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Abstract:
Herein, we disclose the synthesis of selenopyrano[2,3-c]pyrazol-4(1H)-ones and their aryl derivatives for the first time using seleno-pyran ring formation via an in situ generated selenide reacting directly with α-halo-β-ynones bearing substituted pyrazoles to provide concomitant selenopyrano[2,3-c]pyrazol-4(1H)-ones. Subsequent direct C–H arylation of the later compounds effected by palladium catalyzed Heck reaction enables the incorporation of arene substituents on the selenopyrano[2,3-c] pyrazol-4(1H)-ones scaffolds with moderate to good yields, could be useful for the biological screenings.

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Synthesis of Selenopyrano[2,3-c]pyrazol-4(1H)-ones and Their C-H Activation

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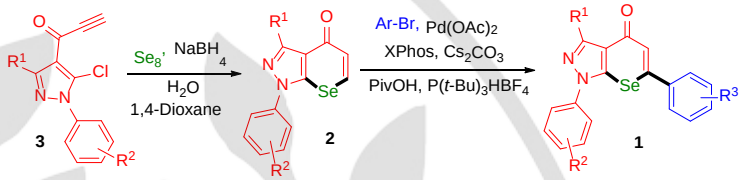

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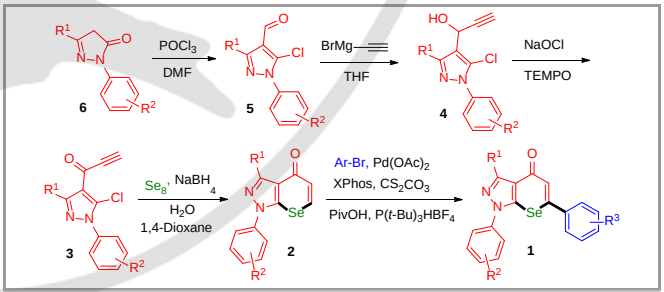
Abstract Herein, we disclose the synthesis of selenopyrano[2,3-c]pyrazol-4(1H)-ones and their aryl derivatives for the first time using seleno-pyran ring formation via an *in situ* generated selenide reacting directly with α-halo-β-ynones bearing substituted pyrazoles to provide concomitant selenopyrano[2,3-c]pyrazol-4(1H)-ones. Subsequent direct C–H arylation of the later compounds effected by palladium catalyzed Heck reaction enables the incorporation of arene substituents on the selenopyrano[2,3-c]pyrazol-4(1H)-ones scaffolds with moderate to good yields, could be useful for the biological screenings.

Key words selenopyrano[2,3-c]pyrazol-4(1H)-ones, carbon-selenium bond formation, C-H activation, Heck reaction, organo-selenide, selenium heterocycles.

Organo-selenium compounds are known to possess broad range of biological activities for therapeutic intervention[1]. Despite, less attention has been paid towards the exploring of organo-selenium compounds and their synthesis[2], our group in 2017 has developed the synthesis of Selenochromen-4-one[3] which showed very good anti-oxidant activities. There are several reports have been surfaced pertaining to the synthesis of organo-selenium-compounds utilizing especially, the C-H activation of arenes or heteroarenes wherein a selenium reagent is needed for installing the selenide functionality under the metal and oxidant driven conditions[3]. Considering the importance of selenium compounds and lack of the structural diversities, there is still room for the development of synthetic methods, wherein a readily prepared selenium heterocycle can be further utilize for the generation of analogs using variety of aryl halides under the cross-coupling reaction conditions. It is noteworthy to explore the selenium containing structural libraries which can be screened for a variety of disease areas would help to highlight the importance of organo-selenium compounds. In this context, we herein, report the straight forward multi-step synthesis of selenium containing heterocyclic scaffold, i.e. selenopyrano[2,3-c]pyrazol-4(1H)-one and more importantly their subsequent direct C-H activation leading to variety of diversely substituted aryl analogs of selenopyrano[2,3-c]pyrazol-4(1H)-ones starting from commercially available pyrazolone derivatives.

In the previous approach reported by our group, the synthesis of selenochromen-4-ones[3], wherein, the Carbon-Selenium (C-Se) bond formation was achieved through the 2-Chloro-3-Carbonyl arenes, selenium and sodium borohydride in DMF solvent at high temperature (135°C) which was then *in situ* cyclized to selenochromen-4-one. Next, the reaction of selenopyrano[2,3-c]pyrazol-4(1H)-ones with aryl halides under the palladium catalyzed cross coupling reaction provided novel aryl substituted selenochromen-4-ones with moderate yields.



Scheme 1: Synthesis of selenopyrano[2,3-c]pyrazol-4(1H)-ones

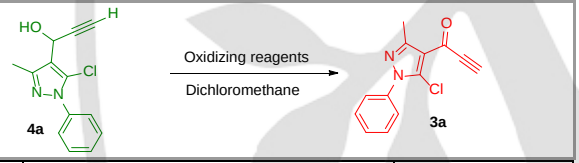
In the present method, the C-Se bond formation[4] was achieved in green solvent water using 1-(5-chloro-1-aryl-1H-pyrazol-4-yl)prop-2-yn-1-one, selenium and sodium borohydride in water at mild reaction temperature (40°C) which was concomitantly *in situ* cyclized to selenopyrano[2,3-c]pyrazol-4(1H)-ones. The present method, seems

environmentally benign and provided the selenopyrano[2,3-c]pyrazol-4(1H)-ones with good yields (**Scheme 1**).

Substituted pyrazolones can be synthesized from hydrazine and alkyl-acetoacetate derivatives[5]. Addition to commercially available pyrazolones, other new analogs were synthesized with substituents such as R^1 and R^2, incorporating various substituents present on phenyl ring.

2-aryl-2,4-dihydro-3H-pyrazol-3-ones **6** were used to transformed to their corresponding 2-chloropyrazol-3-carbaldehydes **5** by means of Vilsmeier–Haack reaction. The formylation occurred very quickly, within 20 minutes. Once the aldehyde functionality is installed on pyrazolone scaffold, the ethynyl group was introduced by Grignard reaction using ethynyl magnesium bromide provided the pyrazole propargylic alcohol **4**. Subsequent oxidation of the propargylic alcohol functionality furnished 1-(5-chloro-1-aryl-1H-pyrazol-4-yl)prop-2-yn-1-ones **3**. This reaction is very important for the subsequent selenide precursor and cyclization, therefore, need to optimized thoroughly. Oxidation of alcohols are well-known and can be achieved by variety of oxidizing agents as summarised in **Table 1**, various oxidizing agents were tested in this reaction. Based on this study, the best oxidizing agent was Sodium hypochlorite and TEMPO for this scaffold. This method made it possible to provide keto-compounds quickly and easily that too with a very good yield compared to our earlier protocol.

Table 1: Optimization study for oxidation of propargylic alcohol[a]

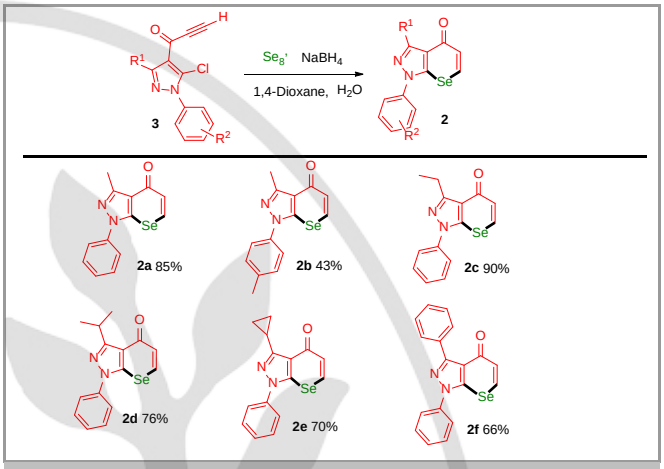


Entry	Oxidizing reagent	Yield (%)[b]
1	Pyridinum chlorochromate	22[c]
2	Manganese dioxide	50[d]
3	Dess Martin Periodinane	88[e]
4	Sodium hypochlorite/TEMPO	98[f]

[a] Reaction Conditions: **4a** (1 mmol), solvent (10 mL), [b] Isolated yields, [c] (1.5 mmol), [d] (10 mmol), [e] (1.8 mmol), [f] (3/0.05 mmol)

In order to achieve cyclization towards selenopyrano[2,3-c]pyrazol-4(1H)-ones from compound **3**, NaHSe was generated in-situ. Initially, following our reported procedure wherein selenium powder and sodium borohydride in anhydrous DMF reacted at 135℃ provided lower yield. Selenide formation is considered to be very important for the intra-molecular cyclization. Knowing the fact that selenide can easily be obtained by using protic solvent such as water, the reaction of selenium powder and sodium borohydride were carried out in water at 40℃ provided selenopyrano[2,3-c]pyrazol-4(1H)-one with high yields. In general, the substituent present at position 3 of the pyrazole ring showed high response in particular EDG turned out with higher yield. The product of both reactions is observed with higher yield of (3-methyl-1-phenylselenopyrano[2,3-c]pyrazole-4(1H)-one) (**Scheme 2**).

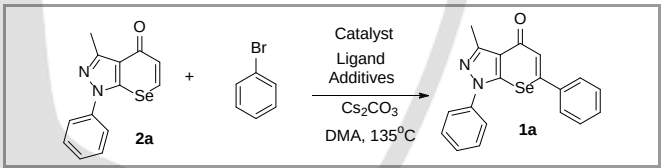
In past, our group has developed C-H activation under the Heck reaction conditions to achieve direct C-H activation of selenopyrano[2,3-c]pyrazol-4(1H)-ones effected by palladium catalyst. As a result, we were able to find the conditions highly suitable for adding a variety of aryl groups onto the Se-C-H bonds of the newly synthesized selenopyrano[2,3-c]pyrazol-4(1H)-ones.



Scheme 2: Substrate scope of selenopyrano[2,3-c]pyrazol-4(1H)-ones

To find a better catalyst system, various palladium catalysts and phosphine ligands were screened for this C-H activation. The established conditions in our previous report provided the best result. With the exception of palladium acetate, the yield of $Pd(Ph_3)_2Cl_2$ catalyzed appeared to be high at 60%, which was fixed and screened using various ligands. However, this yield was not reached to higher level compared to palladium acetate and XPhos (entry 8, **Table 2**). Therefore, various aryl halides were subjected in this condition at 135℃ for 15 hours using palladium acetate, XPhos, cesium carbonate, pivalic acid and tri-tert-butyl phosphonium hydrogen tetrafluoroborate P(*t*-Bu)$_3$HBF$_4$.

Table 2: Optimization study for direct C-H activation[a]



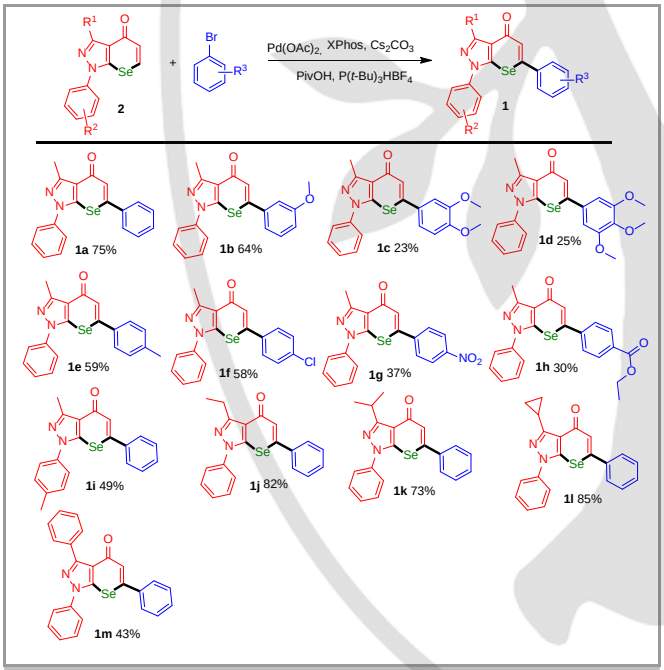
Entry	Catalyst	Ligand	Additives	Yield (%)[b]
1	$Pd(PhCN)_2Cl_2$	XPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	49
2	$Pd(Ph_3)_2Cl_2$	XantPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	17
3	$Pd(Ph_3)_2Cl_2$	SPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	18
4	$Pd(Ph_3)_2Cl_2$	RuPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	38
5	$Pd(Ph_3)_2Cl_2$	JhonPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	39
6	$Pd(Ph_3)_2Cl_2$	tBuXPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	60
7	$Pd(PPh_3)_4$	XPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	46
8	$Pd(OAc)_2$	XPhos	PivOH/P(*t*-Bu)$_3$HBF$_4$	75

[a] Reaction Conditions: **2a** (1 eqv), PhBr (2 eqv), Pd (0.2 eqv), Ligand (40 mol %), PivOH/ P(*t*-Bu)$_3$HBF$_4$ (40 mol%), PivOH (1.5 eqv) Cs_2CO_3 (3 eqv), DMA (0.1M) 15h at 135 ℃, [b] Isolated yields,

The optimized reaction conditions with 20 mol% of $Pd(OAc)_2$, 40 mol% XPhos, 40 mol% P(*t*-Bu)$_3$HBF$_4$, 1.5 eqv of PivOH, 3 eqv of CS_2CO_3, and 2 eqv of aryl halide in DMA (0.1M) provided the

desired C-H arylation of selenopyrano[2,3-c]pyrazol-4(1H)-ones derivatives. The well-known reaction path for palladium-catalyzed direct C-H activation catalyzed by Palladium catalyst is similar to earlier reports[3,6].

Once the established reaction condition is in hand, we began to investigate various aryl bromides with electron-donating groups (EDG) present on the aromatic ring are important for group II secretory phospholipaseA_2 (sPLA_2IIA). activity[7] and electron-withdrawing groups (EWG) as mentioned in scheme 3. Both electron donating and electron withdrawing substituent containing aryl bromide underwent direct C-H activation with established reaction conditions. Both electronic functionalities provided desired C-H activation product with moderate to good yields (**1a-h**). On average, the activity of EDG and EWG looks similar, but a slight higher yield was found in case of electron-donating groups (EDG, Me group) present on 3rd position of pyrazole (**1a**) ring provided better yield compared to phenyl substituent (**1m**). In addition, it was observed that the comparatively higher yields were obtained in case of ethyl, isopropyl, cyclopropyl group (**1j-l**) when it was subject to react with bromobenzene under the established conditions. The presence of electron rich alkyl groups on adjacent carbon may be weakening the electron withdrawing nature of carbonyl bond which could participate as a mild co-ordination in the catalysis process. This method can easily provide C-H arylation products of various selenopyrano[2,3-c]pyrazol-4(1H)-ones with various aryl bromides (**Scheme 3**).



Scheme 3: C-H activation of selenopyrano[2,3-c]pyrazol-4(1H)-ones

In conclusion, we have developed a multi-step synthetic protocol for new selenopyrano[2,3-c]pyrazol-4(1H)-ones and their direct C-H arylation using palladium catalyst. We have also modified the oxidation and cyclization part compared to our previous method and the products were obtained with moderate to higher yields duly confirmed by NMR and HRMS analysis. In general, we attempted to prepare various analogs of this novel scaffold for further biological screenings. Further work on the development of selenium containing other heterocyclic systems is currently under-way in our laboratory and will be reported in due course.

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Click here to insert sources of funding, grant numbers, etc. Do not repeat the same in the acknowledgment.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

Is there **Primary Data** to be associated with this manuscript? Click here, then the arrow, and choose YES or NO.

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(8) General procedure for Vilsmeier-Haack formylation
Phosphoryl chloride (0.12 mol, 11.27mL) was added dropwise to an ice-cold dimethylformamide (0.52 mol, 4 mL) then cooling was removed to reflux system, the mixture was treated with 3-methyl-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3.0 g, 17.22 mmol) and the mixture compound was heated at 120℃ for 20 min. After cooling, the reaction mixture was poured into ice-cold water (200 mL) and stirred for 1h. Then extracted with Ethyl acetate, Organics was washed with water and dried over Sodium sulfate, and concentrated under vacuum. The product was purified by column chromatography on silica gel.
5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (**5a**)

The title compound was prepared from 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3.0 g, 17.22 mmol). Flash chromatography (Hexane/EtOAc=3:1) on silica gel gave 5a as yellow solid (2.5g, 65.8%), mp 143-145℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.53-7.46 (m, 5H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 151.9, 137.1, 133.6, 129.4, 129.3, 125.3, 117.6, 14.0; HRMS (ESI-QTOF) calcd for $C_{11}H_{10}ClN_2O$ 221.0482 $[M+H]^+$, found 221.0480.

(9) General procedure for Grignard reaction

A solution of ethynylmagnesium bromide in THF (0.5 M solution, 8 mmol) was added to the solution of aldehyde **5a** (6 mmol) in anhydrous tetrahydrofuran (THF, 30 mL) at 0℃. The reaction mixture was stirred at 0℃ and then allowed to room temperature for another 2h. After the completion of reaction as indicated by TLC was treated with saturated aqueous ammonium chloride solution and stirred for 30 min after addition of Ethyl acetate. Organics was dried over Sodium sulfate, and concentrated under vacuum and purified by column chromatography on silica gel.

1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (**4a**) The titled compound was prepared from **5a** (1.3 g, 5.9mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (1.4 g, 96%), mp 87-90 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.36 (m, 5H), 5.43 (s, 1H), 3.74 (s, 1H), 2.56 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 137.8, 129.0, 128.3, 125.9, 125.1, 116.5, 82.2, 73.8, 55.3, 13.1; HRMS (ESI-QTOF) calcd for $C_{13}H_{12}ClN_2O$ 247.0638 $[M+H]^+$ found 247.0646.

(10) General procedure for Sodium Hypochlorite oxidation

A solution of NaOCl (12%, 6 mmol) was added to the solution of NaBr (2 mmol), NaHCO3 (4 mmol), TEMPO (0.1 mmol), and secondary alcohol **4a** (2 mmol) in CH_2Cl_2 (10 mL) at 0℃. After the completion of reaction as indicated by TLC was treated with water. Then water and the organic layers were separated, organic was dried over Sodium sulfate, and concentrated under vacuum and purified by column chromatography on silica gel.

1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (**3a**) The title compound was prepared from **4a** (500 mg, 2.03 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2=10:1:2) on silica gel gave white solid (488 mg, 98%), mp 96-99 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, 5H), 3.43 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 166.6, 152.7, 137.2, 129.5, 129.4, 125.6, 81.6, 80.7, 15.2; HRMS (ESI-QTOF) calcd for $C_{13}H_{10}ClN_2O$ 245.0482 $[M+H]^+$, found 245.0479.

(11) General procedure for selenopyrano[2,3-c]pyrazol-4(1H)-ones

A solution of NaHSe (1.2 mmol), which was made from selenium powder (1.1 mmol) and $NaBH_4$ (1.2 mmol) in water (10 mL) at 40℃ stirred for 30 min. A solution of **3a** (1.0 mmol) in 1,4-Dioxane (5 mL) was added at once and the mixture was stirred for another 30 min. To remove the inorganics, it was extracted with ethyl acetate and washed with water. Organics was dried over Sodium sulfate and concentrated purified by column chromatography on silica gel.

3-methyl-1-phenylselenopyrano[2,3-c]pyrazol-4(1H)-one (**2a**)

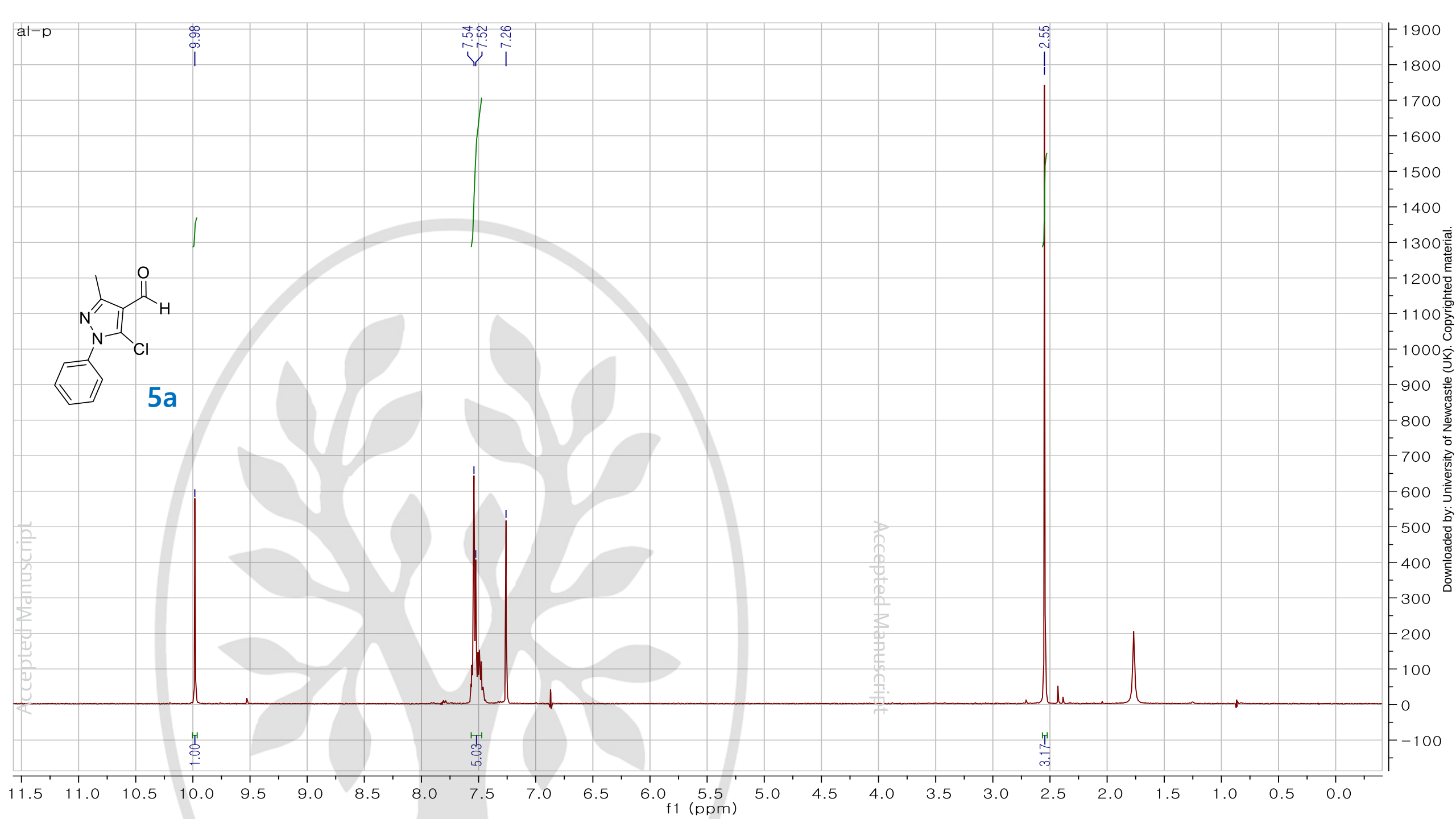
The title compound was prepared from **3a** (100 mg, 0.409 mmol). Flash chromatography (Hexane/EtOAc=2:1) on silica gel gave yellow solid (100 mg, 85%), mp 133-135 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (d, J = 8.0 Hz, 1H), 7.63-7.43 (m, 5H), 7.14-7.12 (d, J = 8.0 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 152.7, 139.1, 136.2, 131.0, 129.9, 129.3, 128.7, 122.8, 118.1, 14.5; HRMS (ESI-QTOF) calcd for $C_{13}H_{11}N_2OSe$ 291.0037 $[M+H]^+$ found 291.0040.

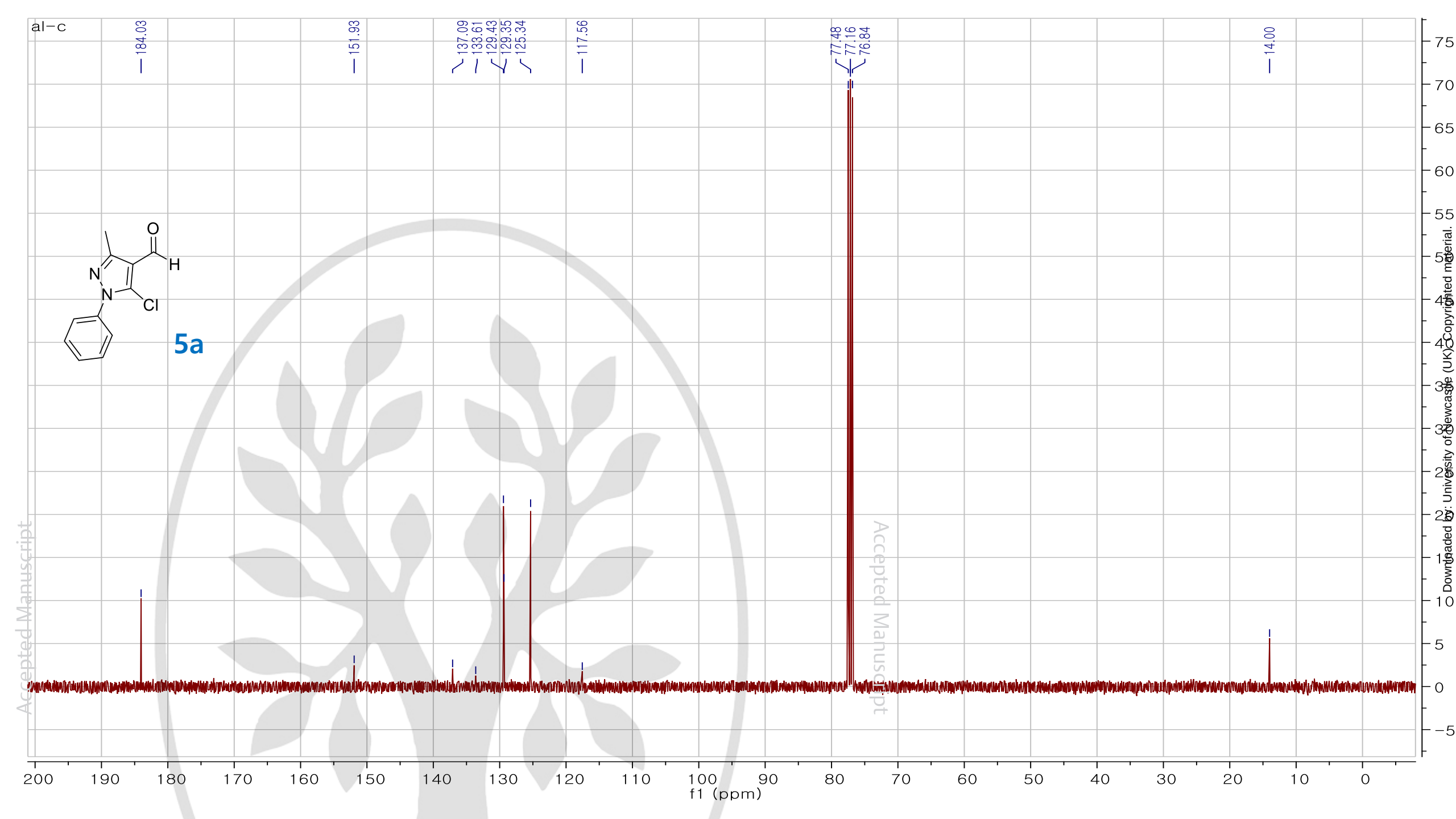
(12) General procedure for Pd-catalyzed direct C-H arylation of selenopyrano[2,3-c]pyrazol-4(1H)-ones

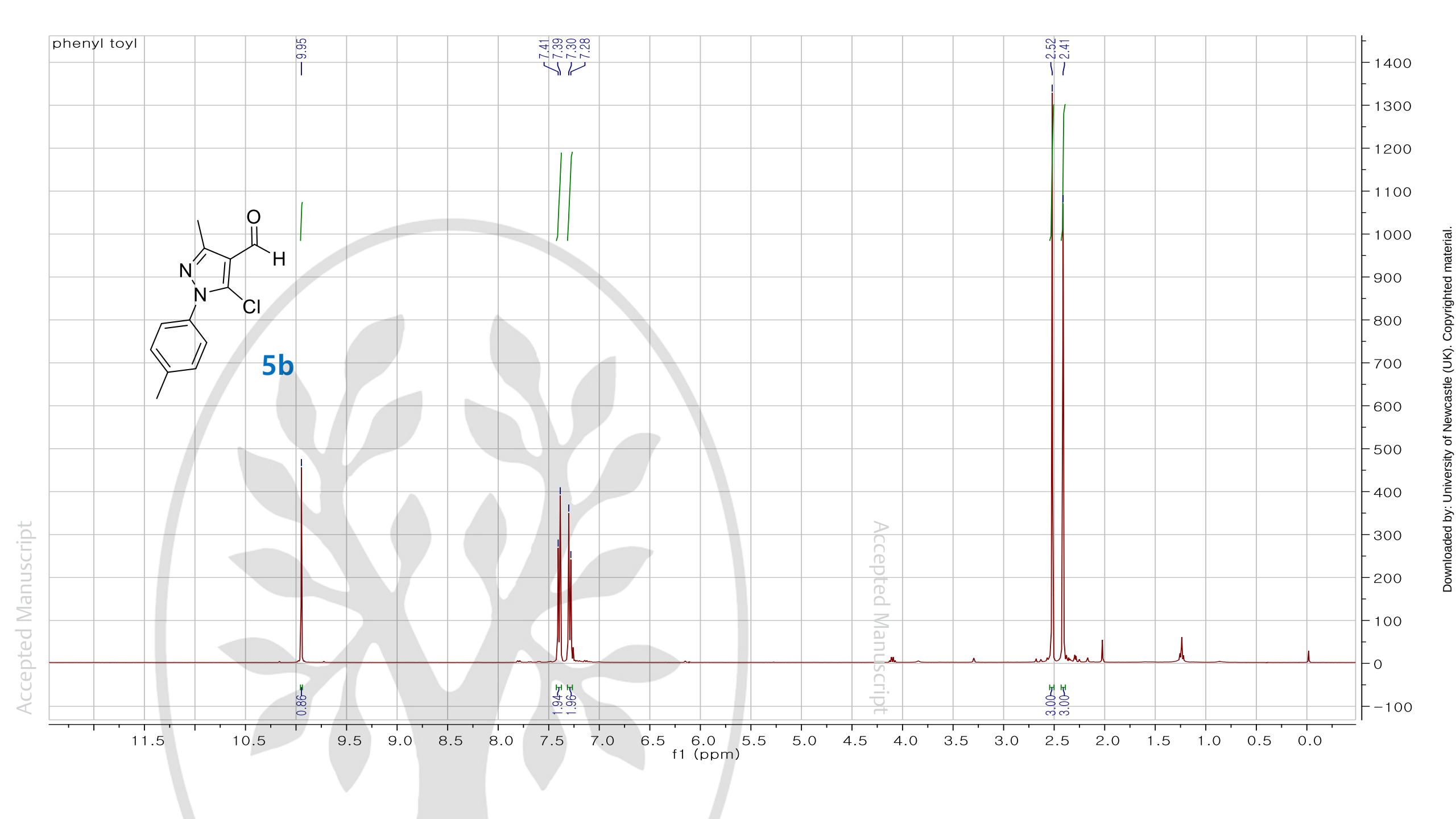
In a two neck flask fitted with reflux-condenser and a septum, $Pd(OAc)_2$ (20 mol%), XPhos (40 mol%), tri-tert-butylphosphonium hydrogen tetrafluoroborate (40 mol%), pivalic acid (0.15 mmol), Cs_2CO_3 (0.3 mmol) and selenopyranopyrazolone 1 (0.1 mmol), in DMA (0.1M) were charged and then treated with aryl halide (0.2 mmol). The flask was set on heating block and was adjusted the temperature to 135℃ with stirring over 15h. After cooling, the mixture was treated with water and EtOAc, dried with Sodium sulfate, concentrated and purified by column chromatography on silica gel.

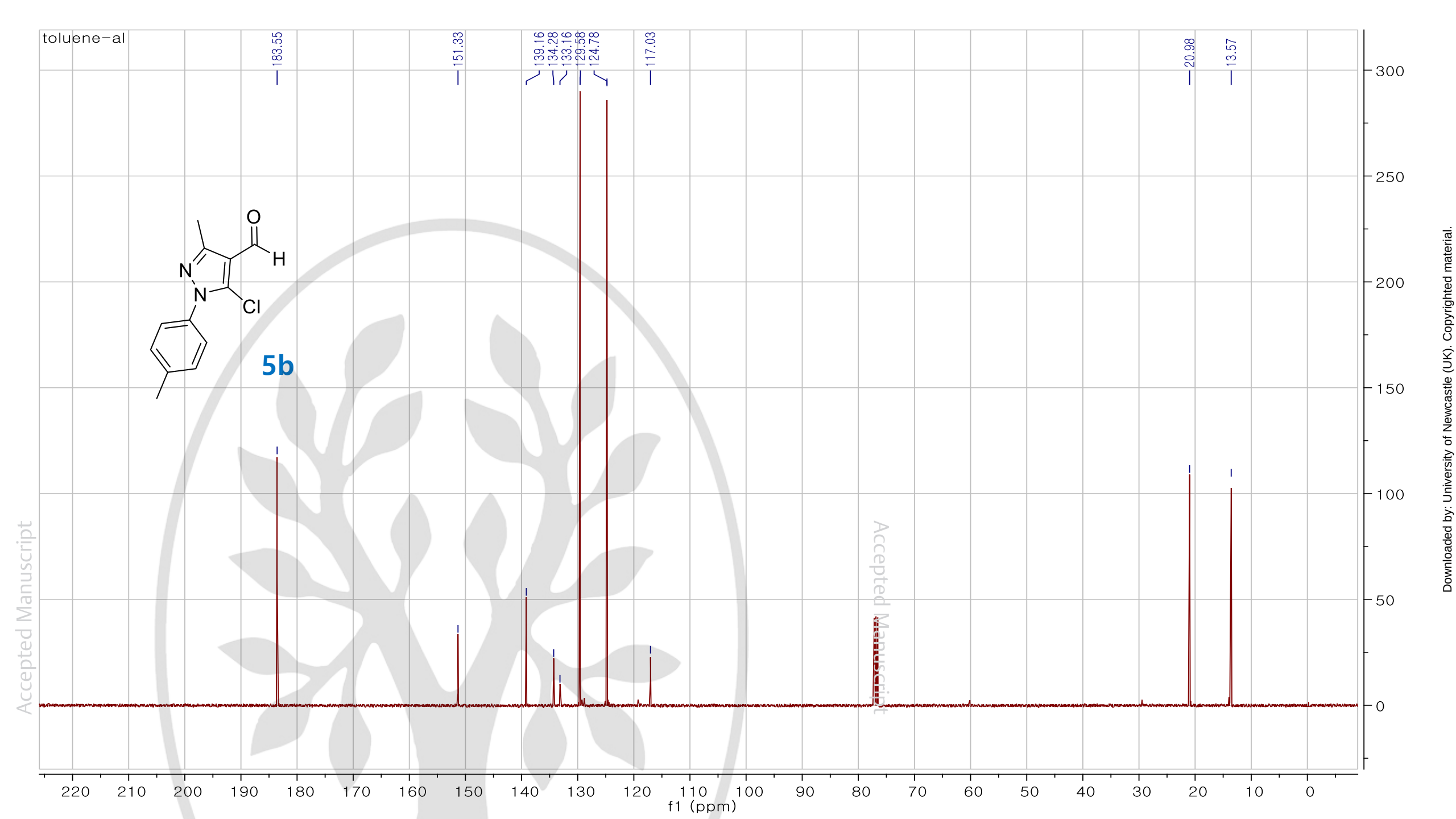
3-methyl-1,6-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (**1a**)

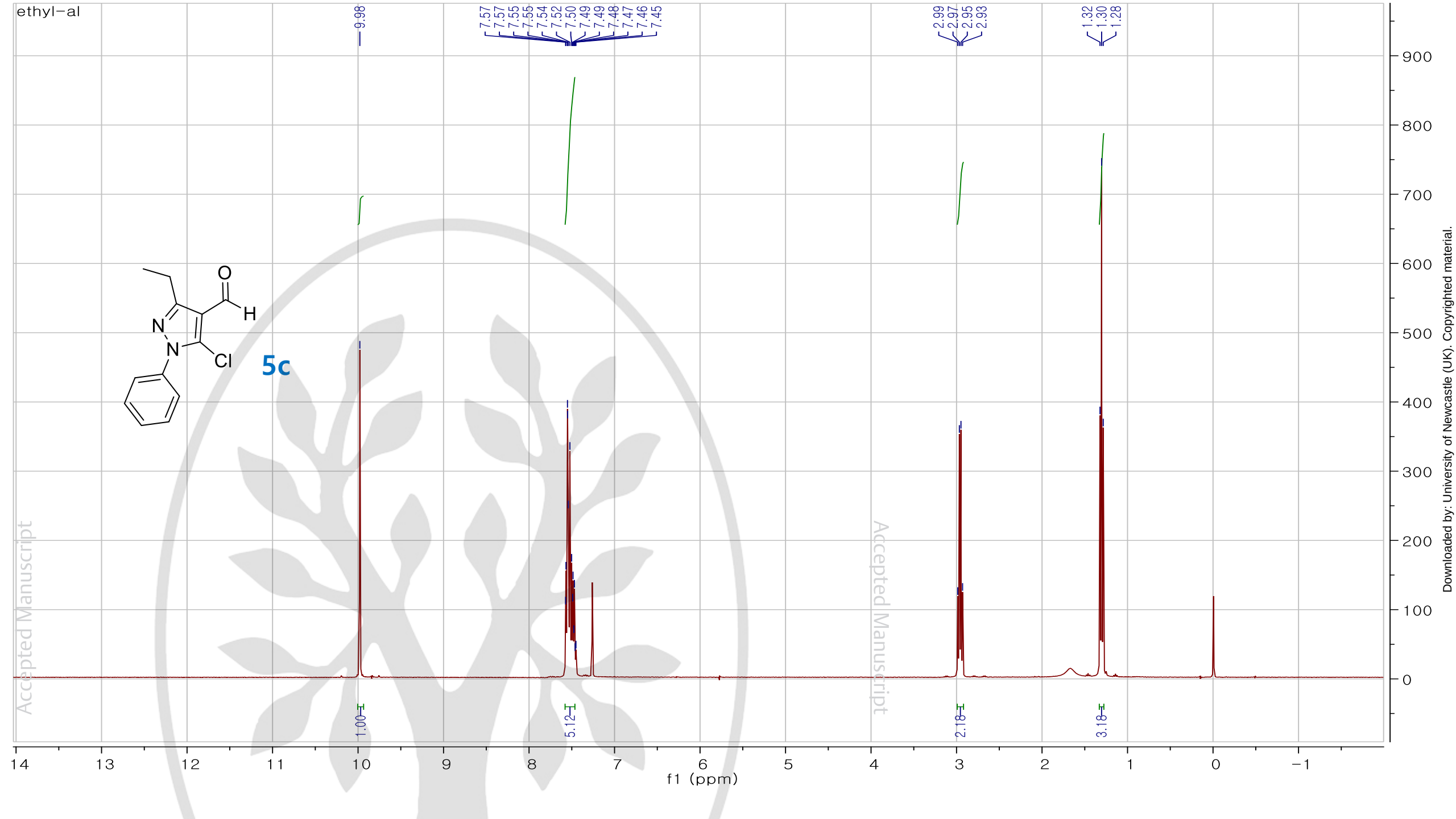
The title compound was prepared from **2a** (30 mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2=5:1:2) on silica gel gave white solid (25.5 mg, 75%), mp 192-193 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (d, J = 8.0 Hz, 2H), 7.57-7.53 (m, 4H), 7.48-7.44 (m, 4H), 7.23 (s, 1H), 2.77 (s, 3H); ^{13C} NMR (101 MHz, $CDCl_3$) δ 180.7, 152.7, 147.3, 139.3, 137.8, 137.7, 130.8, 130.1, 129.5, 128.8, 127.2, 123.0, 117.4, 14.6; HRMS (ESI-QTOF) calcd for $C_{19}H_{15}N_2OSe$ 367.0350 $[M+H]^+$ found 367.0347.







