

Supplementary Information

Ortho-quinone methide driven synthesis of kynurenic acid lactams

Julián Robin Sárík^a, Anasztázia Hetényi^b, Róbert Berkecz^{c,d}, István Szatmári^{a,c,*} and Bálint Lőrinczi^{a,*}

^aInstitute of Pharmaceutical Chemistry, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary

^bDepartment of Medical Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary

^cInstitute of Pharmaceutical Analysis, University of Szeged, H-6720 Szeged, Somogyi u. 4, Hungary

^dDepartment of Forensic Medicine, Albert Szent-Györgyi Health Centre, H-6724 Szeged, Kossuth Lajos sgt. 40, Hungary

^eHUN-REN SZTE Stereochemistry Research Group, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary

Contents

1. ¹ H, ¹³ C, HSQC and HMBC NMR spectra of synthesized compounds	2.
2. HR-MS spectra of synthesized compounds	39.

4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide (7a):

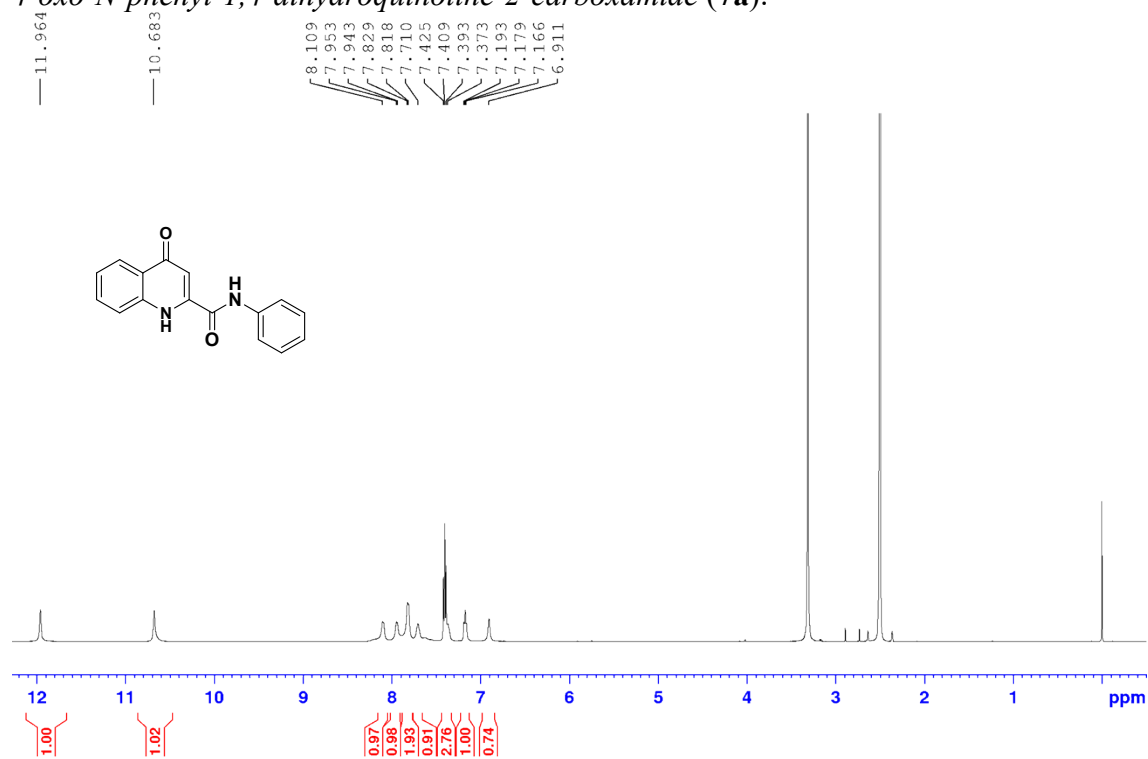


Figure S1. ¹H-NMR spectrum of 7a

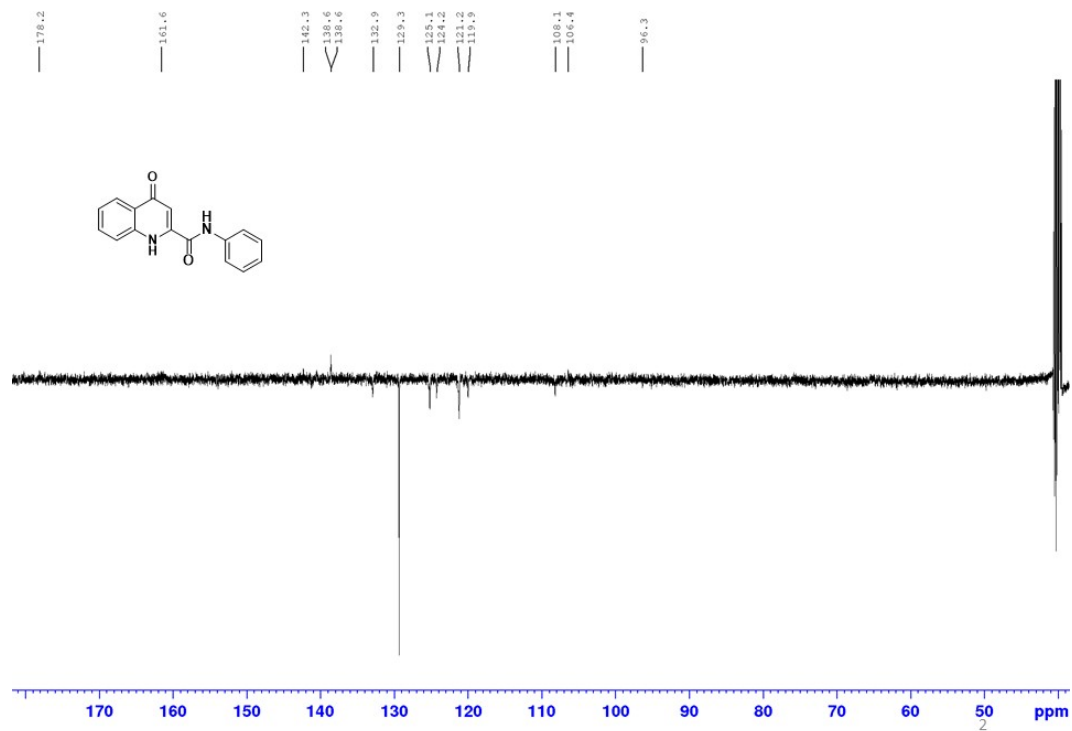
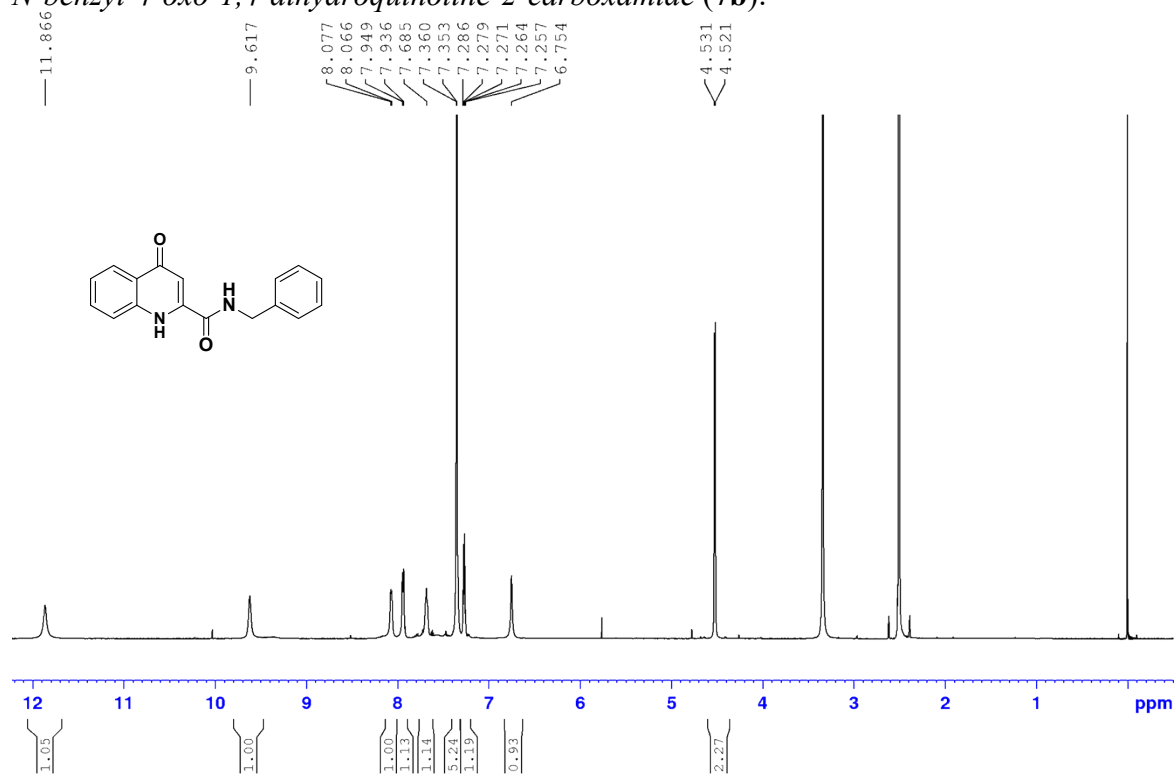


Figure S2. ¹³C-NMR spectrum of 7a

N-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxamide (**7b**):



e S3. ¹H-NMR spectrum of **7b**

Figur

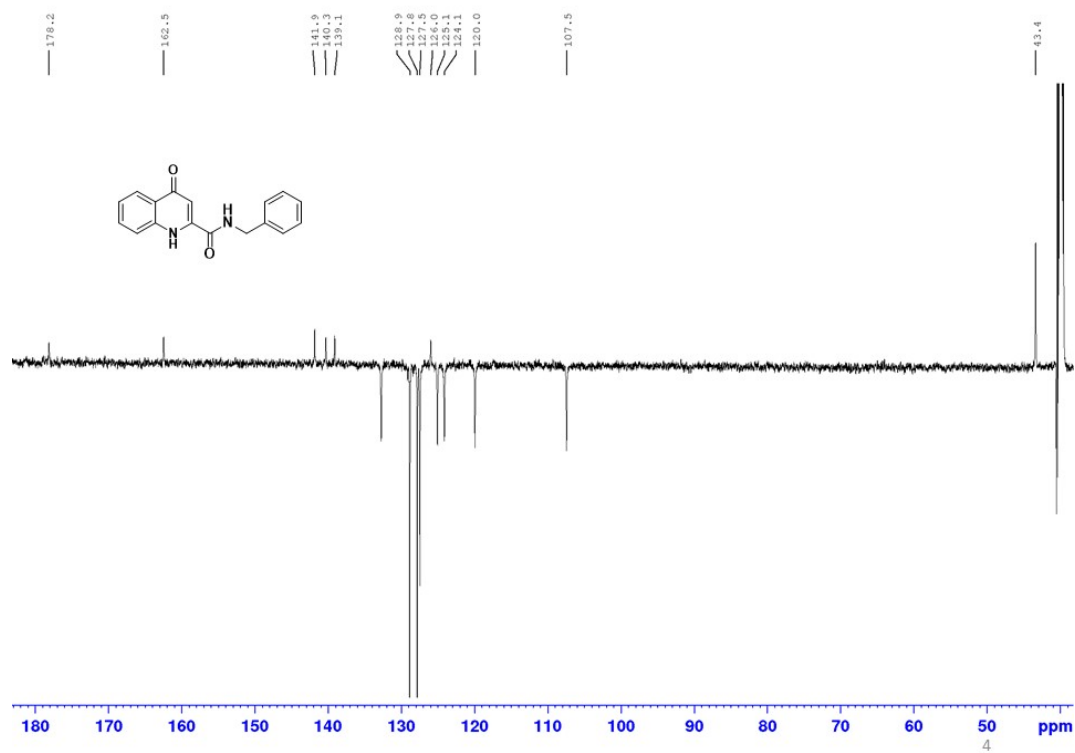
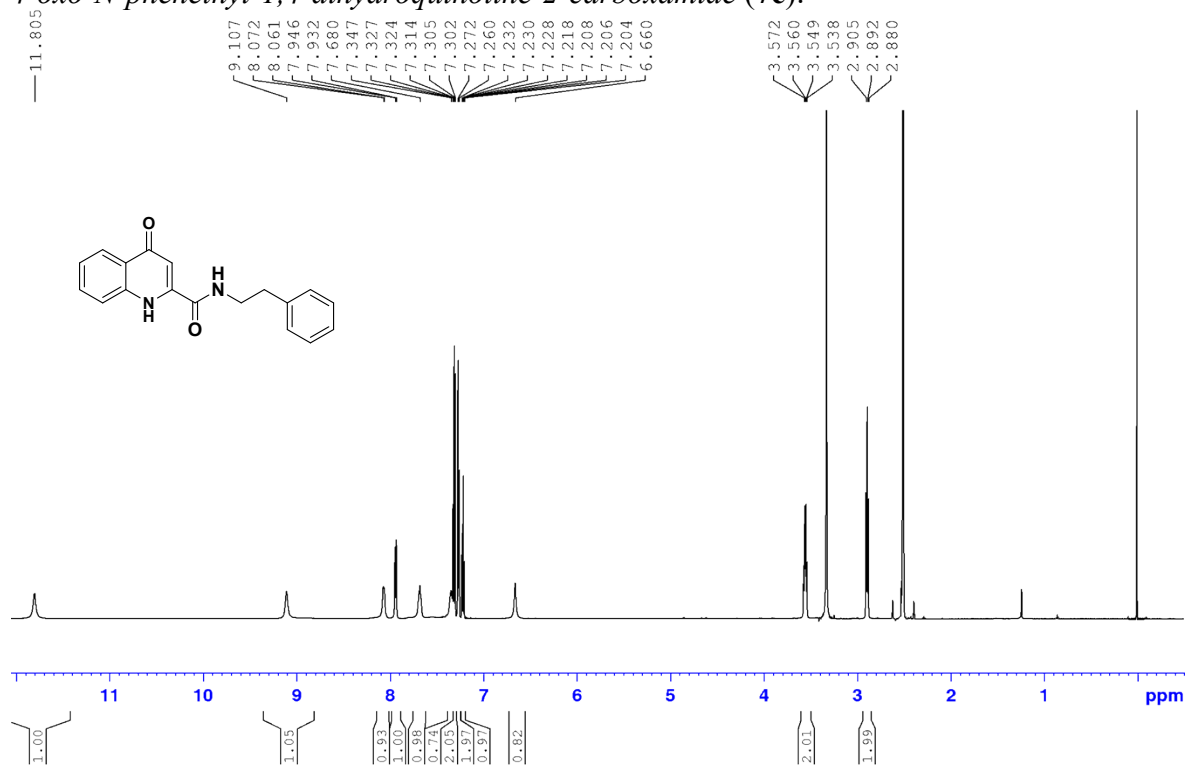


Figure S4. ¹³C-NMR spectrum of **7b**

4-oxo-N-phenethyl-1,4-dihydroquinoline-2-carboxamide (**7c**):



Figure

e S5. ¹H-NMR spectrum of **7c**

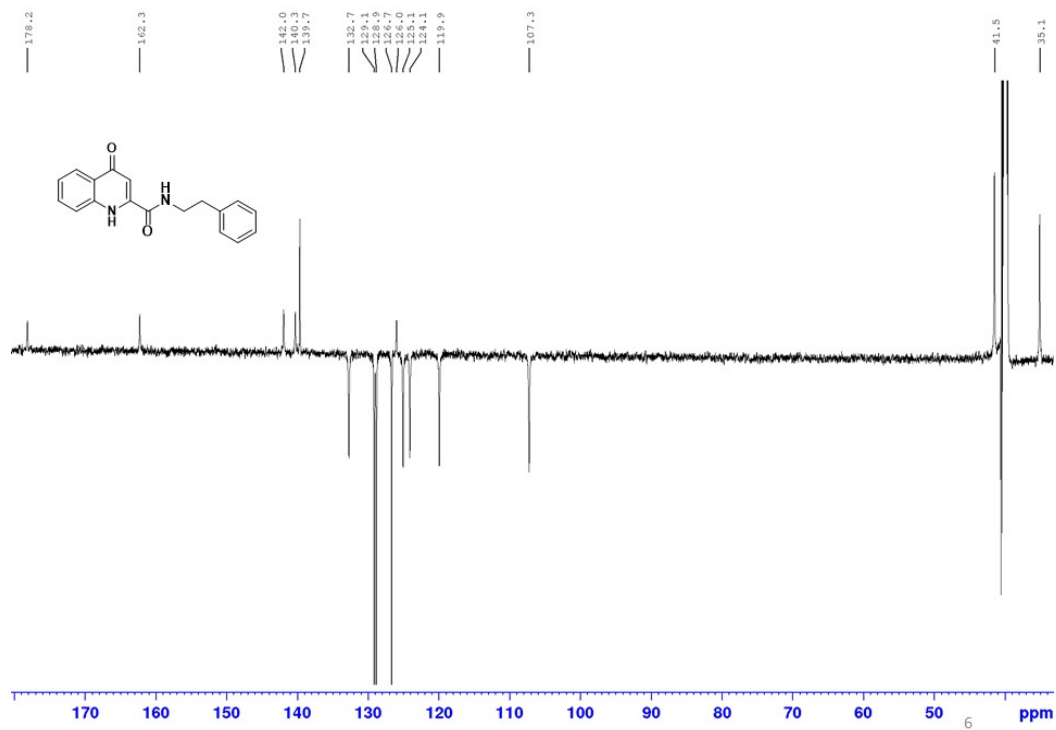
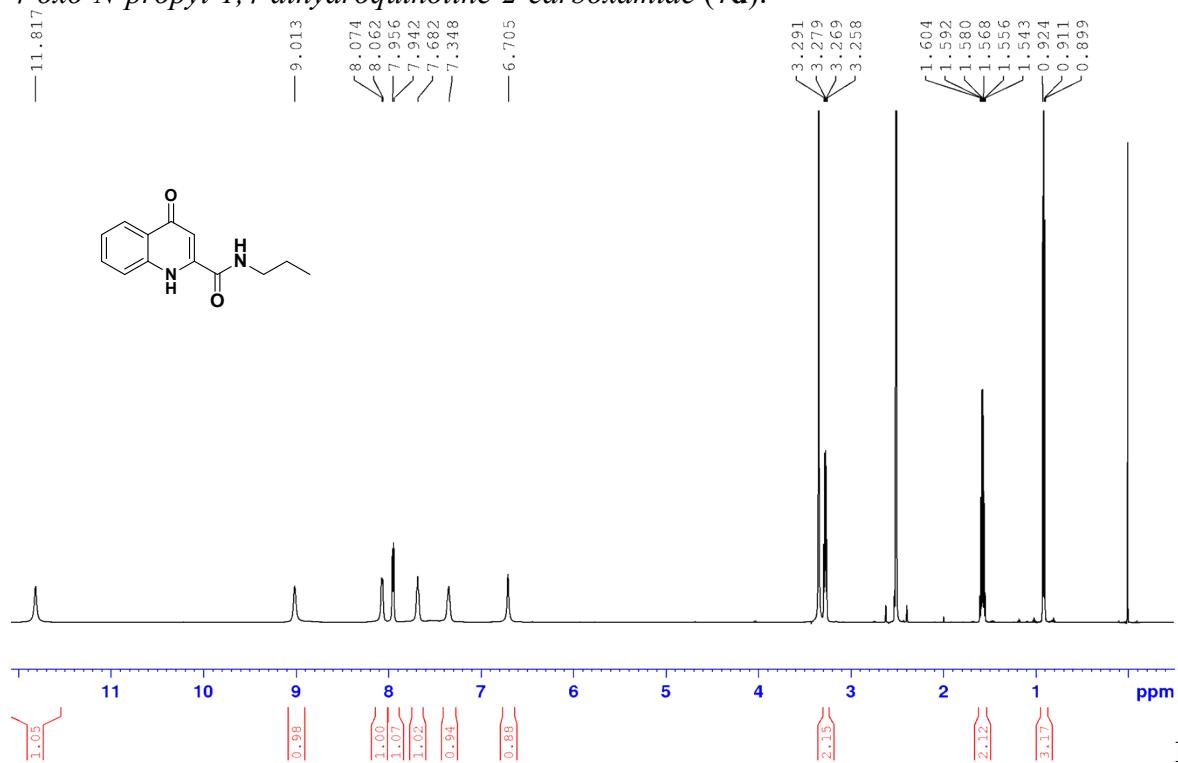


Figure S6. ¹³C-NMR spectrum of **7c**

4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide (7d):



e S7. ¹H-NMR spectrum of 7d

Figur

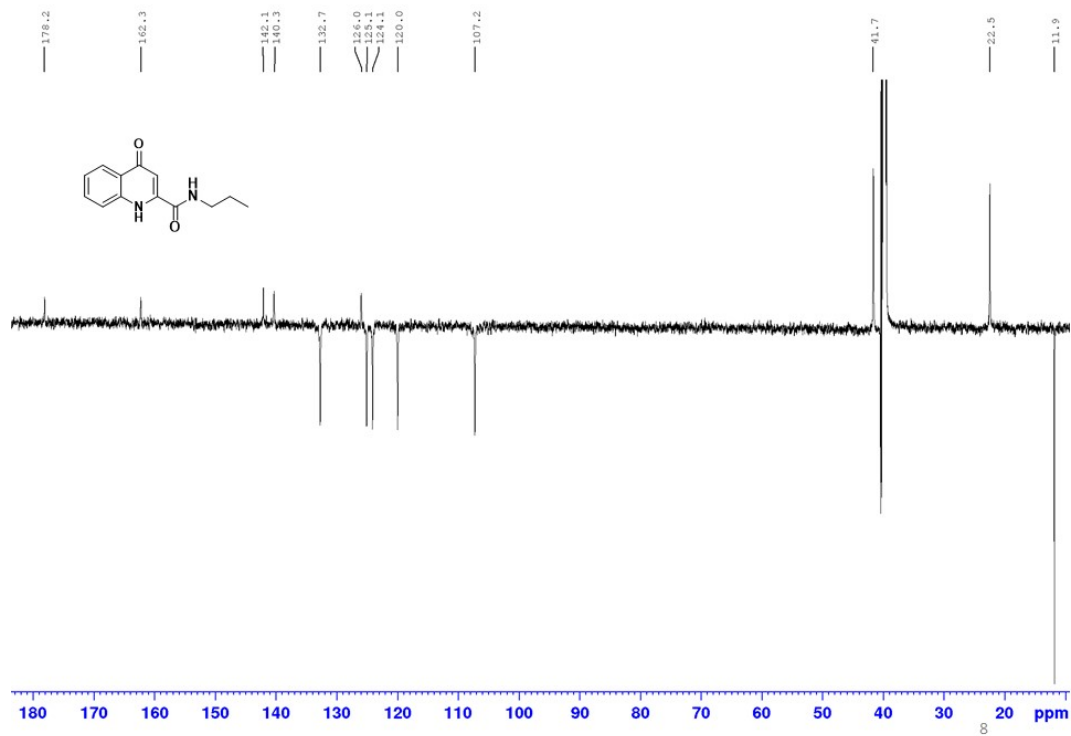
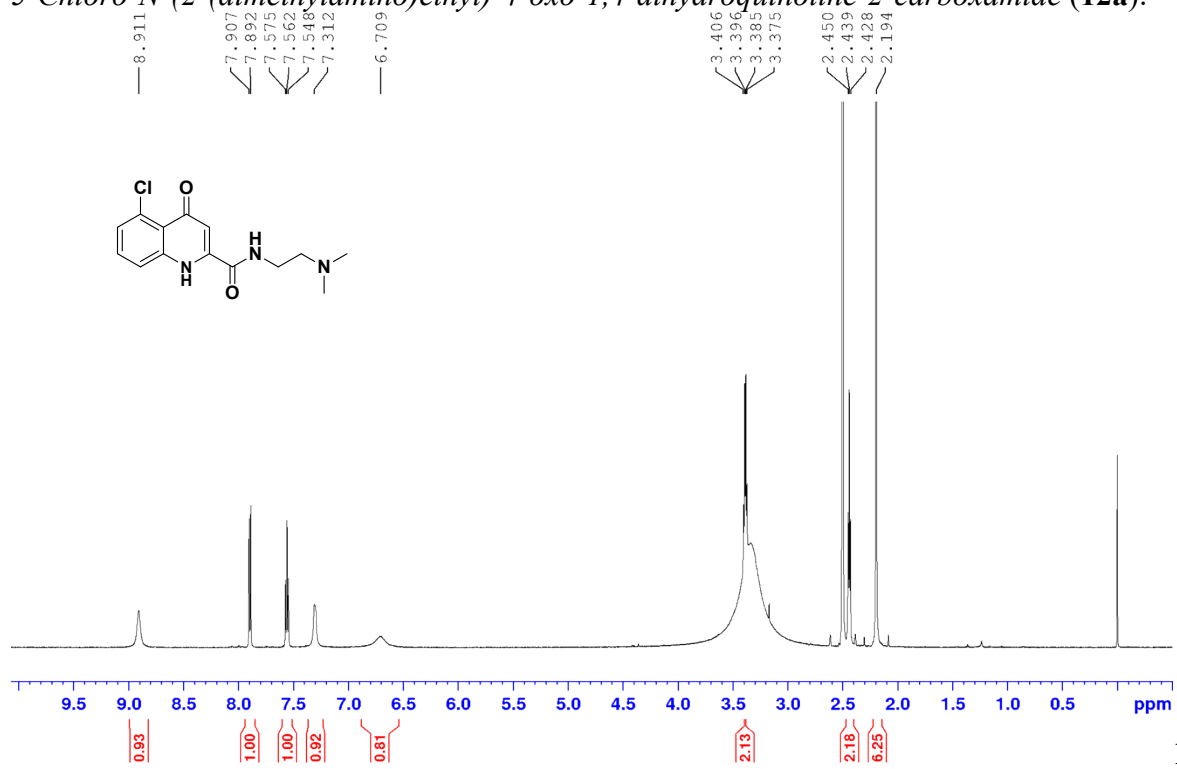


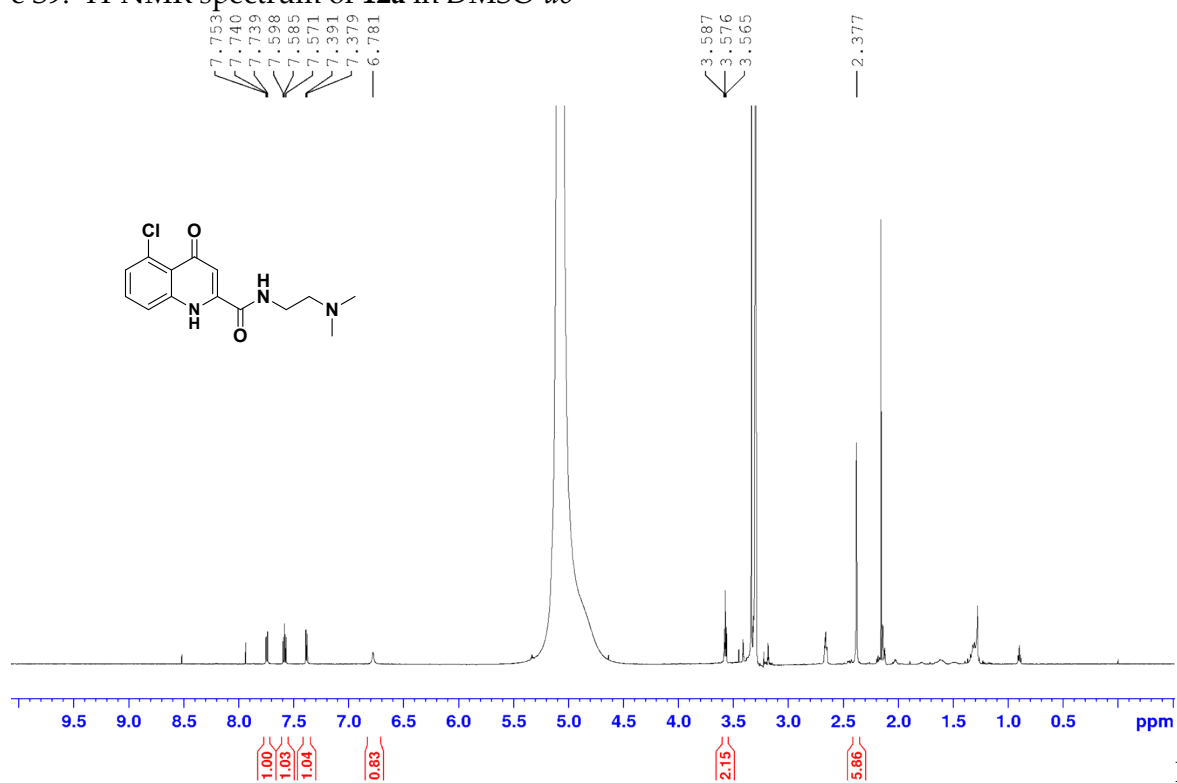
Figure S8. ¹³C-NMR spectrum of 7d

5-Chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**12a**):



Figure

e S9. ¹H-NMR spectrum of **12a** in DMSO-*d*₆



Figure

e S10. ¹H-NMR spectrum of **12a** in MeOD

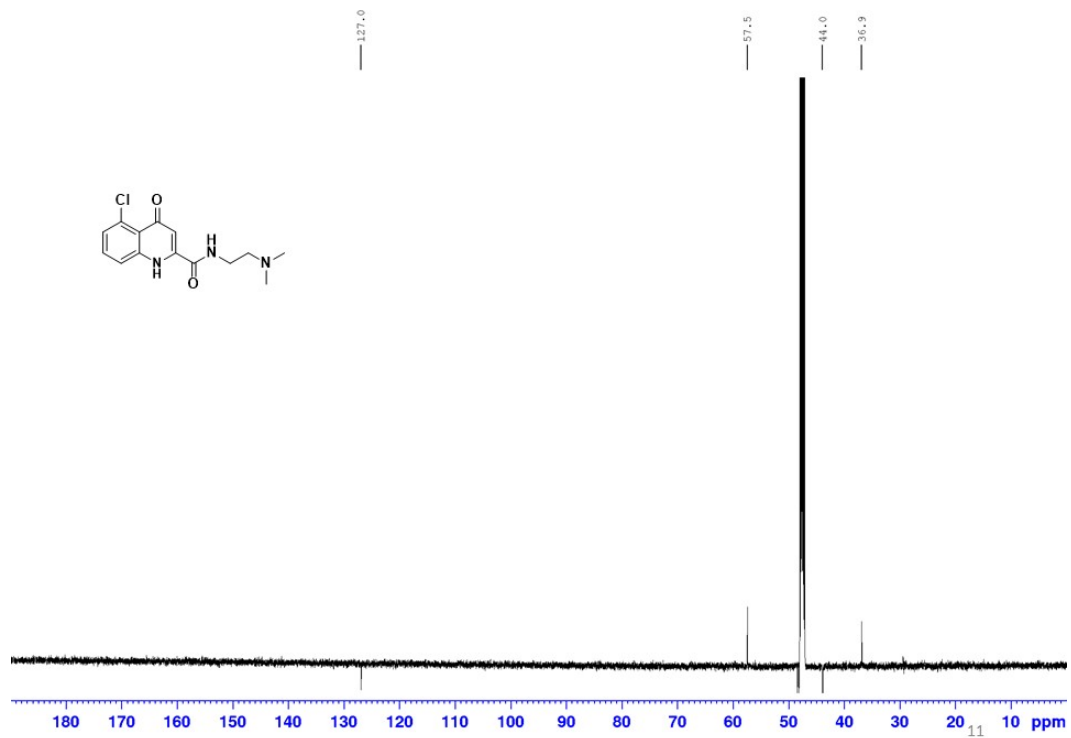


Figure S11. ^{13}C -NMR spectrum of **12a** in MeOD

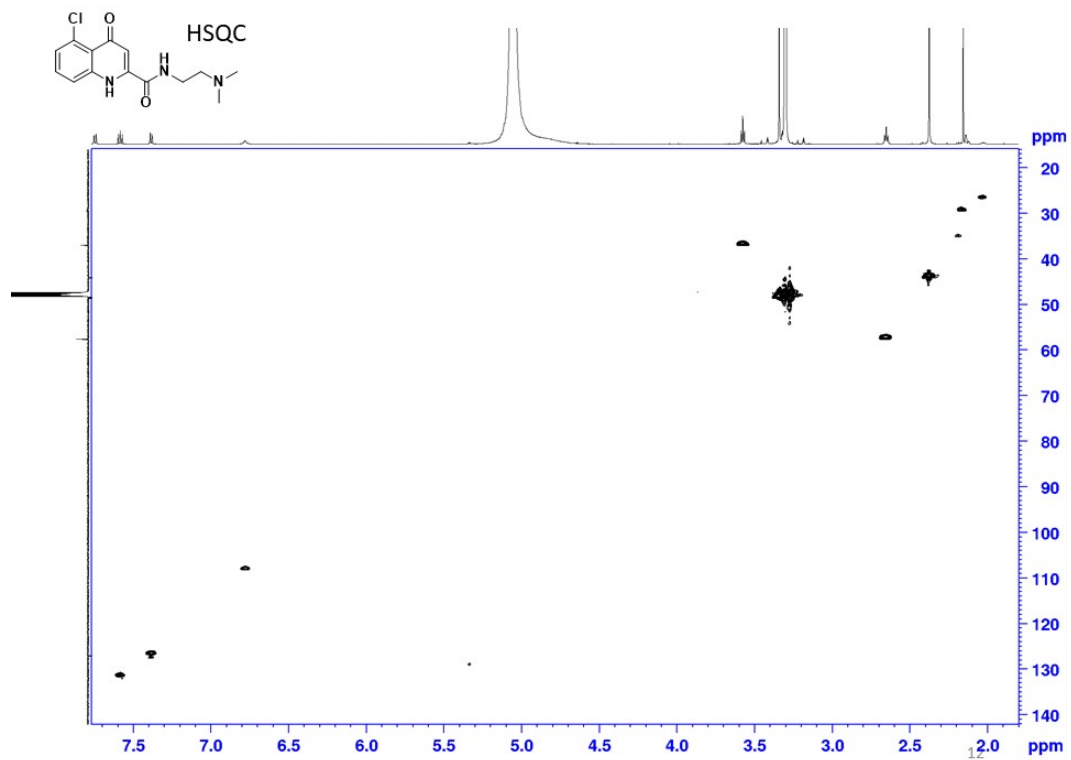


Figure S12. HSQC NMR spectrum of **12a** in MeOD

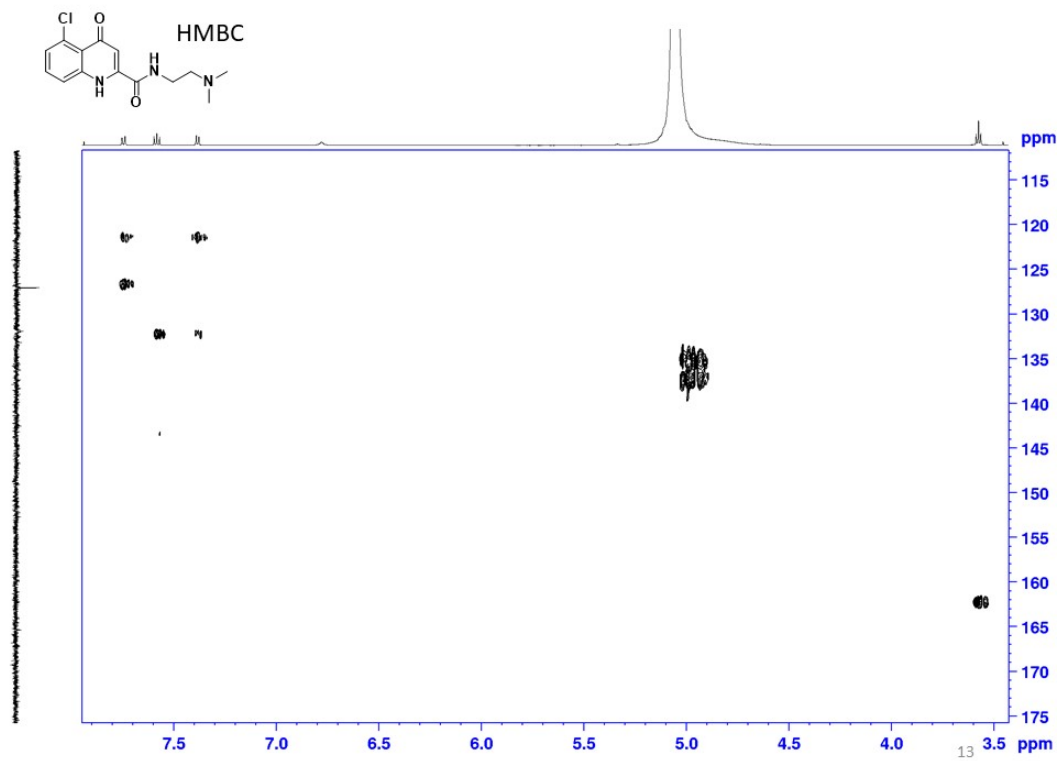
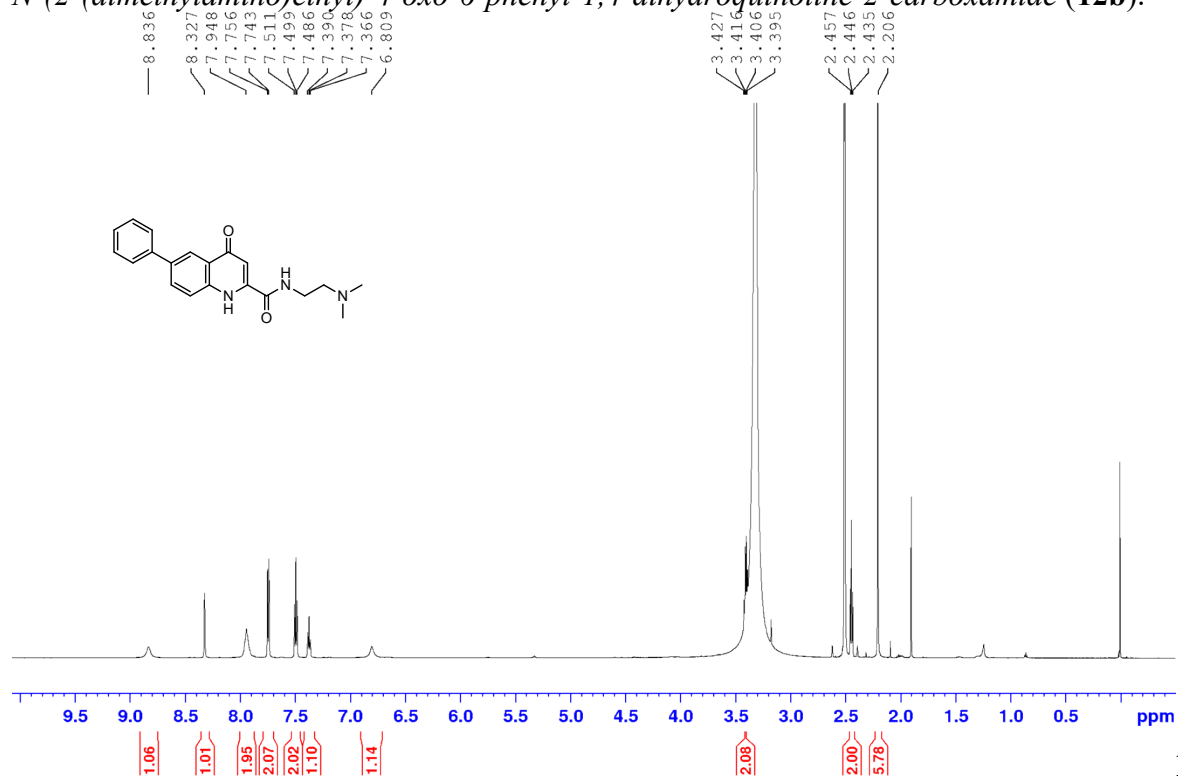


