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## Novel multi-target directed ligands as drug candidates against Alzheimer's disease

Francisco Javier Pérez Areales

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Facultad de Farmacia y Ciencias de la Alimentación  
Departamento de Farmacología, Toxicología y Química Terapéutica  
Unidad de Química Farmacéutica

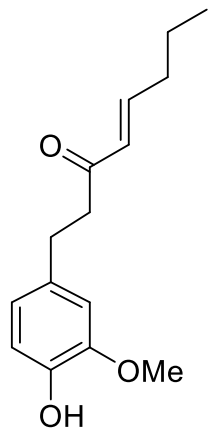
**NOVEL MULTI-TARGET DIRECTED LIGANDS  
AS DRUG CANDIDATES AGAINST ALZHEIMER'S DISEASE**

**Nuclear Magnetic Resonance Spectroscopy  
( $^1\text{H}$  and  $^{13}\text{C}$  spectrum)**

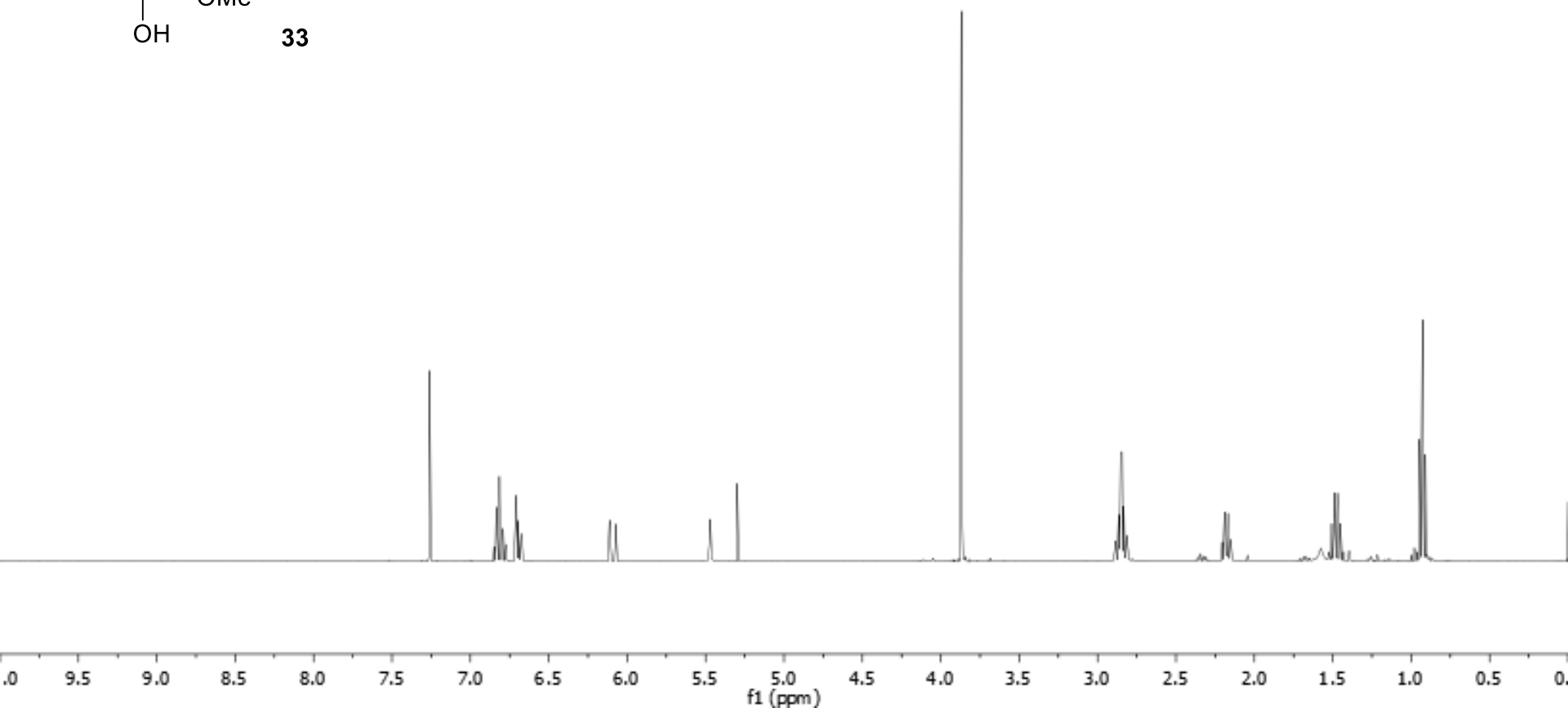
**Francisco Javier Pérez Areales**

Barcelona, 2017

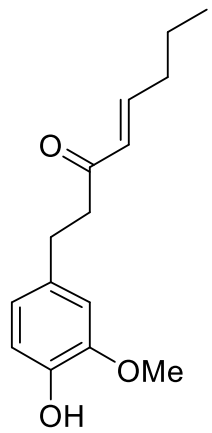
1-(4-hydroxy-3-methoxyphenyl)oct-4-en-3-one, **33** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



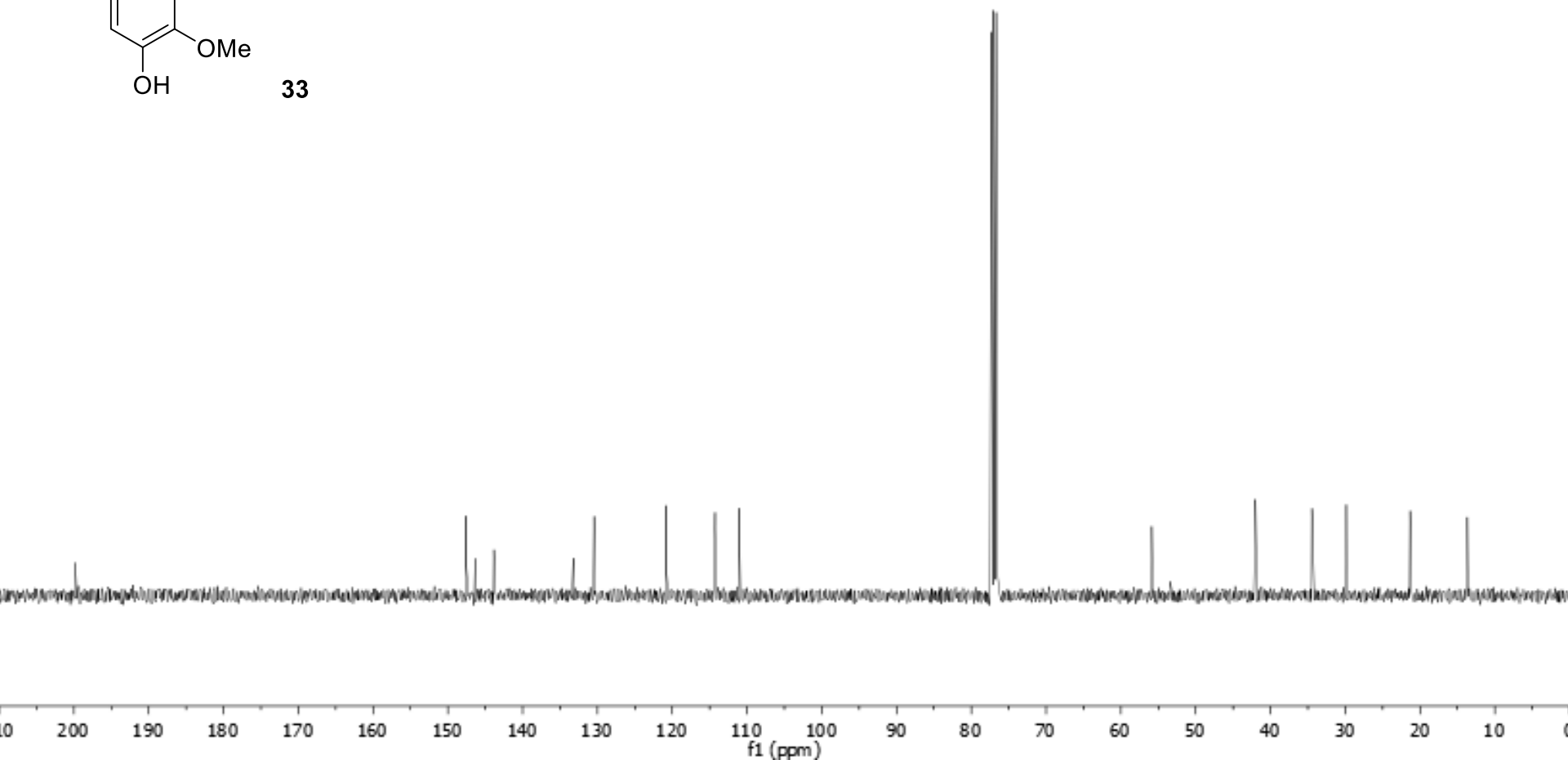
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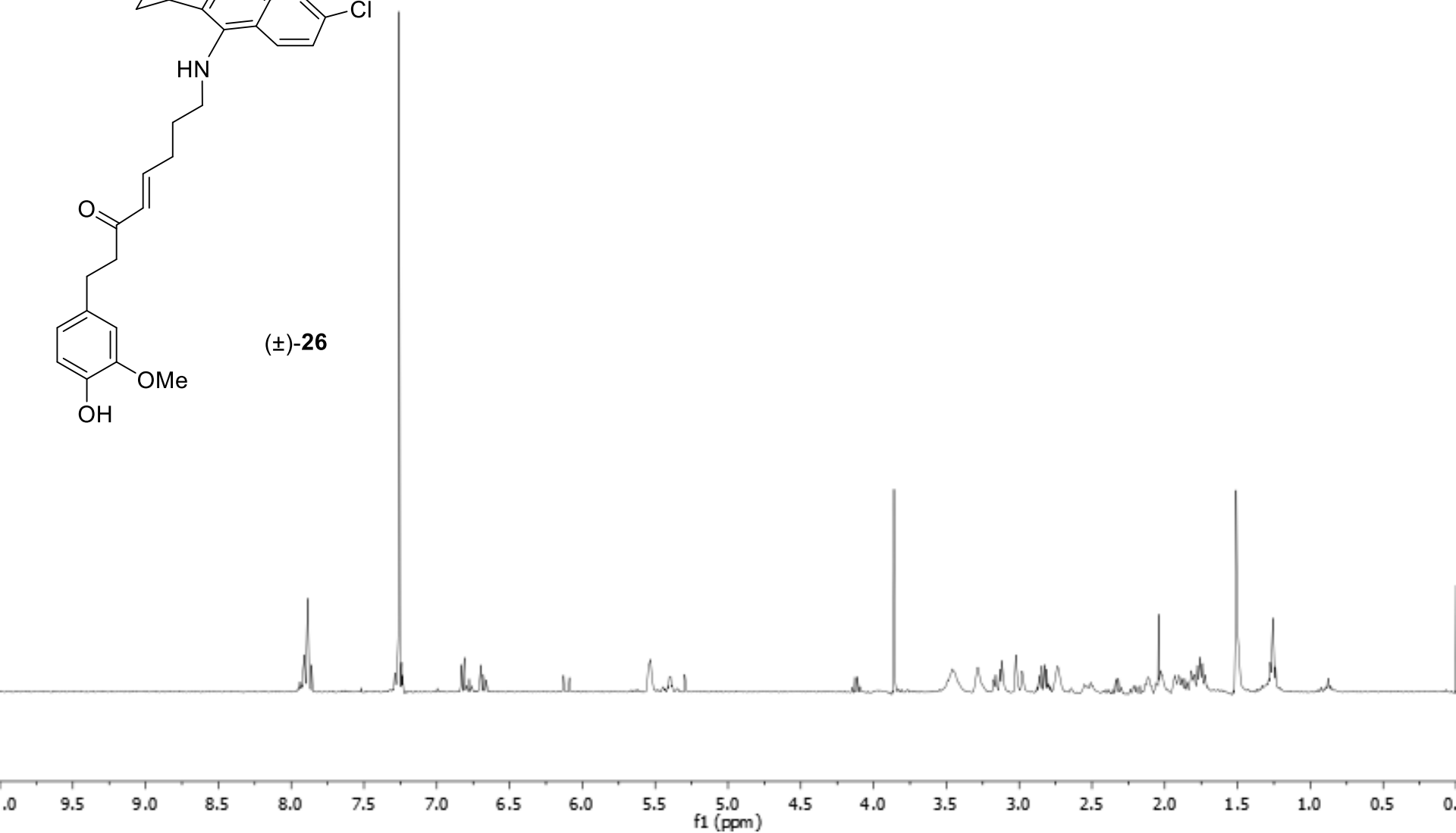
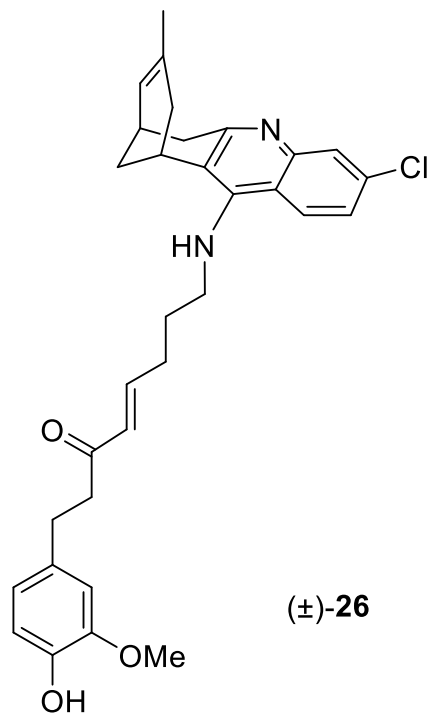
1-(4-hydroxy-3-methoxyphenyl)oct-4-en-3-one, **33** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )



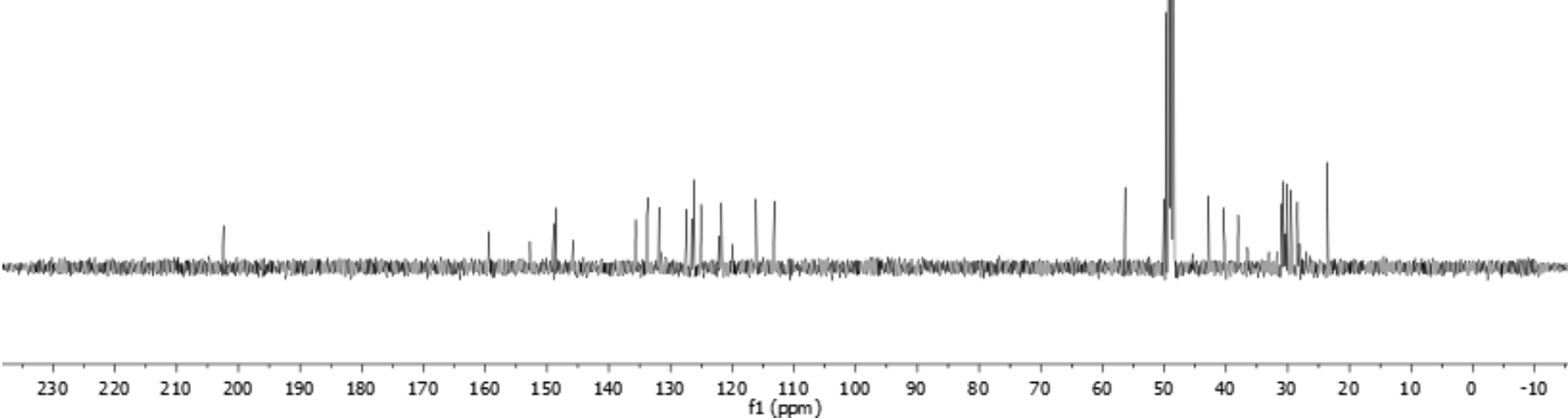
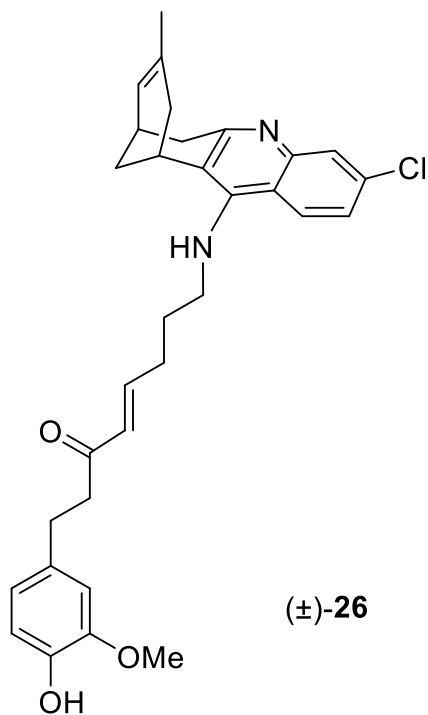
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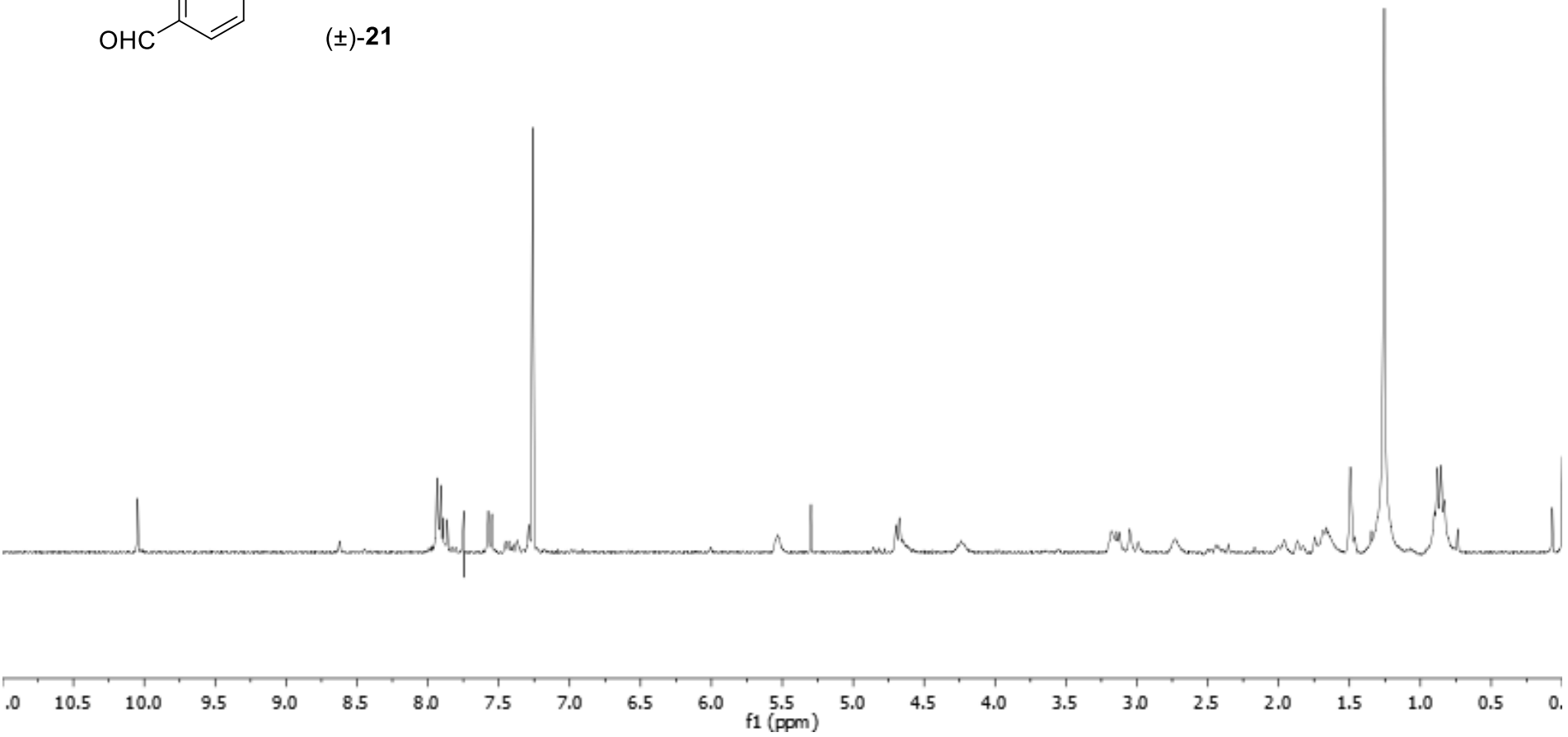
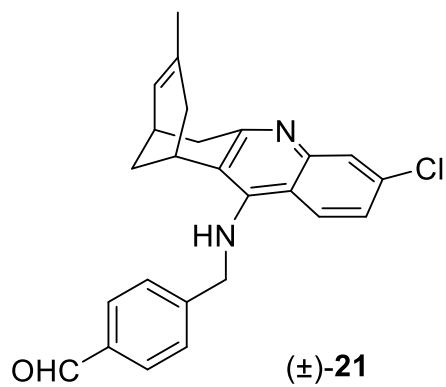
(±)-8-[(3-Chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]-1-(4-hydroxy-3-methoxyphenyl)oct-4-en-3-one, (±)-**26** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



(±)-8-[(3-Chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]-1-(4-hydroxy-3-methoxyphenyl)oct-4-en-3-one, (±)-**26** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

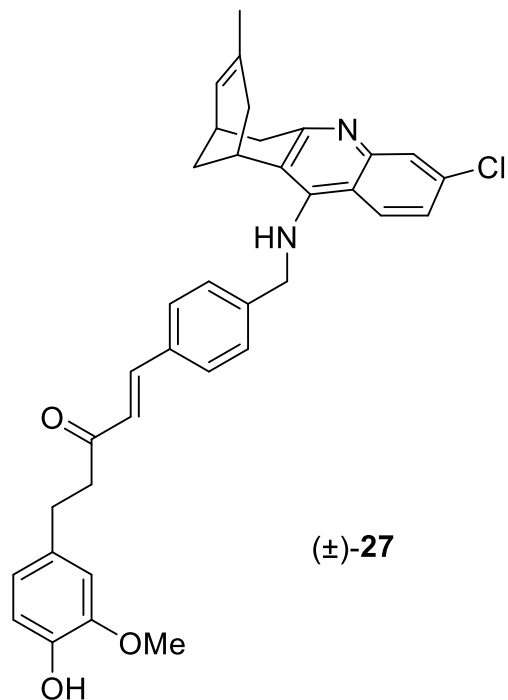


(±)-4-[[[(3-Chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]methyl}benzaldehyde, (±)-**21** –  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

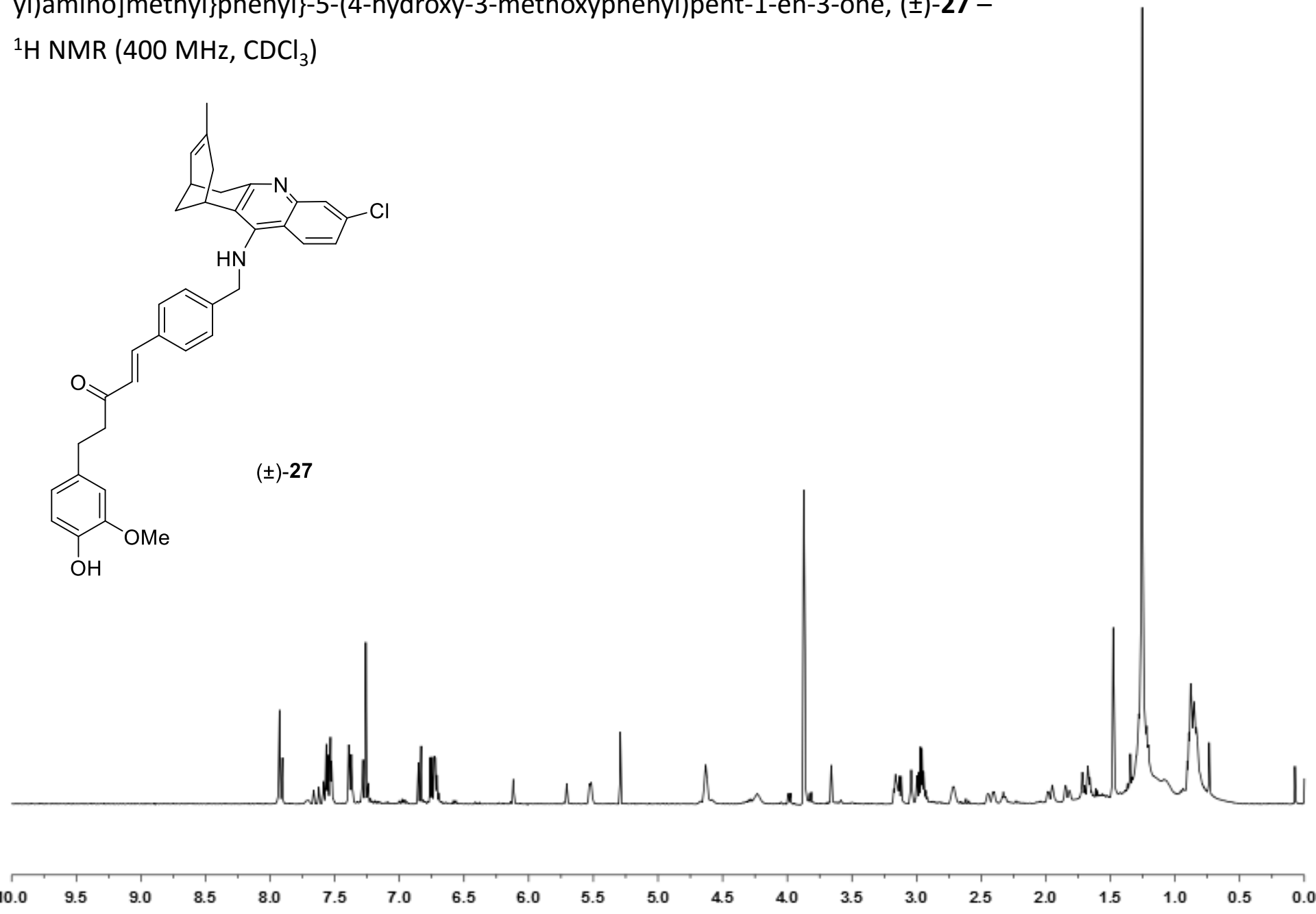


(±)-{4-[[3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]methyl}phenyl}-5-(4-hydroxy-3-methoxyphenyl)pent-1-en-3-one, (±)-**27** –

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

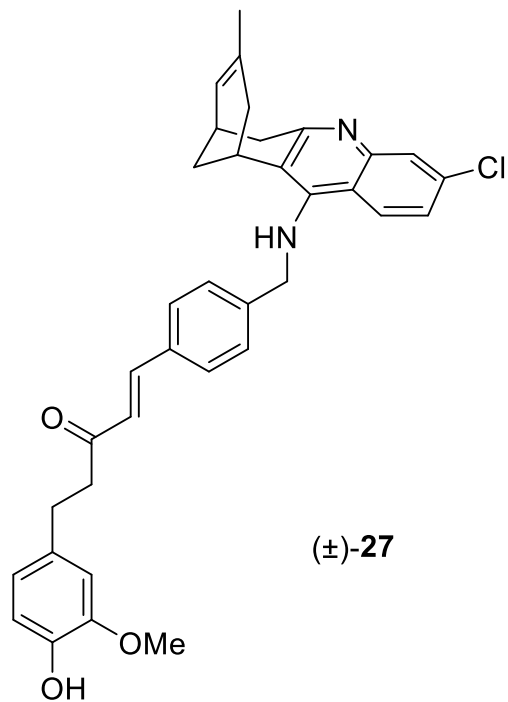


(±)-**27**

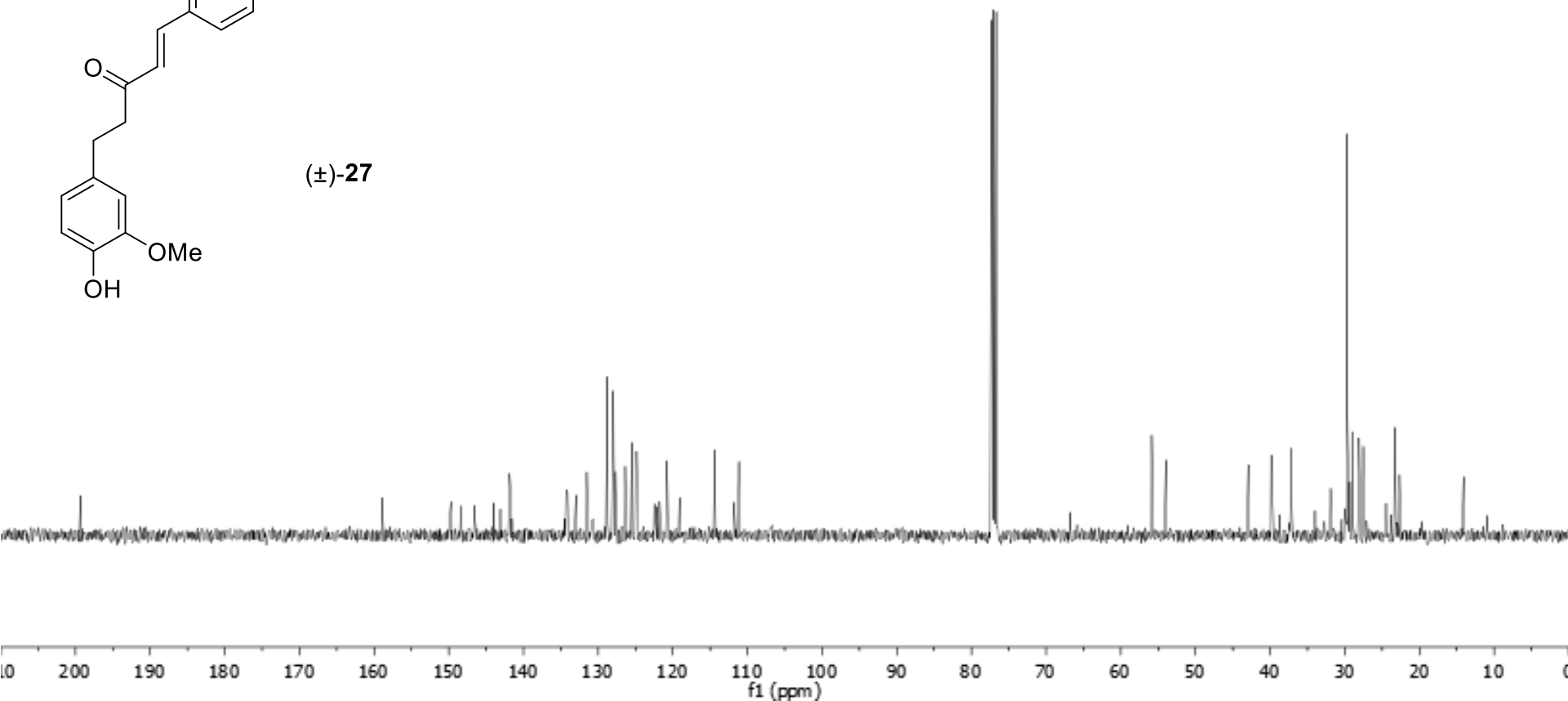




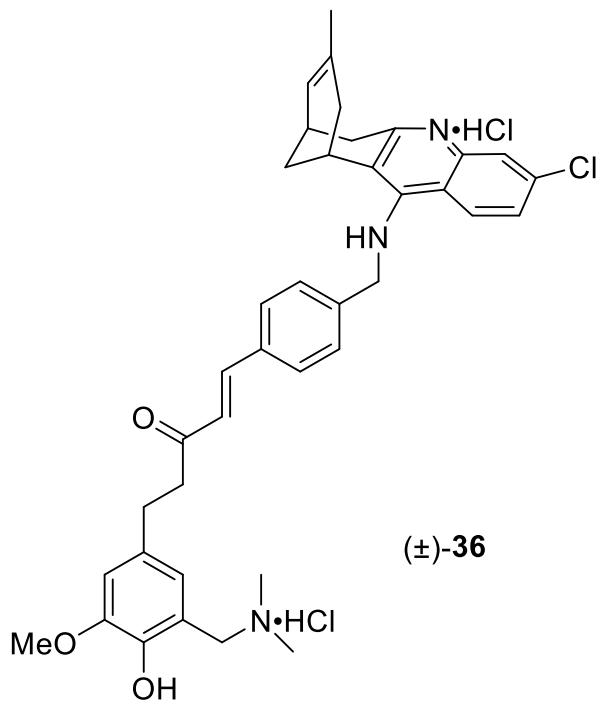
(±)-{4-[[[(3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]methyl}phenyl]-5-(4-hydroxy-3-methoxyphenyl)pent-1-en-3-one, (±)-**27** –  
<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)



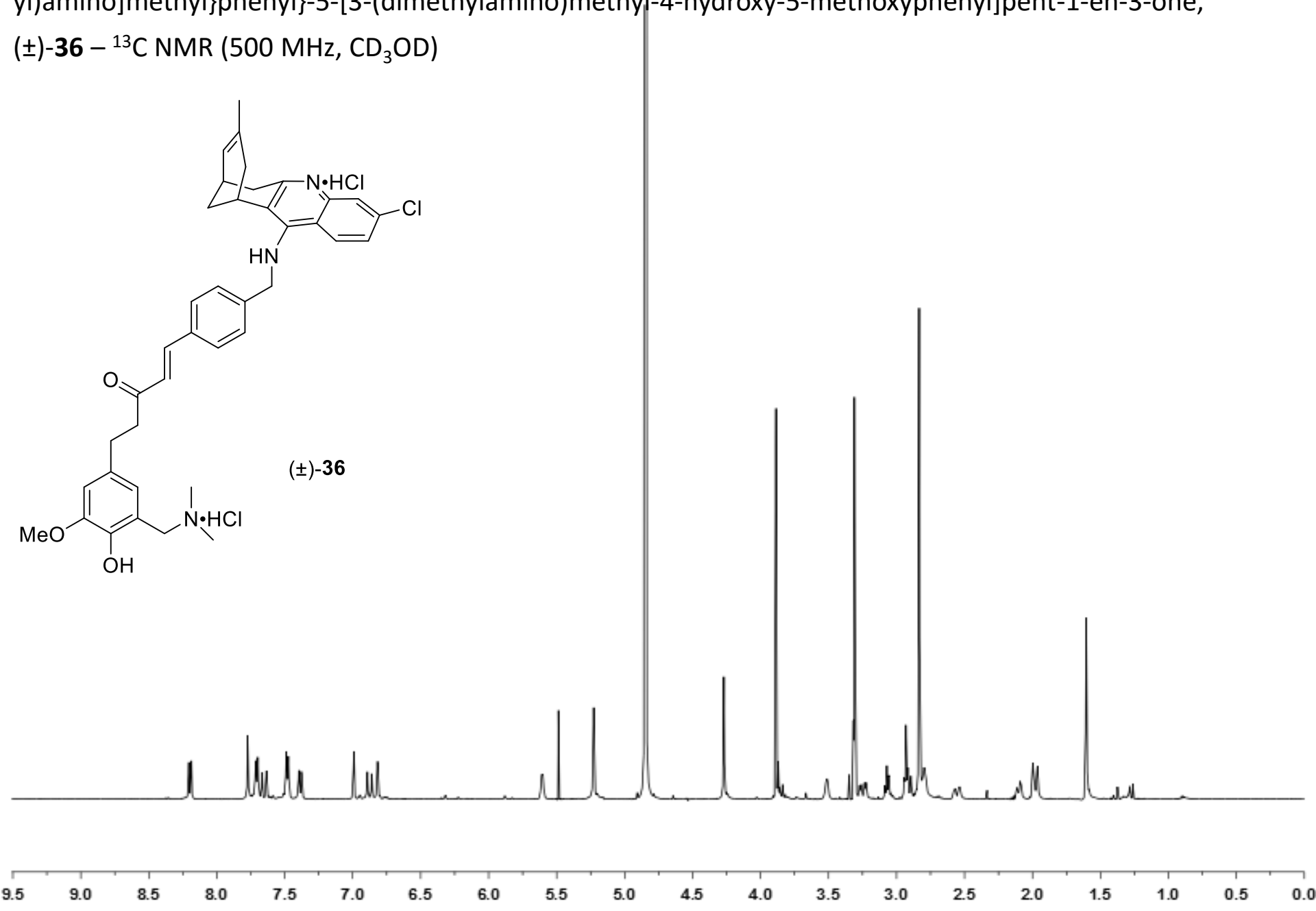
(±)-**27**



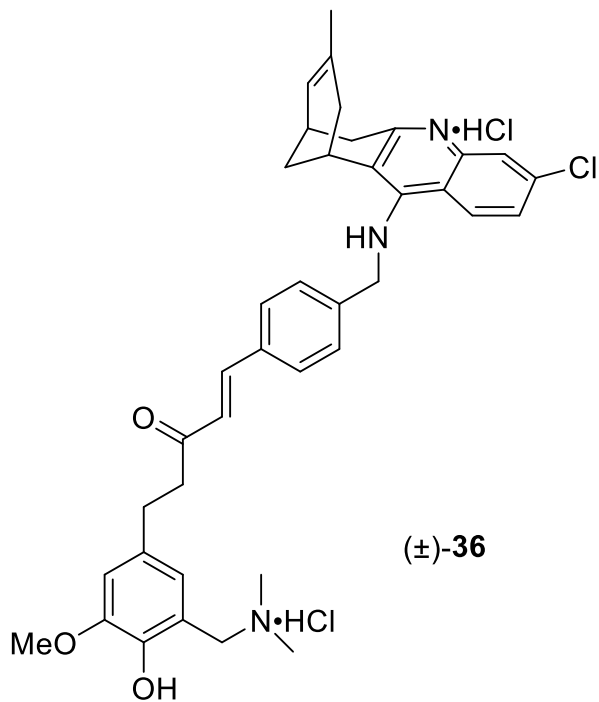
(±)-1-{4-[[3-(3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]methyl]phenyl}-5-[3-(dimethylamino)methyl]-4-hydroxy-5-methoxyphenyl]pent-1-en-3-one, (±)-**36** – <sup>13</sup>C NMR (500 MHz, CD<sub>3</sub>OD)



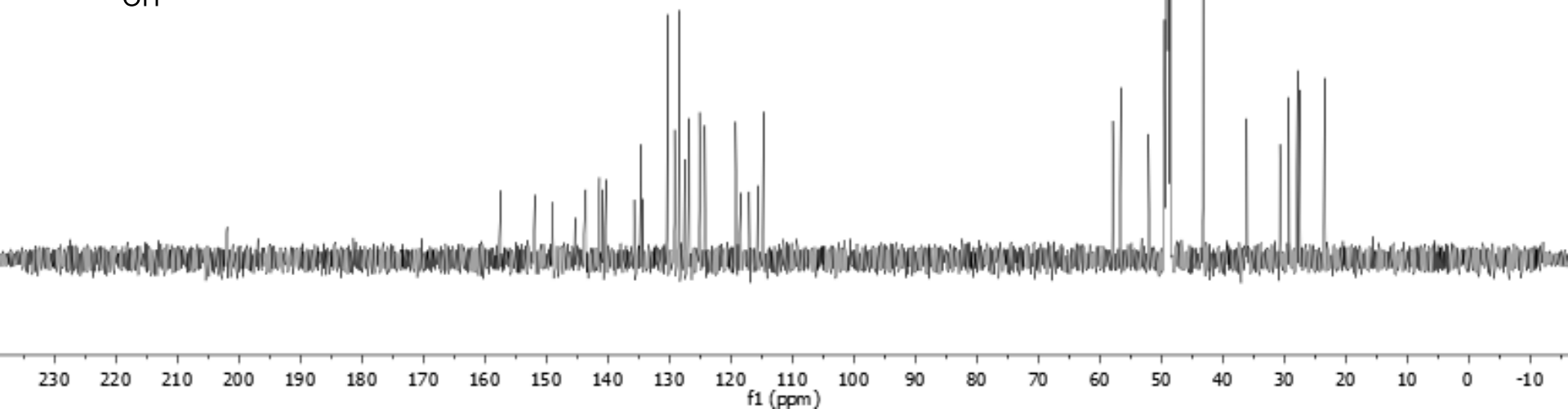
(±)-**36**



(±)-1-{4-[[3-(3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]methyl}phenyl}-5-[3-(dimethylamino)methyl-4-hydroxy-5-methoxyphenyl]pent-1-en-3-one, (±)-**36** –  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CD}_3\text{OD}$ )

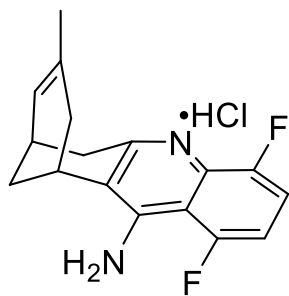


(±)-**36**

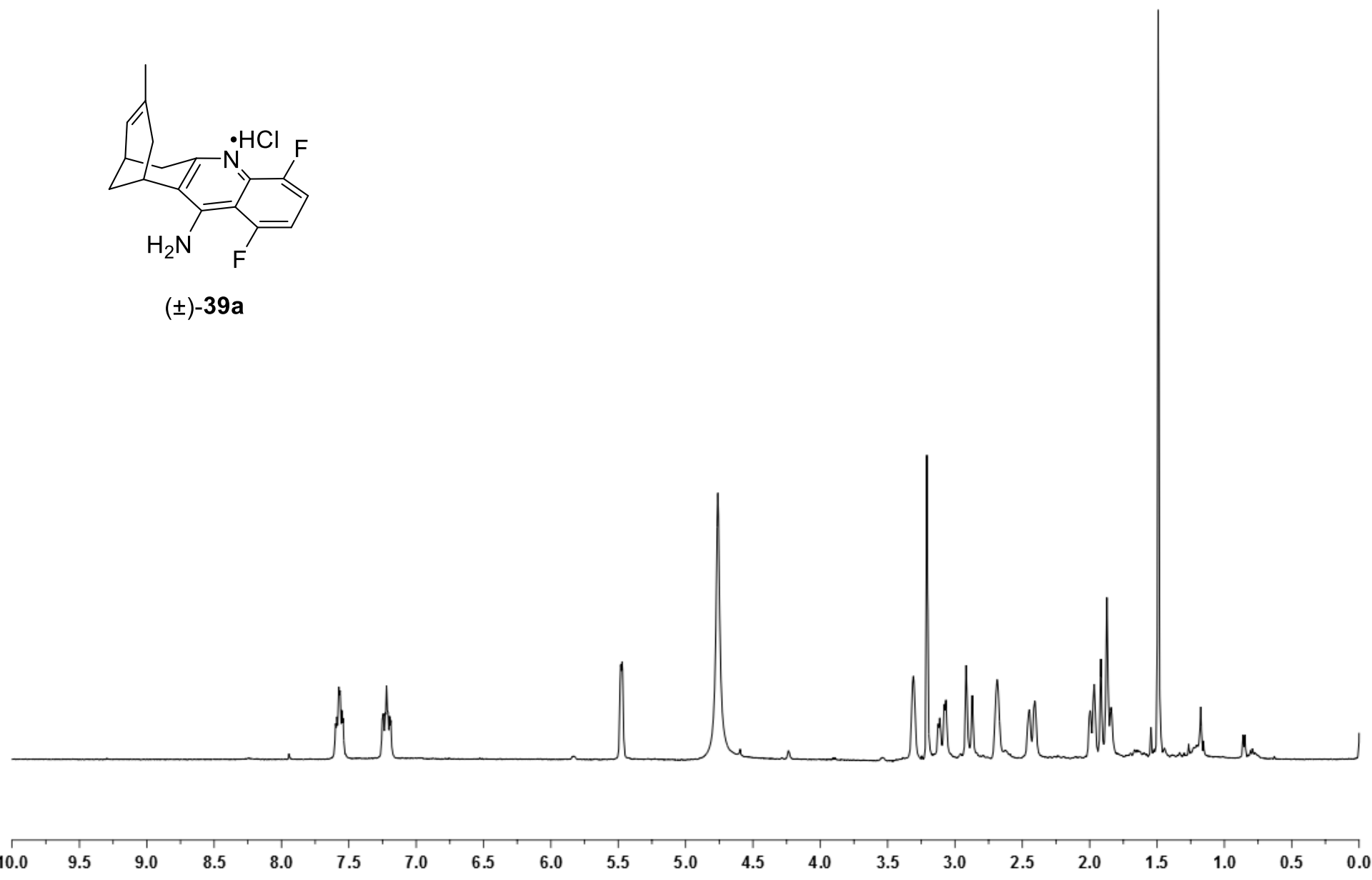


(±)-12-amine-1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinoline, (±)-**39a** –

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)

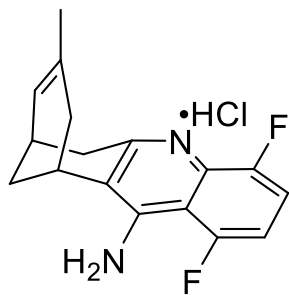


(±)-**39a**

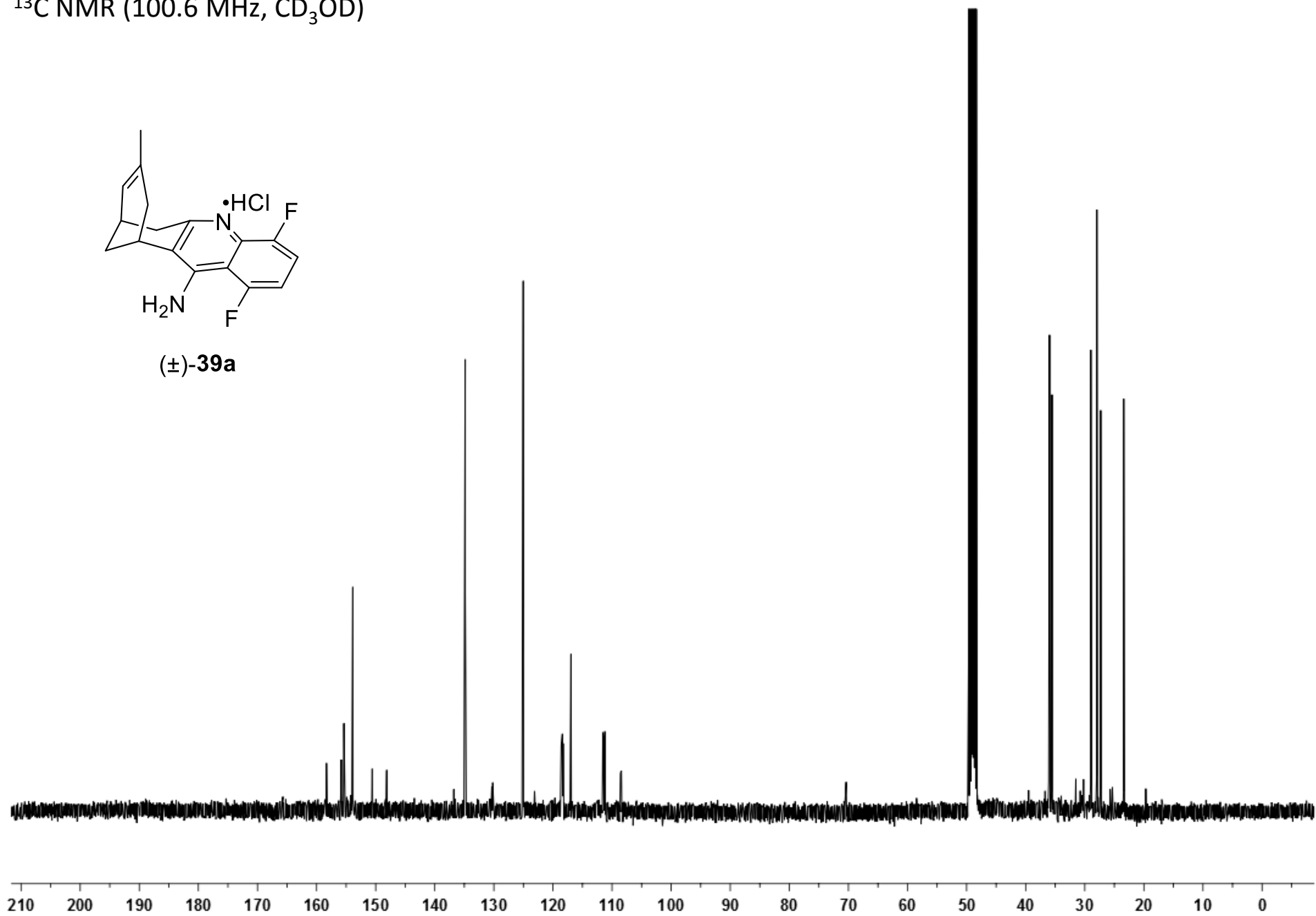


(±)-12-amine-1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinoline, (±)-**39a** –

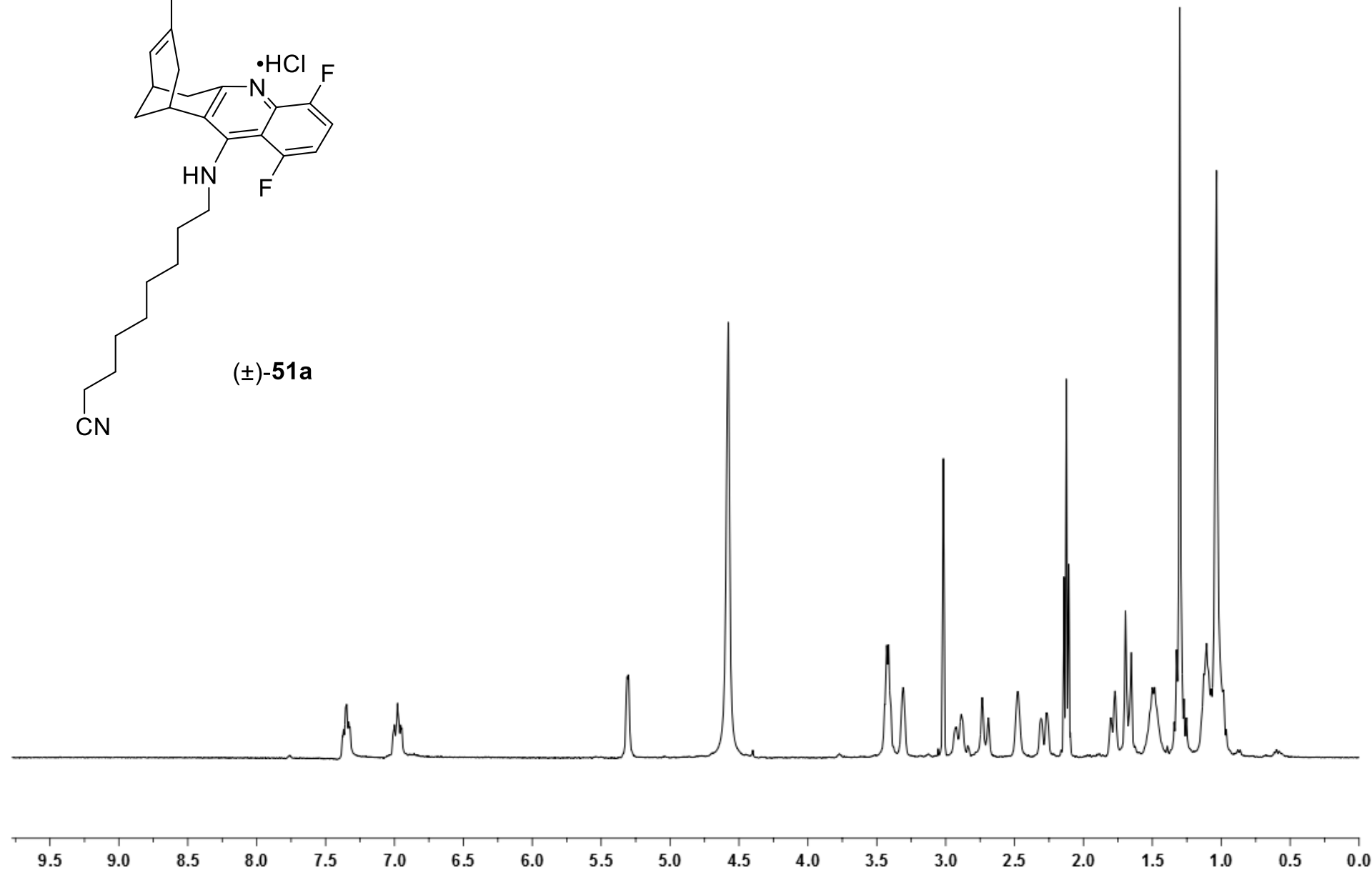
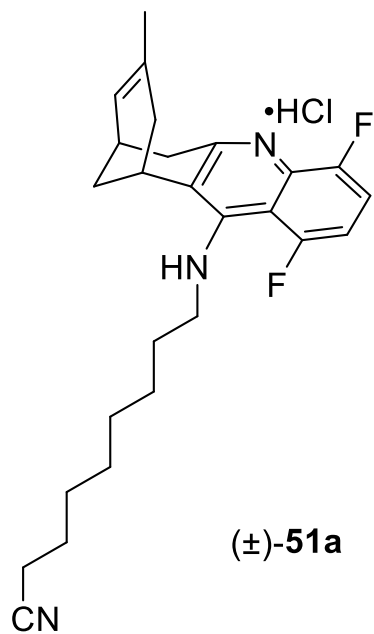
<sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD)



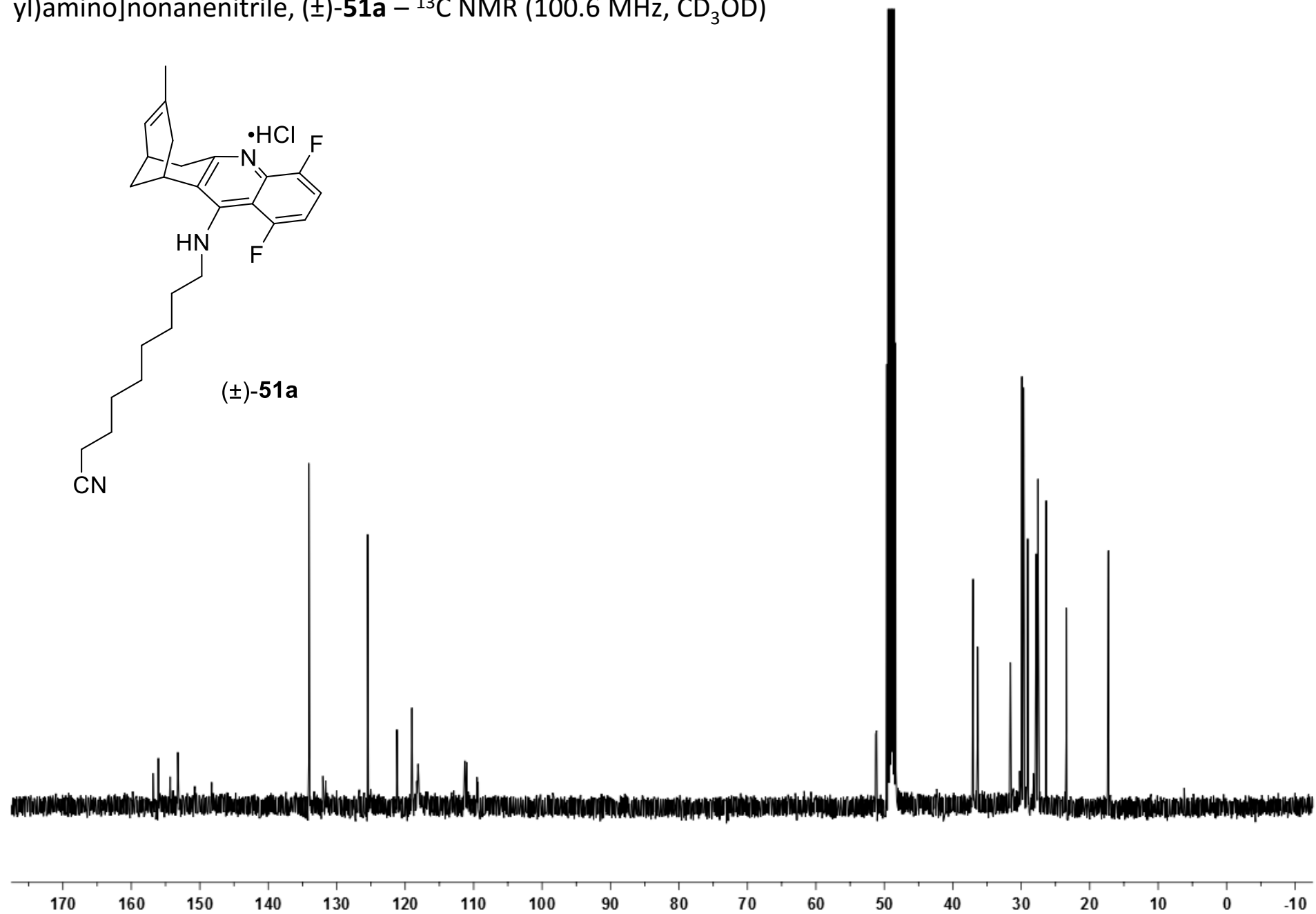
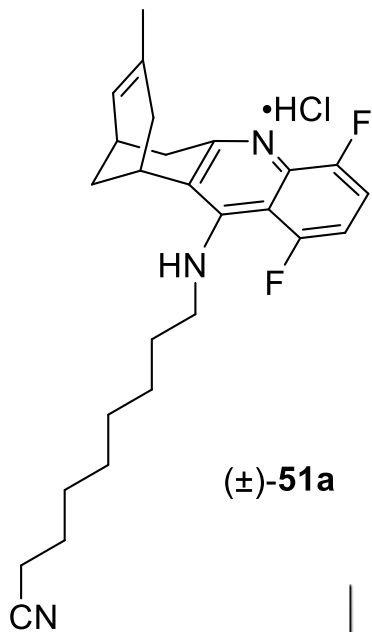
(±)-**39a**



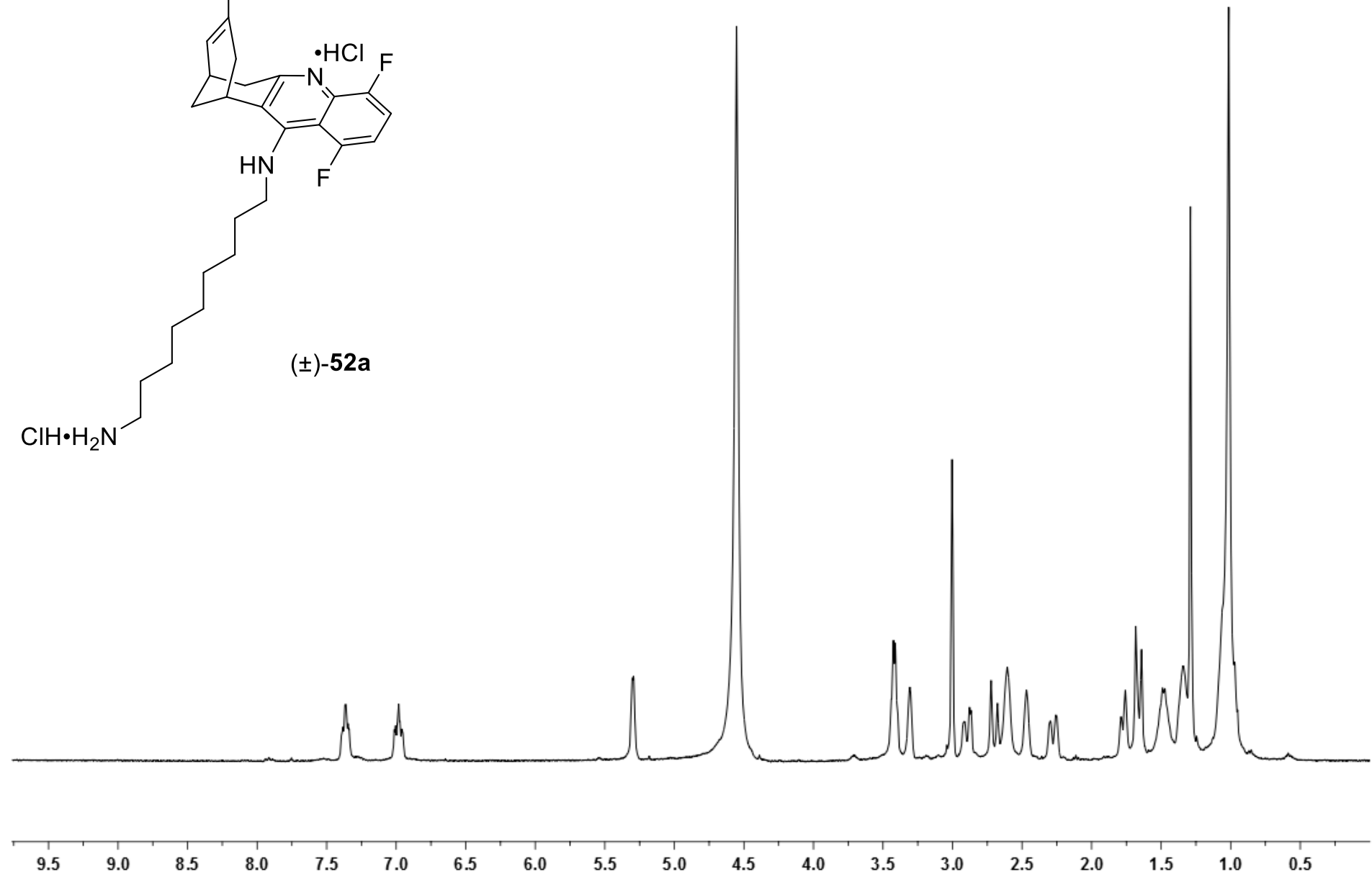
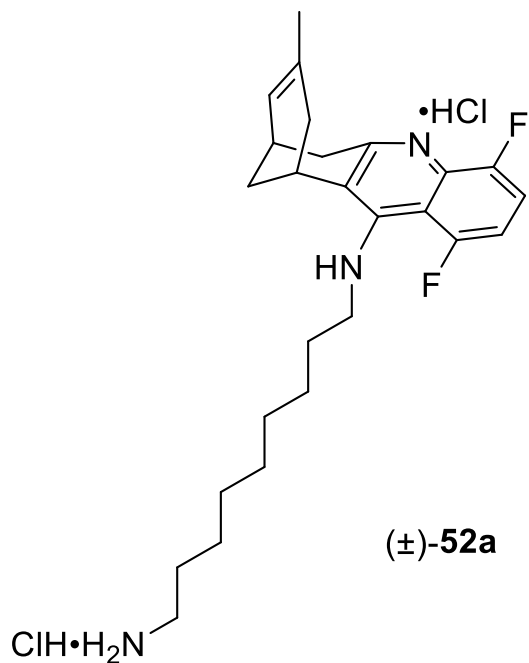
(±)-9-[(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)amino]nonanenitrile, (±)-**51a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



(±)-9-[(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)amino]nonanenitrile, (±)-**51a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

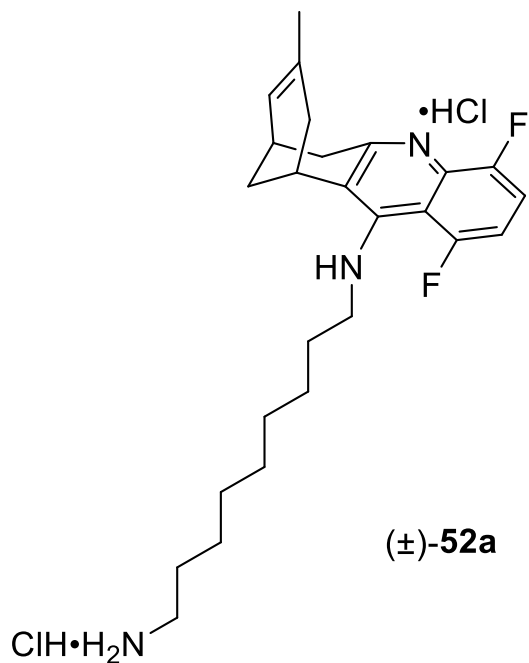


(±)-*N*-(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)nonane-1,9-diamine, (±)-**52a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

