Supporting Information

Palladium-catalyzed arylation of 2*H*-chromene: a new entry to pyrano[2,3-c]carbazoles

K.Ranjith Reddy,[a,b] A. Siva Reddy,[a,b] Devendra K Dhaked[c] ,Sk.Rasheed [a,b], Anup Singh Pathania,[d] Ravi Shankar,[a,b] Fayaz Malik,[d] and Parthasarathi Das[a,b,*]

[a] Academy of Scientific and Innovative Research (AcSIR), New Delhi.
[b] Medicinal Chemistry Division, Indian Institute of Integrative Medicine(CSIR), Canal Road, Jammu-180001, India; E-mail: partha@iiim.ac.in
[c] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S. A. S. Nagar, Mohali, 160062, Punjab, India;
[d] Division of Cancer Pharmacology, Institute of Integrative Medicine(CSIR), Canal Road, Jammu-180001 India,

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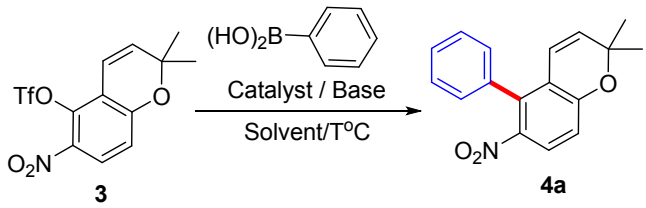
Table 1 Optimization of Suzuki-Miyaura cross-coupling[a]



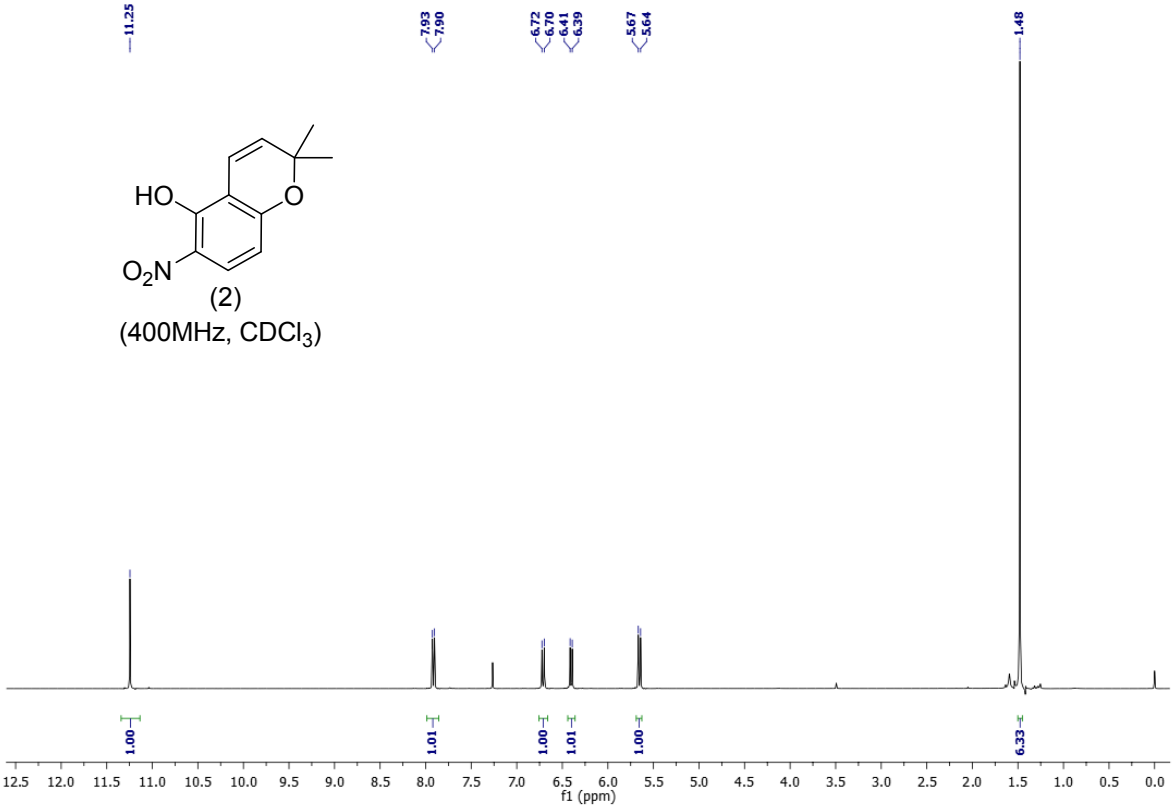
3 **4a**

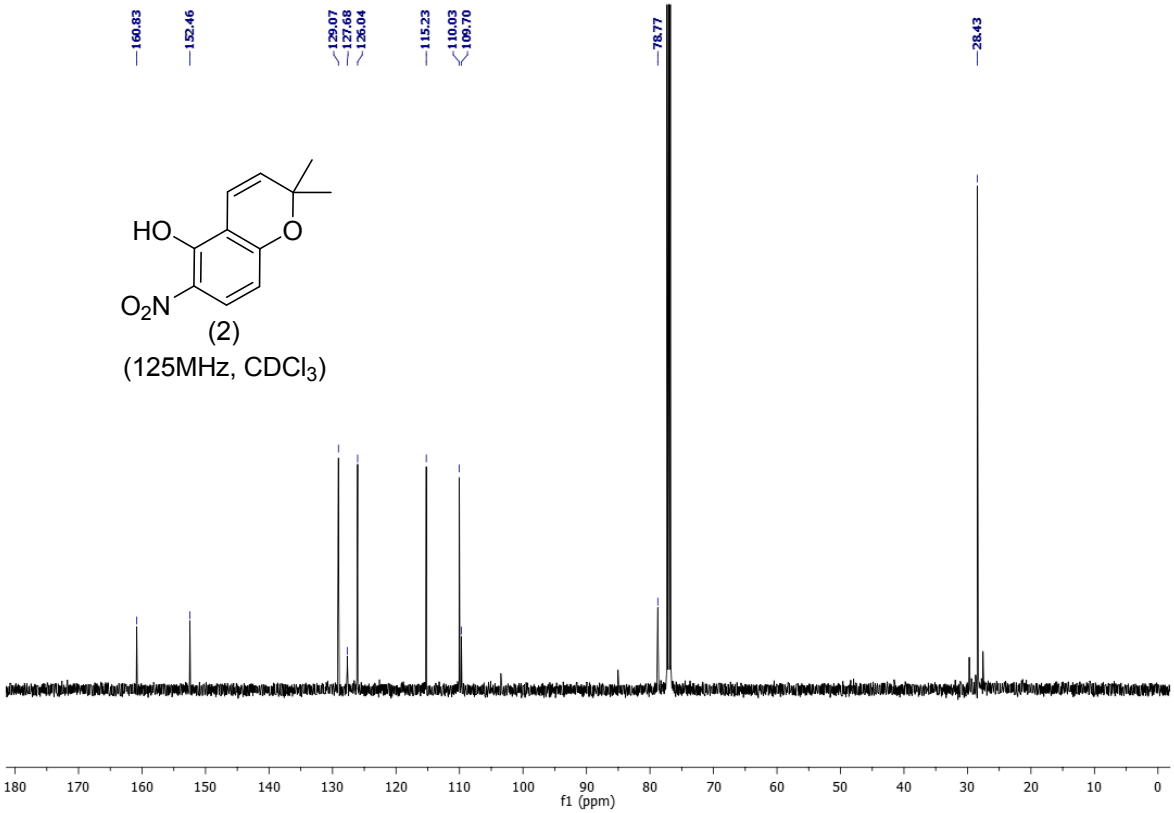
entry	catalyst	base	solvent	T°C	yield(%)[b]
1	$Pd(PPh_3)_4$	Na_2CO_3	1,4 Dioxane	100	45
2	$Pd(PPh_3)_4$	K_2CO_3	1,4 Dioxane	100	68
3	$Pd(PPh_3)_4$	K_3PO_4	1,4 Dioxane	100	77
4	$Pd(PPh_3)_4$	NaOAc	1,4 Dioxane	100	53
5	$Pd(PPh_3)_4$	t-BuOK	1,4 Dioxane	100	65
6	$Pd(PPh_3)_4$	LiOH	1,4 Dioxane	100	60
7	$Pd(PPh_3)_4$	KOH	1,4 Dioxane	100	66
8	$Pd(PPh_3)_4$	K_3PO_4	Toluene	100	50
9	$Pd(PPh_3)_4$	K_3PO_4	DMSO	100	66
10	$Pd(PPh_3)_4$	K_3PO_4	THF	100	65
11	**$Pd(PPh_3)_4$**	**K_3PO_4**	**1,4 Dioxane**	**80**	**80**
12[c]	$Pd(PPh_3)_4$	K_3PO_4	1,4 Dioxane	80	55
13	$Pd(PPh_3)_4$	K_3PO_4	1,4 Dioxane	rt	40
14	$Pd(OAc)_2$	K_3PO_4	1,4 Dioxane	80	55
15	$Pd_2(dba_3)$	K_3PO_4	1,4 Dioxane	80	50

[a]Reaction conditions: **3** (1.0 equiv.), Pd-catalyst (10 mol%); base (1.6 equiv.), phenylboronic acid (1.2 equiv.); solvent , 80 °C, 3h, N_2; [b] isolated yields; [c] catalyst (5 mol%) was used.

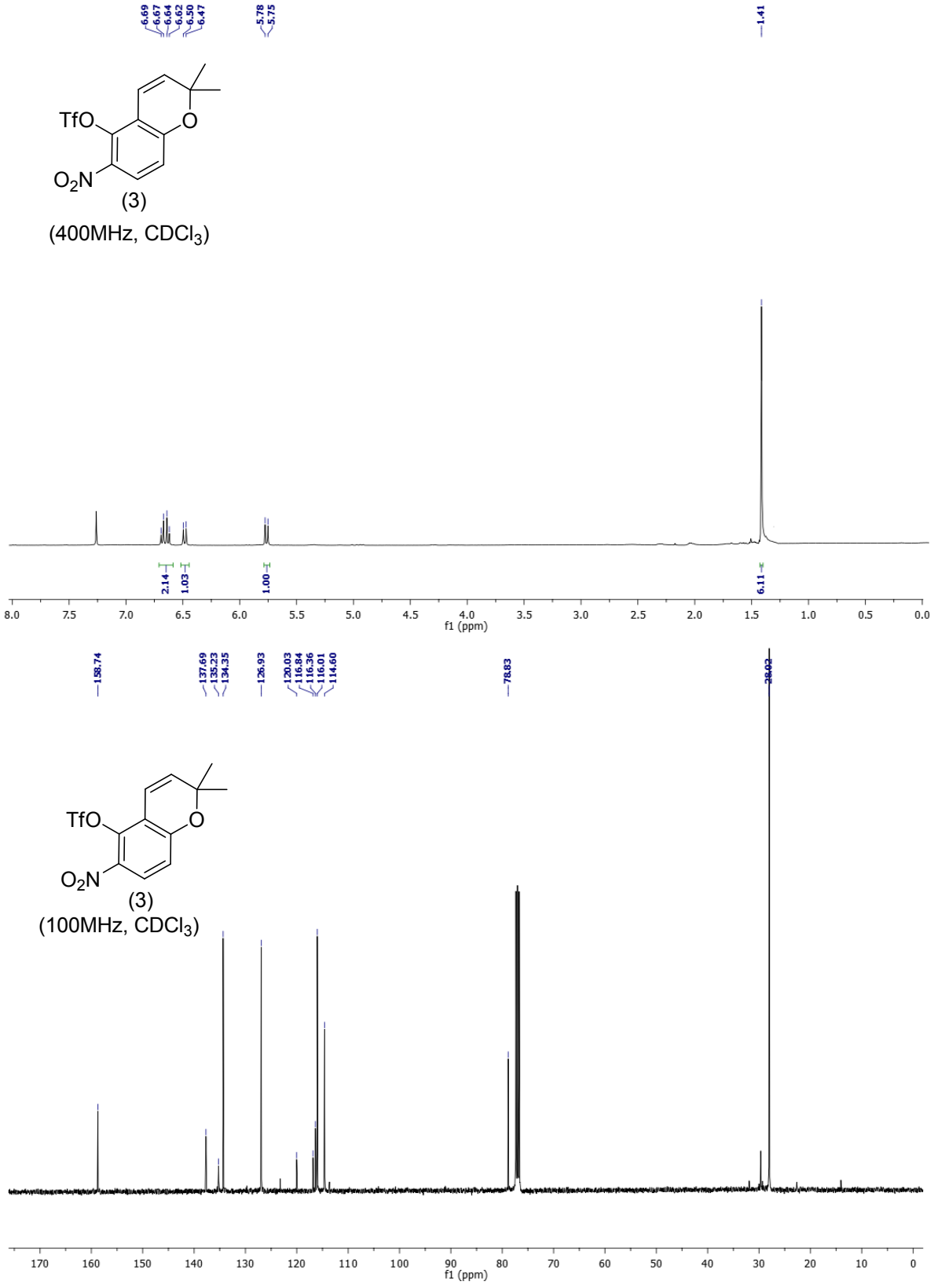
By using simple catalytic system of $Pd(PPh_3)_4/Na_2CO_3$ in 1,4-dioxane at 100 °C then we able to isolate the cross-coupled product in moderate yield (45%) (entry 1, Table 1). Systematic screening of different base like K_2CO_3, K_3PO_4, NaOAc, *t*-BuOK, LiOH, KOH in dioxane (entries 2-7, Table 1) revealed that K_3PO_4 became a base of choice. The use of other common solvents like Toluene (entry 8, table 1), DMSO (entry 9, Table 1) and THF (entry 10, Table 1) proved inferior to 1,4 dioxane (entry 3, Table 1). There is marginal improve in the yield (80%) was observed when the reaction temperature was decreased to 80 °C (entry 11, Table 1). When the loading of catalyst decrease to (5 mol%) , the yield was decreased to 55% (entry 12, Table 1). Whereas, poor yield was observed when reaction was performed at room temperature (entry 13, Table 1). Other palladium complexes such as $Pd(OAc)_2$ (55%) (entry 14, Table 1) and Pd_2dba_3 (50%) (entry 15, Table 1) were moderately effective. In view of efficiency and simplicity we have identified $Pd(PPh_3)_4$/ K_3PO_4/ dioxane/ 80°C as our optimized conditions for the cross-coupling reaction (entry 11, Table 1).

2,2-Dimethyl-6-nitro-2*H*-chromen-5-ol (**2**):





2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl trifluoromethanesulfonate(**3**):



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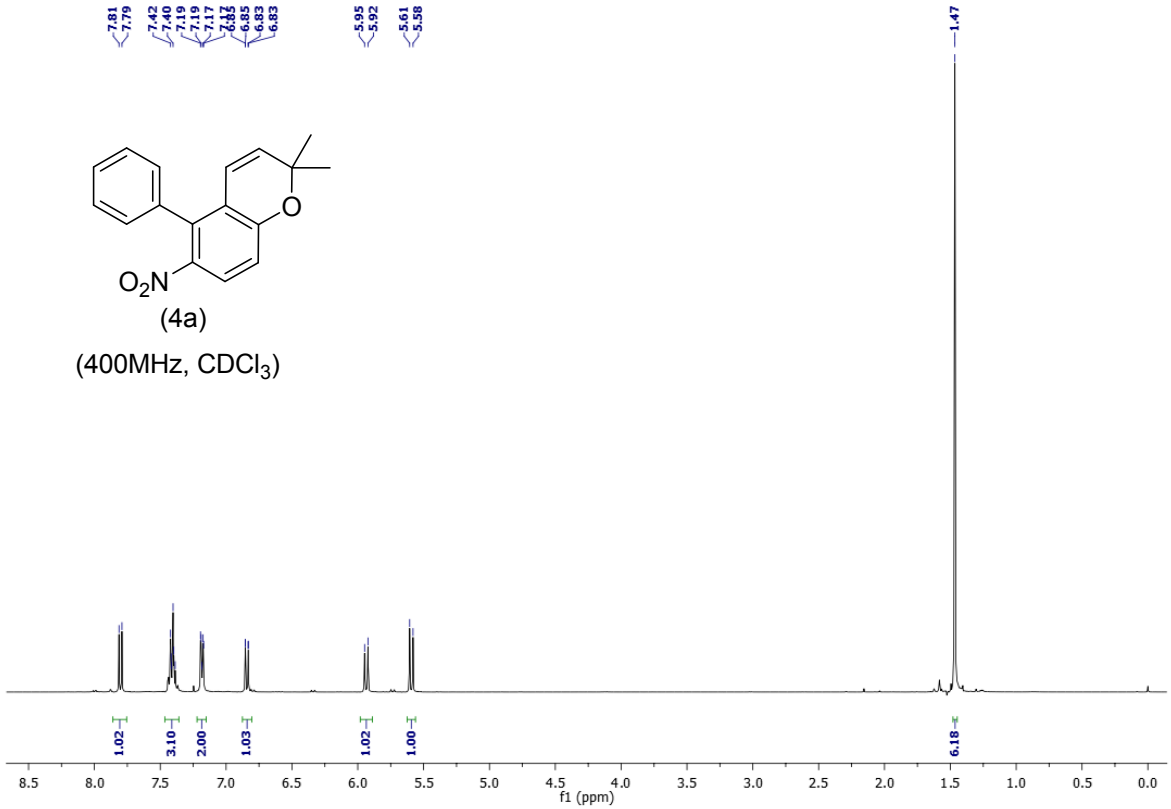

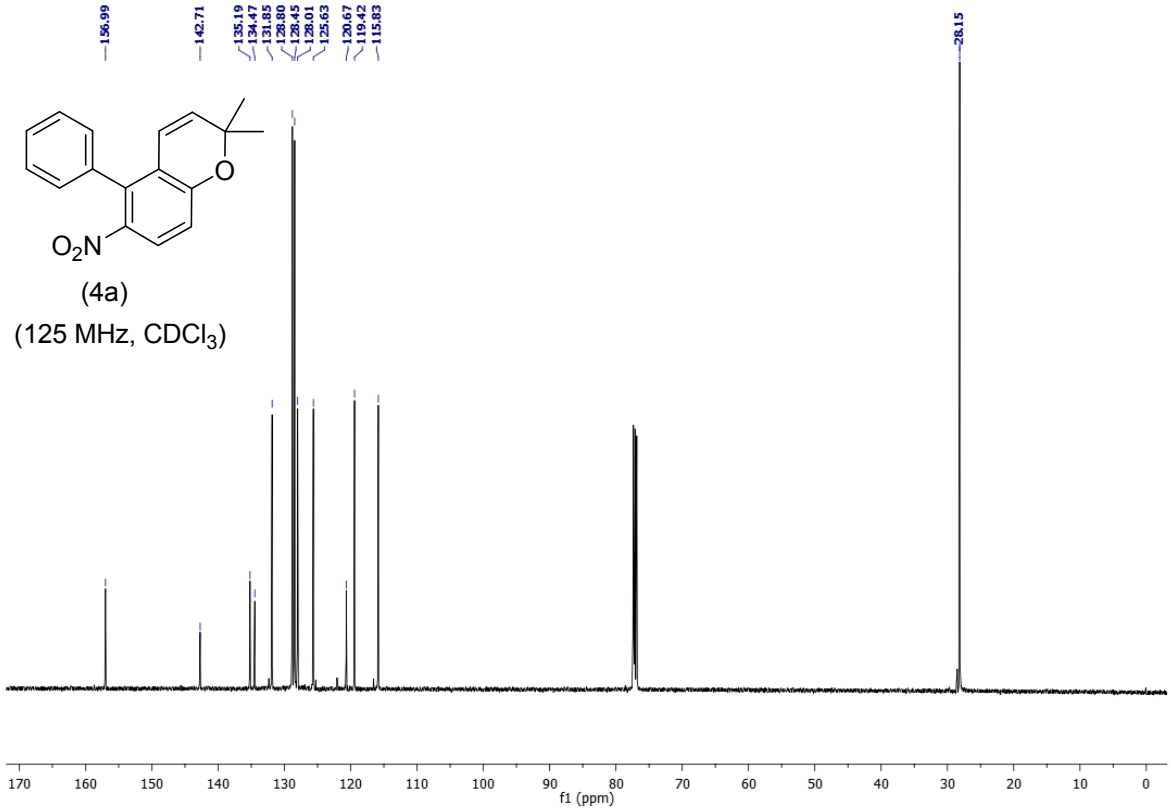

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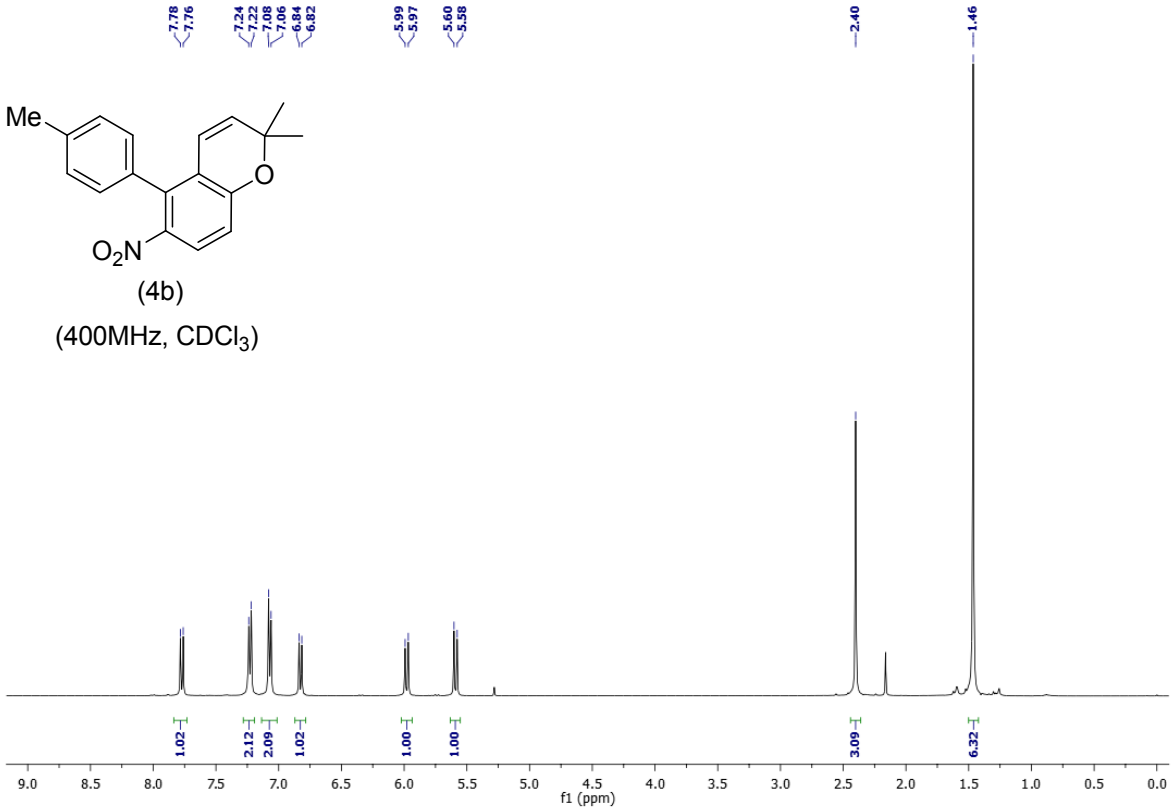
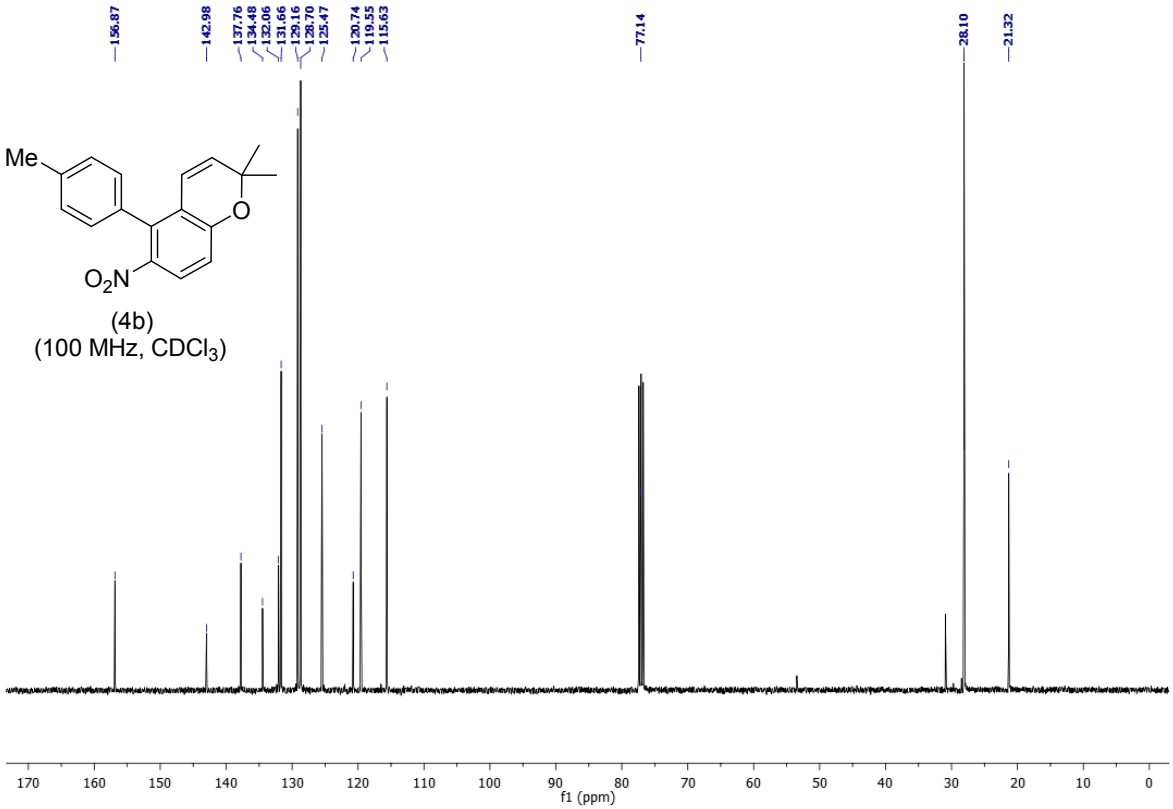
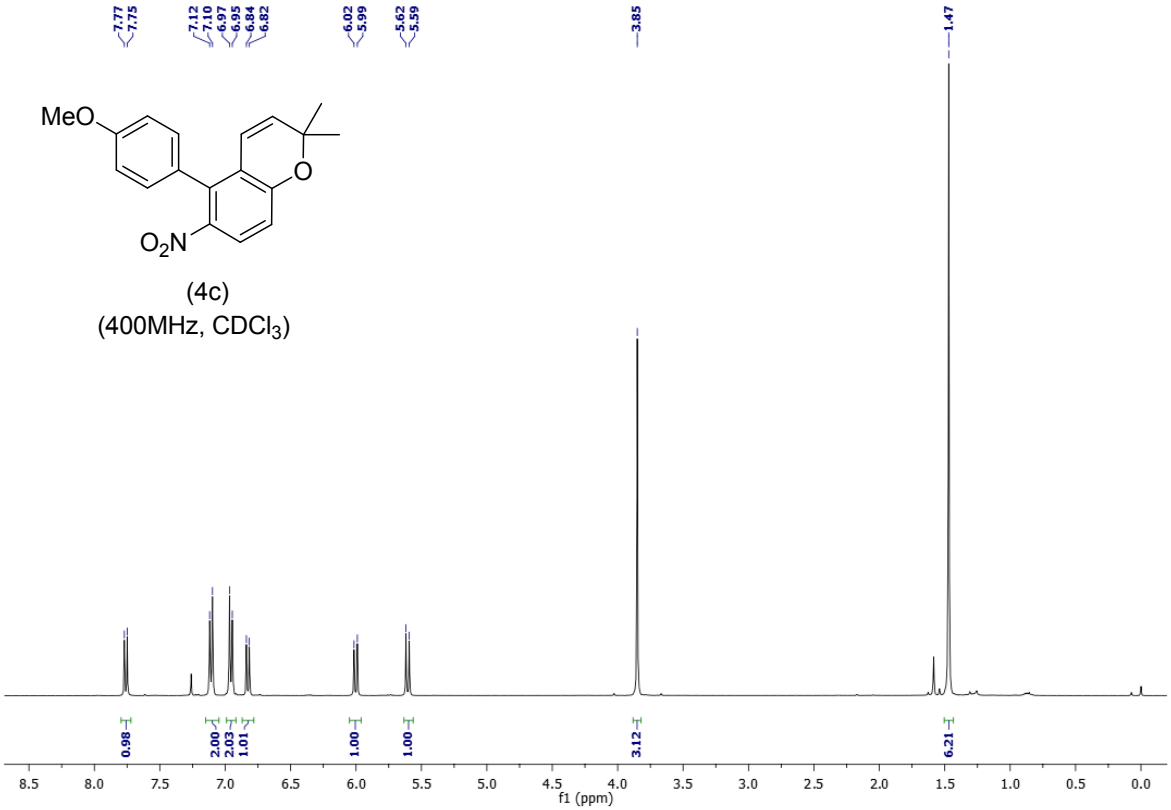
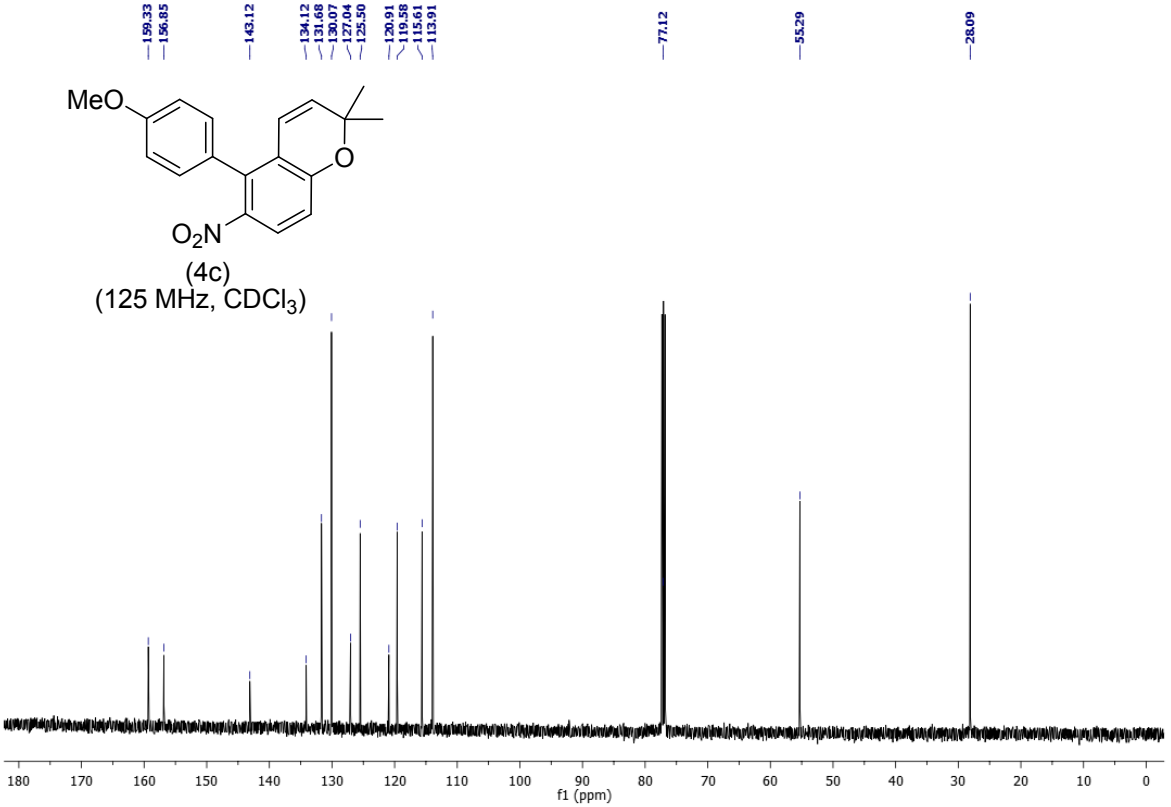


