

Synthesis of 8-Heteroaryl Nitroxoline Analogues via One-Pot Sequential Pd-Catalyzed Coupling Reactions

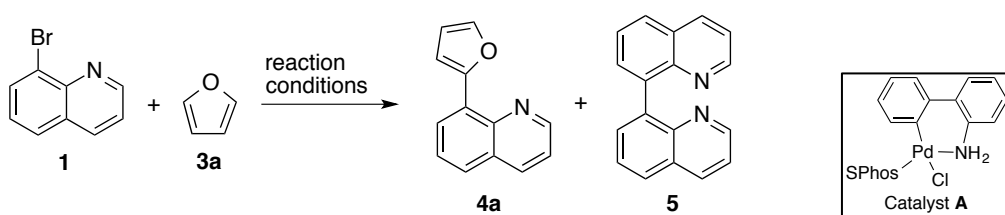
Supplementary Information

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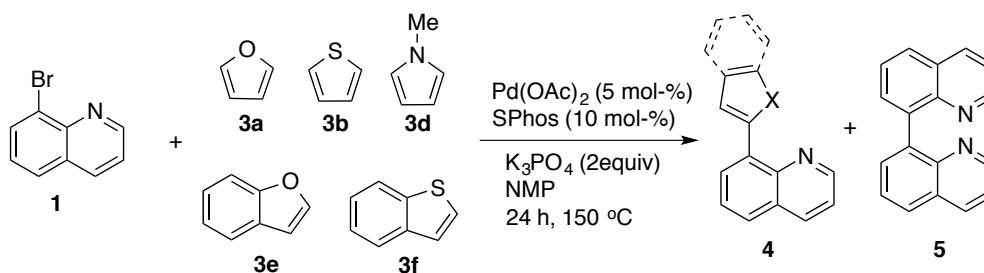
Table 1. C–H activation of furan with 8-bromoquinoline (5 equivalents of furan were used).



Entry	Pd-catalyst(mol-%)	Ligand (mol-%) [additive]	Base	Solvent	T (°C)	Reaction time (h)	Conversion (%) ^a	4a:5a
1	Pd(OAc) ₂ (0.5)	PPh ₃ (1.0)	KOAc (2 eq)	DMAc	150	24	0	-
2	Pd(OAc) ₂ (0.5)	-	KOAc (2 eq)	DMAc	150	24	0	-
3	Pd ₂ (dba) ₃ (0.5)	-	KOAc (2 eq)	DMAc	150	24	0	-
4	PdCl ₂ (0.5)	PPh ₃ (1.0)	KOAc (2 eq)	DMAc	150	24	0	-
5	Pd(acac) ₂ (0.5)	PPh ₃ (1.0)	KOAc (2 eq)	DMAc	150	24	23	1:1
6	Pd(TFA) ₂ (0.5)	PPh ₃ (1.0)	KOAc (2 eq)	DMAc	150	24	0	-
7	Pd(PPh ₃) ₄ (0.5)	-	KOAc (2 eq)	DMAc	150	24	28	1:2
8	Catalyst A (0.5)	-	KOAc (2 eq)	DMAc	150	24	41	1:1.5
9	PdCl ₂ (dipp) (0.5)	PivOH (5.0)	K ₂ CO ₃ (2 eq)	DMAc	150	24	33	2:1
10	PdCl ₂ (dipp) (0.5)	-	K ₃ PO ₄ (2 eq)	DMAc	150	24	29	1:1
11	PdCl ₂ (dipp) (0.5)	-	KAcO (2 eq)	DMAc	150	24	23	1:1
12	Pd(OAc) ₂ (1.0)	Dppe (1.0)	KOAc (2 eq)	DMAc	150	24	29	1:2
13	Pd(OAc)₂ (5.0)	SPhos (10)	K₃PO₄ (2 eq)	NMP	150	48	100	1:2.4
14	Pd(OAc) ₂ (5.0)	SPhos (10)	K ₃ PO ₄ (2 eq)	NMP	120	48	61	2:1
15	Pd(OAc) ₂ (5.0)	SPhos (10)	K ₃ PO ₄ (2 eq)	Dioxane/H ₂ O 4/1 (v/v)	150	48	29	1:1
16	Pd(OAc) ₂ (5.0)	SPhos (10) [Bu ₄ NBr (2 eq)]	K ₃ PO ₄ (2 eq)	NMP	150	24	61	1:1
17	Pd(OAc) ₂ (5.0)	SPhos (10) [Bu ₄ NBr (2 eq)]	K ₃ PO ₄ (2 eq)	NMP	150	48	88	1:1
18	Pd(OAc) ₂ (5.0)	PivOH (30)	K ₂ CO ₃ (2 eq)	DMAc	120	24	52	3:1
19	Catalyst A (5.0)	PivOH (30)	K ₂ CO ₃ (2 eq)	DMAc	150	24	96	1:4.5
20	Pd(OAc) ₂ (5.0)	(t-Bu) ₃ P (10)	K ₂ CO ₃ (2 eq)	Dioxane/H ₂ O 4/1 (v/v)	150	24	33	0:1

^aConversion was determined by ¹H NMR spectroscopy.

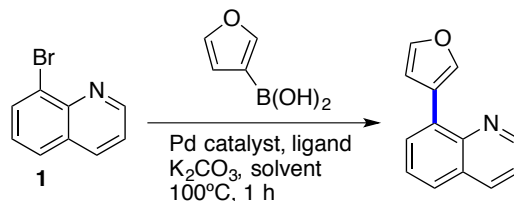
Table 2. C–H activation of **3a**, **3b**, and **3d–3f** with 8-bromoquinoline (5 equivalents of **3a**, **3b**, and **3d–3f** were used).



Heteroarene 3	Conversion-% ^a (ratio 4:5)
furan (3a)	100 (1:2.4)
thiophene (3b)	89 (3.3:1)
1-methyl-1 <i>H</i> -pyrrole (3d)	82 (1:2)
benzo[<i>b</i>]furan (3e)	73 (1:2.7)
benzo[<i>b</i>]thiophene (3f)	100 (2:1)

^aConversion was determined by ¹H NMR spectroscopy.

Table 3. Coupling of **1** with (furan-3-yl)boronic acid under different reaction conditions.



Entry	Catalyst	Ligand	Solvent	Conversion (%) ^a
1	Pd ₂ (dba) ₃	/	Toluene	50
2	PdCl ₂	PPh ₃	Toluene	33
3	Pd(acac) ₂	PPh ₃	Toluene	83
4	Pd(TFA) ₂	PPh ₃	Toluene	100
5	Pd(C), 10%	/	Toluene	0
6	Pd(OAc) ₂	PPh ₃	Toluene	53
7	Pd(PPh ₃) ₄	/	Toluene	45
8	Pd(OAc) ₂	PPh ₃	1,4-Dioxane	77
9	Pd(OAc) ₂	PPh ₃	<i>N</i> -methyl-2-pyrrolidone	23
10	Pd(OAc) ₂	PPh ₃	2-Propanol	100
11	Pd(OAc) ₂	PPh ₃	Water	75
12	Pd(OAc) ₂	PPh ₃	1,4-Dioxane/water 4:1 (v/v)	95
13	Pd(TFA) ₂	PPh ₃	1,4-Dioxane	100
14	Pd(TFA) ₂	PPh ₃	<i>N</i> -methyl-2-pyrrolidone	11
15	Pd(TFA) ₂	PPh ₃	2-Propanol	100
16	Pd(TFA) ₂	PPh ₃	Water	63
17	Pd(TFA) ₂	PPh ₃	1,4-Dioxane/water 4:1 (v/v)	80

^aConversion was determined by ¹H NMR spectroscopy.

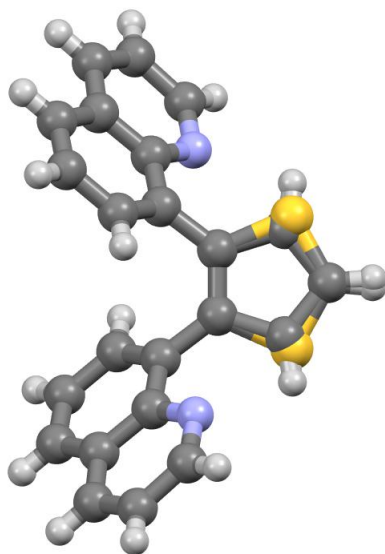


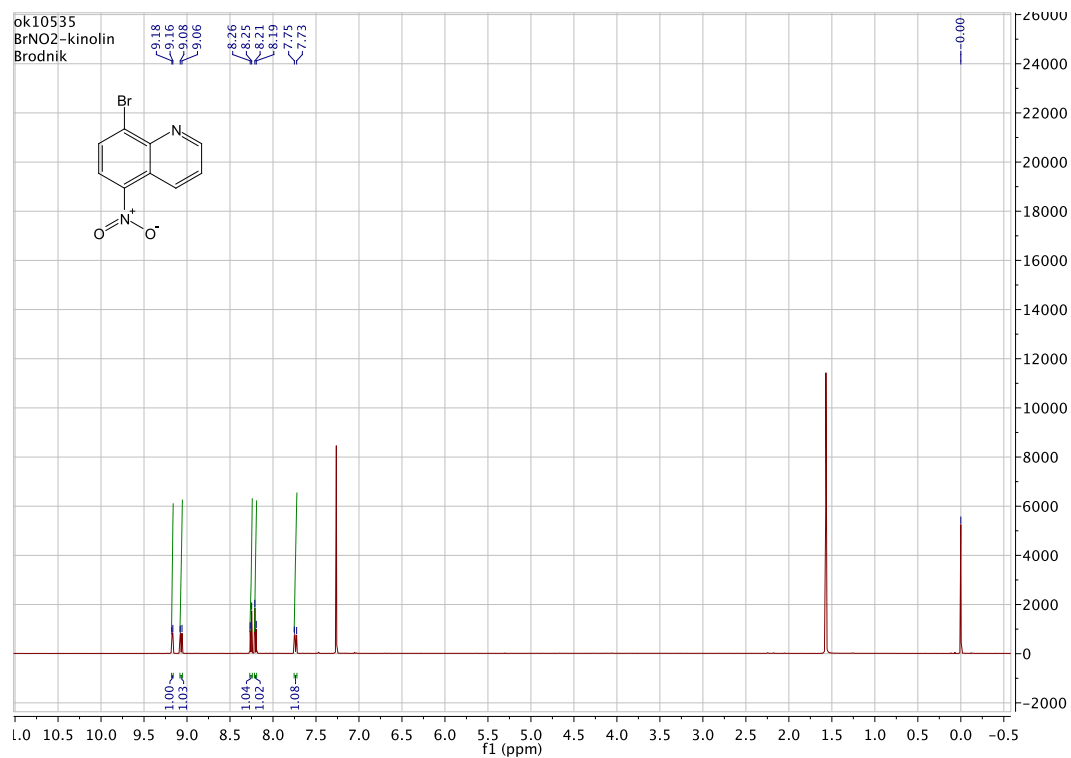
Figure 1. X-ray crystal structure of compound **4I'**.

Synthesis of Pd catalyst A^{1,2}

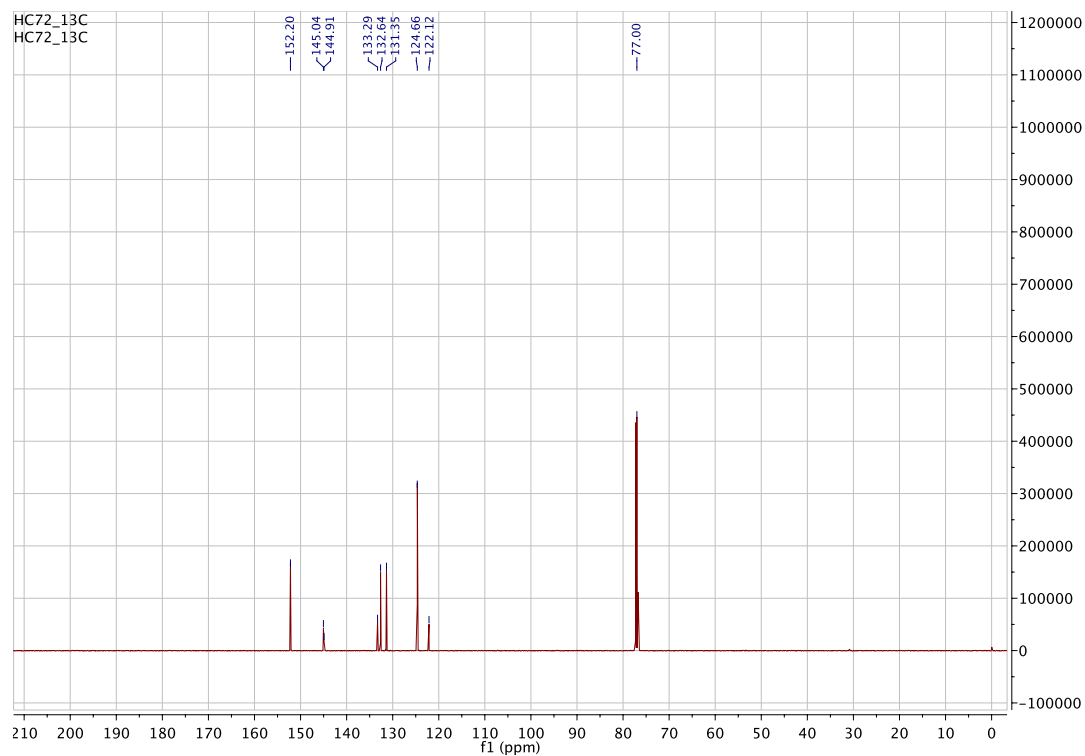
A mixture of Pd(OAc)₂ (84 mg, 0.375 mmol) and 2-amino-biphenyl (63 mg, 0.375 mmol) in toluene (anhydrous, 2 mL) was heated at 60 °C for 1 h, at which the initial red color of the reaction mixture faded and a grey precipitate had formed. The mixture was allowed to cool to r.t., at which the solvent was removed via cannula. The remaining solid was washed with toluene (anhydrous, 2 x 2 mL) and further suspended in acetone (anhydrous, 2 mL). After the addition of lithium chloride (48 mg, 1.125 mmol) the reaction mixture was stirred at room temperature for 24 h to give a dark orange homogenous solution. SPhos (162 mg, 0.394 mmol) was added portionwise over 5 min to which white precipitate had formed. The mixture was stirred for an additional 24 h after which 90 % of the solvent was removed under reduced pressure and the remaining solid was suspended in methyl *tert*-butyl ether (MTBE, 3 mL) and acetone (anhydrous, 0.3 mL). The product was collected by suction filtration, washed with water (3 x 3 mL) and dried under vacuum. White solid (205 mg, 76 %); mp = 181–183 °C; *R*_f (dichloromethane/methanol = 10/1) 0.28. FT-IR (ATR, neat): 3396, 3316, 2912, 2844, 1489, 1246, 1109, 1035, 1001, 780, 758, 723 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.47–7.45 (m, 1H), 7.40–7.31 (m, 2H), 7.22–7.17 (m, 5H), 7.06–7.05 (m, 2H), 6.94–6.91 (m, 1H), 6.70–6.59 (m, 4H), 4.79–4.61 (m, 2H), 3.76–3.66 (m, 6H), 2.04–0.80 (m, 20H). ¹³C NMR (125 MHz, CDCl₃): δ 157.9, 151.5, 140.0, 139.6, 138.5, 138.2, 136.2, 135.3, 133.3, 133.2, 129.5, 128.9, 127.8 (2C), 127.6, 126.5, 126.4, 125.6, 125.1 (2C), 125.0, 124.5, 120.2, 118.9, 104.1, 103.5, 55.3 (2C), 37.0, 35.2, 31.4, 30.9, 28.6, 27.7, 27.6, 27.2 (2C), 26.2. ³¹P NMR (202 MHz, CDCl₃): δ 53.2. HRMS (ESI⁺): *m/z* calcd for C₃₈H₄₅NO₂PPd (M - HCl)⁺: 680.2238; found: 680.2236.