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7.47
7.46
7.45
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2.97
2.95
2.93
1.32
1.30
1.28
O
H
N
N
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Accepted Manuscript
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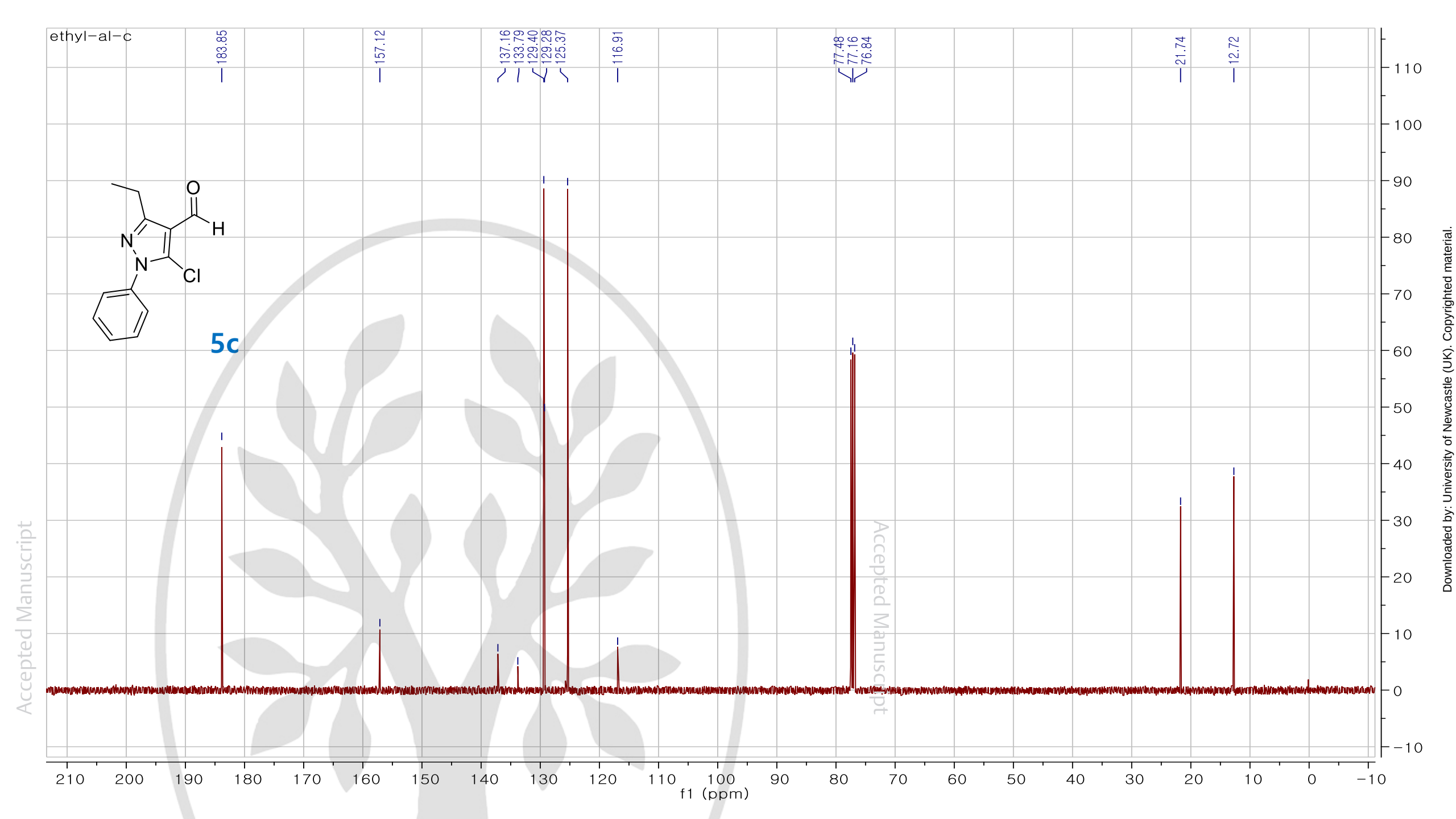

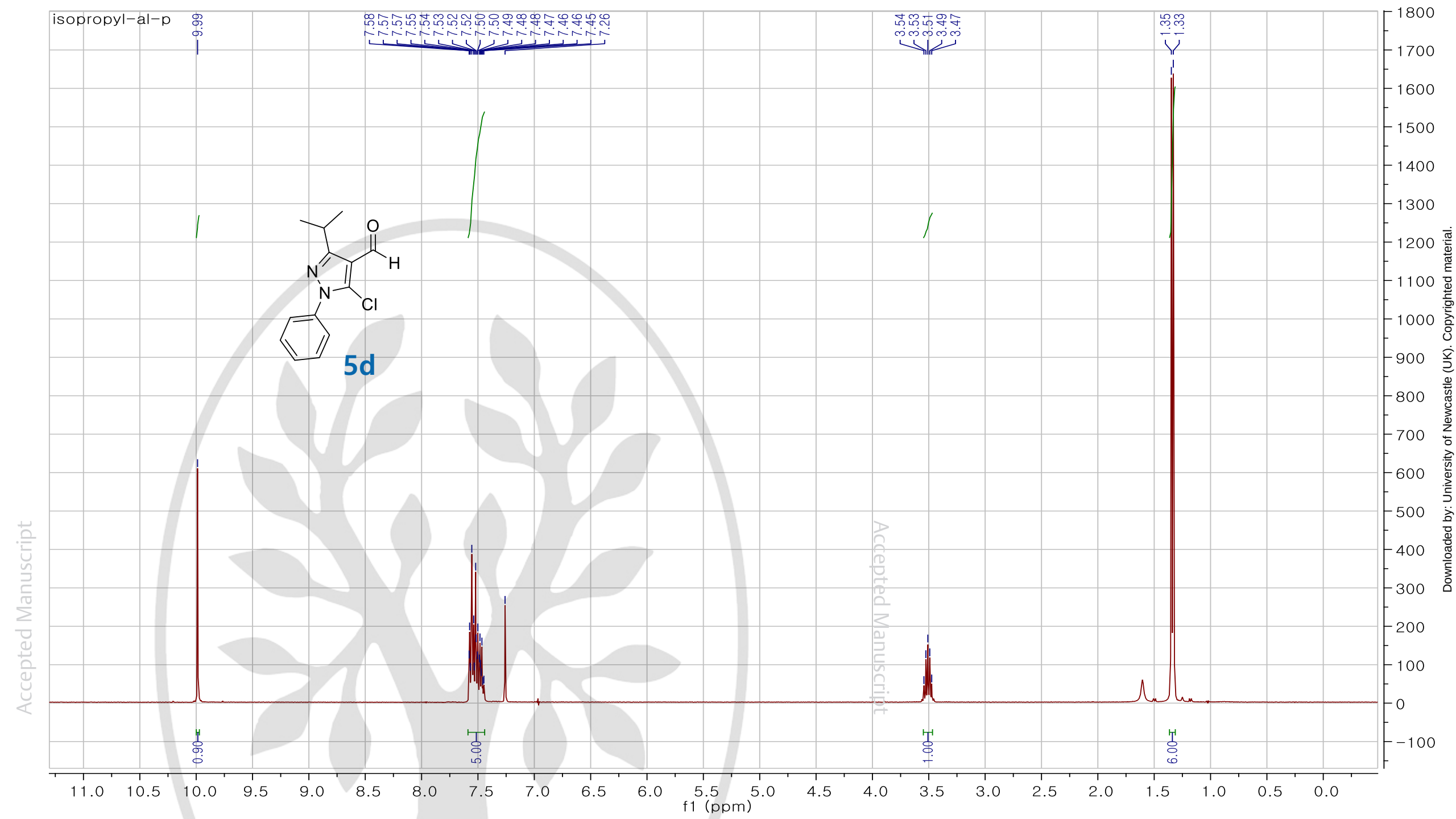
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7.52
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7.46
7.45
7.26
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3.51
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N
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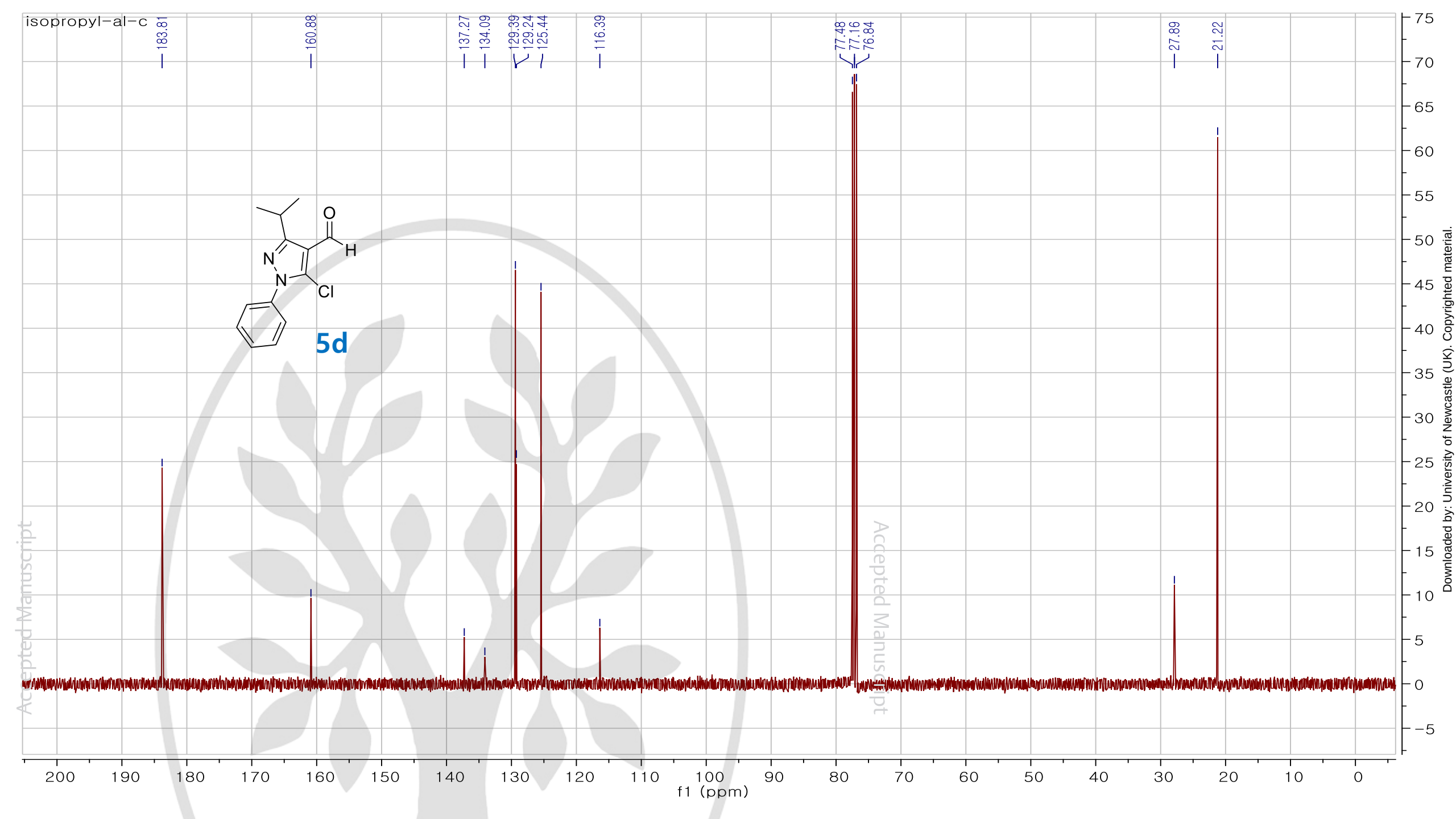
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116.39
77.48
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76.84
27.89
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H
N
N
Cl
5d
f1 (ppm)
Downloaded by: University of Newcastle (UK). Copyrighted material.
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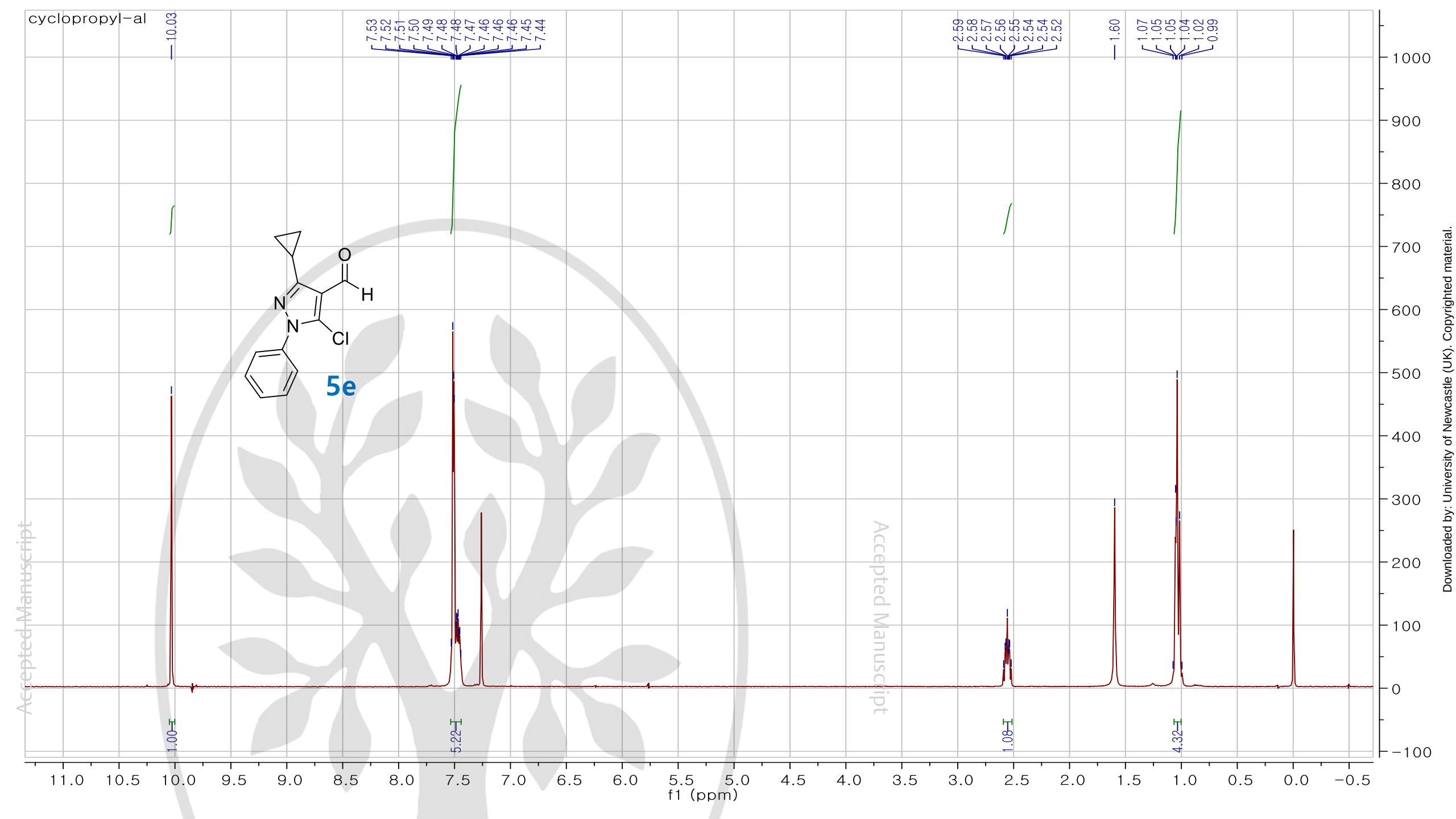
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2.57
2.56
2.55
2.54
2.54
2.52
1.60
1.07
1.05
1.05
1.04
1.02
0.99
O
H
N
N
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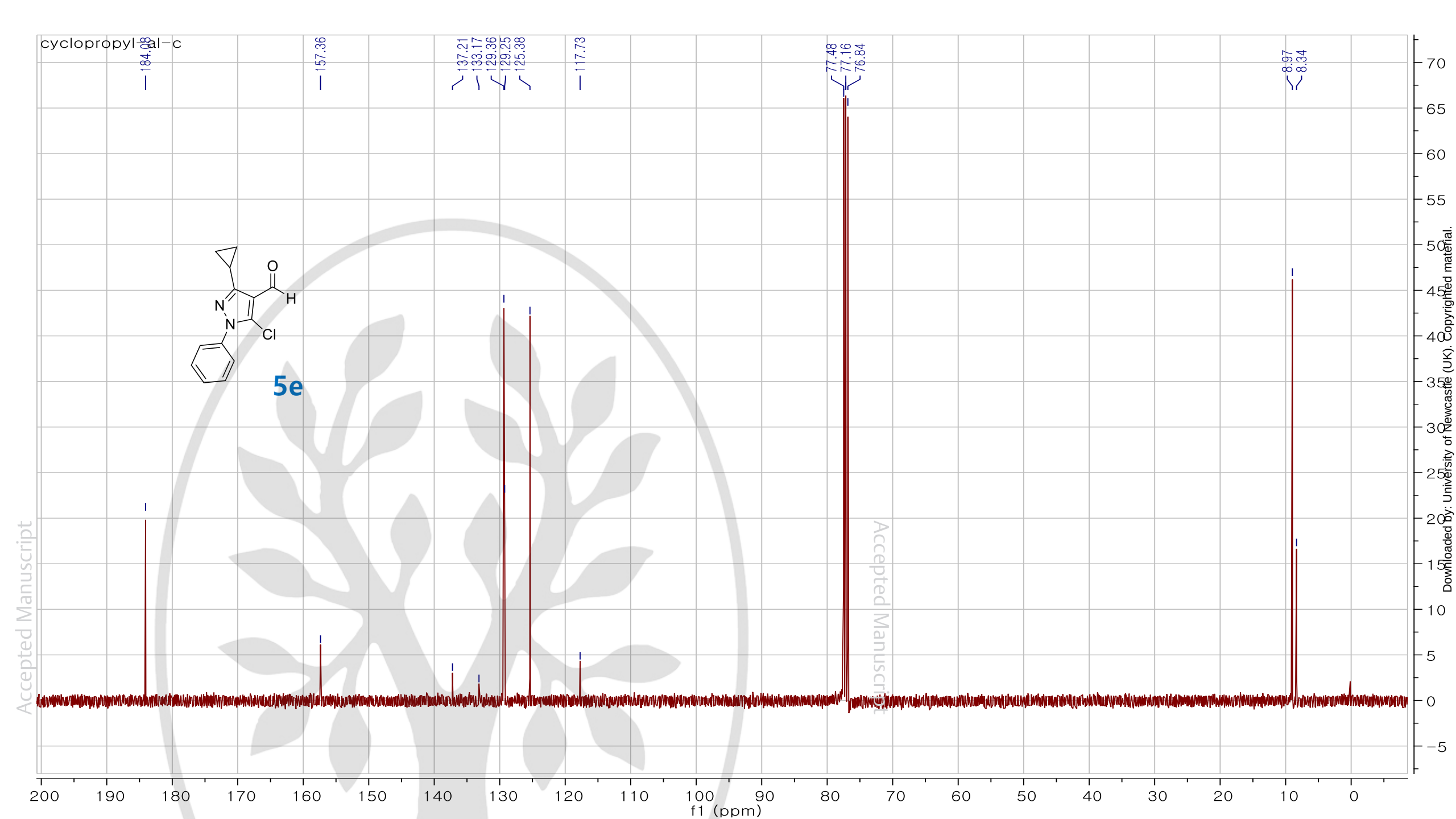

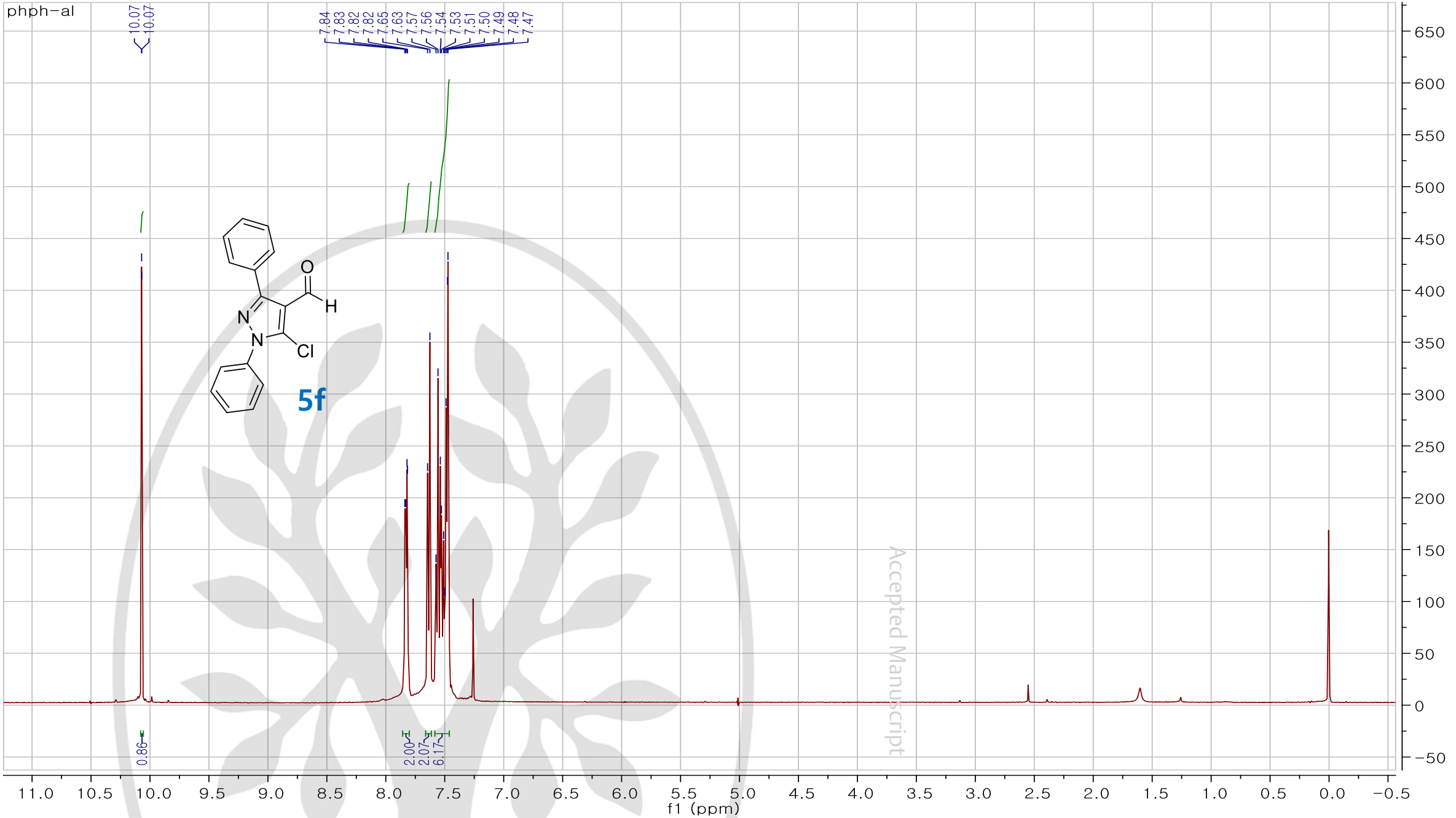

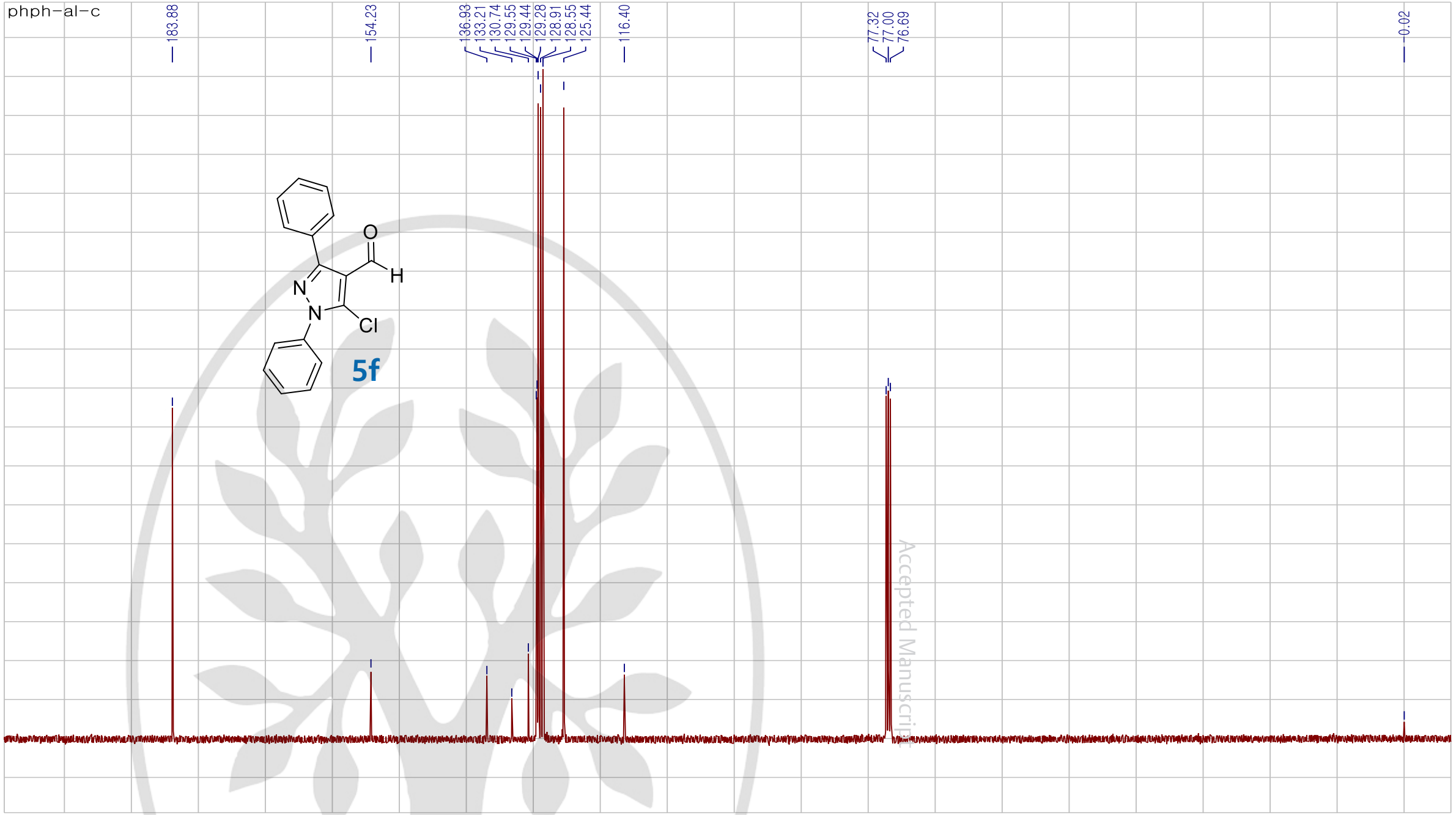

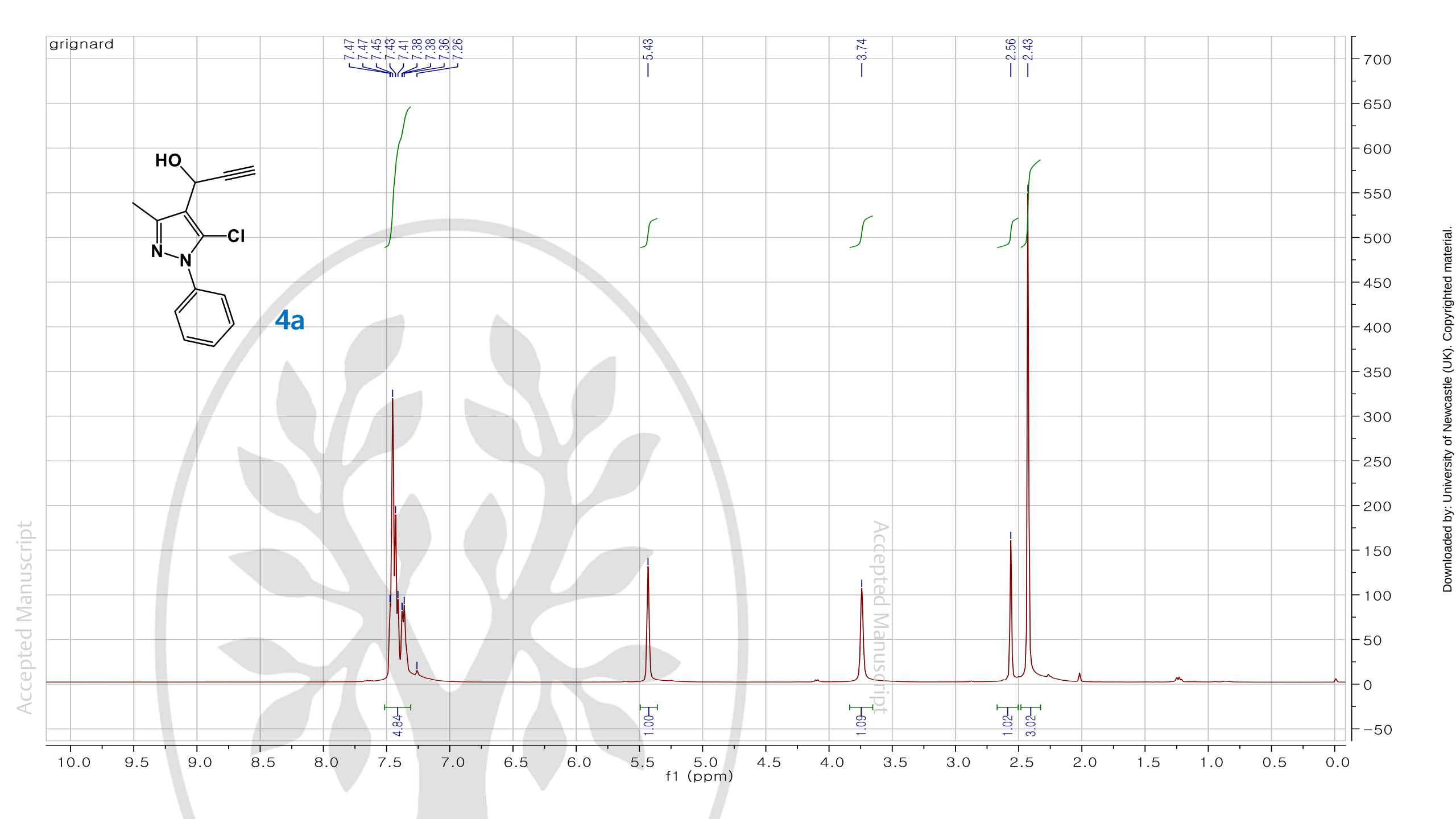

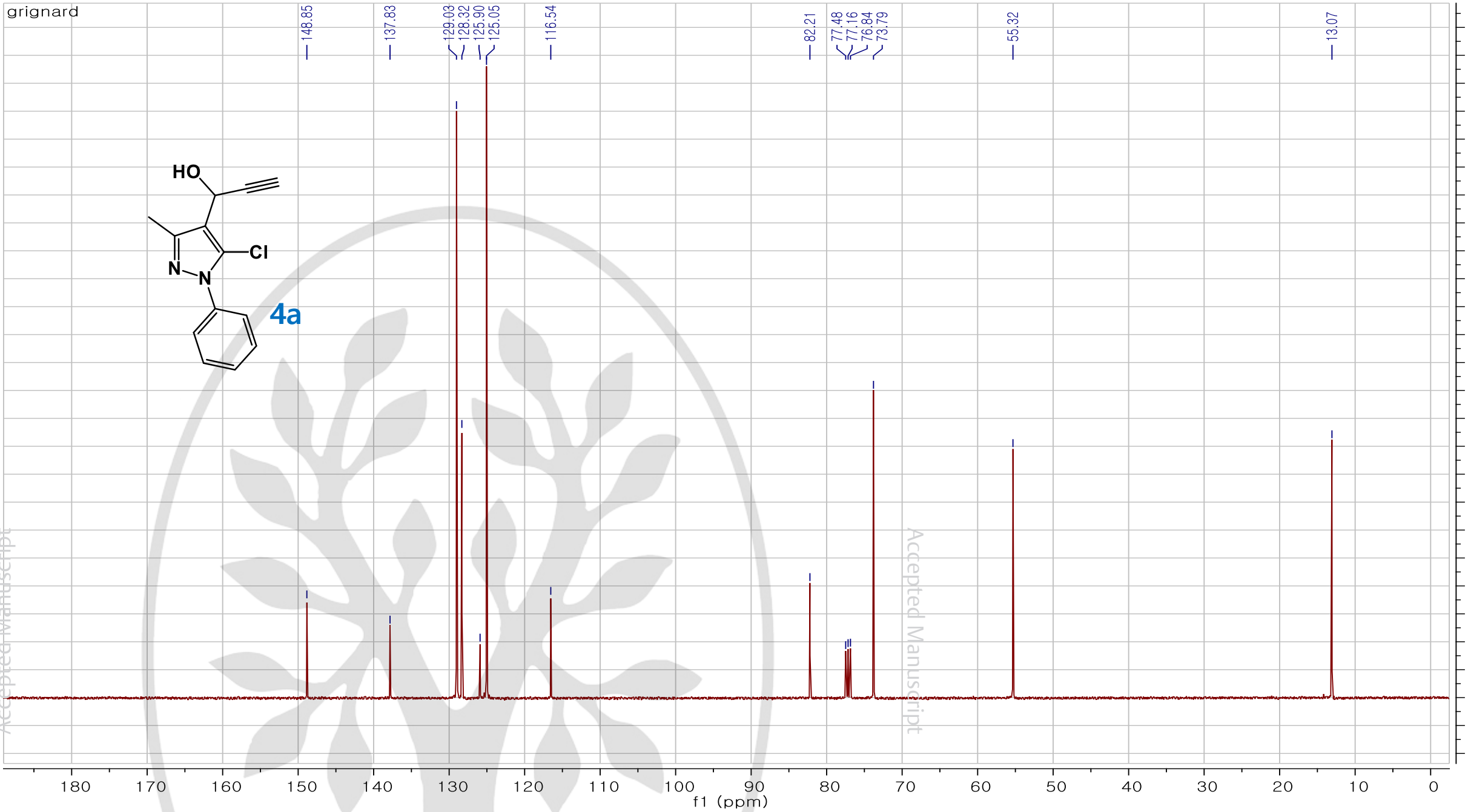

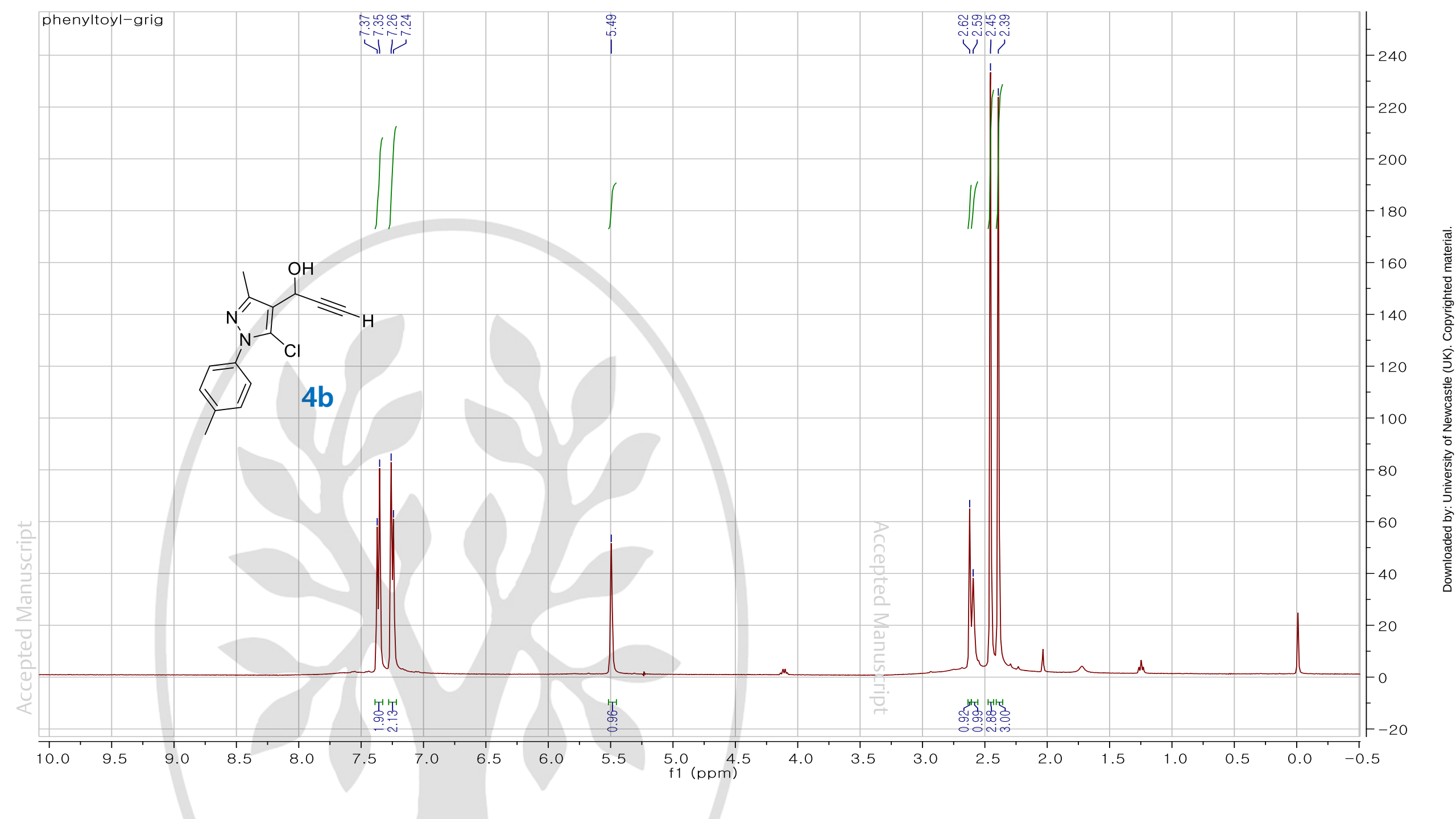

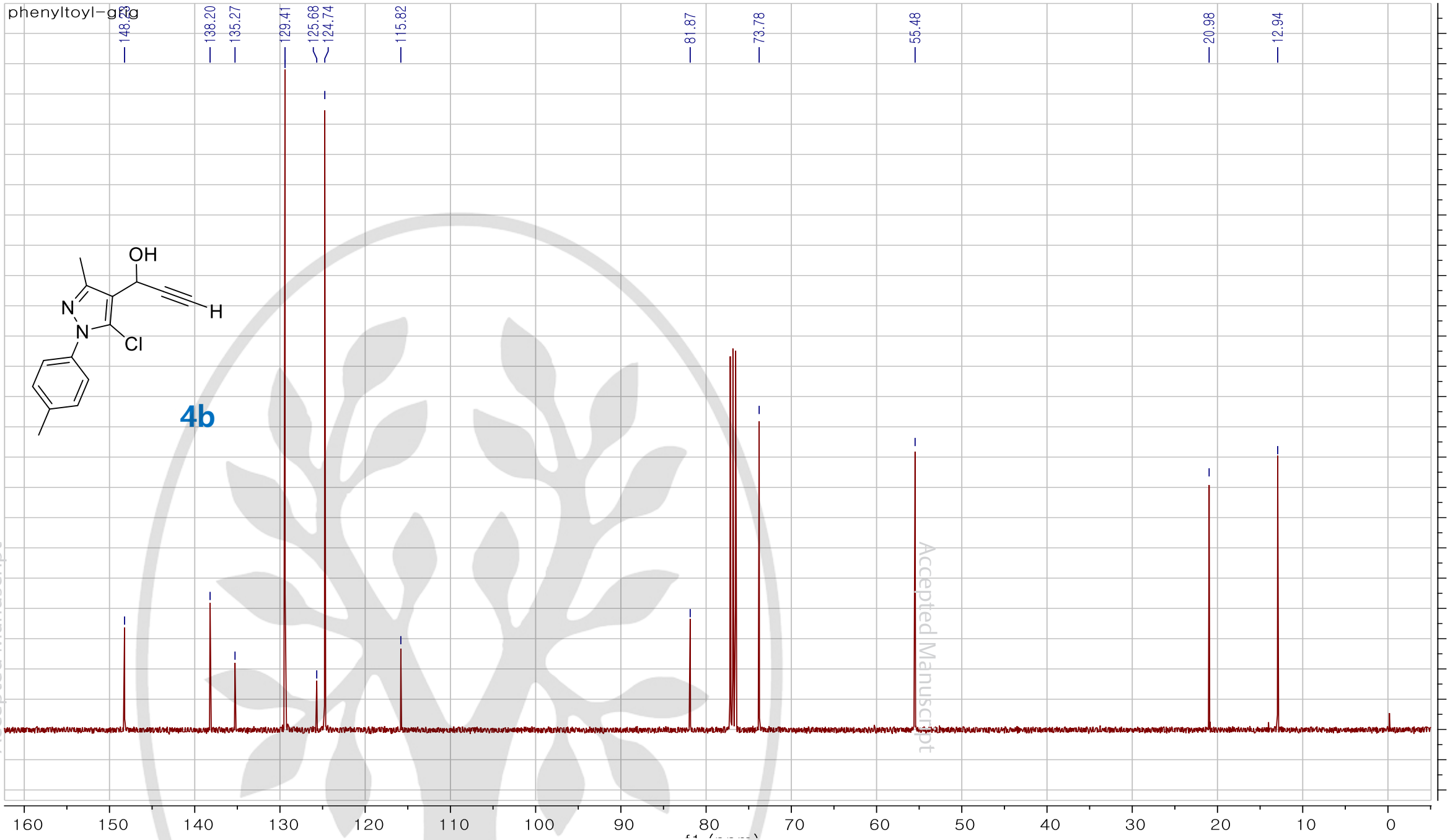

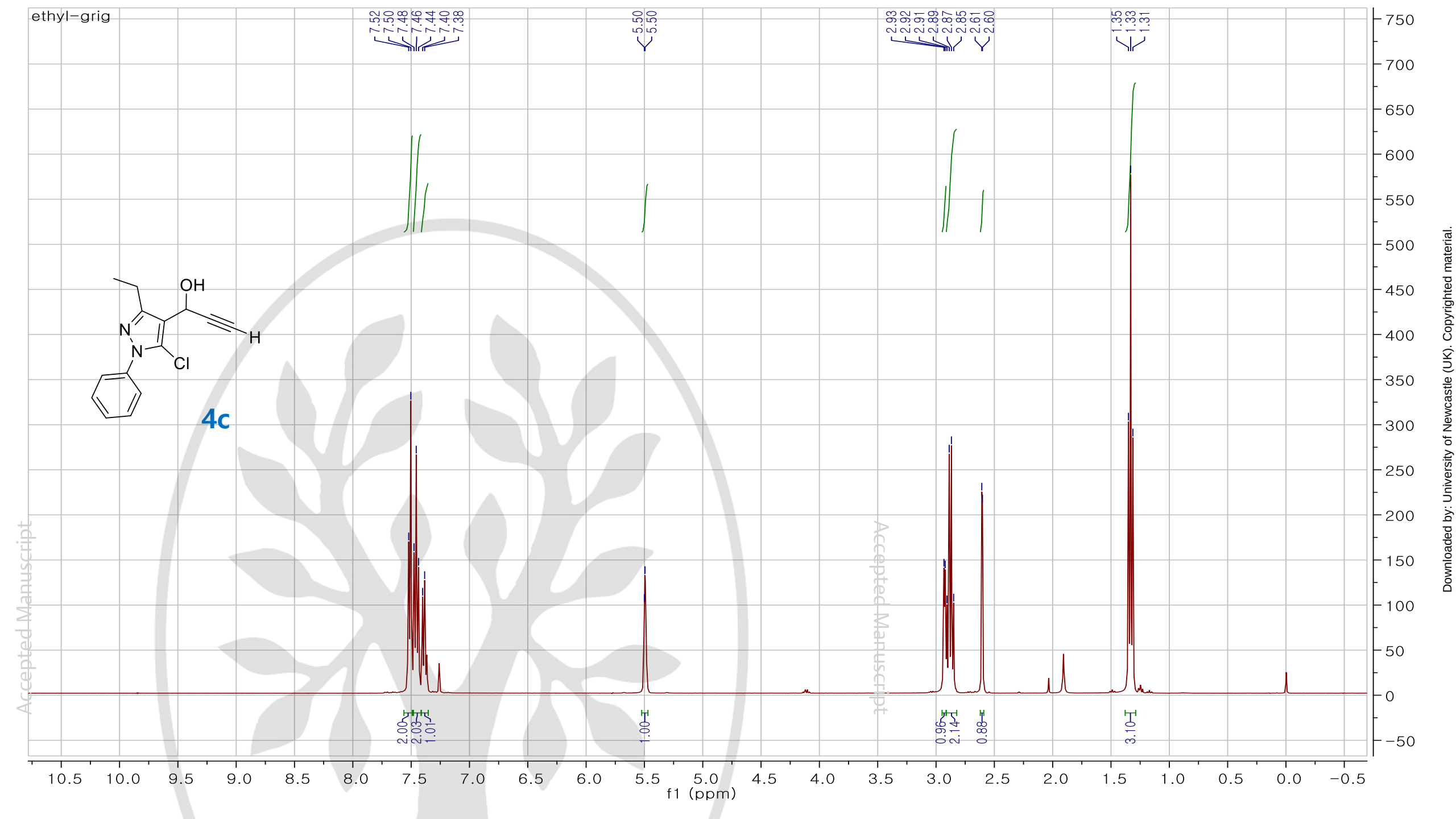
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7.50
7.48
7.46
7.44
7.40
7.38
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5.50
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2.92
2.91
2.89
2.87
2.85
2.61
2.60
1.35
1.33
1.31
OH
N
N
Cl
H
4c
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2.03
1.01
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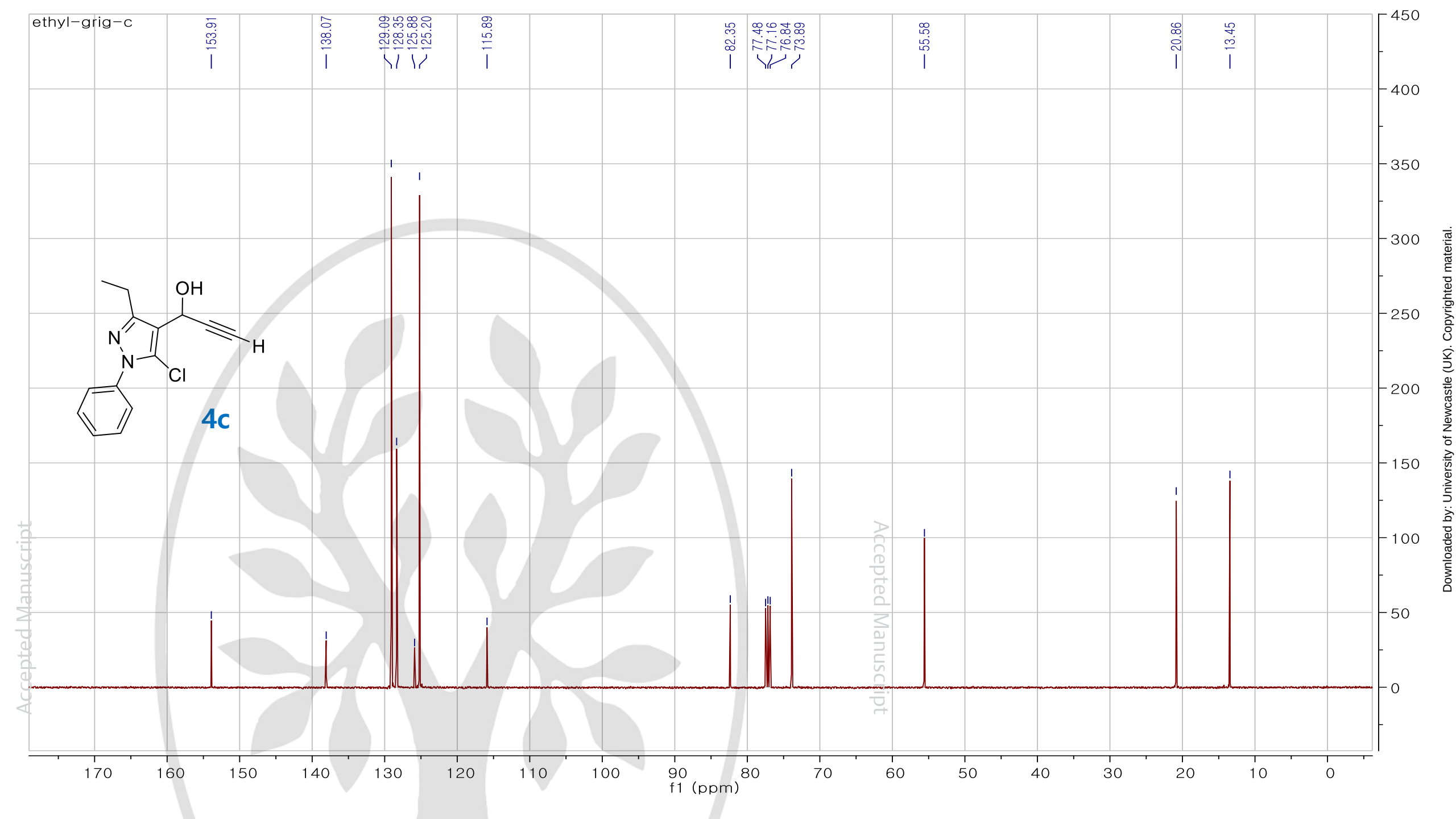

