

# Conjugates of Tacrine and Salicylic Acid Derivatives as New Promising Multitarget Agents for Alzheimer's Disease

Galina F. Makhaeva <sup>1</sup>, Nadezhda V. Kovaleva <sup>1</sup>, Elena V. Rudakova <sup>1</sup>, Natalia P. Boltneva <sup>1</sup>, Maria V. Grishchenko <sup>2</sup>, Sofya V. Lushchekina <sup>1,3</sup>, Tatiana Y. Astakhova <sup>3</sup>, Olga G. Serebryakova <sup>1</sup>, Elena N. Timokhina <sup>3</sup>, Ekaterina F. Zhilina <sup>2</sup>, Evgeny V. Shchegolkov <sup>2</sup>, Mariya V. Ulitko <sup>4</sup>, Eugene V. Radchenko <sup>1,5</sup>, Vladimir A. Palyulin <sup>1,5</sup>, Yanina V. Burgart <sup>2</sup>, Victor I. Saloutin <sup>2</sup>, Sergey O. Bachurin <sup>1</sup> and Rudy J. Richardson <sup>6,7,8,9,\*</sup>

<sup>1</sup> Institute of Physiologically Active Compounds at Federal Research Center of Problems of Chemical Physics and Medicinal Chemistry, Russian Academy of Sciences, Chernogolovka 142432, Russia

<sup>2</sup> Postovsky Institute of Organic Synthesis, Urals Branch of Russian Academy of Sciences, Yekaterinburg 620990, Russia

<sup>3</sup> Emanuel Institute of Biochemical Physics Russian Academy of Sciences, Moscow 119334, Russia

<sup>4</sup> Institute of Natural Sciences and Mathematics of the Ural Federal University Named after the First President of Russia B. N. Yeltsin, Ekaterinburg 620083, Russia

<sup>5</sup> Department of Chemistry, Lomonosov Moscow State University, Moscow 119991, Russia

<sup>6</sup> Department of Environmental Health Sciences, University of Michigan, Ann Arbor, MI 48109, USA

<sup>7</sup> Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA

<sup>8</sup> Center of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA

<sup>9</sup> Michigan Institute for Computational Discovery and Engineering, University of Michigan, Ann Arbor, MI 48109, USA

\* Correspondence: rjrich@umich.edu; Tel.: +1-734-936-0769

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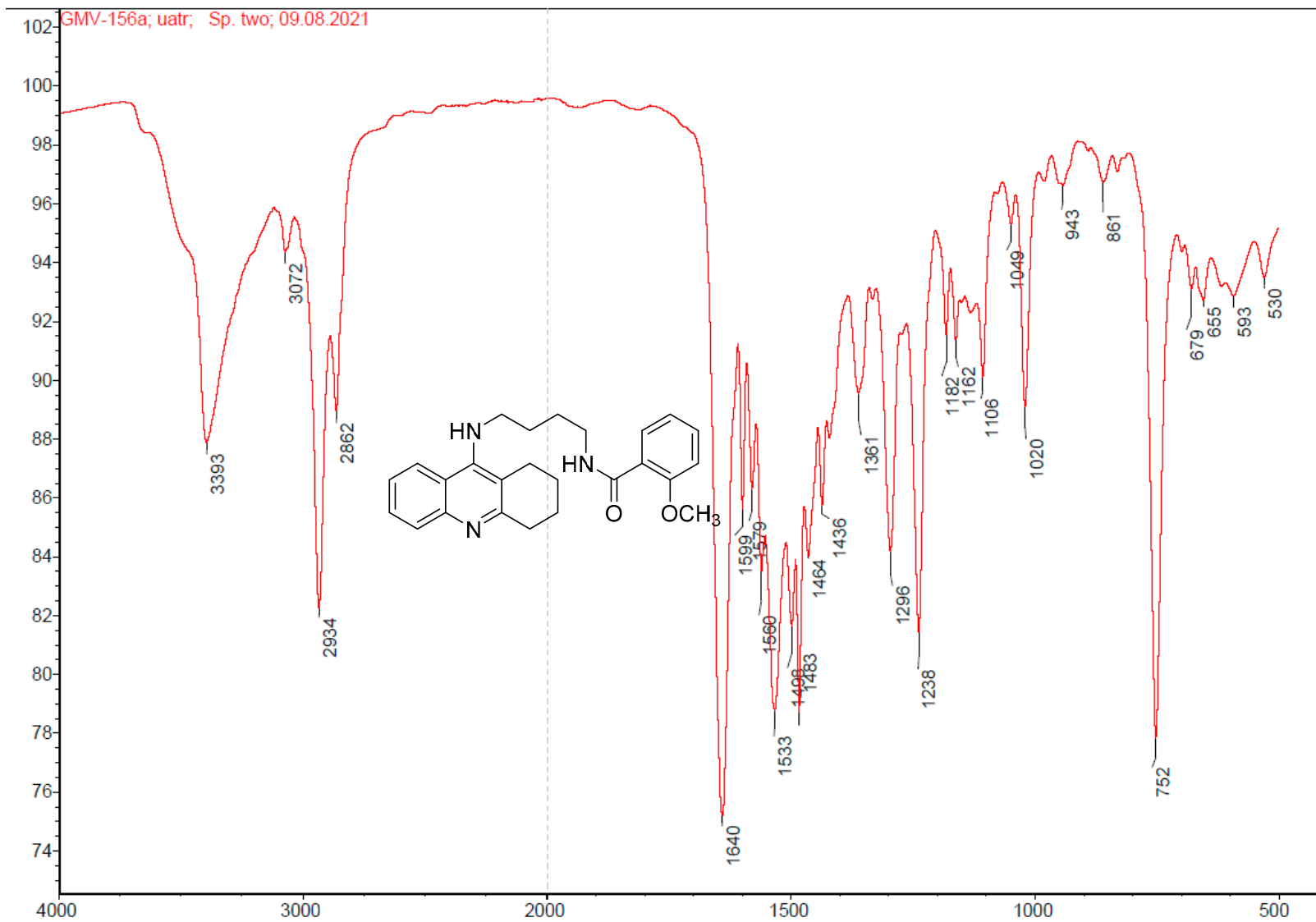


Figure S1. IR spectrum of compound 6a



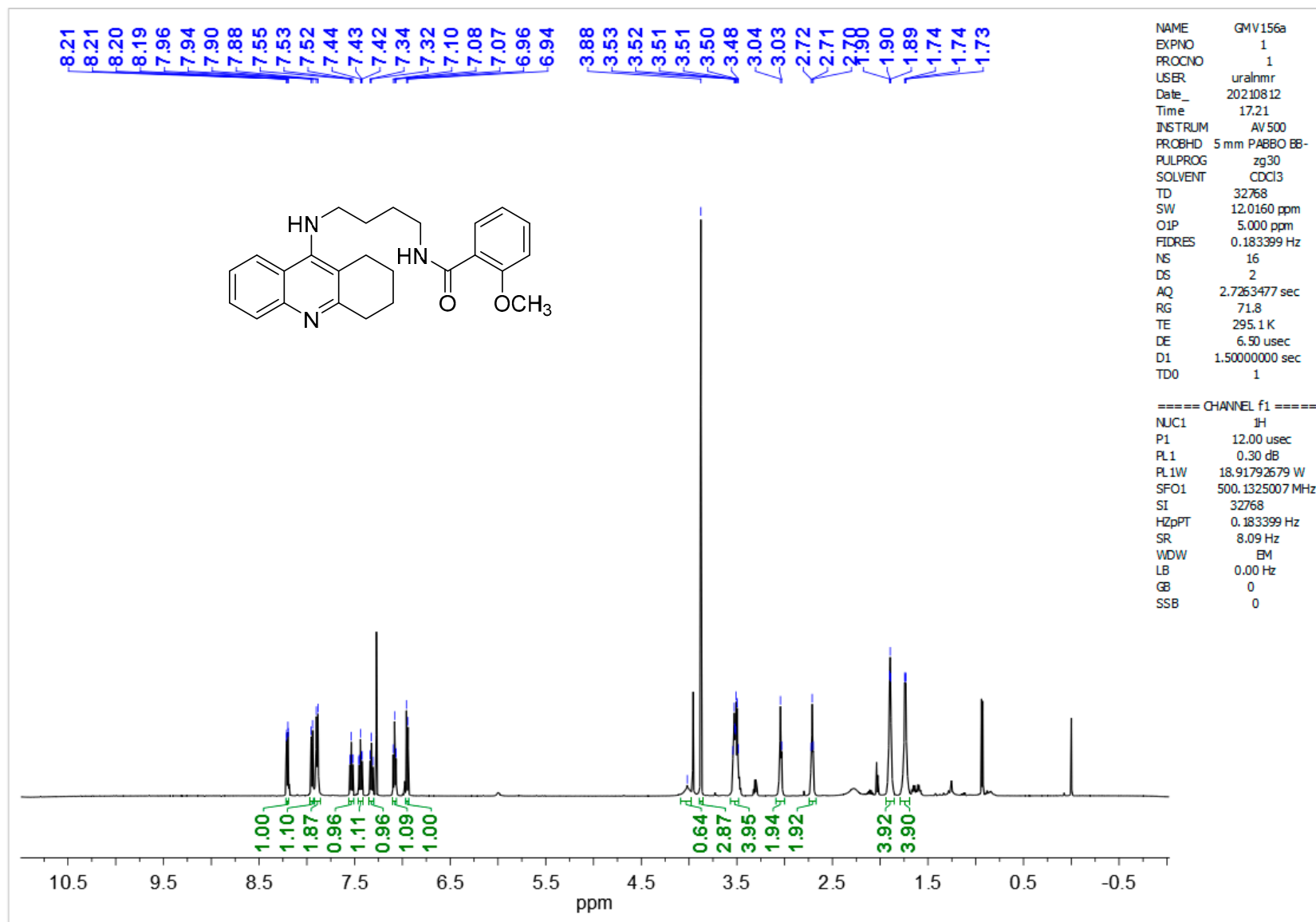


Figure S2. <sup>1</sup>H NMR spectrum of compound 6a

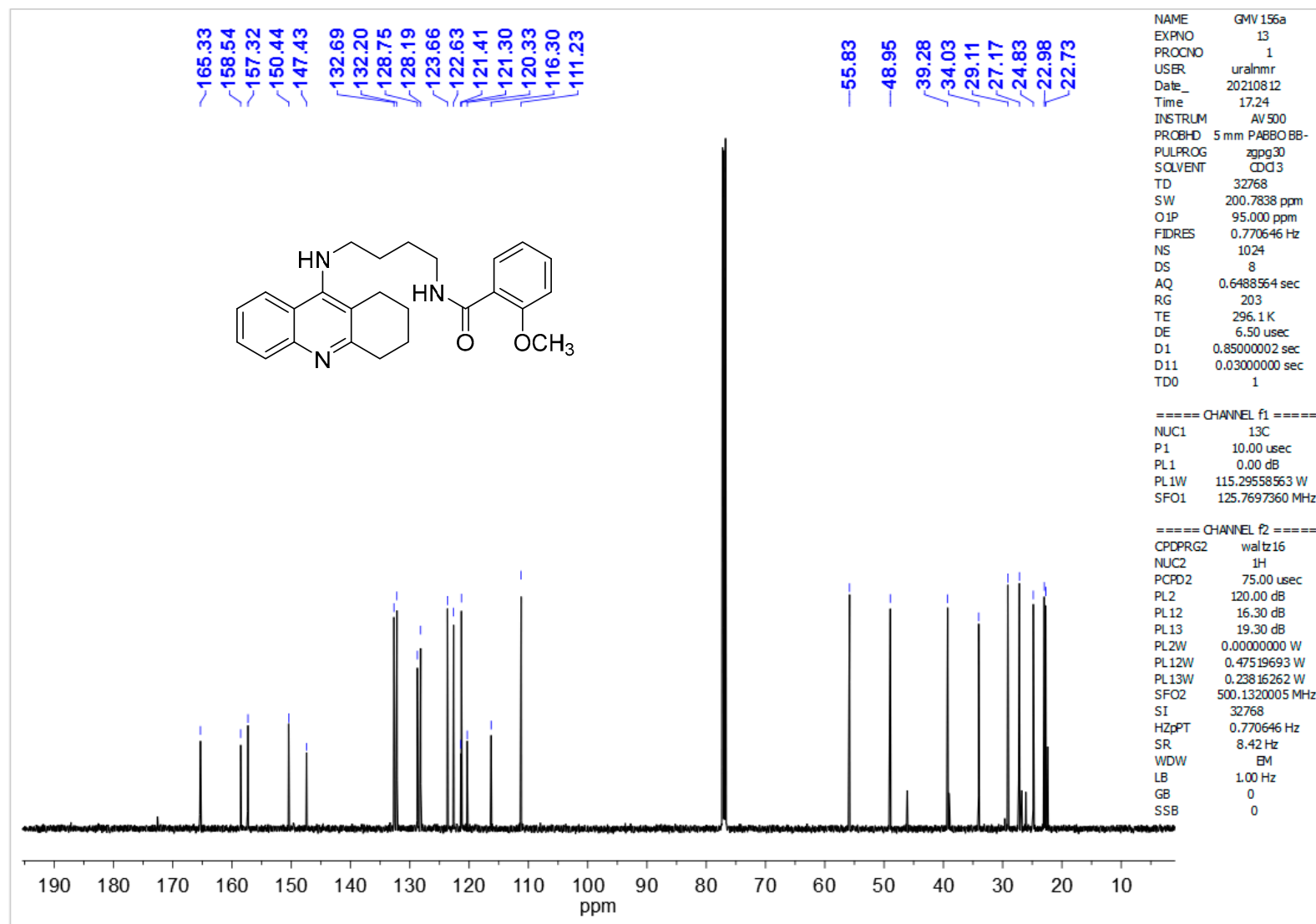


Figure S3. <sup>13</sup>C NMR spectrum of compound 6a

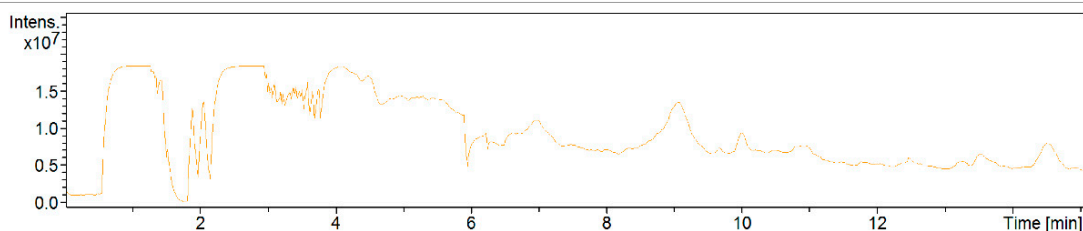
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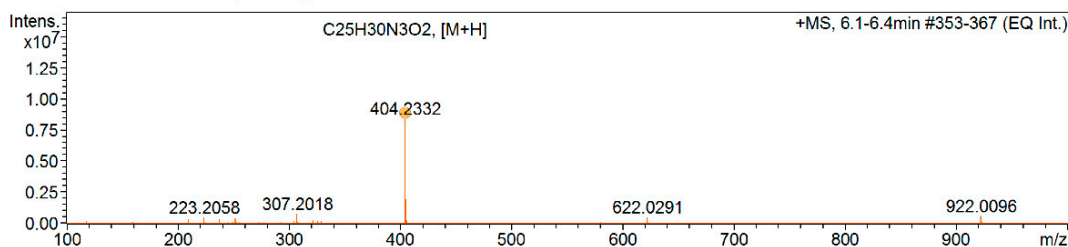
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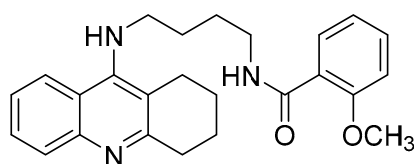
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	3	C25H30N3O2	404.2333	0.1	30.2	3	100.00	12.5	even	ok