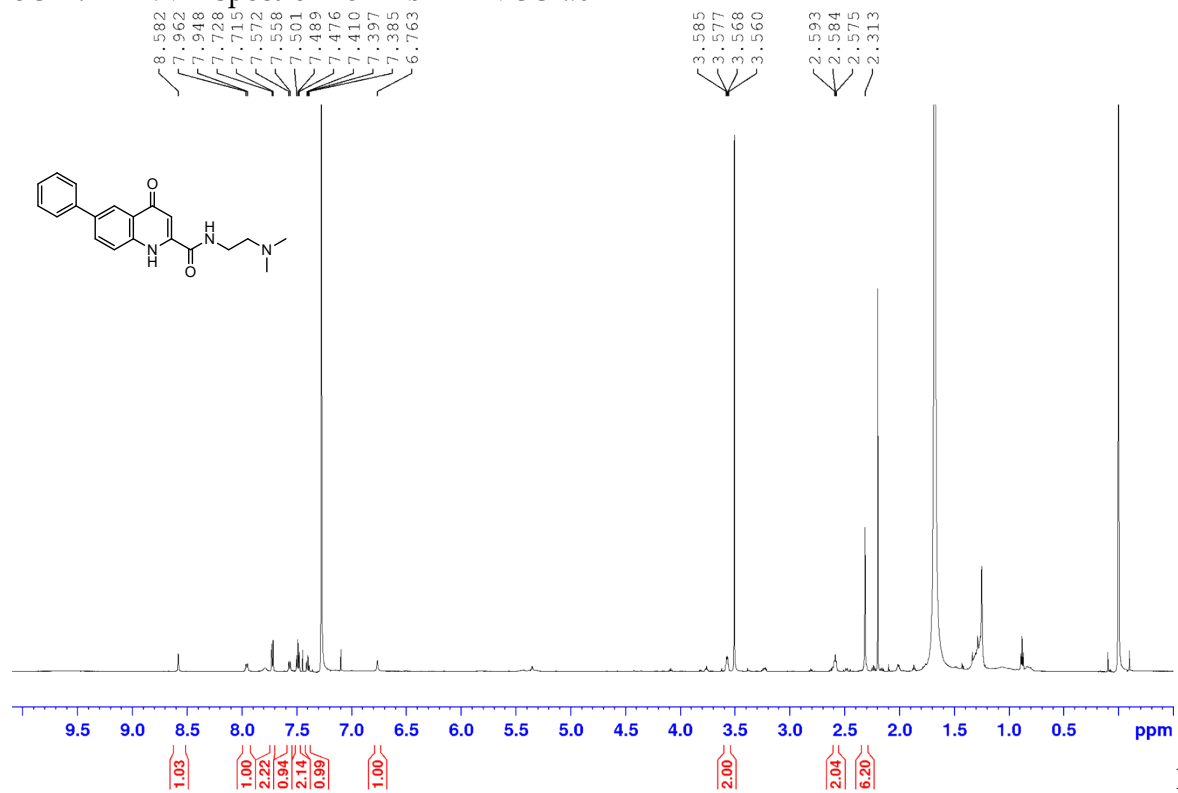
Figure S13. HMBC NMR spectrum of **12a** in MeOD

N-(2-(dimethylamino)ethyl)-4-oxo-6-phenyl-1,4-dihydroquinoline-2-carboxamide (**12b**):



Figur

e S14. ¹H-NMR spectrum of **12b** in DMSO-*d*₆



Figur

e S15. ¹H-NMR spectrum of **12b** in CDCl₃

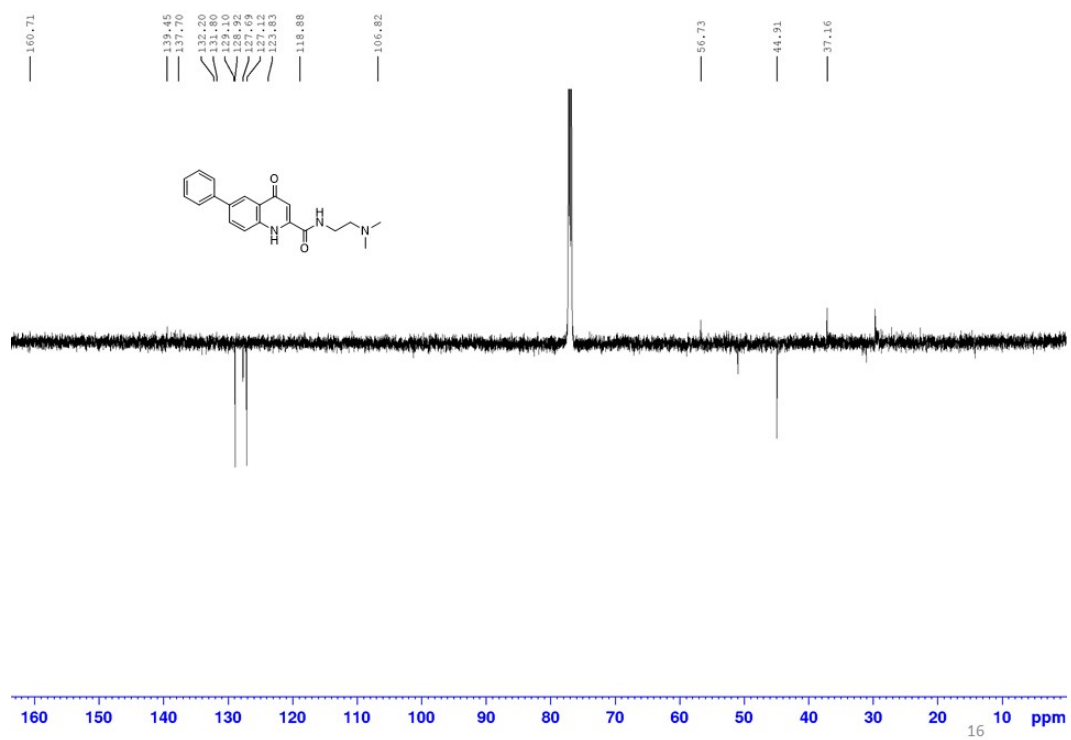


Figure S16. ^{13}C -NMR spectrum of **12b** in CDCl_3

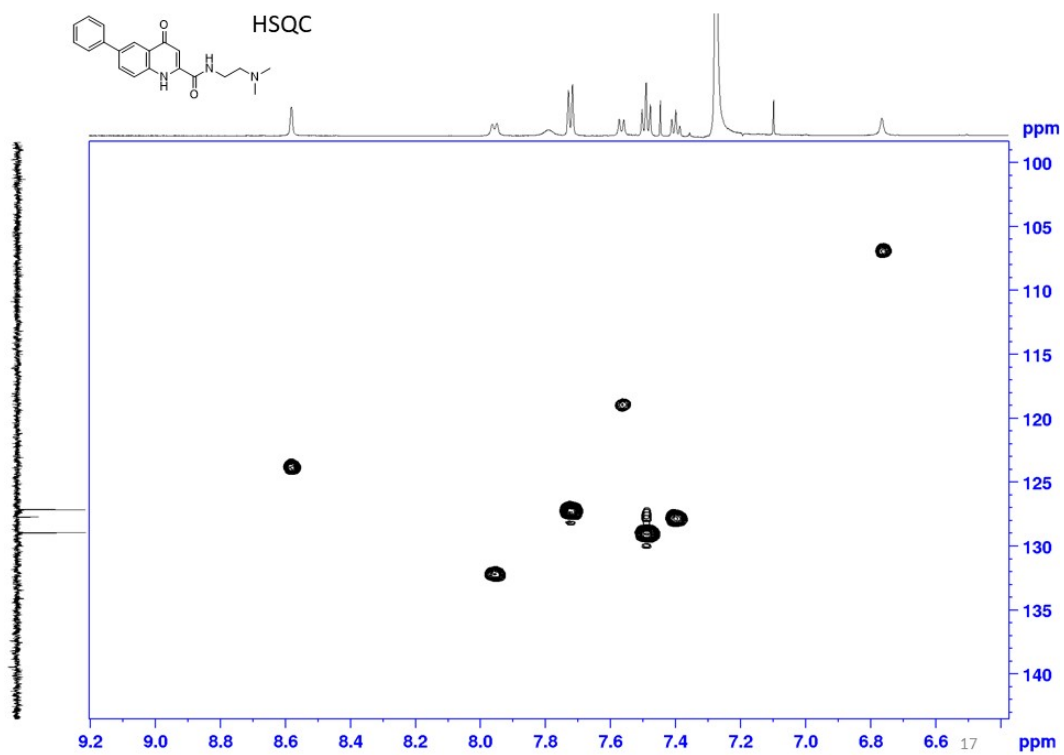


Figure S17. HSQC NMR spectrum of **12b** in CDCl_3

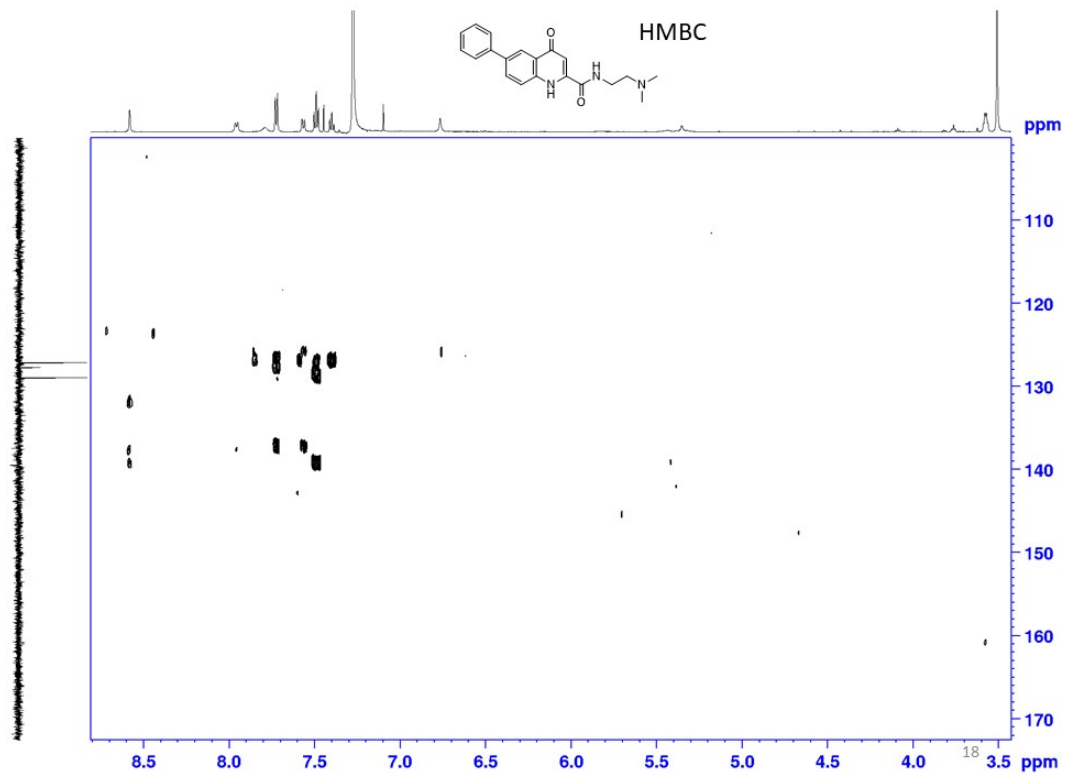
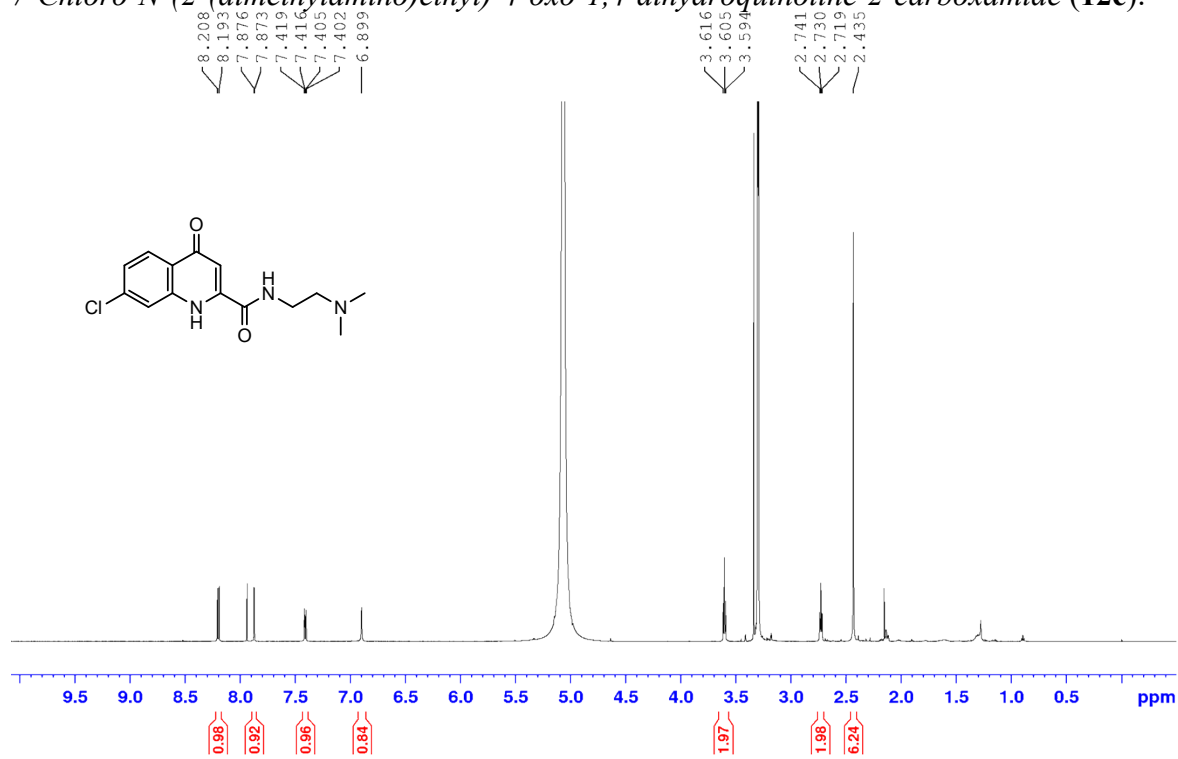


Figure S18. HMBC NMR spectrum of **12b** in CDCl₃

7-Chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**12c**):



Figure

e S19. ¹H-NMR spectrum of **12c**

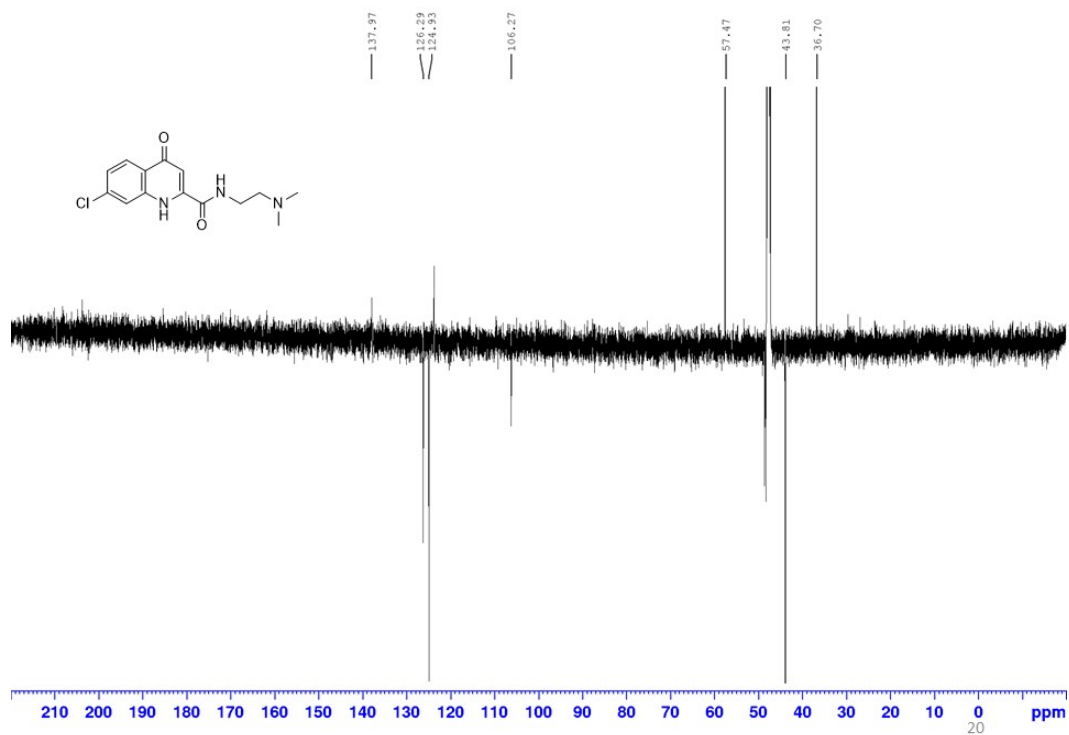


Figure S20. ¹³C-NMR spectrum of **12c**

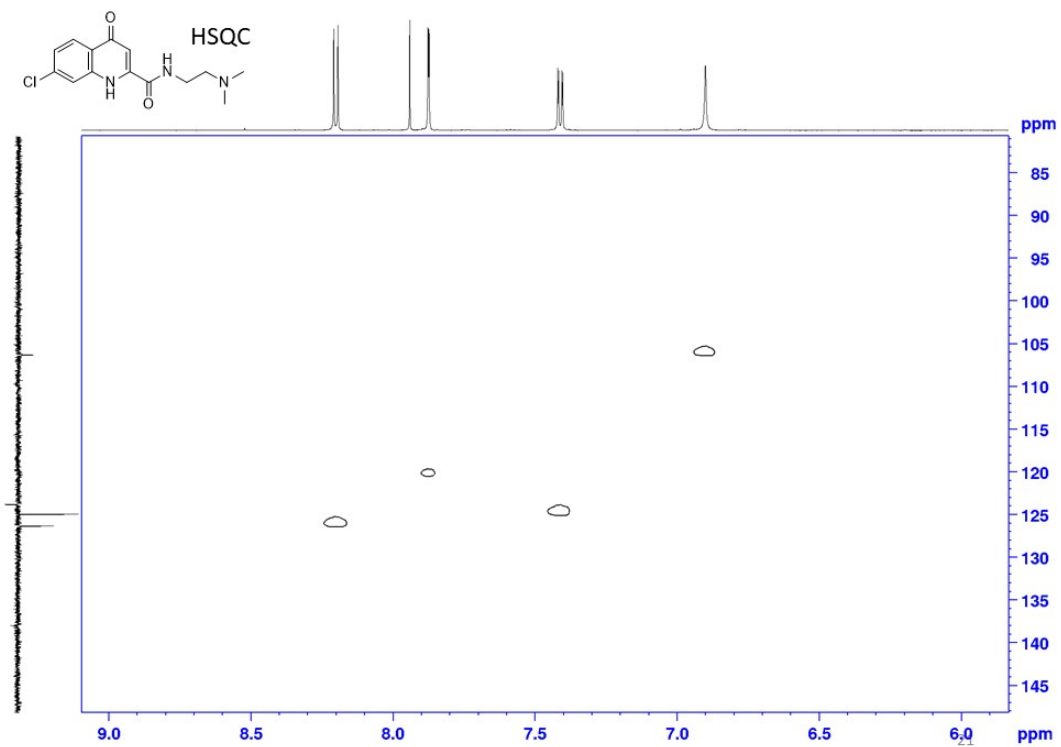
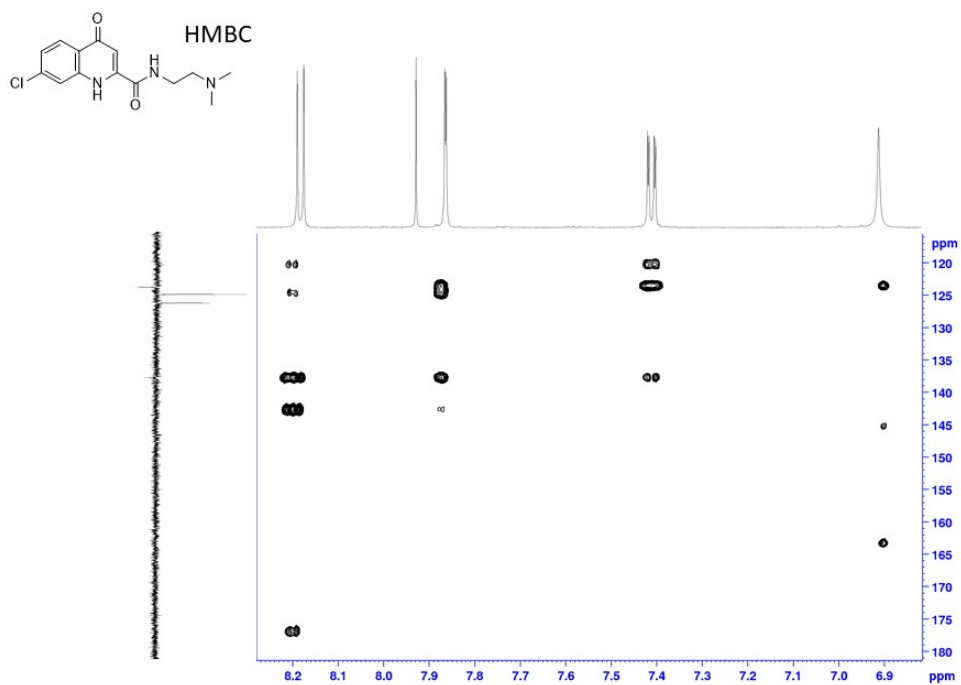


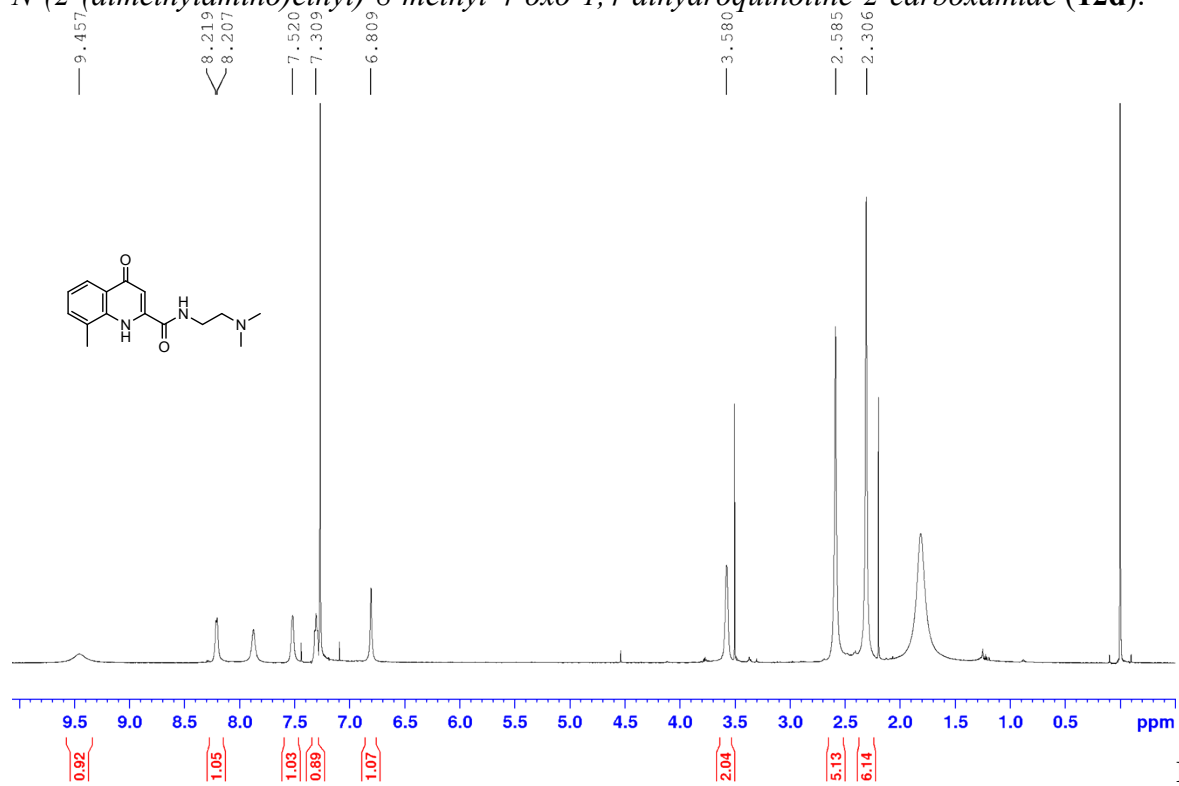
Figure S21. HSQC NMR spectrum of **12c**



22

Figure S22. HMBC NMR spectrum of **12c**

N-(2-(dimethylamino)ethyl)-8-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide (**12d**):



Figur

e S23. ¹H-NMR spectrum of **12d**

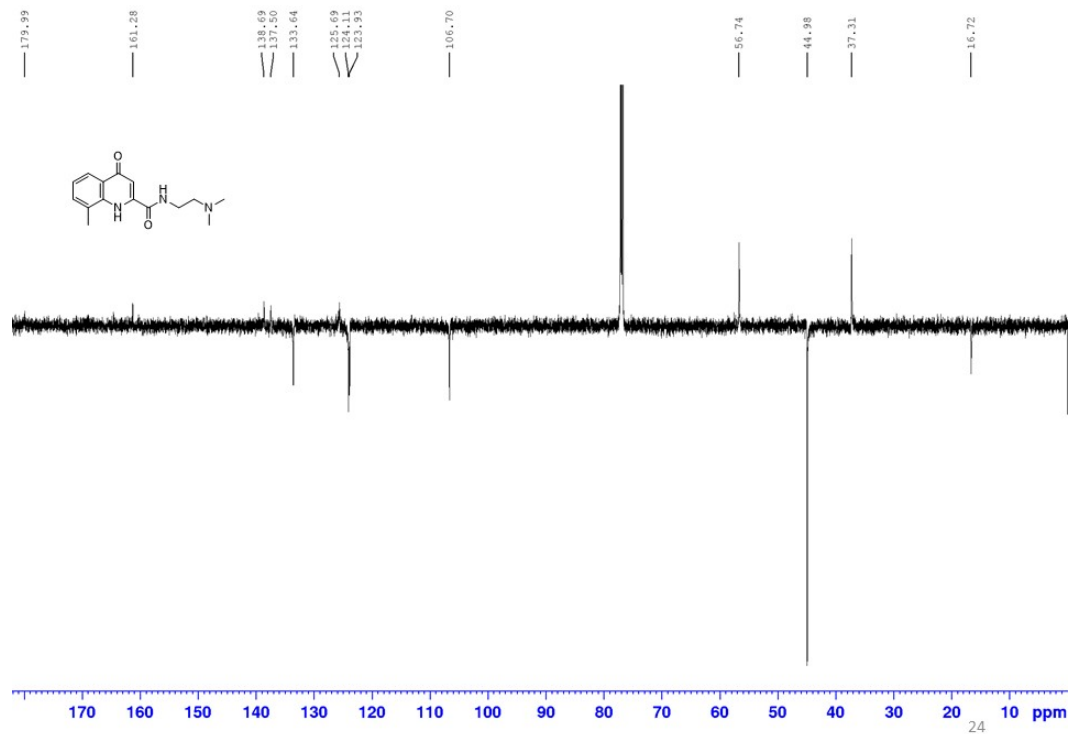
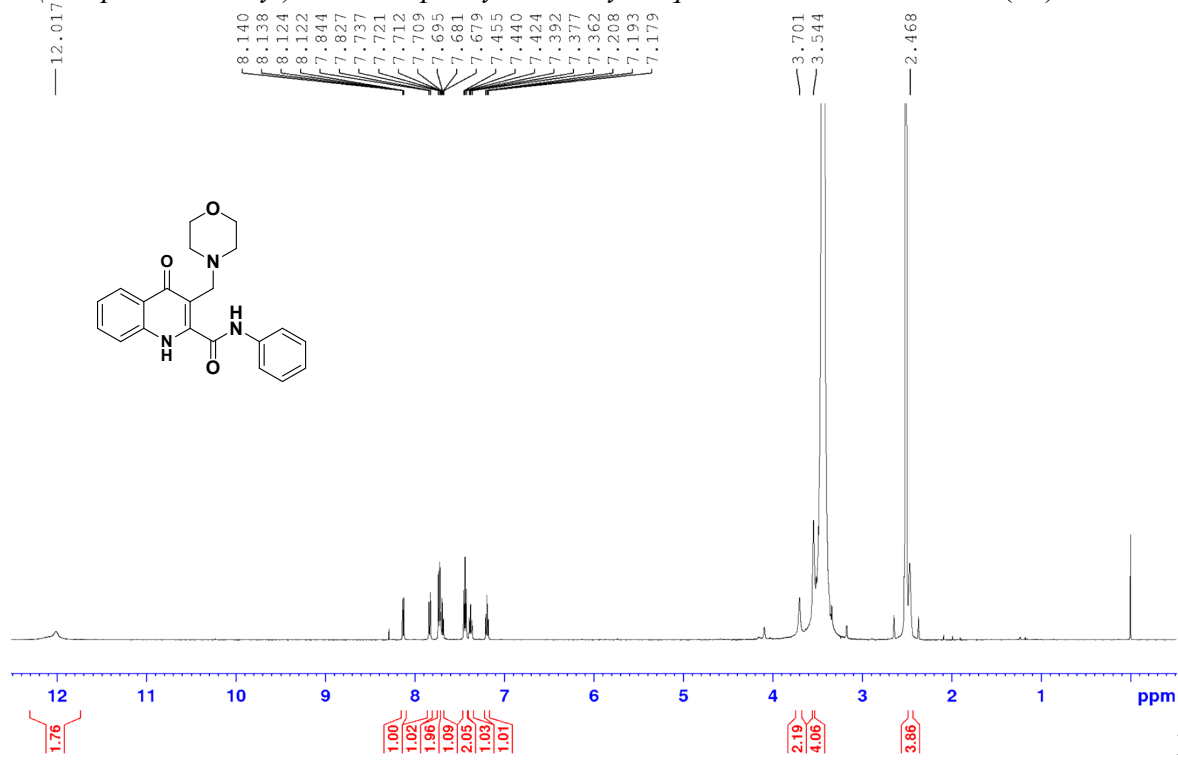


Figure S24. ¹³C-NMR spectrum of **12d**

3-(Morpholinomethyl)-4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide (**8a**):



Figure

S25. ¹H-NMR spectrum of **8a**

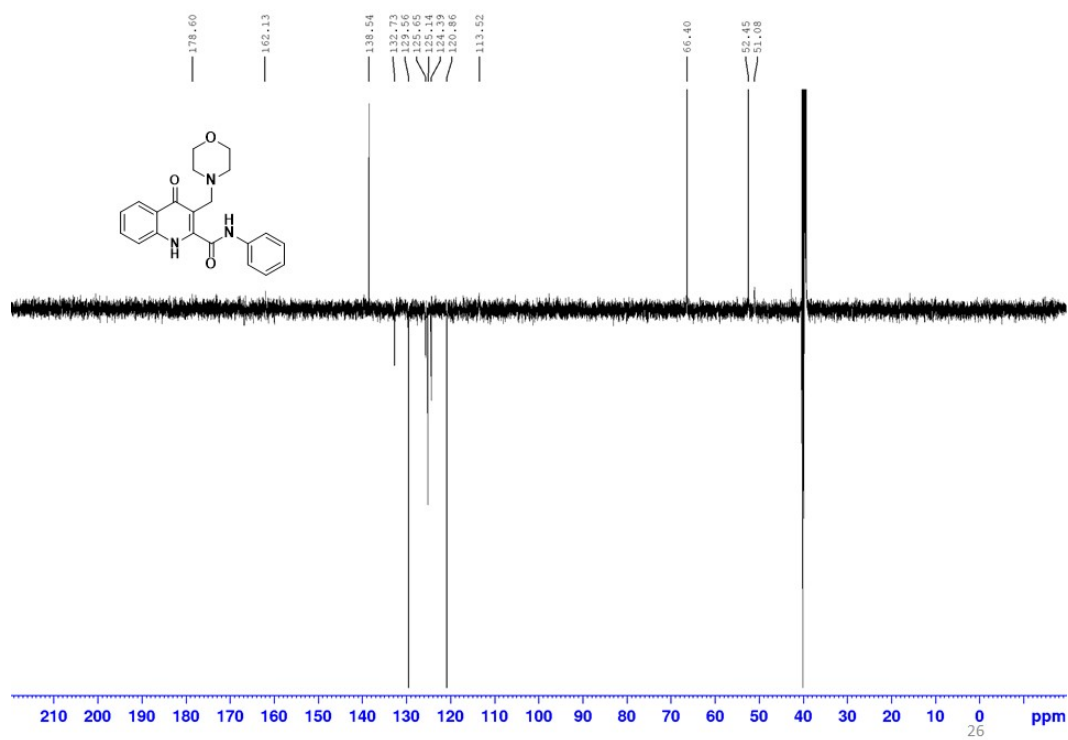
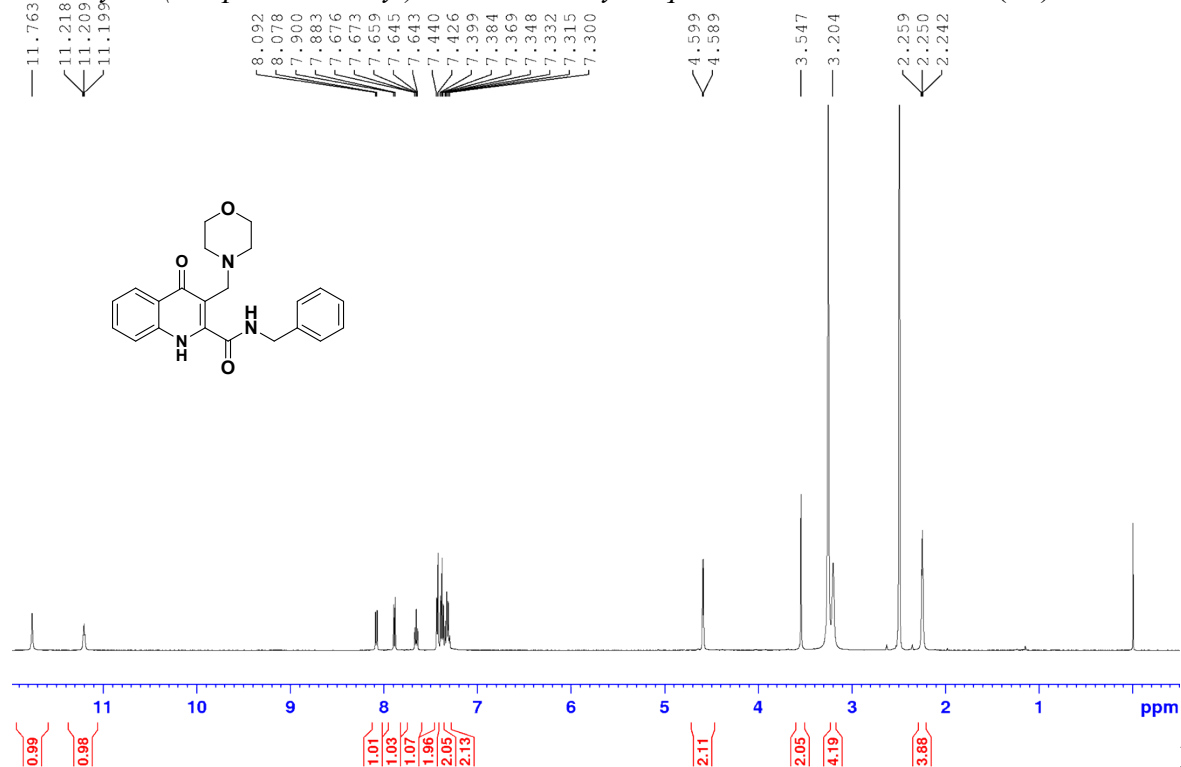


