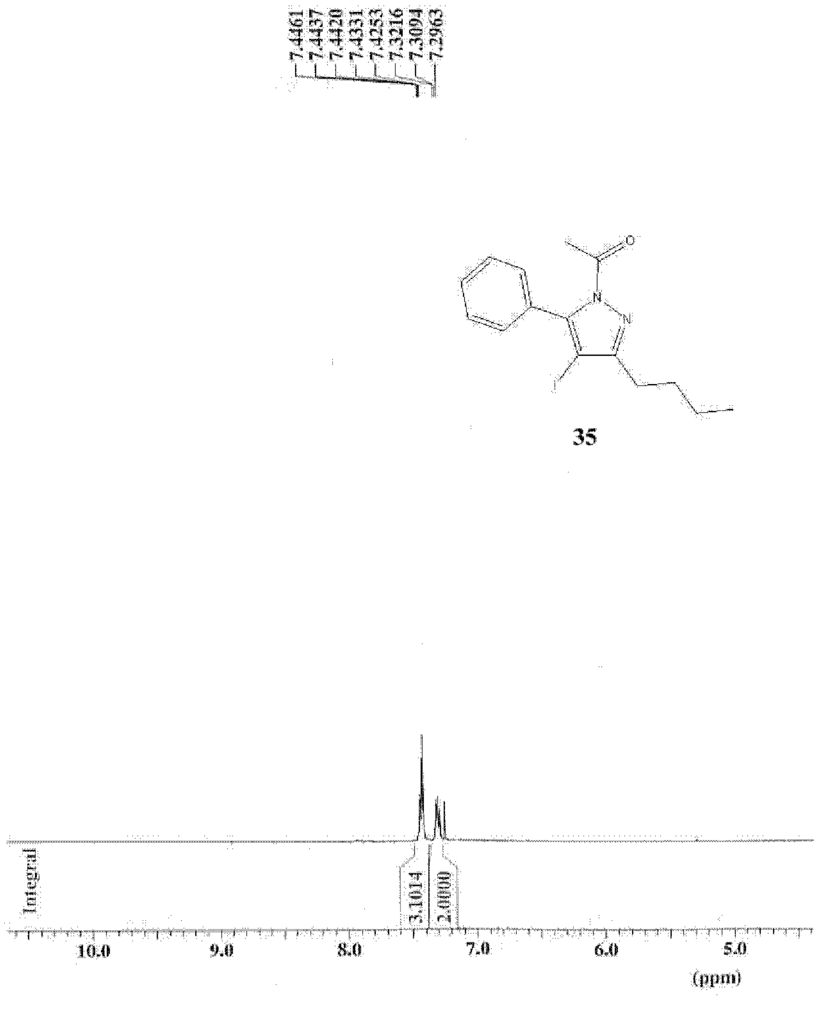

34
8.194
8.188
8.171
8.165
8.160
8.045
8.039
8.023
8.017
7.500
7.497
7.493
7.486
7.478
7.378
7.365
7.353
7.345
7.258
4.460
4.436
4.412
4.389
2.758
1.453
1.429
1.405
0.005
N
N
O
I
CO_2Et
10
9
8
7
6
5
4
3
2
1
pp
1.926
1.786
2.939
1.805
2.001
2.830
2.988

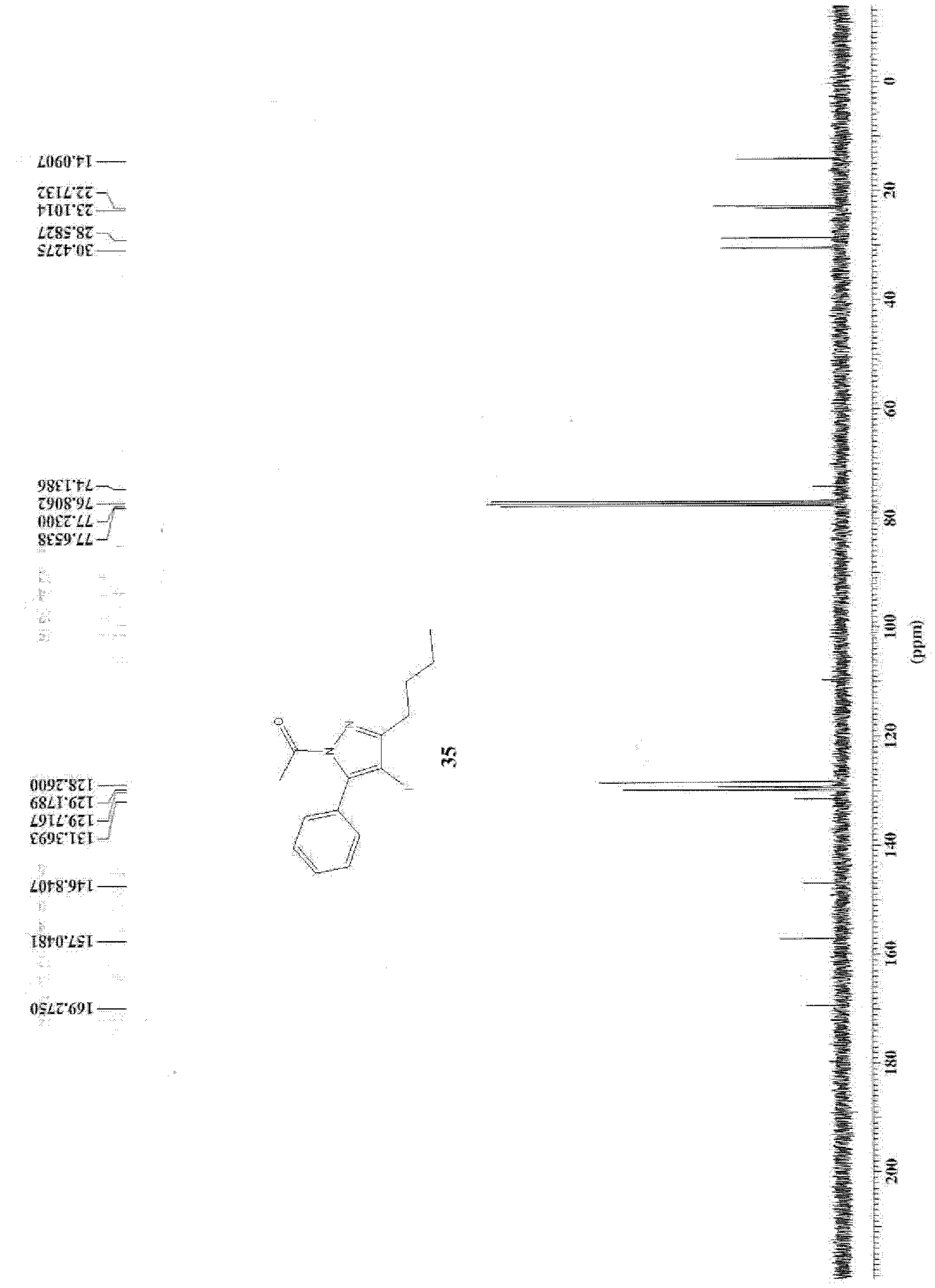


34

169.2821
166.3901
153.1874
148.3757
136.1097
131.2304
131.1057
129.7773
129.4781
128.7907
128.4417
71.3000
61.3739
23.0551
14.5323
CO2Et
N
N
O
I
200
180
160
140
120
100
80
60
40
20
0
(ppm)

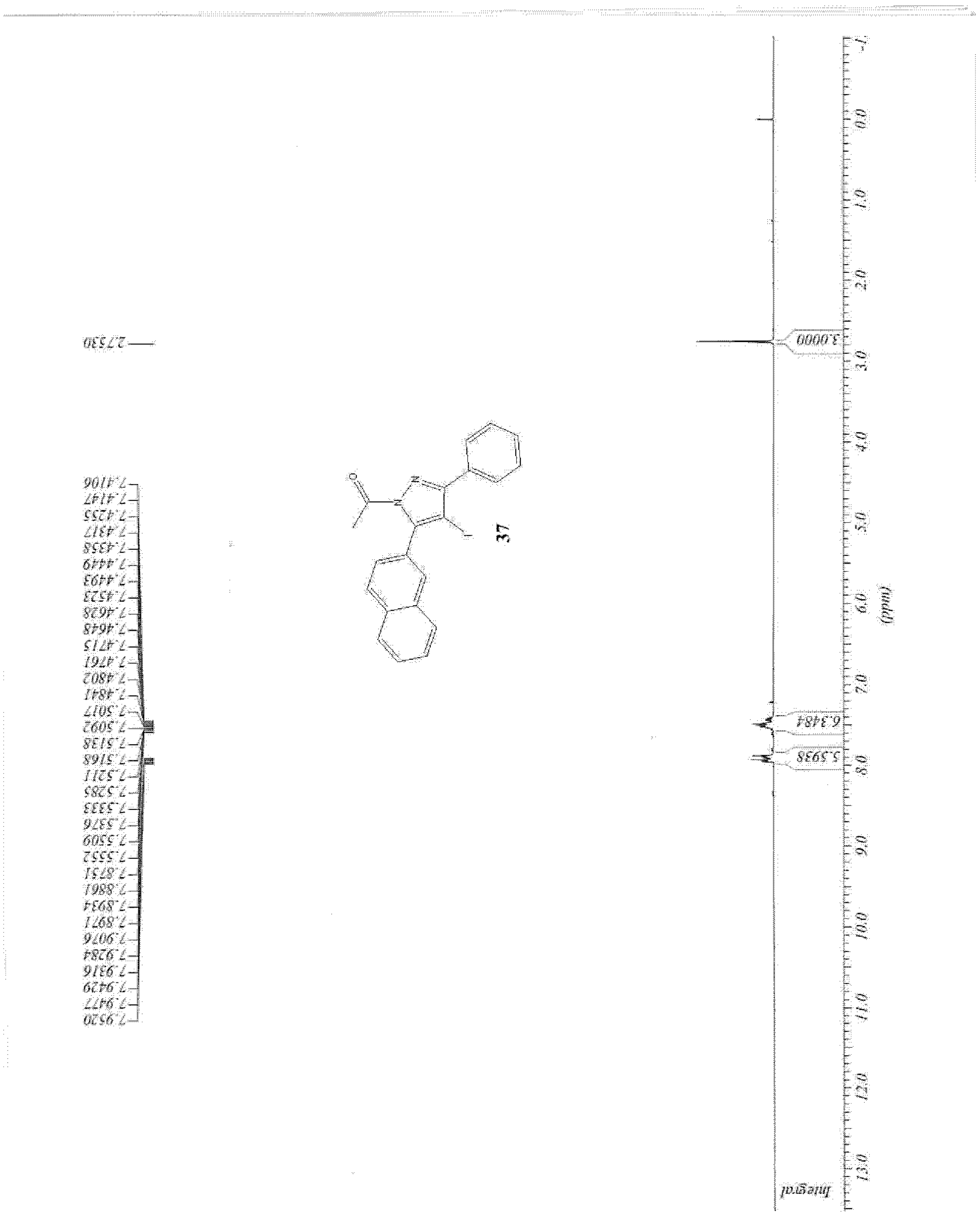

2.6690
2.6576
2.6429
1.7577
1.7516
1.7313
1.7215
1.7057
1.6800
1.5482
1.5054
1.4806
1.4554
1.4313
1.0158
0.9914
0.9670
-0.0000
5.3093
2.2621
2.2584
3.2706
4.0
3.0
2.0
1.0
0.0


7.4461
7.4437
7.4420
7.4331
7.4253
7.3216
7.3094
7.2963
35
Integral
3.1014
2.0000
10.0
9.0
8.0
7.0
6.0
5.0
(ppm)



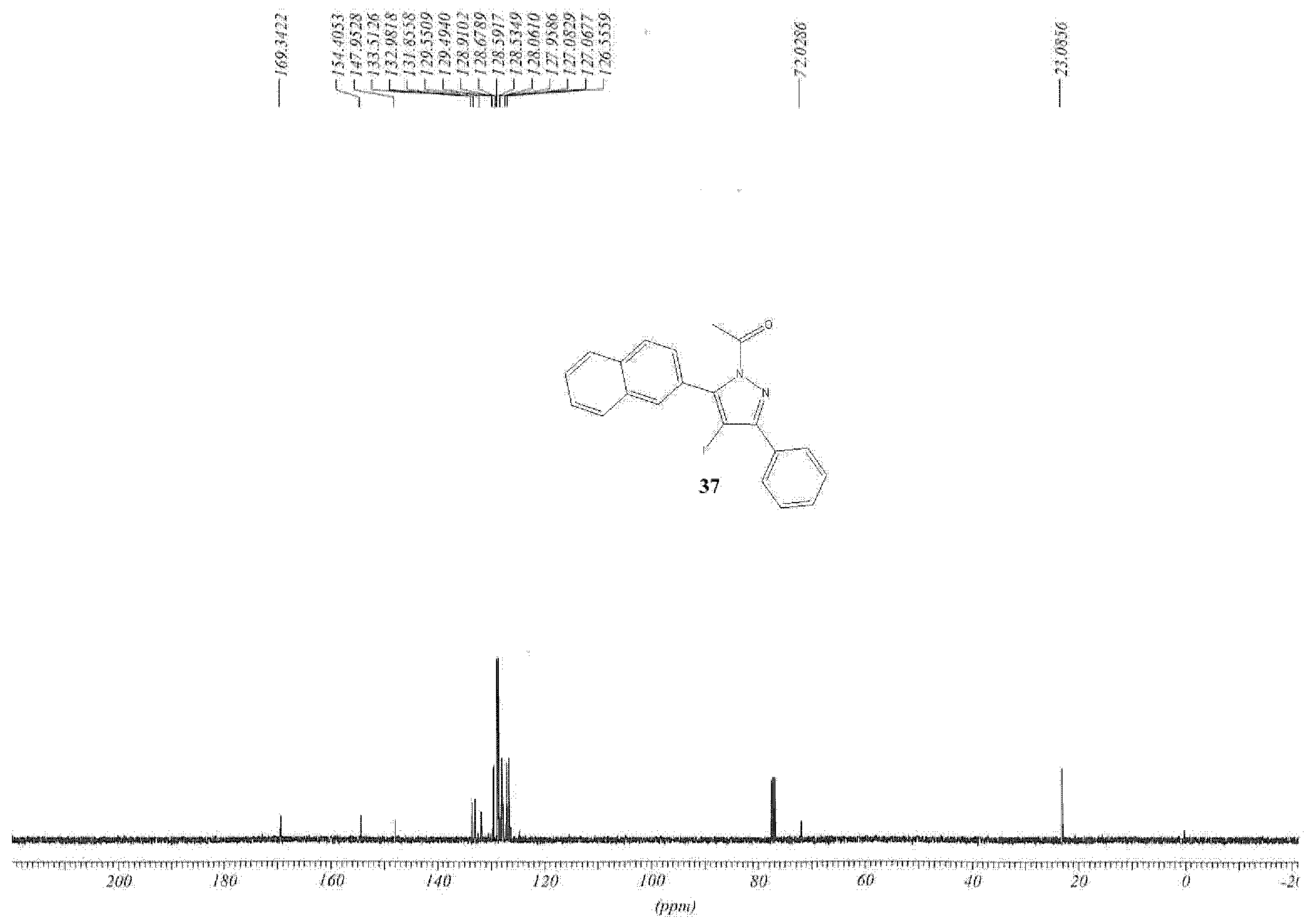
14.0907
22.7132
23.1014
28.5827
30.4275
74.1386
76.8062
77.2300
77.6538
128.2600
129.1789
129.7167
131.3693
146.8407
157.0481
169.2750
N
N
O
0
20
40
60
80
100
120
140
160
180
200
(ppm)

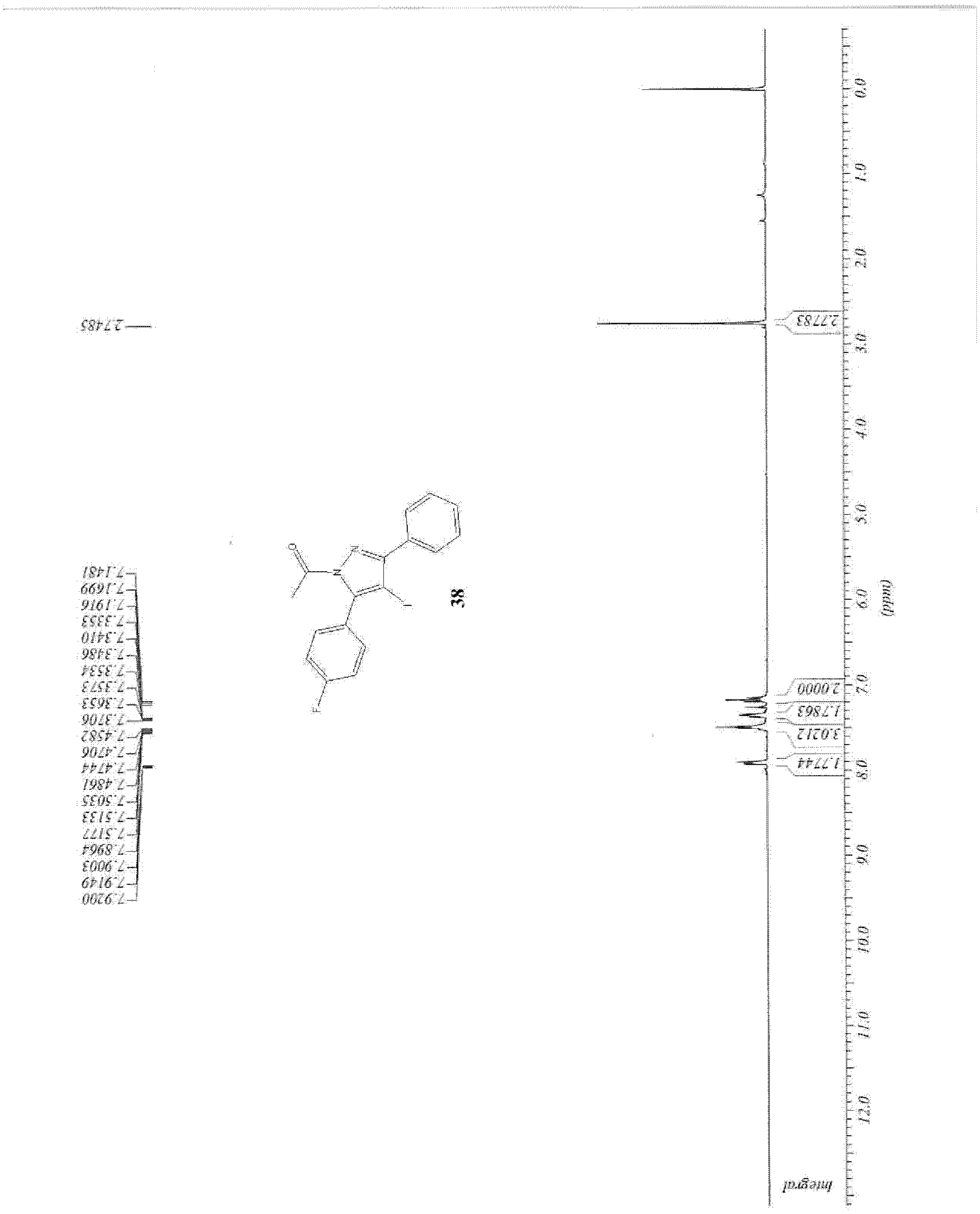
35



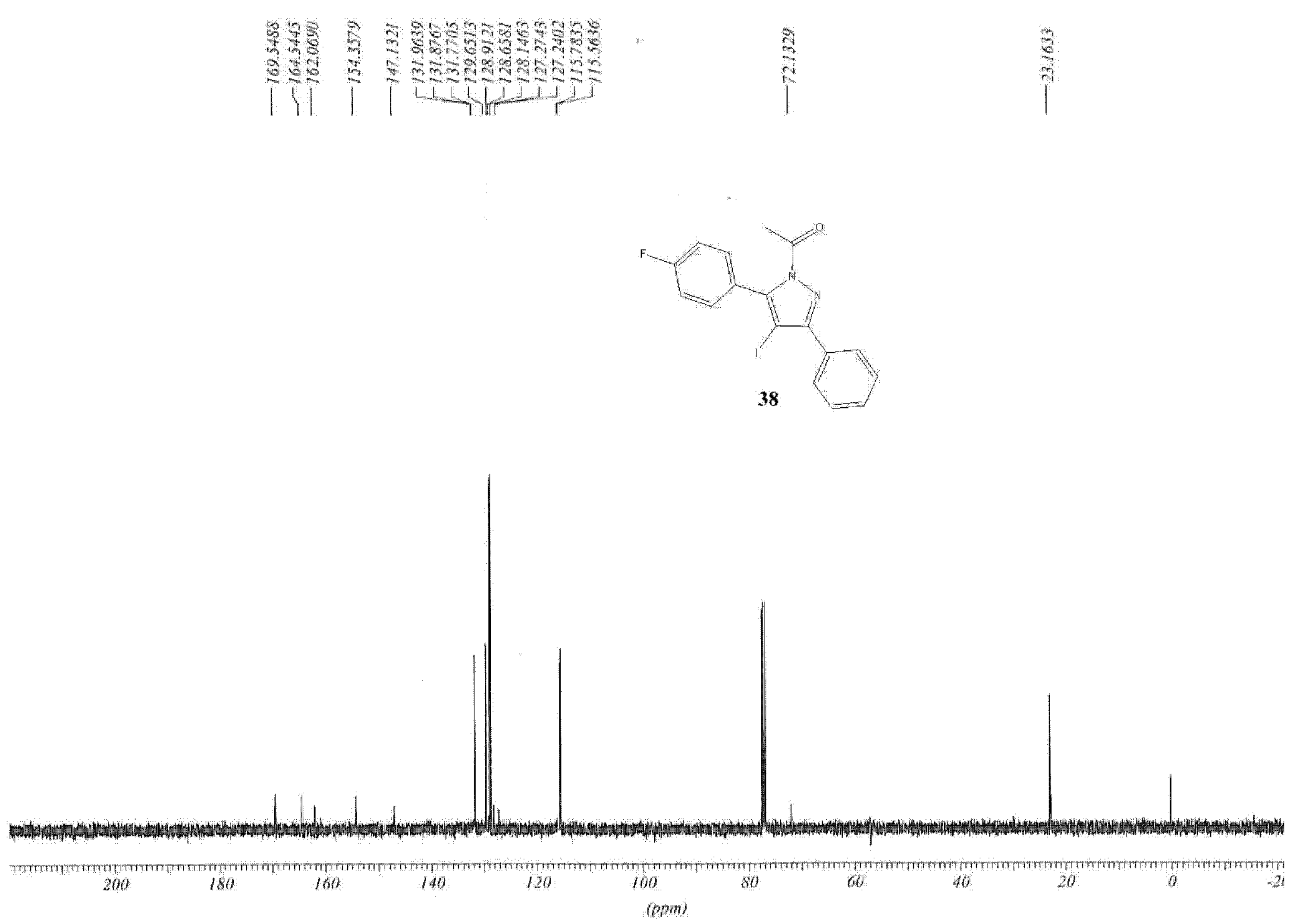
37

2.7530
7.4106
7.4147
7.4255
7.4317
7.4358
7.4449
7.4493
7.4523
7.4628
7.4648
7.4715
7.4761
7.4802
7.4841
7.5017
7.5092
7.5138
7.5168
7.5211
7.5285
7.5333
7.5376
7.5509
7.5552
7.8731
7.8861
7.8934
7.8971
7.9076
7.9284
7.9316
7.9429
7.9477
7.9520
N
N
I
O
3.0000
6.3484
5.5938
Integral
-1.
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

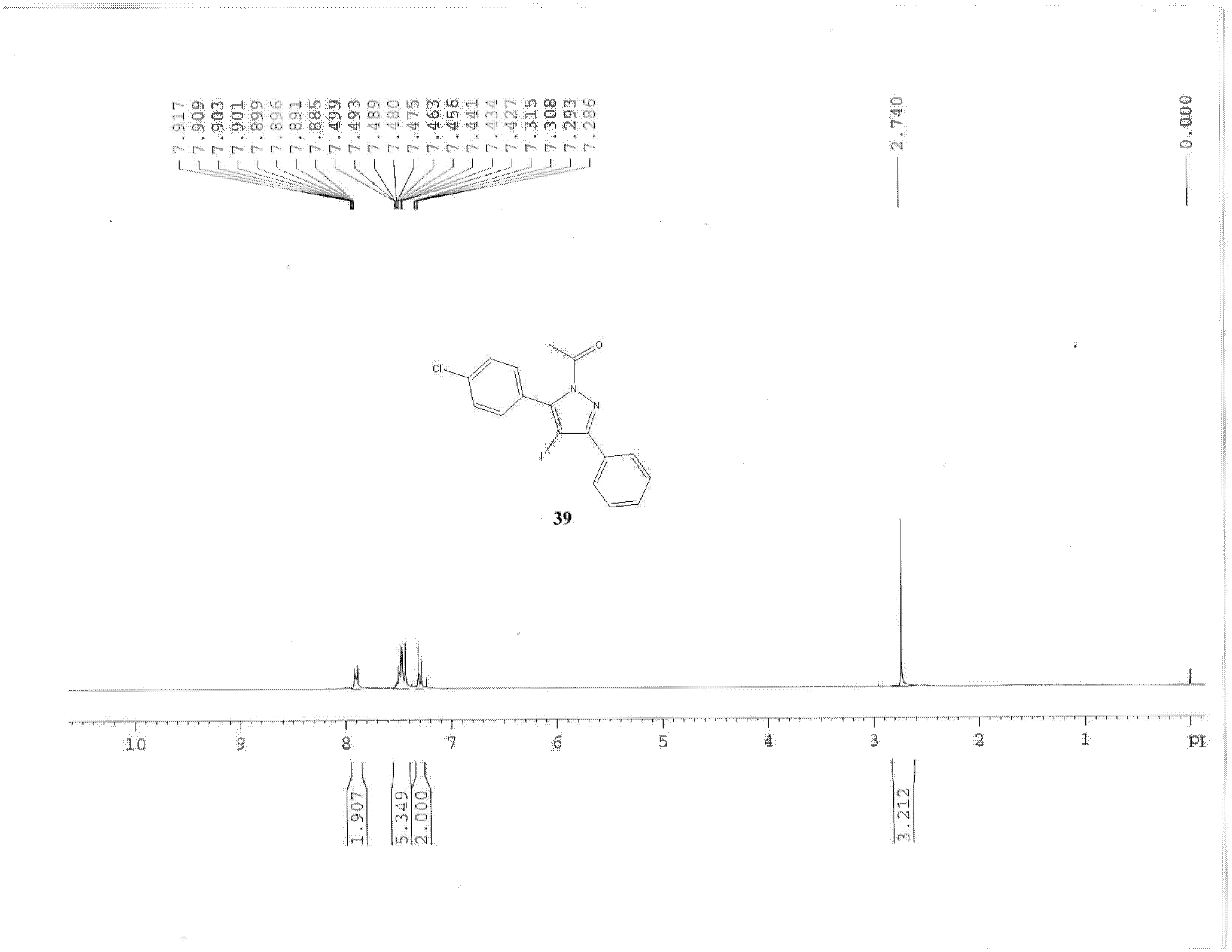

169.3422
154.4053
147.9528
133.5126
132.9818
131.8558
129.5509
129.4940
128.9102
128.6789
128.5917
128.5349
128.0610
127.9586
127.0829
127.0677
126.5559
72.0286
23.0856
37
N
N
O
I
200
180
160
140
120
100
80
60
40
20
0
-2
(ppm)


2.7483
7.1481
7.1699
7.1916
7.3353
7.3410
7.3486
7.3534
7.3573
7.3653
7.3706
7.4582
7.4706
7.4744
7.4861
7.5035
7.5133
7.5177
7.8964
7.9003
7.9149
7.9200
N
N
I
F
2.7783
2.0000
1.7863
3.0212
1.7744
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
(ppm)
integral

38

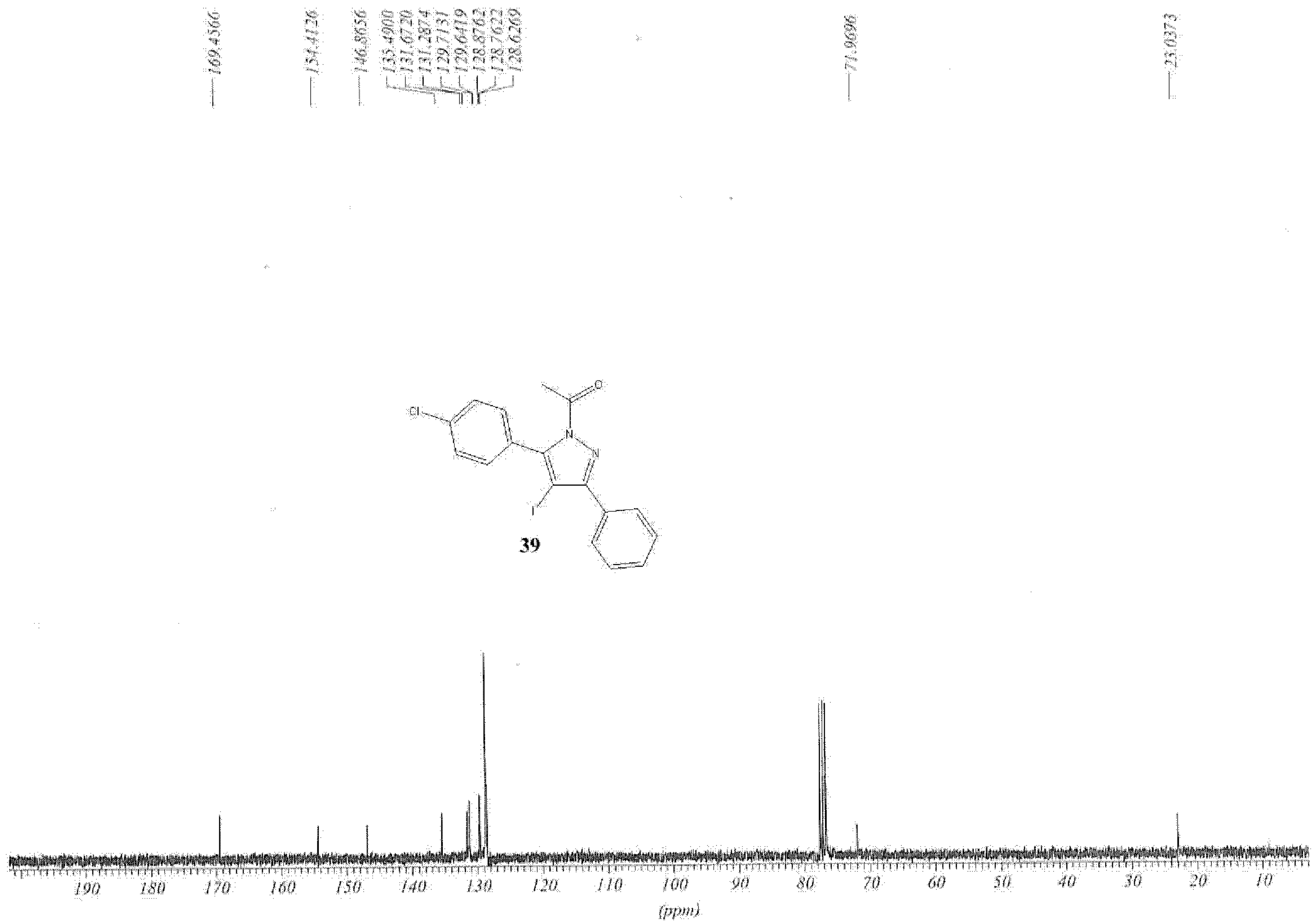

169.5488
164.5445
162.0690
154.3579
147.1321
131.9639
131.8767
131.7705
129.6513
128.9121
128.6581
128.1463
127.2743
127.2402
115.7835
115.5636
72.1329
23.1633
F
N
N
O
I
200
180
160
140
120
100
80
60
40
20
0
-2(
(ppm)

38

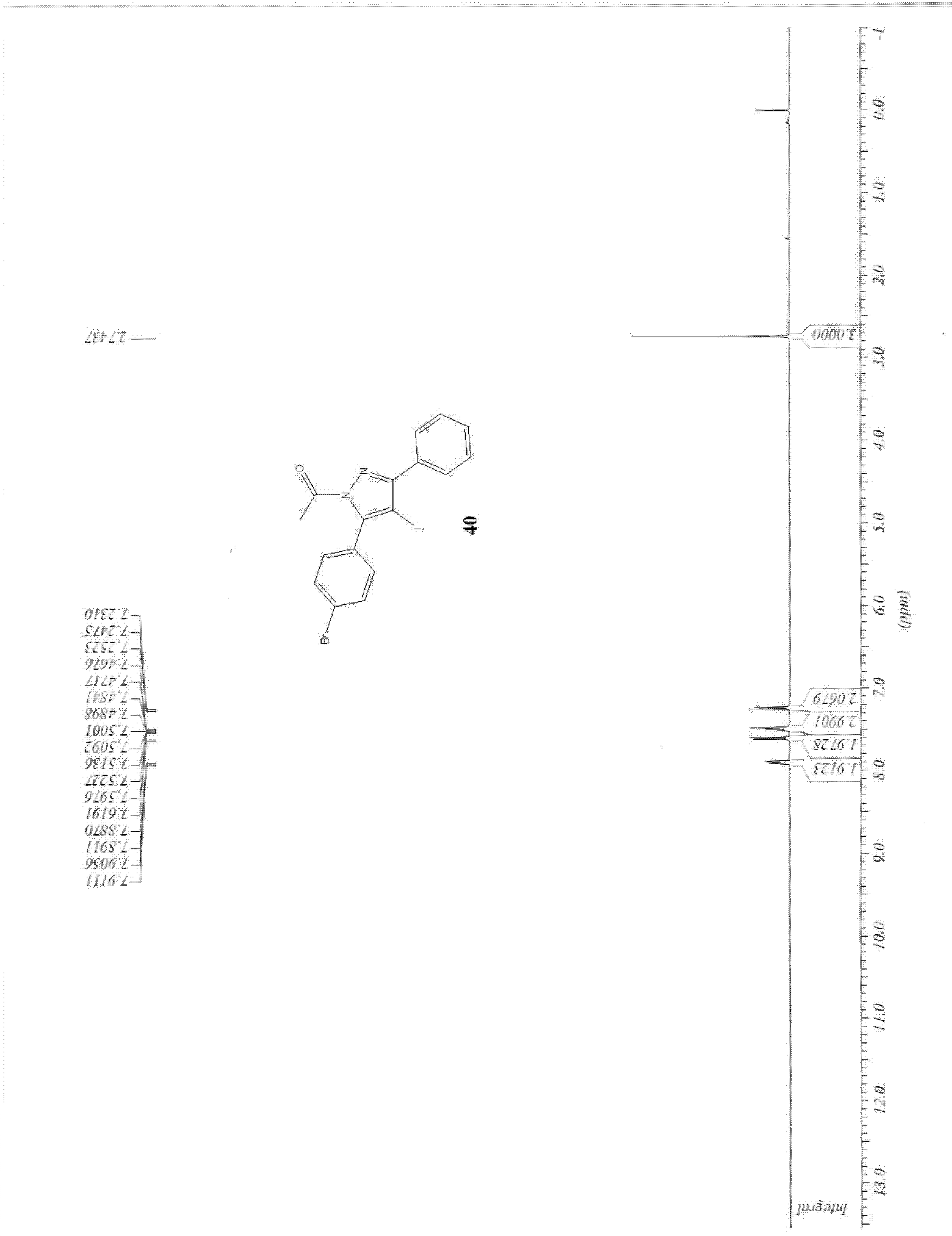


39

7.917
7.909
7.903
7.901
7.899
7.896
7.891
7.885
7.499
7.493
7.489
7.480
7.475
7.463
7.456
7.441
7.434
7.427
7.315
7.308
7.293
7.286
2.740
0.000
Cl
N
N
O
I
10
9
8
7
6
5
4
3
2
1
pI
1.907
5.349
2.000
3.212

