Base mediated synthesis of functionalized 2-(alkynyl)arylnitriles and their molecular docking study with aromatase receptor

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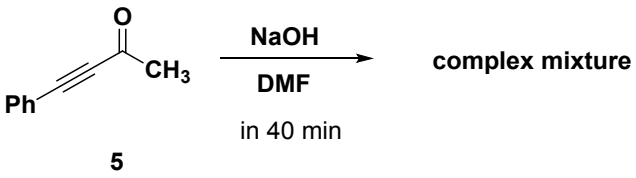
Control Experiments:

To check progress of reaction of starting material **5** was performed under above mentioned conditions to synthesize **6** and **7** without **1**.



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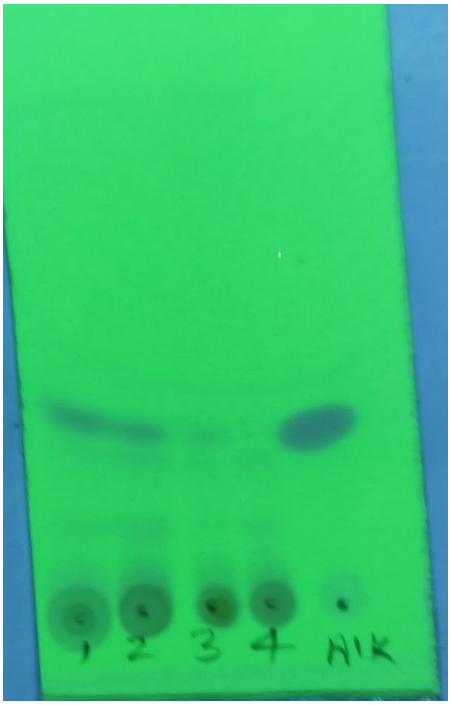


Fig. 1 TLC for the reaction of alkyne **5** with NaOH in DMF.

The progress of reaction was initially monitored by TLC at various time intervals such as 10 minute (Spot 1), 20 minutes (Spot 2), 30 minutes (Spot 3), 40 minutes (Spot 4) and starting material respectively (Figure 1) and further it was confirmed by ^{1}H NMR of reaction at these time intervals (Figure 2). It was observed that within 40 minute starting material **5** decomposes under these reaction conditions.

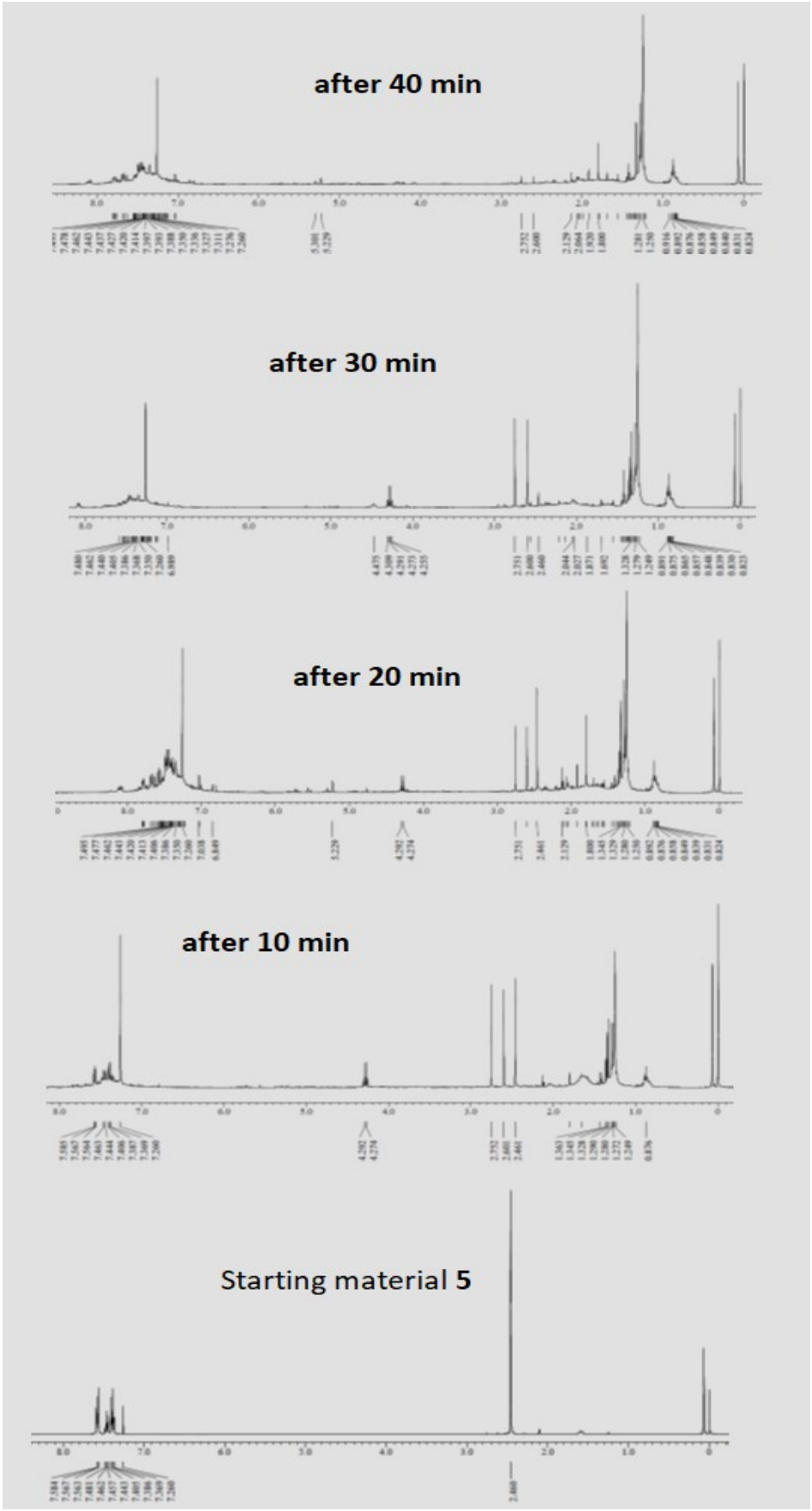


Fig. 2 ^{1}H NMR after different time intervals.

Crystallization procedure (solvent evaporation method): Slow evaporation of a solution of dark-yellow solid **6a** in ethyl acetate: hexanes (1:3) at low-temperature yield white blocks suitable for X-ray analysis. Single crystal diffraction data for **6a** were collected at 298 K temperature with an Oxford XCalibur CCD diffractometer equipped with a graphite monochromatic Mo-Kα radiation (λ = 0.71073 Å).[1] Data reduction was performed with the CrysAllis-PRO.[1] The structure was solved by SHELXT program and refined on F2 using all data by full-matrix least-squares procedures with SHELXL-2014/7 and incorporated in the OLEX2 crystallographic package.[3] The hydrogen atoms were placed at the calculated positions and included in the last cycles of the refinement. All calculations were done using the WinGX software package[4-5] The graphics for publication were prepared by using Mercury software. Crystallographic data collection and structure solution parameters are summarized in Table 1.

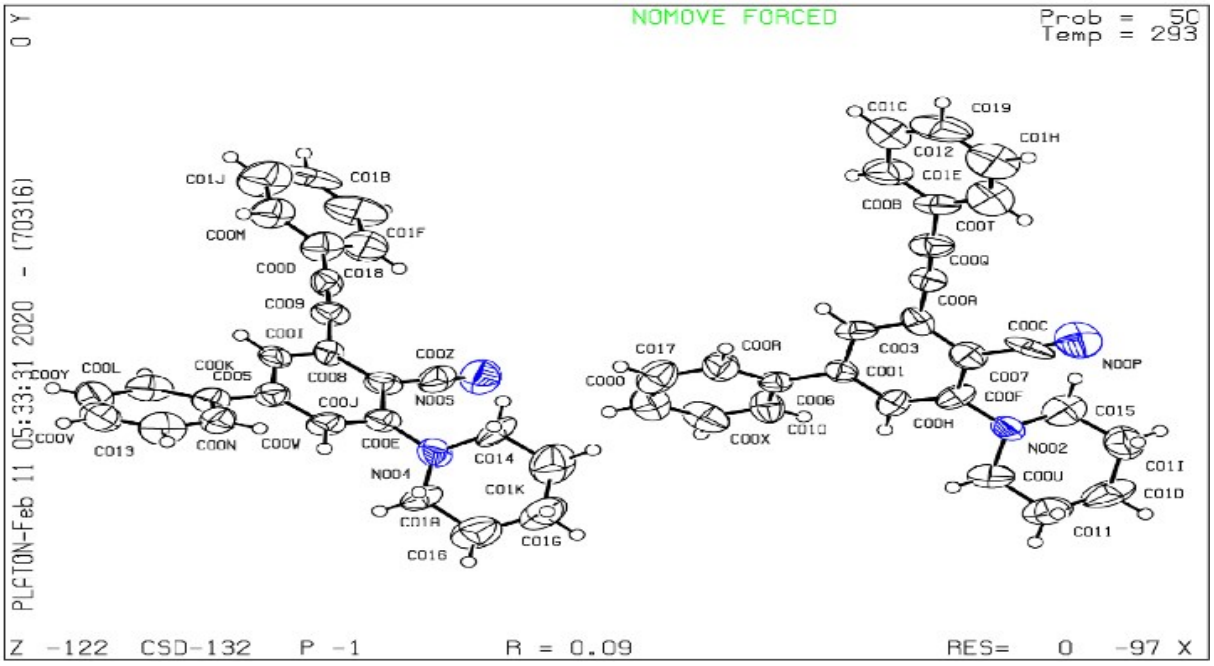


Figure 1. ORTEP diagram of **6a**; thermal ellipsoids are drown at the 50% probability level.

Table 1: Crystallographic data of **6a**

Empirical formula	$C_{26}H_{22}N_2$
CCDC	2059201
Formula weight	362.46
Temperature/K	293
Crystal system	triclinic
Space group	P-1
a/Å	9.9245(14)
b/Å	10.0171(14)
c/Å	c=20.572(3)
α/°	90
β/°	93.914(13)
γ/°	90
Volume/Å^3	2040.4(5)
Z	4
ρ_{calc}g/cm^3	1.180
μ/mm^{-1}	0.069
F(000)	768.0
Crystal size/mm^3	0.5 × 0.5 × 0.5
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	6.86 to 49.7
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -28 ≤ l ≤ 28
Reflections collected	30681
Independent reflections	3804 [R_{int} = 0.189, R_{sigma} = 0.6541]
Data/restraints/parameters	3804/34/505
Goodness-of-fit on F^2	0.897
`Final R indexes [I>=2σ (I)]	R1 = 0.0891, wR2 = 0.1858
Final R indexes [all data]	R_1 = 0.2237, wR_2 = 0.2684
Largest diff. peak/hole / e Å^{-3}	0.61/-0.67

Docking Studies (Methodology)

Molecular modeling studies of alkyne derivatives were performed using Maestro 10.2, (Schrödinger, LLC, New York, NY, 2015) molecular modeling software. The 2D structures of all the synthesized compounds were drawn using ChemBio-office suite Ultra v12.0 (www.cambridgesoft.com). Ligprep module of Schrödinger was used to generate the 3D structures with the lowest energy. Partial atomic charges were computed using the OPLS_2005 force field. The correct Lewis structure, tautomers and ionization states (pH 7.0 ± 2.0) for each of the ligands were generated and optimized with default settings (Ligprep 2.5, Schrödinger, LLC, New York, NY, 2015). The 3D crystal structures of human anticancer targets aromatase (PDB ID: 3EQM; resolution 2.90Å) [**2,3**], were retrieved from protein data bank (www.rcsb.org). The proteins were prepared for docking using Protein Preparation Wizard (Maestro 10.2 Schrödinger, LLC, New York, NY, 2015). Bond order and formal charges were assigned and hydrogen atoms were added to the crystal structure. Further to refine the structure OPLS-2005 force field parameter was used to alleviate steric clashes. The location of co-crystalized ligand Androstenedione structures were used for the center and size of the receptor grid, which was generated using Glide module (Schrödinger, LLC, New York, NY, 2015) with default settings for all parameters. The grid size was chosen sufficiently large to include all active site residues involved in substrate binding. All ligand conformers were docked to each of the receptor grid files using Glide extra precision (XP) mode. Default settings were used for the refinement and scoring. PyMOL software were employed to visualize ligand-protein interactions.

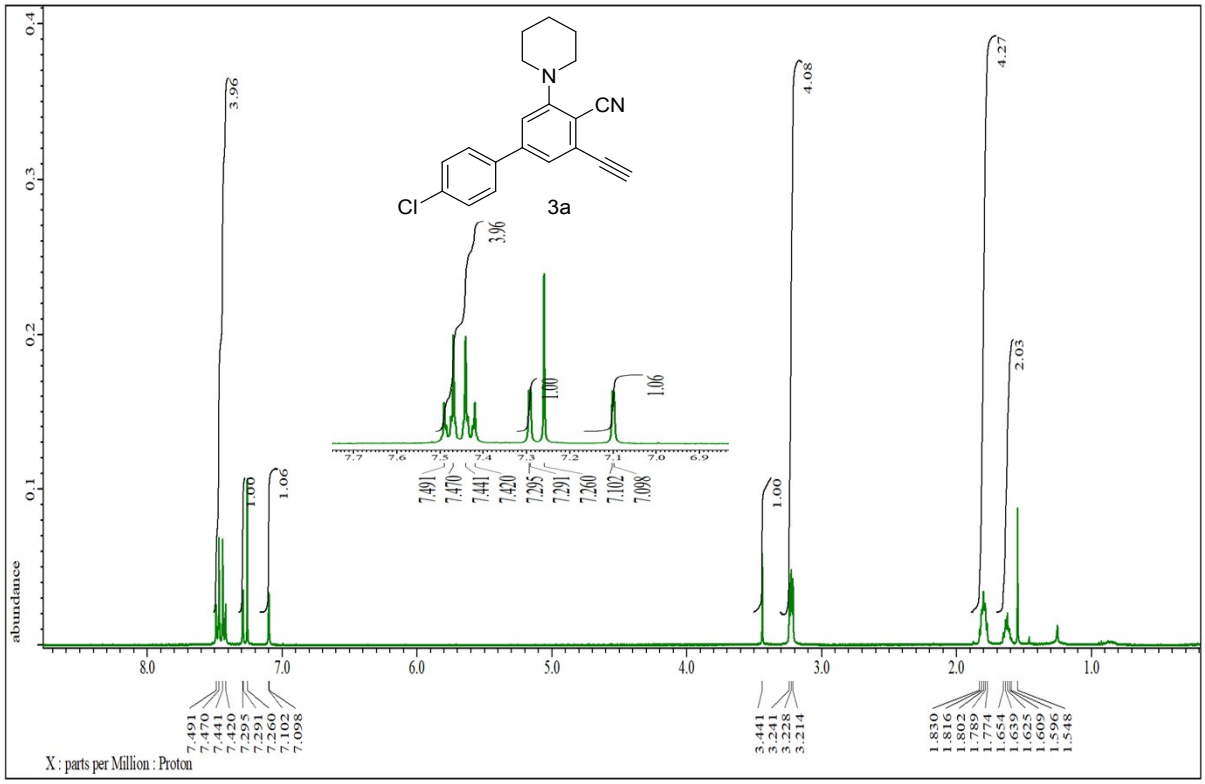
S. No.	**Docking Results with Human Receptor Aromatase**	
Compounds	XP G-Score	Glide Energy
7a	**-8.47**	**-59.83**
6b	**-8.32**	**-56.96**
6a	-8.14	-35.06
7e	-8.86	-47.92
6i	-8.47	-55.57
7d	-8.40	-48.28
6g	-8.27	-52.37

