

Supporting Information

Drug Design Targeting TCF-Driven Epithelial-Mesenchymal Transition as a Therapeutic Strategy for Colorectal Cancer

Adedoyin D. Abraham,[†] Hector Esquer,[†] Qiong Zhou,[†] Nicholas Tomlinson,[†] Brayden D. Hamill,[†] Joshua M. Abbott,[†] Linfeng Li, Laura A. Pike, Sébastien Rinaldetti,[†] Dominique A. Ramirez,[‡] Paul J. Lunghofer,[‡] Jose D. Gomez,[†] Jerome Schaack,[#] Travis Nemkov,[‡] Angelo D'Alessandro,[‡] Kirk C. Hansen,^{‡,°} Daniel L. Gustafson,^{‡,°} Wells A. Messersmith,^{§,°} and Daniel V. LaBarbera^{†,°,*}

[†]The Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Pharmaceutical Sciences; The School of Medicine, Department of [‡]Biochemistry and Molecular Genetics; [#]Department of Immunology and Microbiology, [§]Division of Medical Oncology; and The [°]University of Colorado Cancer Center; The University of Colorado Anschutz Medical Campus, Aurora CO, 80045, U.S.A.

[‡]Clinical Sciences, School of Biomedical Engineering, Colorado State University, Fort Collins CO, 80523, U.S.A.

Corresponding Author *D.V.L.: e-mail, daniel.labarbera@ucdenver.edu

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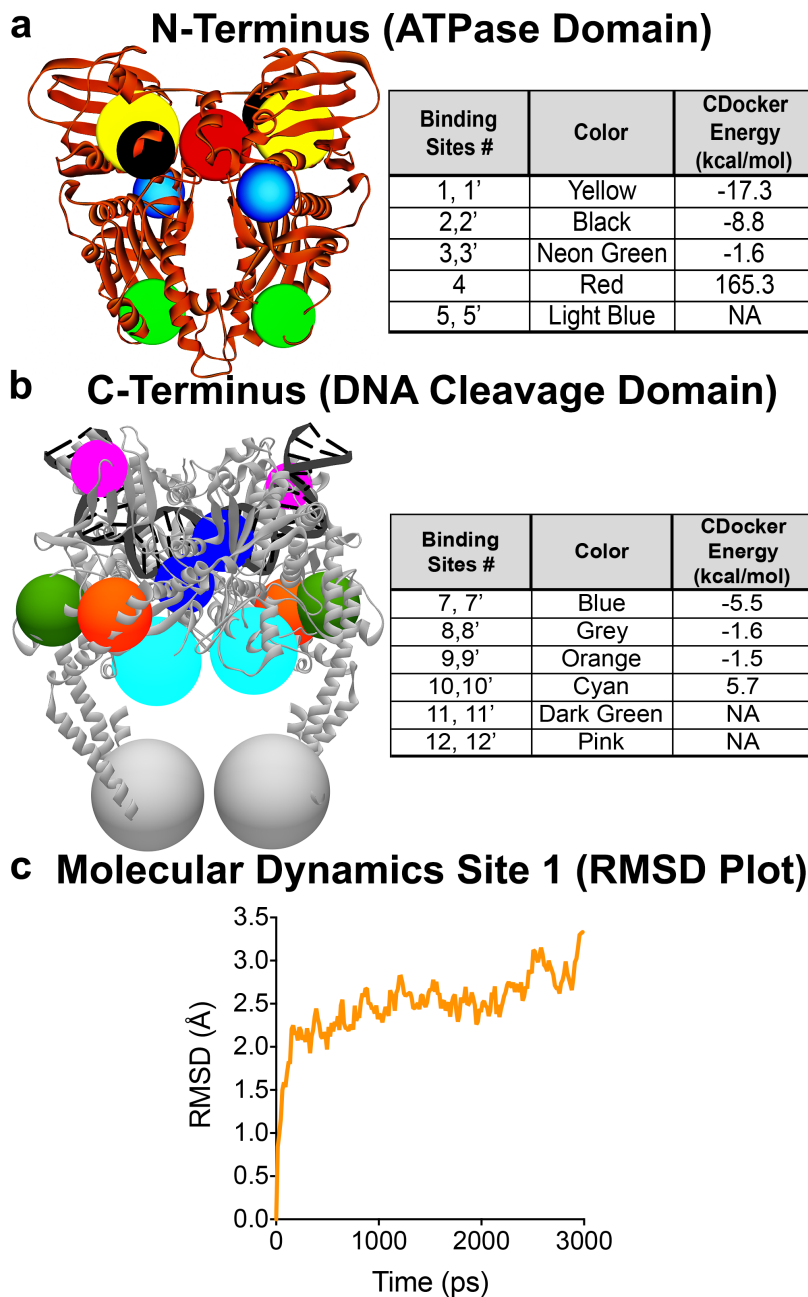


Figure S1. Binding site identification with neo on TOP2A. (a) The potential binding sites identified on the N-terminus, the sites in yellow represent the ATPase site. The site in red represents the allosteric site. Other sites in light blue, black and neon green were also identified for neo in each with respective binding energies (kcal/mol) for each binding site identified on the N-terminus. (b) The potential binding sites identified on the C-terminus, with binding energy (kcal/mol) for neo in each binding site identified on C-terminus. (c) The molecular dynamics of neo-TOP2A (ATPase site1). The average RMSD is 2.48Å

Table S1. The summary of molecular docking interactions of designed TOP2A inhibitors.

















































Analog	R1	R2	R3	R4	Analog-TOP2A Interactions		
					Hydrogen Bonding Interactions	Hydrophobic Interactions	Interaction with Mg ²⁺
3			OCH ₃	OH	Asn91, Arg98, Asn150	π - Lonepair with Ser149 π - Alkyl with Arg98, Ala167 π - donor with Asn150	π - Cation
6			H	OCH ₃	Asn91	π - Alkyl with Ile125 Fluorine with, Asn95	Metal-Acceptor
7			H	OH	Asn91, Asn150, Ser148, Arg98, Ala 167	π - Anion with Asp94	π - Cation, Metal-Acceptor
28			H	OH	Asn91, Asn150, Ala167, Ser148	π - Anion with Asp94	π - Cation Metal-Acceptor
29			H	OH	Asn91, Asn150, Ser149	Fluorine with Asn91, Fluorine with Asn120	Metal-Acceptor
30			H	OH	Asn91, Asn149, Ala167, Ser149, Thr215	π - Anion with Asp94 Fluorine with Asn120	π - Cation, Metal-Acceptor
31			H	OH	Asn91, Asn150, Ala167, Ser148	π - Anion with Asp94 π - Alkyl with Phe142, Ile217 Fluorine with, Asn91	π - Cation, Metal-Acceptor
32			H	OH	Arg98, Gly166, Lys168	π - π with Phe142 π - Alkyl with Ile141, Ala167 Fluorine with Asn95	π - Cation Metal-Acceptor
34			H	OH	Asn91, Asn150, Ala167, Ser148, Thr215	π - Anion with Asp94	π - Cation, Metal-Acceptor
35			H	OH	Asn91, Asn150, Ser148, Asn120, Ala167	None	π - Cation, Metal-Acceptor
36			H	OH	Asn91, Asn95, Asn120, Asn150, Ala167, Ser148	π - Anion with Asp94	π - Cation, Metal-Acceptor
38			H	OH	Asn91, Arg98, Ser148, Ser149	π - Alkyl with Ala92, Ile125	Metal-Acceptor

Table S1 Continued.

Analog	R1	R2	R3	R4	Analog-TOP2A Interactions		
					Hydrogen Bonding Interactions	Hydrophobic Interactions	Interaction with Mg ²⁺
39			H	OH	Asn91, Ser149	π - Alkyl with Ile125, Ile141 π - Amide with Asn91	Metal-Acceptor
40			H	OH	Ser148, Ser149, Asn120, Lys168	π - Alkyl with Ile125, Ile167 π - Amide with Asn91	Metal-Acceptor
41			H	OH	Ser148, Ser149, Lys168	π - Alkyl with Ile125, Ile141, Fluorine bonding with Asn120,	Metal-Acceptor
42			H	OH	Asn91, Ser149, Thr215	π - Alkyl with Ile141 Fluorine with Asn95, Lys123	metal-Acceptor
43			H	OH	Asn91, Ser149, Lys168, Gly164	π - Alkyl with Ile125, Ile141 π - Anion with Asn95	Metal-Acceptor
53			H	OH	Thr147, Ser148	π - Anion with Asp94 π - Alkyl with Ile125	π - Cation, Metal-Acceptor
54			H	OH	Asn91, Asn150, Ala167, Ser148	π - Anion with Asp94 π - Alkyl with Ile125	π - Cation, Metal-Acceptor
56			H	OH	Asn91, Asn150, Ser148, Ala 167	π - Anion with Asp94	π - Cation, Metal-Acceptor
58			H	OH	Asn91, Asn150, Ala167, Ser148	π - Anion with Asp94 π - Sulfur with Phe142	π - Cation, Metal-Acceptor
59			H	OH	Asn91, Ser149	None	Metal-Acceptor
60			H	OH	Ser149, Asn150, Thr147	π - Alkyl with Ile125, Ile141	Metal-Acceptor
61			H	OH	Thr147, Ser149, Lys168	π - Amide Asn91 π - Alkyl with Ile141	Metal-Acceptor

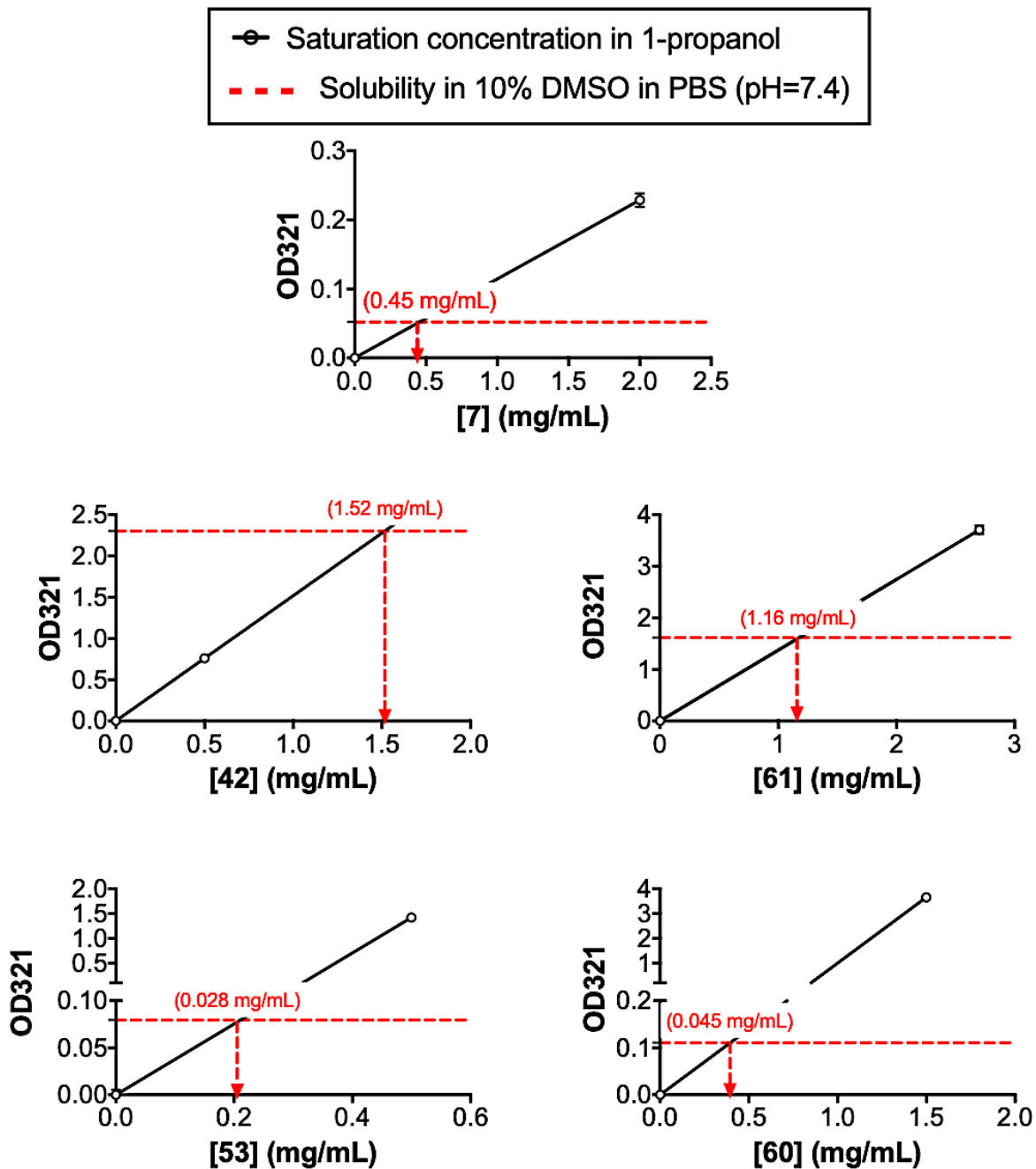


Figure S2. Aqueous solubility studies with morpholine analogs and their respective parent compounds 7 and 53.

Table S2. HPLC purity analysis of final TOP2A inhibitors.

Analogs	Mobile Phase	Retention Time (min)	% Purity	Wave Length (nm)	Analogs	Mobile Phase	Retention Time (min)	% Purity	Wave Length (nm)
2	Water/Acetonitrile	14.7	100	254	38	Water/Acetonitrile	4.45	100	254
3	Water/Acetonitrile	25.77	98.4	254	39	Water/Acetonitrile	22.9	95	254
6	Water/Acetonitrile	16.85	95	254	40	Water/Acetonitrile	29.2	95.2	270
7	Water/Acetonitrile	4.9	100	254	41	Water/Acetonitrile	24.42	95	254
20	Water/Acetonitrile	5.13	100	270	42	Water/Methanol	17.27	100	270
28	Water/Acetonitrile	15.81	100	254	43	Water/Acetonitrile	16.14	100	254
29	Water/Acetonitrile	16.67	100	254	53	Water/Methanol	17.77	100	270
30	Water/Acetonitrile	16.71	100	254	54	Water/Acetonitrile	19.2	100	254
31	Water/Acetonitrile	30.36	95	254	55	Water/Acetonitrile	20.3	100	254
32	Water/Acetonitrile	19.93	100	254	56	Water/Acetonitrile	5.37	100	254
33	Water/Acetonitrile	24.51	96.3	254	57	Water/Methanol	21.37	96	254
34	Water/Acetonitrile	30.4	100	254	58	Water/Acetonitrile	5.93	100	254
35	Water/Acetonitrile	4.32	100	270	59	Water/acetonitrile	3.77	100	254
36	0.1% TFA-Water/ 0.1% TFA- Acetonitrile	3.09	100	270	60	Water/Acetonitrile	19.19	100	254
37	Water/Acetonitrile	31.87	95	254	61	Water/Acetonitrile	21.12	100	270

Table S3. Mouse microsomal stability studies with TOP2A inhibitors.

Microsomal Stability Studies			
Compound Number	Structure	Half-life in Active Microsomes (min)	Half-life in Inactive Microsomes (min)
53		>60	>60
53		>60	>60
53		30.18	>60
53		28.79	>60
61		13.9	>60
42		8.53	>60
7		6.72	>60
3		4.72	>60
28		4.08	>60
58		2.66	>60

Chemical Syntheses

Methyl-2-methoxy-3-nitrobenzoate (S1). To 15 g (81.9 mmol) of 2-hydroxy-3-nitrobenzoic acid in 300 mL of acetone were added 25.8 g (19.4 mL, 204.8 mmol) of dimethyl sulfate and 28.3 g (204.8 mmol), of potassium carbonate and the mixture was stirred for 20 h. The reaction mixture was filtered over a pad of celite, concentrated under a reduced pressure to give an oily residue which was treated with NaHCO₃, and the resulting mixture was extracted with ethyl acetate 3 x (100 mL). The organic layers were combined and dried over anhydrous sodium sulfate, concentrated in vacuo to give 15 g of crude product (87% yield). TLC (ethyl acetate), R_f = 0.74.

2-Methoxy-3-nitrobenzoic acid (S2). To 8.94 g (213 mmol) of (S1) were added lithium hydroxide monohydrate, 50 mL of (THF/H₂O/MeOH). The resulting solution was allowed to stir at room temperature overnight. The solvents were removed *in vacuo*, and the orange residue obtained was acidified with drops of HCl to give a white precipitate that was filtered and dried *in vacuo* to afford 13.8 g (99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.06 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 3.89 (s, 3H).

2-Methyl-2-propanyl [2-(methoxy)-3-nitrophenyl] carbamate (S3). To 11.9 g (60.3 mmol) of (S2) dissolved in 190 mL of tert-butyl alcohol was added 12.6 mL (90.4 mmol) of trimethylamine, followed by dropwise addition of 16.8 mL (78.3 mmol) of diphenylphosphoryl azide (DPPA) at room temperature. The reaction mixture was refluxed for 6 h, and cool to room temperature. The solvents were removed *in vacuo* to give a crude product, which was purified by column chromatography using silica gel and chloroform (CHCl₃) as the solvent to afford the product 13.0 g (80% yield). TLC (40 % ethyl acetate in hexane). R_f = 0.66; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.12 (broad s, 1H), 3.92 (s, 3H), 1.54 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 152.5, 143.0, 142.1, 134.4, 124.4, 123.4, 118.4, 81.7, 62.4, 28.4; IR (neat) ν_{max} 3430.9, 3389.9, 2978.6, 2936.8, 1727.4, 1592.4, 1527.8, 1509.71458.0, 1415.8; ESI-HRMS [M - H]⁻ calculated for C₁₃H₁₅N₄O₅ 267.0986, found 267.0998.

2-Methoxy-3-nitroaniline (S4) from hydrolysis of (S3). To 11.45 g (42.7 mmol) of S3 in 70 mL of methylene chloride was added 32.66 mL (426.92 mmol) of trifluoroacetic acid at room temperature. The reaction was stirred for 4 h and concentrated *in vacuo* to afford the crude product which was purified using silica gel and chloroform as the eluent to afford yellow solid 5.95 g (83% yield). TLC (chloroform) R_f = 0.17; Melting Point 66-67 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.18 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 1.5, 8.0 Hz, 1H) 4.07 (s, 2H), 3.90 (s, 3H).

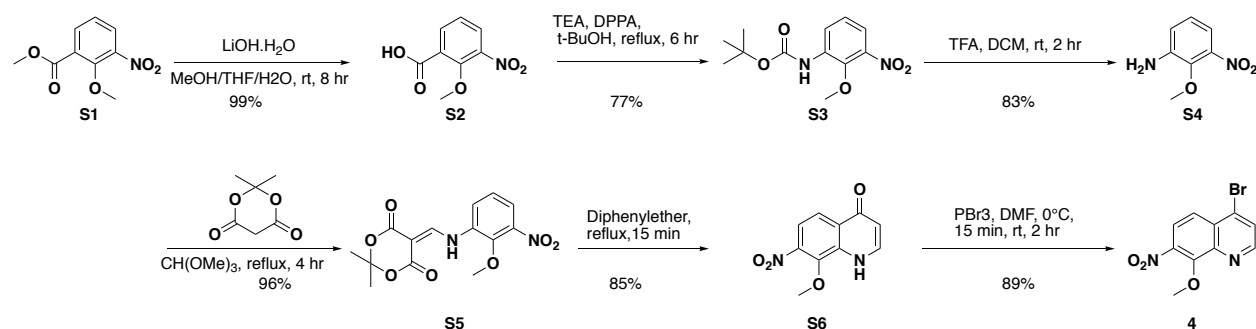
5-[(2-Methoxy-3-nitrophenyl)amino]methylidene}-2,2-dimethyl-4,6-dioxo-1,3-dioxane (S5).

A solution of 687.5 mg (4.77 mmol) Meldrum acid in 7.0 mL of trimethyl orthoformate was refluxed for 2 h, to which 700 mg (4.16 mmol) of 2-methoxy-3-nitroaniline was added and the resulting solution was refluxed for 2 h, and allowed to cool to room temperature, after which the solution was concentrated *in vacuo* to give a yellowish orange solid. The crude product was purified by column chromatography using 40% ethyl acetate in chloroform as the eluent, and silica

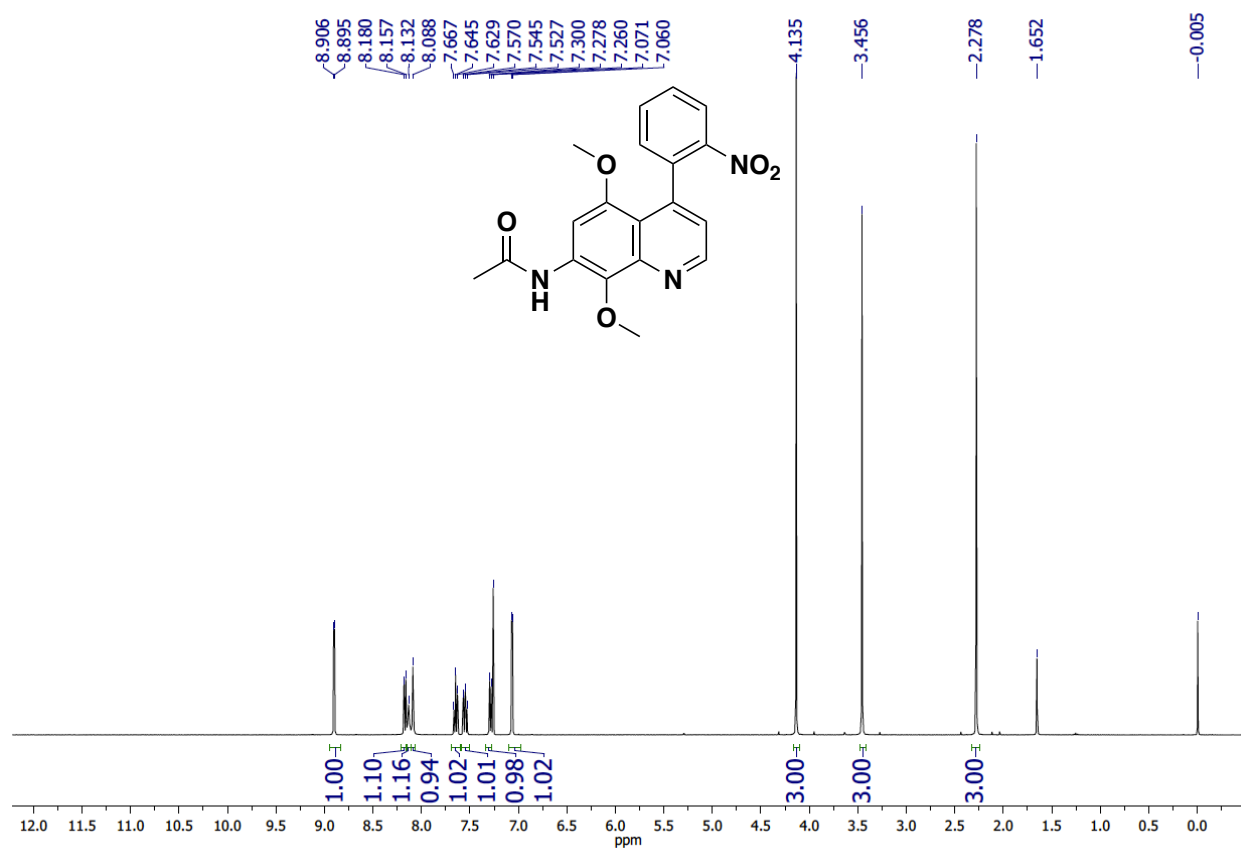
gel as the adsorbent medium to afford light orange solid 1.24g (93 %yield) TLC (40% ethyl acetate in chloroform) $R_f = 0.45$; Melting Point 165-166°C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 11.73 (d, $J = 13.5\text{Hz}$, 1H), 8.67 (d, $J = 14.5\text{Hz}$, 1H), 7.73 (d, $J = 8.5\text{Hz}$, 1H), 7.61 (d, $J = 8.0\text{Hz}$, 1H), 7.32 (t, $J = 8.3\text{Hz}$, 1H), 4.07 (s, 3H), 1.78 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.6, 163.6, 151.4, 144.4, 134.3, 125.3, 122.5, 119.9, 106.0, 89.8, 63.5, 27.6; IR (neat) ν_{max} 3343.8, 2990.5, 2941.6, 2310.8, 1721.7, 1681.7, 1620.8, 1597.1, 1531.4, 1448.1; ESI-HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_7$ 323.0874 found 323.0879.

8-Methoxy-7-nitroquinolin-4(1H)-one (S6). To 250 mg (0.77 mmol) was added 9.0 mL of diphenyl ether, and the mixture was refluxed for 30 min. The reaction mixture was cooled and diluted with hexane. The precipitated crystals were collected by filtration and washed with hexane. The crystals were dried *in vacuo* to give 140 mg (82% yield). TLC (ethyl acetate) $R_f = 0.11$; Melting Point 228-230 °C; $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 11.85 (broad s, 1H), 7.96 (d, $J = 9.5$ Hz, 2H), 7.76 (d, $J = 8.5$ Hz, 1H), 6.18 (d, $J = 6.5$ Hz, 1H) 3.98 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, DMSO-d_6) δ 175.9, 143.5, 143.1, 140.8, 135.1, 128.8, 120.9, 117.6, 110.5, 63.3; IR (neat) ν_{max} 3195.6, 2840.1, 2375.6, 2321.6, 1527.1, 1456.8, 1353.8; ESI-HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_7$ 221.0557, found 221.056

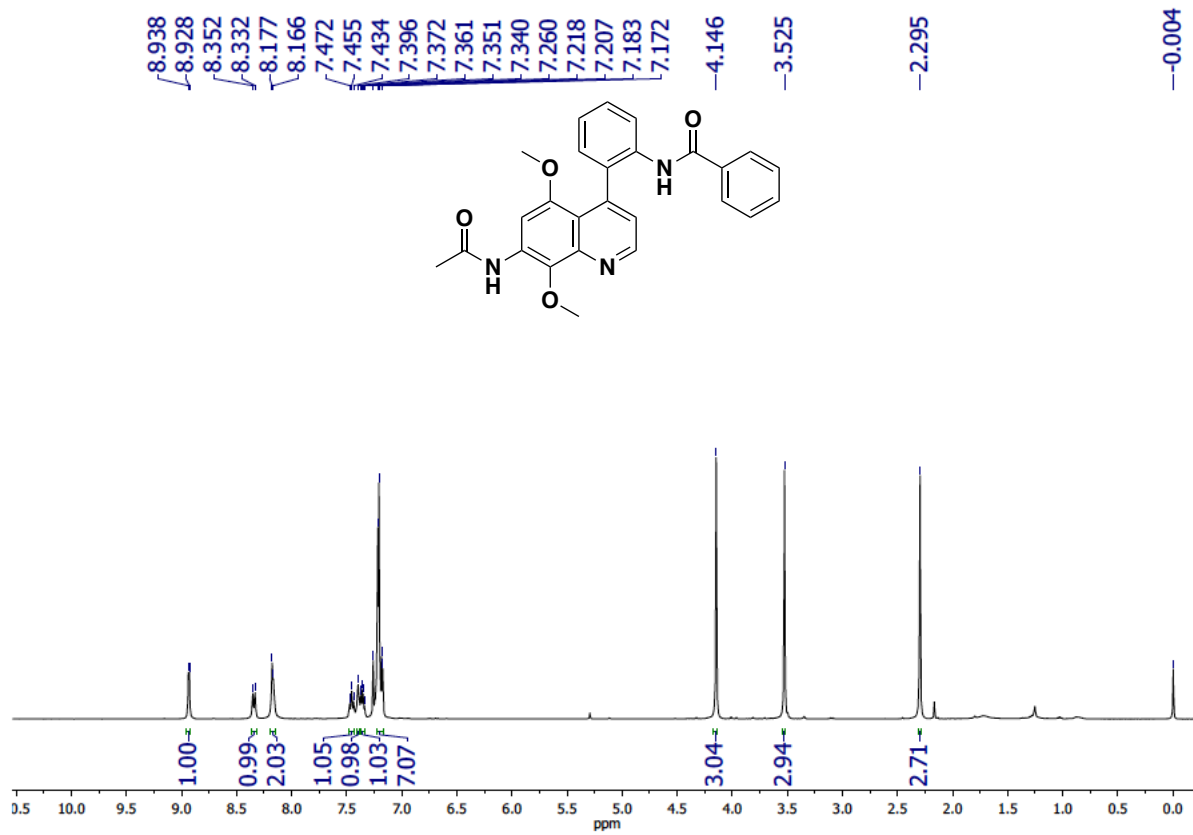
Scheme S1. Synthesis of key halogenated quinoline intermediate 4.



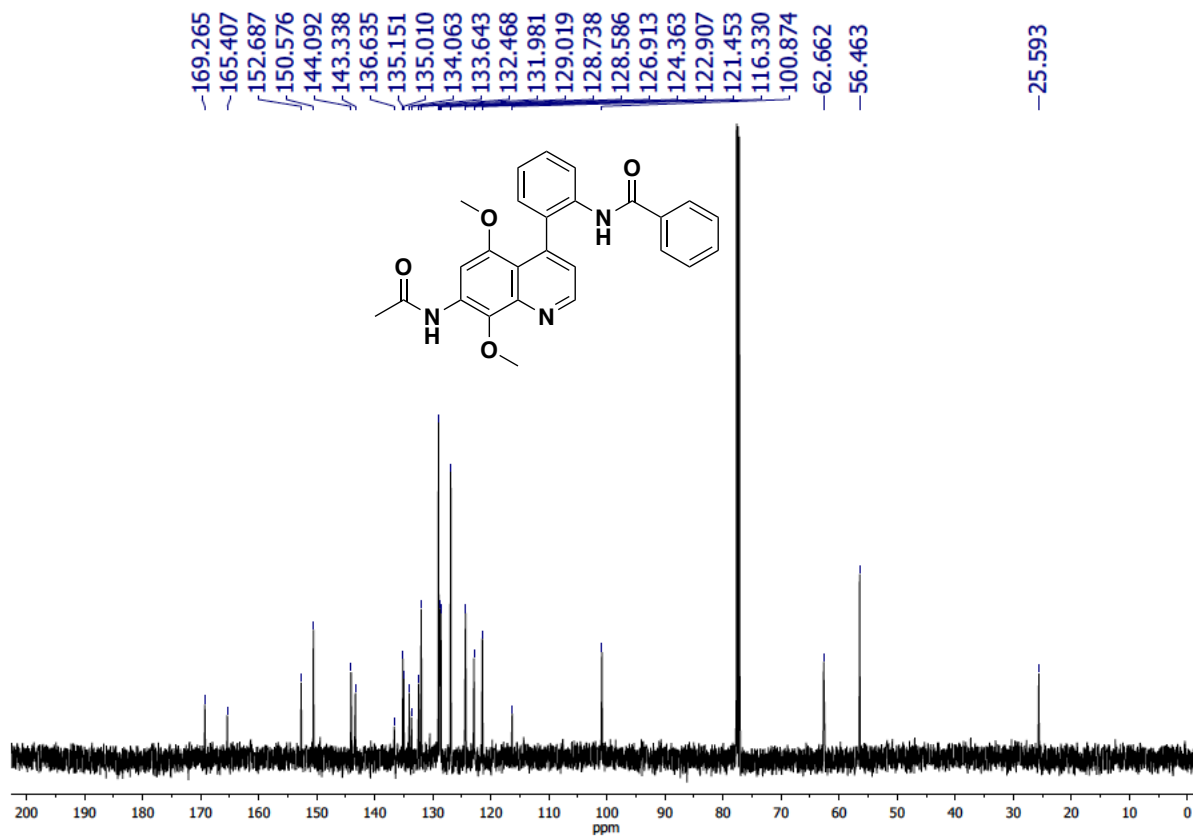
7-Acetamido-4-(2-nitrophenyl)-5,8-dimethoxyquinoline (1)



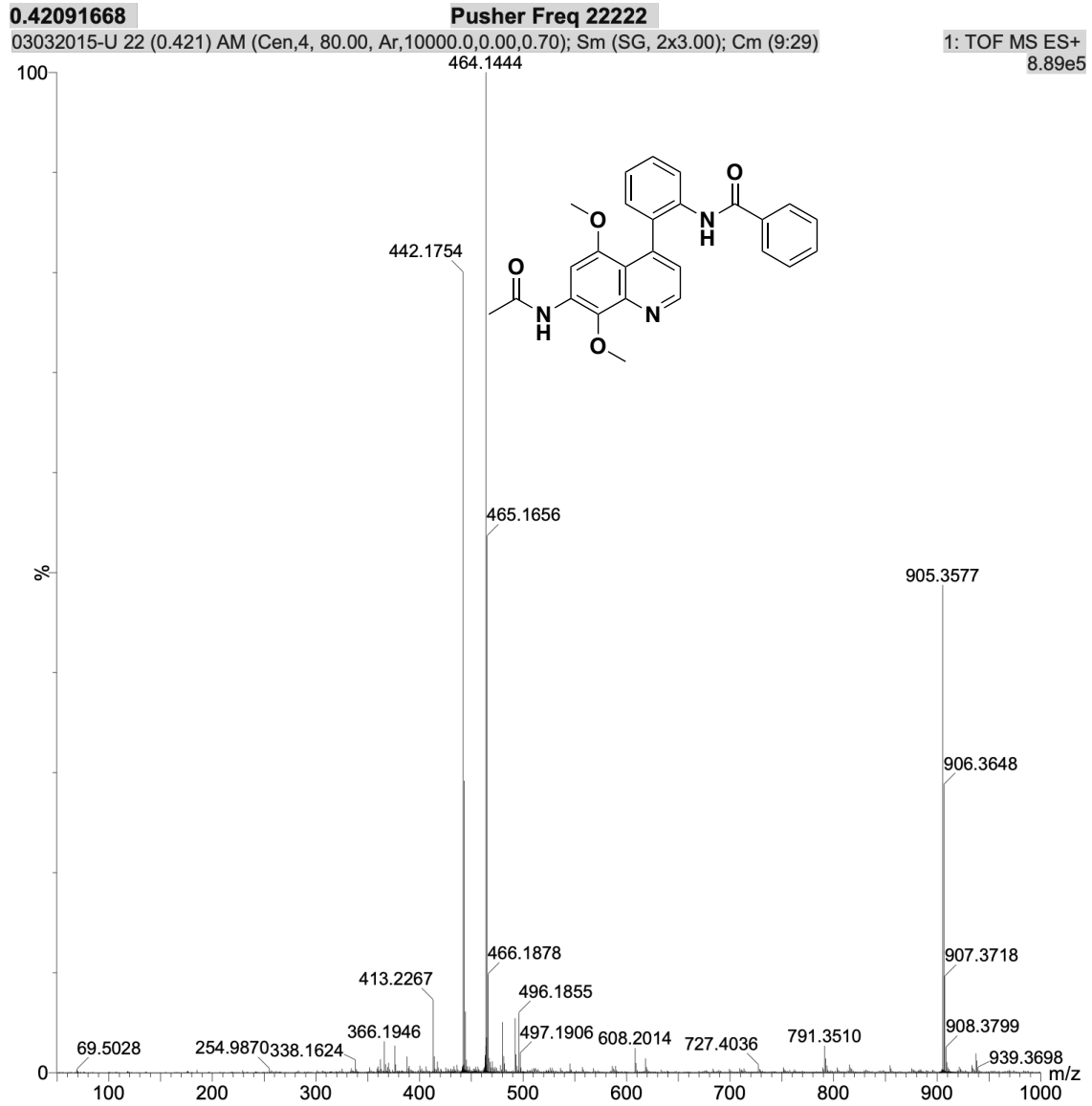
7-Acetamido-4-(2-benzamidophenyl)-5,8-dimethoxyquinoline (2)



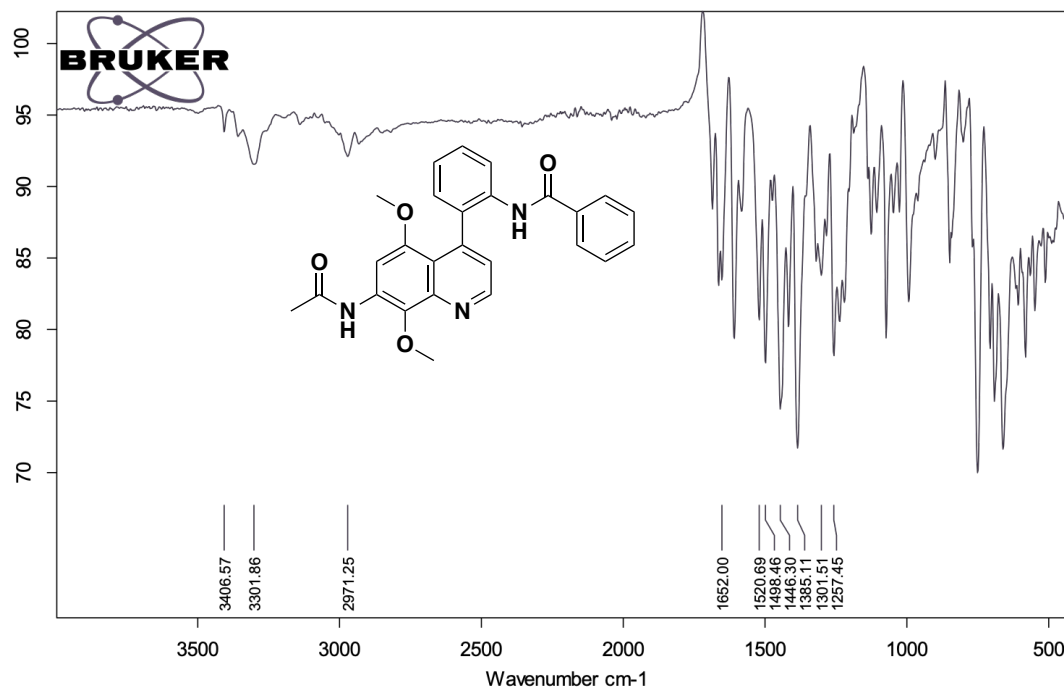
7-Acetamido-4-(2-benzamidophenyl)-5,8-dimethoxyquinoline (2)



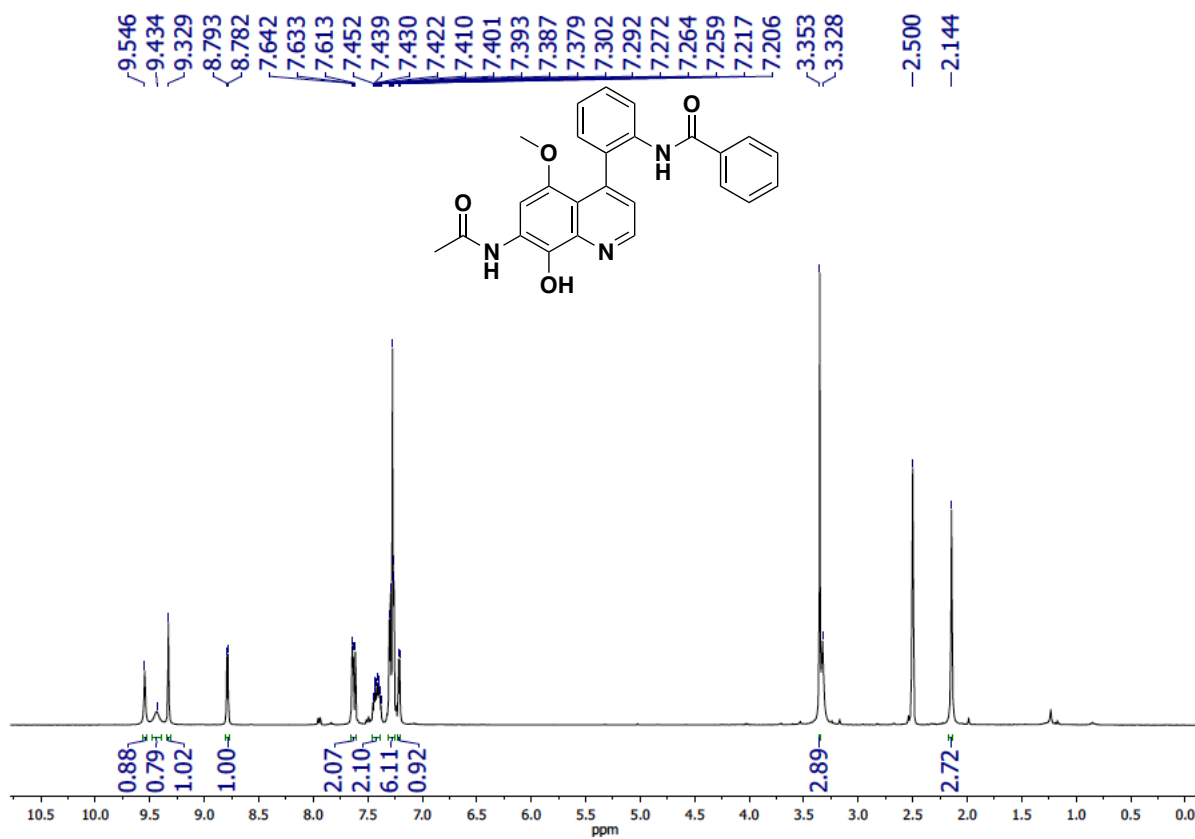
7-Acetamido-4-(2-benzamidophenyl)-5,8-dimethoxyquinoline (2)



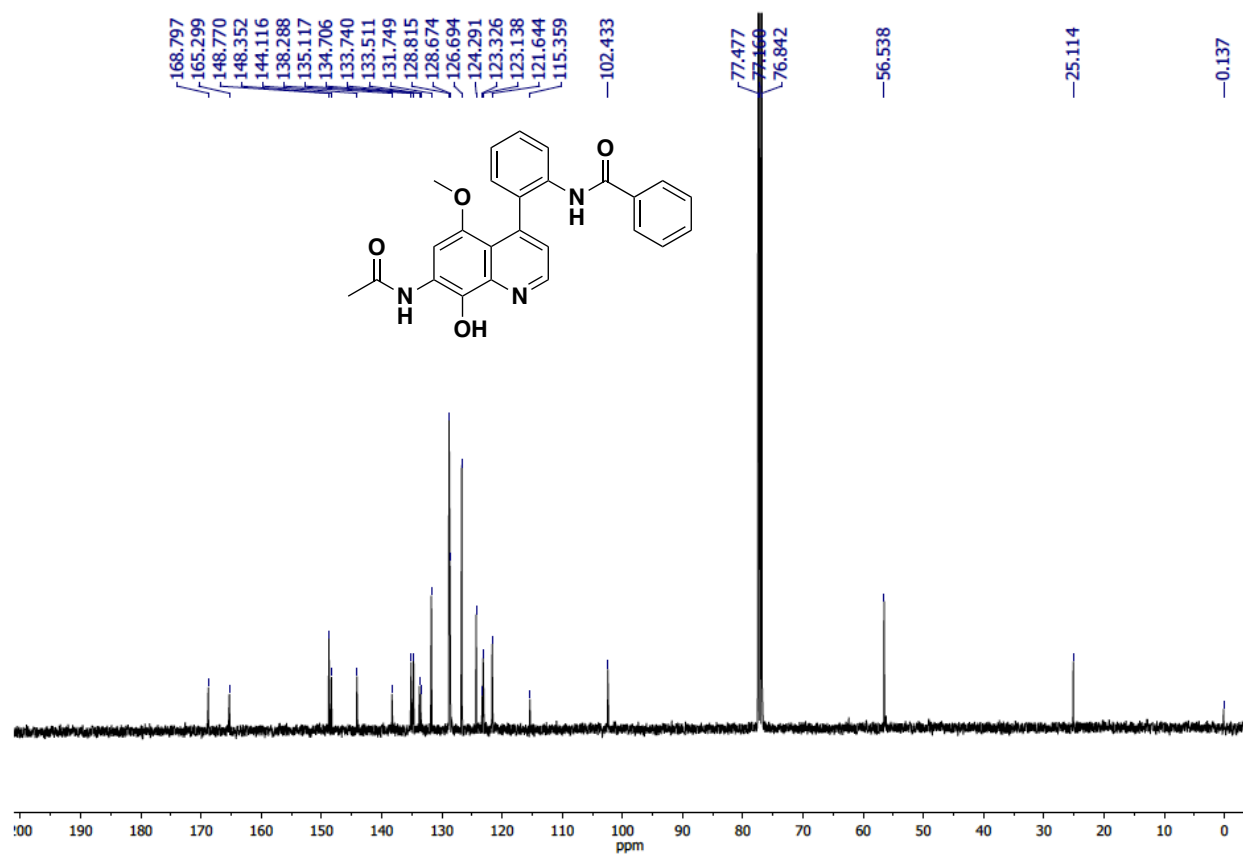
7-Acetamido-4-(2-benzamidophenyl)-5,8-dimethoxyquinoline (2)



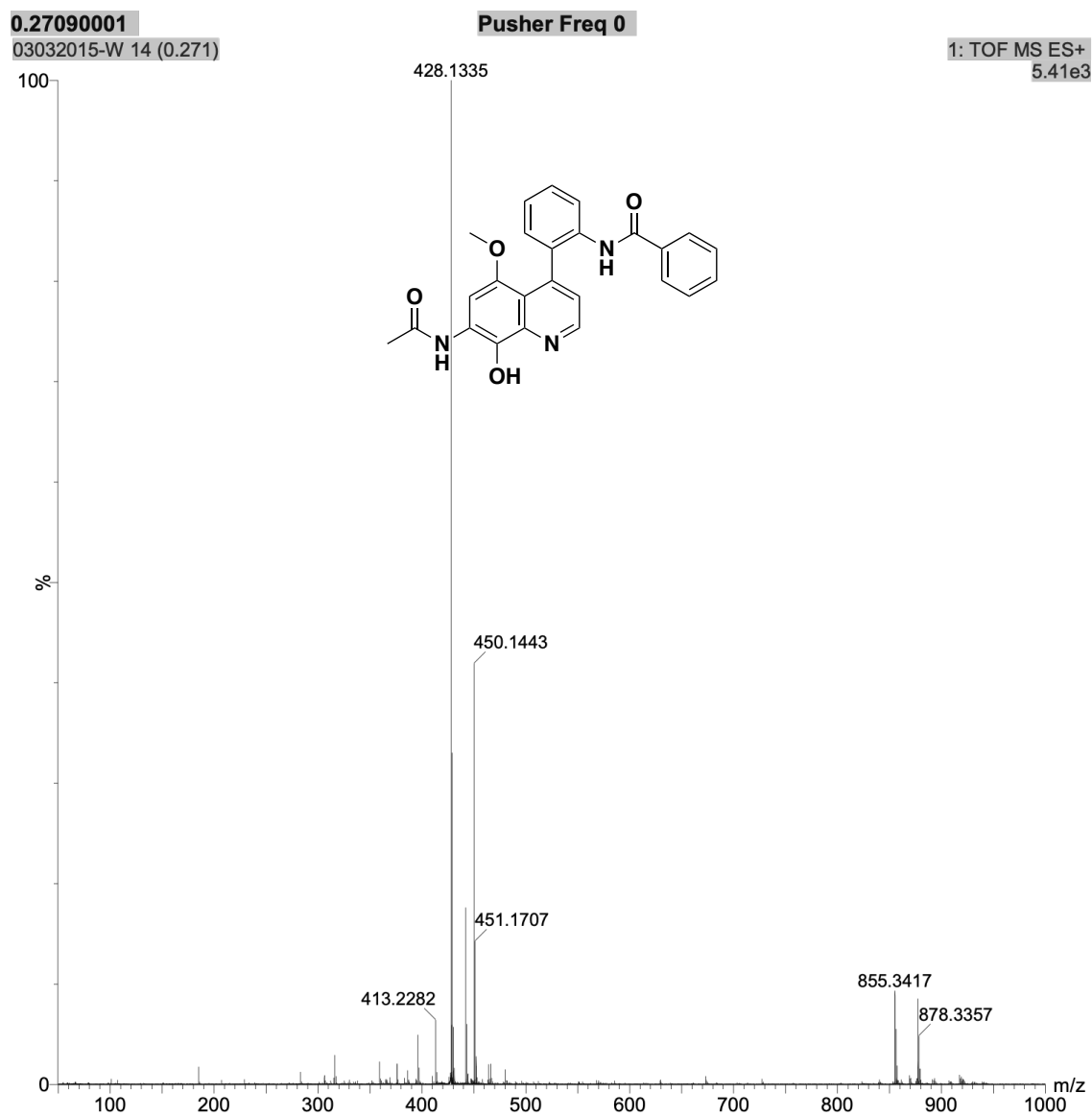
7-Acetamido-4-(2-benzamidophenyl)-8-hydroxy-5-methoxyquinoline (3) in DMSO-d₆



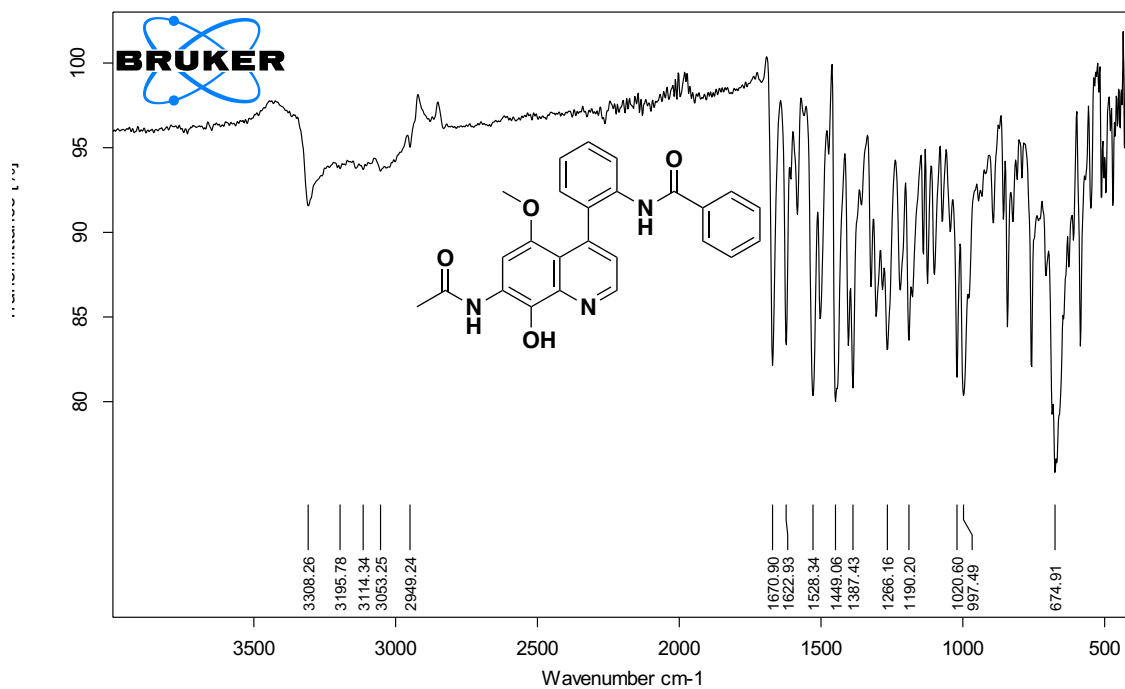
7-Acetamido-4-(2-benzamidophenyl)-8-hydroxy-5-methoxyquinoline (3) in CDCl₃



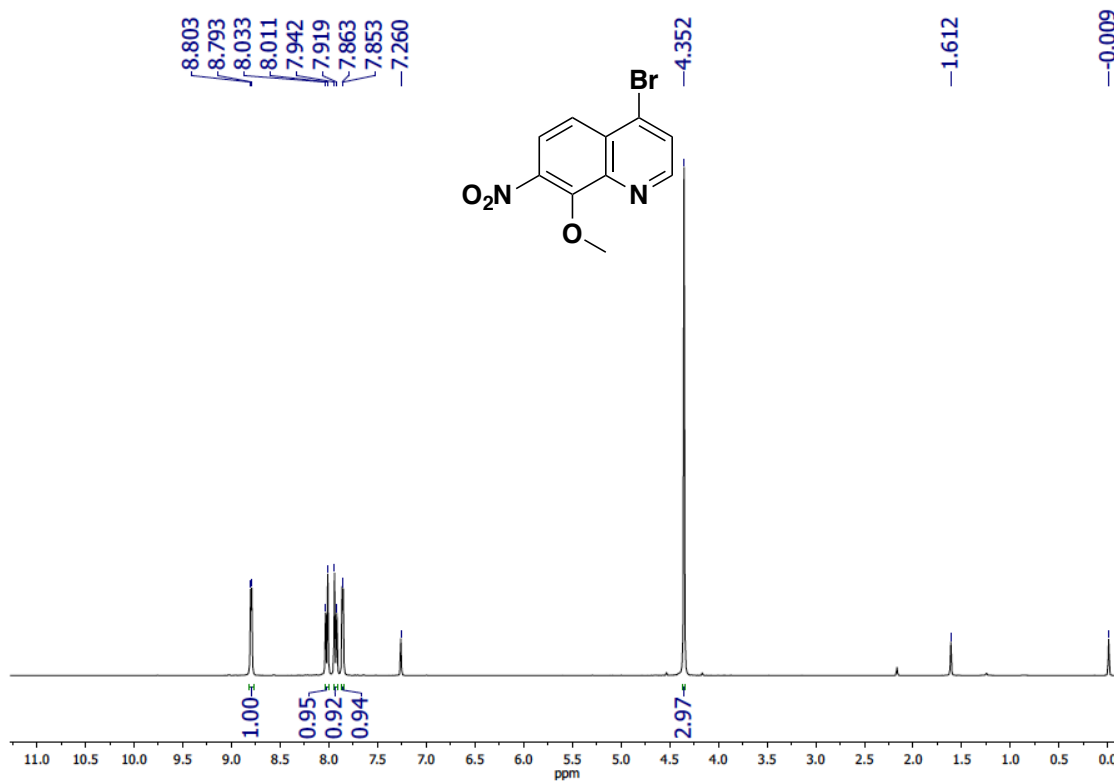
7-Acetamido-4-(2-benzamidophenyl)-8-hydroxy-5-methoxyquinoline (3)



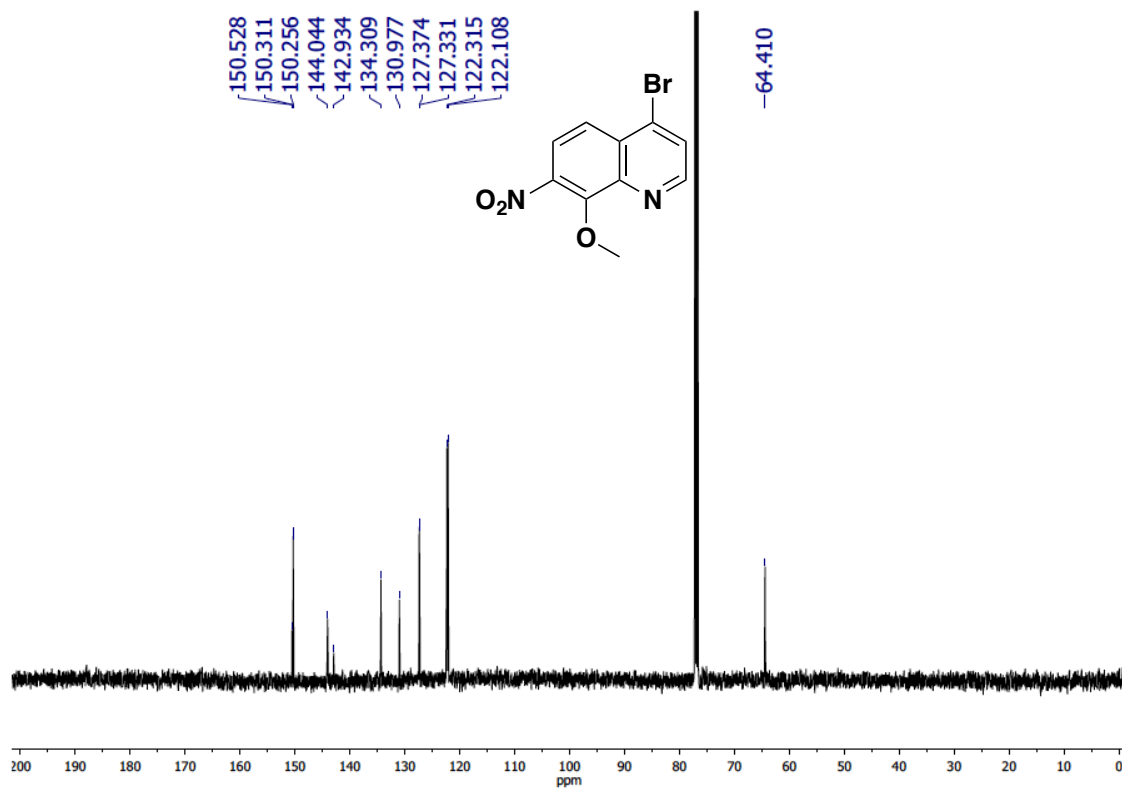
7-Acetamido-4-(2-benzamidophenyl)-8-hydroxy-5-methoxyquinoline (3)



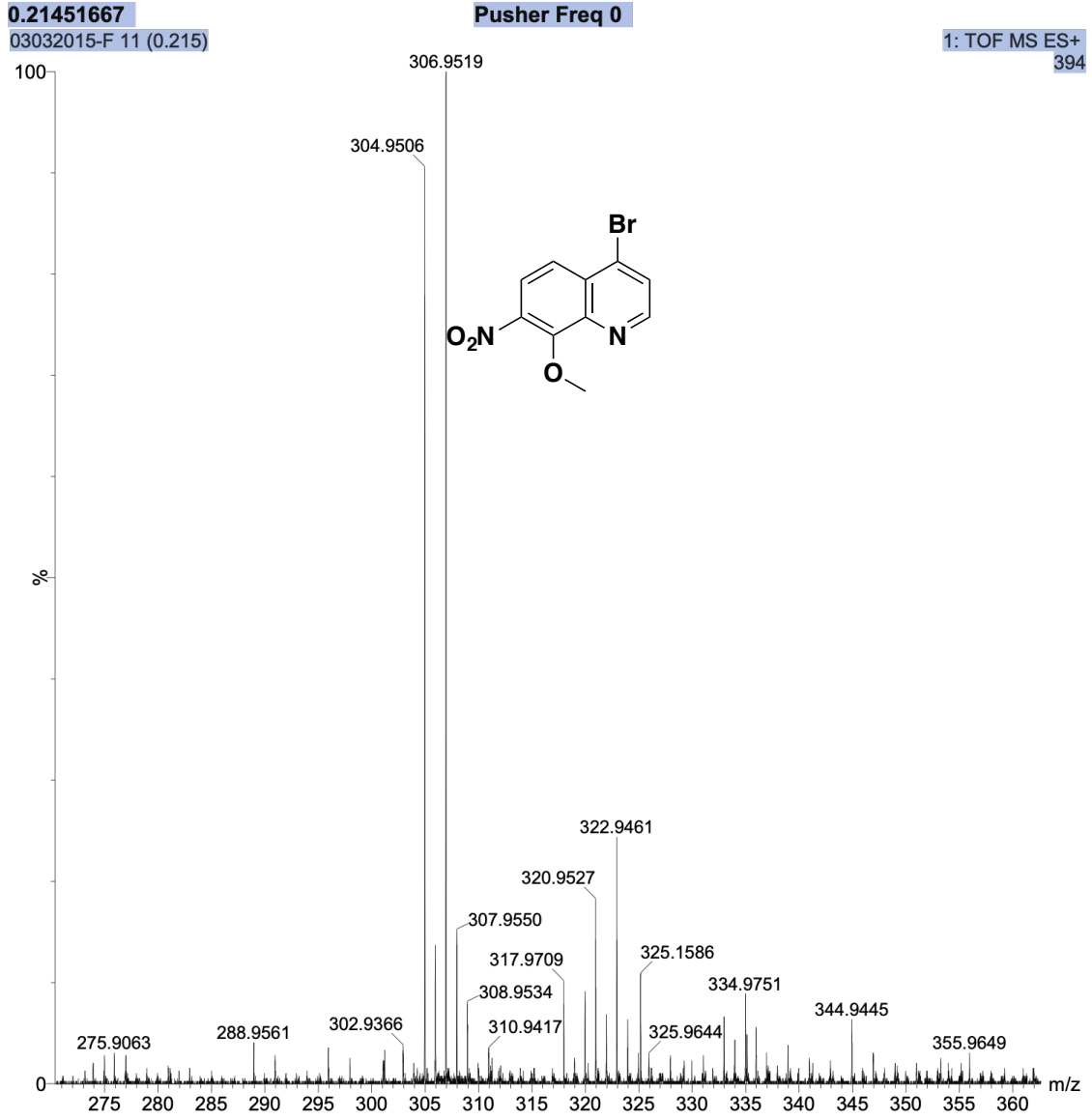
4-Bromo-8-methoxy-7-nitroquinoline (4) in CDCl₃



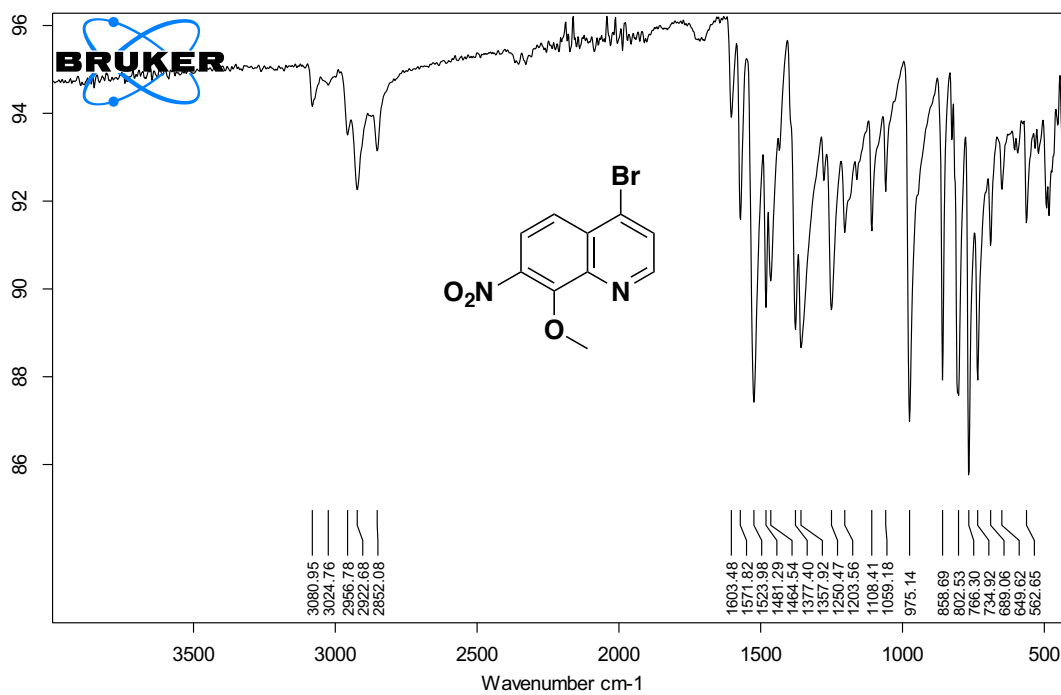
4-Bromo-8-methoxy-7-nitroquinoline (4) in CDCl₃



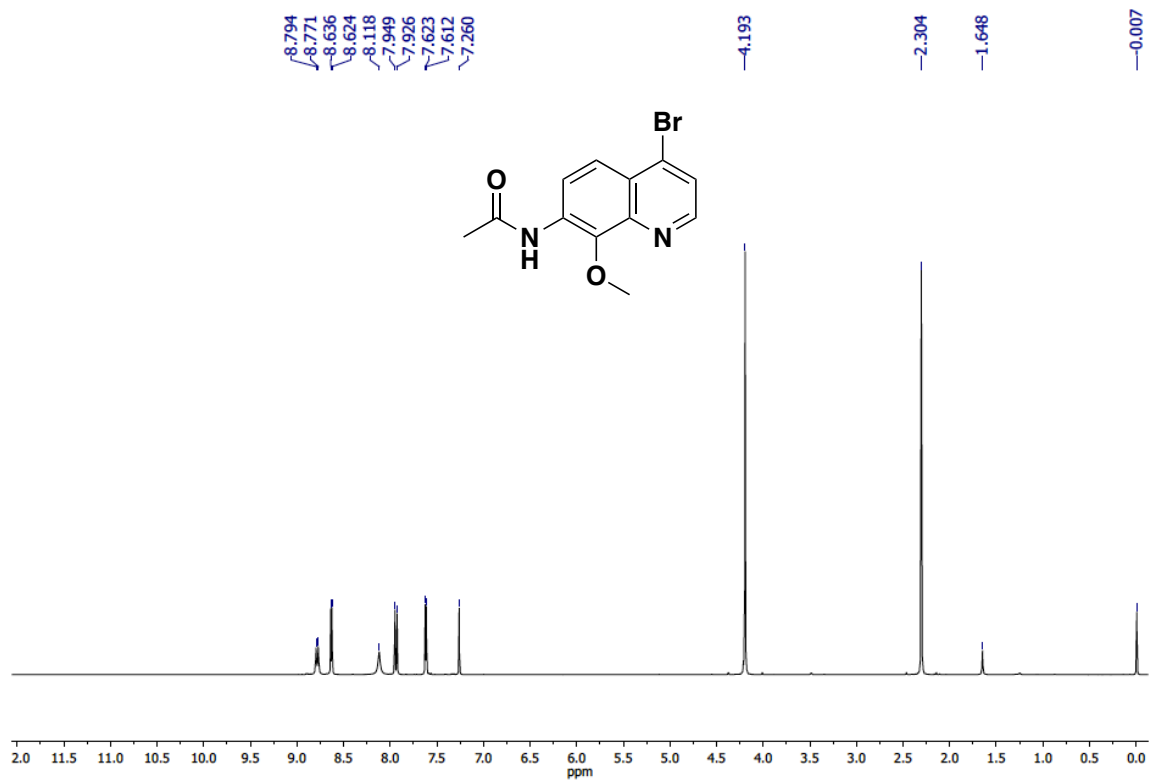
4-Bromo-8-methoxy-7-nitroquinoline (4)



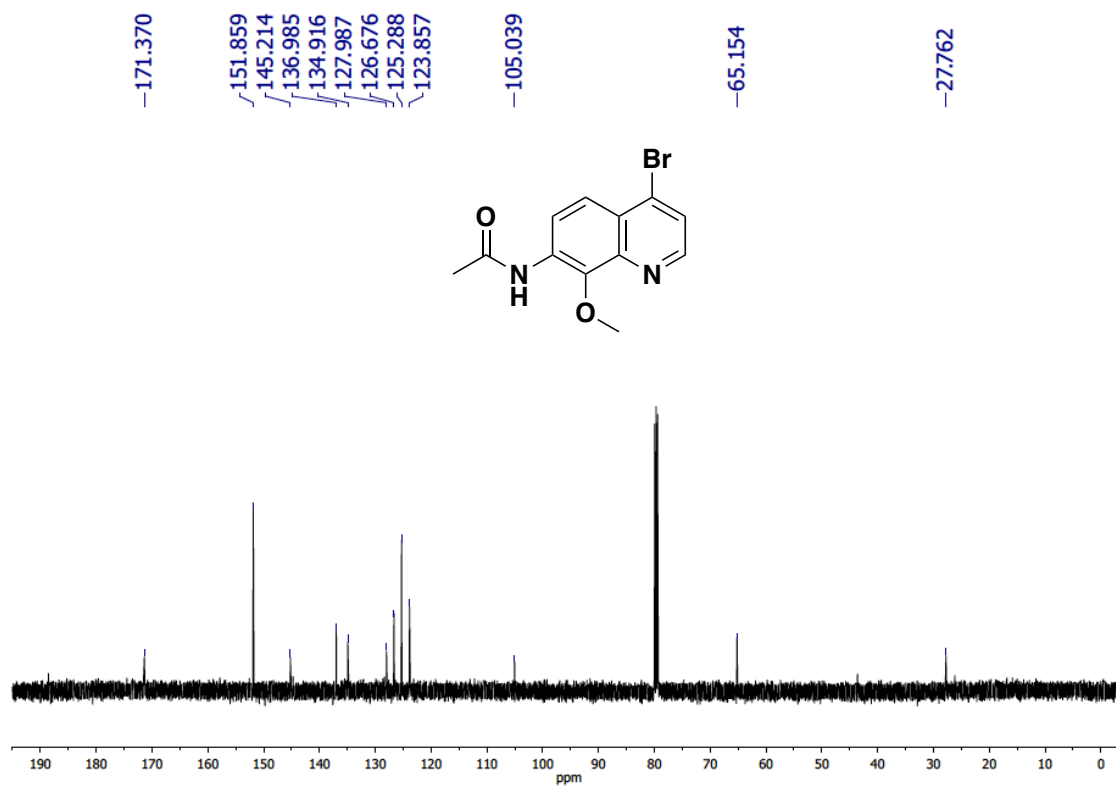
4-Bromo-8-methoxy-7-nitroquinoline (4)



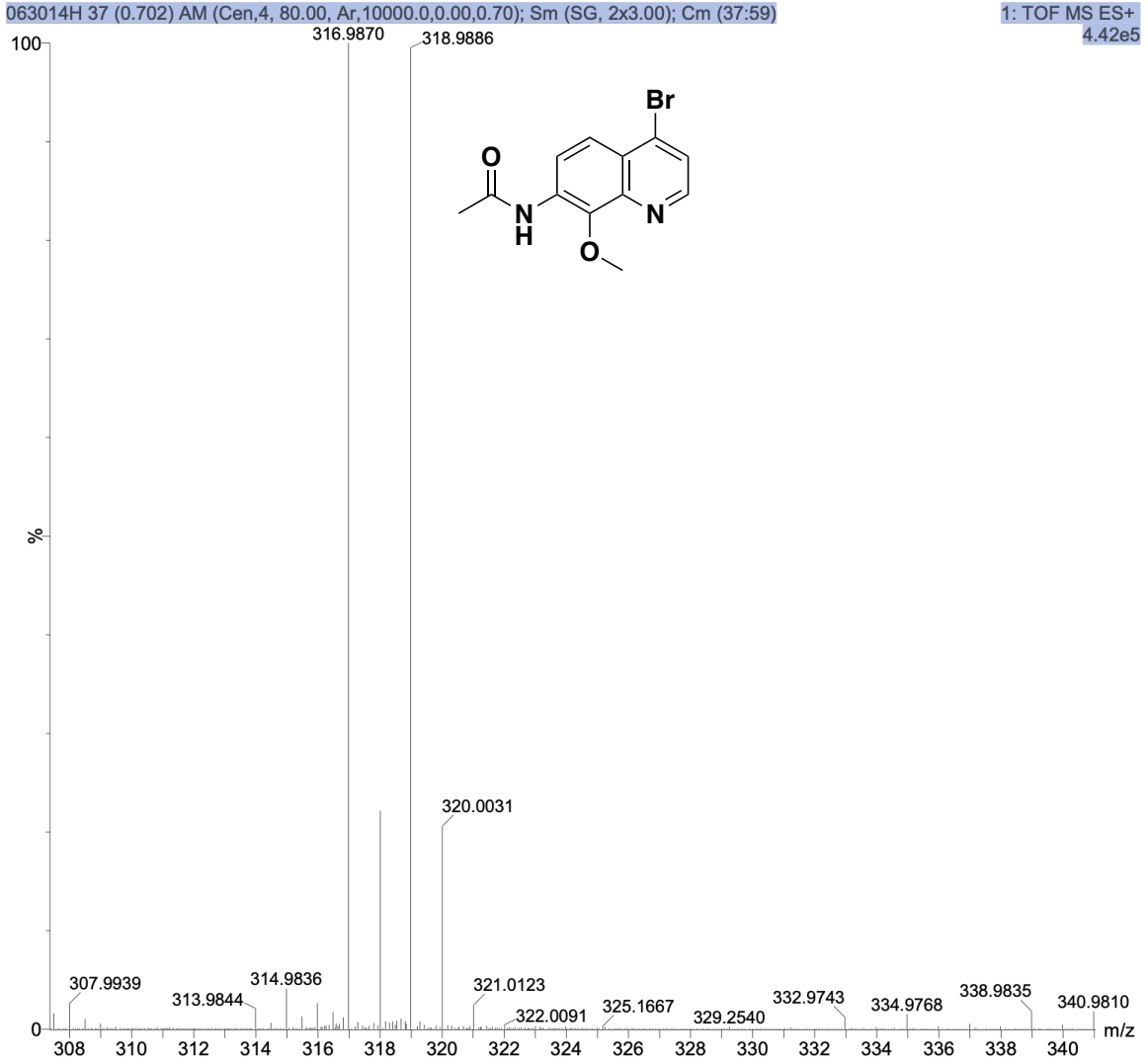
7-Acetamido-4-bromo-8-methoxyquinoline (5) in CDCl₃



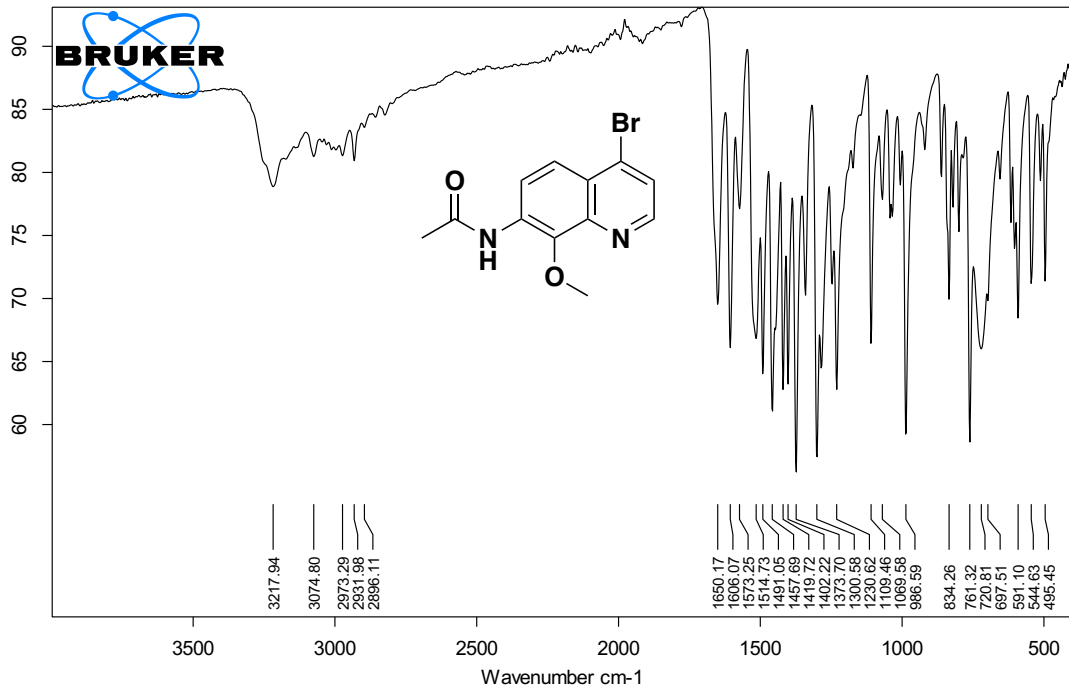
7-Acetamido-4-bromo-8-methoxyquinoline (5) in CDCl₃



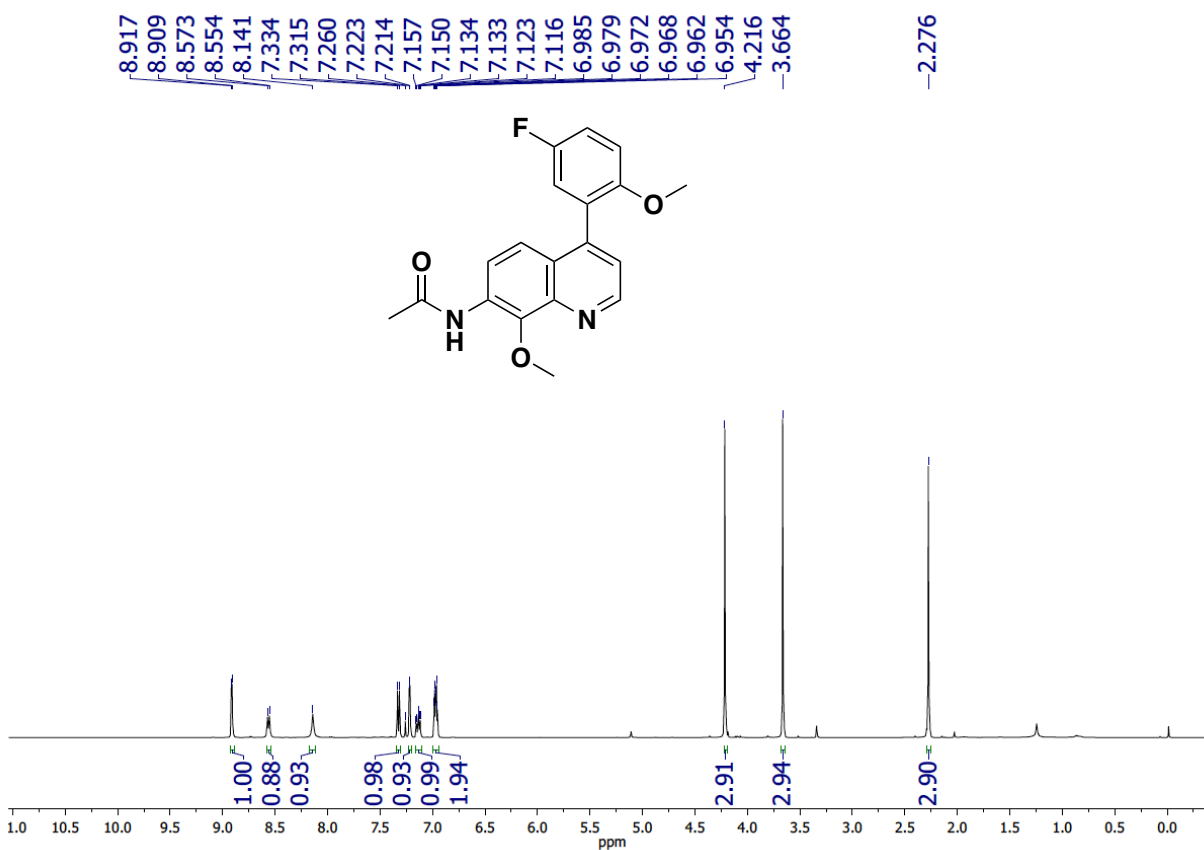
7-Acetamido-4-bromo-8-methoxyquinoline (5)



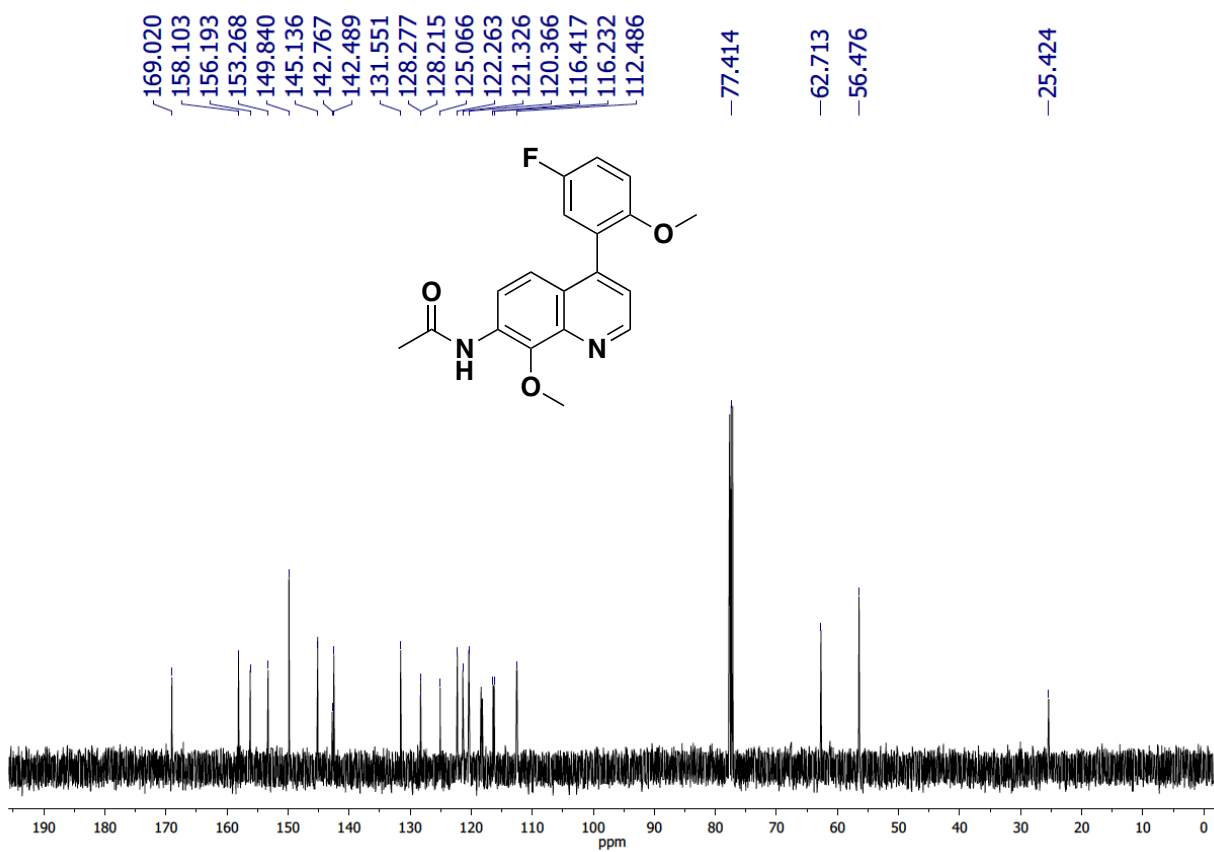
7-Acetamido-4-bromo-8-methoxyquinoline (5)



7-Acetamido-4-(5-fluoro-2-methoxyphenyl)-8-methoxyquinoline (6) in CDCl₃



-Acetamido-4-(5-fluoro-2-methoxyphenyl)-8-methoxyquinoline (6) in CDCl₃

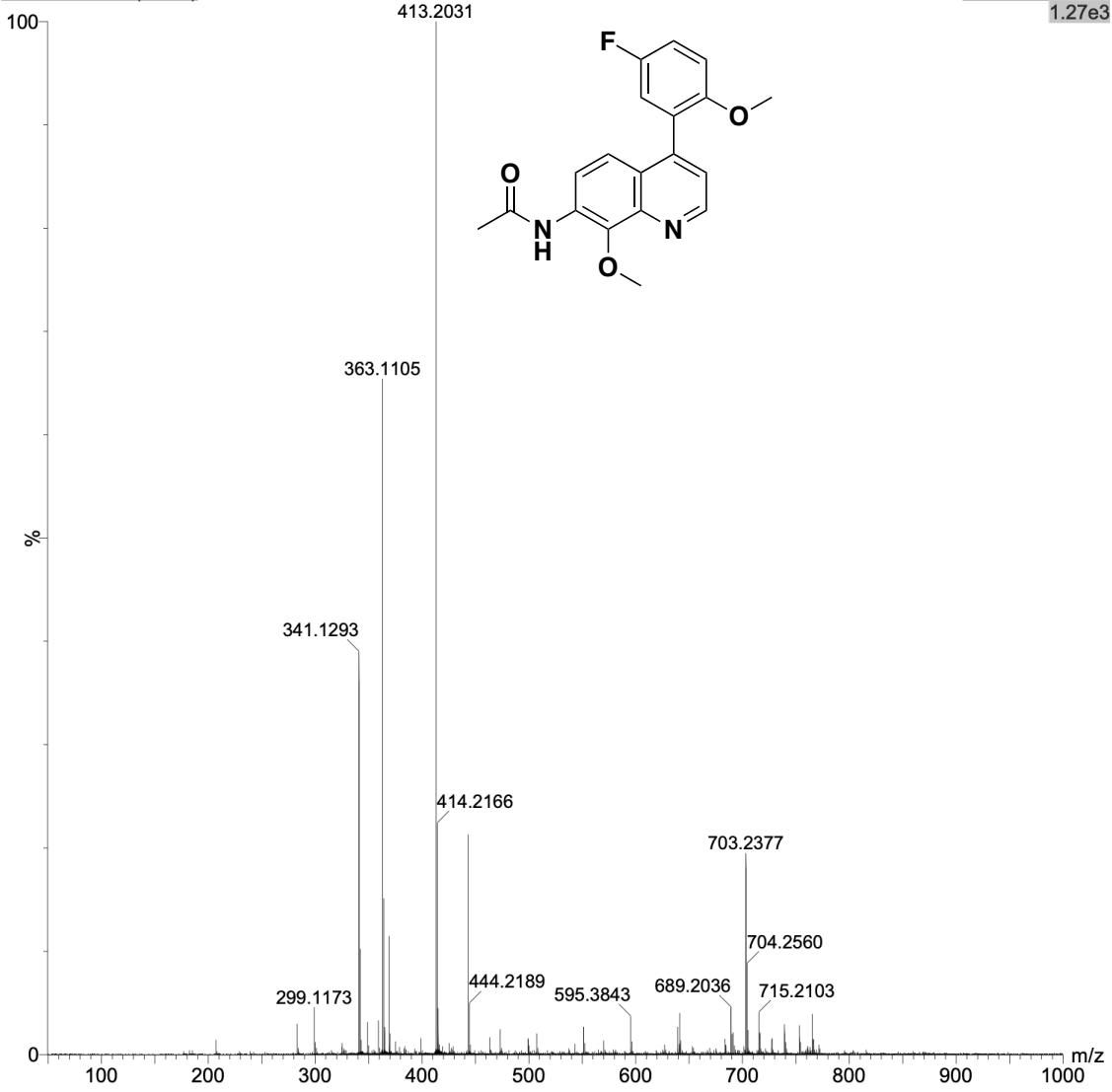


-Acetamido-4-(5-fluoro-2-methoxyphenyl)-8-methoxyquinoline (6)

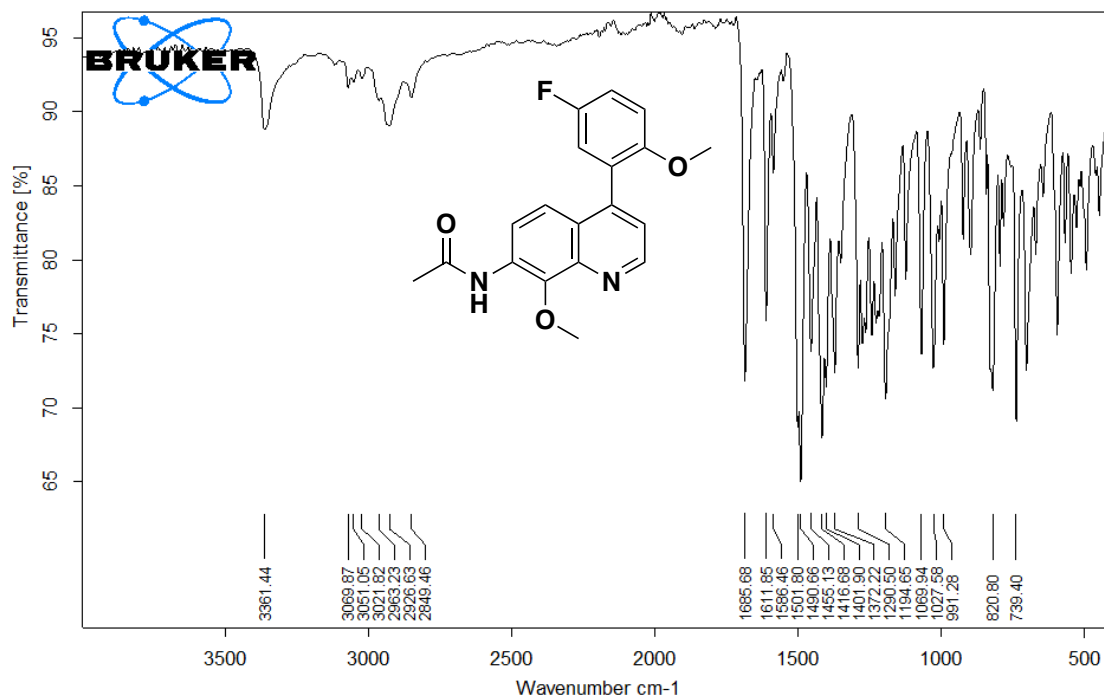
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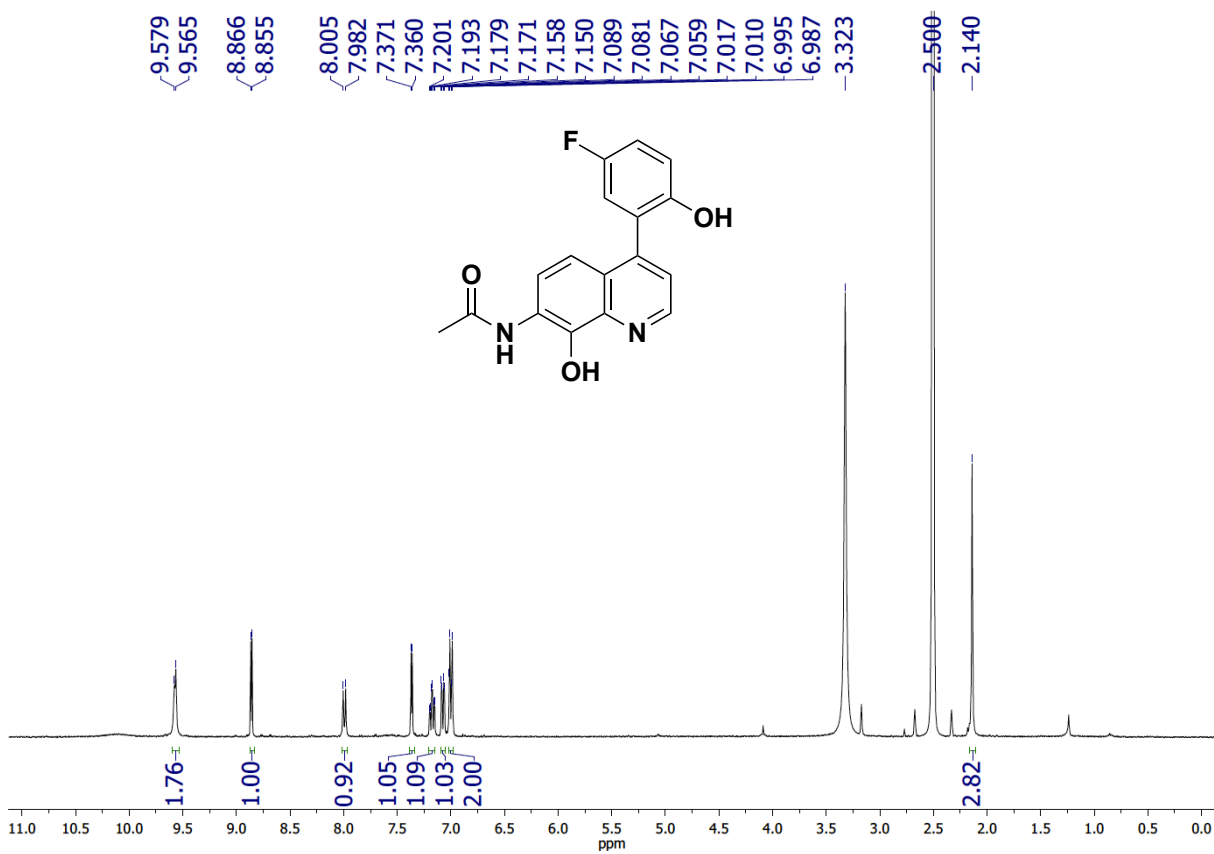
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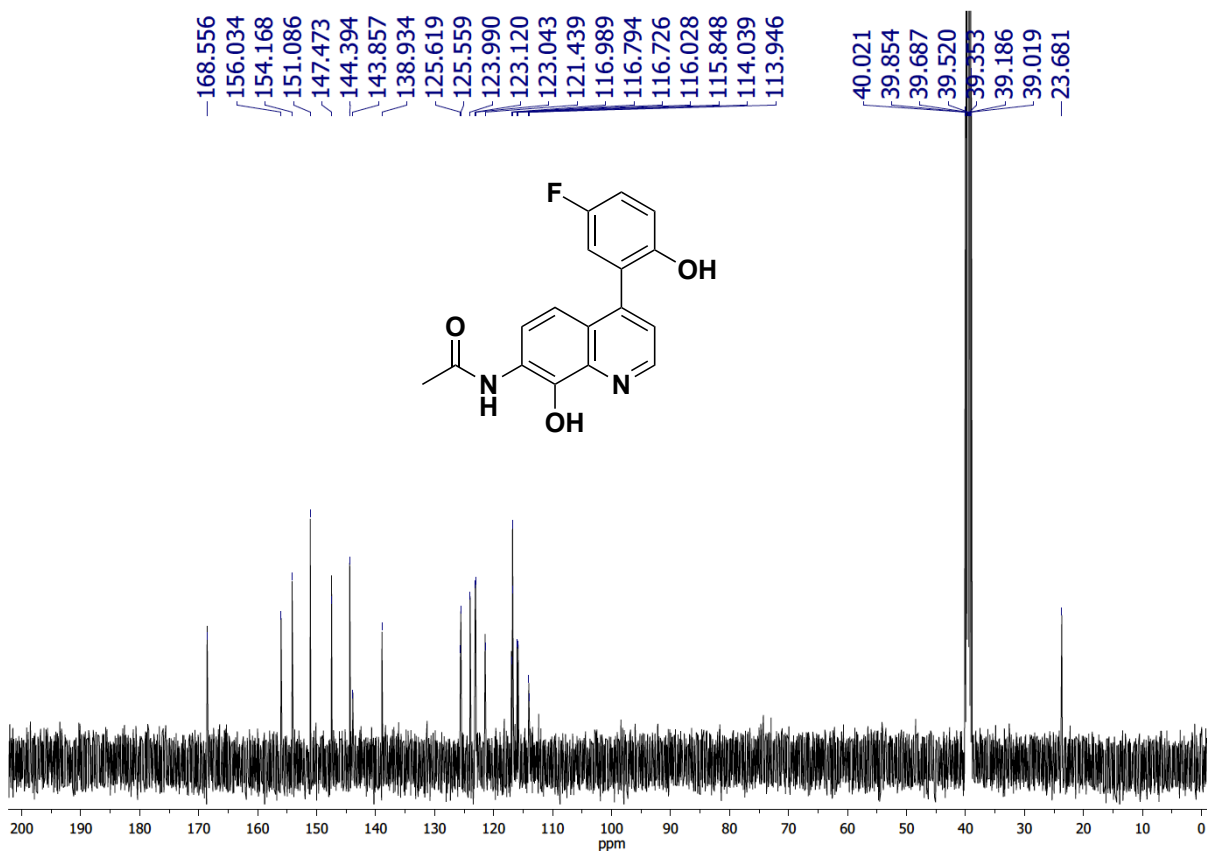
7-Acetamido-4-(5-fluoro-2-methoxyphenyl)-8-methoxyquinoline (6)



7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-hydroxyquinoline (7) in DMSO-d₆



7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-hydroxyquinoline (7) in DMSO-d₆

