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Di Pietro, O; Vicente-Garca, E; Taylor, MC; Berenguer, D; Viayna, E; Lanzoni, A; Sola, I; Sayago, H; Riera, C; Fisa, R; Clos, MV; Prez, B; Kelly, JM; Lavilla, R; Muoz-Torrero, D (2015) Multicomponent reaction-based synthesis and biological evaluation of tricyclic heterofused quinolines with multi-trypanosomatid activity. *European journal of medicinal chemistry*, 105. pp. 120-137. ISSN 0223-5234 DOI: <https://doi.org/10.1016/j.ejmech.2015.10.007>

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DOI: [10.1016/j.ejmech.2015.10.007](https://doi.org/10.1016/j.ejmech.2015.10.007)

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Supplementary Material

Multicomponent reaction-based synthesis and biological evaluation of tricyclic heterofused quinolines with multi-trypanosomatid activity

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E-mail address: dmunoztorrero@ub.edu (D. Muñoz-Torrero).

- S3 **Table S1.** Calculated molecular properties of the tested compounds.
- S4 **Table S2.** Calculated CNS MPO desirability scores of the tested compounds.
- S5 **Table S3.** Reported and experimental permeability values of the commercial drugs used for the PAMPA-BBB assay validation.
- S5 **References.**
- S6 **Copies of ^1H and ^{13}C NMR spectra of the tested compounds.**

Table S1

Calculated molecular properties of the novel heterofused quinolines and related compounds.^a

Compd	miLogP	TPSA	MW	nON	nOHNH	nrotb	volume	nviolations
1	6.64	28.16	442.01	3	1	6	411.95	1
2	5.89	42.15	413.95	3	2	4	377.47	1
3	5.89	42.15	413.95	3	2	4	377.47	1
26	4.30	48.71	305.77	3	1	1	260.85	0
27	4.82	48.71	319.80	3	1	1	277.65	0
28	5.09	48.71	333.82	3	1	1	294.45	1
29	4.82	48.71	319.80	3	1	1	277.65	0
30	3.73	50.94	309.80	3	3	2	272.08	0
31	4.25	50.94	323.83	3	3	2	288.88	0
32	4.52	50.94	337.85	3	3	2	305.68	0
33	4.25	50.94	323.83	3	3	2	288.88	0
35	3.67	62.71	321.81	3	2	4	287.38	0
37	4.31	45.05	324.81	3	1	1	286.44	0
38	5.02	45.92	320.78	3	0	1	274.23	1
39	4.45	48.15	324.81	3	2	2	285.46	0
42	4.40	35.27	285.73	3	0	1	238.94	0
43	5.04	22.13	301.80	2	0	1	248.08	1
44	3.62	46.26	287.75	3	1	4	248.81	0
45	4.26	33.12	303.81	2	1	4	257.96	0
47	4.08	36.68	298.80	2	0	3	250.00	0
49	5.33	16.13	356.92	2	0	5	319.09	1
50	5.68	16.13	358.94	2	0	7	329.45	1

^aMolecular properties (Log P, topological polar surface area (TPSA), molecular weight (MW), number of hydrogen bond acceptors (nON), number of hydrogen bond donors (nOHNH), number of rotatable bonds (nrotb), molecular volume, and number of violations of Lipinski's rules (nviolations)) calculated using Molinspiration (<http://molinspiration.com>).

Table S2

Calculated CNS MPO desirability scores of the novel heterofused quinolines and related compounds.^a

Compd	pK _a ^b	cLogP ^b	cLogD ^b	CNS MPO
1	9.75	7.0	4.44	1.8
2	9.39	6.21	3.98	2.4
3	9.43	6.21	4.13	2.4
26	6.84	4.14	4.03	4.3
27	6.87	4.58	4.47	4.0
28	6.87	5.03	4.91	3.8
29	6.93	4.58	4.46	4.0
30	9.43	3.41	1.31	4.2
31	9.43	3.85	1.74	4.0
32	9.43	4.30	2.19	3.7
33	9.43	3.85	1.74	4.0
35	10.05	4.48	1.99	3.8
37	2.38	3.96	3.96	4.4
38	4.63	4.95	4.95	4.0
39	9.43	4.22	2.23	4.1
42	2.80	4.16	4.16	4.2
43	3.63	4.87	4.87	3.2
44	1.32	3.79	3.79	4.5
45	2.14	4.51	4.51	3.7
47	1.64	4.69	4.69	4.0
49	9.86	5.63	3.20	2.5
50	10.06	5.93	3.33	2.3

^aCNS MPO scores calculated using the algorithm reported in ref. [1]. TPSA values, MW, and the number of hydrogen bond donors (nOHNH), used in the algorithm, are shown in Table S1.

^bMarvin was used for predicting pK_a, cLogP, and cLogD values, Marvin 5.12.0, 2013, ChemAxon (<http://www.chemaxon.com>).

Table S3

Reported and experimental permeability values ($P_e \cdot 10^{-6} \text{ cm s}^{-1}$) of the 14 commercial drugs used for the PAMPA-BBB assay validation.

Compound	Literature value ^a	Experimental value ^b
Cimetidine	0.0	0.70 ± 0.03
Lomefloxacin	1.1	0.70 ± 0.04
Norfloxacin	0.1	0.90 ± 0.02
Ofloxacin	0.8	0.98 ± 0.04
Hydrocortisone	1.9	1.40 ± 0.05
Piroxicam	2.5	1.80 ± 0.02
Clonidine	5.3	6.50 ± 0.05
Corticosterone	5.1	6.70 ± 0.10
Imipramine	13	12.3 ± 0.10
Promazine	8.8	13.8 ± 0.30
Progesterone	9.3	16.8 ± 0.30
Desipramine	12	17.8 ± 0.10
Testosterone	17	23.1 ± 0.20
Verapamil	16	25.8 ± 0.30

^a Taken from ref. [2].

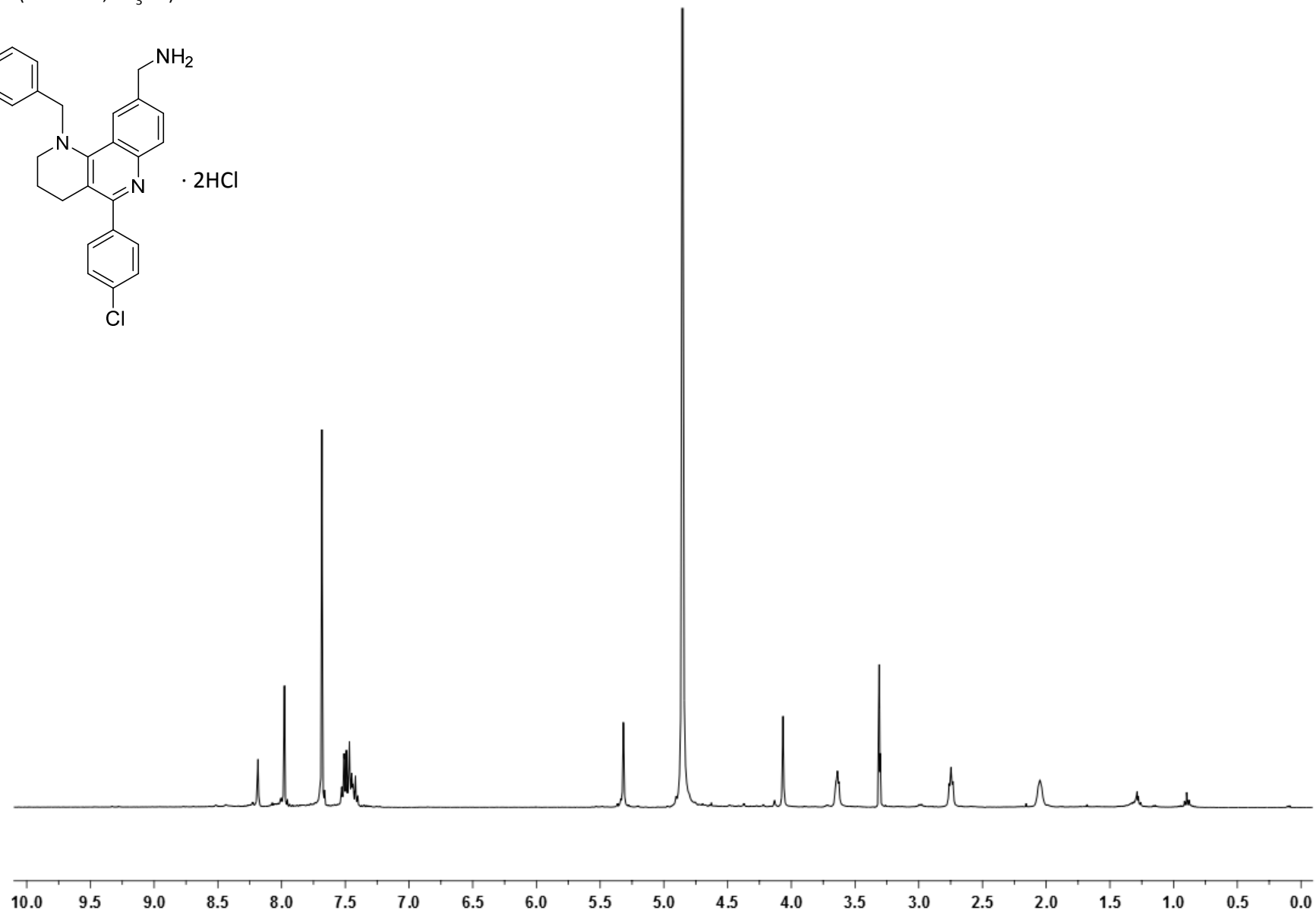
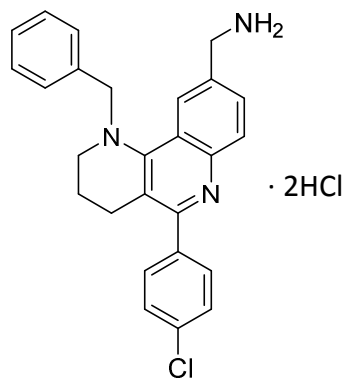
^b Values are expressed as the mean \pm SD of three independent experiments.

References

- [1] T.T. Wager, X. Hou, P.R. Verhoest, A. Villalobos, Moving beyond the rules: The development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties, *ACS Chem. Neurosci.* 1 (2010) 435–449.
- [2] L. Di, E.H. Kerns, K. Fan, O.J. McConnell, G.T. Carter, High throughput artificial membrane permeability assay for blood-brain barrier, *Eur. J. Med. Chem.* 38 (2003) 223–232.

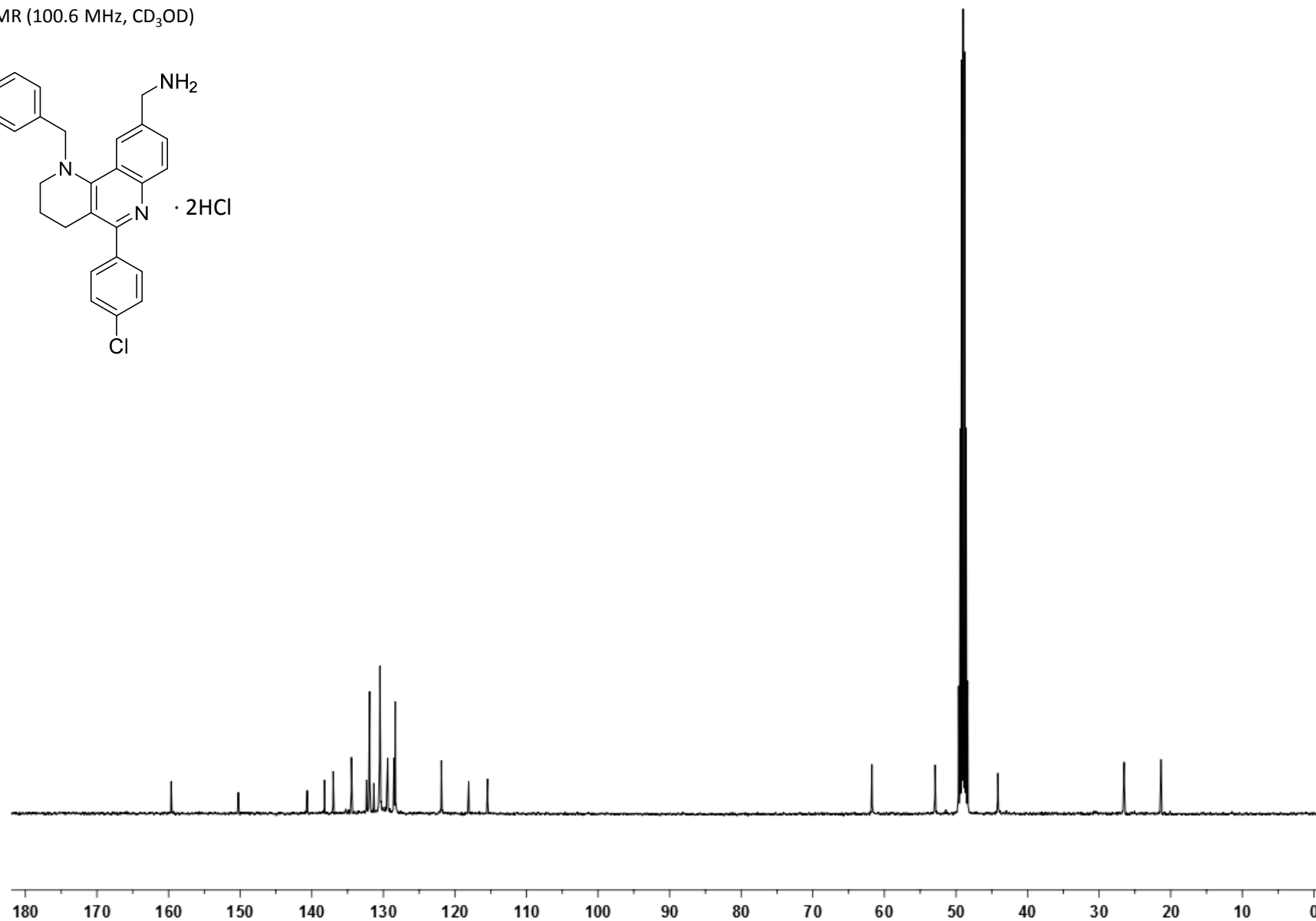
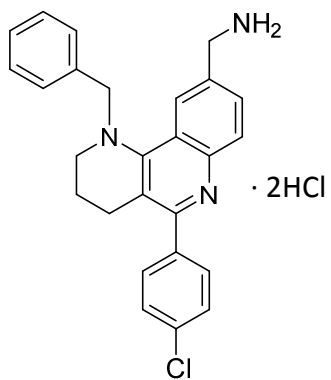
N-{1-Benzyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridin-9-yl}methanamine **2**

¹H NMR (400 MHz, CD₃OD)