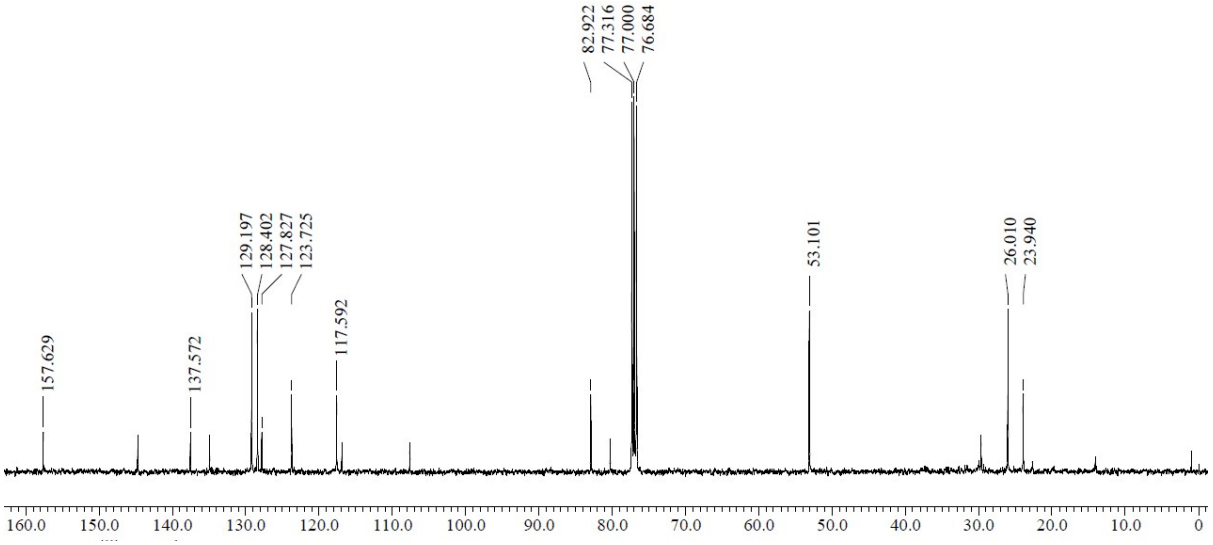
6l	-7.96	-55.08
6e	-7.89	-54.22
6j	-7.75	-48.28
6d	-7.70	-49.98
6c	-7.52	-54.13
6f	-7.49	-55.82
6h	-7.44	-44.82
6k	-7.11	-53.28
7b	-7.07	-52.12
7c	-6.45	-53.06
Doxorubicin	-8.43	-58.62
Tamoxifen	-5.14	-56.03

Table S1. Glide docking energies and docking scores for most active functionalized alkyne derivatives, along with the reference compounds, in human aromatase receptor.

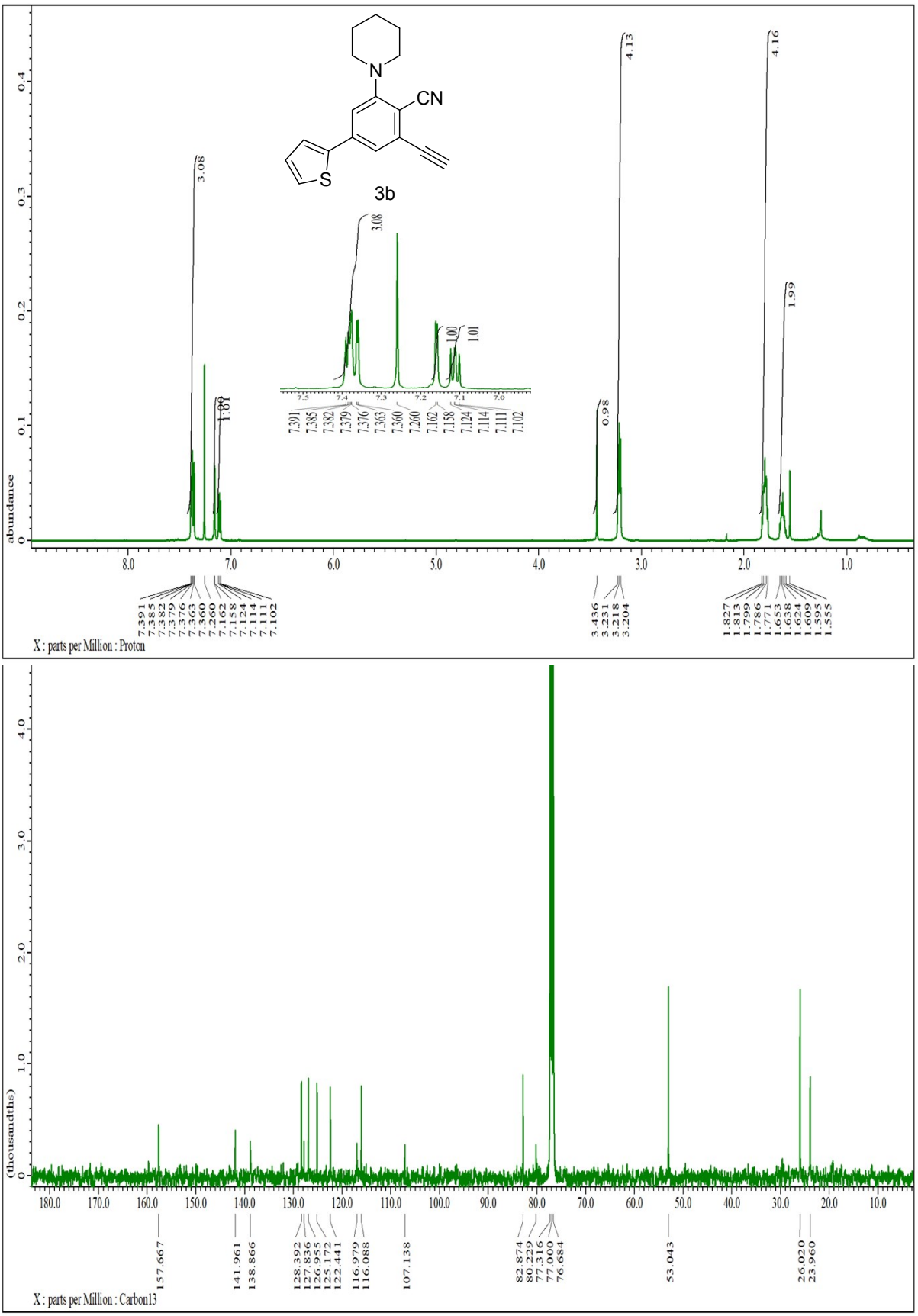
Product data

^{1}H and ^{13}C Spectra of compounds

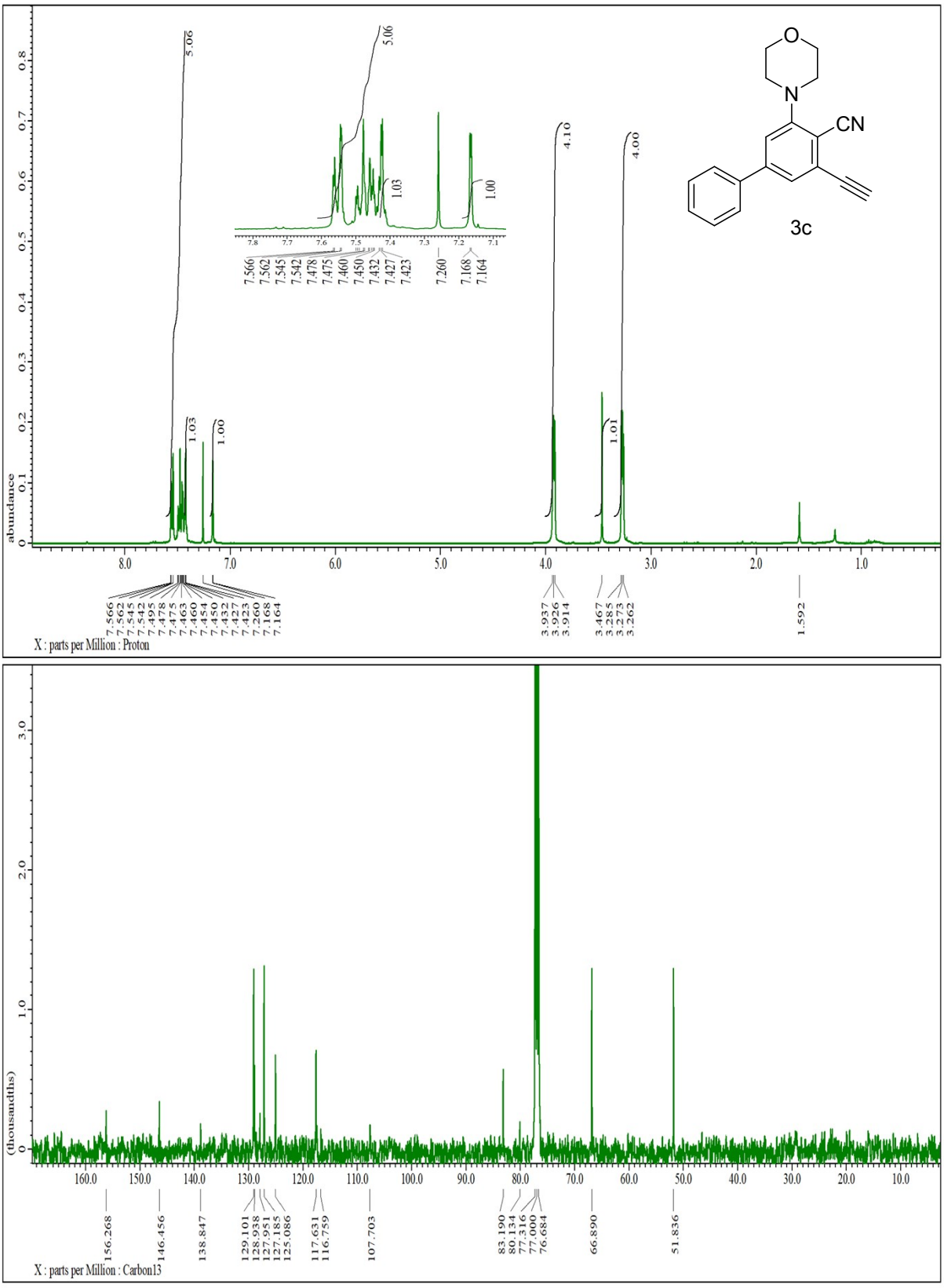




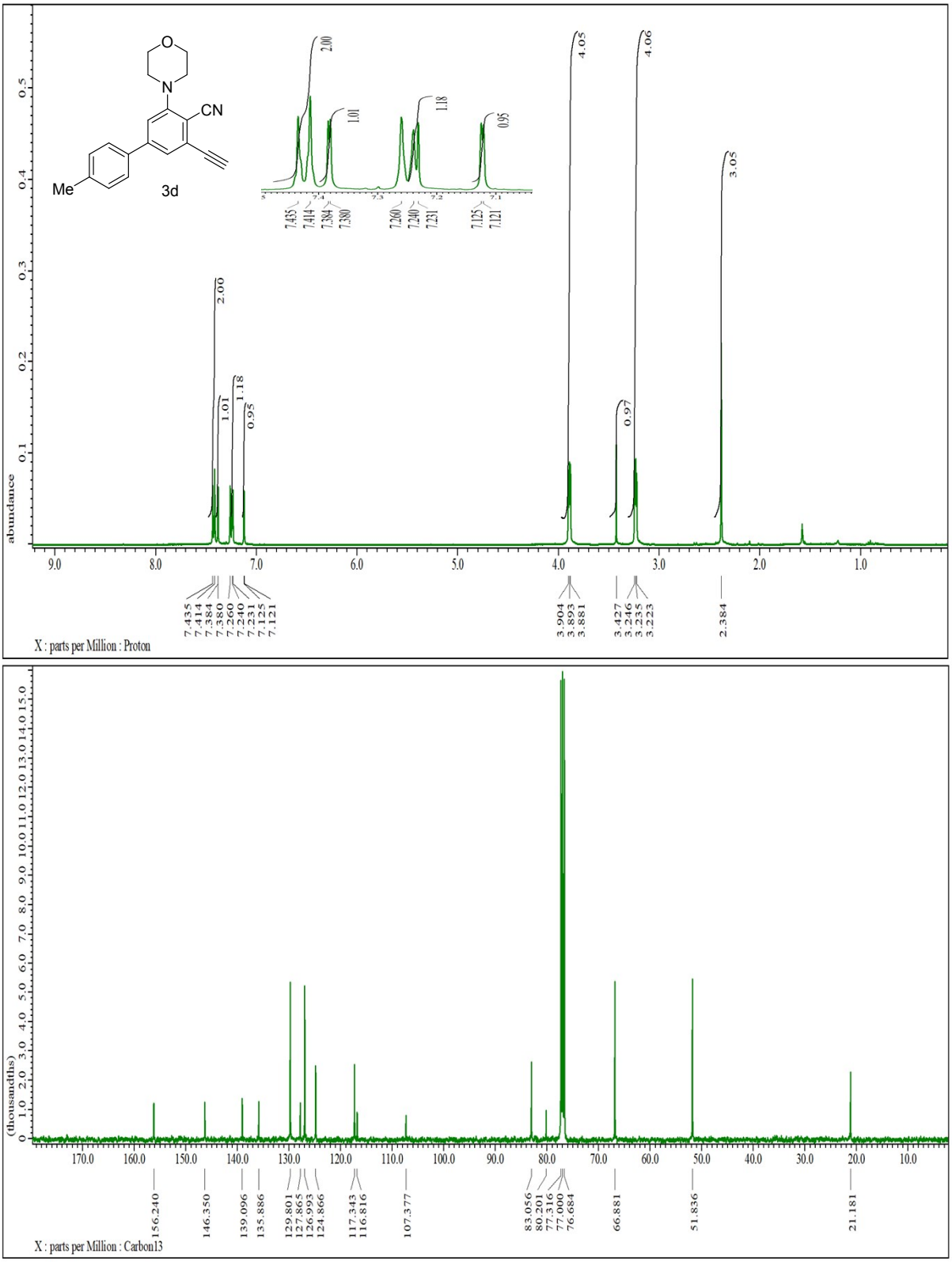
^{1}H NMR and ^{13}C NMR of 4'-chloro-3-ethynyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.