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Institute of Organic Synthesis UB RAS  
 22 S.Kovalevskoy, 20 Akademicheskaya str, Yekaterinburg, Russian Federation  
 Phone: +7 (343) 362-34-56



Figure S4. HMRS spectrum of compound 6a

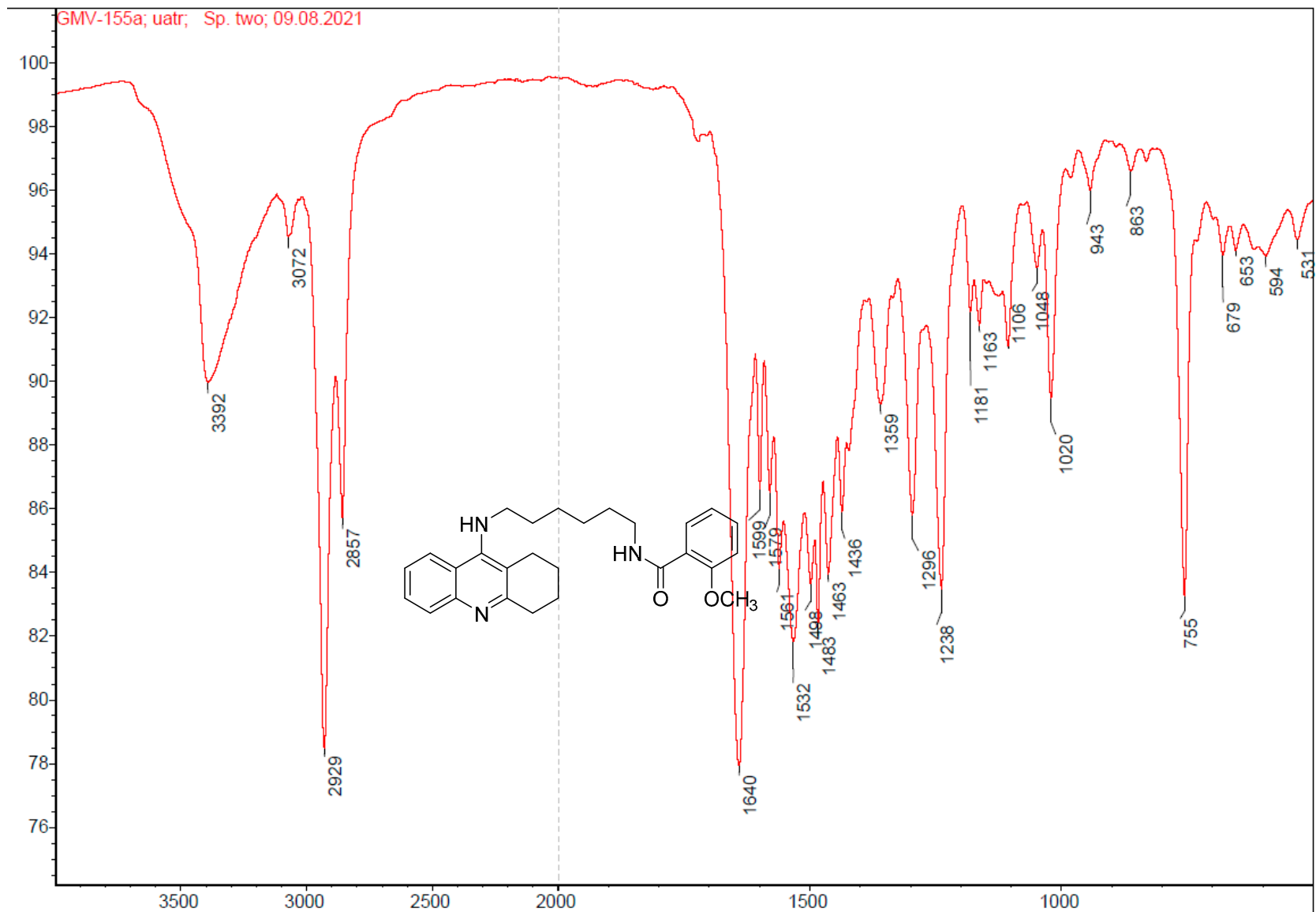


Figure S4. IR spectrum of compound 6b

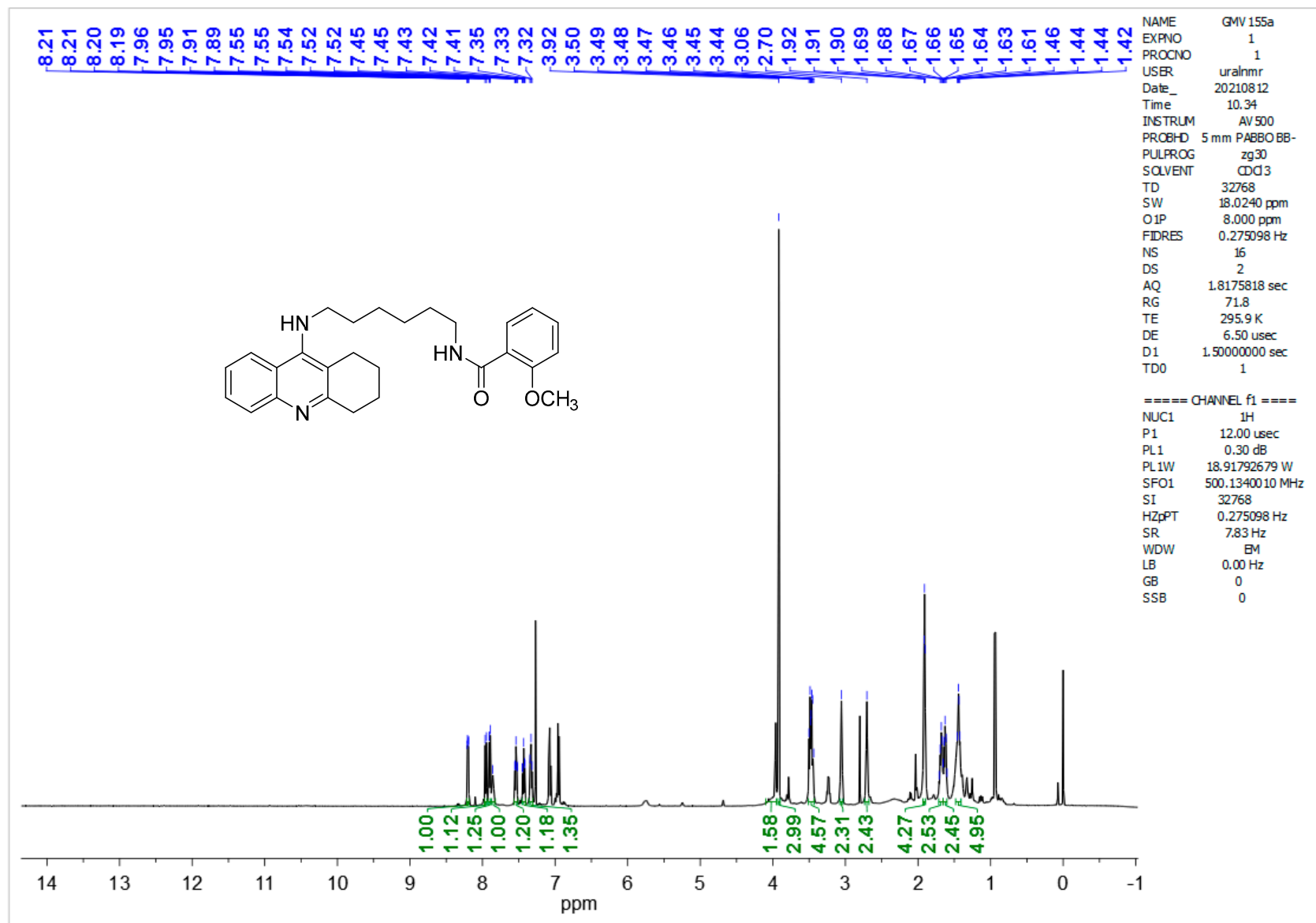


Figure S5. <sup>1</sup>H NMR spectrum of compound 6b

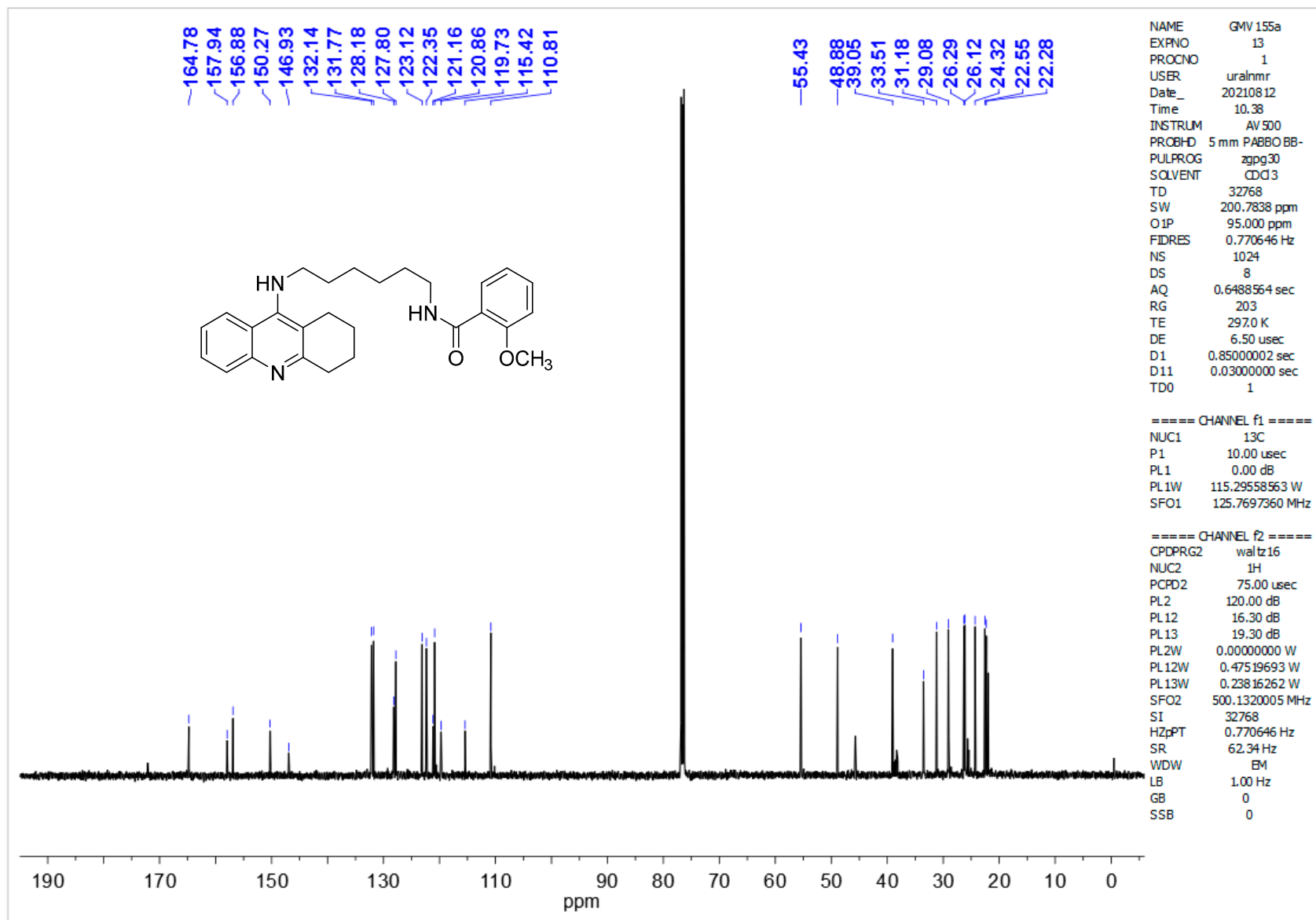


Figure S6. <sup>13</sup>C NMR spectrum of compound **6b**

# Compound Spectrum SmartFormula Report

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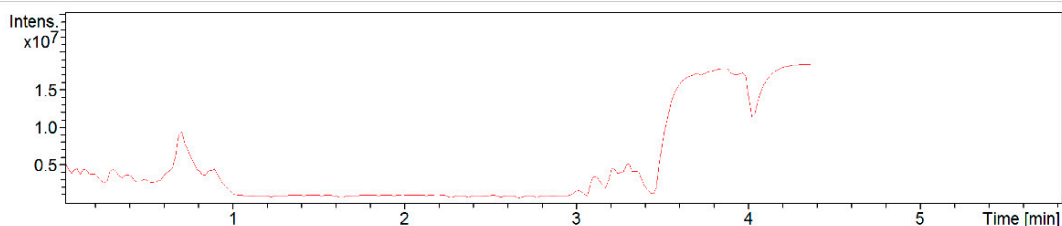
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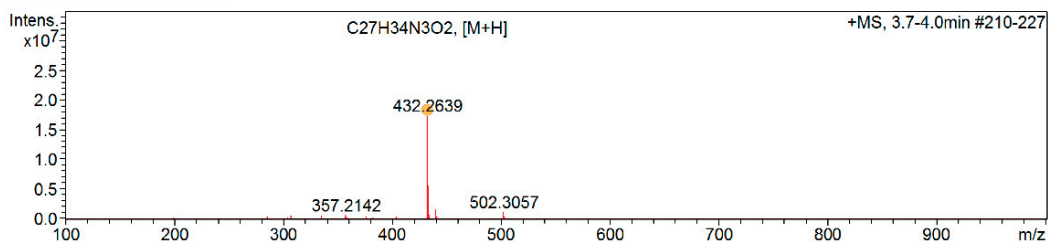
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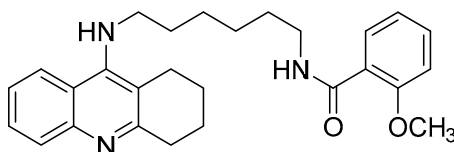
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	2	C23H30N9	432.2619	-4.7	22.7	2	33.17	13.5	even	ok



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**Figure S7.** HMRS spectrum of compound **6b**