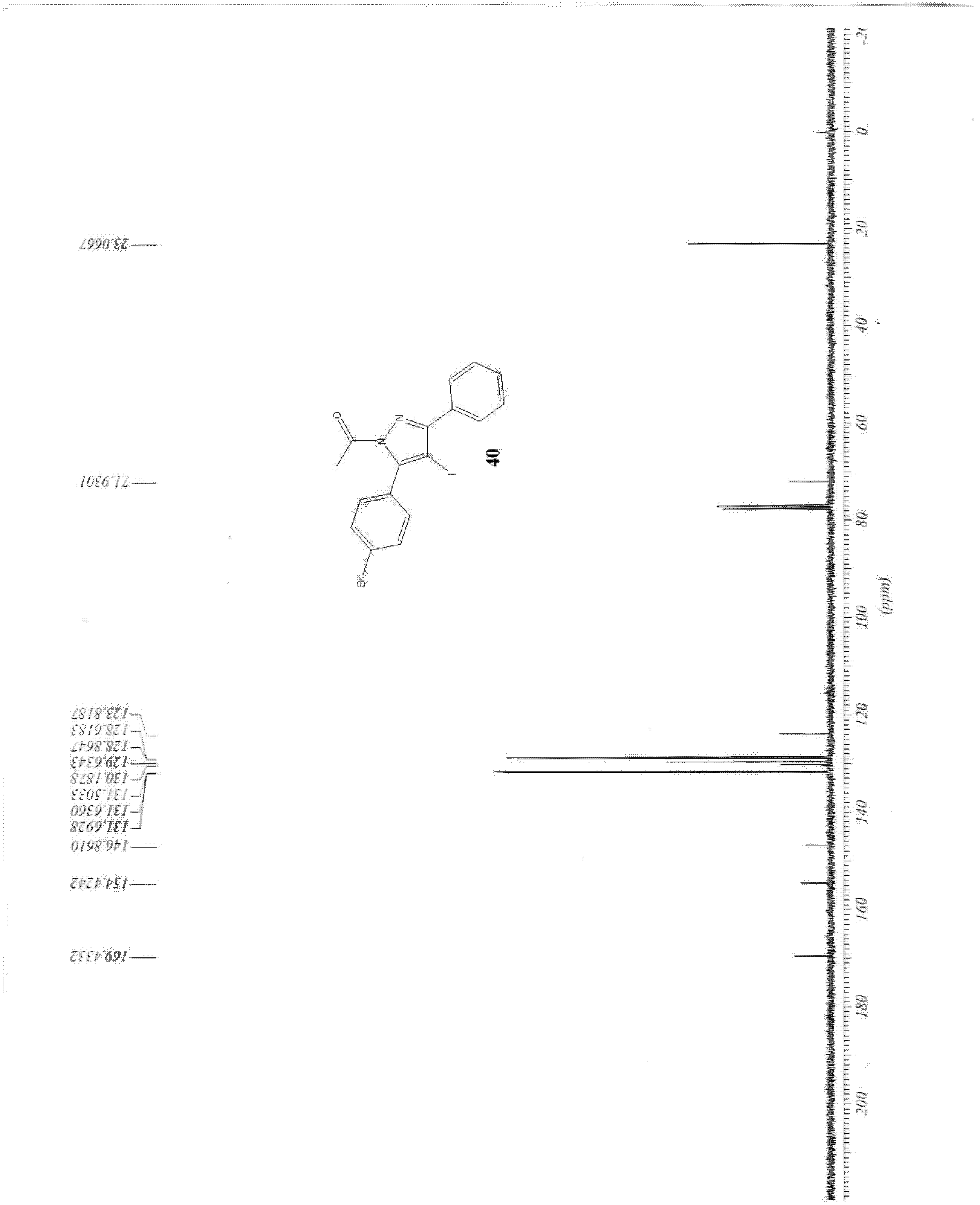

169.4566
154.4126
146.8656
135.4900
131.6720
131.2874
129.7131
129.6419
128.8762
128.7622
128.6269
71.9696
23.0373
Cl
N
N
O
I
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

39



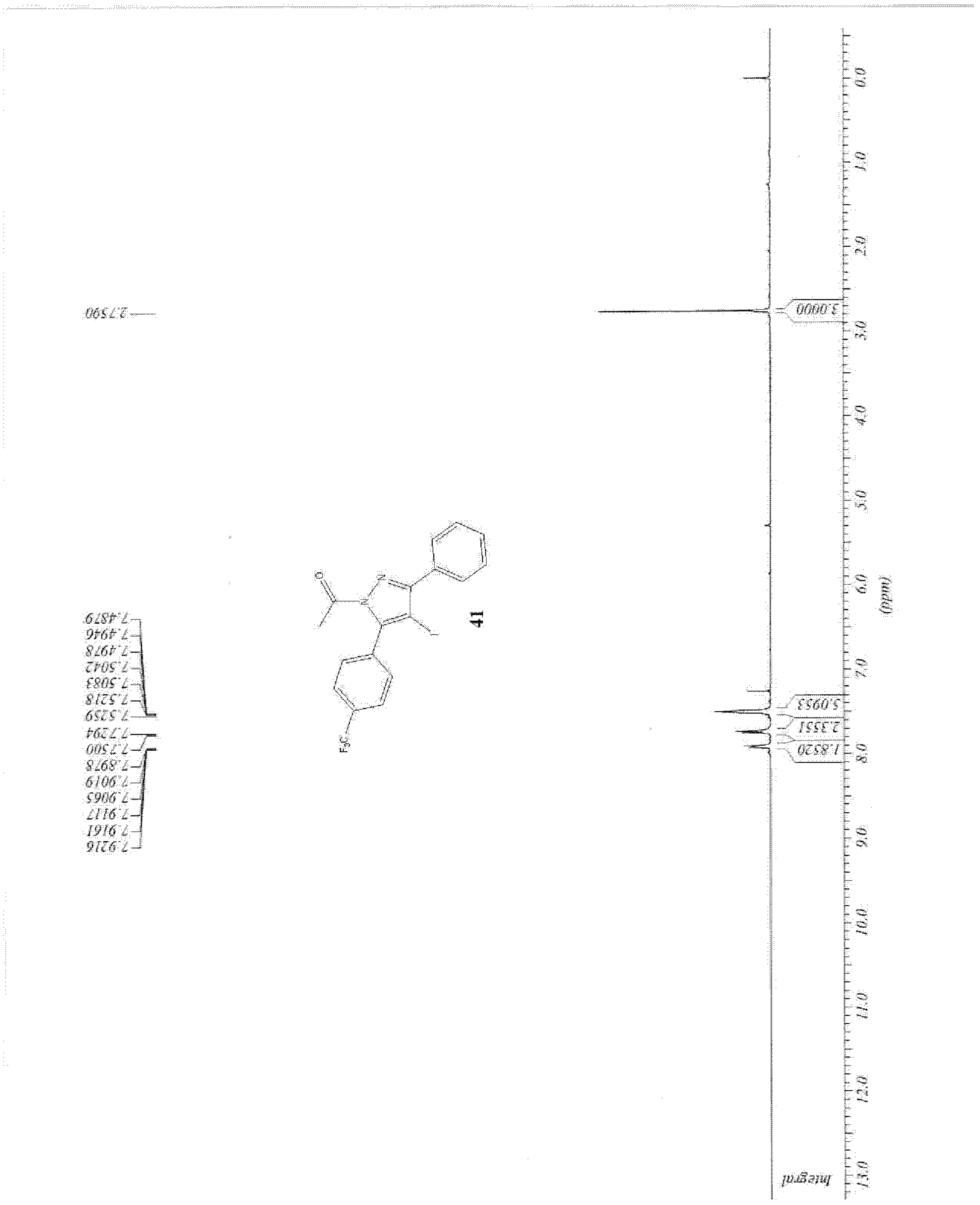
2.7437
7.2310
7.2475
7.2523
7.4676
7.4717
7.4841
7.4898
7.5001
7.5092
7.5136
7.5227
7.5976
7.6191
7.8870
7.8911
7.9056
7.9111
3.0000
2.0679
2.9901
1.9728
1.9123
Integral
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
N
N
O
Br

40

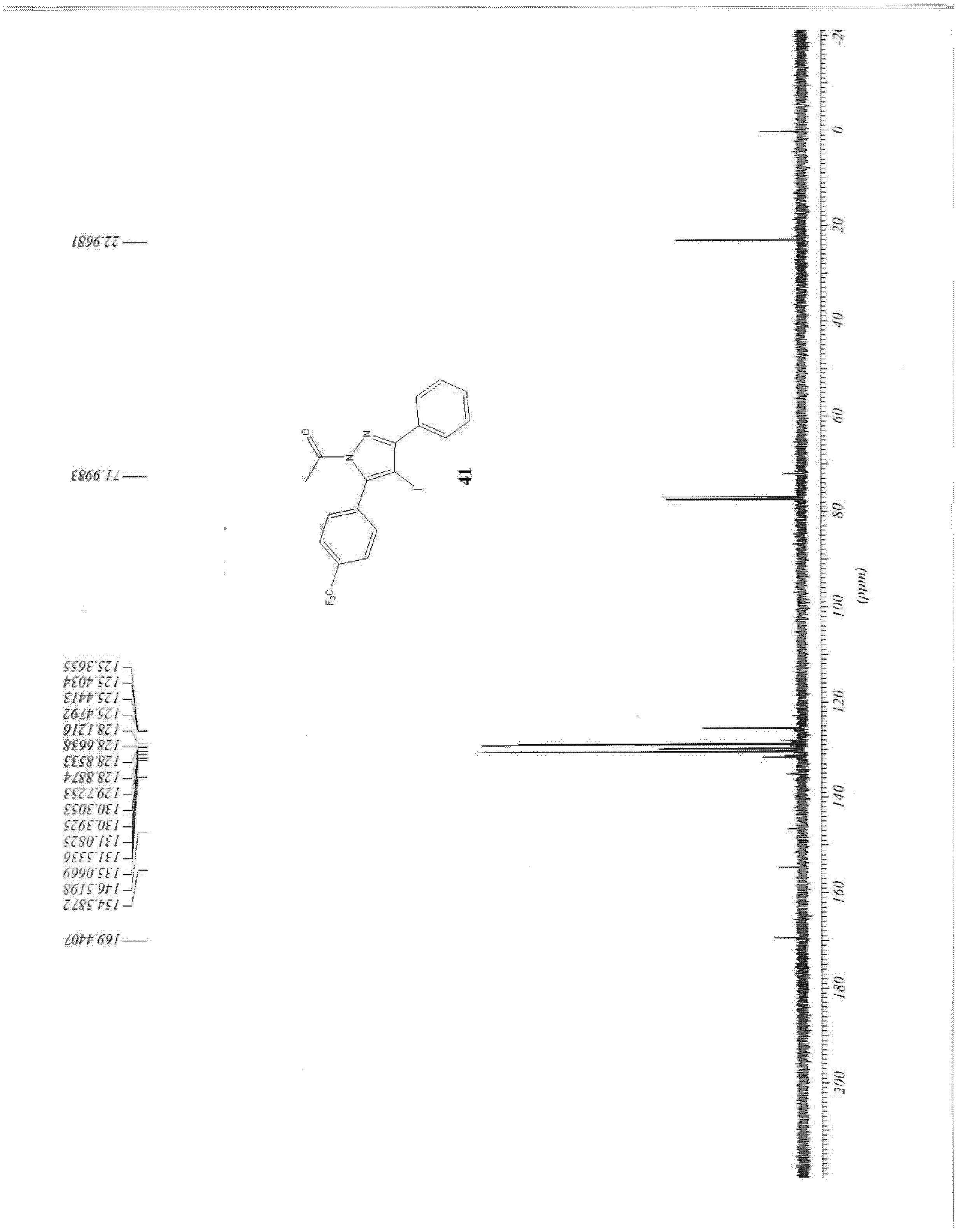


40

23.0667
71.9301
123.8187
128.6183
128.8647
129.6343
130.1878
131.5033
131.6360
131.6928
146.8610
154.4242
169.4332
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

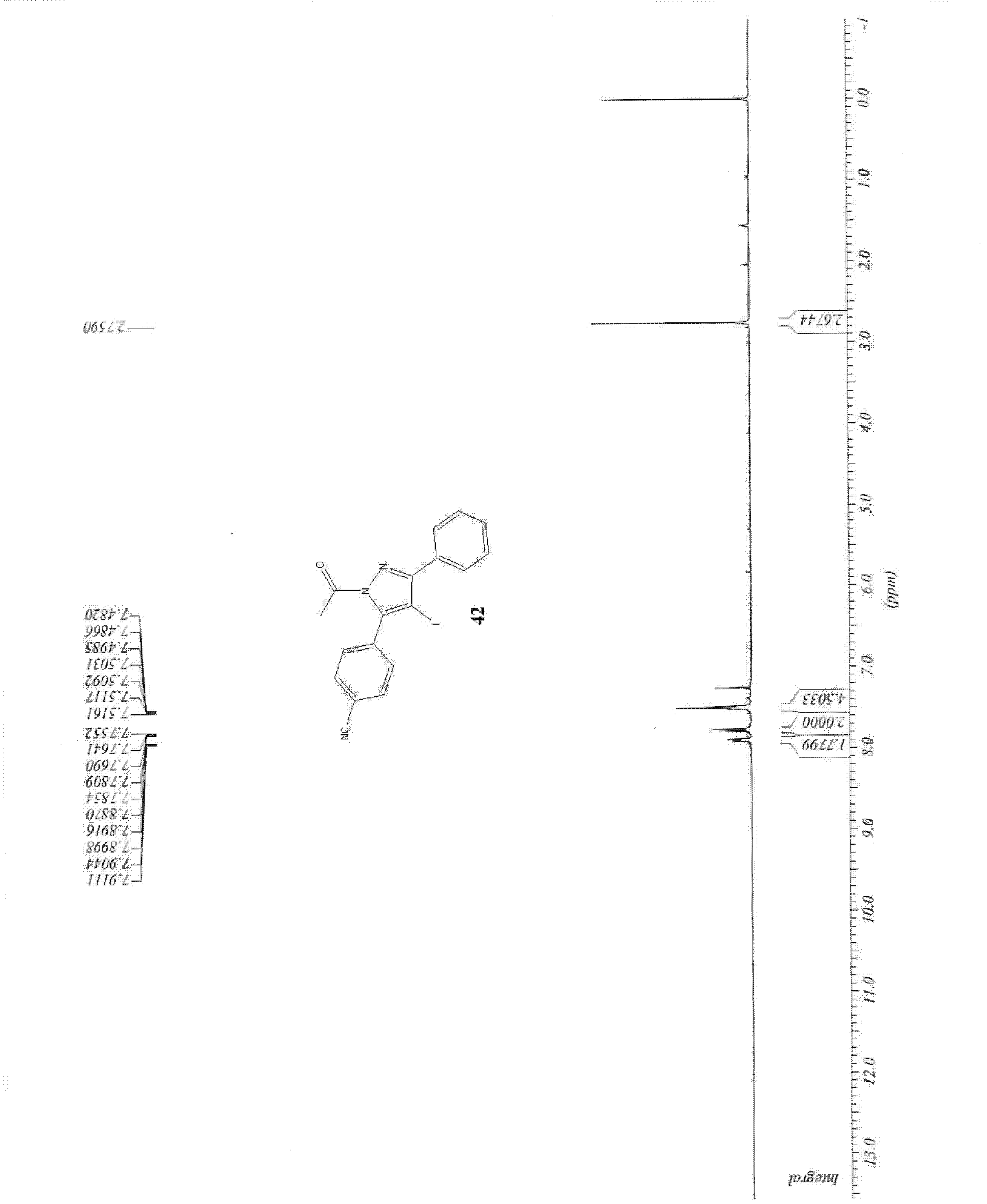

2.7590
7.4879
7.4946
7.4978
7.5042
7.5083
7.5218
7.5259
7.7294
7.7500
7.8978
7.9019
7.9065
7.9117
7.9161
7.9216
F3C
3.0000
5.0953
2.3551
1.8520
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral

41



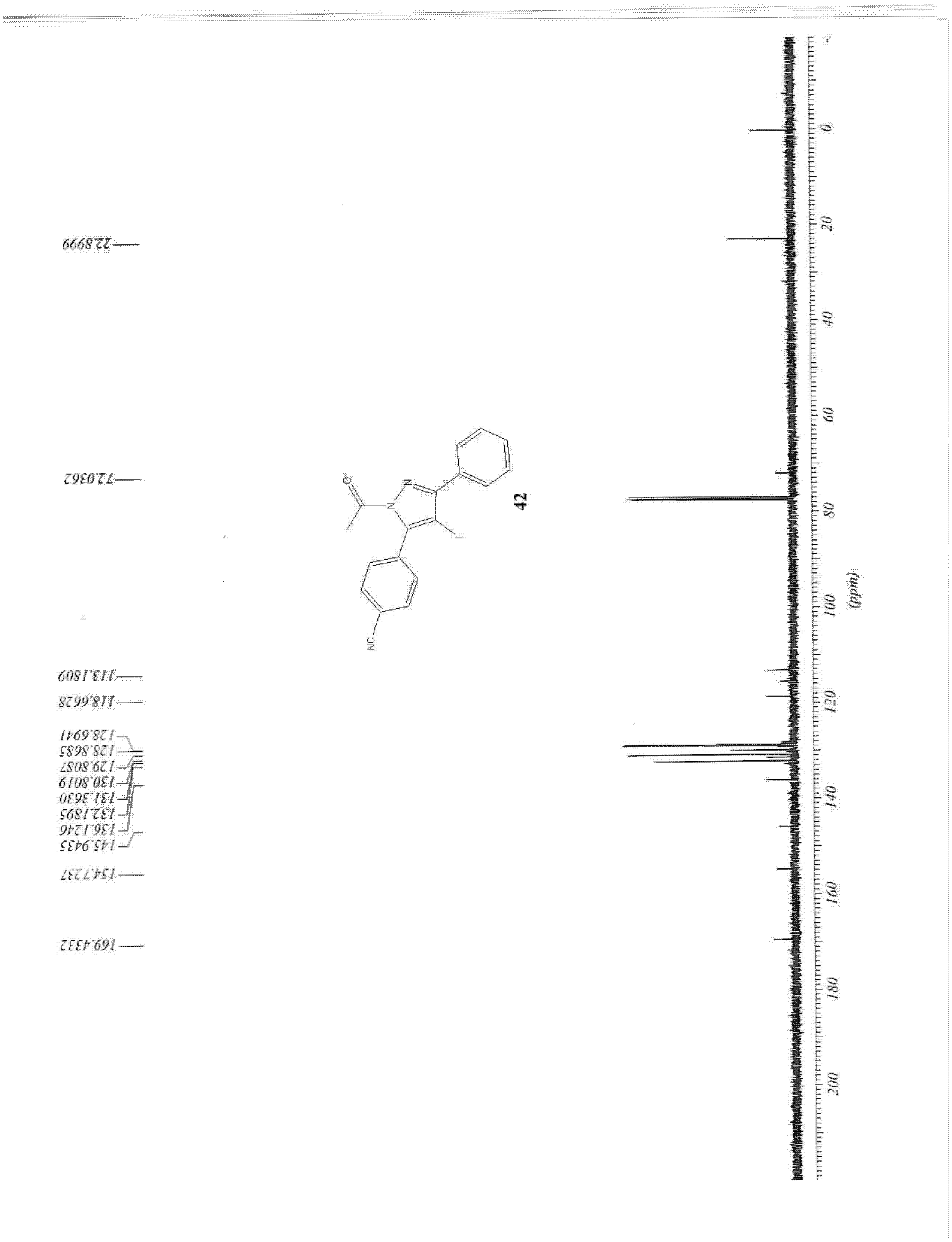
41

22.9681
71.9983
125.3655
125.4034
125.4413
125.4792
128.1216
128.6688
128.8533
128.8874
129.7253
130.3053
130.3925
131.0825
131.5336
133.0669
146.5198
154.5872
169.4407
N
N
O
F3C
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

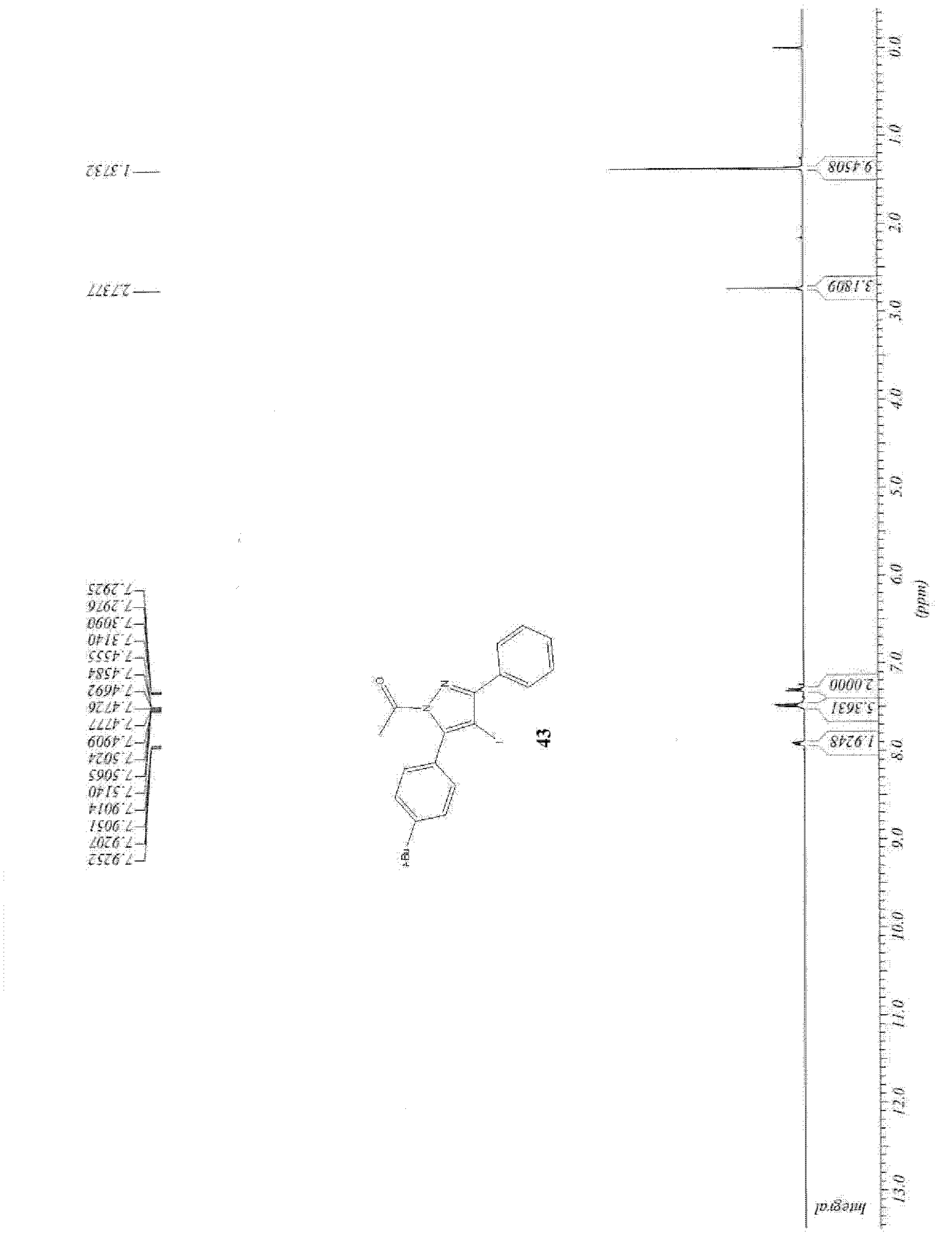


42

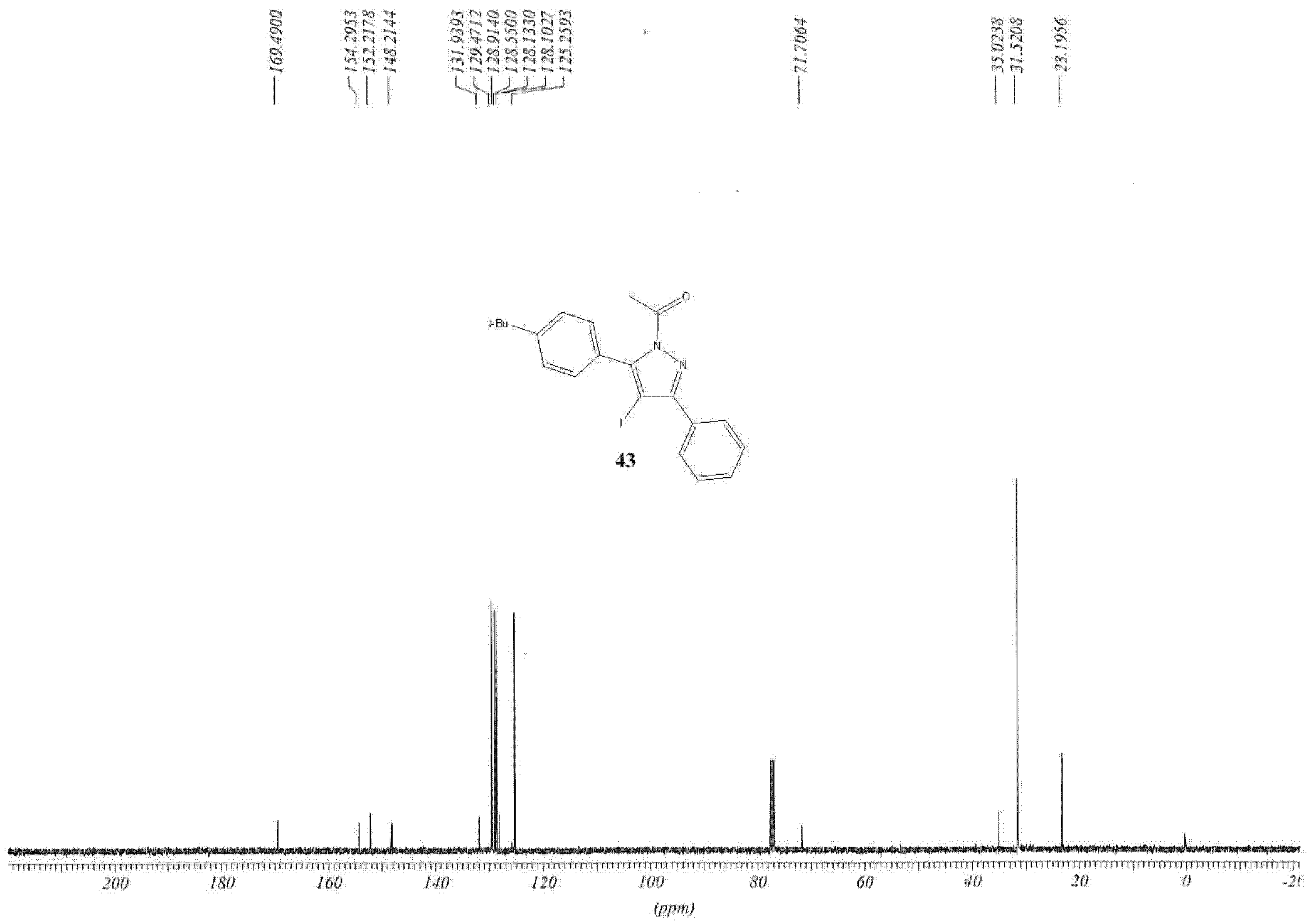
2.7590
7.4820
7.4866
7.4985
7.5031
7.5092
7.5117
7.5161
7.7552
7.7641
7.7690
7.7809
7.7834
7.7870
7.8916
7.8998
7.9044
7.9111
NC
N
N
2.6744
4.5033
2.0000
1.7799
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)


22.8999
72.0362
113.1809
118.6628
128.6941
128.8683
129.8087
130.8019
131.3630
132.1895
136.1246
145.9435
154.7237
169.4332
NC
N
N
0
20
40
60
80
100
120
140
160
180
200
(ppm)

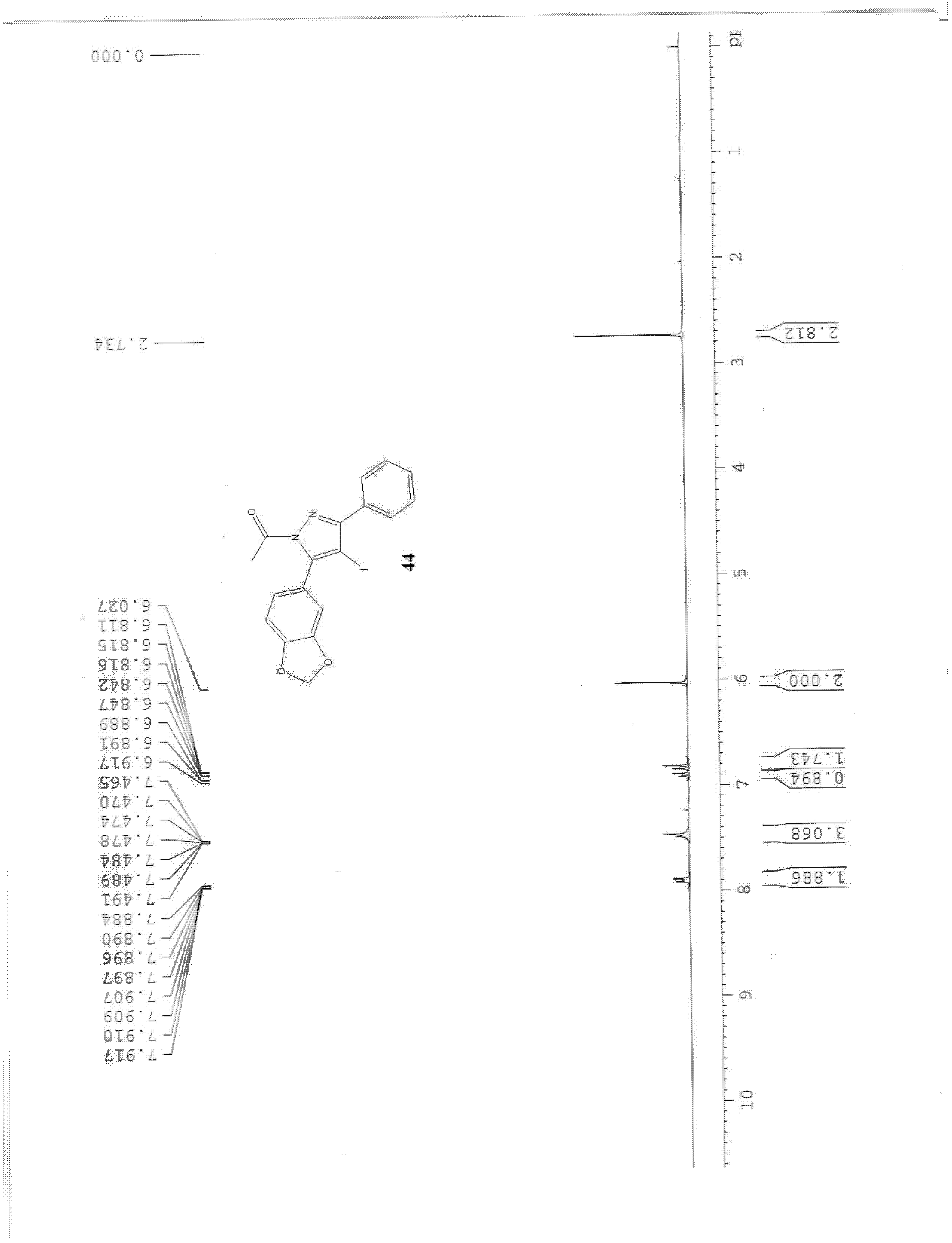
42

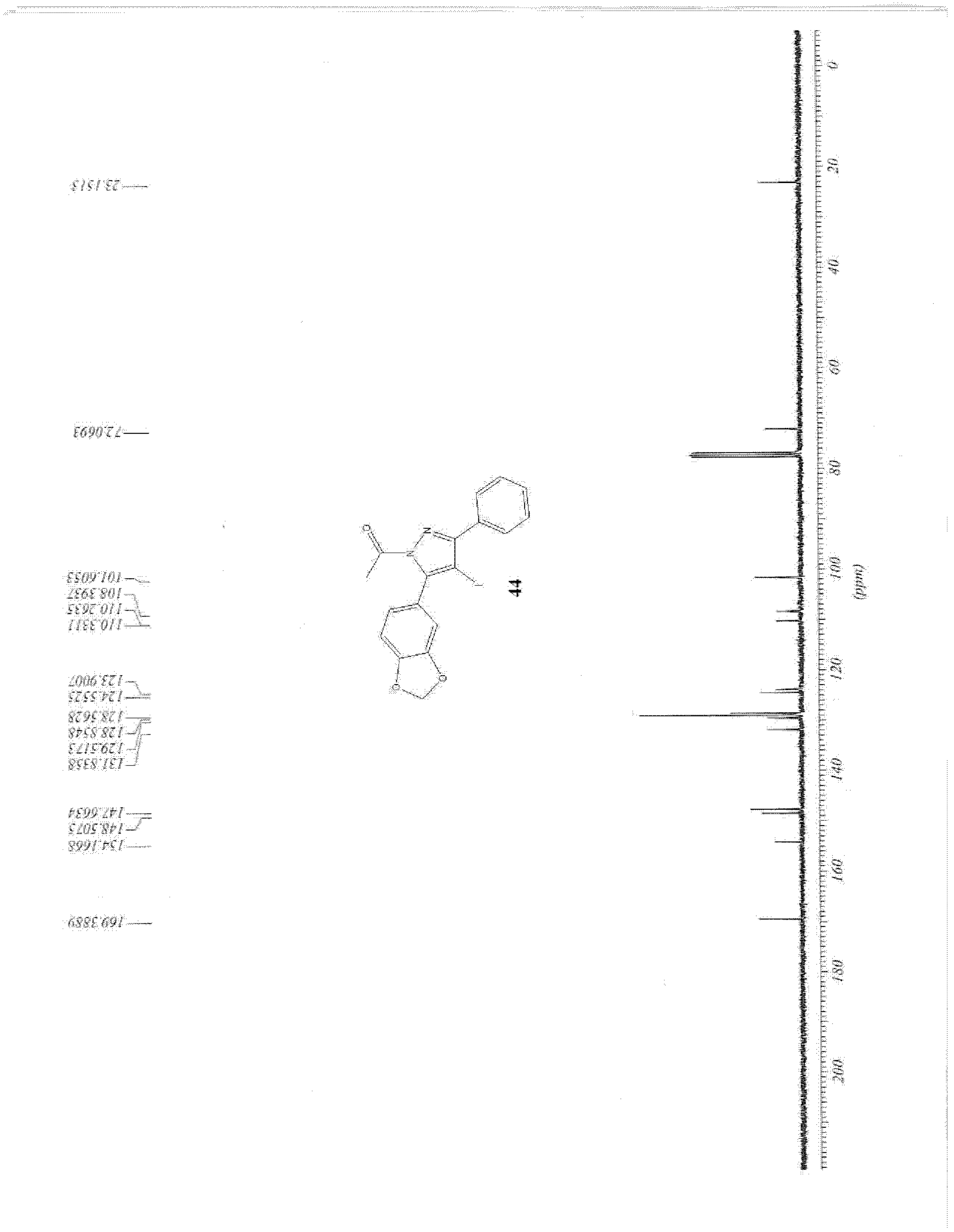

1.3732
2.7377
7.2925
7.2976
7.3090
7.3140
7.4555
7.4584
7.4692
7.4726
7.4777
7.4909
7.5024
7.5065
7.5140
7.9014
7.9051
7.9207
7.9252
N
N
t-Bu
9.4508
3.1809
2.0000
5.3631
1.9248
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