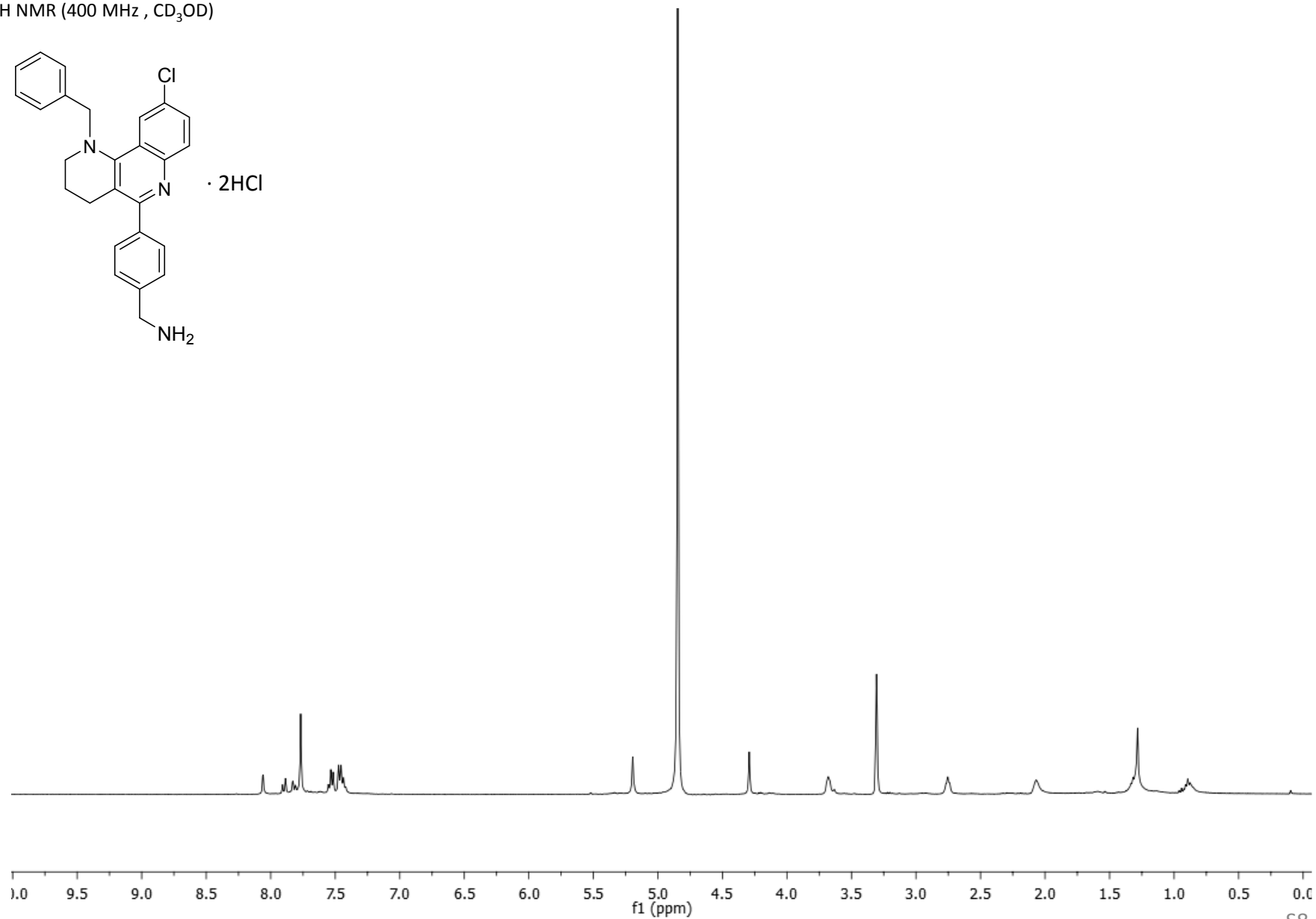
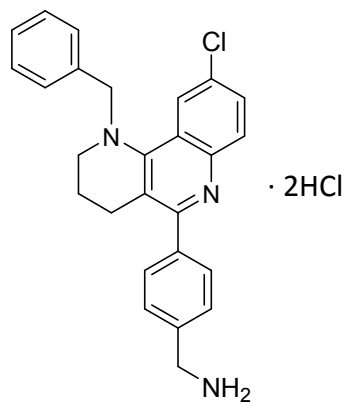
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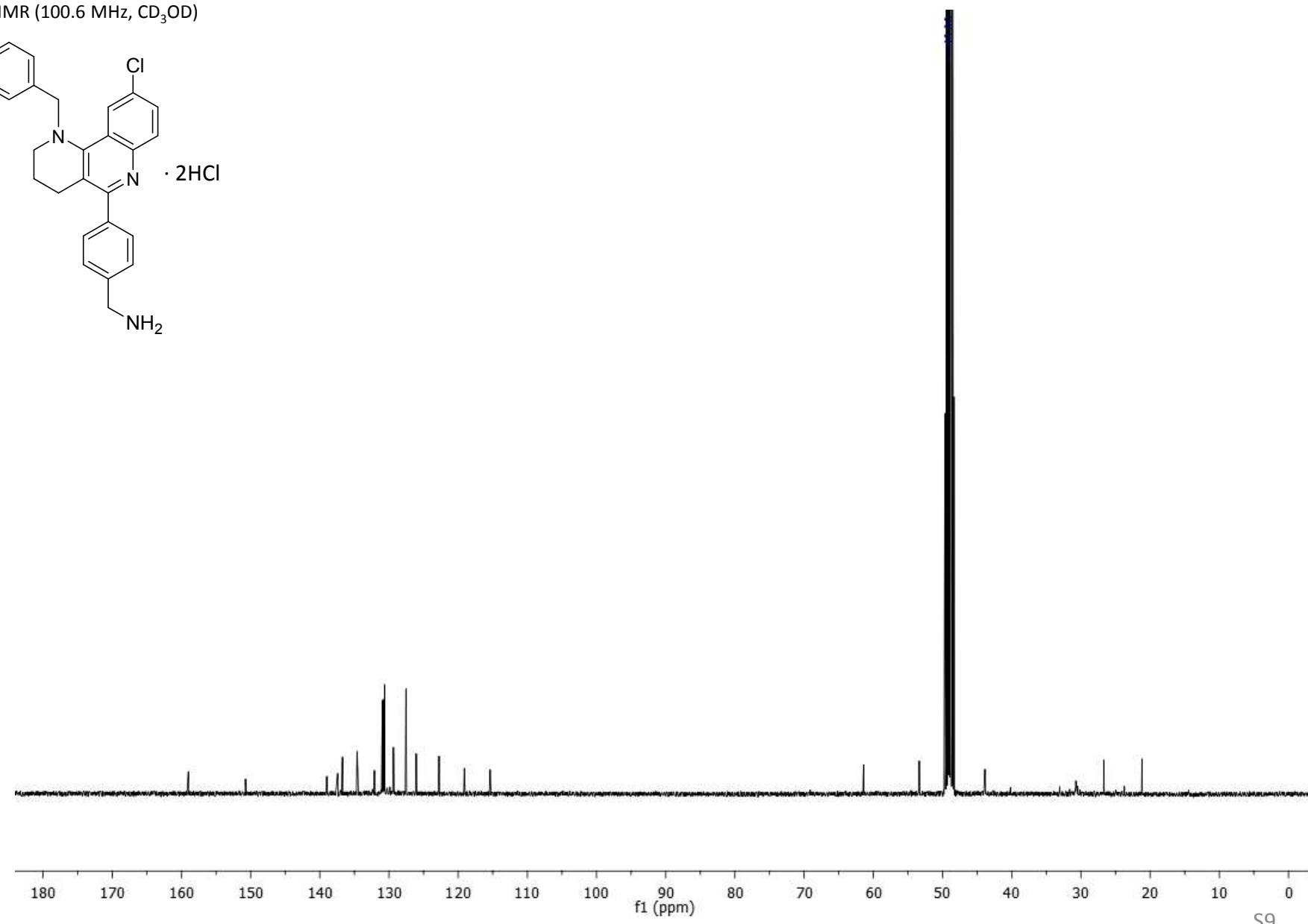
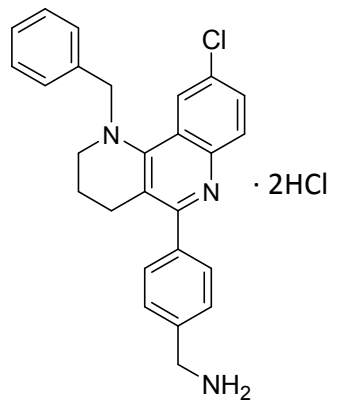
4-{1-Benzyl-9-chloro-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridin-5-yl}benzylamine **3**

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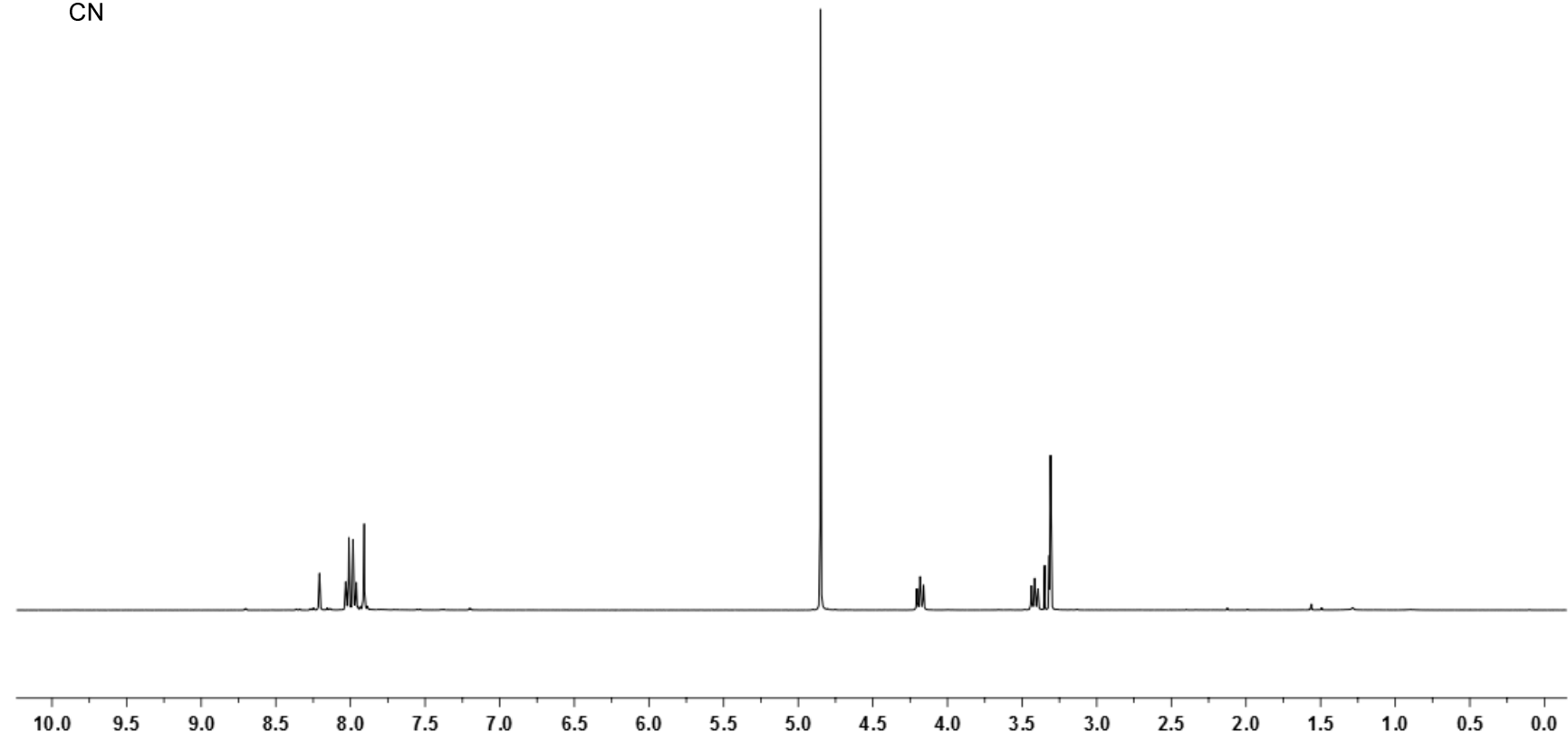
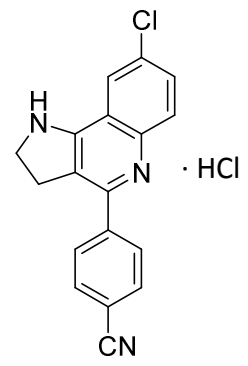
4-{1-Benzyl-9-chloro-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridin-5-yl}benzylamine **3**

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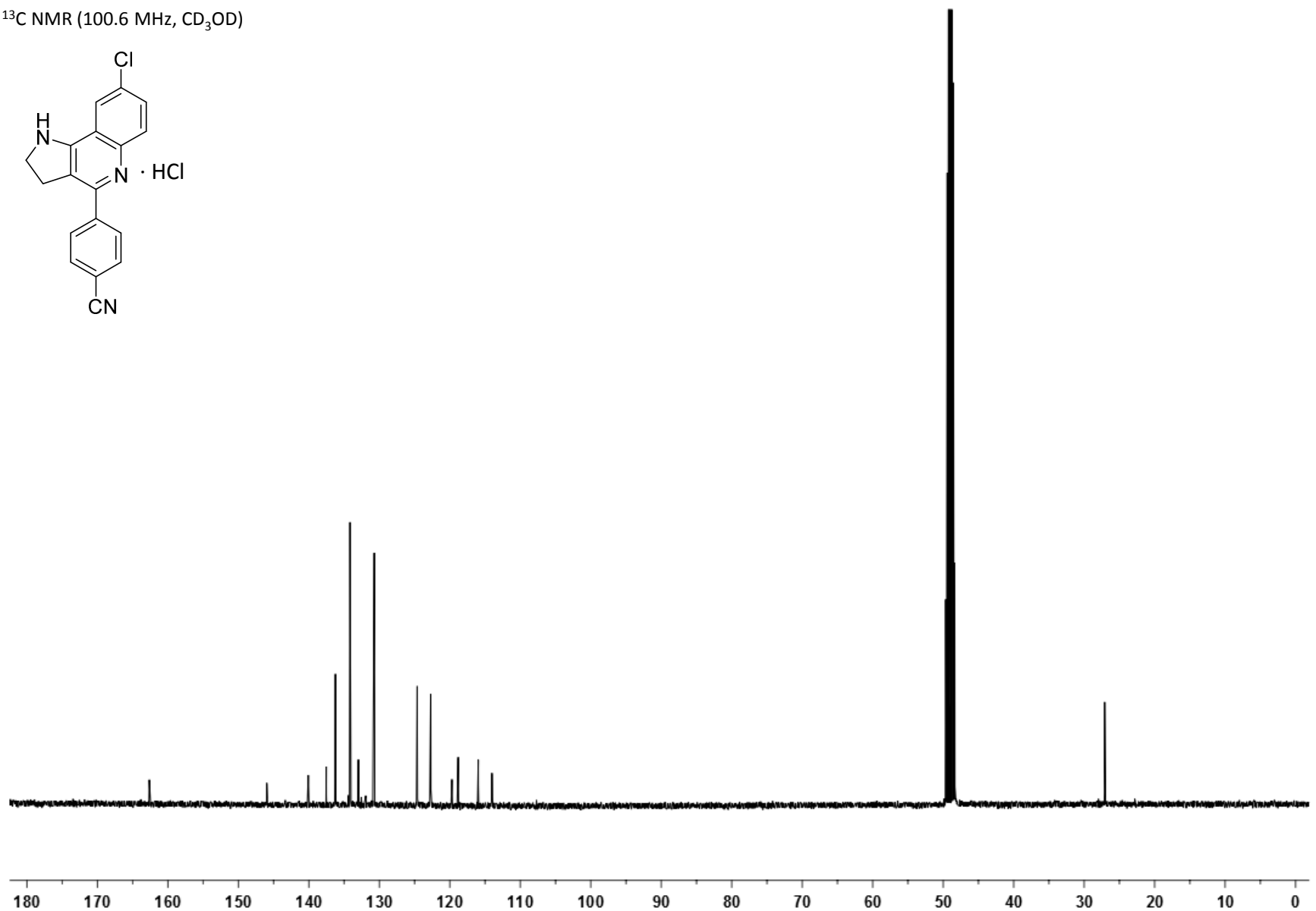
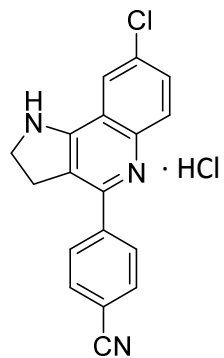
4-{8-Chloro-2,3-dihydro-1H-pyrrolo[3,2-c]quinolin-4-yl}benzonitrile **26**

¹H NMR (400 MHz, CD₃OD)



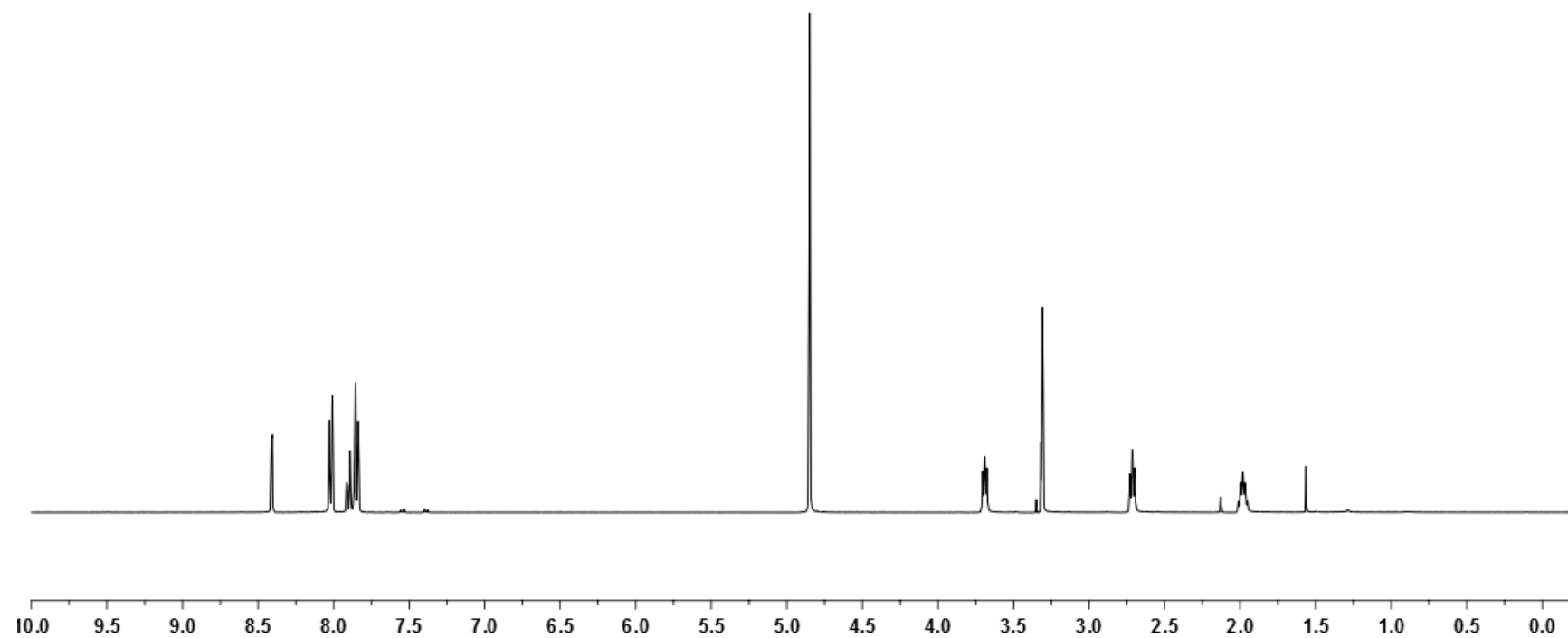
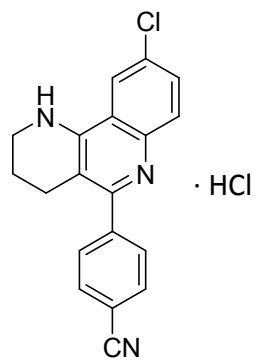
4-{8-Chloro-2,3-dihydro-1H-pyrrolo[3,2-c]quinolin-4-yl}benzotrile **26**

^{13}C NMR (100.6 MHz, CD_3OD)