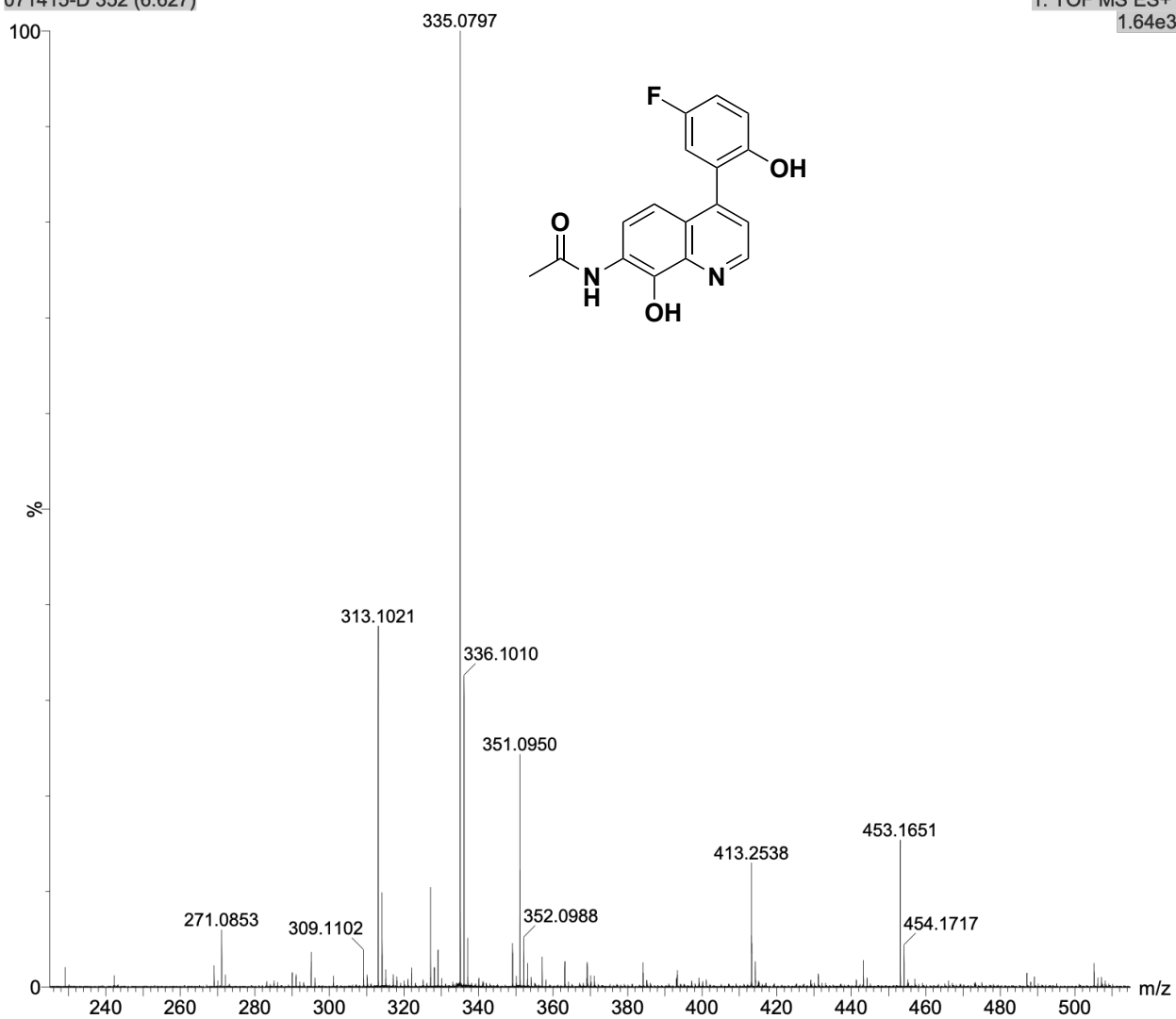


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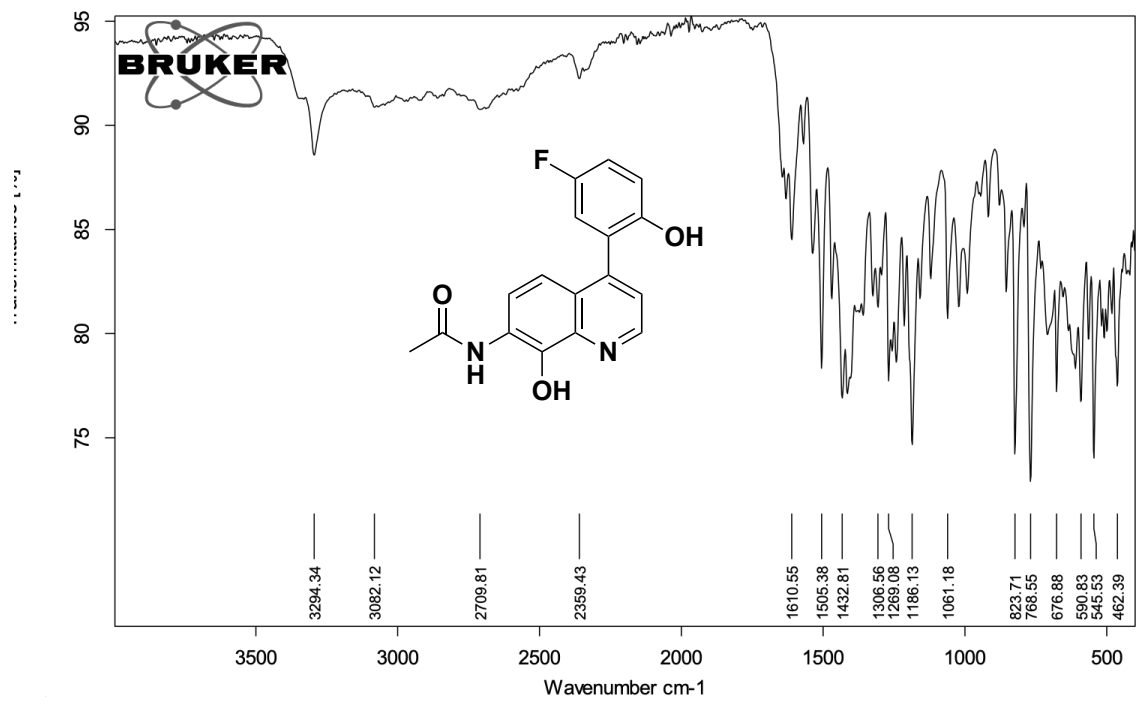
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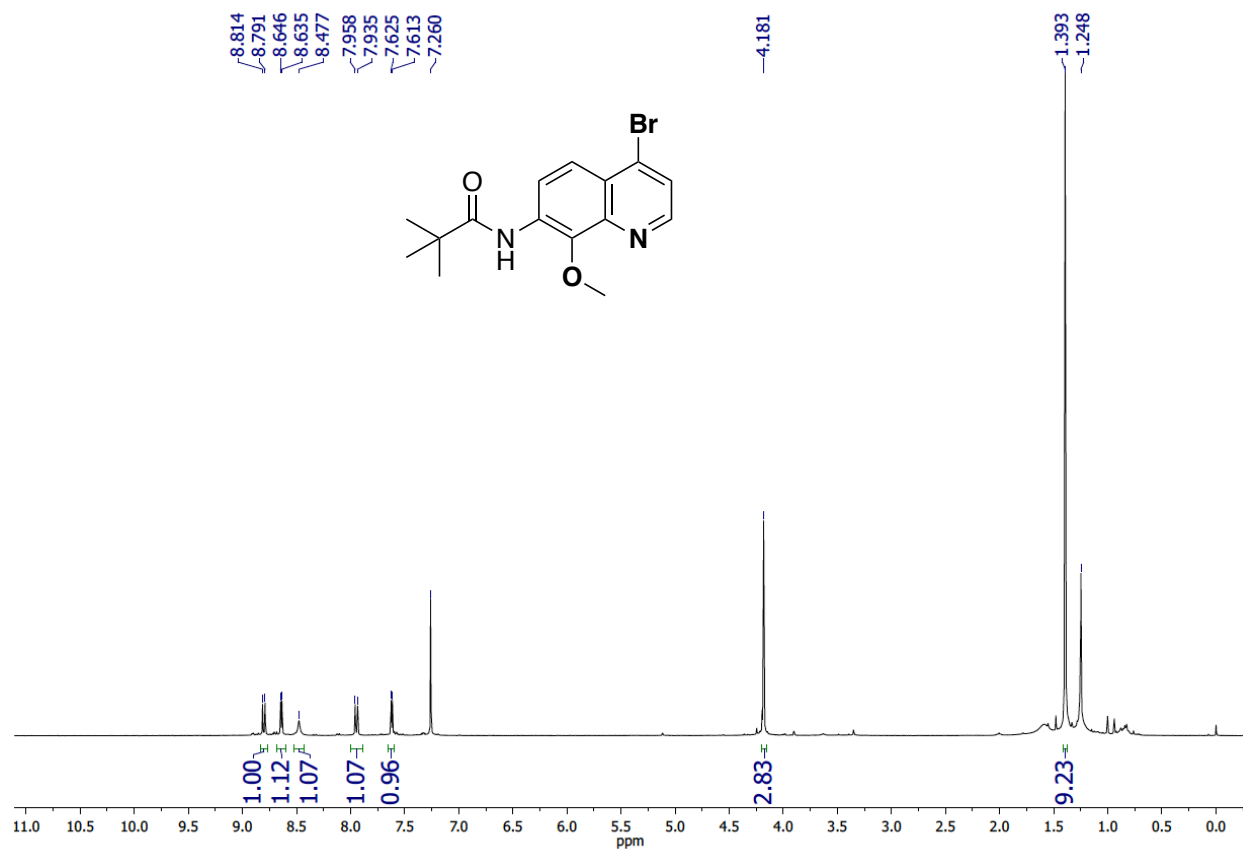
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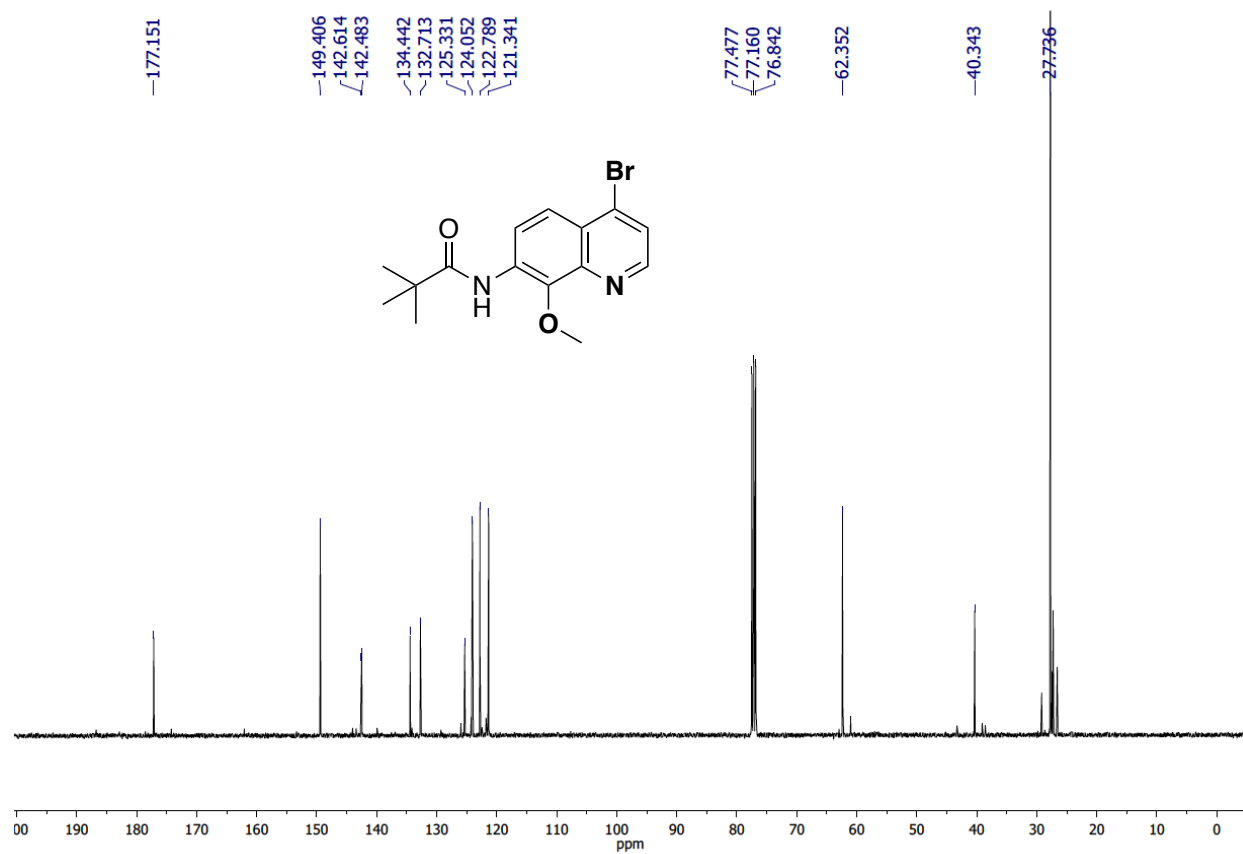
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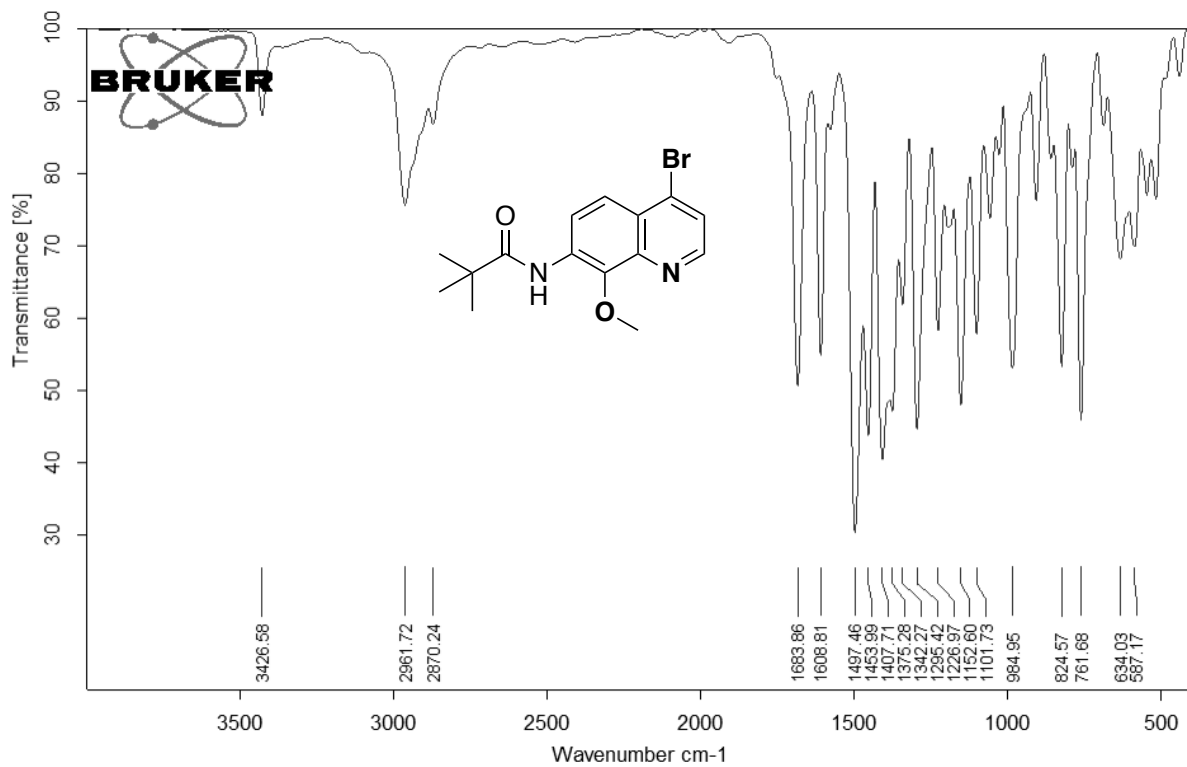
4-Bromo-8-methoxy-7-pivalamidoquinoline (8) in CDCl₃



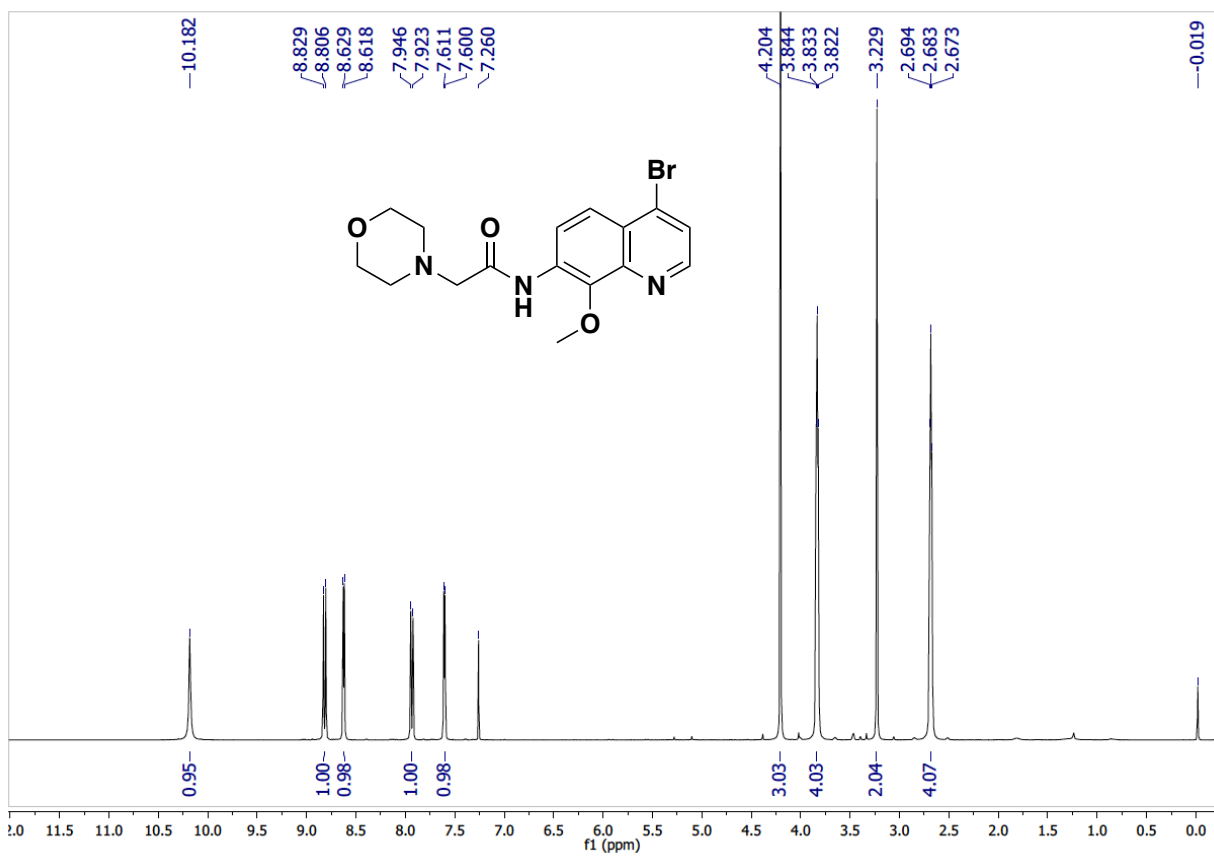
4-Bromo-8-methoxy-7-pivalamidoquinoline (8) in CDCl₃



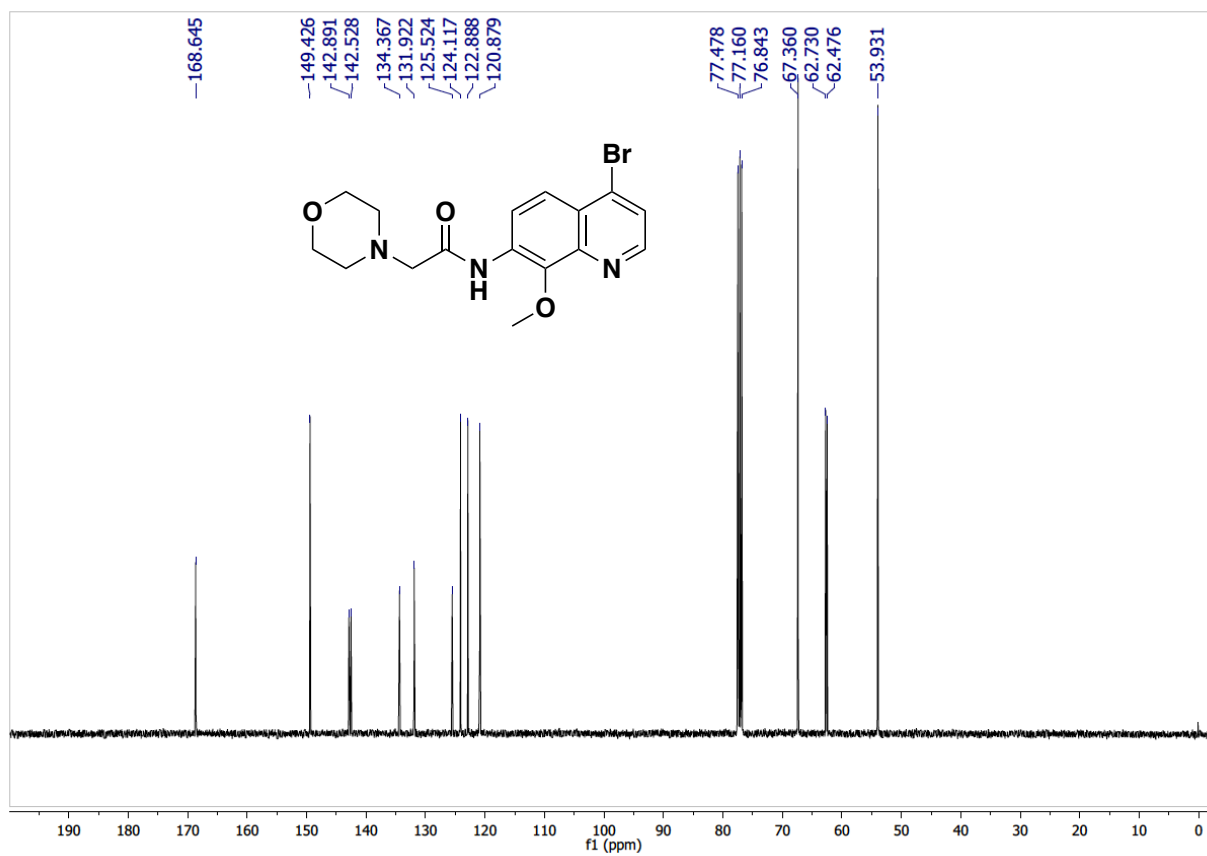
4-Bromo-8-methoxy-7-pivalamidoquinoline (8)



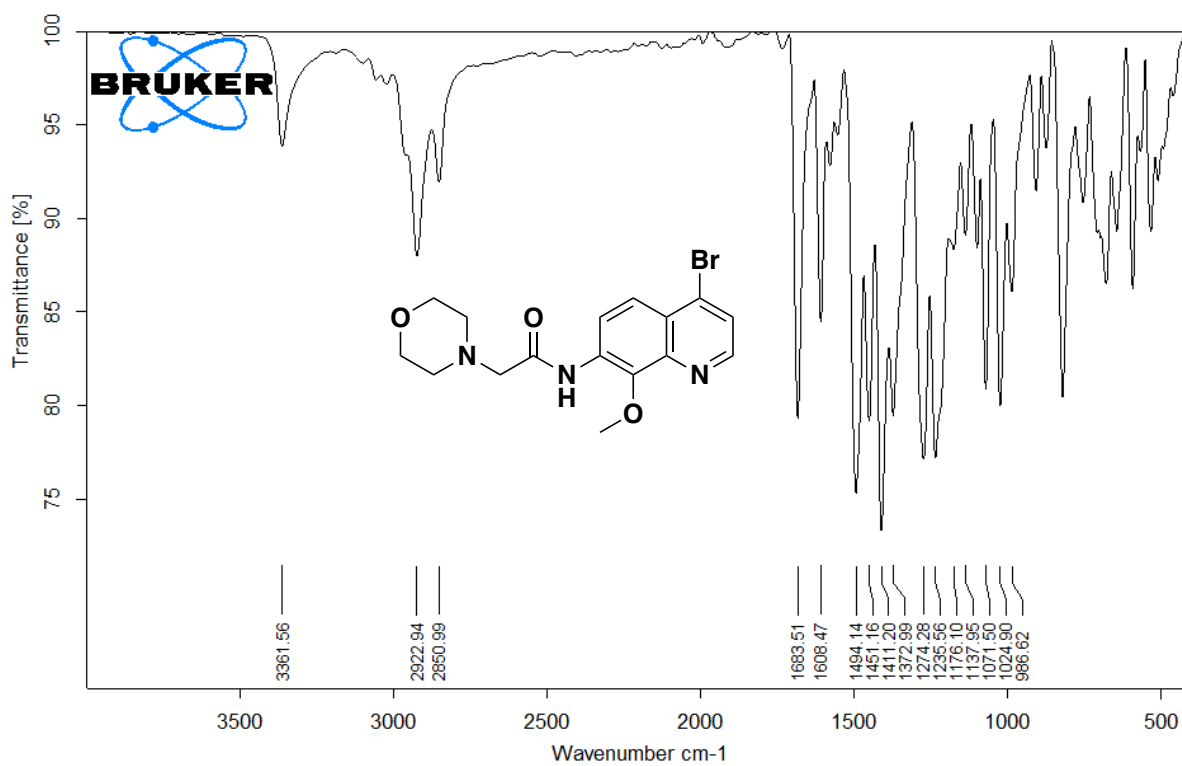
4-Bromo-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (9) in CDCl₃



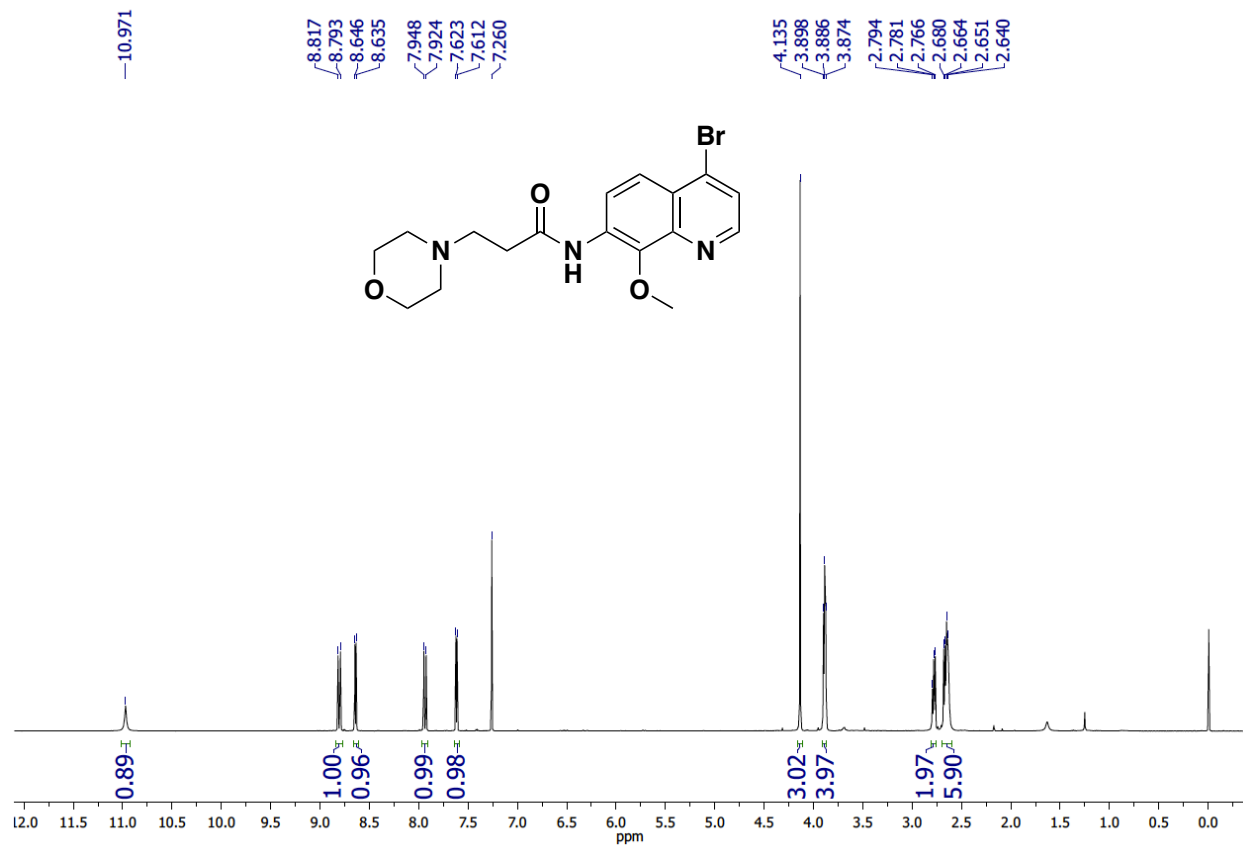
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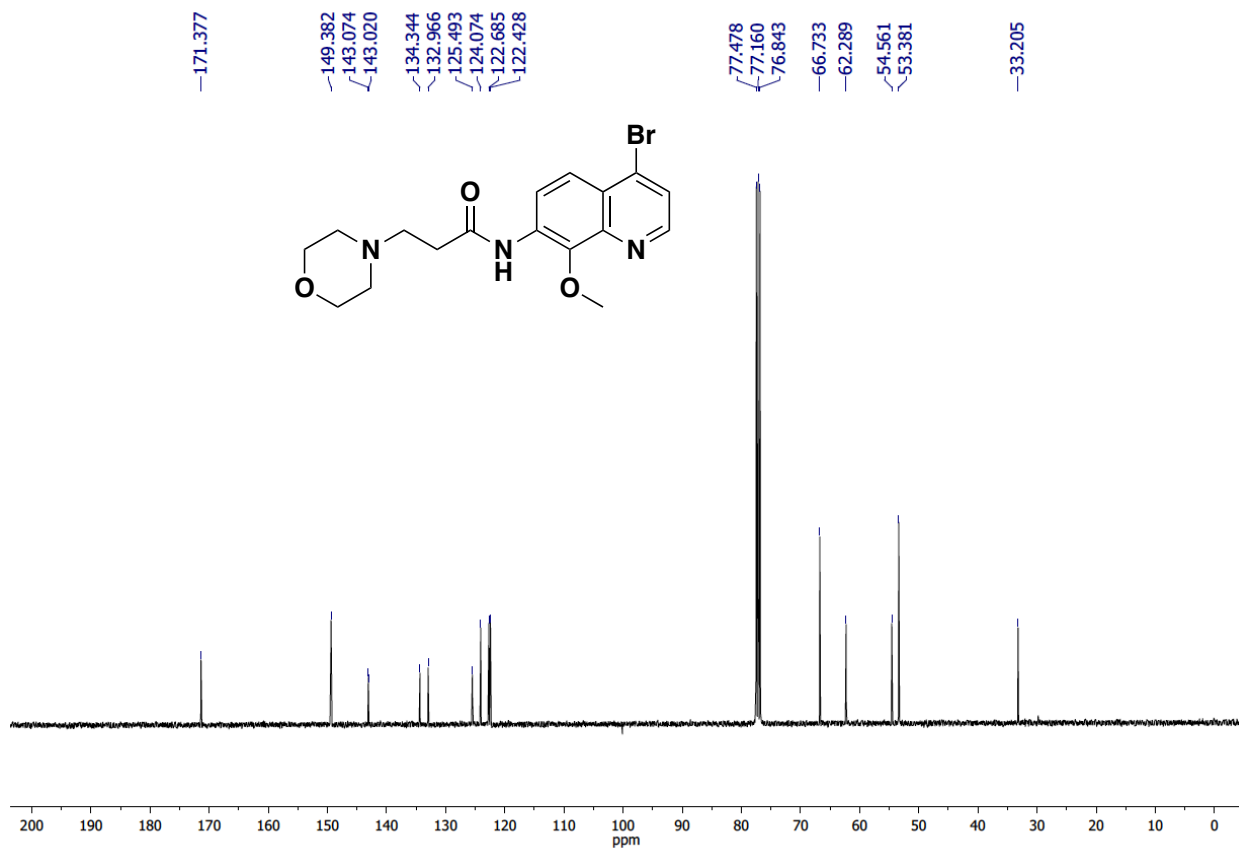
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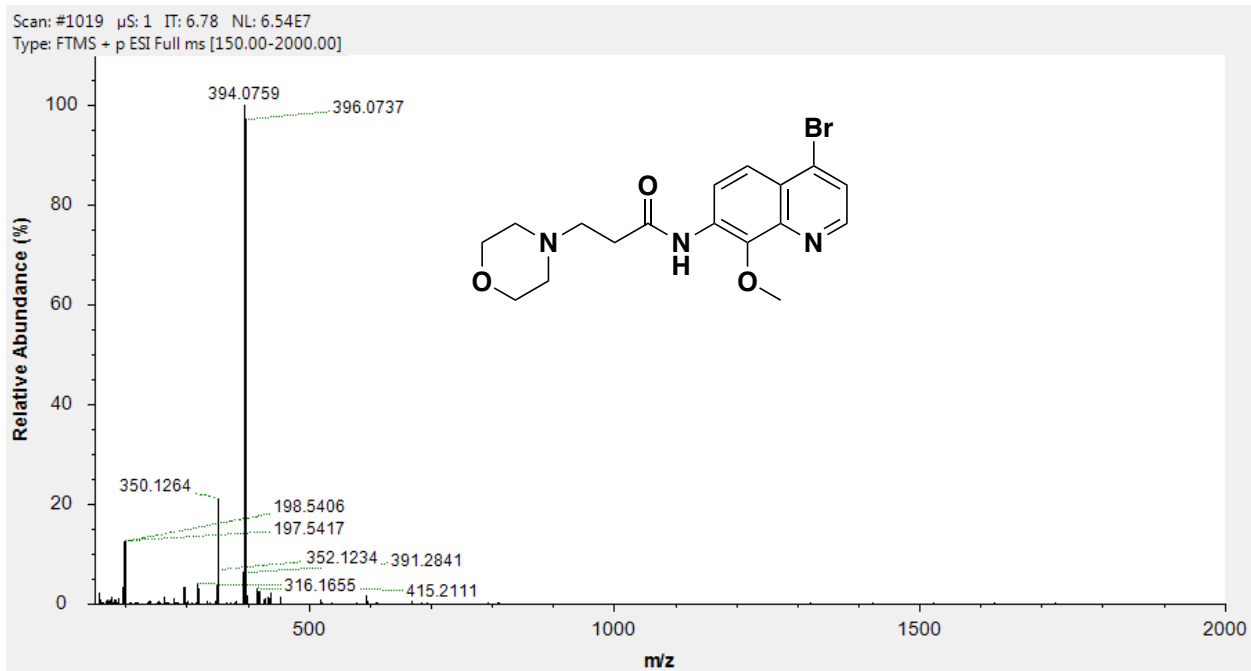
4-Bromo-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (10) in CDCl₃



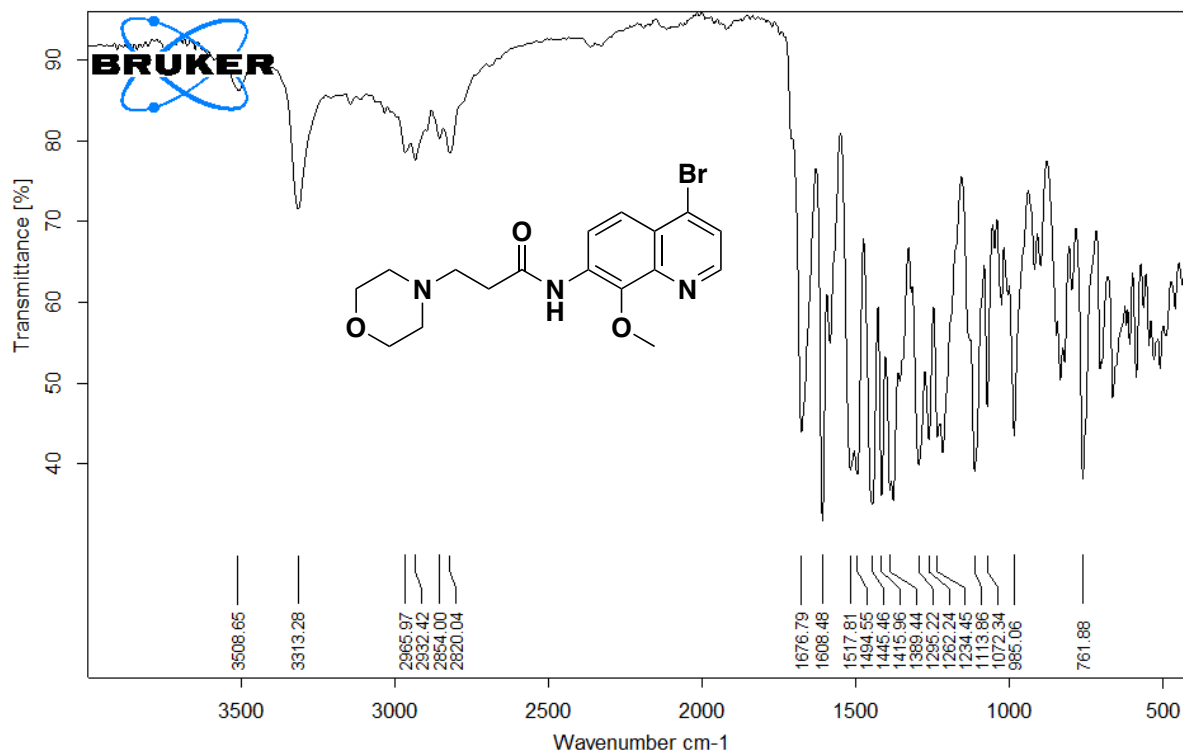
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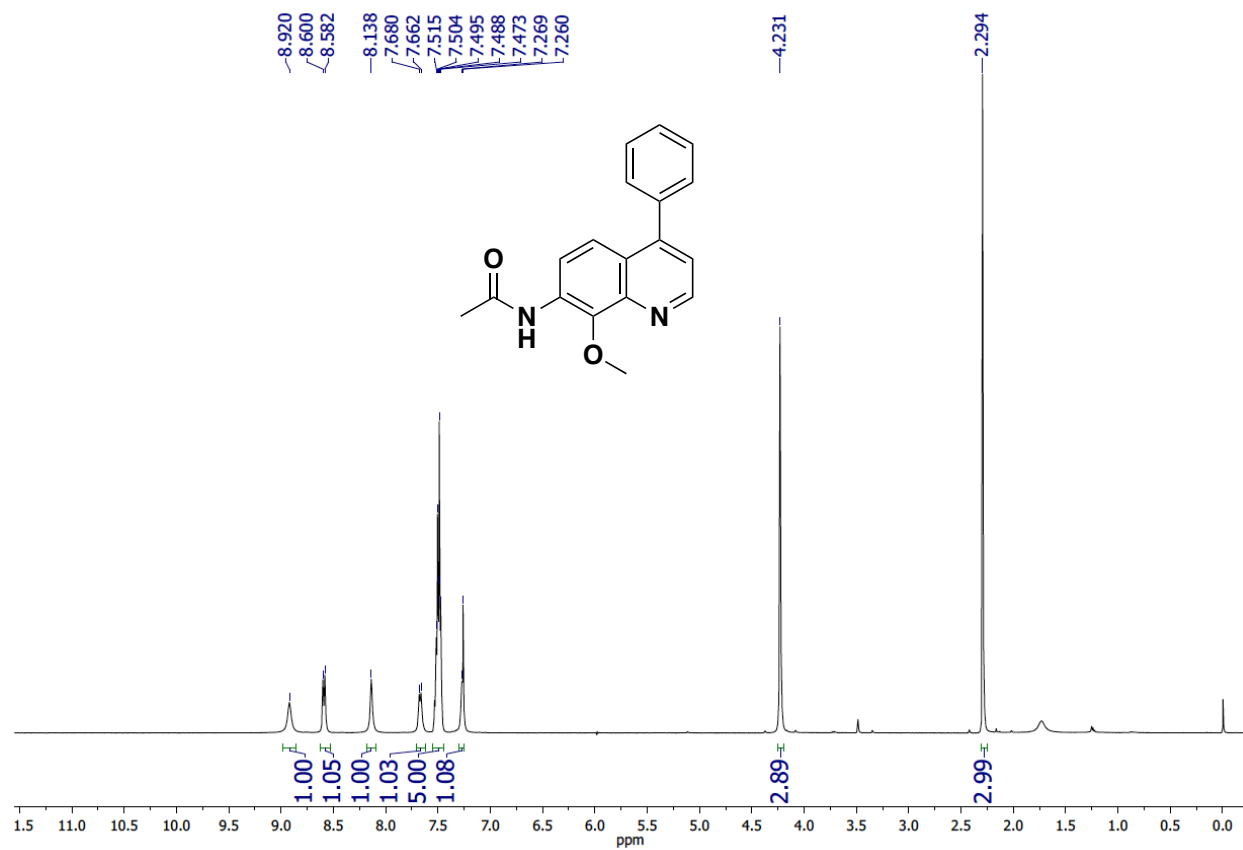
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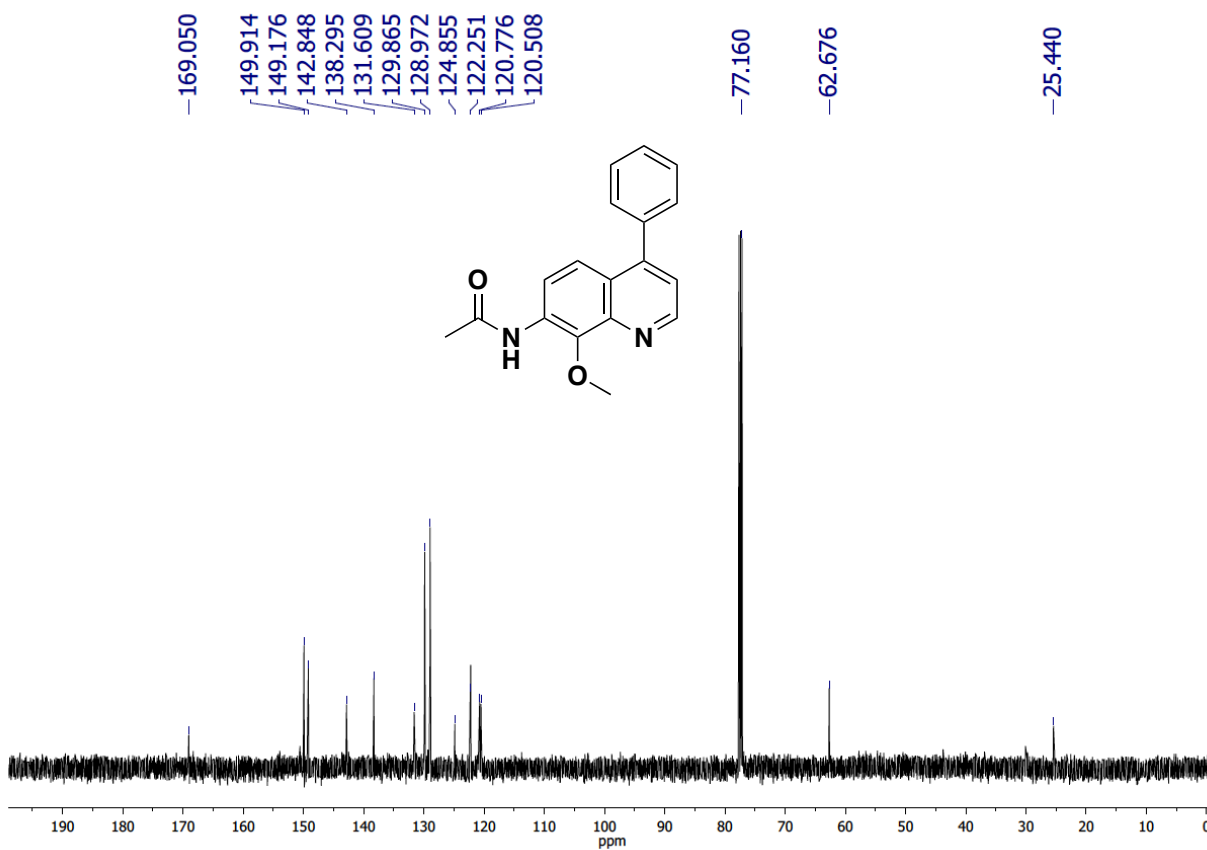
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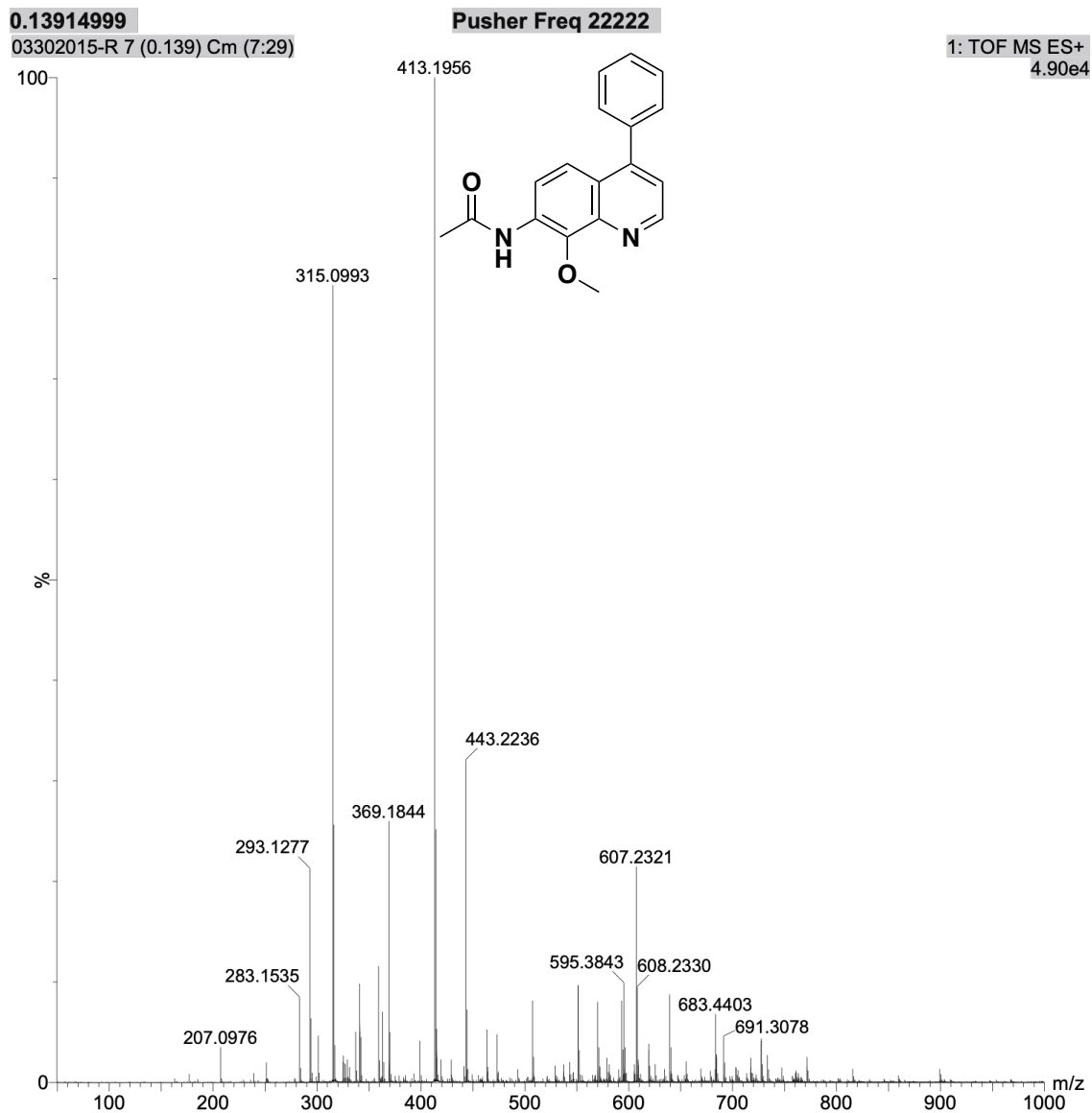
7-Acetamido-4-(phenyl)-8-methoxyquinoline (11) in CDCl₃



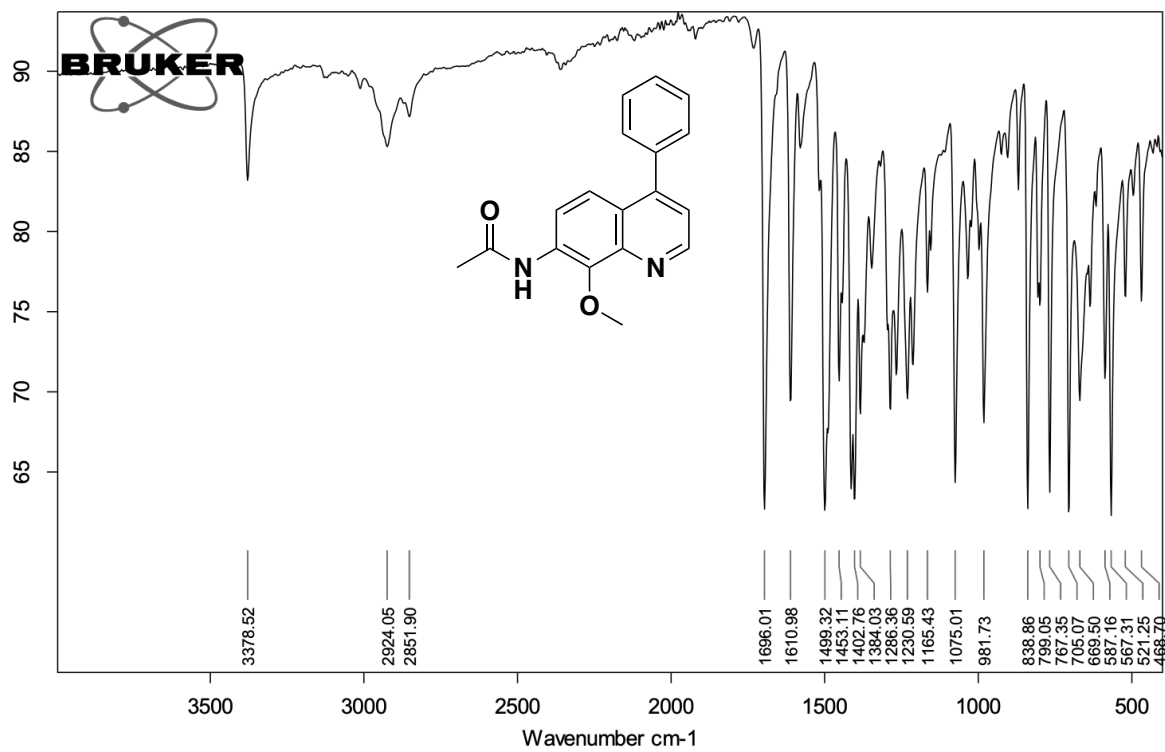
7-Acetamido-4-(phenyl)-8-methoxyquinoline (11) in CDCl₃



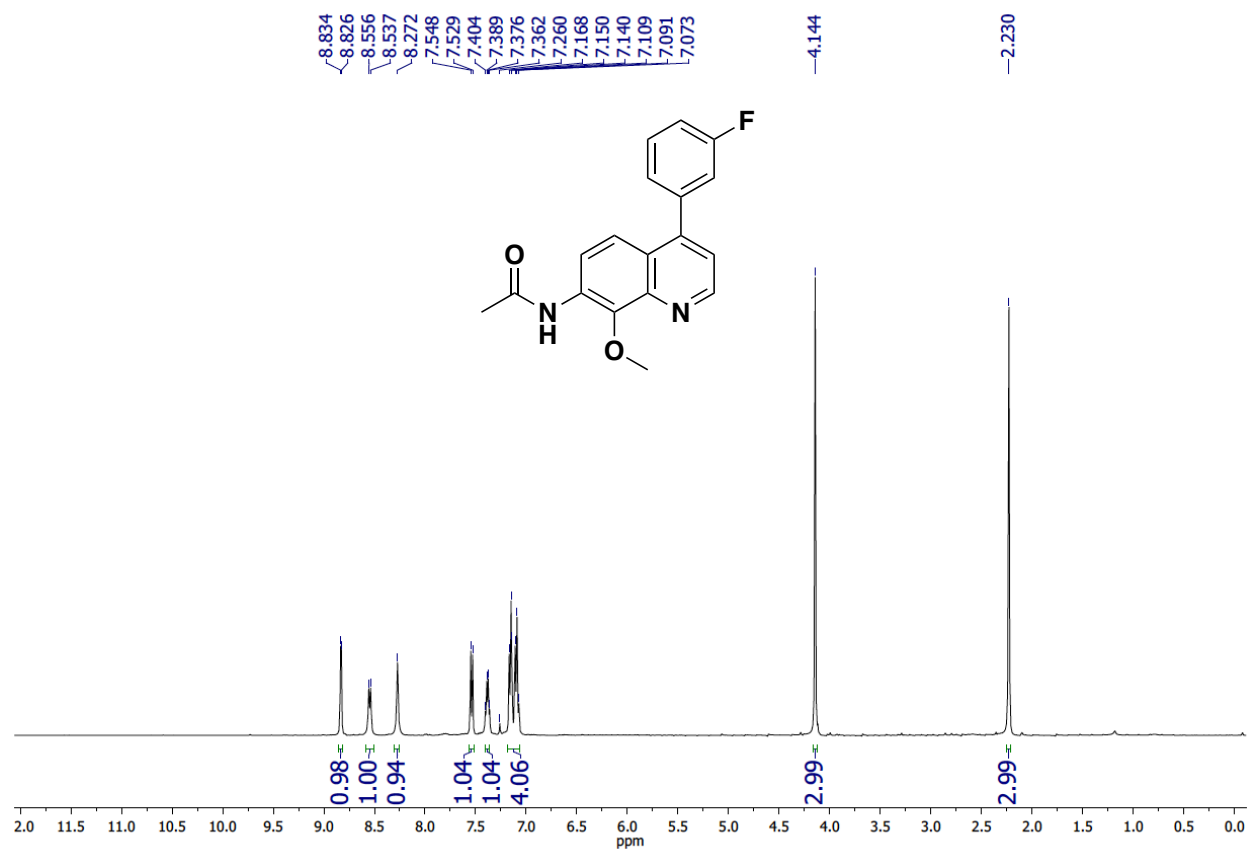
7-Acetamido-4-(phenyl)-8-methoxyquinoline (11)



7-Acetamido-4-(phenyl)-8-methoxyquinoline (11)

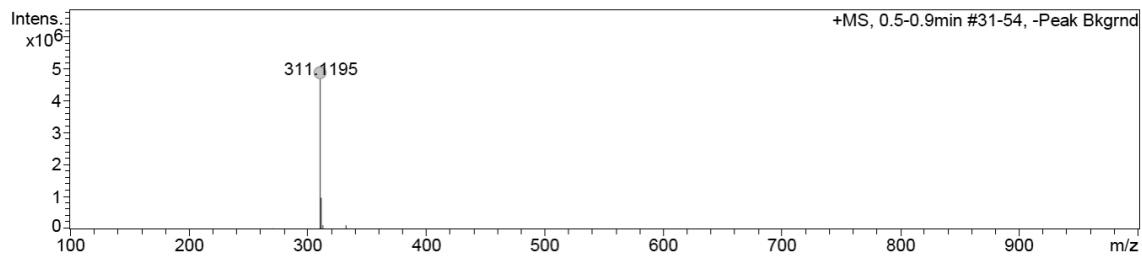
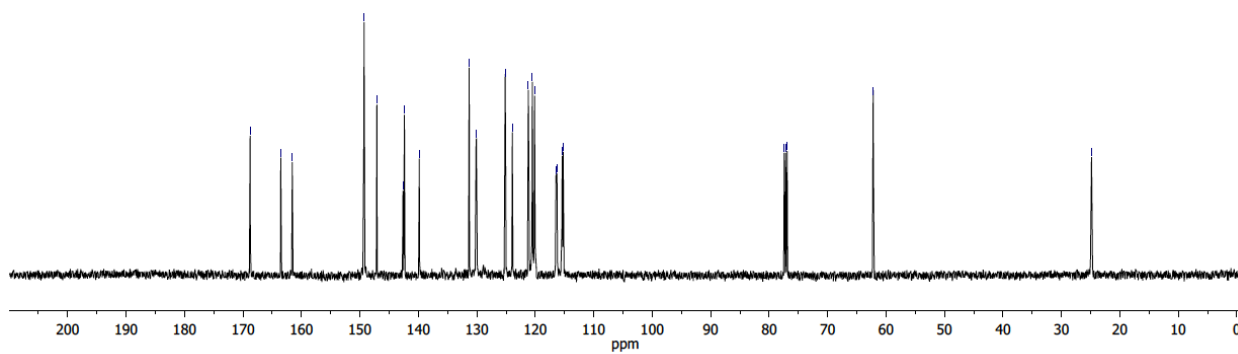
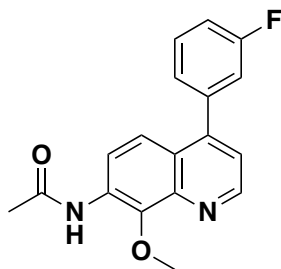


7-Acetamido-4-(3-fluorophenyl)-8-methoxyquinoline (12) in CDCl₃

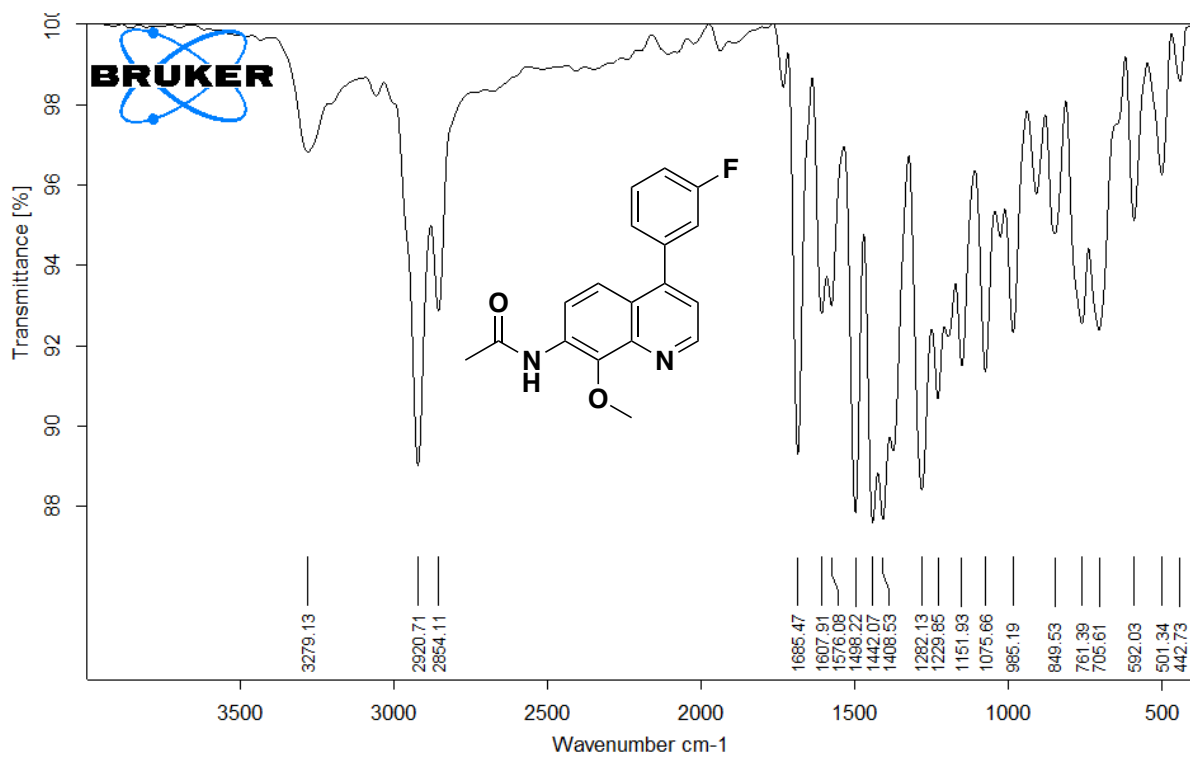


7-Acetamido-4-(3-fluorophenyl)-8-methoxyquinoline (12) in CDCl₃

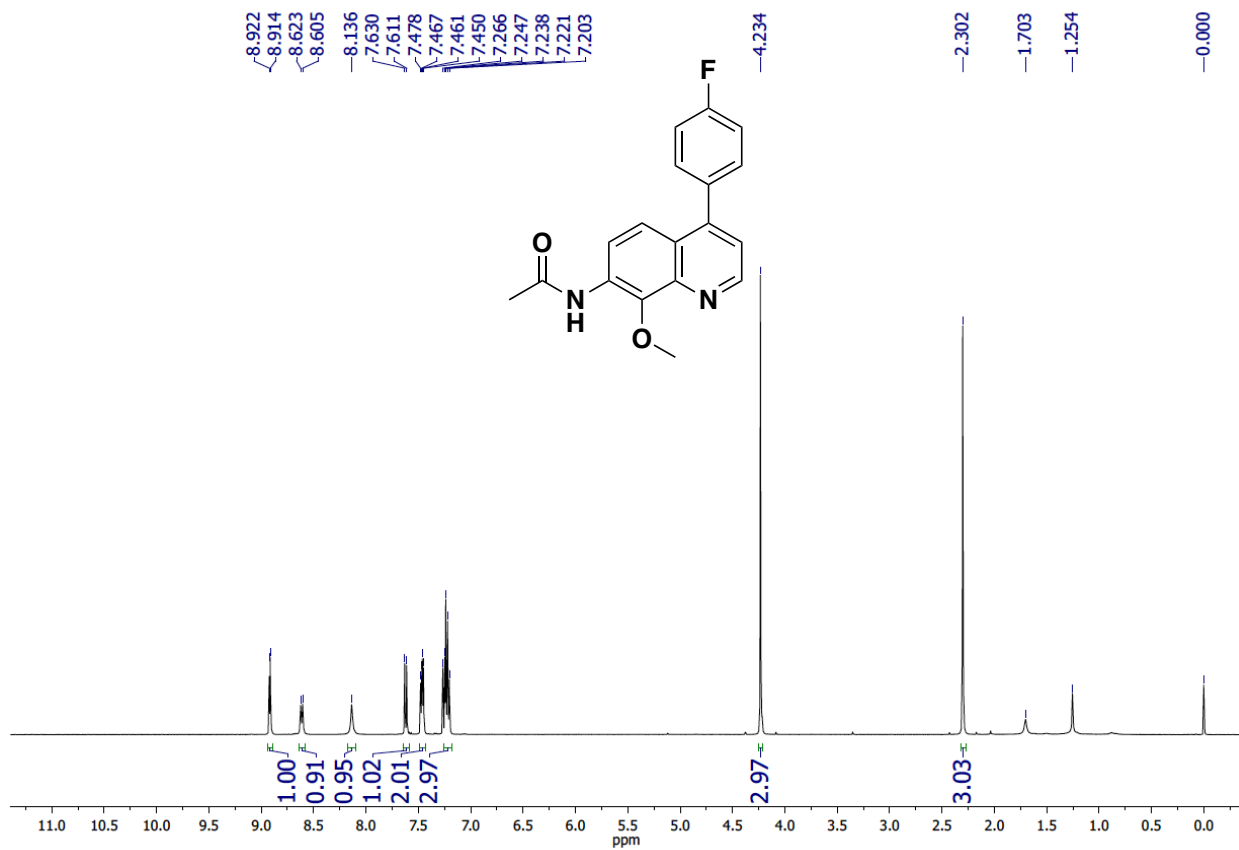
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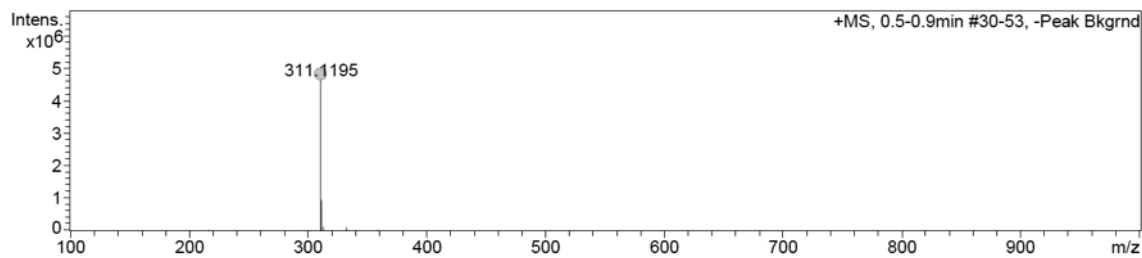
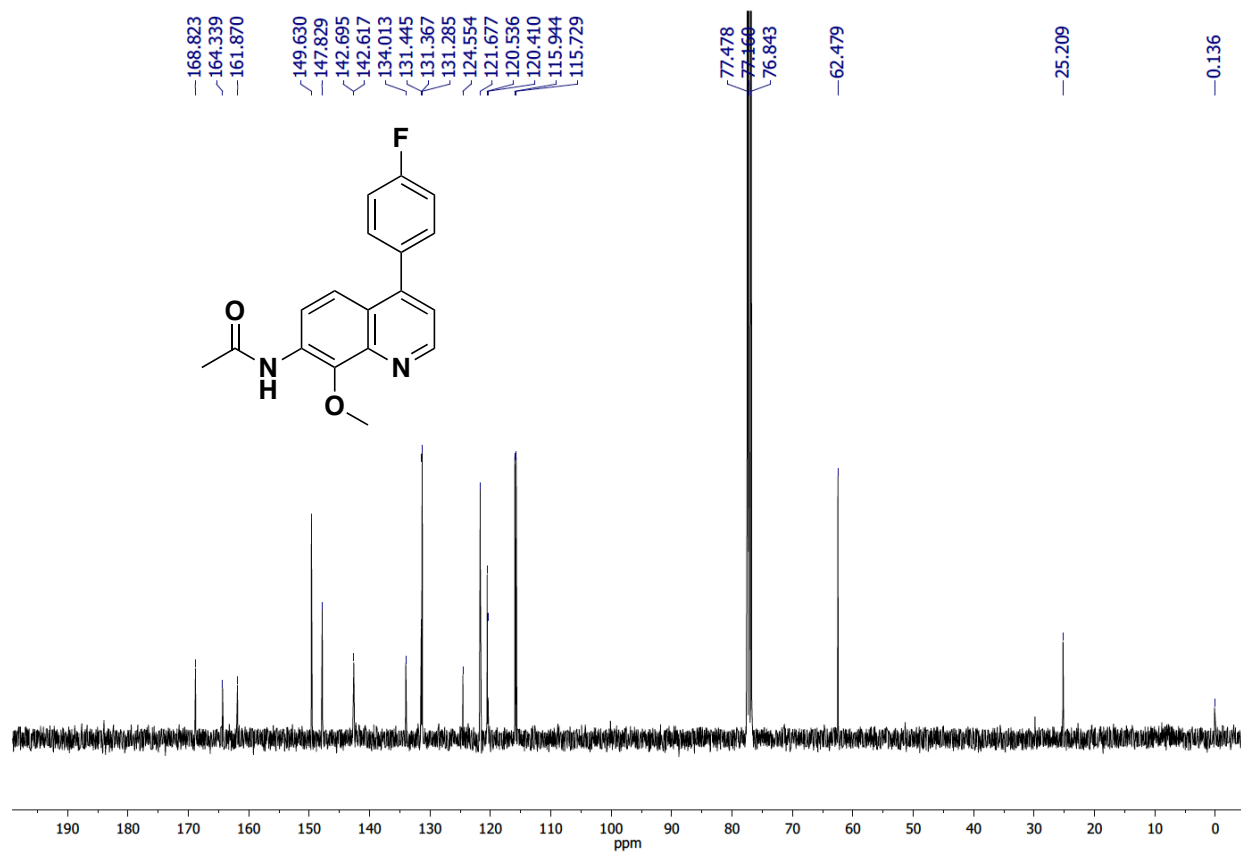
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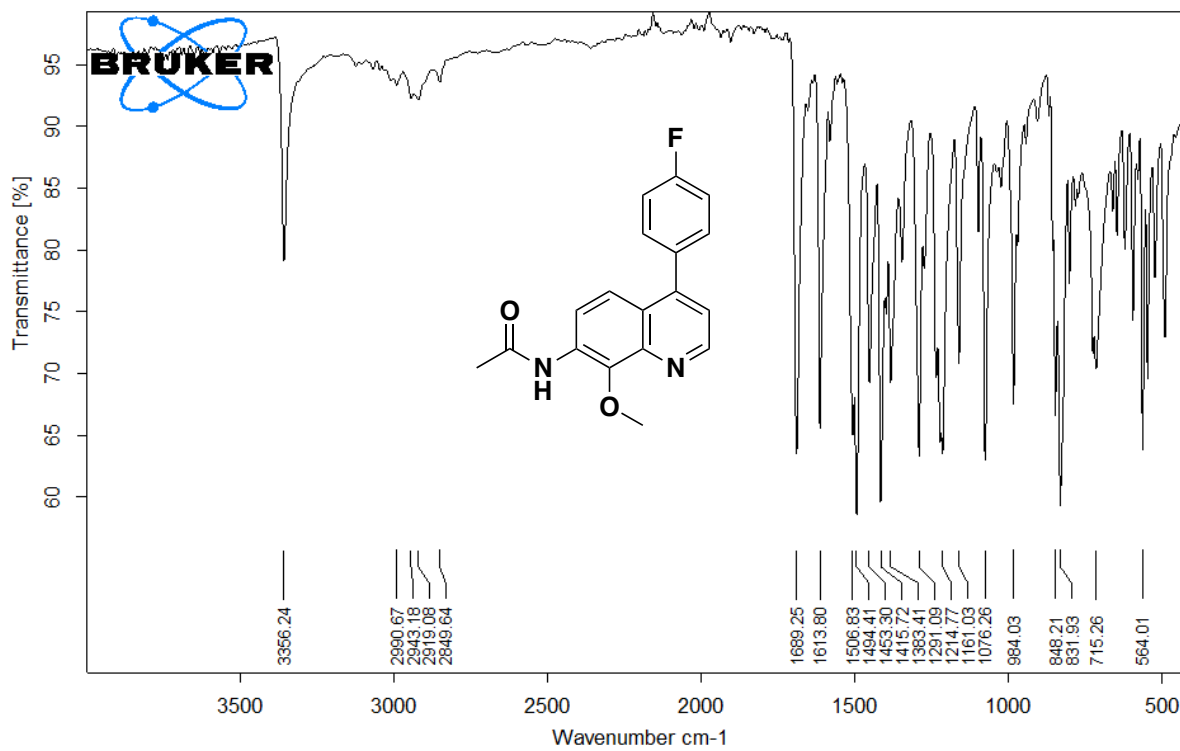
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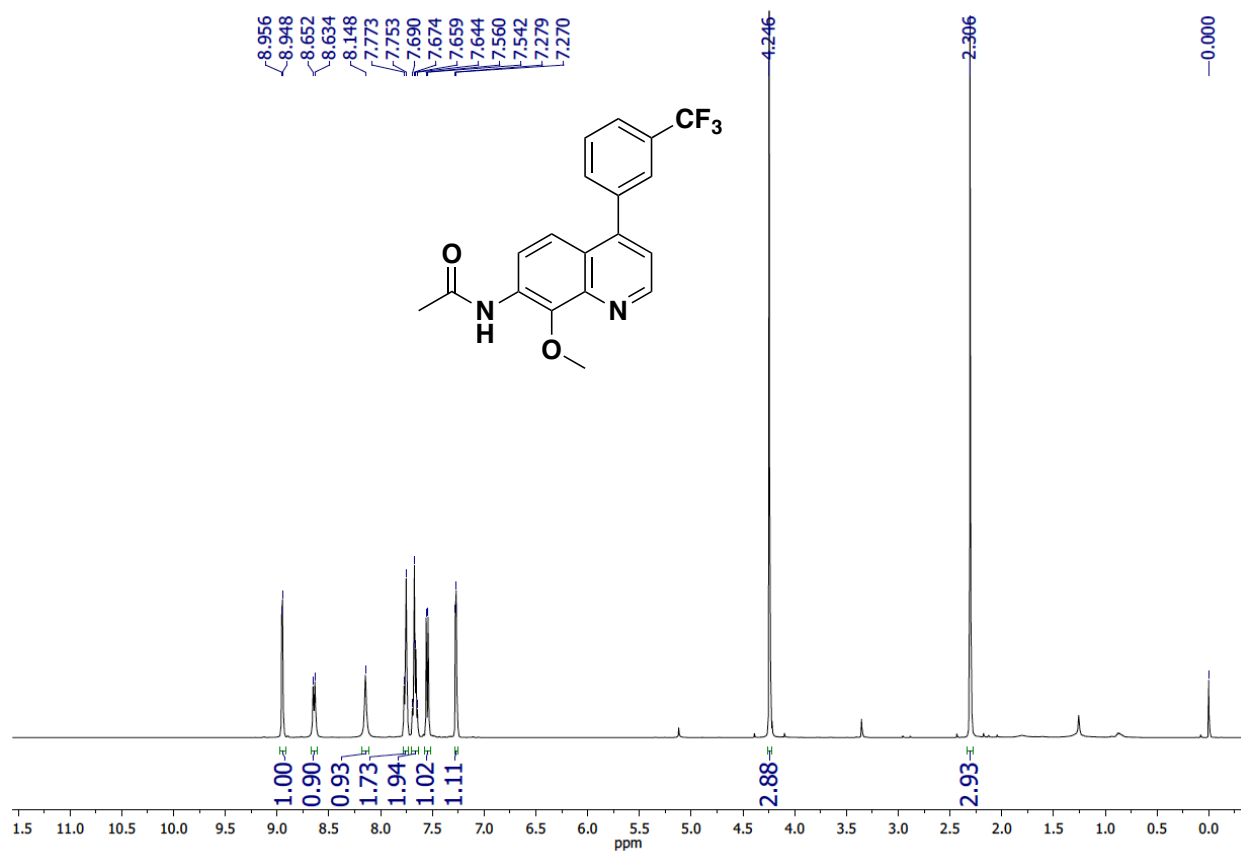
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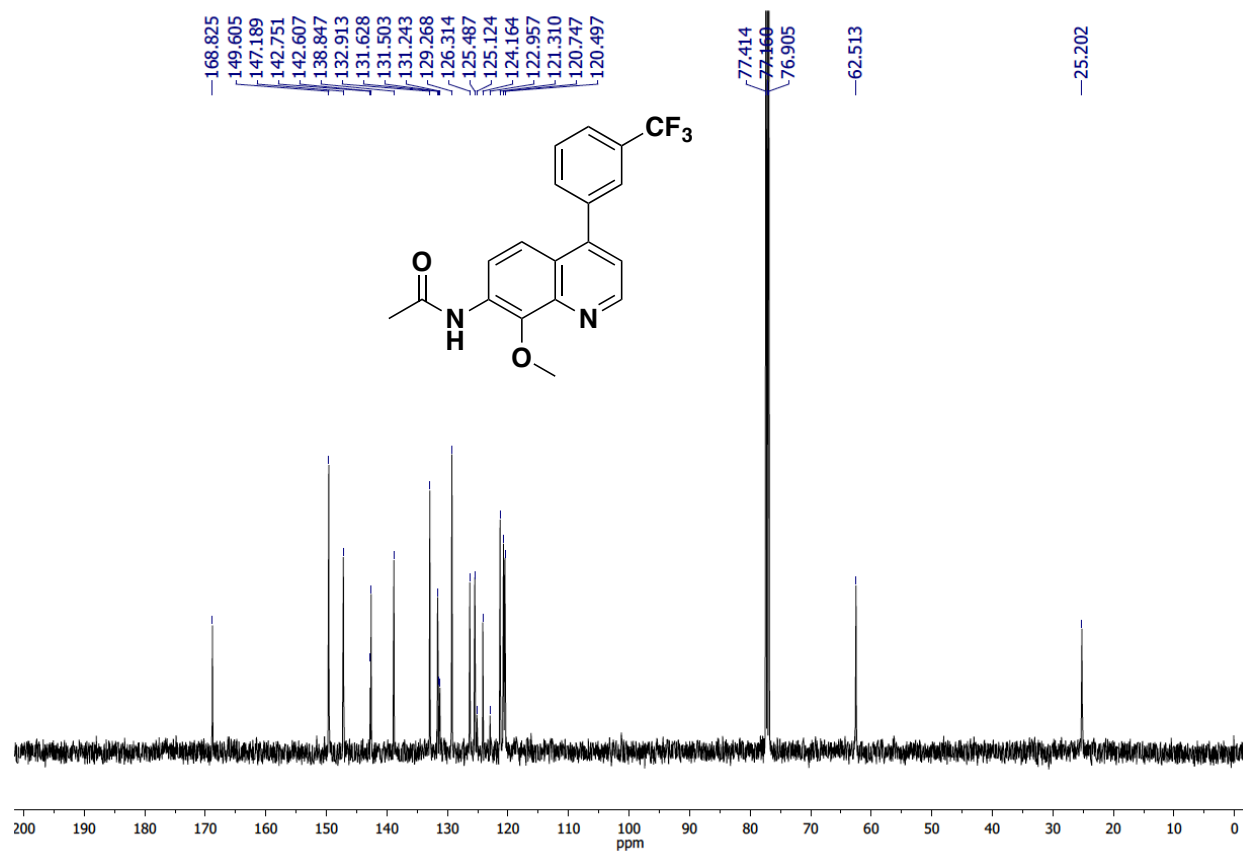
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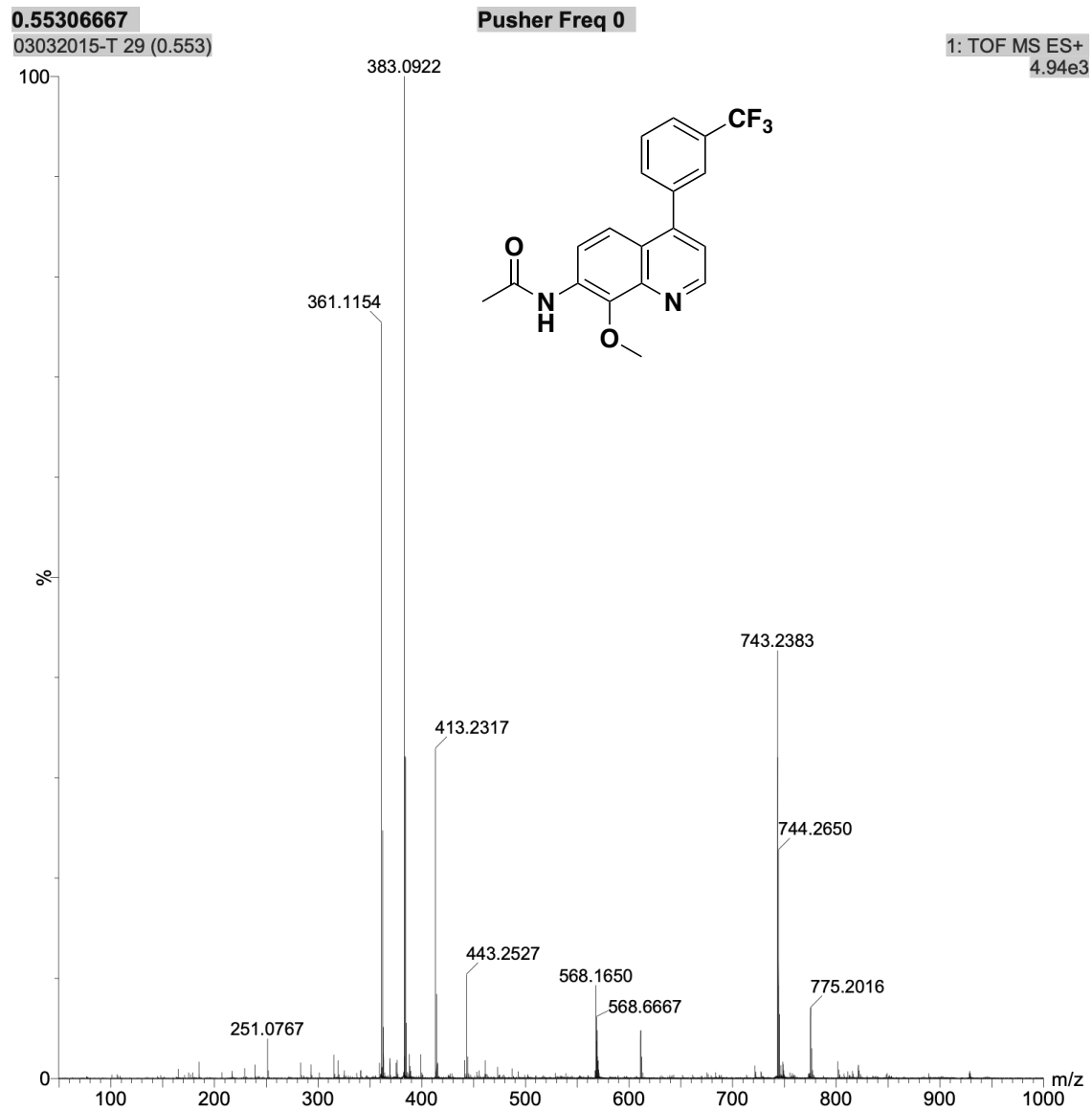
7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-methoxyquinoline (14) in CDCl₃



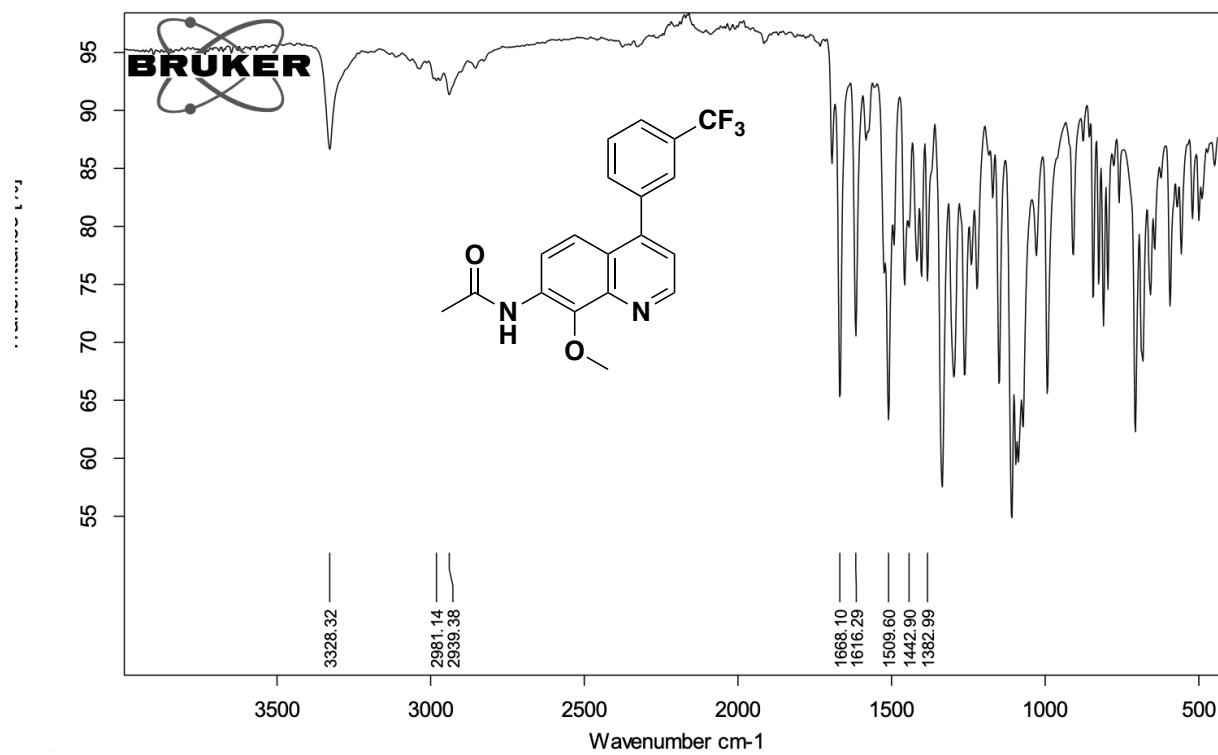
7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-methoxyquinoline (14) in CDCl₃



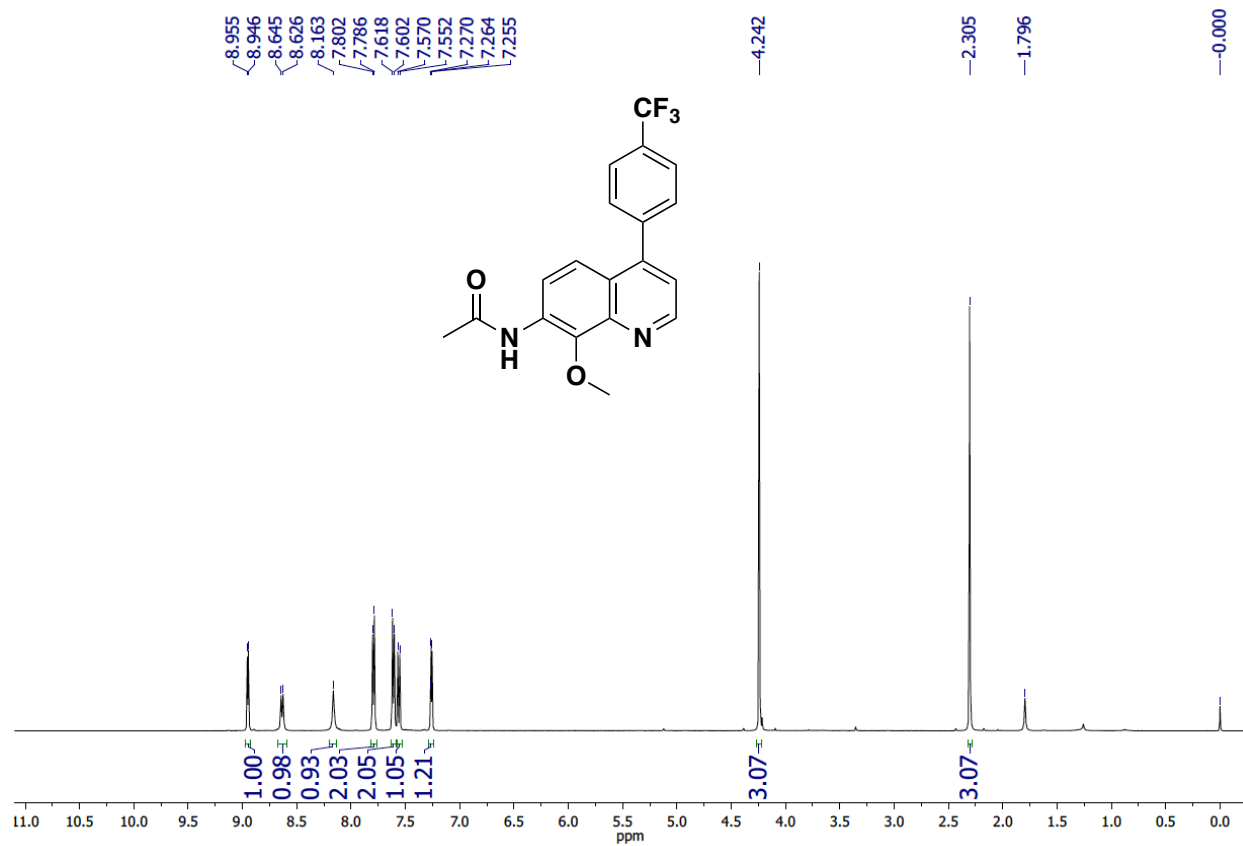
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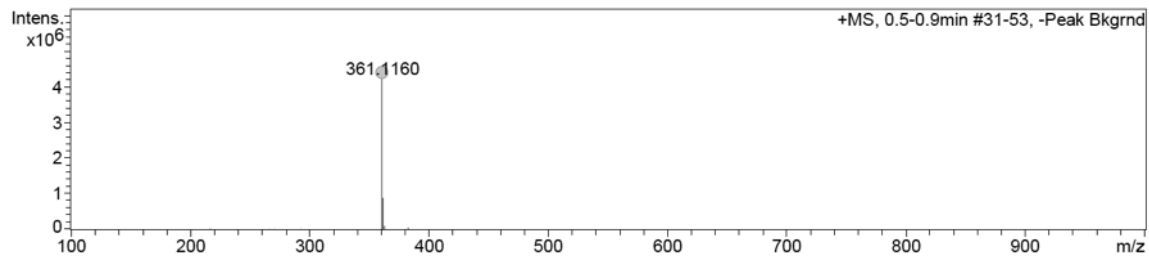
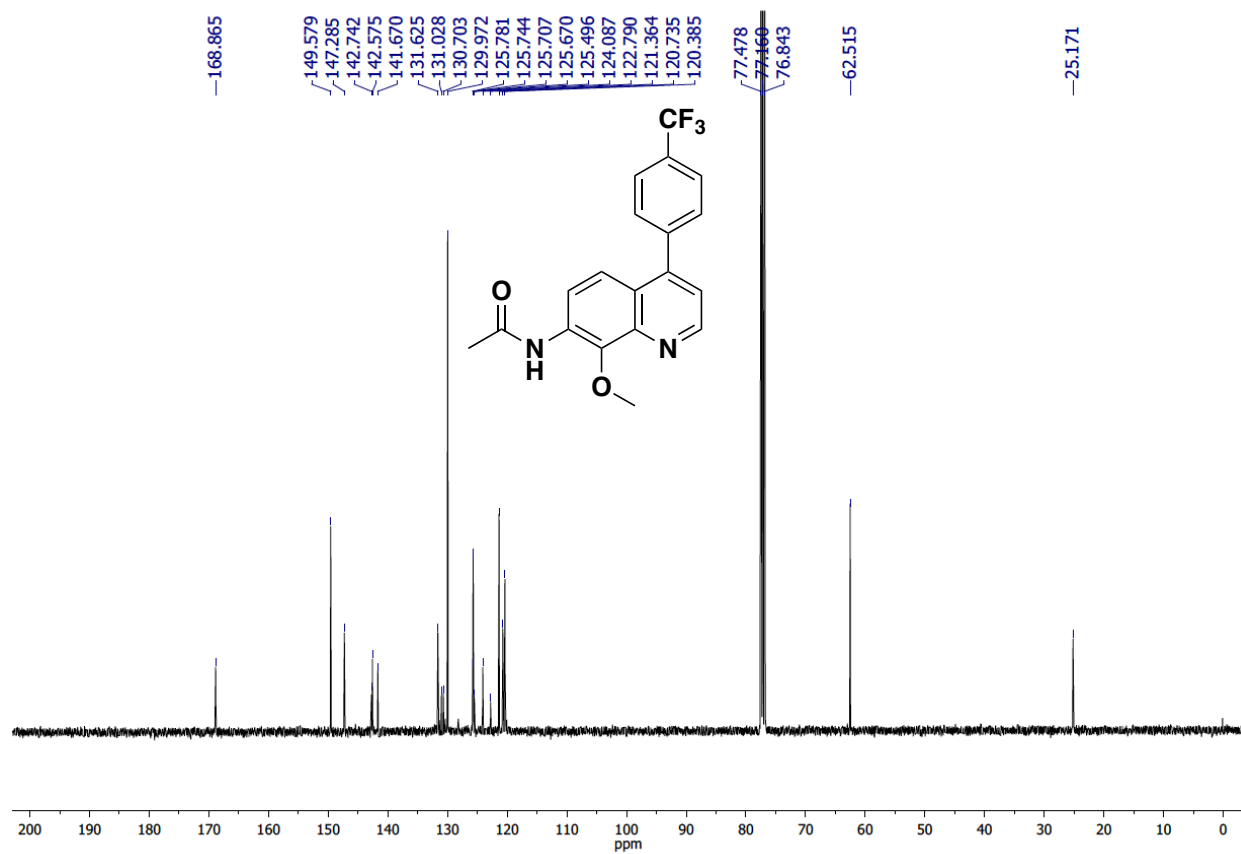
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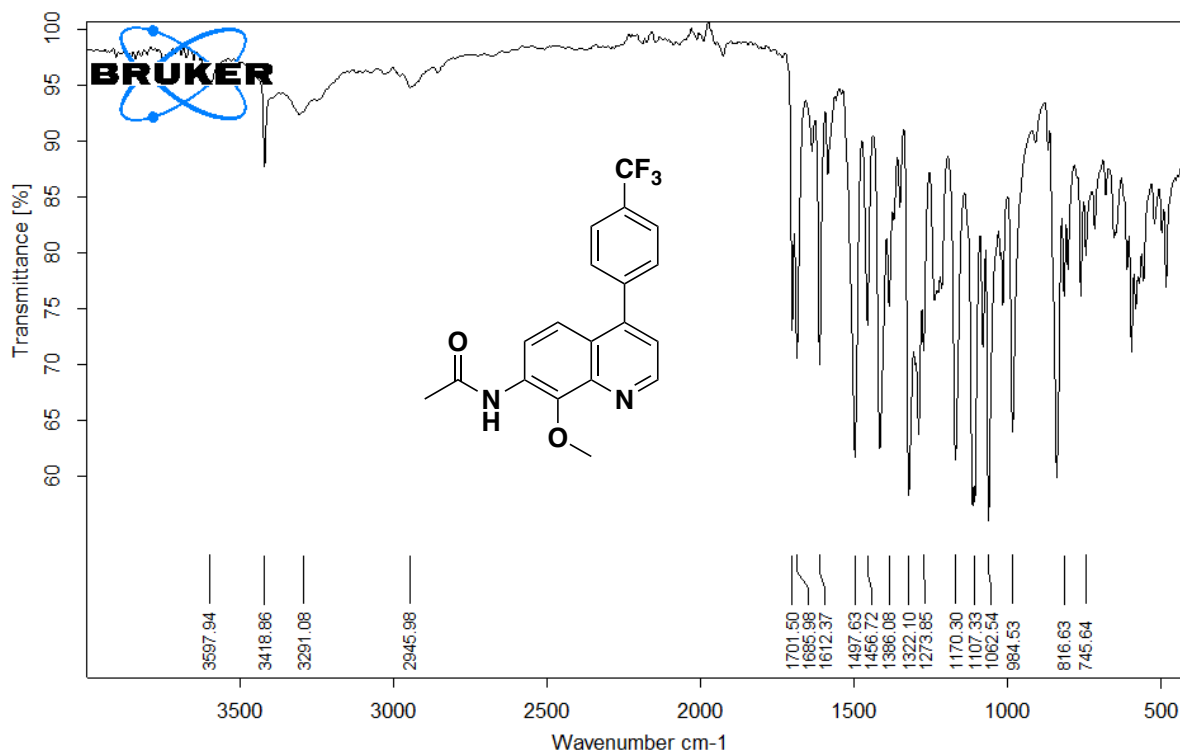
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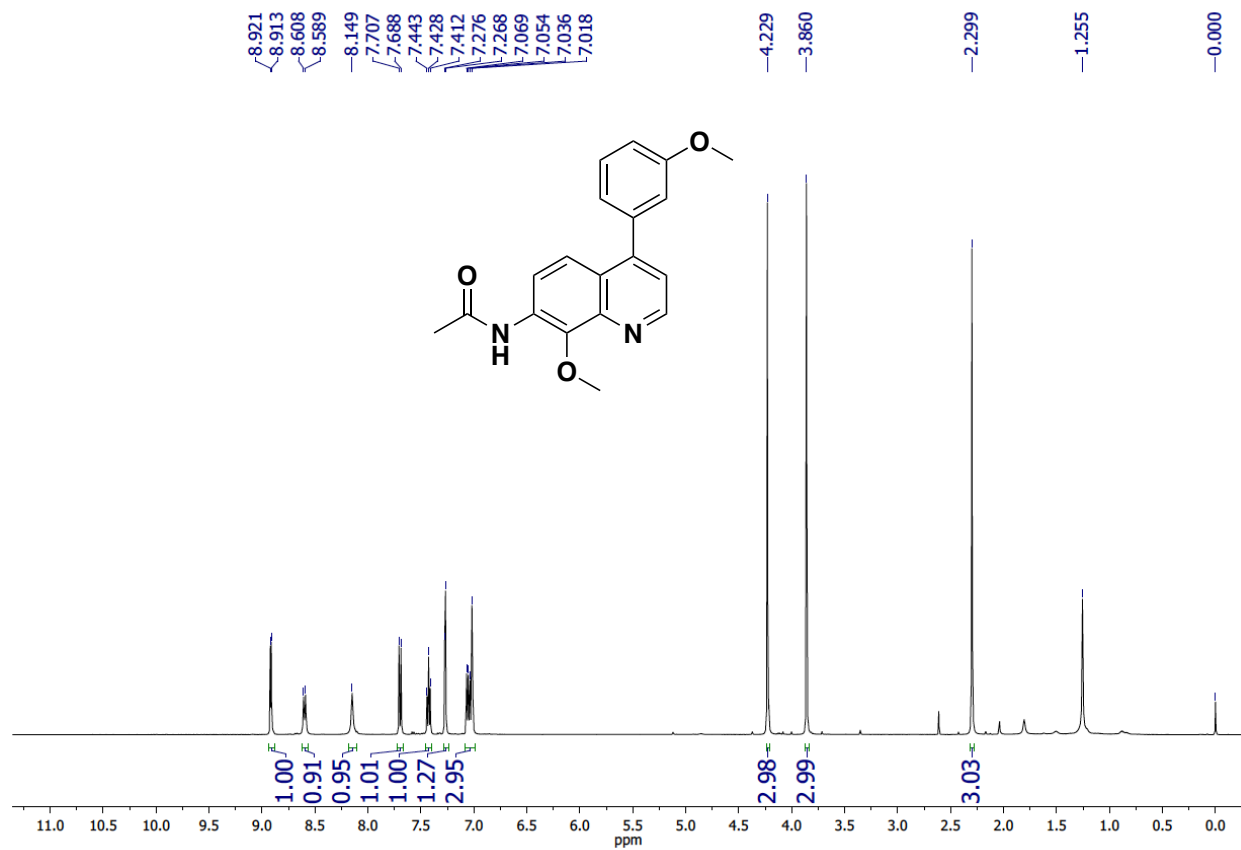
7-Acetamido-4-((4-trifluoromethyl)phenyl)-8-methoxyquinoline (15) in CDCl₃



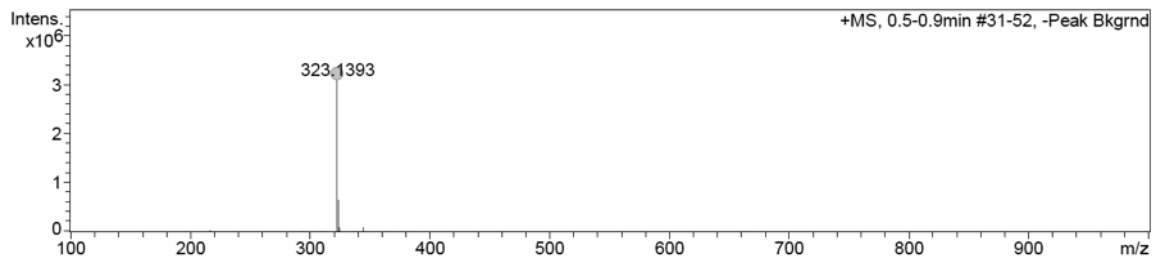
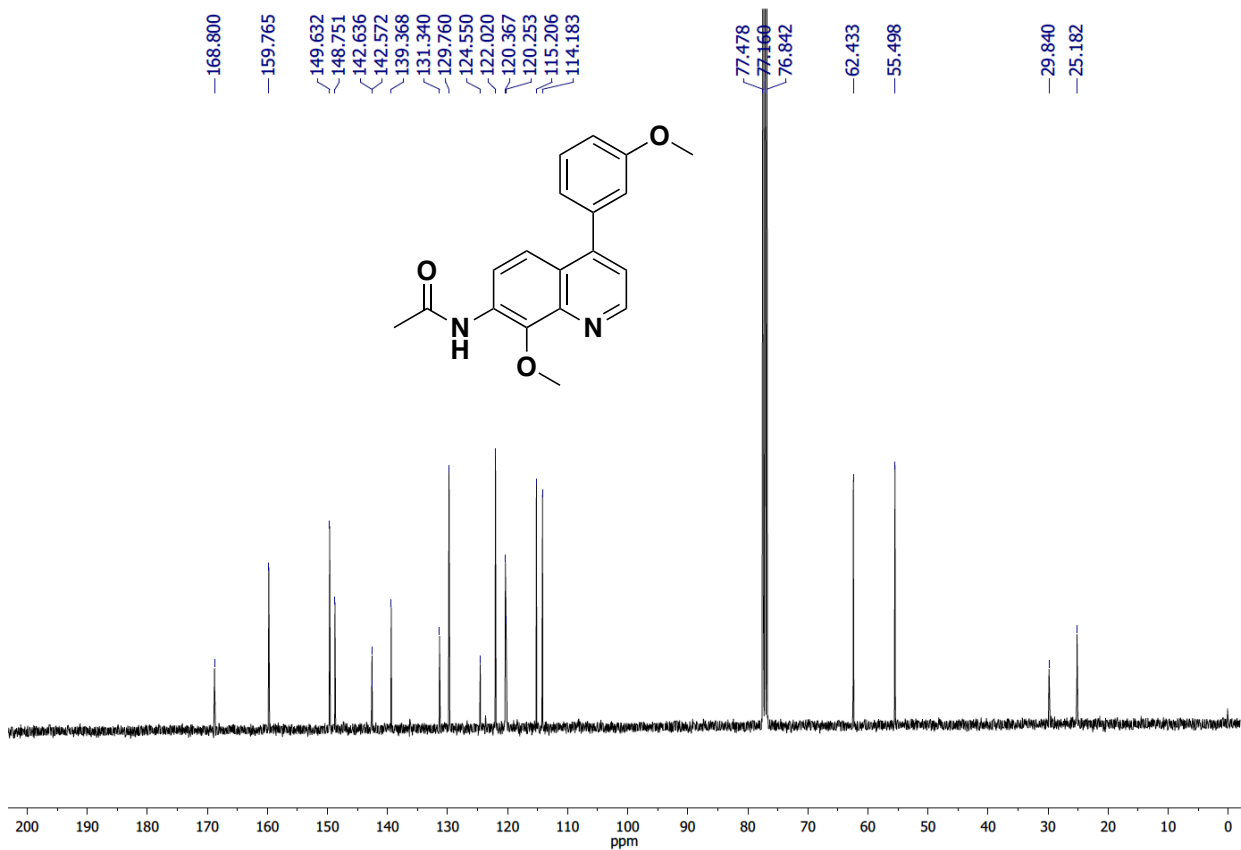
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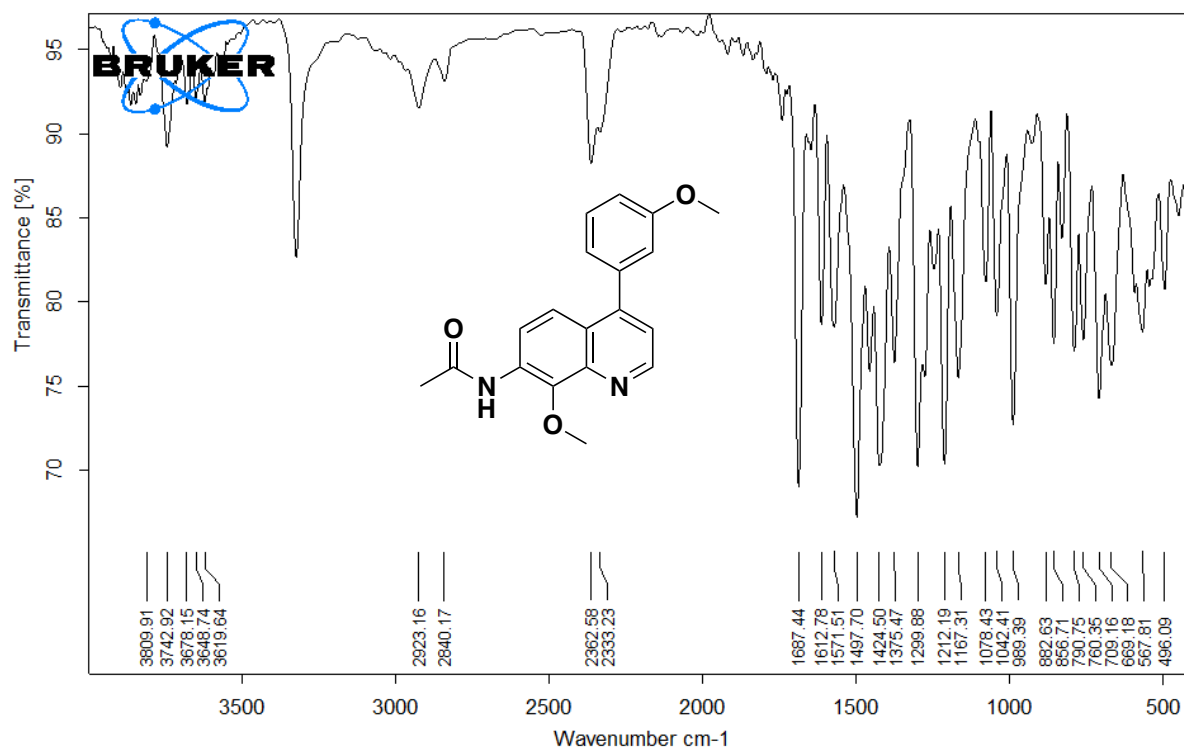
7-Acetamido-4-(3-methoxyphenyl)-8-methoxyquinoline (16) in CDCl₃