Compound 2

^1H NMR

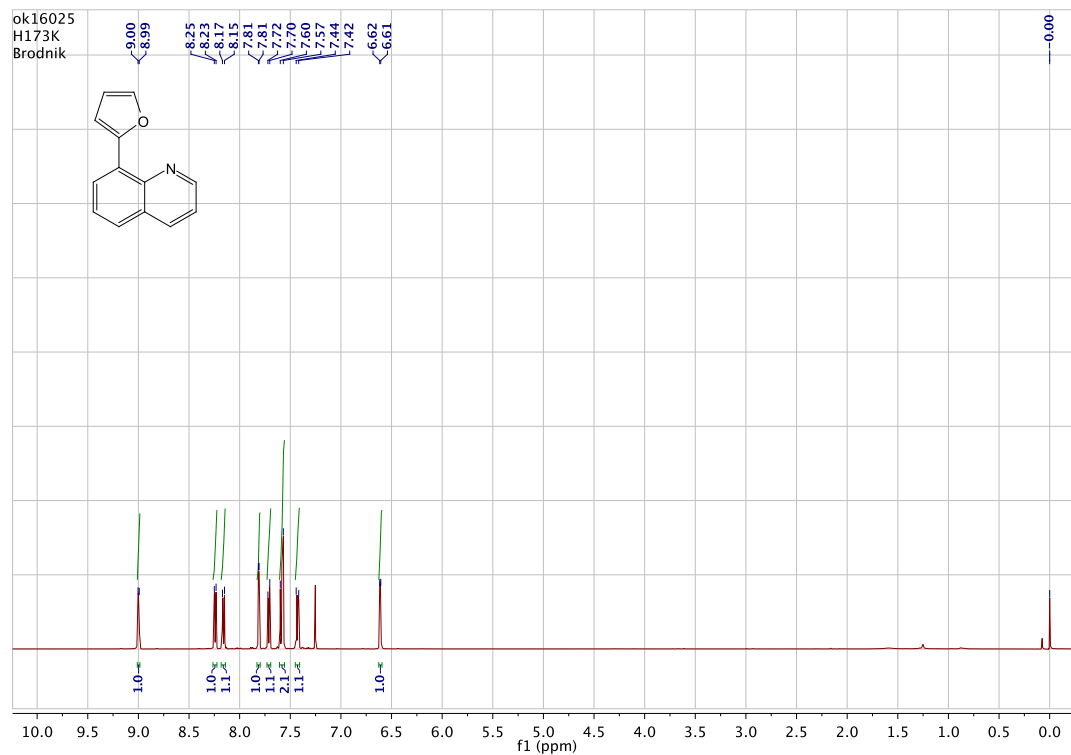


^{13}C NMR

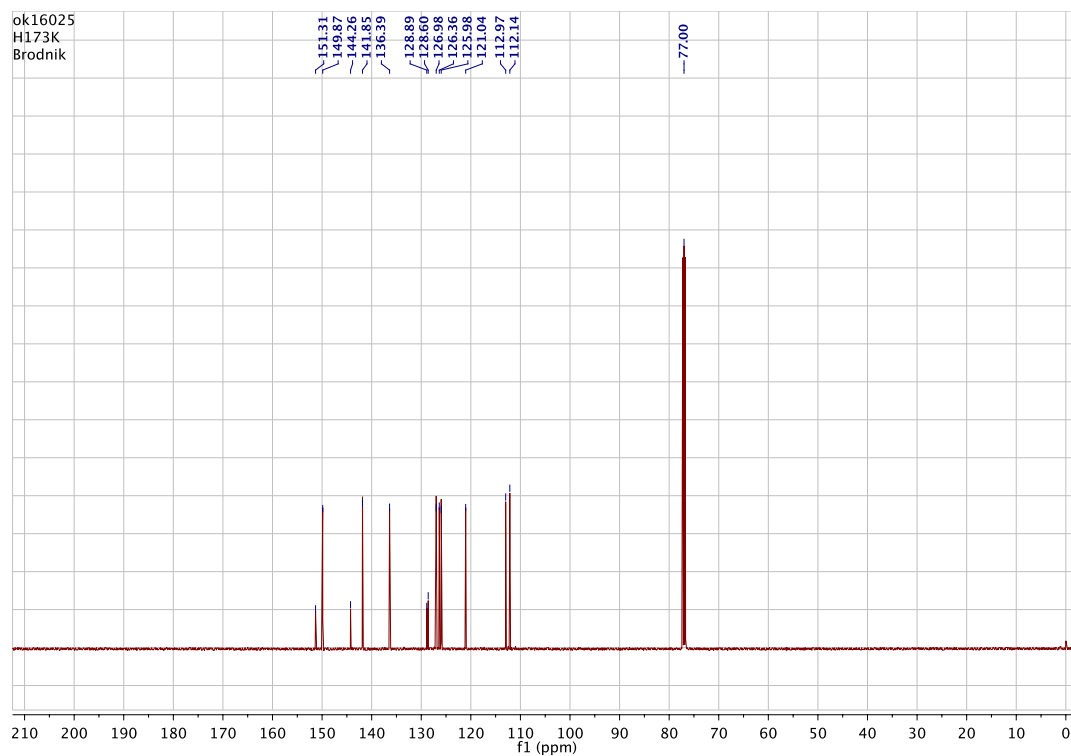


Compound 4a

¹H NMR

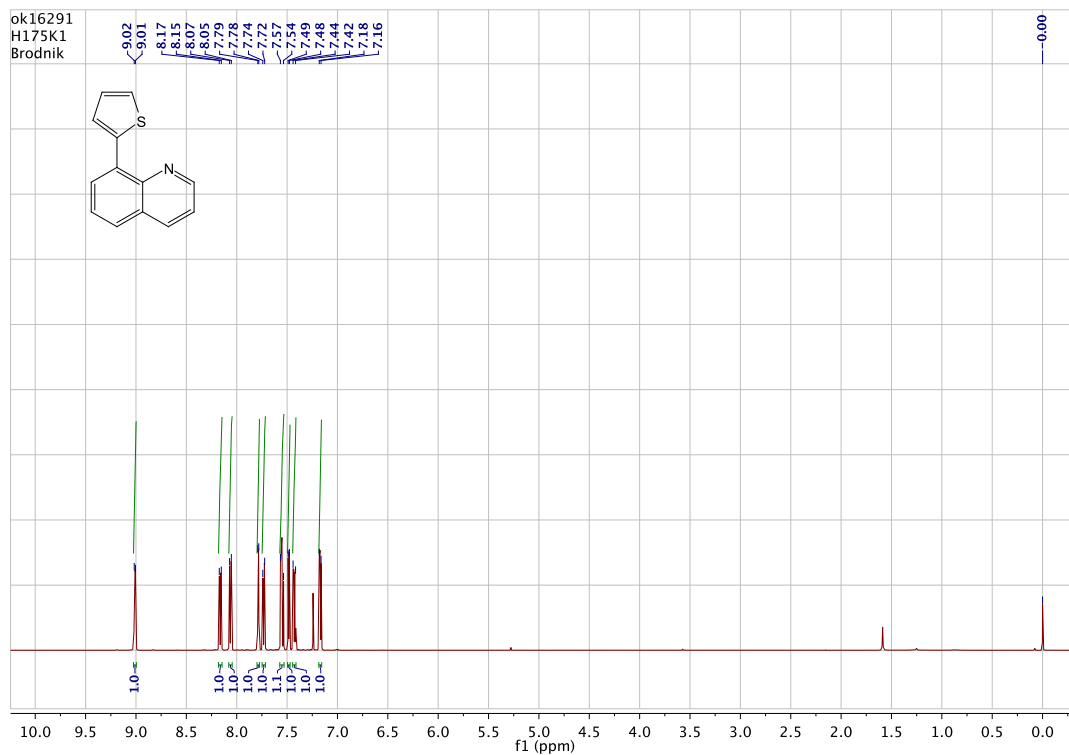


¹³C NMR

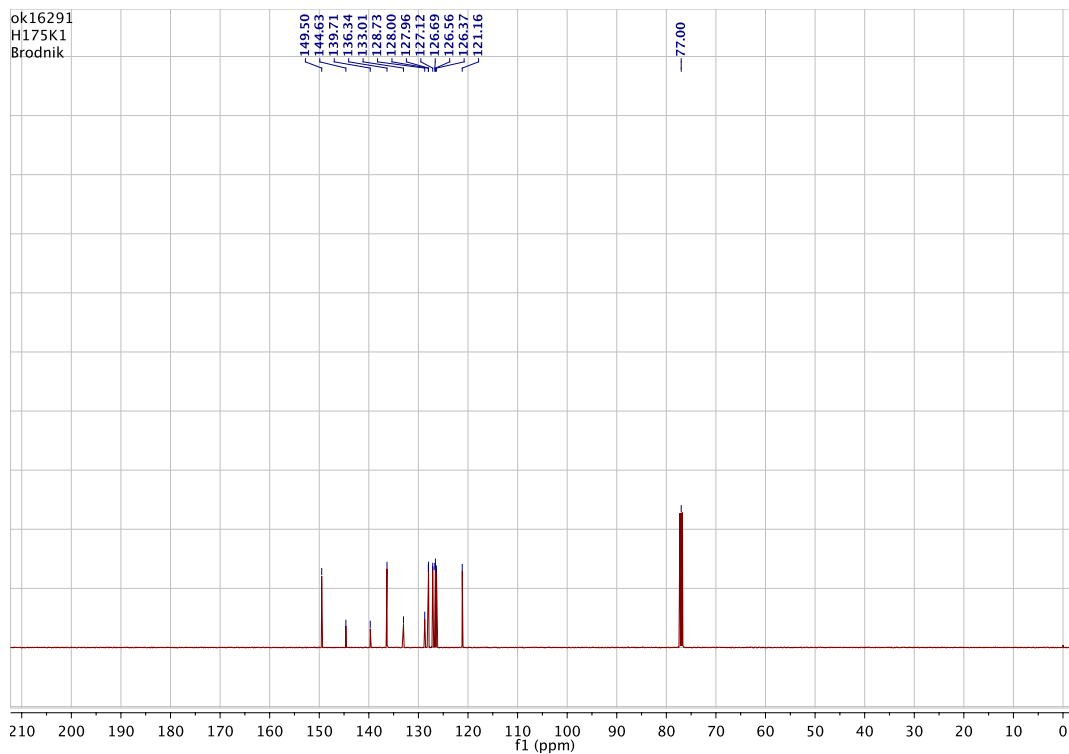


Compound 4b

¹H NMR

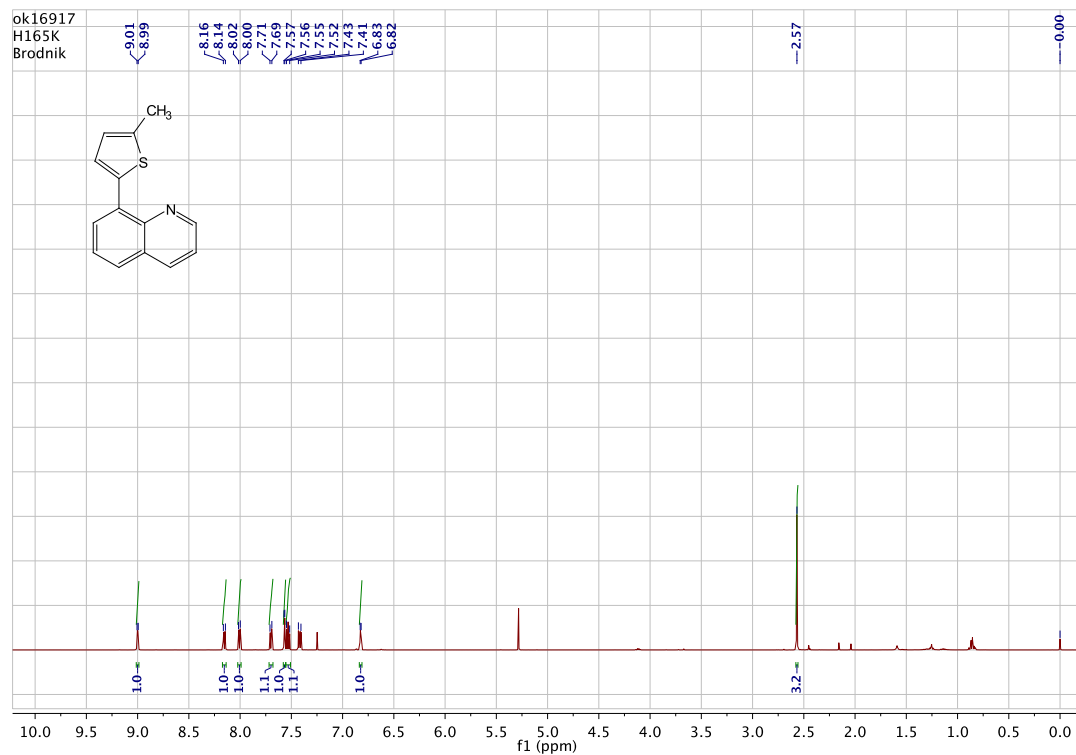


¹³C NMR

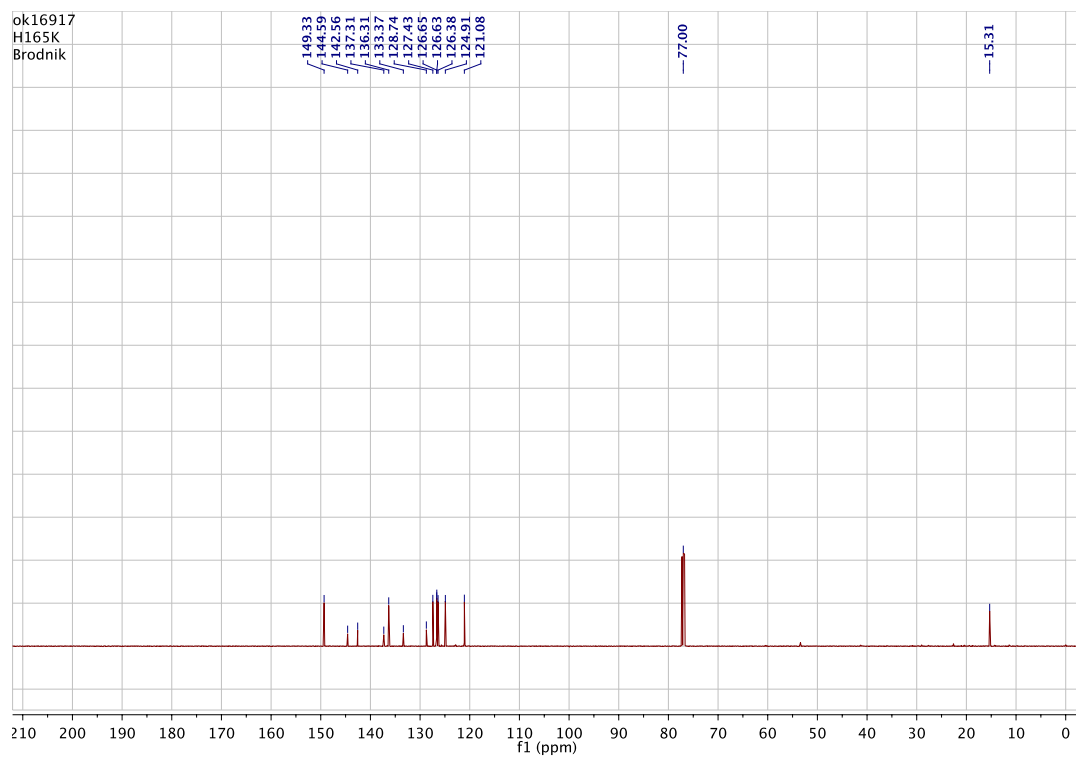


Compound 4c

¹H NMR

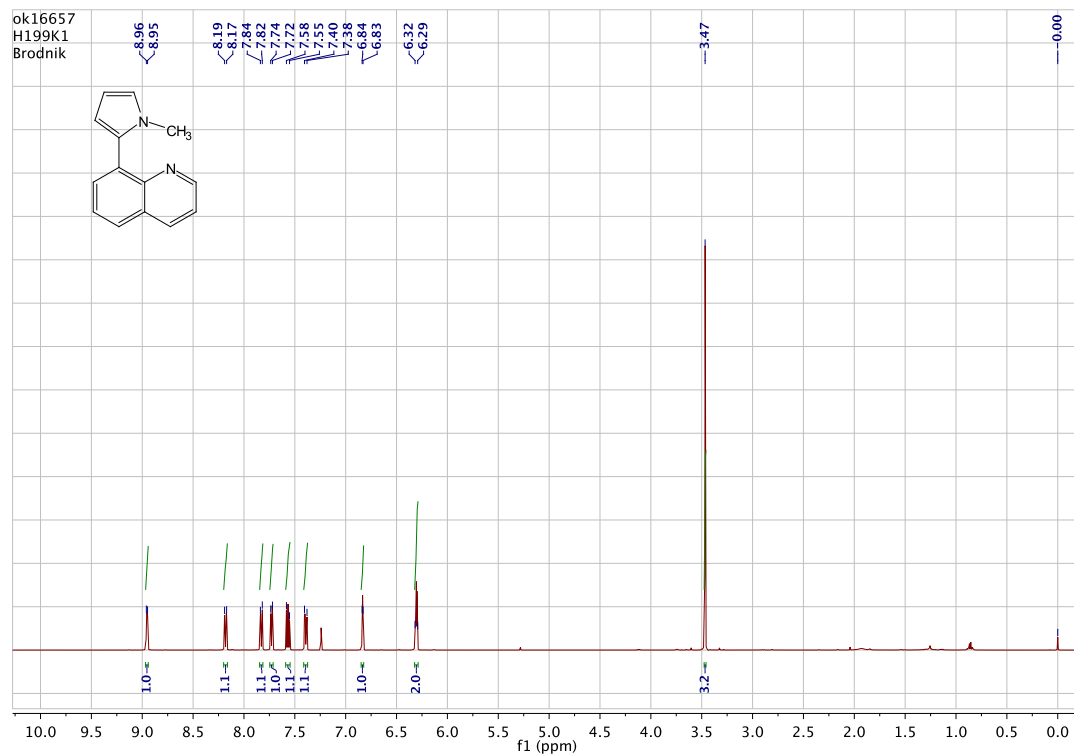


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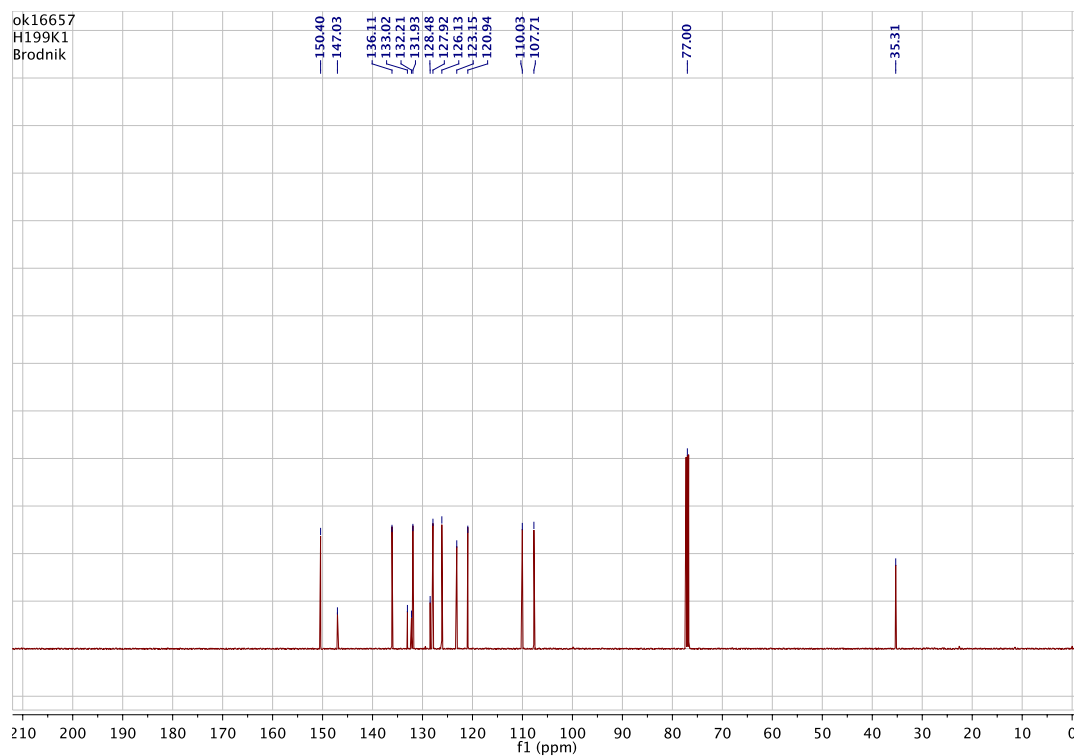


Compound 4d

¹H NMR

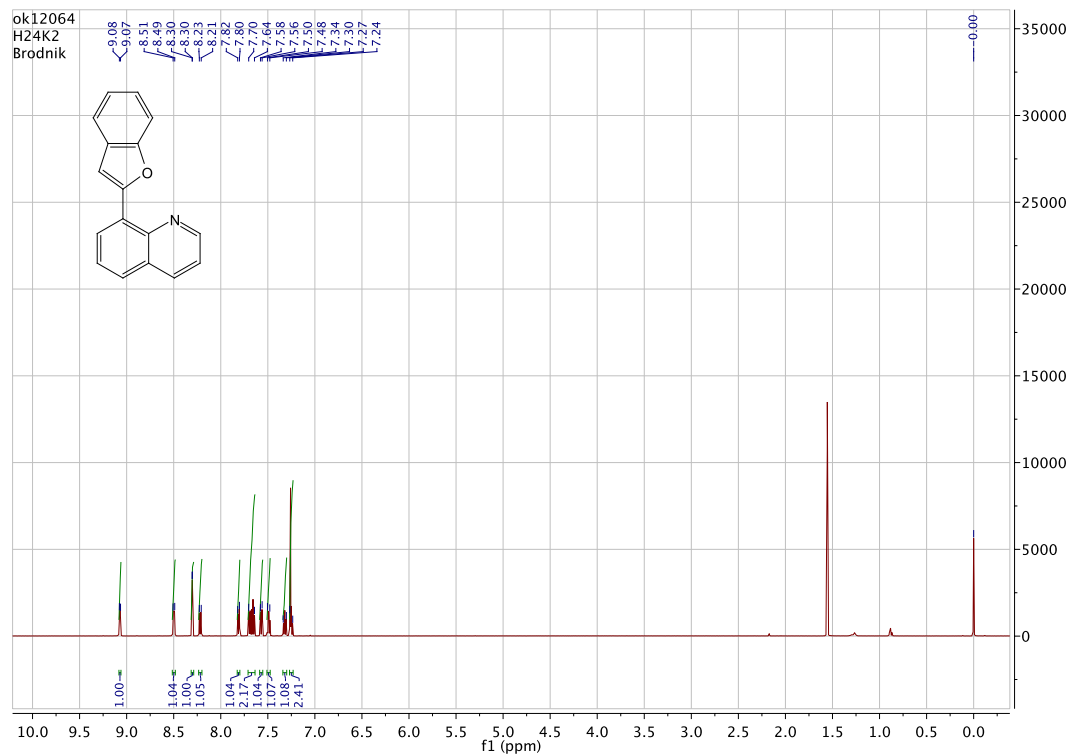


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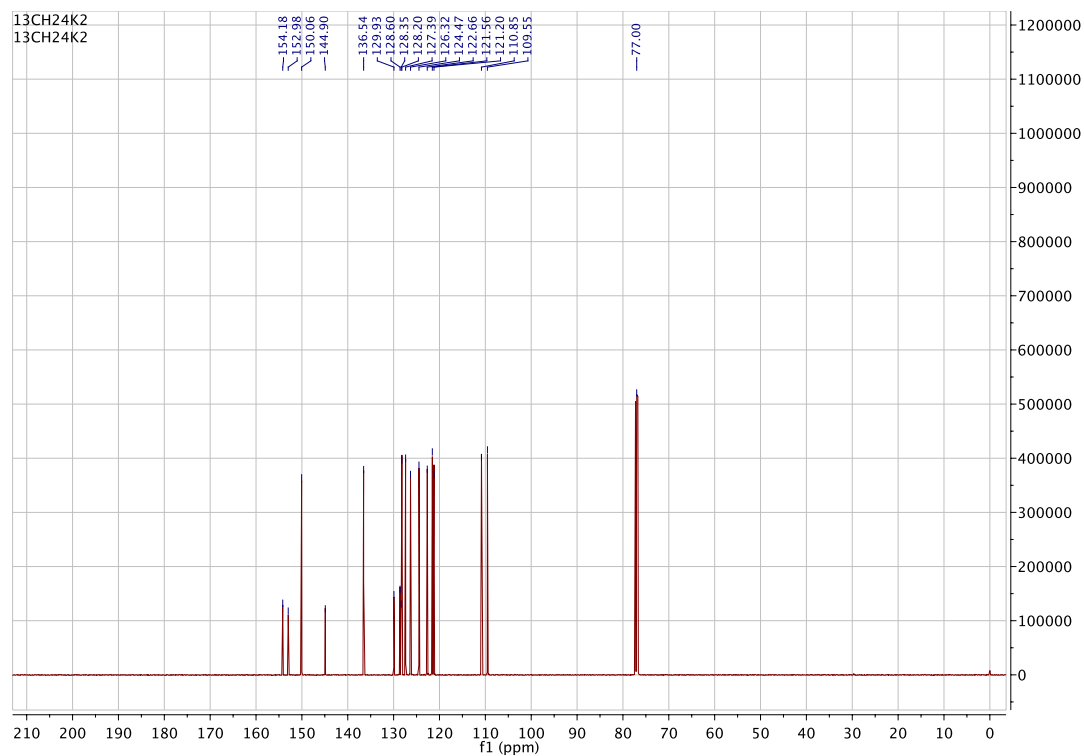


Compound 4e

¹H NMR

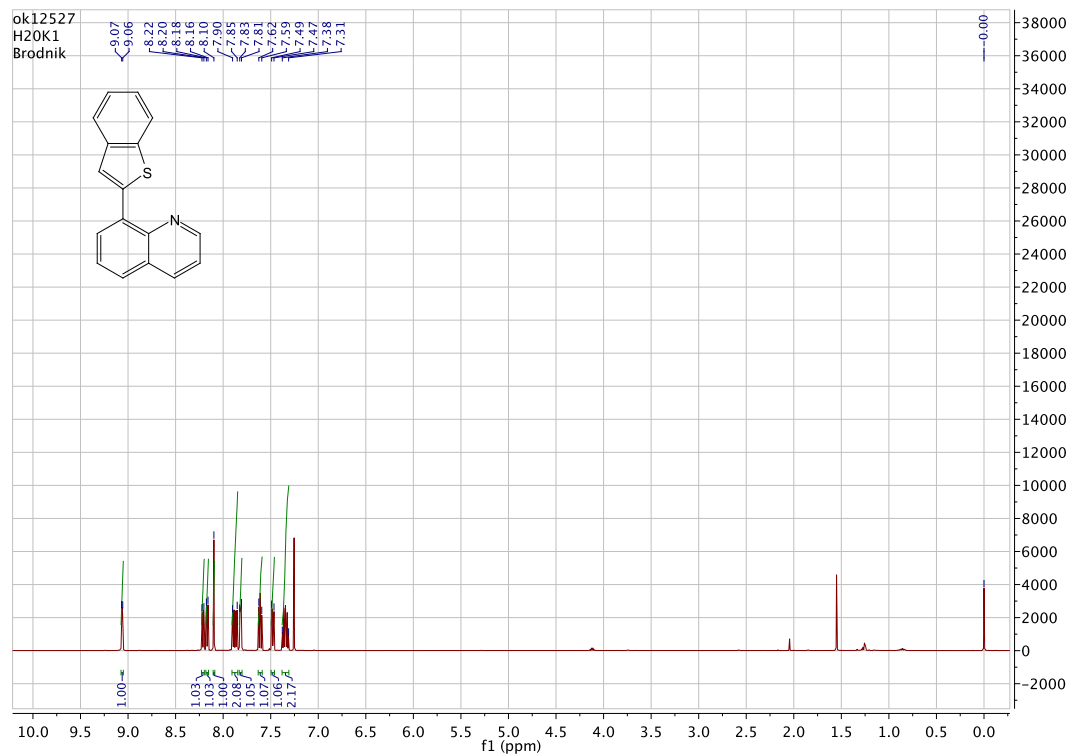


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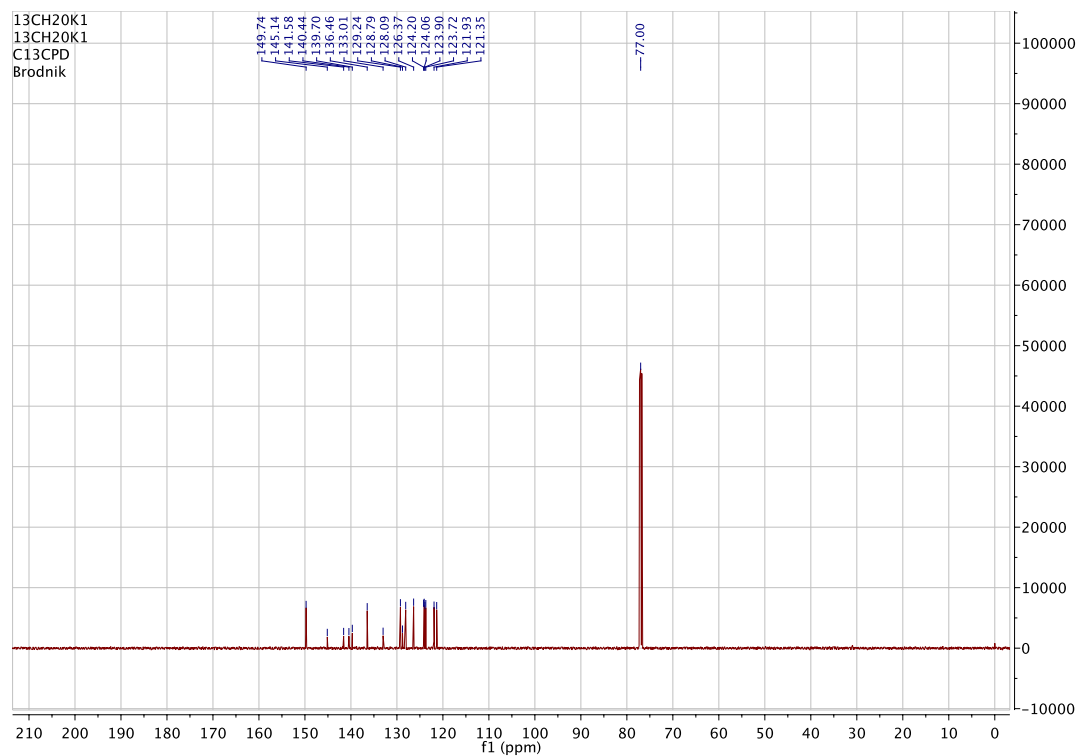


Compound 4f

¹H NMR

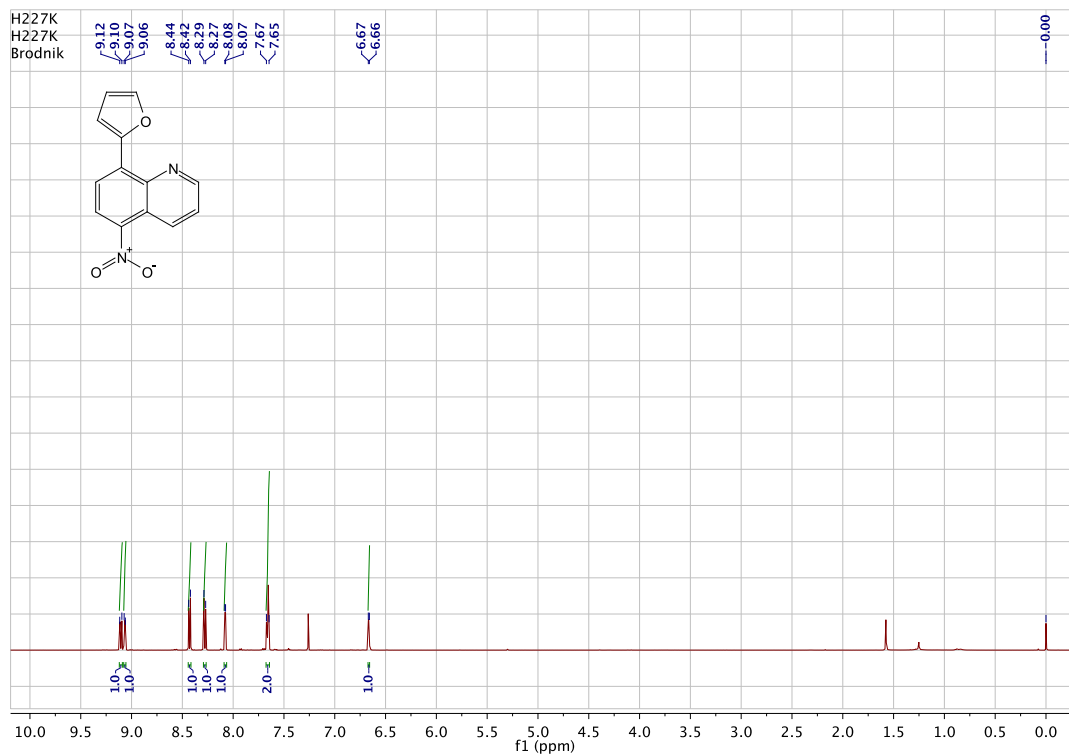


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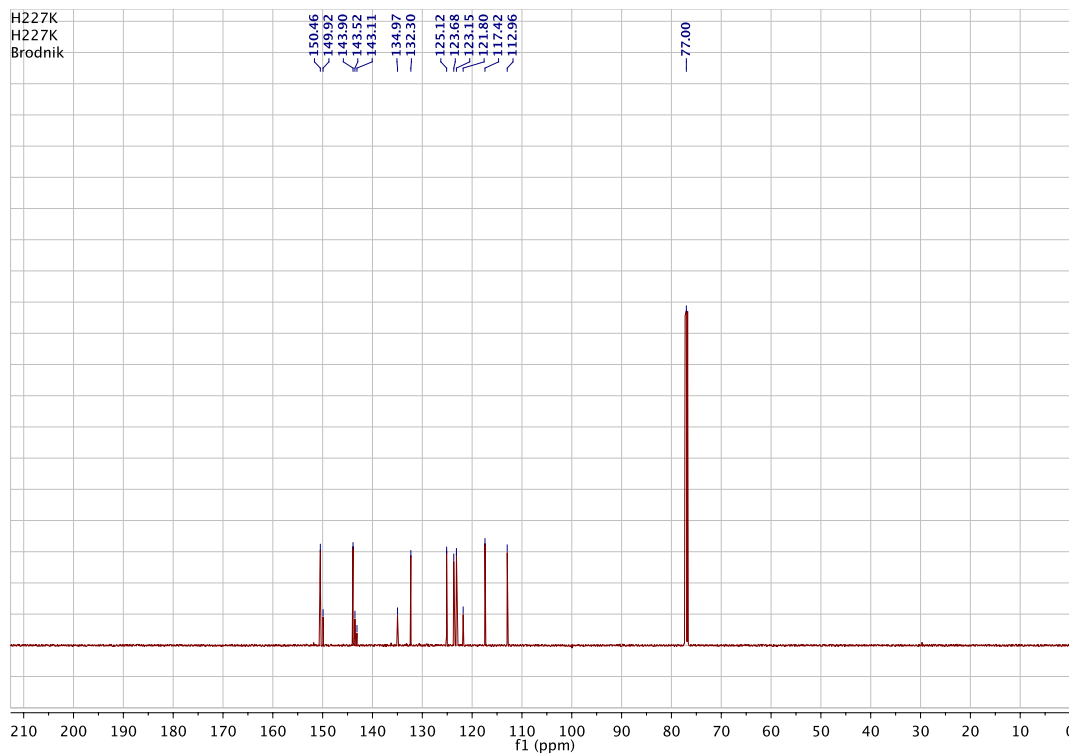


Compound 4g

¹H NMR



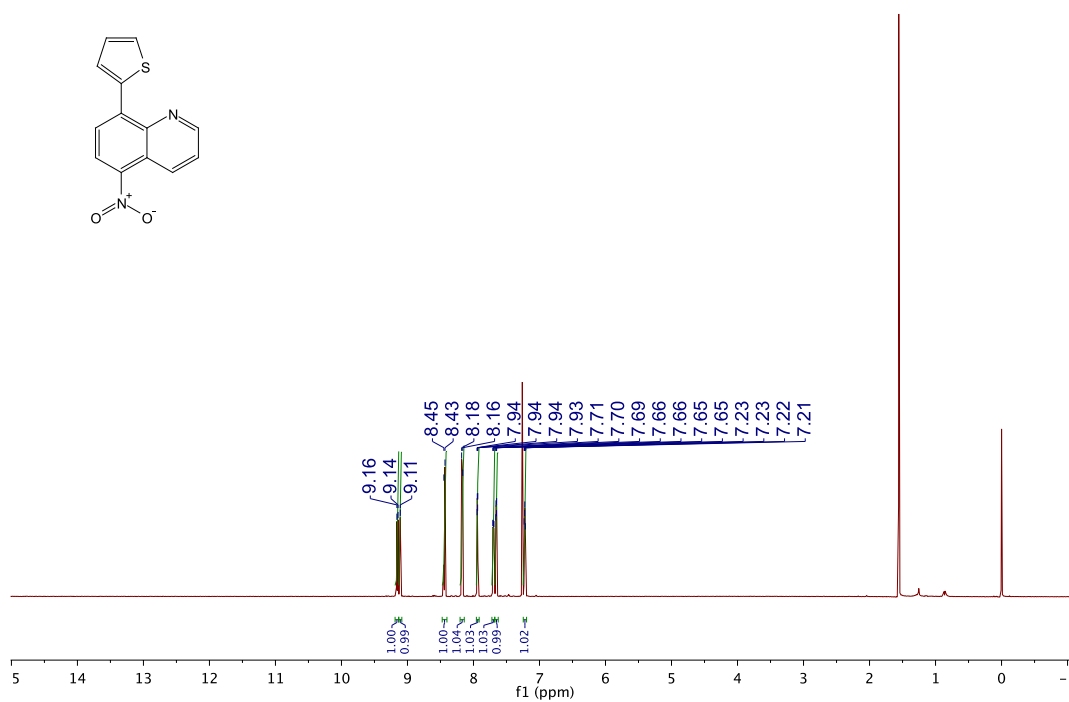
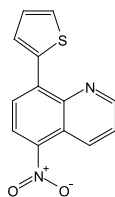
¹³C NMR



Compound 4h

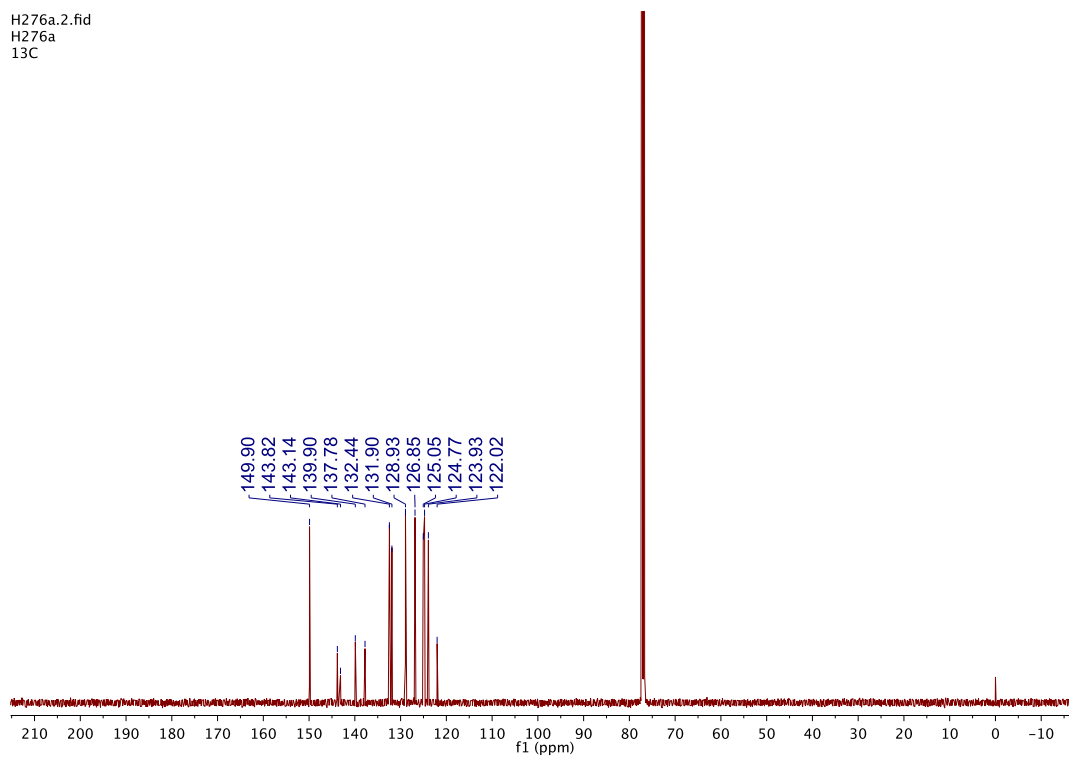
¹H NMR

H276a.1.fid
H276a



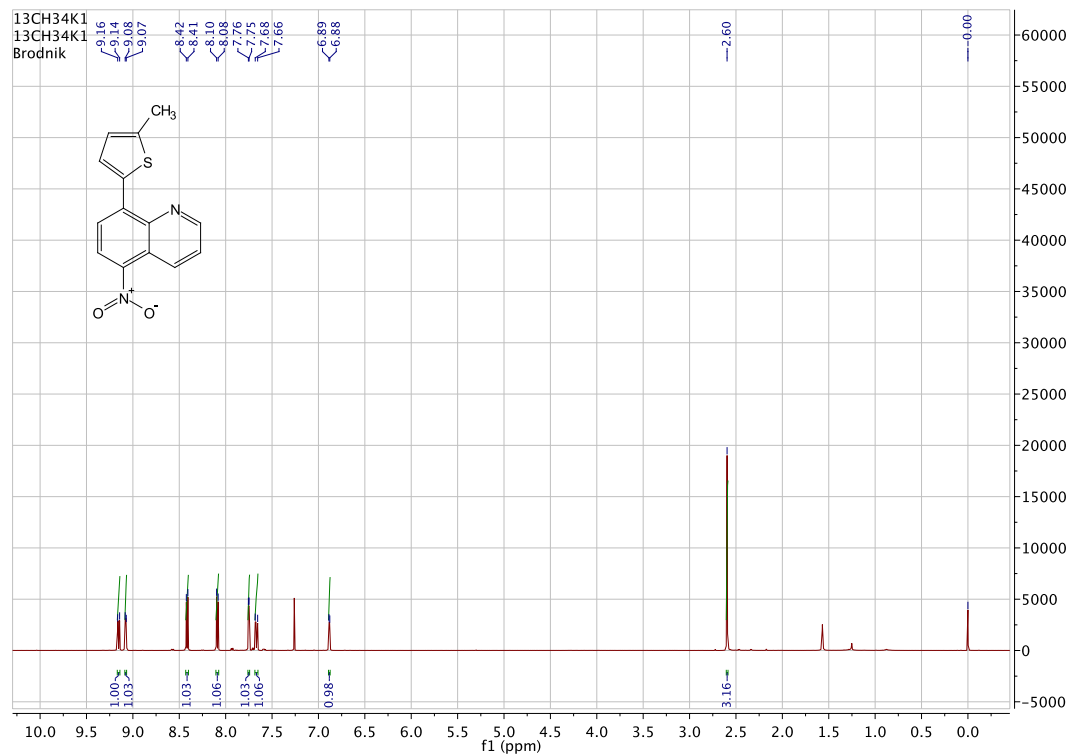
¹³C NMR

H276a.2.fid
H276a
13C

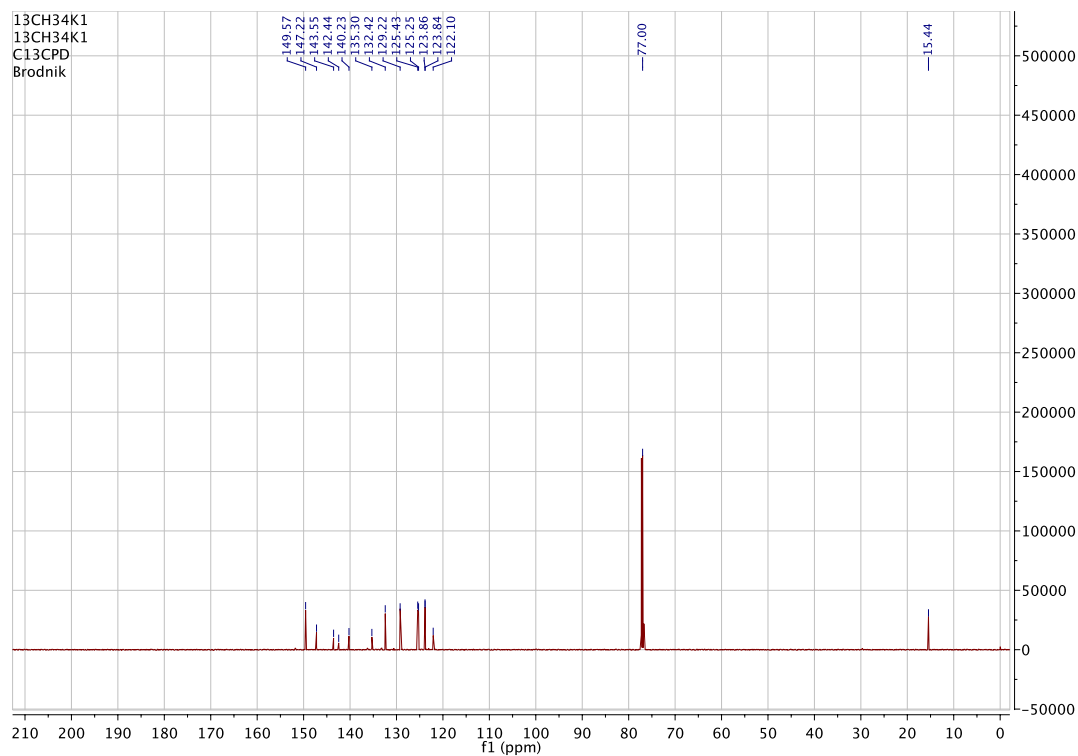


Compound 4i

¹H NMR

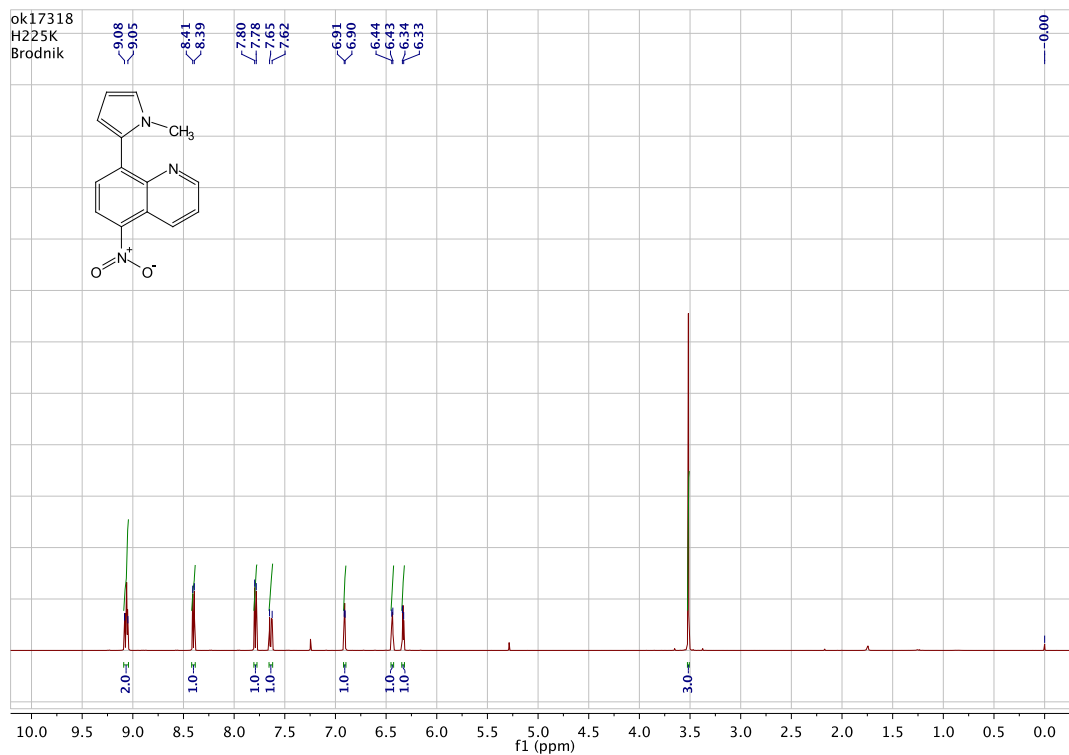


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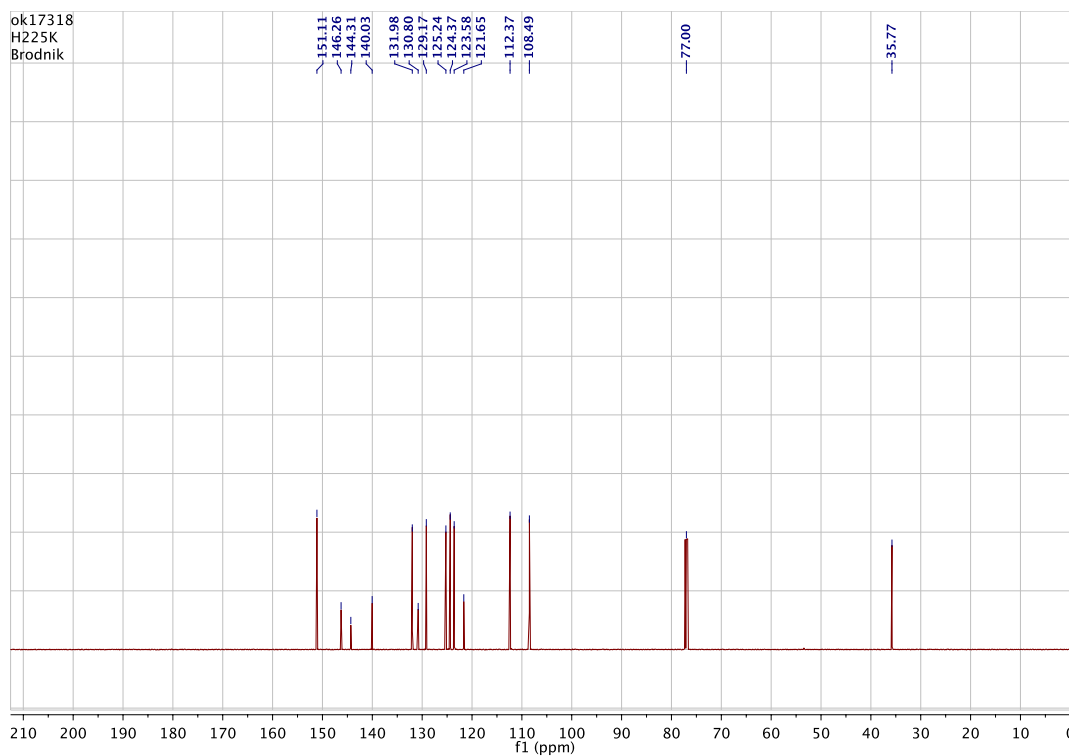