43

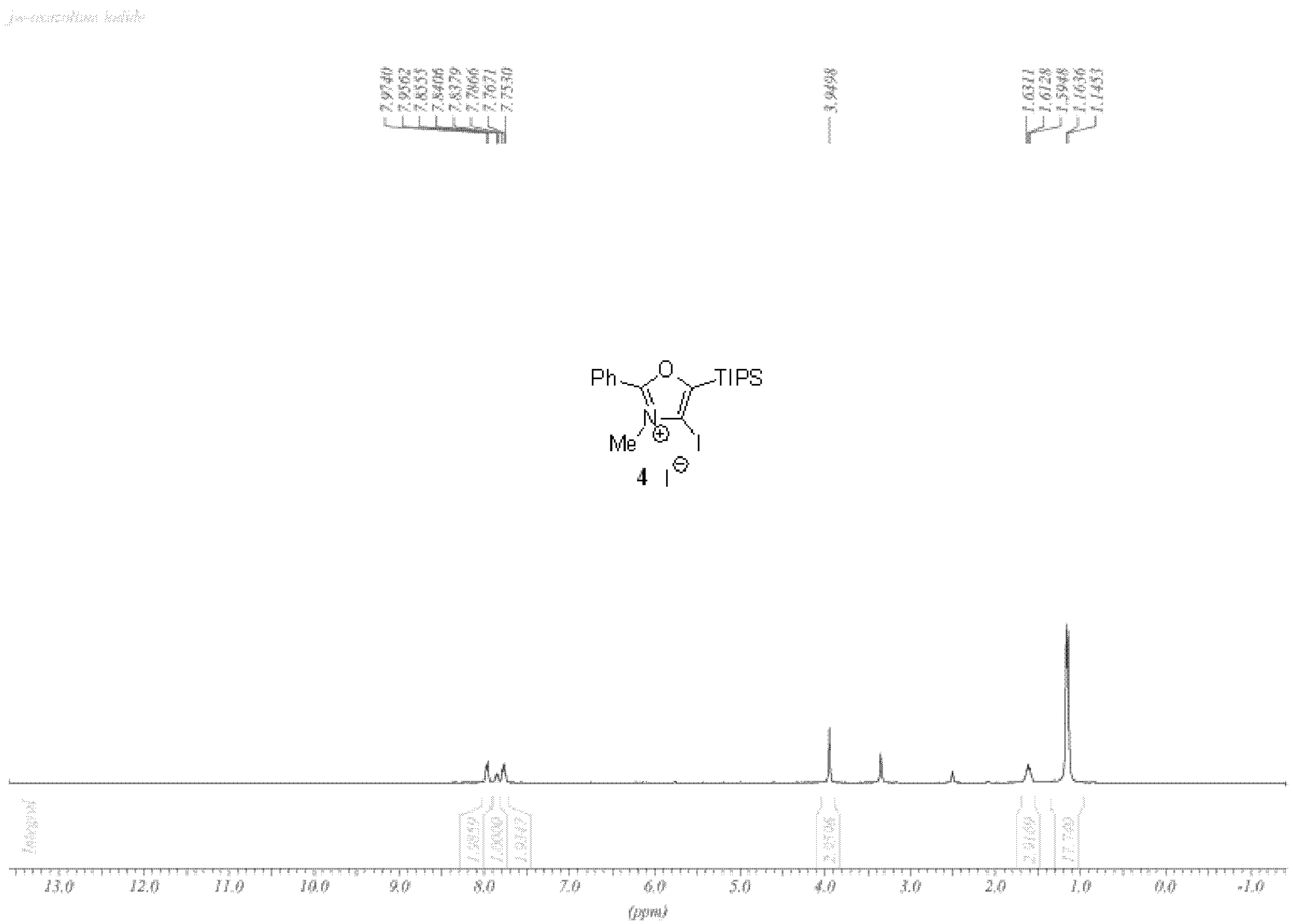

169.4900
154.2953
152.2178
148.2144
131.9393
129.4712
128.9140
128.5500
128.1330
128.1027
125.2593
71.7064
35.0238
31.5208
23.1956
t-Bu
N
N
O
I
200
180
160
140
120
100
80
60
40
20
0
-2
(ppm)

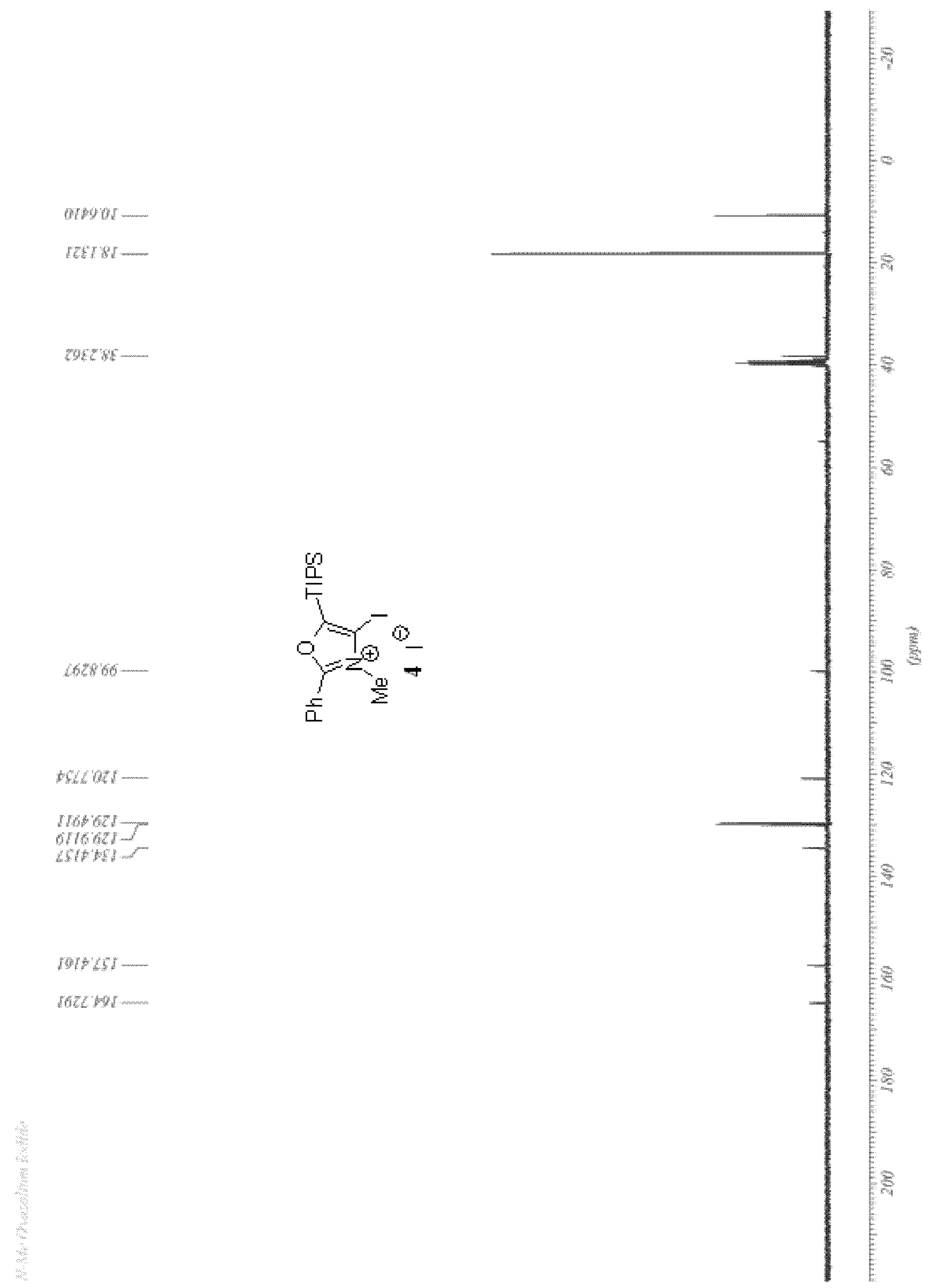
43

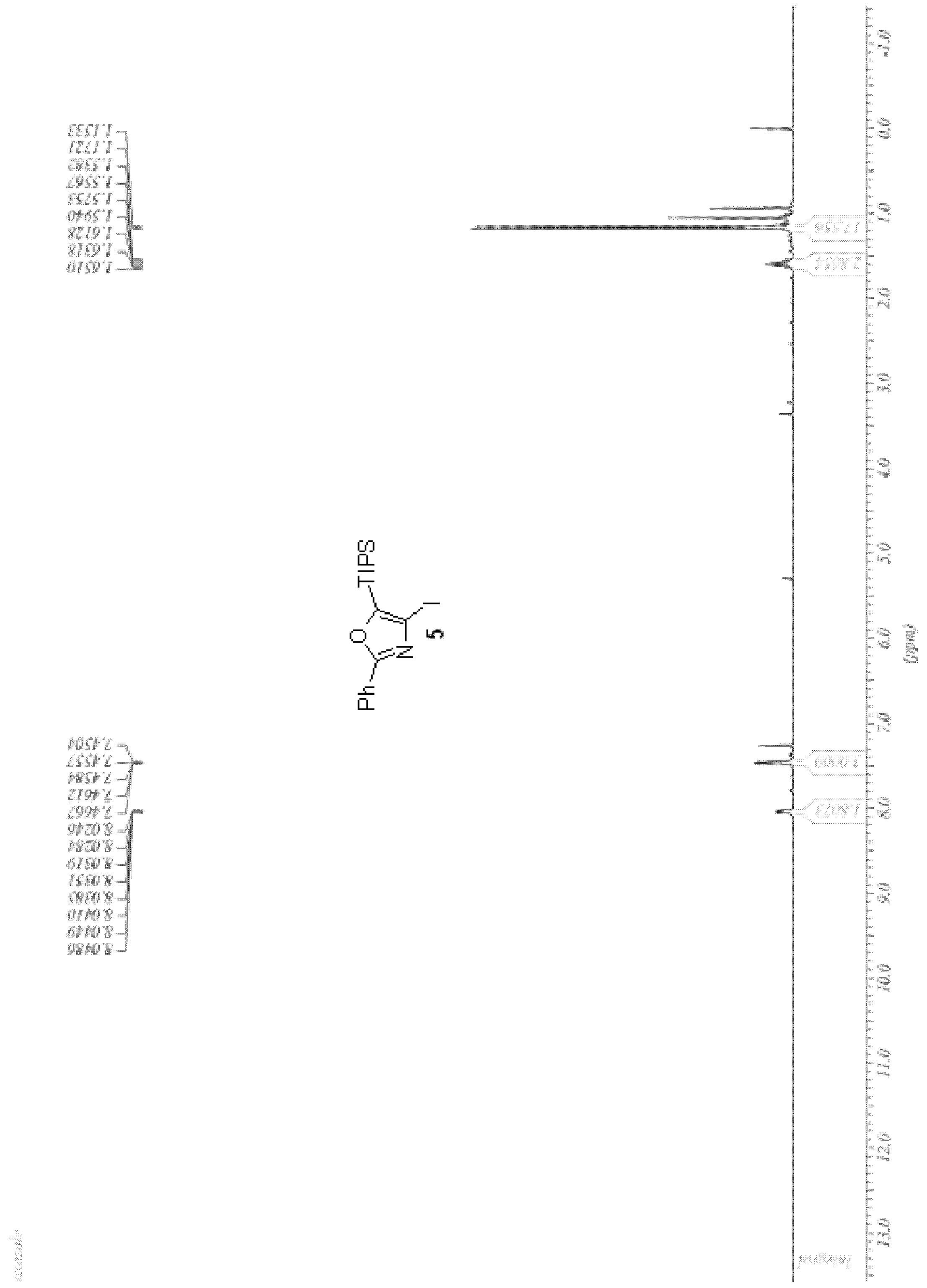

0.000
2.734
6.027
6.811
6.815
6.816
6.842
6.847
6.889
6.891
6.917
7.465
7.470
7.474
7.478
7.484
7.489
7.491
7.884
7.890
7.896
7.897
7.907
7.909
7.910
7.917
44
2.812
2.000
1.743
0.894
3.068
1.886
ppm
1
2
3
4
5
6
7
8
9
10


23.1513
72.0693
101.6053
108.3937
110.2635
110.3311
123.9007
124.5525
128.5628
128.8548
129.5173
131.8358
147.6634
148.5073
154.1668
169.3889
O
N
N
O
O
44
0
20
40
60
80
100
120
140
160
180
200
(ppm)

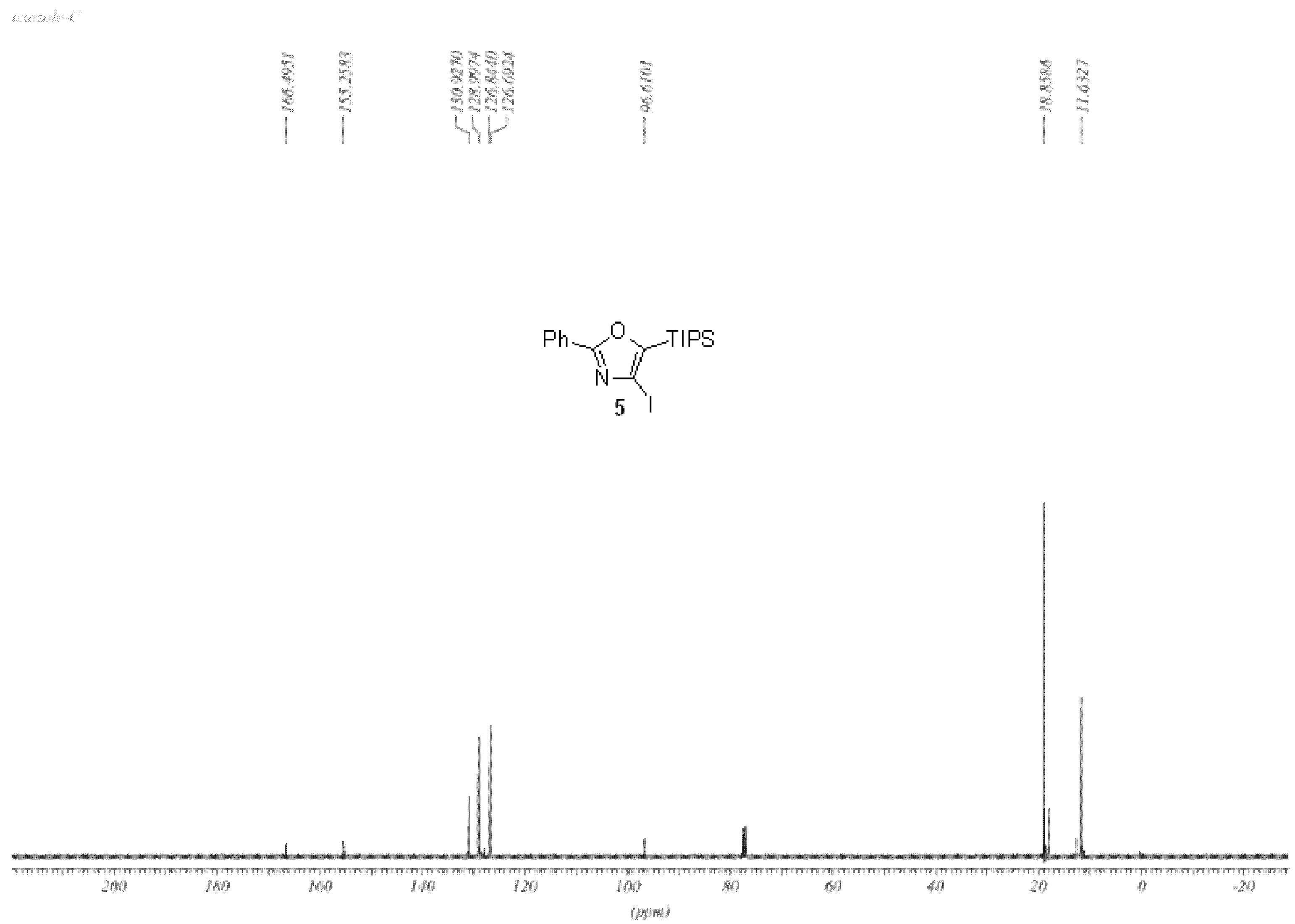
APPENDIX D. CHAPTER 4 ^{1}H AND ^{13}C NMR SPECTRA


jw-oxazolium iodide
7.9740
7.9562
7.8555
7.8406
7.8379
7.7866
7.7671
7.7530
3.9498
1.6311
1.6128
1.5948
1.1636
1.1453
Ph
O
TIPS
N
Me
I
4
I
Integral
1.9859
1.0000
1.9347
2.9596
2.9169
17.740
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

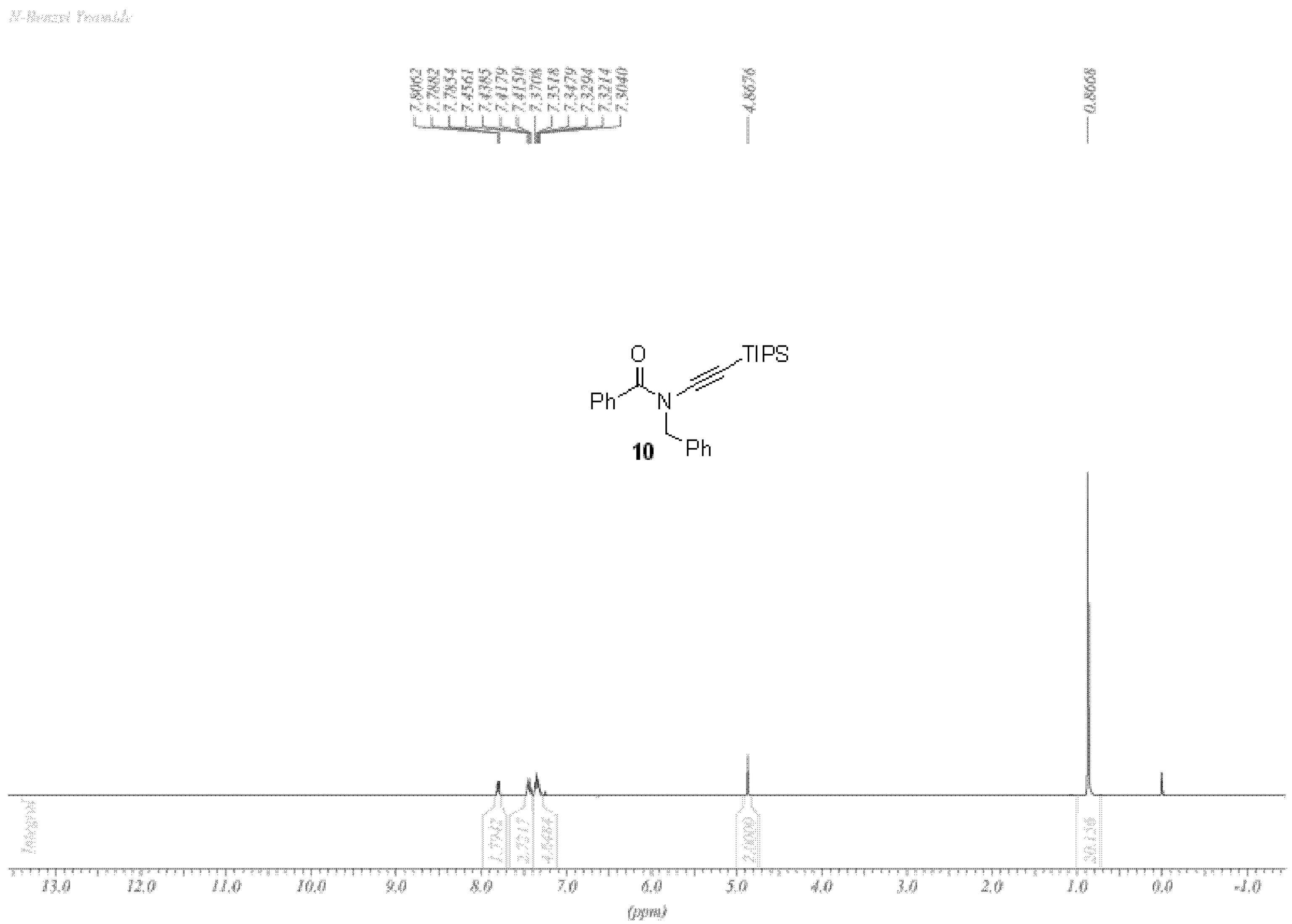

N-Me Oxazolium Iodide
10.6410
18.1321
38.2362
99.8297
120.7734
129.4911
129.9119
134.4157
157.4161
164.7291
Ph
O
N
⊕
Me
TIPS
I
4
I ⊖
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

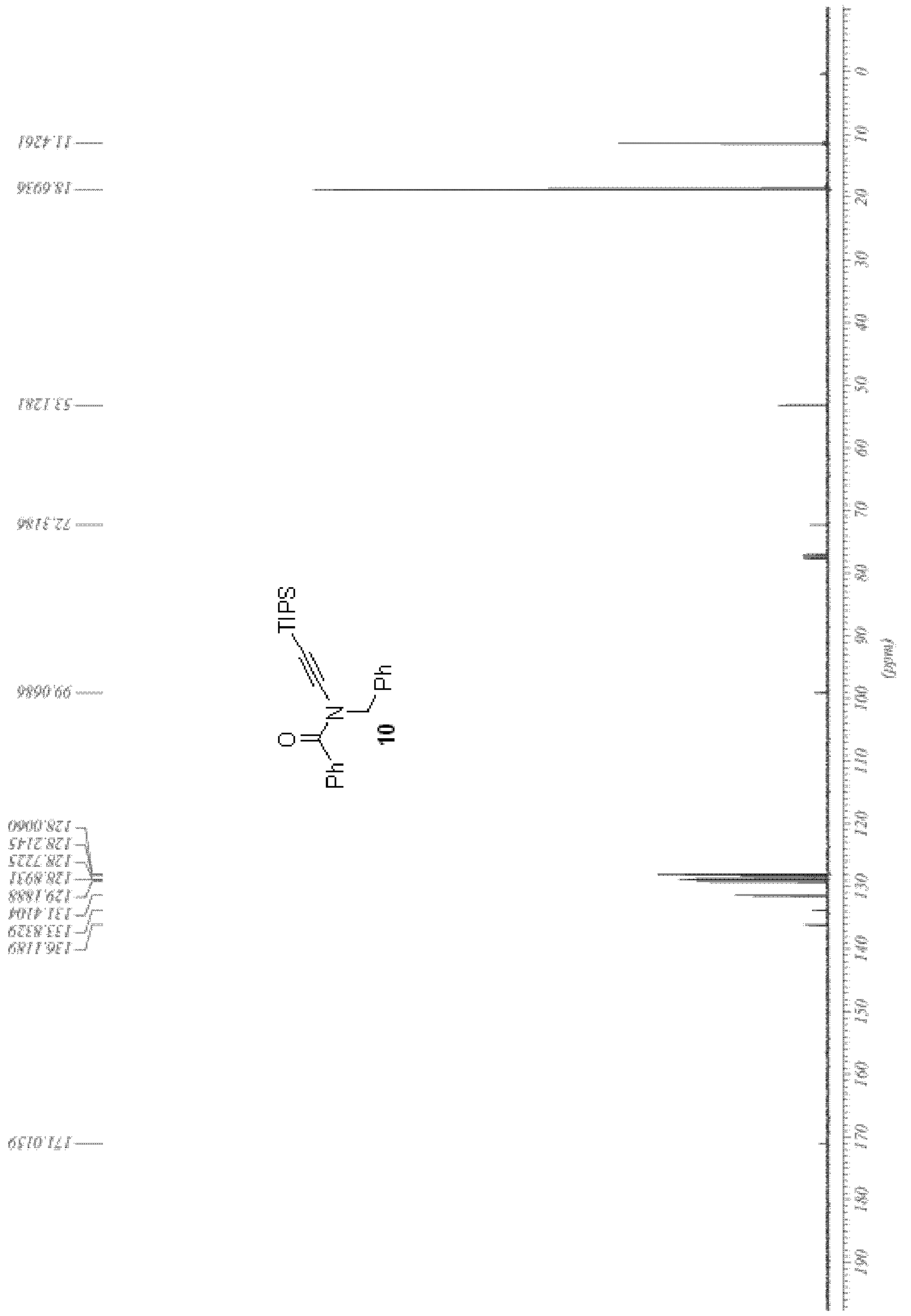


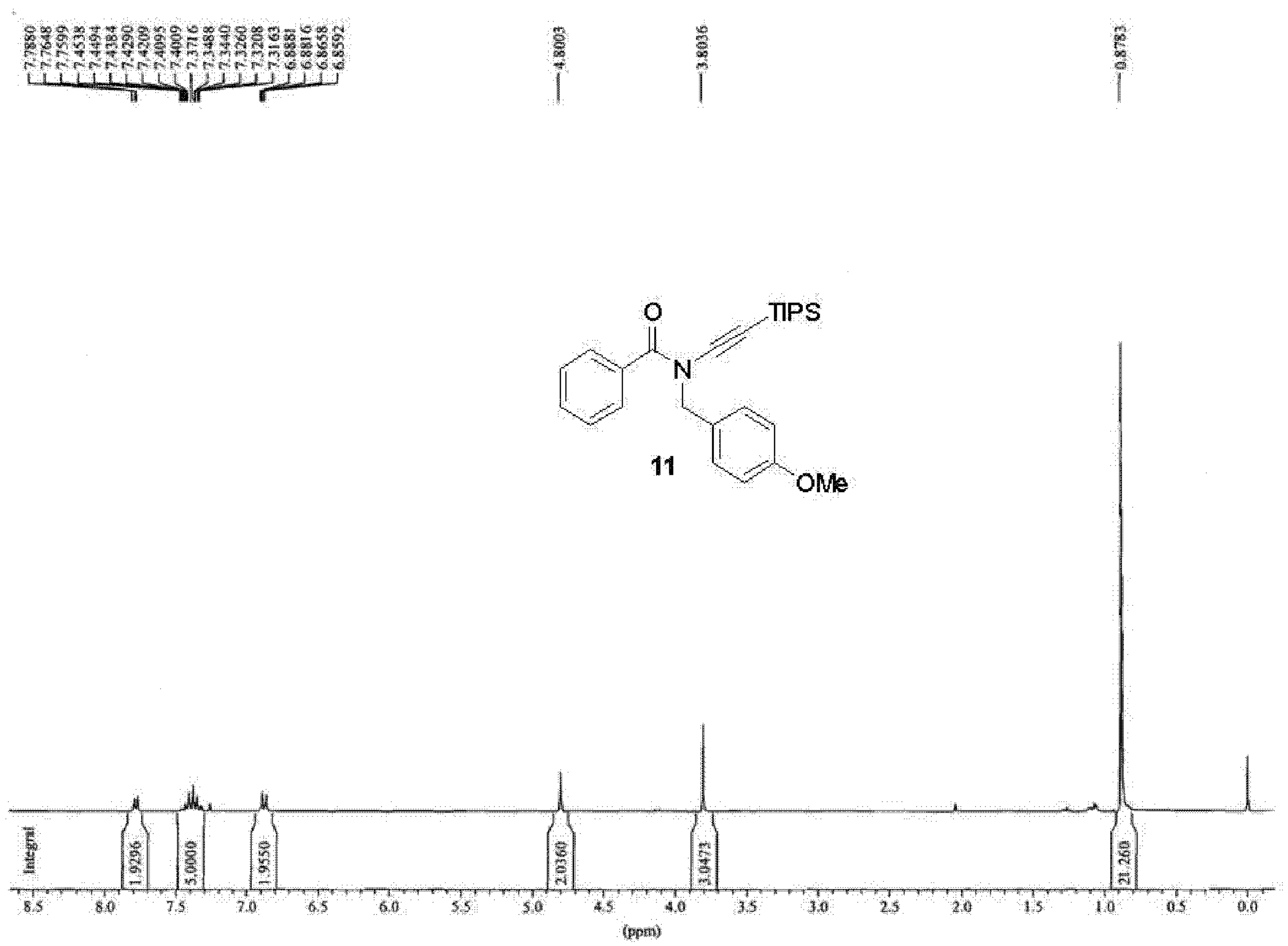
1.1533
1.1721
1.5382
1.5567
1.5755
1.5940
1.6128
1.6318
1.6510
7.4504
7.4557
7.4584
7.4612
7.4667
8.0246
8.0284
8.0319
8.0351
8.0385
8.0410
8.0449
8.0486
Ph
O
N
TIPS
I
5
17.556
2.8654
3.0000
1.8073
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral


5

oxazole-C
166.4951
155.2583
130.9270
128.9974
126.8440
126.6924
96.6101
18.8586
11.6327
Ph
O
N
TIPS
I
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

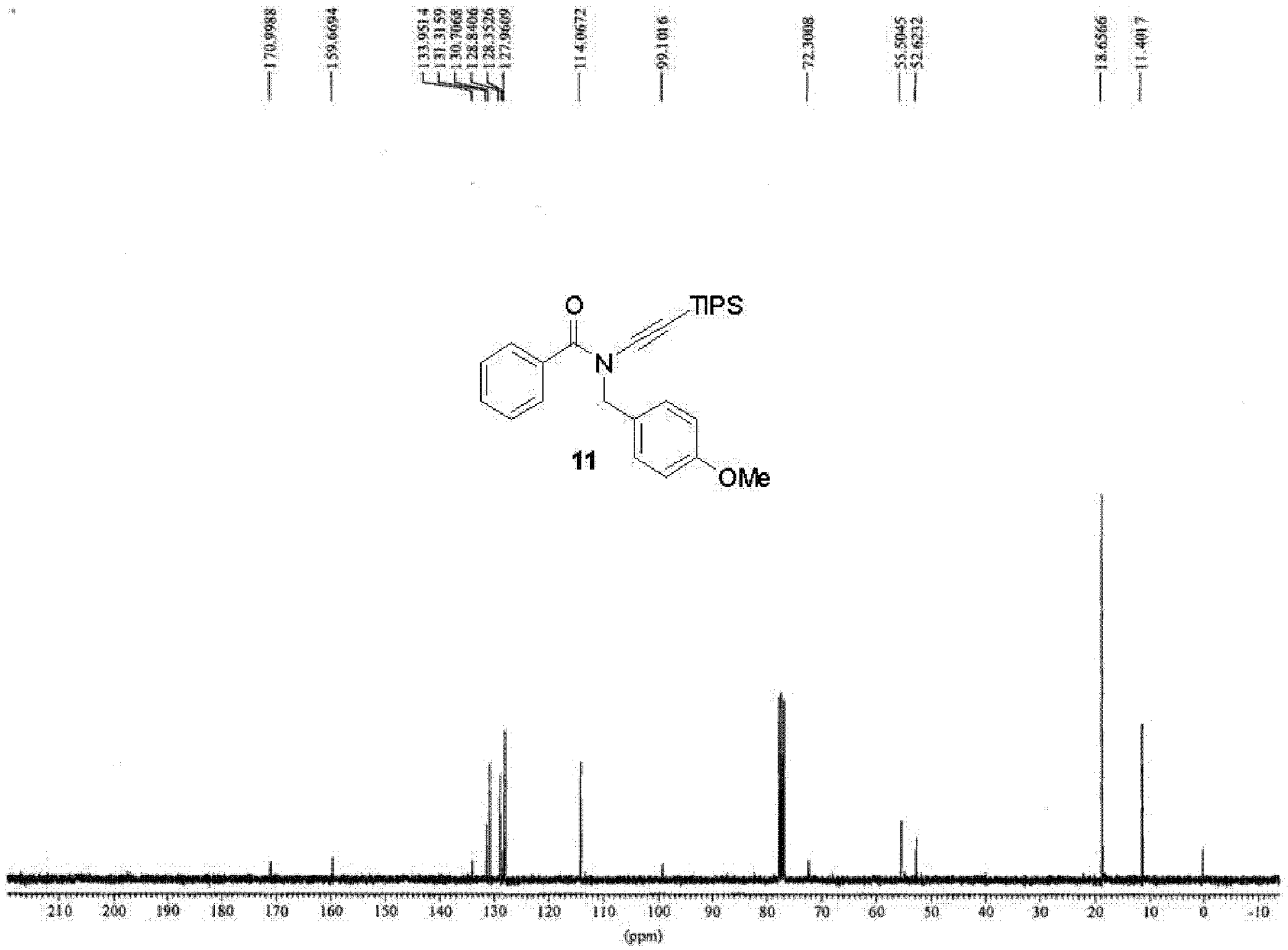

N-Benzyl Ynamide
7.8062
7.7882
7.7854
7.4561
7.4385
7.4179
7.4150
7.3708
7.3518
7.3479
7.3294
7.3214
7.3040
4.8676
0.8668
O
Ph
N
TIPS
Ph
10
Integral
1.7942
2.7217
4.5484
2.0000
20.136
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)


11.4261
18.6936
53.1281
72.3186
99.0686
128.0060
128.2145
128.7225
128.8931
129.1888
131.4104
133.8329
136.1189
171.0159
O
Ph
N
TIPS
Ph
10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
(ppm)



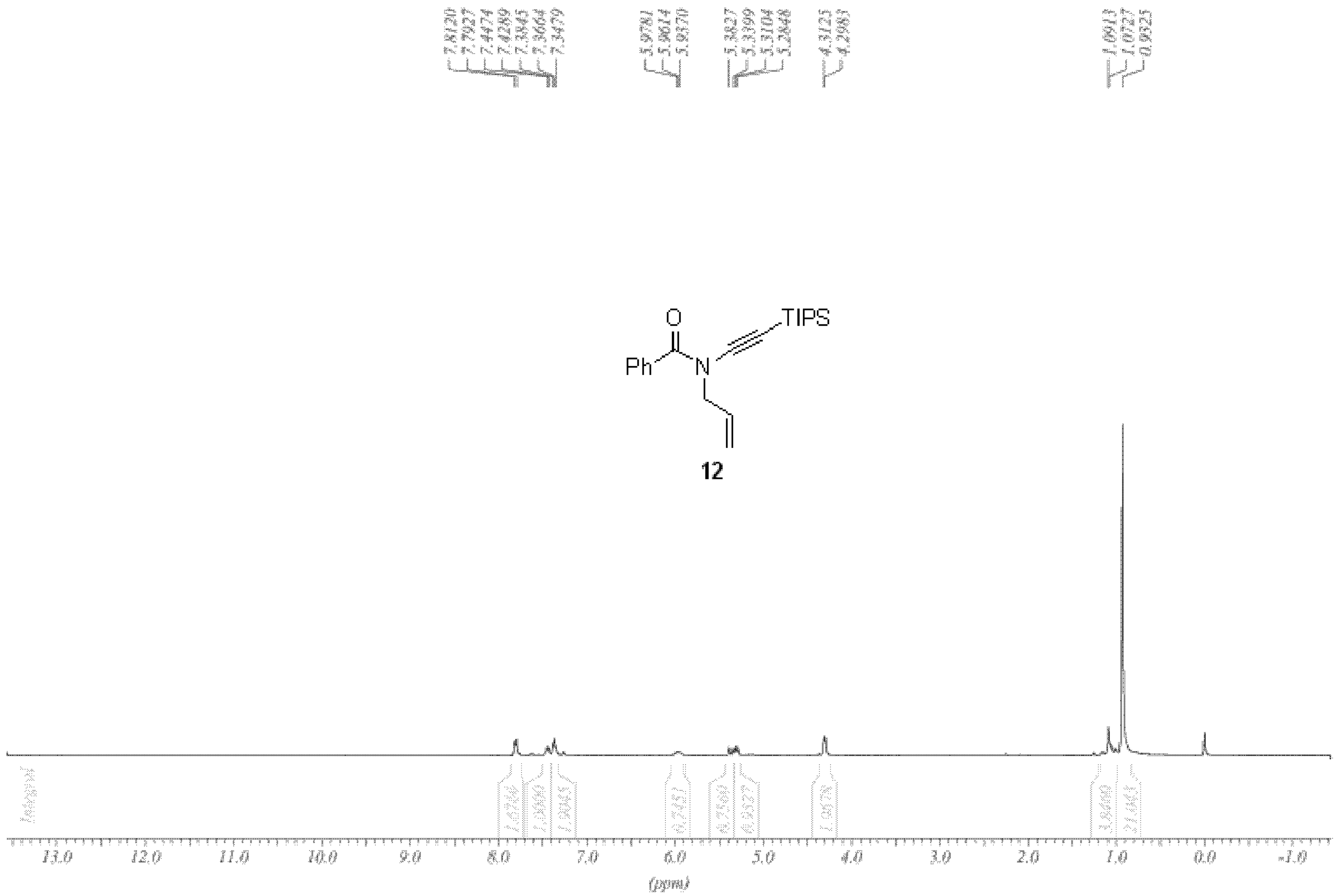
11

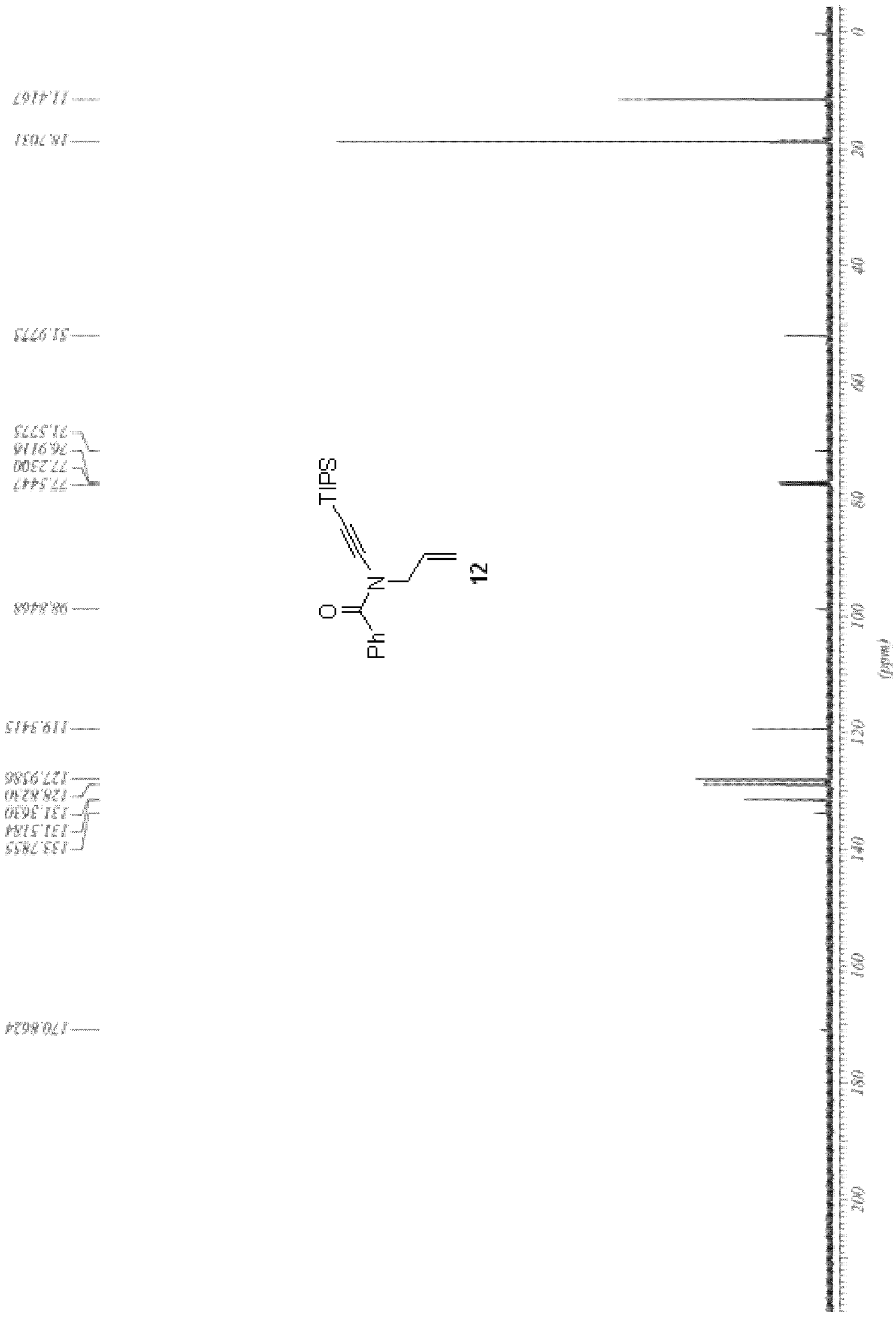
7.7880
7.7648
7.7599
7.4538
7.4494
7.4384
7.4290
7.4209
7.4095
7.4009
7.3716
7.3488
7.3440
7.3260
7.3208
7.3163
6.8881
6.8816
6.8658
6.8592
4.8003
3.8036
0.8783
TIPS
N
O
OMe
Integral
1.9296
5.0000
1.9550
2.0360
3.0473
21.260
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