Figure S26. ¹³C-NMR spectrum of **8a**

N-benzyl-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**8b**):



e S27. ¹H-NMR spectrum of **8b**

Figur

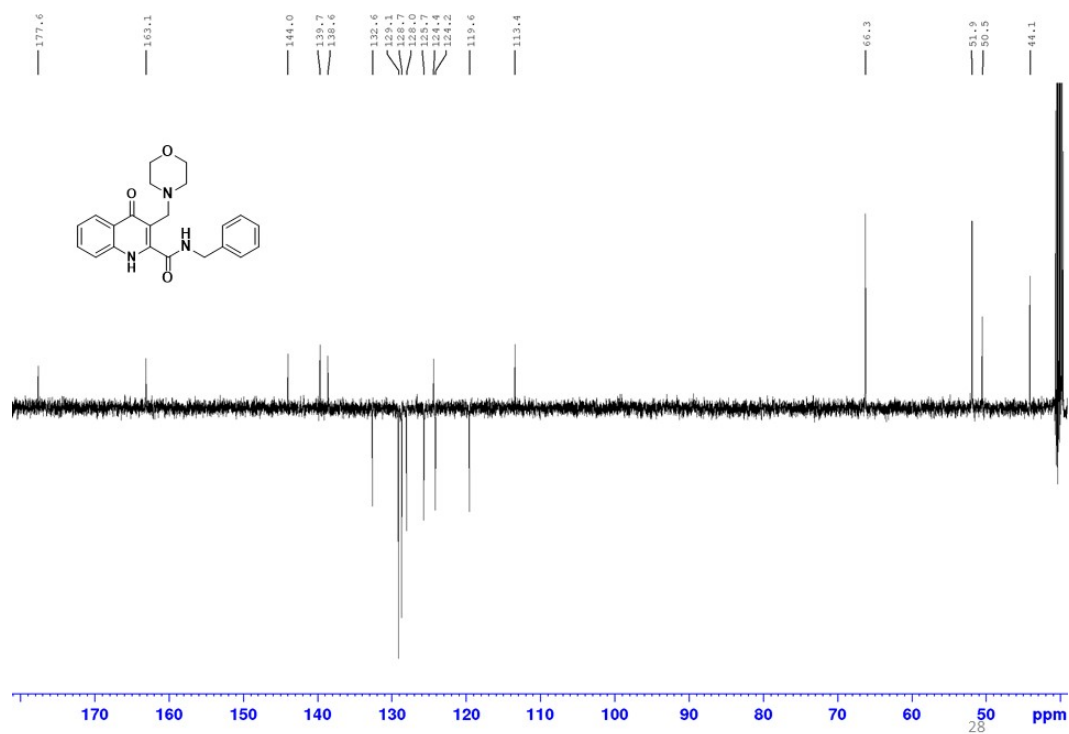
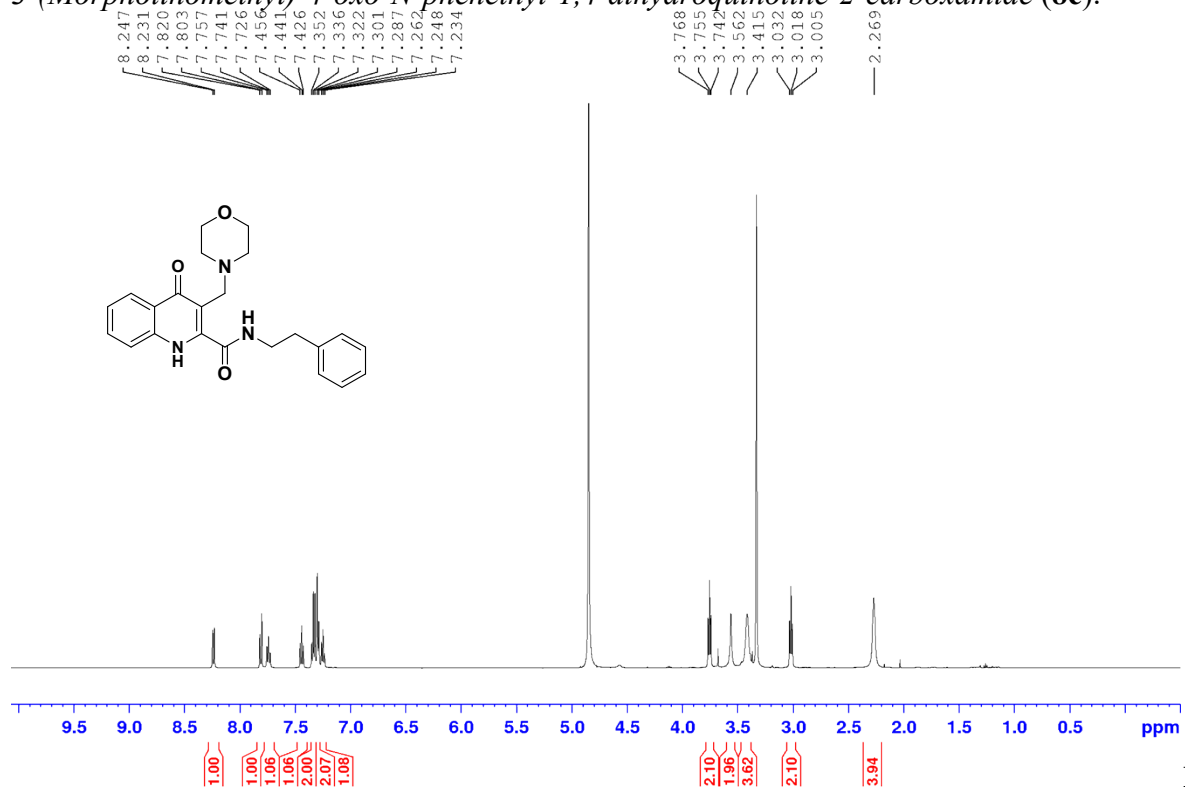


Figure S28. ¹³C-NMR spectrum of **8b**

3-(Morpholinomethyl)-4-oxo-N-phenethyl-1,4-dihydroquinoline-2-carboxamide (**8c**):



e S29. ¹H-NMR spectrum of **8c**

Figur

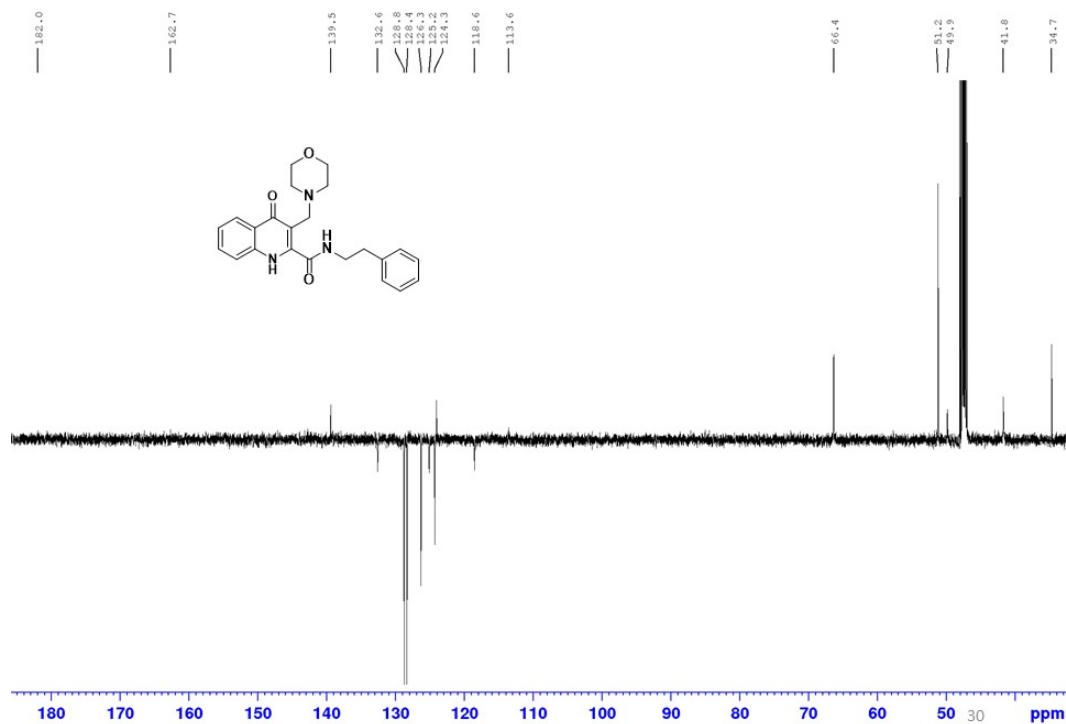
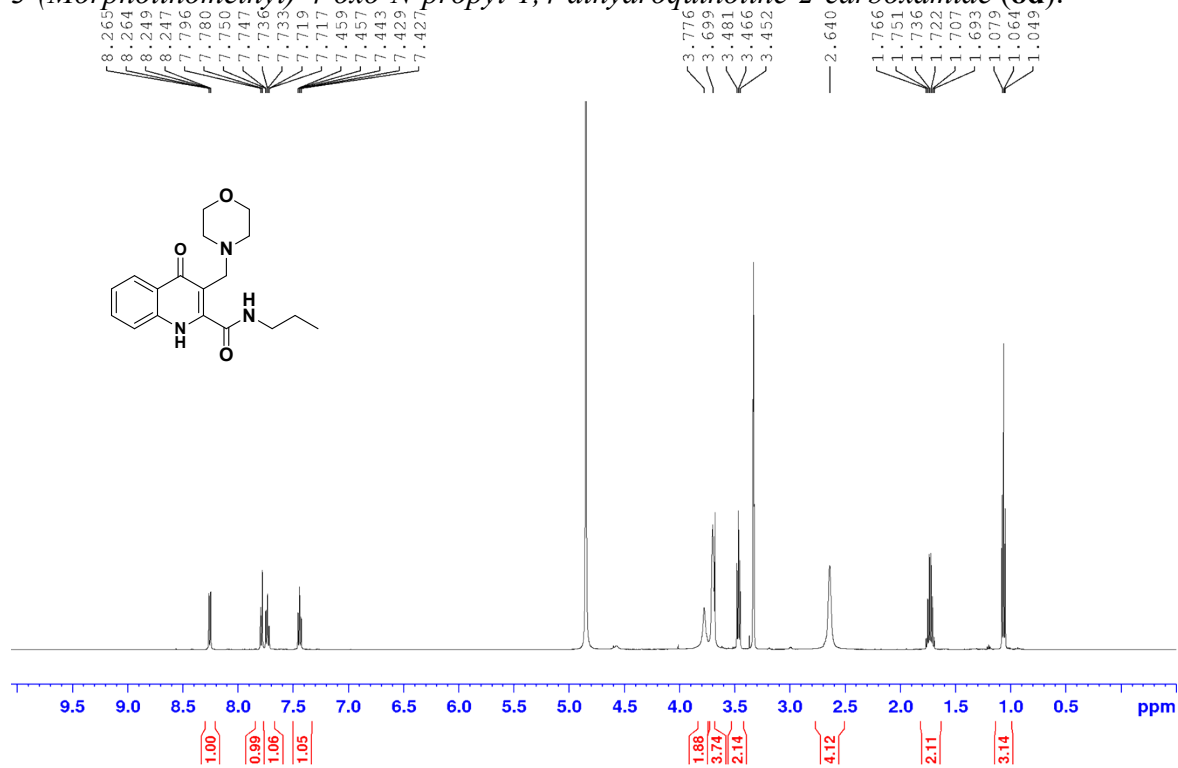


Figure S30. ^{13}C -NMR spectrum of **8c**

3-(Morpholinomethyl)-4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide (8d):



Figur

e S31. ^1H -NMR spectrum of **8d**

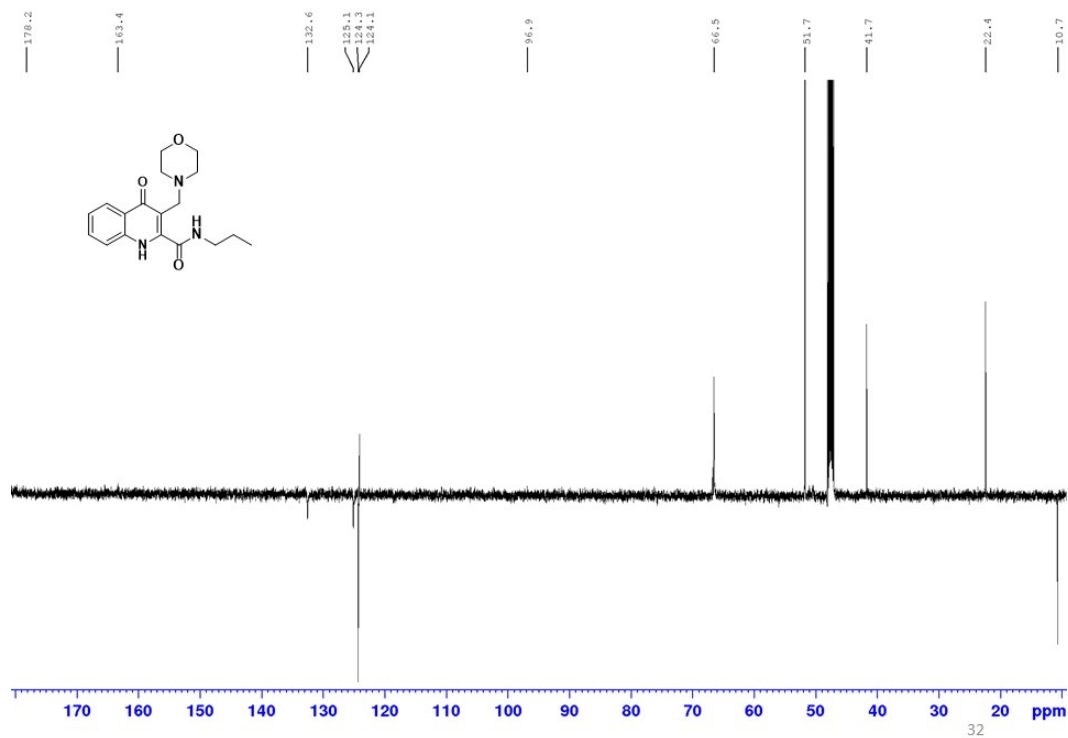
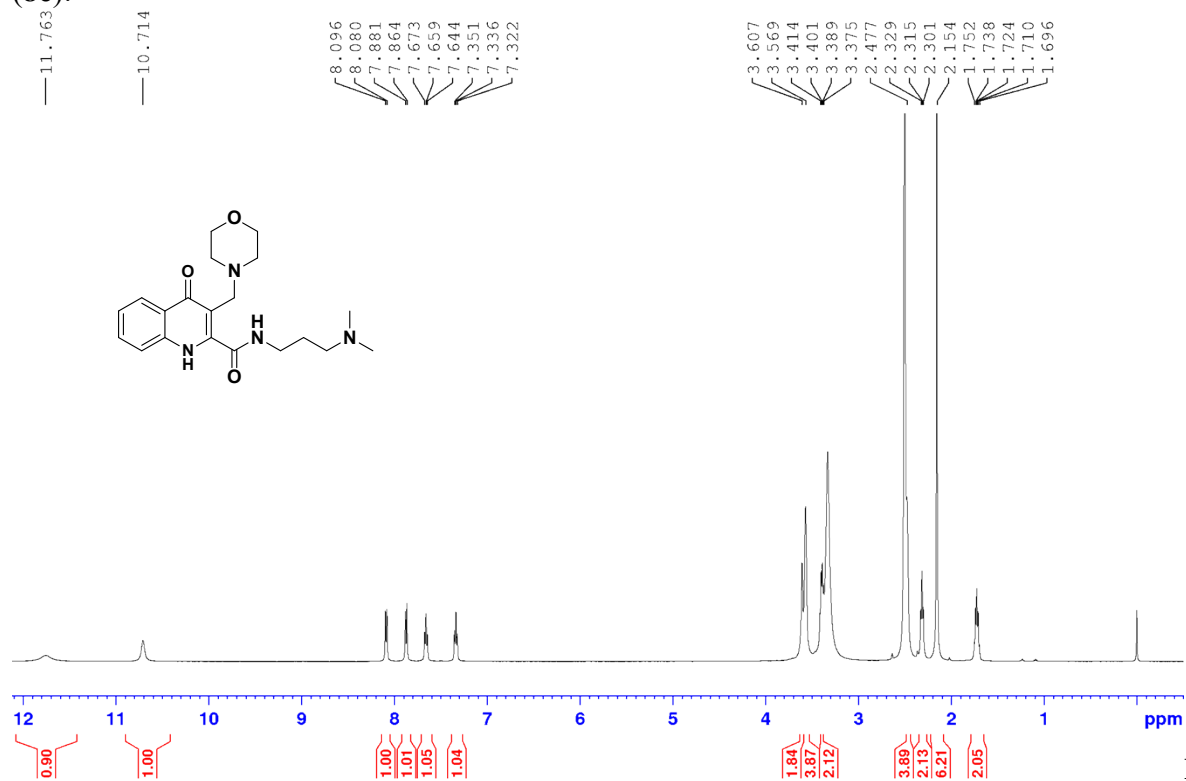


Figure S32. ^{13}C -NMR spectrum of **8d**

N-(3-(dimethylamino)propyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**8e**):



Figur

e S33. ^1H -NMR spectrum of **8e**

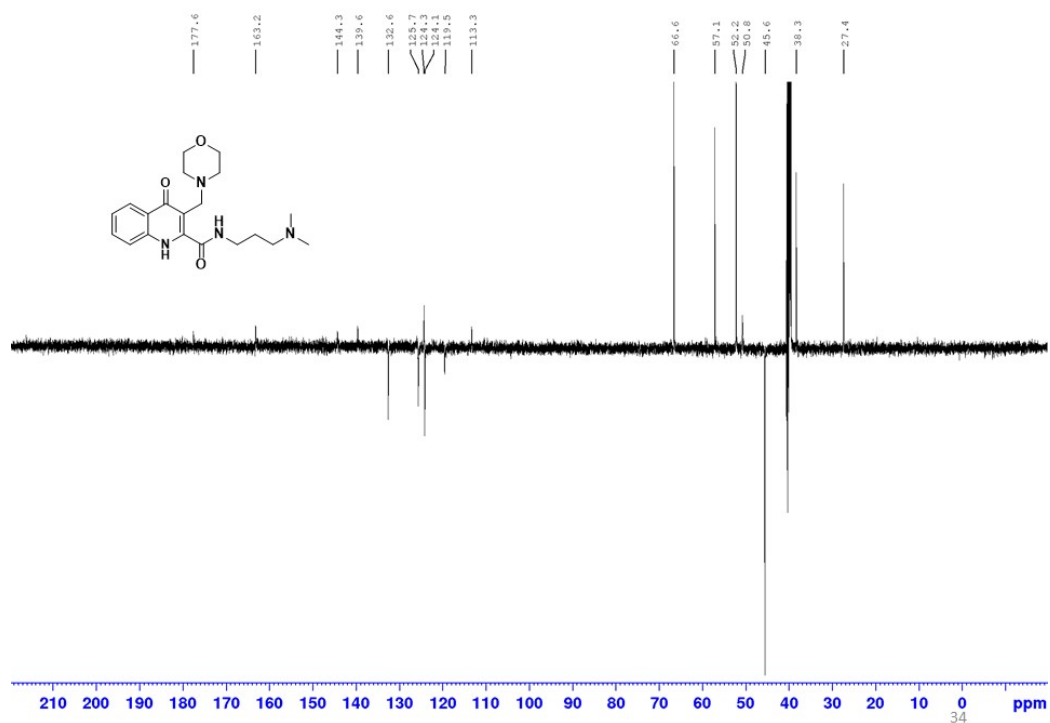
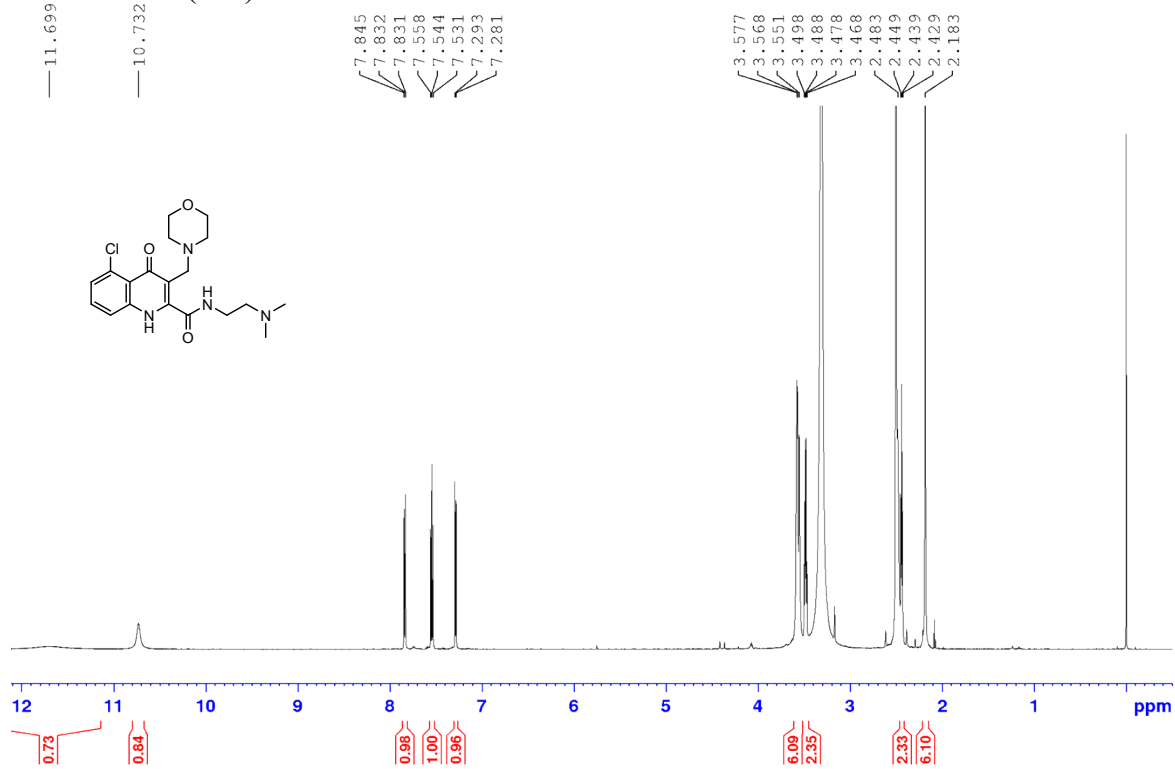


Figure S34. ¹³C-NMR spectrum of **8e**
 5-Chloro-N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**13a**):



e S35. ¹H-NMR spectrum of **13a**

Figur

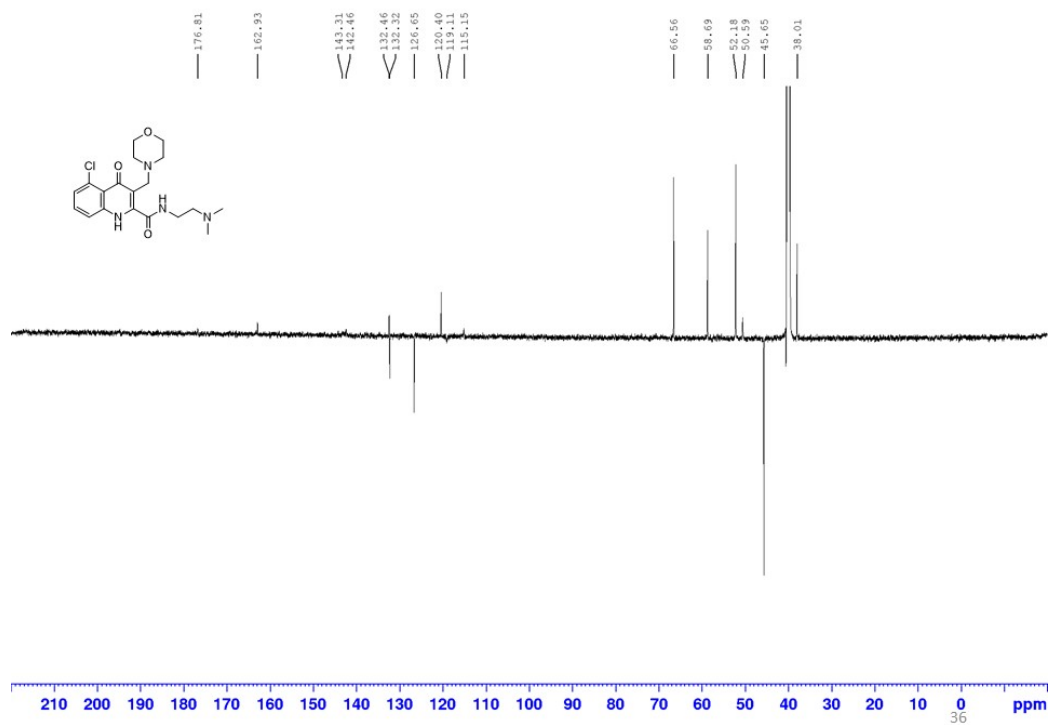


Figure S36. ^{13}C -NMR spectrum of **13a**

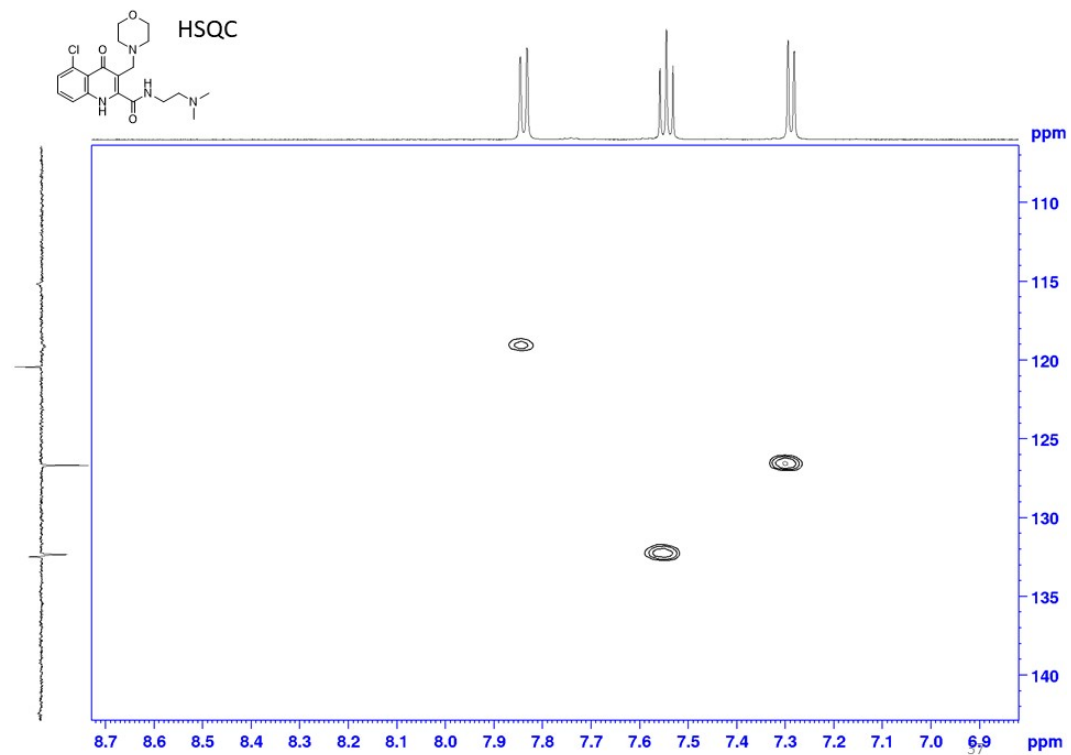


Figure S37. HSQC NMR spectrum of **13a**

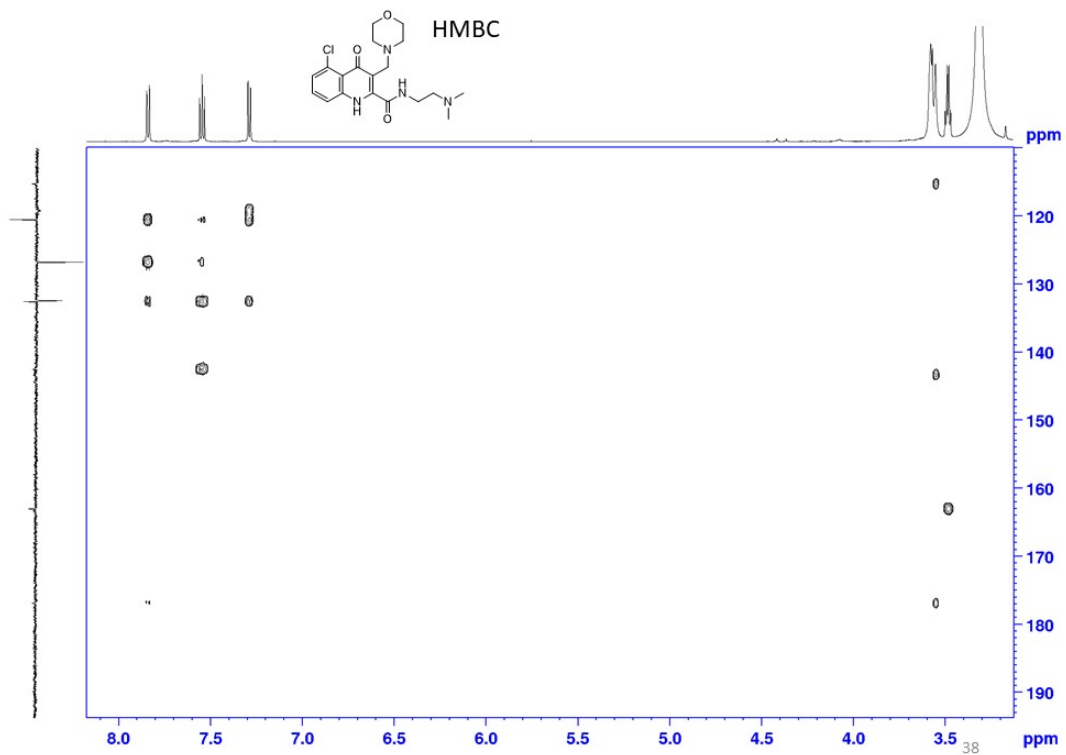


Figure S38. HMBC NMR spectrum of **13a**
N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-6-phenyl-1,4-dihydroquinoline-2-carboxamide (**13b**):

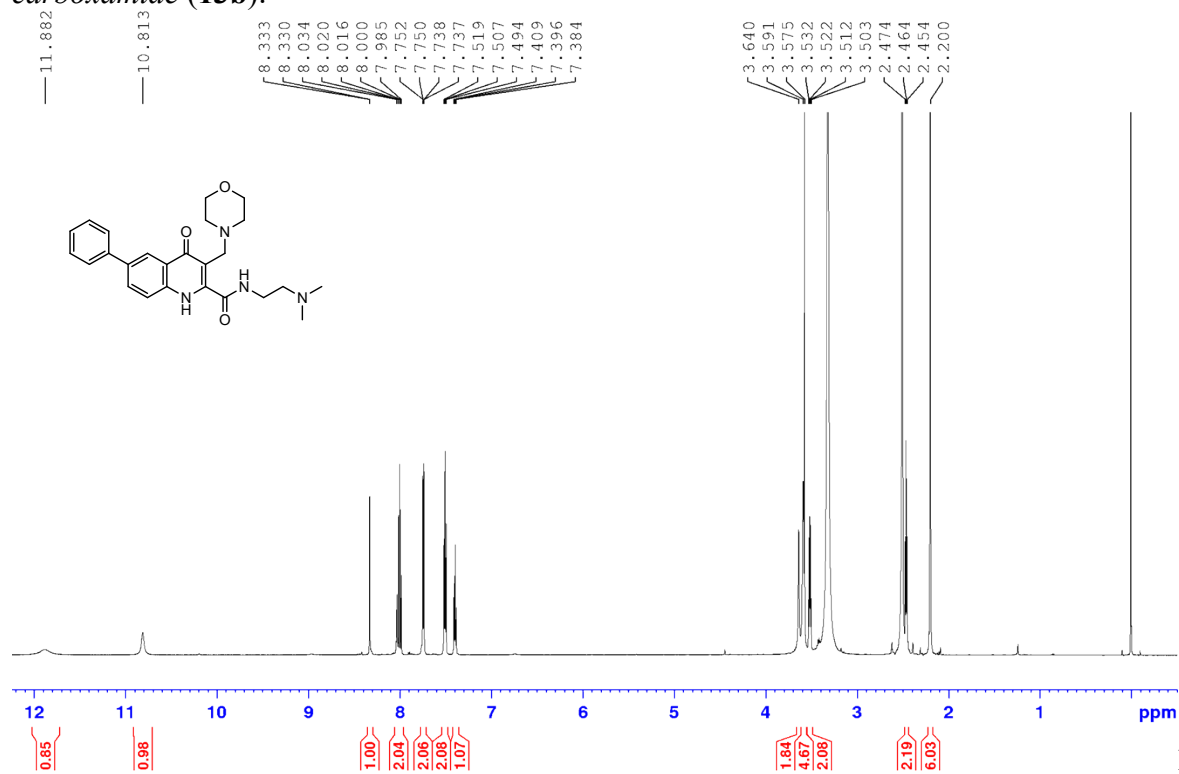


Figure S39. ¹H-NMR spectrum of **13b**

Figure

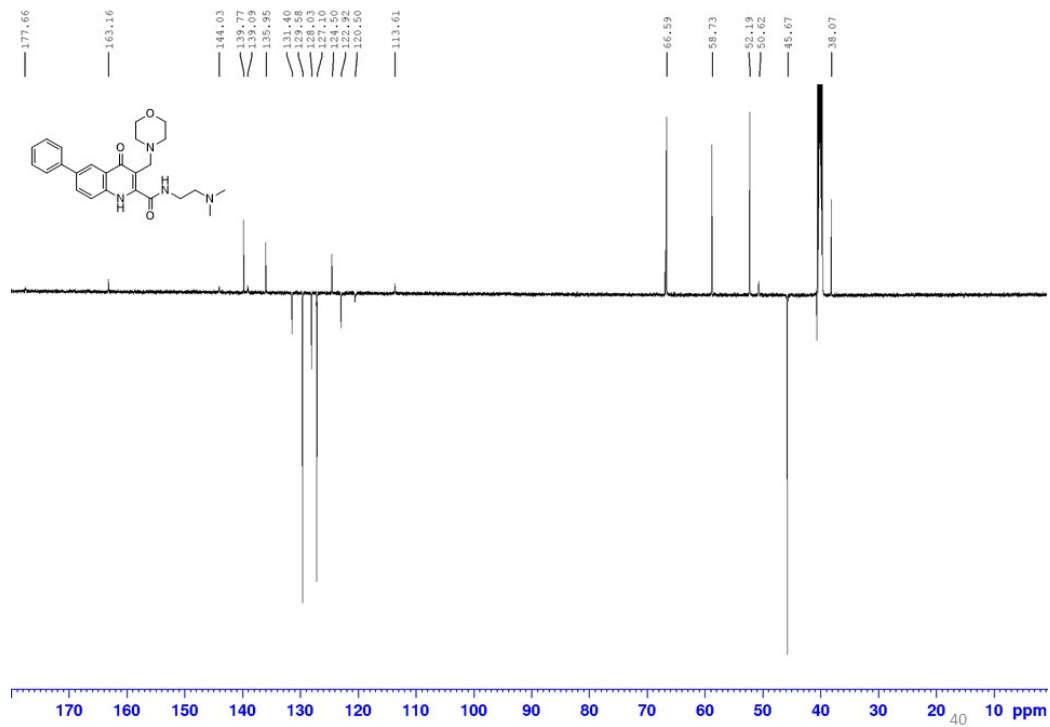


Figure S40. ¹³C-NMR spectrum of **13b**

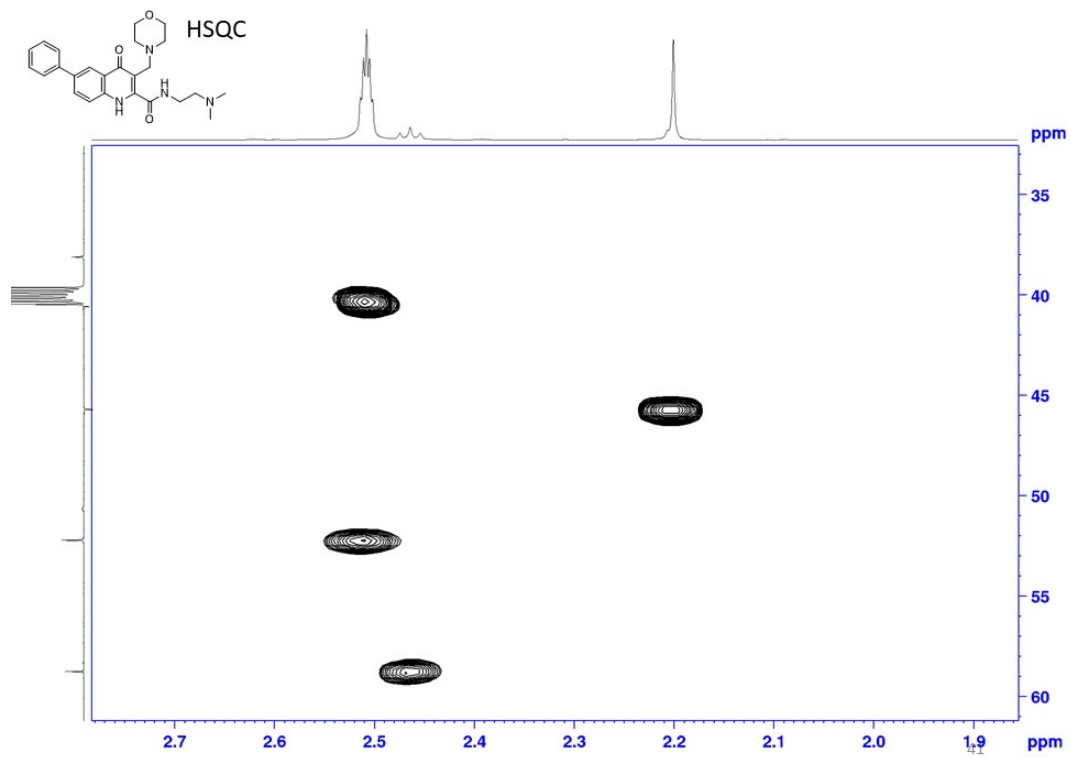


Figure S41. HSQC NMR spectrum of **13a**

7-Chloro-N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**13c**):