Compound 4j

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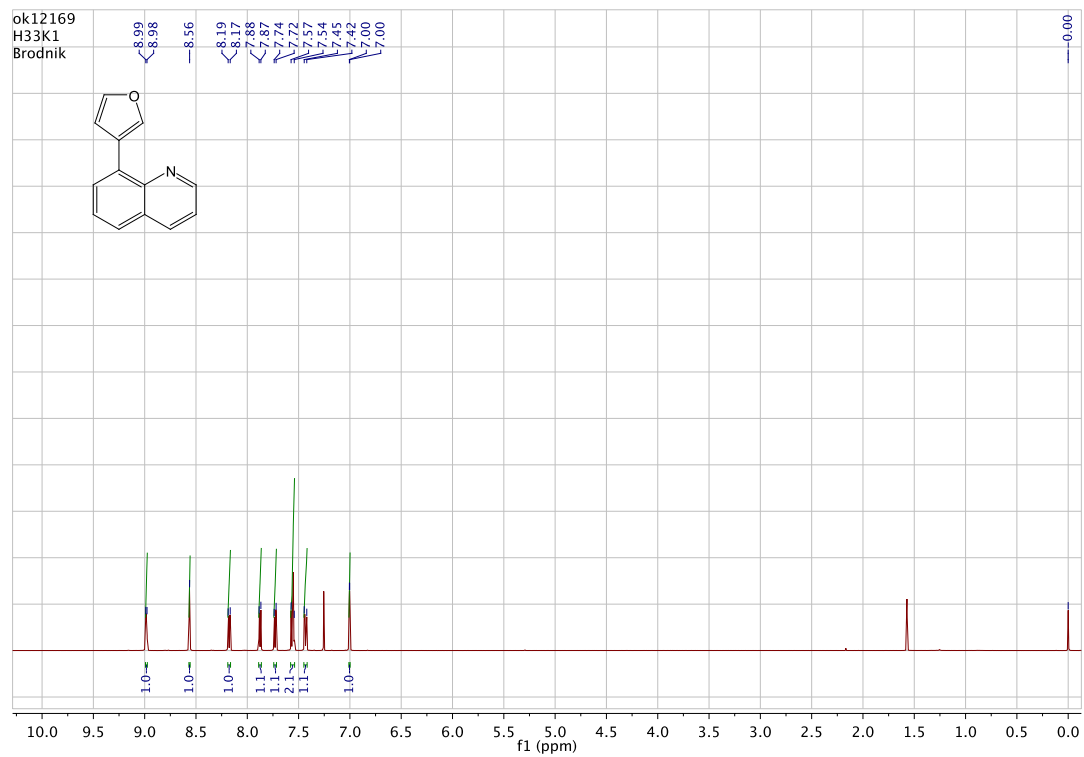


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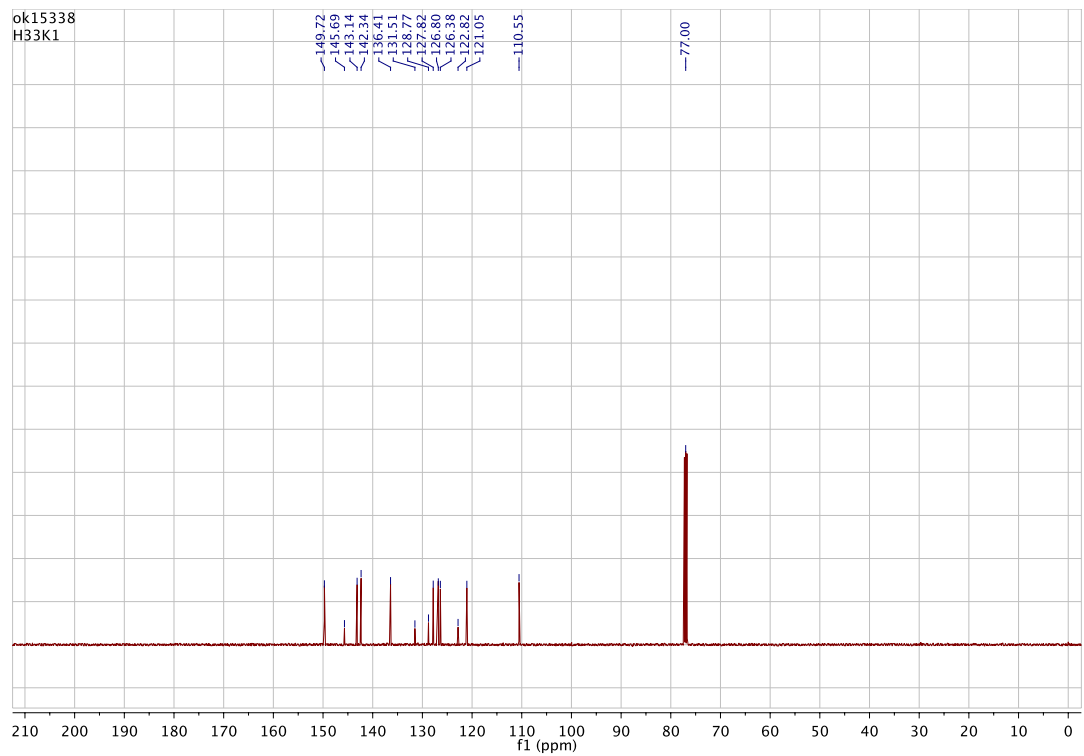


Compound 4k

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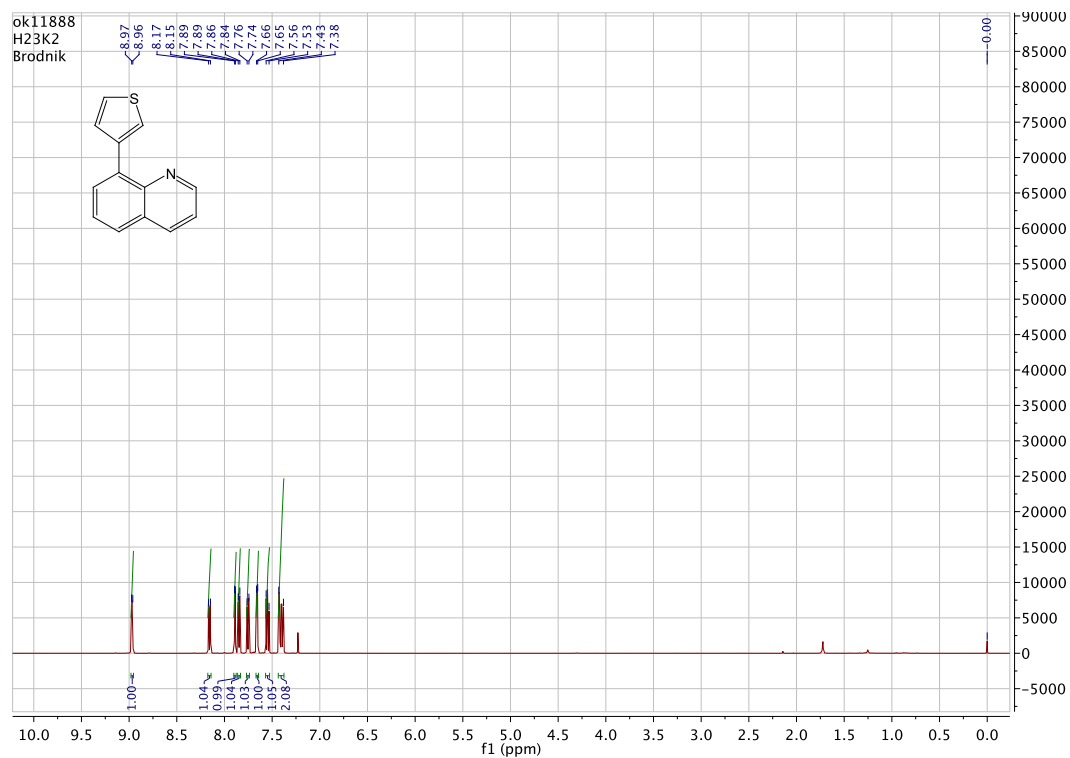


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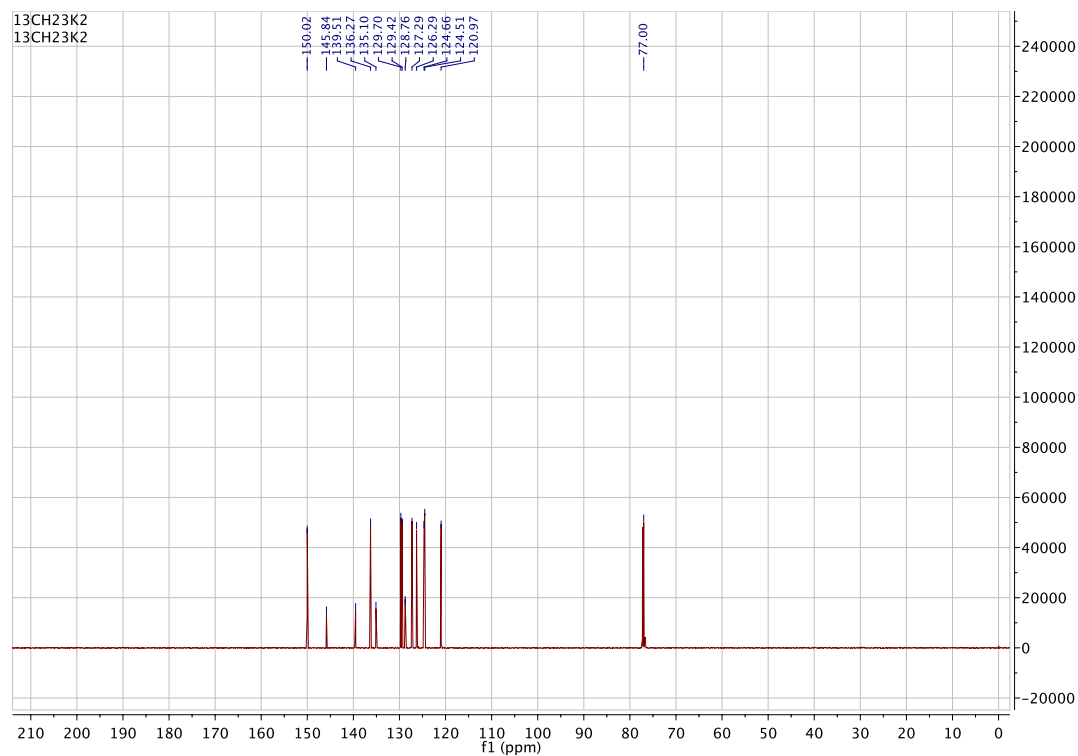


Compound 4l

¹H NMR

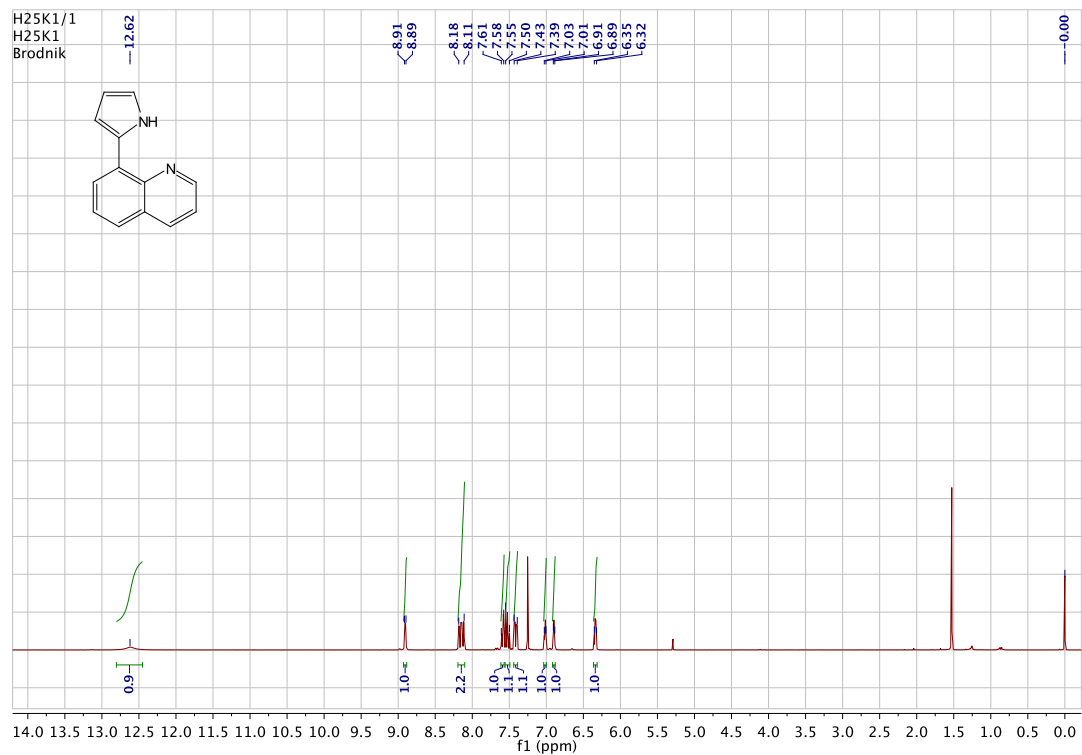


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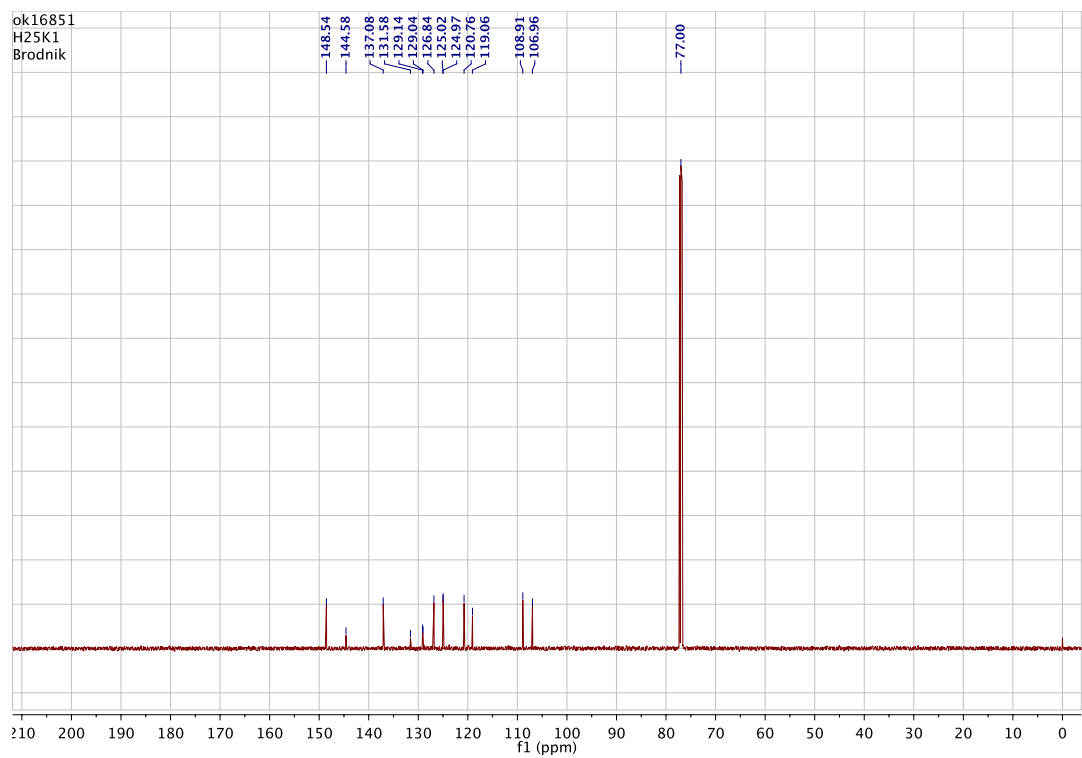


Compound 4m

¹H NMR

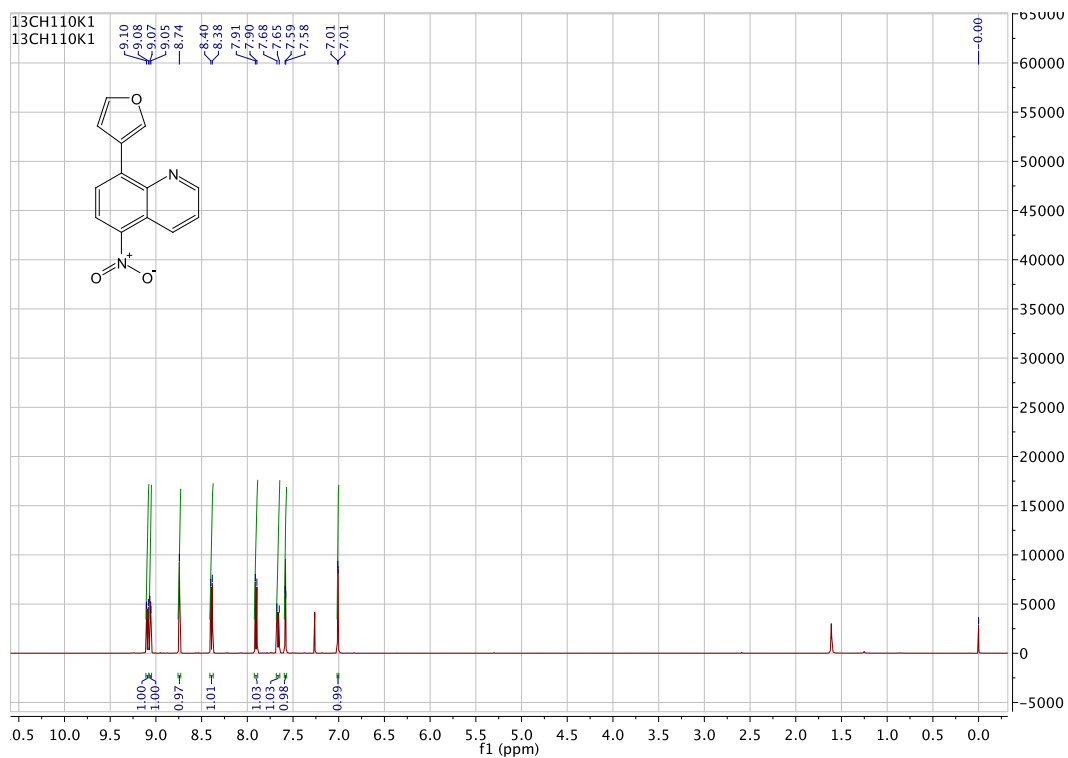


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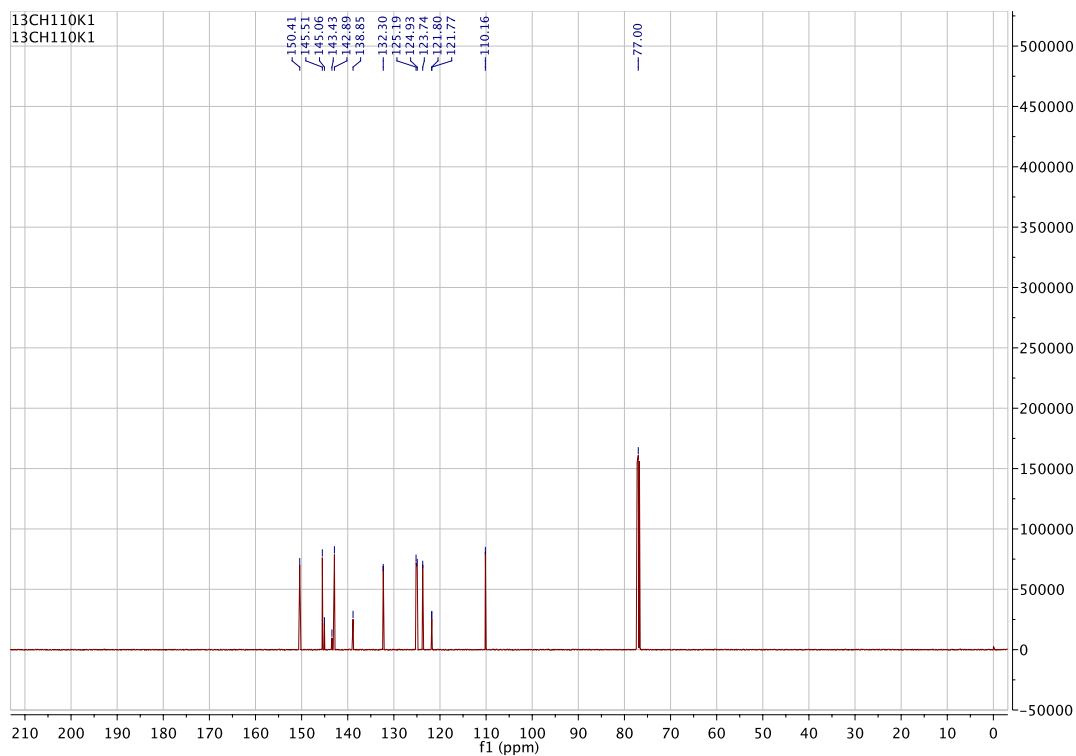


Compound 4n

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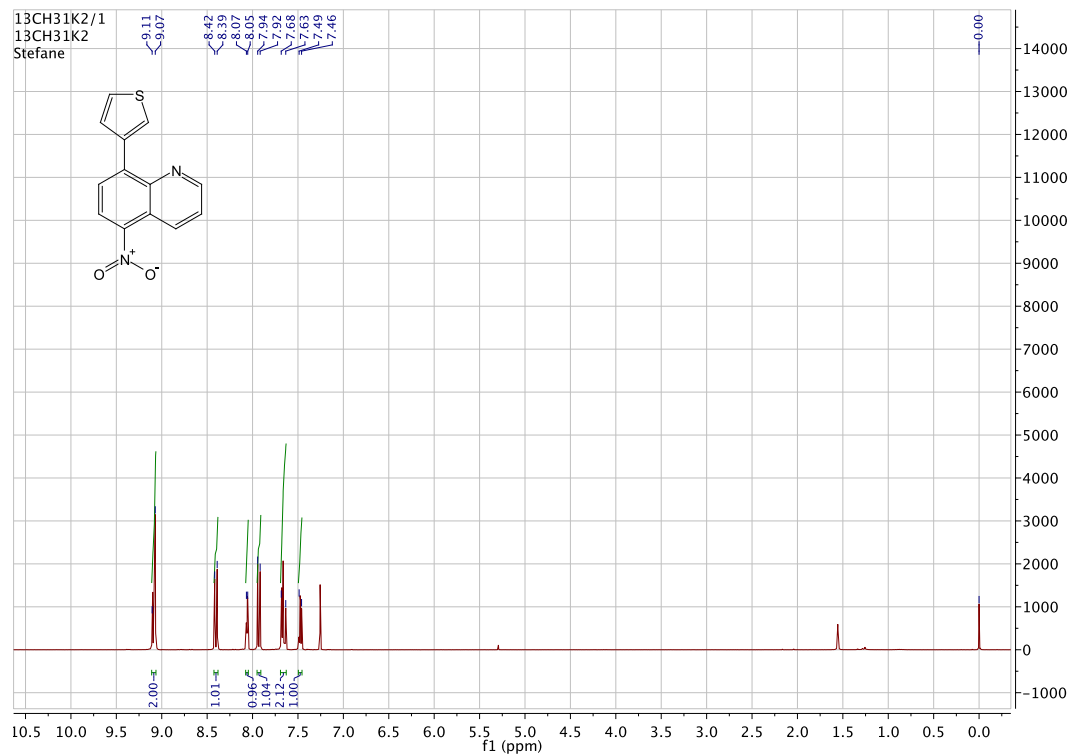


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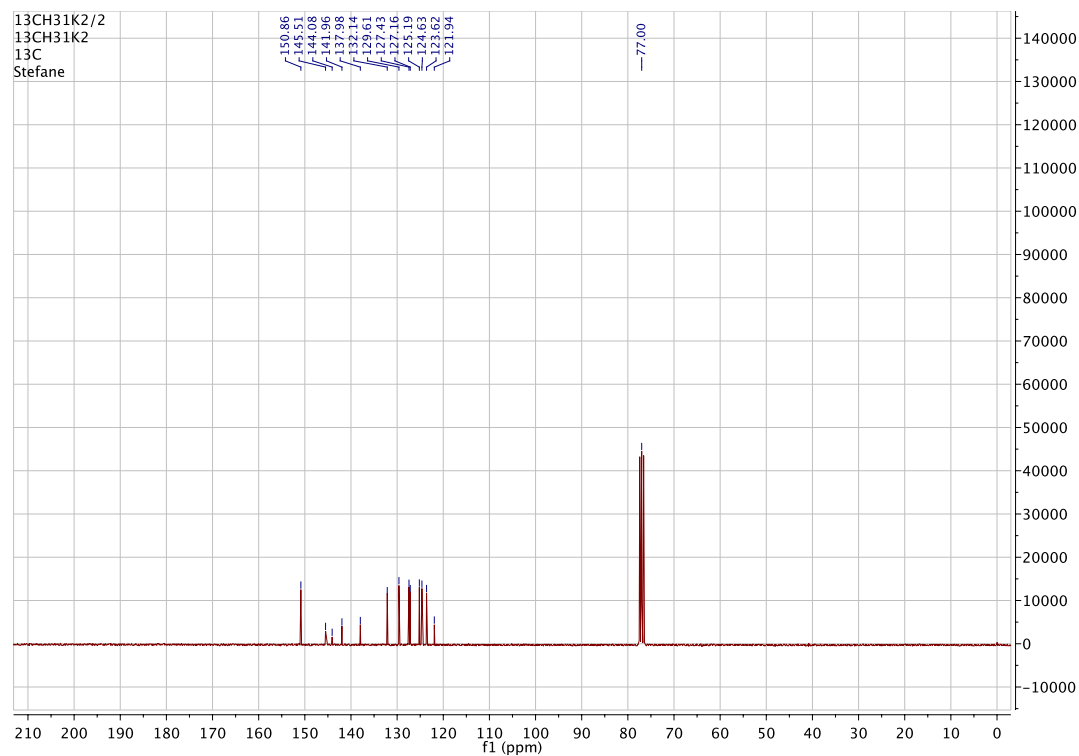