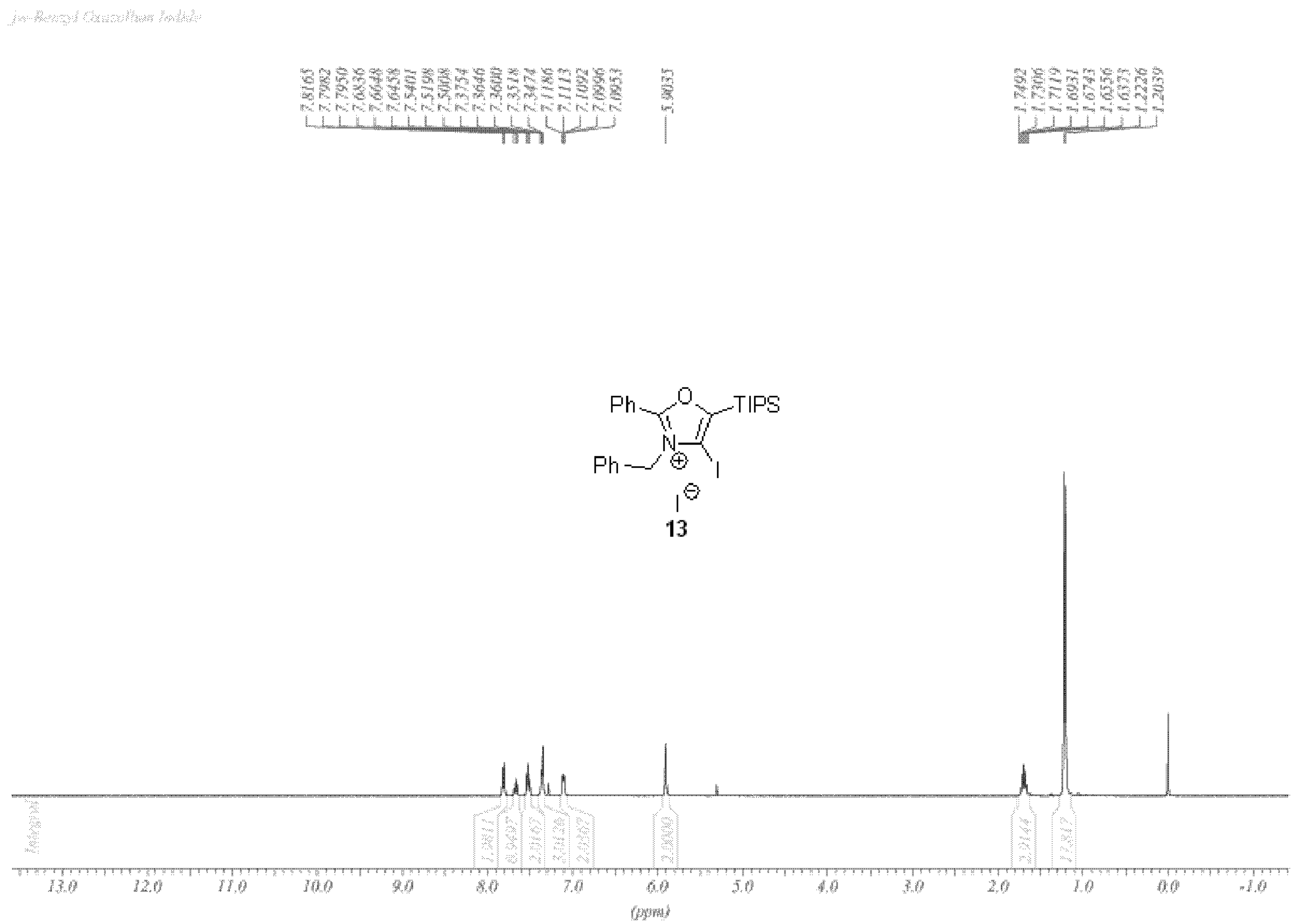


11

170.9988
159.6694
133.9514
131.3159
130.7068
128.8406
128.3526
127.9609
114.0672
99.1016
72.3008
55.5045
52.6232
18.6566
11.4017
O
N
TIPS
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

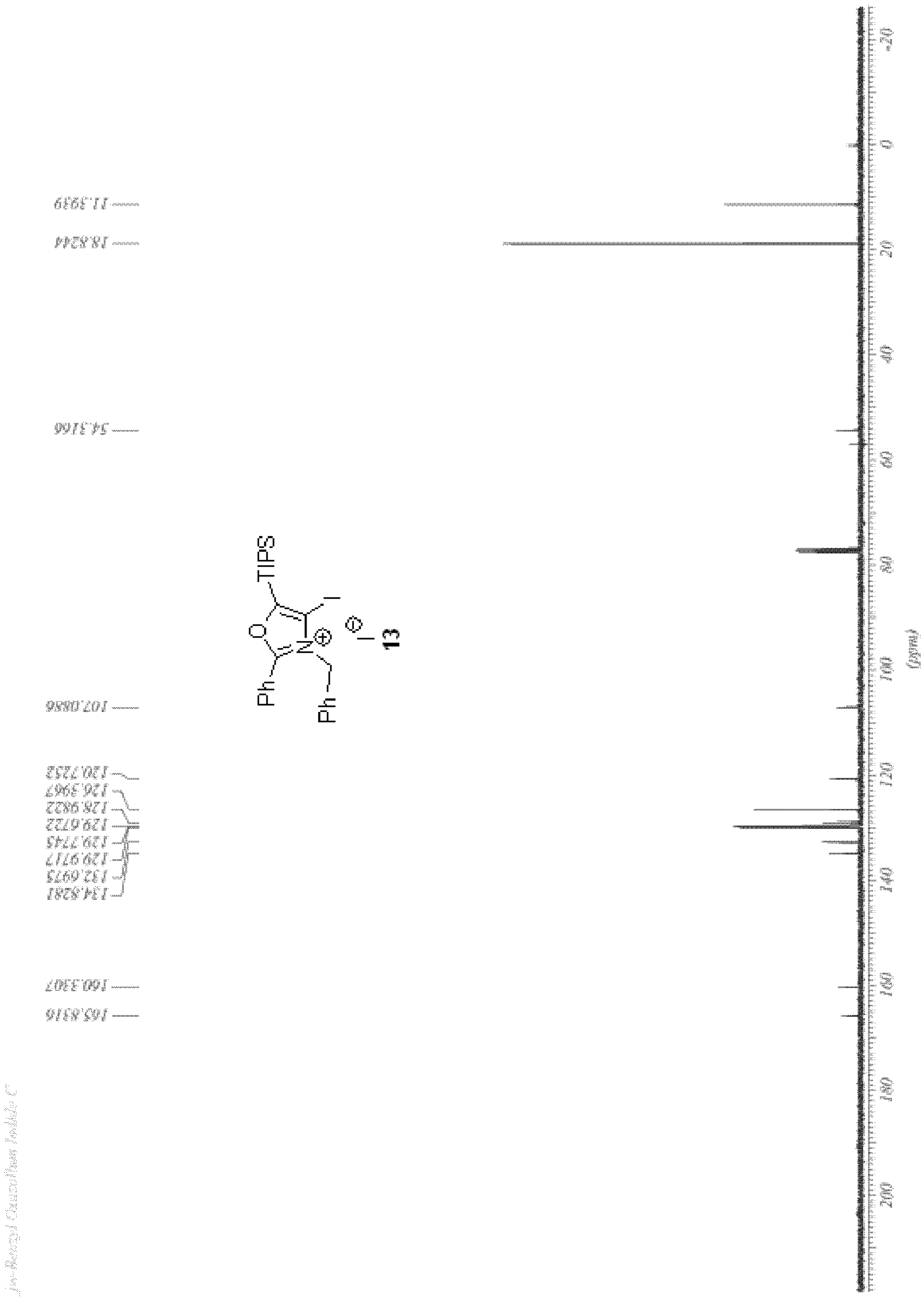

7.8120
7.7927
7.4474
7.4289
7.3845
7.3664
7.3479
5.9781
5.9614
5.9370
5.3827
5.3399
5.3104
5.2848
4.3125
4.2983
1.0913
1.0727
0.9525
O
Ph
N
TIPS
12
Integral
1.6744
1.0000
1.9045
0.7451
0.7560
0.6527
1.3678
3.8480
21.043
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

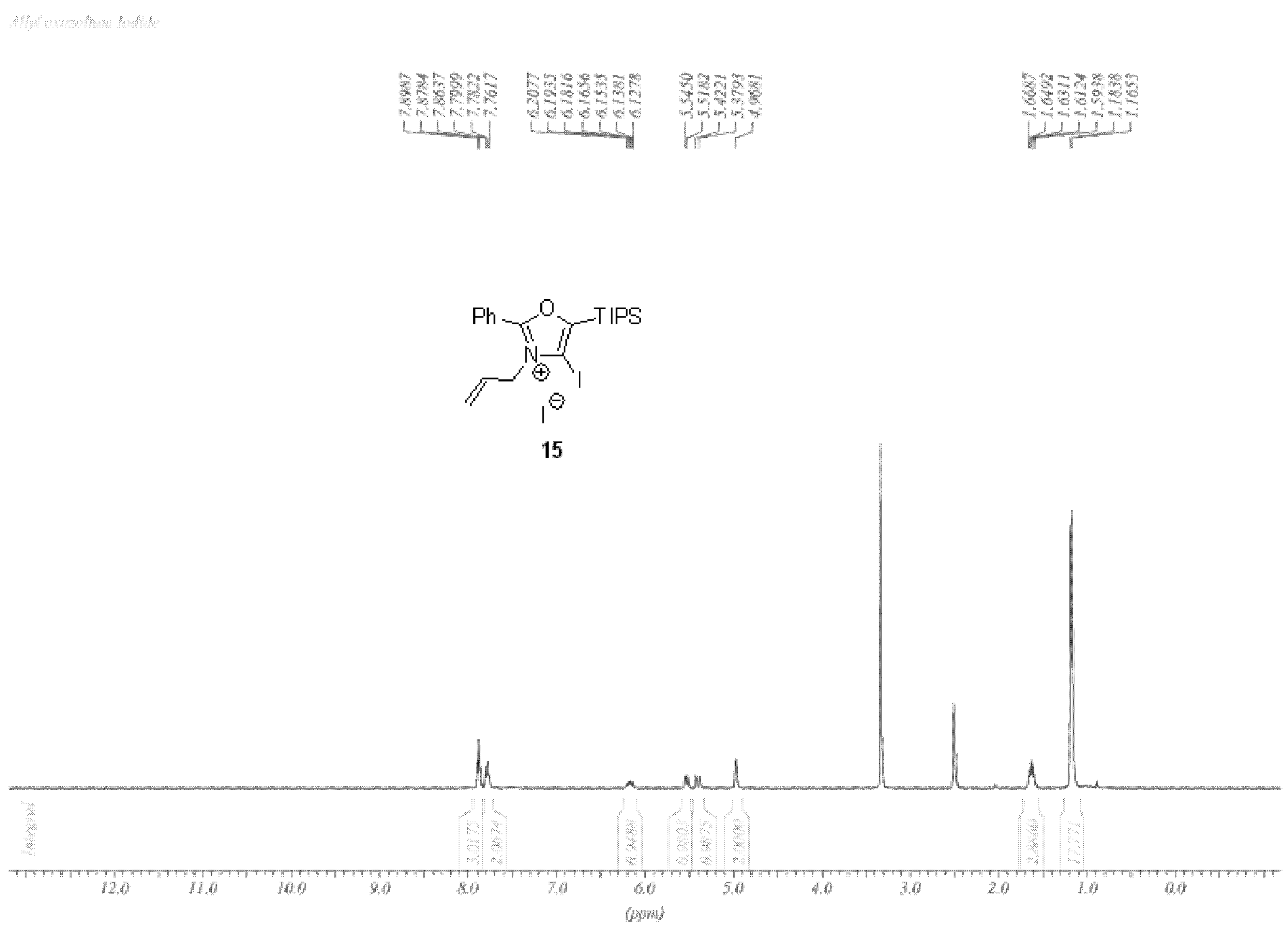

11.4167
18.7031
51.9775
71.5775
76.9116
77.2300
77.5447
98.8468
119.3415
127.9586
128.8230
131.3630
131.5184
133.7855
170.8624
Ph
O
N
TIPS
12
0
20
40
60
80
100
120
140
160
180
200
(ppm)



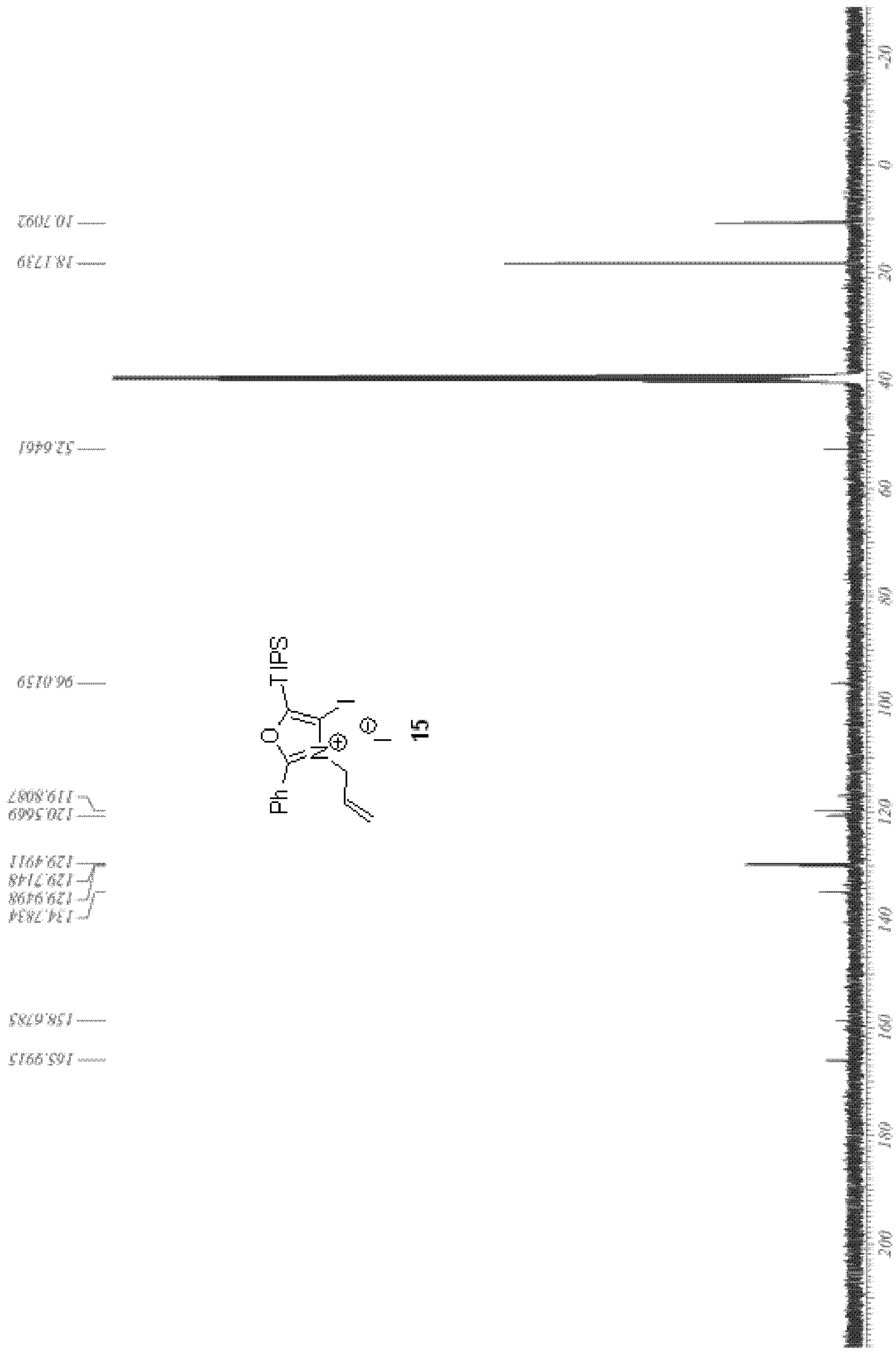
13

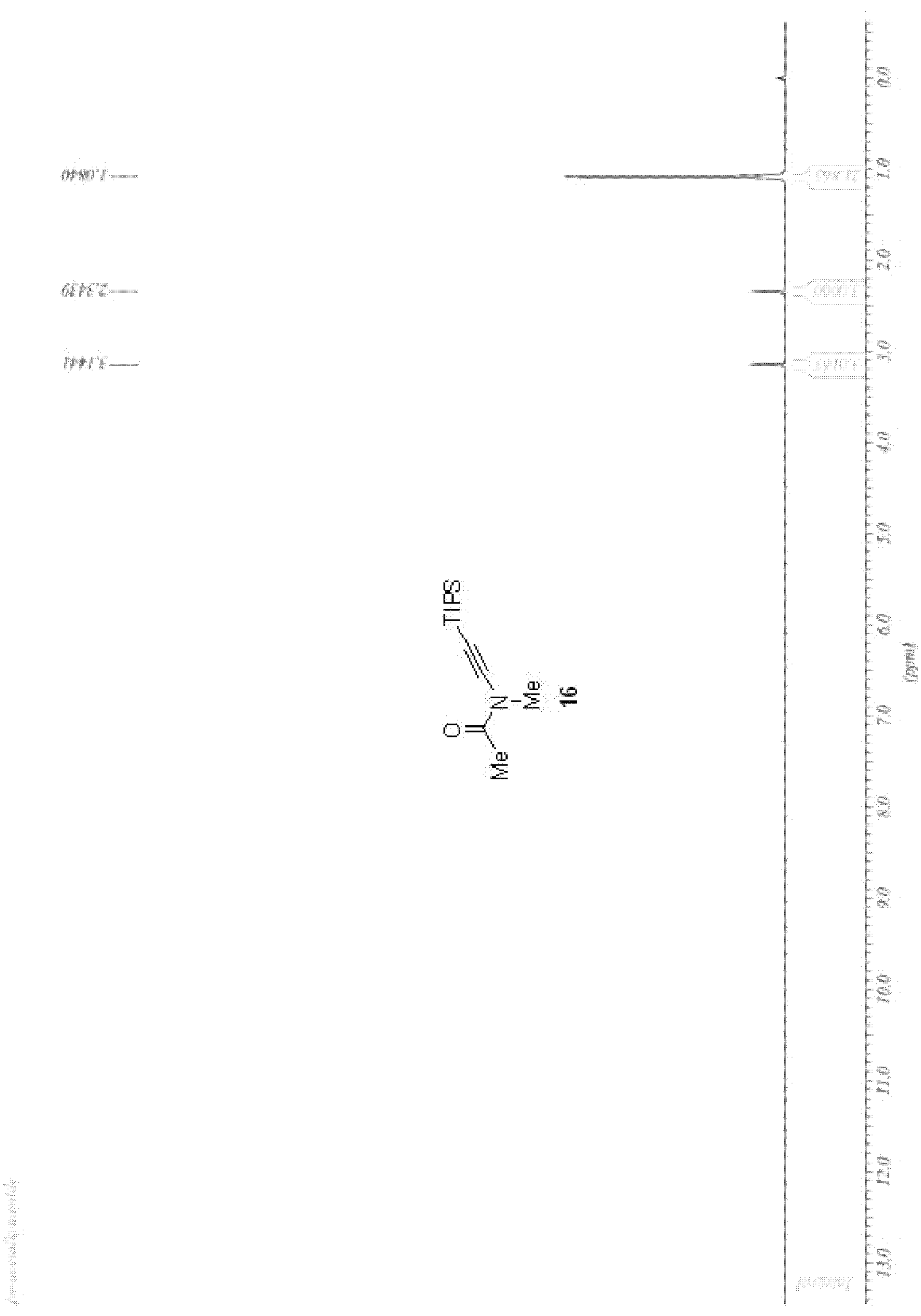
N-Benzyl Oxazolium Iodide
7.8165
7.7982
7.7950
7.6836
7.6648
7.6458
7.5401
7.5198
7.5008
7.3754
7.3646
7.3600
7.3518
7.3474
7.1186
7.1113
7.1092
7.0996
7.0953
5.9035
1.7492
1.7306
1.7119
1.6931
1.6743
1.6556
1.6373
1.2226
1.2039
Ph
O
TIPS
N
⊕
I
I
⊖
Integral
1.9811
0.9497
2.0167
3.0126
2.0567
2.0000
2.0144
17.817
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

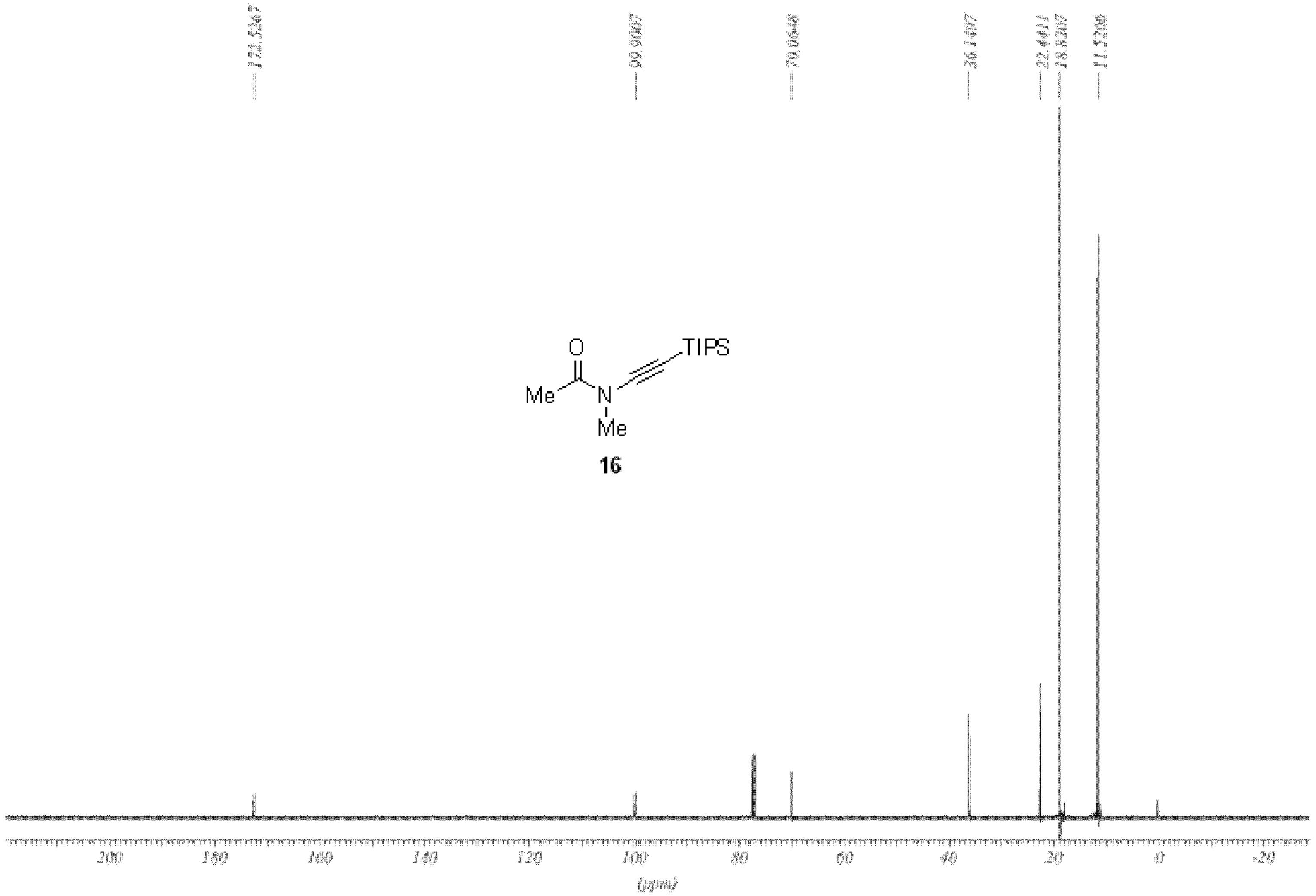

11.3939
18.8244
54.3166
107.0886
120.7252
126.3967
128.9822
129.6722
129.7745
129.9717
132.6975
134.8281
160.3307
165.8316
TIPS
O
I
N
⊕
Ph
Ph
I
⊖
13
(ppm)
-20
0
20
40
60
80
100
120
140
160
180
200
jw-Benzyl Oxazolium Iodide C


Allyl oxazolium Iodide
7.8987
7.8784
7.8637
7.7999
7.7822
7.7617
6.2077
6.1935
6.1816
6.1656
6.1535
6.1381
6.1278
5.5450
5.5182
5.4221
5.3793
4.9681
1.6687
1.6492
1.6311
1.6124
1.5938
1.1838
1.1653
Ph
O
TIPS
N
⊕
I
I
⊖
Integral
3.0175
2.0674
0.9489
0.9803
0.9875
2.0000
2.8660
17.771
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

15


15
10.7092
18.1739
52.6461
96.0159
119.8087
120.5669
129.4911
129.7148
129.9498
134.7834
158.6785
165.9915
Ph
O
TIPS
N
I
I
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

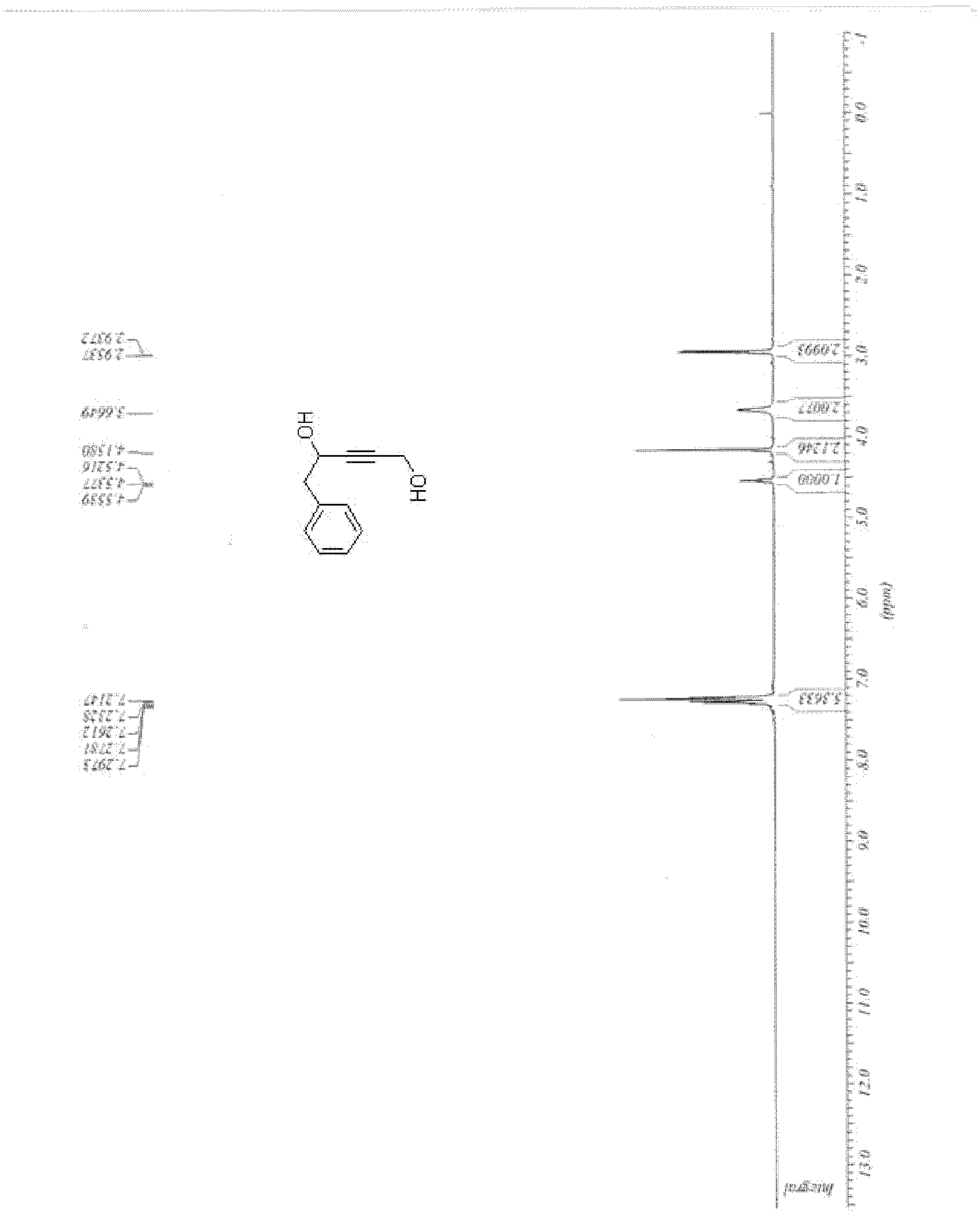

1.0840
2.3439
3.1441
21.863
3.0000
3.0161
TIPS
O
Me
N
Me
16
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral

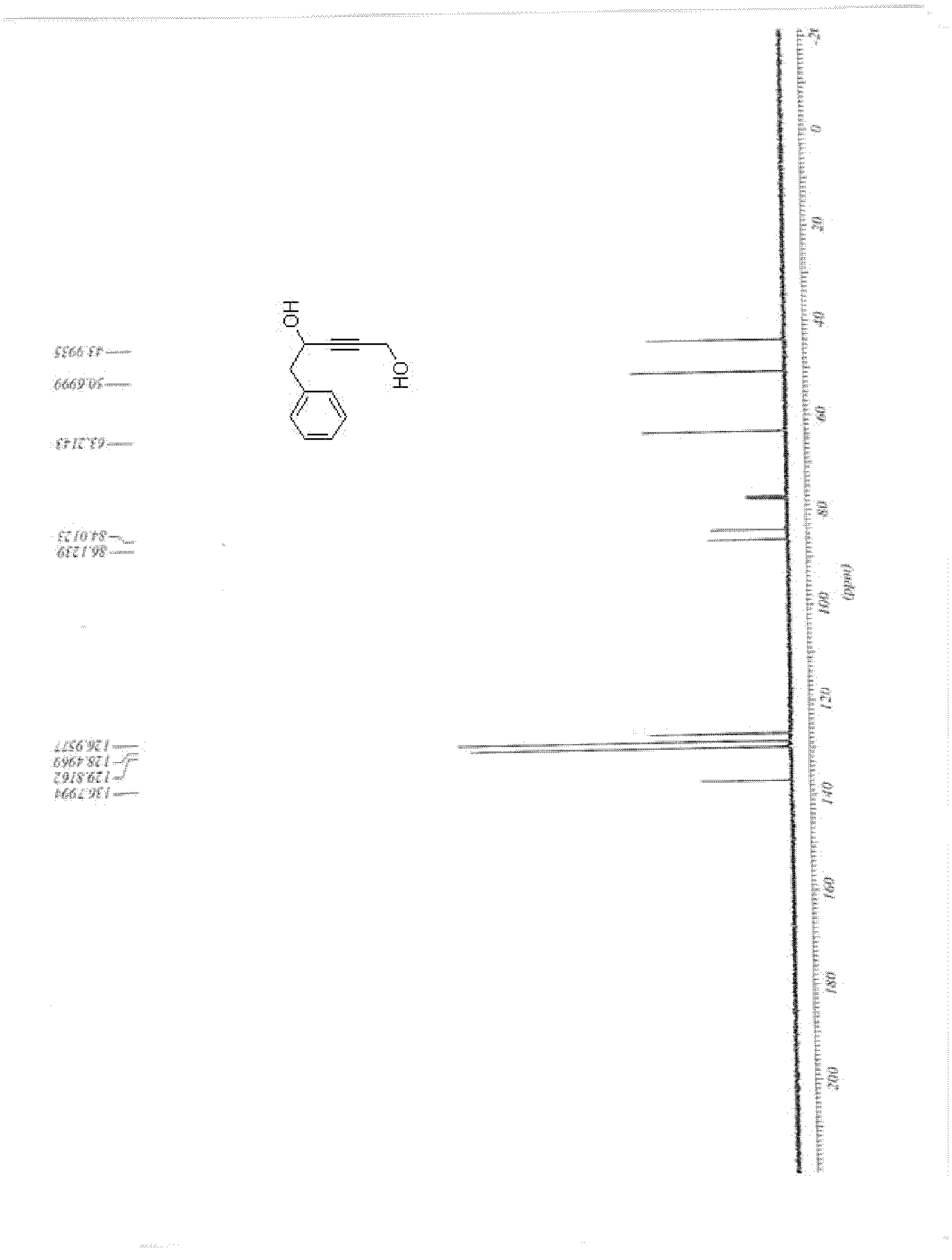


16

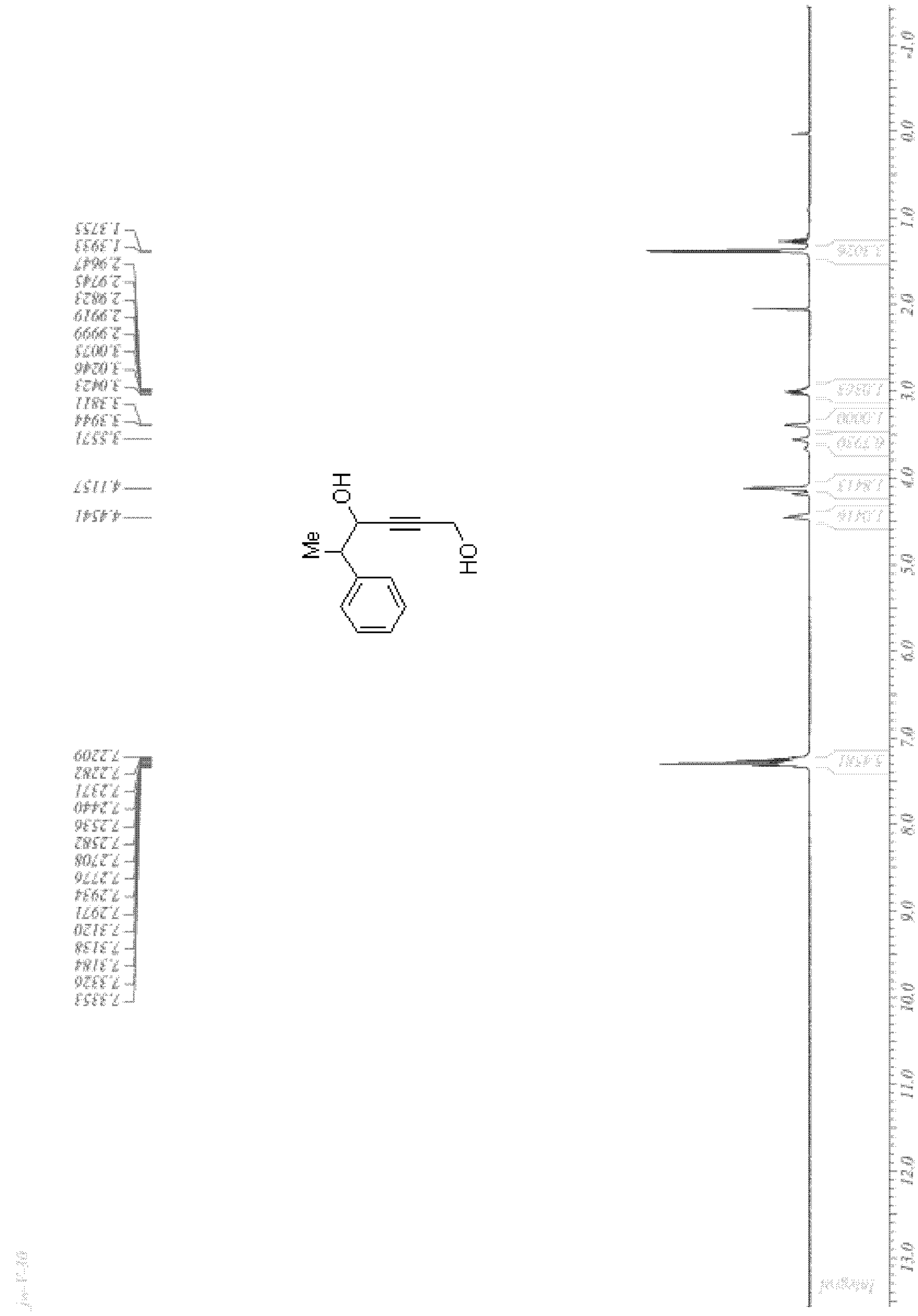
172.5267
99.9007
70.0648
36.1497
22.4411
18.8207
11.5266
O
Me
N
Me
TIPS
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