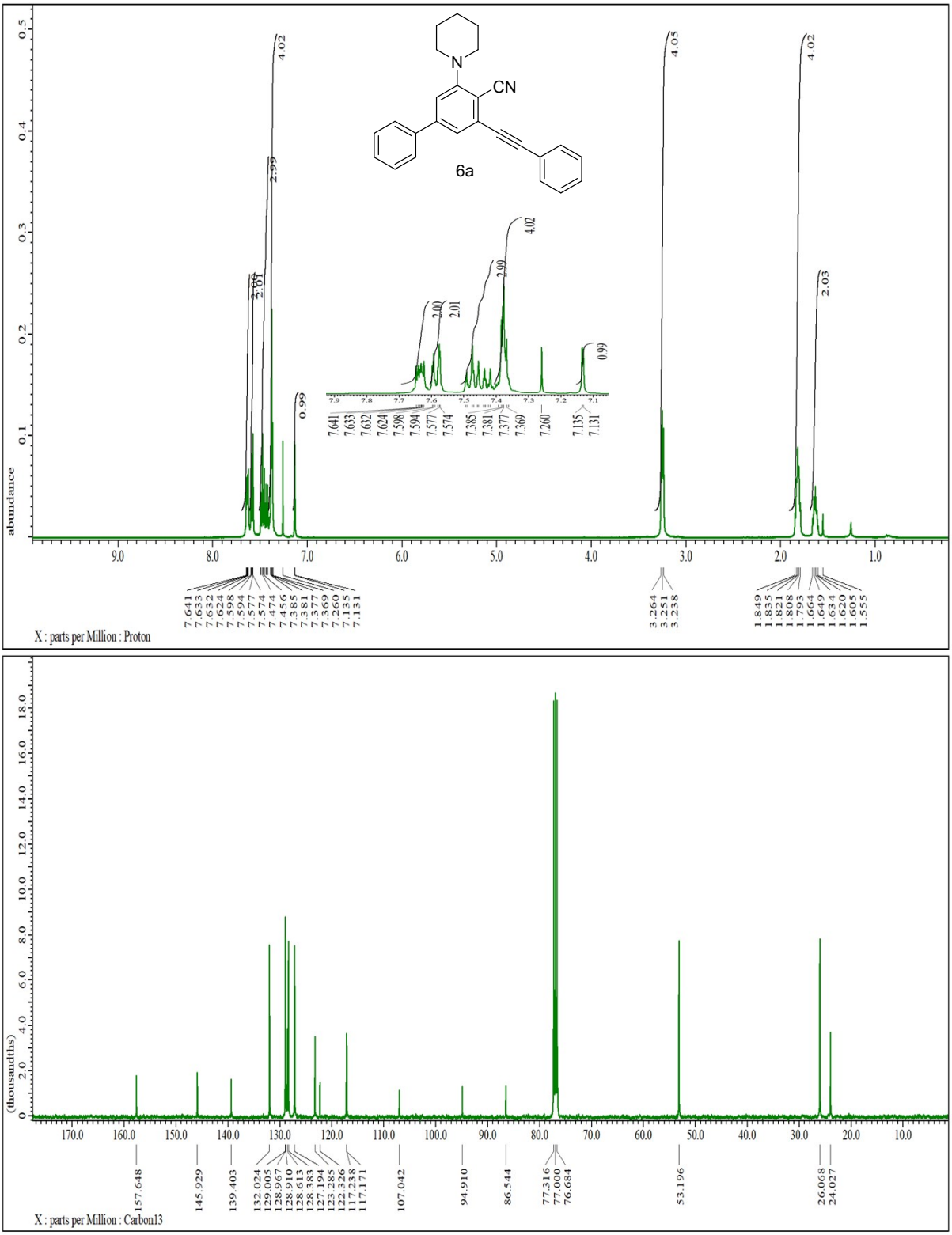
^{1}H NMR and ^{13}C NMR of 2-ethynyl-6-(piperidin-1-yl)-4-(thiophen-2-yl)benzonitrile.



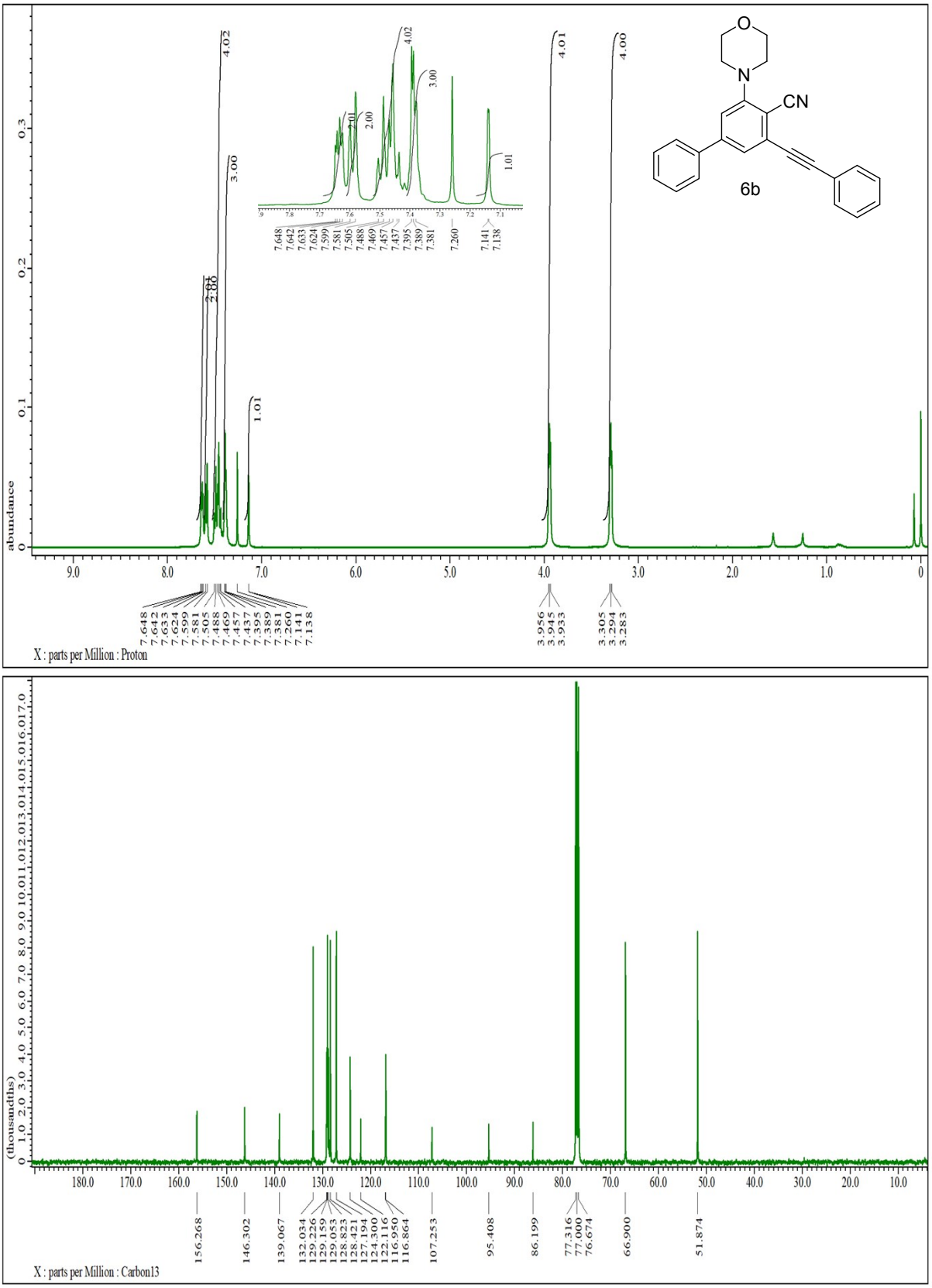
^{1}H NMR and ^{13}C NMR of 3-ethynyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile.



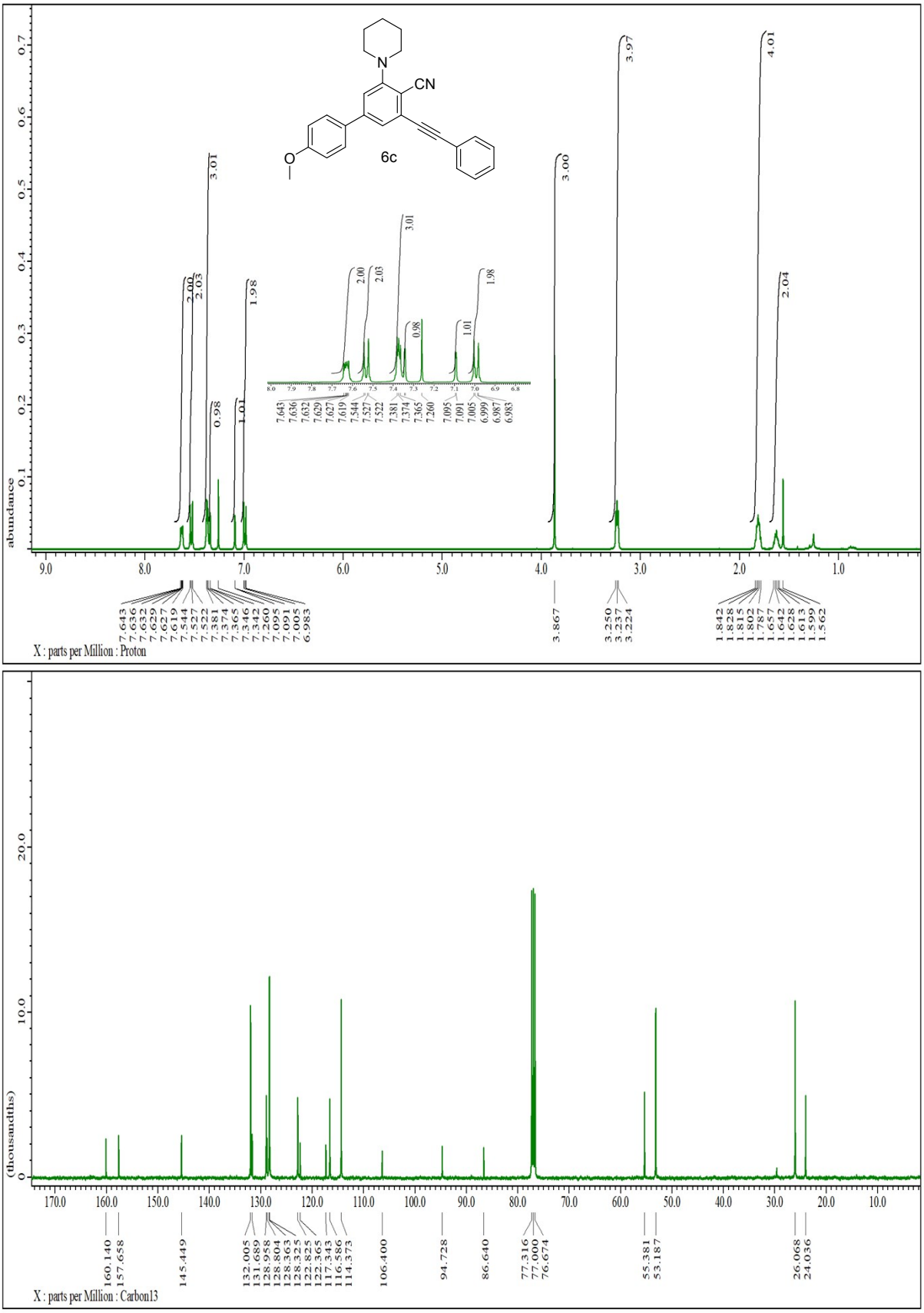
^{1}H NMR and ^{13}C NMR of 3-ethynyl-4'-methyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile.



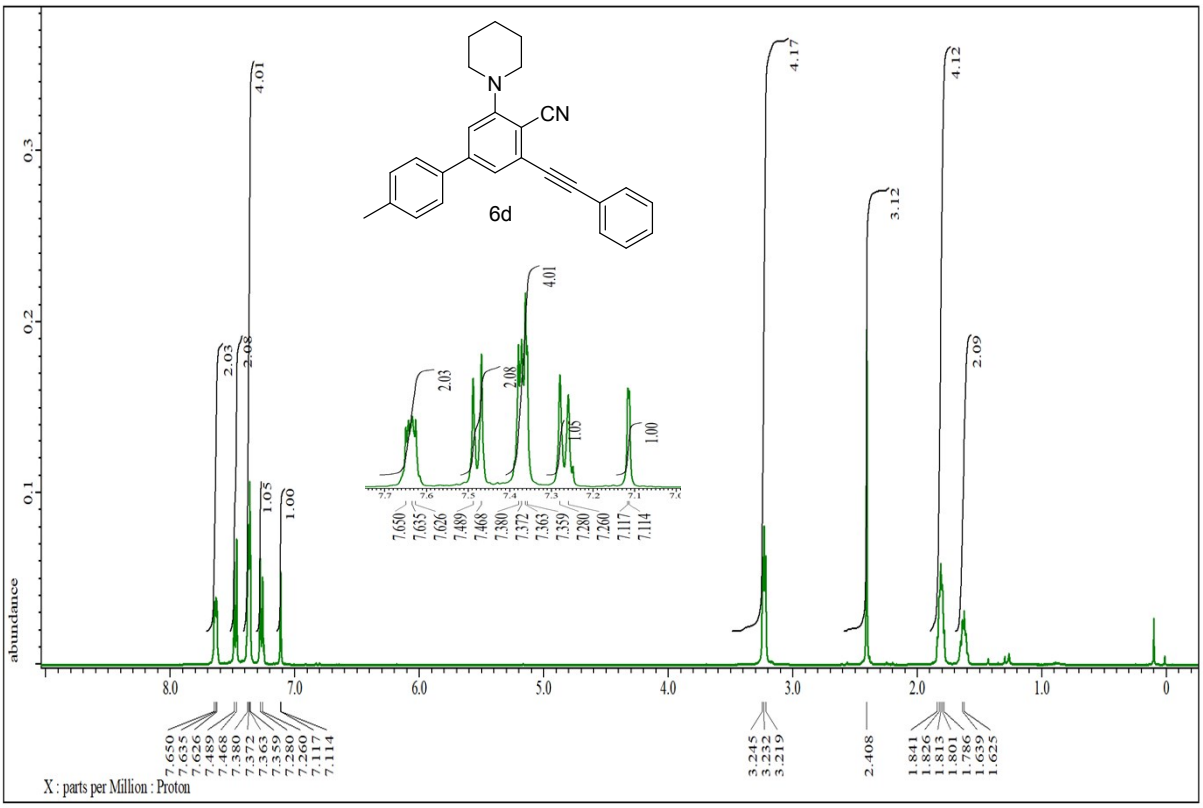
^{1}H NMR and ^{13}C NMR of 3-(phenylethynyl)-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.