Compound 4o

¹H NMR

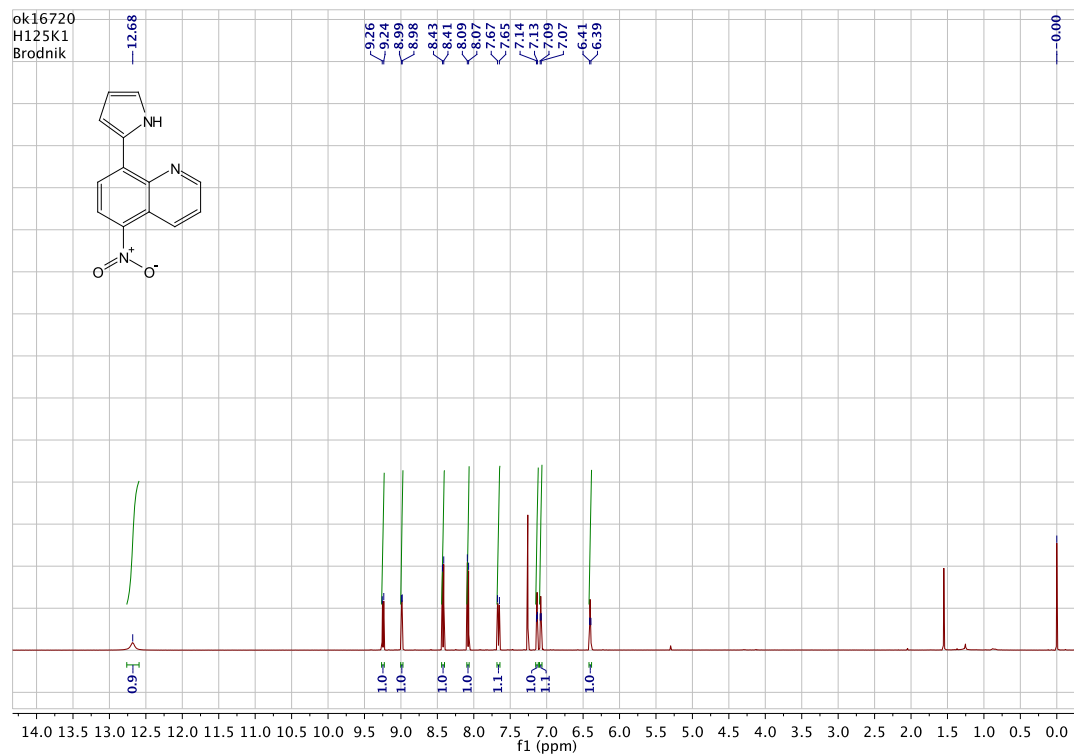


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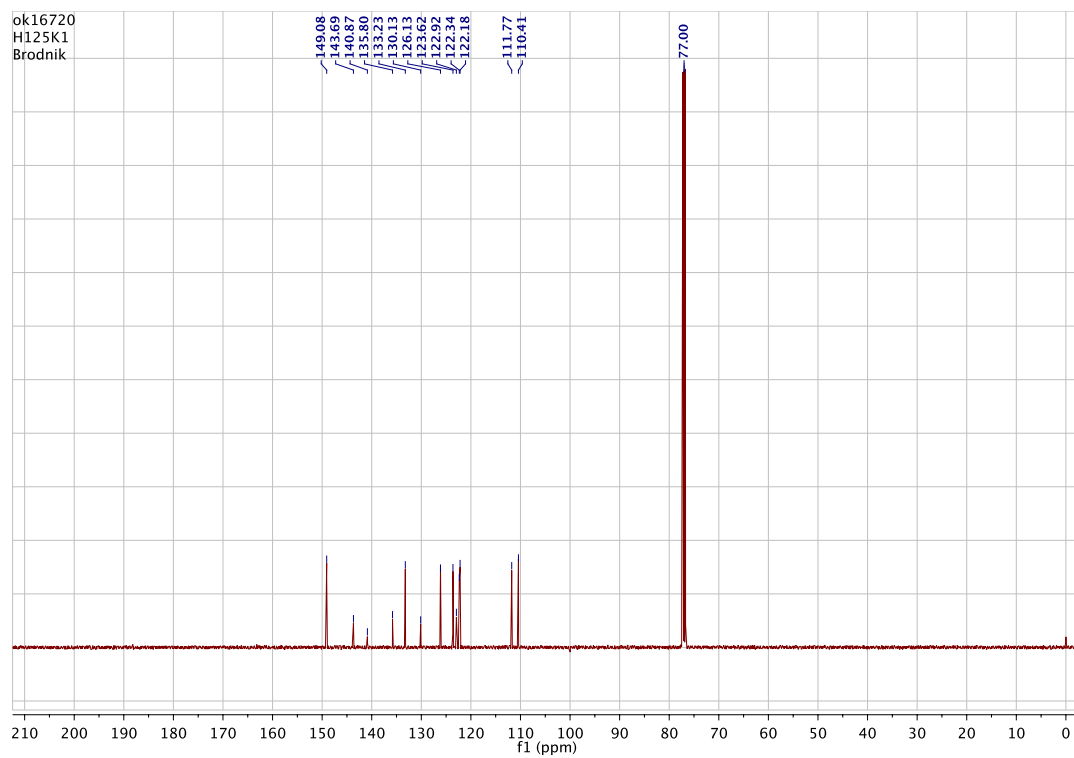


Compound 4p

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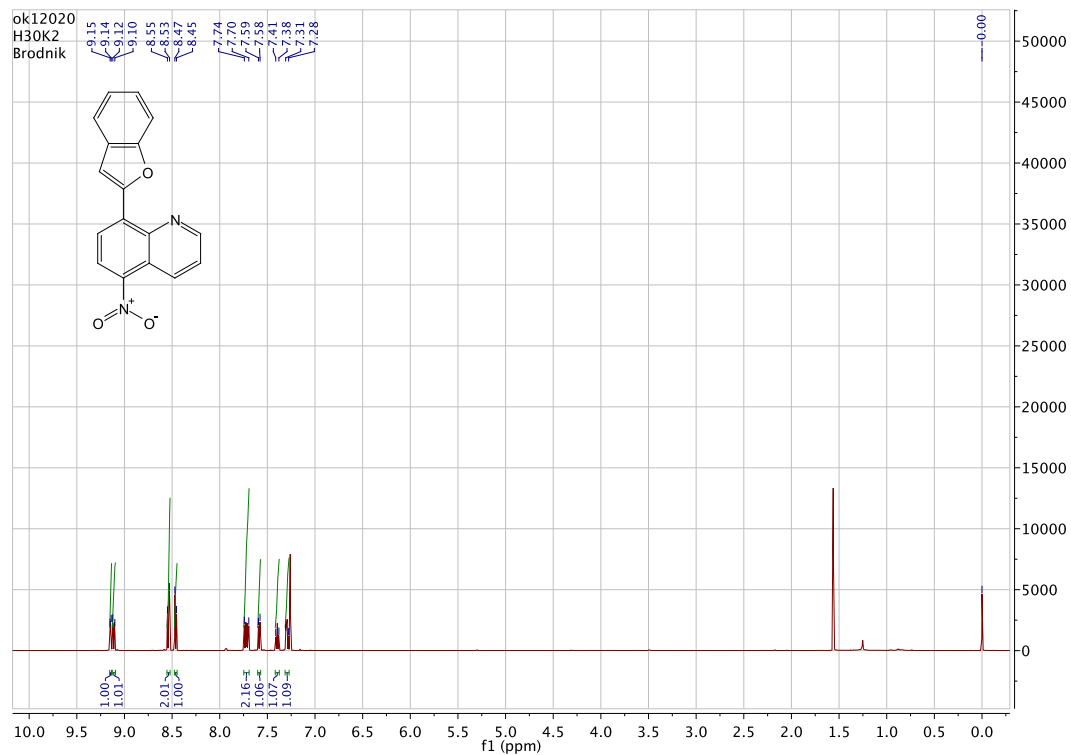


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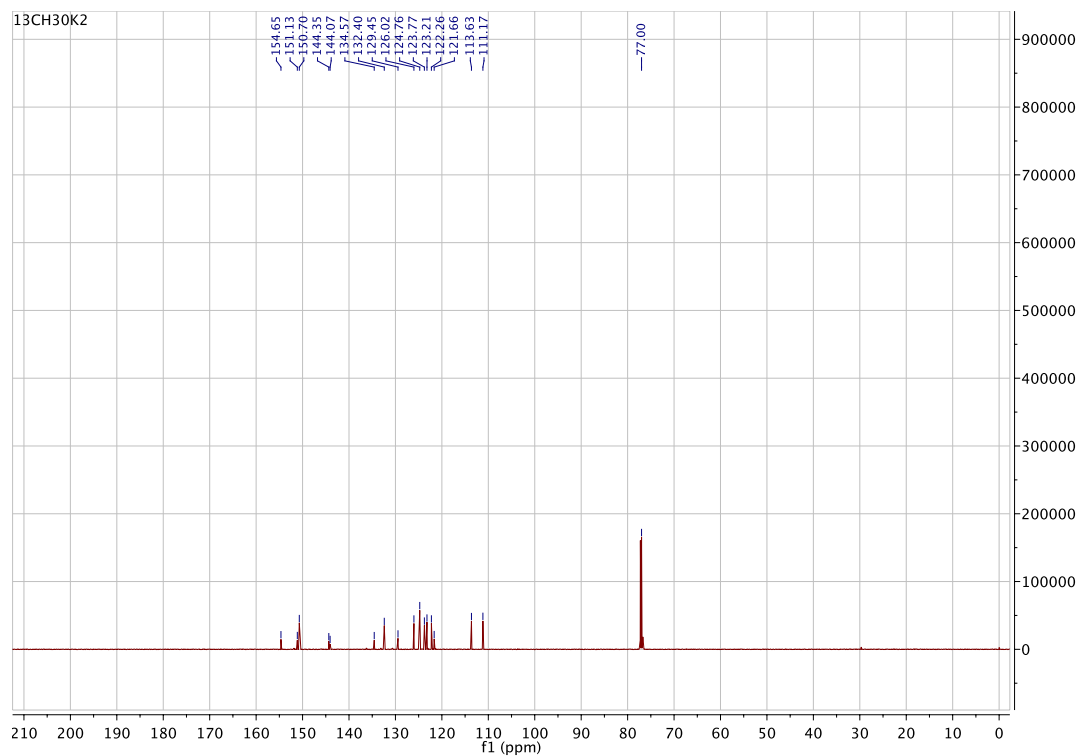


Compound 4q

¹H NMR

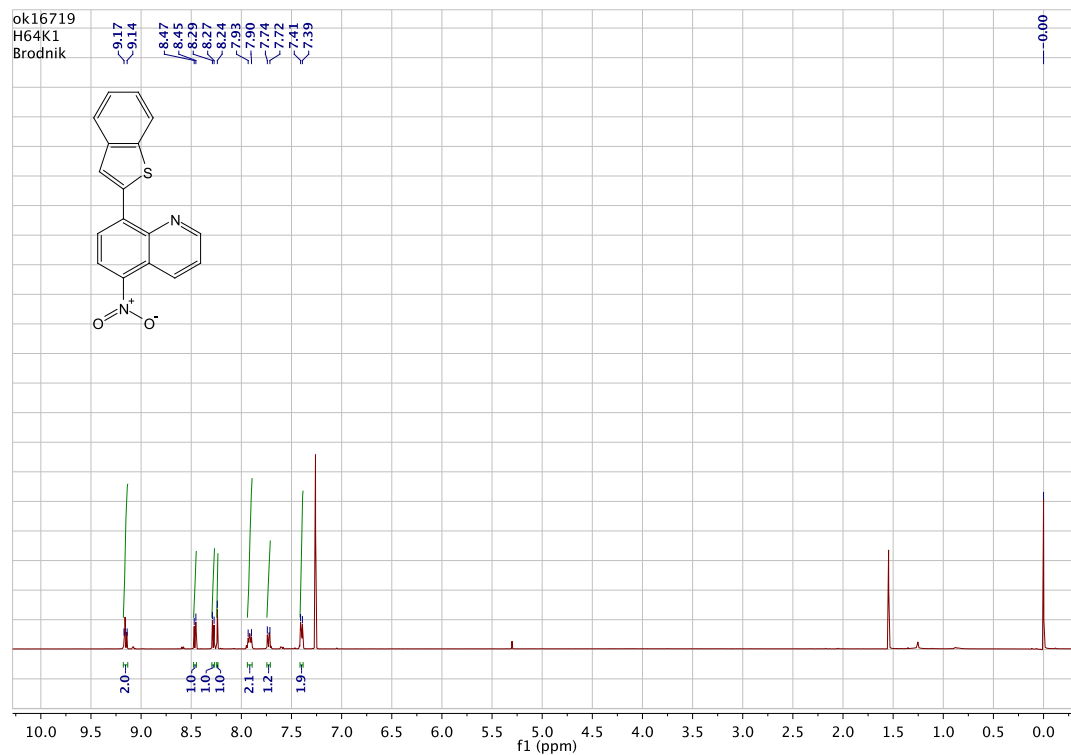


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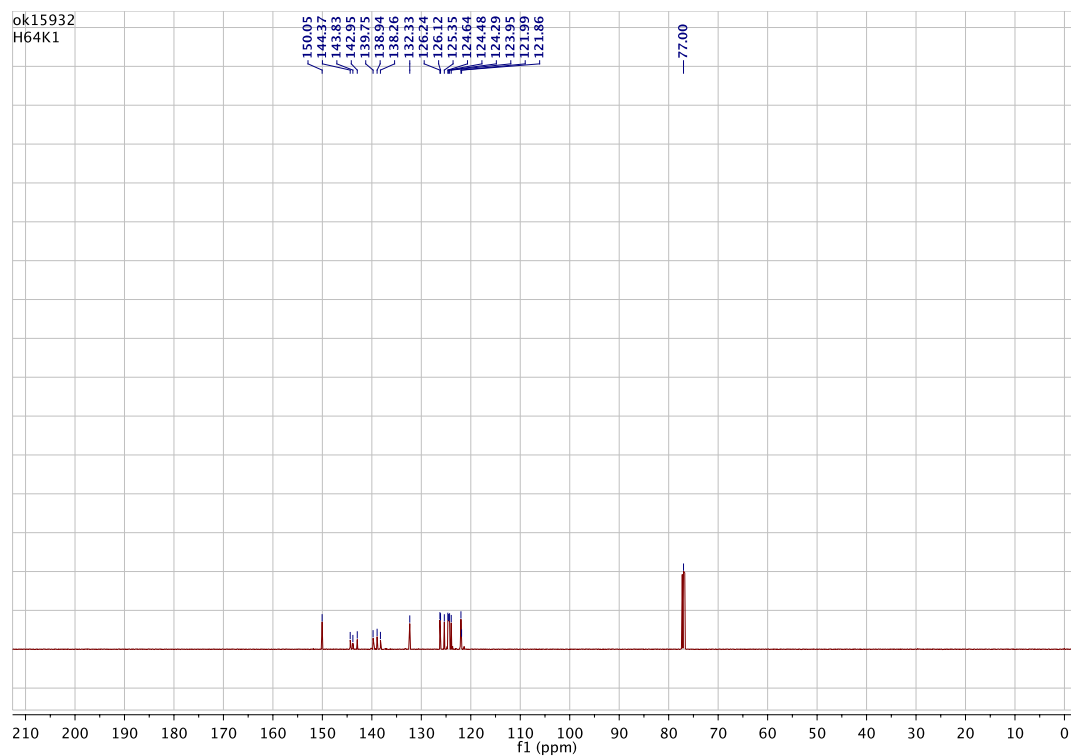


Compound 4r

¹H NMR

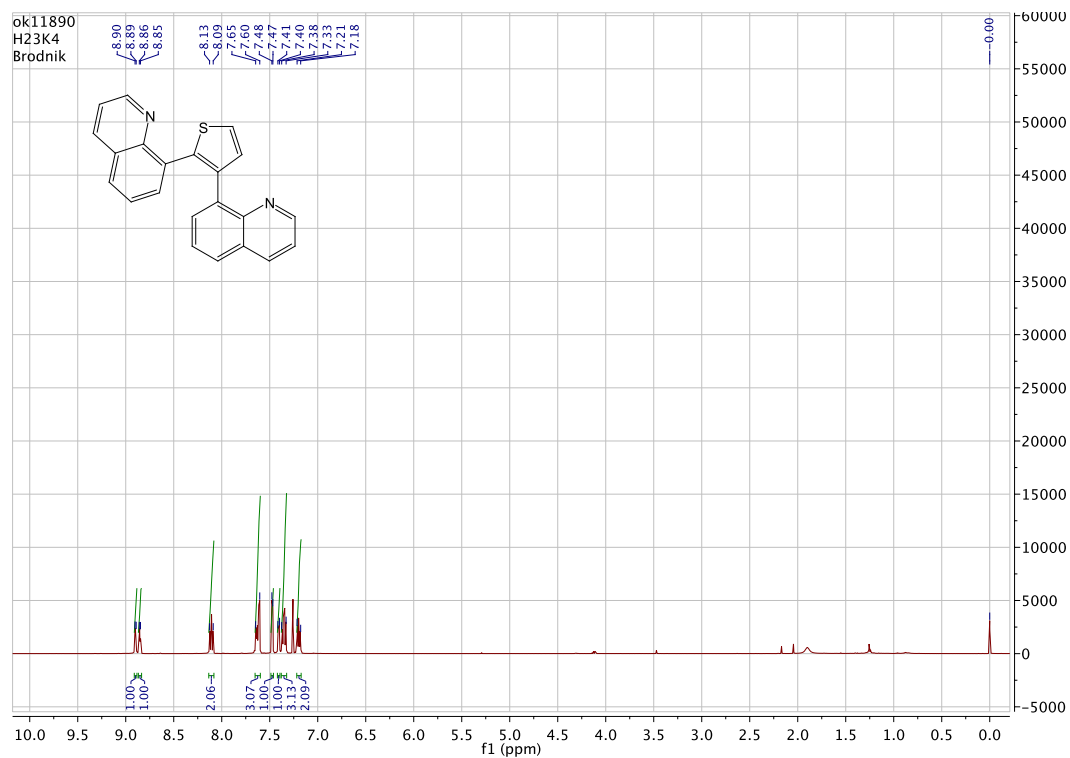


¹³C NMR

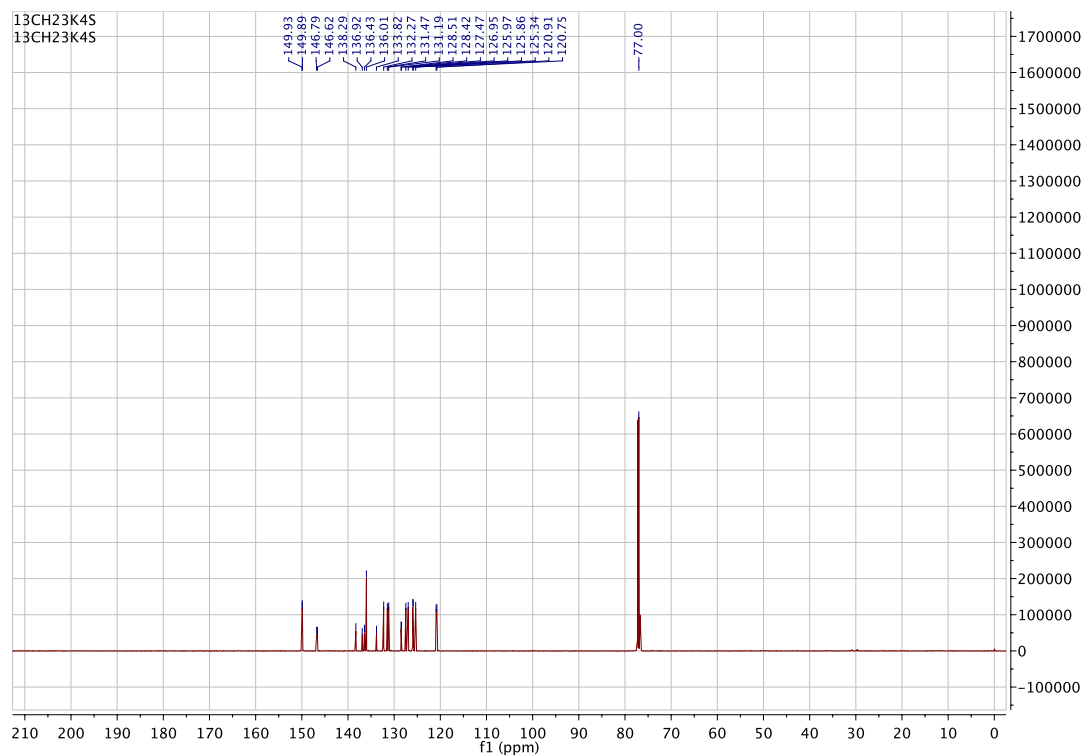


Compound 4I'

¹H NMR

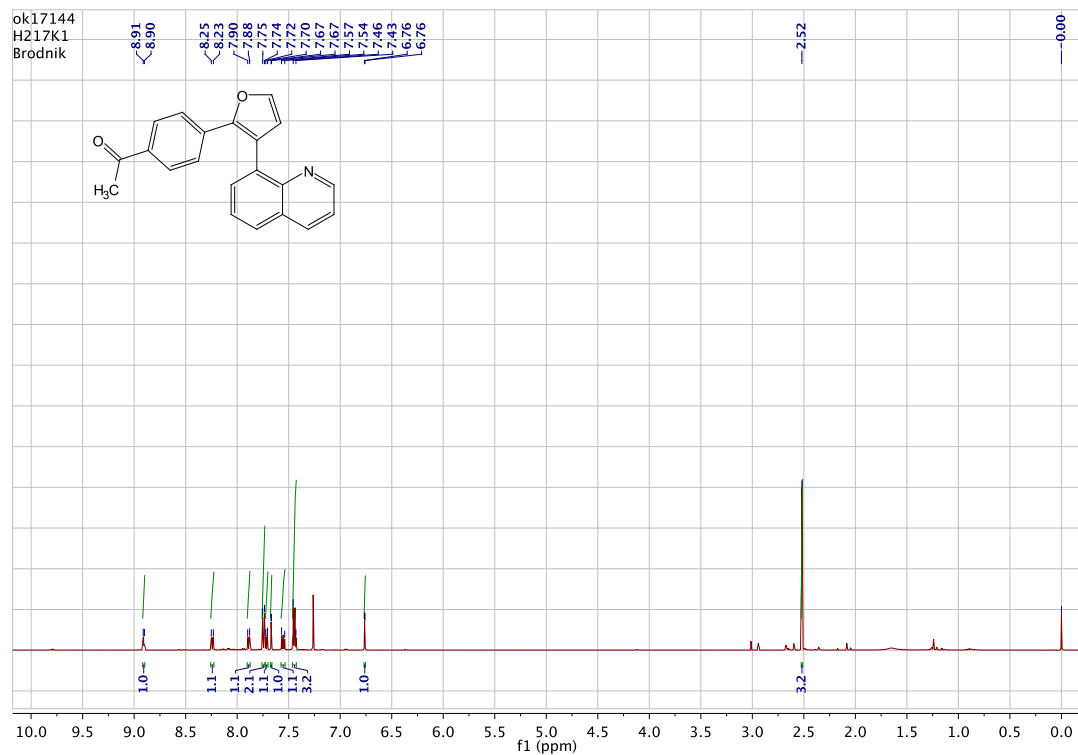


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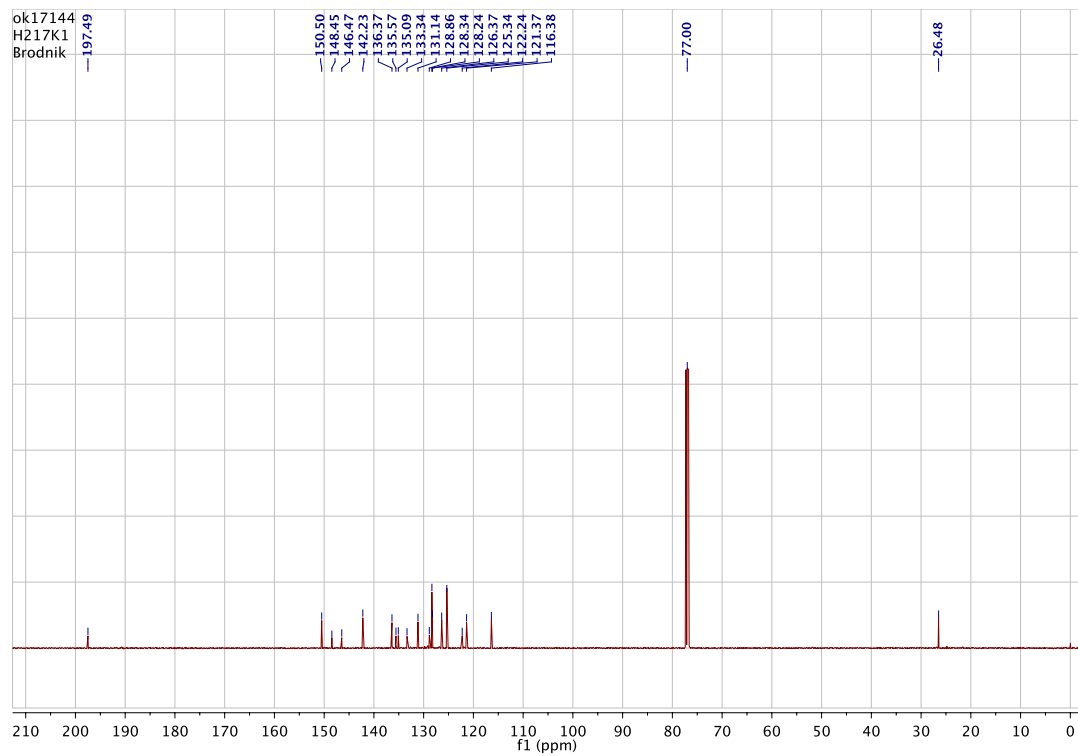


Compound 7a

¹H NMR

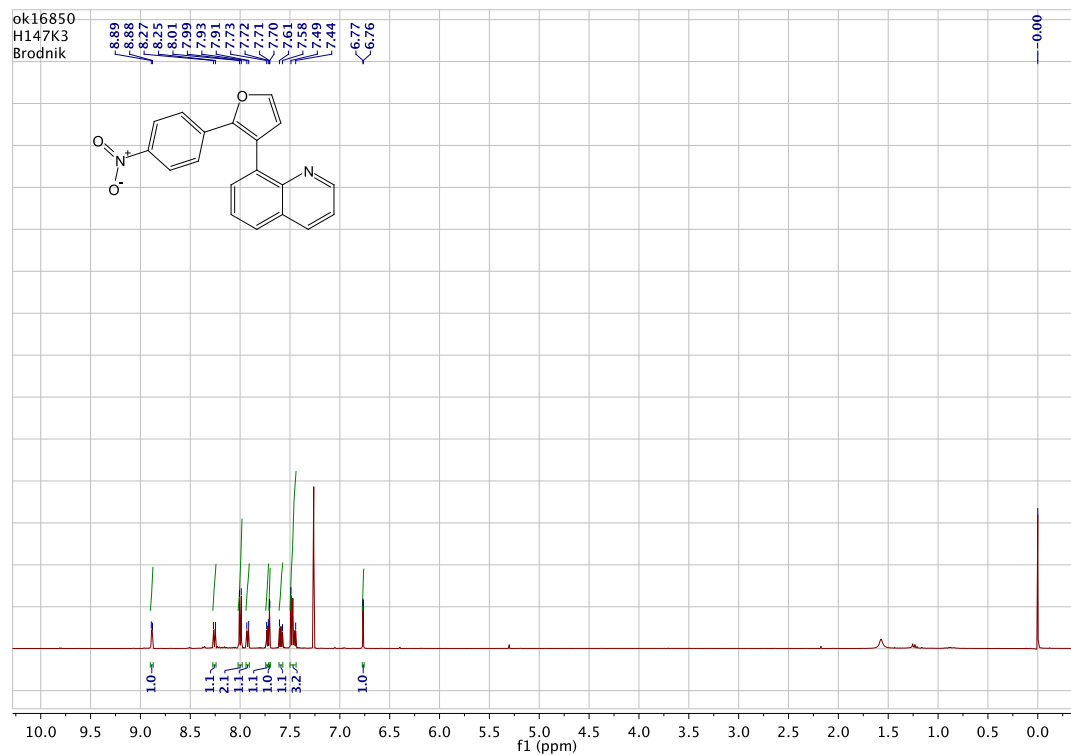


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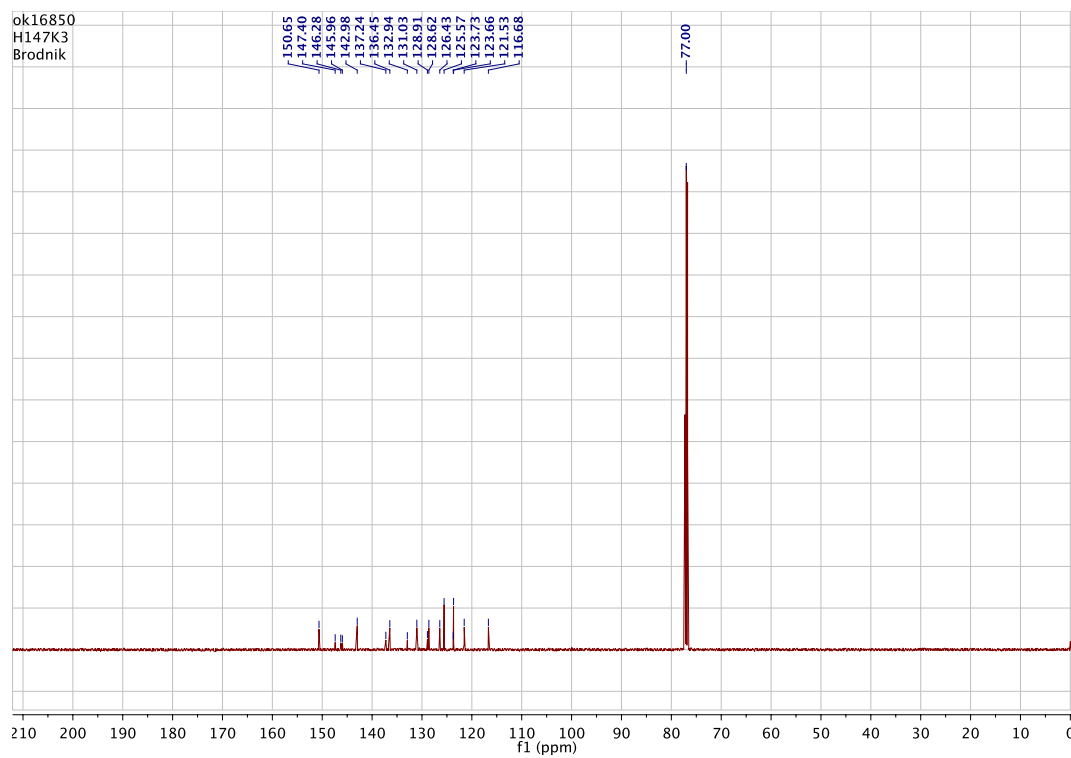