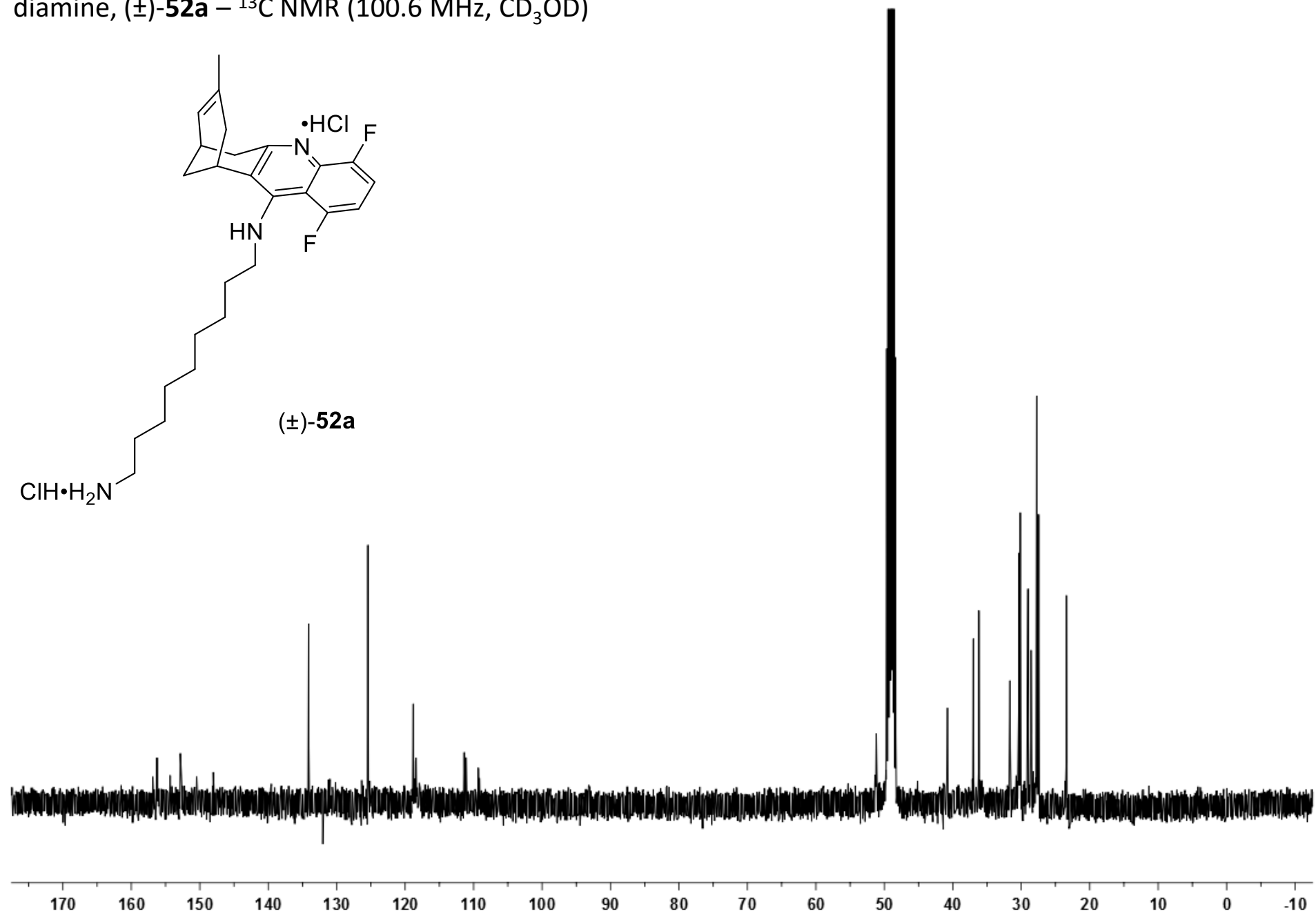




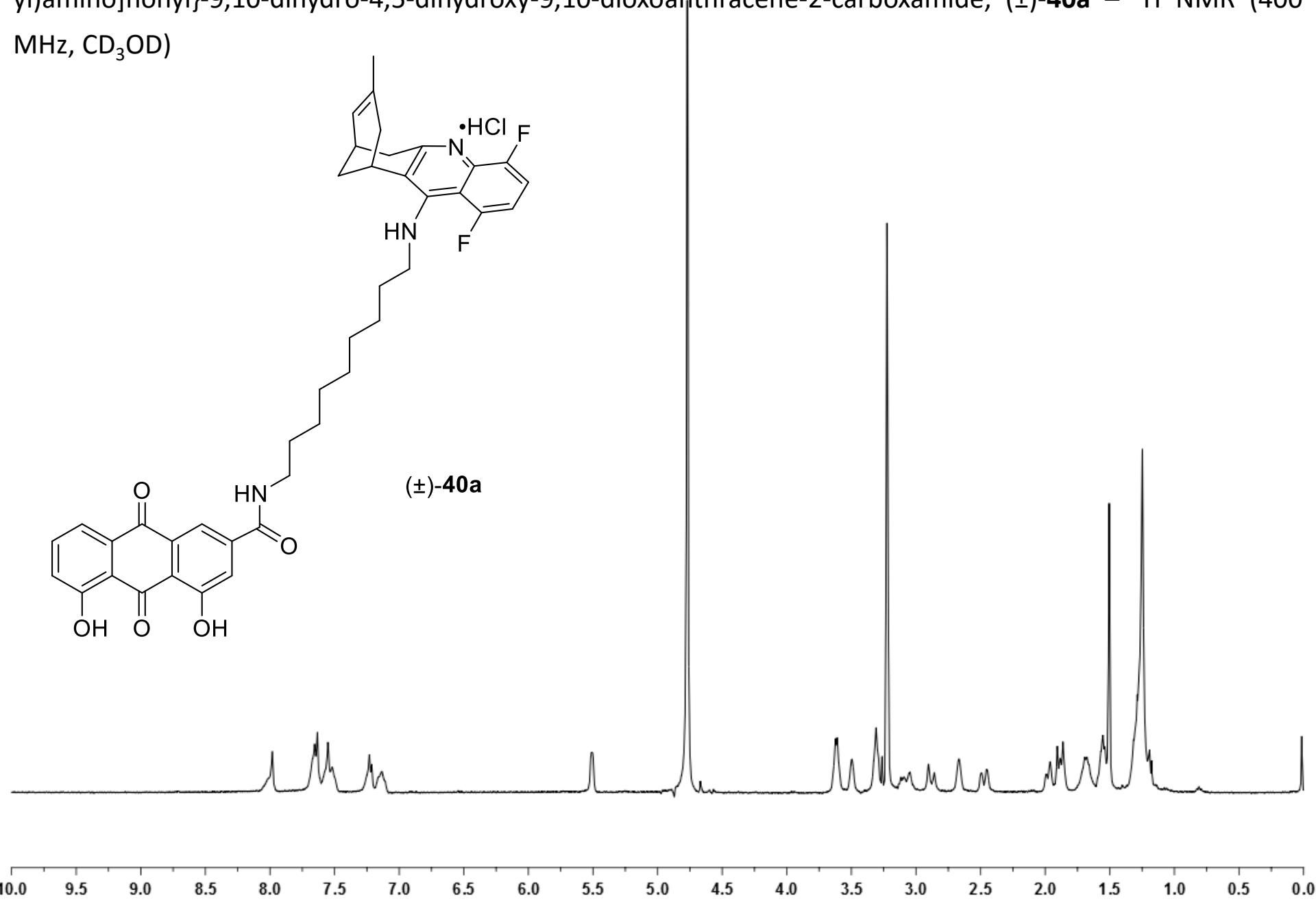
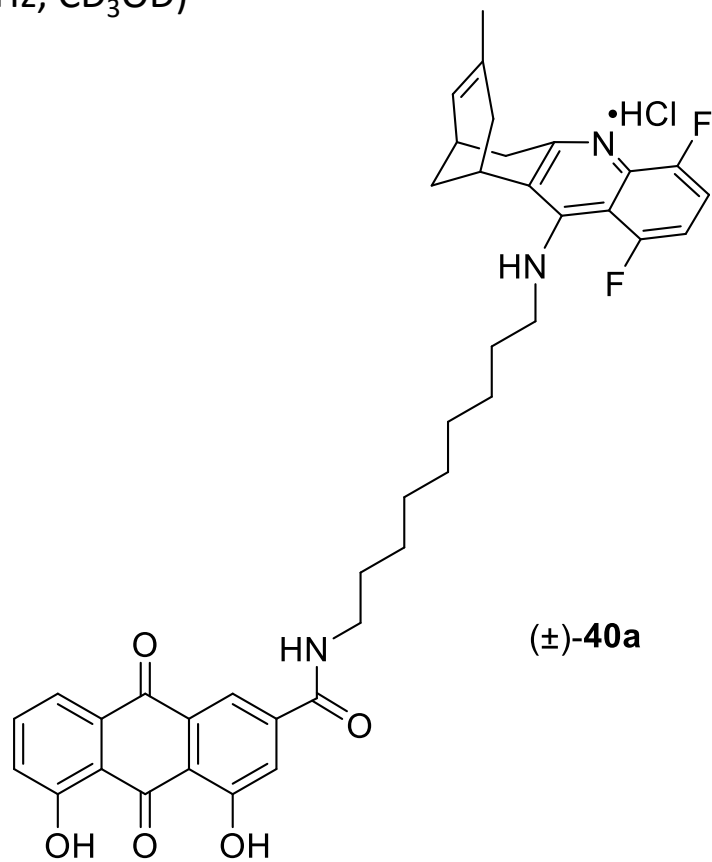
(±)-*N*-(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)nonane-1,9-diamine, (±)-**52a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



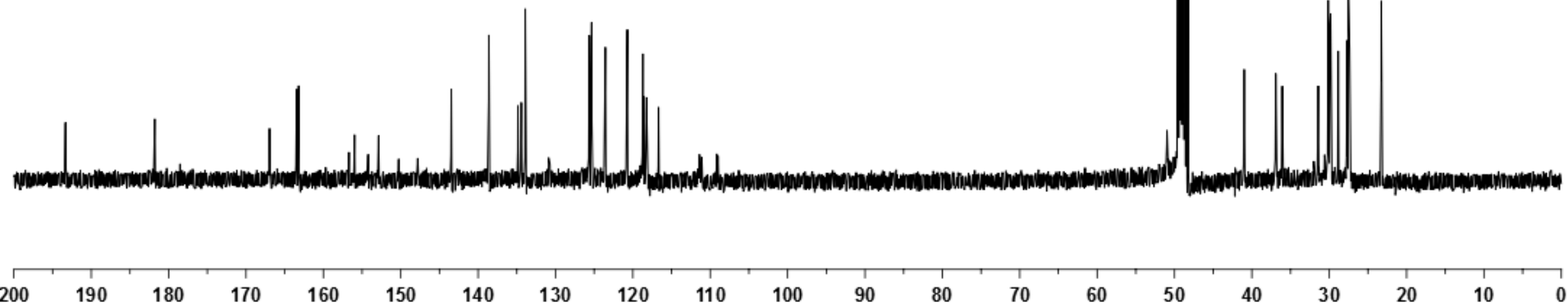
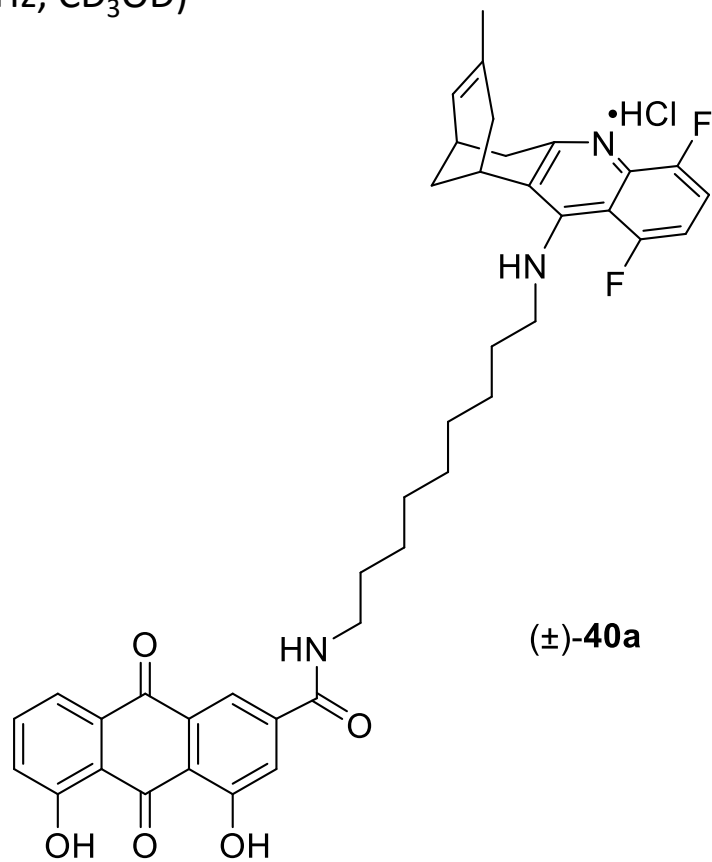
(±)-**52a**



(±)-*N*-{9-[(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)amino]nonyl}-9,10-dihydro-4,5-dihydroxy-9,10-dioxoanthracene-2-carboxamide, (±)-**40a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

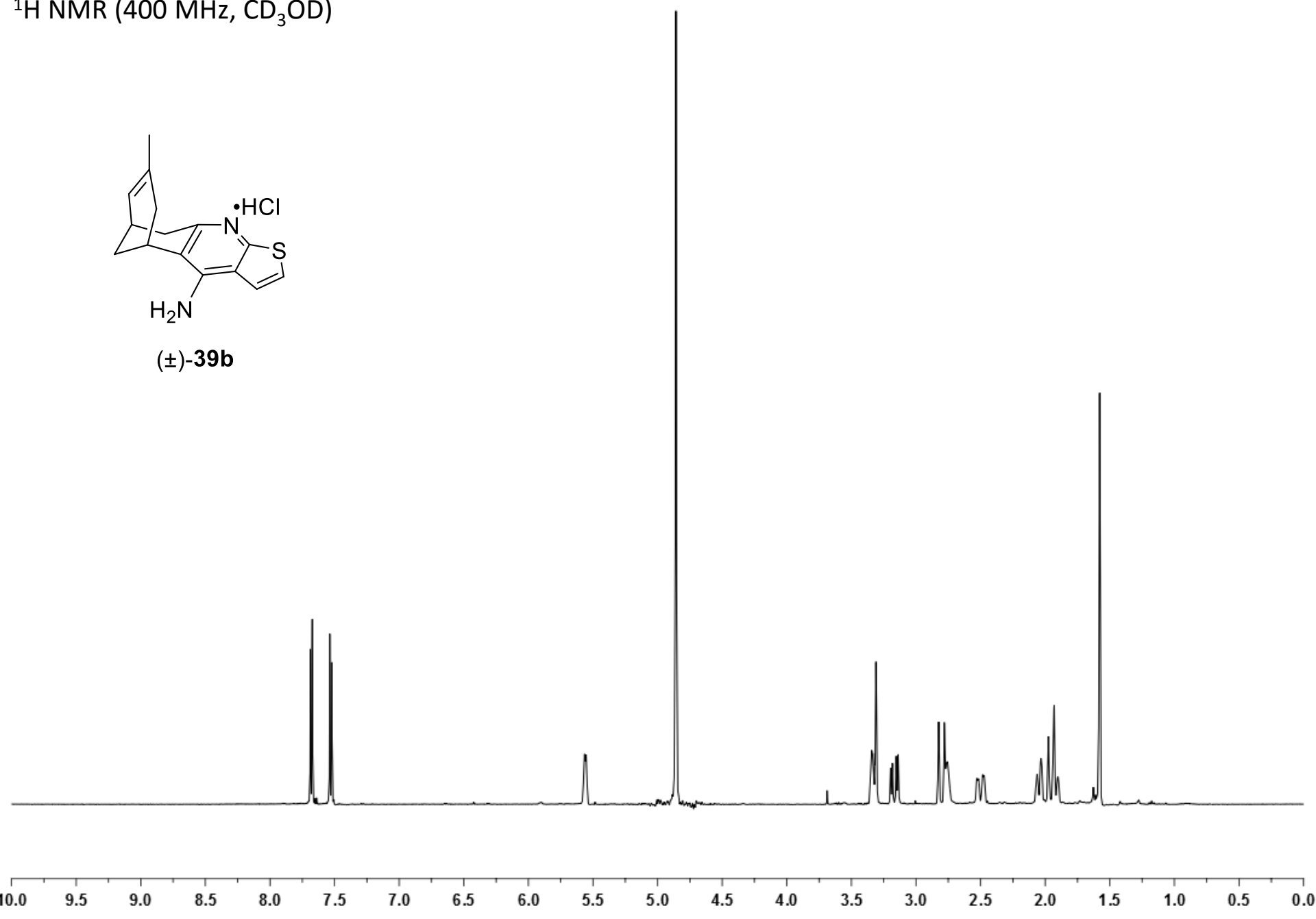
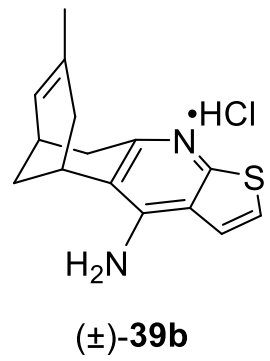


(±)-*N*-{9-[(1,4-difluoro-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*]quinolin-12-yl)amino]nonyl}-9,10-dihydro-4,5-dihydroxy-9,10-dioxoanthracene-2-carboxamide (±)-**40a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

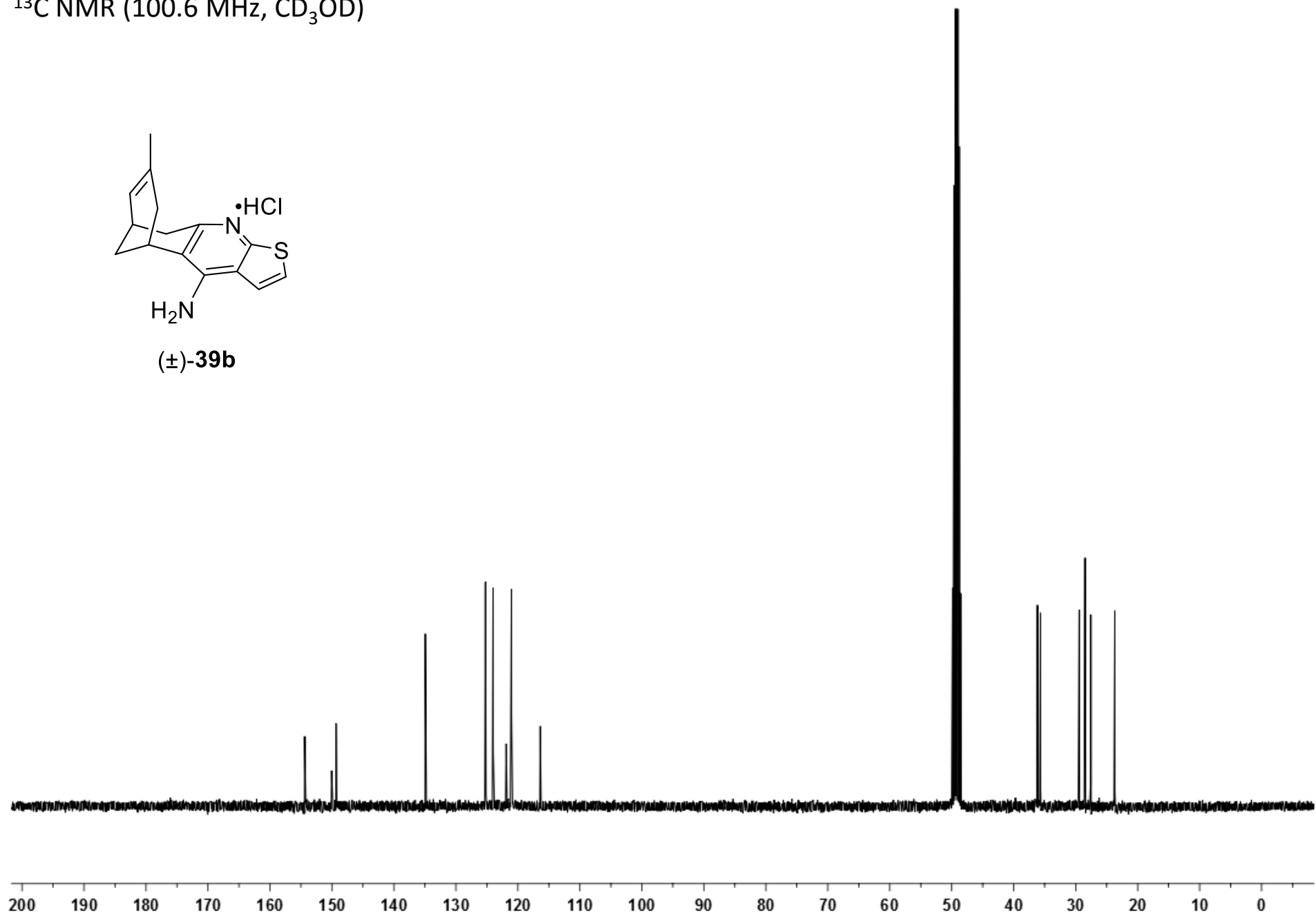
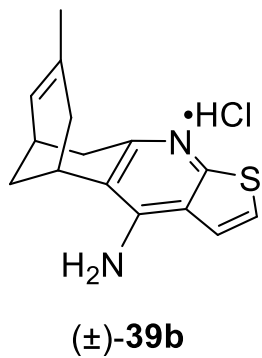


(±)-4-amine-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[2,3-*e*]pyridine, (±)-**39b** –

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)

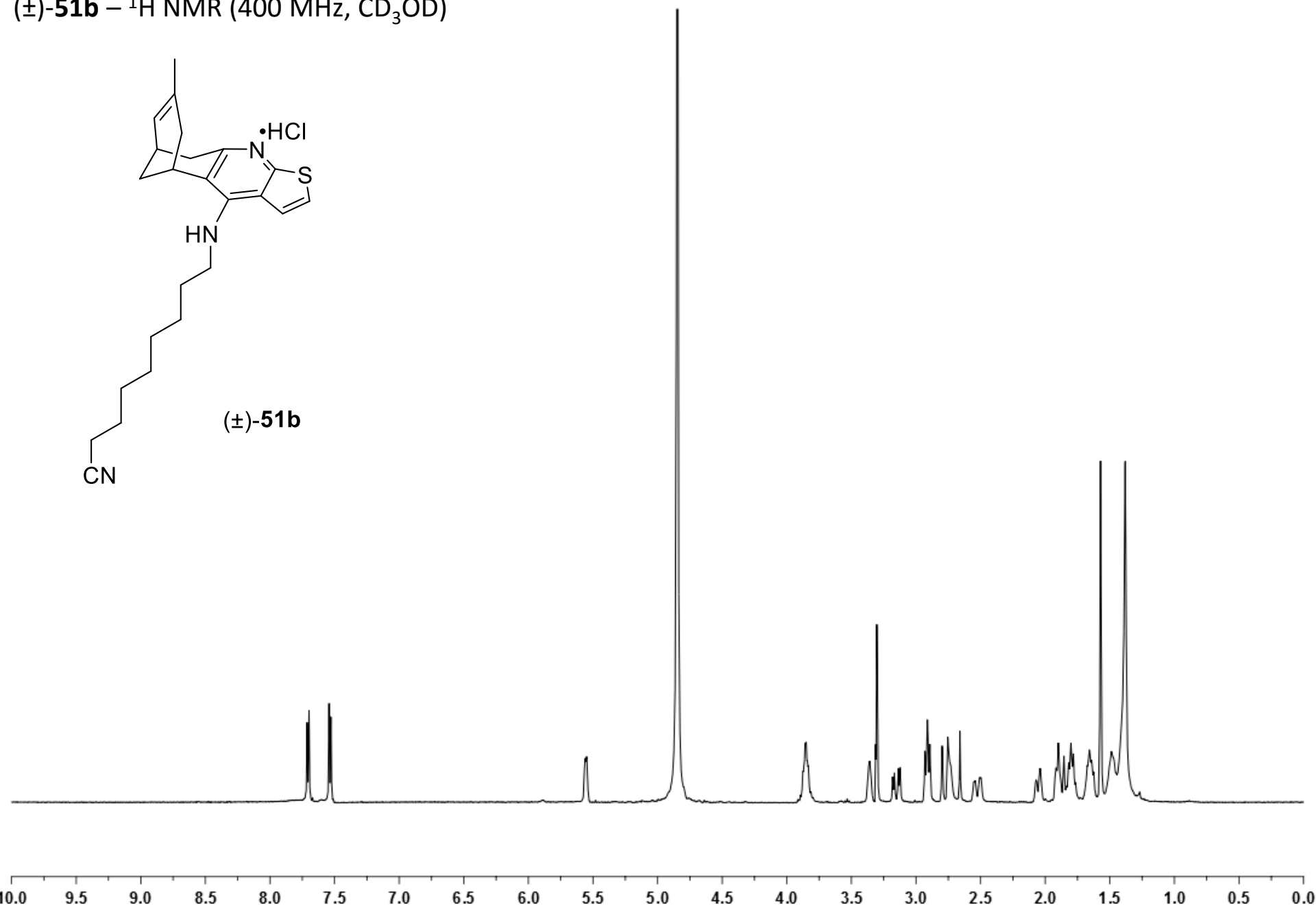
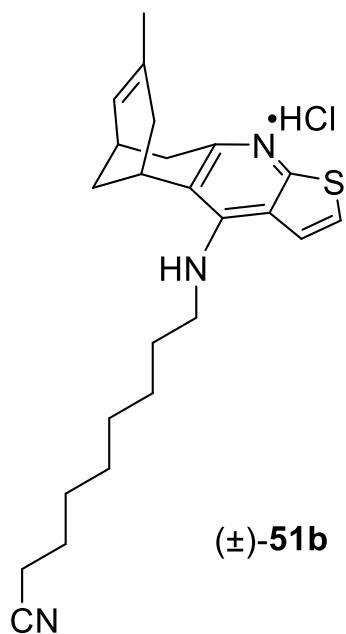


(±)-4-amine-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[2,3-*e*]pyridine, (±)-**39b** –  
<sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD)



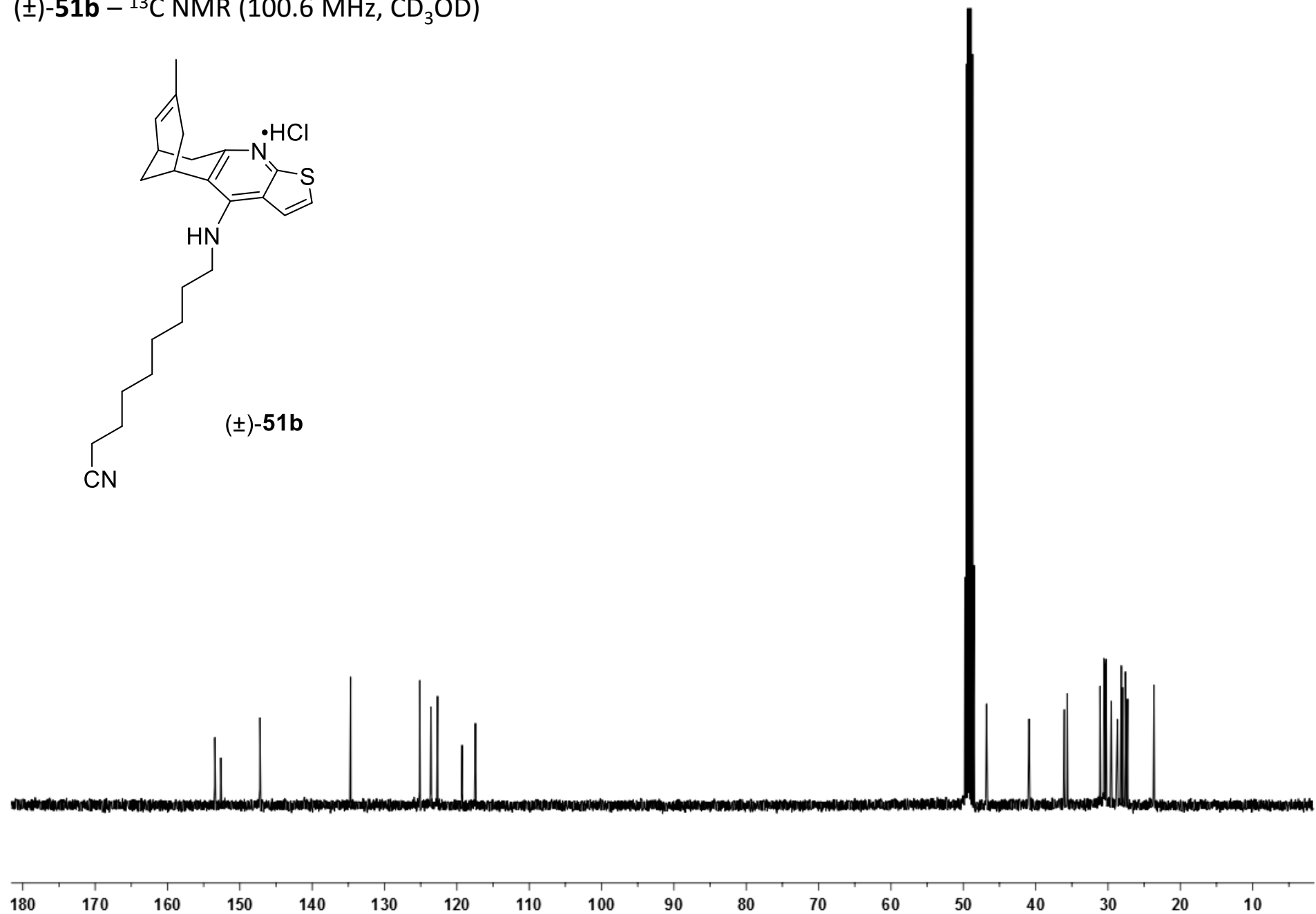
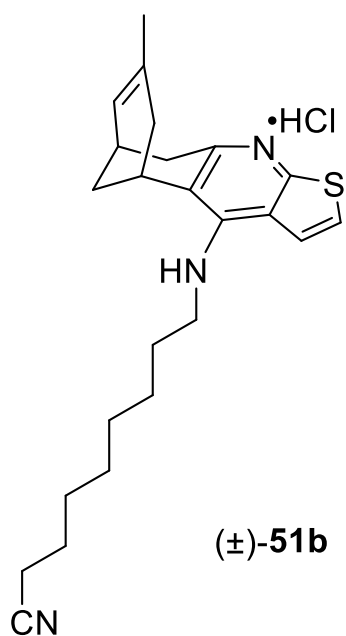
(±)-9-[(7-methyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)amino]nonanenitrile,

(±)-**51b** – <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



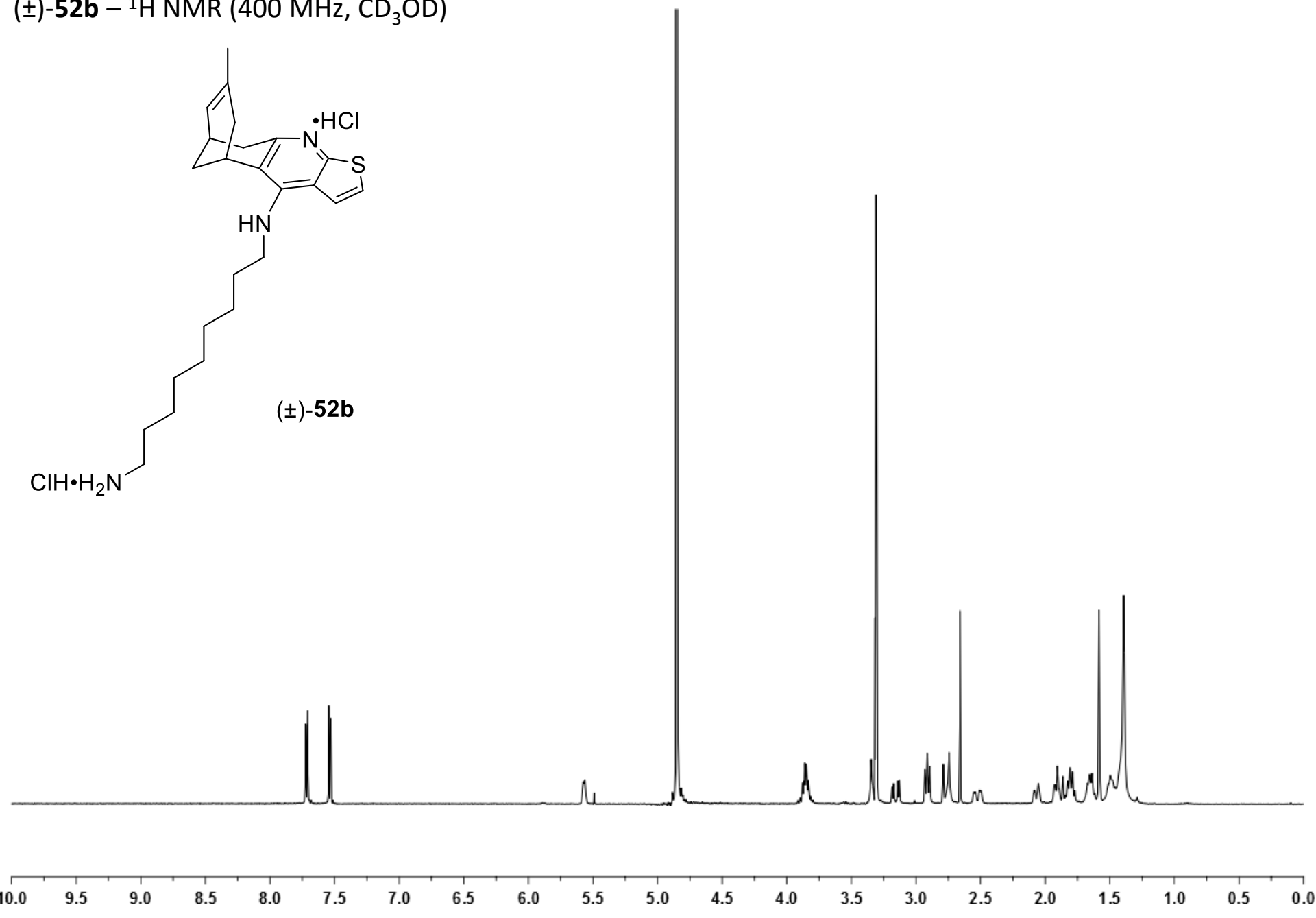
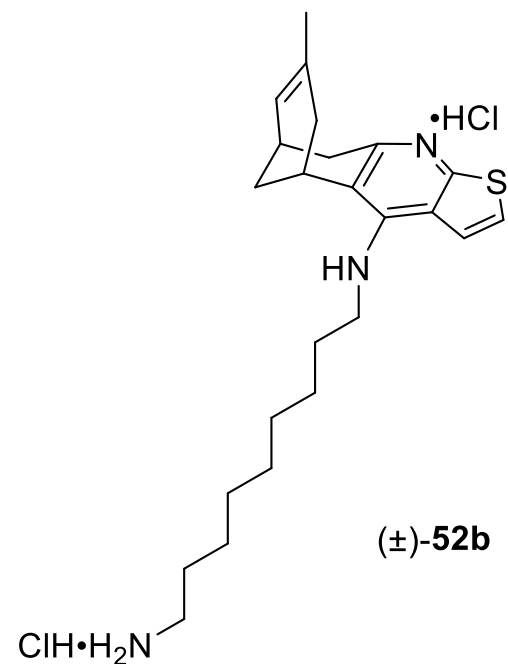
(±)-9-[(7-methyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)amino]nonanenitrile,

(±)-**51b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



(±)-*N*-(5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)nonane-1,9-diamine,

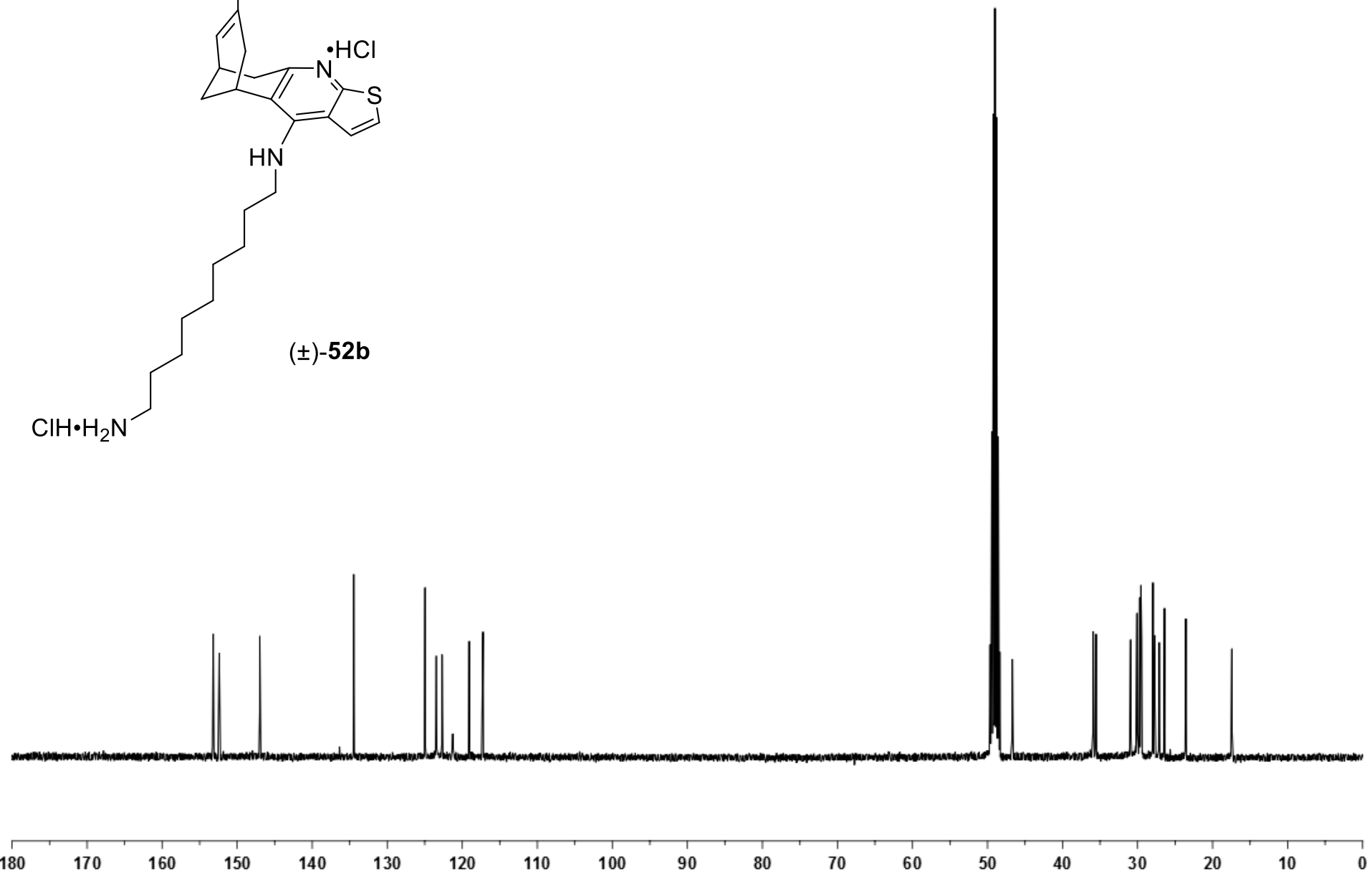
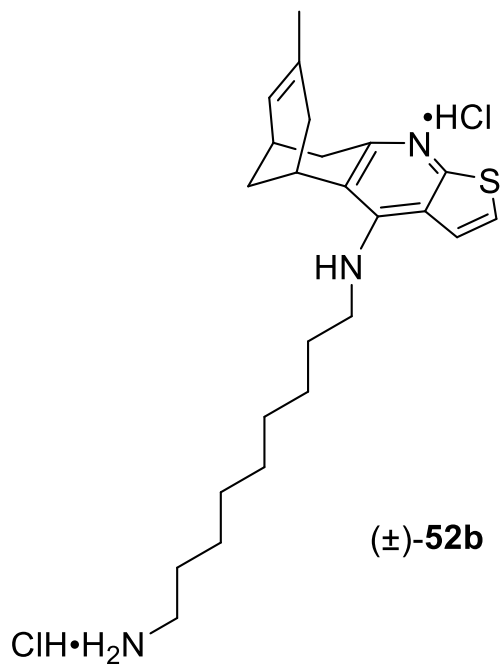
(±)-**52b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



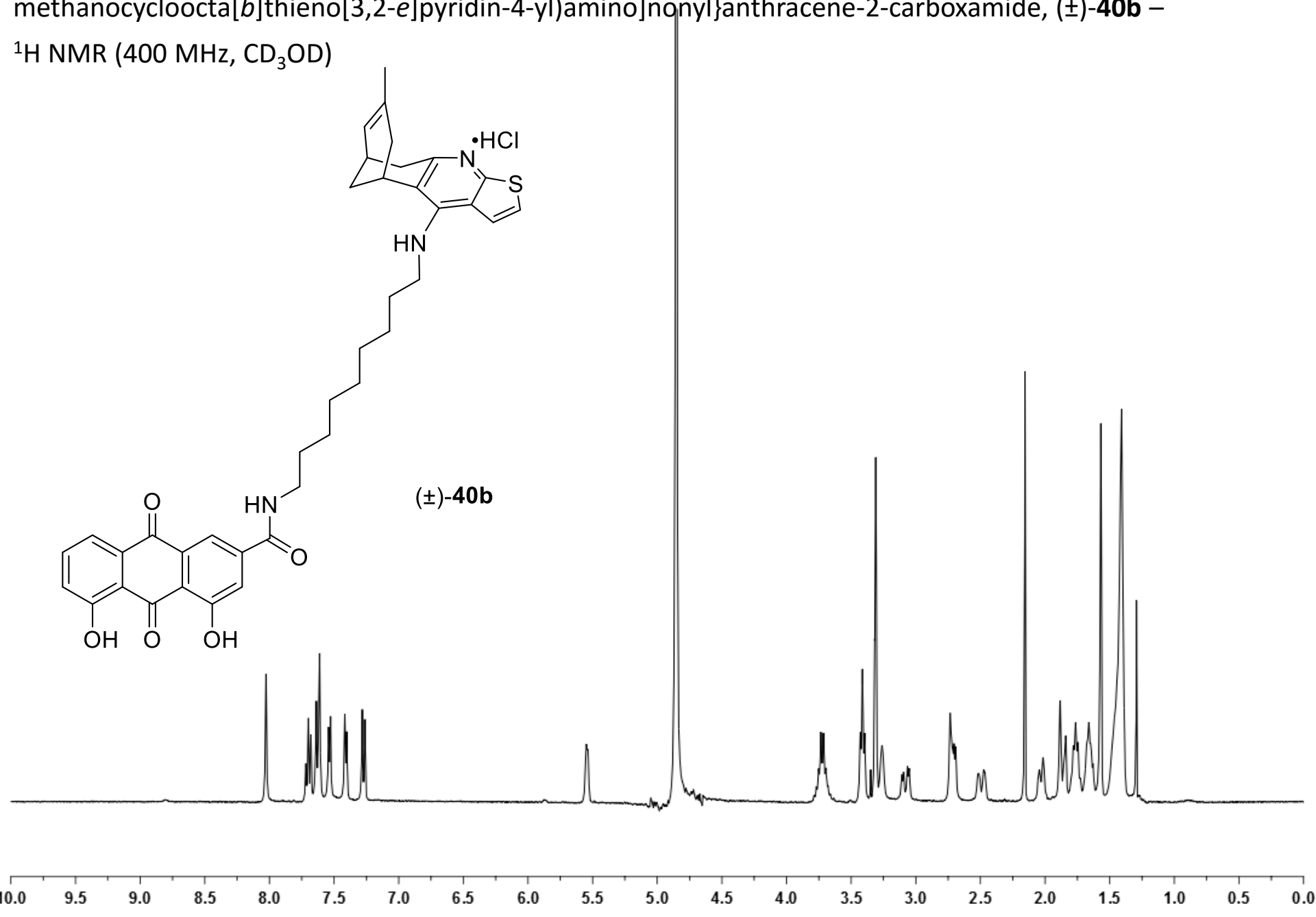
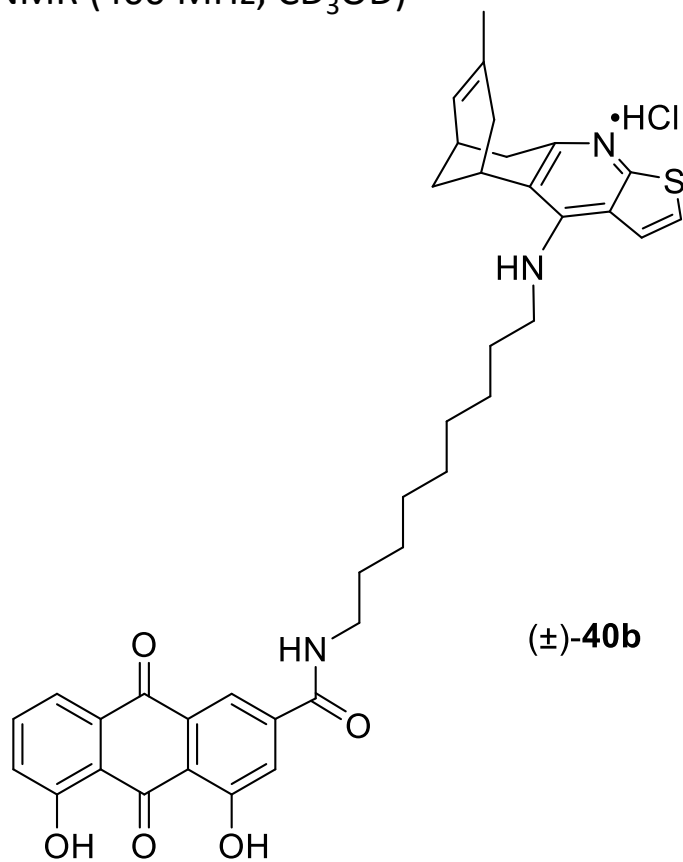


(±)-N-(5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)nonane-1,9-diamine,

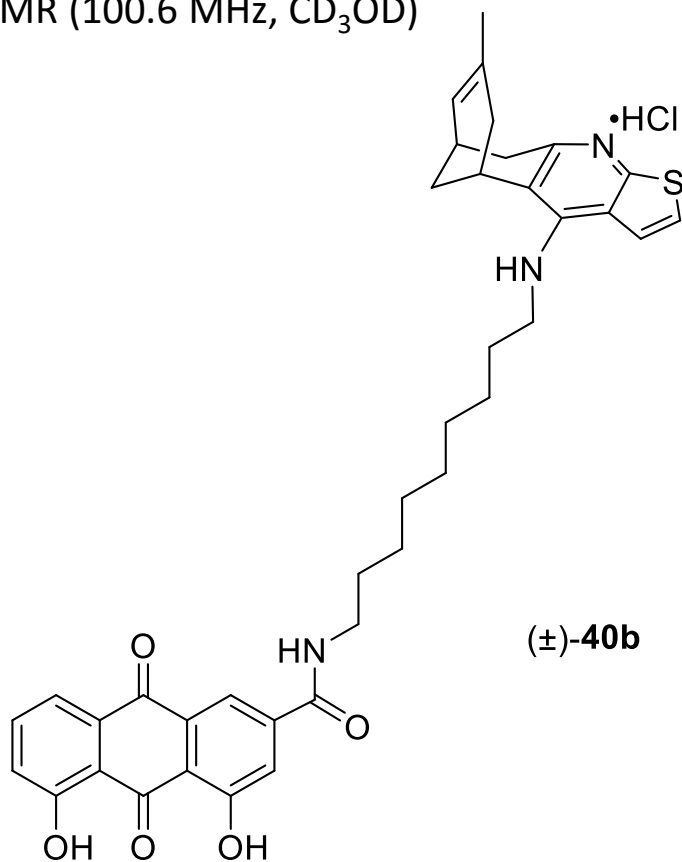
(±)-**52b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



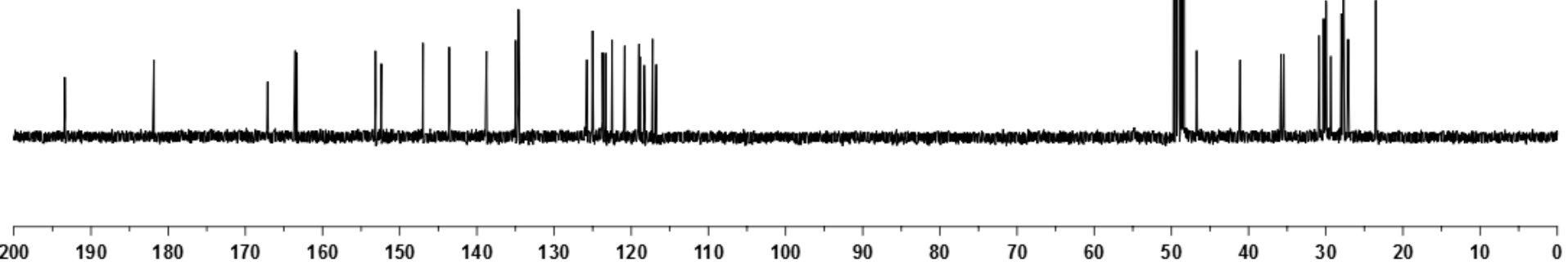
(±)-9,10-dihydro-4,5-dihydroxy-9,10-dioxo-*N*-{9-[(5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)amino]nonyl}anthracene-2-carboxamide, (±)-**40b** – <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



(±)-9,10-dihydro-4,5-dihydroxy-9,10-dioxo-*N*-{9-[(5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]thieno[3,2-*e*]pyridin-4-yl)amino]nonyl}anthracene-2-carboxamide, (±)-**40b** –  
<sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD)

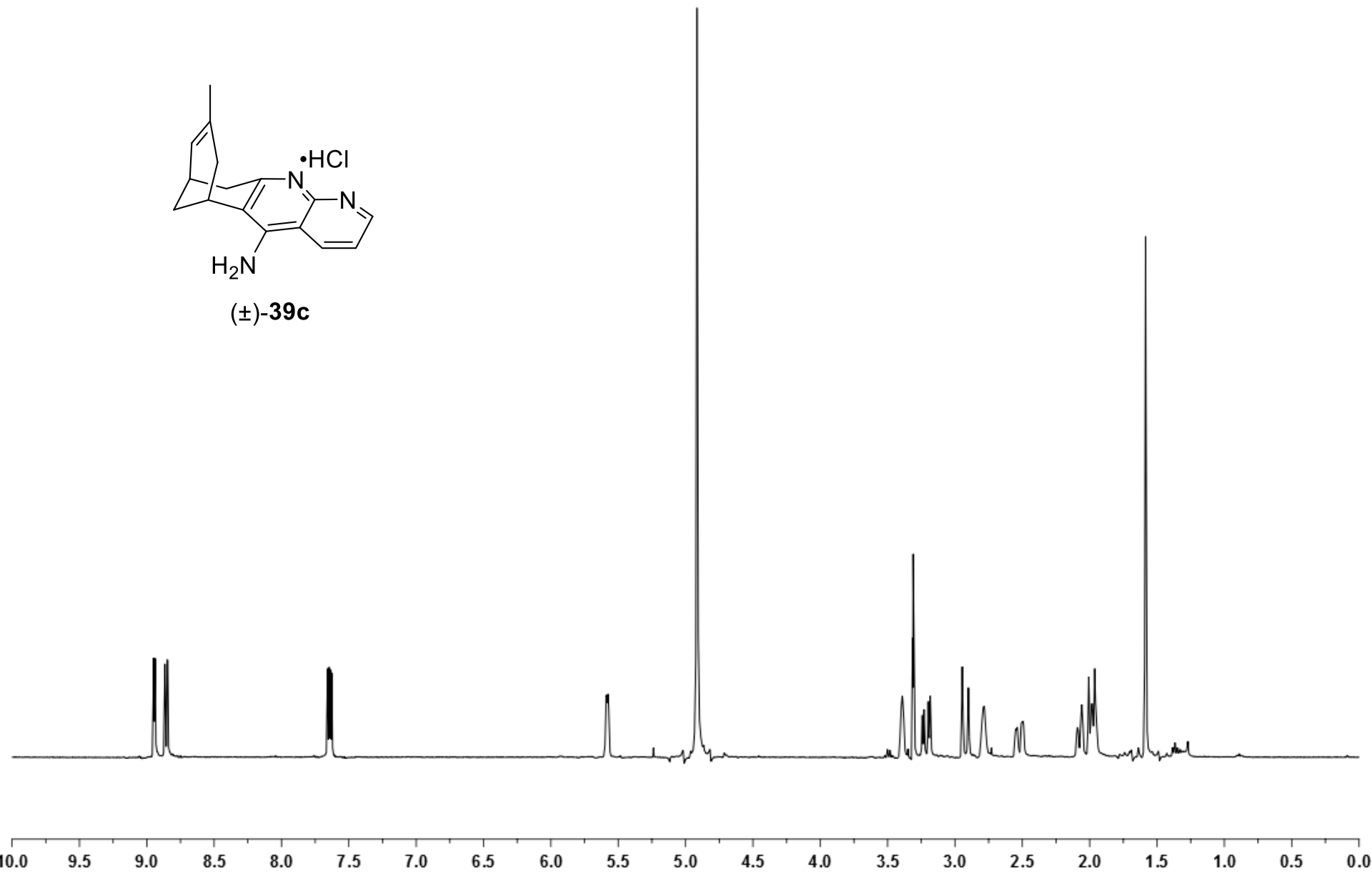
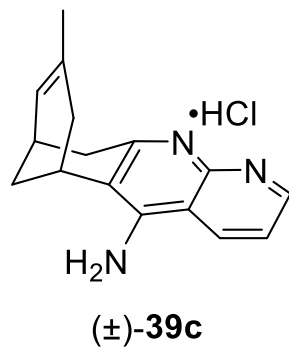


(±)-**40b**



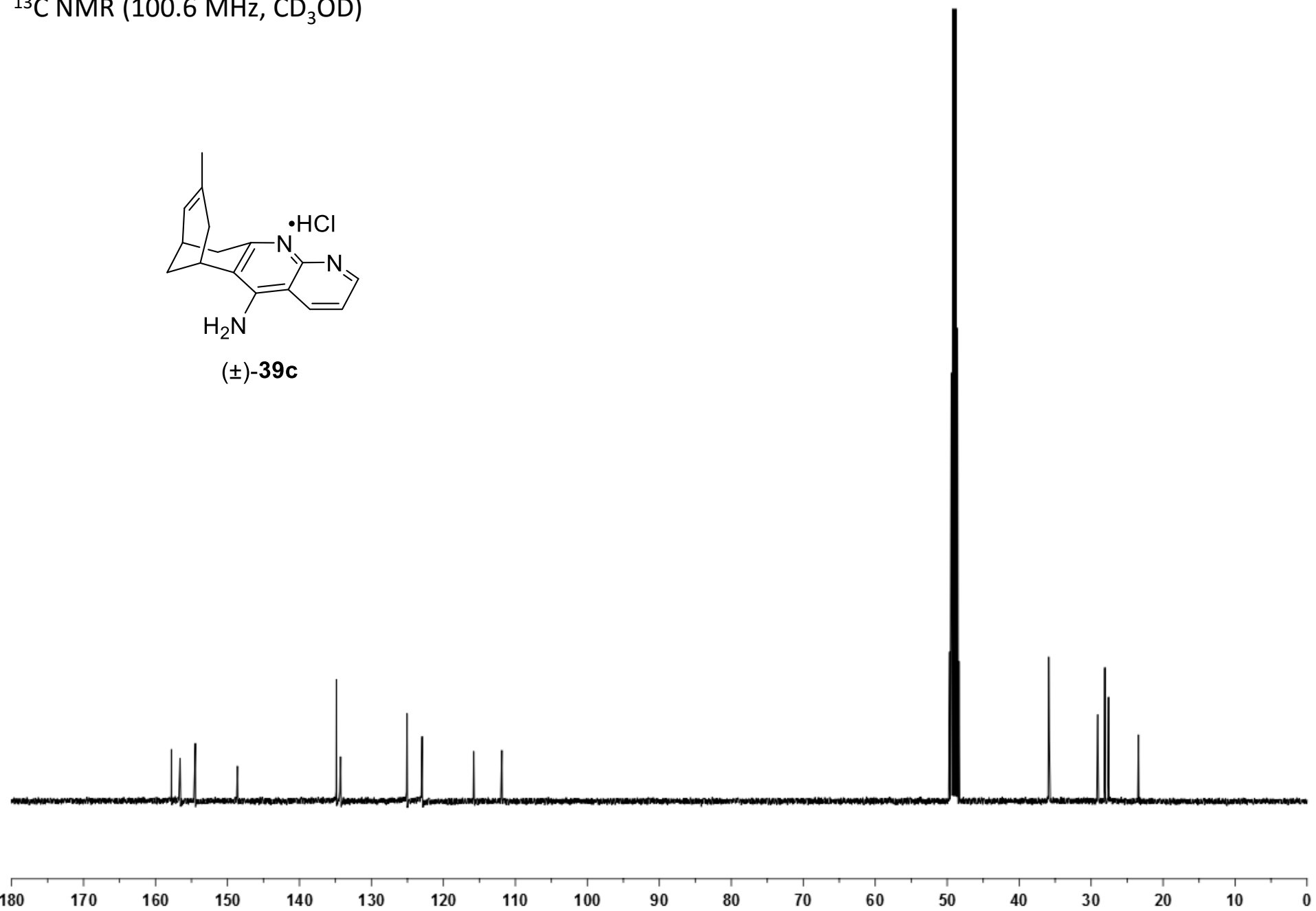
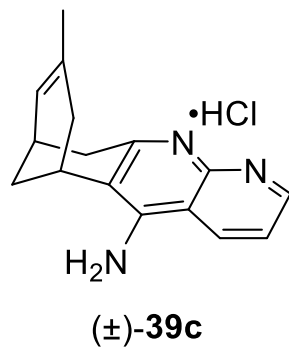
(±)-5-amine-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8] naphthyridine, (±)-**39c** –

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



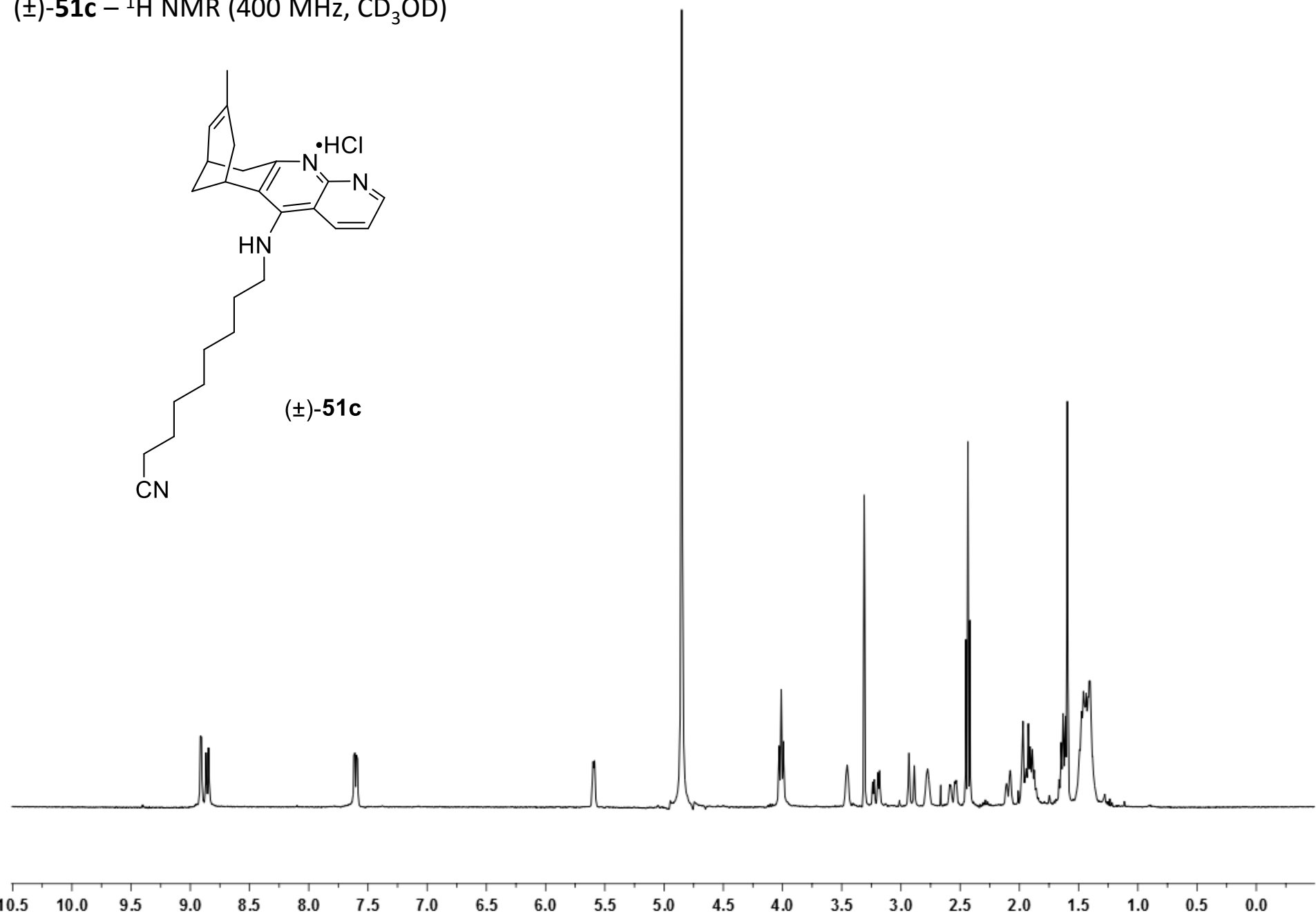
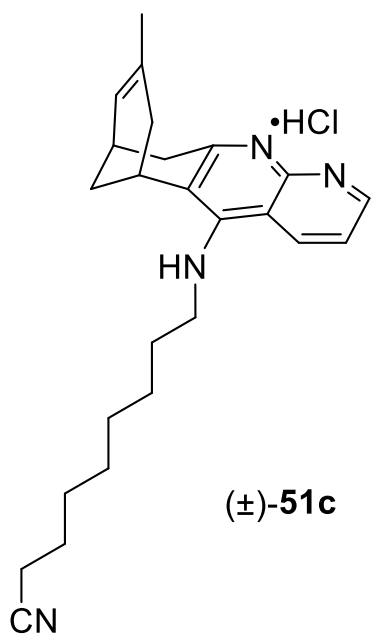
(±)-5-amine-6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8] naphthyridine, (±)-**39c** –