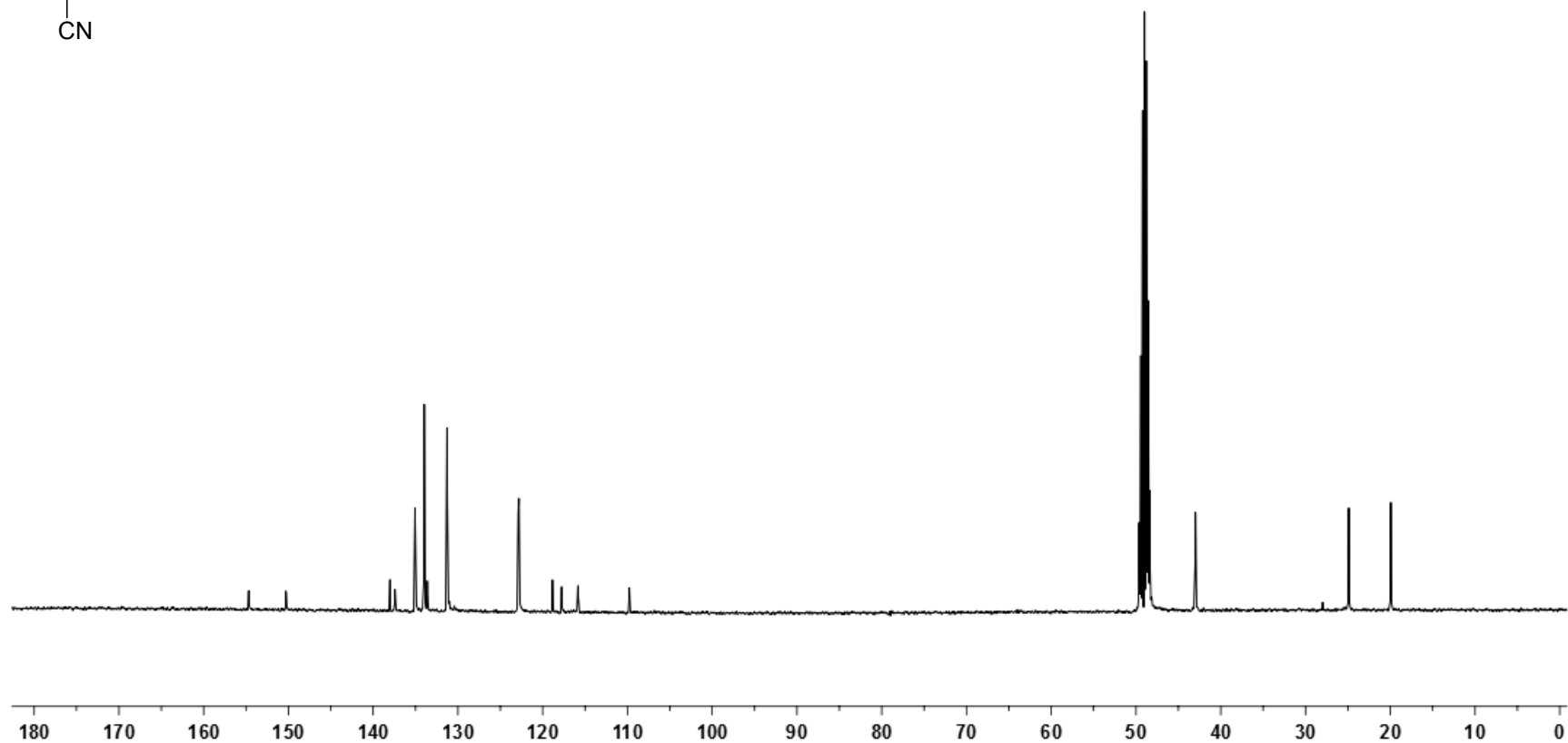
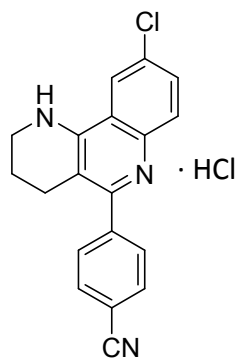
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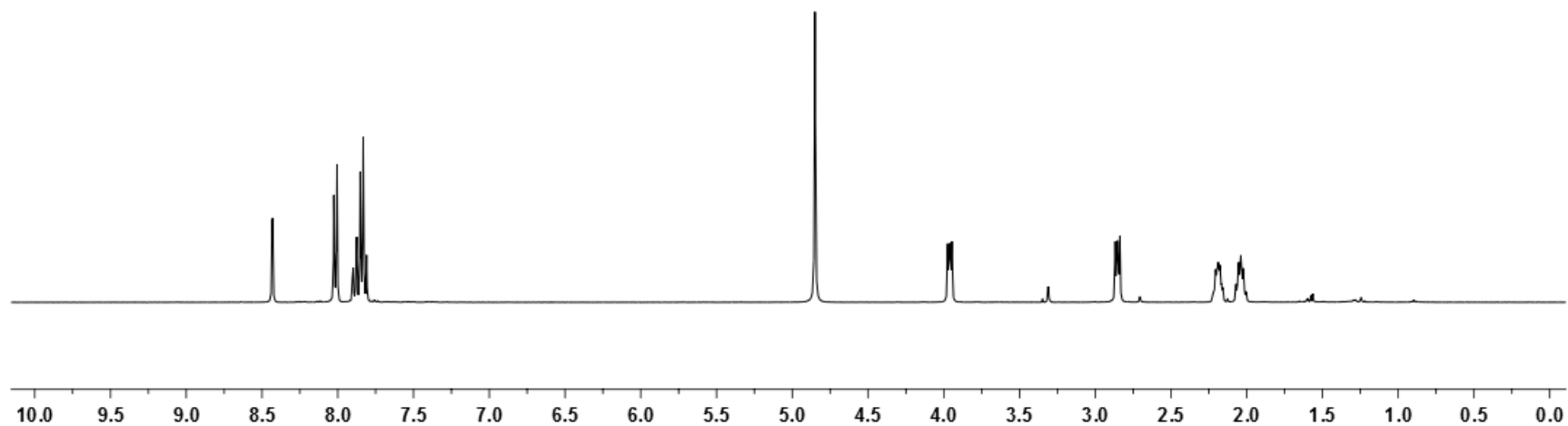
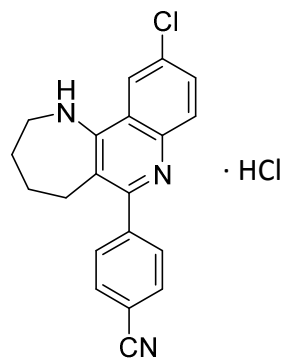
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¹³C NMR (100.6 MHz, CD₃OD)



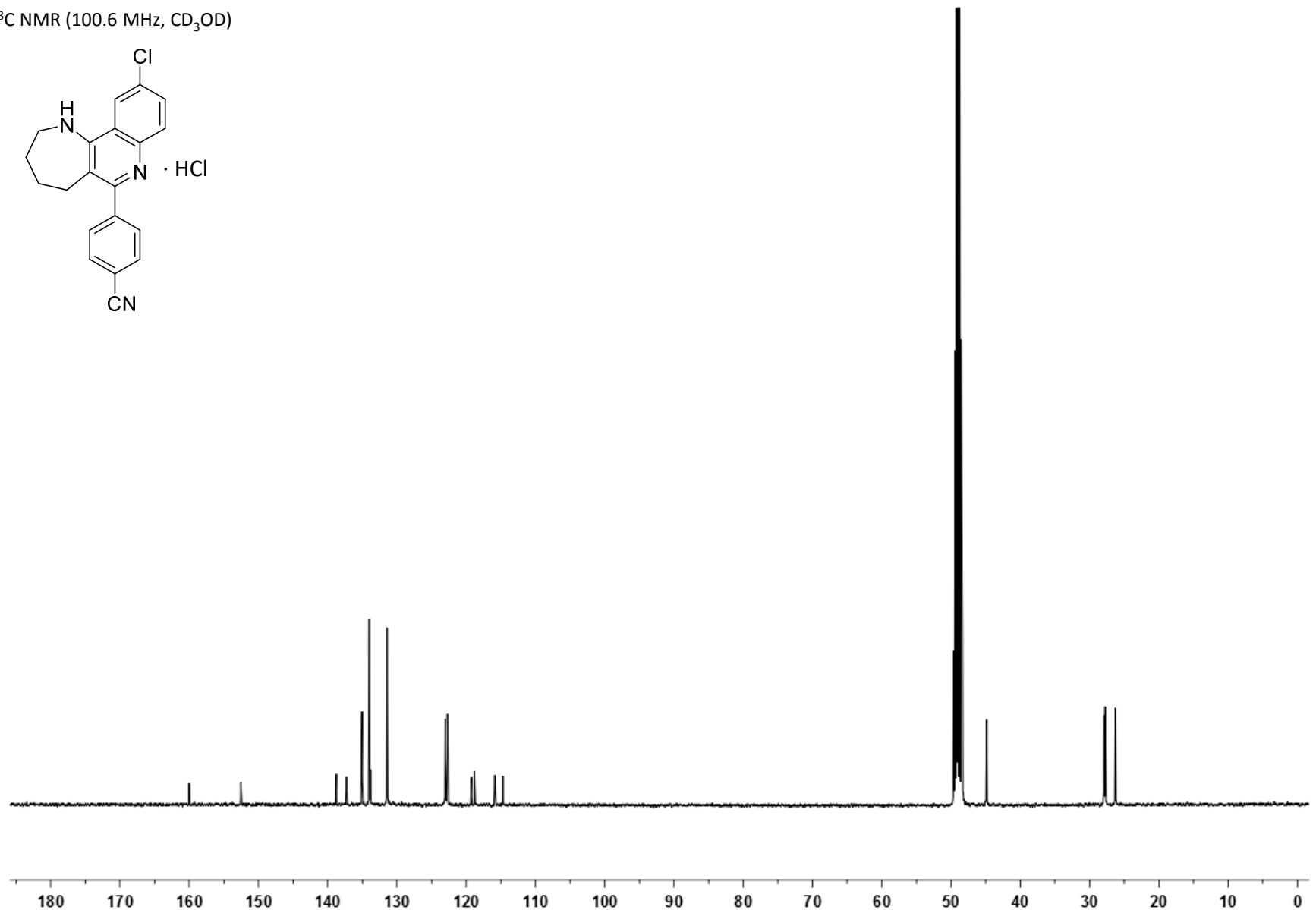
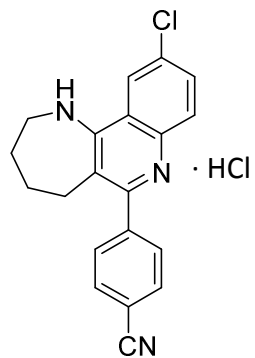
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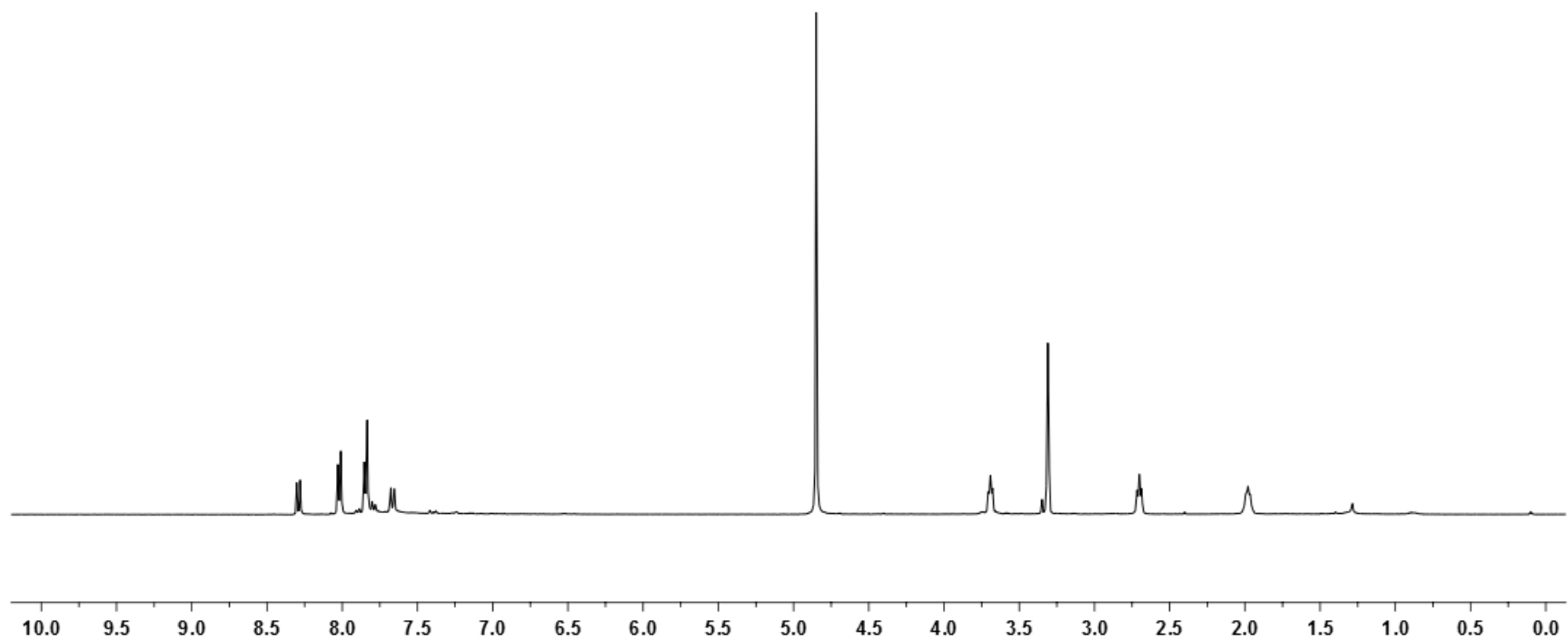
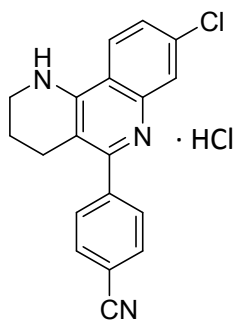
4-{10-Chloro-2,3,4,5-tetrahydro-1H-azepino[3,2-c]quinolin-6-yl}benzotrile **28**

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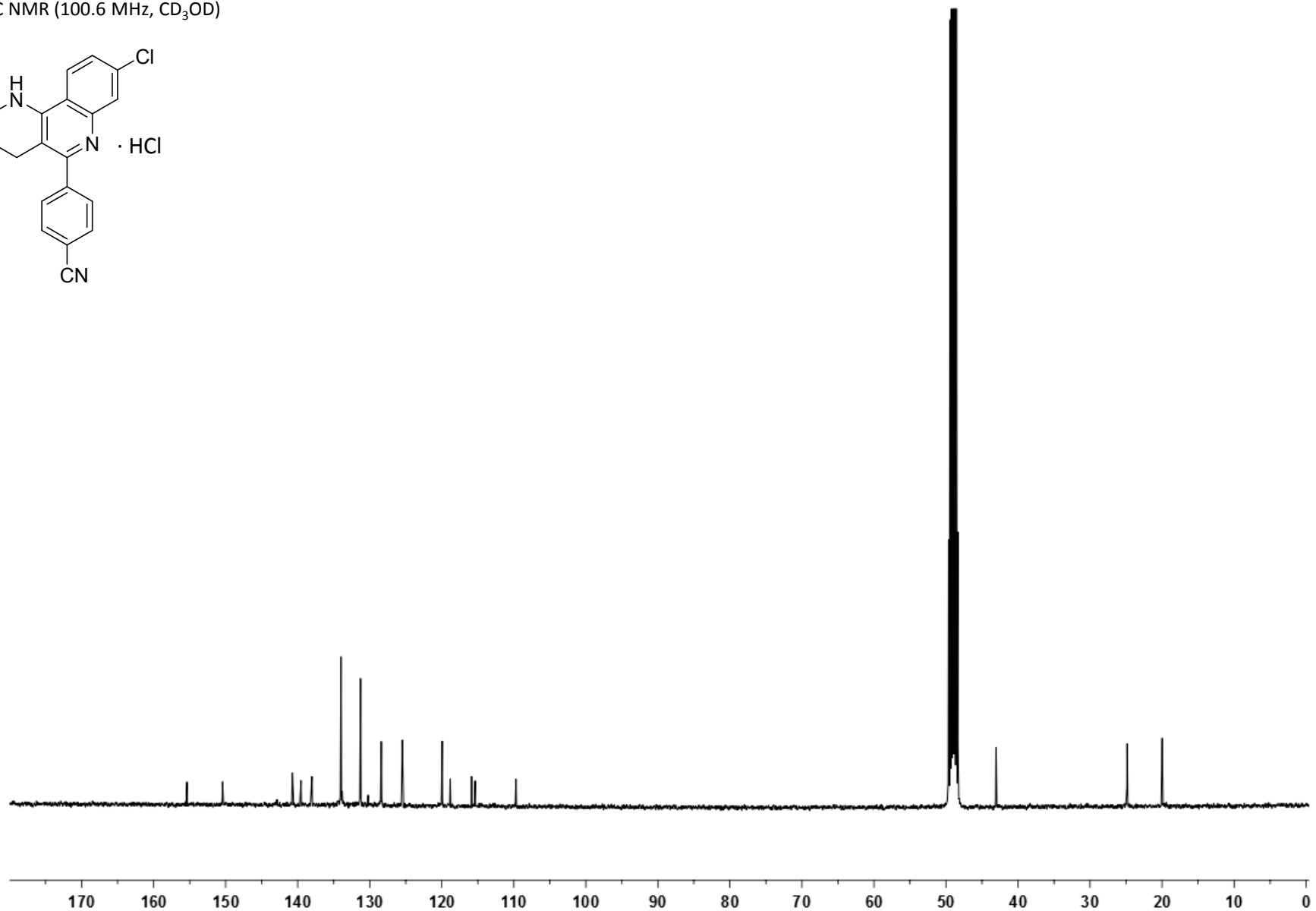
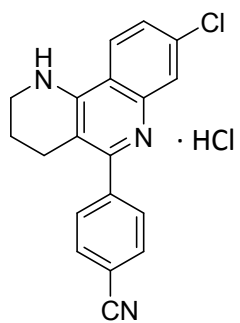
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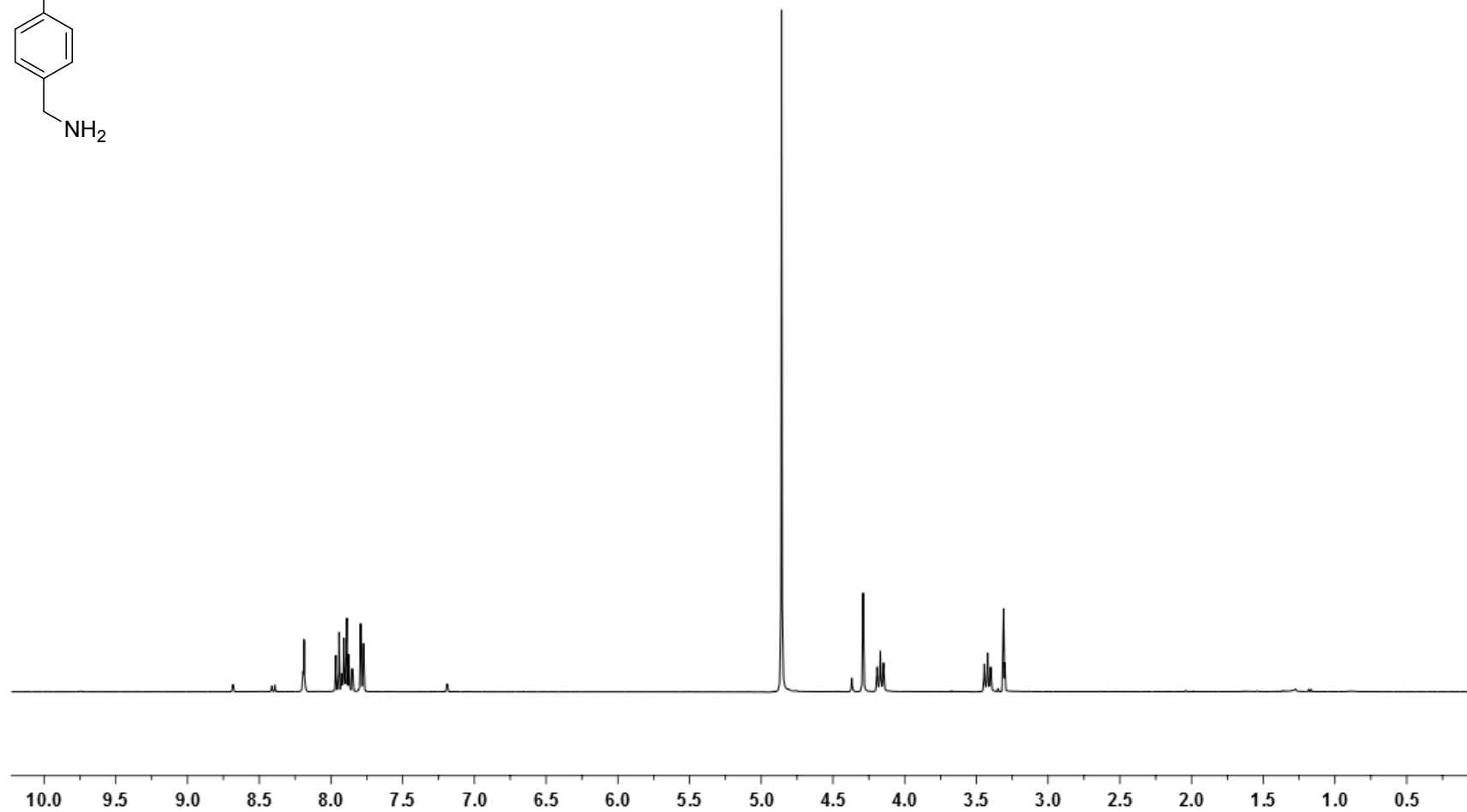
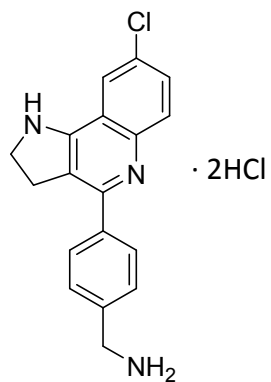
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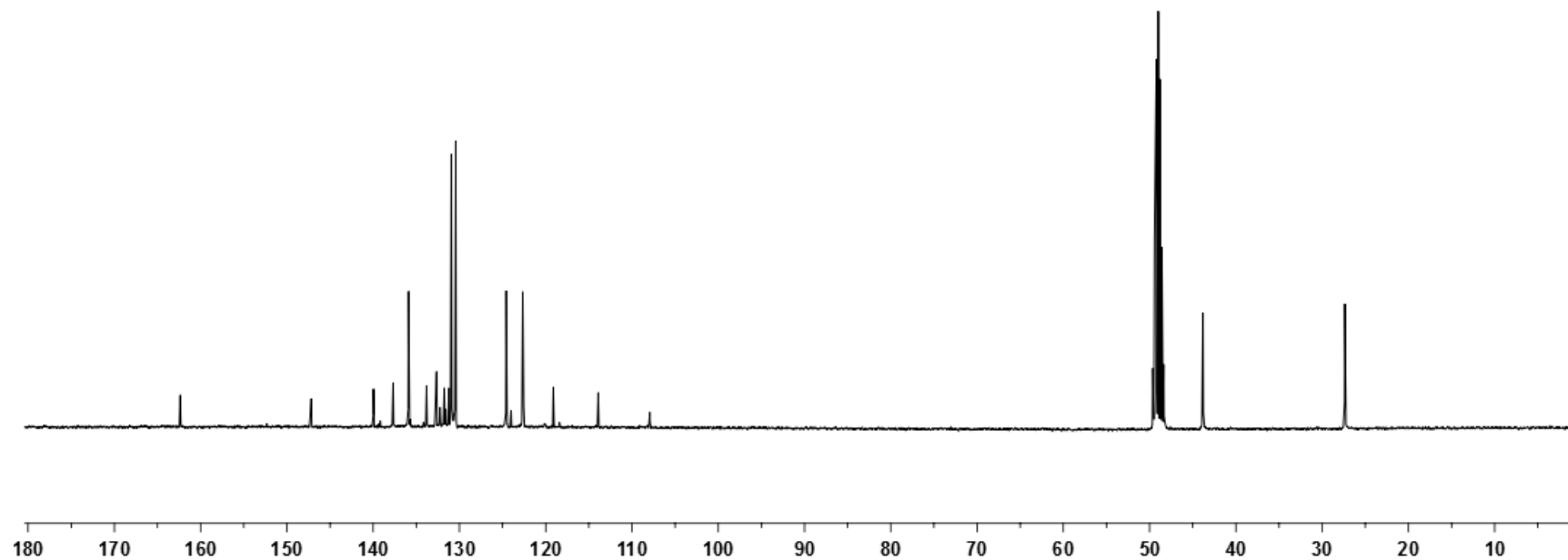
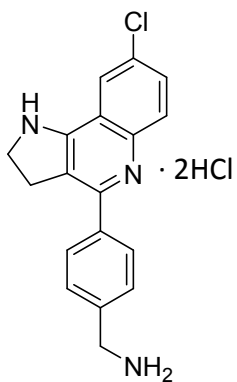
4-{8-Chloro-2,3-dihydro-1H-pyrrolo[3,2-c]quinolin-4-yl}benzylamine **30**