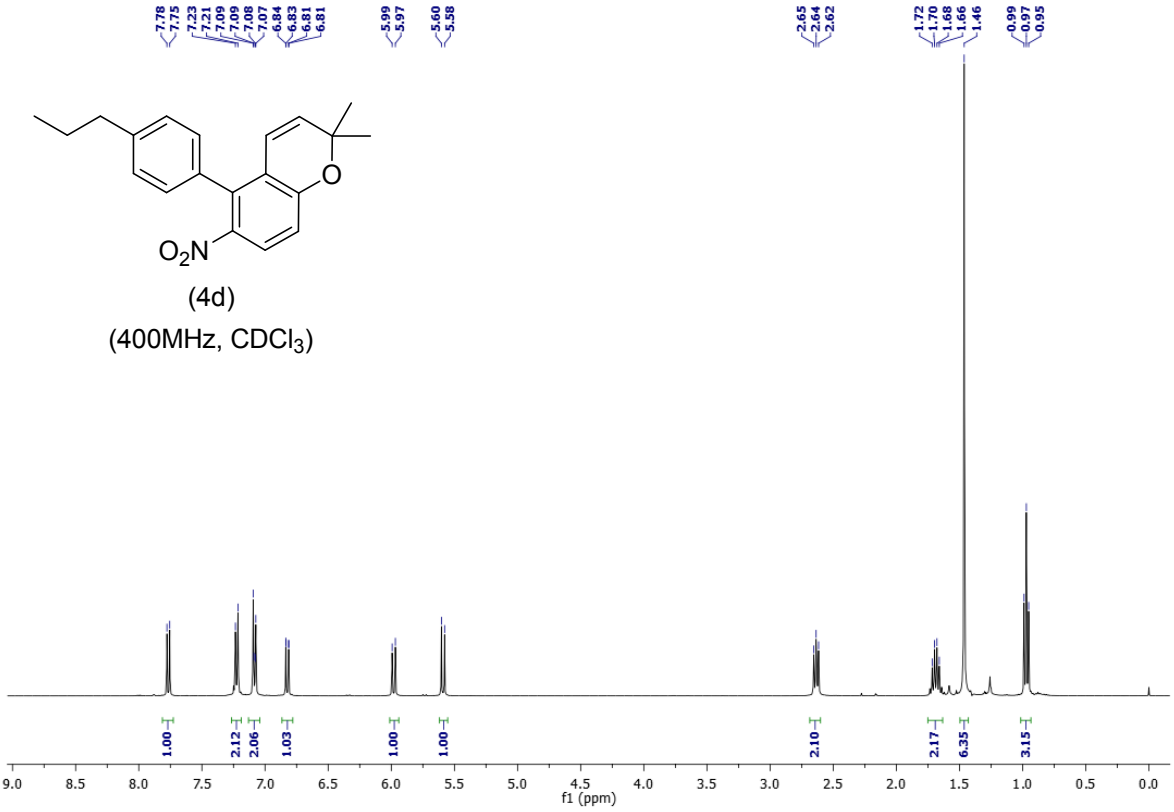


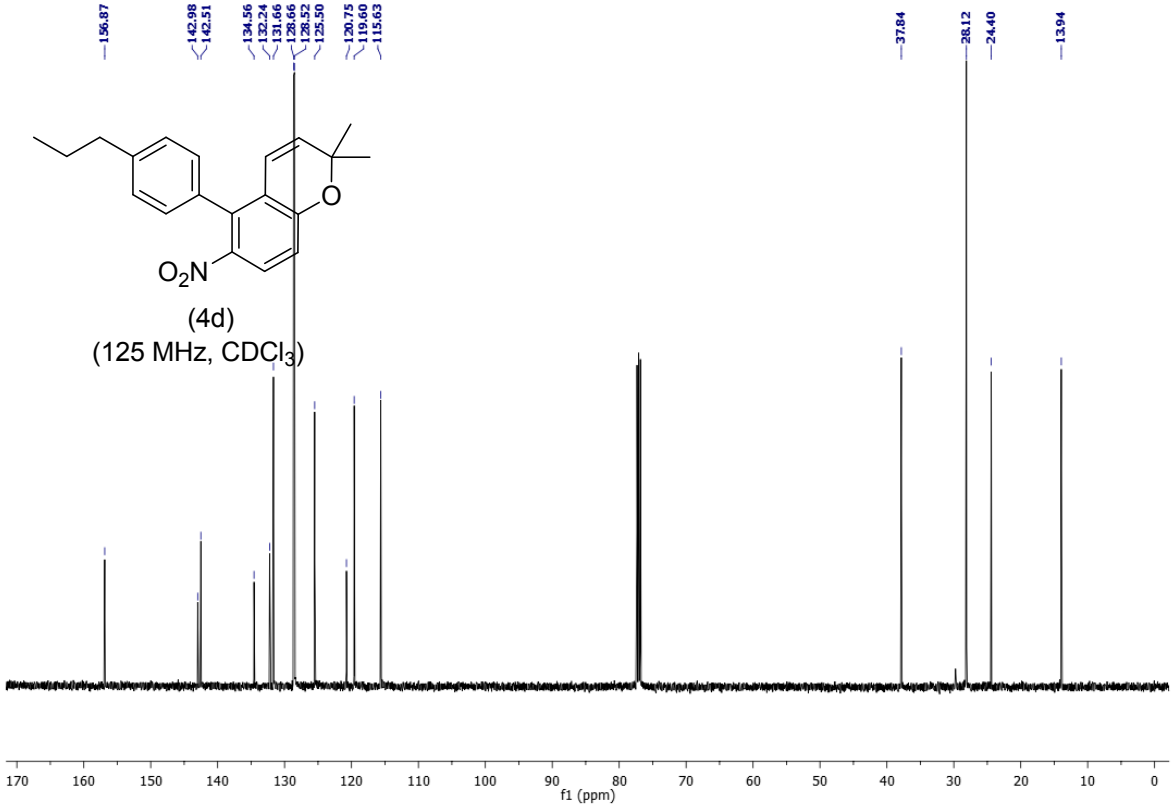
5-(4-Methoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene(**4c**):



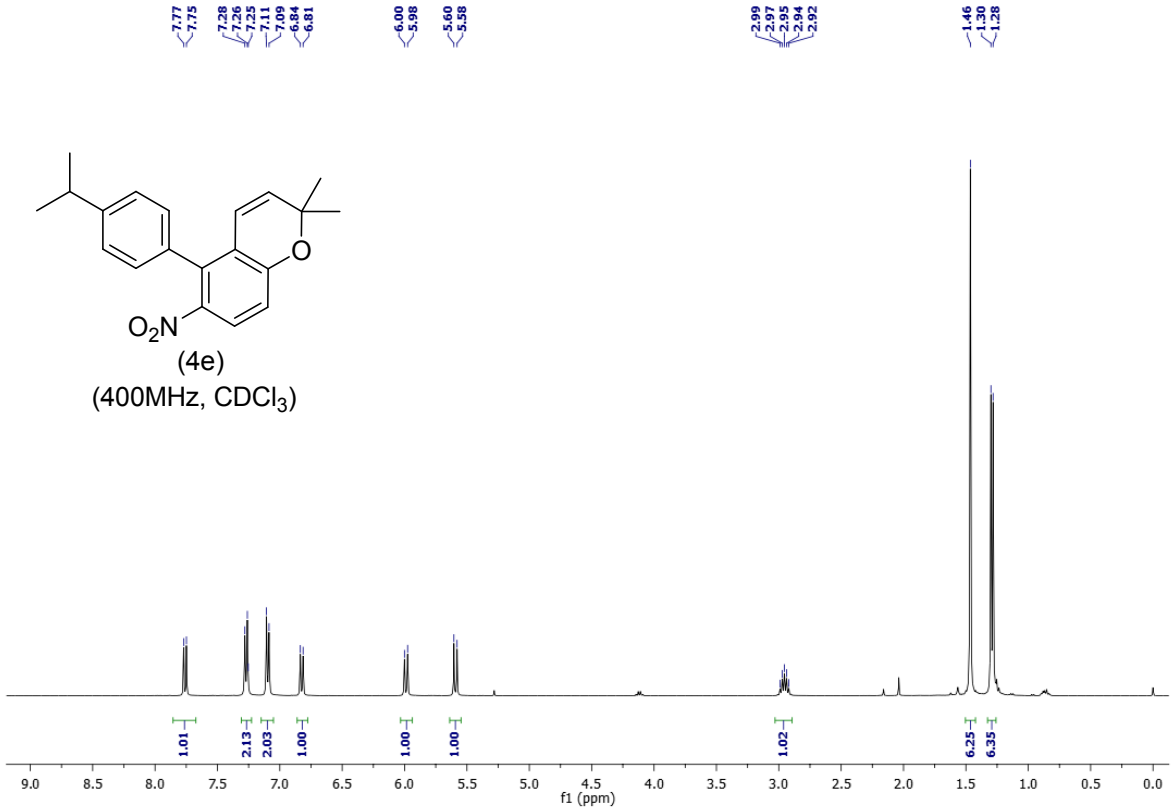


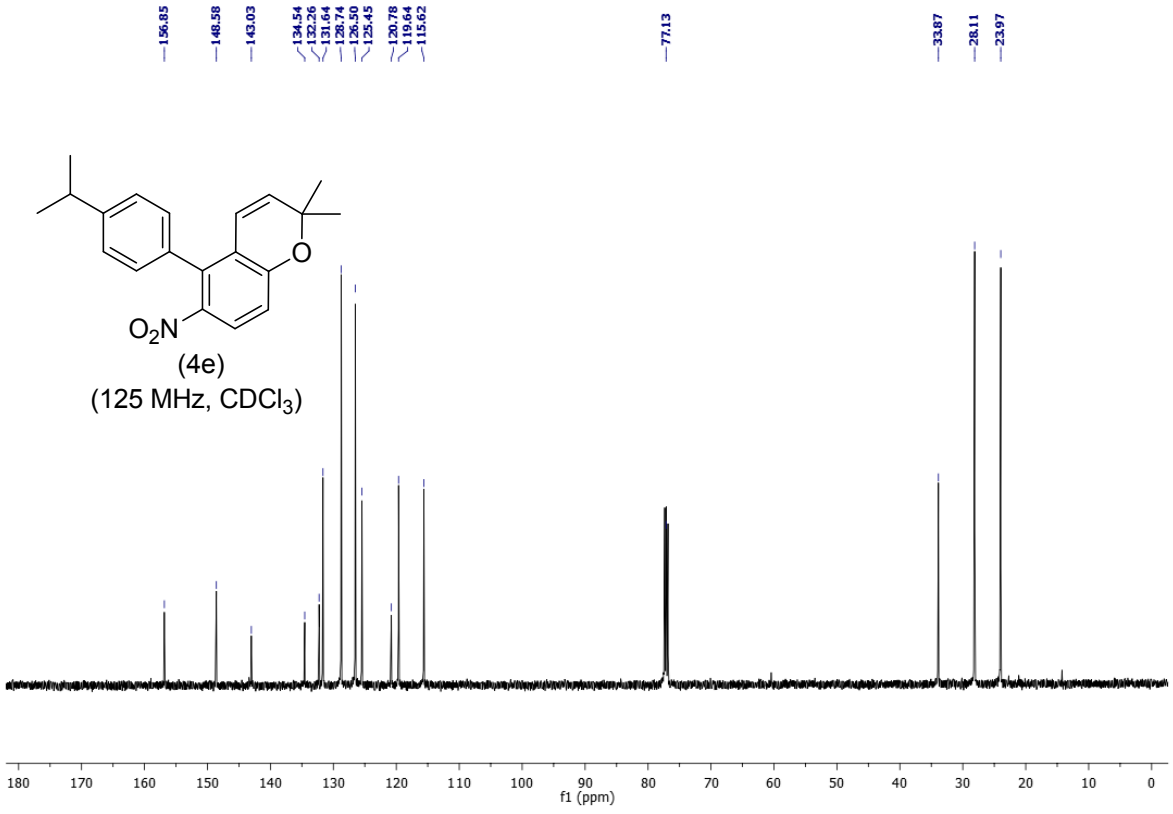
2,2-Dimethyl-6-nitro-5-(4-propylphenyl)-2*H*-chromene (**4d**):





5-(4-Isopropylphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (**4e**):





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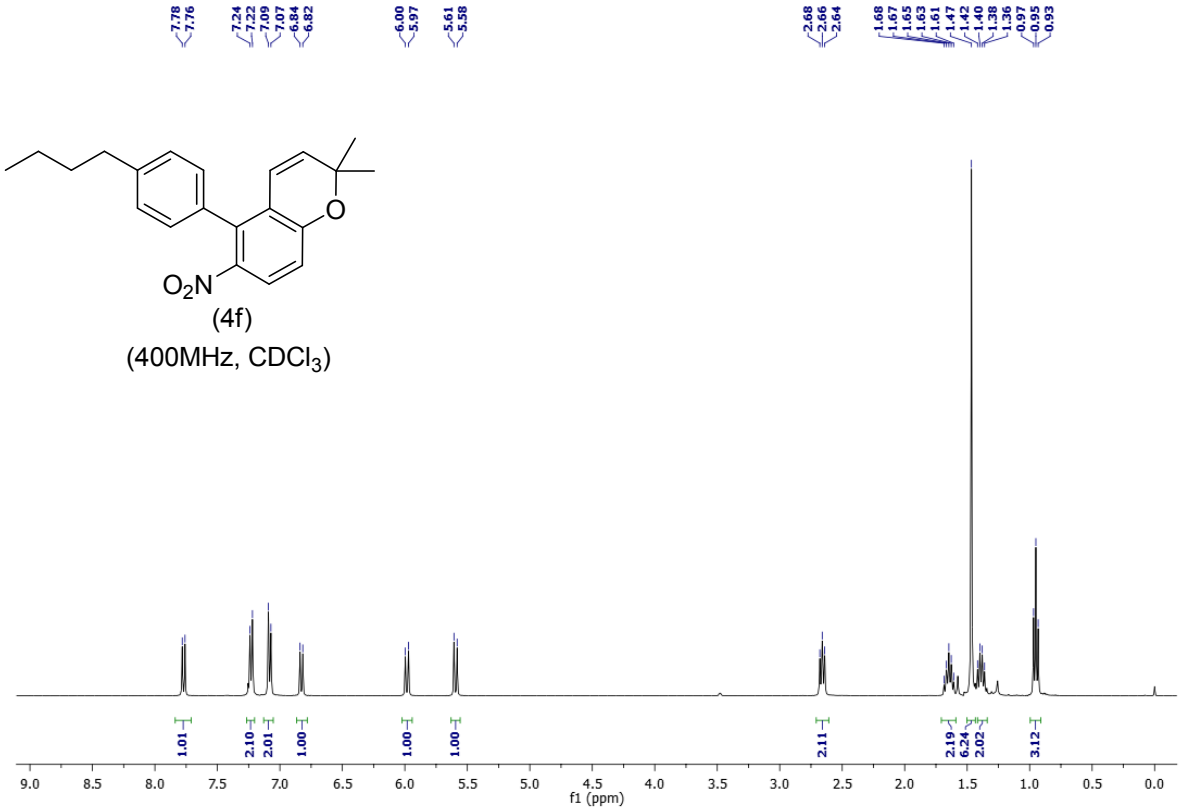
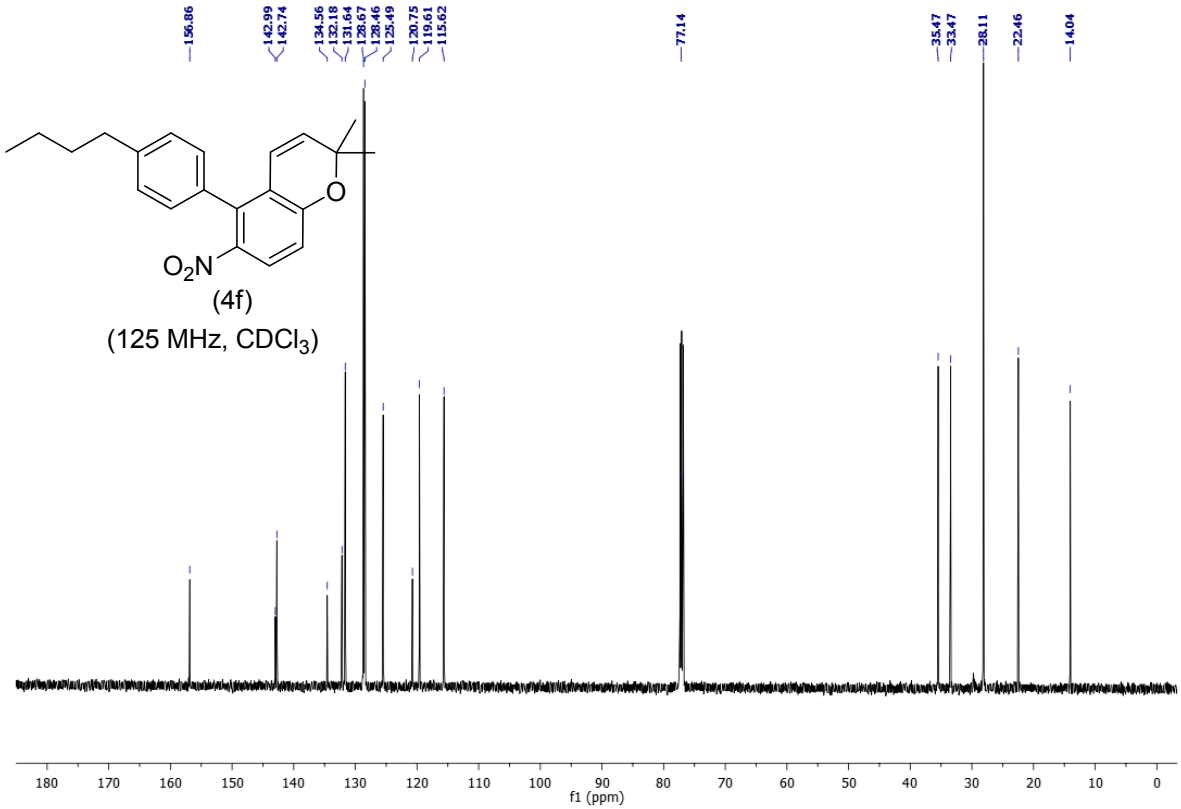
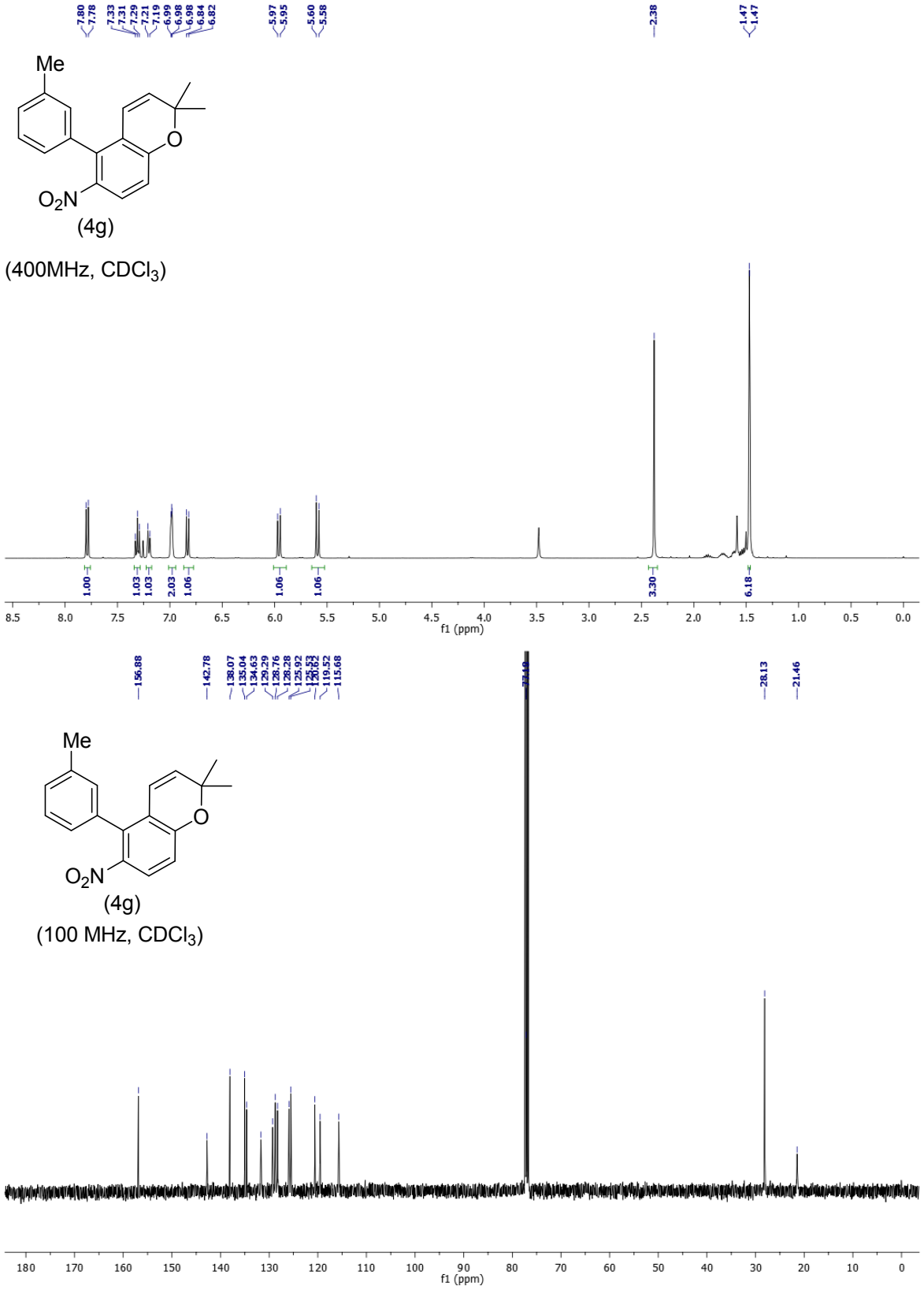
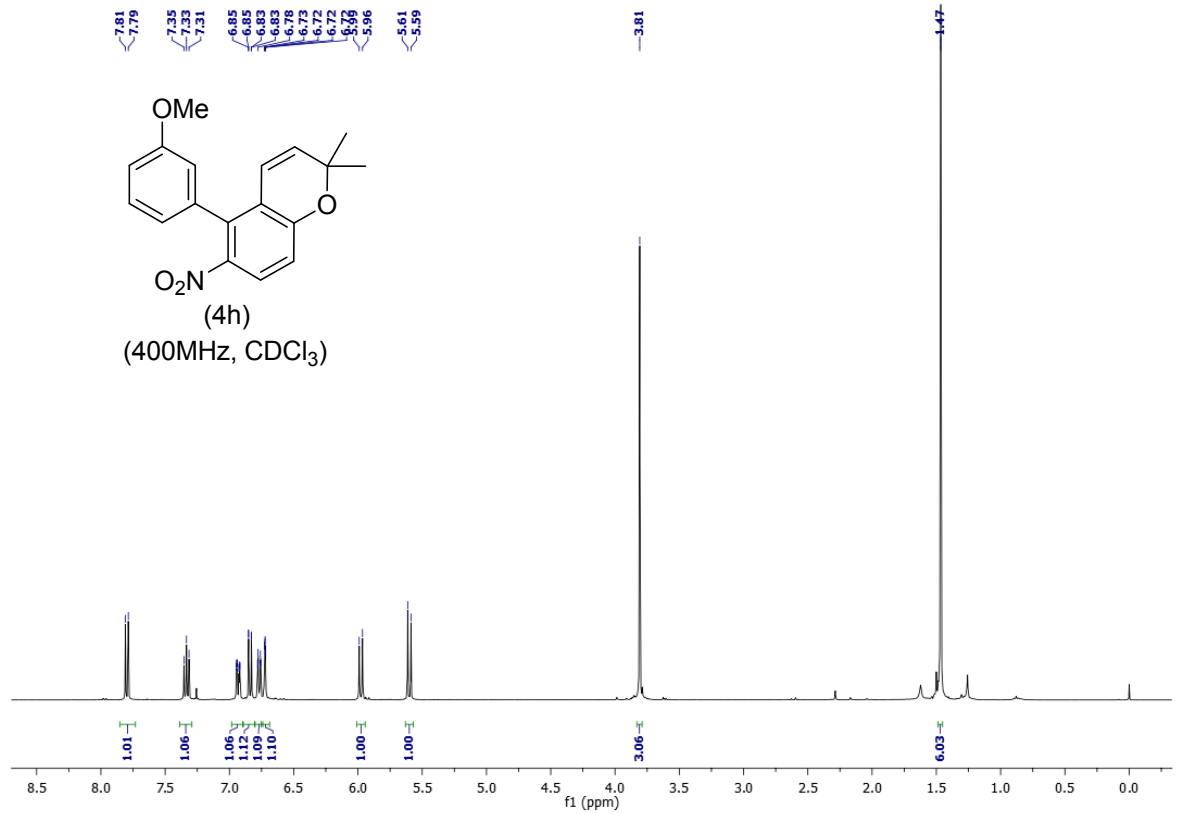


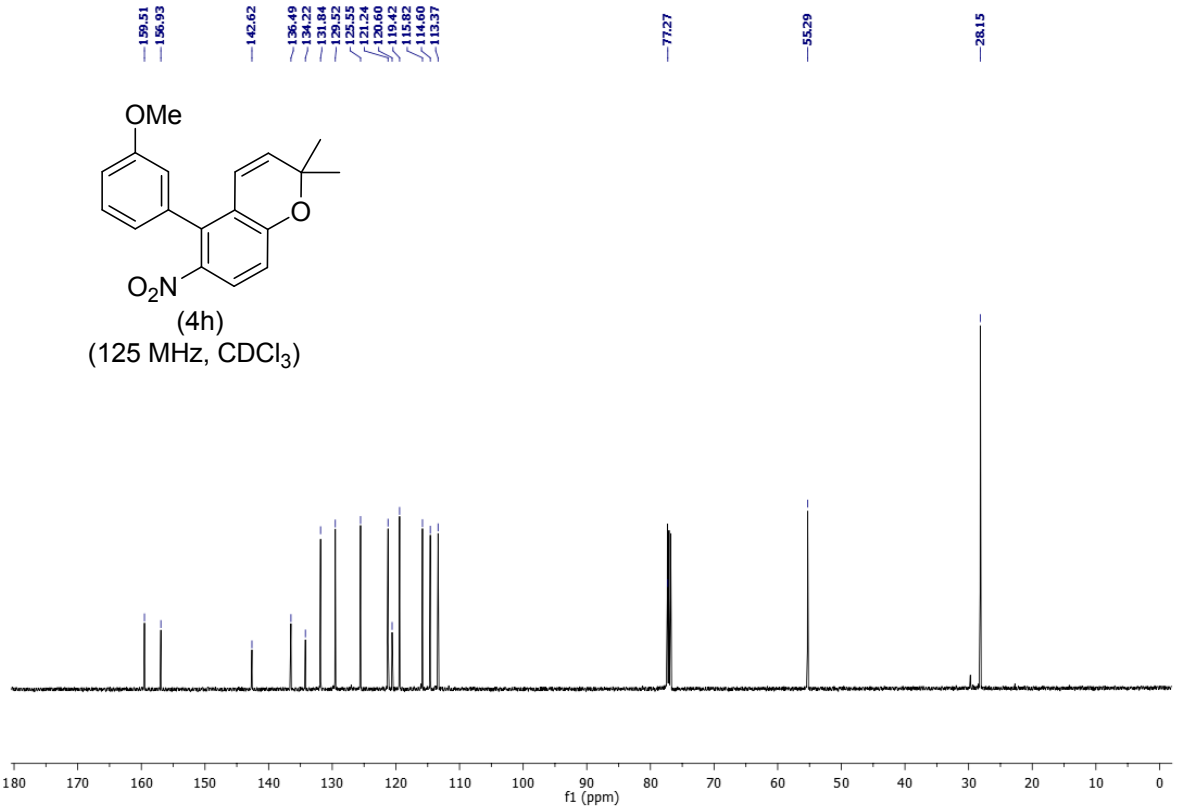


2,2-Dimethyl-6-nitro-5-(*m*-tolyl)-2*H*-chromene (**4g**):

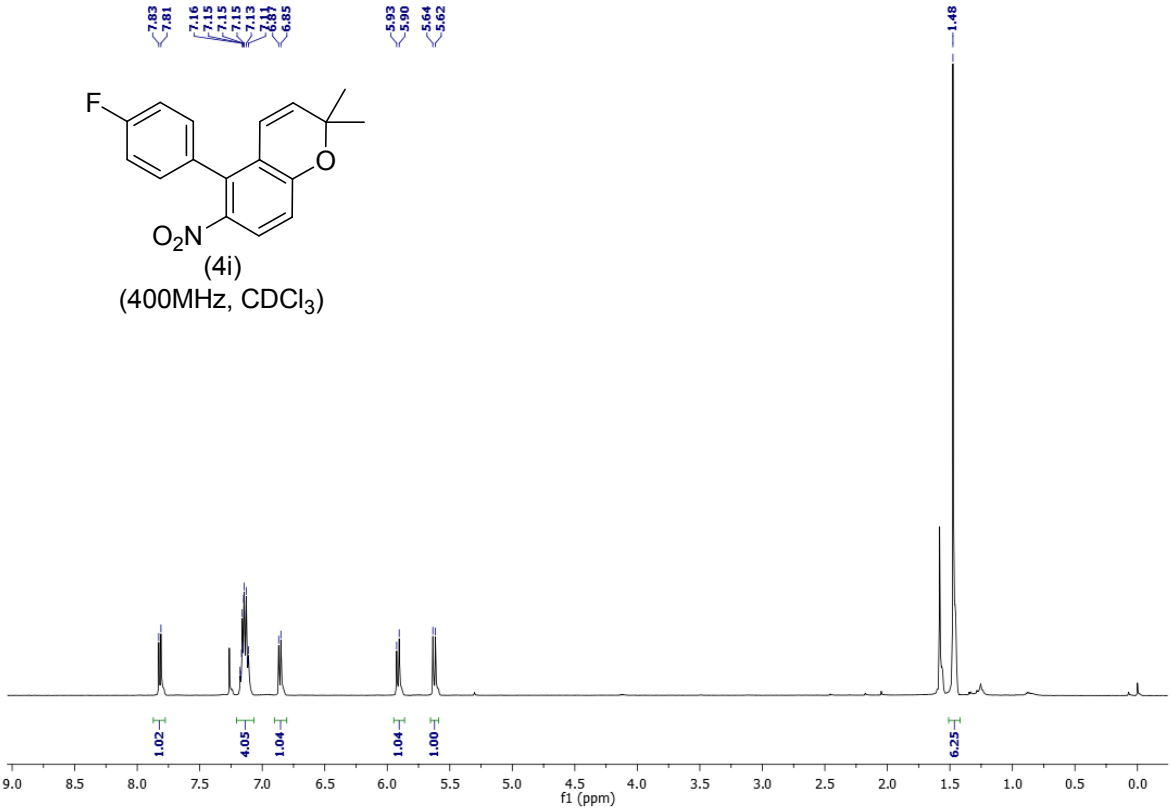


5-(3-Methoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (**4h**):