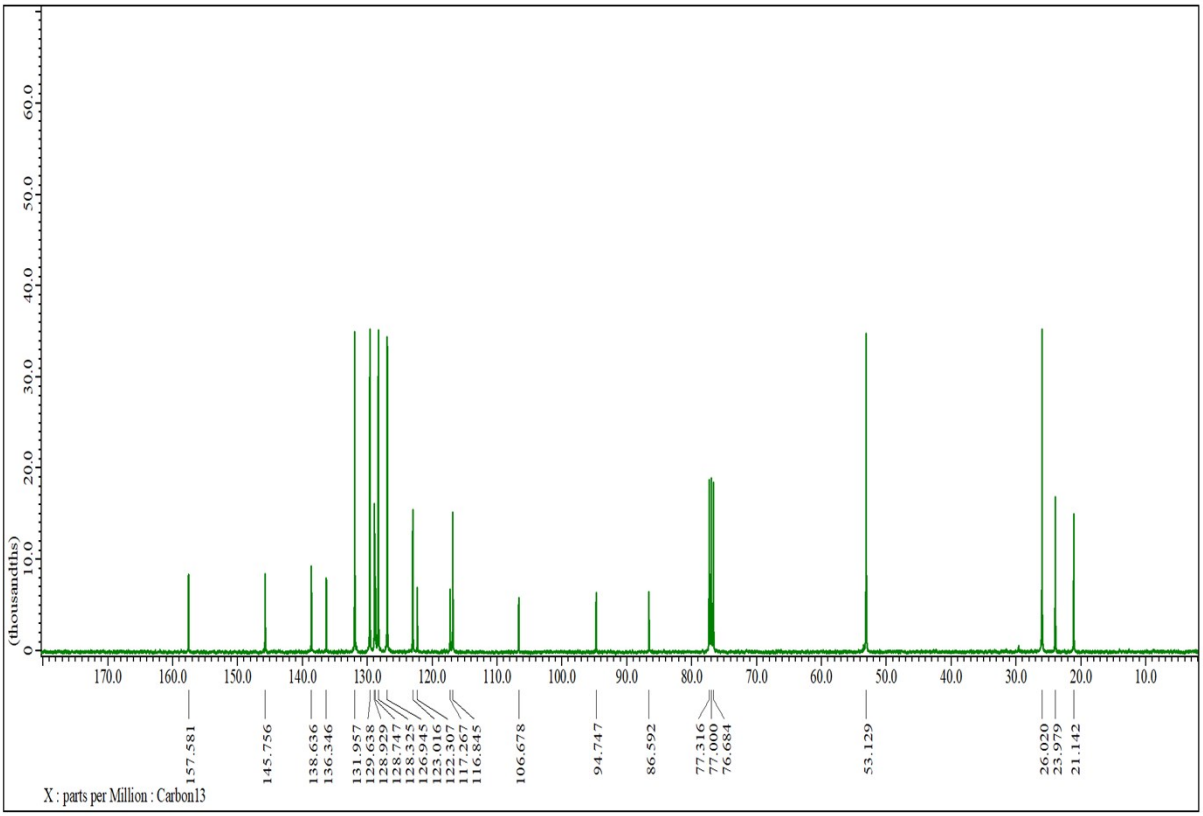


^{1}H NMR and ^{13}C NMR of 3-morpholino-5-(phenylethynyl)-[1,1'-biphenyl]-4-carbonitrile.

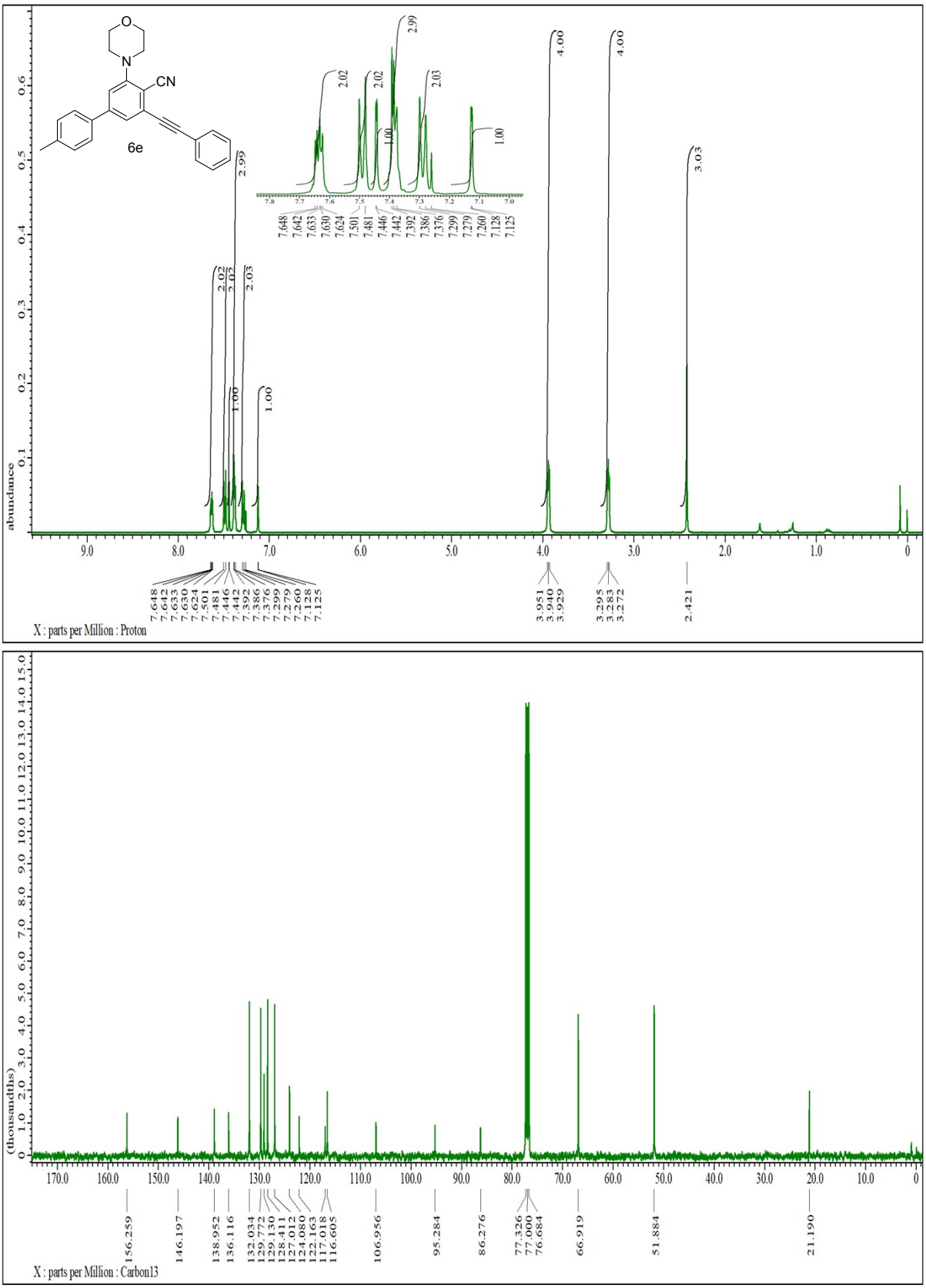


^{1}H NMR and ^{13}C NMR of 4'-methoxy-3-(phenylethynyl)-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.

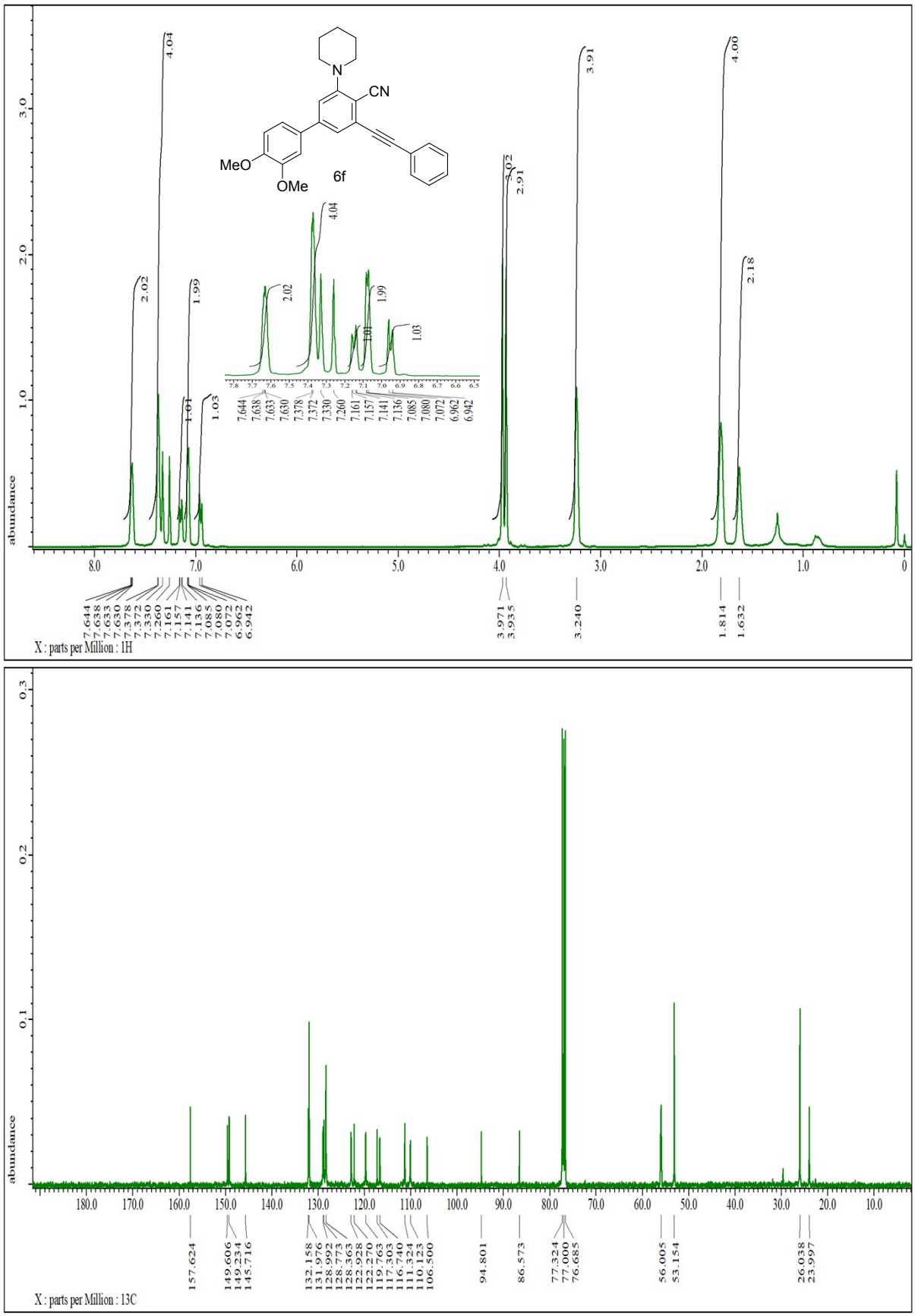




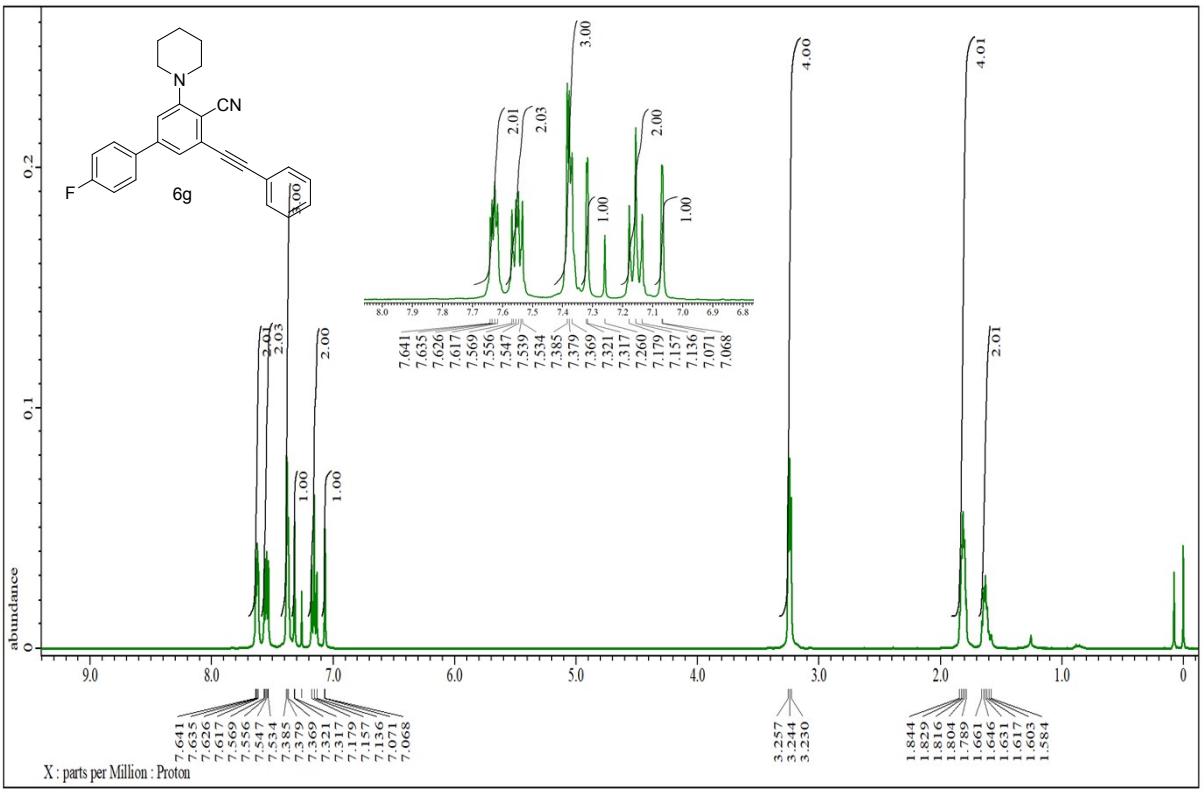
^{1}H NMR and ^{13}C NMR of 4'-methyl-3-(phenylethynyl)-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.