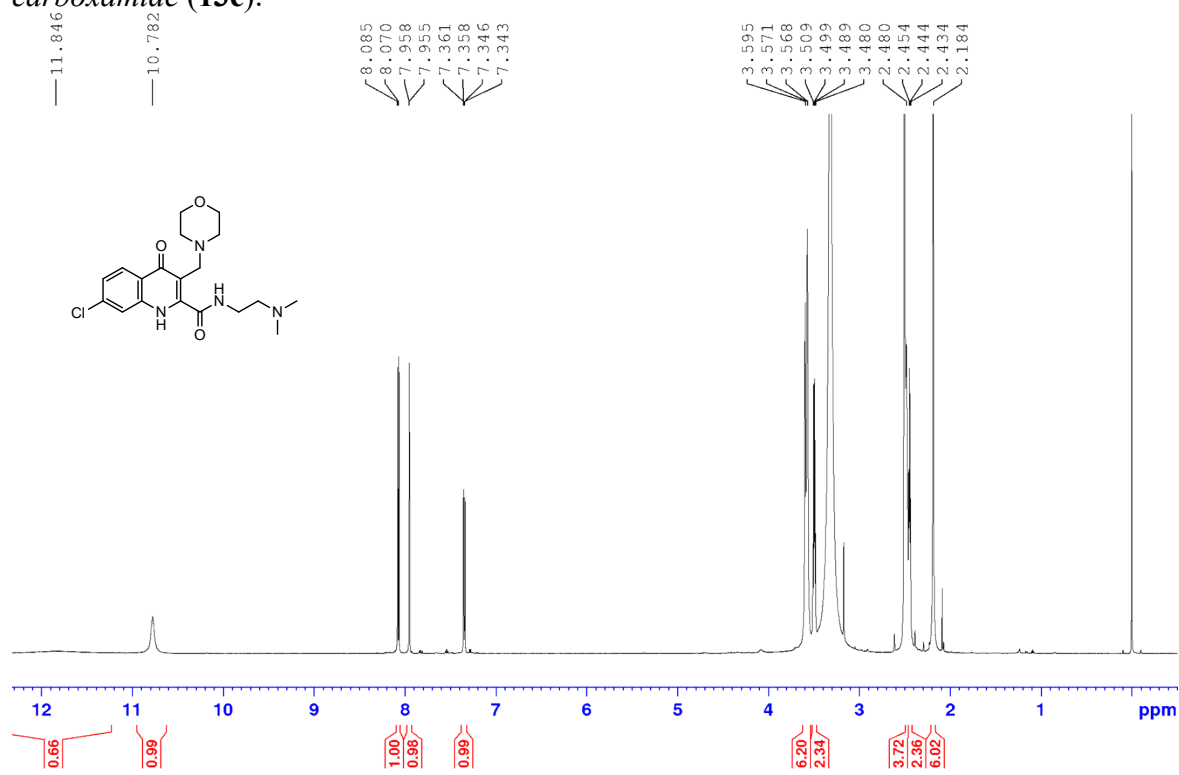


Figure S42. ¹H-NMR spectrum of **13c**

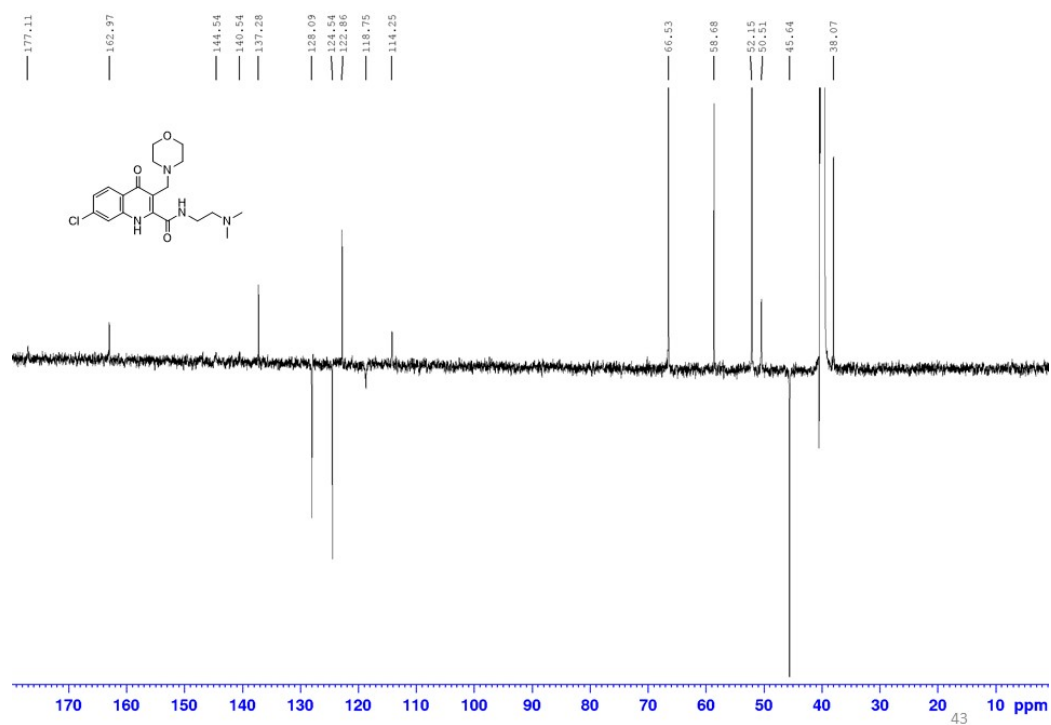


Figure S43. ¹³C-NMR spectrum of **13c**

N-(2-(dimethylamino)ethyl)-8-methyl-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**13d**):

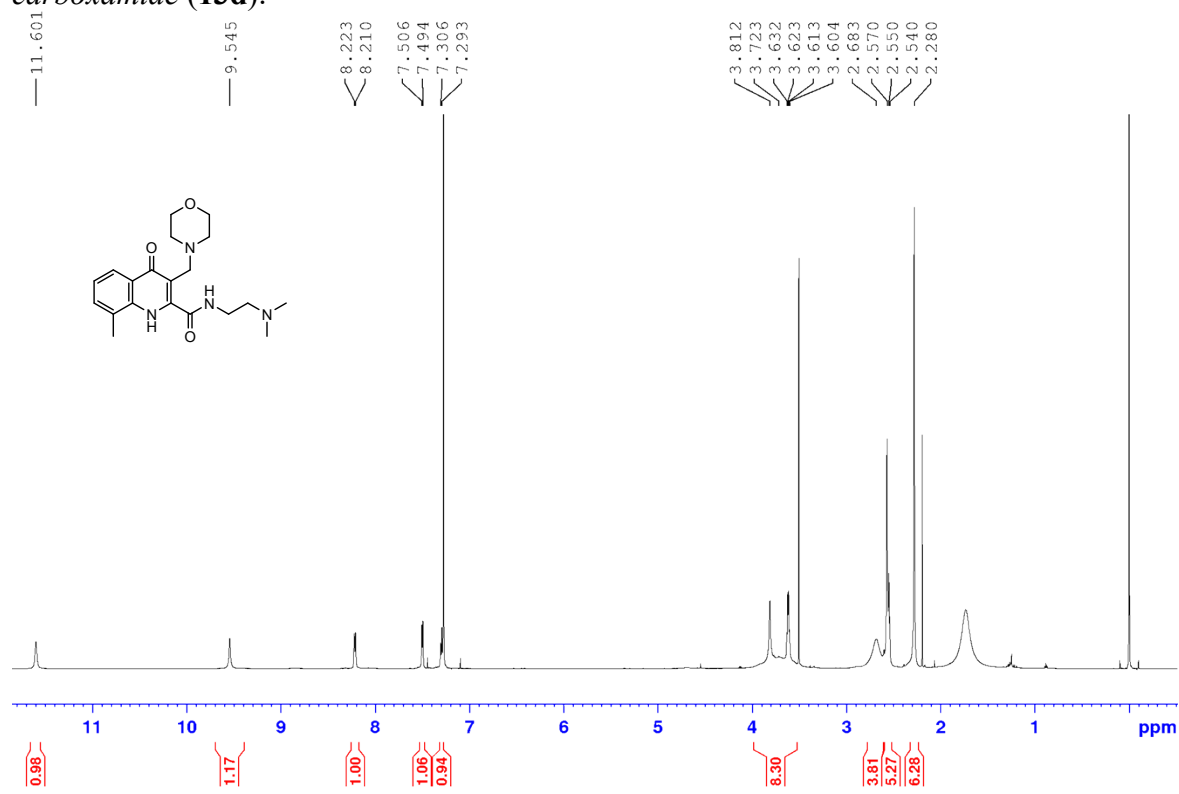


Figure S44. ¹H-NMR spectrum of **13d**

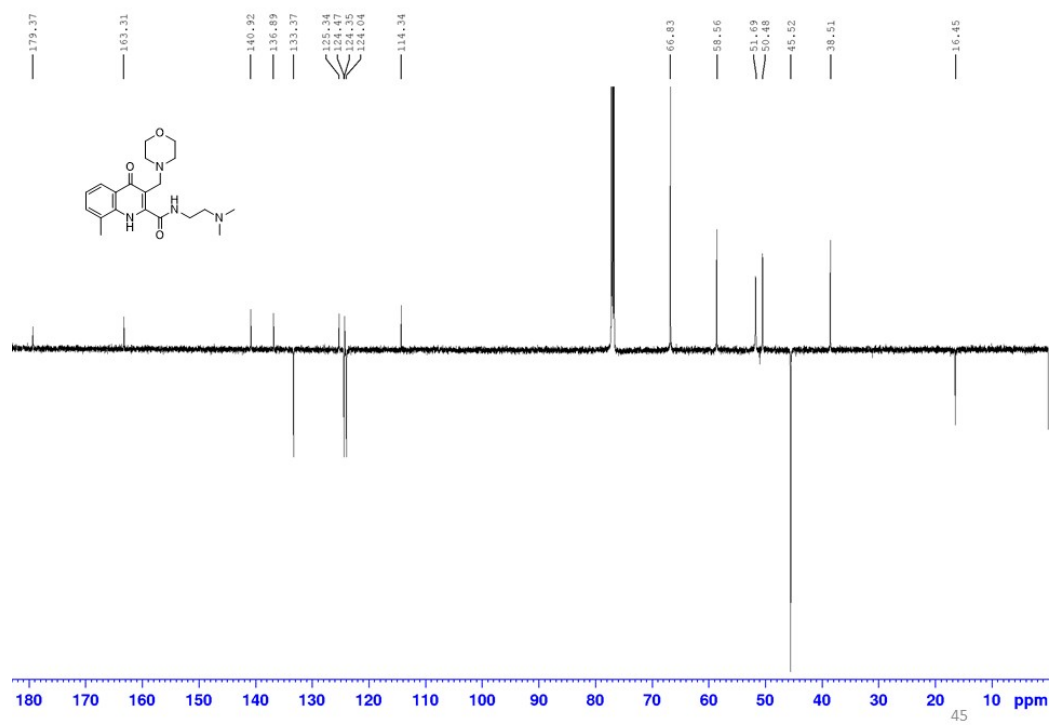
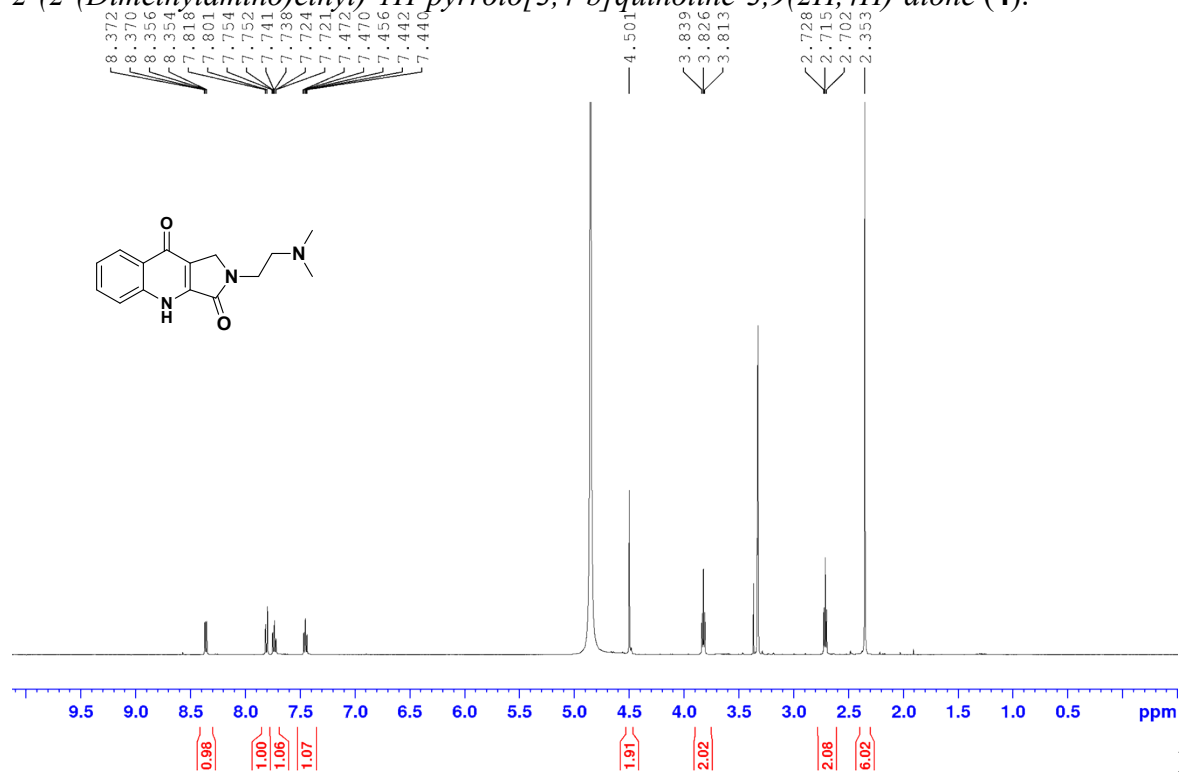


Figure S45. ¹³C-NMR spectrum of **13d**

2-(2-(Dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**4**):



Figure

e S46. ¹H-NMR spectrum of **4**

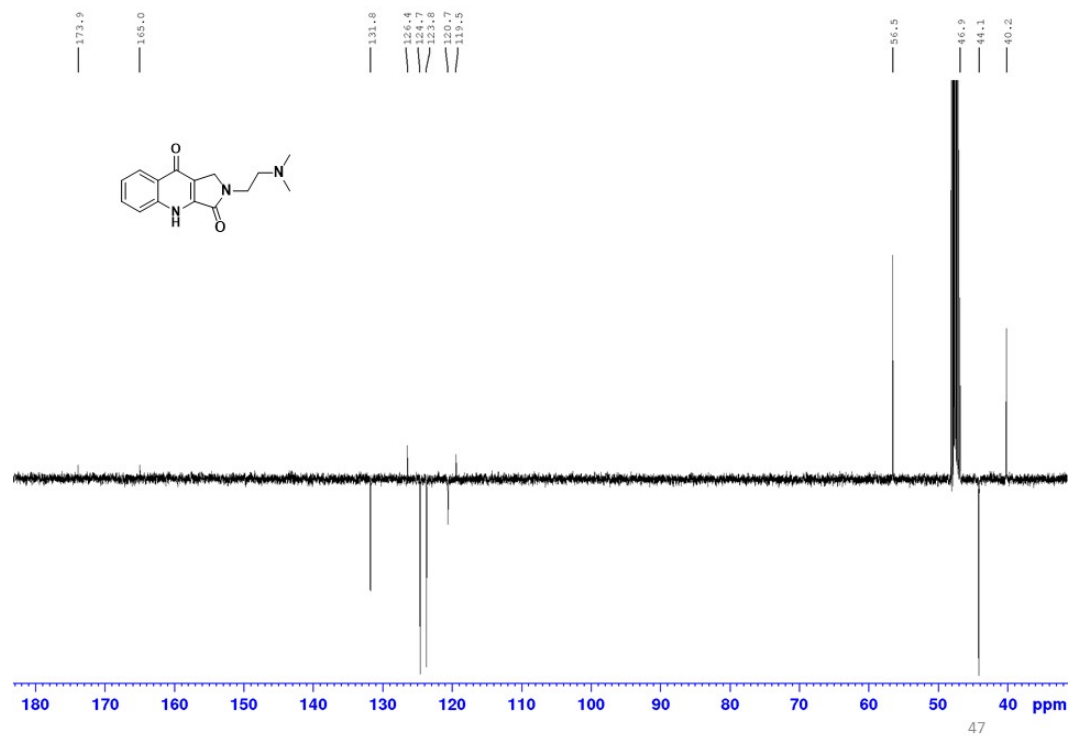
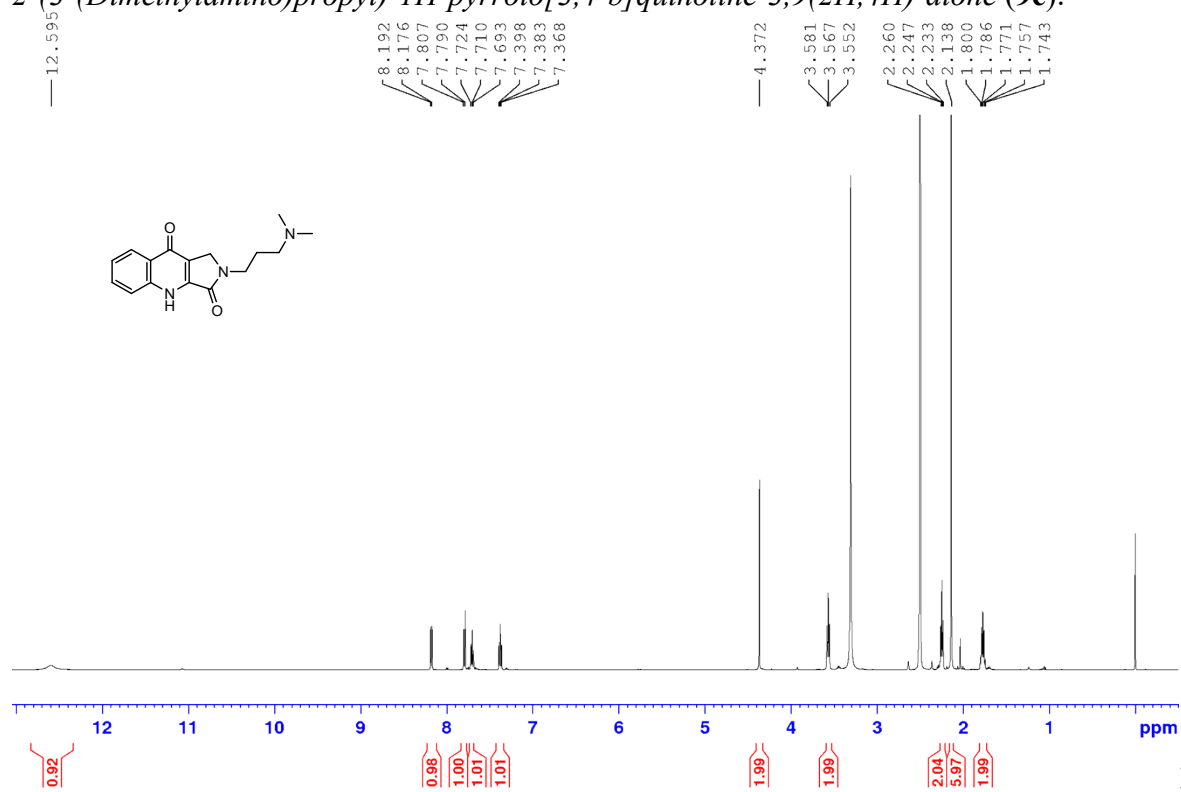


Figure S47. ¹³C-NMR spectrum of **4**

2-(3-(Dimethylamino)propyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**9e**):



Figure

e S48. ¹H-NMR spectrum of **9e**

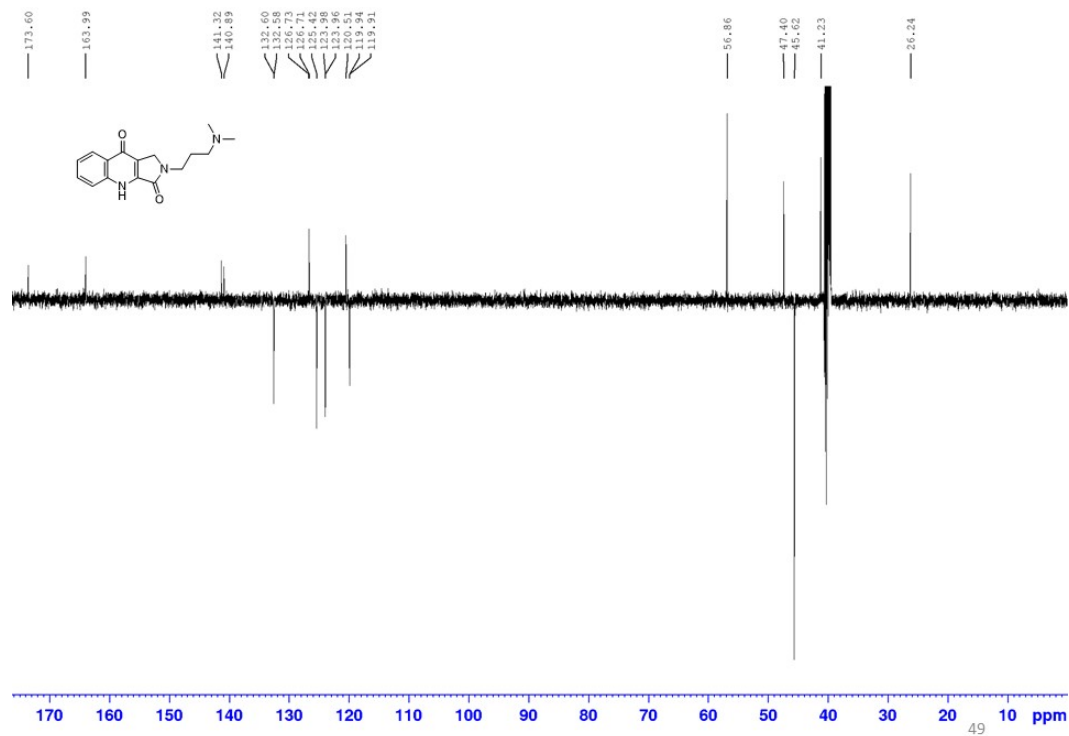
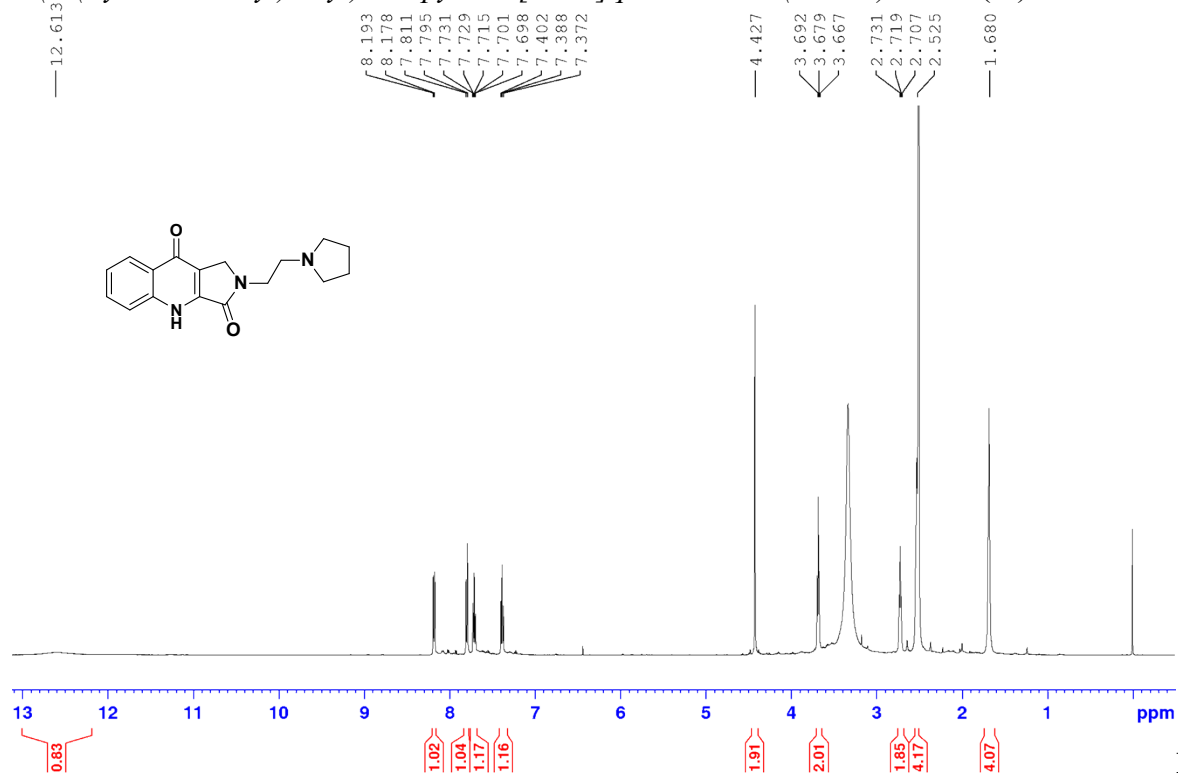


Figure S49. ¹³C-NMR spectrum of **9e**

2-(2-(Pyrrolidin-1-yl)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**9f**):



Figur

e S50. ¹H-NMR spectrum of **9f**

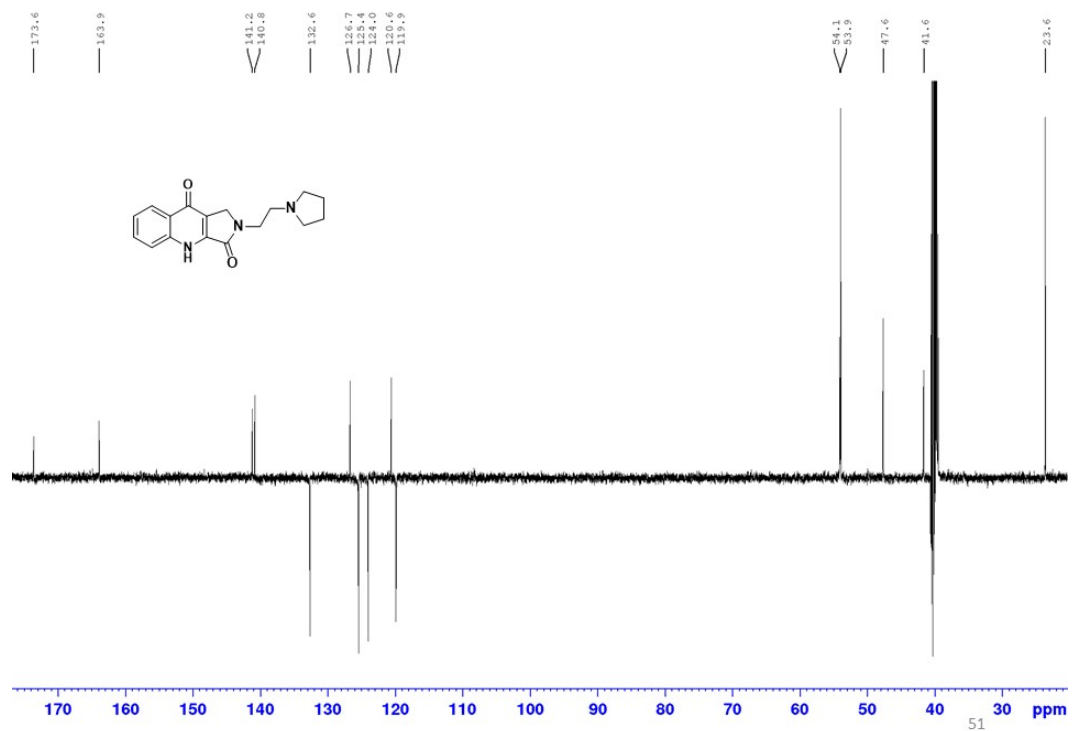


Figure S51. ^{13}C -NMR spectrum of **9f**

8-Chloro-2-(2-(dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (14a):

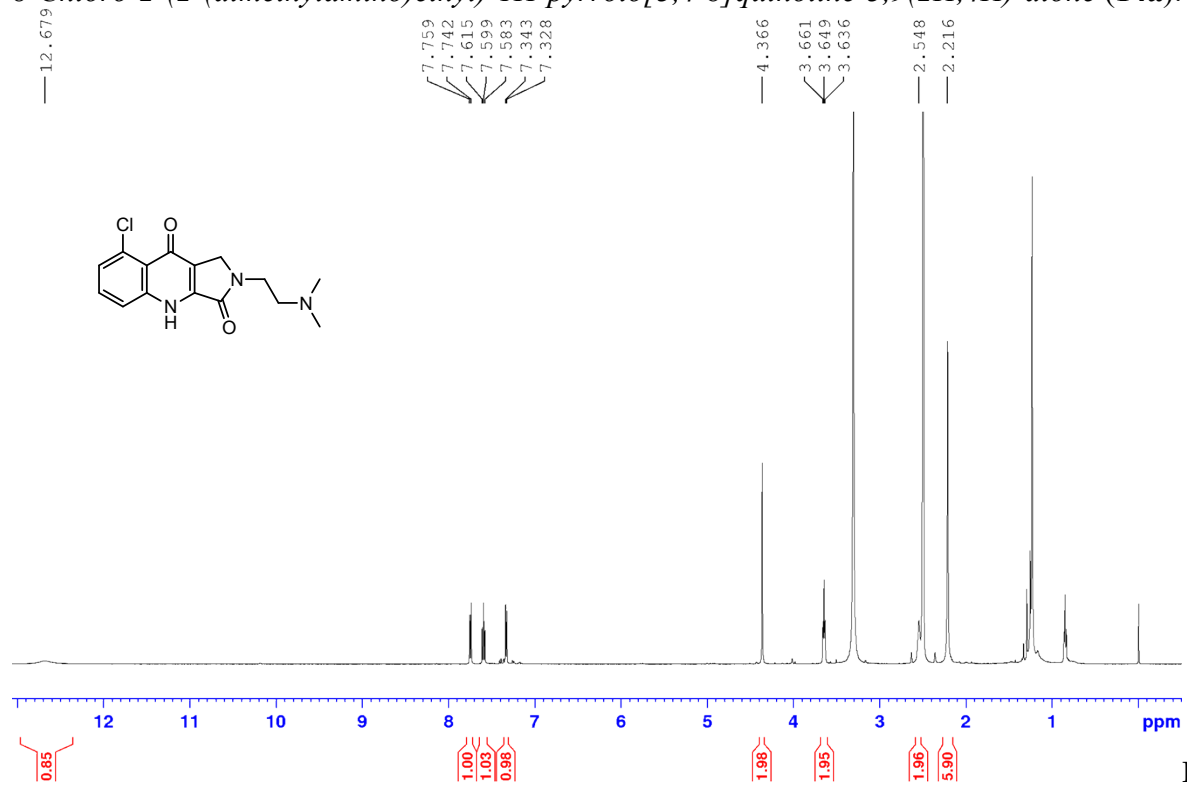


Figure S52. ^1H -NMR spectrum of **14a**



Figur

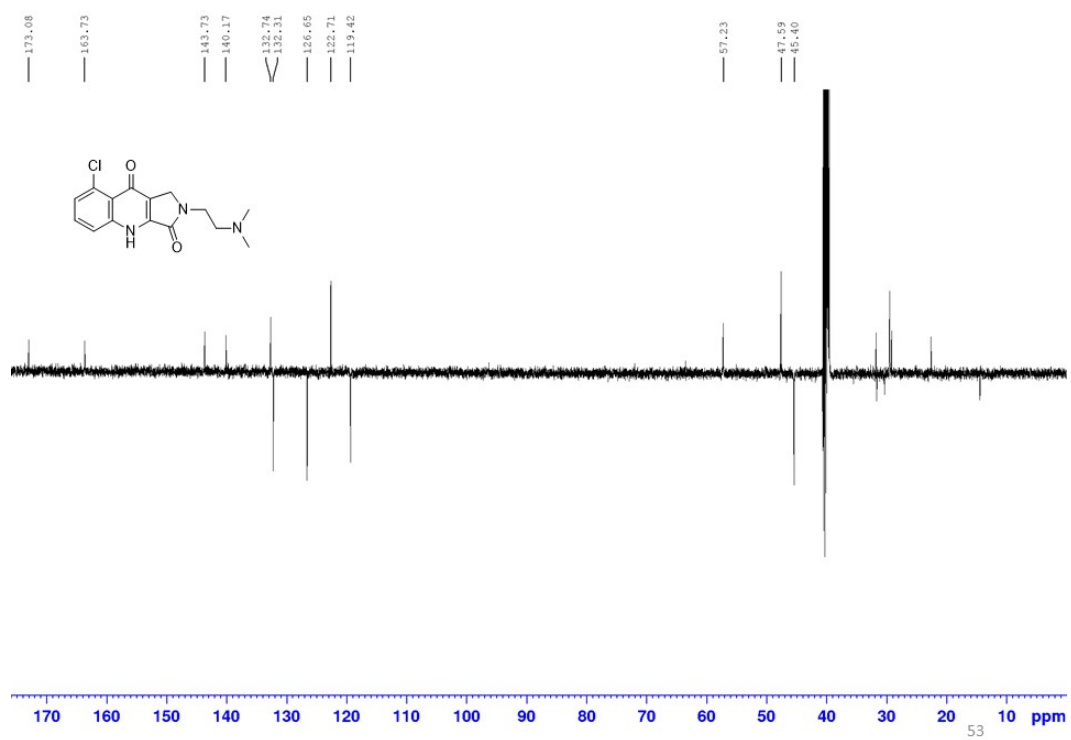


Figure S53. ¹³C-NMR spectrum of **14a**

6-Chloro-2-(2-(dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**14c**):