^1H NMR (400 MHz, CD_3OD)



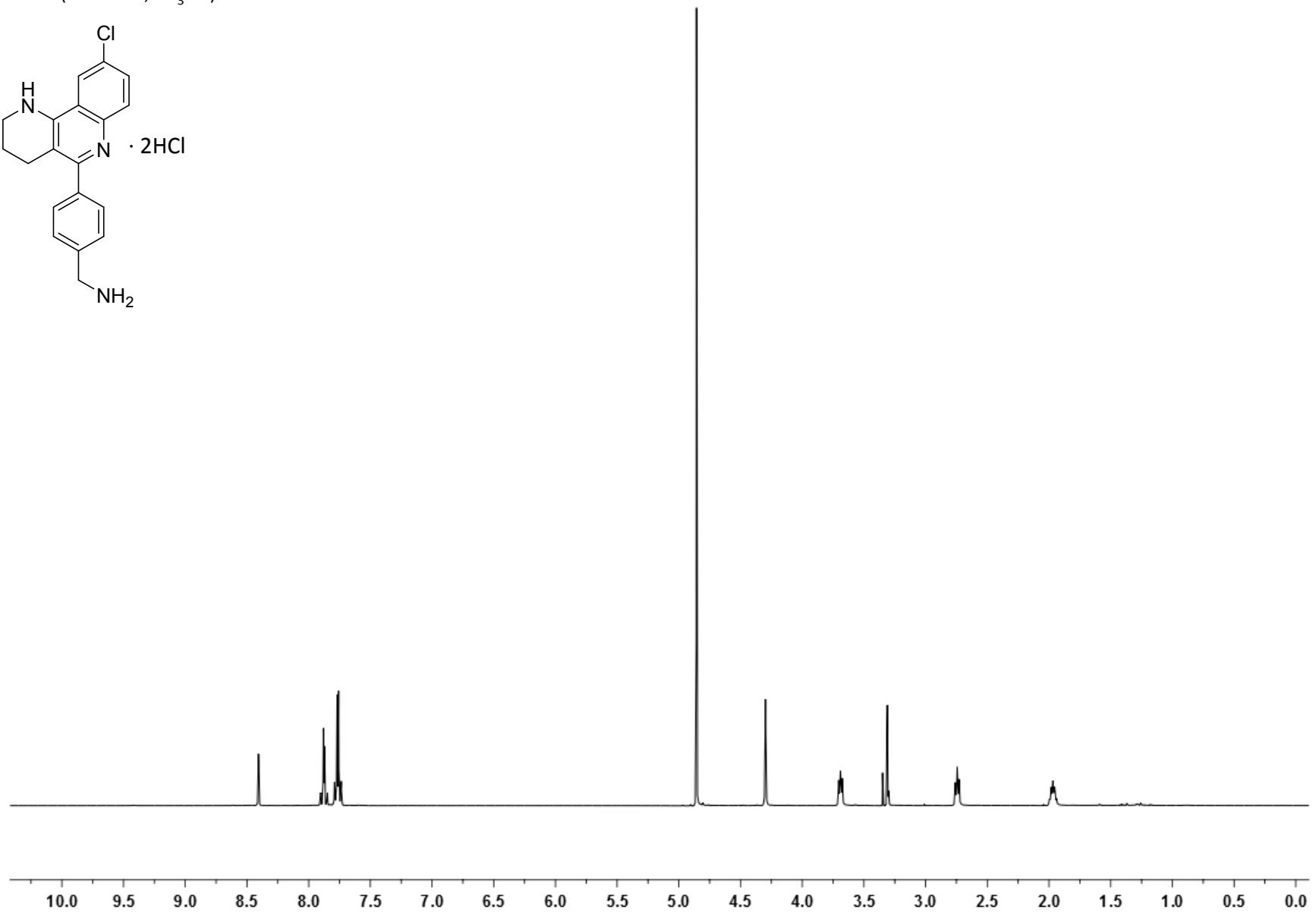
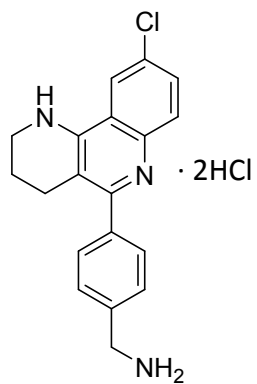
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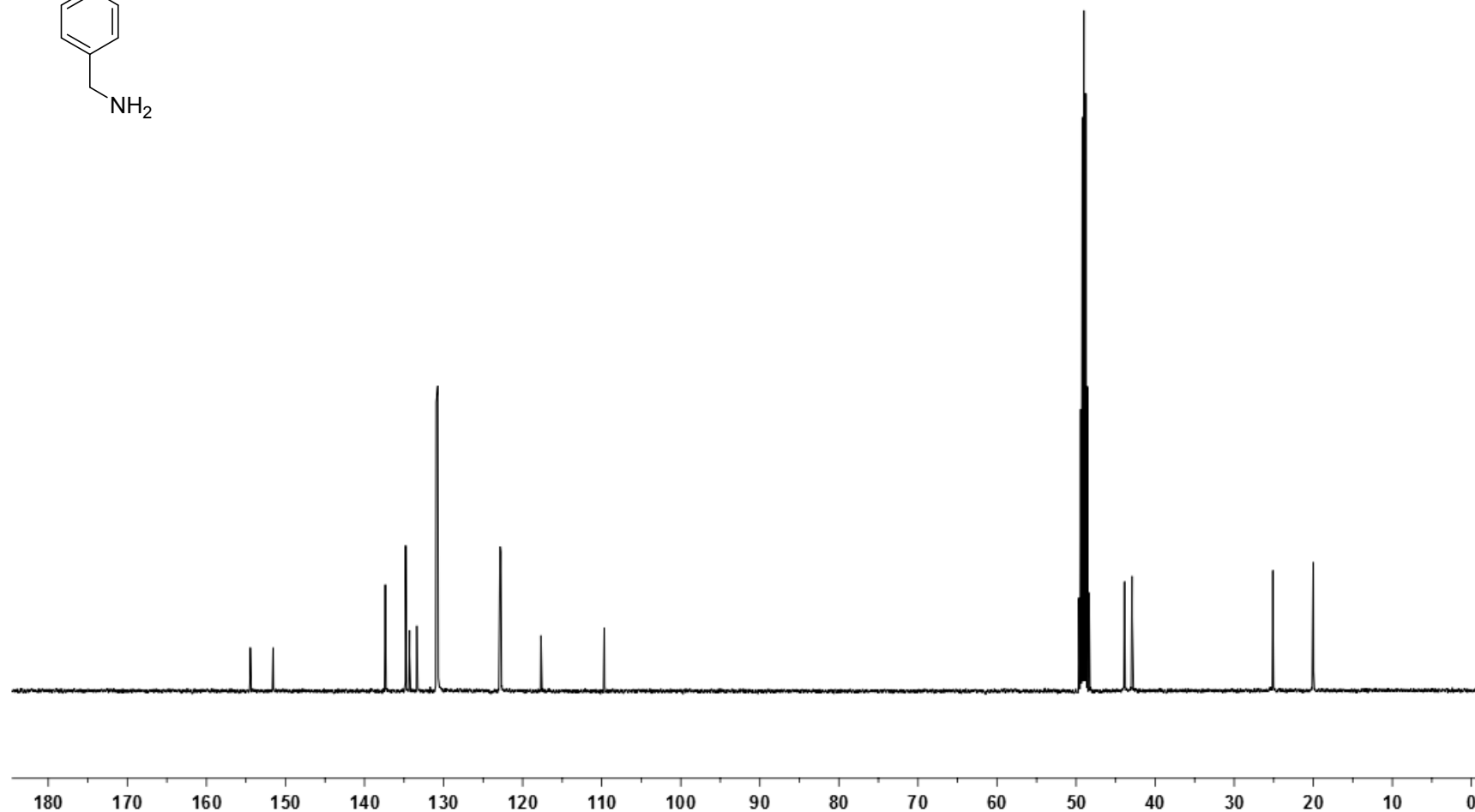
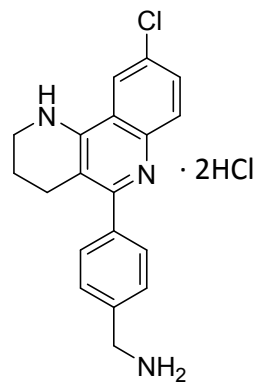
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^1H NMR (400 MHz, CD_3OD)



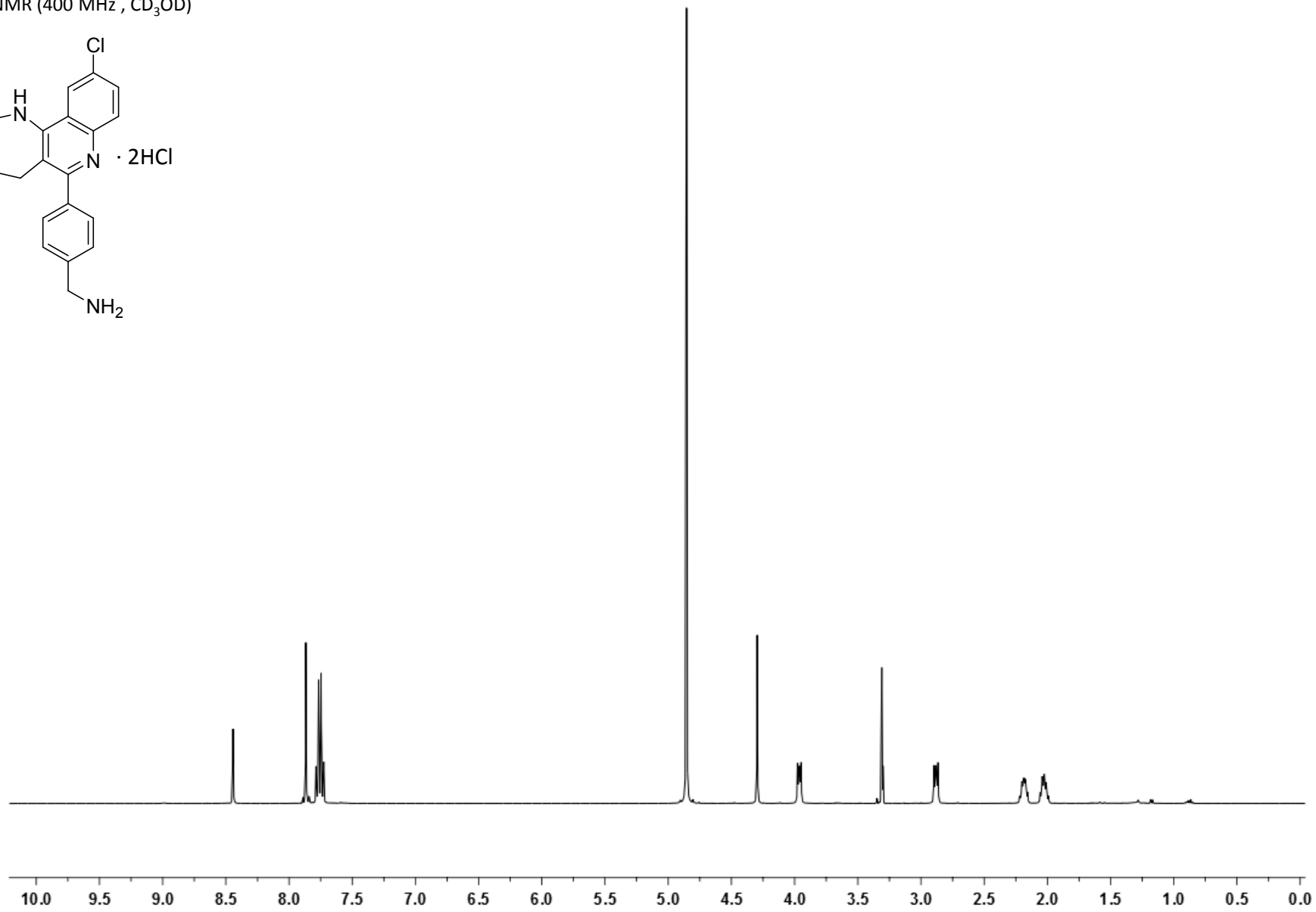
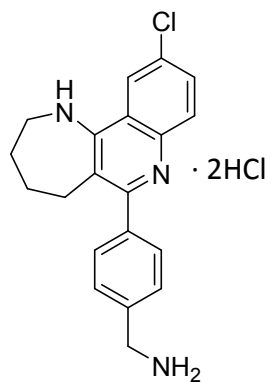
4-{9-Chloro-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridin-5-yl}benzylamine **31**

^{13}C NMR (100.6 MHz, CD_3OD)



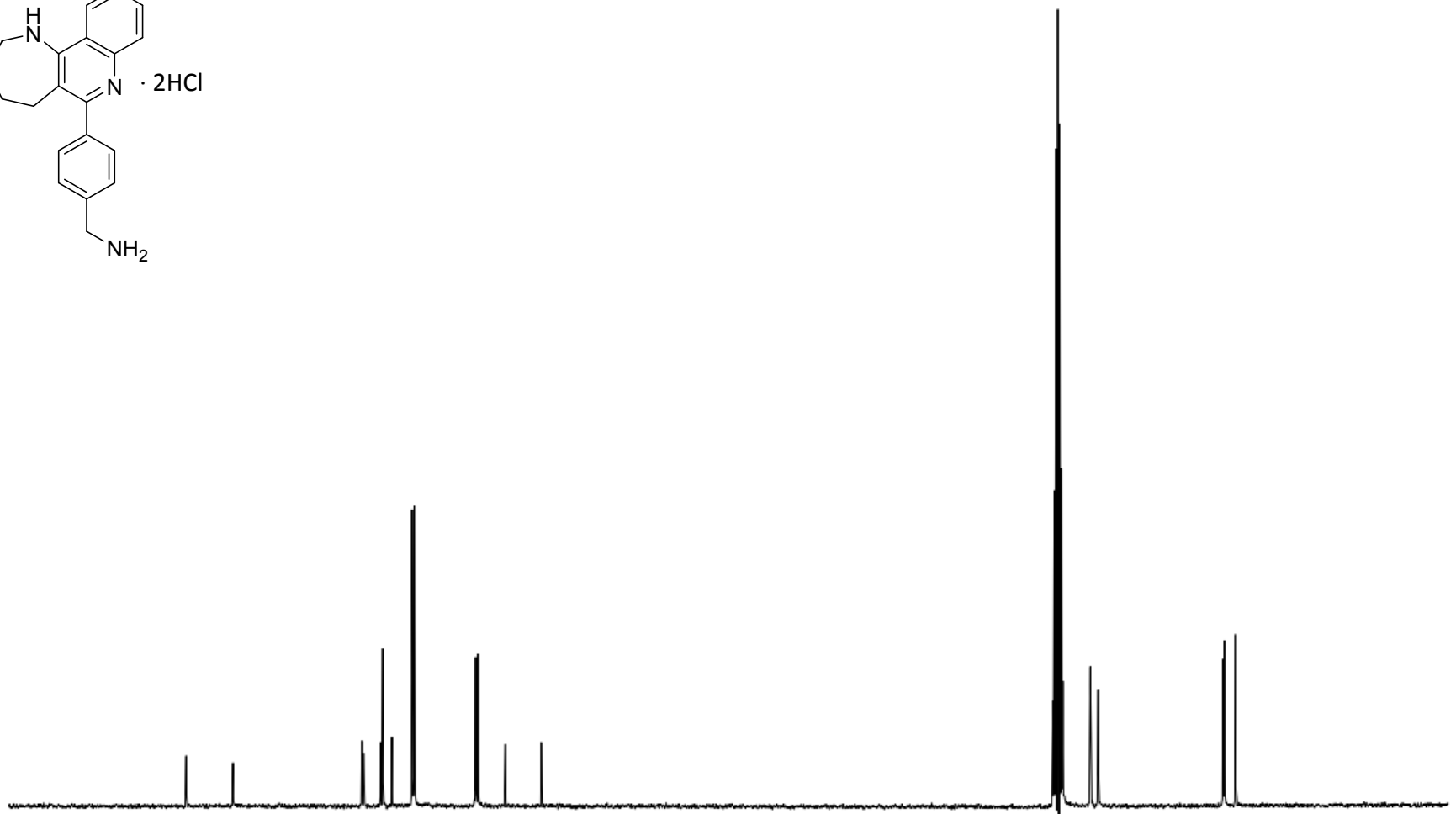
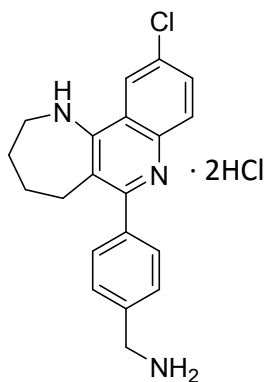
4-{10-Chloro-2,3,4,5-tetrahydro-1H-azepino[3,2-c]quinolin-6-yl}benzylamine **32**