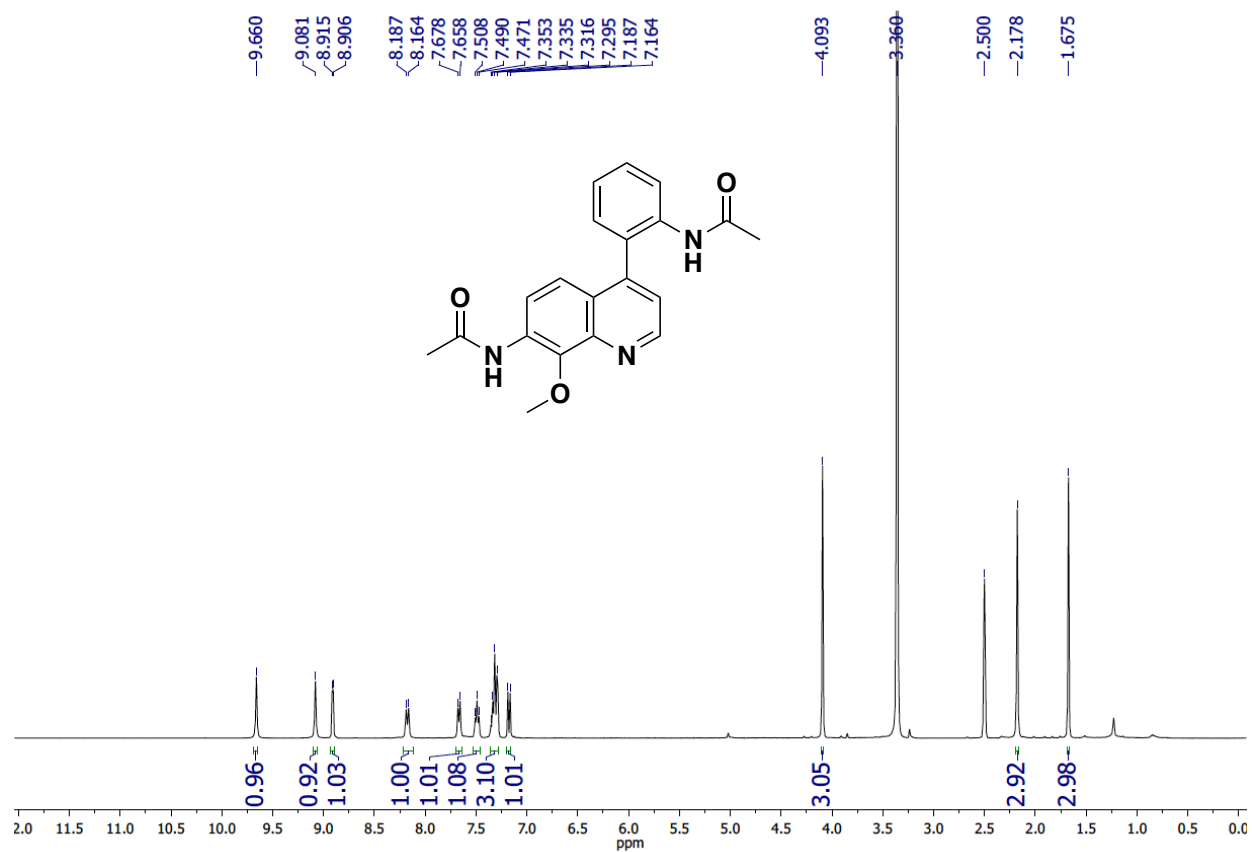
7-Acetamido-4-(3-methoxyphenyl)-8-methoxyquinoline (16) in CDCl₃



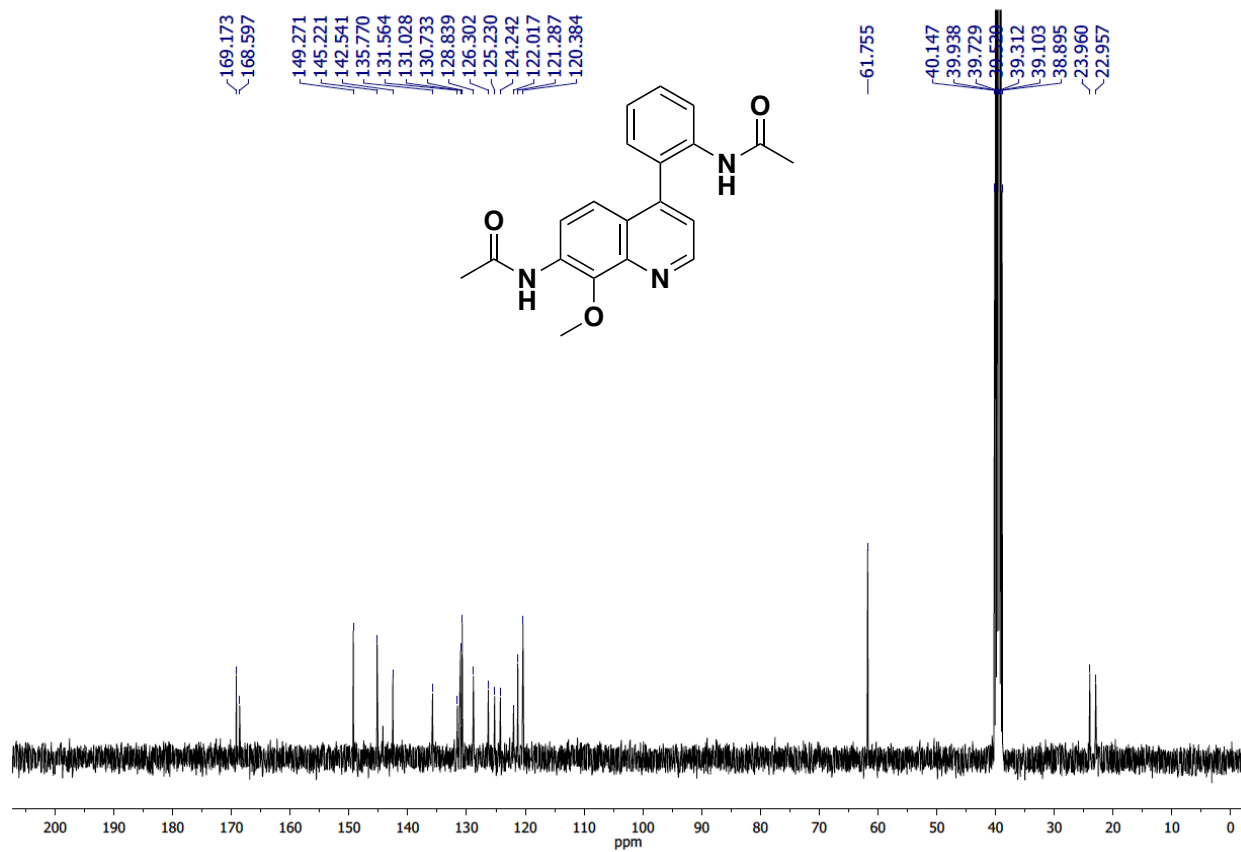
7-Acetamido-4-(3-methoxyphenyl)-8-methoxyquinoline (16)



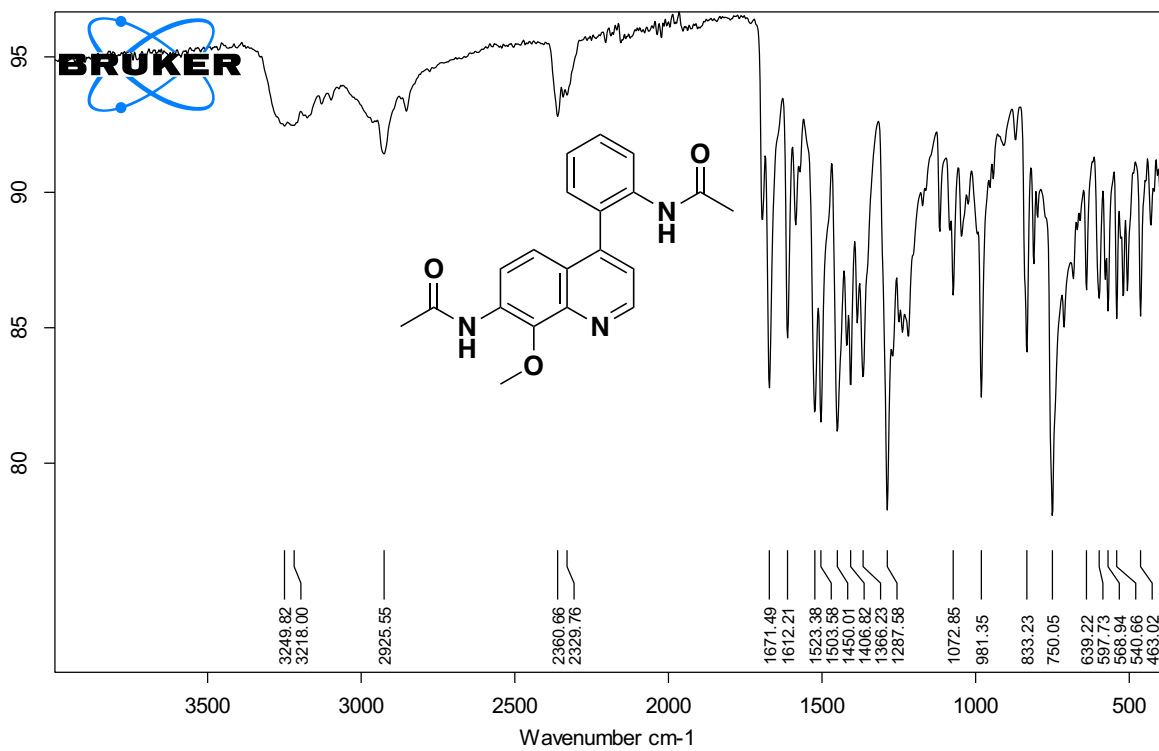
7-Acetamido-4-(2-acetamidophenyl)-8-methoxyquinoline (17) in DMSO-d₆



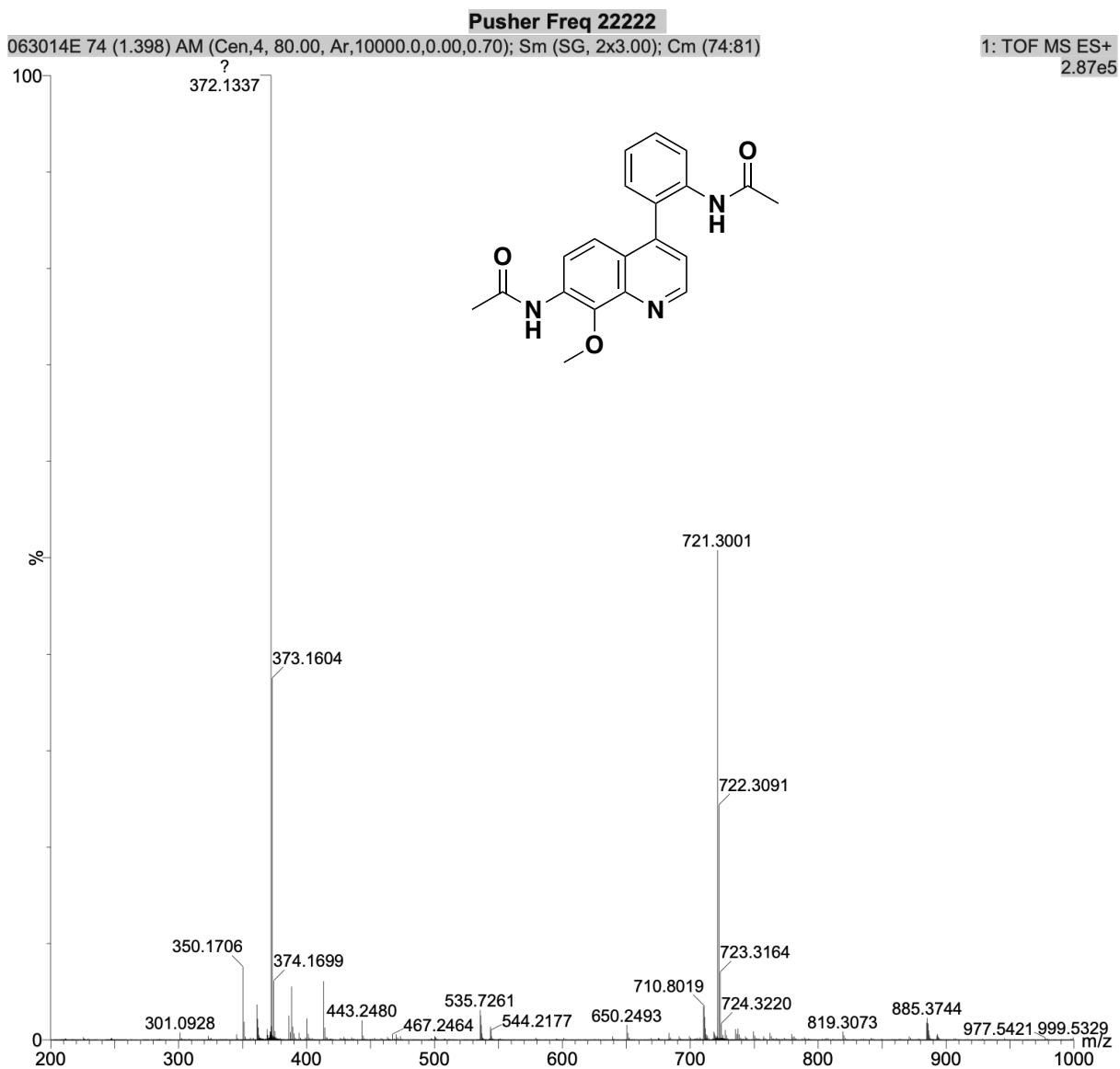
7-Acetamido-4-(2-acetamidophenyl)-8-methoxyquinoline (17) in DMSO-d₆



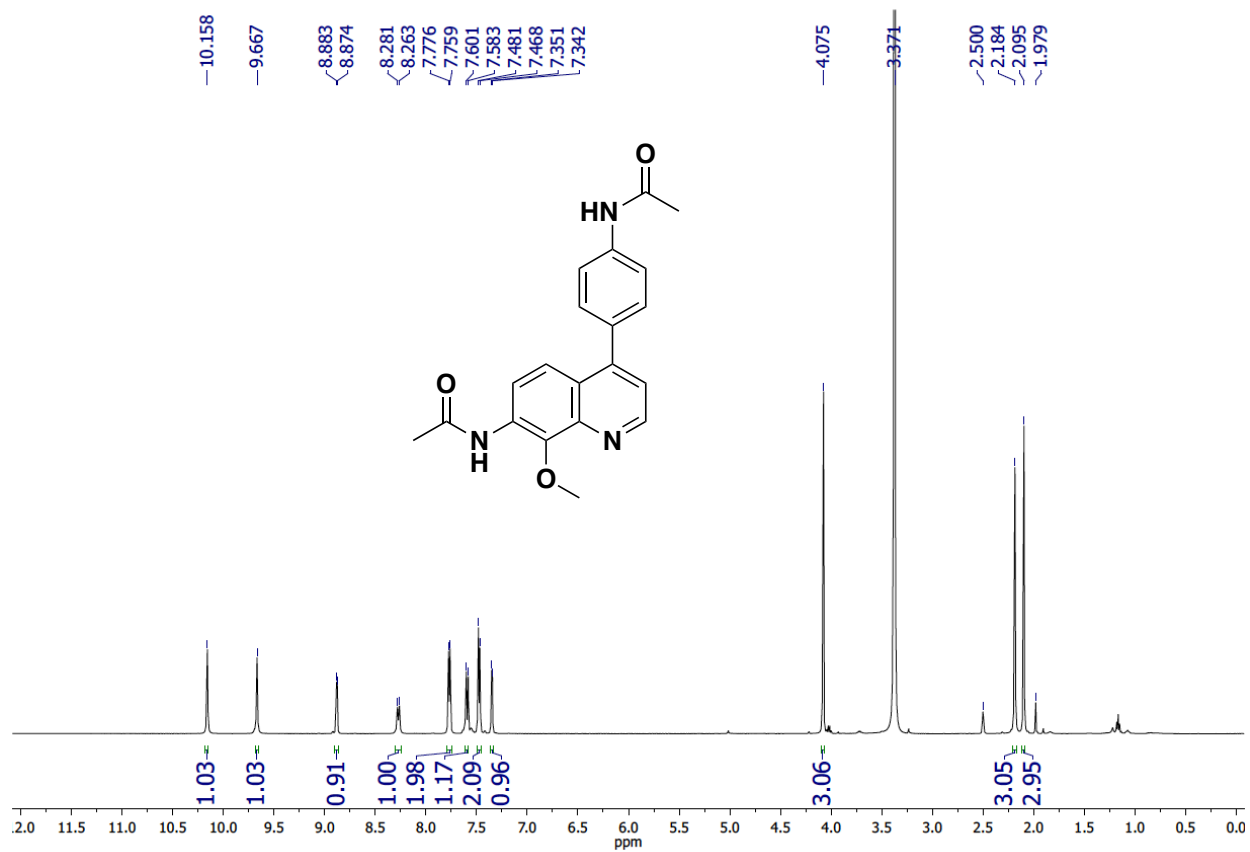
7-Acetamido-4-(2-acetamidophenyl)-8-methoxyquinoline (17)



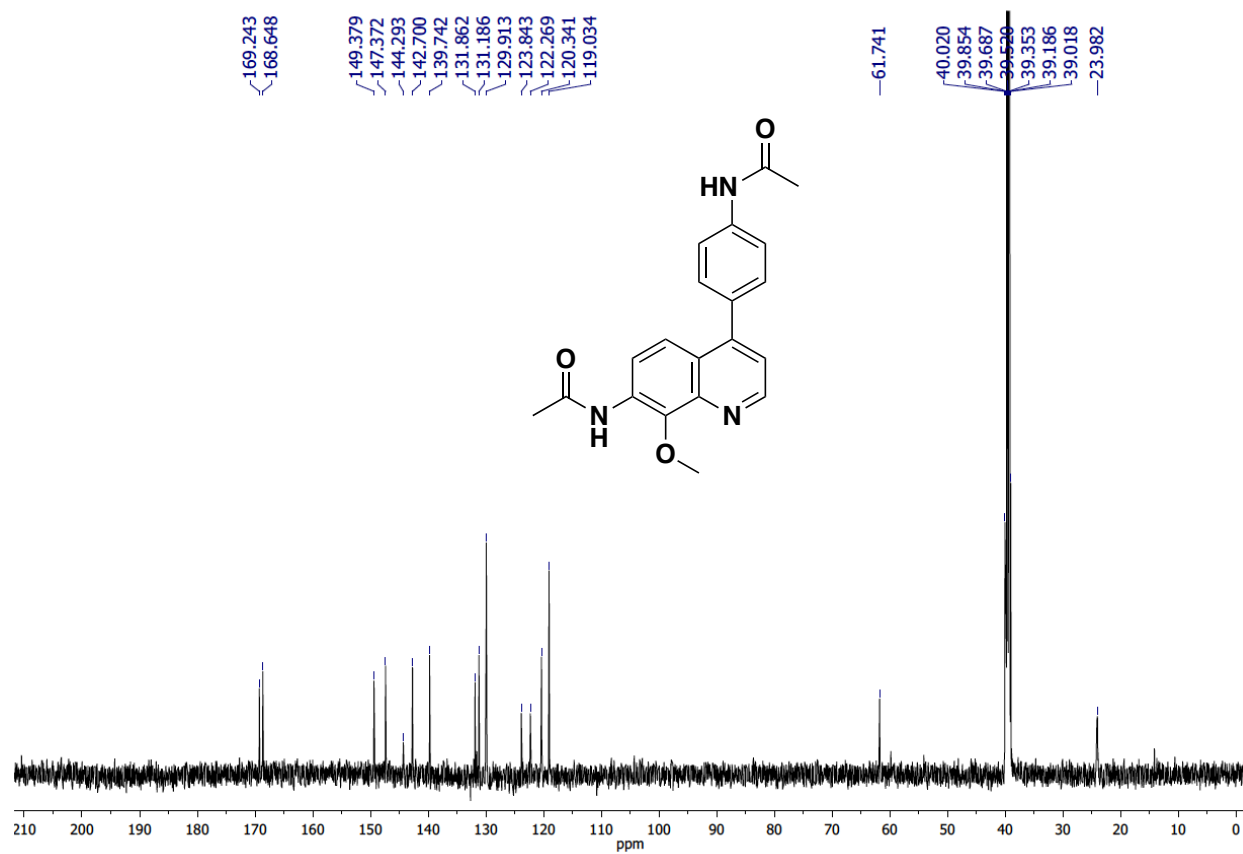
7-Acetamido-4-(2-acetamidophenyl)-8-methoxyquinoline (17)



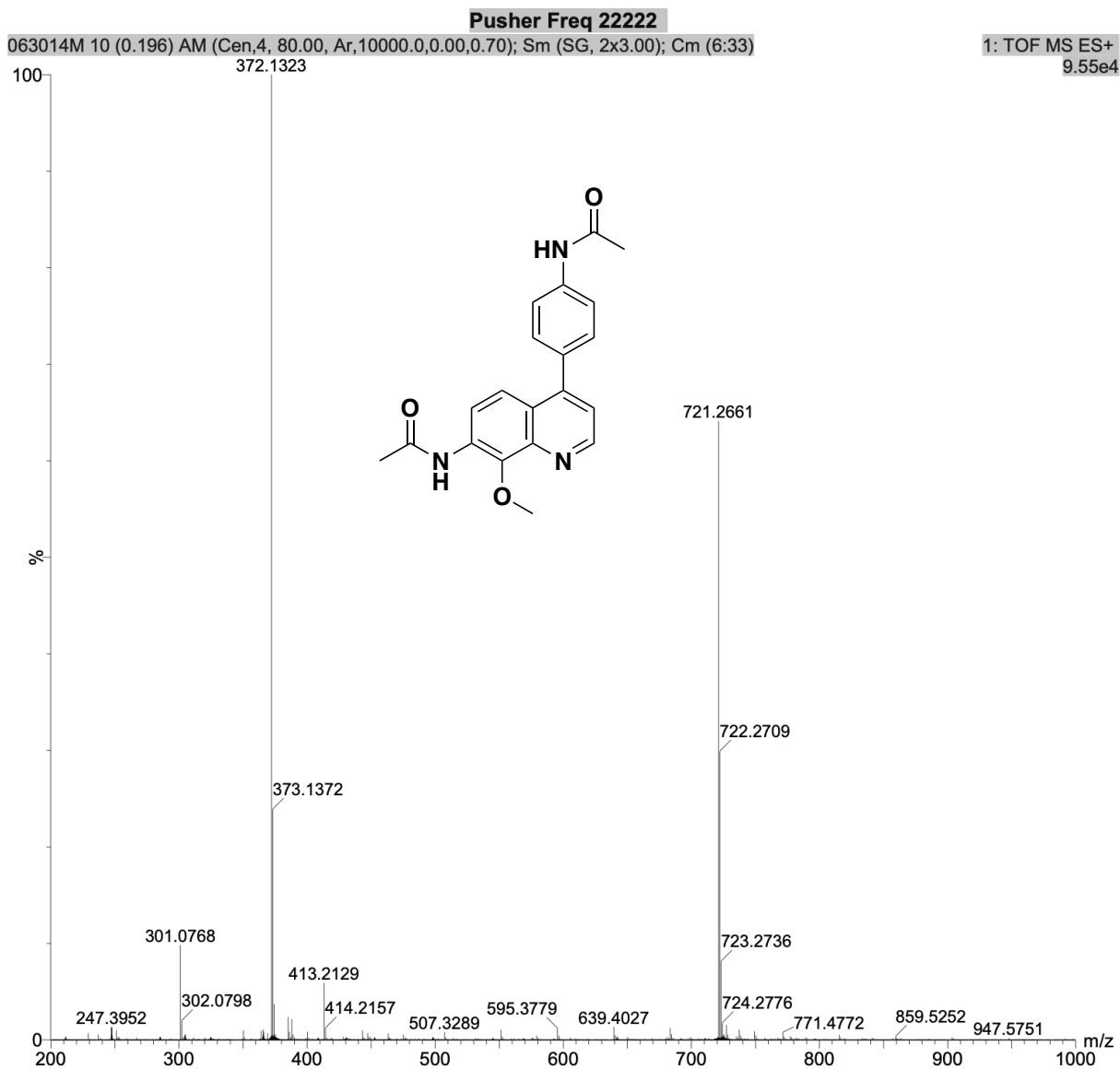
7-Acetamido-4-(4-acetamidophenyl)-8-methoxyquinoline (18) in DMSO



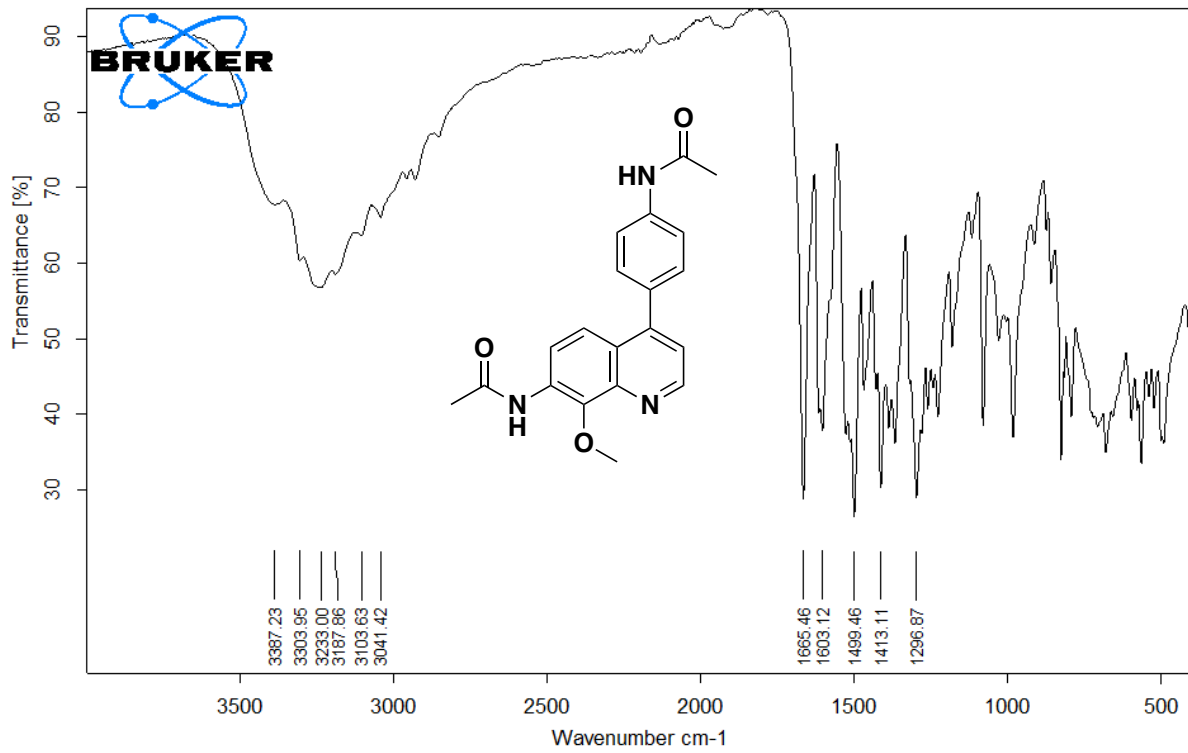
7-Acetamido-4-(4-acetamidophenyl)-8-methoxyquinoline (18) in DMSO



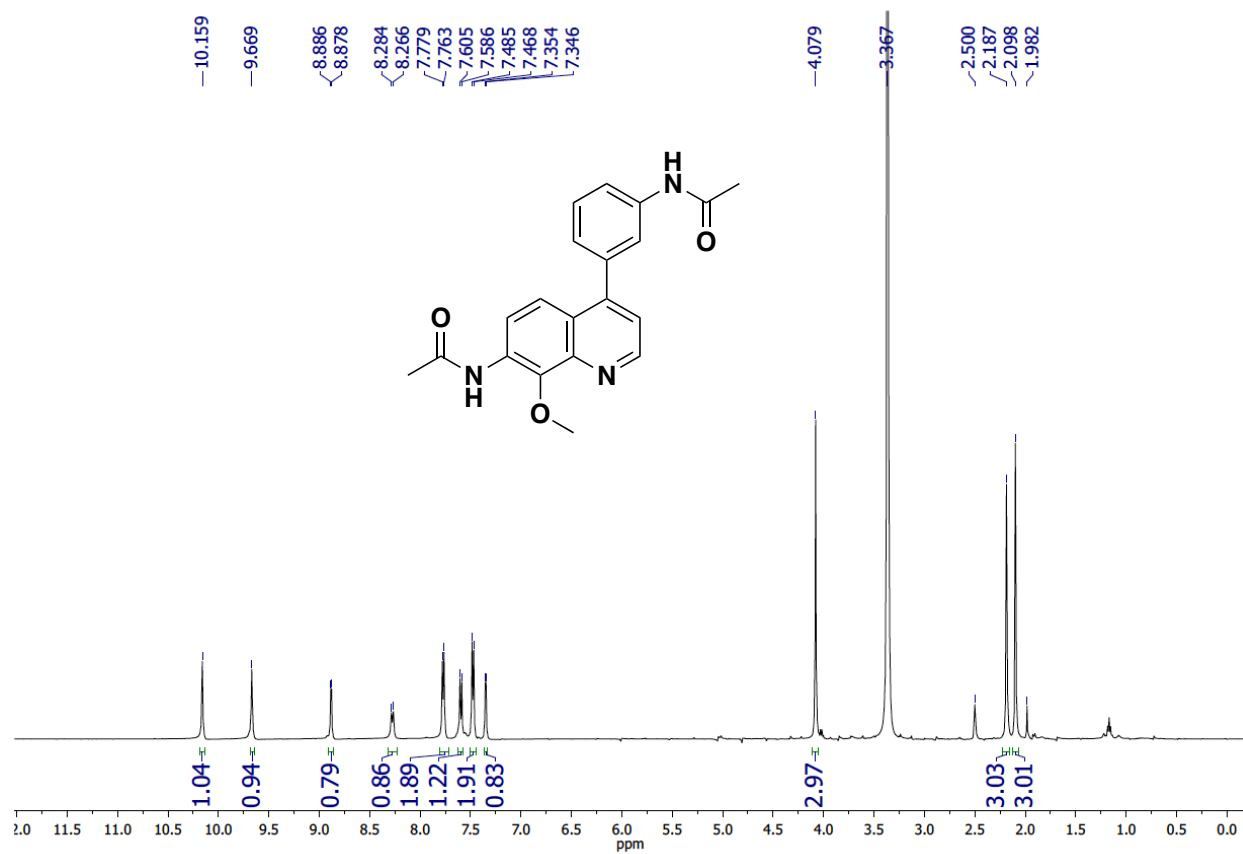
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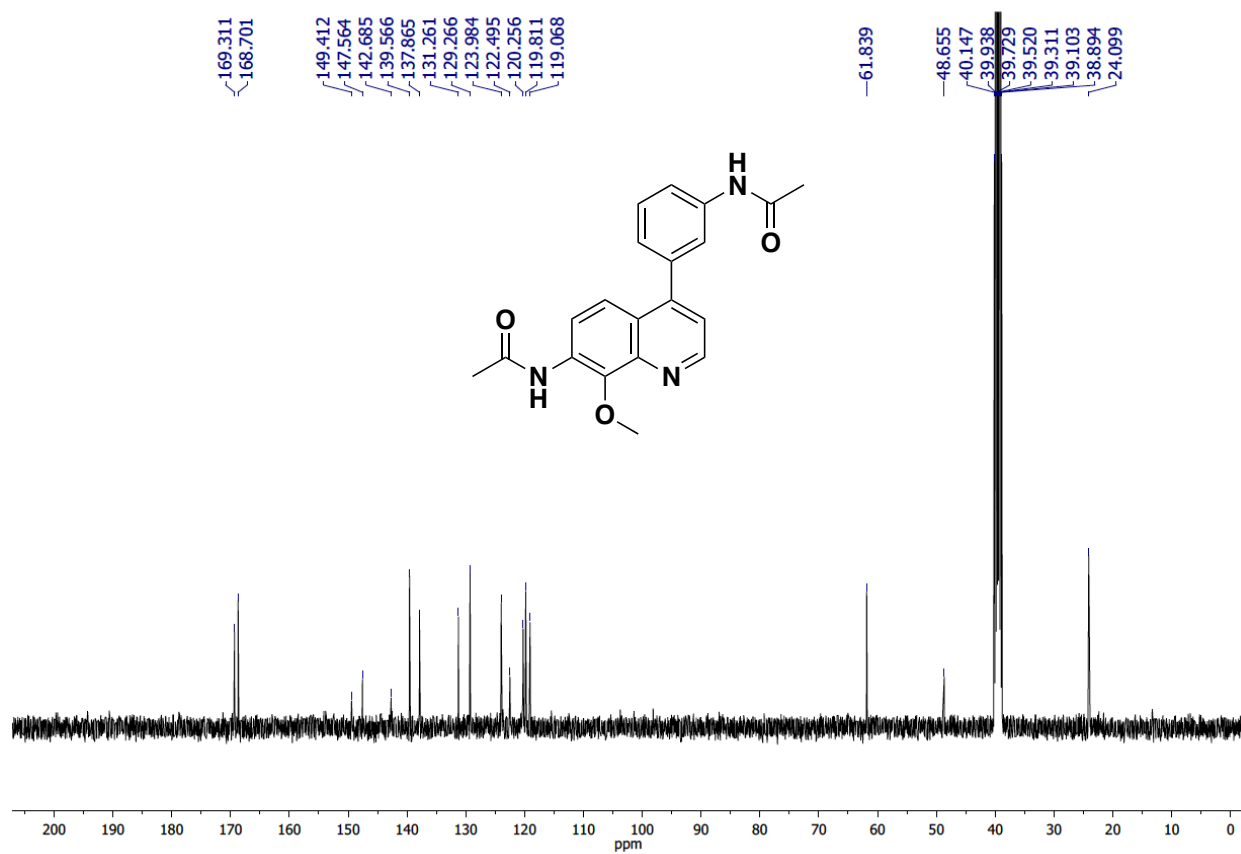
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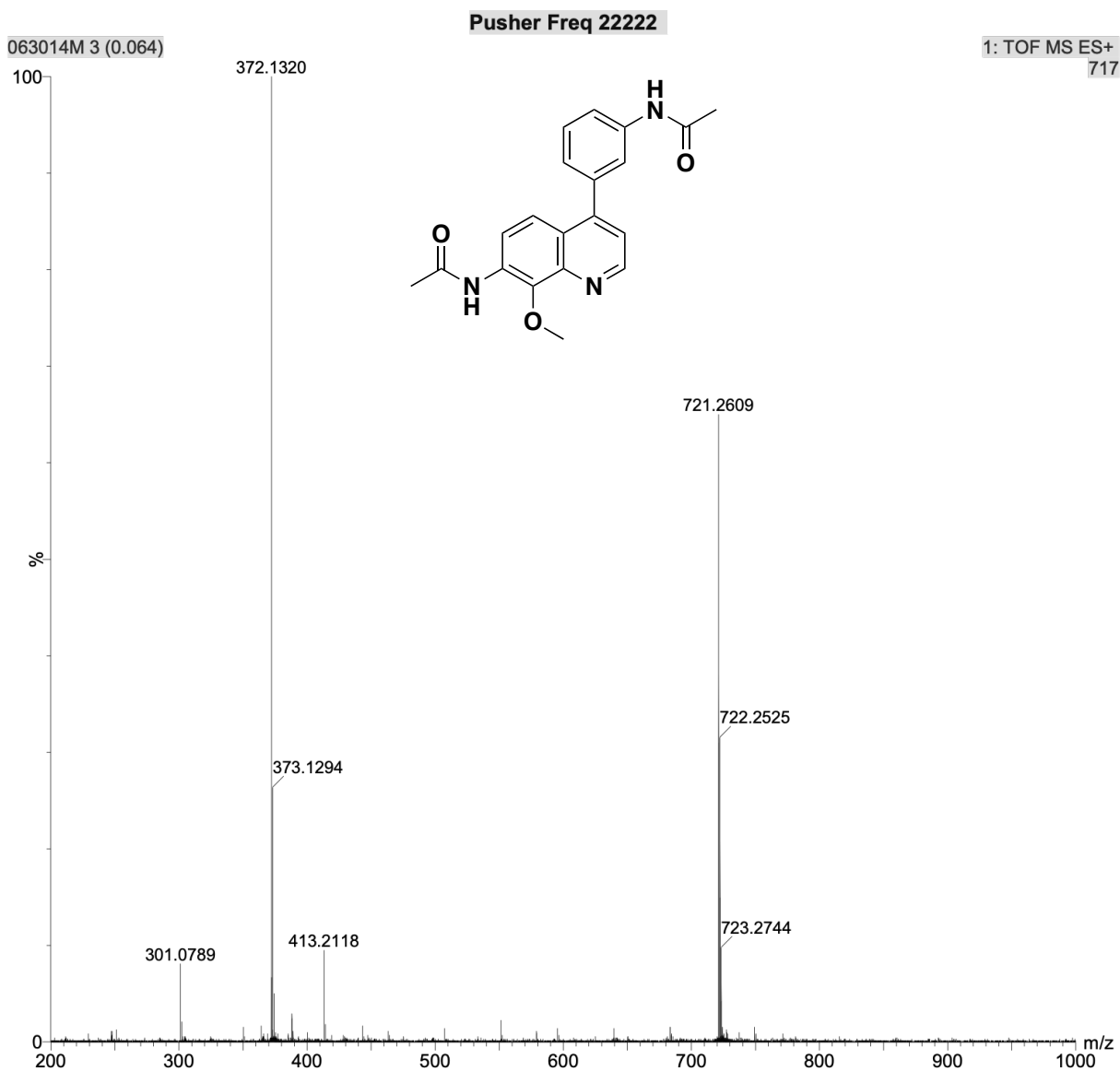
7-Acetamido-4-(3-acetamidophenyl)-8-methoxyquinoline (19) in DMSO



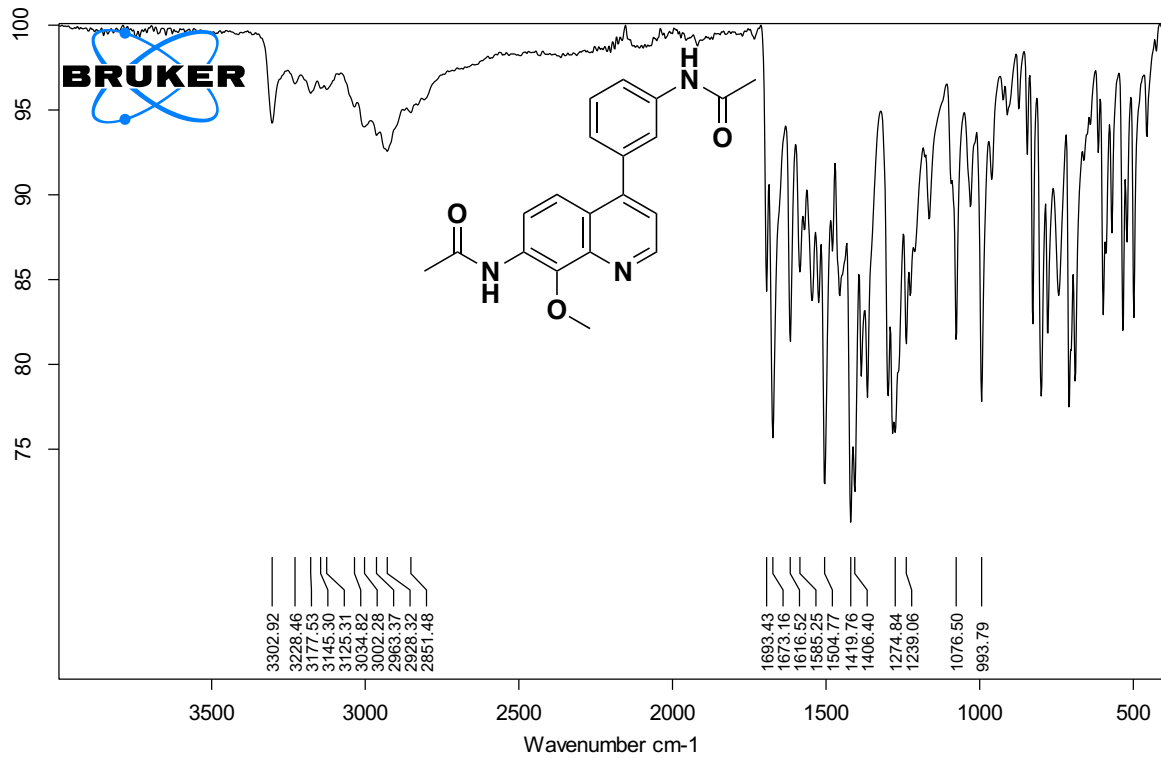
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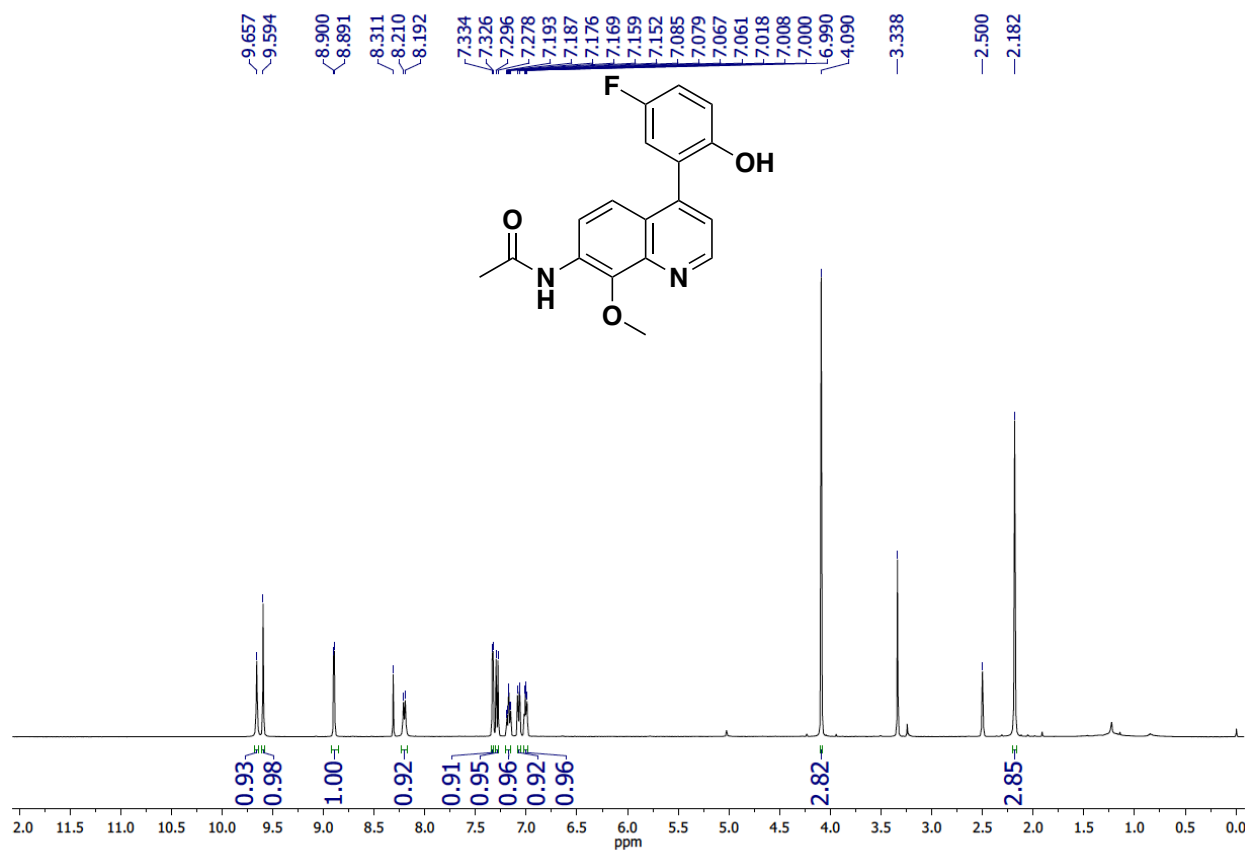
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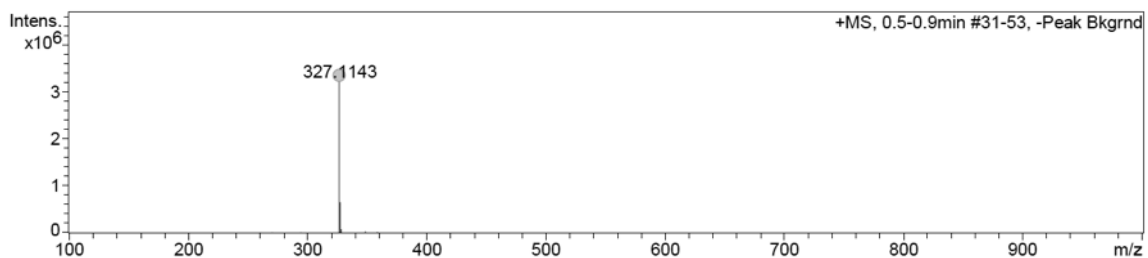
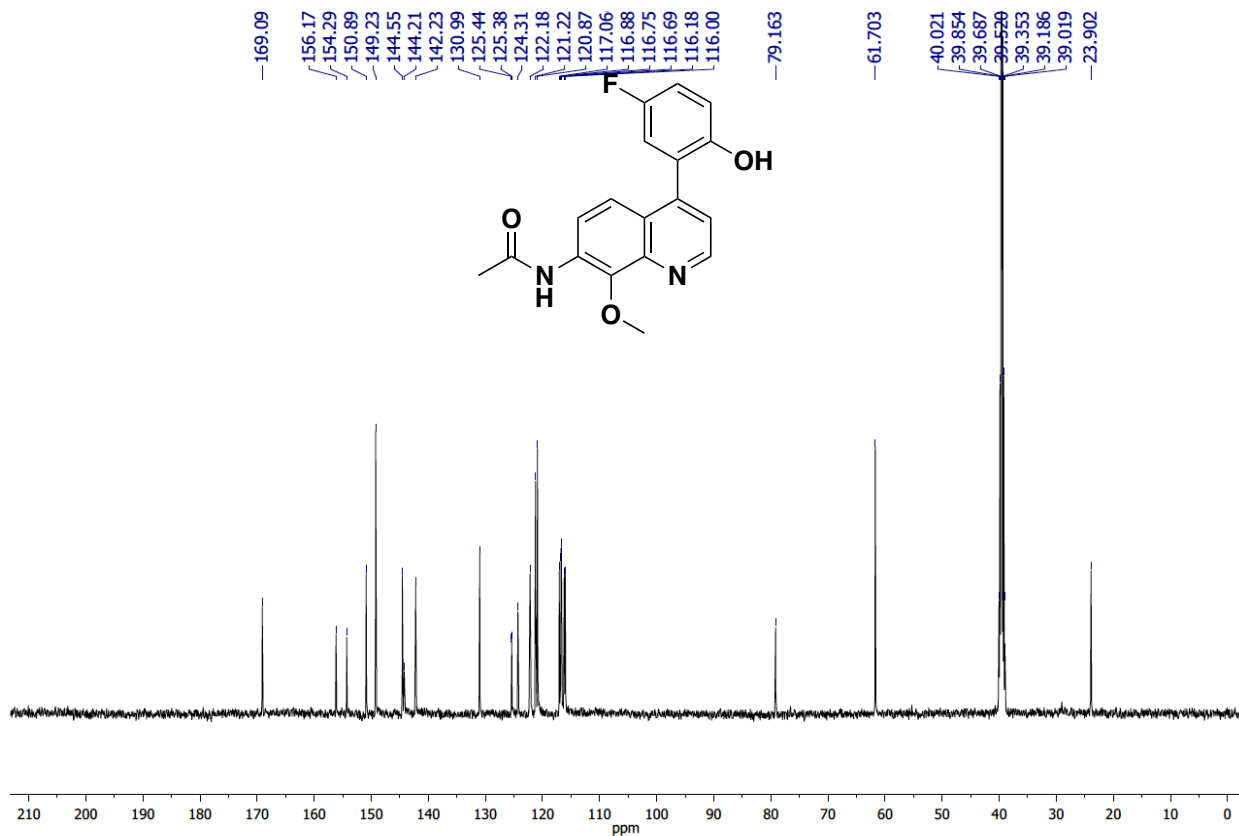
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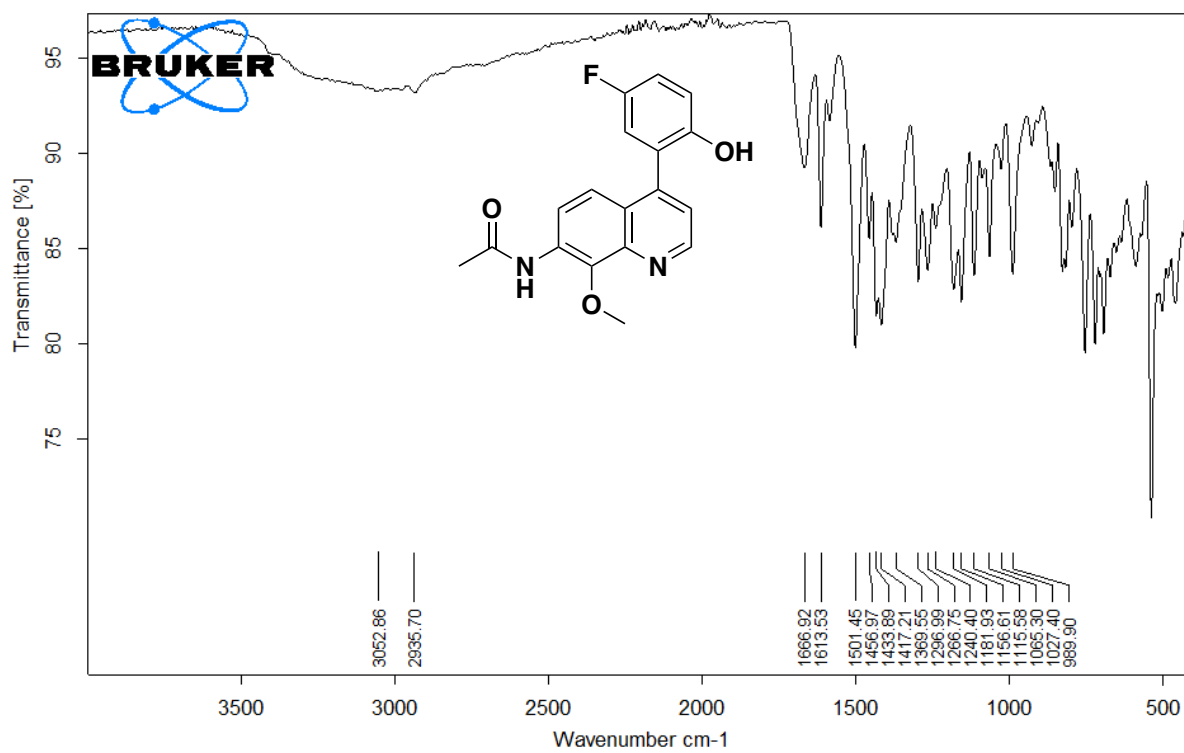
7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-methoxyquinoline (20) in DMSO-d₆



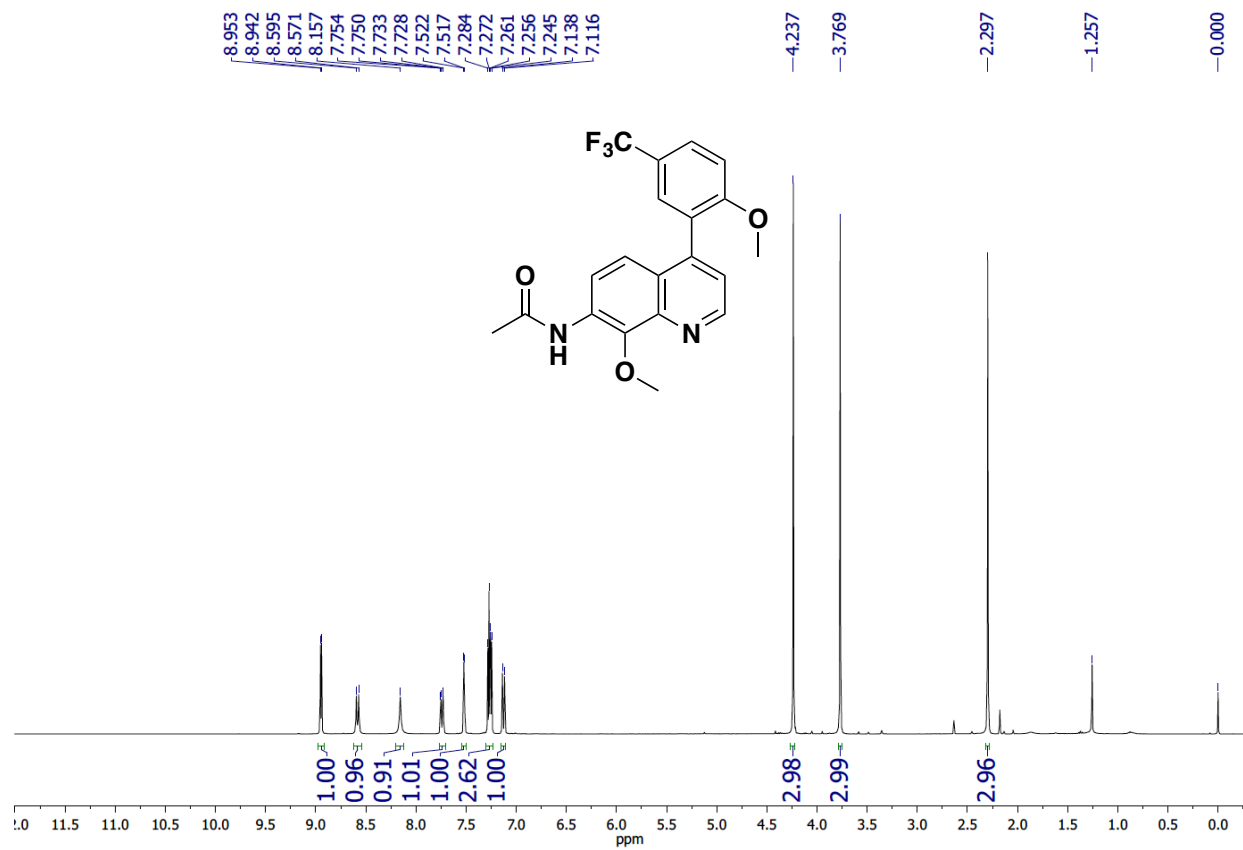
7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-methoxyquinoline (20) in DMSO-d₆



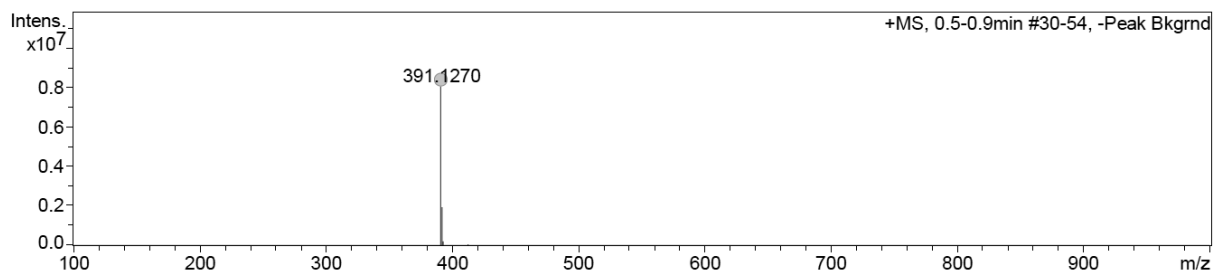
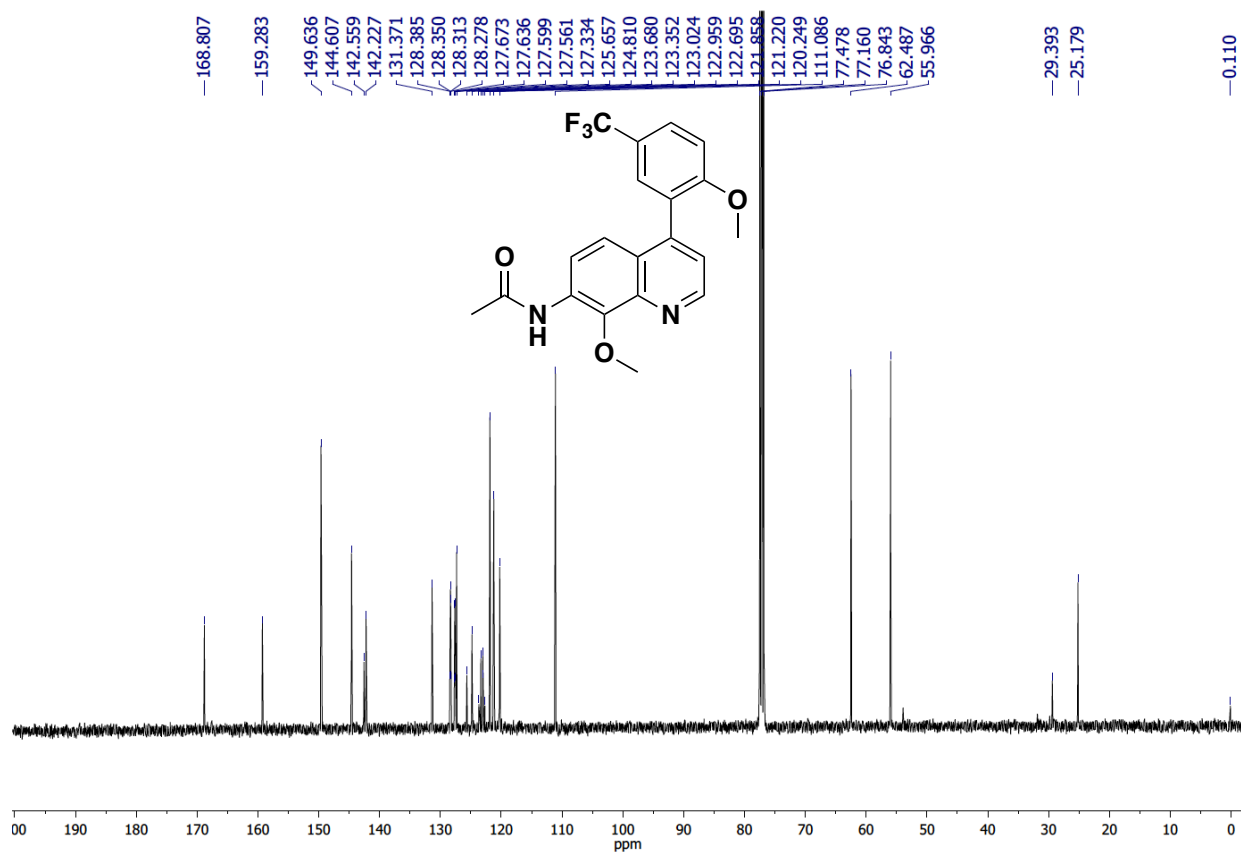
7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-methoxyquinoline (20)



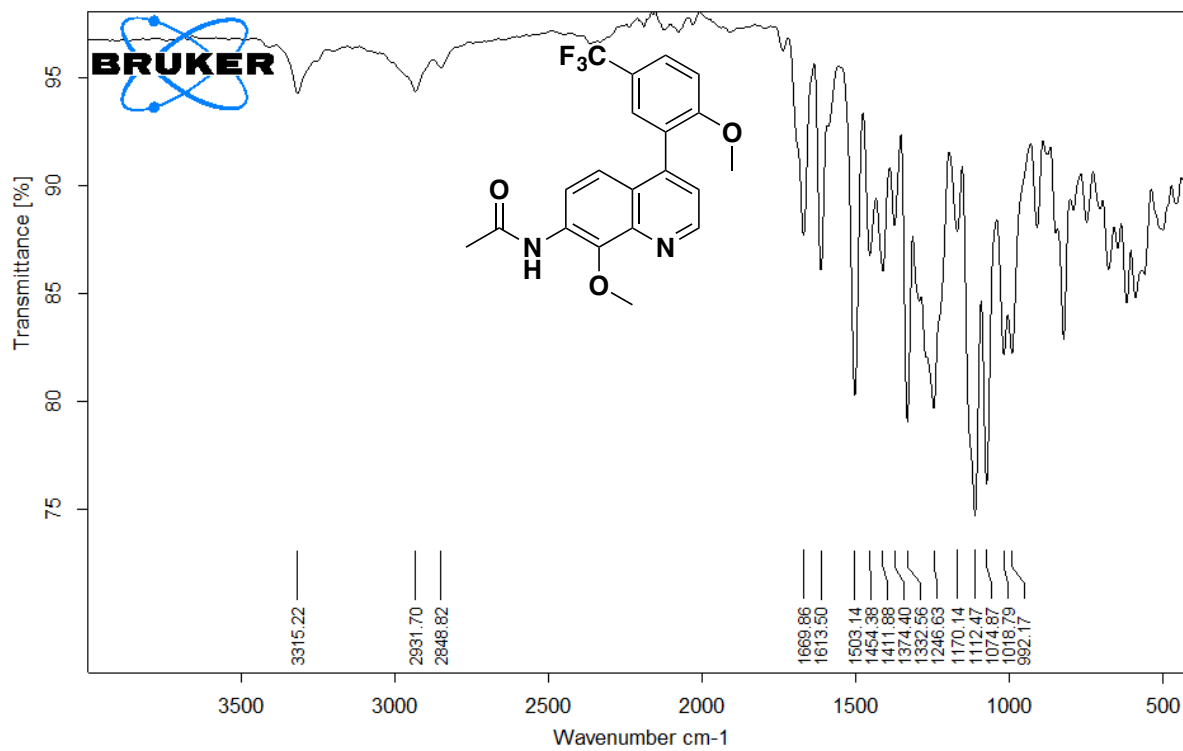
7-Acetamido-4-(2-methoxy-(5-trifluoromethyl)phenyl)-8-methoxyquinoline (21) in CDCl₃



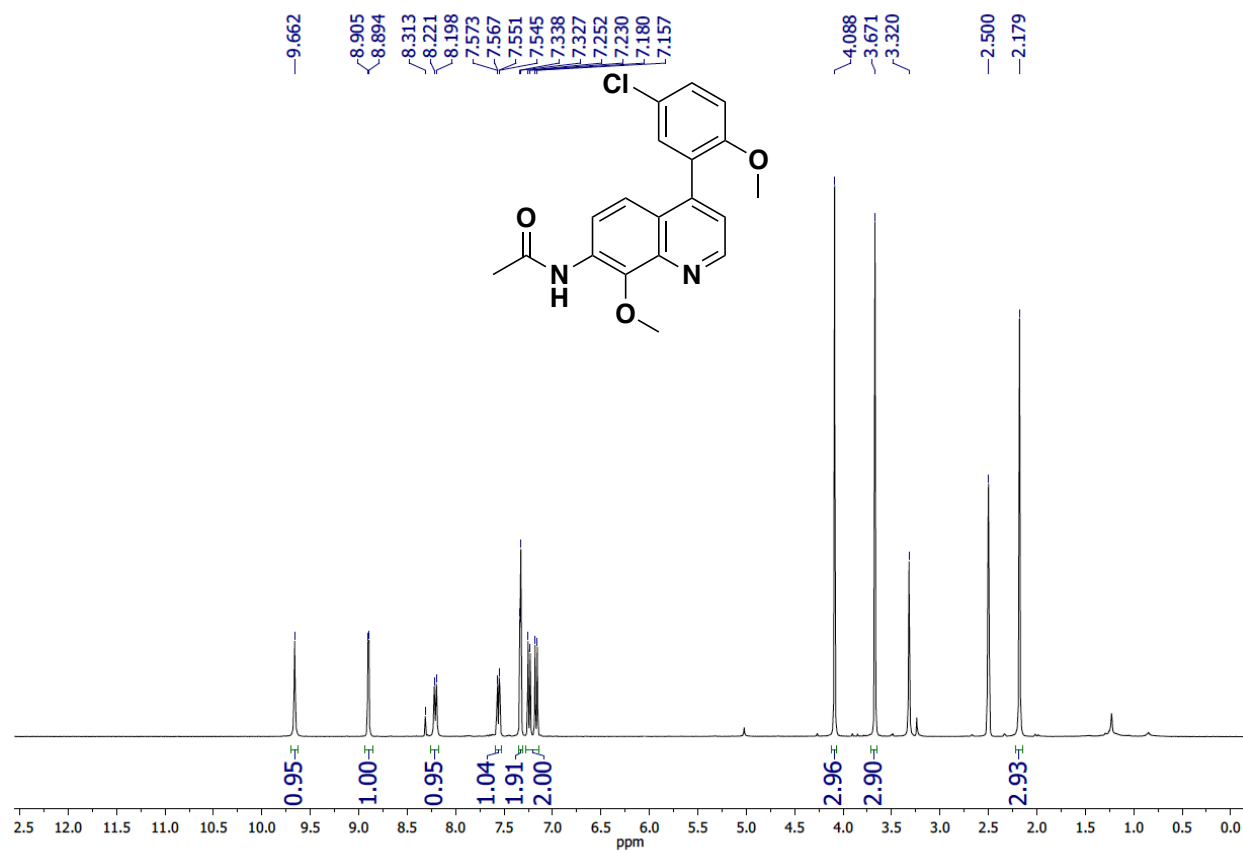
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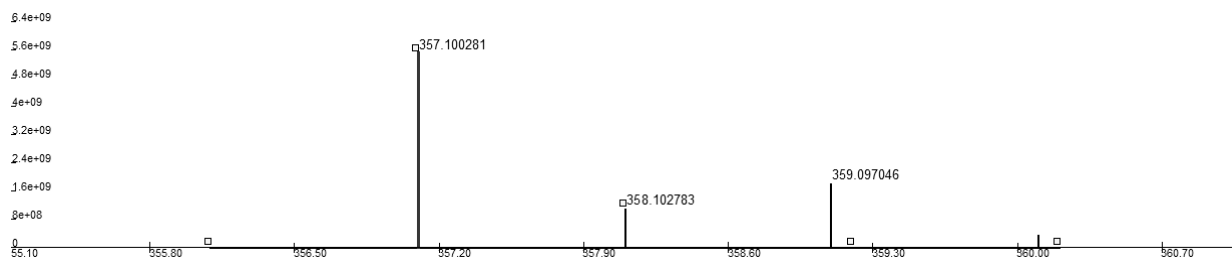
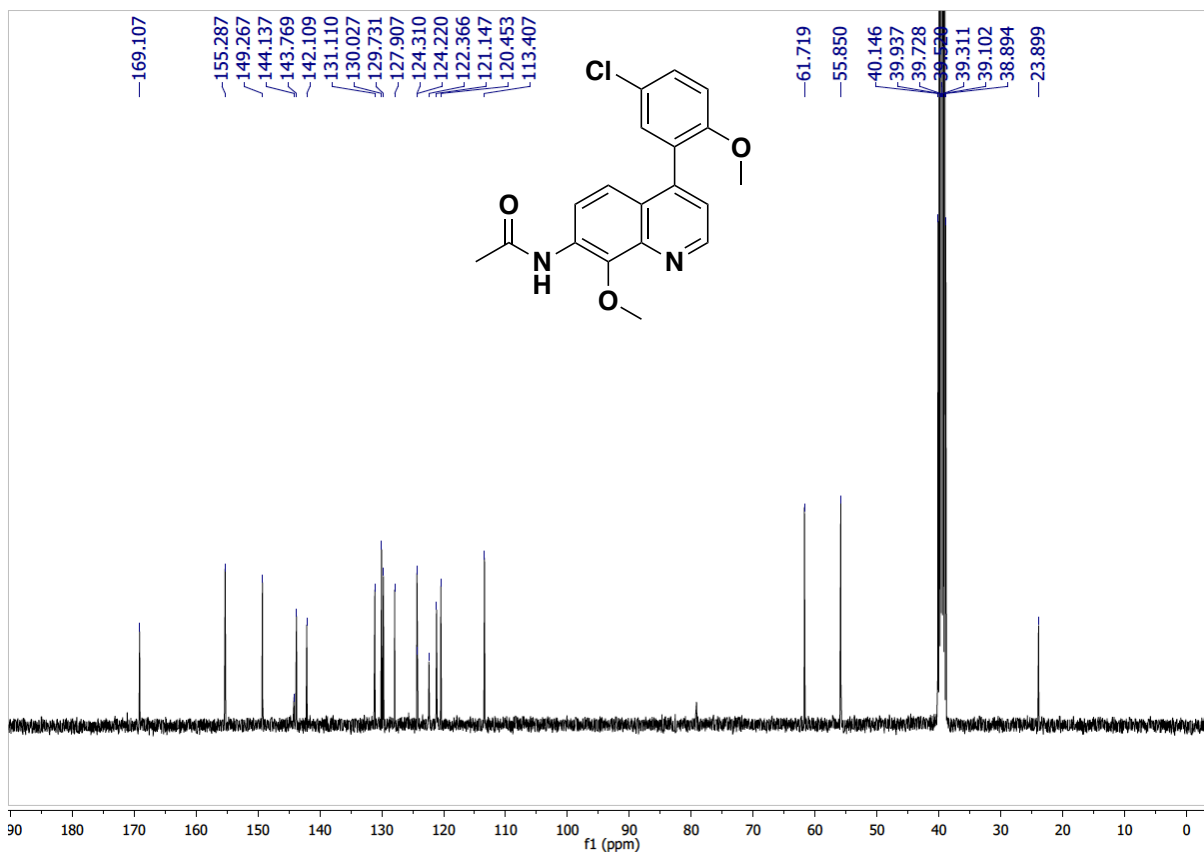
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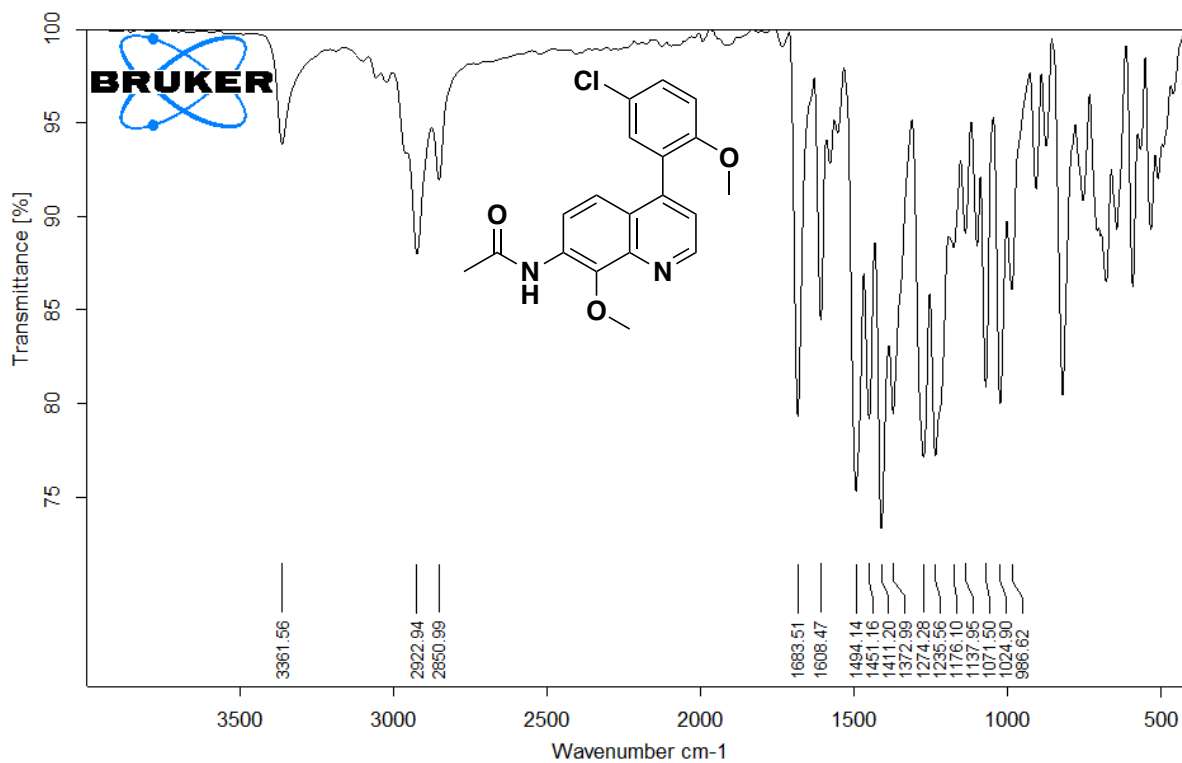
7-Acetamido-4-(5-chloro-2-methoxyphenyl)-8-methoxyquinoline (22) in DMSO



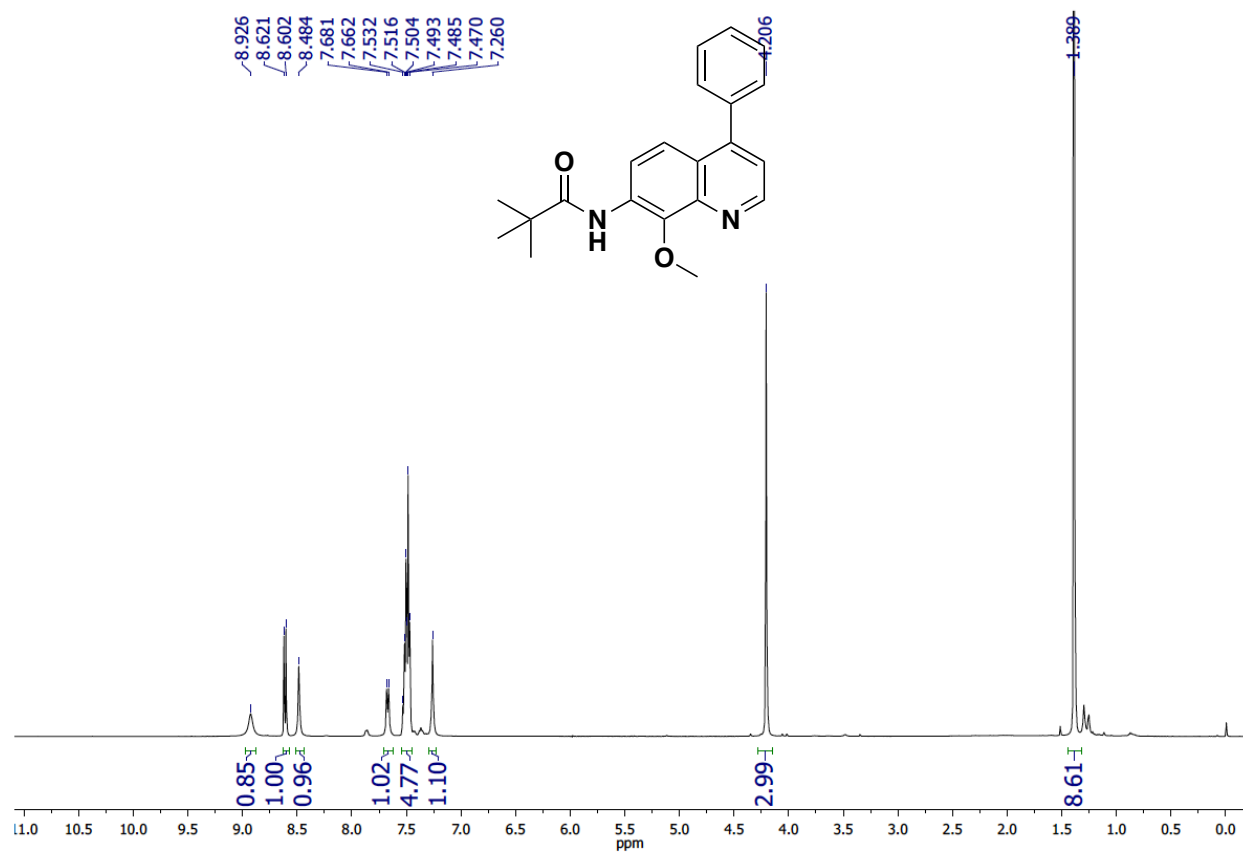
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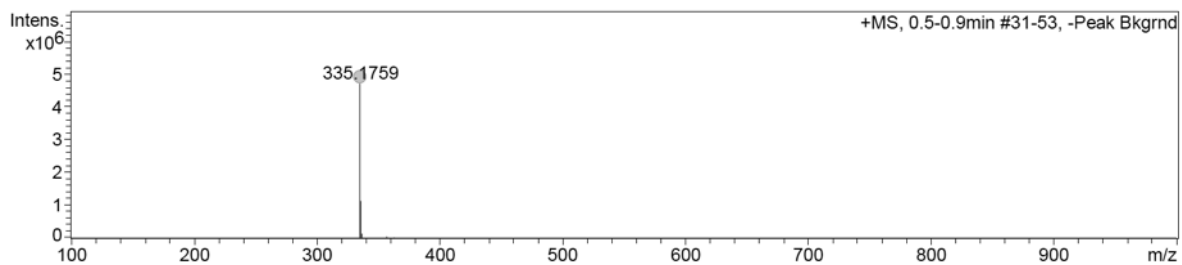
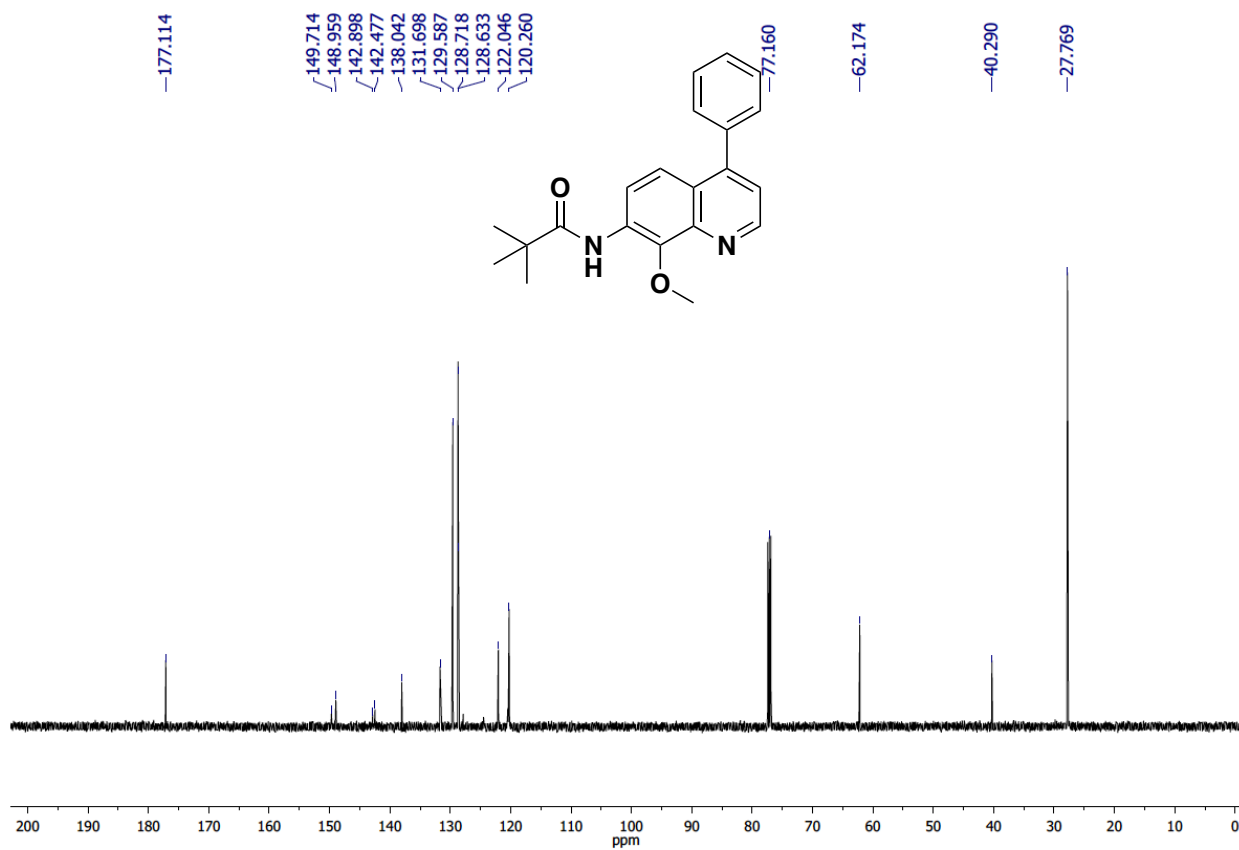
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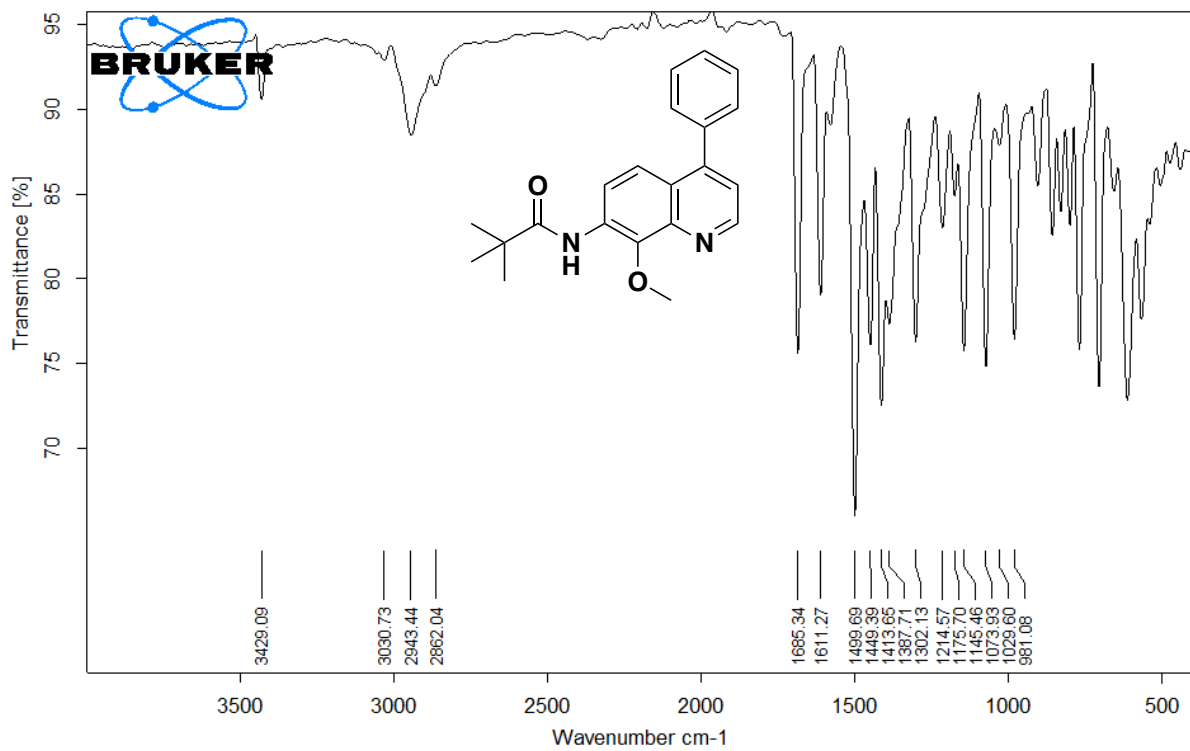
8-Methoxy-4-(phenyl)-7-pivalamidoquinoline (23) in CDCl₃



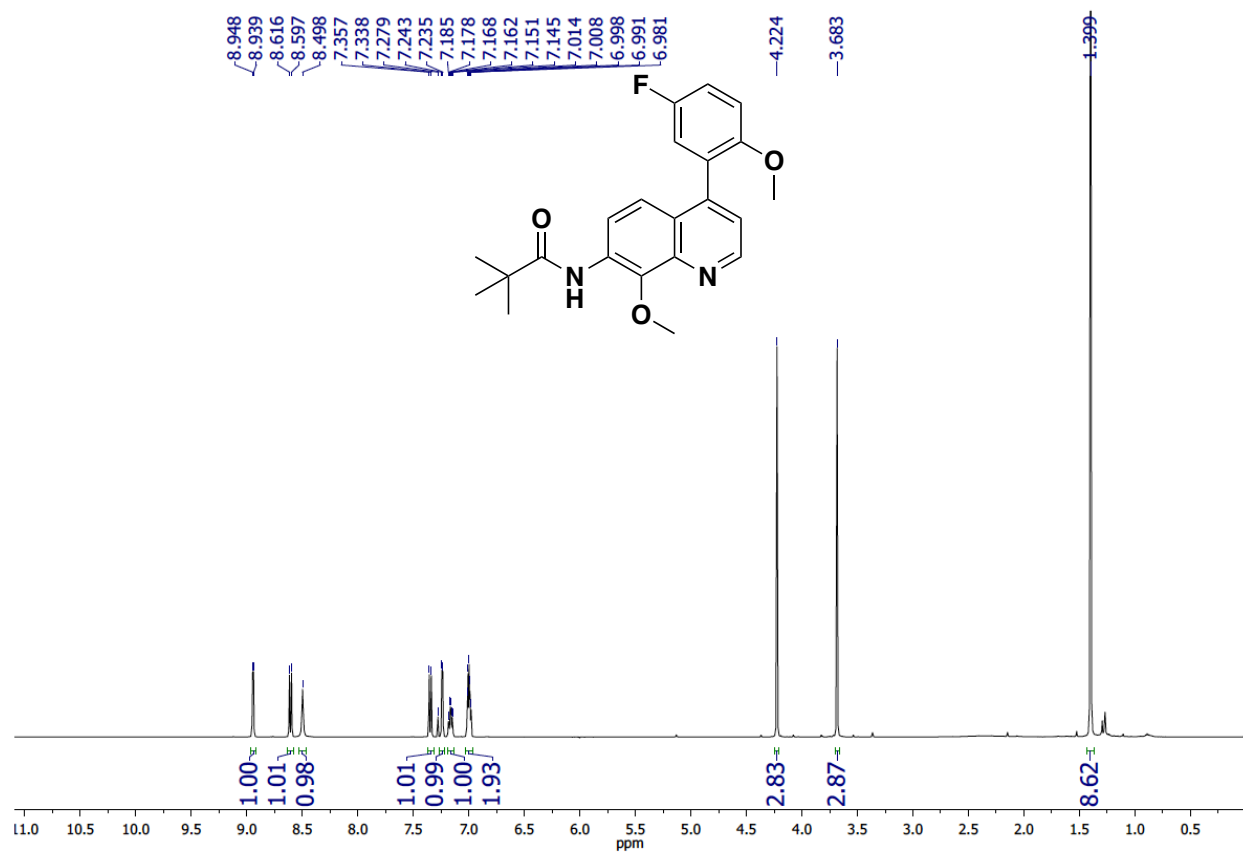
8-Methoxy-4-(phenyl)-7-pivalamidoquinoline (23) in CDCl₃



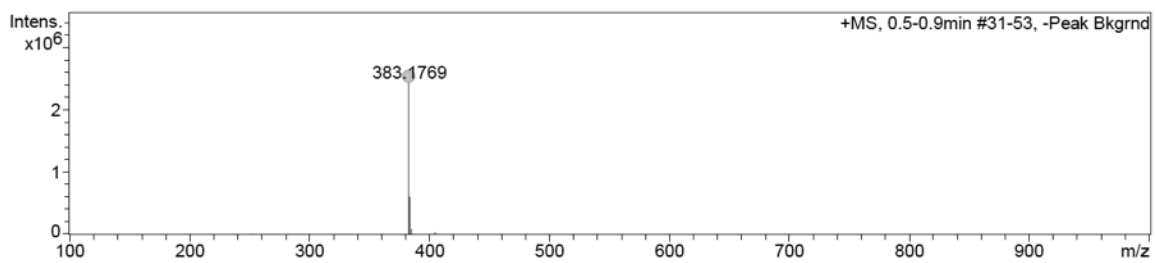
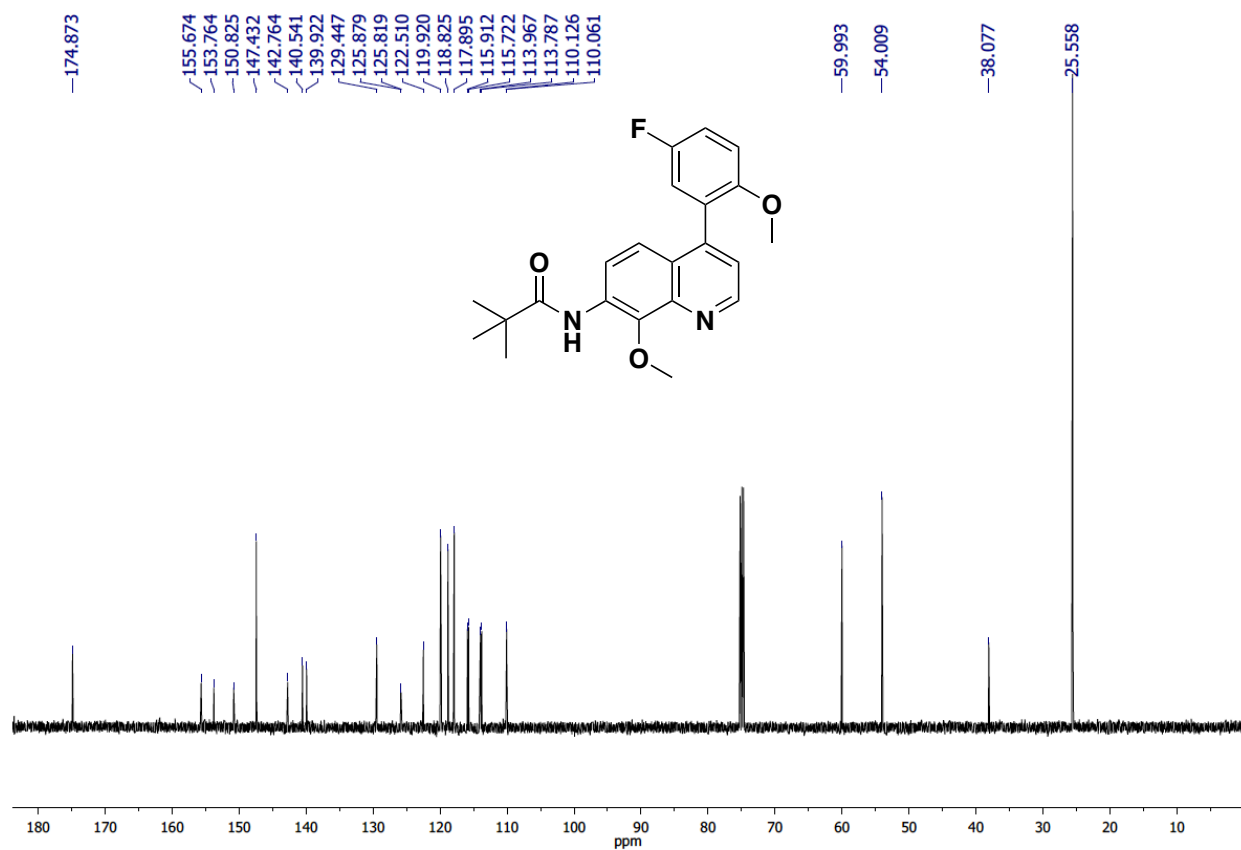
8-Methoxy-4-(phenyl)-7-pivalamidoquinoline (23)



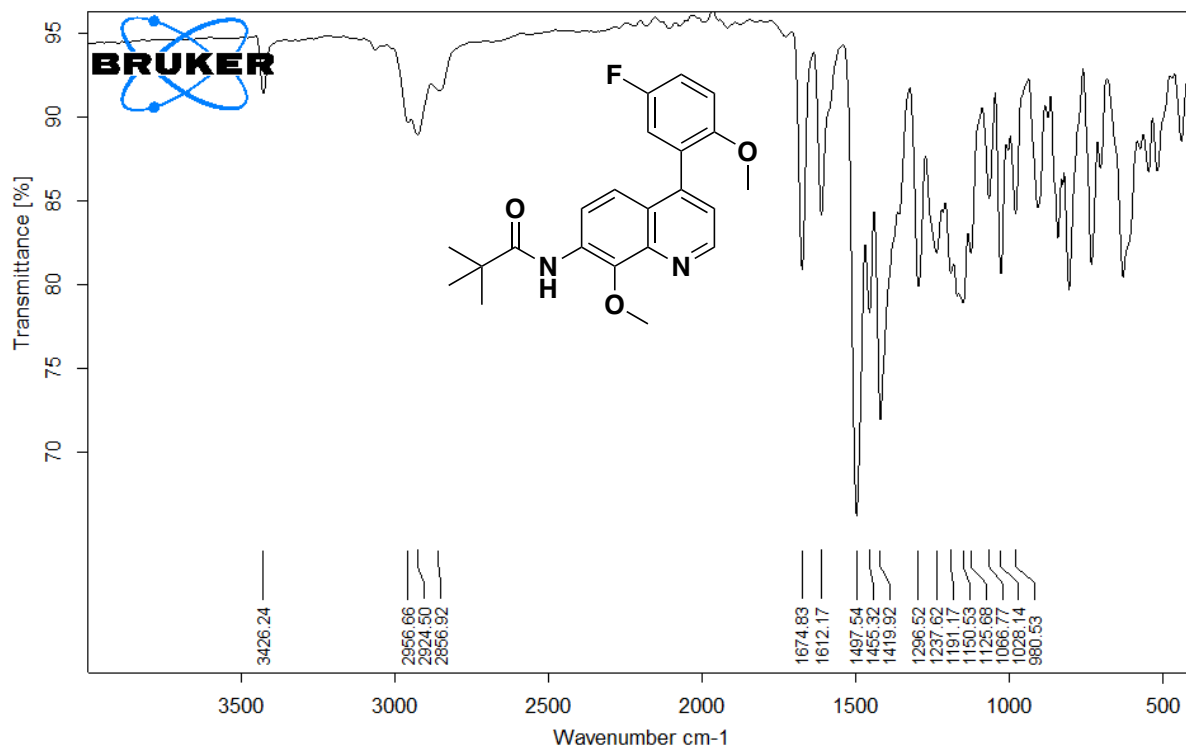
4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-pivalamidoquinoline (24) in CDCl₃



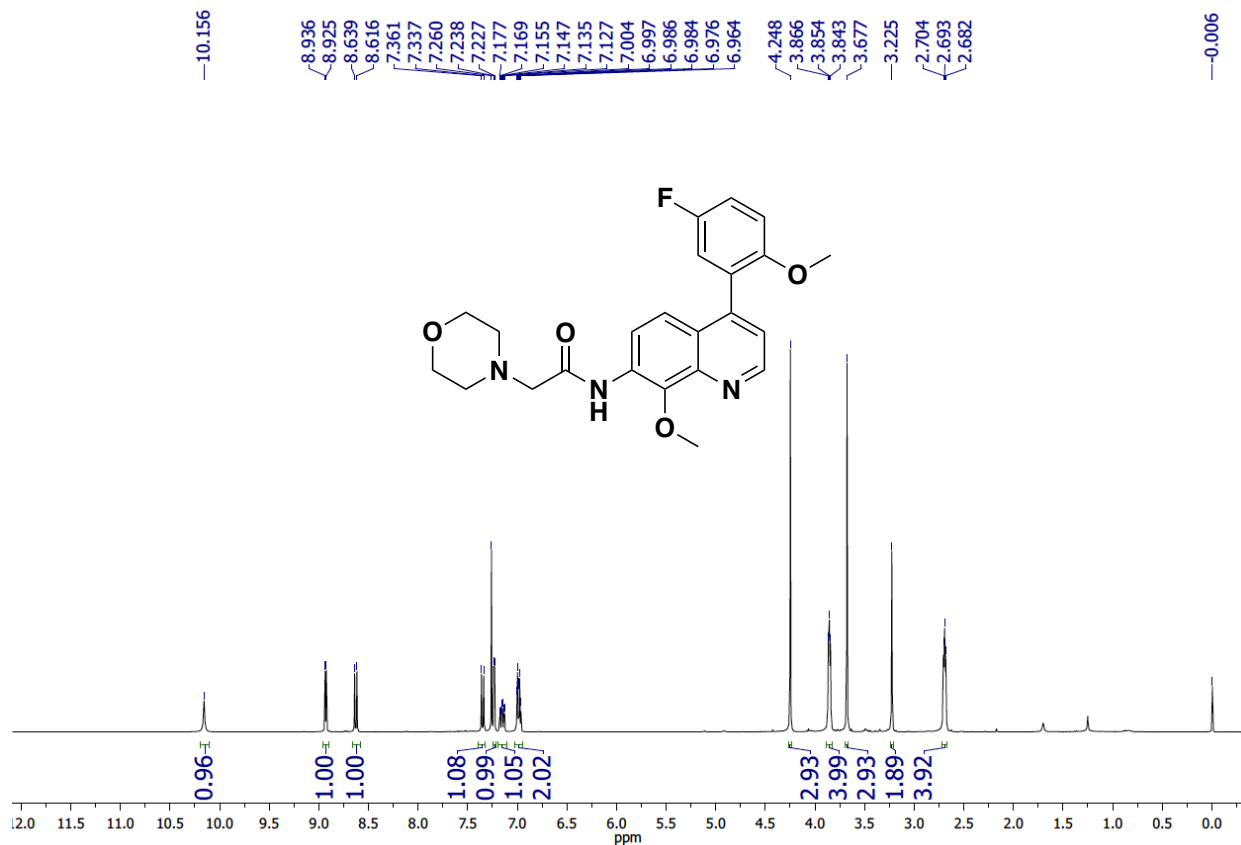
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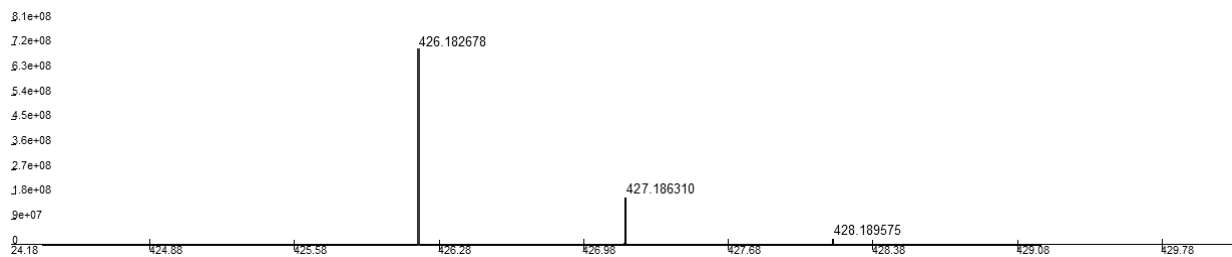
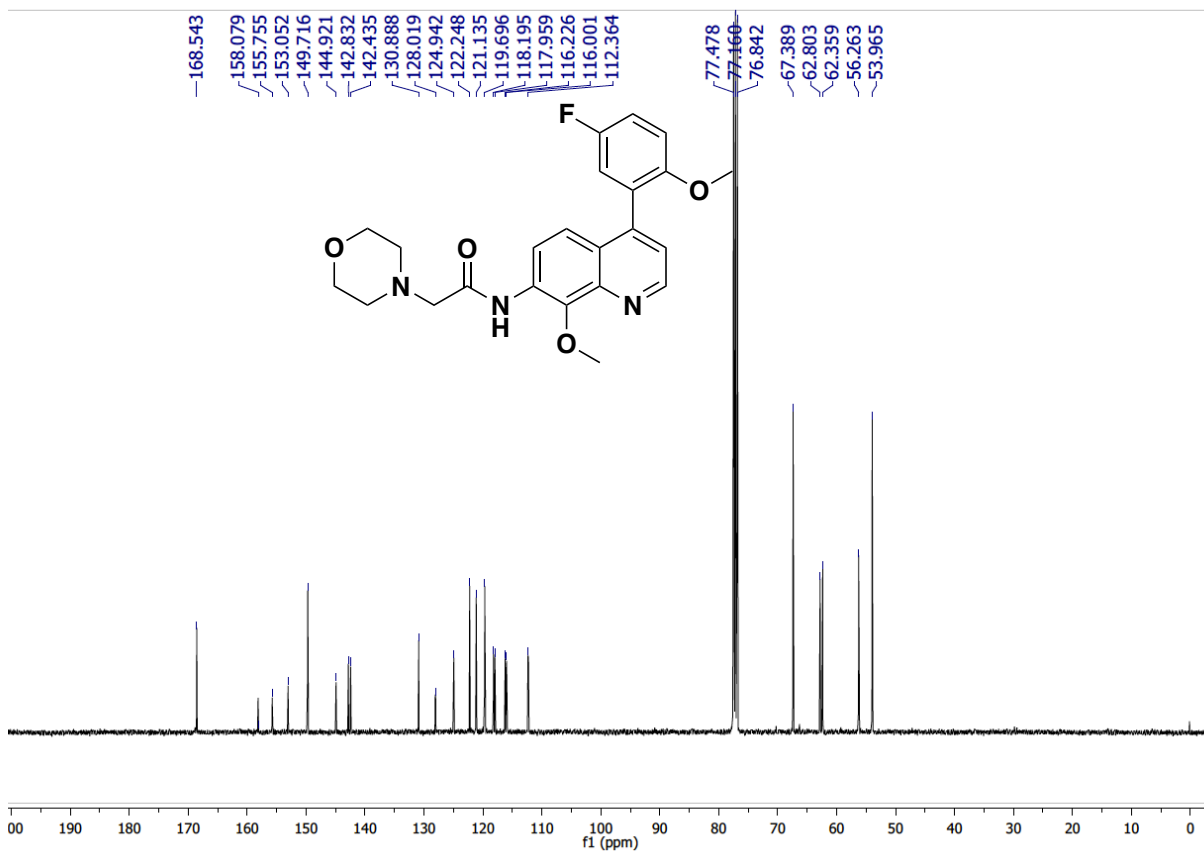
4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-pivalamidoquinoline (24)