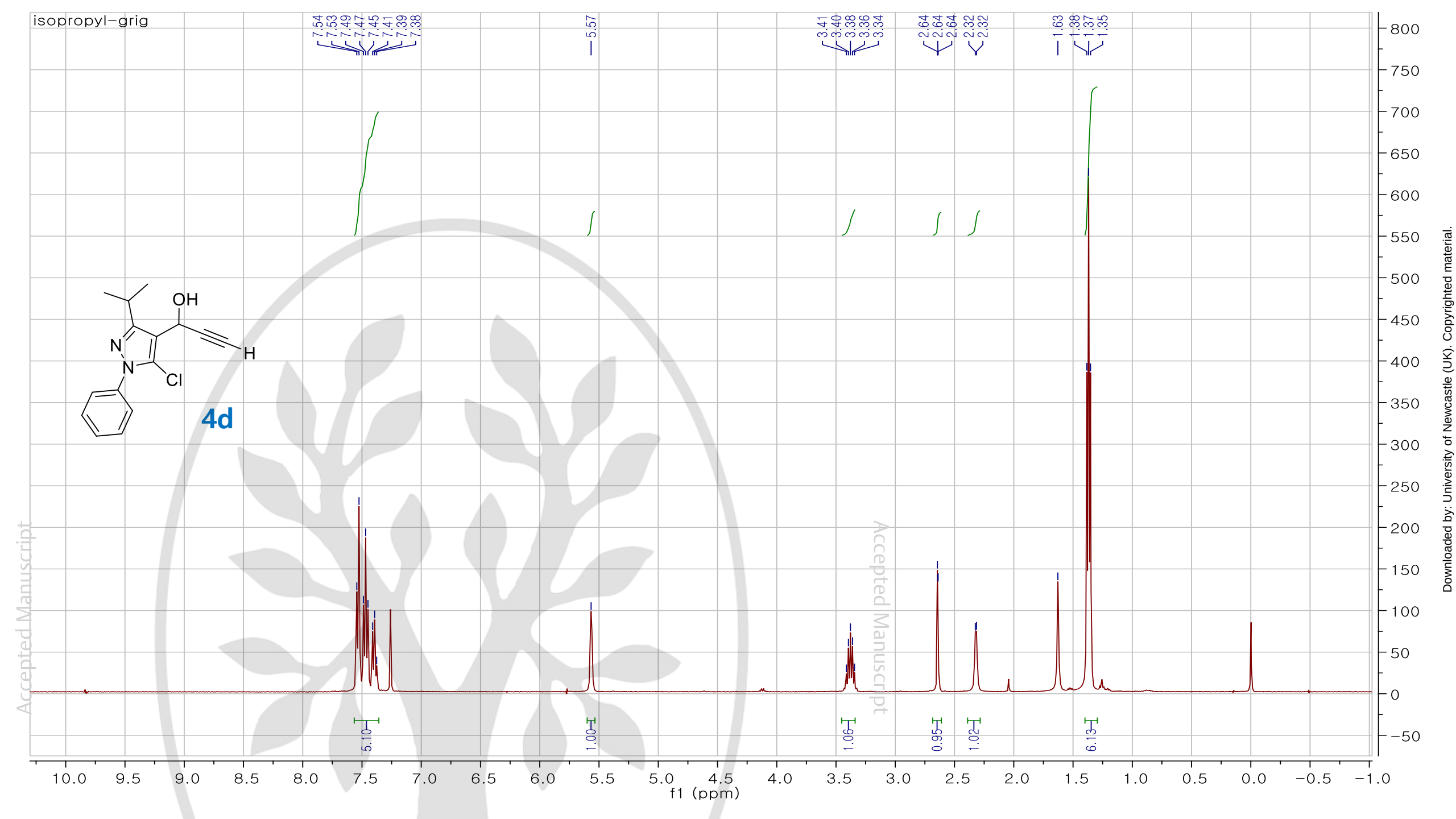
isopropyl-grig
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7.53
7.49
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7.41
7.39
7.38
5.57
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3.36
3.34
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2.64
2.64
2.32
2.32
1.63
1.38
1.37
1.35
OH
N
N
Cl
H
4d
5.10
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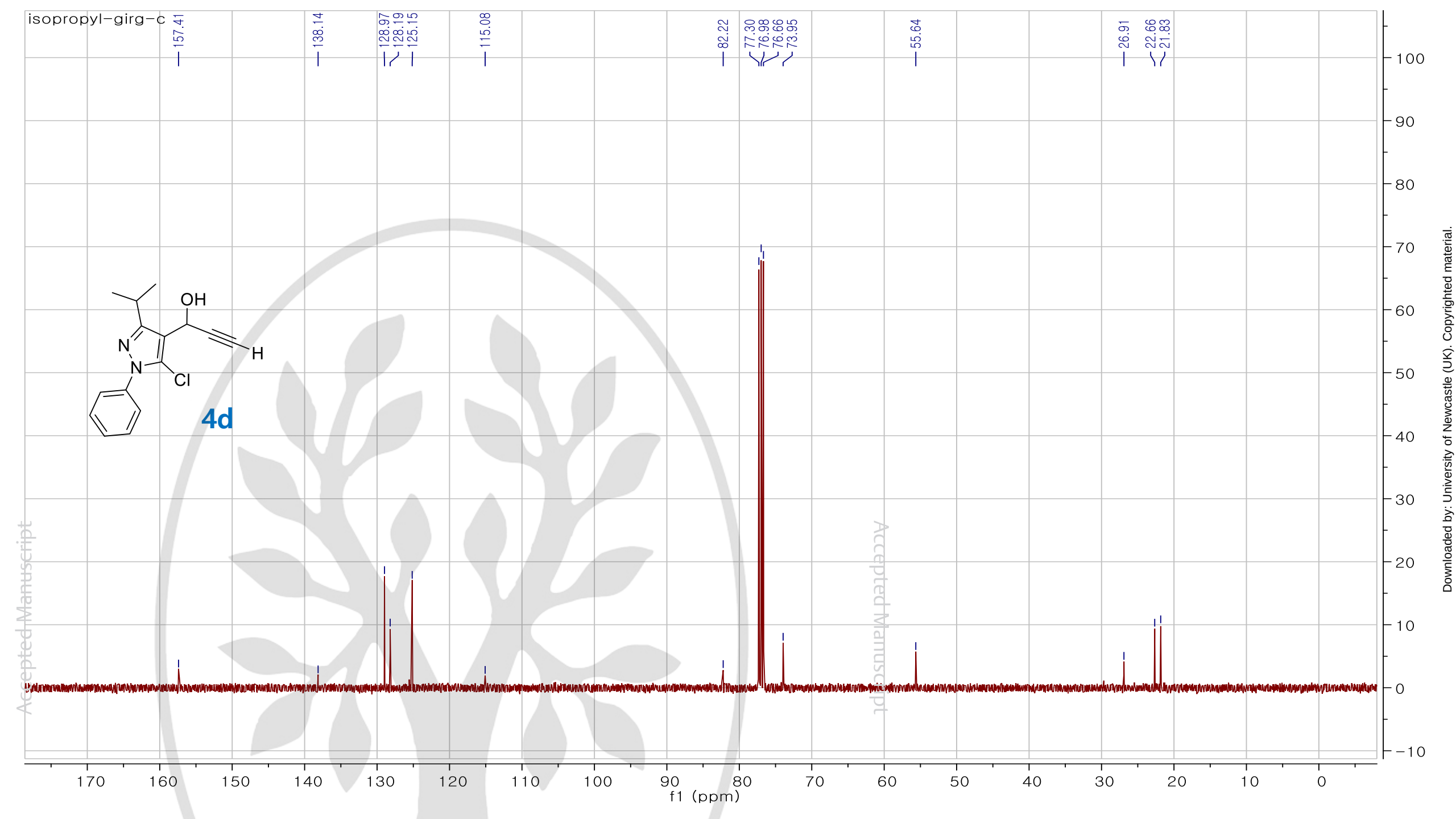

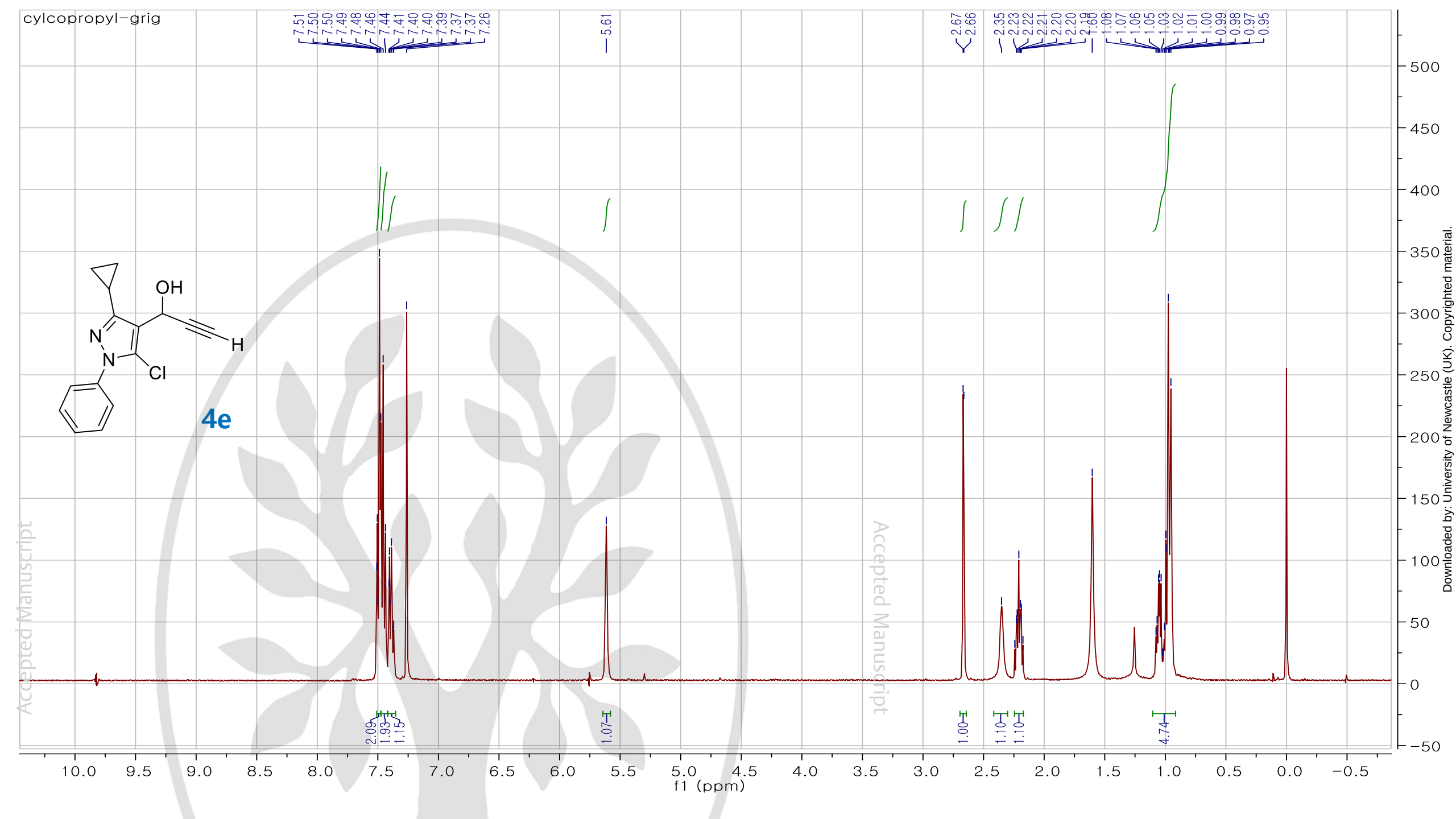
cylcopropyl-grig
7.51 7.50 7.50 7.49 7.48 7.46 7.44 7.41 7.40 7.40 7.39 7.37 7.37 7.26
5.61
2.67 2.66 2.35 2.23 2.22 2.21 2.20 2.20 2.19 1.80 1.08 1.07 1.06 1.05 1.03 1.02 1.01 1.00 0.99 0.98 0.97 0.95
OH
N
N
Cl
H
4e
2.09 1.93 1.15
1.07
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1.10 1.10
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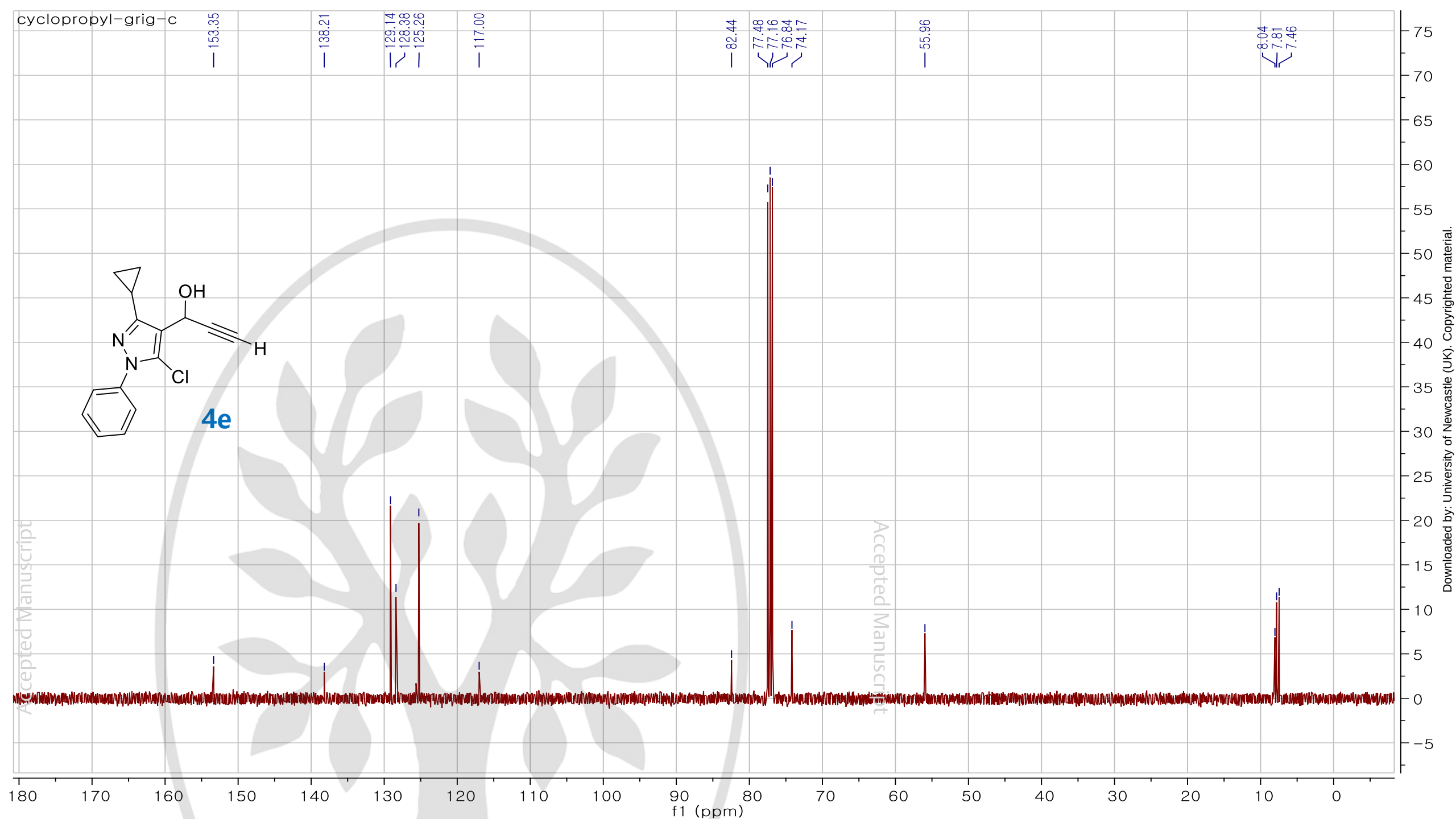