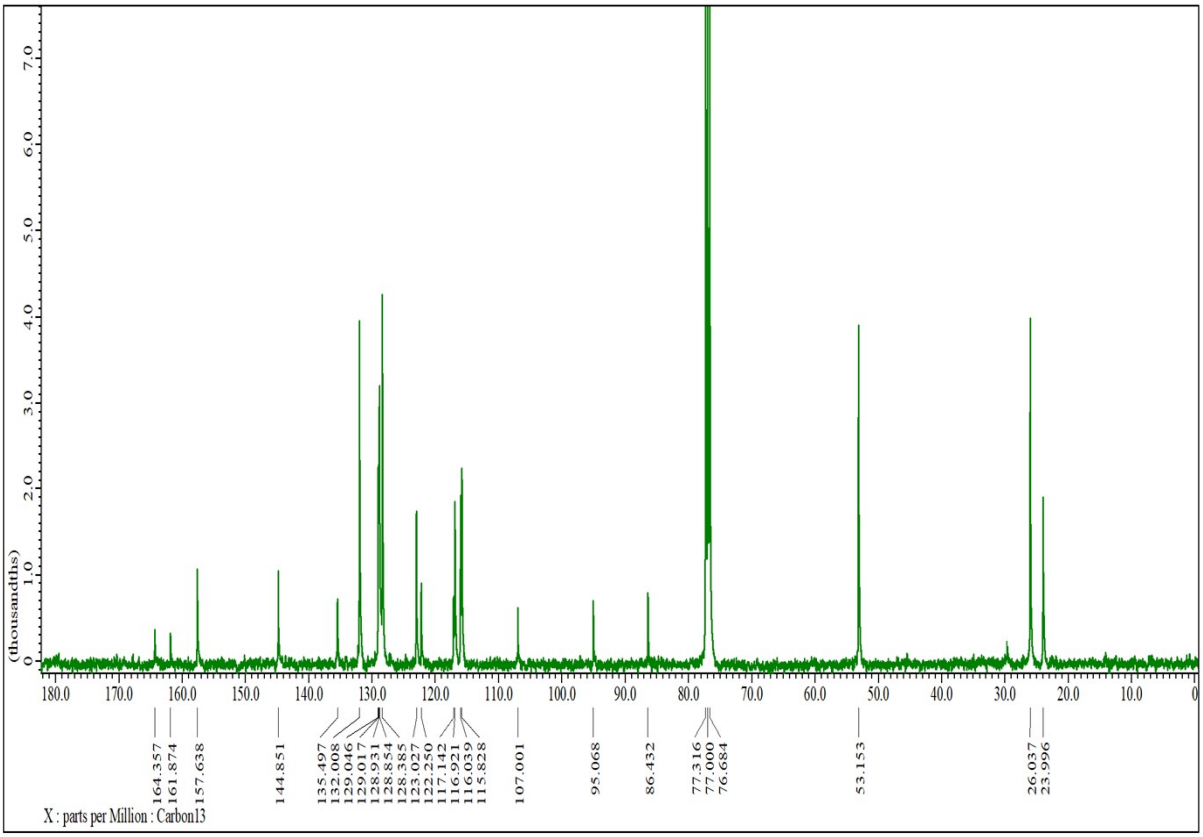


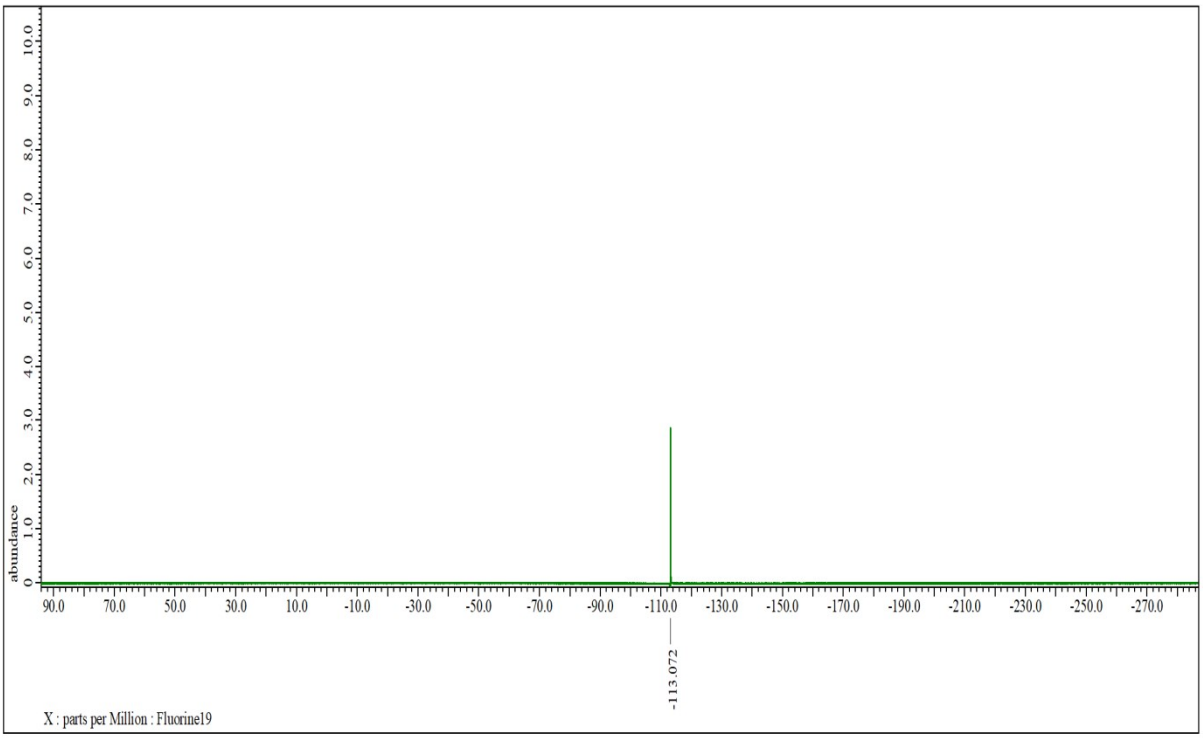
^{1}H NMR and ^{13}C NMR of 4'-methyl-3-morpholino-5-(phenylethynyl)-[1,1'-biphenyl]-4-carbonitrile.



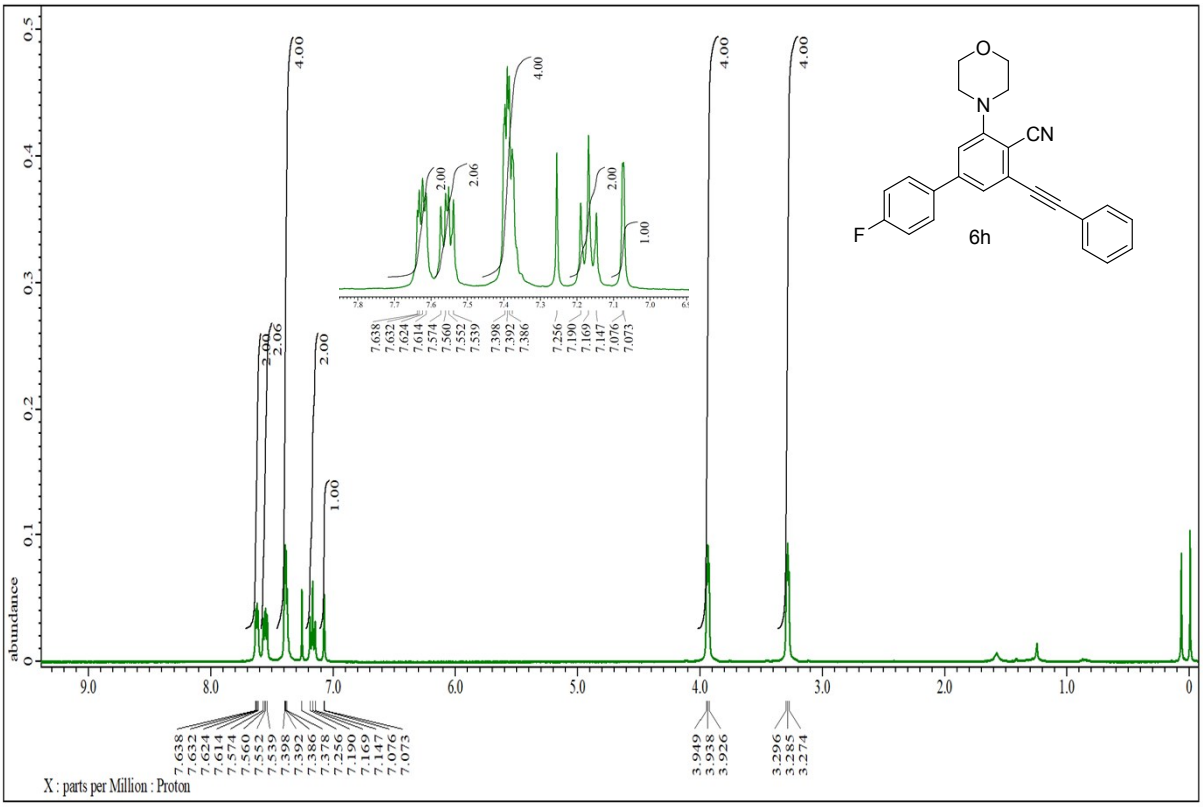
^{1}H NMR and ^{13}C NMR of 3, 4'-dimethoxy-3-(phenylethynyl)-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.

