Supplementary Information

Synthesis of 7-amino-6-halogeno-3-phenylquinoxaline-2-carbonitrile 1,4-dioxides: A way forward for targeting hypoxia and drug resistance of cancer cells

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Legends to Figures and Tables

Copies of NMR Spectra

Figure S1. Copy of ^{1}H NMR spectrum of the derivative **6**.

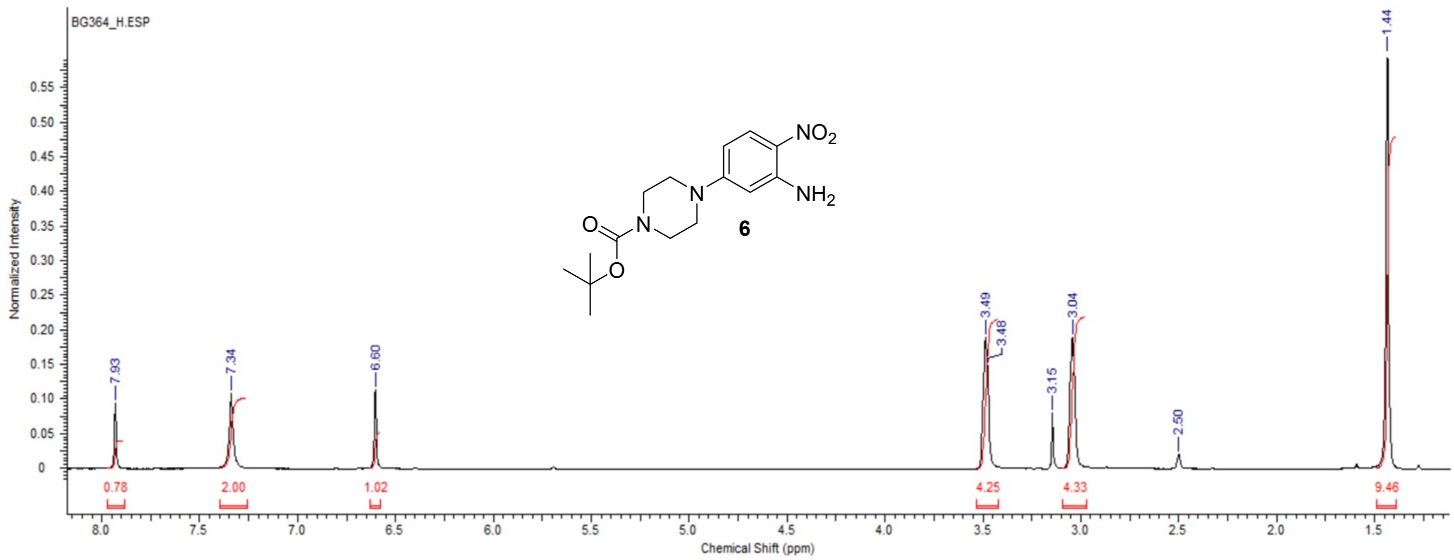


Figure S2. Copy of ^{13}C NMR spectrum of the derivative **6**.

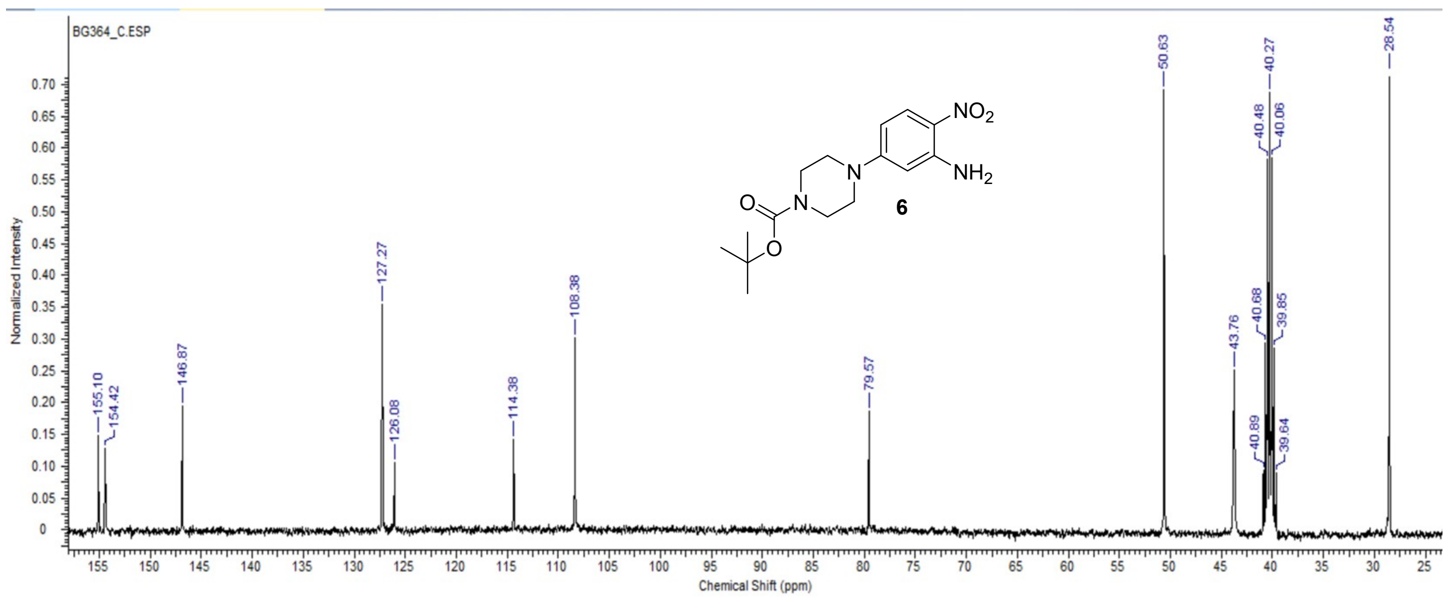


Figure S3. Copy of ^{1}H NMR spectrum of the derivative **7**.

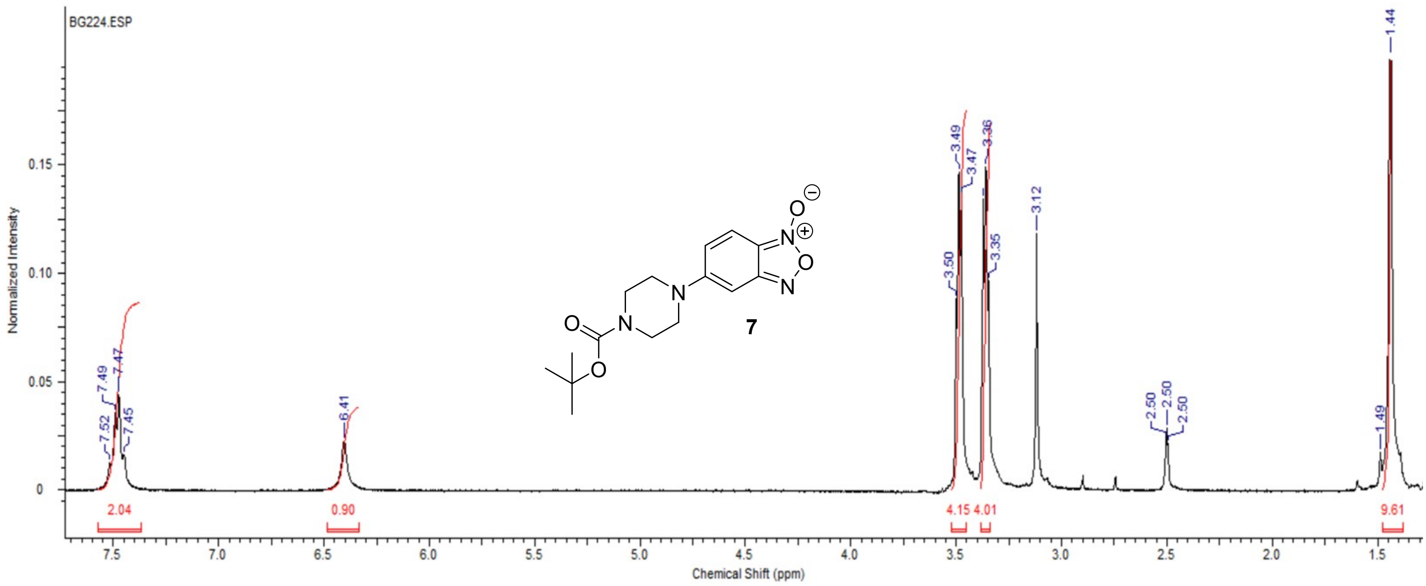


Figure S4. Copy of ^{13}C NMR spectrum of the derivative **7**.

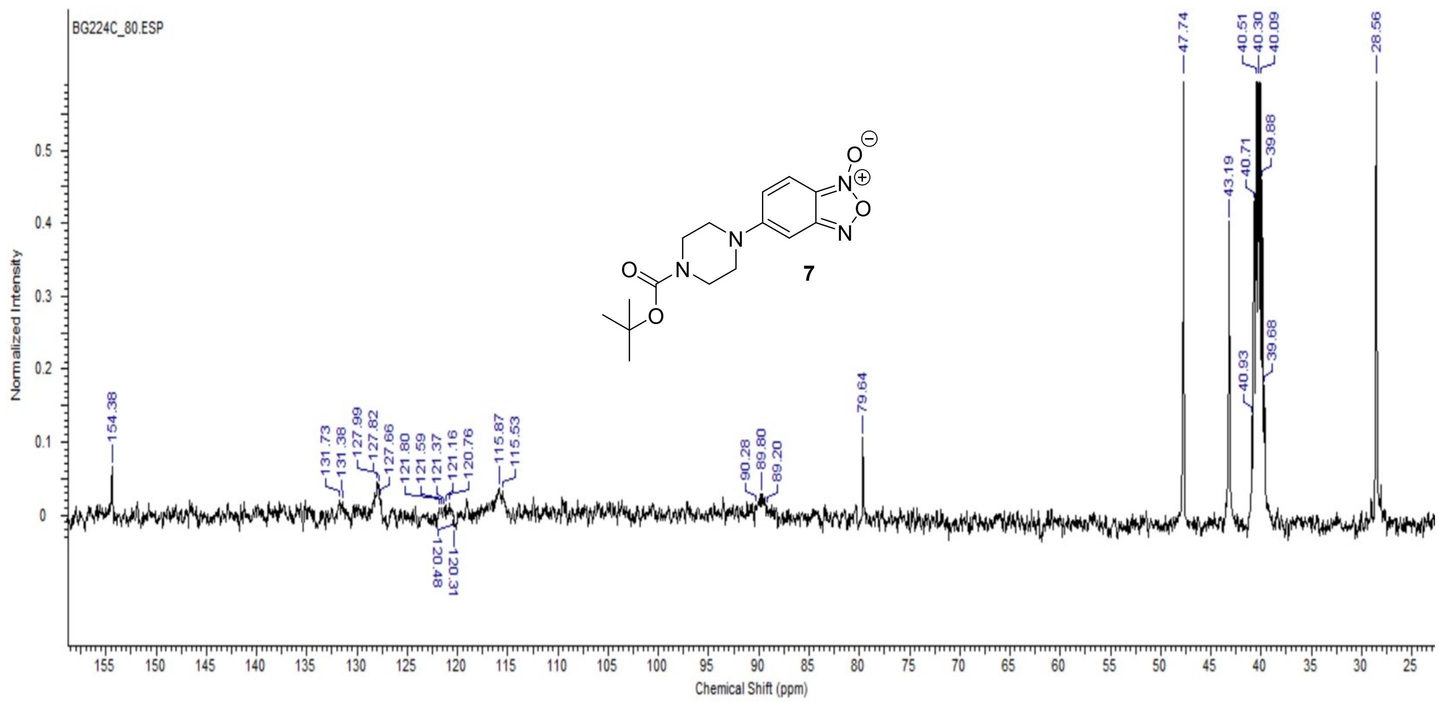


Figure S5. Copy of ^{1}H NMR spectrum of the derivative **9a**.

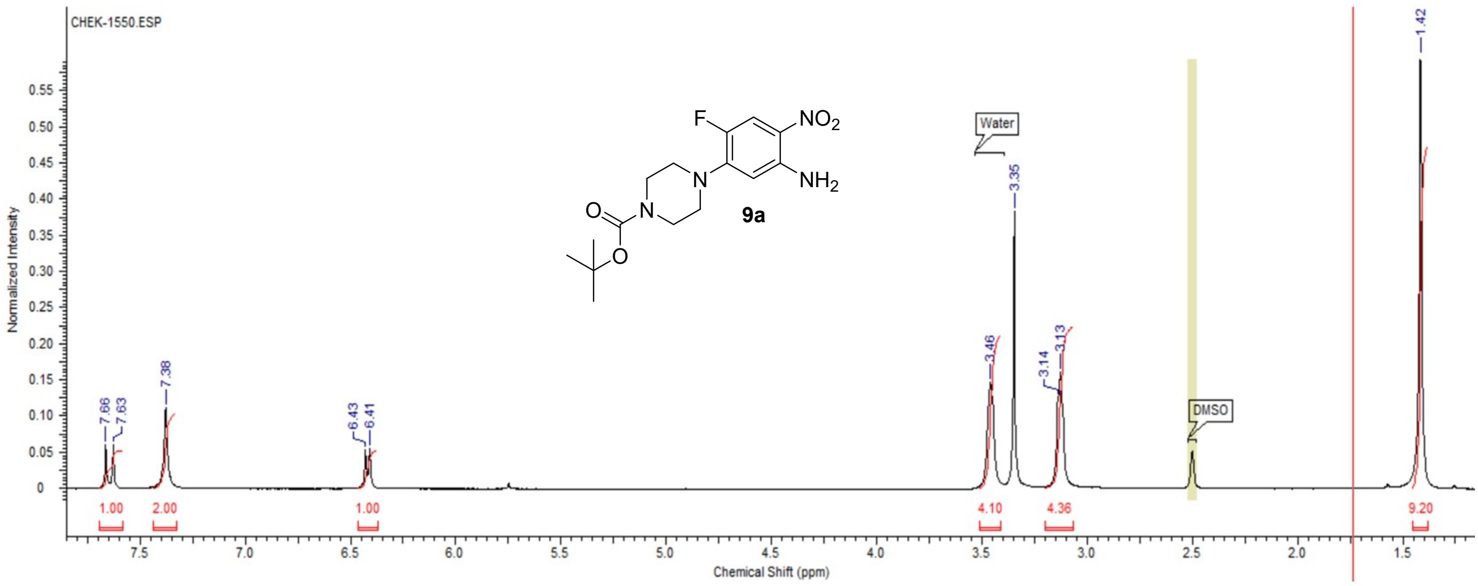


Figure S6. Copy of ^{13}C NMR spectrum of the derivative **9a**.

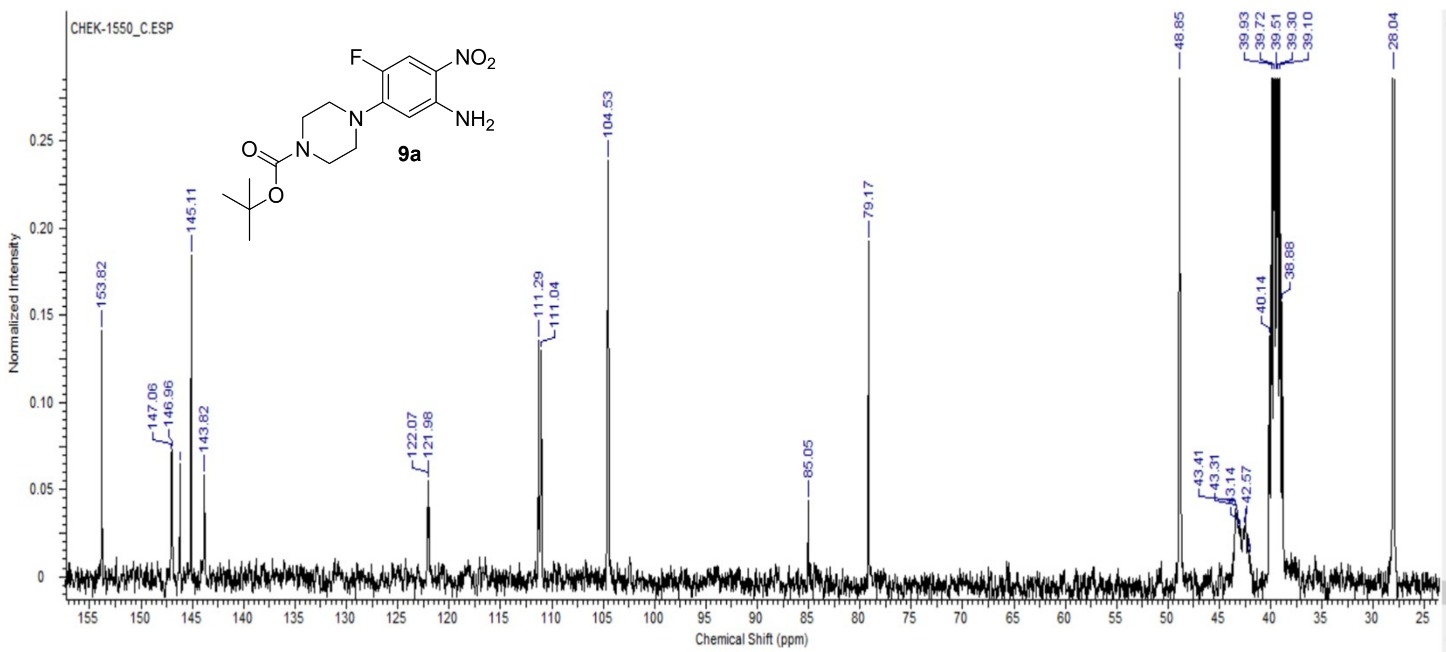


Figure S7. Copy of [1]H NMR spectrum of the derivative **9b**.

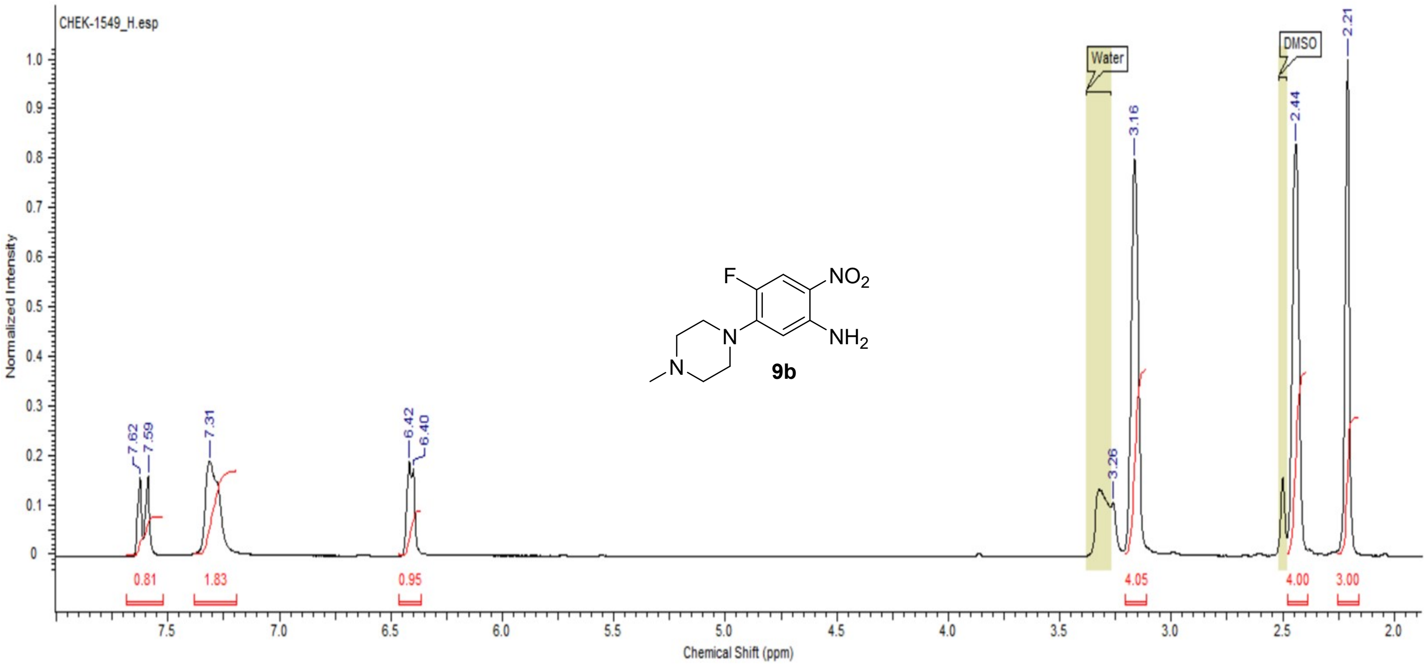


Figure S8. Copy of [13]C NMR spectrum of the derivative **9b**.

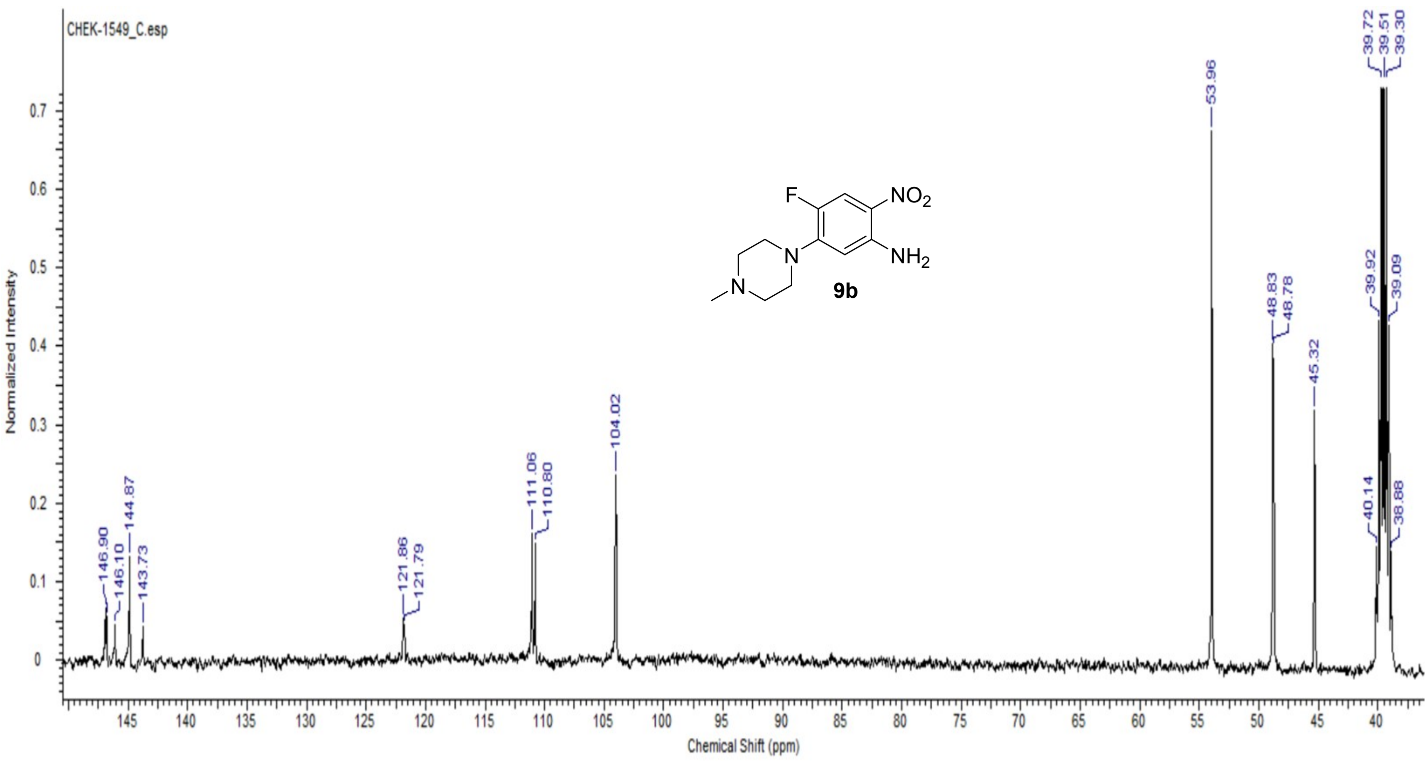


Figure S9. Copy of [1]H NMR spectrum of the derivative **9c**.

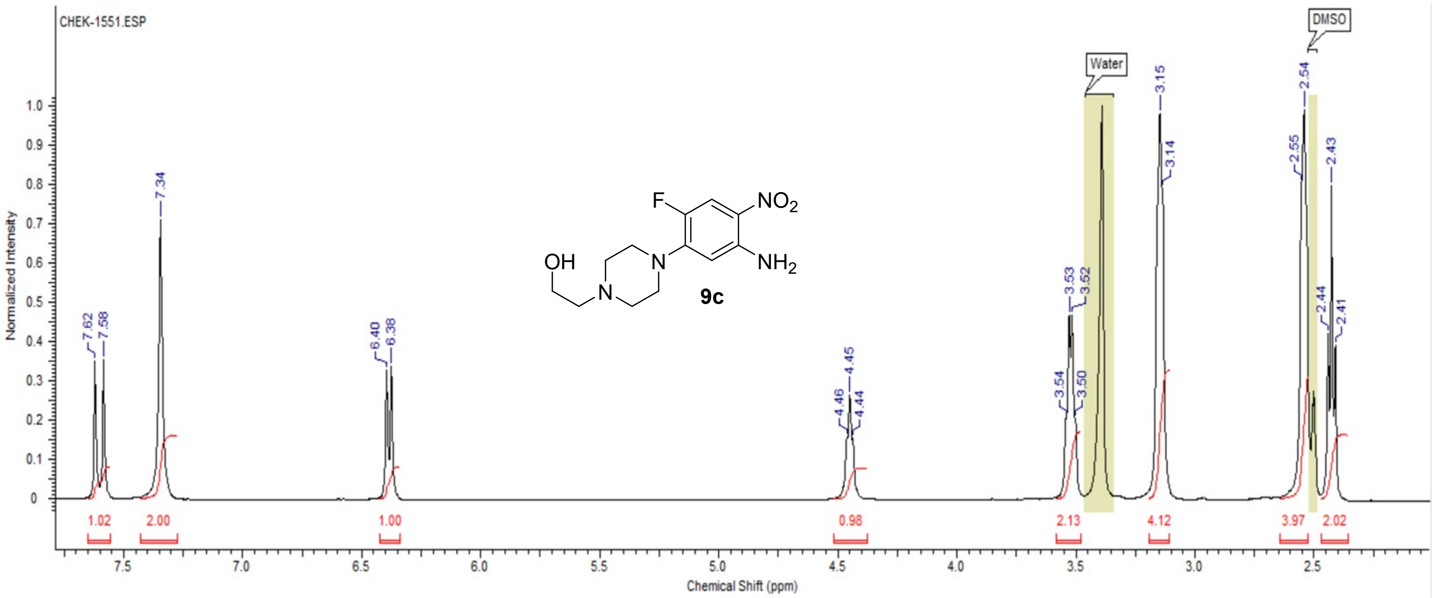


Figure S10. Copy of [13]C NMR spectrum of the derivative **9c**.

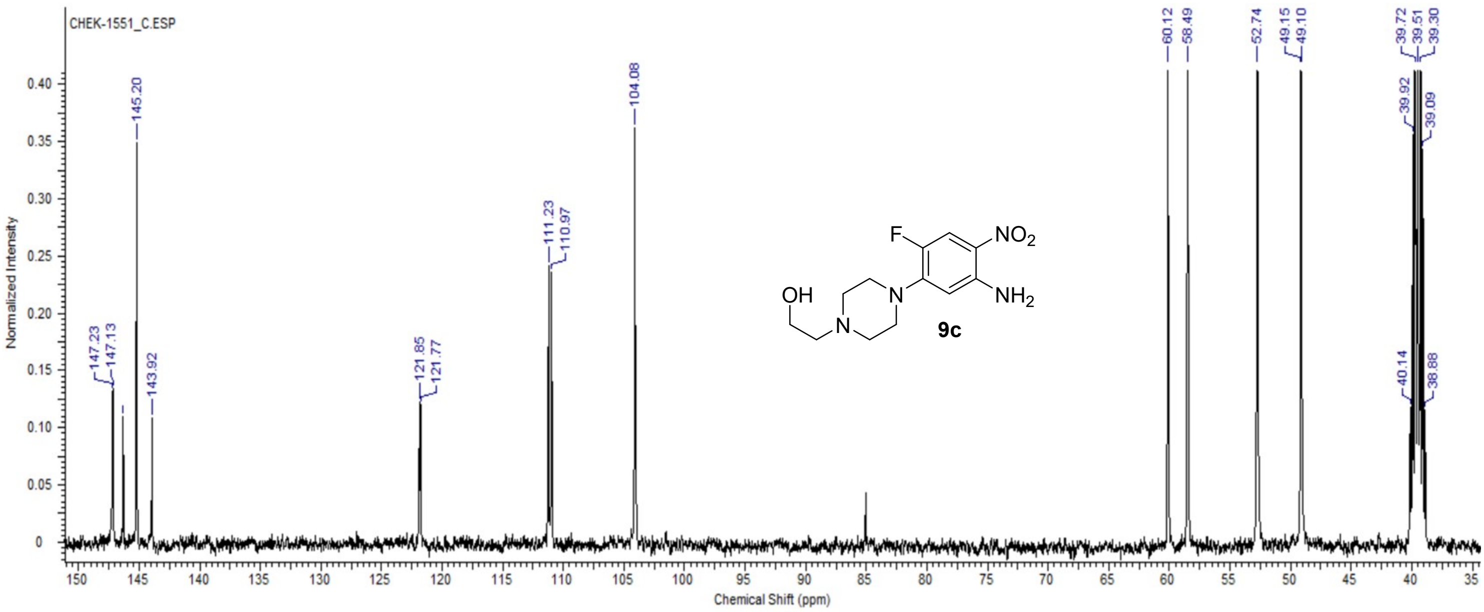


Figure S11. Copy of [1]H NMR spectrum of the derivative **9d**.

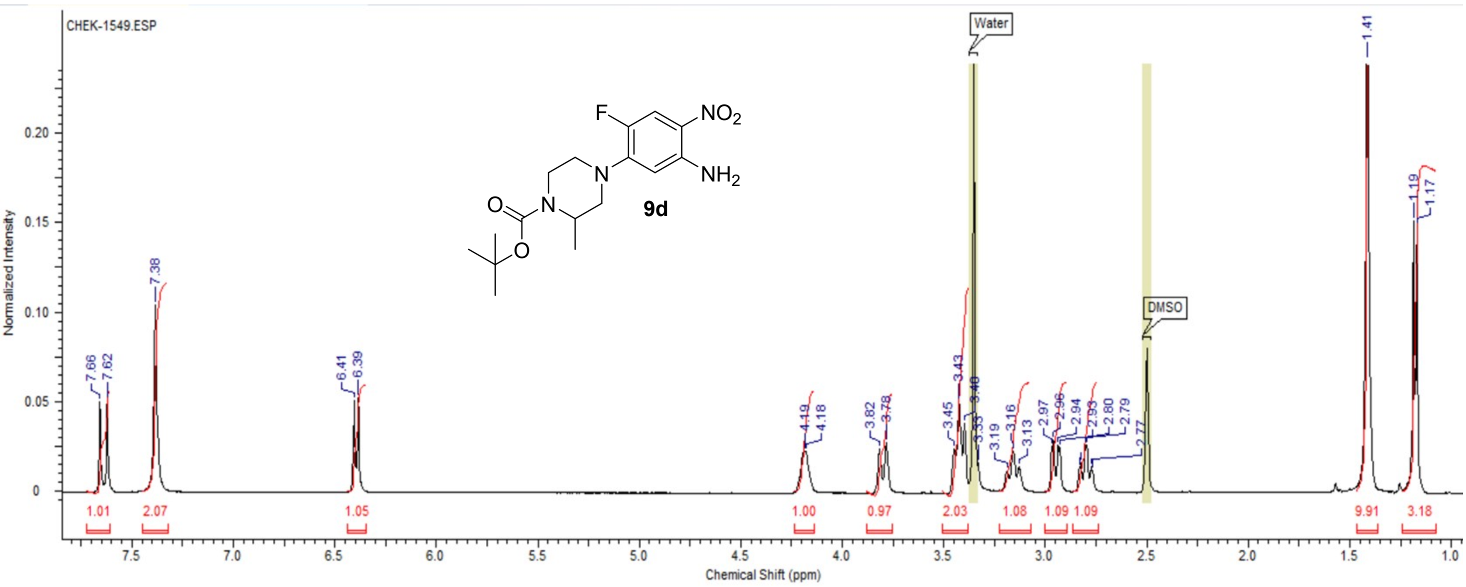


Figure S12. Copy of [13]C NMR spectrum of the derivative **9d**.

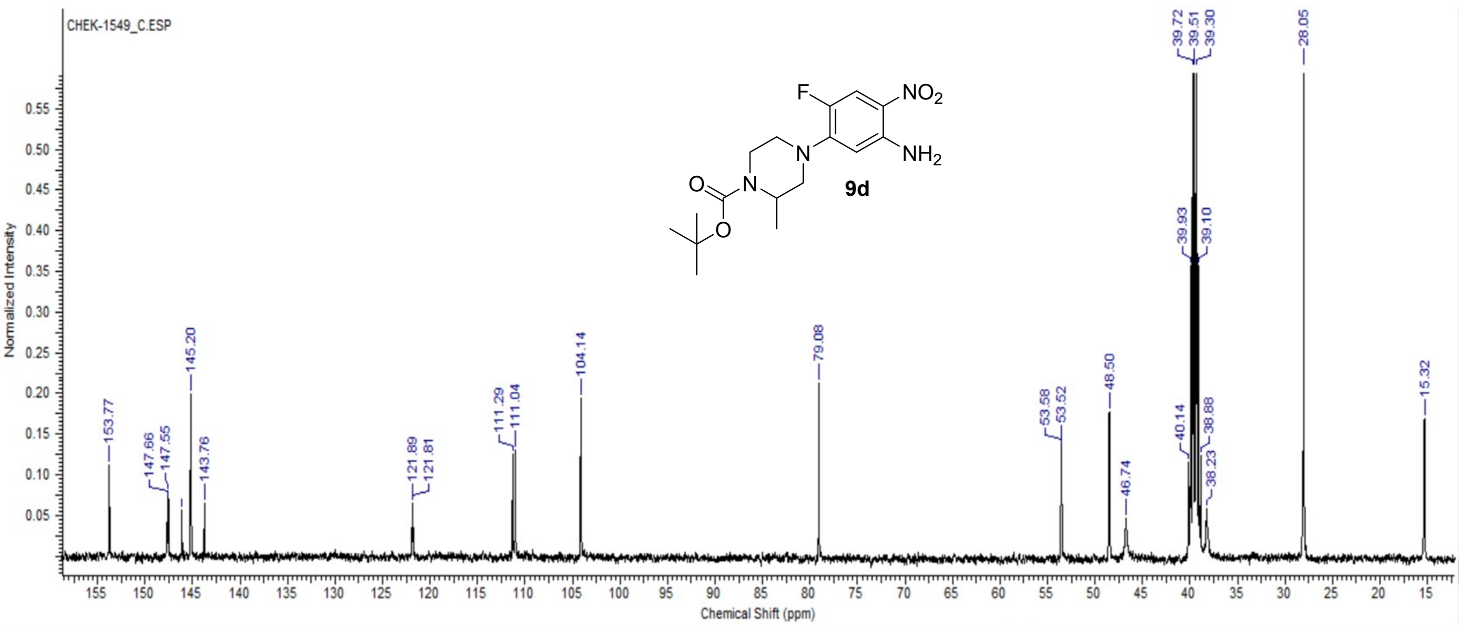


Figure S13. Copy of ^{1}H NMR spectrum of the derivative **9e**.