^1H NMR (400 MHz, CD_3OD)



4-{10-Chloro-2,3,4,5-tetrahydro-1H-azepino[3,2-c]quinolin-6-yl}benzylamine **32**

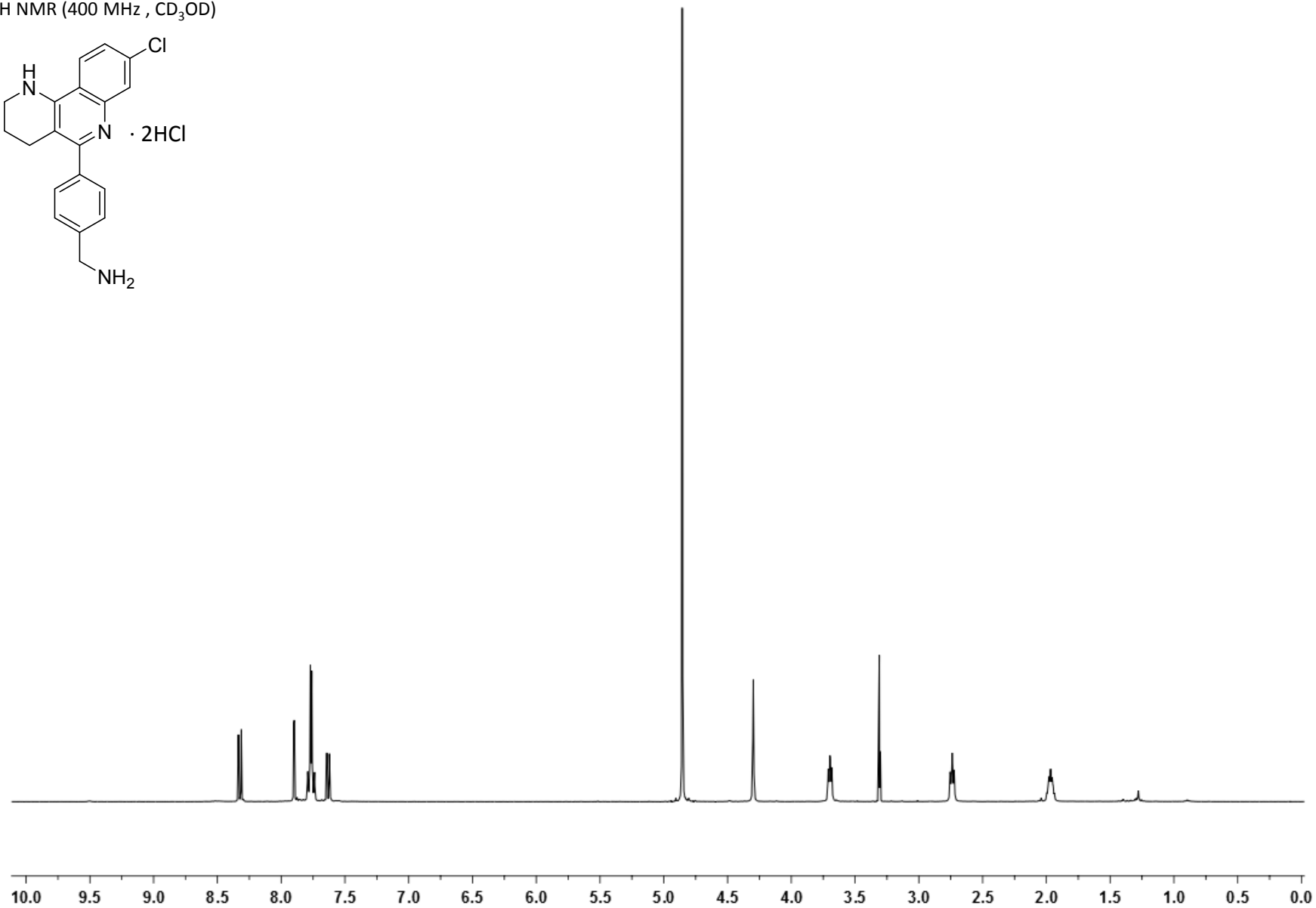
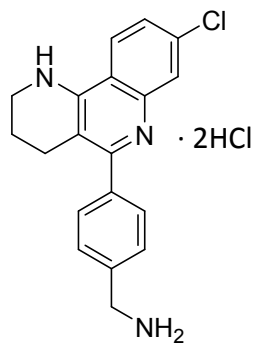
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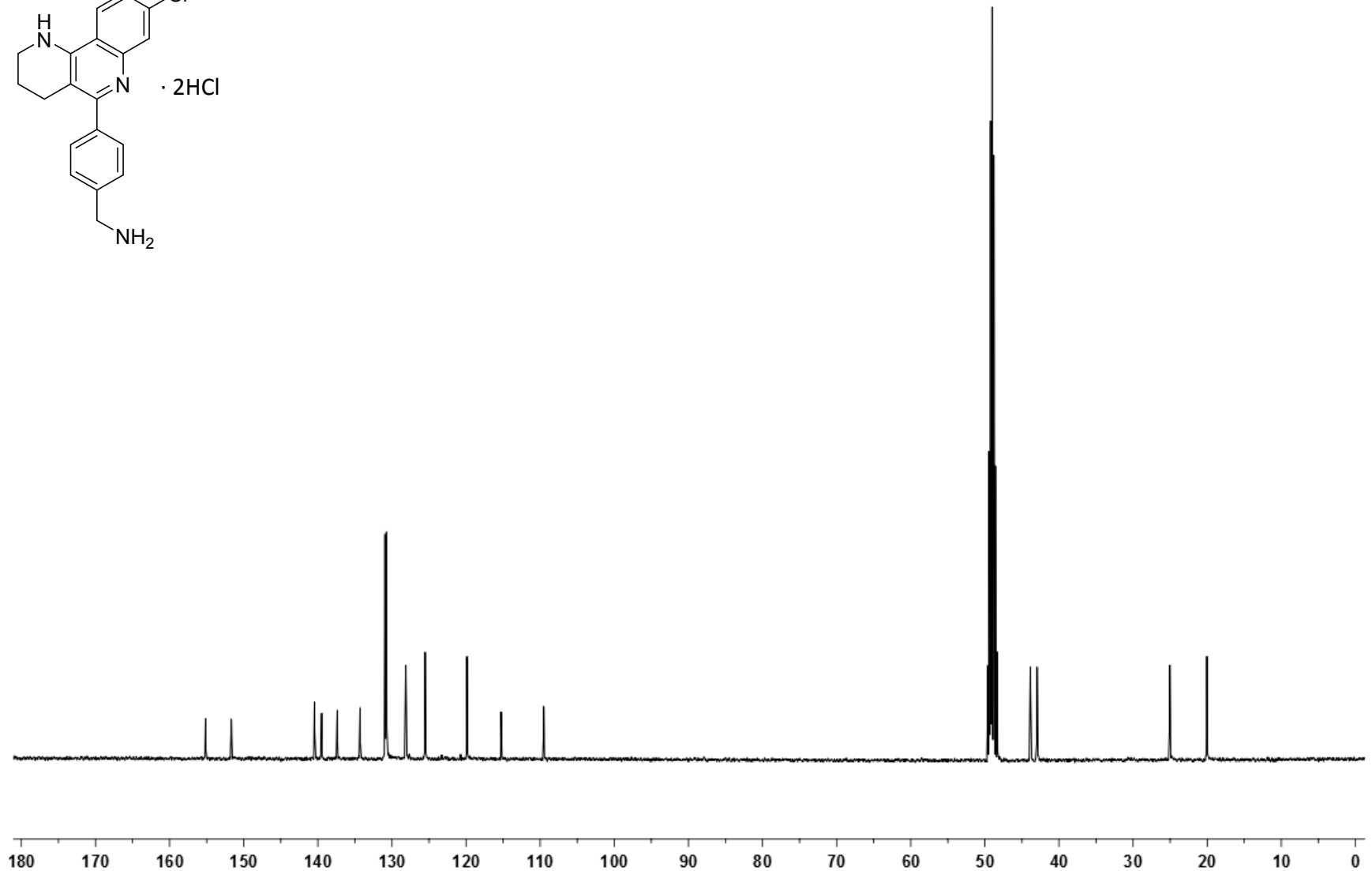
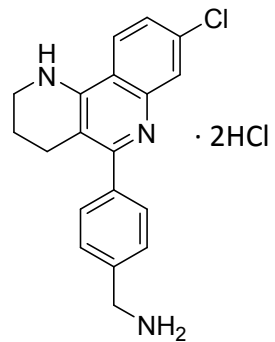
4-{8-Chloro-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridin-5-yl}benzylamine **33**

¹H NMR (400 MHz, CD₃OD)



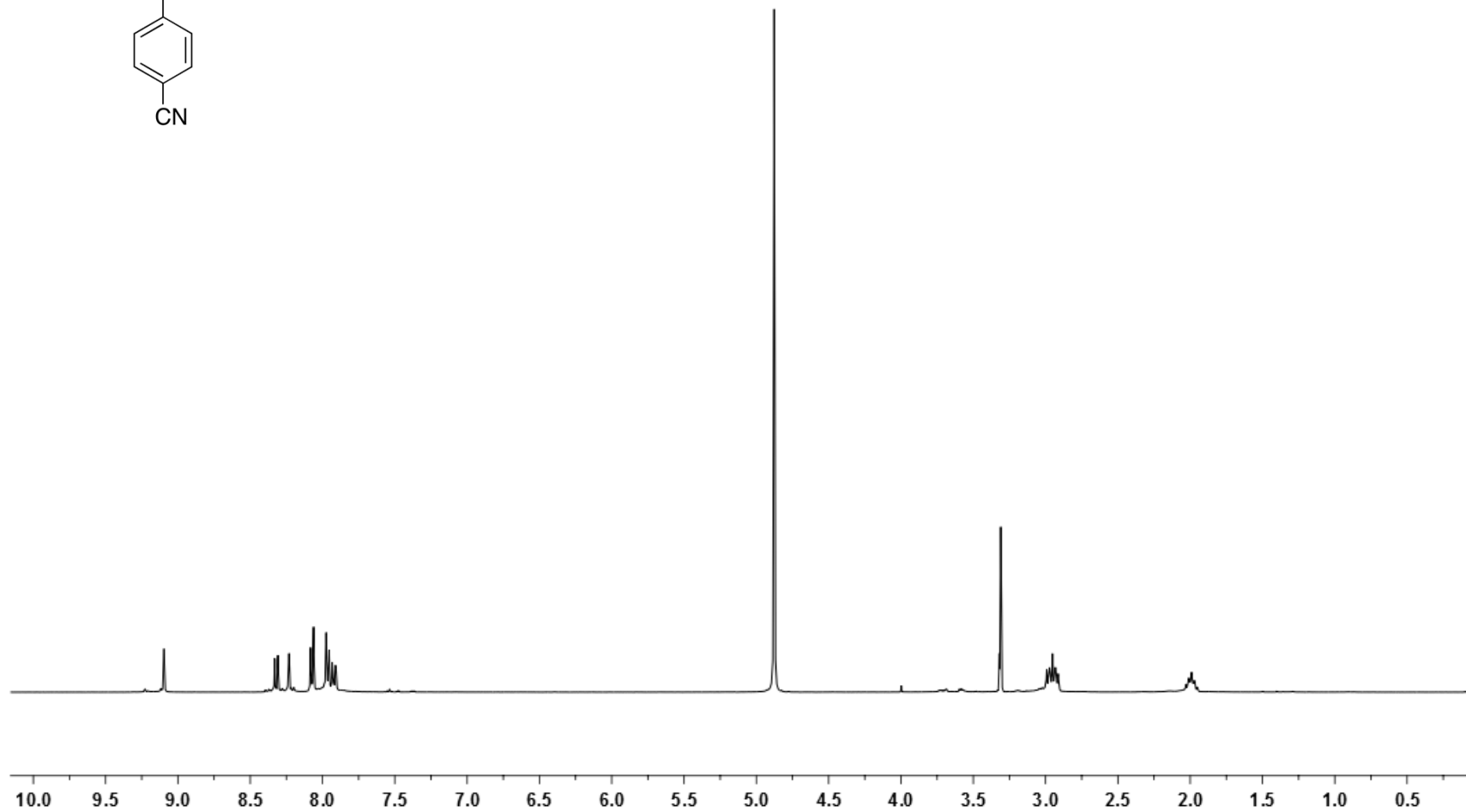
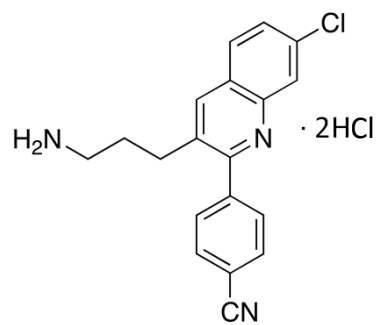
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^{13}C NMR (100.6 MHz, CD_3OD)



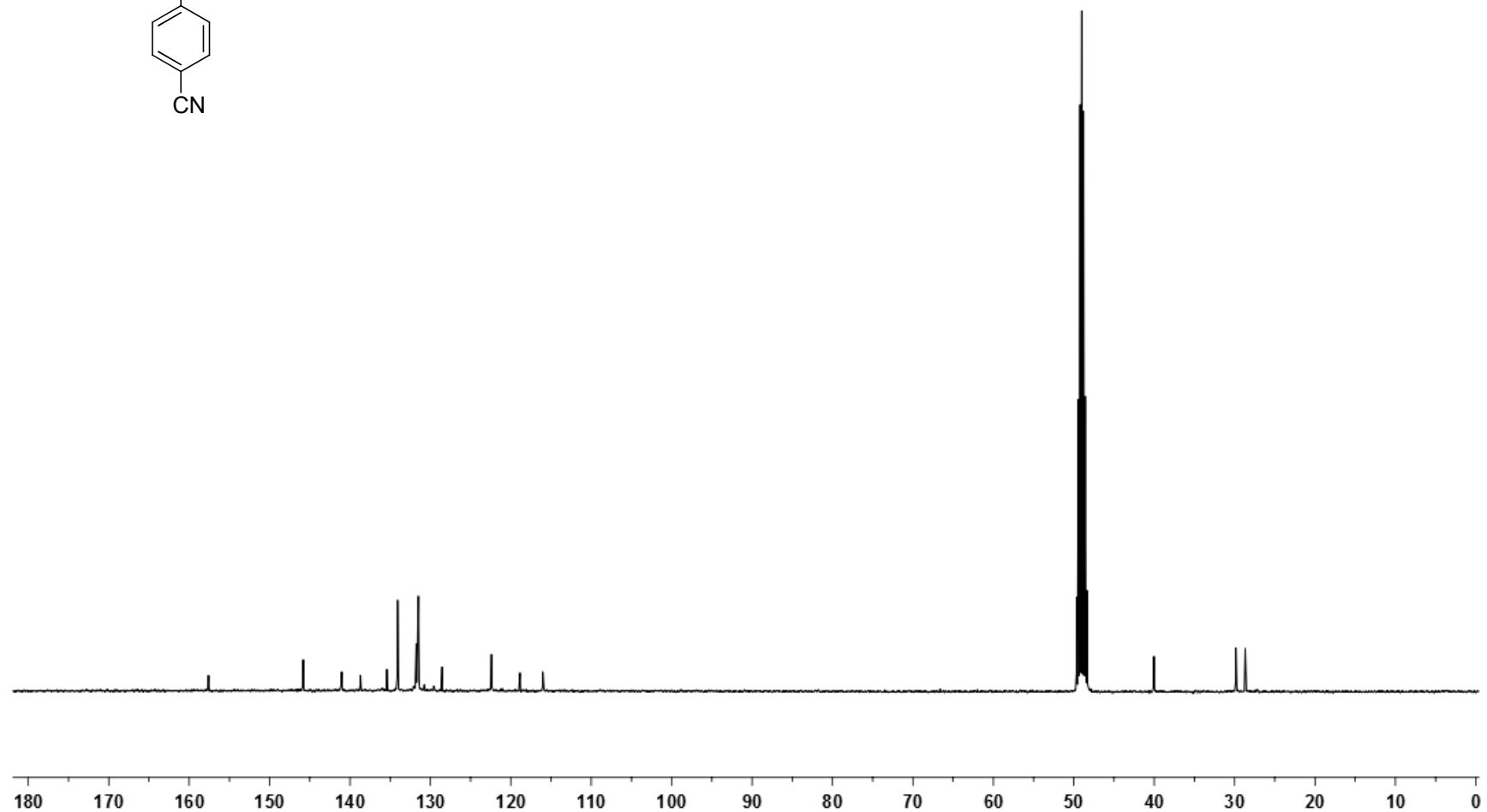
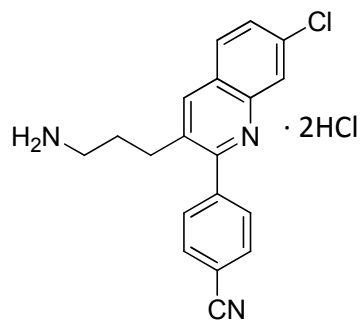
4-[3-(3-Aminopropyl)-7-chloroquinolin-2-yl]benzonitrile 35

$^1\text{H NMR}$ (400 MHz, CD_3OD)