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



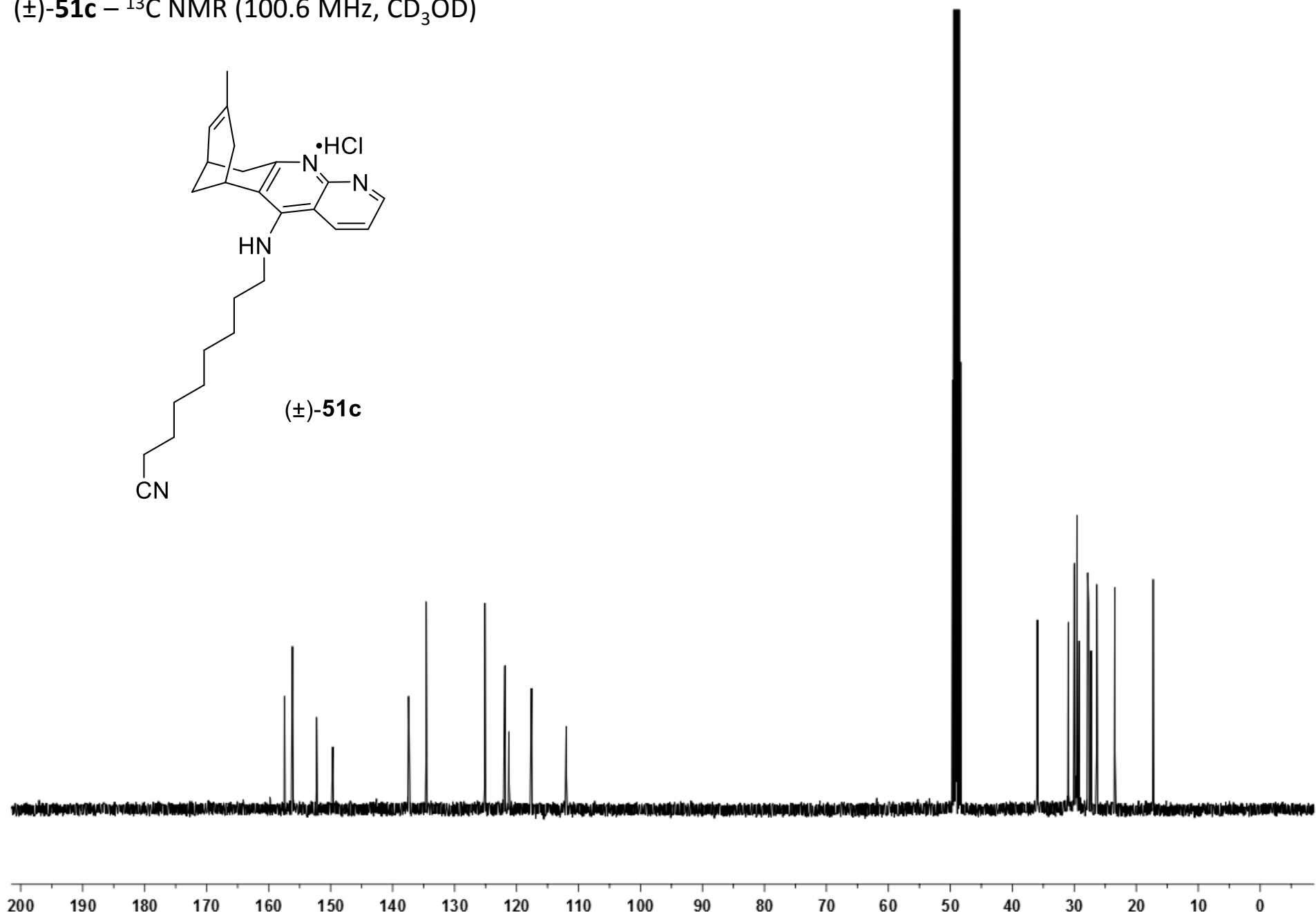
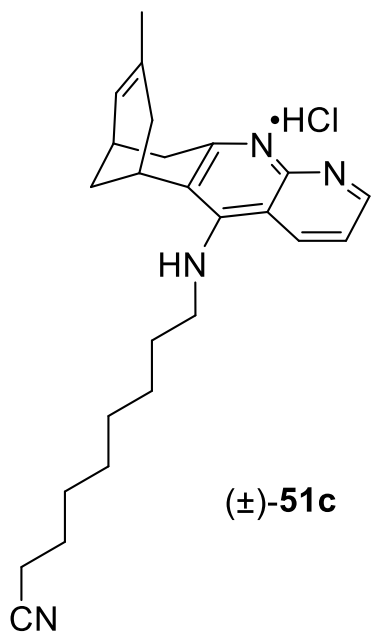
(±)-9-[(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)amino]nonanenitrile,

(±)-**51c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

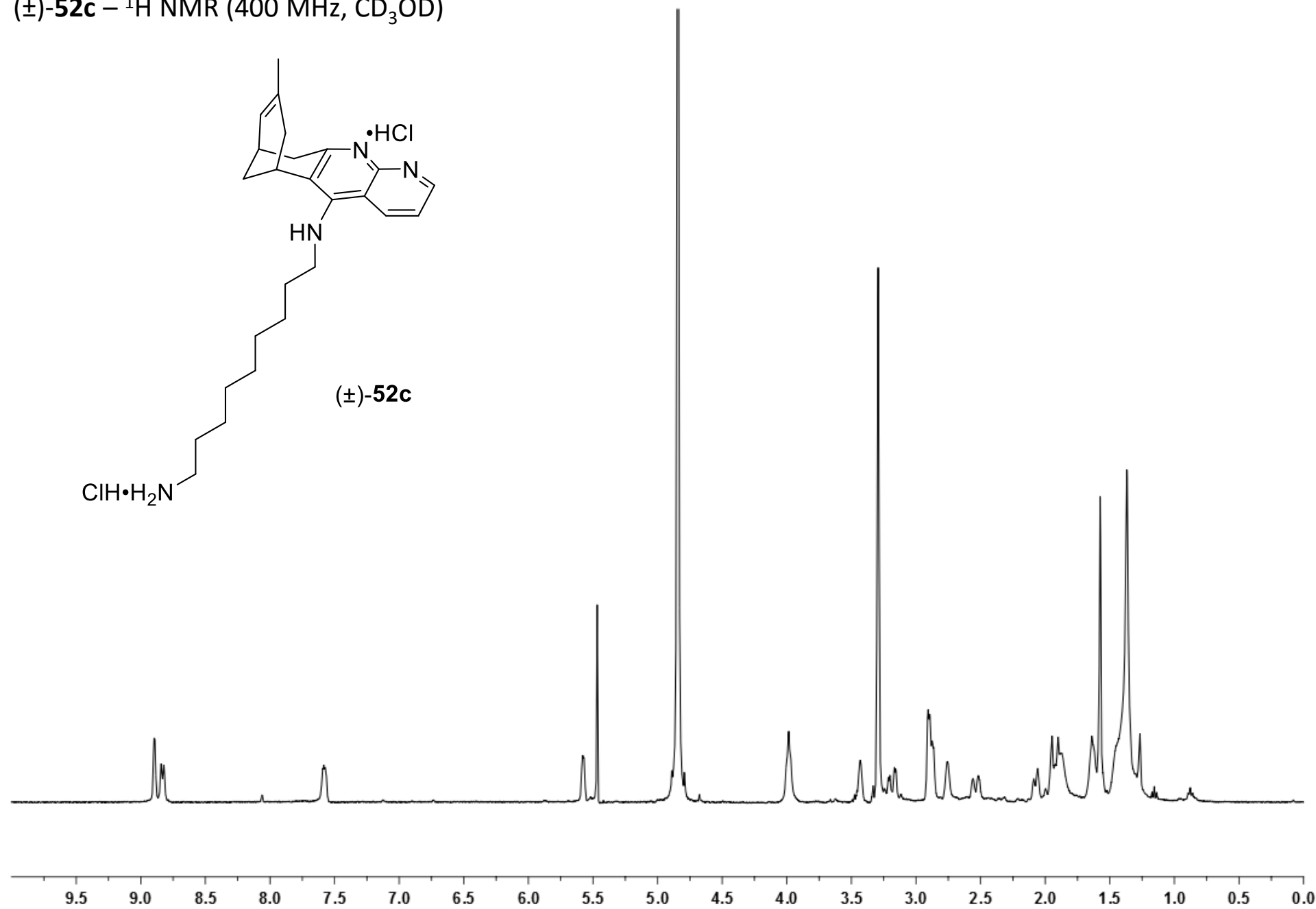
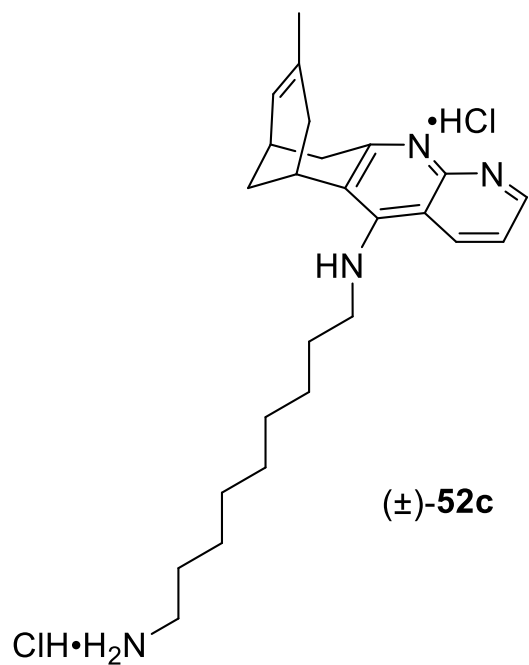


(±)-9-[(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)amino]nonanenitrile,

(±)-**51c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



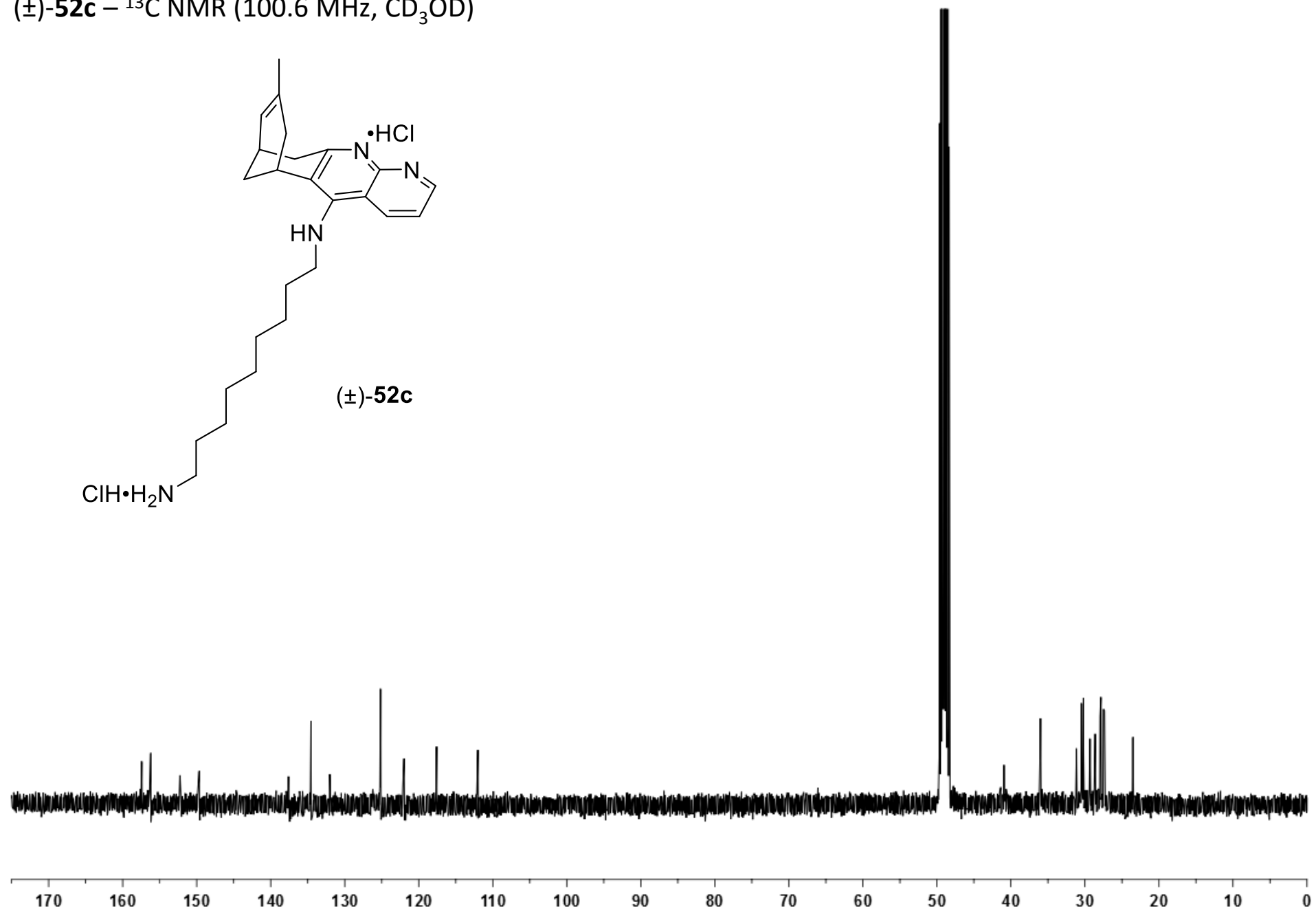
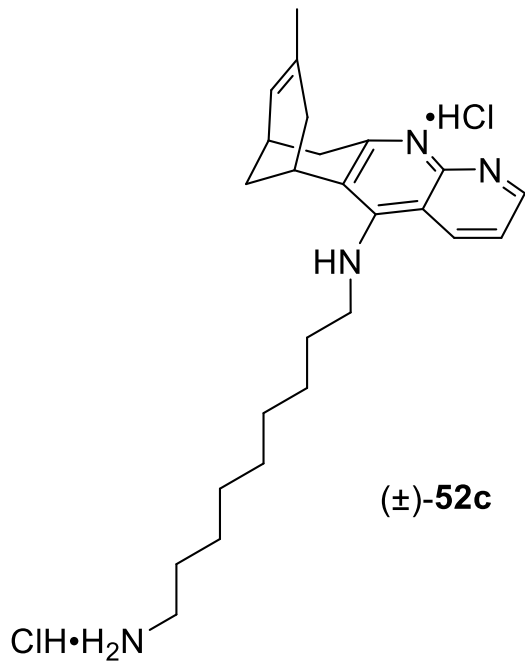
(±)-*N*-(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)-1,9-diaminononane, (±)-**52c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



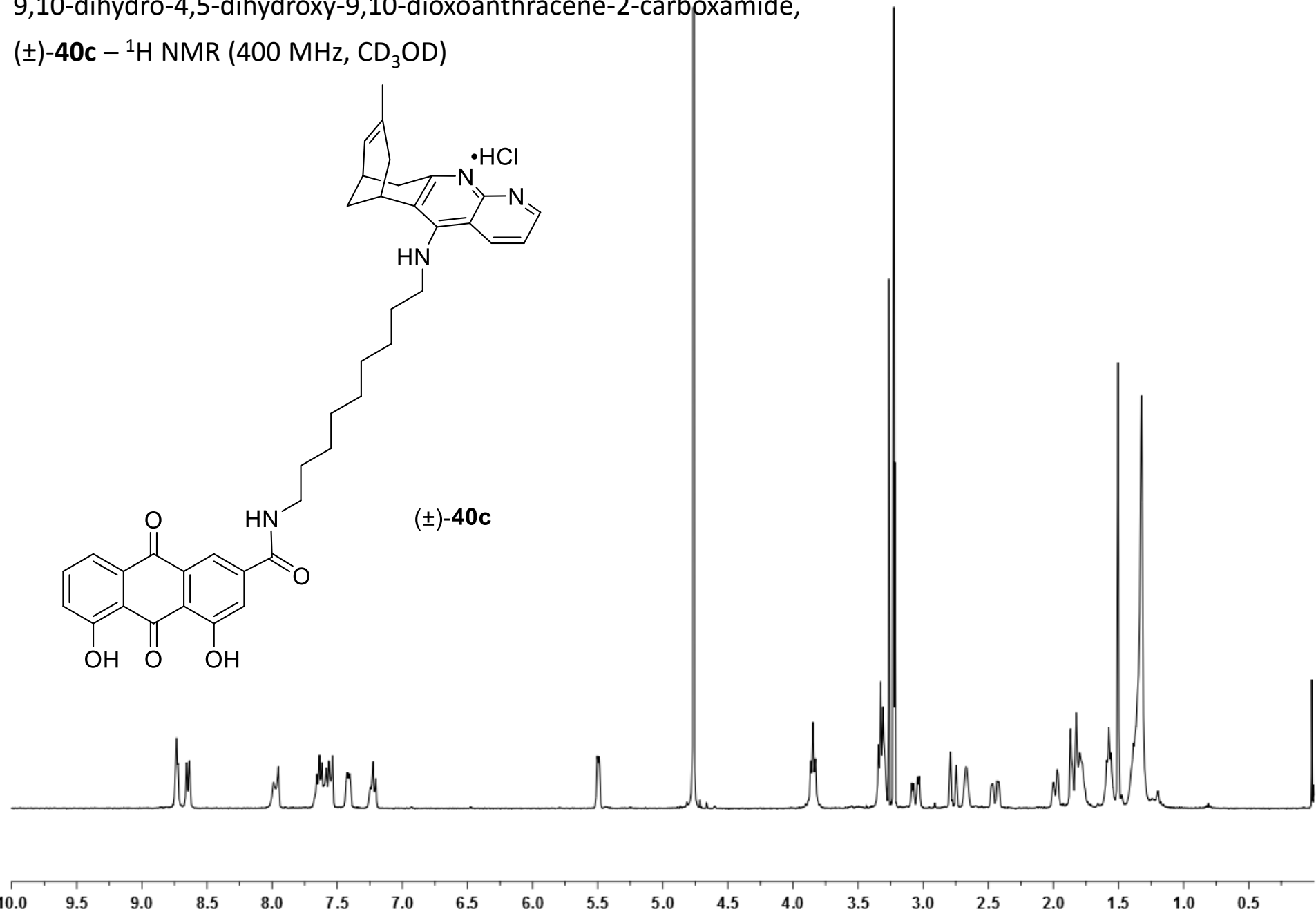
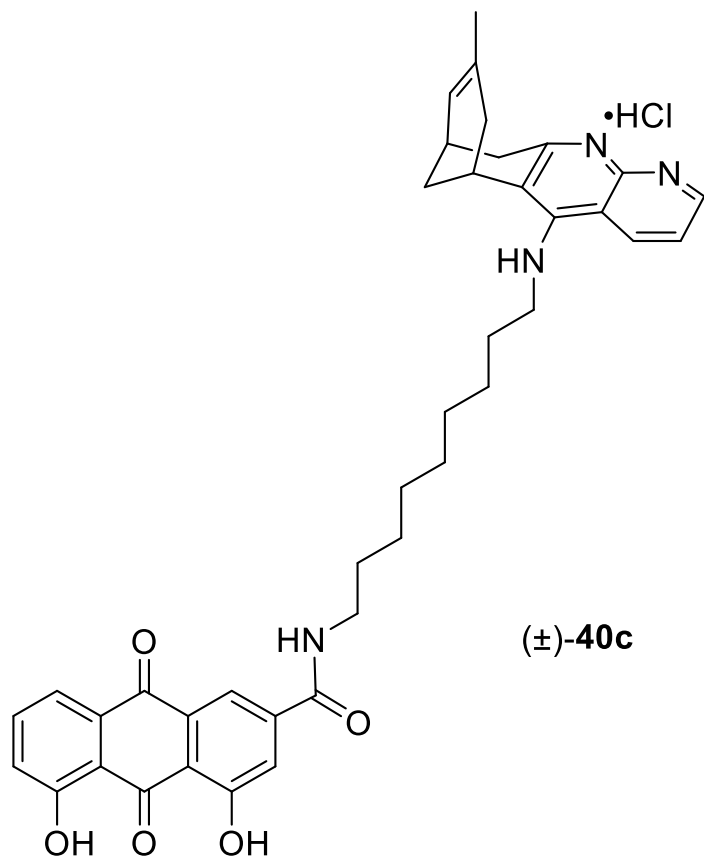


(±)-*N*-(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)-1,9-diaminononane,

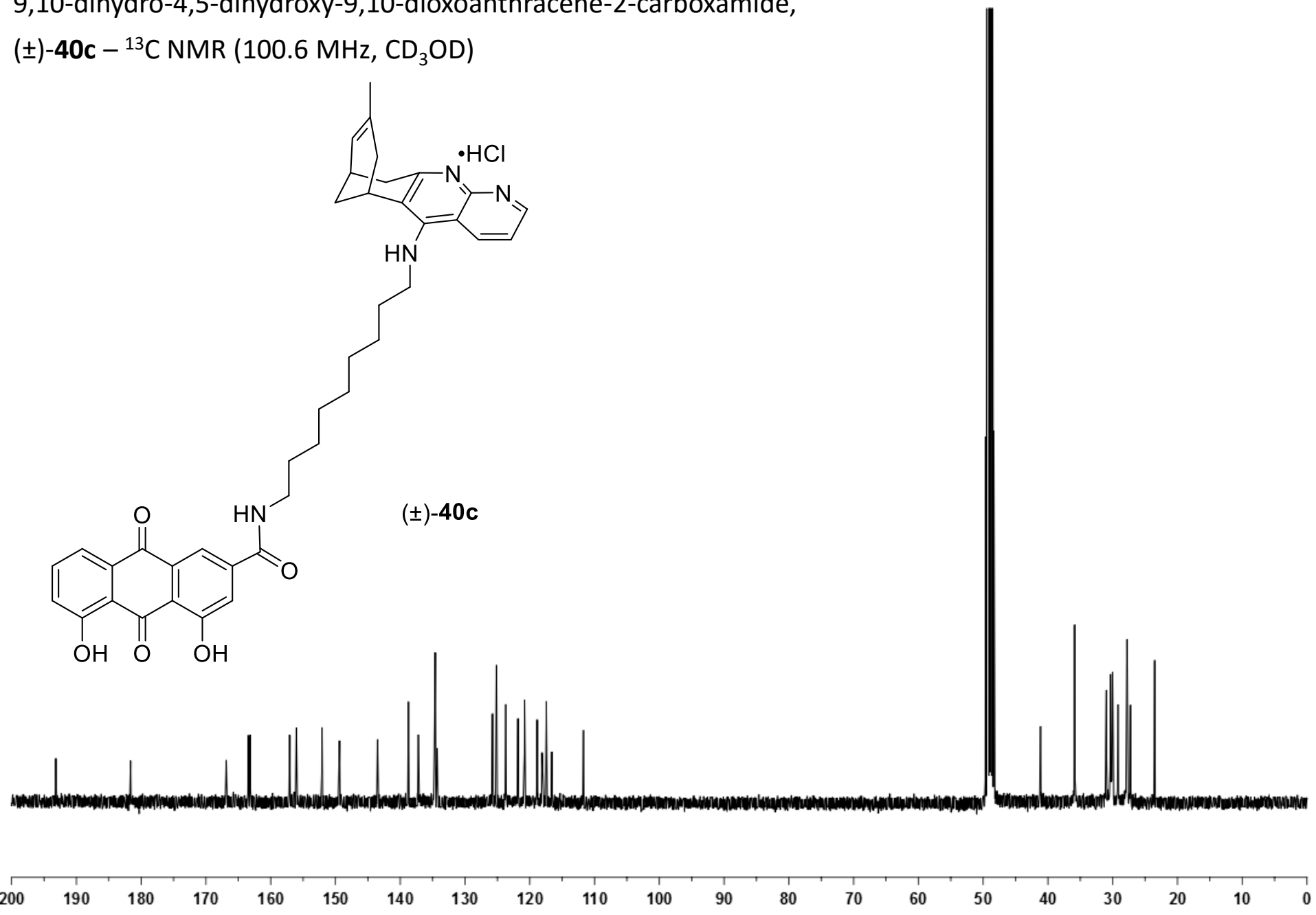
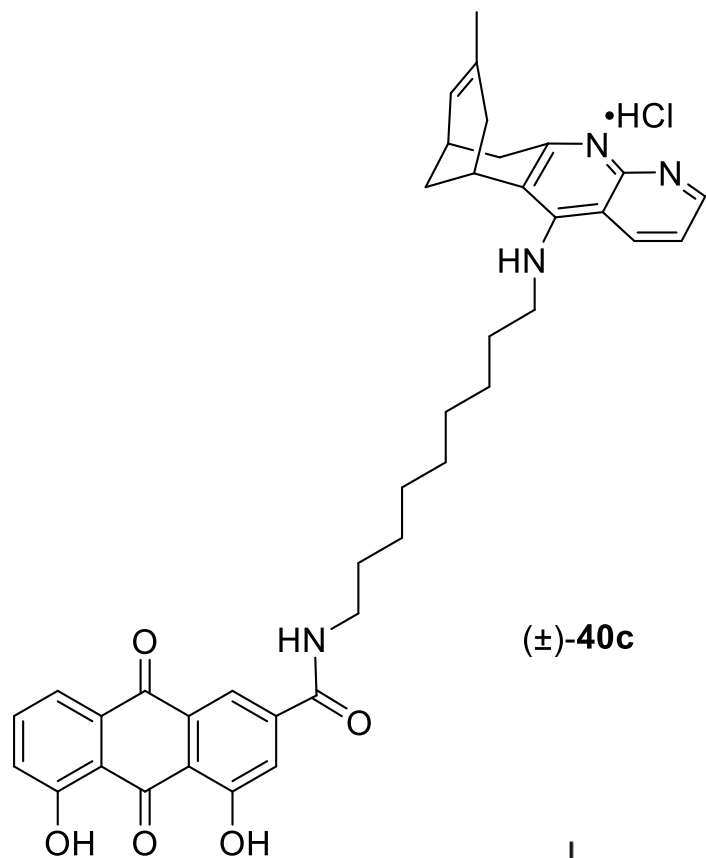
(±)-**52c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



(±)-*N*-{9-[(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)amino]nonyl}-9,10-dihydro-4,5-dihydroxy-9,10-dioxoanthracene-2-carboxamide, (±)-**40c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

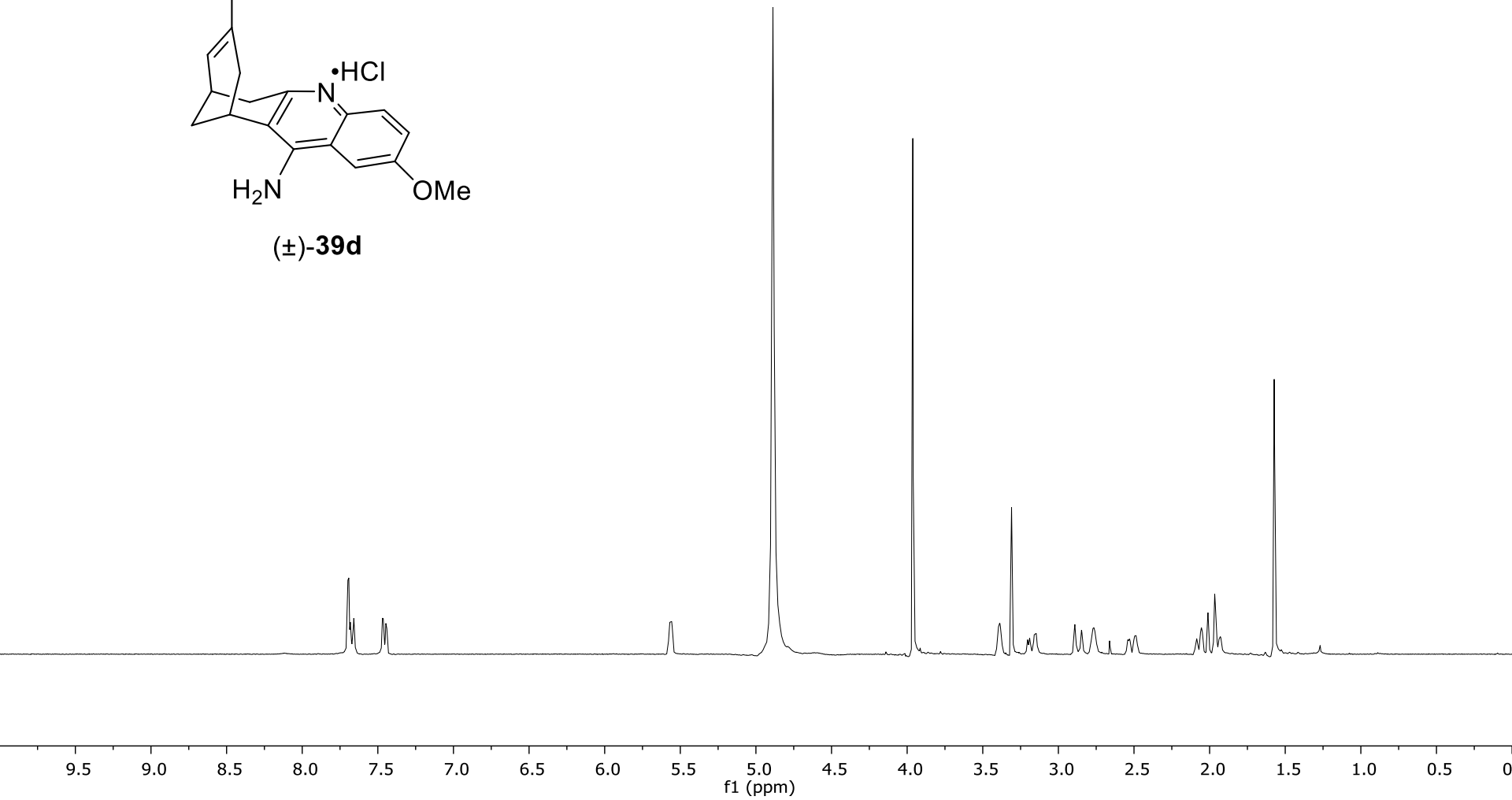
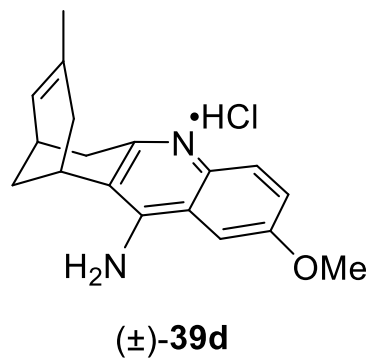


(±)-*N*-{9-[(6,7,10,11-tetrahydro-8-methyl-6,10-methanocycloocta[*b*][1,8]naphthyridin-5-yl)amino]nonyl}-9,10-dihydro-4,5-dihydroxy-9,10-dioxoanthracene-2-carboxamide, (±)-**40c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



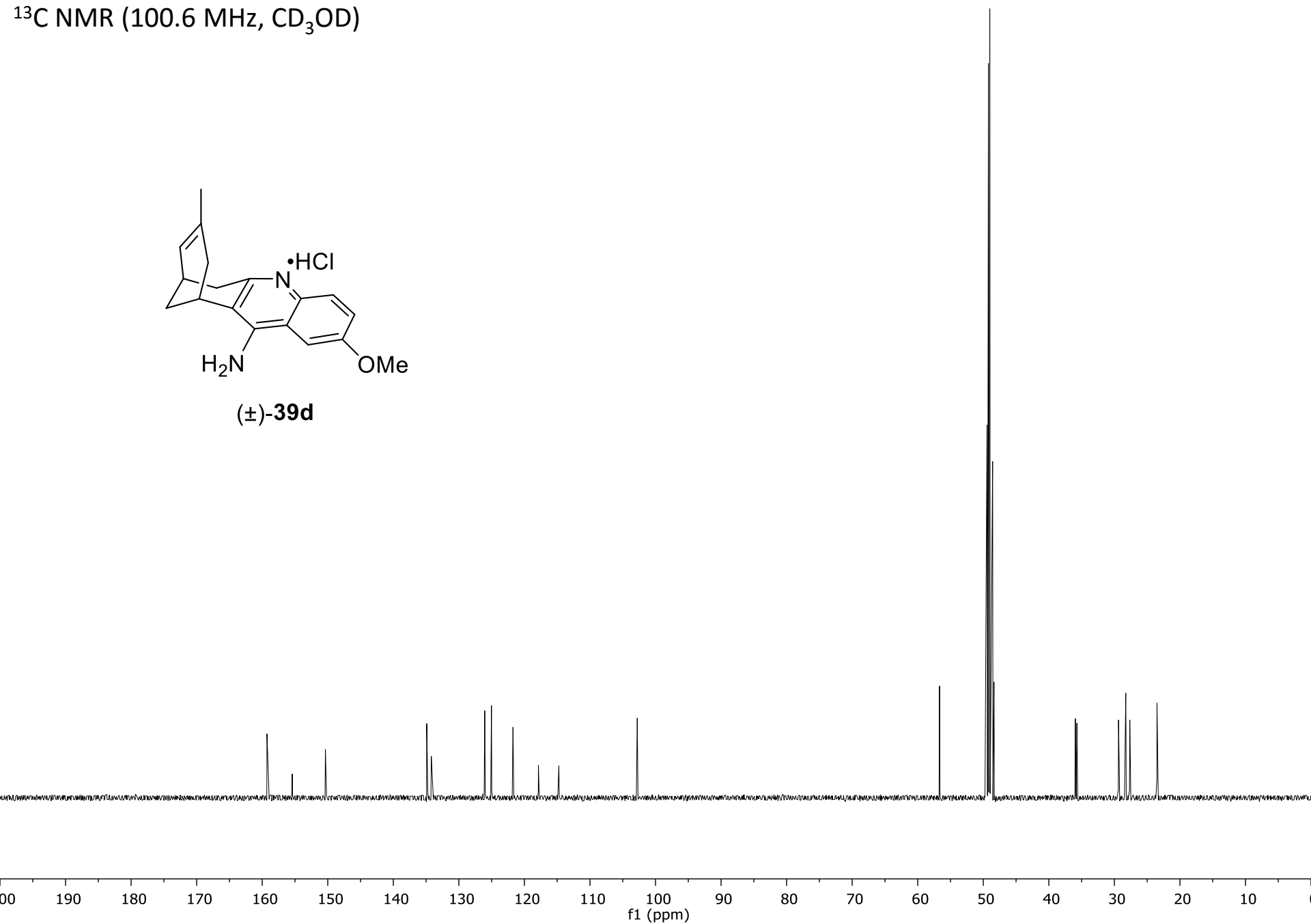
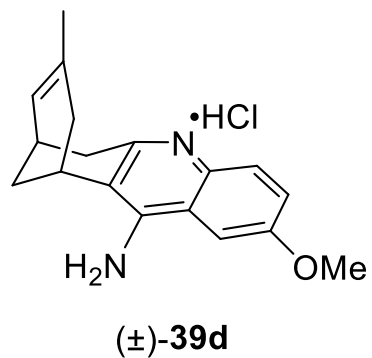
(±)-6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-amine, (±)-**39d** –

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



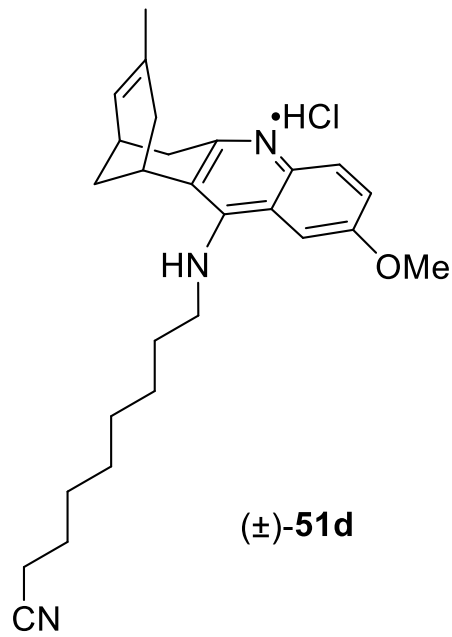
(±)-6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-amine, (±)-**39d** –

<sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD)

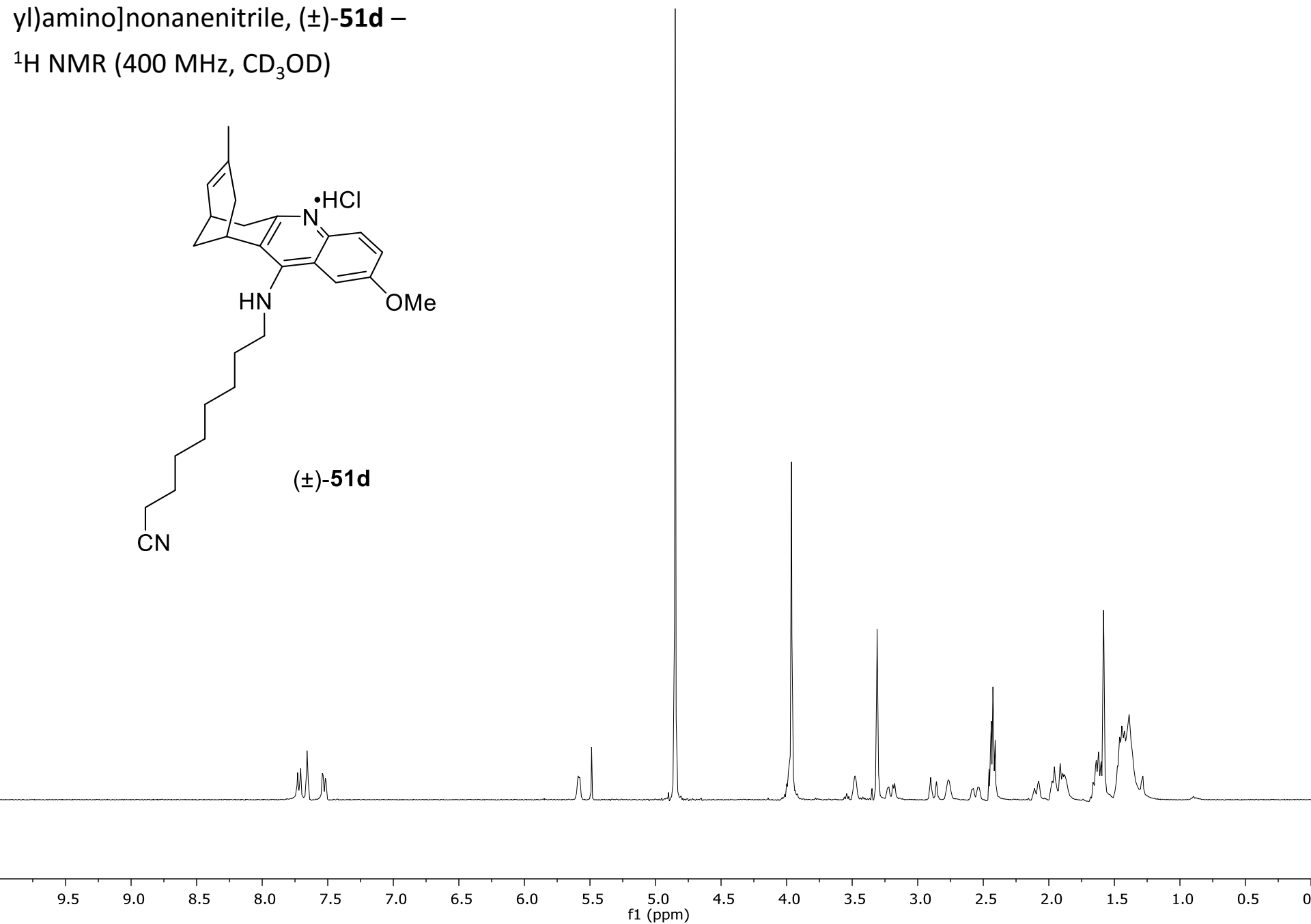


(±)-9-[(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]nonanenitrile, (±)-**51d** –

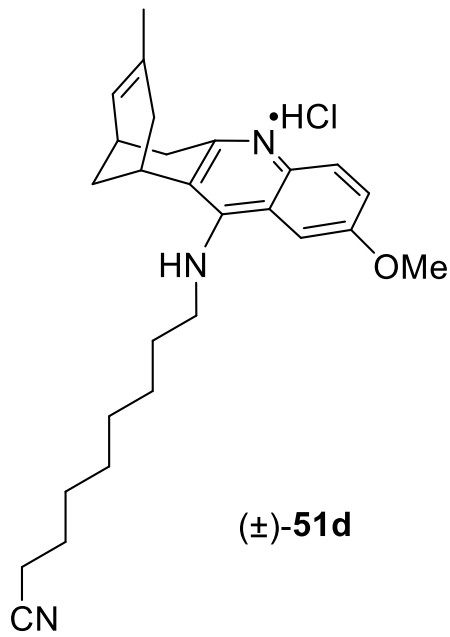
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



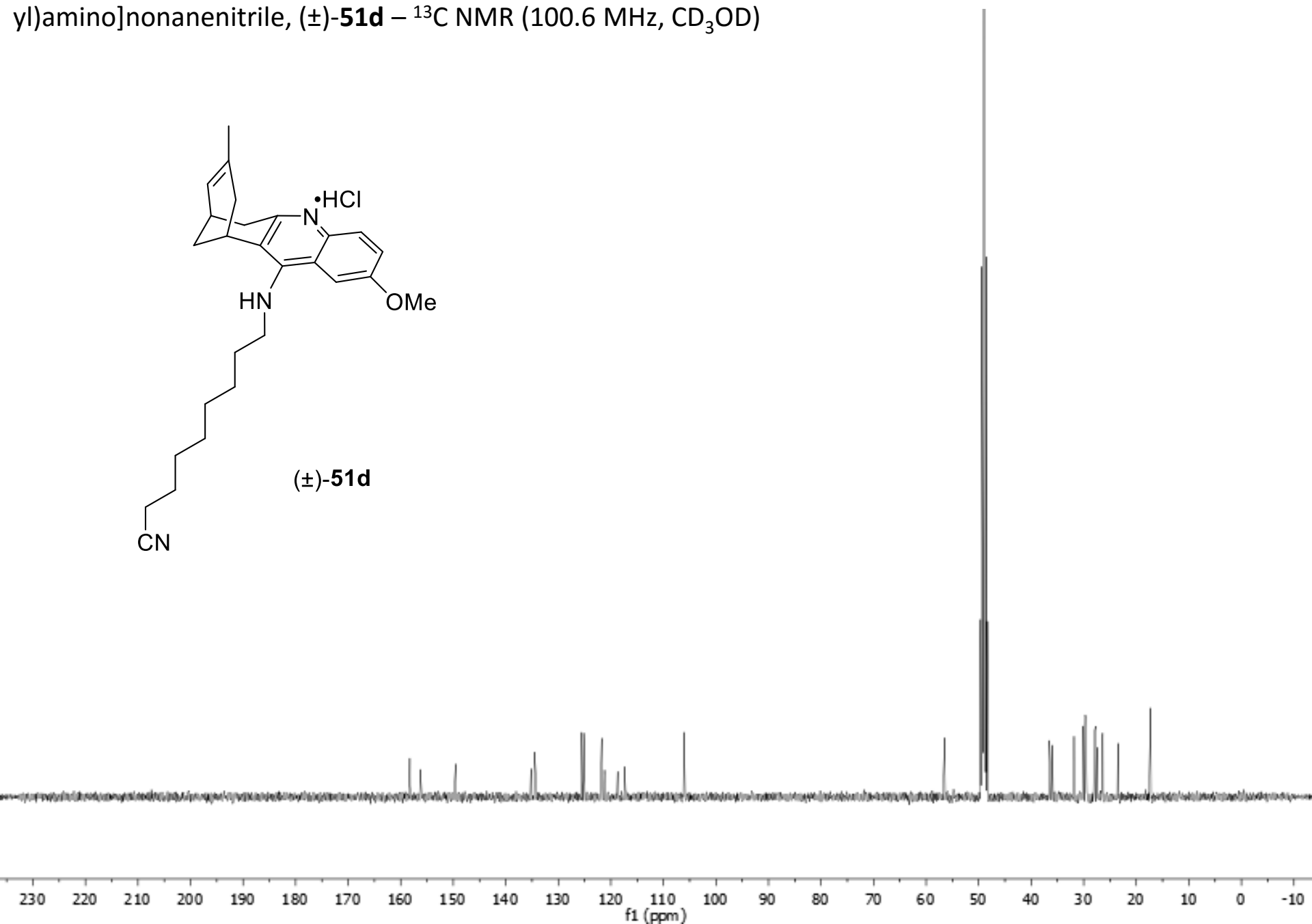
(±)-**51d**



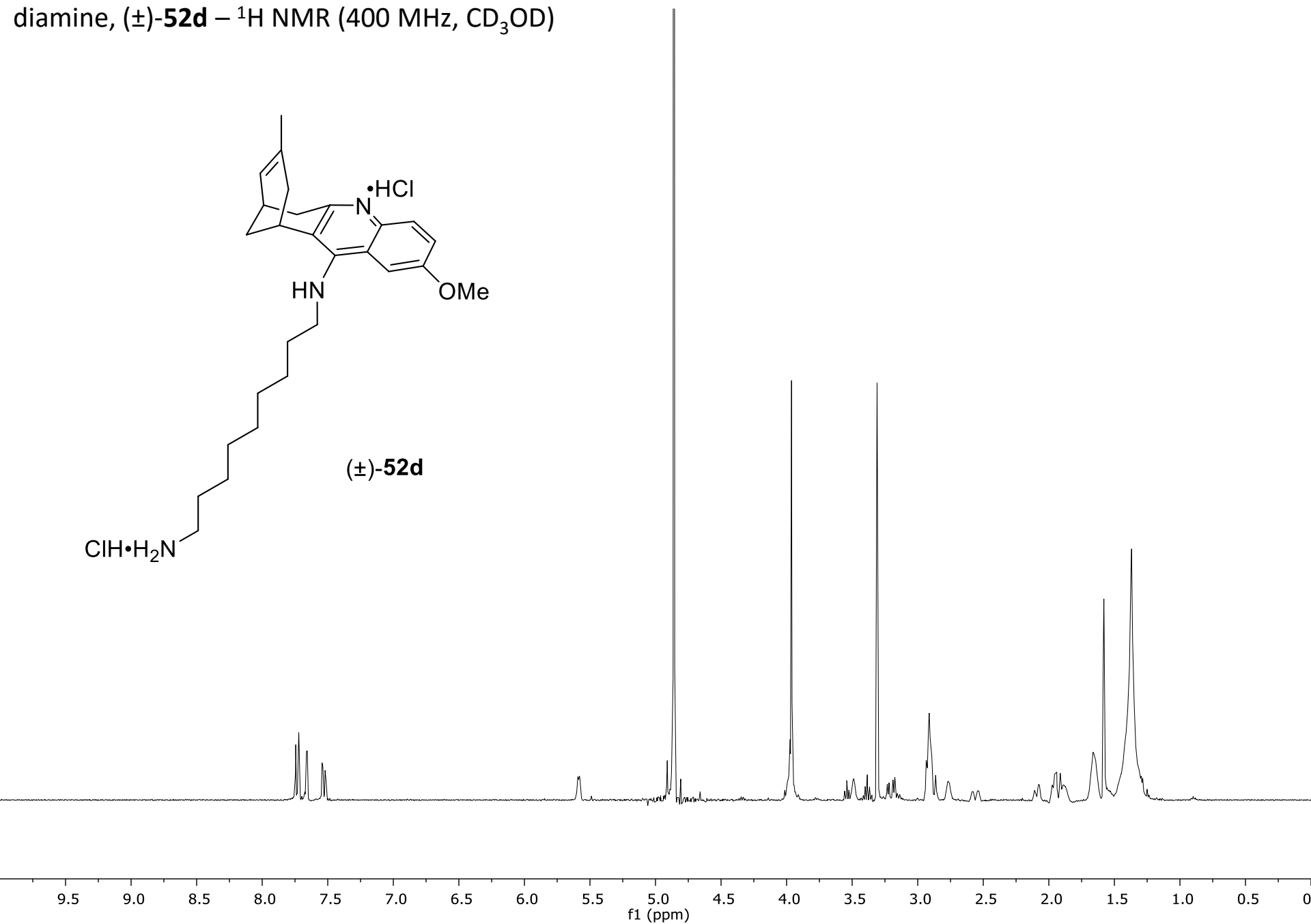
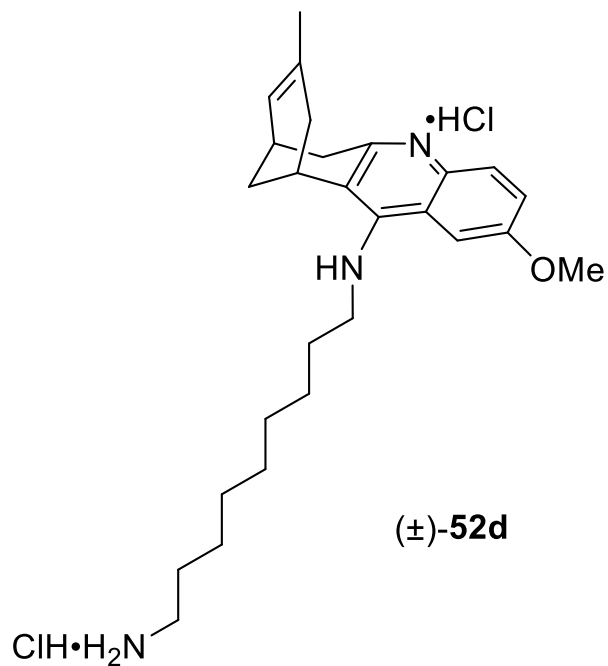
(±)-9-[(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]nonanenitrile, (±)-**51d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



(±)-**51d**

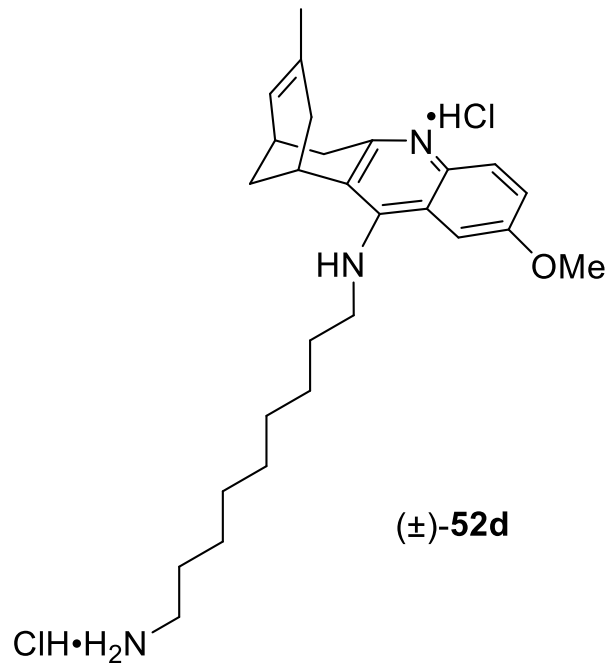


(±)-*N*-(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)nonane-1,9-diamine, (±)-**52d** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

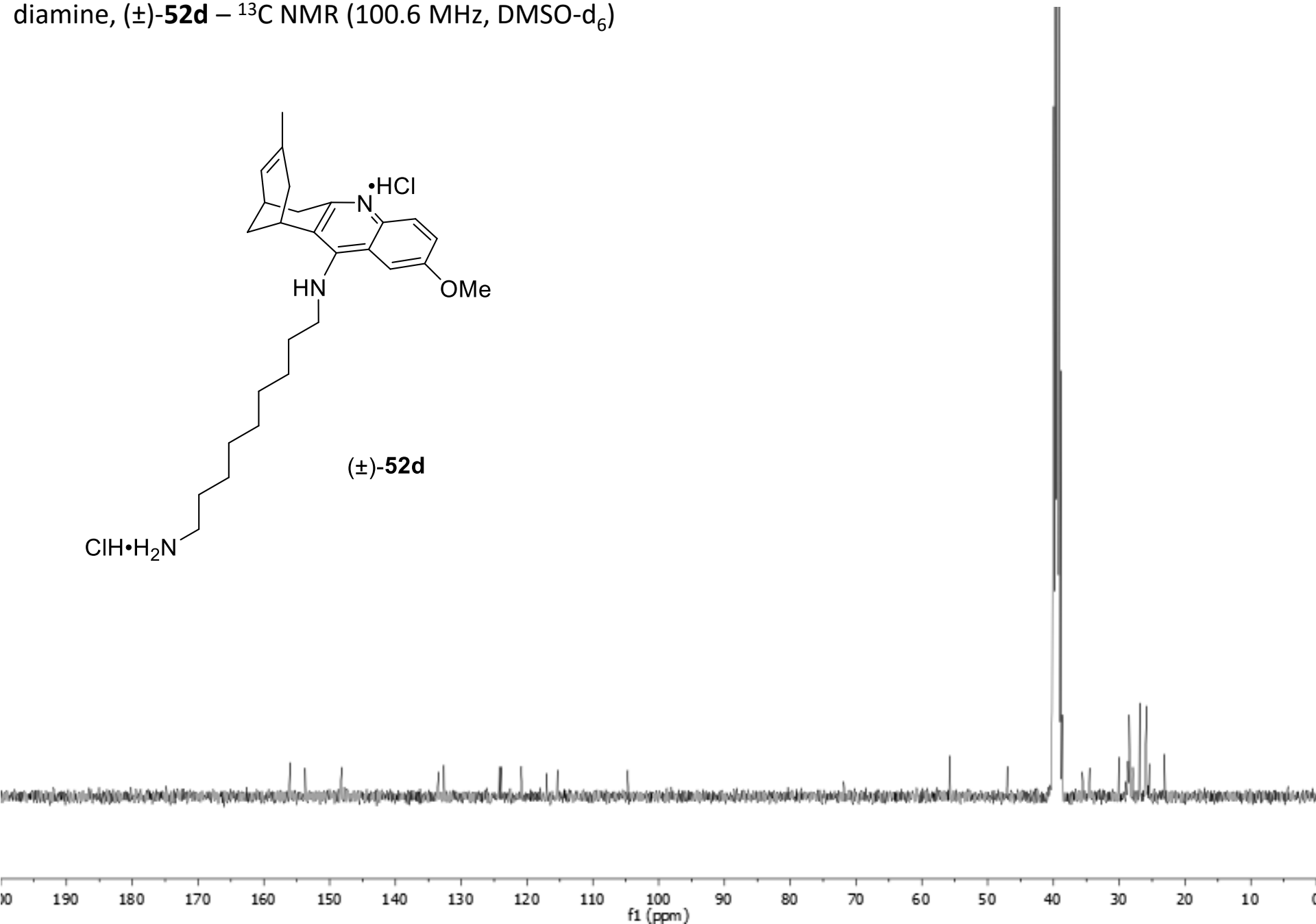




(±)-*N*-(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)nonane-1,9-diamine, (±)-**52d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{DMSO-d}_6$ )

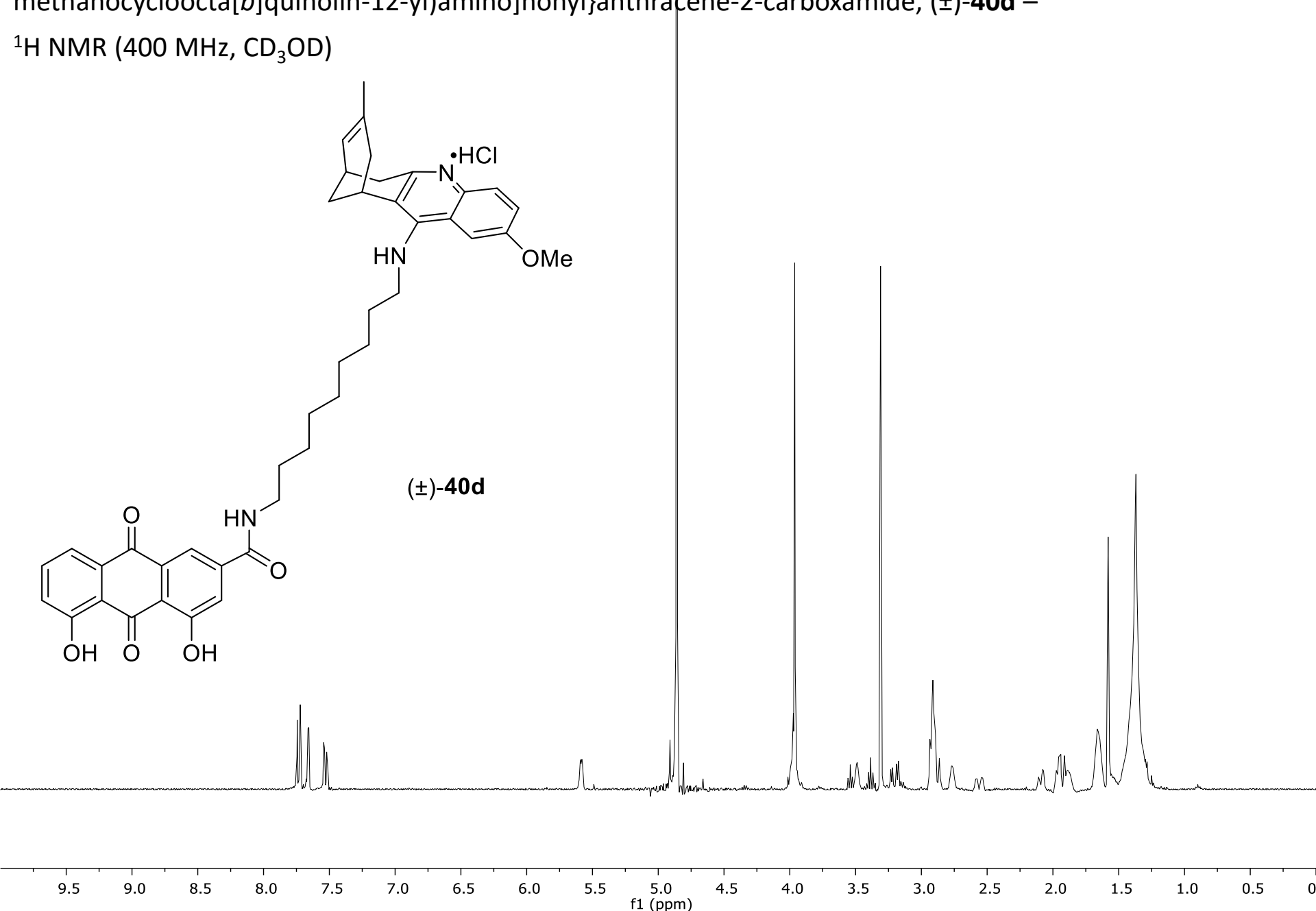
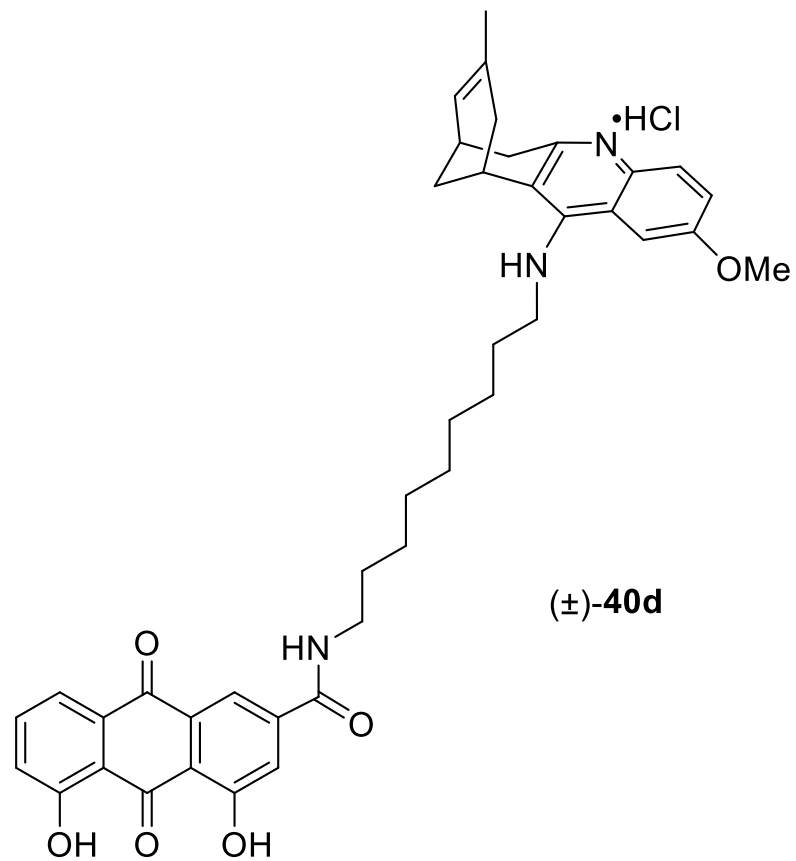


(±)-**52d**

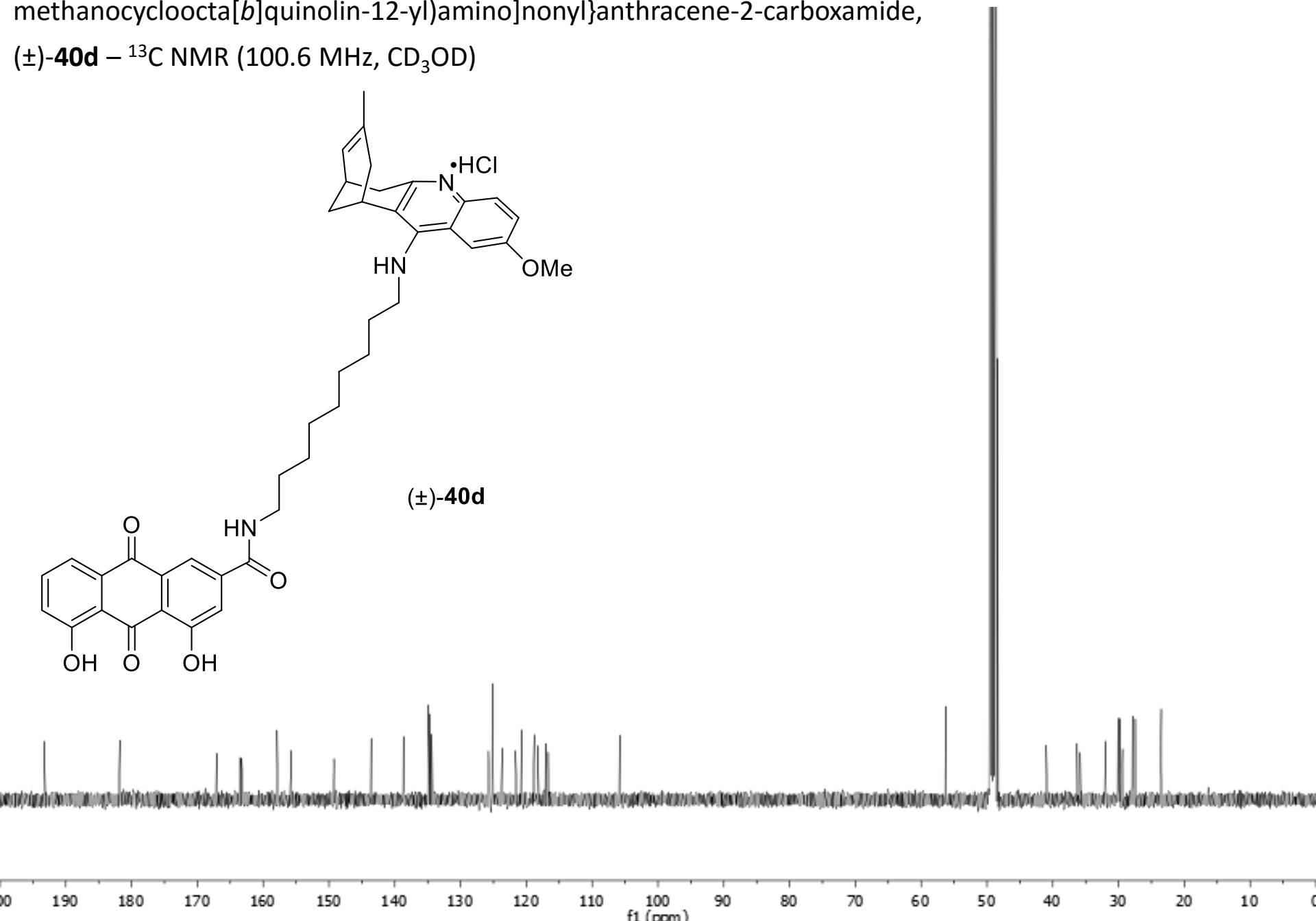
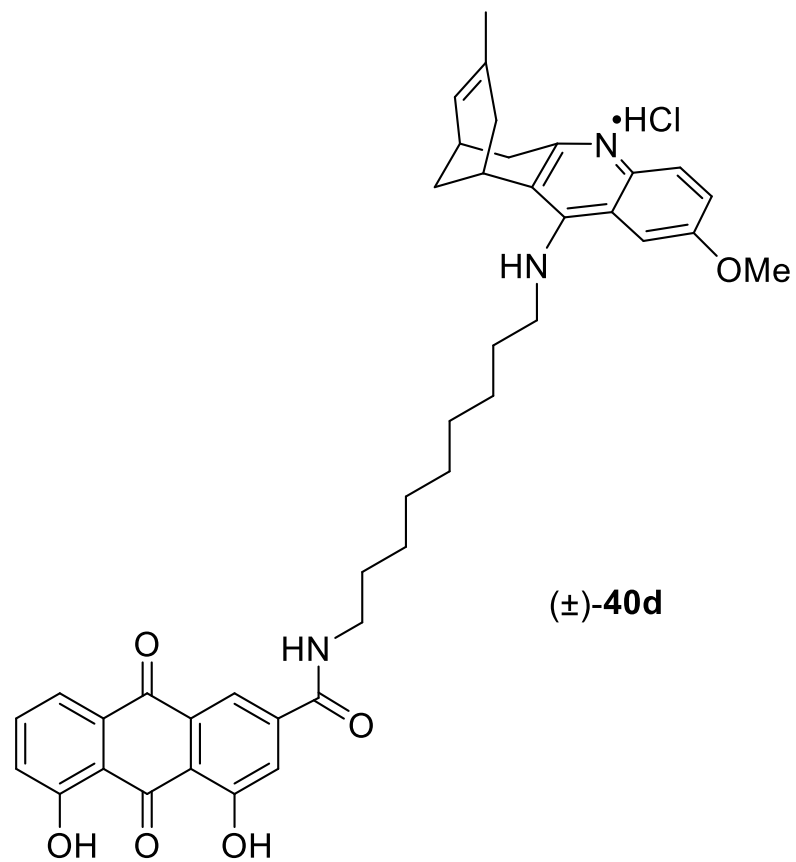