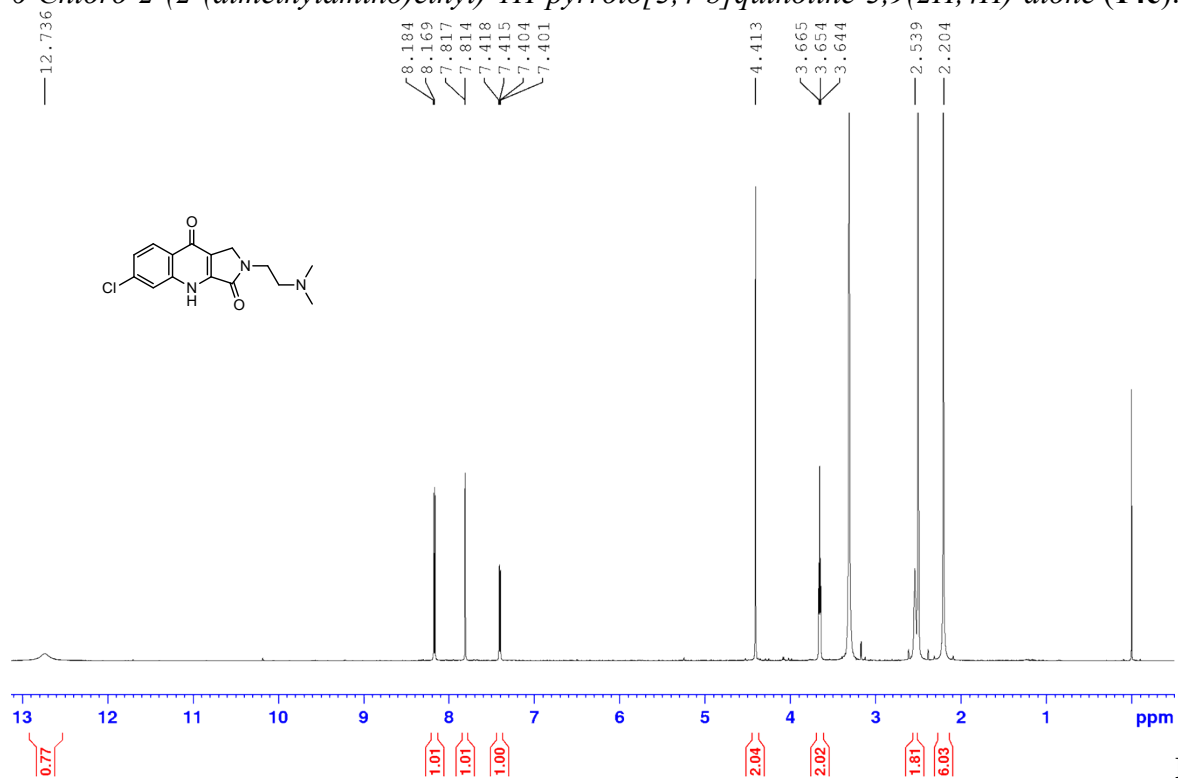


Figure S54. ¹H-NMR spectrum of **14c**

Figur

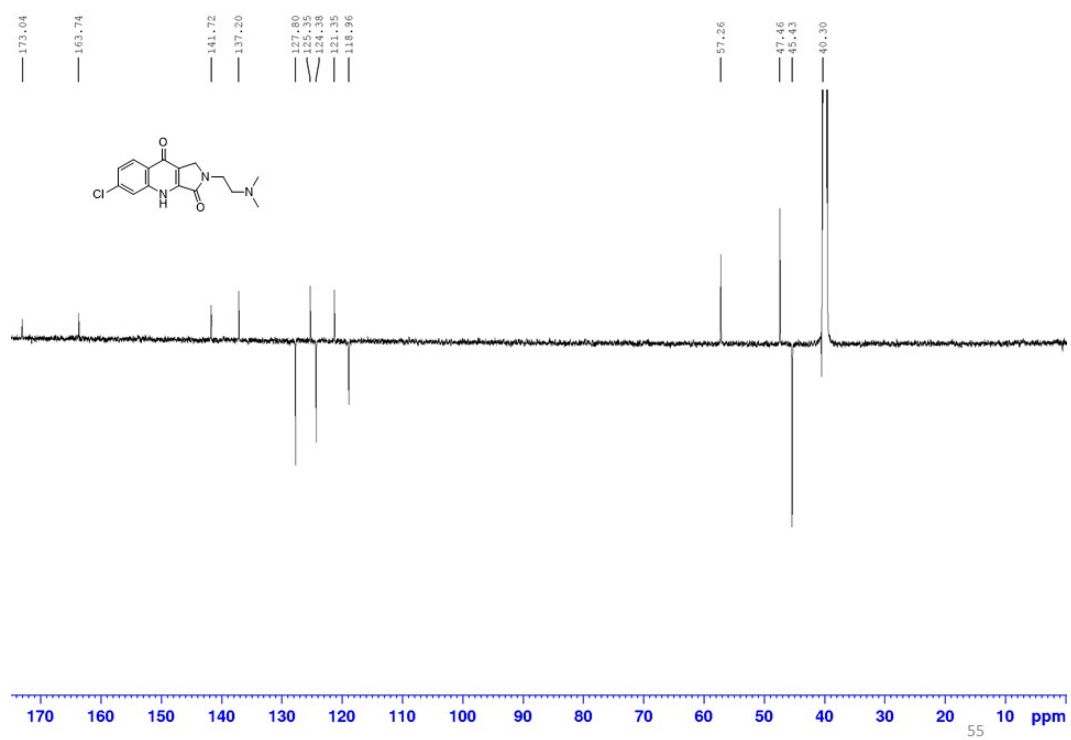


Figure S55. ¹³C-NMR spectrum of **14c**

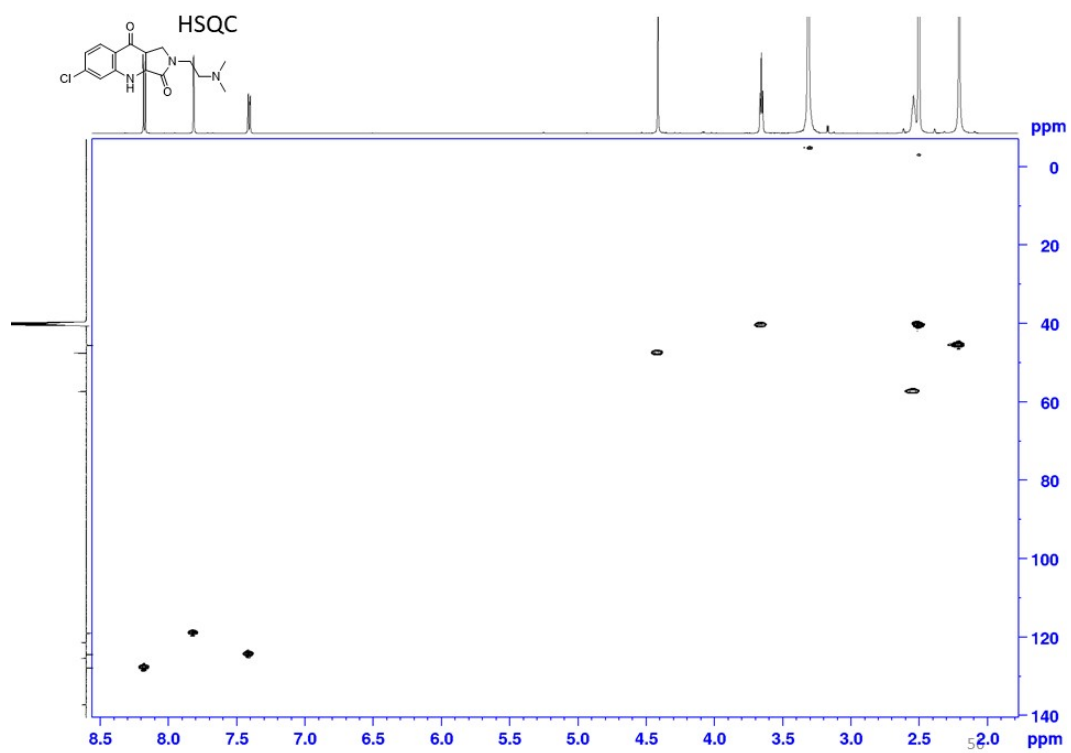
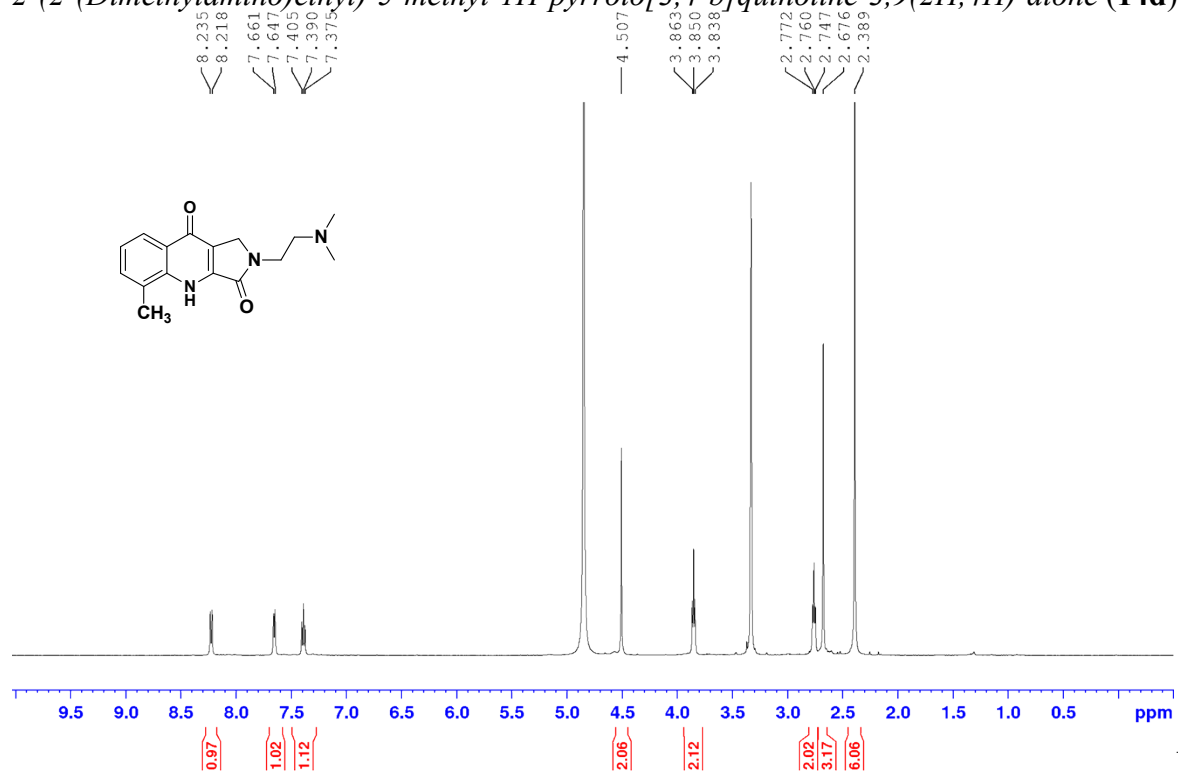


Figure S56. HSQC NMR spectrum of **14c**

2-(2-(Dimethylamino)ethyl)-5-methyl-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**14d**):



Figure

e S57. ¹H-NMR spectrum of **14d**

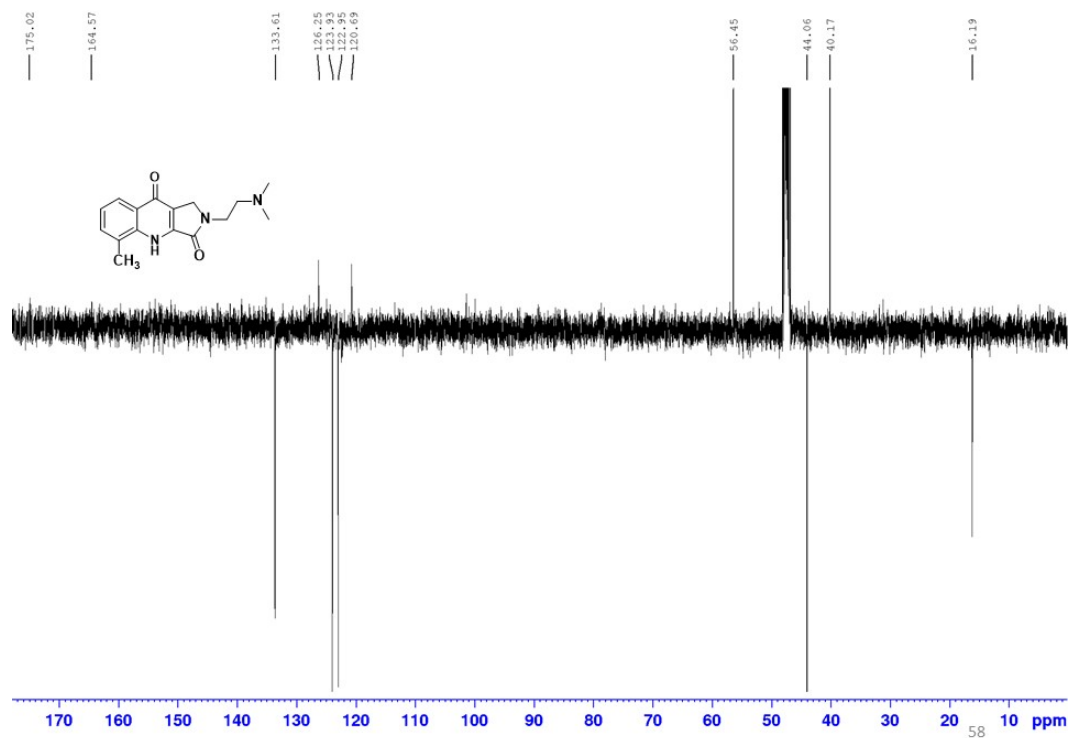
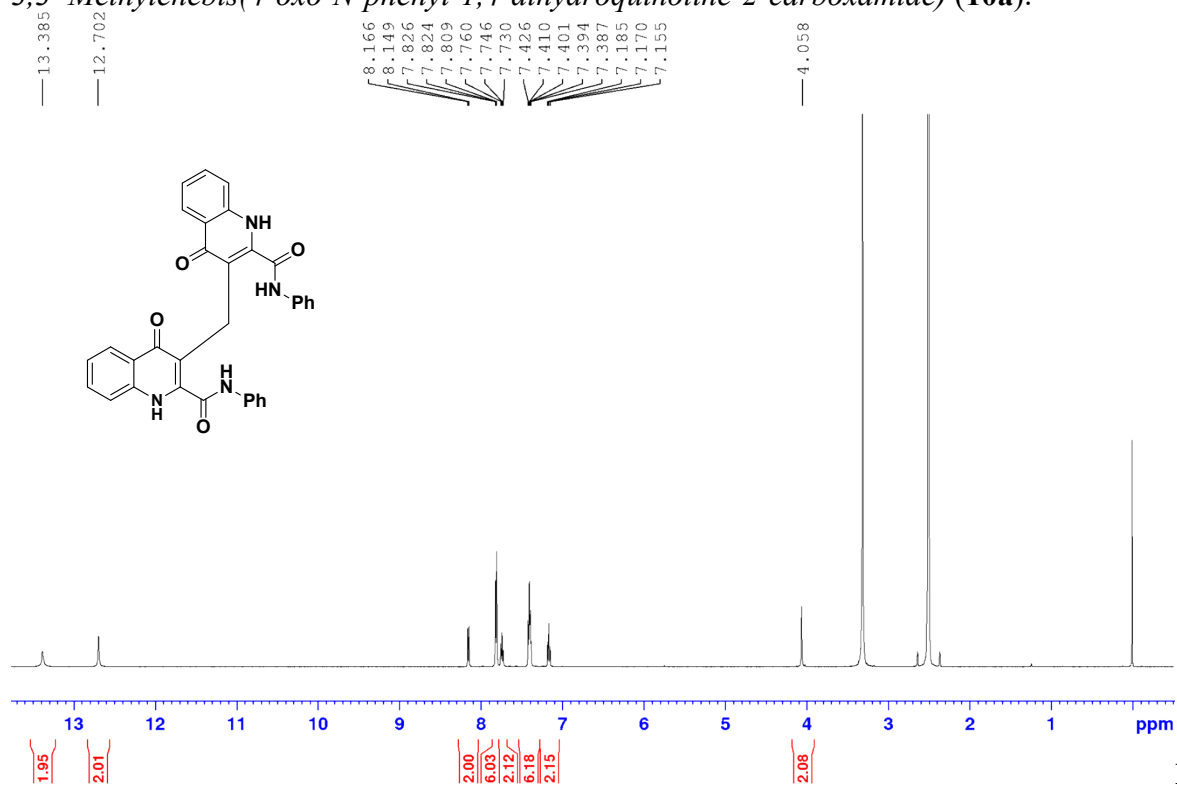


Figure S58. ¹³C-NMR spectrum of **14d**

3,3'-Methylenebis(4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide) (**10a**):



Figur

e S59. $^1\text{H-NMR}$ spectrum of **10a**

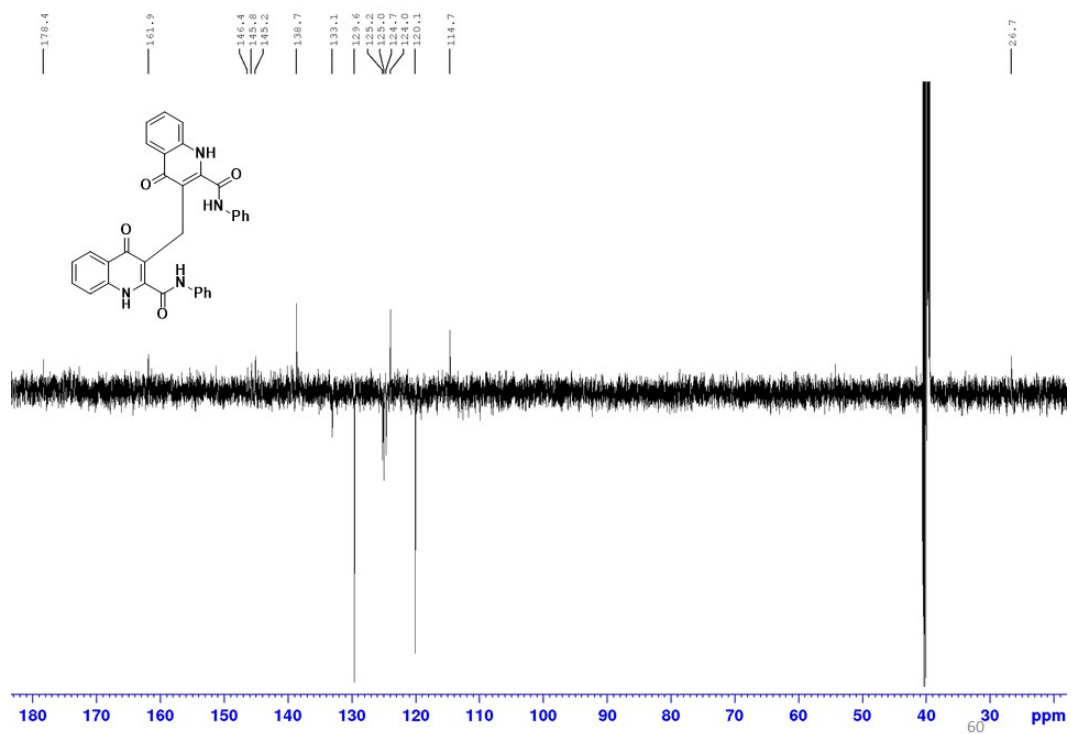


Figure S60. $^{13}\text{C-NMR}$ spectrum of **10a**

3,3'-Methylenebis(N-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxamide) (**10b**):

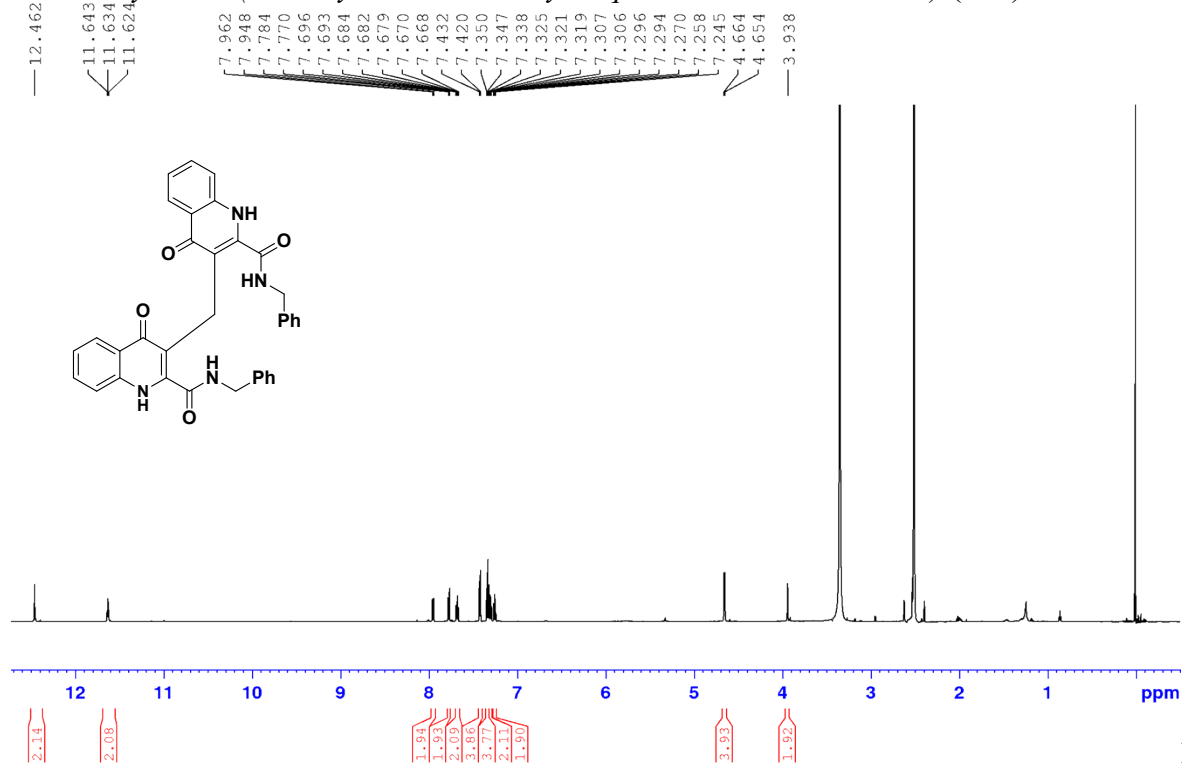


Figure S61. ¹H-NMR spectrum of **10b**

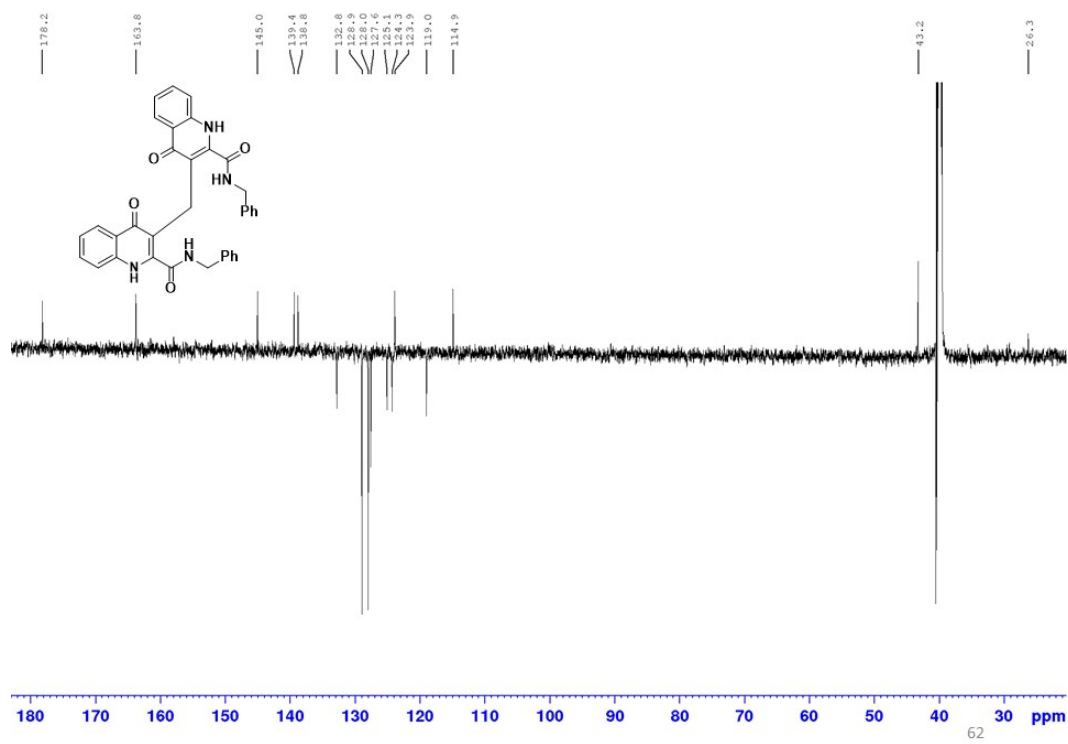
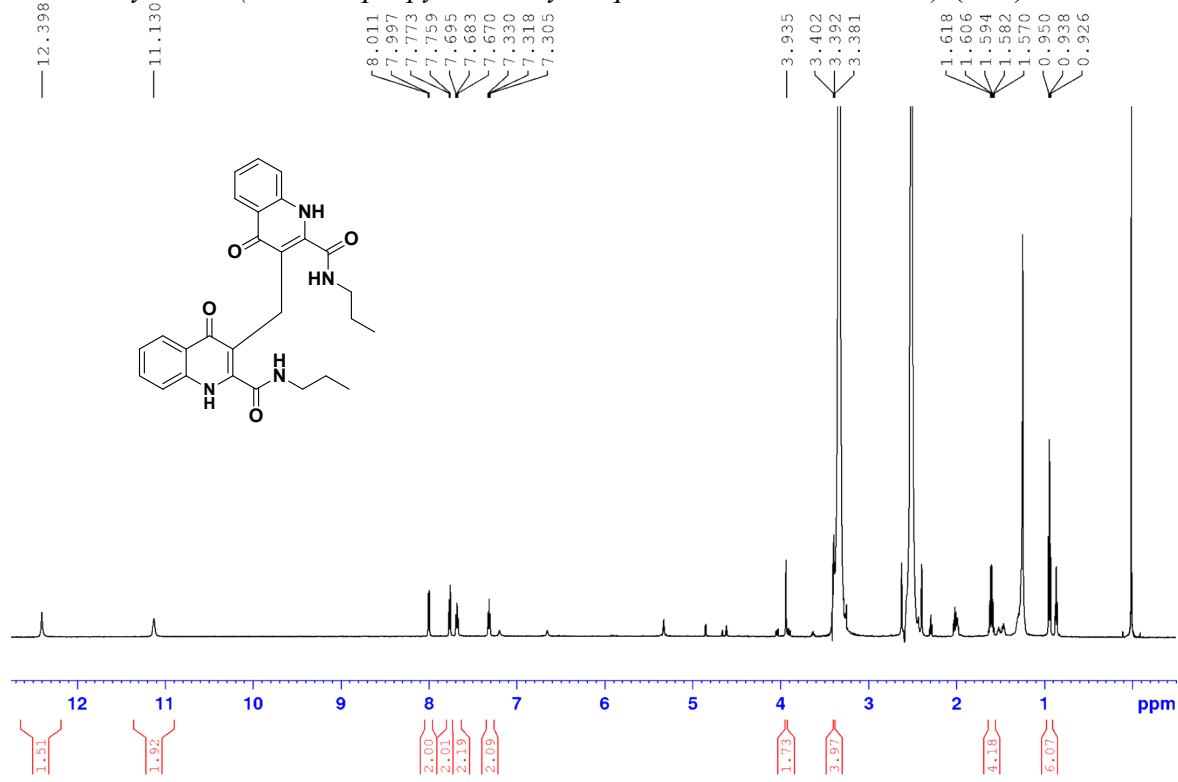


Figure S62. ¹³C-NMR spectrum of **10b**

3,3'-Methylenebis(4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide) (**10d**):



e S63. ¹H-NMR spectrum of **10d**

Figur

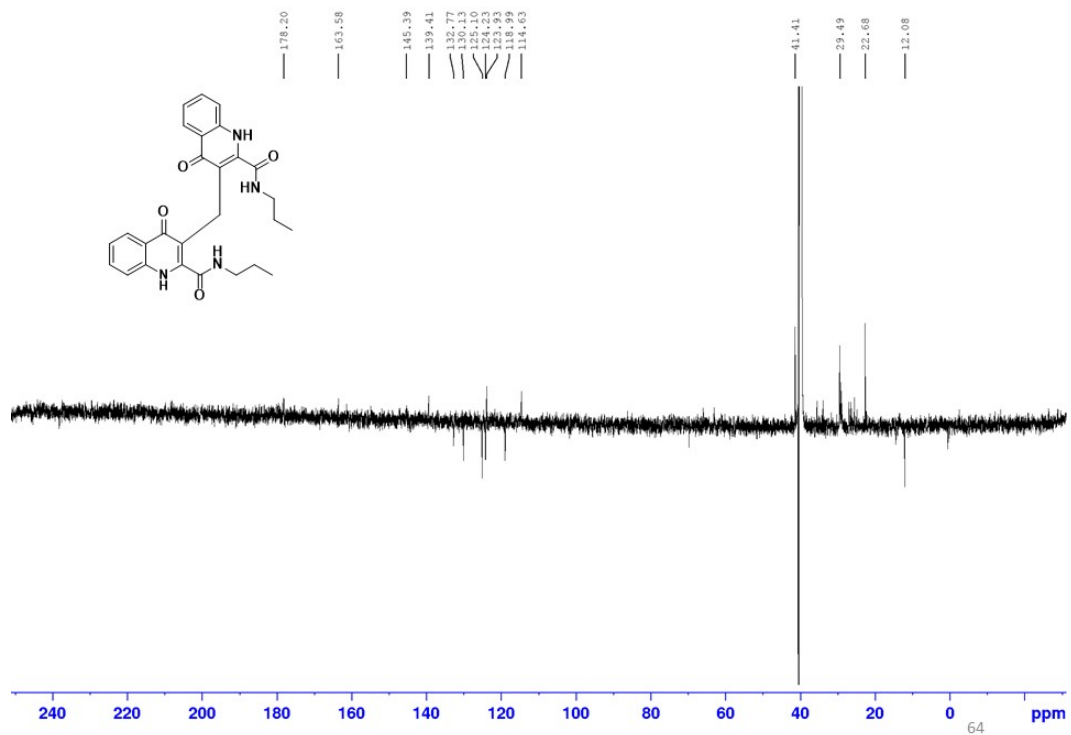
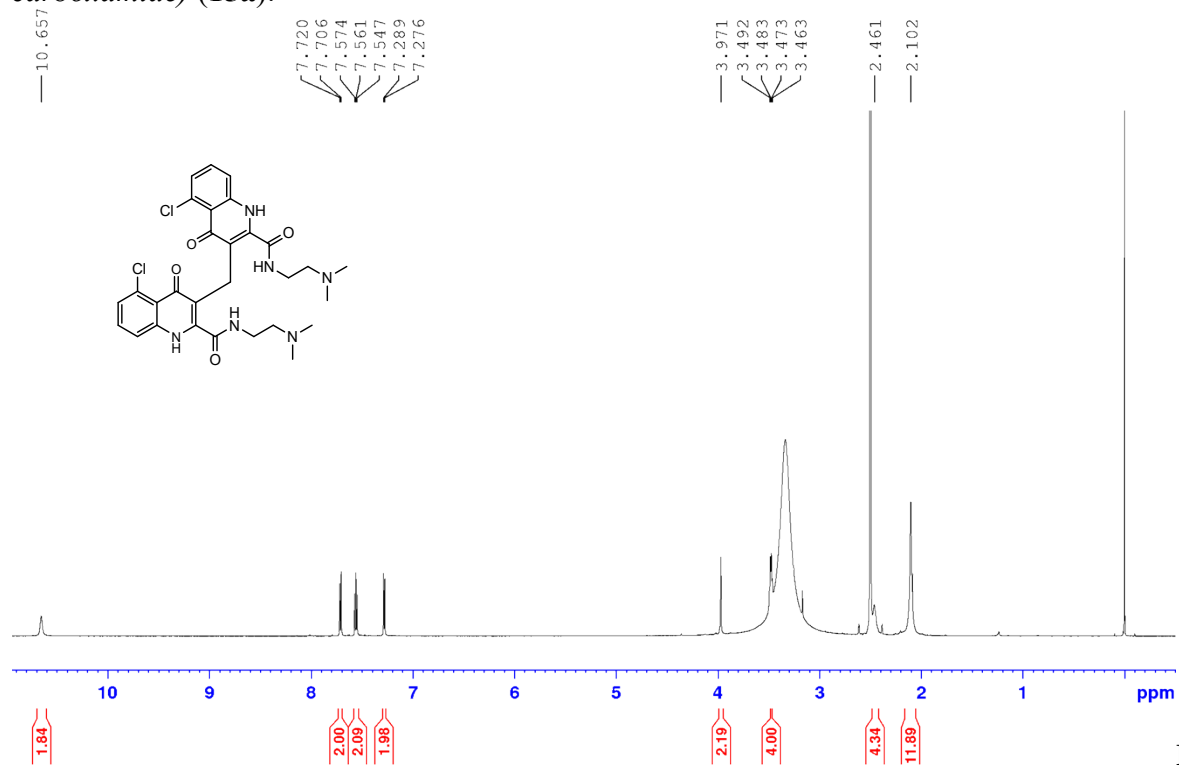


Figure S64. ¹³C-NMR spectrum of **10d**

3,3'-Methylenebis(5-chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide) (**15a**):



Figur

e S65. ¹H-NMR spectrum of **15a**

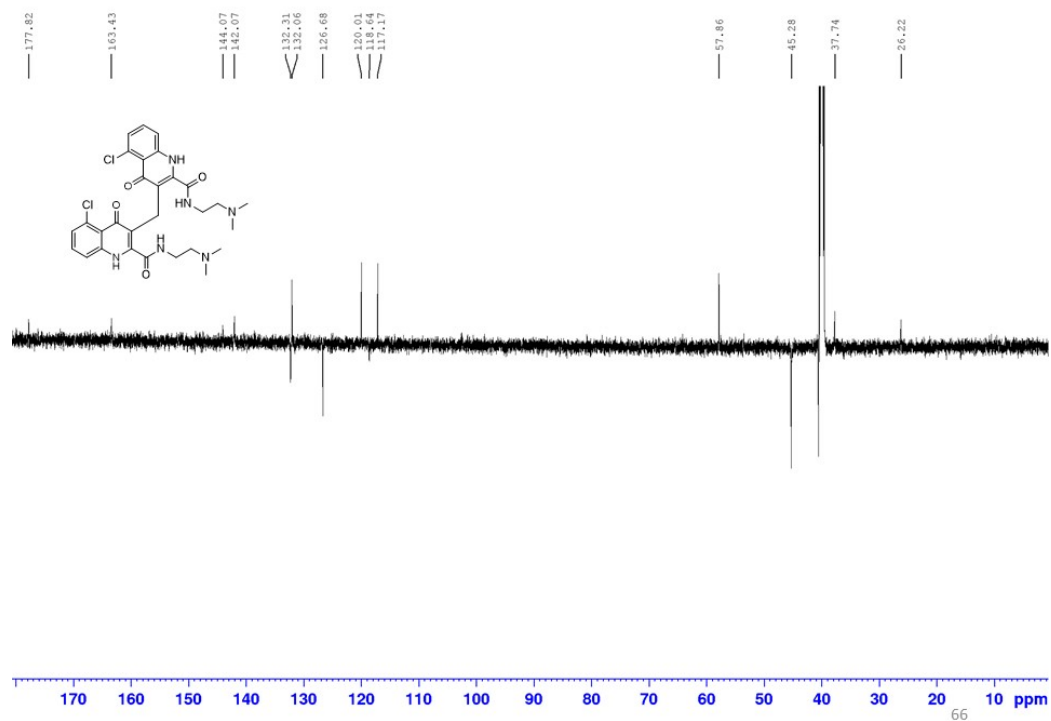
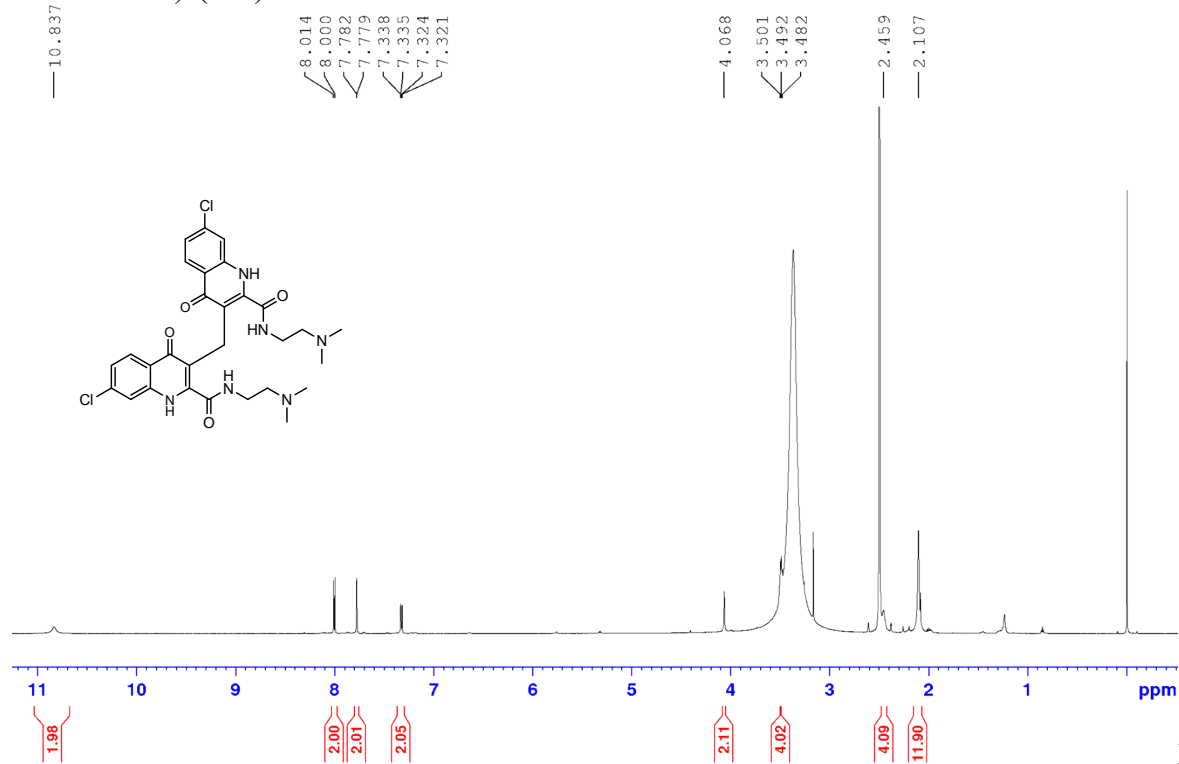


