Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Transition metal free synthesis of sterically hindered allylarenes from 5-hexene-2-one

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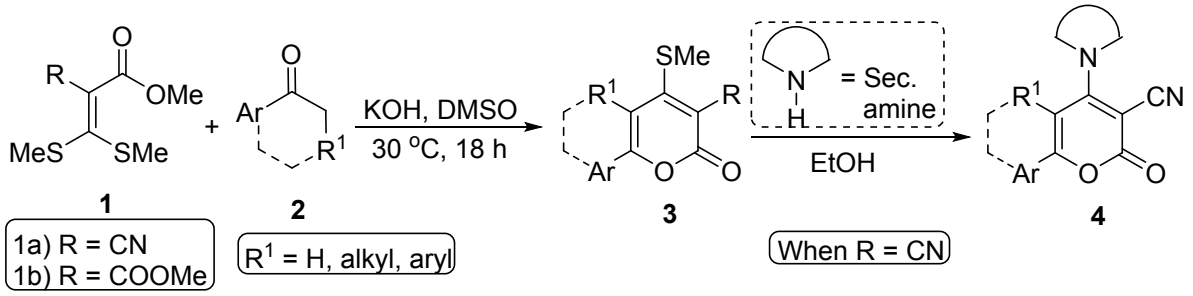
Table of content

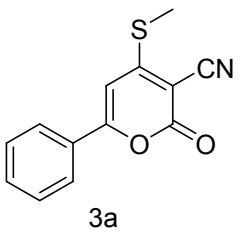
1. Synthesis of precursor 3 and 4

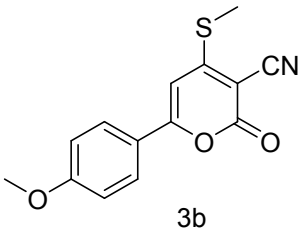
We starts our study from bulk synthesis of methyl 2-cyano/carbomethoxy-3,3-bis(methylthio)acrylates (**1**) from a multicomponent reaction of methyl cyanoacetate or dimethyl malonate, carbon disulfide and dimethyl sulfate in presence of sodium ethoxide in ethanol.[1]To a dry RB flask 3,3-bis(methylthio)acrylate (**1,** 20 mmol), aryl methyl ketone (**2,** 22 mmol) was added followed by addition of KOH (30 mmol)in DMSO (25mL) an mixture was stirred for 18-24 hours at 30 ^{o}C. After completion of reaction, mixture was added drop-wise to crust ice with vigorous stirring. The precipitate obtained was filtered washed with water and dried. The obtained compound was washed with cold ethanol to afford 6-aryl-3-cyano/methyl ester-4-(methylthio)-2*H*-pyran-2-ones (**3**) upto 65-80% yield.[2]

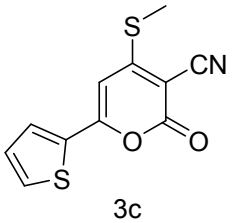
In the second step, precursor 6-aryl-4-(*sec.* amino)-2-oxo-2*H*-pyran-3-carbonitriles **4** weresynthesized by refluxing 6-aryl-4-(methylthio)-2-oxo-2*H*-pyran-3-carbonitriles (**3**) with various secondary amines in ethanol for 6-8 h.

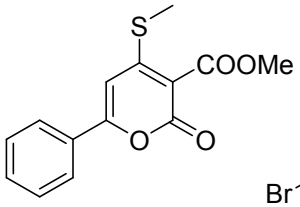
Scheme 1.Synthesis of precursors **3** and **4**

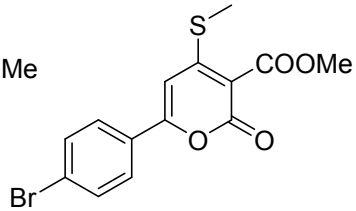


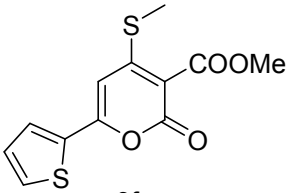


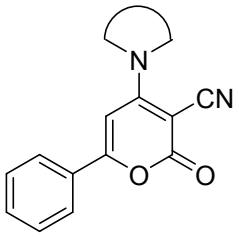




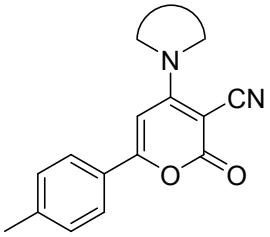




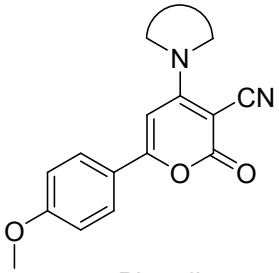




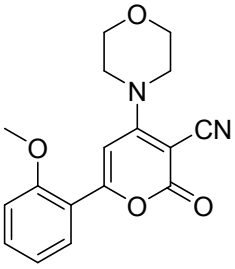
4a; Piperidine
4b; Pyrrolidine



4c; Piperidine
4d; Morpholine



4e; Piperdine
4f; Pyrrolidine



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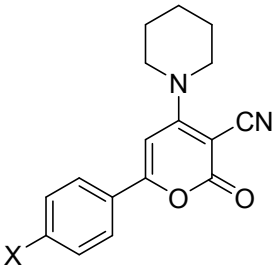
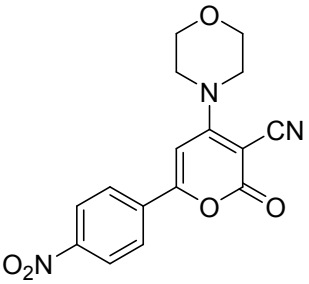


4h; X = F
4i; X = Br



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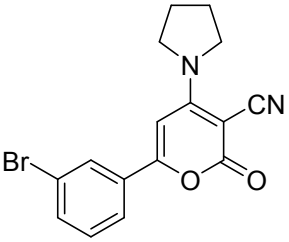

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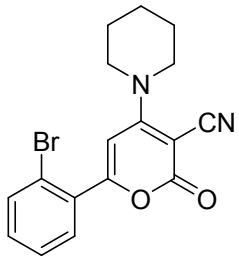

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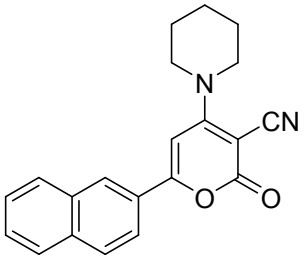

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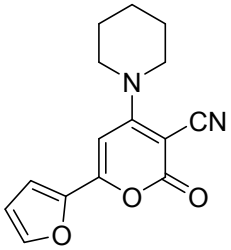

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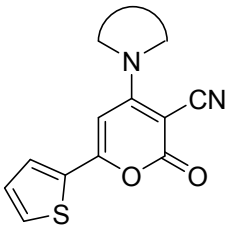
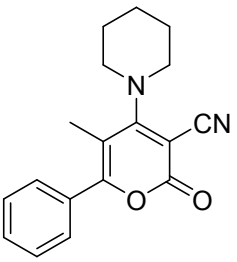
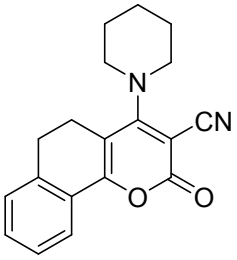


4o; Piperidine
4p; Pyrrolidine
4q; Morpholine



4r



4s

2. Crystallographic data of 2-allyl-3,4'-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (6c) and 2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile (7a)

Intensity data for the compound 2-allyl-3,4'-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (**6c**)and2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile(**7a**) was collected at 298 K on an Agilent Xcalibur, Sapphire3 diffractometer using graphite monochromated Mo-Kα radiation λ = 0.71073 Å. Unit cell determination, data collection were performed with Oxford Diffraction Diffractometer CrysAlisPro.[3] The structure was solved by SHELXT program[4] and refined on F2 using all data by full matrix least-squares procedures with SHELXL-2014/7[5,6]and incorporated in OLEX2 crystallographic package.[7] The hydrogen atoms were placed at the calculated positions and included in the last cycles of the refinement.[8] The C-H, CH_2 and CH_3 hydrogen atoms were placed at their calculated positions (C-H = 0.93 Å, CH_2= 0.97 Å, CH_3= 0.96 Å) followed by their treatment using ariding model with U_{iso} (H, For CH and CH_2) = 1.2Ueq(C) and U_{iso} (For,CH_3) = 1.5Ueq(C). The graphics for publication was prepared by using Mercury software.[9] Crystallographic data collection and structure solution parameters are summarized in the Table S1.CCDC- contains the supplementary crystallographic data for this manuscript.

Table S1. Crystallographic data of 6c and 7a

Compound Code	***6c***	***7a***
Empirical formula	***$C_{23}H_{26}N_2$***	***0.14($C_{18}H_{17}NS$)***
CCDC	2006224	2006225
Formula weight	*330.48*	*0.14(279.39) = 38.48*
Temperature/K	*298*	*298*
Crystal system	*Triclinic*	*monoclinic*
Space group	*P-1*	*$P2_1/c$*
a/Å	*8.2991(6)*	*9.0216(3)*
b/Å	*9.0692(6)*	*10.1719(3)*
c/Å	*13.6609(9)*	*17.3180(7)*
α/°	*94.077(5)*	*90*
β/°	*104.535(6)*	*101.519(4)*
γ/°	*105.981(6)*	*90*
Volume/$Å^3$	*945.91(12)*	*1557.21(10)*
Z	*2*	*29*
$\rho_{calc}g/cm^3$	*1.1602*	*1.1917*
μ/mm^{-1}	*0.068*	*0.198*

F(000)	*356.1*	*592.7*
Crystal size/mm³	*0.1 × 0.1 × 0.1*	*0.1 × 0.1 × 0.1*
Radiation	*Mo Kα (λ = 0.71073)*	*Mo Kα (λ = 0.71073)*
2Θ range for data collection/°	*6.88 to 59*	*6.9 to 58.92*
Index ranges	*-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -18 ≤ l ≤ 18*	*-11 ≤ h ≤ 12, -14 ≤ k ≤ 13, -23 ≤ l ≤ 23*
Reflections collected	*14072*	*22455*
Independent reflections	*4601 [R_{int} = 0.0423, R_{sigma} = 0.0664]*	*3741 [R_{int} = 0.0337, R_{sigma} = 0.0275]*
Data/restraints/parameters	*4601/0/236*	*3741/0/192*
Goodness-of-fit on F^2	*1.043*	*1.053*
`Final R indexes [I>=2σ (I)]	*R_1 = 0.0630, wR_2 = 0.1249*	*R_1 = 0.0455, wR_2 = 0.0920*
Final R indexes [all data]	*R_1 = 0.1232, wR_2 = 0.1583*	*R_1 = 0.0672, wR_2 = 0.1009*
Largest diff. peak/hole / e Å^{-3}	*0.32/-0.33*	*0.25/-0.22*

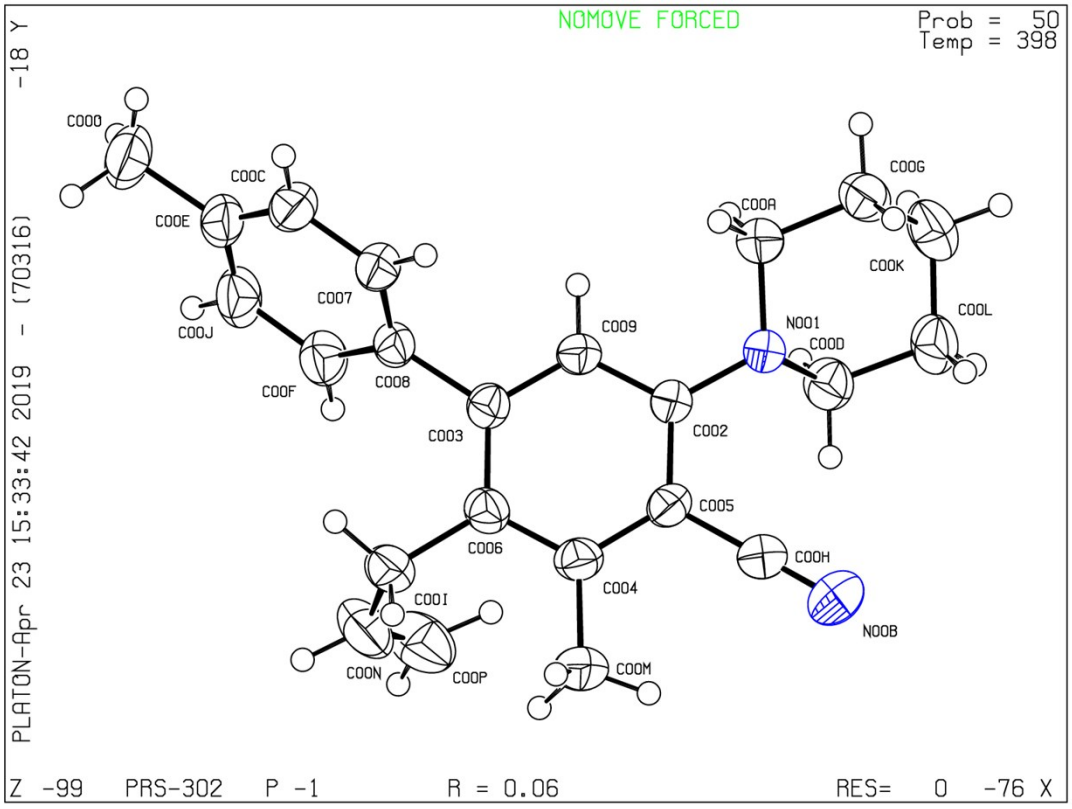


Figure 1. ORTEP image of **6c**at 50% probability with atom numbering scheme

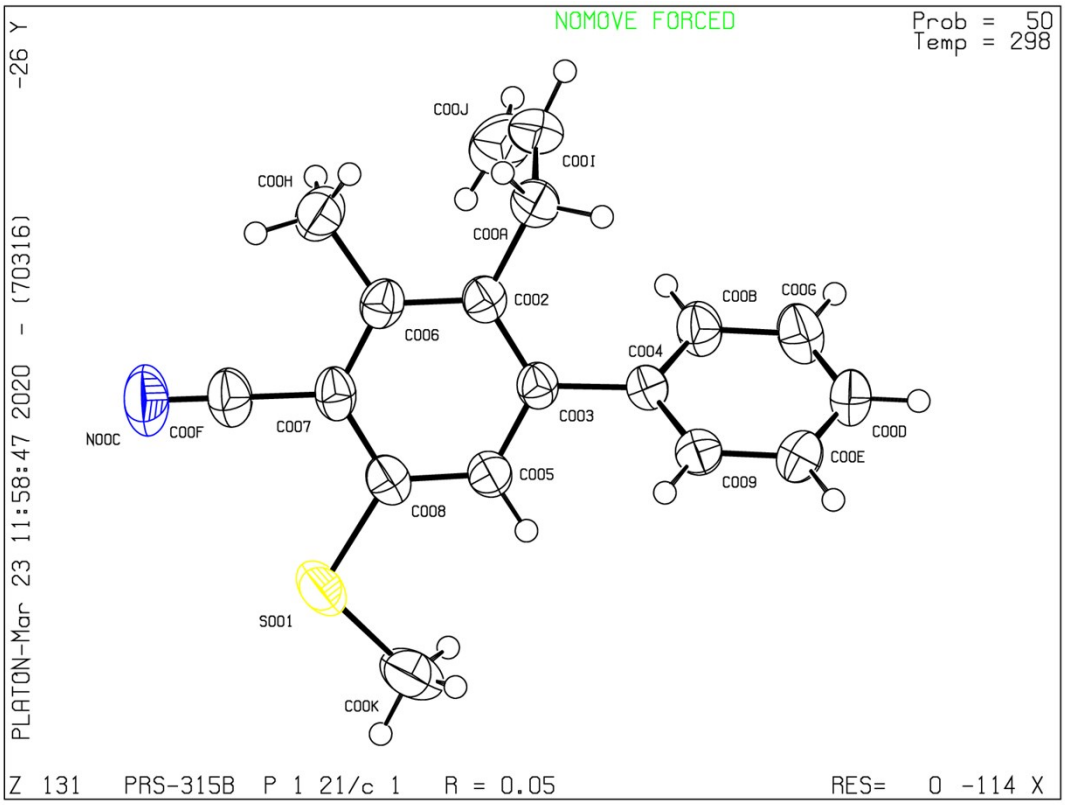


Figure 2. ORTEP image of**7a** at 50% probability with atom numbering scheme

Molecular docking studies (Methodologies)

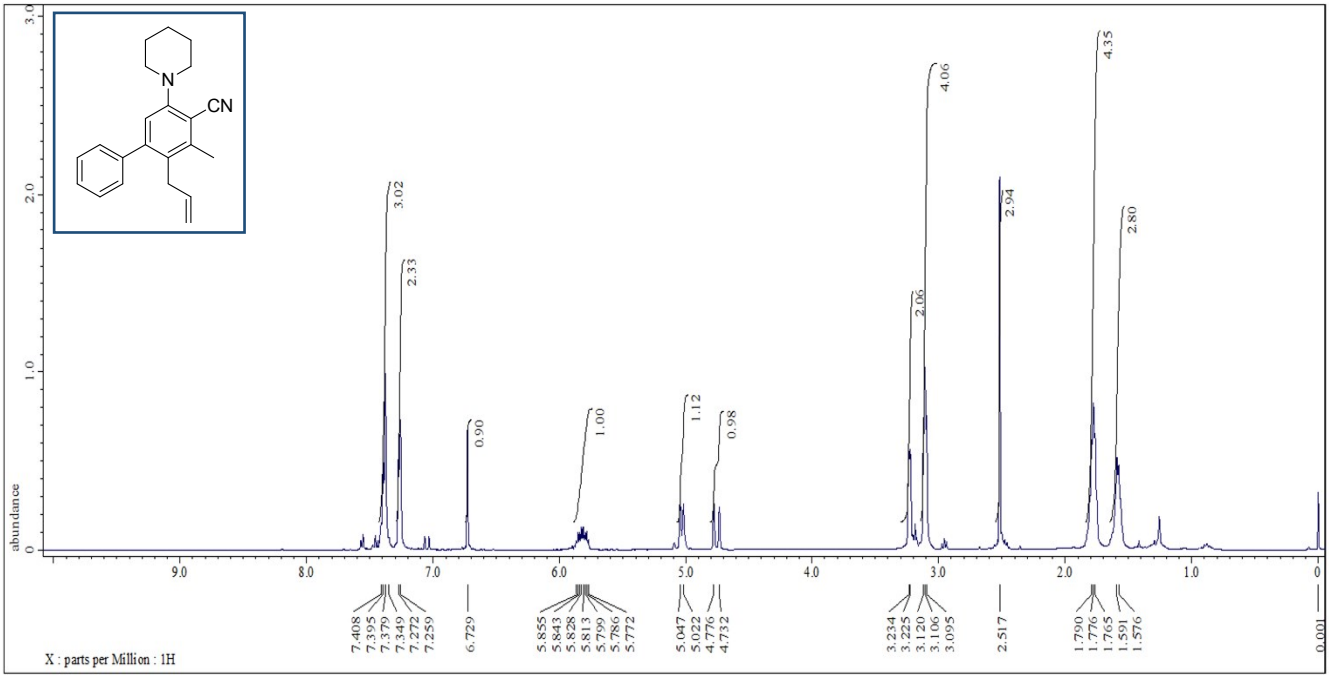
The 2D structures of all the synthesized compounds were drawn using ChemBioDraw Ultra 12.0 (www.cambridgesoft.com). Ligprep module of Schrödinger was used to generate the 3D structures with the lowest energy. Partial atomic charges were computed using the OPLS_2005 force field. The correct Lewis structure, 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 ERα (PDB ID: 2I0J; resolution 2.90Å) and ERβ (PDB ID: 2I0G; resolution 2.50Å), 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 ligandBenzopyrans in bothERsprotein structures were used for the center and size of the receptor grid,which was generated using Glidemodule(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 filesusing Glide extra precision (XP) mode.Default settings were used for the refinement and scoring.

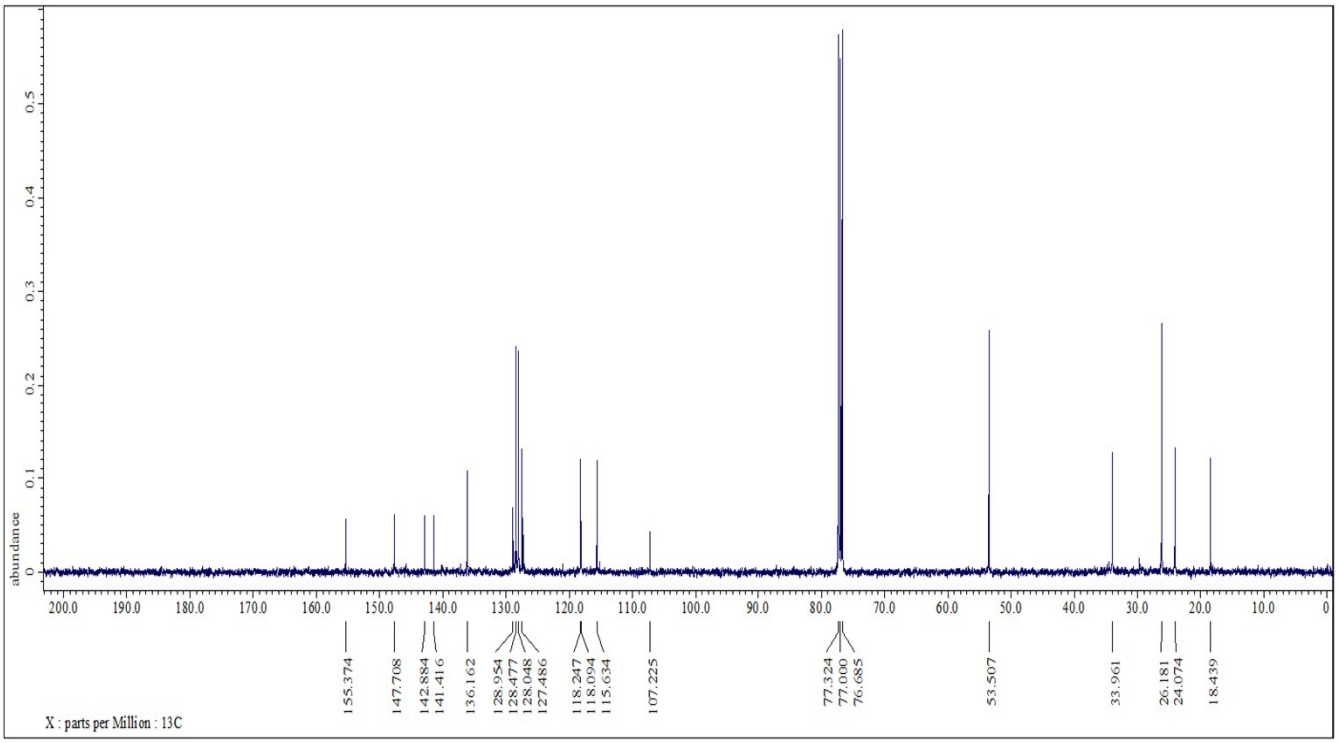
Table S2. Glide docking energies and docking scores for most active functionalized allyl benzenes, along with the reference compounds, in ERα and ERβ.