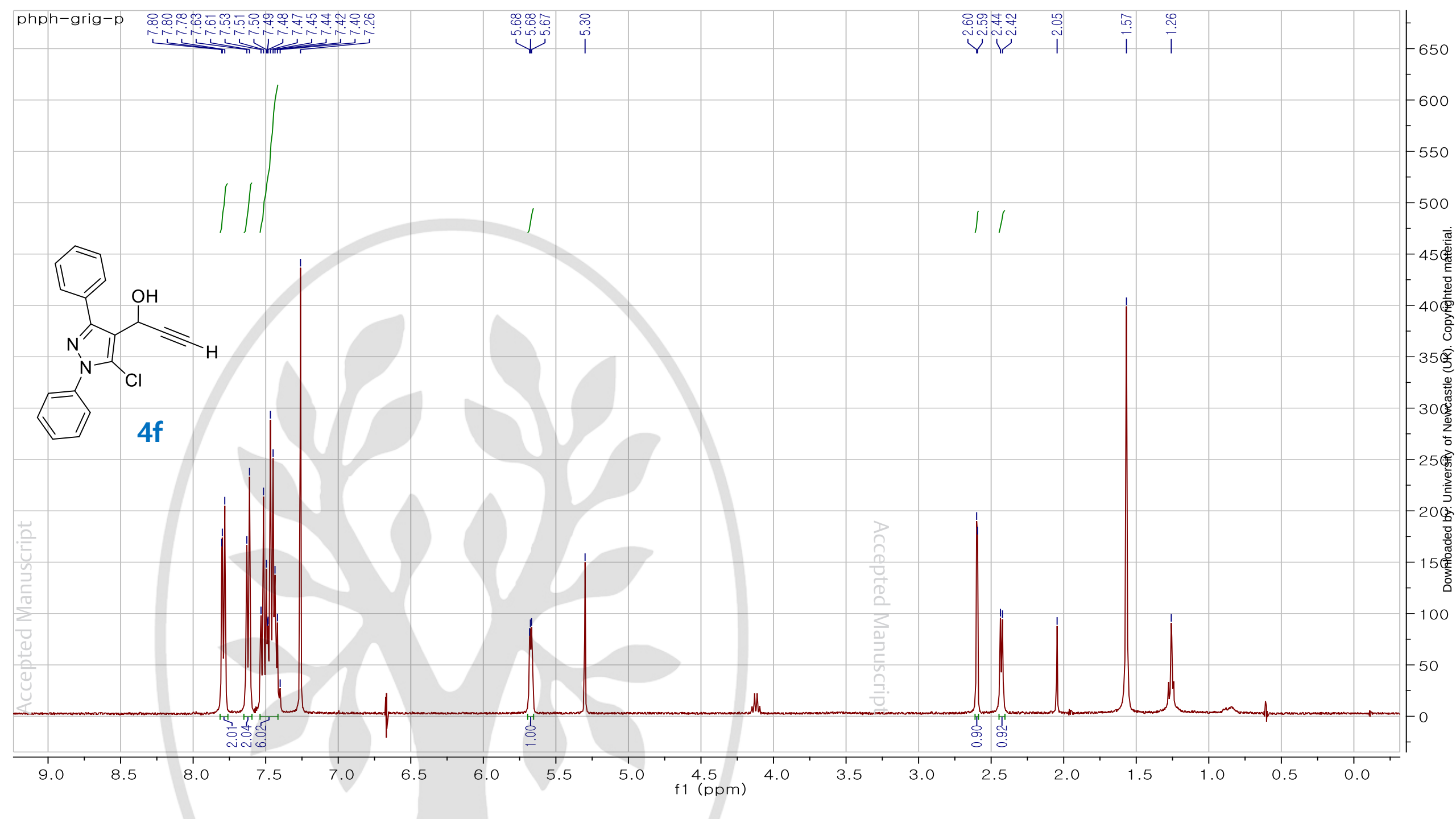

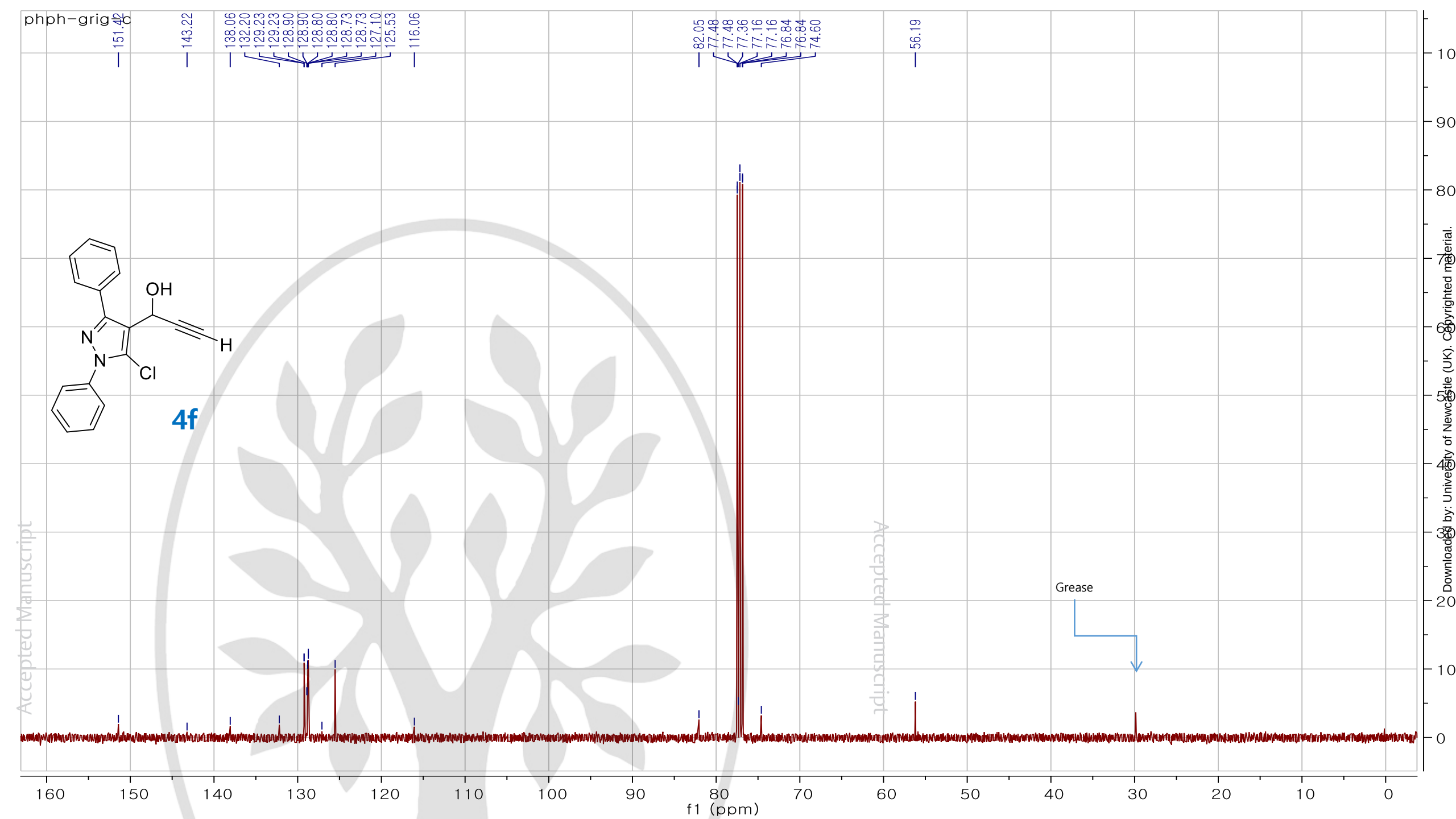

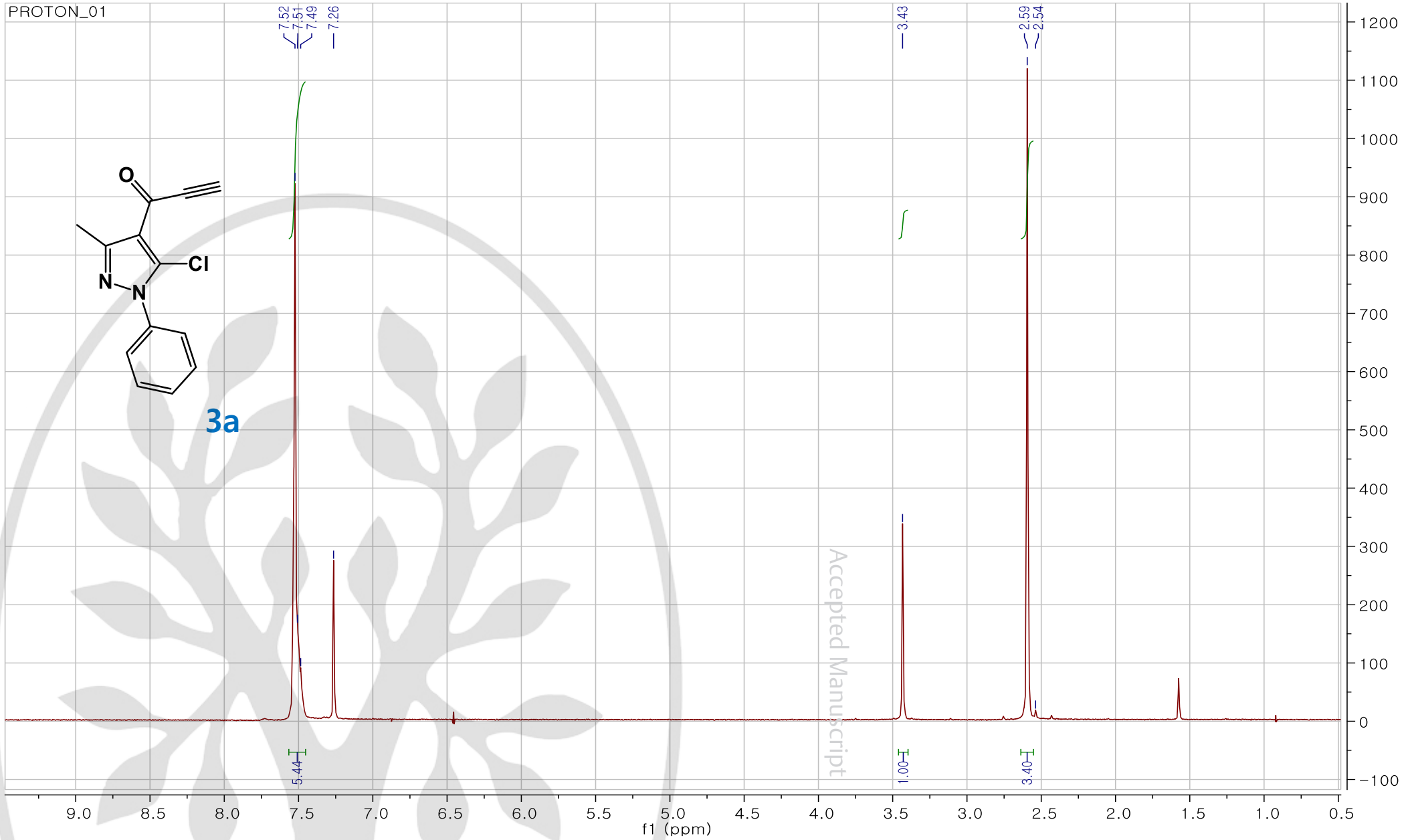

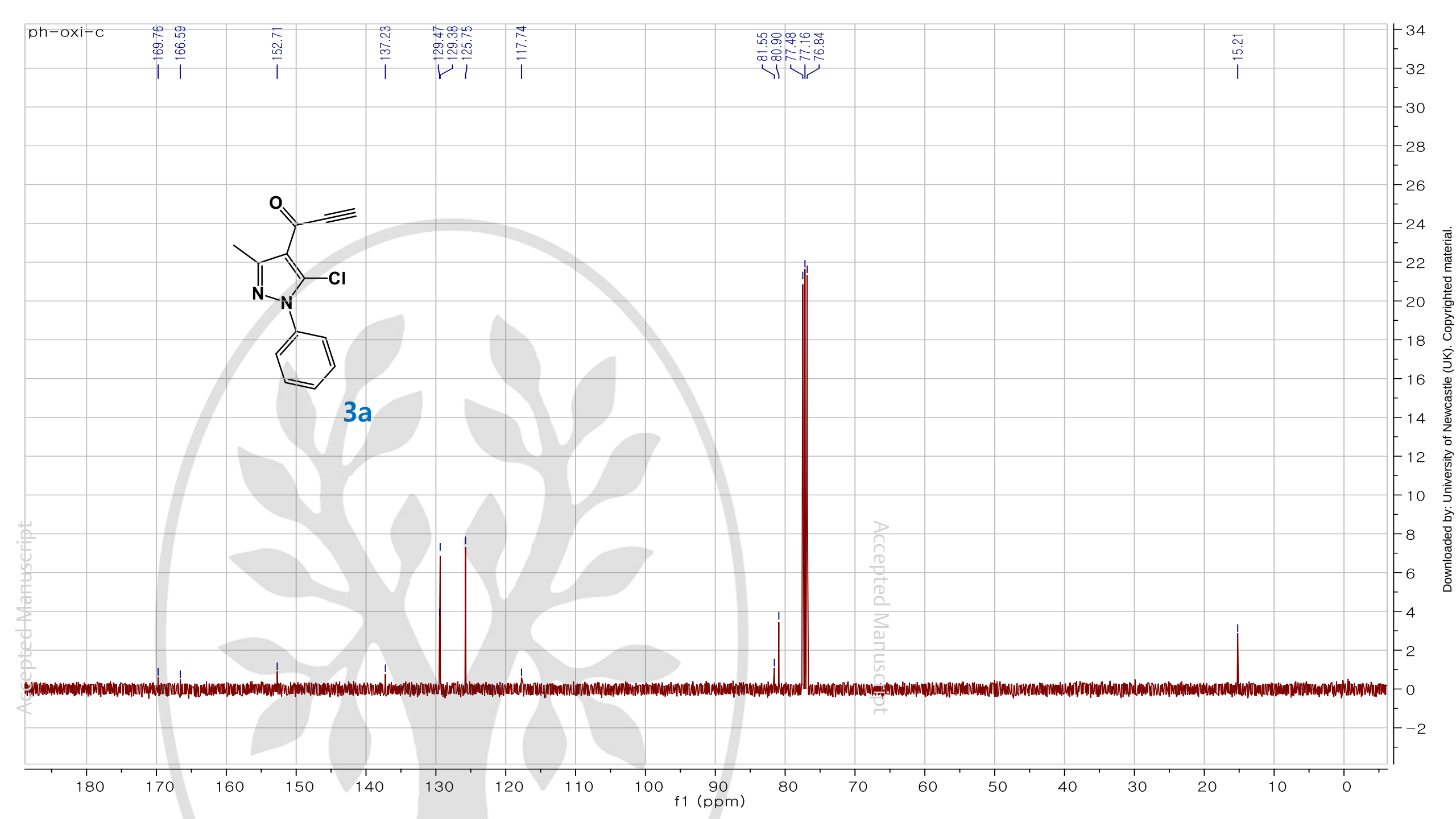

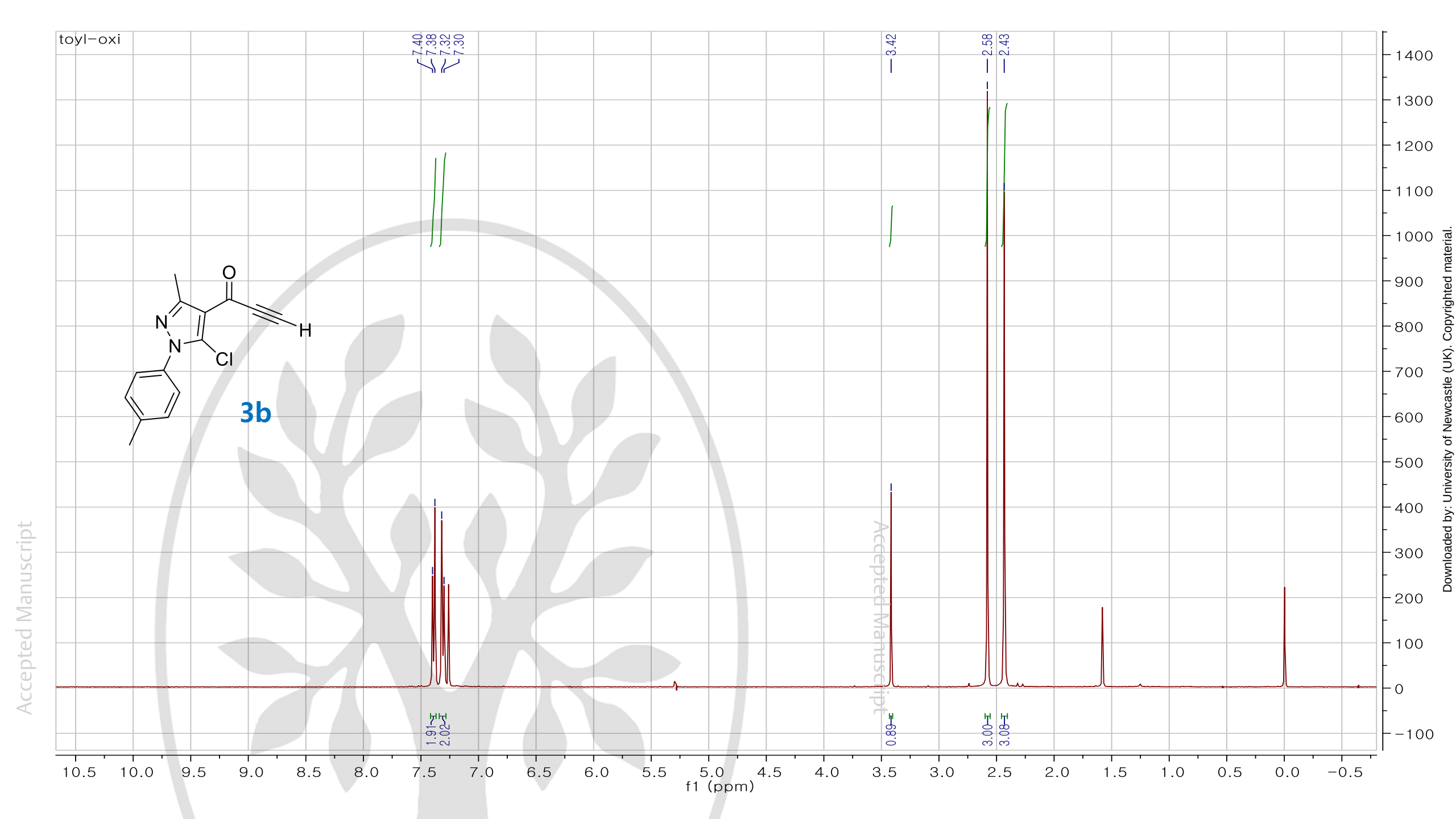

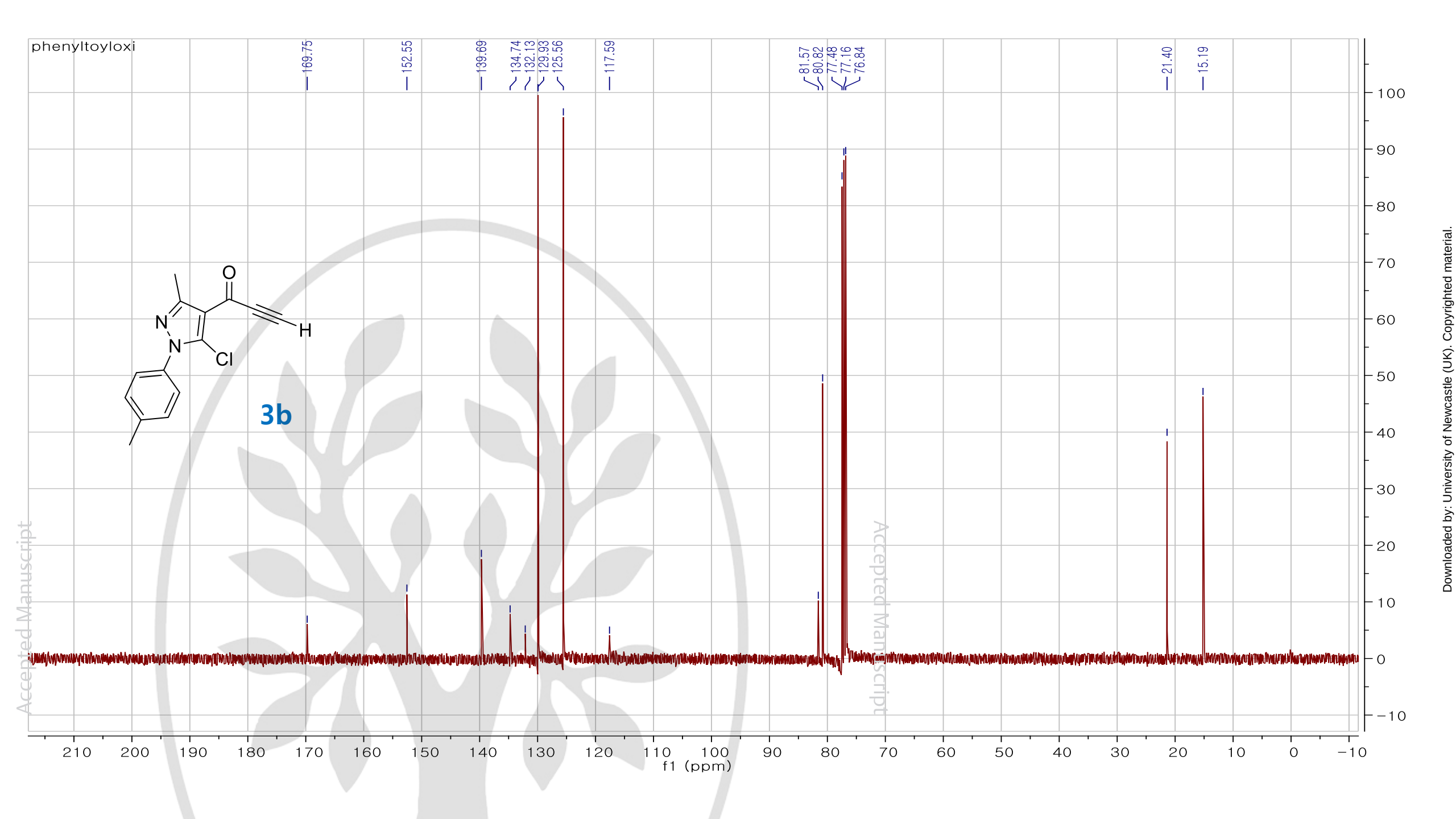

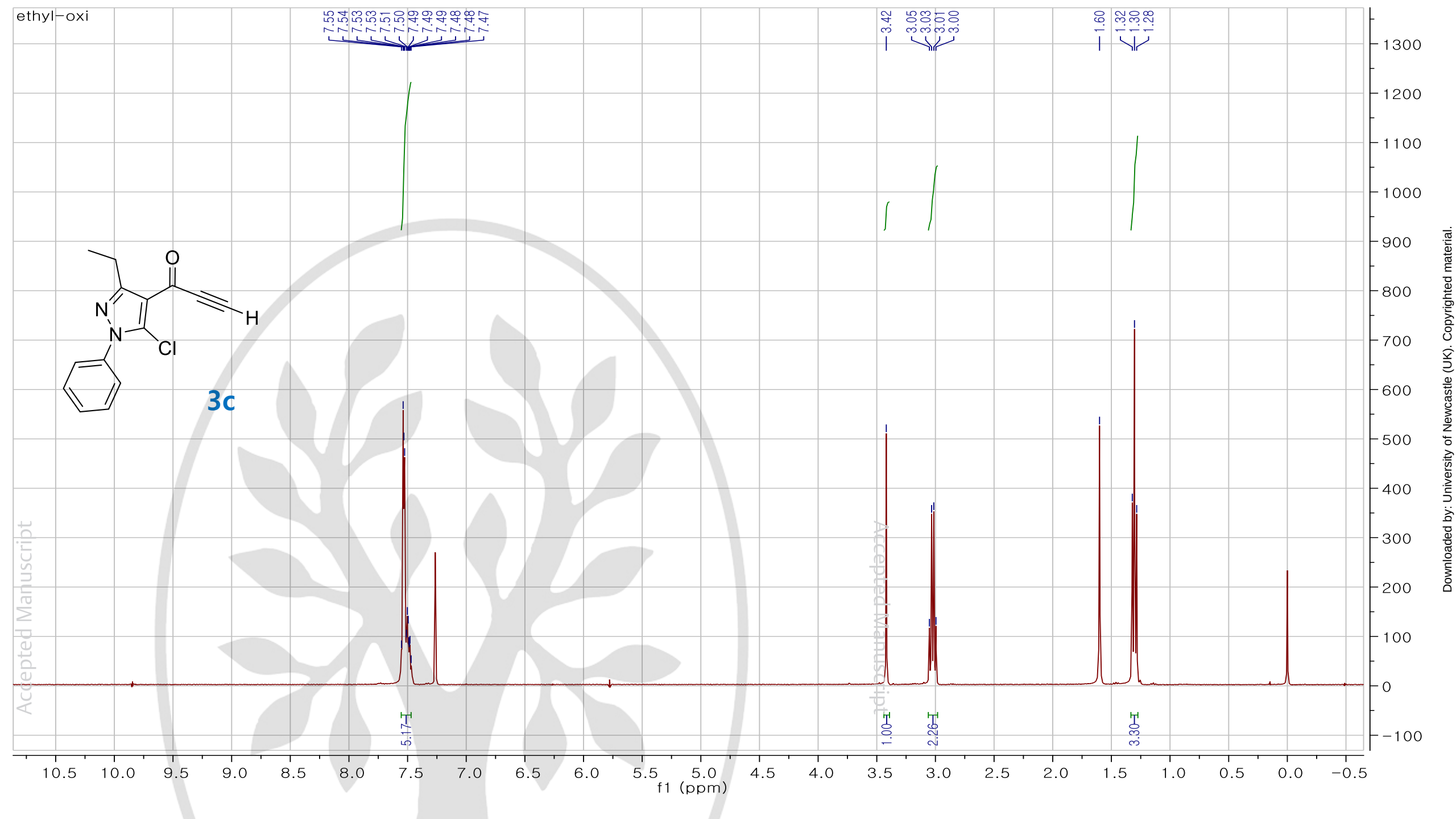
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7.47
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3.03
3.01
3.00
1.60
1.32
1.30
1.28
O
N
N
Cl
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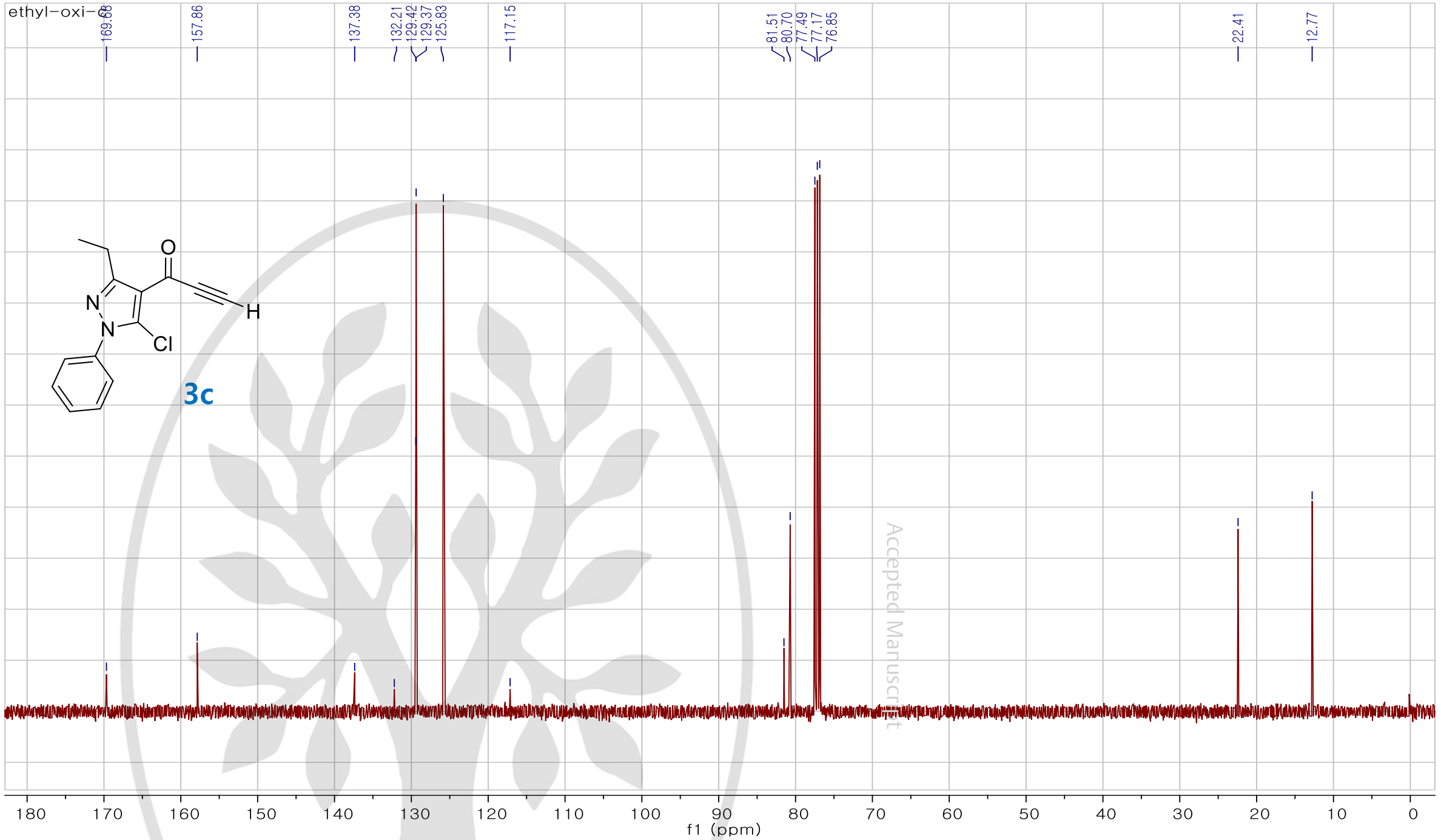

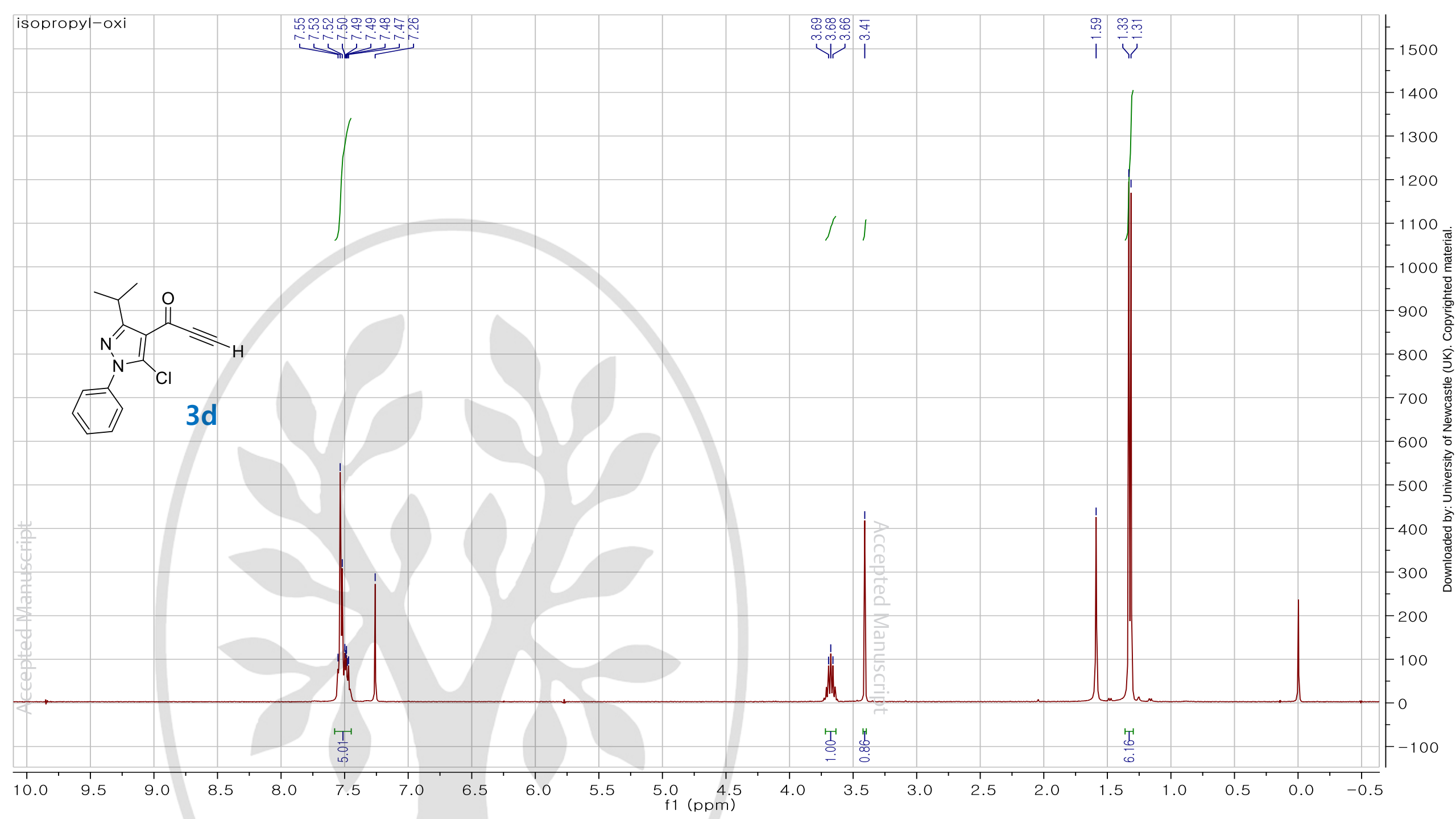
isopropyl-oxi
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7.47
7.26
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3.68
3.66
3.41
1.59
1.33
1.31
O
N
N
Cl
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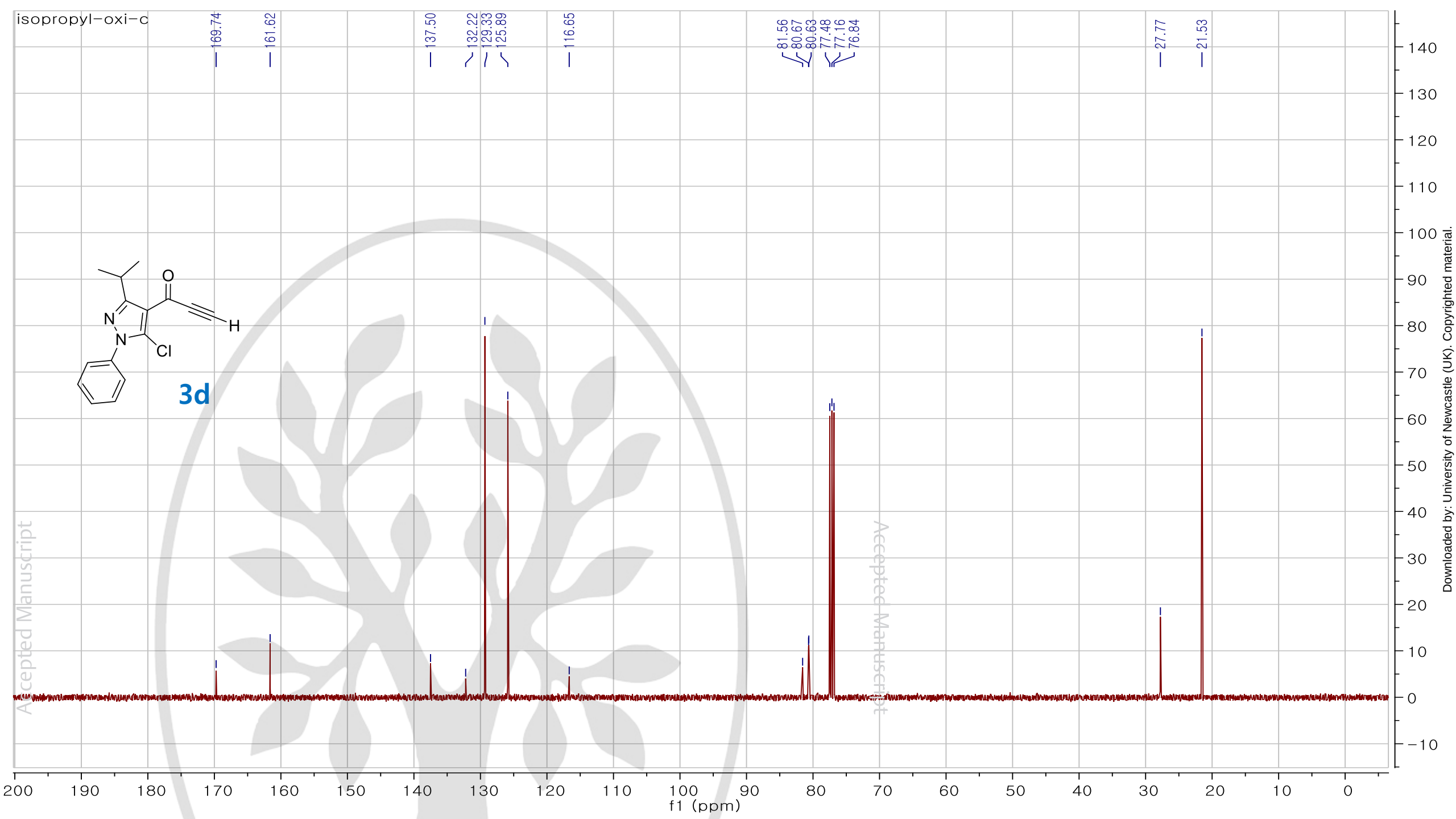
isopropyl-oxi-c
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27.77
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Cl
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3d
f1 (ppm)
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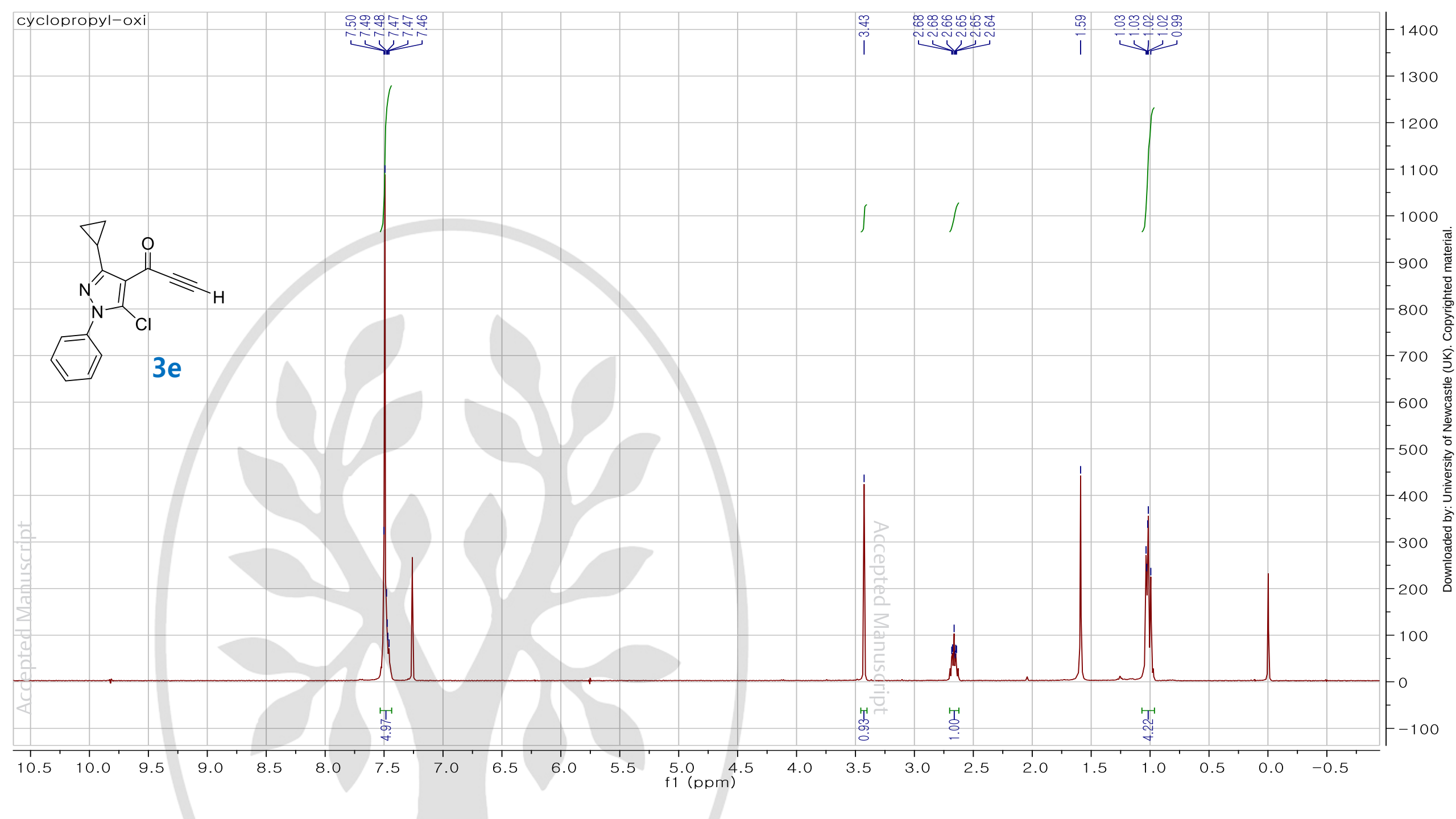
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2.68
2.66
2.65
2.65
2.64
1.59
1.03
1.03
1.02
1.02
0.99
O
N
N
Cl
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1.00
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f1 (ppm)
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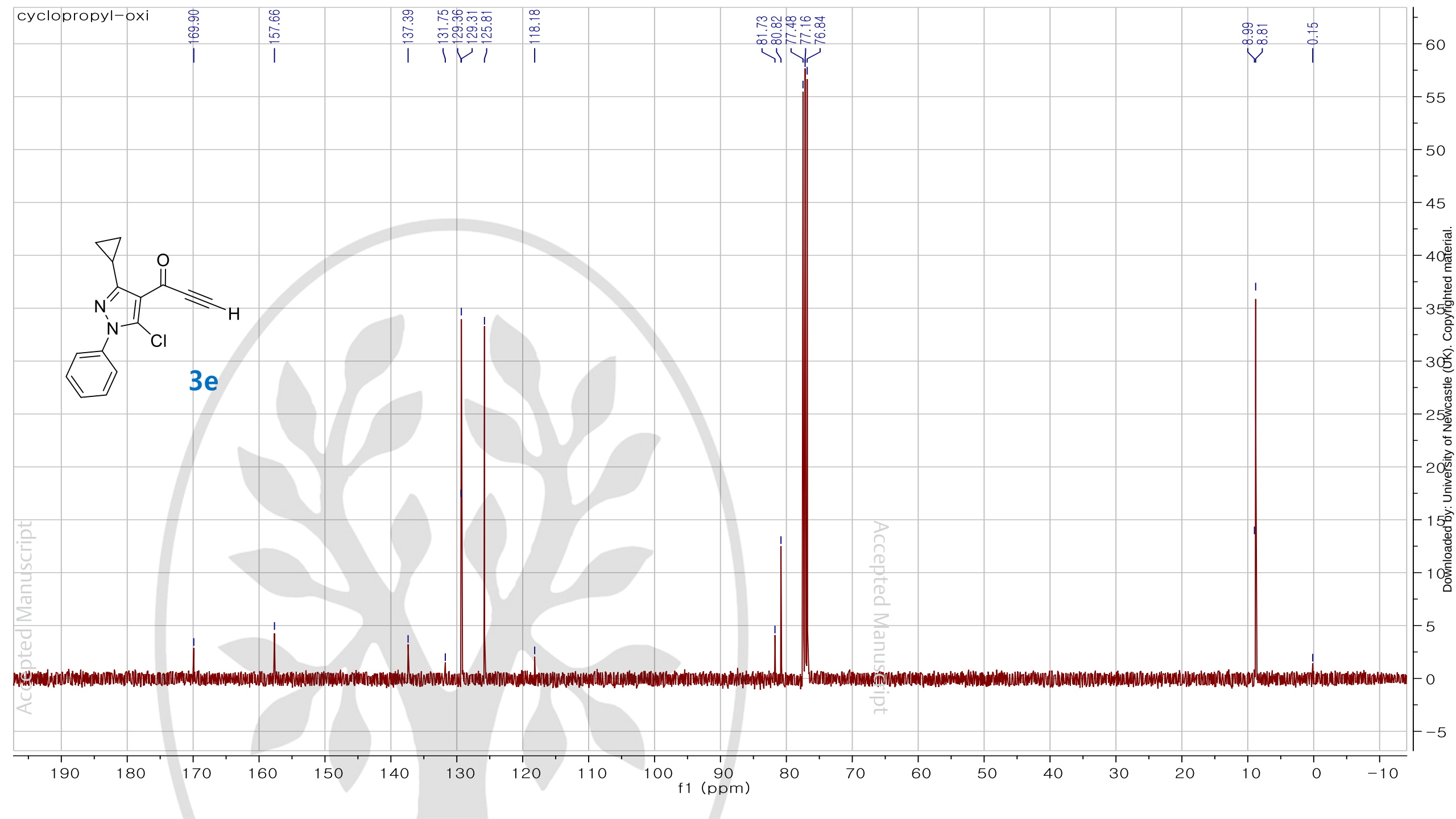

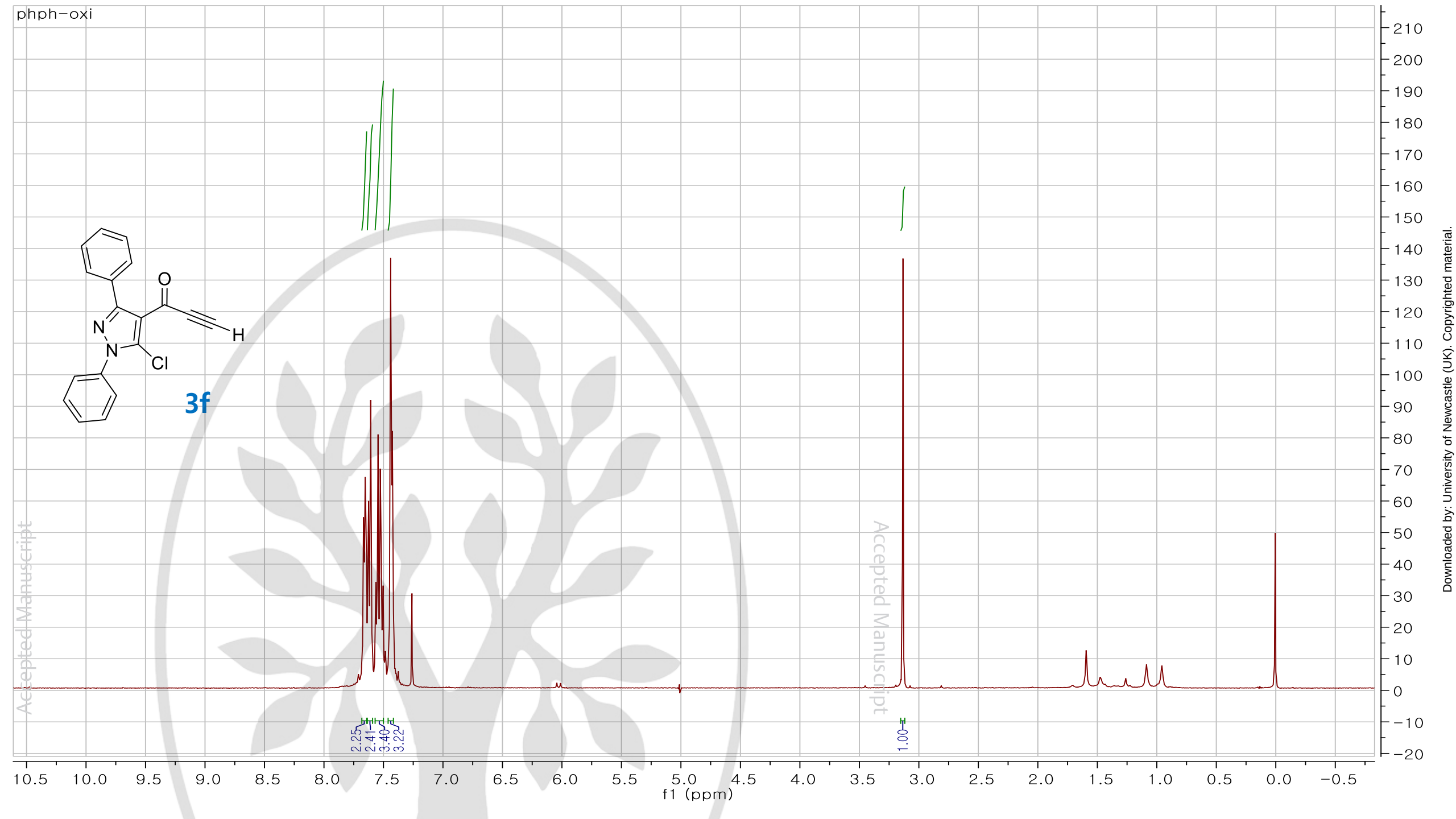

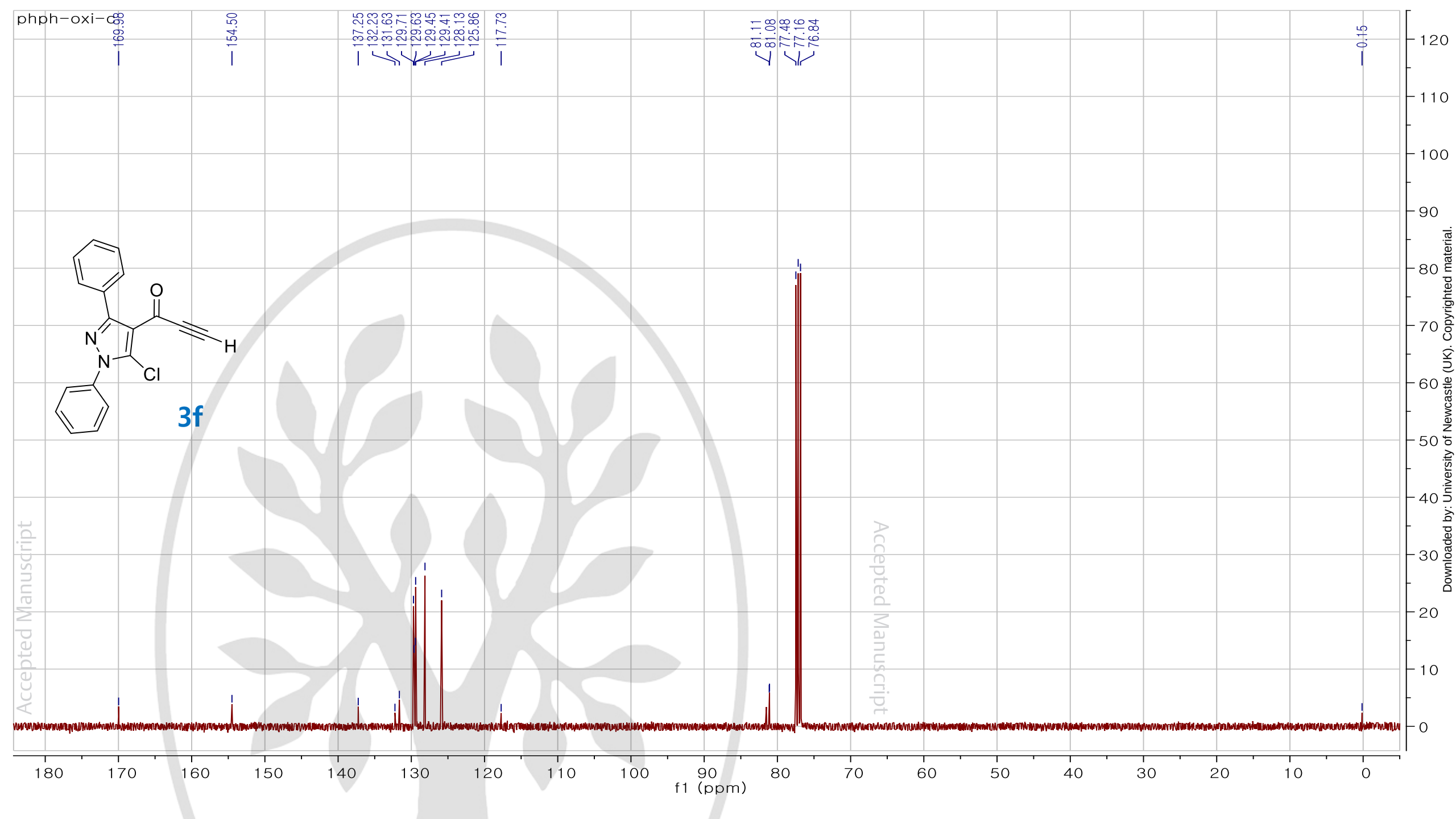
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117.73
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81.08
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76.84
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N
Cl
H
3f
f1 (ppm)
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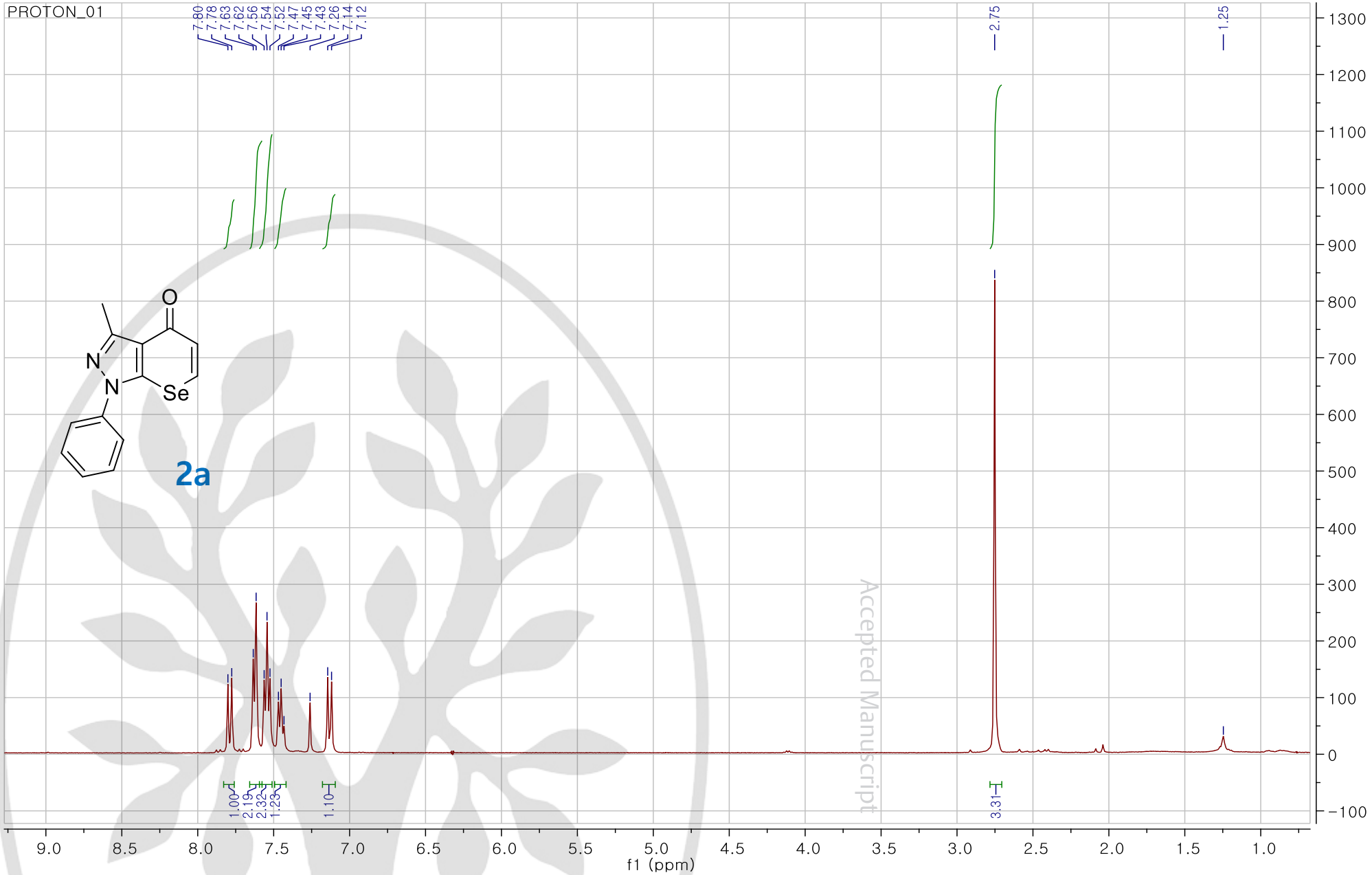
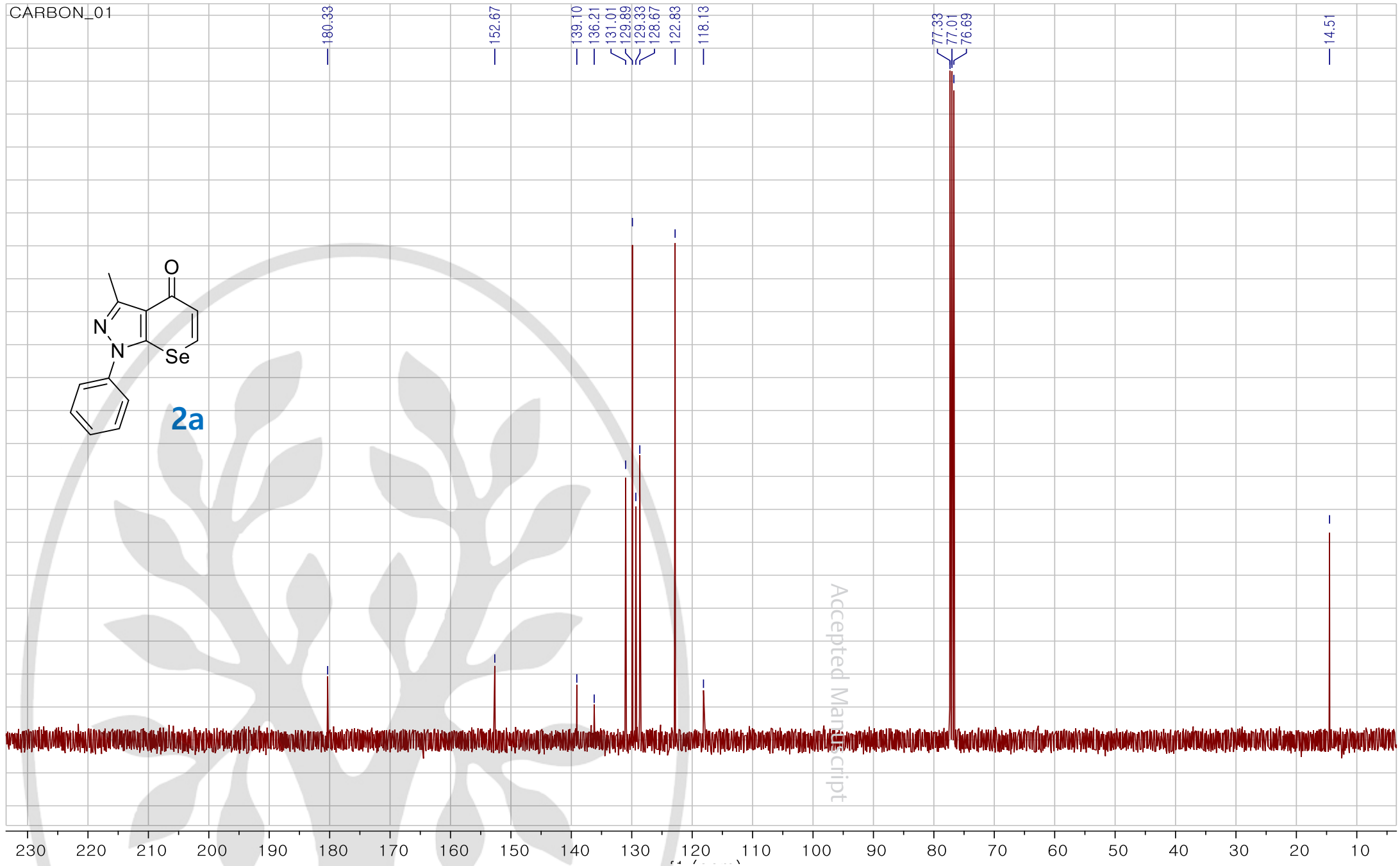
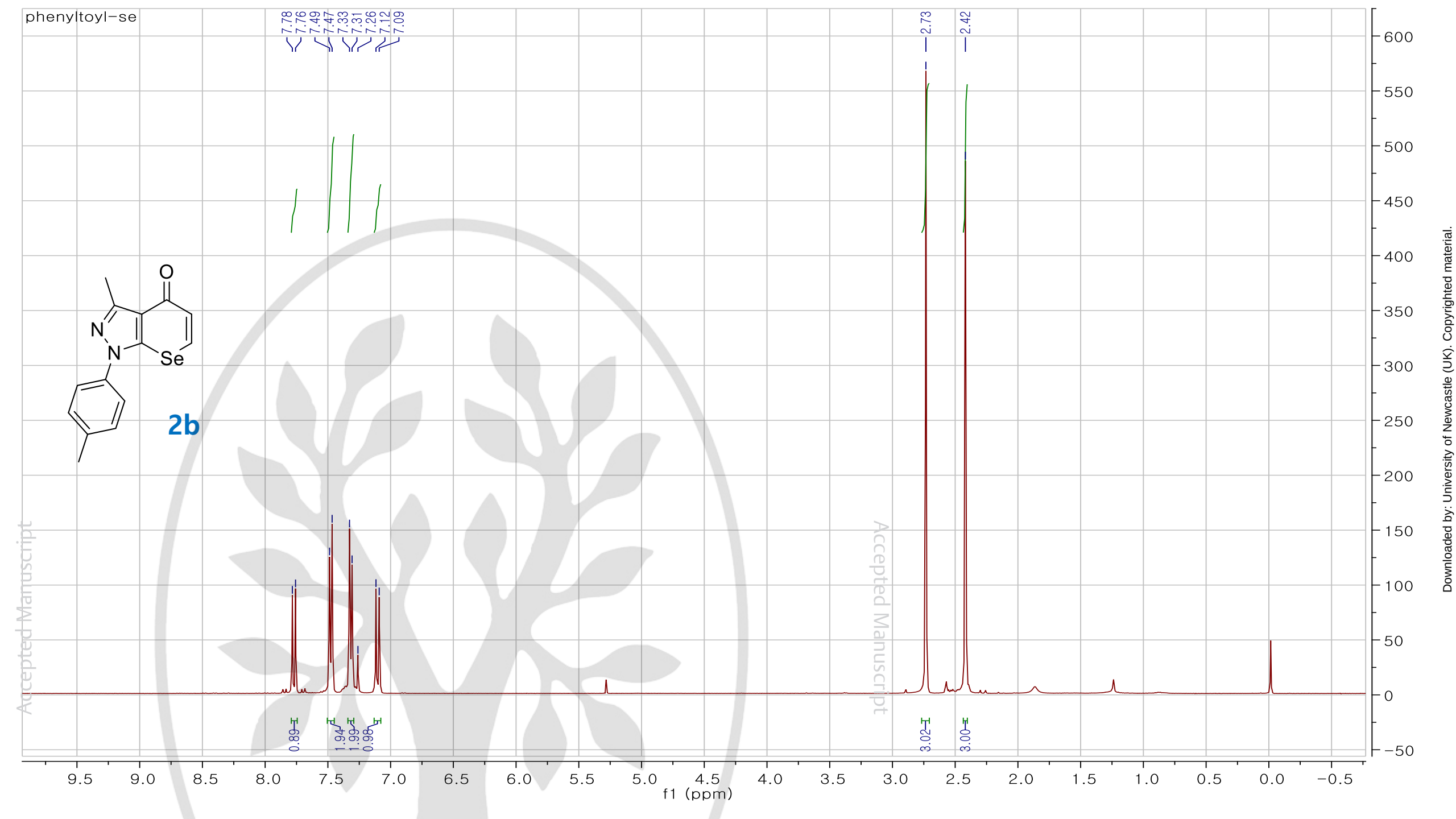
Downloaded by: University of Newcastle (UK). Copyrighted material.