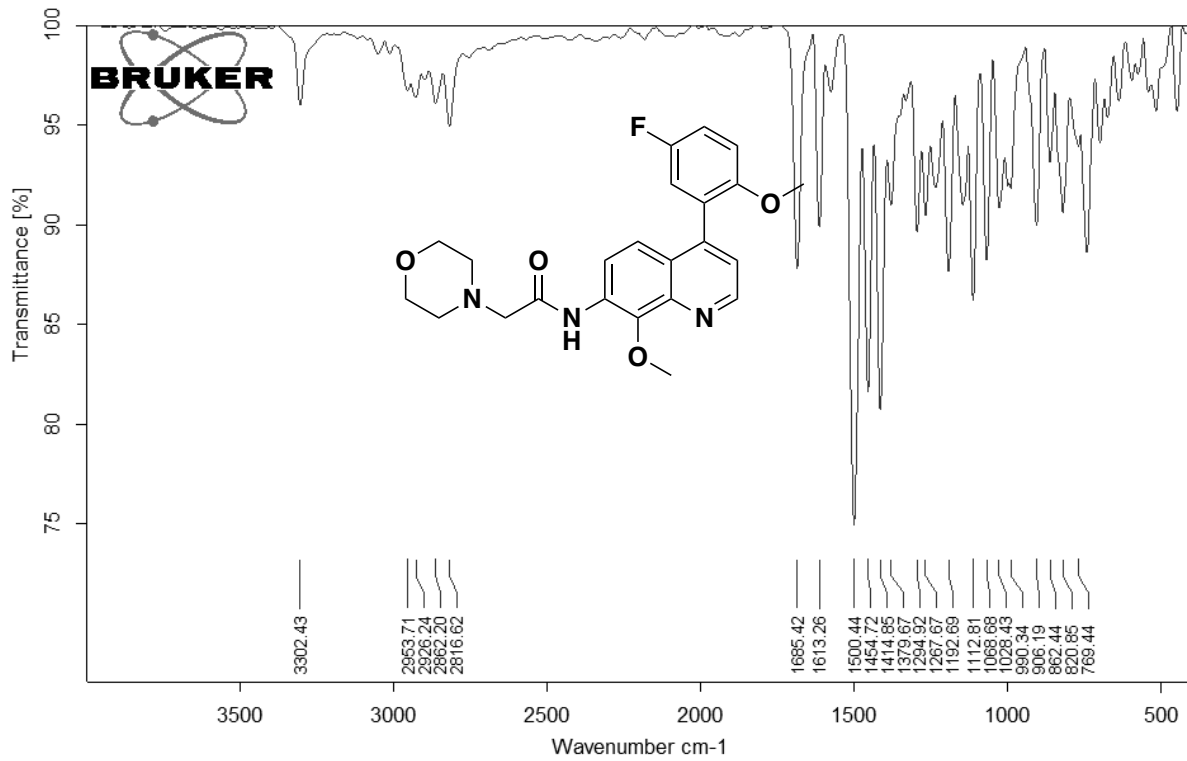
4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (25) in CDCl₃



4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (25) in CDCl₃

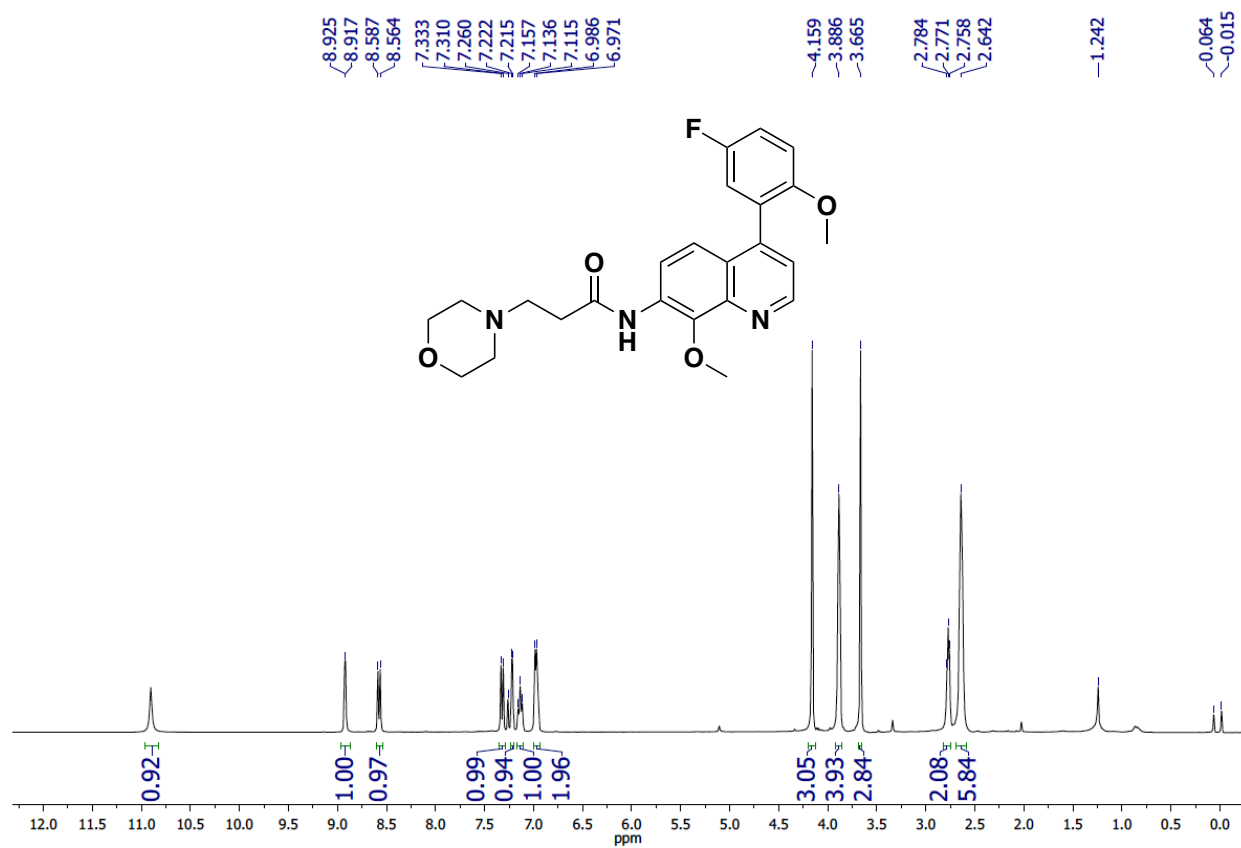


4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (25)



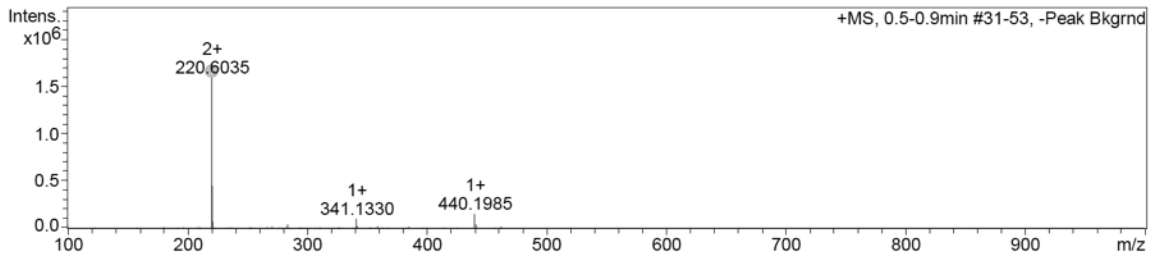
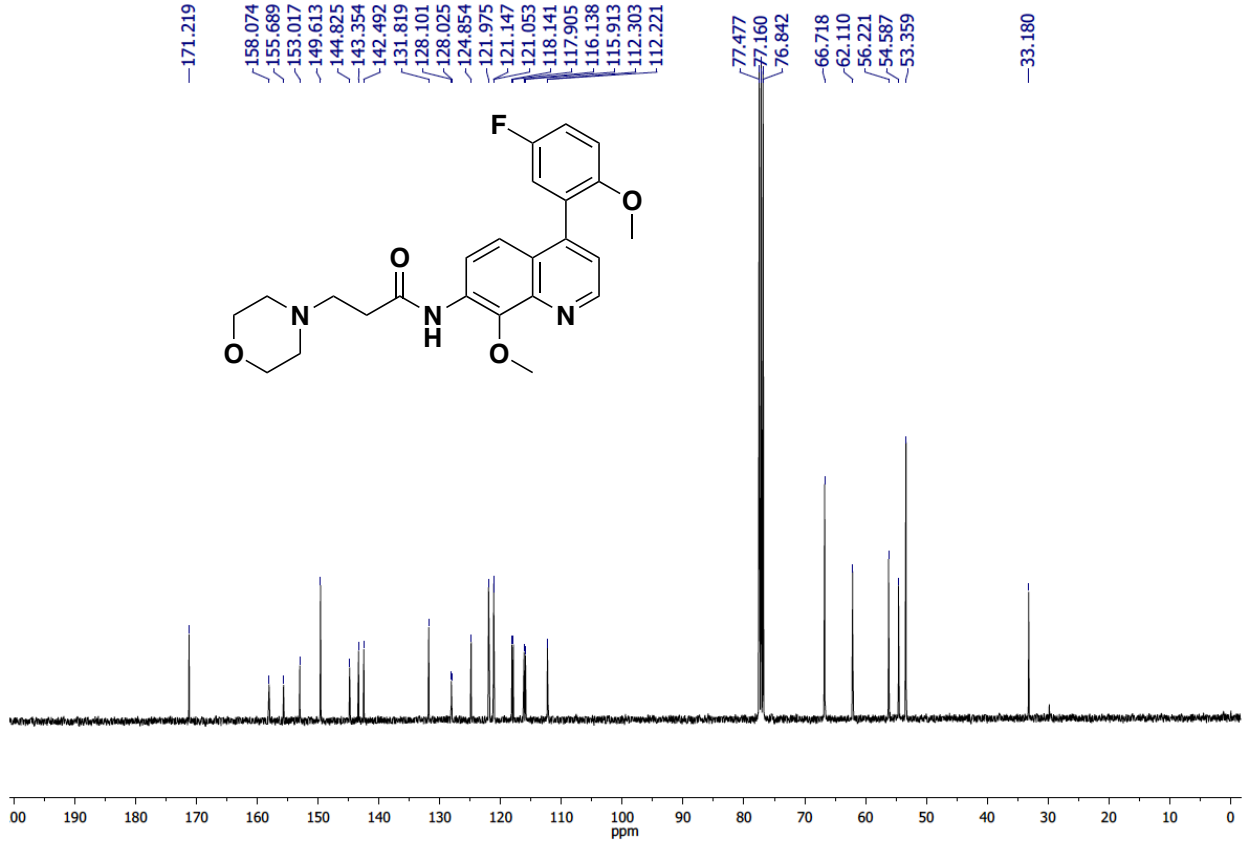
4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (26) in

CDCl₃

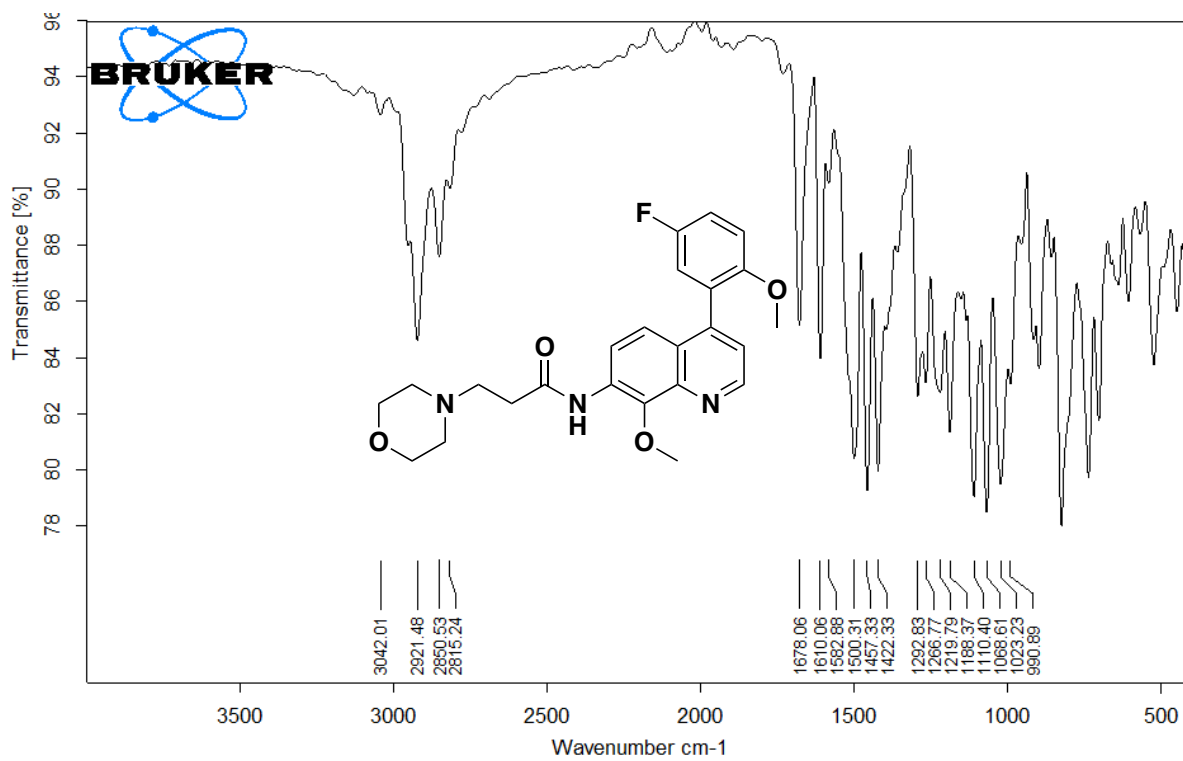


4-(5-fluoro-2-methoxyphenyl)-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (26) in

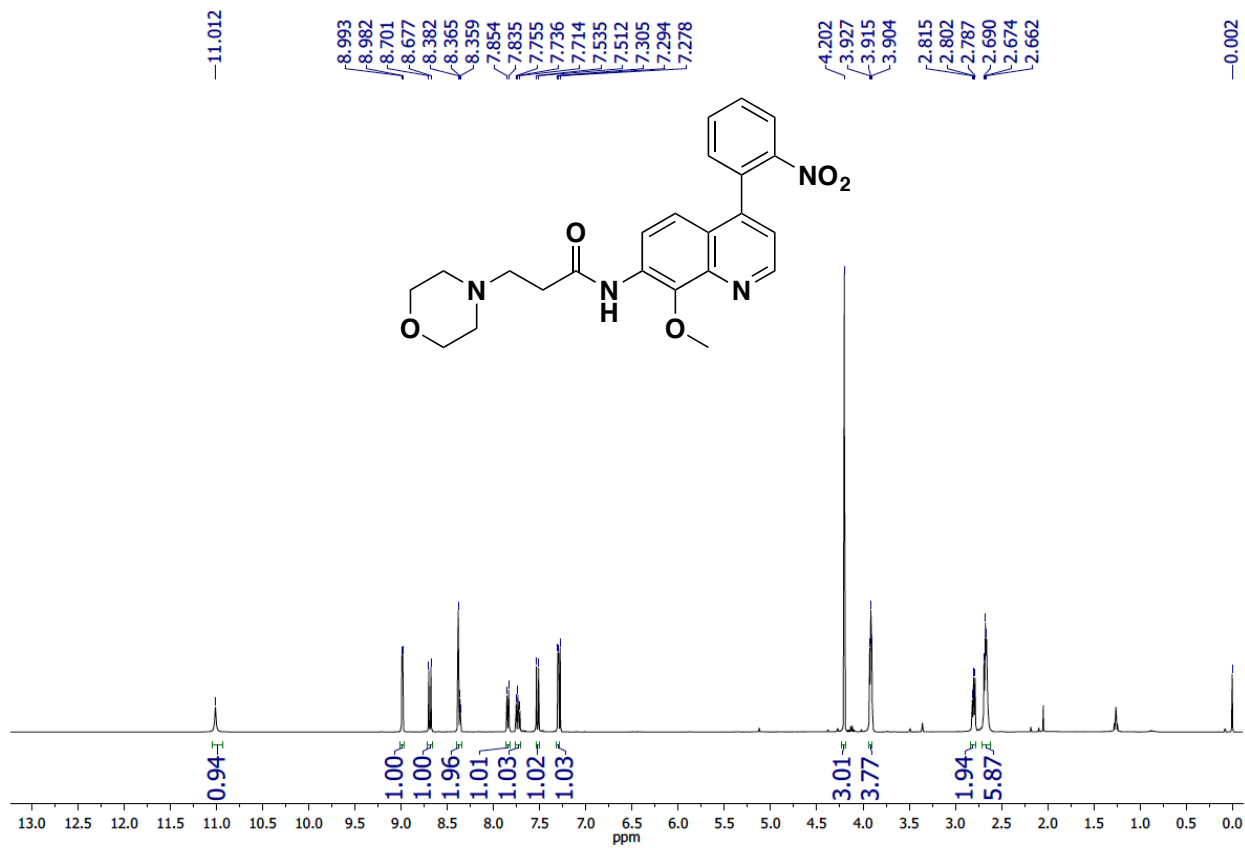
CDCl₃



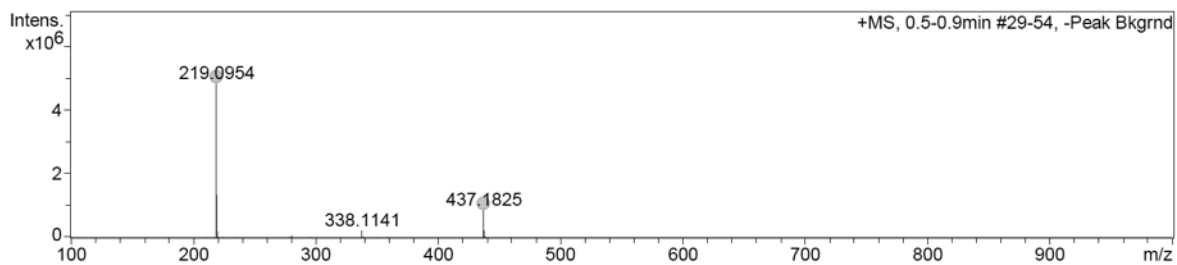
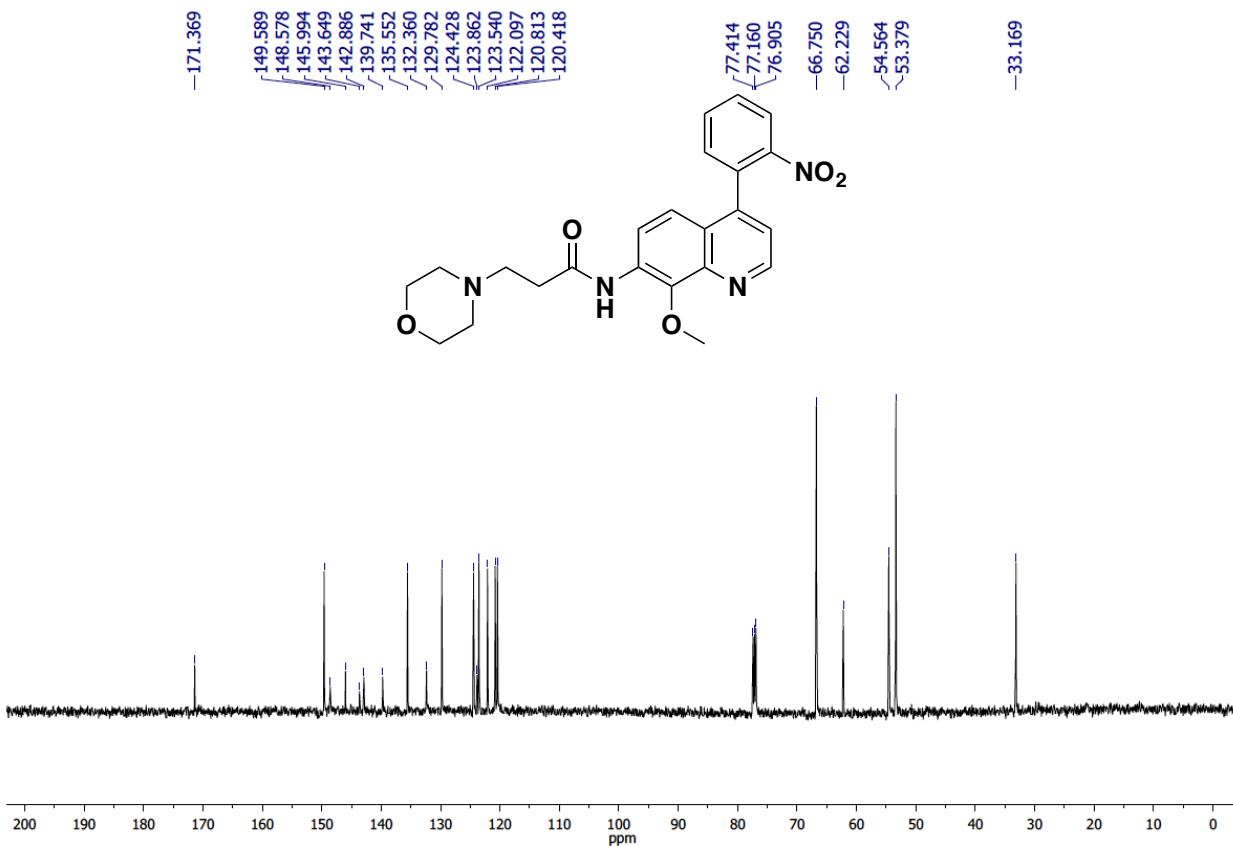
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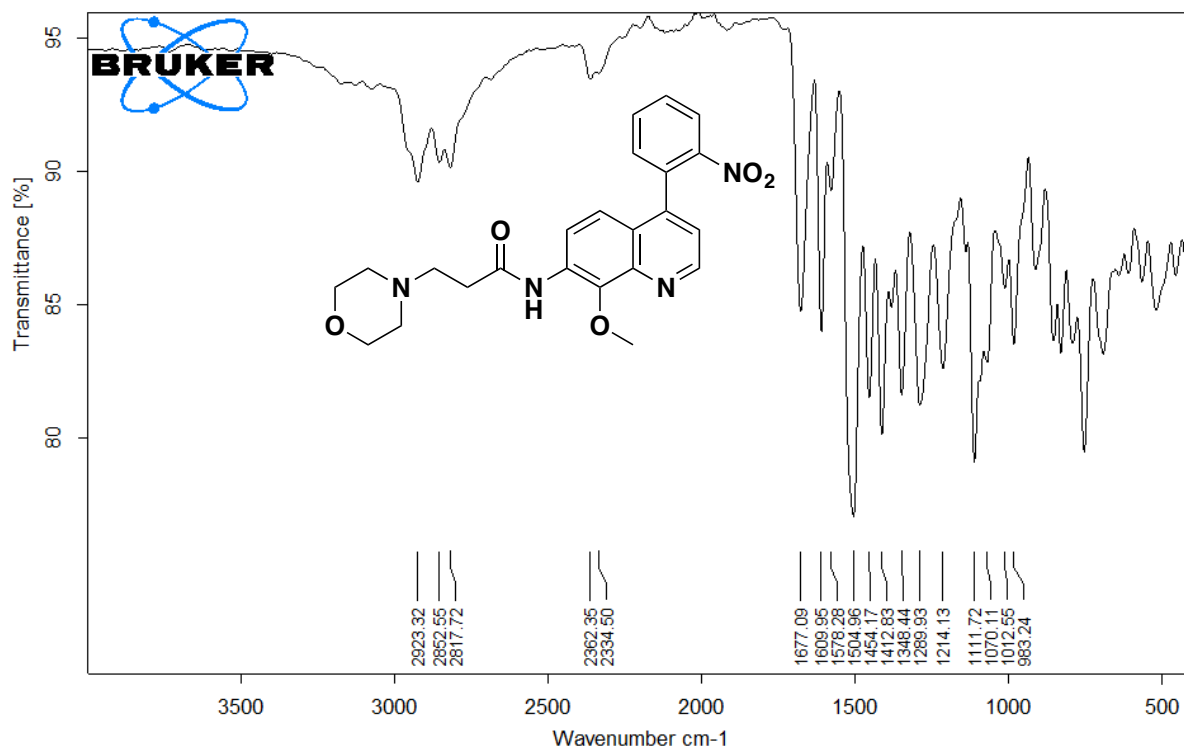
8-Methoxy-7-(3-(morpholin-4-yl)propanamido)-4-(2-nitrophenyl)quinoline in CDCl₃



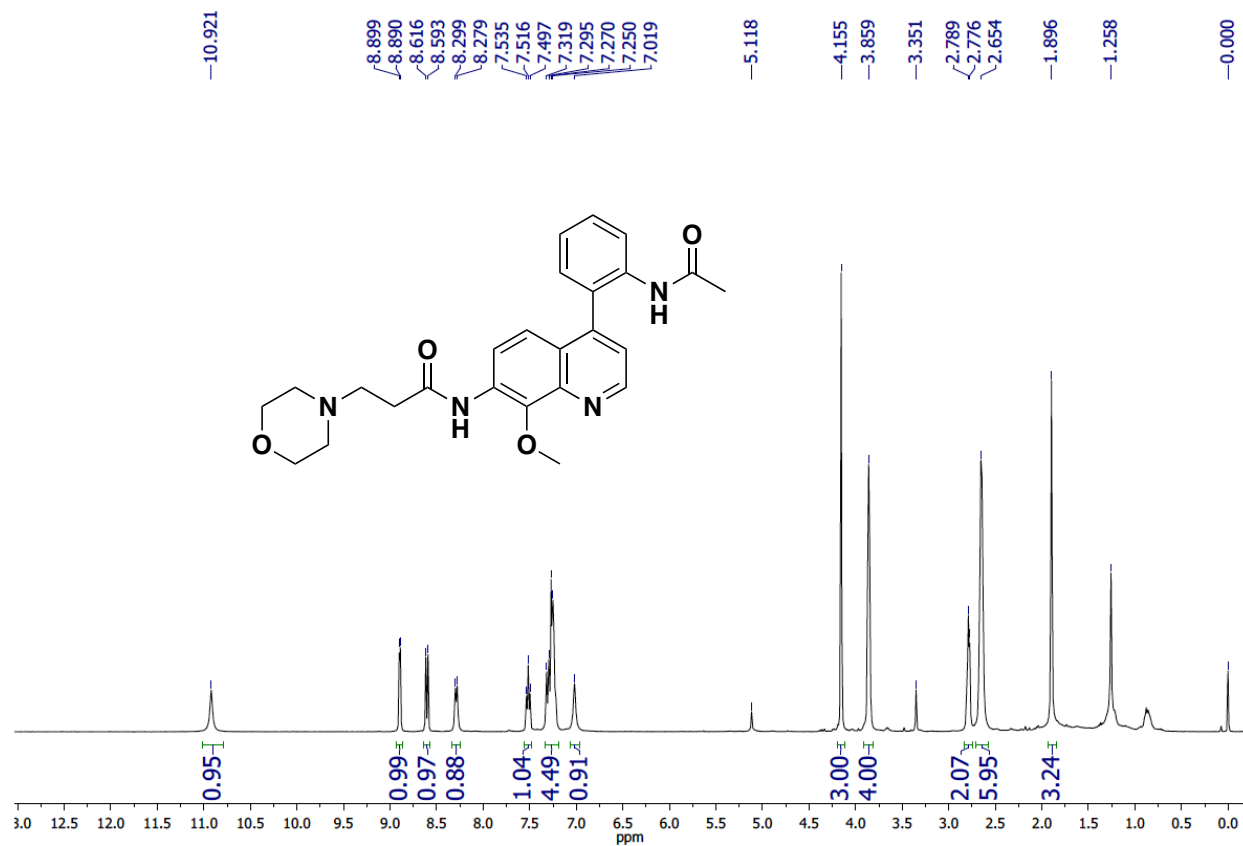
8-Methoxy-7-(3-(morpholin-4-yl)propanamido)-4-(2-nitrophenyl)quinoline in CDCl₃



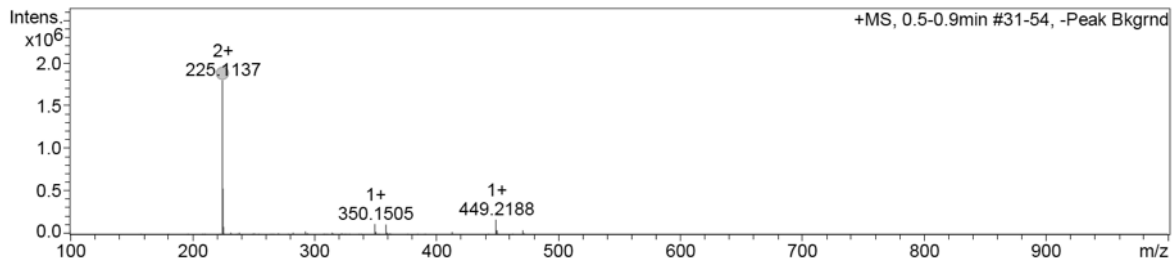
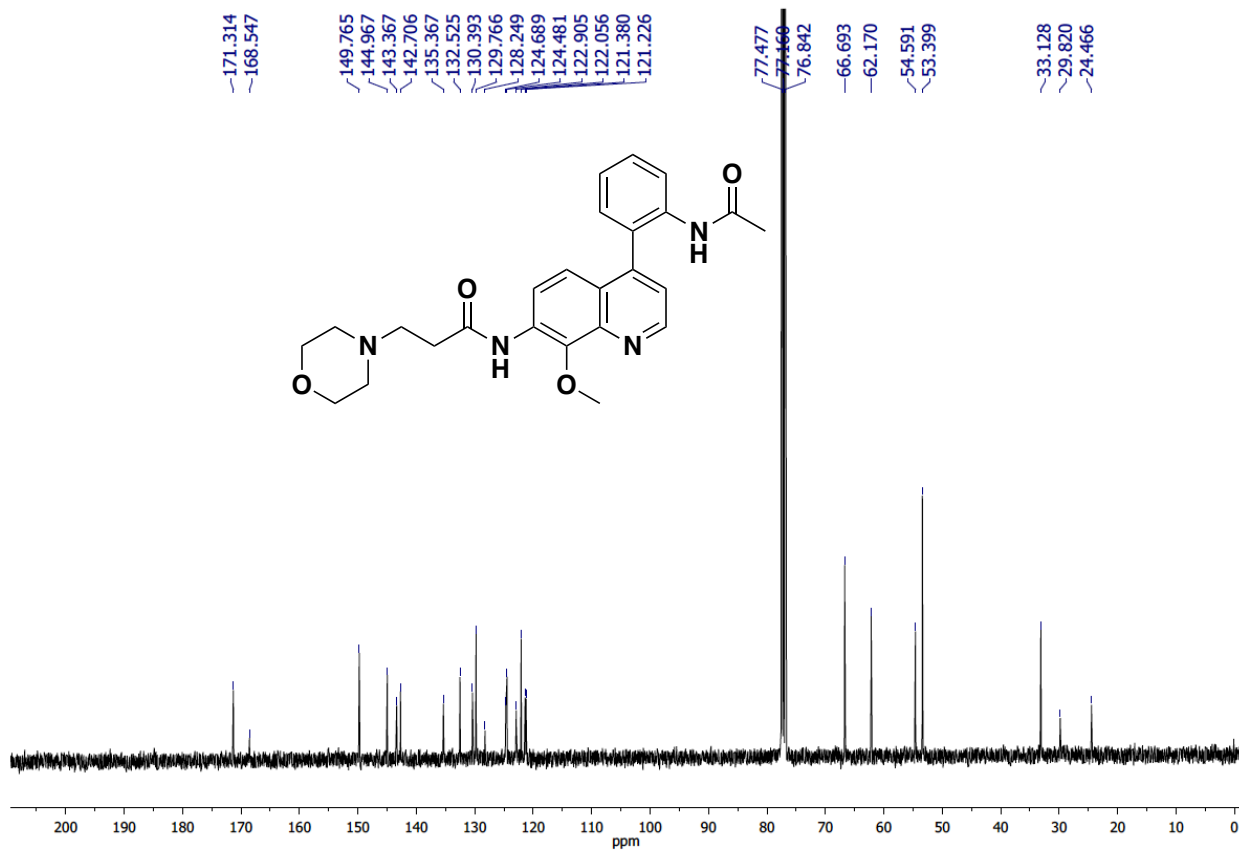
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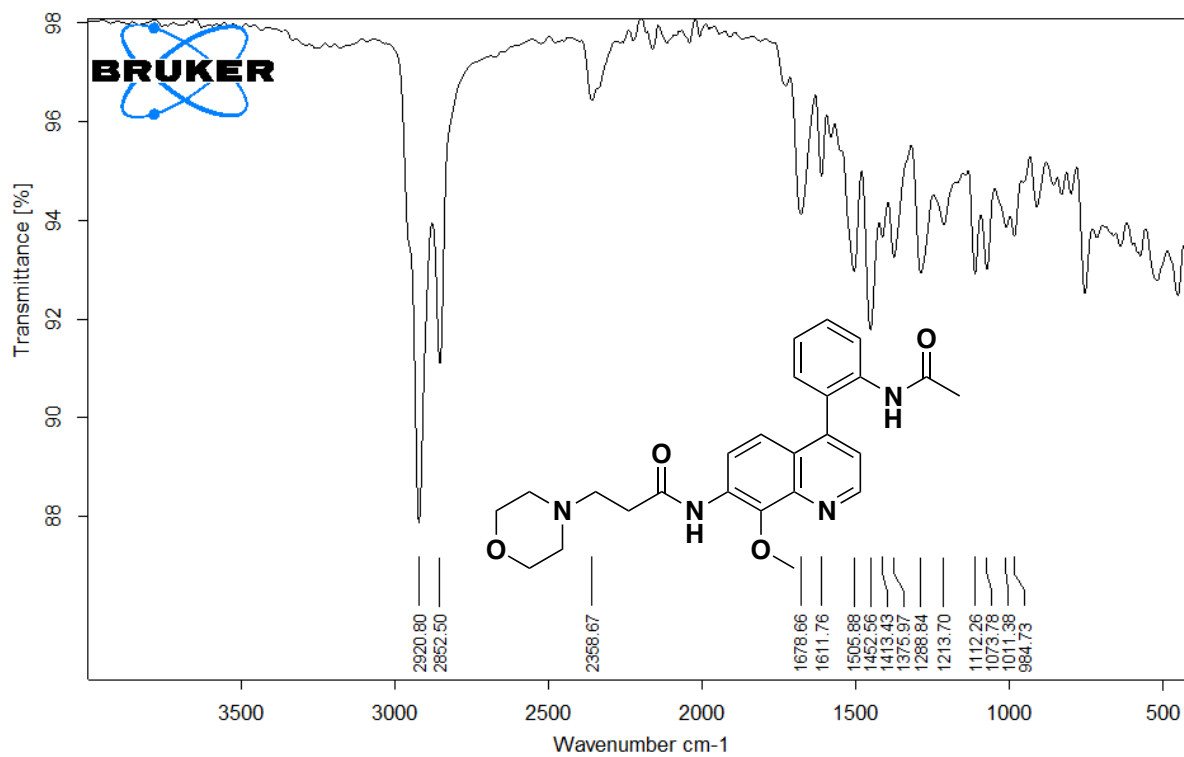
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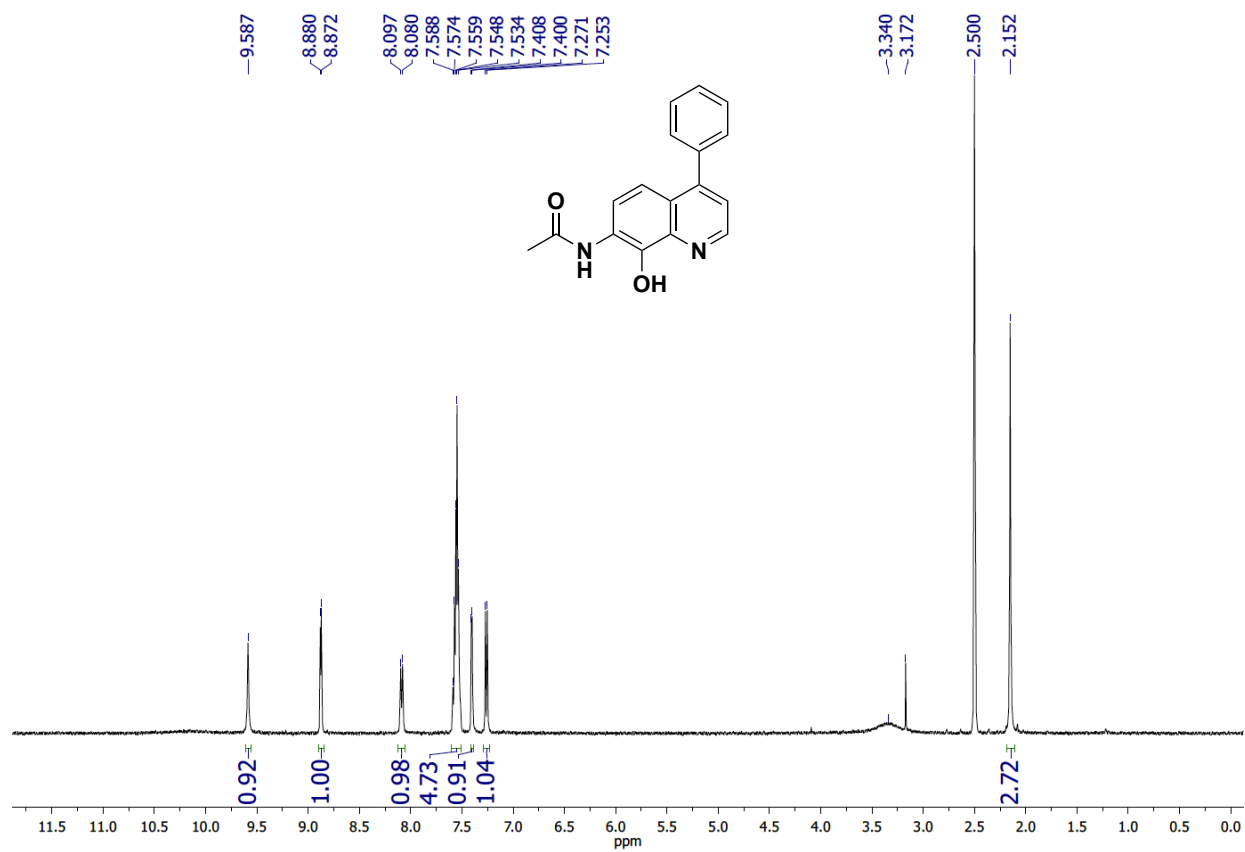
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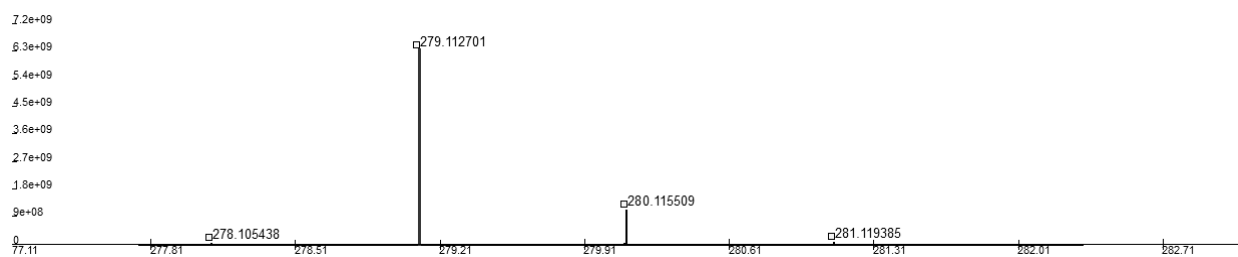
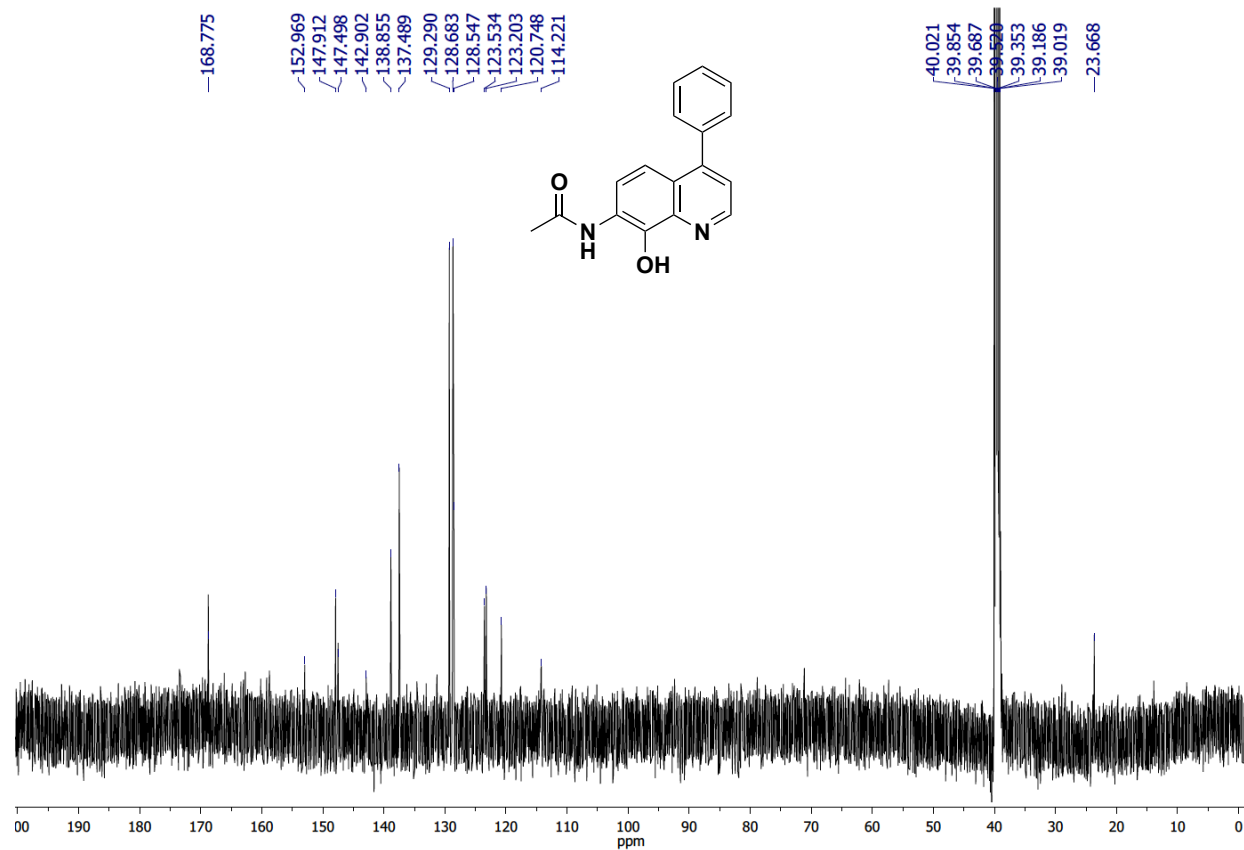
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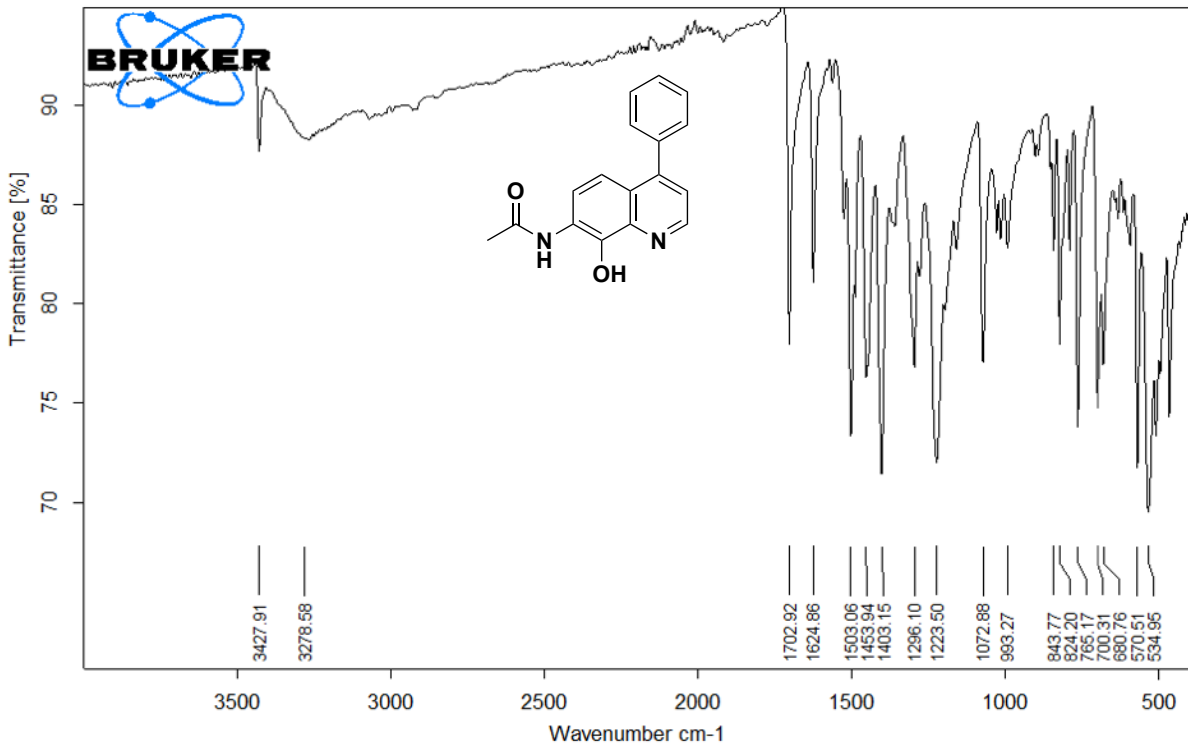
7-Acetamido-4-(phenyl)-8-hydroxyquinoline (28) in DMSO-d₆



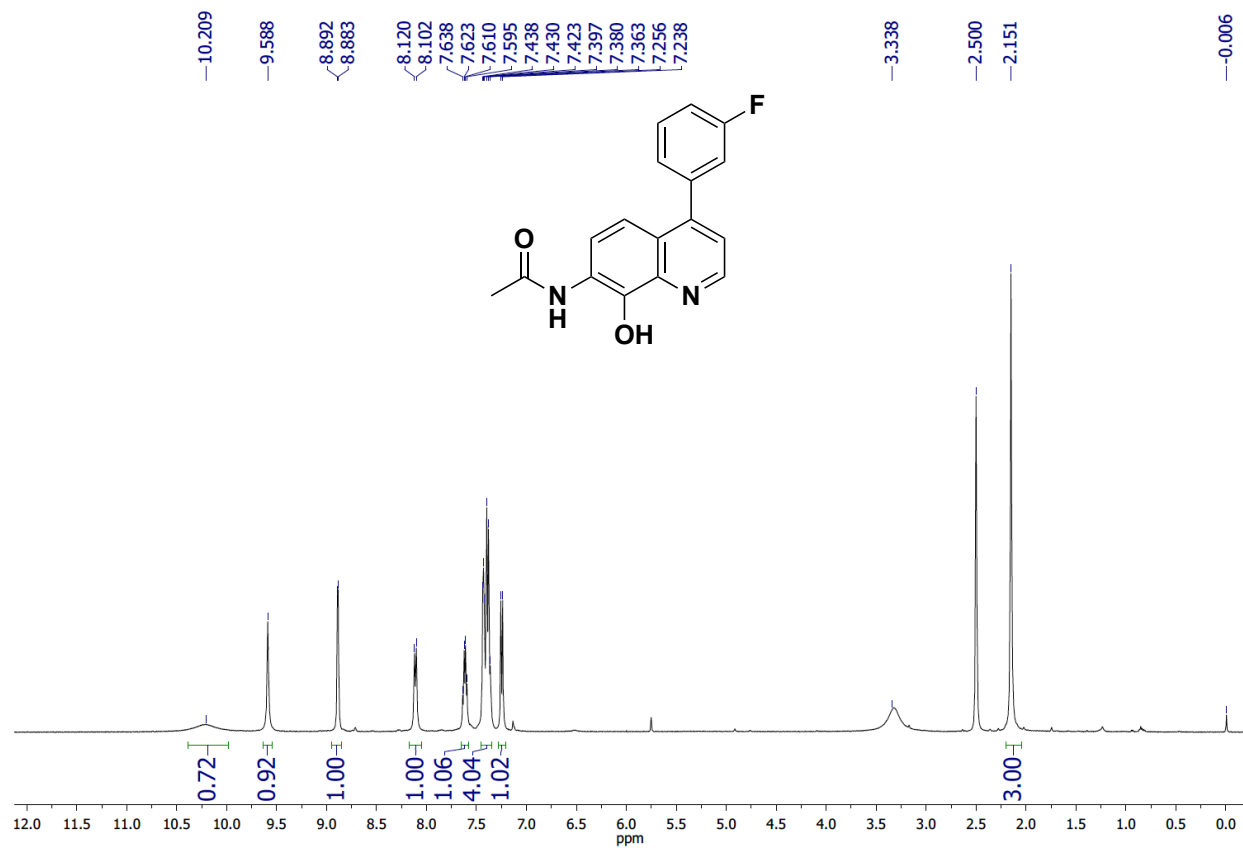
7-Acetamido-4-(phenyl)-8-hydroxyquinoline (28) in DMSO-d₆



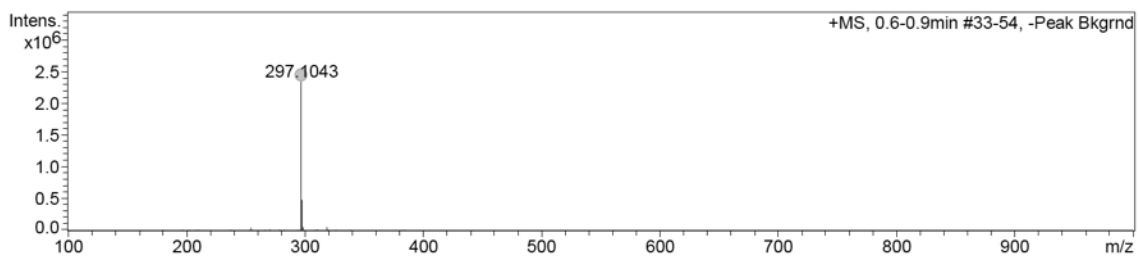
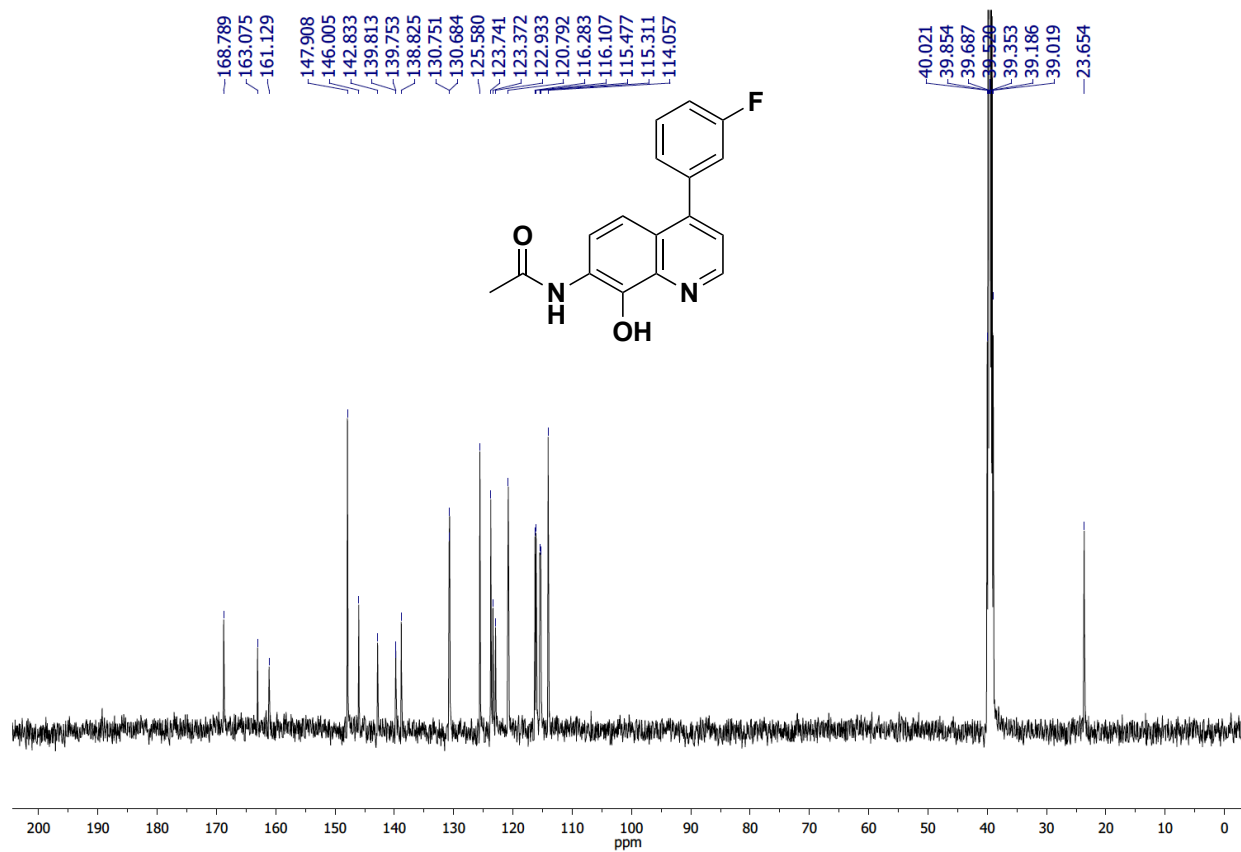
7-Acetamido-4-(phenyl)-8-hydroxyquinoline (28)



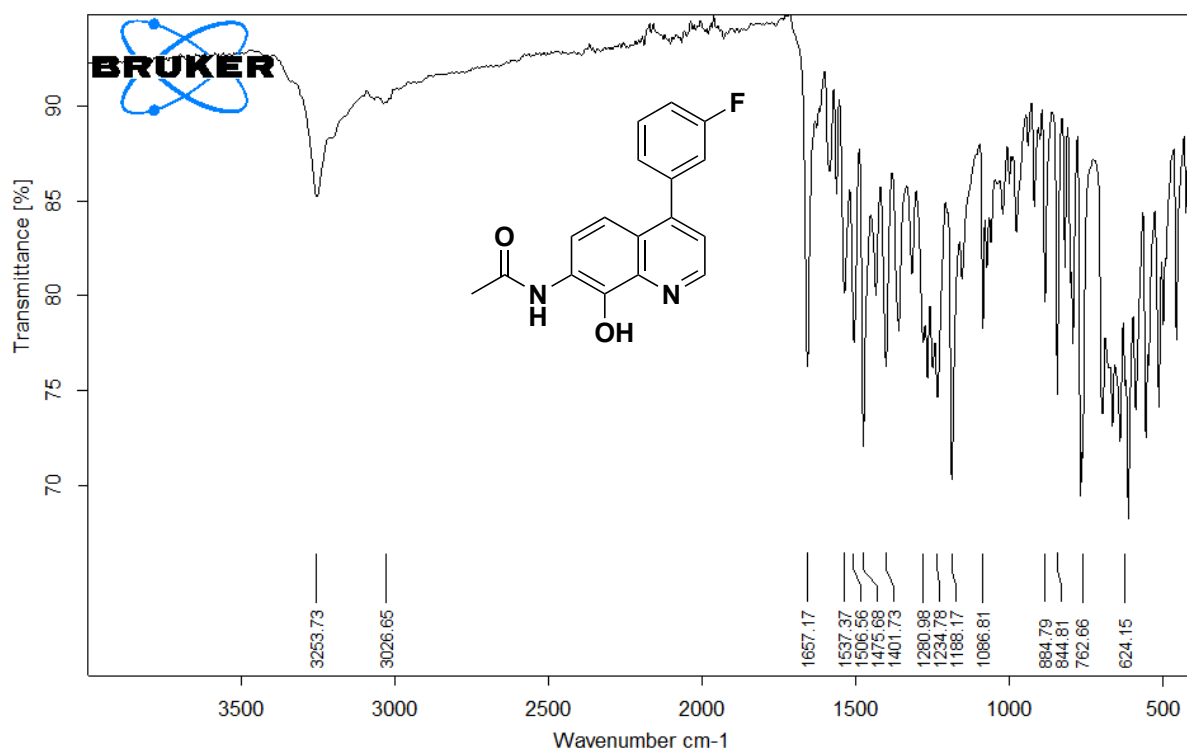
7-Acetamido-4-(3-fluorophenyl)-8-hydroxyquinoline (29) in DMSO-d₆



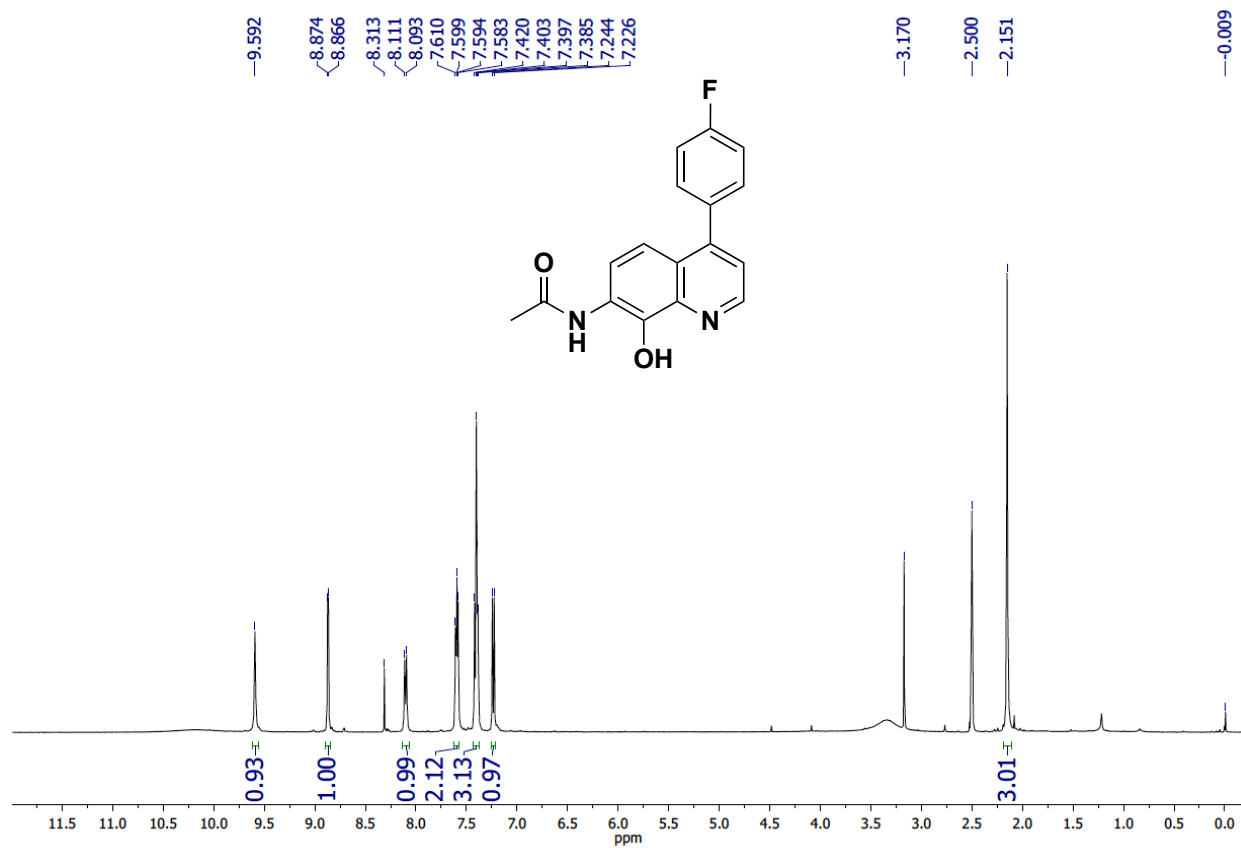
7-Acetamido-4-(3-fluorophenyl)-8-hydroxyquinoline (29) in DMSO-d₆



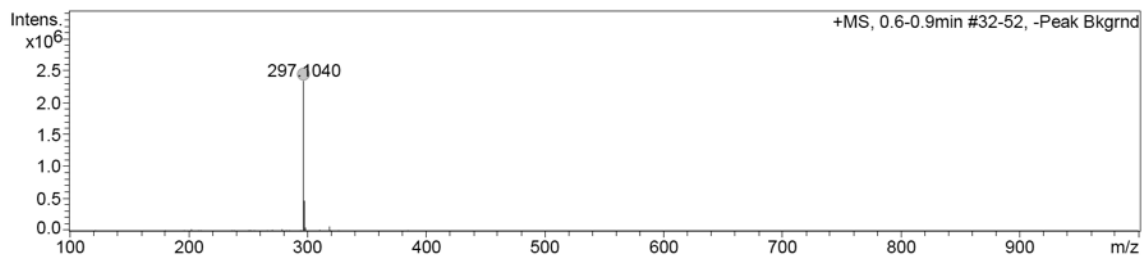
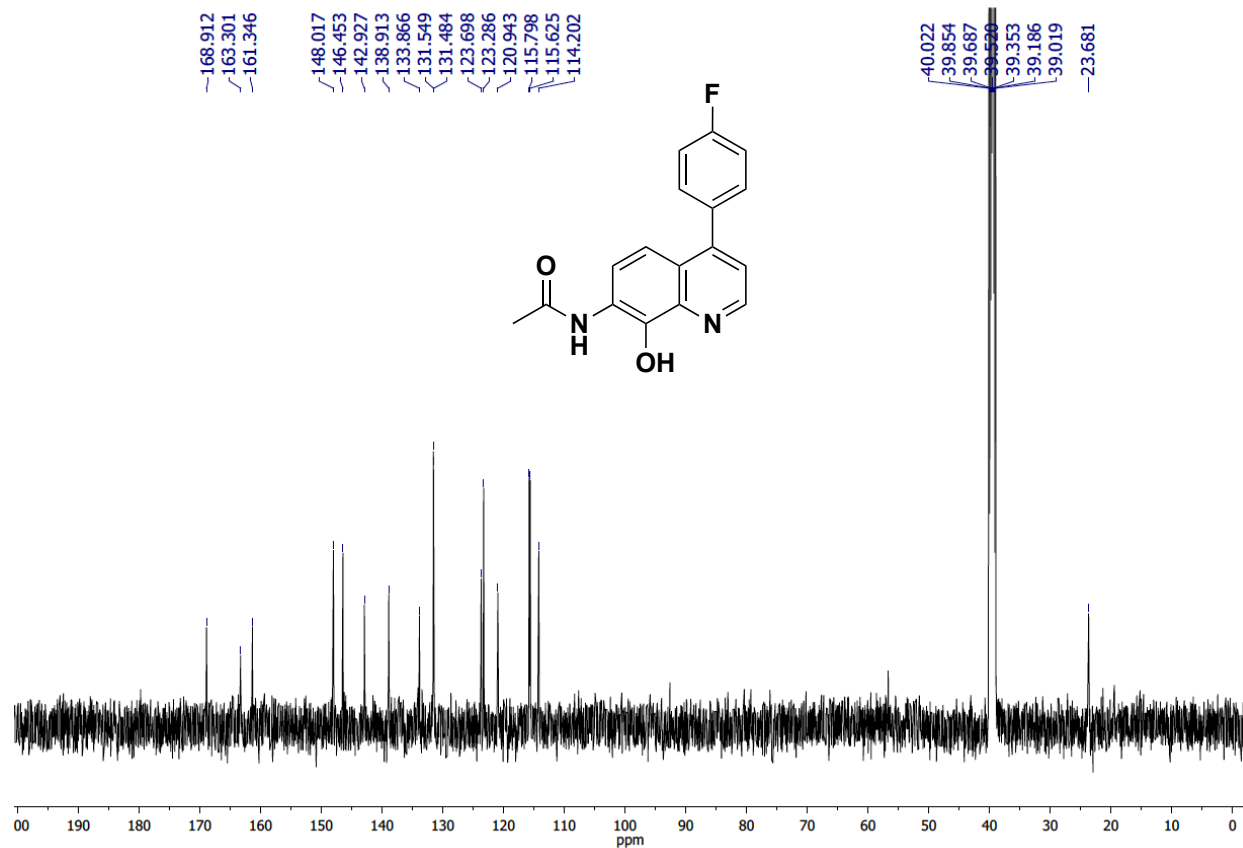
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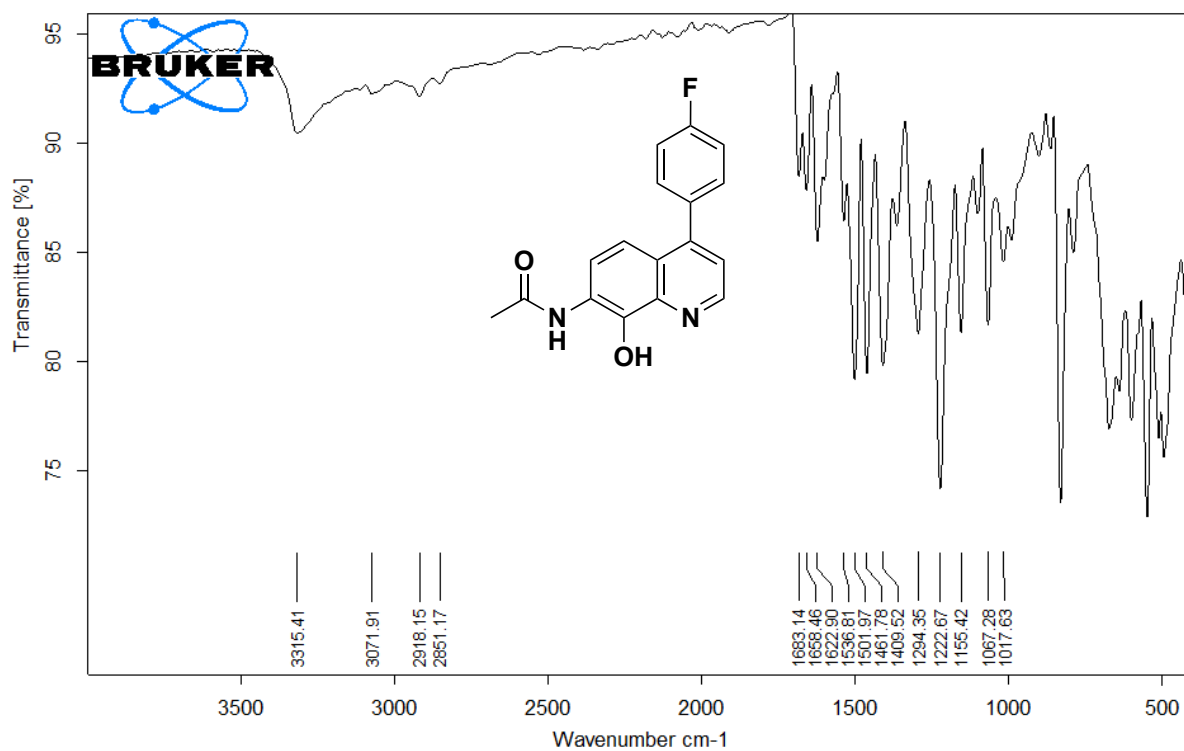
7-Acetamido-4-(4-fluorophenyl)-8-hydroxyquinoline (30) in DMSO-d₆



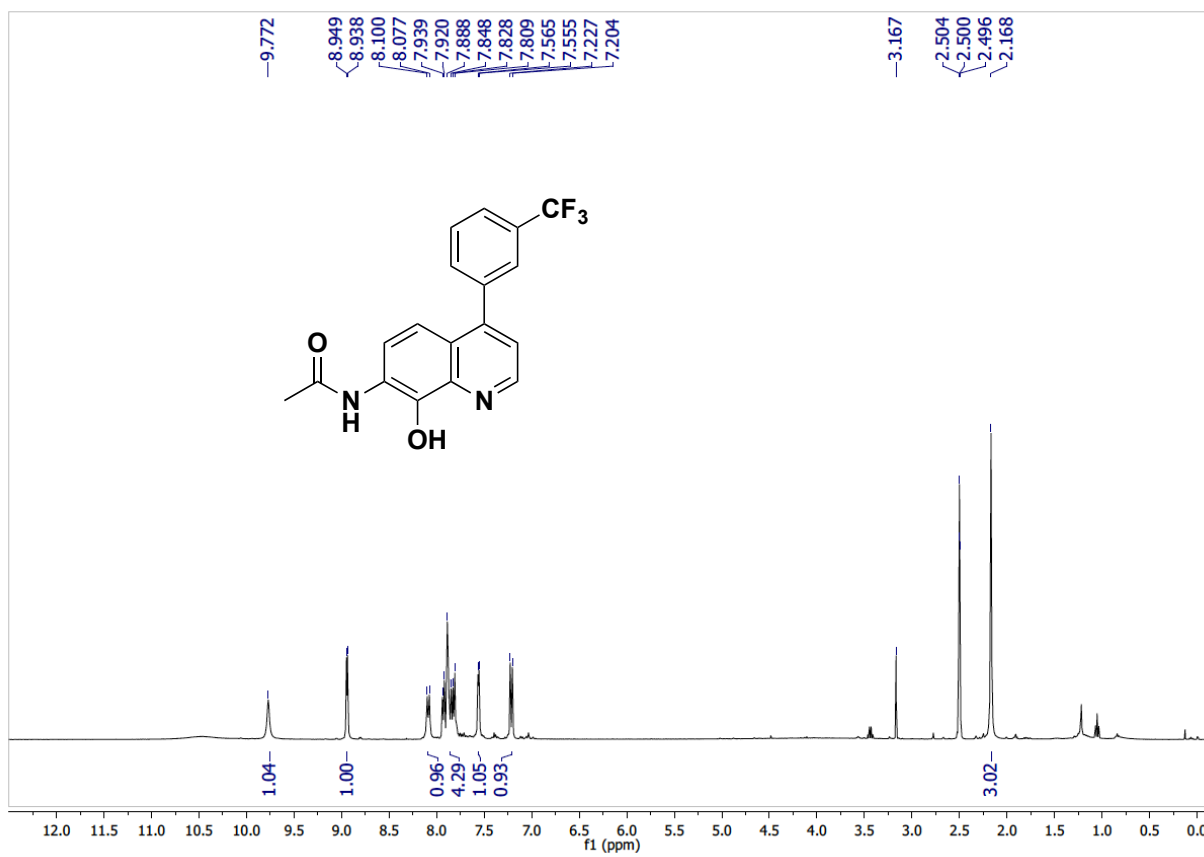
7-Acetamido-4-(4-fluorophenyl)-8-hydroxyquinoline (30) in DMSO-d₆



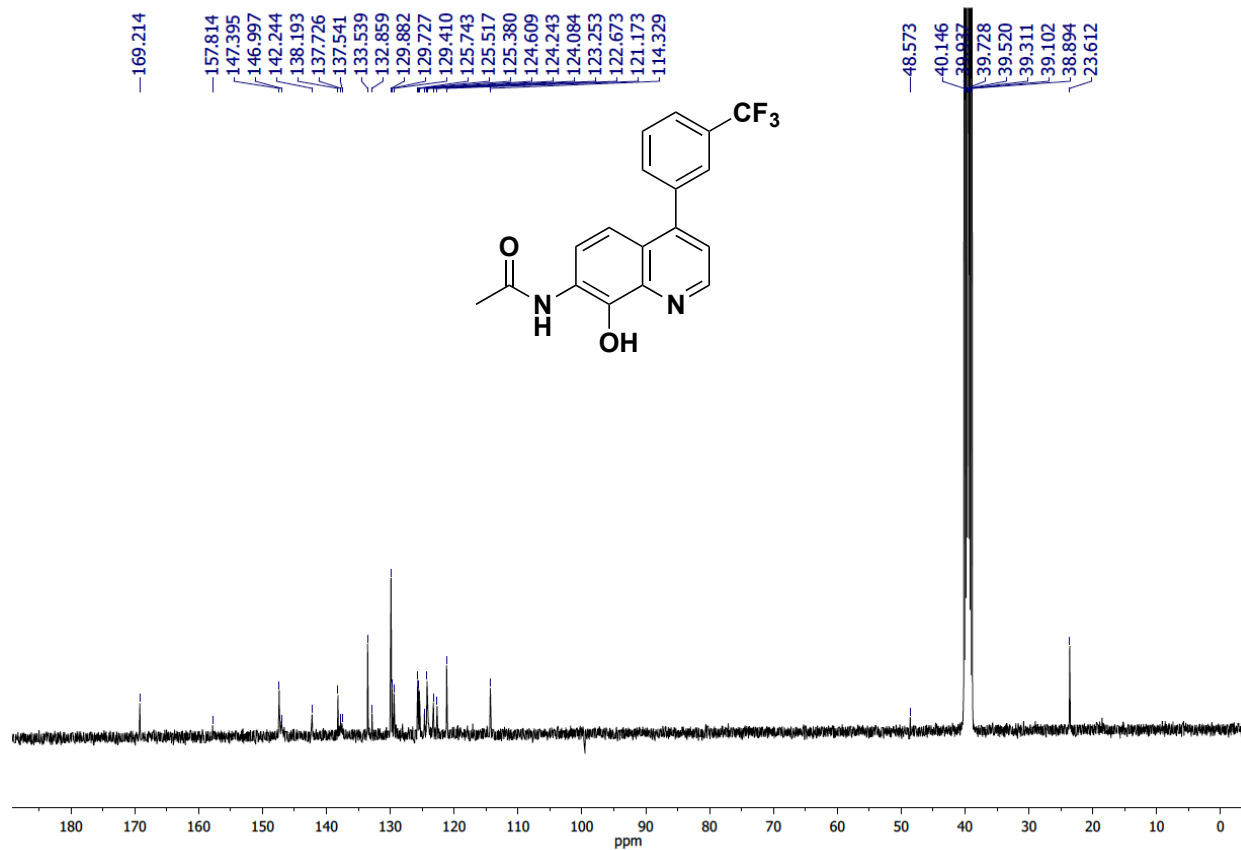
7-Acetamido-4-(4-fluorophenyl)-8-hydroxyquinoline (30)



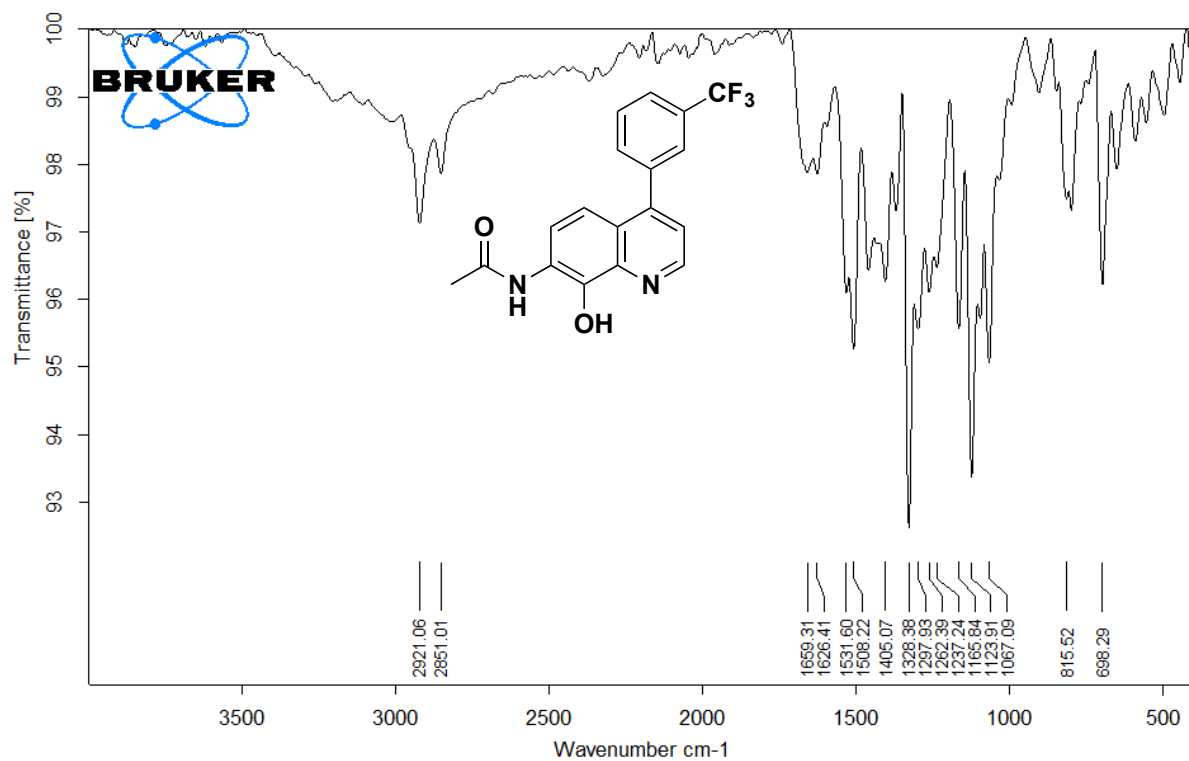
7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-hydroxyquinoline (31) in DMSO-d₆



7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-hydroxyquinoline (31) in DMSO-d₆



7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-hydroxyquinoline (31)



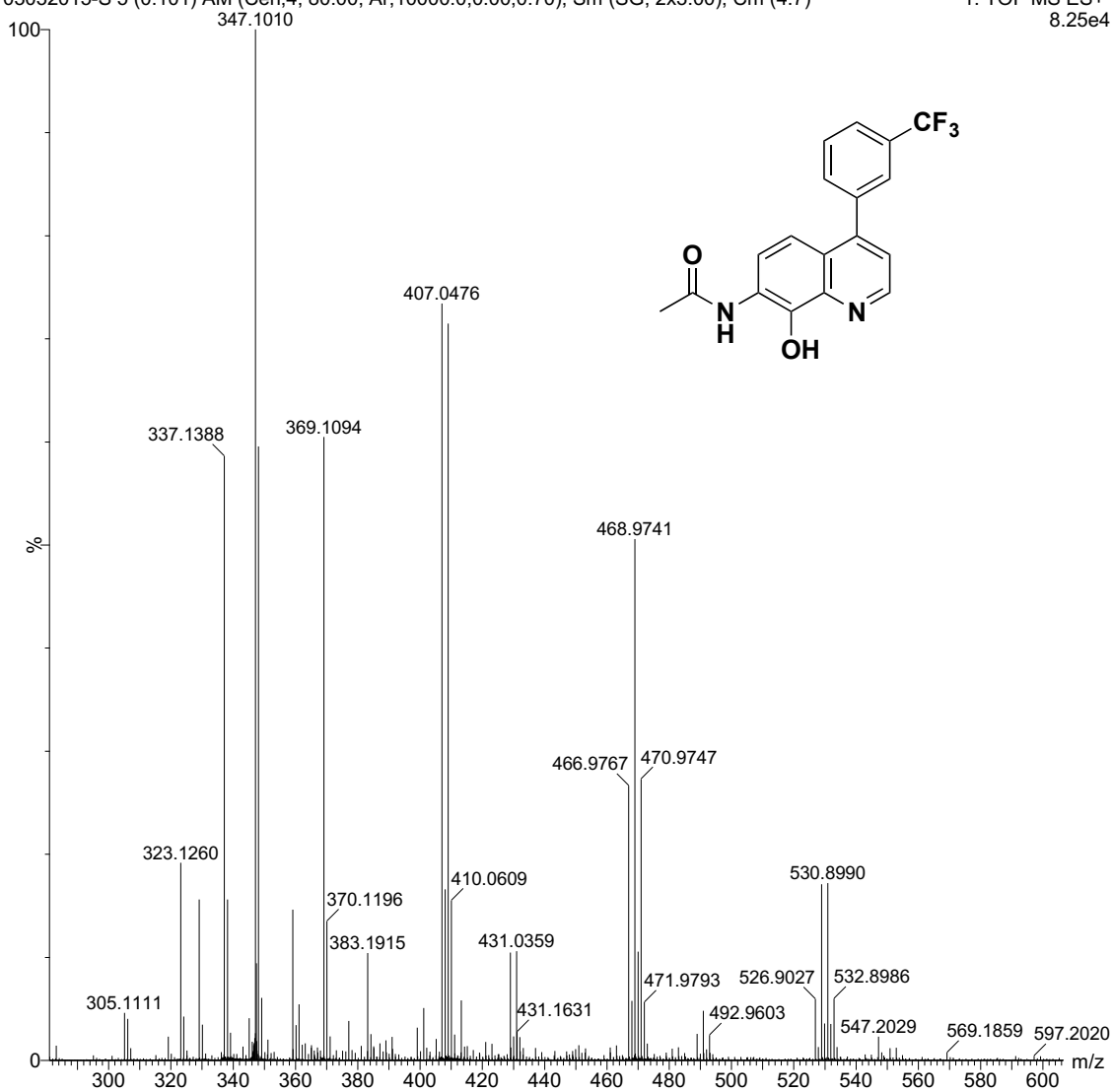
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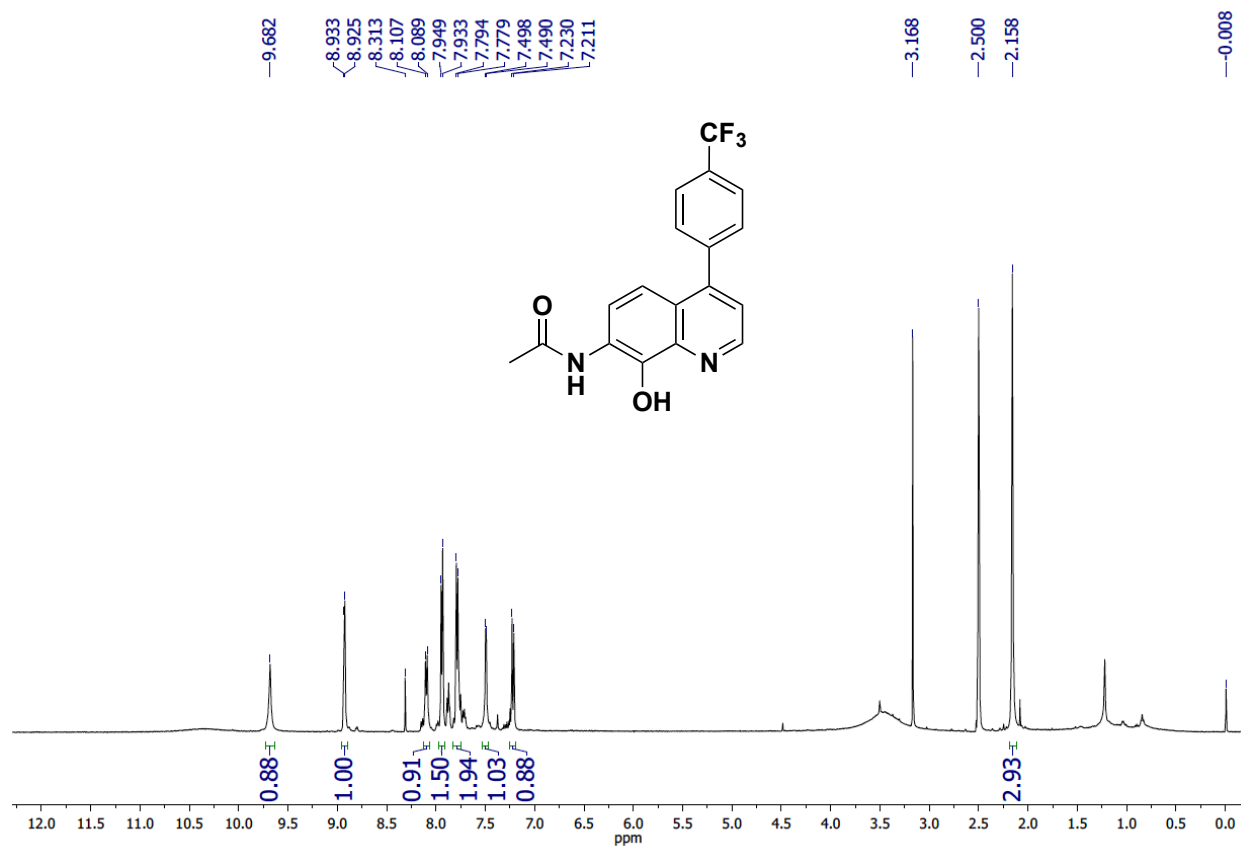
Pusher Freq 22222

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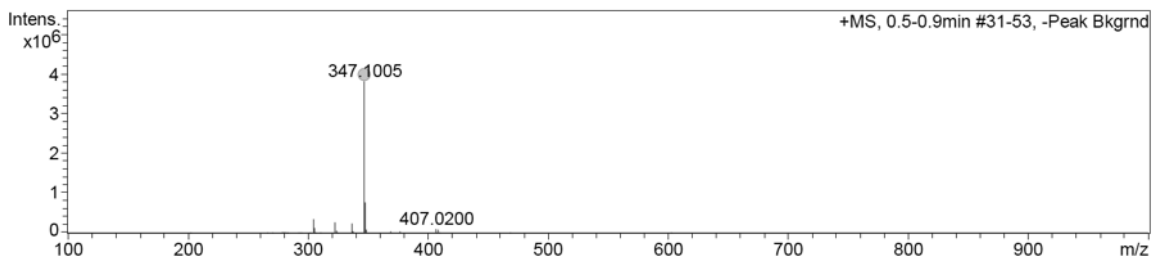
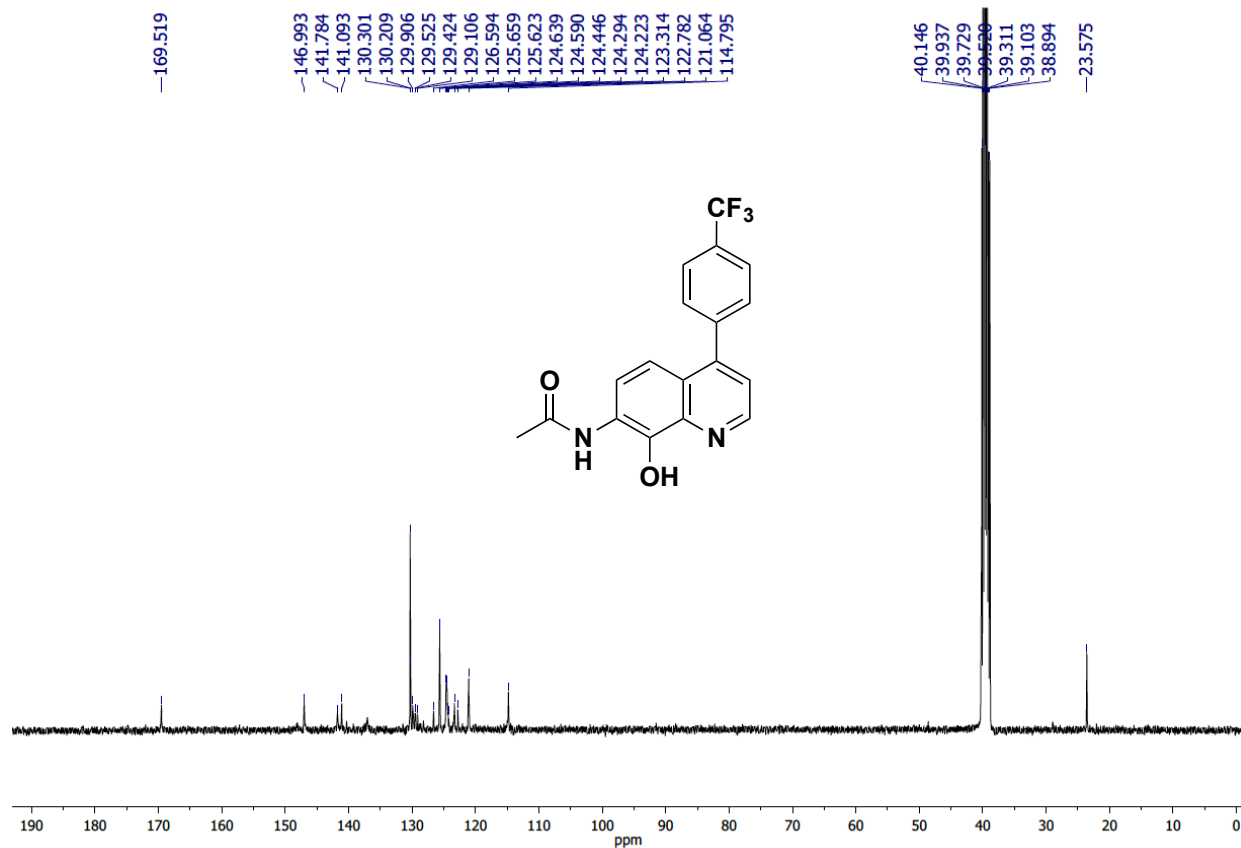
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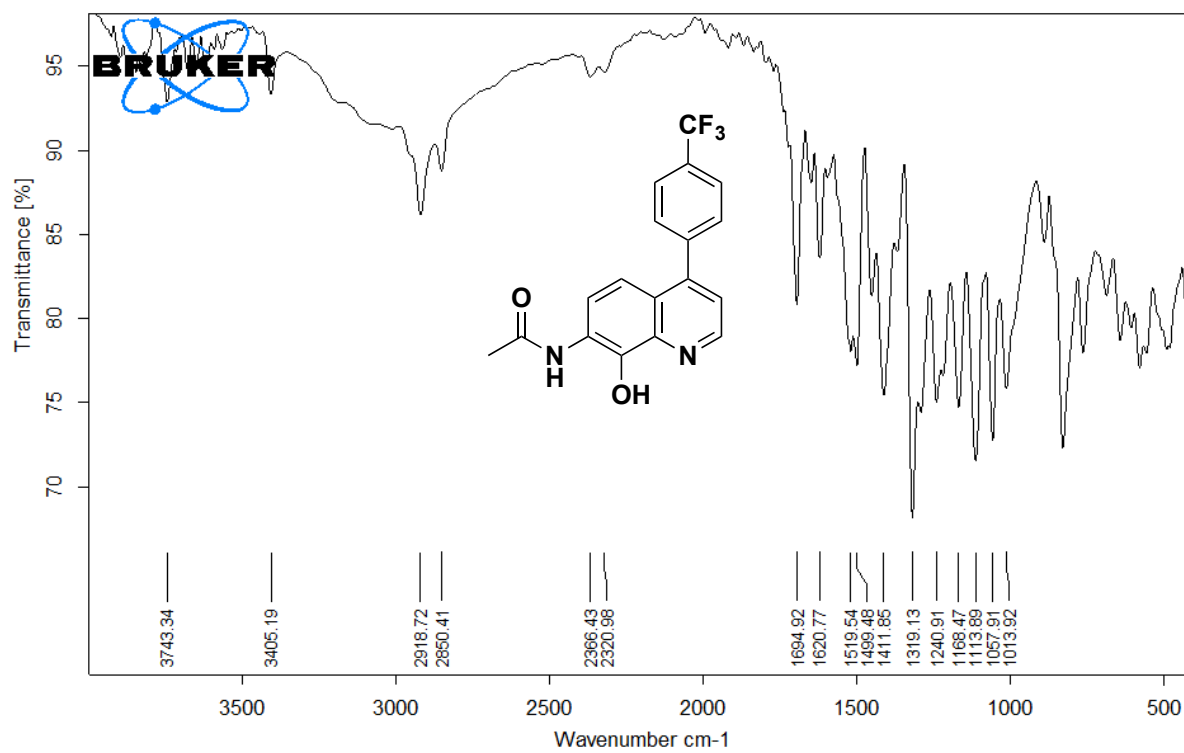
7-Acetamido-4-((4-trifluoromethyl)phenyl)-8-hydroxyquinoline (32) in DMSO-d₆



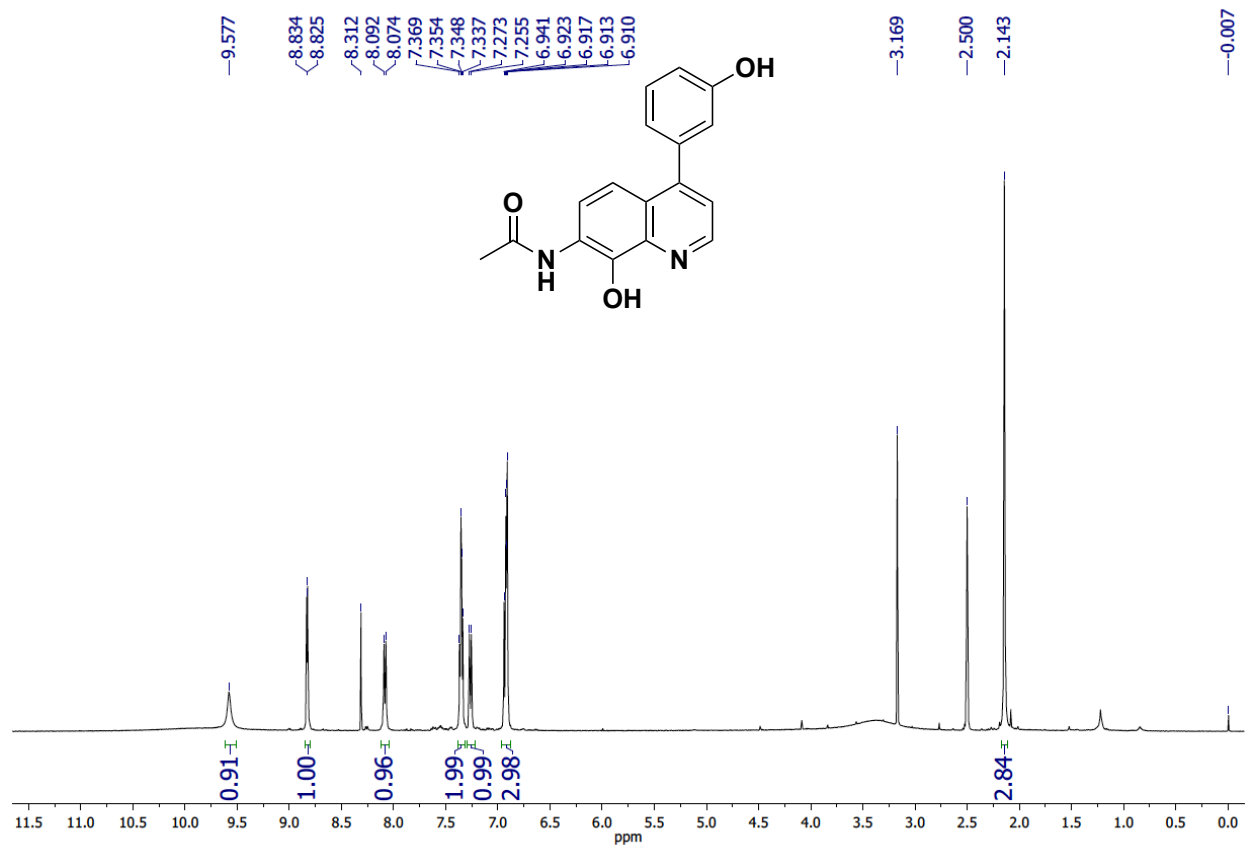
7-Acetamido-4-((4-trifluoromethyl)phenyl)-8-hydroxyquinoline (32) in DMSO-d₆



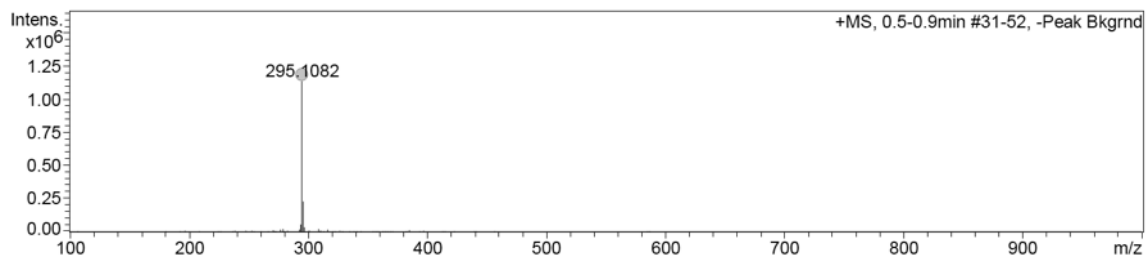
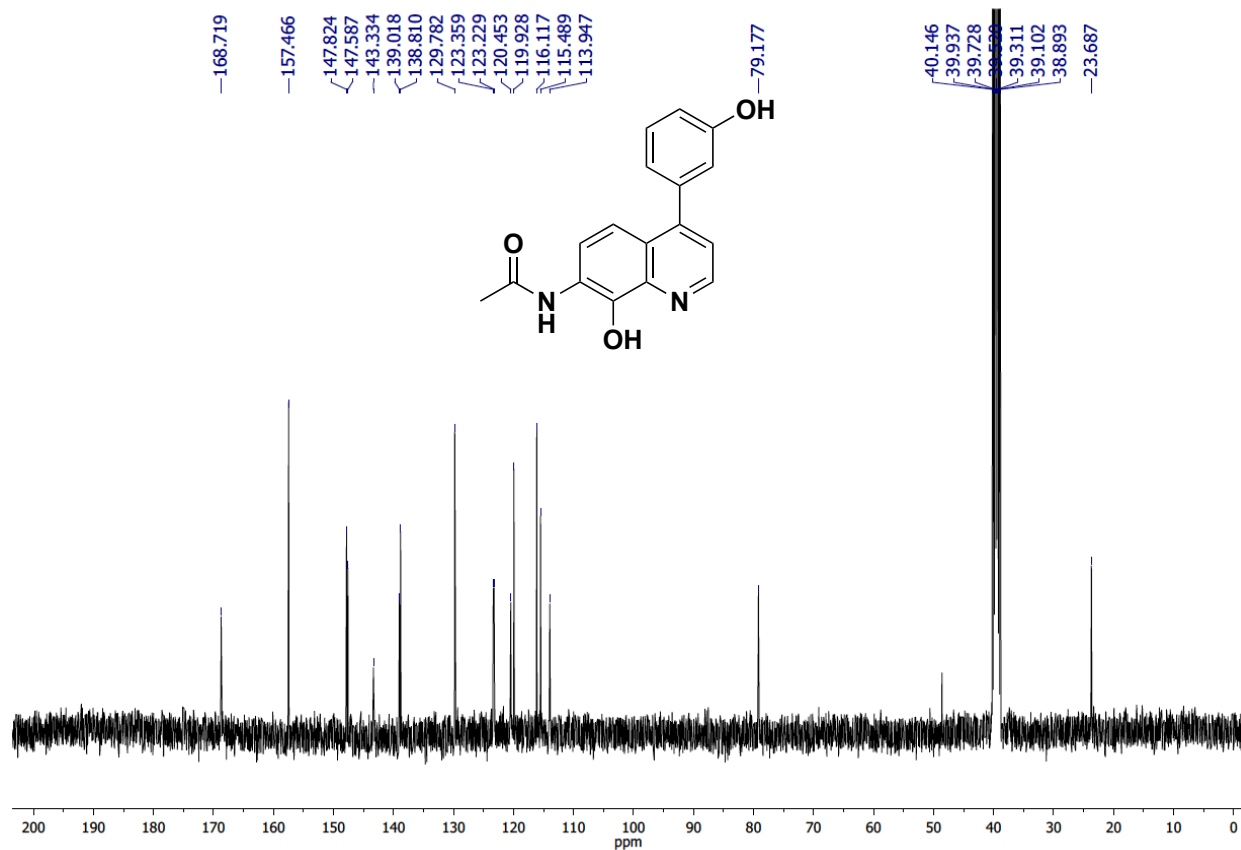
7-Acetamido-4-((4-trifluoromethyl)phenyl)-8-hydroxyquinoline (32)