S. No.	**Docking Results with ERα**		**Docking Results with ERβ**	
Compounds	XP GScore	Glide Energy	XP GScore	Glide Energy
7f	**-8.39**	**-55.11**	**-9.15**	**-58.95**
7d	**-8.76**	**-52.21**	**-9.45**	**-57.14**
7a	-8.80	-50.05	-9.14	-56.23
7c	-8.32	-50.43	-9.17	-55.31

6d	-8.77	-48.05	-8.53	9.5
6p	-8.26	-46.79	-8.52	-0.77
6b	-9.42	-45.92	-8.23	-6.08
6o	-8.22	-39.59	-8.07	6.4
6f	-9.69	-26.61	-7.40	22.31
6c	-9.11	-14.71	-7.22	21.38
6e	-9.64	-20.56	-	-
6a	-9.44	-29.51	-	-
6l	-9.36	-26.08	-	-
6r	-8.88	-13.44	-	-
6m	-7.43	-19.88	-	-
Tamoxifen	**-10.34**	**-61.93**	**-8.59**	**-31.30**

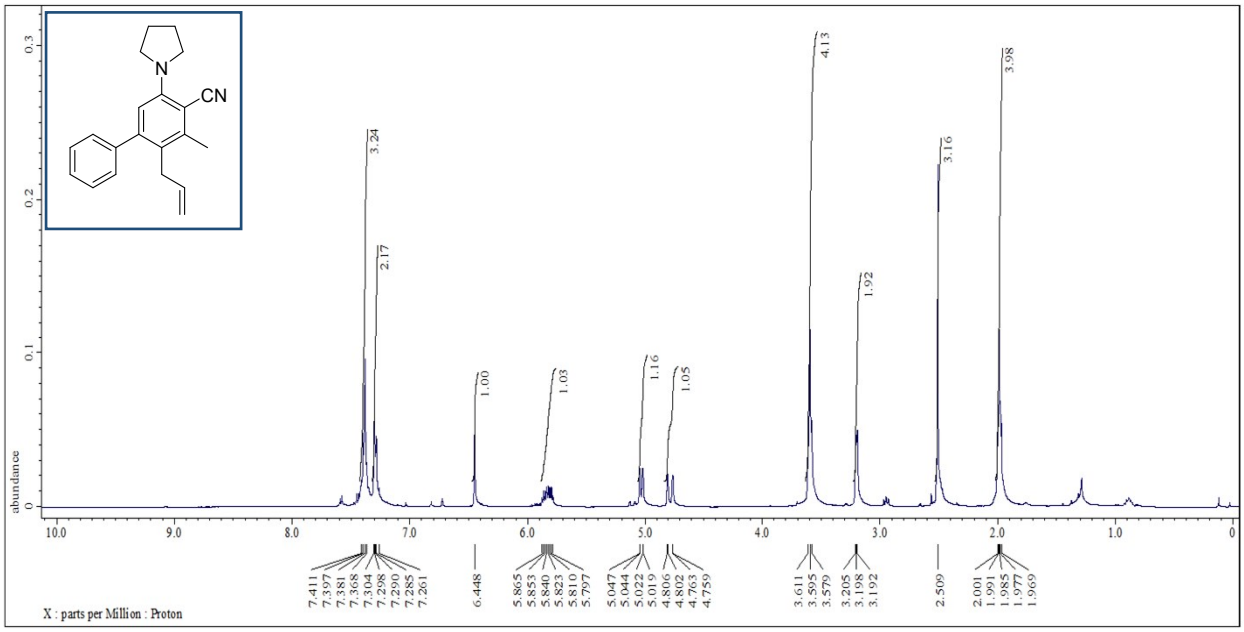
6a. 2-allyl-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

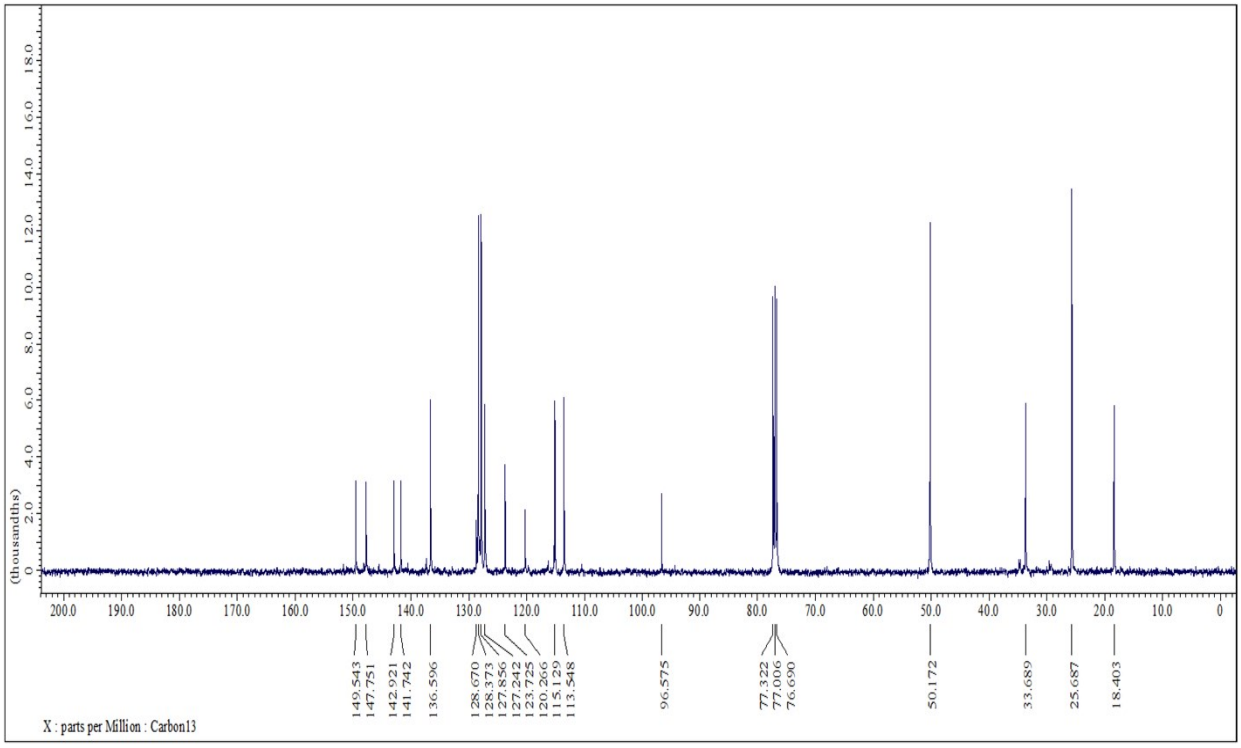




^{1}H and ^{13}C NMR of 2-allyl-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

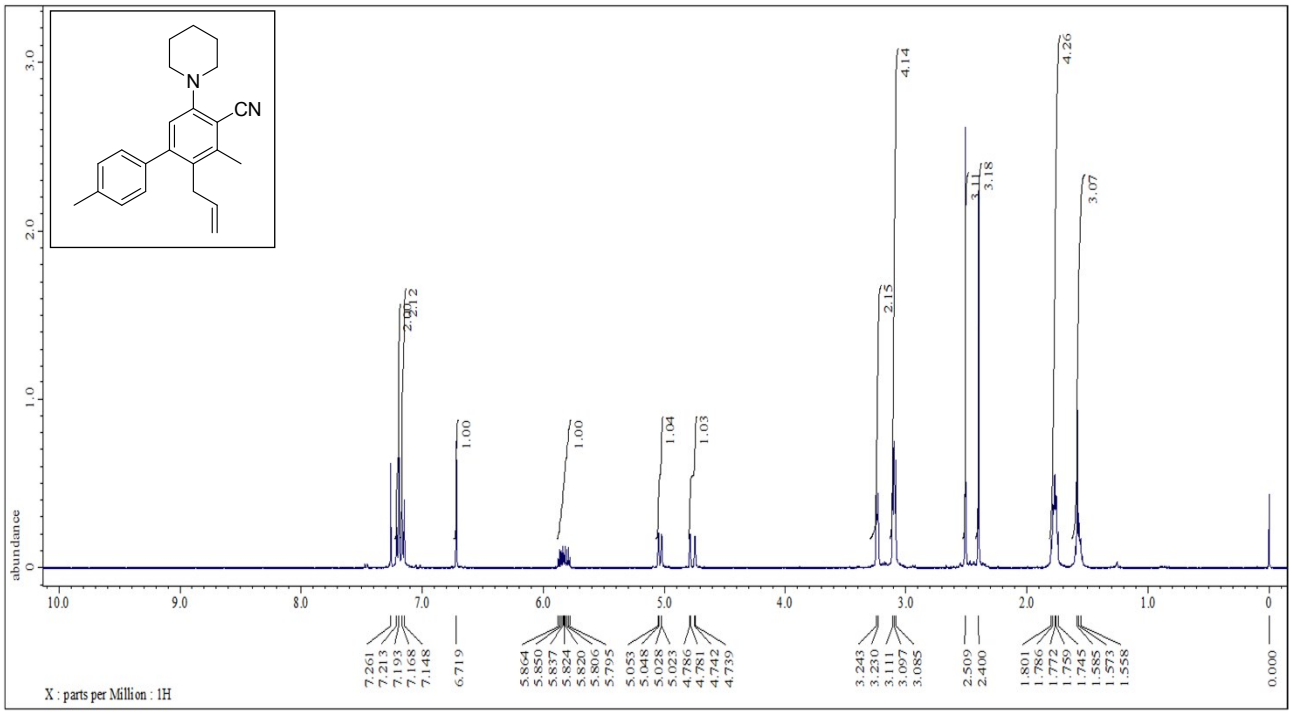
6b. 2-allyl-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

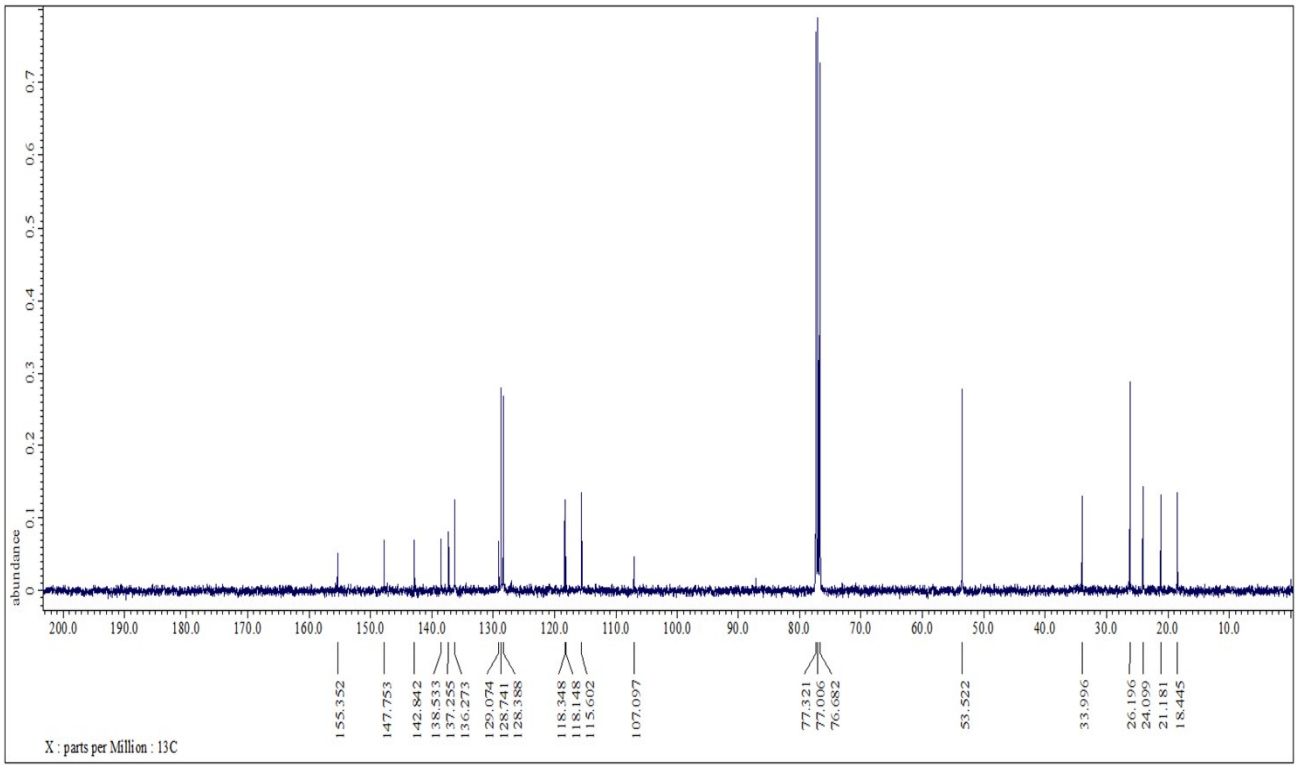




^{1}H and ^{13}C NMR of 2-allyl-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

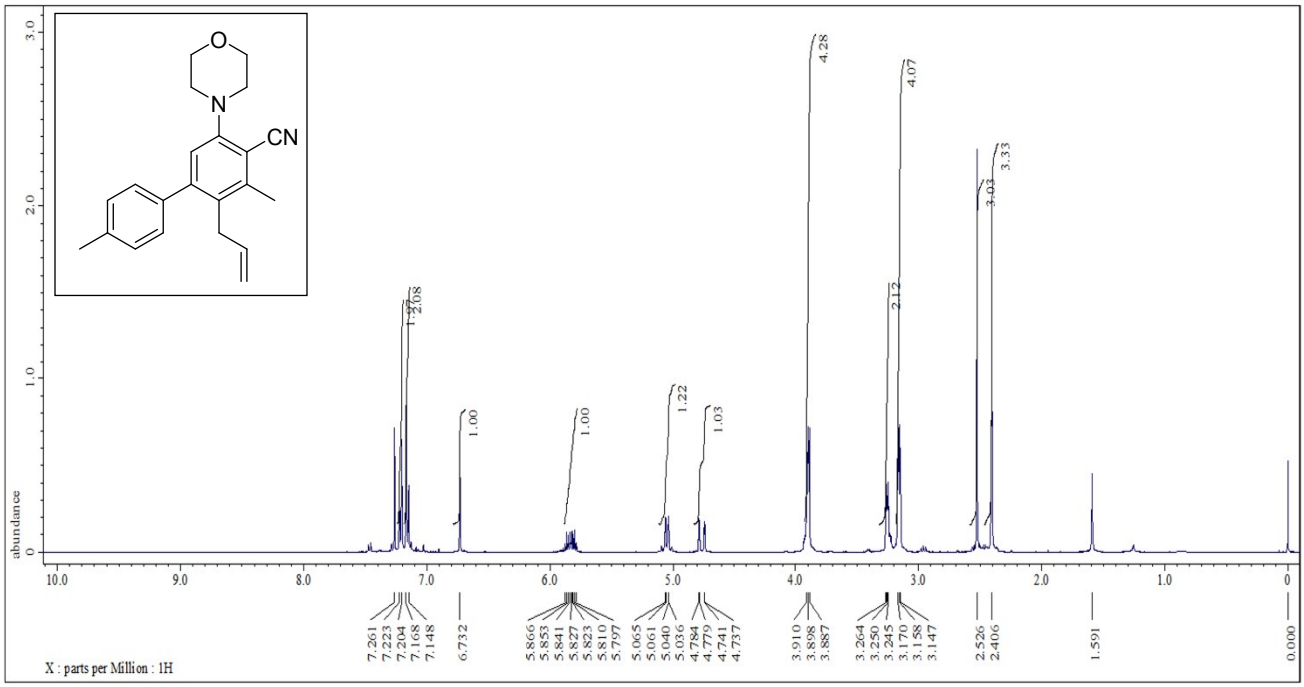
6c. 2-allyl-3,4'-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

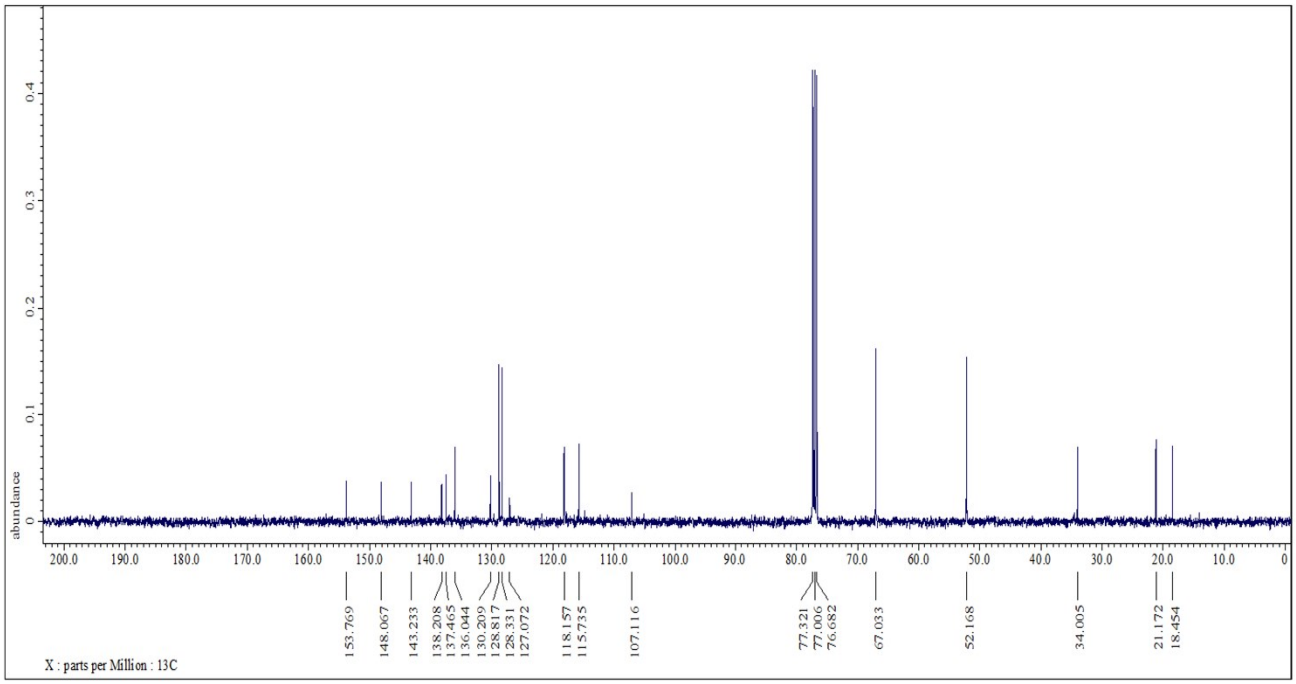




^{1}H and ^{13}C NMR of 2-allyl-3,4'-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

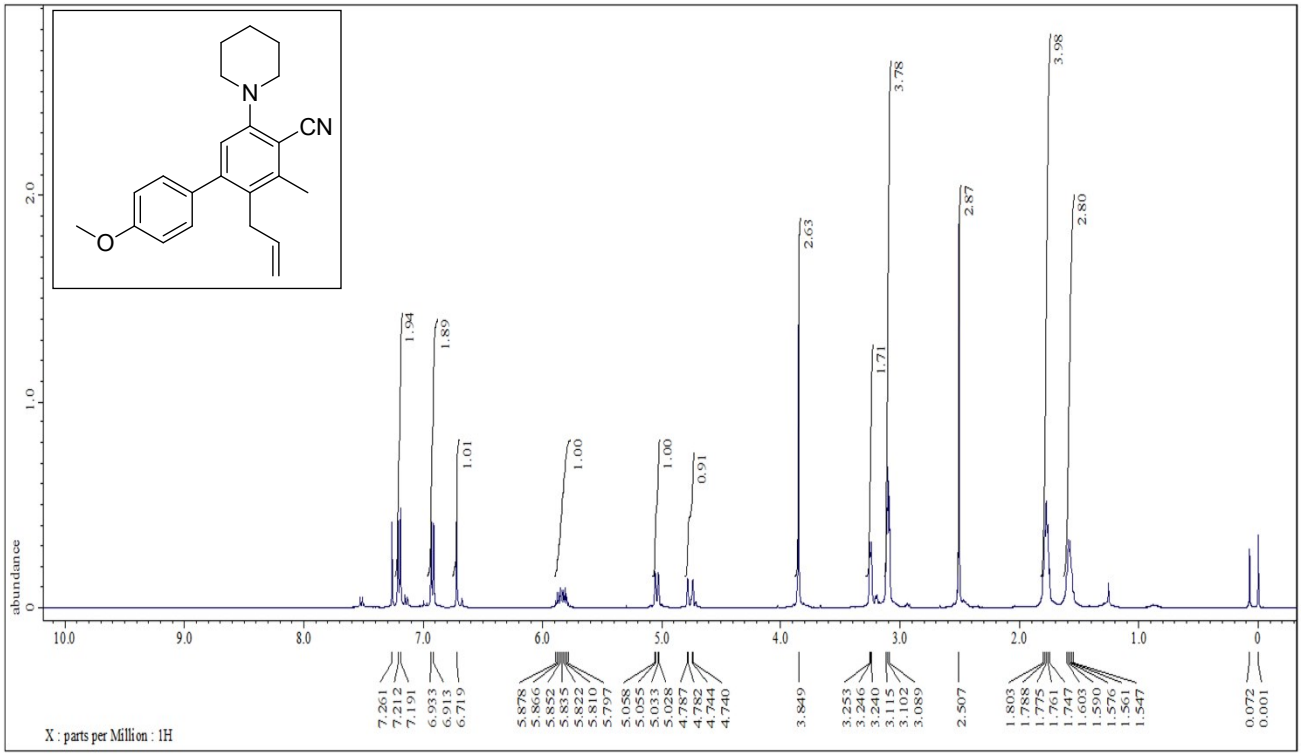
6d. 2-allyl-3,4'-dimethyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile

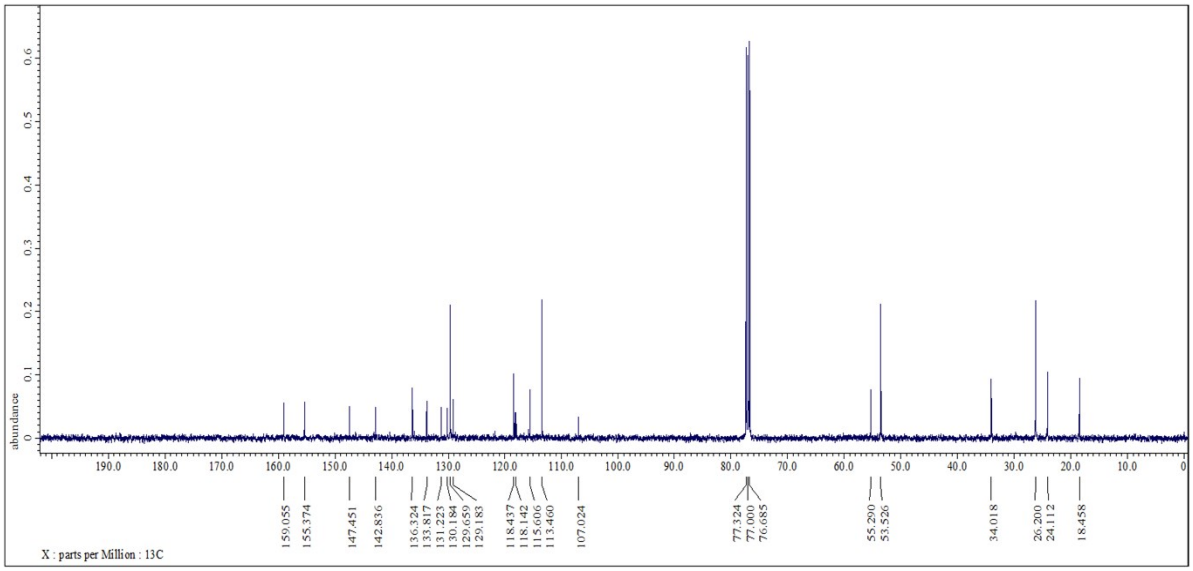




^{1}H and ^{13}C NMR of 2-allyl-3,4'-dimethyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile

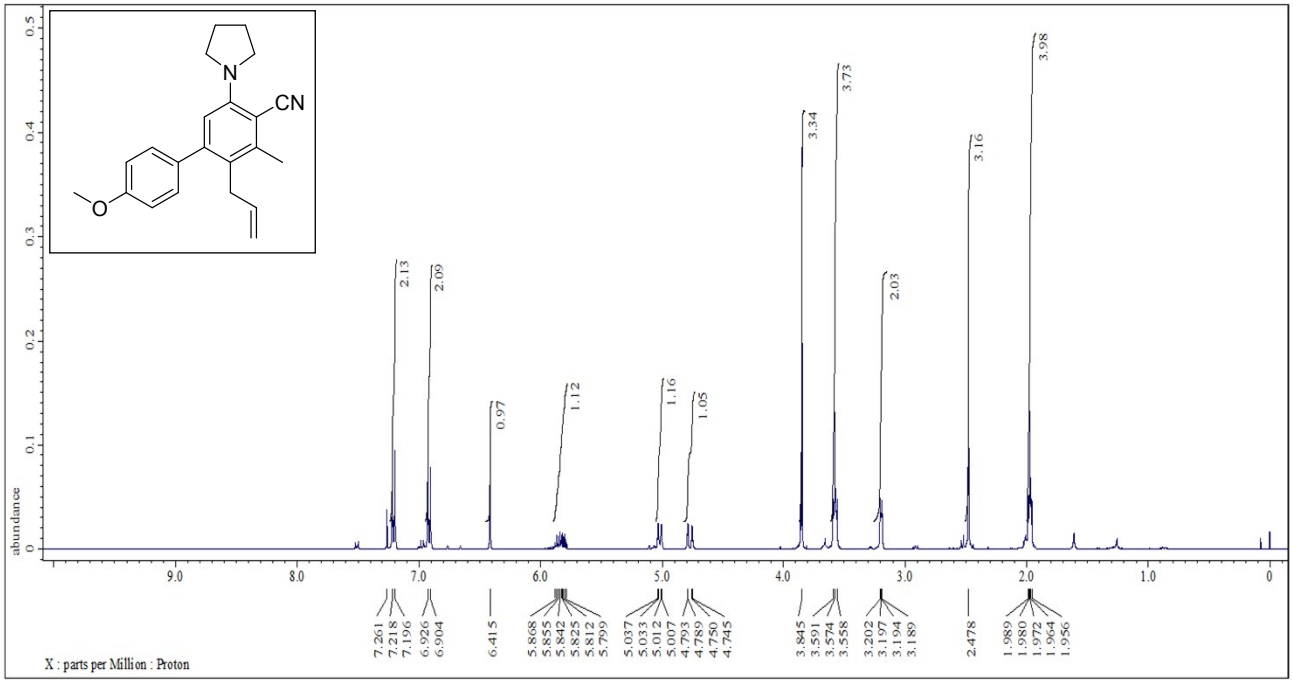
6e. 2-allyl-4'-methoxy-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

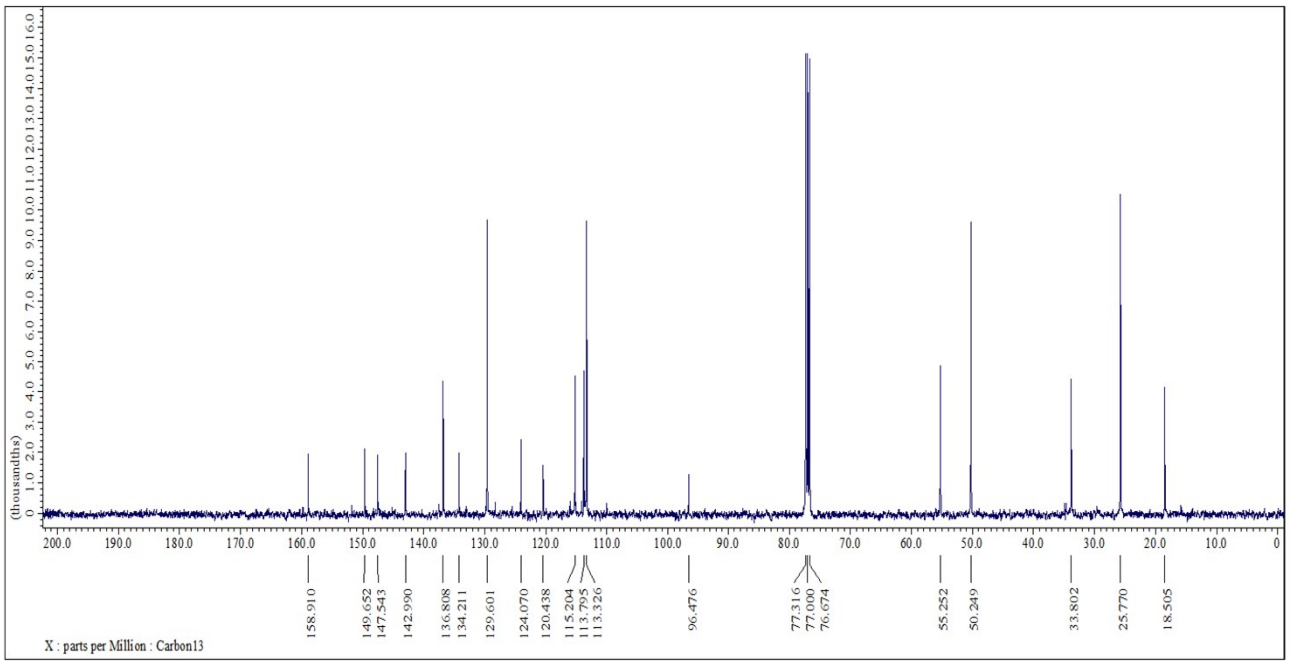




^{1}H and ^{13}C NMR of 2-allyl-4'-methoxy-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