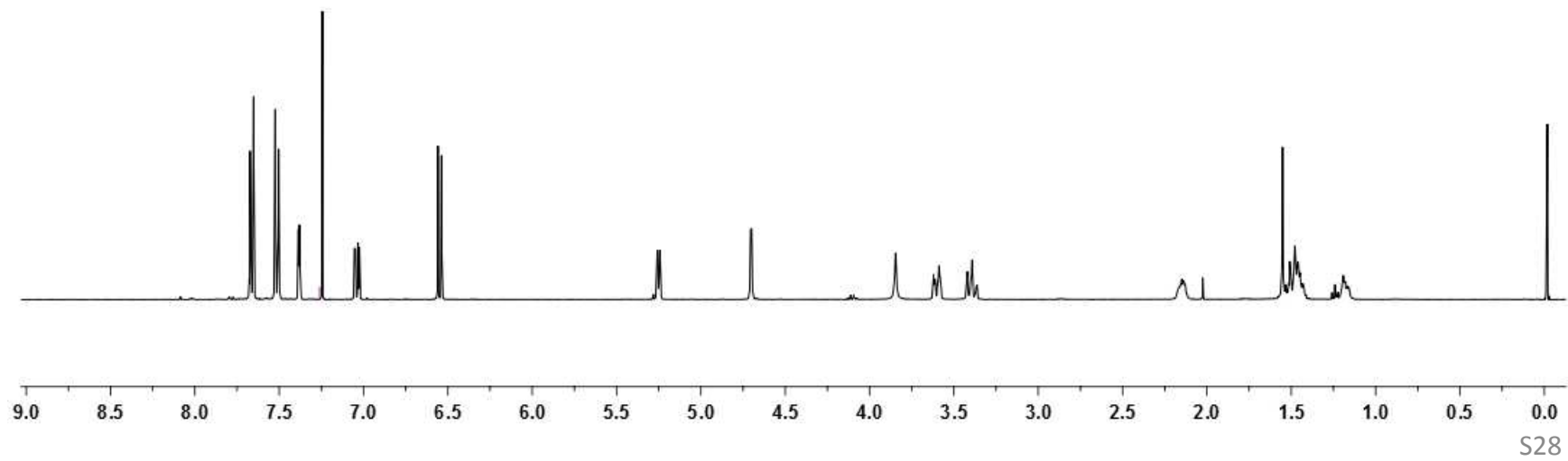
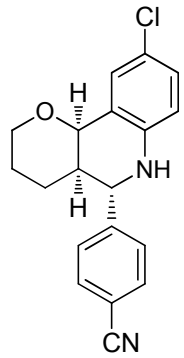
4-[3-(3-Aminopropyl)-7-chloroquinolin-2-yl]benzonitrile 35

^{13}C NMR (100.6 MHz, CD_3OD)



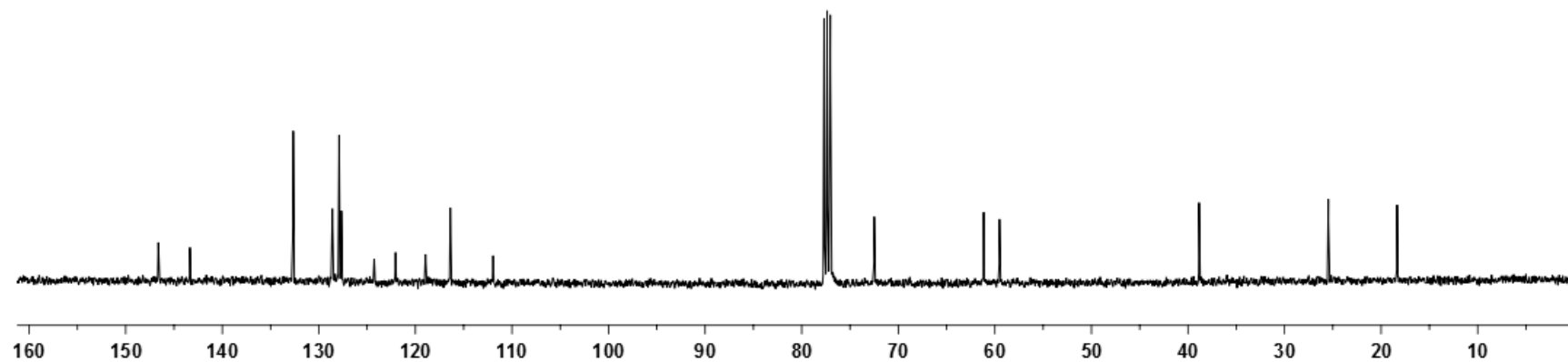
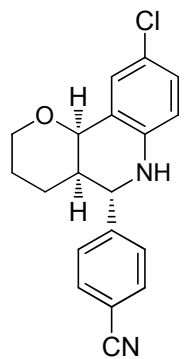
4-{9-Chloro-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-5-yl}benzotrile **37**

¹H NMR (400 MHz, CDCl₃)



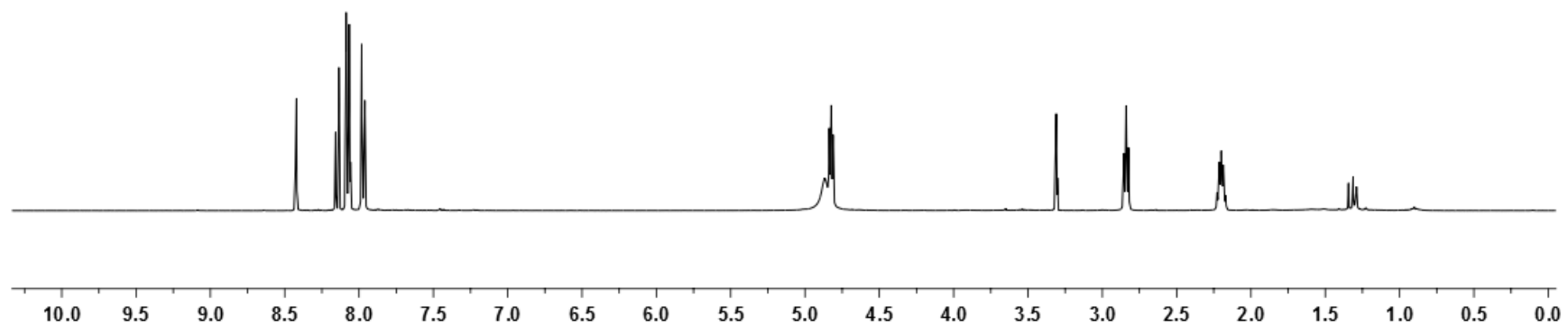
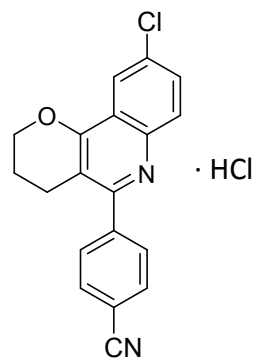
4-{9-Chloro-3,4,4a,5,6,10b -hexahydro-2H-pyrano[3,2-c]quinolin-5-yl}benzonitrile **37**

^{13}C NMR (100.6 MHz, CDCl_3)



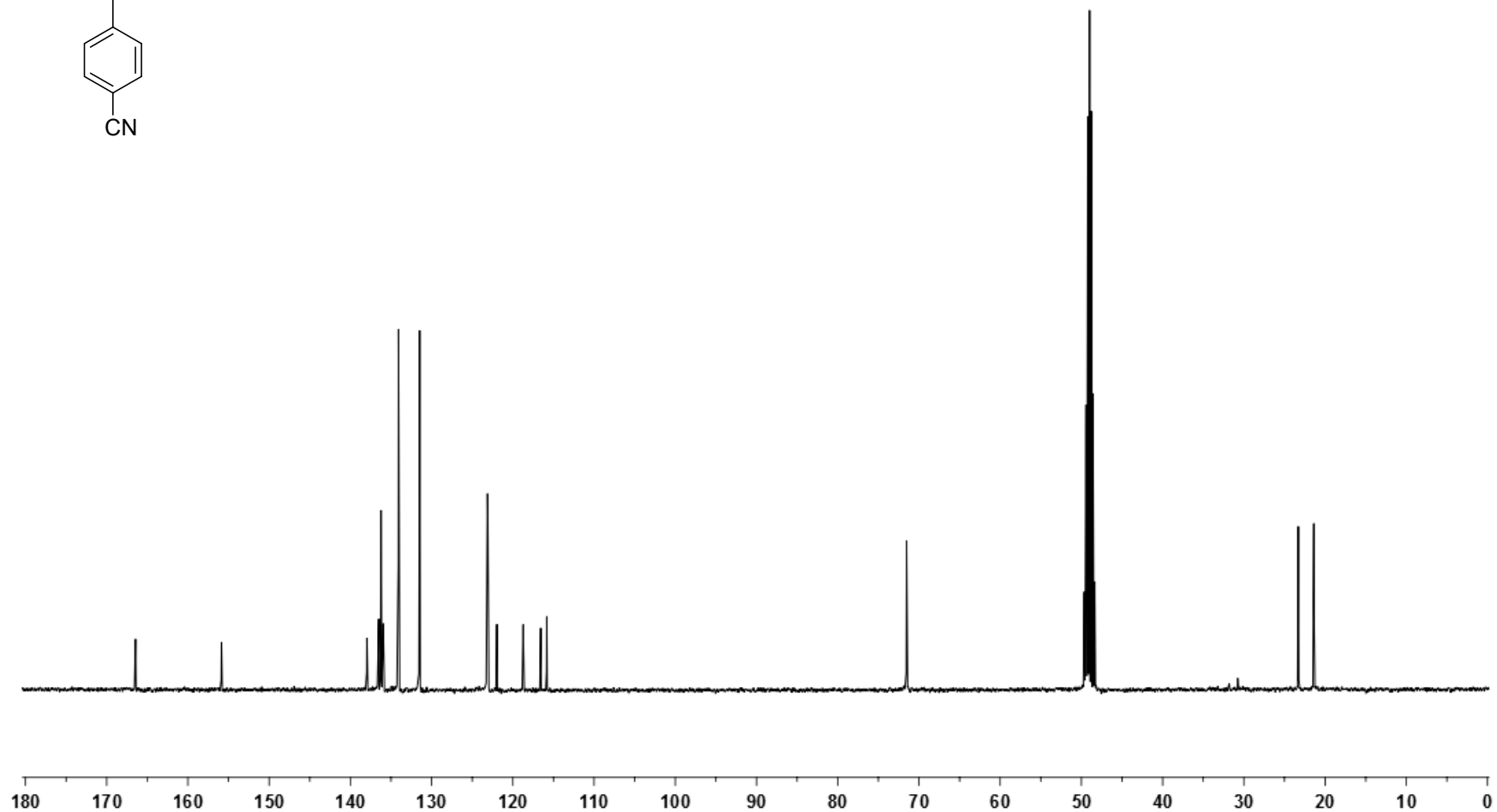
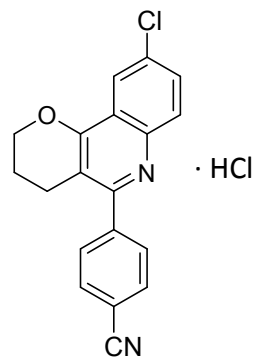
4-{9-Chloro-3,4-dihydro-2H-pyrano[3,2-c]quinolin-5-yl}benzotrile **38**

^1H NMR (400 MHz, CD_3OD)



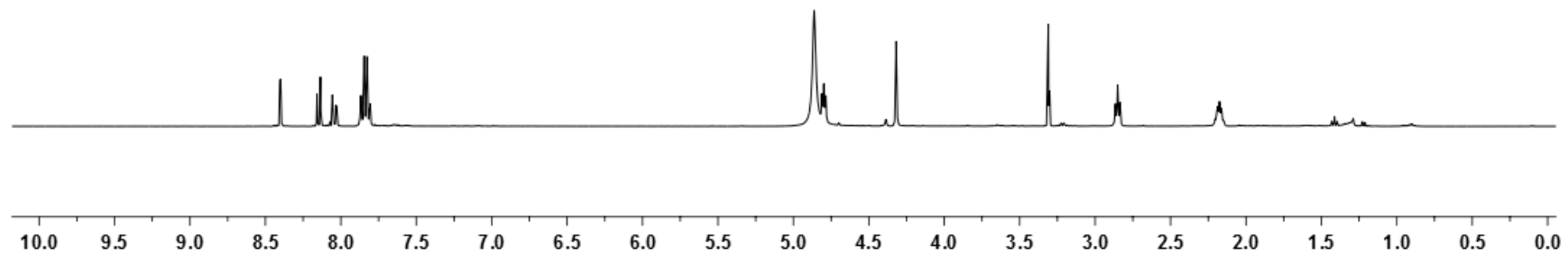
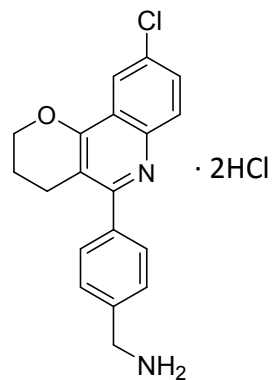
4-{9-Chloro-3,4-dihydro-2H-pyrano[3,2-c]quinolin-5-yl}benzonitrile **38**

^{13}C NMR (100.6 MHz, CD_3OD)



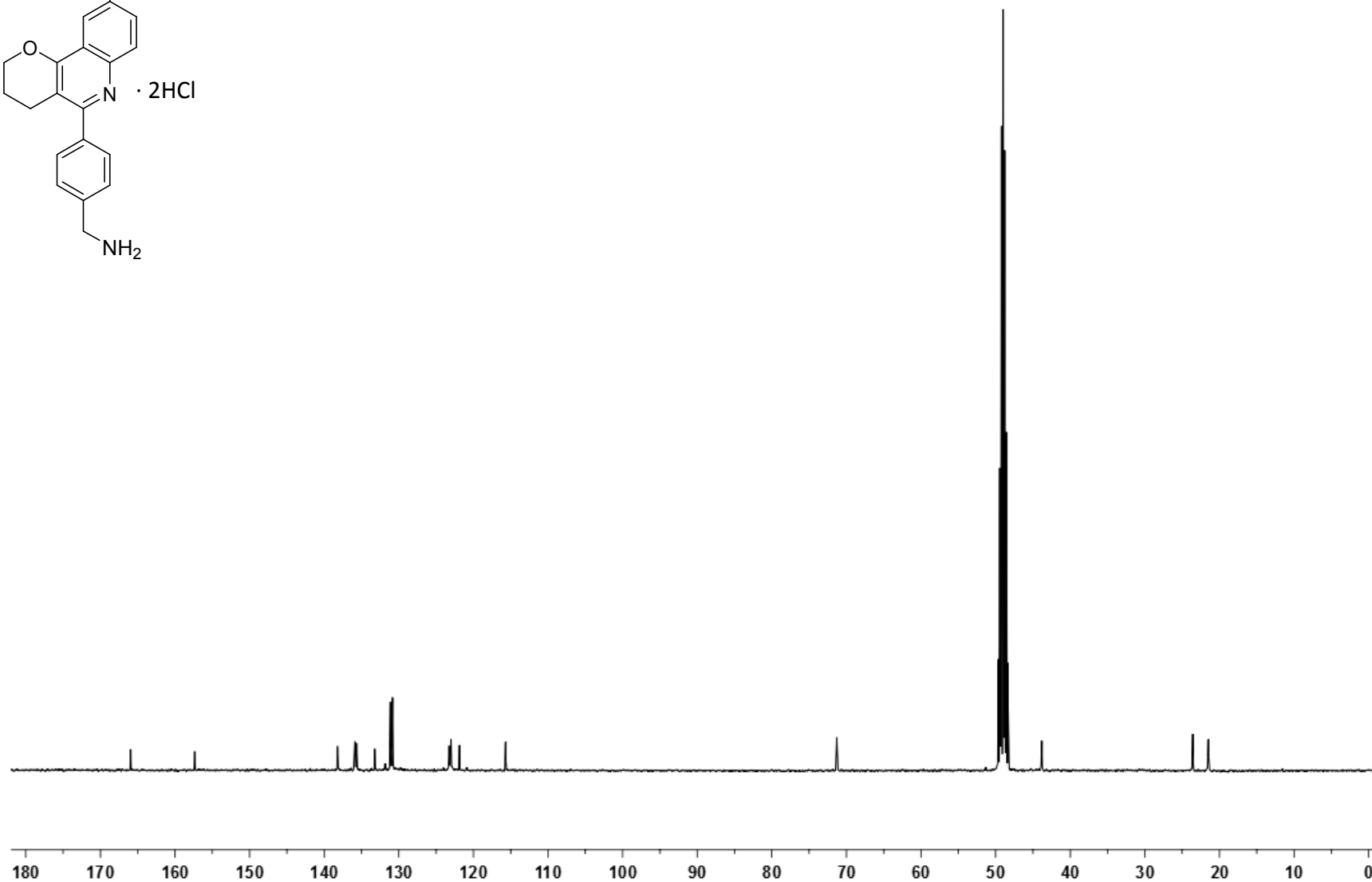
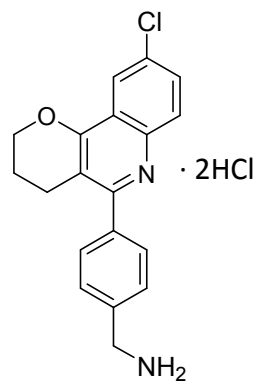
4-{9-Chloro-3,4-dihydro-2H-pyrano[3,2-c]quinolin-5-yl}benzylamine **39**

^1H NMR (400 MHz, CD_3OD)



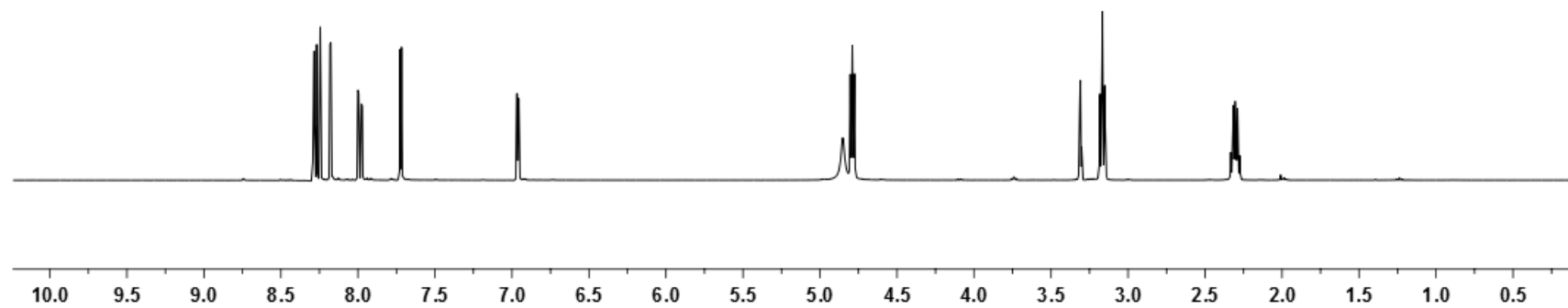
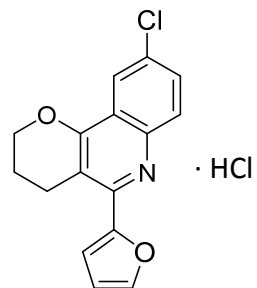
4-{9-Chloro-3,4-dihydro-2H-pyrano[3,2-c]quinolin-5-yl}benzylamine **39**