APPENDIX E. CHAPTER 5 ^{1}H AND ^{13}C NMR SPECTRA

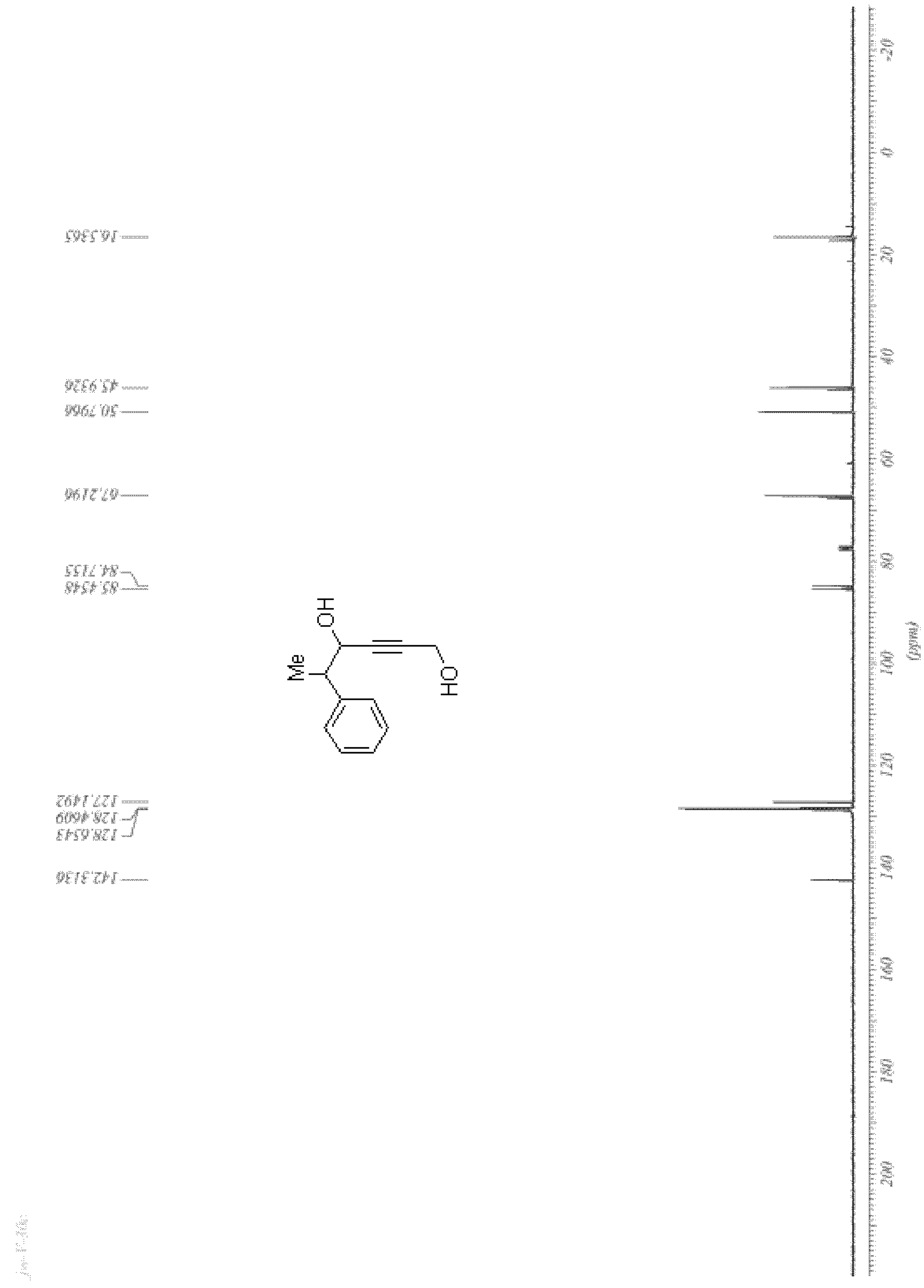

2.9372
2.9537
3.6649
4.1580
4.5216
4.5377
4.5559
7.2147
7.2328
7.2613
7.2781
7.2973
HO
OH
2.0993
2.0077
2.1246
1.0000
5.3633
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)
Integral

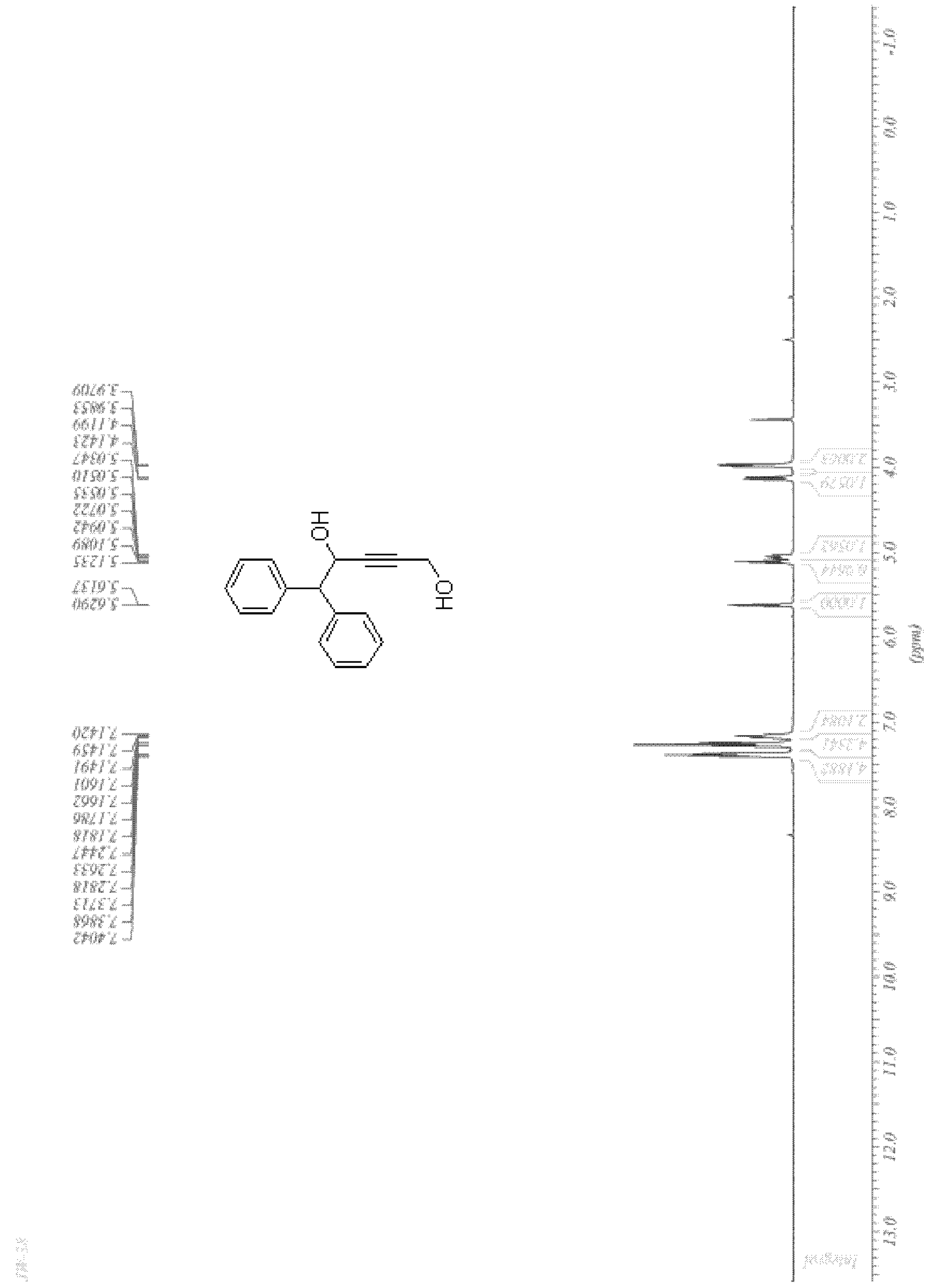


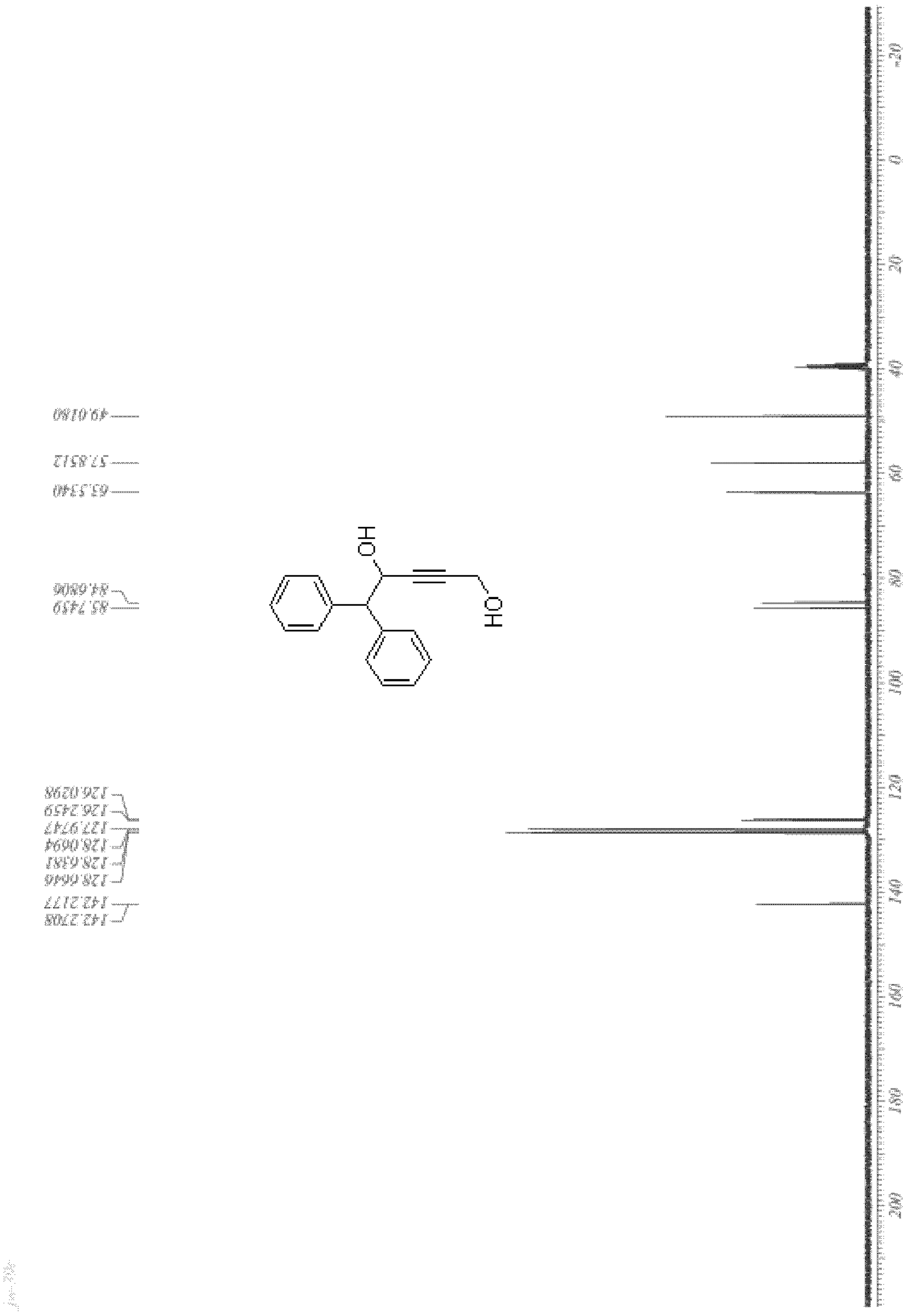
43.9935
50.6999
63.2143
84.0123
86.1239
126.9577
128.4969
129.8162
136.7994
OH
HO
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

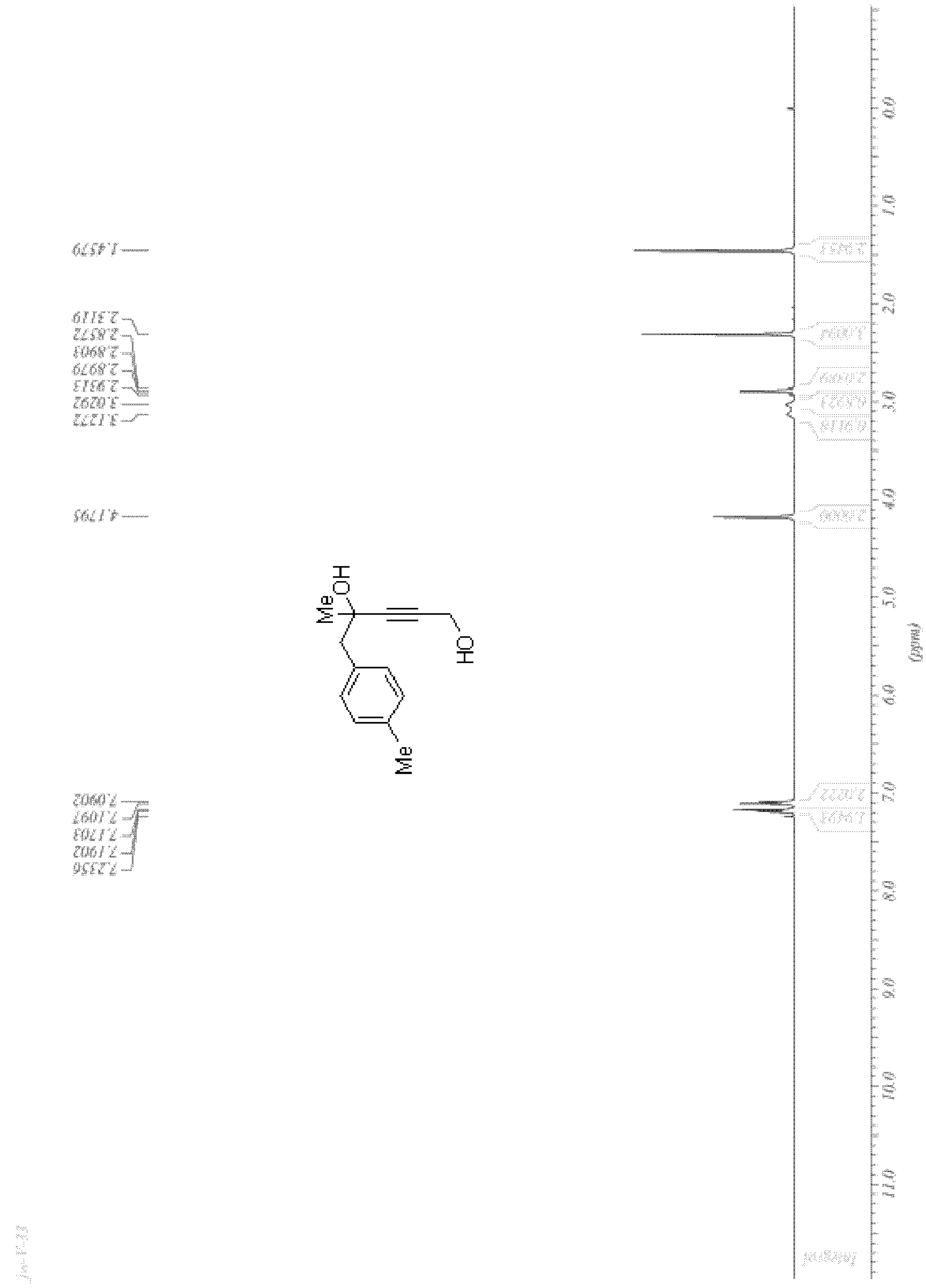


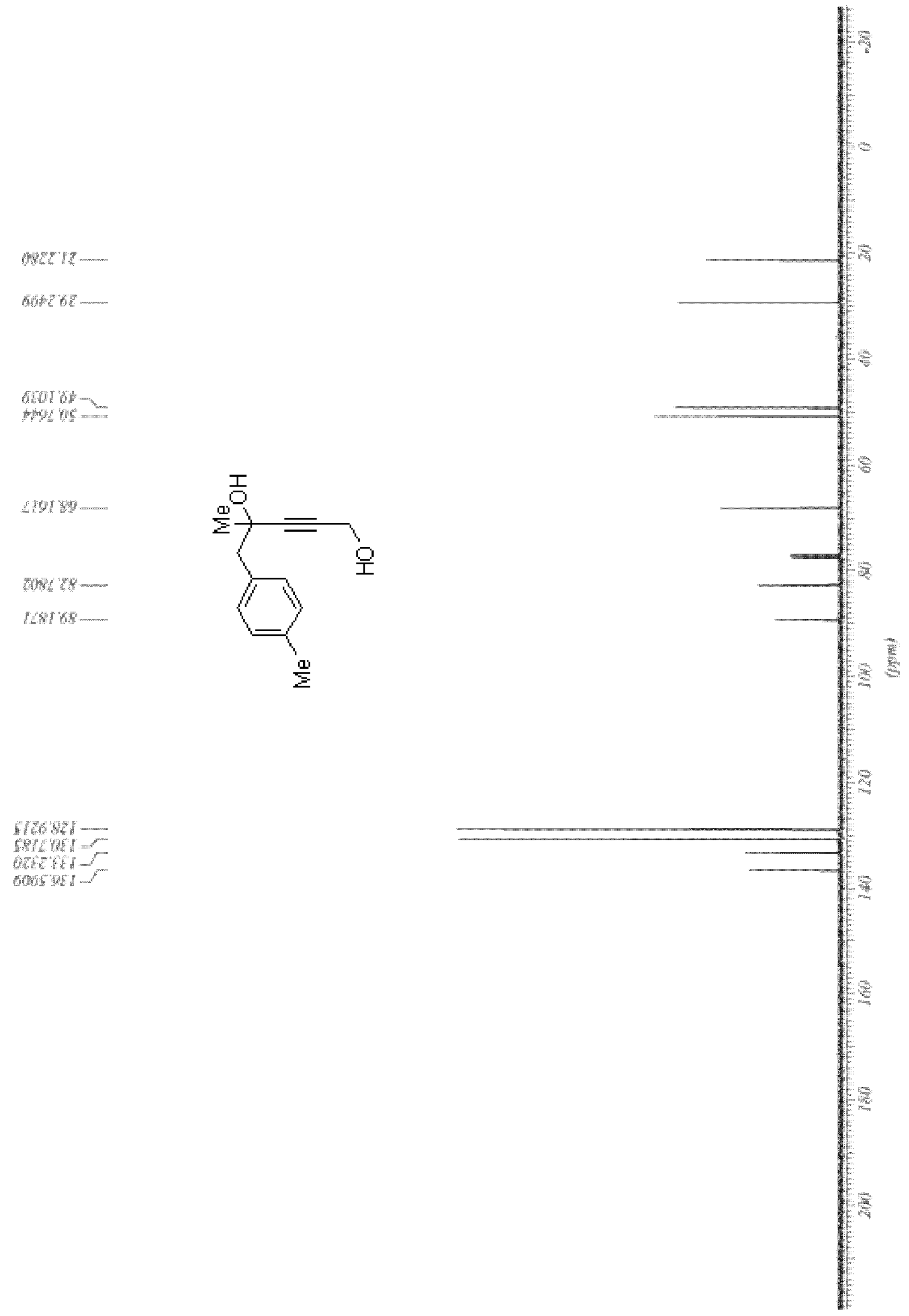
1.3755
1.3933
2.9647
2.9745
2.9823
2.9919
2.9999
3.0075
3.0246
3.0423
3.3811
3.3944
3.5571
4.1157
4.4541
7.2209
7.2282
7.2371
7.2440
7.2536
7.2582
7.2708
7.2776
7.2934
7.2971
7.3120
7.3138
7.3184
7.3326
7.3353
Me
OH
HO
3.3026
1.0565
1.0000
1.8413
Integral
(ppm)
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0

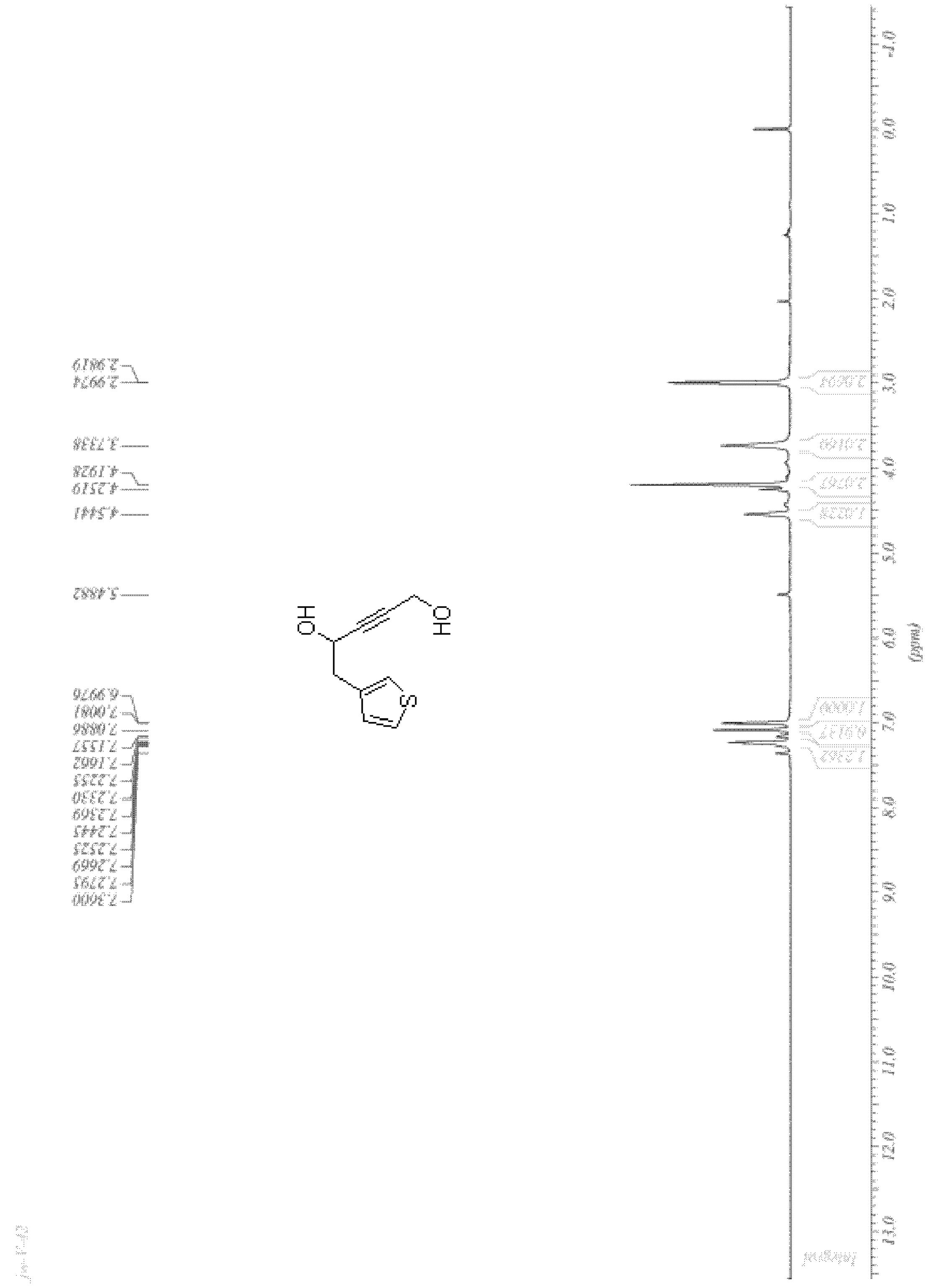

16.5365
45.9326
50.7966
67.2196
84.7155
85.4548
127.1492
128.4609
128.6543
142.3136
Me
OH
HO
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

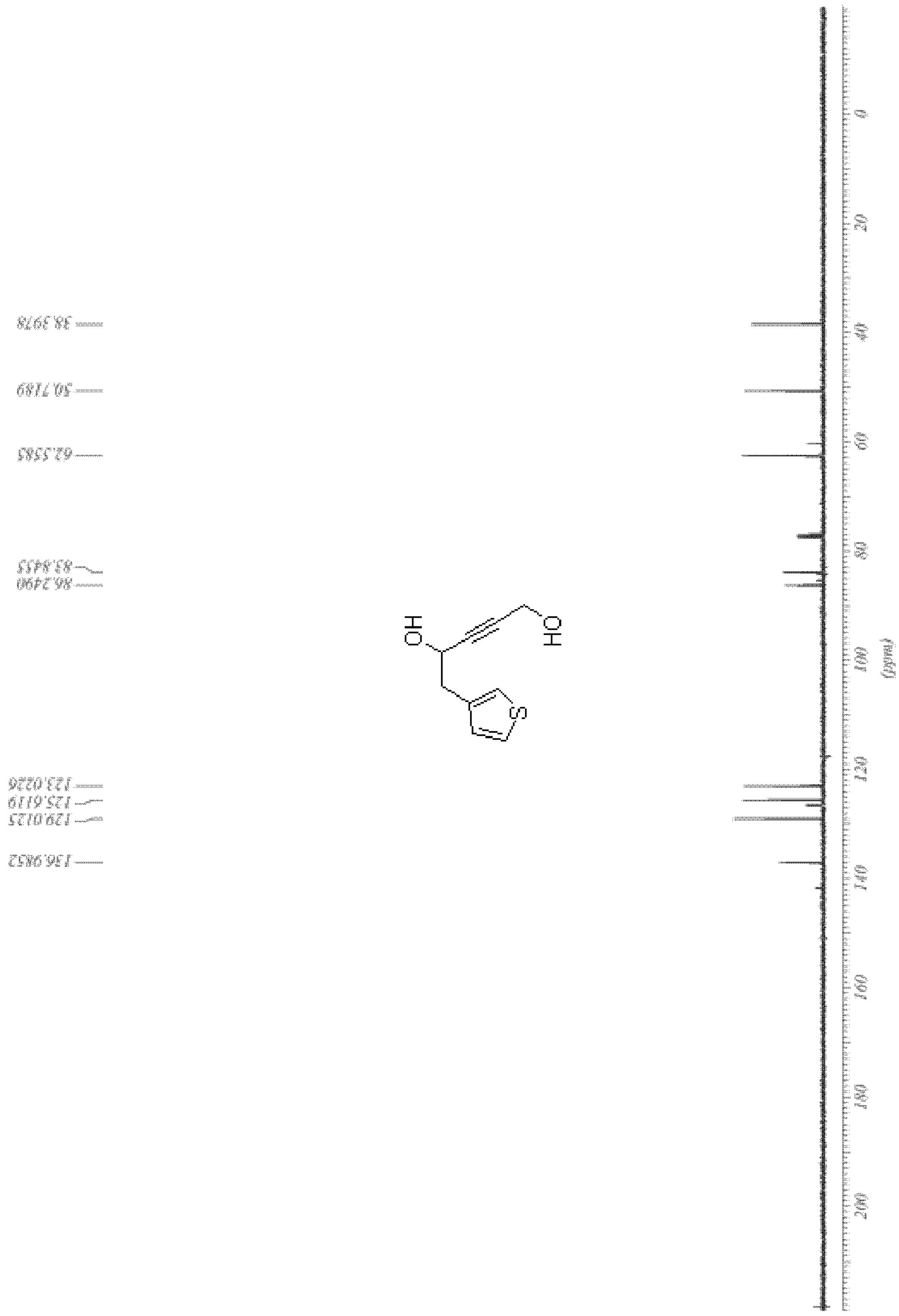

3.9709
3.9853
4.1199
4.1423
5.0347
5.0510
5.0535
5.0722
5.0942
5.1089
5.1235
5.6137
5.6290
7.1420
7.1459
7.1491
7.1601
7.1662
7.1786
7.1818
7.2447
7.2633
7.2818
7.3713
7.3868
7.4042
OH
OH
2.0063
1.0529
1.0582
0.9844
1.0000
2.1084
4.2341
4.1882
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

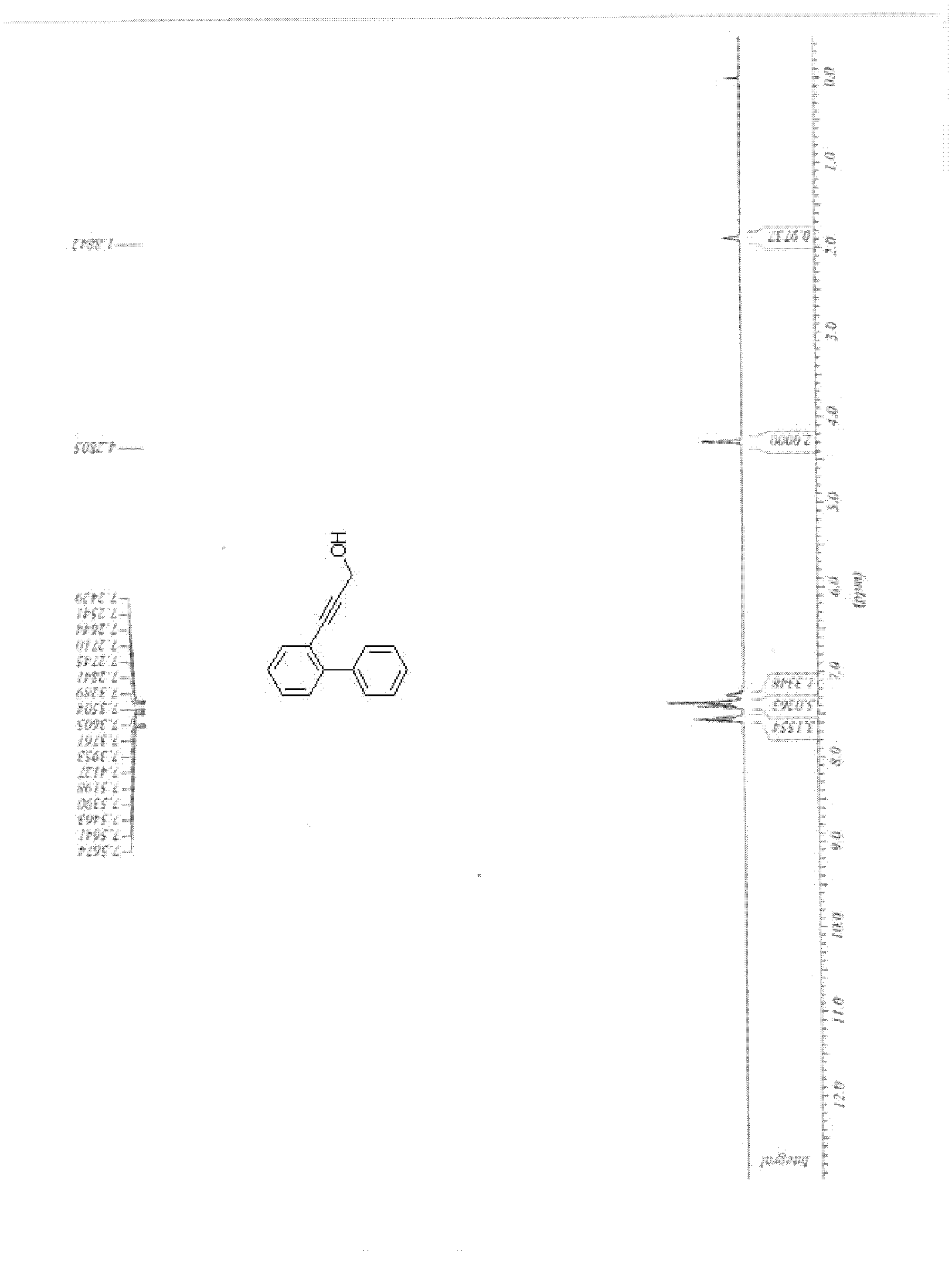

49.0180
57.8512
63.5340
84.6806
85.7459
126.0298
126.2459
127.9747
128.0694
128.6381
128.6646
142.2177
142.2708
OH
HO
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


1.4579
2.3119
2.8572
2.8903
2.8979
2.9513
3.0292
3.1272
4.1795
7.0902
7.1097
7.1703
7.1902
7.2356
Me
OH
HO
Me
2.9433
3.0094
2.0099
0.8921
0.9118
2.0000
2.0222
1.9493
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
(ppm)


21.2280
29.2499
49.1039
50.7644
68.1617
82.7802
89.1871
128.9215
130.7185
133.2320
136.5909
Me
OH
HO
Me
(ppm)
-20
0
20
40
60
80
100
120
140
160
180
200


2.9819
2.9974
3.7338
4.1928
4.2519
4.5441
5.4882
6.9976
7.0081
7.0886
7.1557
7.1662
7.2255
7.2330
7.2369
7.2445
7.2525
7.2669
7.2795
7.3600
OH
OH
S
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)