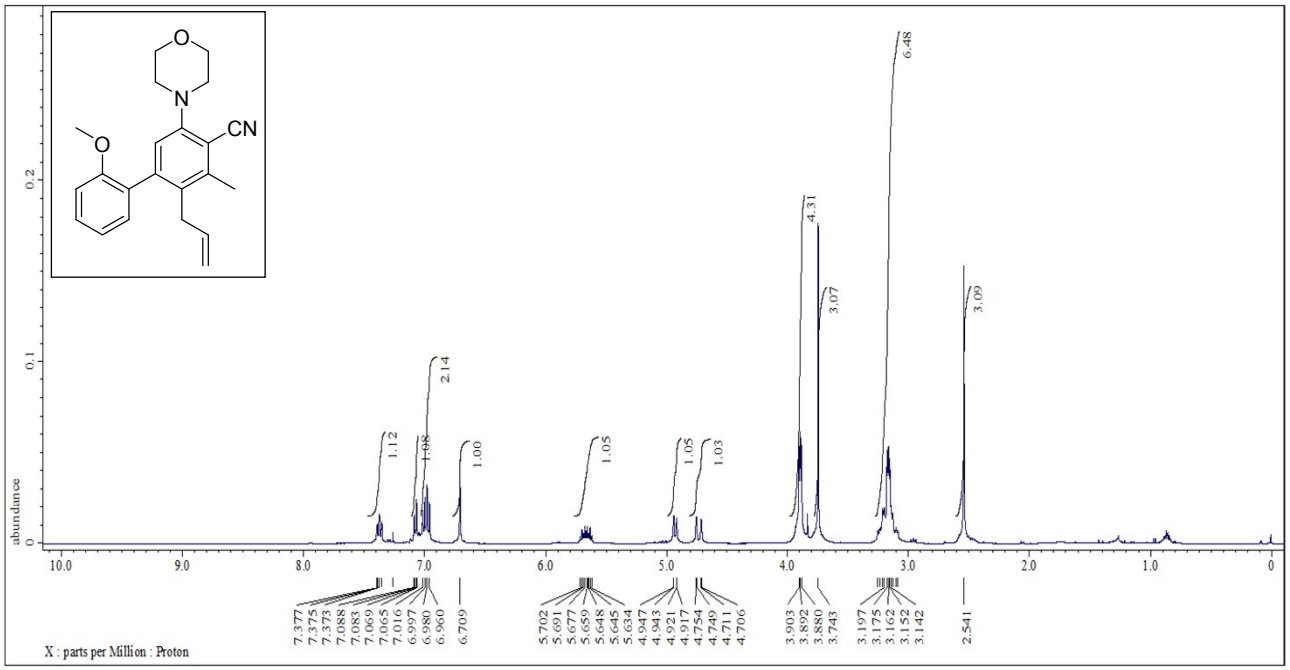
6f. 2-allyl-4'-methoxy-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

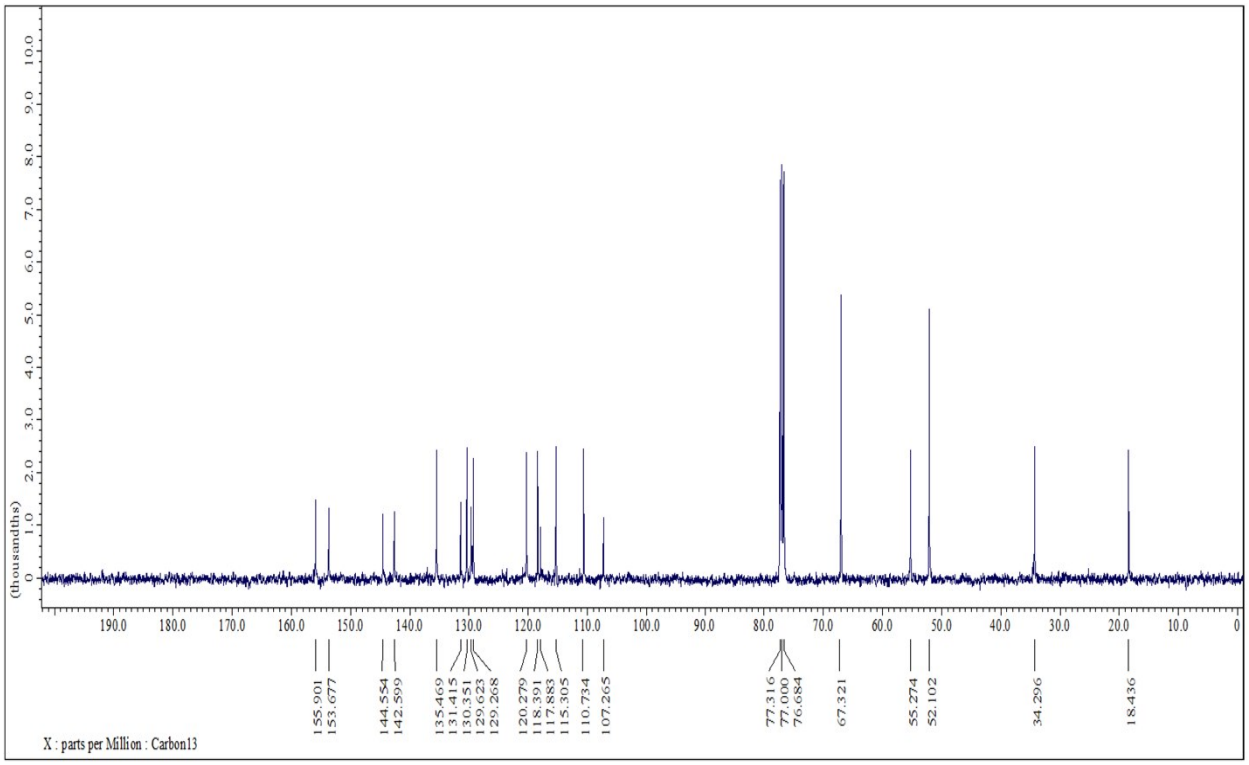




^{1}H and ^{13}C NMR of 2-allyl-4'-methoxy-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

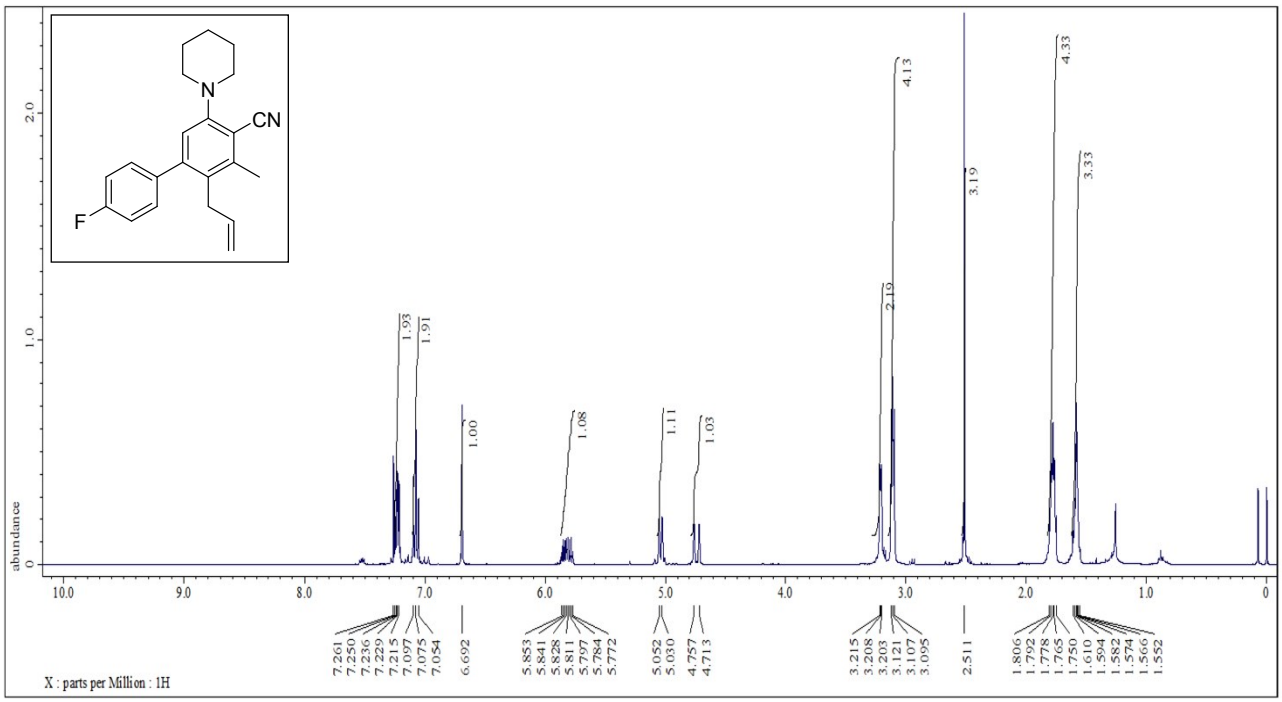
6g. 2-allyl-2'-methoxy-3-methyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile

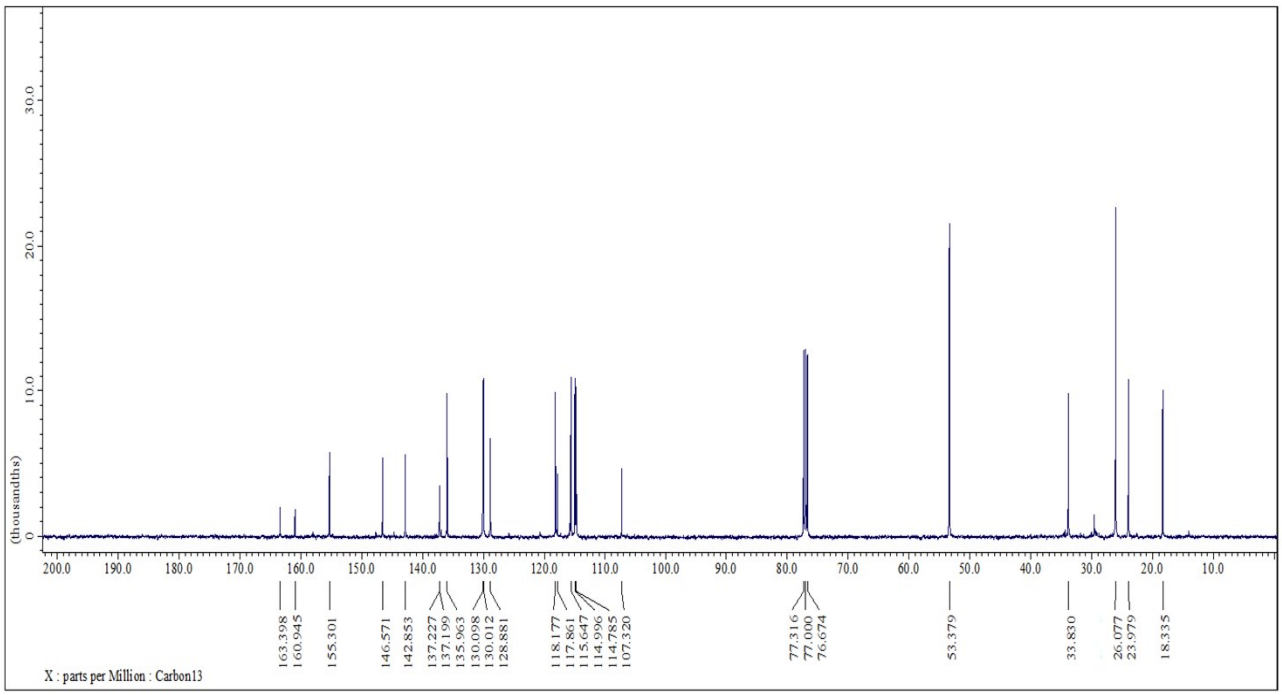




^{1}H and ^{13}C NMR of 2-allyl-2'-methoxy-3-methyl-5-morpholino-[1,1'-biphenyl]-4-carbonitrile

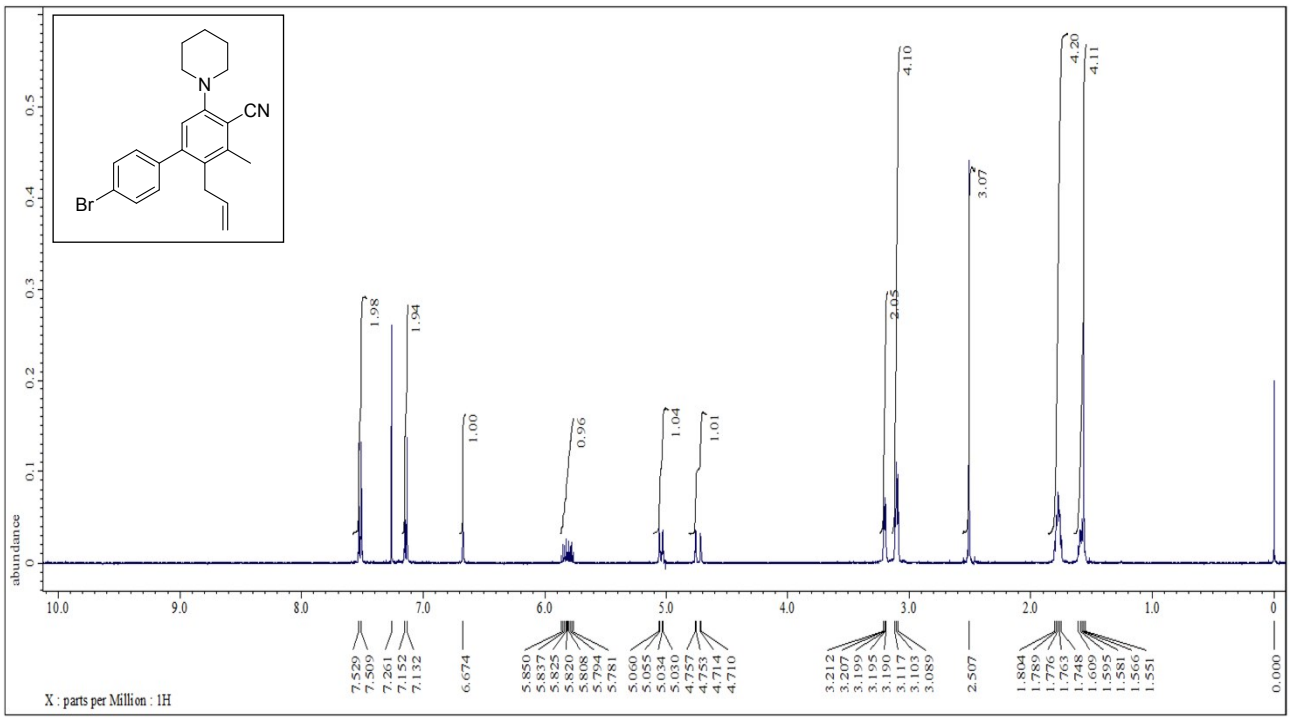
6h. 2-allyl-4'-fluoro-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

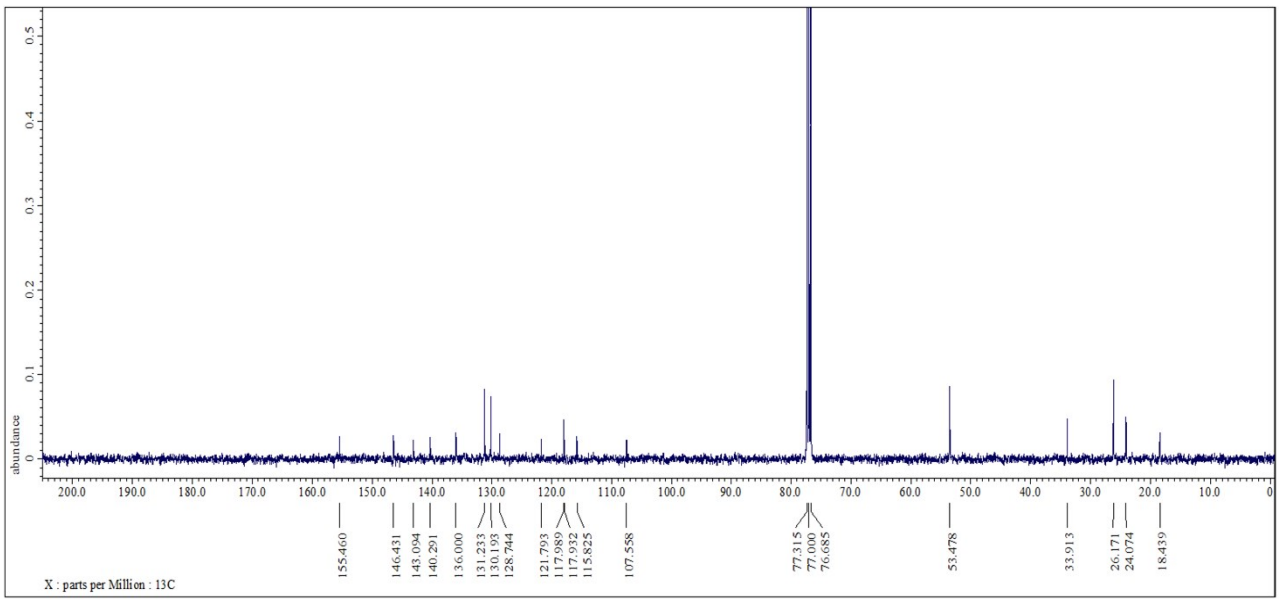




^{1}H and ^{13}C NMR of 2-allyl-4'-fluoro-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

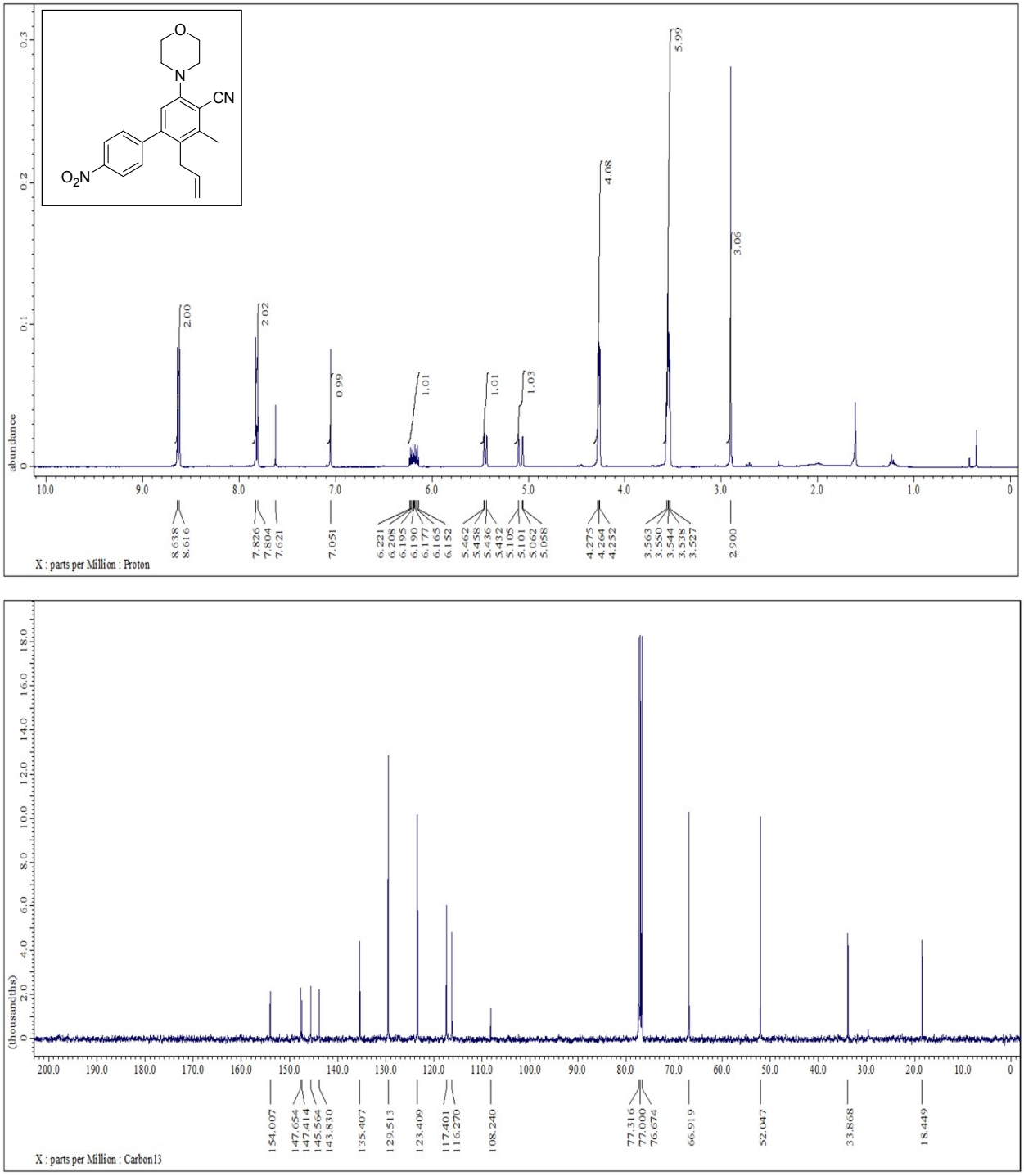
6i. 2-allyl-4'-bromo-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile





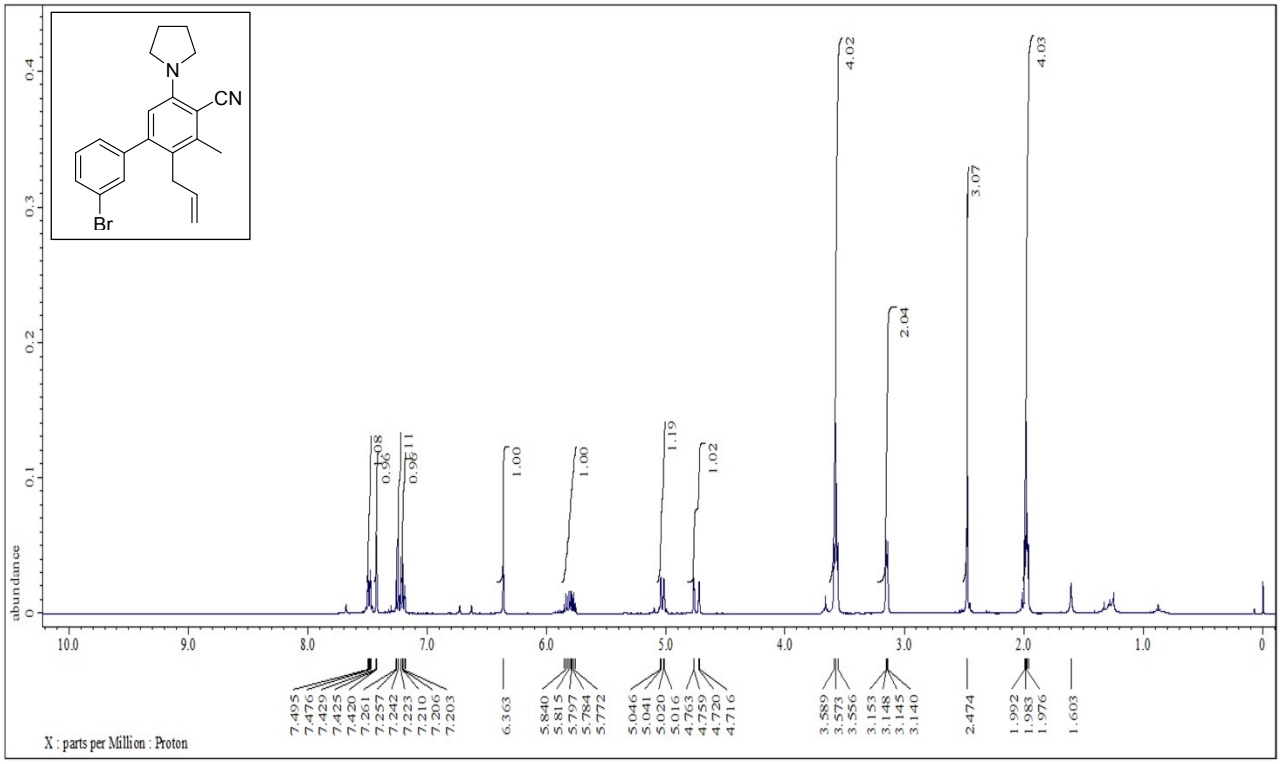
^{1}H and ^{13}C NMR of 2-allyl-4'-bromo-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