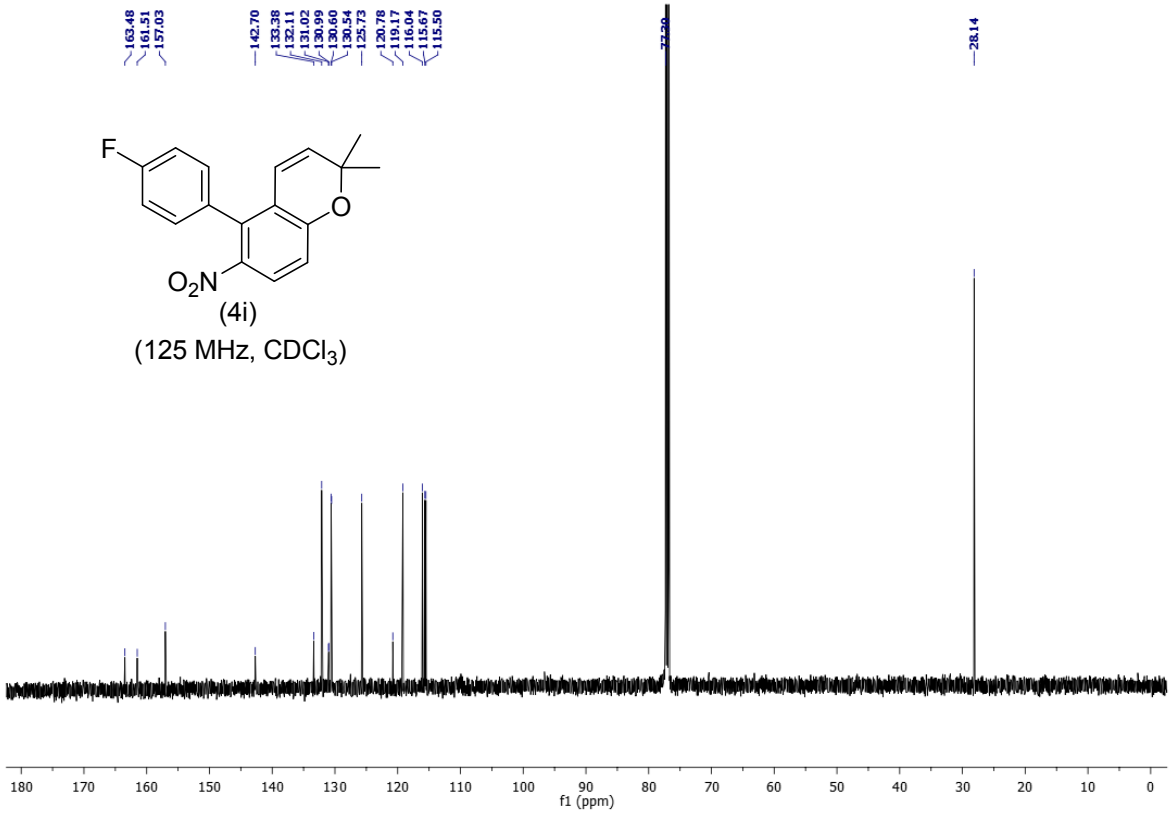


5-(4-Fluorophenyl)-2,2-dimethyl-6-nitro-2*H*-chromene(**4i**):



(4i)

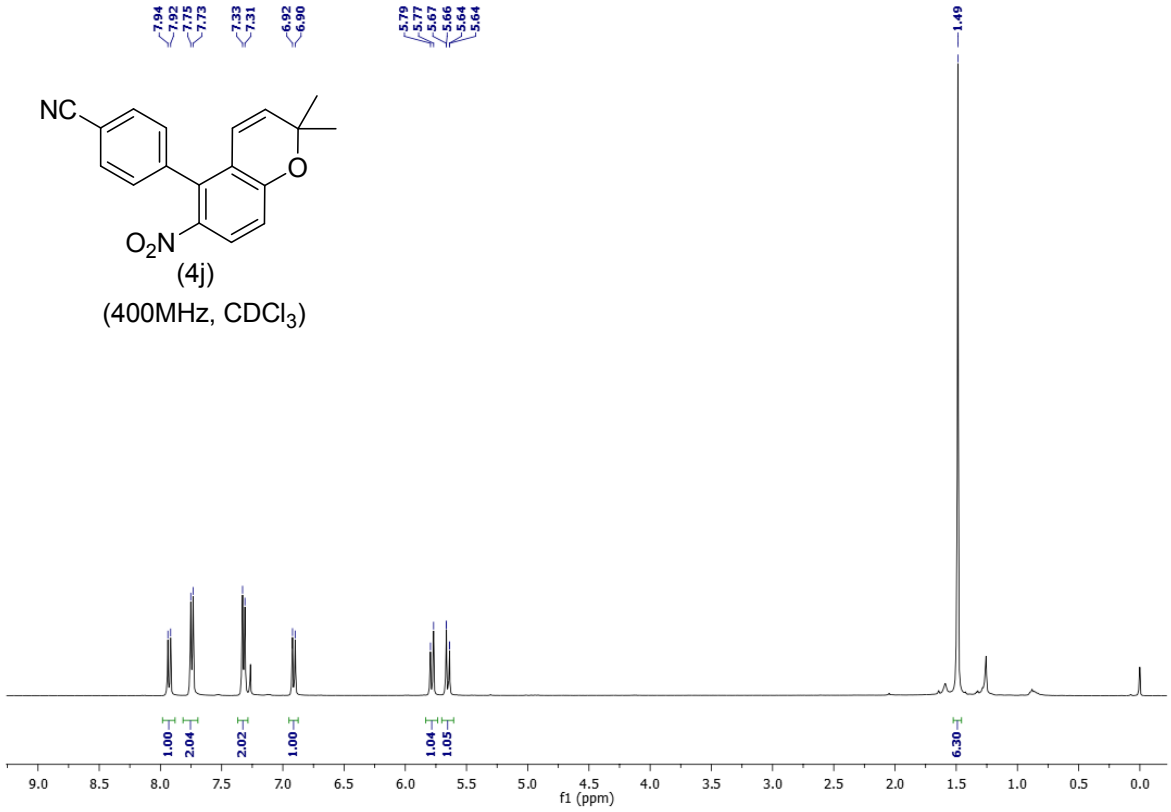
(400MHz, $CDCl_3$)

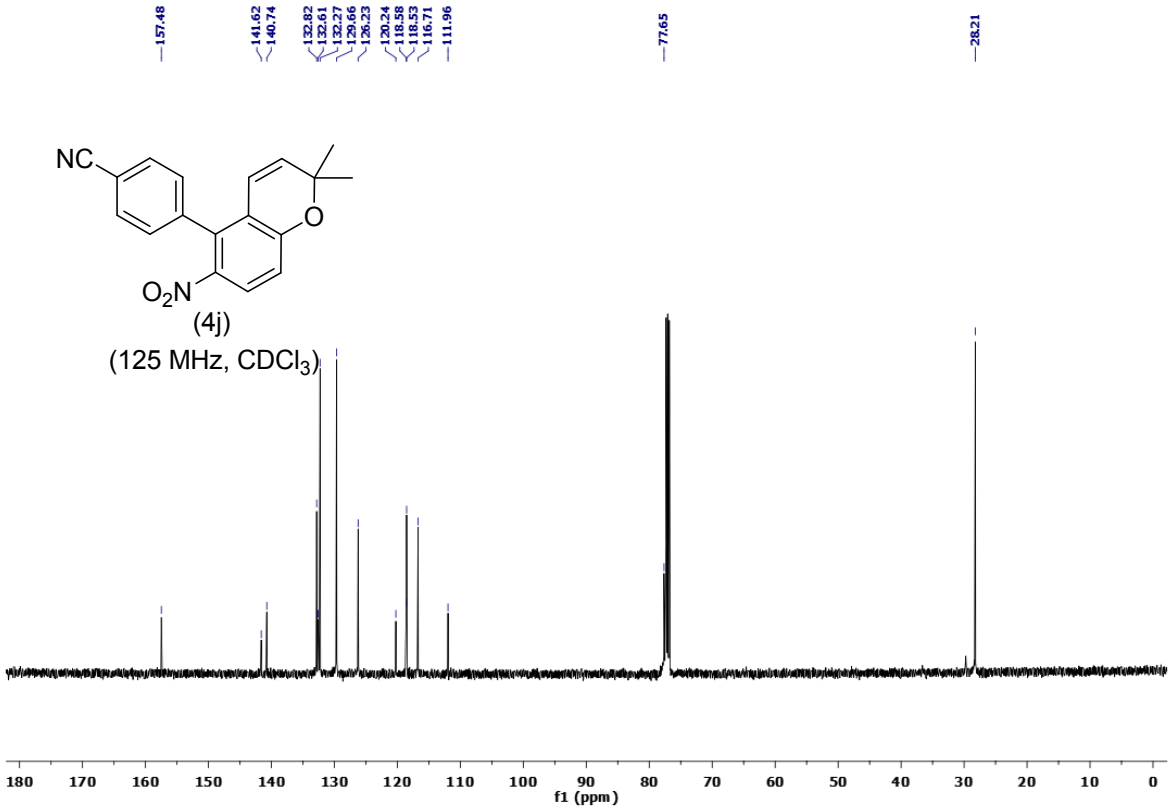


(4i)

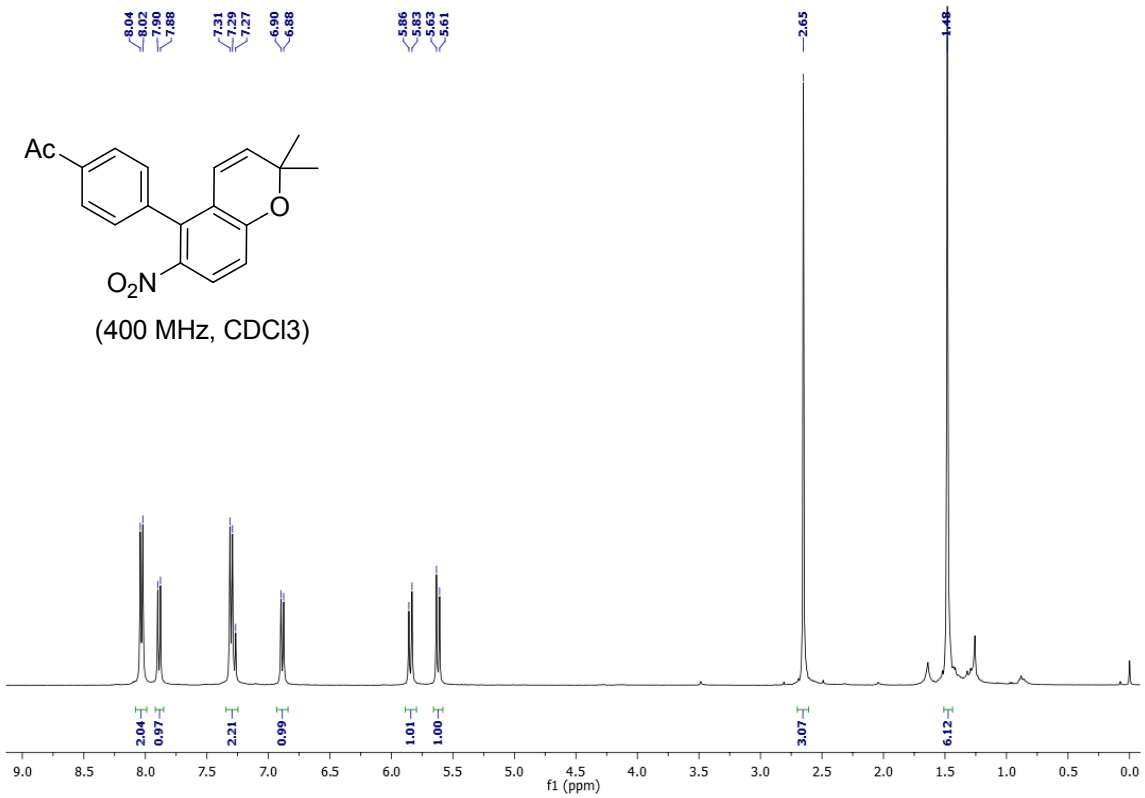
(125 MHz, $CDCl_3$)

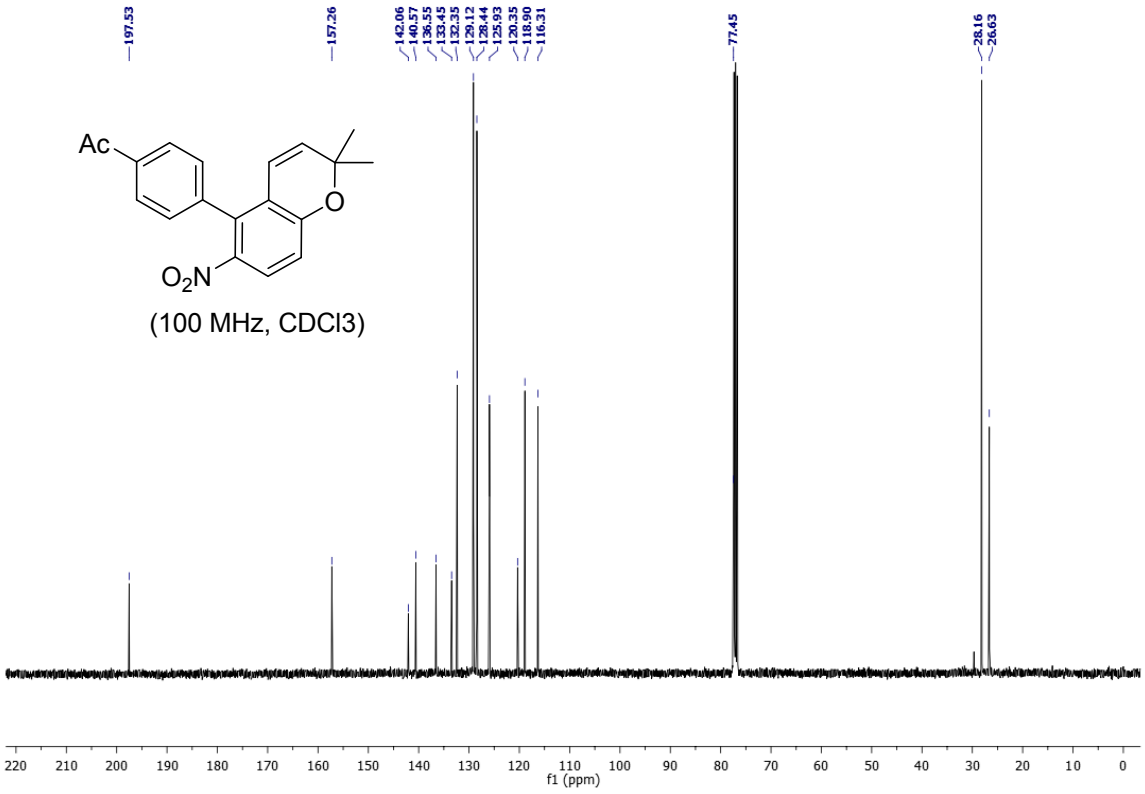
4-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)benzonitrile(**4j**):



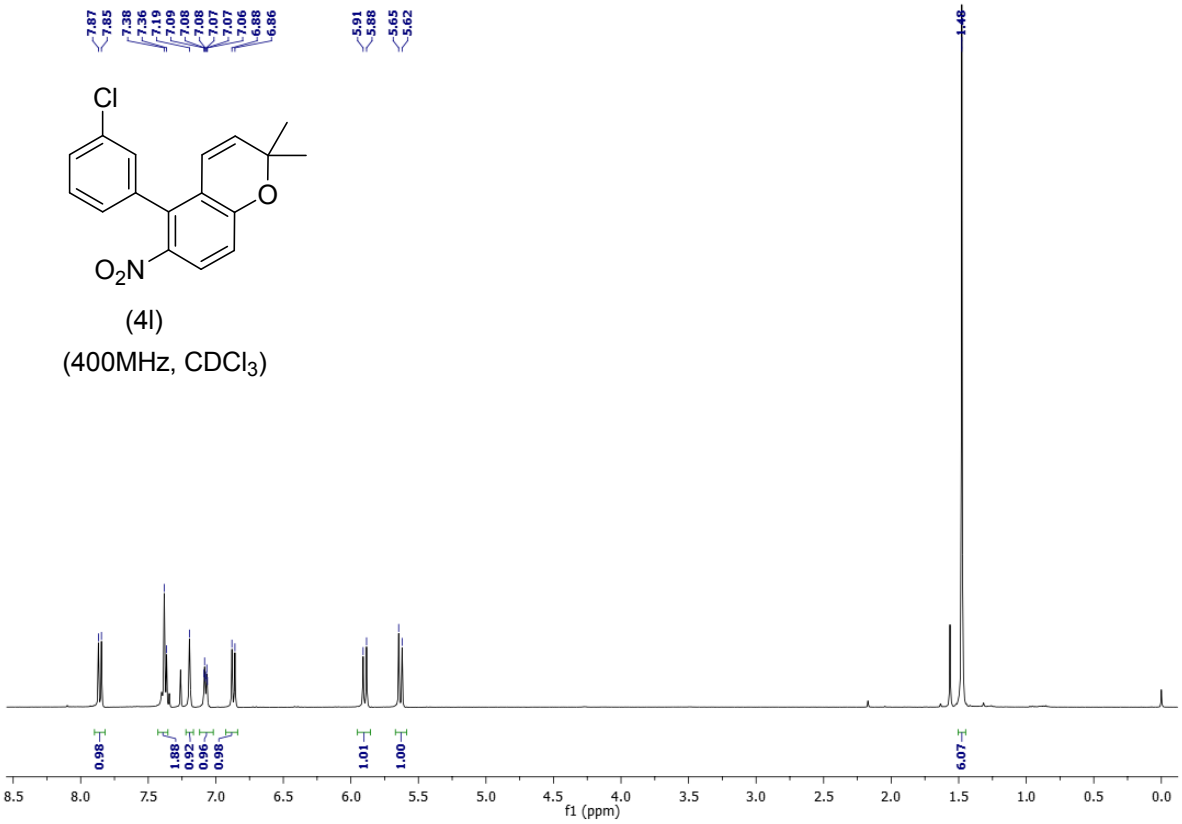


1-(4-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)phenyl)ethanone(**4k)**:



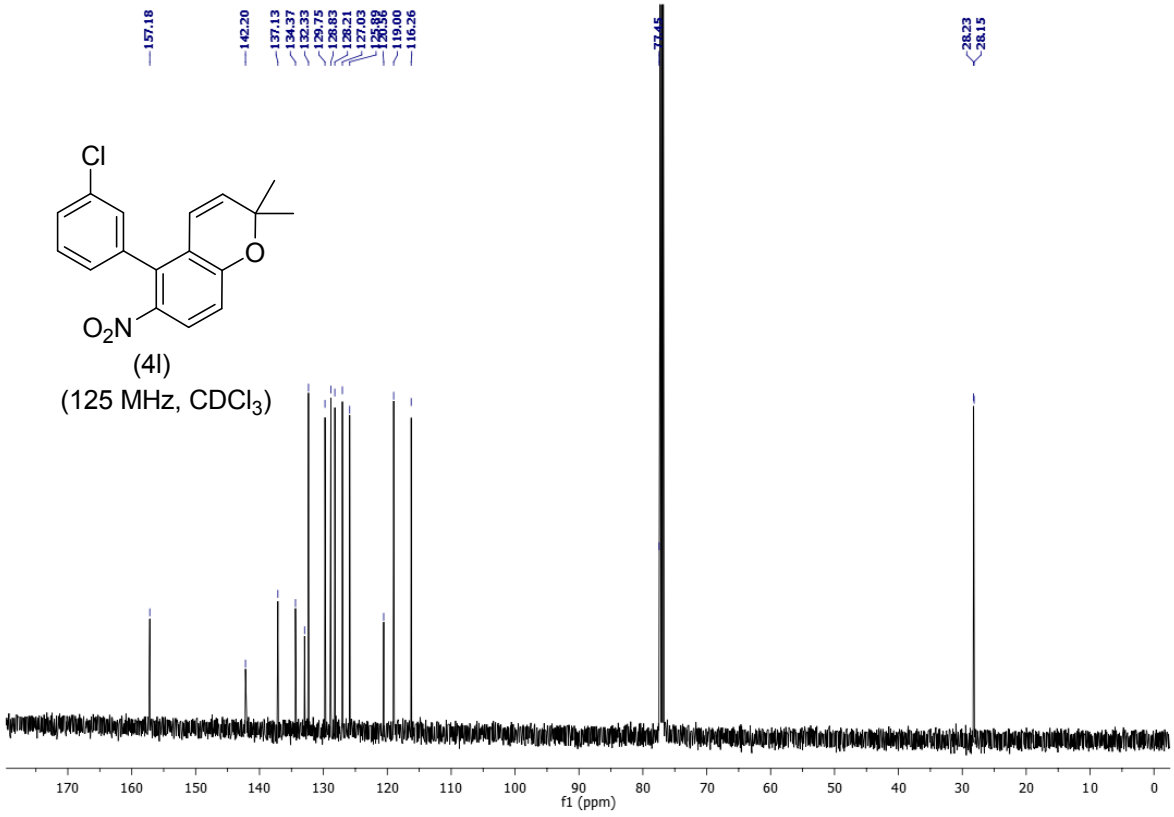


5-(3-Chlorophenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (**4l**) :



(4l)

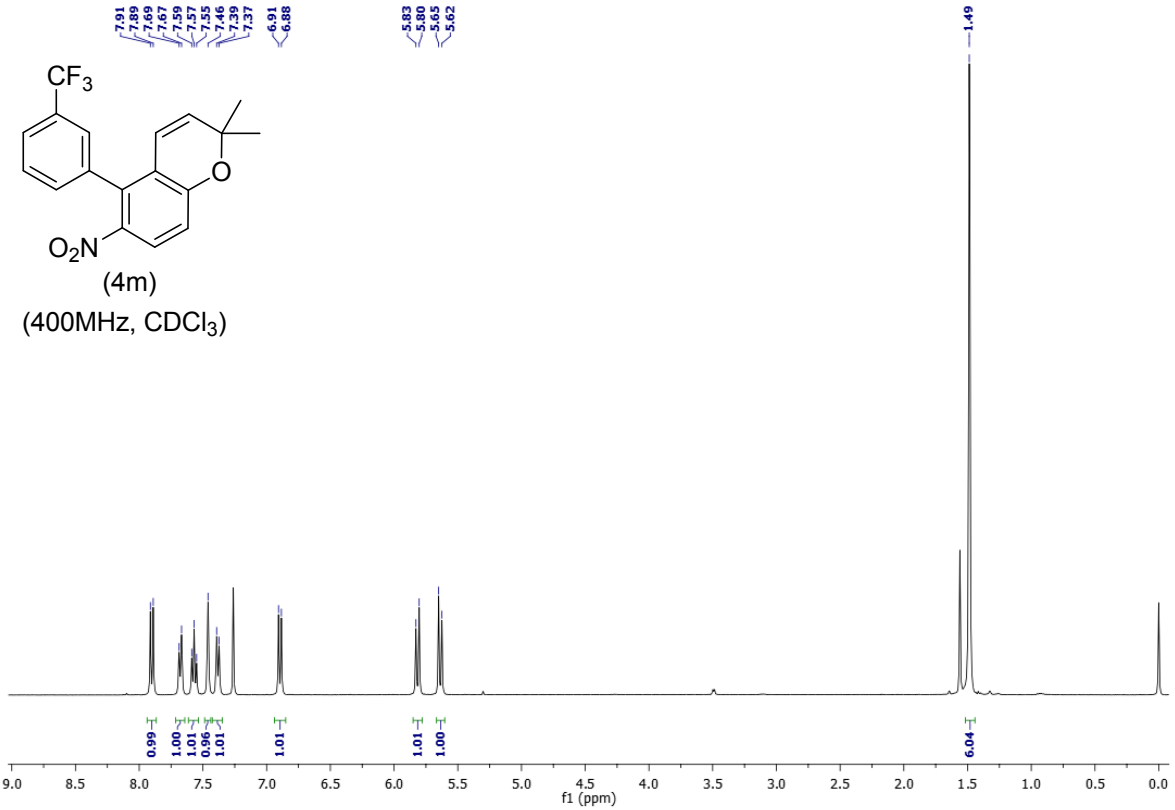
(400MHz, $CDCl_3$)

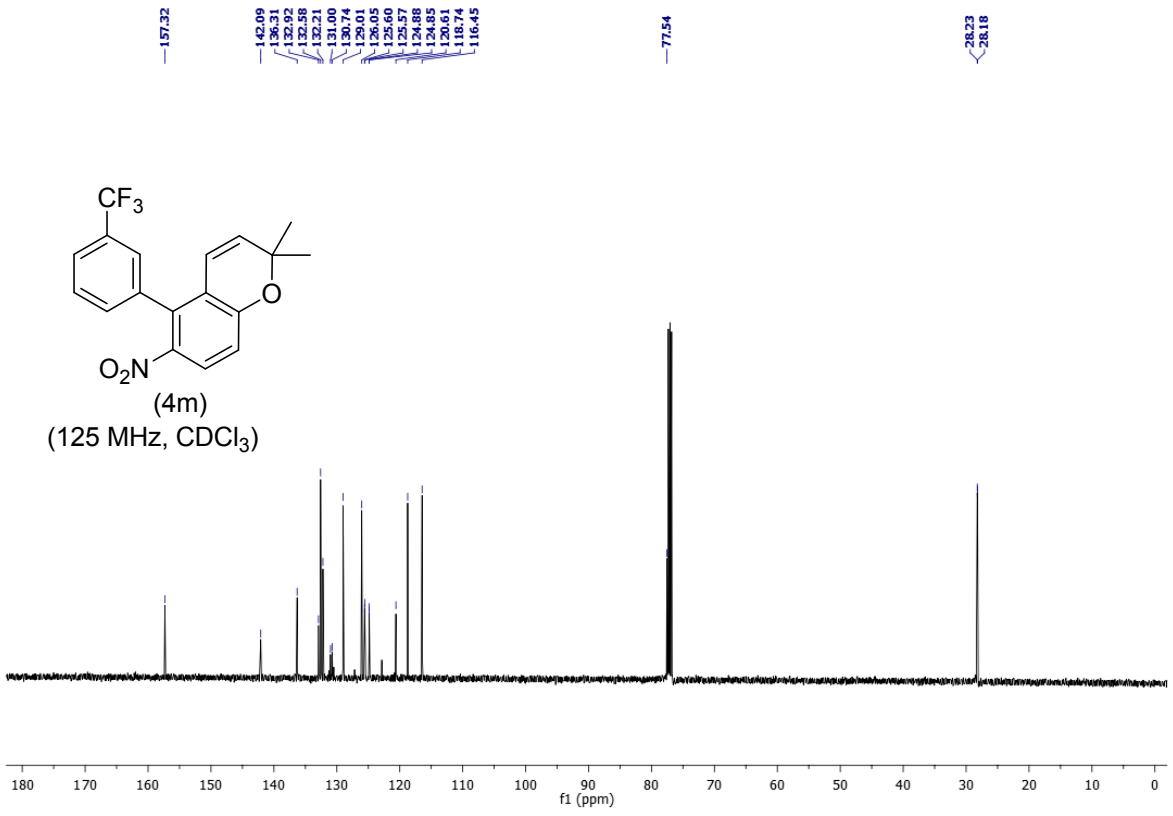


(4l)

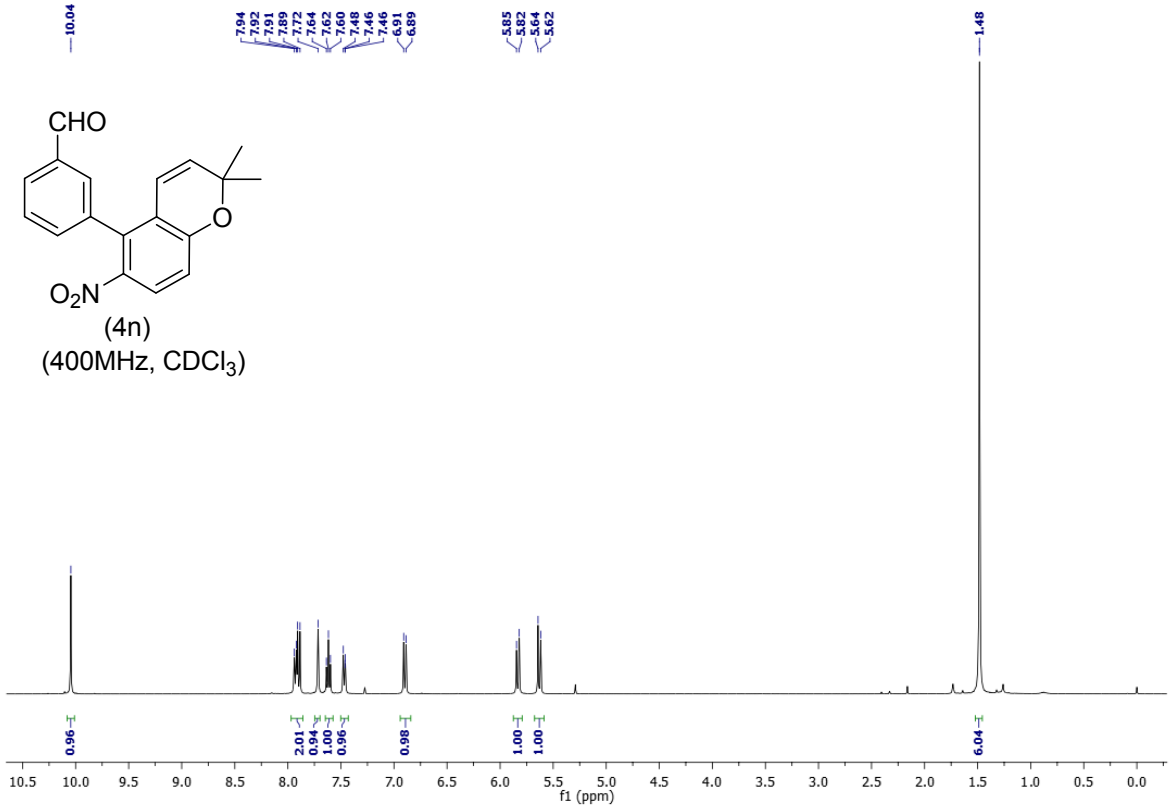
(125 MHz, $CDCl_3$)