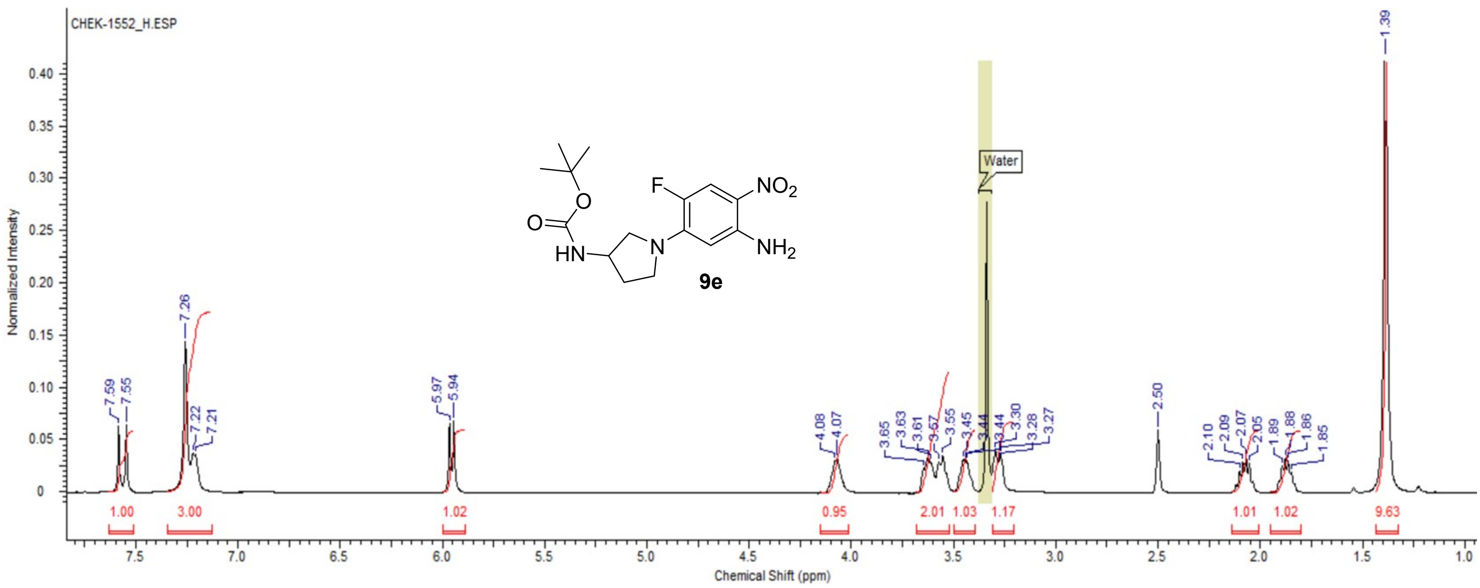


Figure S14. Copy of ^{13}C NMR spectrum of the derivative **9e**

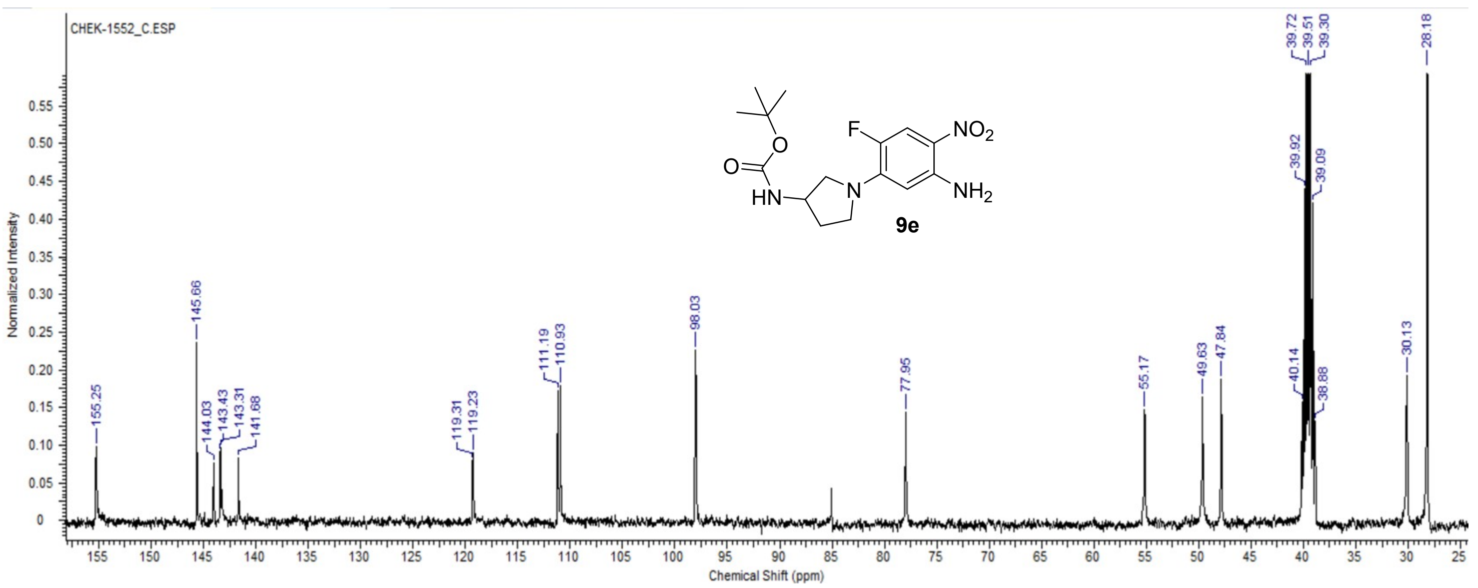


Figure S15. Copy of [1]H NMR spectrum of the derivative **9f**

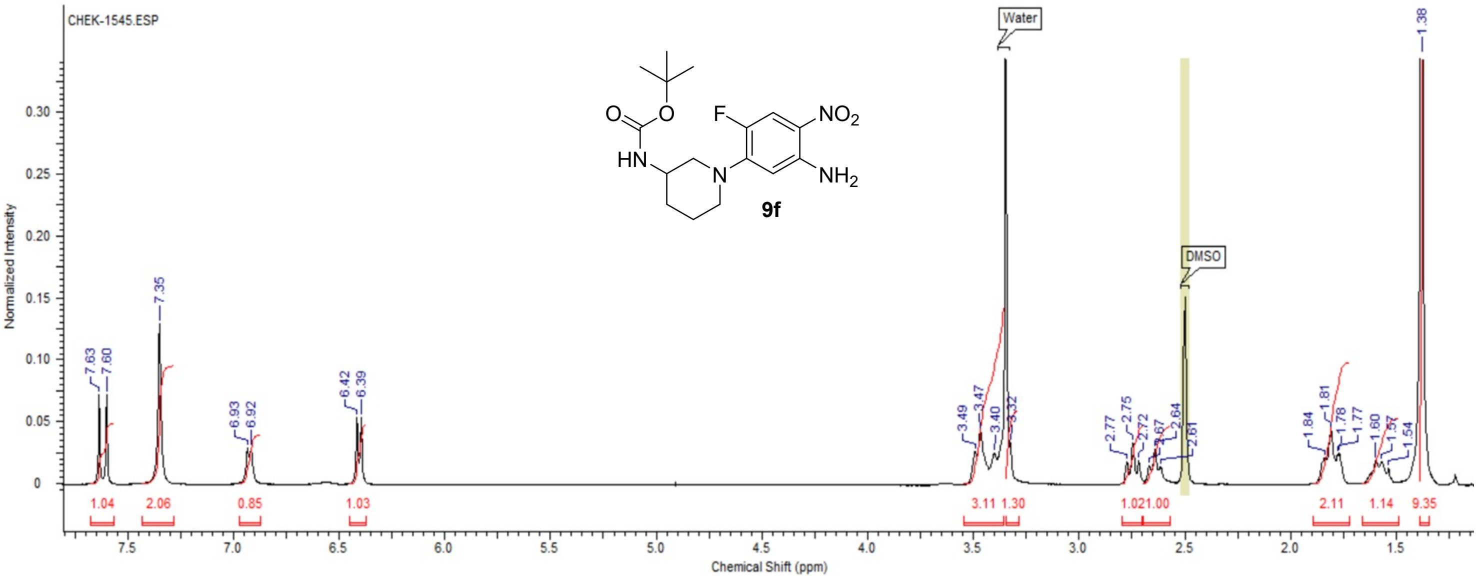


Figure S16. Copy of [13]C NMR spectrum of the derivative **9f**.

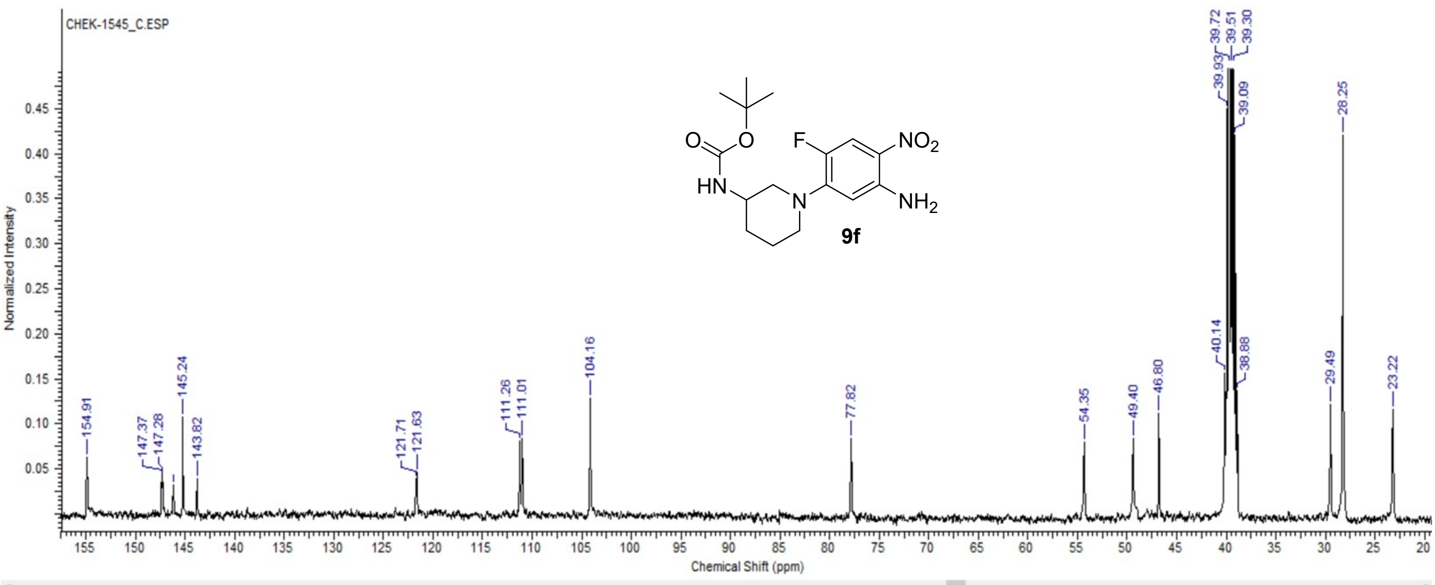


Figure S17. Copy of [1]H NMR spectrum of the derivative **9g**.

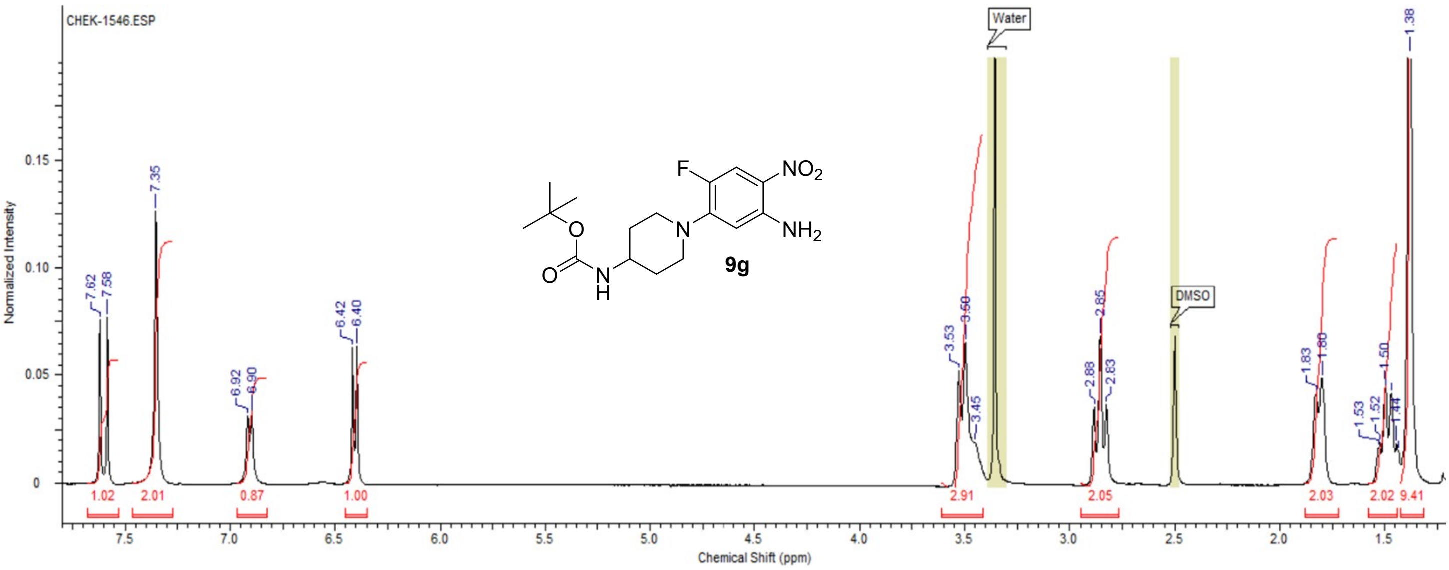


Figure S18. Copy of [13]C NMR spectrum of the derivative **9g**.

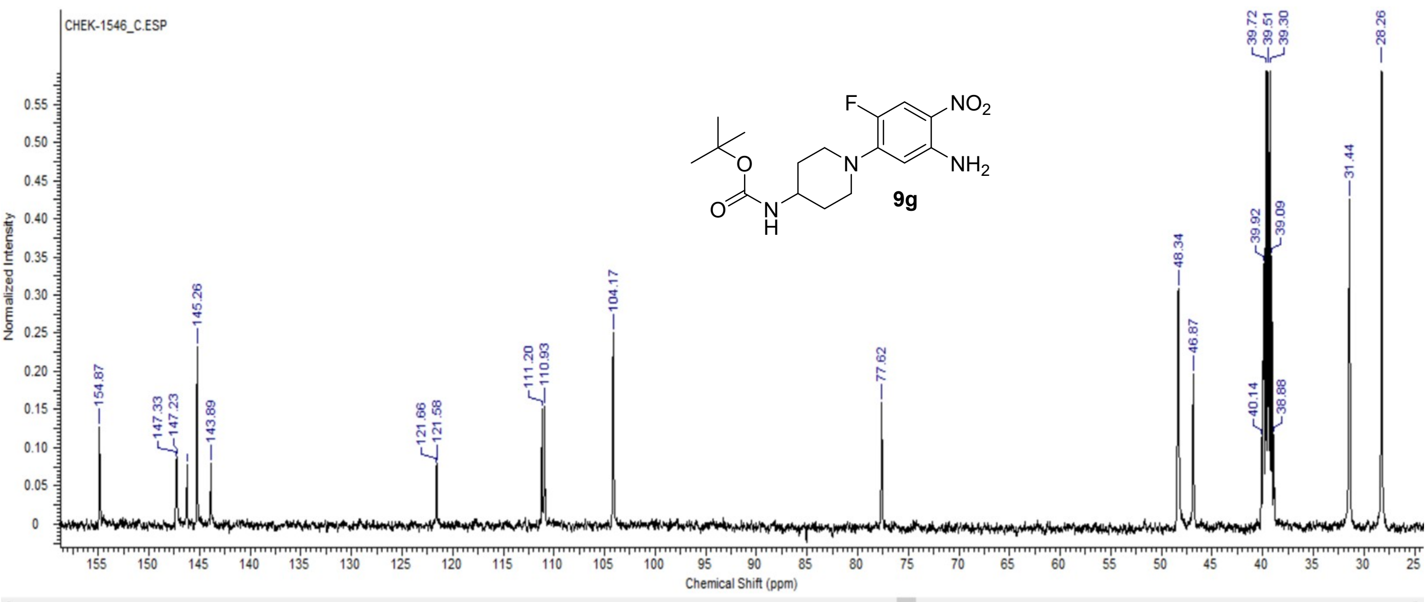


Figure S19. Copy of ^{1}H NMR spectrum of the derivative **9h**.

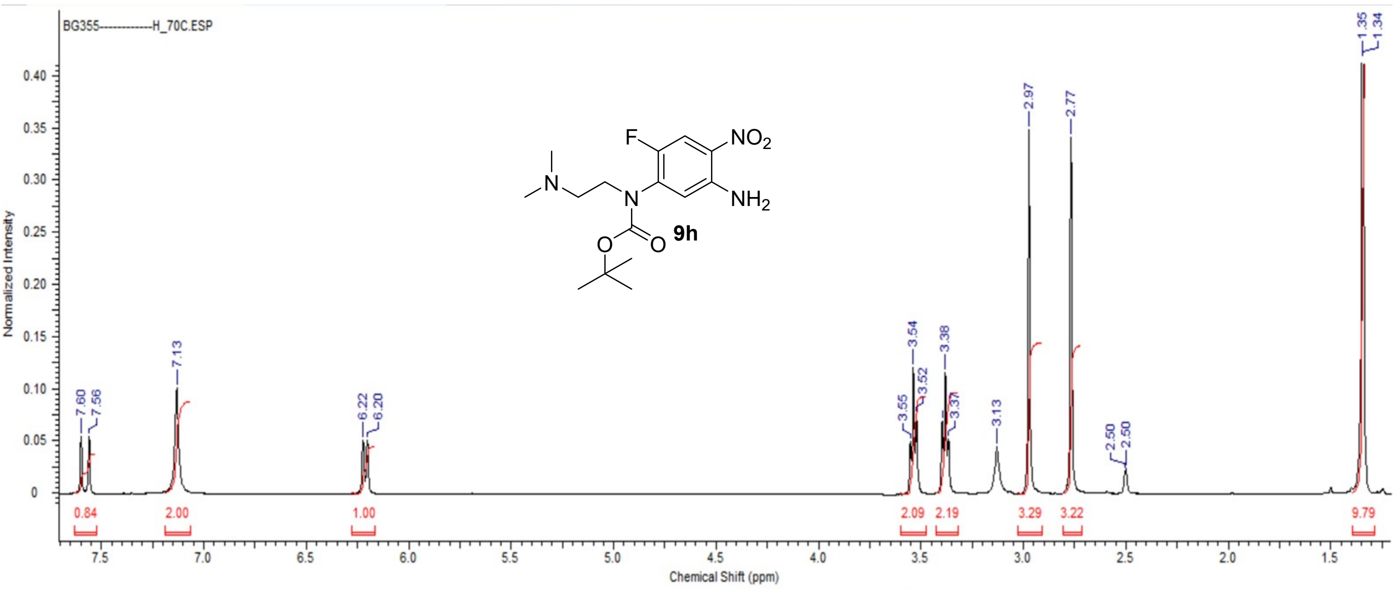


Figure S20. Copy of ^{13}C NMR spectrum of the derivative **9h**.

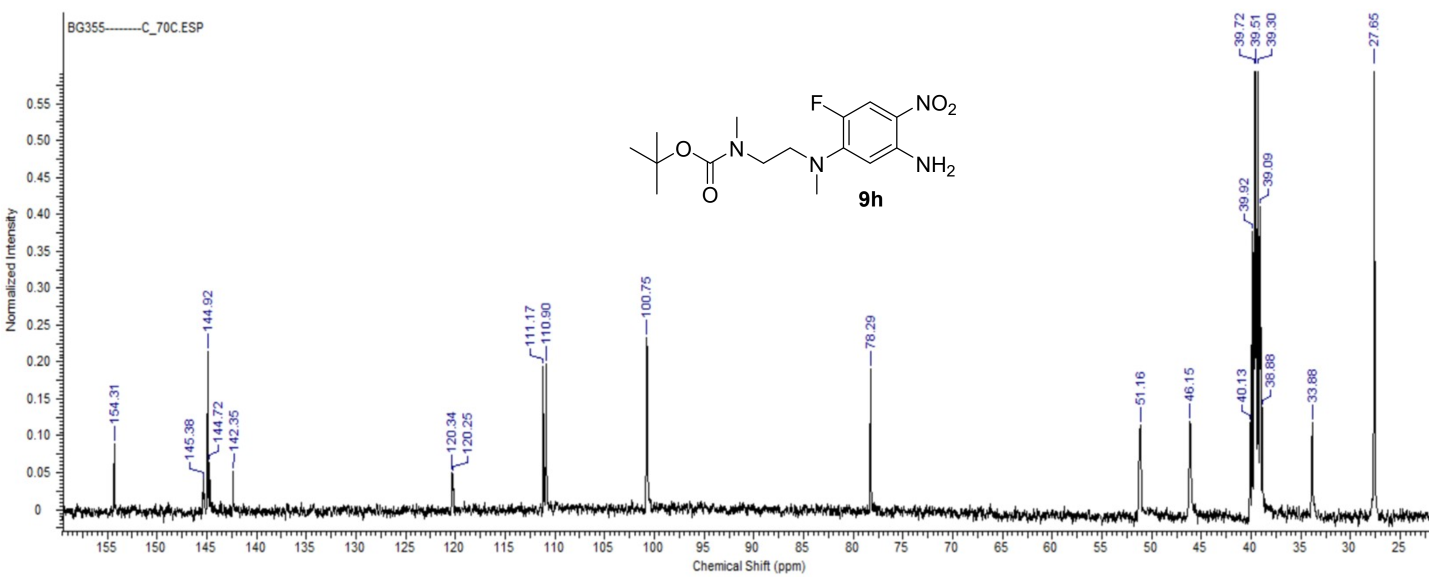


Figure S21. Copy of [1]H NMR spectrum of the derivative **10a**.

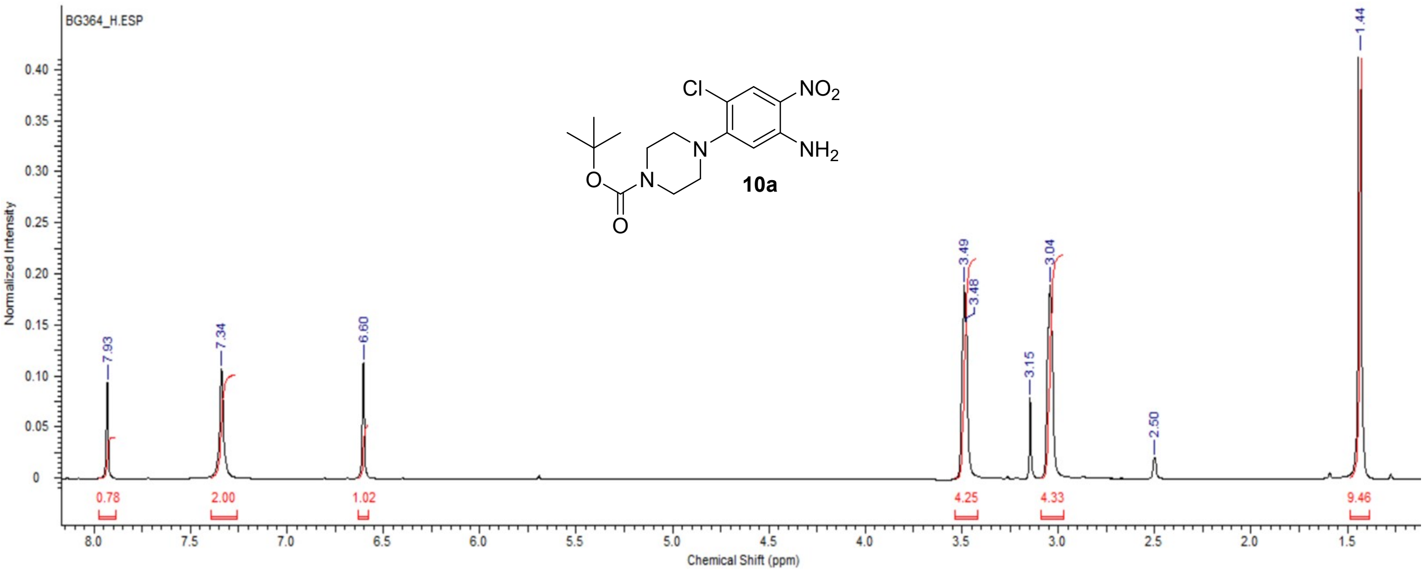


Figure S22. Copy of [13]C NMR spectrum of the derivative **10a**.

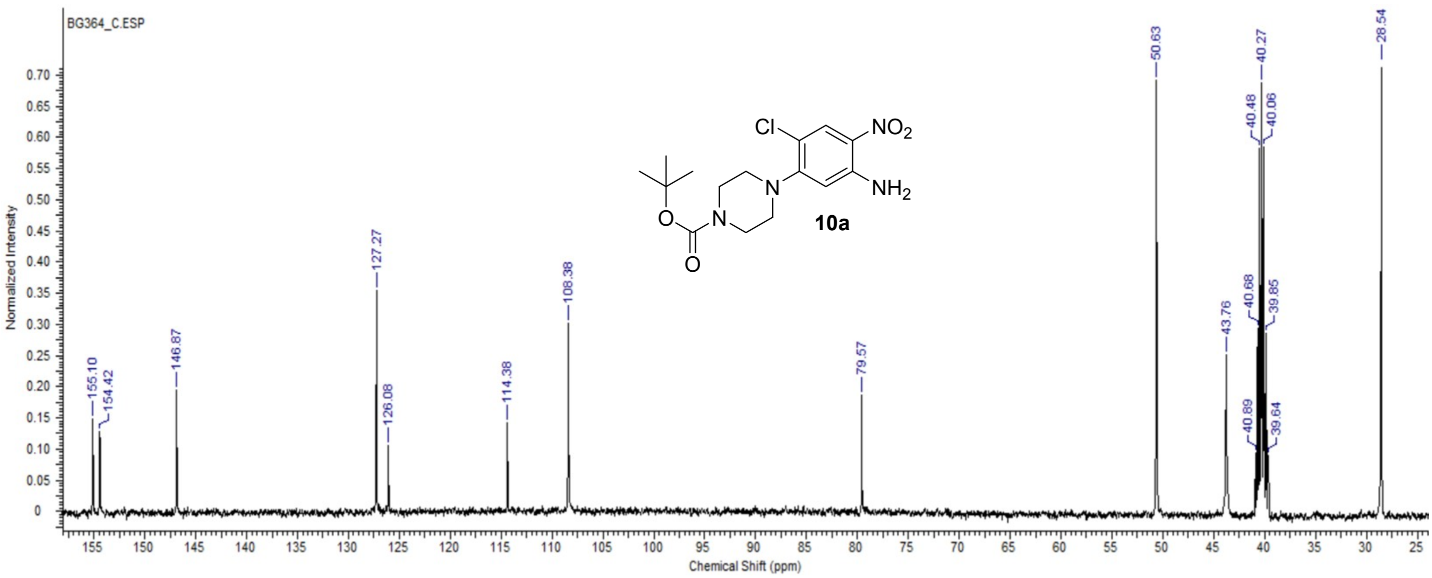


Figure S23. Copy of ^{1}H NMR spectrum of the derivative **10g**.

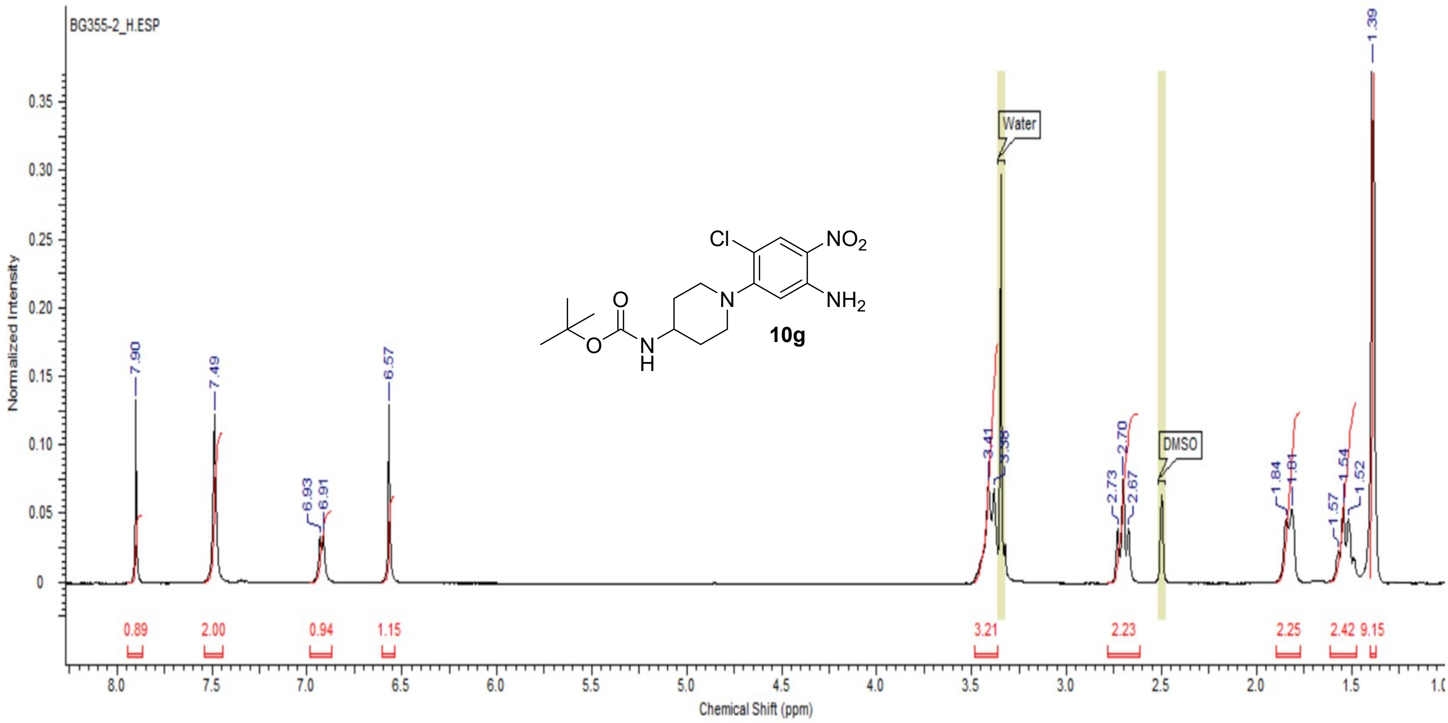


Figure S24. Copy of ^{13}C NMR spectrum of the derivative **10g**.

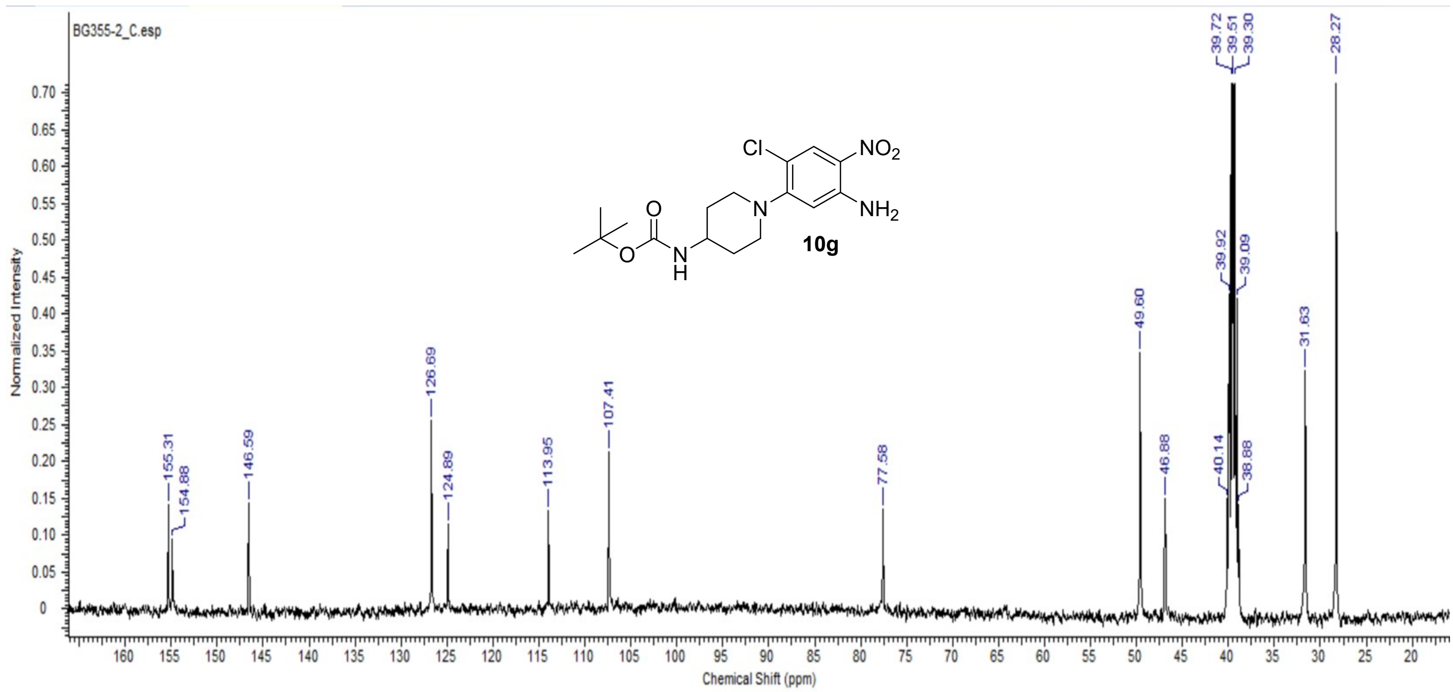


Figure S25. Copy of ^{1}H NMR spectrum of the derivative **11a** at 25 °C.

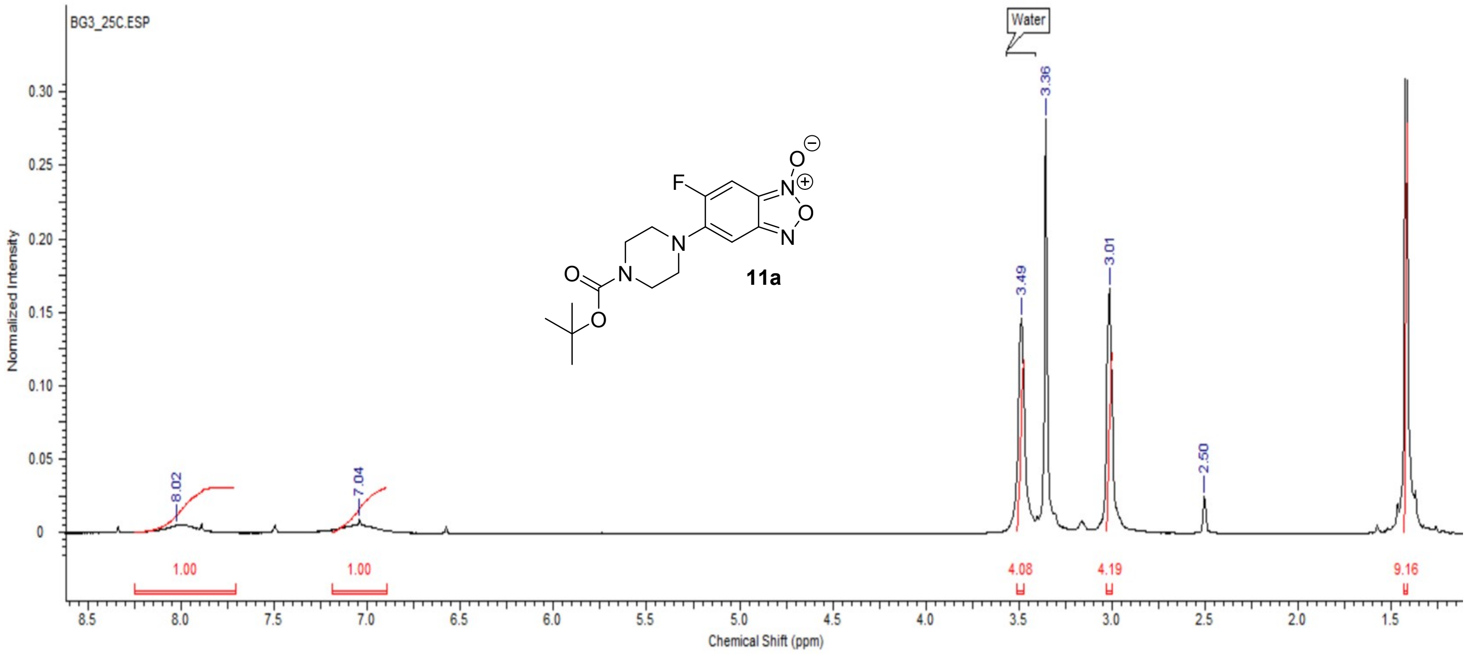


Figure S26. Copy of ^{13}C NMR spectrum of the derivative **11a** at 25 °C.

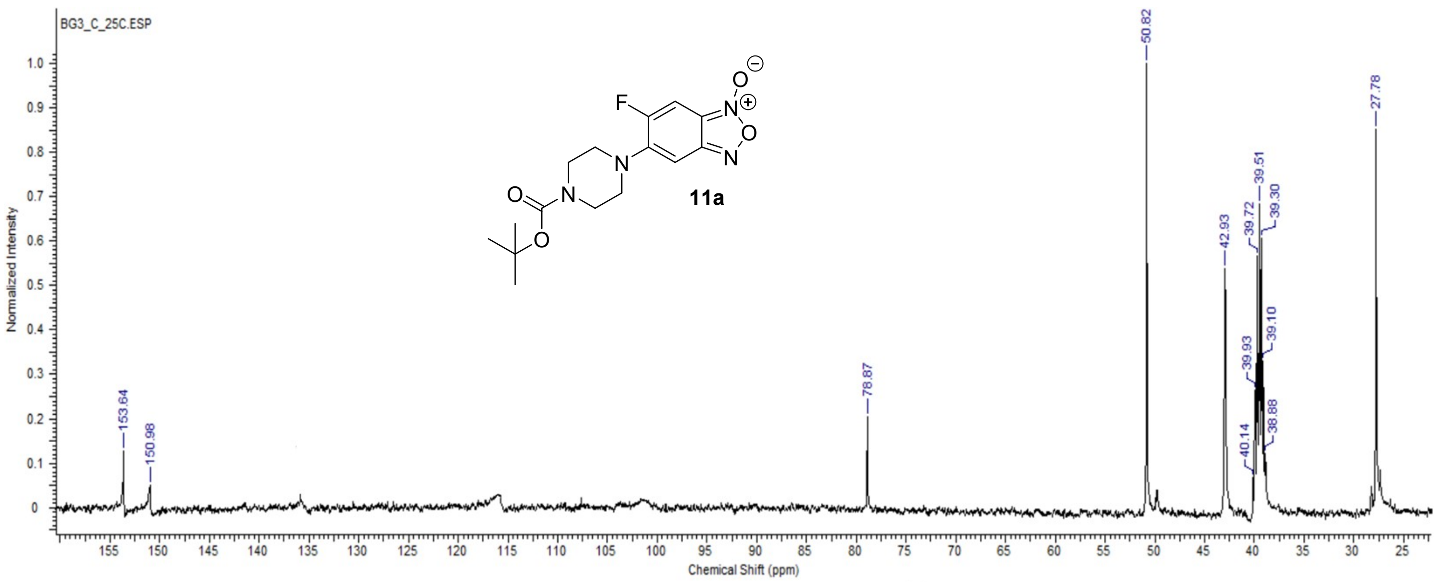


Figure S27. Copy of ^{1}H NMR spectrum of the derivative **11a** at 75 °C.

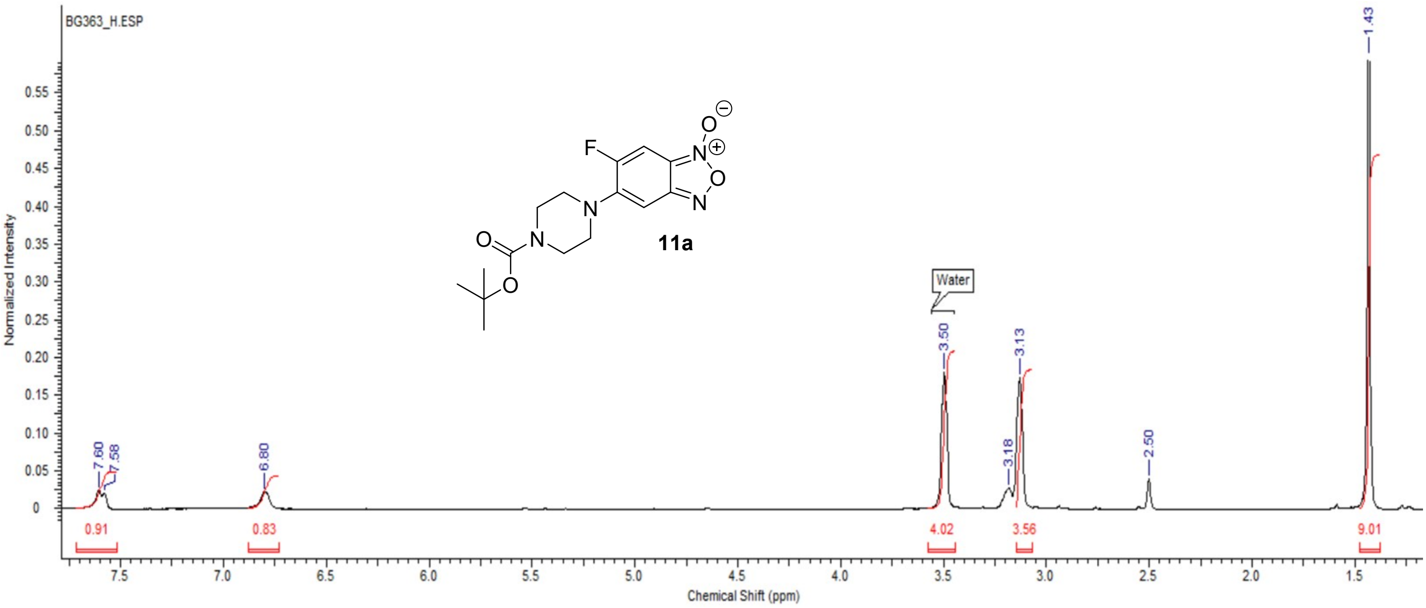


Figure S28. Copy of ^{13}C NMR spectrum of the derivative **11a** at 75 °C.