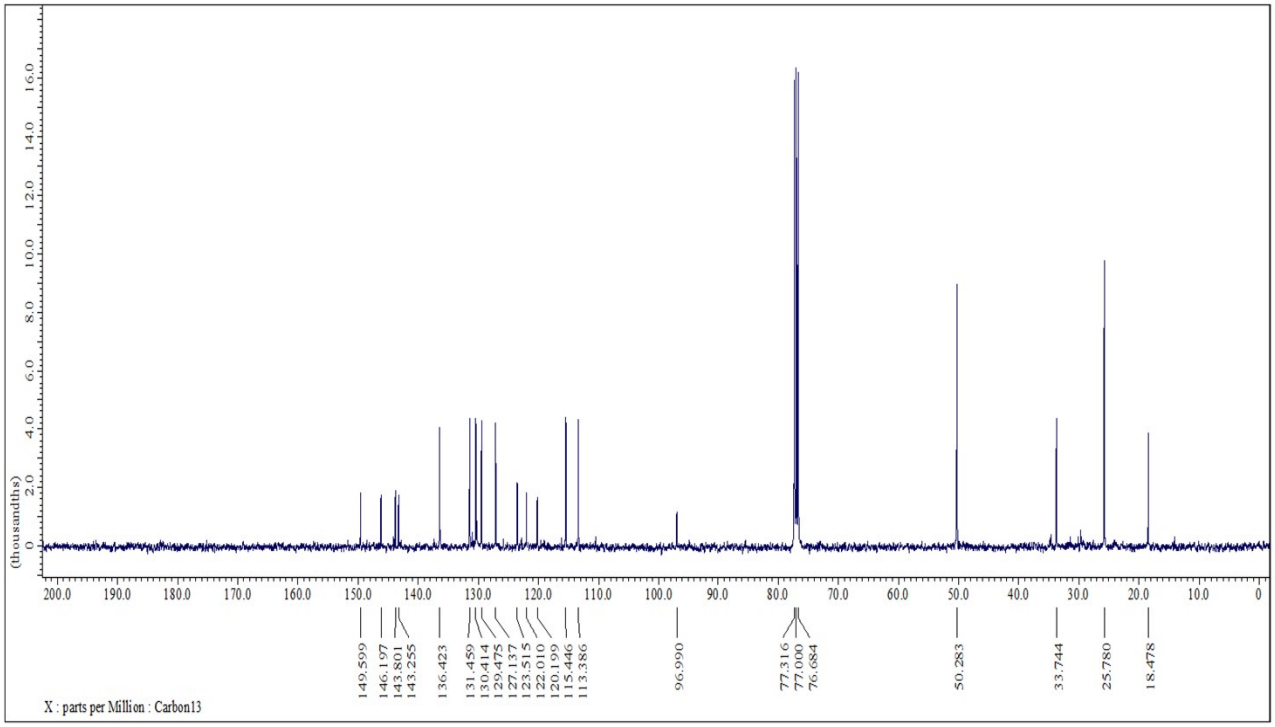
6j. 2-allyl-3-methyl-5-morpholino-4'-nitro-[1,1'-biphenyl]-4-carbonitrile



^{1}H and ^{13}C NMR of 2-allyl-3-methyl-5-morpholino-4'-nitro-[1,1'-biphenyl]-4-carbonitrile

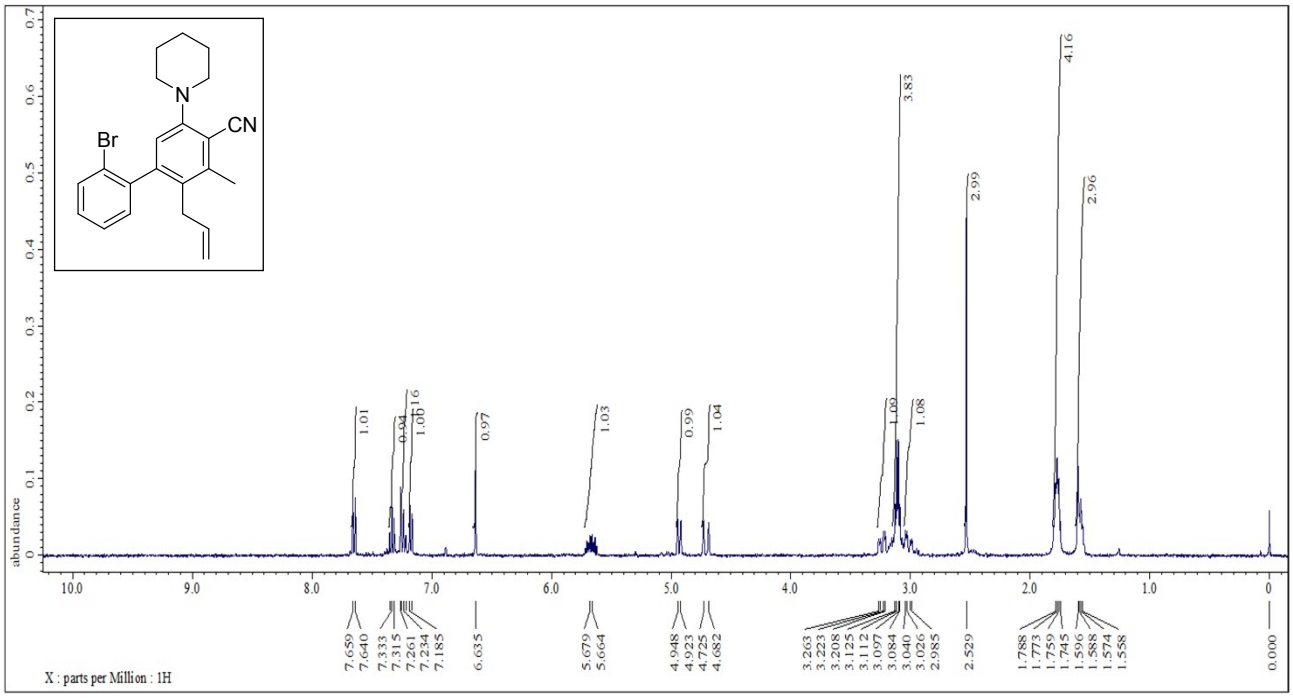
6k. 2-allyl-3'-bromo-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

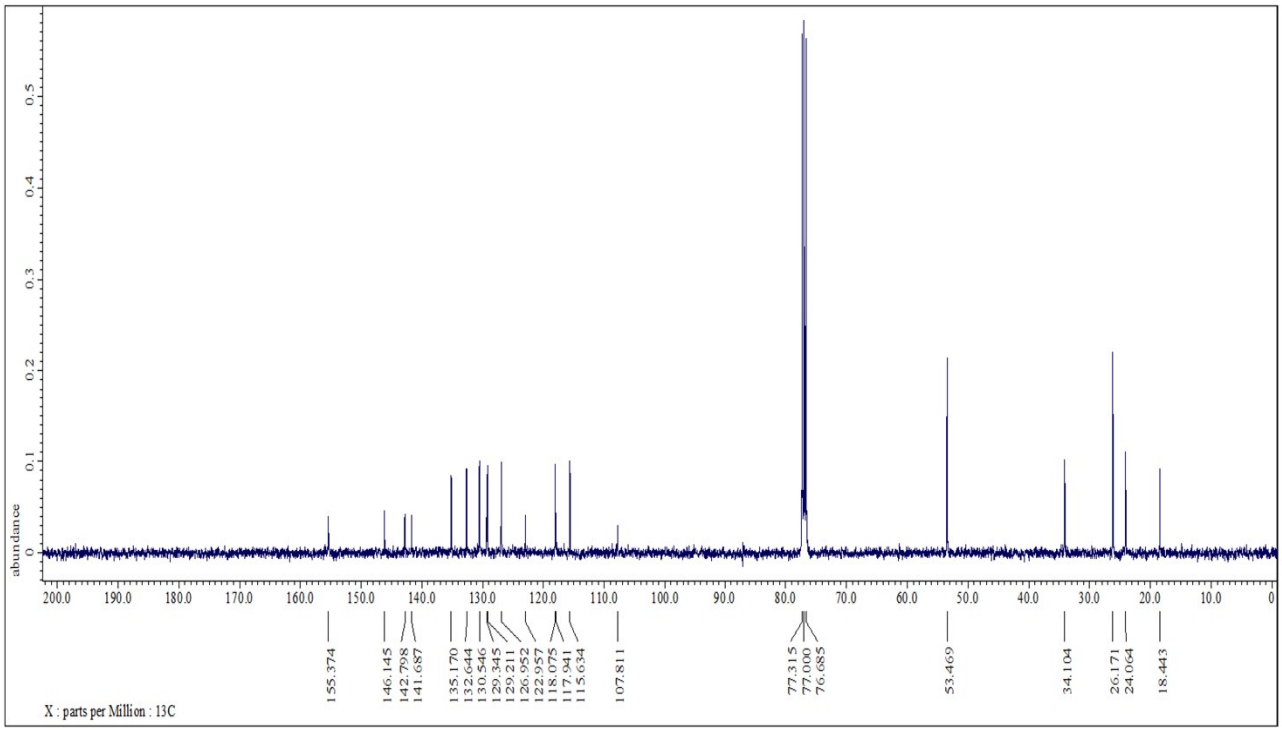




^{1}H and ^{13}C NMR of 2-allyl-3'-bromo-3-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

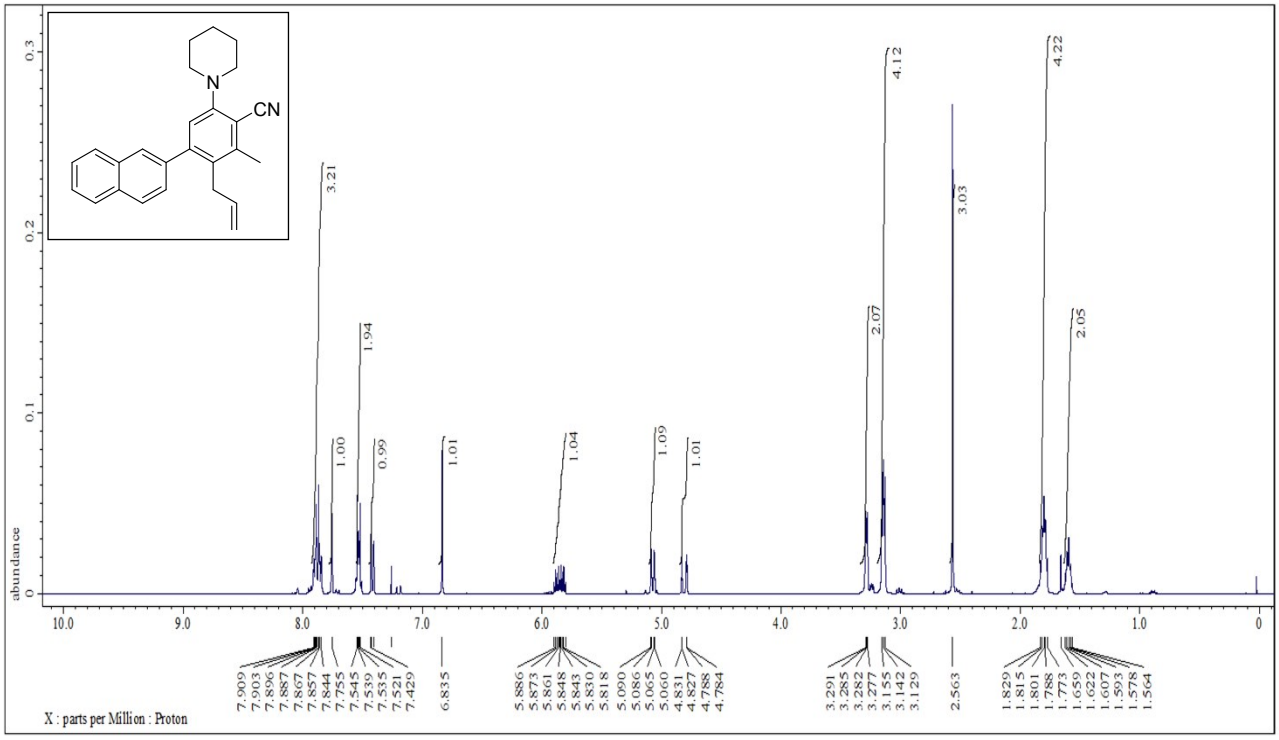
6l. 2-allyl-2'-bromo-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

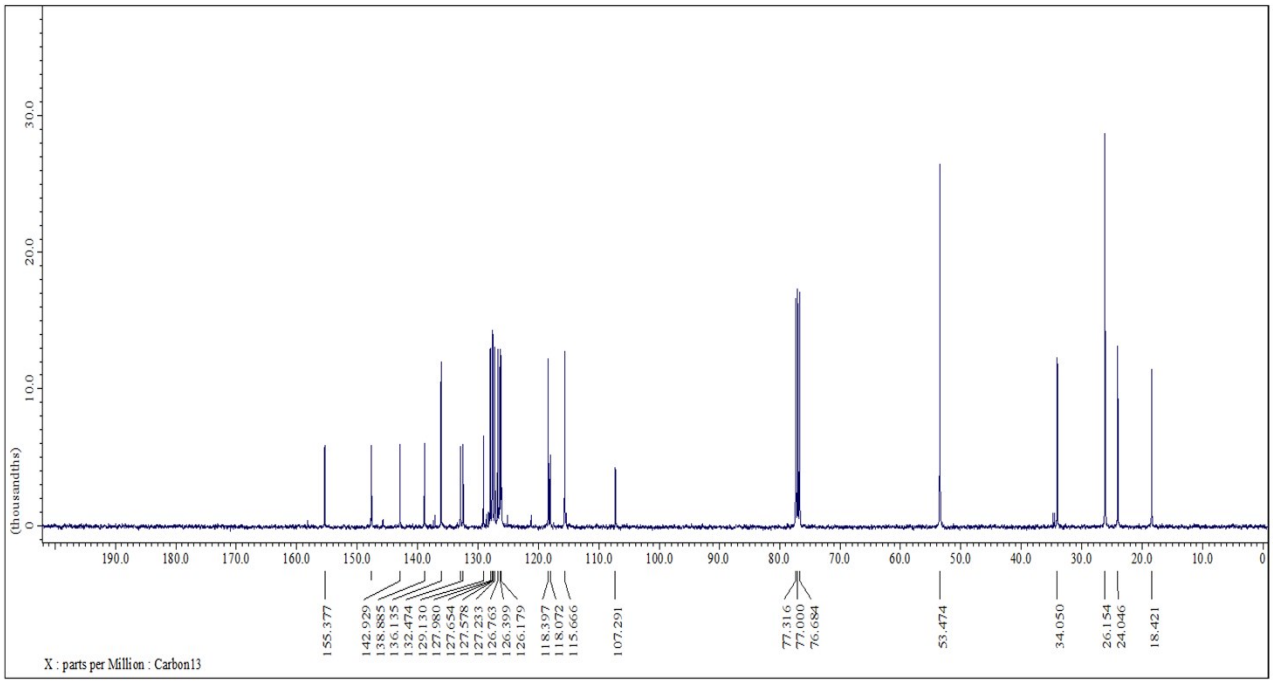




^{1}H and ^{13}C NMR of 2-allyl-2'-bromo-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

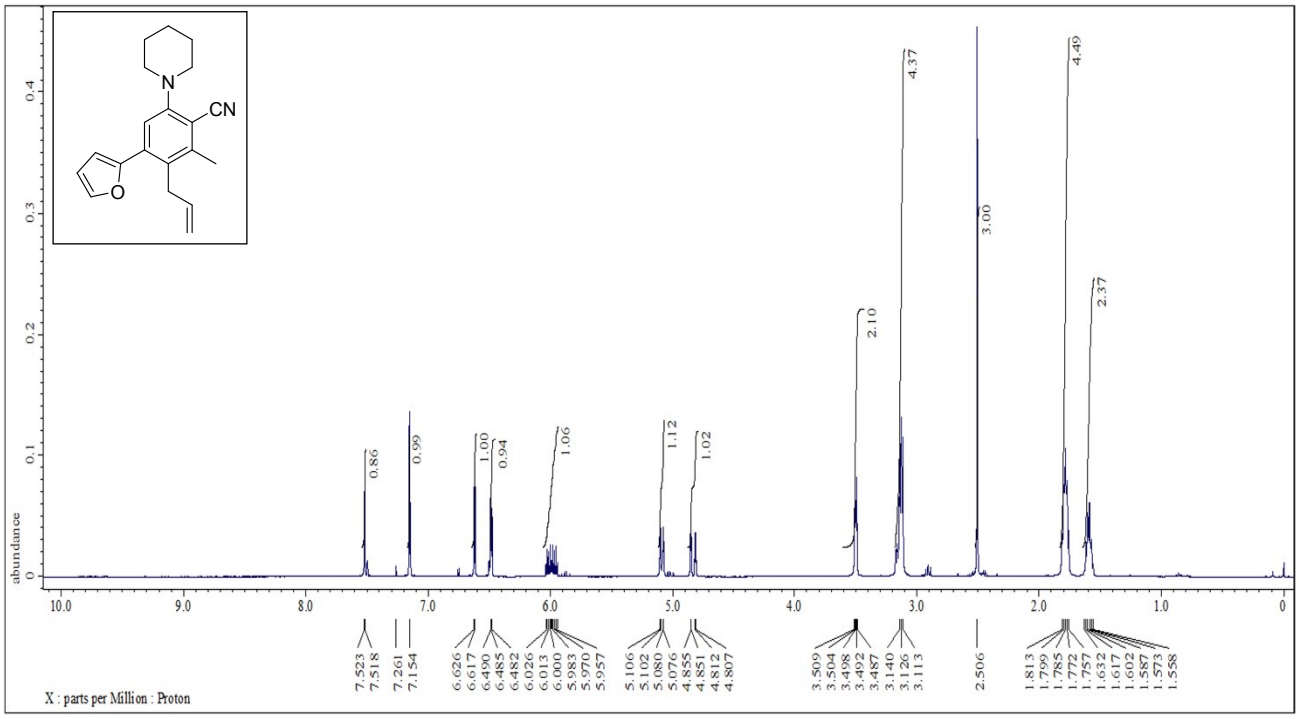
6m. 3-allyl-2-methyl-4-(naphthalen-2-yl)-6-(piperidin-1-yl)benzonitrile

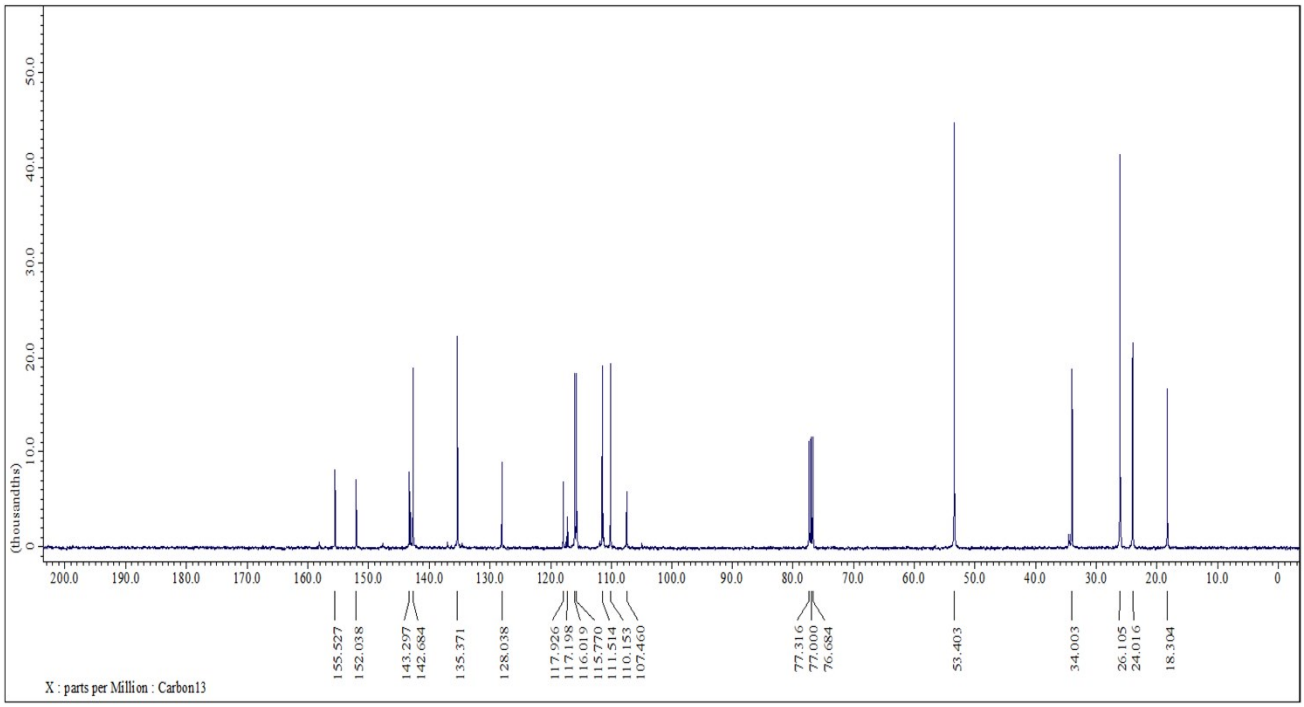




^{1}H and ^{13}C NMR of 3-allyl-2-methyl-4-(naphthalen-2-yl)-6-(piperidin-1-yl)benzonitrile

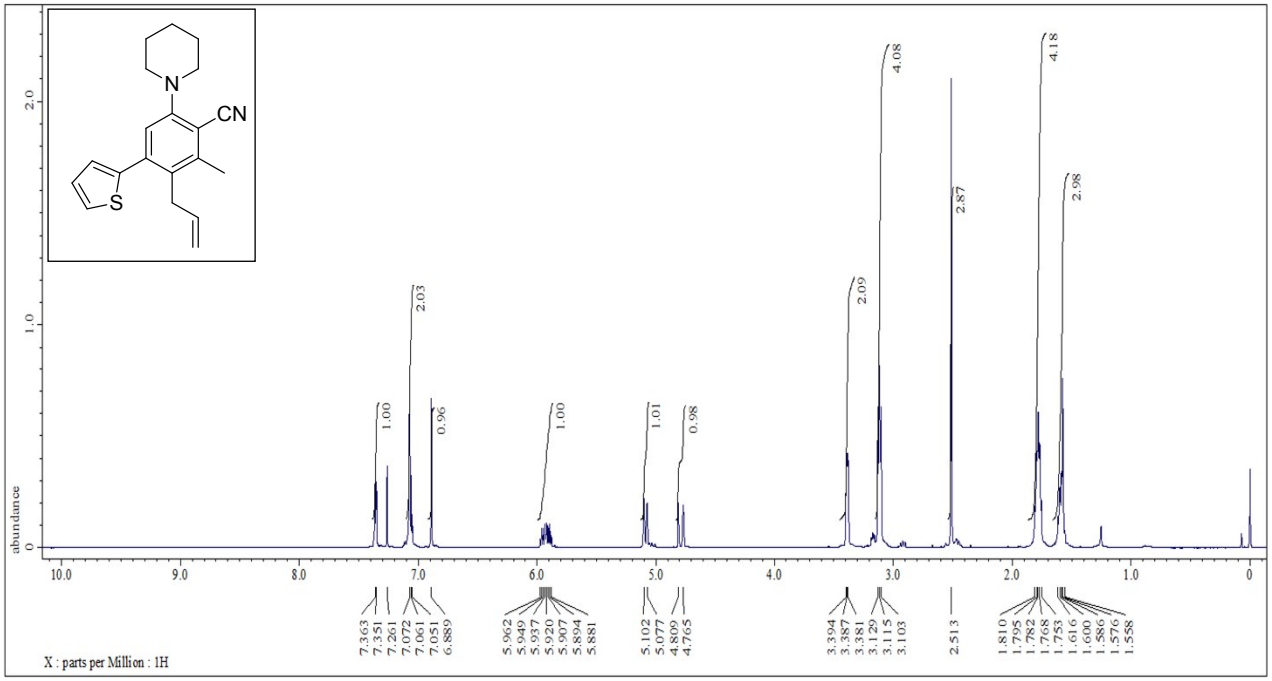
6n. 3-allyl-4-(furan-2-yl)-2-methyl-6-(piperidin-1-yl)benzonitrile

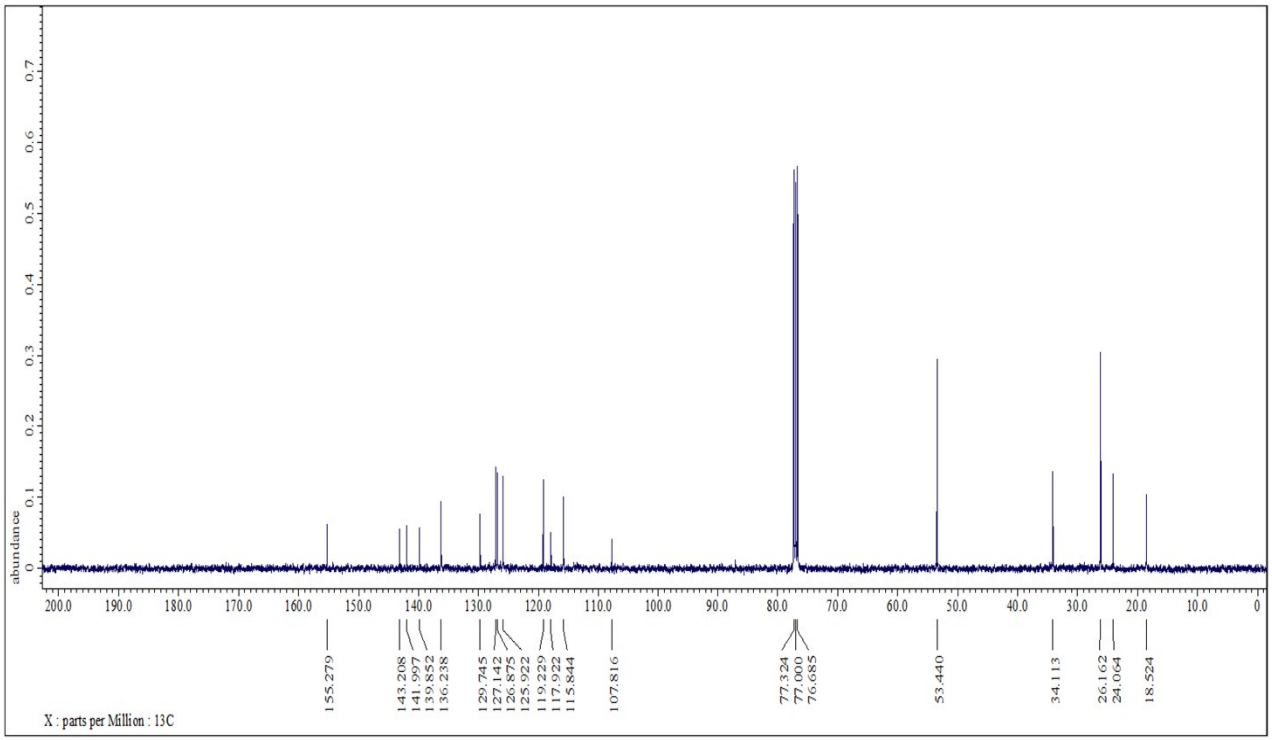




^{1}H and ^{13}C NMR of 3-allyl-4-(furan-2-yl)-2-methyl-6-(piperidin-1-yl)benzonitrile