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O
N
N
Se
2b
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f1 (ppm)
Accepted Manuscript
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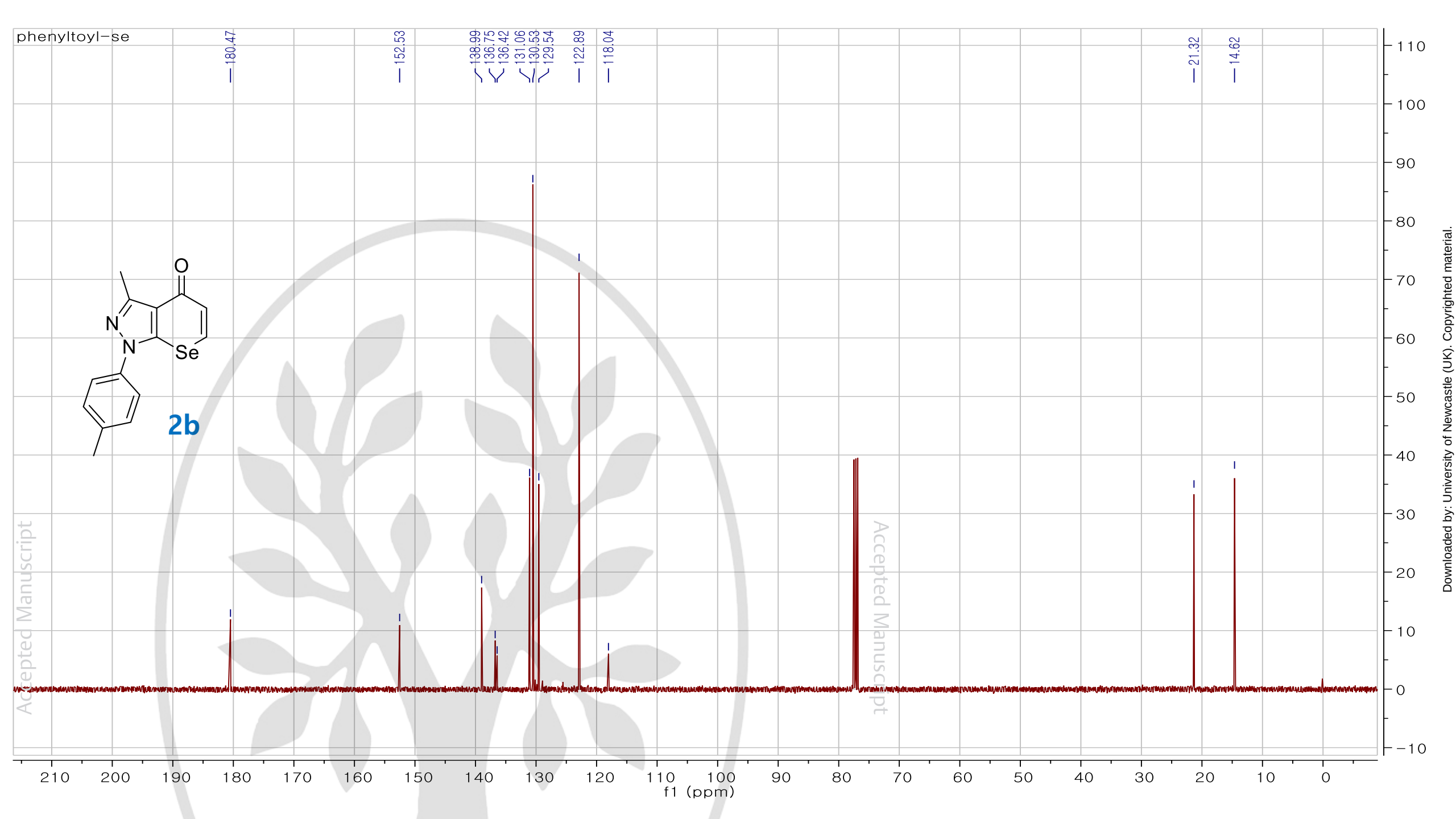
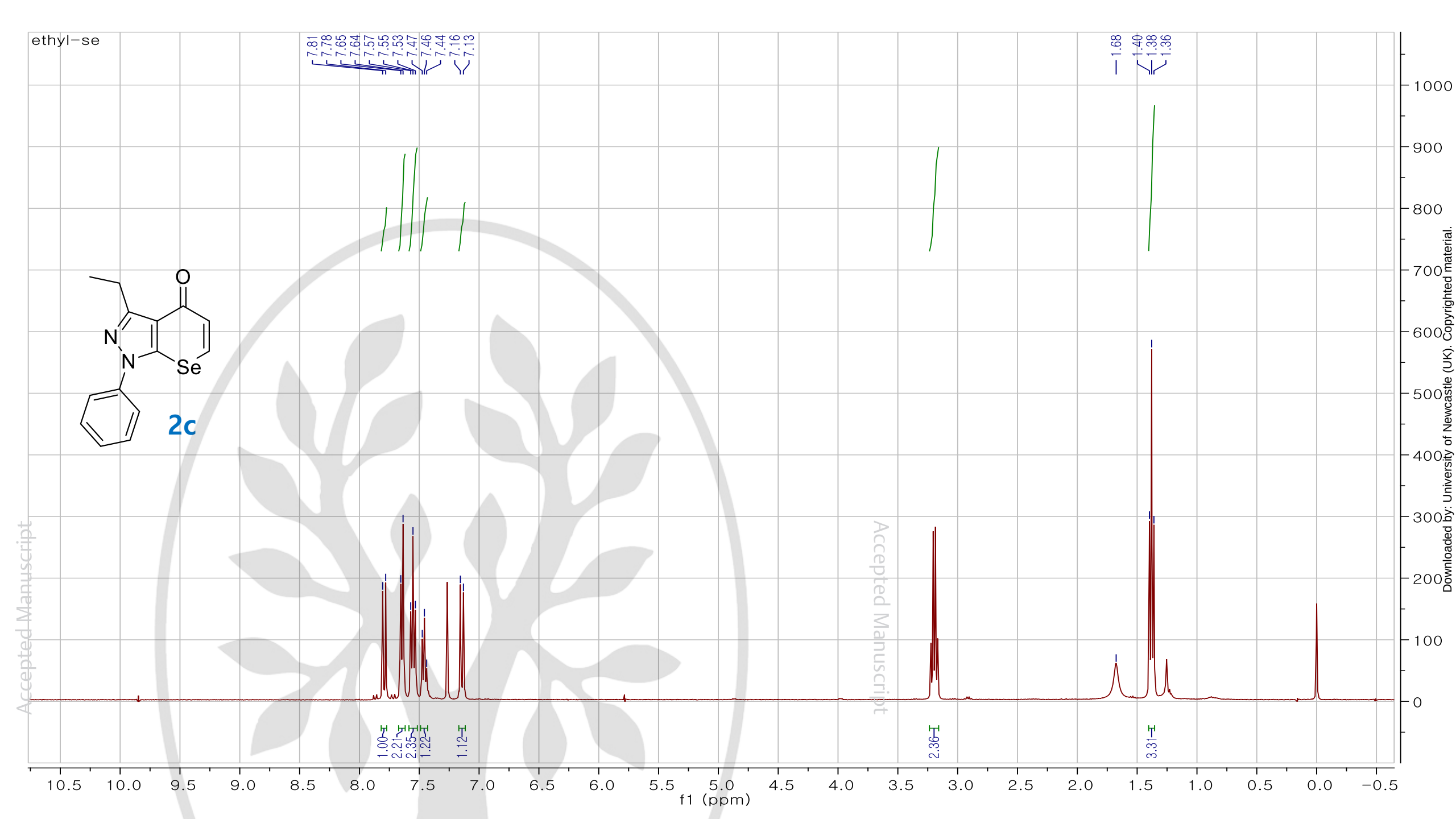
Downloaded by: University of Newcastle (UK). Copyrighted material.




ethyl-se
7.81
7.78
7.65
7.64
7.57
7.55
7.53
7.47
7.46
7.44
7.16
7.13
1.68
1.40
1.38
1.36
O
N
N
Se
2c
1.00
2.21
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3.31
f1 (ppm)
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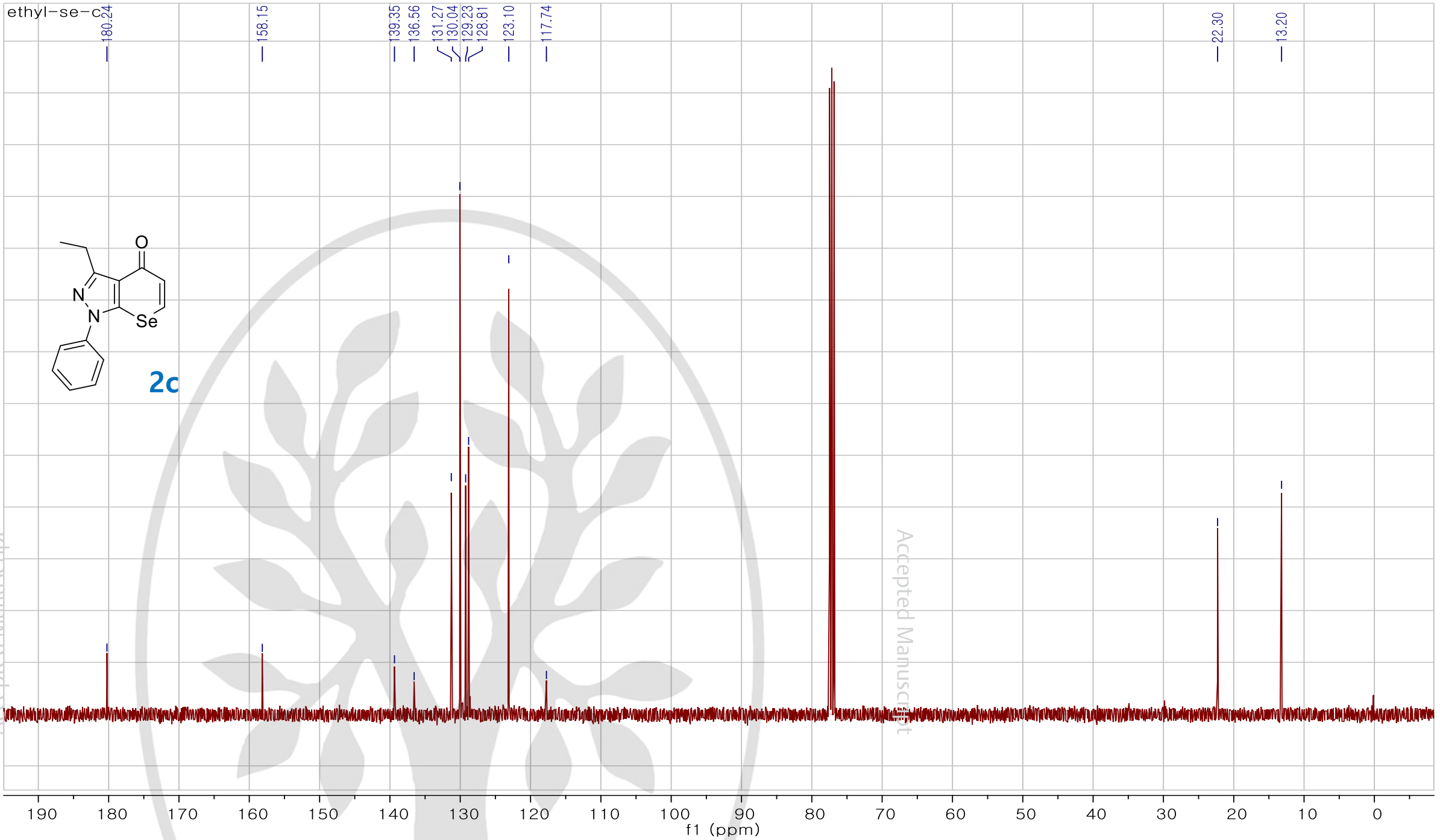
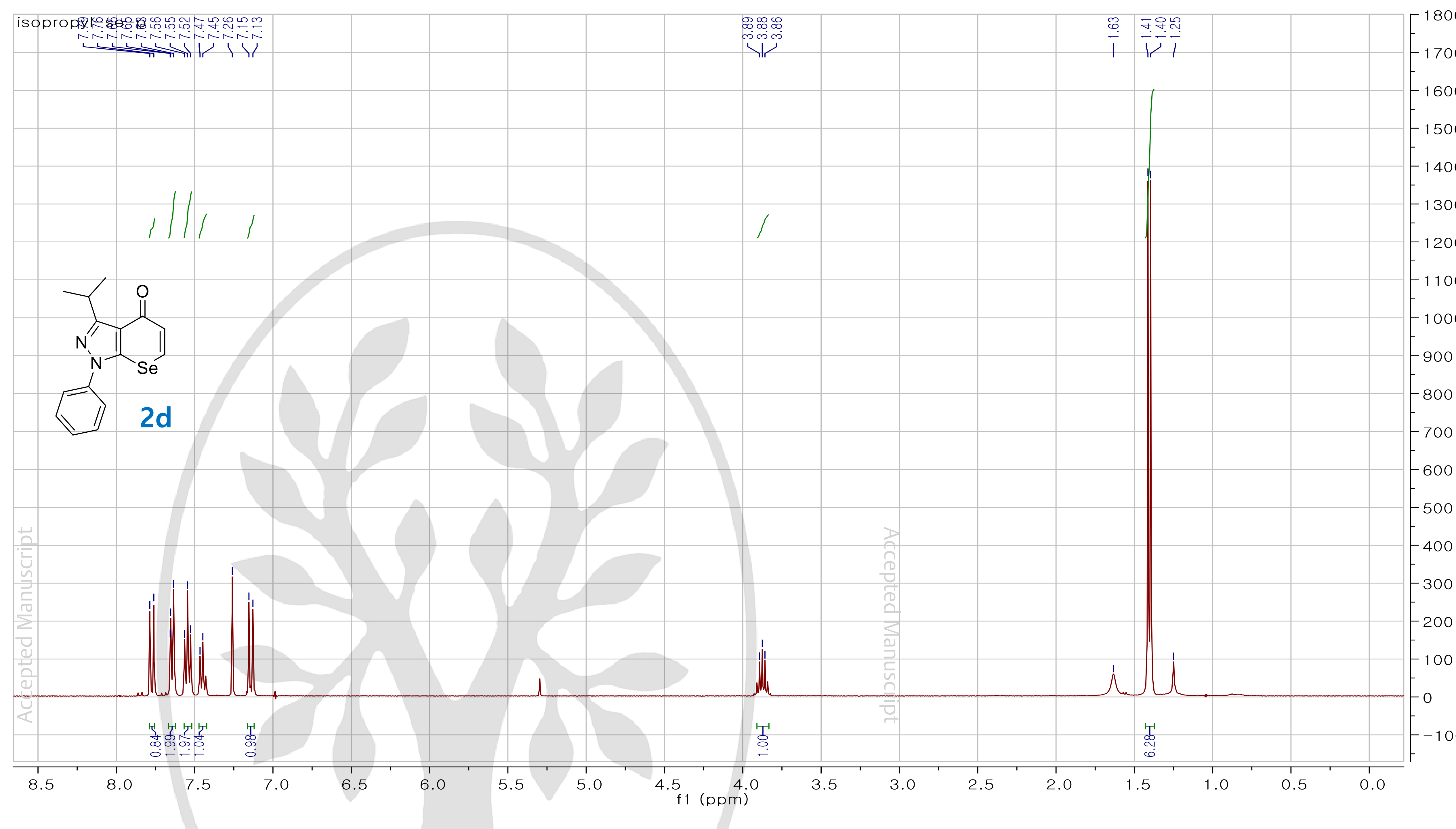
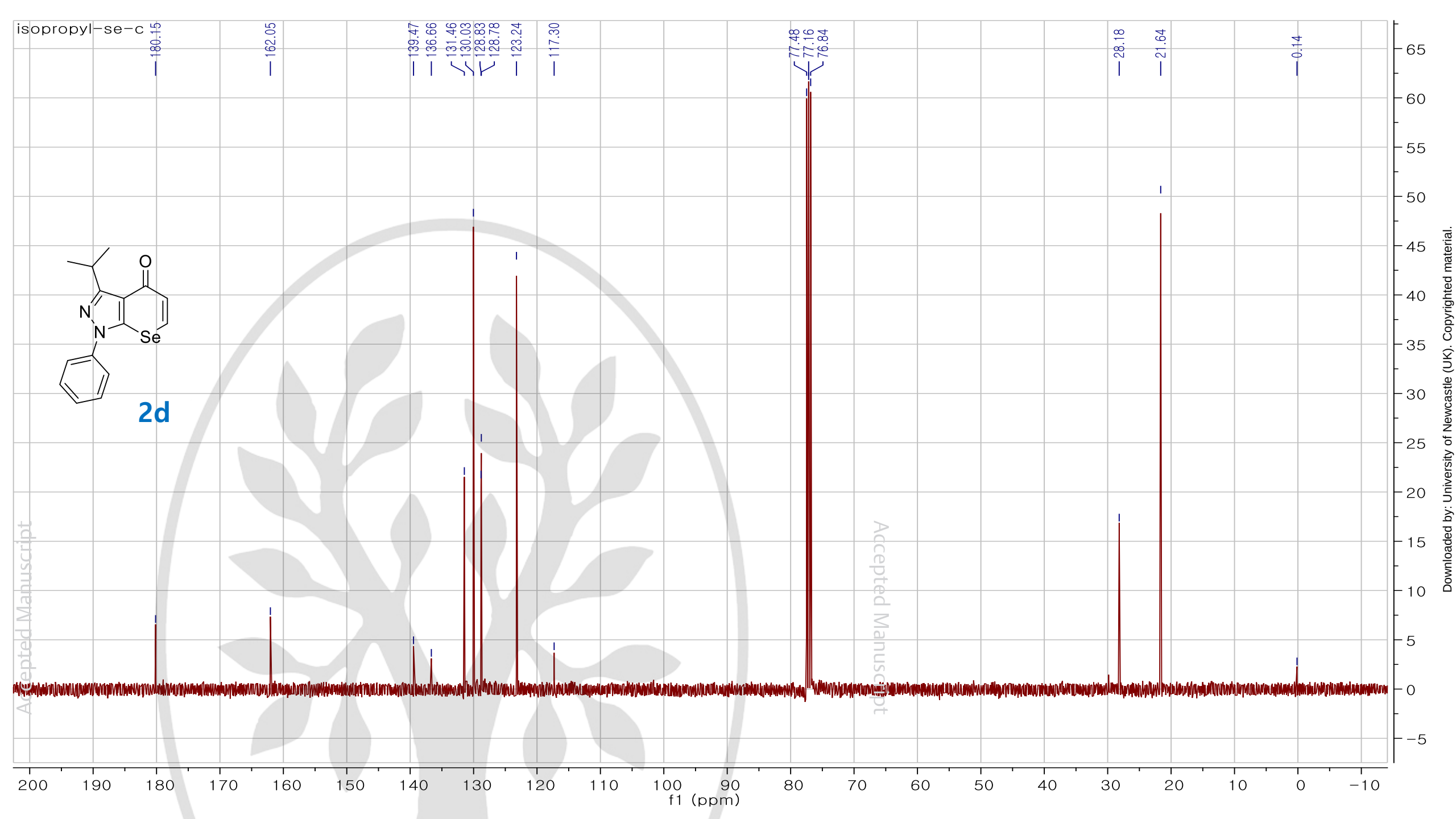
Downloaded by: University of Newcastle (UK). Copyrighted material.



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123.24
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77.16
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28.18
21.64
0.14
O
N
N
Se
2d
f1 (ppm)
Accepted Manuscript
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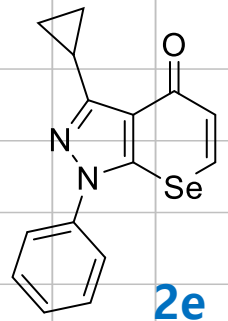
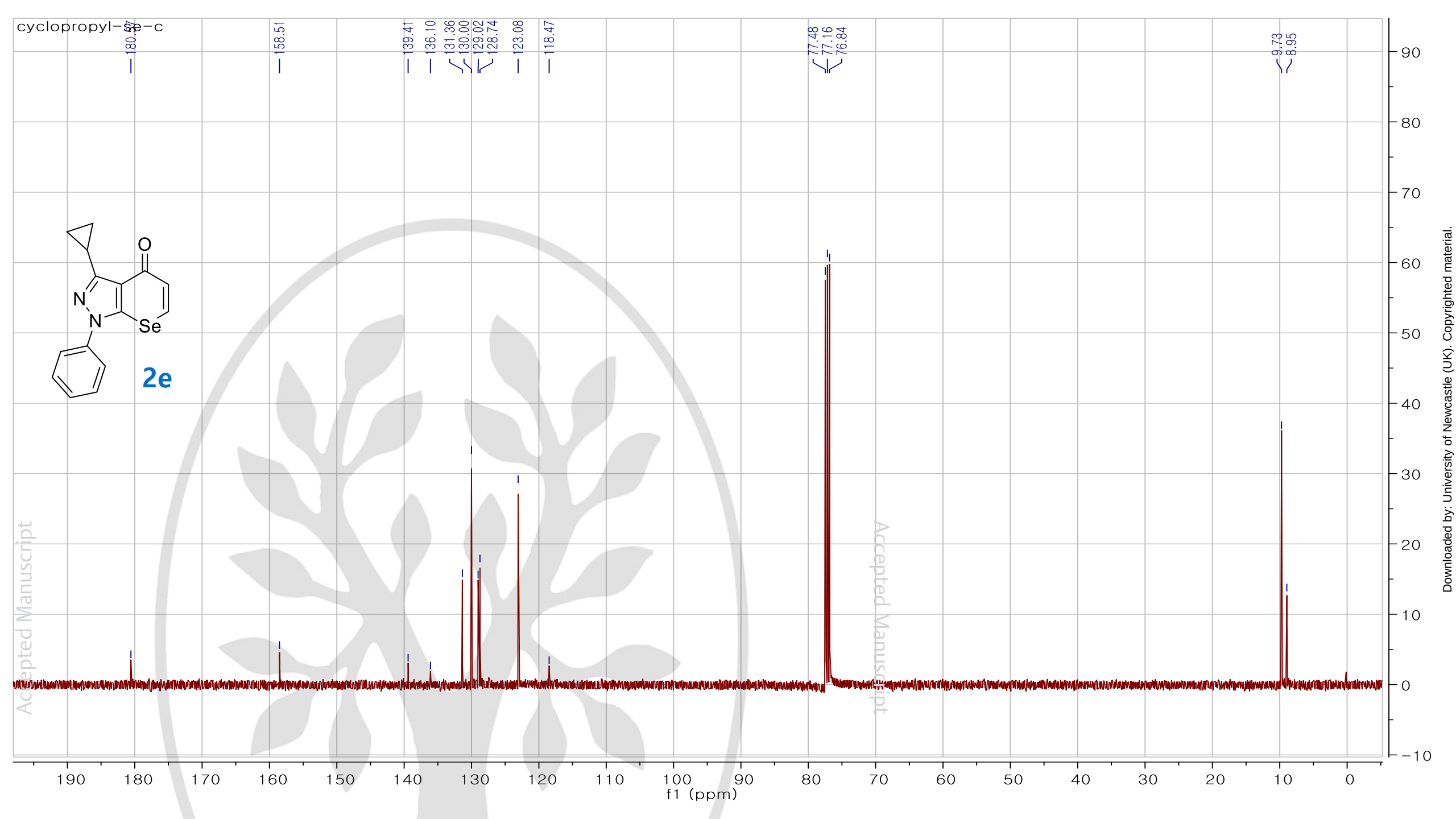
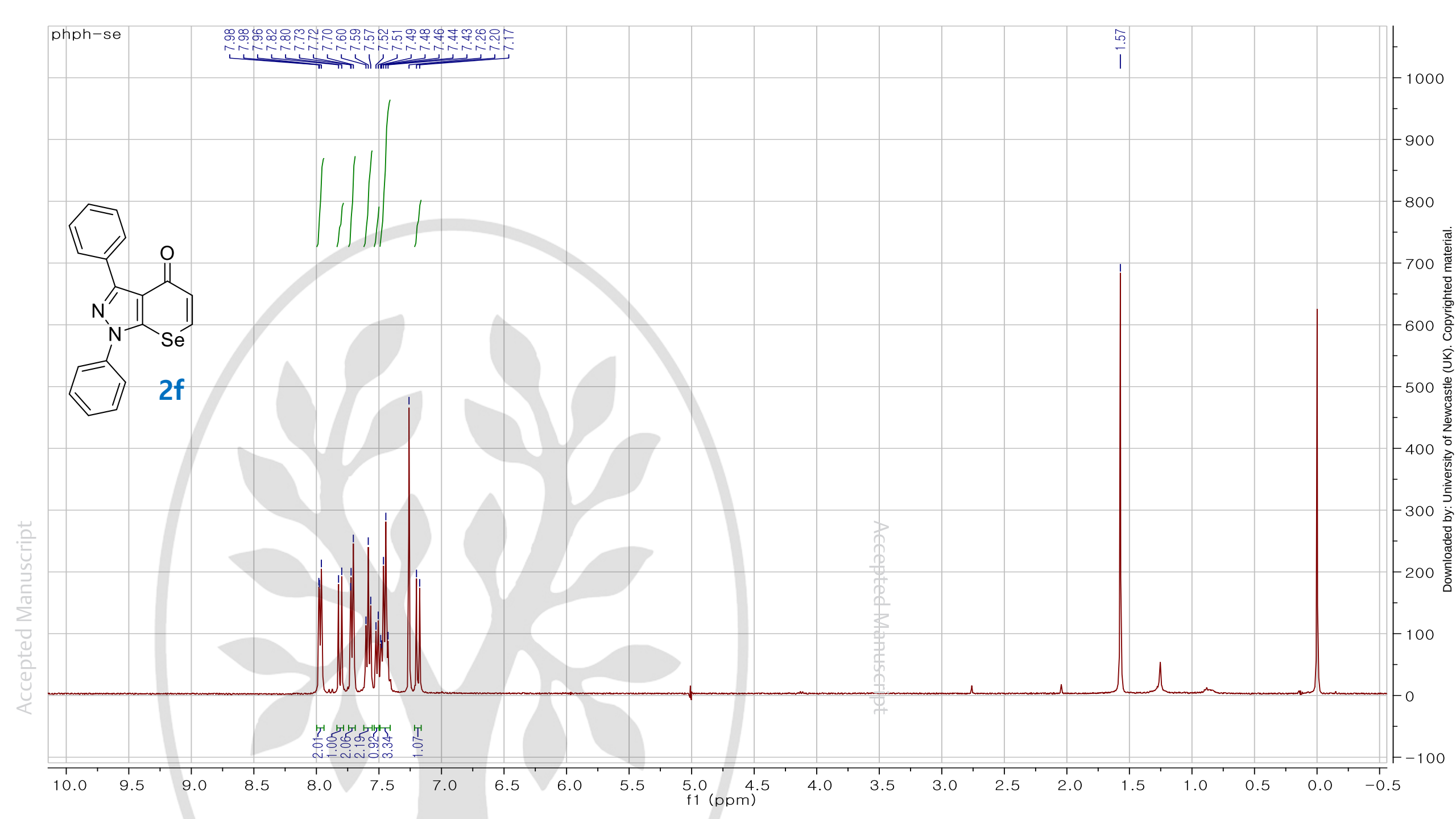
cyclopropyl-se



2e

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7.52
7.51
7.49
7.48
7.46
7.44
7.43
7.26
7.20
7.17
1.57
O
N
N
Se
2f
2.01
1.00
2.06
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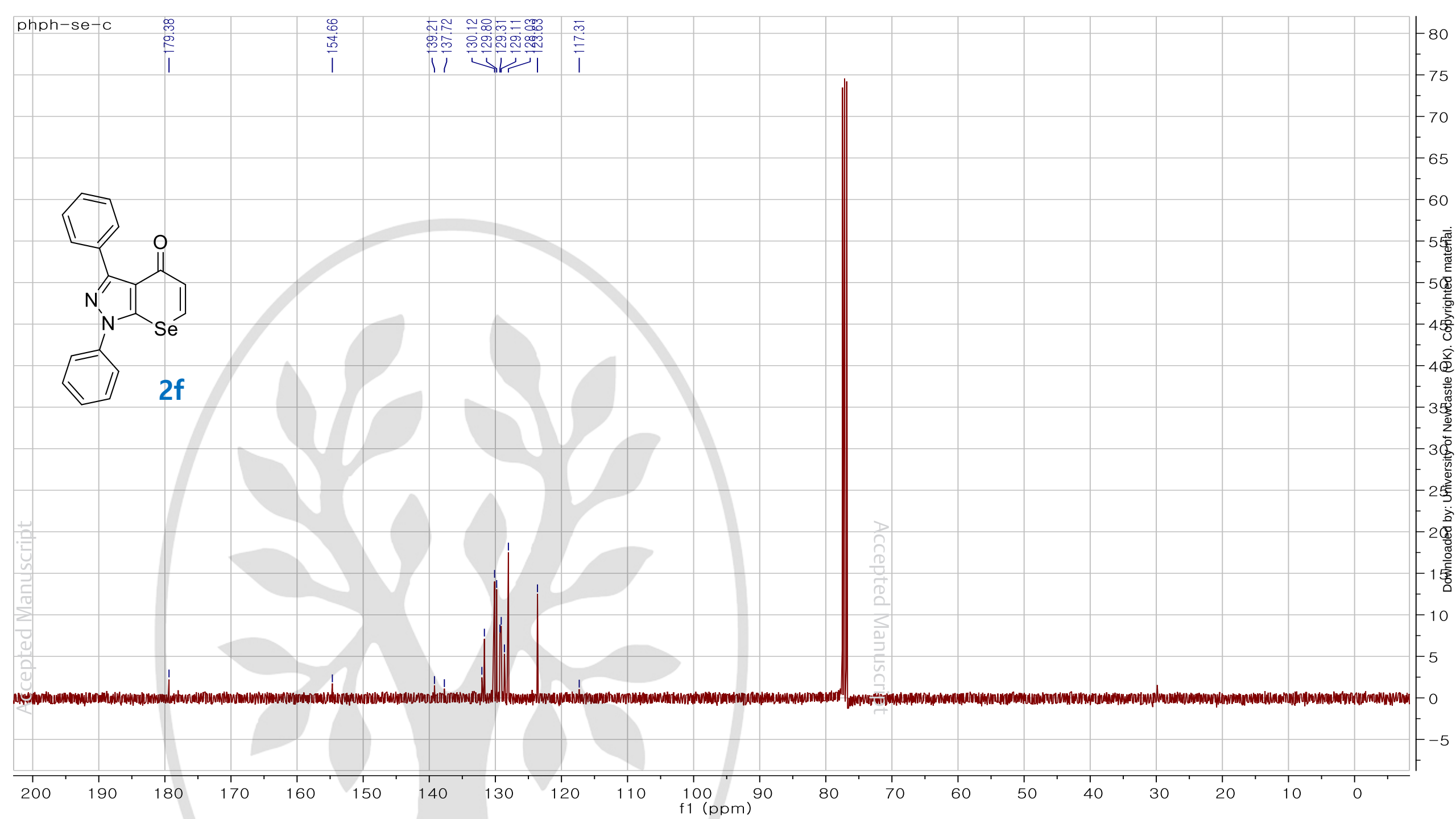