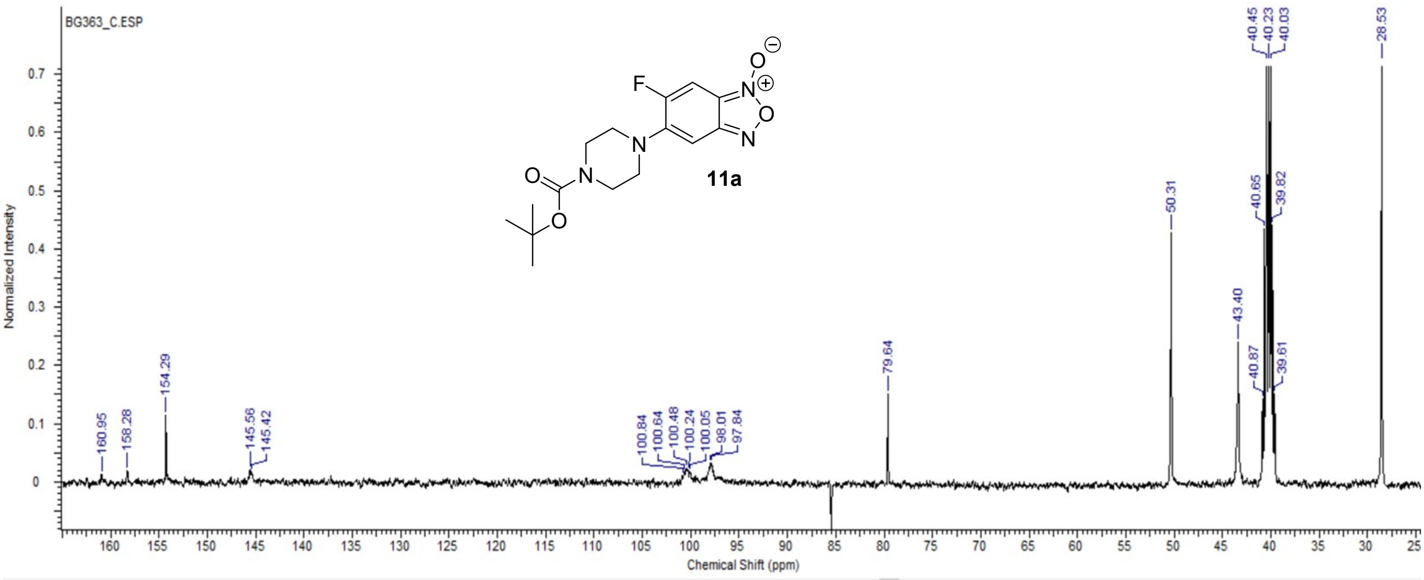


Figure S29. Copy of ^{1}H NMR spectrum of the derivative **11b**.

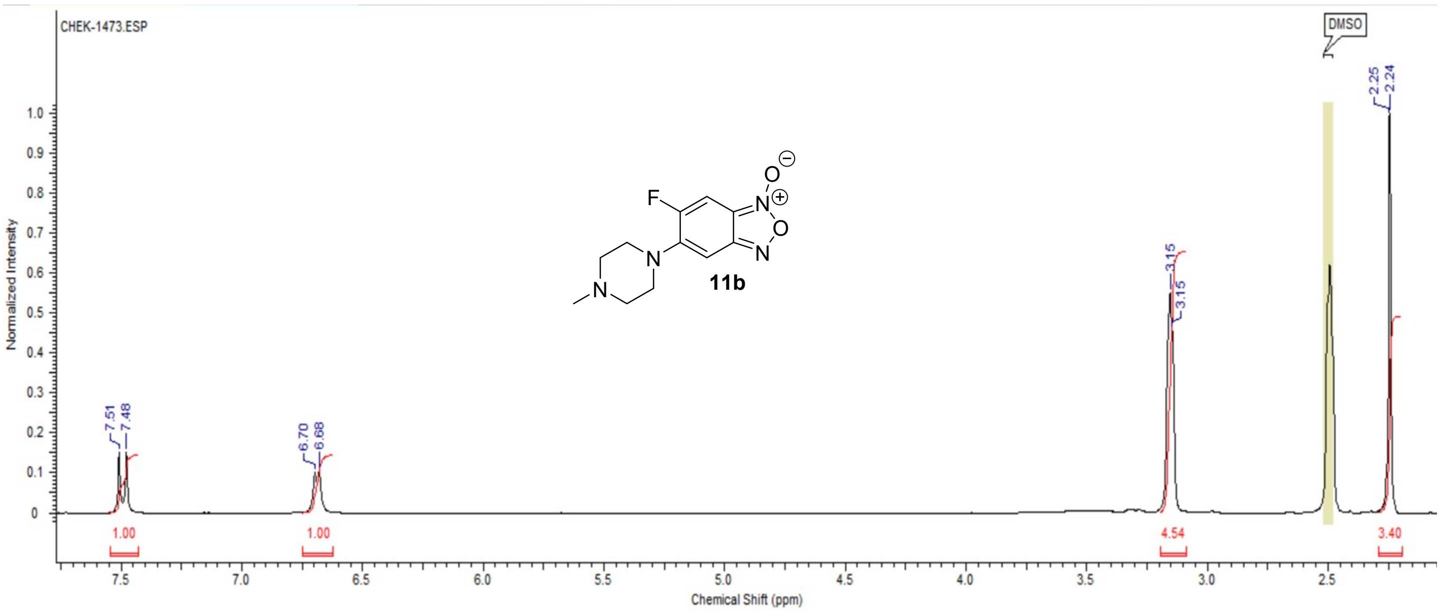


Figure S30. Copy of ^{13}C NMR spectrum of the derivative **11b**.

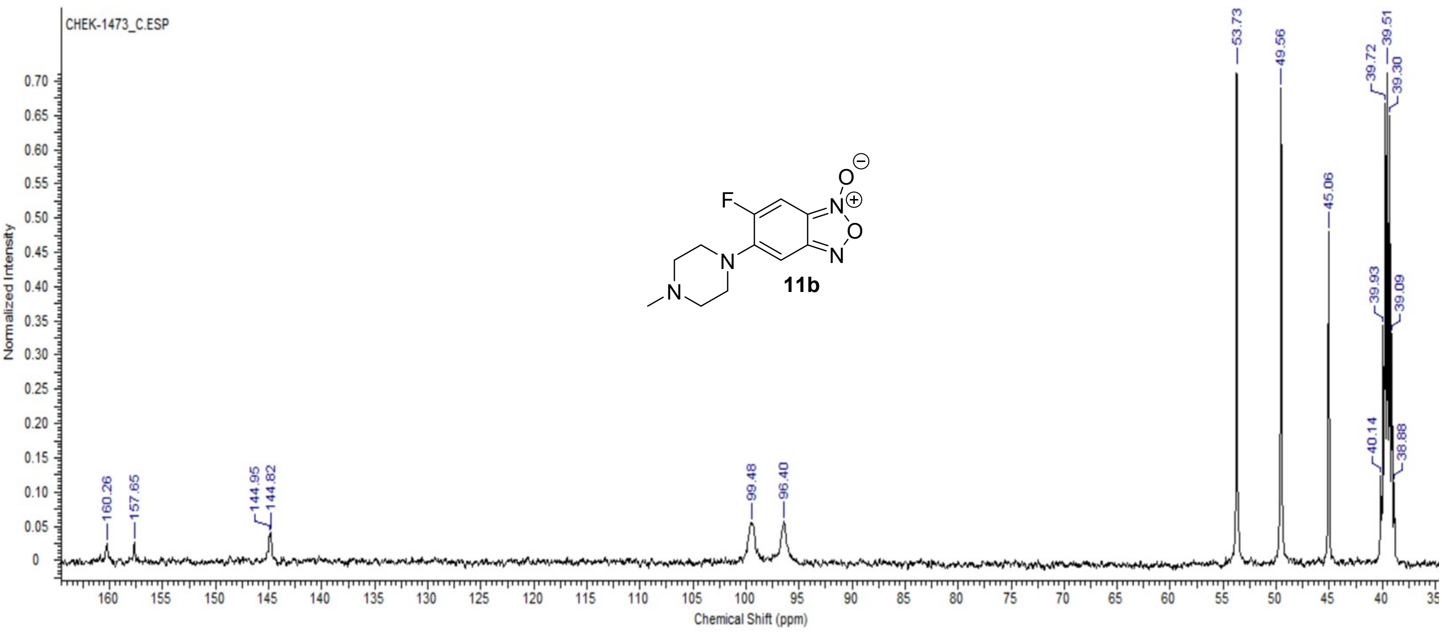


Figure S31. Copy of ^{1}H NMR spectrum of the derivative **11c**.

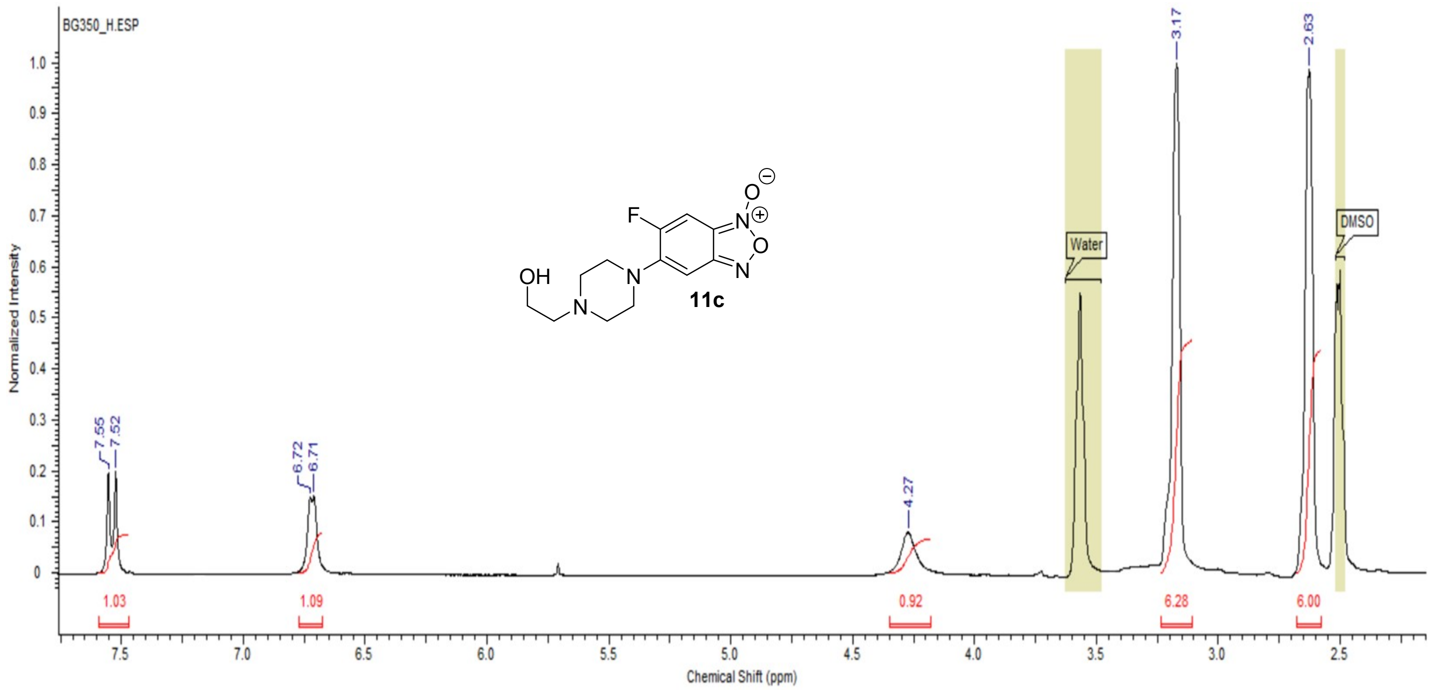


Figure S32. Copy of ^{13}C NMR spectrum of the derivative **11c**.

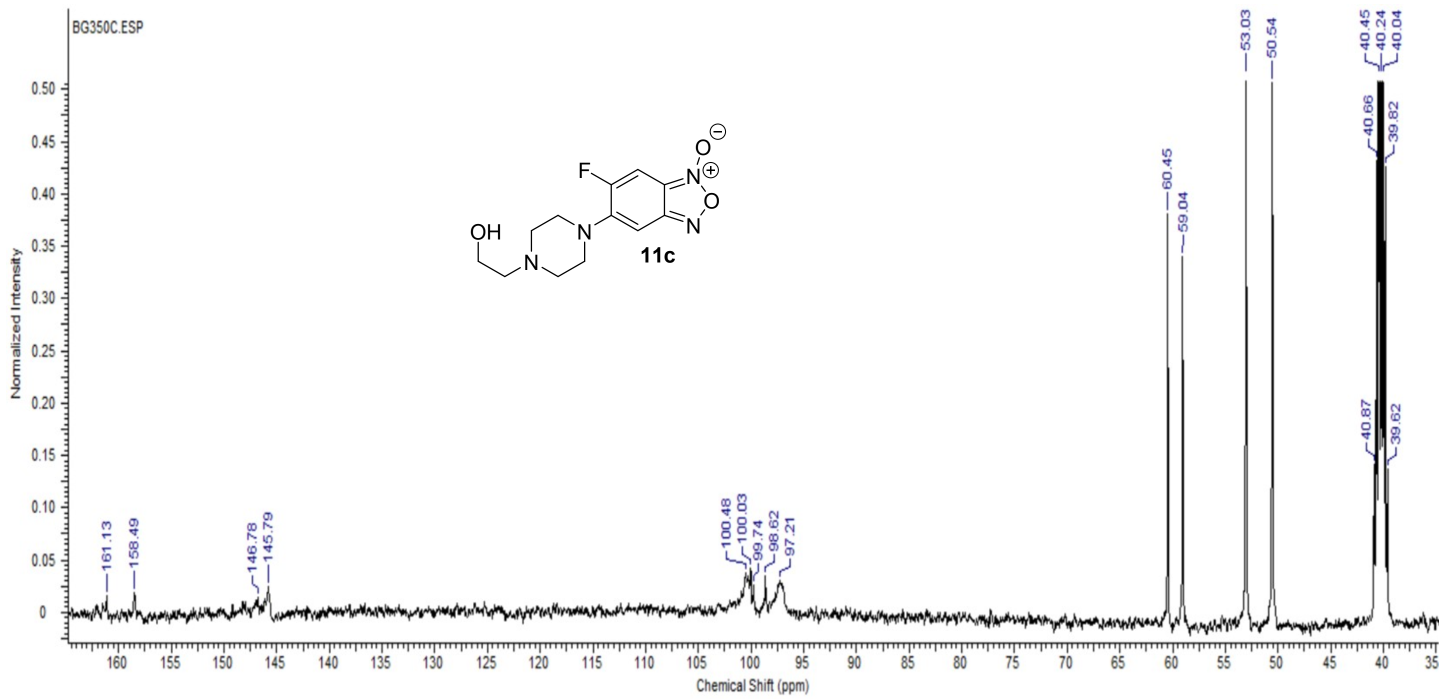


Figure S33. Copy of ^{1}H NMR spectrum of the derivative **11d**.

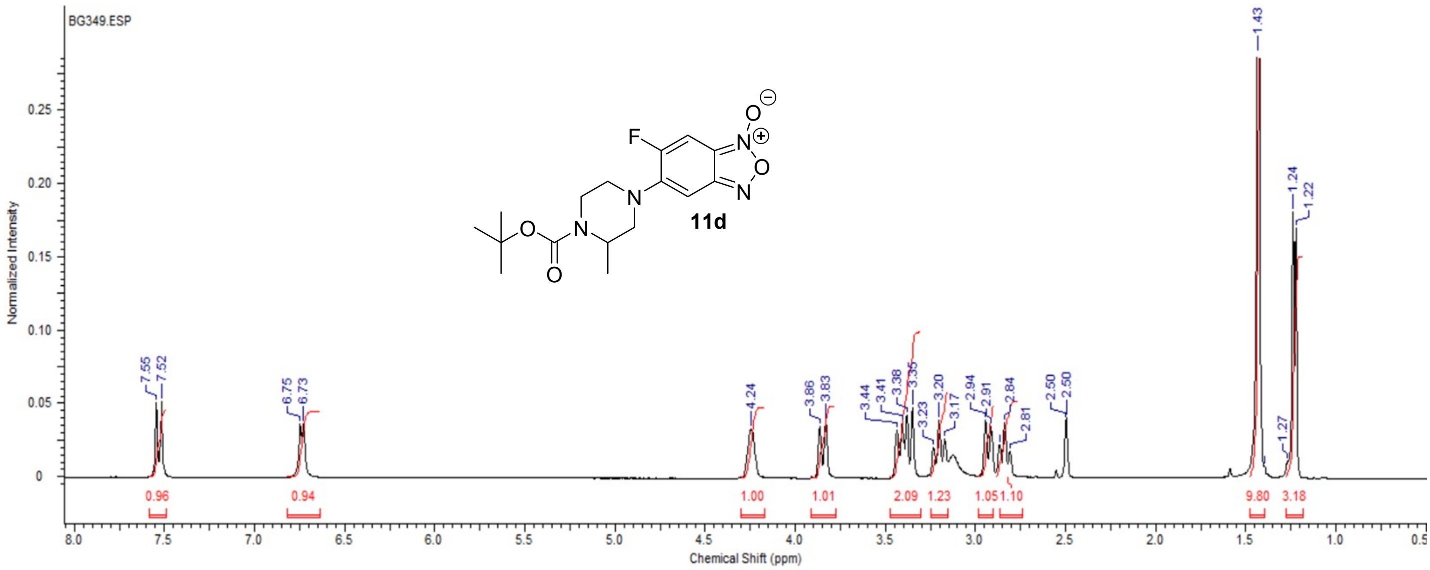


Figure S34. Copy of ^{13}C NMR spectrum of the derivative **11d**.

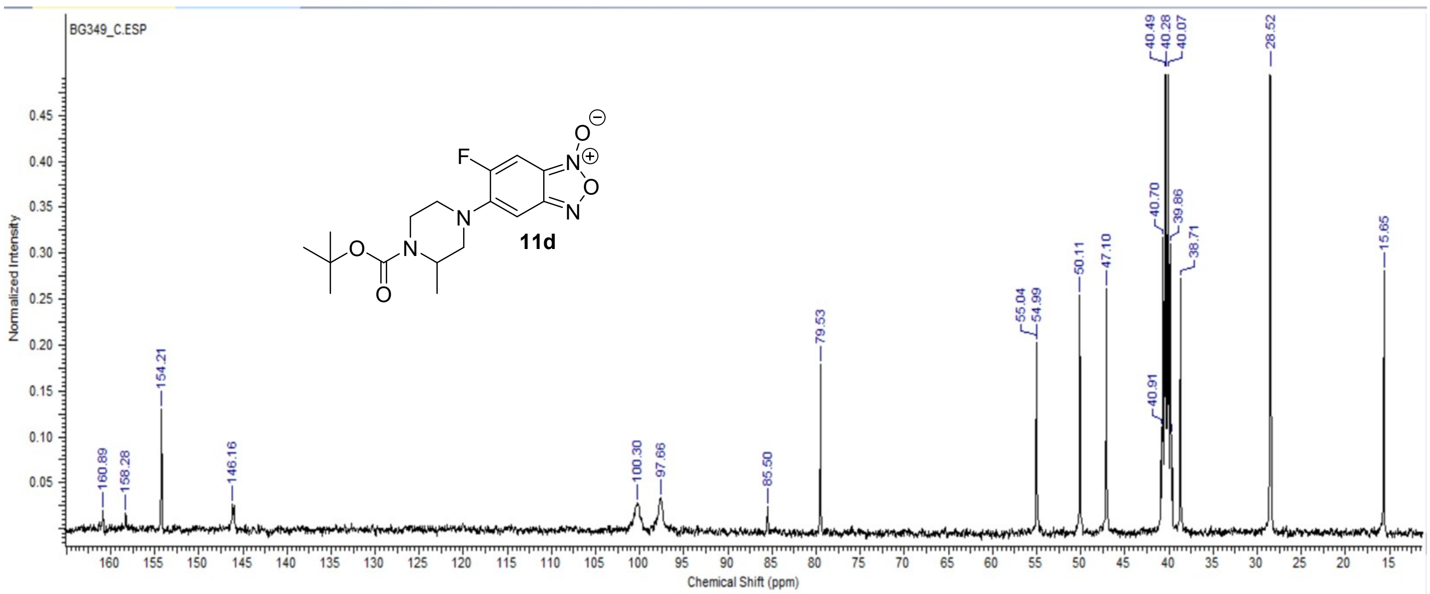


Figure S35. Copy of [1]H NMR spectrum of the derivative **11e**.

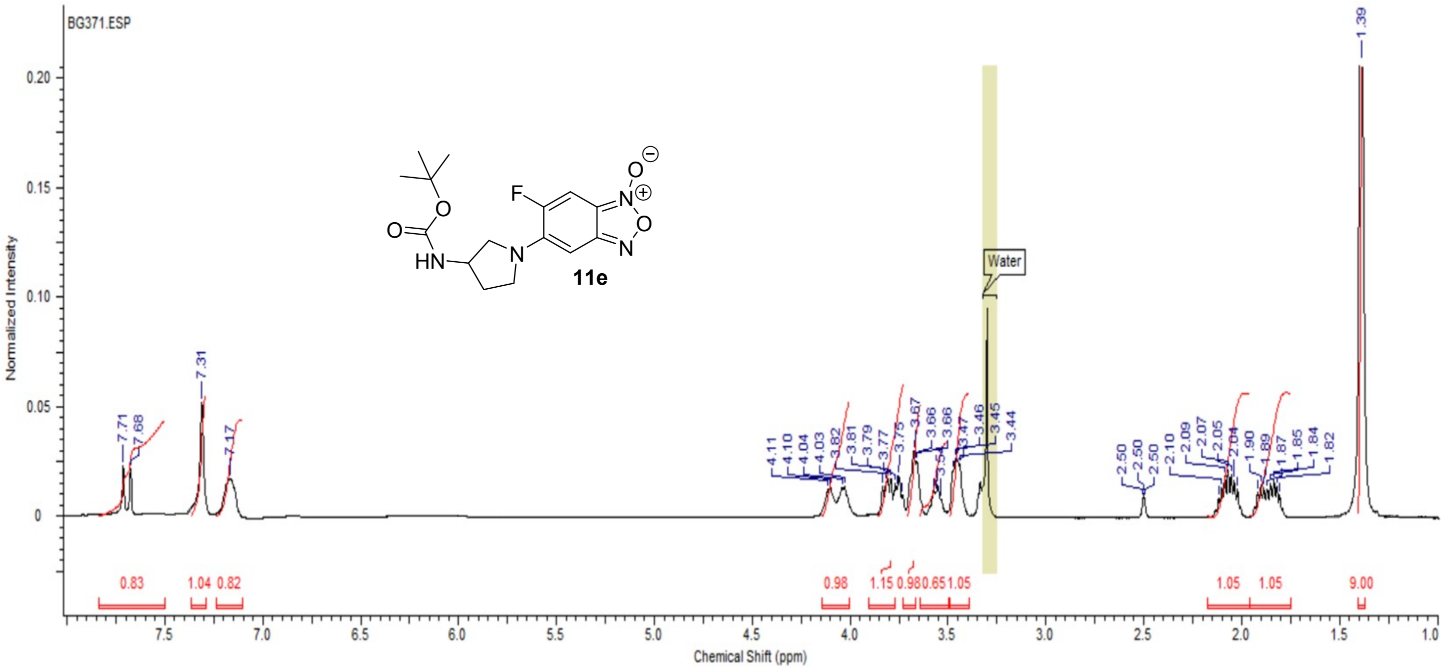


Figure S36. Copy of [13]C NMR spectrum of the derivative **11e**.

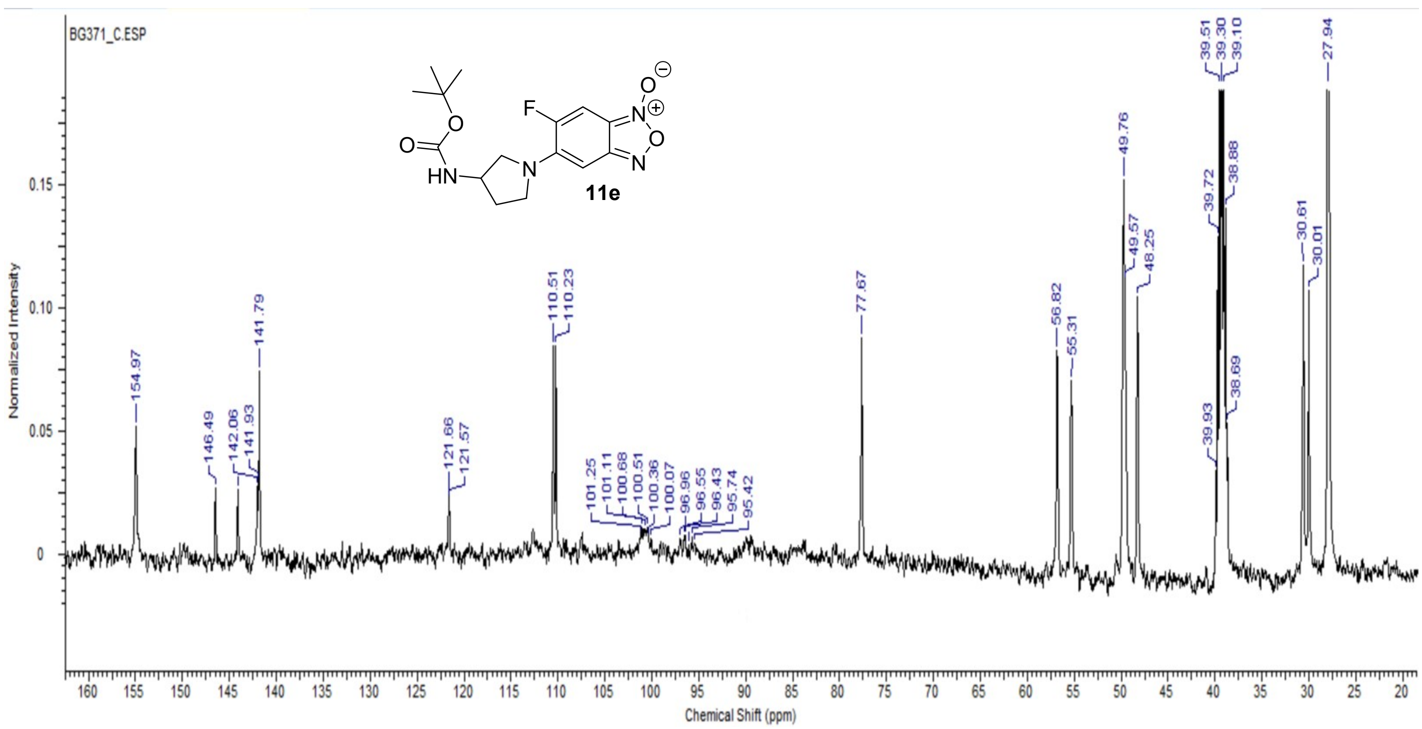


Figure S37. Copy of ^{1}H NMR spectrum of the derivative **11f**.

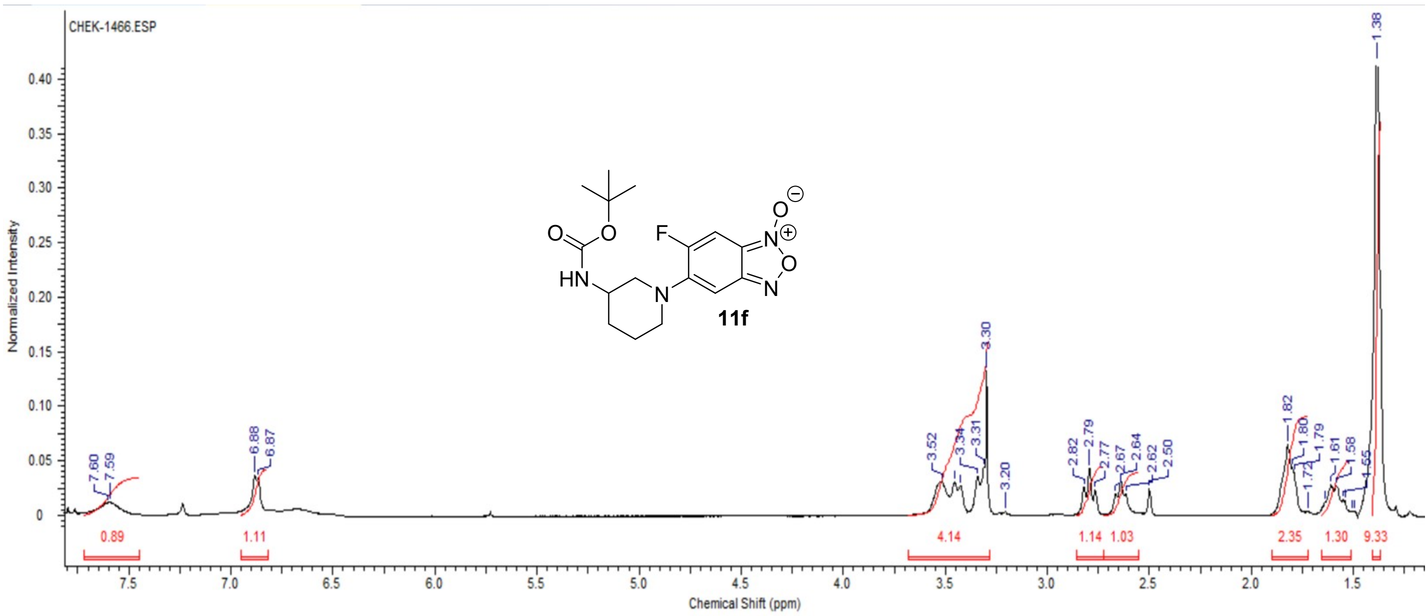


Figure S38. Copy of ^{13}C NMR spectrum of the derivative **11f**.

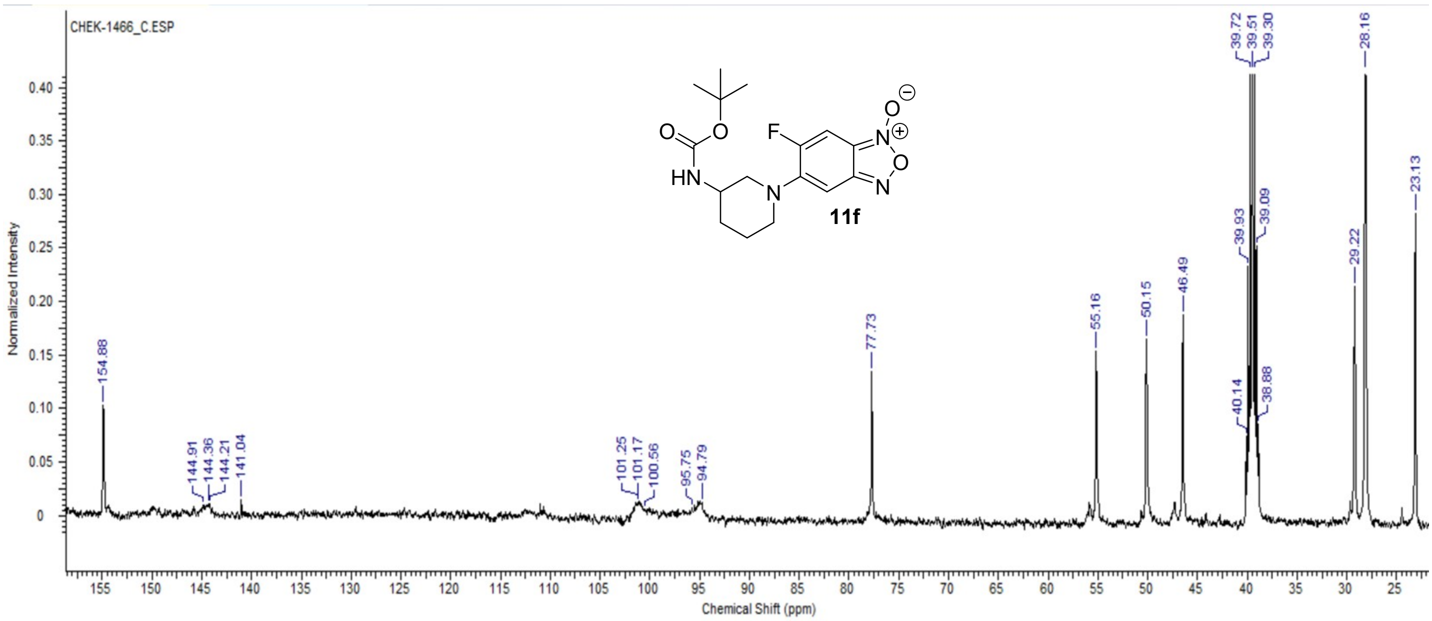


Figure S39. Copy of ^{1}H NMR spectrum of the derivative **11g**.

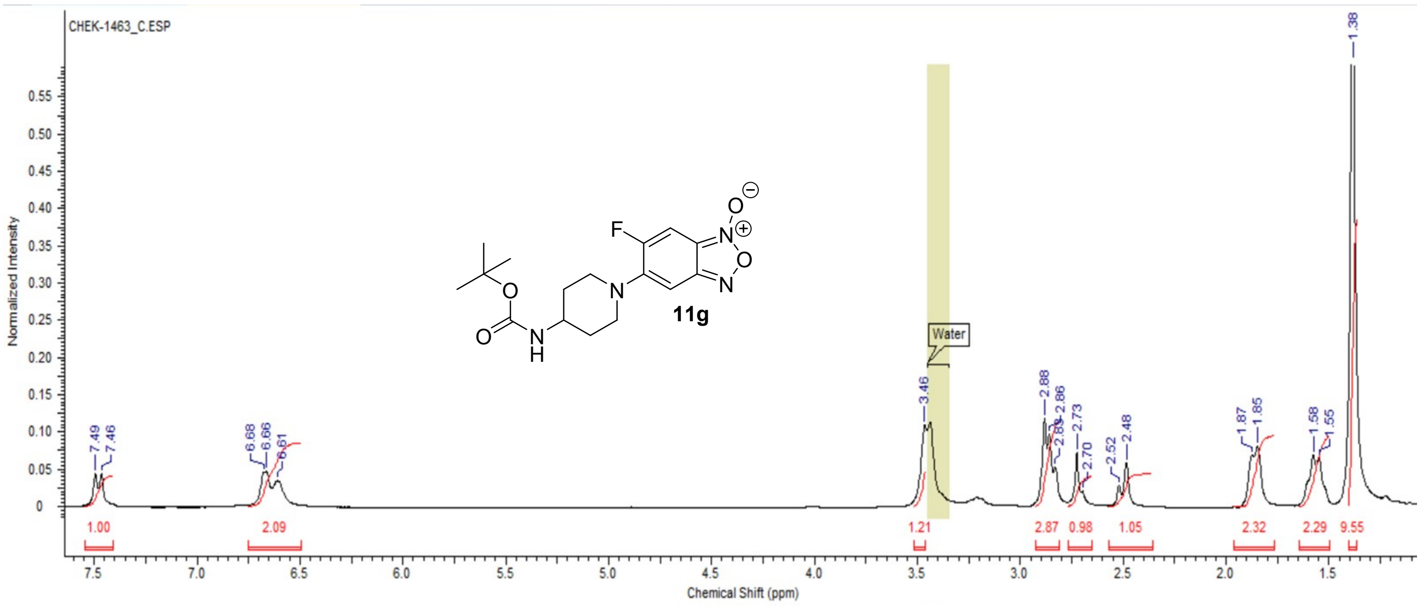


Figure S40. Copy of ^{13}C NMR spectrum of the derivative **11g**.

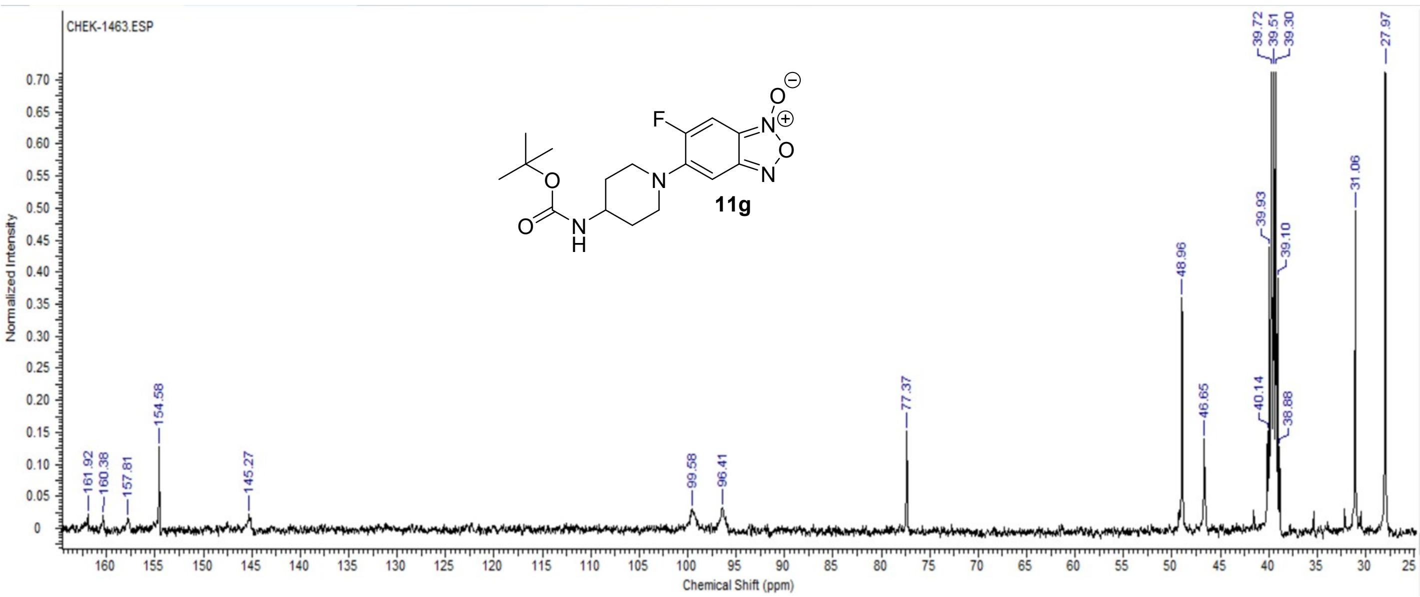


Figure S41. Copy of [1]H NMR spectrum of the derivative **11h**.