(±)-9,10-dihydro-4,5-dihydroxy-9,10-dioxo-*N*-{9-[(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]nonyl}anthracene-2-carboxamide, (±)-**40d** –

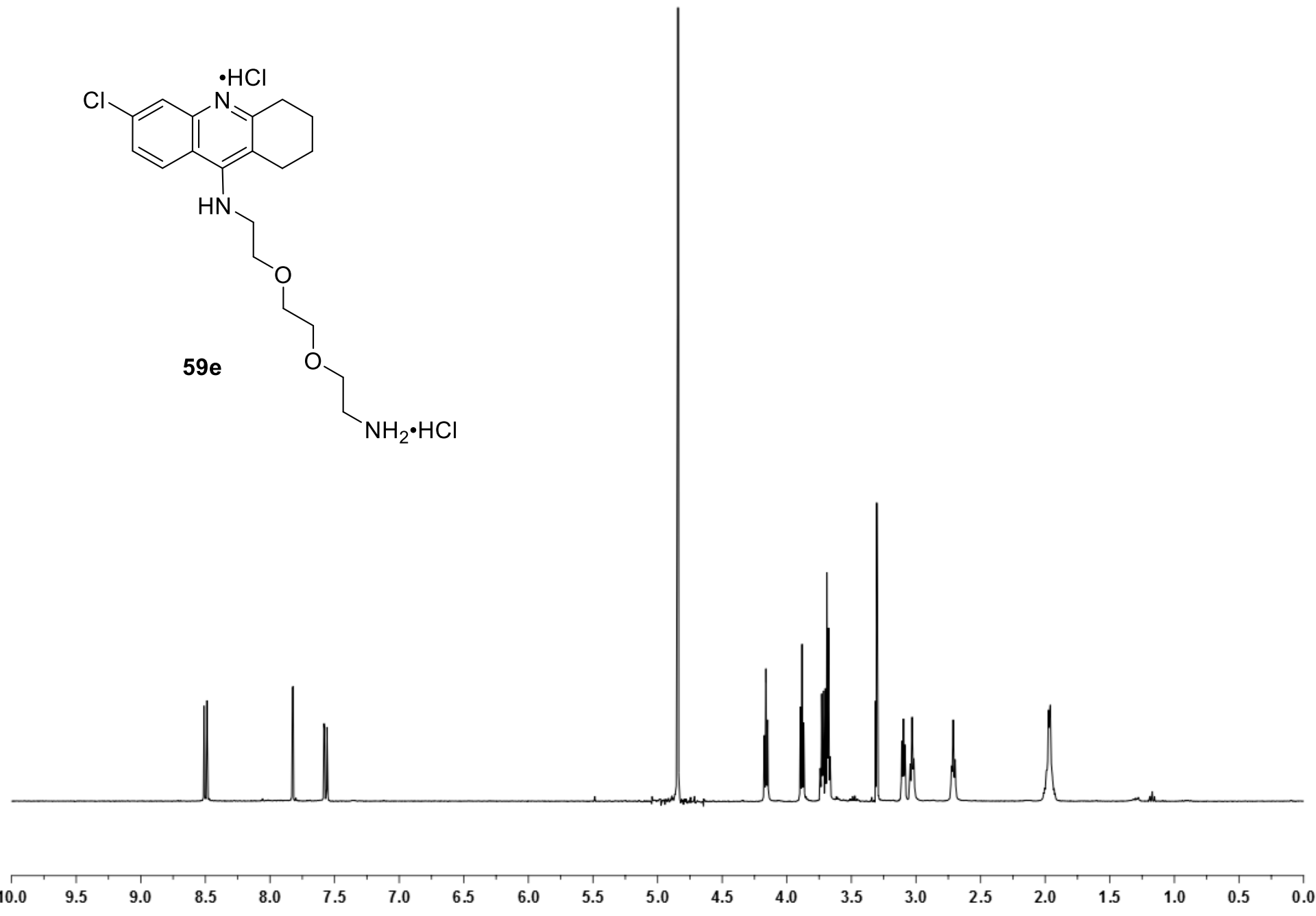
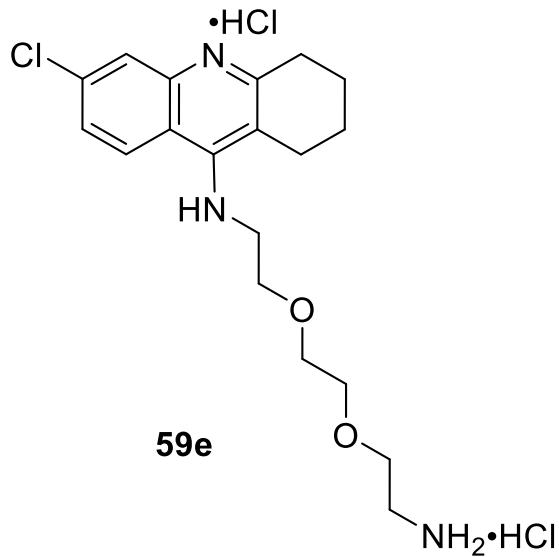
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



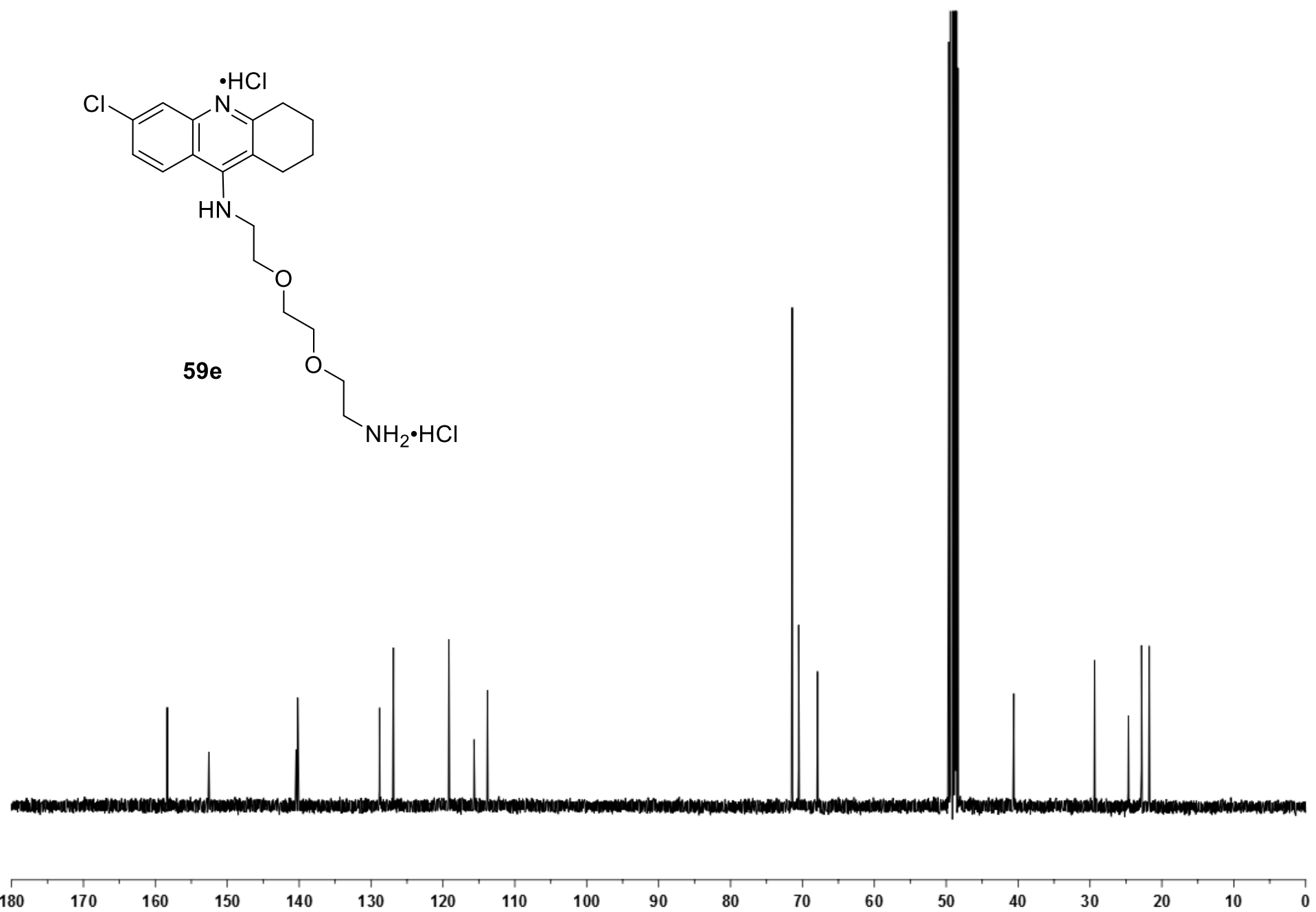
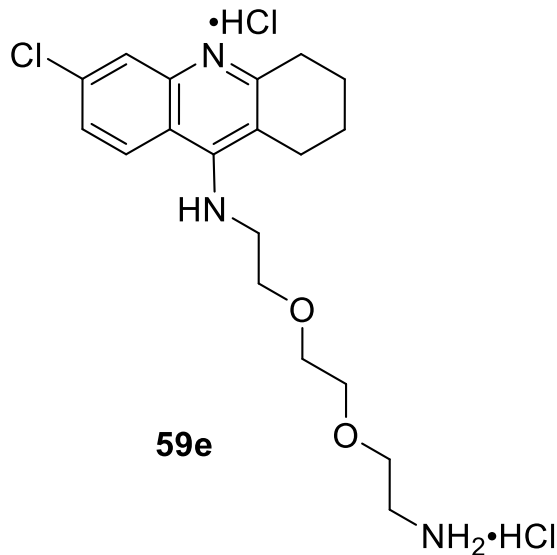
(±)-9,10-dihydro-4,5-dihydroxy-9,10-dioxo-*N*-{9-[(6,7,10,11-tetrahydro-2-methoxy-9-methyl-7,11-methanocycloocta[*b*]quinolin-12-yl)amino]nonyl}anthracene-2-carboxamide, (±)-**40d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



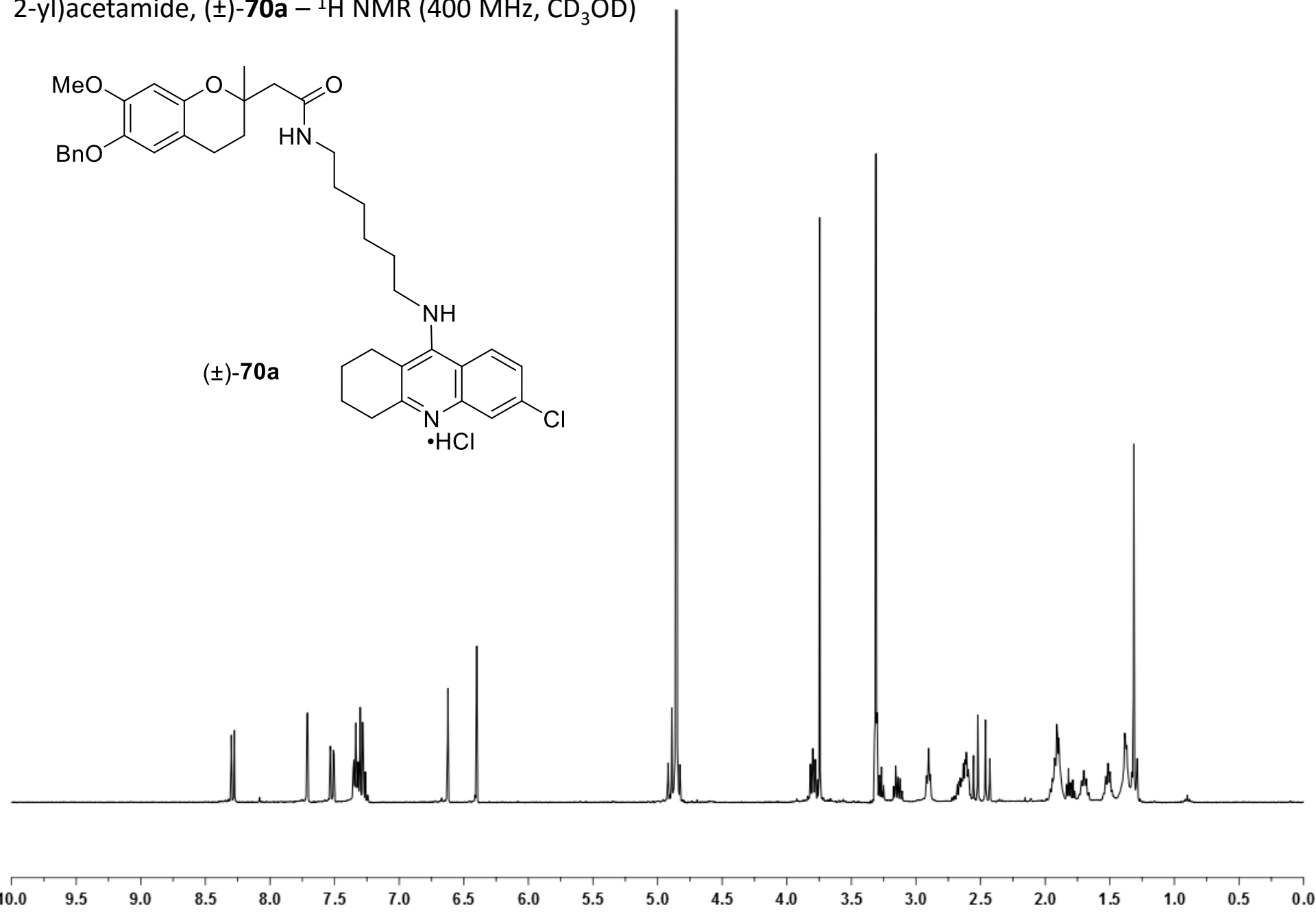
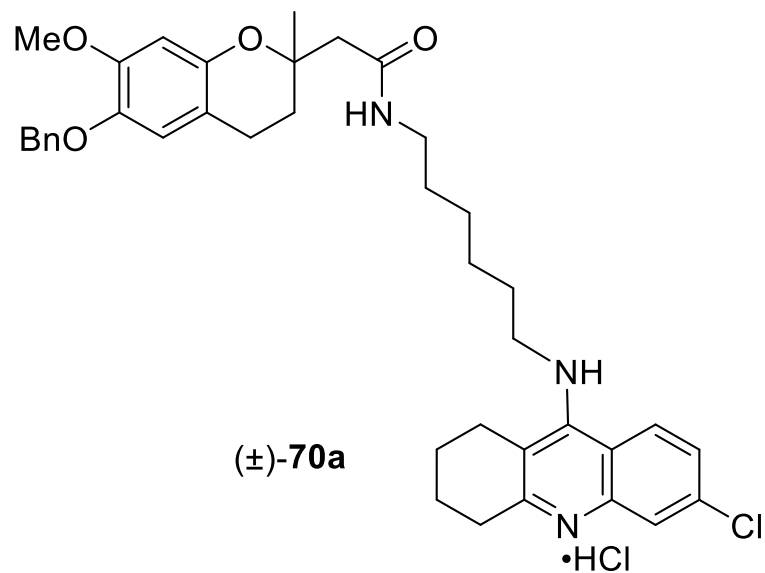
*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-3,6-dioxaoctane-1,8-diamine, **59e** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



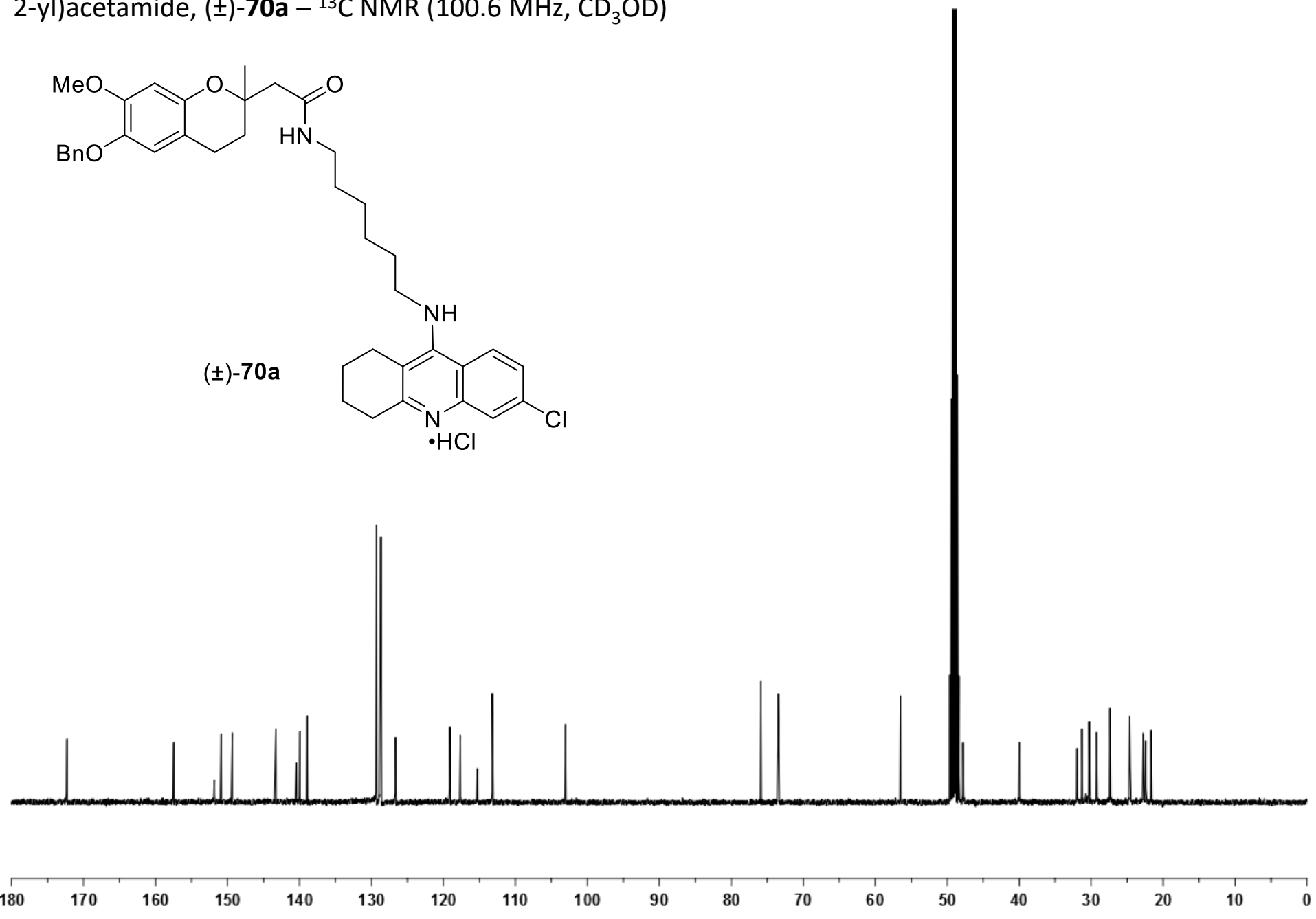
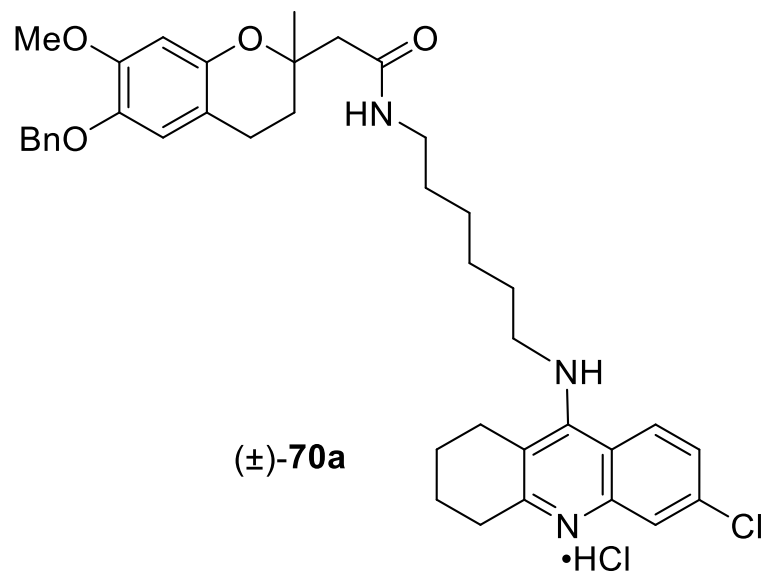
*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-3,6-dioxaoctane-1,8-diamine, **59e** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



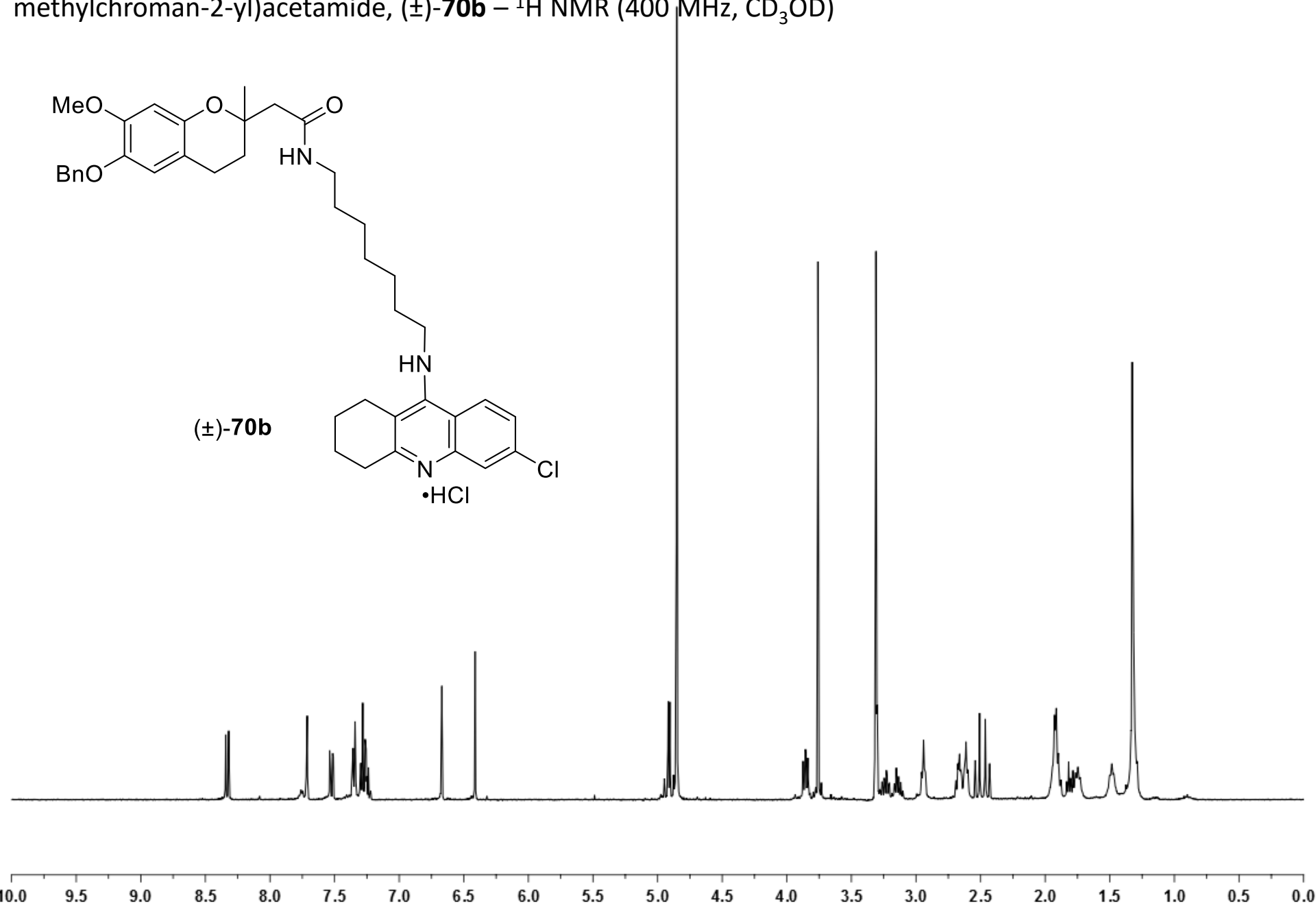
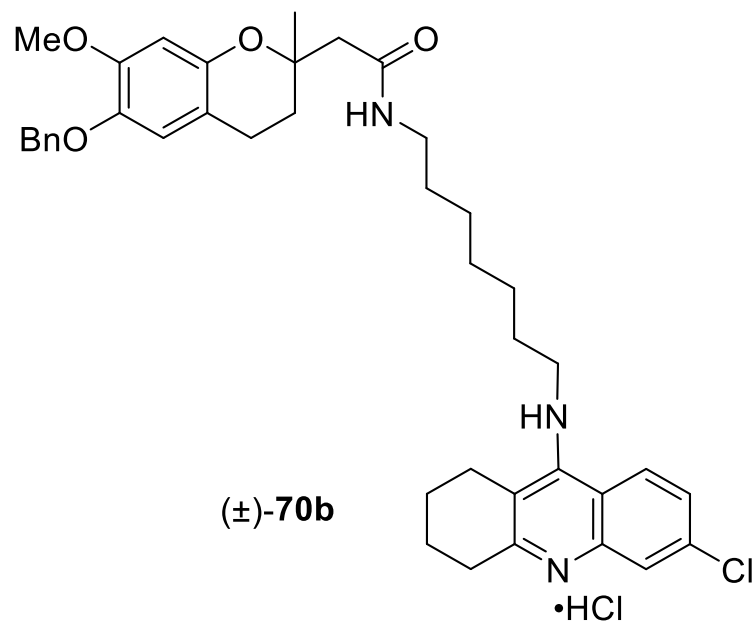
(±)-*N*-{6-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]hexyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



(±)-*N*-{6-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]hexyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

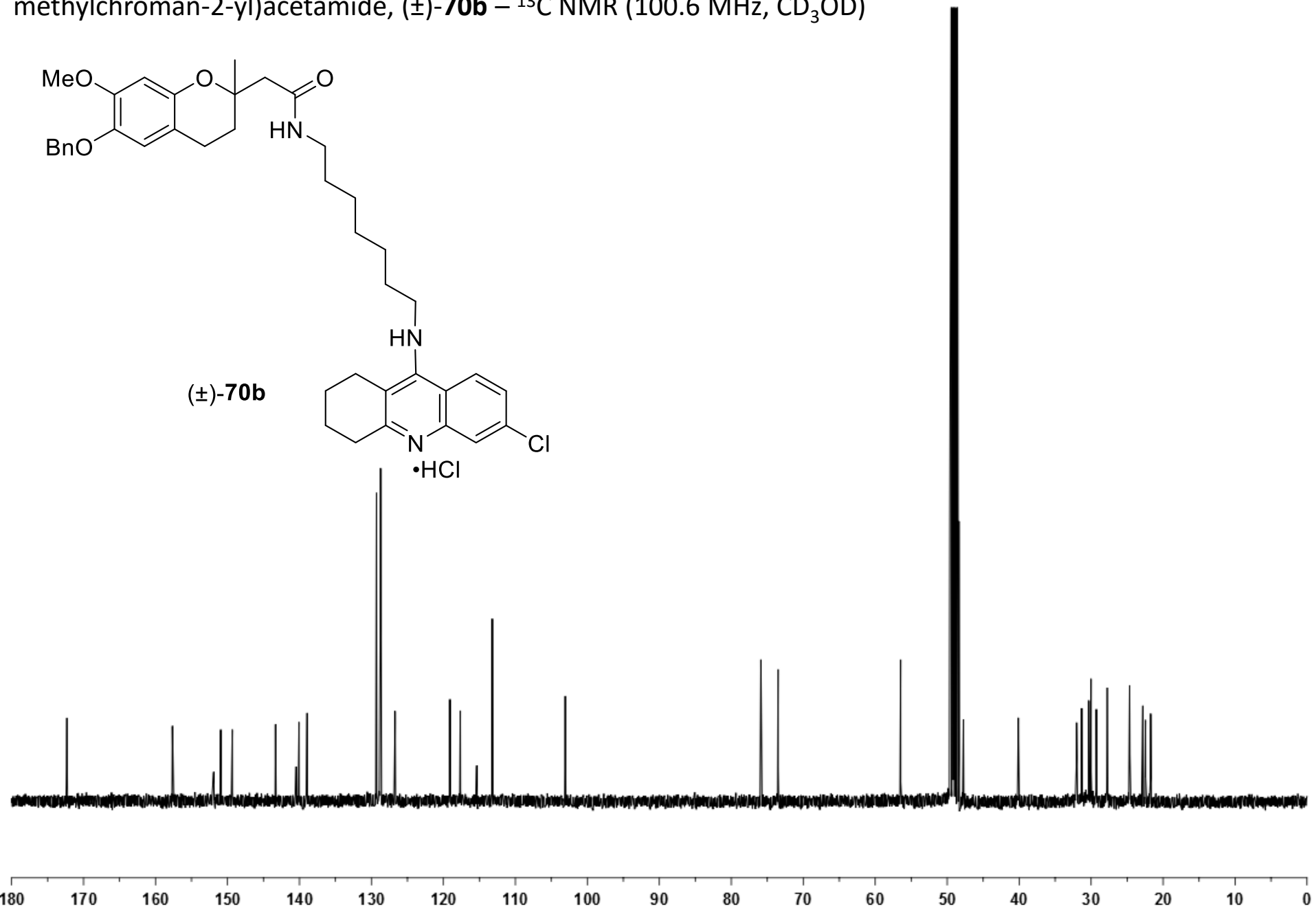
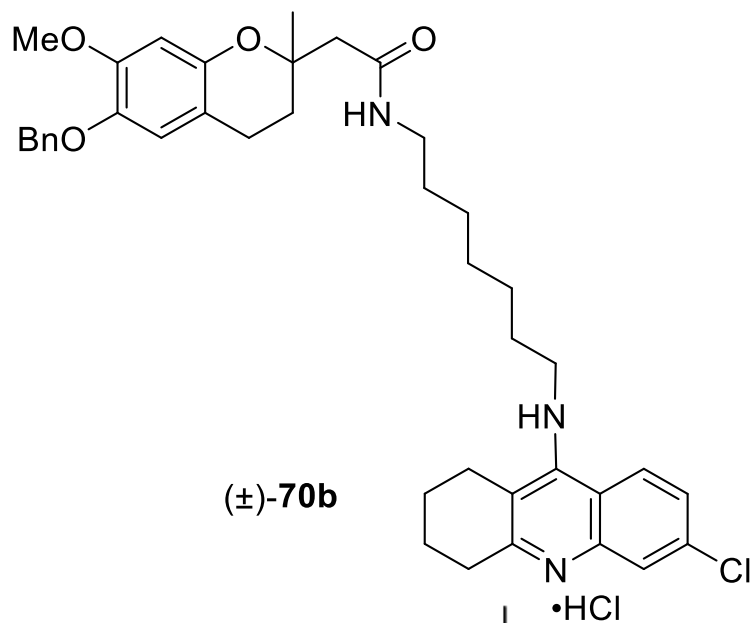


(±)-*N*-{7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

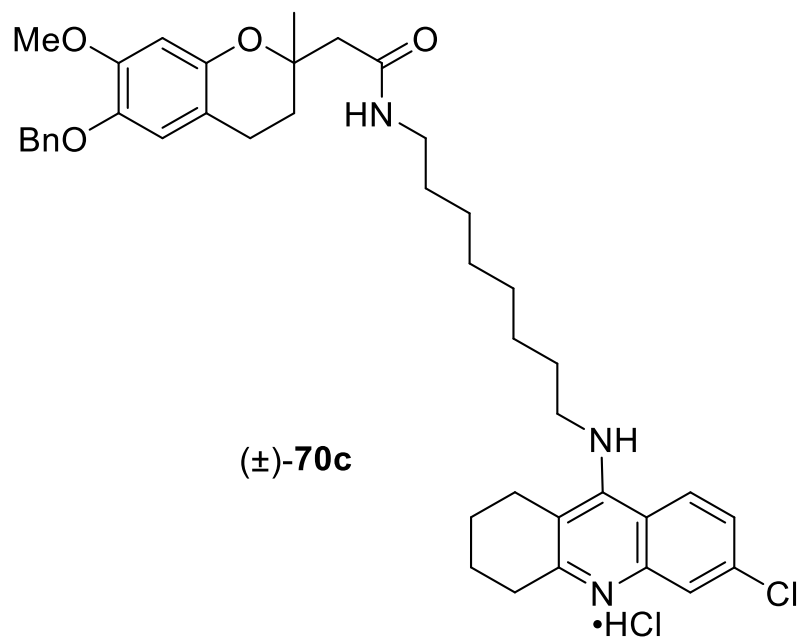




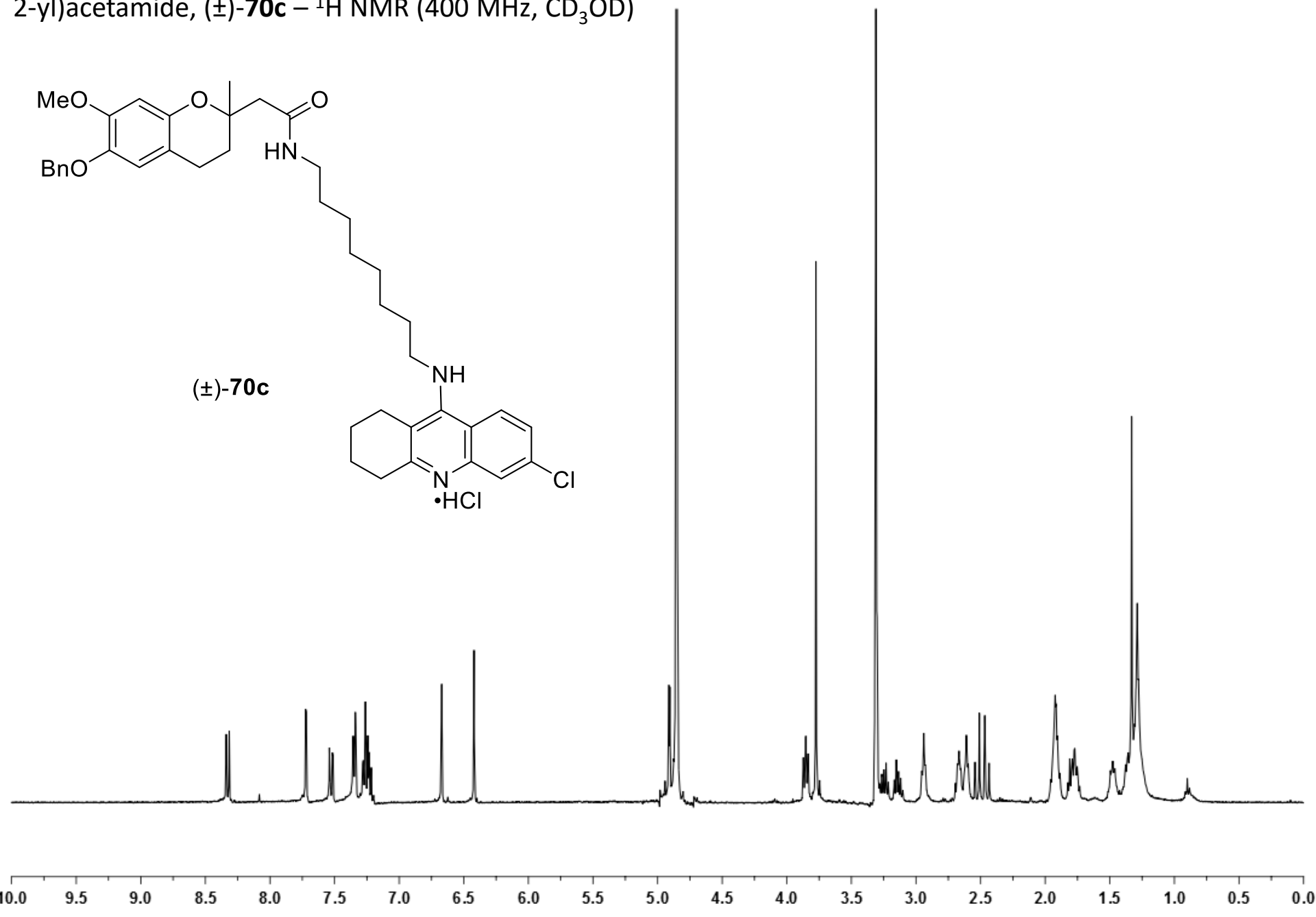
(±)-*N*-{7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



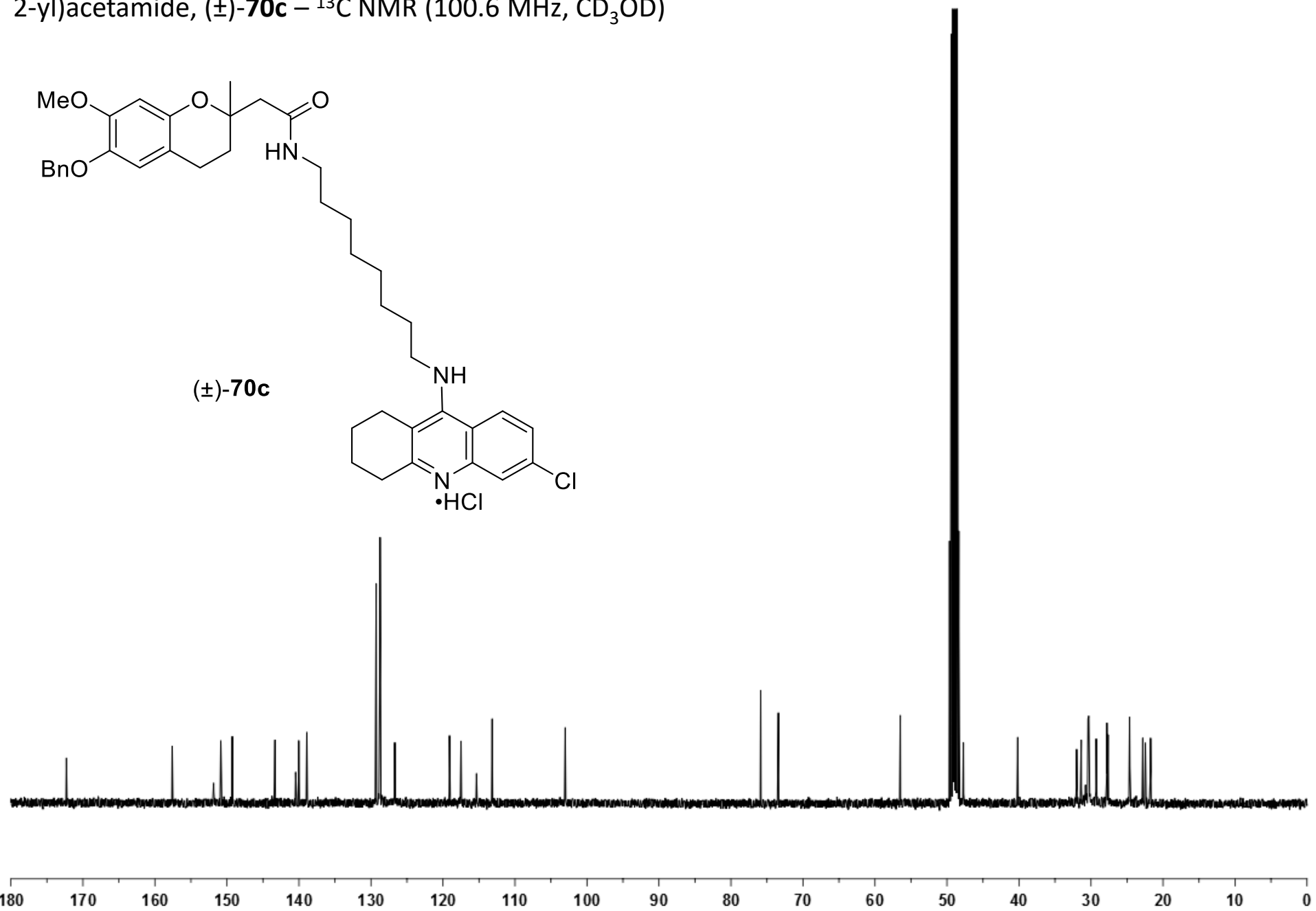
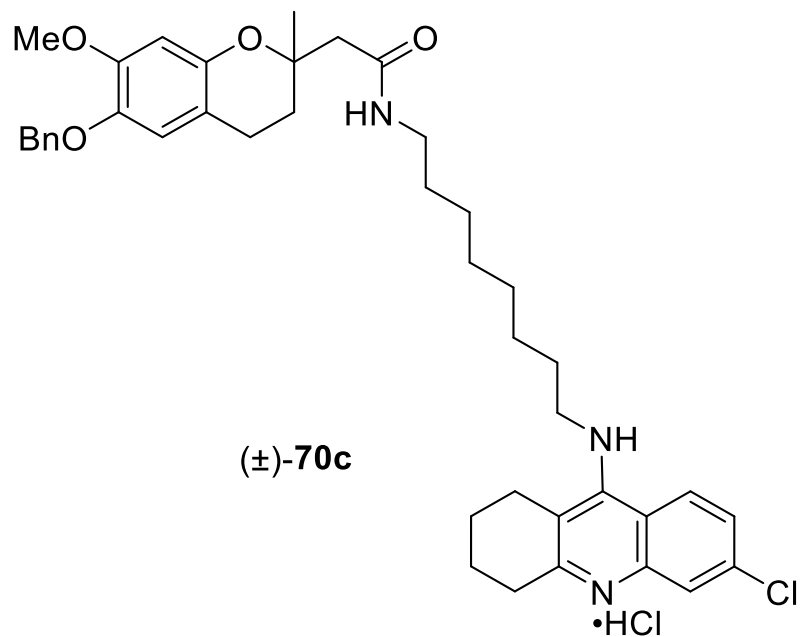
(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



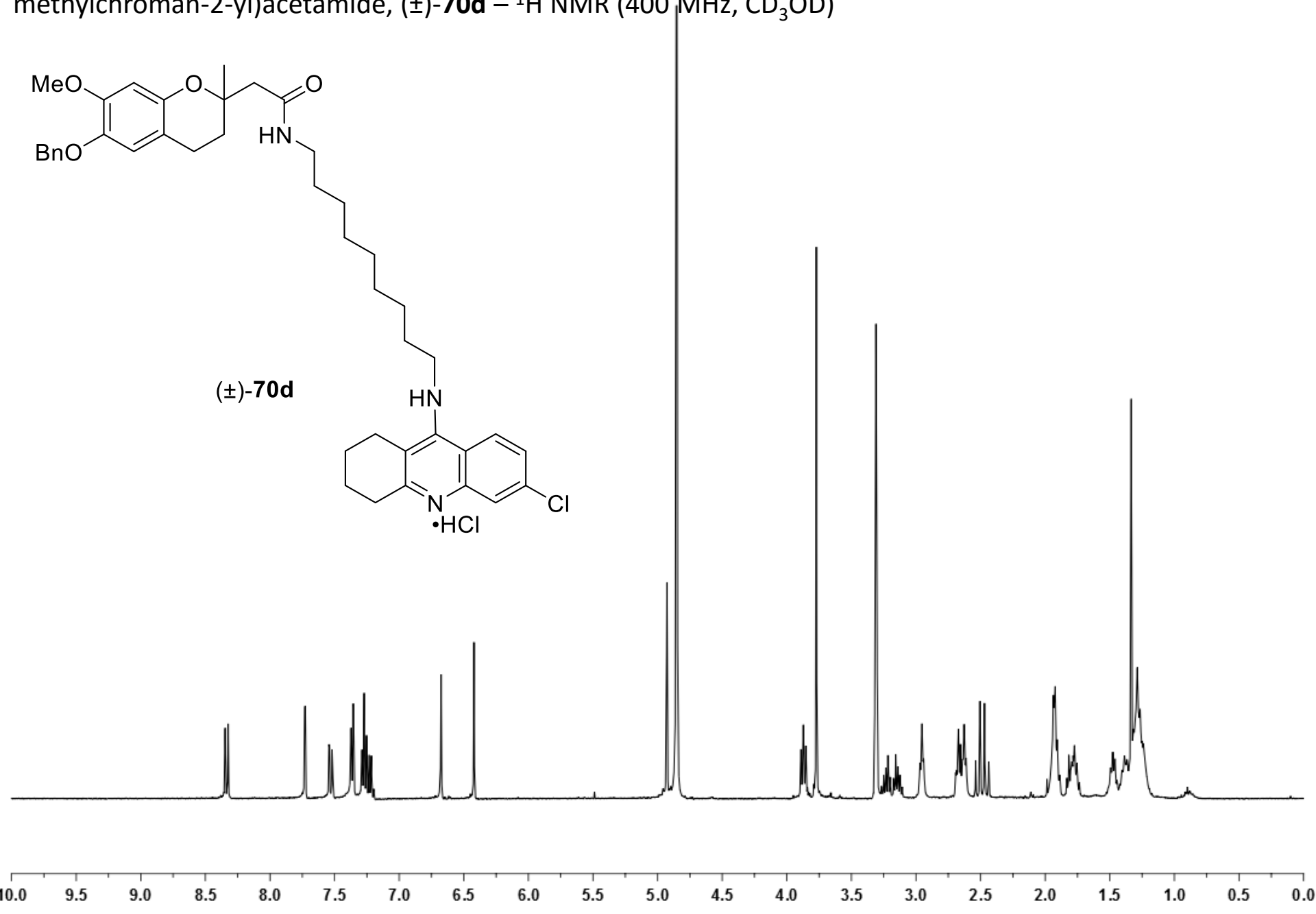
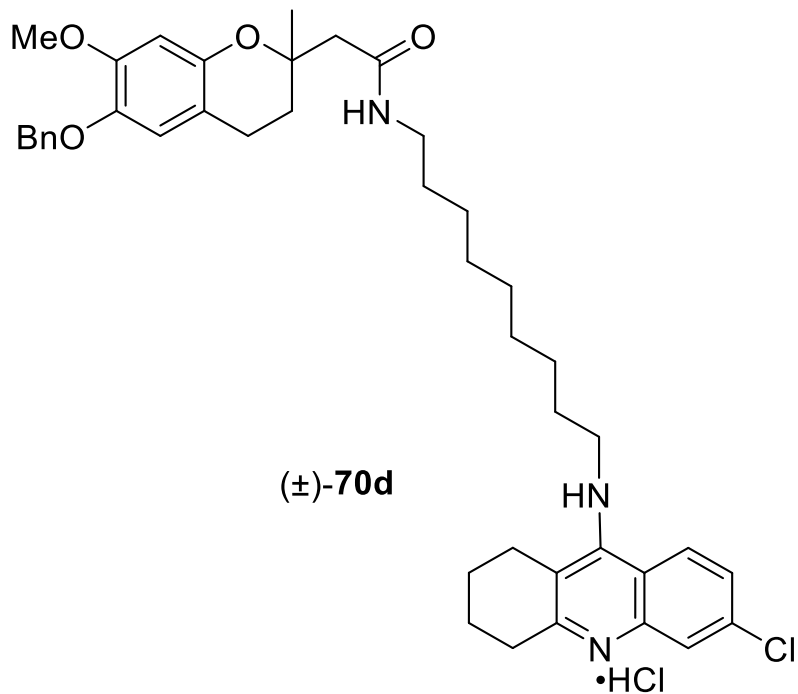
(±)-**70c**



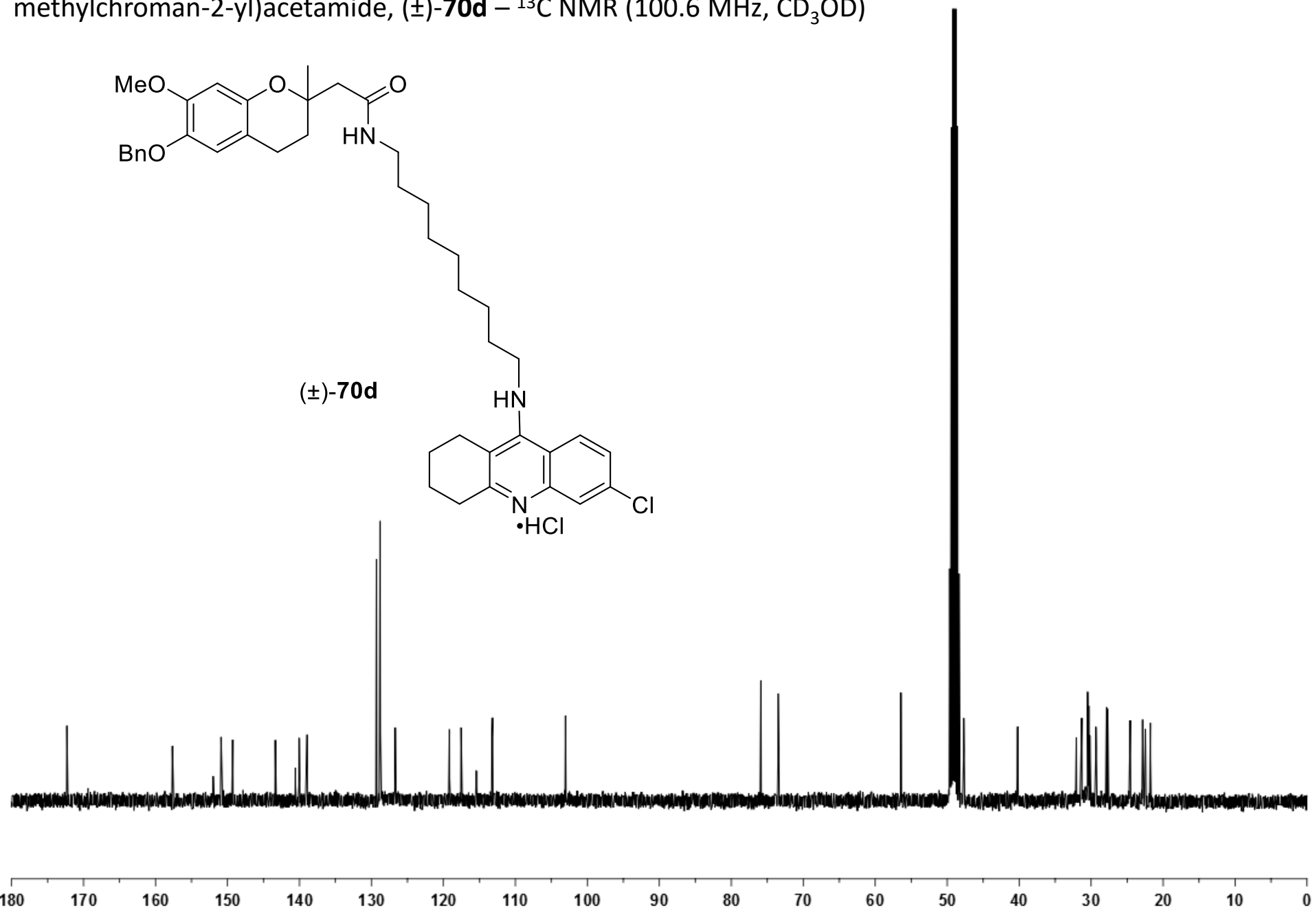
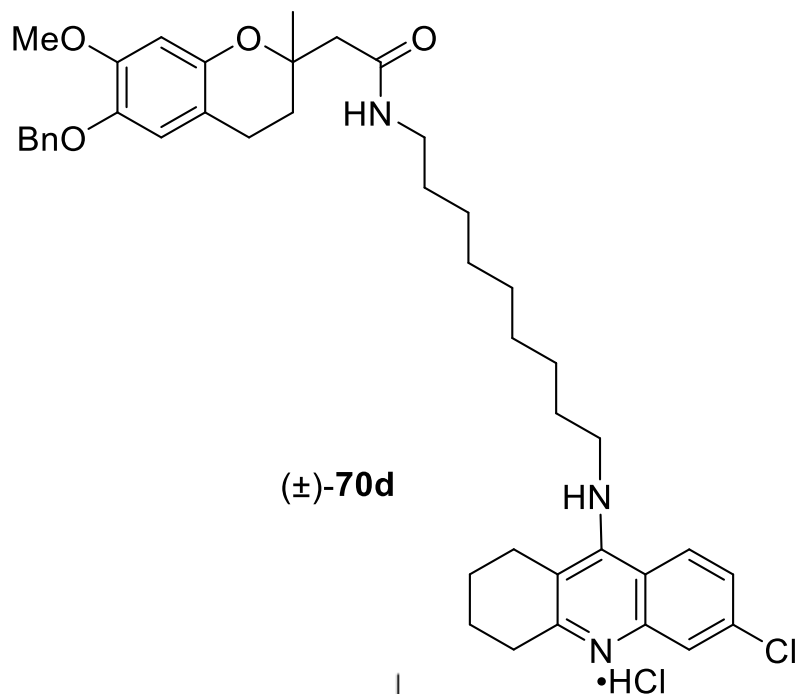
(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



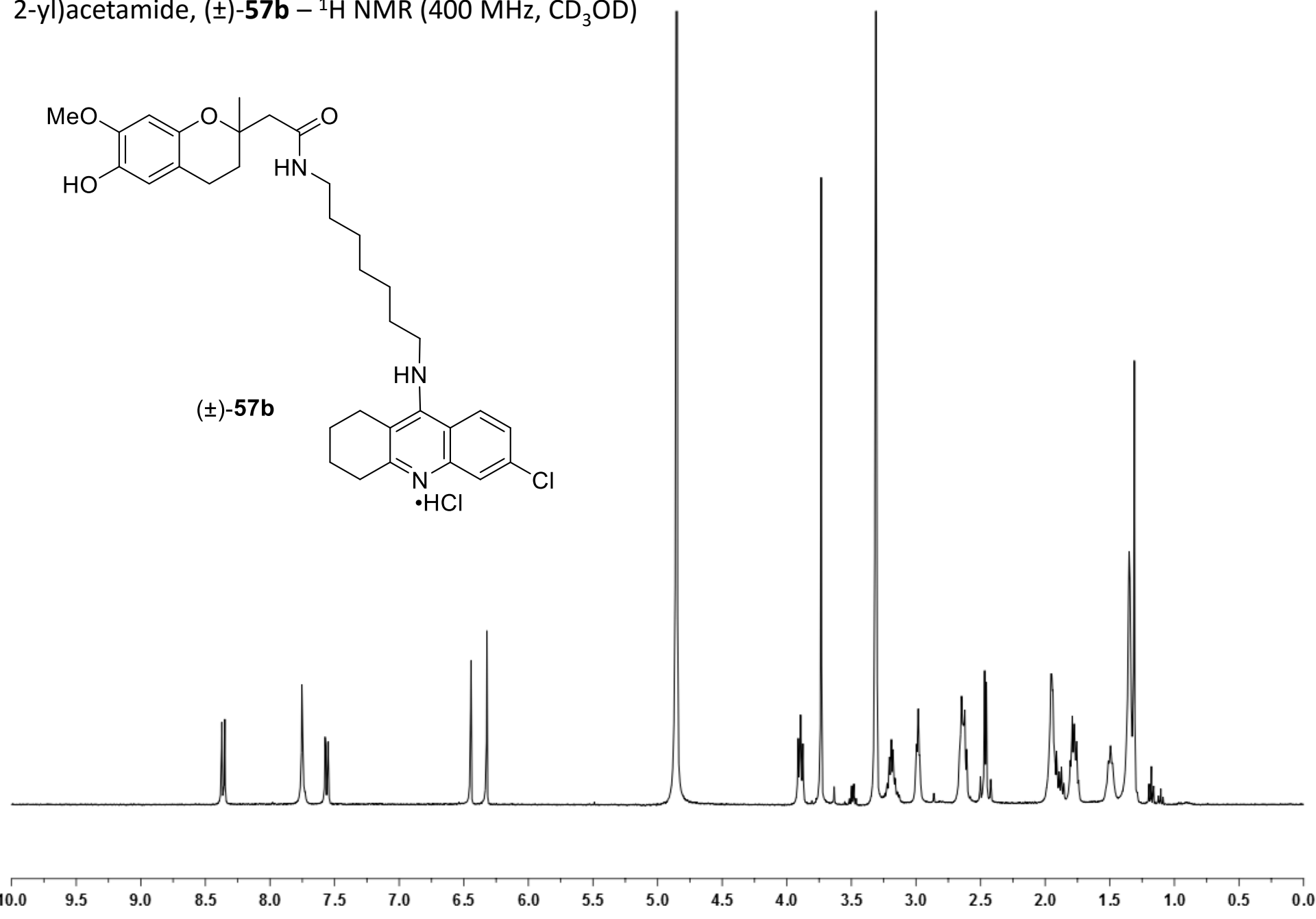
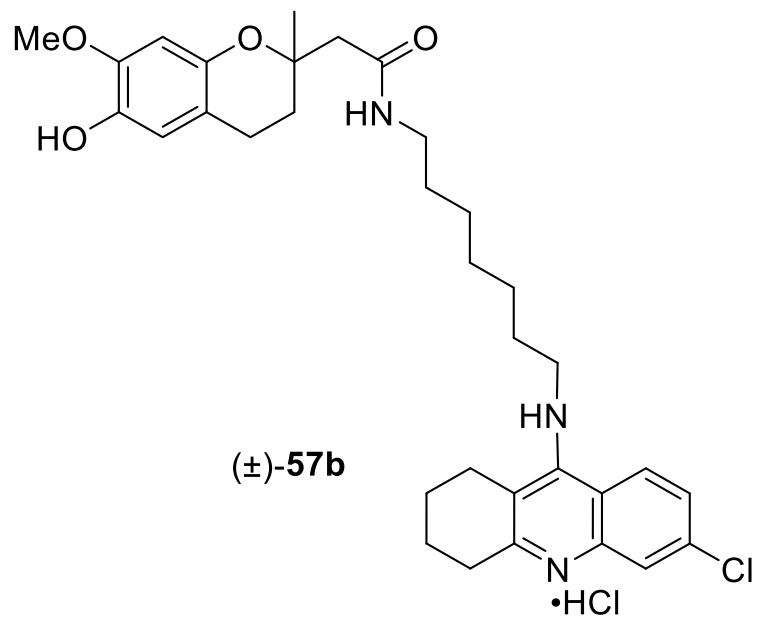
(±)-*N*-{9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70d** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



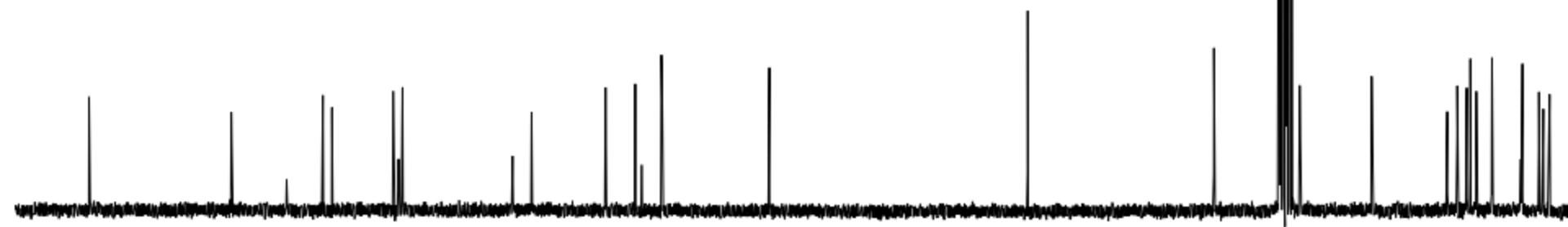
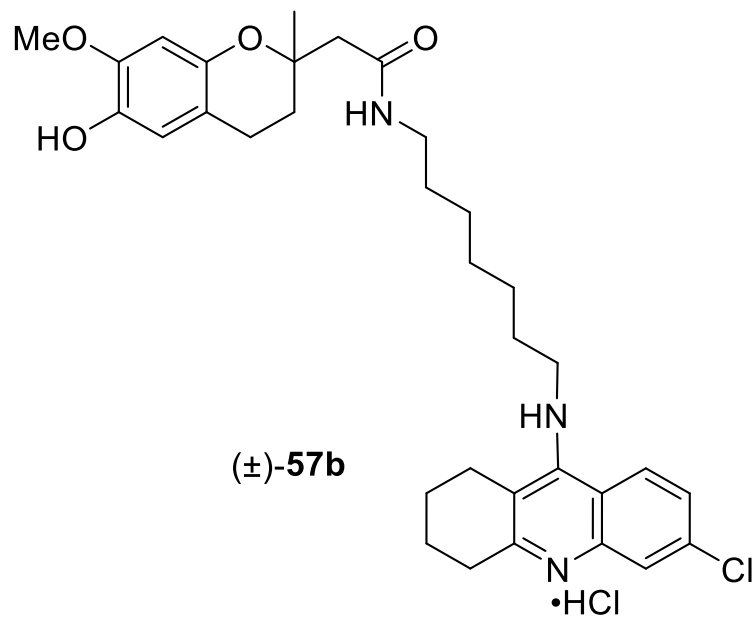
(±)-*N*-{9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonyl}-2-(6-benzyloxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**70d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