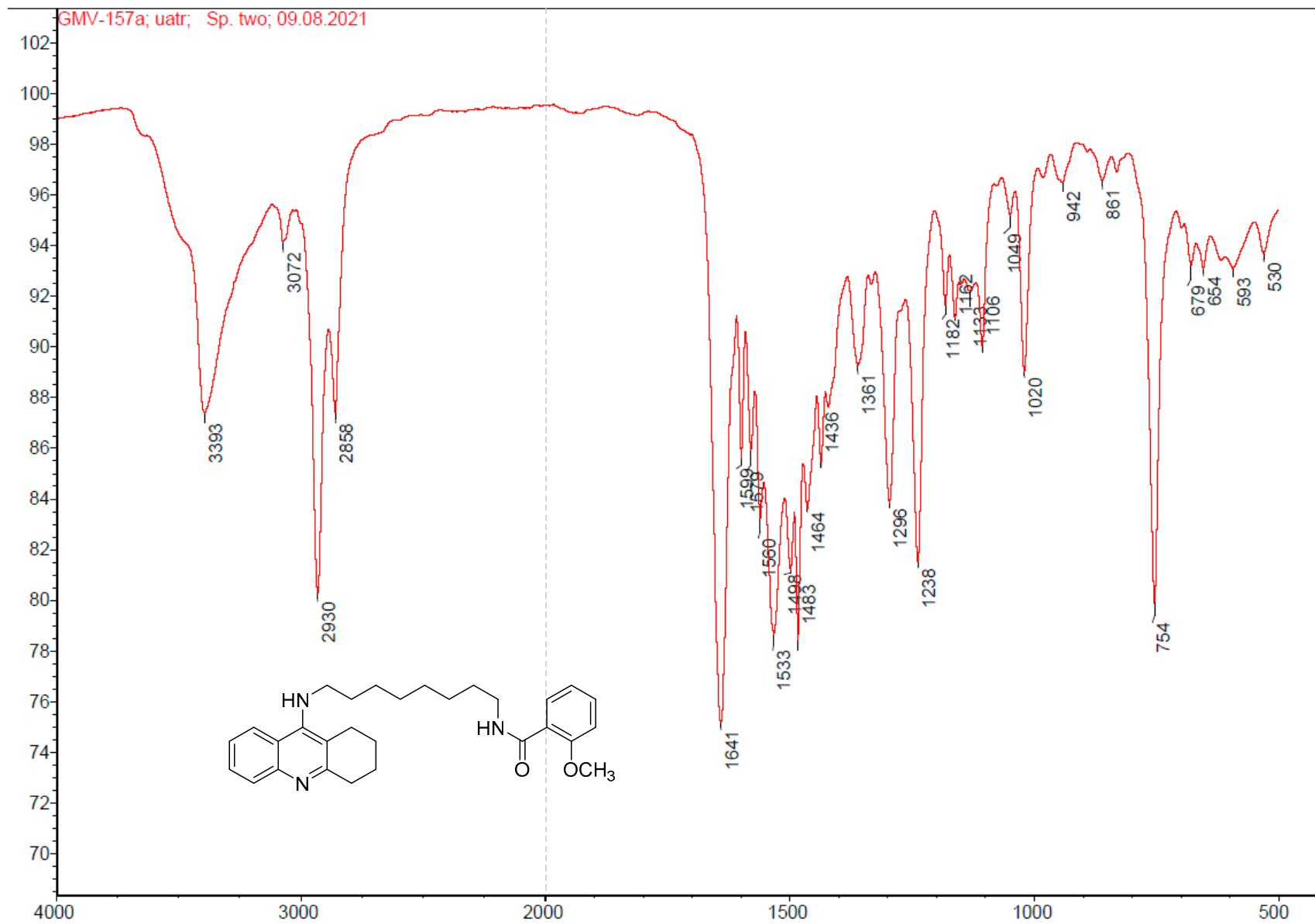


Figure S7. IR spectrum of compound 6c



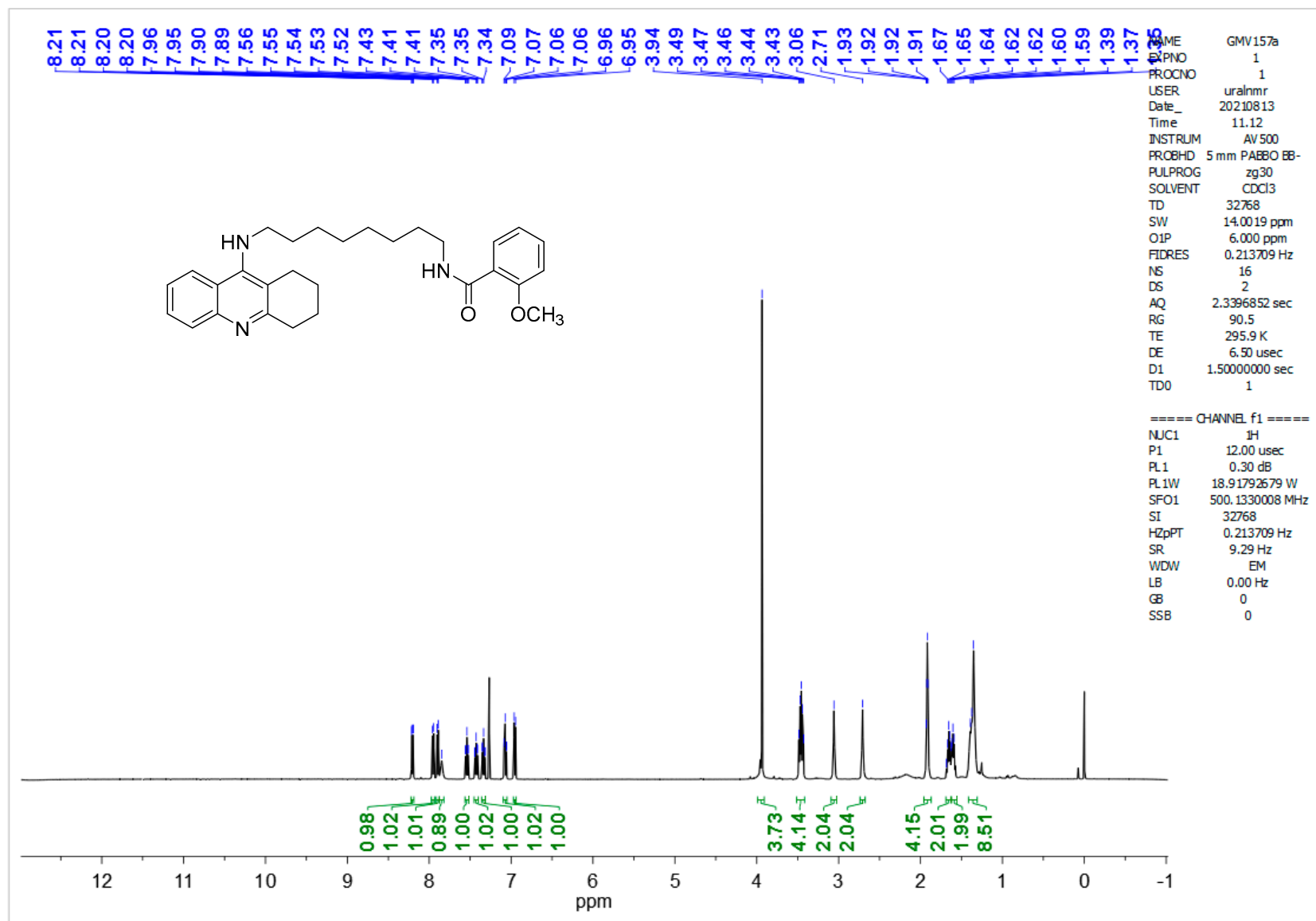


Figure S8. <sup>1</sup>H NMR spectrum of compound 6c

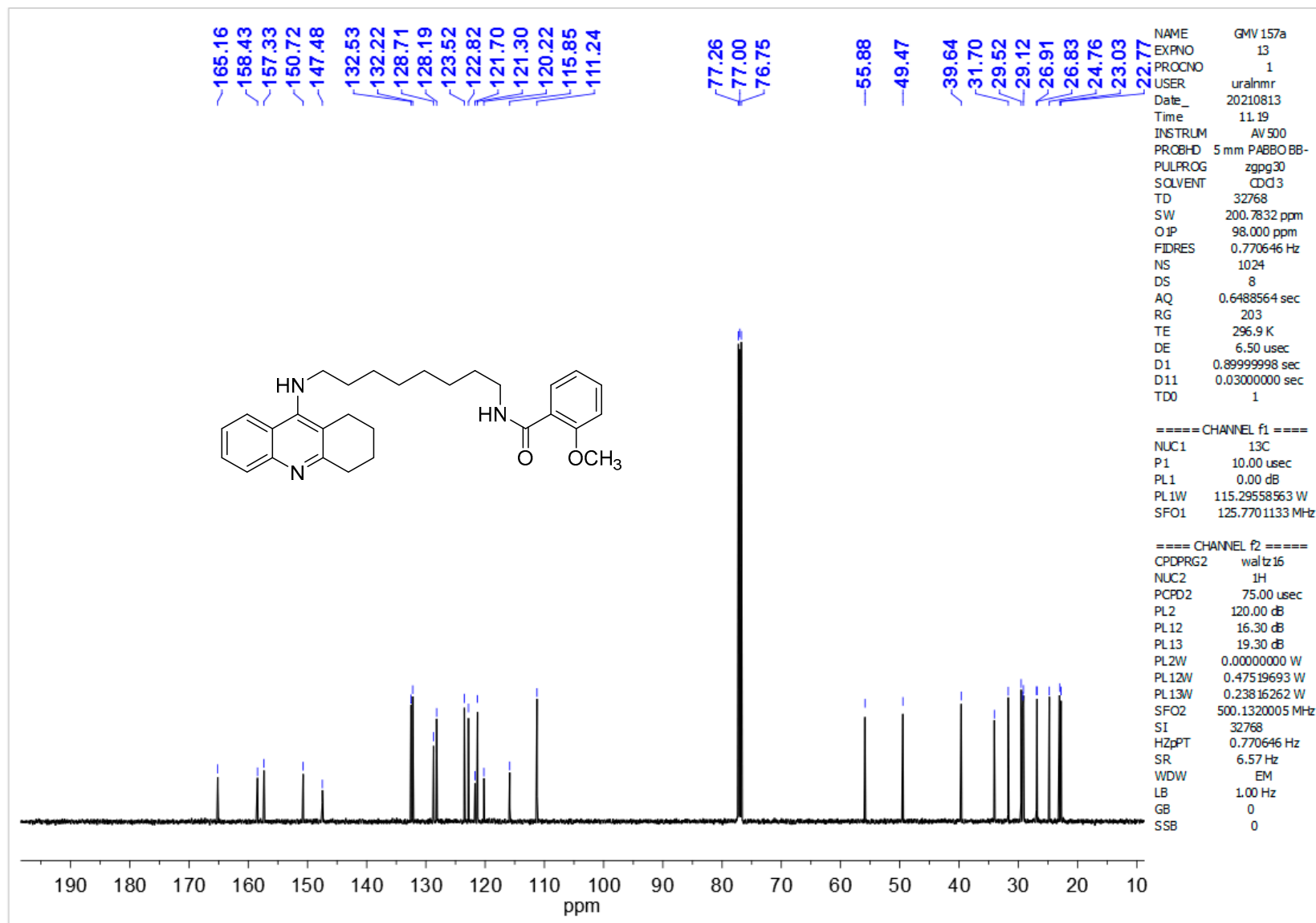


Figure S9. <sup>13</sup>C NMR spectrum of compound 6c

# Compound Spectrum SmartFormula Report

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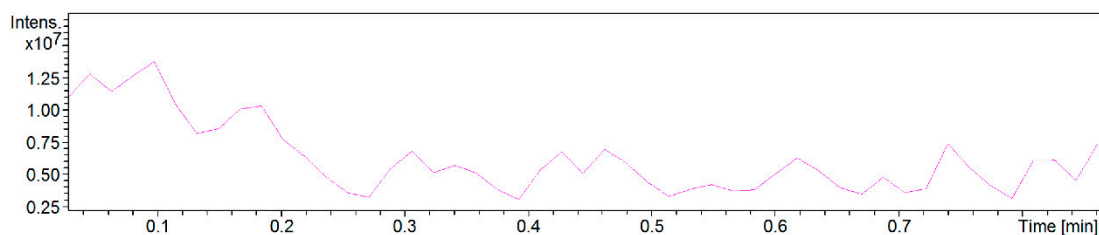
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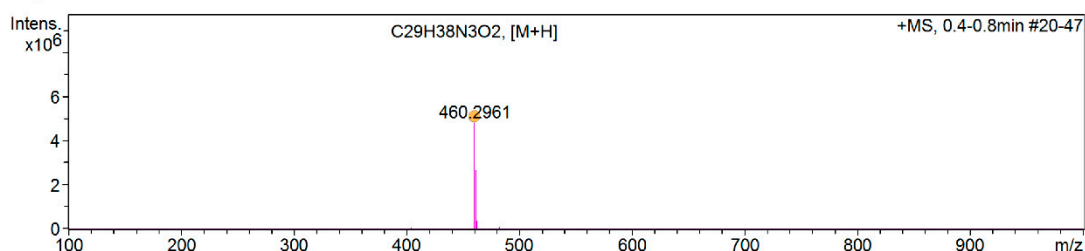
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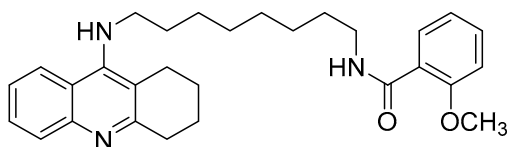
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	2	C17H42N5O9	460.2977	3.5	199.6	2	0.33	-0.5	even	ok
	3	C14H34N15O3	460.2964	0.6	200.1	3	0.67	5.5	even	ok
	4	C13H38N11O7	460.2950	-2.4	213.1	4	0.14	0.5	even	ok



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Figure S10. HRMS spectrum of compound 6c