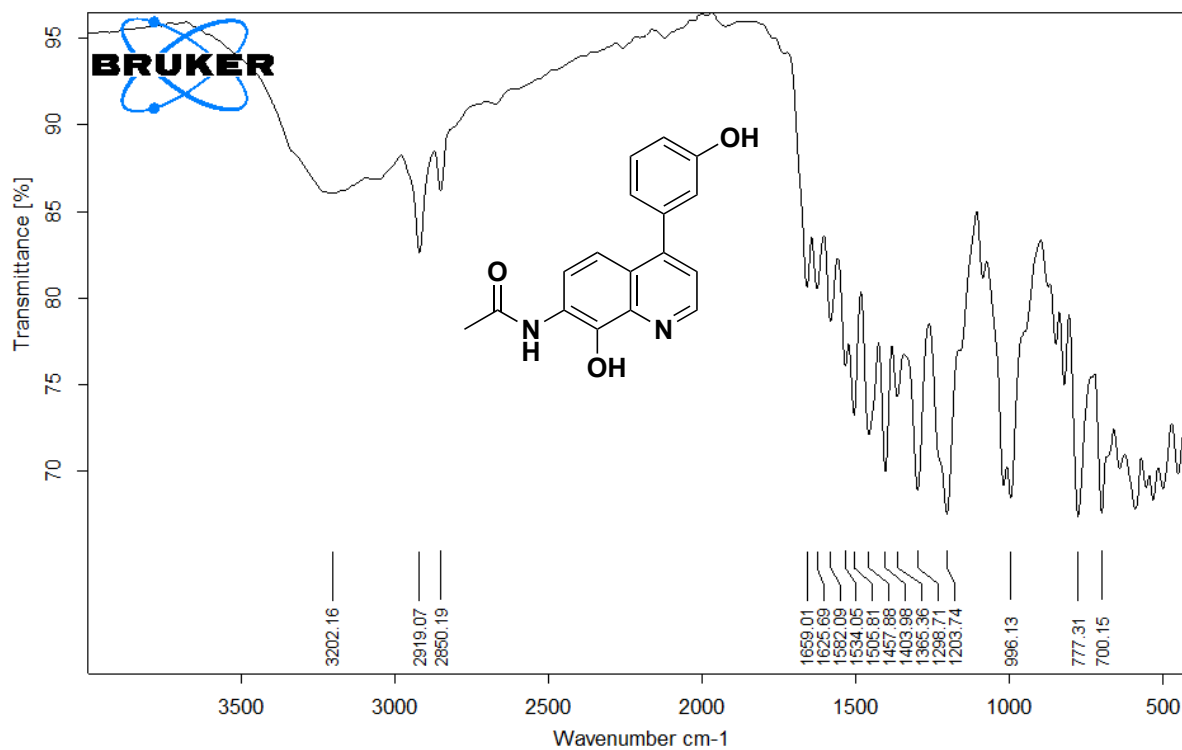
7-Acetamido-4-(3-hydroxyphenyl)-8-hydroxyquinoline (33) in DMSO-d₆



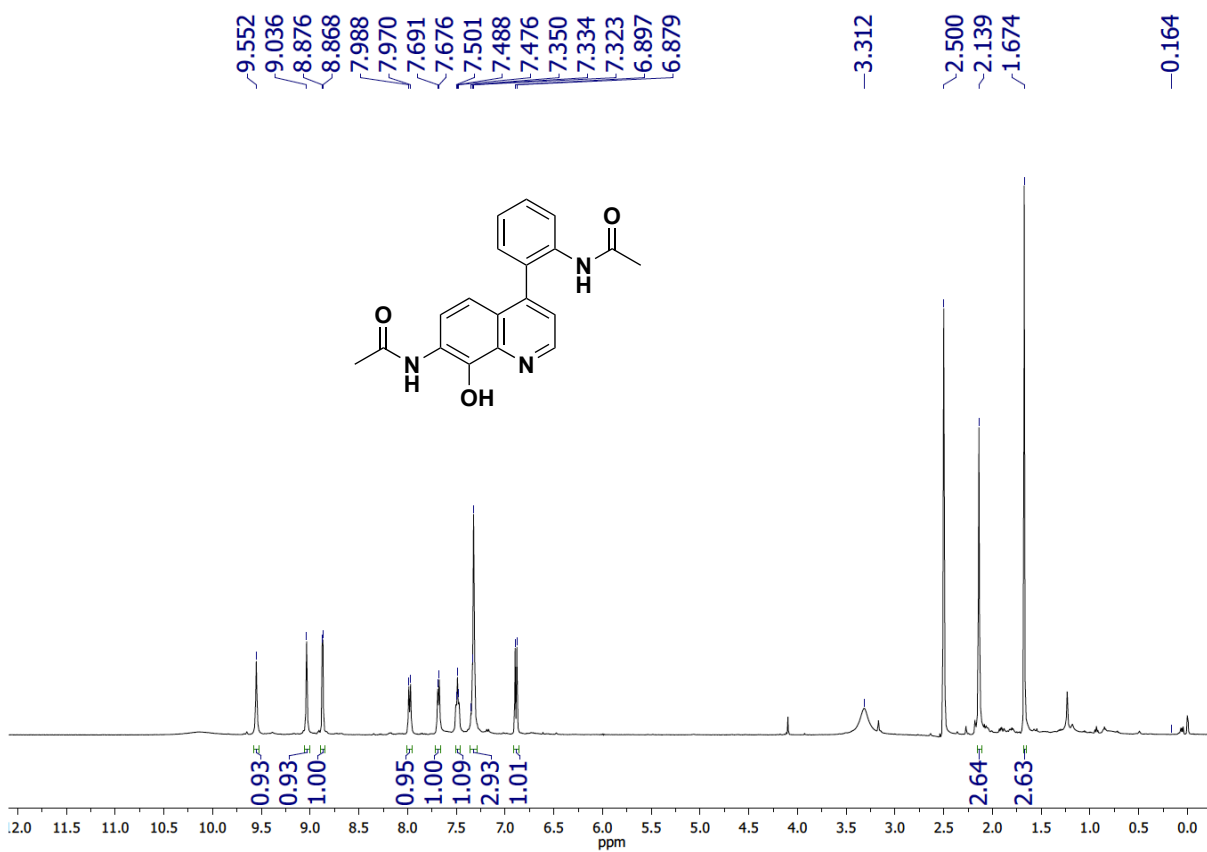
7-Acetamido-4-(3-hydroxyphenyl)-8-hydroxyquinoline (33) in DMSO-d₆



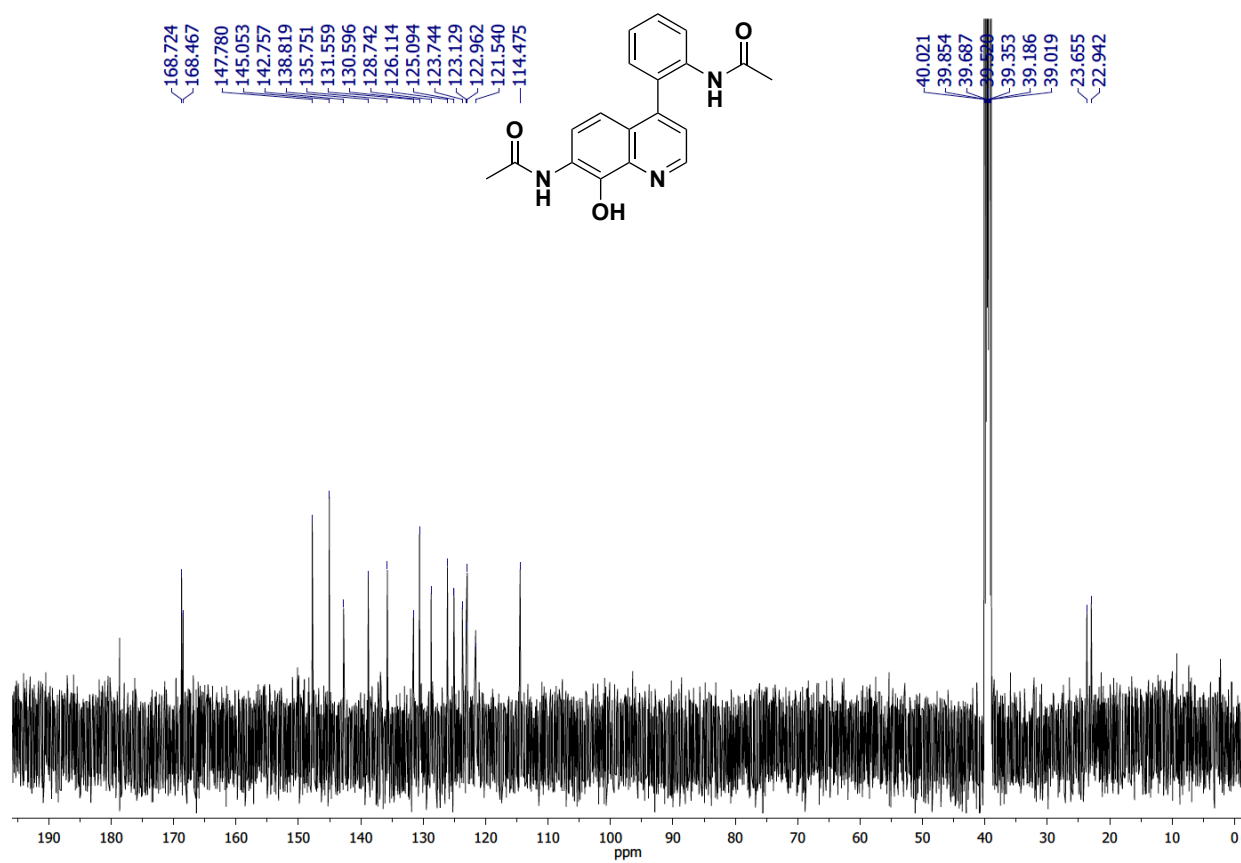
7-Acetamido-4-(3-hydroxyphenyl)-8-hydroxyquinoline (33)



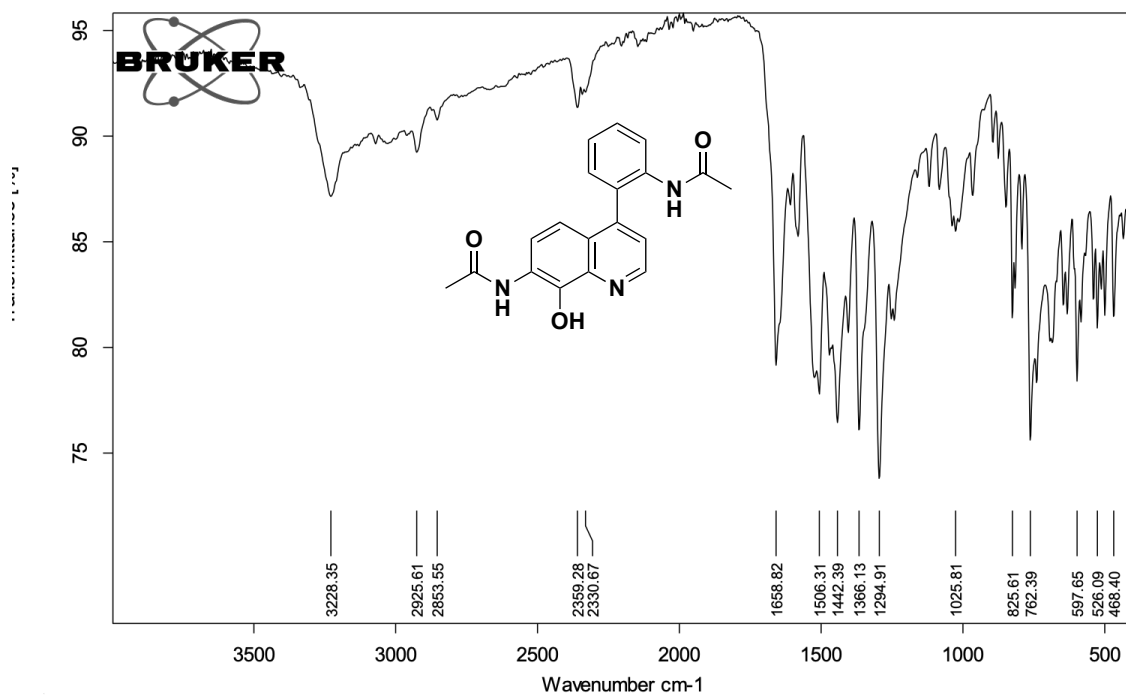
7-Acetamido-4-(2-acetamidophenyl)-8-hydroxyquinoline (34) in DMSO-d₆



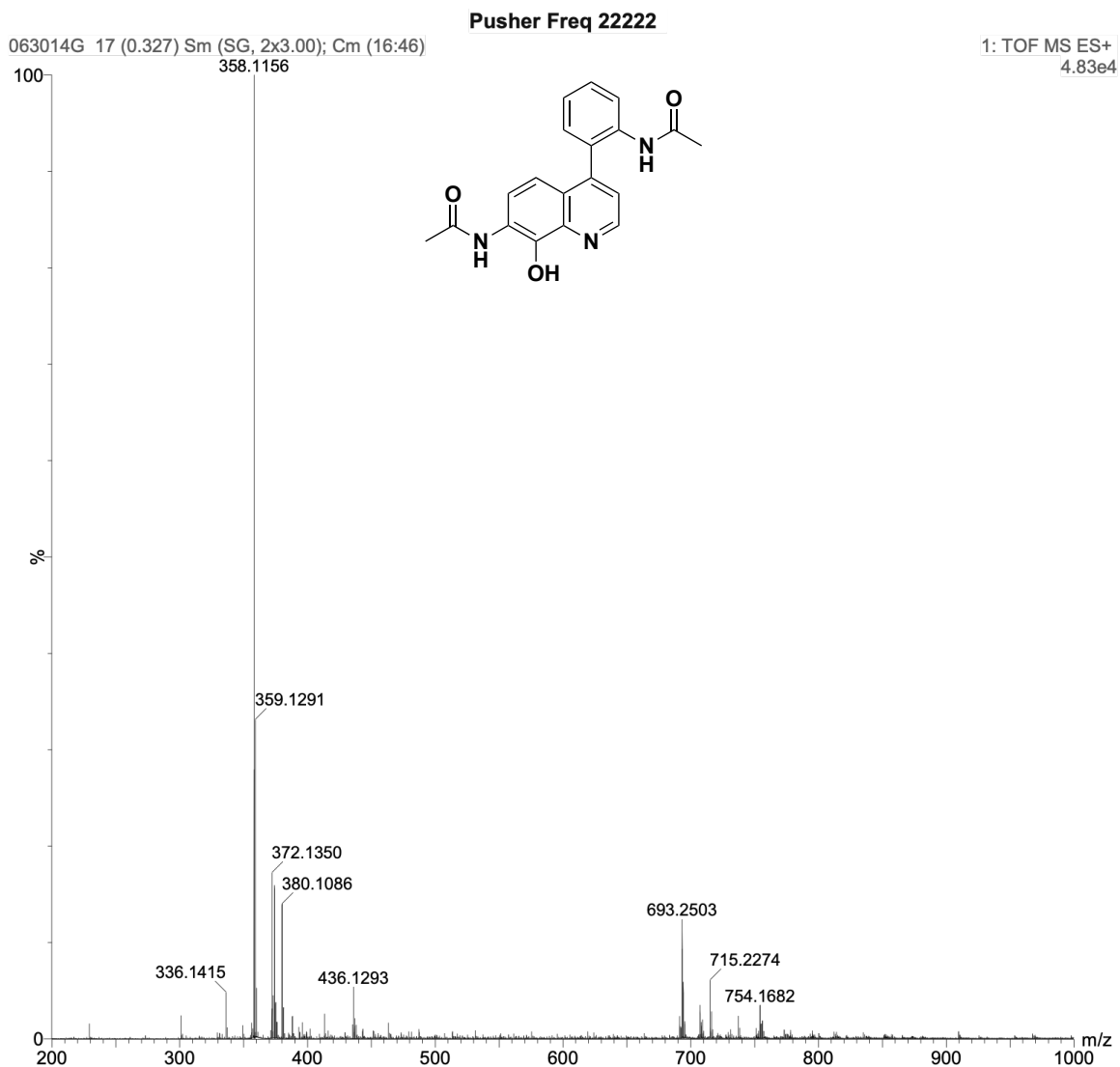
7-Acetamido-4-(2-acetamidophenyl)-8-hydroxyquinoline (34) in DMSO-d₆



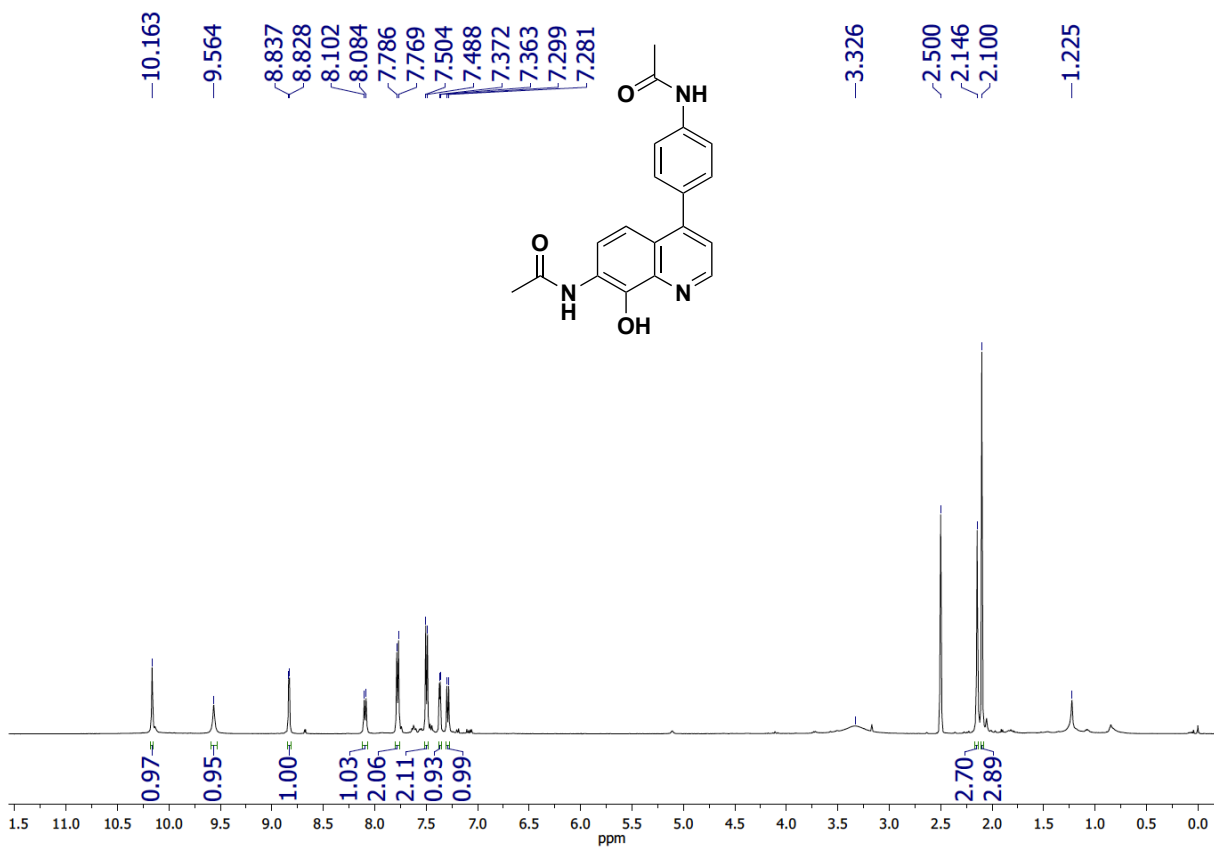
7-Acetamido-4-(2-acetamidophenyl)-8-hydroxyquinoline (34) in DMSO



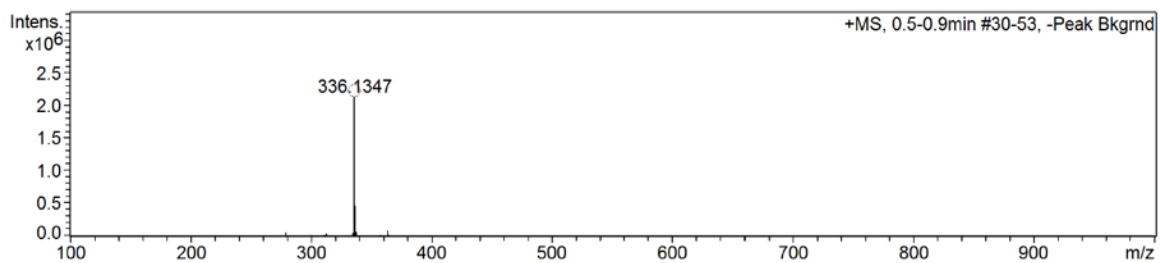
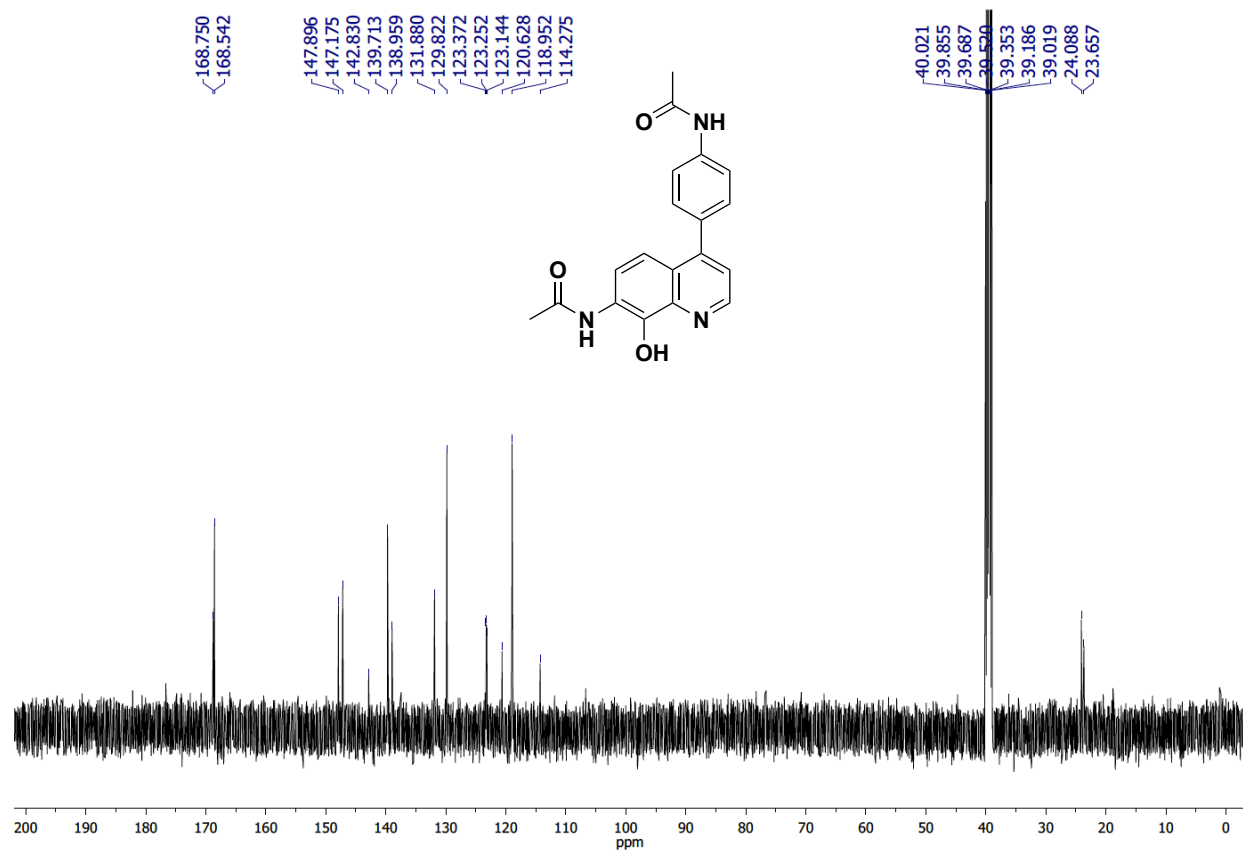
7-Acetamido-4-(2-acetamidophenyl)-8-hydroxyquinoline (34)



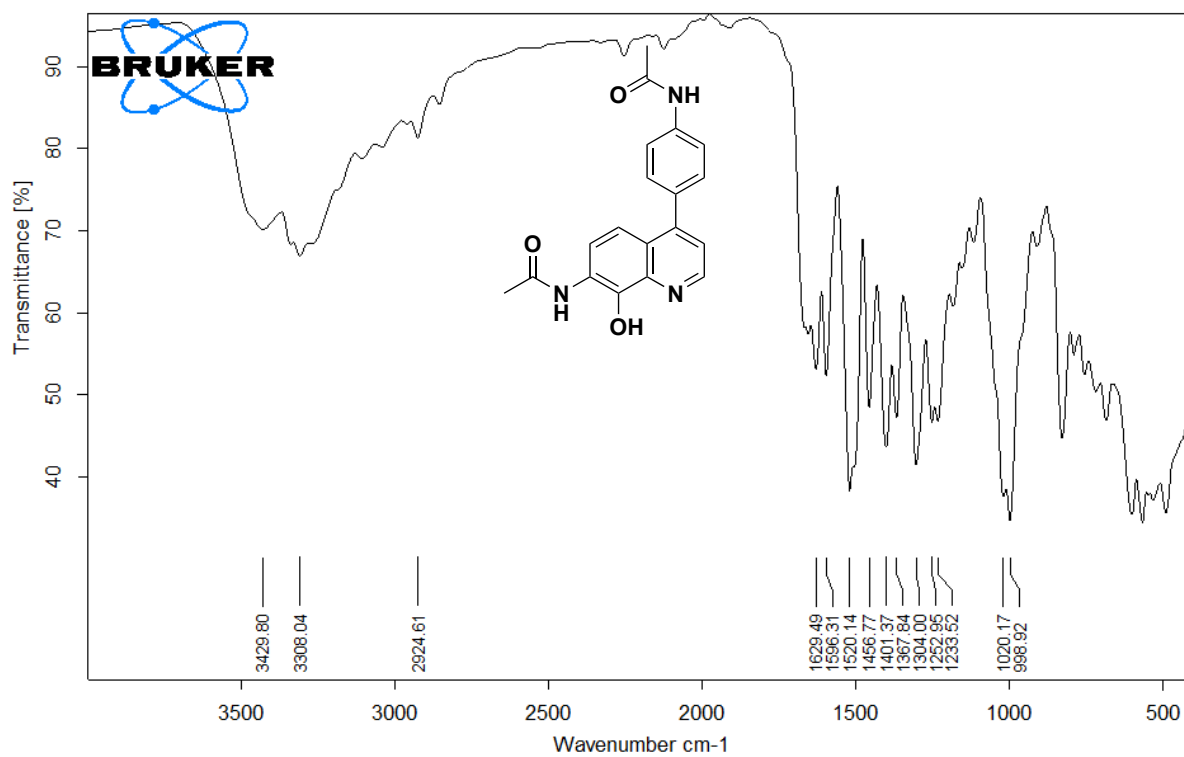
7-Acetamido-4-(4-acetamidophenyl)-8-hydroxyquinoline (35) in DMSO-d₆



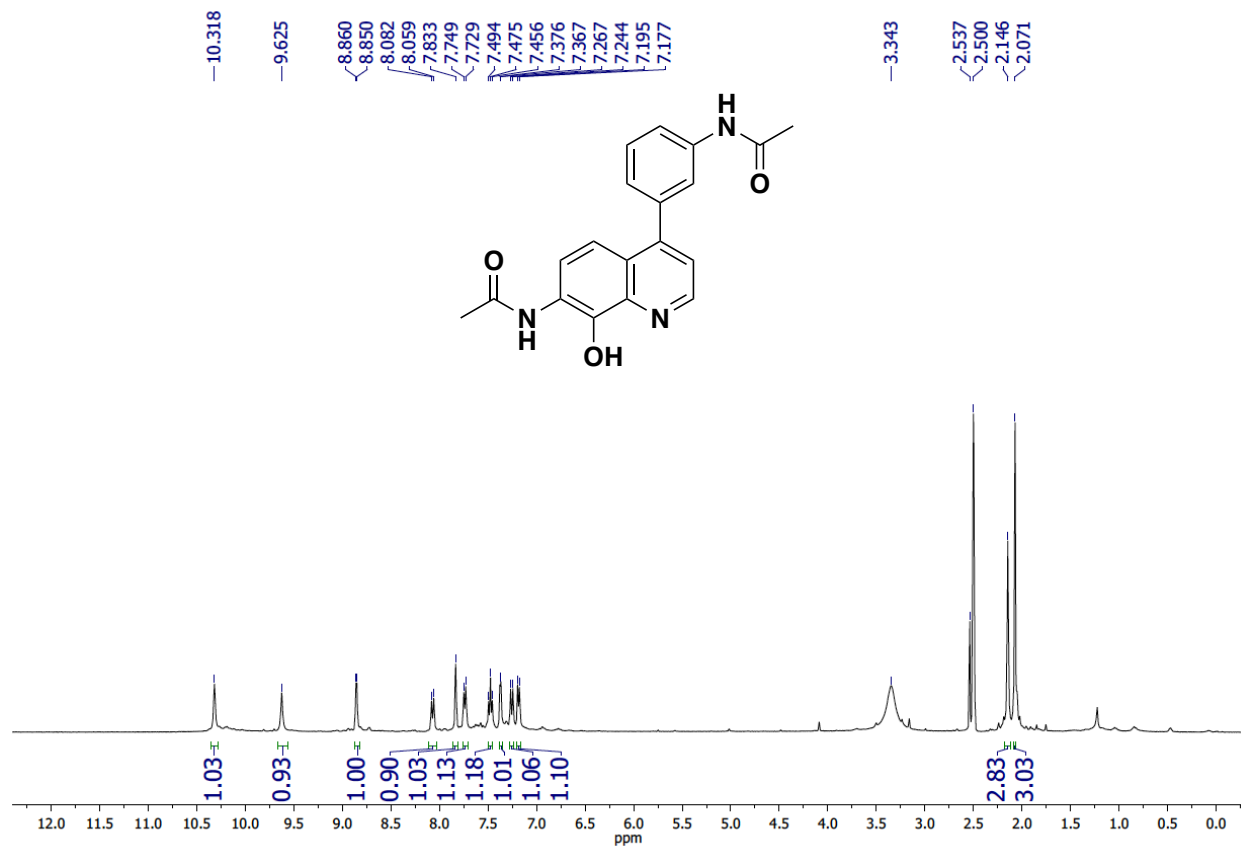
7-Acetamido-4-(4-acetamidophenyl)-8-hydroxyquinoline (35) in DMSO-d₆



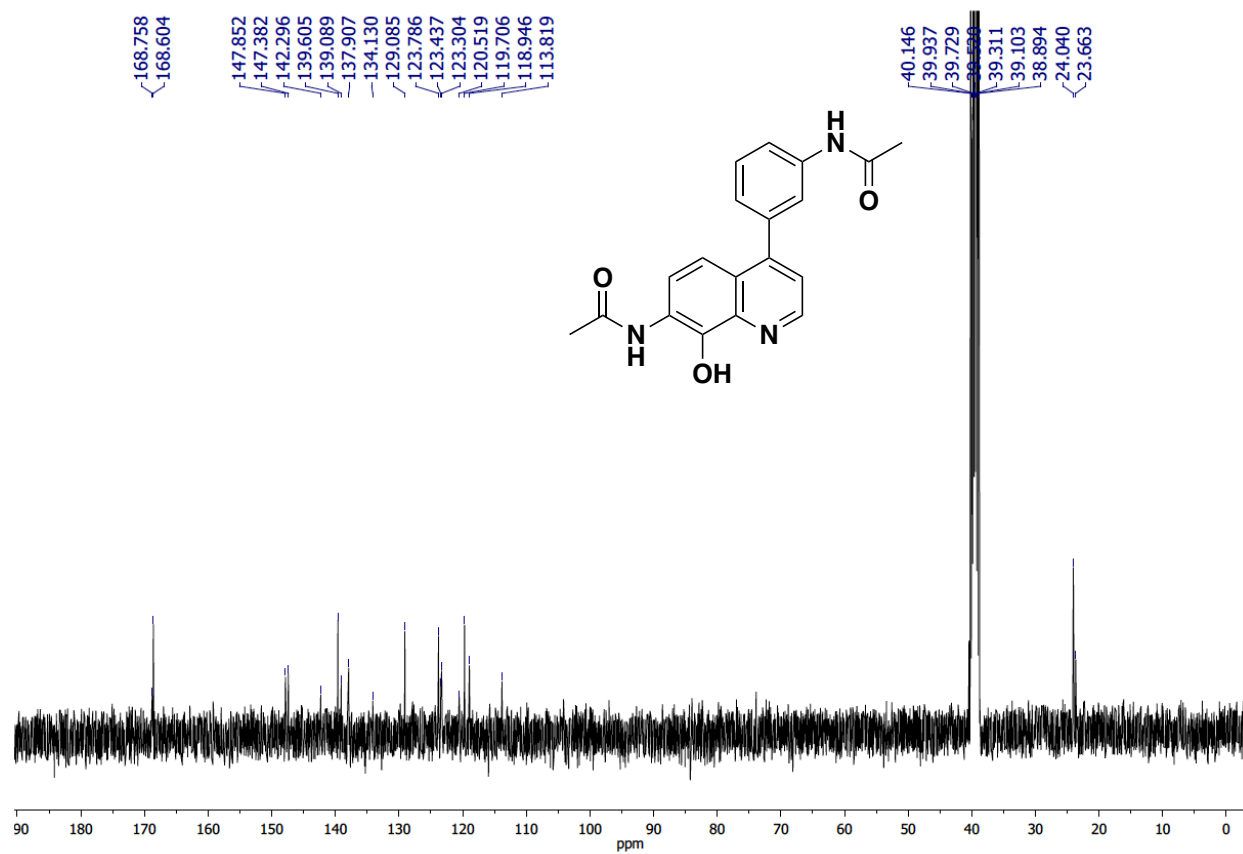
7-Acetamido-4-(4-acetamidophenyl)-8-hydroxyquinoline (35)



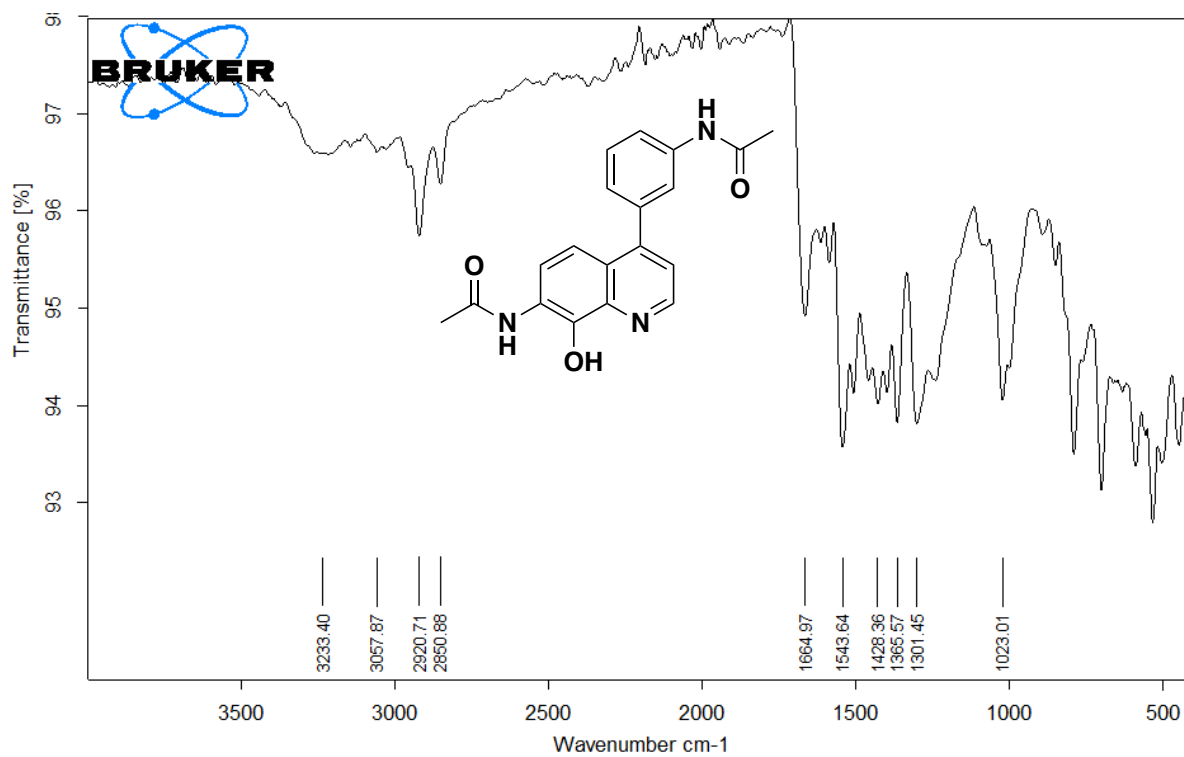
7-Acetamido-4-(3-acetamidophenyl)-8-hydroxyquinoline (36) in DMSO-d₆



7-Acetamido-4-(3-acetamidophenyl)-8-hydroxyquinoline (36) in DMSO-d₆



7-Acetamido-4-(3-acetamidophenyl)-8-hydroxyquinoline (36)



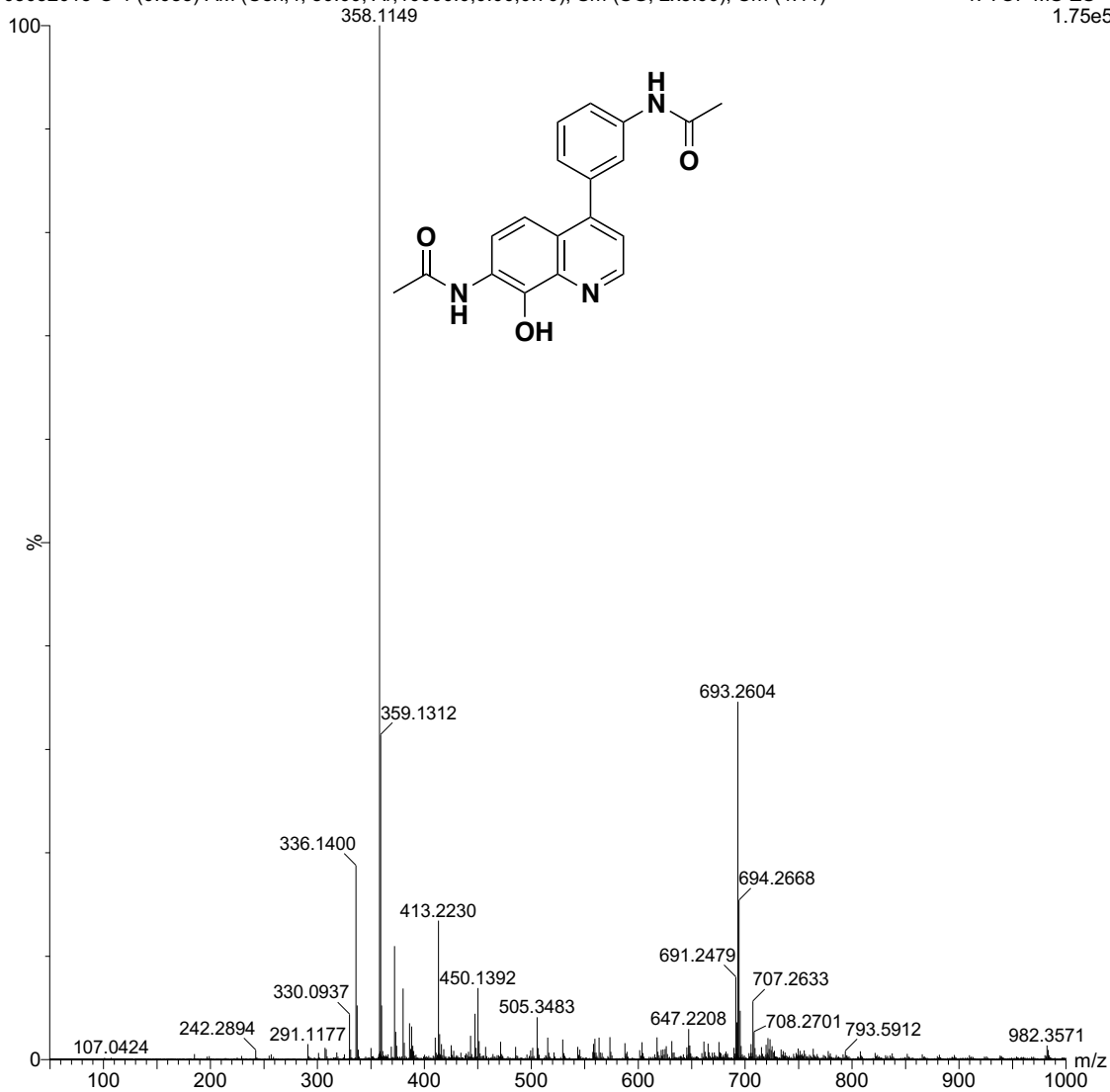
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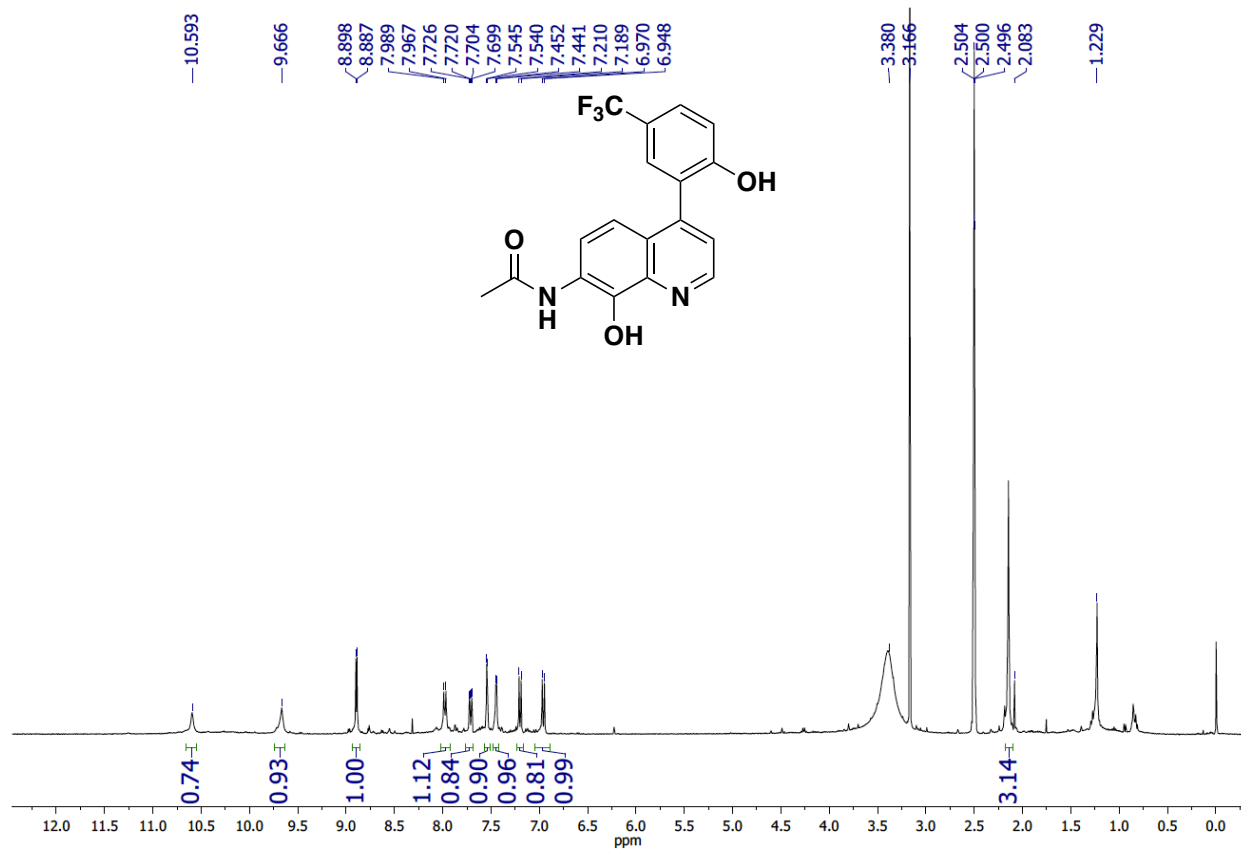
Pusher Freq 22222

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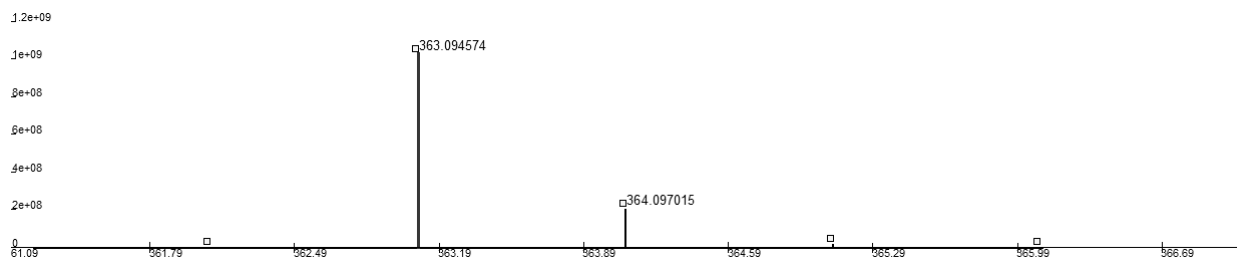
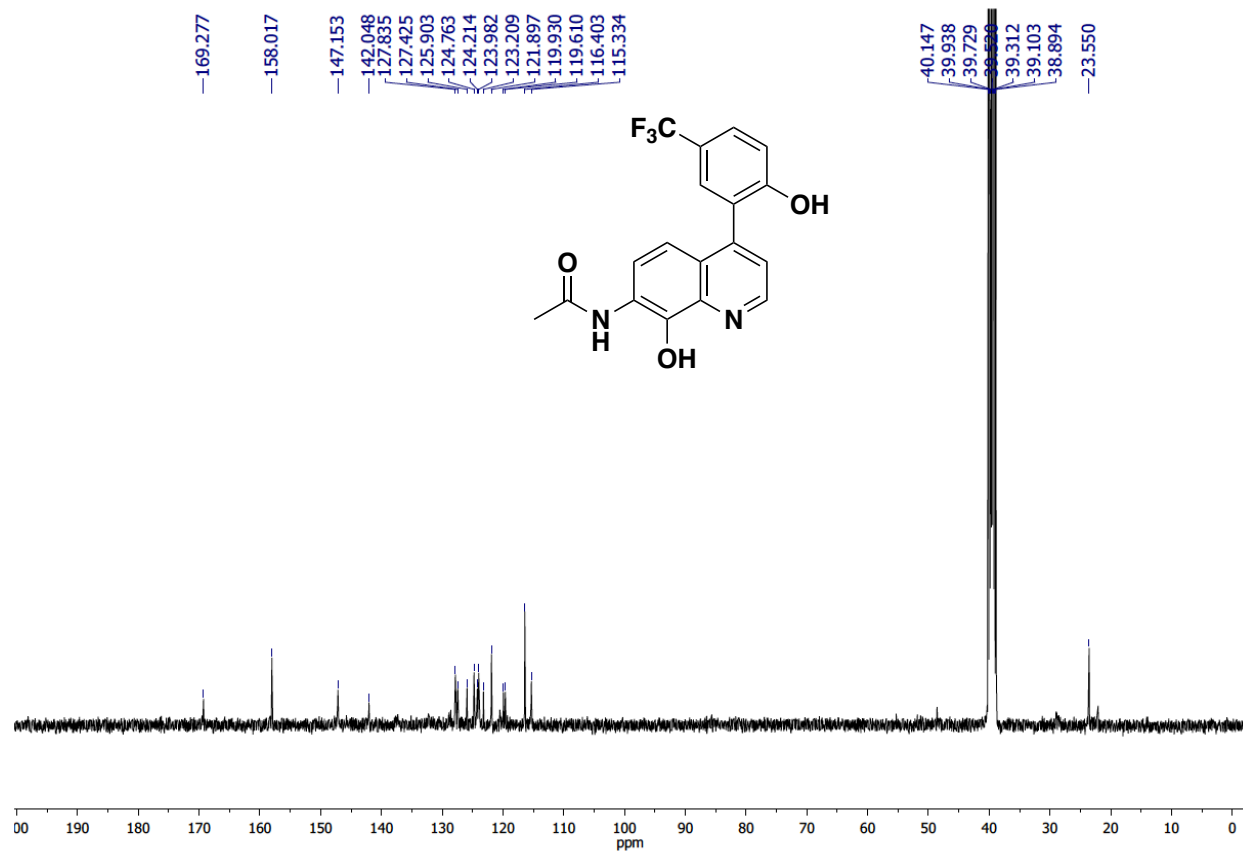
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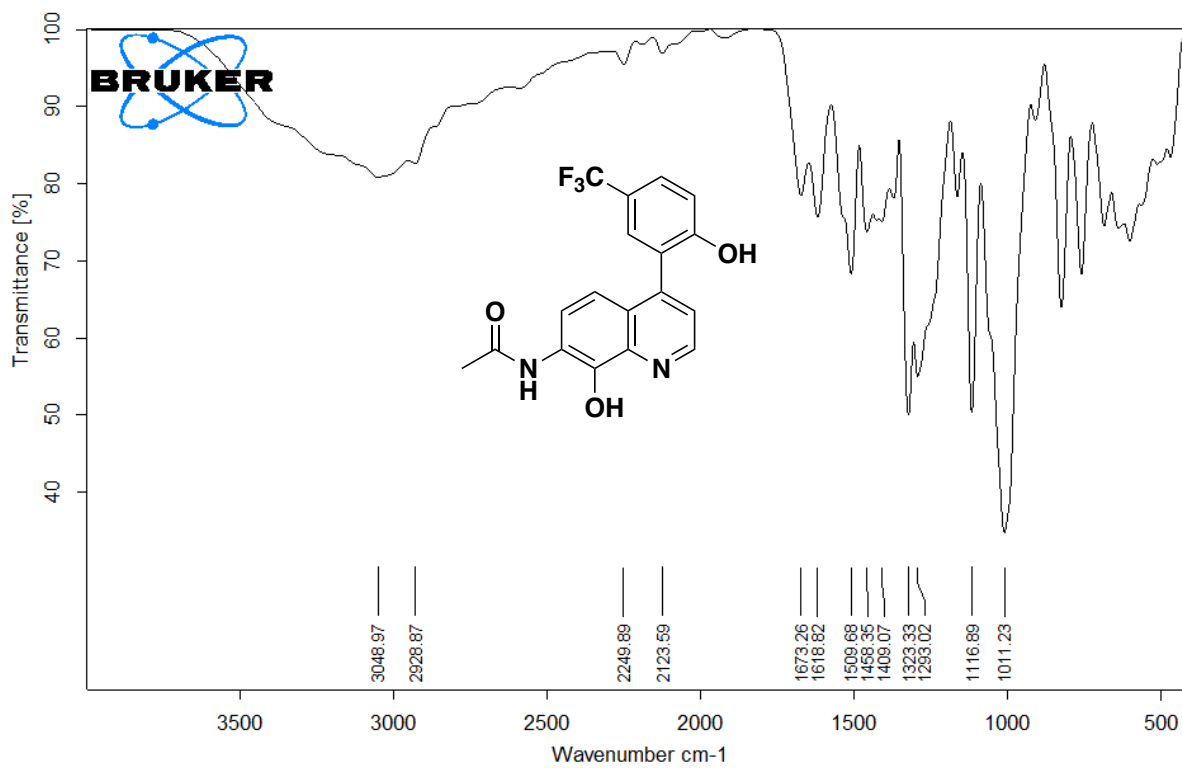
7-Acetamido-4-(2-hydroxy-(5-trifluoromethyl)phenyl)-8-hydroxyquinoline (37) in DMSO-d₆



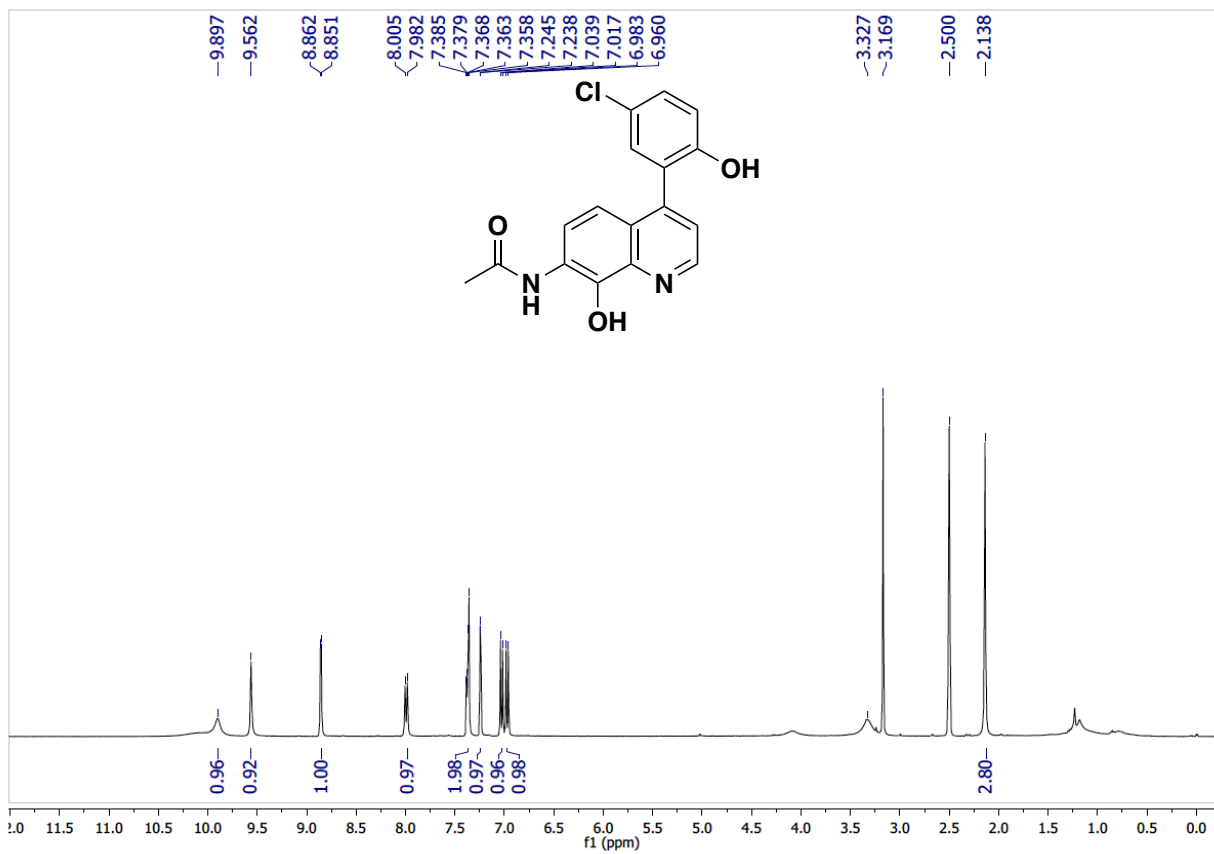
7-Acetamido-4-(2-hydroxy-(5-trifluoromethyl)phenyl)-8-hydroxyquinoline (37) in DMSO-d₆



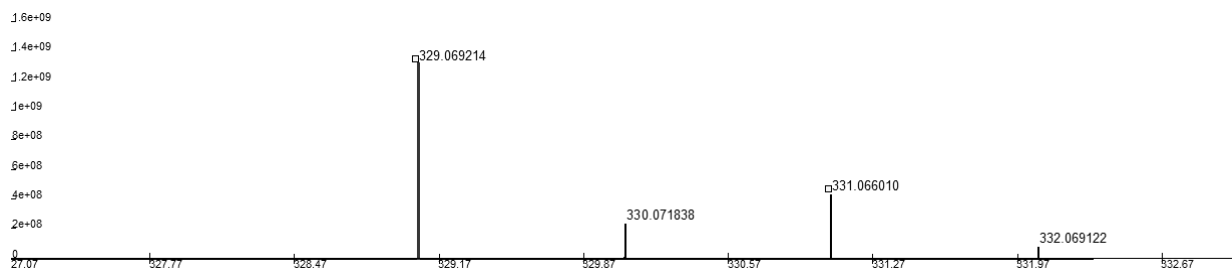
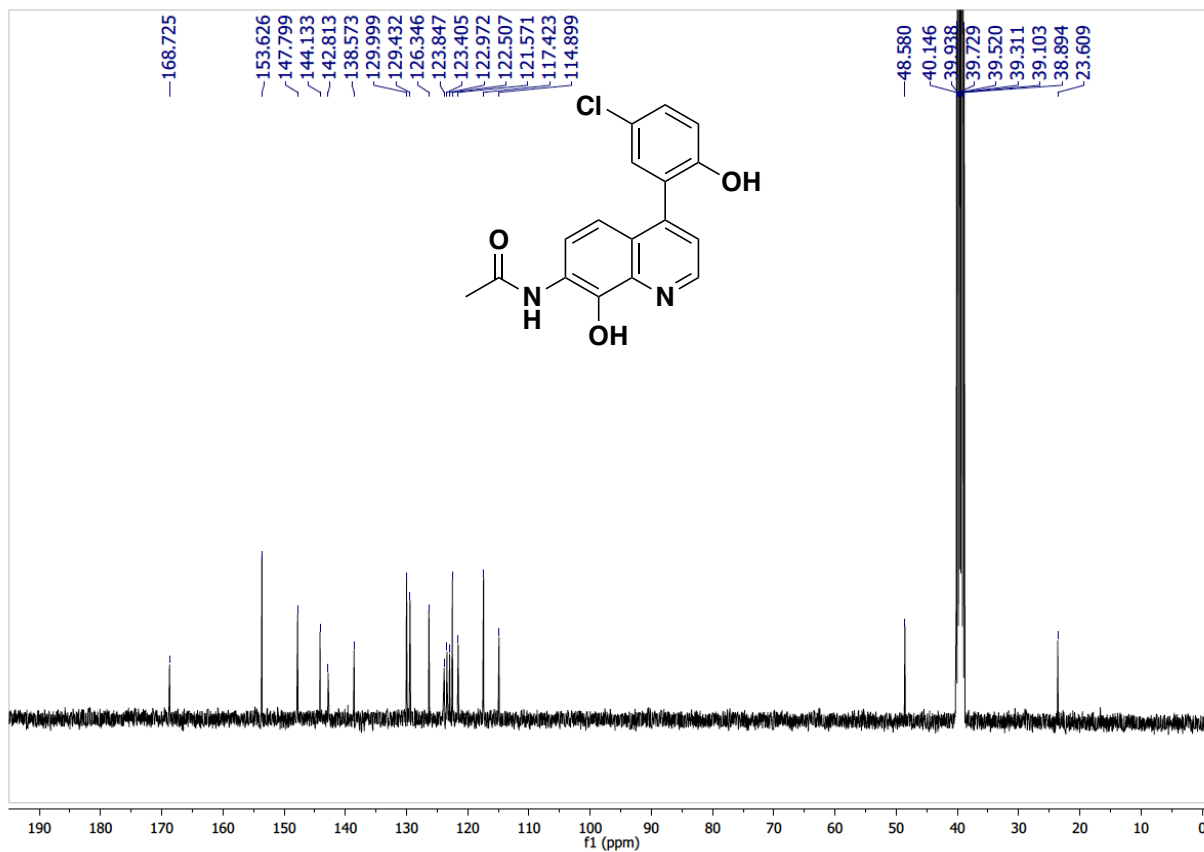
7-Acetamido-4-(2-hydroxy-(5-trifluoromethyl)phenyl)-8-hydroxyquinoline (37)



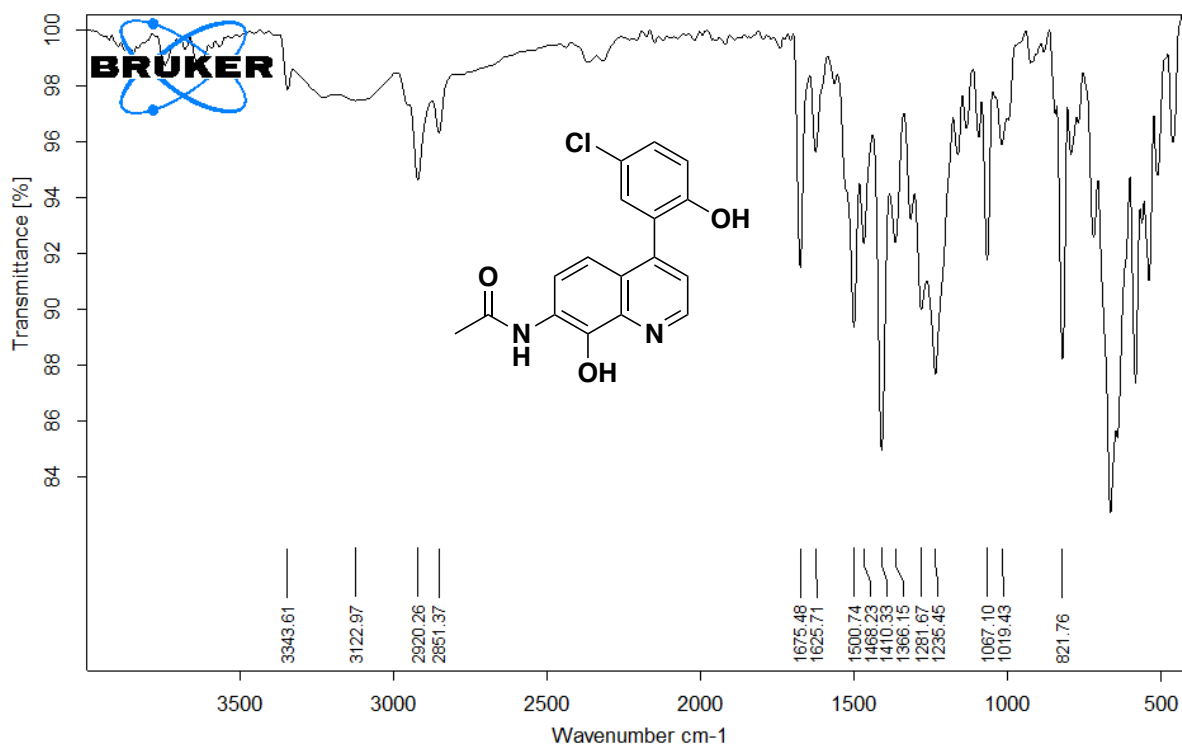
7-Acetamido-4-(5-chloro-2-hydroxyphenyl)-8-hydroxyquinoline (38) in DMSO-d₆



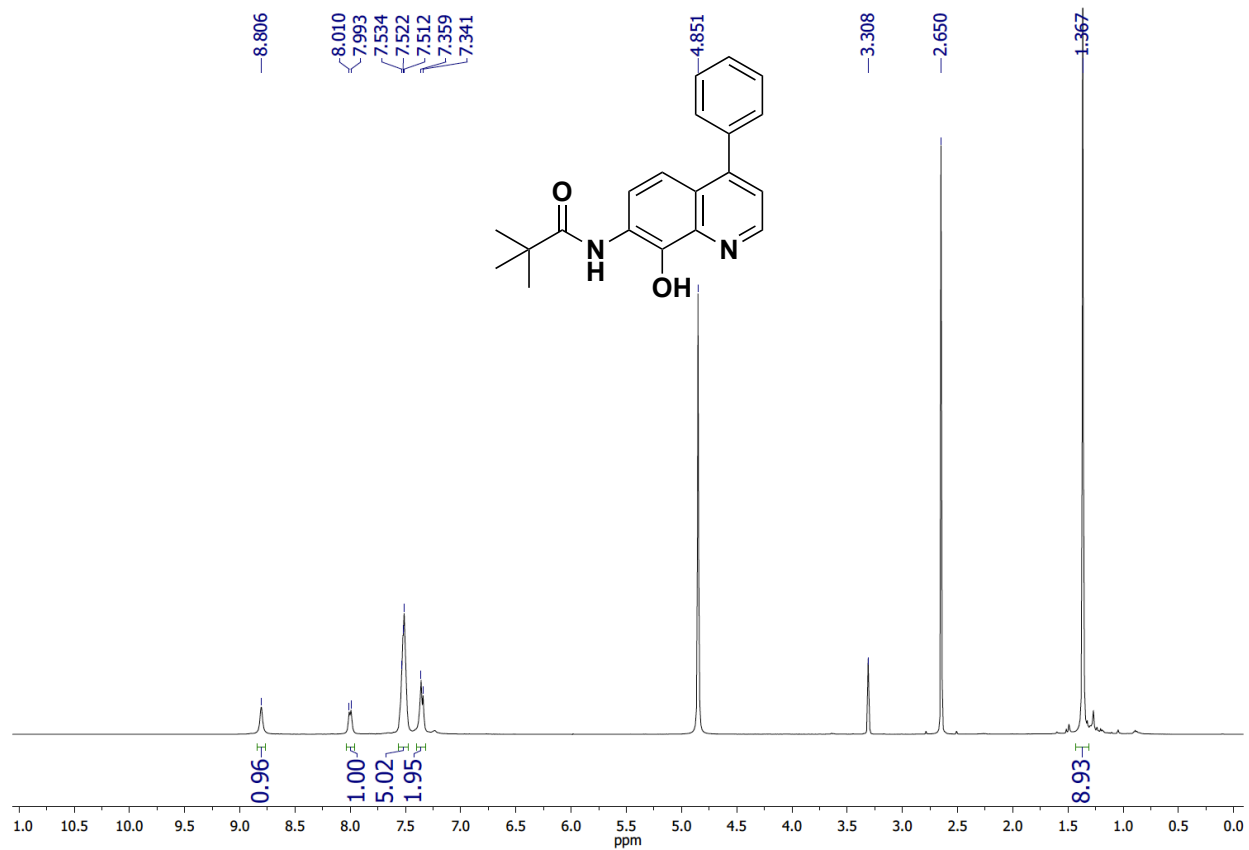
7-Acetamido-4-(5-chloro-2-hydroxyphenyl)-8-hydroxyquinoline (38) in DMSO-d₆



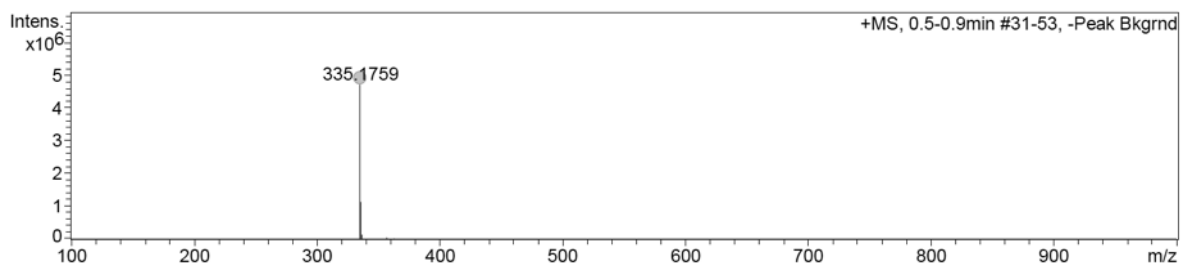
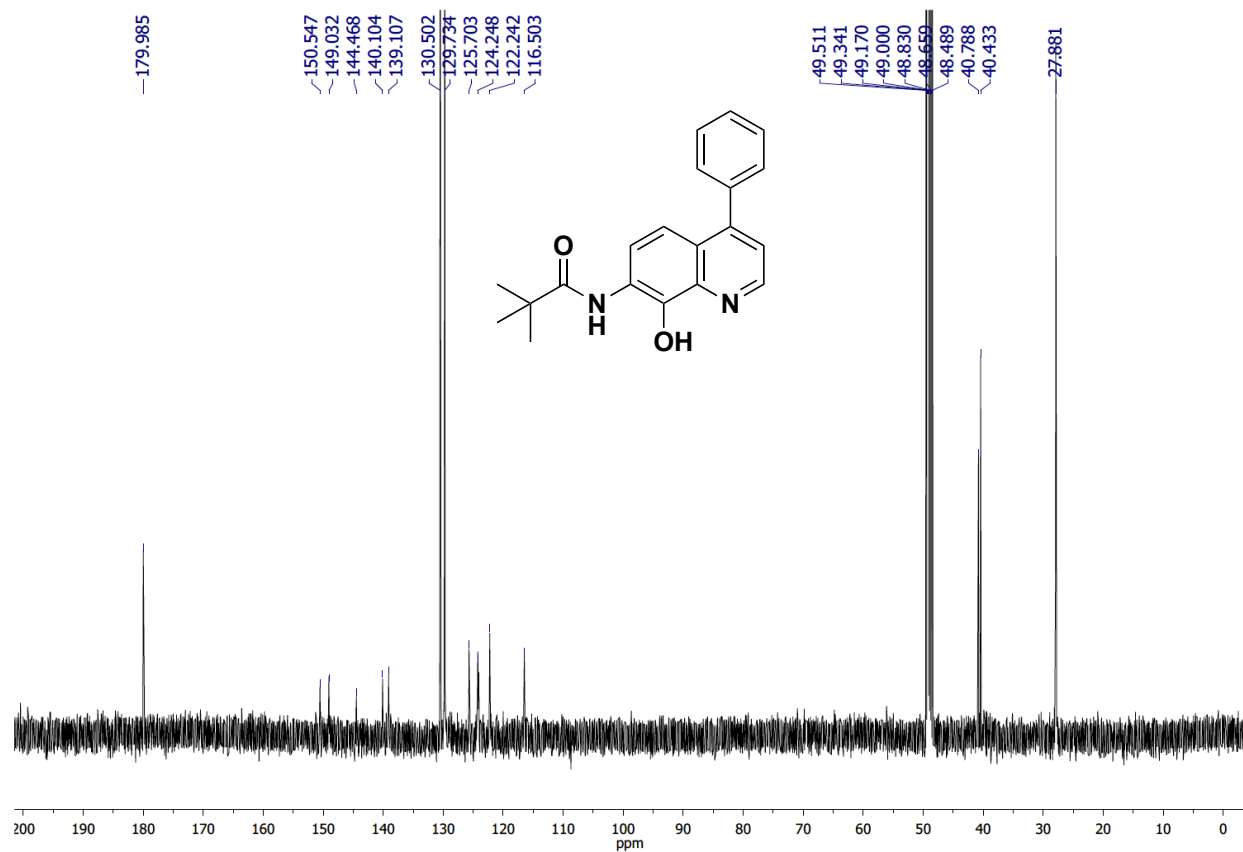
7-Acetamido-4-(5-chloro-2-hydroxyphenyl)-8-hydroxyquinoline (38)



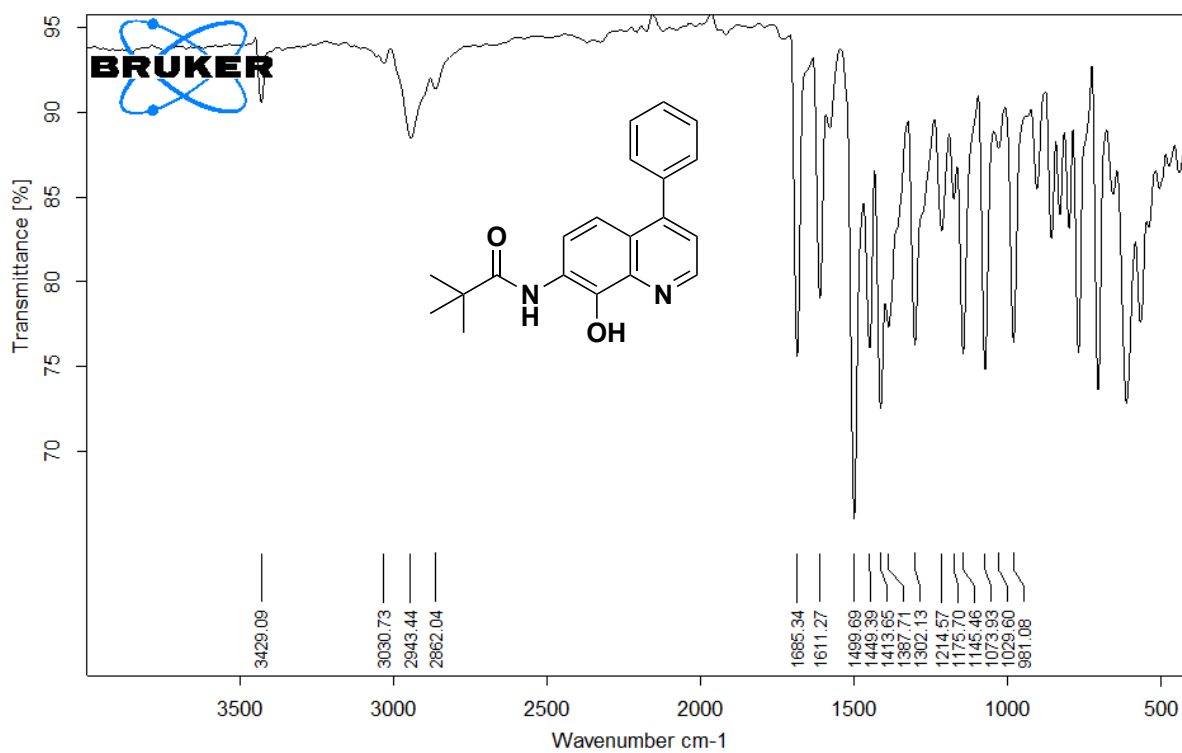
8-Hydroxy-4-(phenyl)-7-pivalamidoquinoline (39) in CD₃OD



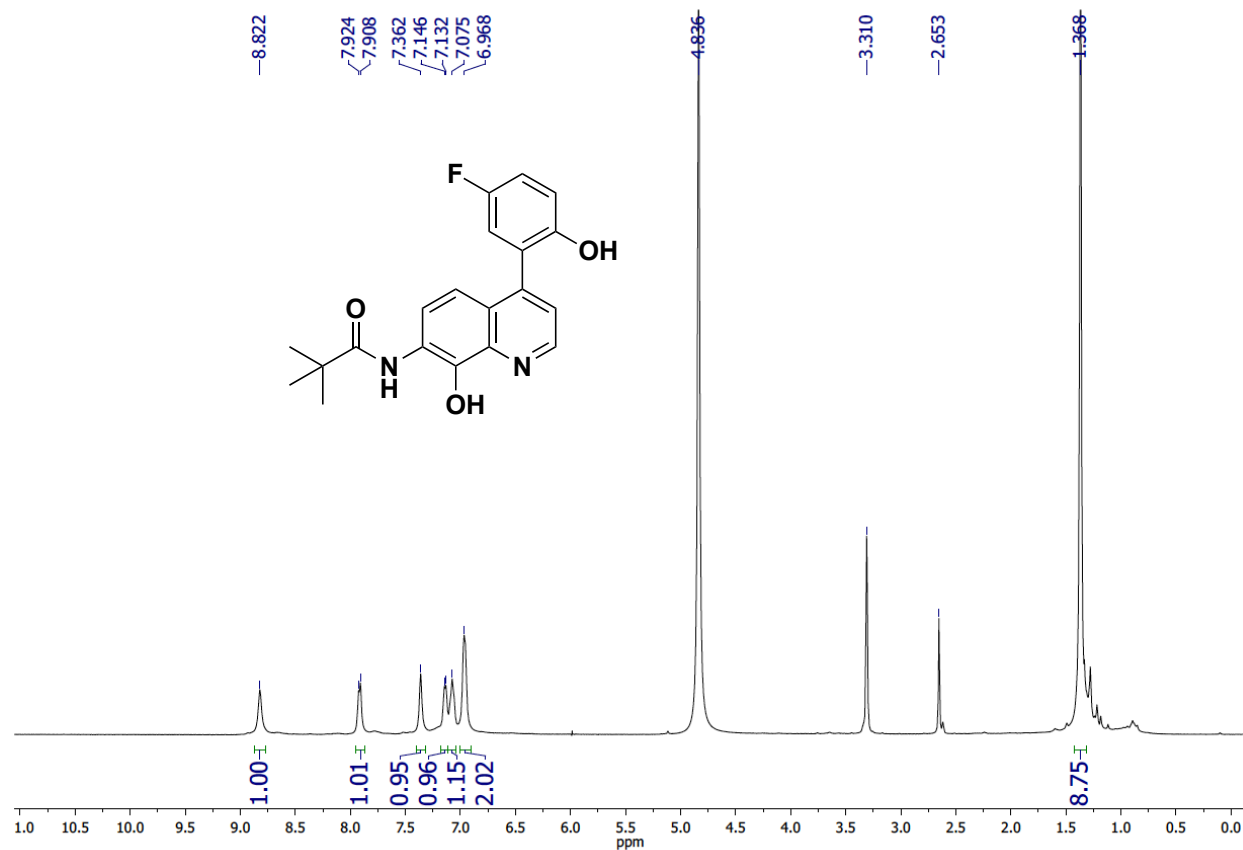
8-Hydroxy-4-(phenyl)-7-pivalamidoquinoline (39) in CD₃OD



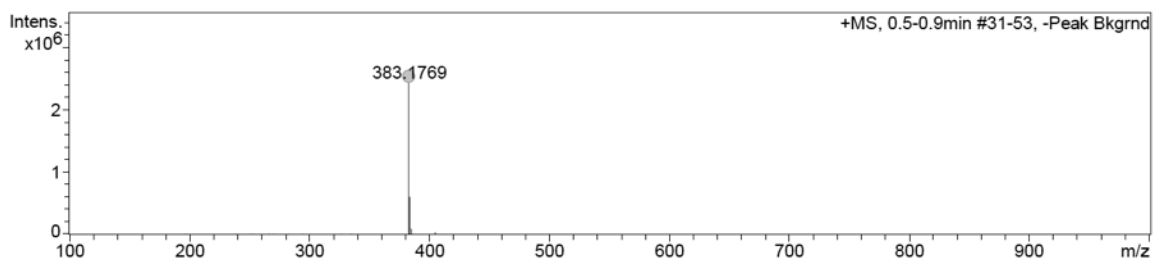
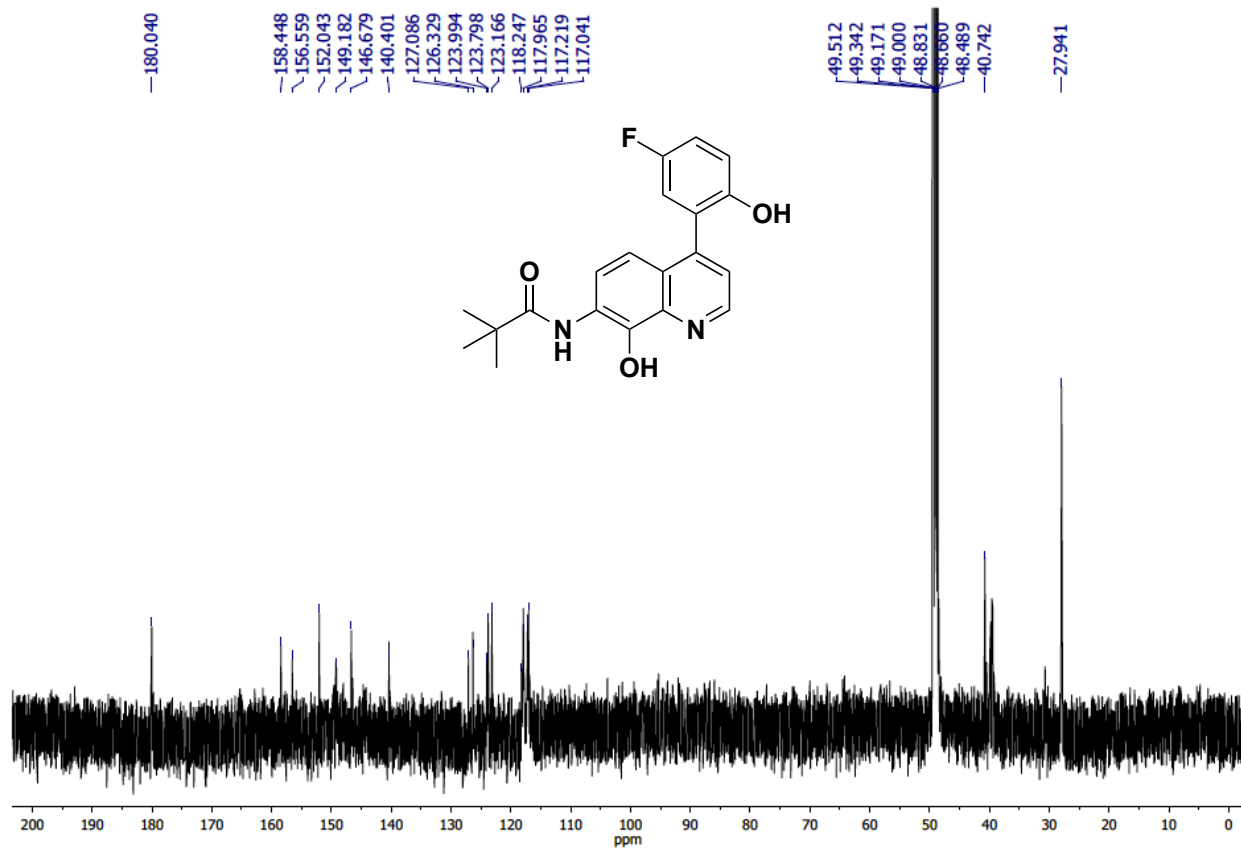
8-Hydroxy-4-(phenyl)-7-pivalamidoquinoline (39)



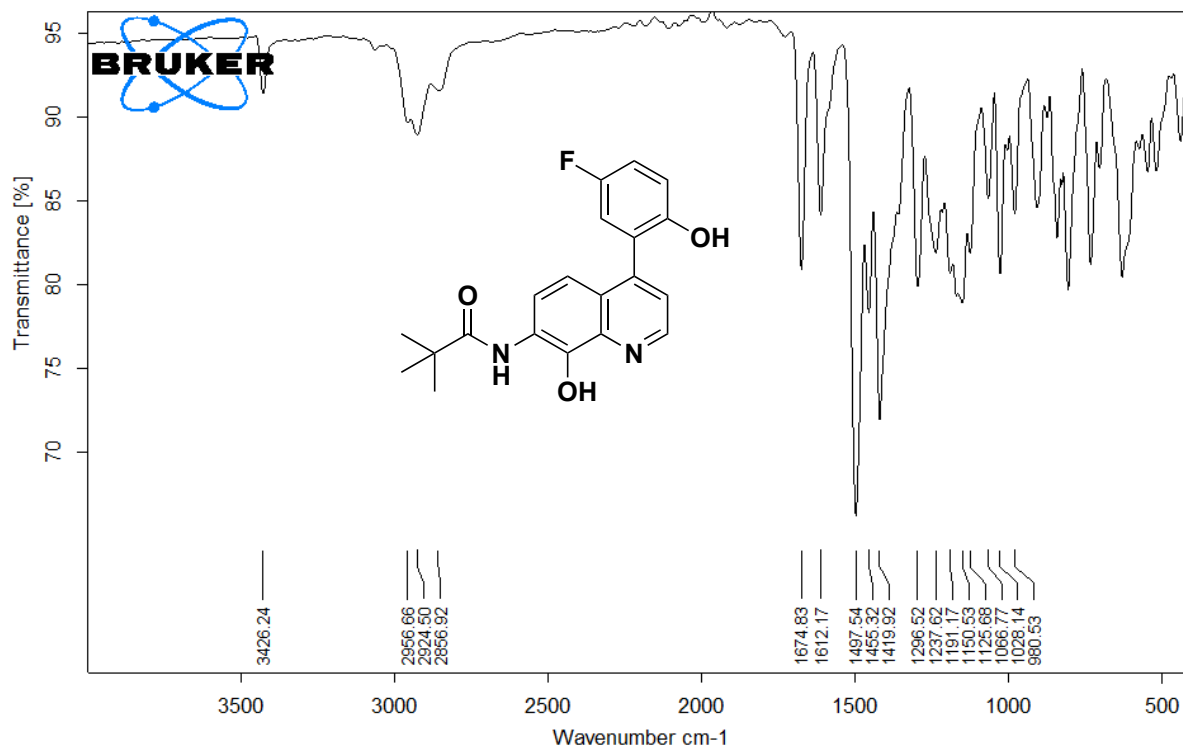
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-pivalamidoquinoline (40) in CD₃OD



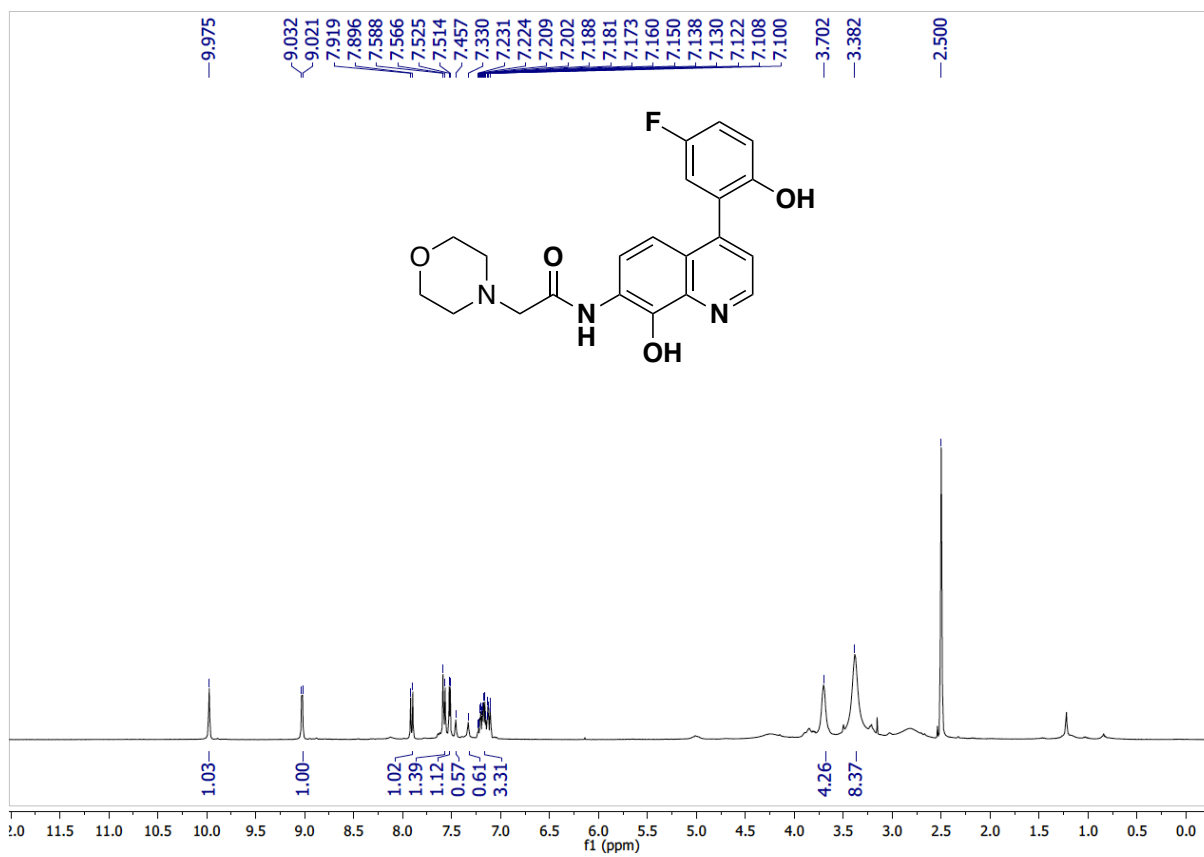
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-pivalamidoquinoline (40) in CD₃OD



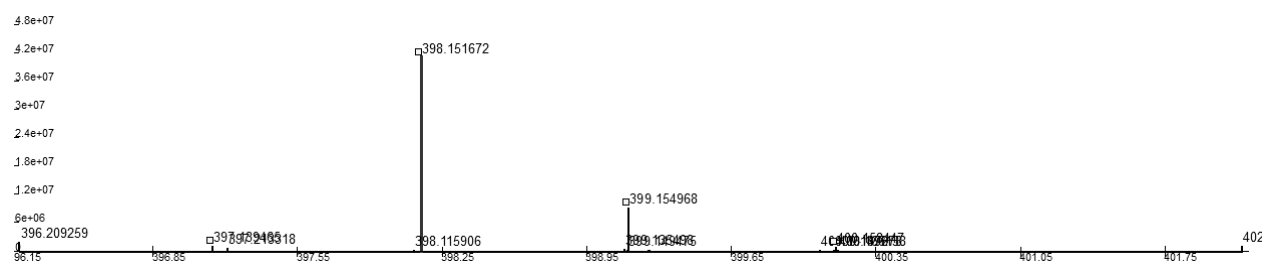
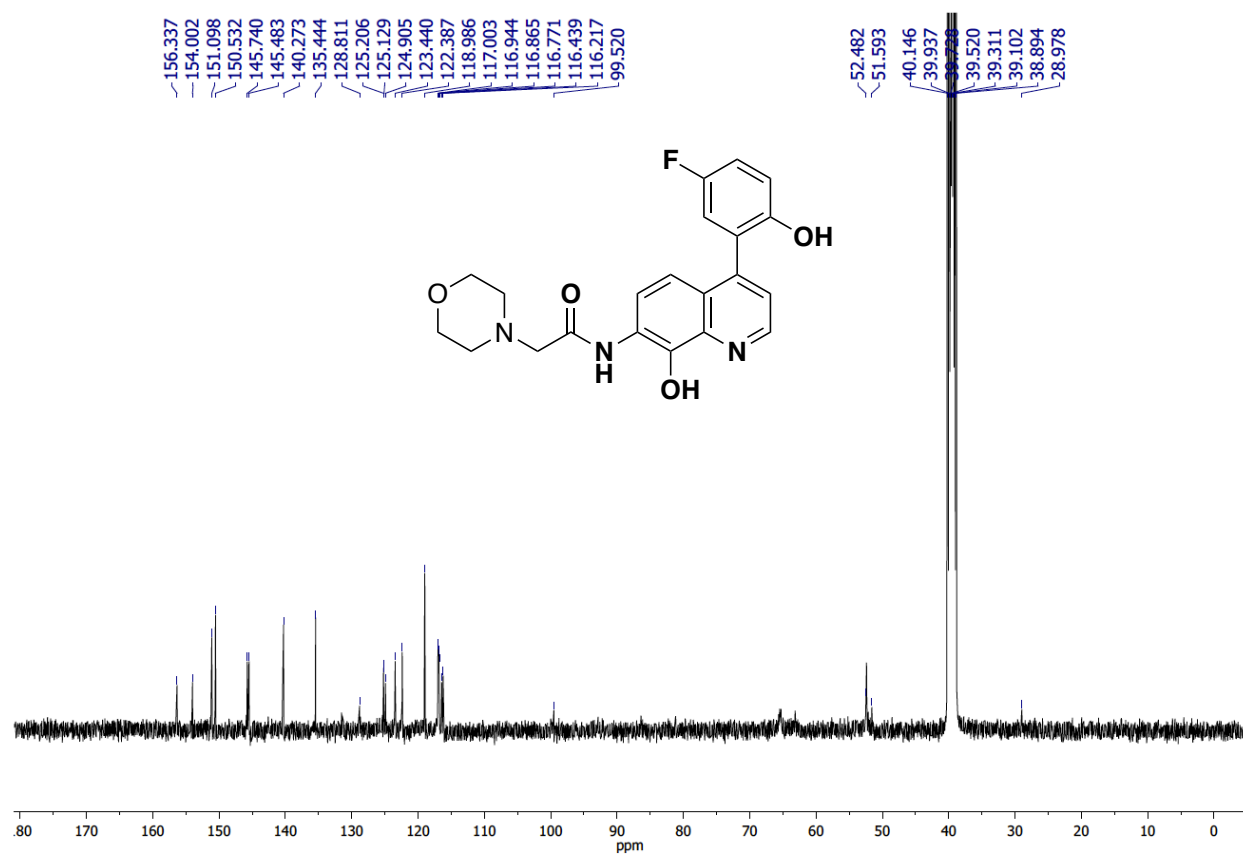
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-pivalamido-quinoline (40)



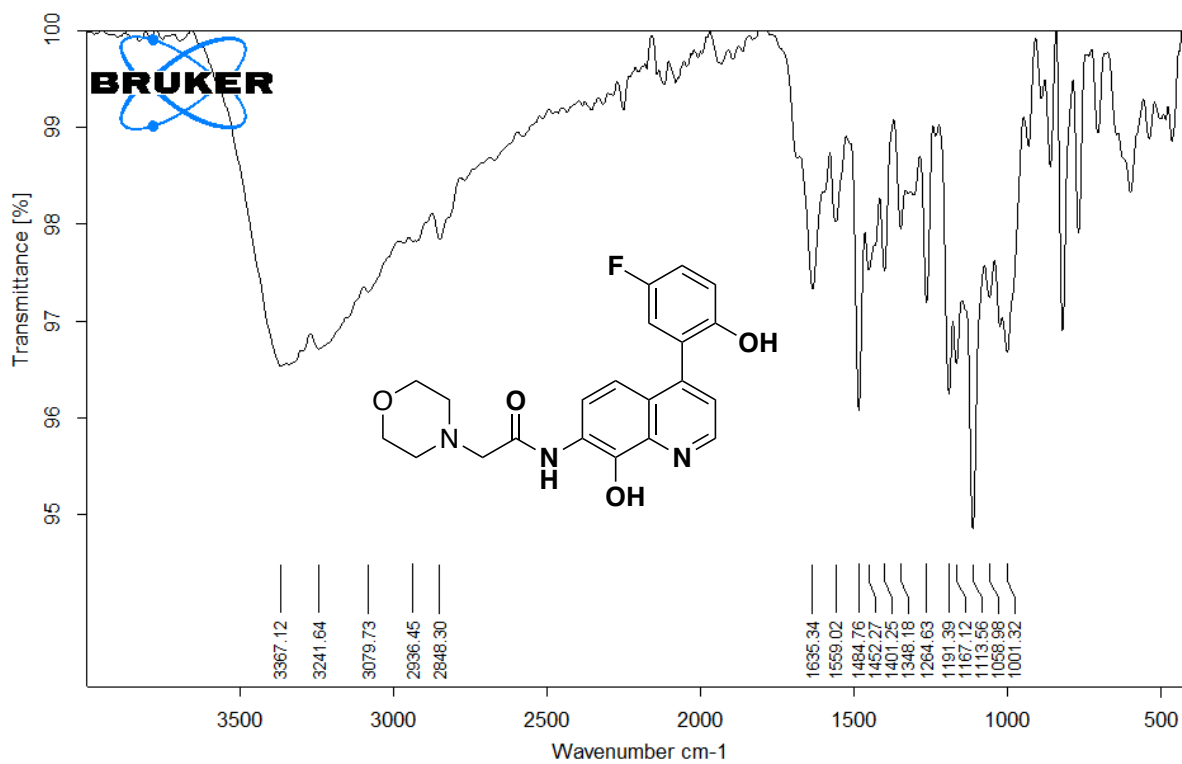
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (41) in DMSO



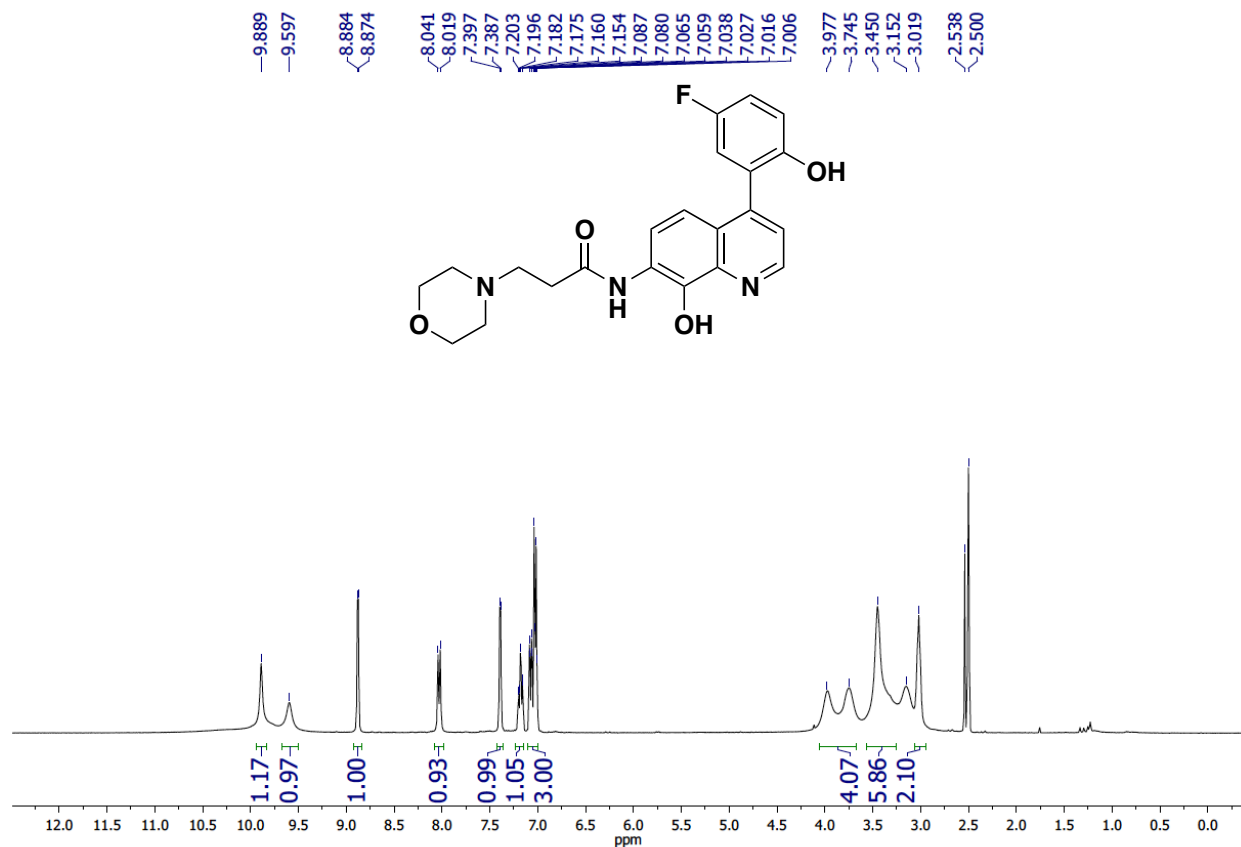
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (41) in DMSO