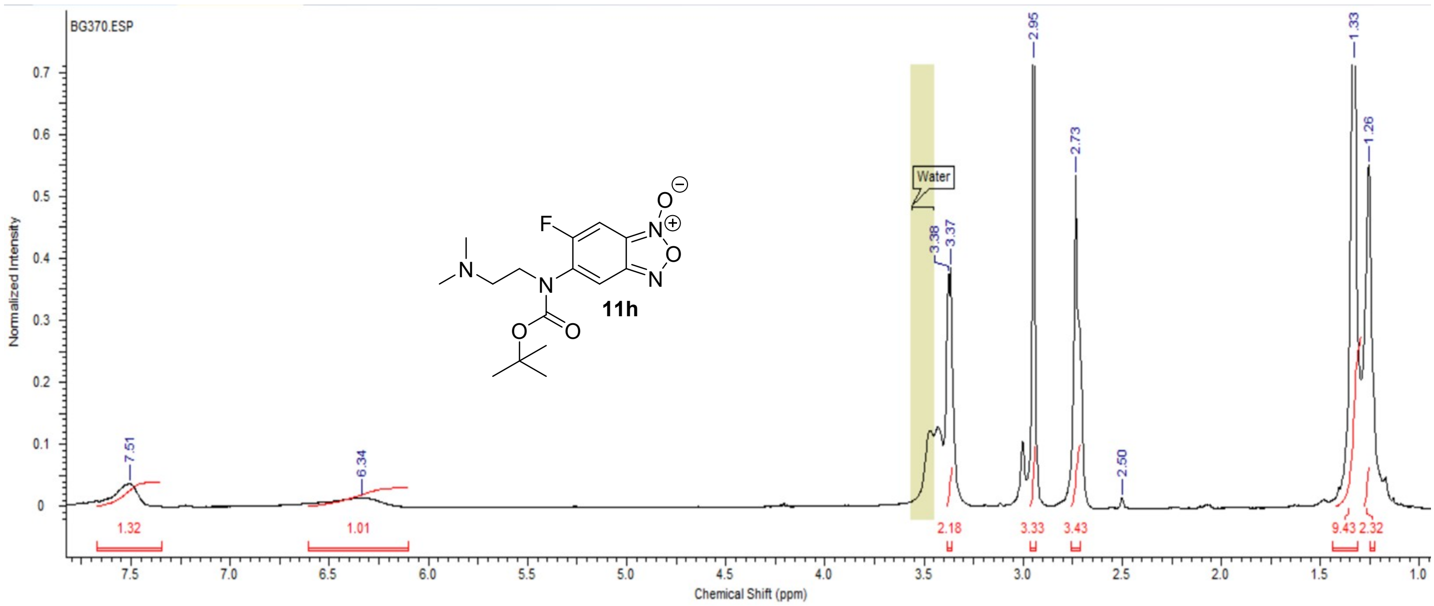


Figure S42. Copy of [13]C NMR spectrum of the derivative **11h**.

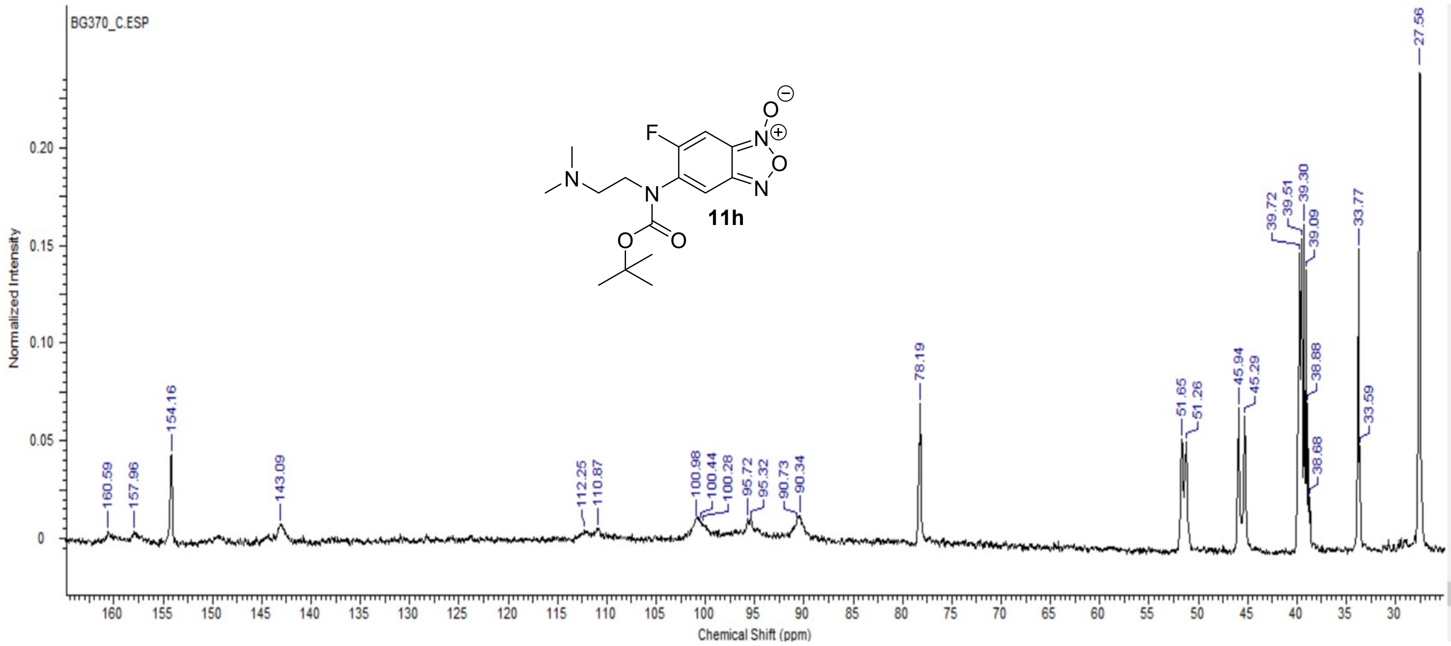


Figure S43. Copy of ^{1}H NMR spectrum of the derivative **12a**.

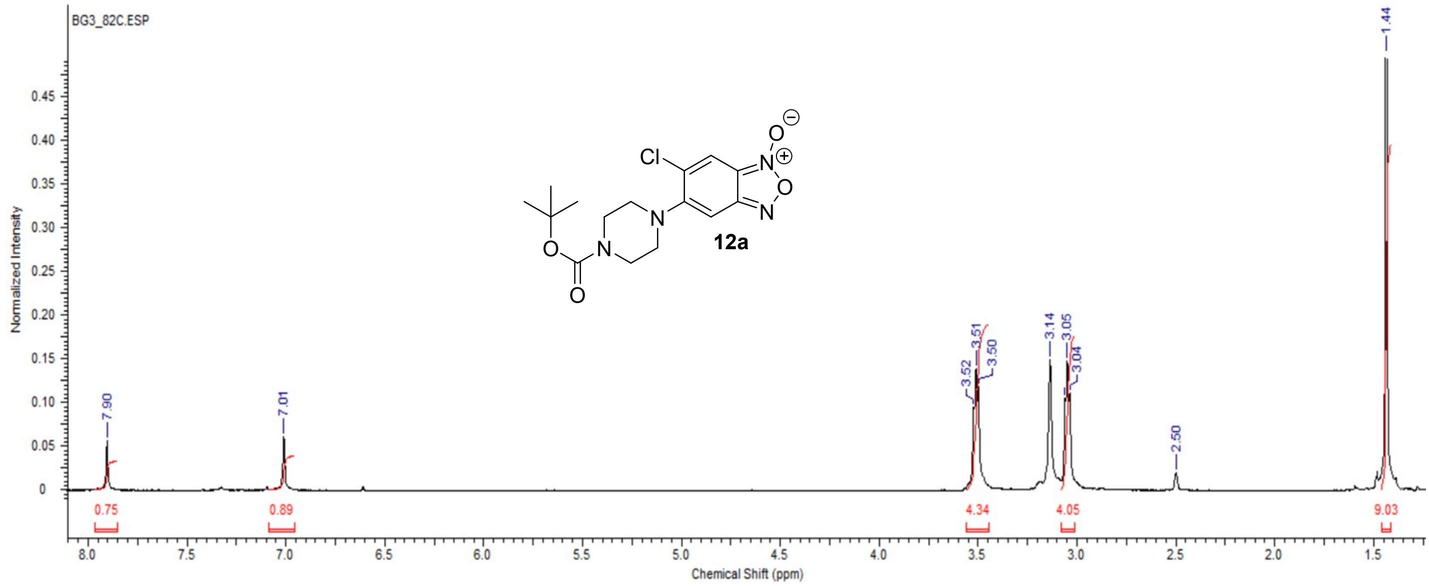


Figure S44. Copy of ^{13}C NMR spectrum of the derivative **12a**.

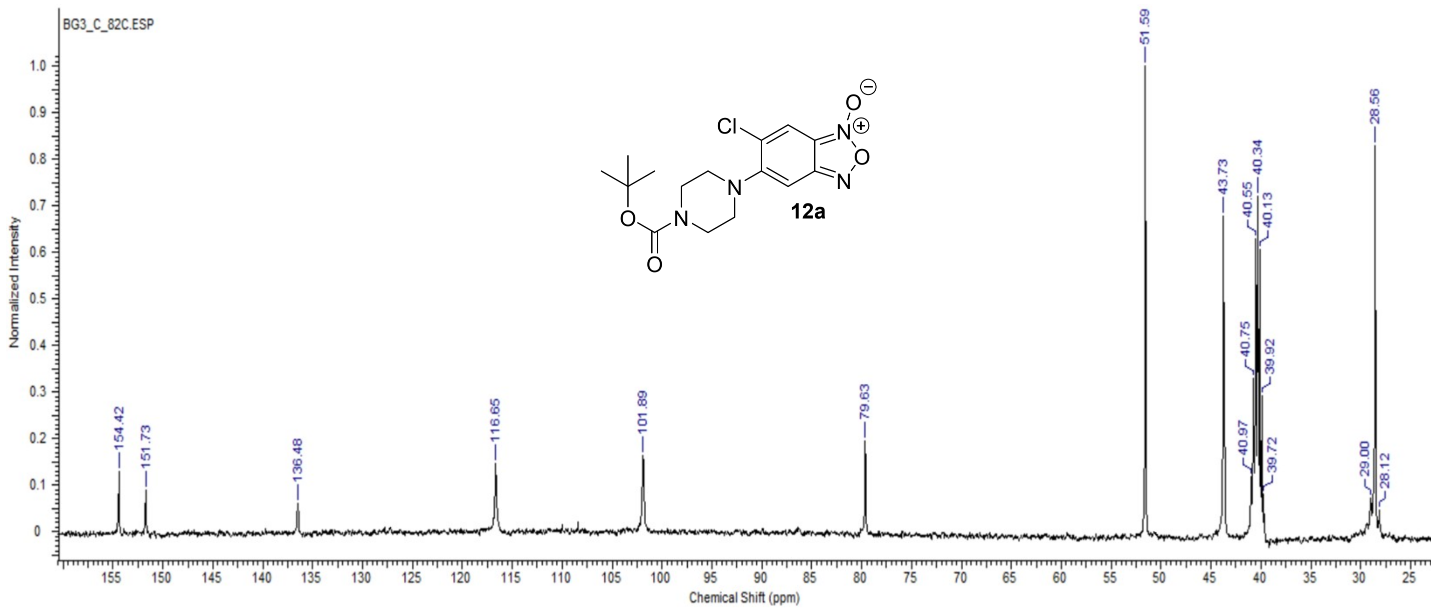


Figure S45. Copy of ^{1}H NMR spectrum of the derivative **12b**.

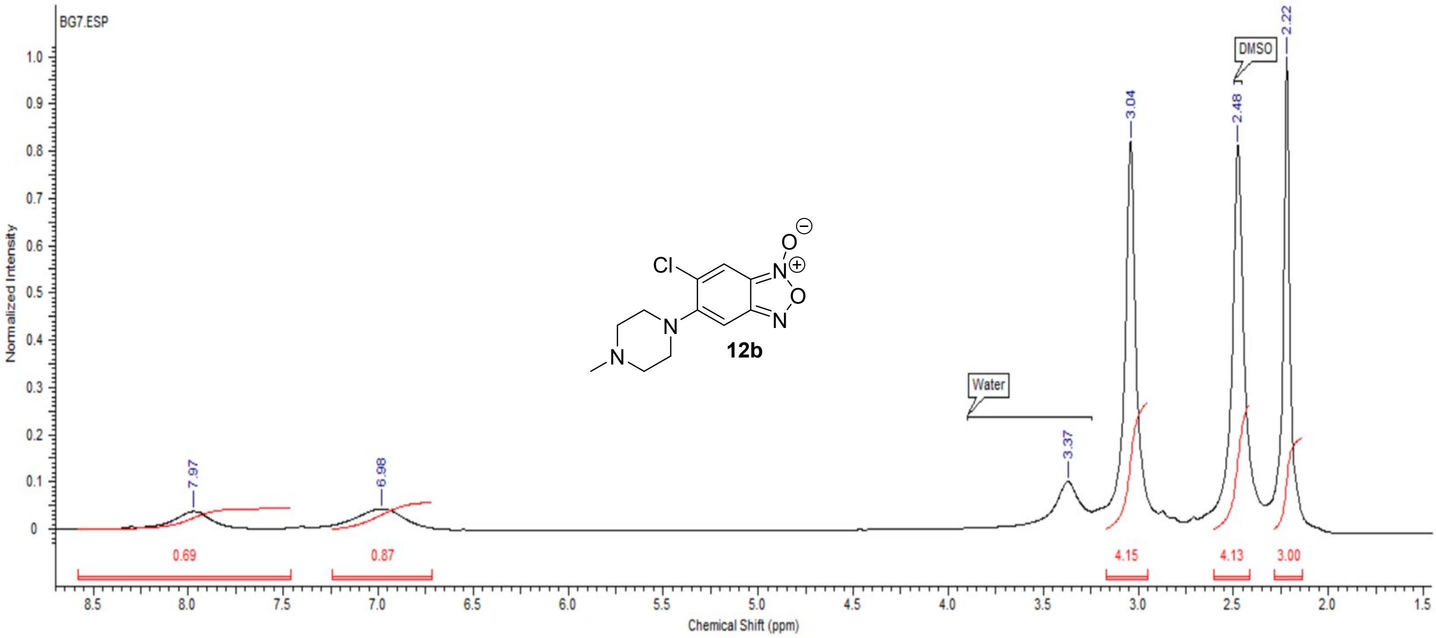


Figure S46. Copy of ^{13}C NMR spectrum of the derivative **12b**.

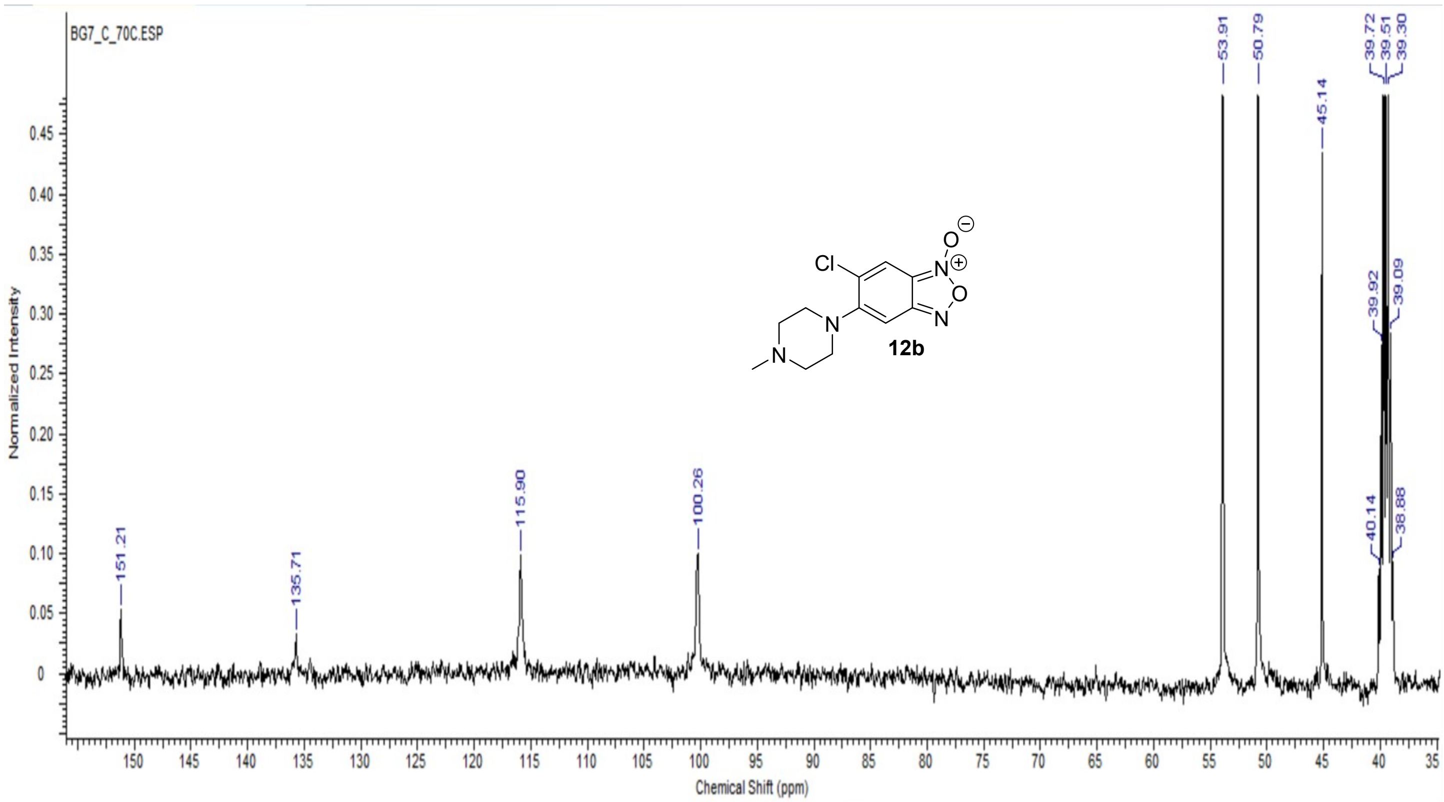


Figure S47. Copy of ^{1}H NMR spectrum of the derivative **12g**.

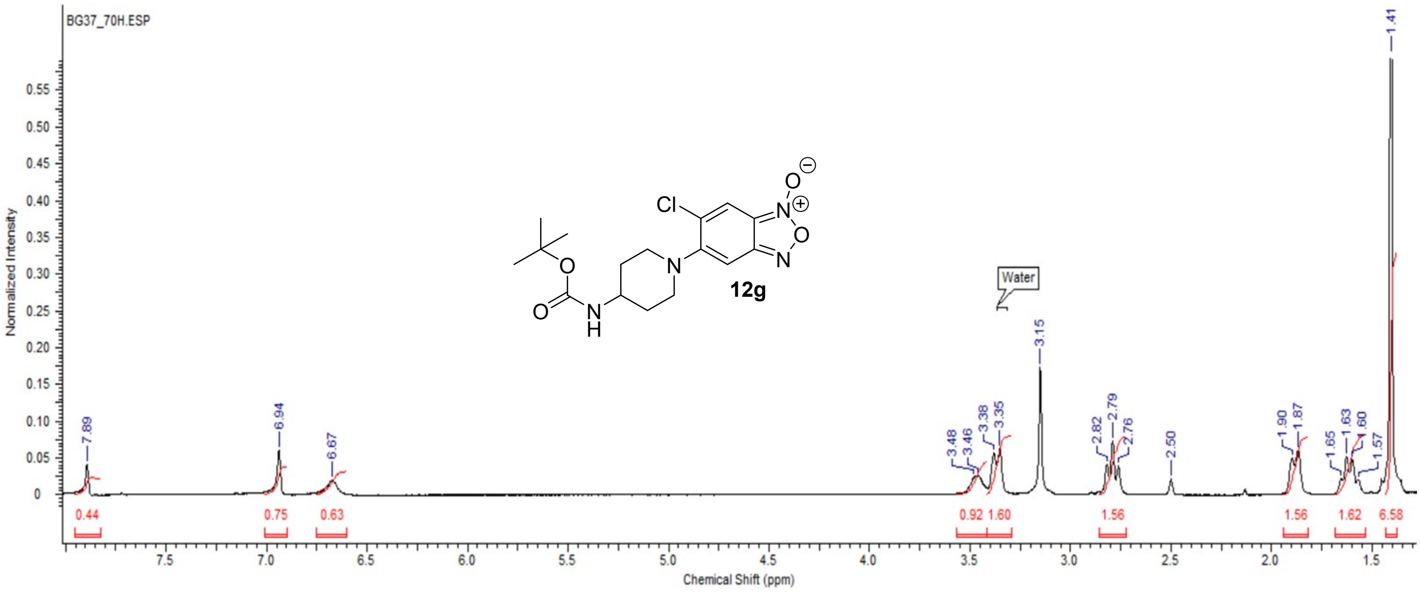


Figure S48. Copy of ^{13}C NMR spectrum of the derivative **12g**.

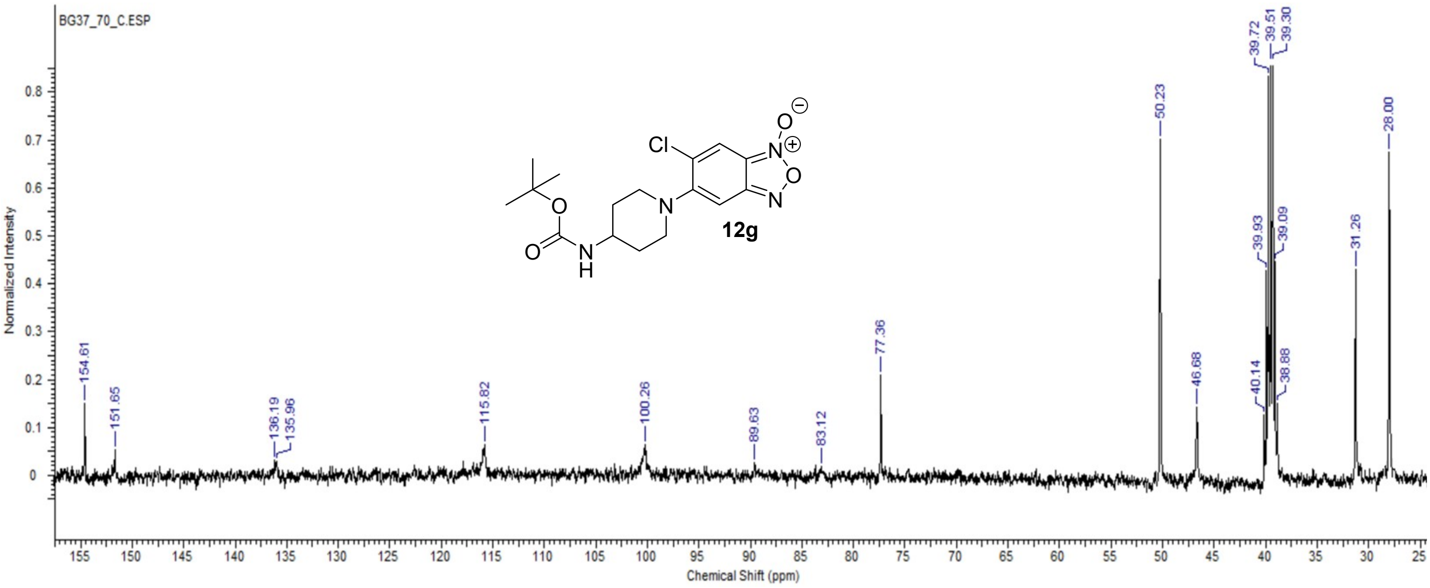


Figure S49. Copy of ^{1}H NMR spectrum of the derivative **13a**.

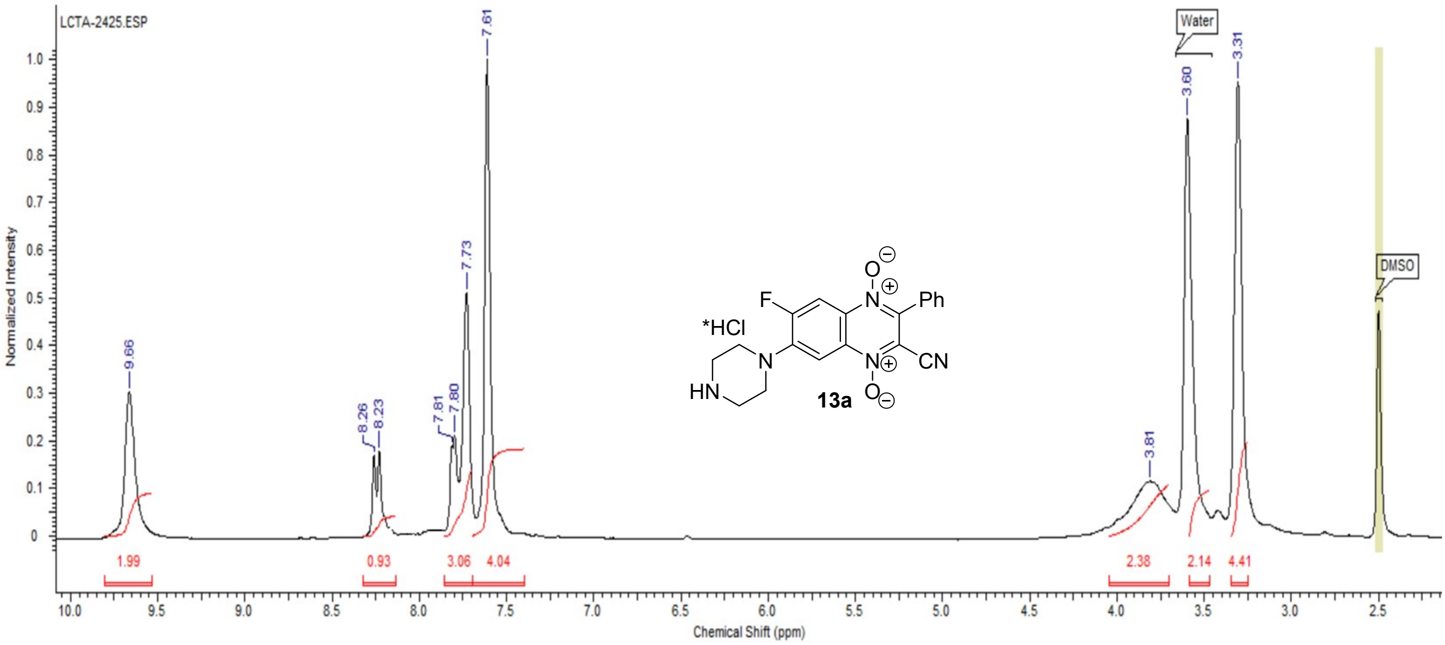


Figure S50. Copy of ^{13}C NMR spectrum of the derivative **13a**.

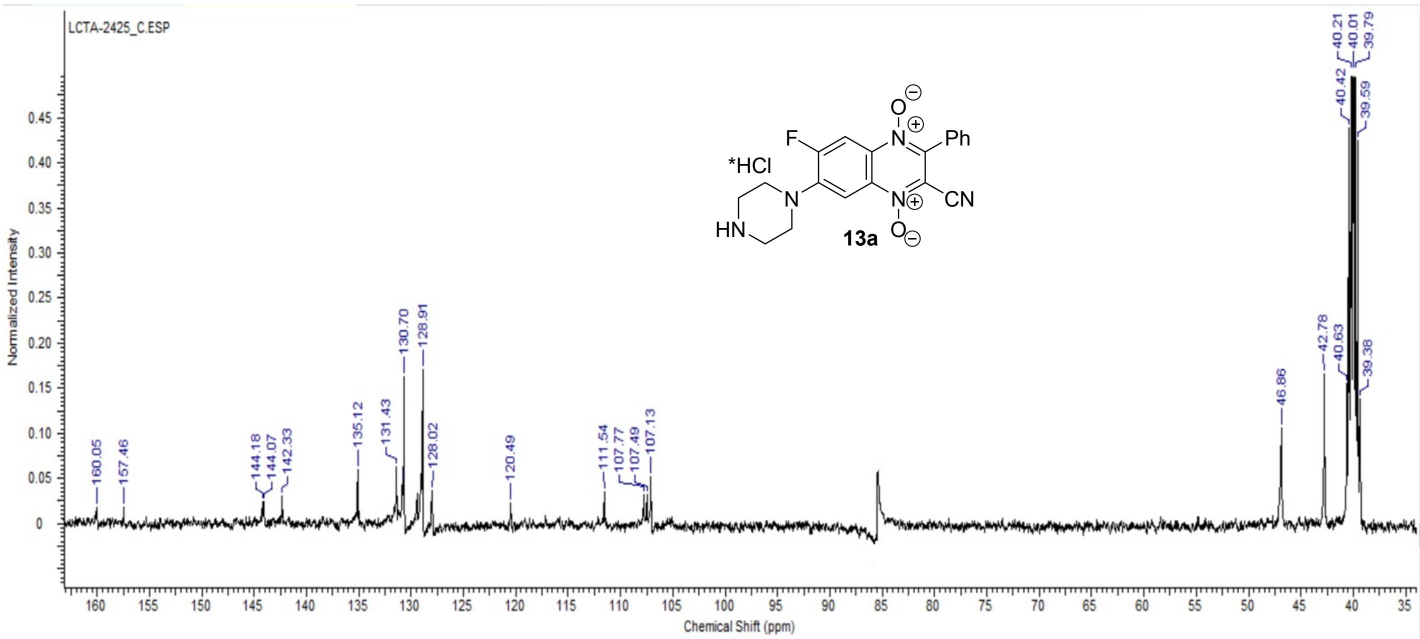


Figure S51. Copy of ^{1}H NMR spectrum of the derivative **13b**.

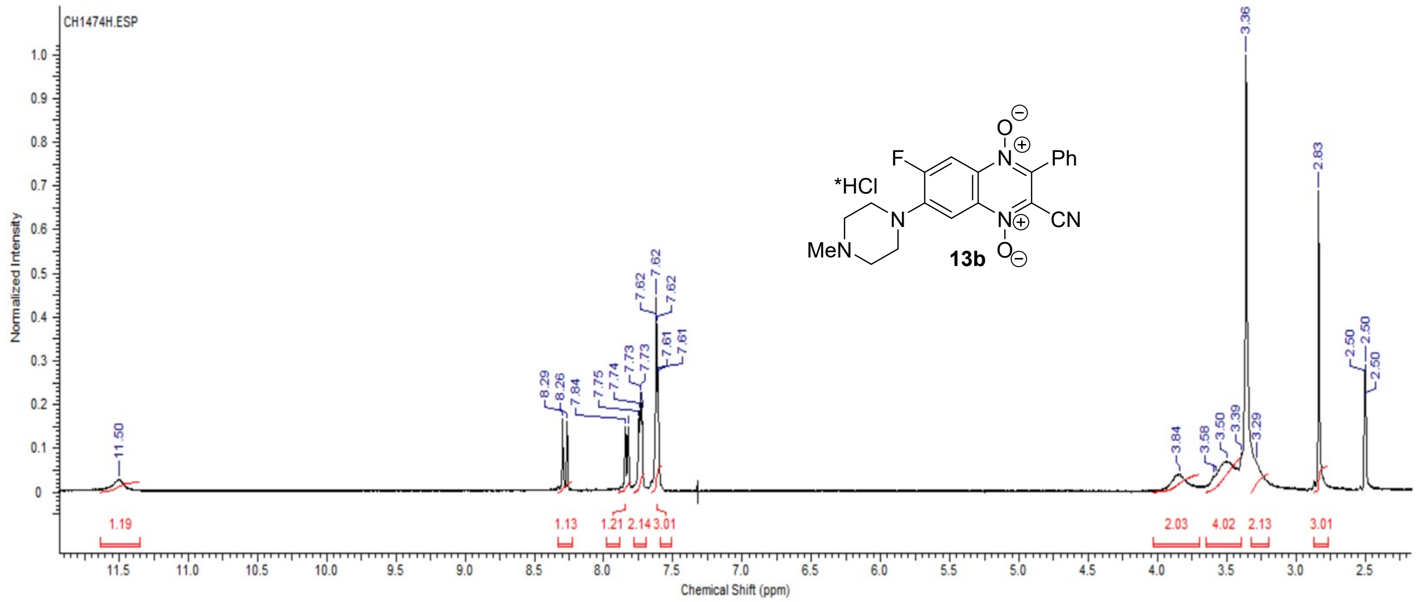


Figure S52. Copy of ^{13}C NMR spectrum of the derivative **13b**.

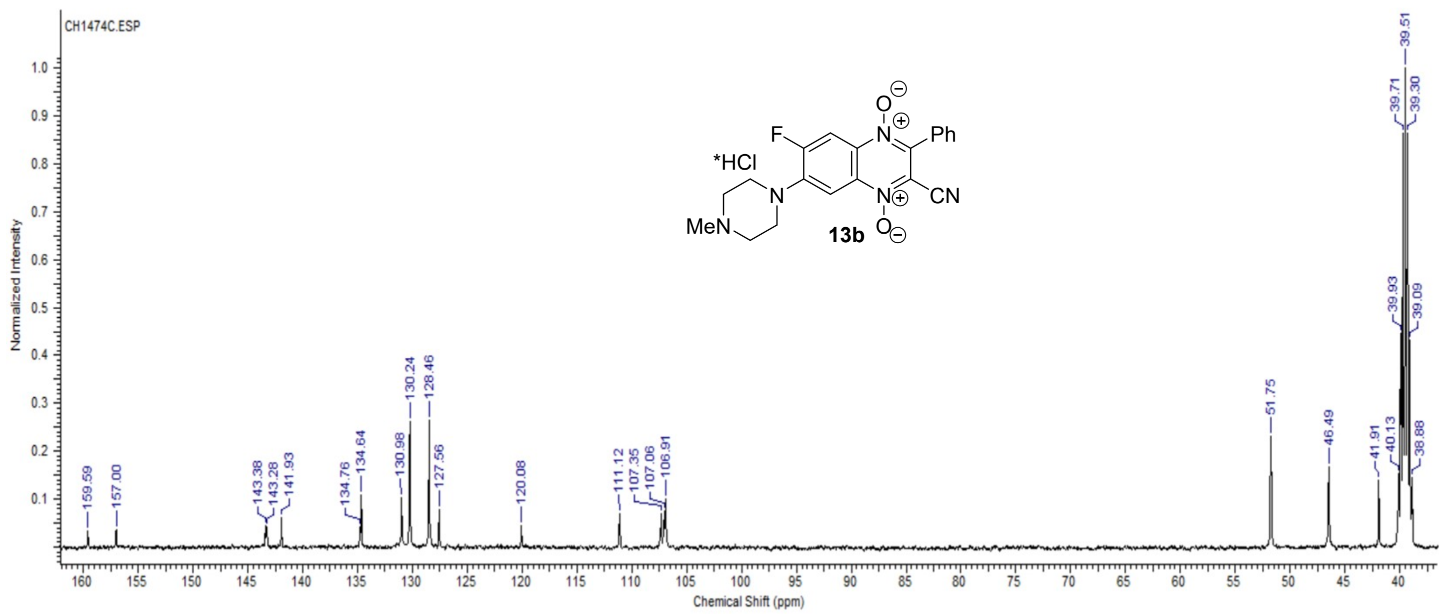


Figure S53. Copy of ^{1}H NMR spectrum of the derivative **13c**.

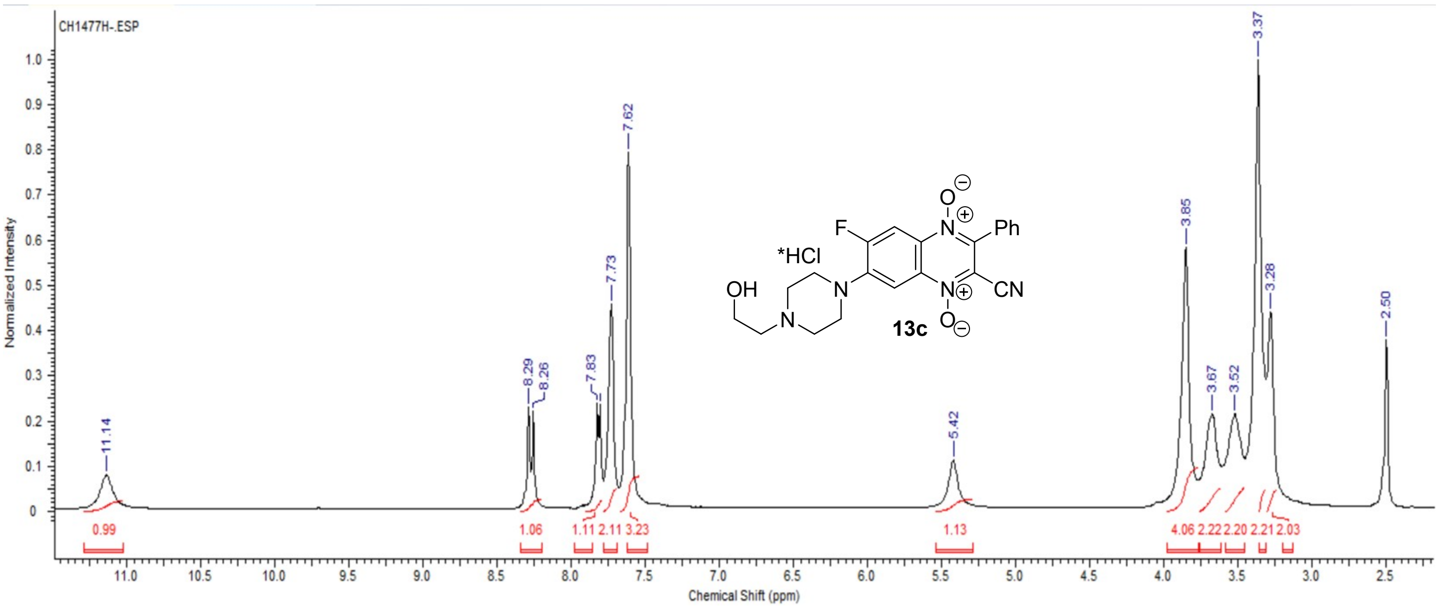


Figure S54. Copy of ^{13}C NMR spectrum of the derivative **13c**.