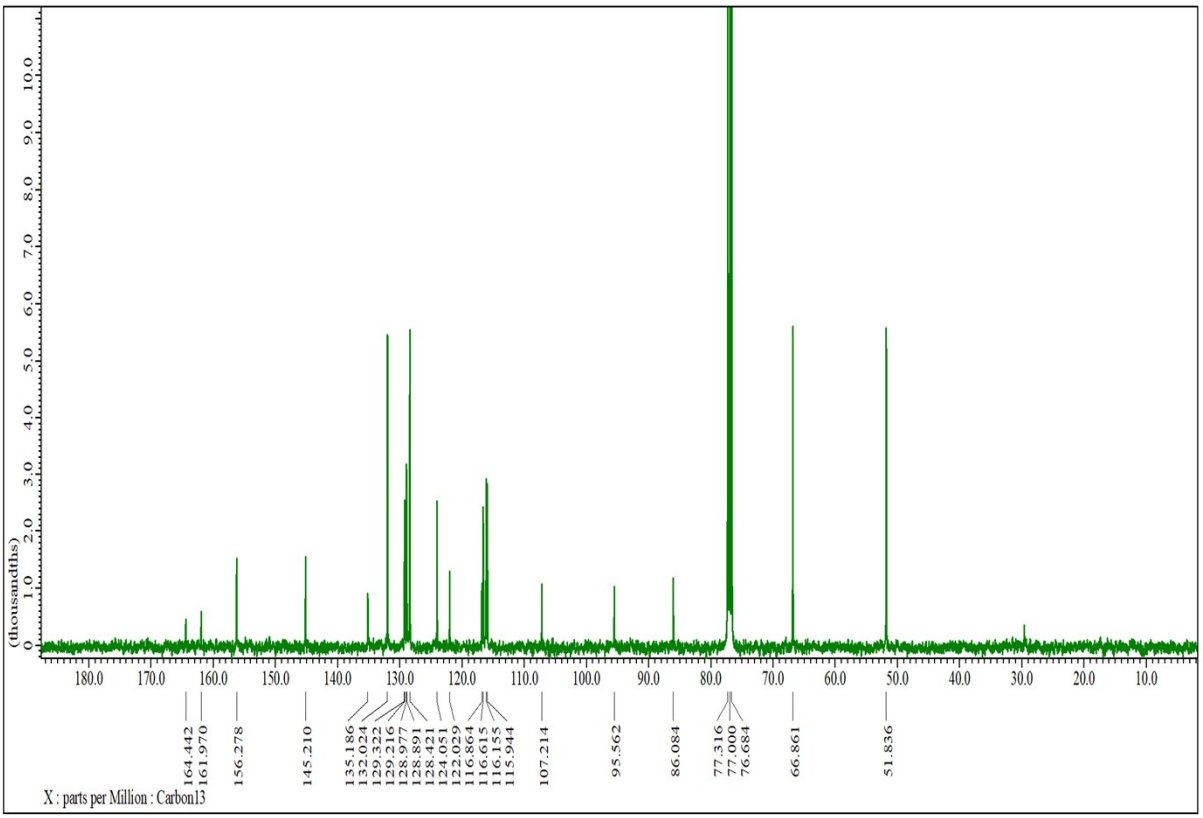

N
CN
F
6g
abundance
X : parts per Million : Proton

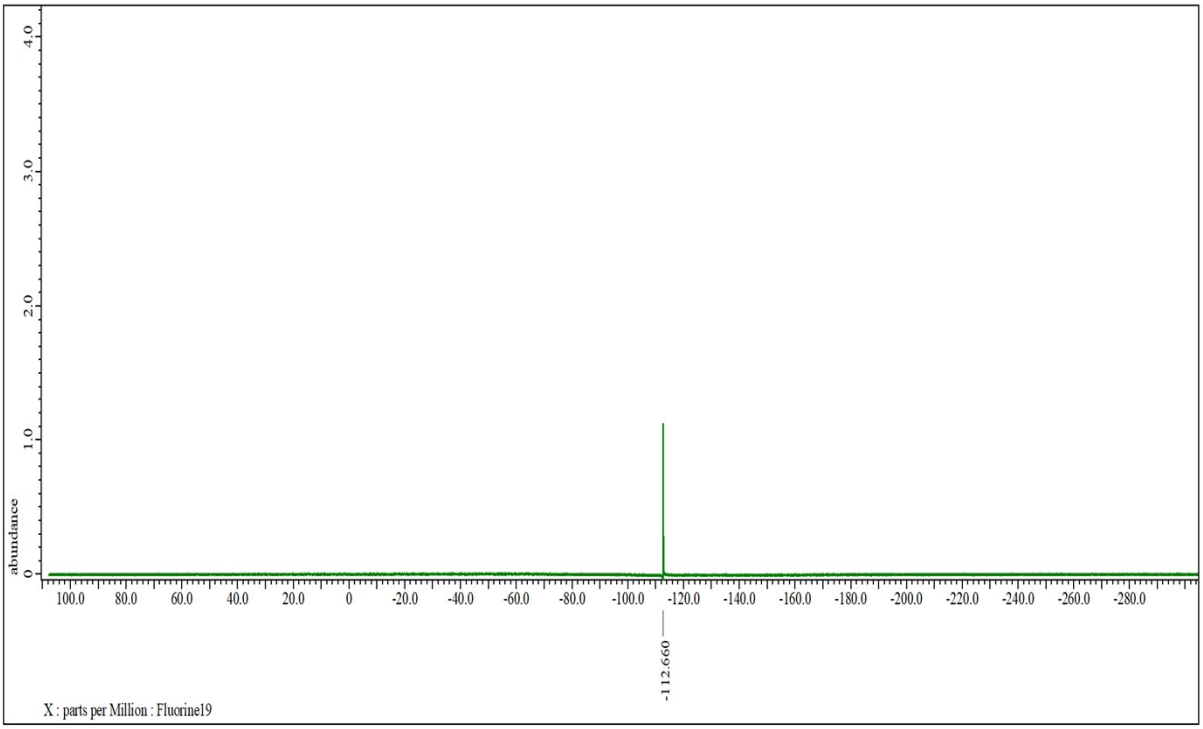

(thousandths)
X : parts per Million : Carbon13



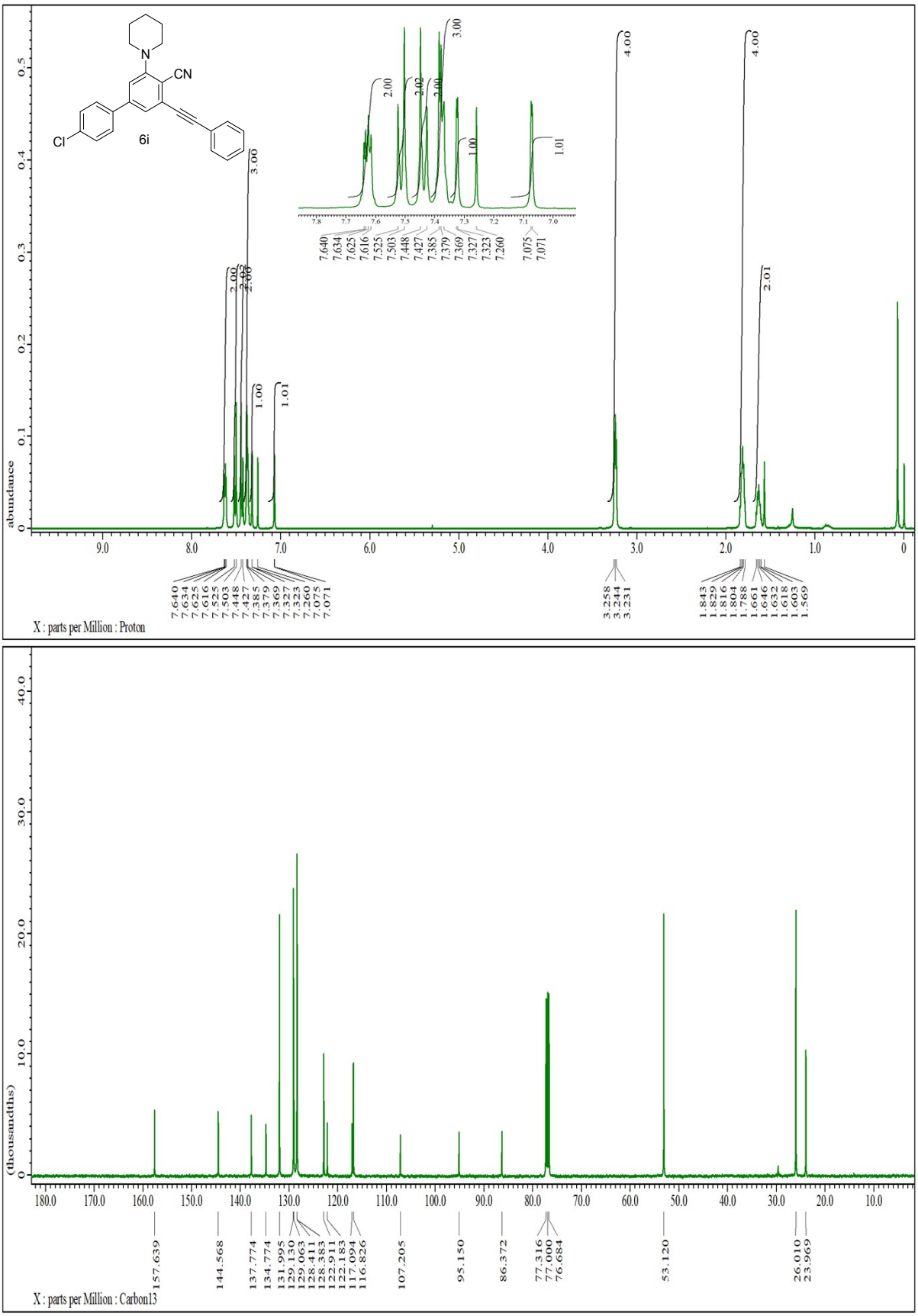
^{1}H NMR, ^{13}C NMR and ^{19}F NMR of 4'-fluoro-3-(phenylethynyl)-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile.







^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS of 4'-fluoro-3-morpholino-5-(phenylethynyl)-[1,1'-biphenyl]-4-carbonitrile.



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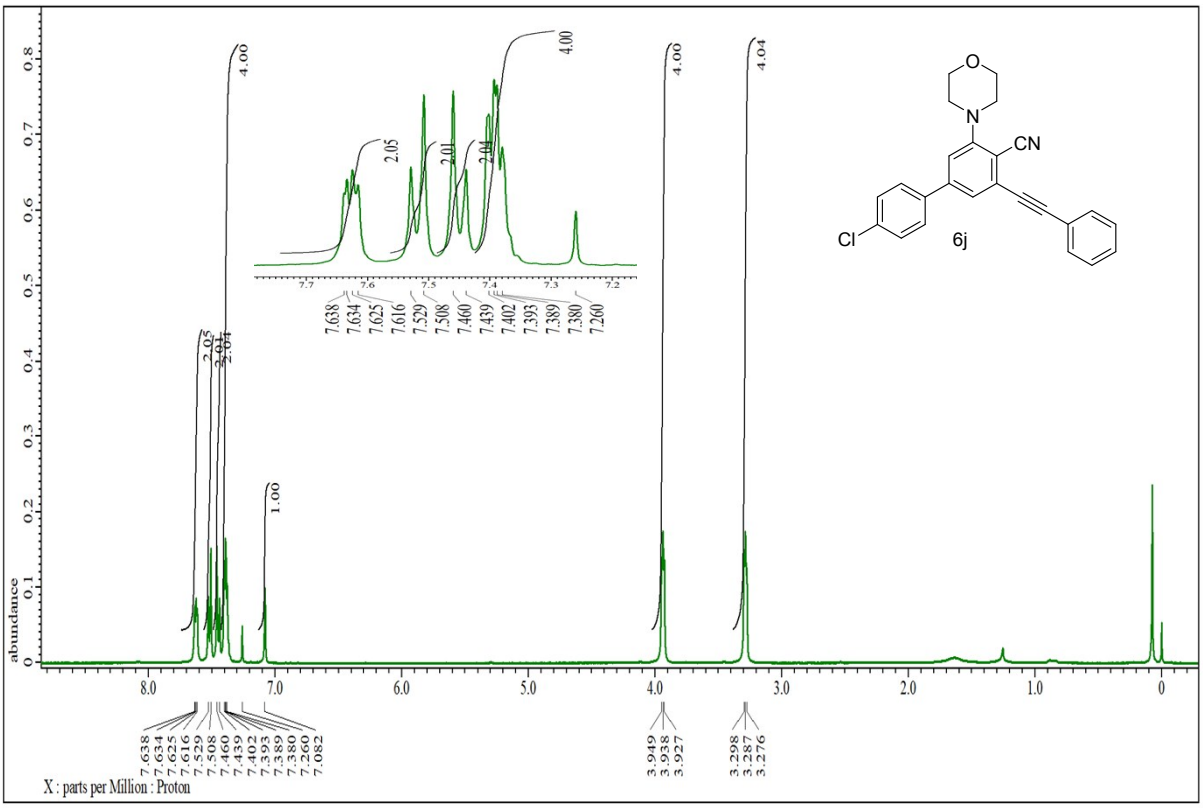
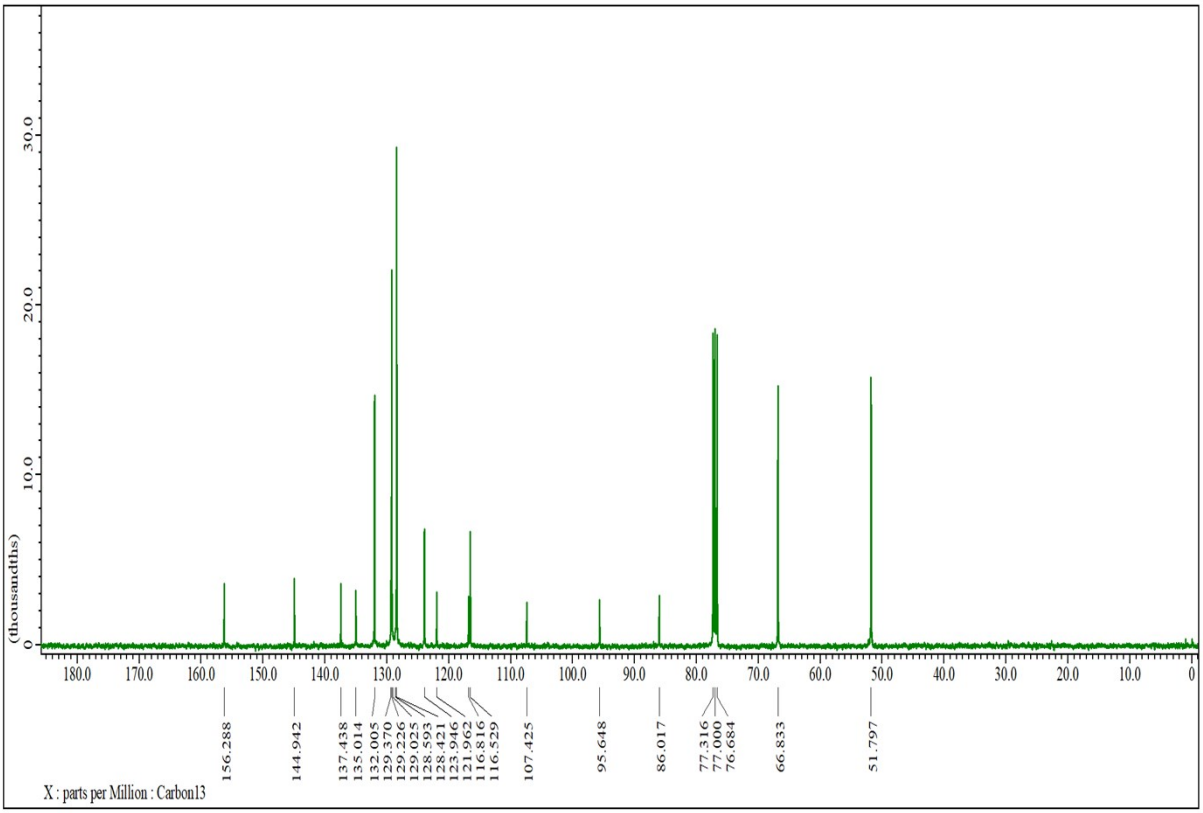
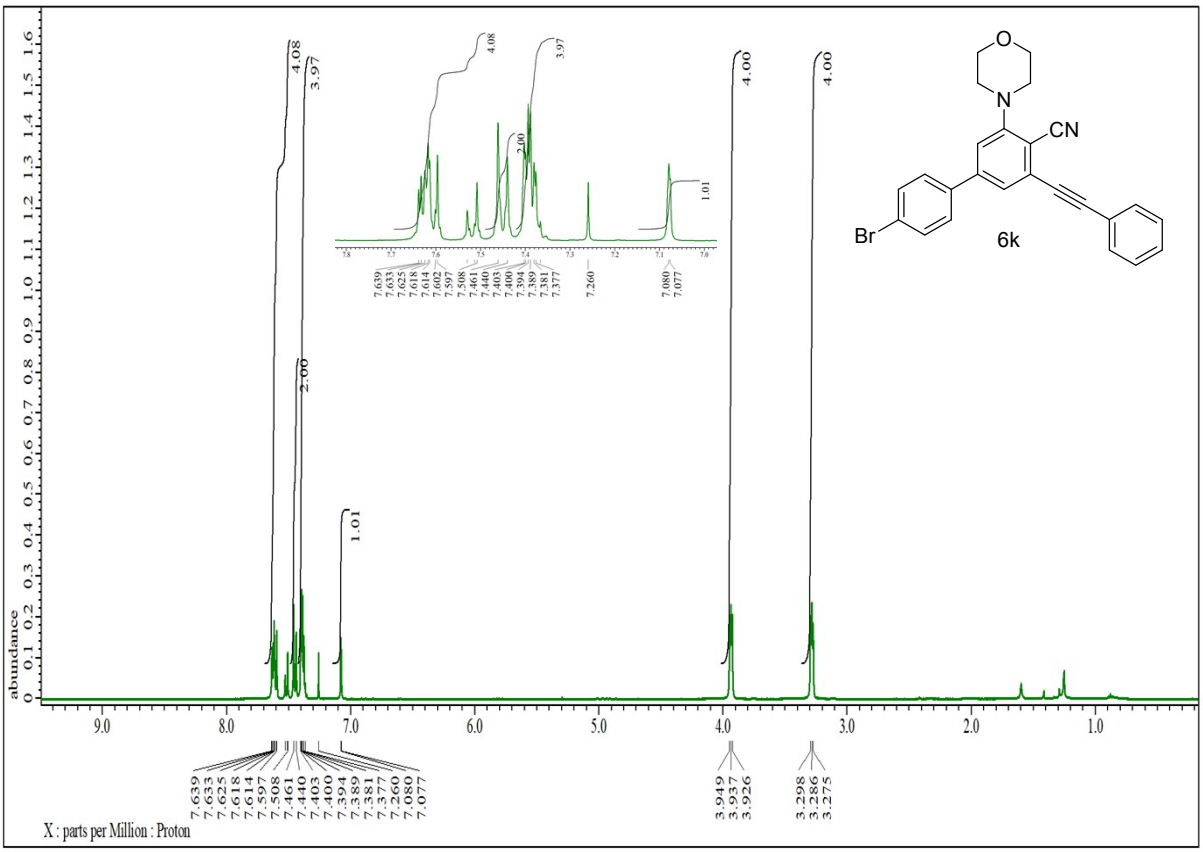
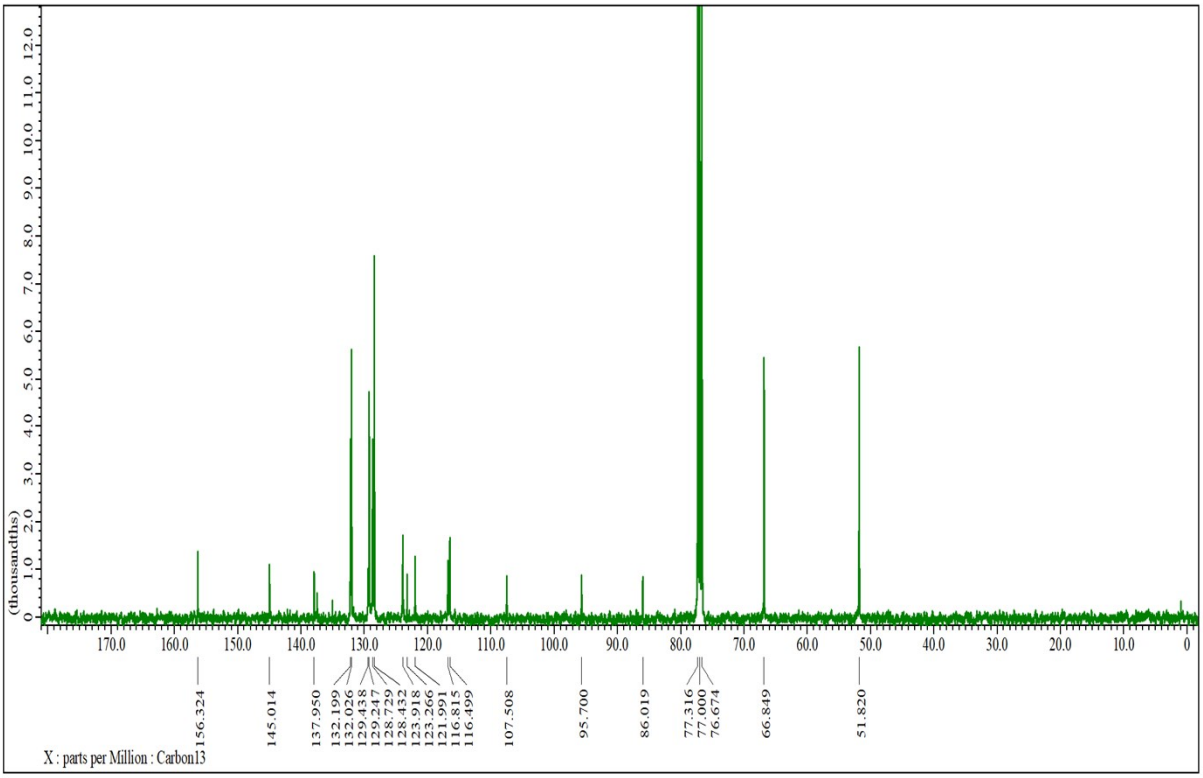