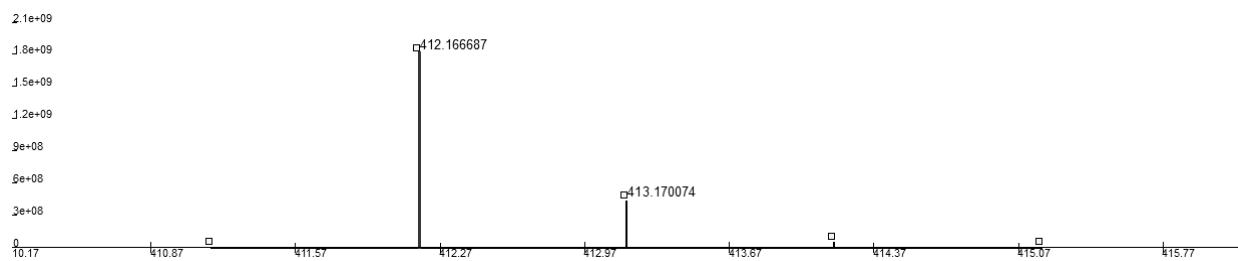
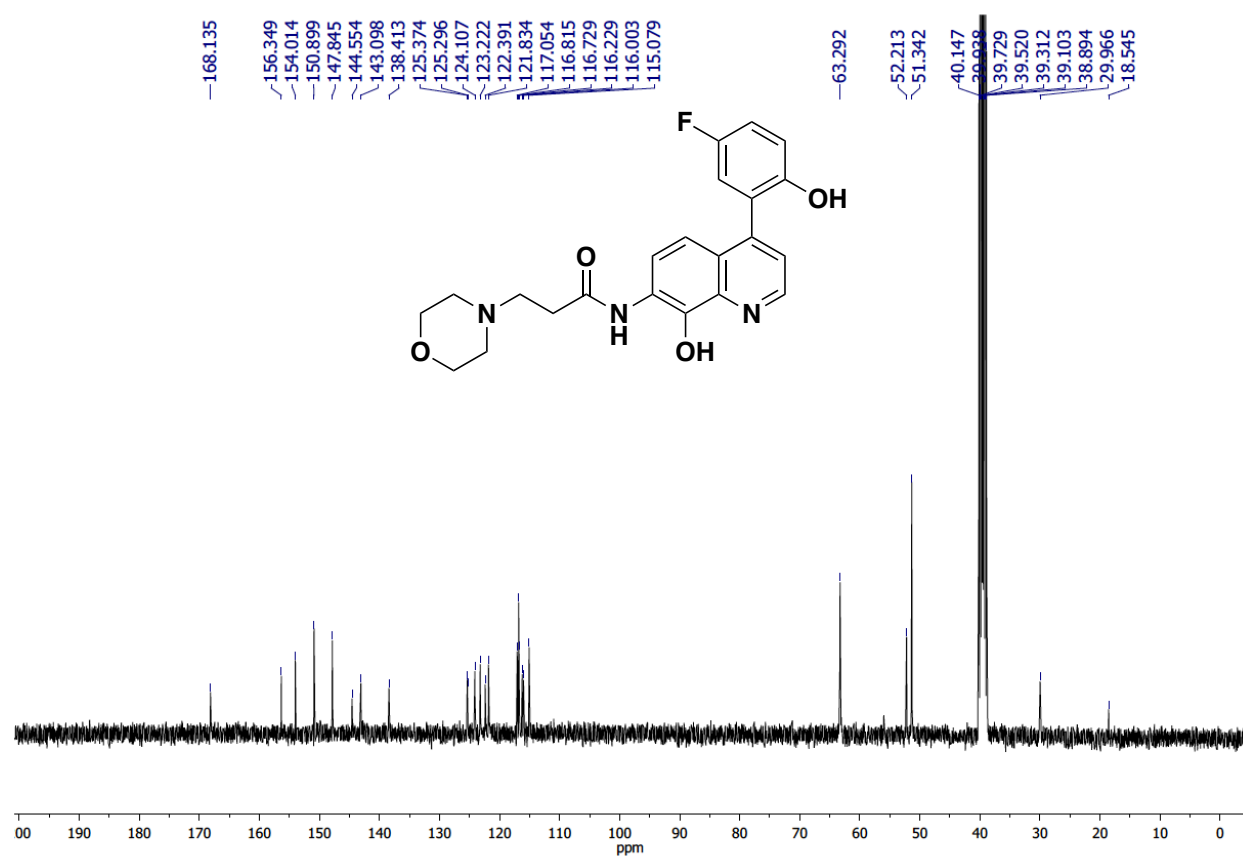
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (41)



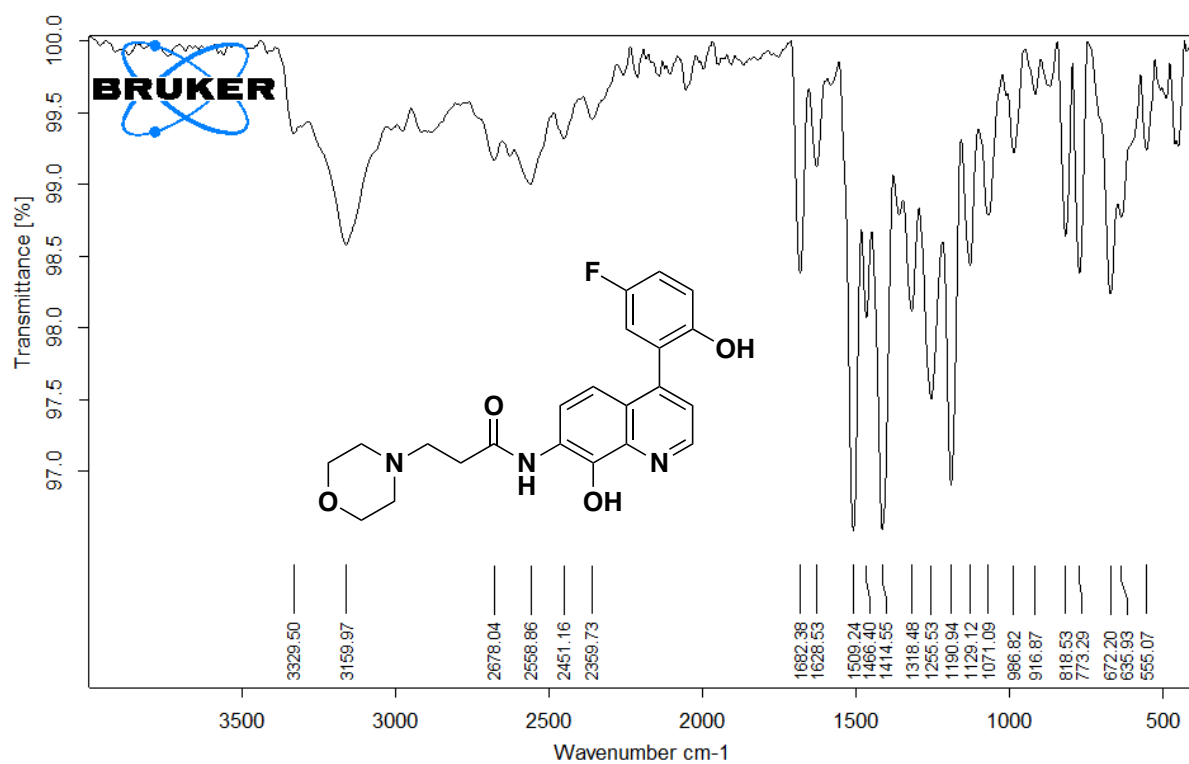
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (42)



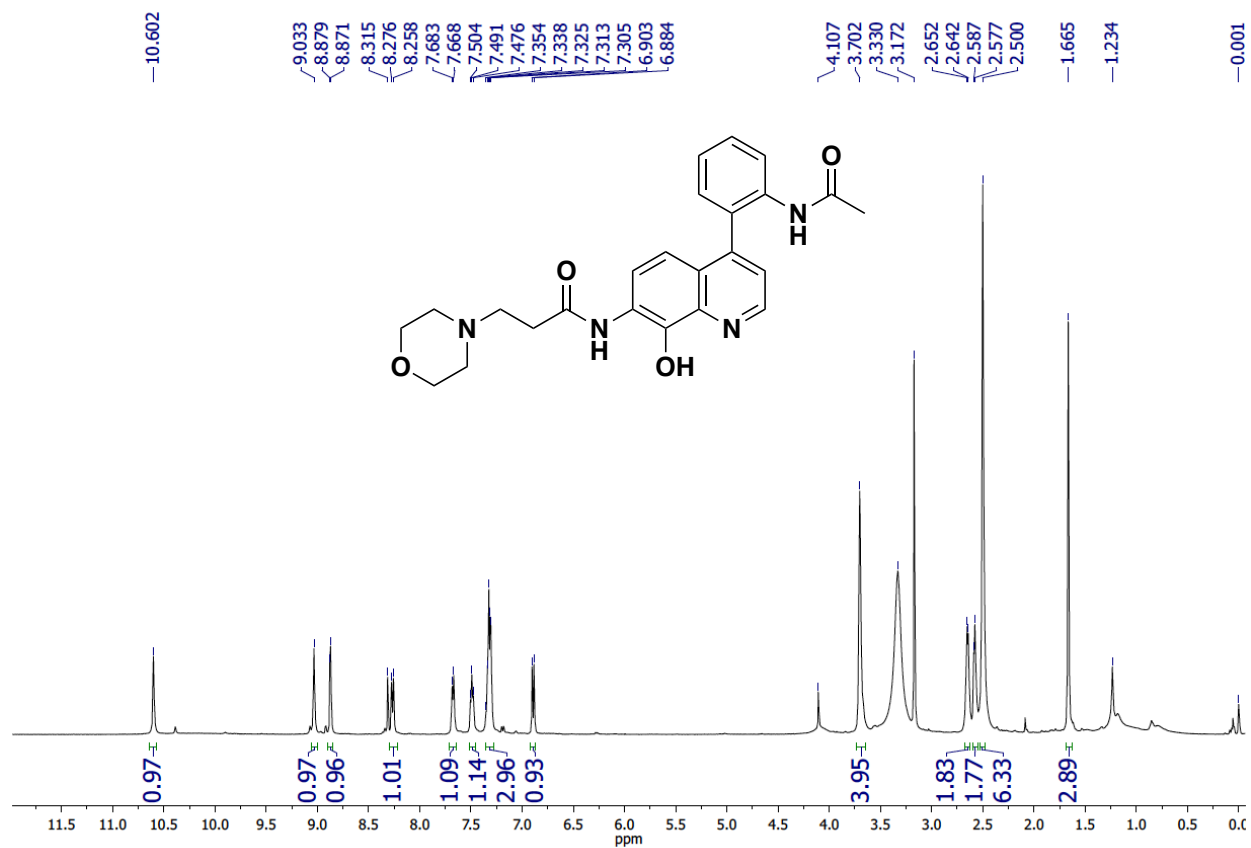
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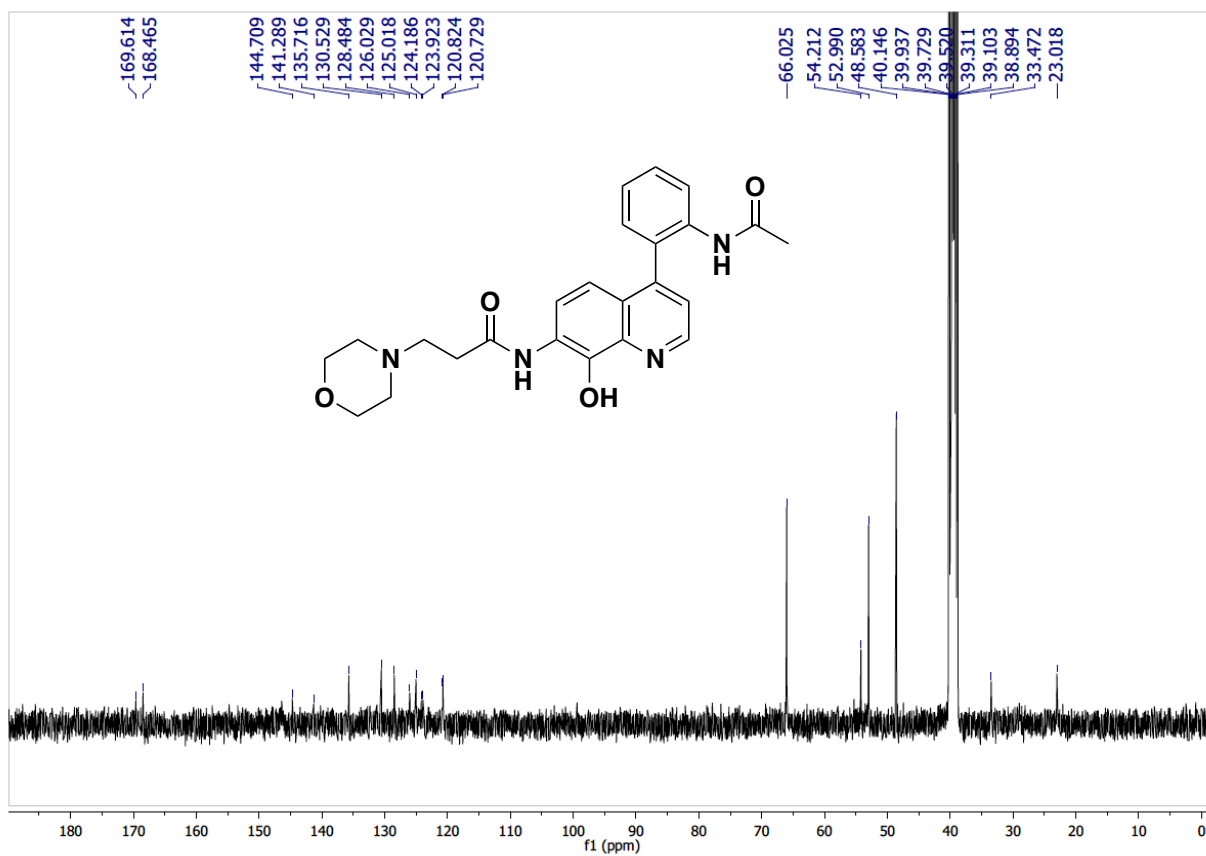
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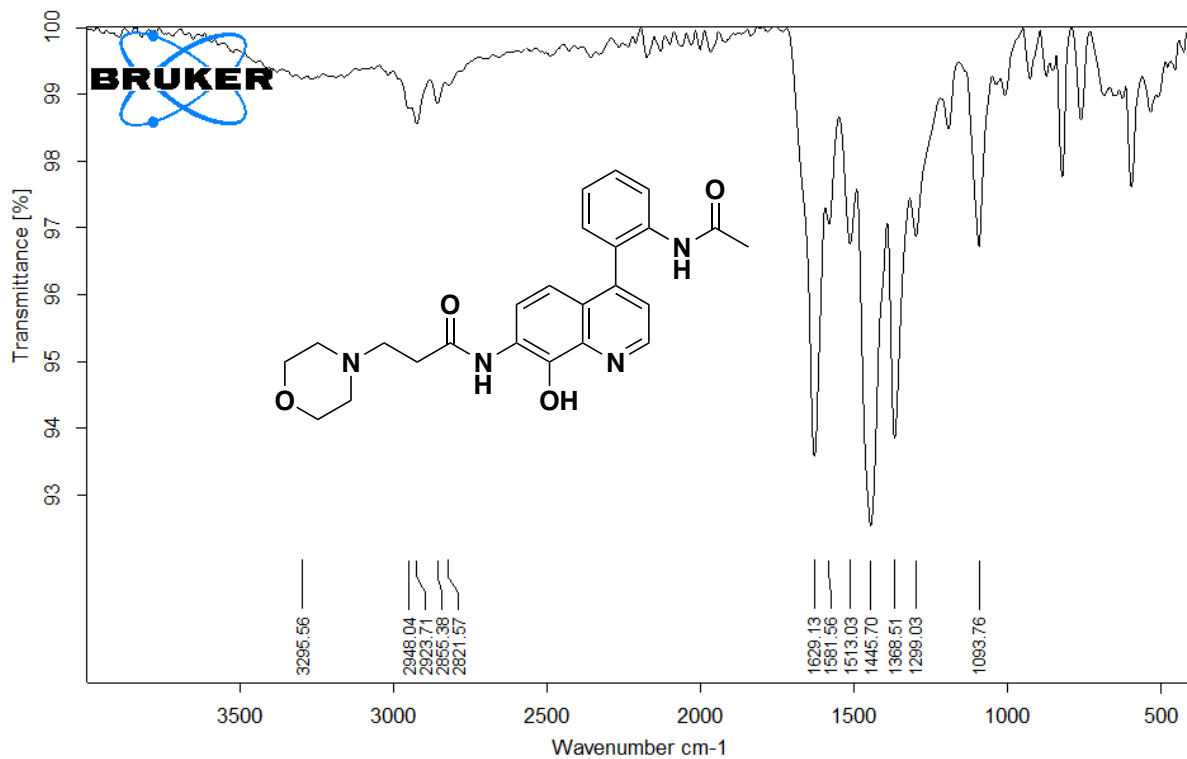
4-(2-Acetamidophenyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (43) in DMSO-d₆



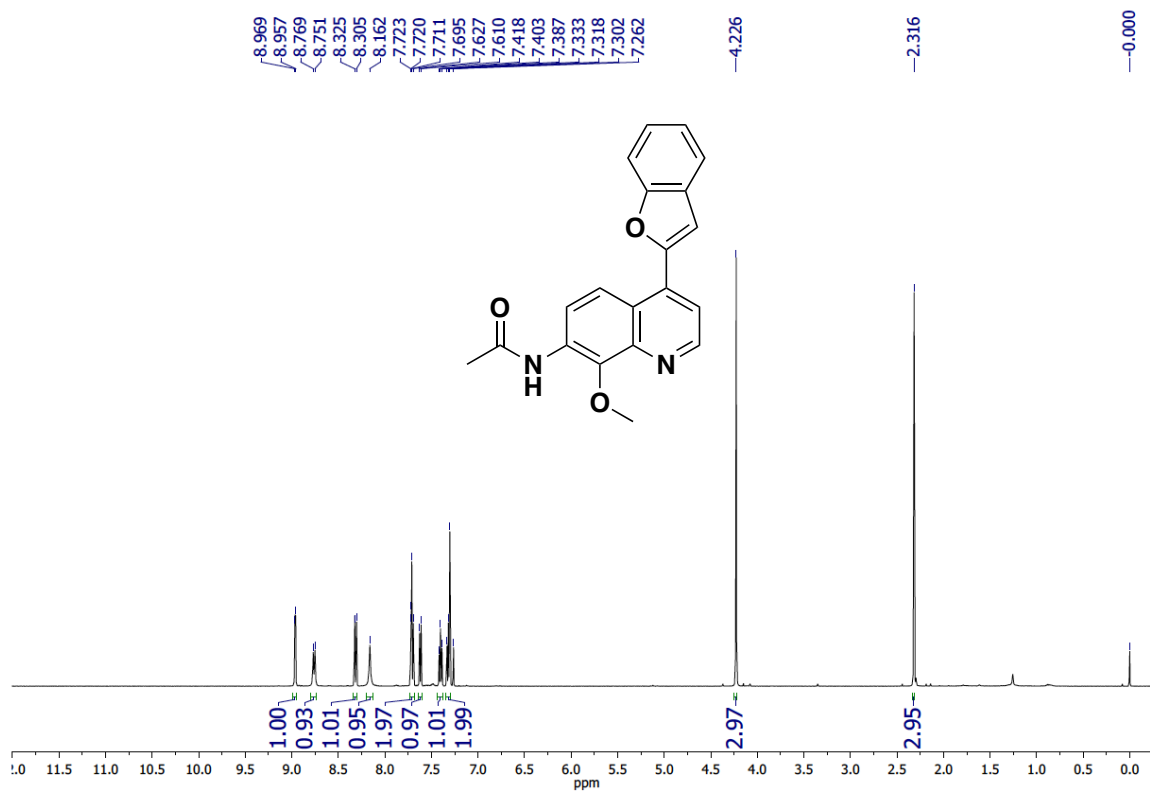
4-(2-Acetamidophenyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (43) in DMSO-d₆



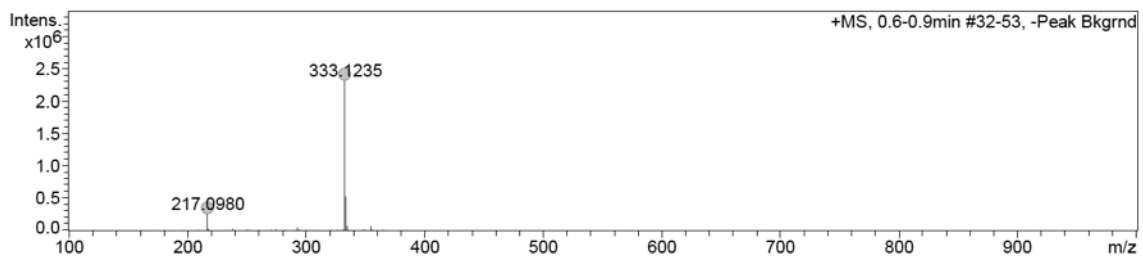
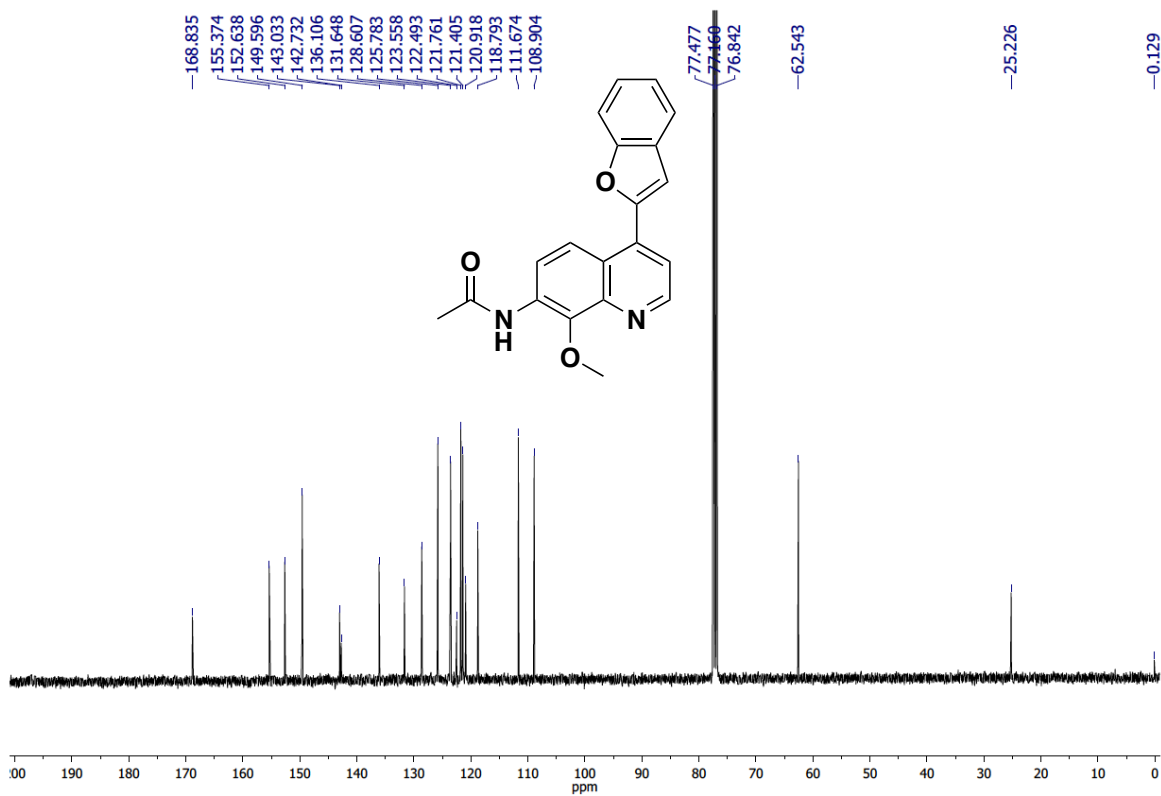
4-(2-Acetamidophenyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (43)



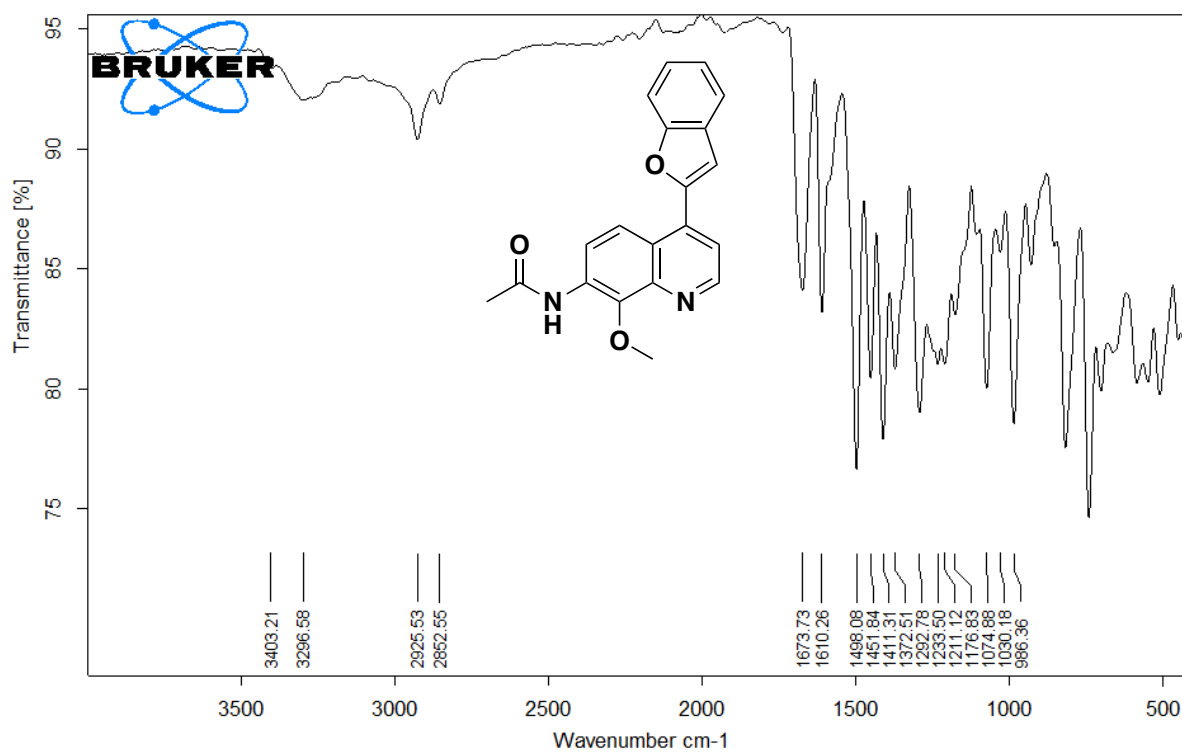
7-Acetamido-4-(2-benzofuranyl)-8-methoxyquinoline (45) in CDCl₃



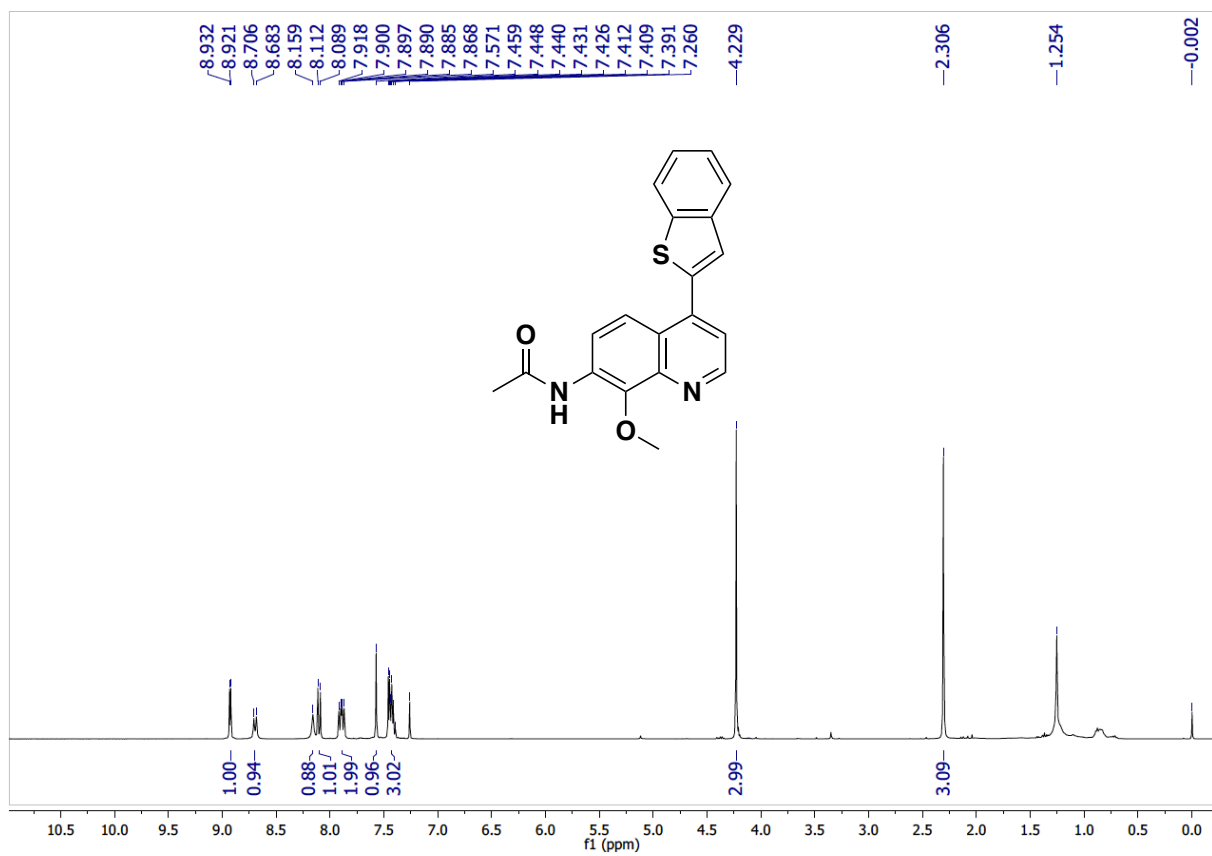
7-Acetamido-4-(2-benzofuranyl)-8-methoxyquinoline (45) in CDCl₃



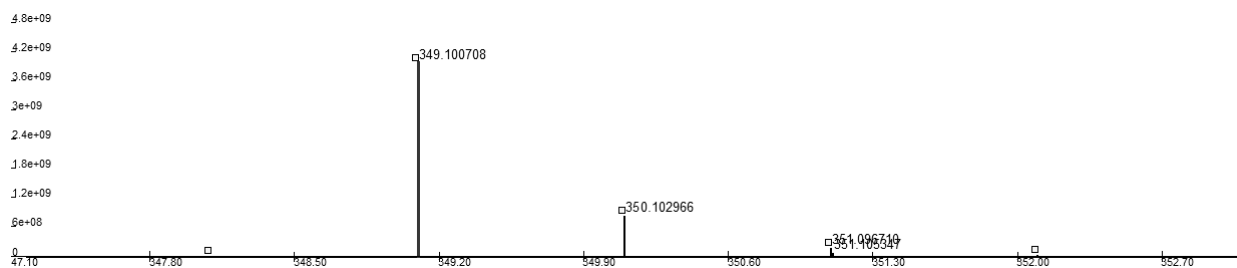
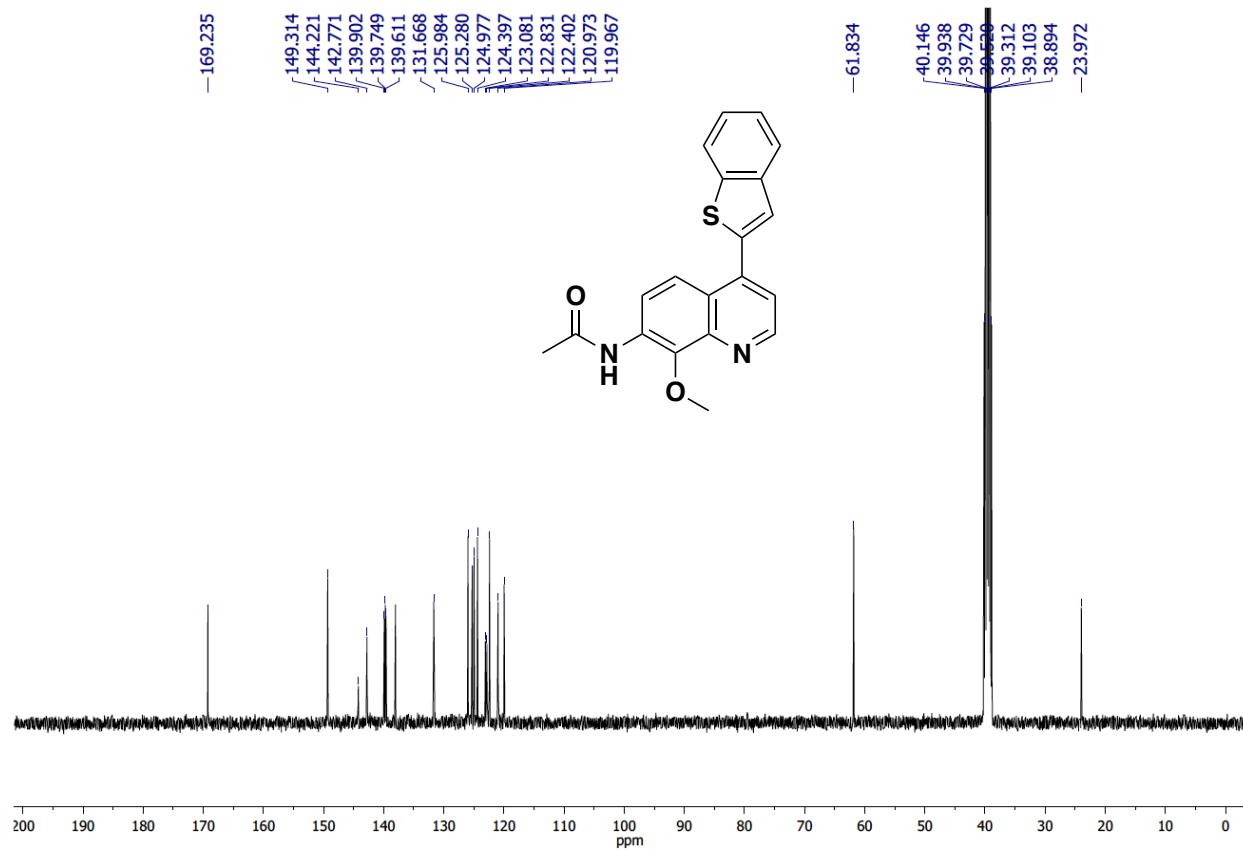
7-Acetamido-4-(2-benzofuranyl)-8-methoxyquinoline (45)



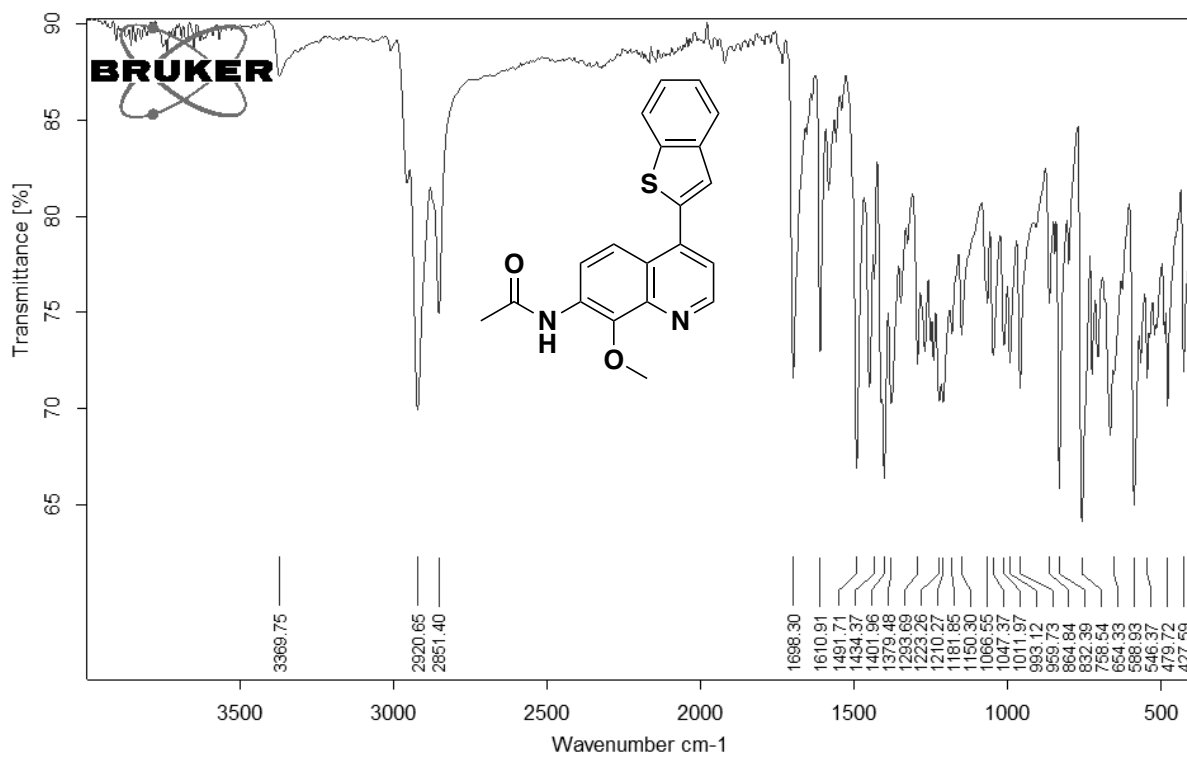
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-methoxyquinoline (45) in CDCl₃



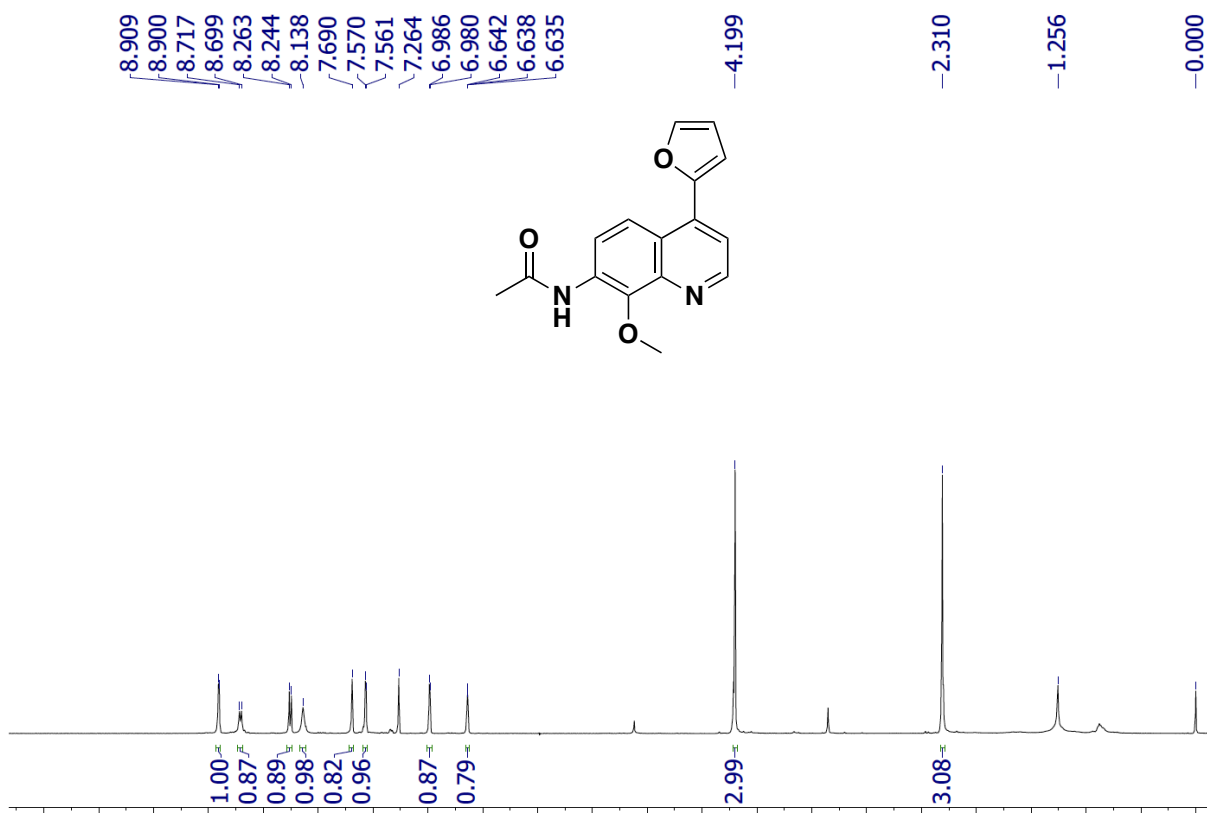
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-methoxyquinoline (45) in DMSO



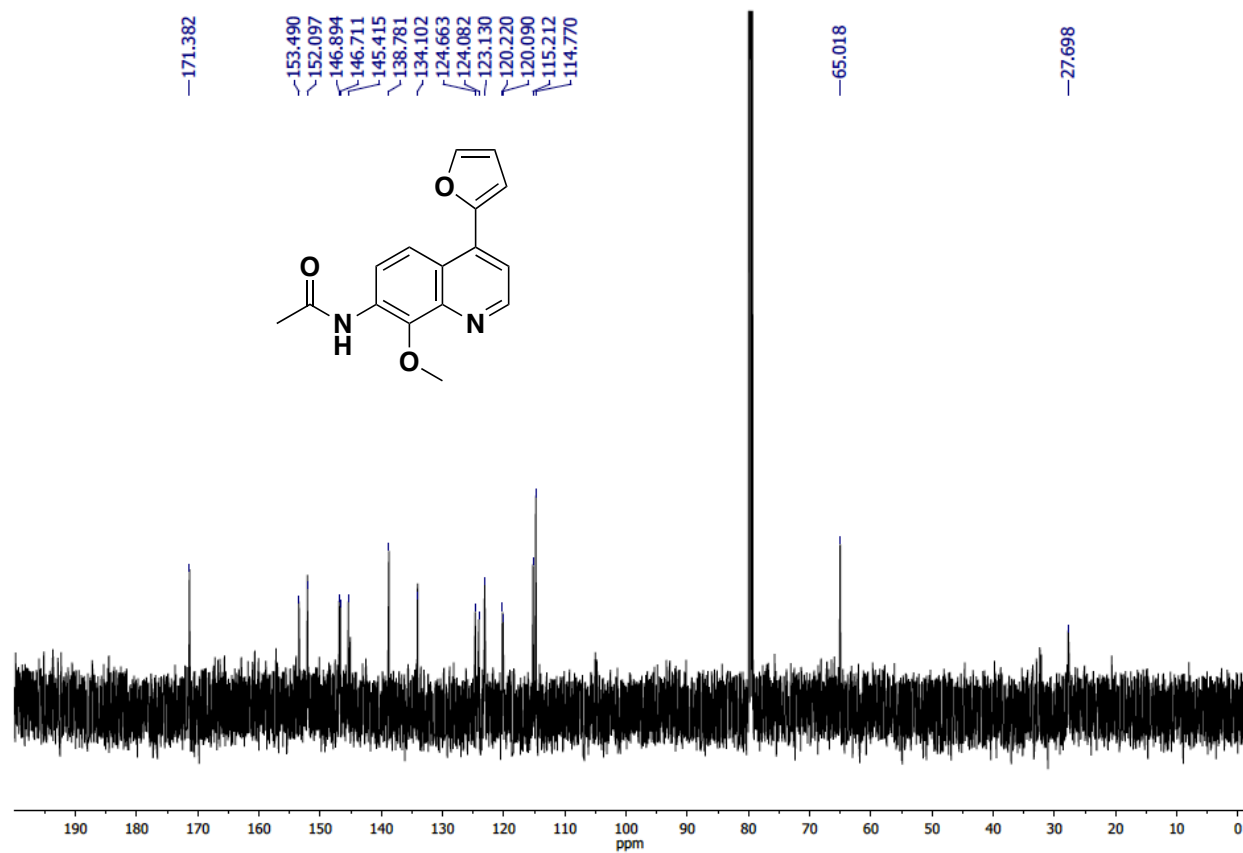
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-methoxyquinoline (45)



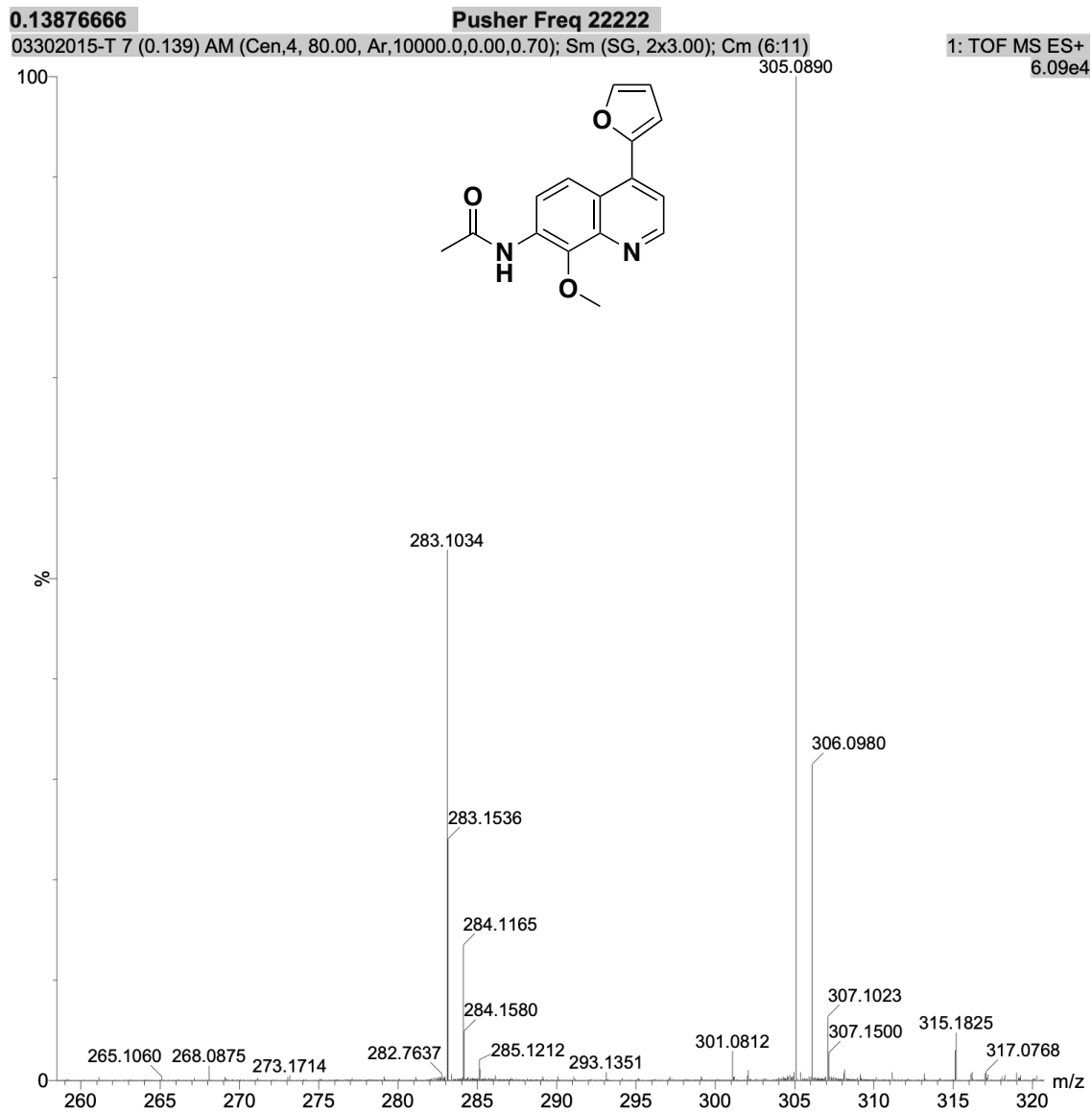
7-Acetamido-4-(2-furanyl)-8-methoxyquinoline (46) in CDCl₃



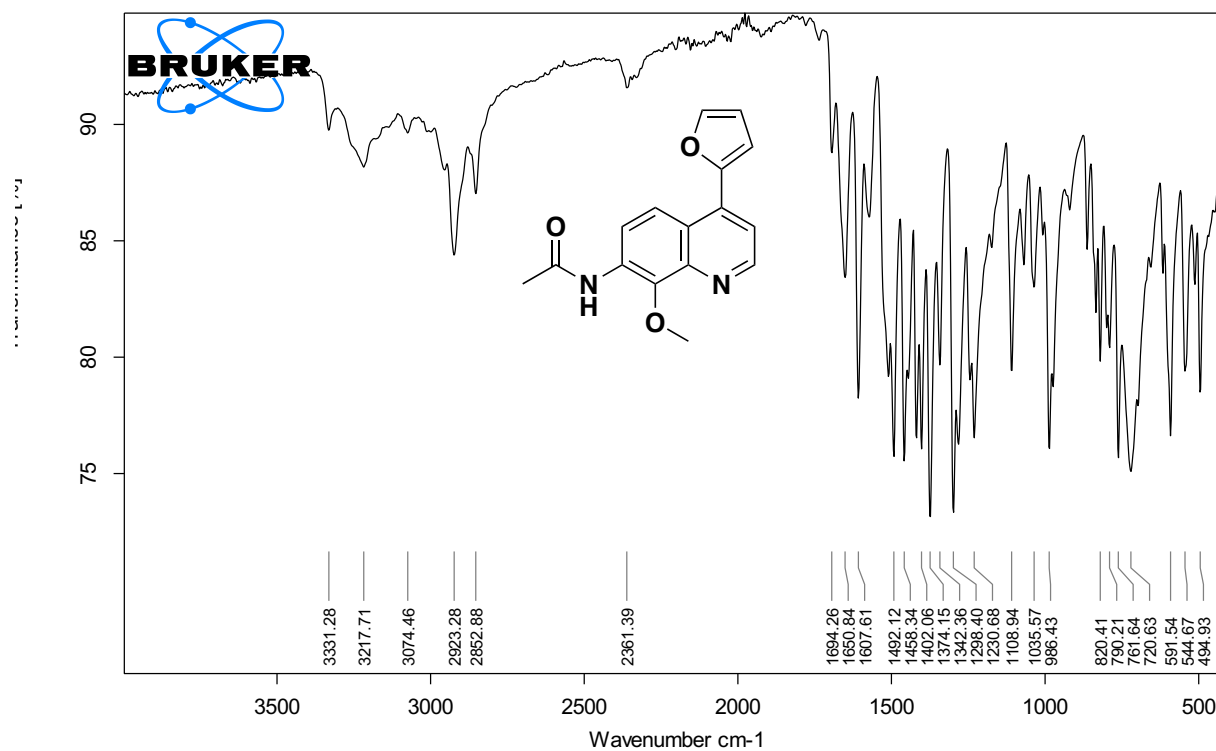
7-Acetamido-4-(2-furanyl)-8-methoxyquinoline (46) in CDCl₃



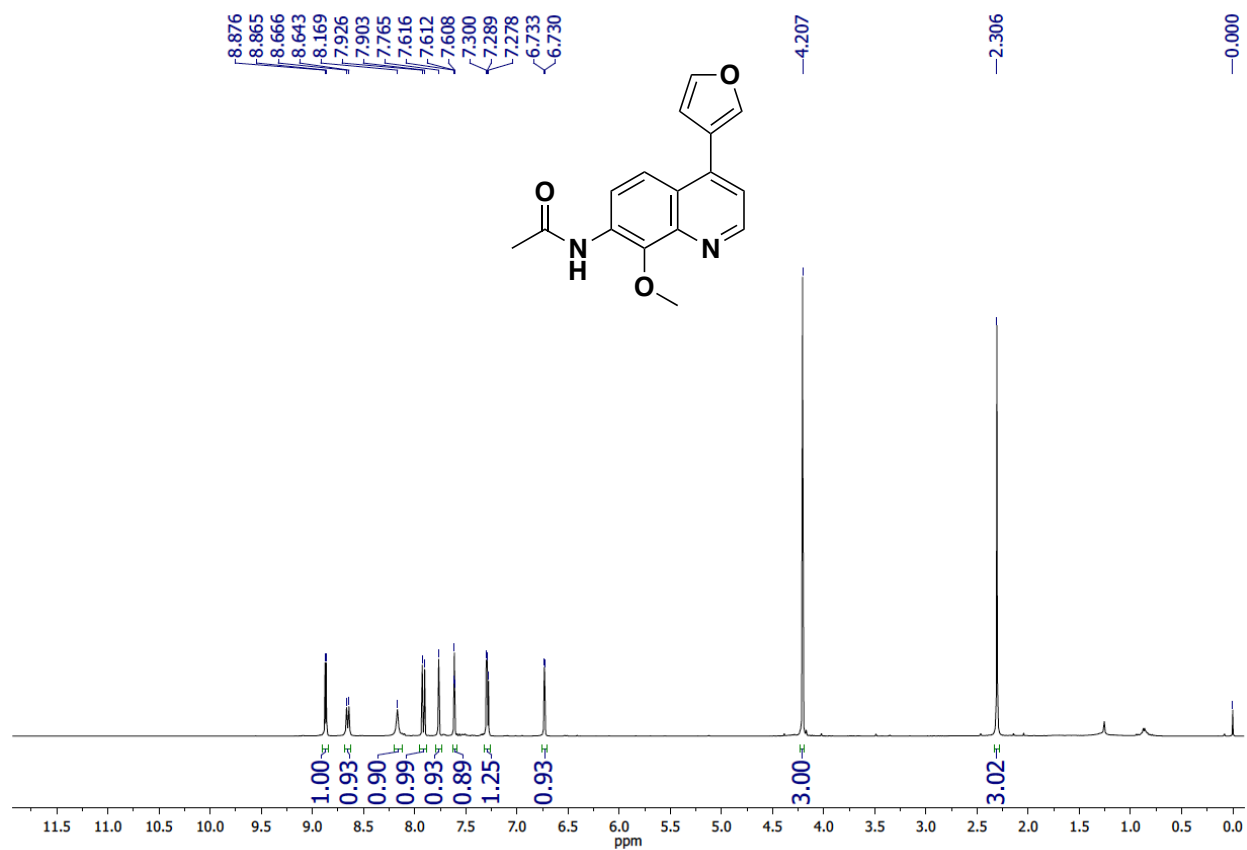
7-Acetamido-4-(2-furanyl)-8-methoxyquinoline (46)



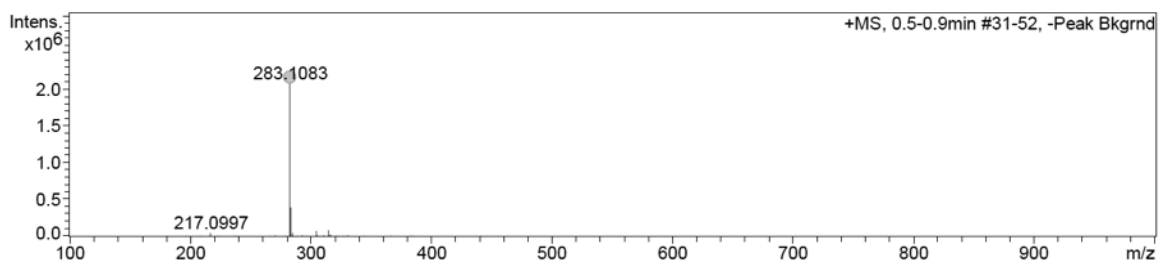
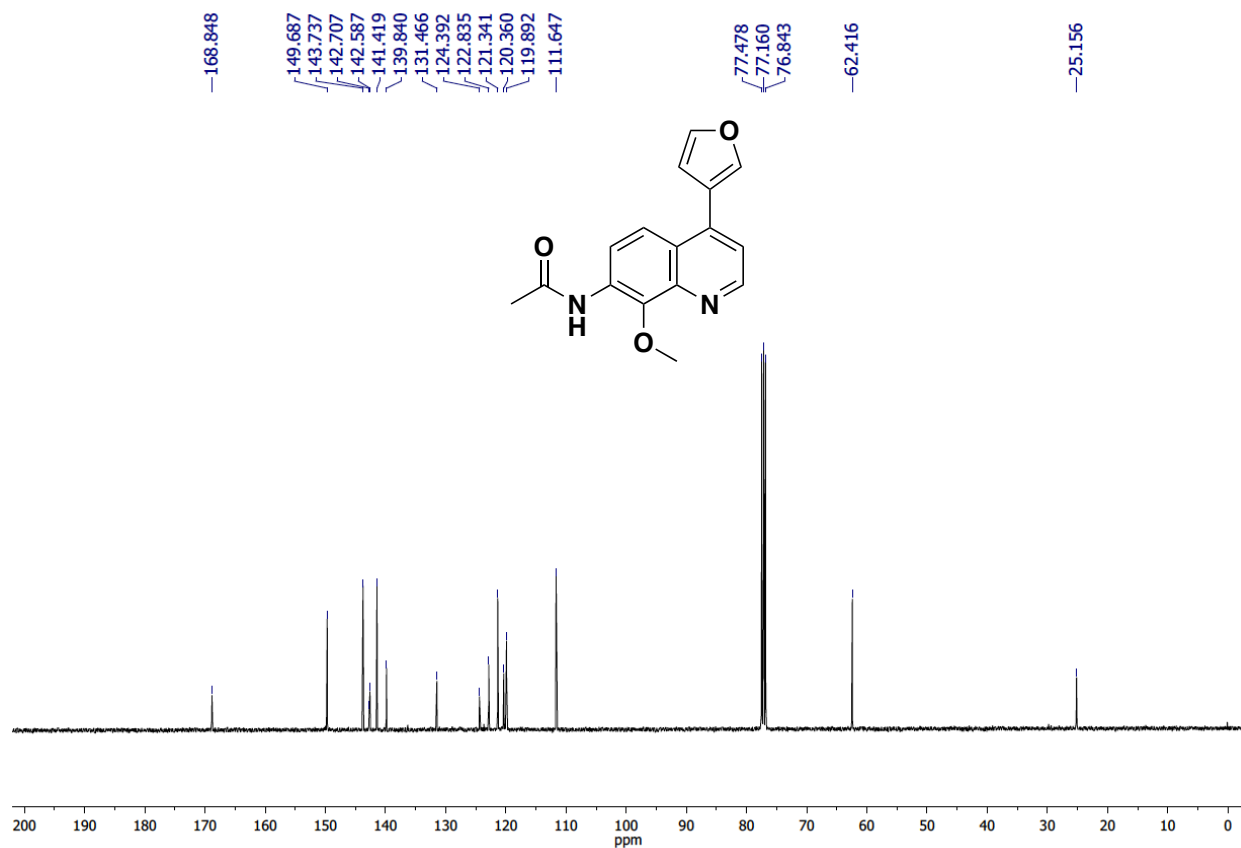
7-Acetamido-4-(2-furanyl)-8-methoxyquinoline (46)



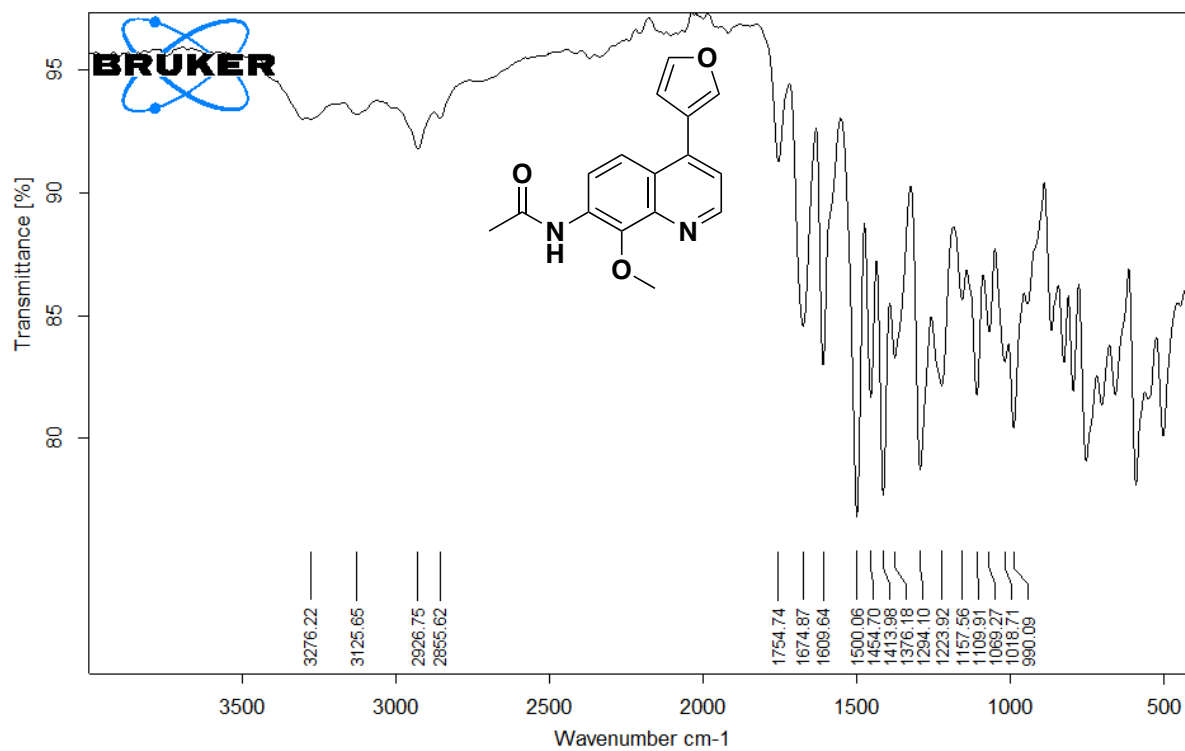
7-Acetamido-4-(3-furanyl)-8-methoxyquinoline (47) in CDCl₃



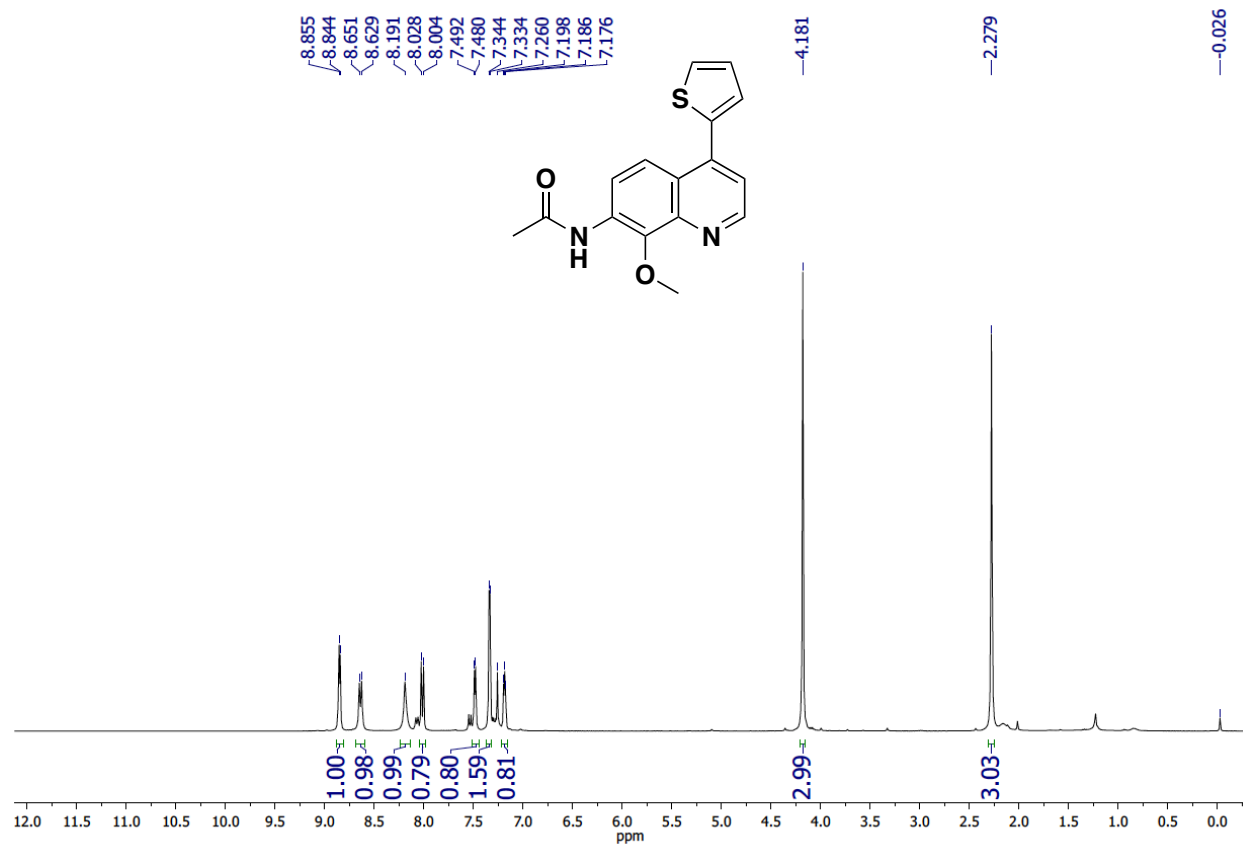
7-Acetamido-4-(3-furanyl)-8-methoxyquinoline (47) in CDCl₃



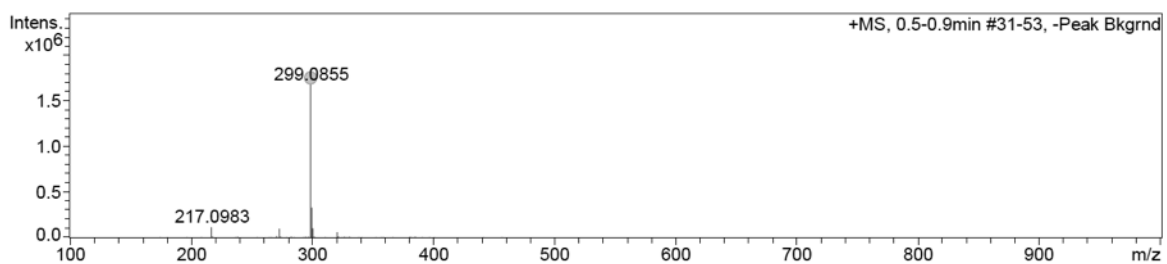
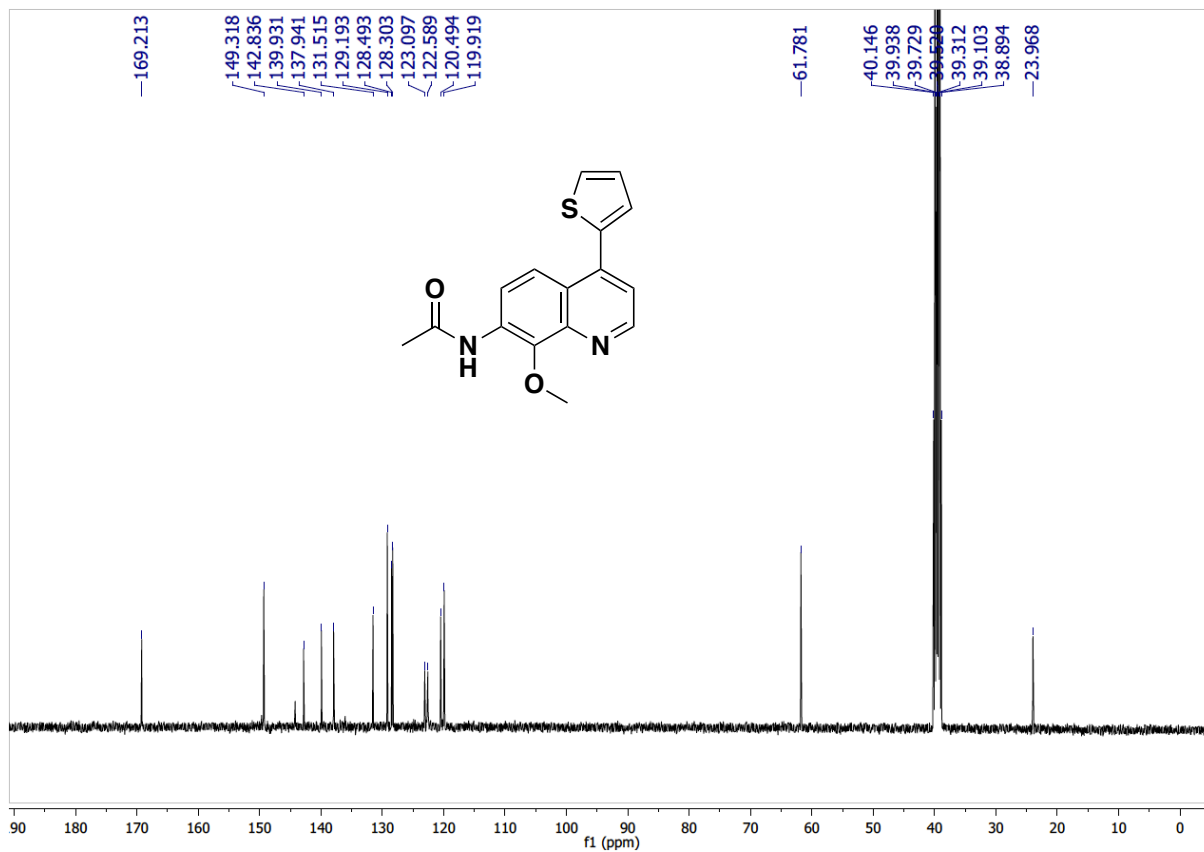
7-Acetamido-4-(3-furanyl)-8-methoxyquinoline (47)



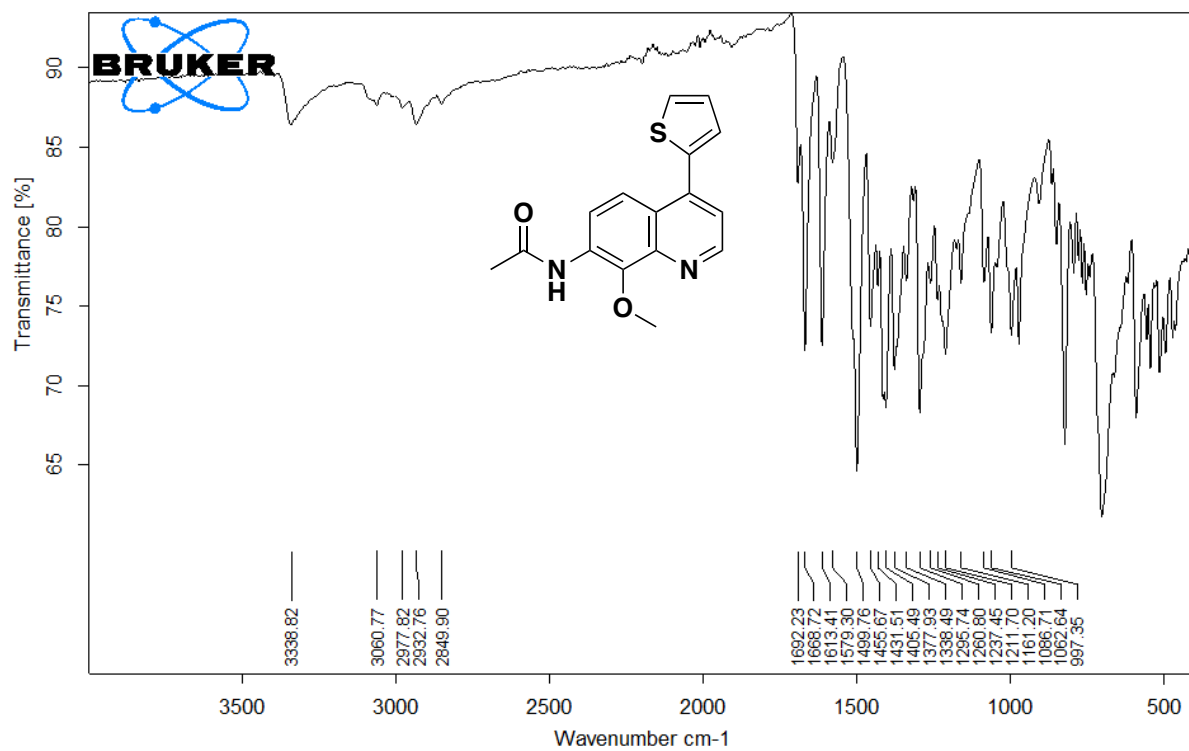
7-Acetamido-4-(thiophen-2-yl)-8-methoxyquinoline (48) in CDCl₃



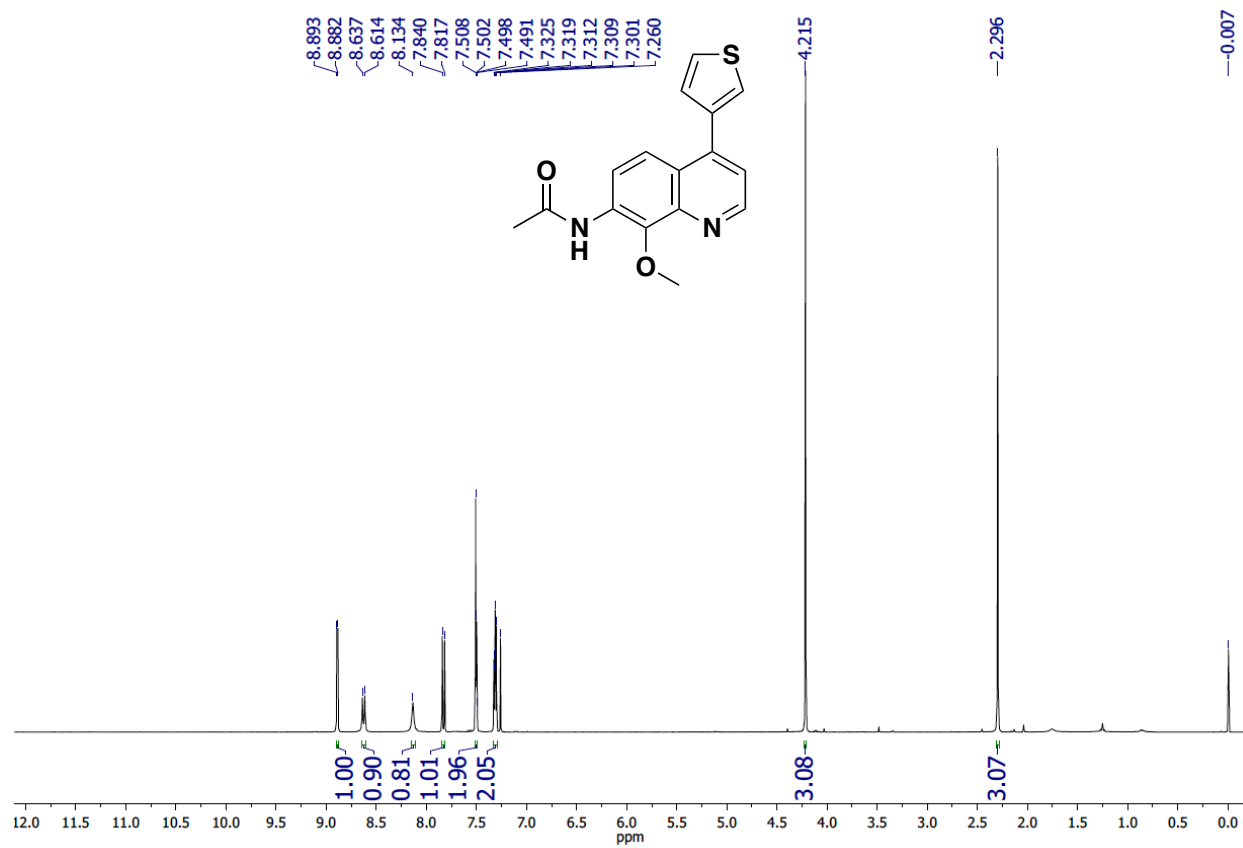
7-Acetamido-4-(thiophen-2-yl)-8-methoxyquinoline (48) in DMSO



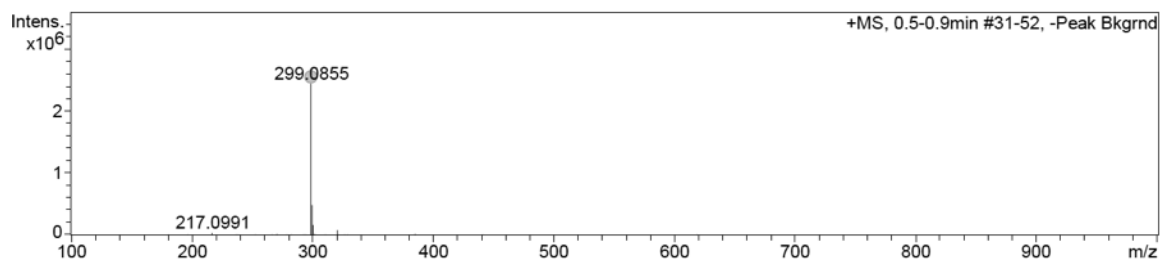
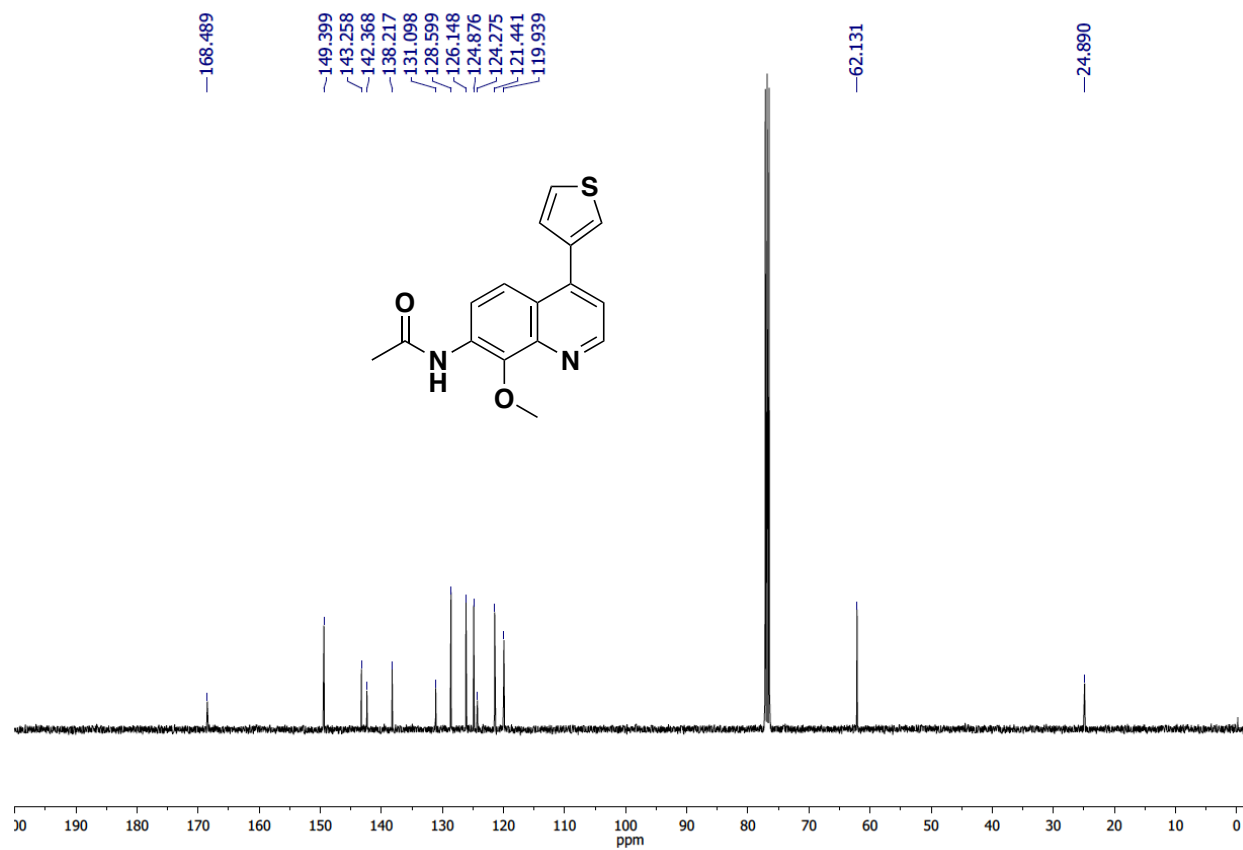
7-Acetamido-4-(thiophen-2-yl)-8-methoxyquinoline



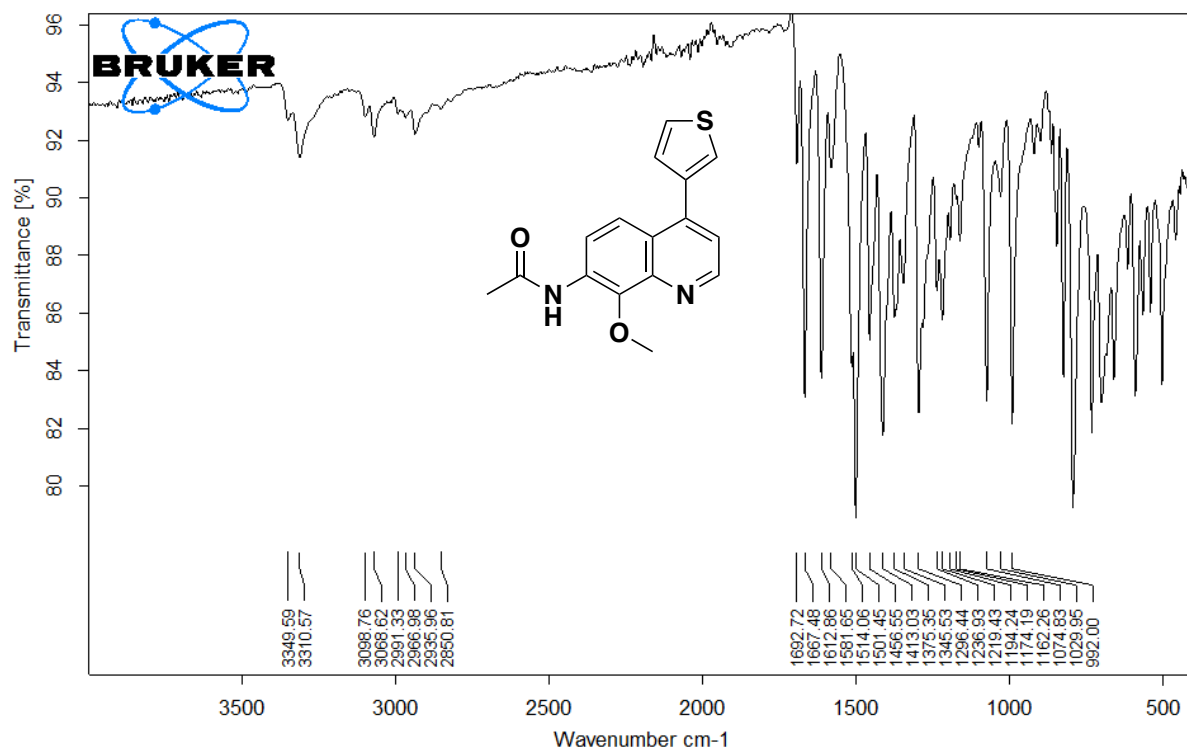
7-Acetamido-4-(thiophen-3-yl)-8-methoxyquinoline (49) in CDCl₃



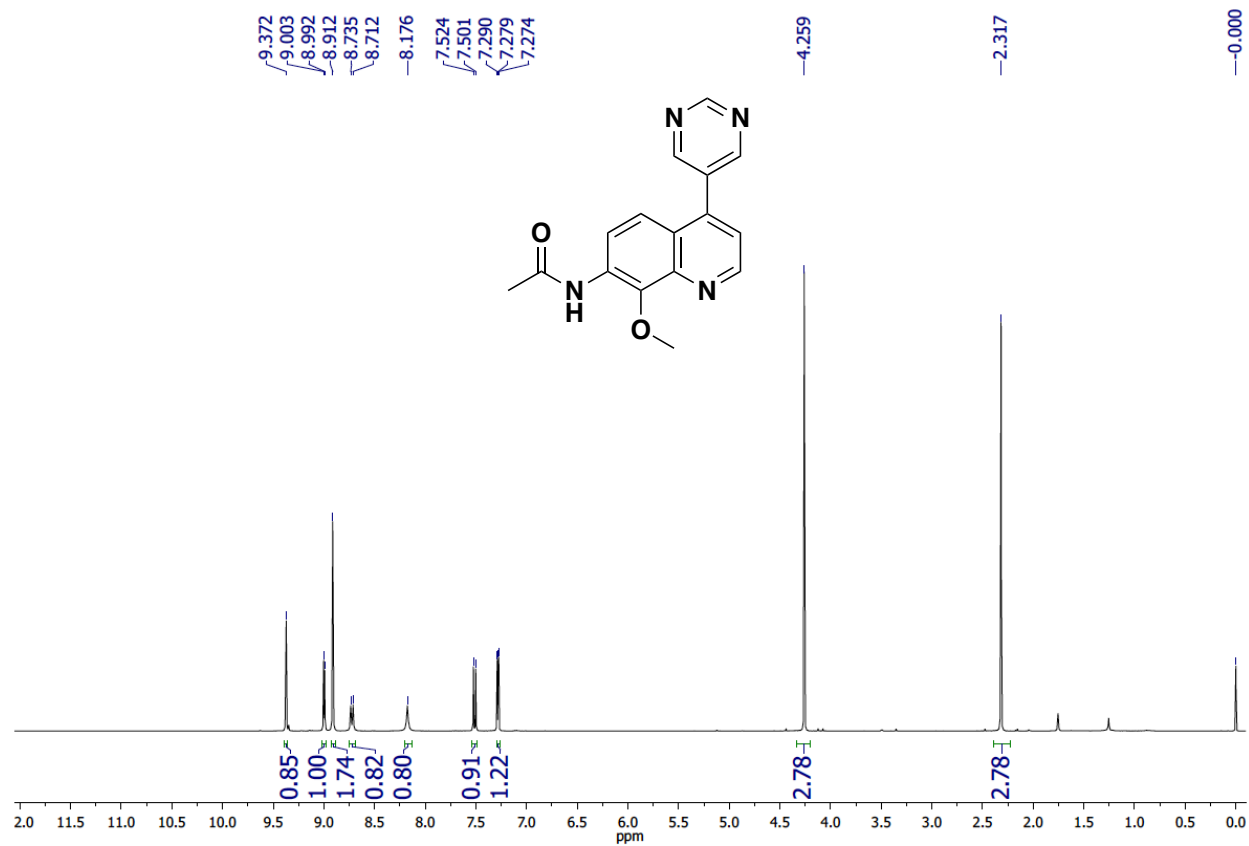
7-Acetamido-4-(thiophen-3-yl)-8-methoxyquinoline (49) in CDCl₃



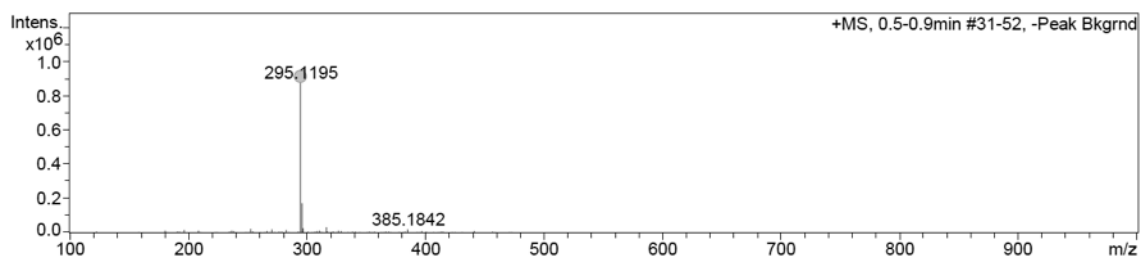
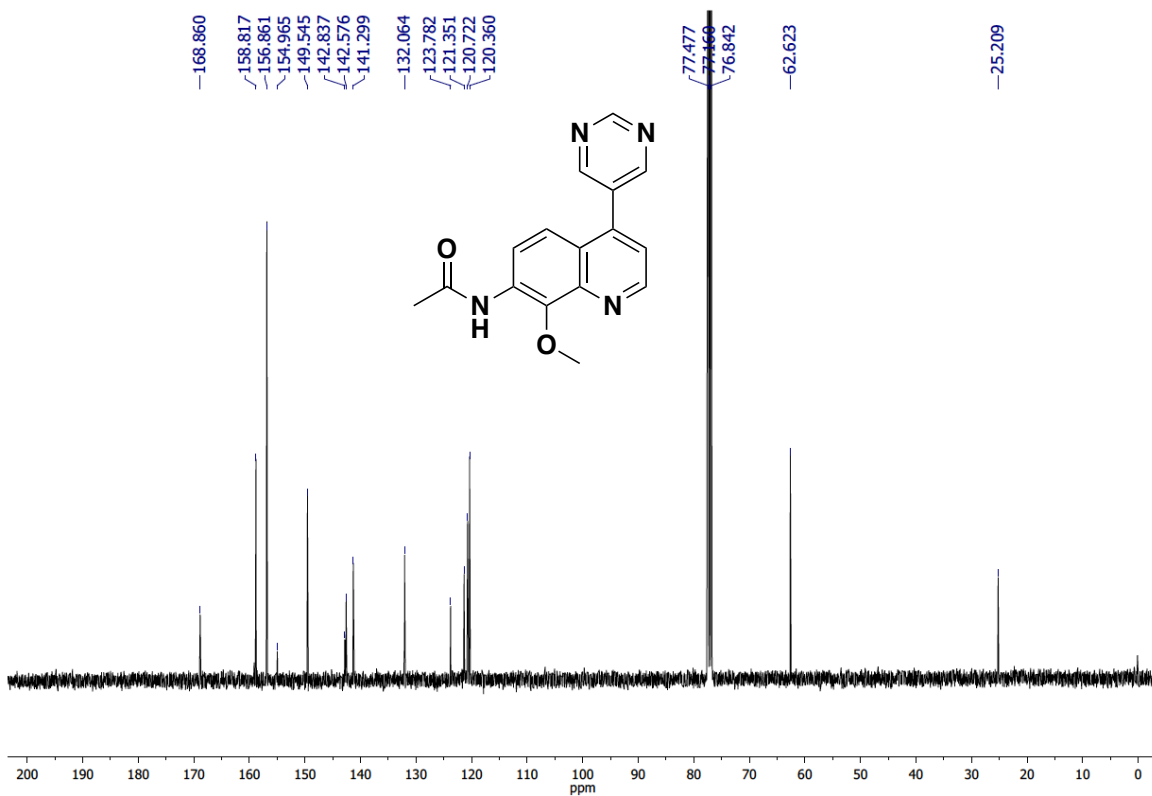
7-Acetamido-4-(thiophen-3-yl)-8-methoxyquinoline



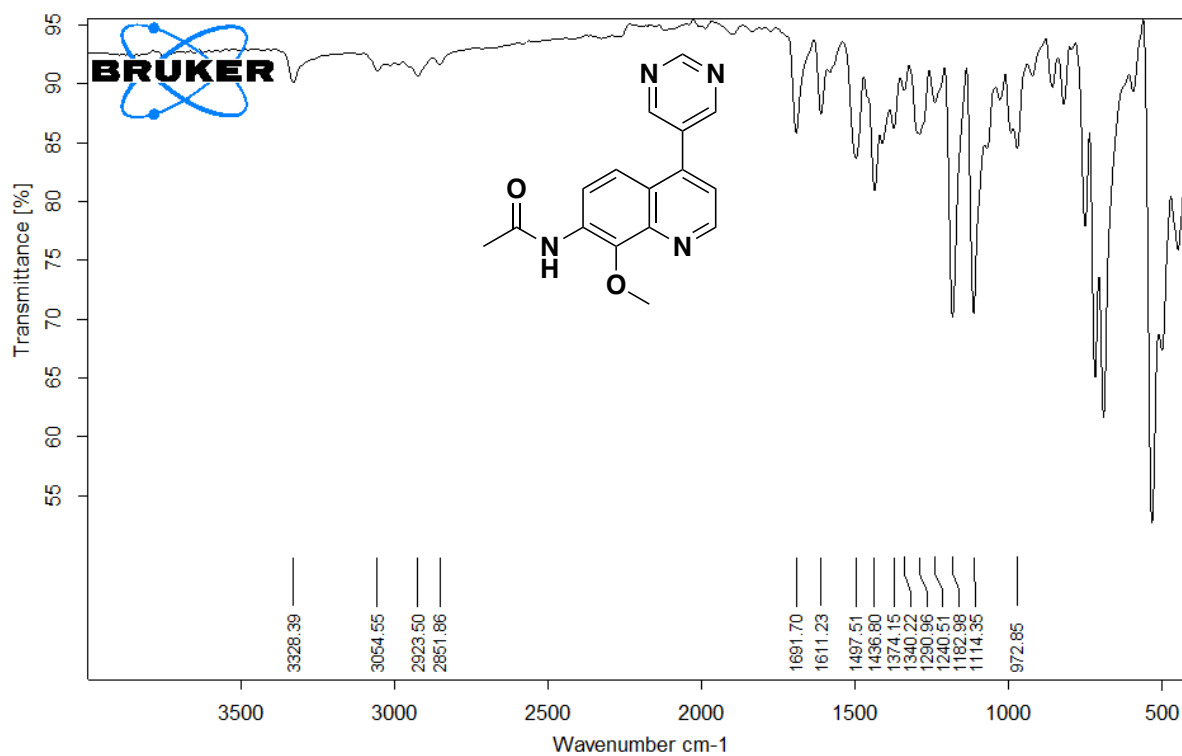
7-Acetamido-4-(5-pyrimidinyl)-8-methoxyquinoline (50) in CDCl₃



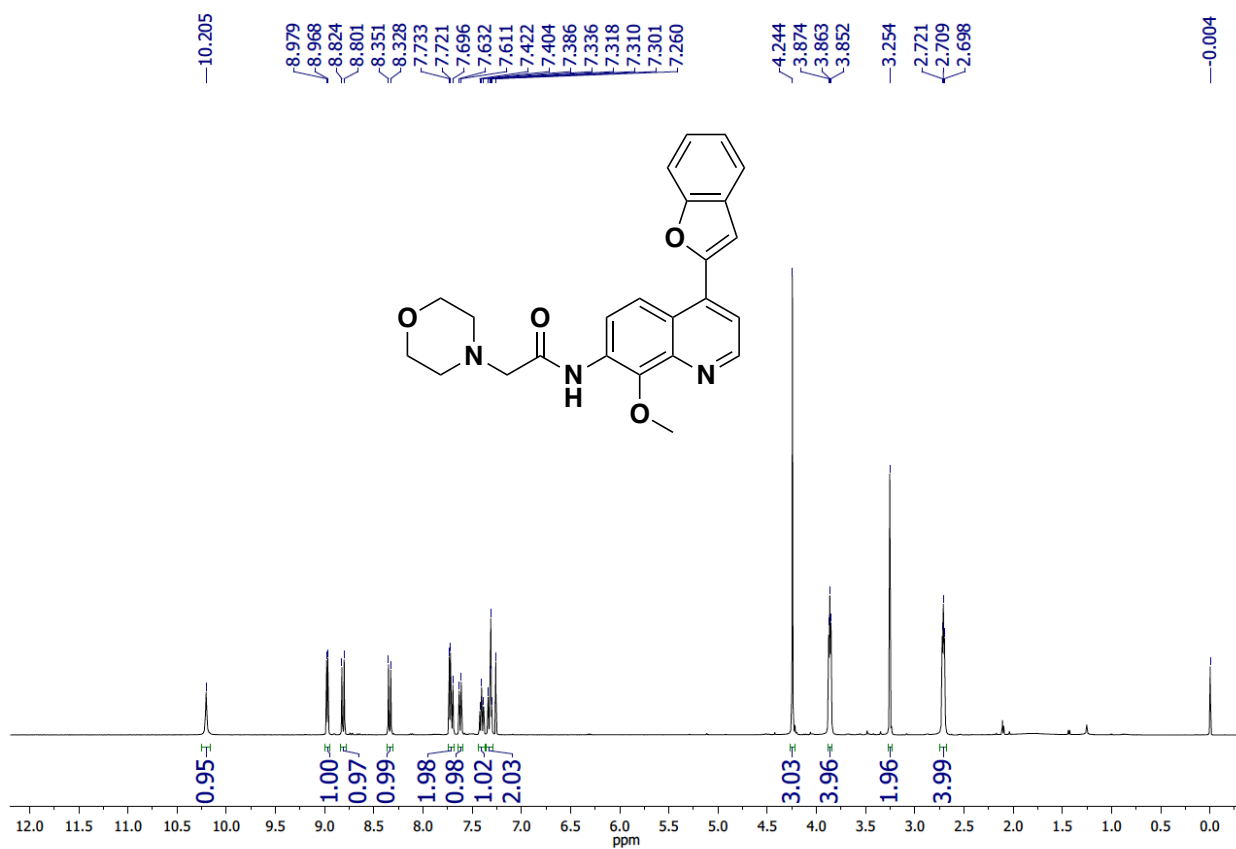
7-Acetamido-4-(5-pyrimidinyl)-8-methoxyquinoline (50) in CDCl₃



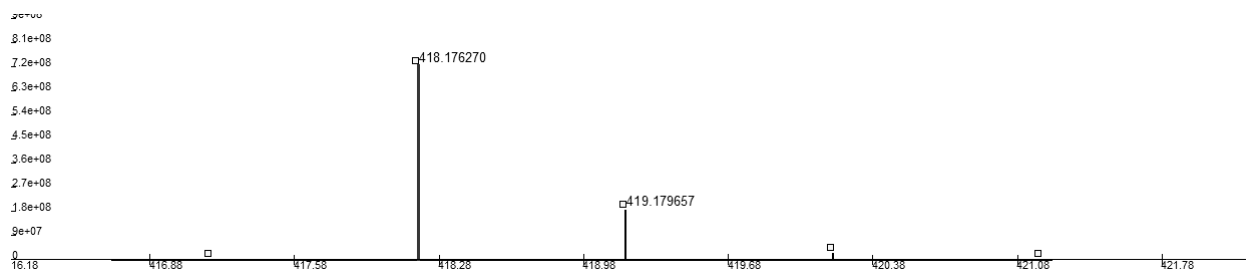
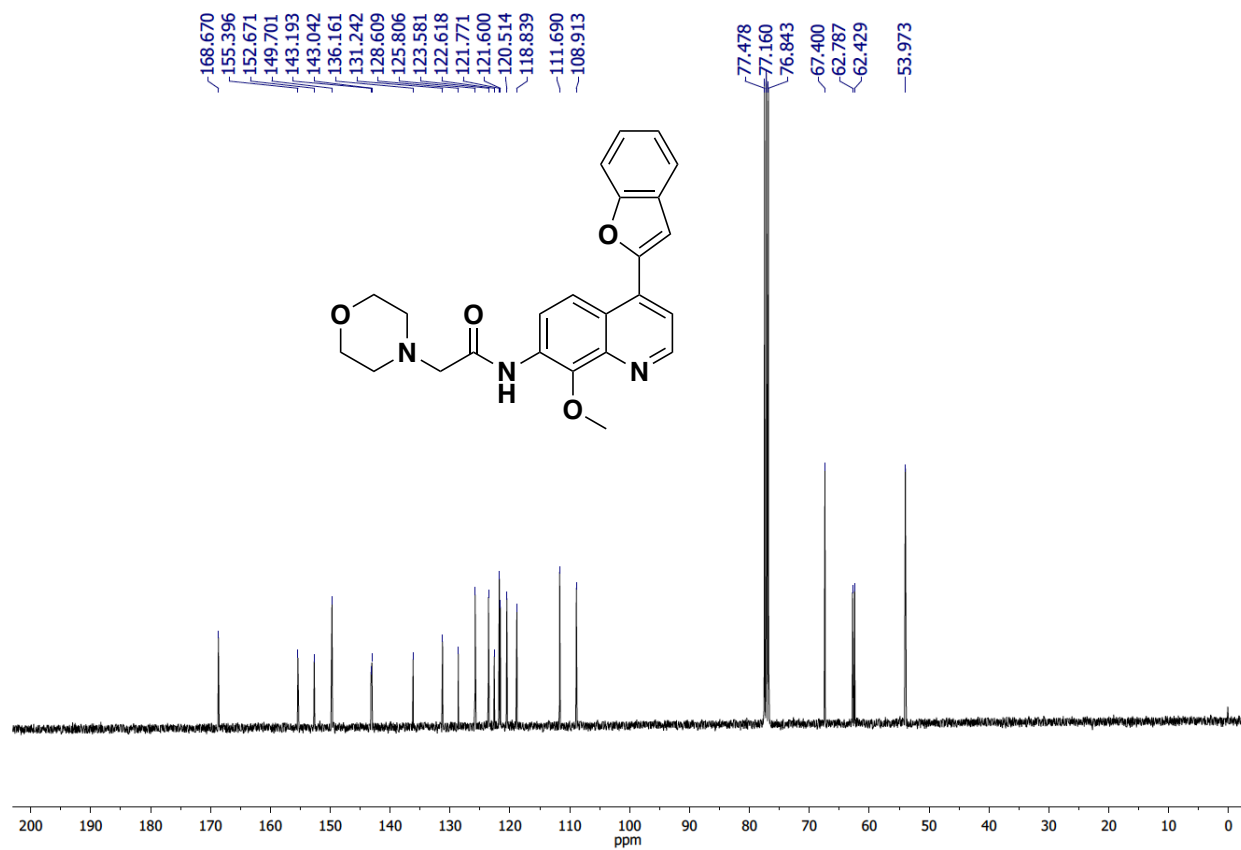
7-Acetamido-4-(5-pyrimidinyl)-8-methoxyquinoline (50)