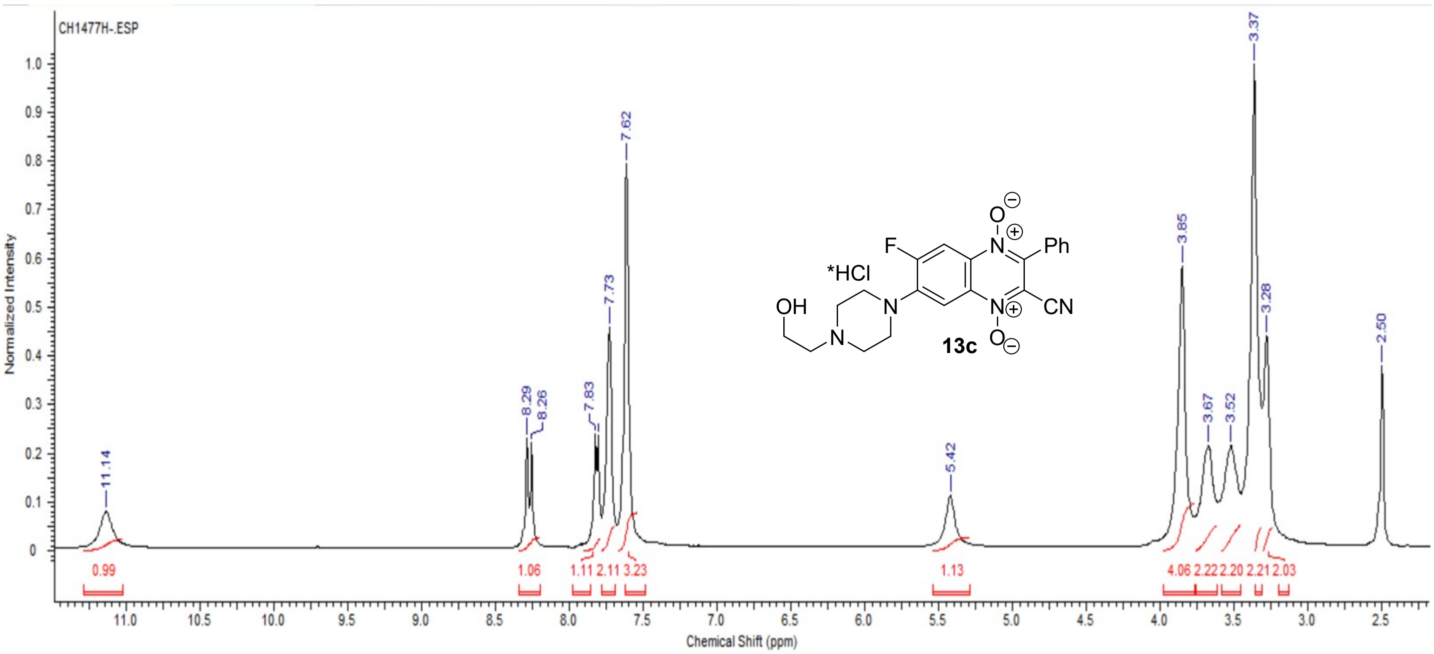


Figure S55. Copy of ^{1}H NMR spectrum of the derivative **13d**.

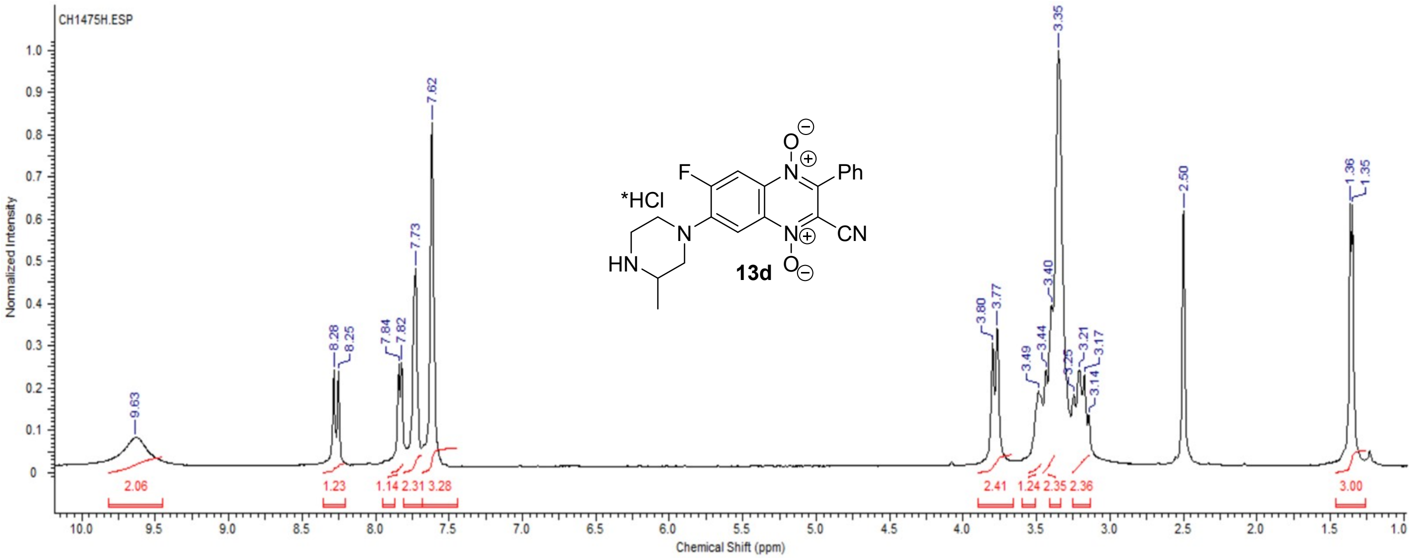


Figure S56. Copy of ^{13}C NMR spectrum of the derivative **13d**.

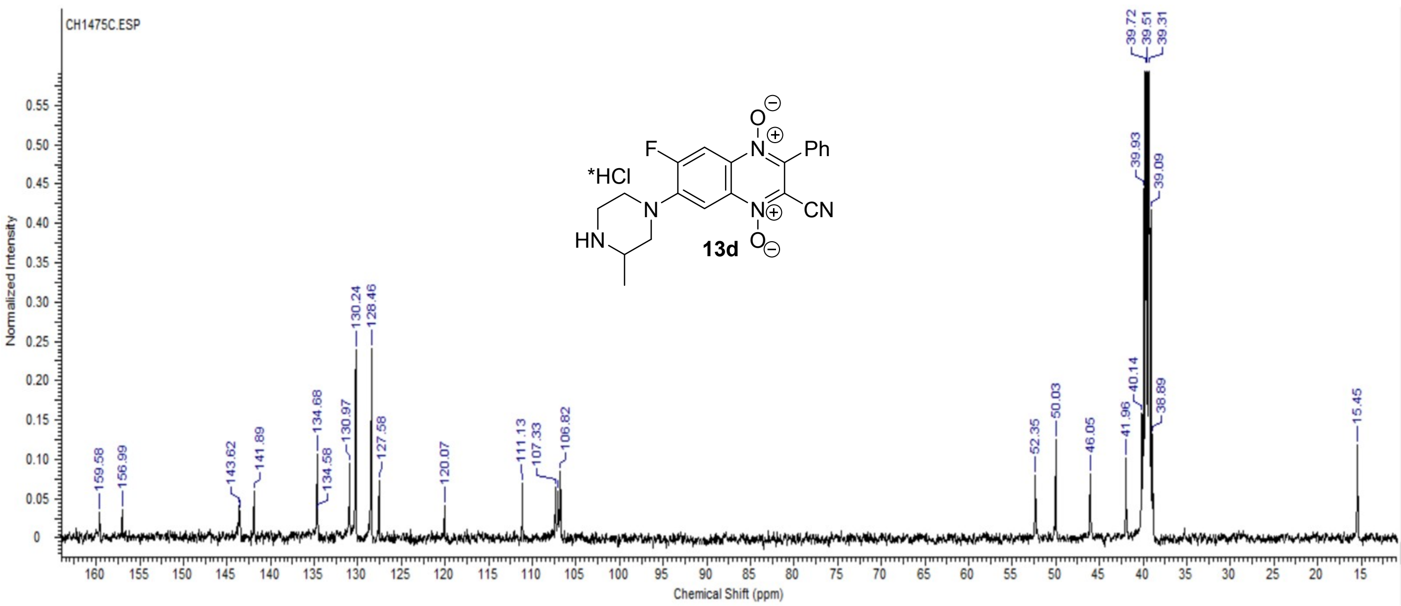


Figure S57. Copy of ^{1}H NMR spectrum of the derivative **13e**.

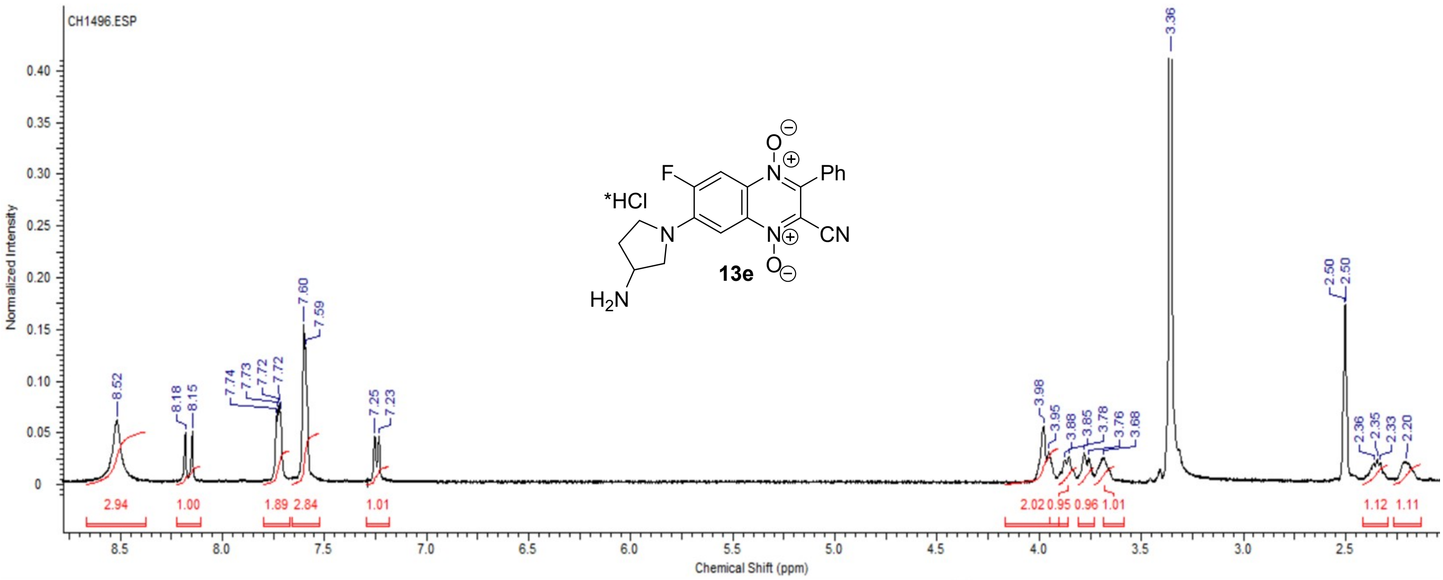


Figure S58. Copy of ^{13}C NMR spectrum of the derivative **13e**.

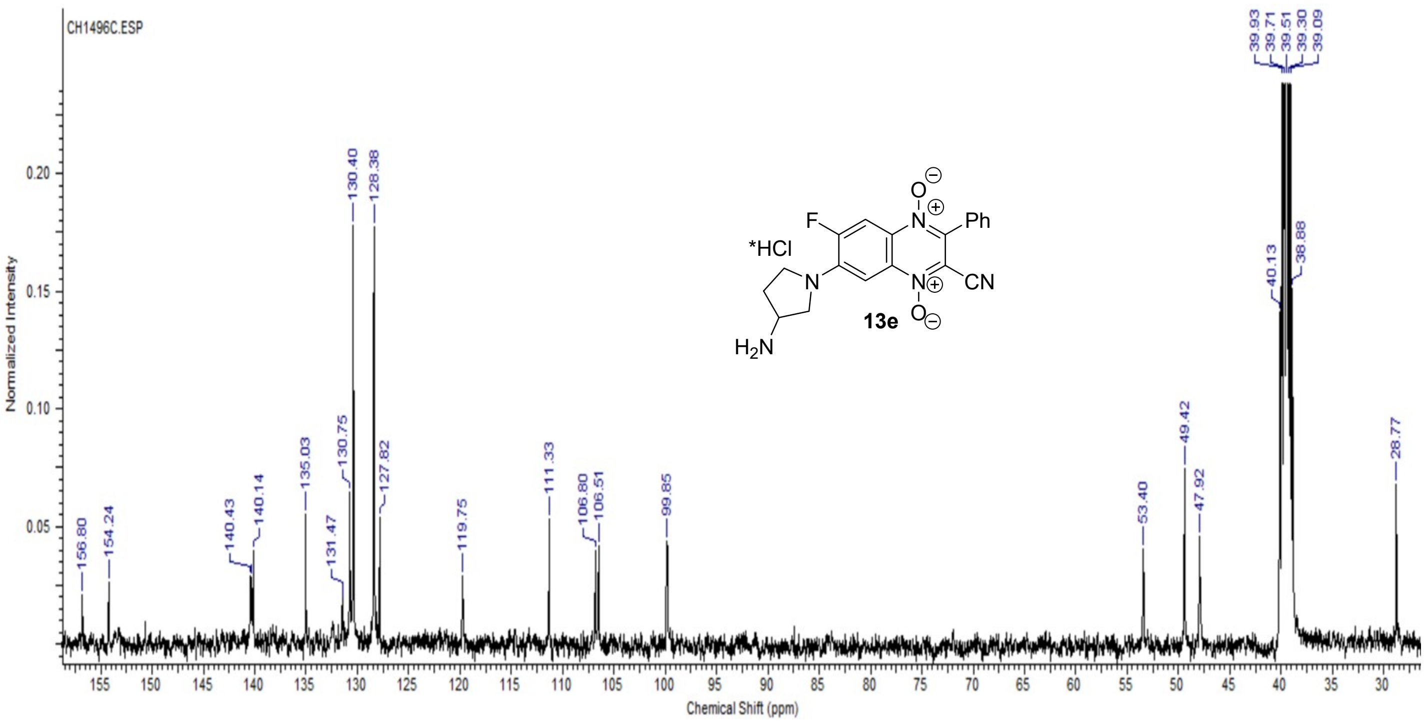


Figure S59. Copy of [1]H NMR spectrum of the derivative **13f**.

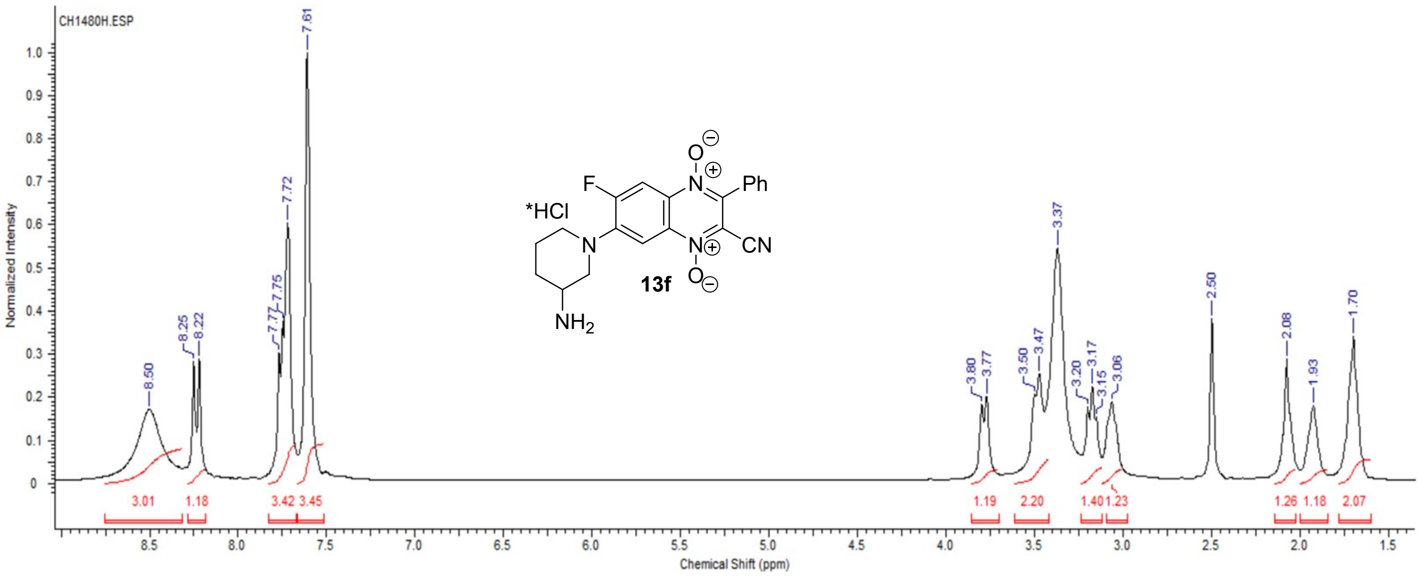


Figure S60. Copy of [13]C NMR spectrum of the derivative **13f**.

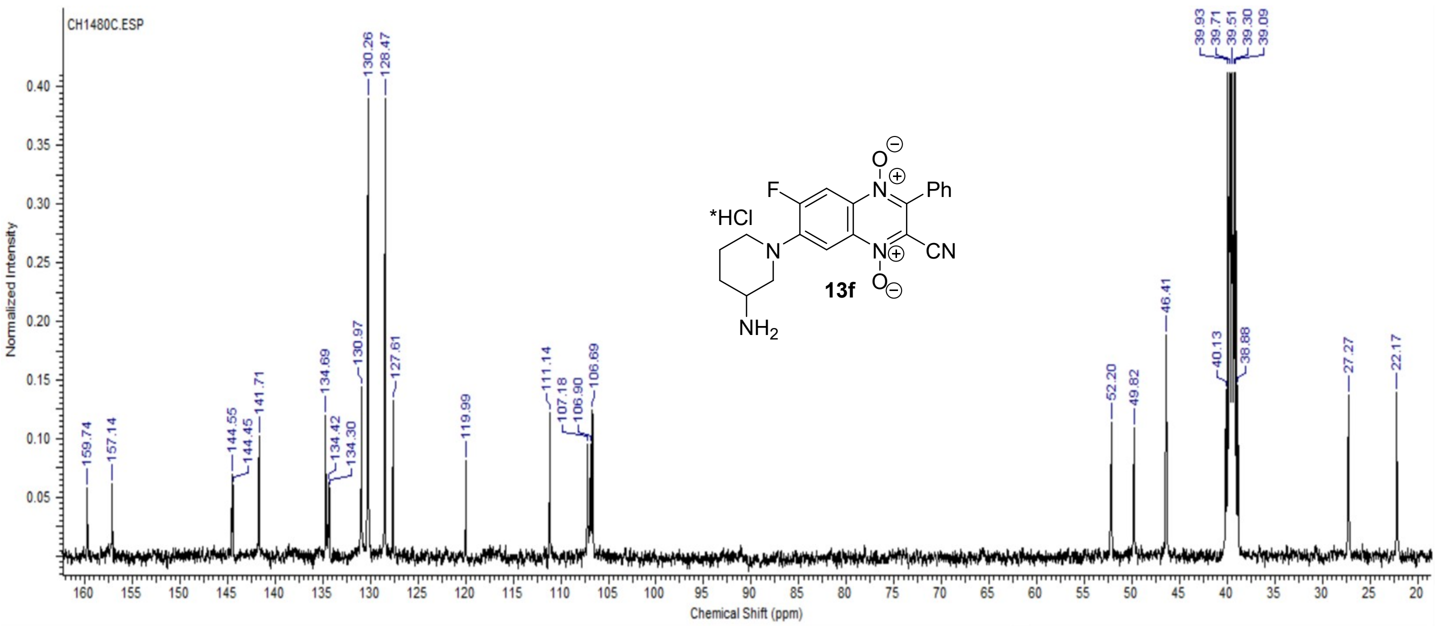


Figure S61. Copy of [1]H NMR spectrum of the derivative **13g**.

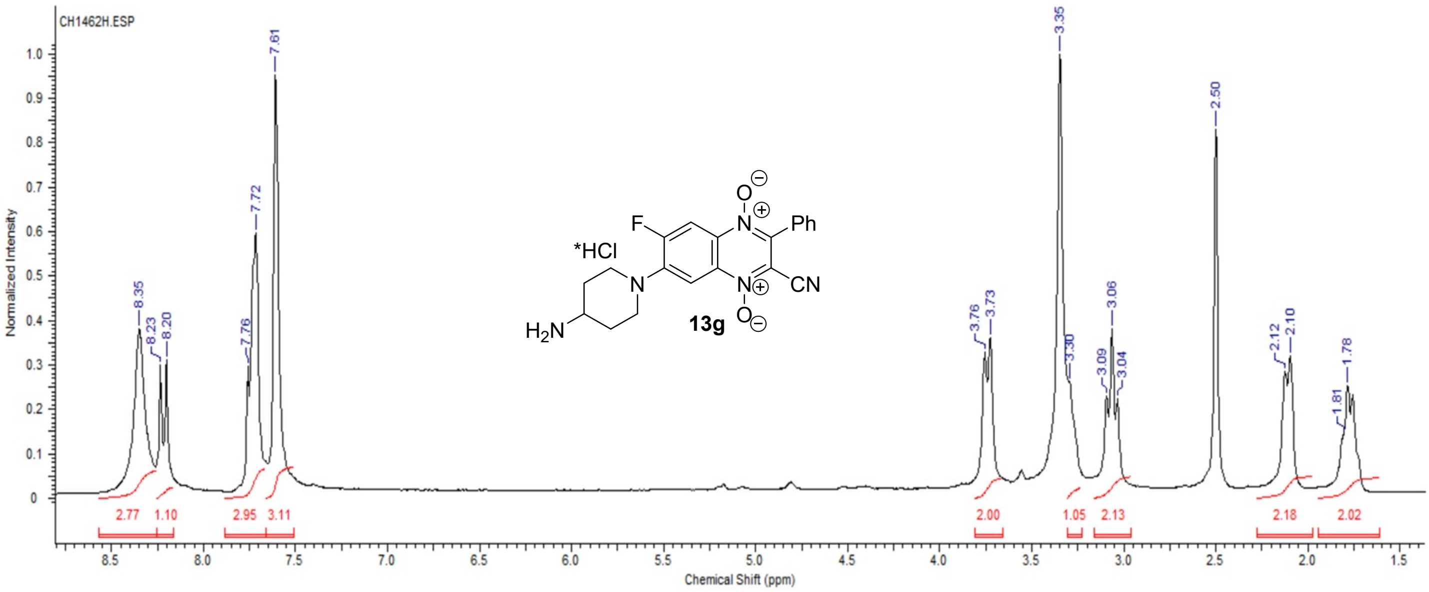


Figure S62. Copy of [13]C NMR spectrum of the derivative **13g**.

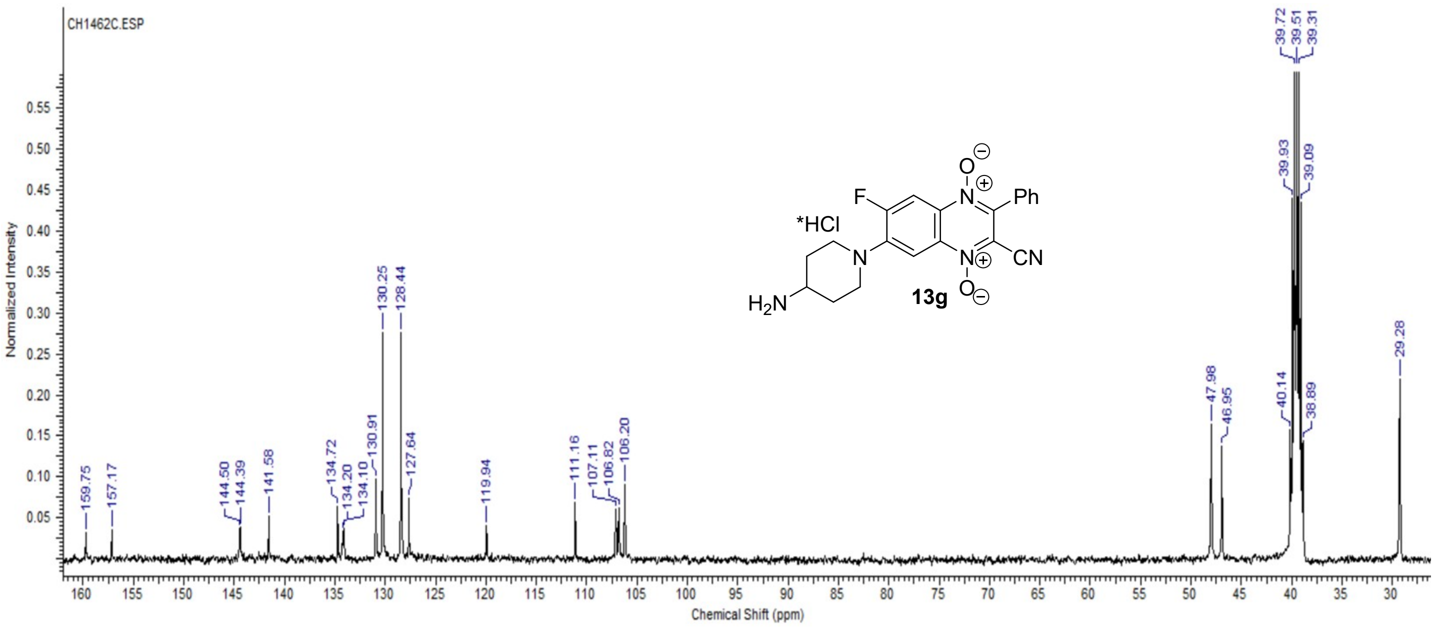


Figure S63. Copy of ^{1}H NMR spectrum of the derivative **13h**.

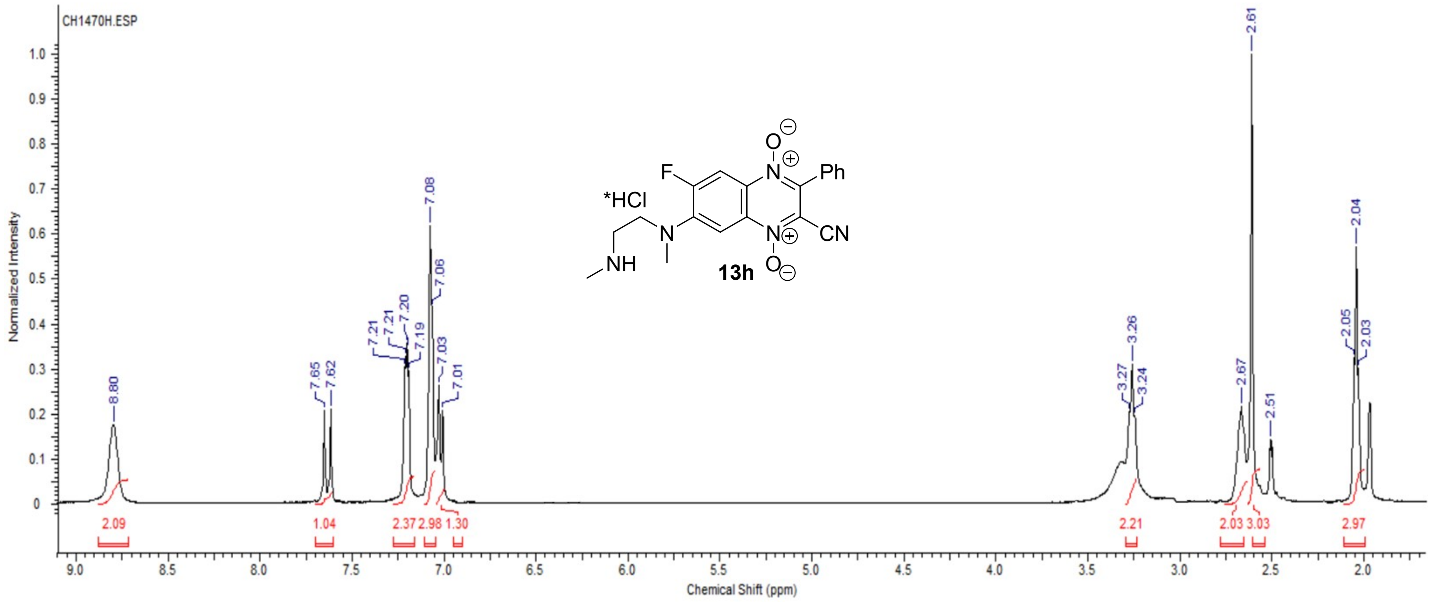


Figure S64. Copy of ^{13}C NMR spectrum of the derivative **13h**.

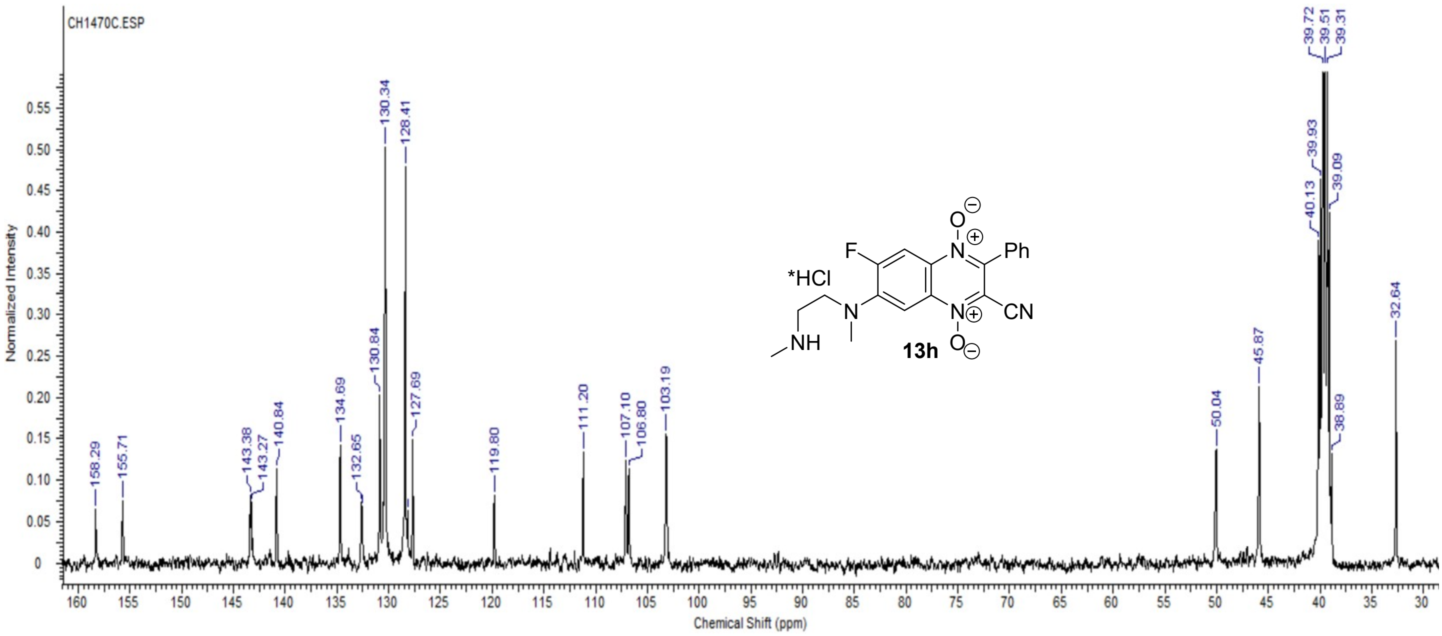


Figure S65. Copy of [1]H NMR spectrum of the derivative **14a**.

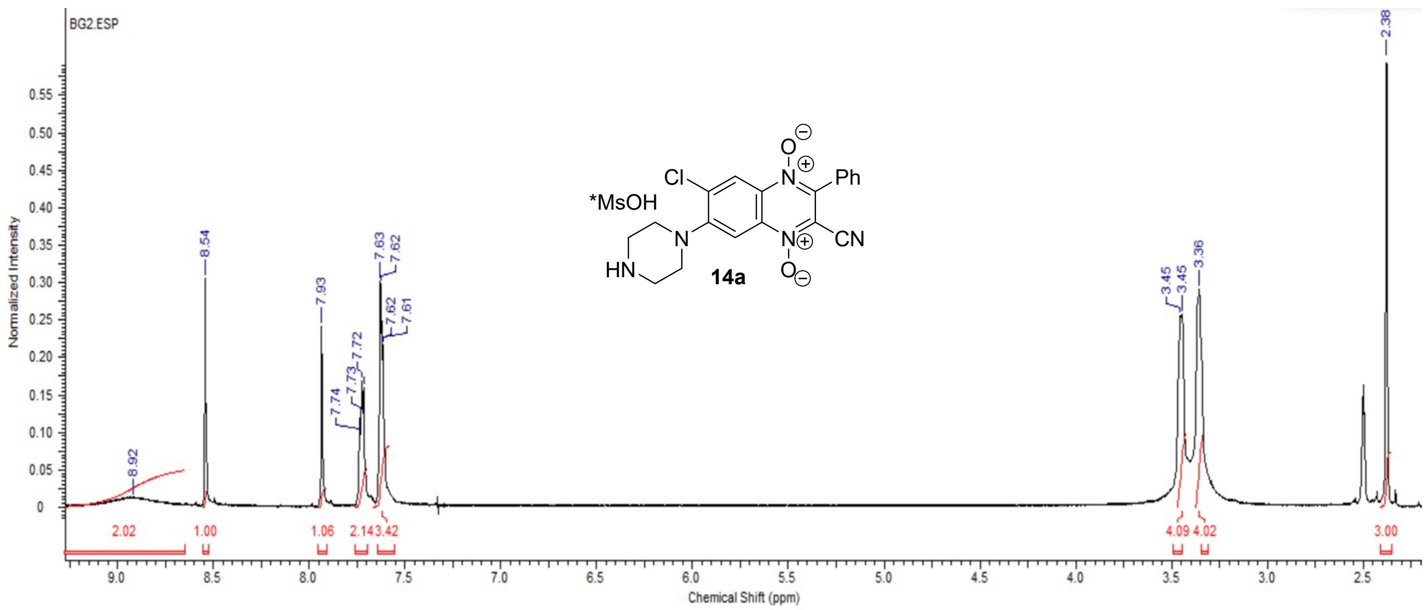


Figure S66. Copy of [13]C NMR spectrum of the derivative **14a**.

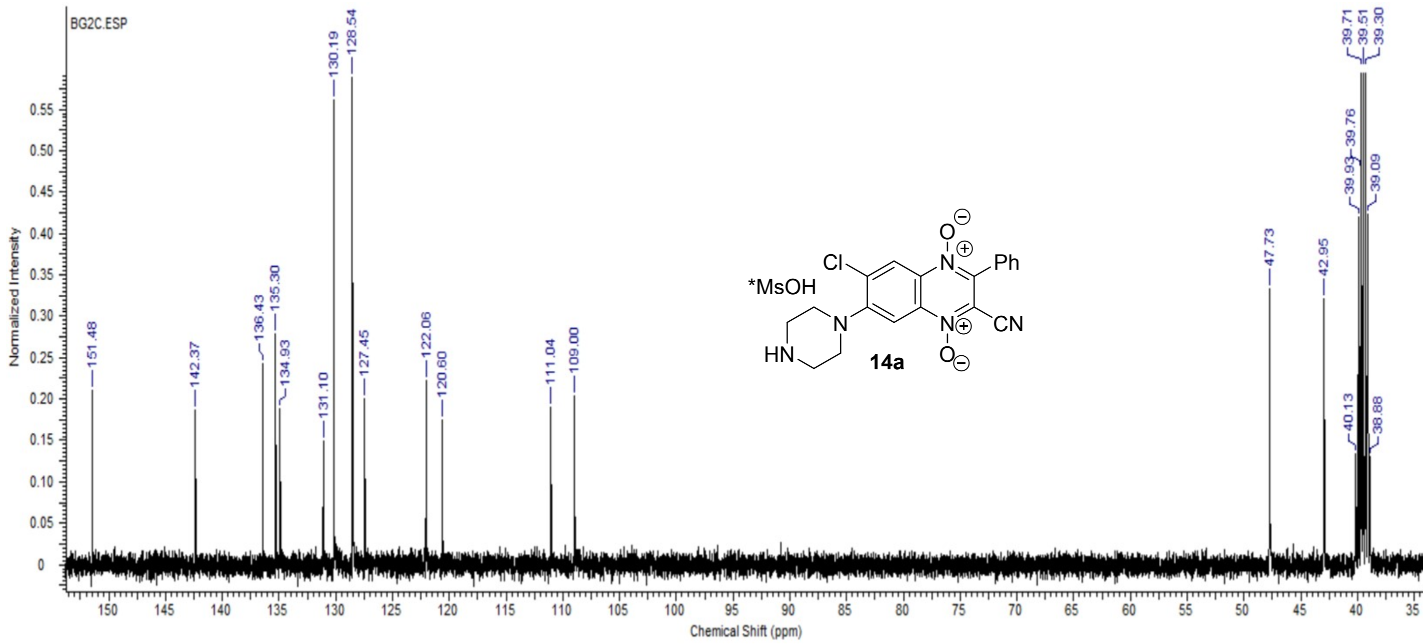


Figure S67. Copy of ^{1}H NMR spectrum of the derivative **14b**.

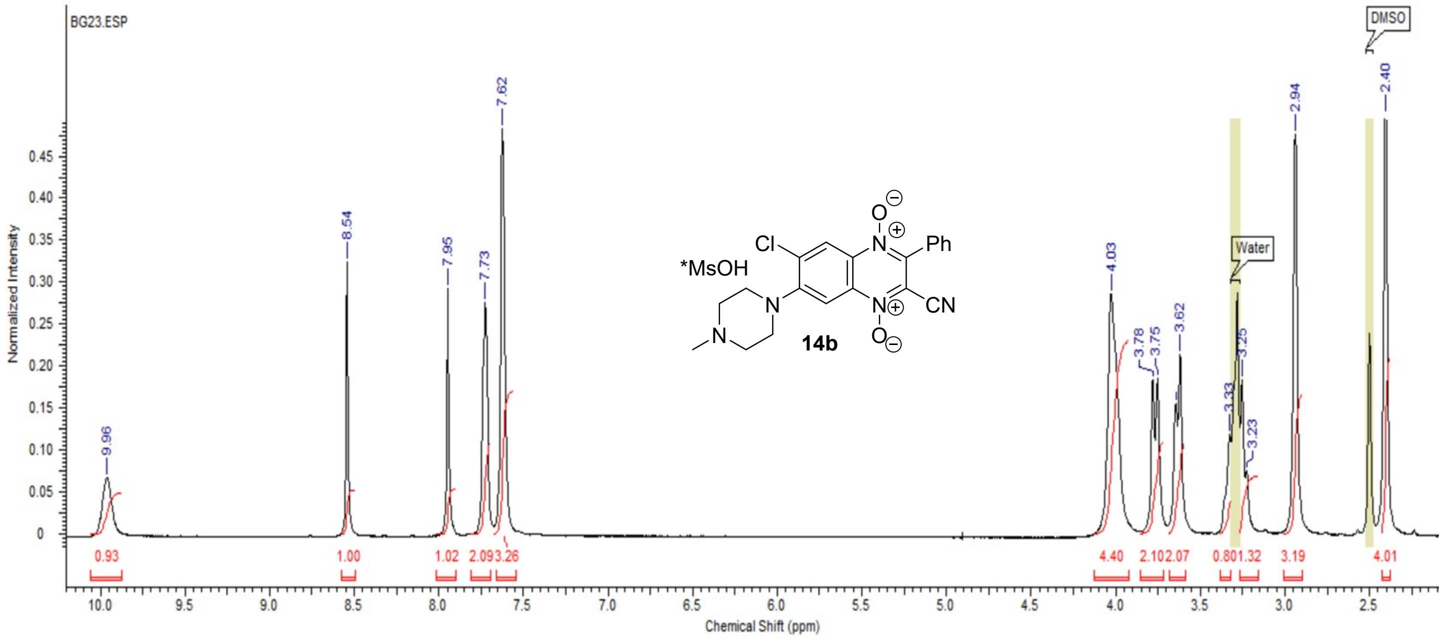


Figure S68. Copy of ^{13}C NMR spectrum of the derivative **14b**.