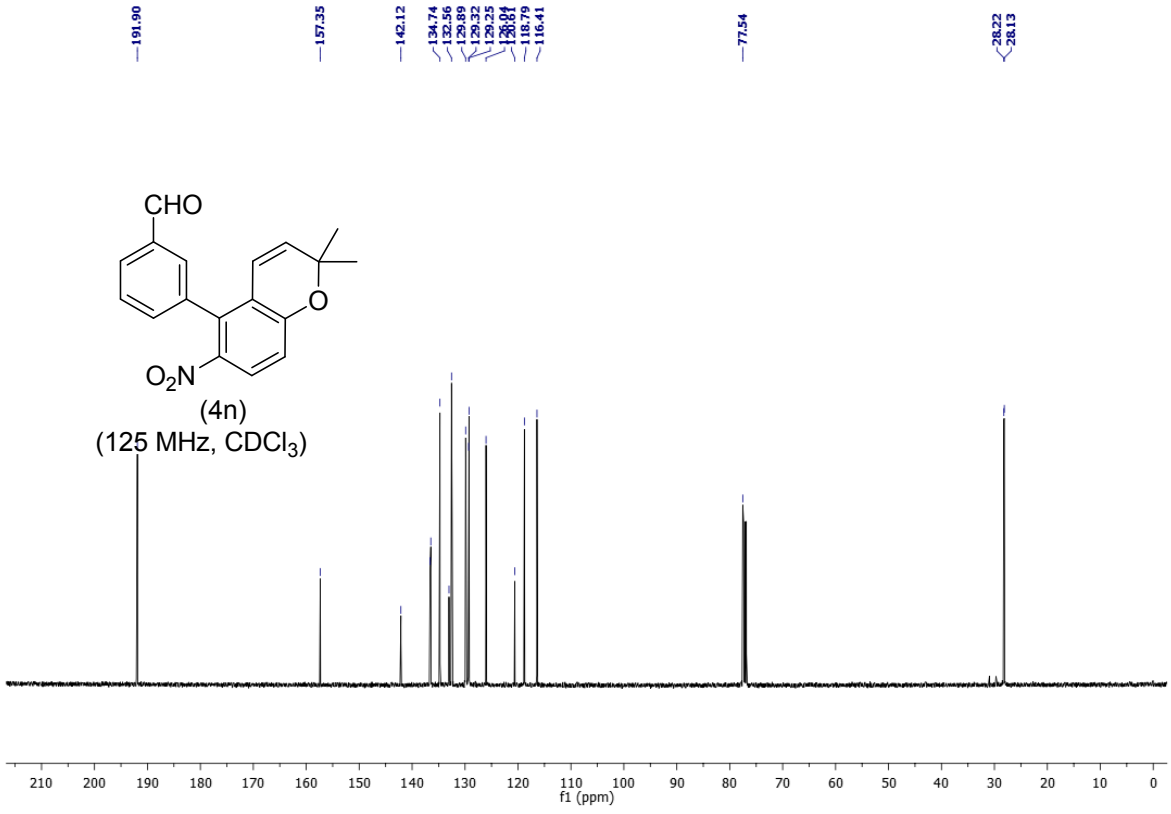
2,2-Dimethyl-6-nitro-5-(3-(trifluoromethyl)phenyl)-2*H*-chromene (**4m**):



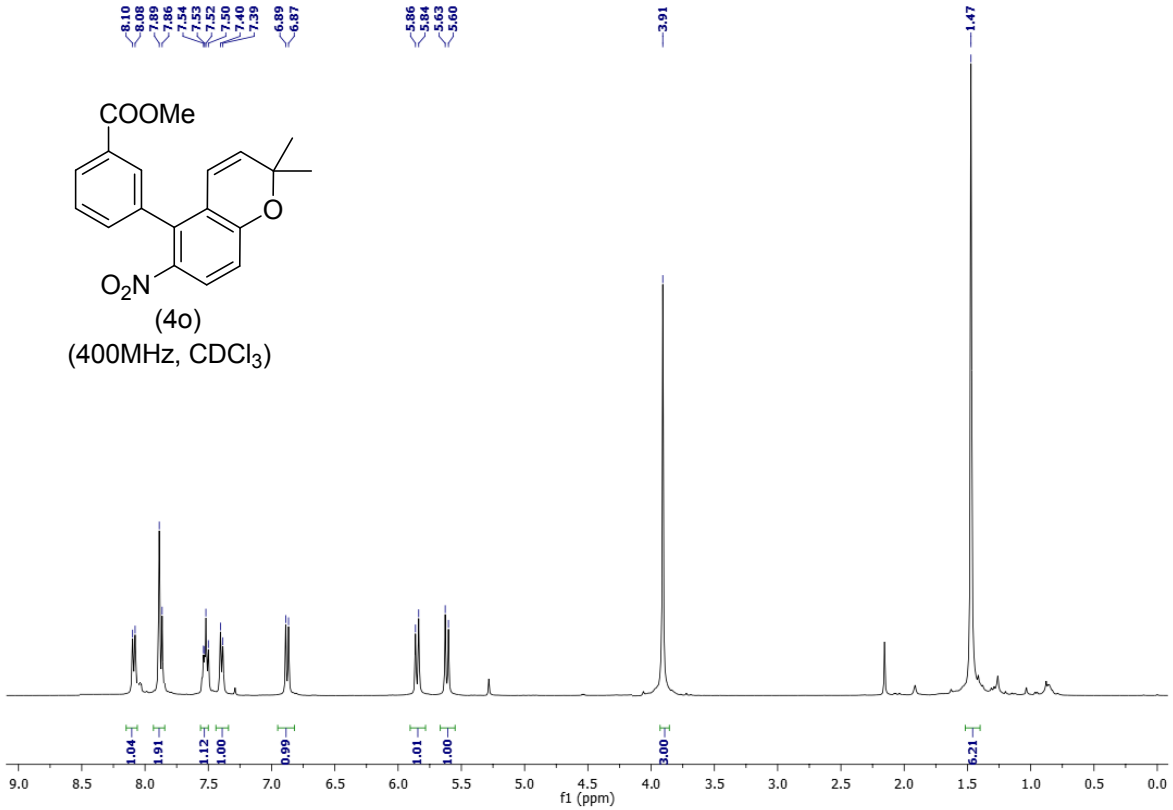


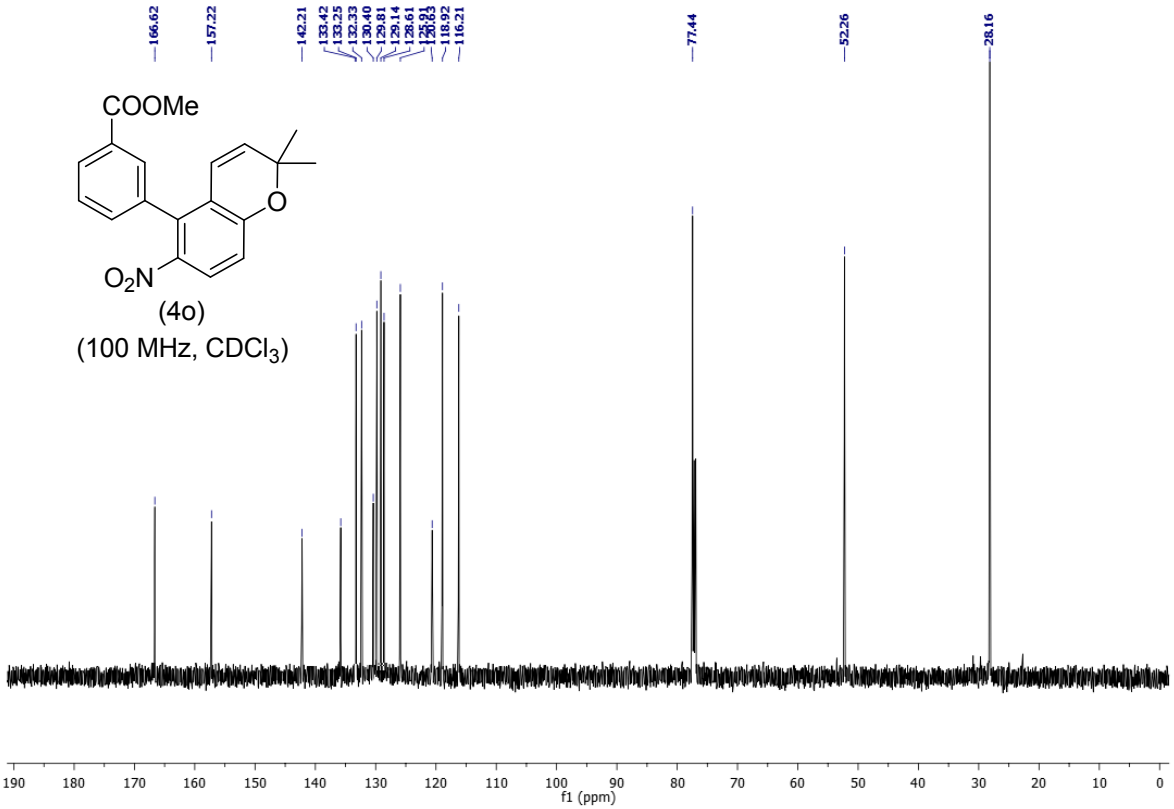
3-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)benzaldehyde(**4n**):



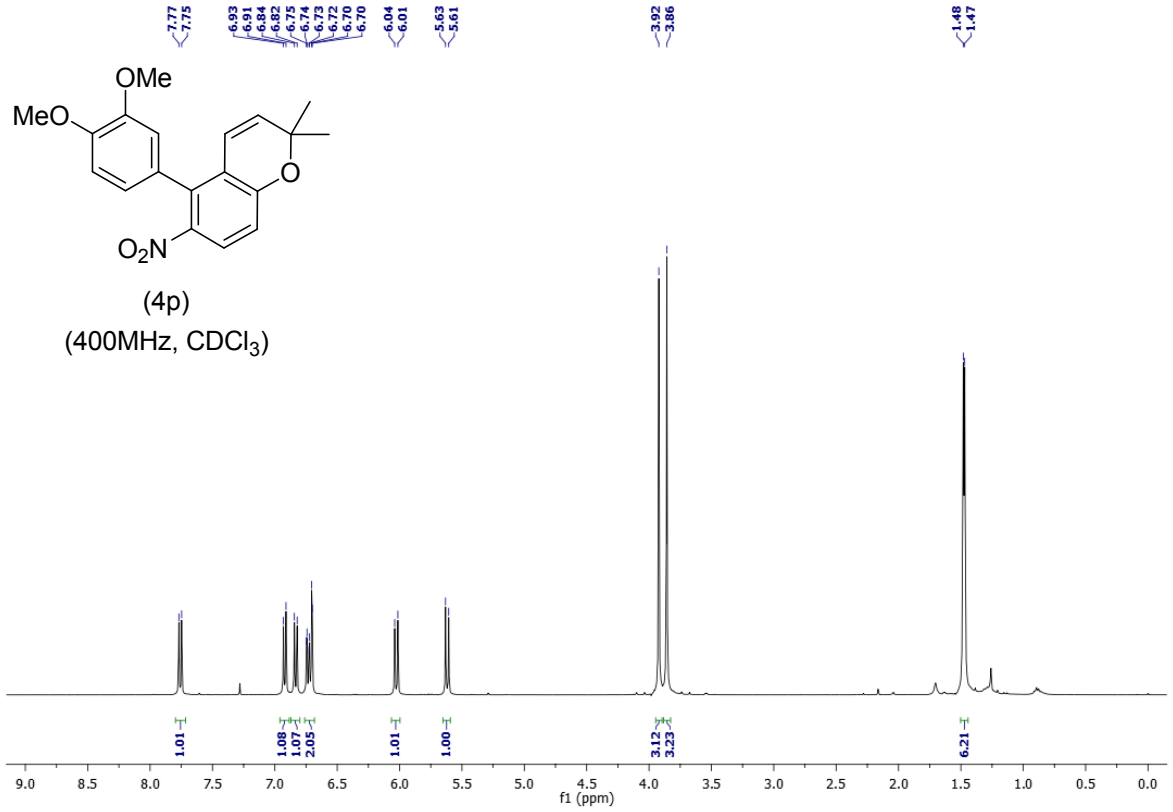


Methyl 3-(2,2-dimethyl-6-nitro-2*H*-chromen-5-yl)benzoate (**4o**) :

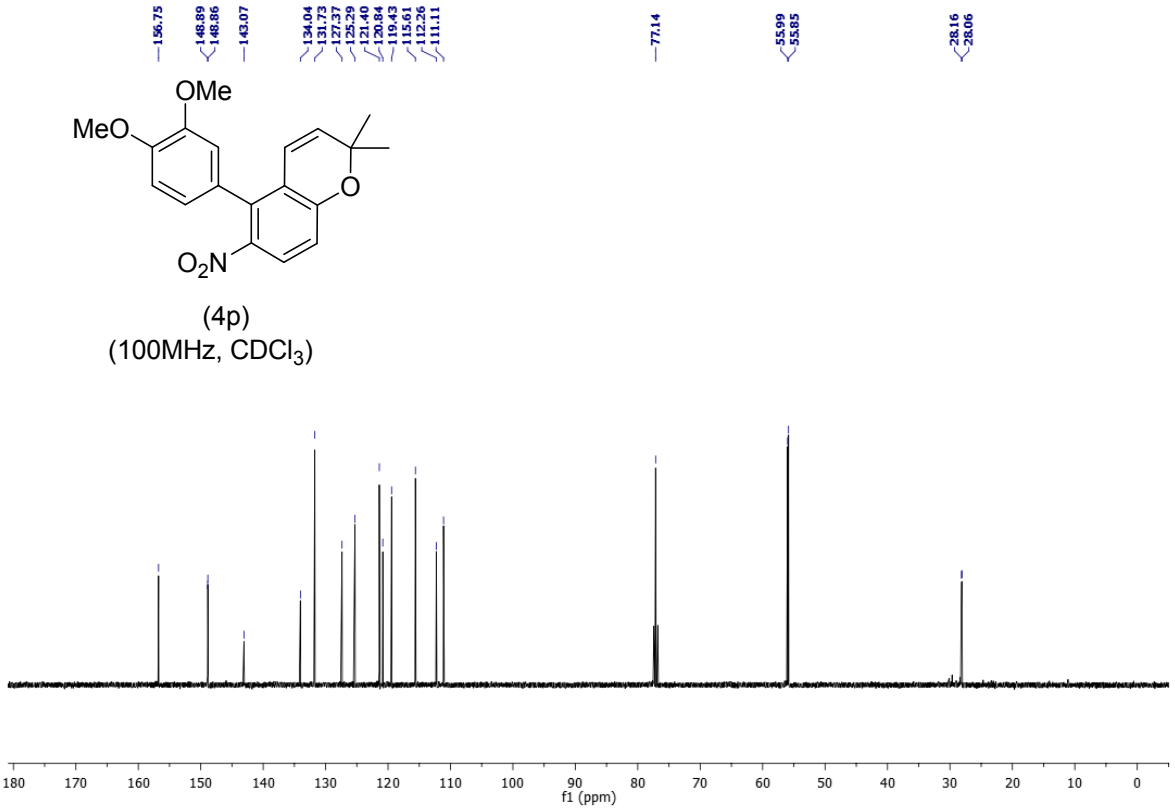




5-(3,4-Dimethoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene(**4p**):



(4p)
(400MHz, $CDCl_3$)



(4p)
(100MHz, $CDCl_3$)

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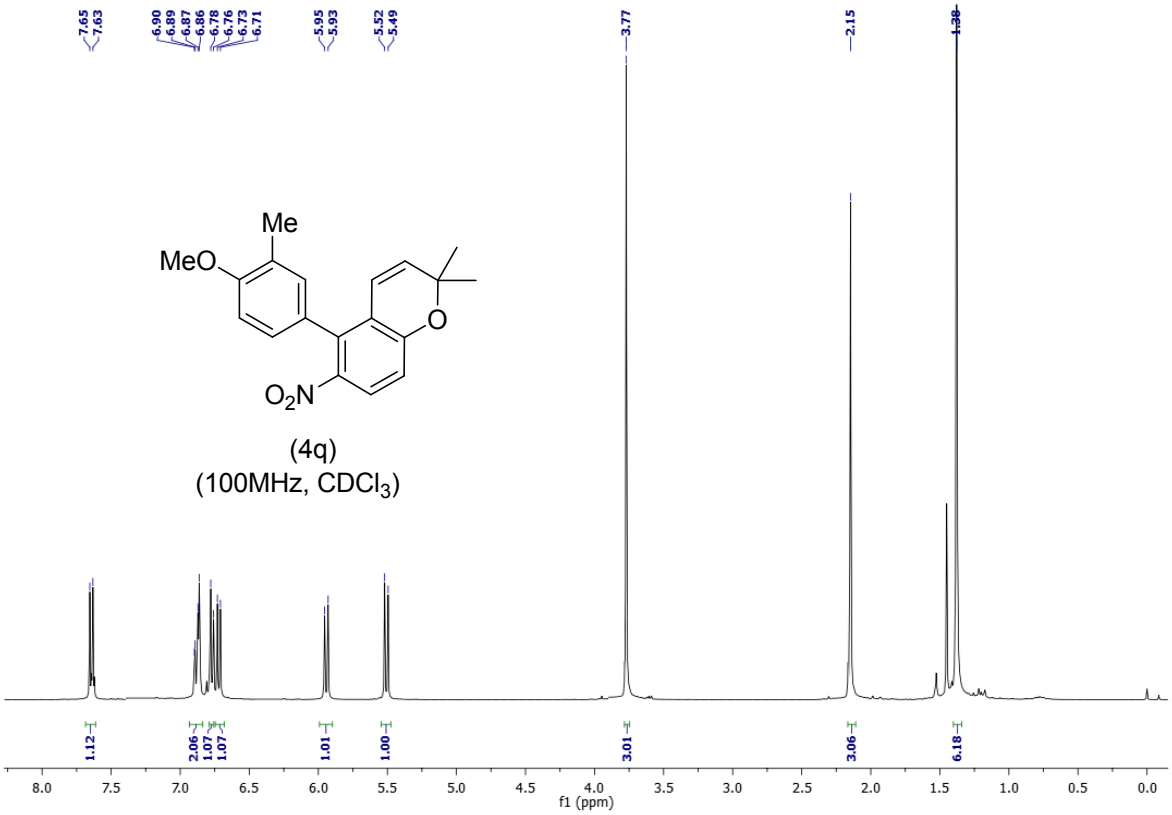
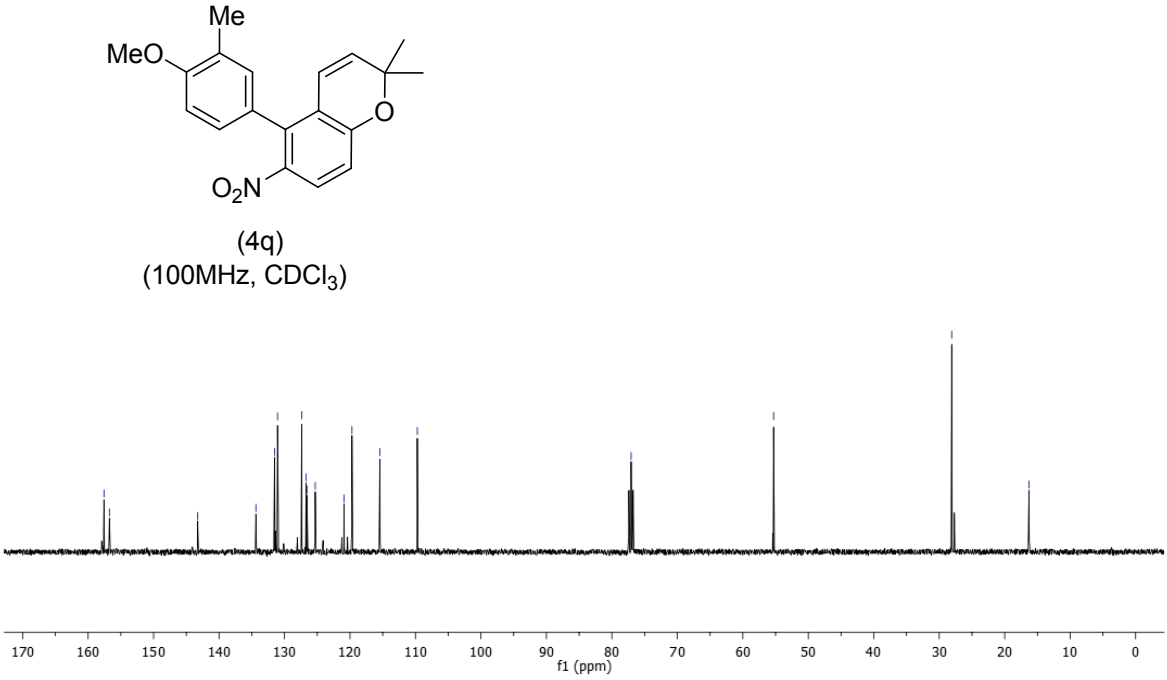
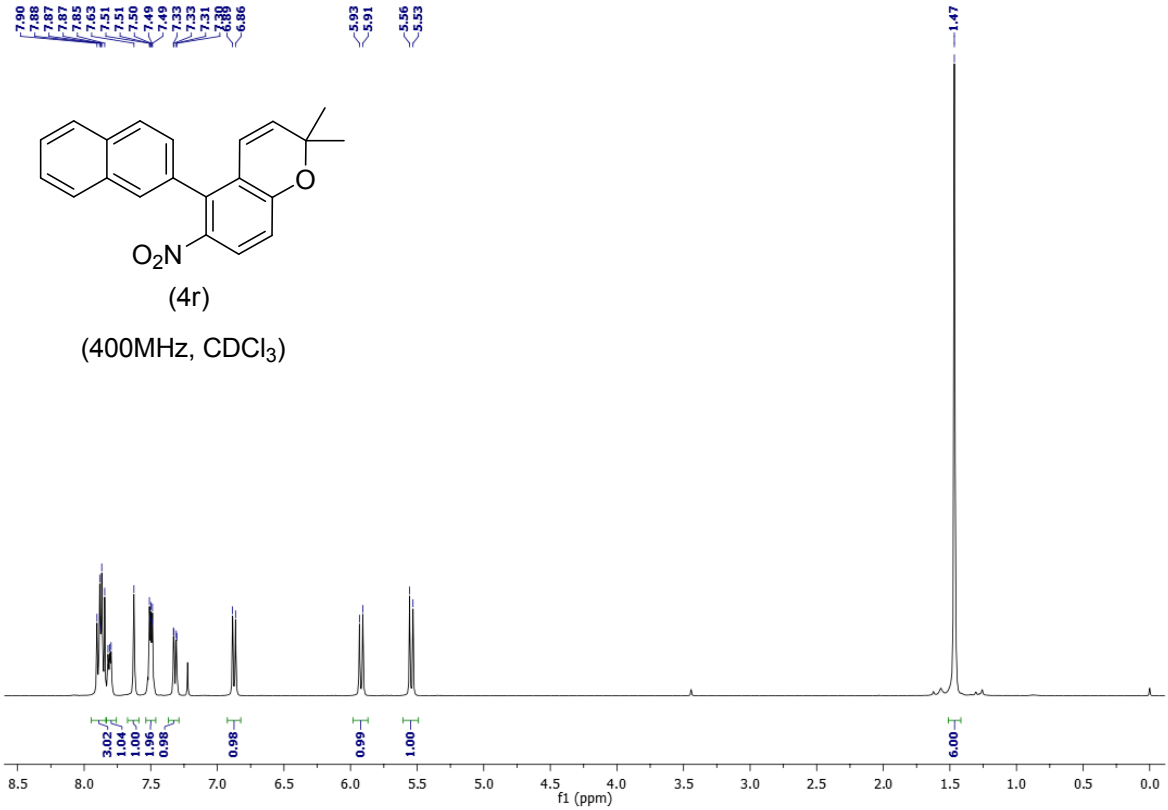


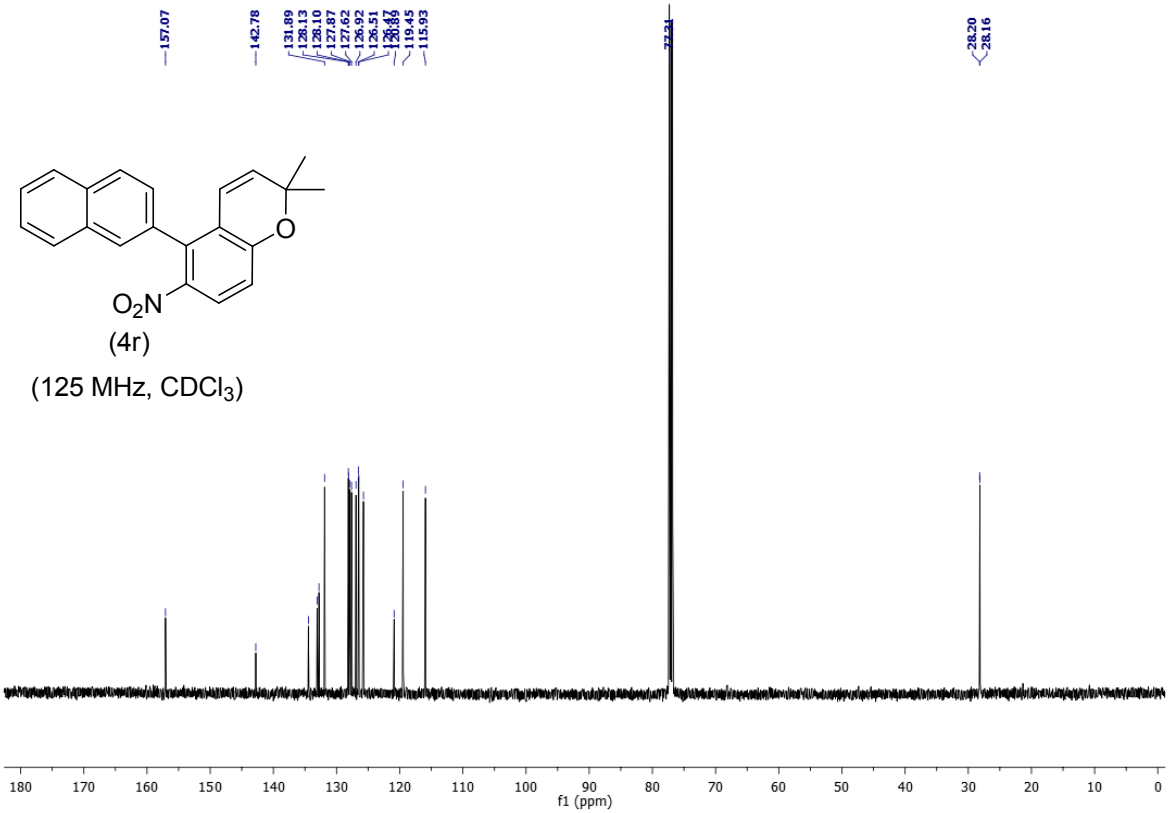


2,2-Dimethyl-5-(naphthalen-2-yl)-6-nitro-2*H*-chromene(**4r**):



(4r)

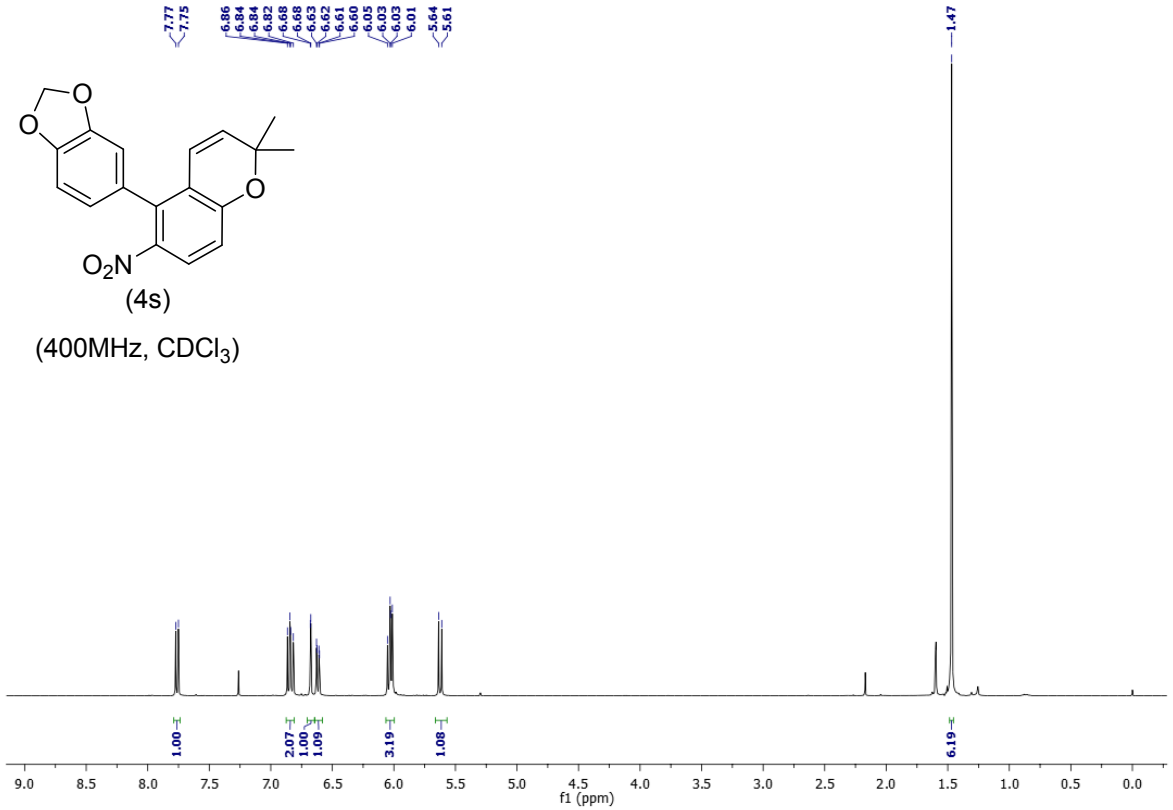
(400MHz, $CDCl_3$)



(4r)

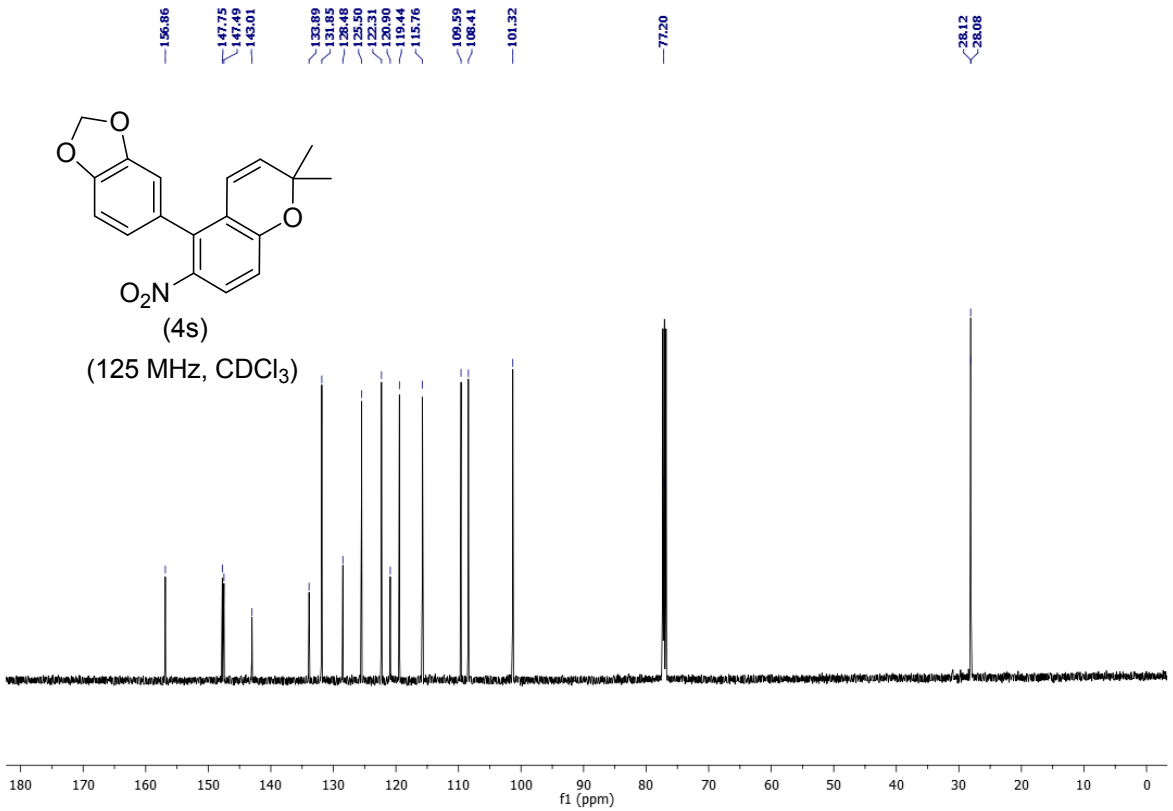
(125 MHz, $CDCl_3$)