Figure S66. ^{13}C -NMR spectrum of **15a**
 3,3'-Methylenebis(7-chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide) (**15c**):



Figur

e S67. ^1H -NMR spectrum of **15c**

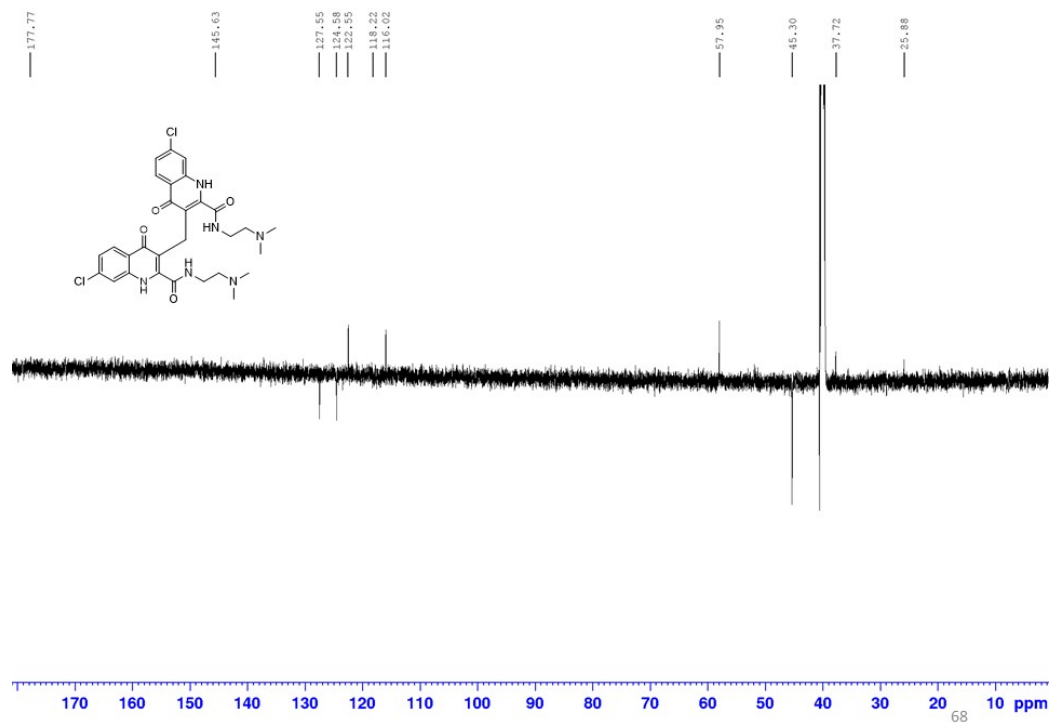


Figure S68. ^{13}C -NMR spectrum of **15c**

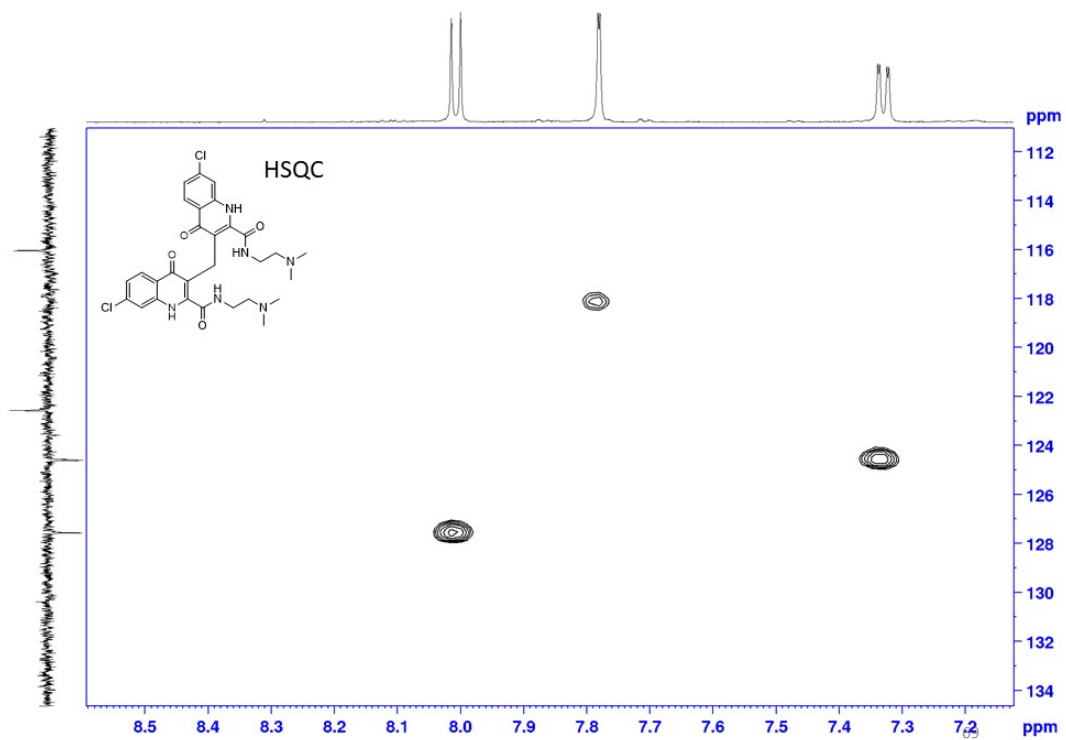


Figure S69. HSQC NMR spectrum of **15c**

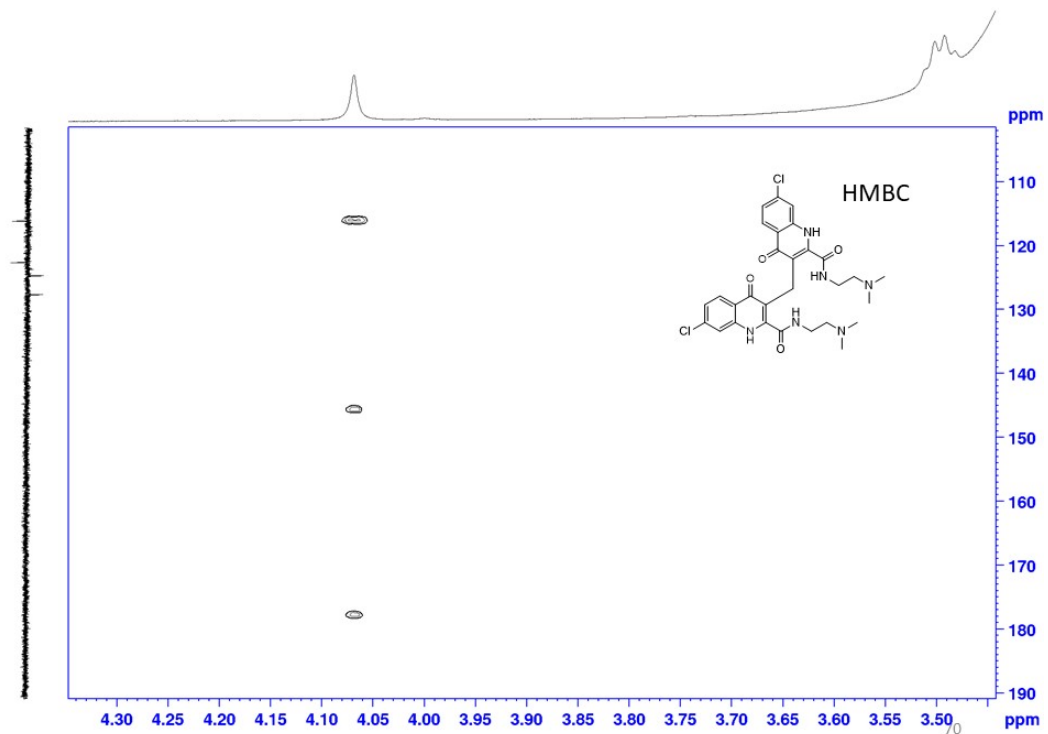


Figure S70. HMBC NMR spectrum of **15c**

4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide (7a):

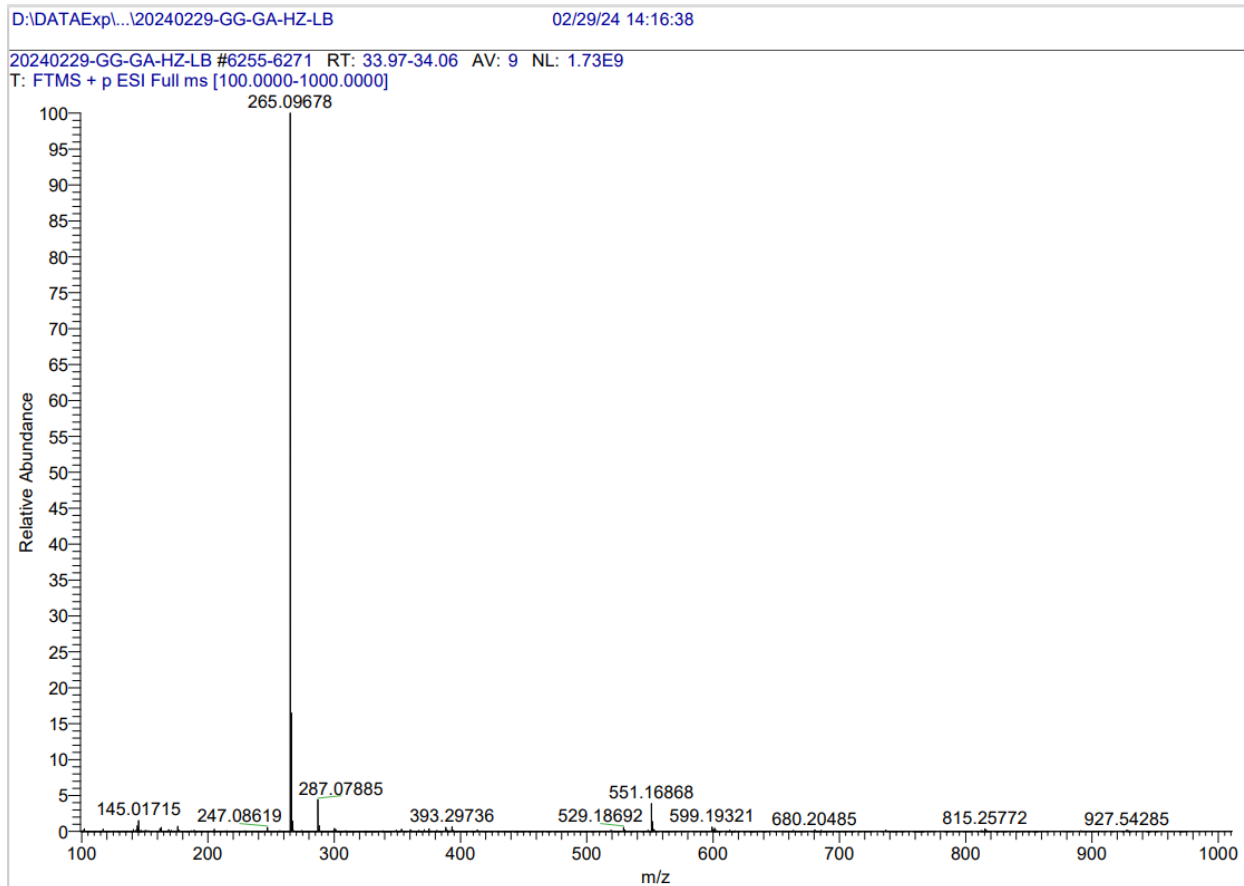


Figure S71. HR-MS spectrum of **7a** (mass accuracy of - 2.5 ppm)

N-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxamide (**7b**):

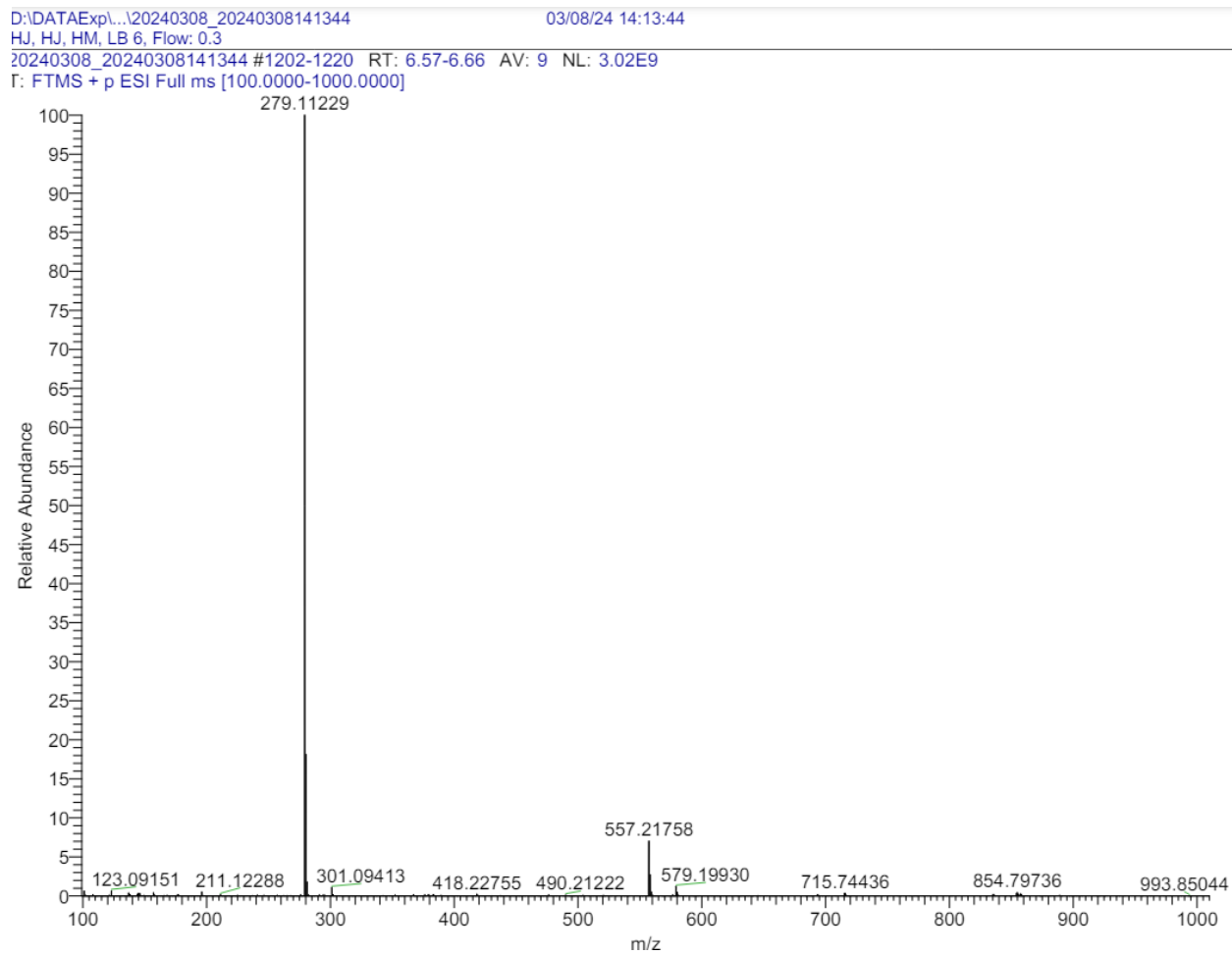


Figure S72. HR-MS spectrum of **7b** (mass accuracy of - 1.8 ppm)

4-oxo-N-phenethyl-1,4-dihydroquinoline-2-carboxamide (**7c**):

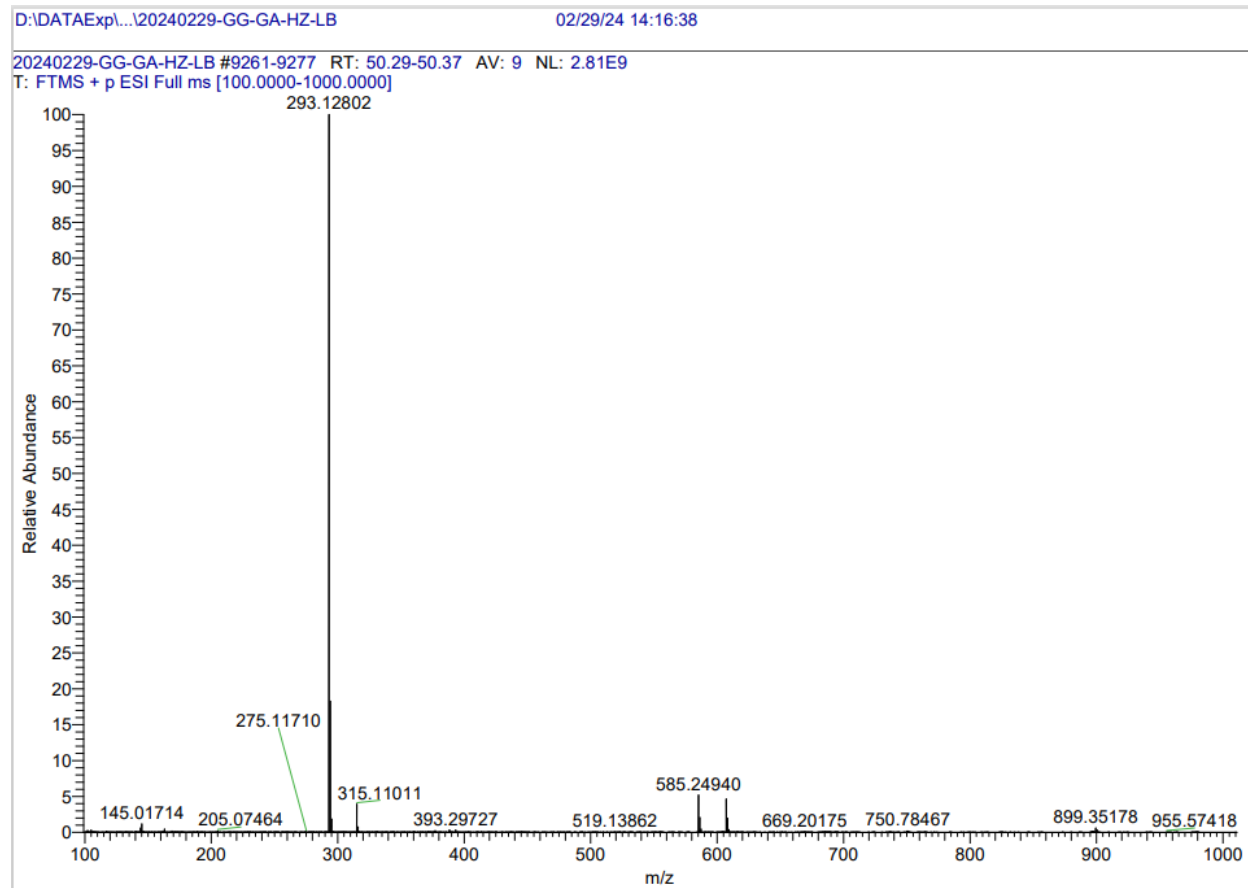


Figure S73. HR-MS spectrum of **7c** (mass accuracy of -1.5 ppm)

4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide (7d):

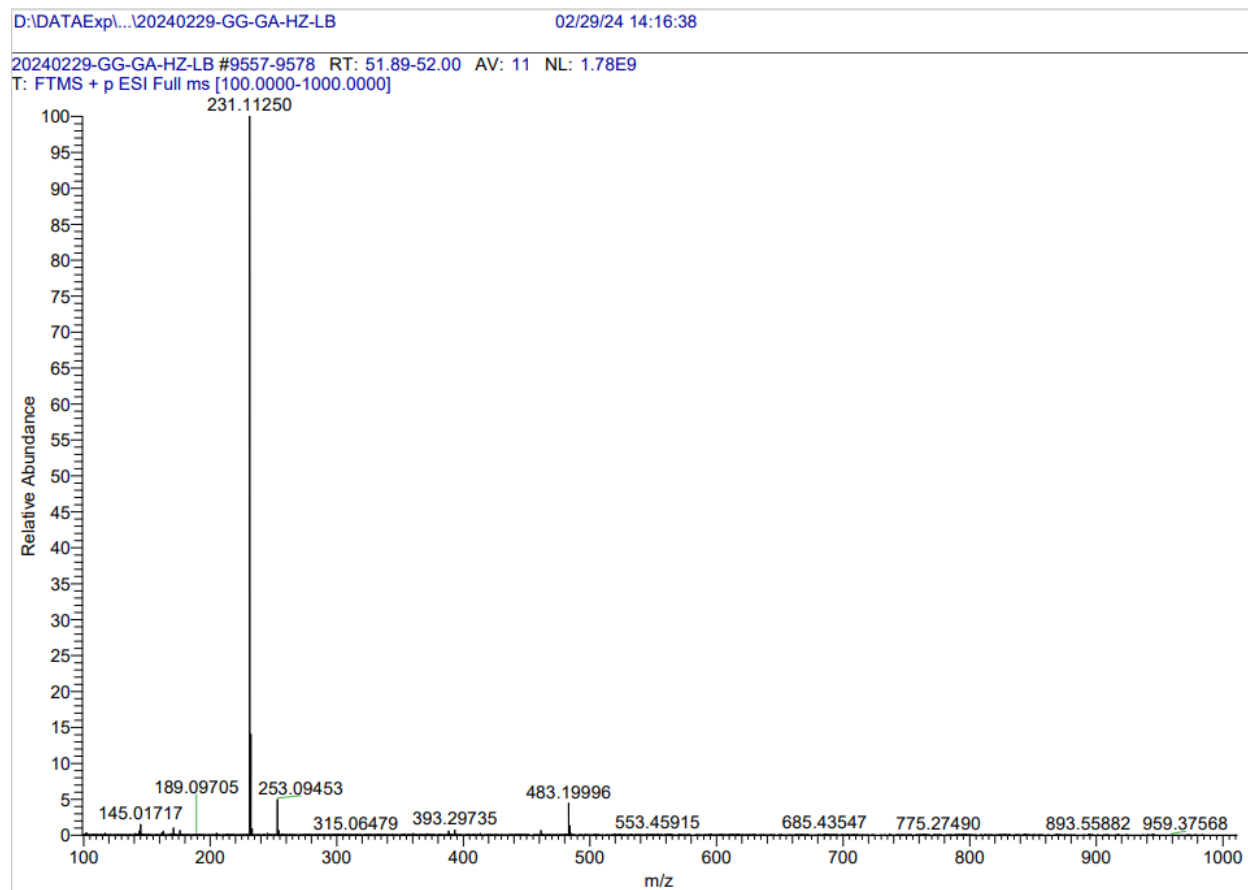


Figure S74. HR-MS spectrum of **7d** (mass accuracy of -1.3 ppm)

5-Chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (12a):

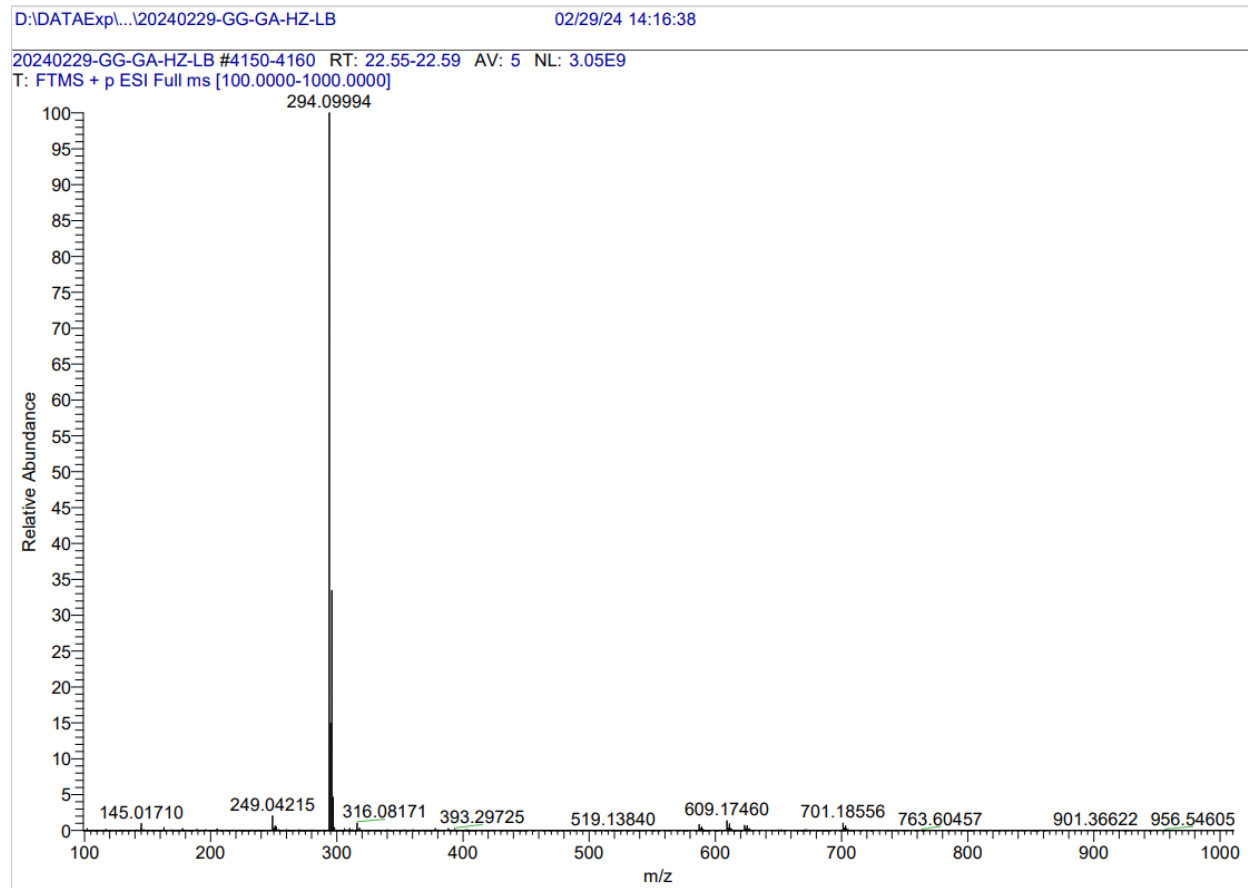


Figure S75. HR-MS spectrum of **12a** (mass accuracy of -1.5 ppm)

N-(2-(dimethylamino)ethyl)-4-oxo-6-phenyl-1,4-dihydroquinoline-2-carboxamide (**12b**):

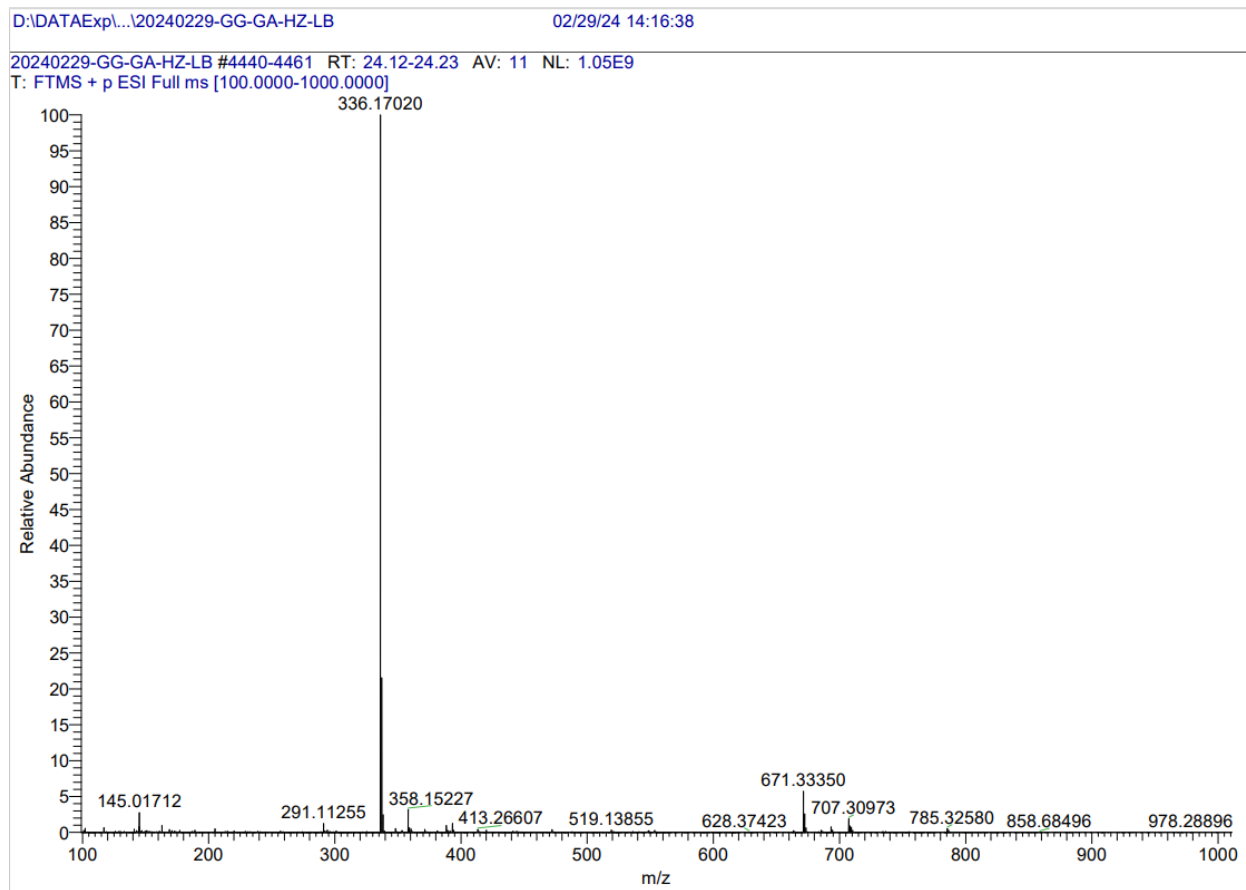


Figure S76. HR-MS spectrum of **12b** (mass accuracy of -1.3 ppm)

7-Chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**12c**):

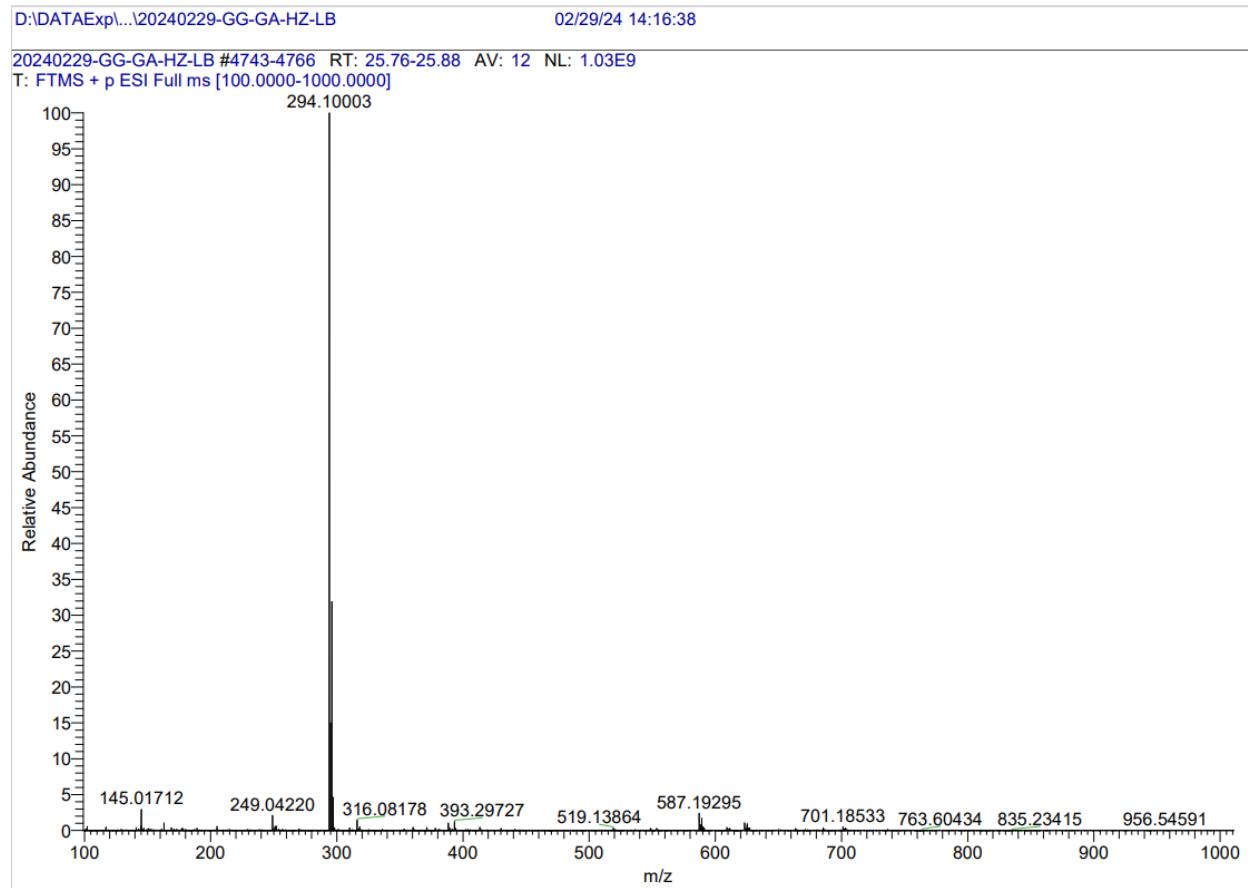


Figure S77. HR-MS spectrum of **12c** (mass accuracy of -1.2 ppm)

N-(2-(dimethylamino)ethyl)-8-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide (**12d**):

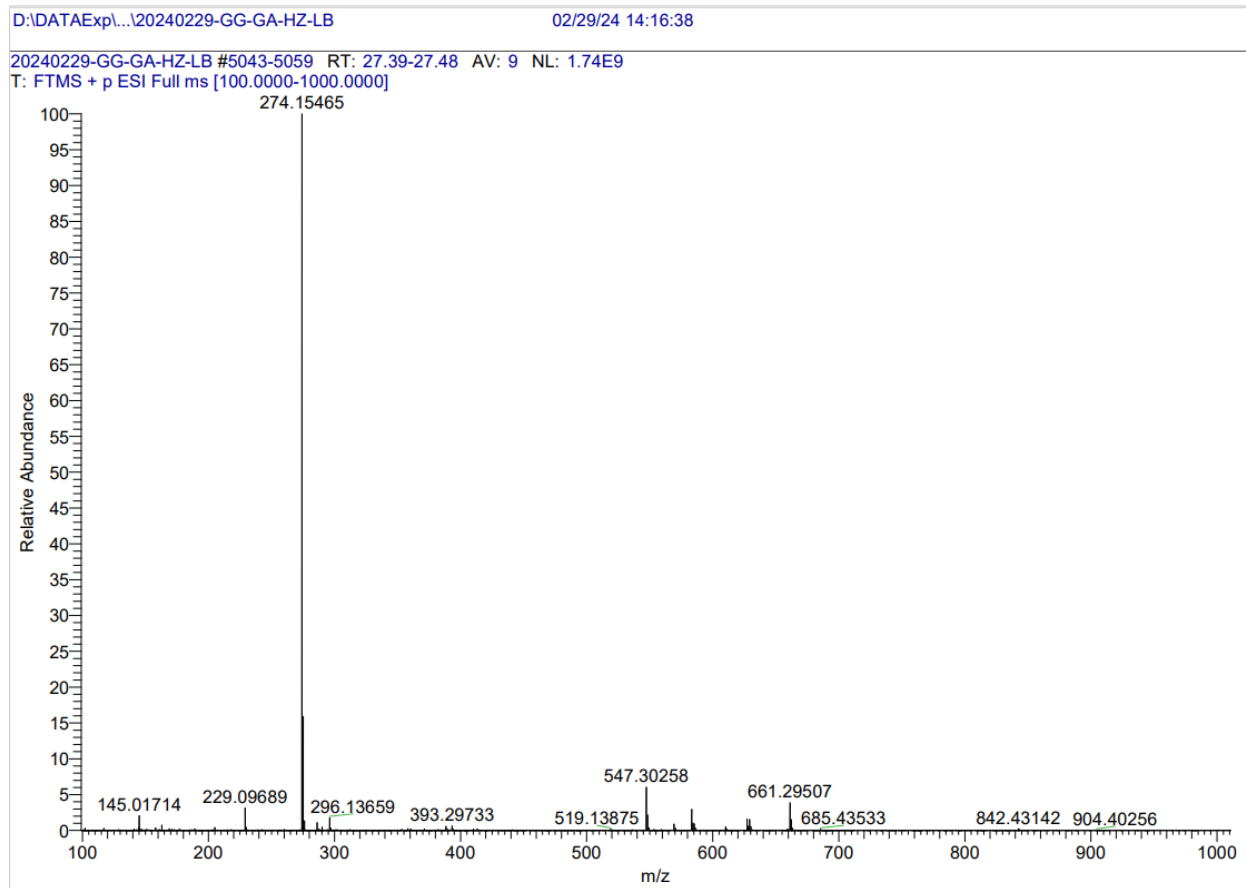


Figure S78. HR-MS spectrum of **12d** (mass accuracy of -1.3 ppm)