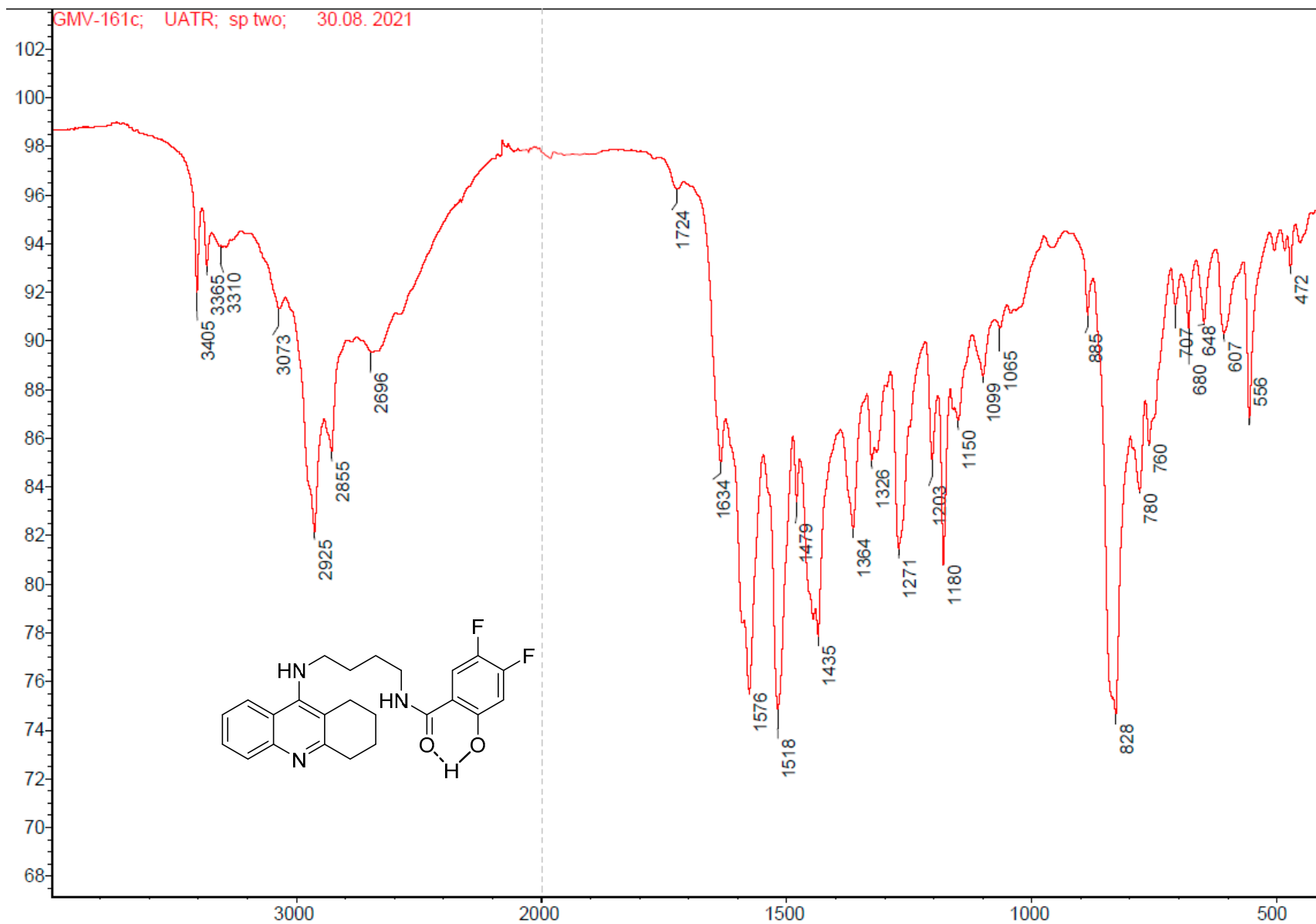


Figure S11. IR spectrum of compound 7a

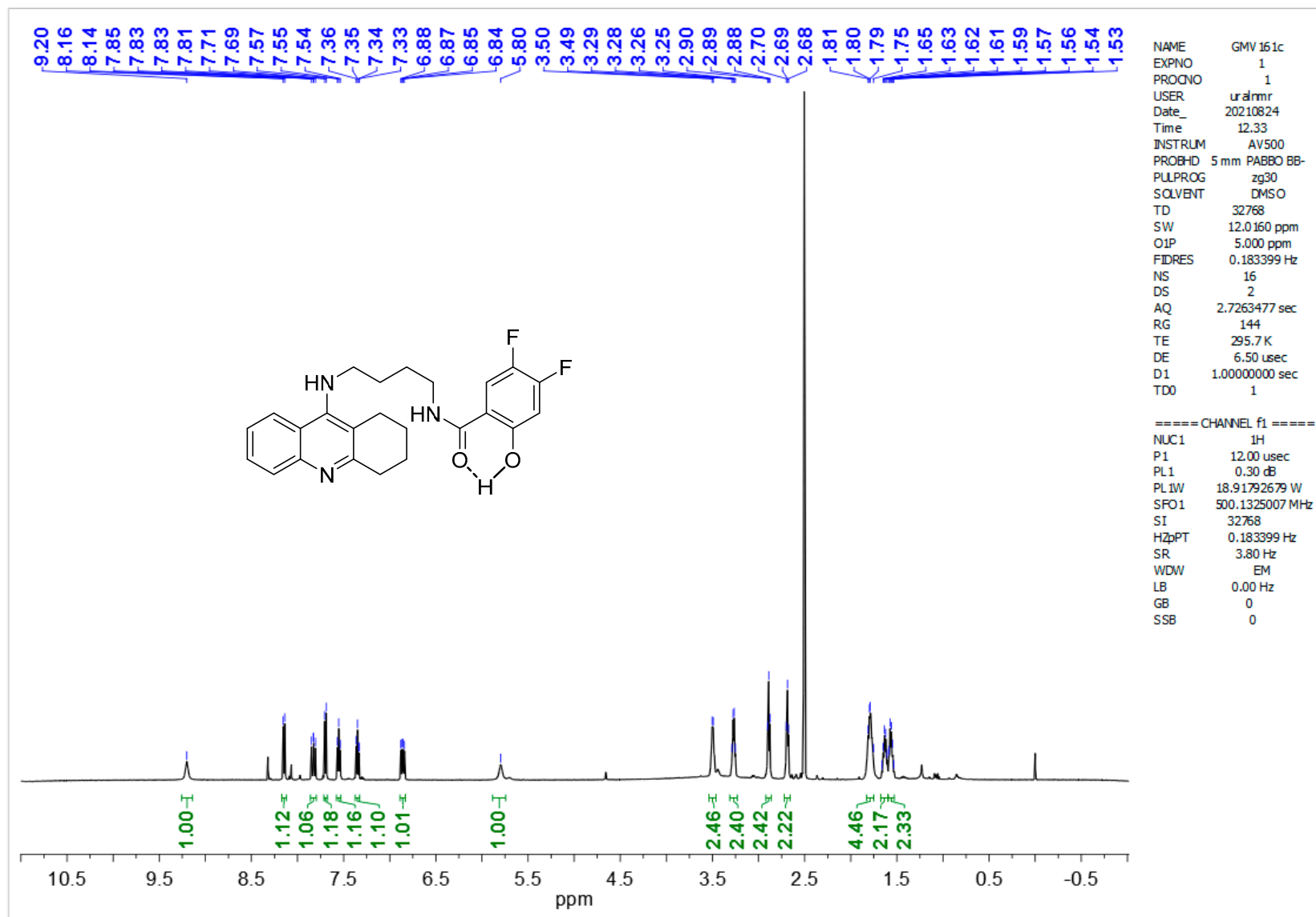


Figure S12. <sup>1</sup>H NMR spectrum of compound 7a

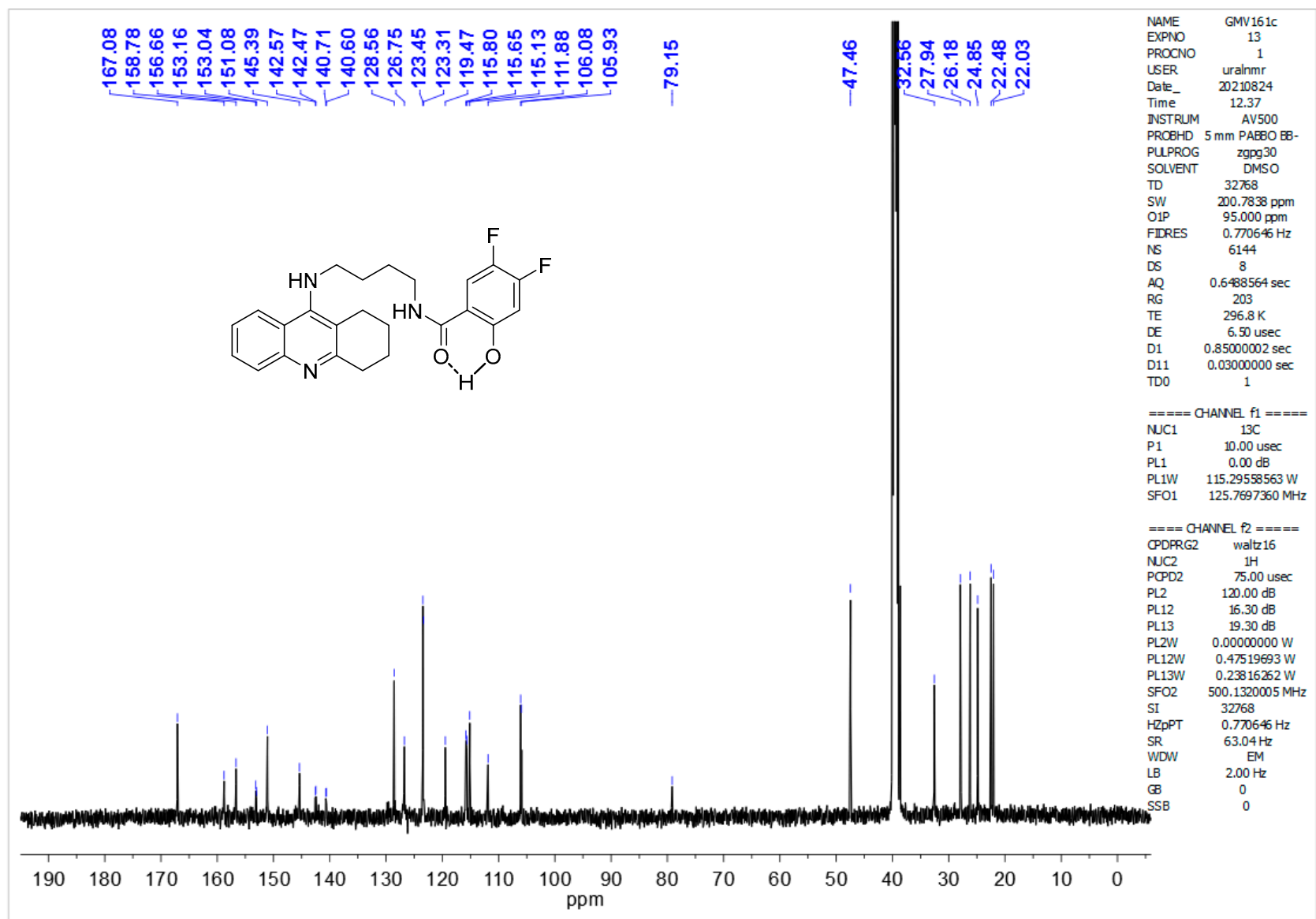


Figure S13. <sup>13</sup>C NMR spectrum of compound 7a

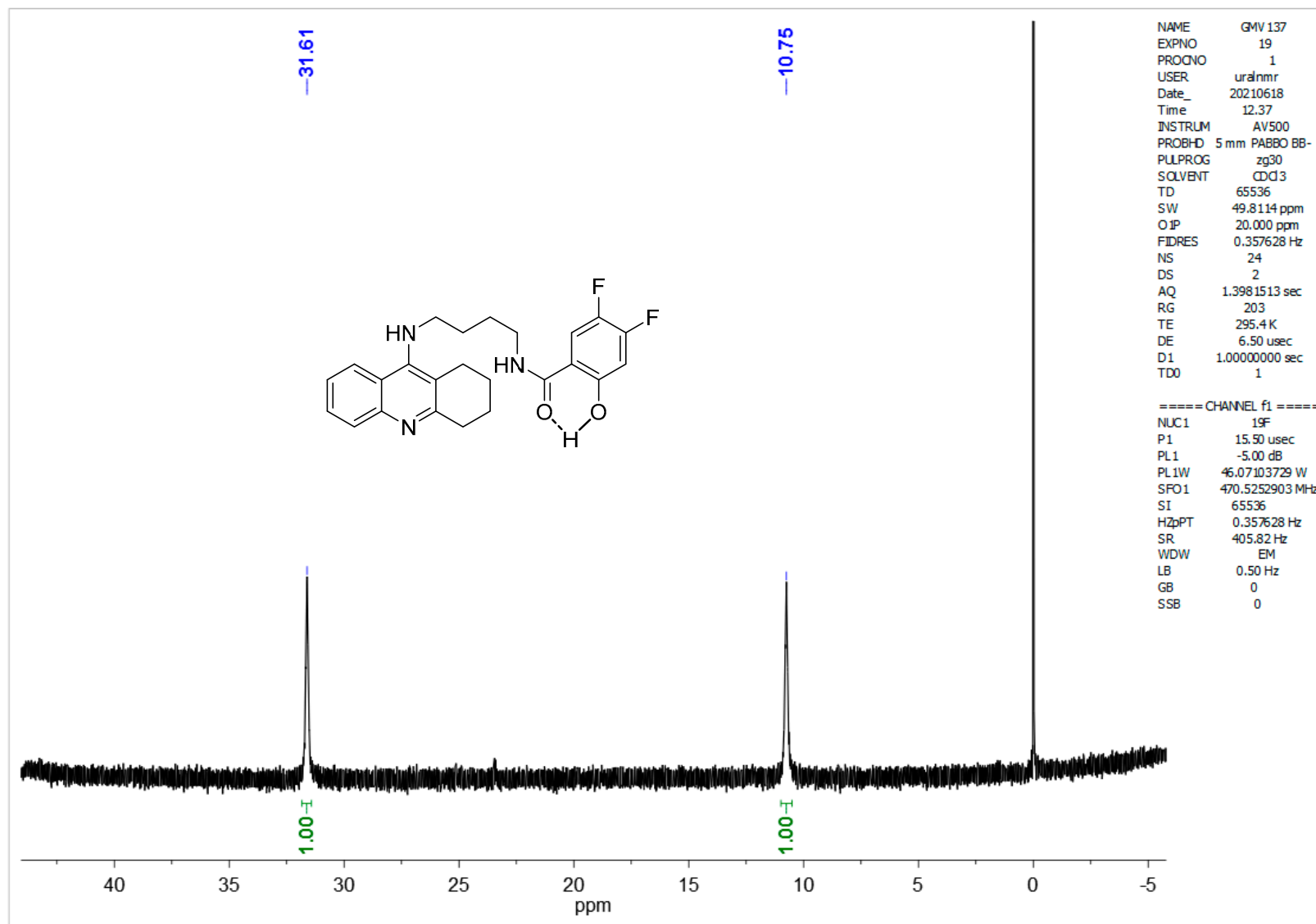


Figure S14. <sup>19</sup>F NMR spectrum of compound 7a

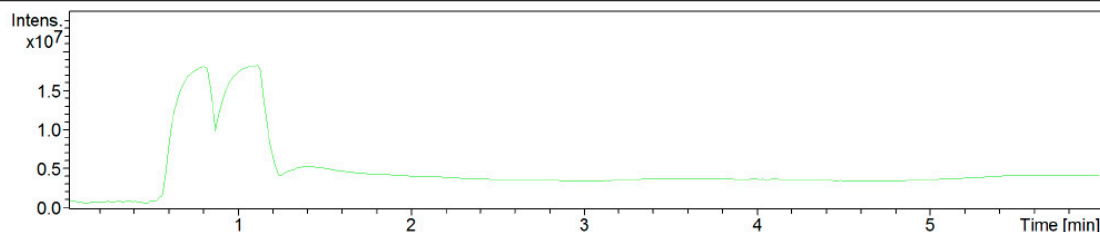
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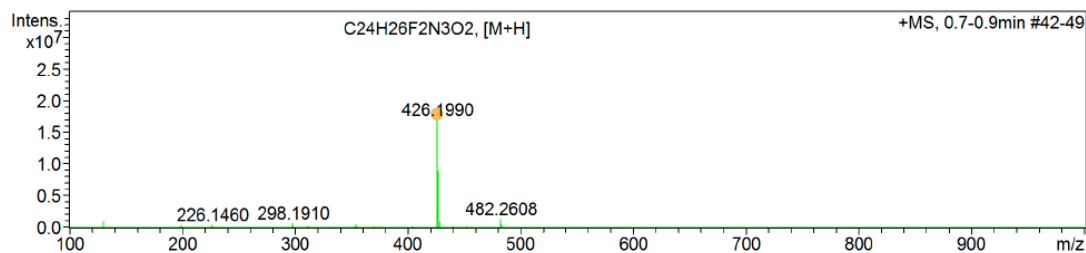
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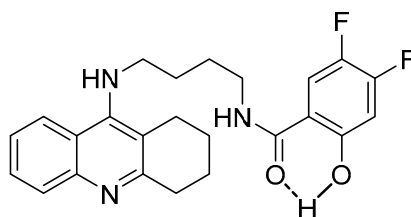
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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 0.7-0.9min #42-49