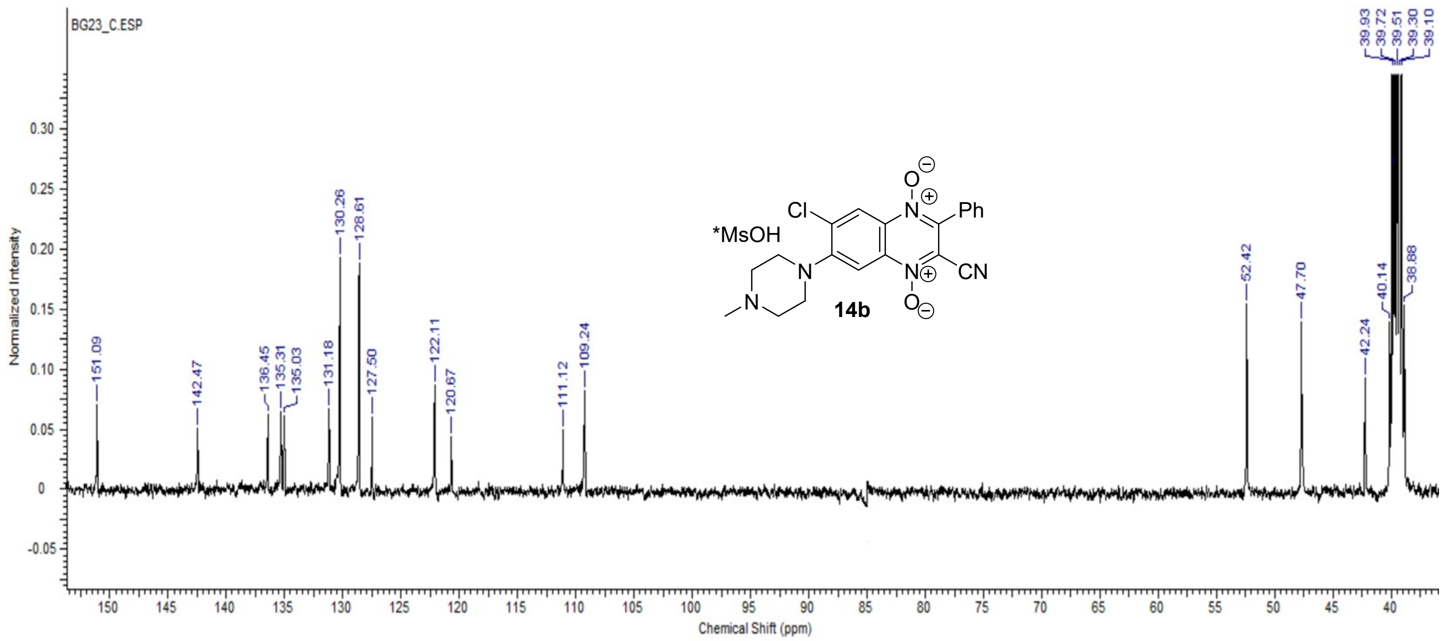


Figure S69. Copy of ^{1}H NMR spectrum of the derivative **14g**.

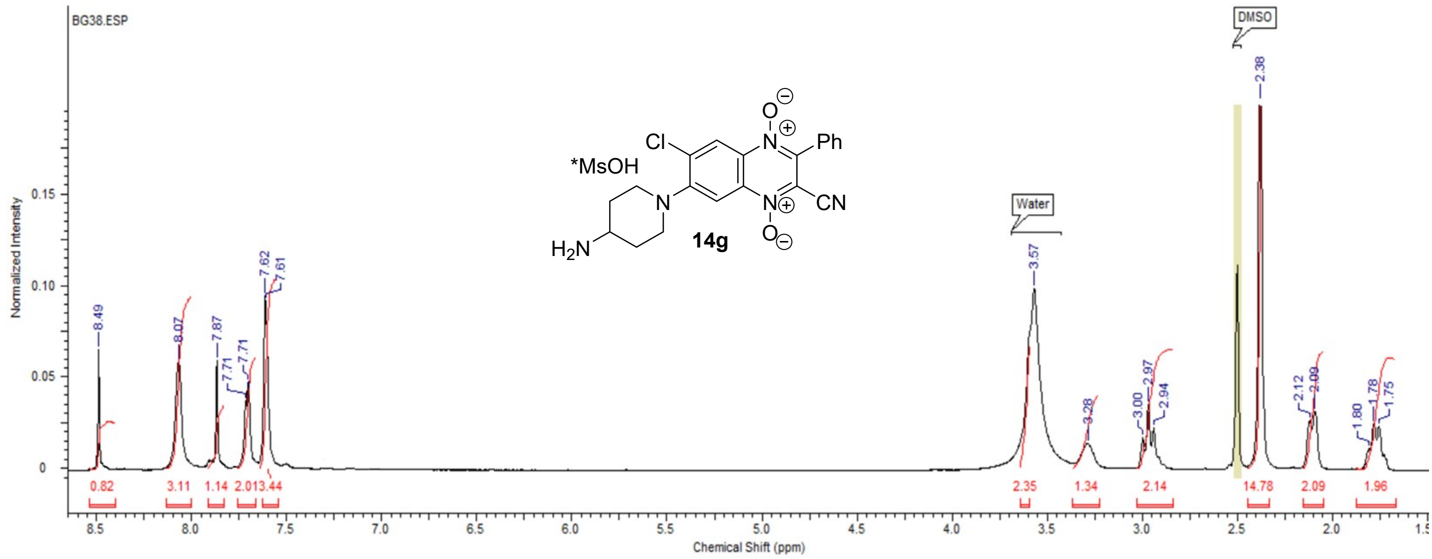


Figure S70. Copy of ^{13}C NMR spectrum of the derivative **14g**.

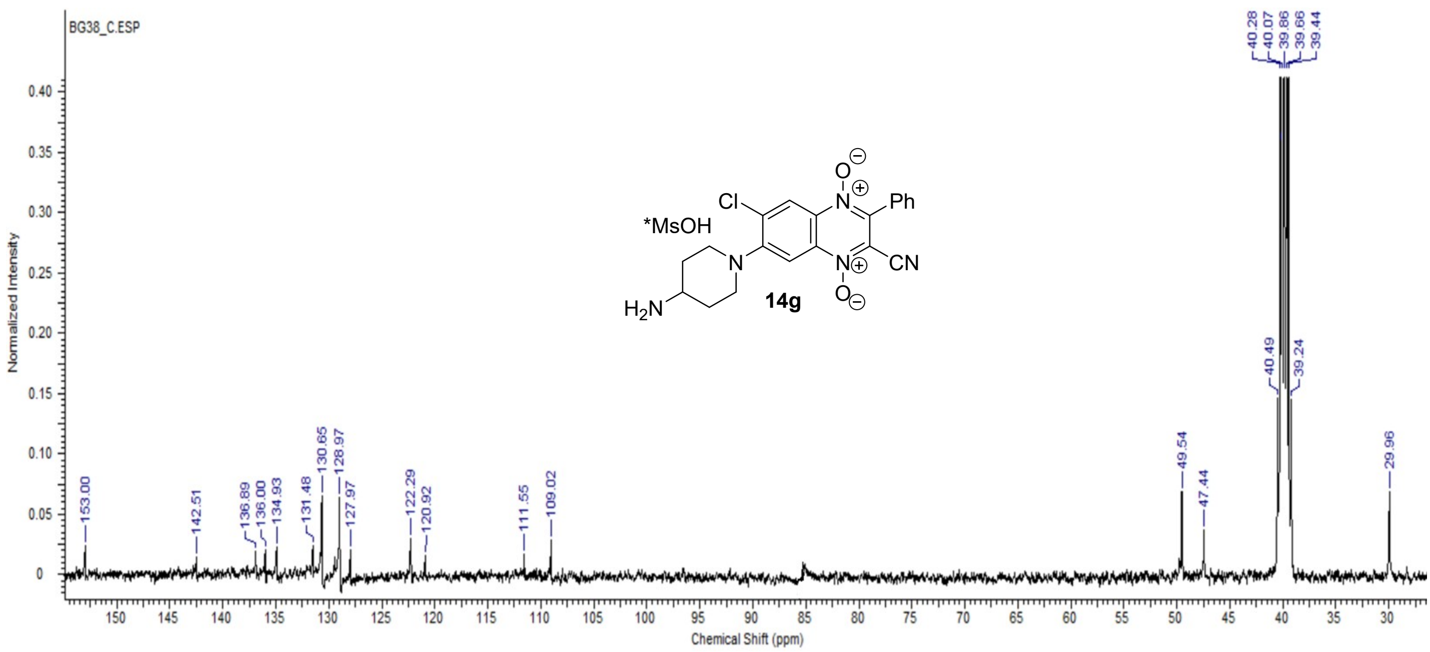
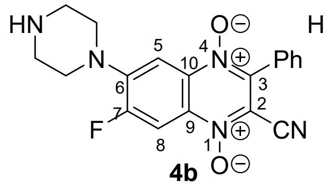
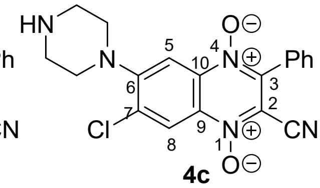
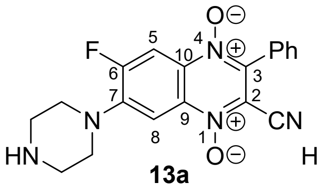
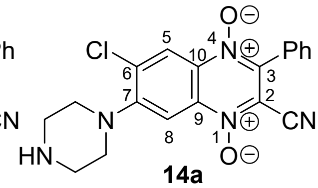


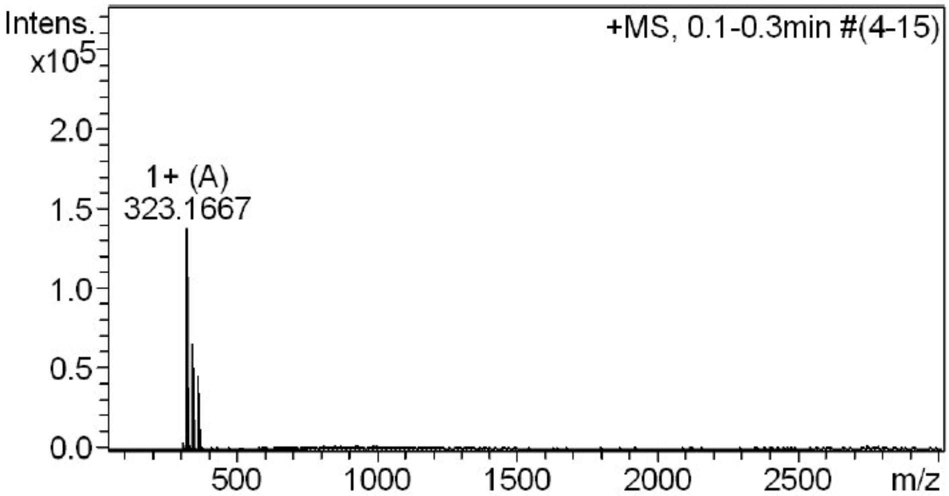
Table S1. ^{13}C chemical shifts (δ_C, ppm) and characteristic increments (I^C) for the ^{13}C chemical shift differences (relative to 3-phenylquinoxaline-2-carbonitrile 1,4-dioxide[8]) for the piperazine group for **4b–c** and **13–14a**.

Position	 **4b**		 **4c**		 **13a**		 **14a**	
	δ_C (J, Hz)	I^C	δ_C	I^C	δ_C (J, Hz)	I^C	δ_C	I^C
C-2	118.8	-1.6	119.4	−1.0	120.5	+0.1	120.6	+0.2
C-3	142.9	+0.2	143.3	+0.6	142.3	−0.4	142.4	−0.3
C-9	131.9 (10.7)	−5.5	133.4	−4.0	135.1	−2.3	136.4	−1.0
C-10	136.9	−2.5	138.6	−0.8	130.8 (13.8)	−8.6	135.3	−4.1

Copies of HRMS ESI Analysis

Figure S71. Copy of HRMS ESI analysis of the derivatives **6**.

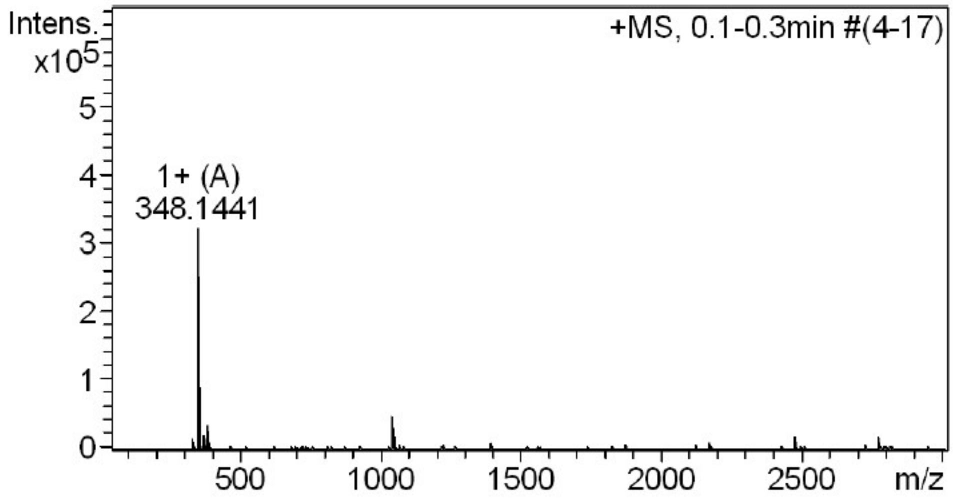
+MS, 0.1-0.3min #(4-15)



#	m/z	Res.	S/N	I	I %
1	323.1667	10491	1184.0	138173	100.0
2	324.1701	11068	245.2	28731	20.8
3	345.1481	12043	524.0	65562	47.4
4	346.1513	10555	86.1	10837	7.8
5	361.1235	10516	349.0	45655	33.0

Figure S72. Copy of HRMS ESI analysis of the derivatives **3**.

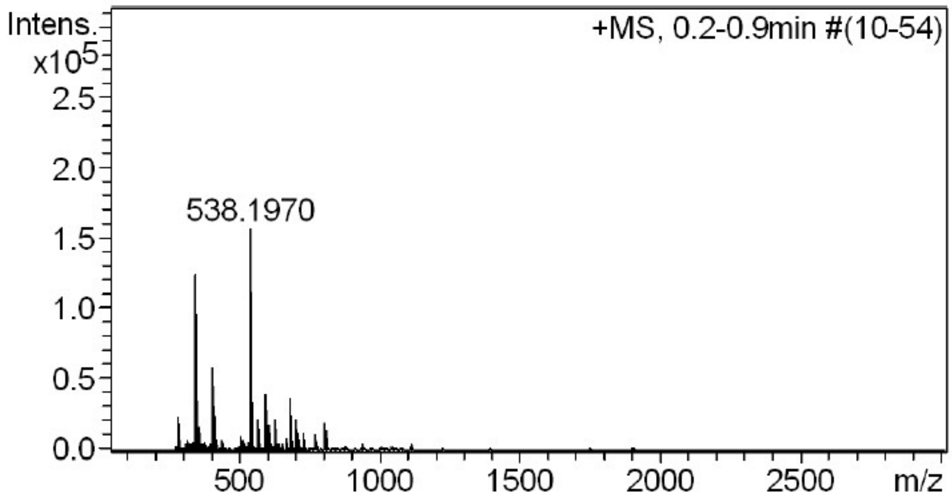
+MS, 0.1-0.3min #(4-17)



#	m/z	Res.	S/N	I	I %
1	348.1441	10507	4549.4	323109	100.0
2	349.1470	10479	1005.8	71684	22.2
3	386.0987	11765	402.8	32340	10.0
4	1042.4199	12987	271.1	47264	14.6
5	1043.4241	11425	171.7	29963	9.3

Figure S73. Copy of HRMS ESI analysis of the derivatives **9a**.

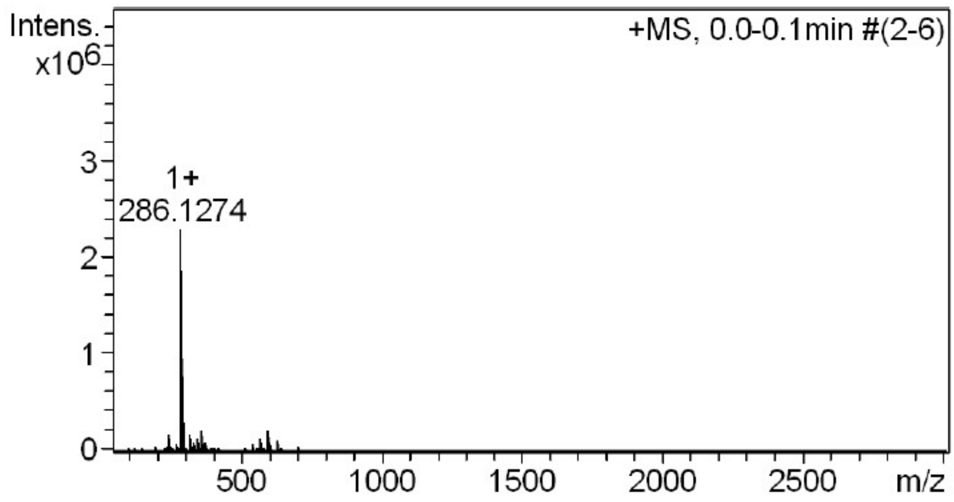
+MS, 0.2-0.9min #(10-54)



#	m/z	Res.	S/N	I	I %
1	341.1615	6186	2400.5	124409	79.6
2	407.1279	6647	849.3	58537	37.4
3	537.6982	7465	434.7	44717	28.6
4	538.1970	7409	1520.7	156325	100.0
5	538.6981	7474	833.3	85759	54.9
6	539.1972	7466	1031.7	106137	67.9
7	539.6984	7516	501.9	51691	33.1
8	540.1958	7498	451.8	46536	29.8
9	596.5933	7646	388.5	39528	25.3
10	681.3122	7832	364.0	36324	23.2

Figure S74. Copy of HRMS ESI analysis of the derivatives **9c**.

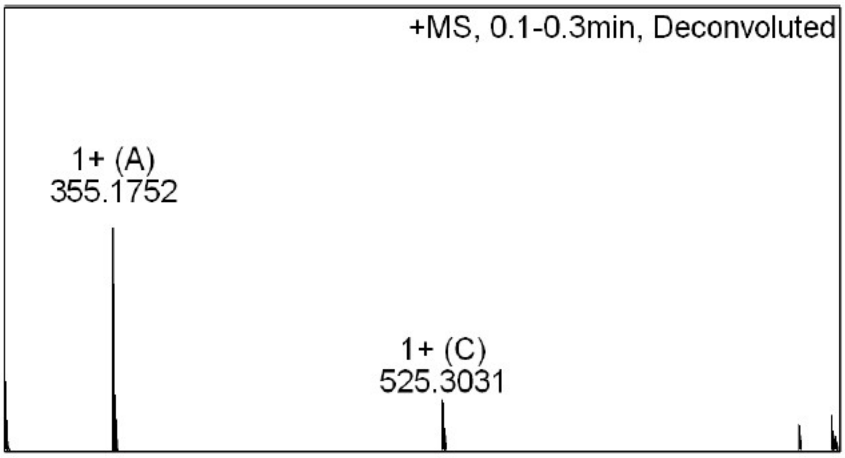
+MS, 0.0-0.1min #(2-6)



#	m/z	Res.	S/N	I	I %
1	241.0994	8849	279.4	165378	7.2
2	285.5196	7452	465.7	337865	14.8
3	285.6874	5215	237.4	172574	7.5
4	285.8654	4690	206.7	150411	6.6
5	286.1274	13215	3150.3	2288924	100.0
6	287.1255	10478	1296.2	945975	41.3
7	314.3248	10264	184.3	150065	6.6
8	358.3499	10242	231.7	200397	8.8
9	568.5367	10931	217.6	114785	5.0
10	596.5670	11585	403.2	197296	8.6

Figure S75. Copy of HRMS ESI analysis of the derivatives **9d**.

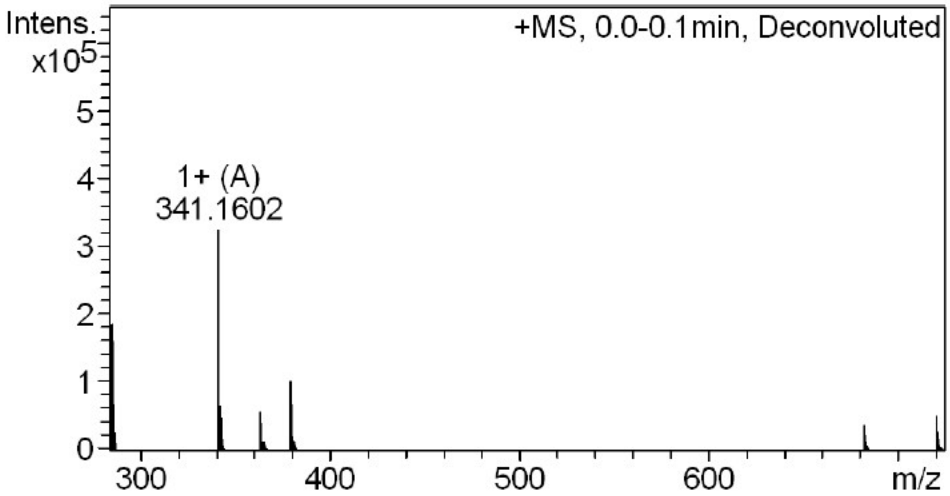
+MS, 0.1-0.3min #(4-18)



#	m/z	Res.	S/N	I	I %
1	299.1131			28241	35.4
2	355.1752			79705	100.0
3	525.3031			16442	20.6
4	709.3426			8367	10.5
5	726.3561			11800	14.8

Figure S76. Copy of HRMS ESI analysis of the derivatives **9e**.

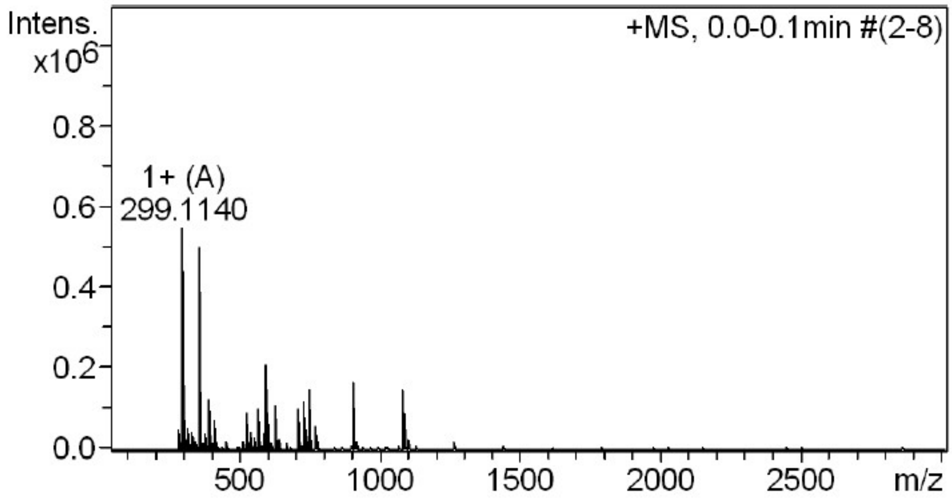
+MS, 0.0-0.1min #(2-6)



#	m/z	Res.	S/N	I	I %
1	285.1067			188810	57.6
2	341.1602			328025	100.0
3	363.1260			57258	17.5
4	379.1140			102691	31.3
5	681.3132			36198	11.0
6	719.2680			50911	15.5

Figure S77. Copy of HRMS ESI analysis of the derivatives **9f**.

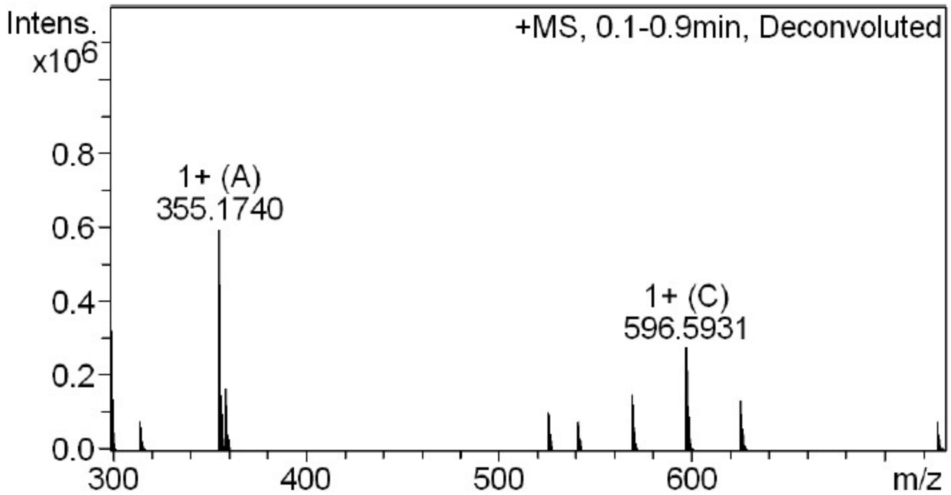
+MS, 0.0-0.1min #(2-8)



#	m/z	Res.	S/N	I	I %	FWHM
1	299.1140	5083	4484.2	546241	100.0	0.0588
2	355.1753	5514	3231.3	498293	91.2	0.0644
3	358.3645	6013	894.1	138079	25.3	0.0596
4	393.1296	6251	794.2	123863	22.7	0.0629
5	596.5926	7055	1300.8	208096	38.1	0.0846
6	747.2982	7569	944.9	144953	26.5	0.0987
7	905.4062	7959	1232.3	167370	30.6	0.1138
8	905.9061	8107	1201.1	163081	29.9	0.1117
9	1082.4914	8141	1002.7	127968	23.4	0.1330
10	1082.9904	8502	1132.3	144472	26.4	0.1274

Figure S78. Copy of HRMS ESI analysis of the derivatives **9g**.

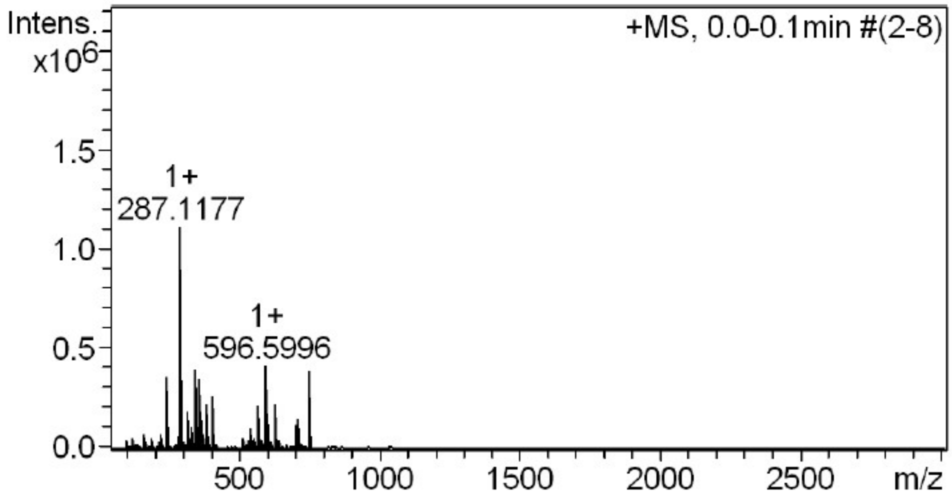
+MS, 0.1-0.9min #(5-56)



#	m/z	Res.	S/N	I	I %
1	299.1118			375742	62.7
2	314.3364			81458	13.6
3	355.1740			599323	100.0
4	358.3635			174195	29.1
5	525.3037			105914	17.7
6	540.5301			79141	13.2
7	568.5614			153397	25.6
8	596.5931			279540	46.6
9	624.6231			136199	22.7
10	726.3692			78817	13.2

Figure S79. Copy of HRMS ESI analysis of the derivatives **9h**.

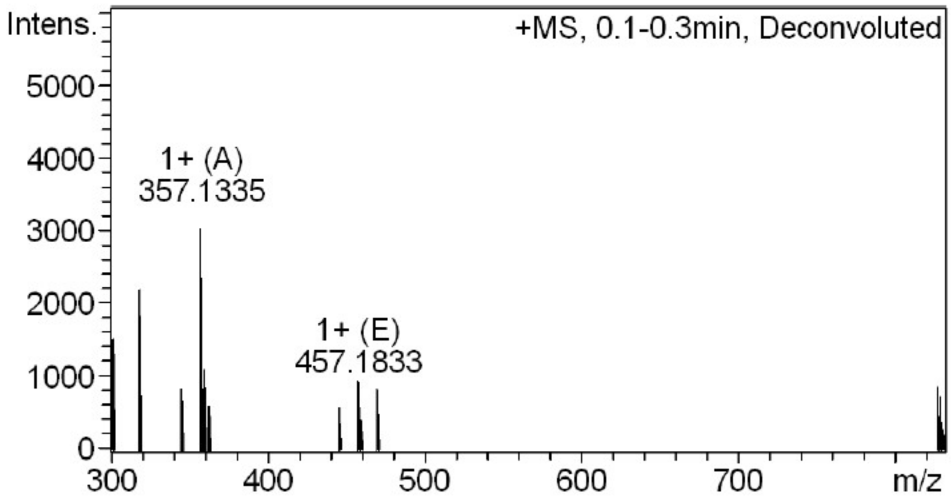
+MS, 0.0-0.1min #(2-8)



#	m/z	I	I %
1	243.1273	349825	31.6
2	287.1177	1107864	100.0
3	343.1791	395890	35.7
4	358.3692	347849	31.4
5	381.1345	220083	19.9
6	405.1004	258392	23.3
7	568.5675	213342	19.3
8	596.5996	411364	37.1
9	624.6299	216912	19.6
10	747.2730	381052	34.4

Figure S80. Copy of HRMS ESI analysis of the derivatives **10a**.

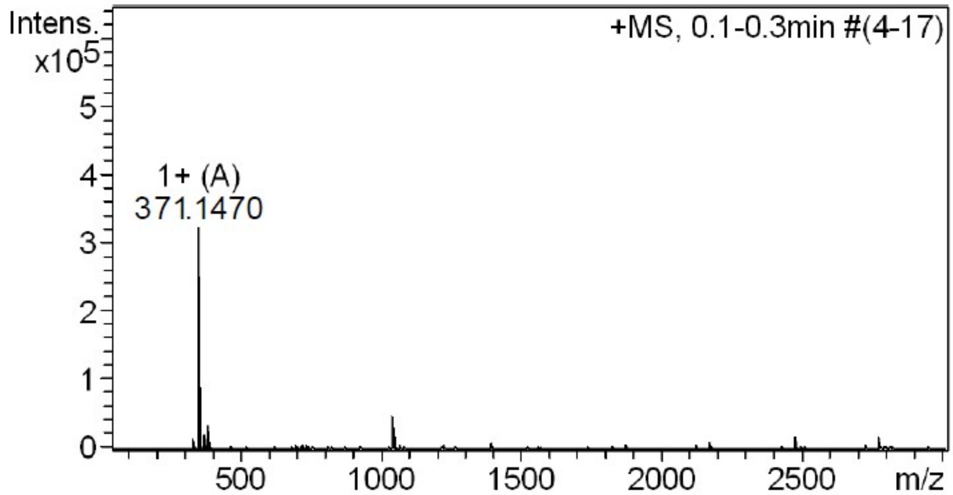
+MS, 0.1-0.3min #(4-18)



#	m/z	Res.	S/N	I	I %
1	301.0711			1611	49.1
2	318.3005			2422	73.8
3	345.0605			866	26.4
4	357.1335			3283	100.0
5	359.1312			1155	35.2
6	362.3269			670	20.4
7	457.1833			951	29.0
8	469.1845			872	26.6
9	825.3071			888	27.0
10	827.3023			755	23.0

Figure S81. Copy of HRMS ESI analysis of the derivatives **10g**.

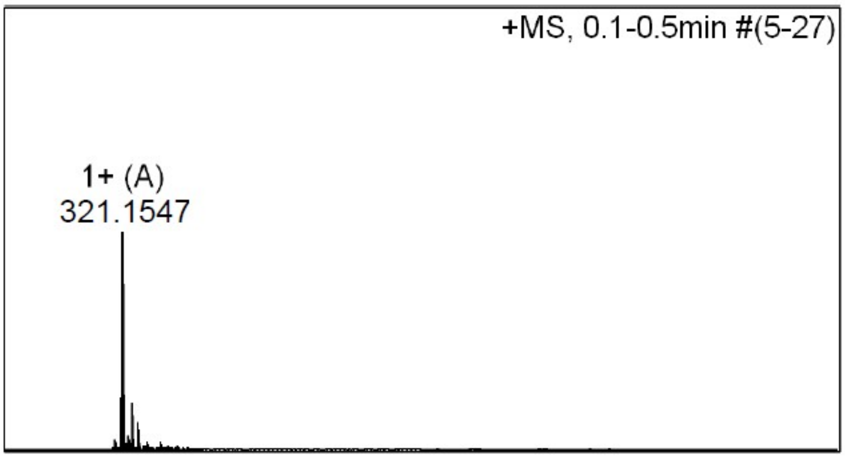
+MS, 0.1-0.3min #(4-17)



#	m/z	Res.	S/N	I	I %
1	371.1470	10507	4549.4	323109	100.0
2	349.4199	10479	1005.8	71684	22.2
3	386.0987	11765	402.8	32340	10.0
4	1042.2873	12987	271.1	47264	14.6
5	1043.4241	11425	171.7	29963	9.3

Figure S82. Copy of HRMS ESI analysis of the derivatives **6**.

+MS, 0.1-0.5min #(5-27)



#	m/z	Res.	S/N	I	I %
1	321.1547	8146	1447.4	26111	100.0
2	323.1701	8022	346.5	6118	23.4
3	324.1739	7723	266.2	4855	18.6
4	345.1506	7926	241.0	5371	20.6

Figure S83. Copy of HRMS ESI analysis of the derivatives **11a**.

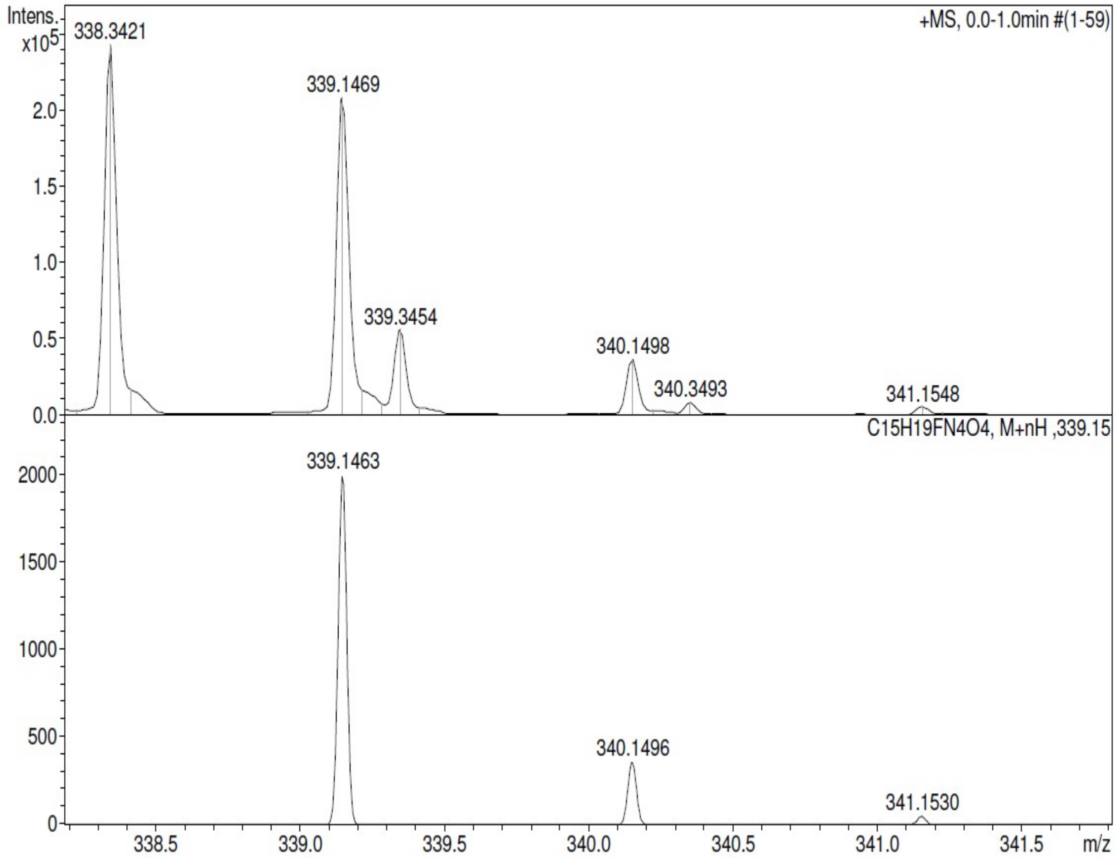


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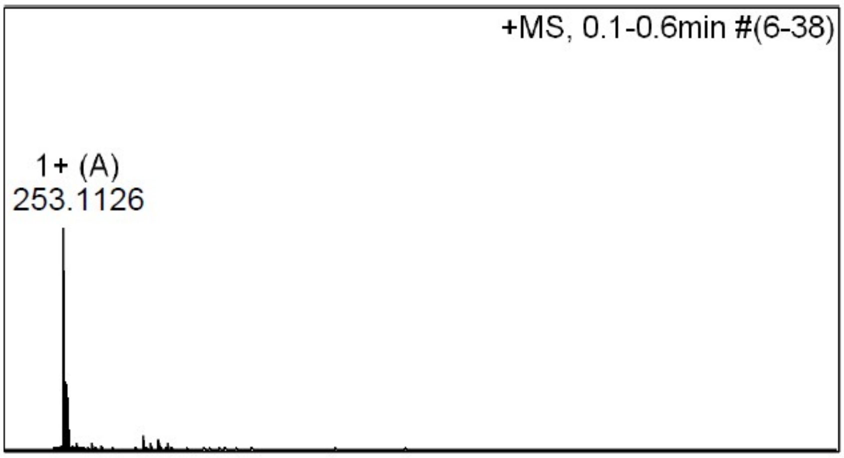
Figure S84. Copy of HRMS ESI analysis of the derivatives **11b**.



#	m/z	I	I %
1	253.1126	43917	100.0
2	254.1153	5964	13.6
3	255.1264	2900	6.6
4	269.1068	12812	29.2
5	270.1115	1830	4.2
6	537.2022	2520	5.7
7	596.5955	1875	4.3

Figure S85. Copy of HRMS ESI analysis of the derivatives **11c**.