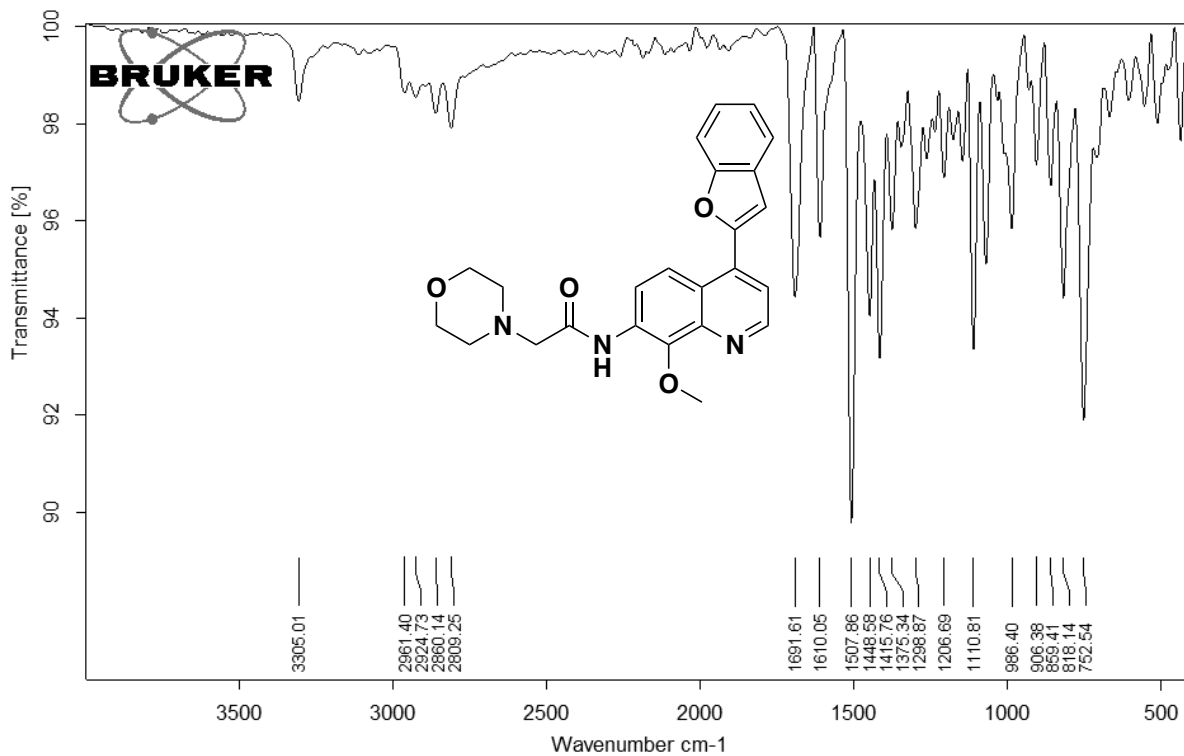
4-(2-benzofuranyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (51) in CDCl₃



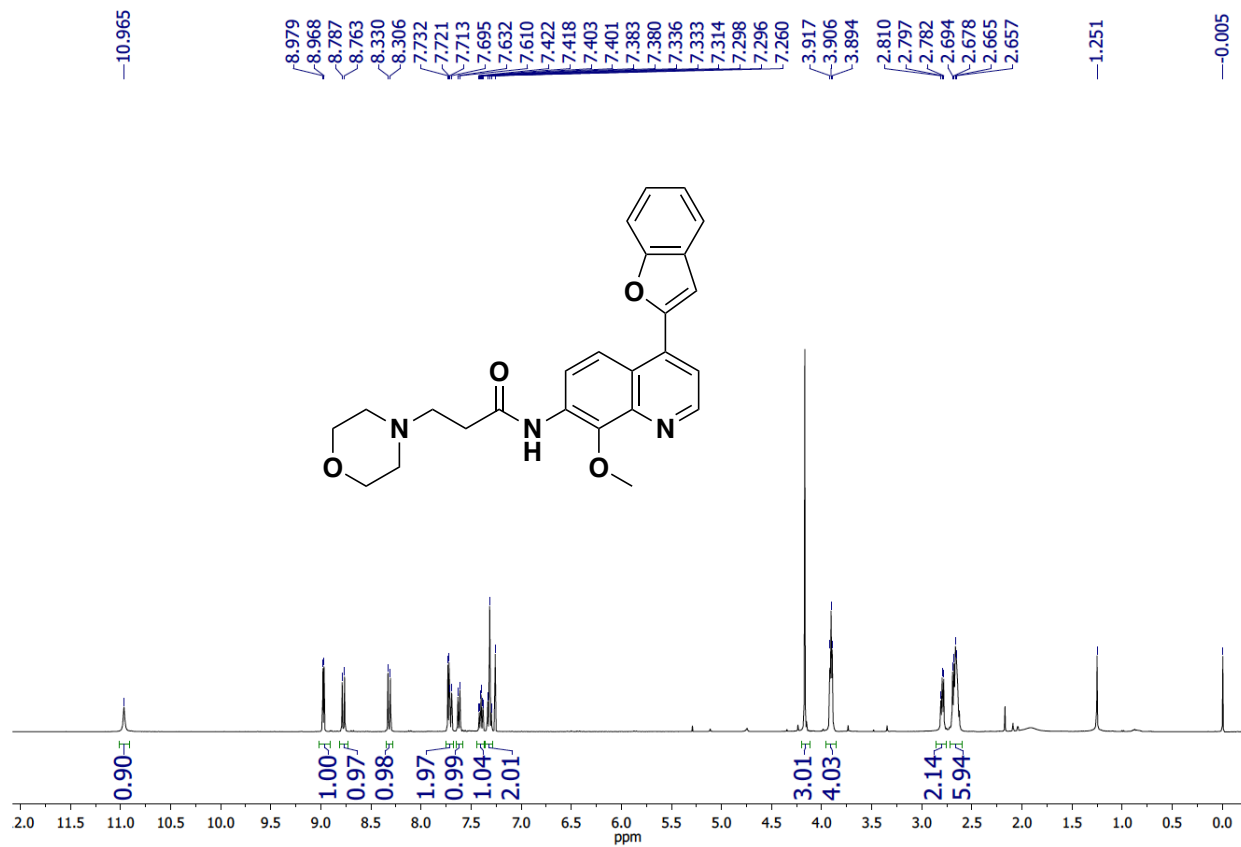
4-(2-benzofuranyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (51) in CDCl₃



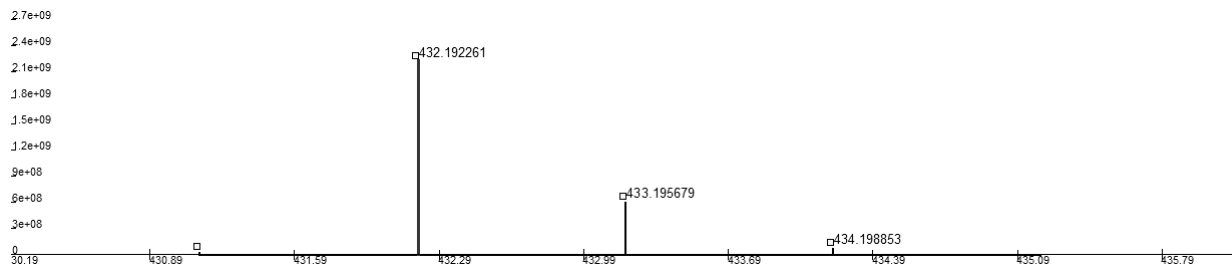
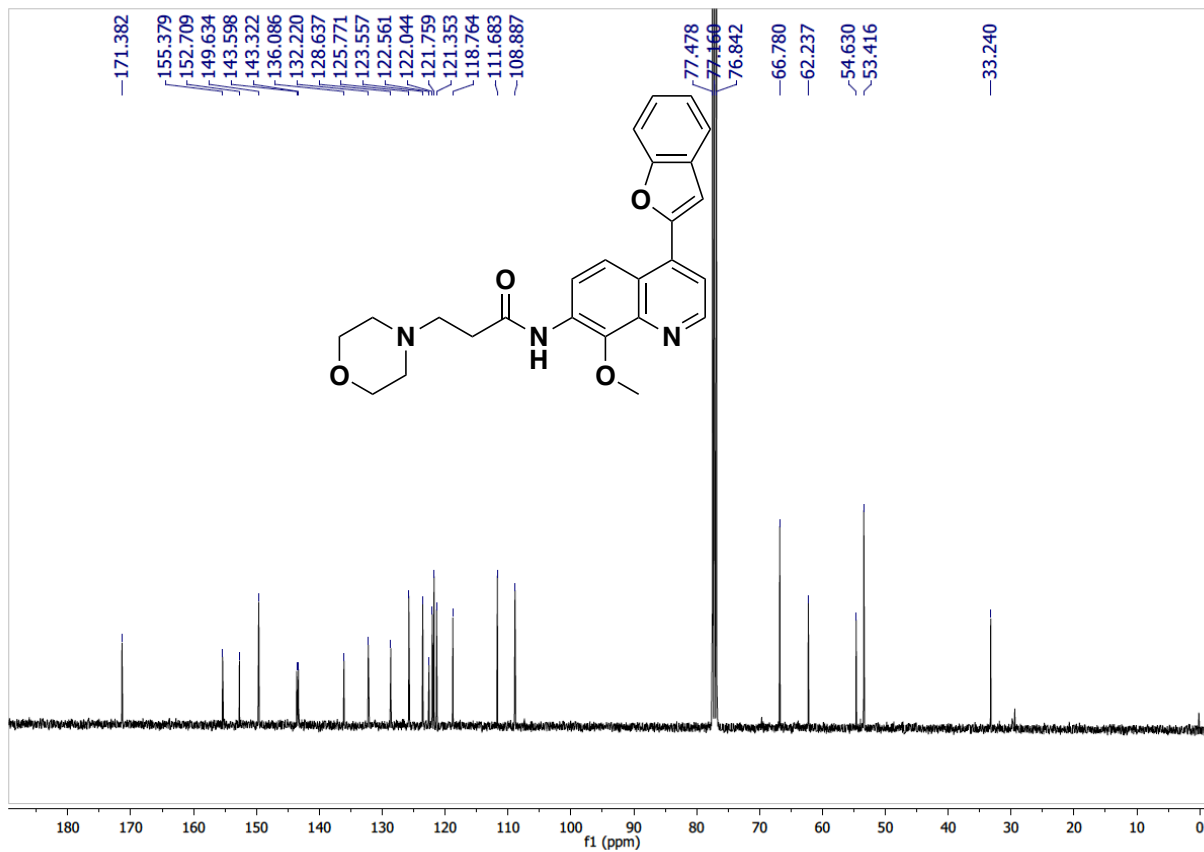
4-(2-benzofuranyl)-8-methoxy-7-(2-(morpholin-4-yl)acetamido)quinoline (51)



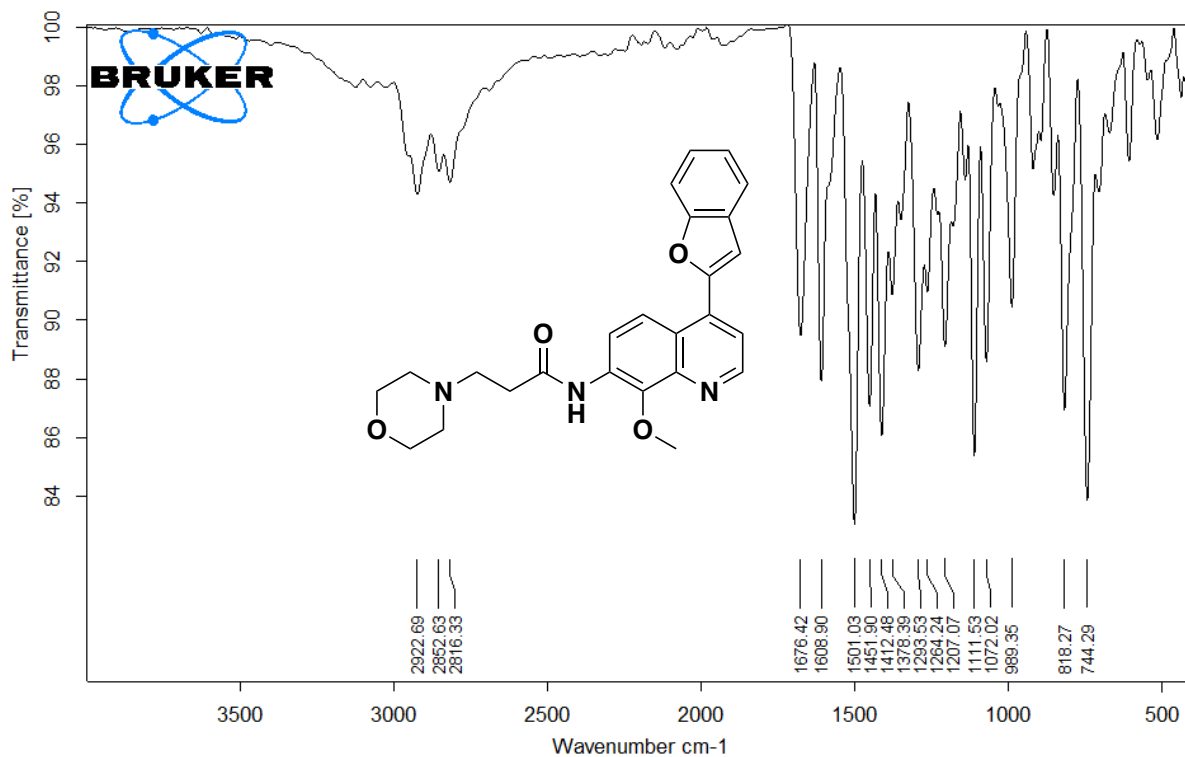
4-(2-benzofuranyl)-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (52) in CDCl₃



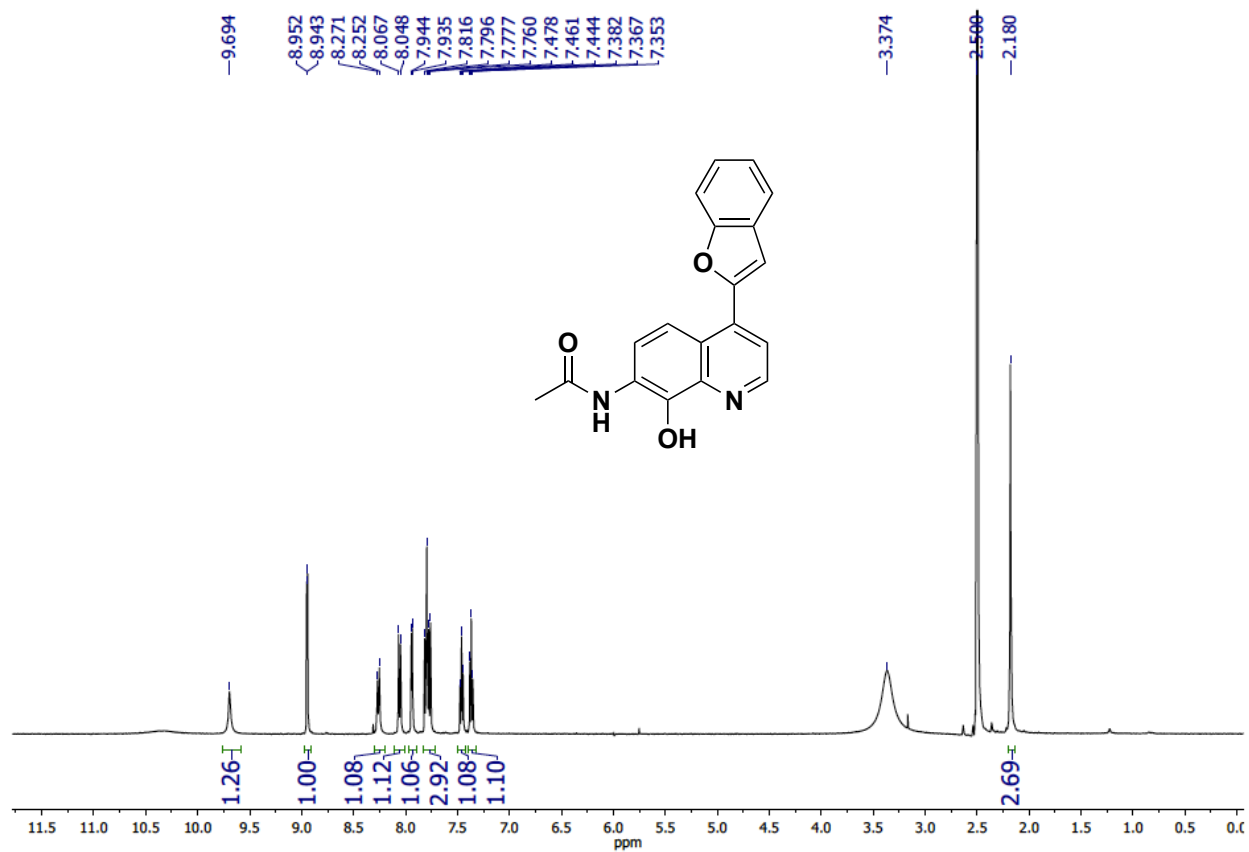
4-(2-benzofuranyl)-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (52) in CDCl₃



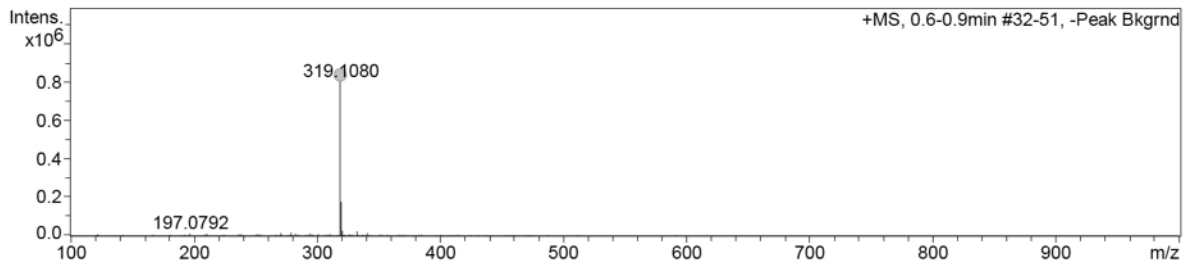
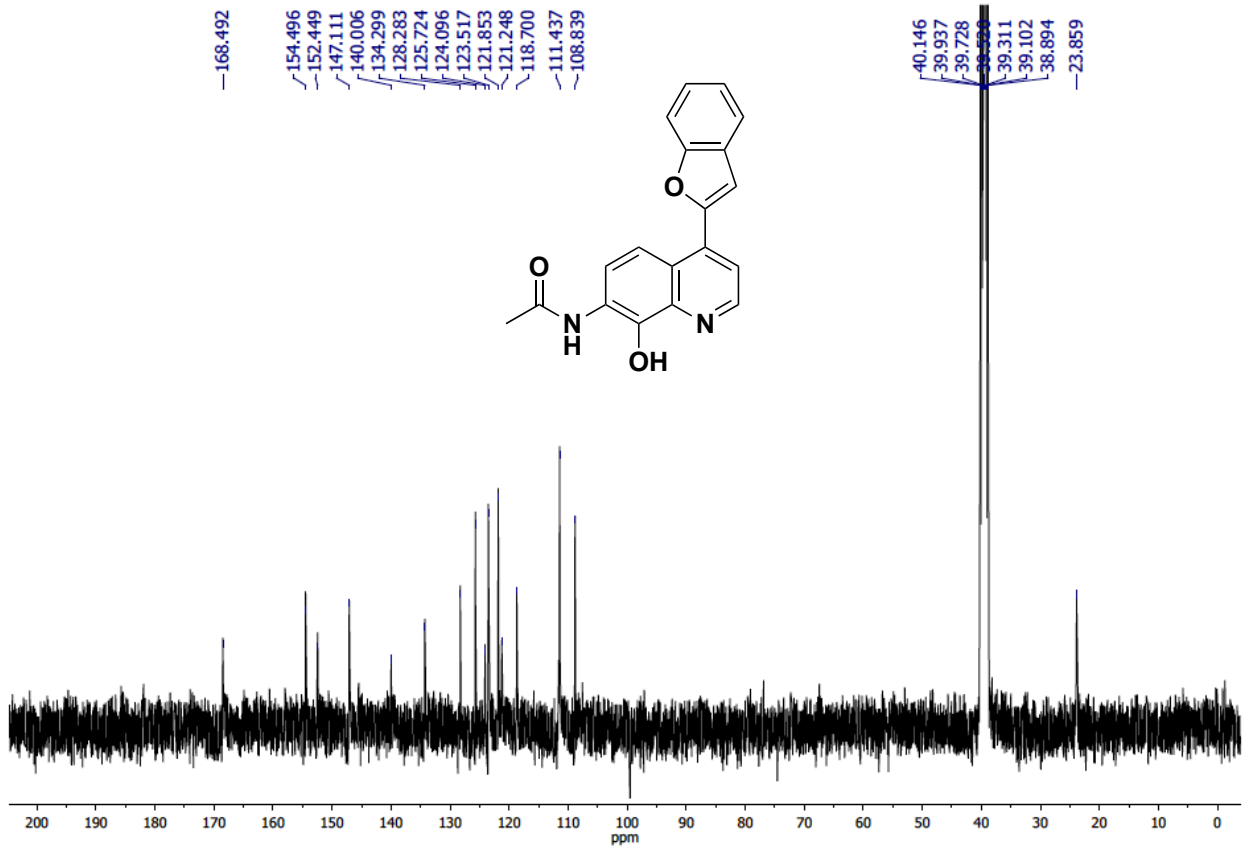
4-(2-benzofuranyl)-8-methoxy-7-(3-(morpholin-4-yl)propanamido)quinoline (52)



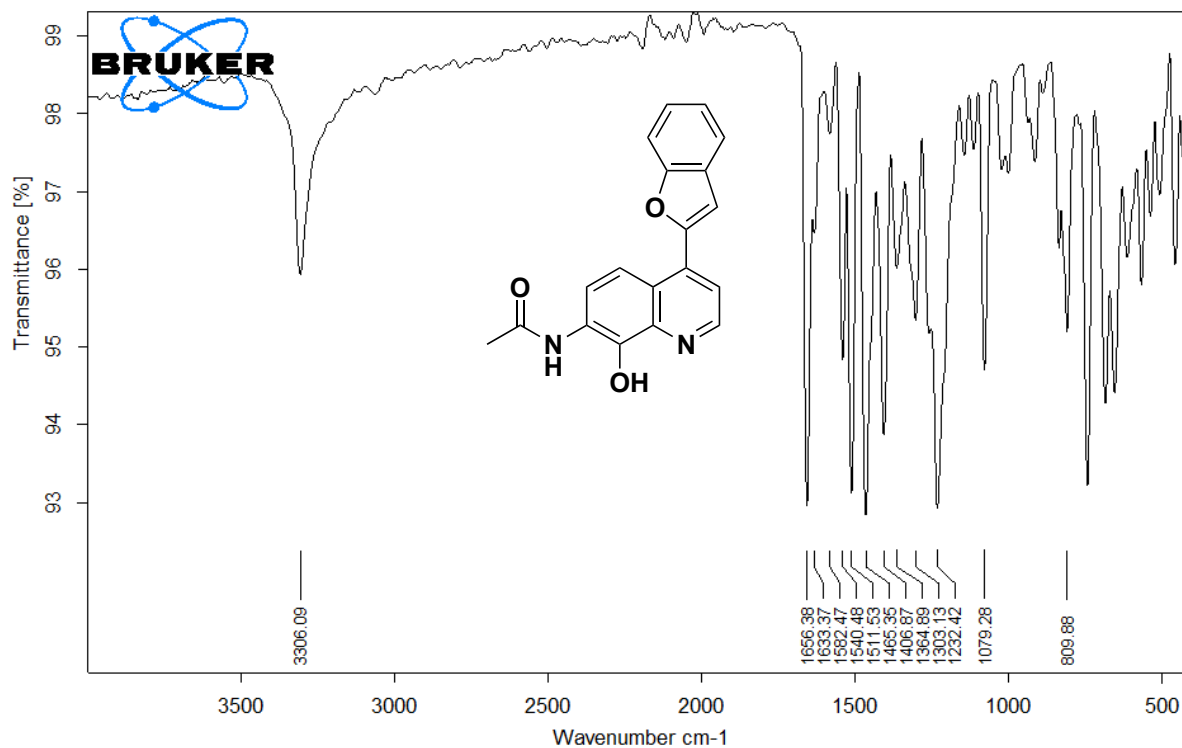
7-Acetamido-4-(2-benzofuranyl)-8-hydroxyquinoline (53) in DMSO-d₆



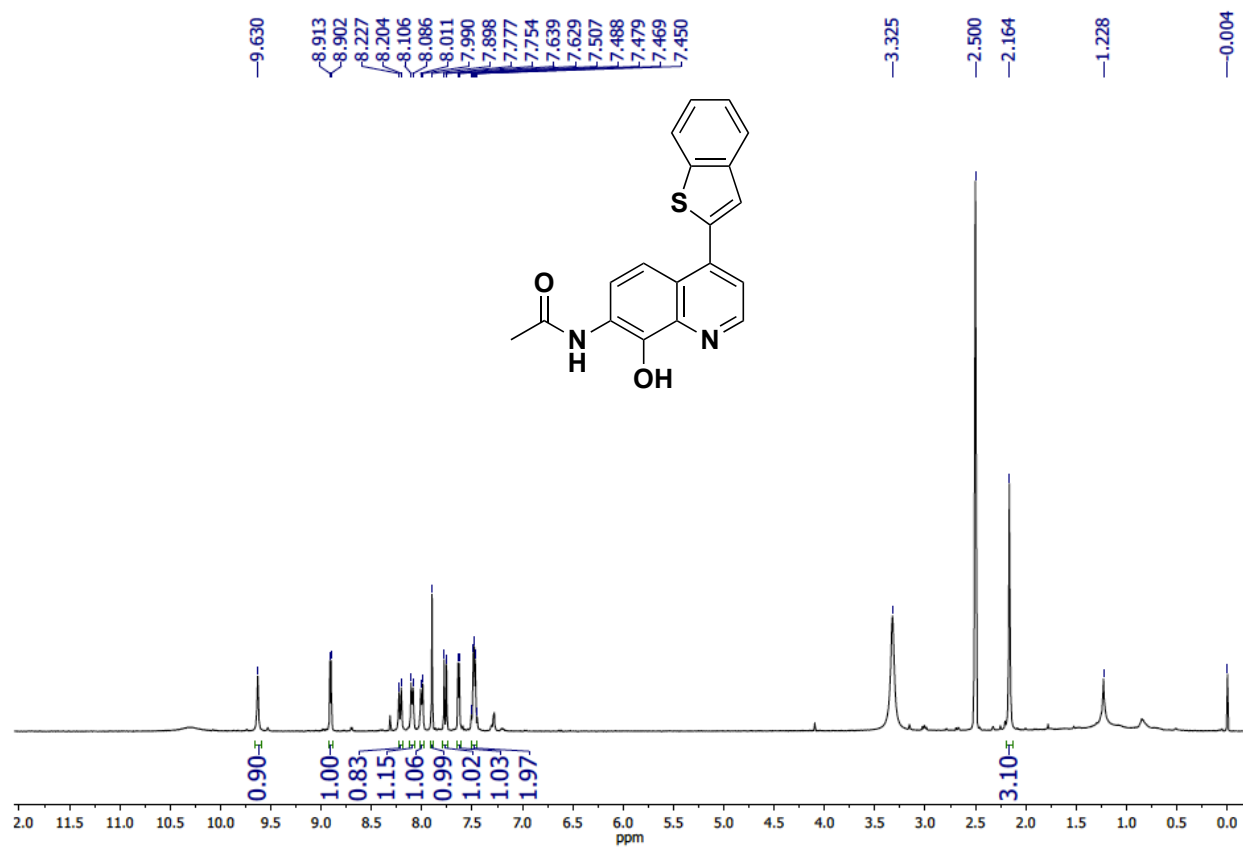
7-Acetamido-4-(2-benzofuranyl)-8-hydroxyquinoline (53) in DMSO-d₆



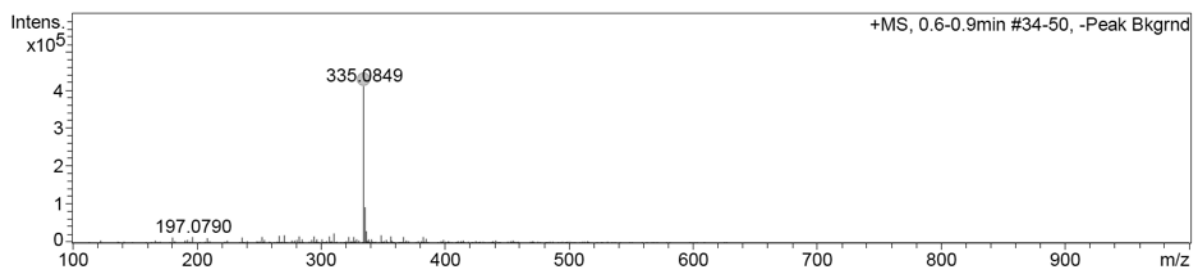
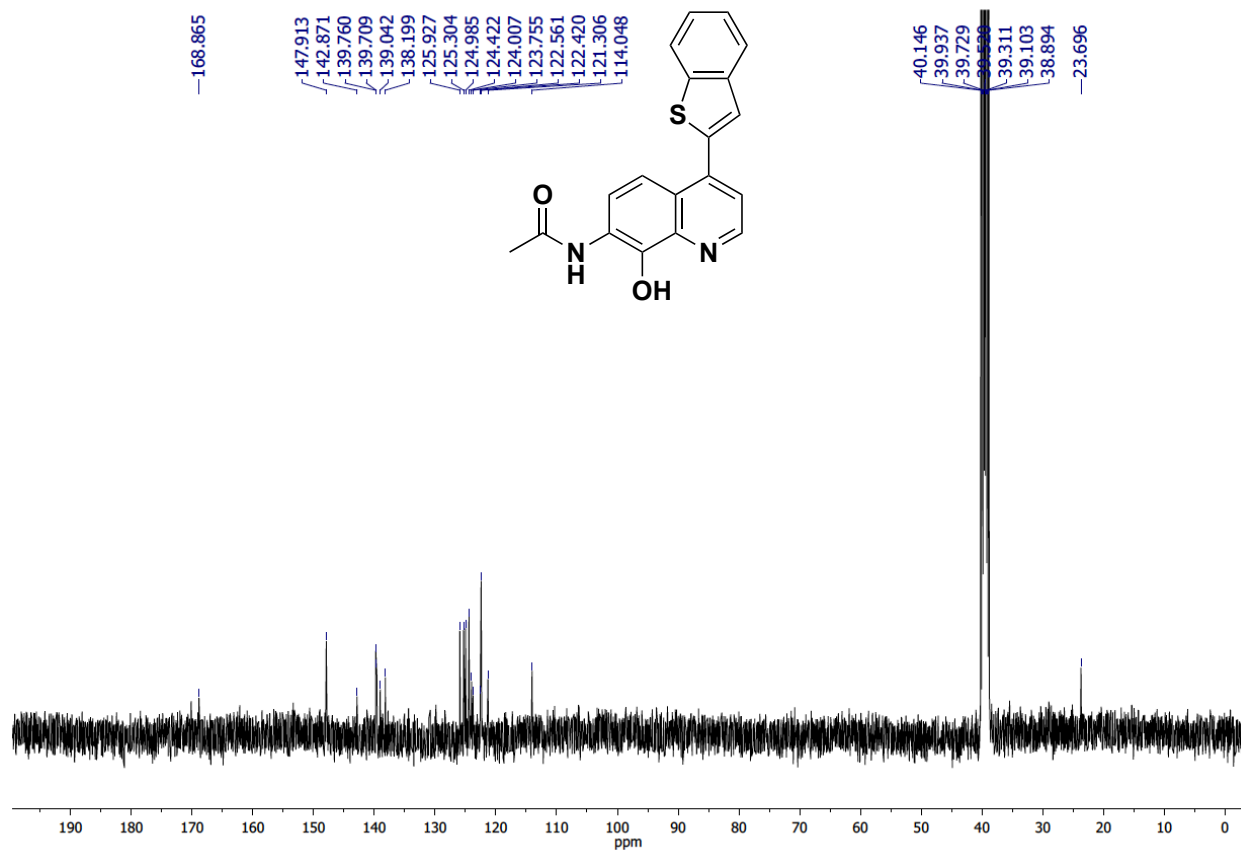
7-Acetamido-4-(2-benzofuranyl)-8-hydroxyquinoline (53)



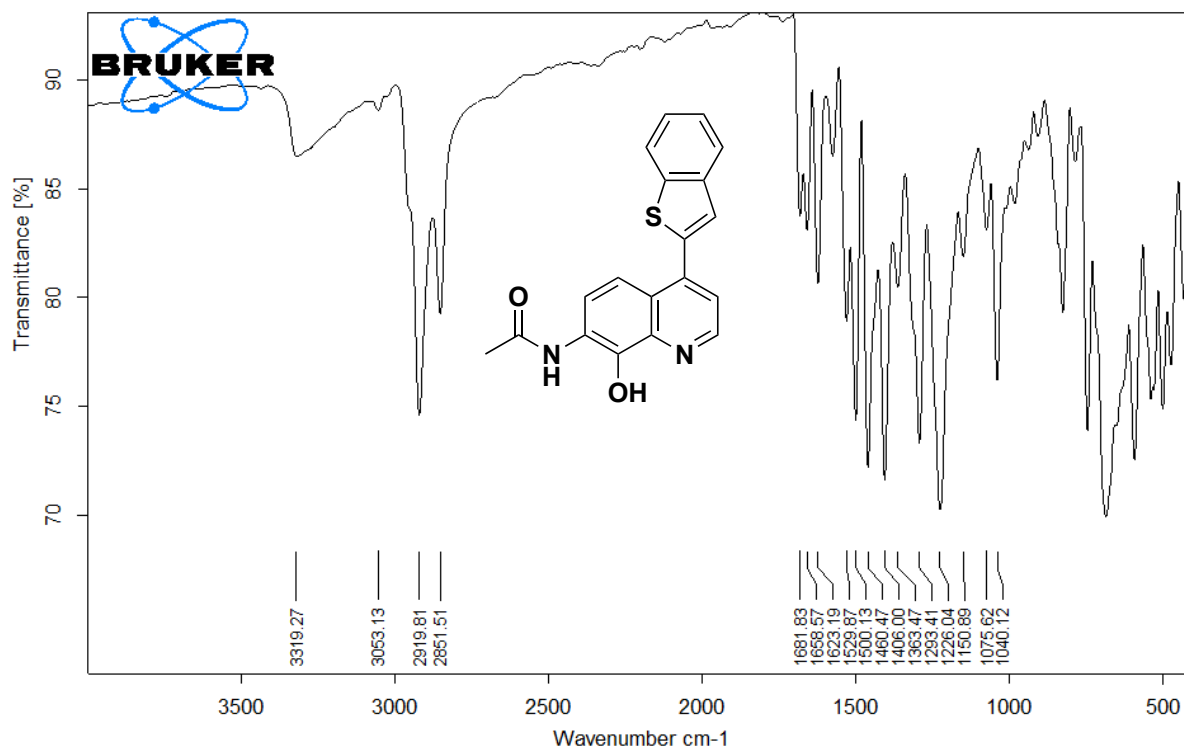
7- Acetamido-4-(benzo[b]thiophen-2-yl)-8-hydroxyquinoline (54) in DMSO-d₆



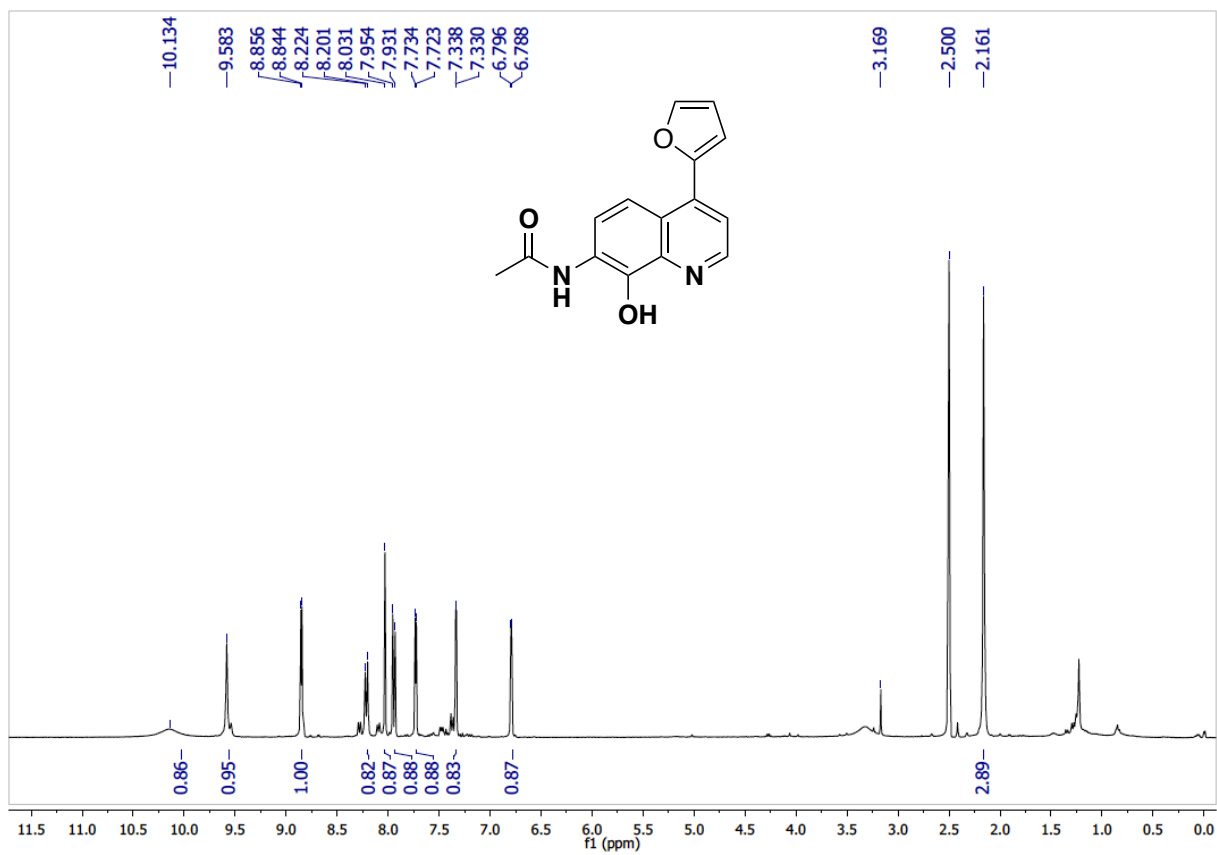
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-hydroxyquinoline (54) in DMSO-d₆



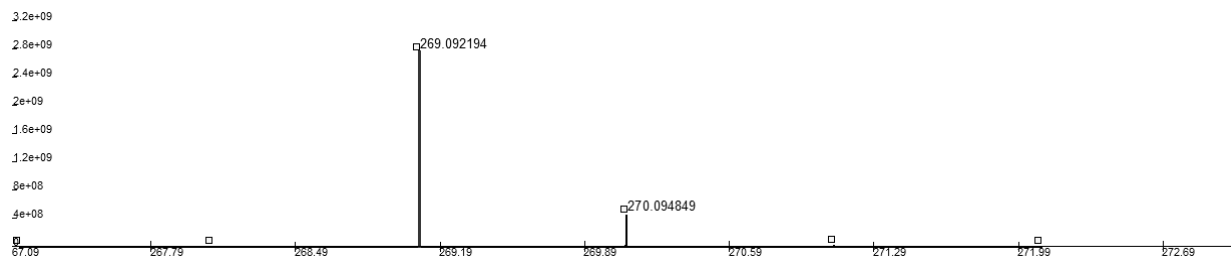
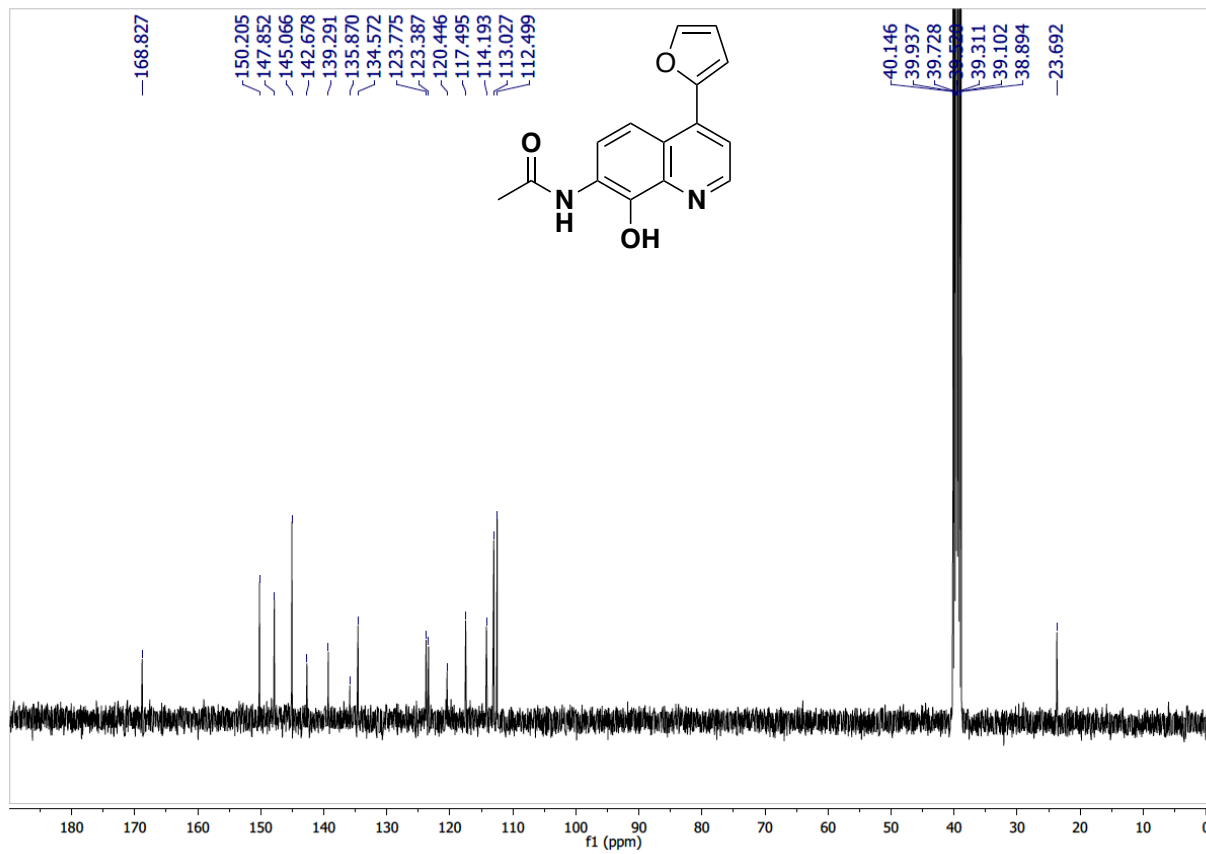
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-hydroxyquinoline (54)



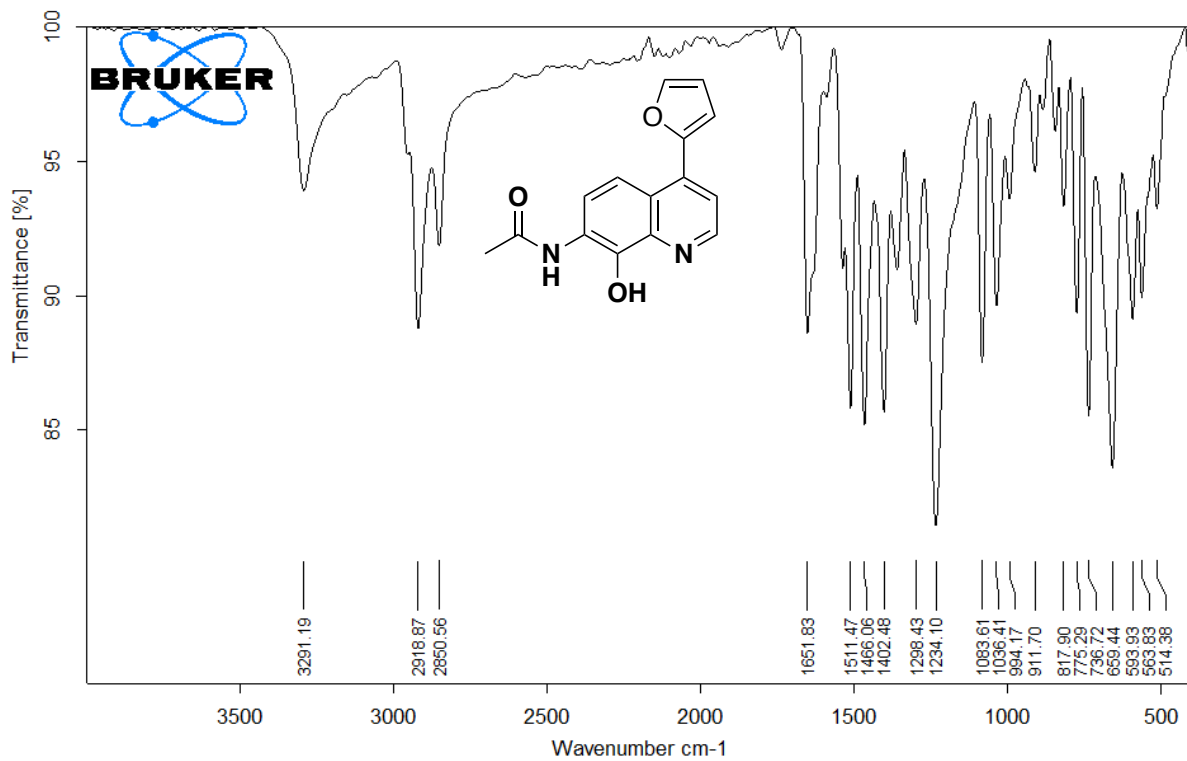
7-Acetamido-4-(2-furanyl)-8-hydroxyquinoline (55) in DMSO-d₆



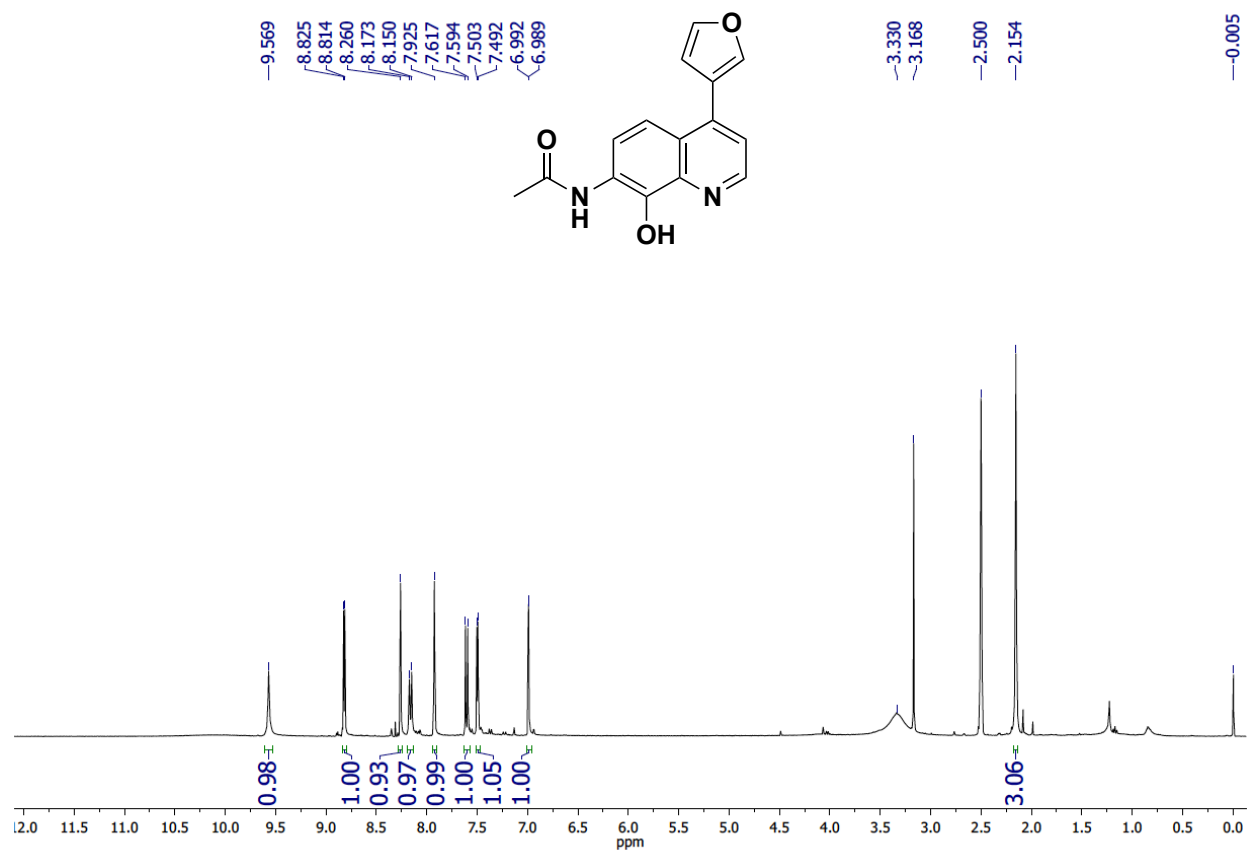
7-Acetamido-4-(2-furanyl)-8-hydroxyquinoline (55) in DMSO-d₆



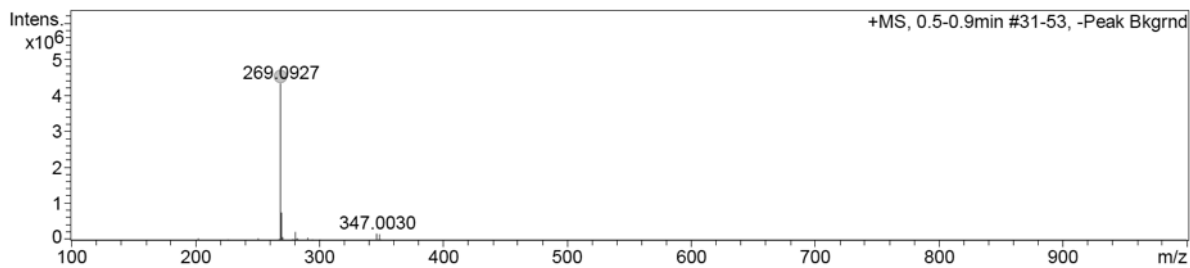
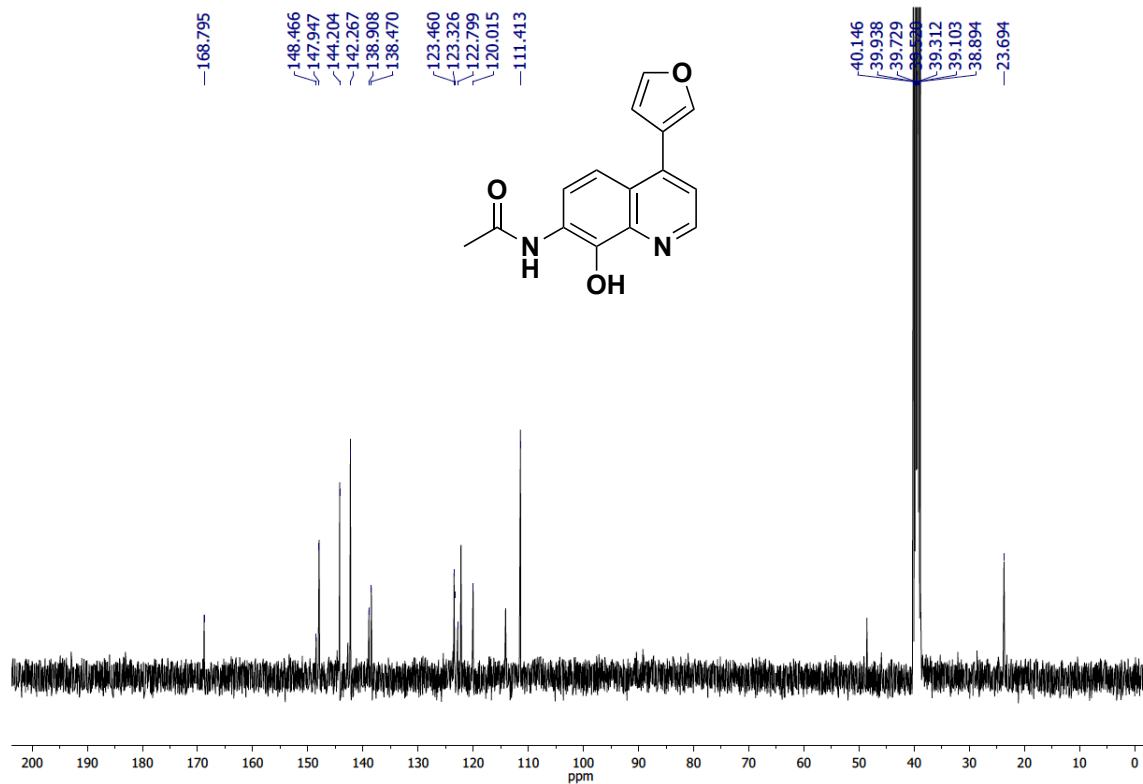
7-Acetamido-4-(2-furanyl)-8-hydroxyquinoline (55)



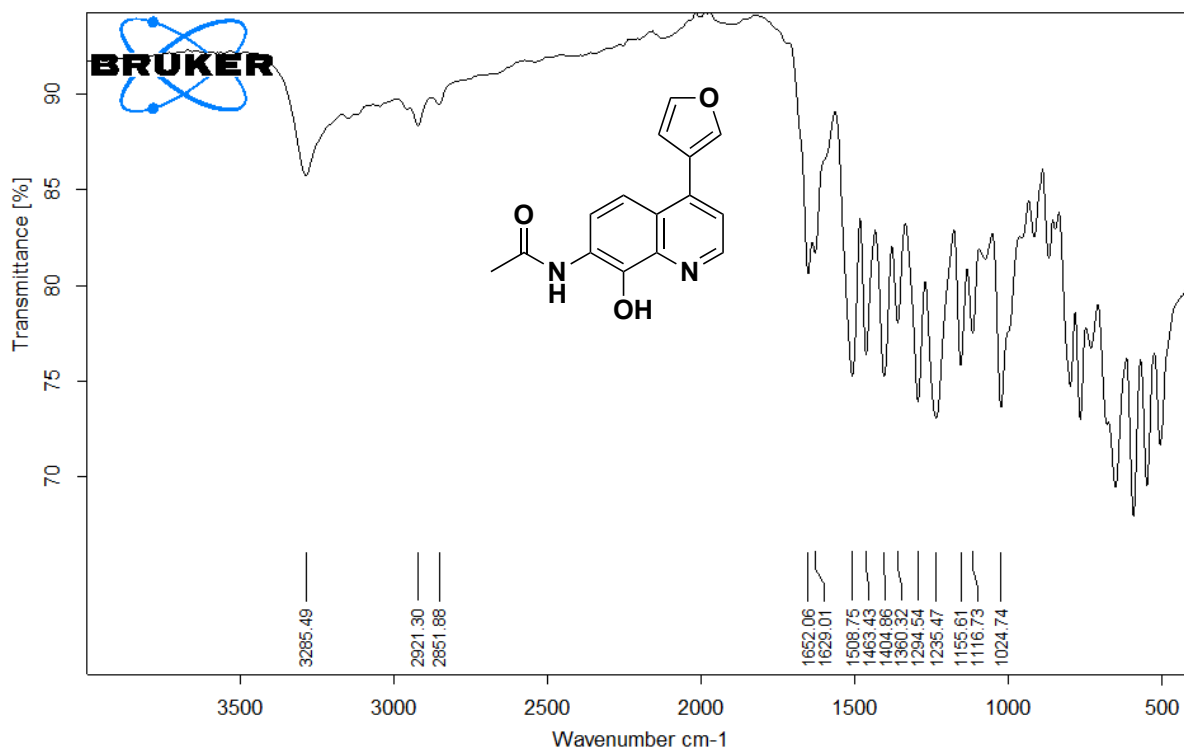
7-Acetamido-4-(3-furanyl)-8-hydroxyquinoline (56) in DMSO-d₆



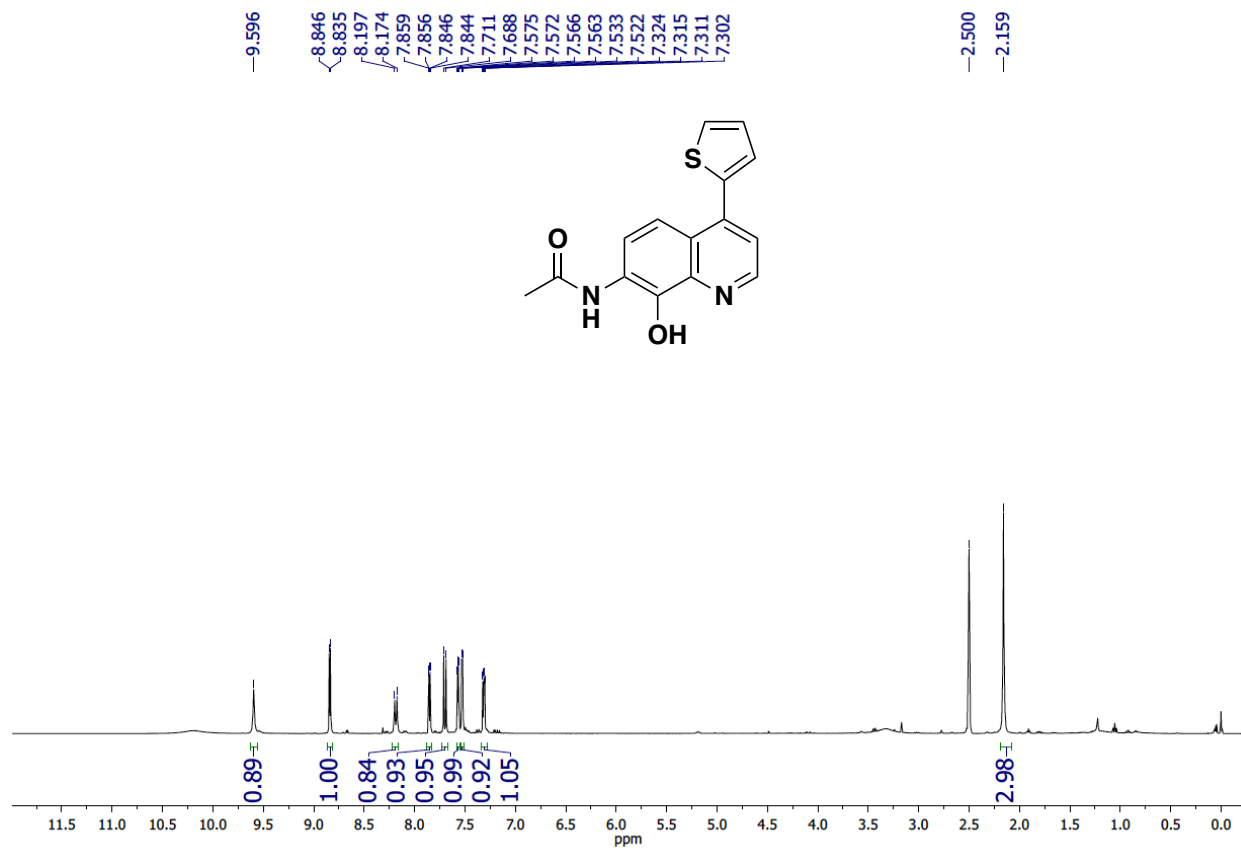
7-Acetamido-4-(3-furanyl)-8-hydroxyquinoline (56) in DMSO-d₆



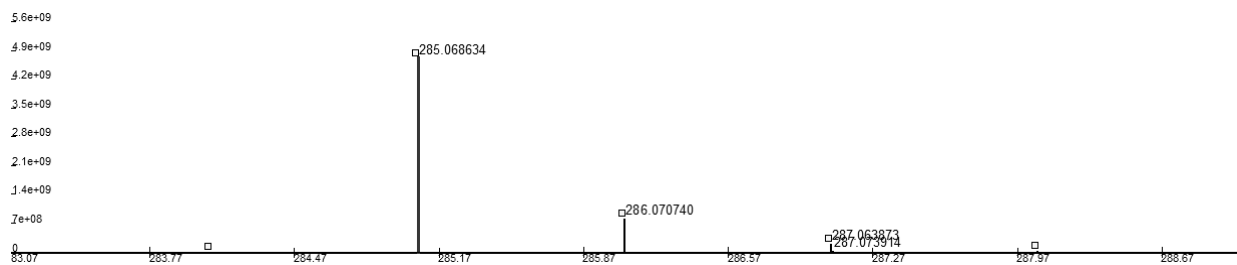
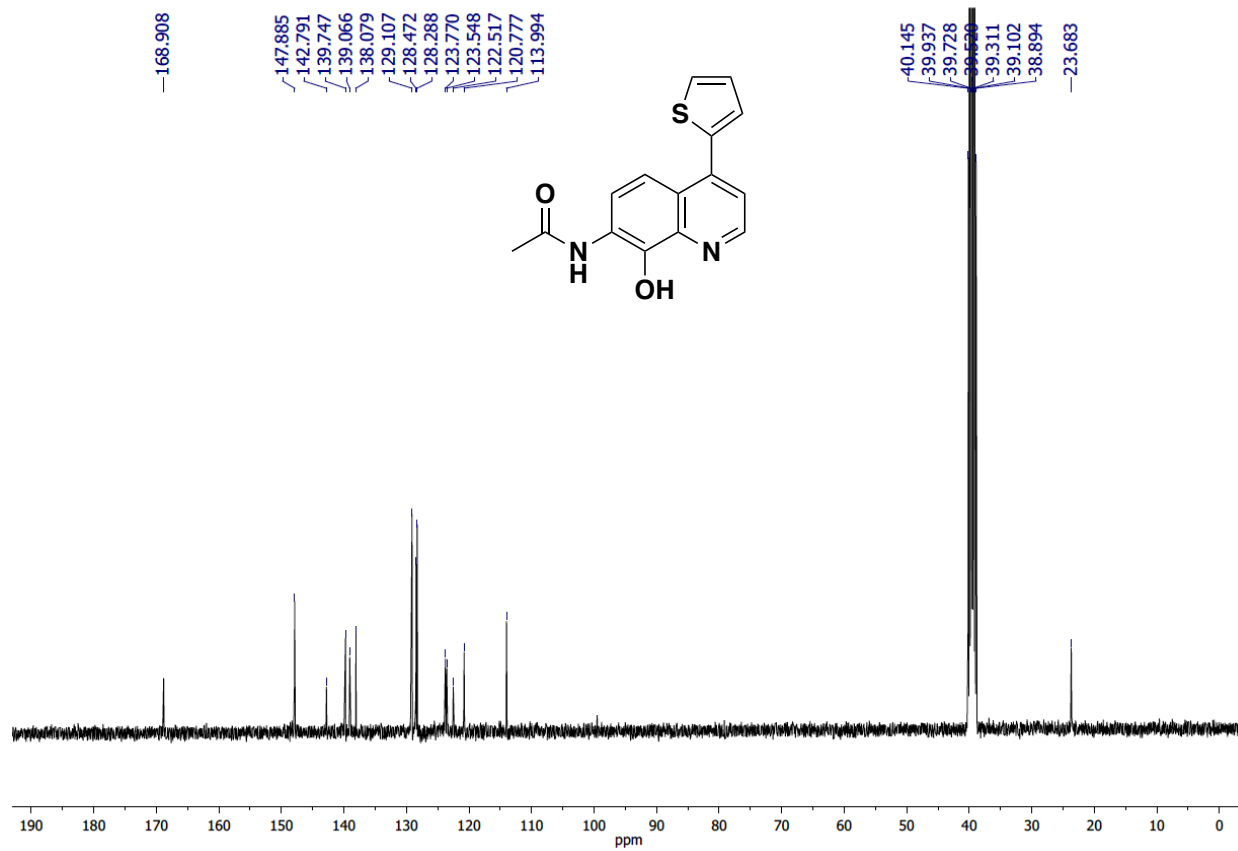
7-Acetamido-4-(3-furanyl)-8-hydroxyquinoline (56)



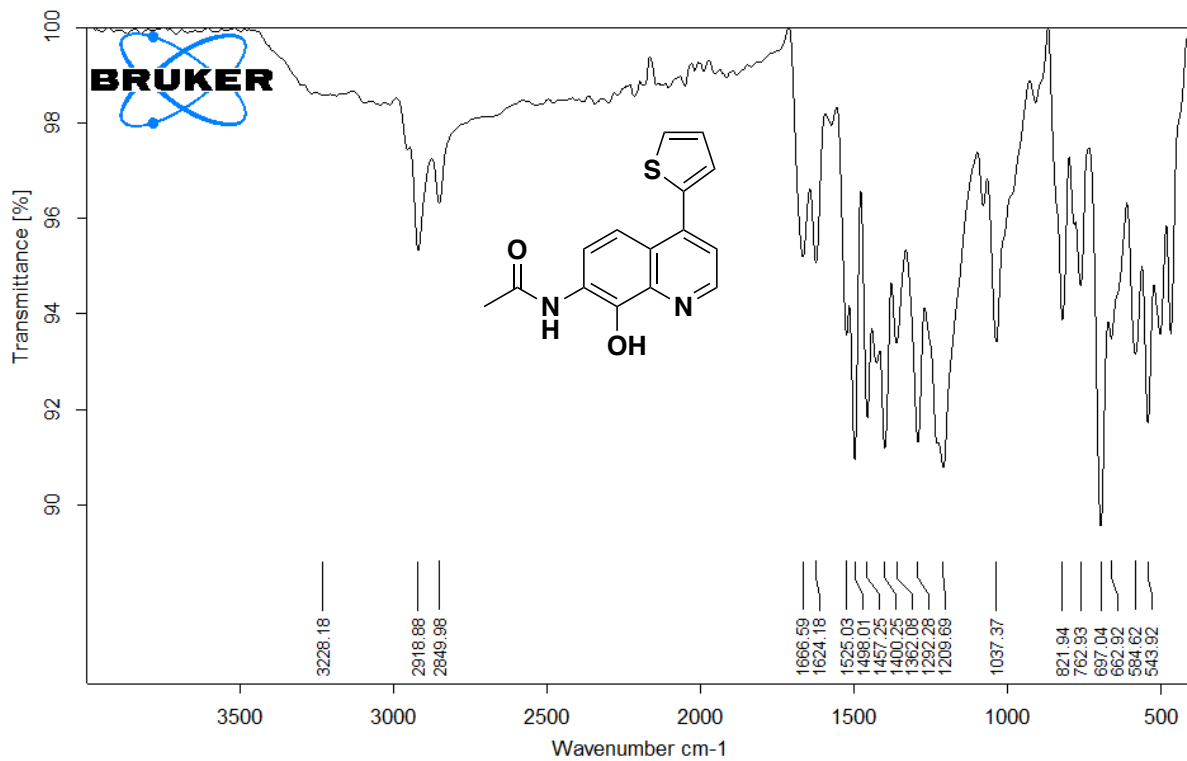
7-Acetamido-4-(thiophen-2-yl)-8-hydroxyquinoline (57) in DMSO-d₆



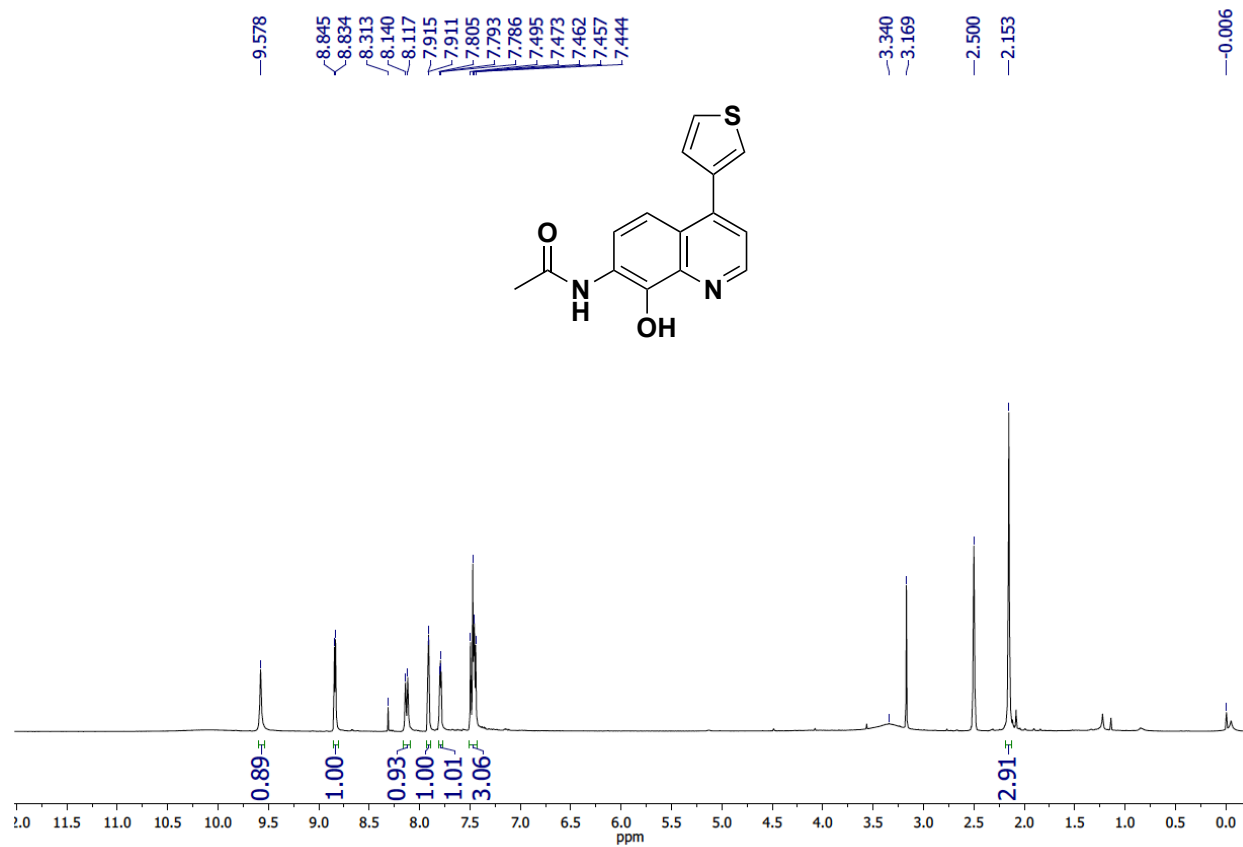
7-Acetamido-4-(thiophen-2-yl)-8-hydroxyquinoline (57) in DMSO-d₆



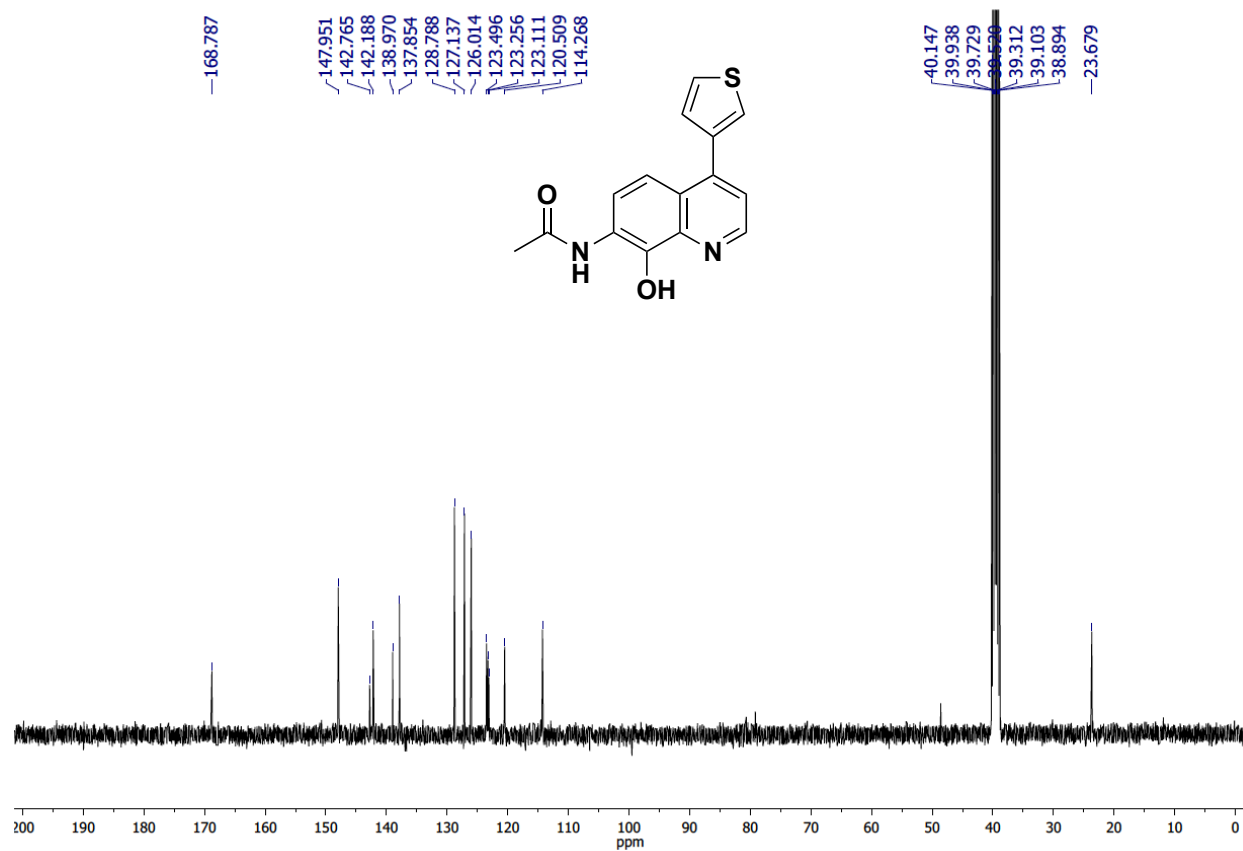
7-Acetamido-4-(thiophen-2-yl)-8-hydroxyquinoline (57)

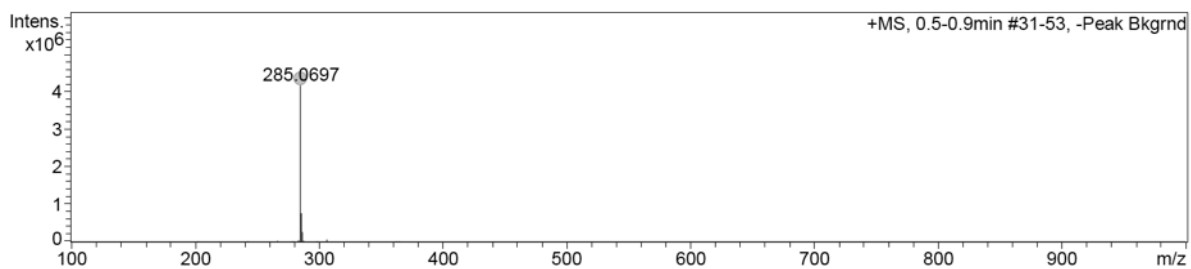


7-Acetamido-4-(thiophen-3-yl)-8-hydroxyquinoline (58) in DMSO-d₆

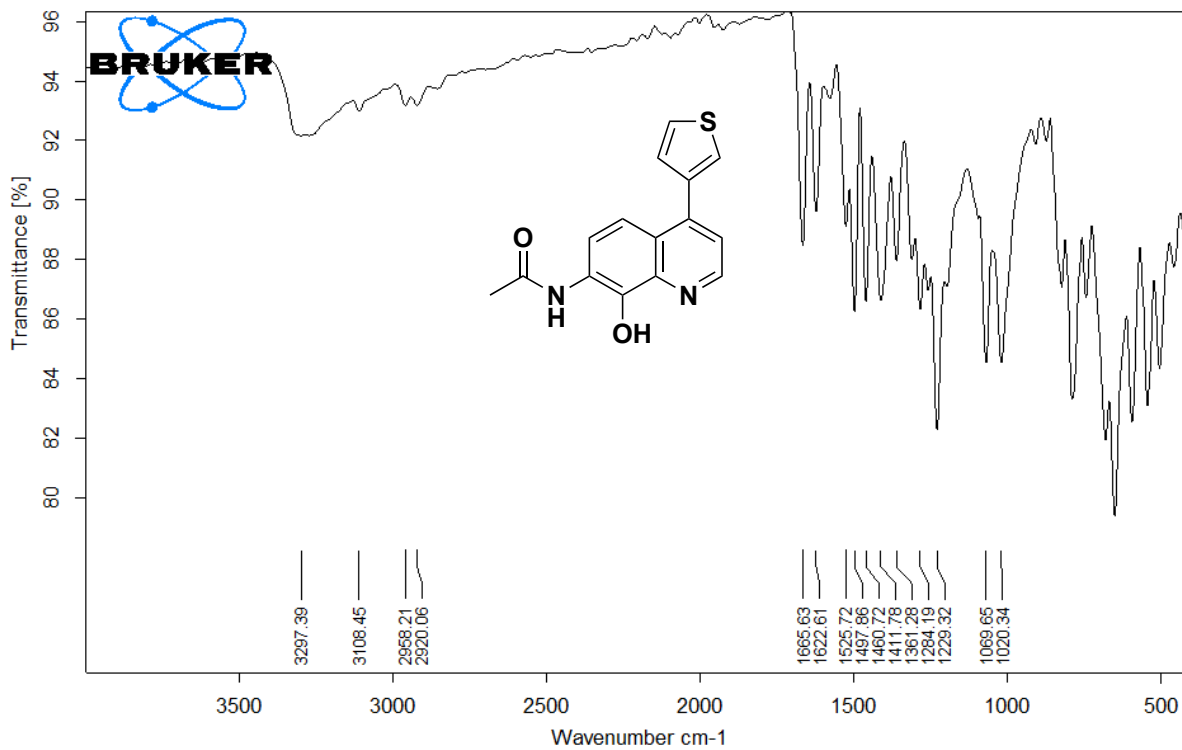


7-Acetamido-4-(thiophen-3-yl)-8-hydroxyquinoline (58) in DMSO-d₆

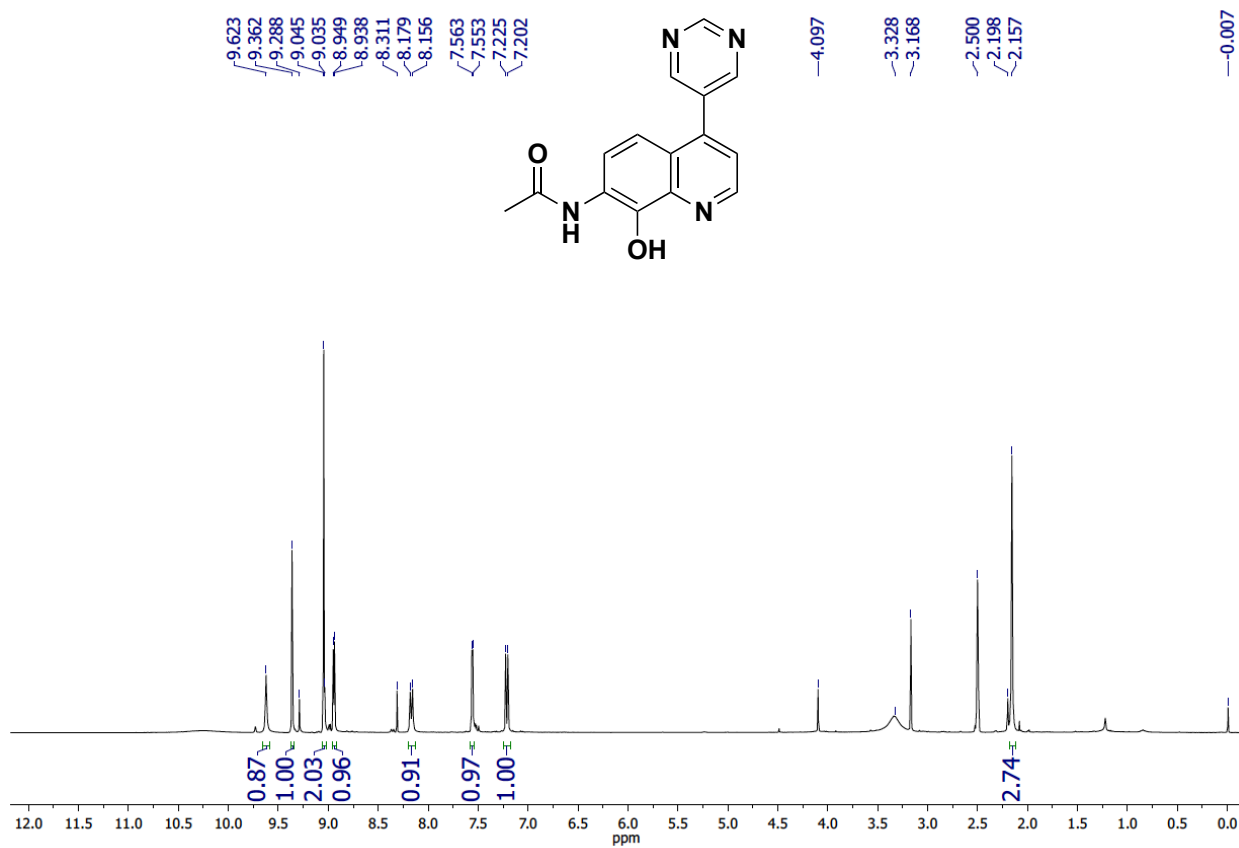




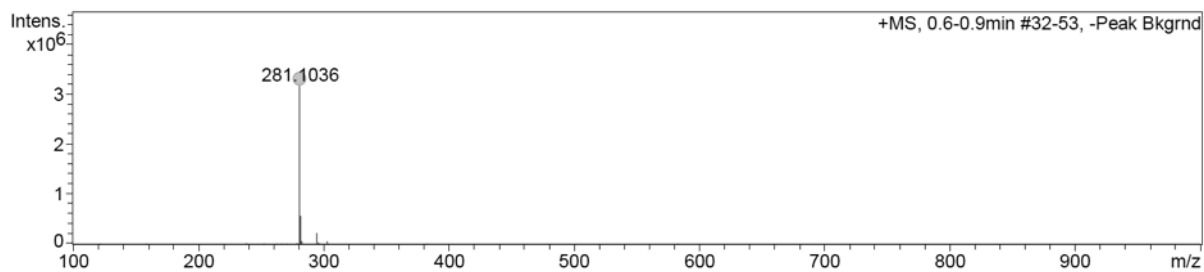
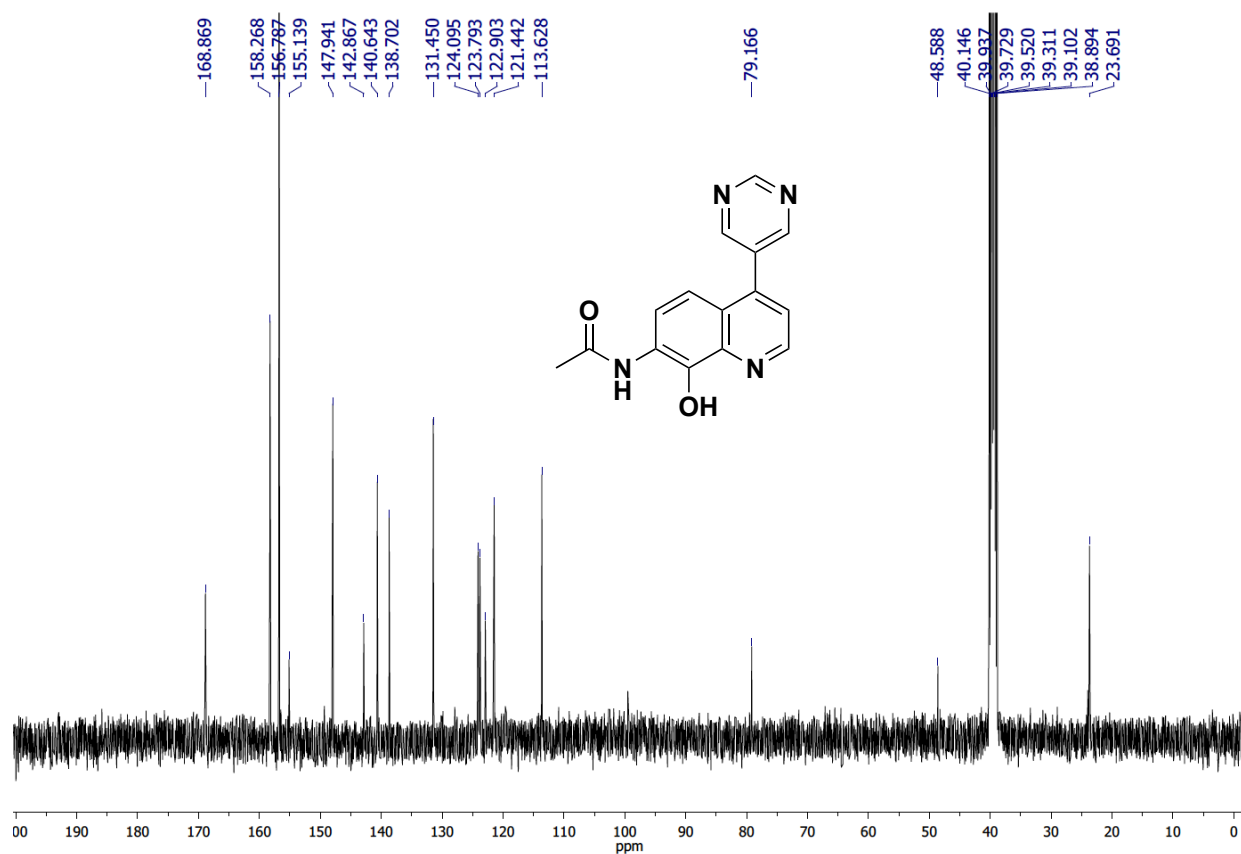
7-Acetamido-4-(thiophen-3-yl)-8-hydroxyquinoline (58)



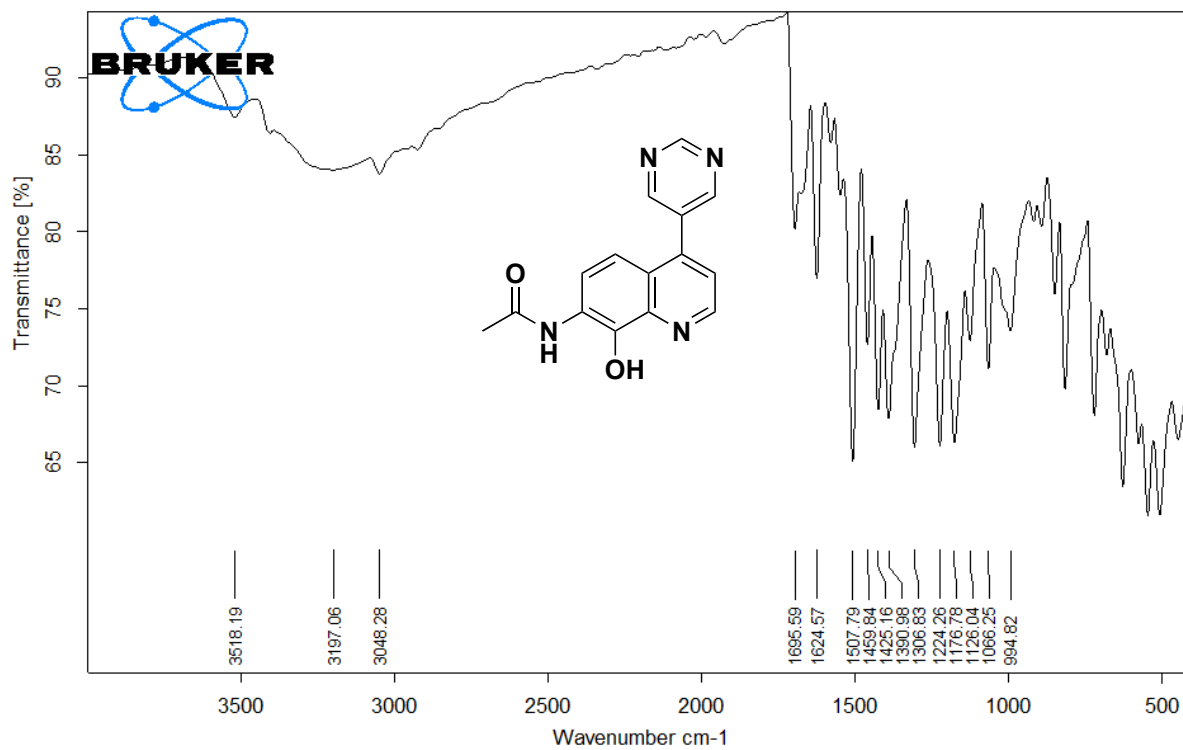
7-Acetamido-4-(5-pyrimidinyl)-8-hydroxyquinoline (59) in DMSO-d₆



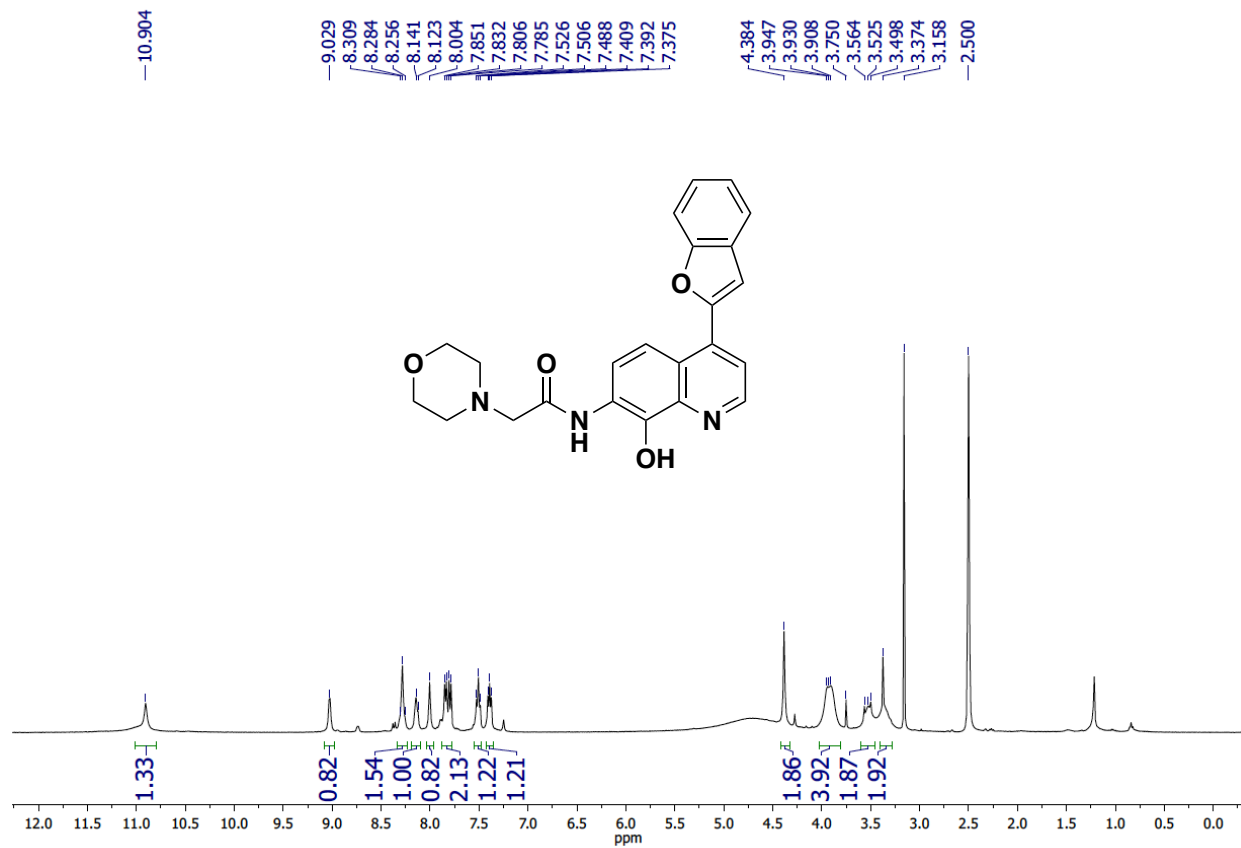
7-Acetamido-4-(5-pyrimidinyl)-8-hydroxyquinoline (59) in DMSO-d₆



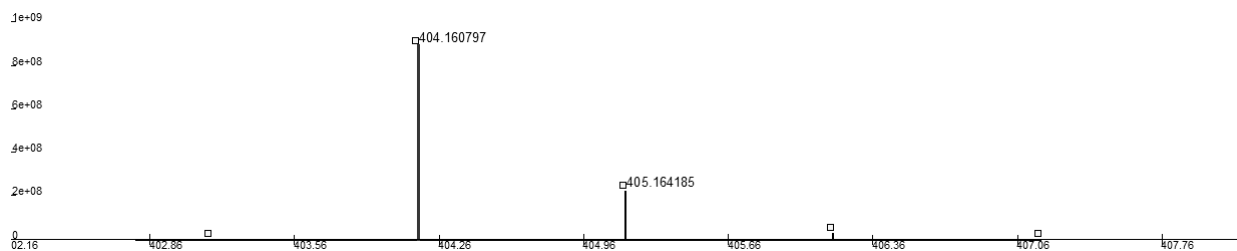
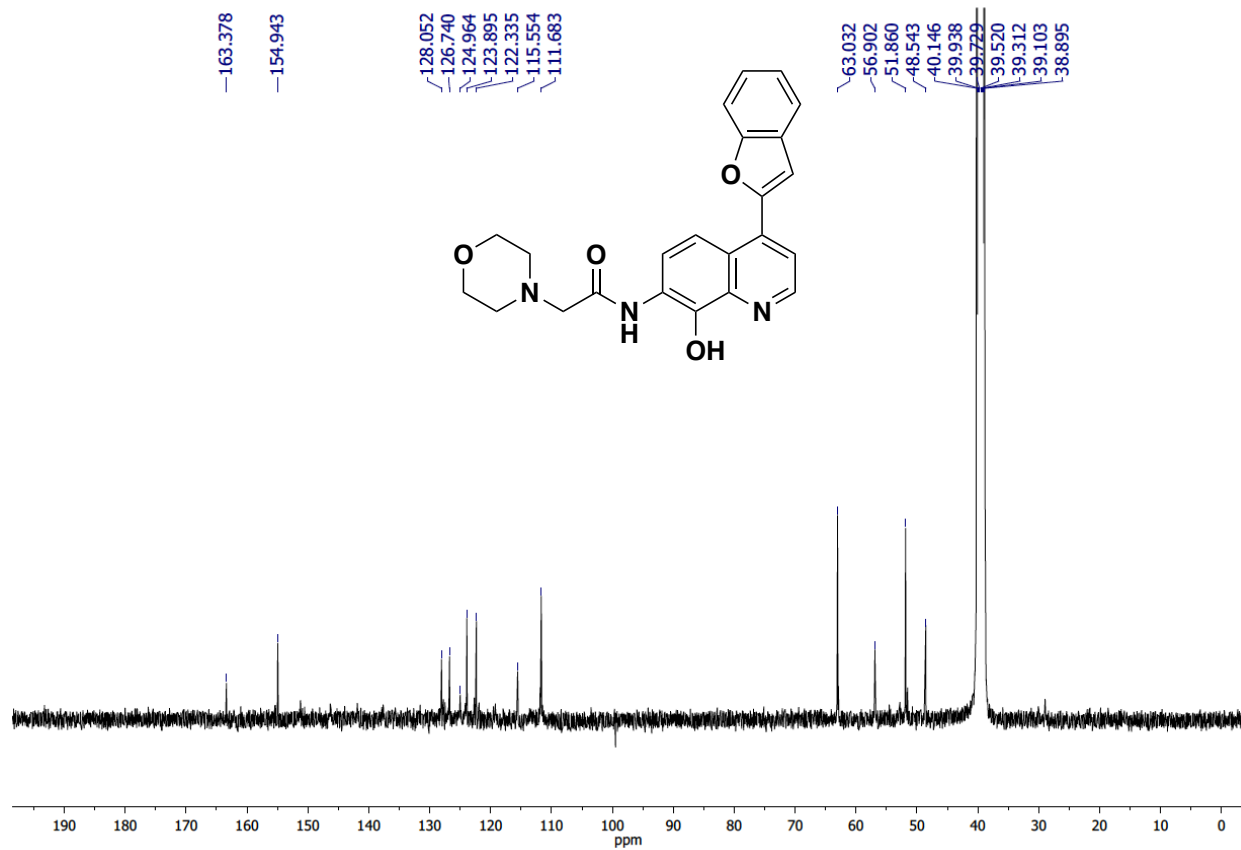
7-Acetamido-4-(5-pyrimidinyl)-8-hydroxyquinoline (59)



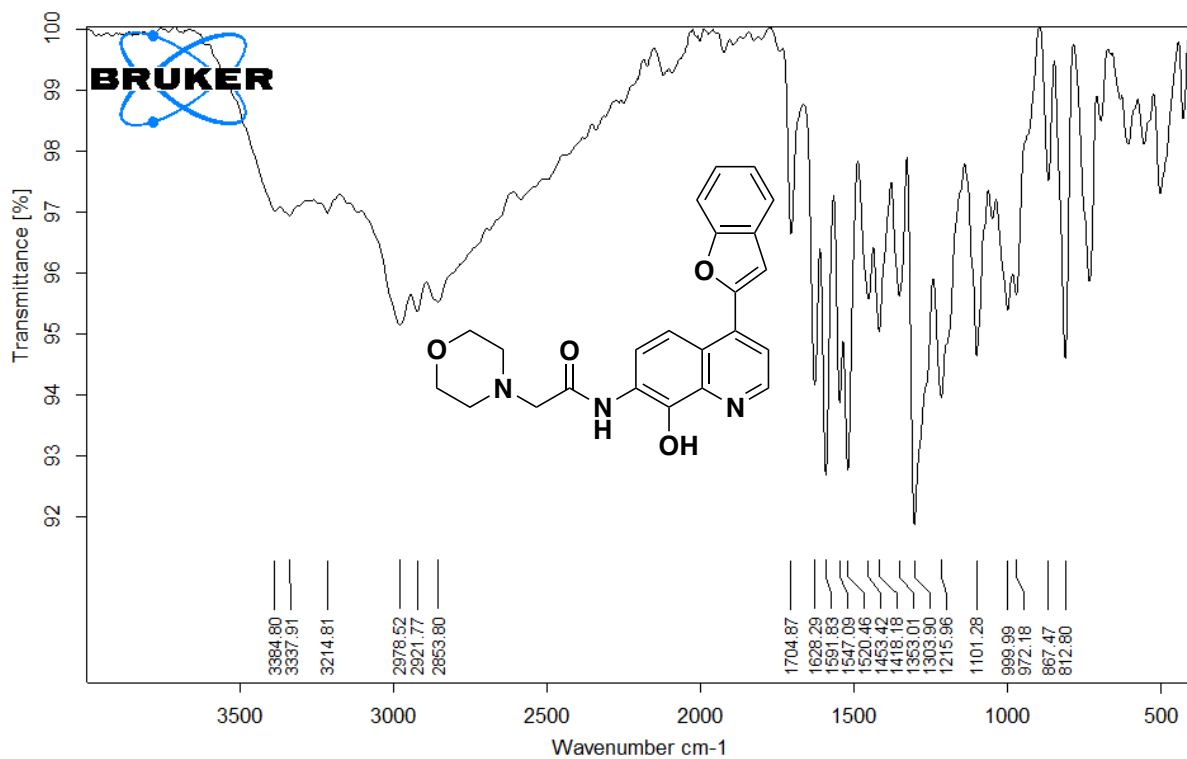
4-(2-benzofuranyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (60) in DMSO-d₆