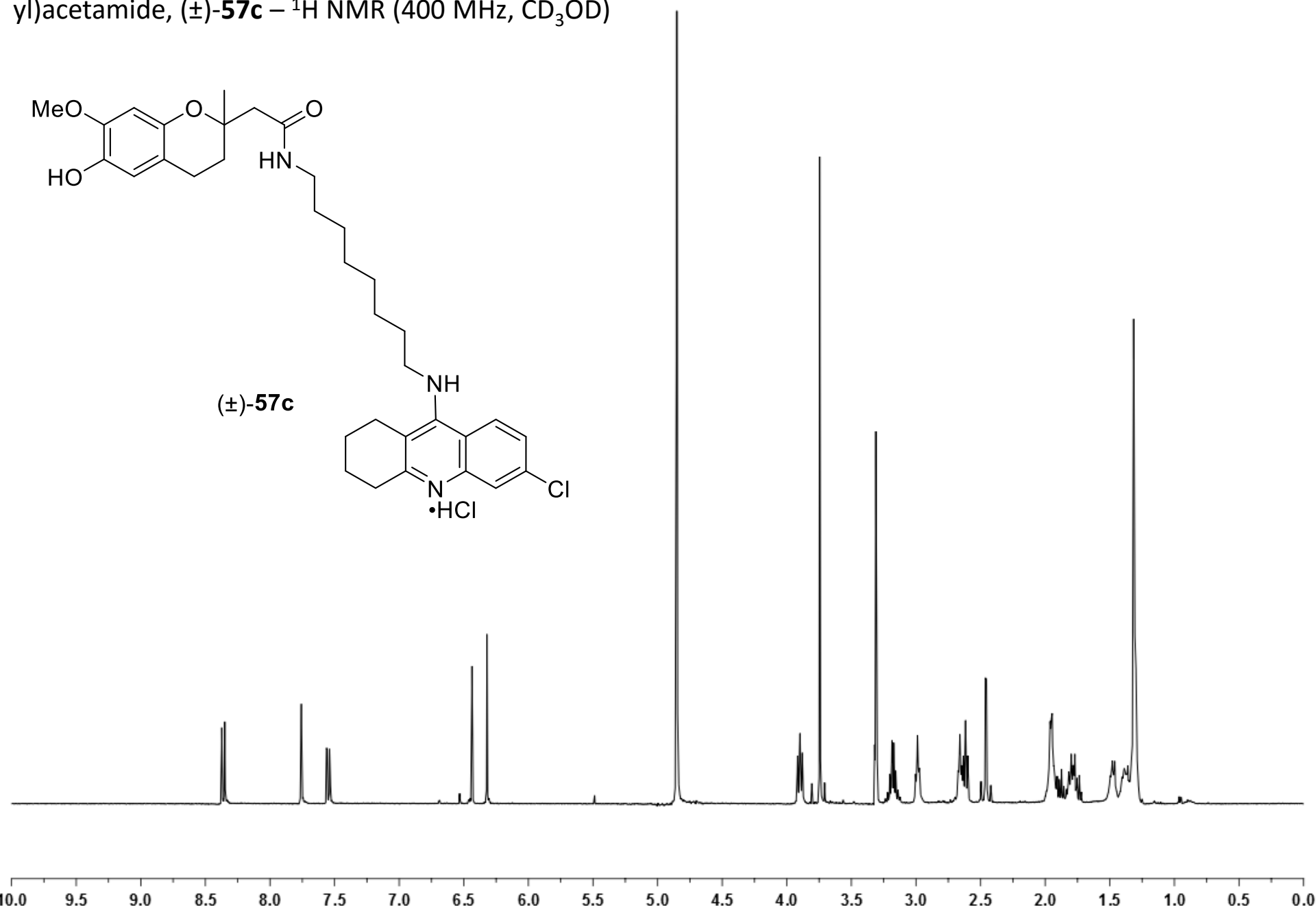
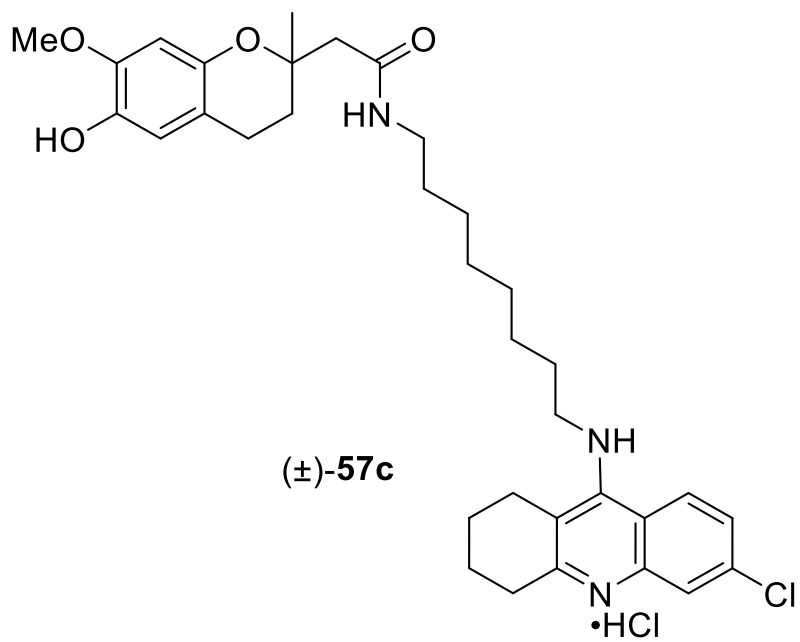
(±)-*N*-{7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



(±)-*N*-{7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

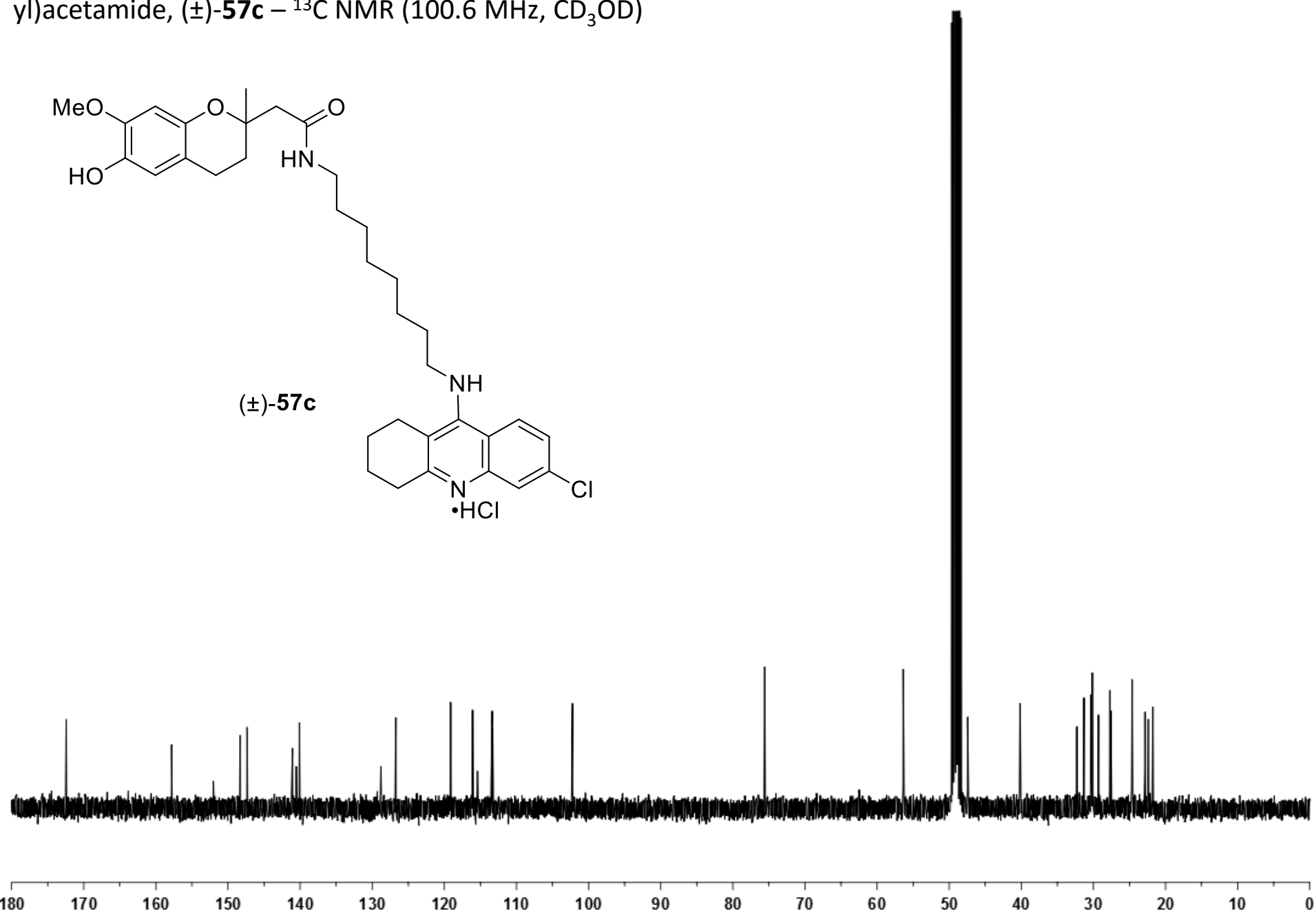
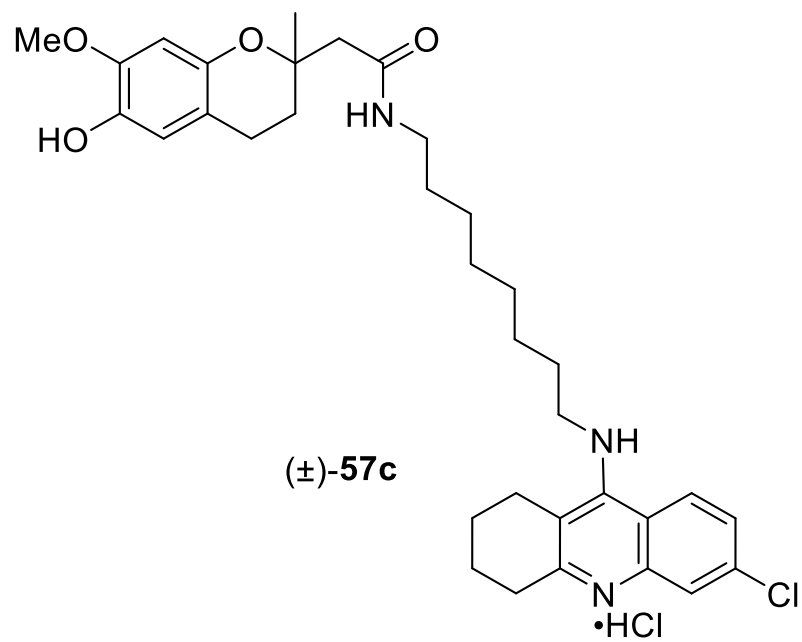


(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

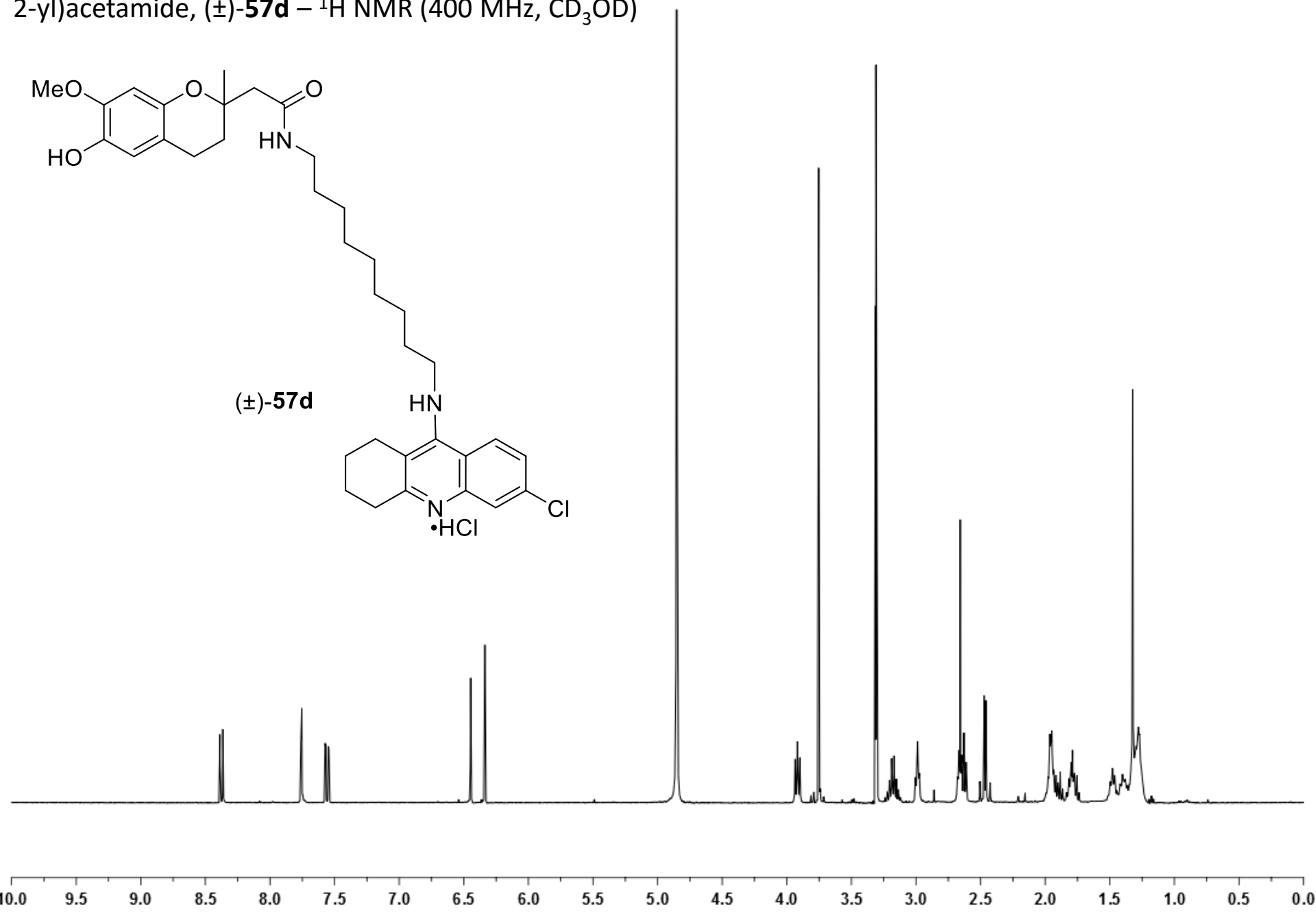
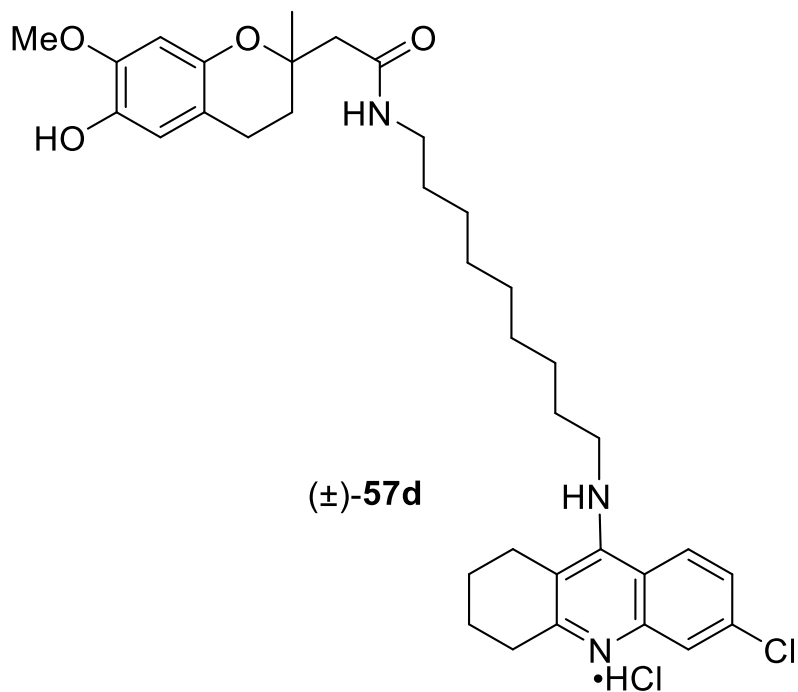




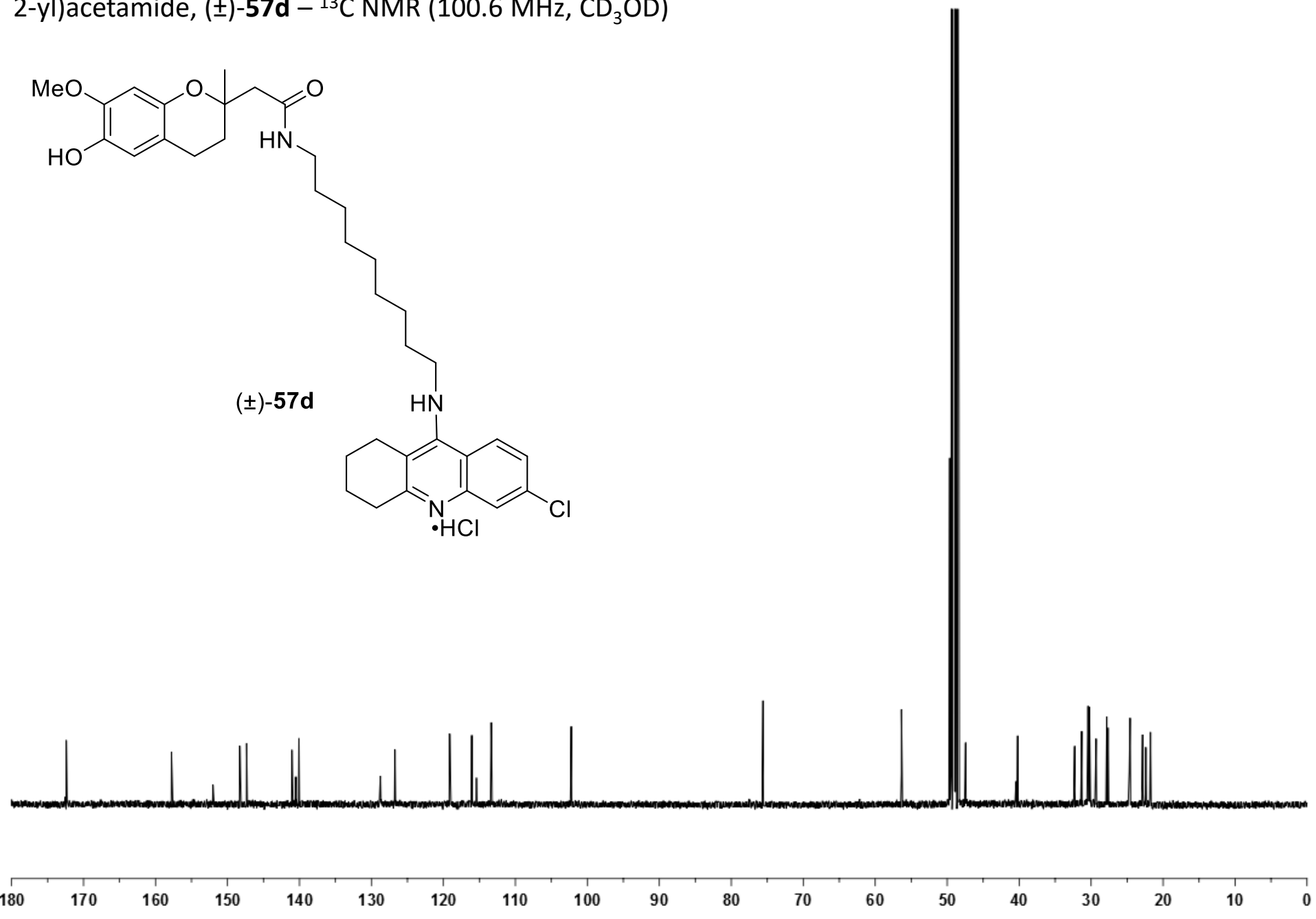
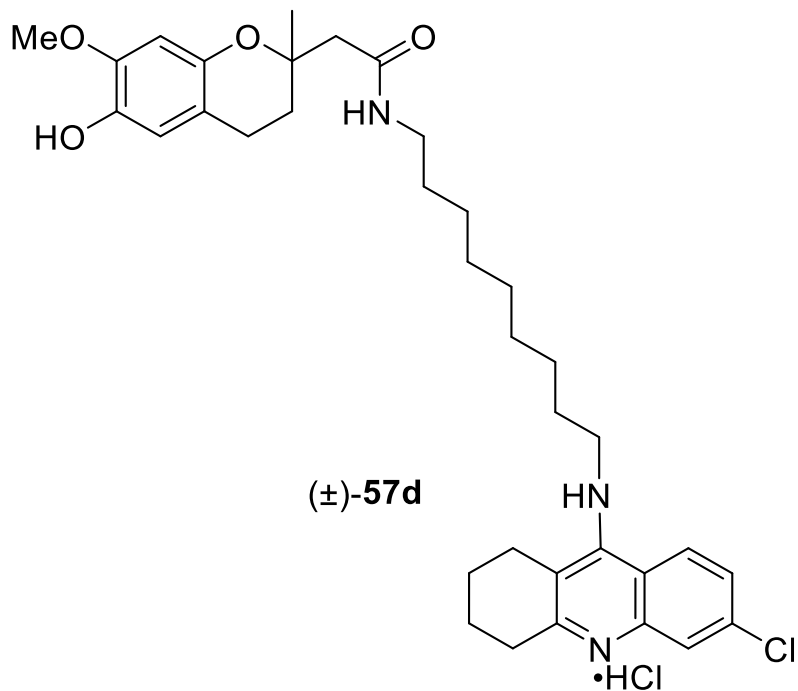
(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



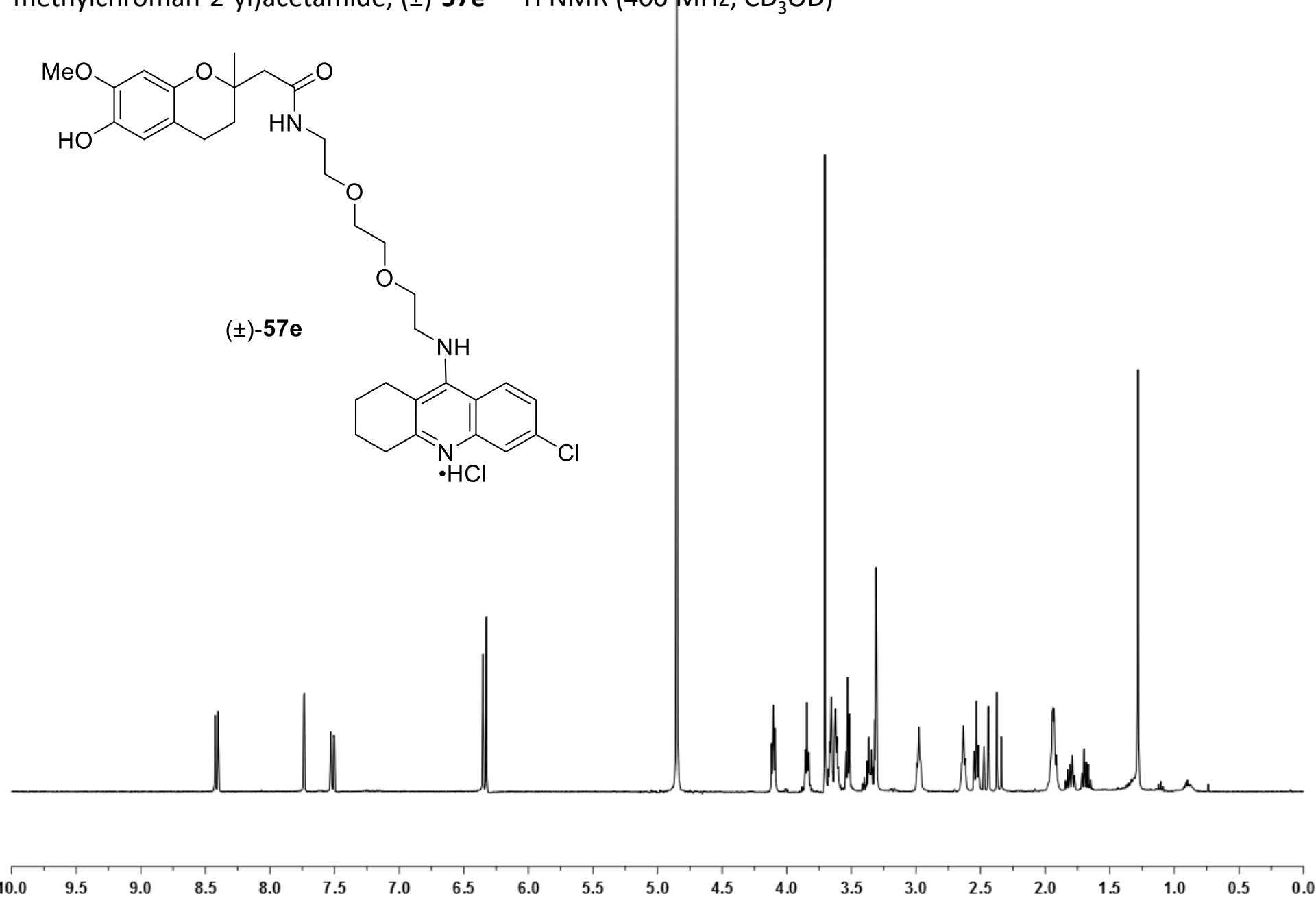
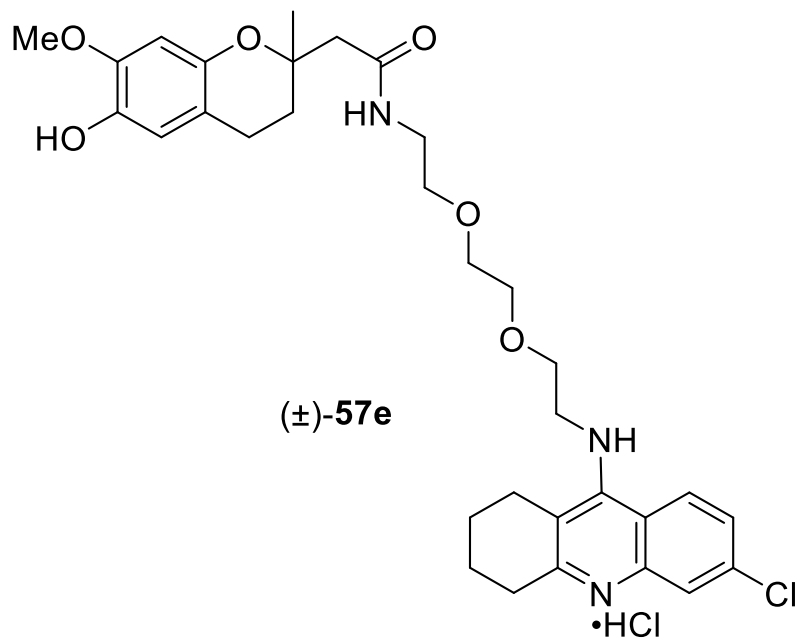
(±)-*N*-{9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57d** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



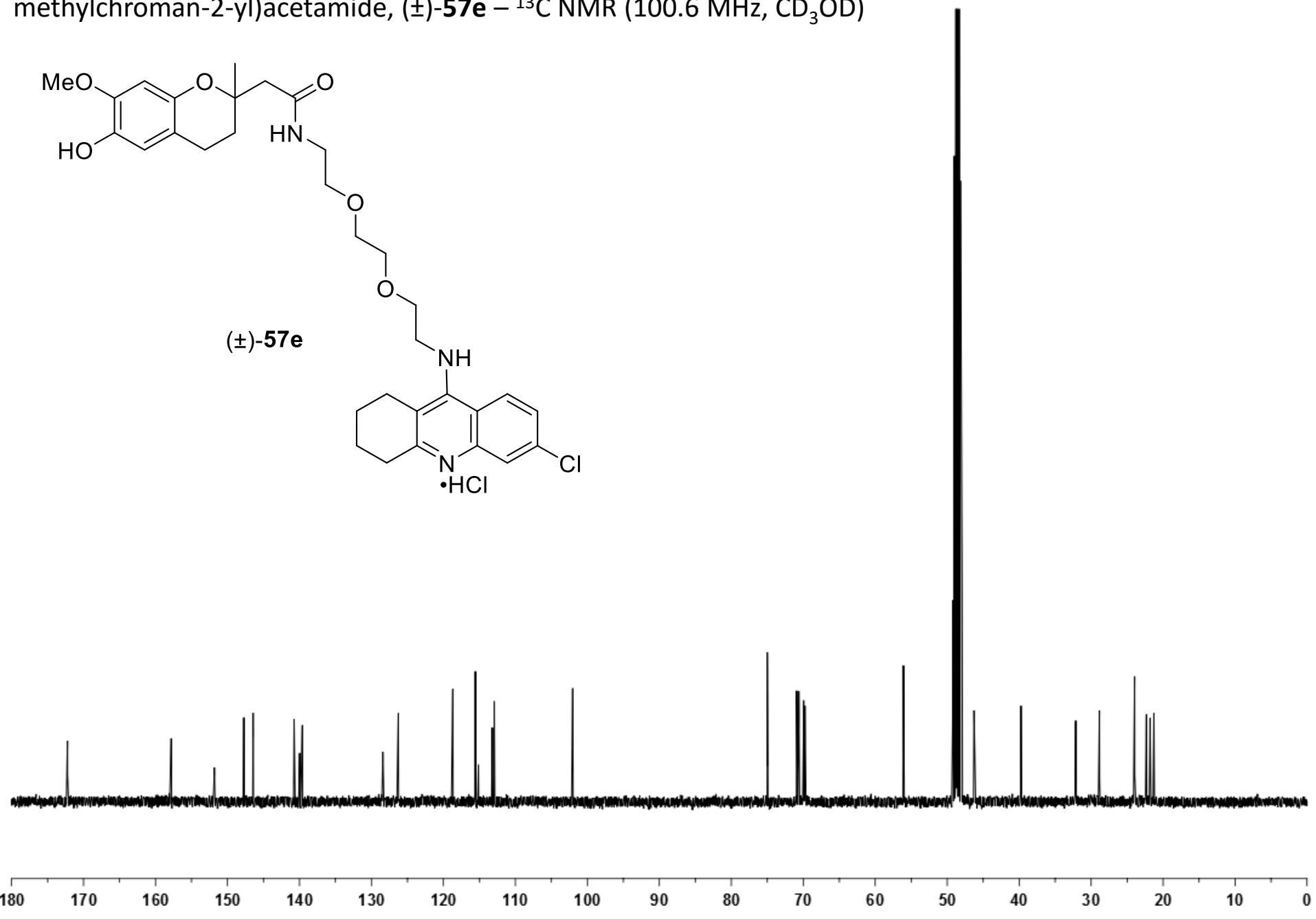
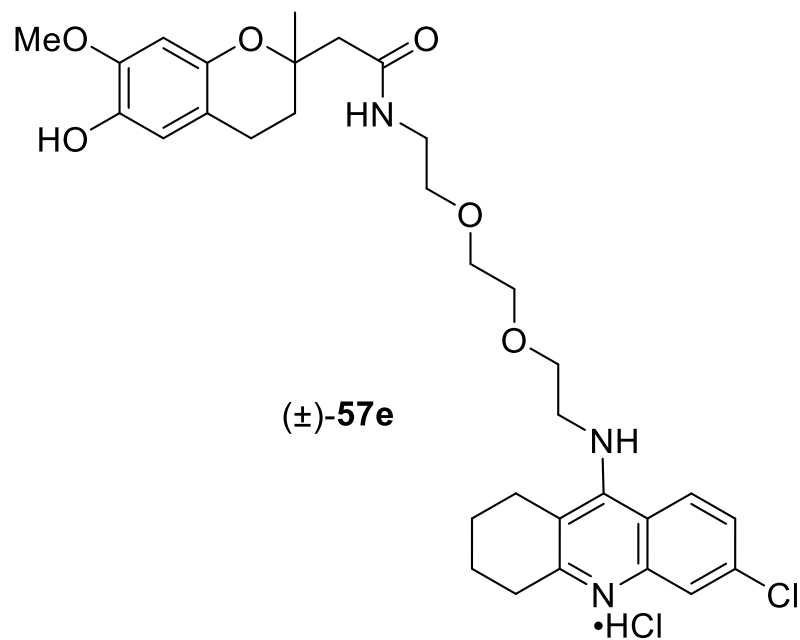
(±)-*N*-{9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



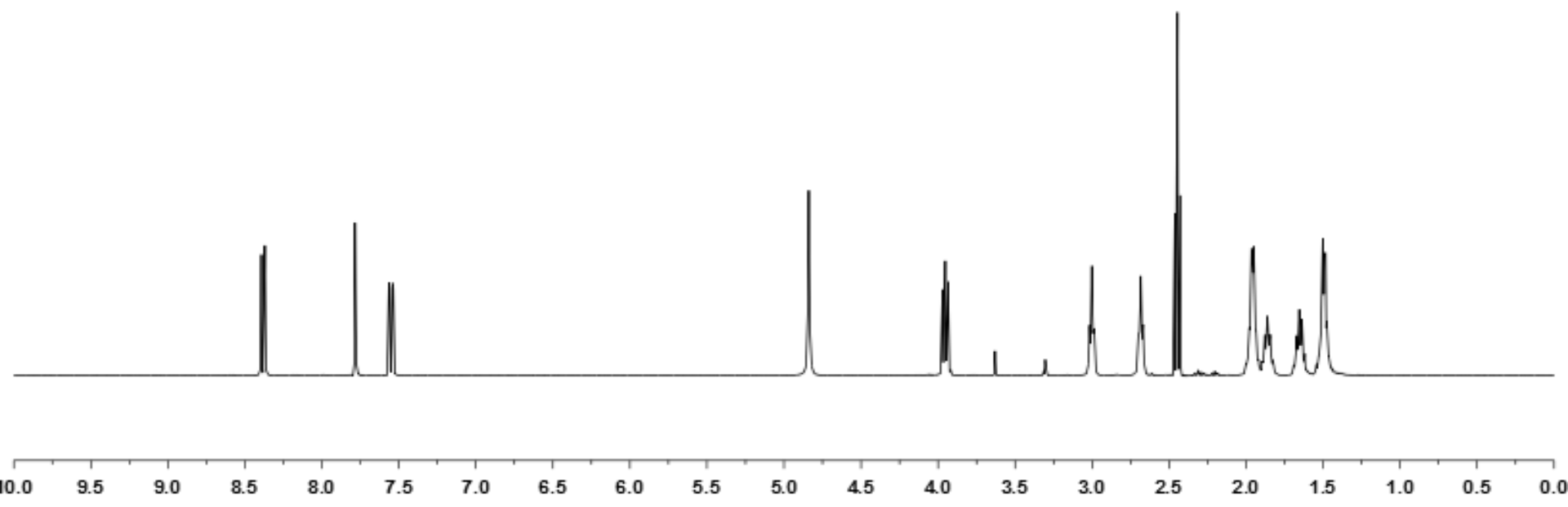
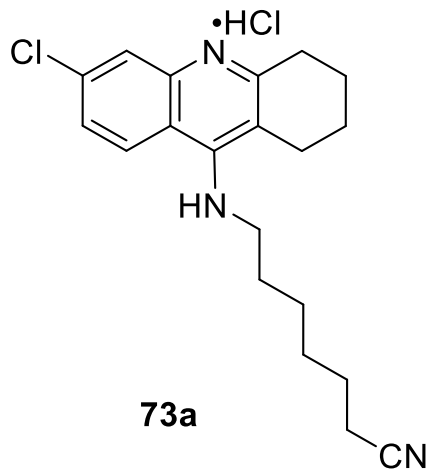
(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-3,6-dioxaoctyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57e** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



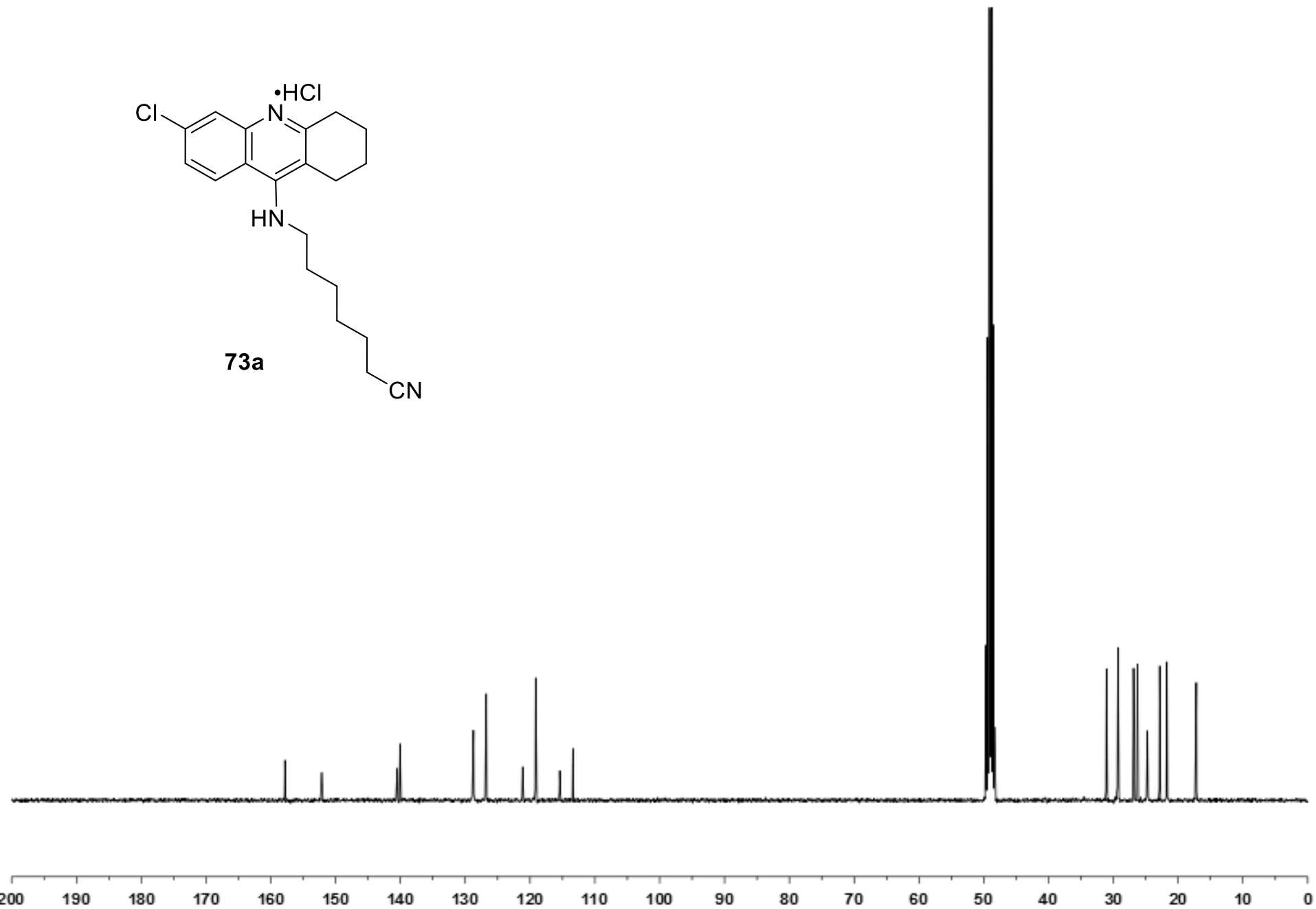
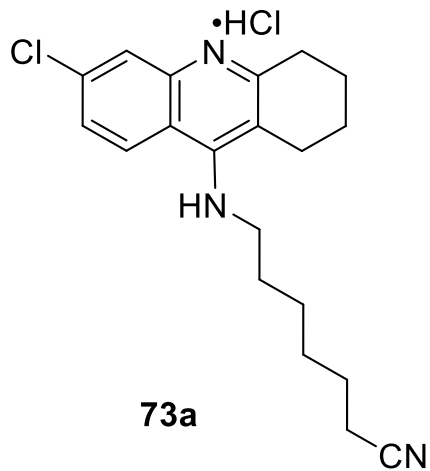
(±)-*N*-{8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-3,6-dioxaoctyl}-2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)acetamide, (±)-**57e** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



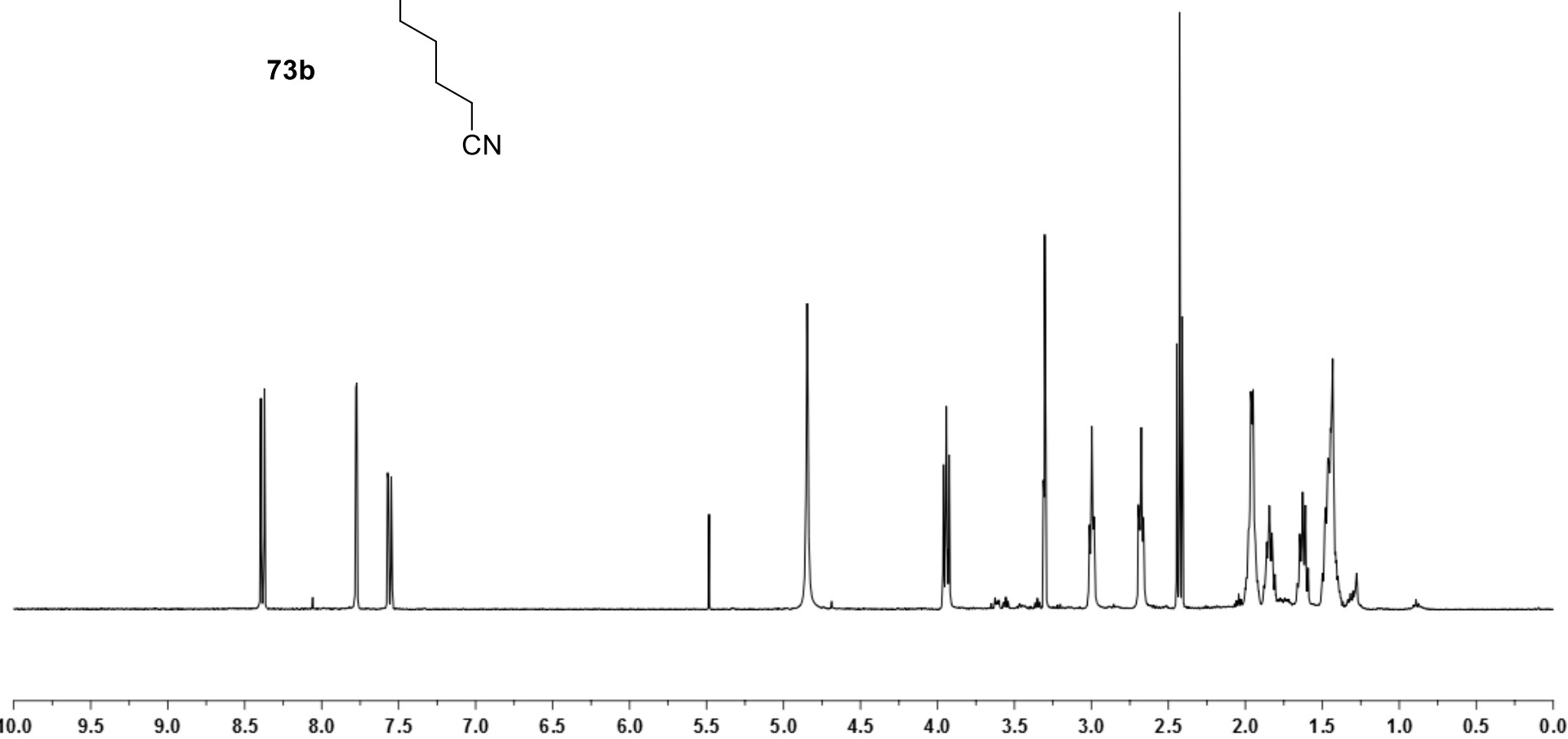
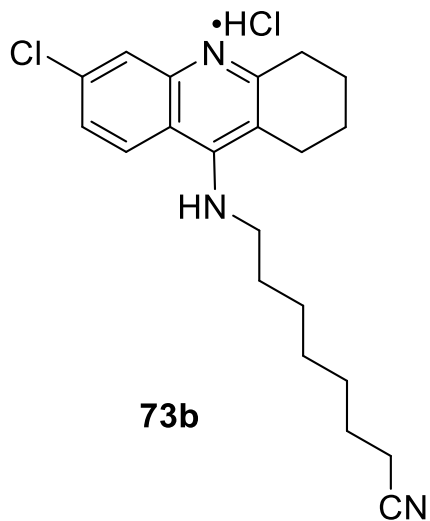
7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptanenitrile, **73a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]heptanenitrile, **73a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

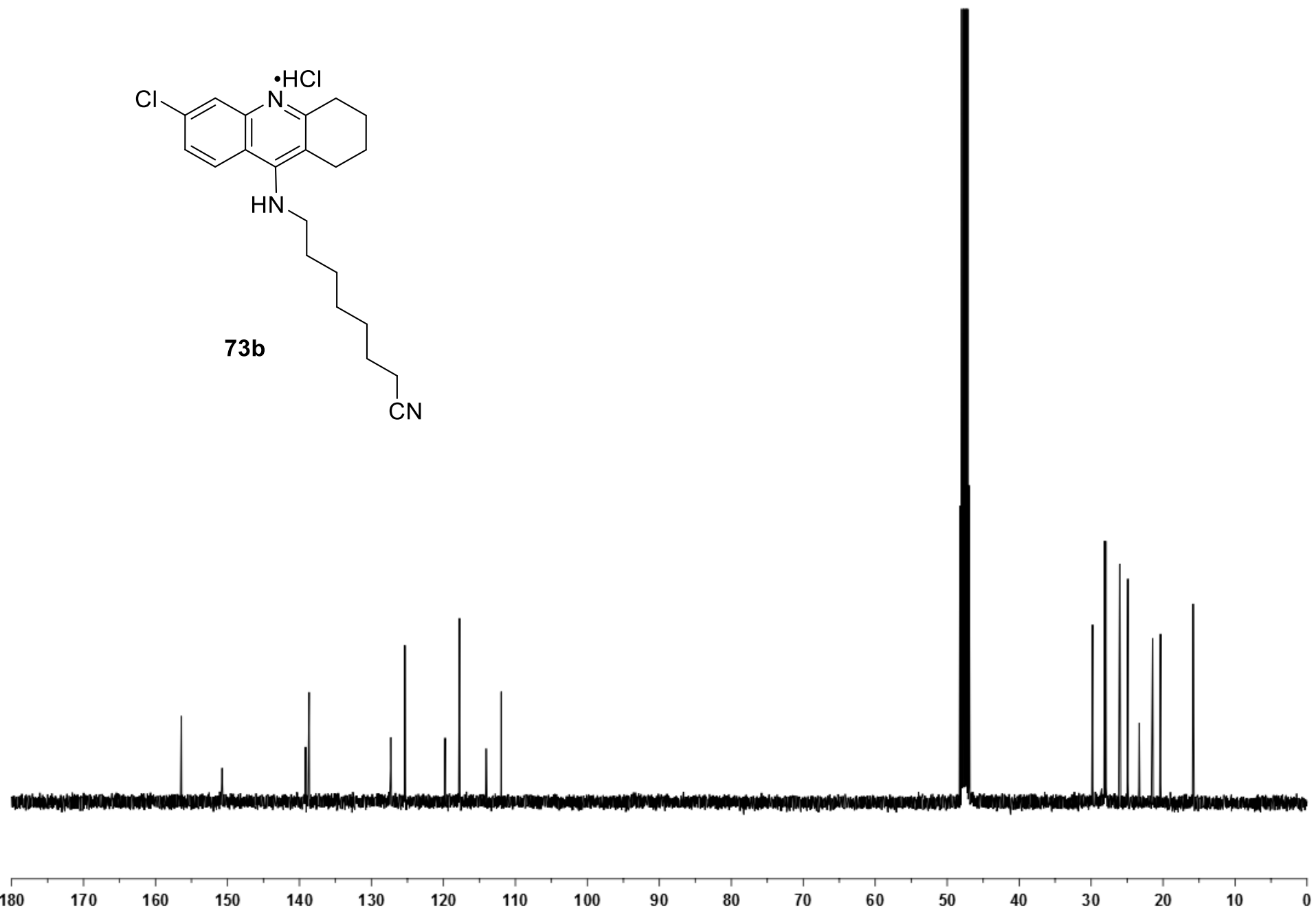
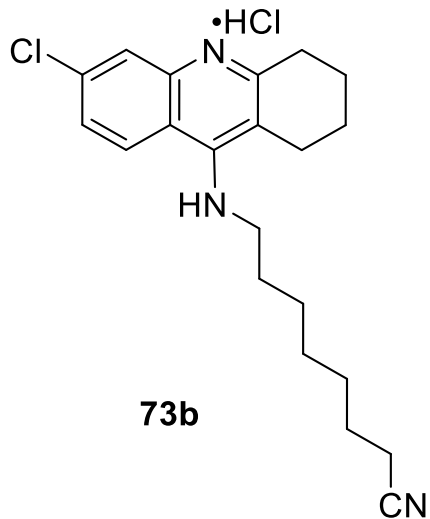


8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octanenitrile, **73b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

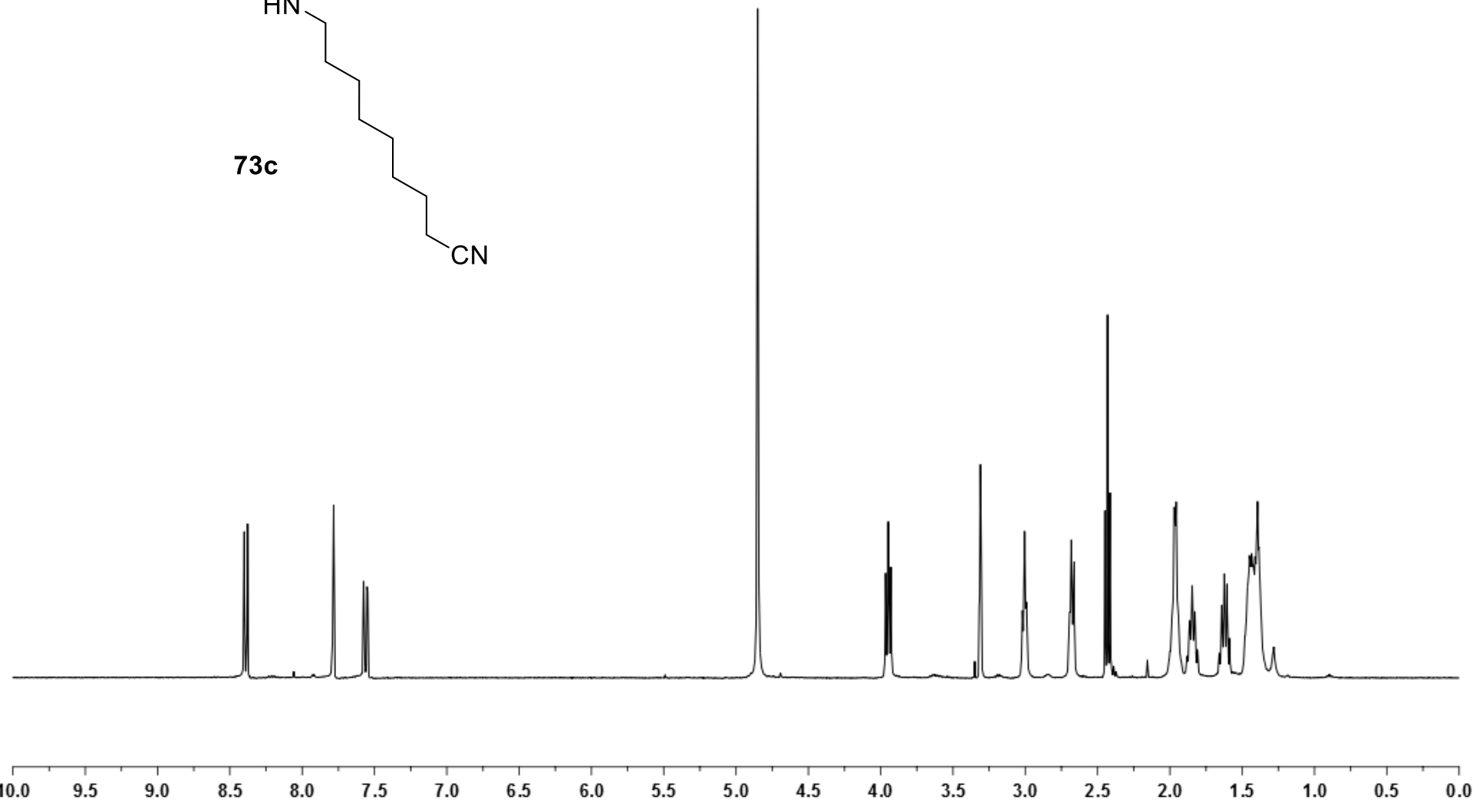
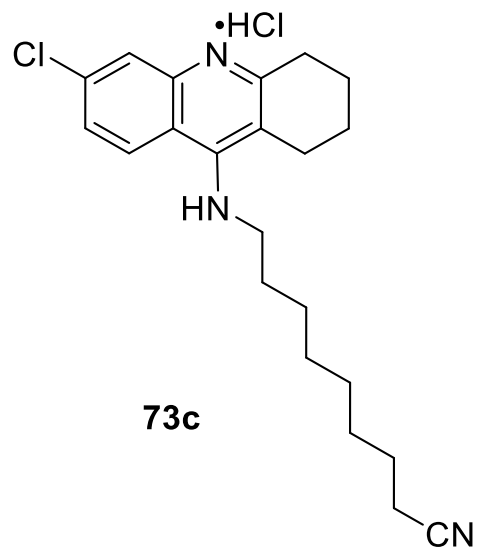




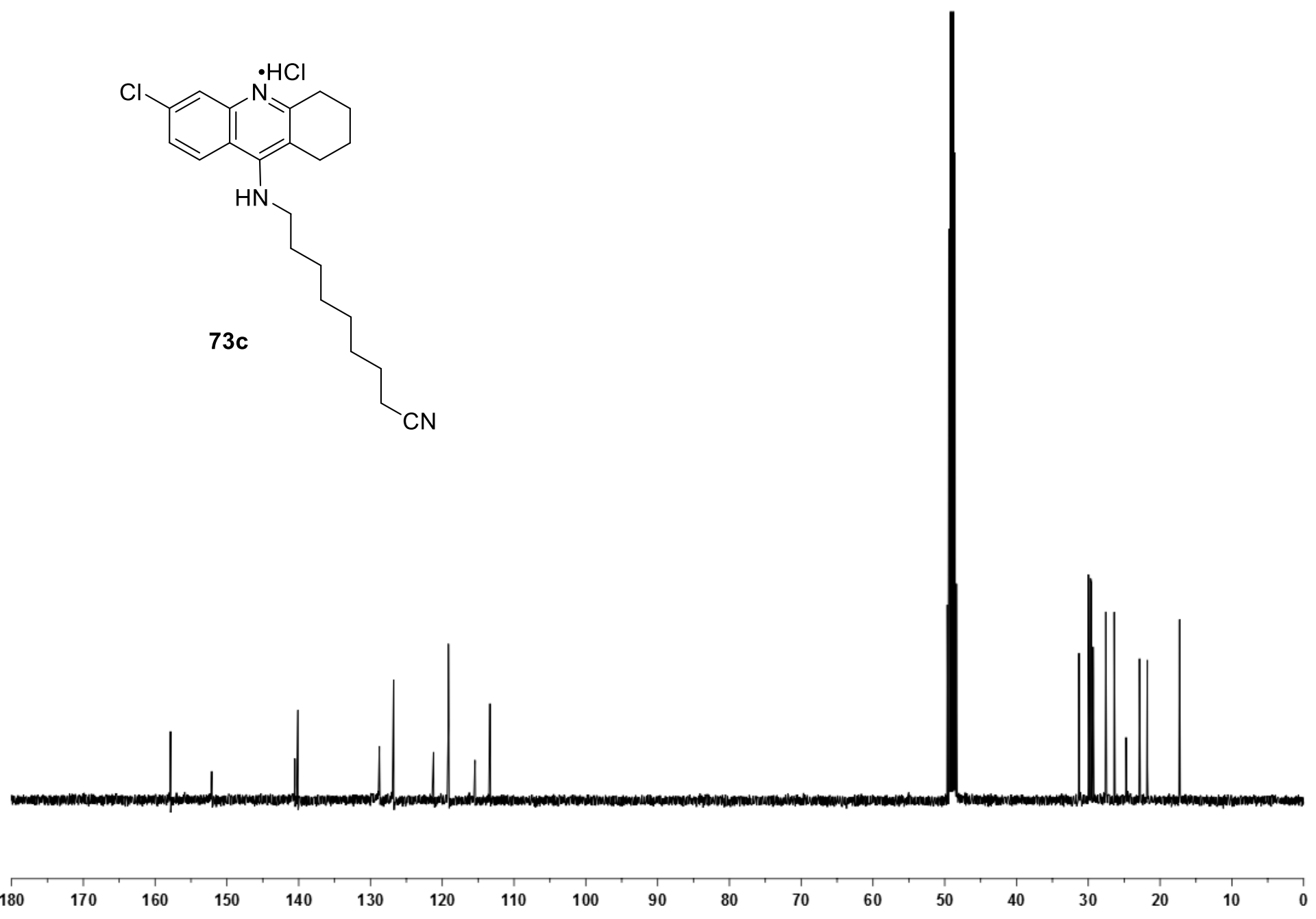
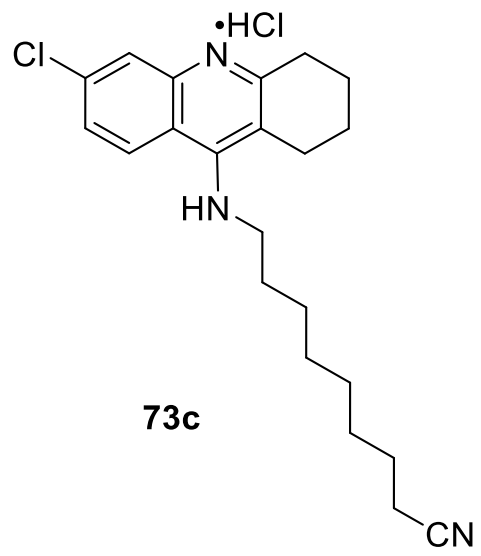
8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]octanenitrile, **73b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



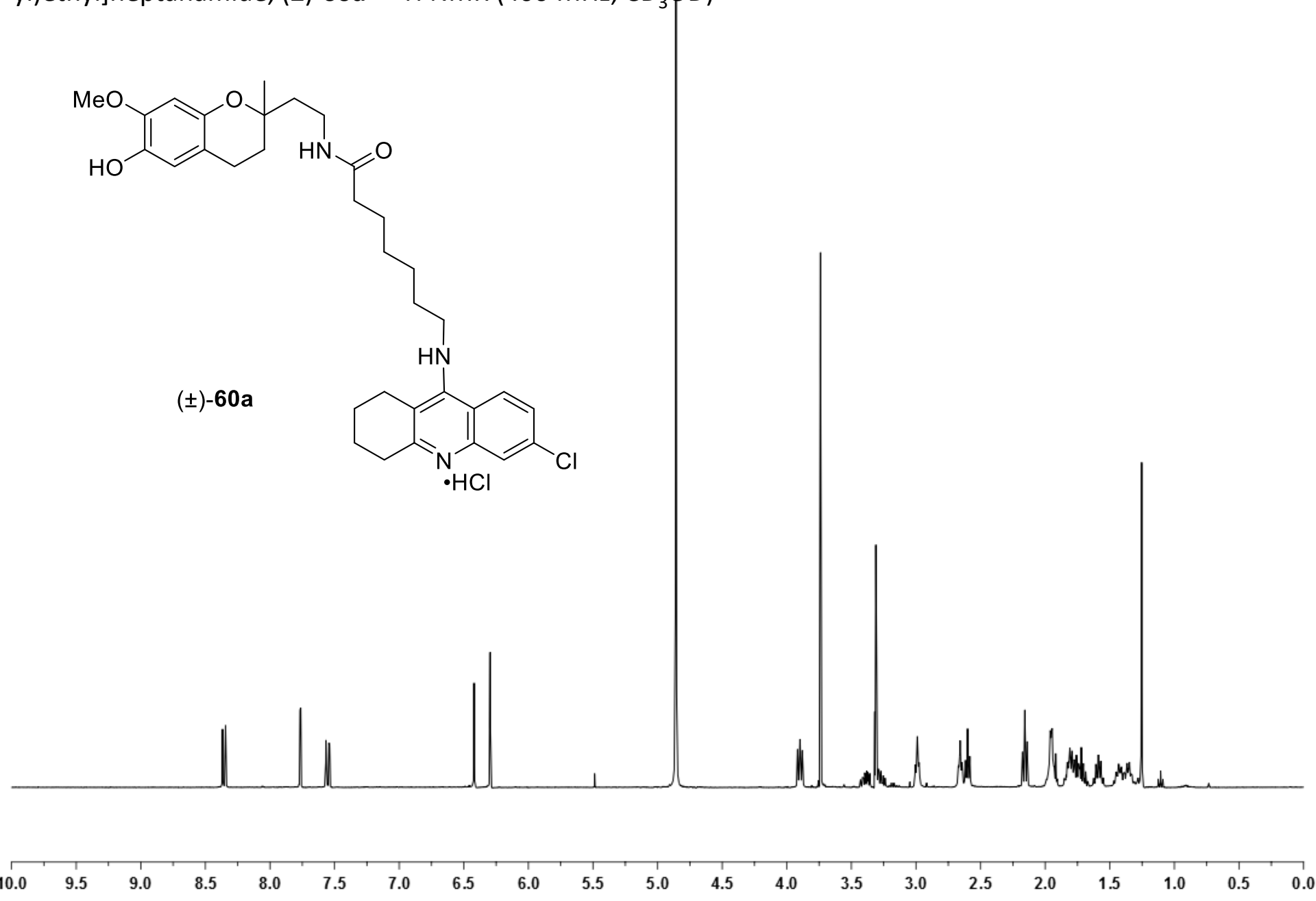
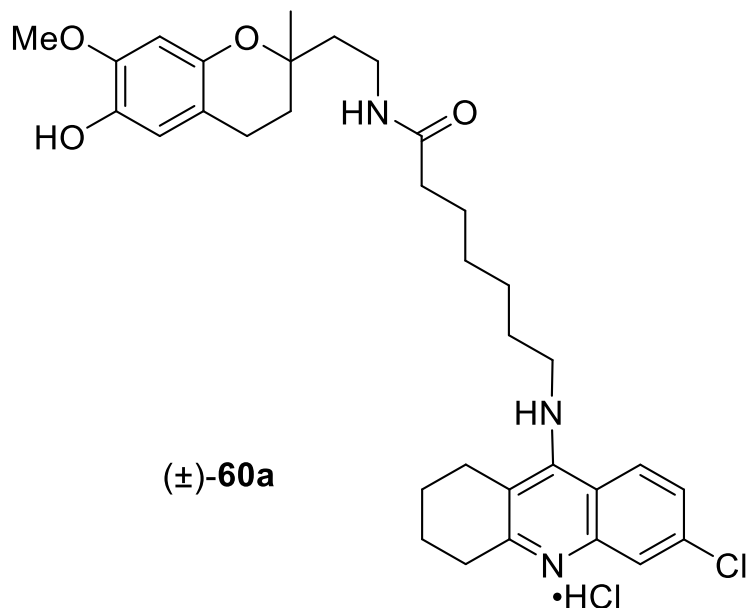
9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonanenitrile, **73c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