38.3978
50.7189
62.5585
83.8455
86.2490
123.0226
125.6119
129.0125
136.9852
0
20
40
60
80
100
120
140
160
180
200
(ppm)
OH
HO
S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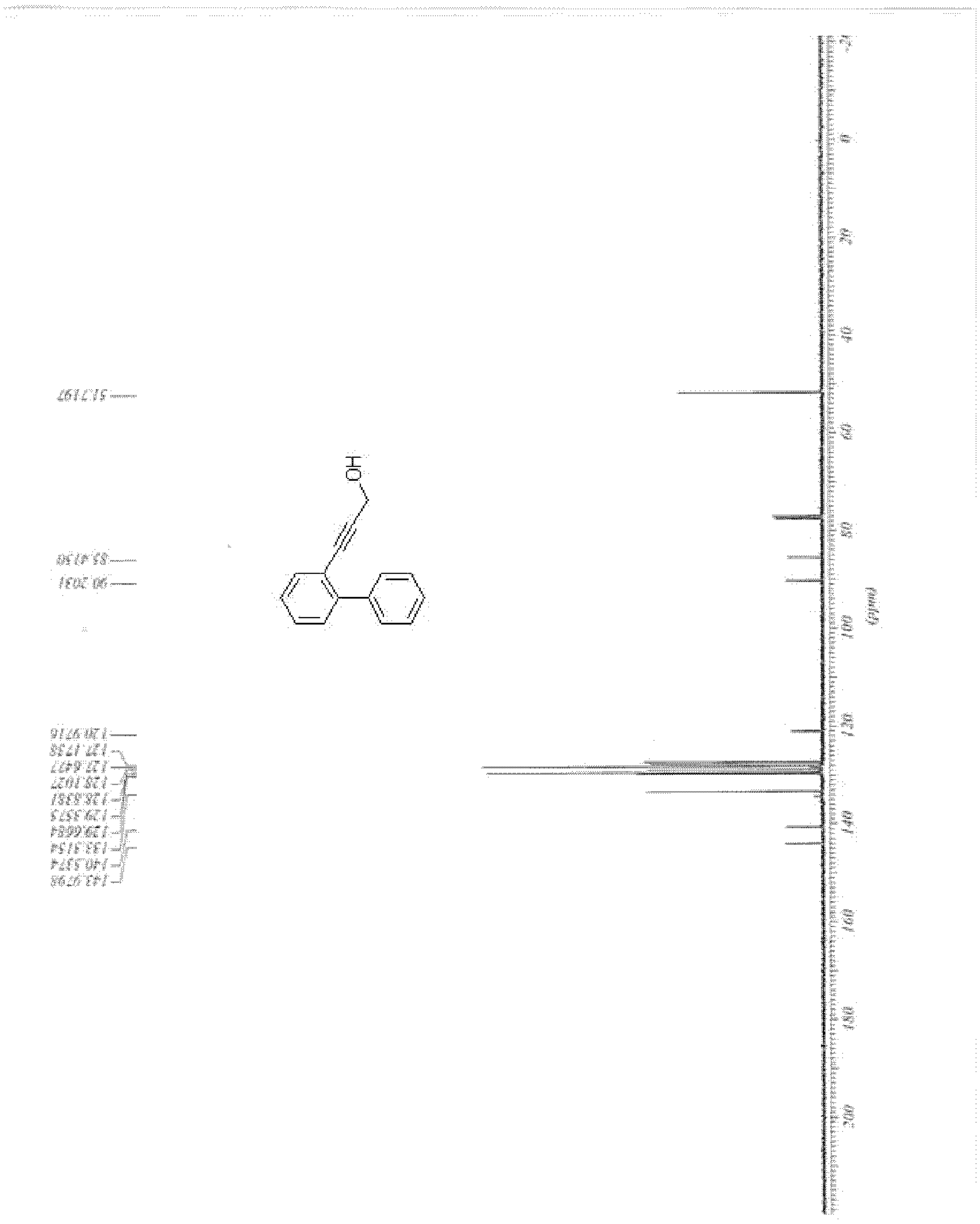
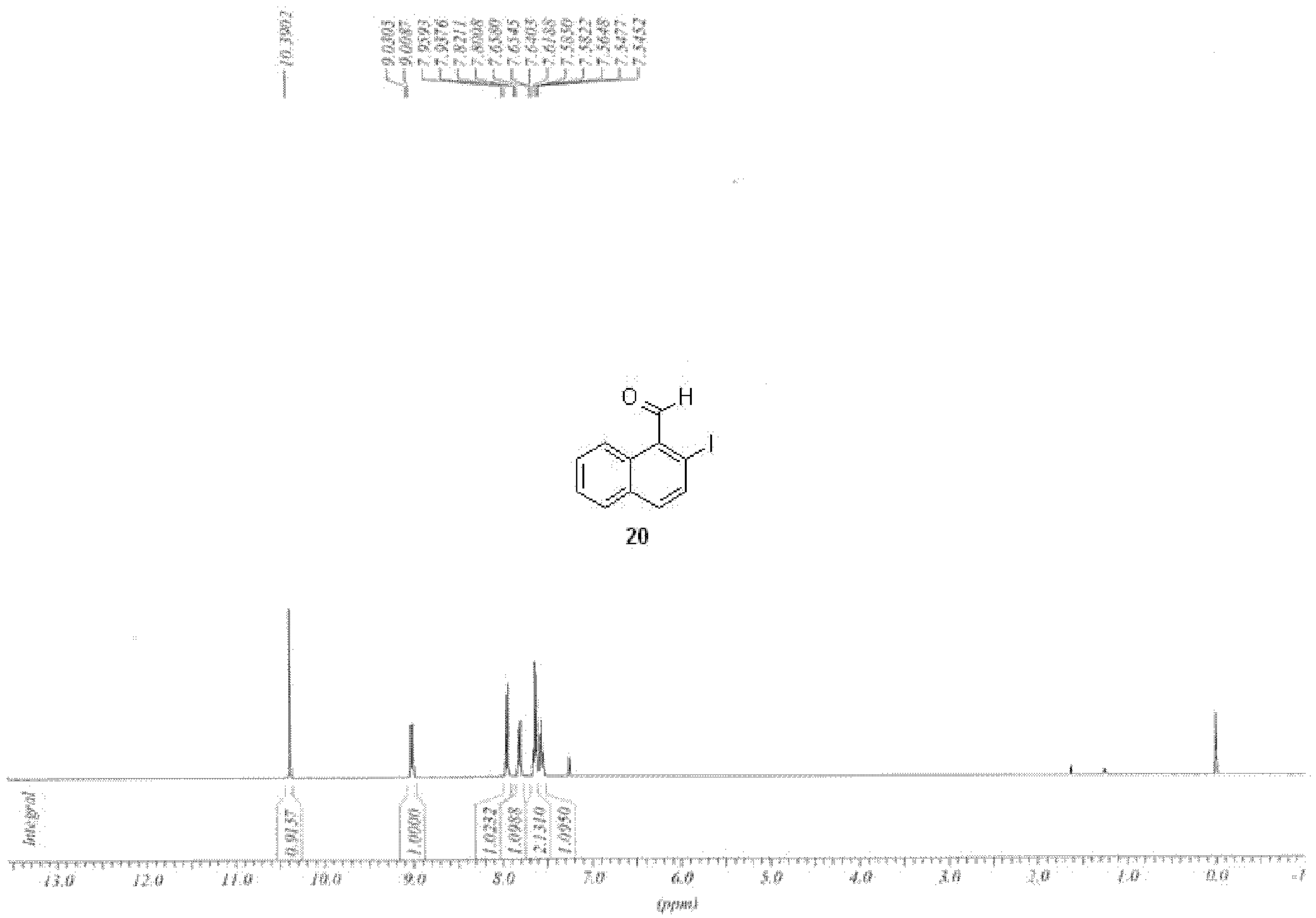
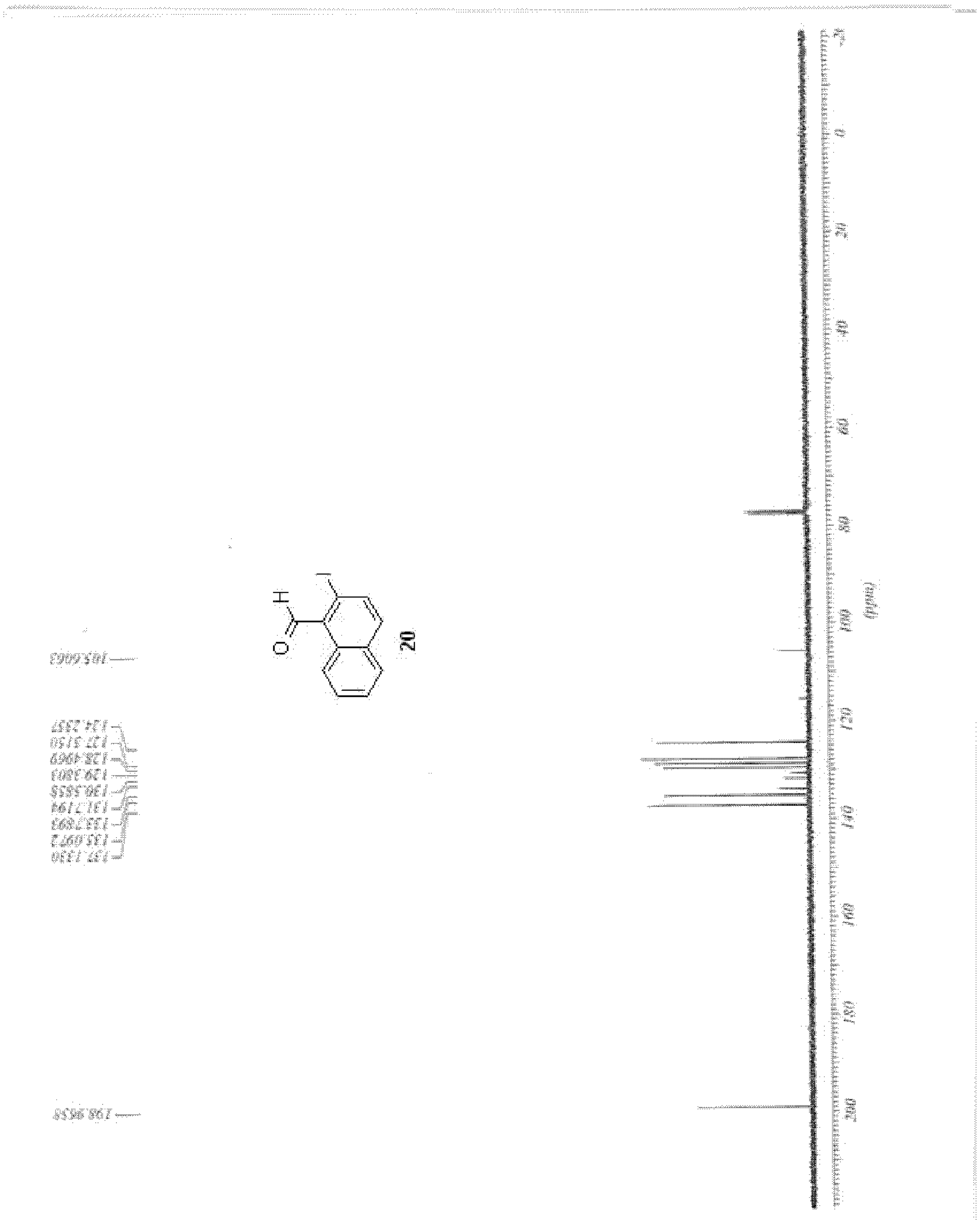
4.2805
7.2429
7.2541
7.2644
7.2710
7.2745
7.2841
7.3289
7.3504
7.3605
7.3761
7.3953
7.4127
7.5198
7.5390
7.5463
7.5641
7.5674
OH
0.9737
2.0000
1.3348
5.0363
3.1554
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
(ppm)
Integral

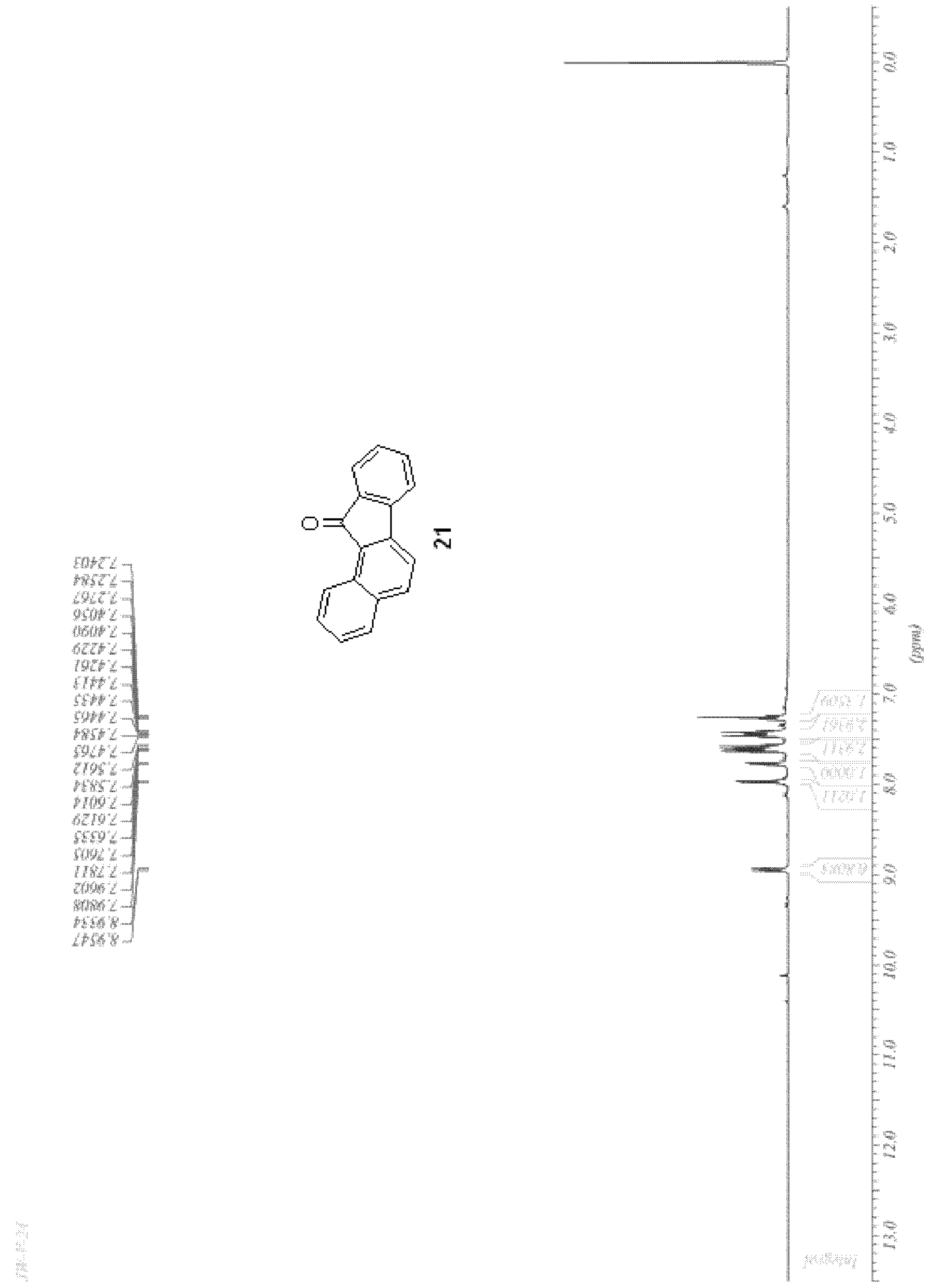


51.7197
85.4150
90.2031
120.9716
127.1738
127.6437
128.1027
128.8381
129.3575
129.6684
133.3154
140.5374
143.9798
HO
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


10.3902
9.0305
9.0087
7.9593
7.9376
7.8211
7.8008
7.6580
7.6545
7.6403
7.6188
7.5850
7.5822
7.5648
7.5477
7.5452
O
H
I
Integral
0.9137
1.0000
1.0232
1.0988
2.1310
1.0950
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
(ppm)

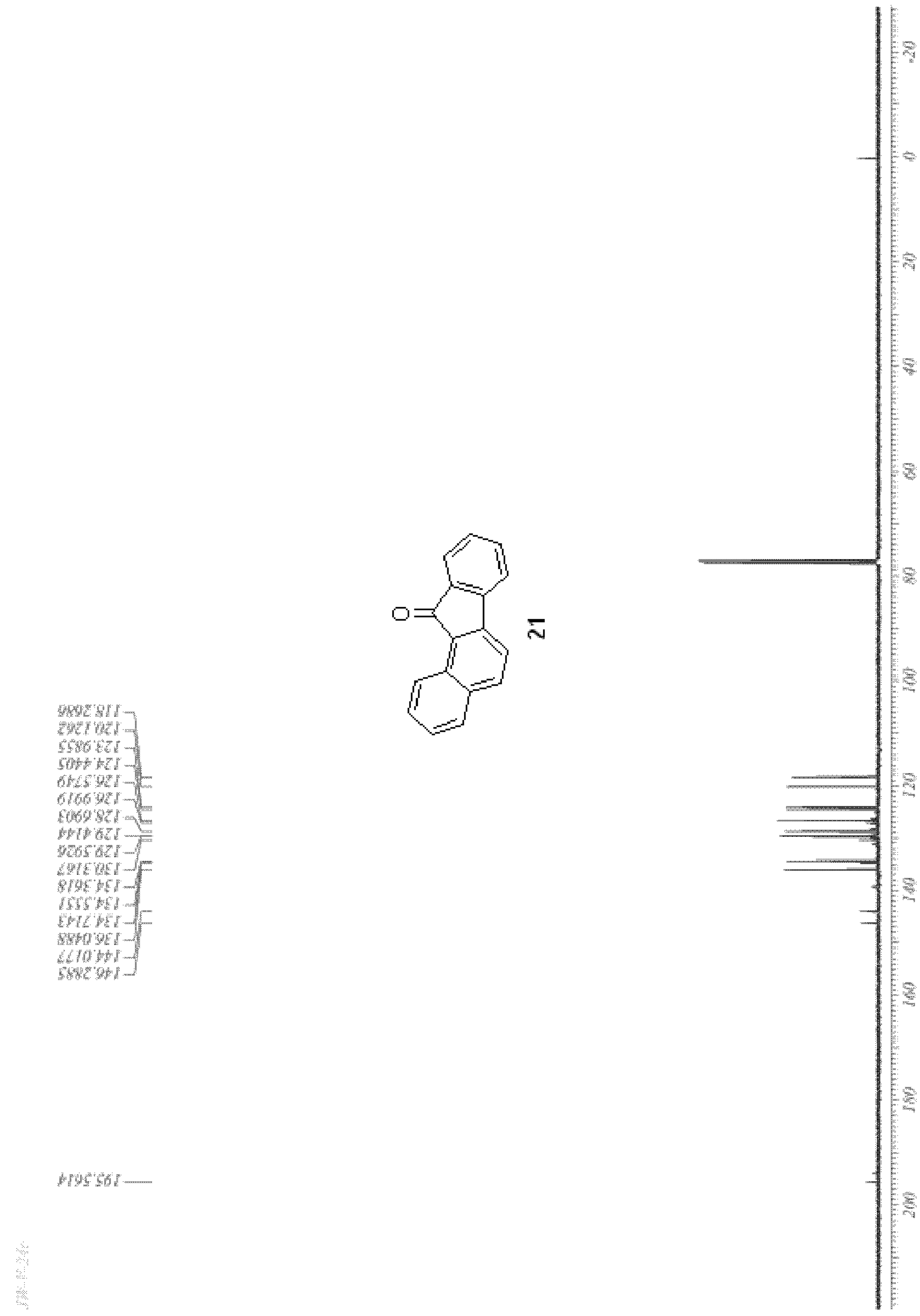
20


20
105.6063
124.2357
127.5150
128.4969
129.3803
130.5855
131.7194
133.7893
135.0972
137.1330
198.9658
O
H
I
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)



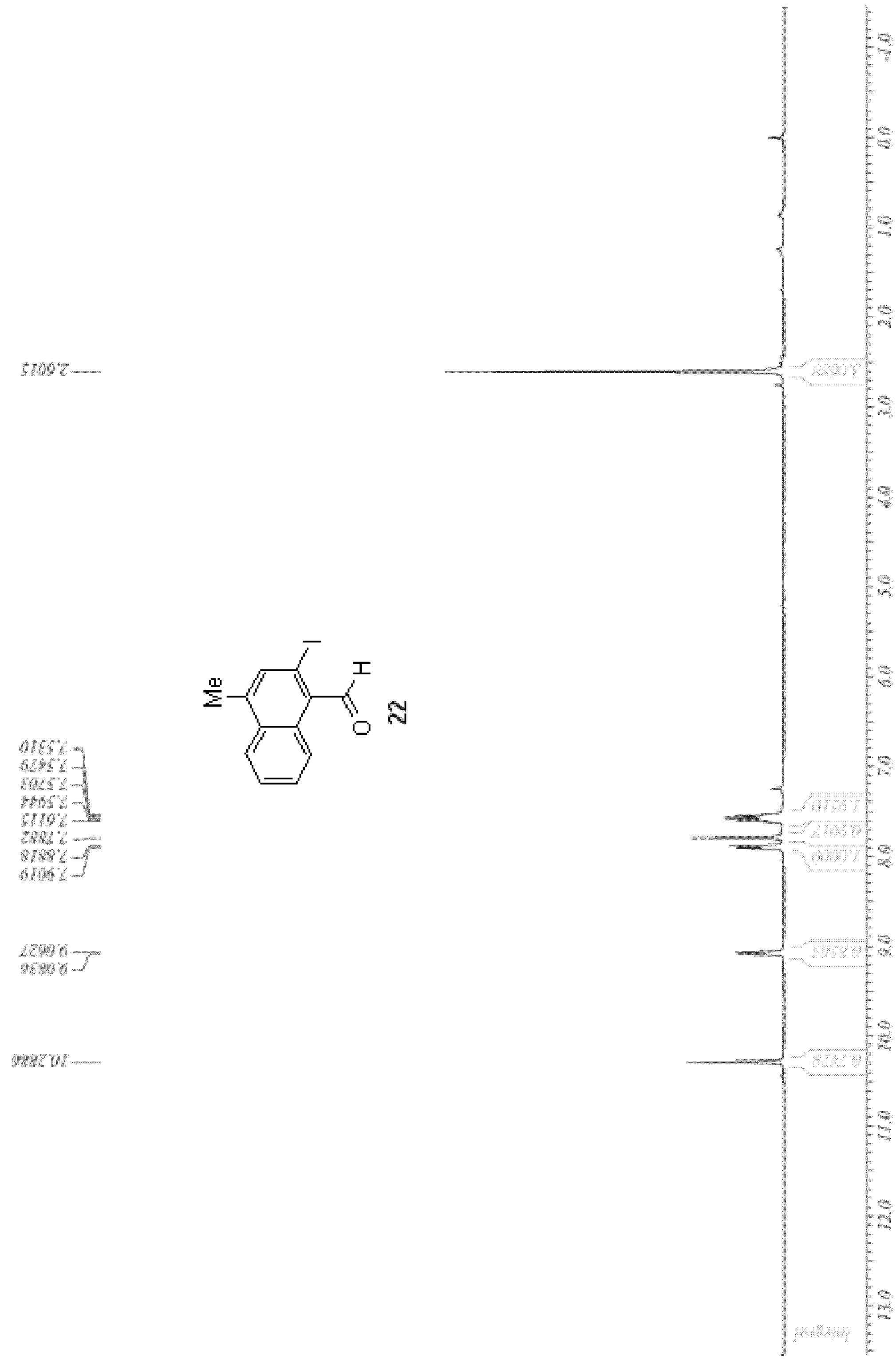
21

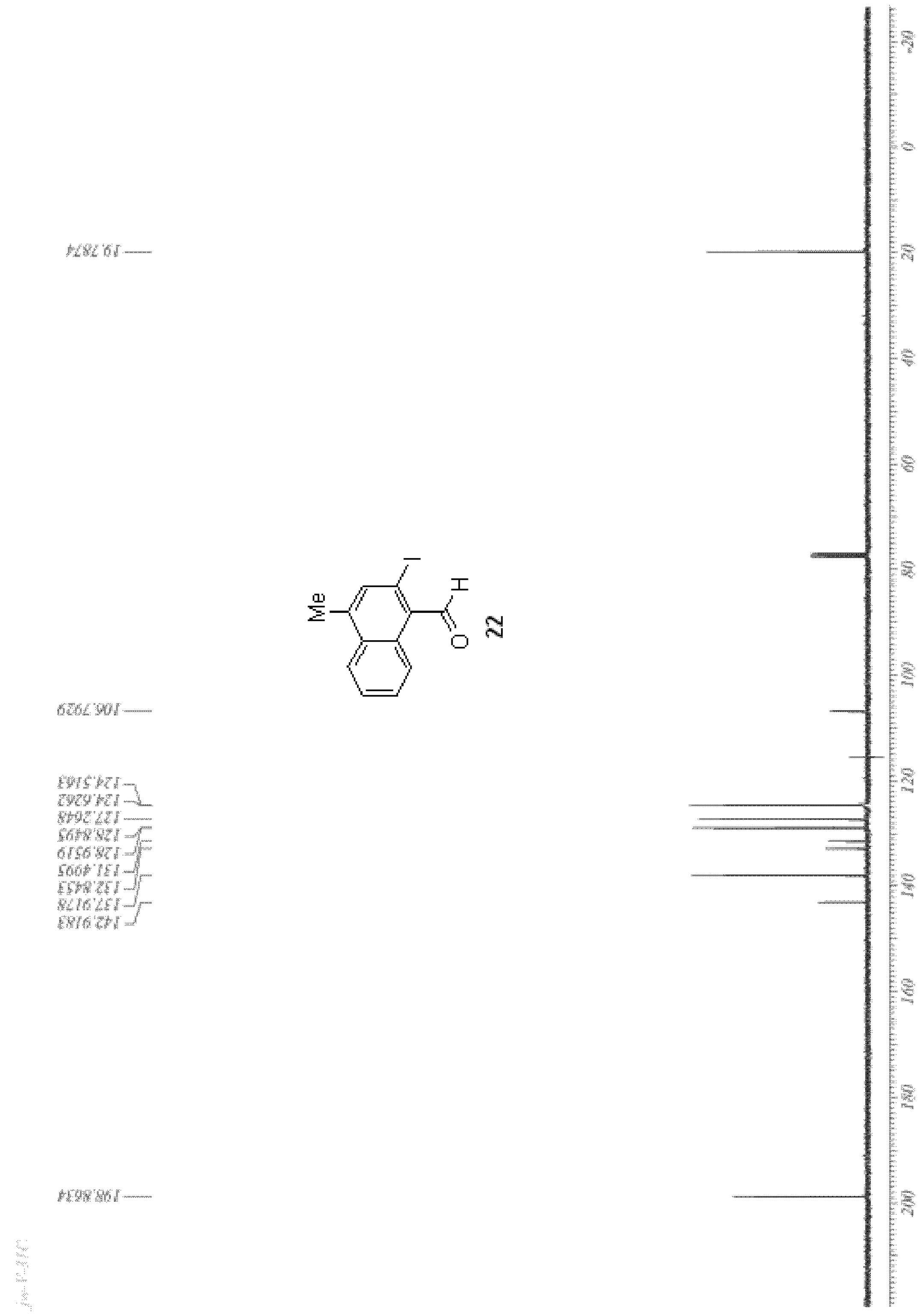
7.2403
7.2584
7.2767
7.4056
7.4090
7.4229
7.4261
7.4413
7.4435
7.4465
7.4584
7.4763
7.5612
7.5834
7.6014
7.6129
7.6335
7.7605
7.7811
7.9602
7.9808
8.9334
8.9547
O
1.1509
2.9561
2.2911
1.0000
1.0211
0.8085
Integral
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)



21

118.2686
120.1262
123.9855
124.4405
126.5749
126.9919
128.6903
129.4144
129.5926
130.3167
134.3618
134.5551
134.7143
136.0488
144.0177
146.2885
195.5614
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)


2.6015
7.5310
7.5479
7.5703
7.5944
7.6115
7.7882
7.8818
7.9019
9.0627
9.0836
10.2886
Me
I
O
H
22
3.0688
1.9510
0.9017
1.0000
0.8563
0.7428
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)