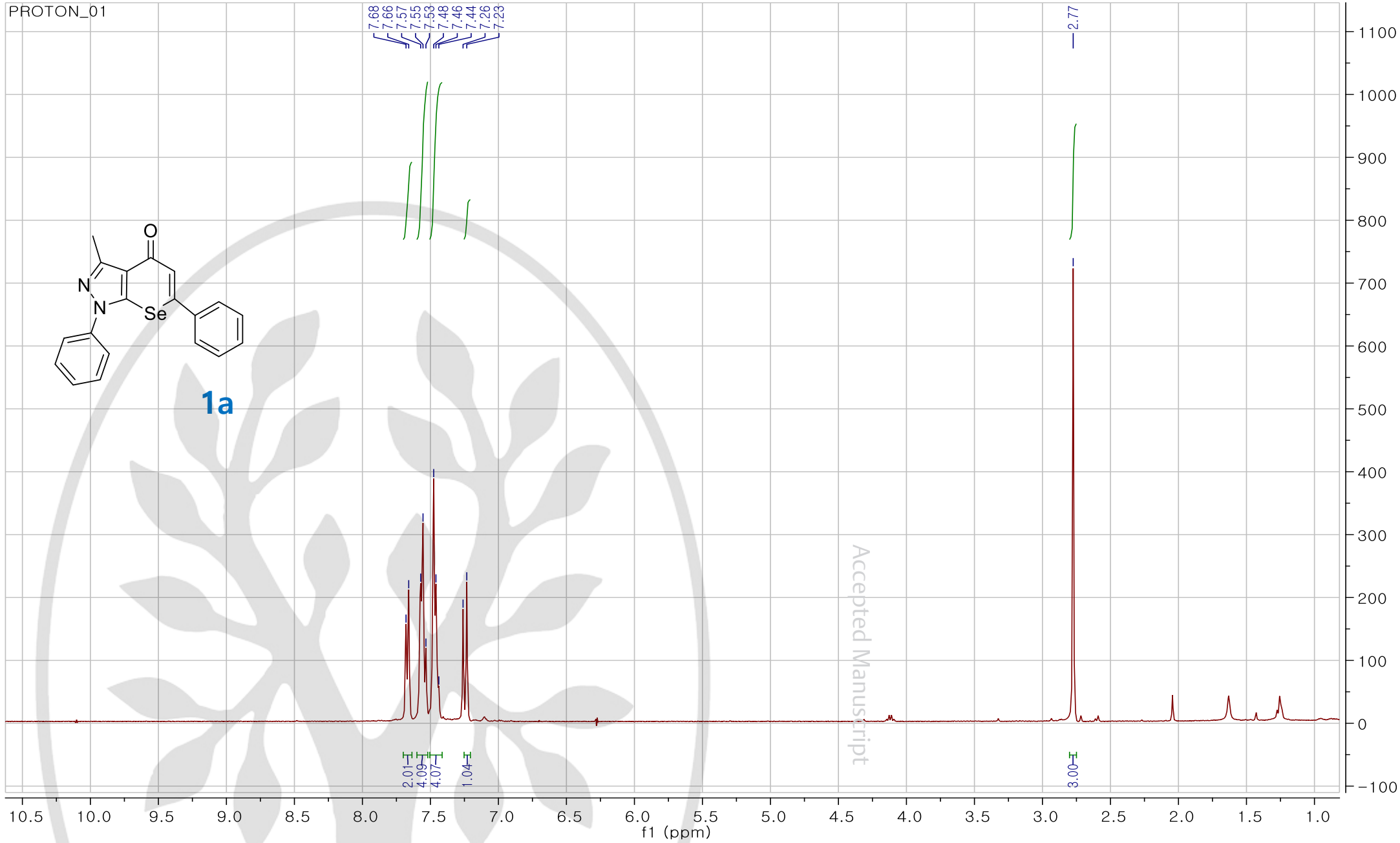

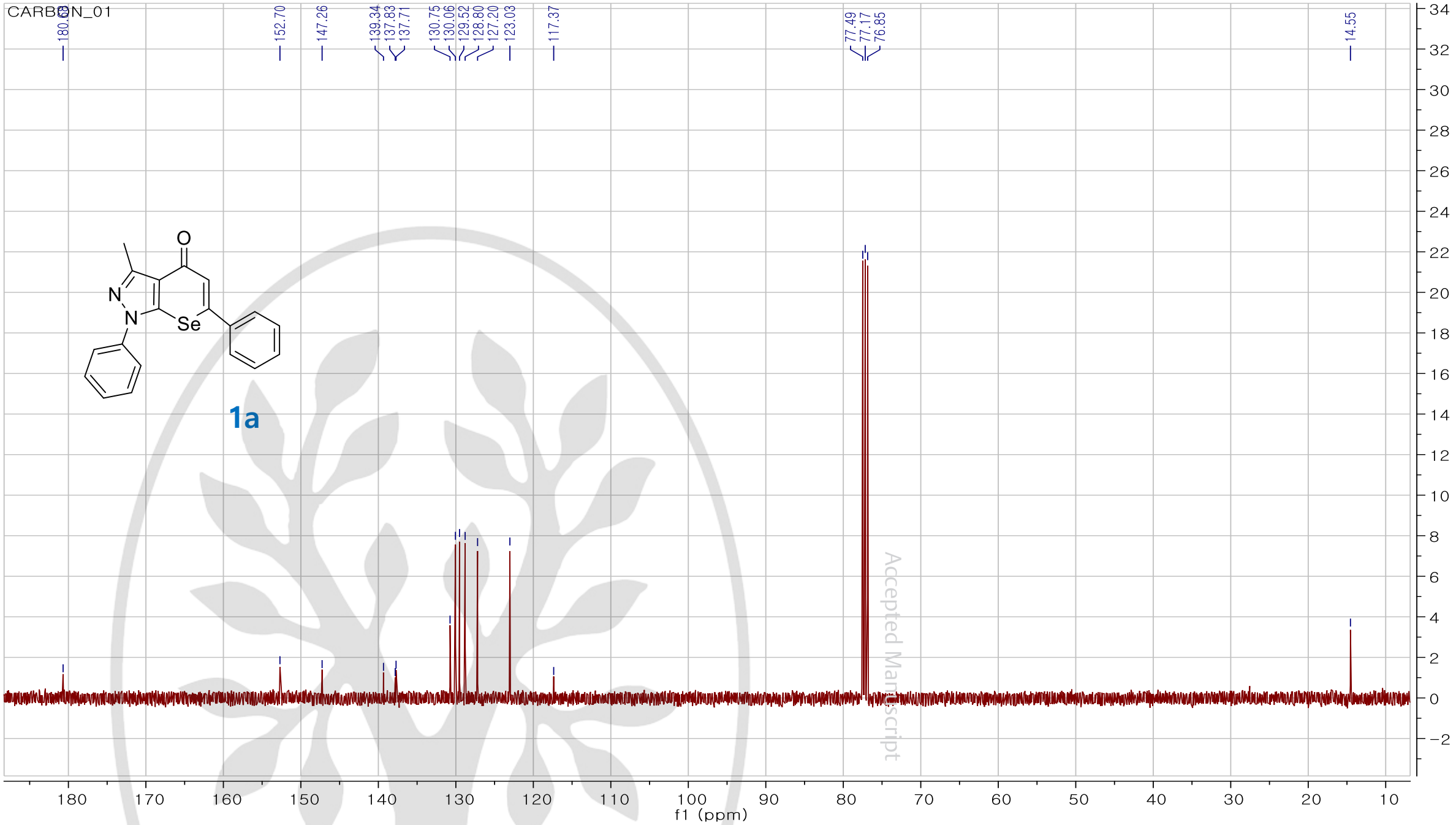

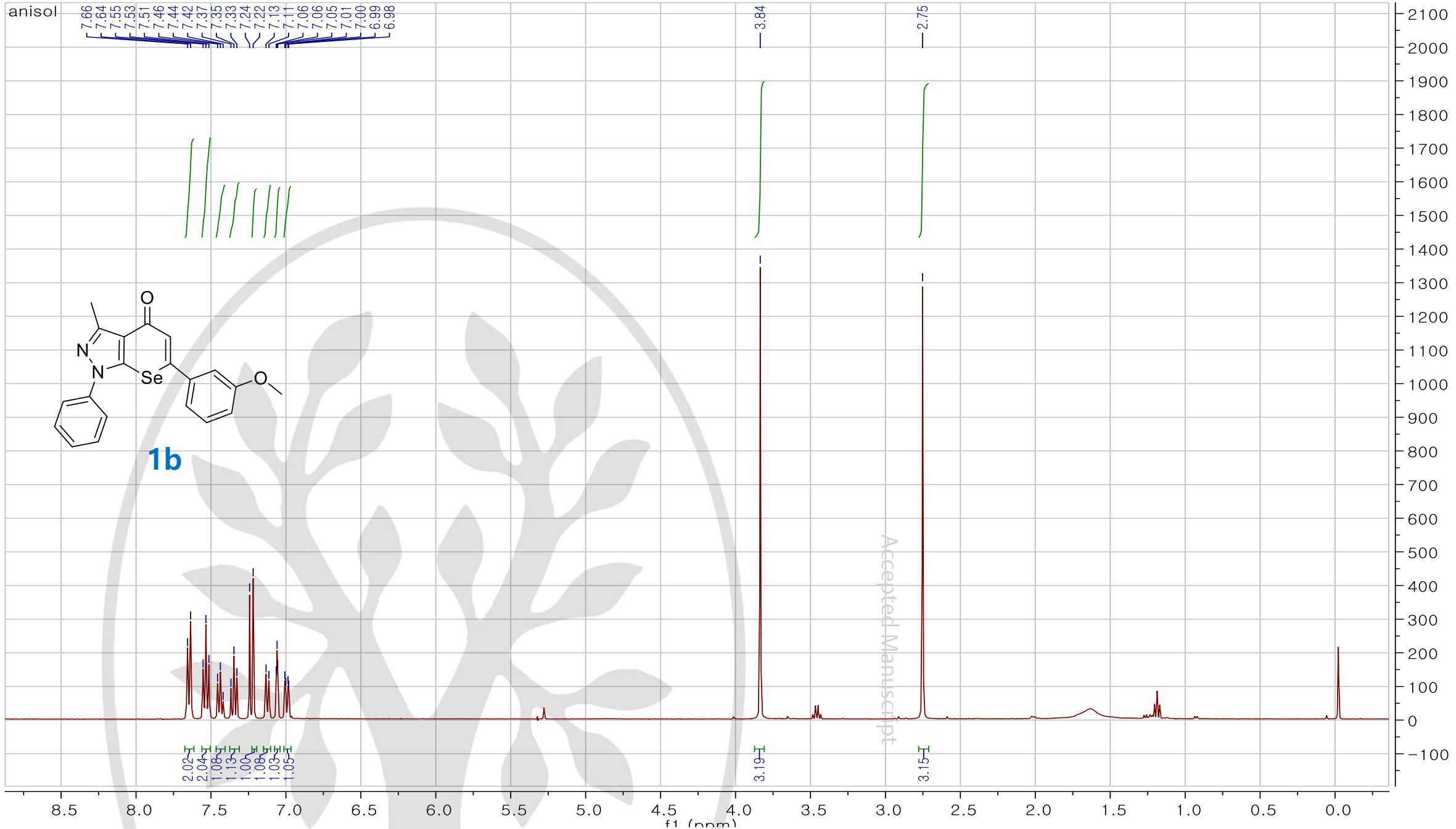

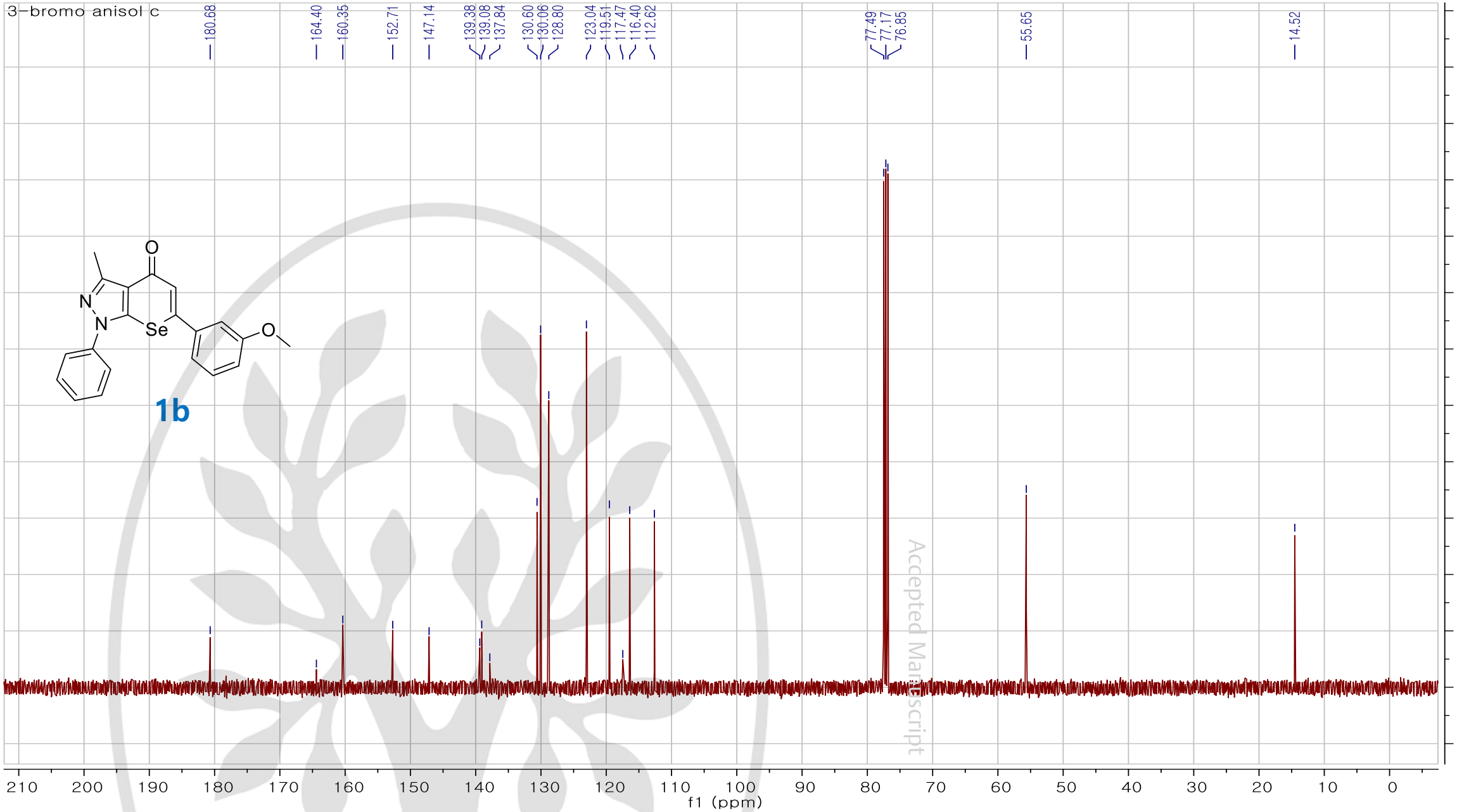

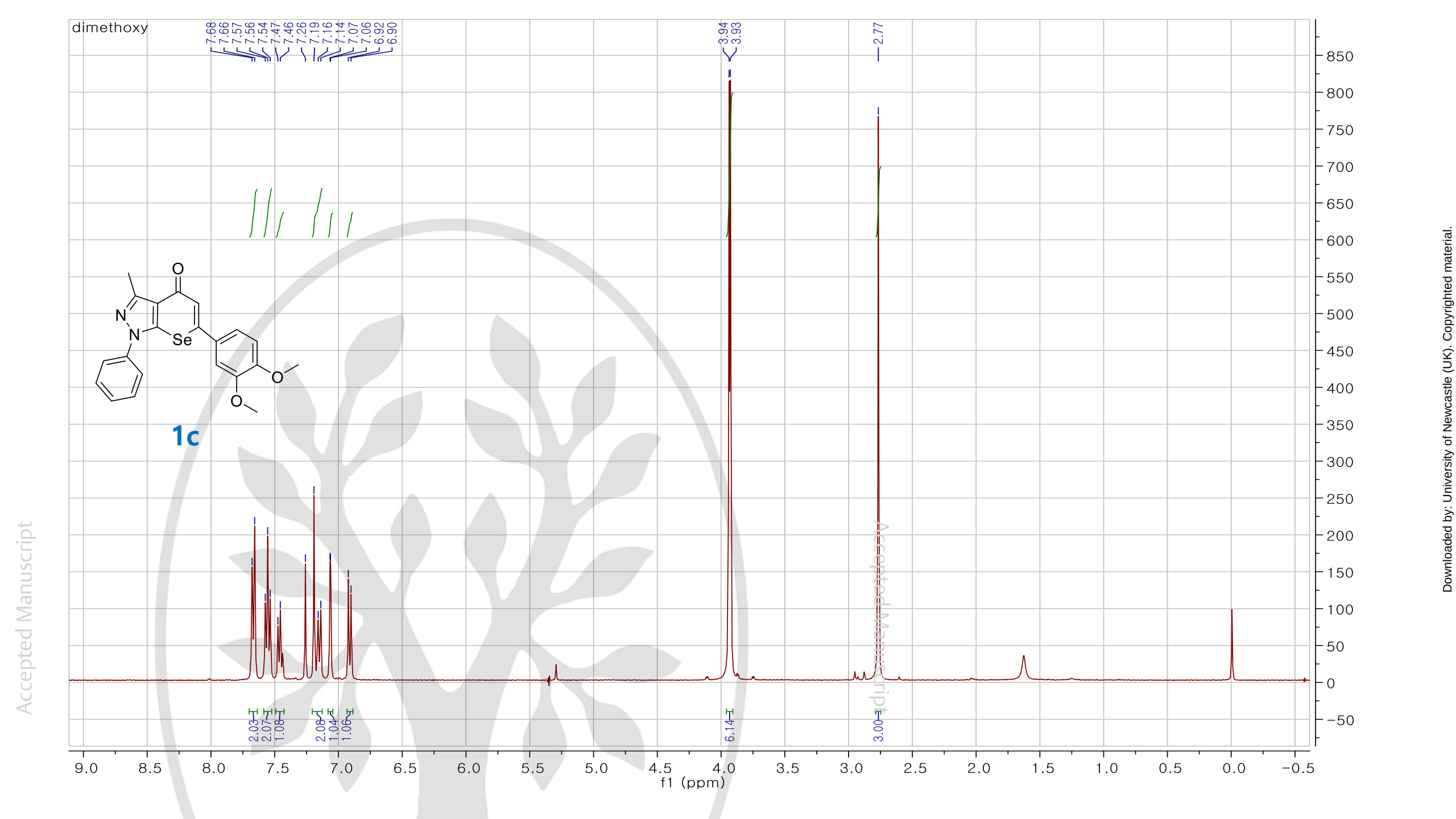

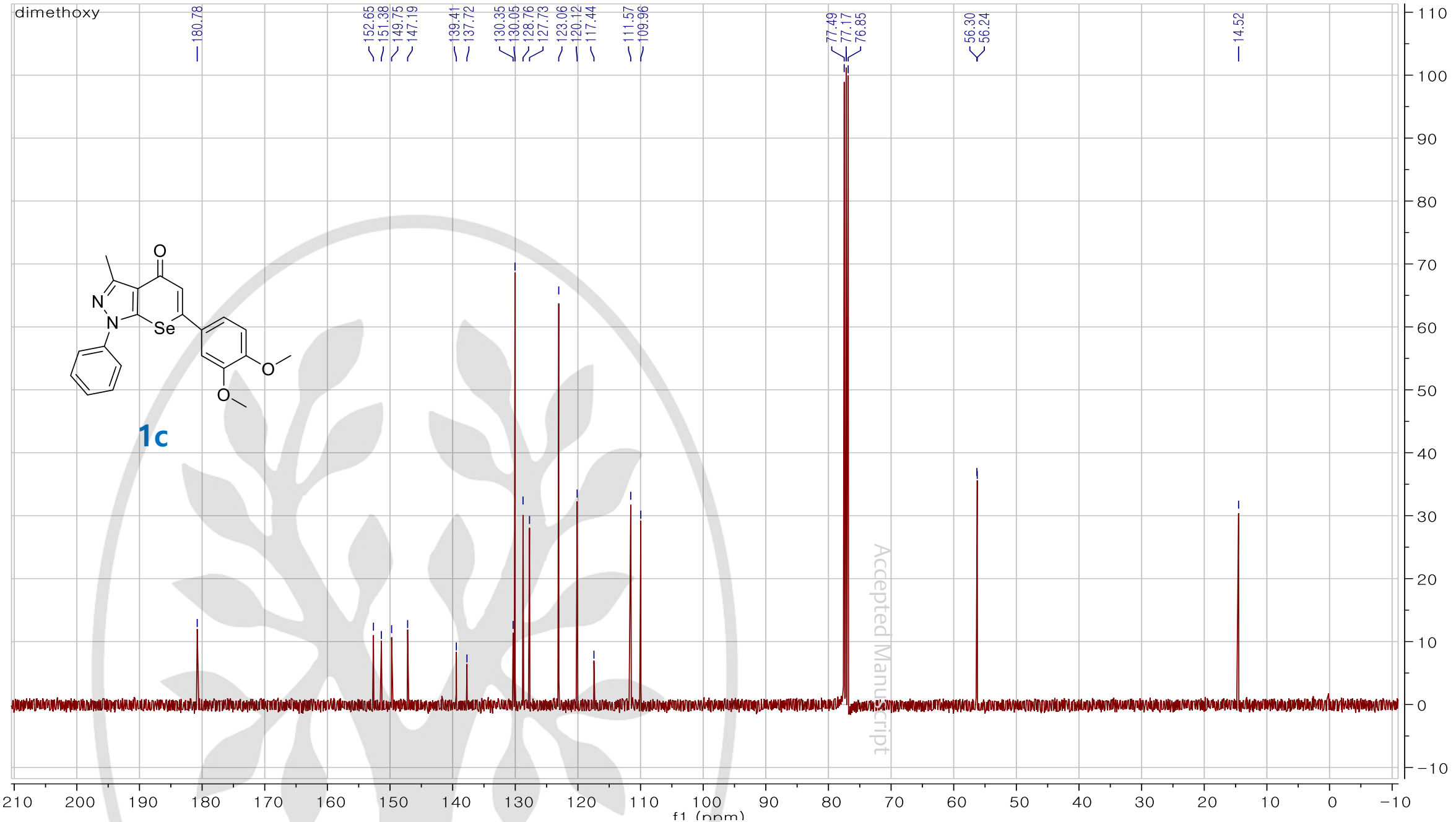

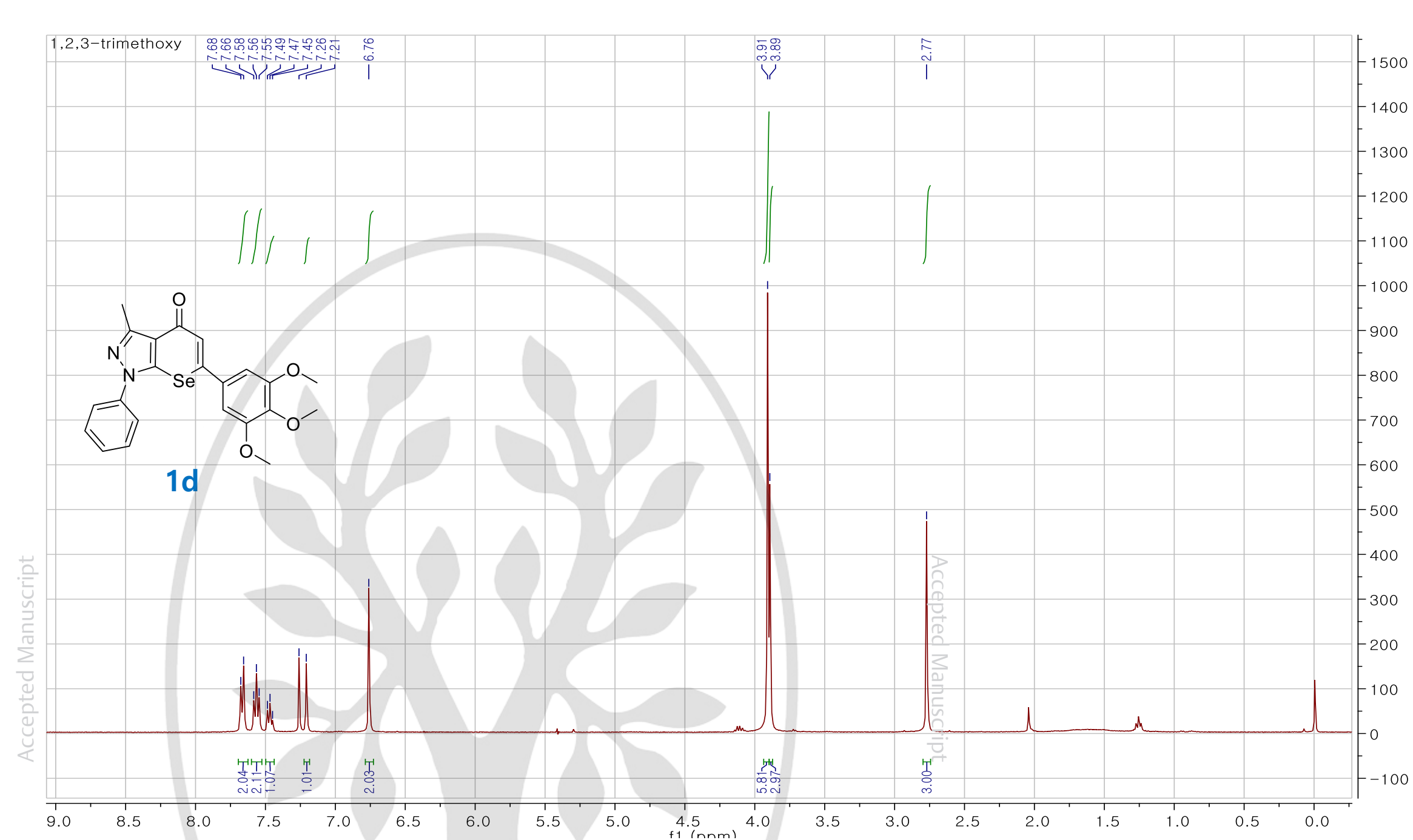

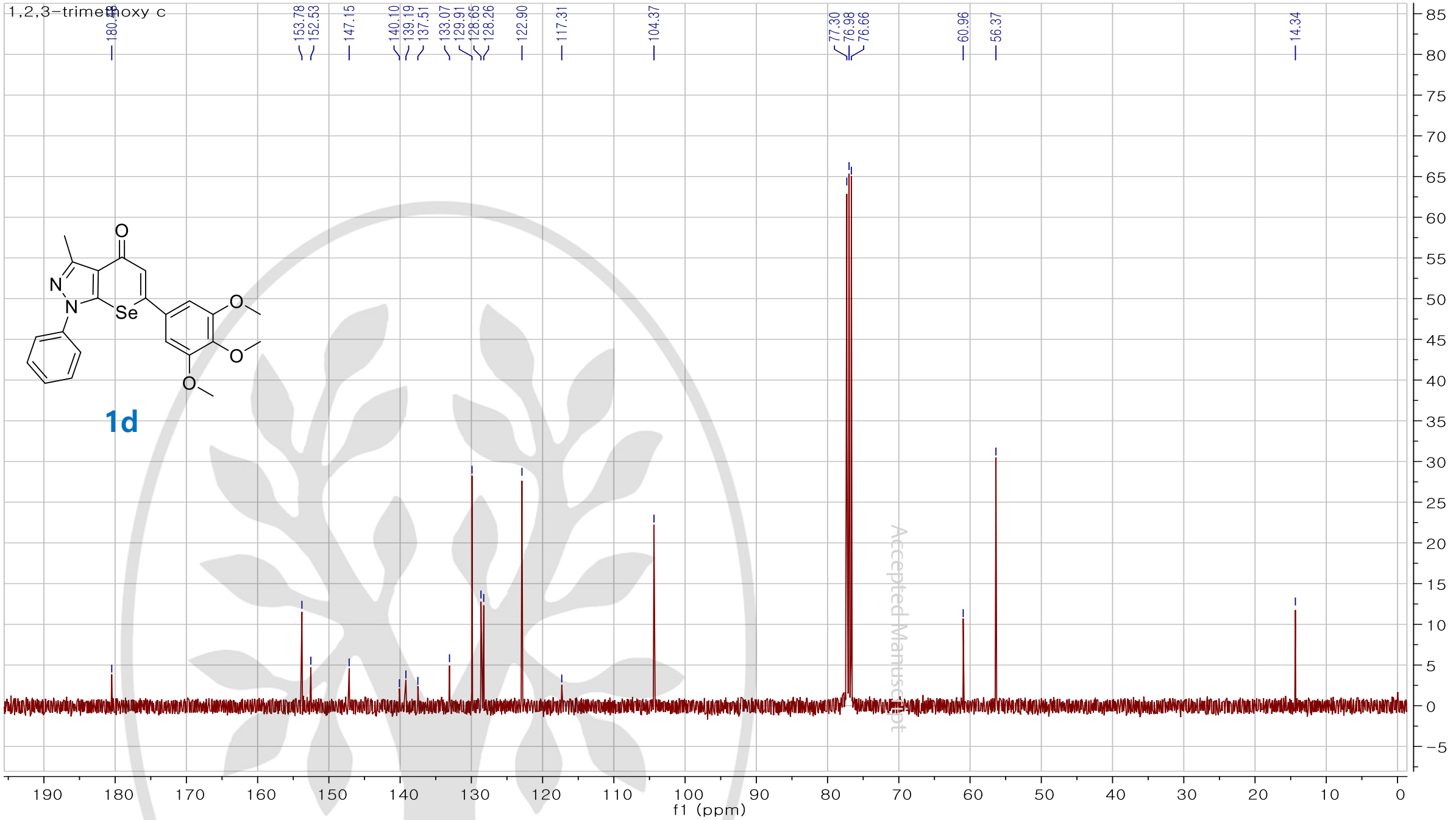

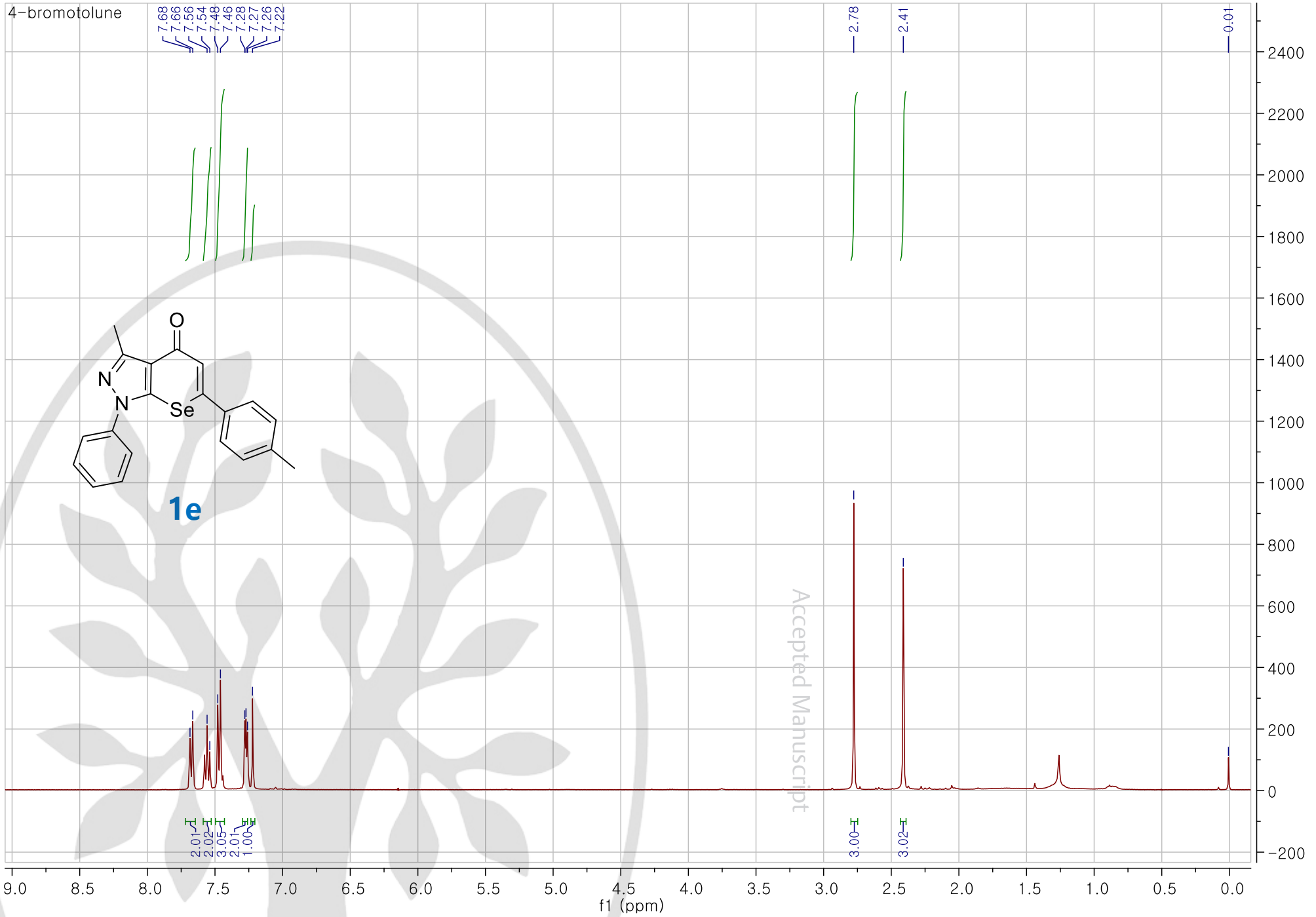

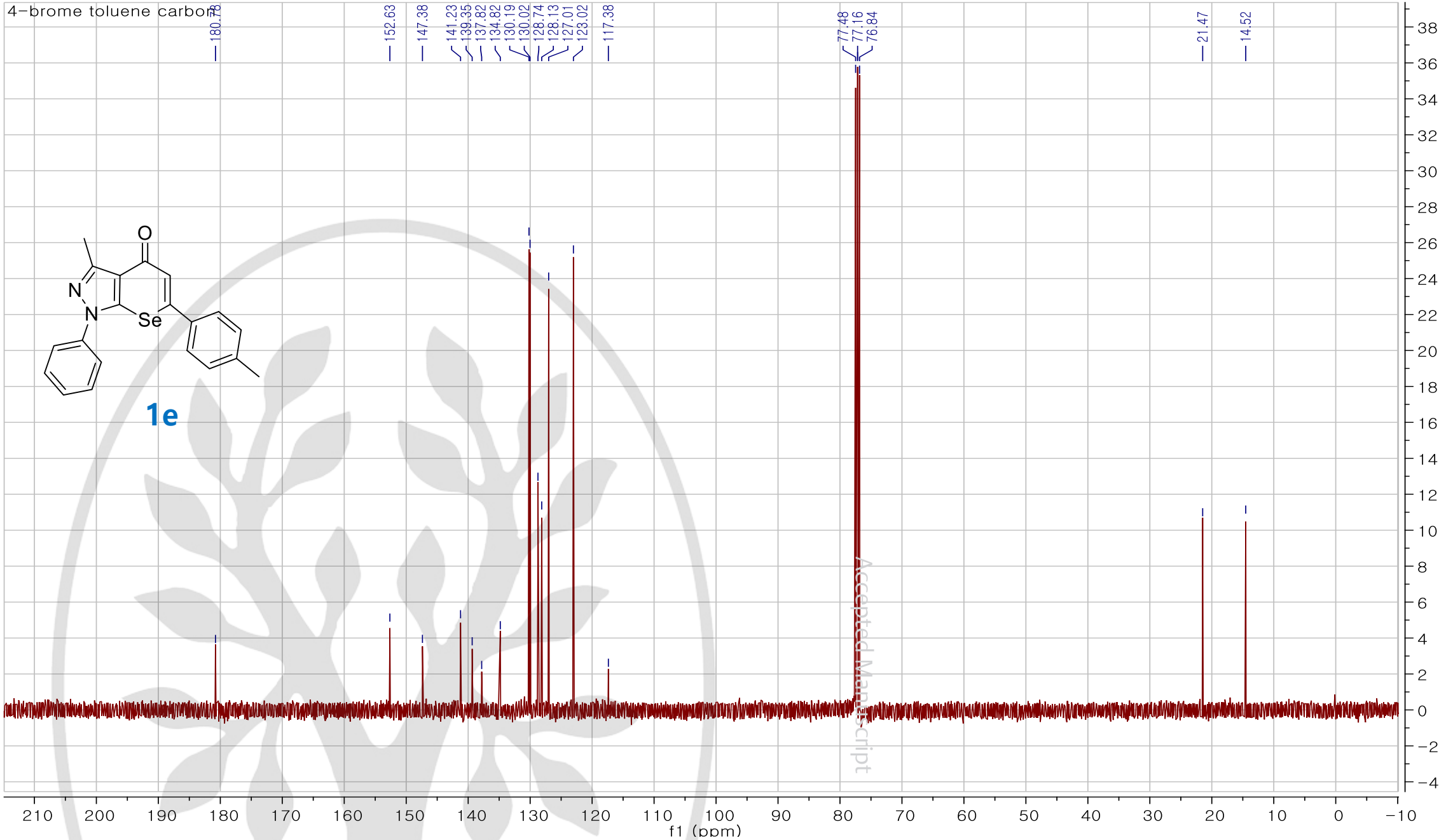

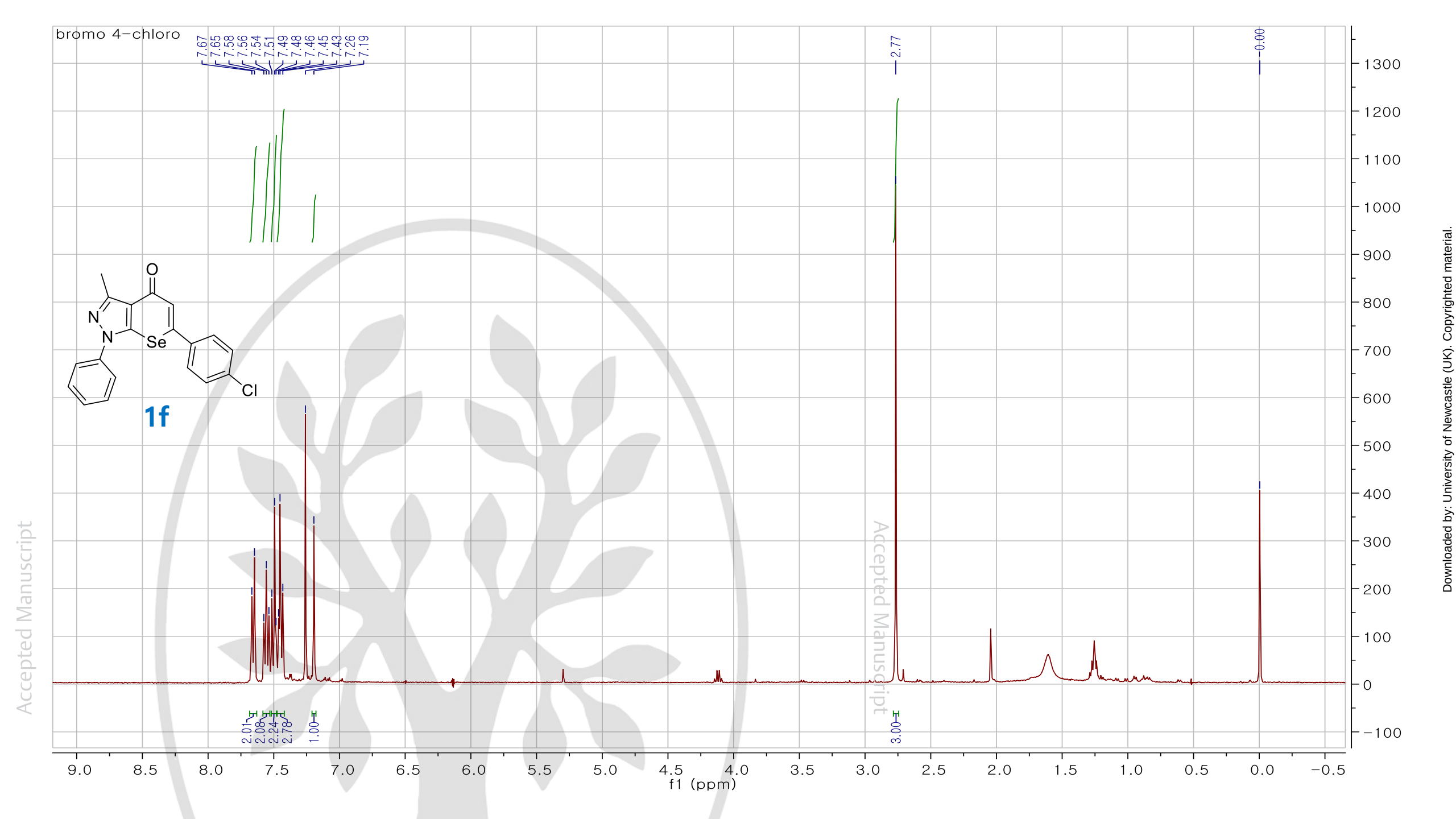
bromo 4-chloro
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7.56
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7.51
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7.48
7.46
7.45
7.43
7.26
7.19
2.77
0.00
O
N
N
Se
Cl
1f
2.01
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2.78
1.00
3.00
f1 (ppm)
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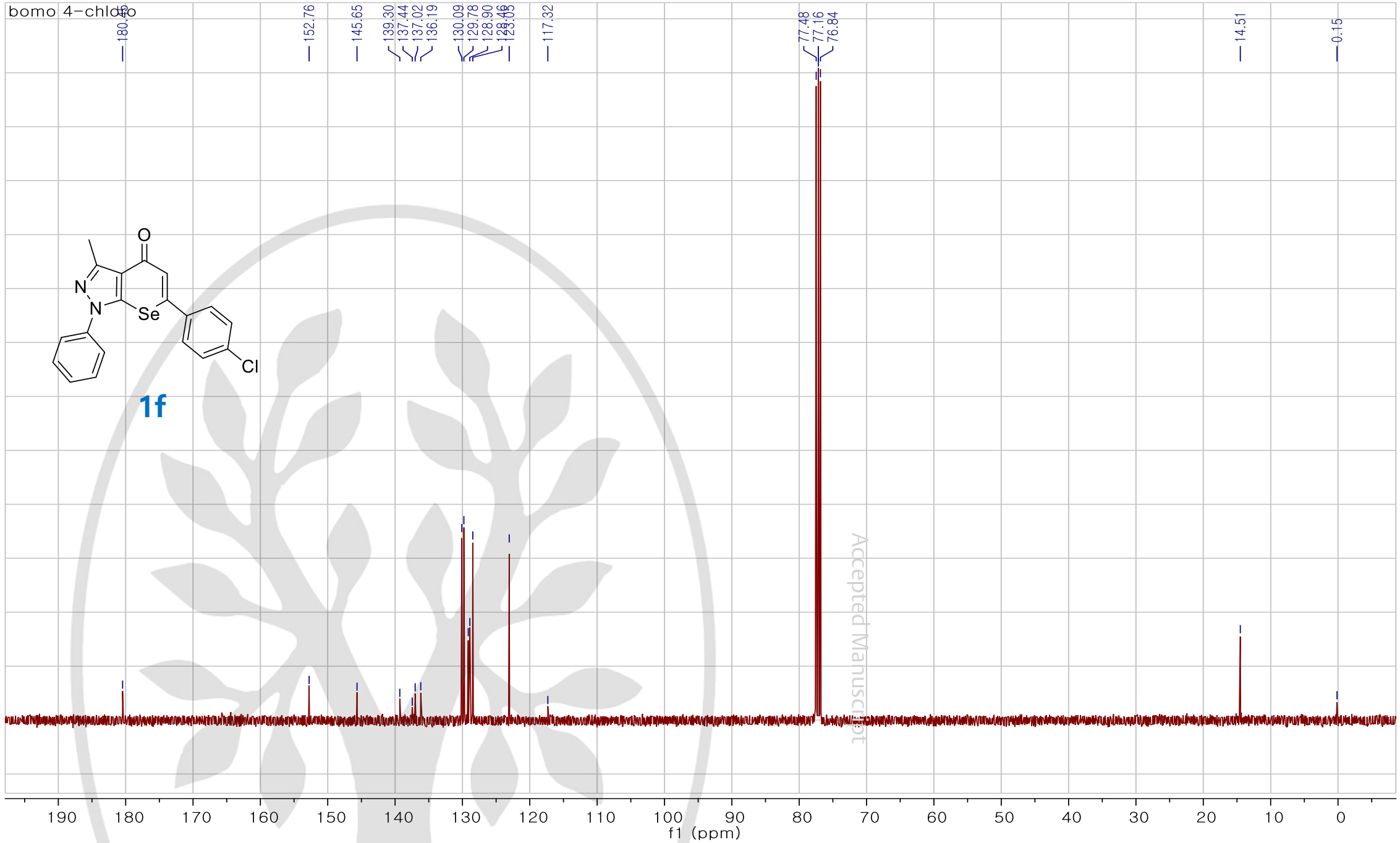