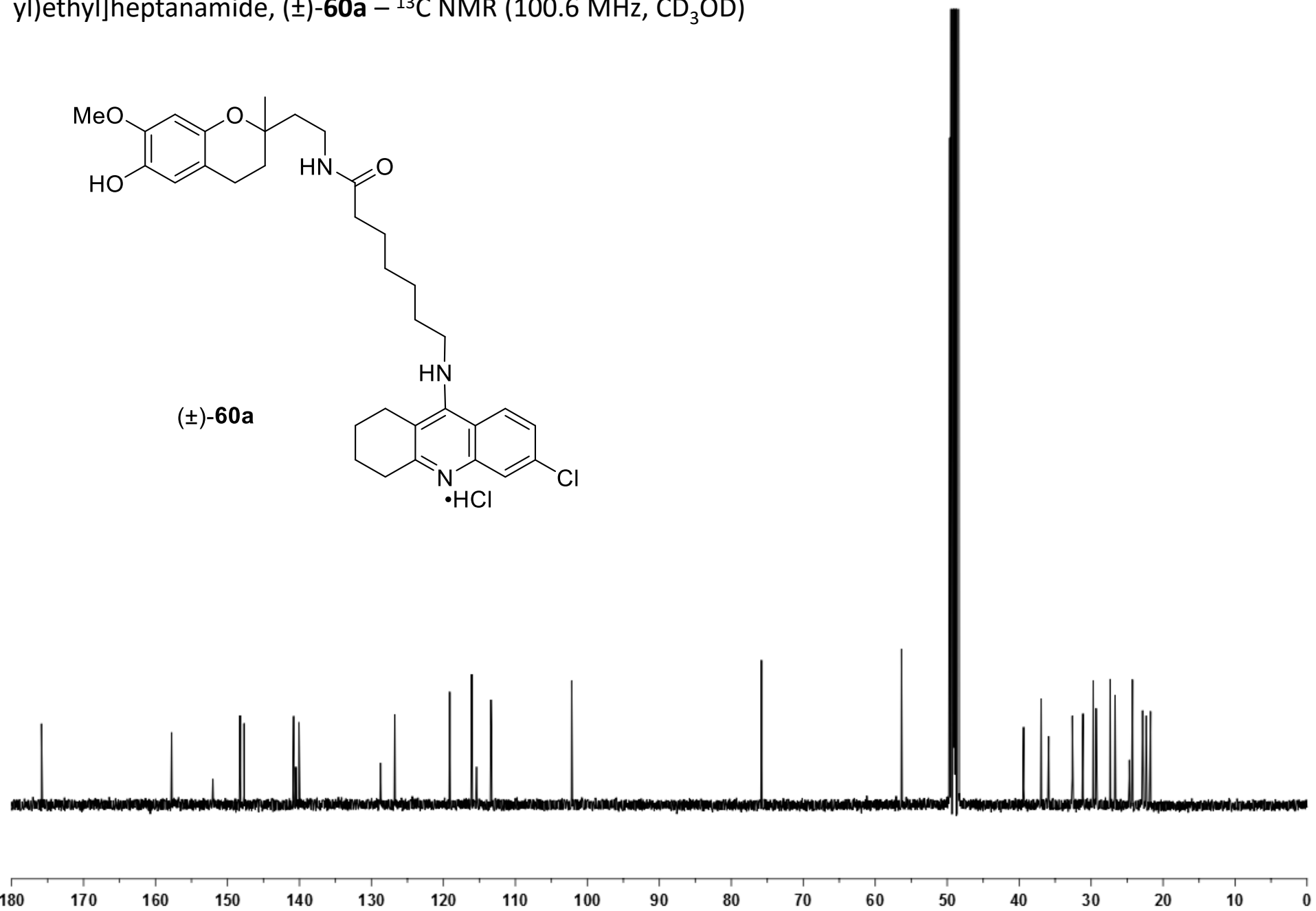
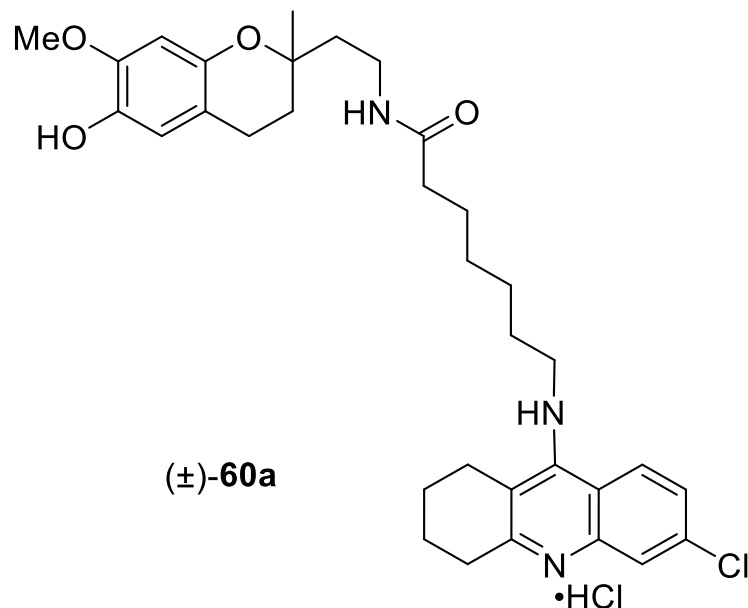
9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]nonanenitrile, **73c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



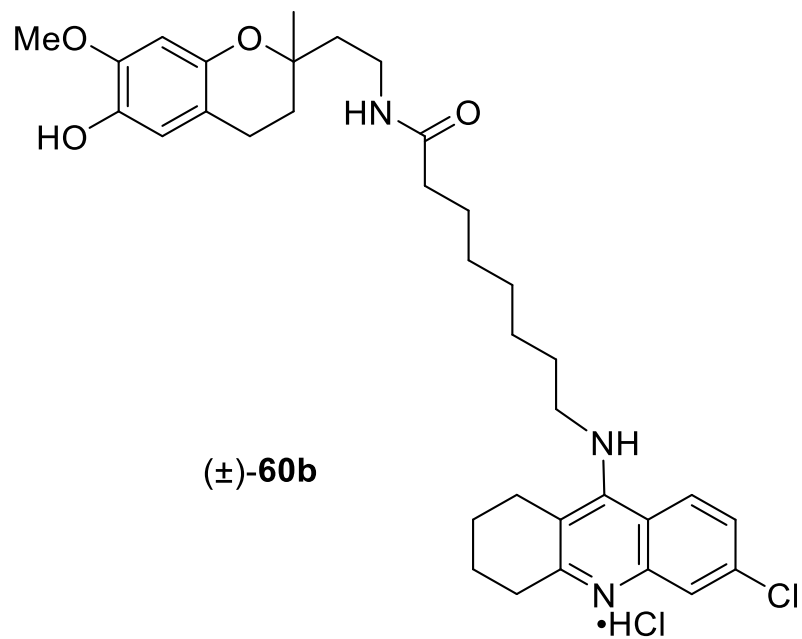
(±)-7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]heptanamide, (±)-**60a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



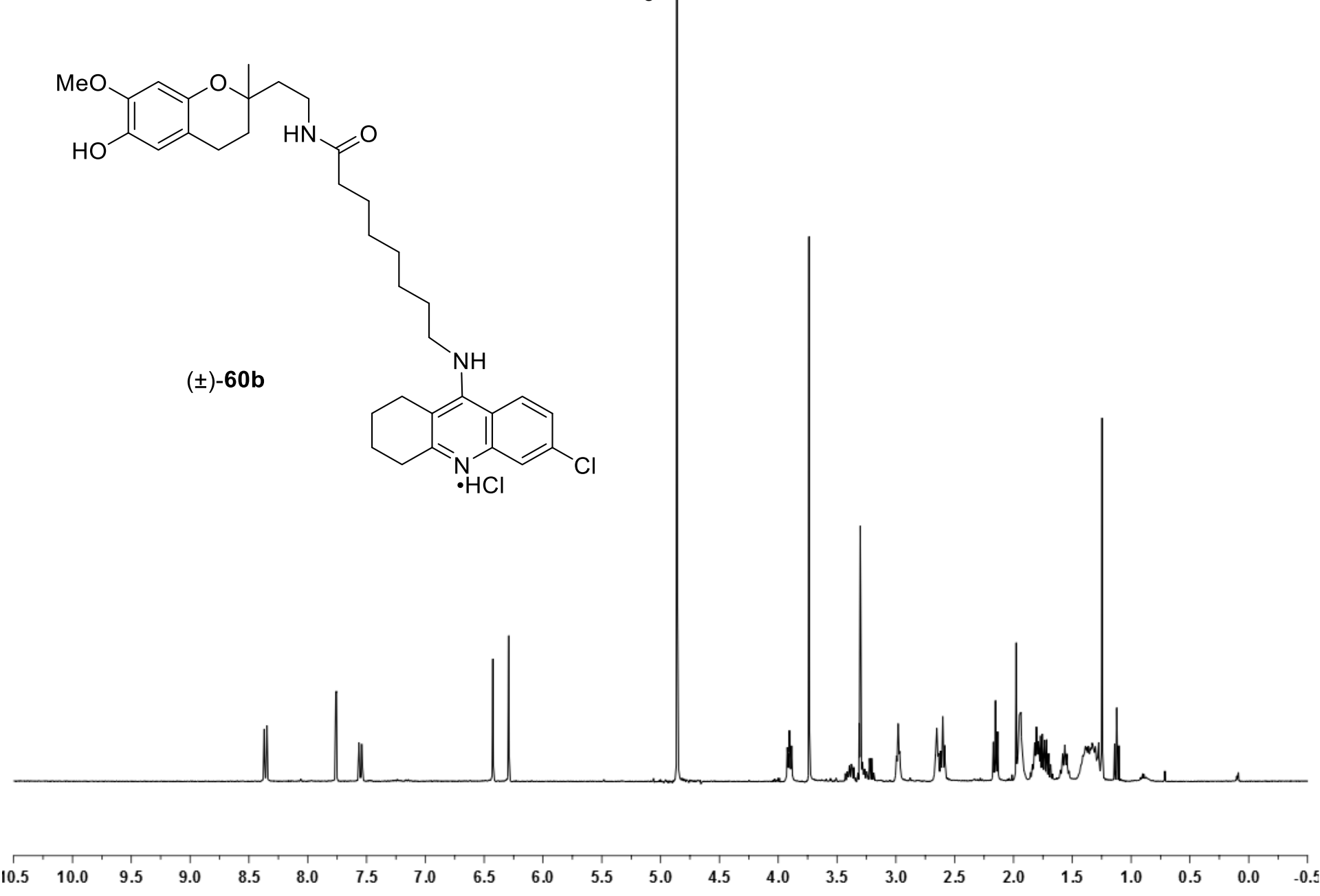
(±)-7-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]heptanamide, (±)-**60a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



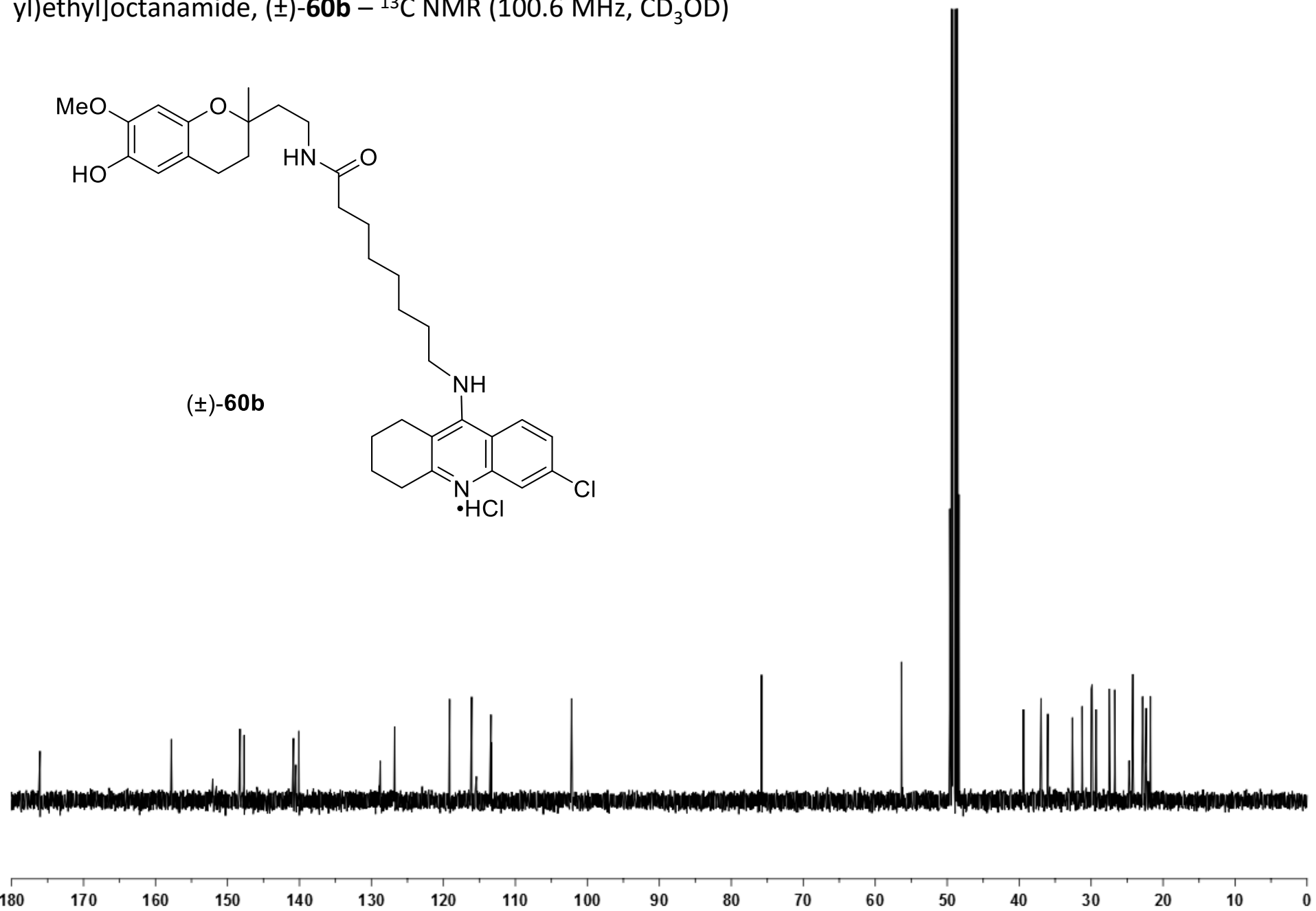
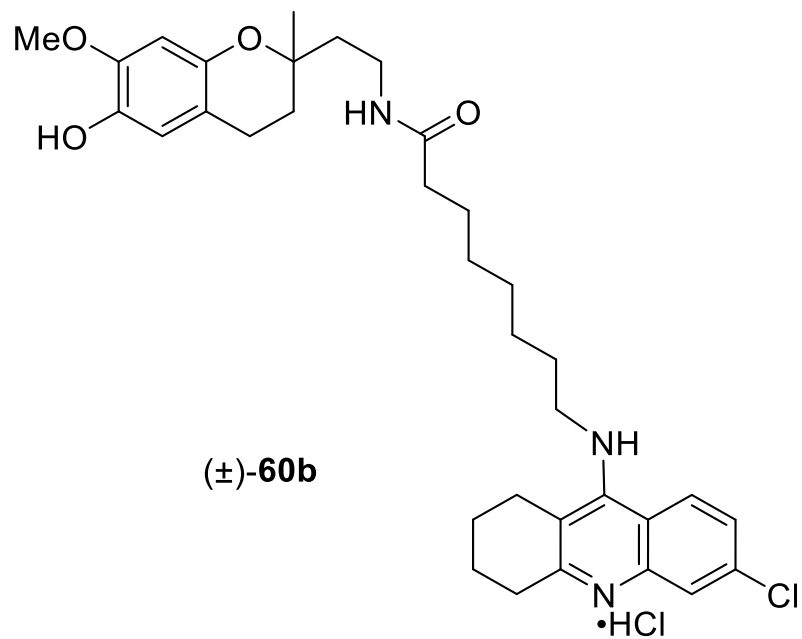
(±)-8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]octanamide, (±)-**60b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



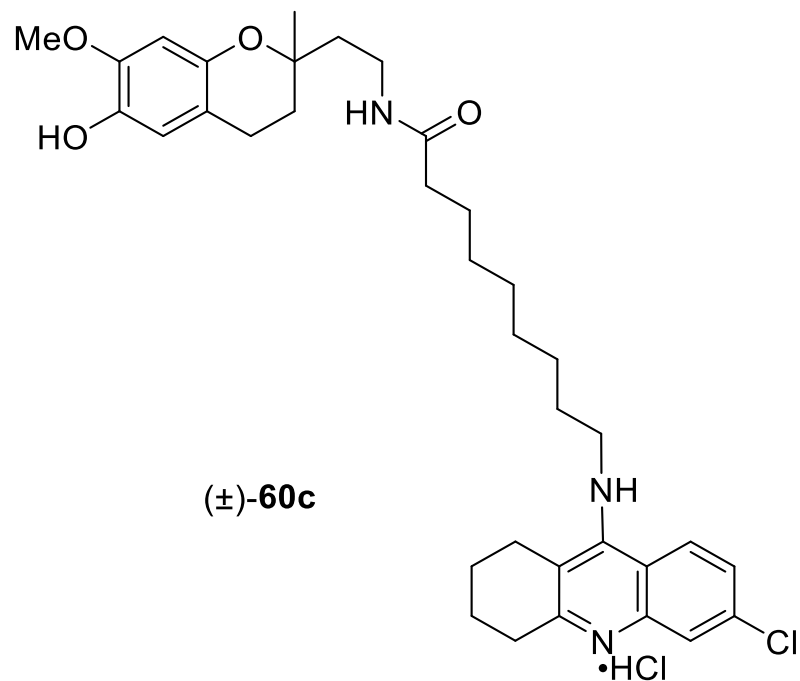
(±)-**60b**



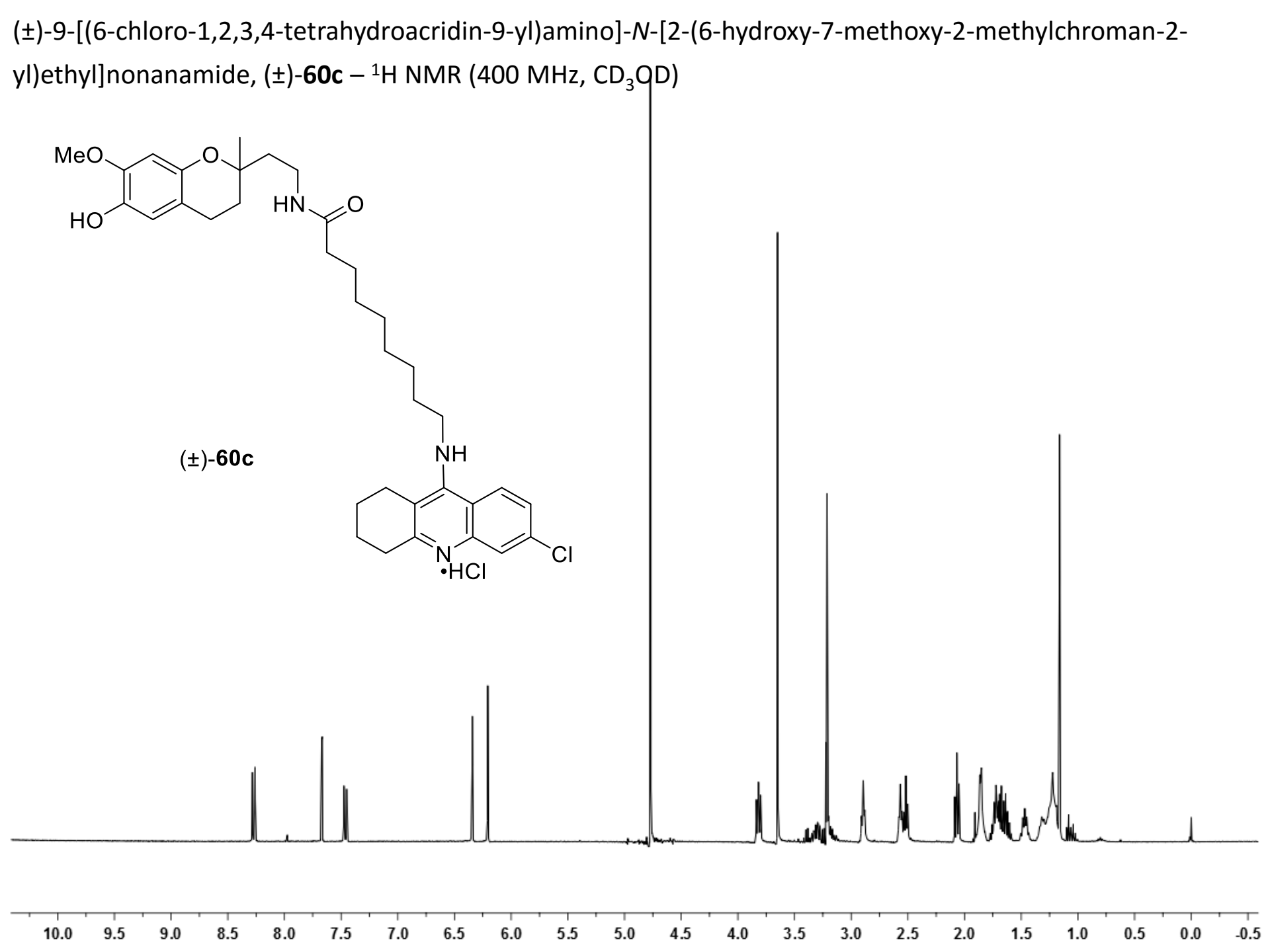
(±)-8-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]octanamide, (±)-**60b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



(±)-9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]nonanamide, (±)-**60c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

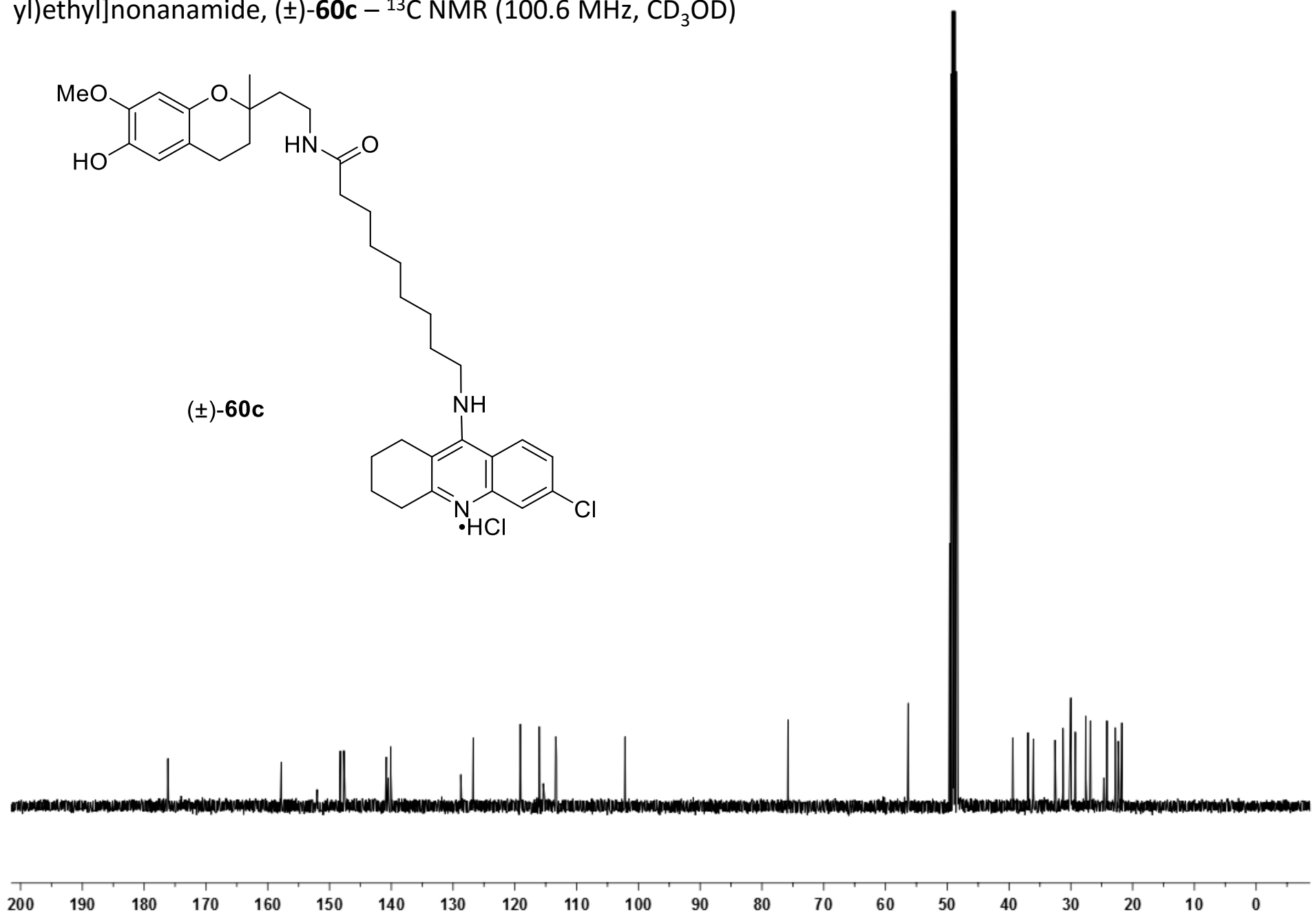
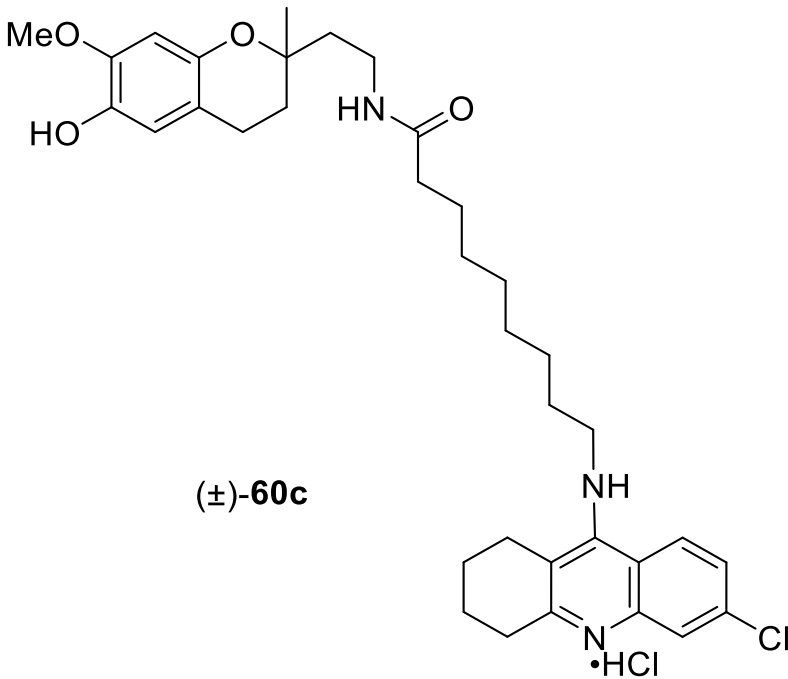


(±)-**60c**

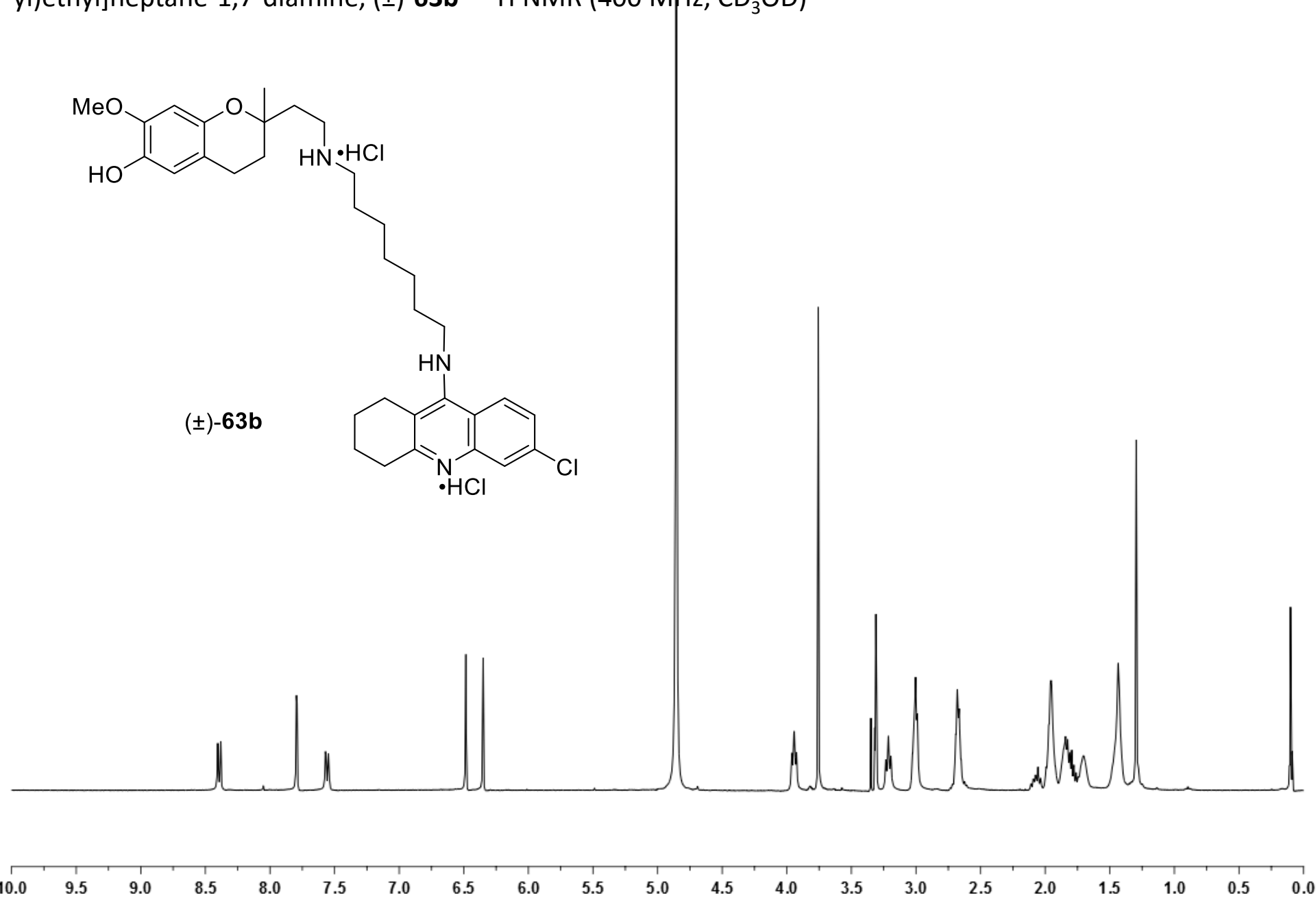
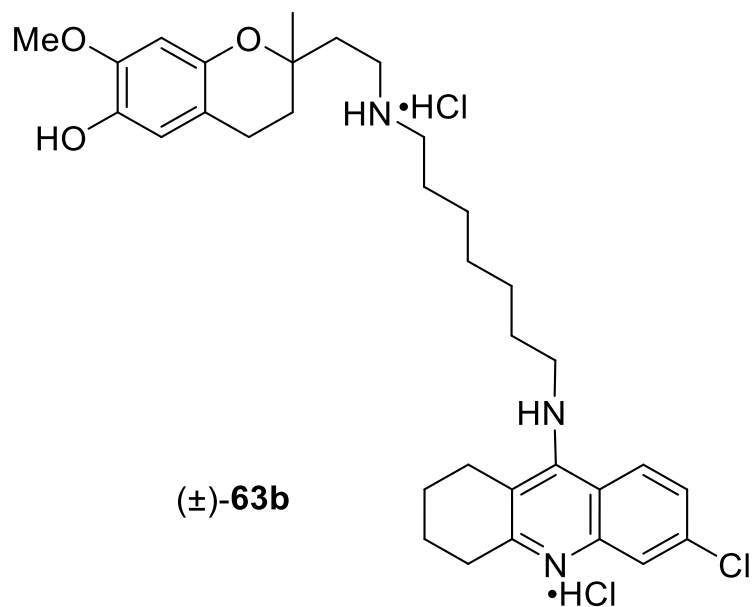




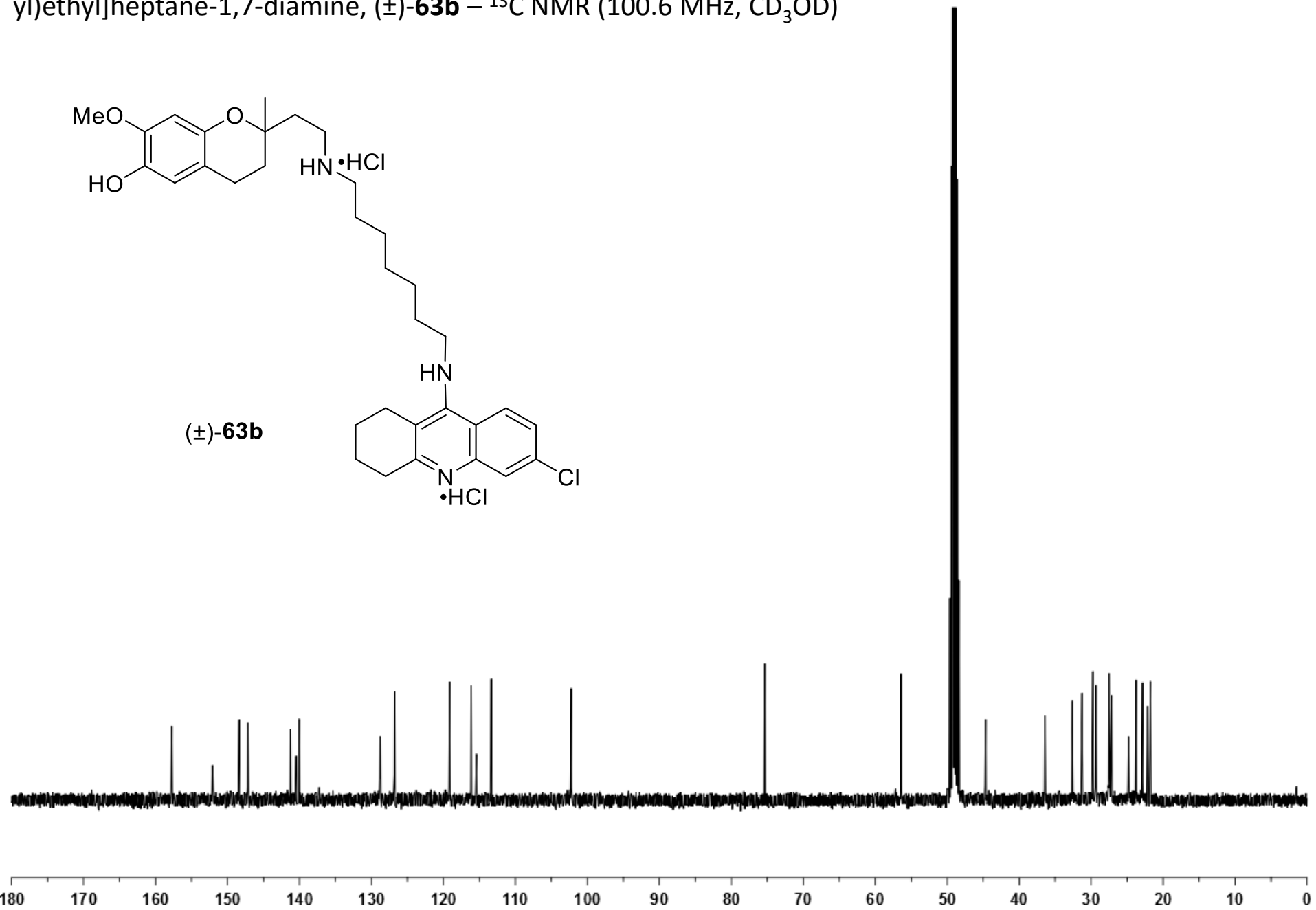
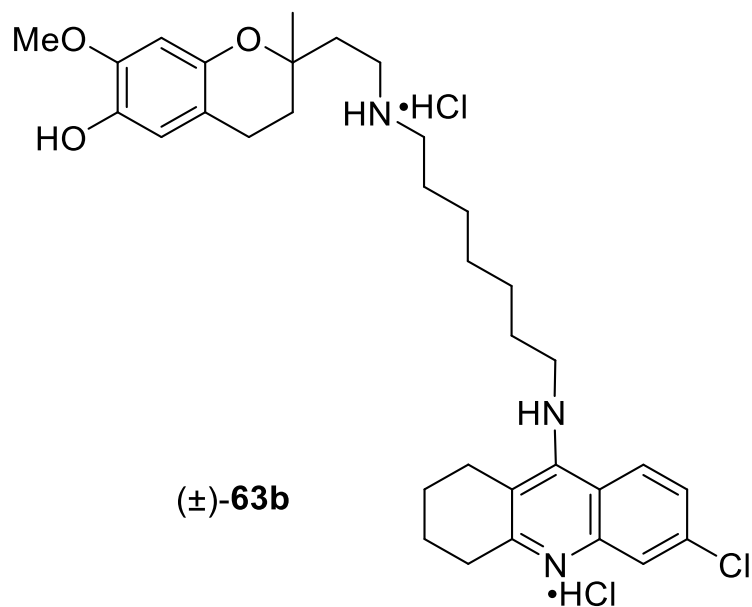
(±)-9-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]nonanamide, (±)-**60c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



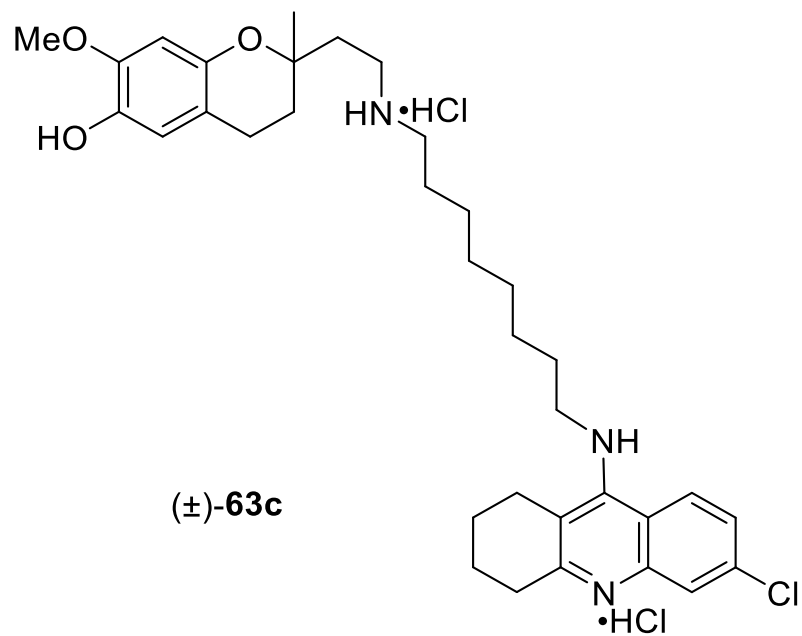
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]heptane-1,7-diamine, (±)-**63b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



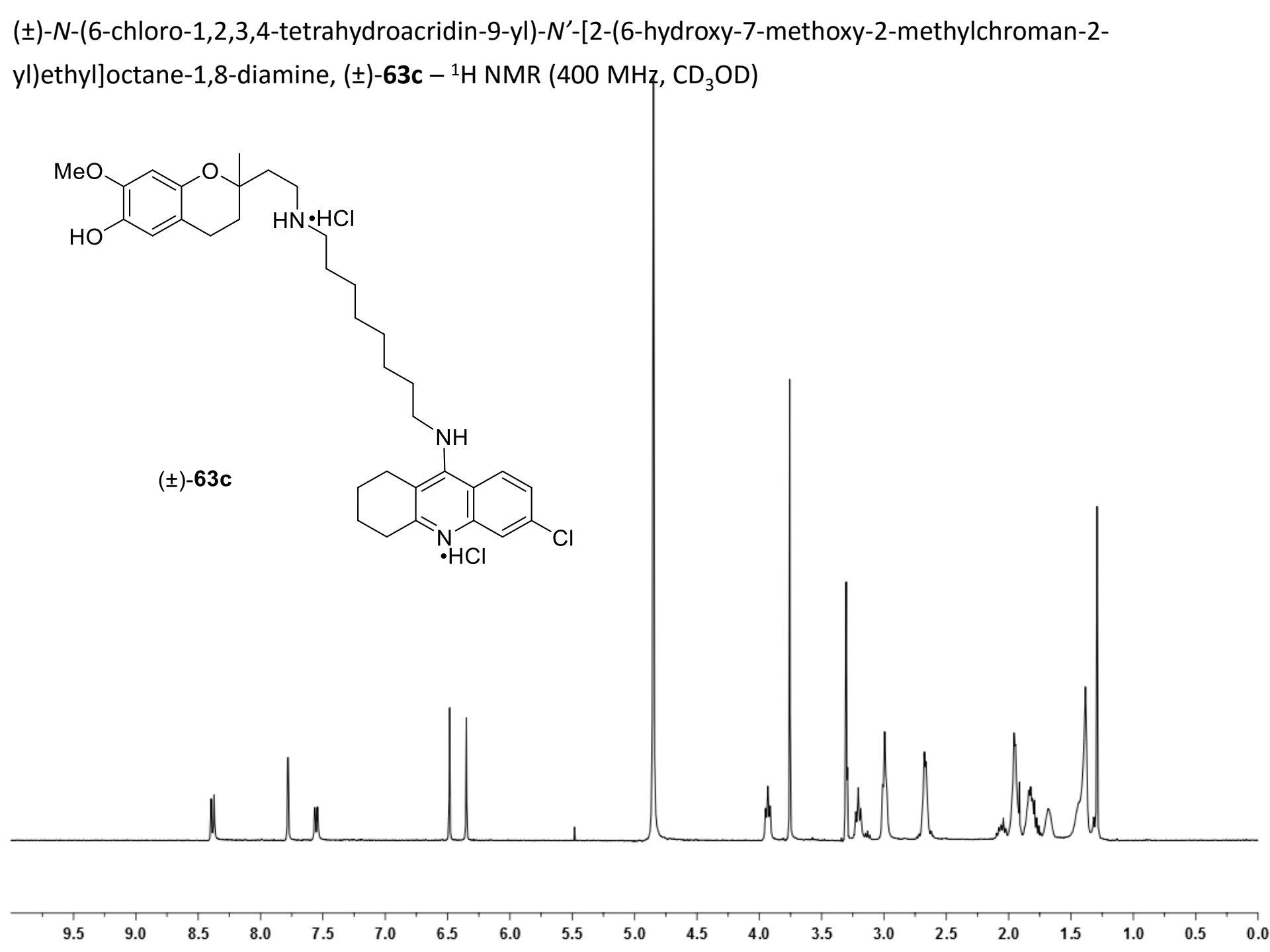
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]heptane-1,7-diamine, (±)-**63b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



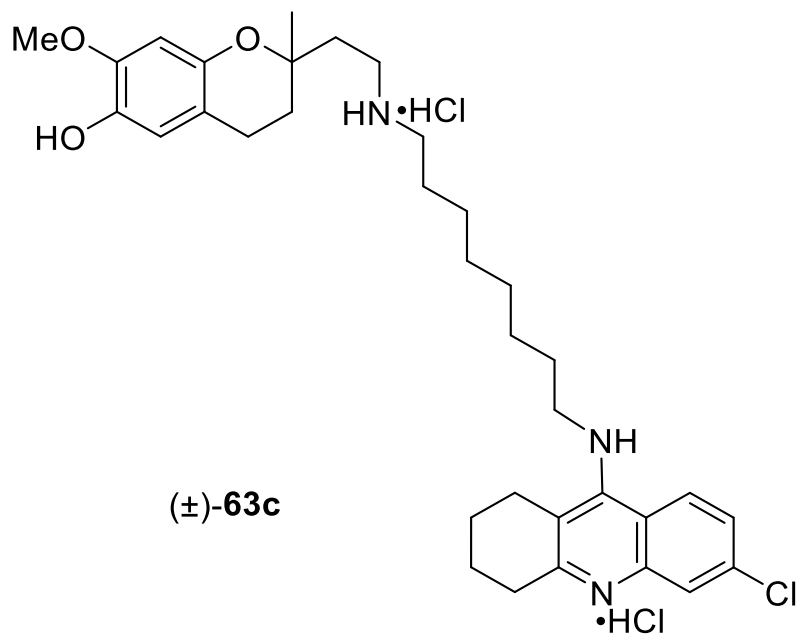
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]octane-1,8-diamine, (±)-**63c** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



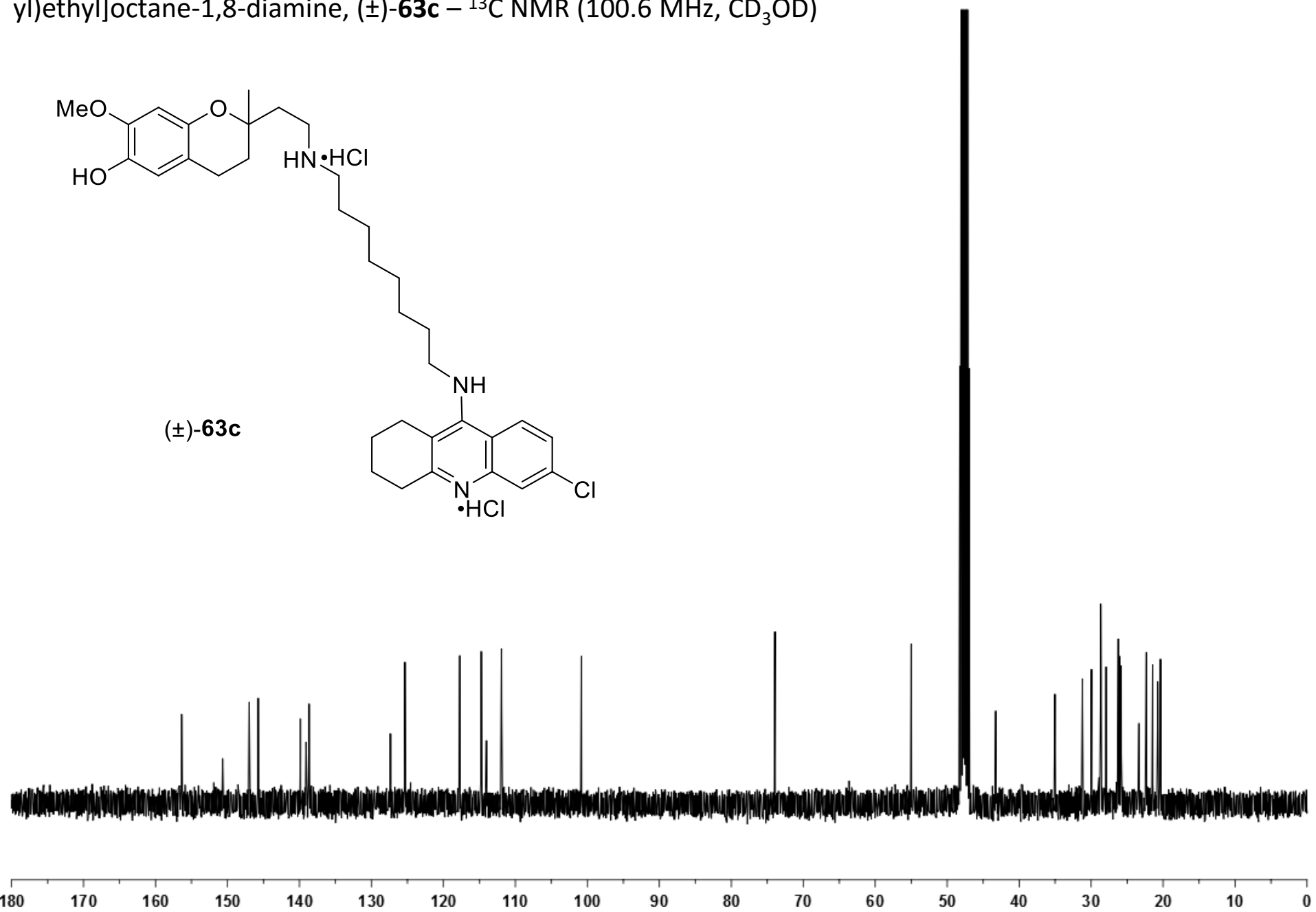
(±)-**63c**



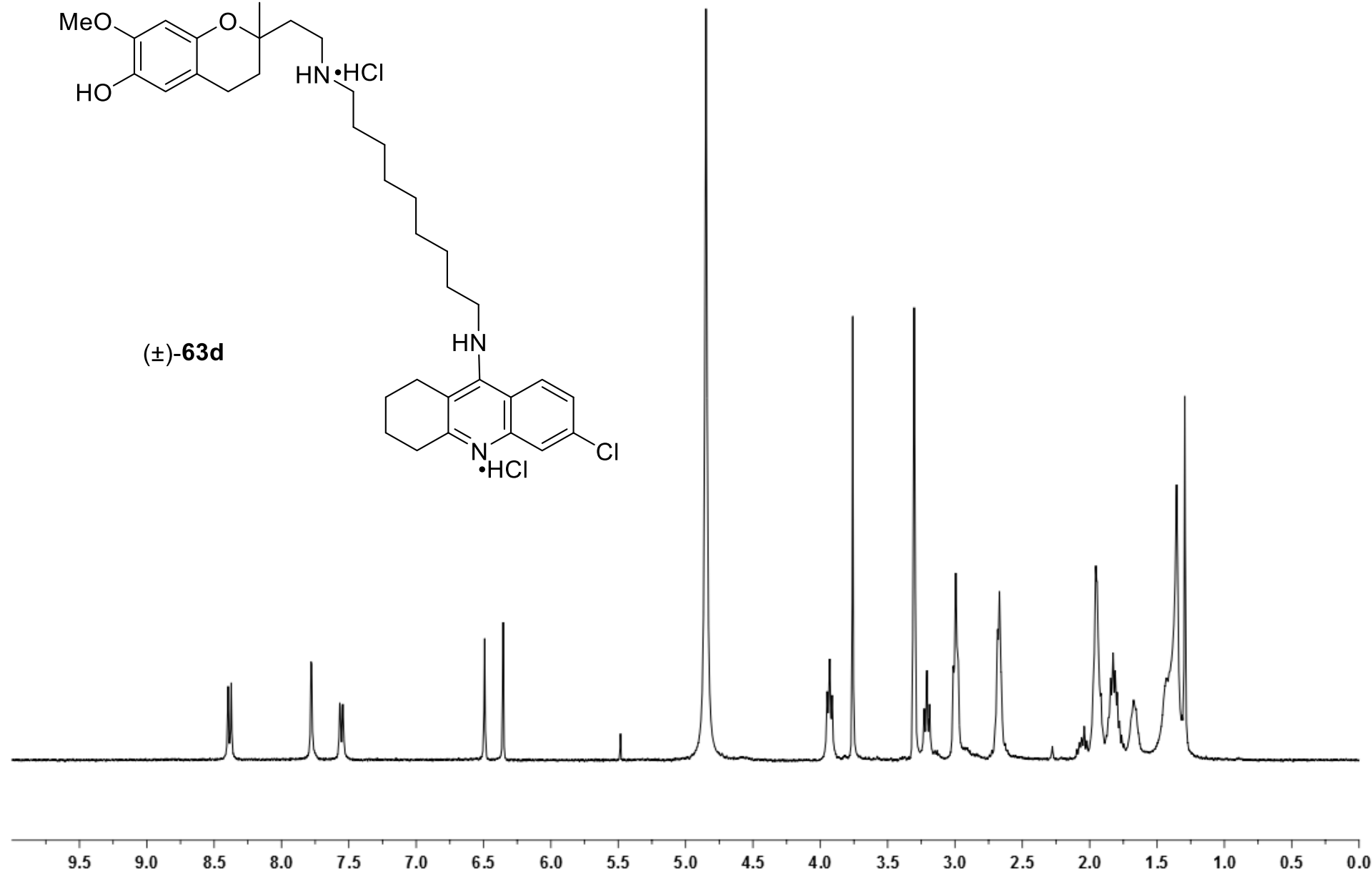
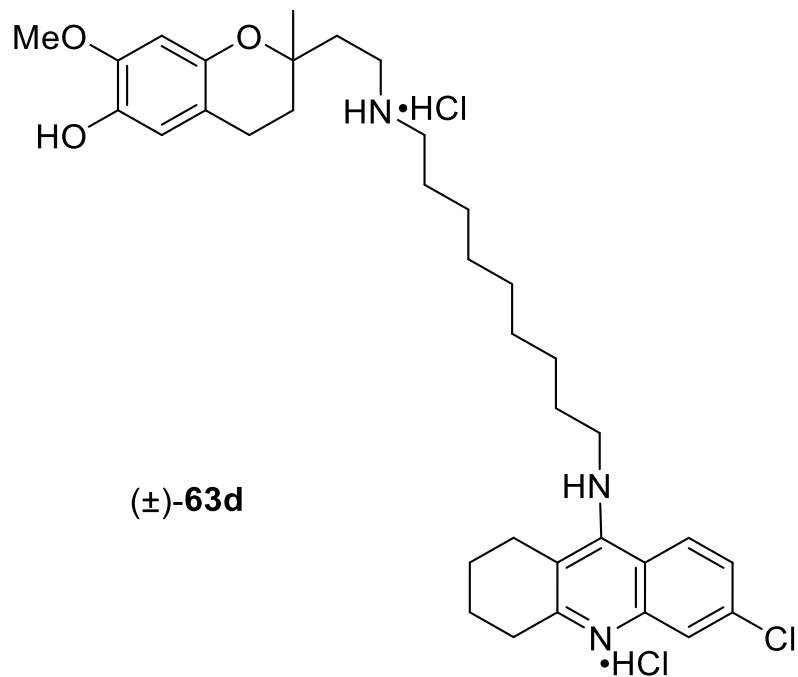
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]octane-1,8-diamine, (±)-**63c** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



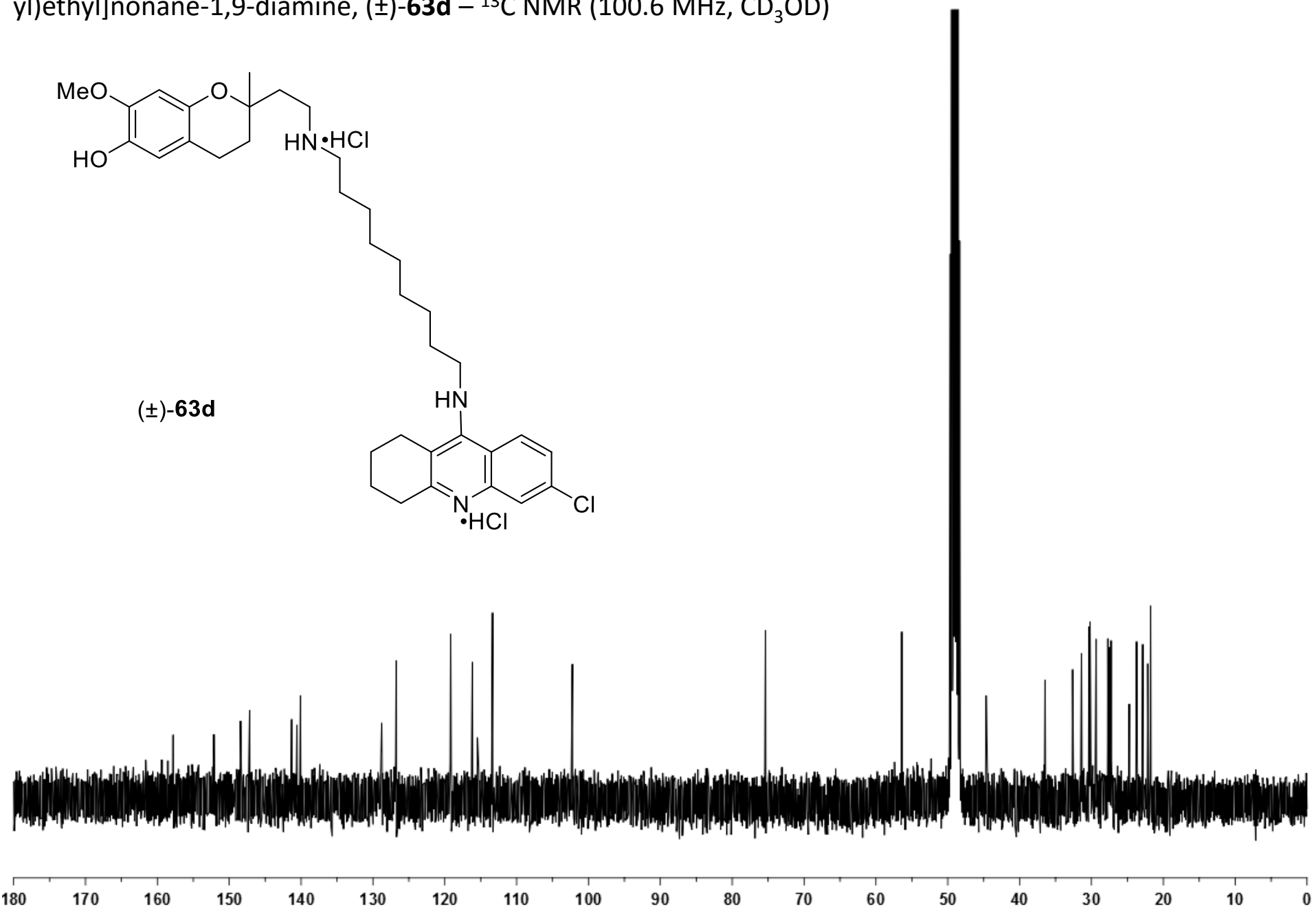
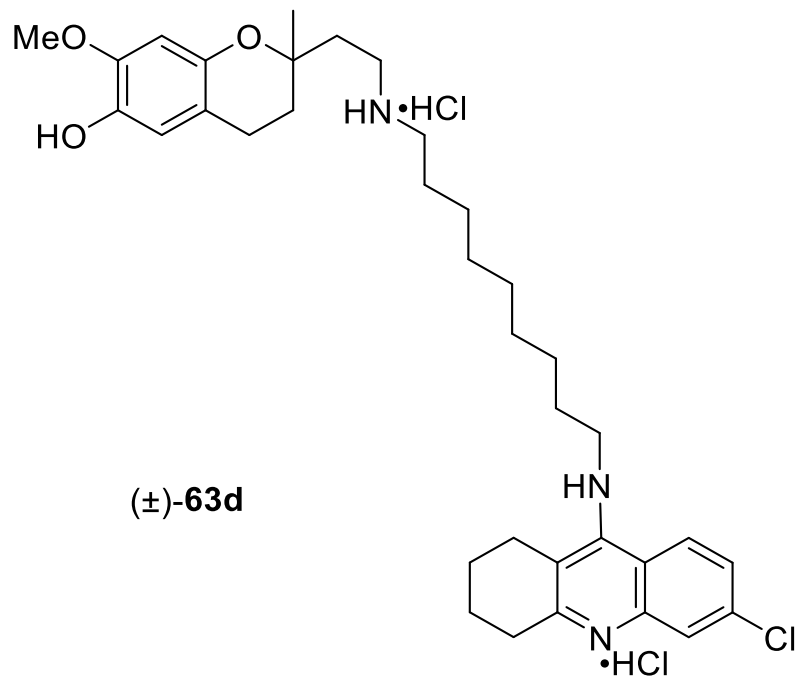
(±)-**63c**



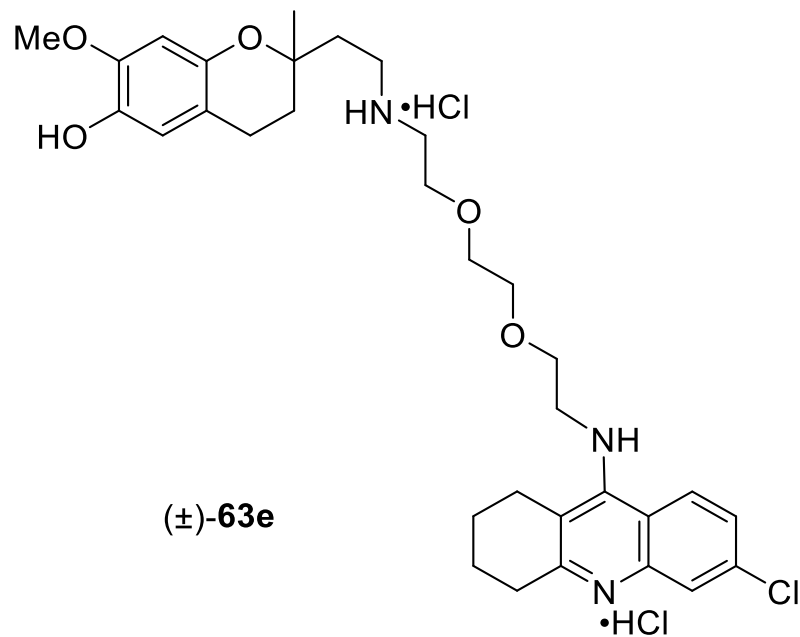
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]nonane-1,9-diamine, (±)-**63d** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



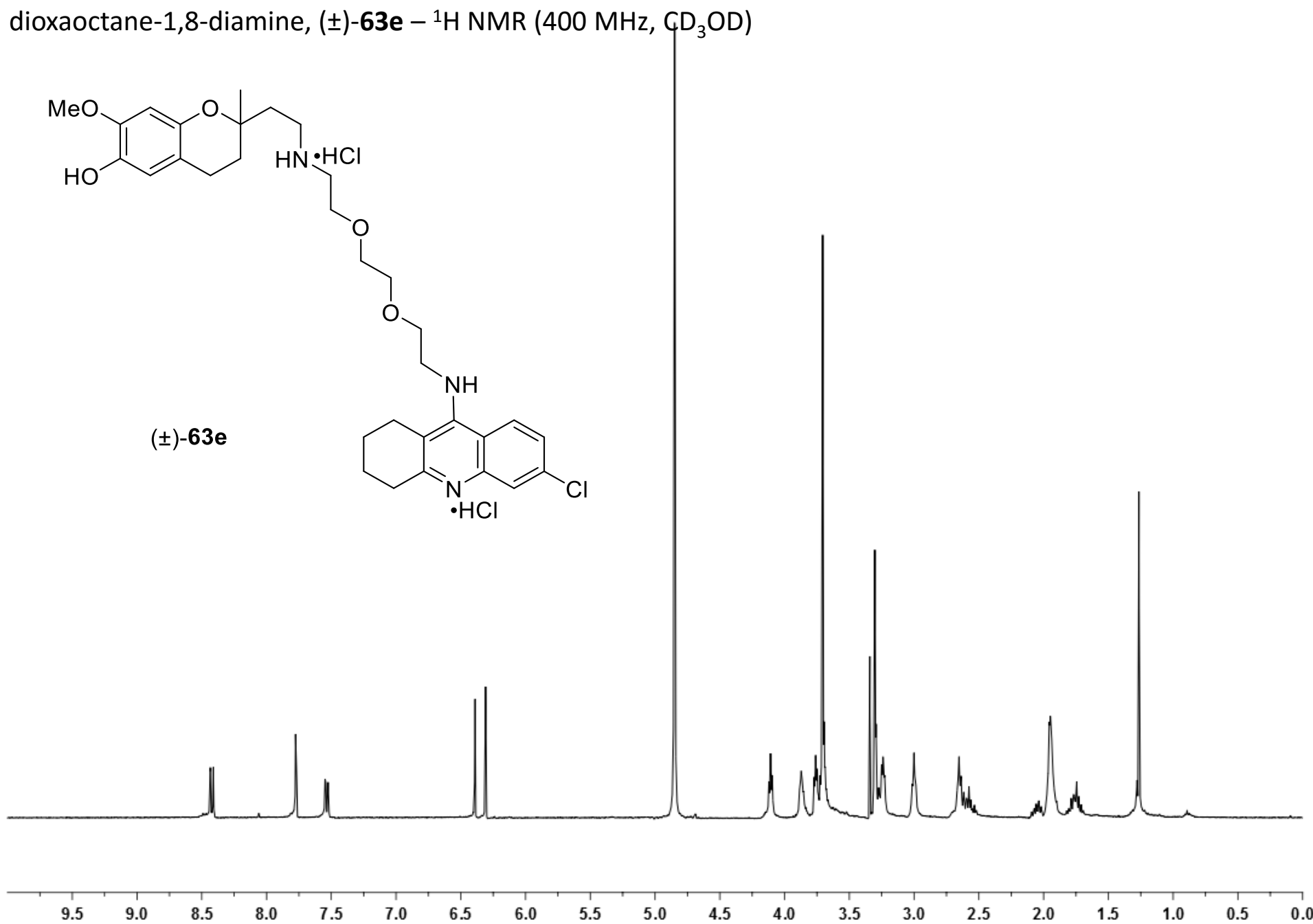
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]nonane-1,9-diamine, (±)-**63d** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]ethane-1,2-diamine, (±)-**63e** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