Compound 7b

¹H NMR

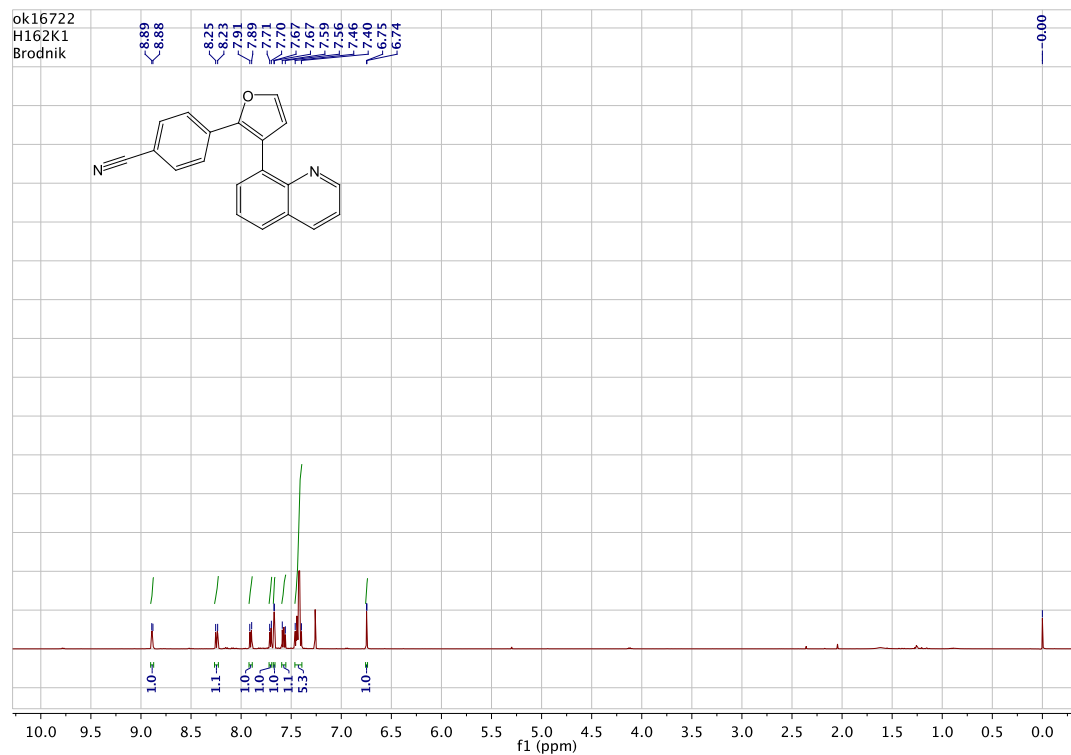


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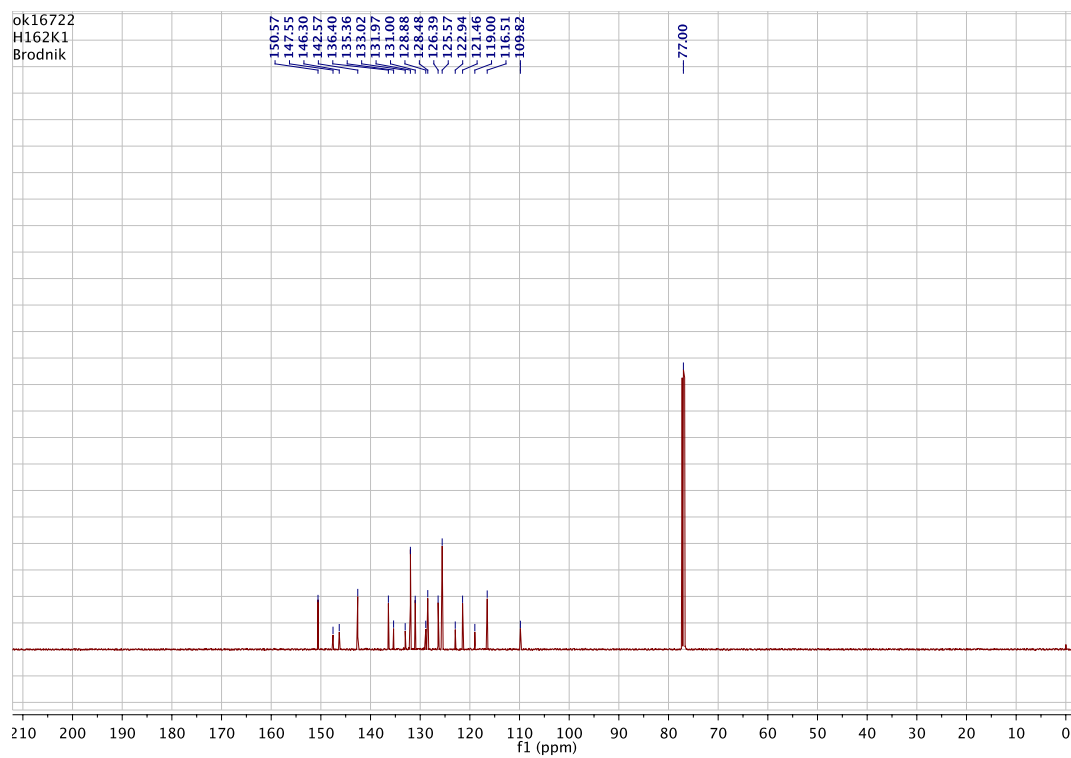


Compound 7c

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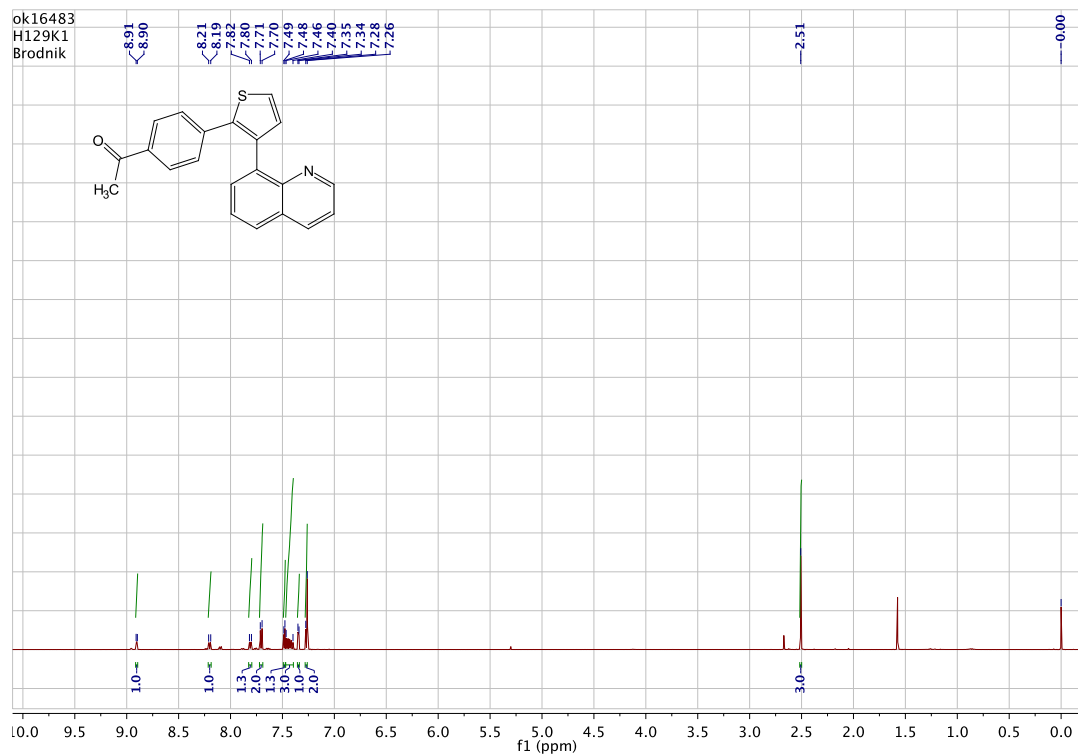


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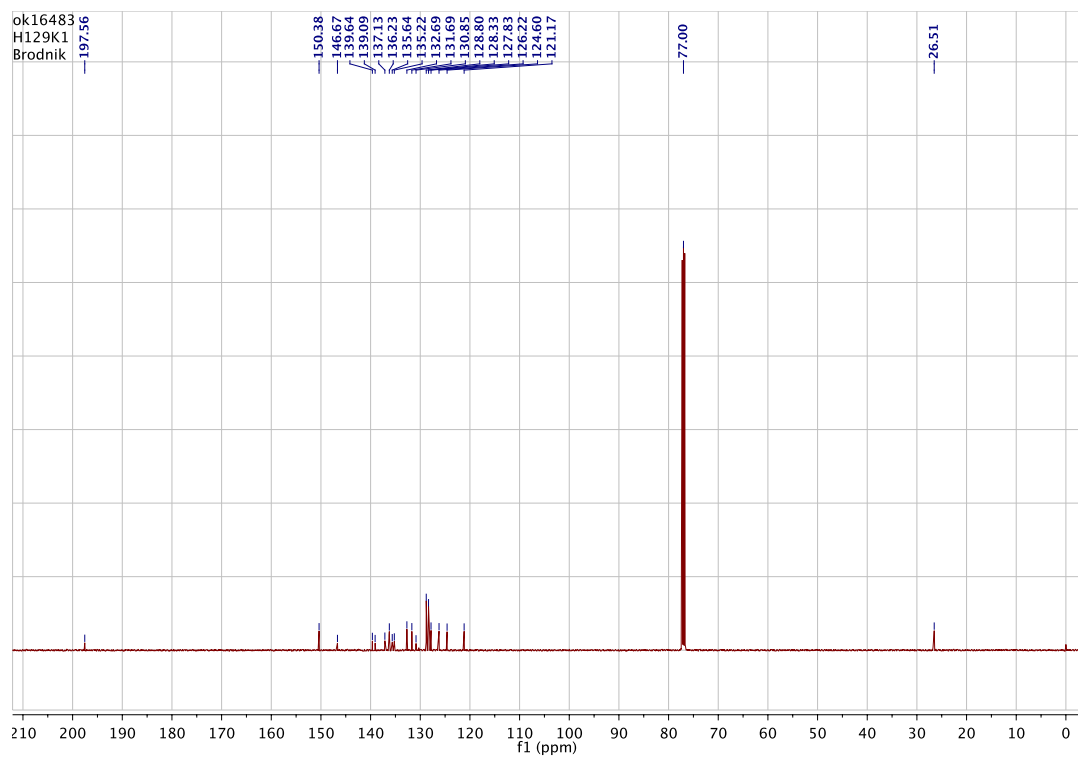


Compound 7d

¹H NMR

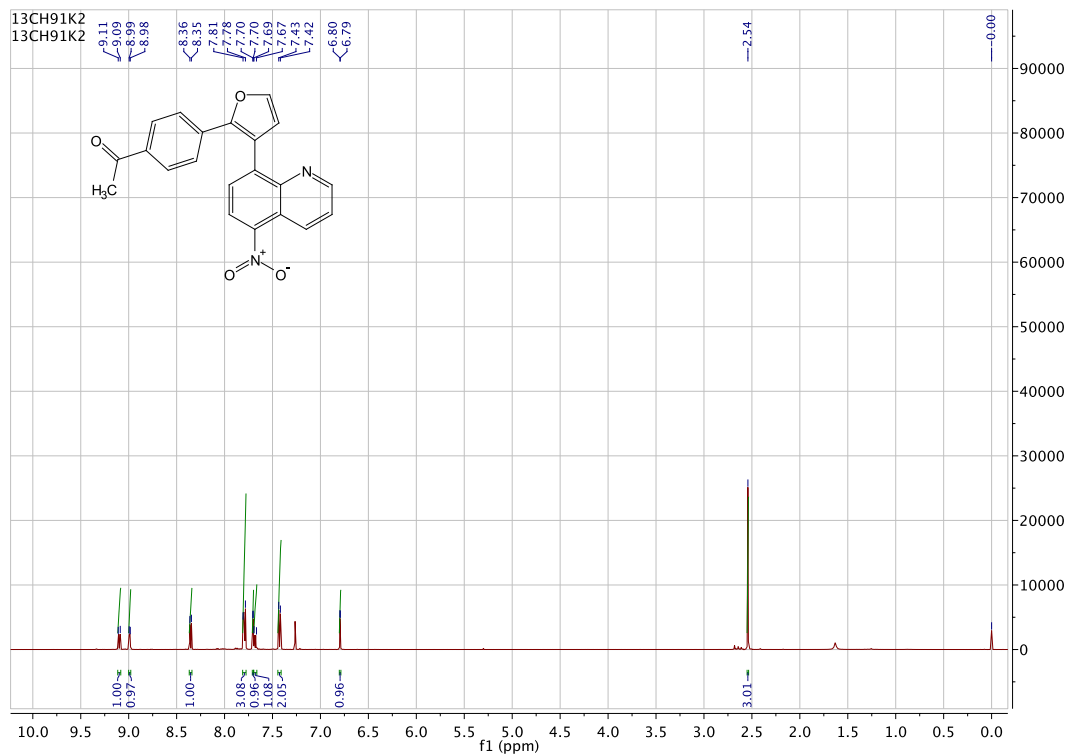


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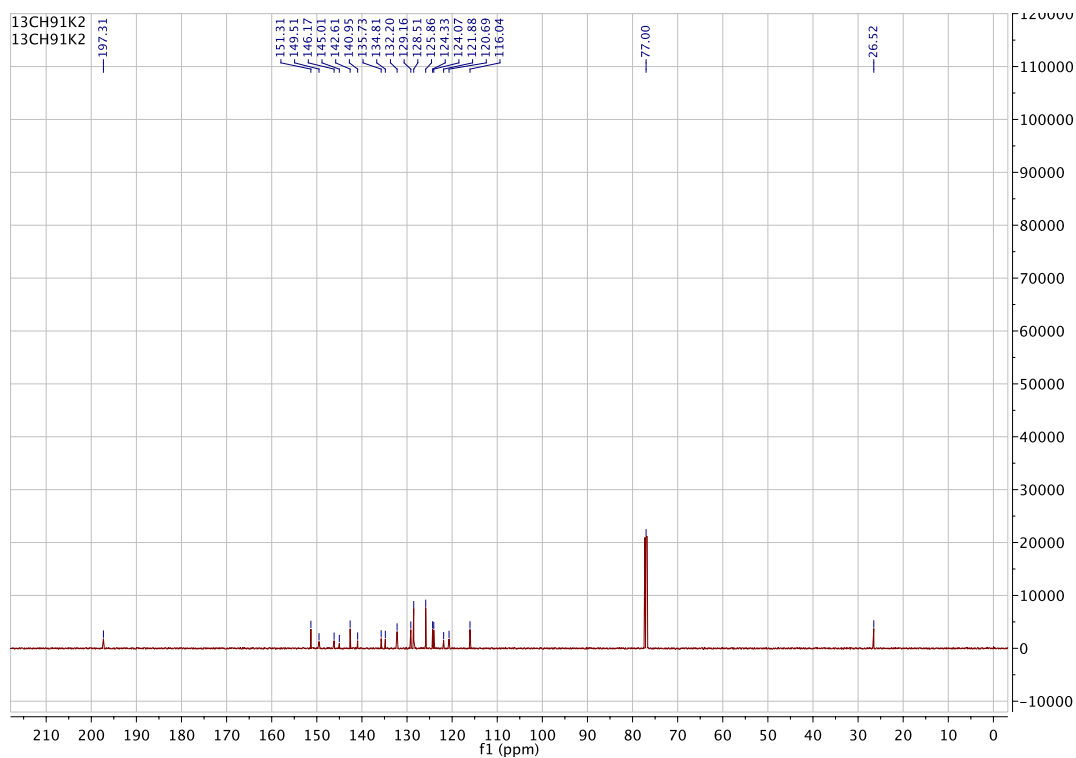


Compound 7e

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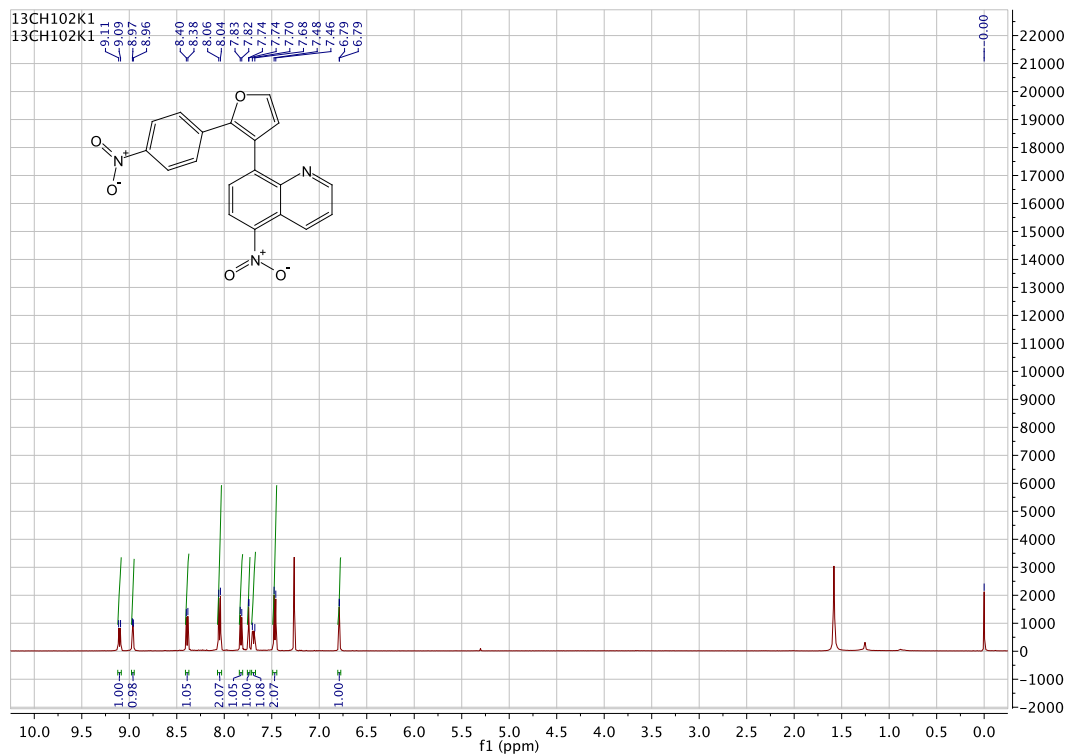


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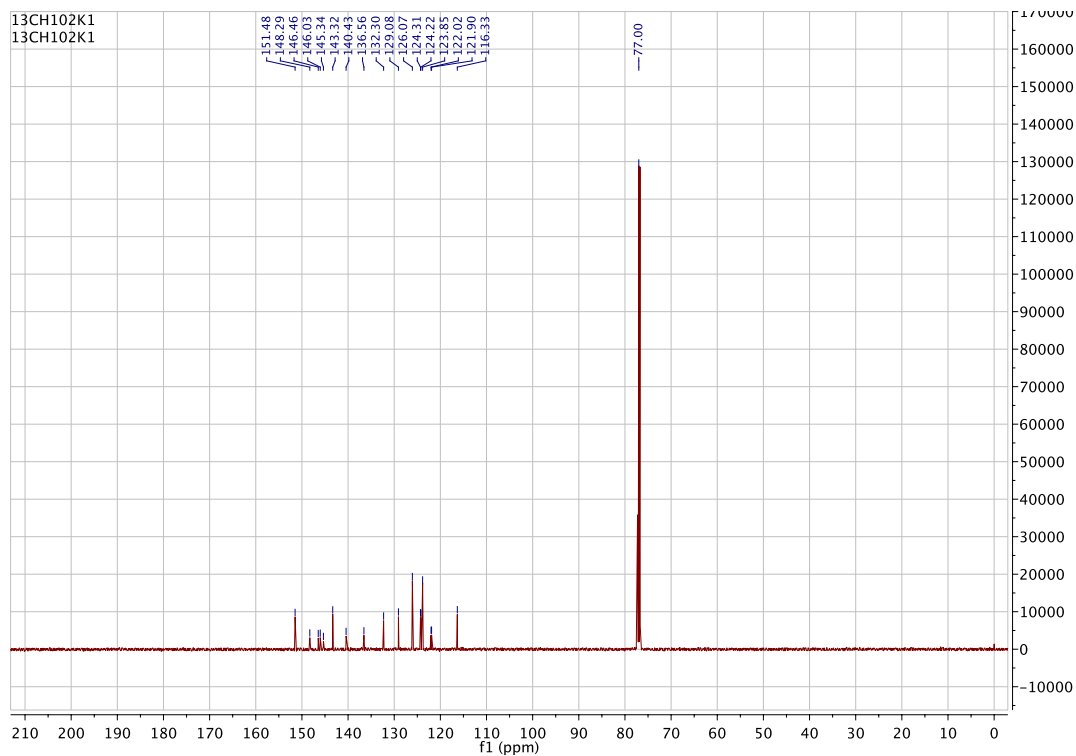


Compound 7f

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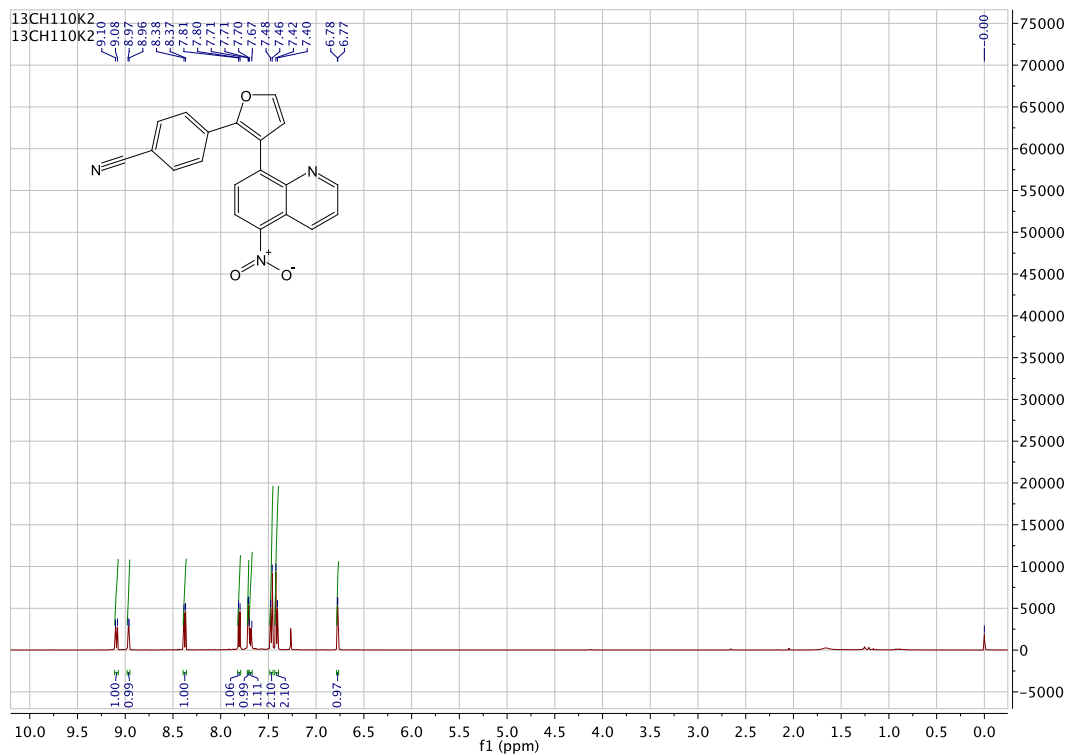