^{13}C NMR (100.6 MHz, CD_3OD)



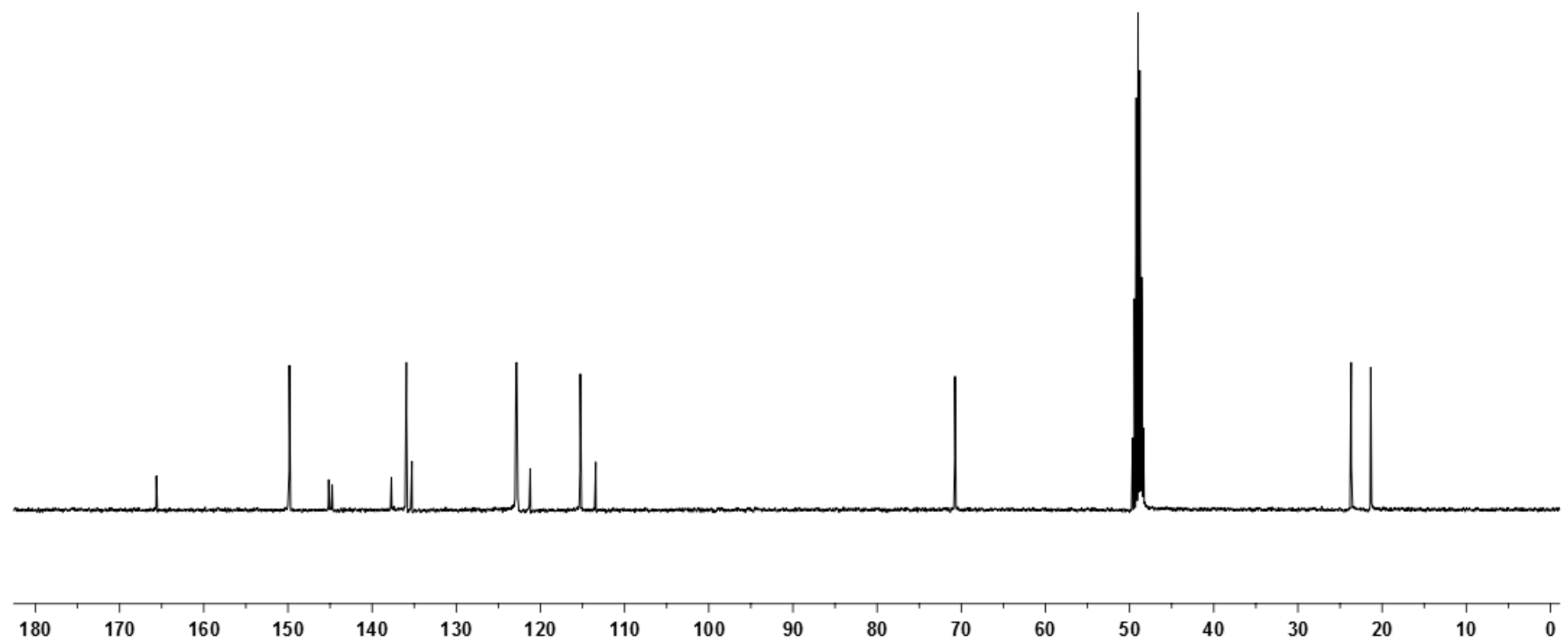
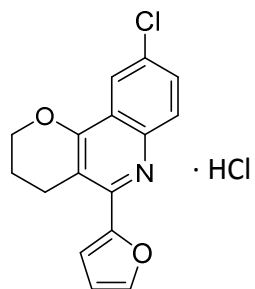
9-Chloro-5-(2-furyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline **42**

^1H NMR (400 MHz, CD_3OD)



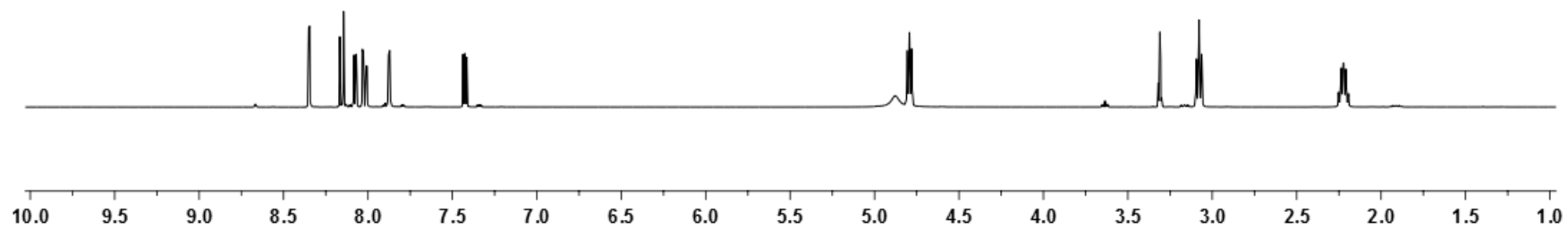
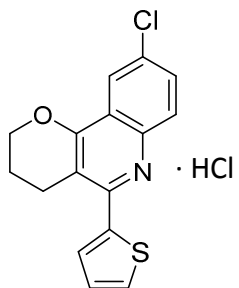
9-Chloro-5-(2-furyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline **42**

^{13}C NMR (100.6 MHz, CD_3OD)



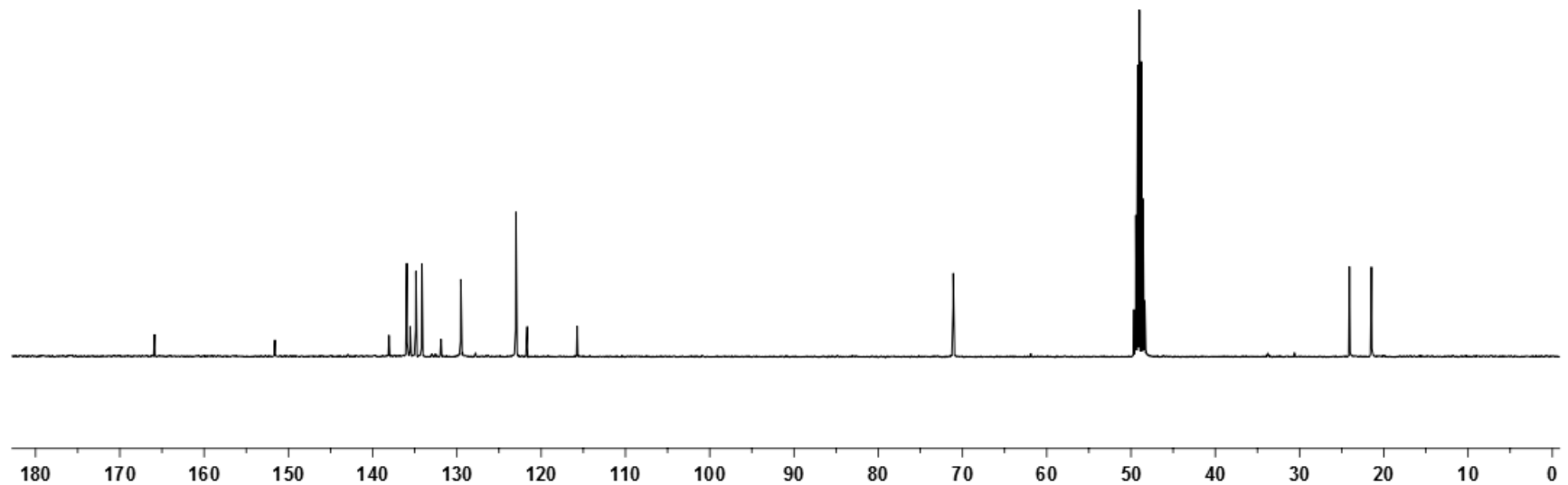
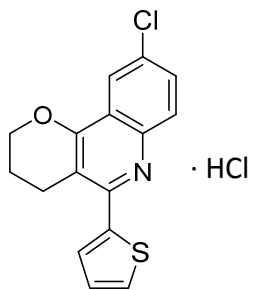
9-Chloro-3,4-dihydro-5-(2-thienyl)-2H-pyrano[3,2-c]quinoline 43

¹H NMR (400 MHz, CD₃OD)



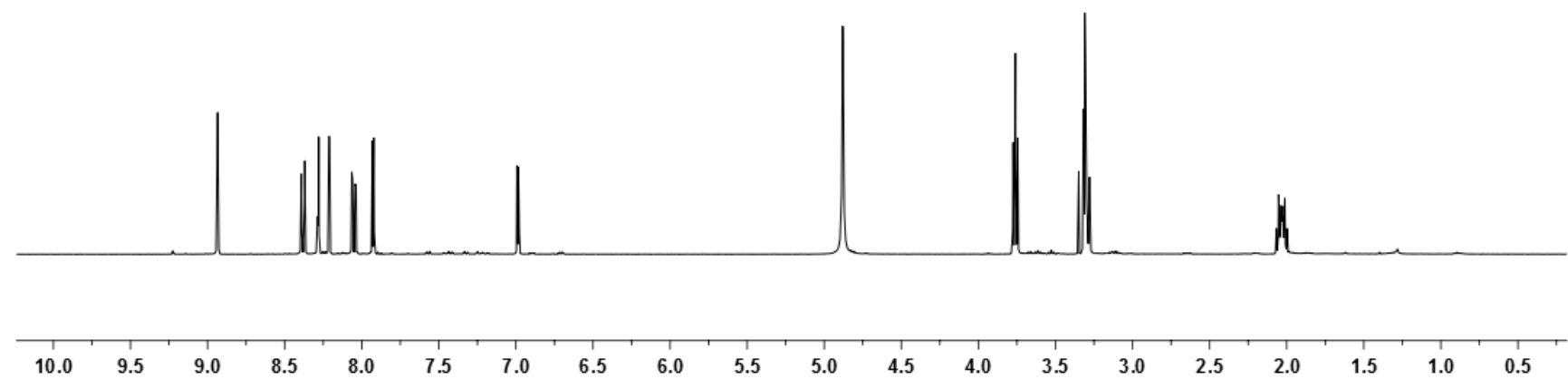
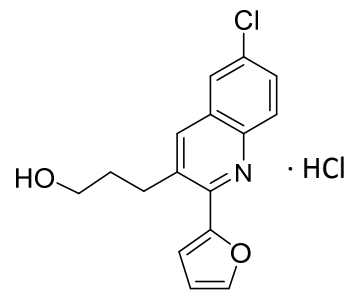
9-Chloro-3,4-dihydro-5-(2-thienyl)-2H-pyrano[3,2-c]quinoline 43

¹³C NMR (100.6 MHz, CD₃OD)



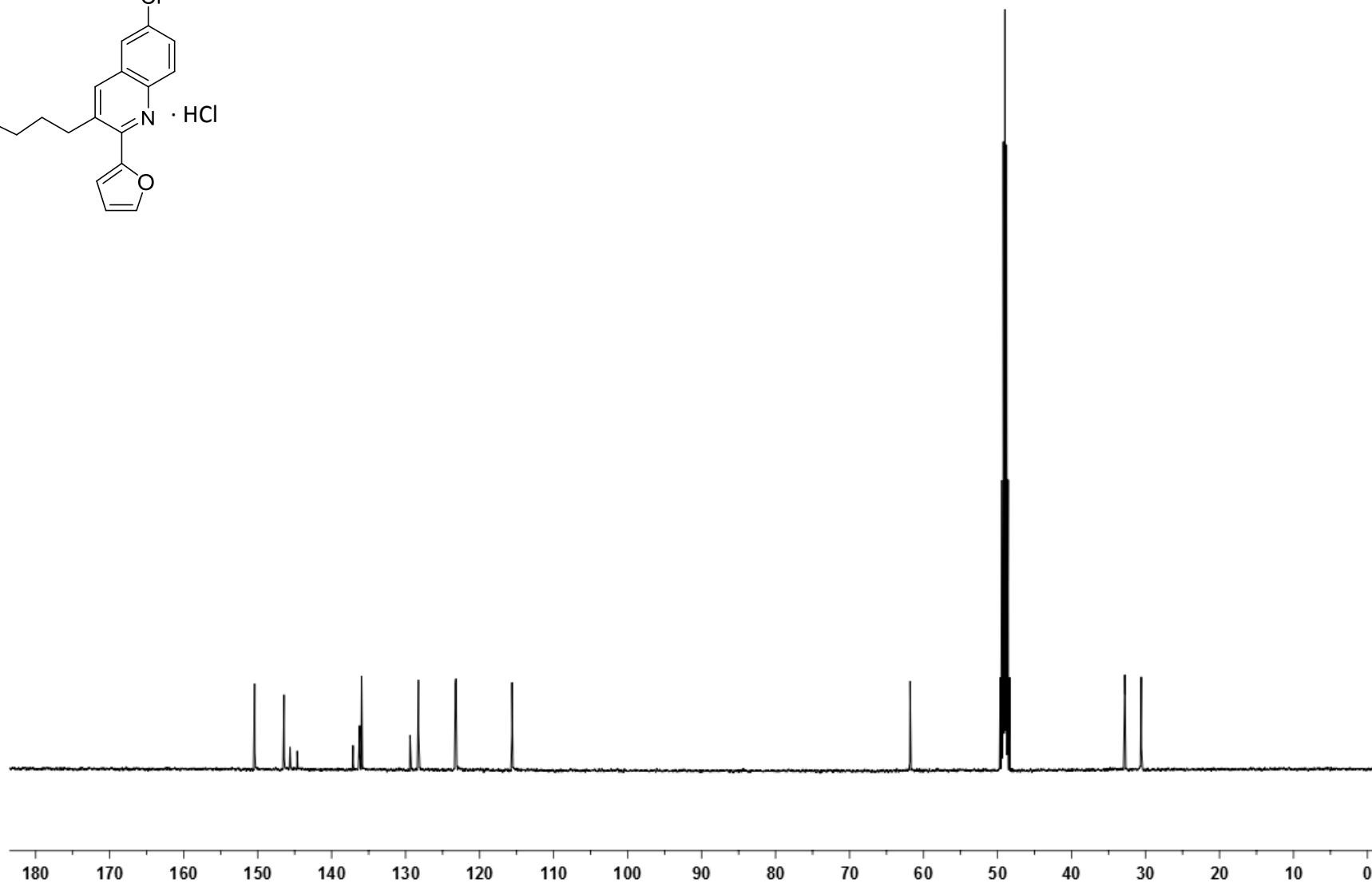
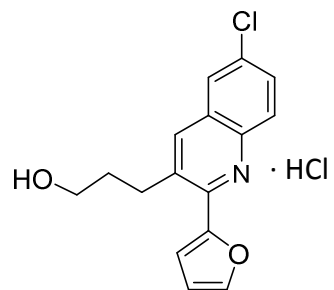
3-[6-Chloro-2-(2-furyl)quinolin-3-yl]-1-propanol **44**

¹H NMR (400 MHz, CD₃OD)



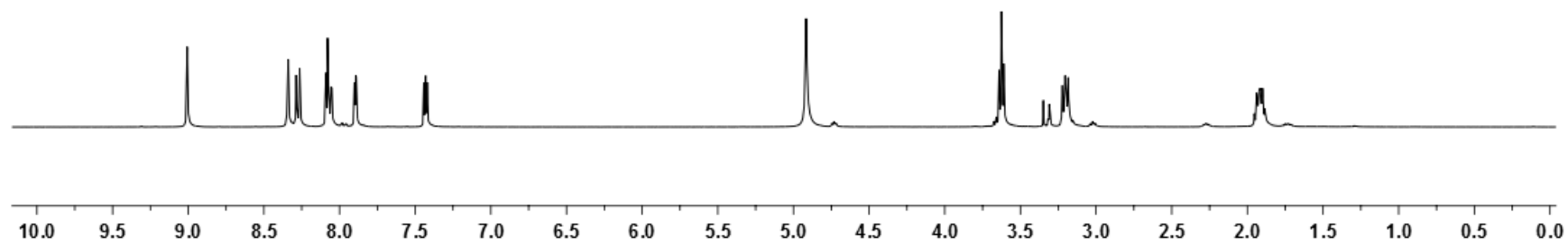
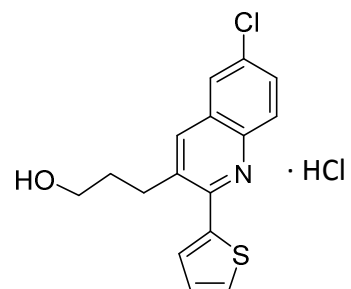
3-[6-Chloro-2-(2-furyl)quinolin-3-yl]-1-propanol **44**

¹³C NMR (100.6 MHz, CD₃OD)



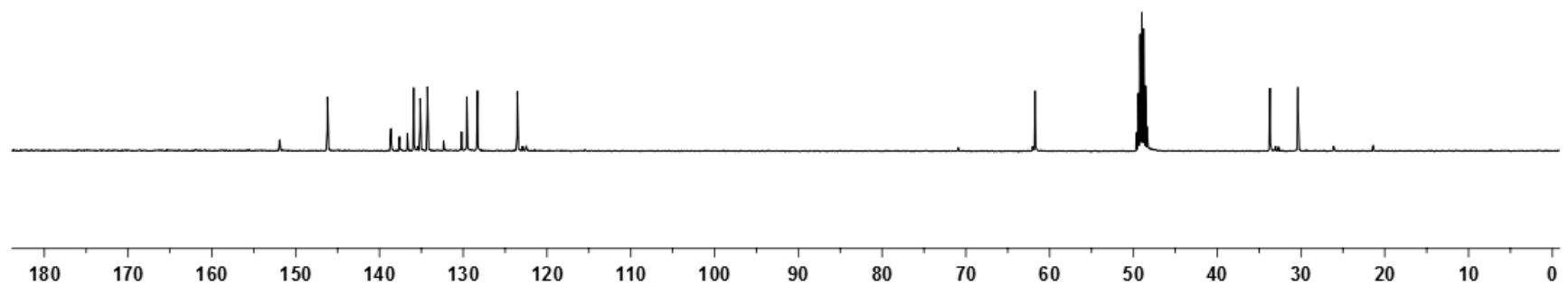
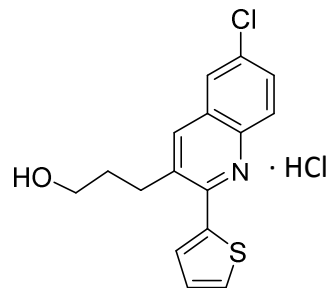
3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]-1-propanol 45

¹H NMR (400 MHz, CD₃OD)