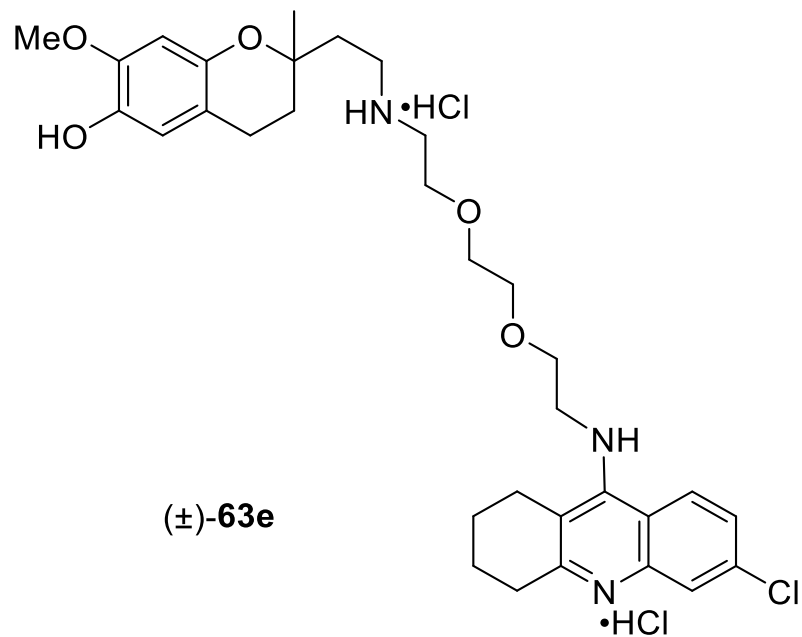


(±)-**63e**

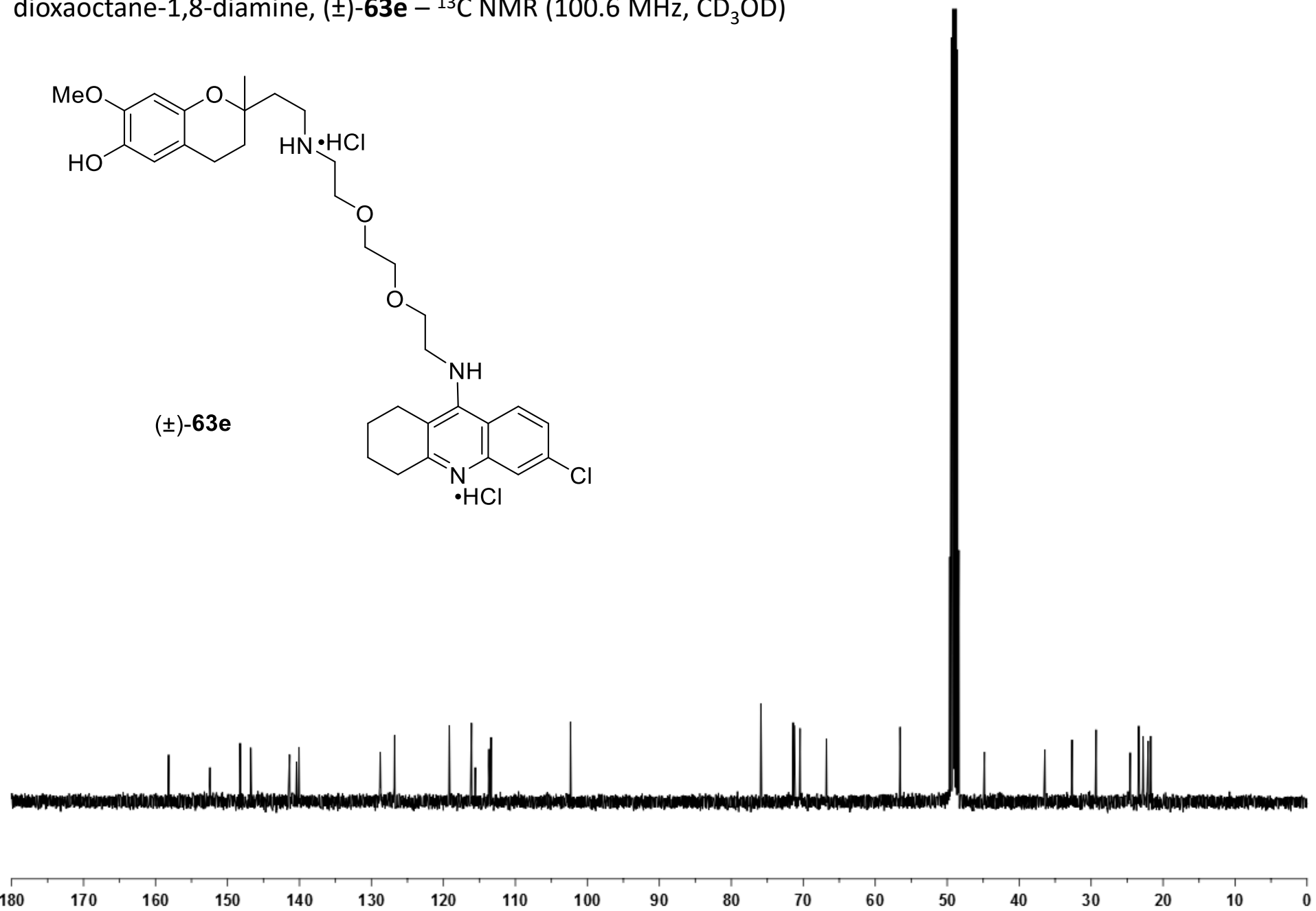




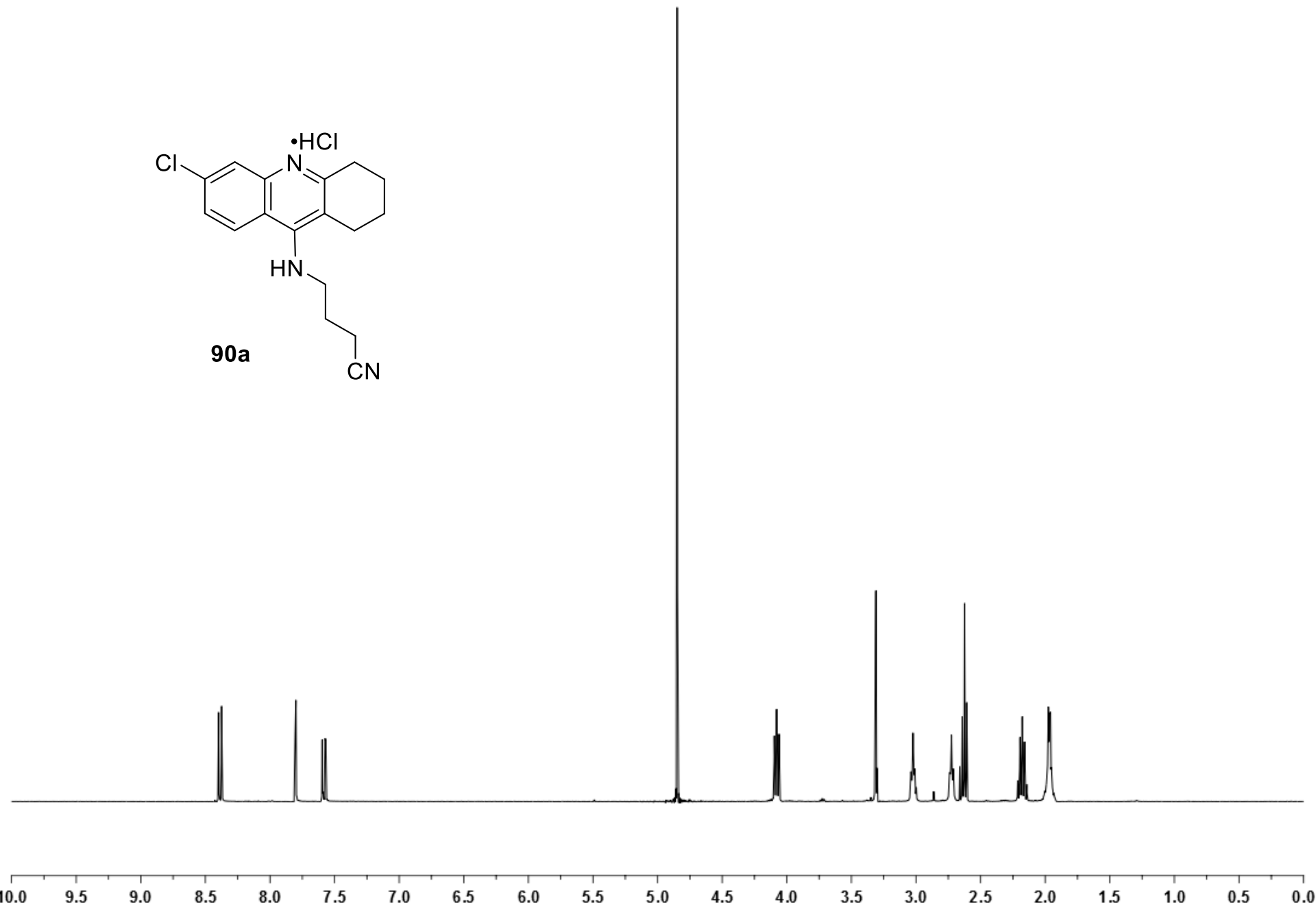
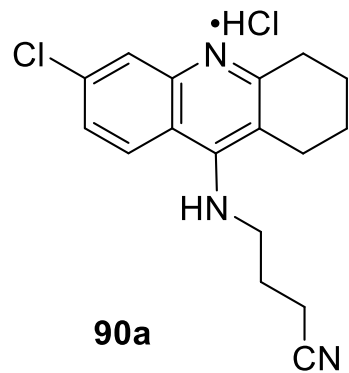
(±)-*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-[2-(6-hydroxy-7-methoxy-2-methylchroman-2-yl)ethyl]ethyl-3,6-dioxaoctane-1,8-diamine, (±)-**63e** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



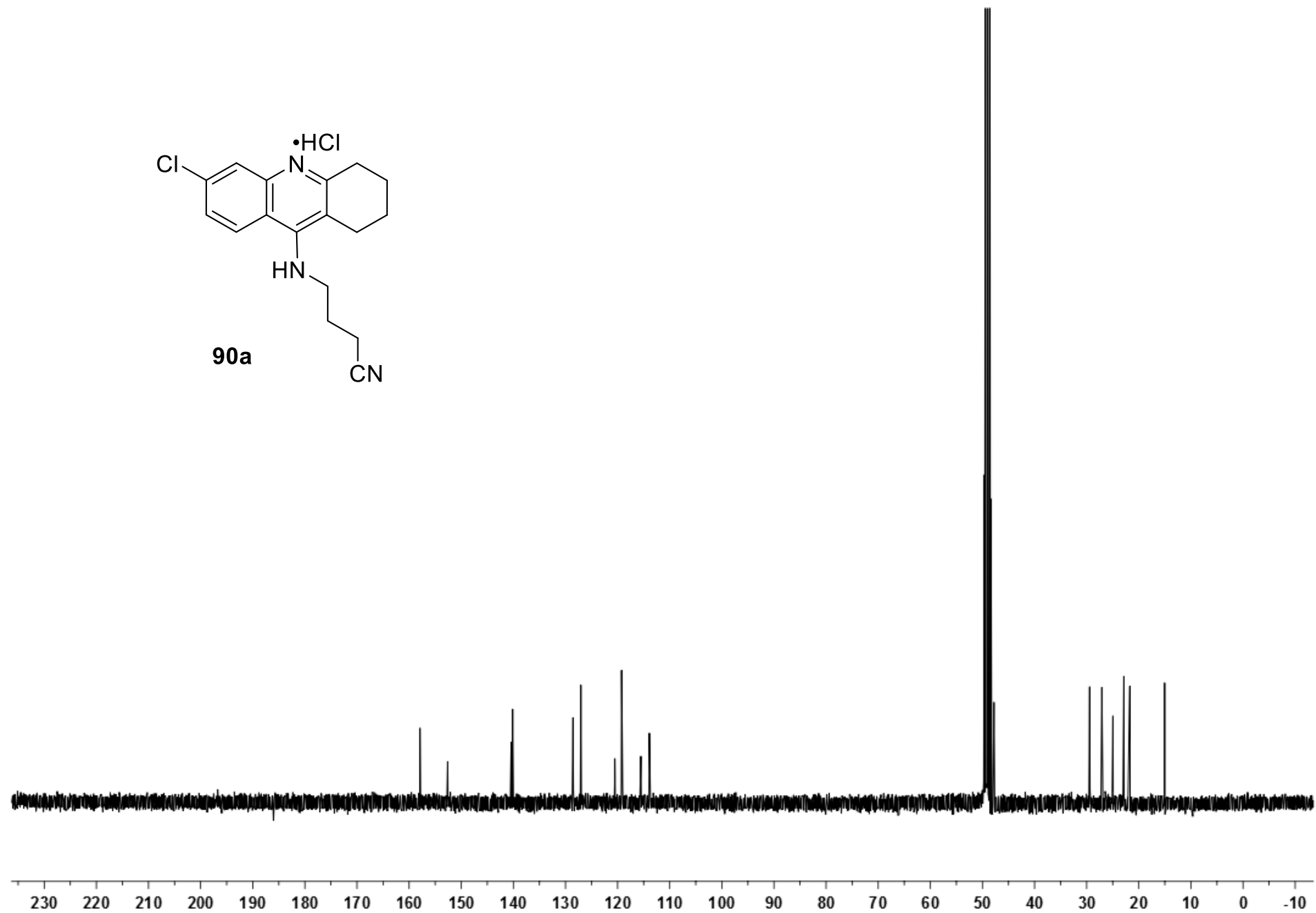
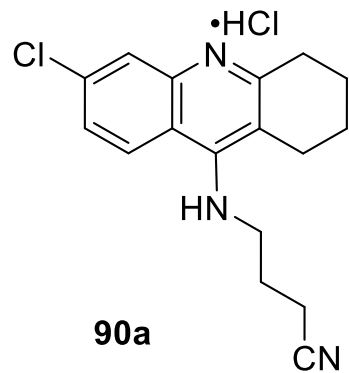
(±)-**63e**



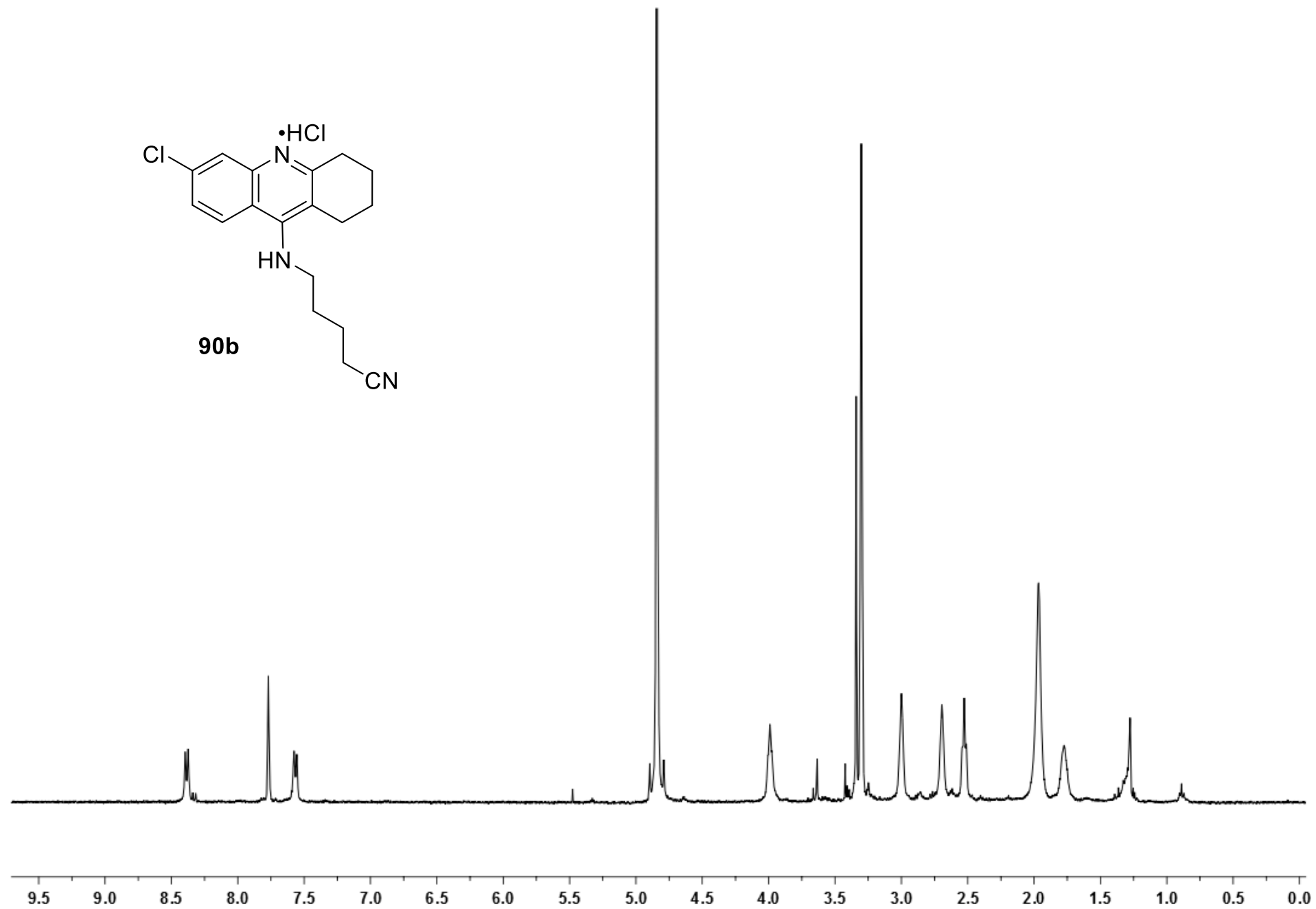
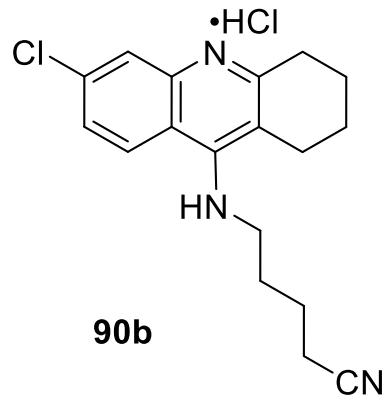
4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butanenitrile, **90a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



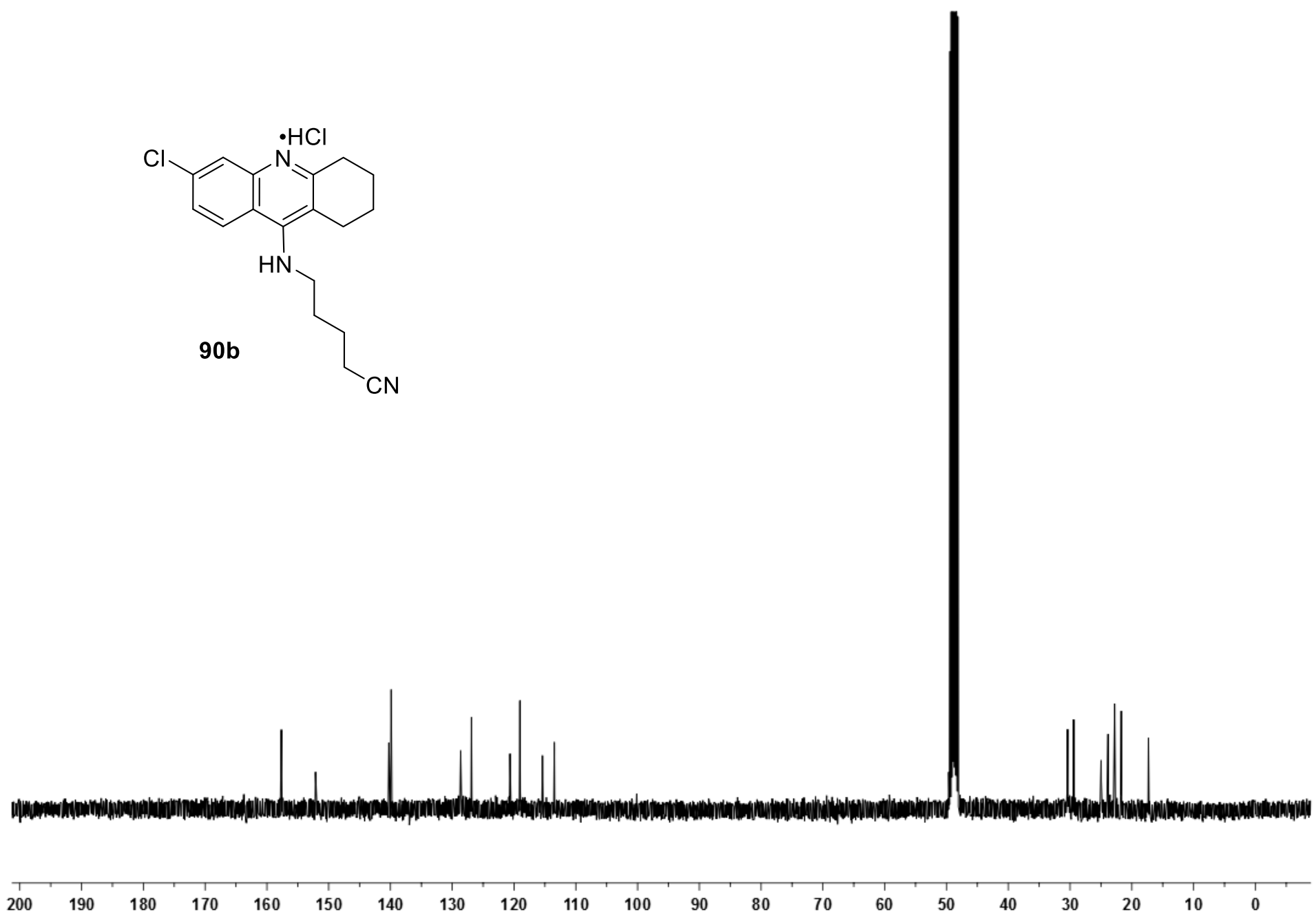
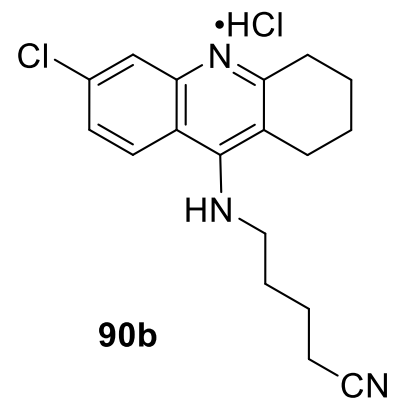
4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butanenitrile, **90a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentanenitrile, **90b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

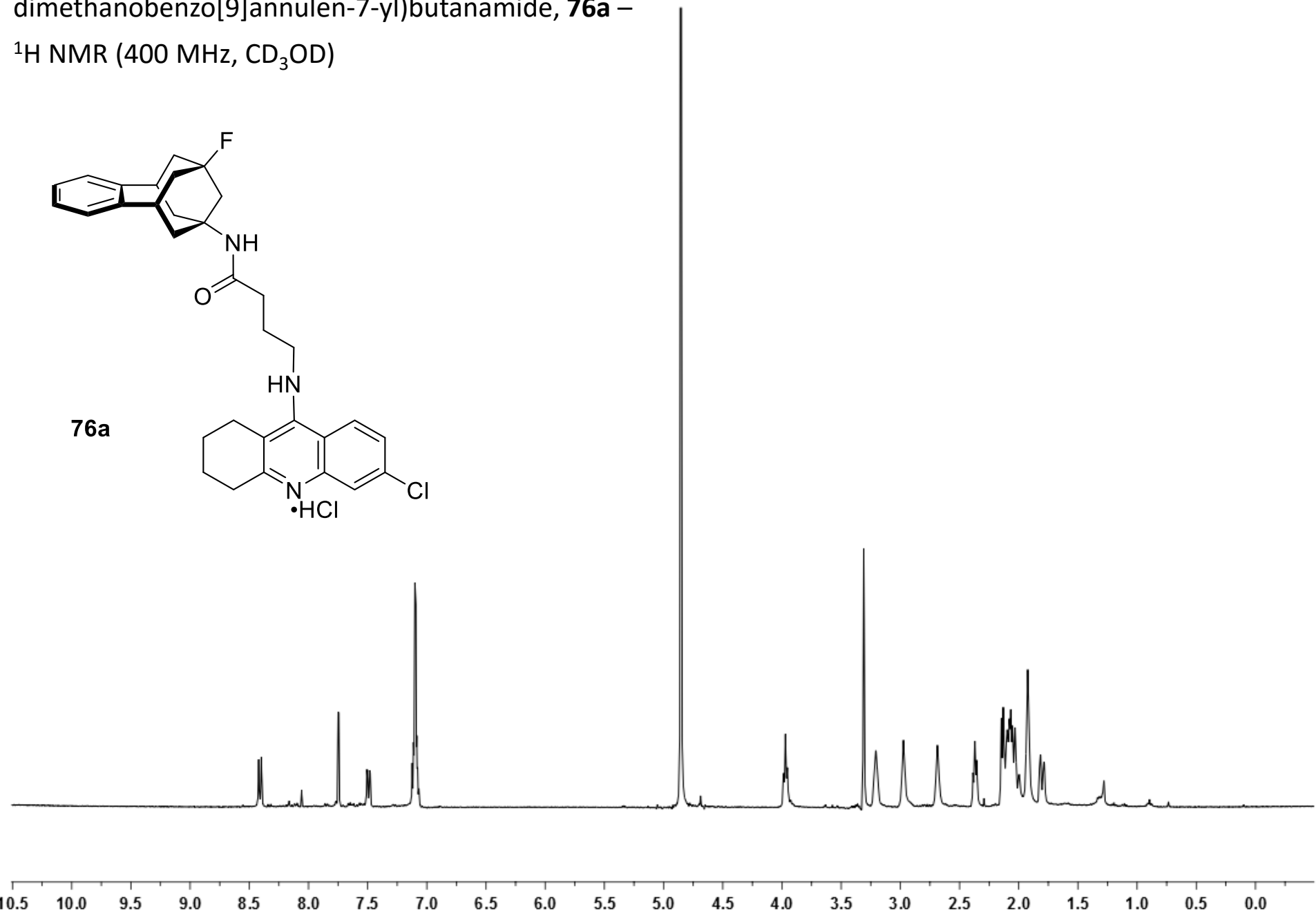
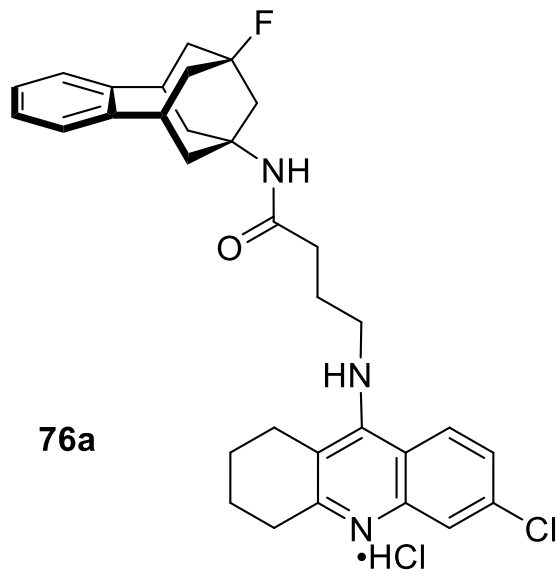


5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentanenitrile, **90b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



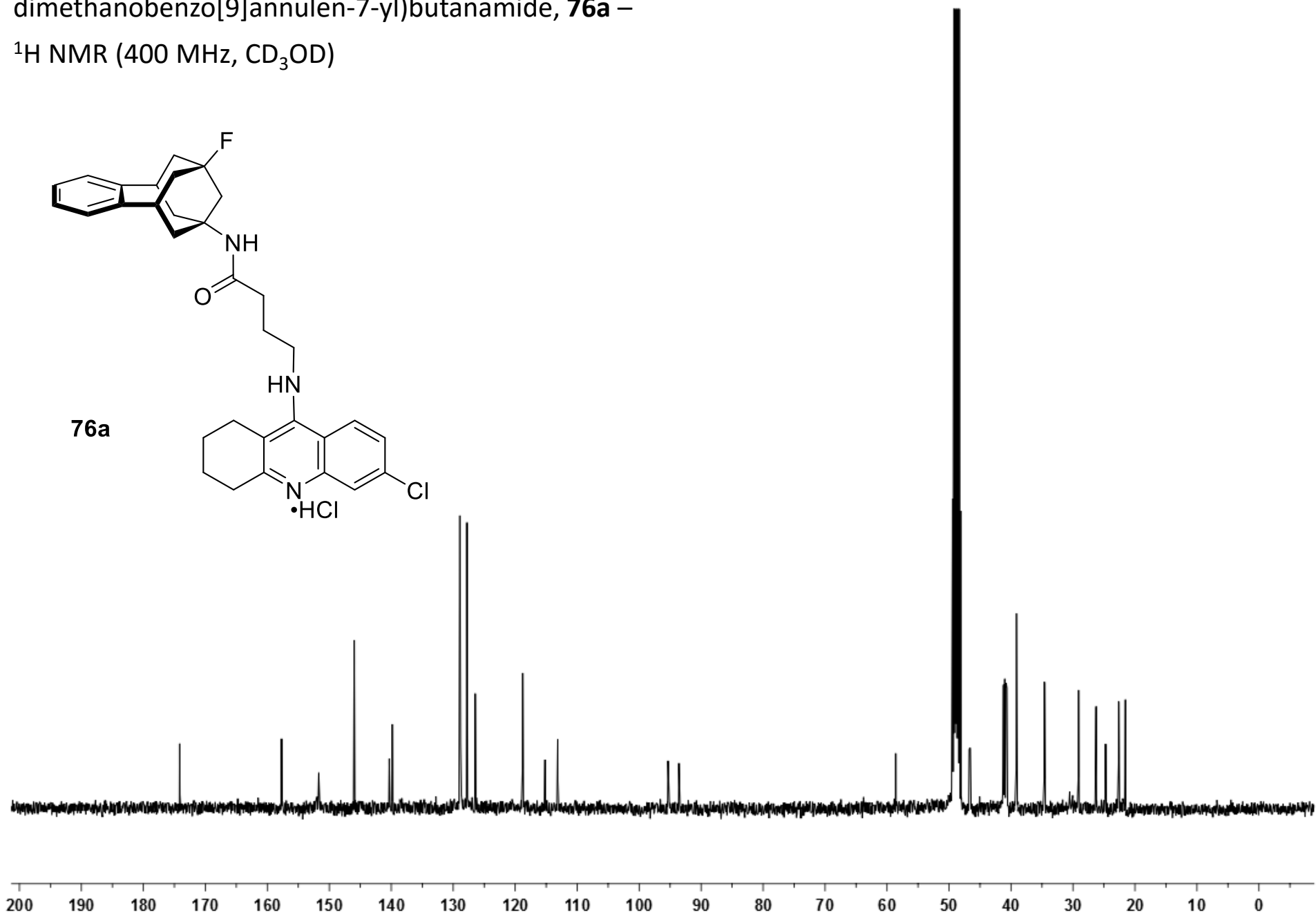
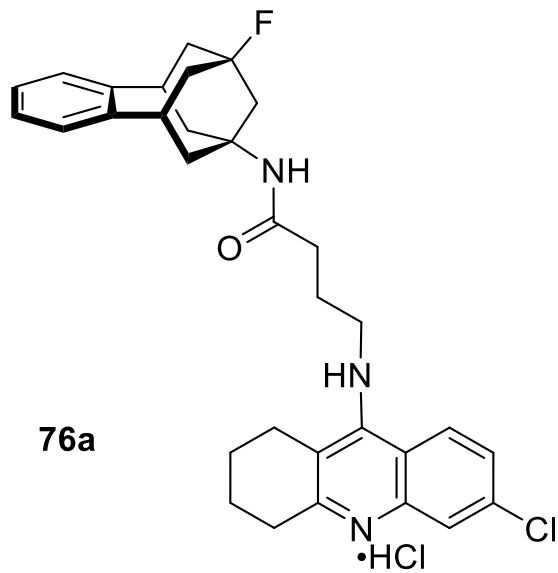
4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)butanamide, **76a** –

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



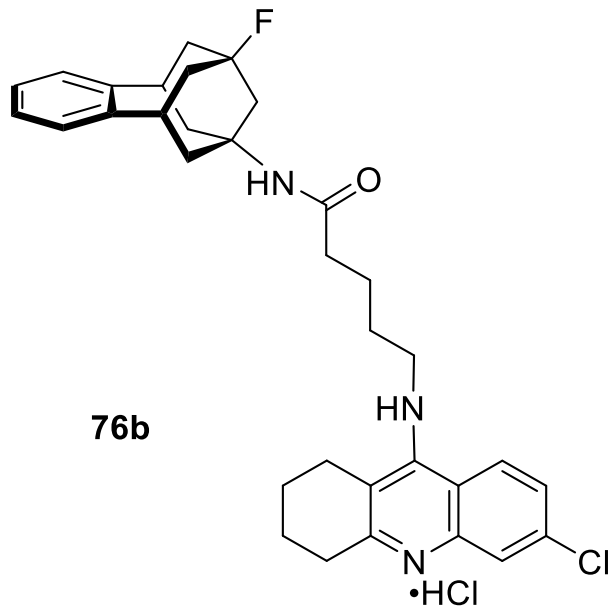
4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)butanamide, **76a** –

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

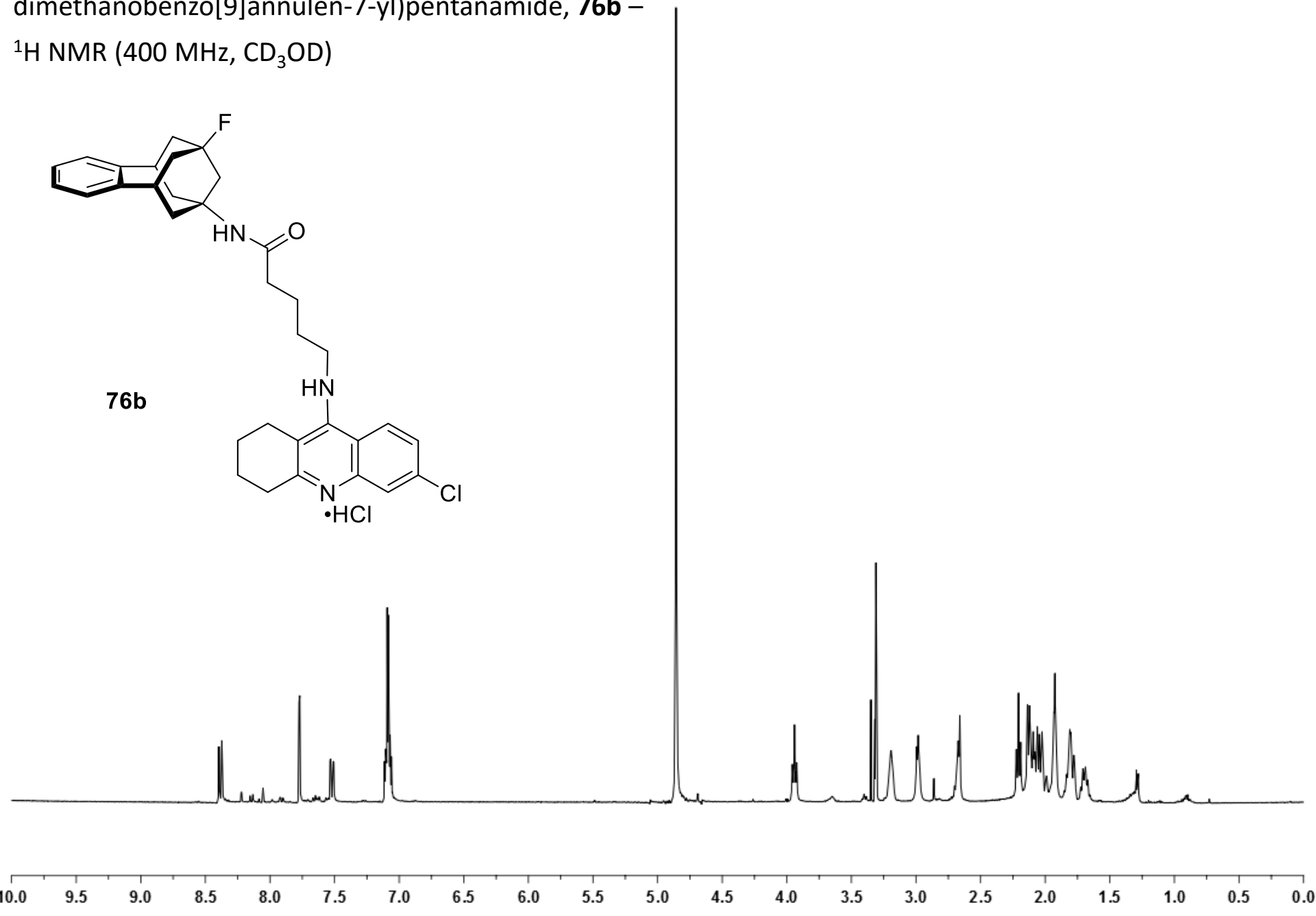


5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)pentanamide, **76b** –

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



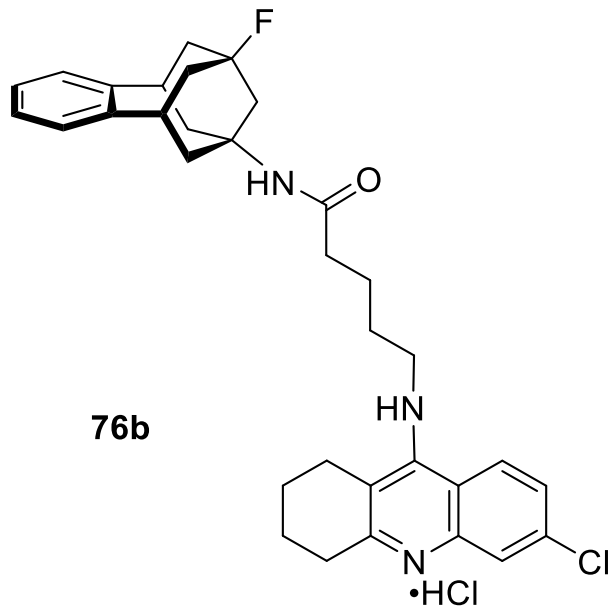
**76b**



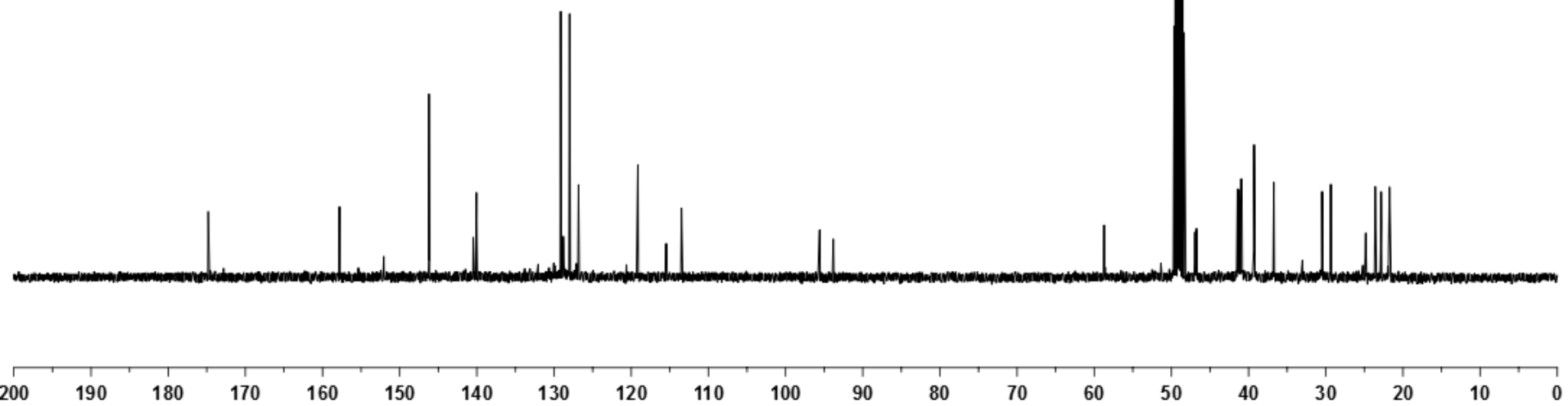


5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]-*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)pentanamide, **76b** –

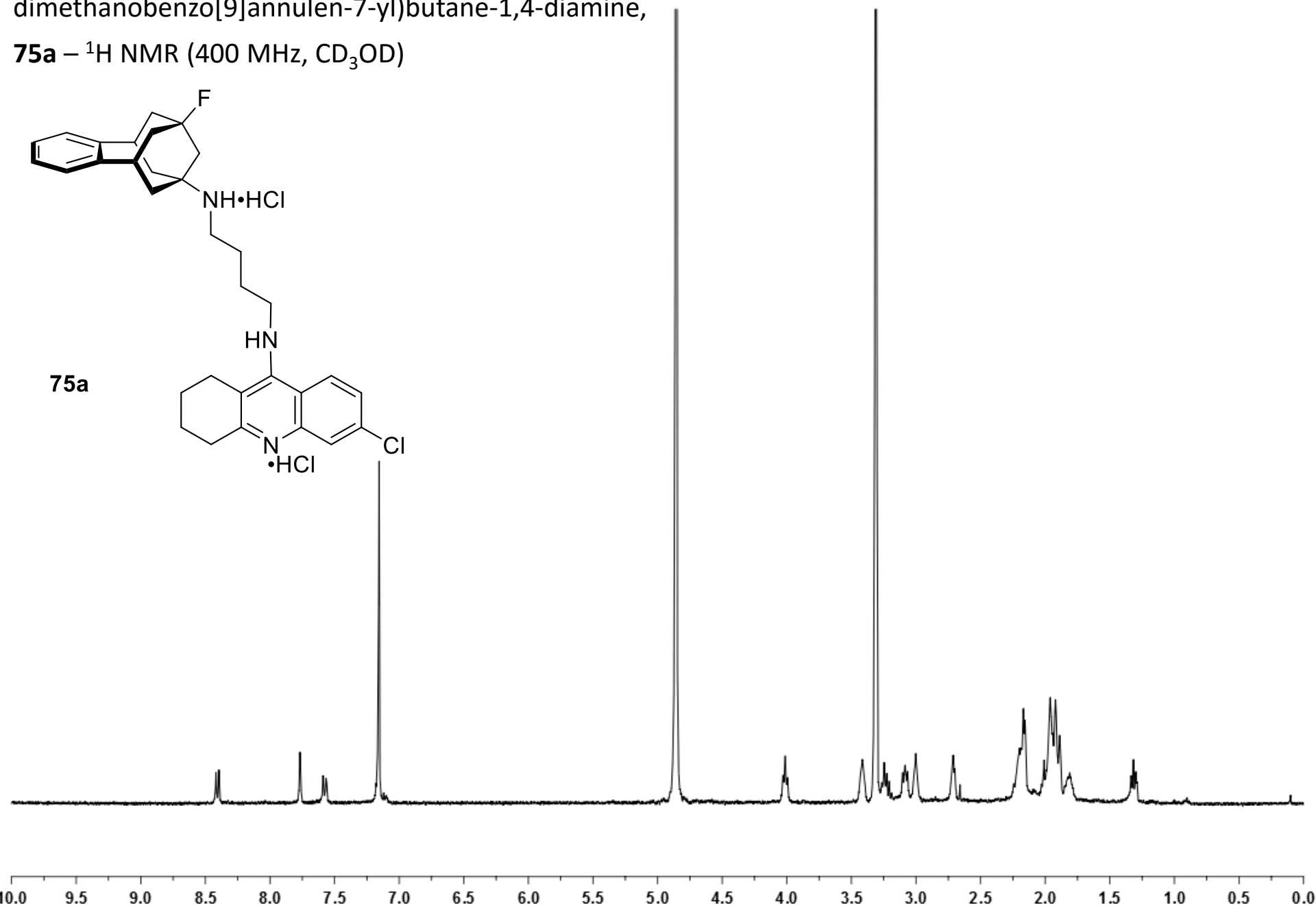
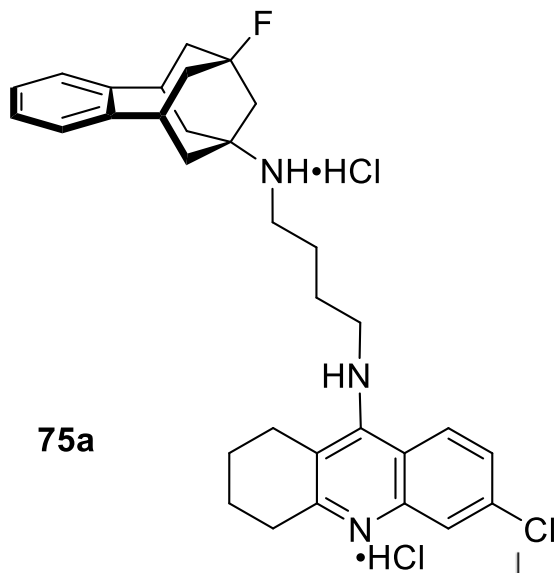
$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



**76b**

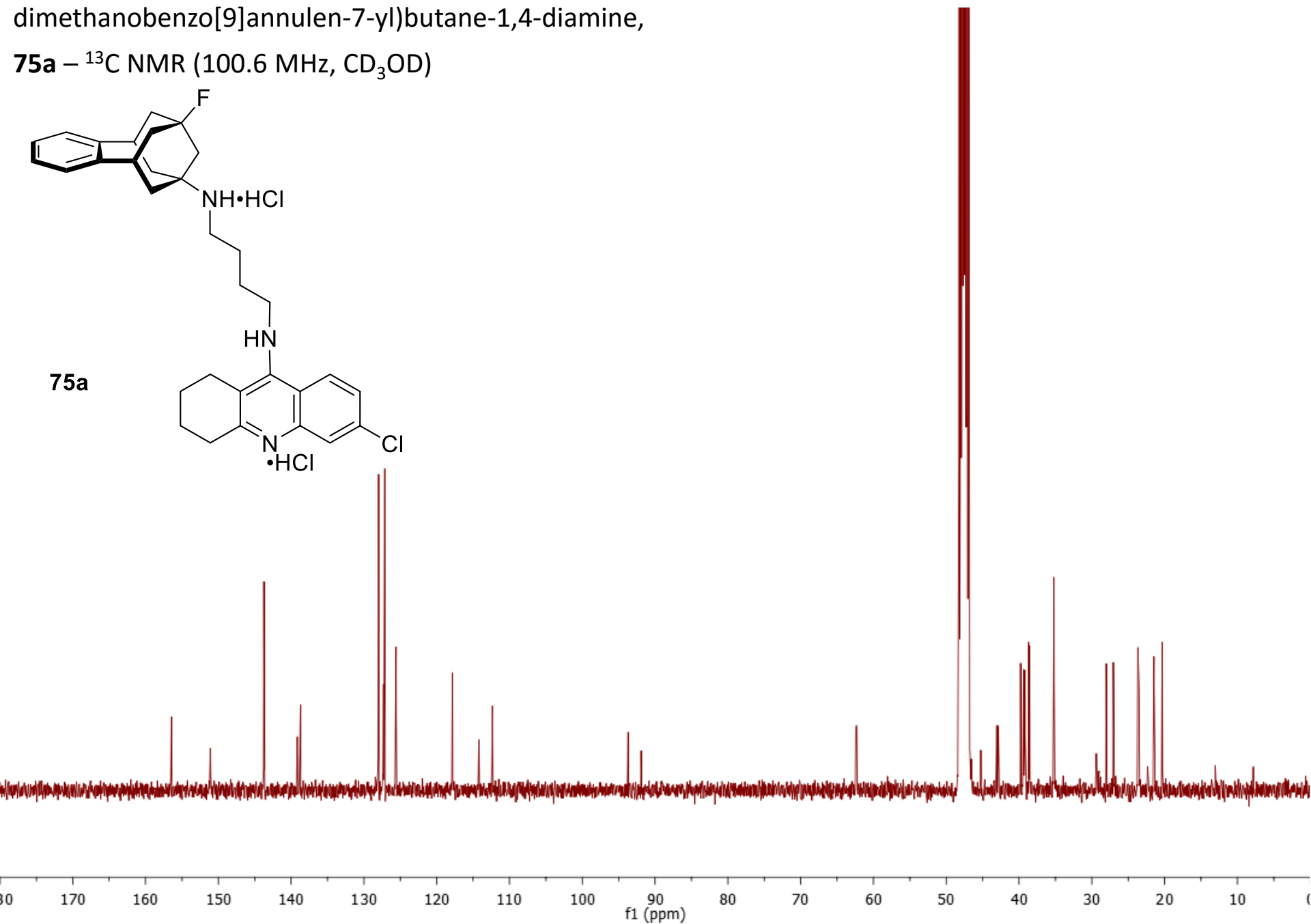
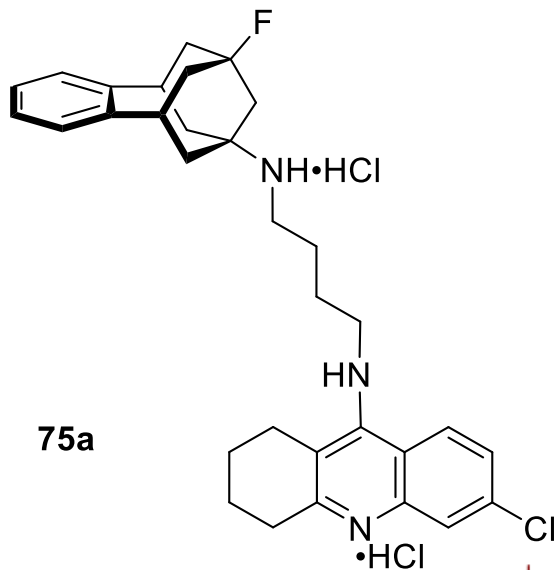


*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)butane-1,4-diamine, **75a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

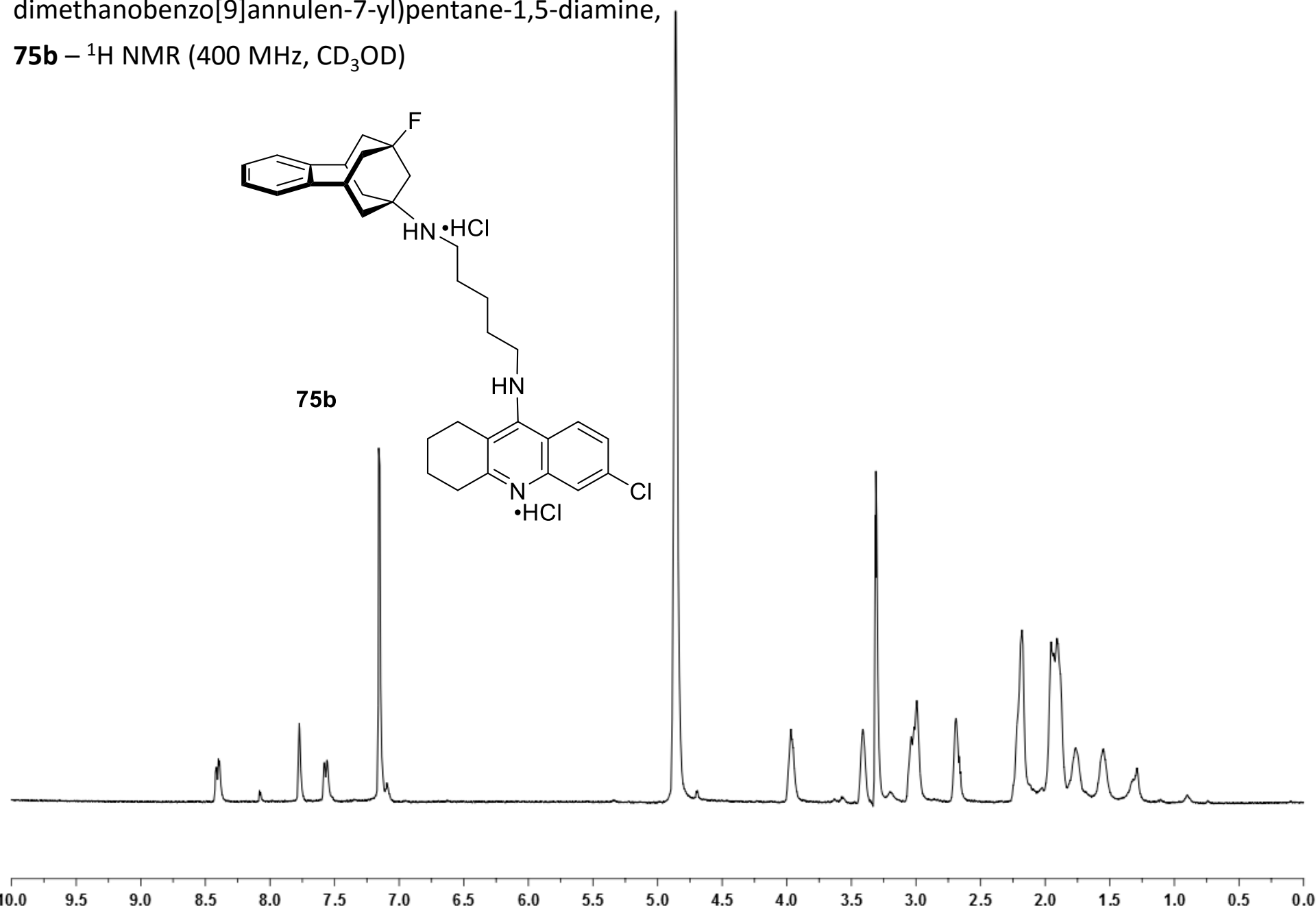
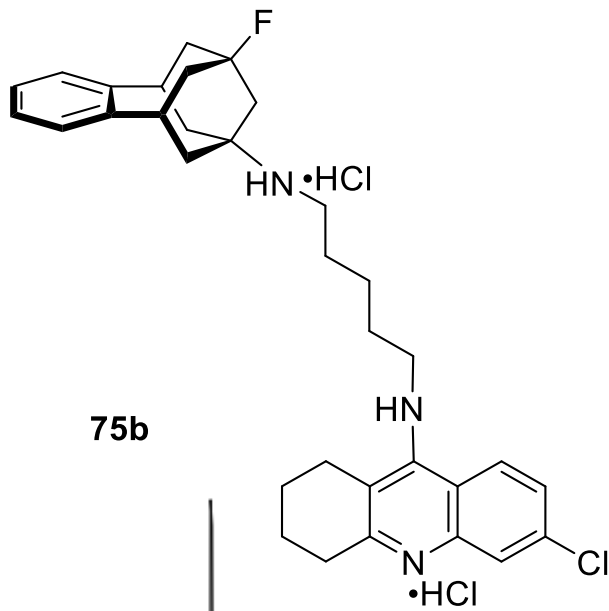


*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)butane-1,4-diamine,

**75a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

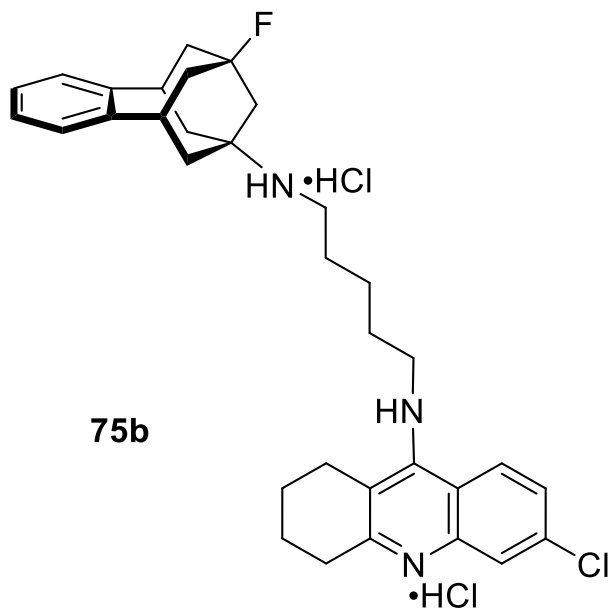


*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)pentane-1,5-diamine, **75b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

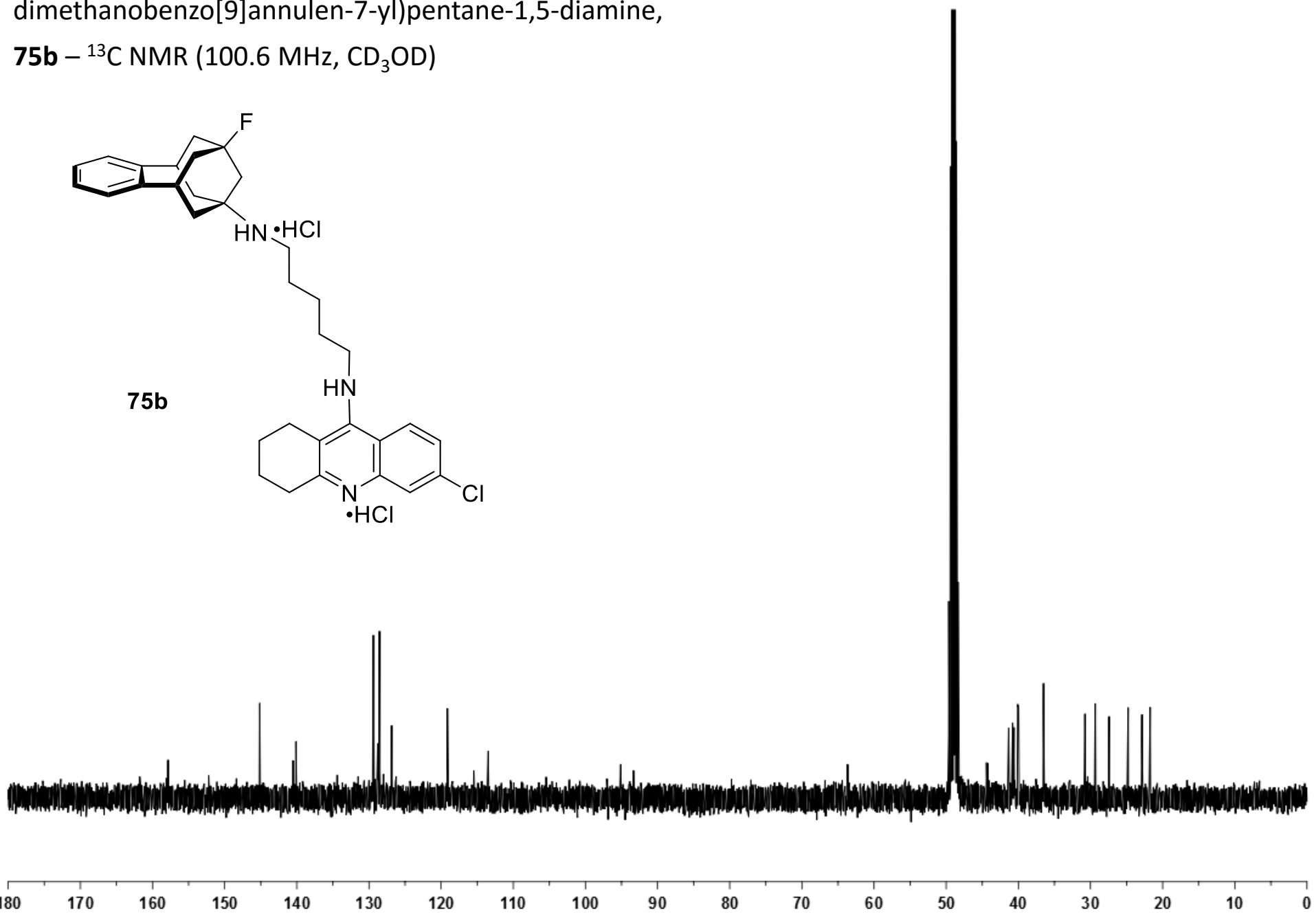


*N*-(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)-*N'*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-

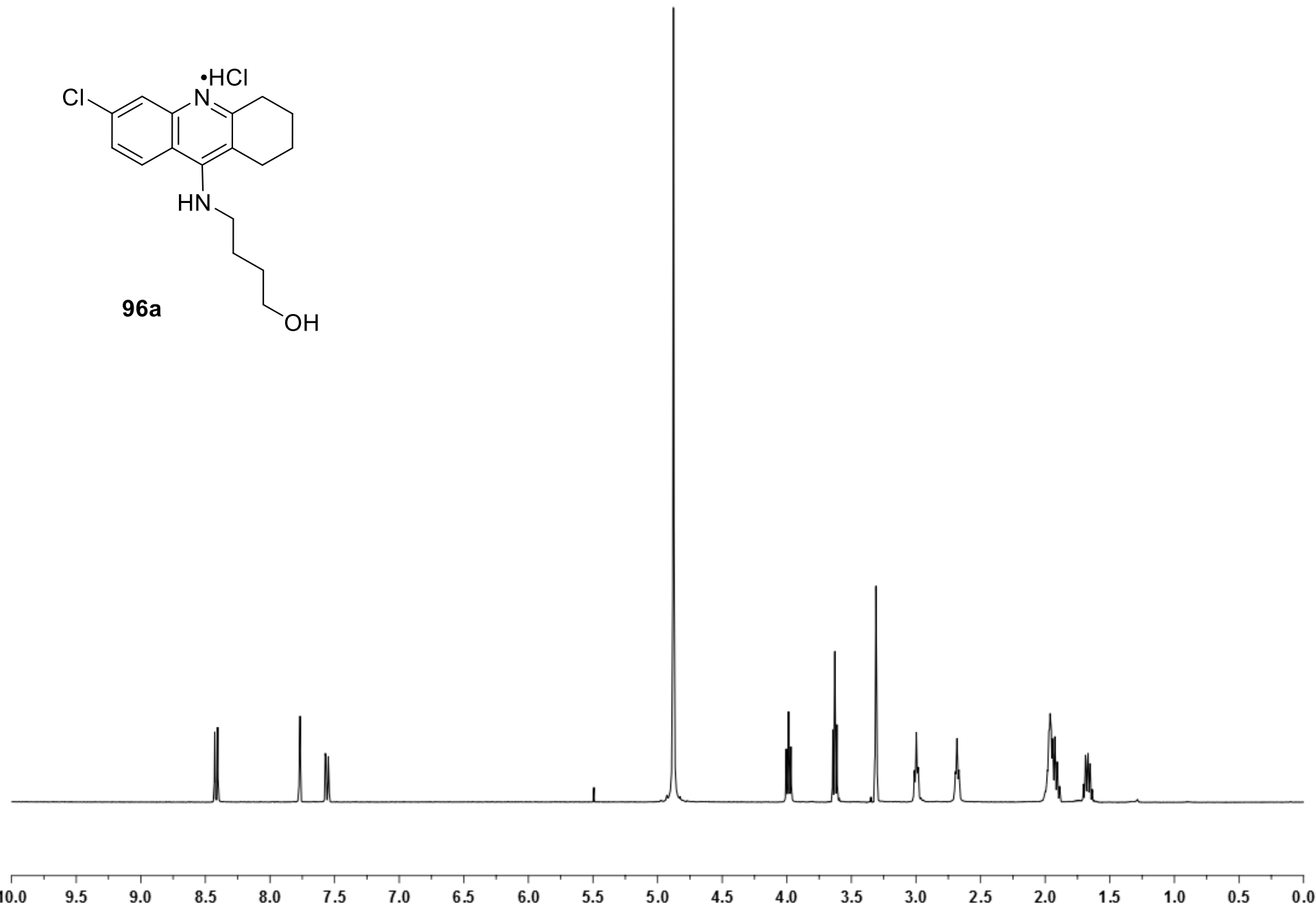
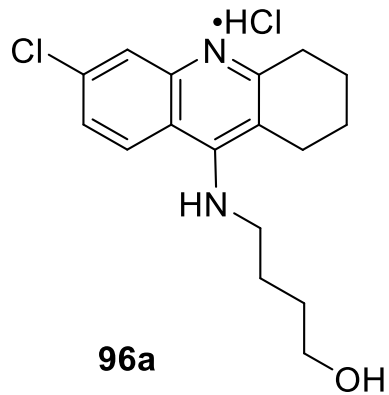
dimethanobenzo[9]annulen-7-yl)pentane-1,5-diamine,  
**75b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