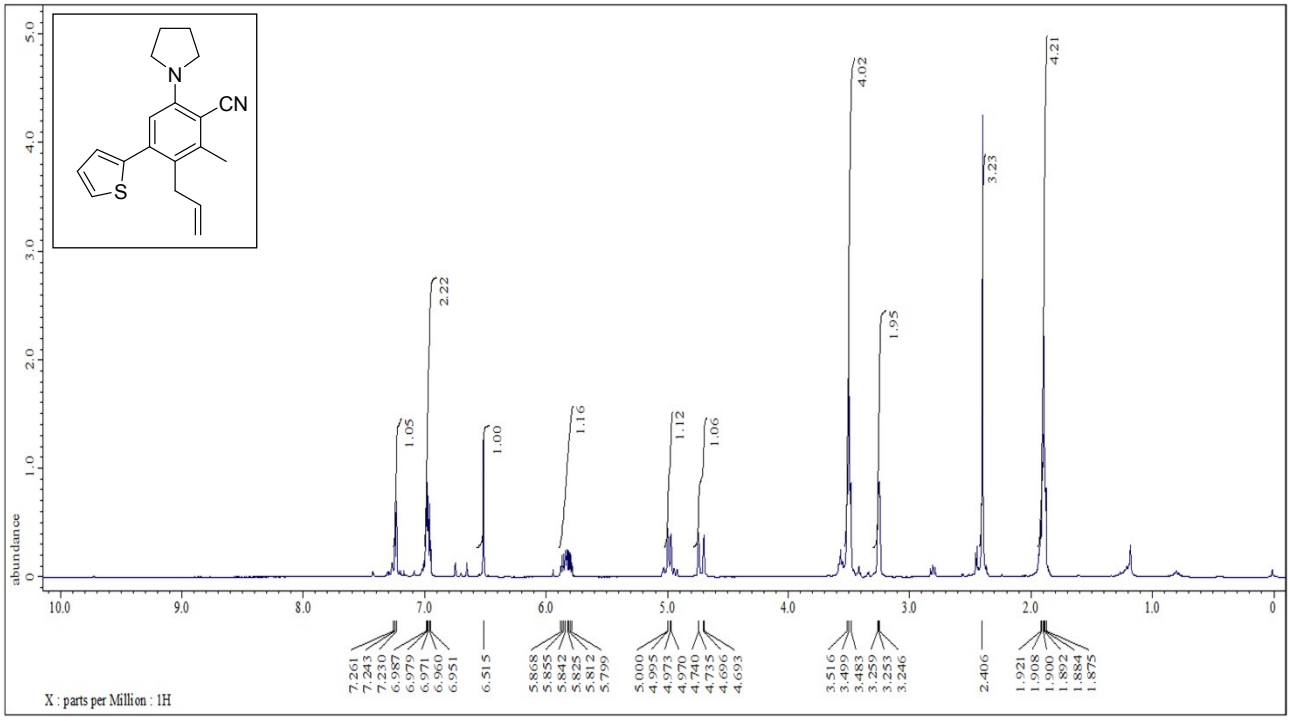
6o. 3-allyl-2-methyl-6-(piperidin-1-yl)-4-(thiophen-2-yl)benzonitrile

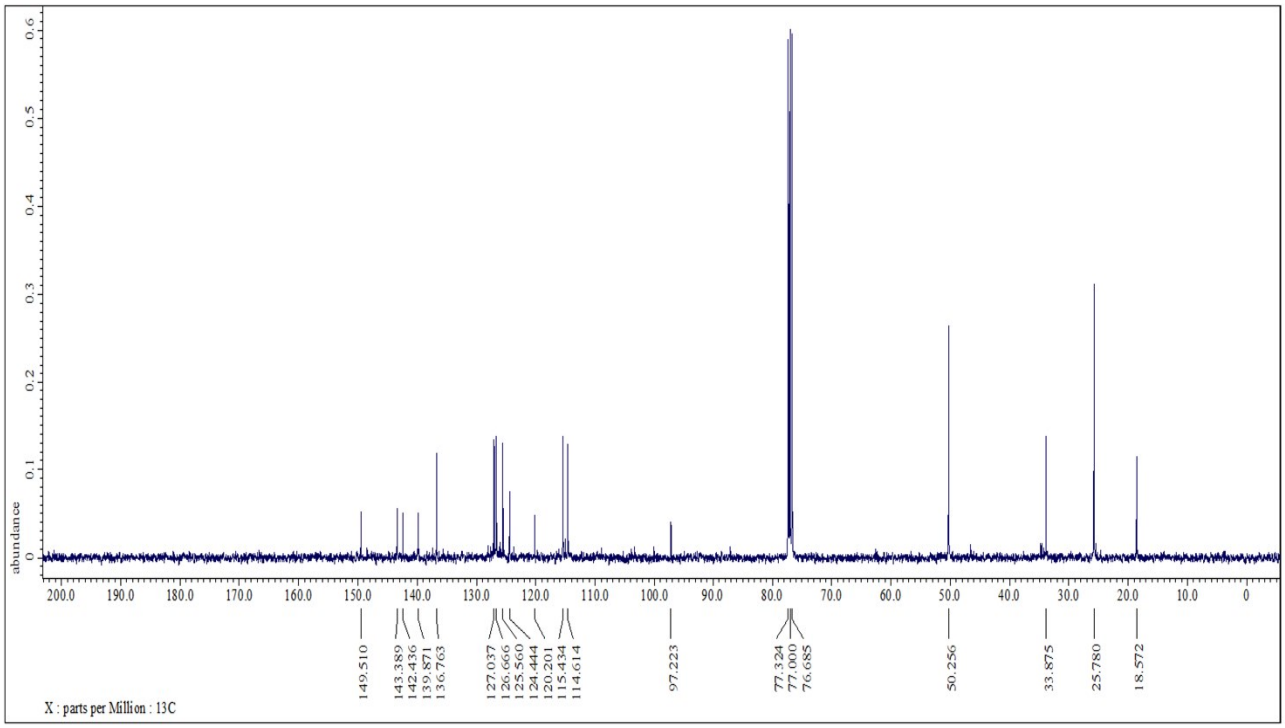




^{1}H and ^{13}C NMR of 3-allyl-2-methyl-6-(piperidin-1-yl)-4-(thiophen-2-yl)benzonitrile

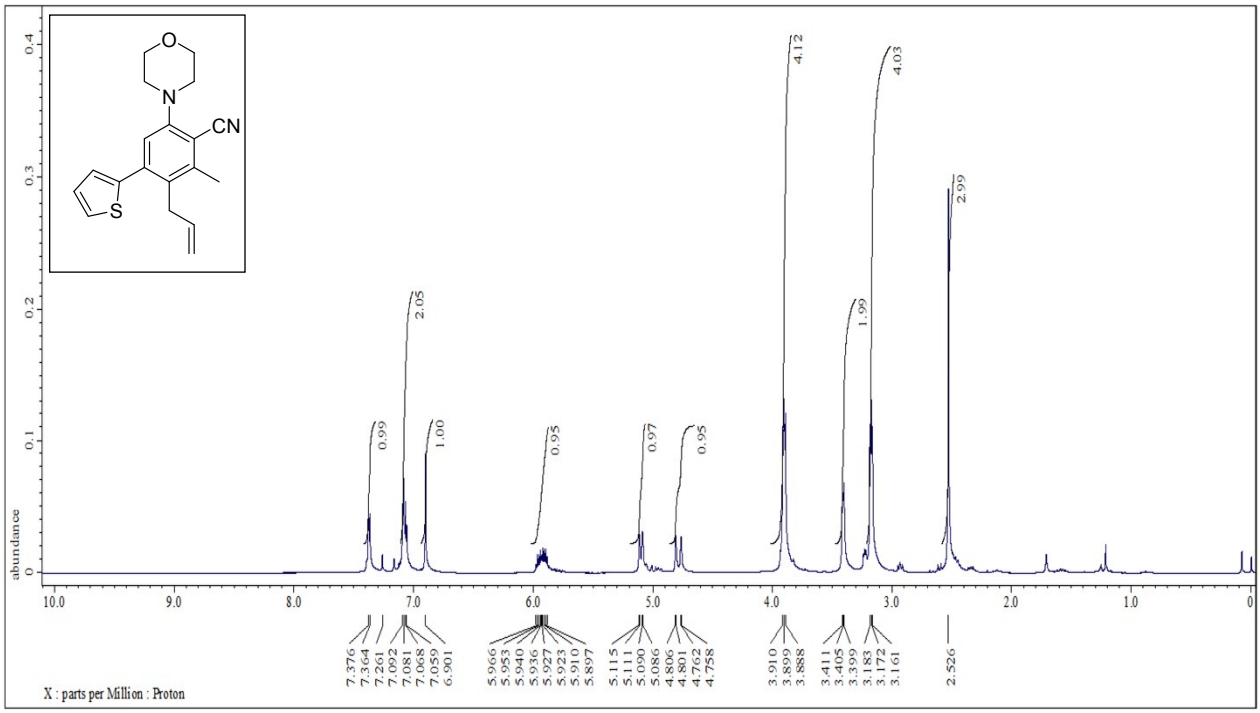
6p. 3-allyl-2-methyl-6-(pyrrolidin-1-yl)-4-(thiophen-2-yl)benzonitrile

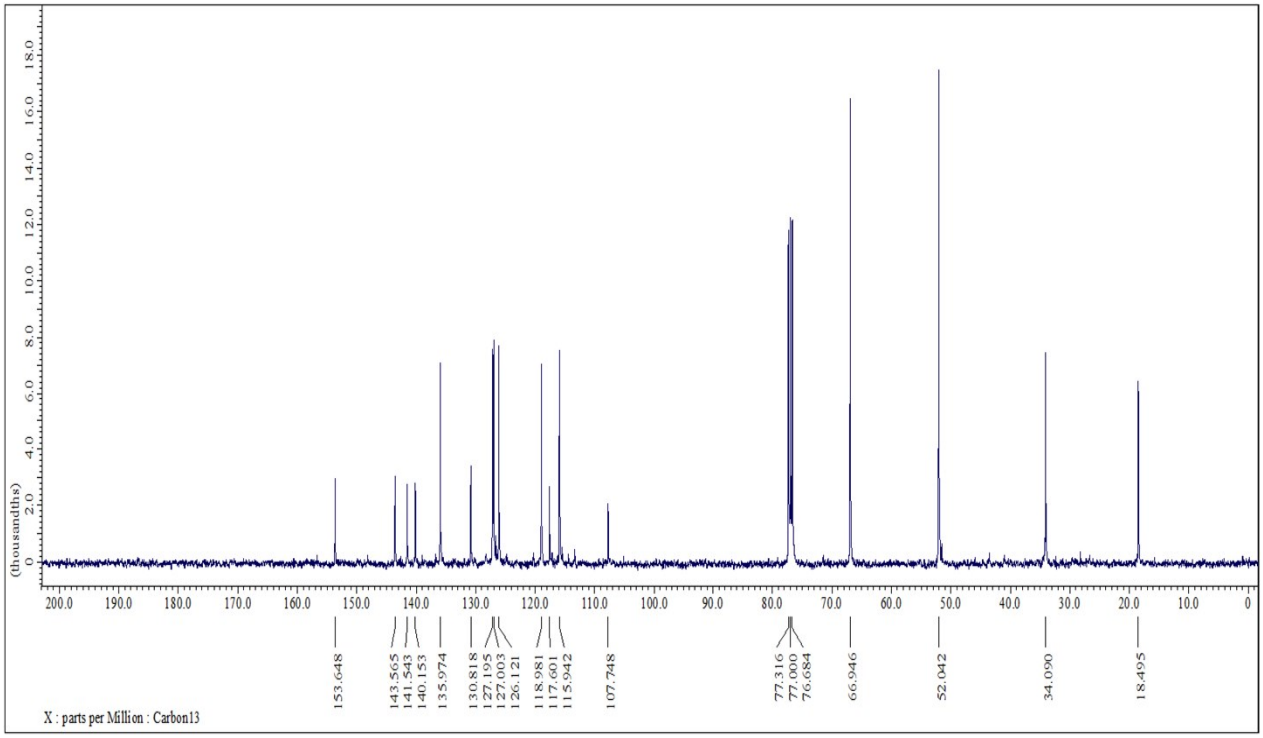




^{1}H and ^{13}C NMR of 3-allyl-2-methyl-6-(pyrrolidin-1-yl)-4-(thiophen-2-yl)benzonitrile

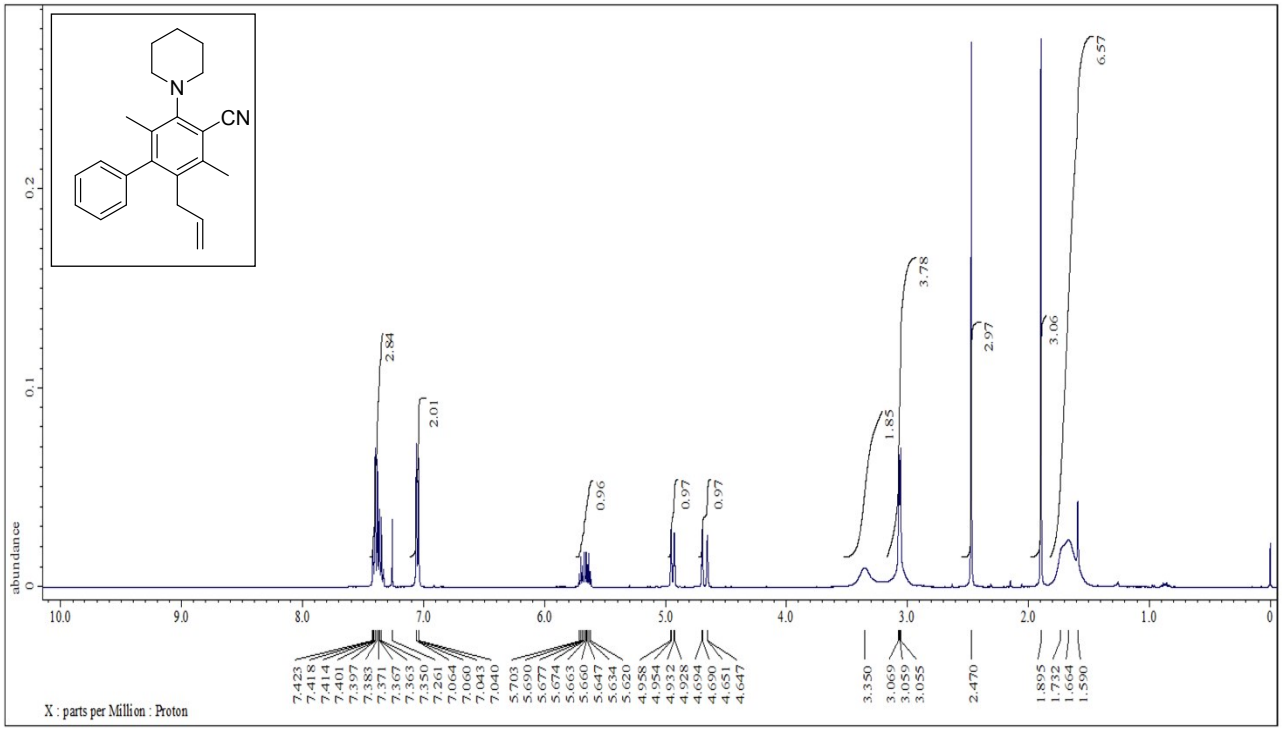
6q. 3-allyl-2-methyl-6-morpholino-4-(thiophen-2-yl)benzonitrile

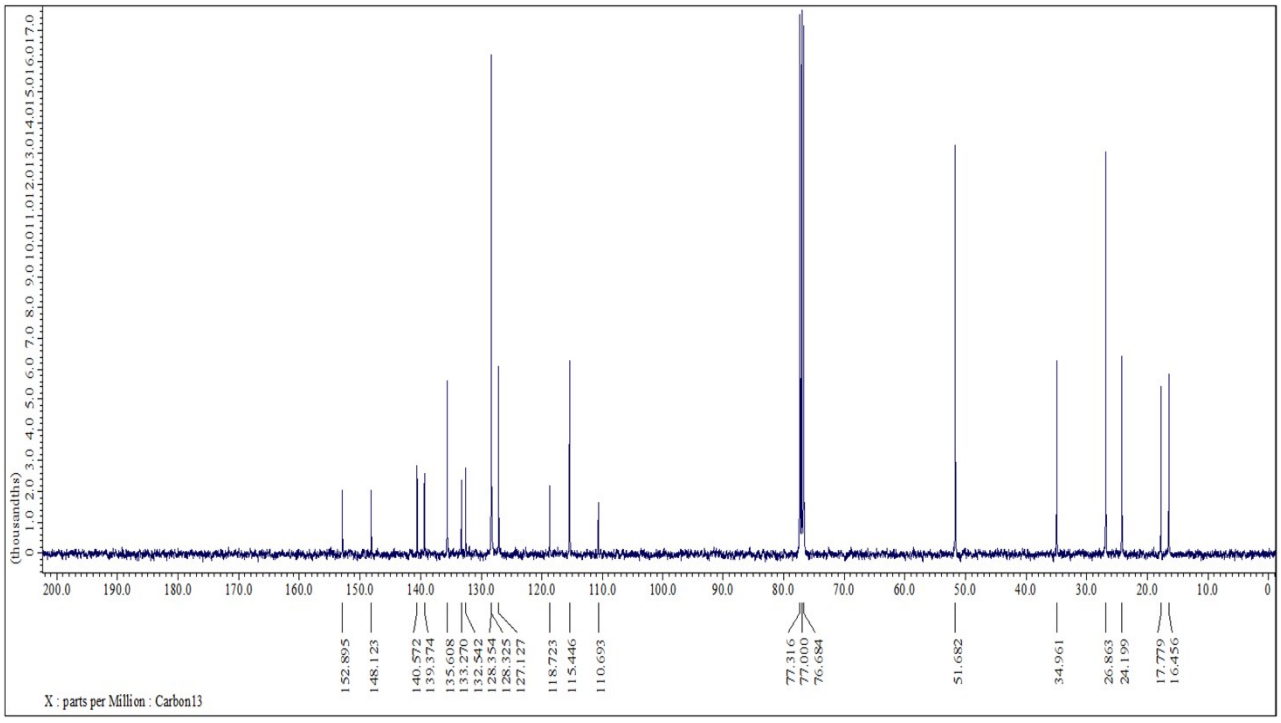




^{1}H and ^{13}C NMR of 3-allyl-2-methyl-6-morpholino-4-(thiophen-2-yl)benzonitrile

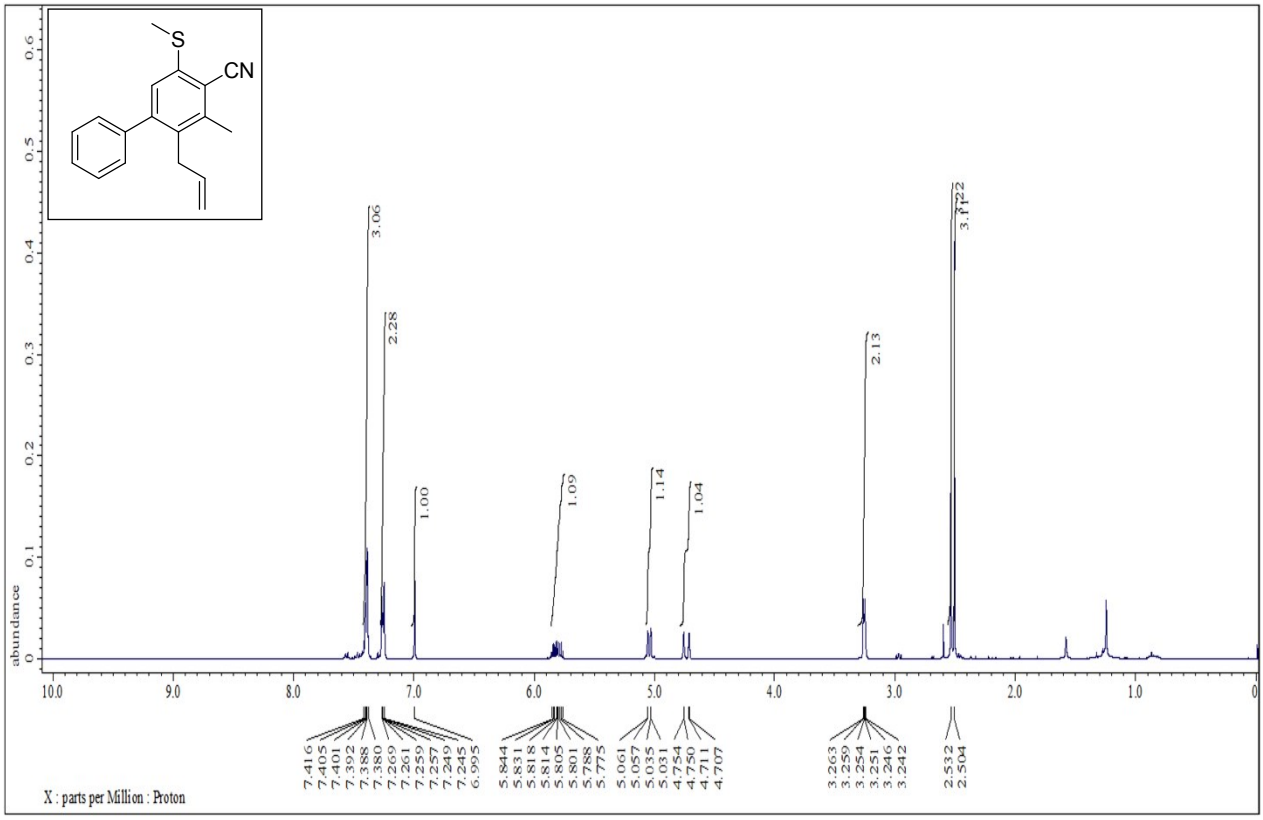
6r. 2-allyl-3,6-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

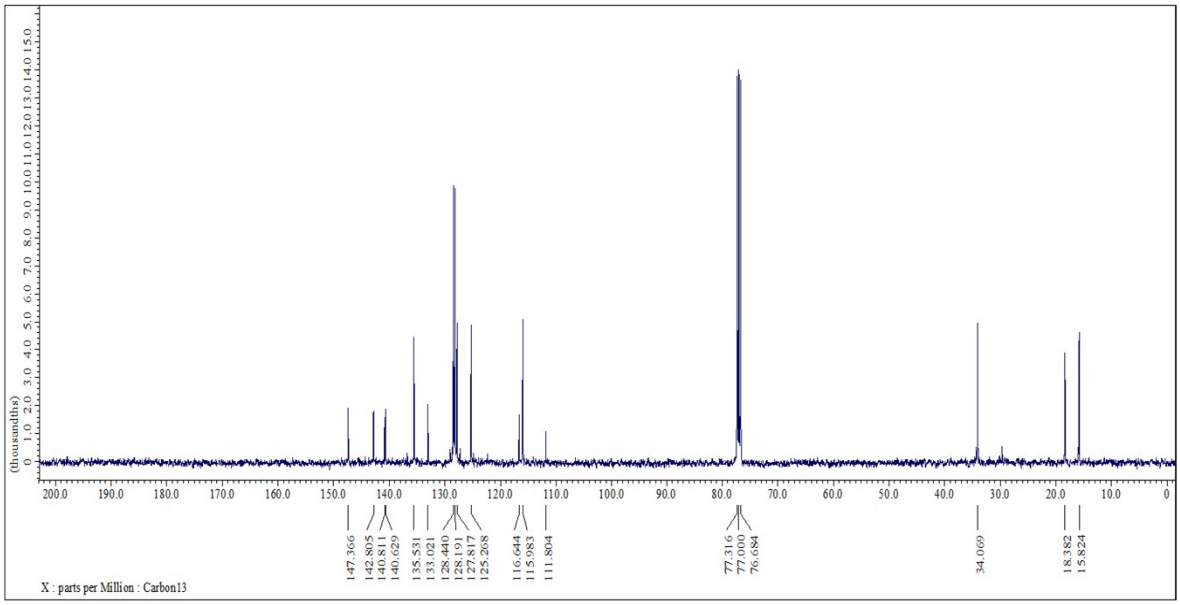




^{1}H and ^{13}C NMR of 2-allyl-3,6-dimethyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile

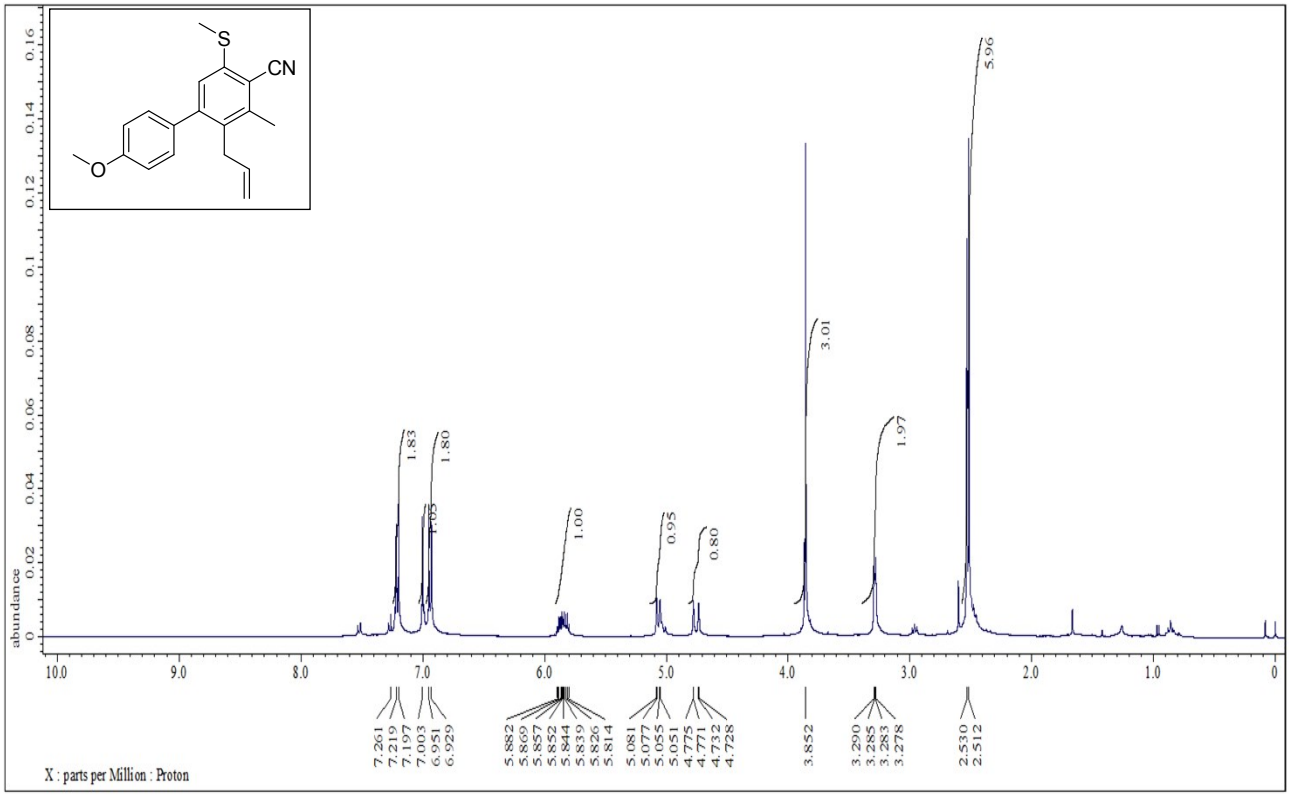
7a. 2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile