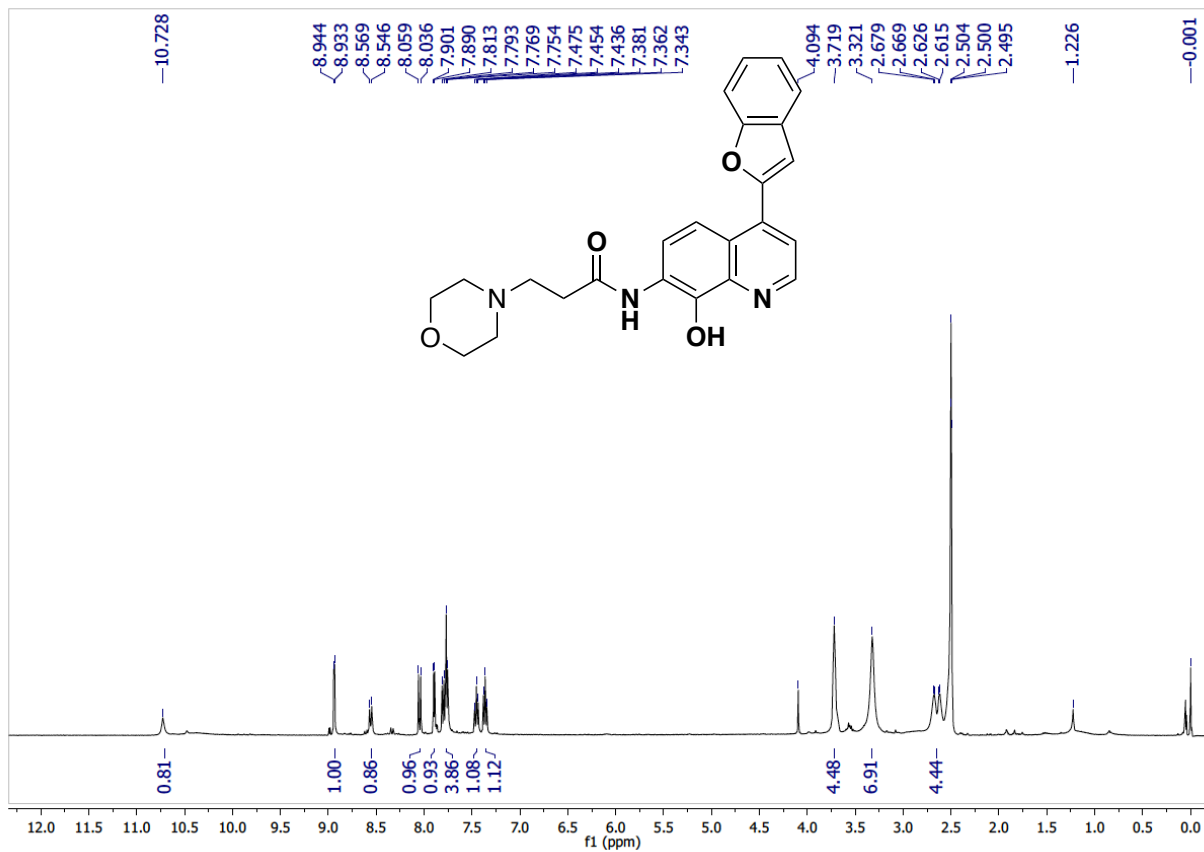
4-(2-benzofuranyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (60) in DMSO-d₆



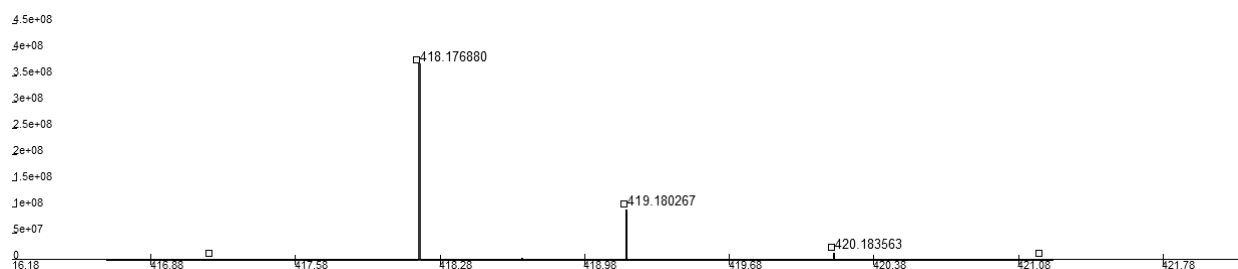
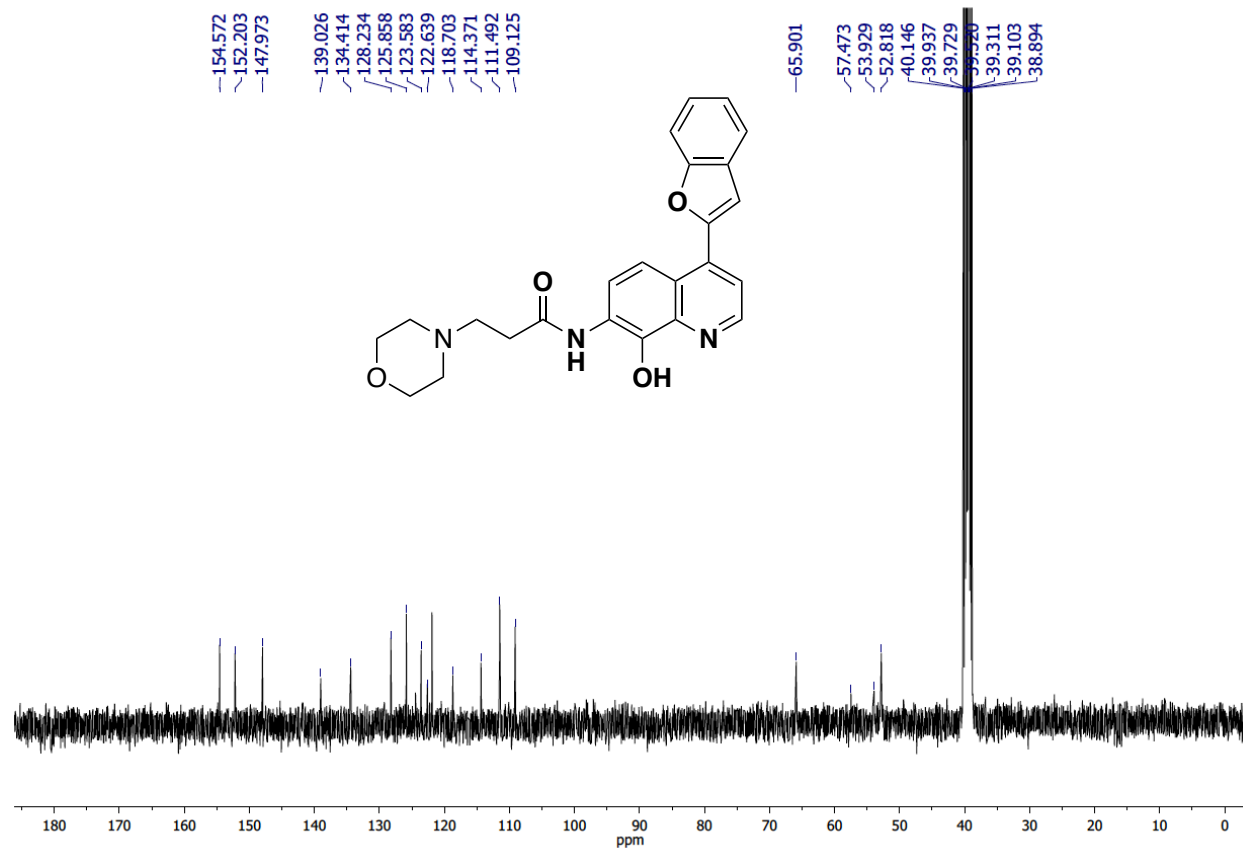
4-(2-benzofuranyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (60)



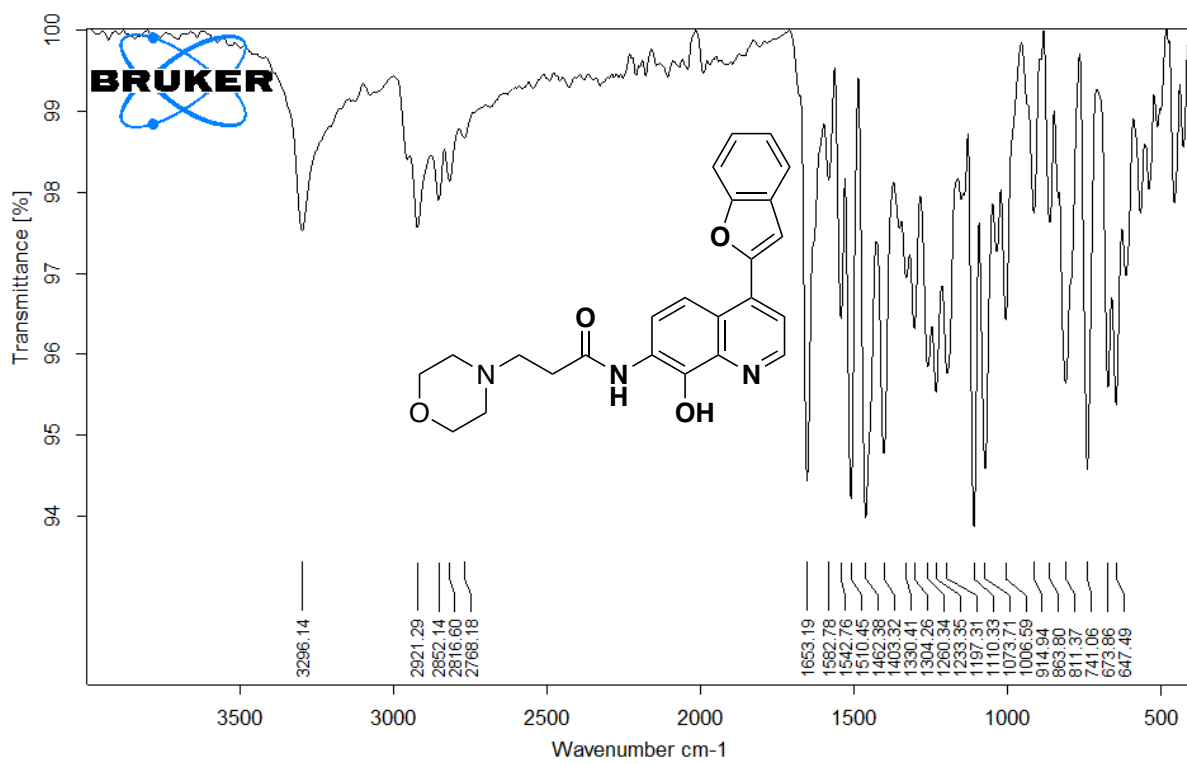
4-(2-benzofuranyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (61) in DMSO-d₆



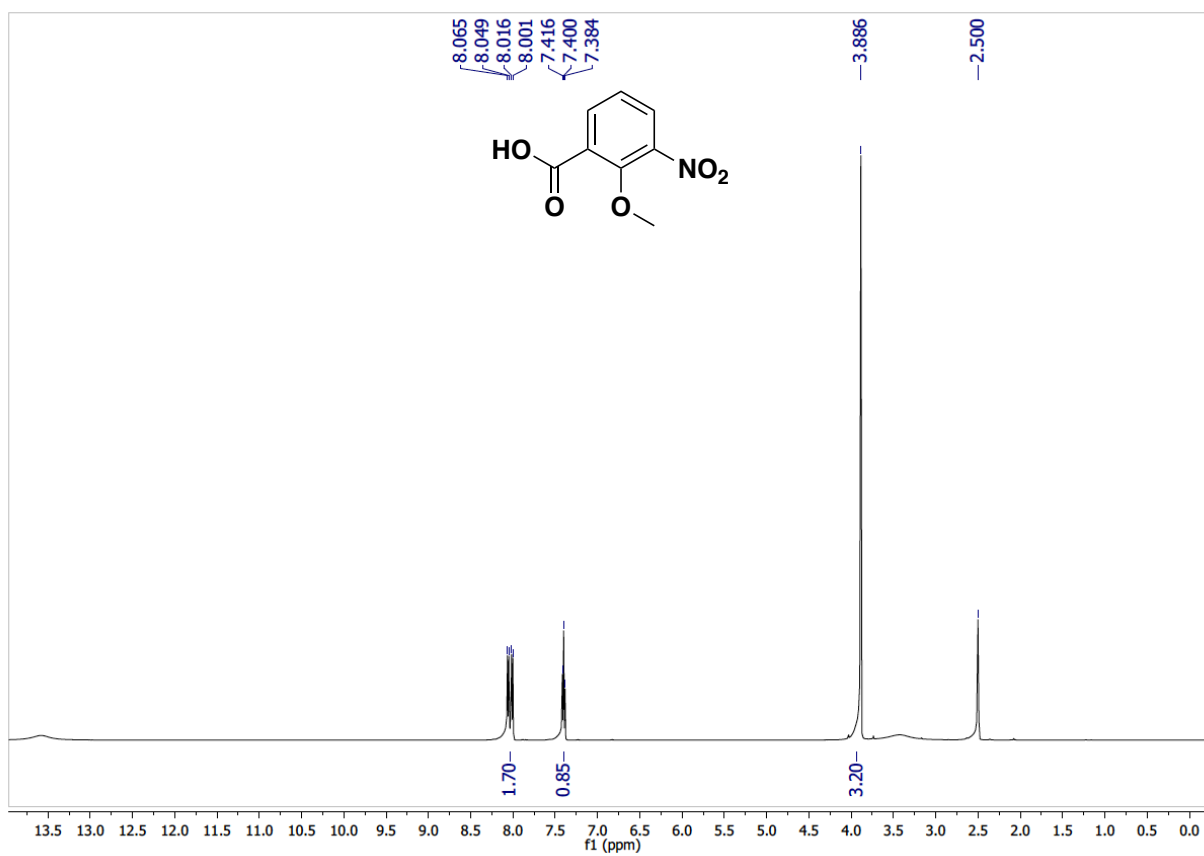
4-(2-benzofuranyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (61) in DMSO-d₆



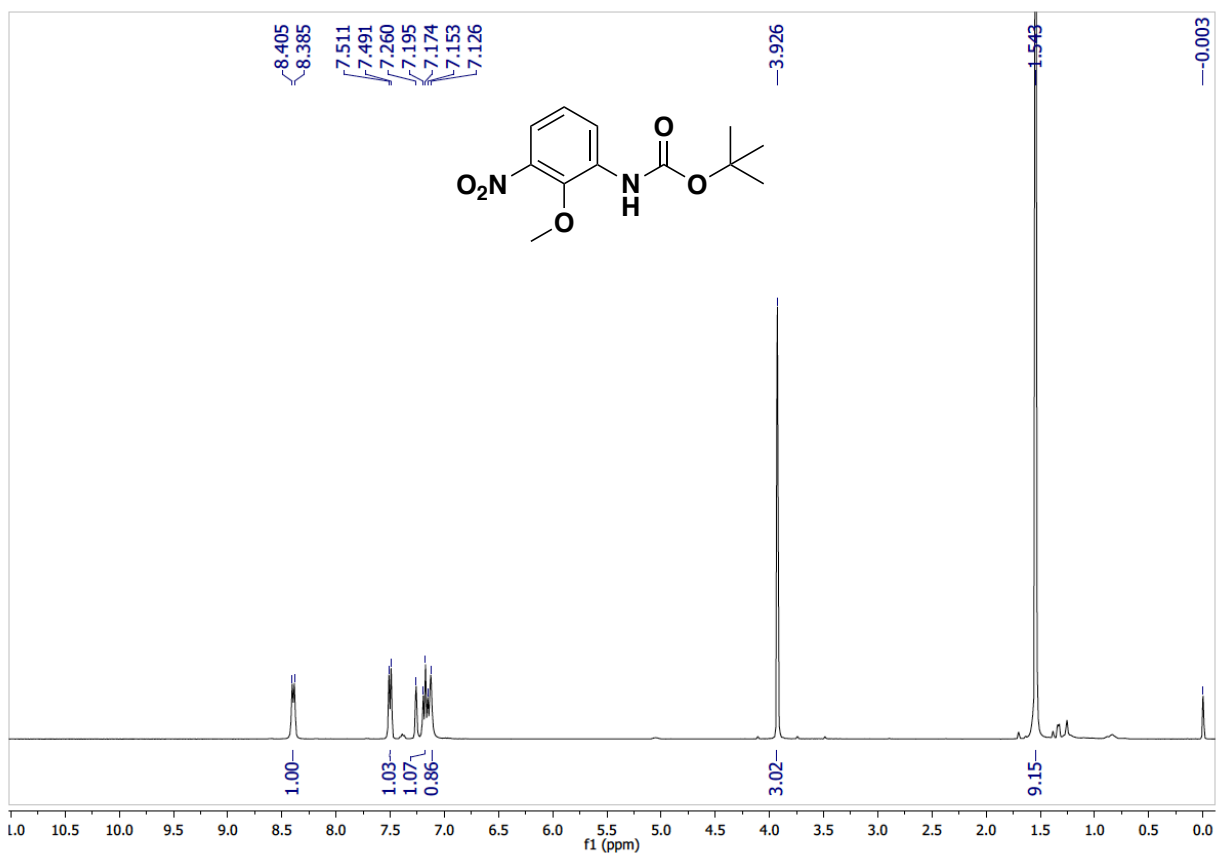
4-(2-benzofuranyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (61)



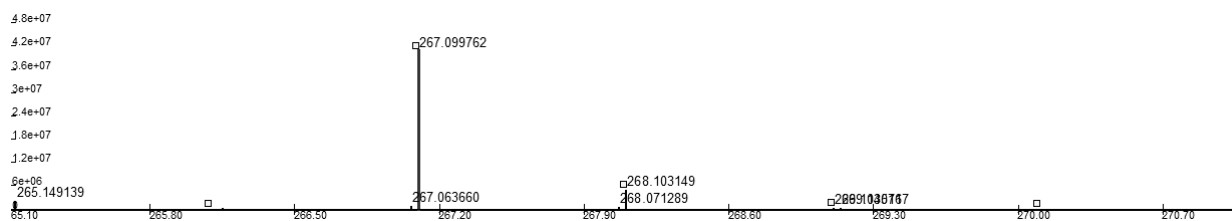
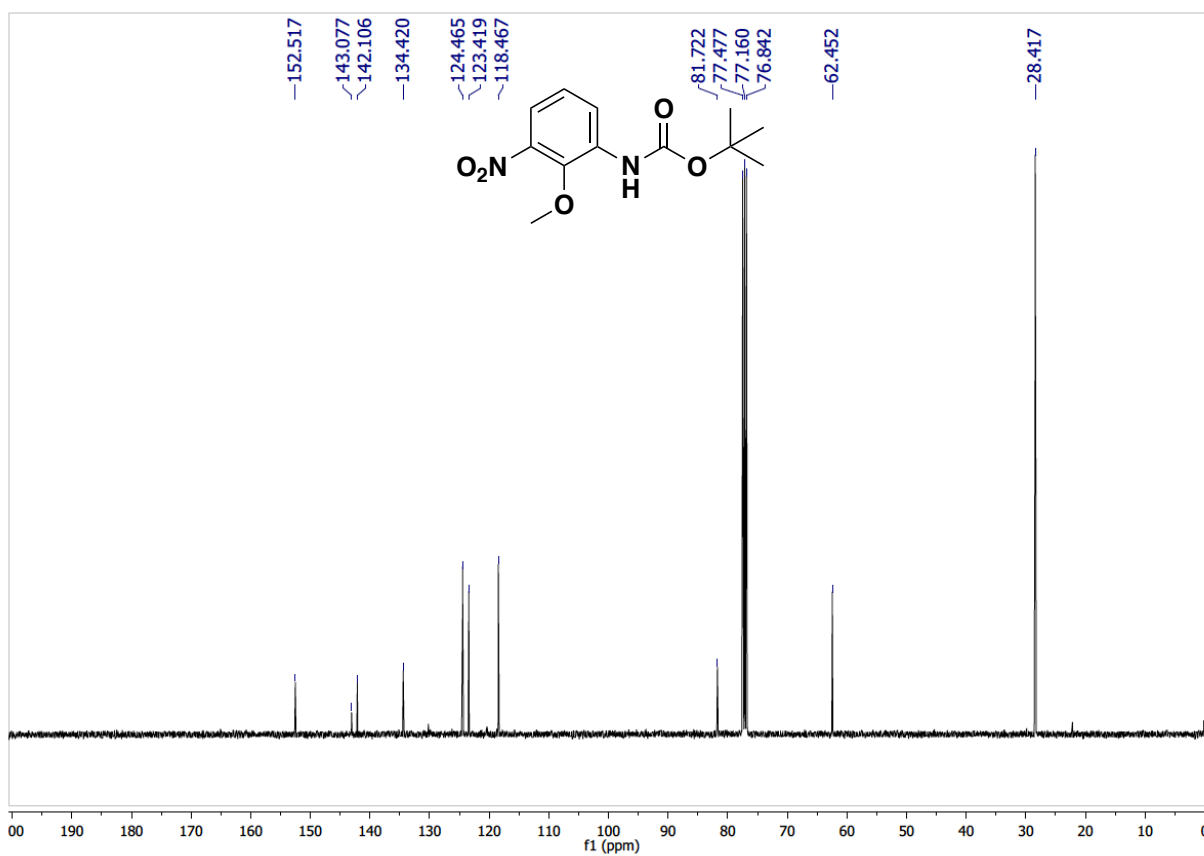
2-Methoxy-3-nitrobenzoic acid (S1)



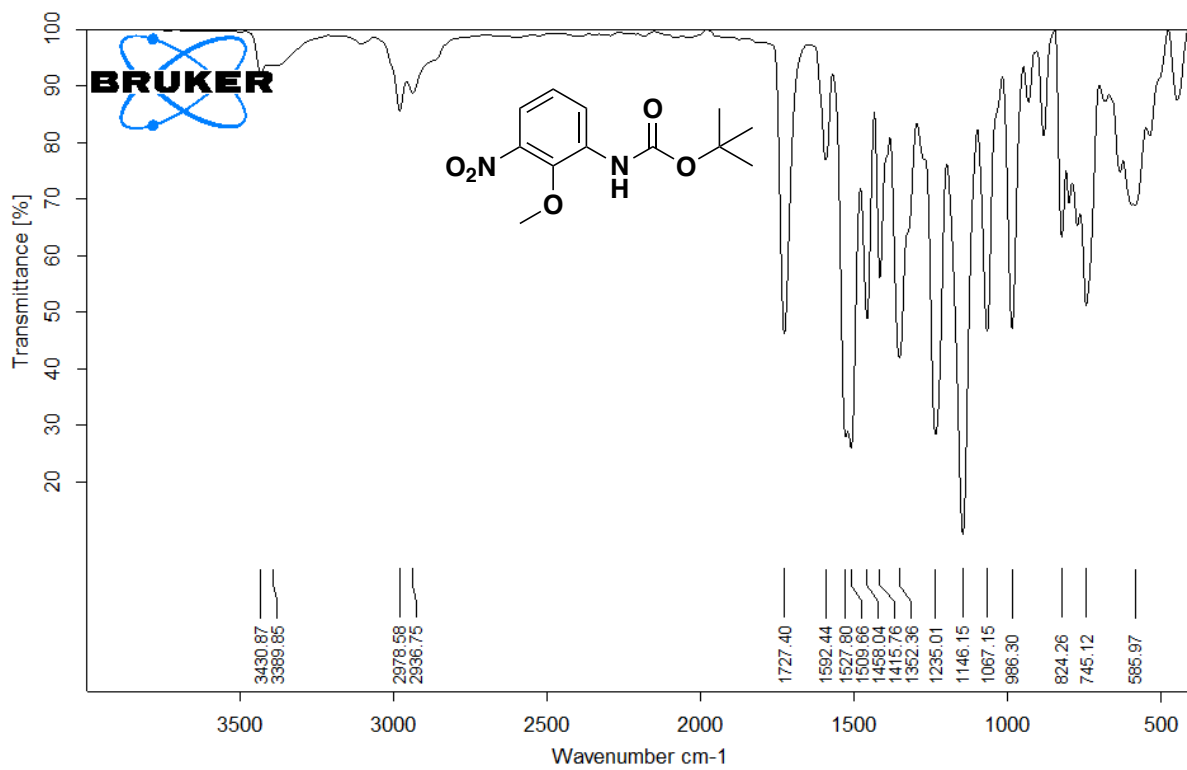
2-Methyl-2-propanyl [2-(methoxy)-3-nitrophenyl] carbamate (S3) in CDCl₃



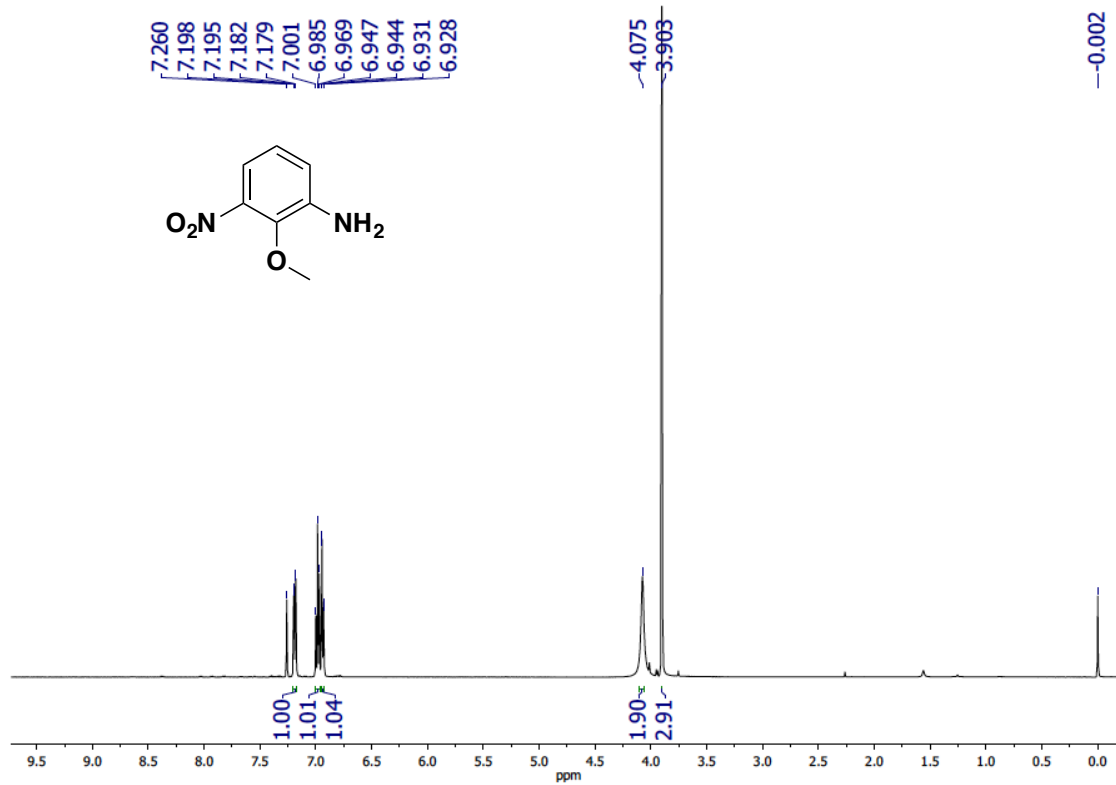
2-Methyl-2-propanyl [2-(methoxy)-3-nitrophenyl] carbamate (S3) in CDCl₃



2-Methyl-2-propanyl [2-(methoxy)-3-nitrophenyl] carbamate (S3)

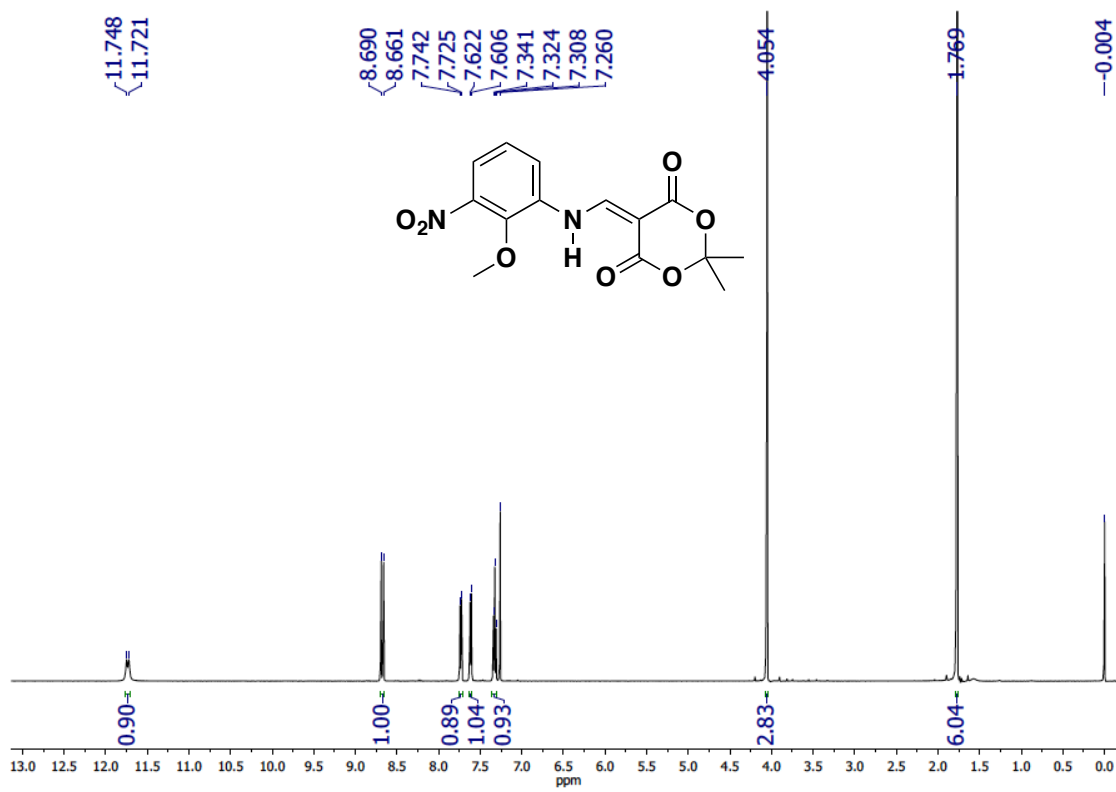


2-Methoxy-3-nitroaniline (S4) in CDCl₃



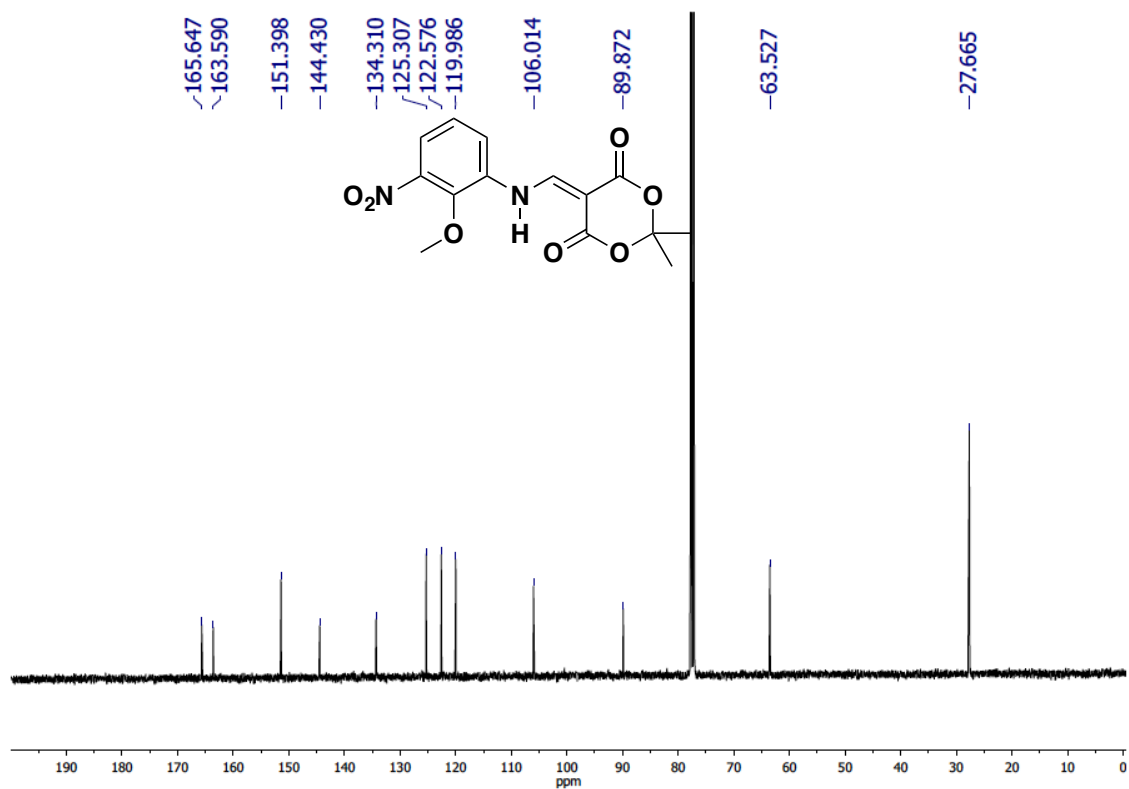
5-[[2-Methoxy-3-nitrophenyl] amino] methyldene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane

(S5) in CDCl₃.



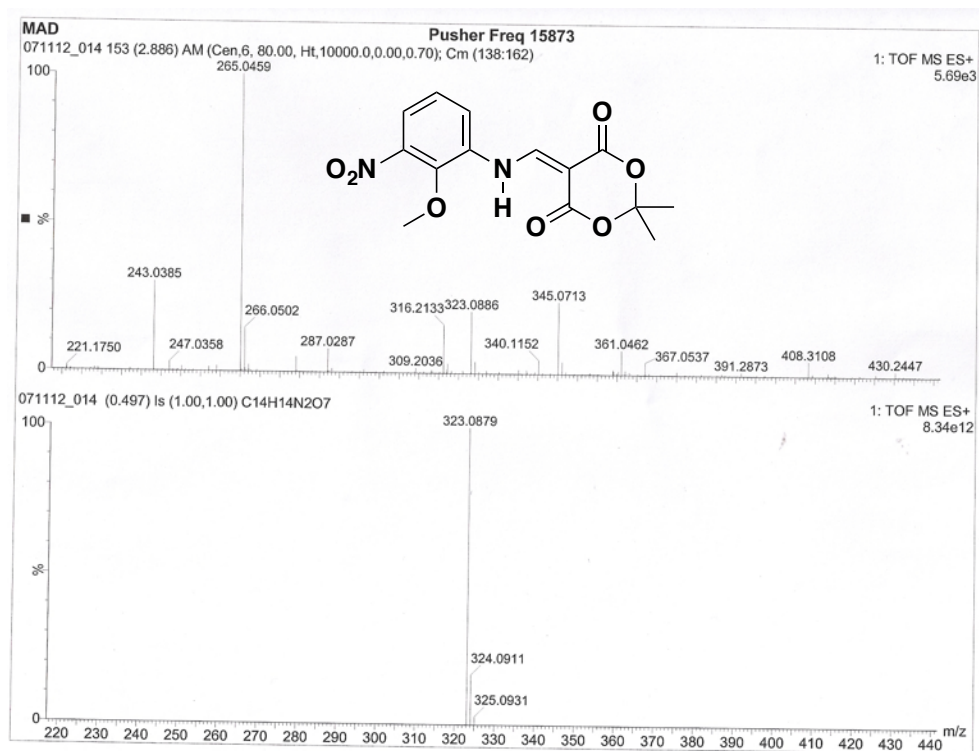
55-[(2-Methoxy-3-nitrophenyl) amino] methylene}-2,2-dimethyl-4,6-dioxo-1,3-dioxane

(S5) in CDCl₃



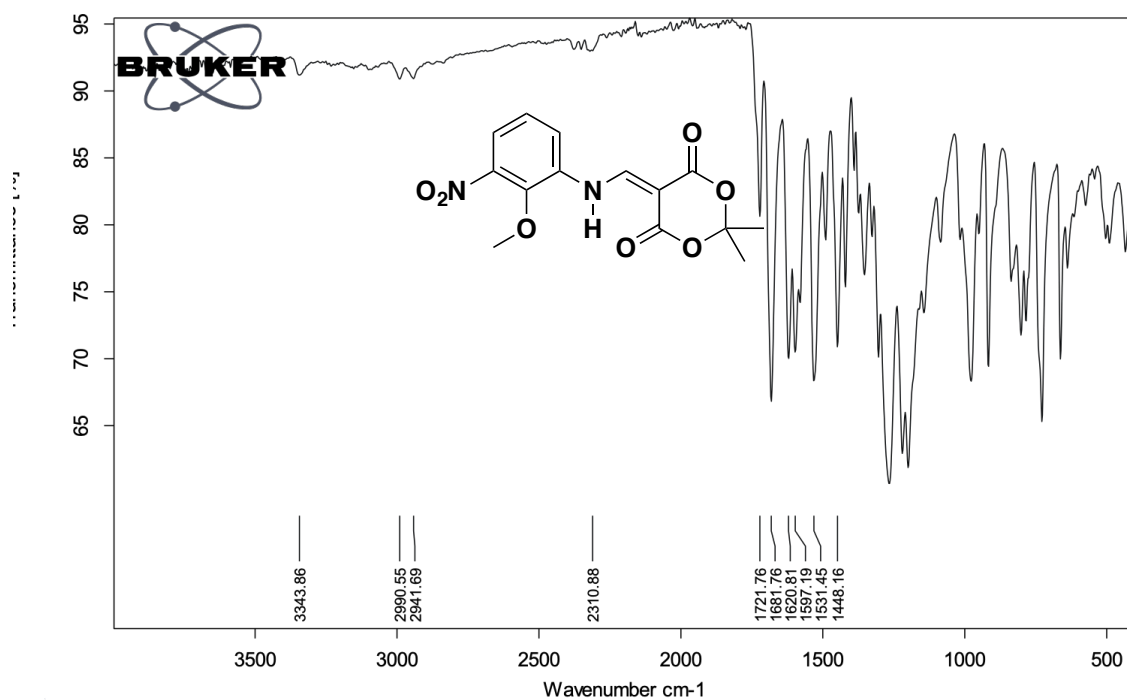
5-[(2-Methoxy-3-nitrophenyl) amino] methyldene}-2,2-dimethyl-4,6-dioxo-1,3-dioxane

(S5)

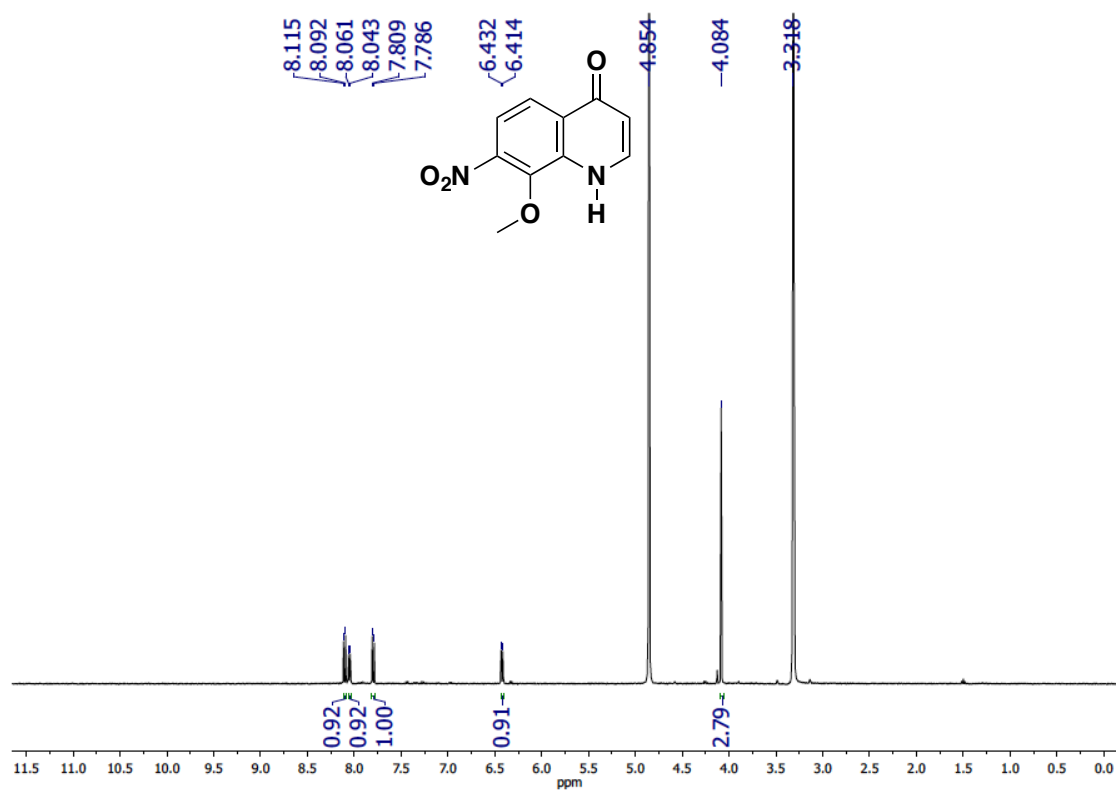


5-[[2-Methoxy-3-nitrophenyl] amino] methyldene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane

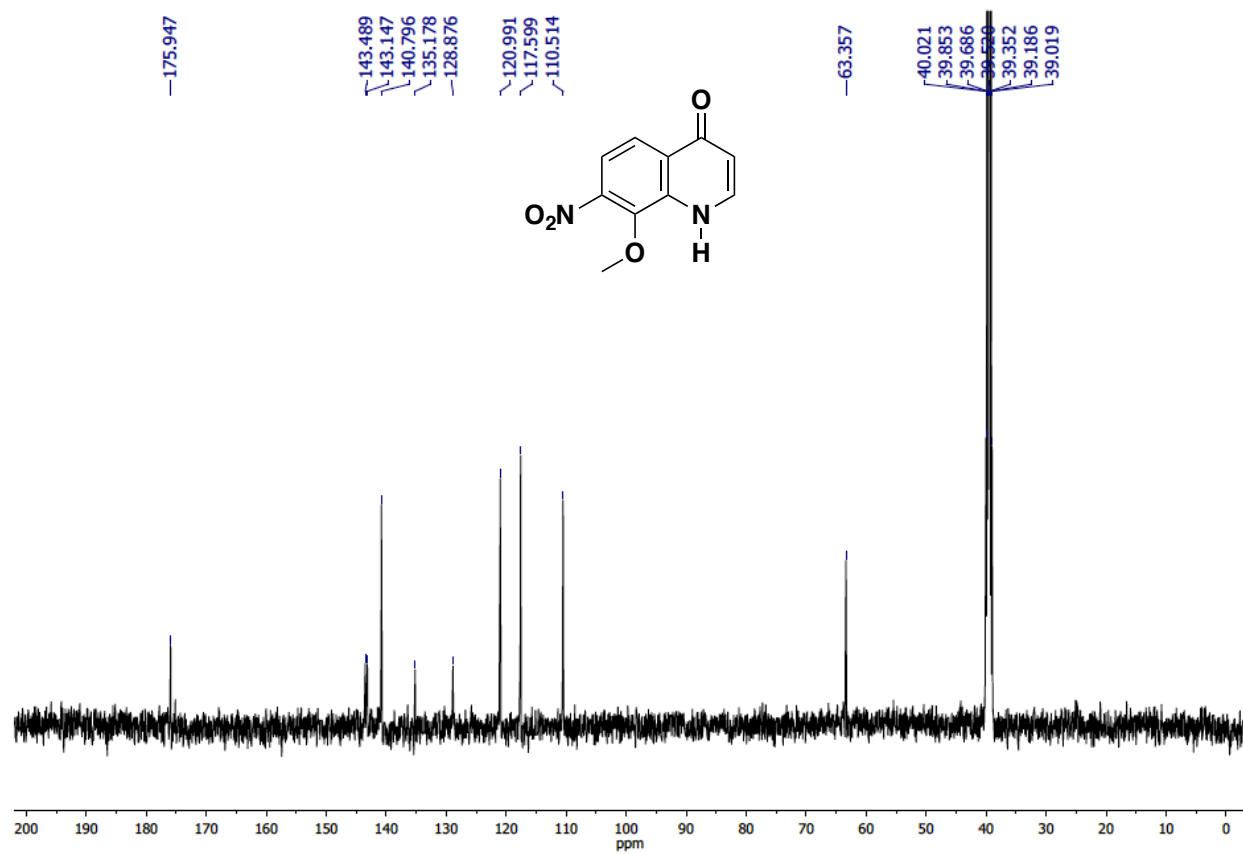
(S5)



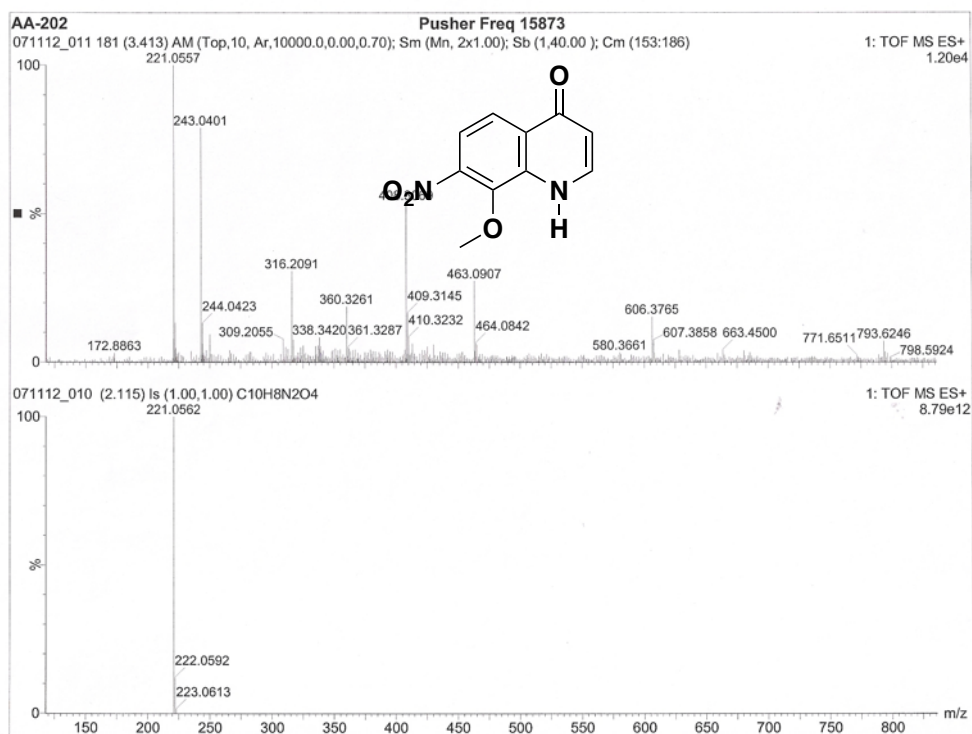
8-Methoxy-7-nitroquinolin-4(1H)-one (S6) in DMSO-d₆



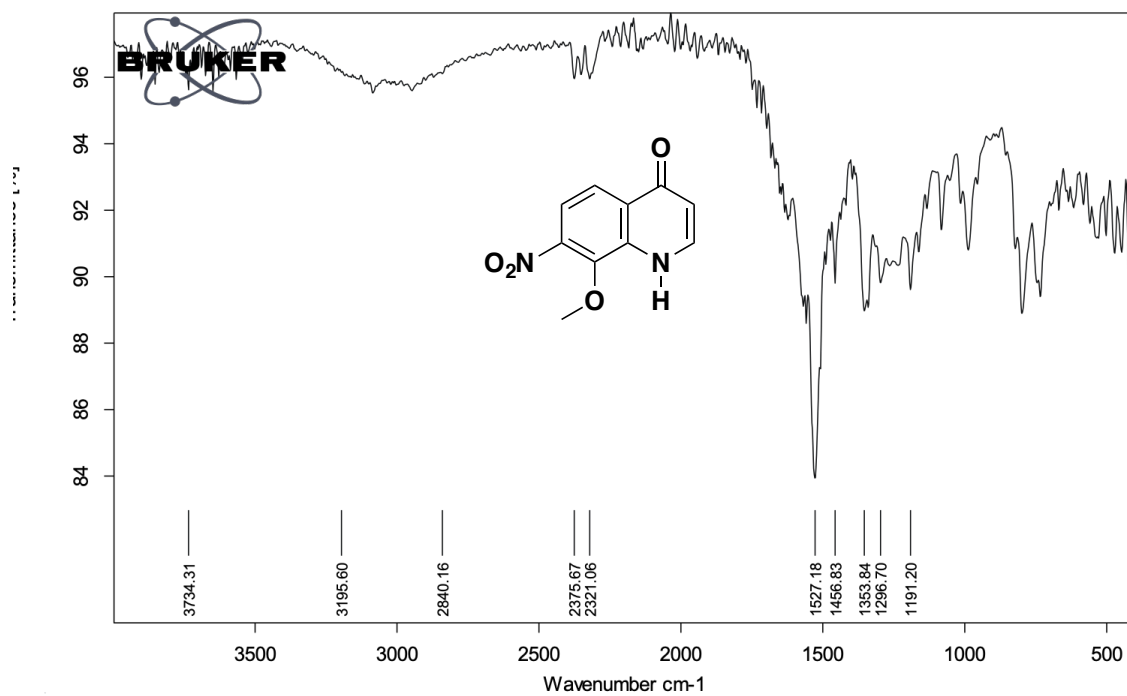
8-Methoxy-7-nitroquinolin-4(1H)-one (S6) in DMSO-d₆



8-Methoxy-7-nitroquinolin-4(1H)-one (S6)

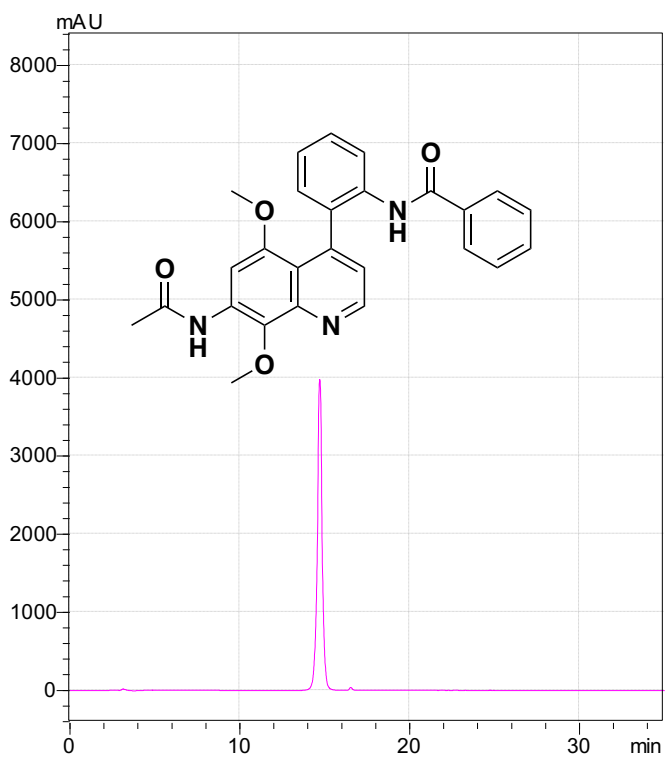


8-Methoxy-7-nitroquinolin-4(1H)-one (S6) DMSO

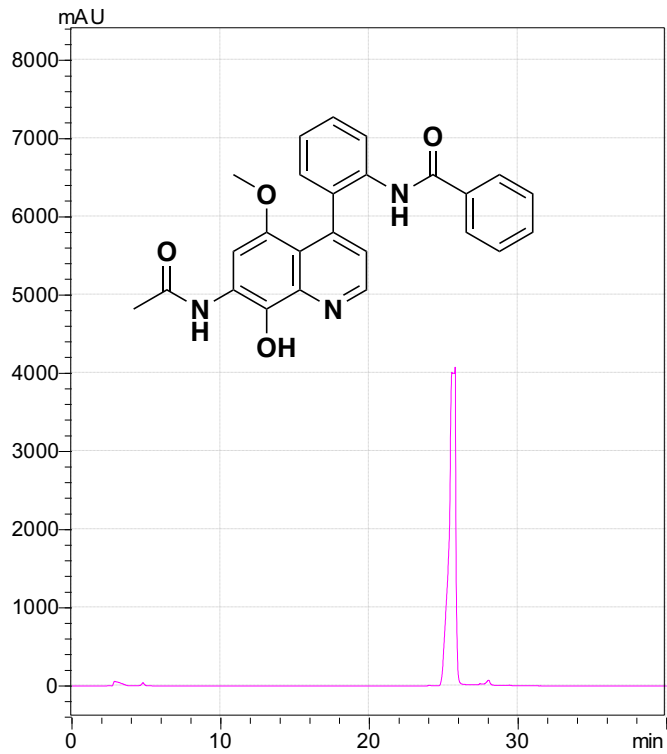


HPLC trace of final analogs

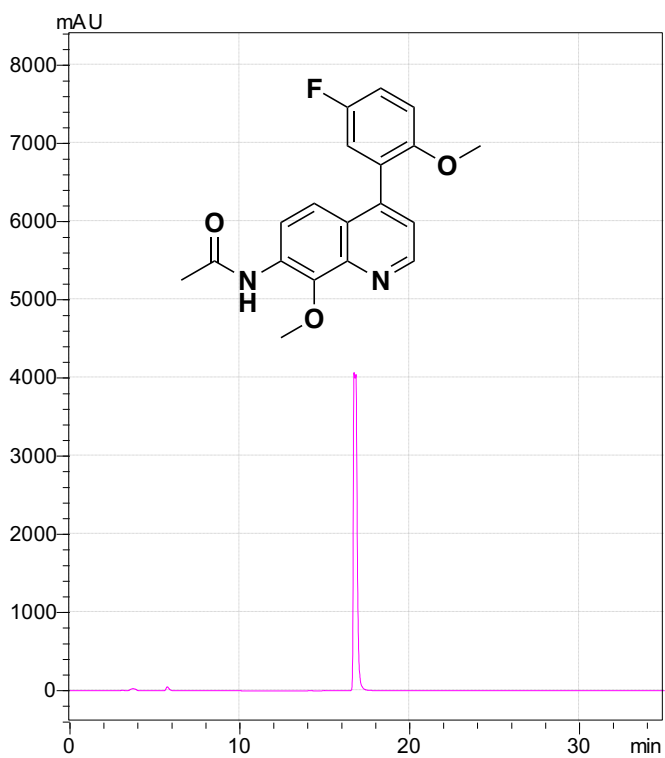
7-Acetamido-4-(2-benzamidophenyl)-8-methoxyquinoline (2)



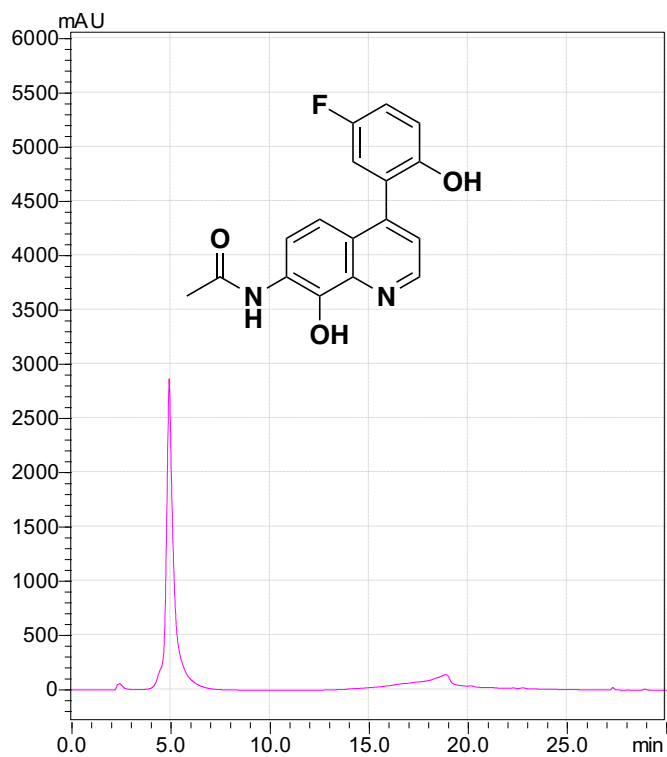
7-Acetamido-4-(2-benzamidophenyl)-8-hydroxyquinoline (3)



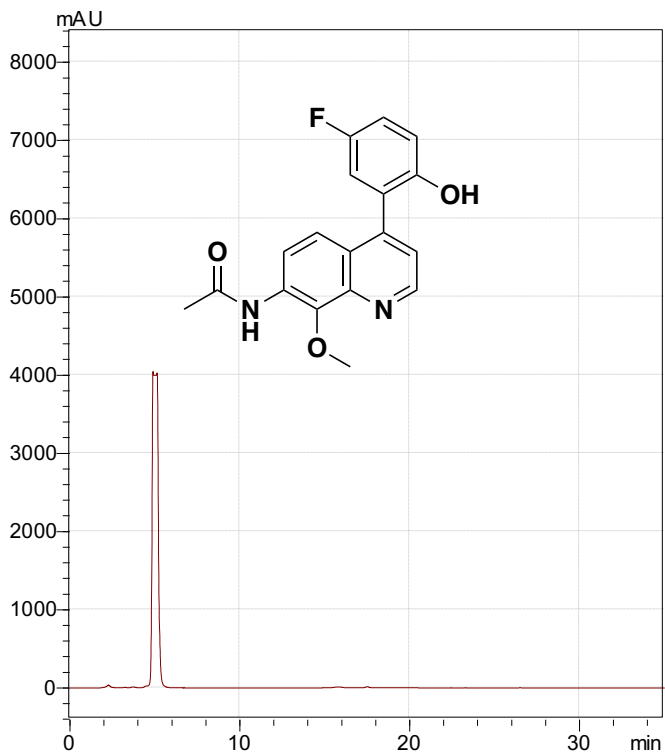
7-Acetamido-4-(5-fluoro-2-methoxyphenyl)-8-methoxyquinoline (6)



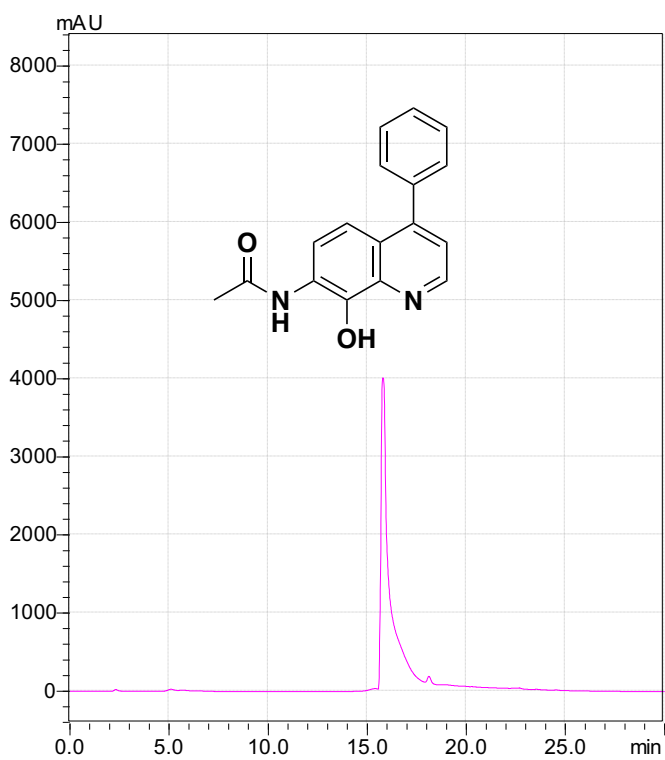
7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-hydroxyquinoline (7)



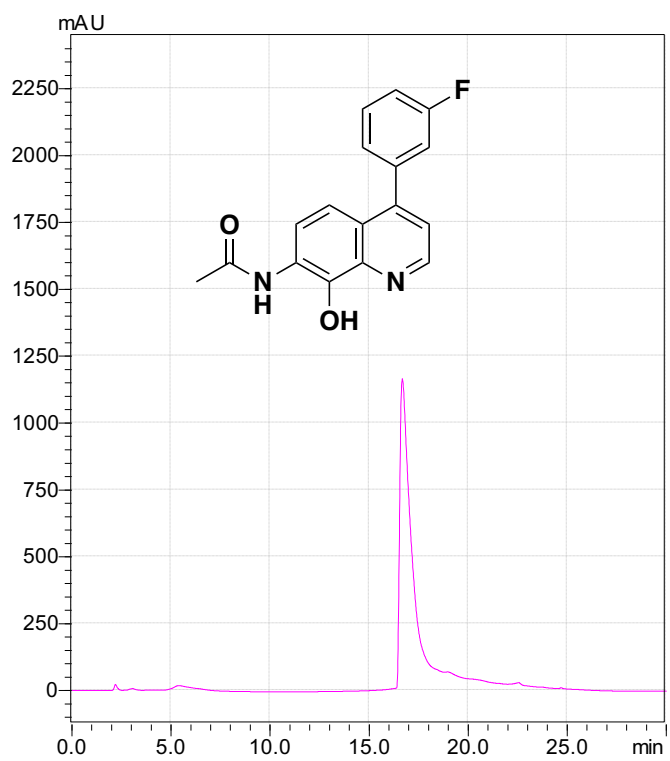
7-Acetamido-4-(5-fluoro-2-hydroxyphenyl)-8-methoxyquinoline (20)



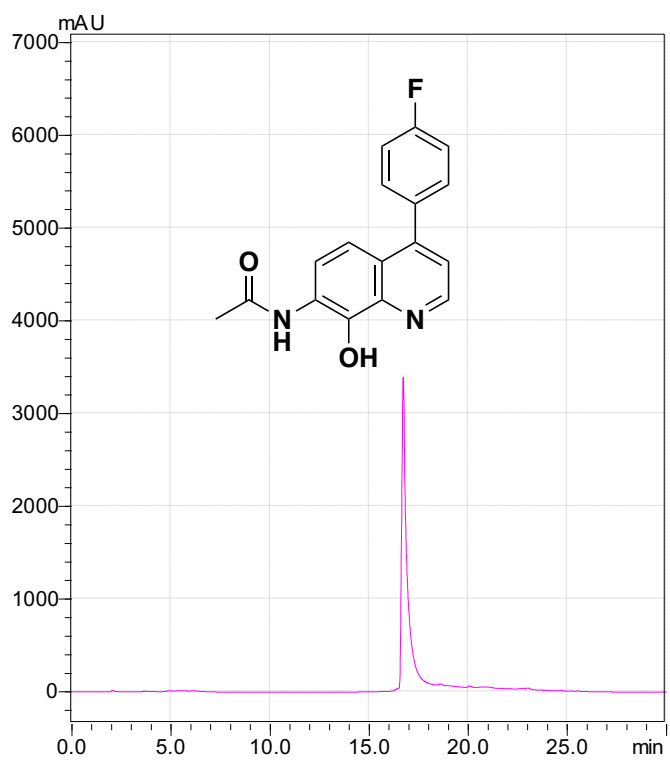
7-Acetamido-4-(phenyl)-8-hydroxyquinoline (28)



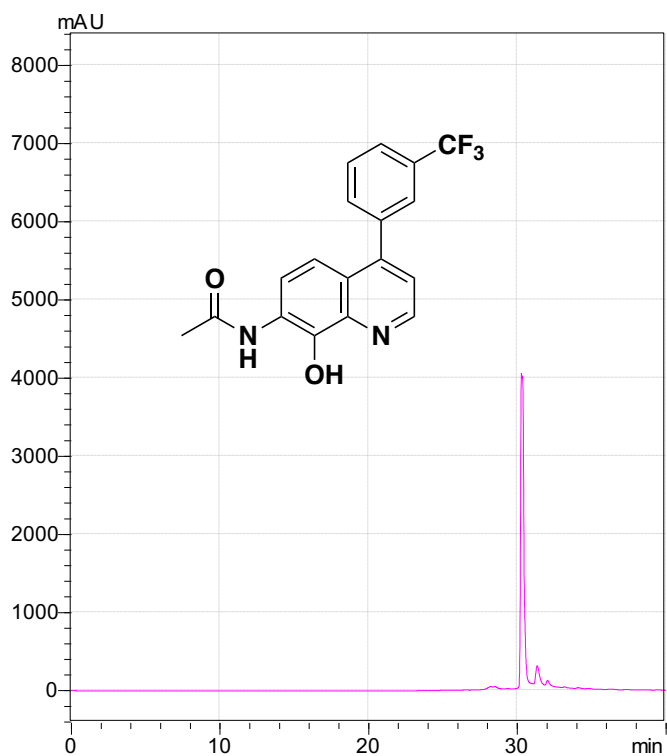
7-Acetamido-4-(3-fluorophenyl)-8-hydroxyquinoline (29)



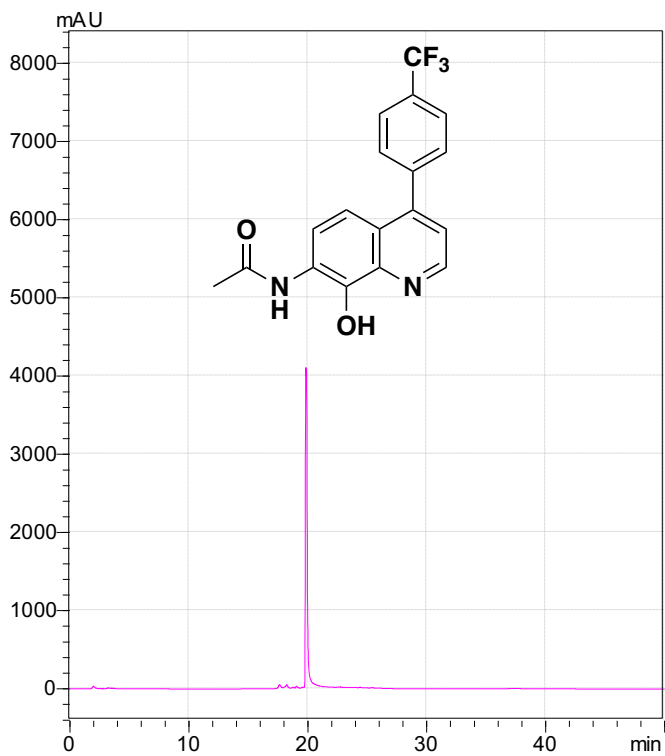
7-Acetamido-4-(4-fluorophenyl)-8-hydroxyquinoline (30)



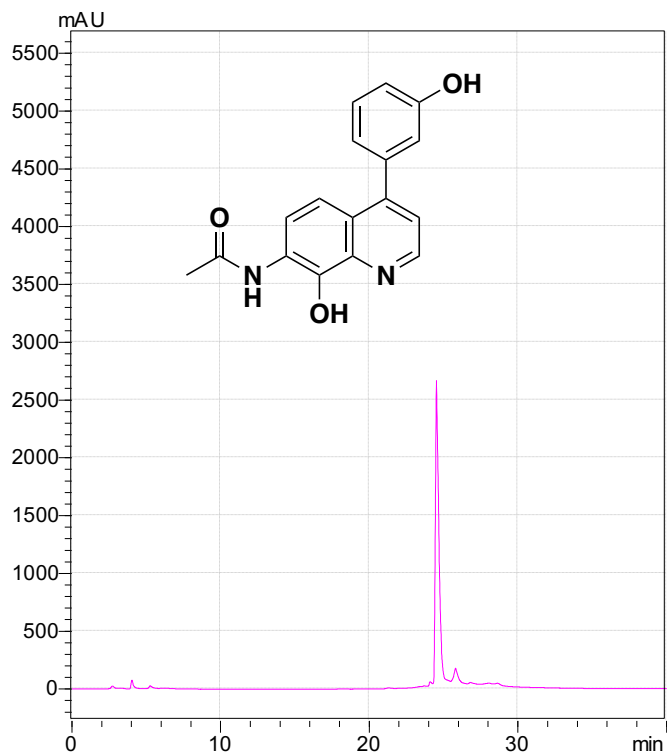
7-Acetamido-4-((3-trifluoromethyl)phenyl)-8-hydroxyquinoline (31).



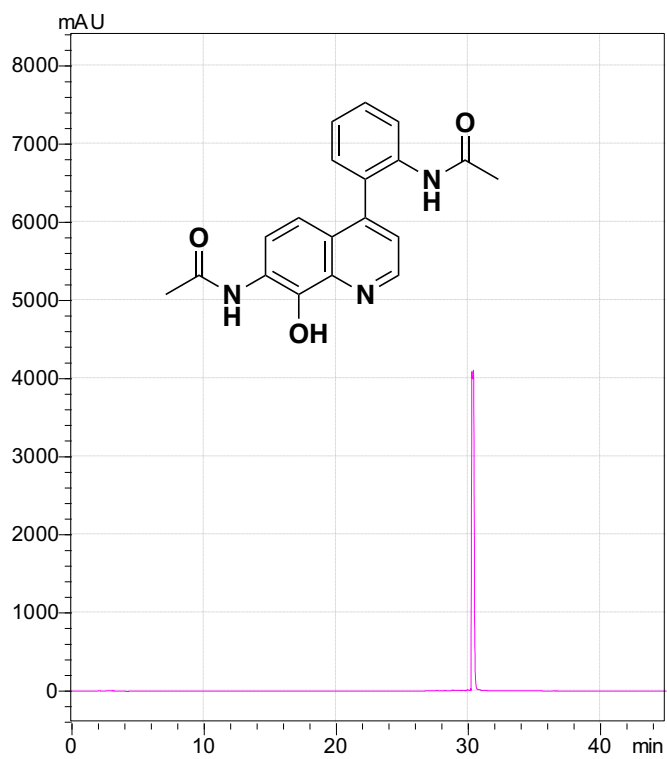
7-Acetamido-4-((4-trifluoromethyl)phenyl)-8-hydroxyquinoline (32)



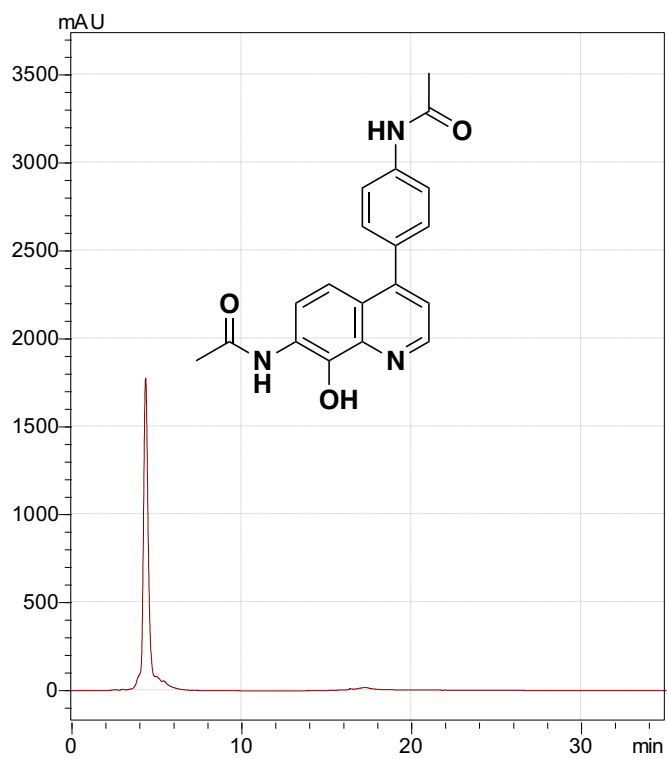
7-Acetamido-4-(3-hydroxyphenyl)-8-hydroxyquinoline (33).



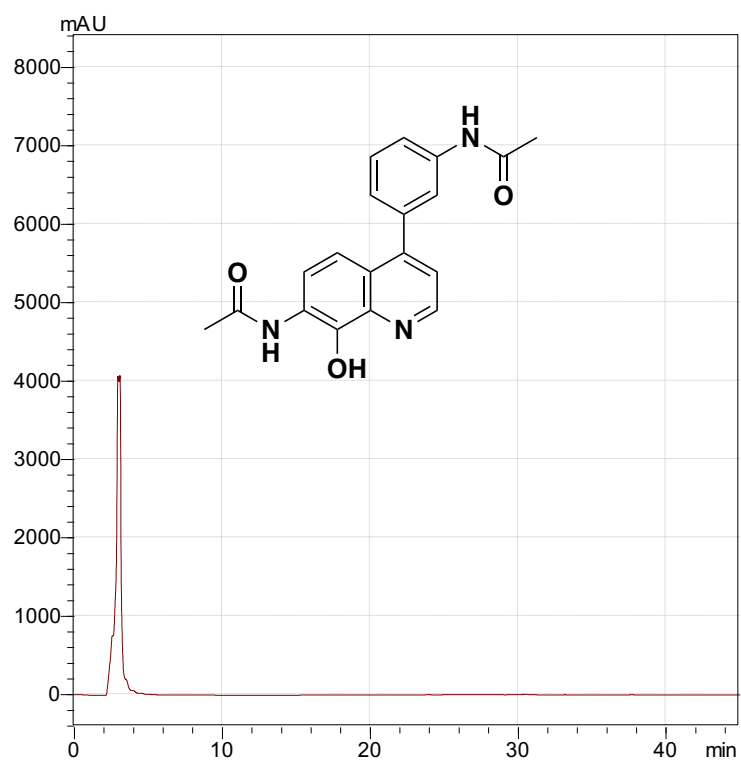
7-Acetamido-4-(2-acetamidophenyl)-8-hydroxyquinoline (34).



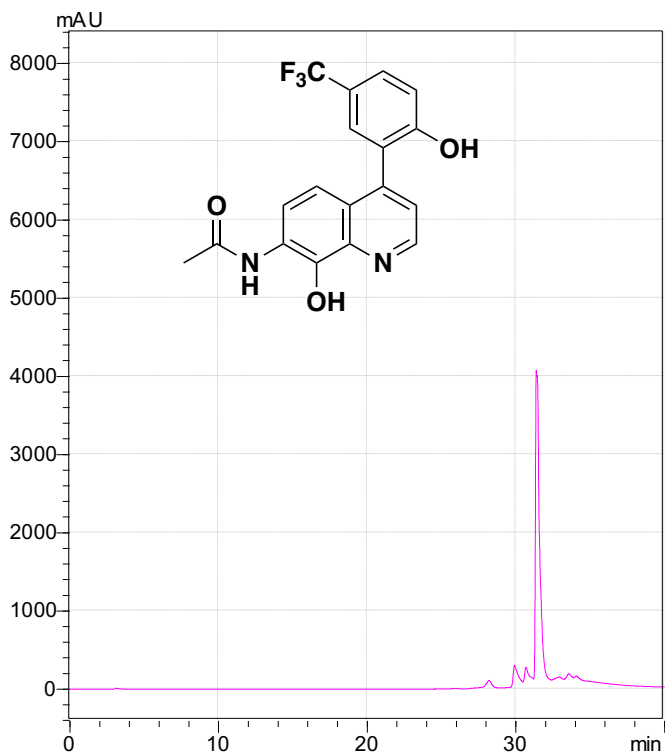
7-Acetamido-4-(4-acetamidophenyl)-8-hydroxyquinoline (35)



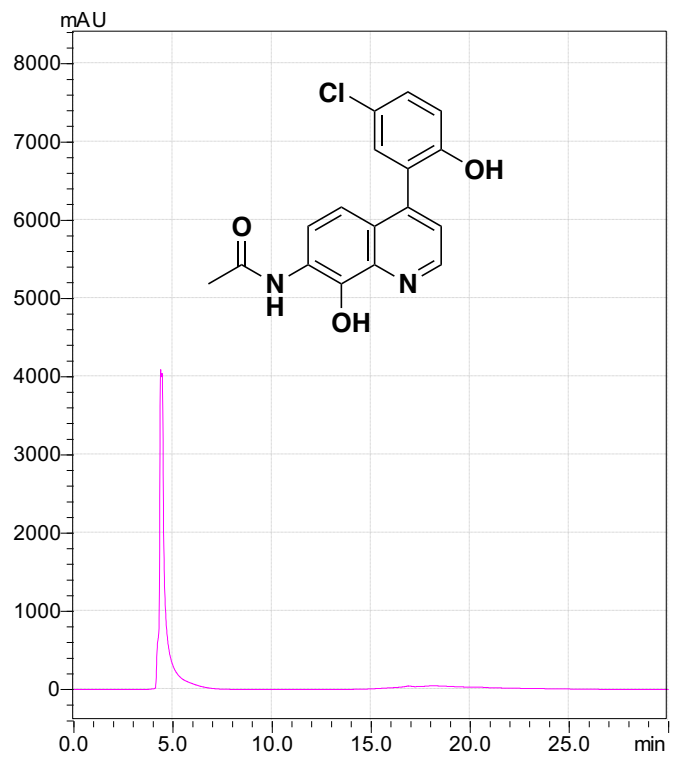
7-Acetamido-4-(3-acetamidophenyl)-8-hydroxyquinoline (36)



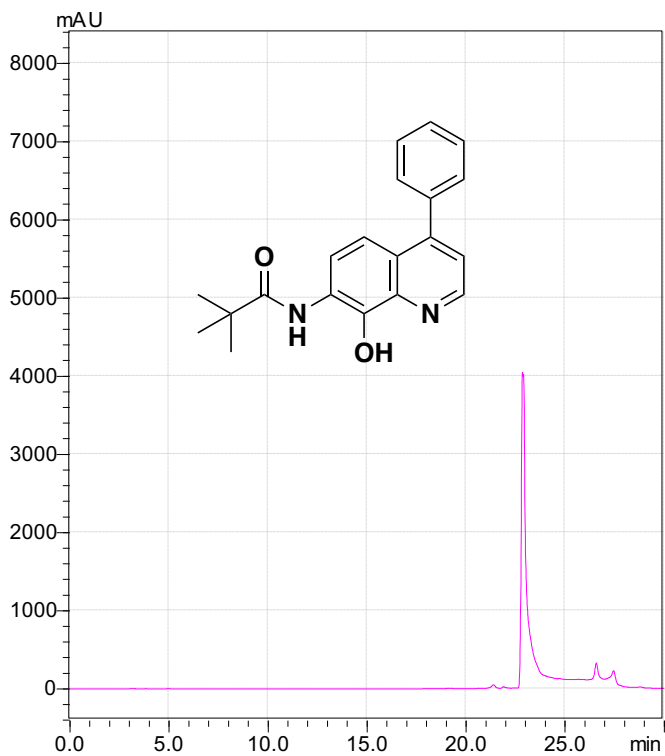
7-Acetamido-4-(2-hydroxy-(5-trifluoromethyl)phenyl)-8-hydroxyquinoline (37)



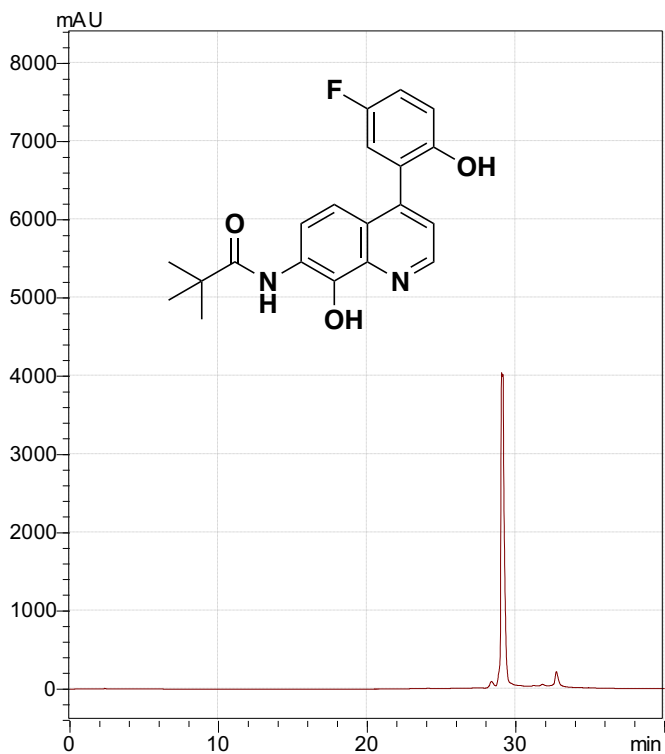
7-Acetamido-4-(5-chloro-2-hydroxyphenyl)-8-hydroxyquinoline (38)



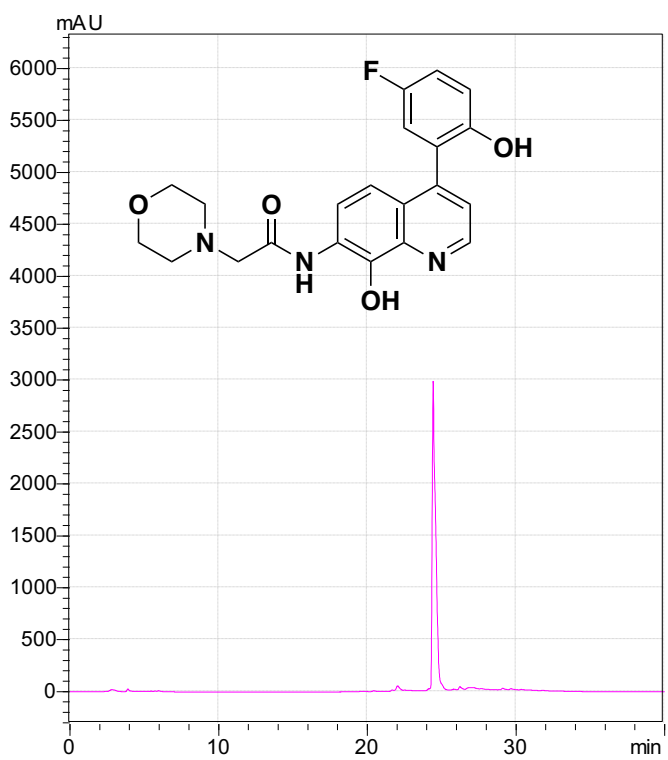
4-(Phenyl)-8-hydroxy-7-pivalamidoquinoline (39)



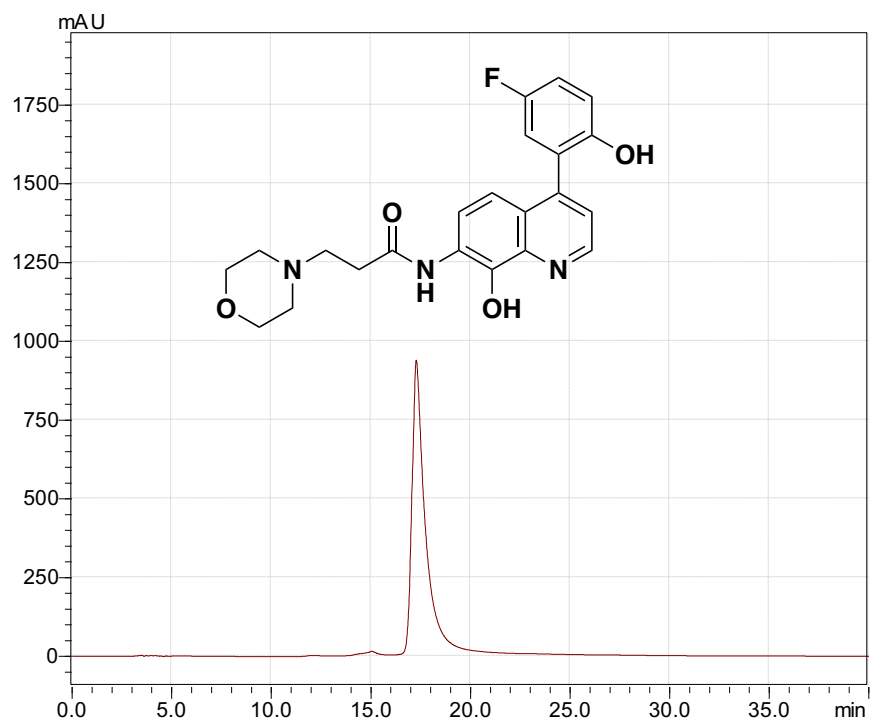
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-pivalamido-quinoline (40)



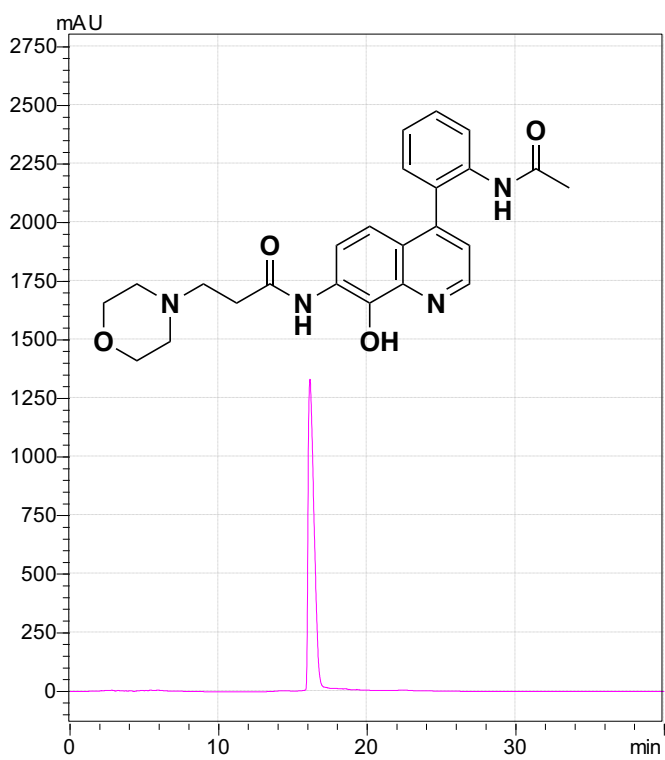
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (41).



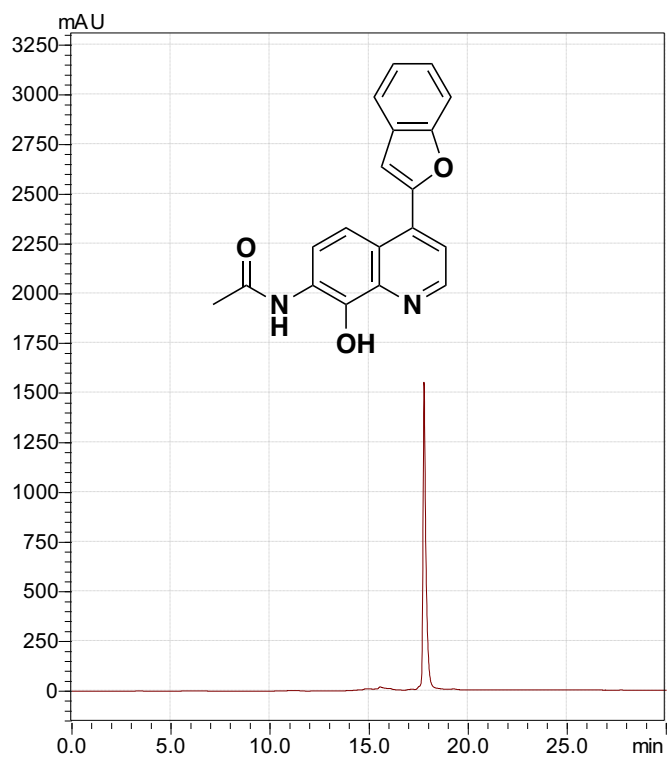
4-(5-fluoro-2-hydroxyphenyl)-8-hydroxy-7-(2-(morpholin-4-yl)propanamido)quinoline (42).



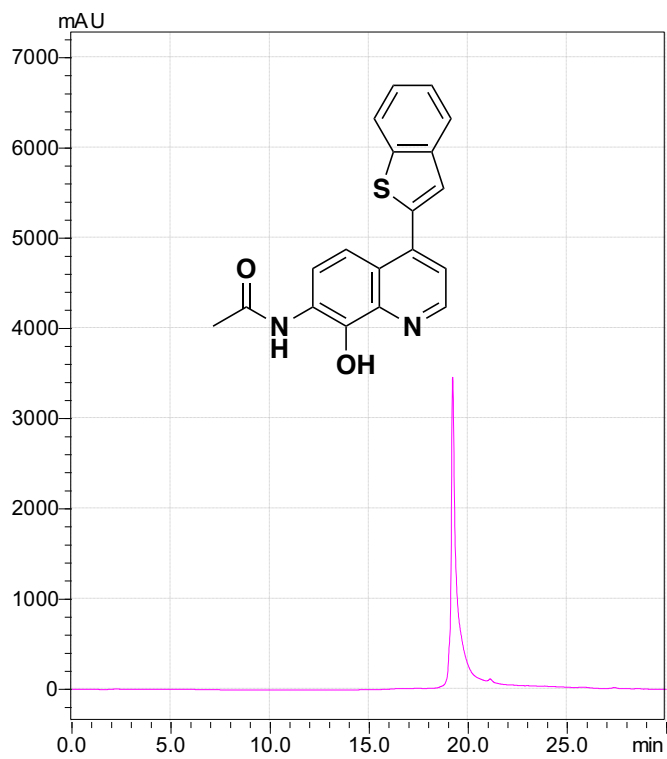
4-(2-Acetamidophenyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (43).



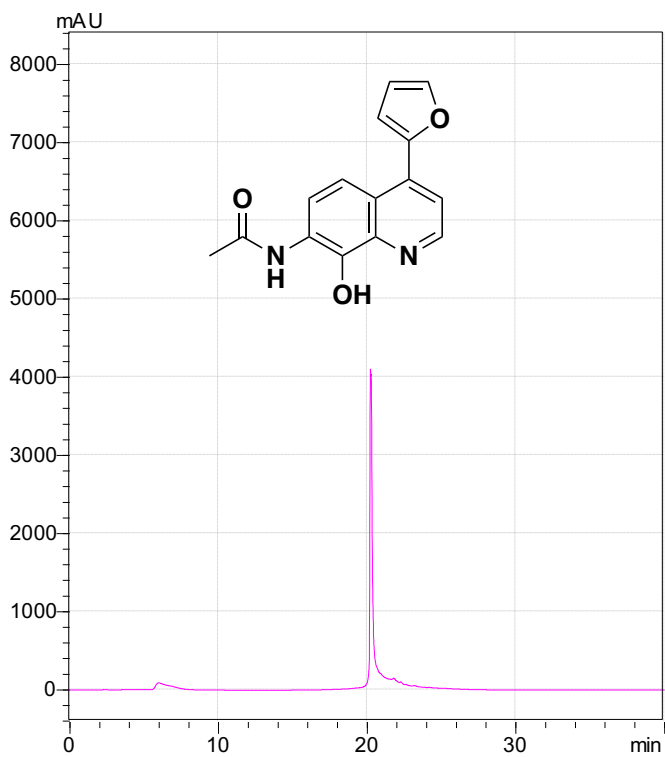
7-Acetamido-4-(2-benzofuranyl)-8-hydroxyquinoline (53)



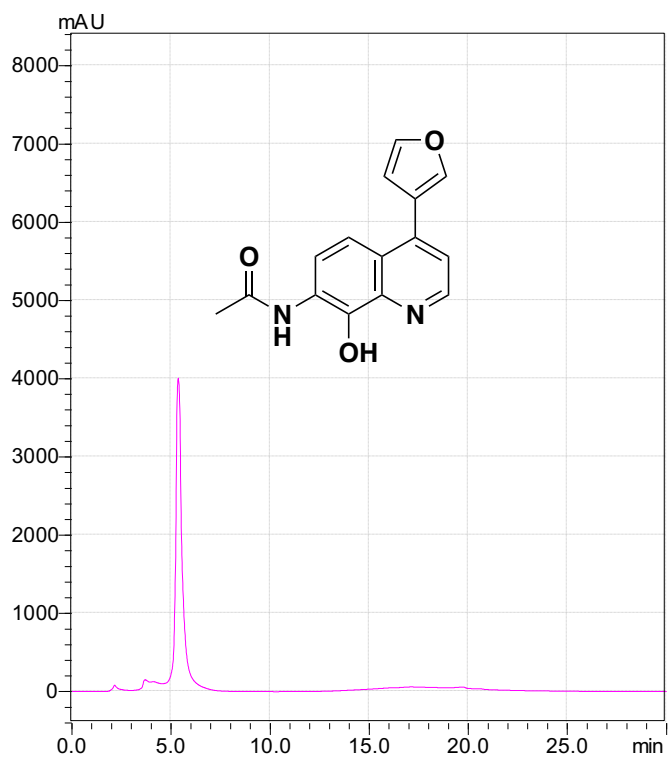
7-Acetamido-4-(benzo[b]thiophen-2-yl)-8-hydroxyquinoline (54)



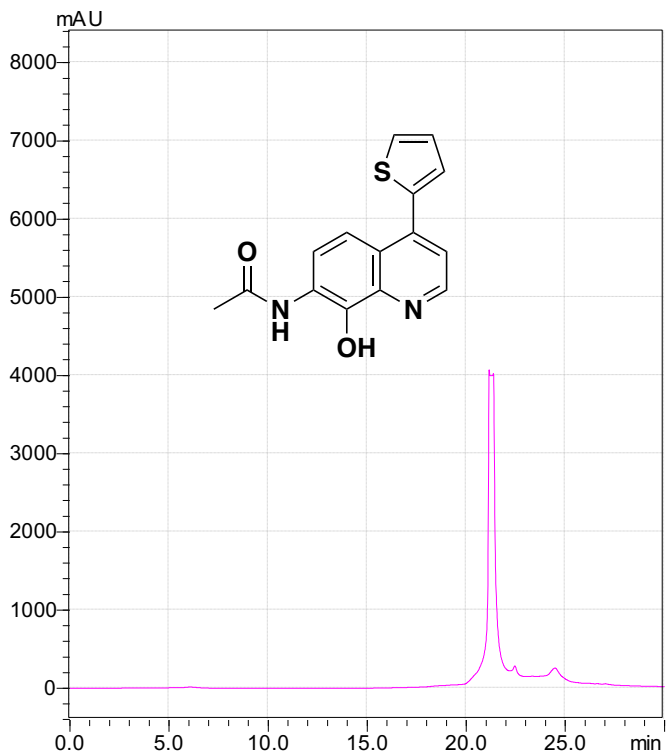
7-Acetamido-4-(2-furanyl)-8-hydroxyquinoline (55)



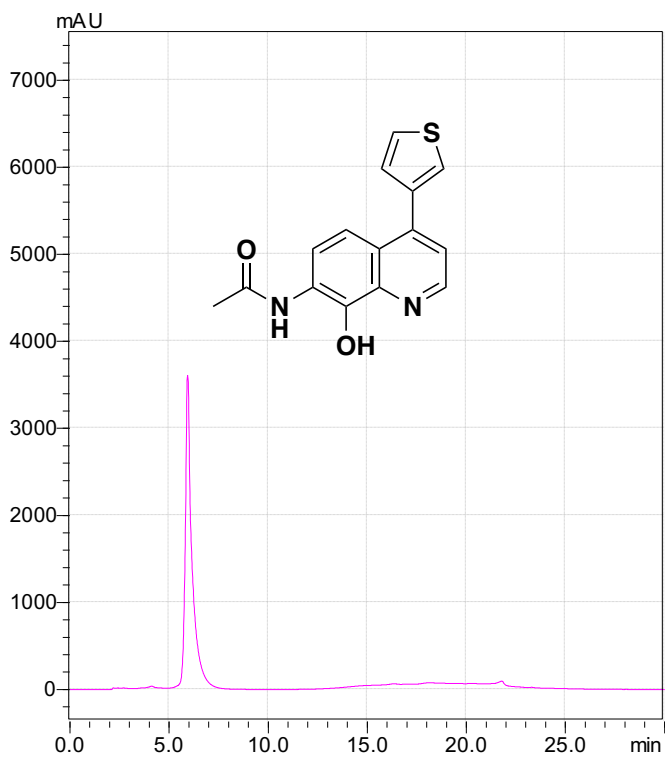
7-Acetamido-4-(3-furanyl)-8-hydroxyquinoline (56)



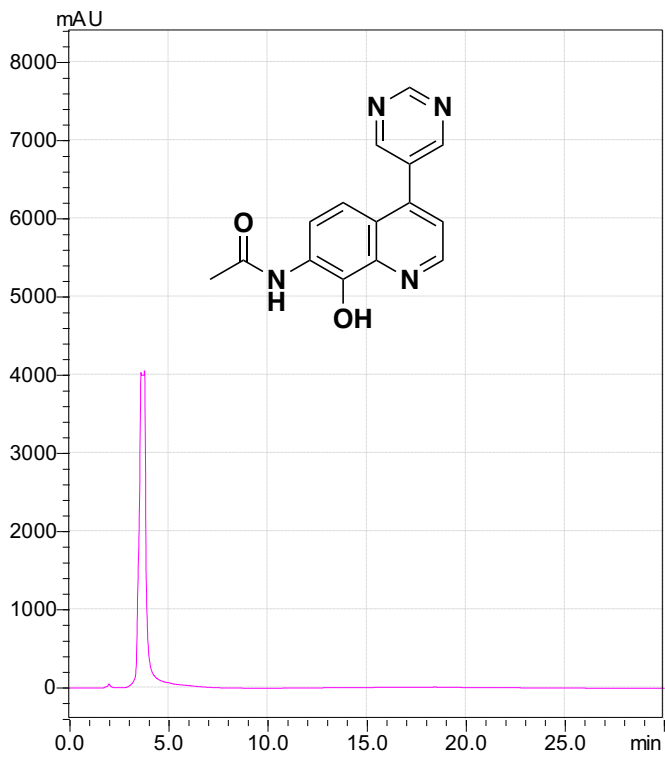
7-Acetamido-4-(thiophen-2-yl)-8-hydroxyquinoline (57)



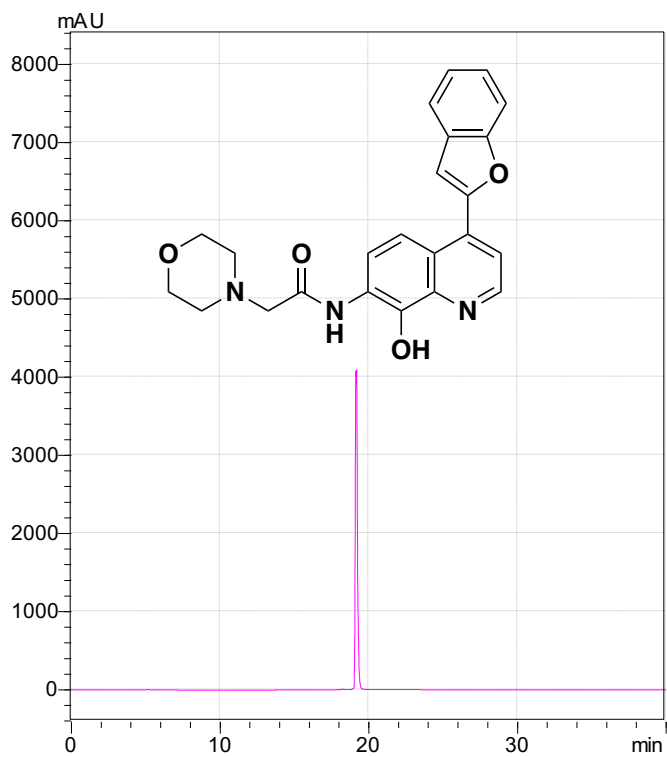
7-Acetamido-4-(thiophen-3-yl)-8-hydroxyquinoline (58)



7-Acetamido-4-(5-pyrimidinyl)-8-hydroxyquinoline (59)



4-(2-benzofuranyl)-8-hydroxy-7-(2-(morpholin-4-yl)acetamido)quinoline (60)



4-(2-benzofuranyl)-8-hydroxy-7-(3-(morpholin-4-yl)propanamido)quinoline (61)