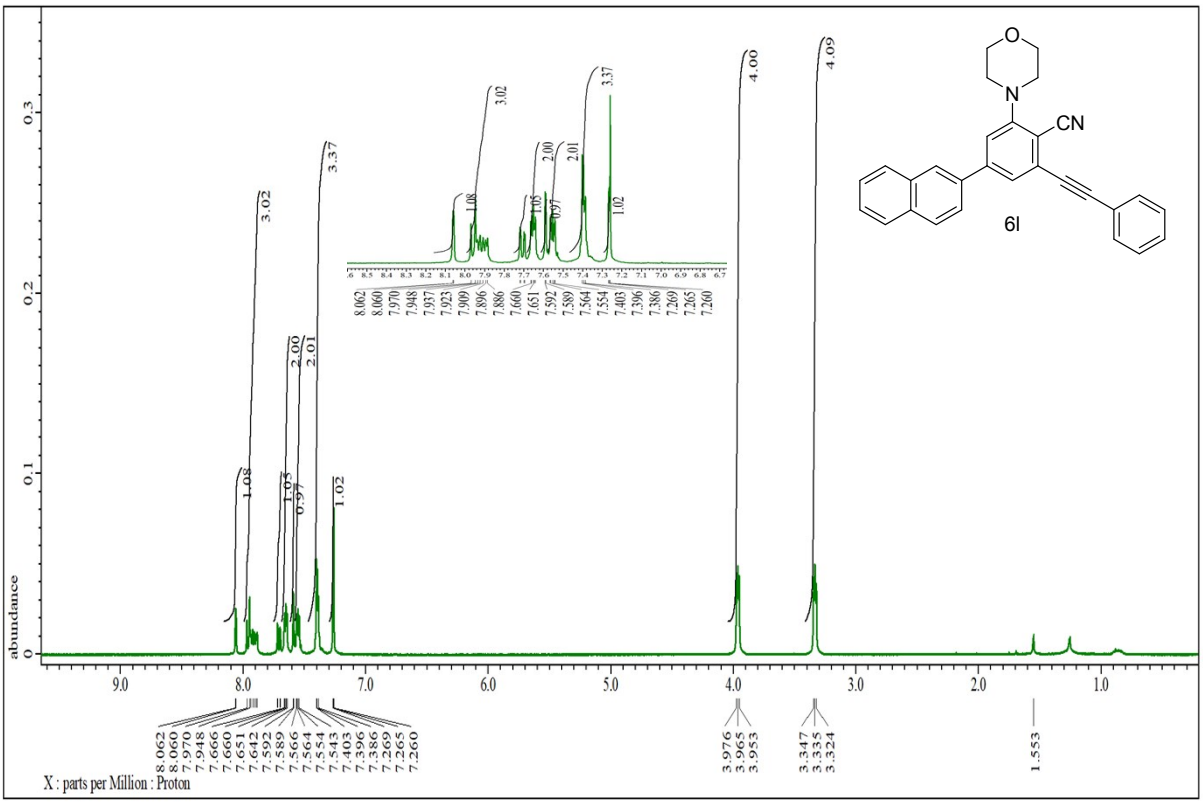


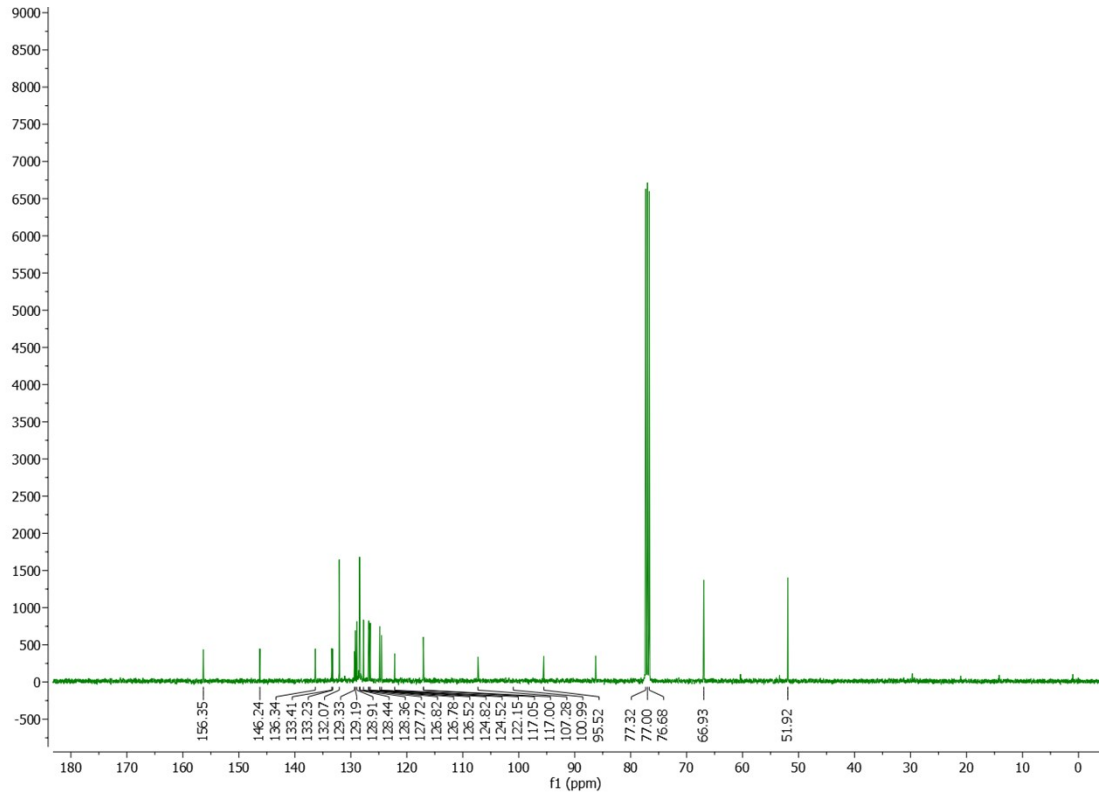
^{1}H NMR and ^{13}C NMR of 4'-chloro-3-morpholino-5-(phenylethynyl)-[1, 1'-biphenyl]-4-carbonitrile.



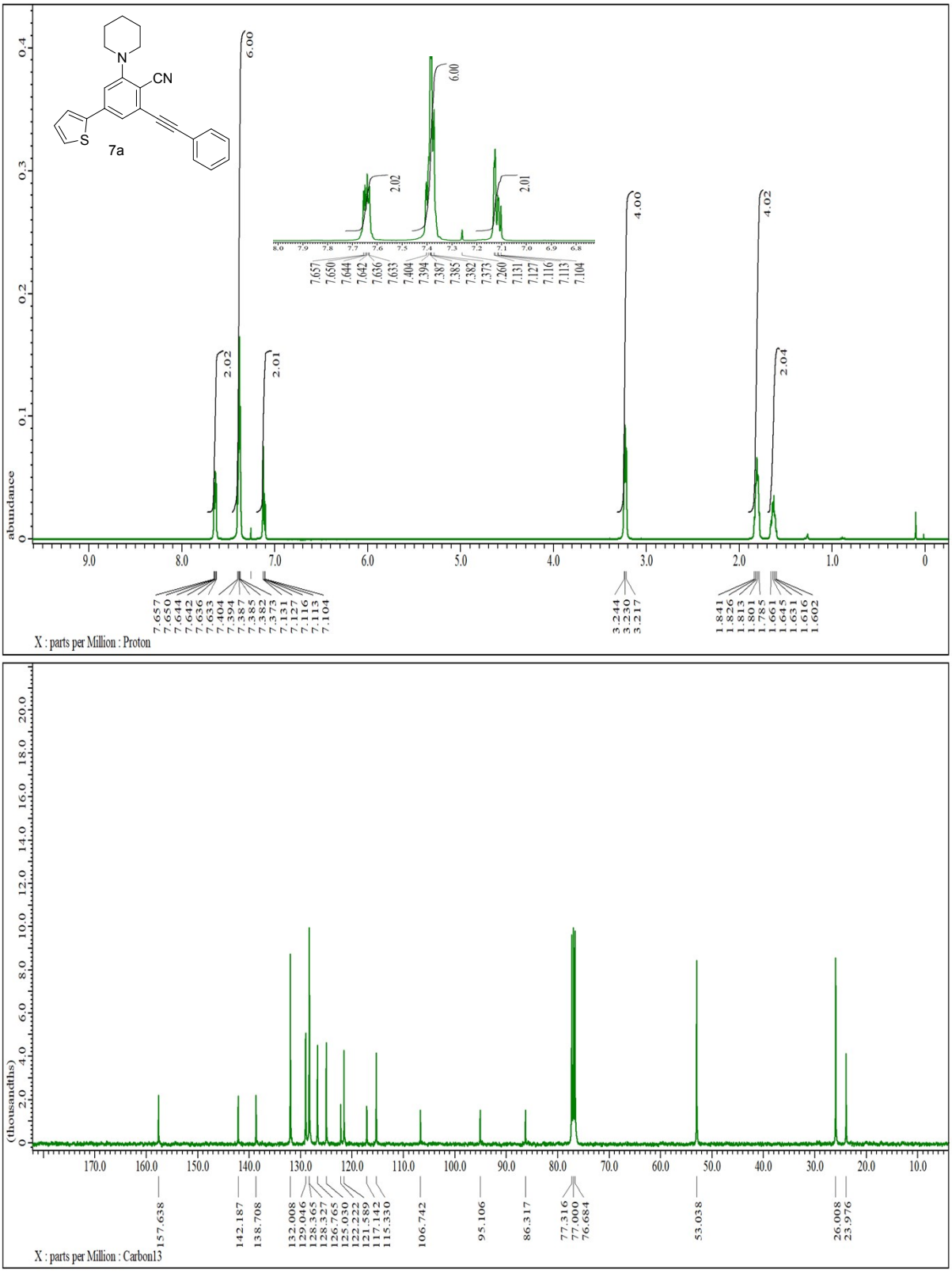


^{1}H NMR and ^{13}C NMR of 4'-bromo-3-morpholino-5-(phenylethynyl)-[1,1'-biphenyl]-4-carbonitrile.