22

jw-V-31C
19.7874
106.7929
124.5143
124.6262
127.2648
128.8495
128.9519
131.4995
132.8453
137.9178
142.9183
198.8634
Me
I
H
O
-20
0
20
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100
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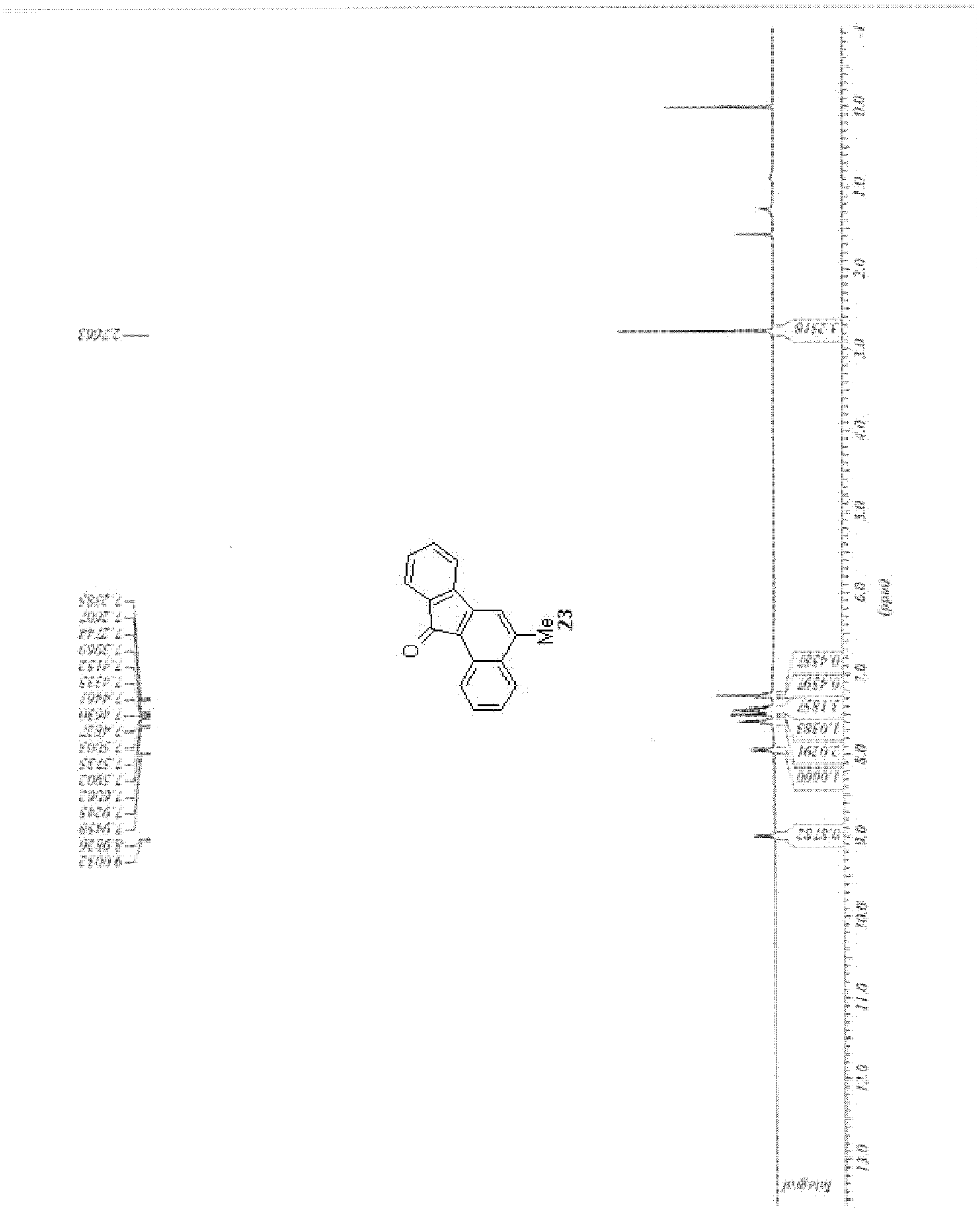
160
180
200
(ppm)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7.9245
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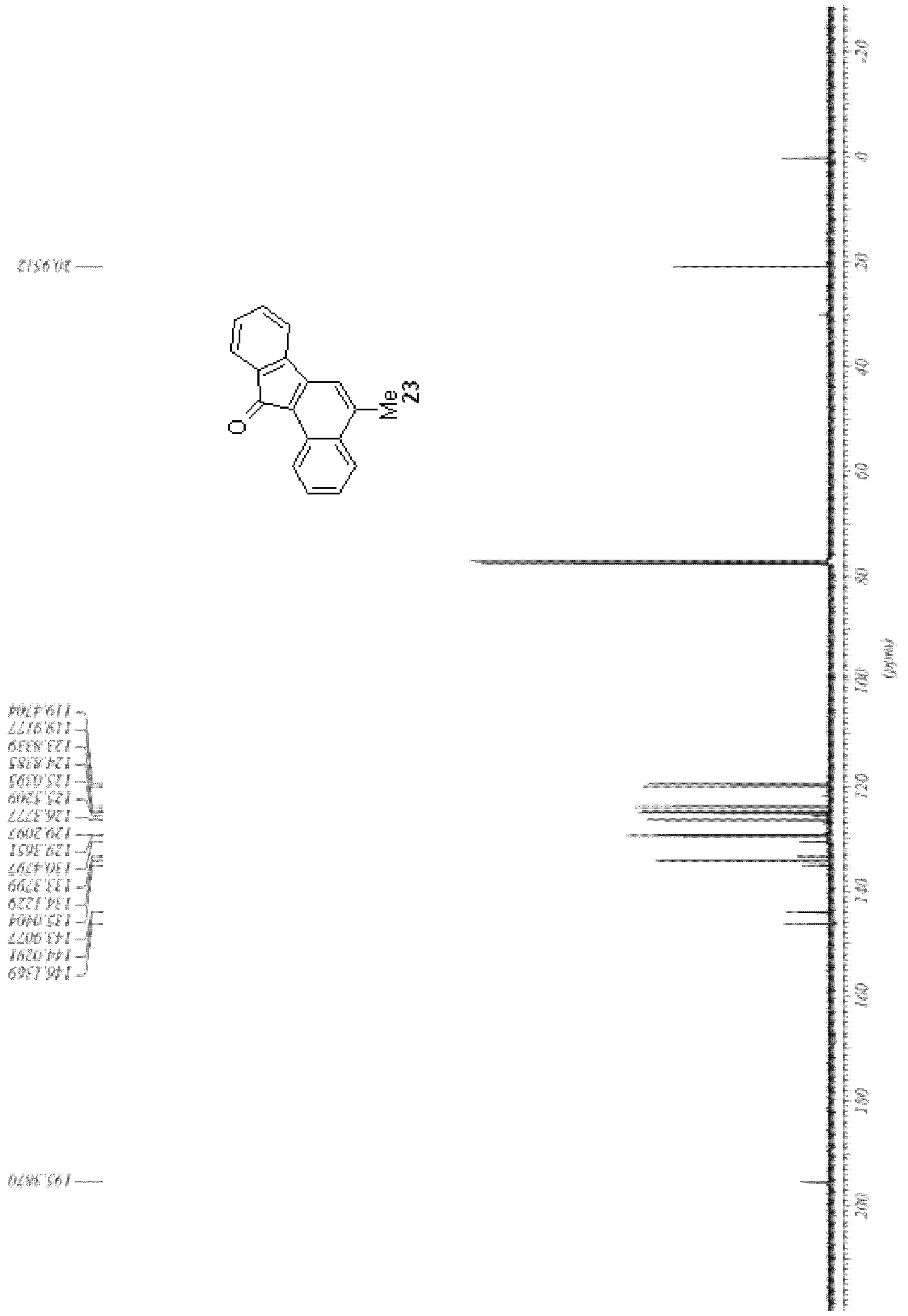
7.5902
7.5735
7.5003
7.4827
7.4630
7.4461
7.4335
7.4152
7.3969
7.2744
7.2607
7.2355
2.7663
O
Me
23
0.8782
1.0000
2.0291
1.0383
3.1857
0.4597
0.4557
3.2318
Integral
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
(ppm)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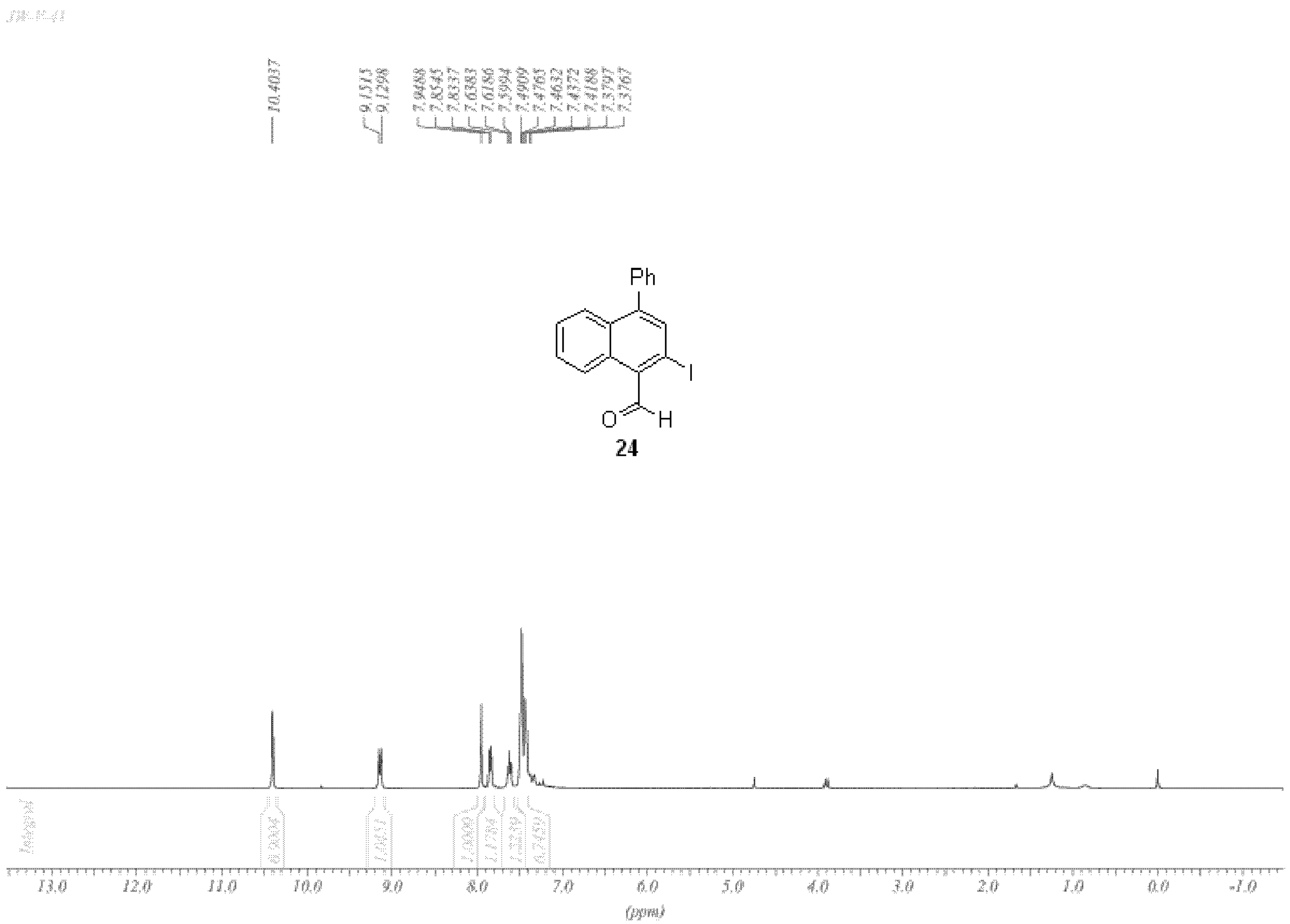
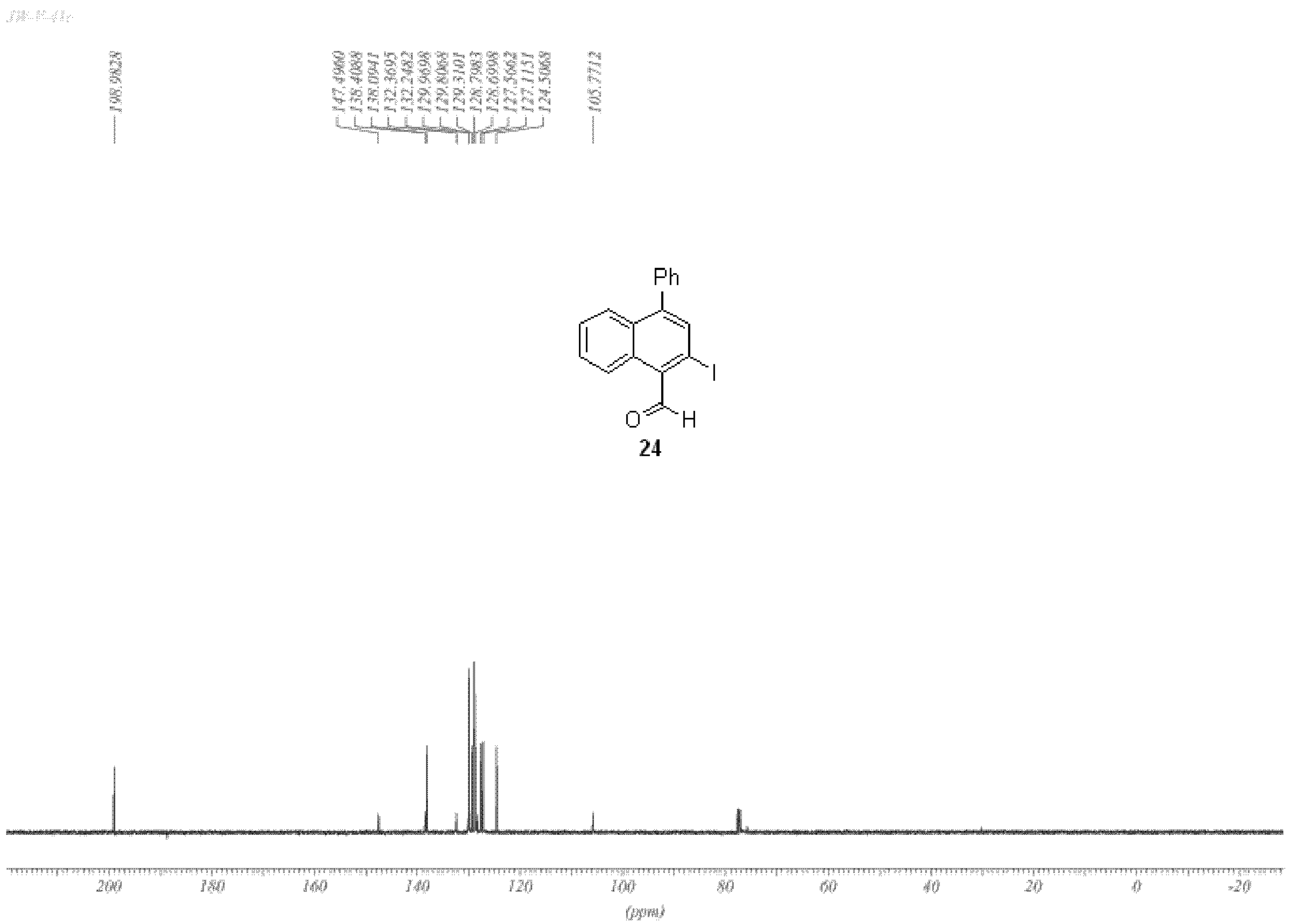
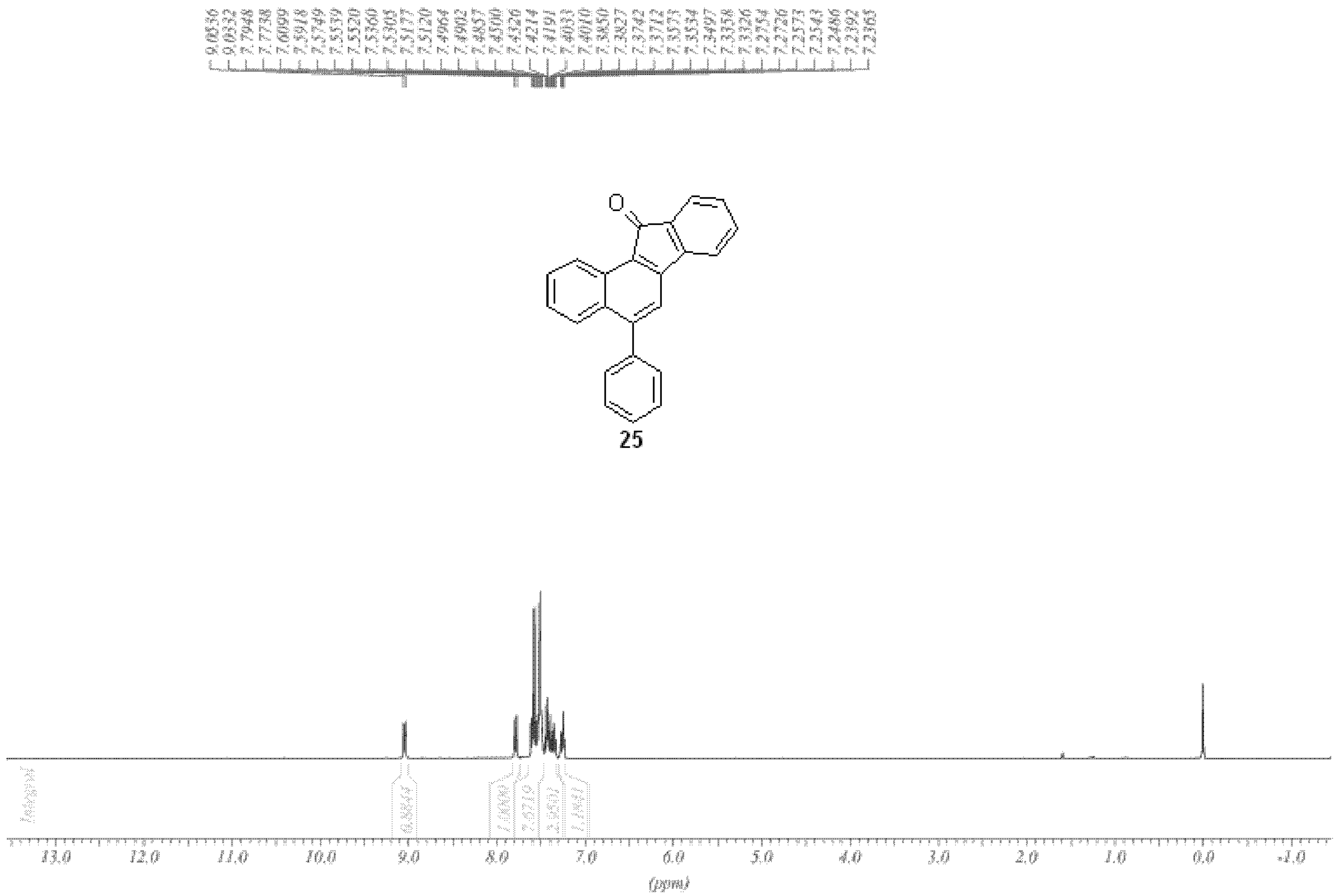
119.4704
119.9177
123.8339
124.8385
125.0395
125.5209
126.3777
129.2097
129.3651
130.4797
133.3799
134.1229
135.0404
143.9077
144.0291
146.1369
195.3870
O
Me
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

23


JW-V-41
10.4037
9.1515
9.1298
7.9488
7.8545
7.8337
7.6383
7.6186
7.5994
7.4909
7.4765
7.4632
7.4372
7.4188
7.3797
7.3767
Ph
I
O
H
24
Integral
0.9004
1.0451
1.0000
1.1784
1.2239
6.7459
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)


JW-V-41c
198.9828
147.4960
138.4088
138.0941
132.3695
132.2482
129.9698
129.8068
129.3101
128.7983
128.6998
127.5662
127.1151
124.5068
105.7712
Ph
I
O
H
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

24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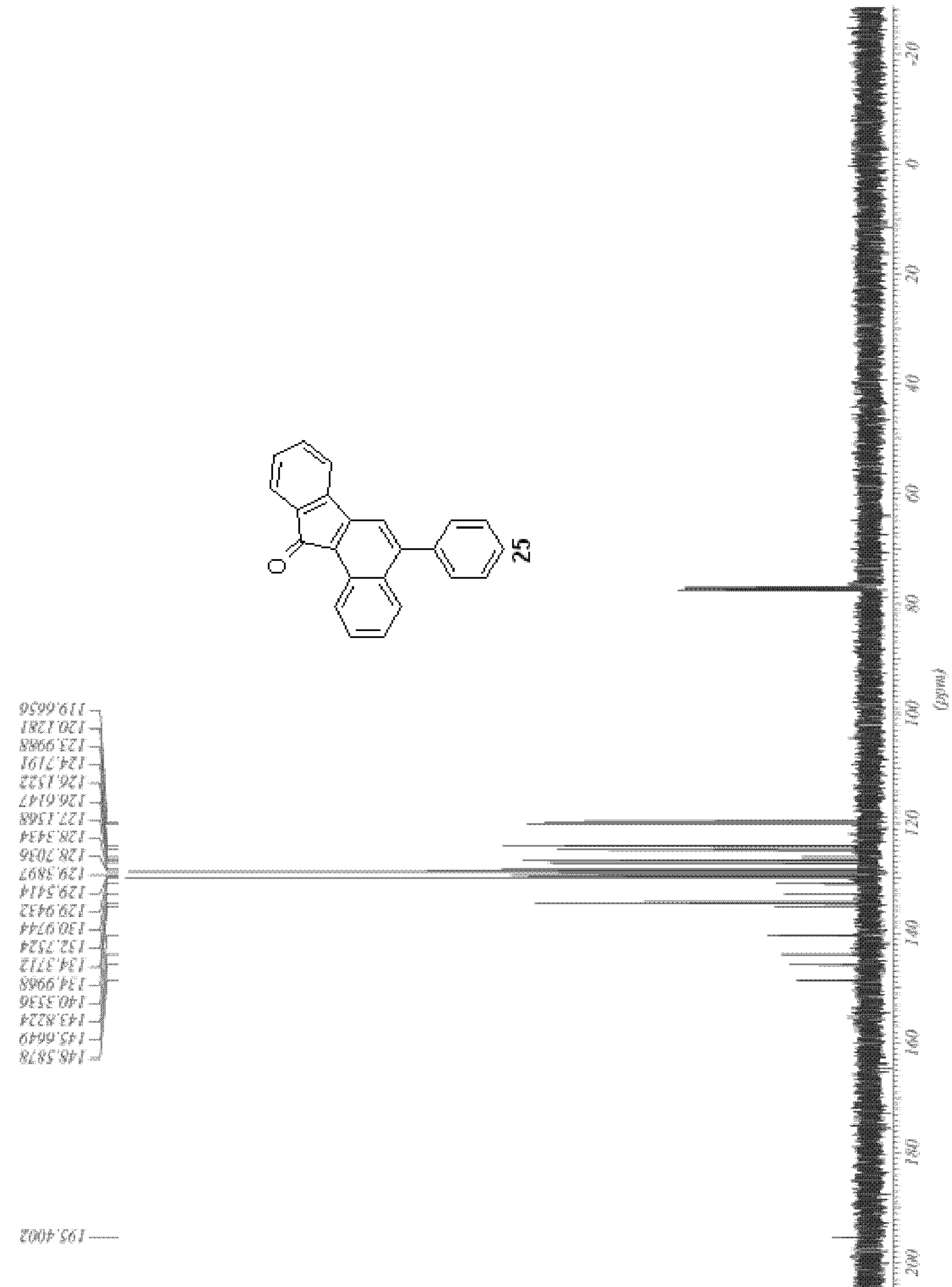
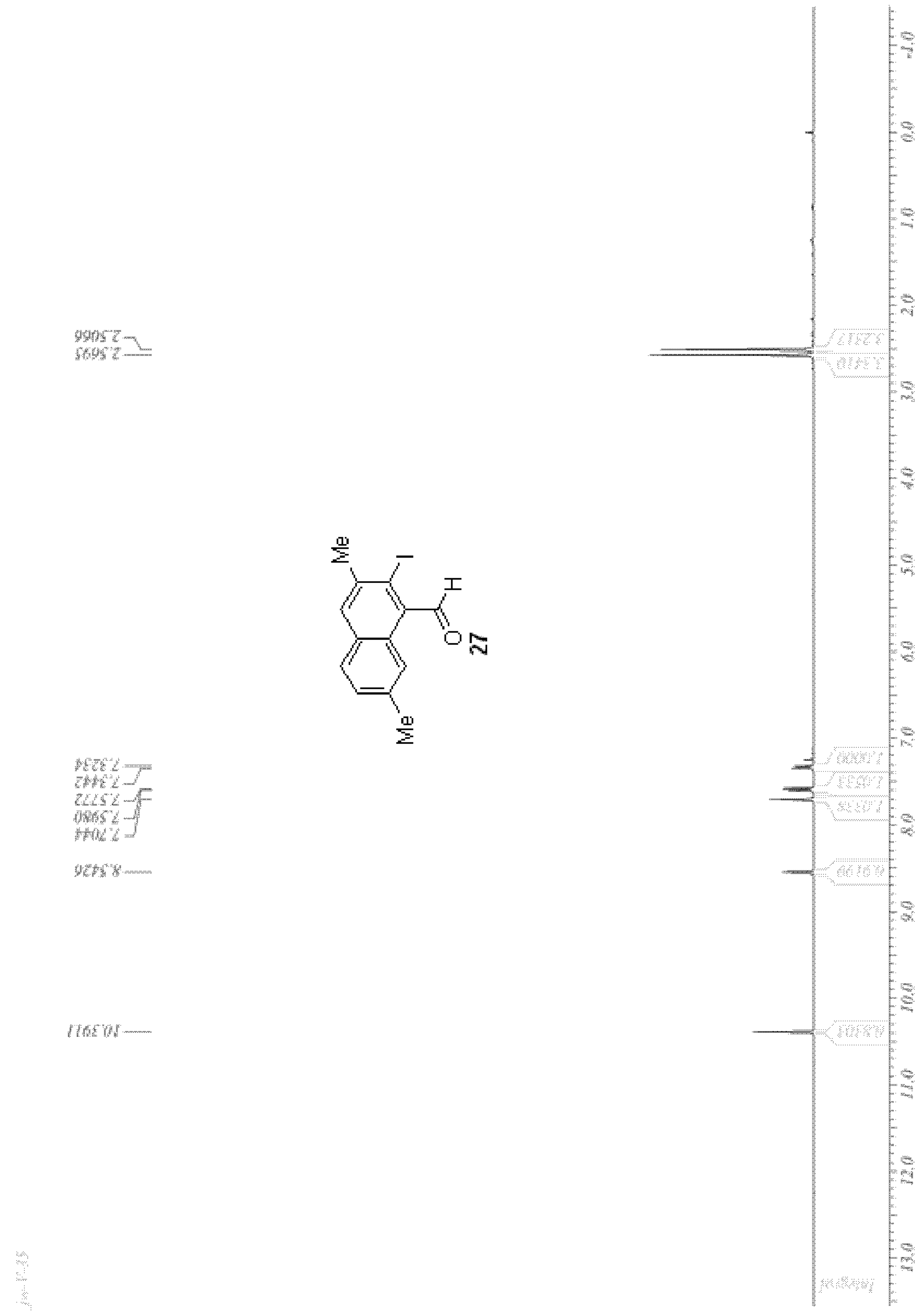
9.0332
7.7948
7.7738
7.6099
7.5918
7.5749
7.5539
7.5520
7.5360
7.5305
7.5177
7.5120
7.4964
7.4902
7.4857
7.4500
7.4326
7.4214
7.4191
7.4033
7.4010
7.3850
7.3827
7.3742
7.3712
7.3573
7.3534
7.3497
7.3358
7.3326
7.2754
7.2726
7.2573
7.2543
7.2486
7.2392
7.2365
O
Integral
0.8844
1.0000
2.6219
2.9501
1.1841
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

25


25

195.4002
148.5878
145.6649
143.8224
140.5336
134.9968
134.3712
132.7524
130.9744
129.9432
129.5414
129.3897
128.7036
128.3434
127.1568
126.6147
126.1522
124.7191
123.9988
120.1281
119.6656
O
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)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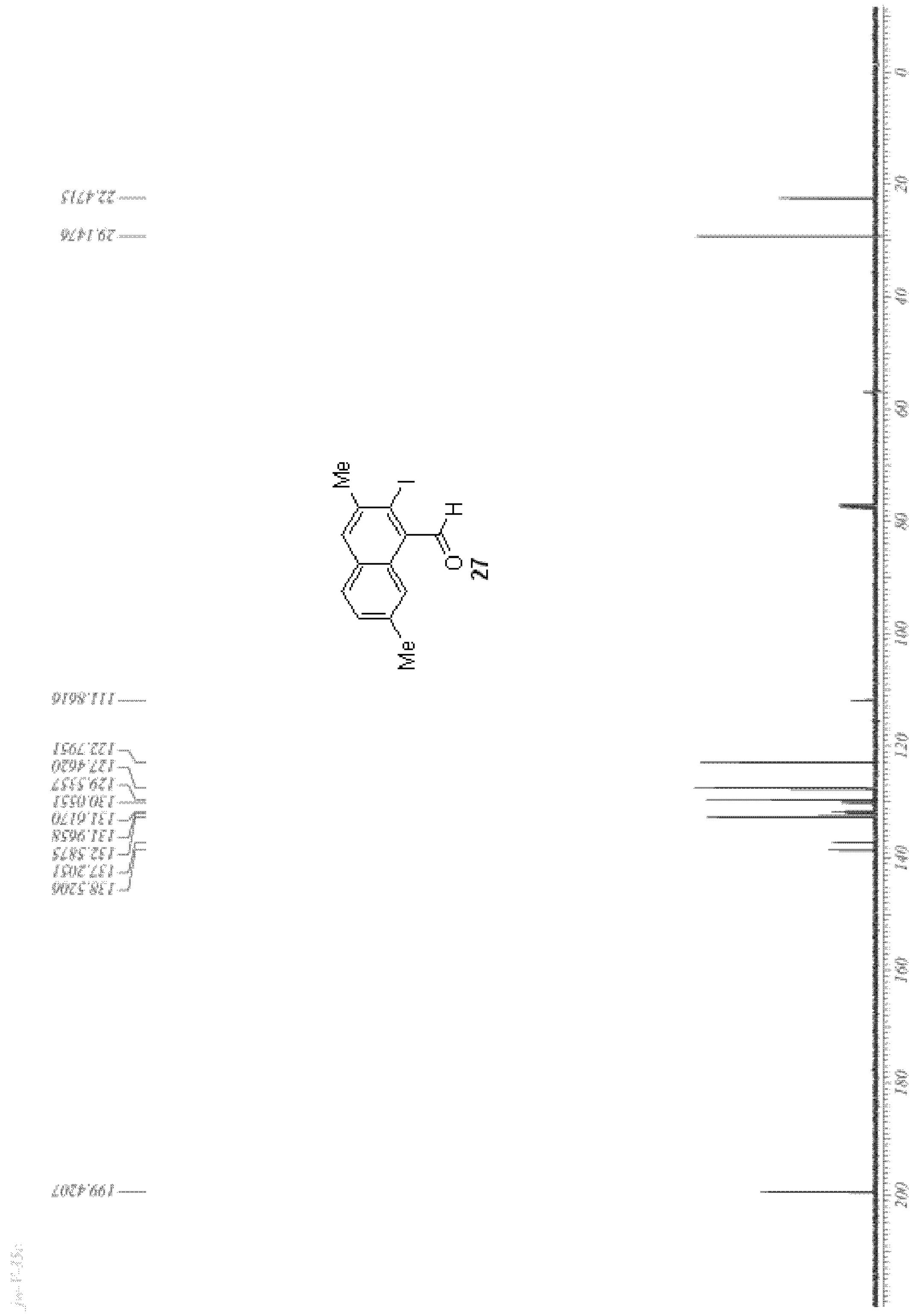
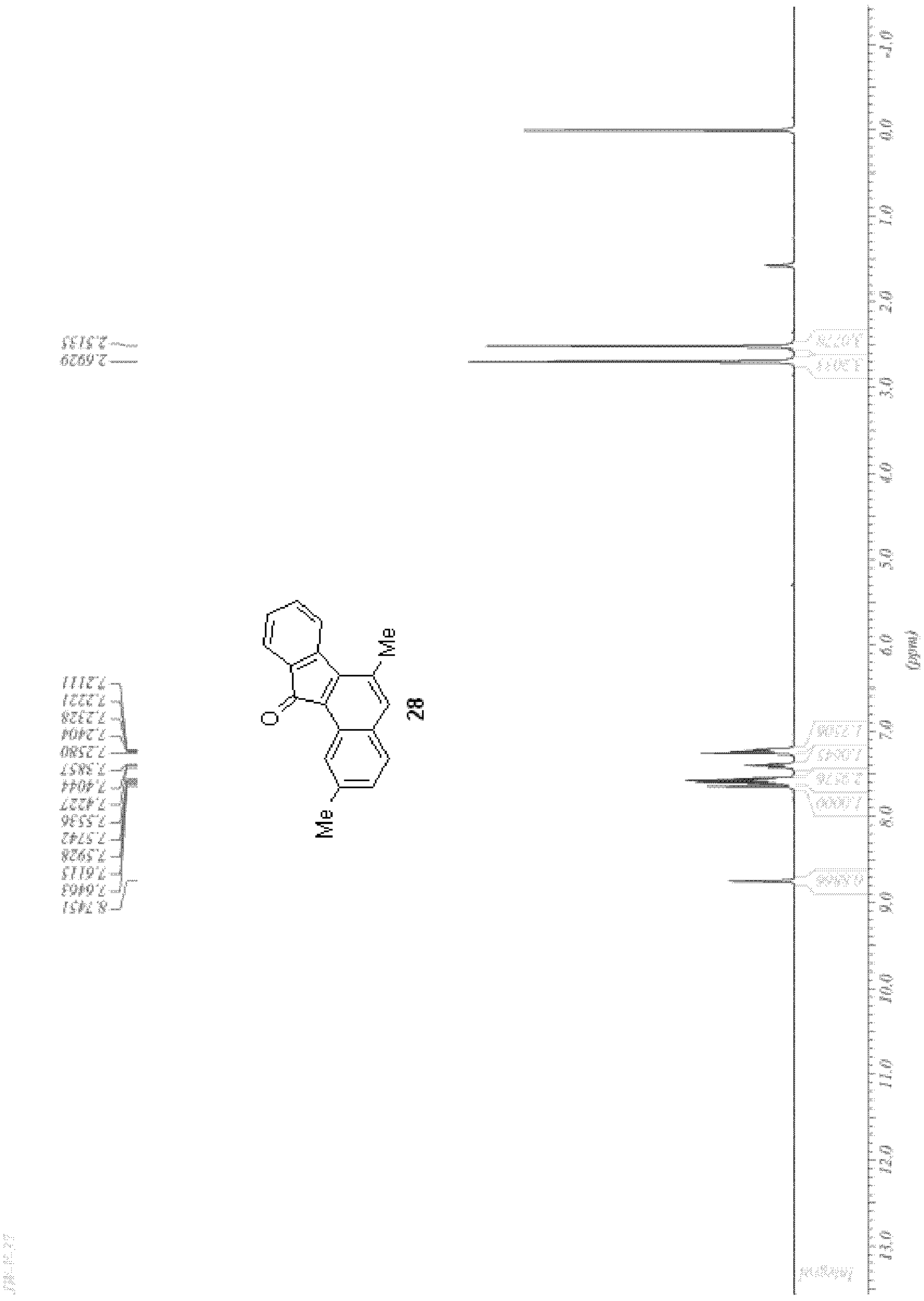
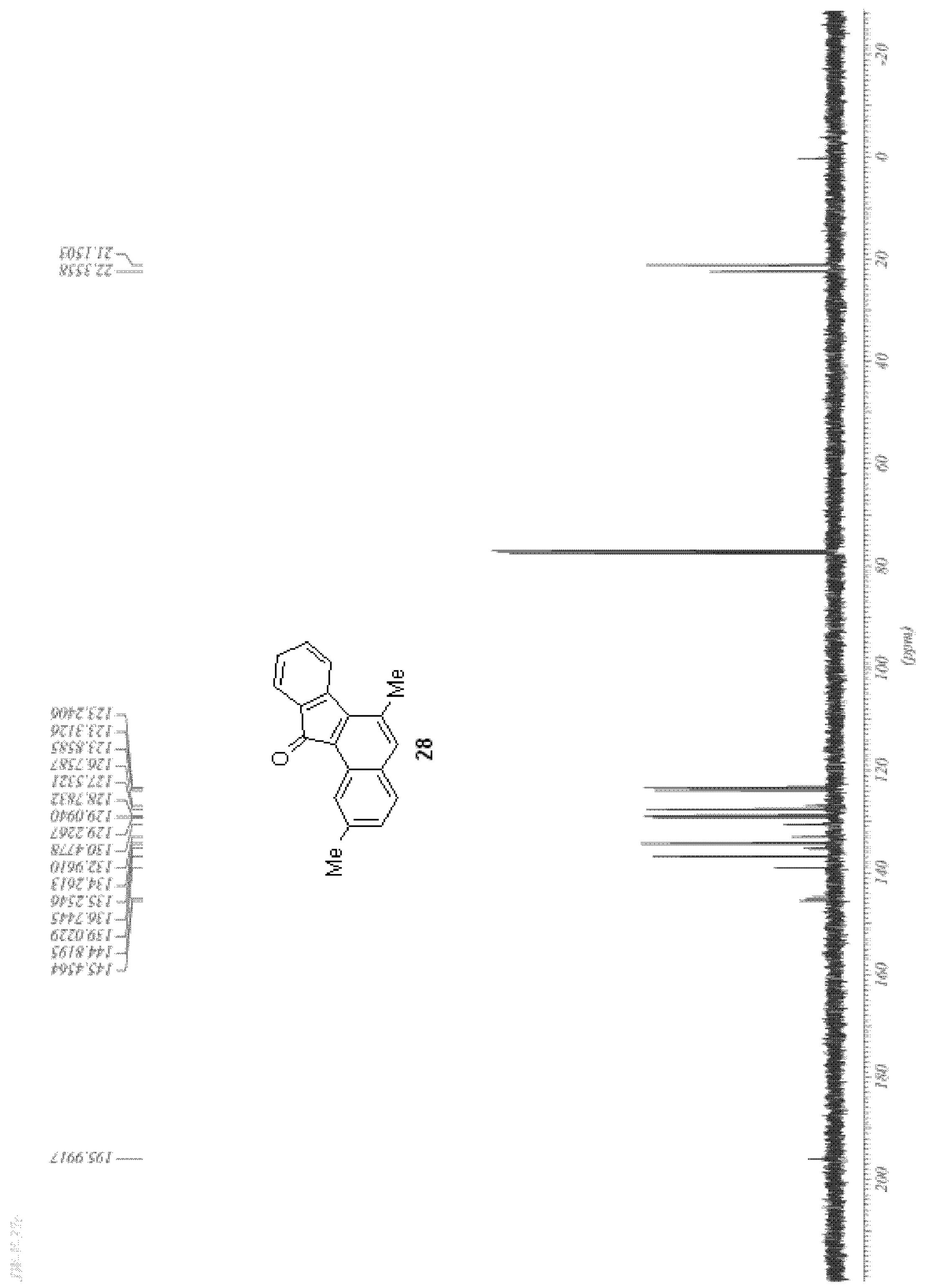
2.5695
7.3234
7.3442
7.5772
7.5980
7.7044
8.5426
10.3911
Me
I
H
O
27
Me
3.2317
3.3410
1.0000
1.0533
1.0338
0.9199
0.8301
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)



27

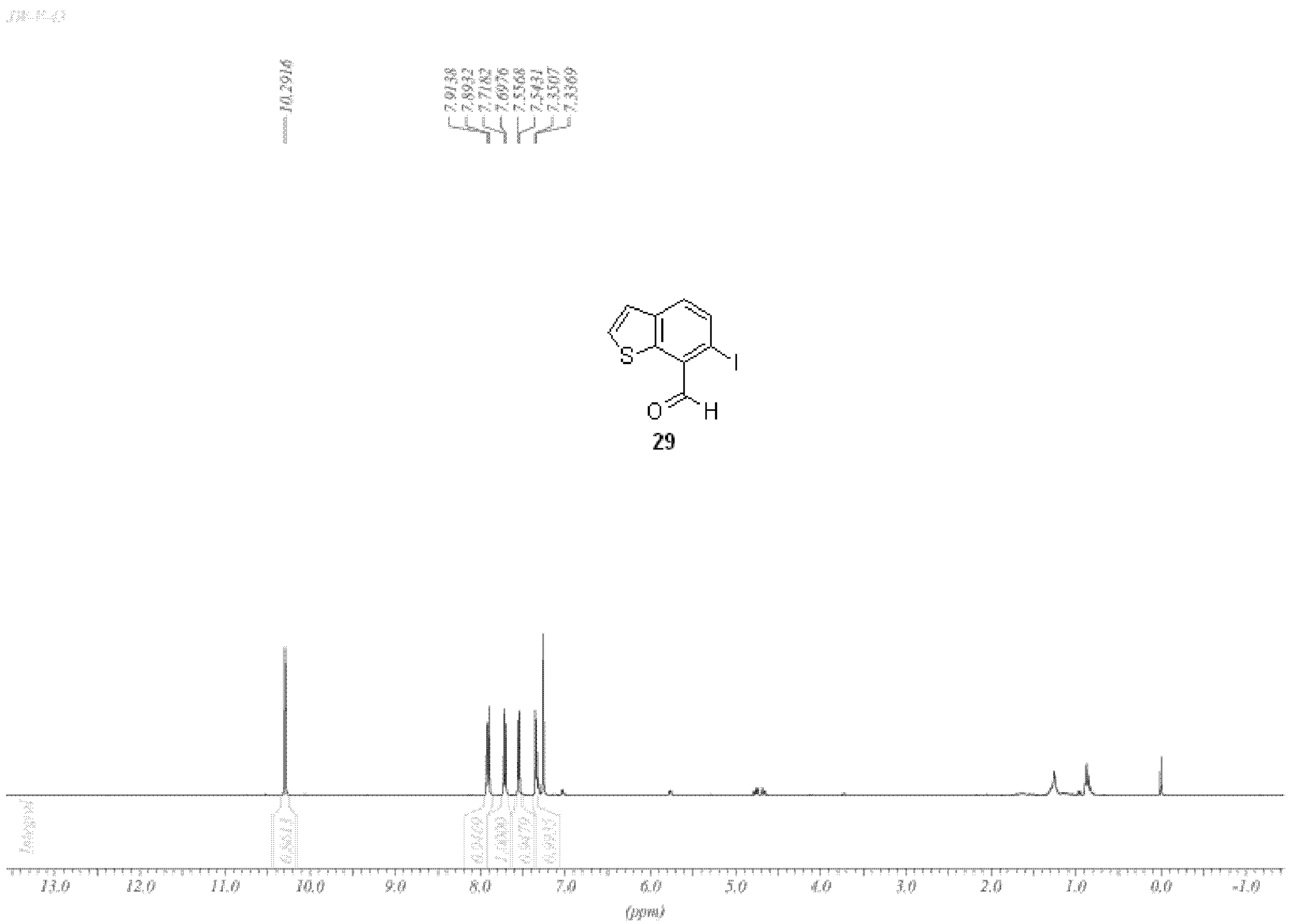
22.4715
29.1476
111.8616
122.7951
127.4620
129.5357
130.0551
131.6170
131.9658
132.5875
137.2051
138.5206
199.4207
Me
I
H
O
Me
0
20
40
60
80
100
120
140
160
180
200
(ppm)
jw-1-35c


2.5135
2.6929
7.2111
7.2221
7.2328
7.2404
7.2580
7.3857
7.4044
7.4227
7.5536
7.5742
7.5928
7.6115
7.6463
8.7451
O
Me
Me
28
Integral
(ppm)
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0