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
426.1990	1	C24H26F2N3O2	426.1988	-0.7	150.0	1	100.00	12.5	even	ok
	2	C21H27F3N3O3	426.1999	2.0	168.7	2	20.59	8.5	even	ok
	3	C19H24N9O3	426.1997	1.5	168.7	3	23.31	12.5	even	ok
	4	C18H28N5O7	426.1983	-1.7	182.0	4	8.16	7.5	even	ok
	5	C15H29FN5O8	426.1995	1.0	200.6	5	2.08	3.5	even	ok
	6	C9H22F2N15O3	426.1993	0.5	219.3	6	0.44	5.5	even	ok



GMV-161c.23i-C.EP180.6240\_23i1300.d

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Figure S15. HMRS spectrum of compound 7a



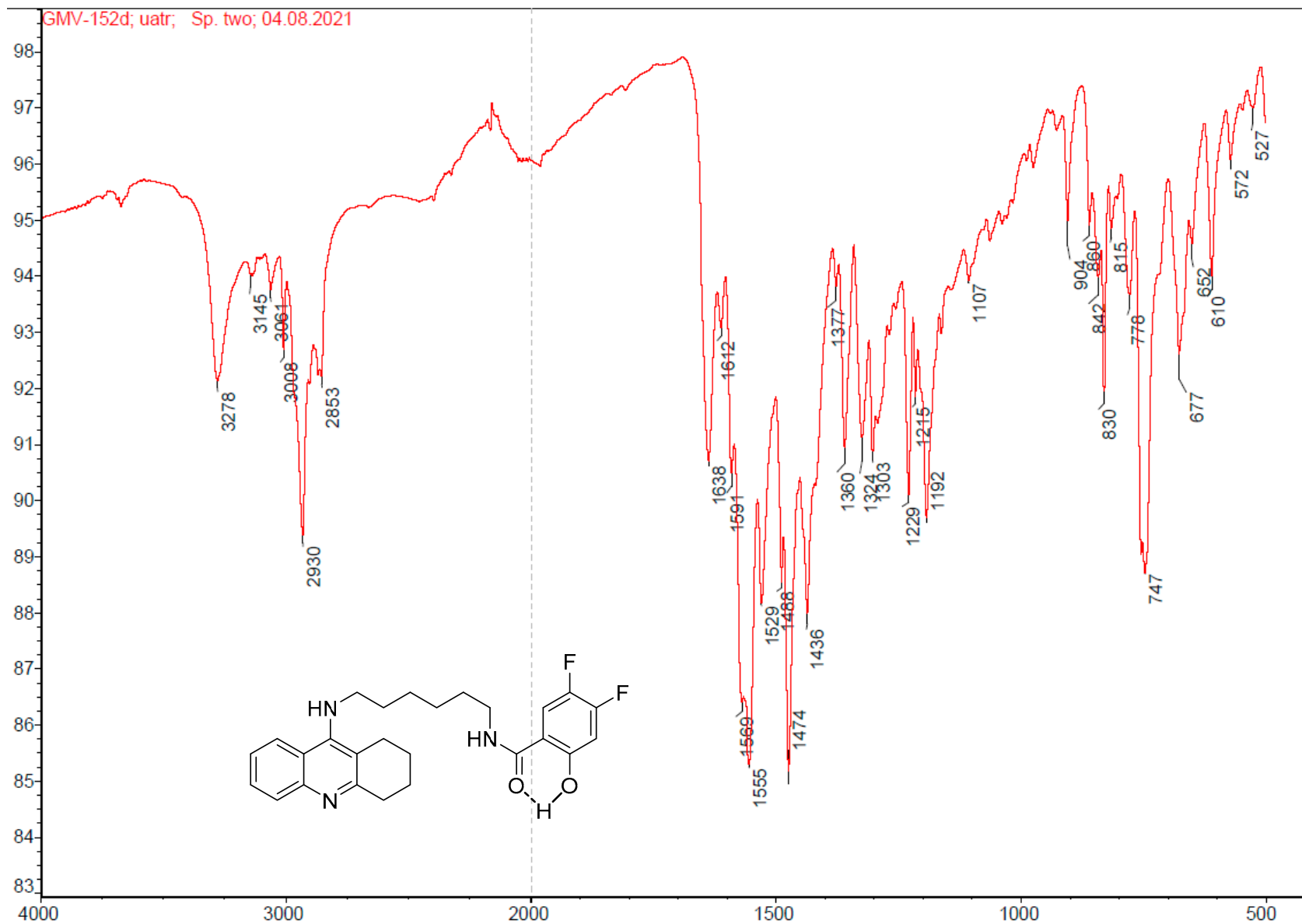


Figure S16. IR spectrum of compound **7b**

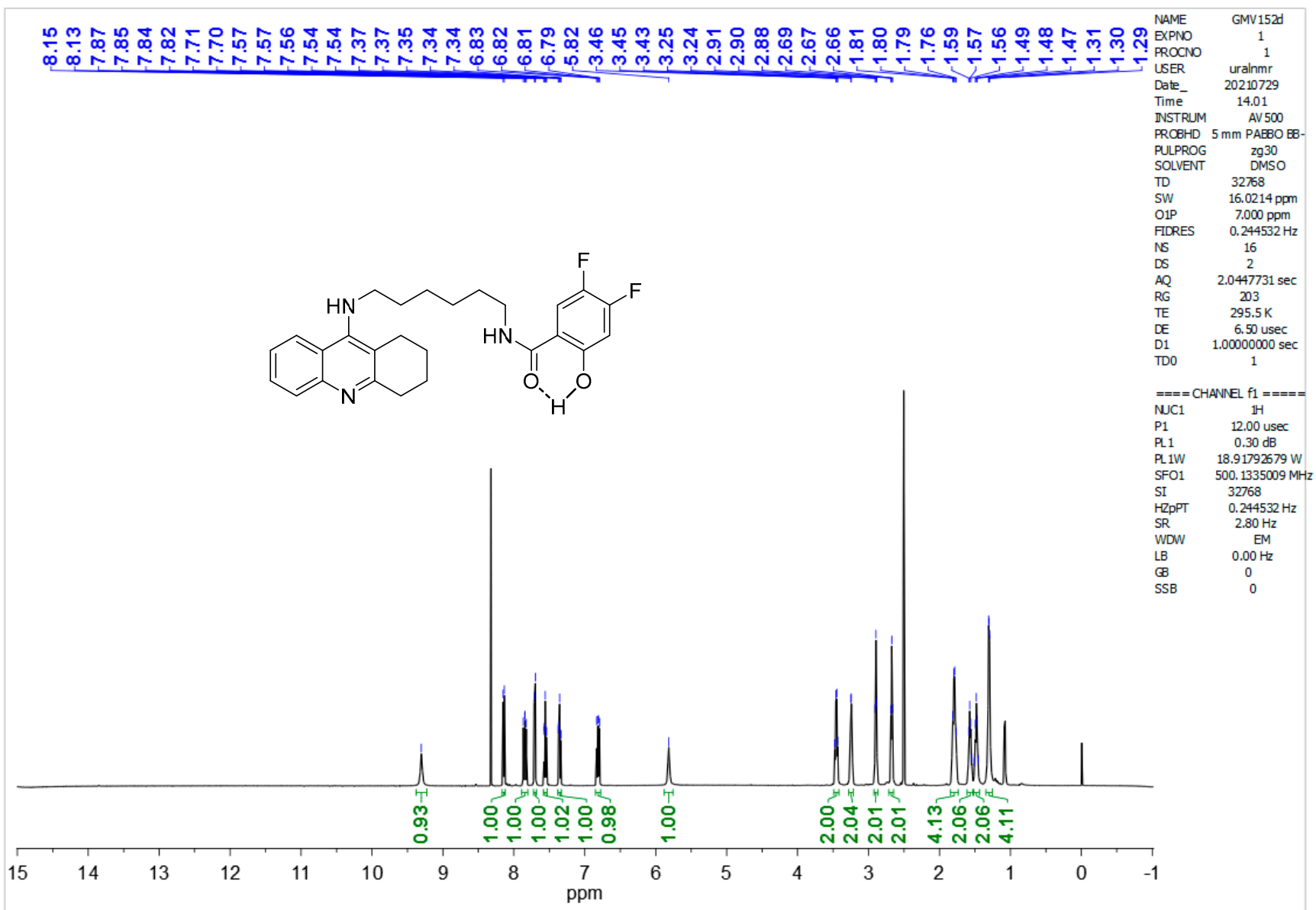
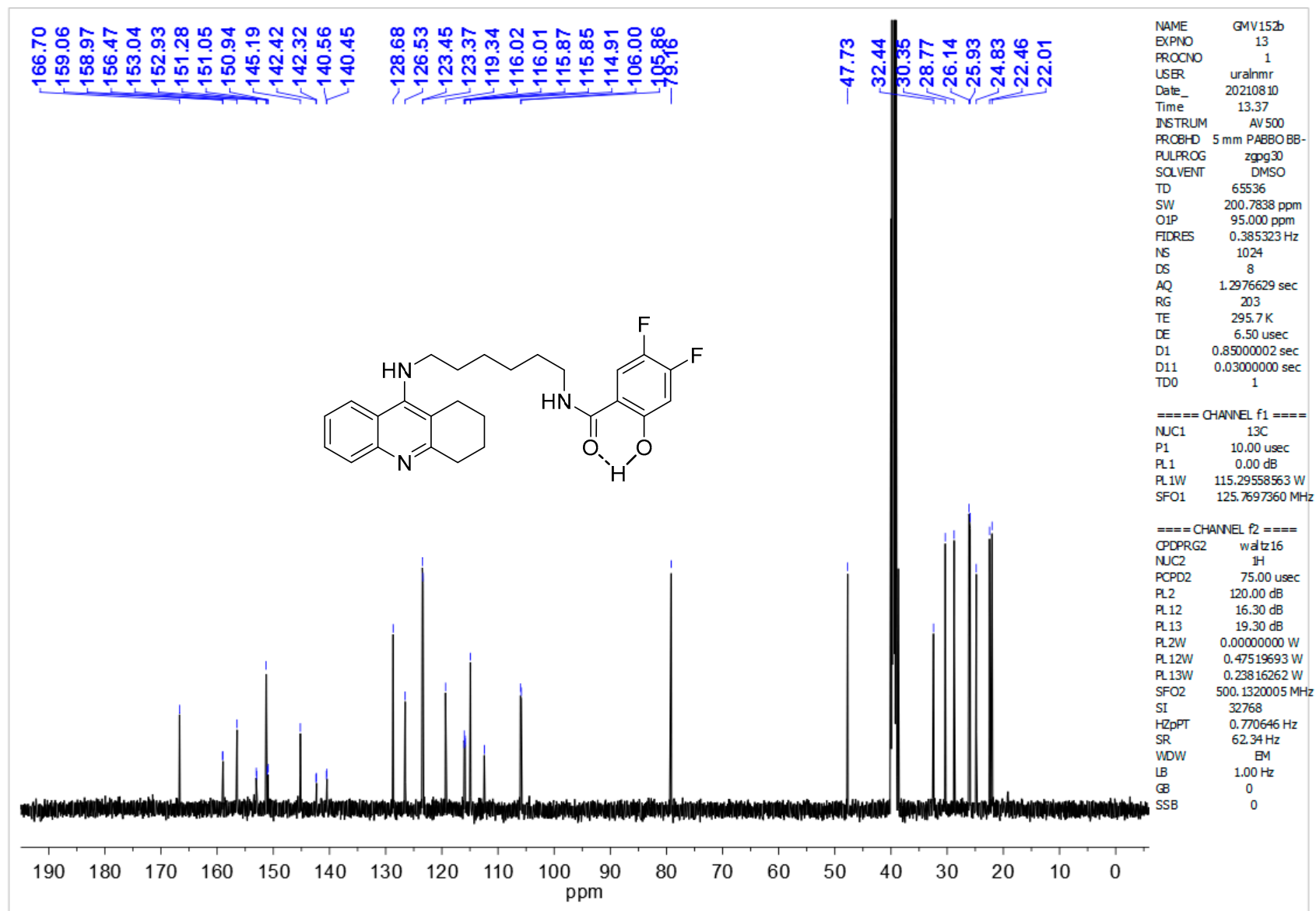