¹³C NMR

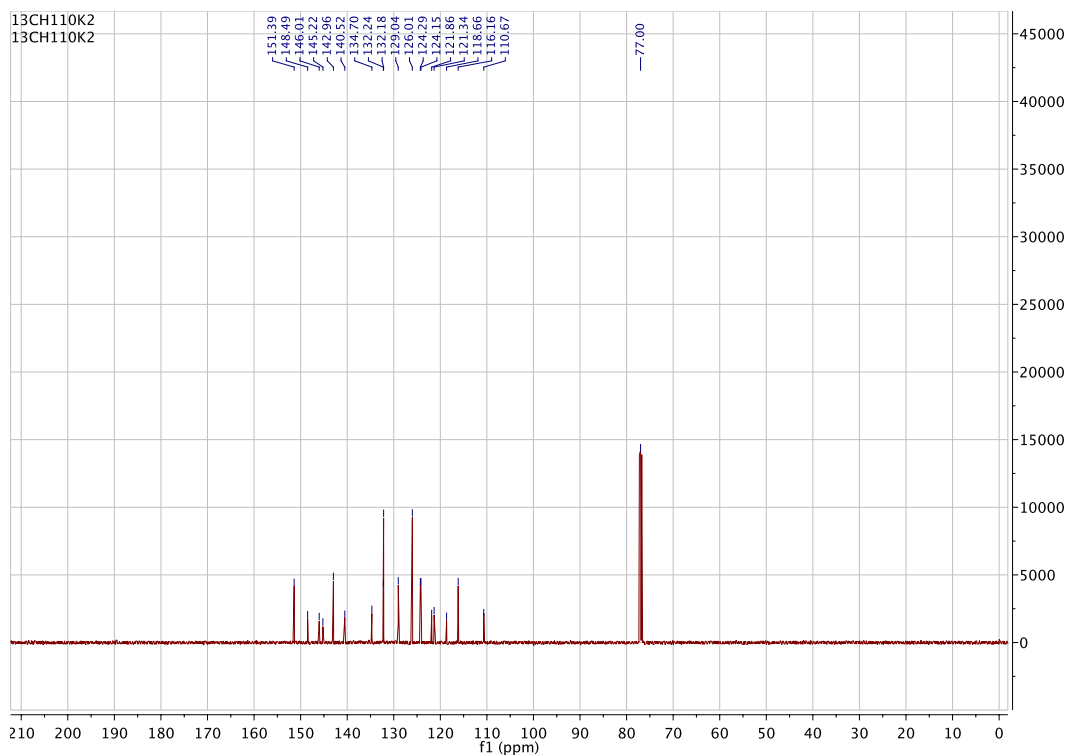


Compound 7g

¹H NMR

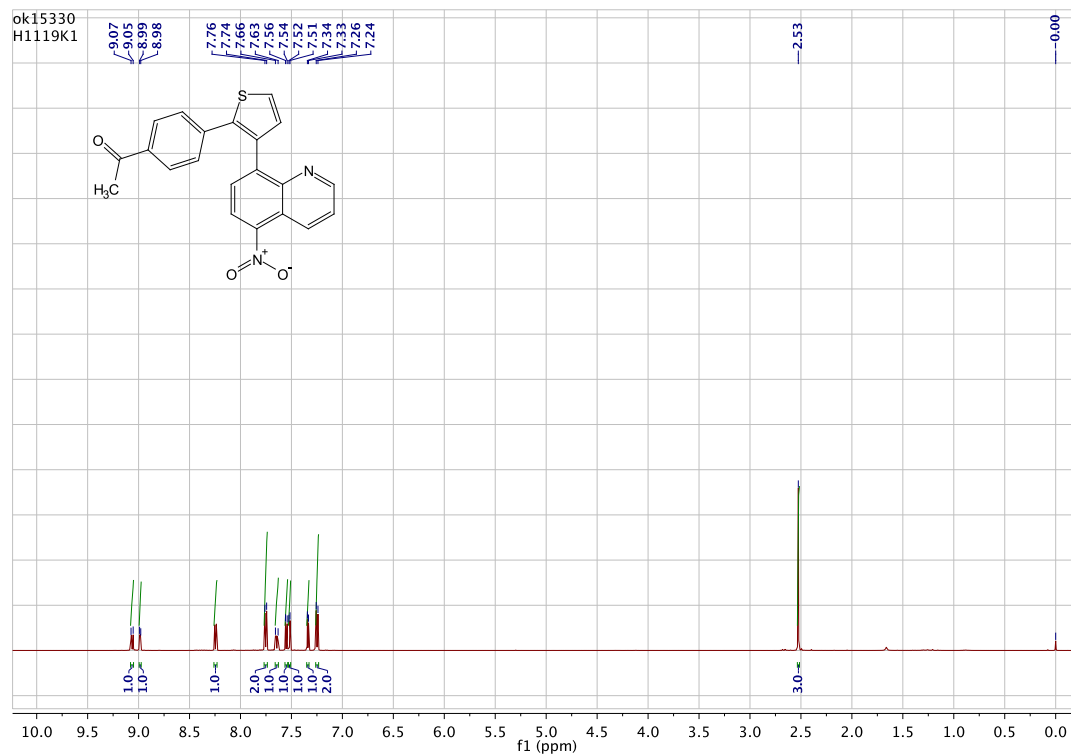


¹³C NMR

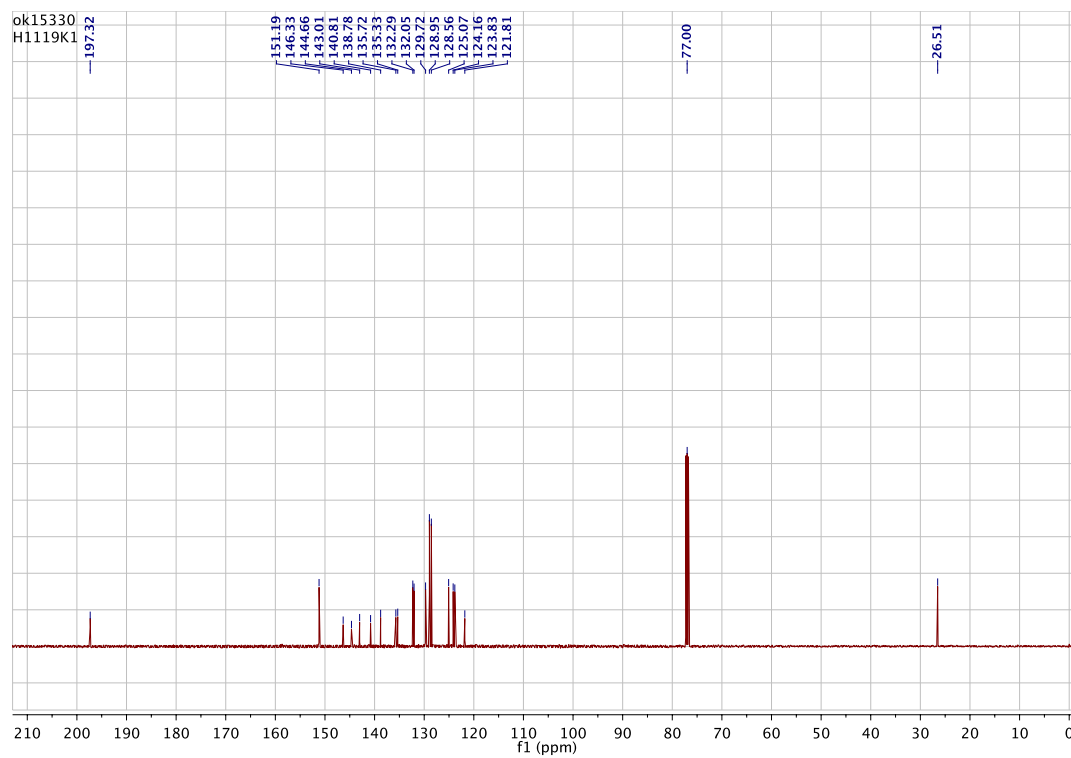


Compound 7h

¹H NMR

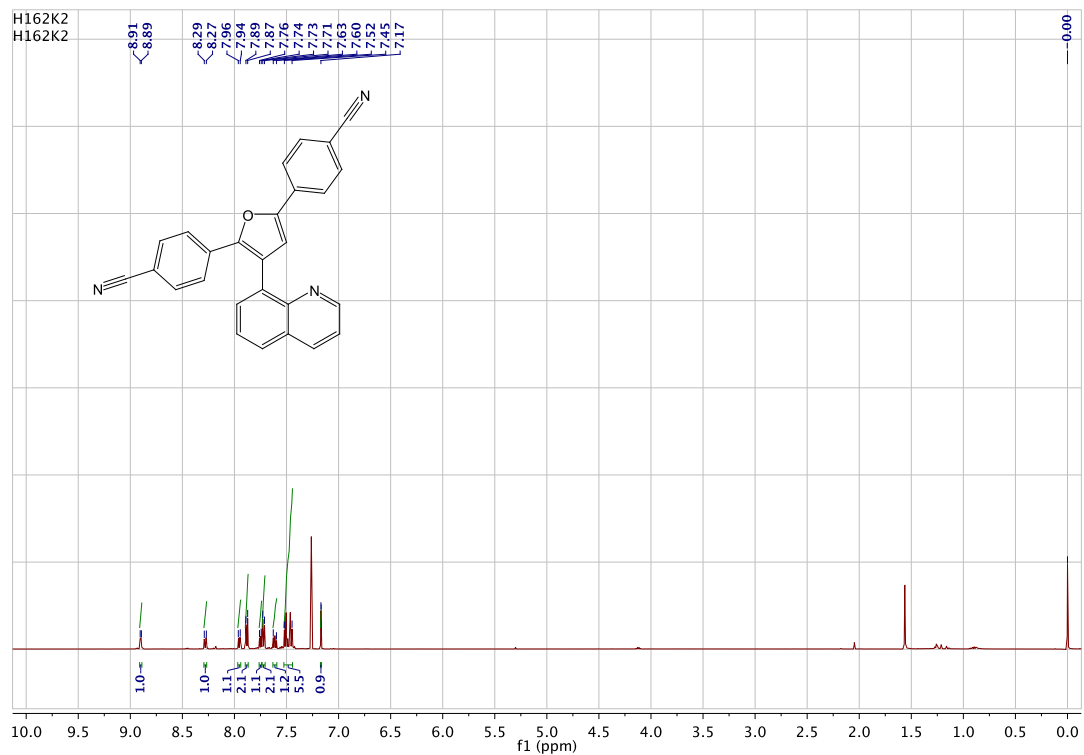


¹³C NMR

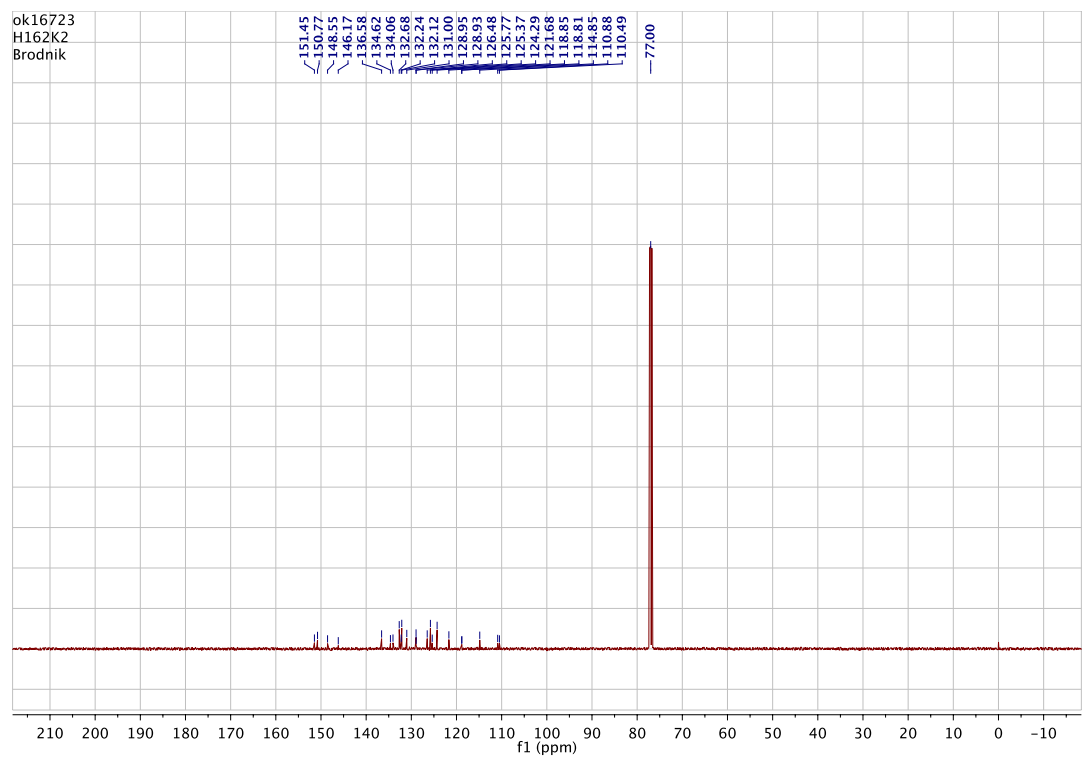


Compound 7ca

¹H NMR

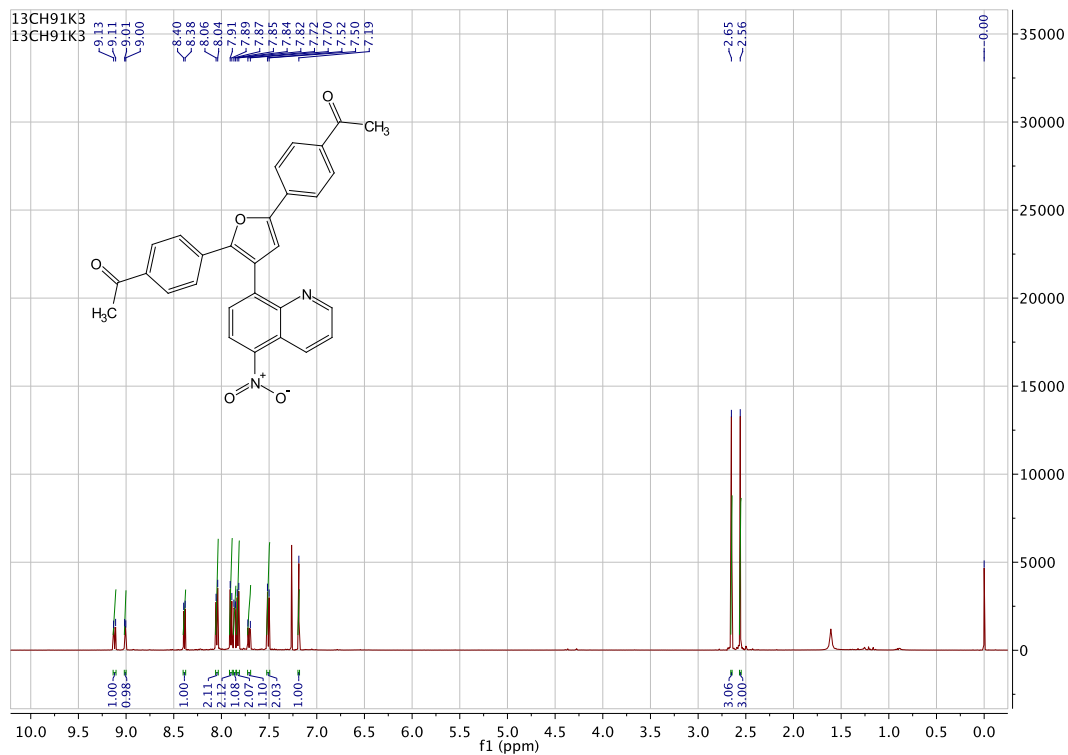


¹³C NMR

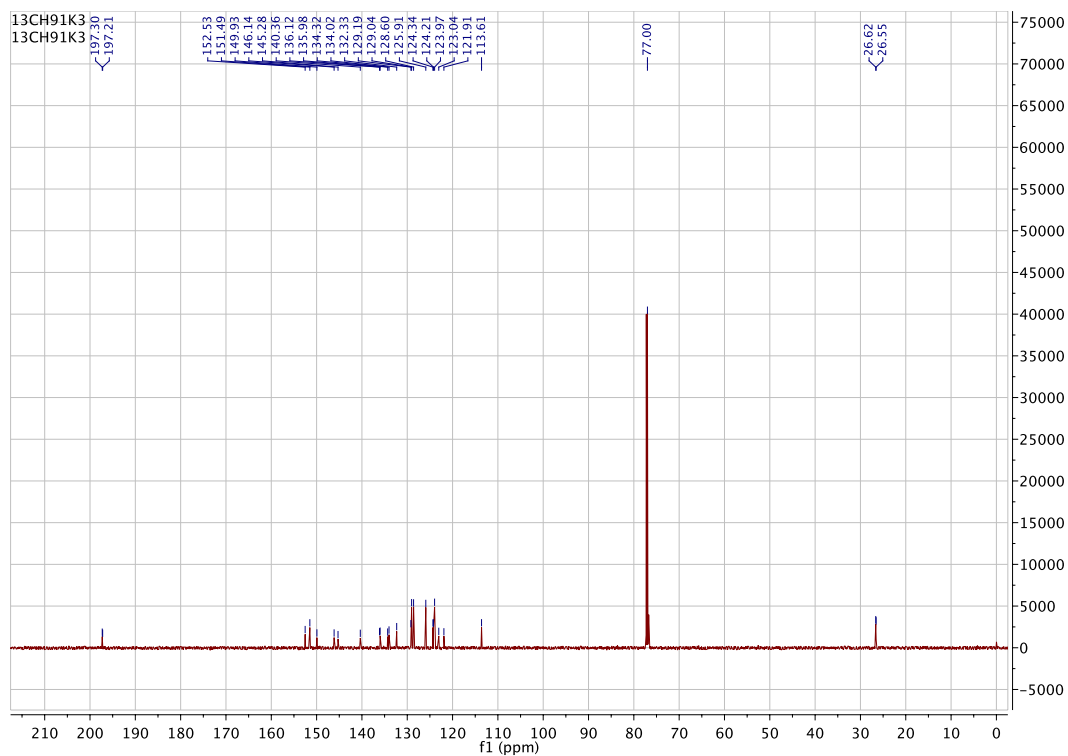


Compound 7ea

¹H NMR

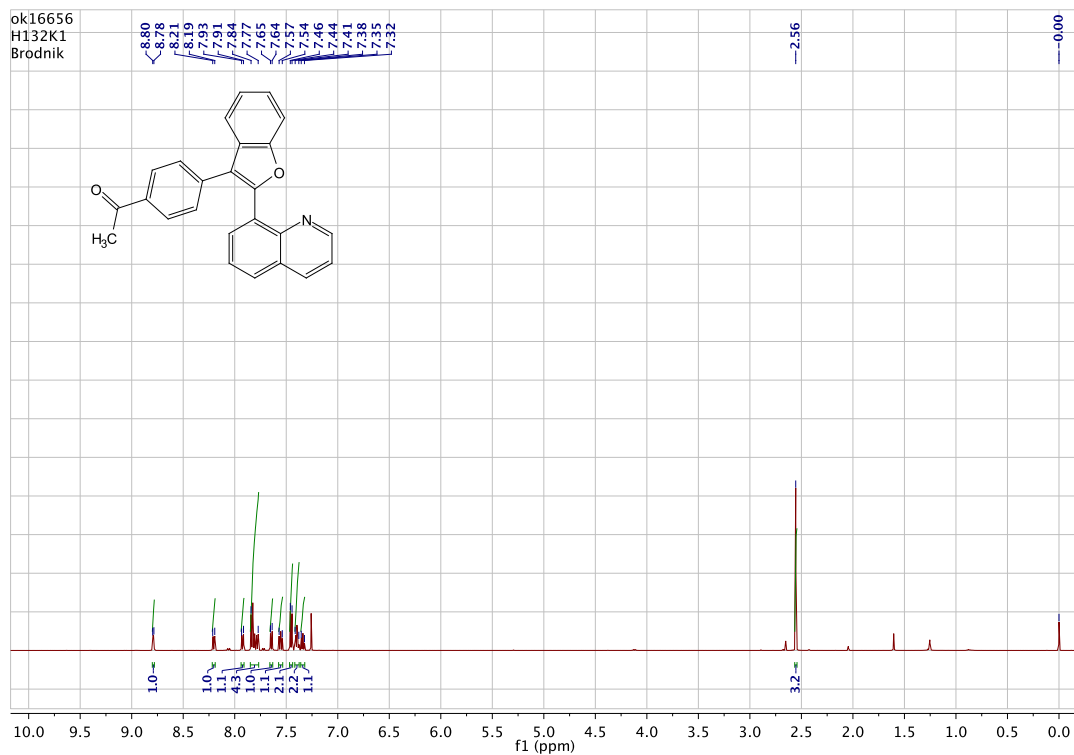


¹³C NMR

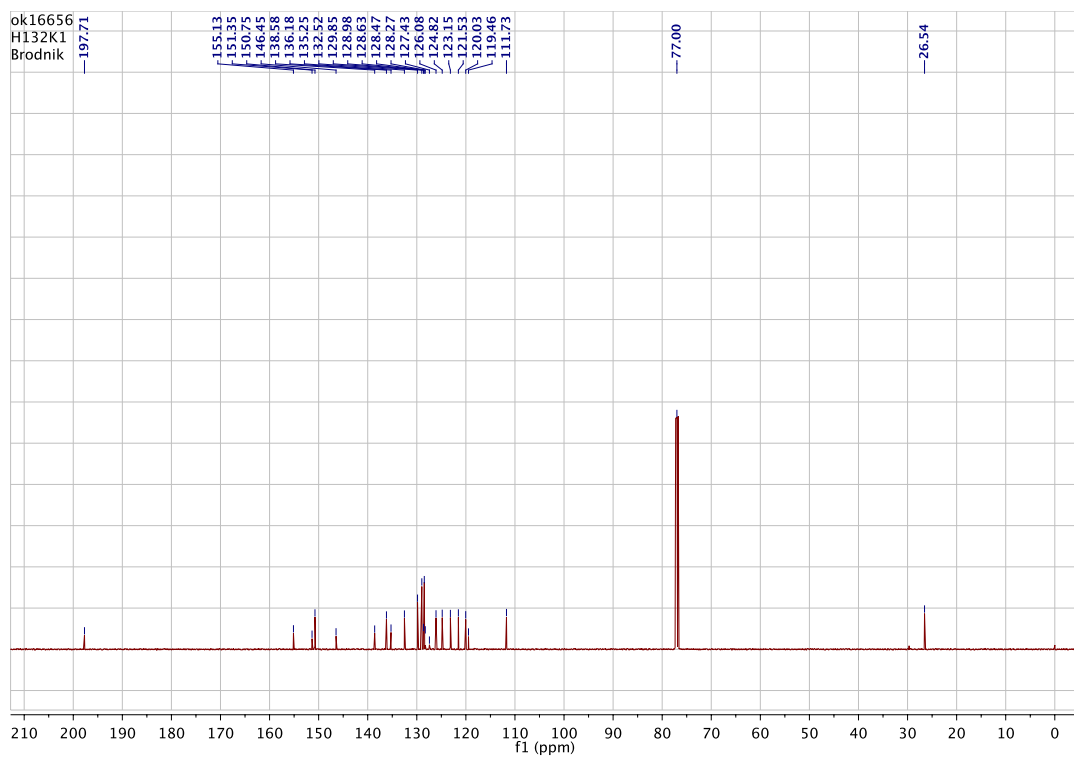


Compound 7i

¹H NMR

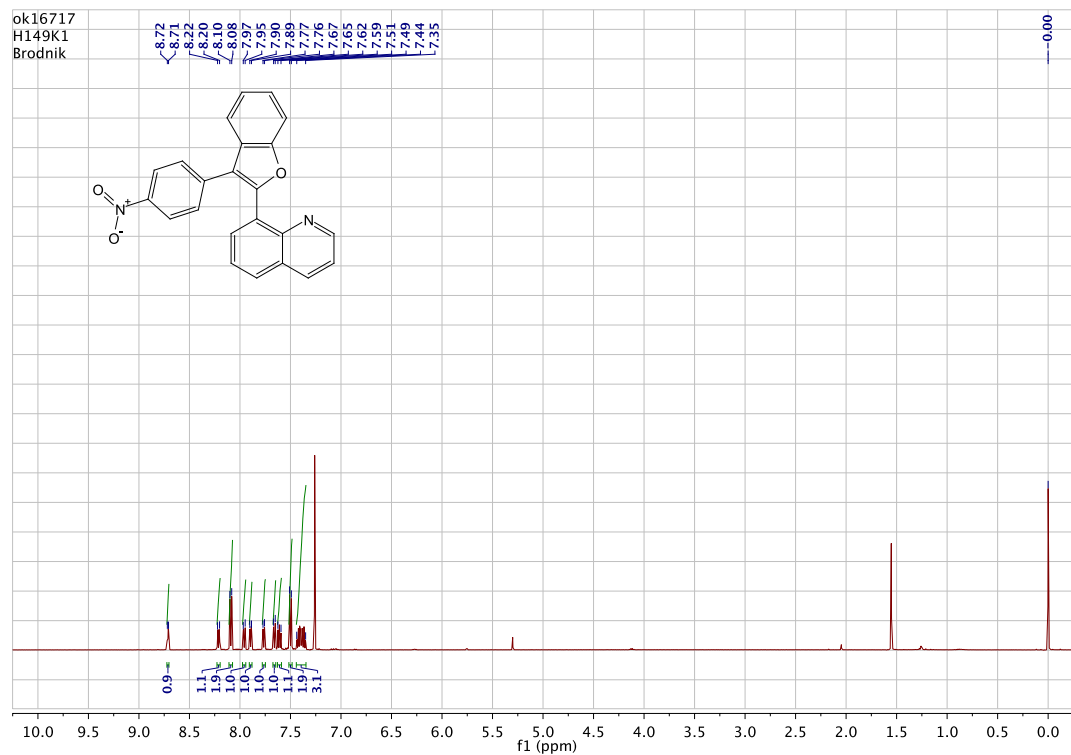


¹³C NMR

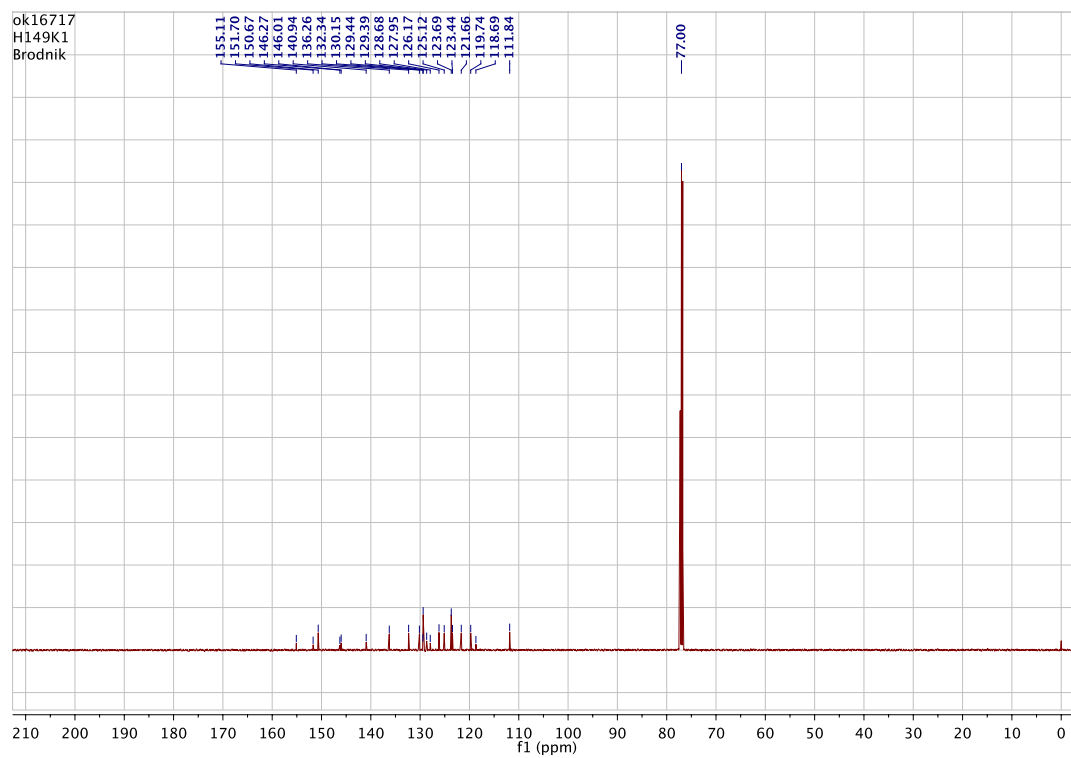


Compound 7j

¹H NMR

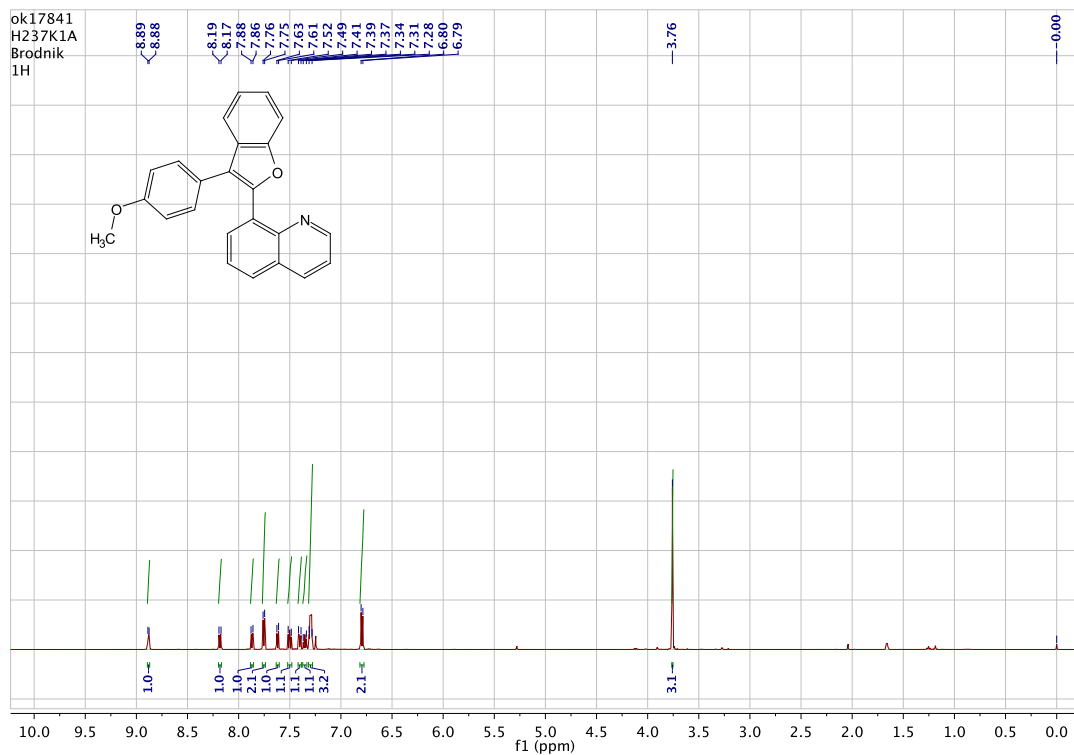


¹³C NMR

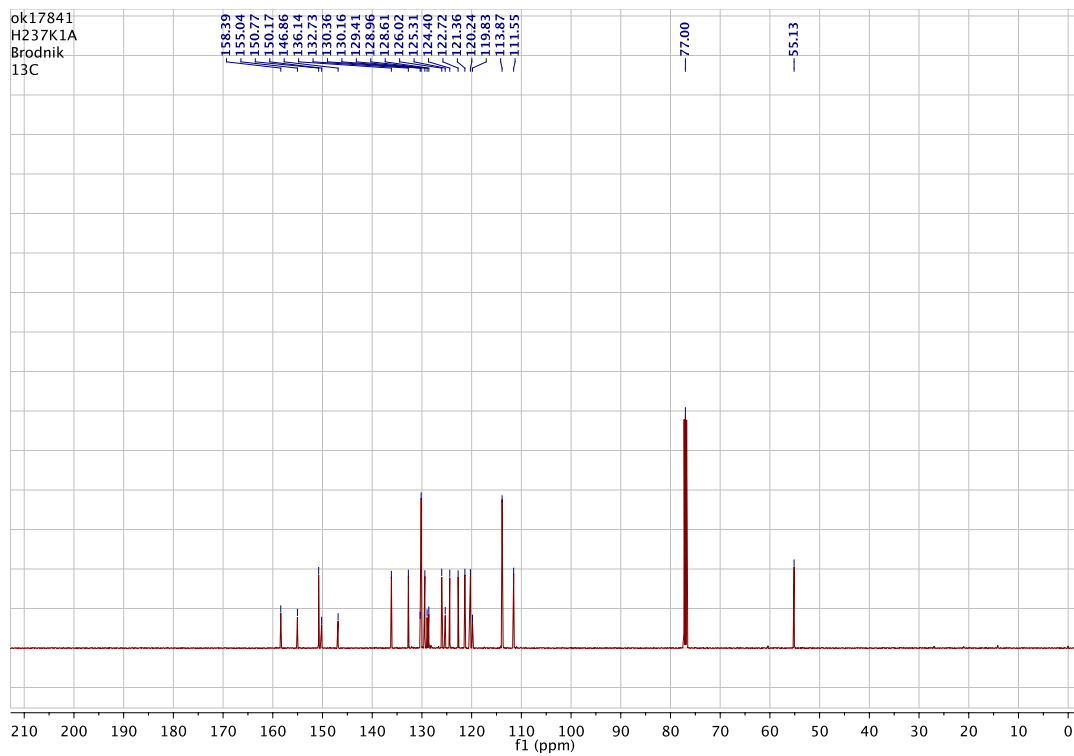


Compound 71

¹H NMR

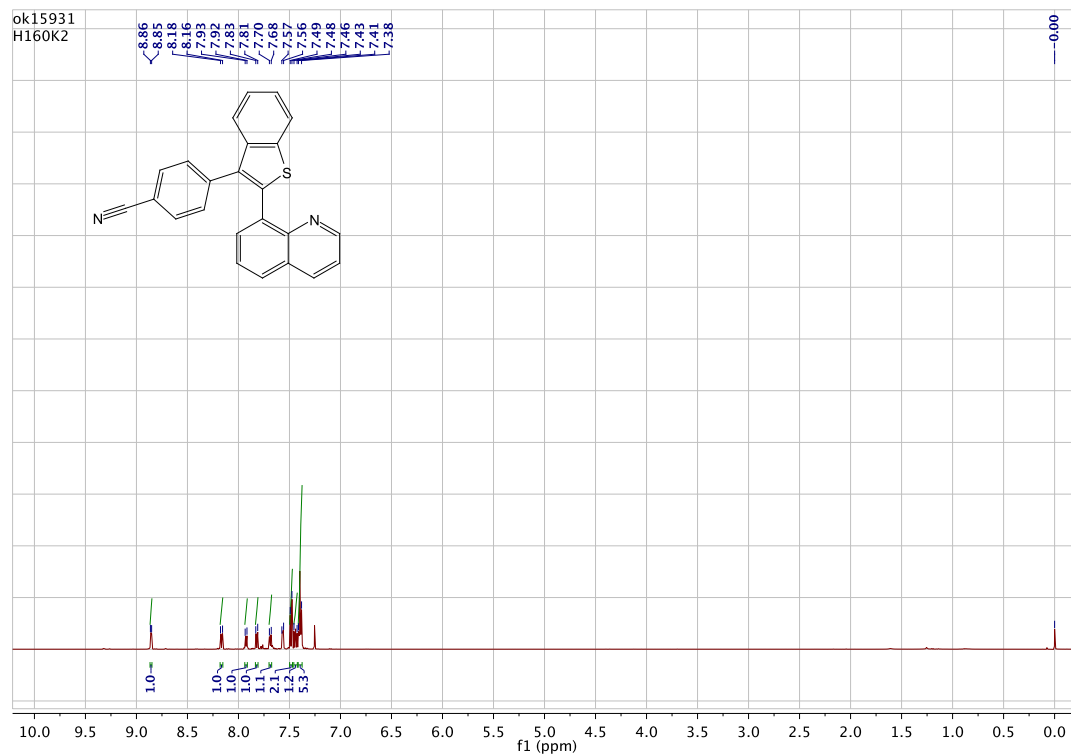


¹³C NMR