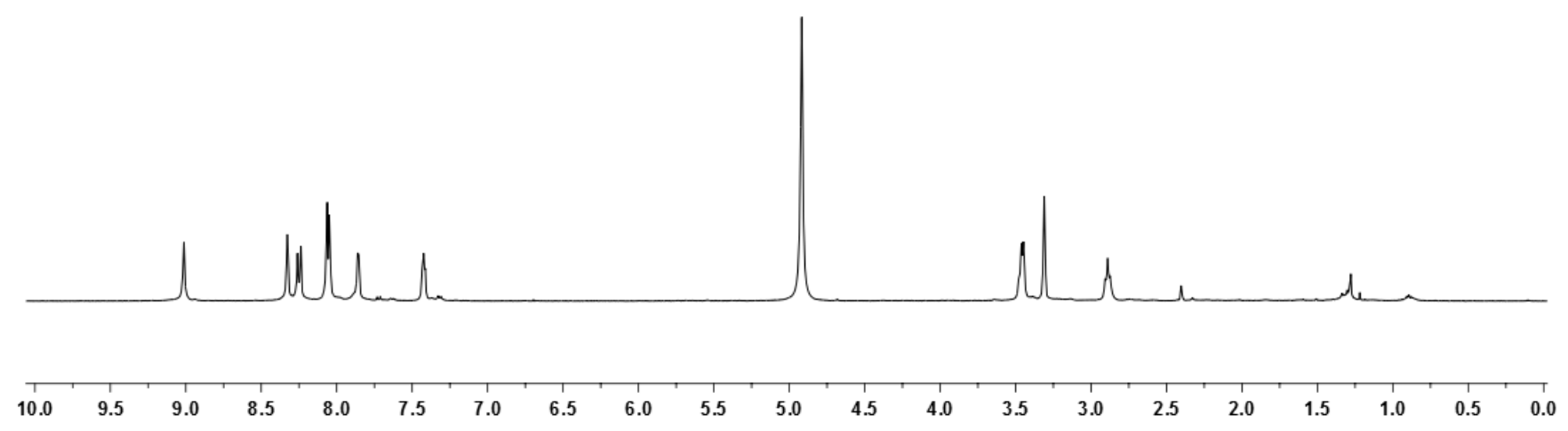
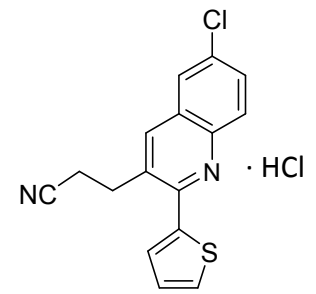
3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]-1-propanol 45

¹³C NMR (100.6 MHz, CD₃OD)



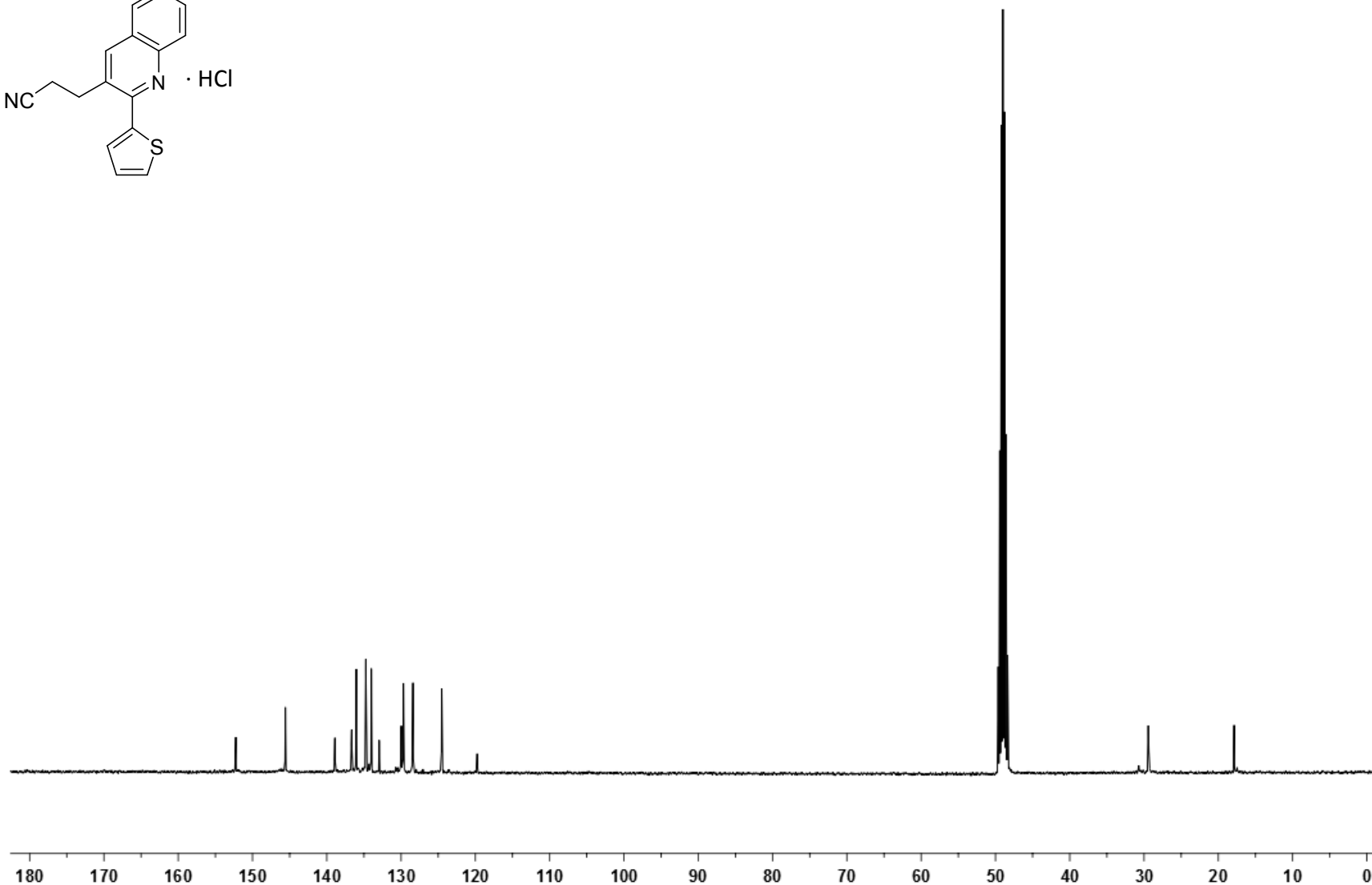
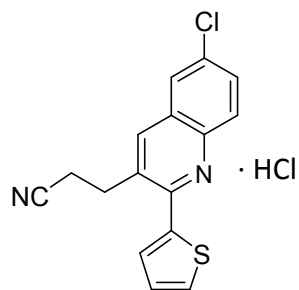
3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propanenitrile 47

¹H NMR (400 MHz, CD₃OD)



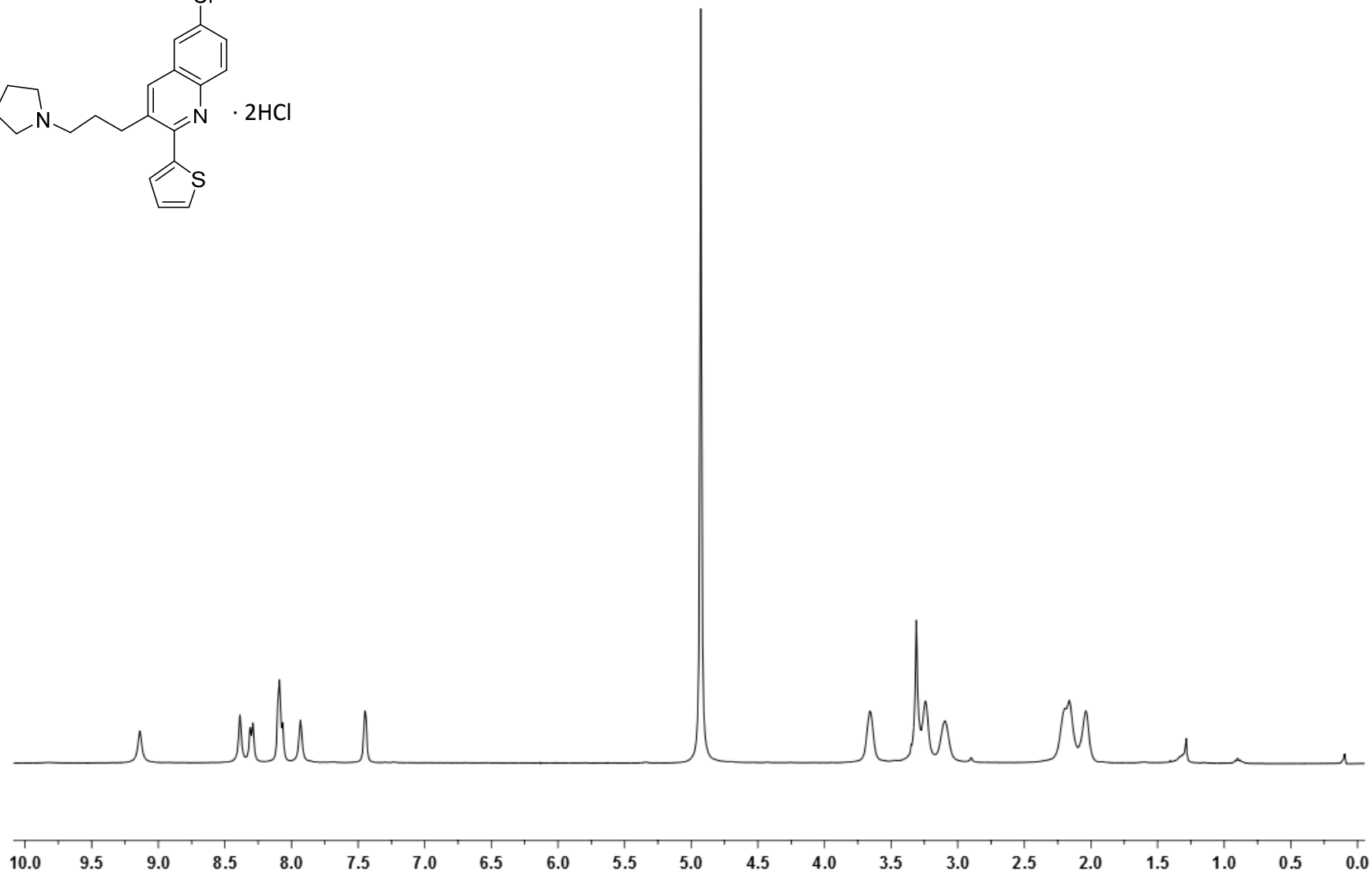
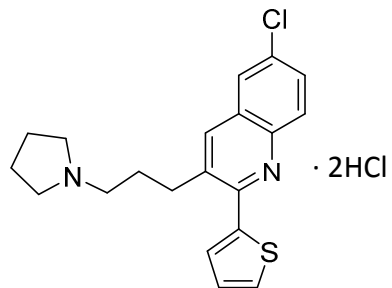
3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propanenitrile 47

¹³C NMR (100.6 MHz, CD₃OD)



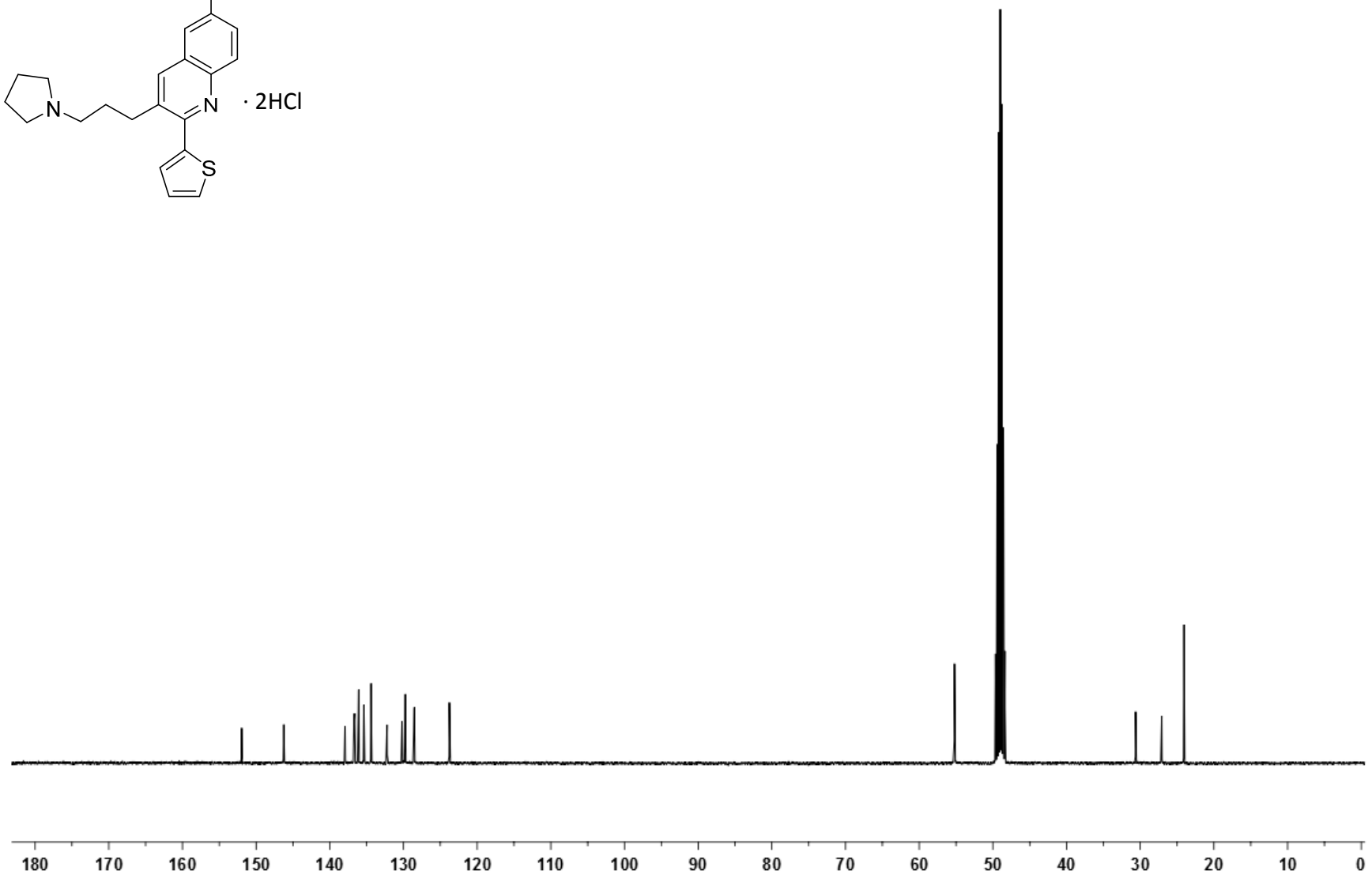
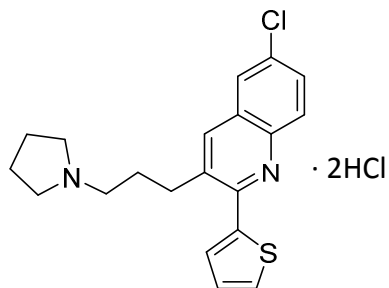
N*-{3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propyl}pyrrolidine **49*

¹H NMR (400 MHz, CD₃OD)



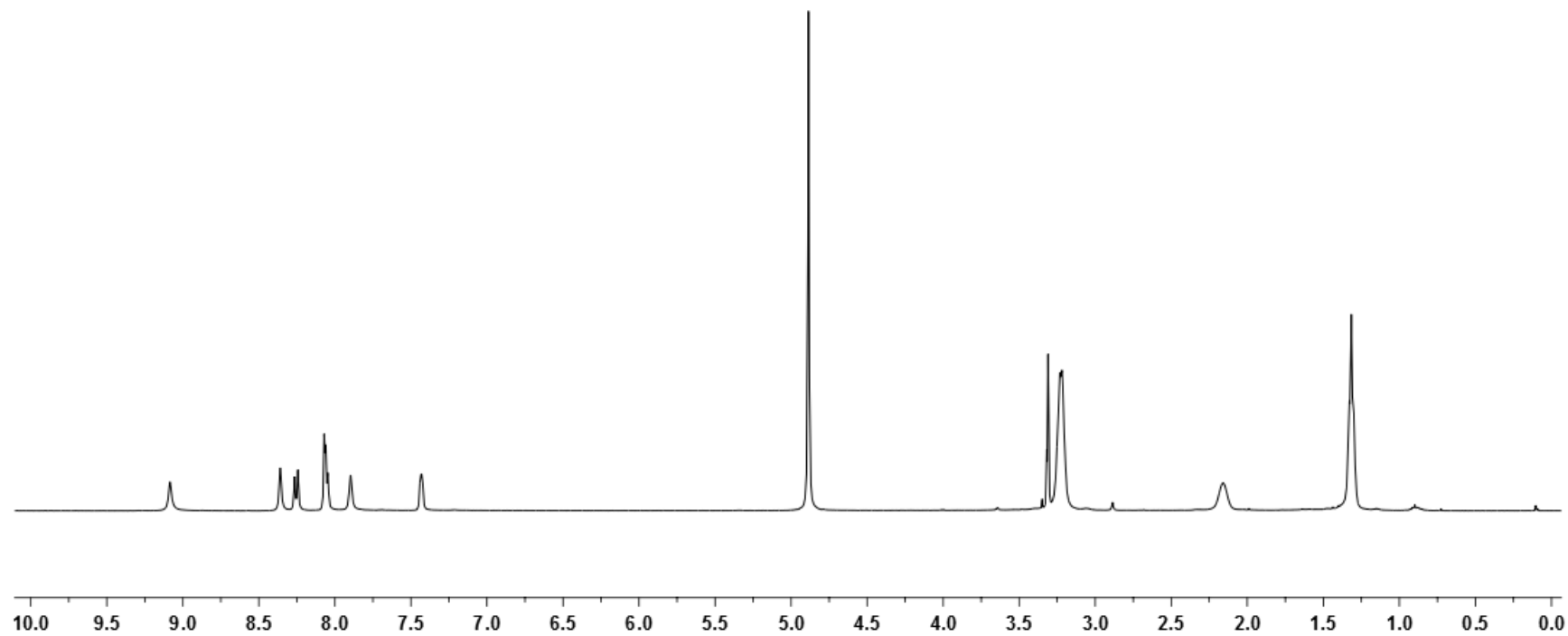
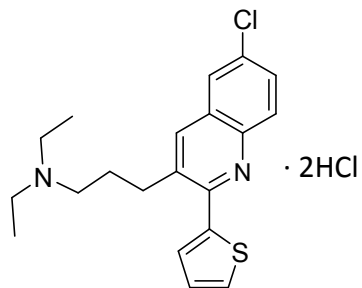
N-{3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propyl}pyrrolidine **49**

¹³C NMR (100.6 MHz, CD₃OD)



N-{3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propyl}-*N,N*-diethylamine **50**

^1H NMR (400 MHz, CD_3OD)



N-{3-[6-Chloro-2-(2-thienyl)quinolin-3-yl]propyl}-*N,N*-diethylamine **50**

¹³C NMR (100.6 MHz, CD₃OD)