Figure S17. <sup>1</sup>H NMR spectrum of compound **7b**



**Figure S18.** <sup>13</sup>C NMR spectrum of compound **7b**

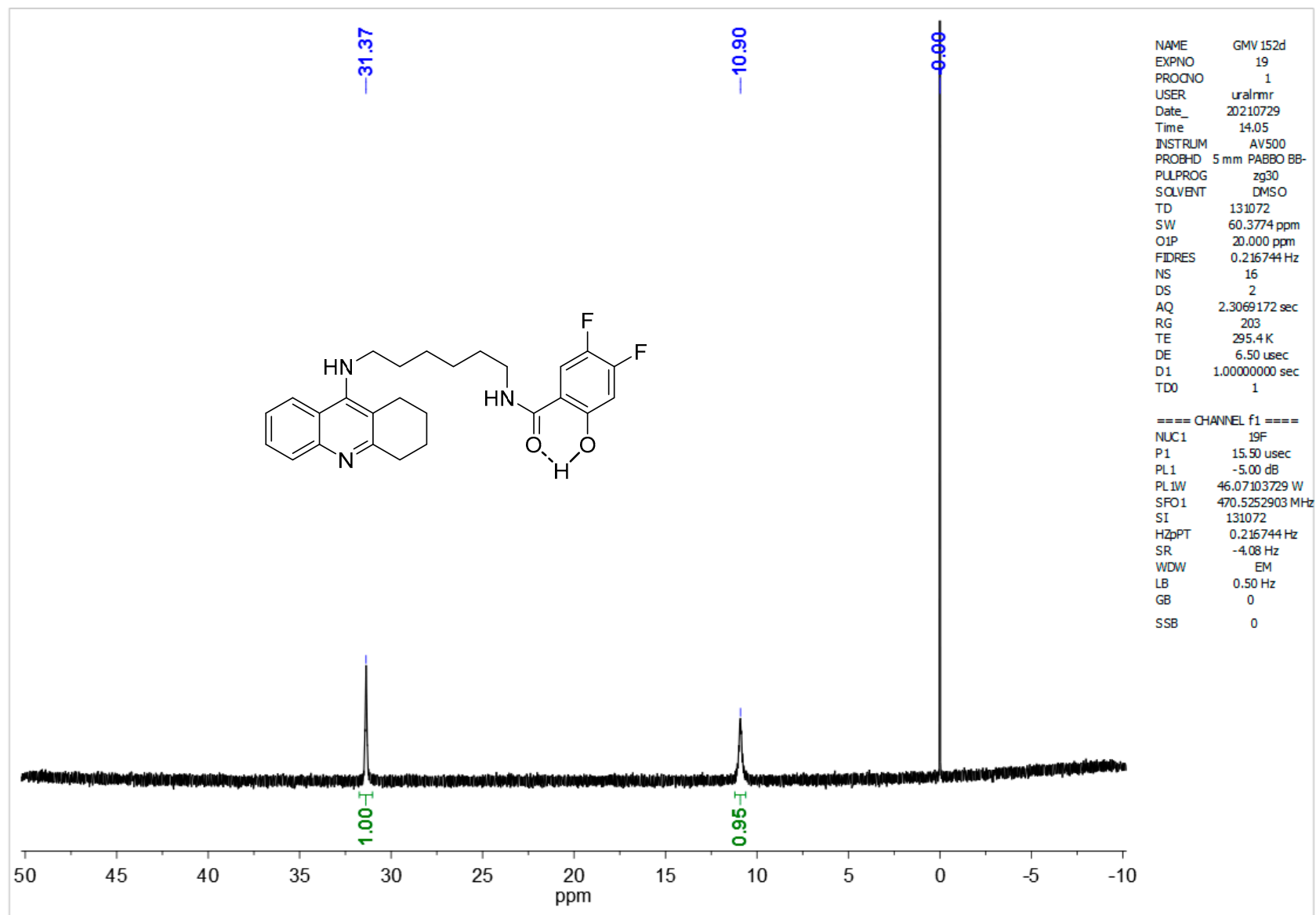


Figure S19. <sup>19</sup>F NMR spectrum of compound **7b**

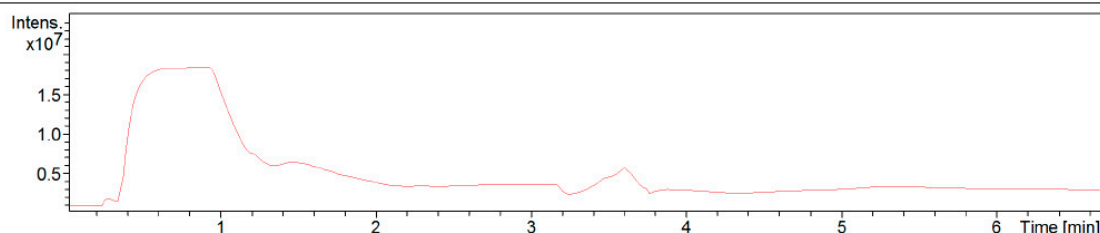
# Compound Spectrum SmartFormula Report

## Analysis Info

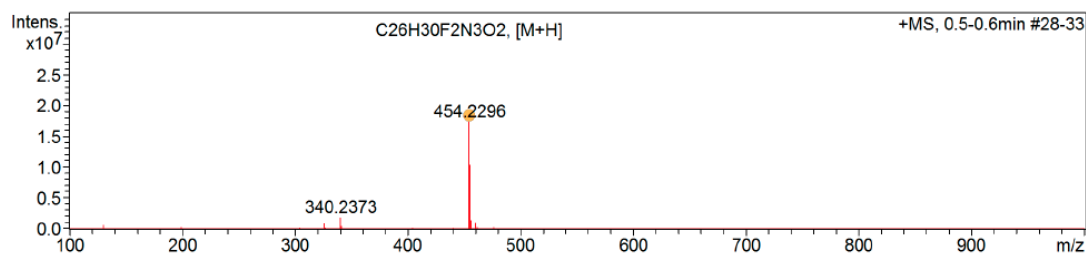
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 Sample Name 70ie5lm70ce10pps6crf300-1200tt40-110\_F3x1\_Segm1.m Instrument maXis impact 1819696.00172  
 Comment 2/09/2022: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2\*e4): 102.13 (NEt3); 132.91 (\*2-PrOH); 391.28&413.26 (DOP); 86.10, 113.13, 140.07, 149.02, 158.96, 167.03, 187.07. 194.10, 203.14, 207.17, 209.19, 214.25, 217.10, 223.21, 227.23, 237.22, 245.19, 249.22, 251.24, 255.27, 259.20, 263.23, 265.25, 273.22, 279.16, 291.27, 293.28, 304.30, 307.30, 321.31, 326.38, 332.33, 335.33, 349.35, 413.27, 1259.95, 1307.08, 1559.93: background (prev. analyzed samples and impurities); 188.09 (#6216); 588.32 (#6218); 404.23 (#6219); 376.20 (#6220); 440.21 (#6221); 460.30 (#6224)

## Acquisition Parameter

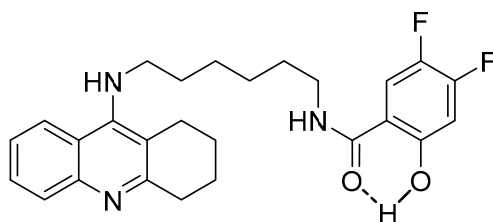
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Focus	Active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 0.5-0.6min #28-33



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
454.2296	1	C29H29FN3O	454.2289	-1.5	158.3	1	100.00	16.5	even	ok
	2	C26H30F2N3O2	454.2301	1.0	177.1	2	28.33	12.5	even	ok
	3	C20H32N5O7	454.2296	0.1	209.2	3	2.48	7.5	even	ok
	4	C14H25FN15O2	454.2294	-0.4	228.1	4	0.41	9.5	even	ok
	5	C10H30F2N11O7	454.2292	-0.8	259.8	5	0.02	0.5	even	ok



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Figure S20. HRMS spectrum of compound 7b