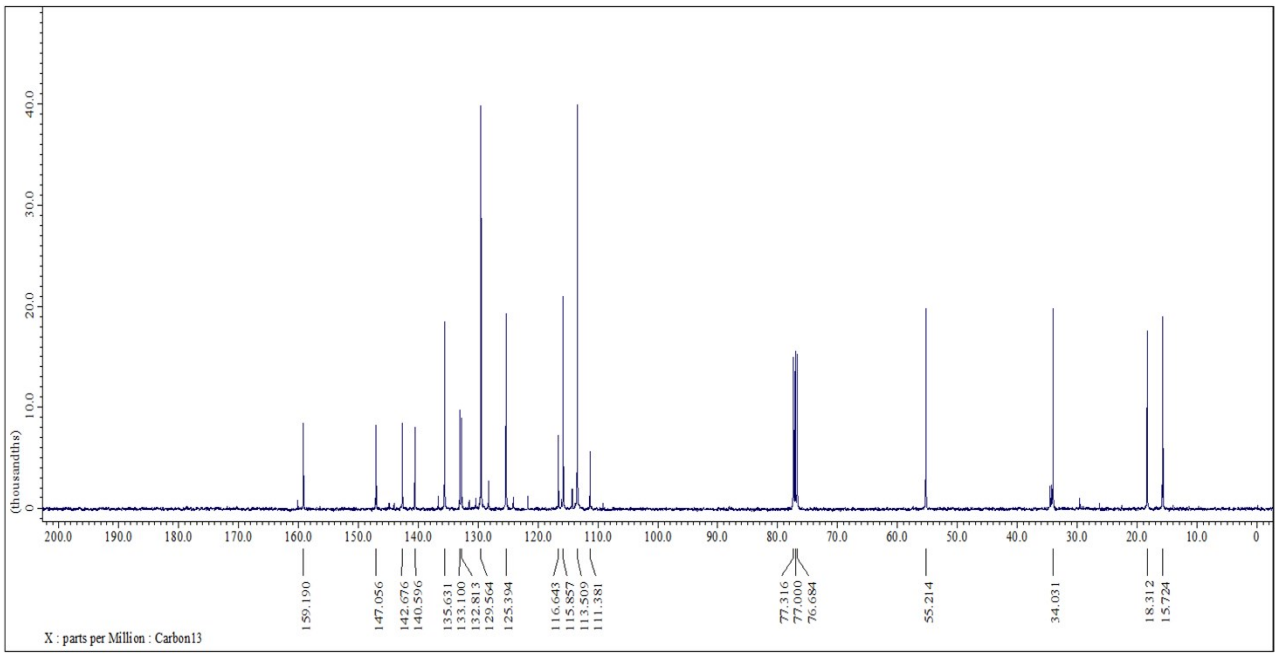




^{1}H and ^{13}C NMR of 2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile

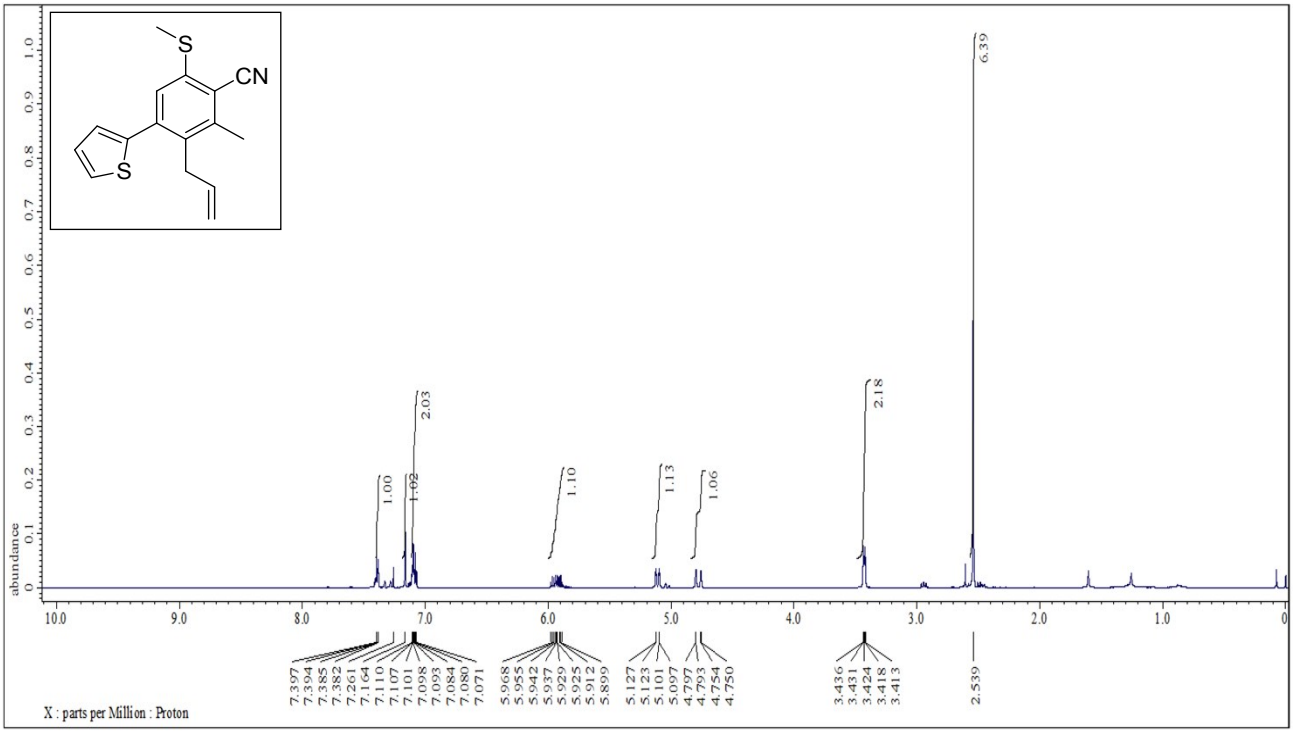
7b. 2-allyl-4'-methoxy-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile

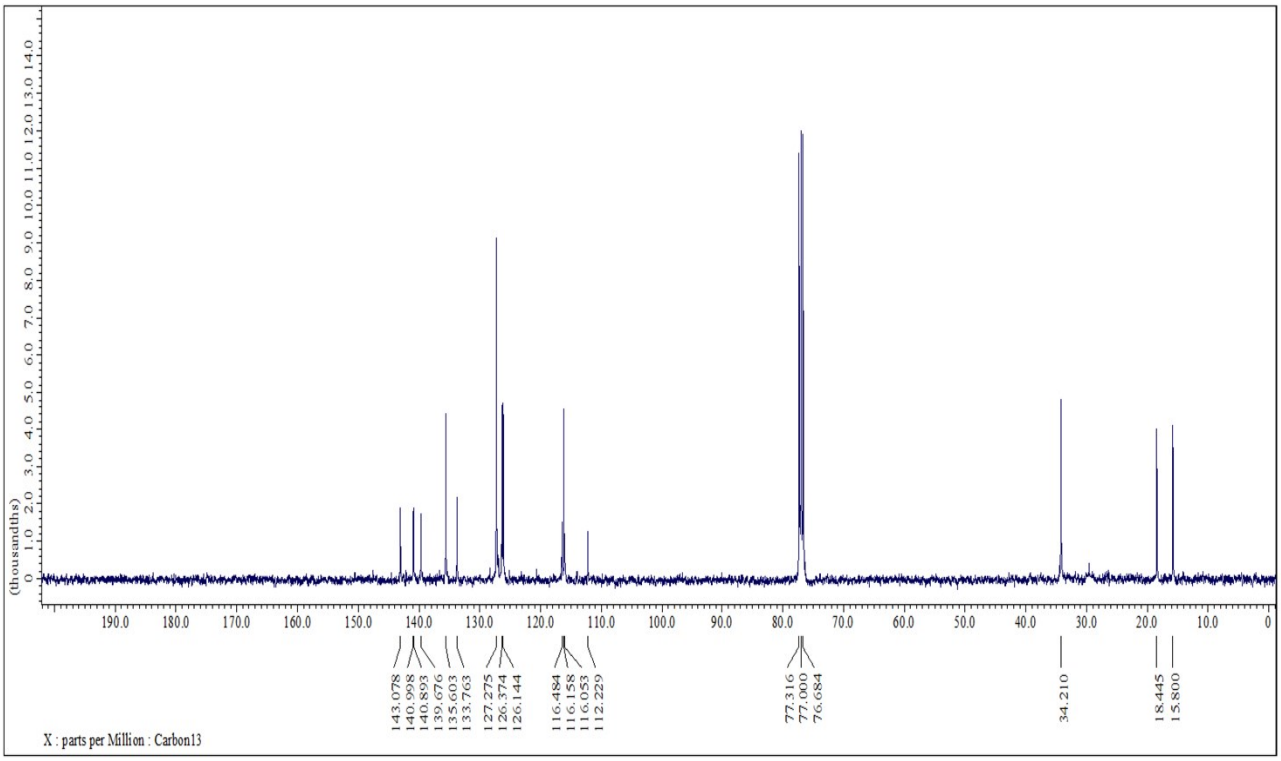




^{1}H and ^{13}C NMR of 2-allyl-4'-methoxy-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carbonitrile

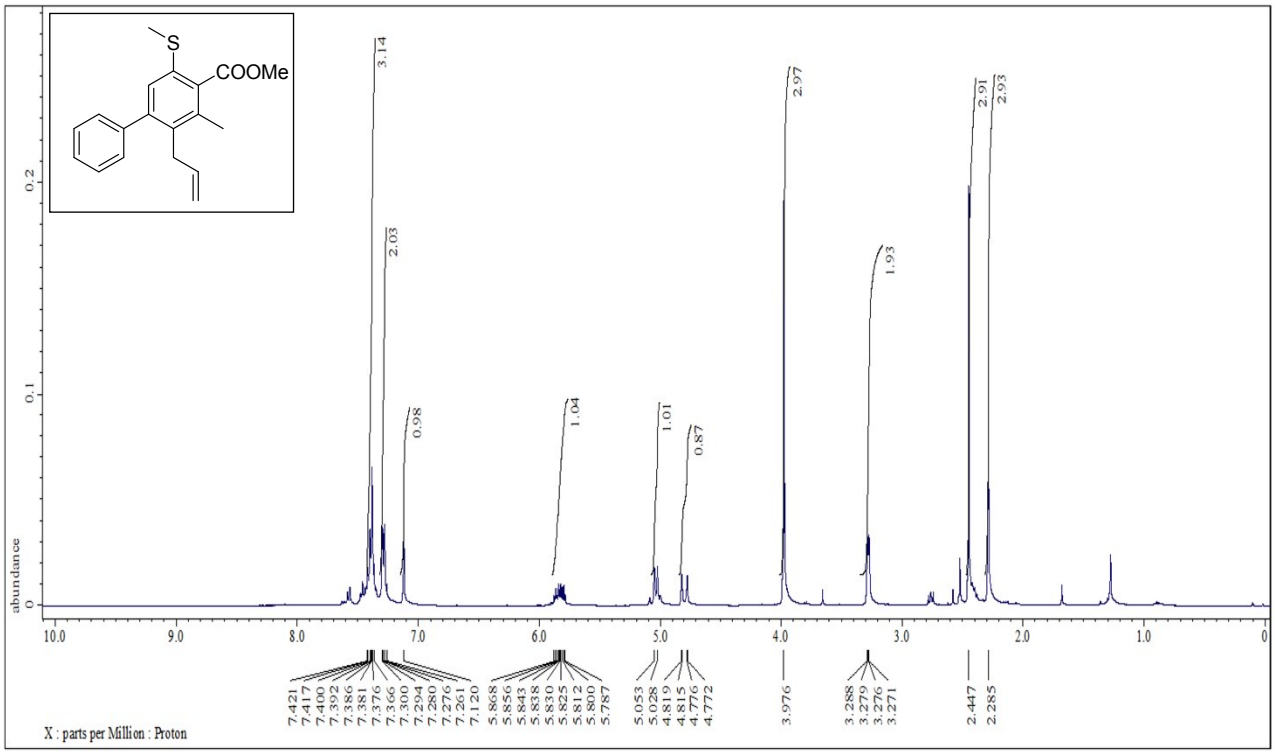
7c. 3-allyl-2-methyl-6-(methylthio)-4-(thiophen-2-yl)benzonitrile

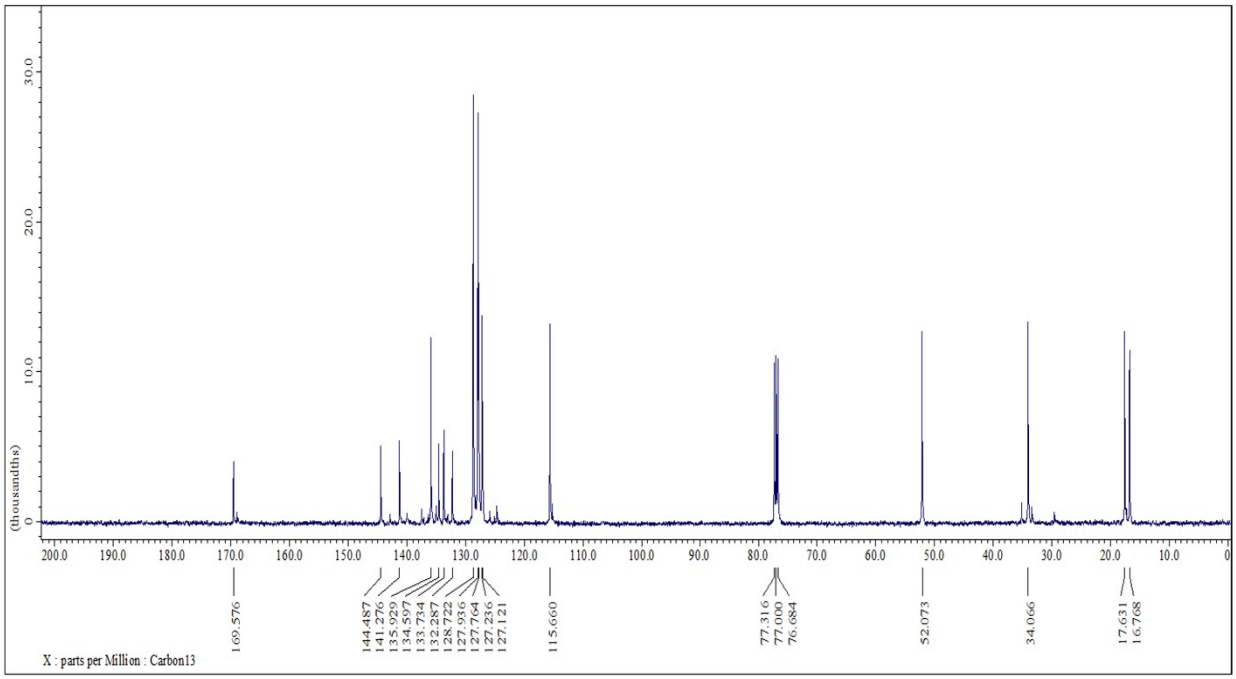




^{1}H and ^{13}C NMR of 3-allyl-2-methyl-6-(methylthio)-4-(thiophen-2-yl)benzonitrile

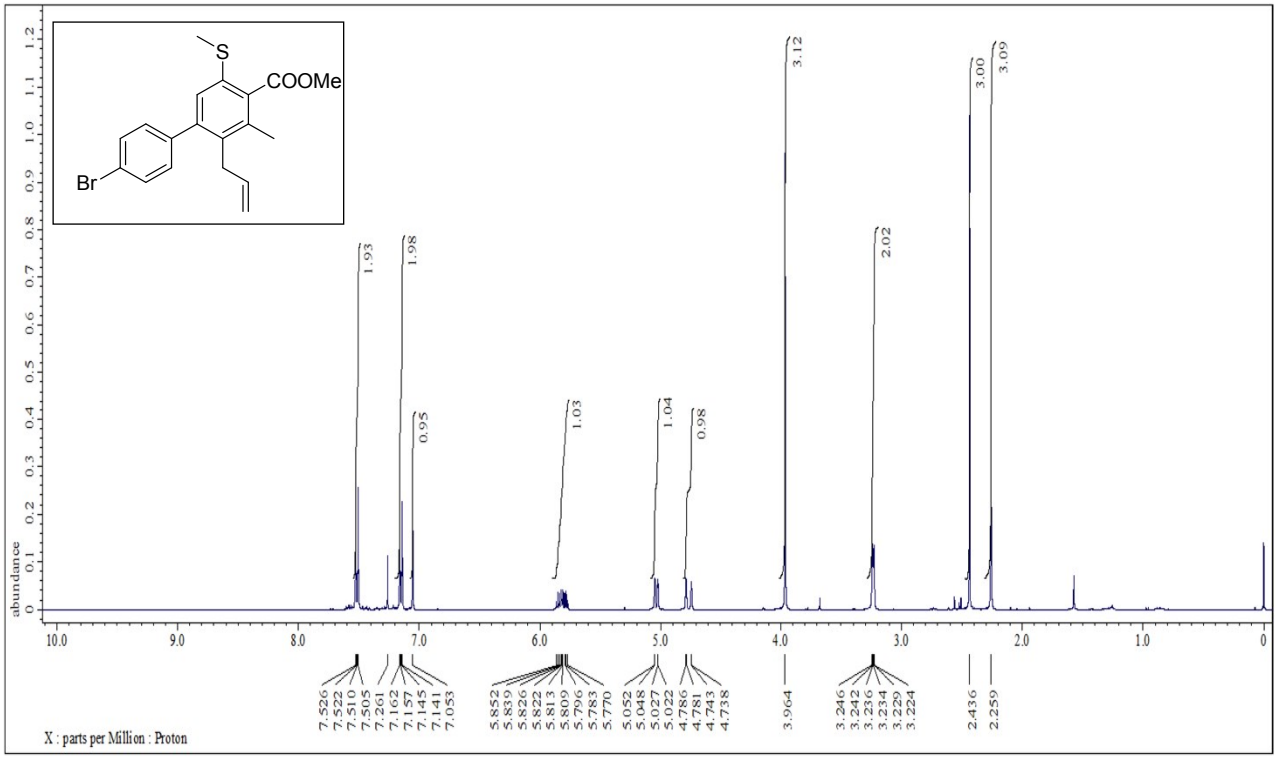
7d. methyl 2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carboxylate

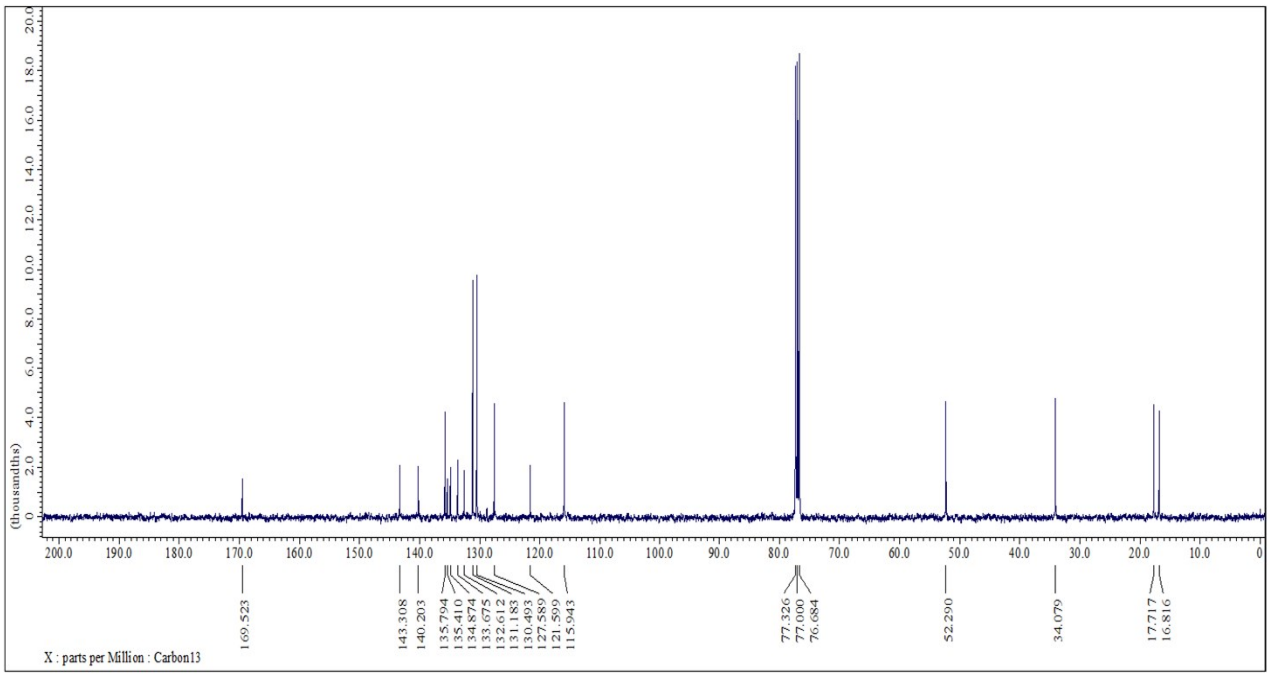




^{1}H and ^{13}C NMR of methyl 2-allyl-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carboxylate

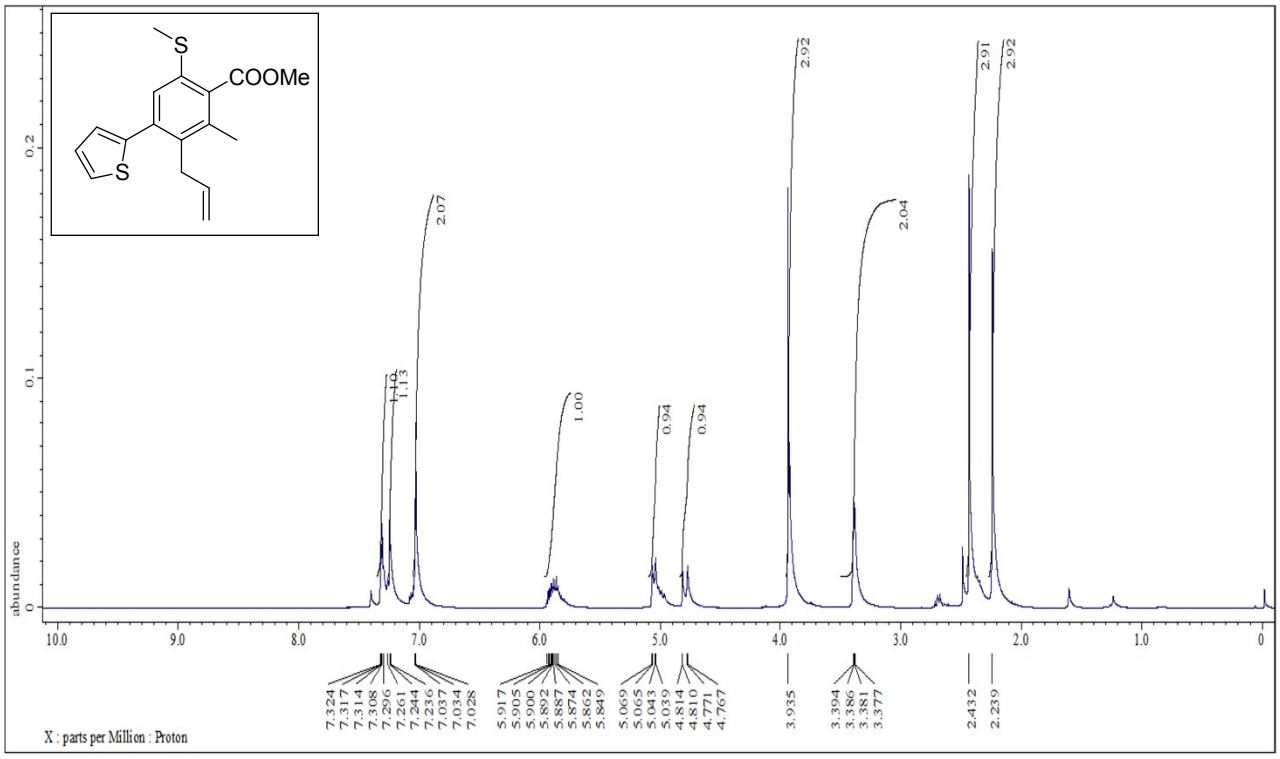
7e. methyl 2-allyl-4'-bromo-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carboxylate