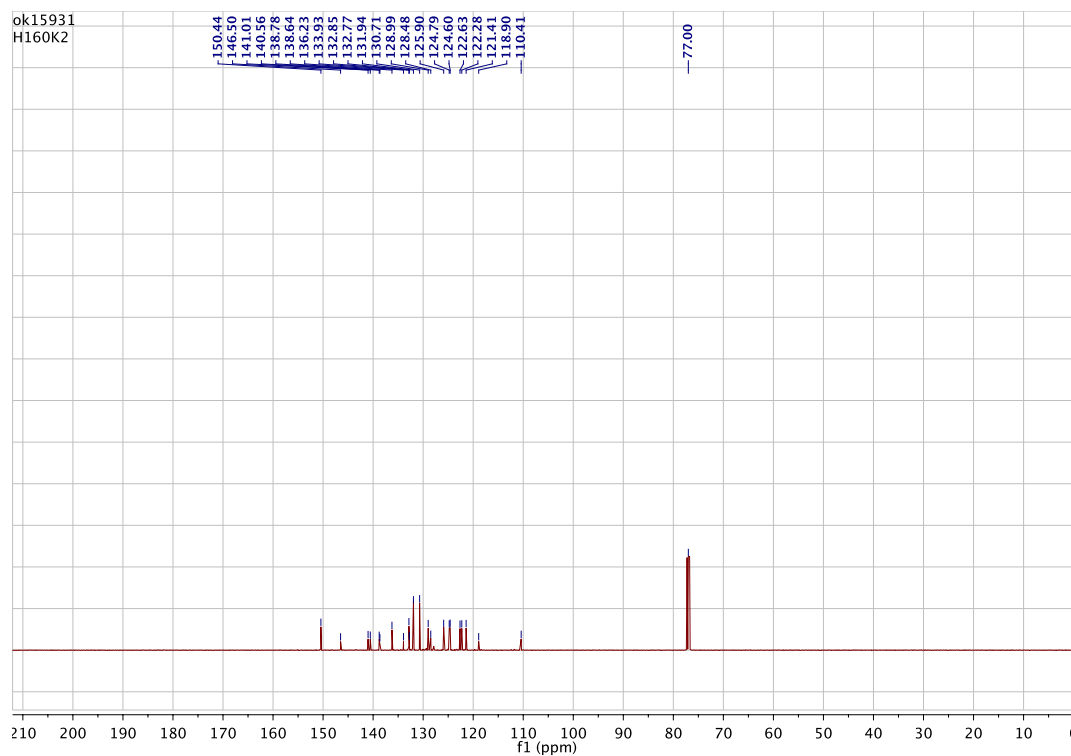


Compound 7m

¹H NMR

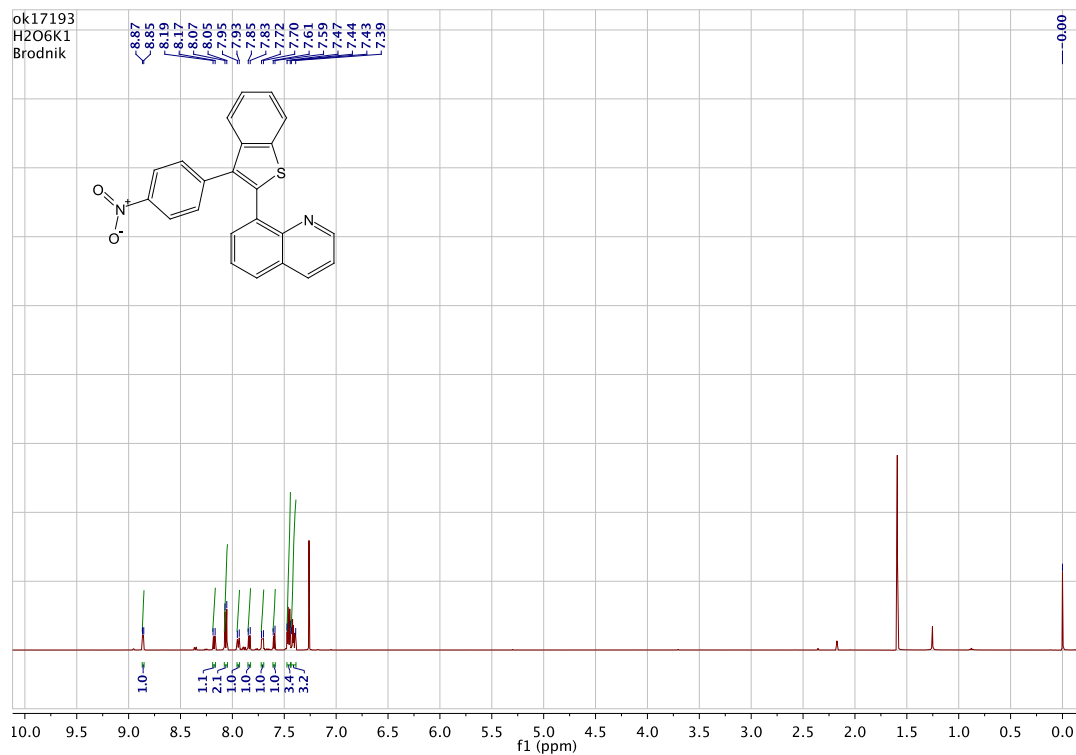


¹³C NMR

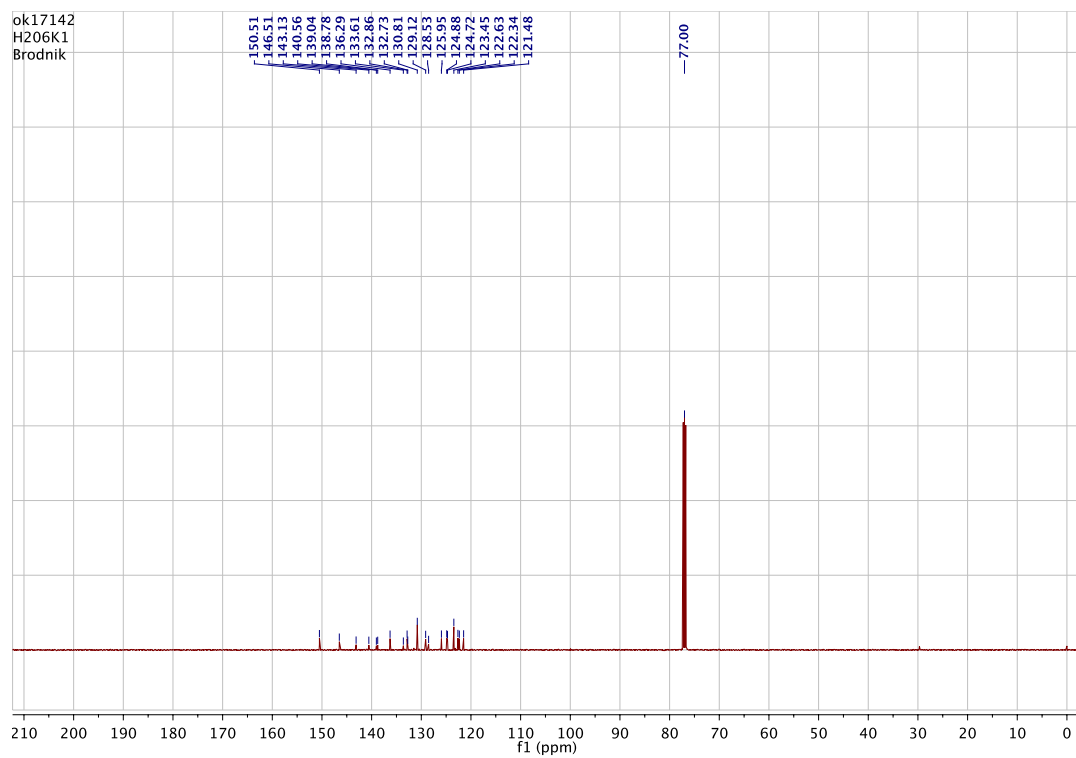


Compound 7n

¹H NMR

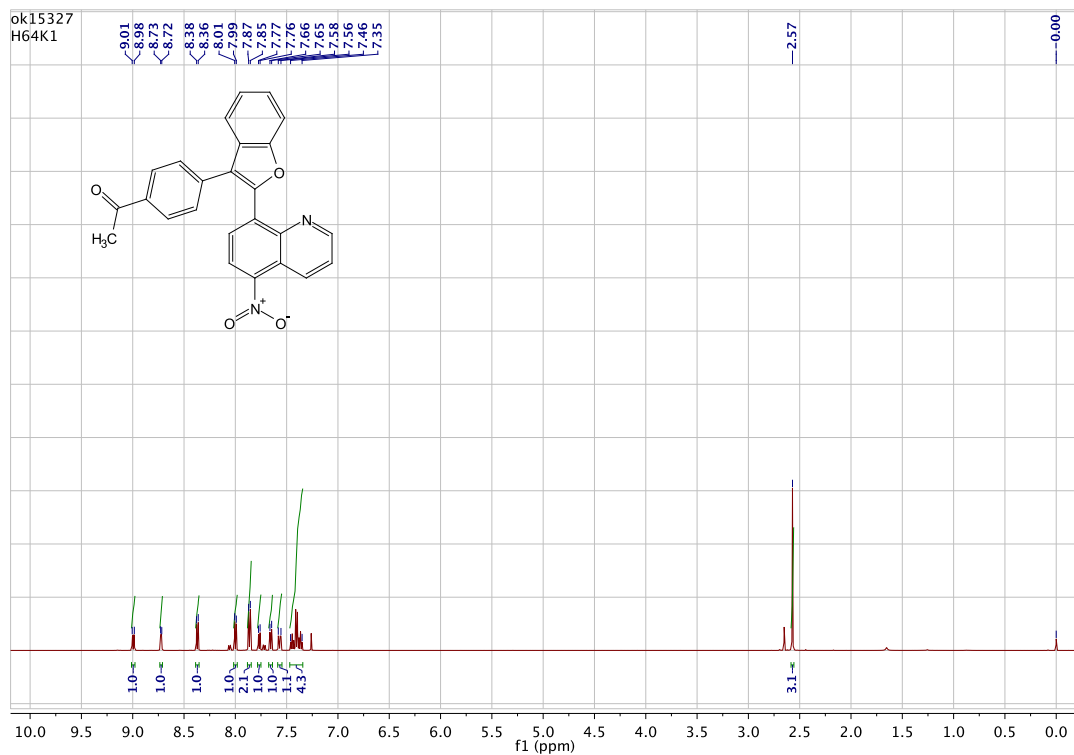


¹³C NMR

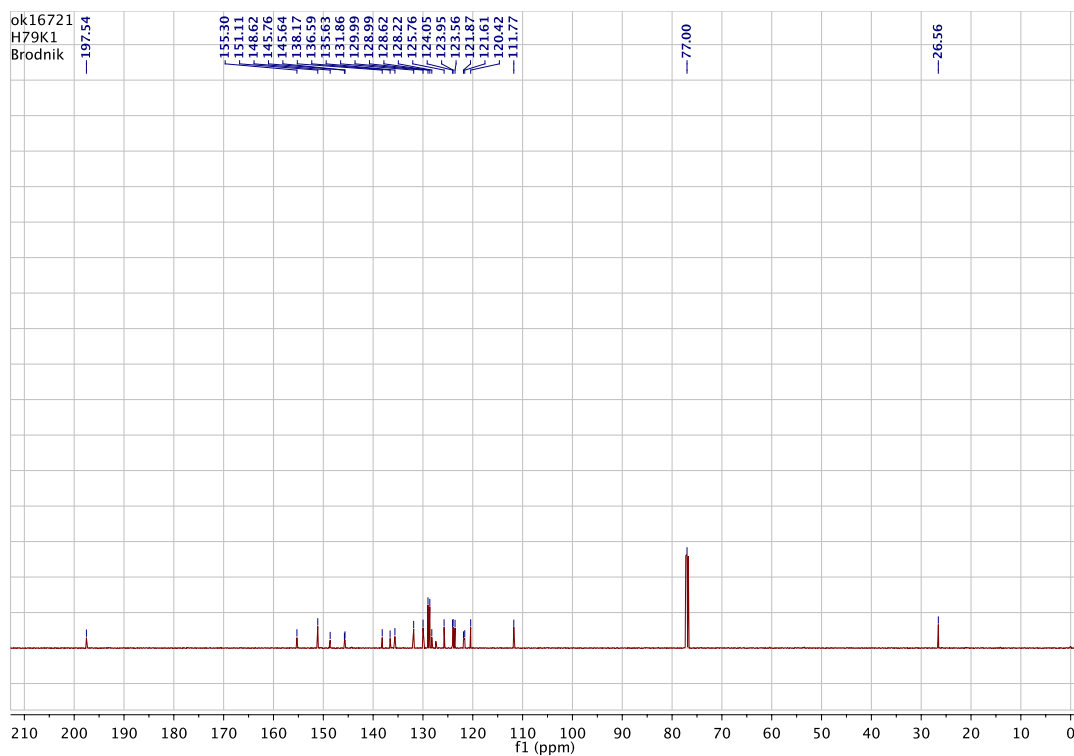


Compound 7o

¹H NMR

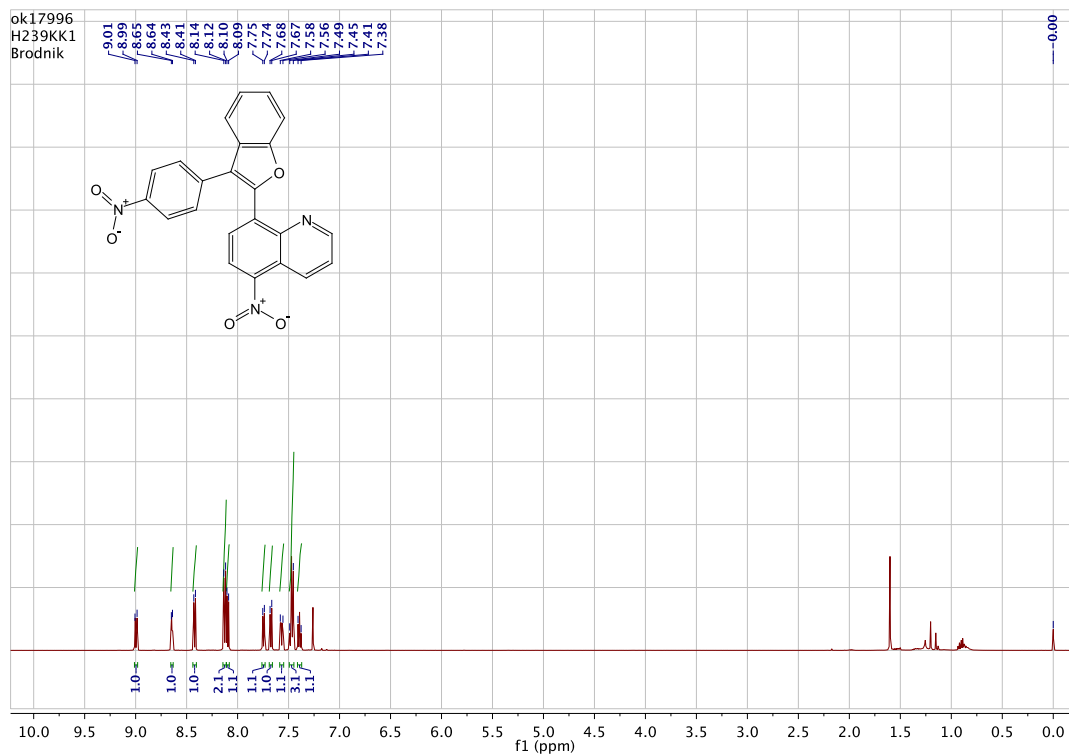


¹³C NMR

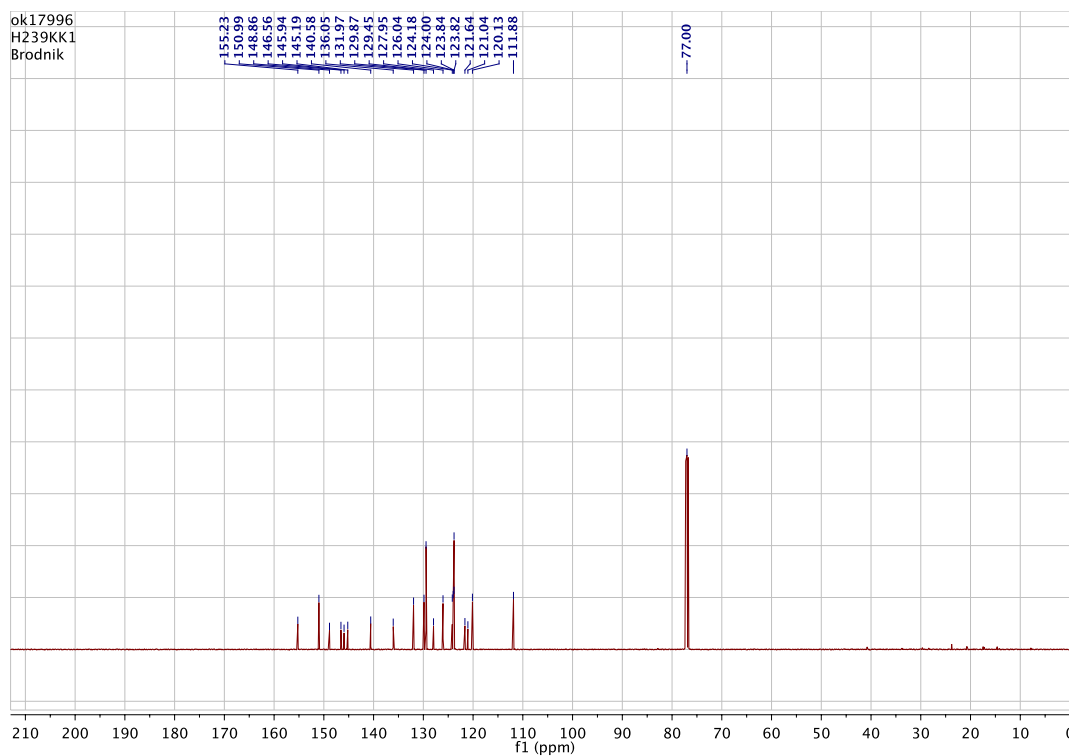


Compound 7p

¹H NMR

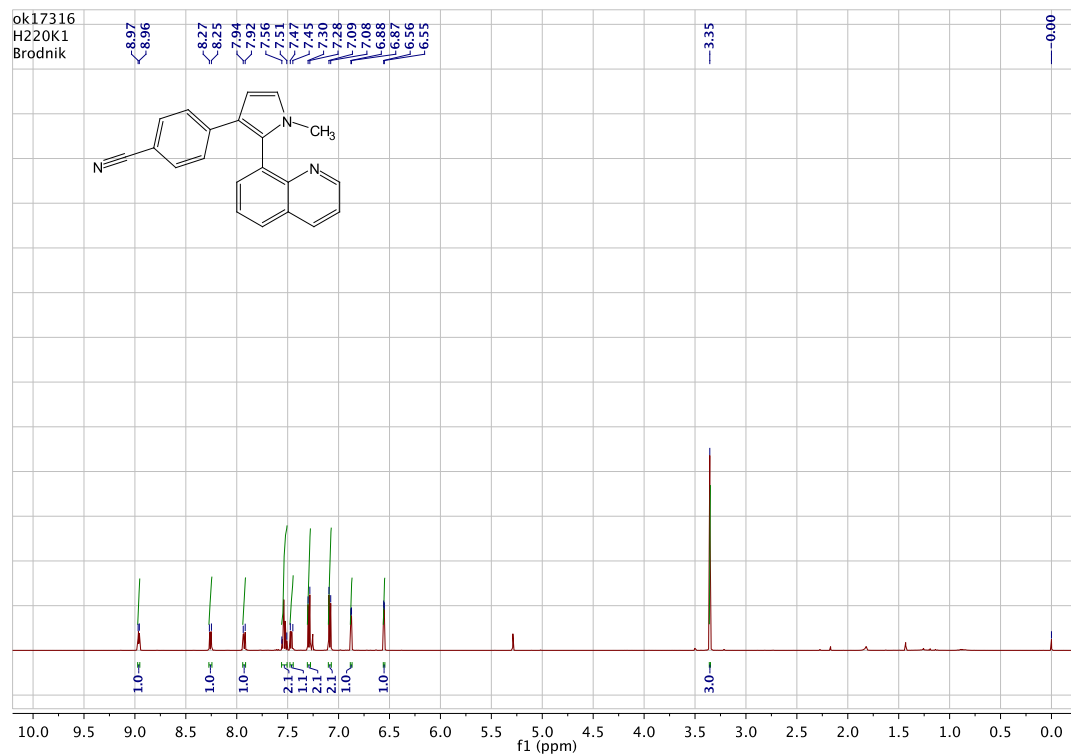


¹³C NMR

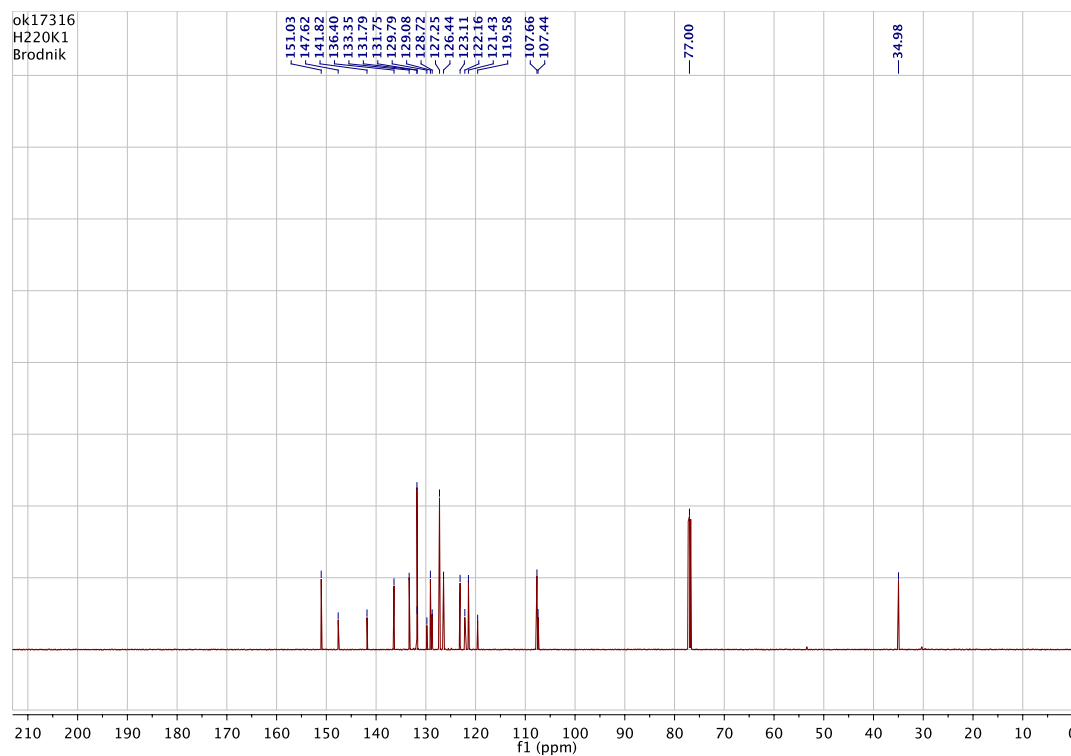


Compound 7q

¹H NMR

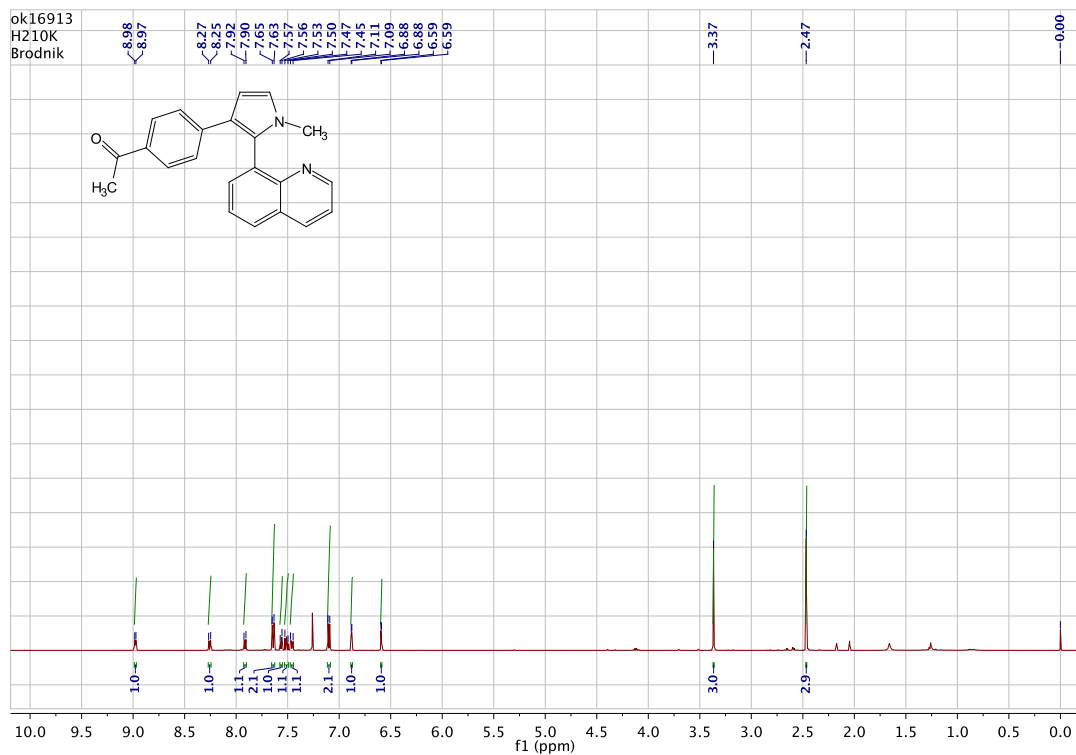


¹³C NMR

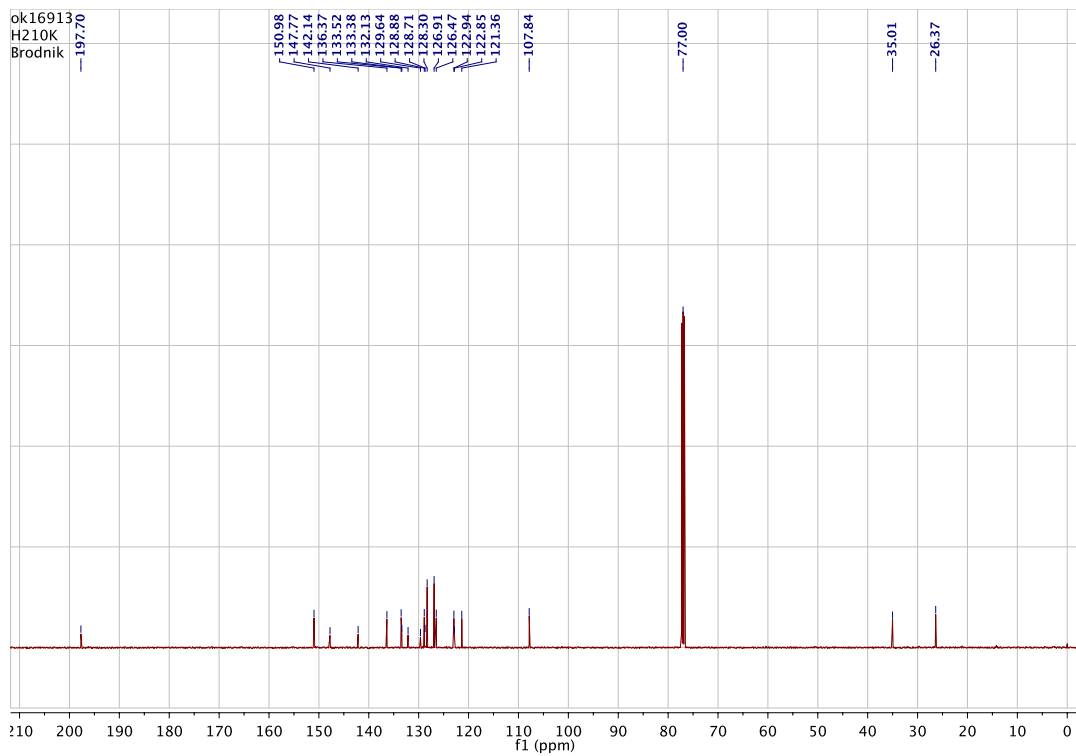


Compound 7s

¹H NMR

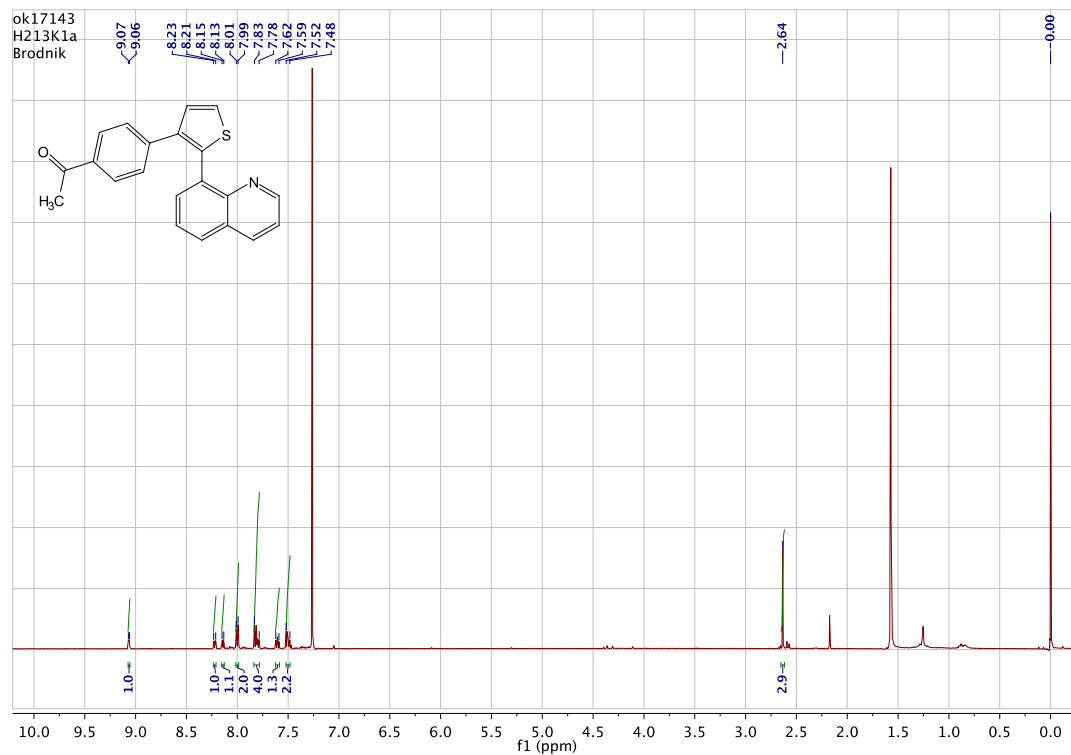


¹³C NMR

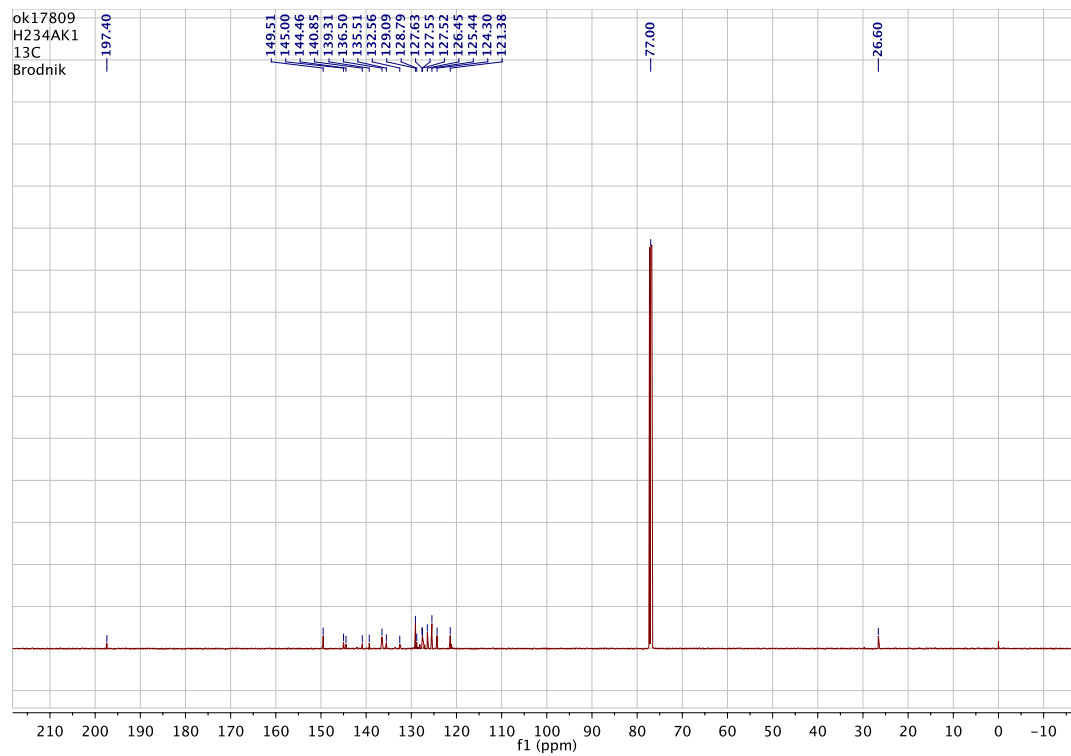


Compound 7t

¹H NMR

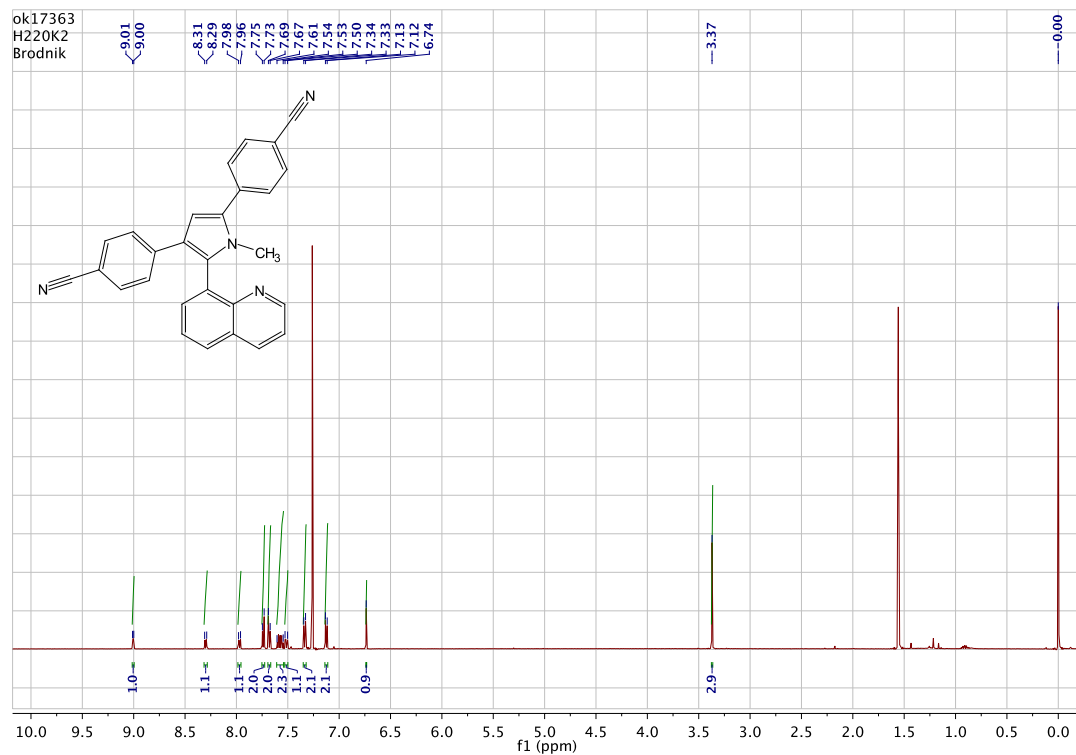


¹³C NMR

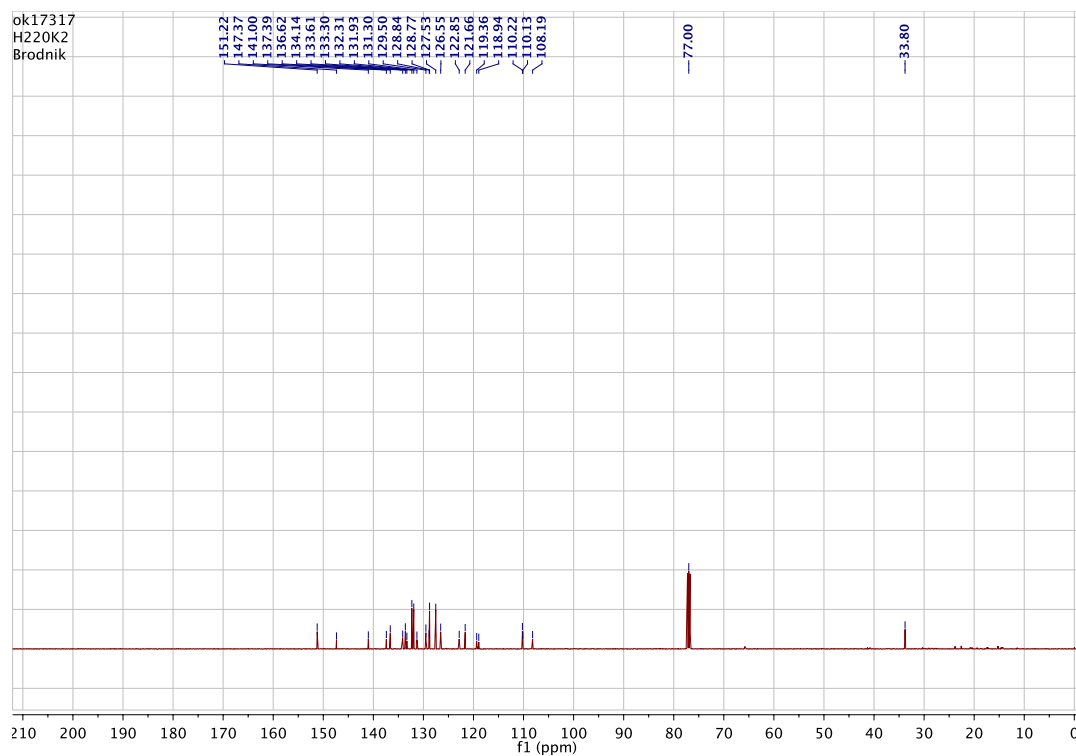