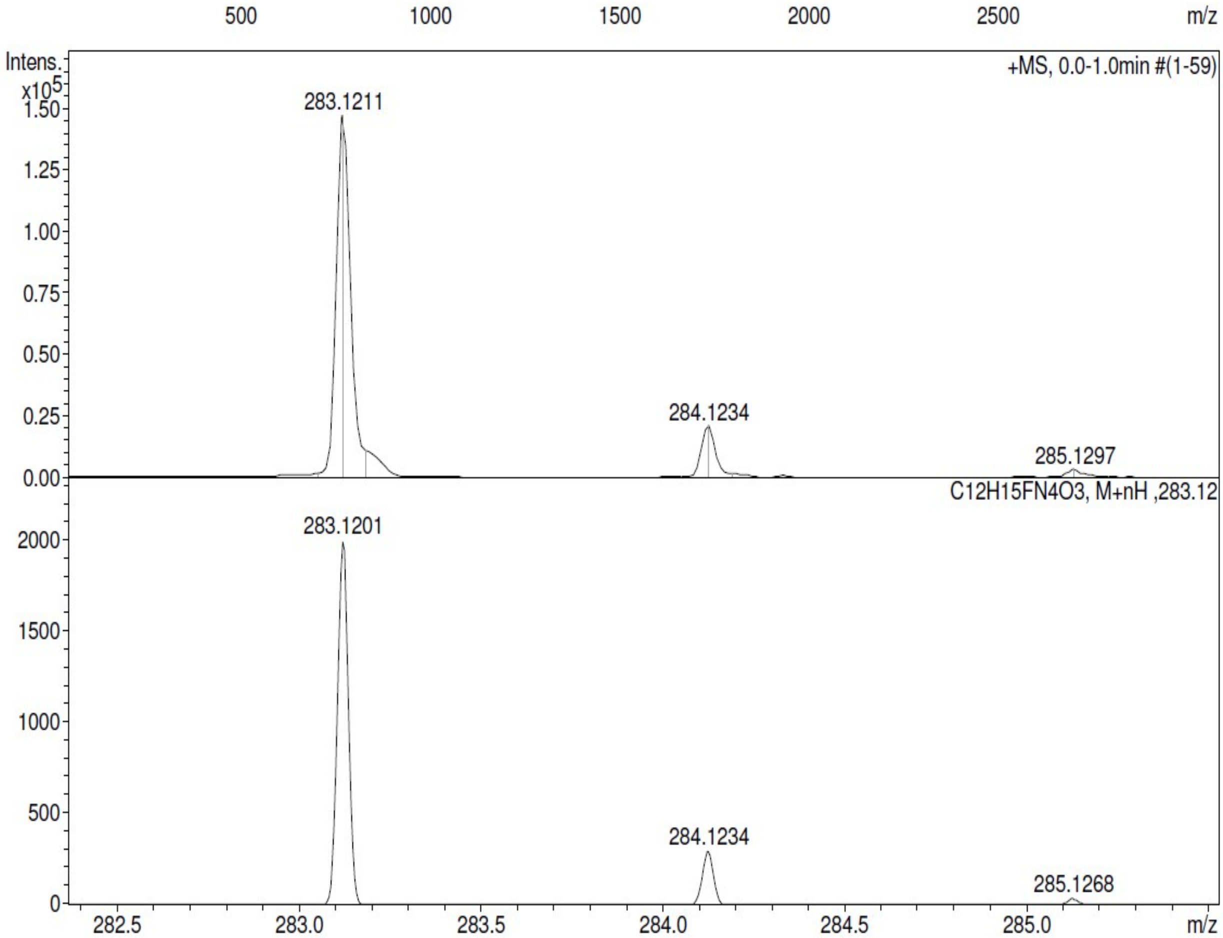


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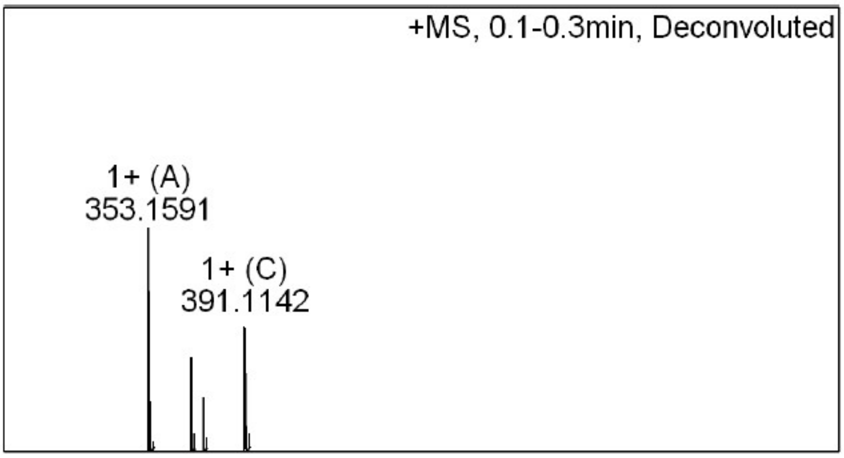
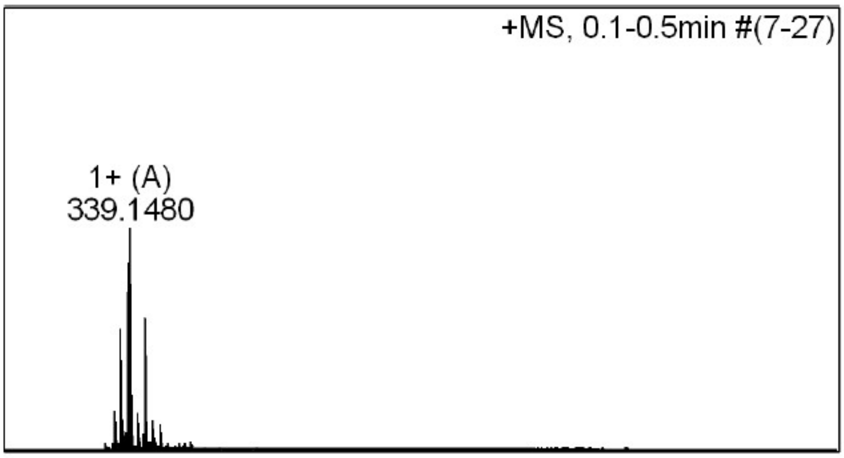
Figure S86. Copy of HRMS ESI analysis of the derivatives **11d**.



#	m/z	Res.	S/N	I	I %
1	353.1591			7416	100.0
2	370.1853			3472	46.8
3	375.1400			1736	23.4
4	391.1142			4330	58.4

Figure S87. Copy of HRMS ESI analysis of the derivatives **11e**.

+MS, 0.1-0.5min #(7-27)



#	m/z	Res.	S/N	I	I %
1	319.0638	7519	388.8	7650	54.1
2	339.1480	7736	588.8	14134	100.0
3	375.1244	7834	270.8	8437	59.7
4	377.1115	7654	176.6	5521	39.1

Figure S88. Copy of HRMS ESI analysis of the derivatives **11f**.

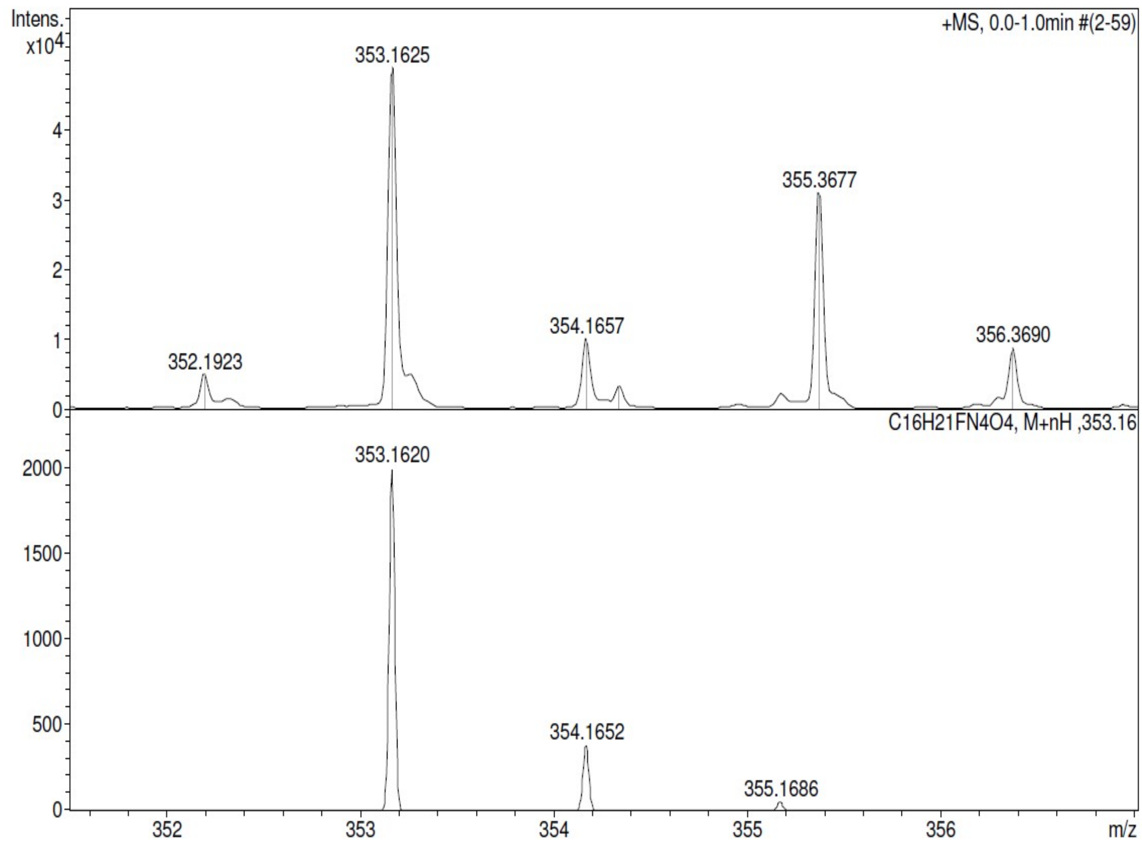


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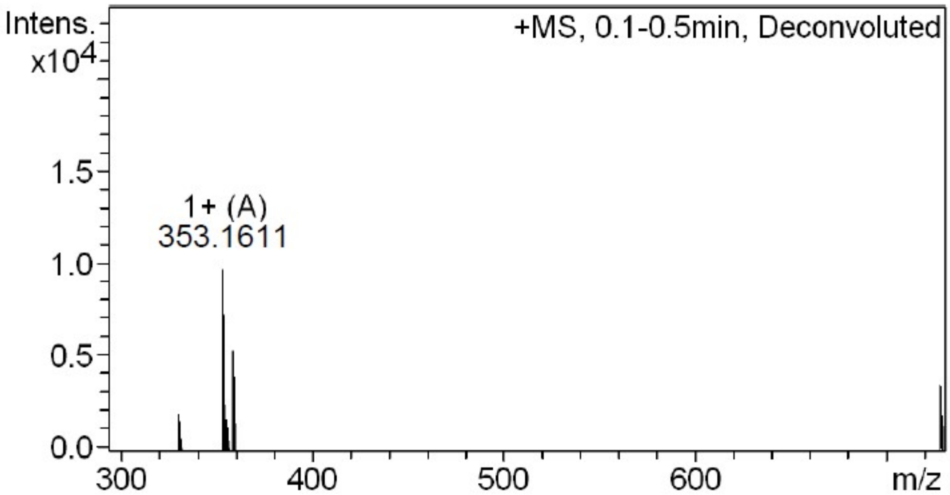
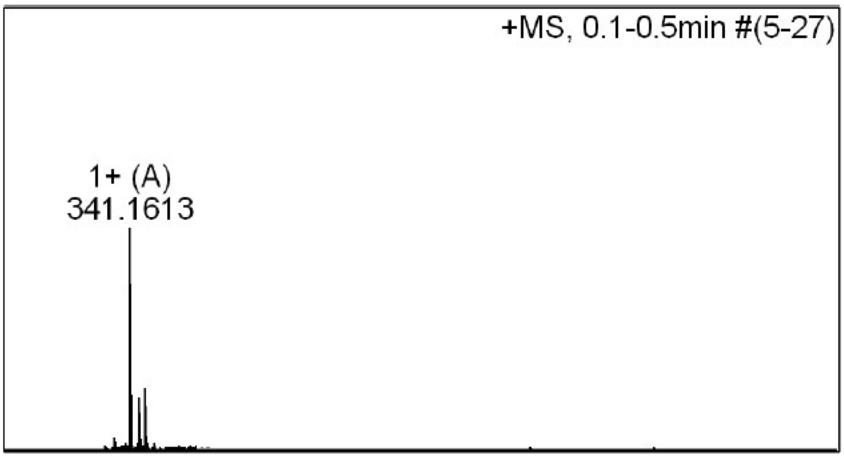
Figure S89. Copy of HRMS ESI analysis of the derivatives **11g**.



#	m/z	Res.	S/N	I	I %
1	353.1611			9981	78.6
2	358.3710			12698	100.0

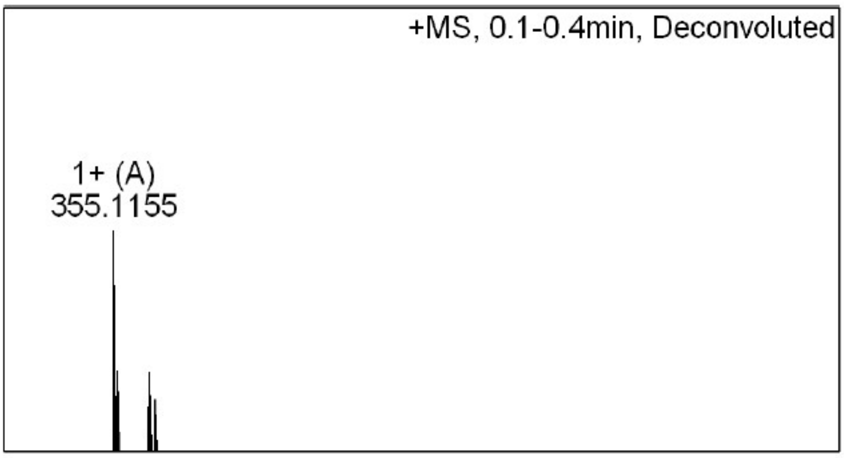
Figure S90. Copy of HRMS ESI analysis of the derivatives **11h**.

+MS, 0.1-0.5min #(5-27)



#	m/z	Res.	S/N	I	I %
1	341.1613	8349	1862.3	49932	100.0
2	342.1639	8044	338.7	9166	18.4
3	363.1412	8508	364.5	11685	23.4
4	379.1153	8442	395.1	13837	27.7

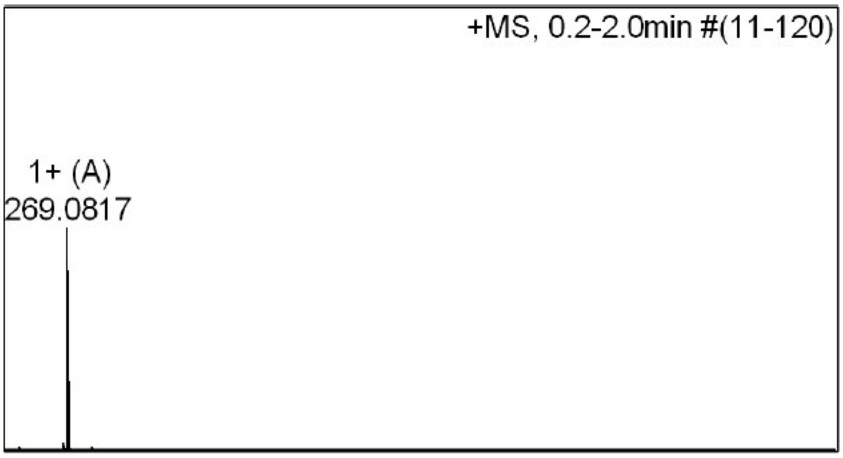
Figure S91. Copy of HRMS ESI analysis of the derivatives **12a**.



#	m/z	Res.	S/N	I	I %
1	355.1155			69565	100.0
2	357.1136			25547	36.7
3	374.1391			24889	35.8
4	377.0968			16095	23.1

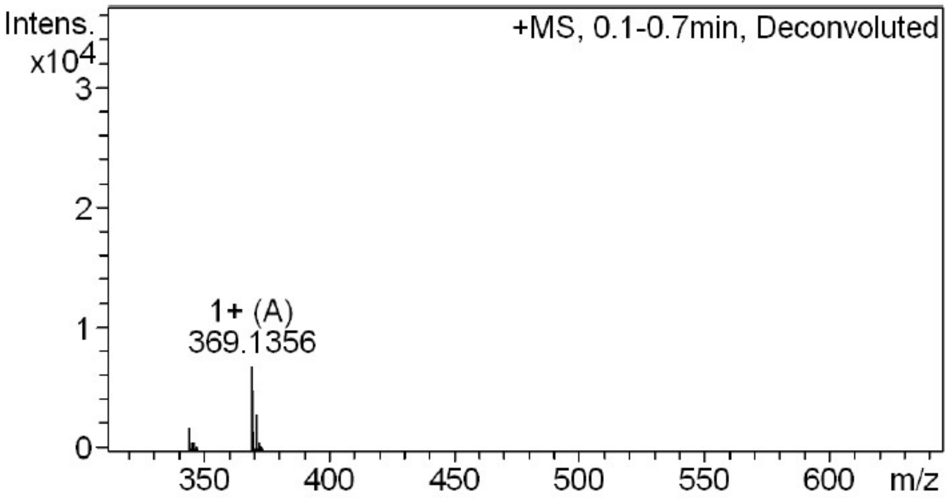
Figure S92. Copy of HRMS ESI analysis of the derivatives **12b**.

+MS, 0.2-2.0min #(11-120)



#	m/z	I	I %
1	258.1736	32261	2.6
2	269.0817	1258314	100.0
3	270.0831	150913	12.0
4	271.0792	381093	30.3
5	272.0813	50373	4.0

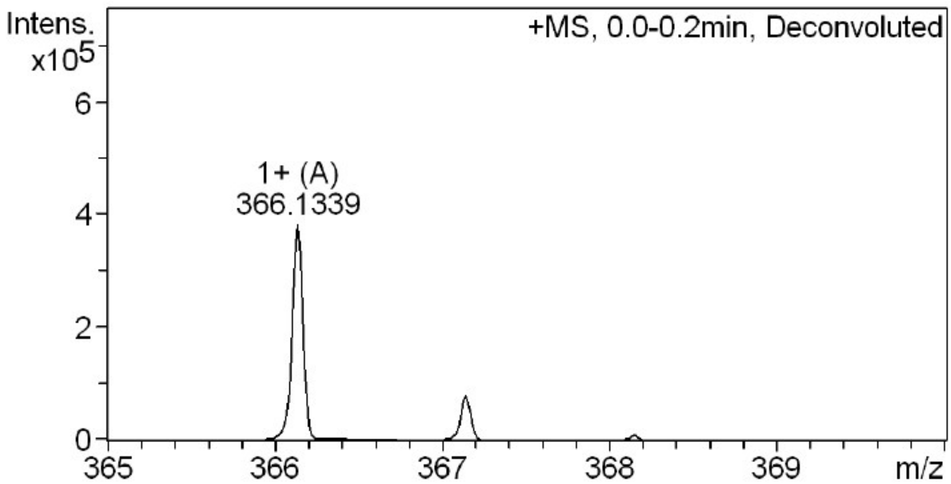
Figure S93. Copy of HRMS ESI analysis of the derivatives **12g**.



#	m/z	Res.	S/N	I	I %
1	369.1356			7297	100.0
2	371.1334			2917	15.9

Figure S94. Copy of HRMS ESI analysis of the derivatives **13a**.

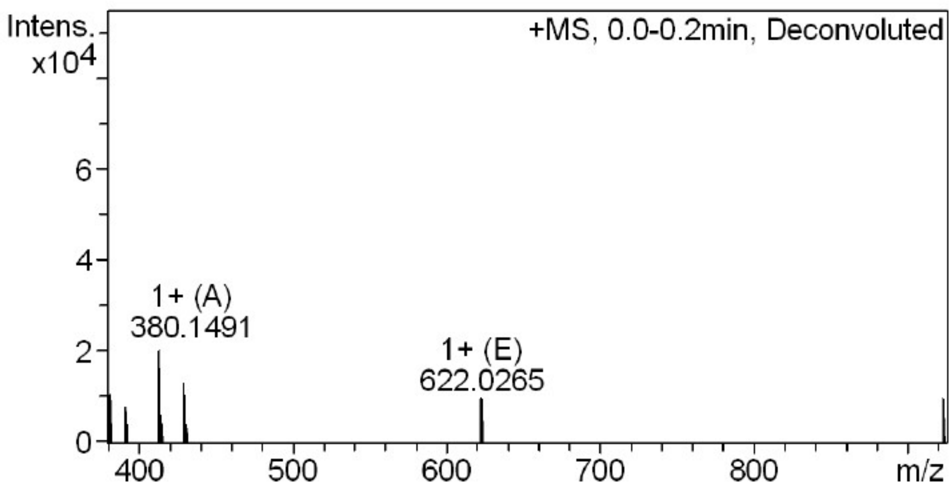
+MS, 0.0-0.2min #(2-11)



#	m/z	Res.	S/N	I	I %
1	366.1339			384624	100.0

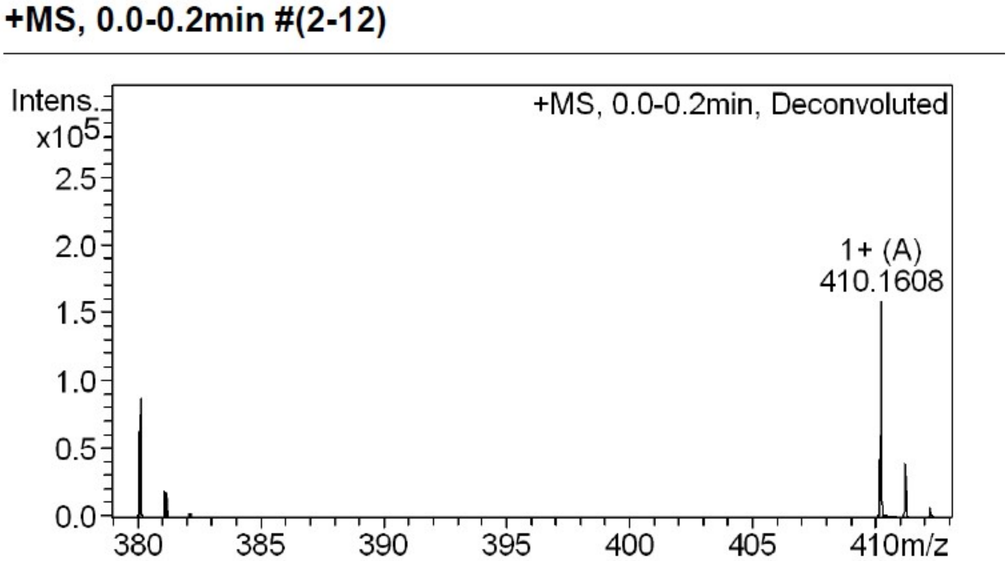
Figure S95. Copy of HRMS ESI analysis of the derivatives **13b**.

+MS, 0.0-0.2min #(2-12)



#	m/z	Res.	S/N	I	I %
1	380.1488			49242	100.0
2	391.2805			7882	16.0
3	413.2630			20647	41.9
4	429.2354			13356	27.1
5	622.0265			9571	19.4
6	922.0062			10780	21.9

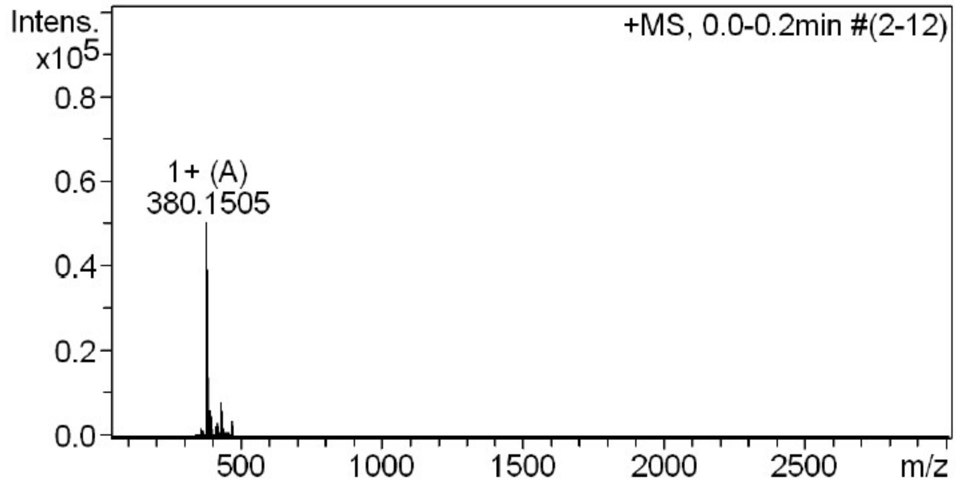
Figure S96. Copy of HRMS ESI analysis of the derivatives **13c**.



#	m/z	Res.	S/N	I	I %
1	380.1504			87953	55.1
2	410.1608			159636	100.0

Figure S97. Copy of HRMS ESI analysis of the derivatives **13d**.

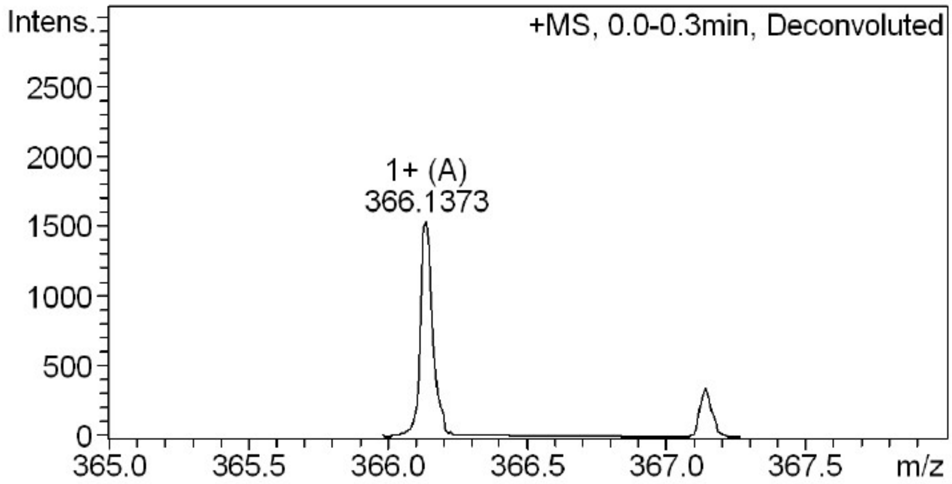
+MS, 0.0-0.2min #(2-12)



#	m/z	Res.	S/N	I	I %
1	380.1505	8777	975.2	50279	100.0
2	381.1529	6749	214.3	11104	22.1
3	391.2816	7260	112.7	6061	12.1
4	413.2659	7579	40.4	2356	4.7
5	421.1741	10829	50.0	2985	5.9
6	429.2353	7645	127.1	7741	15.4

Figure S98. Copy of HRMS ESI analysis of the derivatives **13e**.

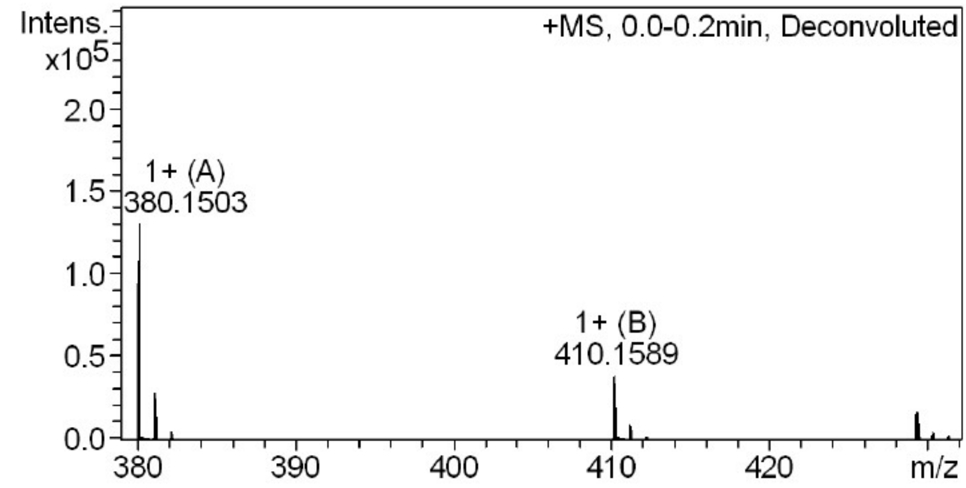
+MS, 0.0-0.3min #(2-16)



#	m/z	Res.	S/N	I	I %
1	366.1373			1545	100.0

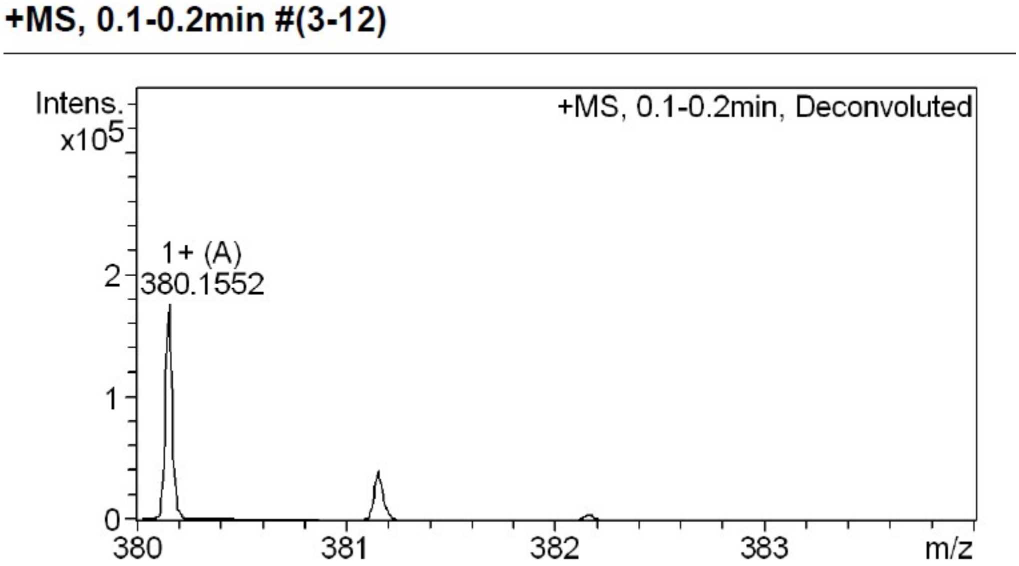
Figure S99. Copy of HRMS ESI analysis of the derivatives **13f**.

+MS, 0.0-0.2min #(2-12)



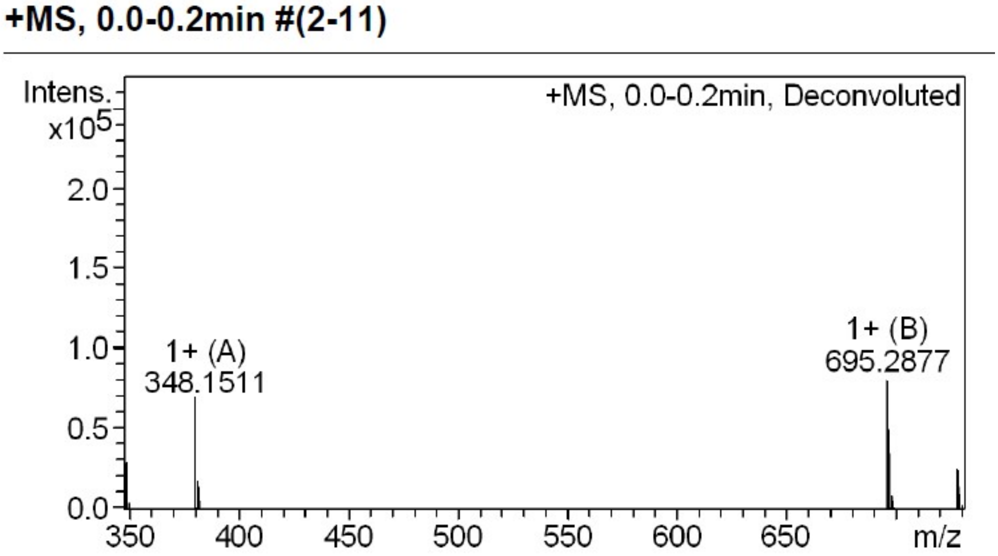
#	m/z	Res.	S/N	I	I %
1	380.1501			131624	100.0
2	410.1589			41115	31.2
3	429.2359			17399	13.2

Figure S100. Copy of HRMS ESI analysis of the derivatives **13g**.



#	m/z	Res.	S/N	I	I %
1	380.1544			185072	100.0

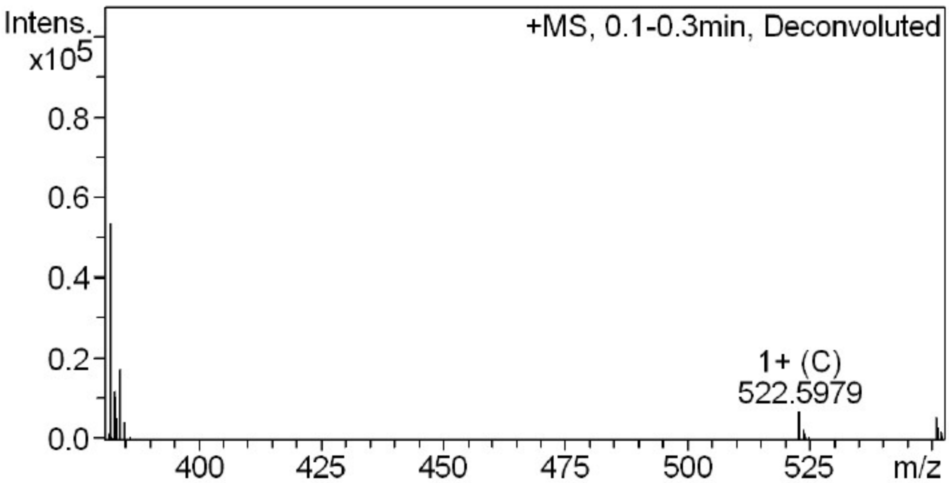
Figure S101. Copy of HRMS ESI analysis of the derivatives **13h**.



#	m/z	Res.	S/N	I	I %
1	348.1507			135065	100.0
2	380.1568			72628	53.8
3	695.2877			81033	60.0
4	727.2929			24782	18.3

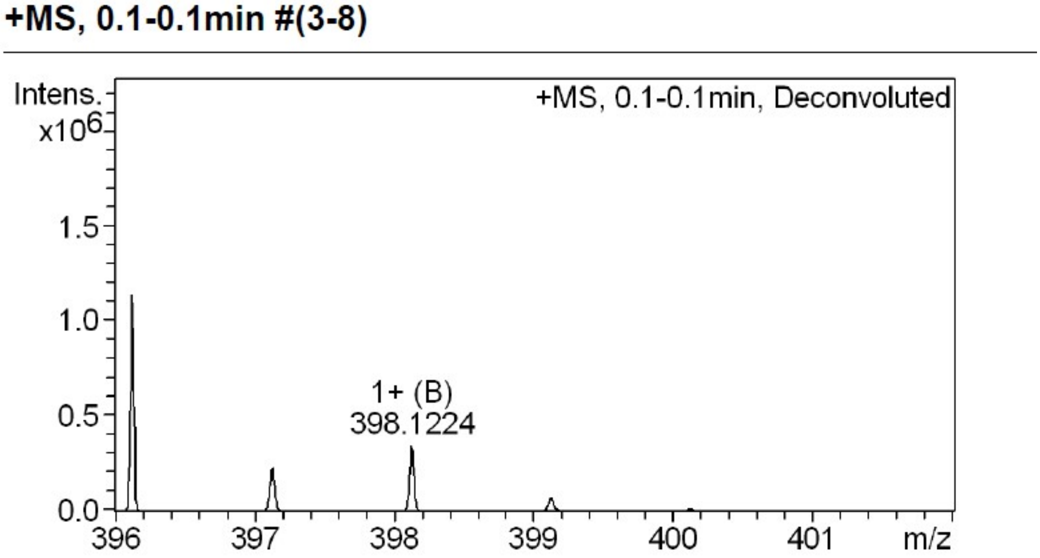
Figure S102. Copy of HRMS ESI analysis of the derivatives **14a**.

+MS, 0.1-0.3min #(3-16)



#	m/z	Res.	S/N	I	I %
1	382.1086			56623	100.0
2	384.1055			17602	31.1
3	522.5979			7201	12.7
4	550.6308			6284	11.1

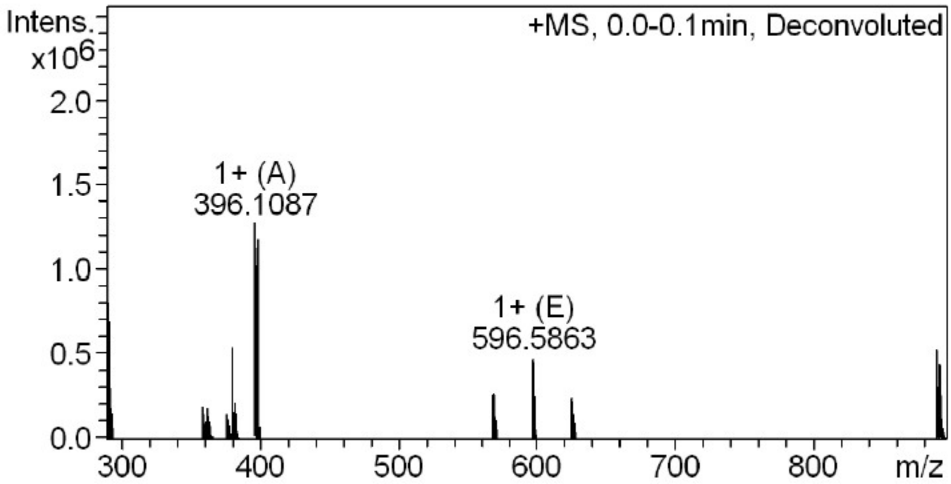
Figure S103. Copy of HRMS ESI analysis of the derivatives **14b**.



#	m/z	Res.	S/N	I	I %
1	396.1255			1137519	100.0
2	398.1224			365607	32.1

Figure S104. Copy of HRMS ESI analysis of the derivatives **14g**.