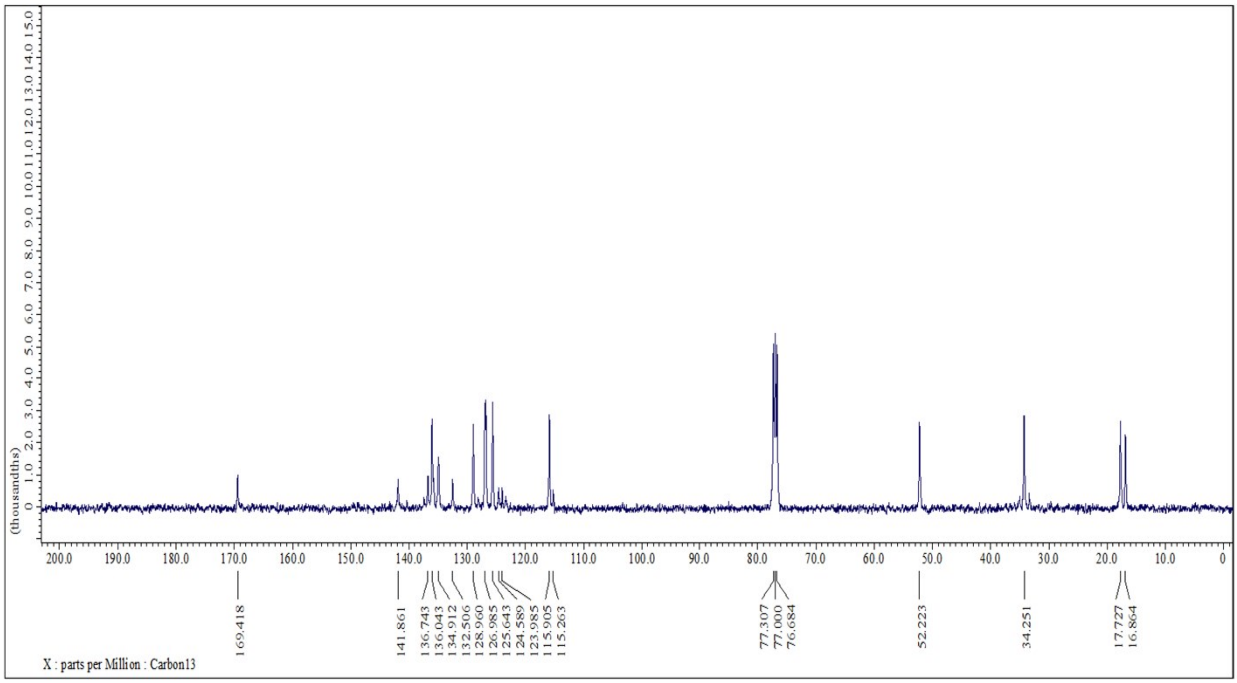




^{1}H and ^{13}C NMR ofmethyl 2-allyl-4'-bromo-3-methyl-5-(methylthio)-[1,1'-biphenyl]-4-carboxylate

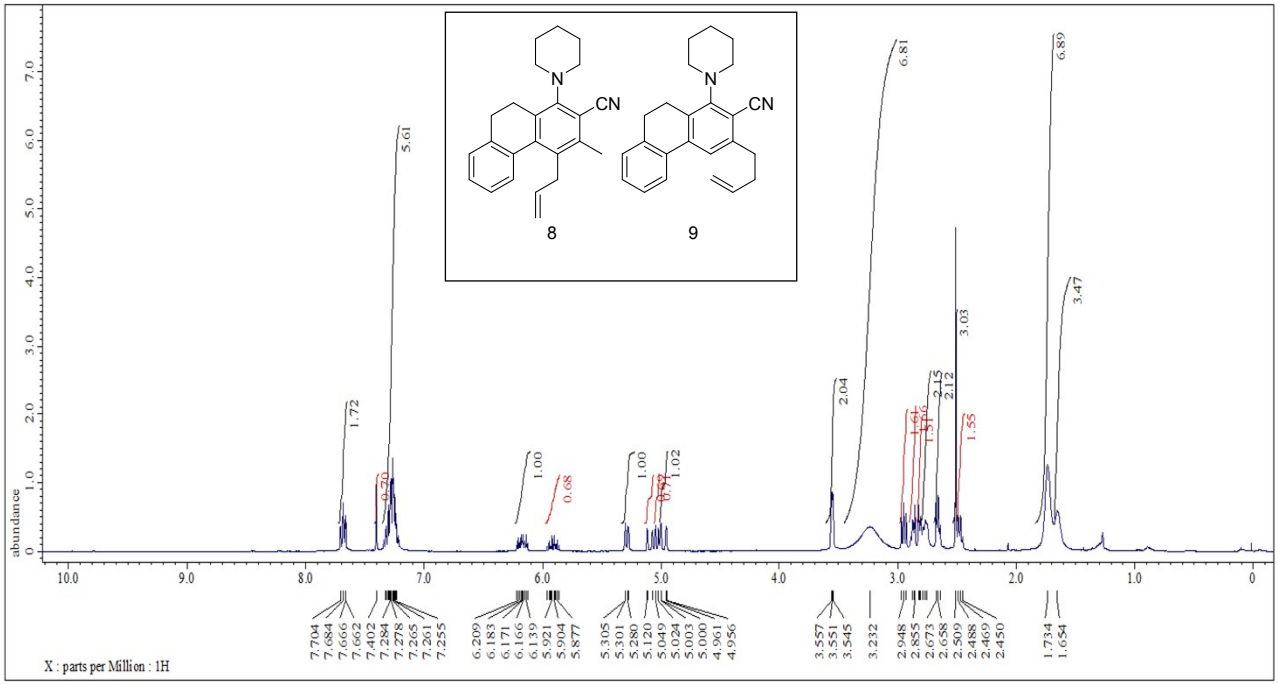
7f. methyl 3-allyl-2-methyl-6-(methylthio)-4-(thiophen-2-yl)benzoate

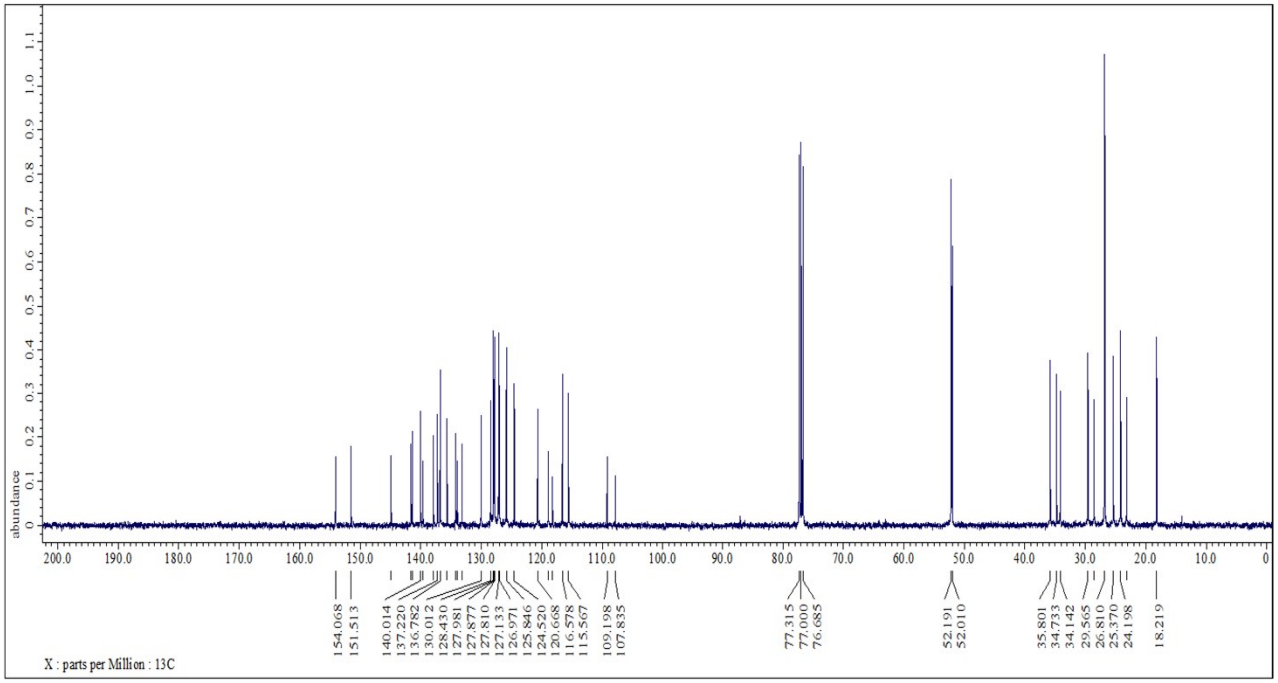




^{1}H and ^{13}C NMR of methyl 3-allyl-2-methyl-6-(methylthio)-4-(thiophen-2-yl)benzoate

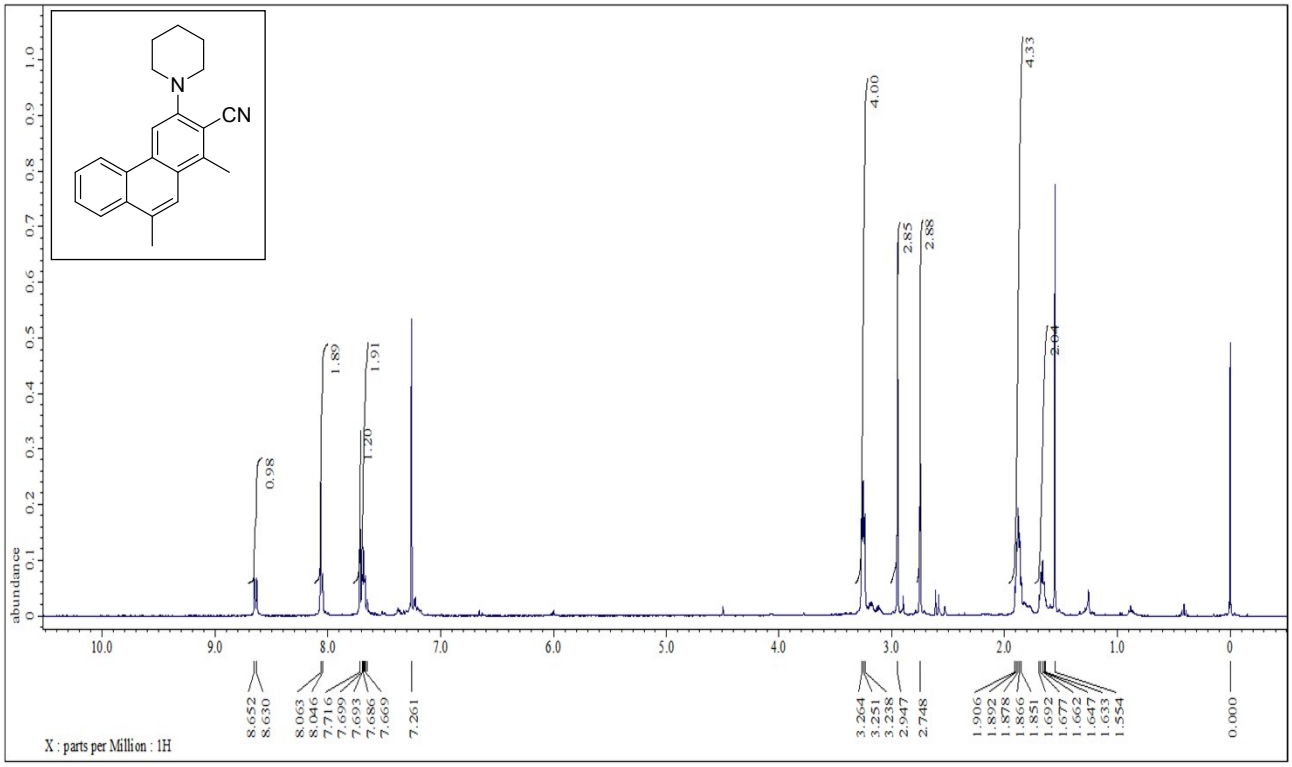
8. 4-allyl-3-methyl-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile and 9. 3-(but-3-en-1-yl)-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile

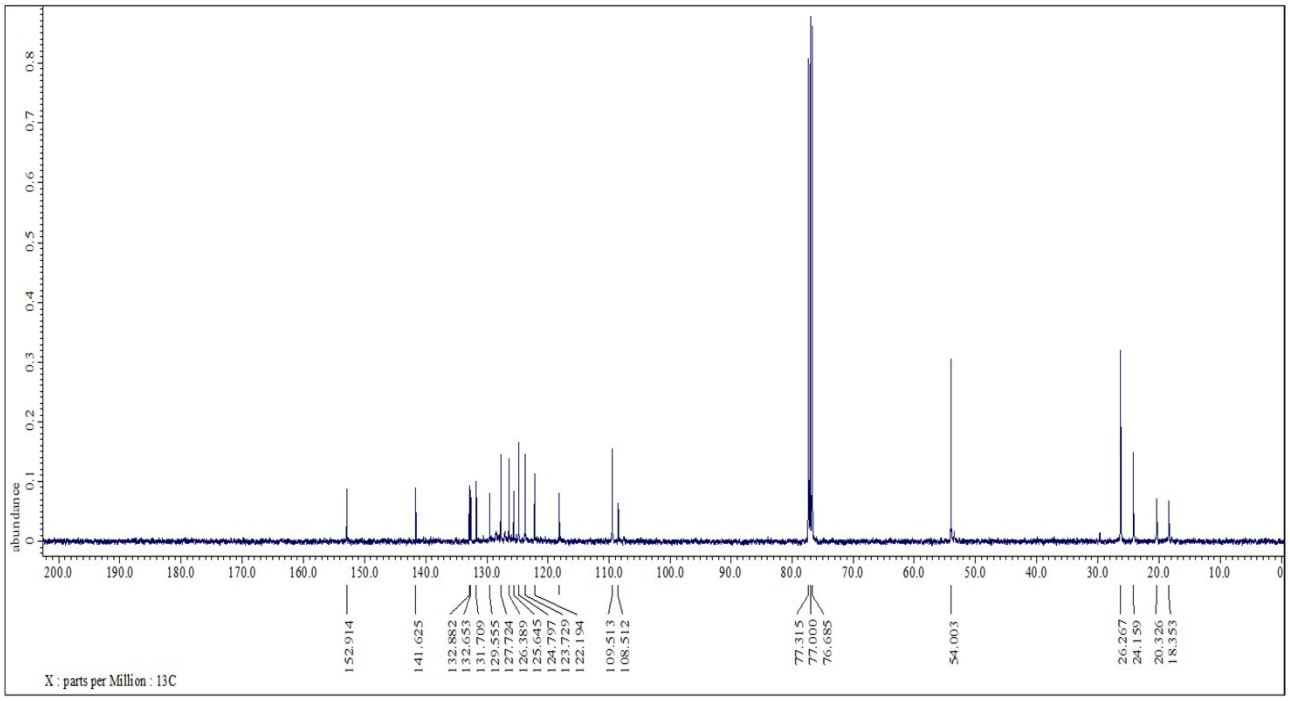




^{1}H and ^{13}C NMR of 4-allyl-3-methyl-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile and 3-(but-3-en-1-yl)-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile

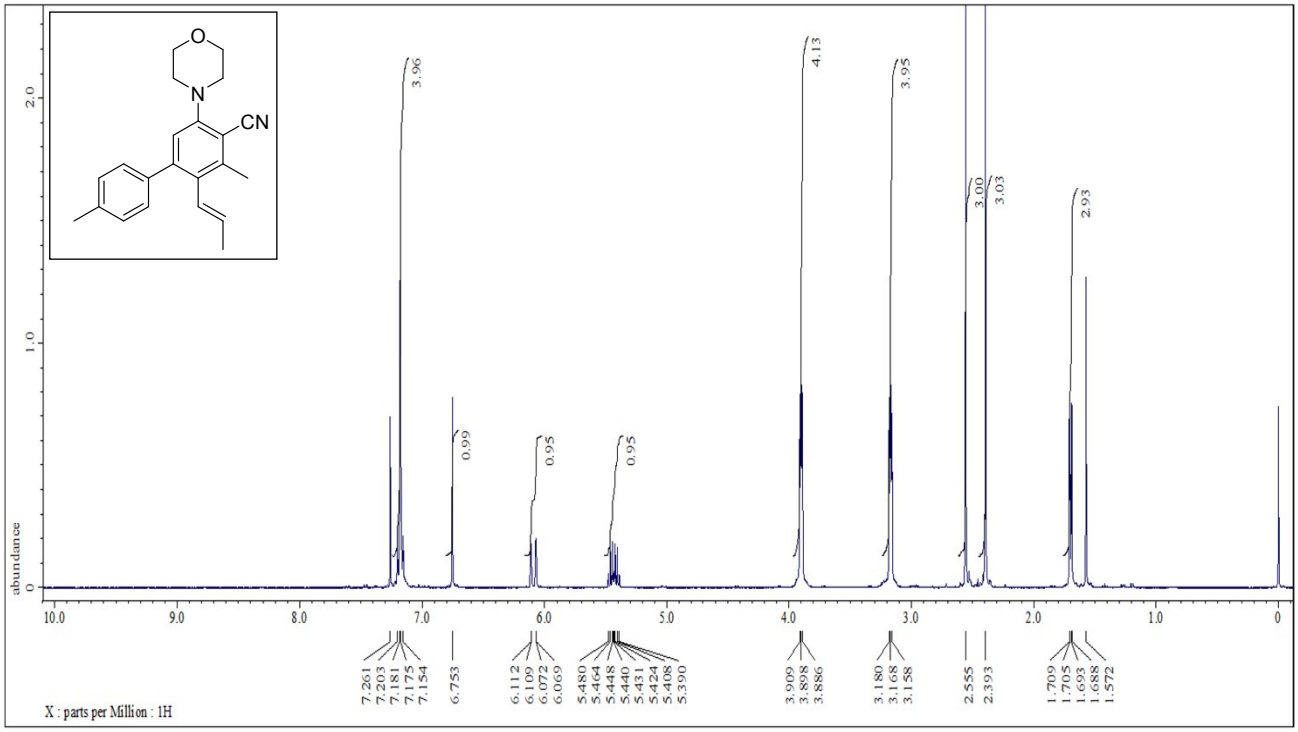
10. 1,9-dimethyl-3-(piperidin-1-yl)phenanthrene-2 carbonitrile

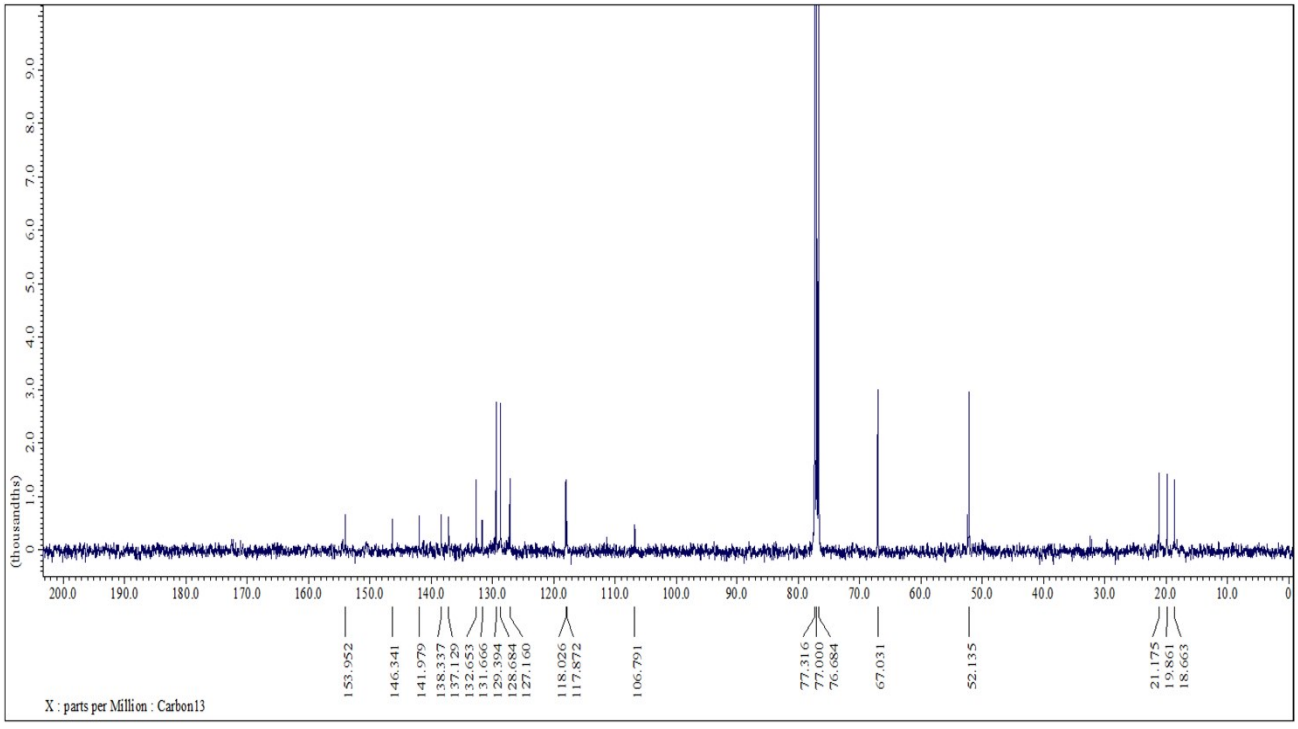




^{1}H and ^{13}C NMR of1,9-dimethyl-3-(piperidin-1-yl)phenanthrene-2 carbonitrile

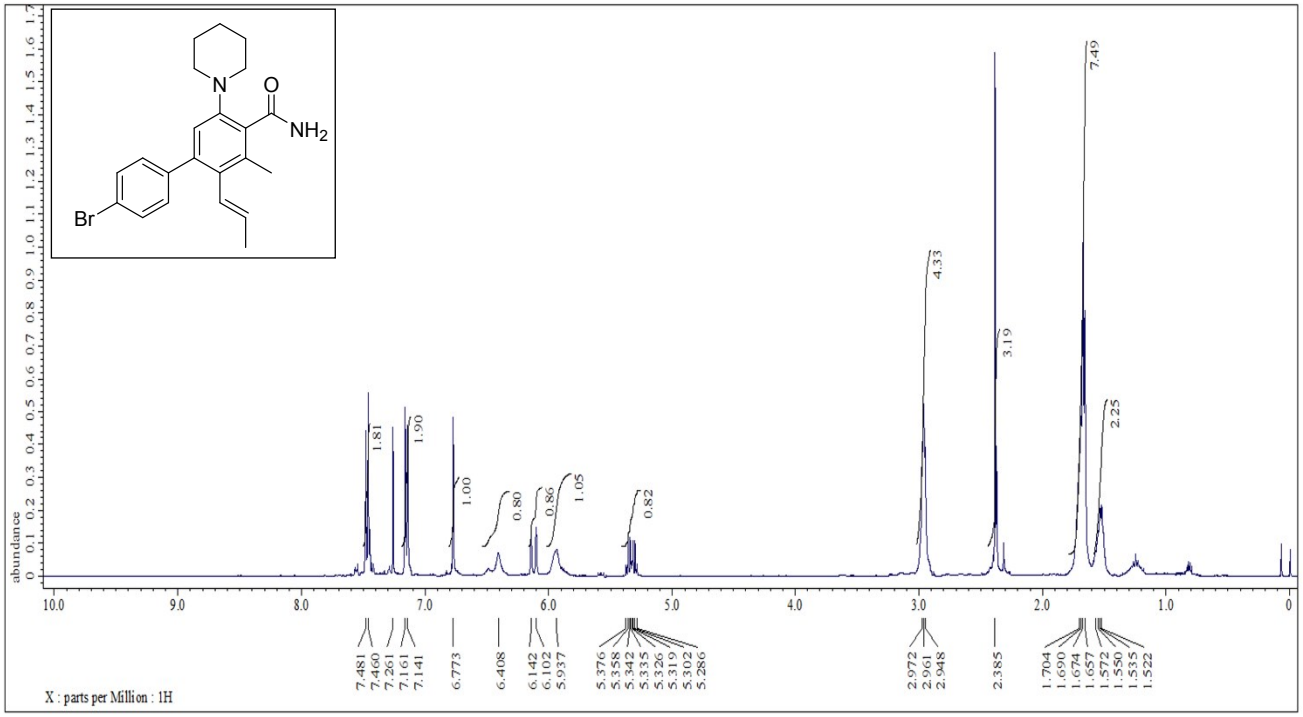
11. 3,4'-dimethyl-5-morpholino-2-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carbonitrile

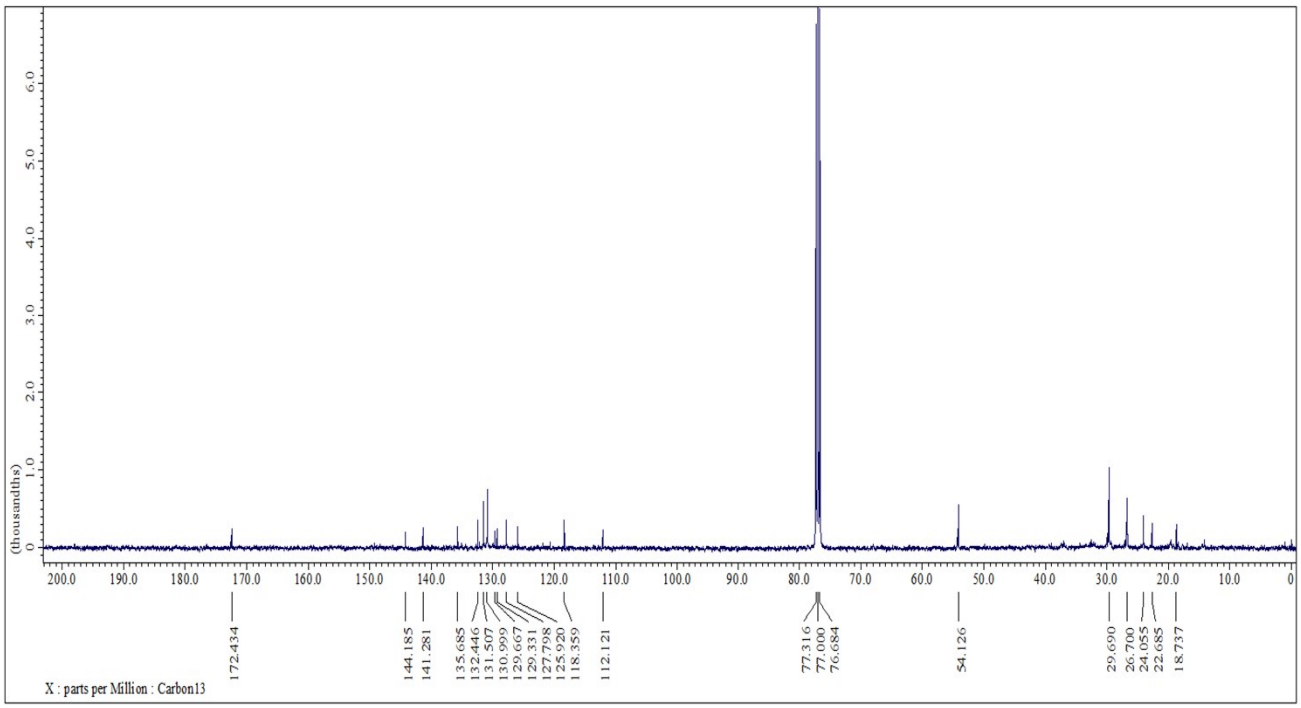




^{1}H and ^{13}C NMR of 3,4'-dimethyl-5-morpholino-2-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carbonitrile