Compound 7qa

¹H NMR

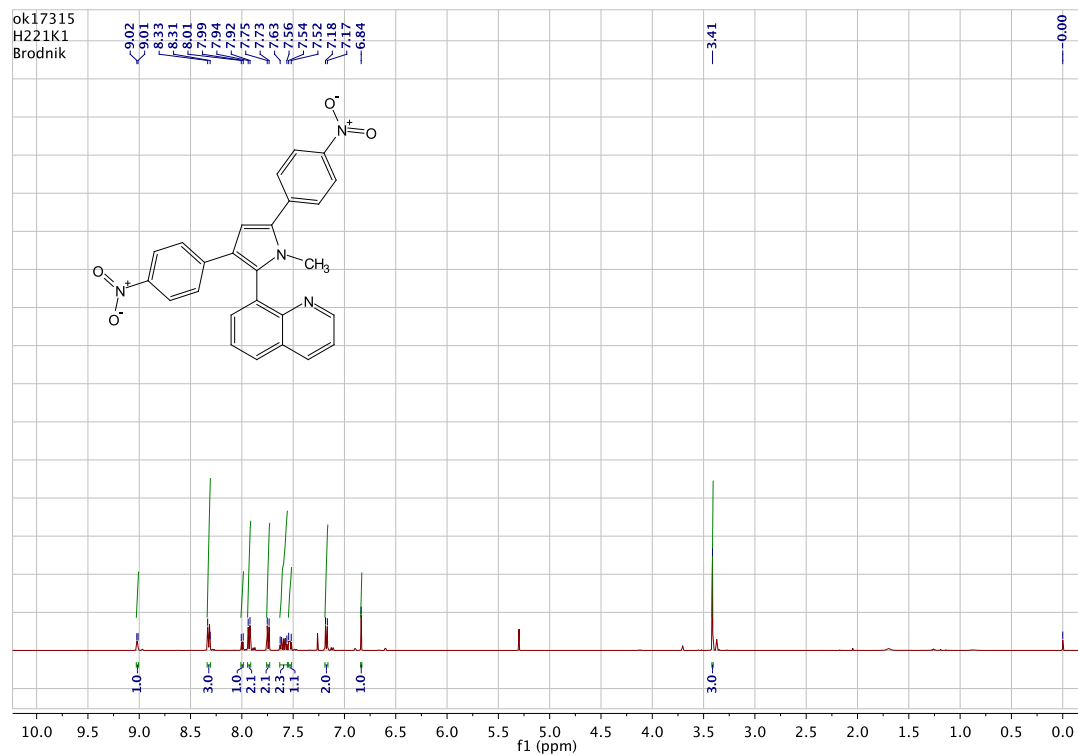


¹³C NMR

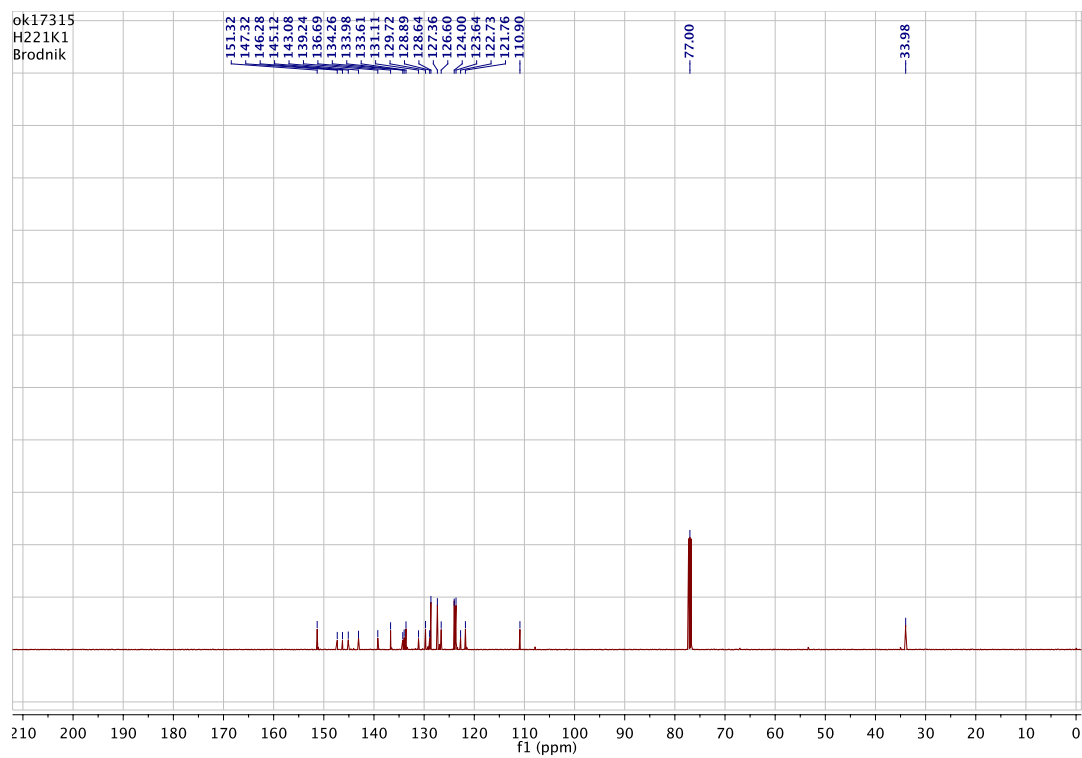


Compound 7ra

^1H NMR

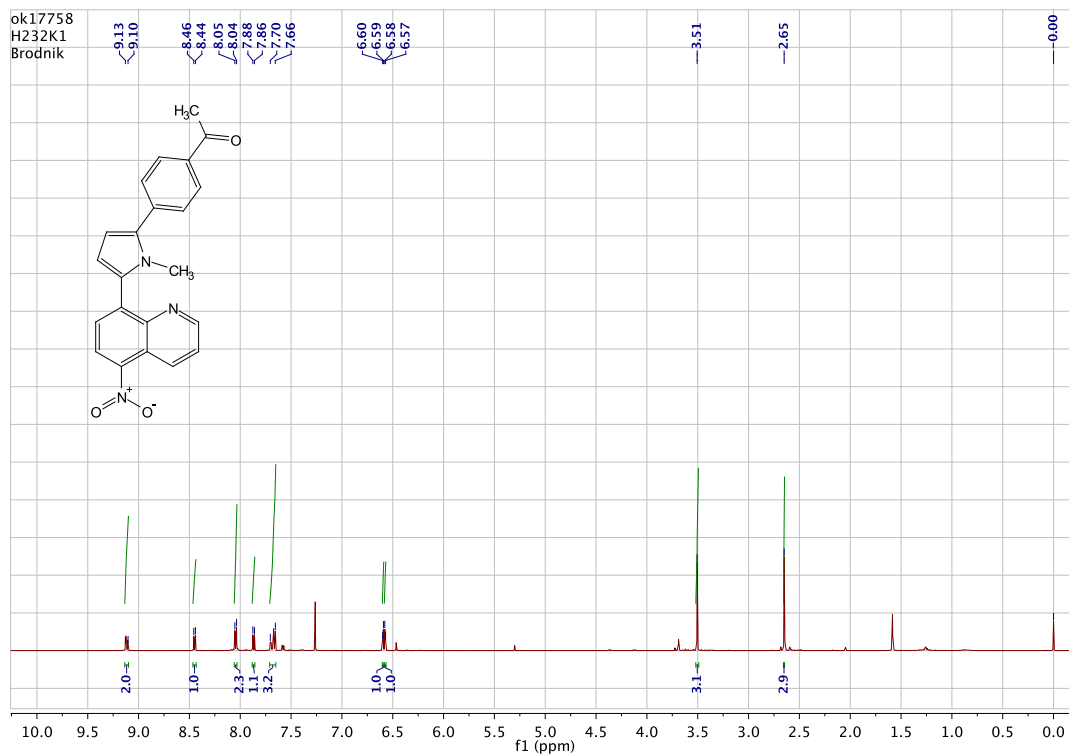


^{13}C NMR

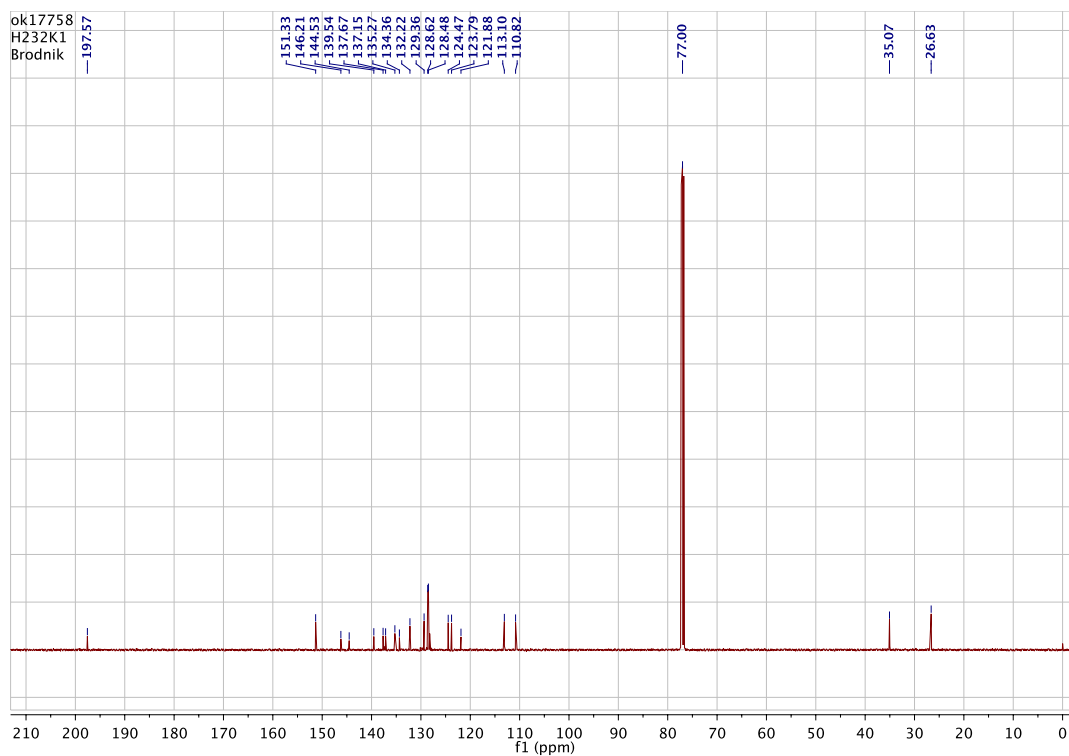


Compound 7u

¹H NMR

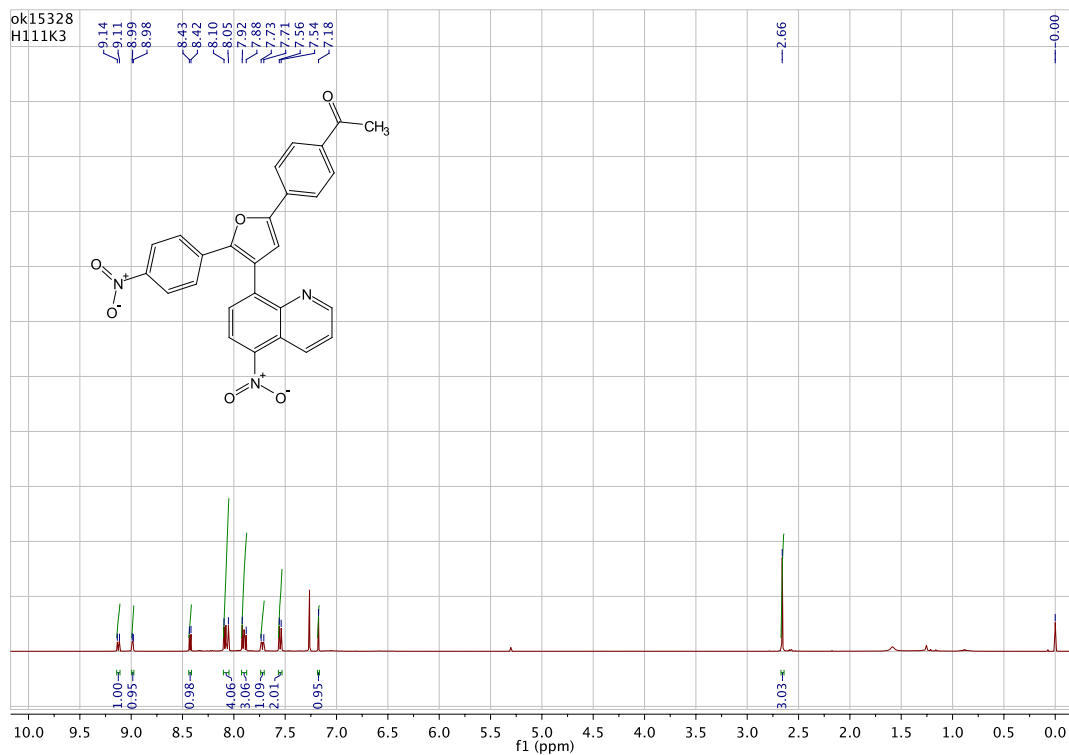


¹³C NMR

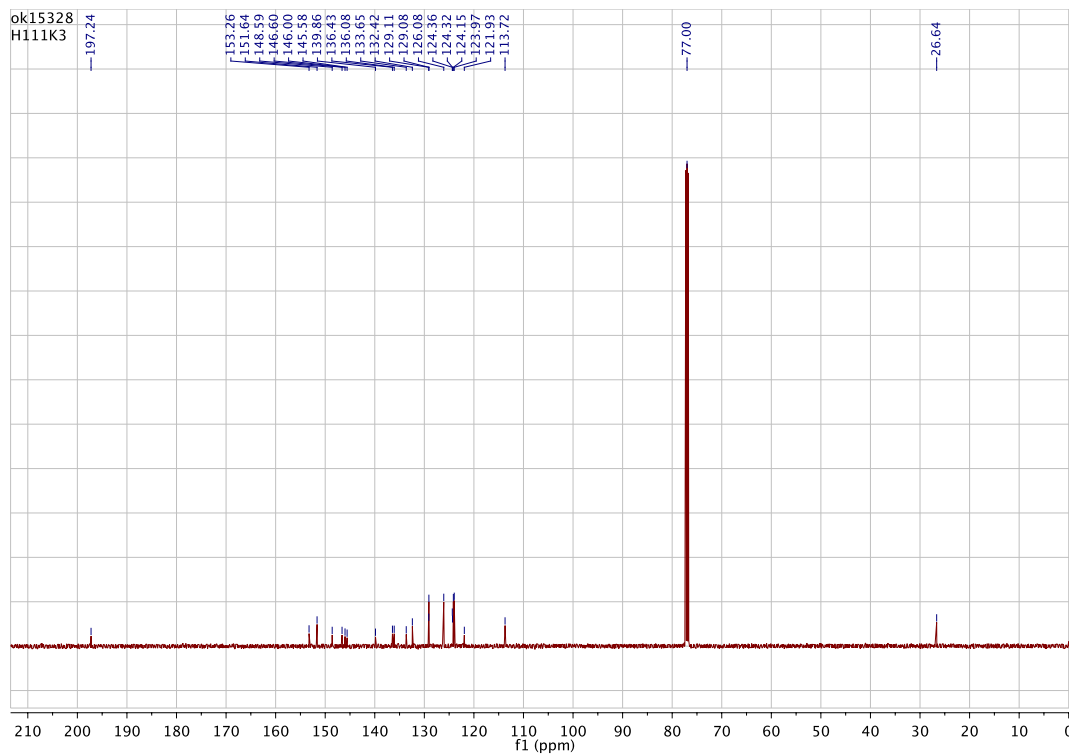


Compound 8

¹H NMR

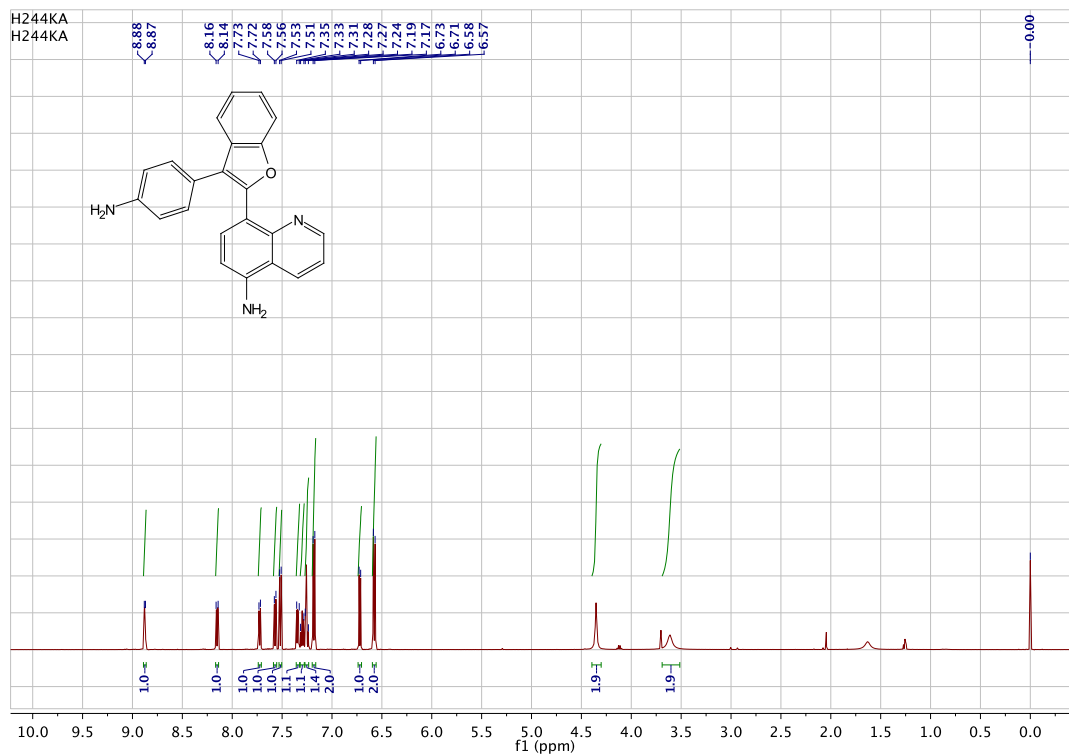


¹³C NMR

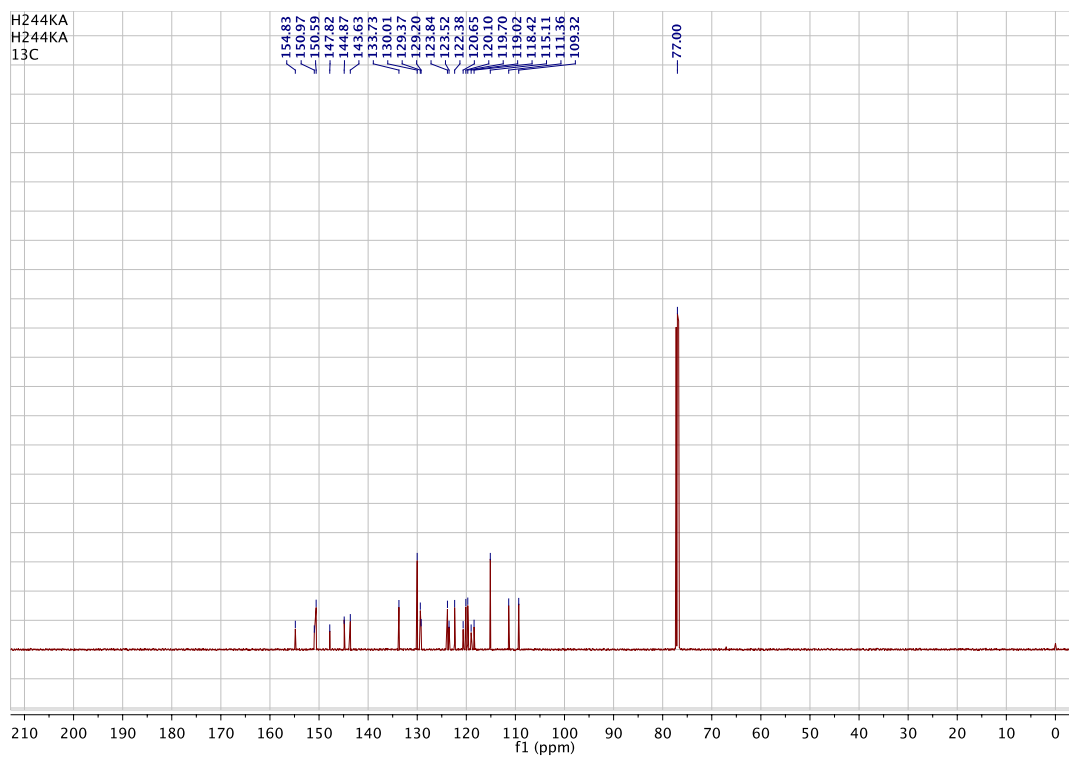


Compound 9

¹H NMR

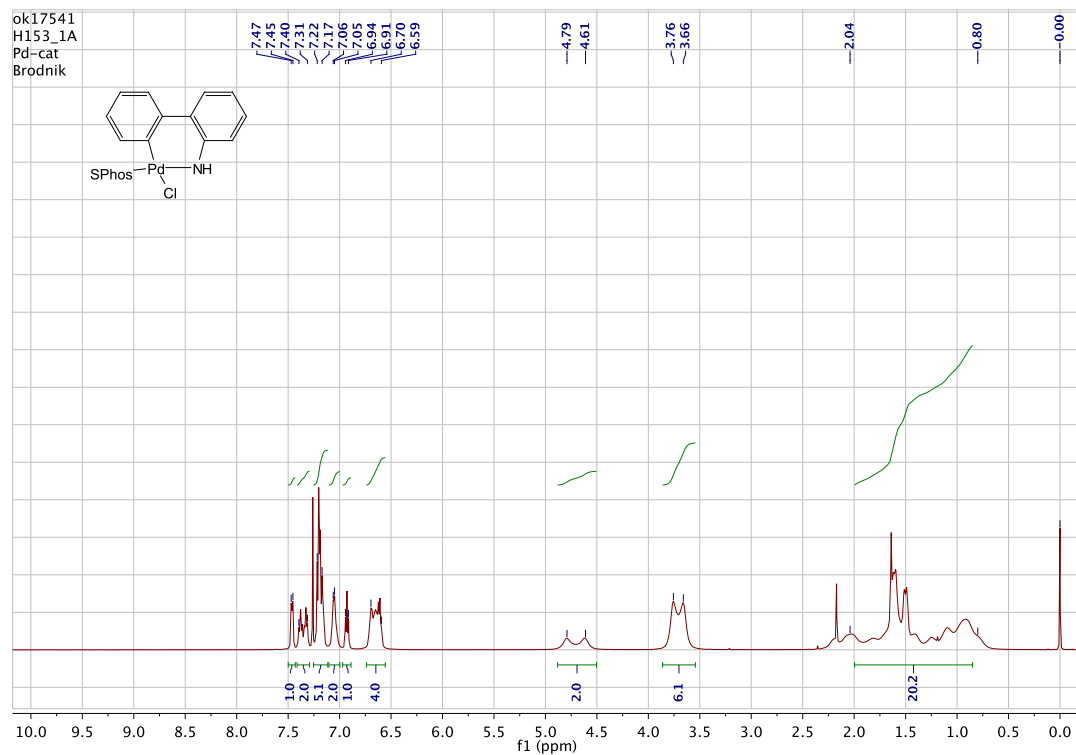


¹³C NMR

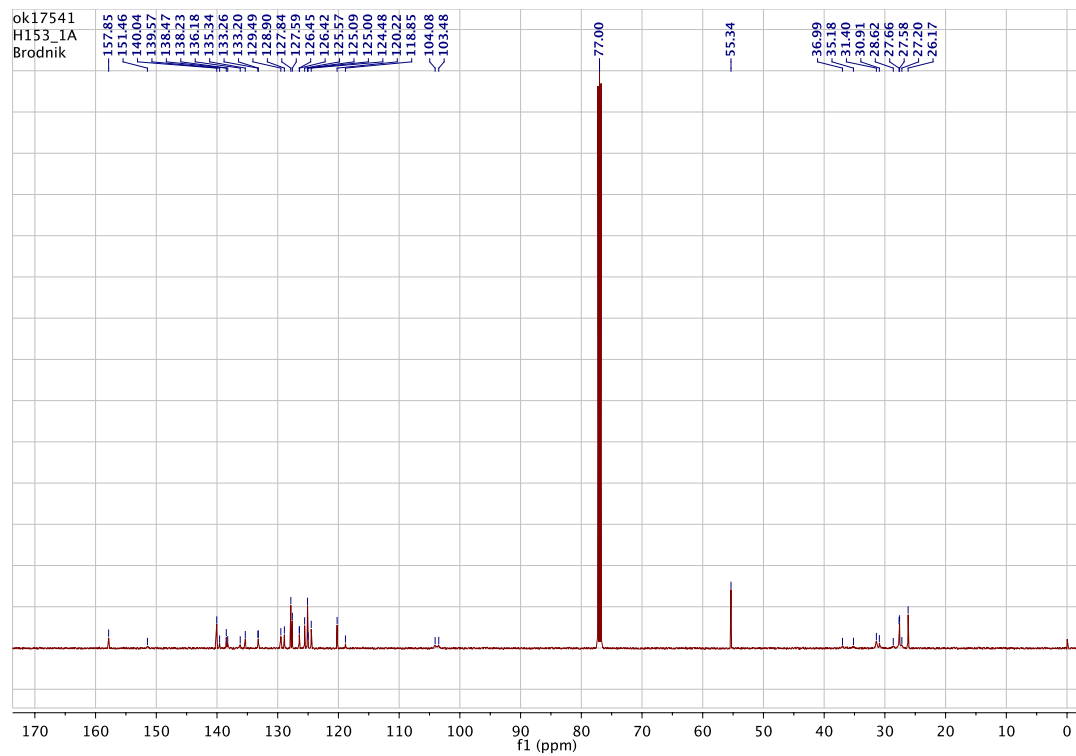


Pd catalyst A

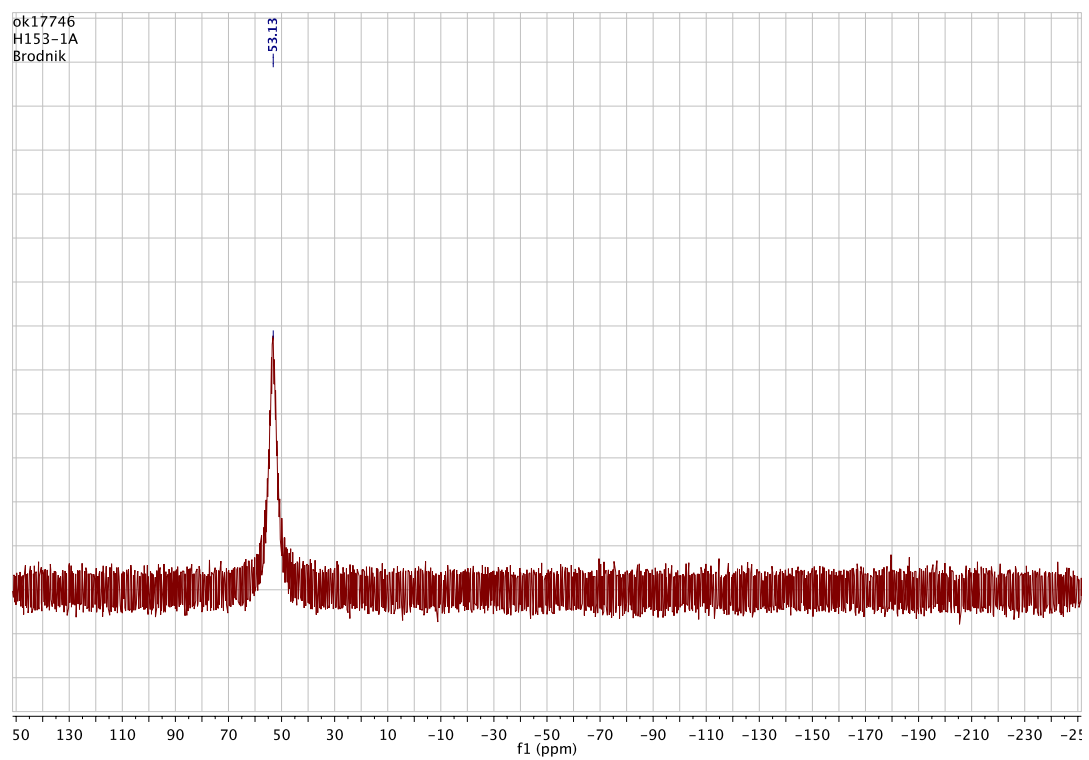
¹H NMR



¹³C NMR



³¹P NMR



¹ T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073.

² J. Albert, J. Granell, J. Zafrilla, M. Font-Barida, X. Solans, *J. Organometallic Chem.* **2005**, *690*, 422.