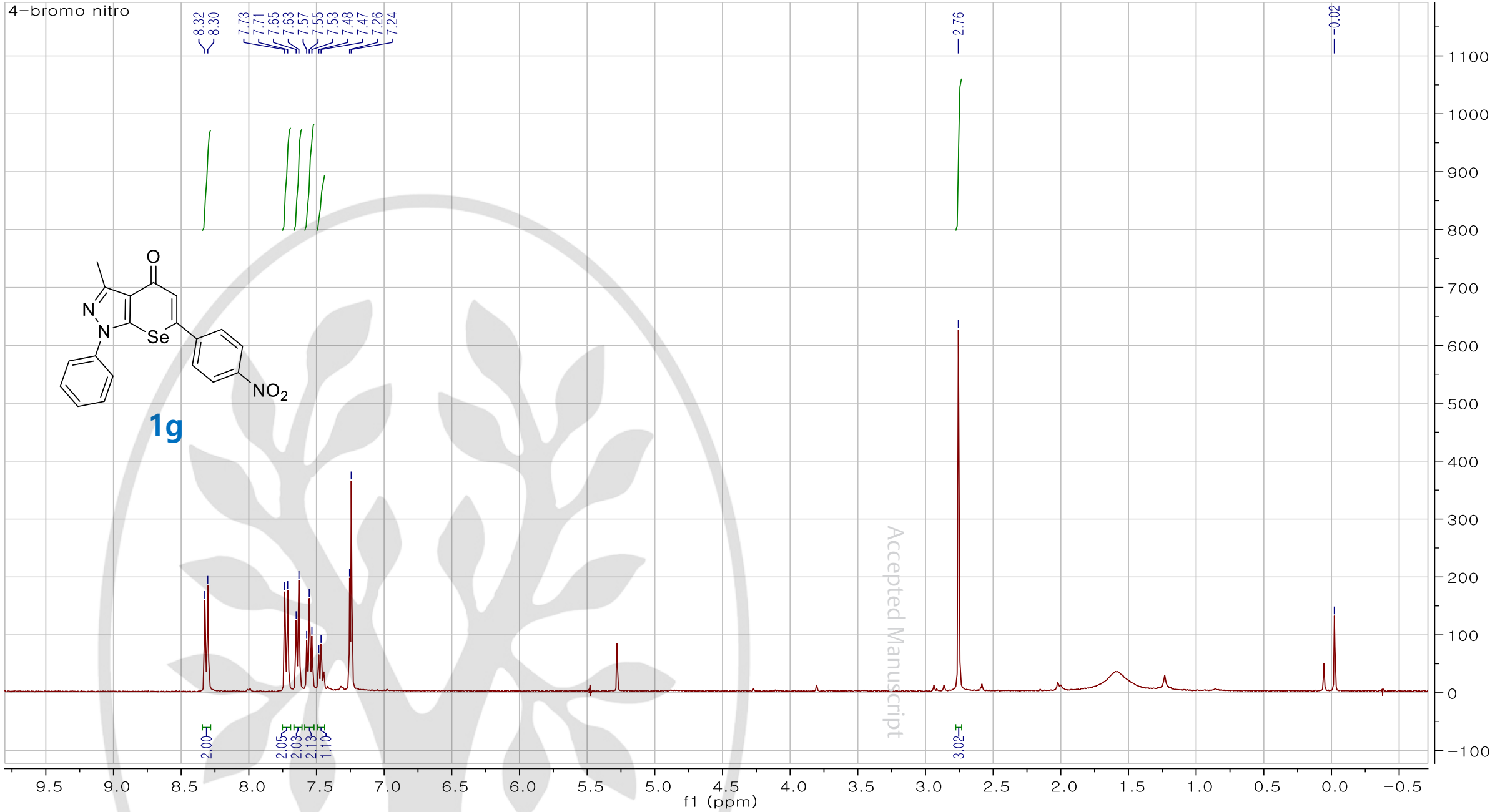

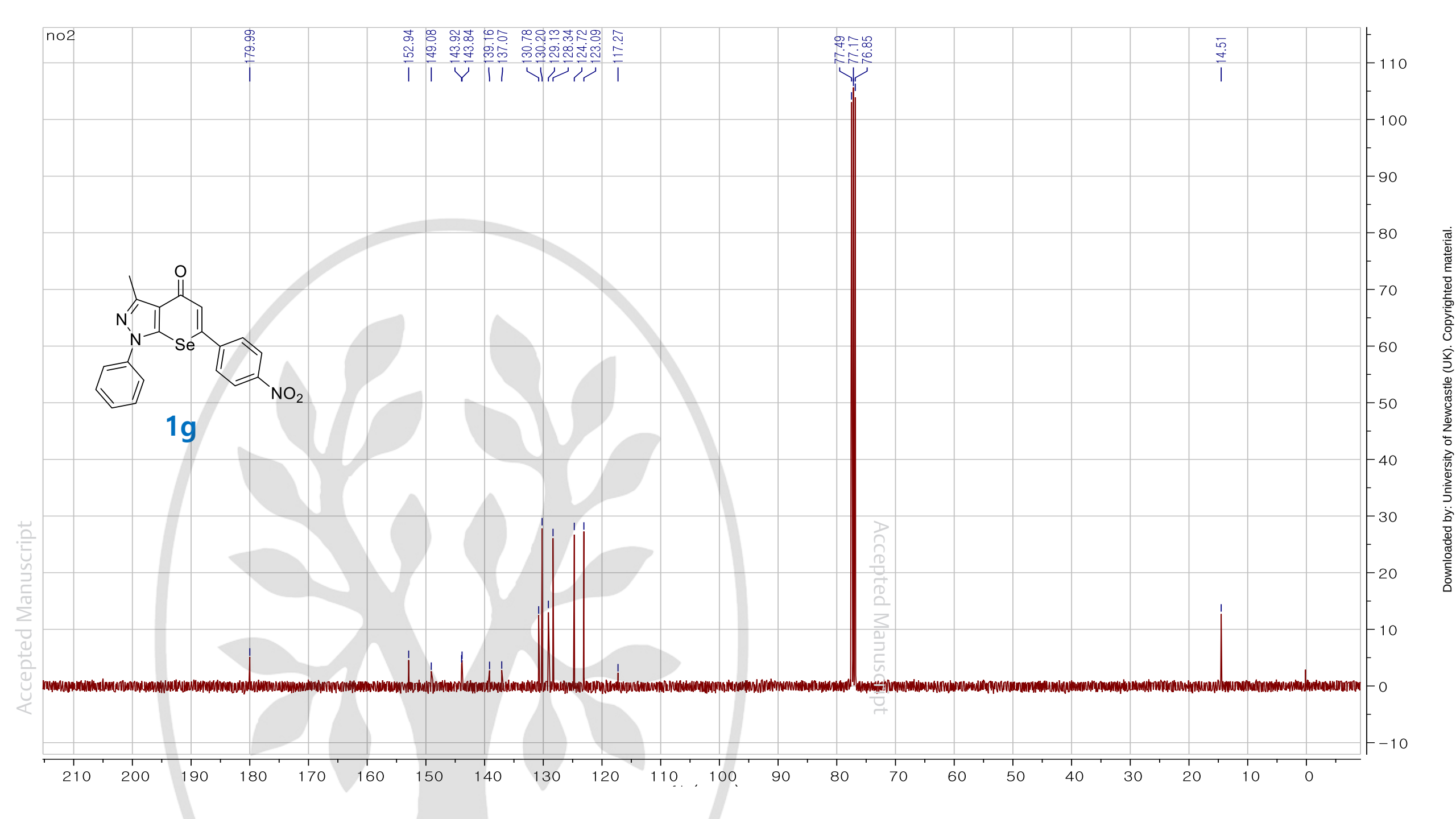

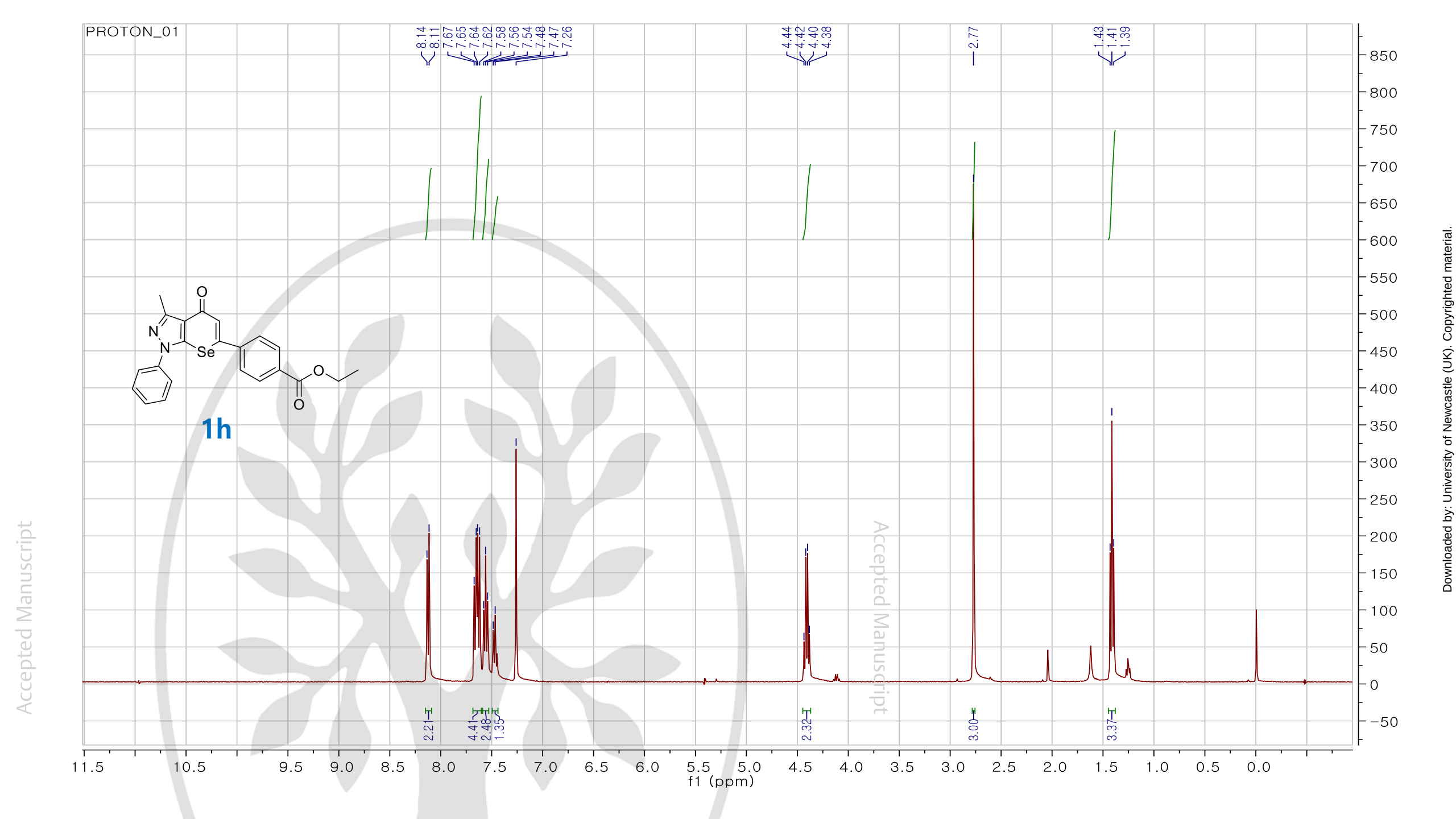

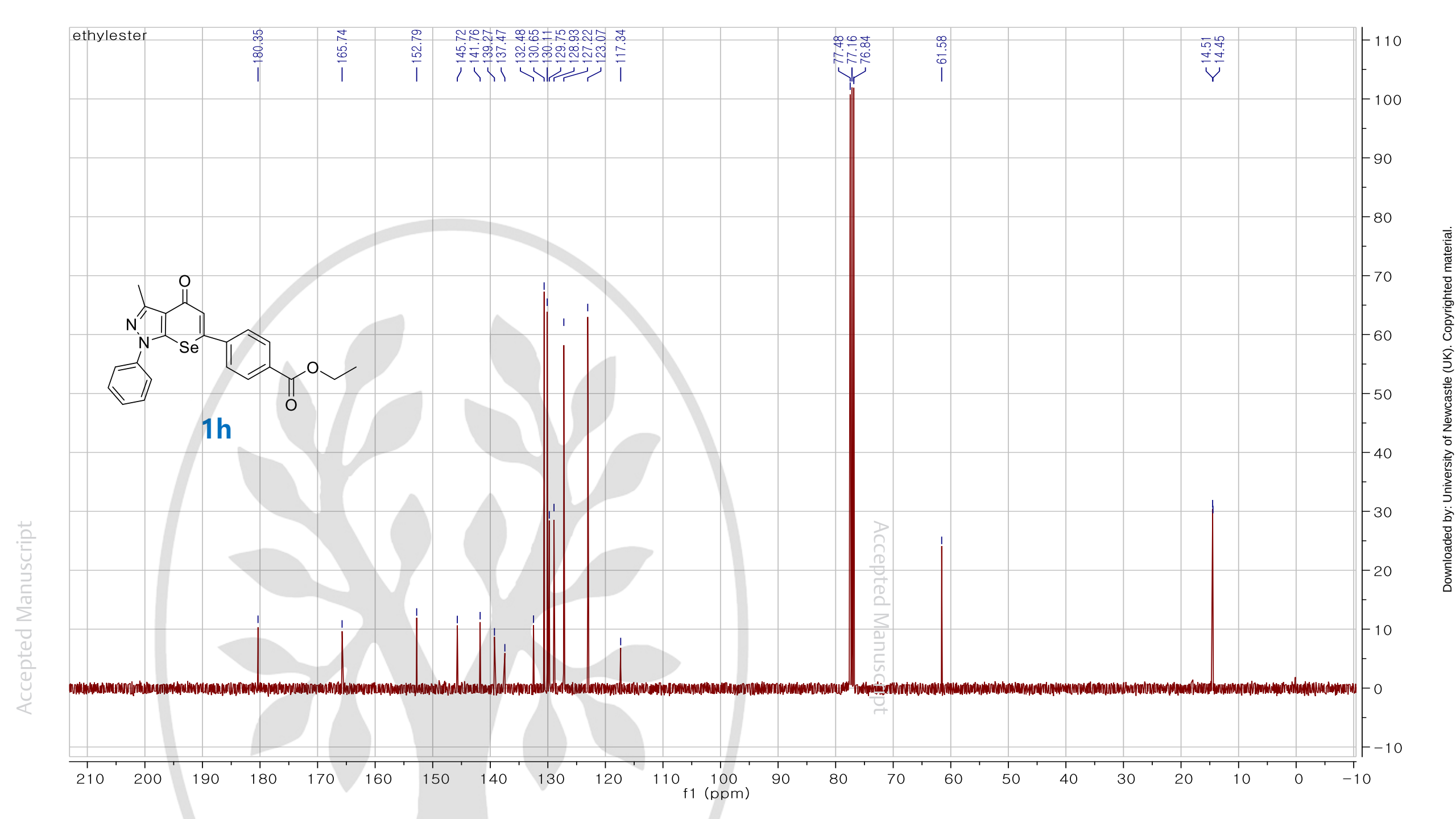

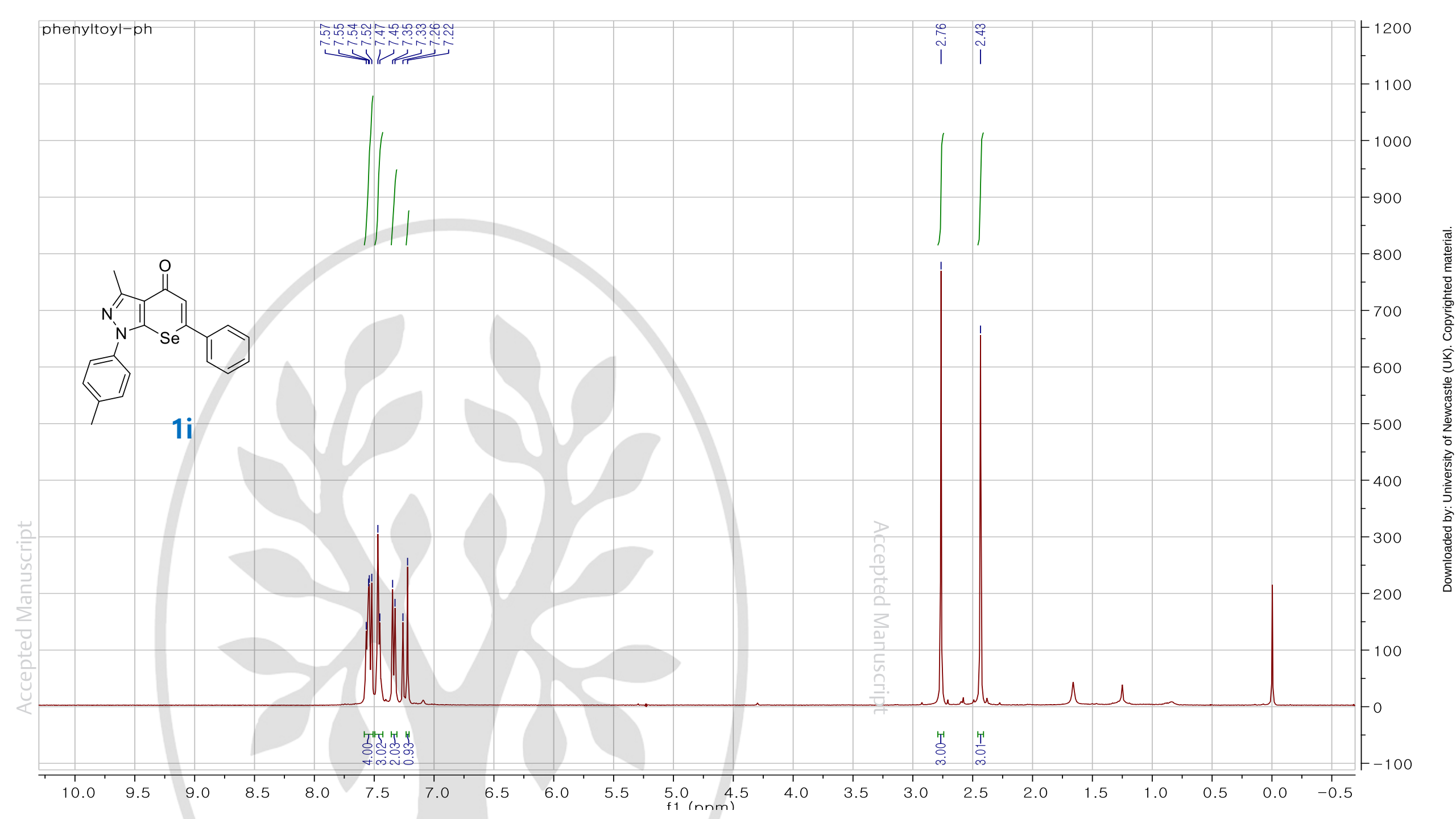

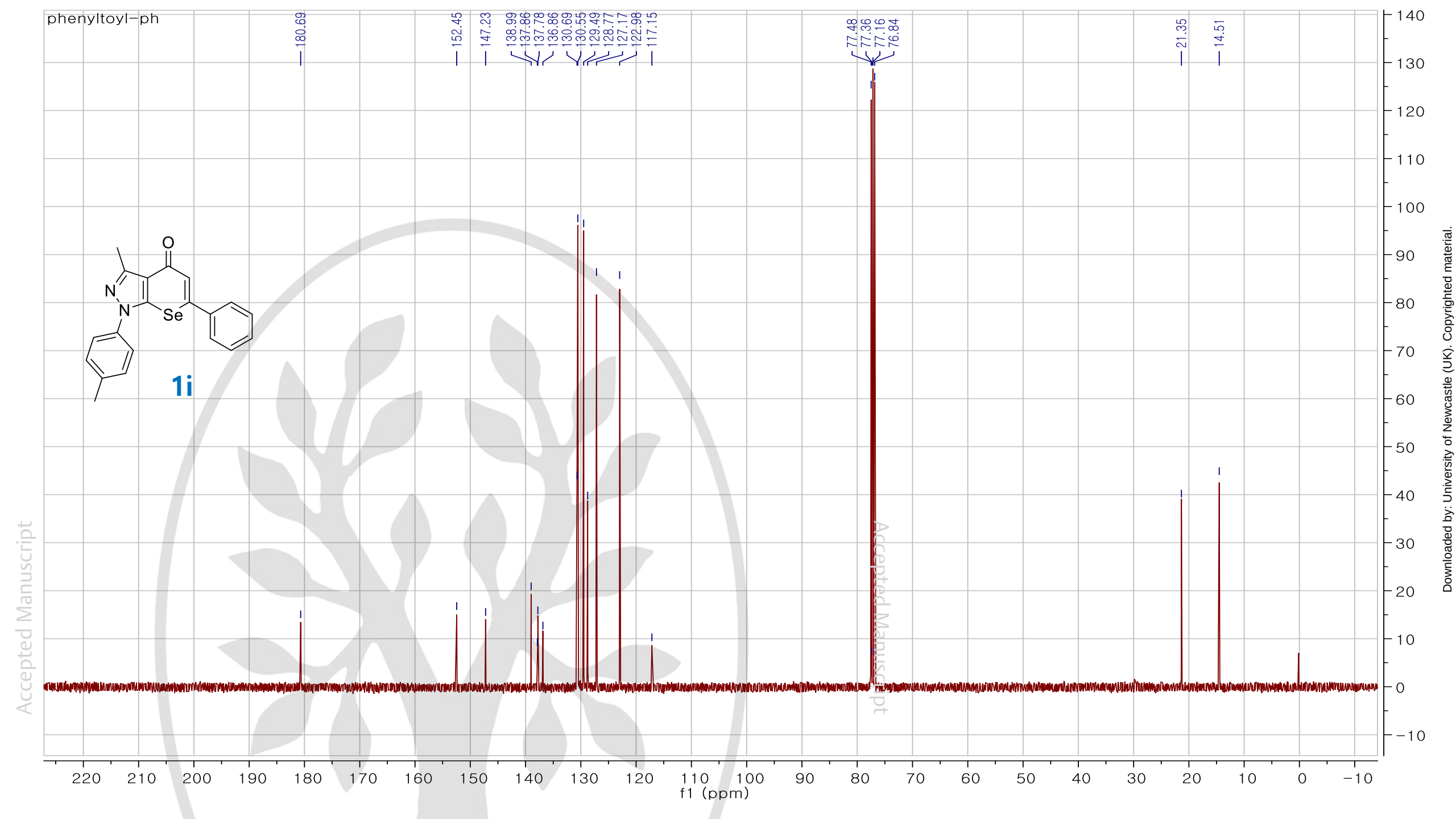
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76.84
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14.51
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N
N
Se
1i
f1 (ppm)
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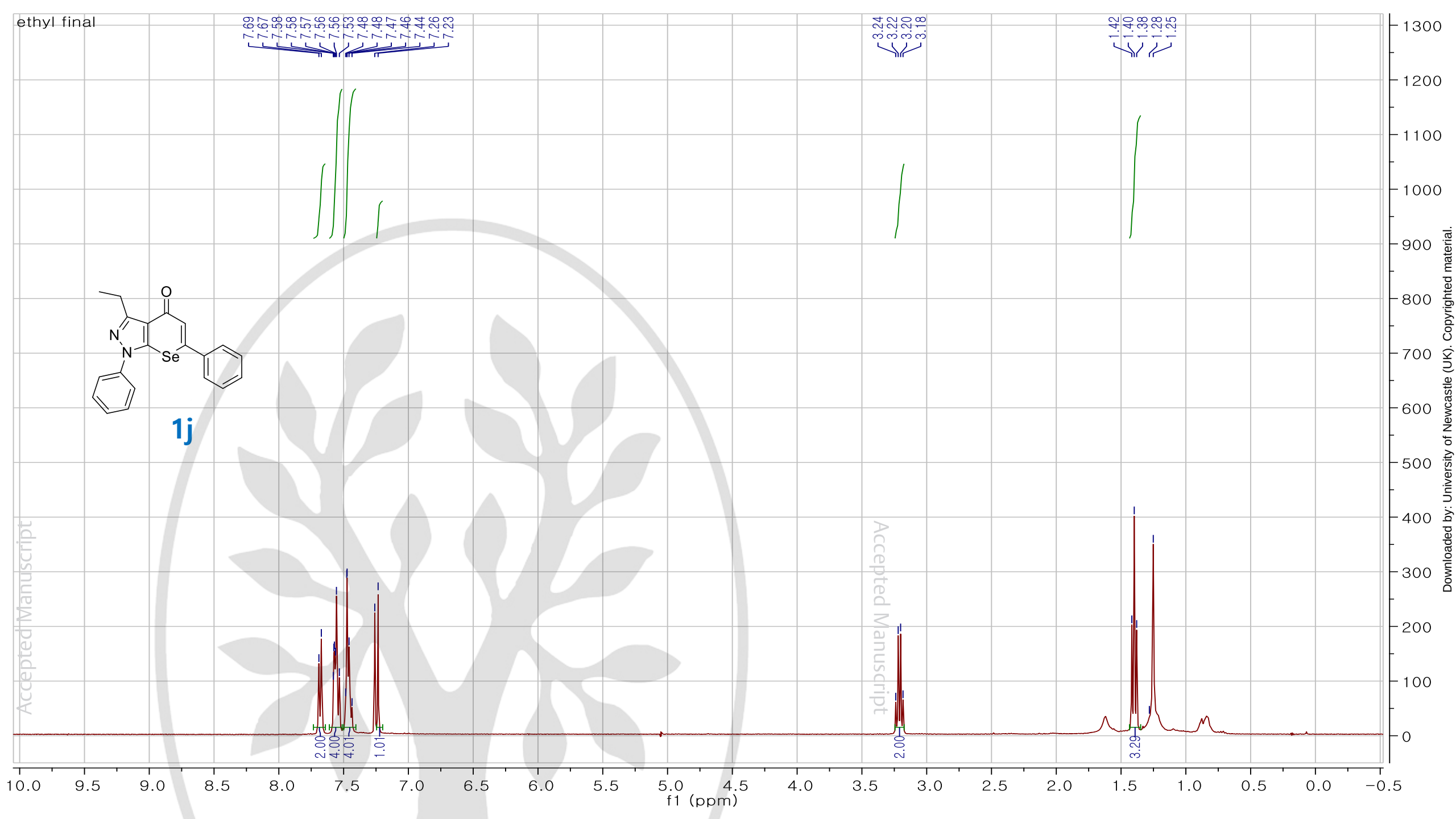
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7.53
7.48
7.48
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7.44
7.26
7.23
3.24
3.22
3.20
3.18
1.42
1.40
1.38
1.28
1.25
O
N
N
Se
1j
2.00
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f1 (ppm)
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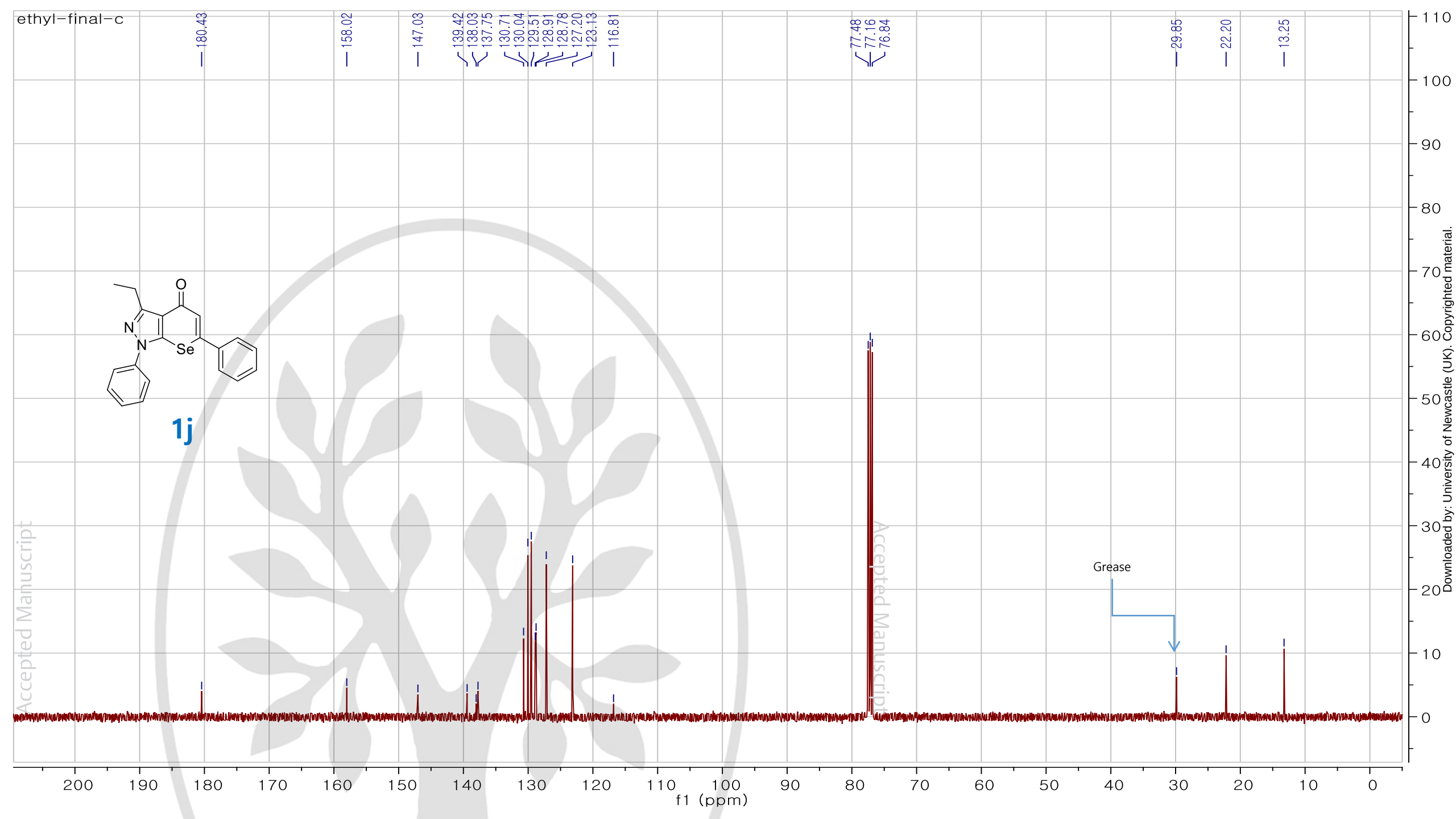
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127.20
123.13
116.81
77.48
77.16
76.84
29.85
22.20
13.25
O
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N
Se
1j
Grease
f1 (ppm)
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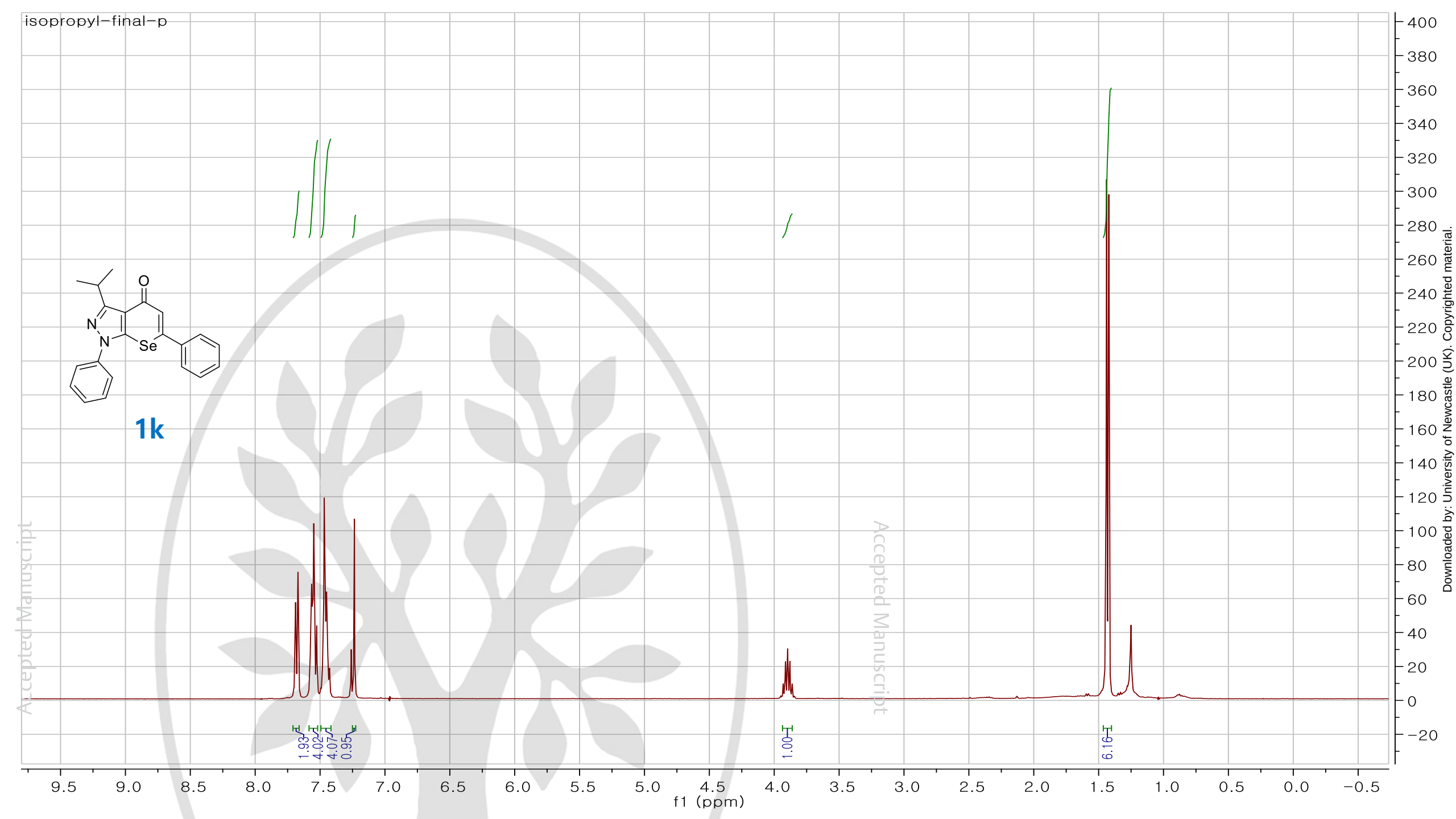
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N
N
Se
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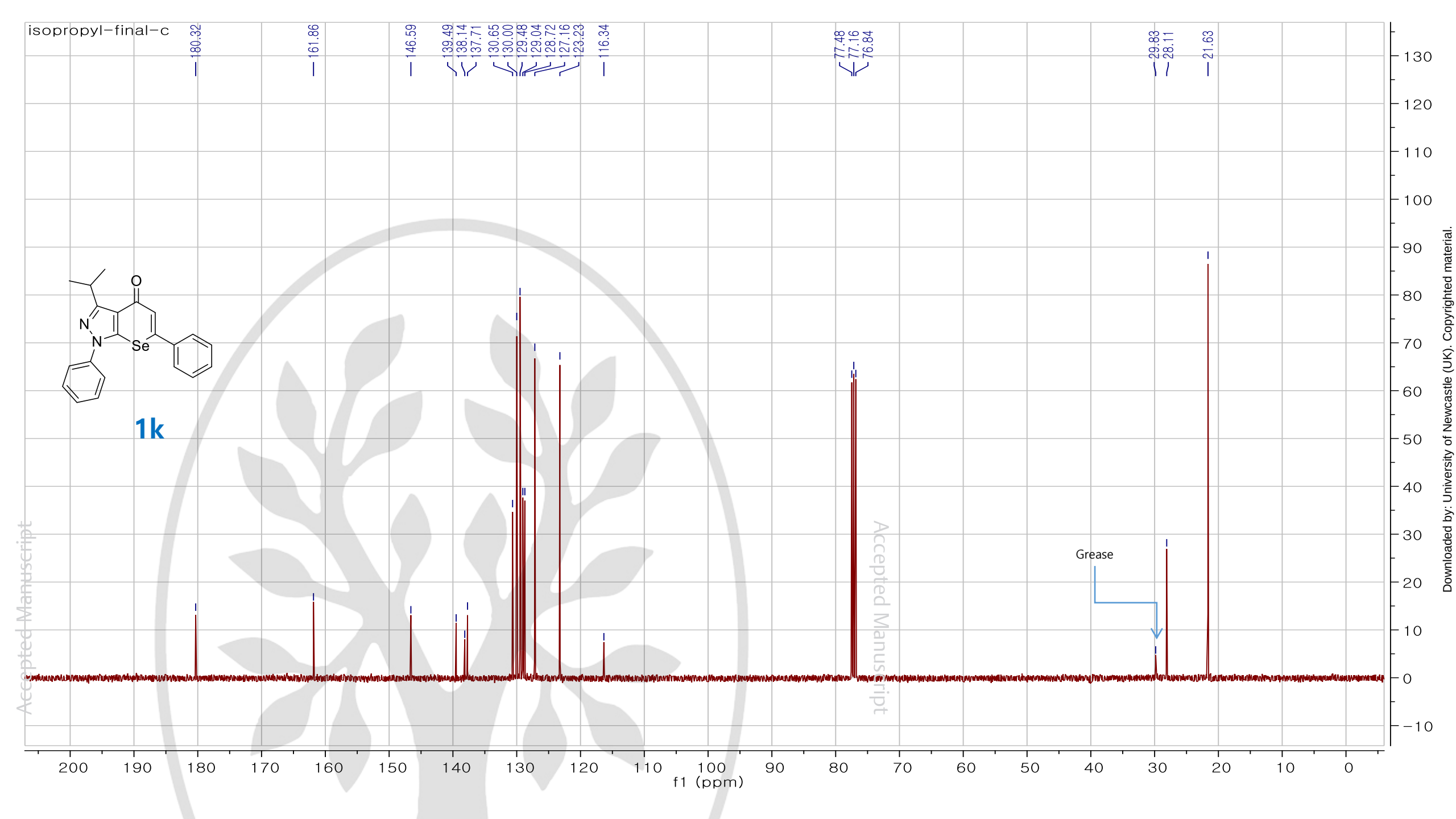
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146.59
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137.71
130.65
130.00
129.48
129.04
128.72
127.16
123.23
116.34
77.48
77.16
76.84
29.83
28.11
21.63
O
N
N
Se
1k
Grease
f1 (ppm)
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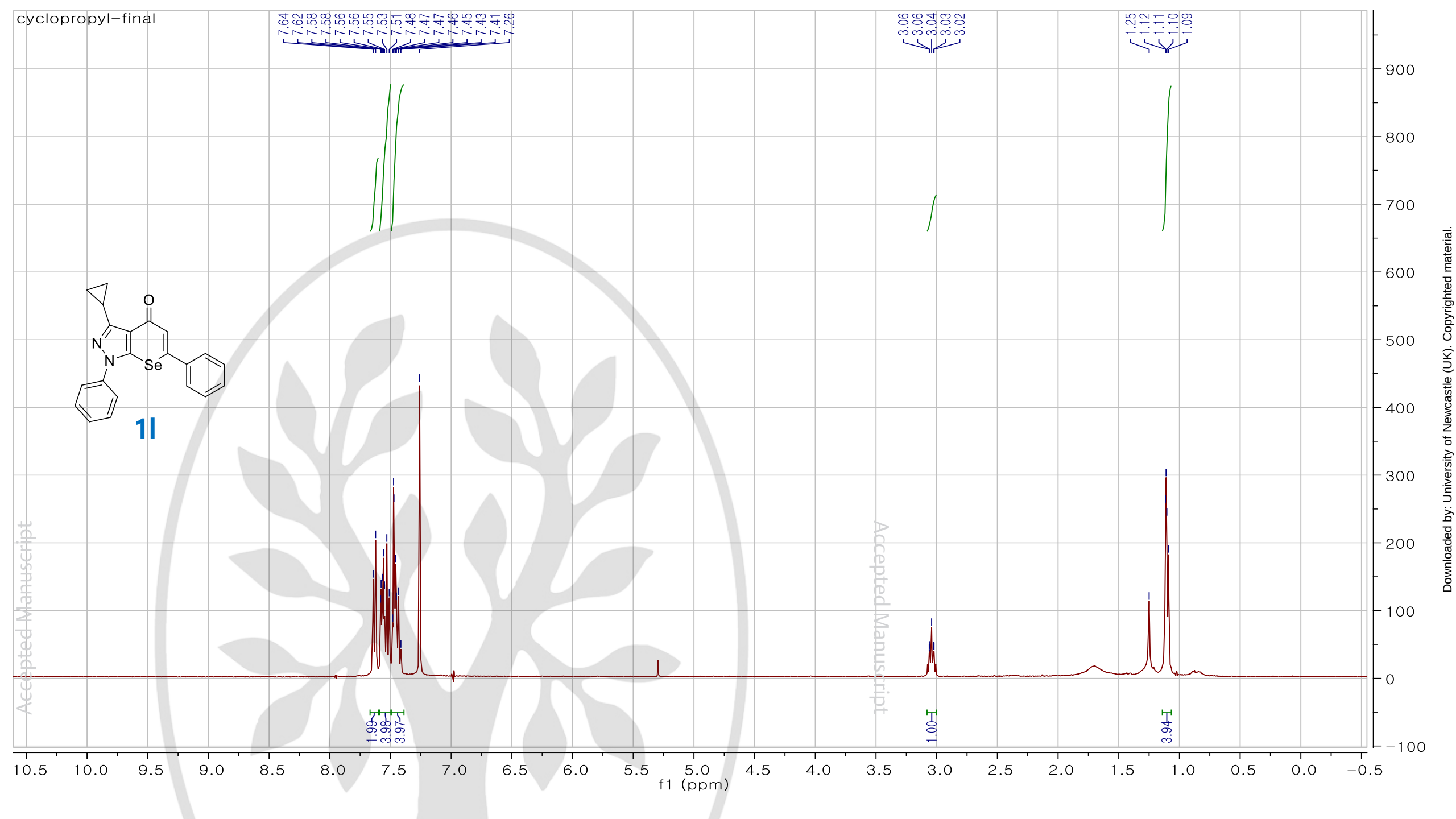
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7.51
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7.26
3.06
3.06
3.04
3.03
3.02
1.25
1.12
1.11
1.10
1.09
O
N
N
Se
1l
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3.97
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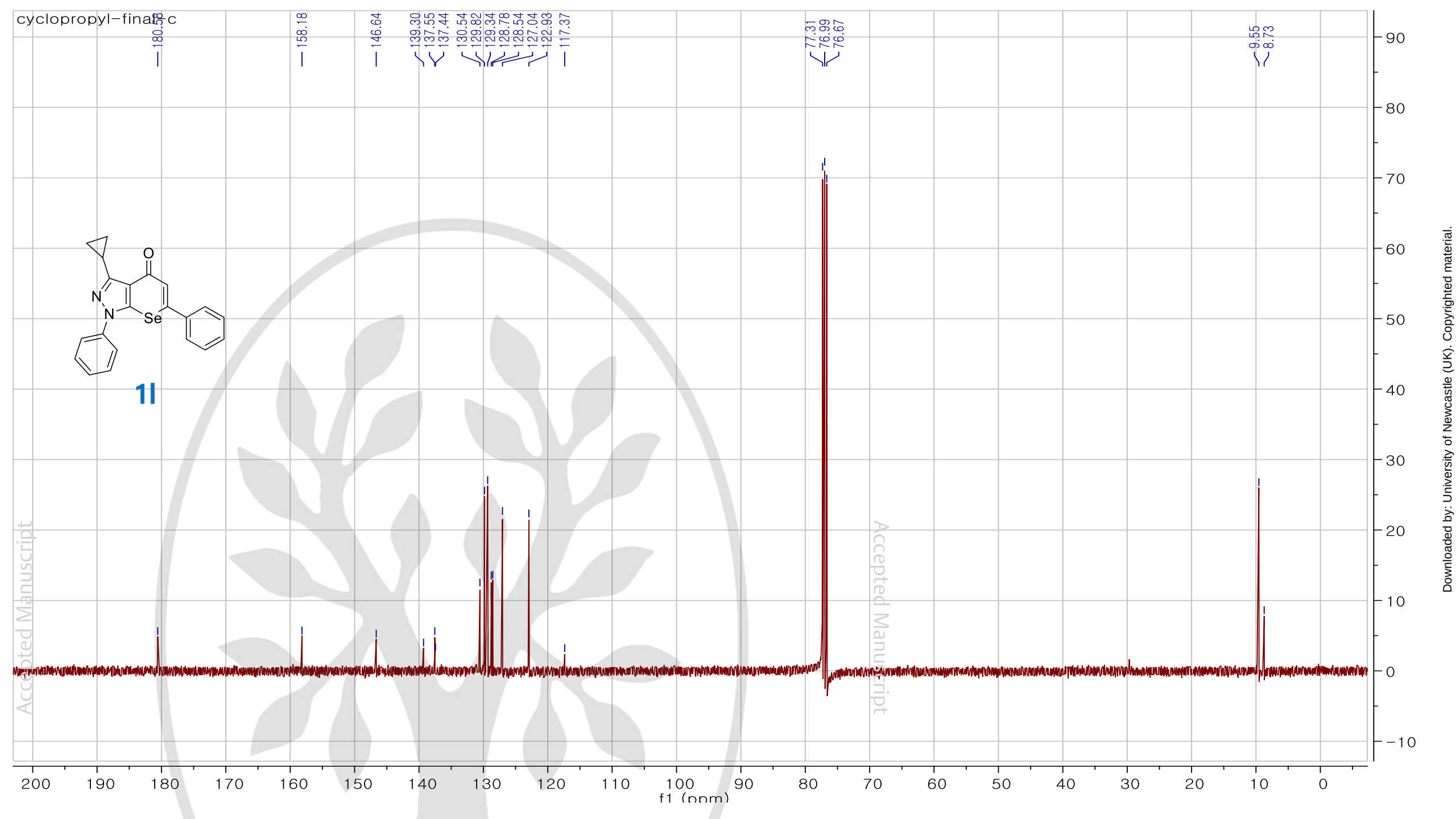