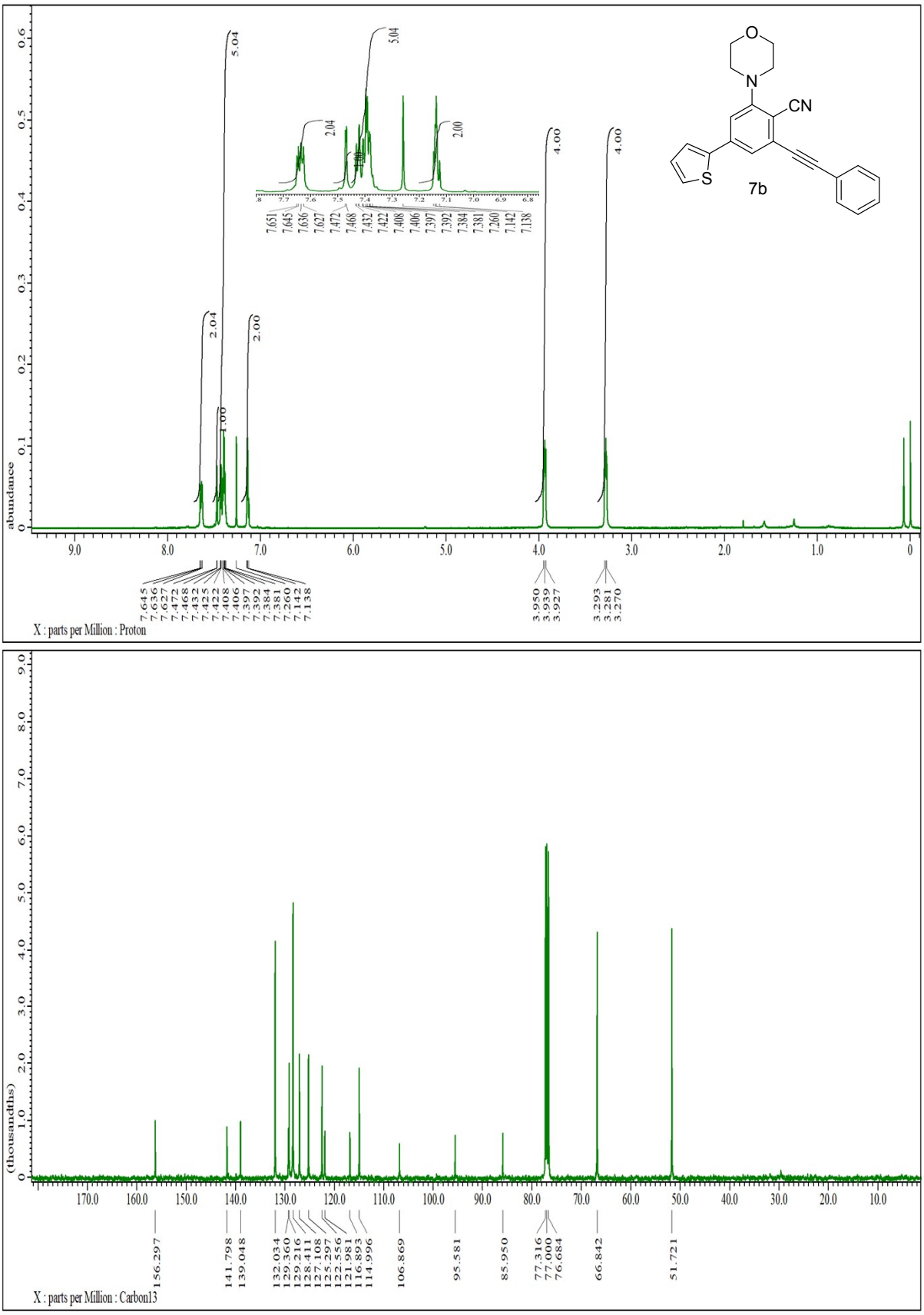




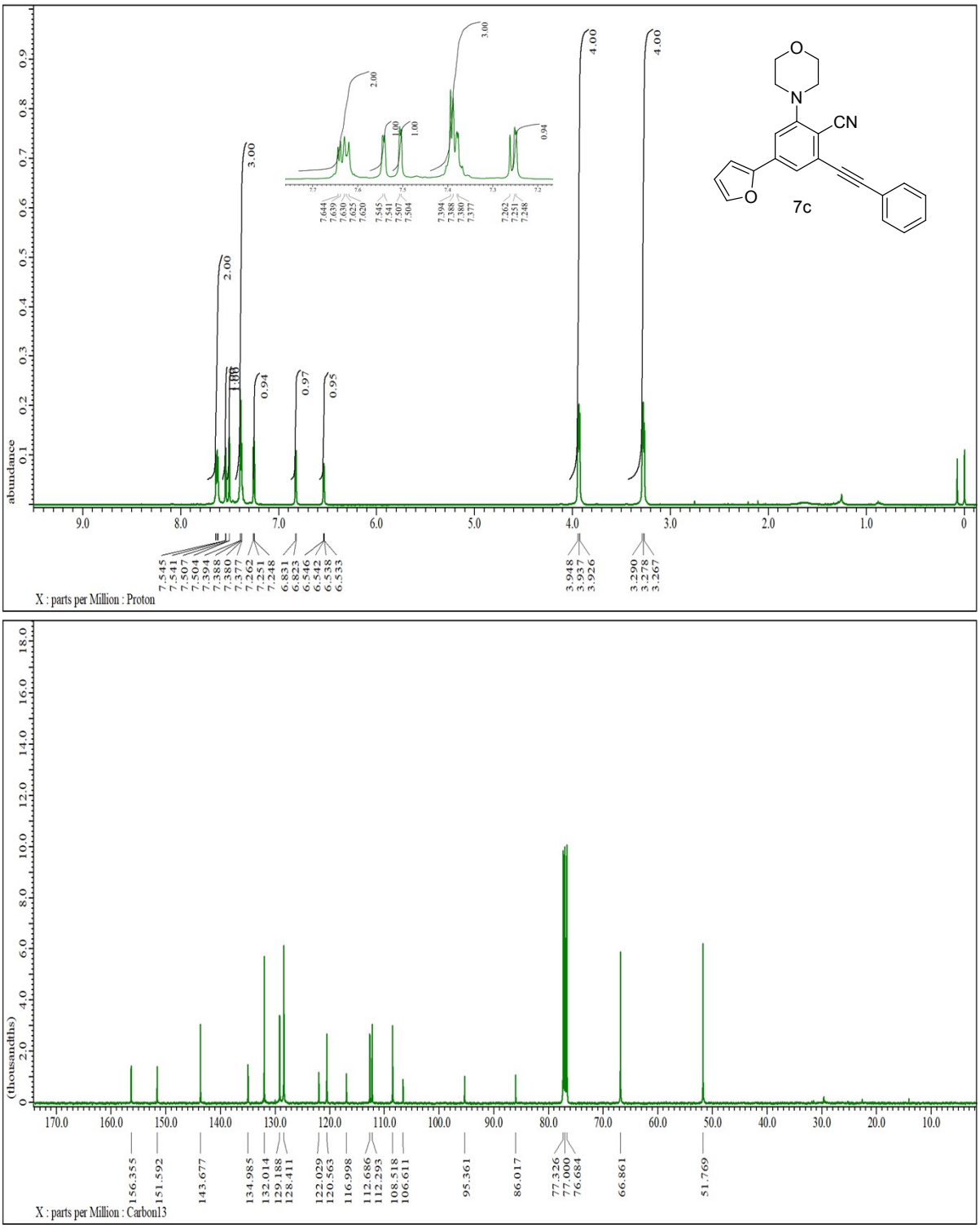
^{1}H NMR and ^{13}C NMR of 2-morpholino-4-(naphthalen-2-yl)-6-phenylethynyl)benzonitrile.



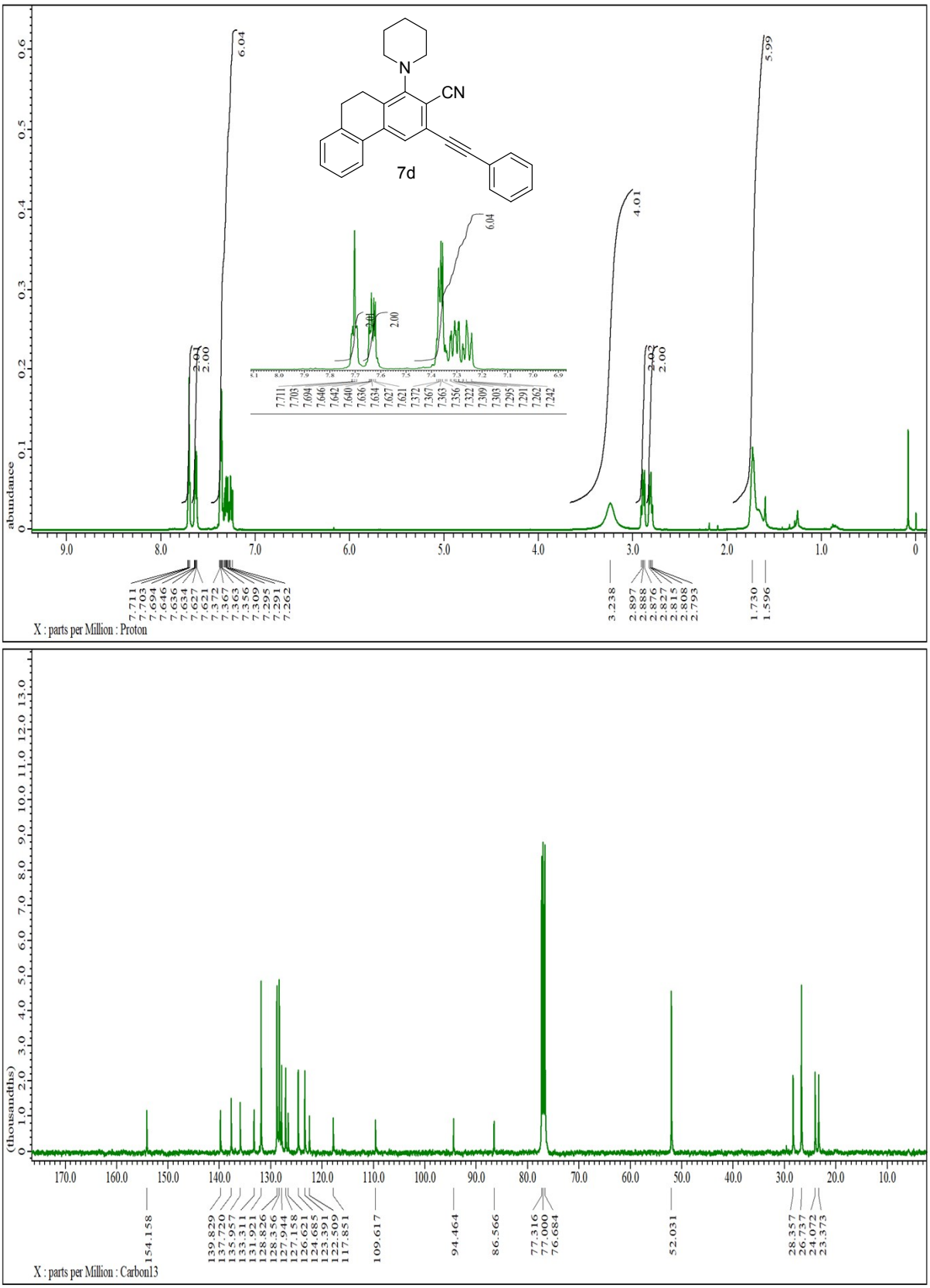
^{1}H NMR and ^{13}C NMR of 2-(phenylethynyl)-6-(piperidin-1-yl)-4-(thiophen-2-l)benzonitrile.



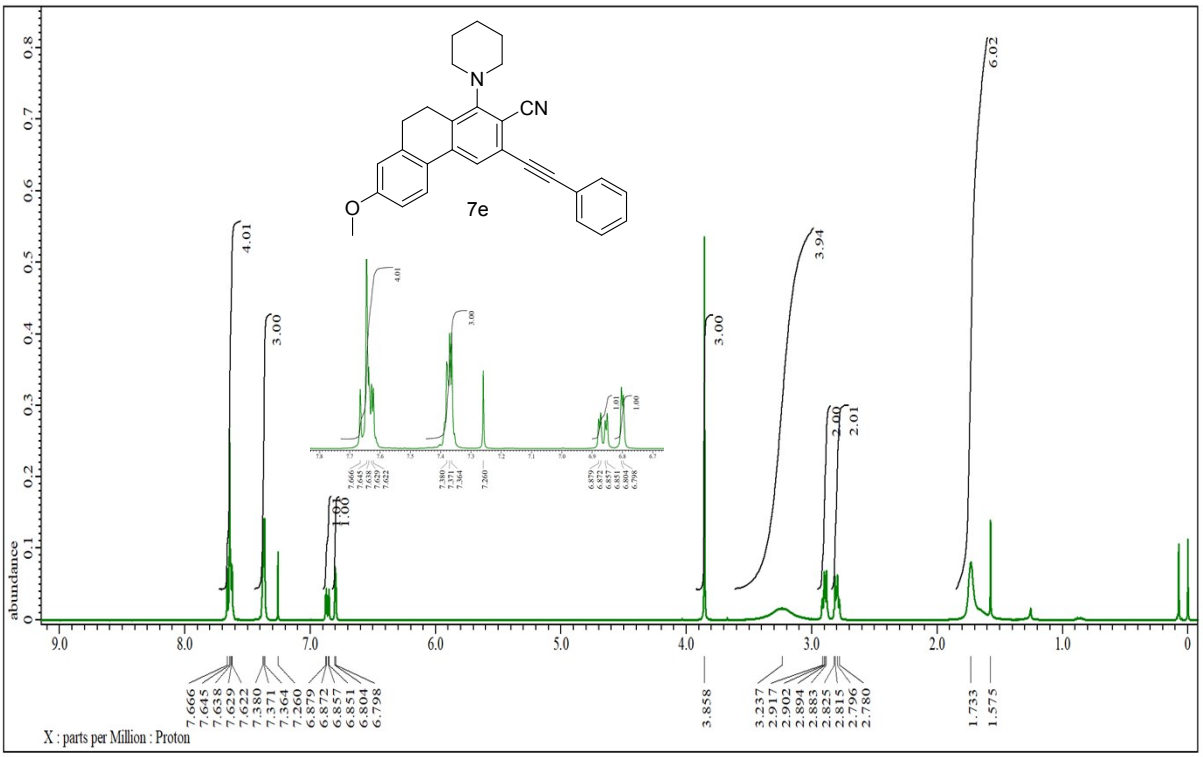
^{1}H NMR and ^{13}C NMR of 2-morpholino-6-(phenylethynyl)-4-(thiophen-2-yl)benzonitrile.

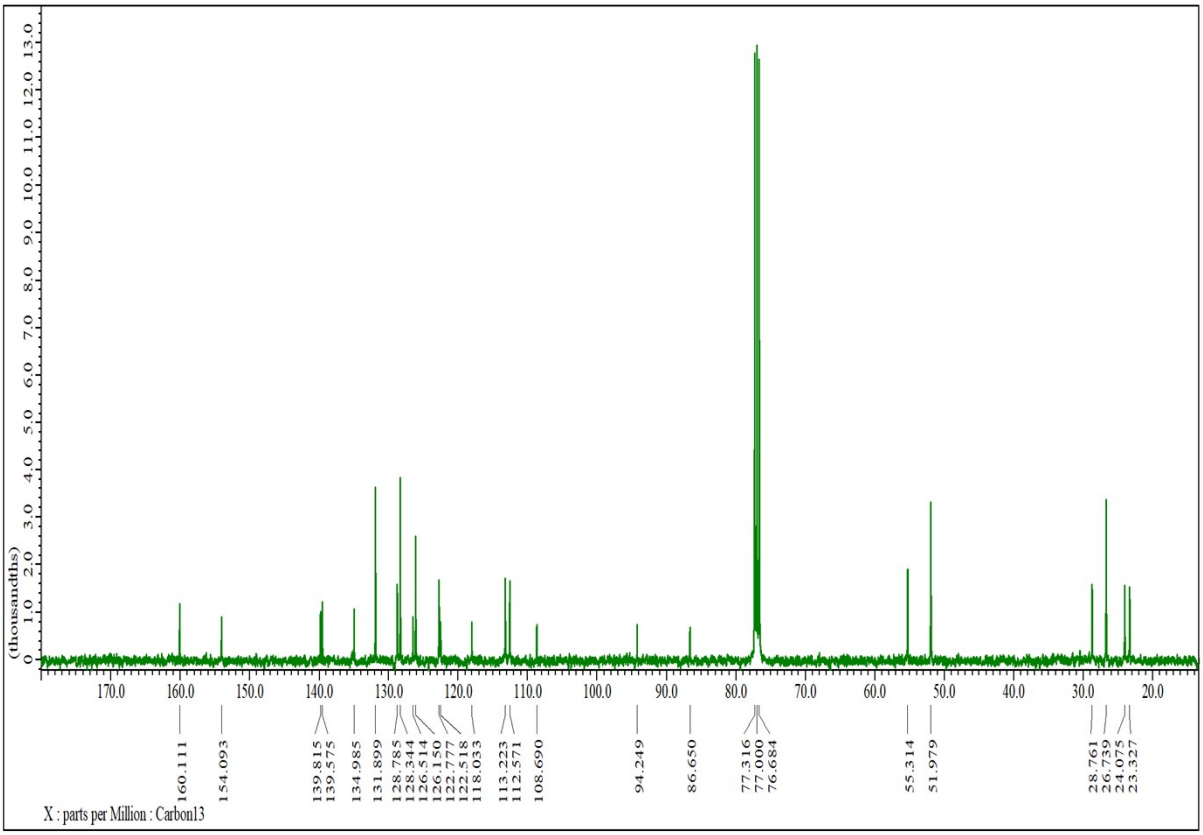


^{1}H NMR and ^{13}C NMR of 4-(furan-2-yl)-2-morpholino-6-(phenylethynyl)benzonitrile.



^{1}H NMR and ^{13}C NMR of 3-(phenylethynyl)-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile.





^{1}H NMR and ^{13}C NMR of 7-methoxy-3-(phenylethynyl)-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile.

References

1. CrysAlisPro, v. 1.171.33.49b, Oxford Diffraction Ltd., 2009.
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4. G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr*., 2008, **64**, 112
5. L. J. Farrugia, "*WinGX version 1.64, an integrated system of windows programs for the solution, refinement and analysis of single-crystal X-ray diffraction data." University of Glasgow, Glasgow* 2003.