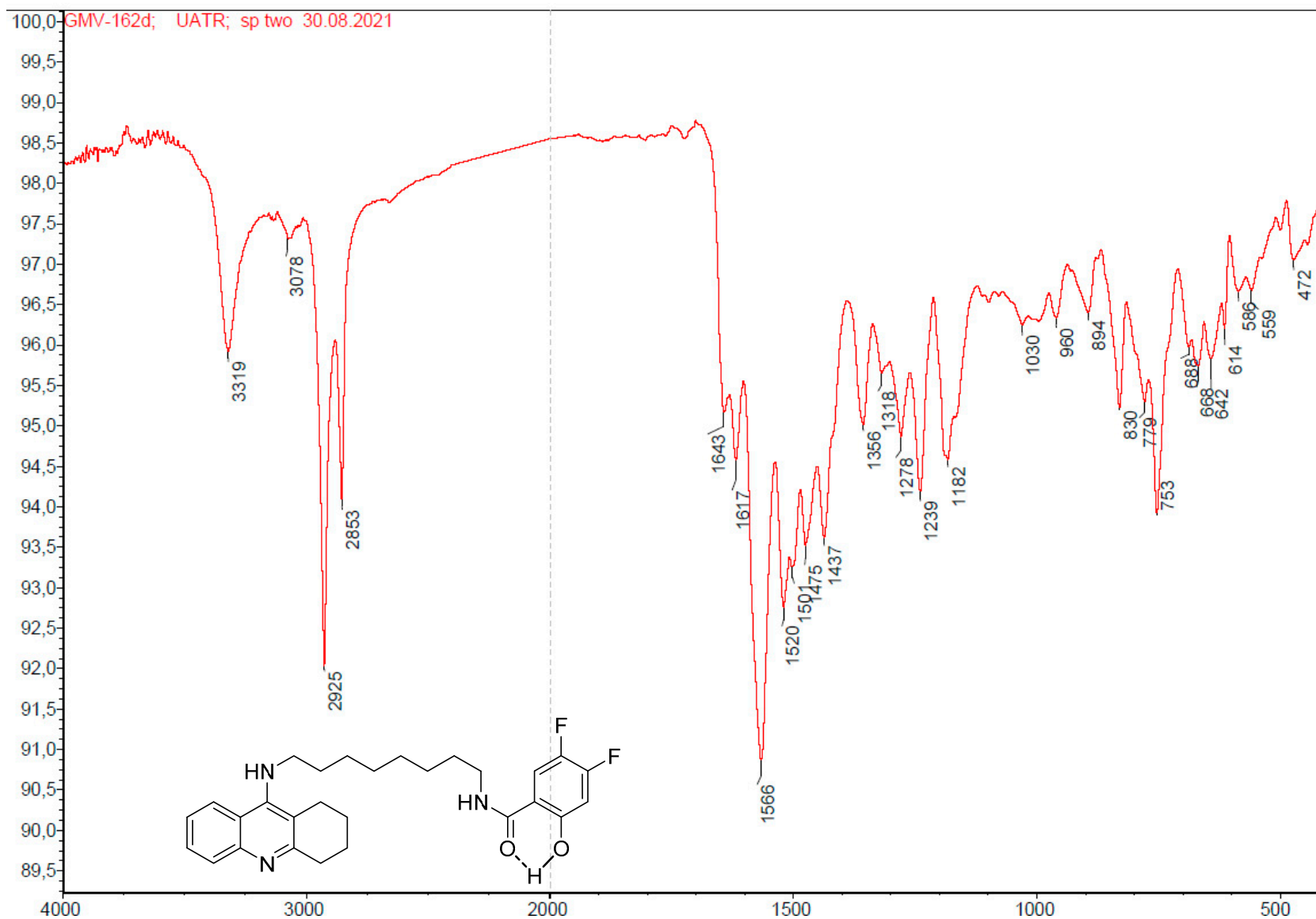


Figure S21. IR spectrum of compound 7c

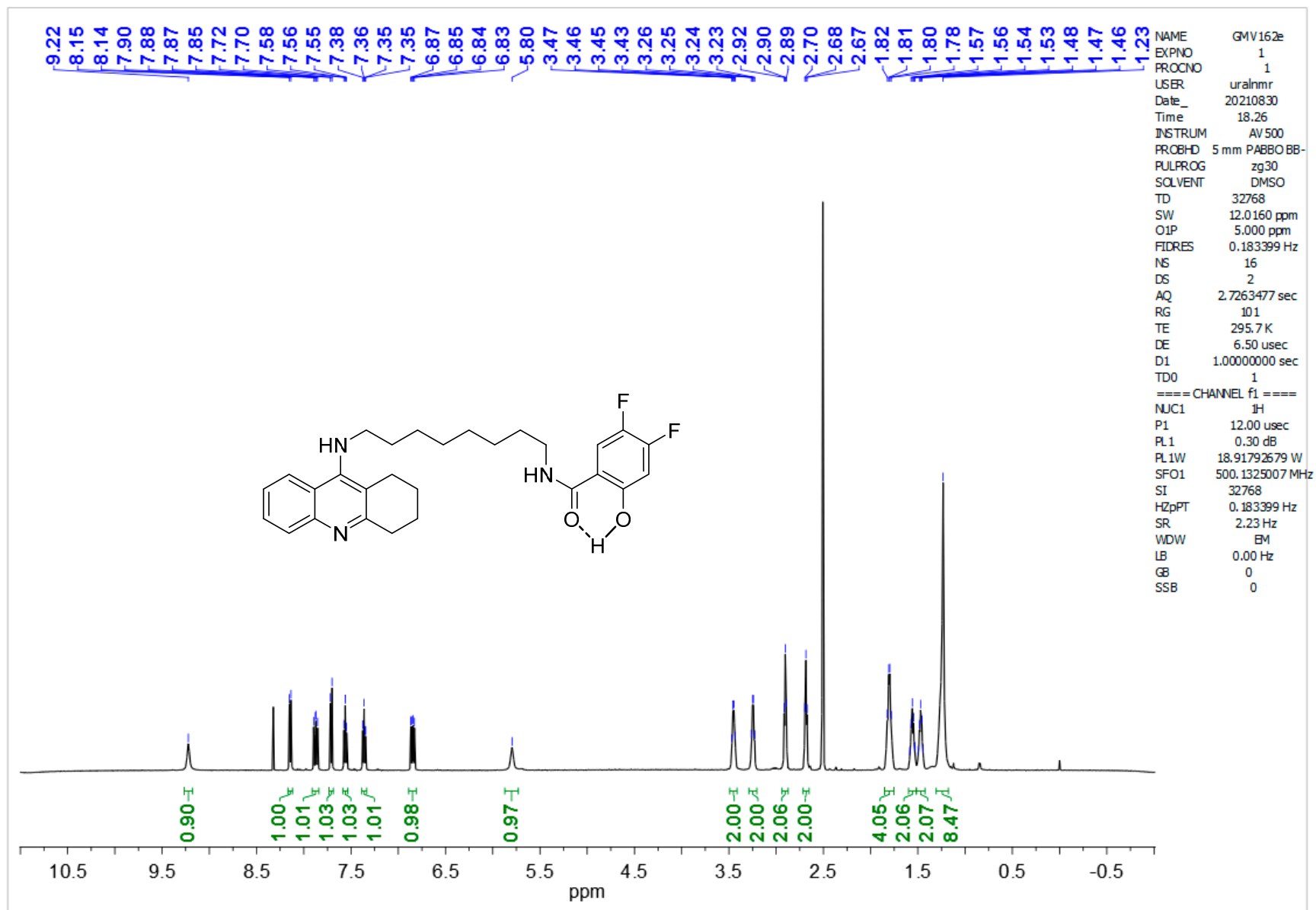


Figure S22. <sup>1</sup>H NMR spectrum of compound 7c

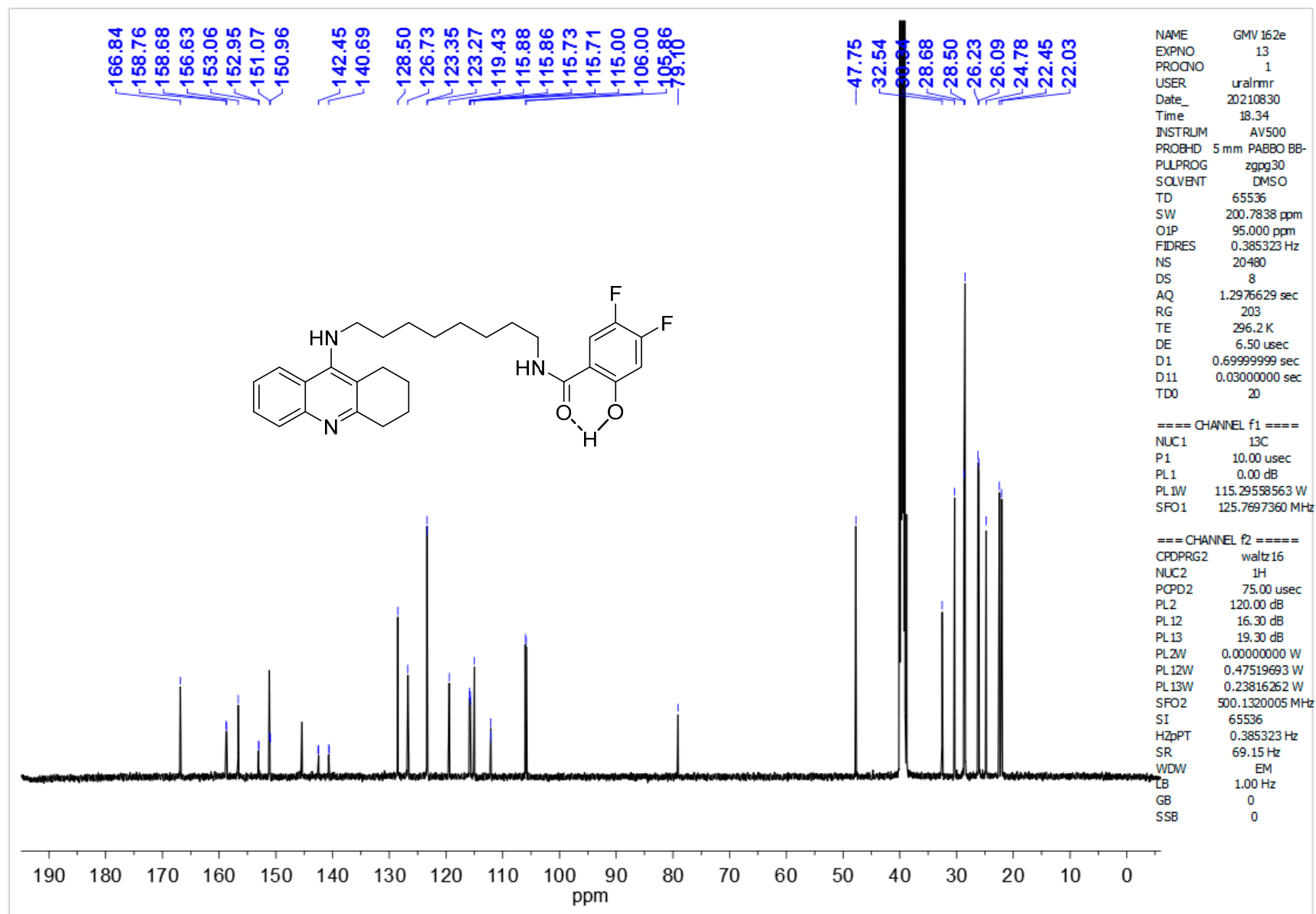


Figure S23. <sup>13</sup>C NMR spectrum of compound 7c



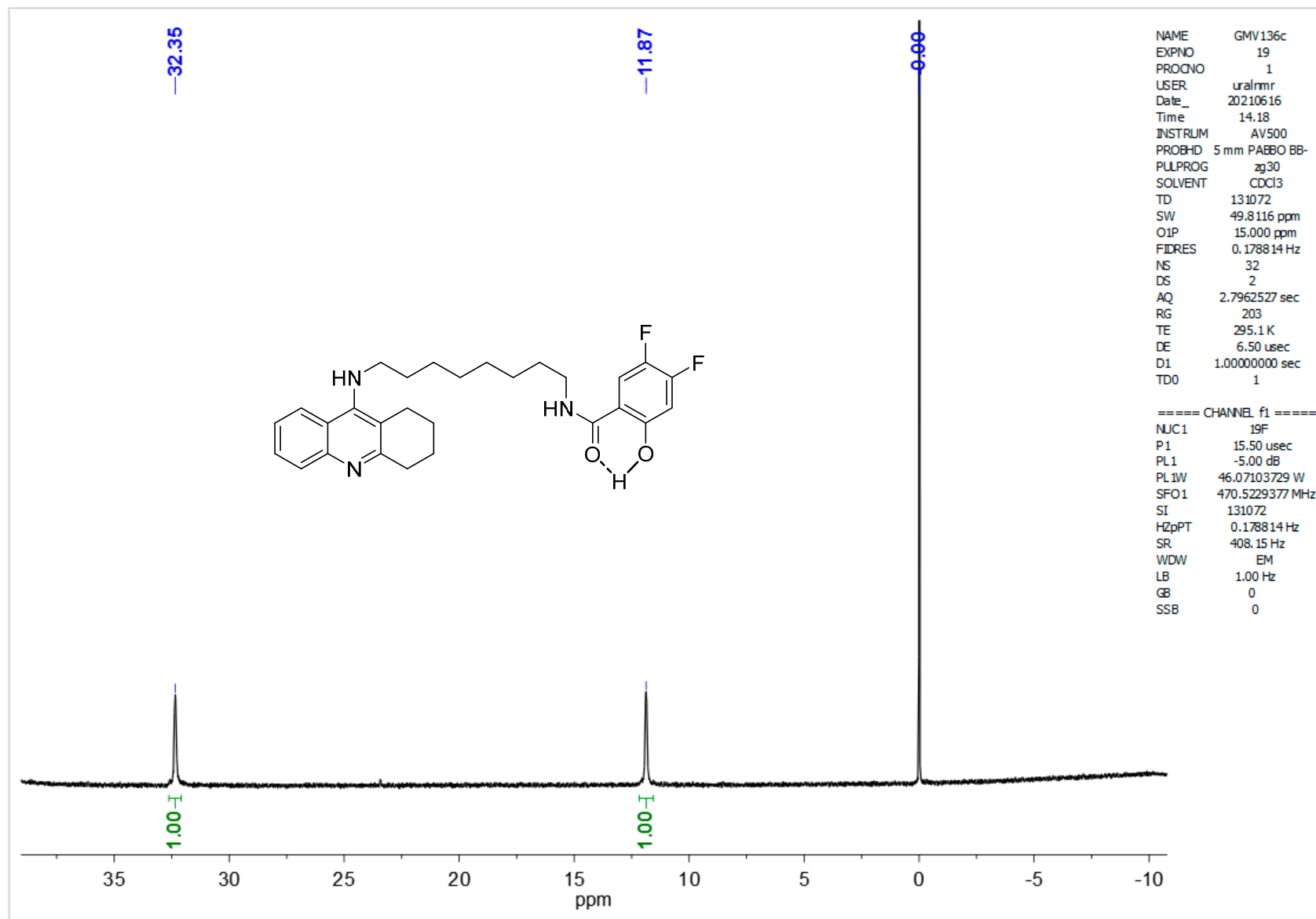


Figure S24. <sup>19</sup>F NMR spectrum of compound 7c

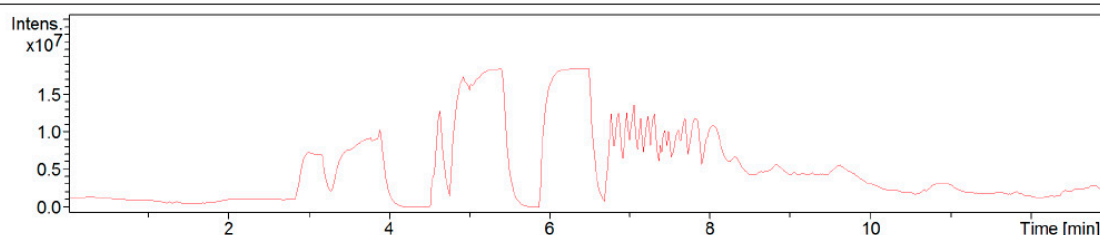
# Compound Spectrum SmartFormula Report

## Analysis Info

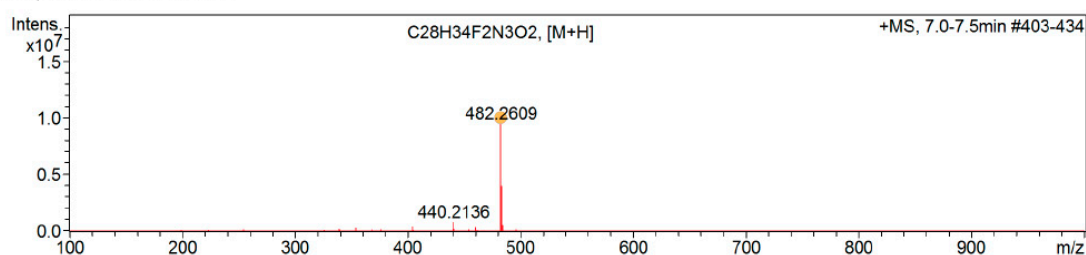
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 Sample Name 70ie5lm70ce10pps6crf300-1200tt40-110\_F3x1\_Segm1.m Instrument maXis impact 1819696.00172  
 Comment 2/09/2022: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2\*e4): 102.13 (NEt3); 132.91 (\*2-PrOH); 391.28&413.26 (DOP); 86.10, 113.13, 140.07, 149.02, 158.96, 167.03, 187.07. 194.10, 203.14, 207.17, 209.19, 214.25, 217.10, 223.21, 227.23, 237.22, 245.19, 249.22, 251.24, 255.27, 259.20, 263.23, 265.25, 273.22, 279.16, 291.27, 293.28, 304.30, 307.30, 321.31, 326.38, 332.33, 335.33, 349.35, 413.27, 1259.95, 1307.08, 1559.93: background (prev. analyzed samples and impurities); 188.09 (#6216); 588.32 (#6218); 404.23 (#6219); 376.20 (#6220); 440.21 (#6221); 460.30 (#6224)

## Acquisition Parameter

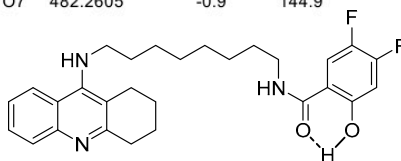
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Scan End	1600 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 7.0-7.5min #403-434



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdB	e <sup>-</sup>	Conf	N-Rule
482.2609	1	C31H33FN3O	482.2602	-1.5	37.9	1	100.00	16.5	even		ok
	2	C28H34F2N3O2	482.2614	0.9	62.1	2	41.94	12.5	even		ok
	3	C23H32N9O3	482.2623	2.7	80.8	3	12.69	12.5	even		ok
	4	C21H40NO11	482.2596	-2.8	93.3	4	9.61	2.5	even		ok
	5	C22H36N5O7	482.2609	-0.1	94.3	5	13.78	7.5	even		ok
	6	C21H31F3N9O	482.2598	-2.3	94.3	6	7.92	9.5	even		ok
	7	C19H28N15O	482.2596	-2.8	94.4	7	6.81	13.5	even		ok
	8	C19H37FN5O8	482.2621	2.3	112.9	8	3.23	3.5	even		ok
	9	C16H29FN15O2	482.2607	-0.5	113.1	9	5.04	9.5	even		ok
	10	C13H30F2N15O3	482.2619	1.9	131.7	10	1.28	5.5	even		ok
	11	C12H34F2N11O7	482.2605	-0.9	144.9	11	0.73	0.5	even		ok



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Figure S25. HMRS spectrum of compound 7c