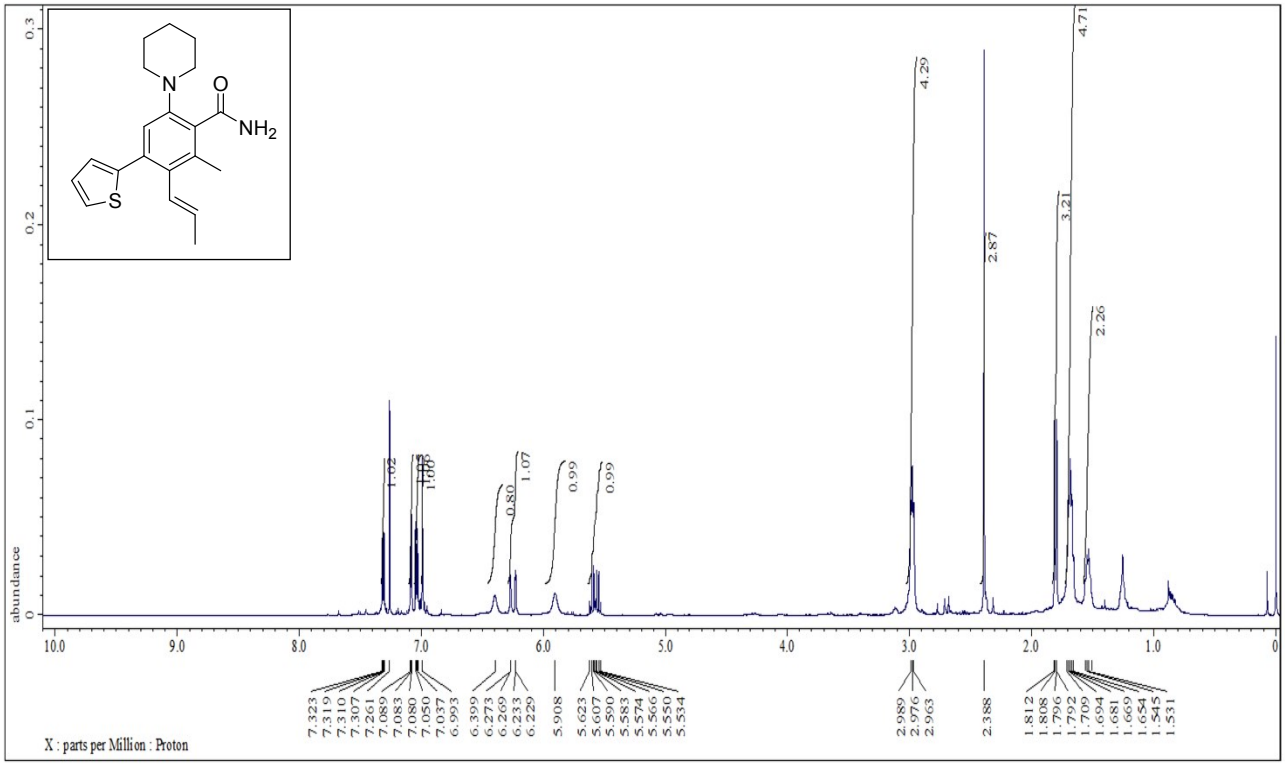
12a. 4'-bromo-3-methyl-5-(piperidin-1-yl)-2-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxamide

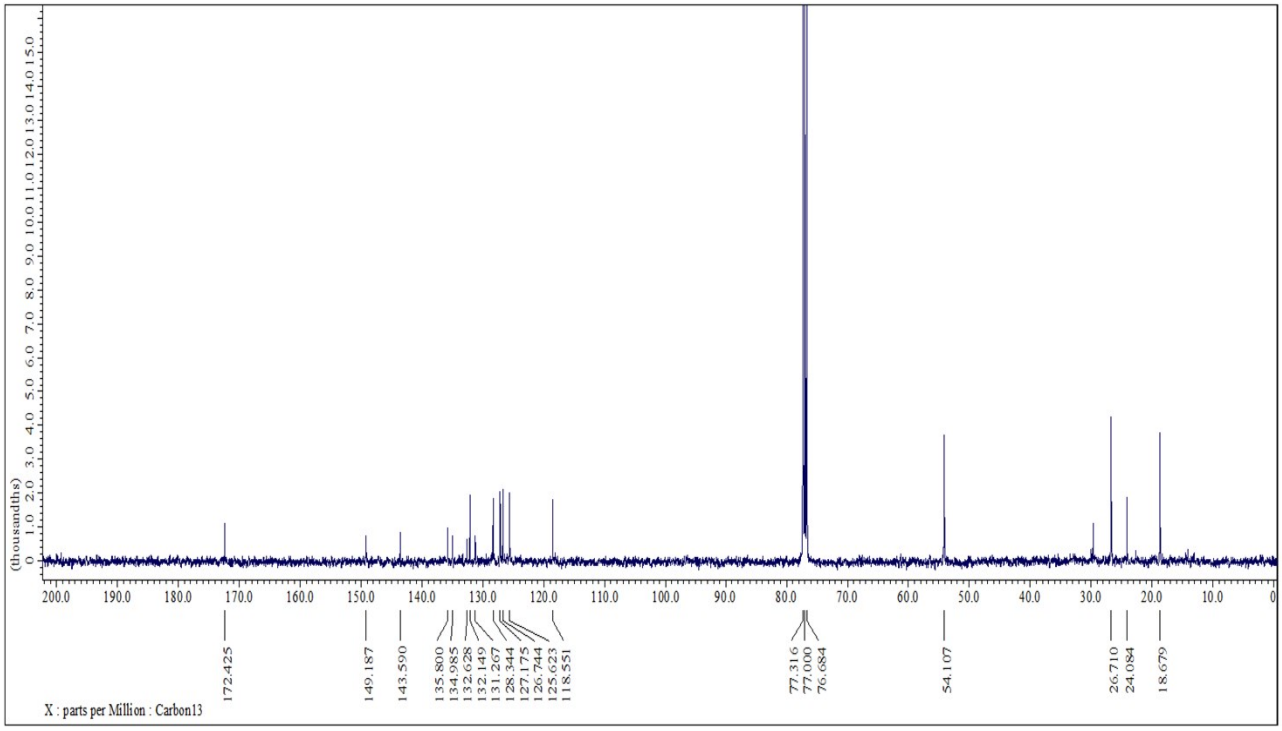




^{1}H and ^{13}C NMR of 4'-bromo-3-methyl-5-(piperidin-1-yl)-2-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxamide

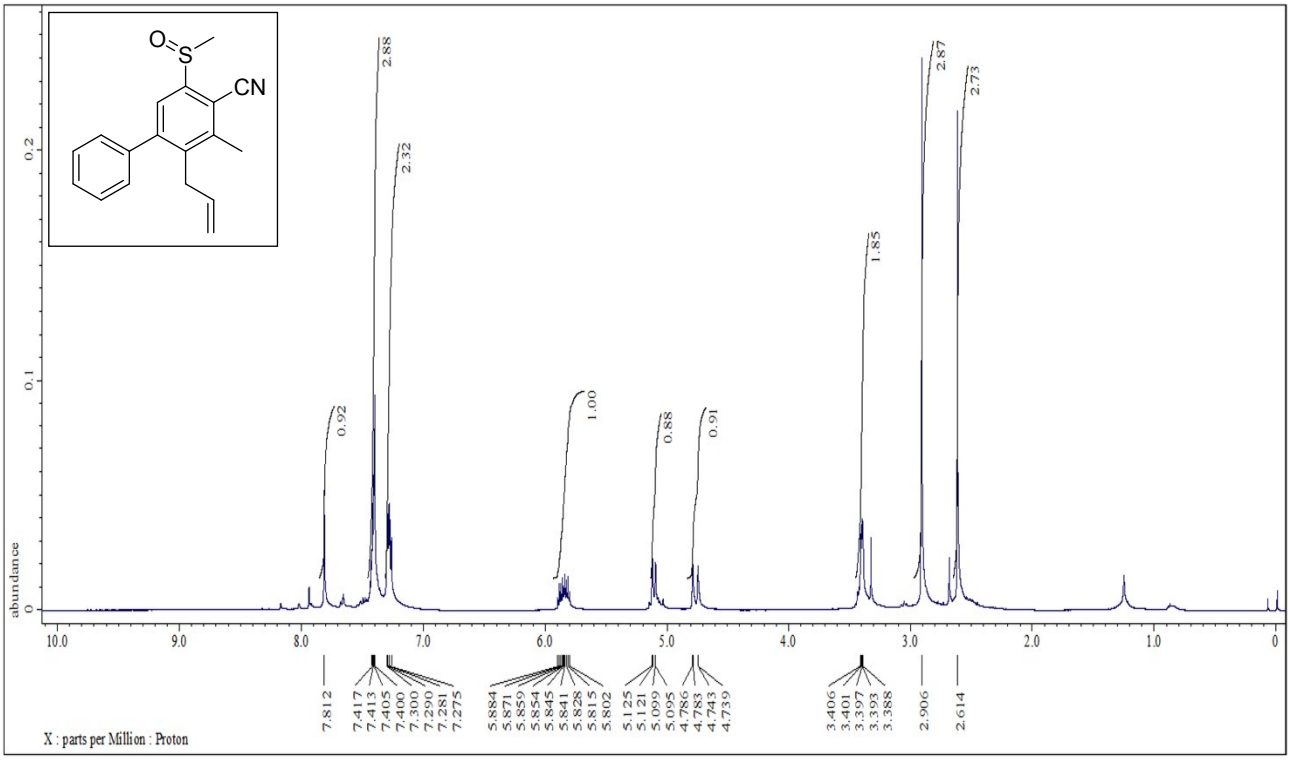
12b. 2-methyl-6-(piperidin-1-yl)-3-(prop-1-en-1-yl)-4-(thiophen-2-yl)benzamide

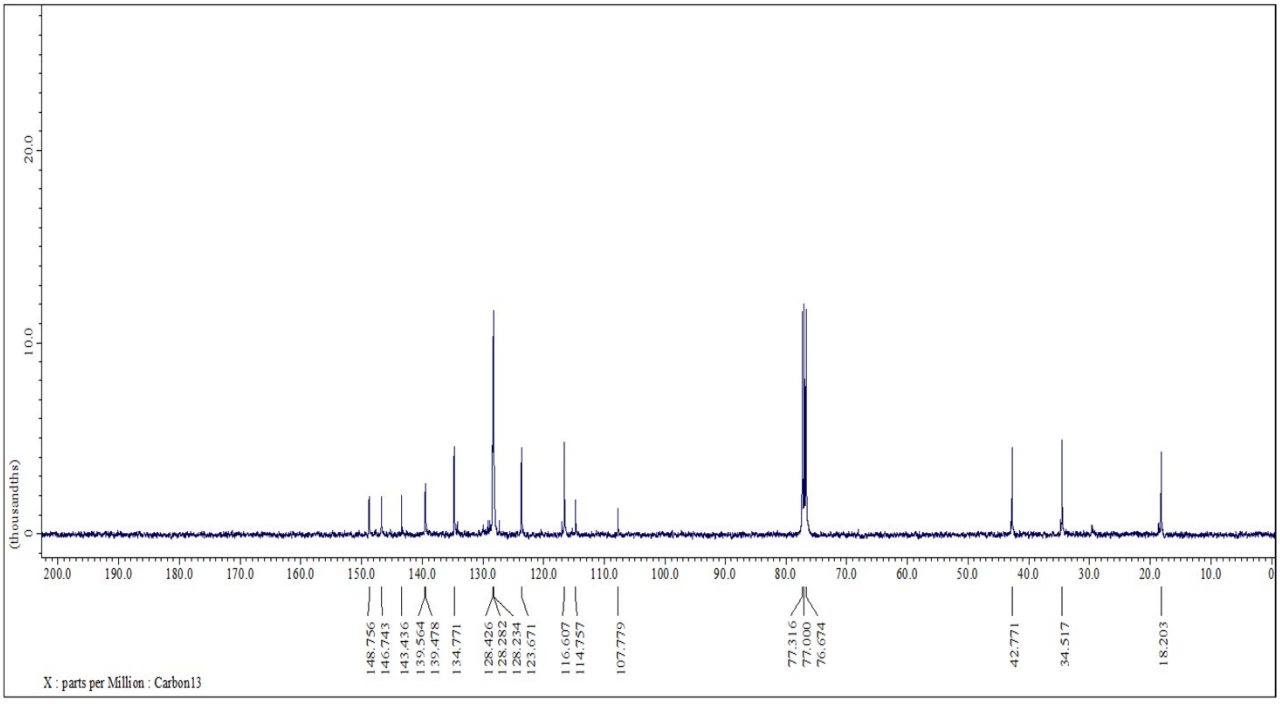




^{1}H and ^{13}C NMR of 2-methyl-6-(piperidin-1-yl)-3-(prop-1-en-1-yl)-4-(thiophen-2-yl)benzamide

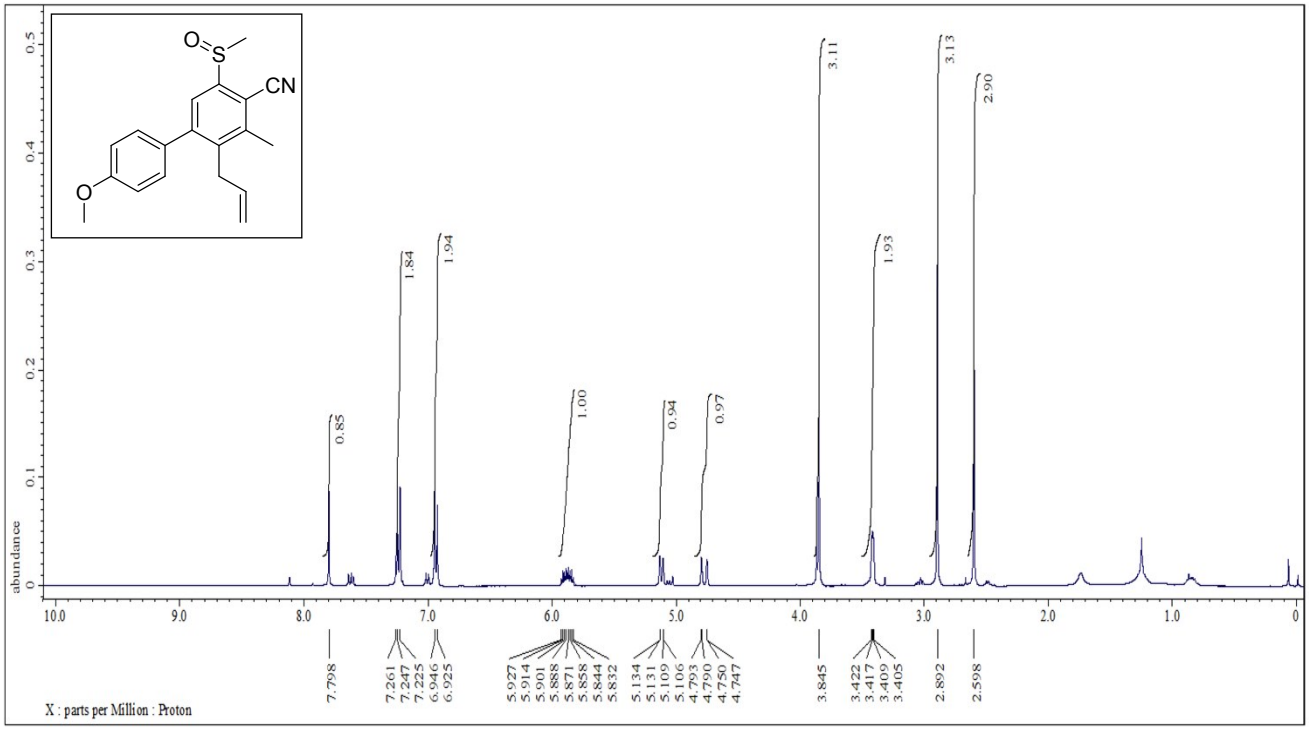
13a. 2-allyl-3-methyl-5-(methylsulfinyl)-[1,1'-biphenyl]-4-carbonitrile

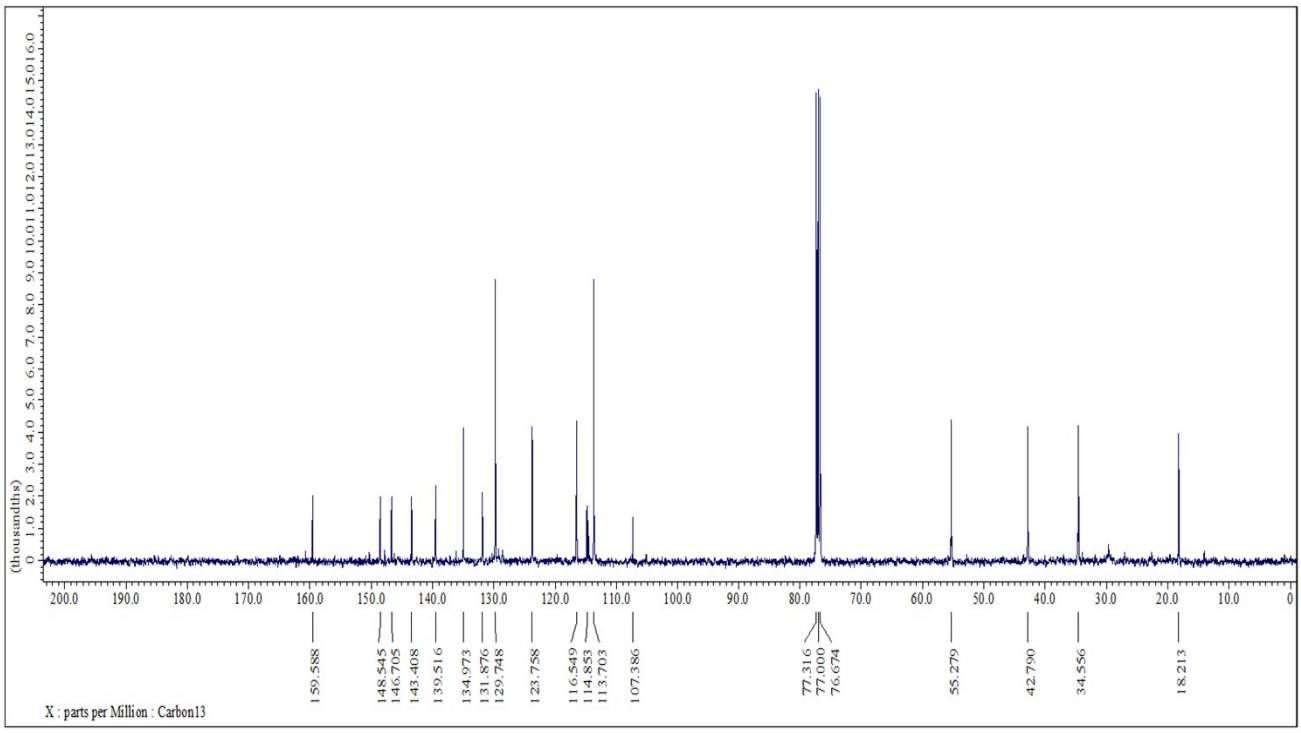




^{1}H and ^{13}C NMR of 2-allyl-3-methyl-5-(methylsulfinyl)-[1,1'-biphenyl]-4-carbonitrile

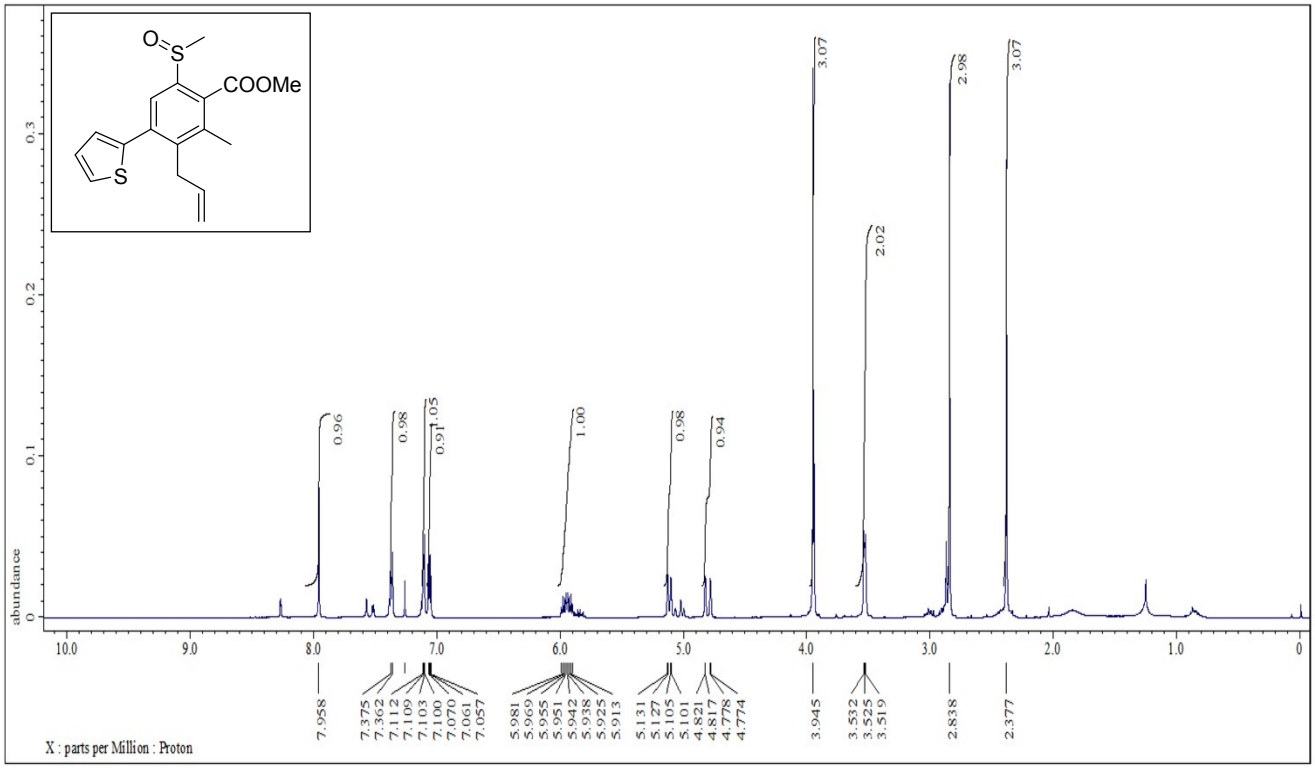
13b. 2-allyl-4'-methoxy-3-methyl-5-(methylsulfinyl)-[1,1'-biphenyl]-4-carbonitrile

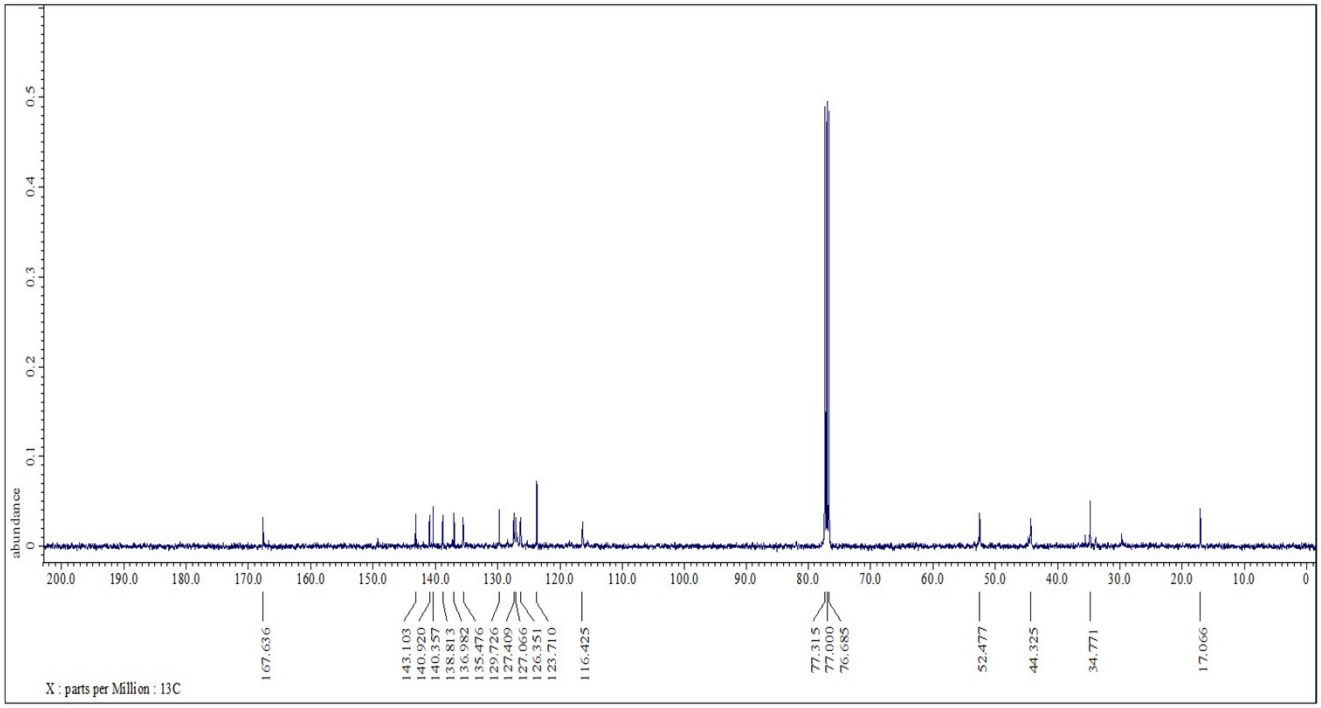




^{1}H and ^{13}C NMR of 2-allyl-4'-methoxy-3-methyl-5-(methylsulfinyl)-[1,1'-biphenyl]-4-carbonitrile

13c. methyl 3-allyl-2-methyl-6-(methylsulfinyl)-4-(thiophen-2-yl)benzoate





^{1}H and ^{13}C NMR of methyl 3-allyl-2-methyl-6-(methylsulfinyl)-4-(thiophen-2-yl)benzoate

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