+MS, 0.0-0.1min #(2-4)



#	m/z	Res.	S/N	I	I %
1	290.9614			817120	64.1
2	359.0622			189521	14.9
3	380.1145			548338	43.0
4	382.1122			214165	16.8
5	396.1087			1274941	100.0
6	568.5549			273014	21.4
7	596.5863			489719	38.4
8	624.6170			244564	19.2
9	887.2170			536545	42.1
10	889.2124			450347	35.3

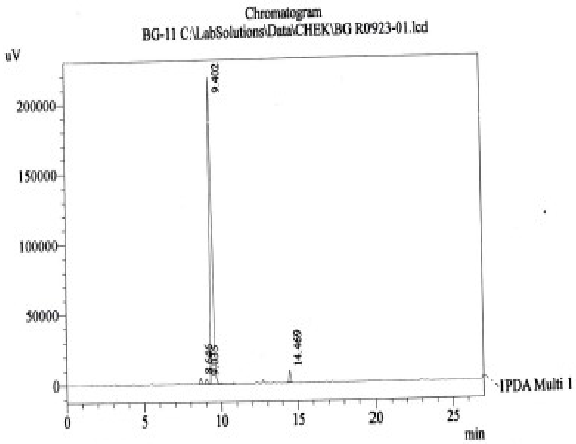
Copies of HPLC Analysis

Figure S105. Copy HPLC analysis of the derivative **3**.

a Compound **3** prepared from quinoxaline 1,4-dioxide **2** (R_1=H, R_2=F) as described in [10]

b Compound **3** prepared as described in **Scheme 1**

a



1 PDA Multi 1 / 360nm 4nm

PDA Ch1 360nm 4nm

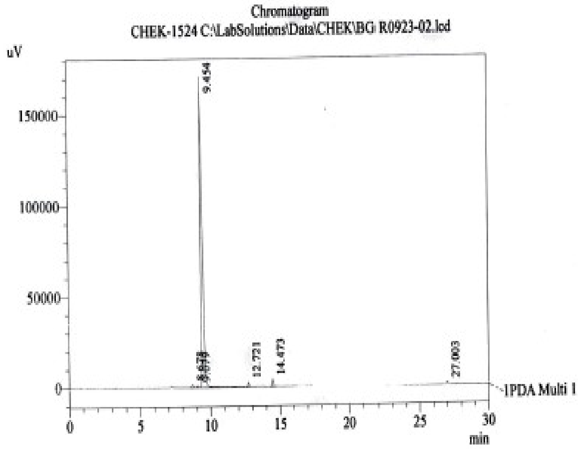
Peak#	Ret. Time	Area	Height	Area %
1	8.646	31039	4329	1.252
2	9.035	29715	3596	1.199
3	9.402	2359039	217226	95.148
4	14.469	59535	8658	2.401
Total		2479328	233809	100.000

Method Filename : FOS Av.lcm 23.09.2021 12:28:24

Time	Unit	Command	Valu
0.01	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
45.00	Controller	Stop	

Shimadzu LC-20 AD; System - FOS Colon- Kromasil-100-5mkm. C-18, 4,6x250 mm. N 62511
Elution: A - H3PO4 0,01M pH 2,6; B - MeCN, fl - 1.0 ml/min, loop 20 mkl

b



1 PDA Multi 1 / 360nm 4nm

PDA Ch1 360nm 4nm

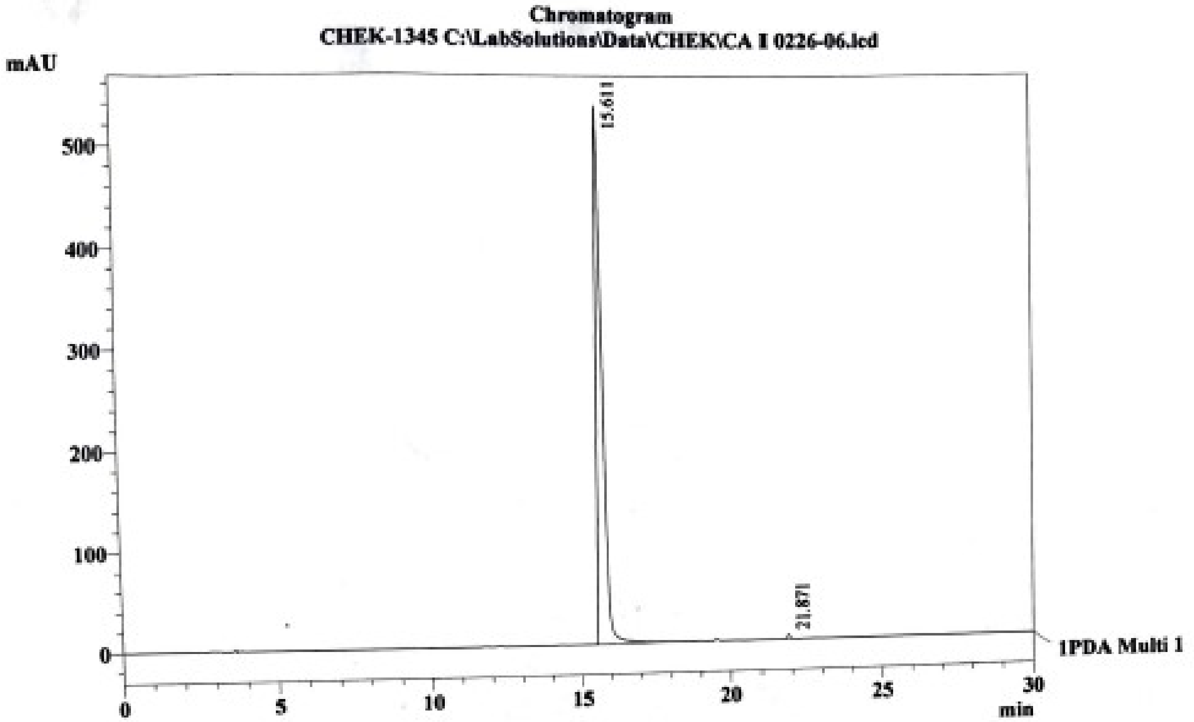
Peak#	Ret. Time	Area	Height	Area %
1	8.678	12957	1614	0.735
2	9.079	10517	1126	0.597
3	9.454	1681663	171300	95.395
4	12.721	17831	2672	1.011
5	14.473	30036	4304	1.704
6	27.003	9841	1284	0.558
Total		1762845	182300	100.000

Method Filename : FOS Av.lcm 23.09.2021 13:18:44

Time	Unit	Command	Valu
0.01	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
45.00	Controller	Stop	

Shimadzu LC-20 AD; System - FOS Colon- Kromasil-100-5mkm. C-18, 4,6x250 mm. N 62511
Elution: A - H3PO4 0,01M pH 2,6; B - MeCN, fl - 1.0 ml/min, loop 20 mkl

Figure S106. Copy HPLC analysis of the derivative **13a**.



1 PDA Multi 1 / 294nm 4nm

PeakTable

PDA Ch1 294nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	15.611	7505673	538266	99.566
2	21.871	32699	4659	0.434
Total		7538372	542925	100.000

Method

<<LC Program>>

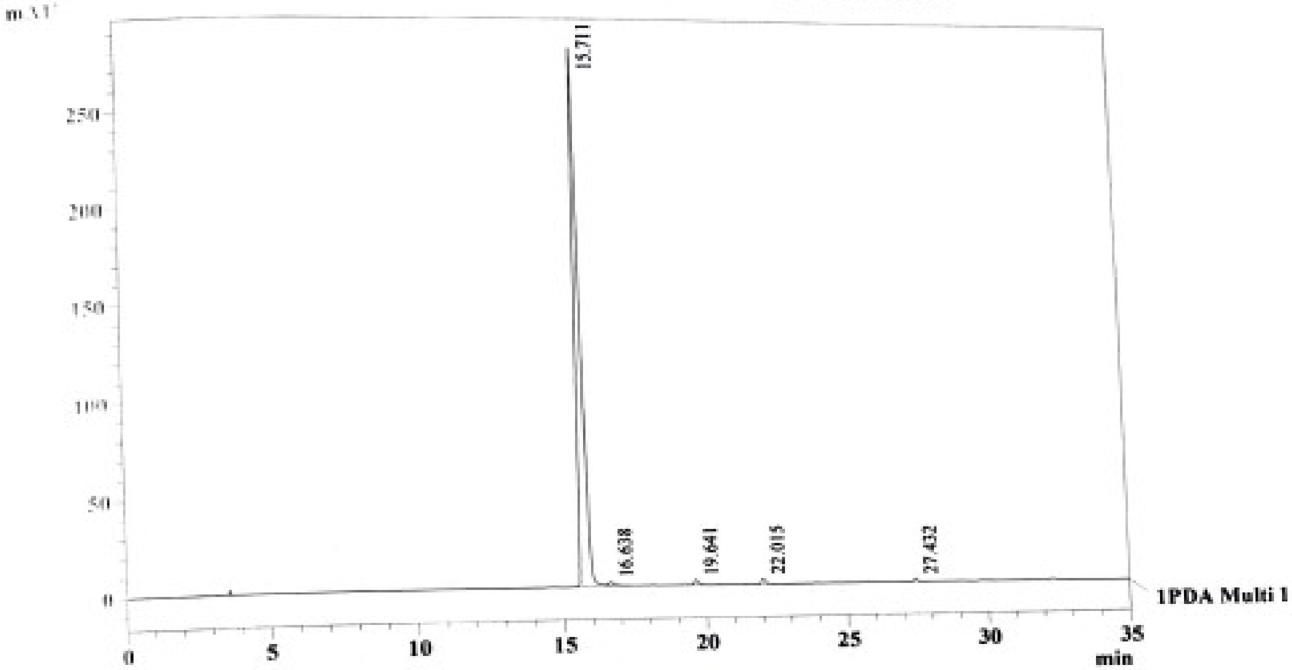
Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 62512
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S107. Copy HPLC analysis of the derivative **13b**.

Chromatogram
CHEK-1474 C:\LabSolutions\Data\CHEK\CA L 0209-07.lcd



1 PDA Multi 1 / 290nm 4nm

PeakTable

PDA Ch1 290nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	15.711	3221582	281274	97.672
2	16.638	16986	1511	0.515
3	19.641	23291	2536	0.706
4	22.015	26181	2720	0.794
5	27.432	10320	1551	0.313
Total		3298360	289593	100.000

Method

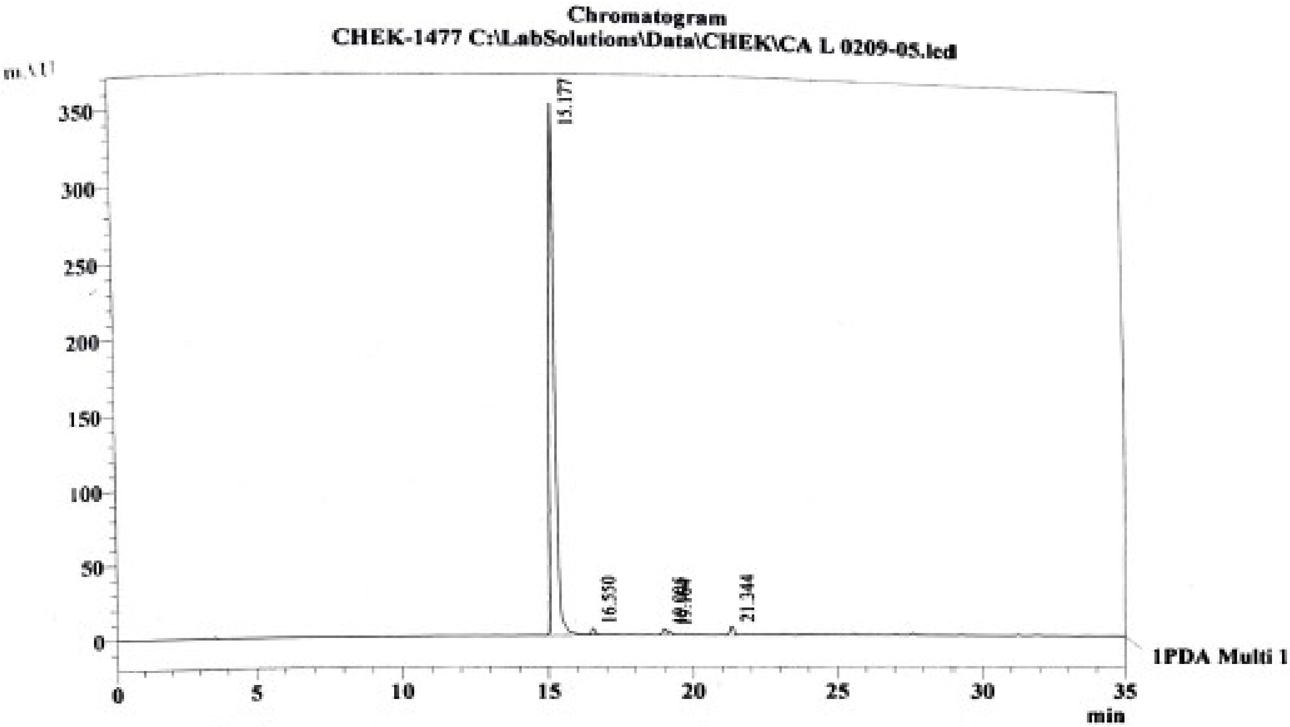
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Eluent: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S108. Copy HPLC analysis of the derivative **13c**.



1 PDA Multi 1 / 290nm 4nm

PeakTable

PDA Ch1 290nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	15.177	4146836	350548	96.756
2	16.550	32828	3927	0.766
3	19.005	36713	3821	0.857
4	19.164	21933	2689	0.512
5	21.344	47561	5519	1.110
Total		4285871	366503	100.000

Method

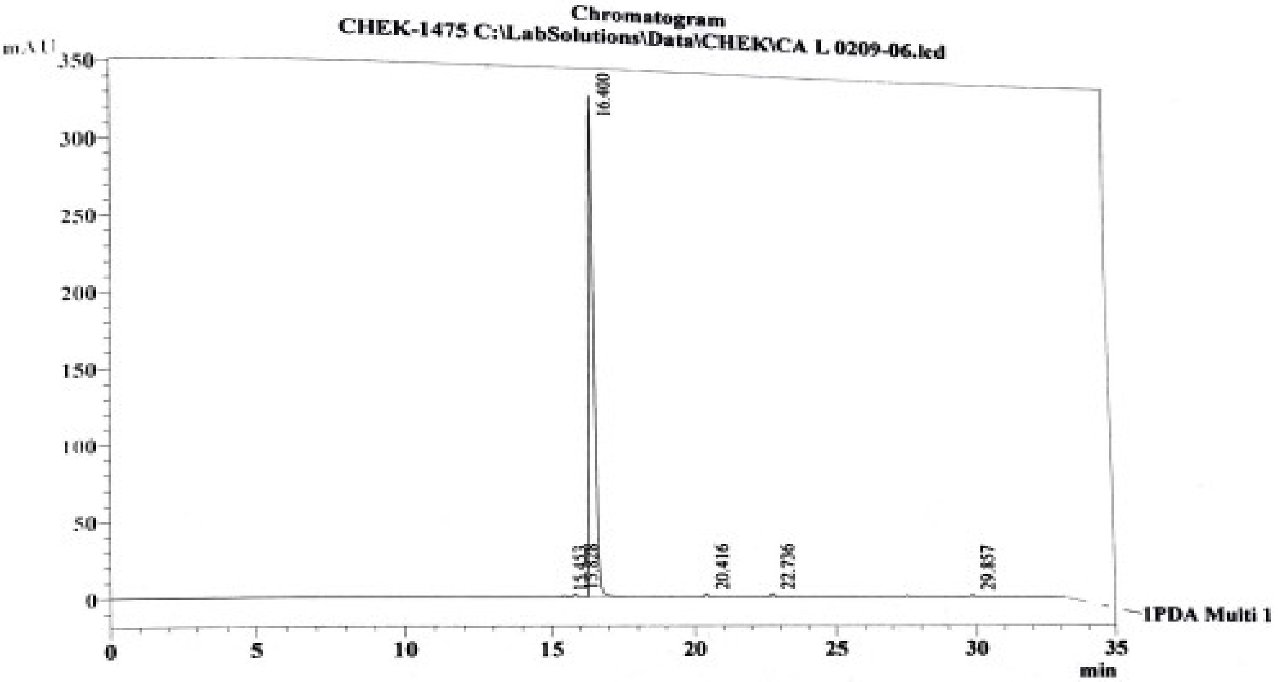
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S109. Copy HPLC analysis of the derivative **13d**.



1 PDA Multi 1 / 290nm 4nm

PeakTable

PDA Ch1 290nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	15.453	14912	1063	0.371
2	15.828	17387	2006	0.432
3	16.400	3942125	332461	98.019
4	20.416	17626	1987	0.438
5	22.736	18688	2134	0.465
6	29.857	11054	1759	0.275
Total		4021792	341409	100.000

Method

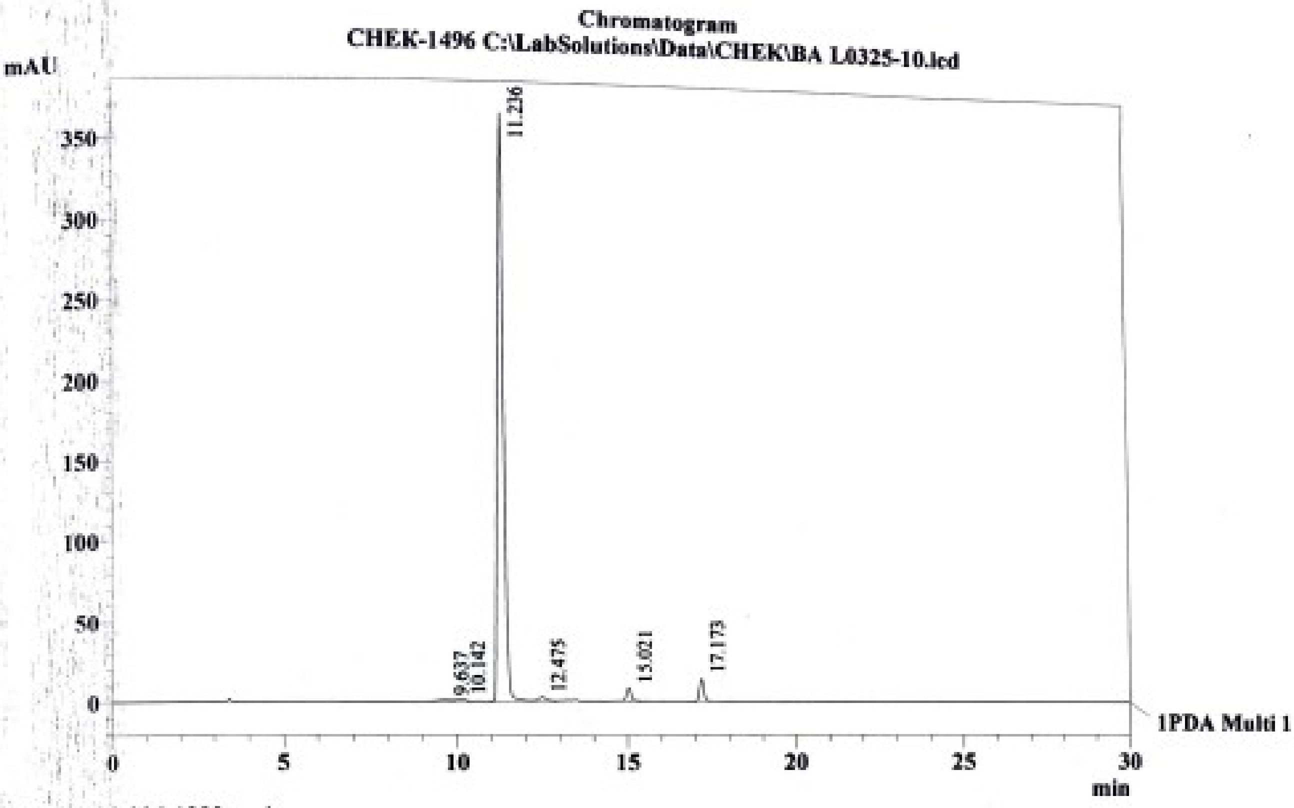
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S110. Copy HPLC analysis of the derivative **13e**.



1 PDA Multi 1 / 300nm 4nm

PeakTable

PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.637	29688	989	0.609
2	10.142	30974	1715	0.636
3	11.236	4550228	366255	93.362
4	12.475	48296	2787	0.991
5	15.021	84025	8431	1.724
6	17.173	130534	14623	2.678
Total		4873746	394799	100.000

Method

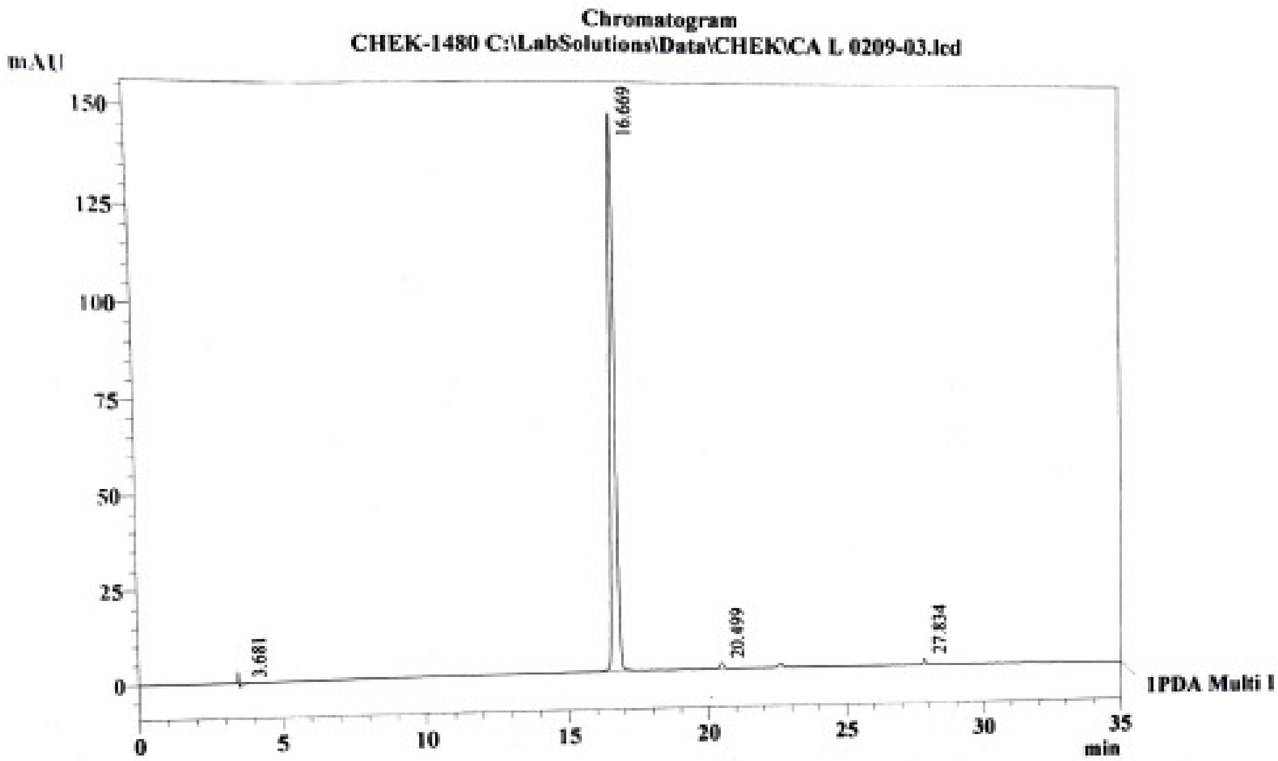
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
43.00	Controller	Stop	

Method Filename : FOS Bv.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S111. Copy HPLC analysis of the derivative **13f**.



1 PDA Multi 1 / 290nm 4nm

PeakTable

PDA Ch1 290nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	3.681	10073	805	0.573
2	16.669	1723323	146937	98.044
3	20.499	13562	1595	0.772
4	27.834	10753	1751	0.612
Total		1757712	151087	100.000

Method

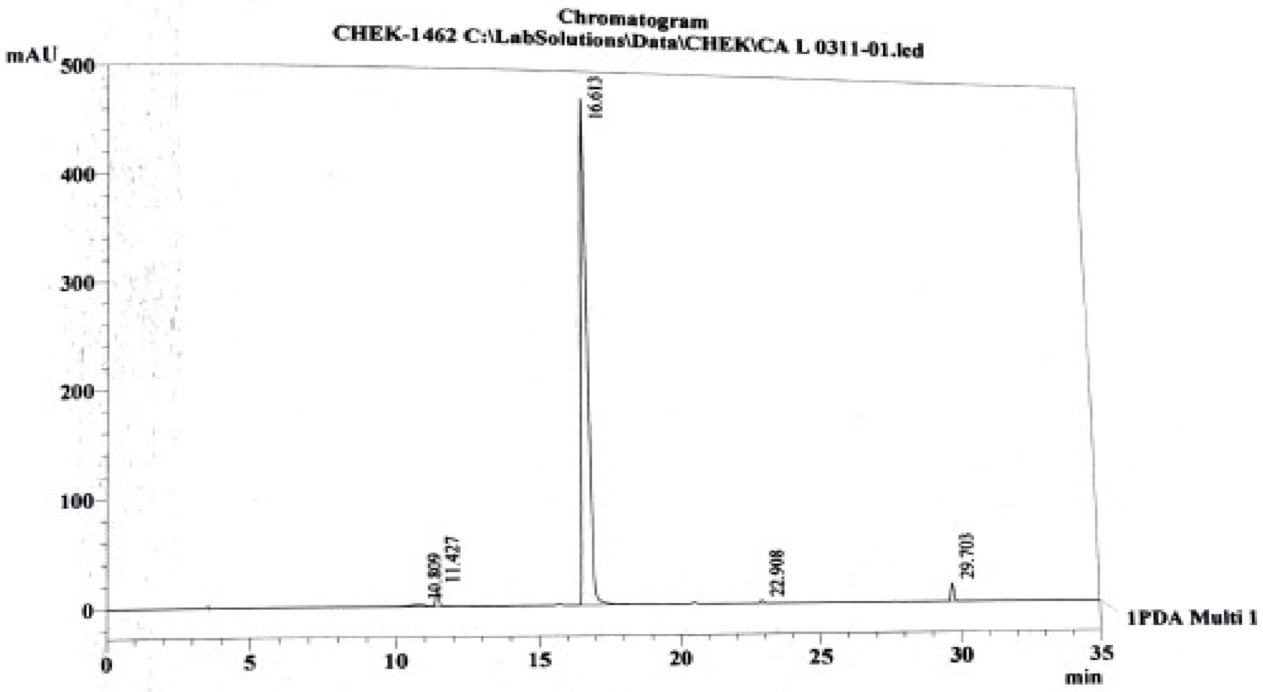
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S112. Copy HPLC analysis of the derivative **13g**.



1 PDA Multi 1 / 298nm 4nm

PeakTable

PDA Ch1 298nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	10.809	58271	1728	0.795
2	11.427	132338	16936	1.807
3	16.613	7001975	473677	95.585
4	22.908	22119	2471	0.302
5	29.703	110656	16629	1.511
Total		7325359	511440	100.000

Method

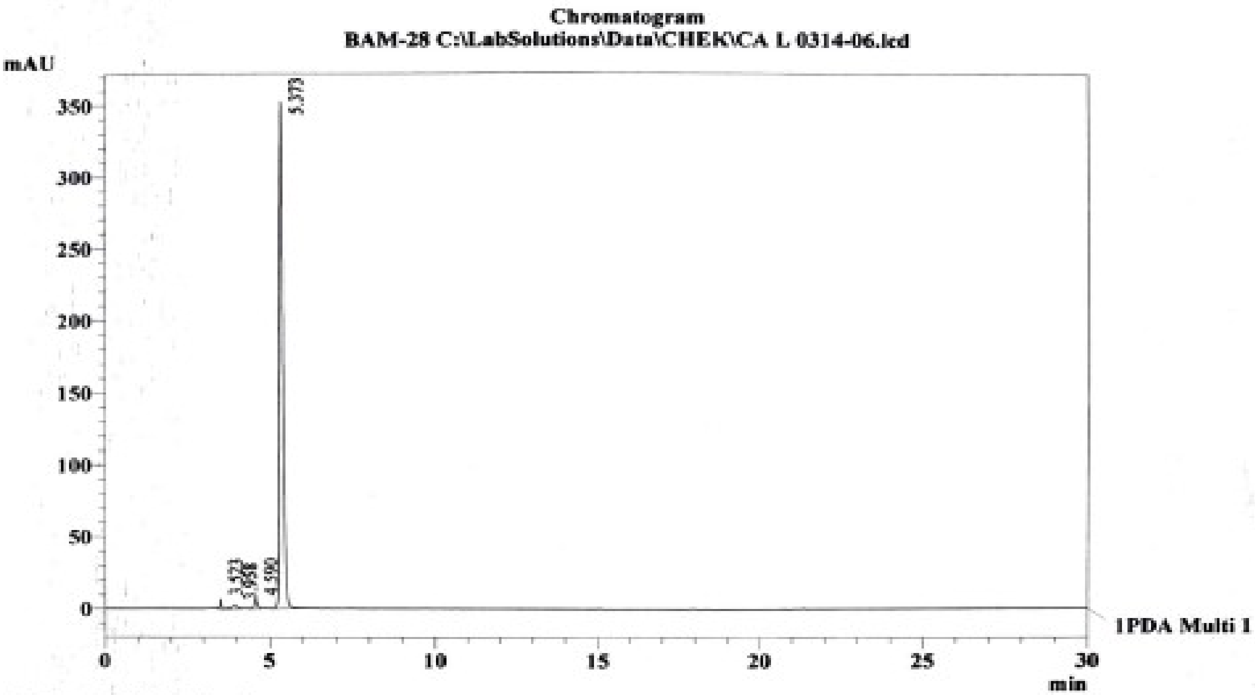
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	15
20.00	Pumps	B.Conc	40
30.00	Pumps	B.Conc	70
33.00	Pumps	B.Conc	15
45.00	Controller	Stop	

Method Filename : FOS Av.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18,.size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S113. Copy HPLC analysis of the derivative **13h**.



1 PDA Multi 1 / 335nm 4nm

PeakTable

PDA Ch1 335nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	3.523	25023	6981	0.926
2	3.958	39531	3345	1.463
3	4.590	44279	6801	1.638
4	5.373	2593718	352686	95.973
Total		2702551	369814	100.000

Method

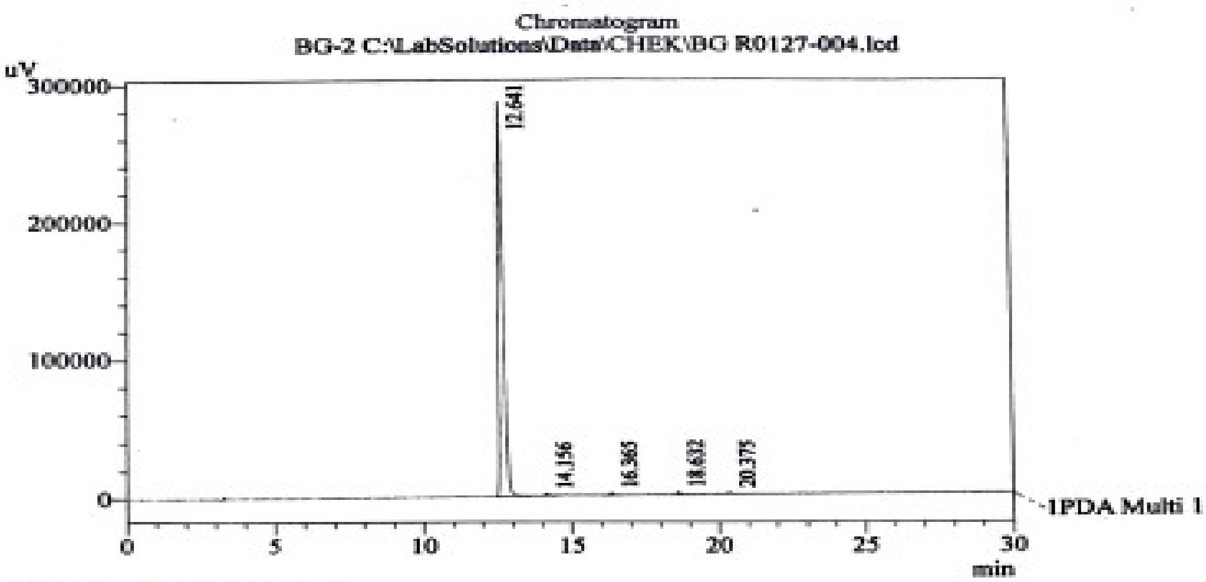
<<LC Program>>

Time	Unit	Command	Value
0.10	Pumps	B.Conc	30
30.00	Pumps	B.Conc	70
32.00	Pumps	B.Conc	30
43.00	Controller	Stop	

Method Filename : FOS B.lcm

Shimadzu LC-20AD; 2-System FOS, Colon Kromasil 100-C18, size 5mkm, 4,6*250mm, N 86912
Elution: A - H3PO4 0.01M pH 2.6; B - MeCN, fl. 1,0 ml/min, loop 20mkl.

Figure S114. Copy HPLC analysis of the derivative **14a**.



1 PDA Multi 1 / 290nm 4nm

PDA Ch1 290nm 4nm

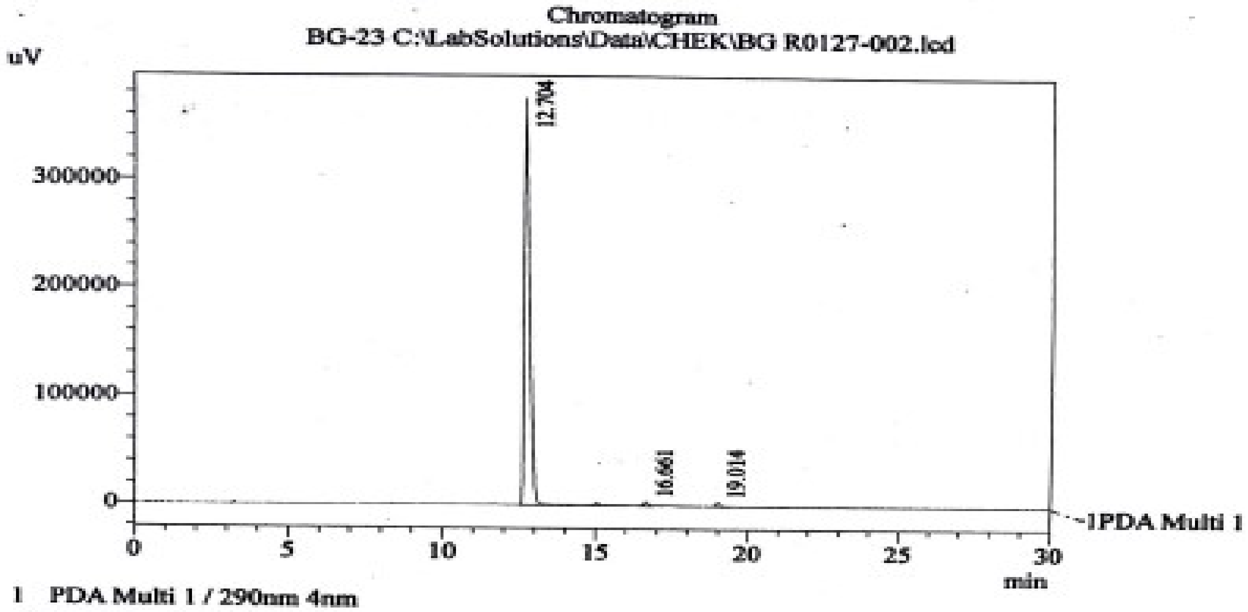
Peak#	Ret. Time	Area	Height	Area %
1	12.641	3308849	285189	98.464
2	14.156	18139	1426	0.540
3	16.365	13052	1671	0.388
4	18.632	16172	1987	0.481
5	20.375	4251	1222	0.127
Total		3360462	291494	100.000

Method Filename : FOS Av1.lcm 27.01.2021 15:04:11

Time	Unit	Command	Valu
0.01	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
45.00	Controller	Stop	

Shimadzu LC-20 AD; System - FOS Colon- Kromasil-100-5mkm. C-18, 4,6x250 mm. N 62511
Elution: A - H3PO4 0,01M pH 2,6; B - MeCN, f1 - 1.0 ml/min, loop 20 mkl

Figure S115. Copy HPLC analysis of the derivative **14b**.



1 PDA Multi 1 / 290nm 4nm

PDA Ch1 290nm 4nm

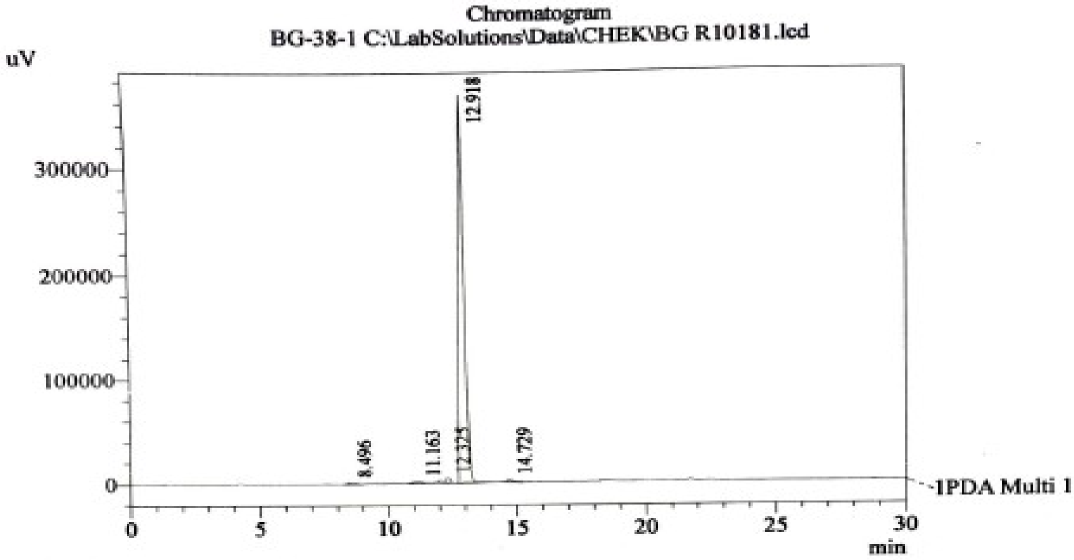
Peak#	Ret. Time	Area	Height	Area %
1	12.704	5196493	374968	98.549
2	16.661	38639	4417	0.733
3	19.014	37890	4288	0.719
Total		5273023	383673	100.000

Method Filename : FOS Av1.lcm 27.01.2021 13:27:12

Time	Unit	Command	Valu
0.01	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
45.00	Controller	Stop	

Shimadzu LC-20 AD; System - FOS Colon- Kromasil-100-5mkm. C-18, 4,6x250 mm. N 62511
Elution: A - H3PO4 0,01M pH 2,6; B - MeCN, fl - 1.0 ml/min, loop 20 mkl

Figure S116. Copy HPLC analysis of the derivative **14g**.



1 PDA Multi 1 / 290nm 4nm

PDA Ch1 290nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	8.496	26901	1561	0.485
2	11.163	41047	1813	0.741
3	12.325	73221	4391	1.321
4	12.918	5368240	367525	96.859
5	14.729	32935	2543	0.594
Total		5542343	377833	100.000

Method Filename : FOS Av1.lcm 18.10.2021 15:08:02

Time	Unit	Command	Valu
0.01	Pumps	B.Conc	20
30.00	Pumps	B.Conc	60
33.00	Pumps	B.Conc	20
45.00	Controller	Stop	

Shimadzu LC-20 AD; System - FOS Colon- Kromasil-100-5mkm. C-18, 4,6x250 mm. N 62511
Elution: A - H3PO4 0,01M pH 2,6; B - MeCN, fl - 1.0 ml/min, loop 20 mkl

Table S2. Experimental parameters of aqueous solubility (pH=7) of some derivatives **4a-c**, **13a** and **14a** at 23 °C.

Compound	**Experimental solubility (mg/mL)**
4a*HCl	14.3±0.3
4b*HCl	1.2±0.1
4c*HCl	0.17±0.02
13a*HCl	0.9±0.1
14a*HCl	0.03±0.05
14a*MsOH	0.6±0.1