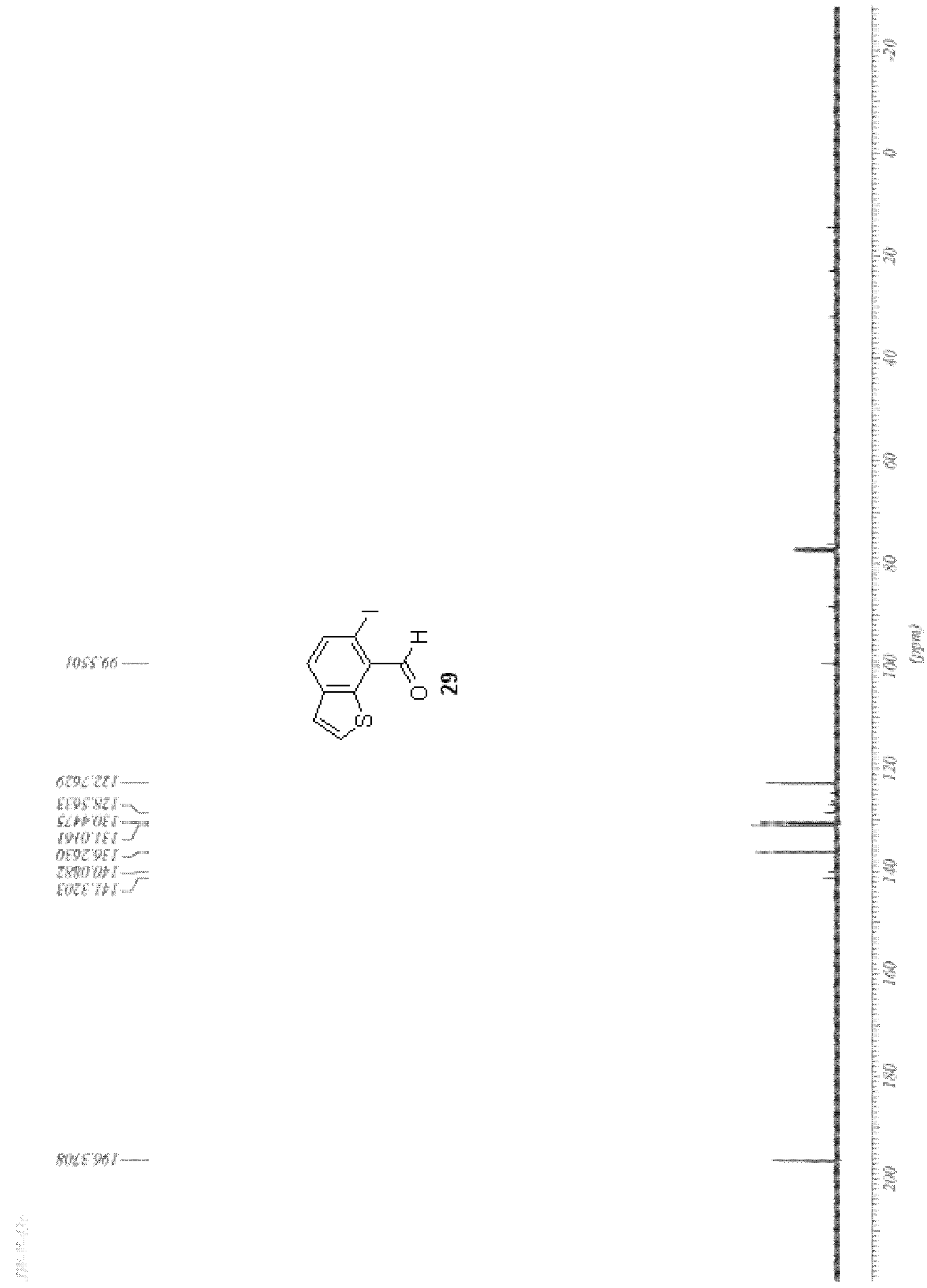
28

21.1503
22.3558
123.2400
123.3126
123.8585
126.7587
127.5321
128.7832
129.0940
129.2267
130.4778
132.9610
134.2613
135.2546
136.7445
139.0229
144.8195
145.4564
195.9917
O
Me
Me
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

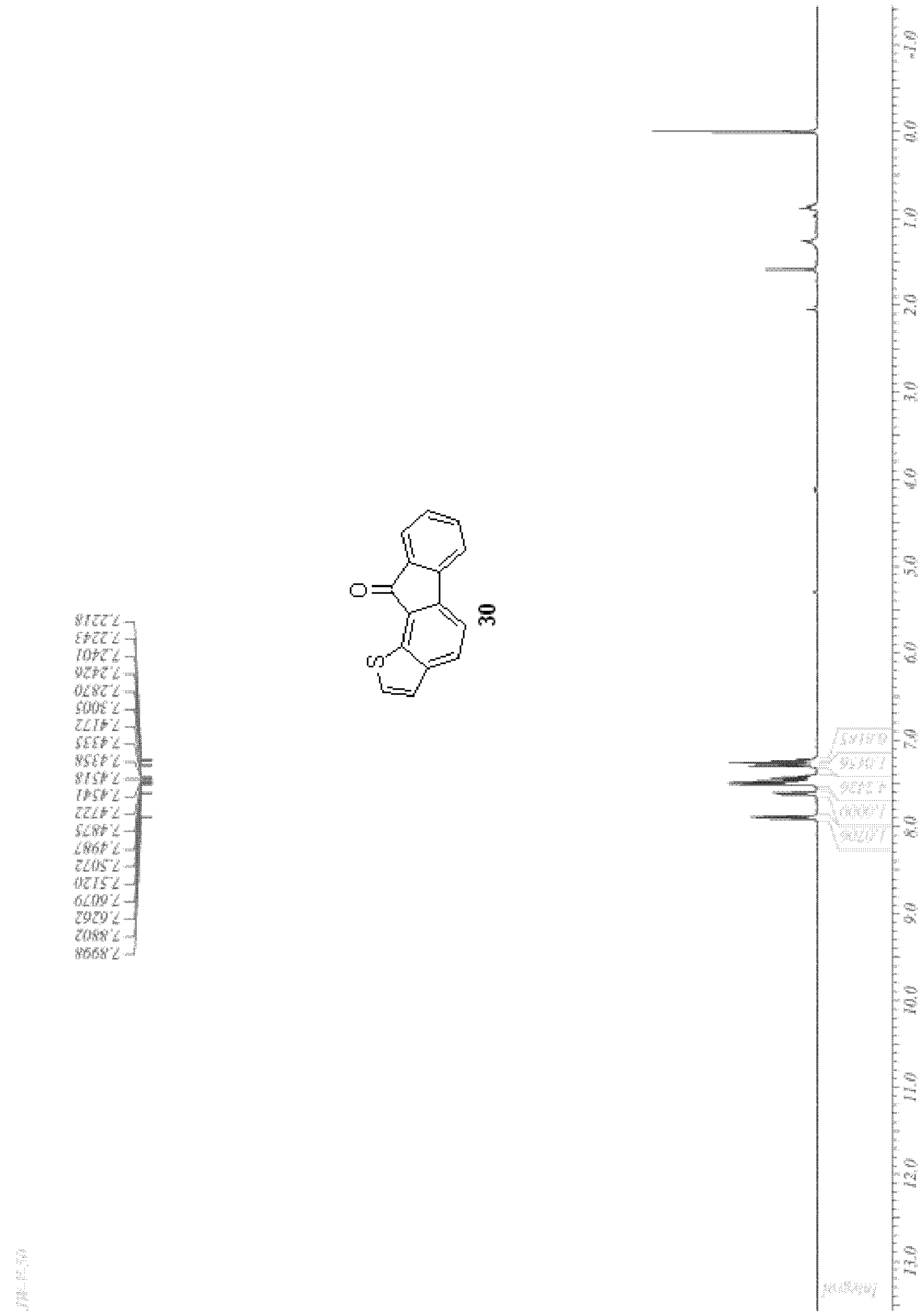


29

JW-V-43
10.2916
7.9138
7.8932
7.7182
7.6976
7.5568
7.5431
7.3507
7.3369
S
O
H
I
Integral
0.9613
0.9469
1.0000
0.9479
0.9935
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)


99.5501
122.7629
128.5633
130.4473
131.0161
136.2630
140.0882
141.3203
196.3708
S
O
H
I
-20
0
20
40
60
80
100
120
140
160
180
200
(ppm)

29



30

7.2218
7.2243
7.2401
7.2426
7.2870
7.3005
7.4172
7.4335
7.4358
7.4518
7.4541
7.4722
7.4875
7.4987
7.5072
7.5120
7.6079
7.6262
7.8802
7.8898
O
S
0.6185
1.0476
4.2426
1.0000
1.0206
Integral
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
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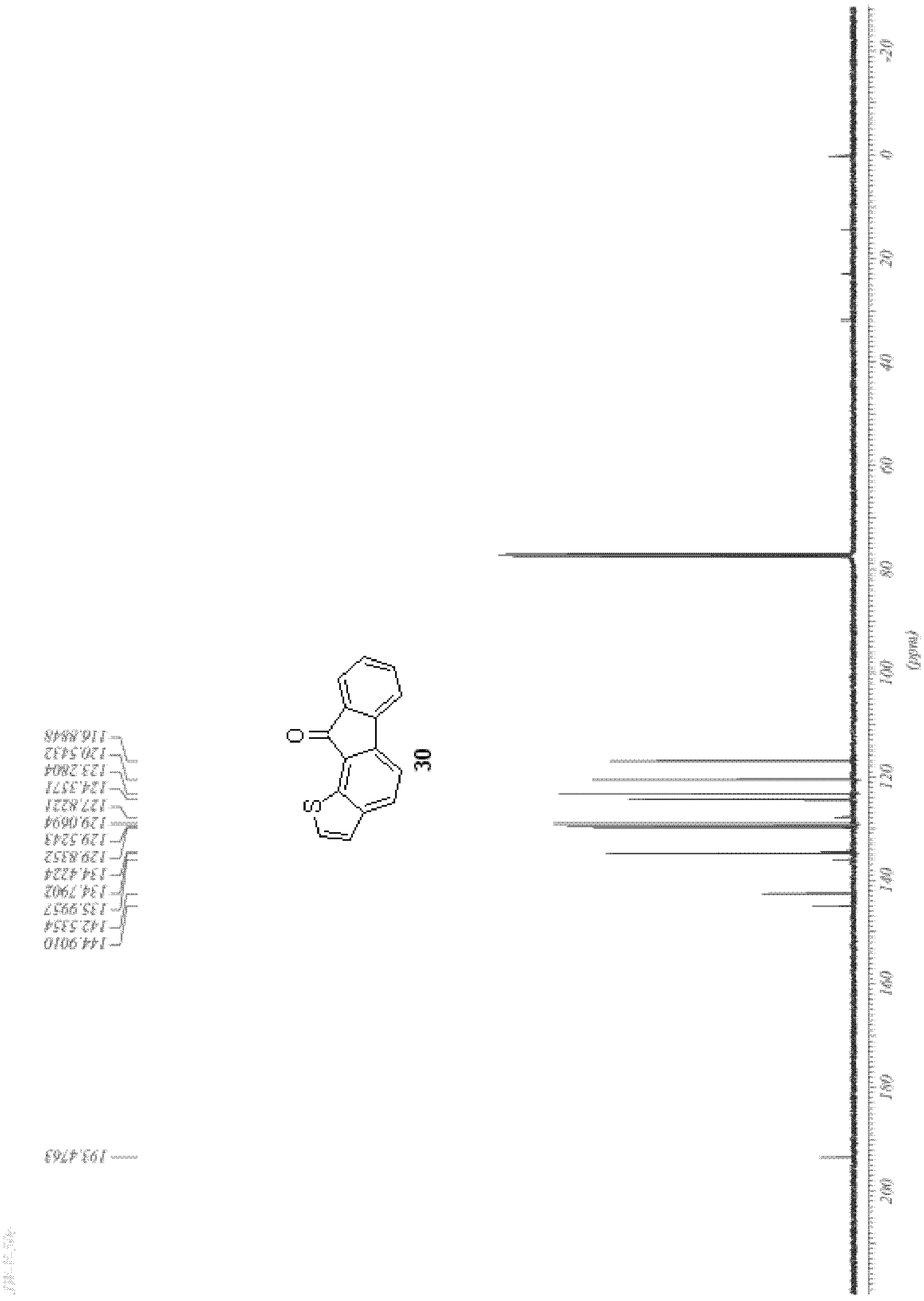
10.0
11.0
12.0
13.0
(ppm)


144.9010
142.5354
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134.7902
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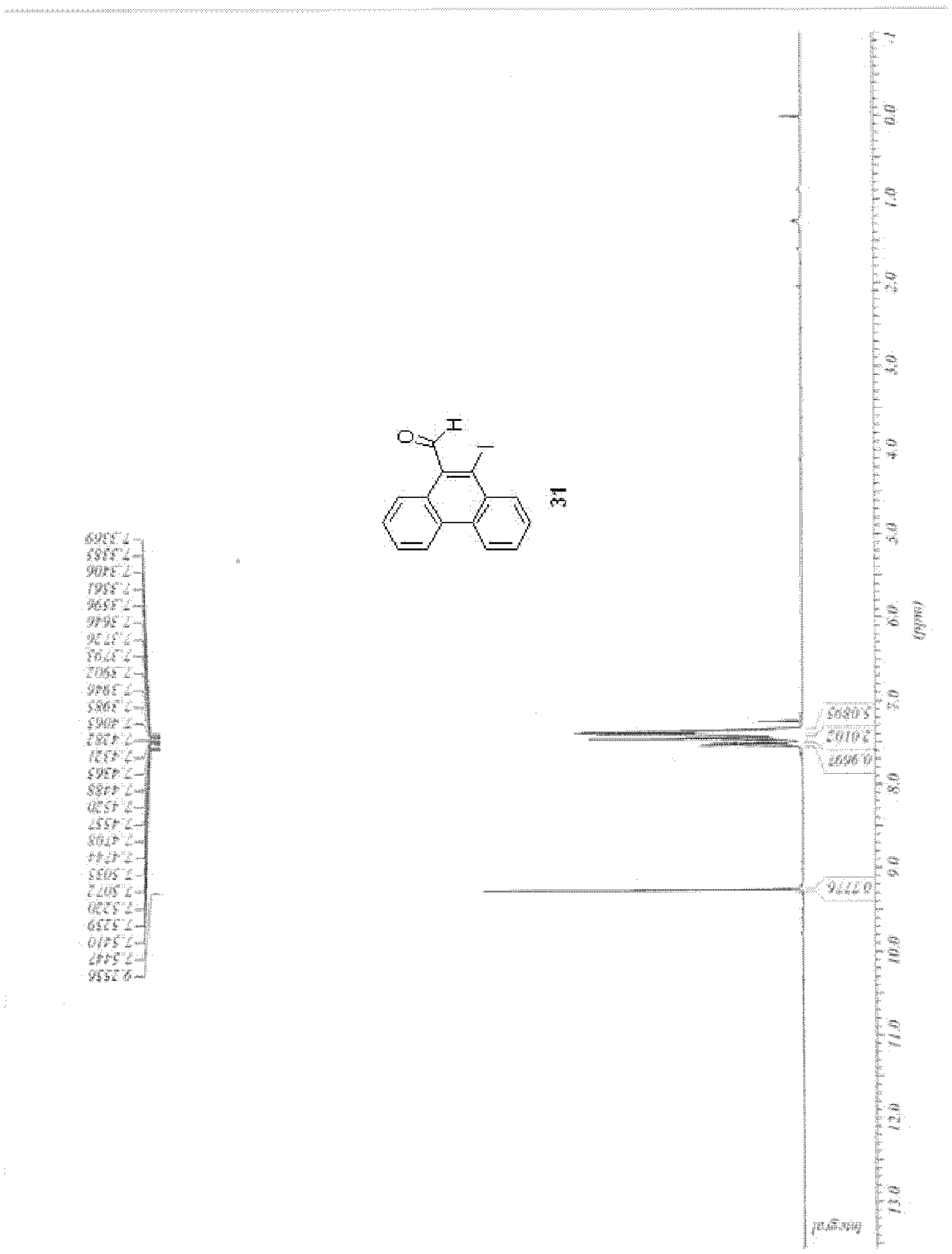
129.5243
129.0694
127.8221
124.3571
123.2804
120.5432
116.8848
193.4763
S
O
30
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)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7.3406
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7.3596
7.3646
7.3726
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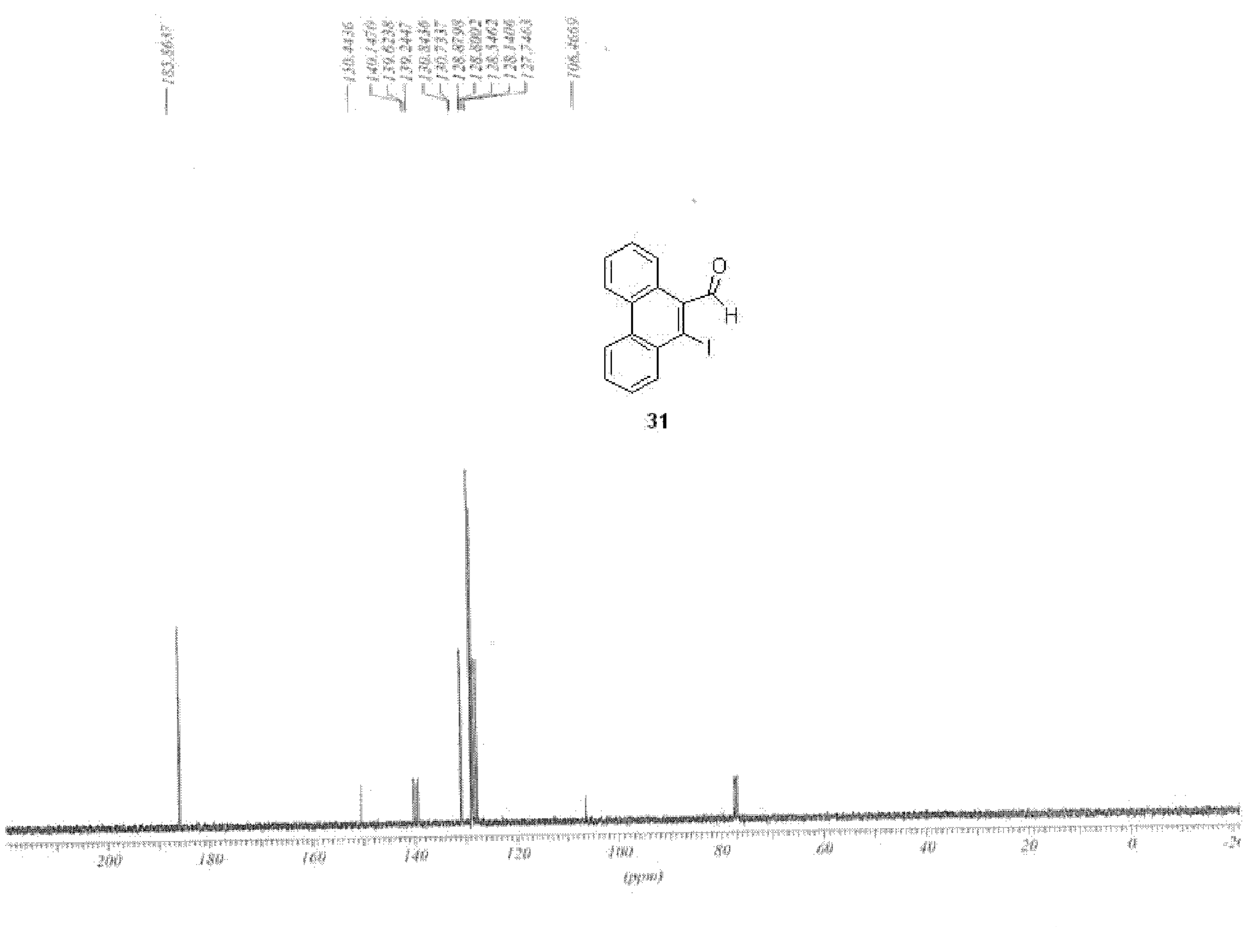
7.3902
7.3946
7.3985
7.4065
7.4282
7.4321
7.4365
7.4488
7.4520
7.4557
7.4708
7.4744
7.5055
7.5072
7.5320
7.5359
7.5410
7.5447
9.2556
5.0895
2.0102
0.9662
0.9776
Integral
-1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
(ppm)

31



31

183.8647
150.4436
140.1470
139.6238
139.2447
130.8436
130.7337
128.8798
128.8002
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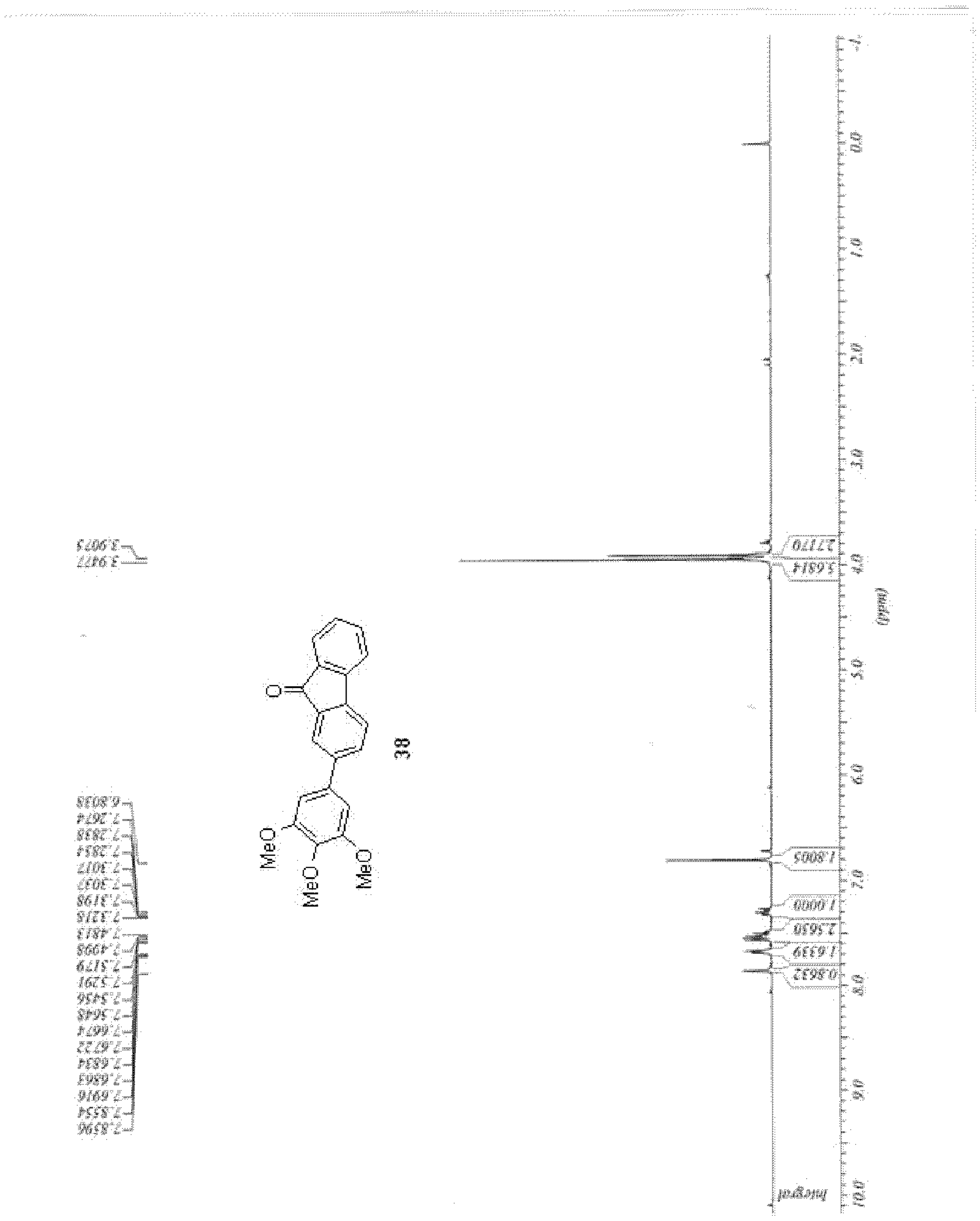
128.1406
127.7463
106.4669
O
H
I
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)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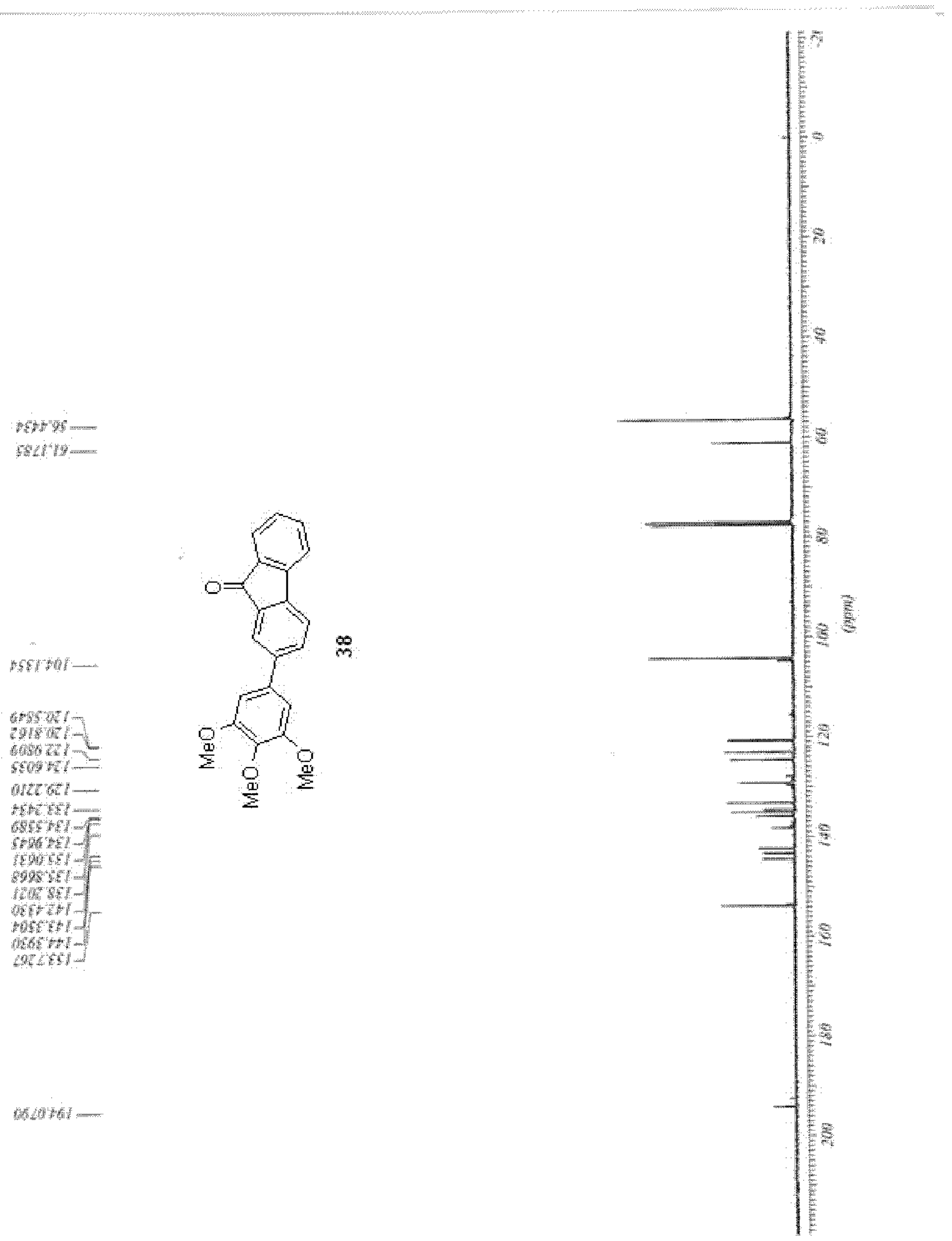
3.9477
6.8038
7.2674
7.2838
7.2854
7.3017
7.3037
7.3198
7.3216
7.4813
7.4998
7.5179
7.5291
7.5456
7.5648
7.6674
7.6722
7.6834
7.6883
7.6916
7.8554
7.8596
MeO
MeO
MeO
O
2.7170
5.6814
1.8005
1.0000
2.5650
1.6339
0.8632
Integral
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.
(ppm)

38



38

56.4454
61.1785
104.1354
120.5549
120.8162
122.9809
124.6035
129.2210
133.2434
134.5589
134.9645
135.0631
135.8668
138.2021
142.4330
143.3504
144.3930
153.7267
194.0790
MeO
MeO
MeO
O
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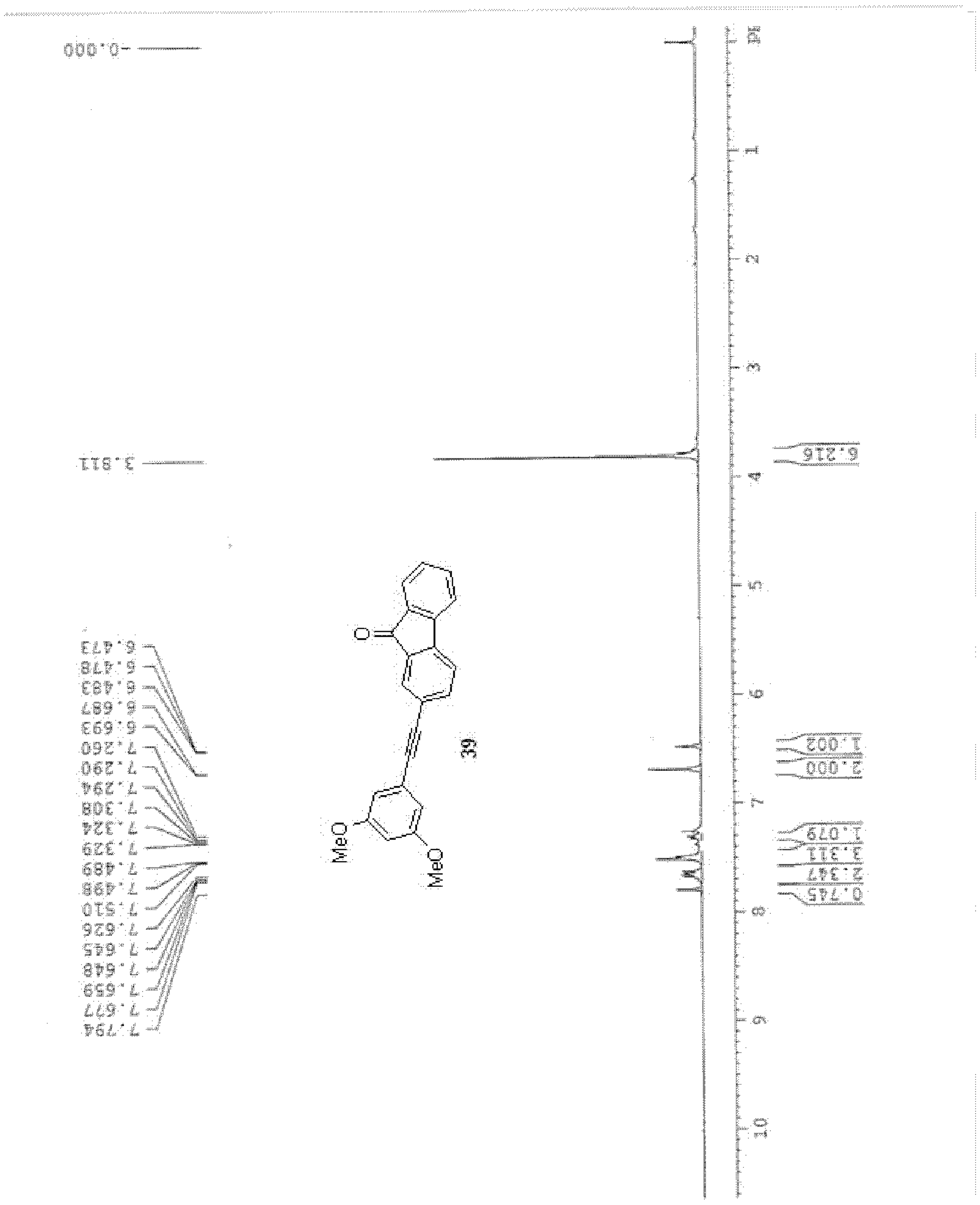
0
20
40
60
80
100
120
140
160
180
200
(ppm)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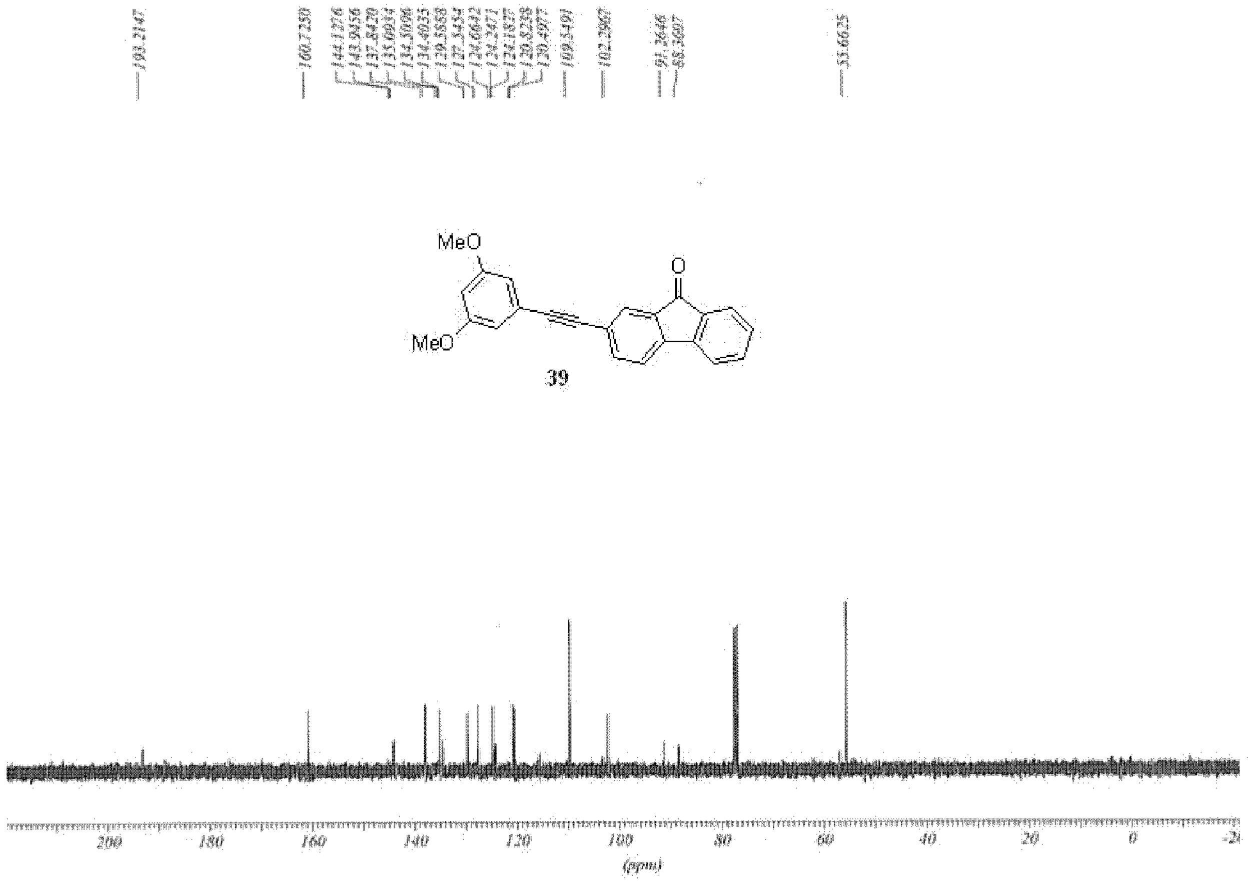
6.473
6.478
6.483
6.687
6.693
7.260
7.290
7.294
7.308
7.324
7.329
7.489
7.498
7.510
7.626
7.645
7.648
7.659
7.677
7.794
O
MeO
MeO
39
6.216
1.002
2.000
1.079
3.311
2.347
0.745
ppm
1
2
3
4
5
6
7
8
9
10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143.9456
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135.6934
134.5096
134.4035
129.5888
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124.6642
124.2471
124.1837
120.8238
120.4977
109.5491
102.2967
91.2646
88.3607
55.6625
MeO
MeO
O
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

39