5-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-6-nitro-2*H*-chromene (**4s**):



(4s)

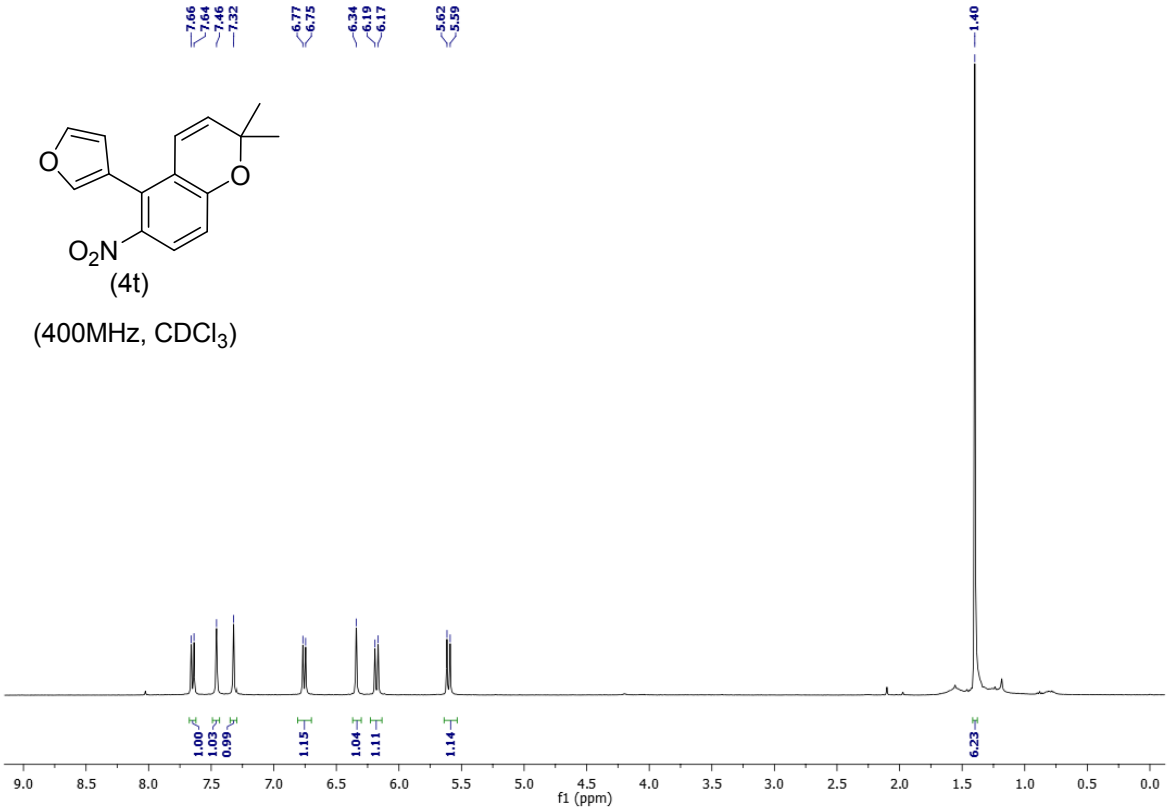
(400MHz, $CDCl_3$)



(4s)

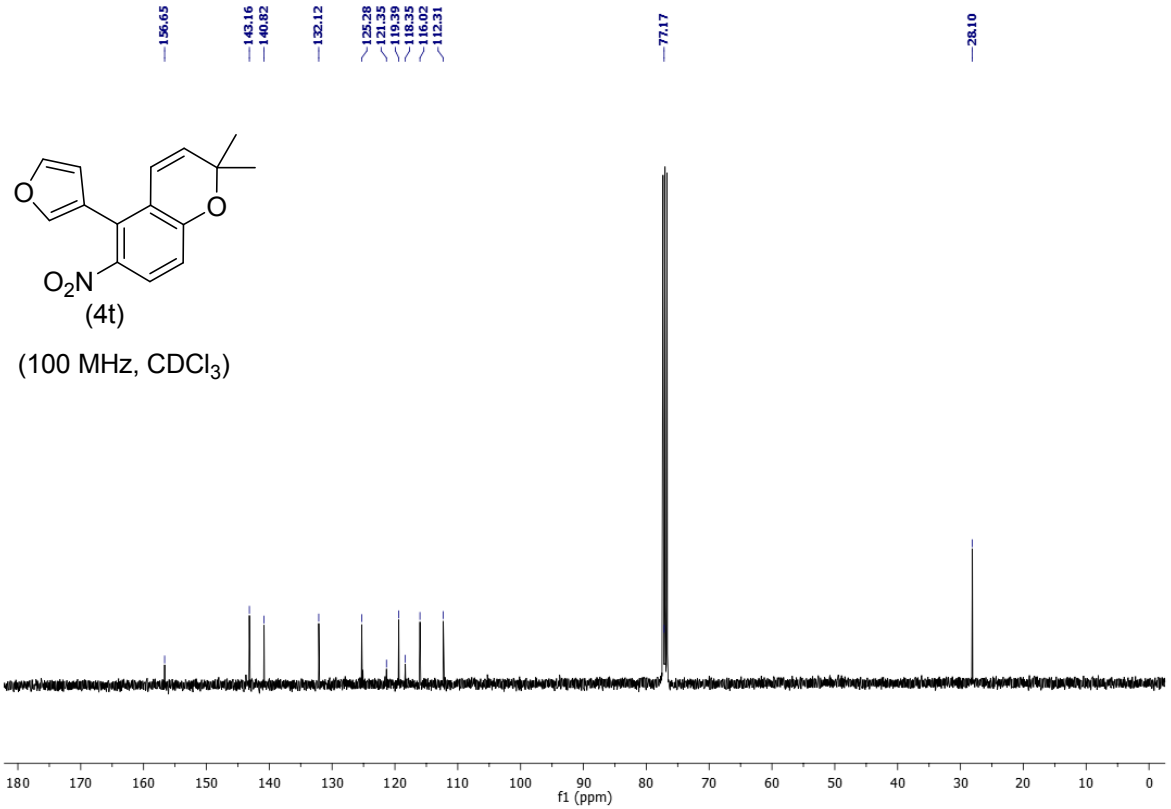
(125 MHz, $CDCl_3$)

5-(Furan-3-yl)-2,2-dimethyl-6-nitro-2*H*-chromene(**4t**);



(4t)

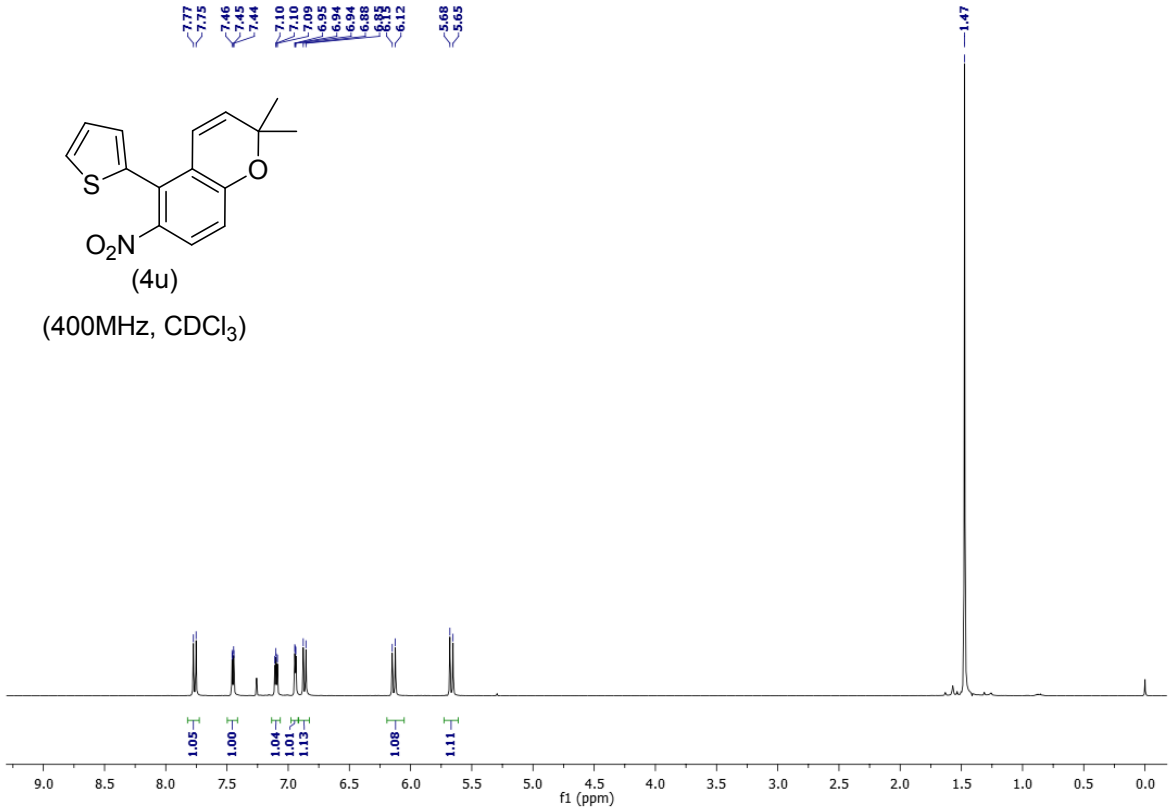
(400MHz, $CDCl_3$)



(4t)

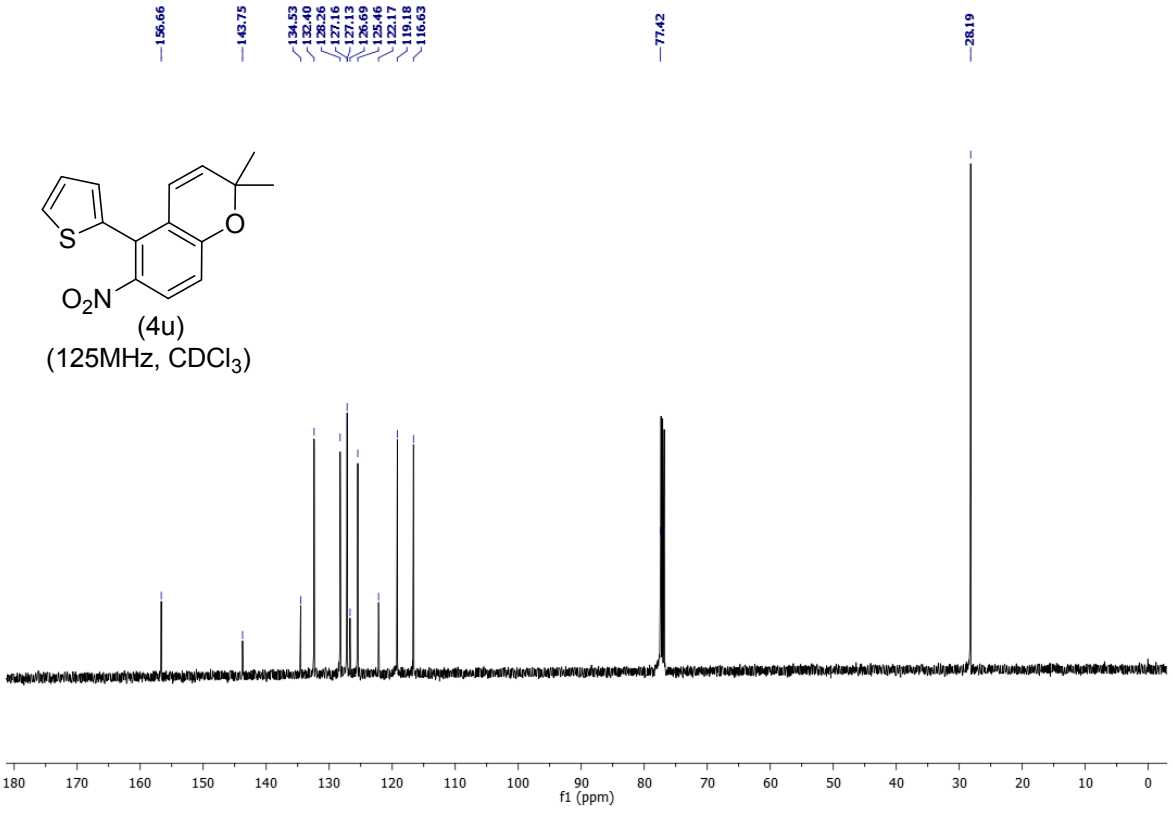
(100 MHz, $CDCl_3$)

2,2-Dimethyl-6-nitro-5-(thiophen-2-yl)-2*H*-chromene(**4u**):



(4u)

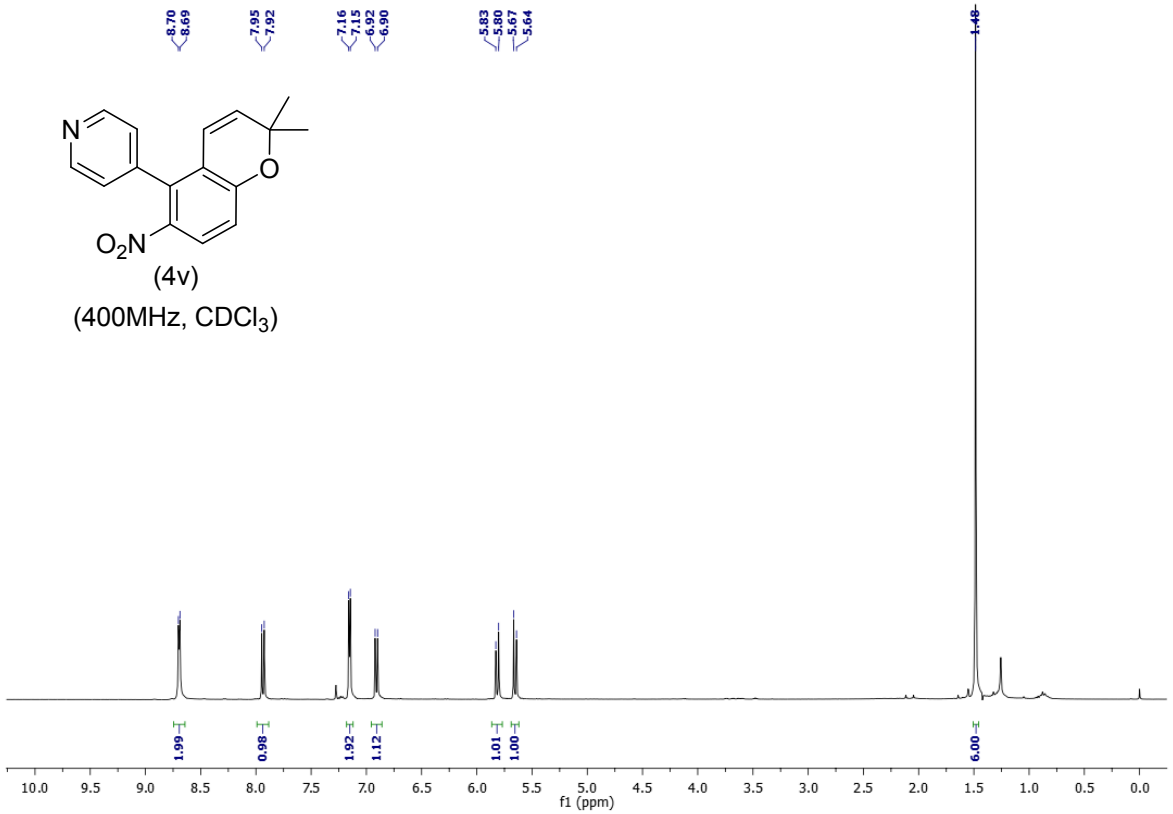
(400MHz, $CDCl_3$)

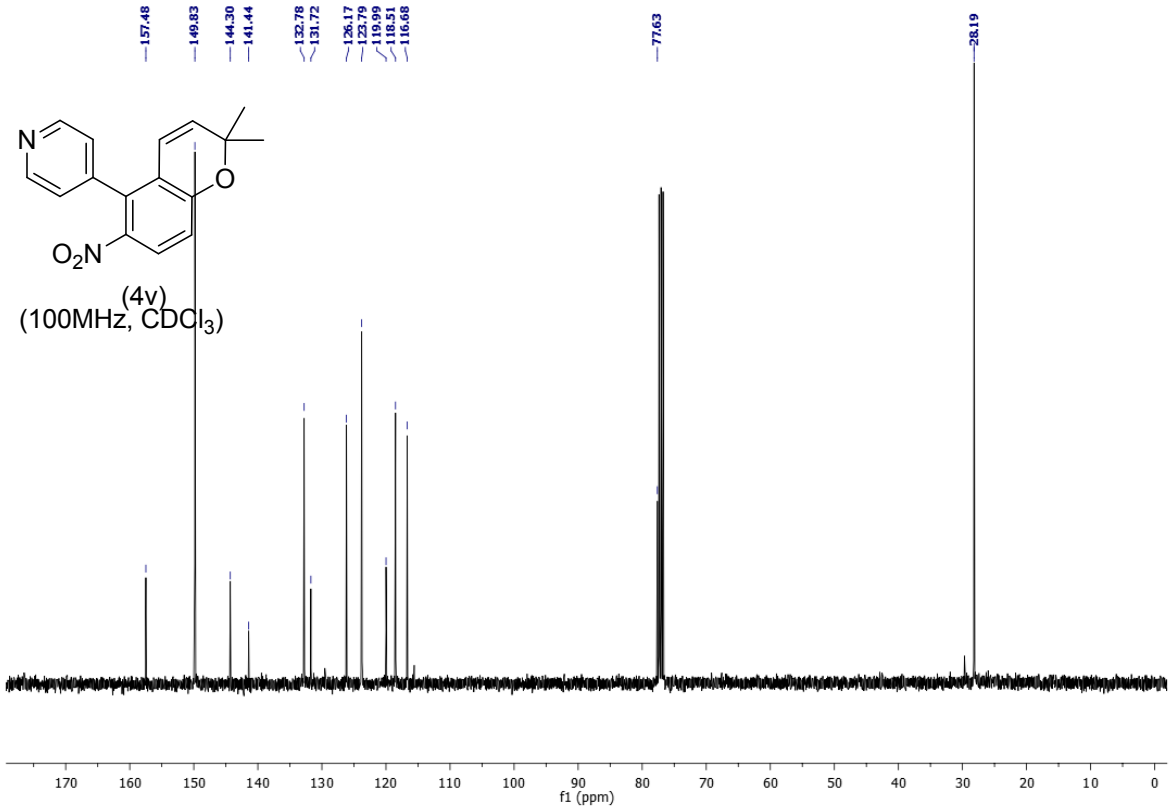


(4u)

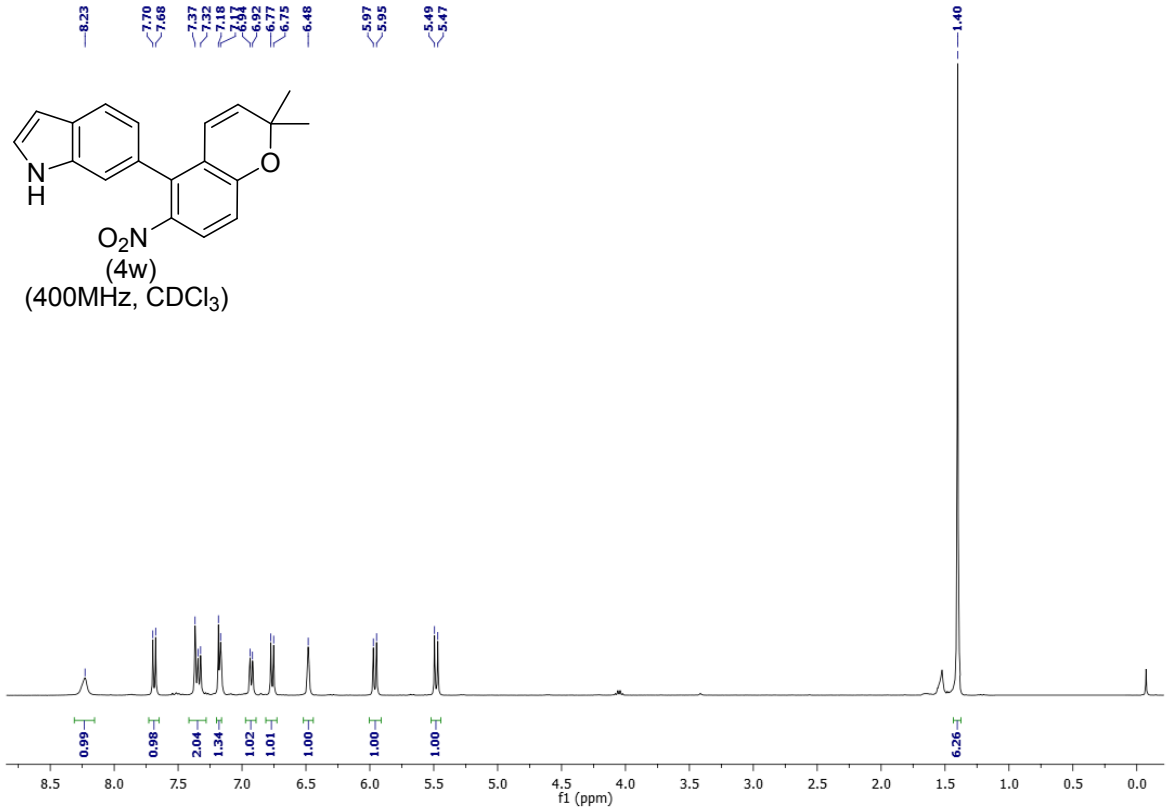
(125MHz, $CDCl_3$)

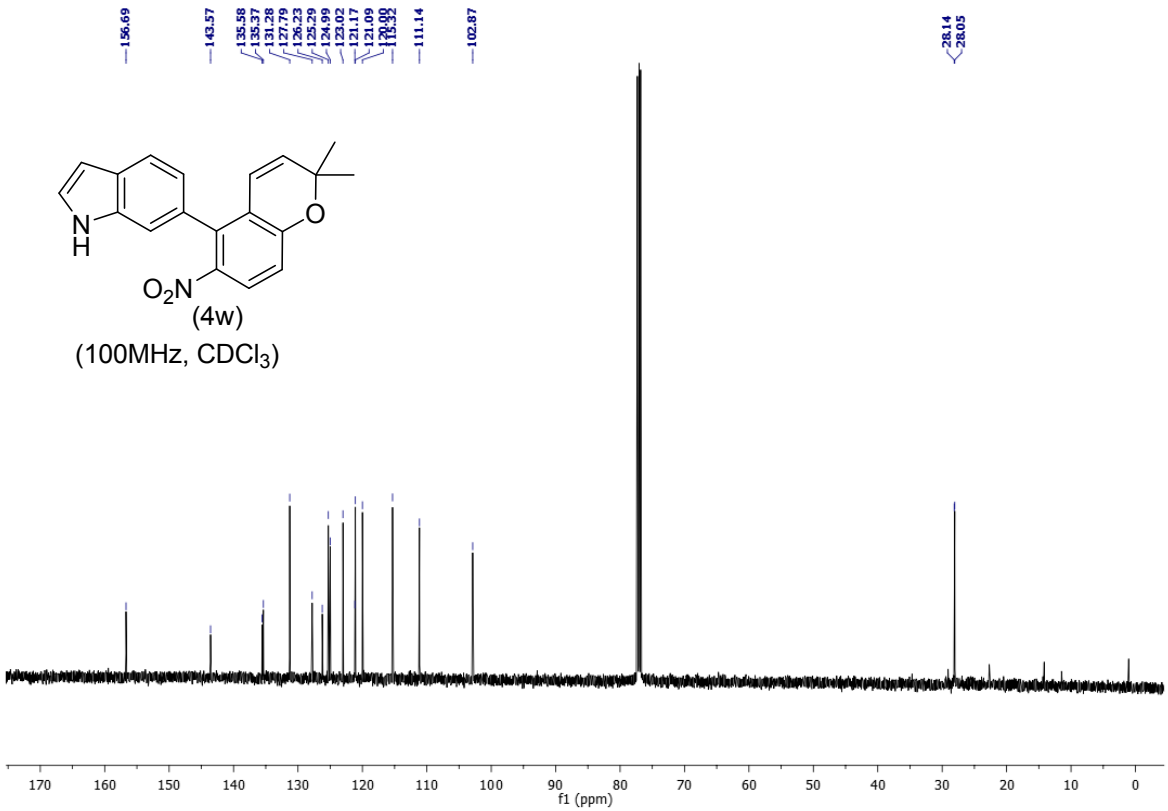
4-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)pyridine (**4v**):



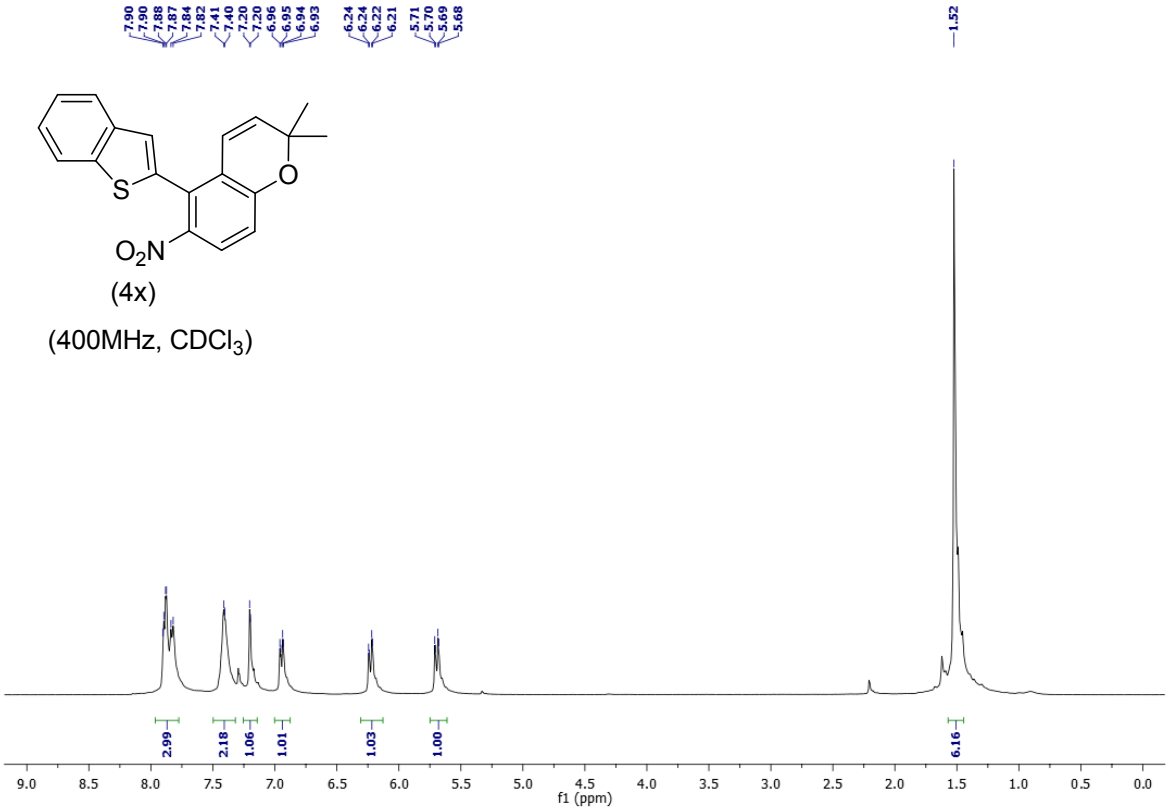


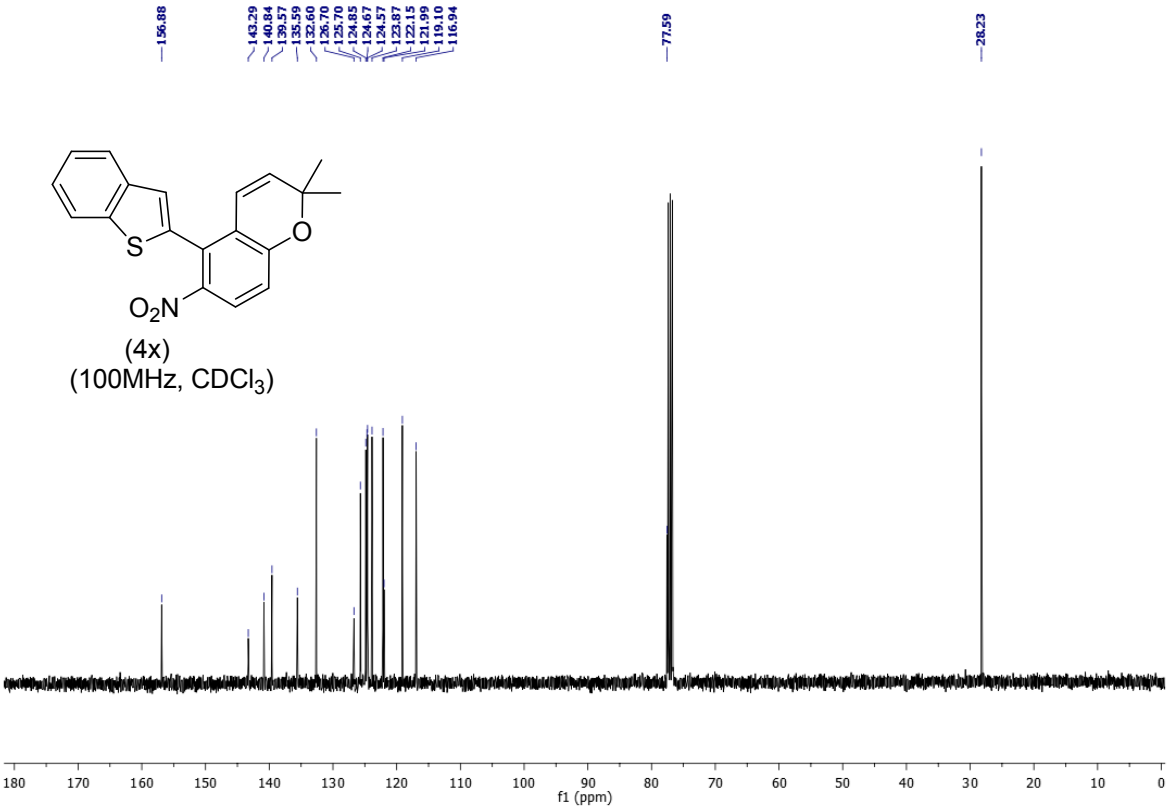
6-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)-1*H*-indole(**4w**):