3-(Morpholinomethyl)-4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide (**8a**):

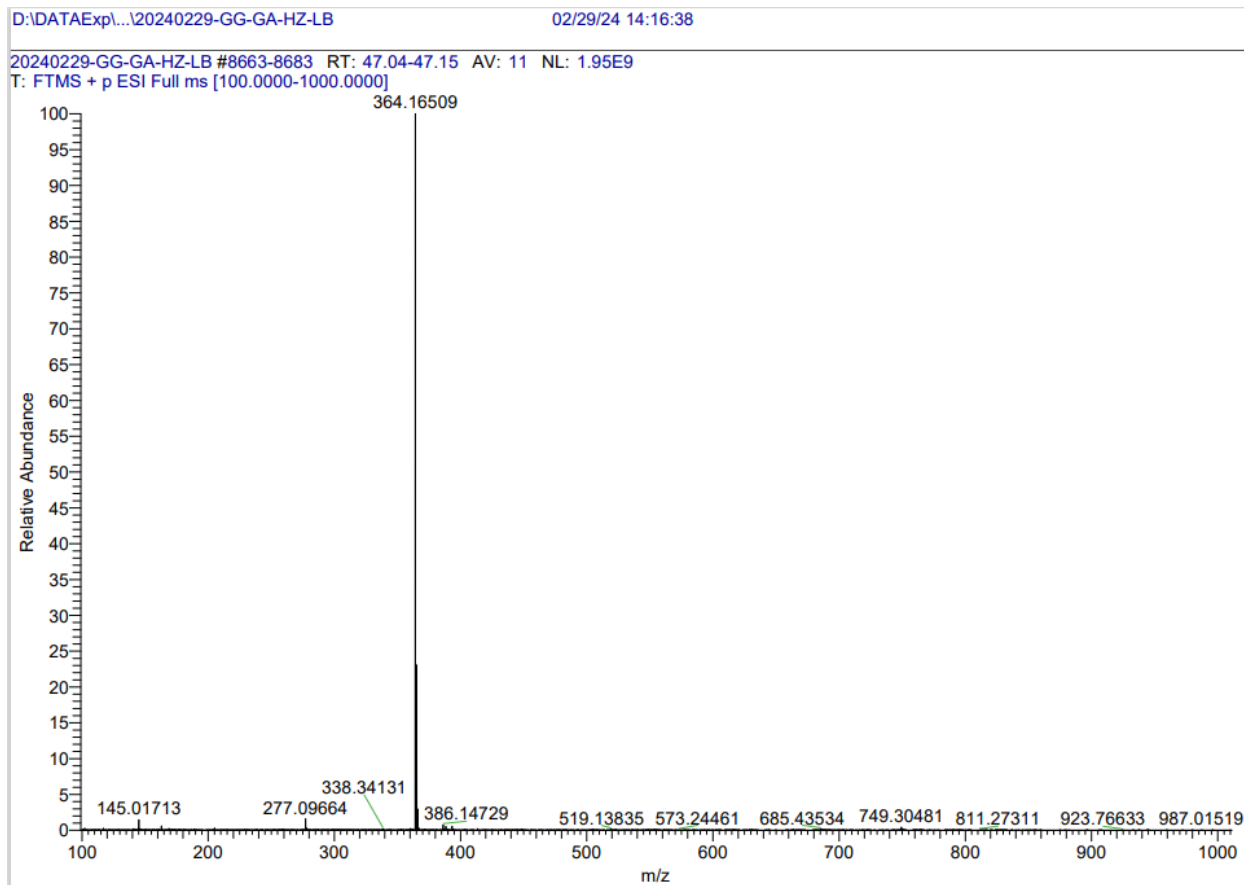


Figure S79. HR-MS spectrum of **8a** (mass accuracy of -1.3 ppm)

N-benzyl-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**8b**):

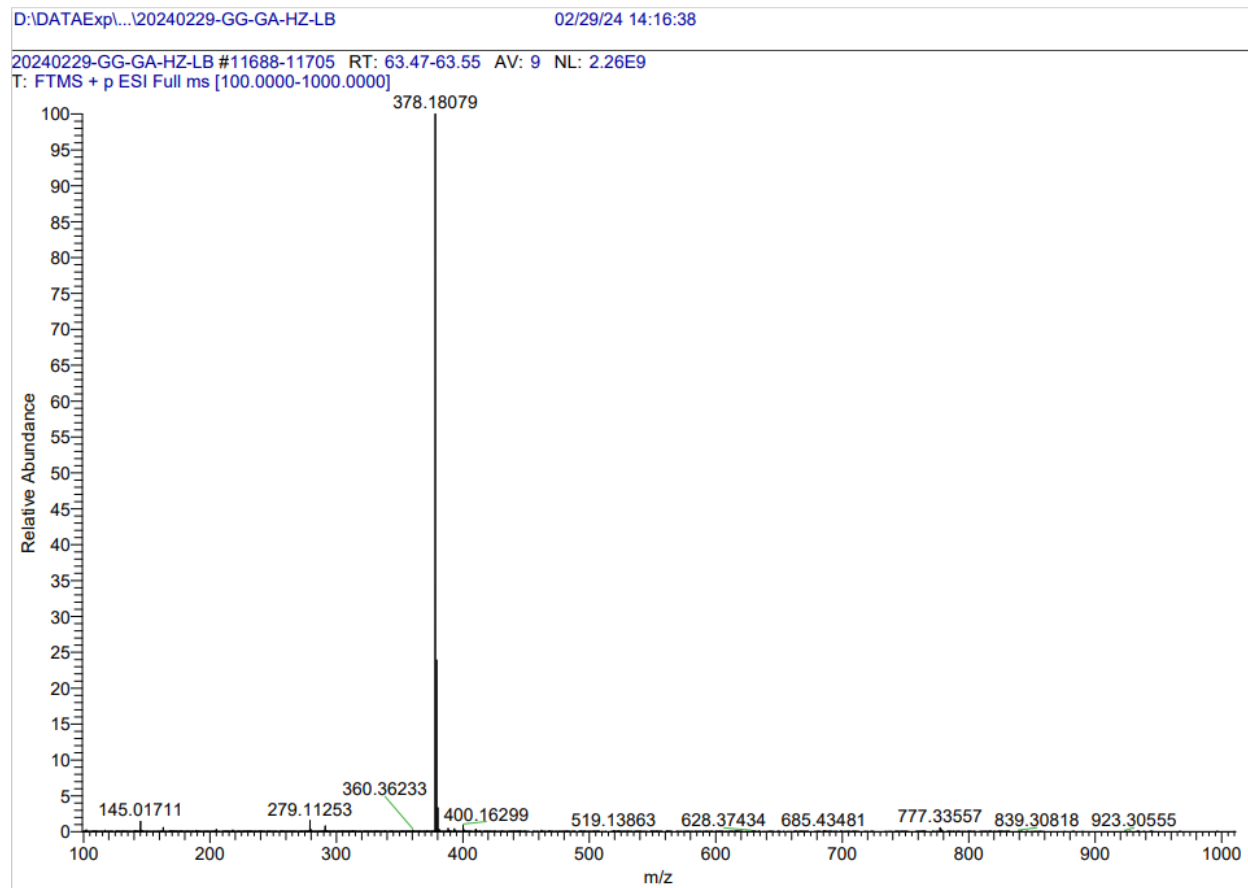


Figure S80. HR-MS spectrum of **8b** (mass accuracy of -1.1 ppm)

3-(Morpholinomethyl)-4-oxo-N-phenethyl-1,4-dihydroquinoline-2-carboxamide (8c):

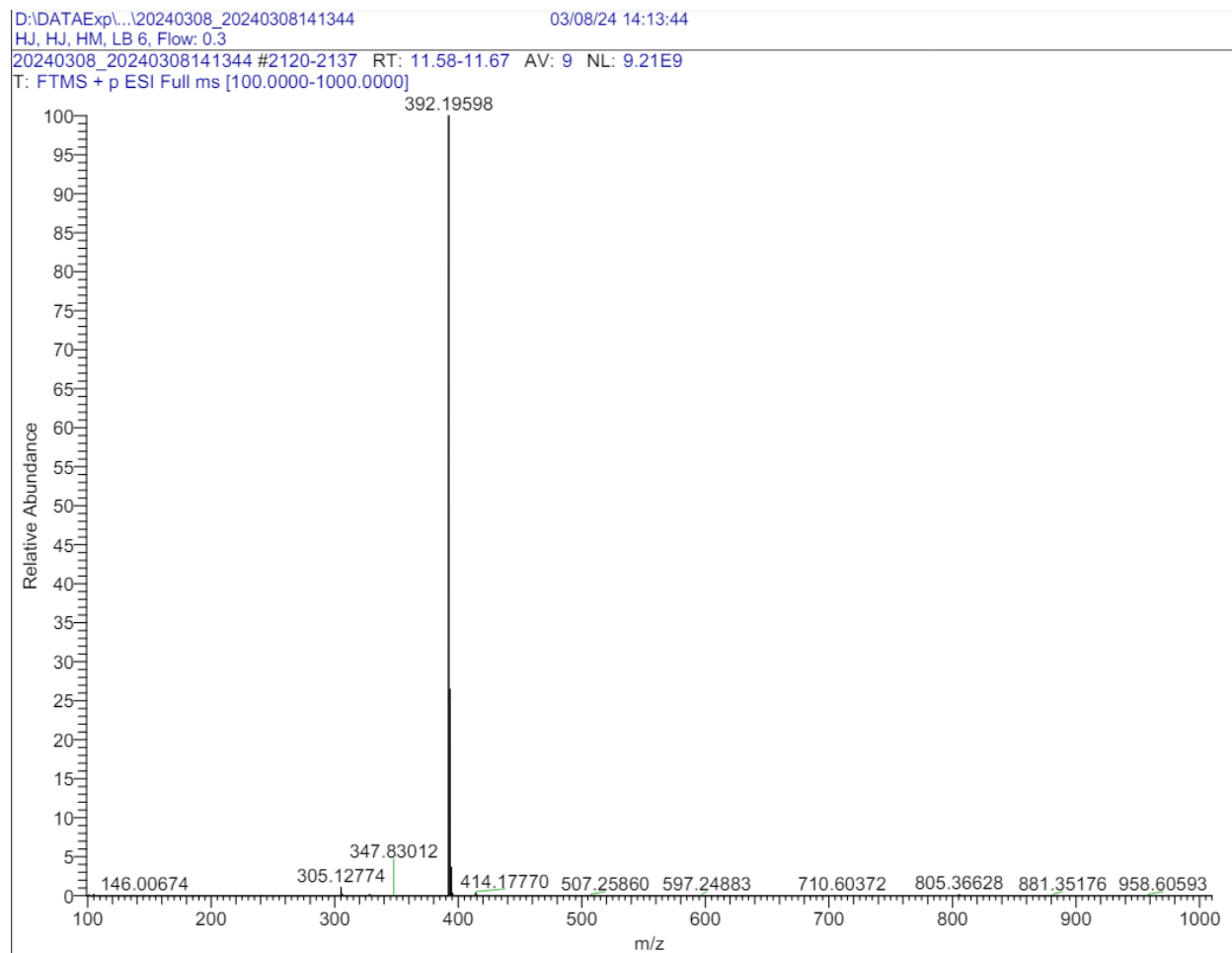


Figure S81. HR-MS spectrum of **8c** (mass accuracy of -2.3 ppm)

3-(Morpholinomethyl)-4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide (8d):

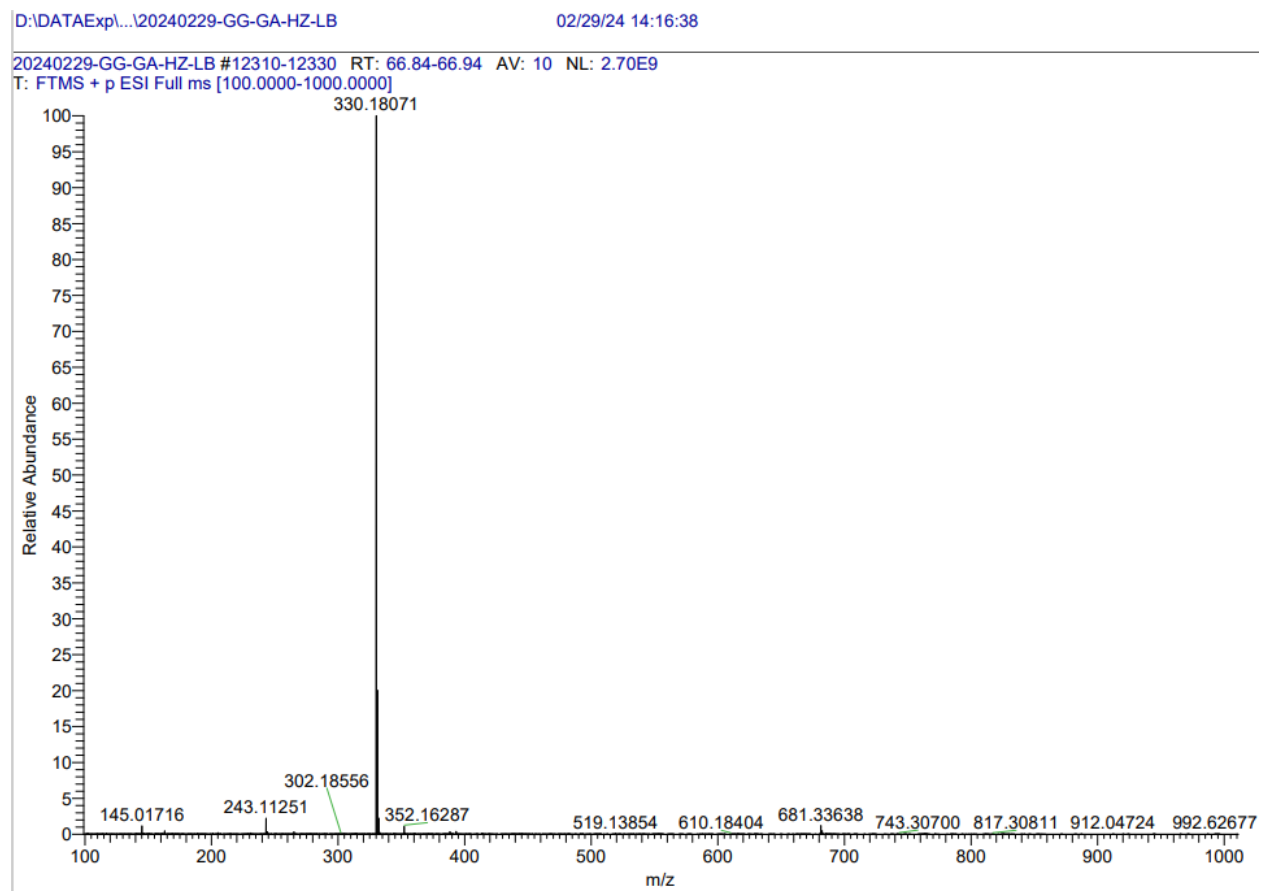


Figure S82. HR-MS spectrum of **8d** (mass accuracy of -1.5 ppm)

N-(3-(dimethylamino)propyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**8e**):

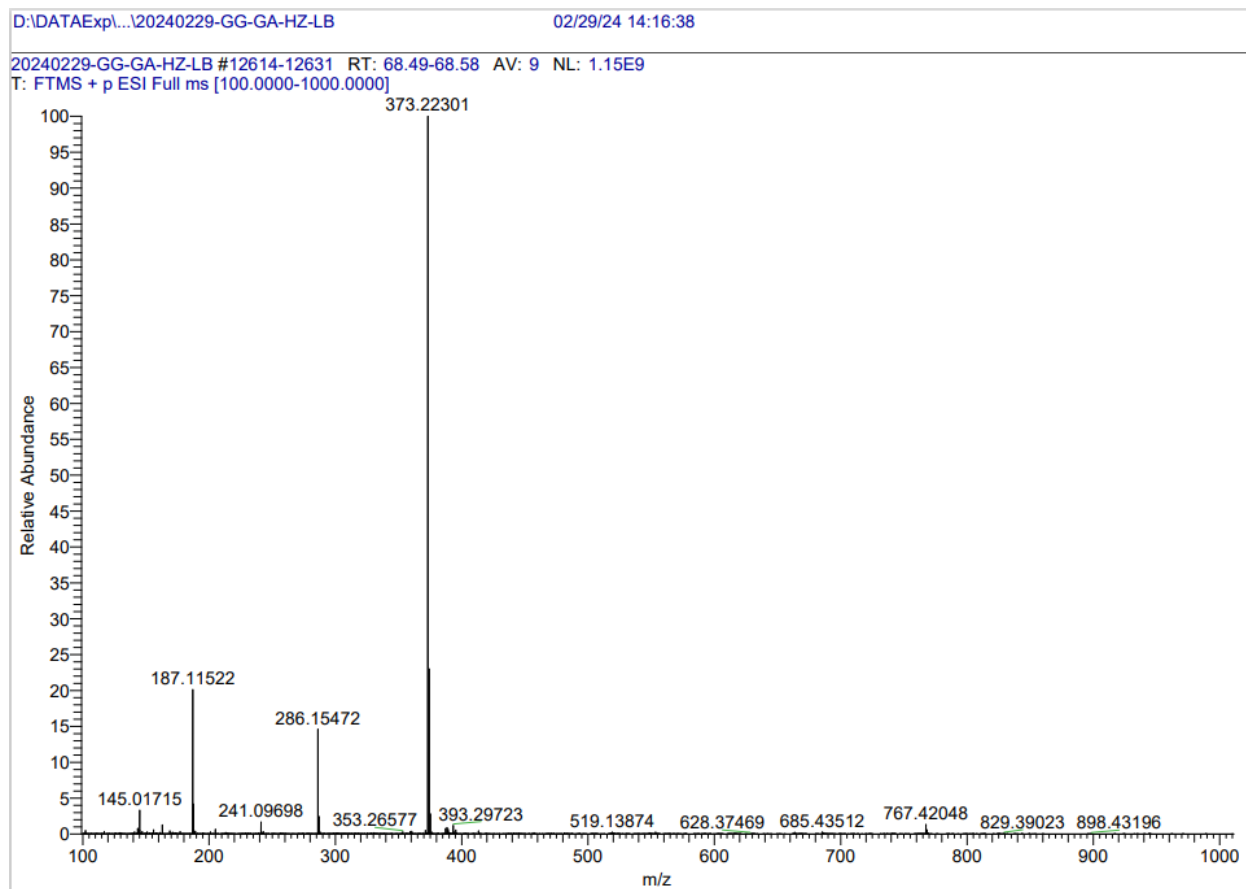


Figure S83. HR-MS spectrum of **8e** (mass accuracy of -1.1 ppm)

5-Chloro-N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (13a):

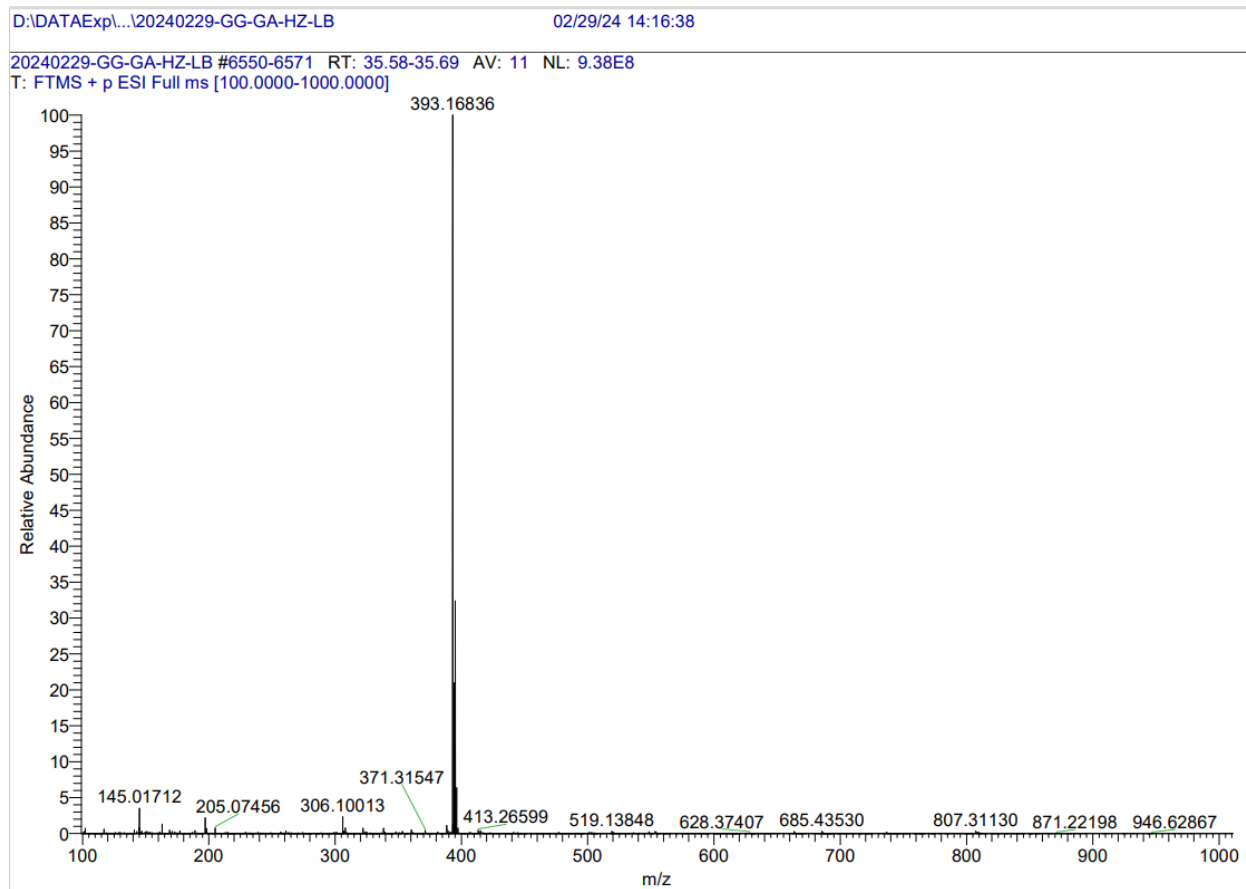


Figure S84. HR-MS spectrum of **13a** (mass accuracy of -1.1 ppm)

N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-6-phenyl-1,4-dihydroquinoline-2-carboxamide (**13b**):

D:\DATAExp\...20240229-GG-GA-HZ-LB

02/29/24 14:16:38

20240229-GG-GA-HZ-LB #6850-6874 RT: 37.21-37.32 AV: 12 NL: 1.10E9

T: FTMS + p ESI Full ms [100.0000-1000.0000]

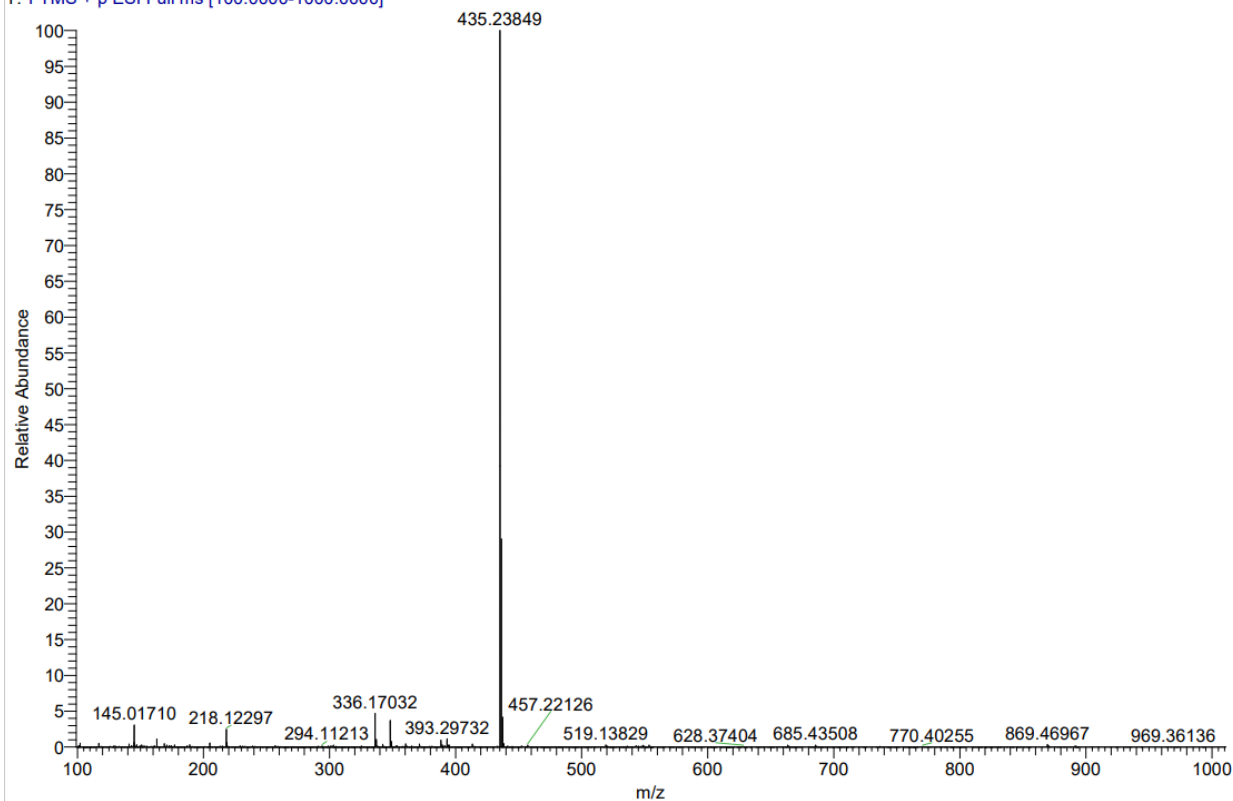


Figure S85. HR-MS spectrum of **13b** (mass accuracy of -1.3 ppm)

7-Chloro-N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**13c**):

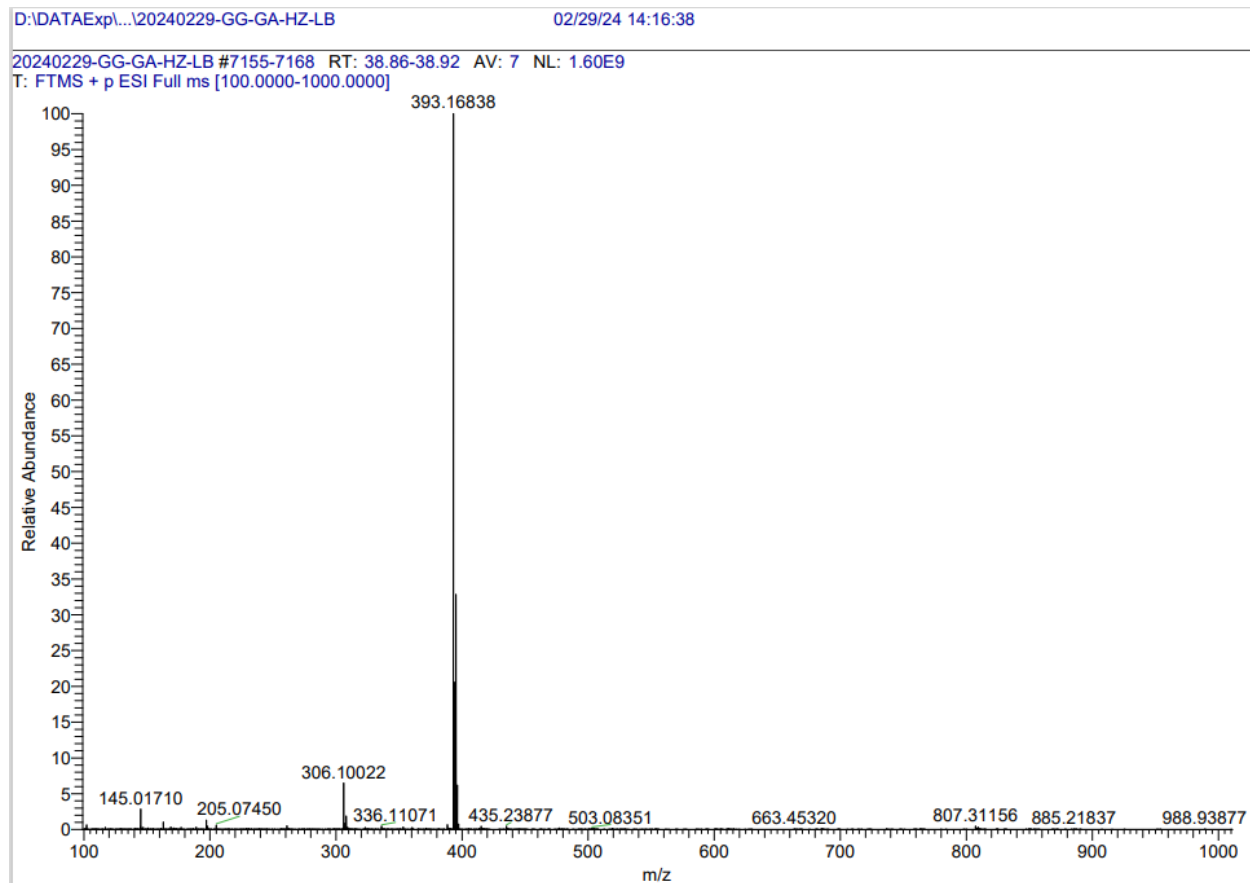


Figure S86. HR-MS spectrum of **13c** (mass accuracy of -1.1 ppm)

N-(2-(dimethylamino)ethyl)-8-methyl-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (**13d**):

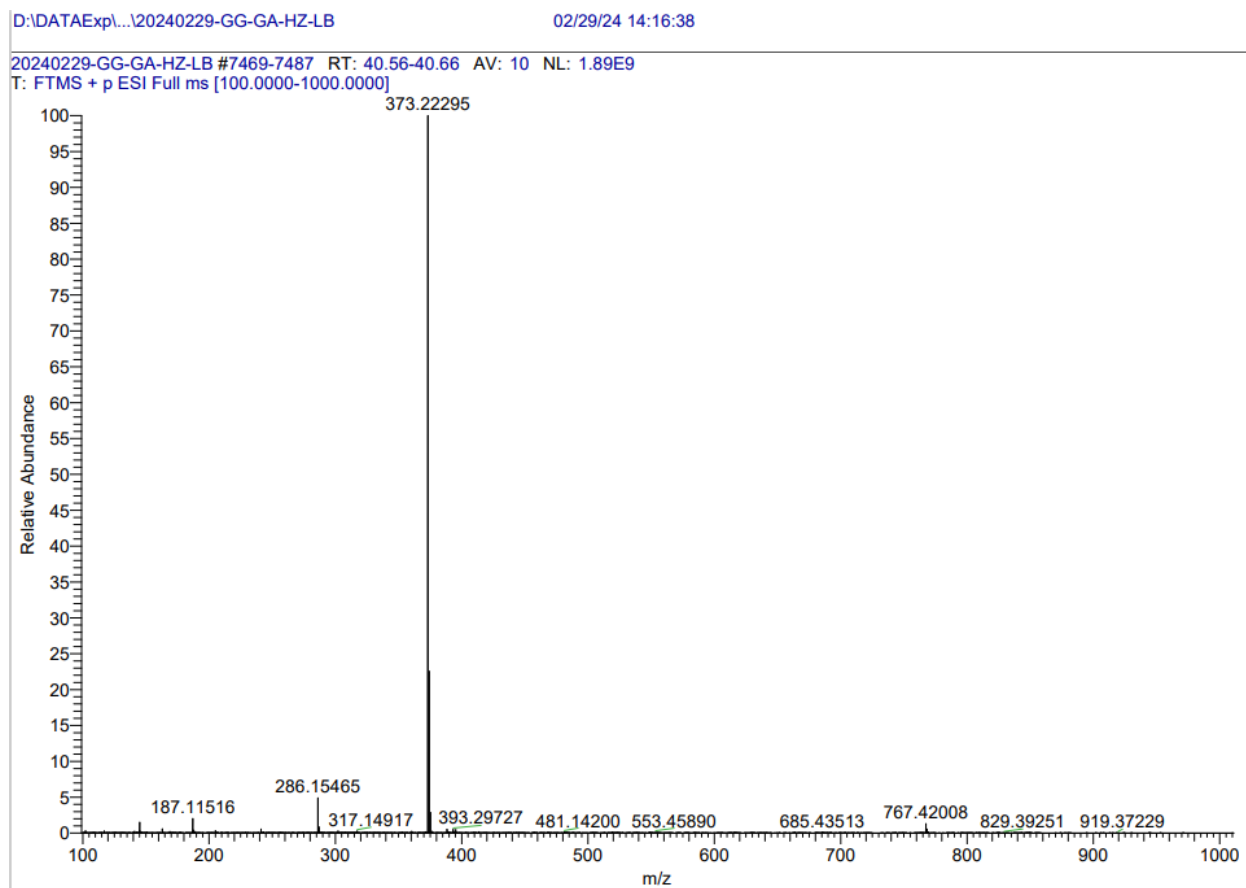


Figure S87. HR-MS spectrum of **13d** (mass accuracy of -1.3 ppm)

2-(2-(Dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**4**):

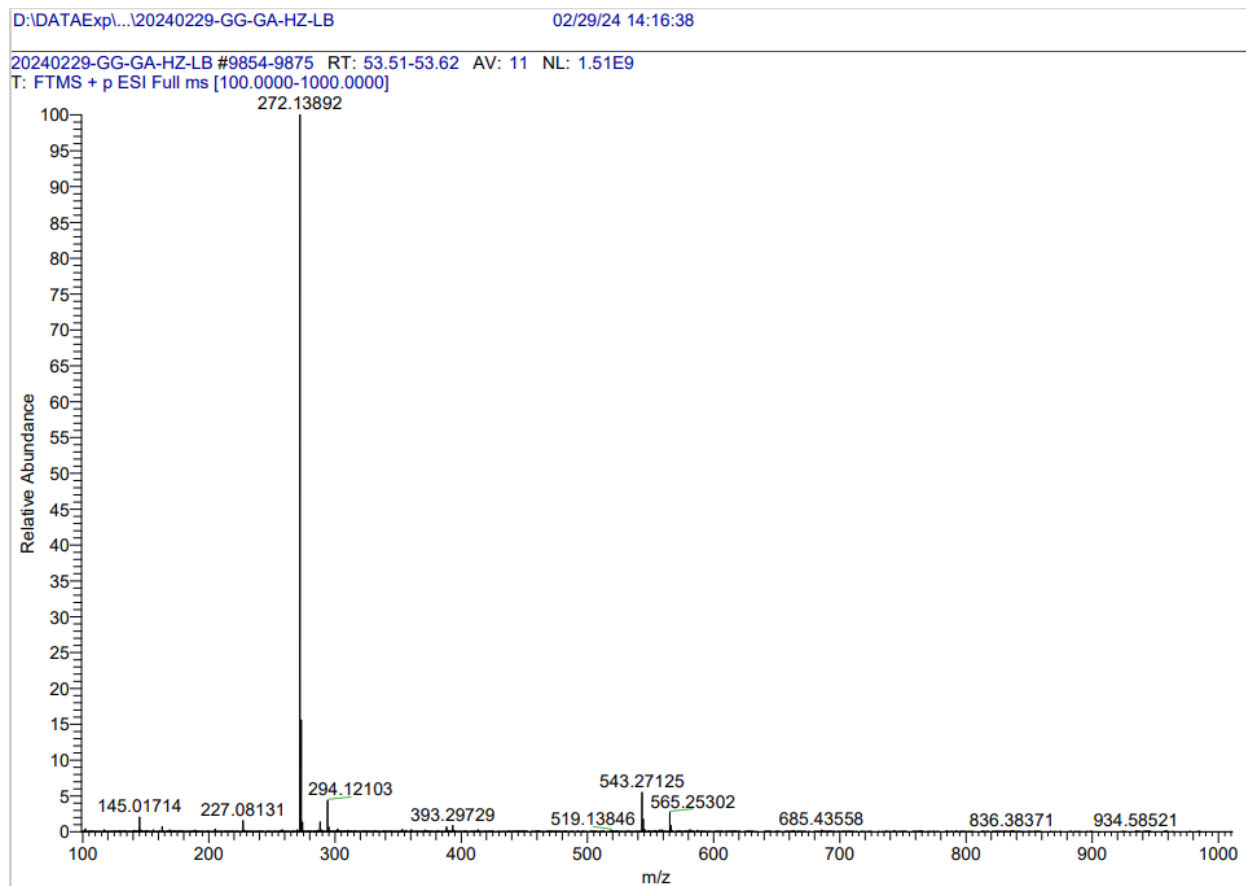


Figure S88. HR-MS spectrum of **4** (mass accuracy of -1.6 ppm)

2-(3-(Dimethylamino)propyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**9e**):