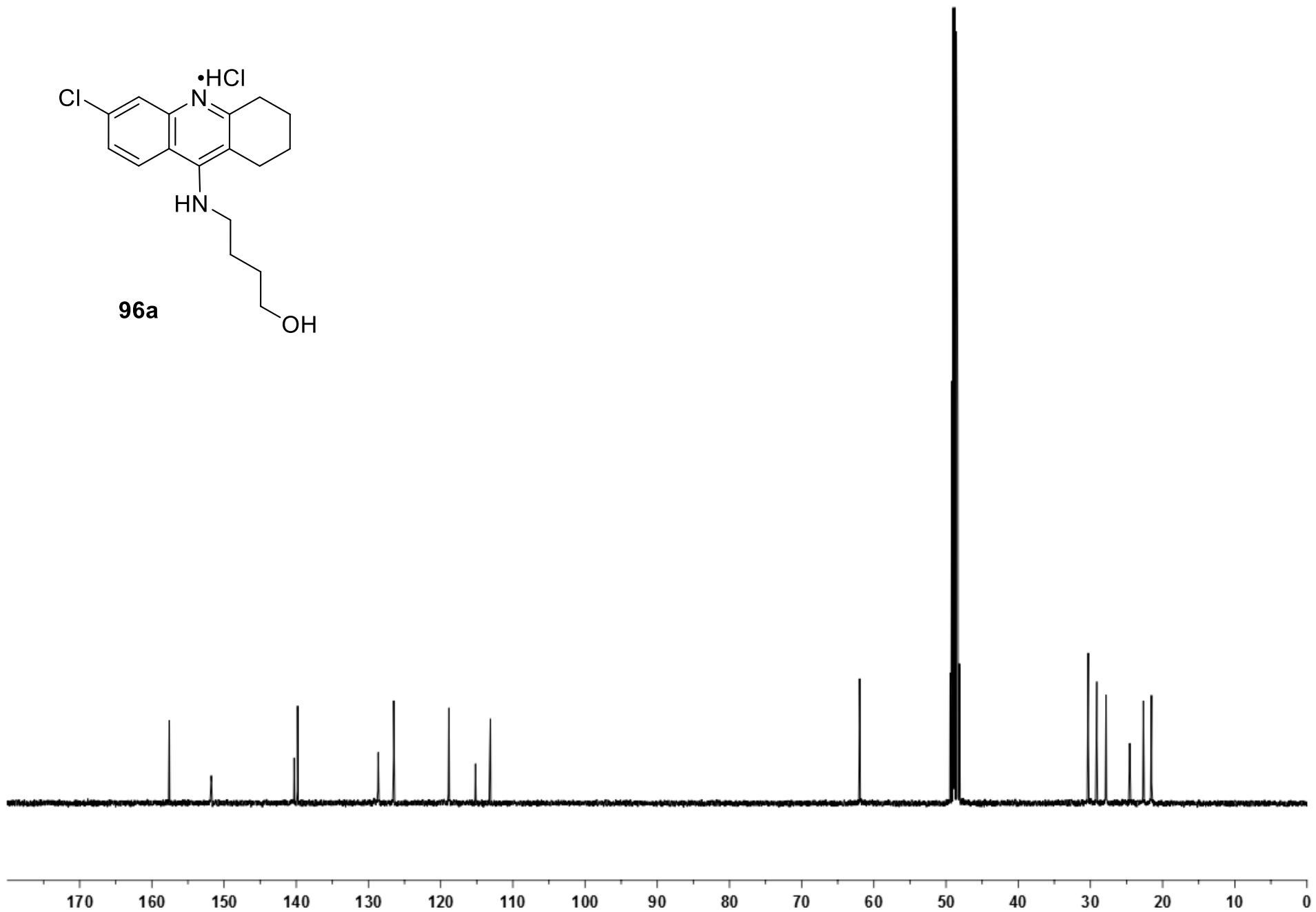
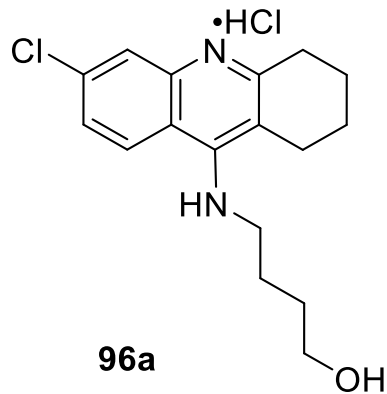
**75b**



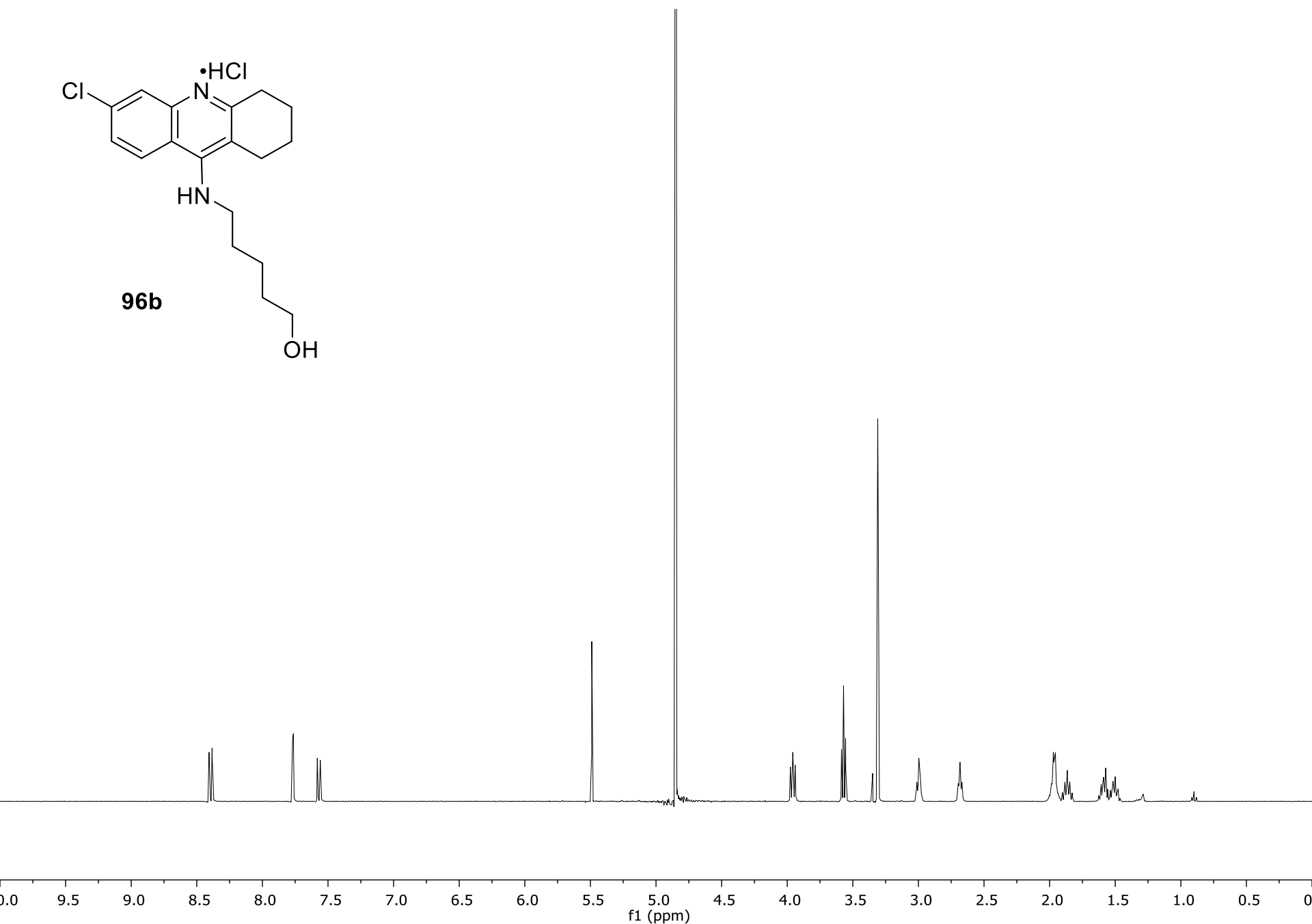
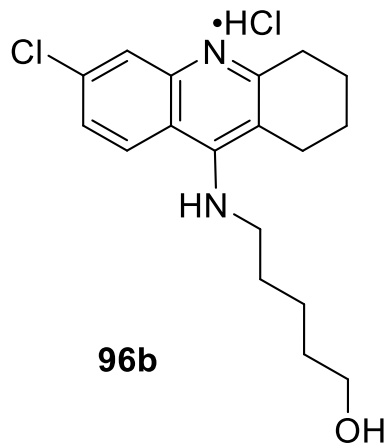
4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butan-1-ol, **96a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butan-1-ol, **96a** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

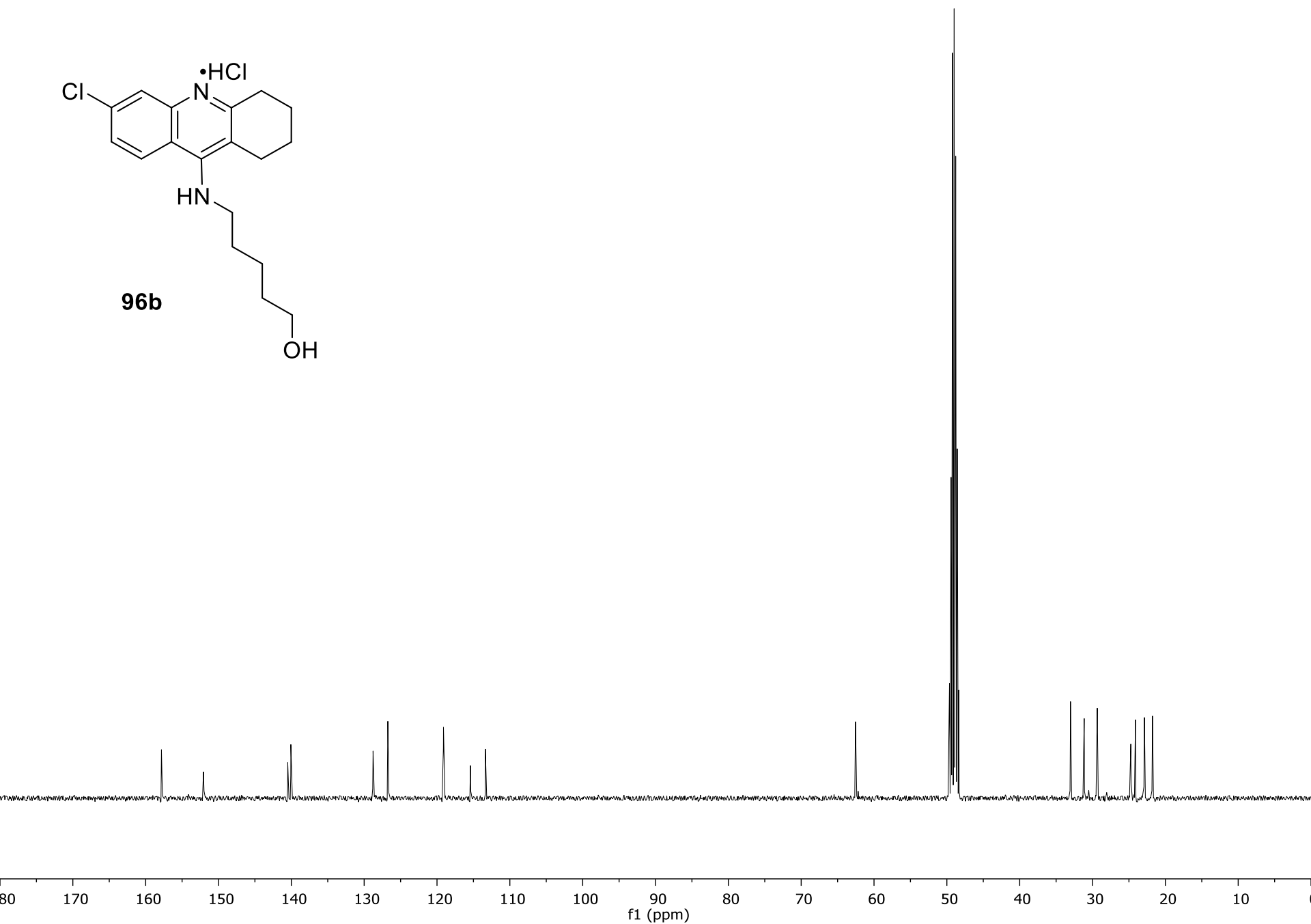
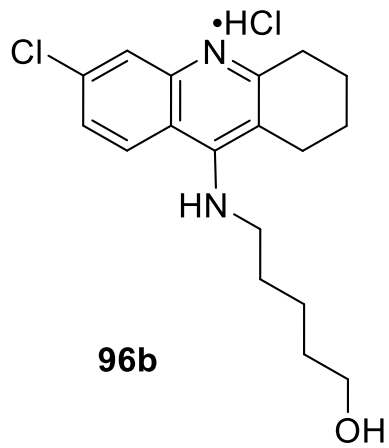


5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentan-1-ol, **96b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

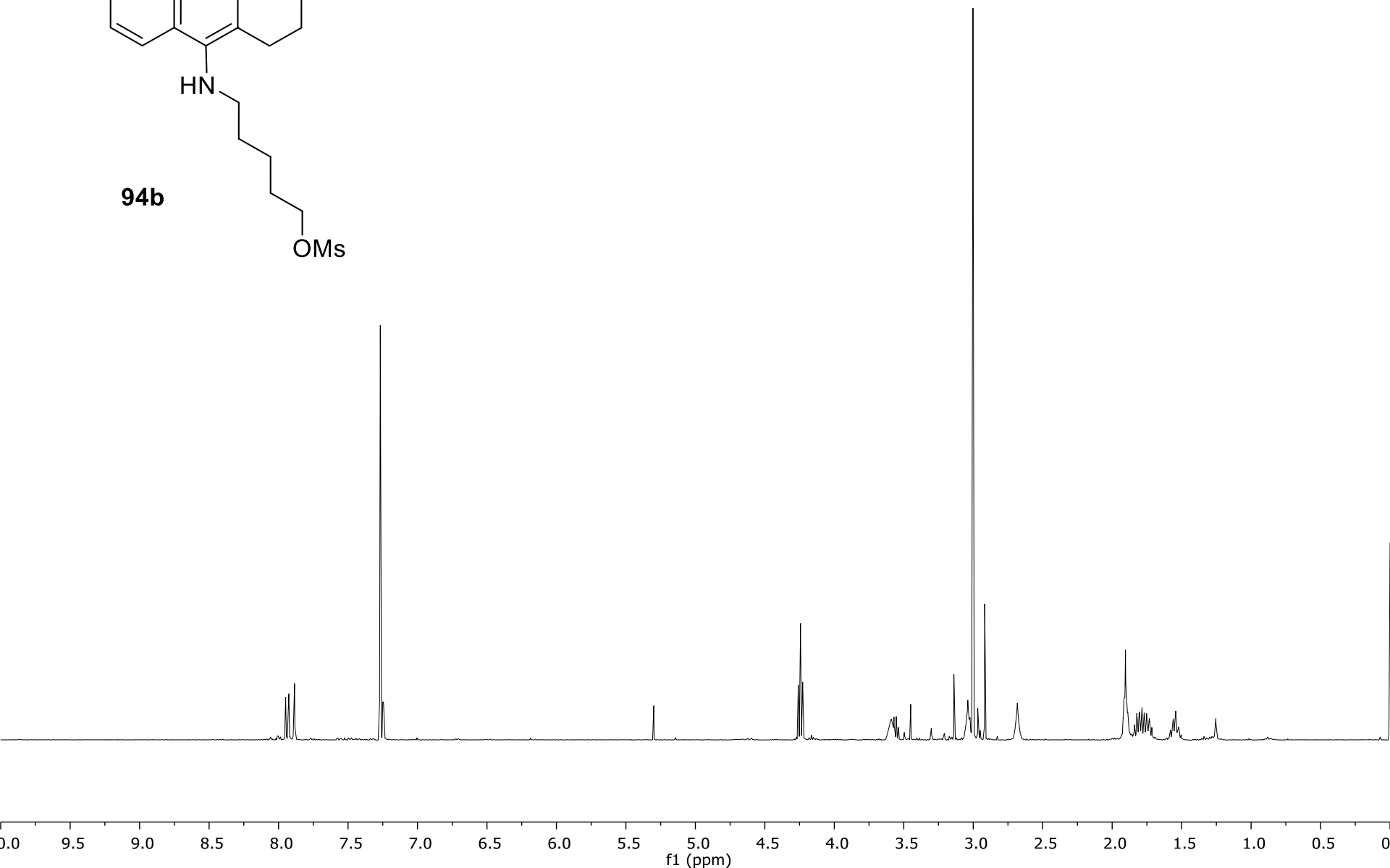
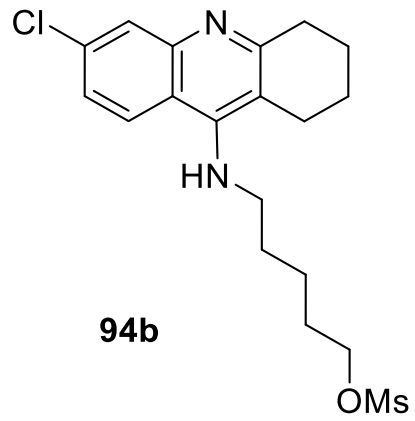




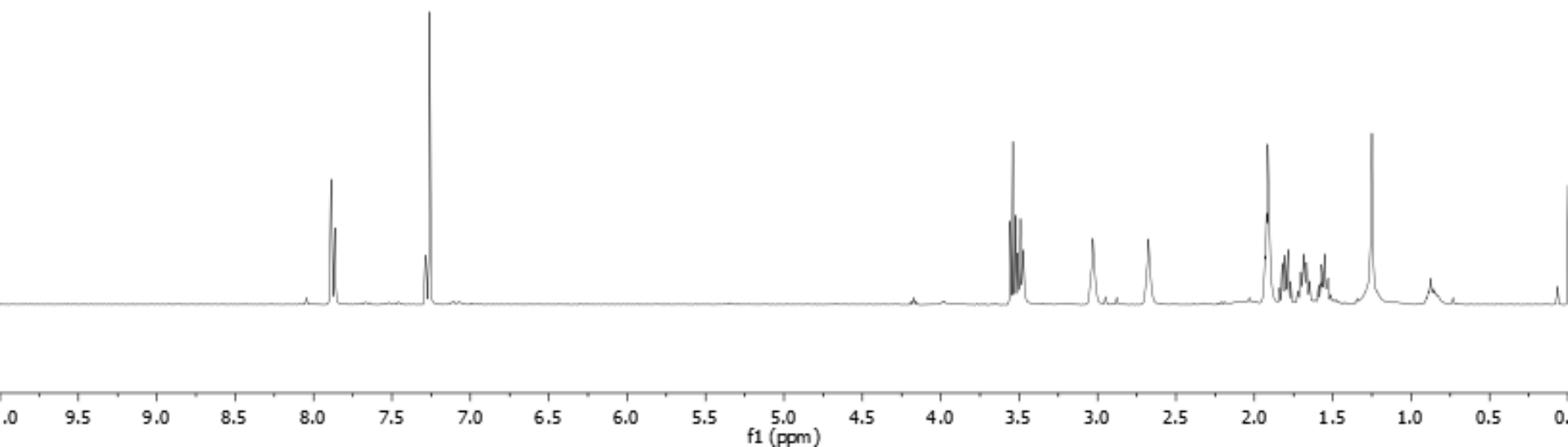
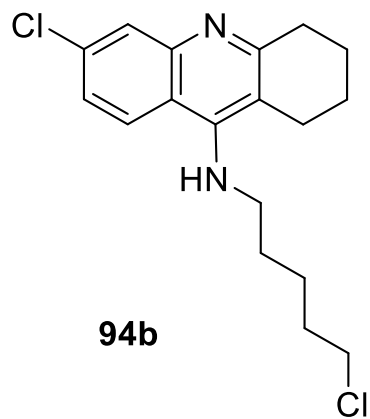
5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentan-1-ol, **96b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



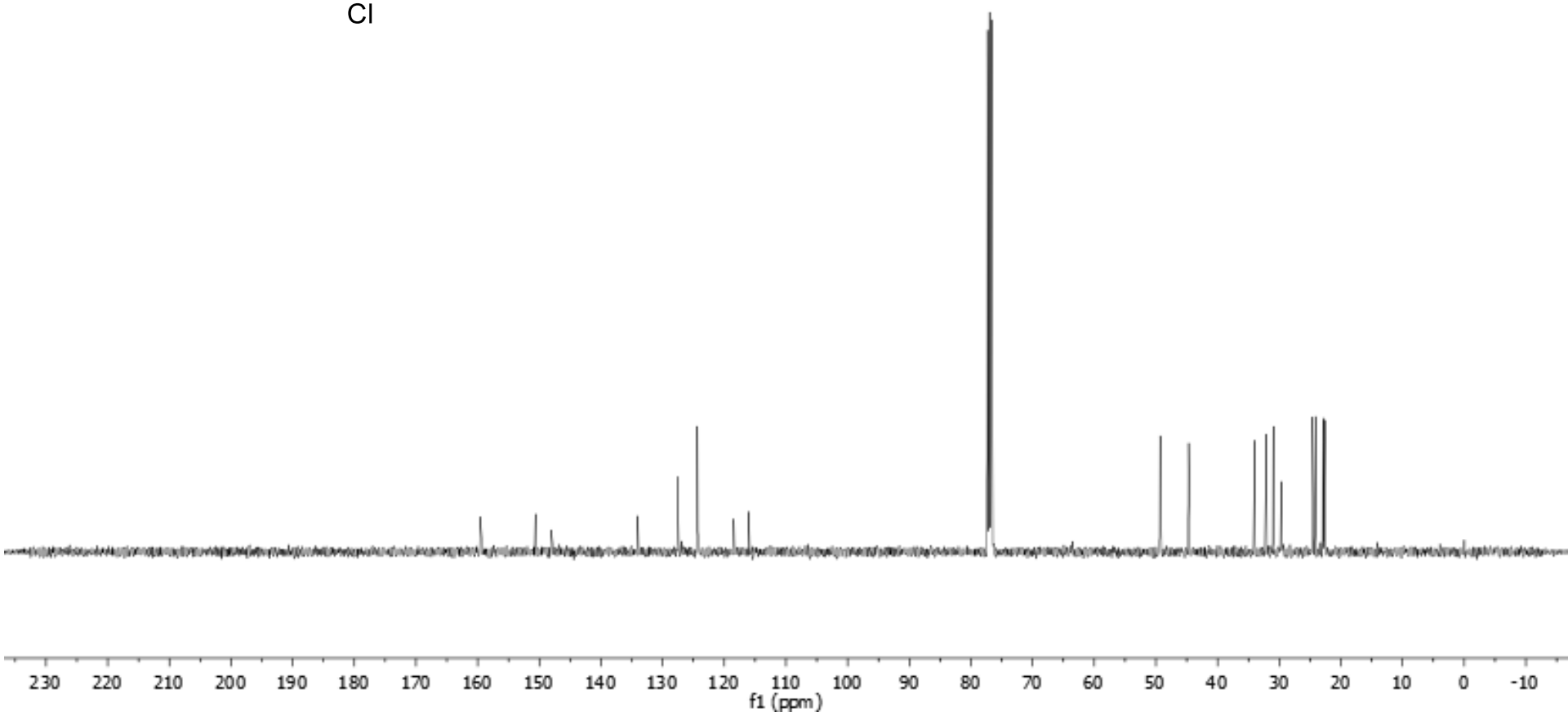
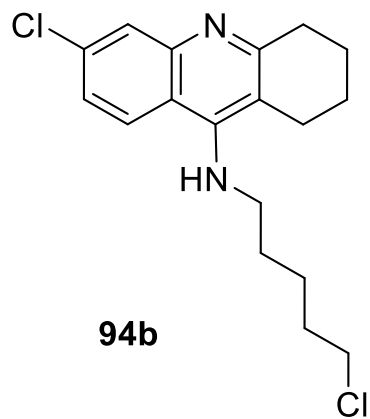
5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentyl methanesulfonate, **94b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



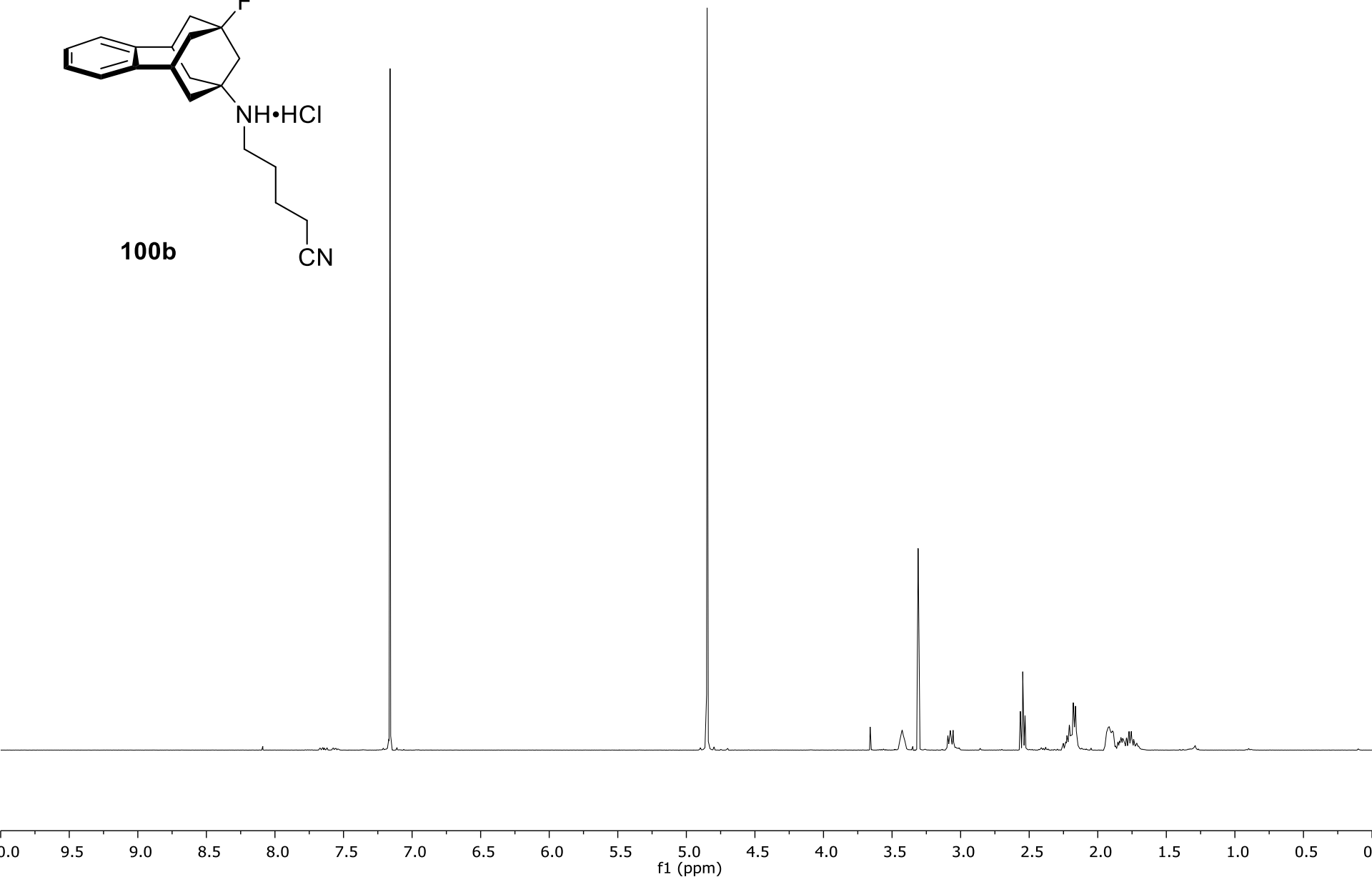
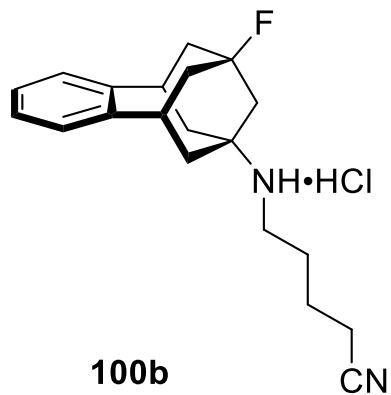
6-chloro-*N*-(5-chloropentyl)-1,2,3,4-tetrahydroacridin-9-amine, **97** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



6-chloro-*N*-(5-chloropentyl)-1,2,3,4-tetrahydroacridin-9-amine, **97** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )

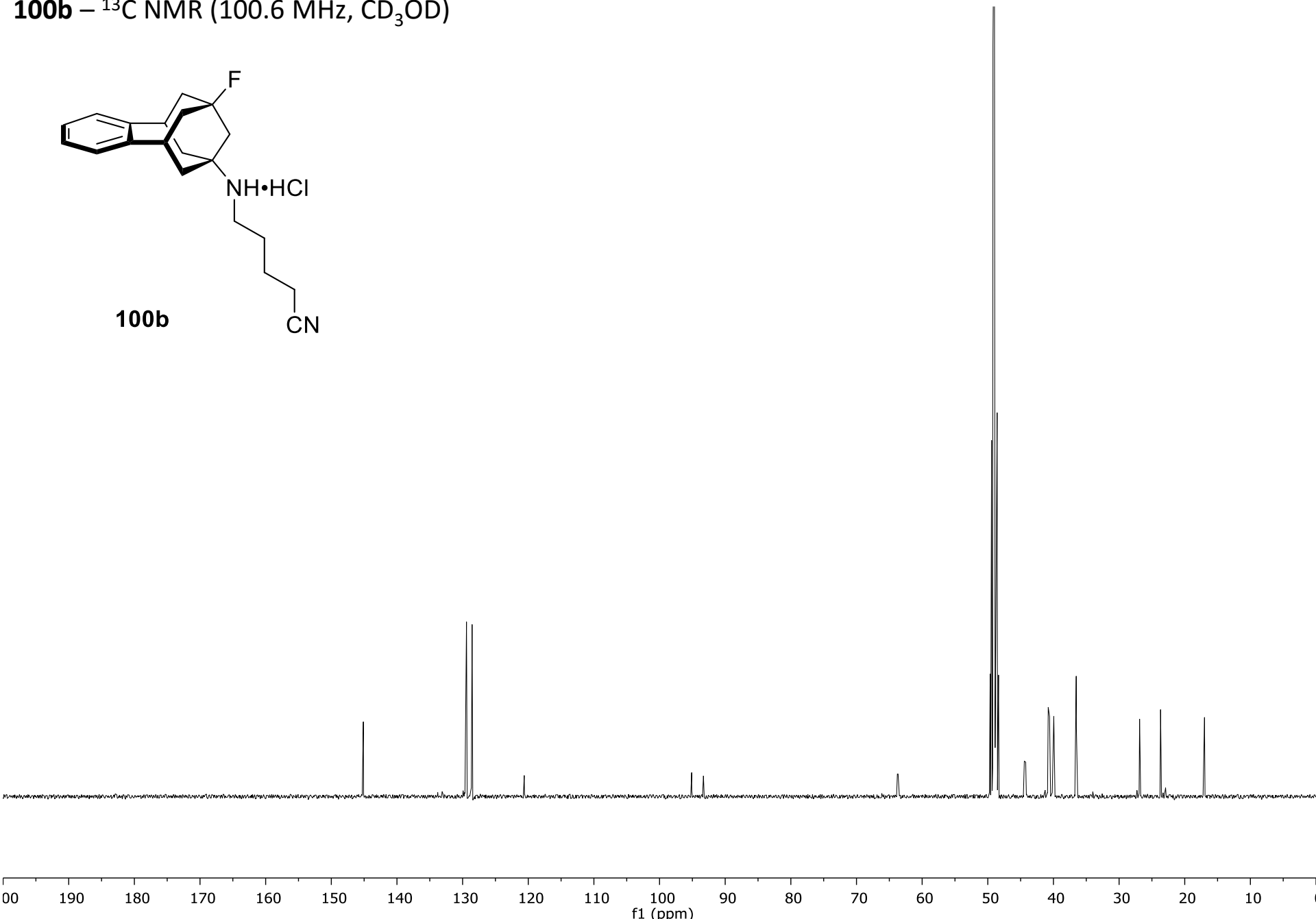
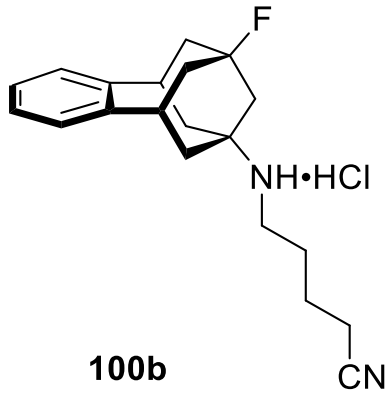


5-[(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)amino]pentanenitrile,  
**100b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

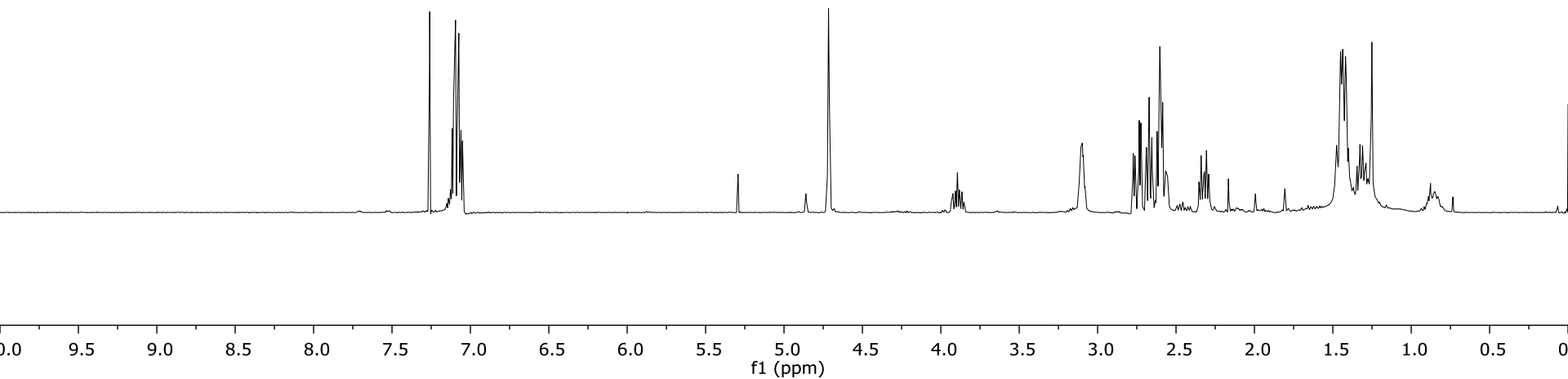
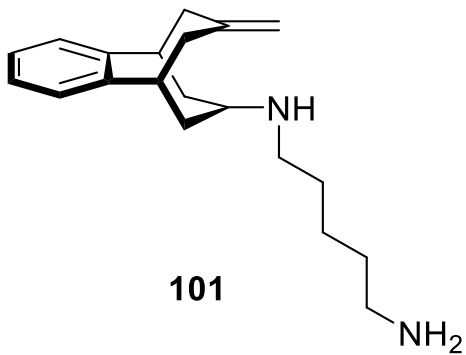


5-[(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)amino]pentanenitrile,

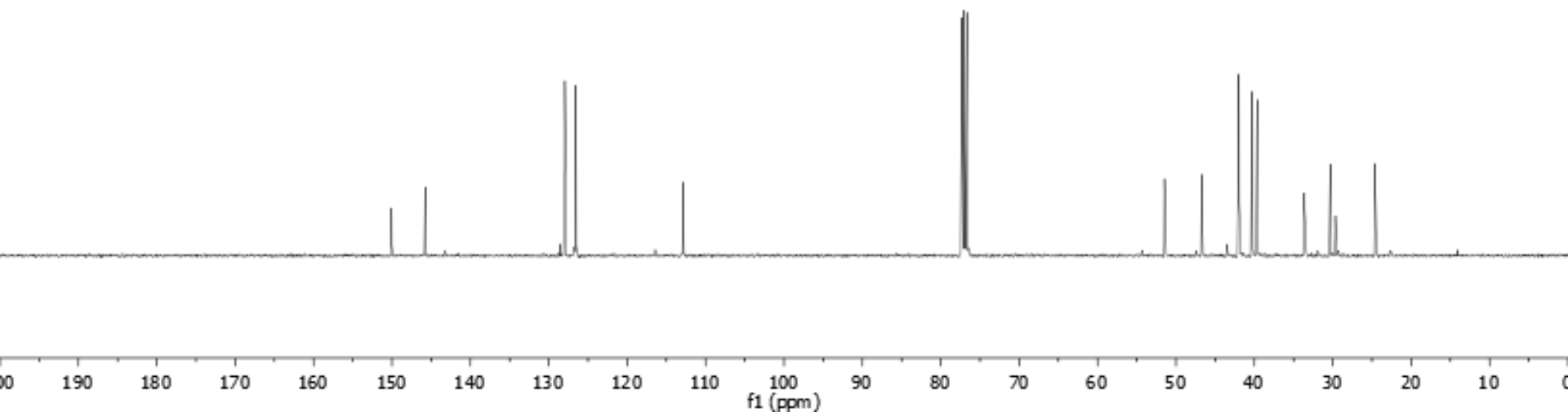
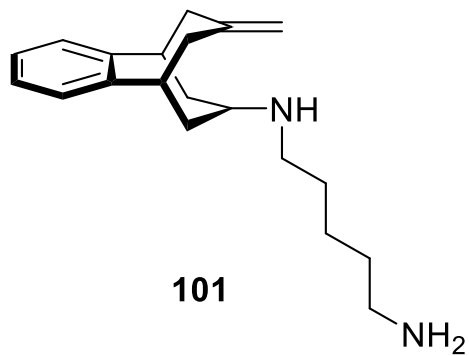
**100b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)pentane-1,5-diamine,  
**99b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

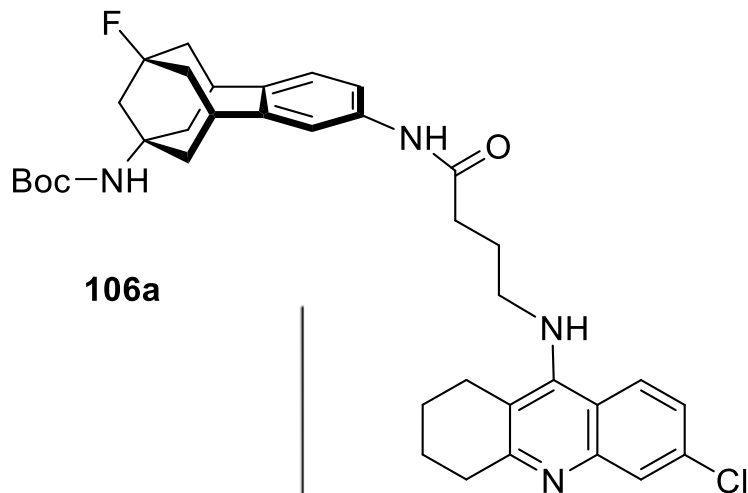


*N*-(9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-7-yl)pentane-1,5-diamine, **99b** –  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )

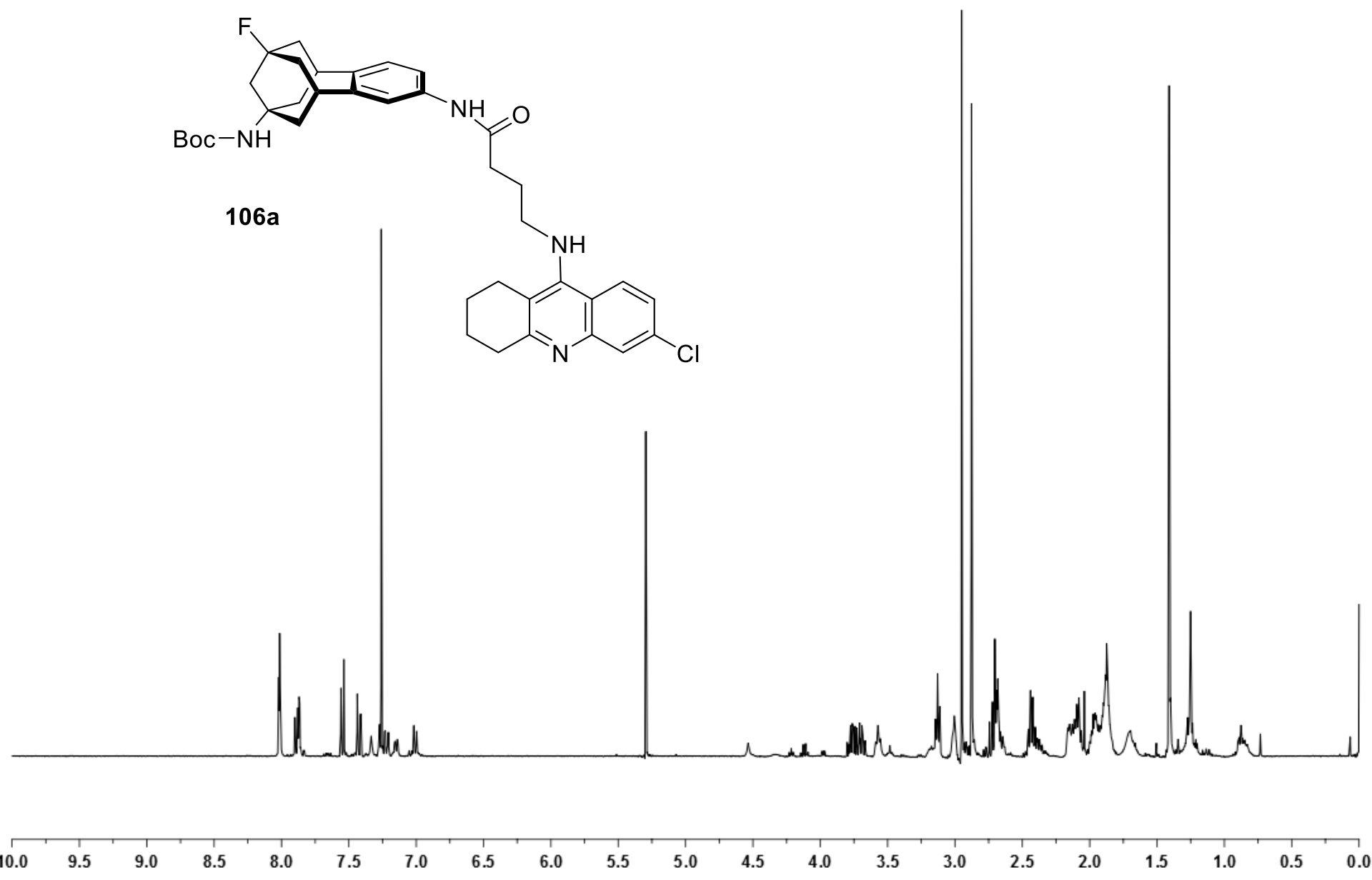




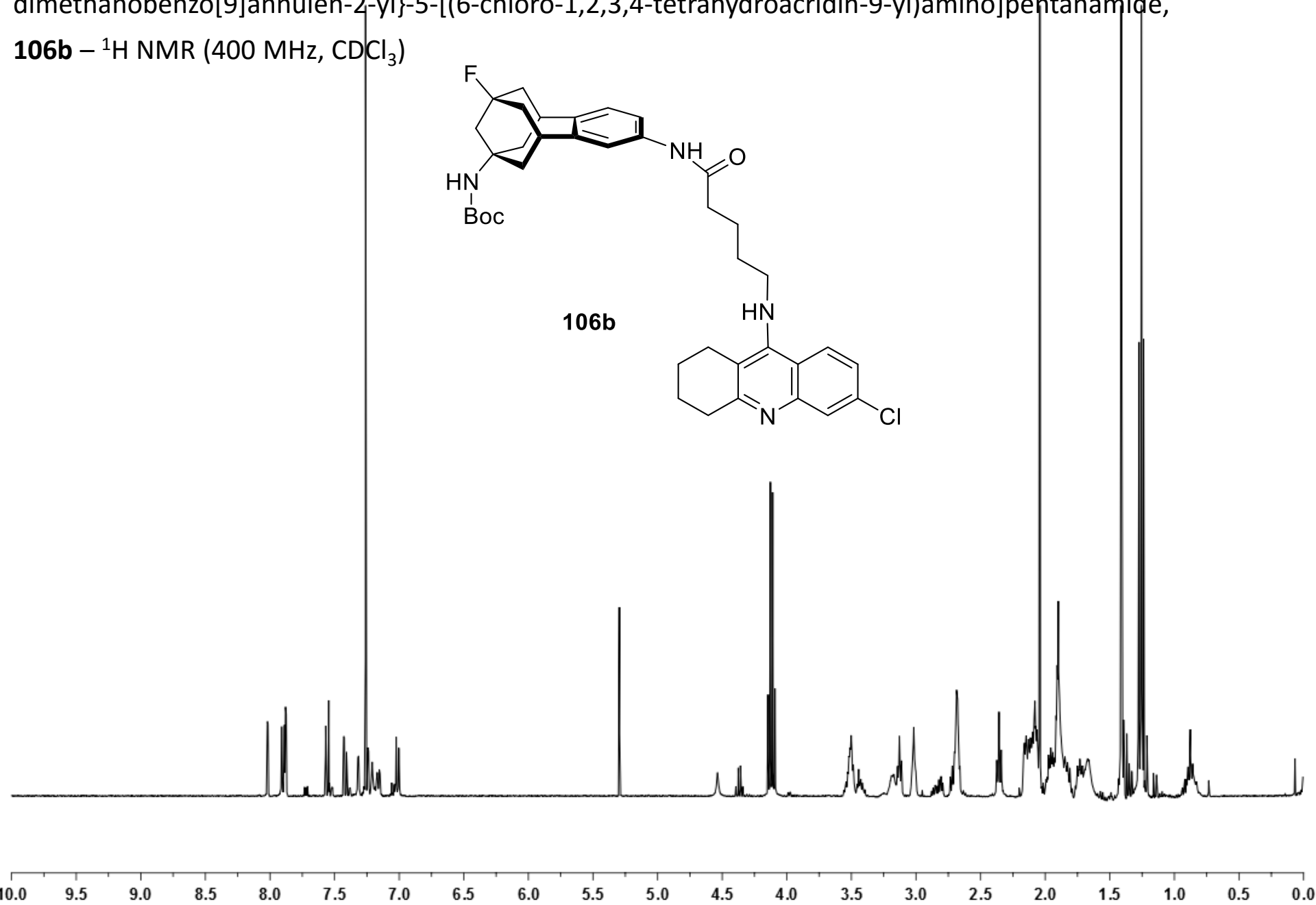
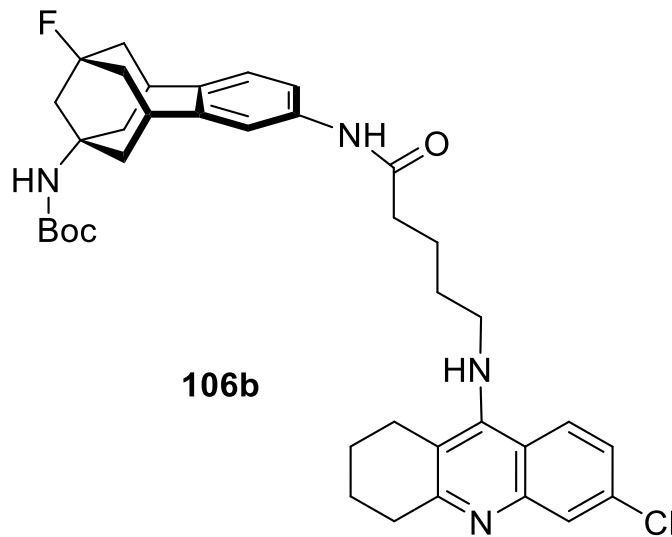
*N*-{7-[(*tert*-butyloxycarbonyl)amino]-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl}-4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butanamide, **106a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



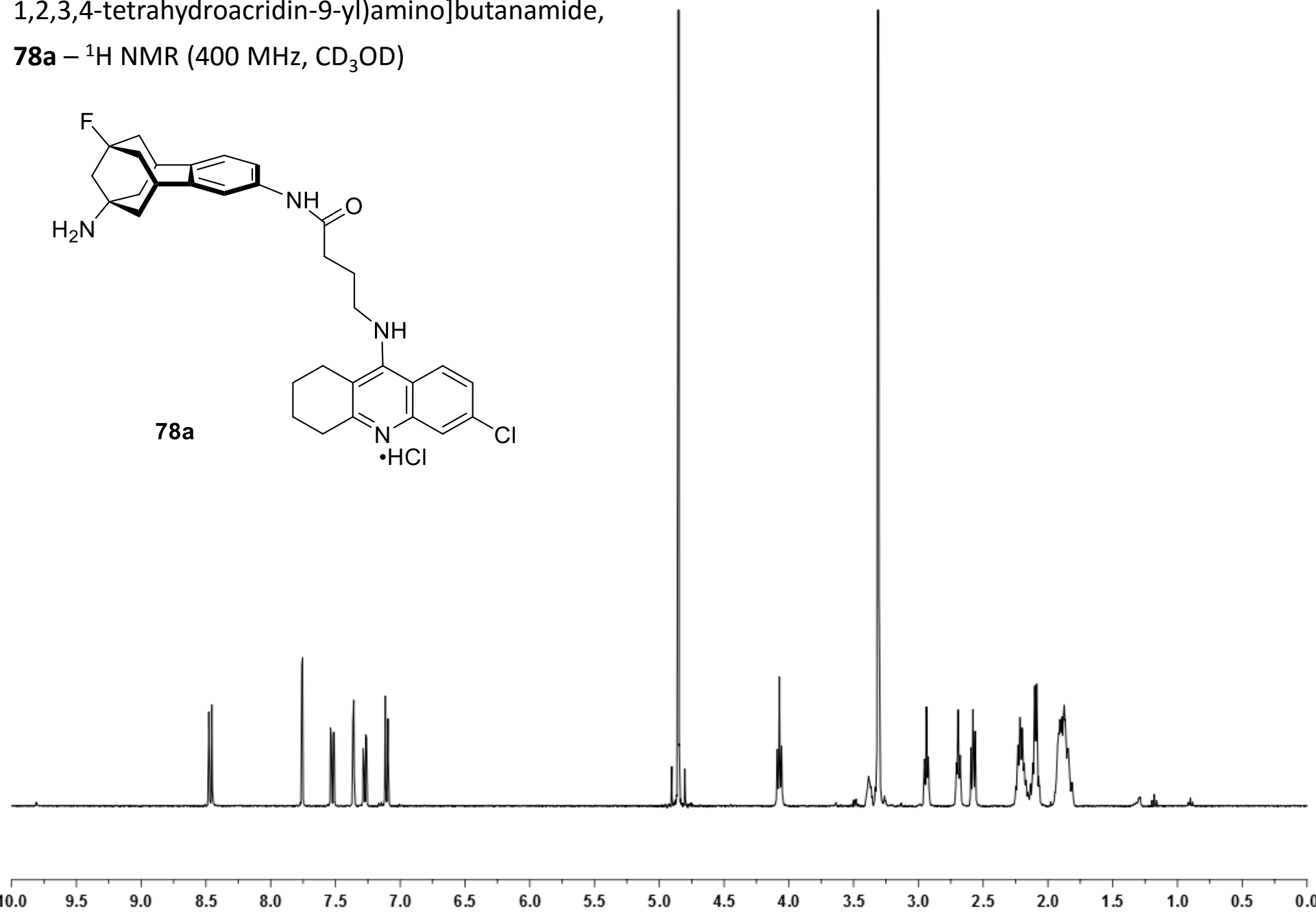
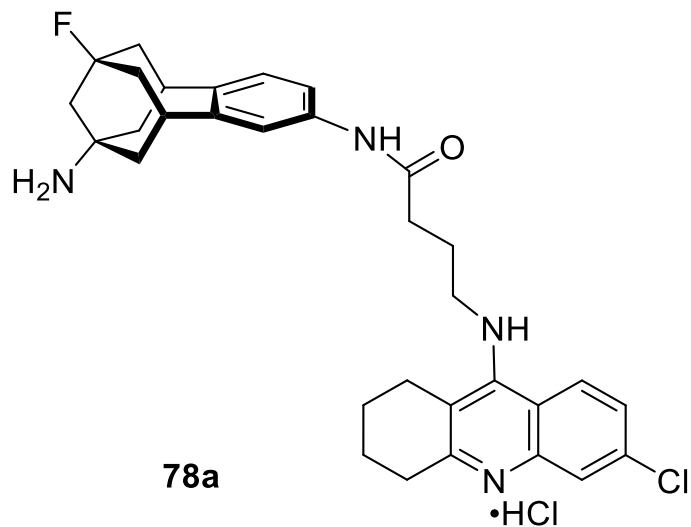
**106a**



*N*-{7-[(*tert*-butyloxycarbonyl)amino]-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl}-5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentanamide, **106b** –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

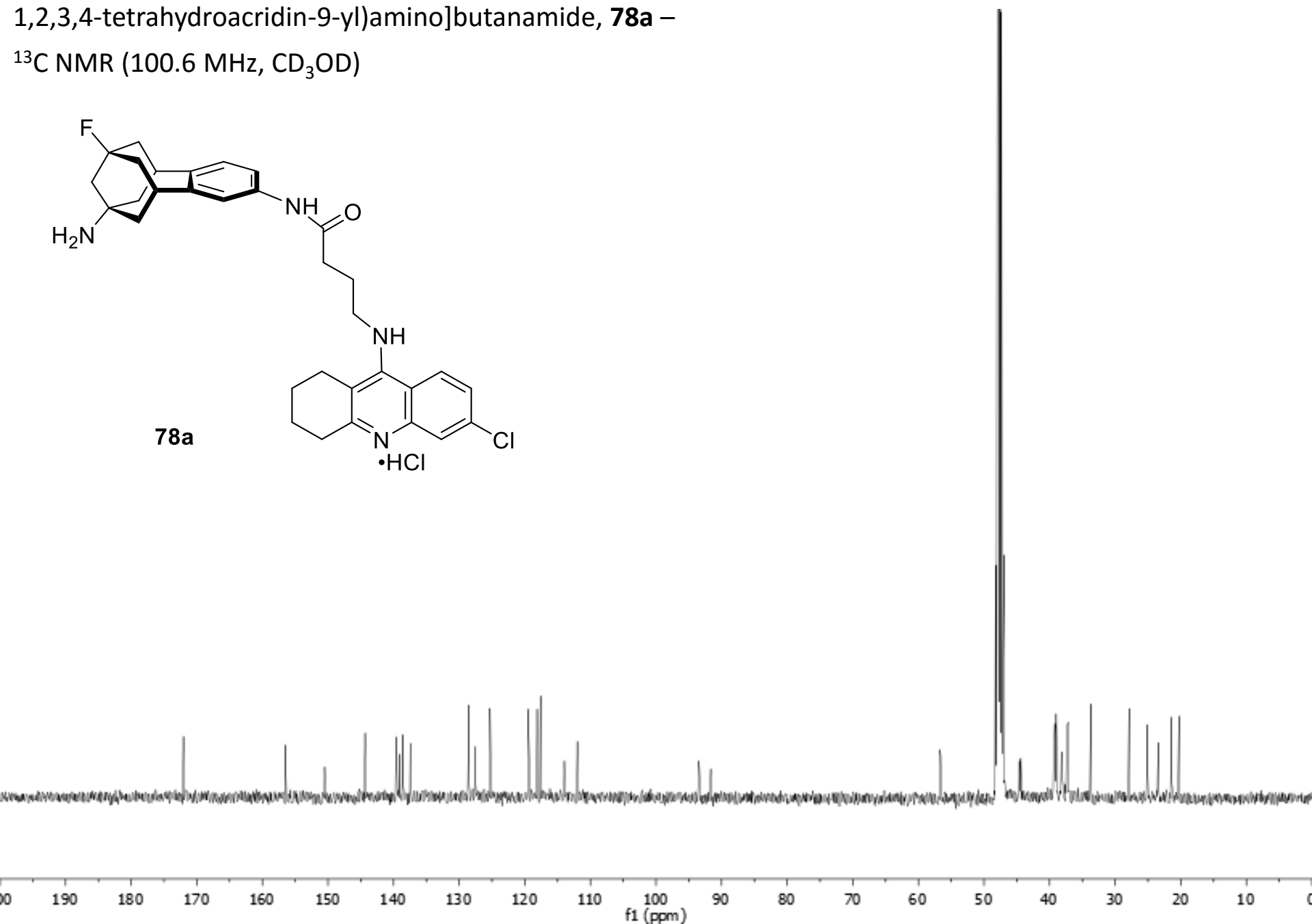
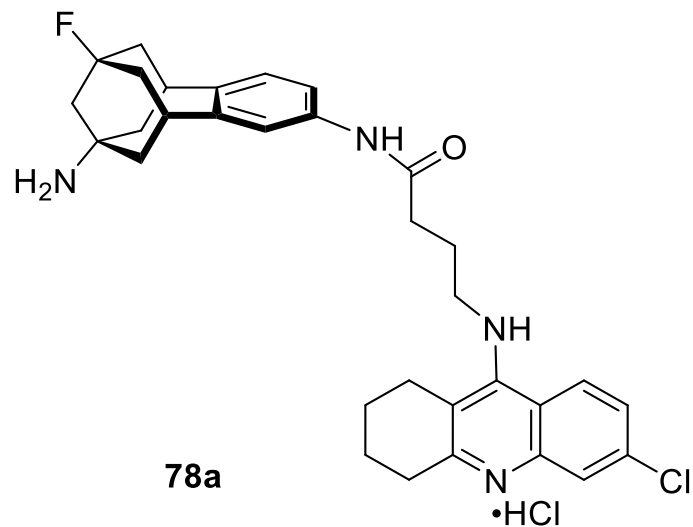


*N*-(7-amino-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl)-4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butanamide,  
**78a** –  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )

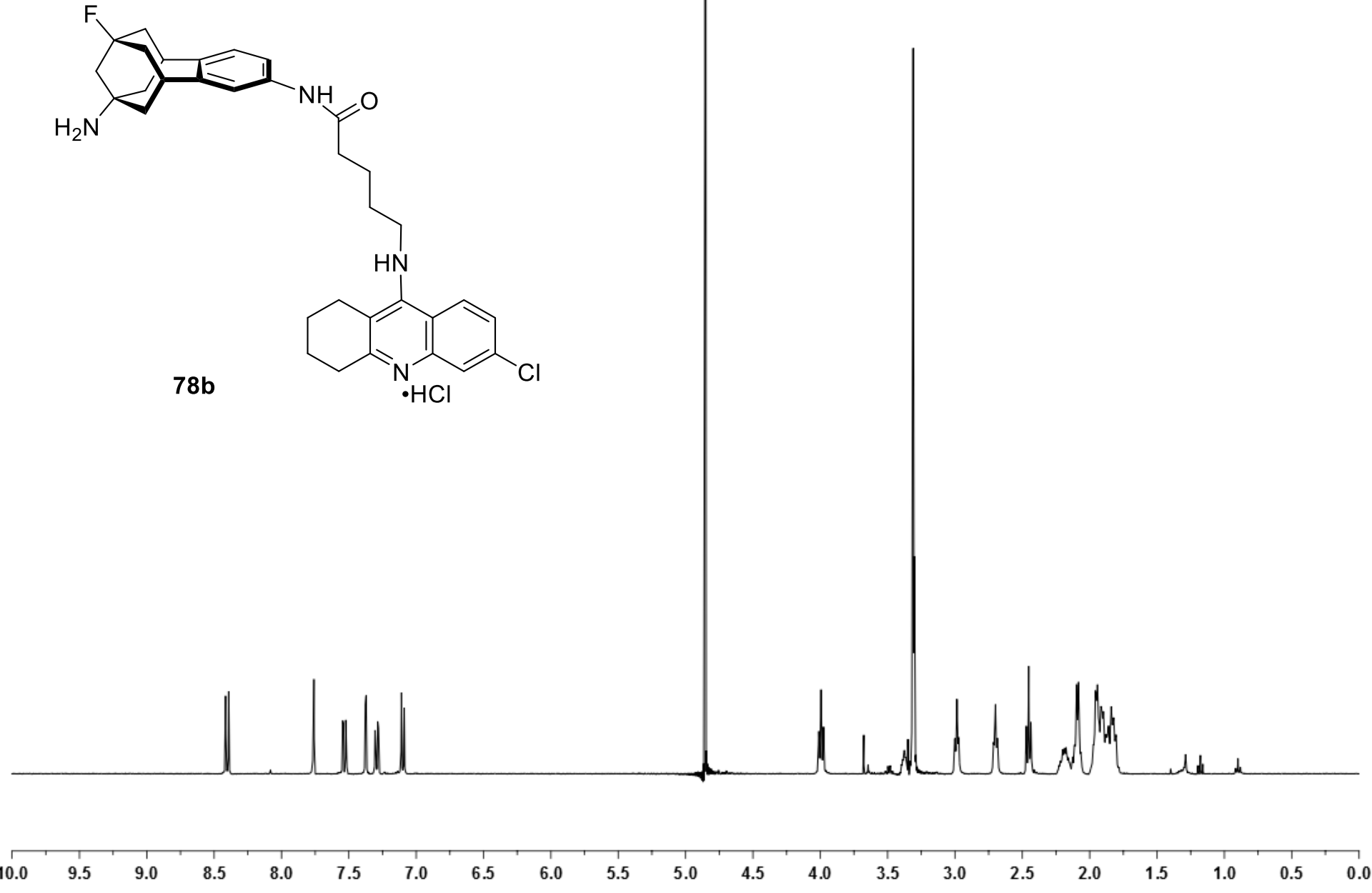
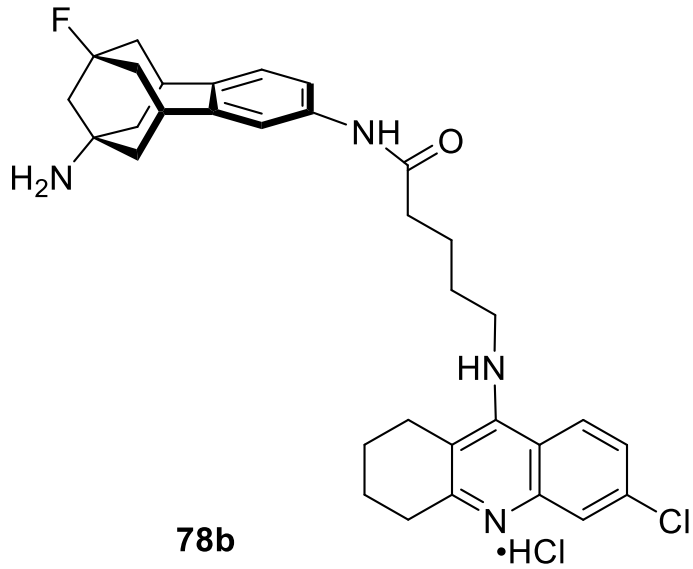


*N*-(7-amino-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl)-4-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]butanamide, **78a** –

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )



*N*-(7-amino-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl)-5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentanamide, **78b** —  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )



*N*-(7-amino-9-fluoro-7*H*-5,6,8,9,10,11-hexahydro-5,9:7,11-dimethanobenzo[9]annulen-2-yl)-5-[(6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]pentanamide, **78b** –

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ )