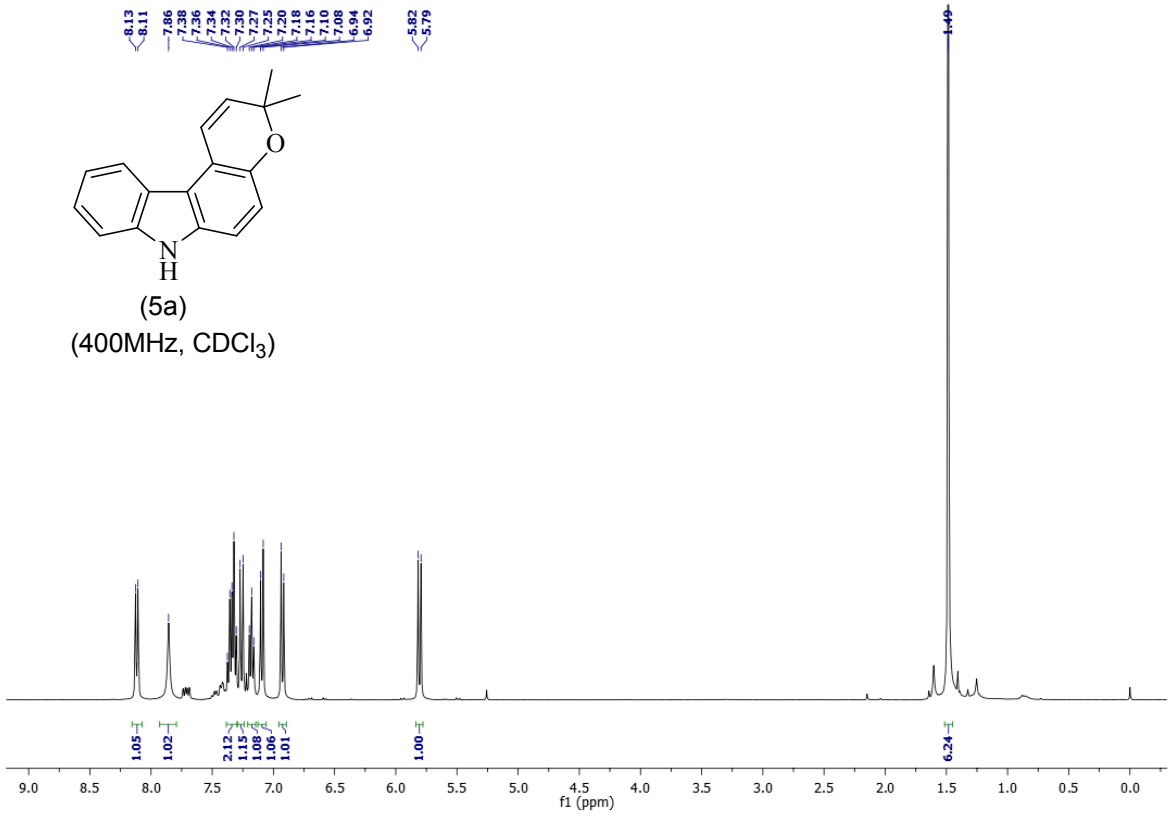


5-(Benzo[*b*]thiophen-2-yl)-2,2-dimethyl-6-nitro-2*H*-chromene(**4x**):



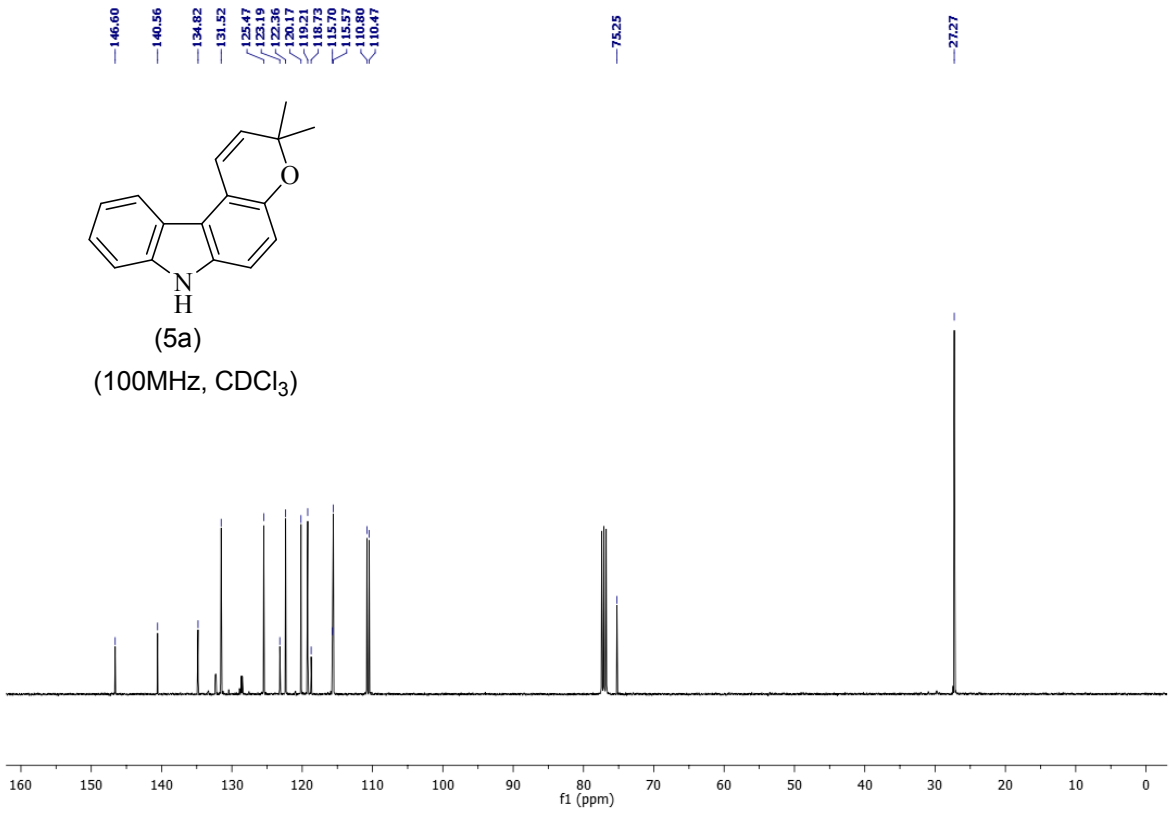


3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5a**):



(5a)

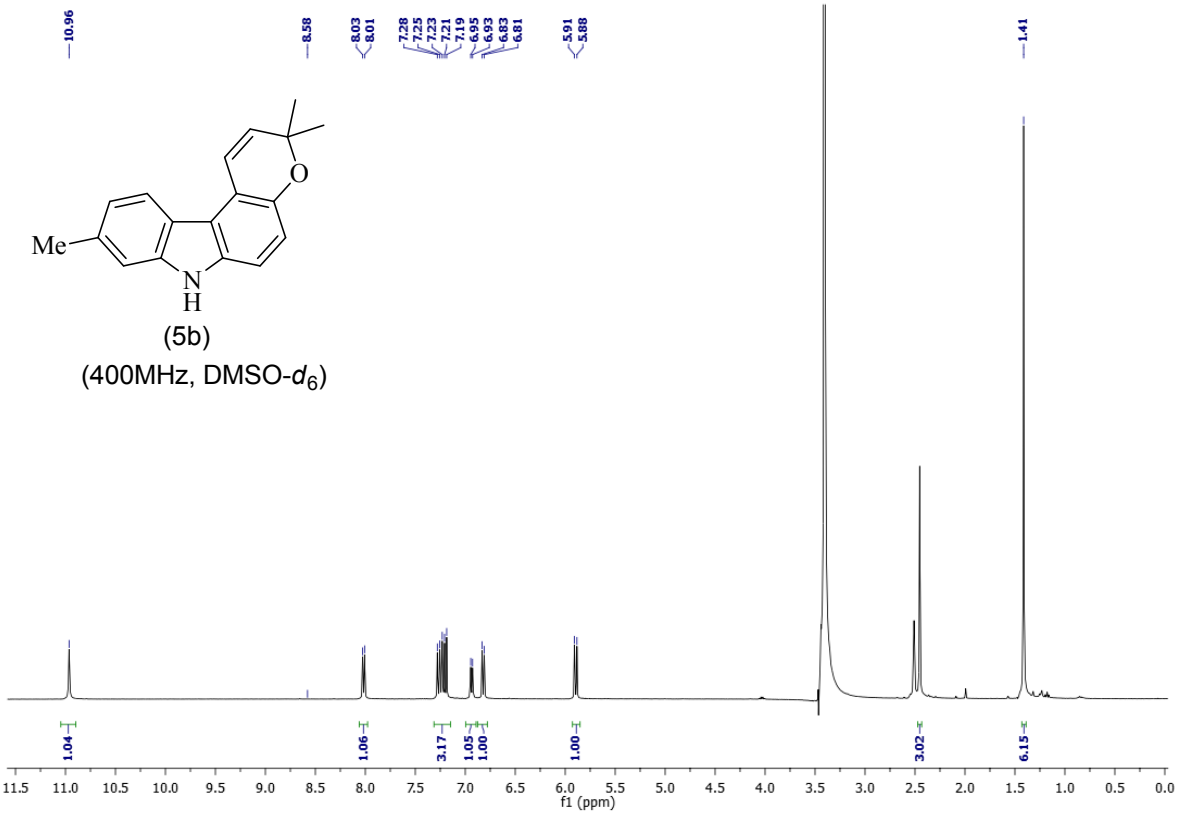
(400MHz, $CDCl_3$)



(5a)

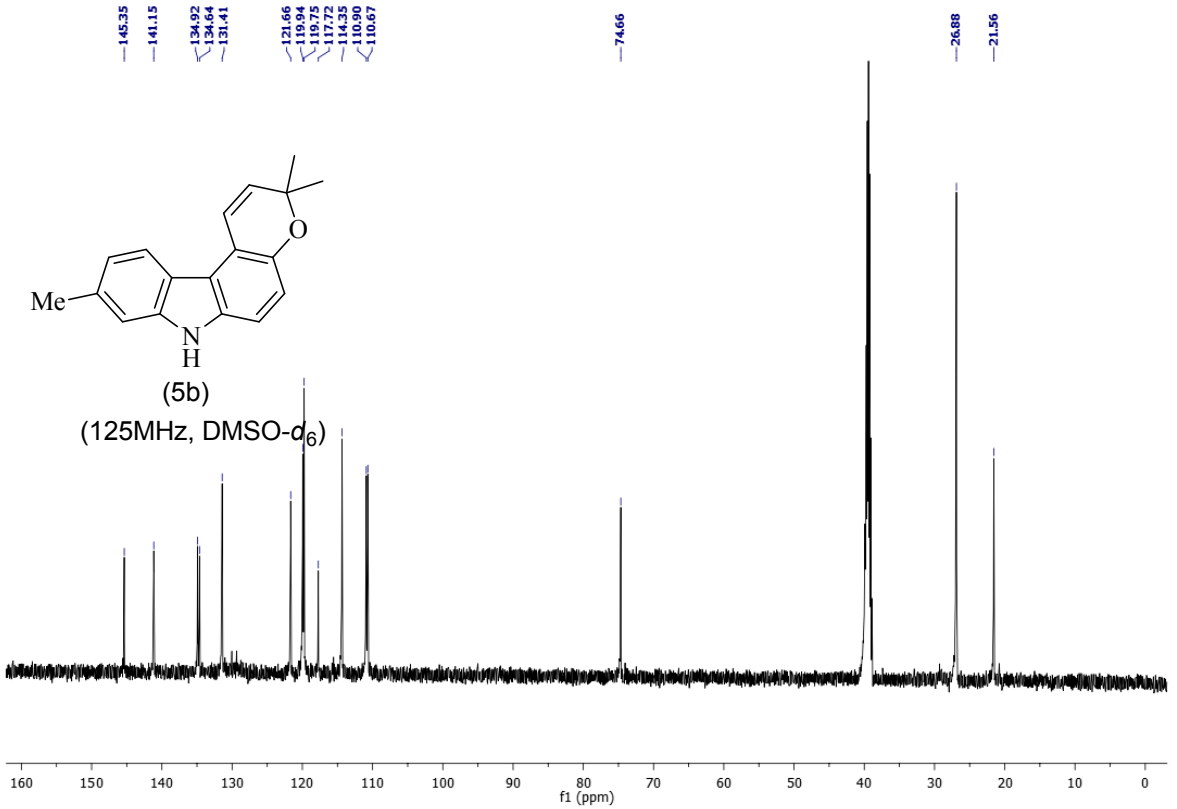
(100MHz, $CDCl_3$)

3,3,9-Trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5*b***):



(5b)

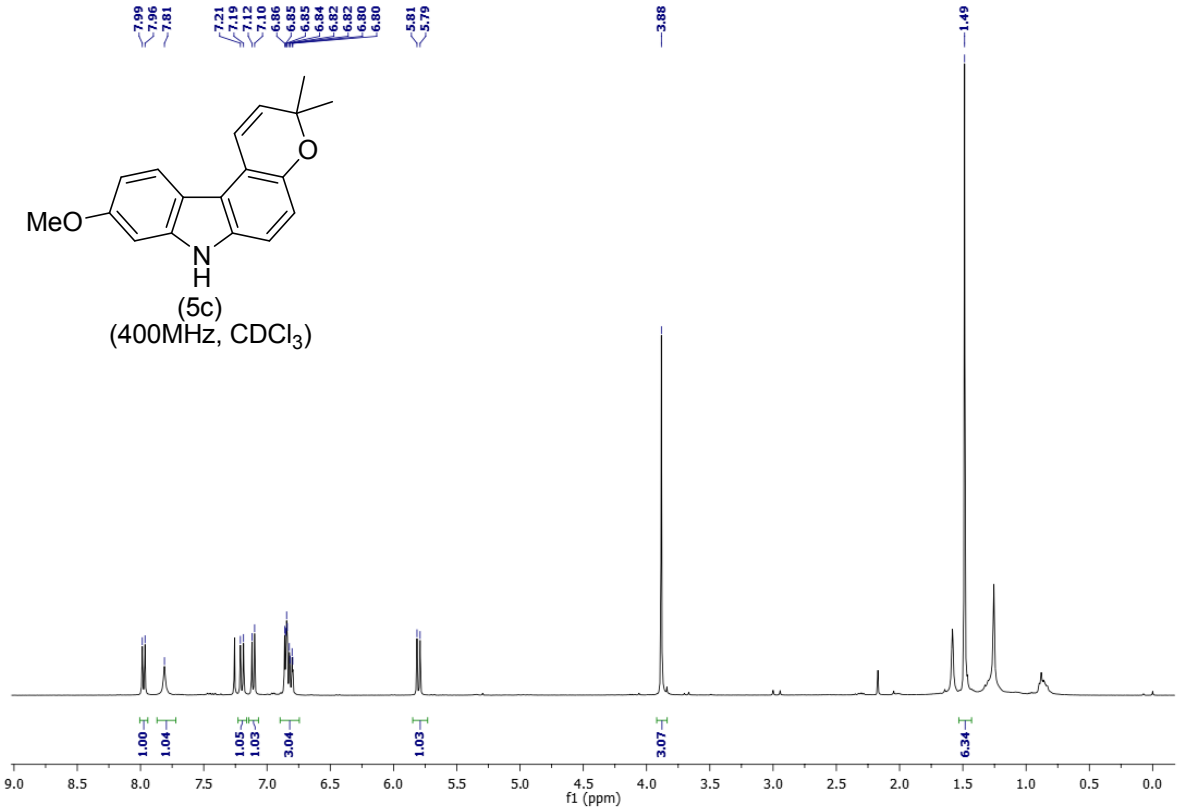
(400MHz, DMSO-d_6)

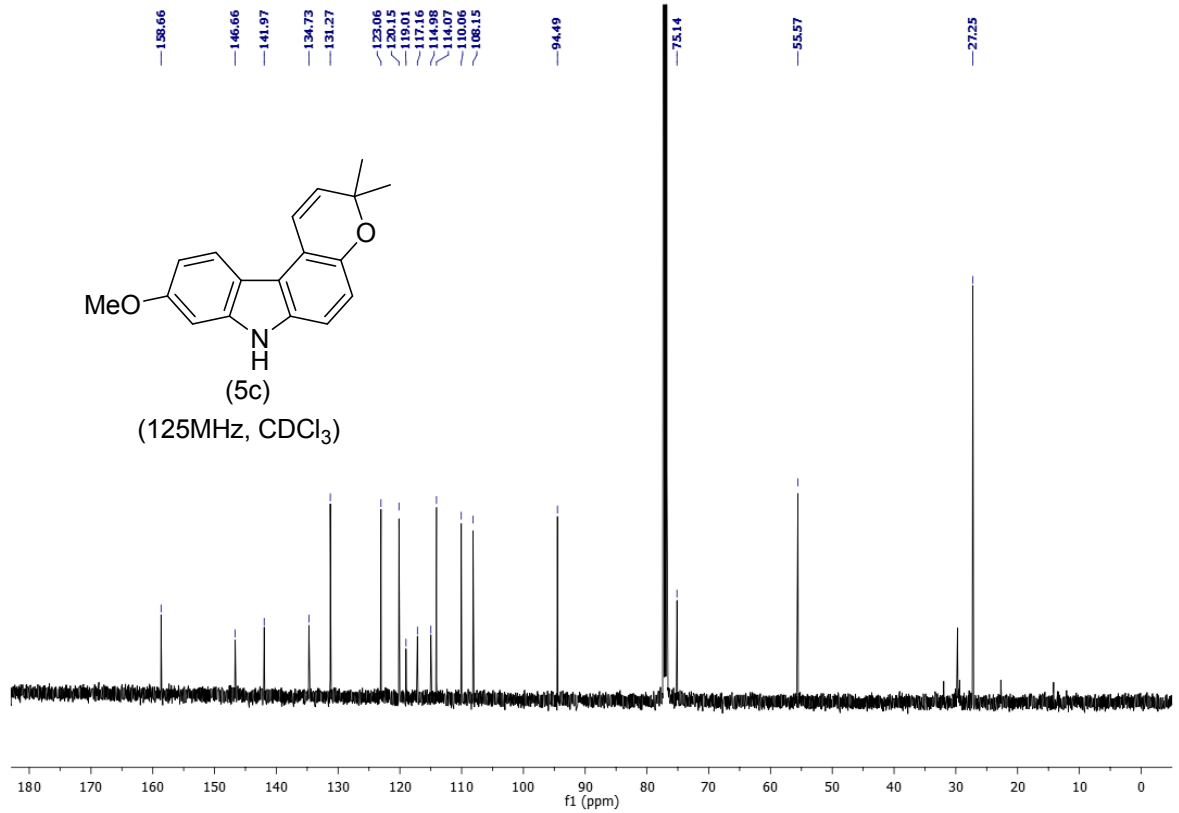


(5b)

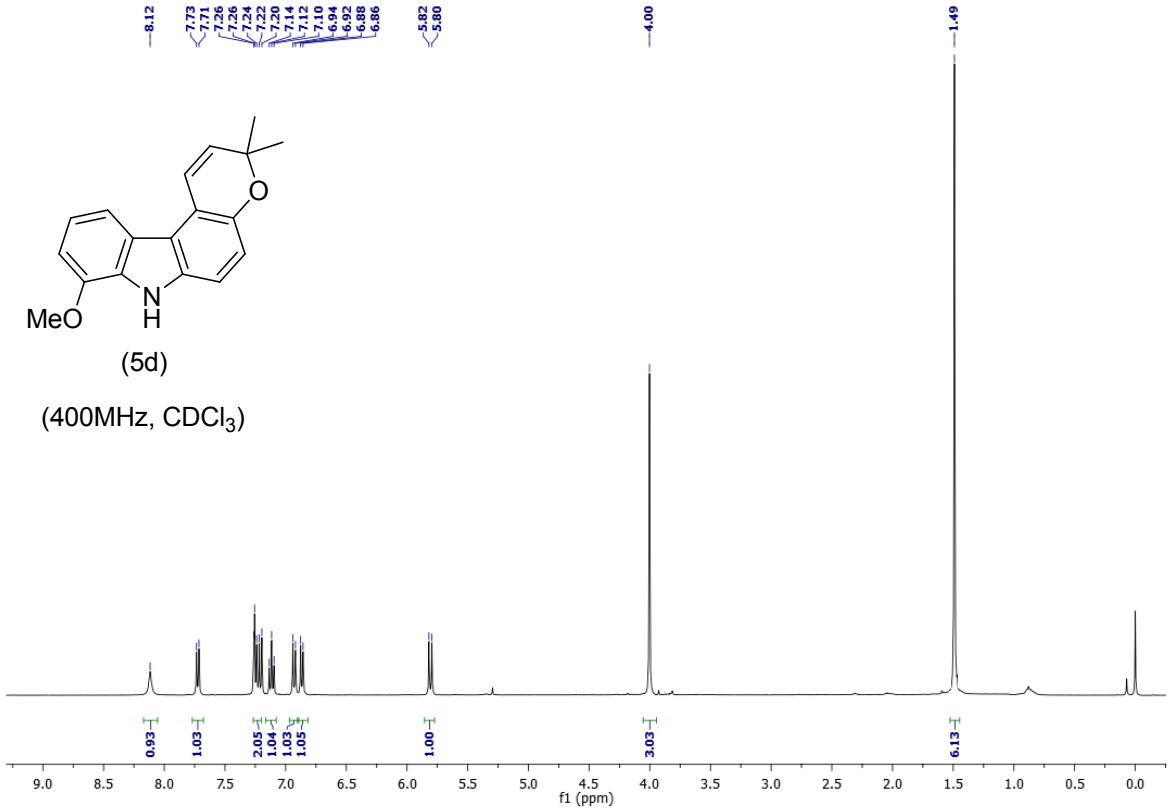
(125MHz, DMSO-d_6)

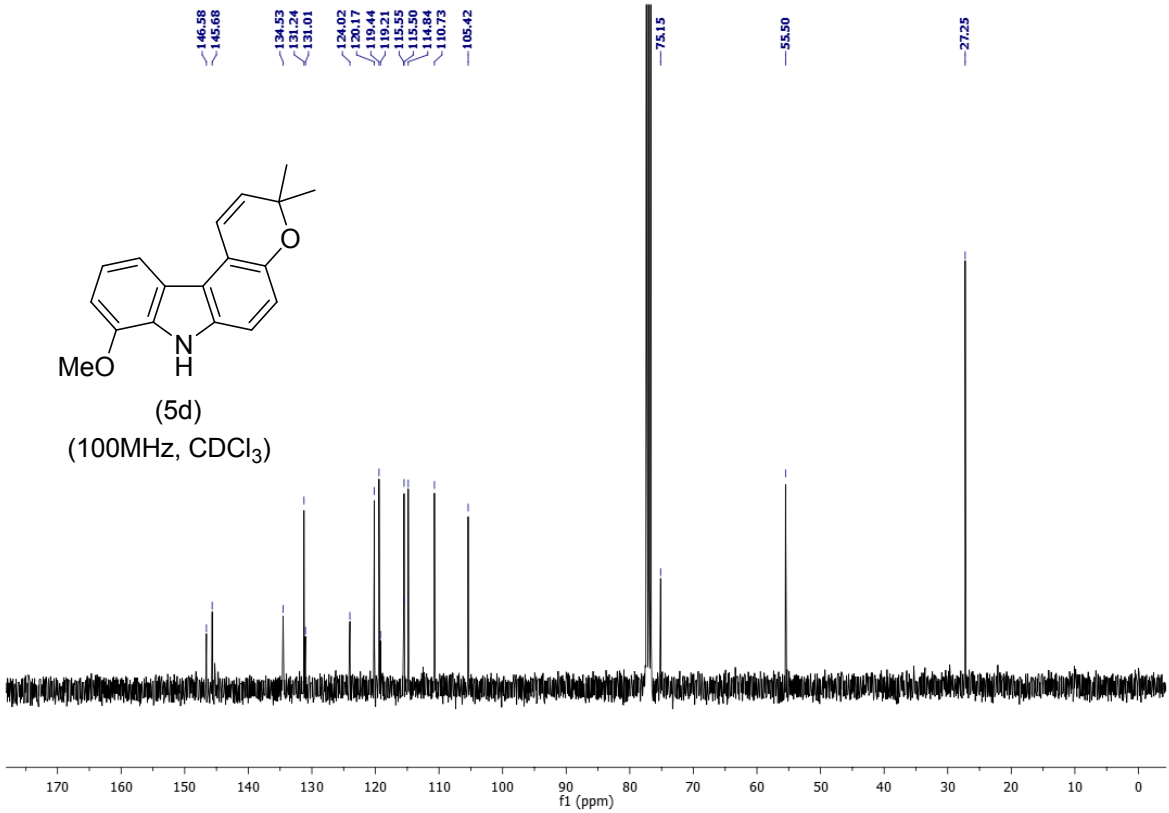
9-Methoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5c)**:



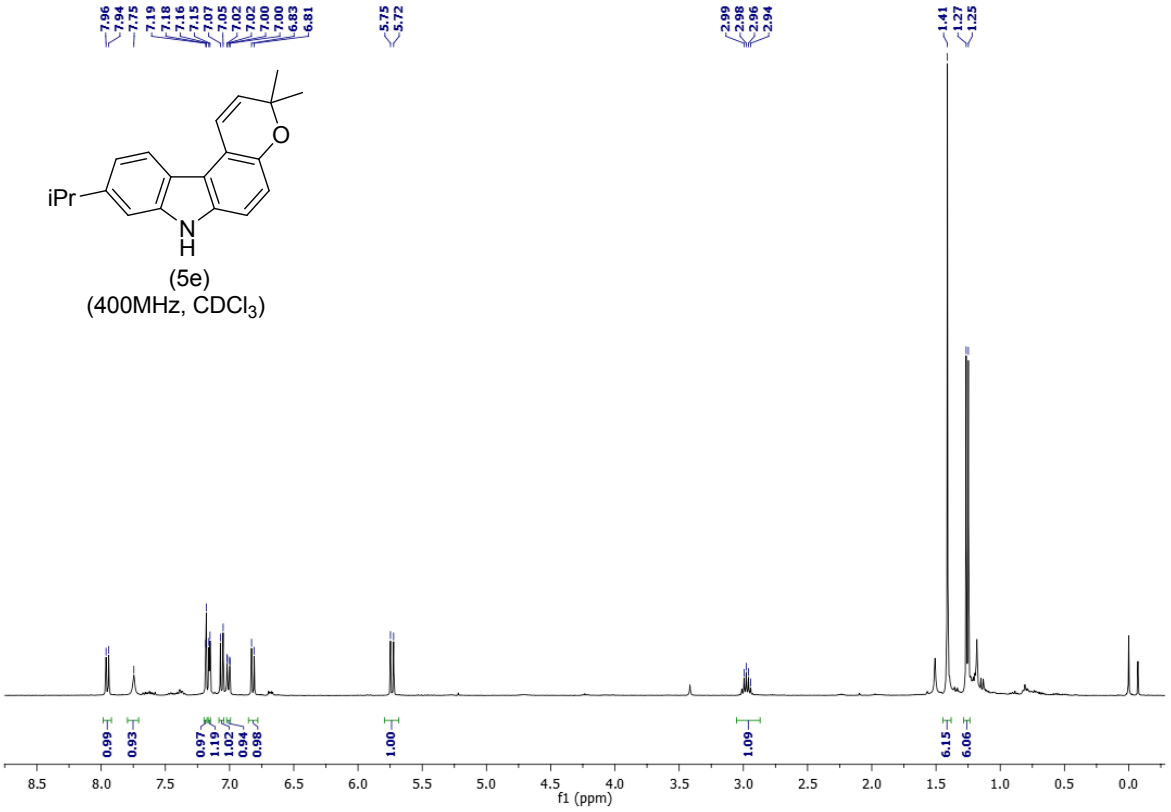


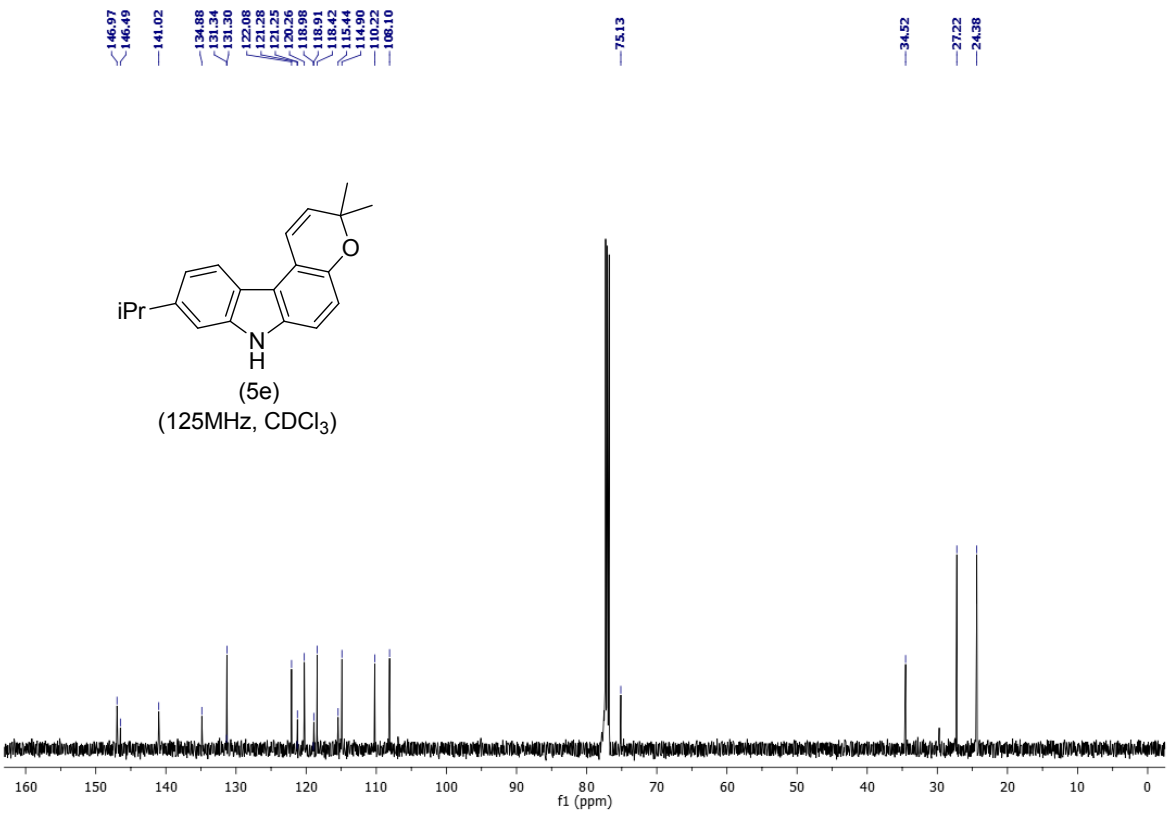
8-Methoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole**(5d)**:



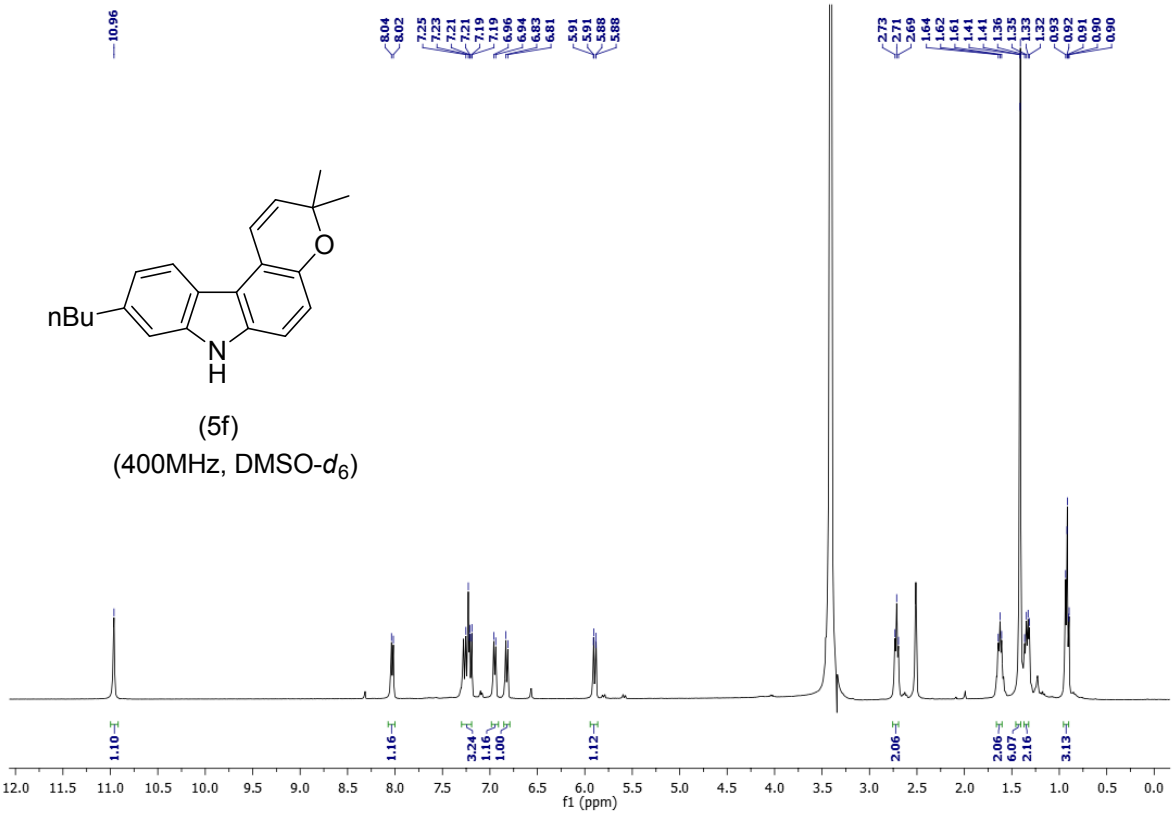


9-Isopropyl-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5e)**:

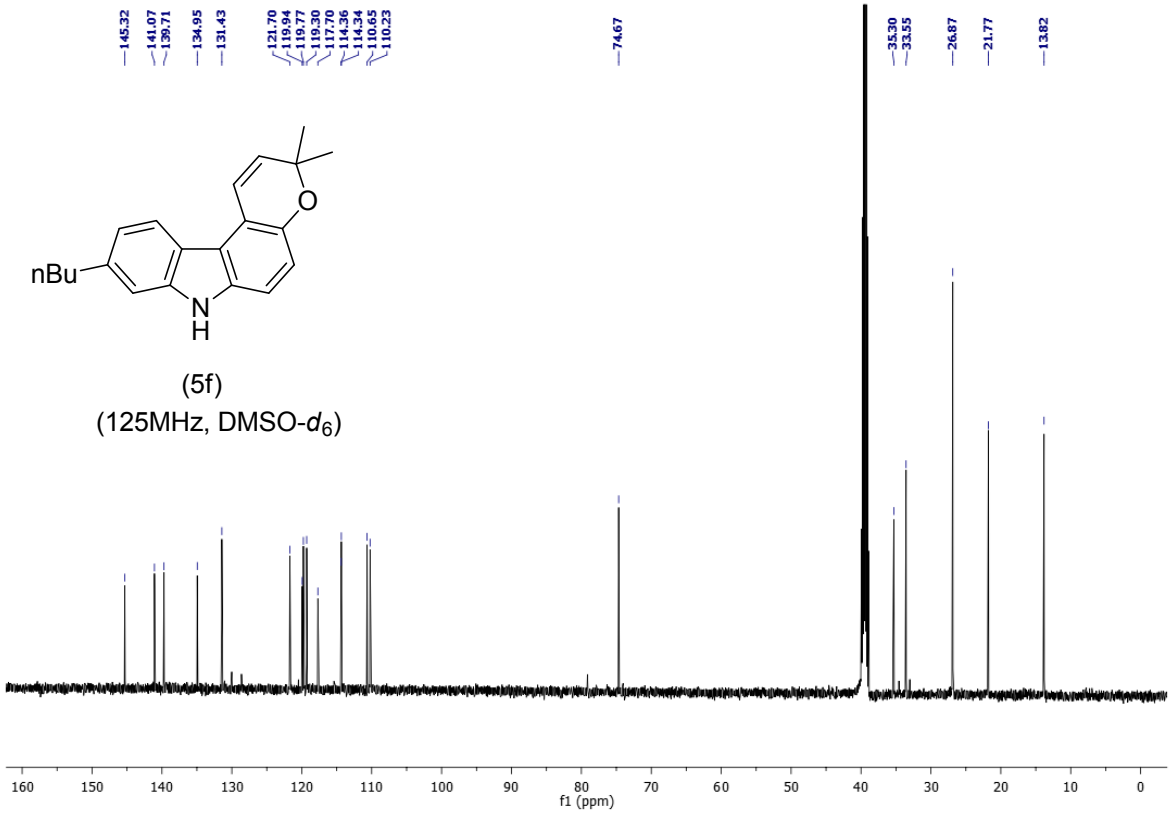




9-Butyl-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5f**):

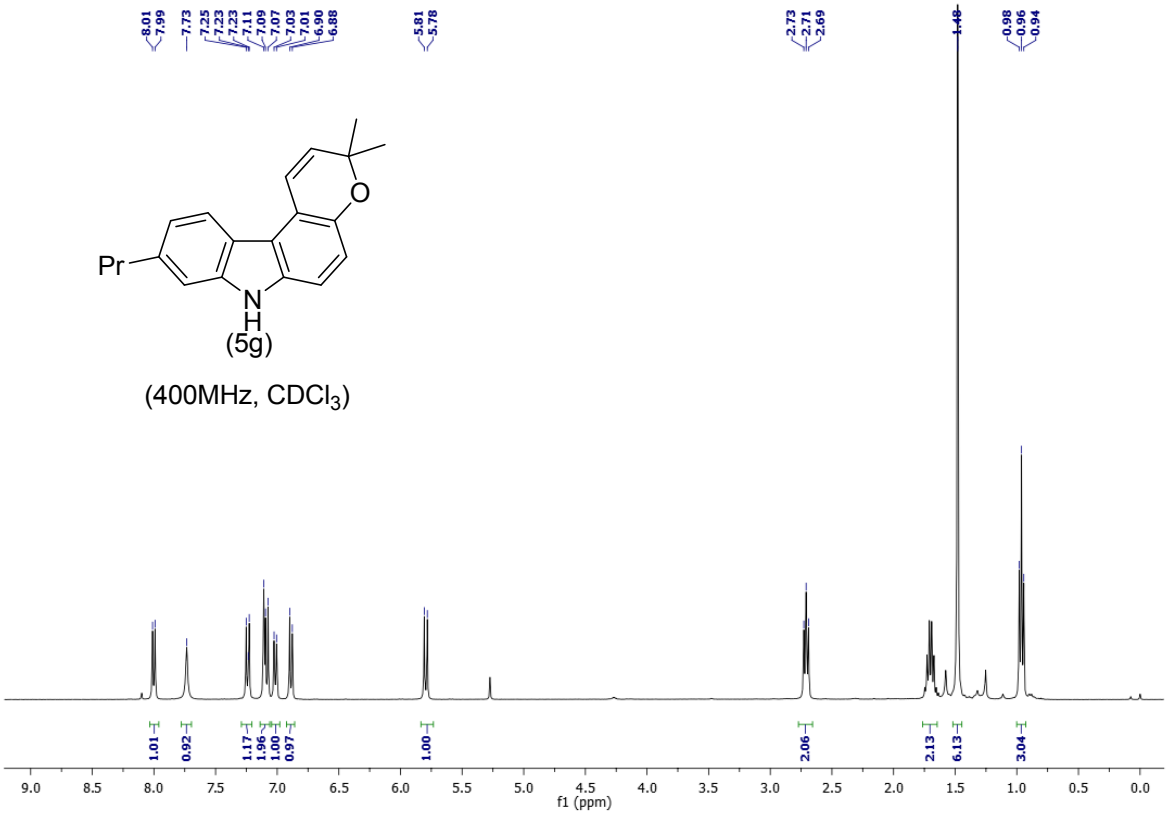


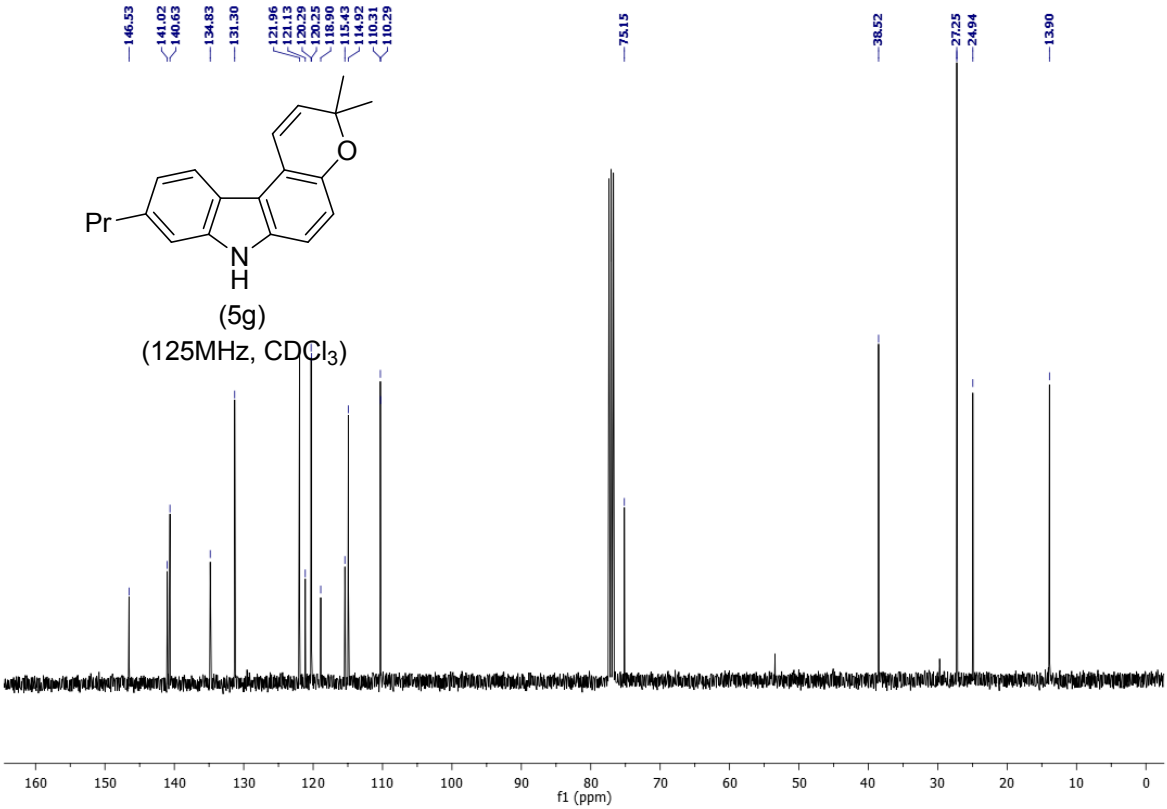
(5f)
(400MHz, DMSO-d_6)



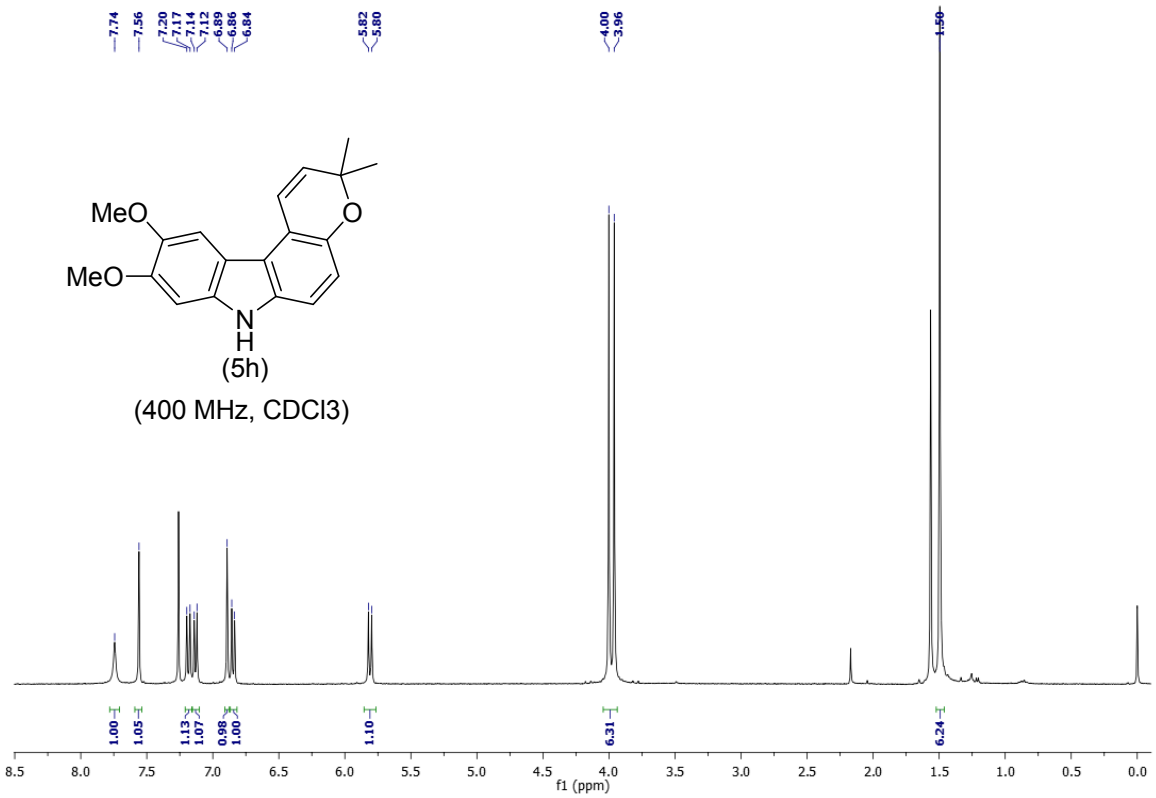
(5f)
(125MHz, DMSO-d_6)

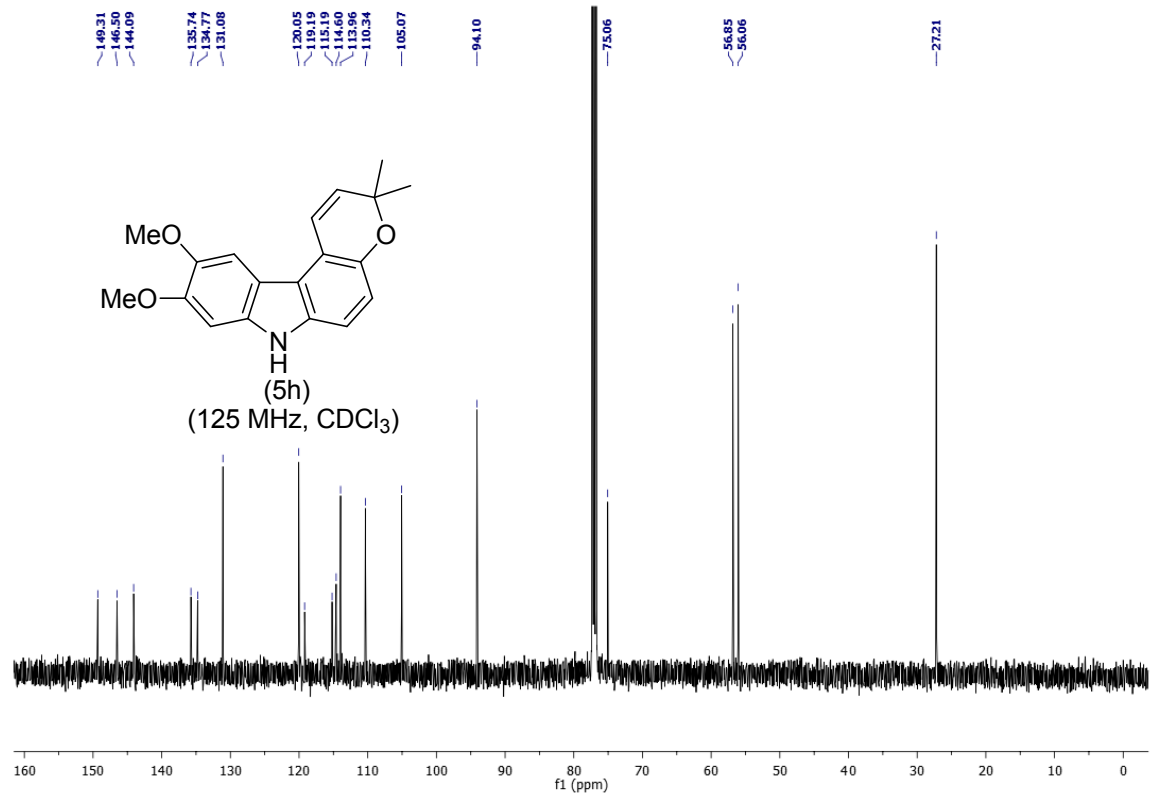
3,3-Dimethyl-9-propyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5g**):



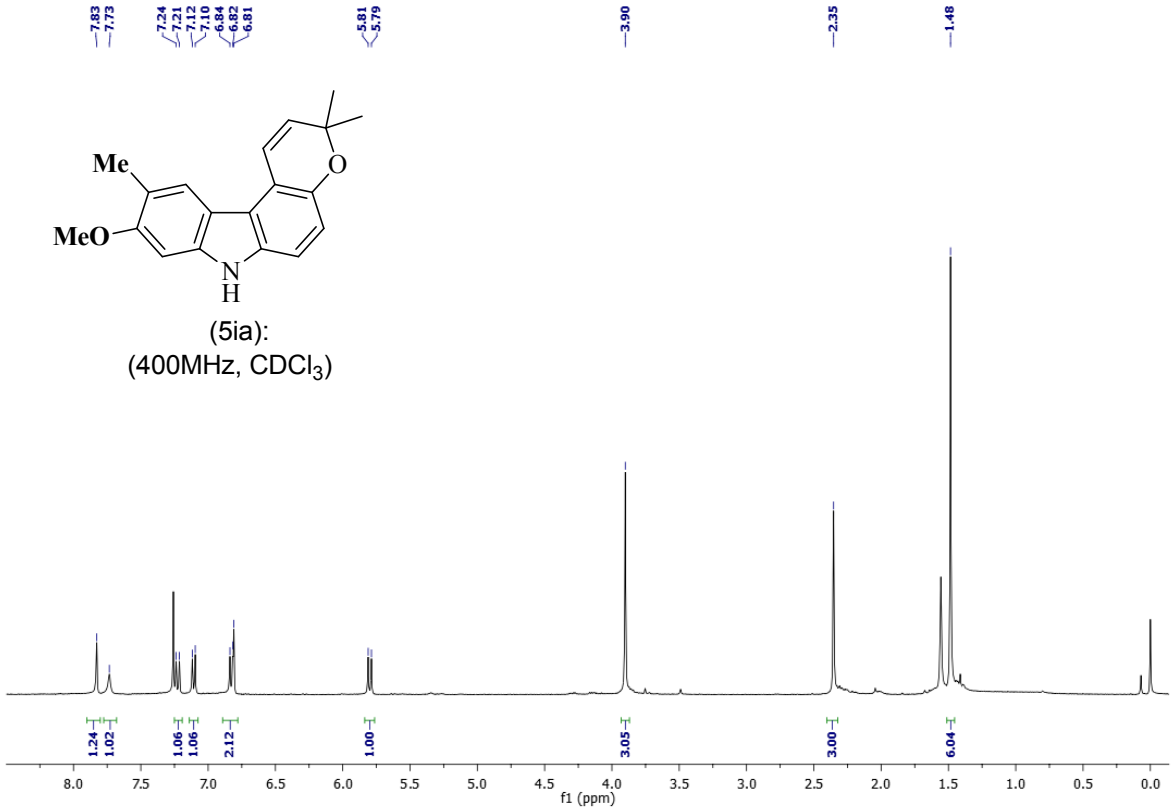


9,10-Dimethoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5h)**:

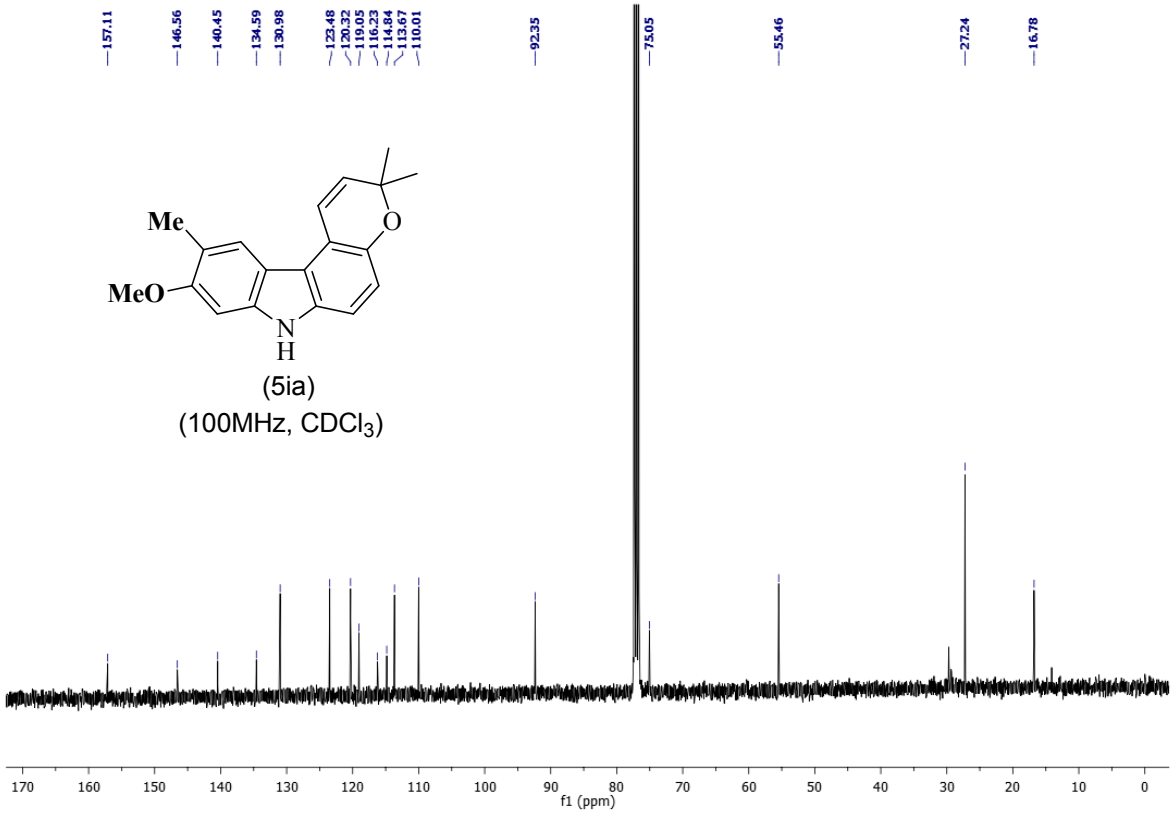




9-Methoxy-3,3,10-trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5ia**):

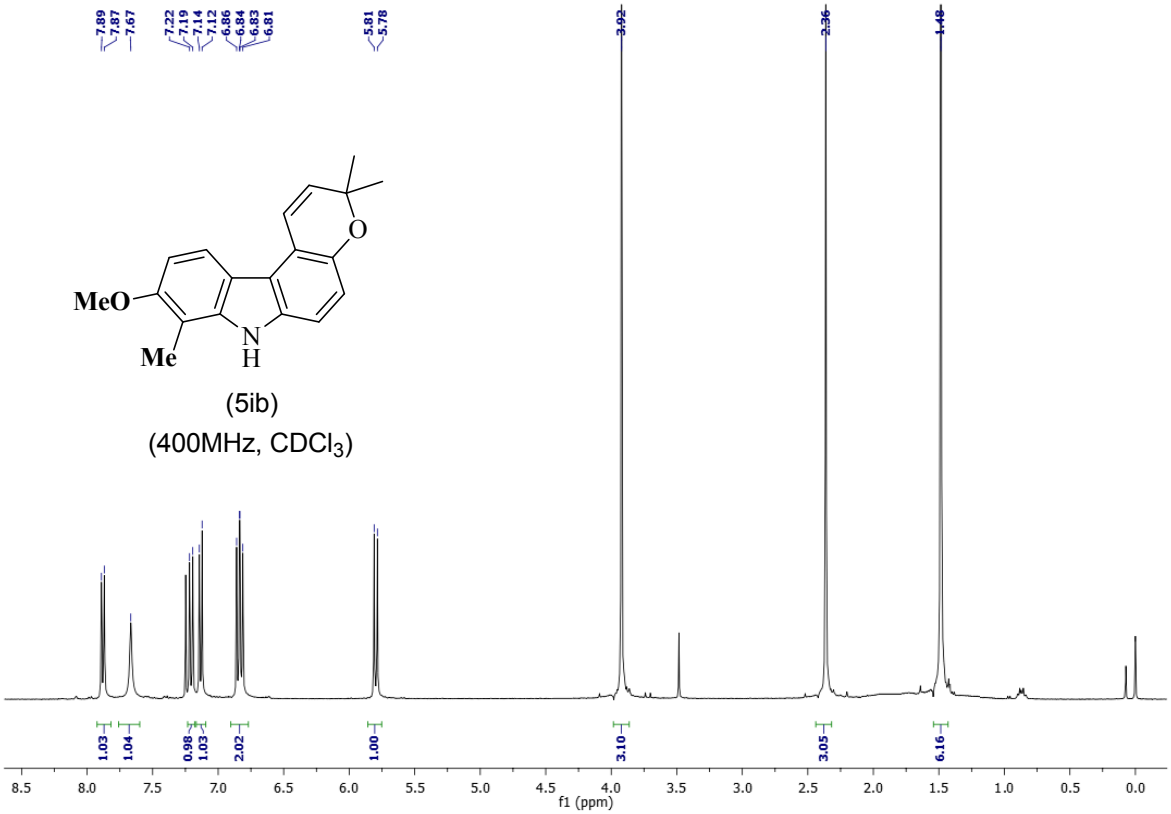


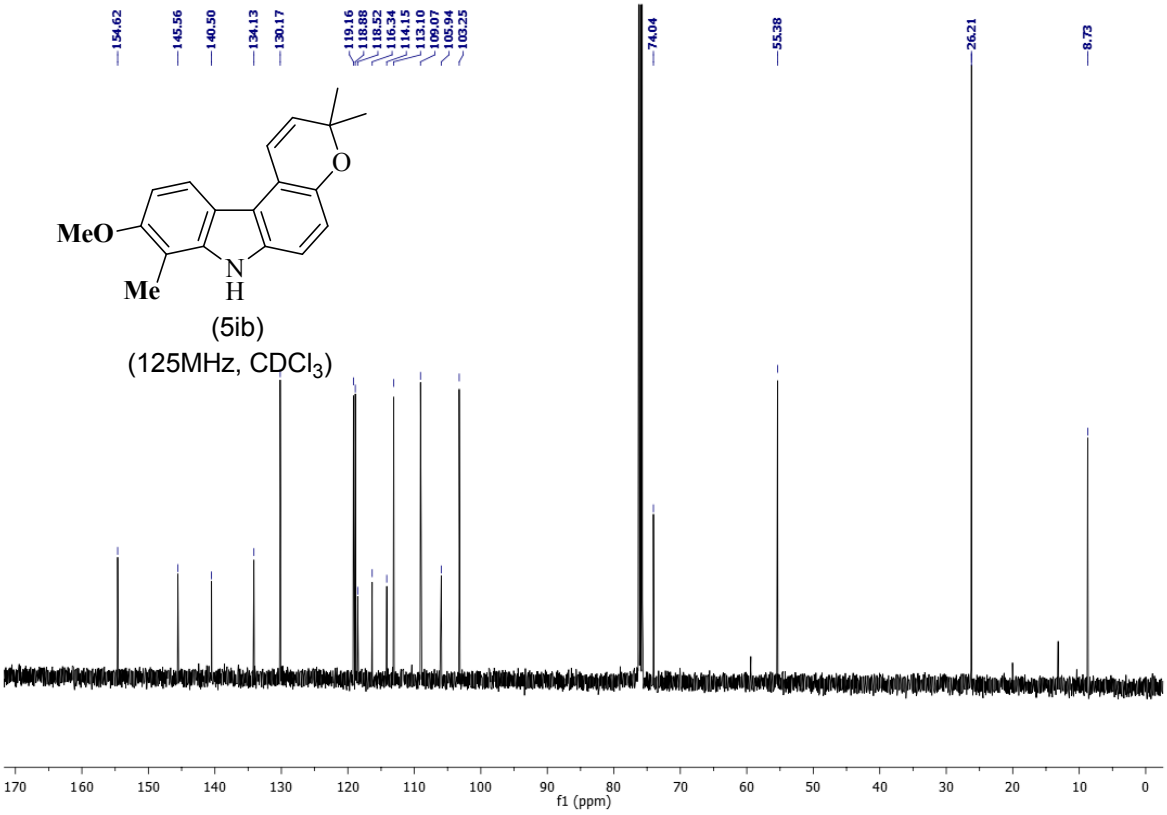
(5ia):
(400MHz, $CDCl_3$)



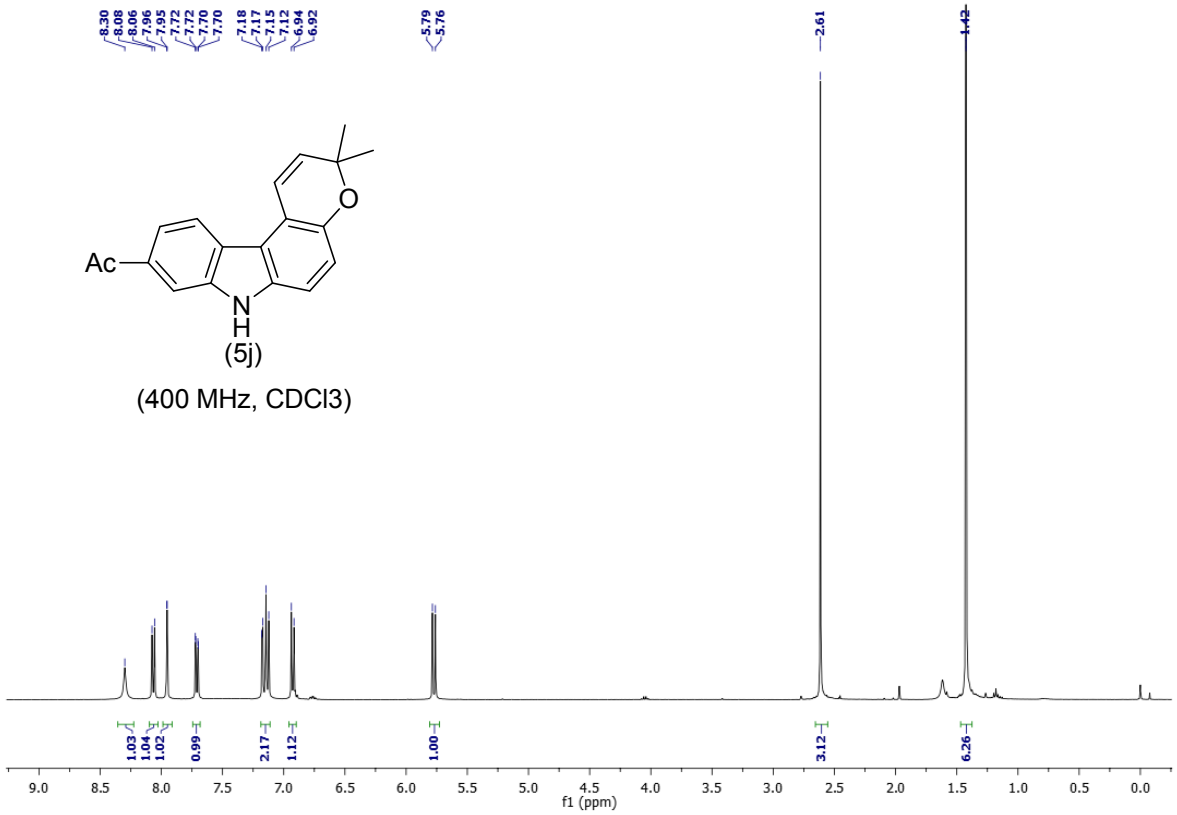
(5ia)
(100MHz, $CDCl_3$)