D:\DATAExp\...20240229-GG-GA-HZ-LB

02/29/24 14:16:38

20240229-GG-GA-HZ-LB #12918-12938 RT: 70.14-70.24 AV: 10 NL: 1.38E9

T: FTMS + p ESI Full ms [100.0000-1000.0000]

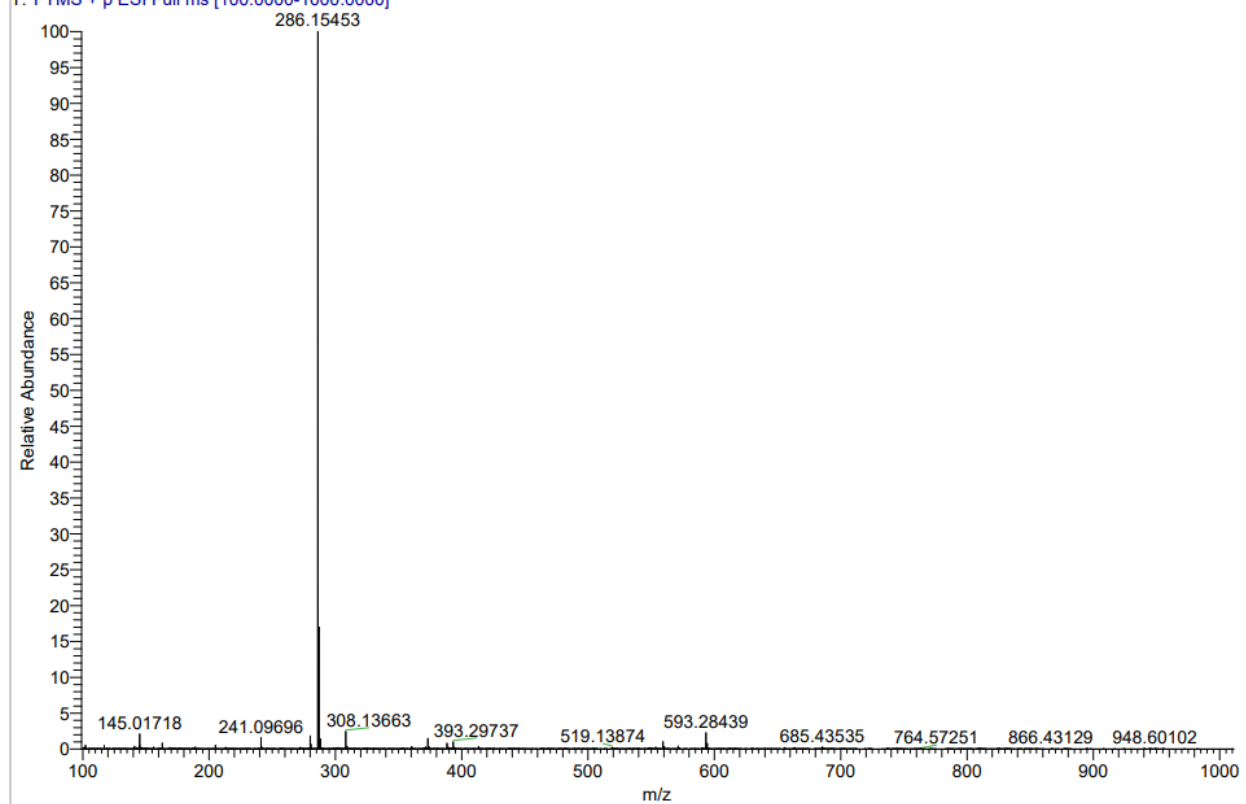


Figure S89. HR-MS spectrum of **9e** (mass accuracy of -1.7 ppm)

2-(2-(Pyrrolidin-1-yl)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**9f**):

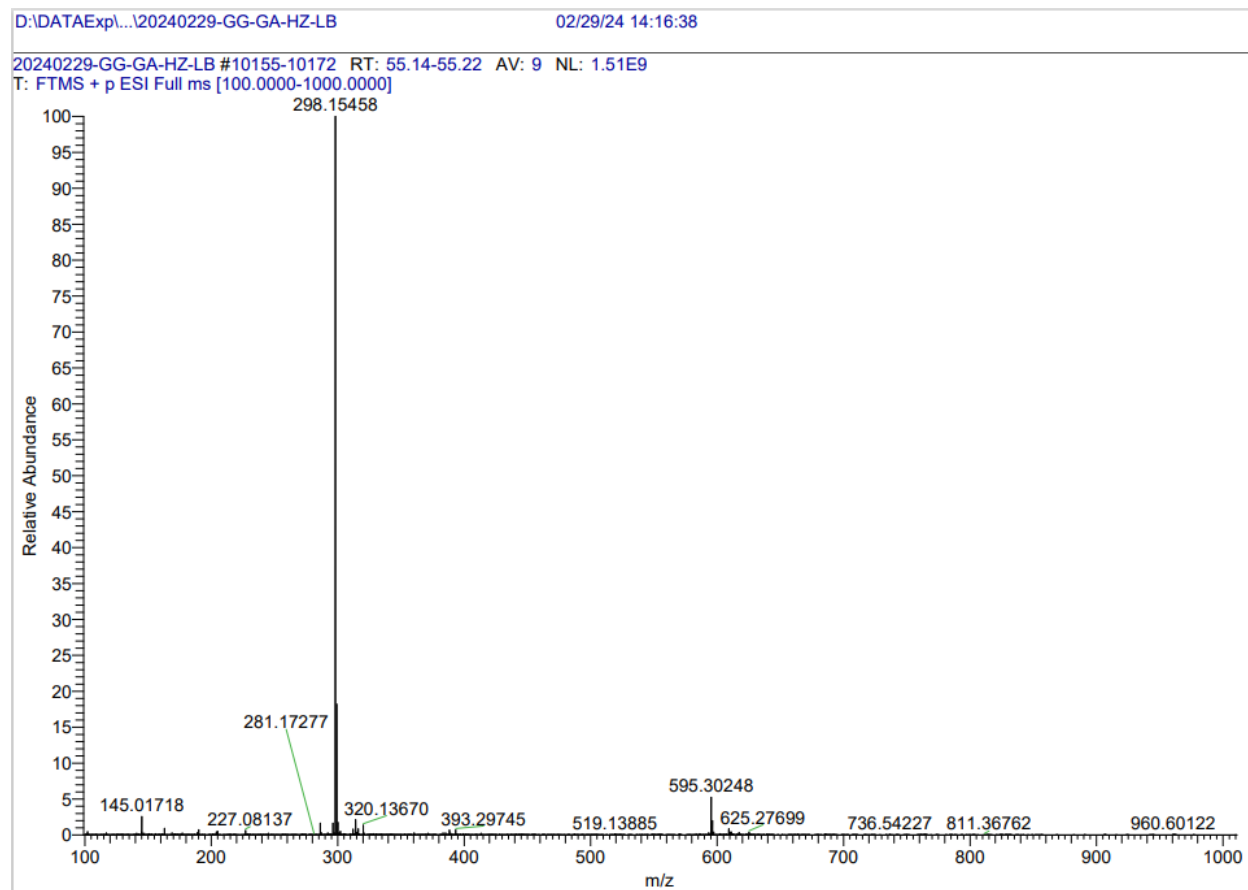


Figure S90. HR-MS spectrum of **9f** (mass accuracy of -1.4 ppm)

8-Chloro-2-(2-(dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (14a):

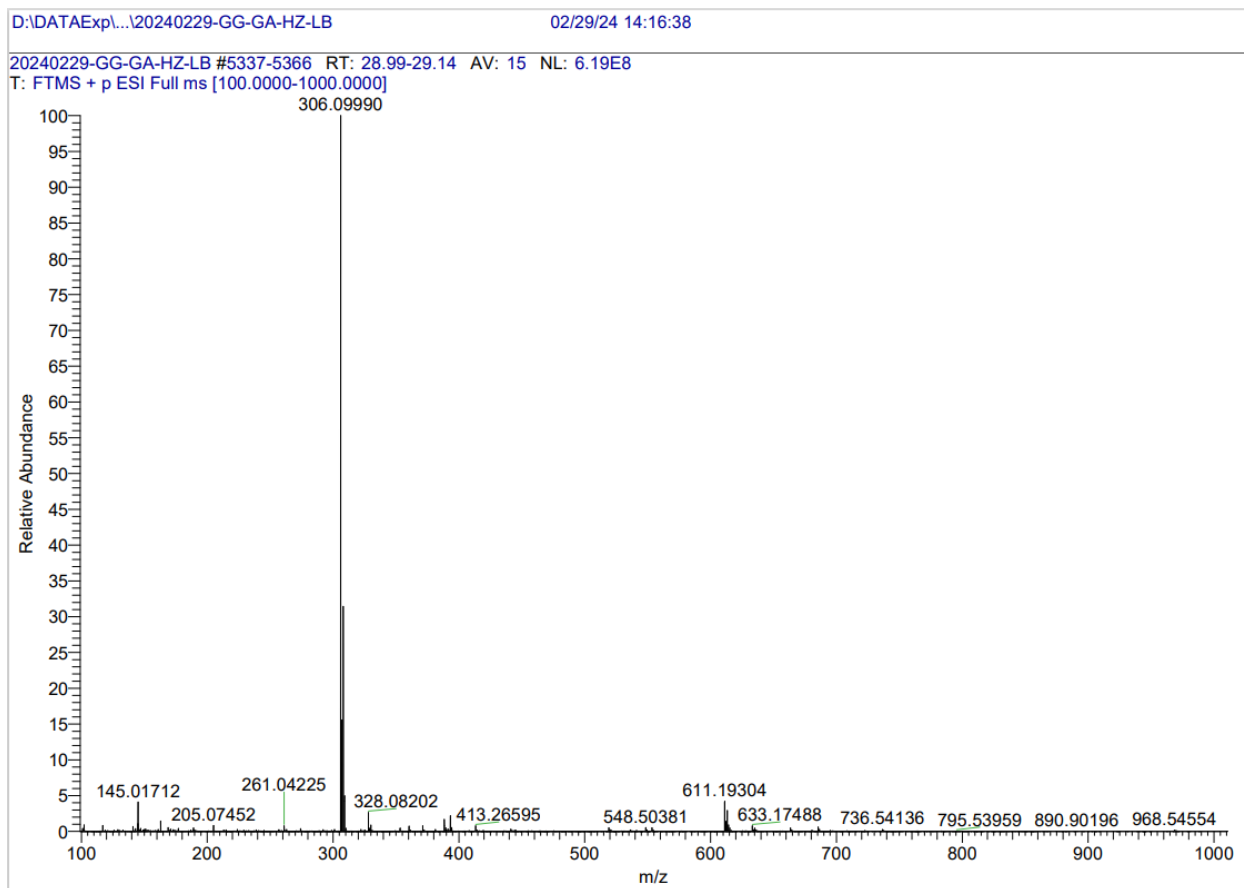


Figure S91. HR-MS spectrum of **14a** (mass accuracy of -1.6 ppm)

6-Chloro-2-(2-(dimethylamino)ethyl)-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**14c**):

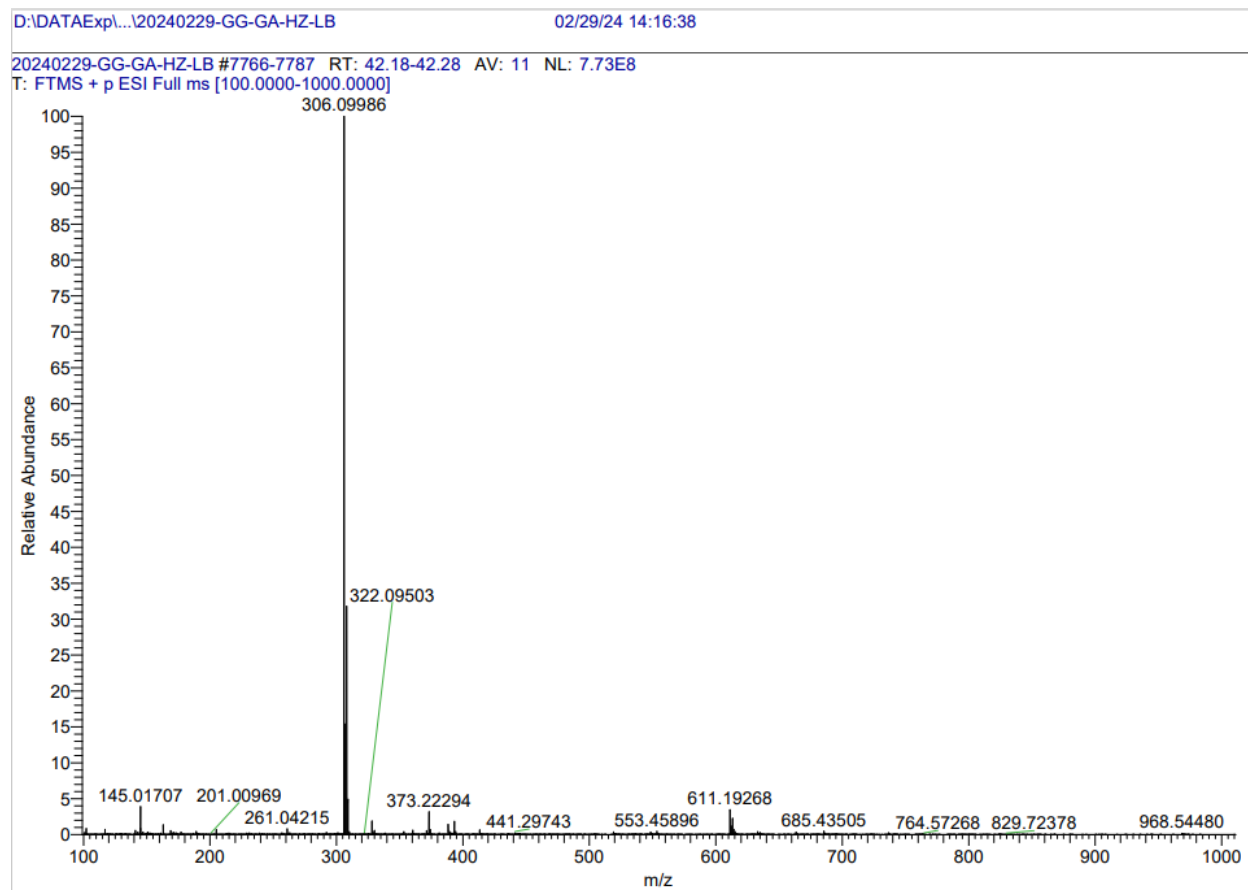


Figure S92. HR-MS spectrum of **14c** (mass accuracy of -1.7 ppm)

2-(2-(Dimethylamino)ethyl)-5-methyl-1H-pyrrolo[3,4-b]quinoline-3,9(2H,4H)-dione (**14d**):

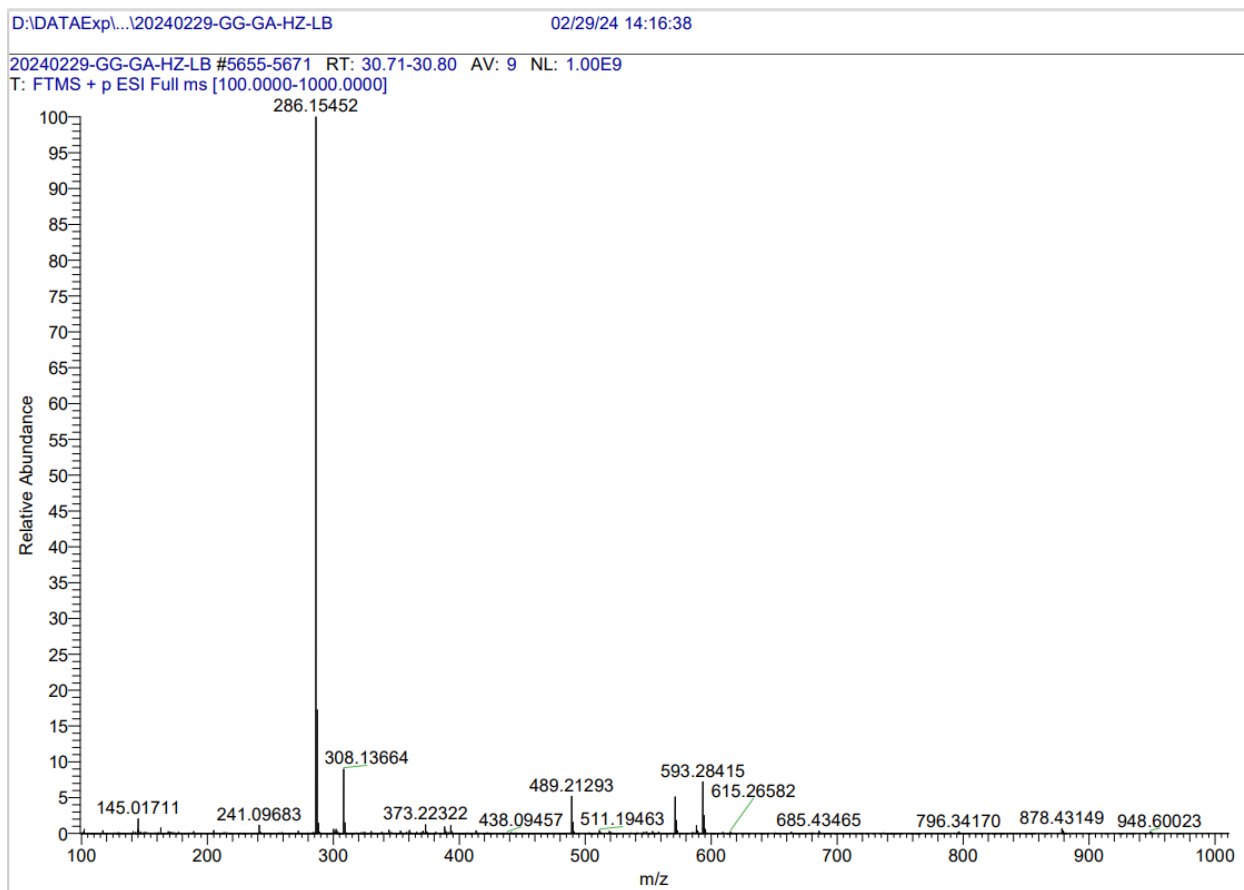


Figure S93. HR-MS spectrum of **14d** (mass accuracy of -1.7 ppm)

3,3'-Methylenebis(4-oxo-N-phenyl-1,4-dihydroquinoline-2-carboxamide) (**10a**):

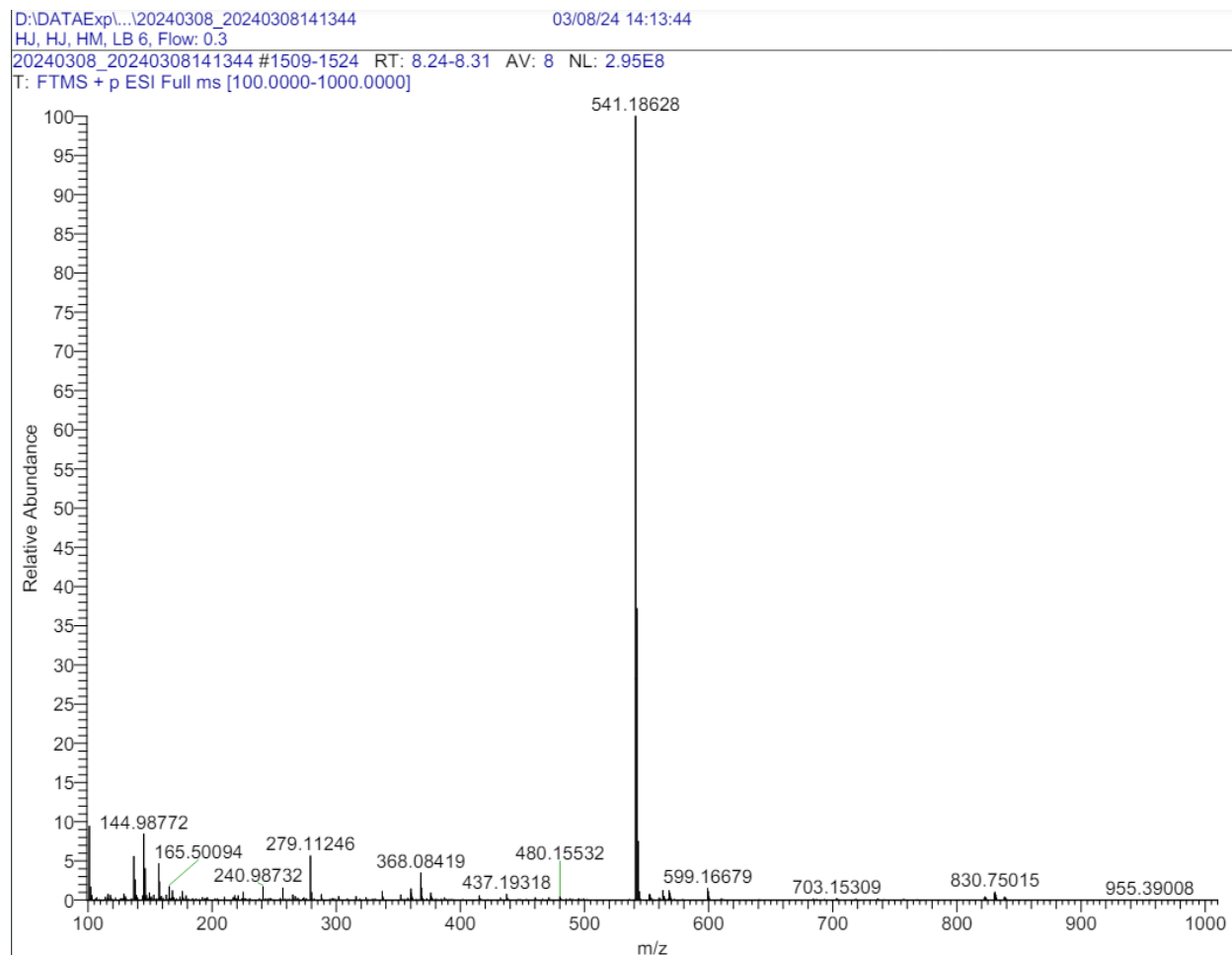


Figure S94. HR-MS spectrum of **10a** (mass accuracy of -1.4 ppm)

3,3'-Methylenebis(N-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxamide) (**10b**):

D:\DATA\Exp\...20240308_20240308141344

03/08/24 14:13:44

HJ, HJ, HM, LB 6, Flow: 0.3

20240308_20240308141344 #2442-2452 RT: 13.34-13.38 AV: 5 NL: 3.06E8

T: FTMS + p ESI Full ms [100.0000-1000.0000]

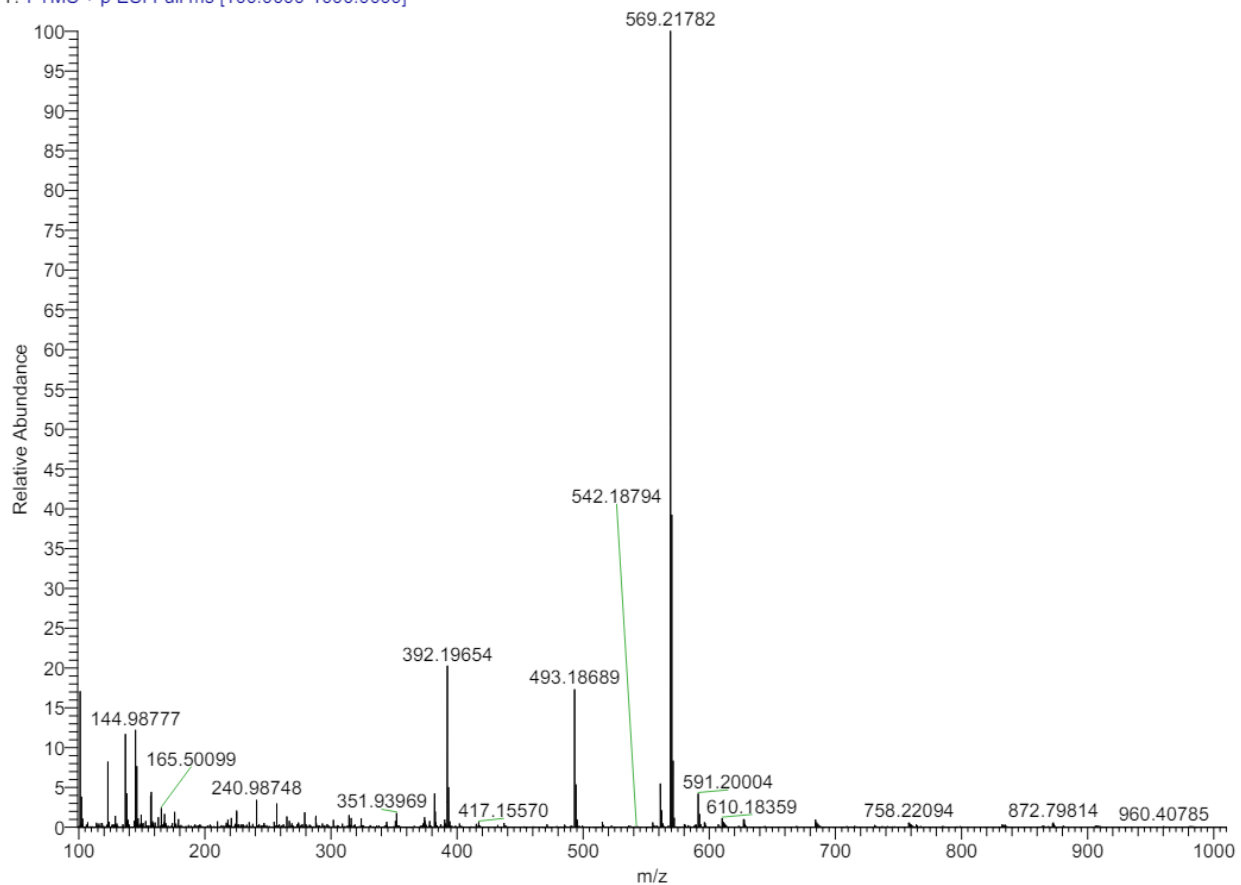


Figure S95. HR-MS spectrum of **10b** (mass accuracy of -0.9 ppm)

3,3'-Methylenebis(4-oxo-N-propyl-1,4-dihydroquinoline-2-carboxamide) (**10d**):

D:\DATAExp\...20240308_20240308141344 03/08/24 14:13:44
HJ, HJ, HM, LB 6, Flow: 0.3
20240308_20240308141344 #2738-2752 RT: 14.96-15.02 AV: 7 NL: 5.69E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

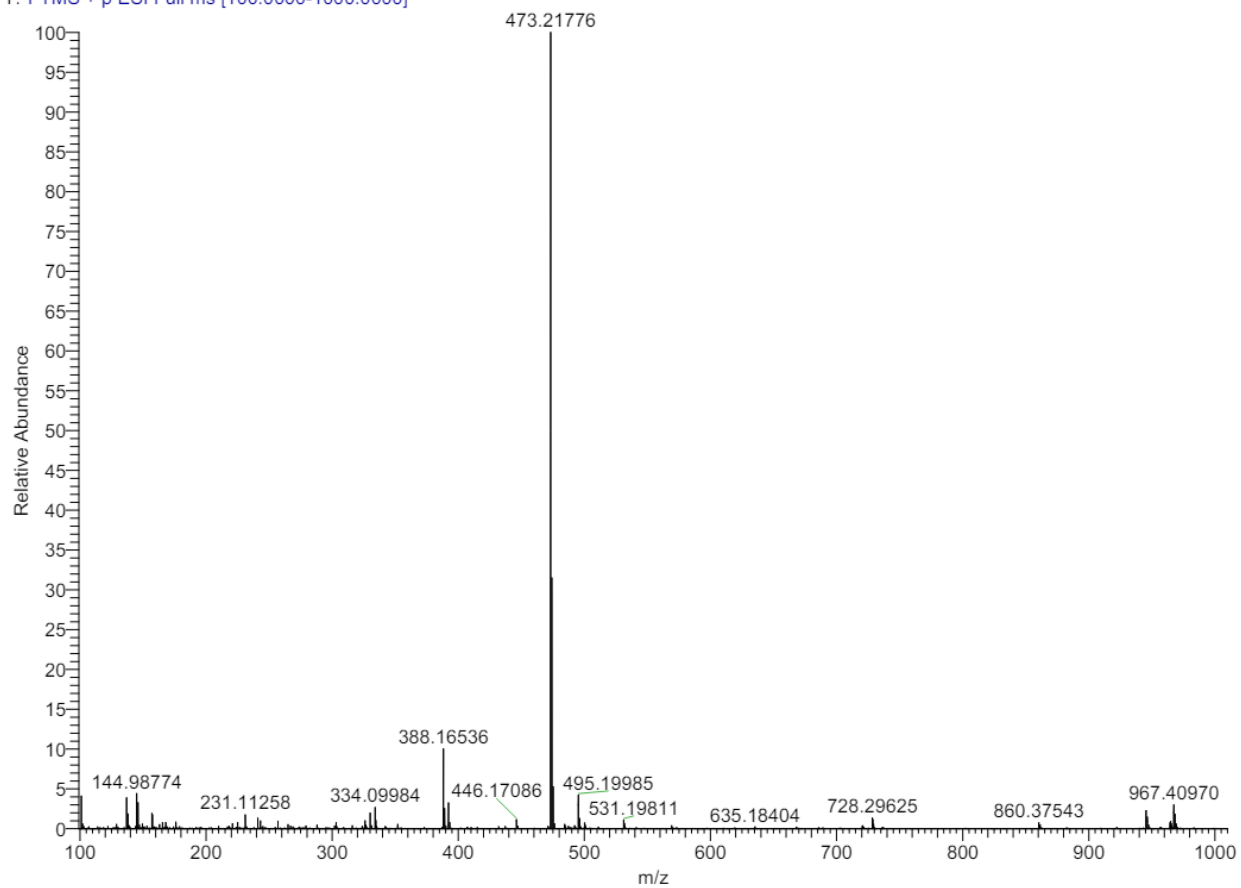


Figure S96. HR-MS spectrum of **10d** (mass accuracy of -1.2 ppm)

3,3'-Methylenebis(5-chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide) (15a):

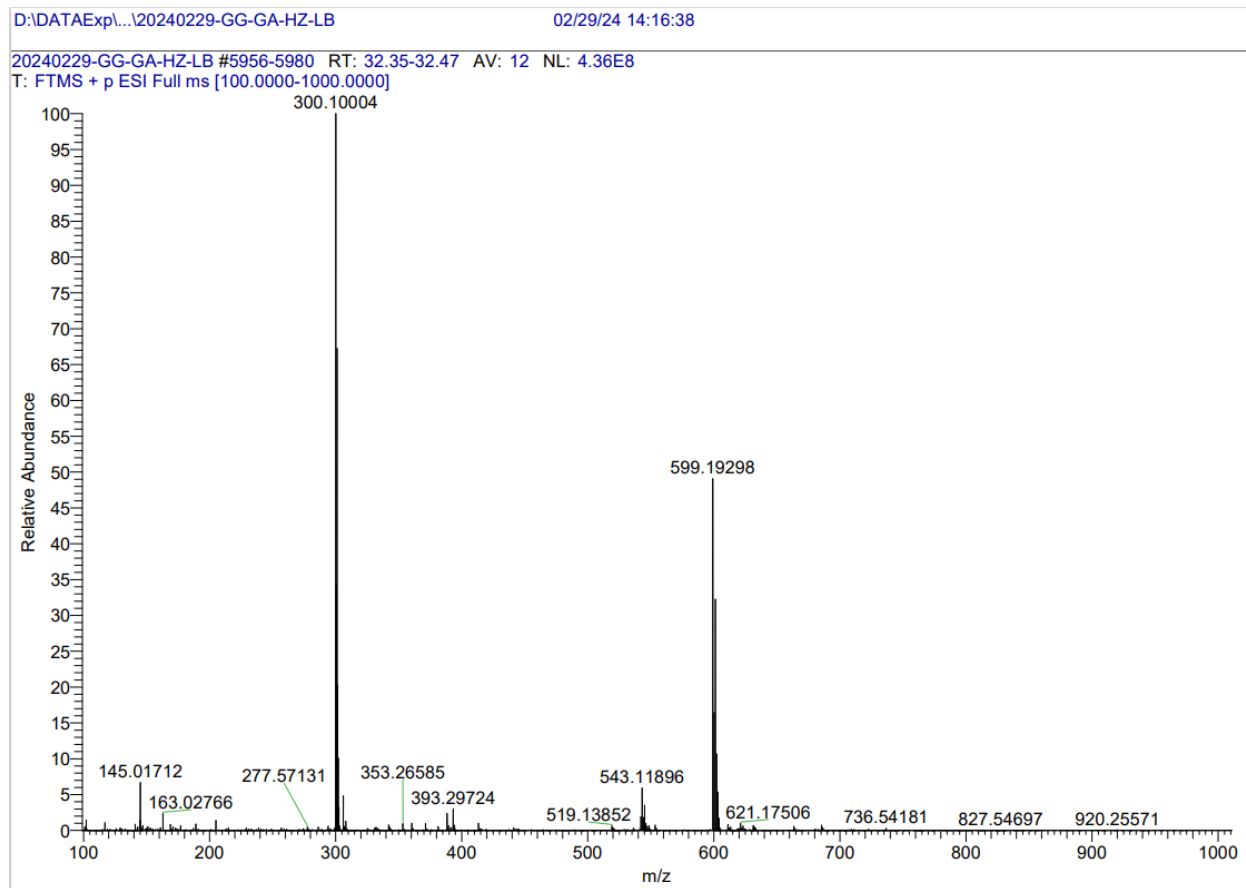


Figure S97. HR-MS spectrum of **15a** (mass accuracy of -0.8 ppm)

3,3'-Methylenebis(7-chloro-N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide) (15c):

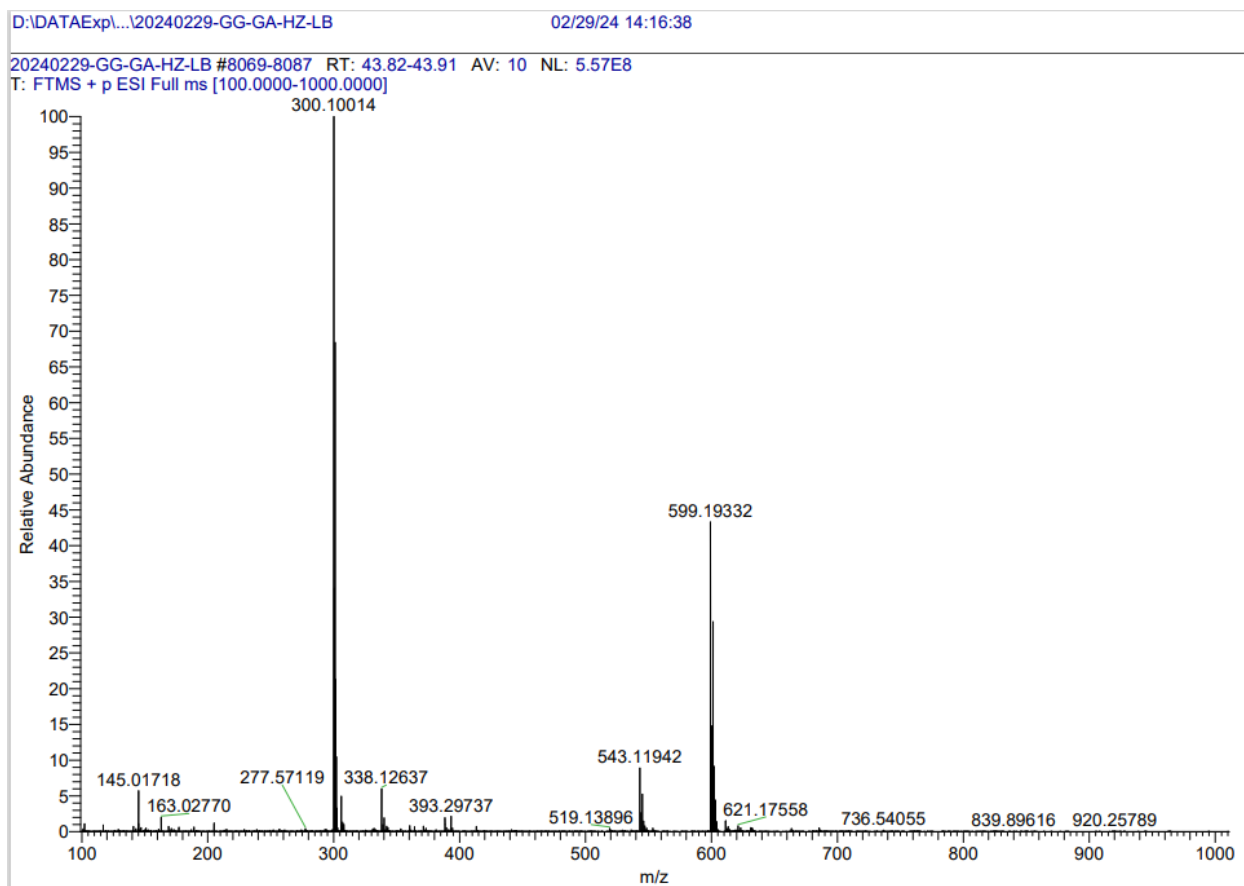


Figure S98. HR-MS spectrum of **15c** (mass accuracy of -0.3 ppm)