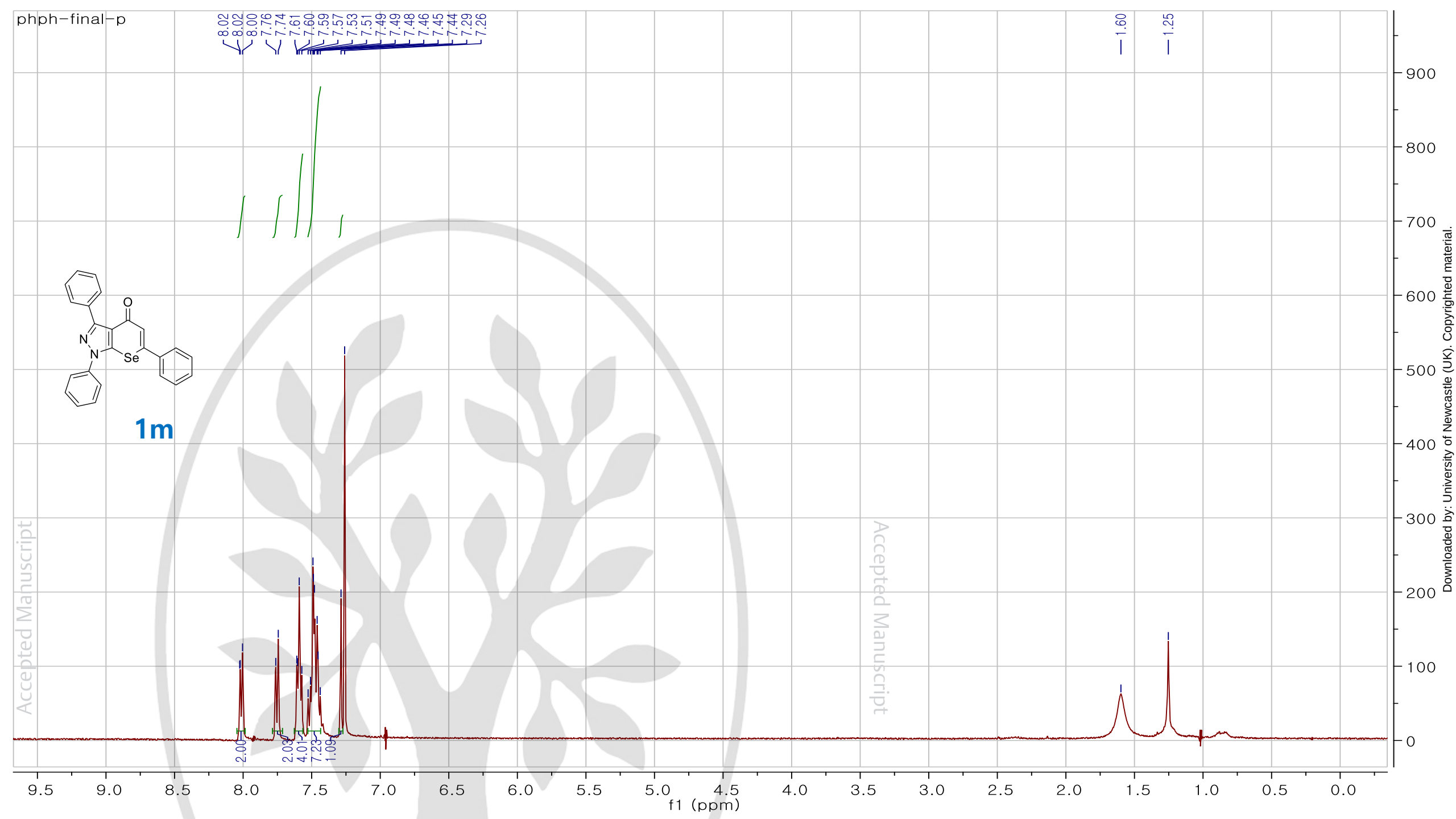
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7.60
7.59
7.57
7.53
7.51
7.49
7.49
7.48
7.46
7.45
7.44
7.29
7.26
1.60
1.25
O
N
N
Se
1m
2.00
2.03
4.01
7.23
1.09
f1 (ppm)
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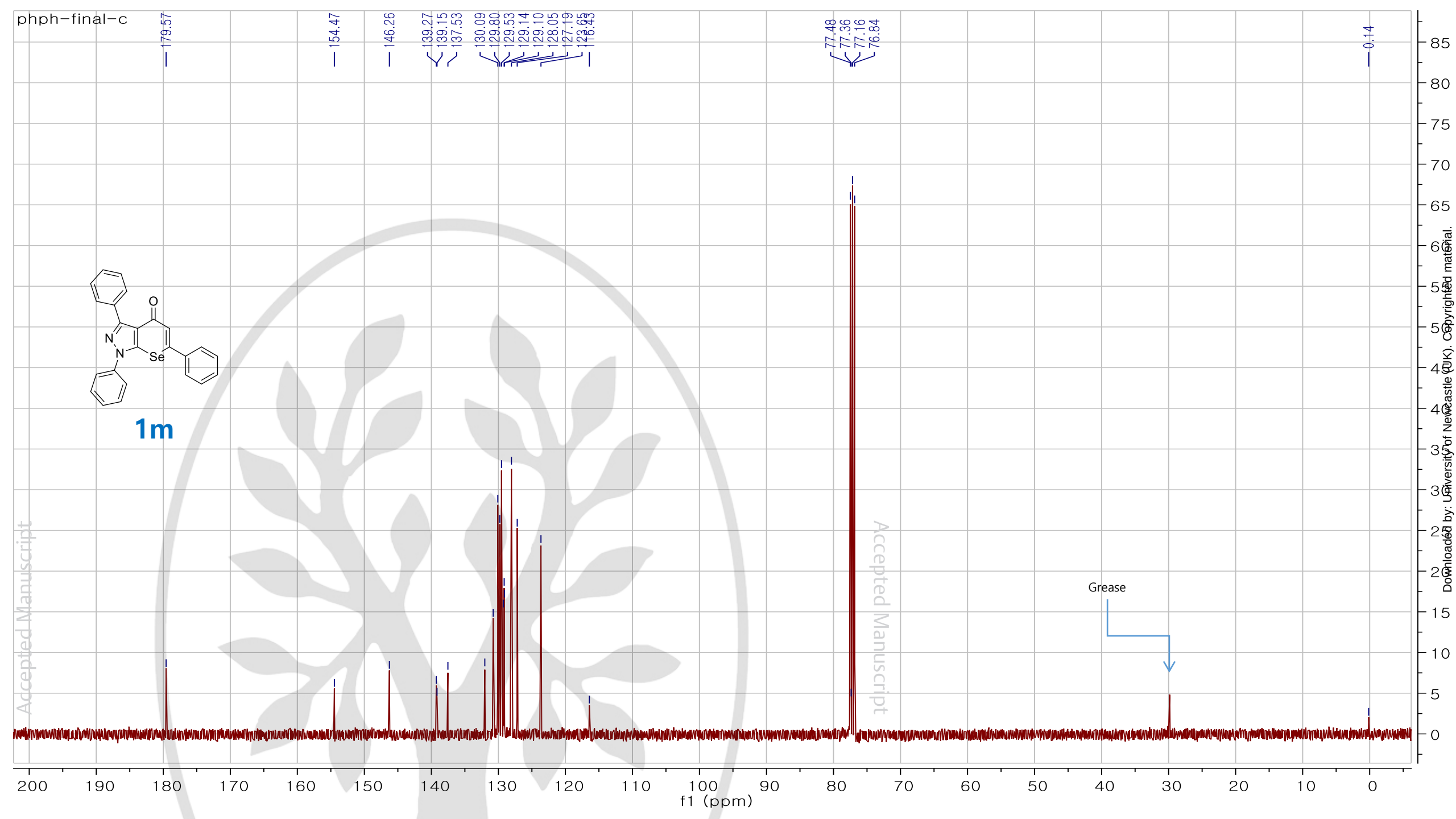
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137.53
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128.05
127.19
123.65
116.43
77.48
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77.16
76.84
0.14
O
N
N
Se
1m
Grease
f1 (ppm)
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Supporting Information

Synthesis of Selenopyrano[2,3-c]pyrazol-4(1H)-ones and Their C-H Activation

In-Hui Choi[a], Hitesh B. Jalani[a,b]*, Jin-Hyun, Jeong[a]*

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[b] Smart BioPharm, 310-Pilotplant, Incheon Techno-Park, 12-Gaetbeol-ro, Yeonsu-gu, Incheon 21999, South Korea.

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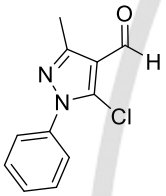
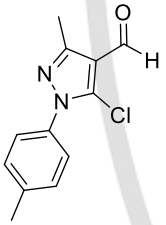
General procedure for Vilsmeier-Formylation reaction

Phosphoryl chloride (0.12 mol, 11.27 mL) was added drop-wise to an ice-cold N,N'-dimethylformamide (0.52 mol, 4 mL) then cooling was removed to reflux system, the mixture was treated with 3-methyl- 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3.0 g, 17.22 mmol) and the mixture compound was heated at 120℃ for 20 min. After cooling, the reaction mixture was poured into ice-cold water (200 mL) and stirred for 1 h. Then extracted with Ethyl acetate, Organics was washed with water and dried over Sodium sulfate, and concentrated under vacuum. The product was purified by column chromatography on silica gel.

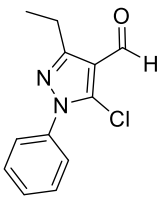


5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (5a)

The compound was prepared from 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3.0g, 17.22mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (2.5 g, 11.33 mmol, 66% yield), mp 143-145℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.98 (s, 1H), 7.53 (d, *J* = 6.2 Hz, 5H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 151.9, 137.1, 129.4, 129.4, 125.3, 117.6, 14.0; HRMS (ESI-QTOF) calcd for $C_{11}H_{10}ClN_2O$ 221.0482 ($[M + H]^+$), found 221.0480

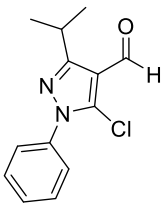


5-chloro-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbaldehyde (5b) The compound was prepared from 5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (5.0g, 26.56mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (2.6g, 11.08 mmol, 41.71% yield), mp 178-180℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.95 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 2.52 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.6, 151.3, 139.2, 134.3, 133.2, 129.6, 124.8, 117.0, 21.0, 13.6; HRMS (ESI-QTOF) calcd for $C_{12}H_{12}ClN_2O$ 235.0638 ($[M + H]^+$), found 235.0640

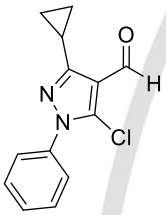


5-chloro-3-ethyl-1-phenyl-1H-pyrazole-4-carbaldehyde (5c)

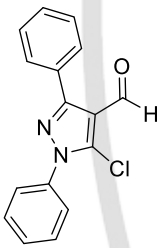
The title compound was prepared from 5-ethyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2.0g, 10.63mmol). Flash chromatography (Hexane/EtOAc = 30:1) on silica gel gave yellow solid (2.0g, 8.52 mmol, 80.21% yield), mp 57-58℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.98 (s, 1H), 7.58 - 7.46 (m, 5H), 2.96 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.9, 157.1, 137.2, 133.8, 129.4, 129.3, 125.4, 116.9, 21.7, 12.7; HRMS (ESI-QTOF) calcd for $C_{12}H_{12}ClN_2O$ 235.0638 ($[M + H]^+$), found 235.0632



5-chloro-3-isopropyl-1-phenyl-1H-pyrazole-4-carbaldehyde (5d) The title compound was prepared from 5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2.5g, 12.36mmol). Flash chromatography (Hexane/EtOAc = 30:1) on silica gel gave yellow liquid (918mg, 3.69 mmol, 29.86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.99 (s, 1H), 7.58 – 7.45 (m, 5H), 3.51 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CDCl3) δ = 183.8, 160.9, 137.3, 134.1, 129.4, 129.3, 125.4, 116.4, 27.9, 21.2; HRMS (ESI-QTOF) calcd for $C_{13}H_{14}ClN_2O$ 249.0795 ($[M + H]^+$), found 249.0797



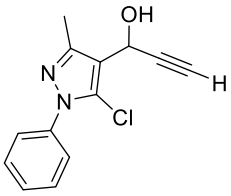
5-chloro-3-cyclopropyl-1-phenyl-1H-pyrazole-4-carbaldehyde (5e) The title compound was prepared from 5-cyclopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2.0g, 9.99mmol). Flash chromatography (Hexane/EtOAc = 20:1) on silica gel gave white solid (2.1g, 0.278 mmol, 85.23% yield), mp 82-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.03 (s, 1H), 7.53 - 7.45 (m, 5H), 2.55 (dq, *J* = 8.1, 5.4 Hz, 1H), 1.04 (dd, *J* = 8.9, 5.2 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 184.1, 157.4, 137.2, 129.4, 129.3, 125.4, 117.7, 9.0, 8.3; HRMS (ESI-QTOF) calcd for $C_{13}H_{12}ClN_2O$ 247.0638 ($[M + H]^+$), found 247.0636



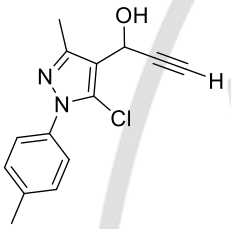
5-chloro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (5f) The title compound was prepared from 2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one (3.5g, 14.81mmol). Flash chromatography (Hexane/EtOAc = 30:1) on silica gel gave yellow solid (2.3g, 8.14 mmol, 53.94% yield), mp 106-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.07 (s, 1H), 7.83 (dd, *J* = 6.8, 2.1 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.58 - 7.46 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.9, 154.2, 136.9, 133.2, 130.7, 129.6, 129.4, 129.3, 128.9, 128.6, 125.4, 116.4; HRMS (ESI-QTOF) calcd for $C_{16}H_{12}ClN_2O$ 283.0638 ($[M + H]^+$), found 283.0641.

General procedure for Grignard reaction

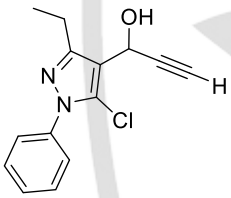
A solution of ethynylmagnesium bromide in THF (0.5 M solution, 8 mmol) was added to the solution of aldehyde 5a (6 mmol) in anhydrous tetrahydrofuran (THF, 30 mL) at 0°C. The reaction mixture was stirred at 0°C and then allowed to room temperature for another 2h. After the completion of reaction as indicated by TLC was treated with saturated aqueous ammonium chloride solution and stirred for 30 min after addition of Ethyl acetate. Organics was dried over Sodium sulfate, and concentrated under vacuum and purified by column chromatography on silica gel.



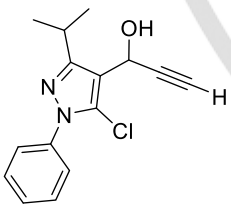
1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (4a) The title compound was prepared from **5a** (1.3g, 5.98mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (1.4g, 5.68 mmol, 96% yield), mp 87-90 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (ddd, *J* = 19.9, 7.8, 3.5 Hz, 5H), 5.43 (s, 1H), 3.74 (s, 1H), 2.56 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.9, 137.8, 129.0, 128.3, 125.9, 125.1, 116.5, 82.2, 73.8, 55.3, 13.1; HRMS (ESI-QTOF) calcd for $C_{13}H_{12}ClN_2O$ 247.0638 ($[M + H]^+$), found 247.0646



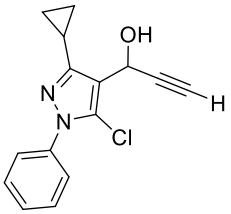
1-(5-chloro-3-methyl-1-(p-tolyl)-1H-pyrazol-4-yl)prop-2-yn-1-ol (4b) The title compound was prepared from **5b** (1.0g, 4.26mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow liquid (810mg, 3.11mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 2H), 5.49 (s, 1H), 2.62 (s, 1H), 2.59 (s, 1H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.2, 138.2, 135.3, 129.4, 125.7, 124.7, 115.8, 81.9, 73.8, 55.4, 21.0, 12.9; HRMS (ESI-QTOF) calcd for $C_{14}H_{14}ClN_2O$ 261.0795 ($[M + H]^+$), found 261.0788



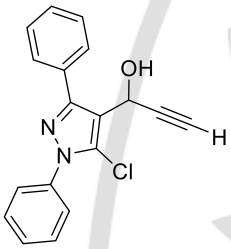
1-(5-chloro-3-ethyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (4c) The title compound was prepared from **5c** (1.0g, 4.26mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (670mg, 2.57 mmol, 60.31% yield), mp 108-110 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 6.9 Hz, 1H), 5.50 (s, 1H), 2.93 (d, *J* = 4.1 Hz, 1H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.60 (d, *J* = 2.3 Hz, 1H), 1.33 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.9, 138.1, 129.1, 128.4, 125.9, 125.2, 115.9, 82.4, 73.9, 55.6, 20.9, 13.5; HRMS (ESI-QTOF) calcd for $C_{14}H_{14}ClN_2O$ 261.0795 ($[M + H]^+$), found 261.0801



1-(5-chloro-3-isopropyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (4d) The title compound was prepared from **5d** (500mg, 2.01mmol). Flash chromatography (Hexane/ EtOAc = 3:1) on silica gel gave yellow liquid (330mg, 1.2 mmol, 59.75% yield), mp 119-120 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (ddd, *J* = 29.4, 17.9, 7.1 Hz, 5H), 5.57 (s, 1H), 3.38 (dt, *J* = 13.7, 6.9 Hz, 1H), 2.68 - 2.61 (m, 1H), 2.32 (d, *J* = 3.9 Hz, 1H), 1.37 (t, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.4, 138.1, 129.0, 128.2, 125.2, 125.2, 115.1, 74.0, 55.6, 26.9, 22.7, 21.8; HRMS (ESI-QTOF) calcd for $C_{15}H_{16}ClN_2O$ 275.0951 ($[M + H]^+$), found 275.0954



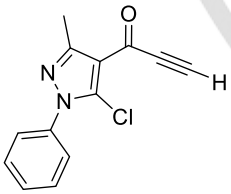
1-(5-chloro-3-cyclopropyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (4e) The title compound was prepared from **5e** (1.0g, 4.05mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave white solid (1.0g, 3.67 mmol, 90.45% yield), mp 129-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 - 7.48 (m, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.42 - 7.35 (m, 1H), 5.61 (s, 1H), 2.67 (d, *J* = 2.3 Hz, 1H), 2.35 (s, 1H), 2.21 (ddd, *J* = 10.1, 7.9, 5.4 Hz, 1H), 1.10 - 0.91 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.4, 138.2, 129.1, 128.4, 125.3, 125.2, 117.0, 82.4, 74.2, 56.0, 8.0, 7.8, 7.5; HRMS (ESI-QTOF) calcd for $C_{15}H_{14}ClN_2O$ 273.0795 ($[M + H]^+$), found 273.0815



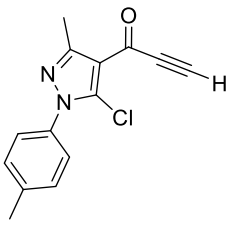
1-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)prop-2-yn-1-ol (4f) The title compound was prepared from **5f** (1.5g, 5.31mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave white solid (1.1g, 3.47 mmol, 65.32% yield), mp 195-197 °C. ^{1}H NMR (400 MHz, $cdcl_3$) δ = 7.81 - 7.76 (m, 2H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.54 - 7.42 (m, 6H), 5.68 - 5.67 (m, 1H), 2.60 (d, *J* = 2.4 Hz, 1H), 2.43 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $cdcl_3$) δ = 151.2, 138.1, 132.2, 129.2, 129.2, 128.9, 128.8, 128.7, 127.1, 125.5, 116.1, 82.1, 74.6, 56.2; HRMS (ESI-QTOF) calcd for $C_{18}H_{14}ClN_2O$ 309.0795 ($[M + H]^+$), found 309.0820

General procedure for Sodium hypochlorite-TEMPO oxidation

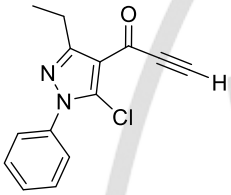
A solution of NaOCl (12%, 6 mmol) was added to the solution of NaBr (2 mmol), NaHCO3 (4 mmol), TEMPO (0.1 mmol), and propargyl alcohol **4a** (2 mmol) in CH_2Cl_2 (10 mL) at 0°C. After the completion of reaction as indicated by TLC it was treated with water. Then water and the organic layers were separated, organic was dried over Sodium sulfate, and concentrated under vacuum and purified by column chromatography on silica gel.



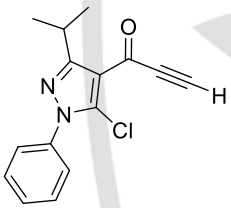
1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (3a) The title compound was prepared from **4a** (500mg, 2.03mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 10:1:2) on silica gel gave white solid (488mg, 1.99 mmol, 98% yield), mp 96-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 - 7.49 (m, 5H), 3.43 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 166.6, 152.7, 137.2, 129.5, 129.4, 125.8, 81.6, 80.9, 15.0; HRMS (ESI-QTOF) calcd for $C_{13}H_{10}ClN_2O$ 245.0482 ($[M + H]^+$), found 245.0479



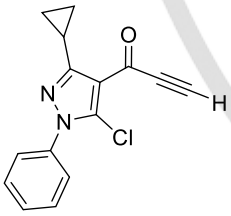
1-(5-chloro-3-methyl-1-(p-tolyl)-1H-pyrazol-4-yl)prop-2-yn-1-one (3b) The title compound was prepared from **4b** (600mg, 2.30mmol). Flash chromatography (Hexane/EtOAc = 2:1) on silica gel gave white solid (580mg, 2.24 mmol, 97% yield), mp 110-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 3.42 (s, 1H), 2.58 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 152.6, 139.7, 134.7, 132.1, 129.9, 125.6, 117.6, 81.6, 80.8, 21.4, 15.2; HRMS (ESI-QTOF) calcd for $C_{14}H_{12}ClN_2O$ 259.0638 ($[M + H]^+$), found 259.0632



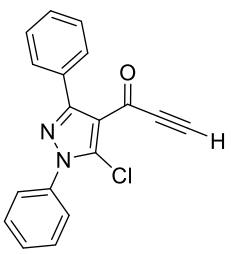
1-(5-chloro-3-ethyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (3c) The title compound was prepared from **4c** (500mg, 1.92mmol). Flash chromatography (Hexane/EtOAc = 30:1) on silica gel gave yellow solid (390mg, 1.51 mmol, 78.61% yield), mp 93-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 - 7.47 (m, 5H), 3.42 (s, 1H), 3.02 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.9, 157.9, 137.4, 132.2, 129.4, 129.4, 125.8, 117.1, 81.5, 80.7, 22.4, 12.8; HRMS (ESI-QTOF) calcd for $C_{14}H_{12}ClN_2O$ 259.0638 ($[M + H]^+$), found 259.0632



1-(5-chloro-3-isopropyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (3d) The title compound was prepared from **4d** (250mg, 0.91mmol). Flash chromatography (Hexane/ EtOAc = 3:1) on silica gel gave yellow solid (240mg, 0.88 mmol, 96.71% yield), mp 102-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 - 7.47 (m, 5H), 3.72 - 3.64 (m, 1H), 3.41 (s, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 161.6, 137.5, 132.2, 129.3, 125.9, 116.7, 81.6, 80.7, 27.8, 21.5; HRMS (ESI-QTOF) calcd for $C_{15}H_{14}ClN_2O$ 273.0795 ($[M + H]^+$), found 273.0798



1-(5-chloro-3-cyclopropyl-1-phenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (3e) The title compound was prepared from **4e** (500mg, 1.83mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 20:1:2) on silica gel gave white solid (445mg, 1.64 mmol, 89.66% yield), mp 100-103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (dt, *J* = 6.3, 3.8 Hz, 5H), 3.43 (s, 1H), 2.68 - 2.64 (m, 1H), 1.03 - 0.99 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.9, 157.7, 137.4, 131.8, 129.4, 129.3, 125.8, 118.2, 81.7, 80.8, 9.0, 8.9; HRMS (ESI-QTOF) calcd for $C_{15}H_{12}ClN_2O$ 271.0638 ($[M + H]^+$), found 271.0611



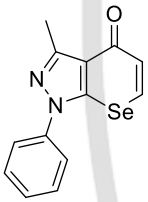
1-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)prop-2-yn-1-one (3f)

The title compound was prepared from **4f** (500mg, 1.62mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 20:1:2) on silica gel gave yellow solid (390mg, 1.27 mmol, 78.51% yield), mp 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 - 7.64 (m, 2H), 7.64 - 7.59 (m, 2H), 7.54 (tdd, *J* = 6.4, 4.5, 2.0 Hz, 3H), 7.46 - 7.42 (m, 3H), 3.13 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.0, 154.5, 137.3, 132.2, 131.6, 129.7, 129.6, 129.5, 129.4, 128.1, 125.9, 117.7, 81.1, 81.1; HRMS (ESI-QTOF) calcd for $C_{18}H_{12}ClN_2O$ 307.0638 ($[M + H]^+$), found 307.0641

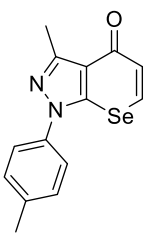
General procedure for selenopyranopyrazolones

A solution of NaHSe (1.2 mmol) prepared from selenium powder (1.1 mmol) and $NaBH_4$ (1.2 mmol) in water (10 mL) at 40°C stirred for 30 min. A solution of **3a** (1.0 mmol) in 1,4-Dioxane (5 mL) was added at once and the mixture was stirred for another 30 min. To remove the inorganics, it was extracted with ethyl acetate and washed with water. Organics was dried over Sodium sulfate, concentrated and purified by column chromatography on silica gel.

3-methyl-1-phenylselenopyrano[2,3-c]pyrazol-4(1H)-one (2a)

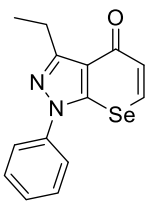


The title compound was prepared from **3a** (100mg, 0.409mmol). Flash chromatography (Hexane/EtOAc = 2:1) on silica gel gave yellow solid (100mg, 0.356 mmol, 85% yield), mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 10.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 10.2 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.3, 152.7, 139.1, 136.2, 131.0, 129.9, 129.3, 128.7, 122.8, 118.1, 14.5; HRMS (ESI-QTOF) calcd for $C_{13}H_{11}N_2OSe$ 291.0037 ($[M + H]^+$), found 291.0040



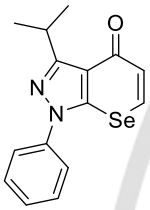
3-methyl-1-(p-tolyl)selenopyrano[2,3-c]pyrazol-4(1H)-one (2b)

The title compound was prepared from **3b** (100mg, 0.387mmol). Flash chromatography (Hexane/EtOAc = 2:1) on silica gel gave yellow solid (38.78mg, 0.102 mmol, 43% yield), mp 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78-7.76 (d, *J* = 8.0 Hz, 1H), 7.49-7.47 (d, *J* = 8.0 Hz, 2H), 7.33-7.31 (d, *J* = 8.0 Hz, 2H), 7.22-7.19 (d, *J* = 10.2 Hz, 1H), 2.73 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.5, 152.5, 139.0, 136.8, 131.1, 130.5, 129.5, 122.9, 118.0, 21.3, 14.6; HRMS (ESI-QTOF) calcd for $C_{14}H_{13}N_2OSe$ 305.0193 ($[M + H]^+$), found 305.0188



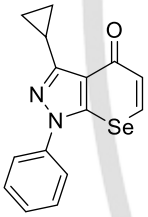
3-ethyl-1-phenylselenopyrano[2,3-c]pyrazol-4(1H)-one (2c)

The title compound was prepared from **3c** (100mg, 0.387mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (112mg, 0.369 mmol, 95.56% yield), mp 134-136 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 10.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 10.2 Hz, 1H), 3.20 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.2, 158.2, 139.4, 136.6, 131.3, 130.0, 129.2, 128.8, 123.1, 117.7, 22.3, 13.2; HRMS (ESI-QTOF) calcd for $C_{14}H_{13}N_2OSe$ 305.0193 ($[M + H]^+$), found 305.0210

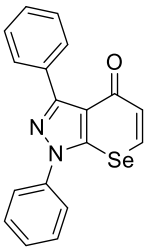


3-isopropyl-1-phenylselenopyrano[2,3-c]pyrazol-4(1H)-one (2d)

The title compound was prepared from **3d** (100mg, 0.367mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (88.2mg, 0.278 mmol, 75.82% yield), mp 175-176 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 10.2 Hz, 1H), 7.67 - 7.62 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 10.2 Hz, 1H), 3.91 – 3.83 (m, 1H), 1.40 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.2, 162.1, 139.5, 136.7, 131.5, 130.0, 128.8, 128.8, 123.2, 117.3, 28.2, 21.6; HRMS (ESI-QTOF) calcd for $C_{15}H_{15}N_2OSe$ 319.0350 ($[M + H]^+$), found 319.0353



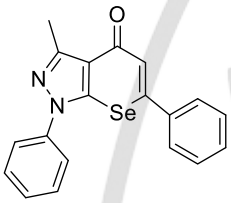
3-cyclopropyl-1-phenylselenopyrano[2,3-c]pyrazol-4(1H)-one (2e) The title compound was prepared from **3e** (100mg, 0.369mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave white solid (81mg, 0.257 mmol, 69.56% yield), mp 183-184 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 10.2 Hz, 1H), 7.62 - 7.57 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.17 - 7.14 (m, 1H), 3.06 - 2.99 (m, 1H), 1.09 - 1.07 (t, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.6, 158.5, 139.4, 136.1, 131.4, 130.0, 129.0, 128.7, 123.1, 118.5, 9.7, 9.0; HRMS (ESI-QTOF) calcd for $C_{15}H_{13}N_2OSe$ 317.0193 ($[M + H]^+$), found 317.0209



1,3-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (2f) The title compound was prepared from **3f** (100mg, 0.326mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (75mg, 0.214 mmol, 65.49% yield), mp 195-196 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 - 7.94 (m, 2H), 7.81 (d, *J* = 10.2 Hz, 1H), 7.74 - 7.69 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.49 - 7.41 (m, 3H), 7.19 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.4, 154.7, 139.2, 137.7, 132.1, 131.2, 131.1, 130.1, 129.8, 129.3, 129.1, 128.0, 123.6, 117.3; HRMS (ESI-QTOF) calcd for $C_{18}H_{13}N_2OSe$ 353.0193 ($[M + H]^+$), found 353.0178

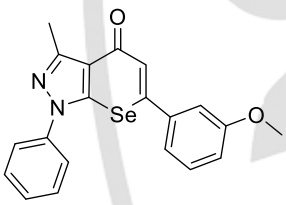
*General procedure for Pd-catalyzed direct C-H arylation of selenopyranopyrazolone with aryl halides (**1**)*

In a two neck flask fitted with reflux-condenser and a septum, $Pd(OAc)_2$ (20 mol%), XPhos (40 mol%), tri-tert-butylphosphonium hydrogen tetrafluoroborate (40 mol%), pivalic acid (0.15 mmol), Cs_2CO_3 (0.3 mmol) and selenopyranopyrazolone 1 (0.1 mmol), in DMA (0.1 M) were charged and then treated with aryl halide (0.2 mmol). The flask was set on heating block with temperature adjusted to 135°C and stirred for 15 h. After cooling, the mixture was treated with water and EtOAc, organics were dried over sodium sulfate, concentrated and purified by column chromatography on silica gel.

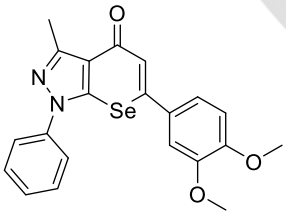


3-methyl-1,6-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (1a)

The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 5:1:2) on silica gel gave as white solid (25.5mg, 0.078 mmol, 75% yield), mp 192-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 4H), 7.50 - 7.41 (m, 4H), 7.23 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.7, 152.7, 147.3, 139.3, 137.8, 137.7, 130.8, 130.1, 129.5, 128.8, 127.2, 123.0, 117.4, 14.6; HRMS (ESI-QTOF) calcd for $C_{19}H_{15}N_2OSe$ 367.0350 ($[M + H]^+$), found 367.0347

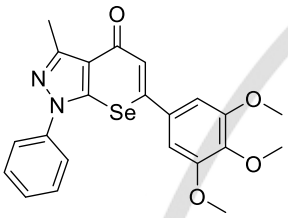


6-(3,4-dimethoxyphenyl)-3-methyl-1-phenylseleno-pyrano[2,3-c]pyrazole -4(1H)-one (1b) The heading compound was prepared from **2a** (33.6mg, 0.116 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 5:1:2) on silica gel gave white solid (23.4mg, 0.064 mmol, 64% yield), mp 222-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.21 - 7.13 (m, 2H), 7.06 (d, *J* = 1.6 Hz, 1H), 7.01 (d, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 6H), 2.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.7, 164.4, 160.4, 152.7, 147.1, 139.4, 139.1, 137.8, 130.6, 130.1, 128.8, 123.0, 119.5, 117.5, 116.4, 112.6, 55.7, 14.5; HRMS (ESI-QTOF) calcd for $C_{21}H_{19}N_2O_3Se$ 427.0561 ($[M + H]^+$), found 427.0559

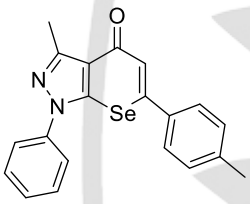


6-(3-methoxyphenyl)-3-methyl-1-phenylselenoPyrano[2,3-c]pyrazol-4(1H) -one (1c) The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave pale yellow solid (26.4mg, 0.062 mmol, 59% yield), mp 169-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.07 - 7.06 (d, 1H), 6.92-6.90 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H),

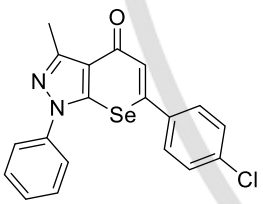
2.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.8, 152.7, 151.4, 149.8, 147.2, 139.4, 137.7, 130.4, 130.1, 128.8, 127.7, 123.1, 120.1, 117.4, 111.6, 110.0, 56.3, 56.2, 14.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}N_2O_2Se$ 397.0455 ($[M + H]^+$), found 379.0454



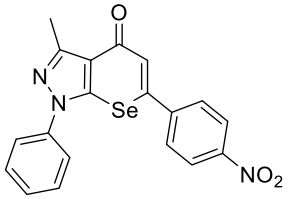
3-methyl-1-phenyl-6-(3,4,5-trimethoxyphenyl)Seleno-pyrano[2,3-c]pyrazol -4(1H)-one (1d) The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 3:1:2) on silica gel gave white solid (11.6mg, 0.025 mmol, 25% yield), mp 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.21 (s, 1H), 6.76 (s, 2H), 3.91 (s, 6H), 3.89 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.5, 153.8, 152.5, 147.2, 140.1, 139.2, 129.9, 128.7, 128.3, 122.9, 117.3, 104.4, 61.0, 56.4, 14.3; HRMS (ESI-QTOF) calcd for $C_{22}H_{21}N_2O_4Se$ 457.0667 ($[M + H]^+$), found 457.0661



6-(4-chlorophenyl)-3-methyl-1-phenylselenopyrano-[2,3-c]pyrazol-4(1H)-one (1e) The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave white solid (19.70mg, 0.052 mmol, 50% yield), mp 189-191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 6.5 Hz, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 2.78 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.8, 152.6, 147.4, 141.2, 139.4, 137.8, 134.8, 130.2, 130.0, 128.7, 128.1, 127.0, 123.0, 117.4, 21.5, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{14}ClN_2OSe$ 400.9960 ($[M + H]^+$), found 400.9961

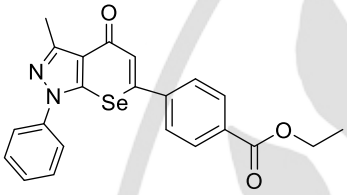


3-methyl-1-phenyl-6-(p-tolyl)selenopyrano[2,3-c] pyrazol-4 (1H)-one (1f) The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc/CH_2Cl_2 = 5:1:2) on silica gel gave yellow solid (17.0mg, 0.0425 mmol, 41% yield), mp 169-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.52 (dd, *J* = 10.5, 8.1 Hz, 2H), 7.46 (m, 3H), 7.19 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.5, 152.8, 145.7, 139.3, 137.4, 137.0, 136.2, 130.1, 129.8, 128.9, 128.5, 123.1, 117.3, 14.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}N_2OSe$ 381.0506 ($[M + H]^+$), found 381.0505

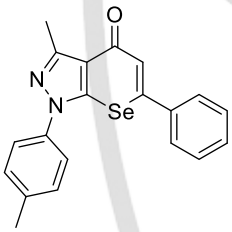


3-methyl-6-(4-nitrophenyl)-1-phenylselenopyrano-[2,3-c]pyrazol-4 (1H)-one (1g) The title compound was prepared from **2a** (30mg, 0.104 mmol).

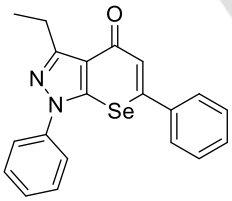
Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave yellow solid (15.9mg, 0.039 mmol, 37.36% yeild), mp 251-253 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (d, *J* = 6.9 Hz, 1H), 7.24 (s, 1H), 2.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.0, 152.9, 149.1, 143.9, 143.8, 139.2, 137.1, 130.8, 130.2, 129.1, 128.3, 124.7, 123.1, 117.3, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{14}N_3O_3Se$ 412.0200 ($[M + H]^+$), found 412.0194



ethyl 4-(3-methyl-4-oxo-1-phenyl-1,4-dihydroseleno-pyrano[2,3-c] pyrazole-6-yl)benzoate (1h) The title compound was prepared from **2a** (30mg, 0.104 mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave white solid (13.8mg, 0.032 mmol, 30% yield), mp 172-174 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.3 Hz, 2H), 7.65 (dd, *J* = 13.4, 8.2 Hz, 4H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.77 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.4, 165.7, 152.8, 145.7, 141.8, 139.3, 137.5, 132.5, 130.7, 130.1, 129.8, 128.9, 127.2, 123.1, 117.3, 61.6, 14.5, 14.5; HRMS (ESI-QTOF) calcd for $C_{22}H_{19}N_2O_3Se$ 439.0561 ($[M + H]^+$), found 439.0561



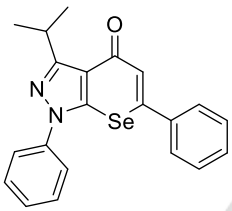
3-methyl-6-phenyl-1-(p-tolyl)selenopyrano[2,3-c]pyrazol-4(1H)-one (1i) The title compound was prepared from **2b** (30mg, 0.989 mmol). Flash chromatography (Hexane/EtOAc = 3:1) on silica gel gave yellow solid (18.24mg, 0.048 mmol, 49% yield), mp 161-163 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 10.5, 8.1 Hz, 4H), 7.46 (d, *J* = 6.6 Hz, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.22 (s, 1H), 2.76 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.7, 152.5, 147.2, 139.0, 137.9, 137.8, 136.9, 130.7, 130.6, 129.5, 128.8, 127.2, 123.0, 117.2, 21.4, 14.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}N_2OSe$ 381.0506 ($[M + H]^+$), found 381.0492



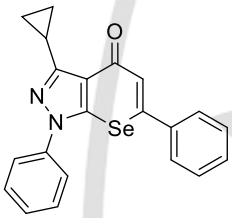
3-ethyl-1,6-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (1j)

The title compound was prepared from **2c** (30mg, 0.099 mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave yellow solid (30.70mg, 0.081 mmol, 82% yield), mp 119-120 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 7.5 Hz, 2H), 7.56 (dt, *J* = 11.8, 5.4 Hz, 4H), 7.50 - 7.41 (m, 4H), 7.23 (s, 1H), 3.21 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.4, 158.0, 147.0, 139.4, 138.0, 137.8, 130.7, 130.0, 129.5, 128.9, 128.8, 127.2, 123.1, 116.8, 22.2, 13.3; HRMS (ESI-QTOF) calcd

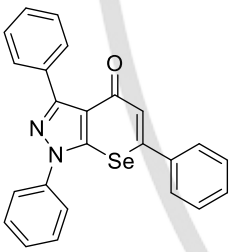
for $C_{20}H_{17}N_2OSe$ 381.0506 ($[M + H]^+$), found 381.0515



3-isopropyl-1,6-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (1k) The title compound was prepared from **2d** (30mg, 0.095 mmol). Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave yellow solid (27.10mg, 0.069 mmol, 73% yield), mp °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 - 7.66 (m, 2H), 7.59 - 7.52 (m, 4H), 7.49 - 7.42 (m, 4H), 7.24 (s, 1H), 3.90 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.3, 161.9, 146.6, 139.5, 138.1, 137.7, 130.7, 130.0, 129.5, 129.0, 128.7, 127.2, 123.2, 116.3, 28.1, 21.6; HRMS (ESI-QTOF) calcd for $C_{21}H_{19}N_2OSe$ 395.0663 ($[M + H]^+$), found 395.0661



3-cyclopropyl-1,6-diphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (1l) The title compound was prepared from **2e** (30mg, 0.095 mmol) Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave yellow solid (31.50mg, 0.080 mmol, 85% yield), mp 148-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.62 (m, 2H), 7.59 - 7.50 (m, 4H), 7.50 - 7.40 (m, 4H), 7.26 (merged with $CDCl_3$ s, 1H), 3.08 - 3.00 (m, 1H), 1.15 - 1.06 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.6, 158.2, 146.6, 139.3, 137.6, 137.4, 130.5, 129.8, 129.3, 128.8, 128.5, 127.0, 122.9, 117.4, 9.6, 8.7; HRMS (ESI-QTOF) calcd for $C_{21}H_{17}N_2OSe$ 393.0506 ($[M + H]^+$), found 393.0529



1,3,6-triphenylselenopyrano[2,3-c]pyrazol-4(1H)-one (1m) The title compound was prepared from **2f** (30mg, 0.085 mmol) Flash chromatography (Hexane/EtOAc = 5:1) on silica gel gave yellow solid (15.75mg, 0.037 mmol, 43% yield), mp °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 - 7.99 (m, 2H), 7.75 (d, *J* = 7.3 Hz, 2H), 7.59 (dd, *J* = 9.8, 4.8 Hz, 4H), 7.53 - 7.43 (m, 7H), 7.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.6, 154.5, 146.3, 139.3, 139.2, 137.5, 132.0, 130.8, 130.1, 129.8, 129.5, 129.4, 129.1, 129.0, 128.1, 127.2, 123.7, 116.4; HRMS (ESI-QTOF) calcd for $C_{24}H_{17}N_2OSe$ 429.0506 ($[M + H]^+$), found 429.0501