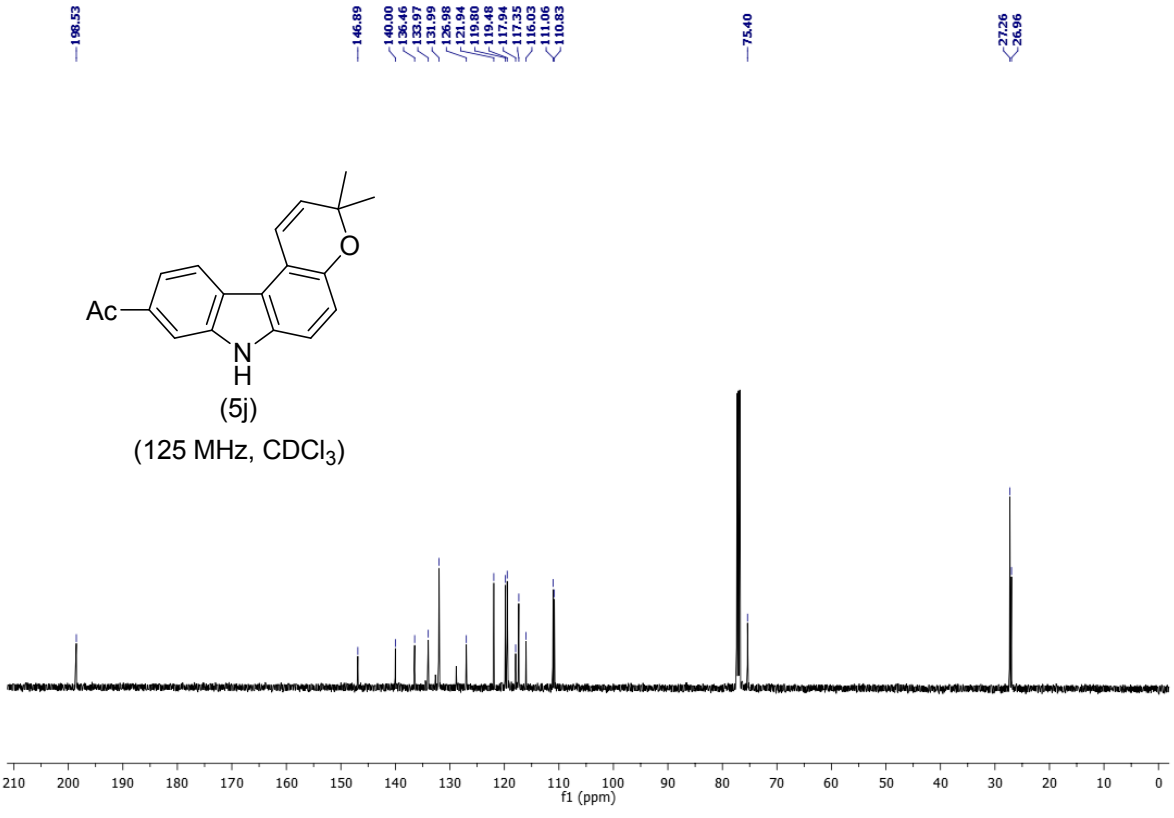
9-Methoxy-3,3,8-trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(**5ib**):



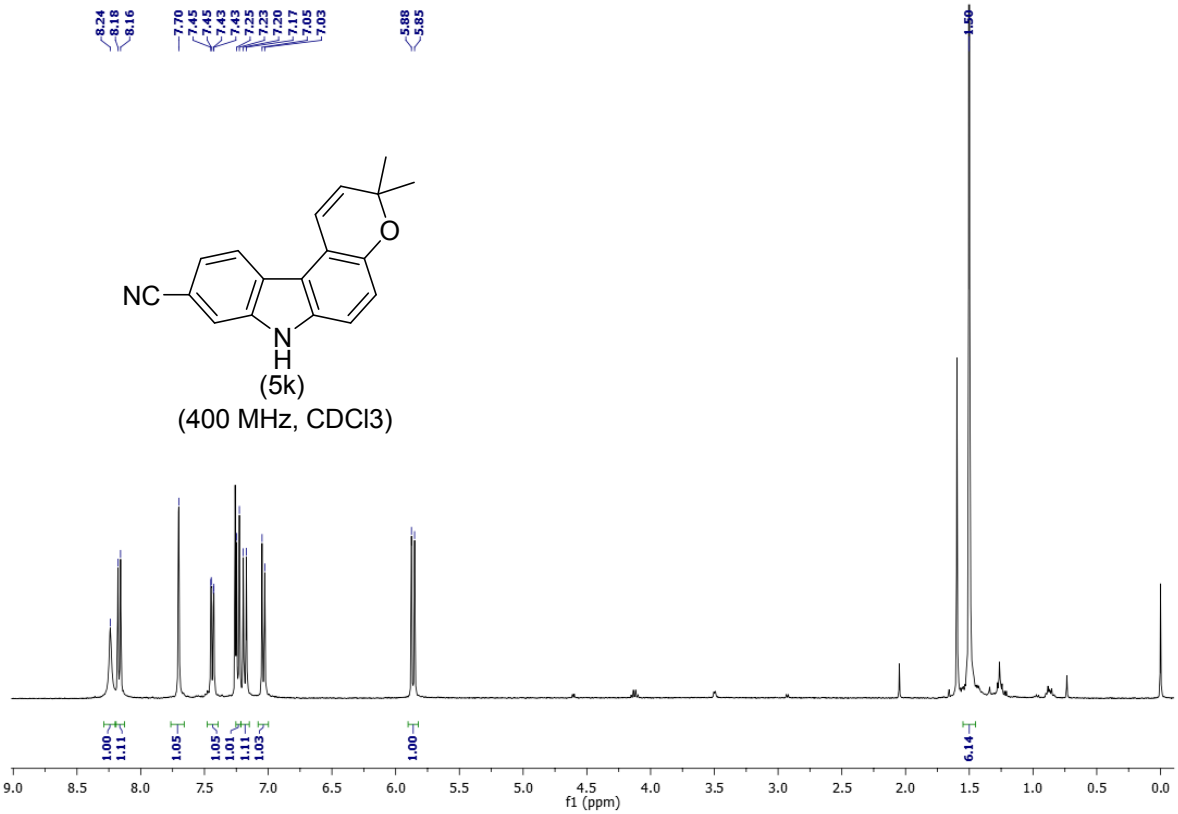


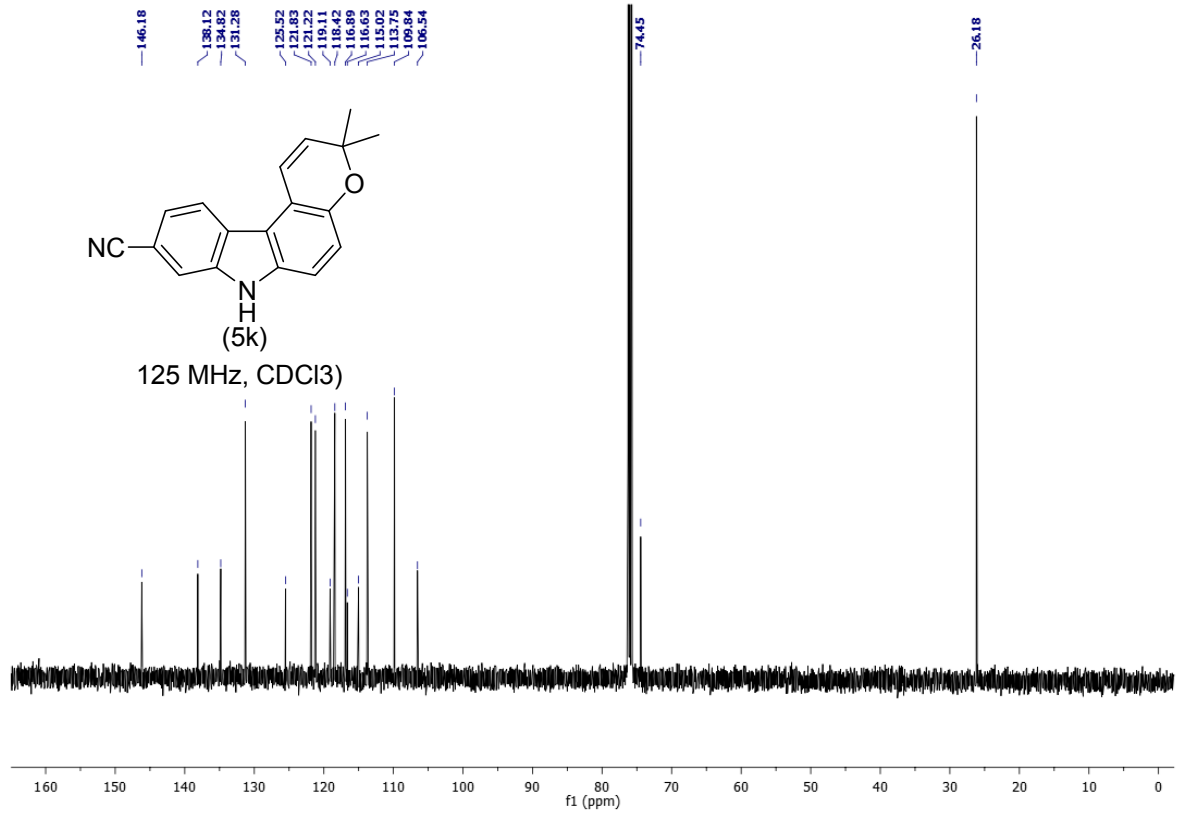
1-(3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazol-9-yl)ethanone(**5j)**:



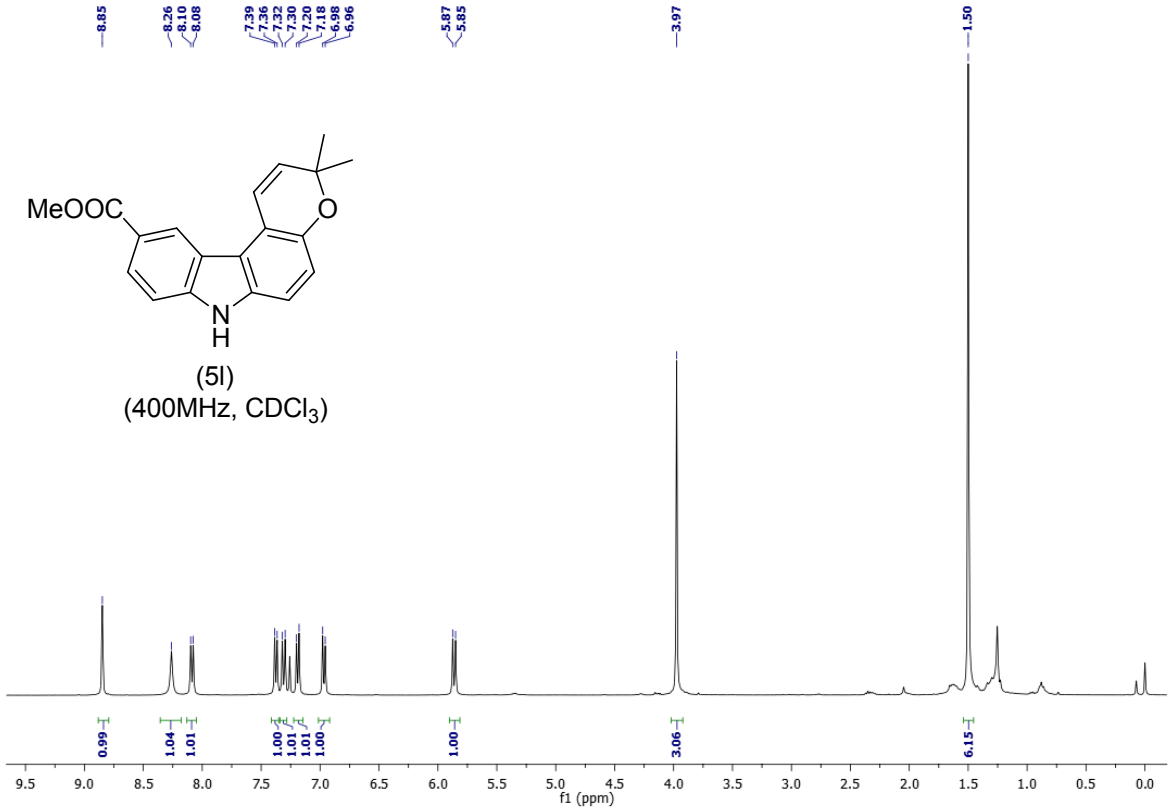


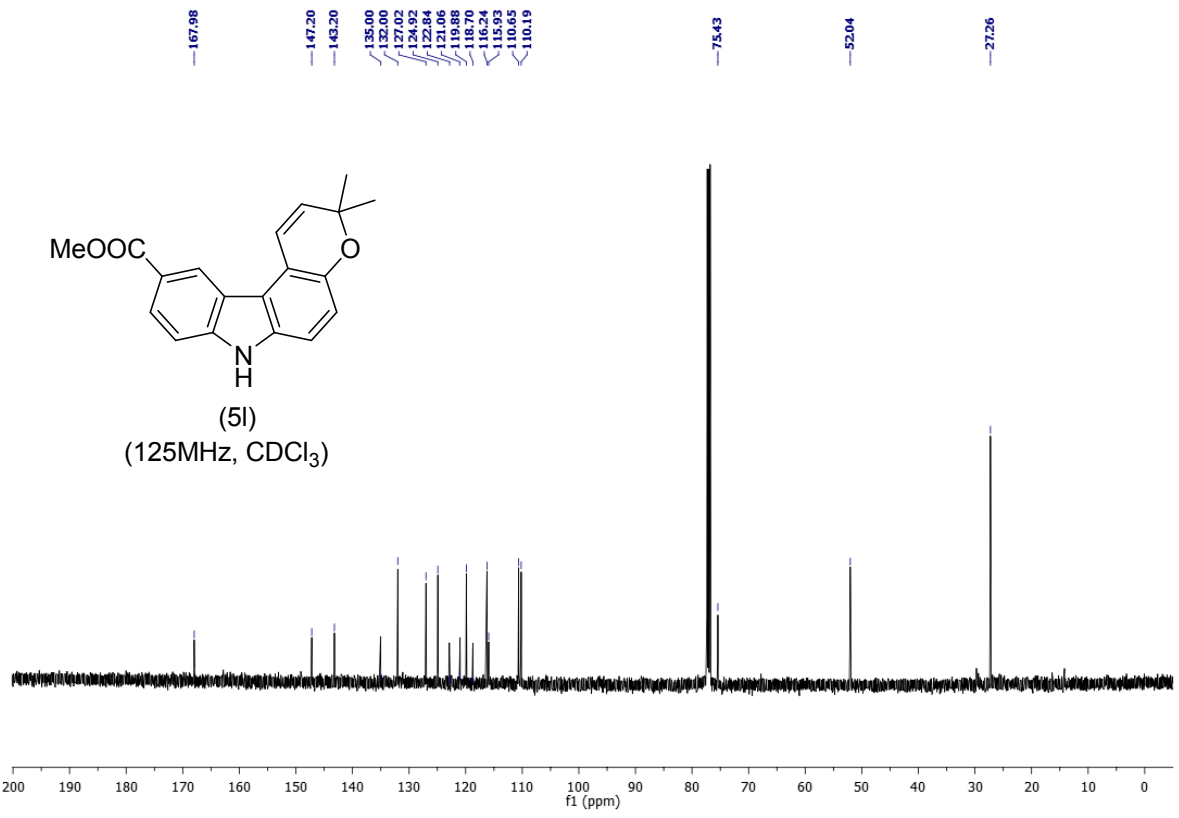
3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole-9-carbonitrile(**5k**):



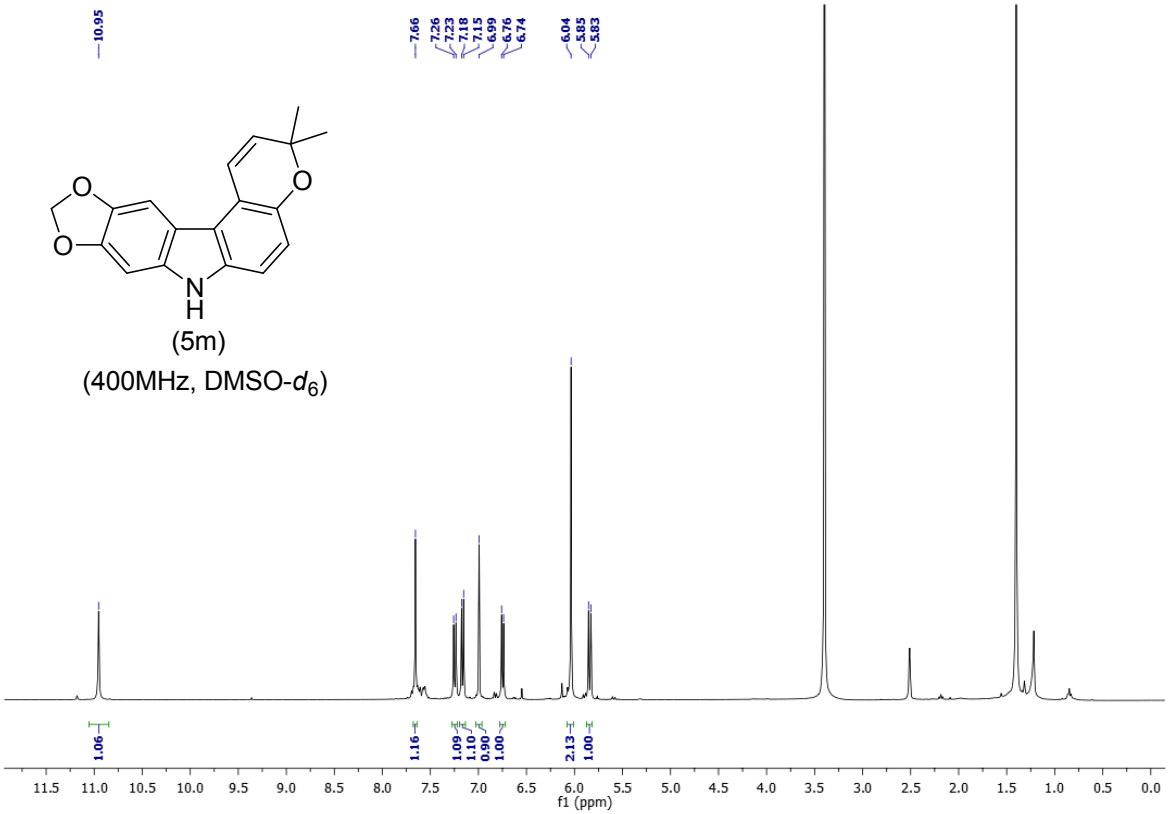


Methyl 3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole-10-carboxylate(**5l**):



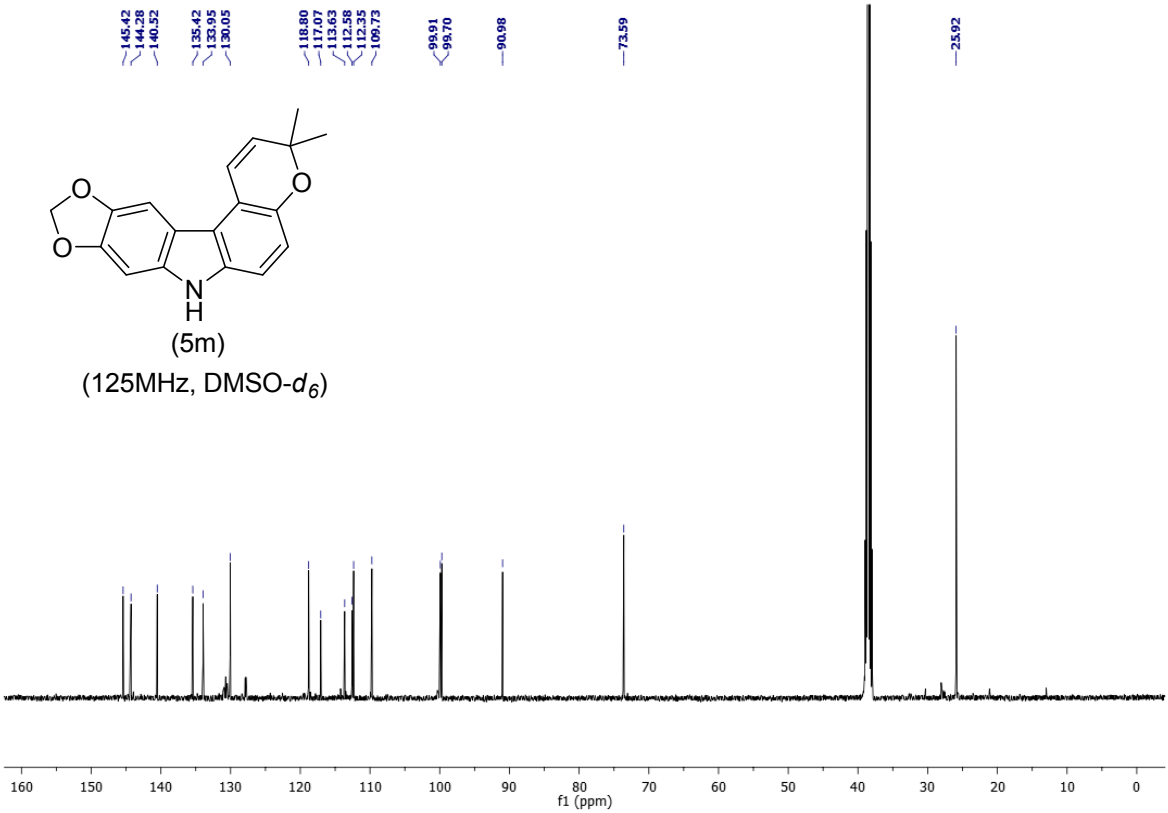


3,3-Dimethyl-3,7-dihydro-[1,3]dioxolo[4,5-*b*]pyrano[3,2-*g*]carbazole(**5m**):



(5m)

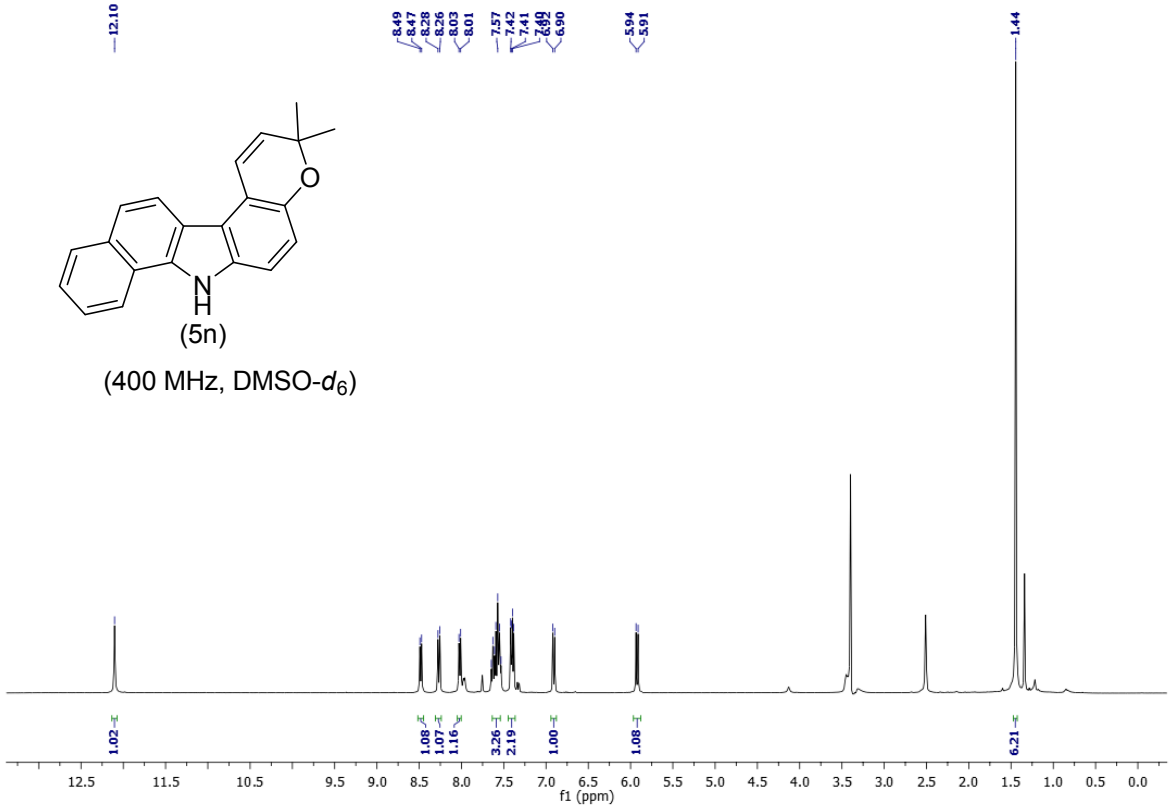
(400MHz, DMSO-d_6)



(5m)

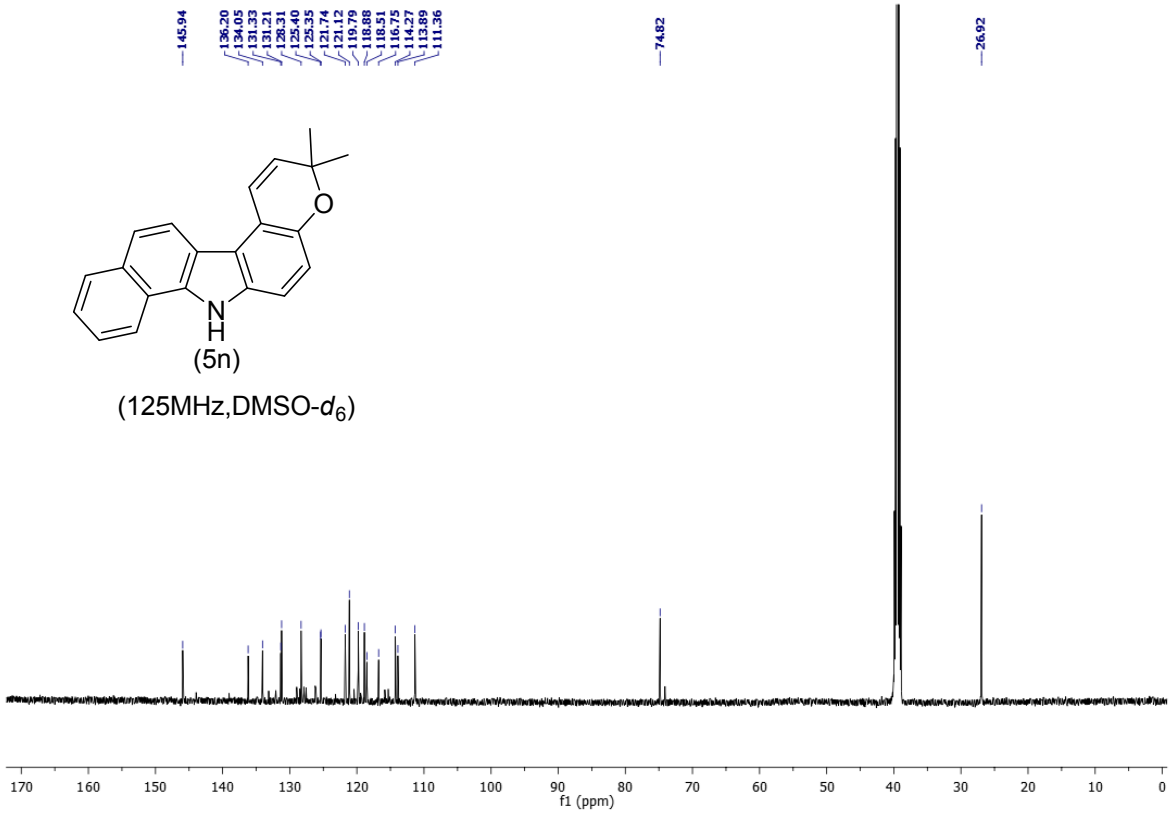
(125MHz, DMSO-d_6)

3,3-Dimethyl-3,7-dihydrobenzo[*a*]pyrano[3,2-*g*]carbazole (**5n**):



(5n)

(400 MHz, DMSO-d_6)



(5n)

(125MHz,DMSO-d_6)

Table 1. The molecular docking scores of the designed molecules and Podophyllotoxin

Molecule	Glide gScore	Hydrogen Bonding/ NH···π Interaction	Residues within 5Å
Podophy-llotoxin	-6.913	Asn*α*101, Leu*β*248	Gln*α*11, Ser*α*178, Thr*α*179, Ala*α*180, Val*α*181, Cys*β*241, Gln*β*247, Asn*β*249, Ala*β*250, Lys*β*254, Leu*β*255, Asn*β*258, Met*β*259, Ala*β*316, Lys*β*352, Thr*β*353, Ala*β*354
5b	-7.858	Asn*β*258	Asn*α*101, Ser*α*178, Thr*α*179, Ala*α*180, Glu*α*183, Cys*β*241, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5a	-7.229	Asn*β*258	Asn*α*101, Ser*α*178, Thr*α*179, Ala*α*180, Glu*α*183, Cys*β*241, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
9i	-7.032	Gln*α*11, Thr*β*353, Lys*β*254	Asn*α*101, Ser*α*178, Thr*α*179, Ala*α*180,Tyr*α*224,Cys*β*241, Gln*β*247, Leu*β*248, Asn*β*249, Ala*β*250, Leu*β*255, Asn*β*258, Met*β*259, Val*β*315,Ala*β*316, Lys*β*352, Ala*β*354
5d	-6.415	Asn*α*101	Gly*α*143, Ser*α*178, Glu*α*183, Cys*β*241, Lys*β*254, Leu*β*255, Asn*β*258, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5n	-6.362		Gln*α*11, Asn*α*101, Ser*α*178, Thr*α*179, Ala*α*180, Val*α*181, Glu*α*183, Tyr*α*224, Cys*β*241, Gln*β*247, Ala*β*250, Lys*β*254, Leu*β*255, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5l	-6.359	Ser*α*178, Asn*β*258	Gln*α*11, Asn*α*101, Thr*α*179, Ala*α*180, Val*α*181, Glu*α*183, Tyr*α*224, Cys*β*241, Gln*β*247, Ala*β*250, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354, Ile*β*378
5g	-6.033	Asn*β*258	Gln*α*11, Asn*α*101, Thr*α*179, Ala*α*180, Val*α*181, Glu*α*183, Tyr*α*224, Cys*β*241, Gln*β*247, Ala*β*250, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354, Ile*β*378
5m	-5.958	Asn*β*258	Gln*α*11, Asn*α*101, Ala*α*180, Tyr*α*224, Cys*β*241, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5c	-5.919	Asn*β*258	Gln*α*11, Asn*α*101, Ala*α*180, Glu*α*183, Tyr*α*224, Cys*β*241, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5f	-5.512		Gln*α*11, Asn*α*101, Ala*α*180, Tyr*α*224, Cys*β*241, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354
5e	-5.219		Gln*α*11, Asn*α*101, Thr*α*179, Ala*α*180, Tyr*α*224, Cys*β*241,Gln*β*247, Leu*β*248, Asn*β*249, Ala*β*250, Lys*β*254, Leu*β*255, Met*β*259, Ala*β*316, Thr*β*317, Ile*β*318, Lys*β*352, Thr*β*353, Ala*β*354

MTT assay

% Growth Inhibition (30 μM)

Time: 48 h

Compound's Name	MOLT-4 (Lymphoid leukemia)	Colo 205 (Colorectal carcinoma)
5a	40.5	28.4
5f	46.3	25.8
5l (clauraila C)	33.8	25.1