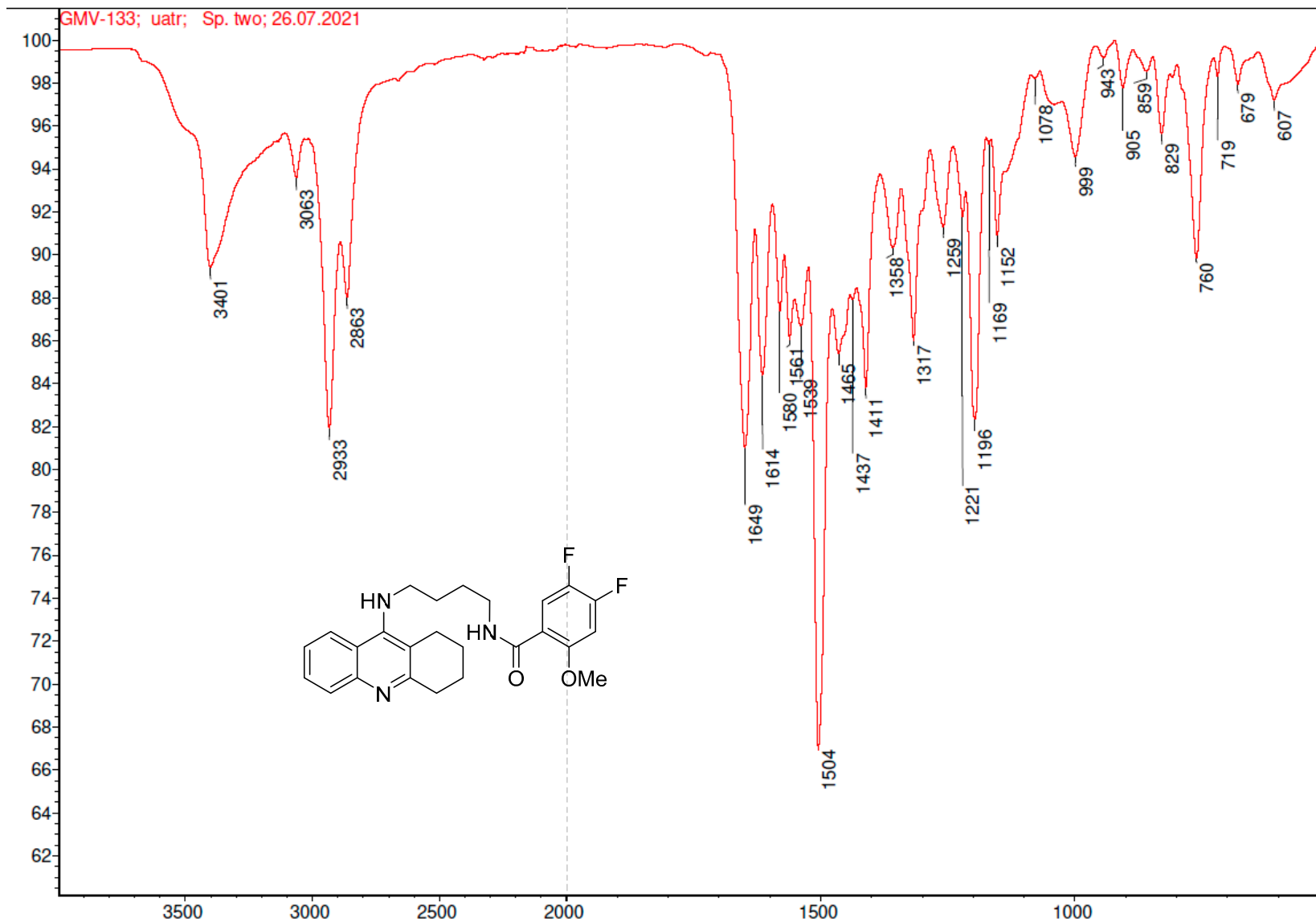


Figure S26. IR spectrum of compound 8a

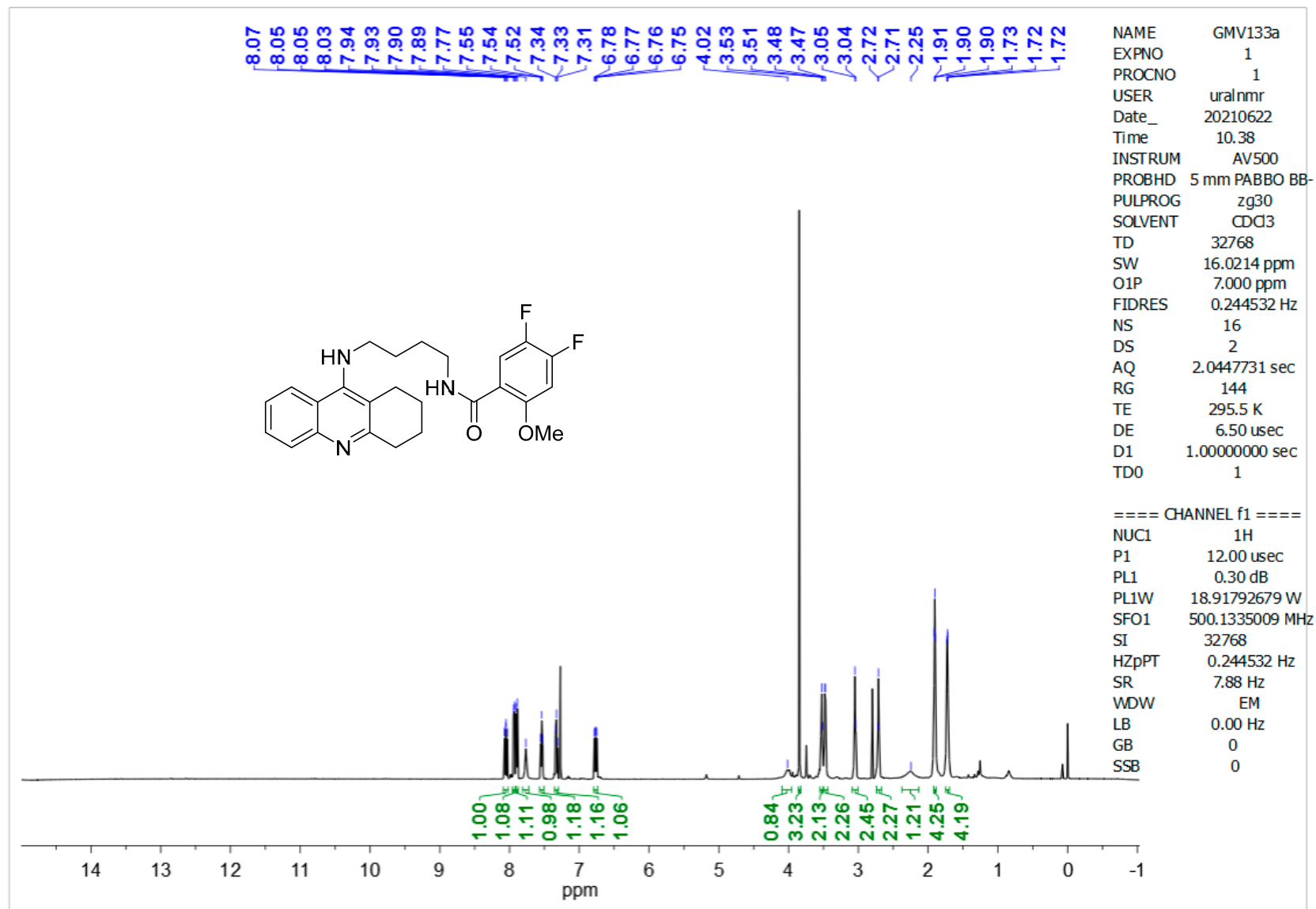


Figure S26. <sup>1</sup>H NMR spectrum of compound 8a

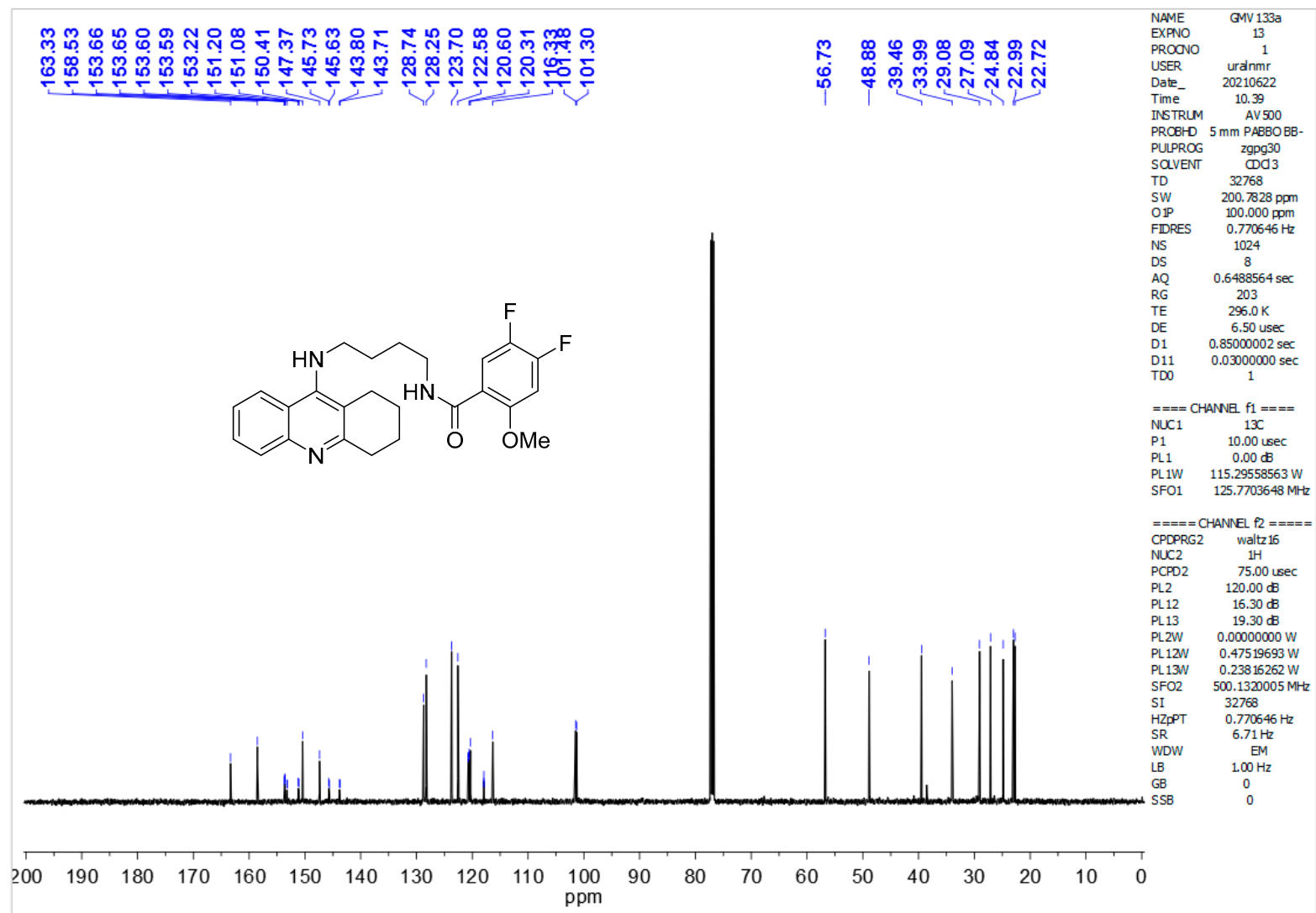


Figure S27. <sup>13</sup>C NMR spectrum of compound 8a

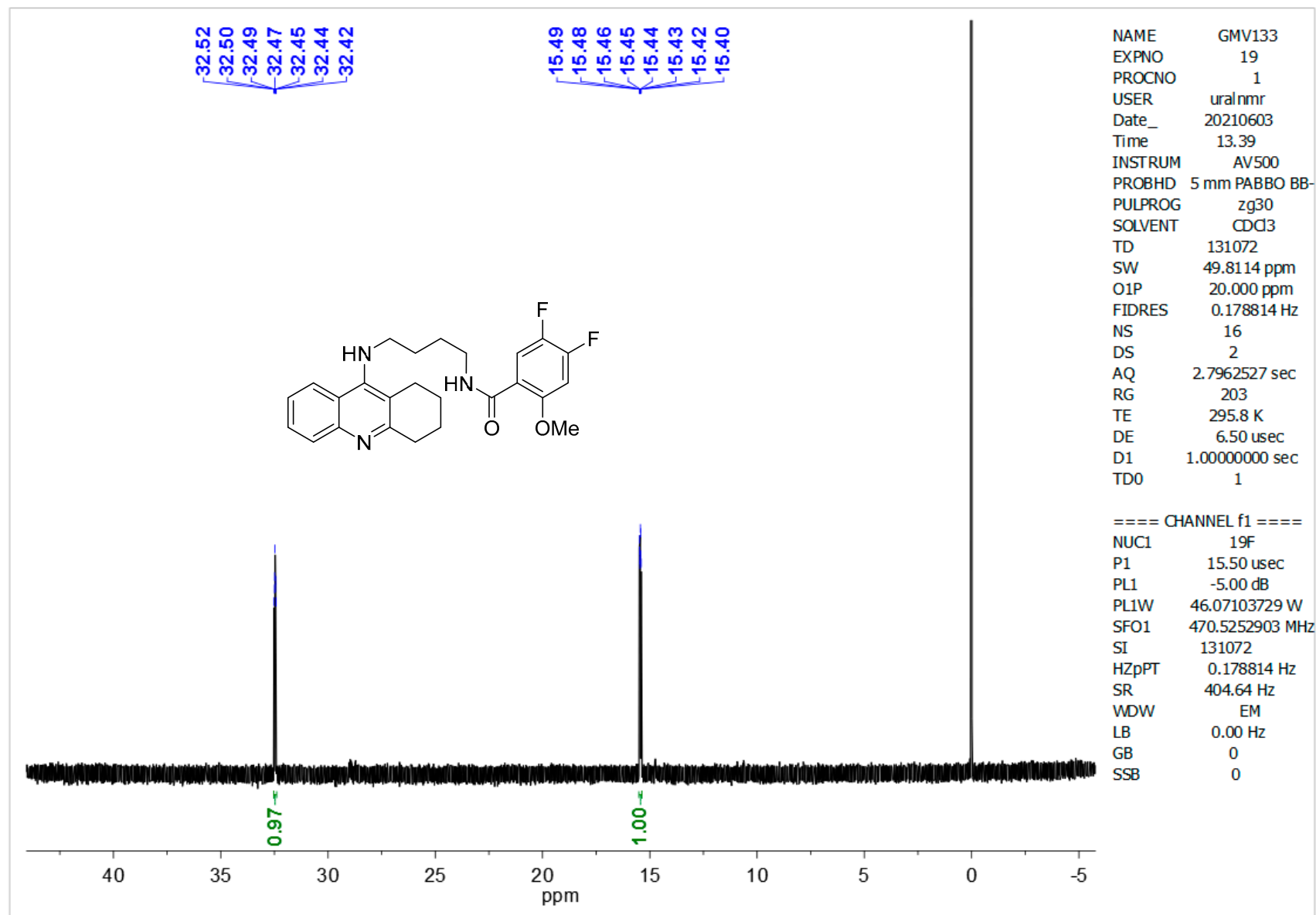


Figure S28. <sup>19</sup>F NMR spectrum of compound 8a

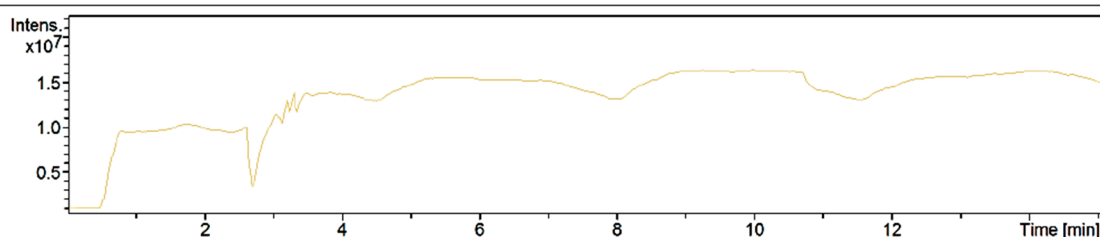
# Compound Spectrum SmartFormula Report

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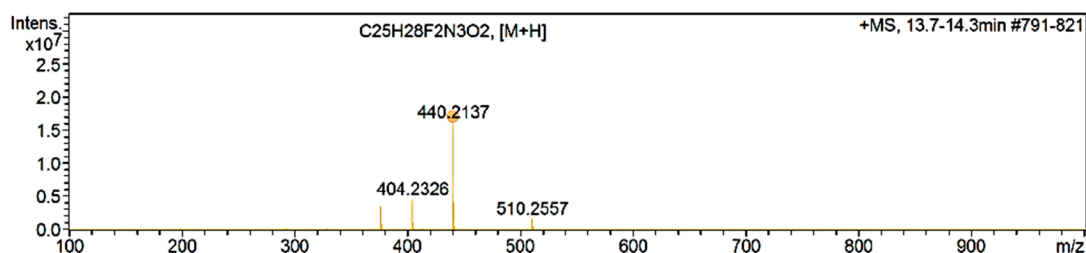
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 Comment 22/09/2022: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2\*e4): 102.13 (NEt3); 132.91 (\*2-PrOH); 391.28&413.26 (DOP); 86.10, 113.13, 140.07, 149.02, 158.96, 167.03, 187.07, 194.10, 203.14, 207.17, 209.19, 214.25, 217.10, 223.21, 227.23, 237.22, 245.19, 249.22, 251.24, 255.27, 259.20, 263.23, 265.25, 273.22, 279.16, 291.27, 293.28, 304.30, 307.30, 321.31, 326.38, 332.33, 335.33, 349.35, 413.27, 1259.95, 1307.08, 1559.93: background (prev. analyzed samples and impurities); 188.09 (#6216); 588.32 (#6218); 404.23 (#6219); 376.20 (#6220)

## Acquisition Parameter

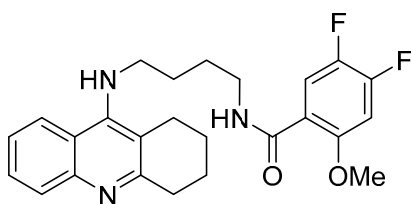
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Scan End	1600 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 13.7-14.3min #791-821



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	2	C19H30N5O7	440.2140	0.7	18.8	2	100.00	7.5	even	ok
	3	C28H27FN3O	440.2133	-0.9	33.8	3	67.65	16.5	even	ok



GMV-133.22i-C.EP180.6221\_22i1440.d

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Figure S29. HRMS spectrum of compound 8a

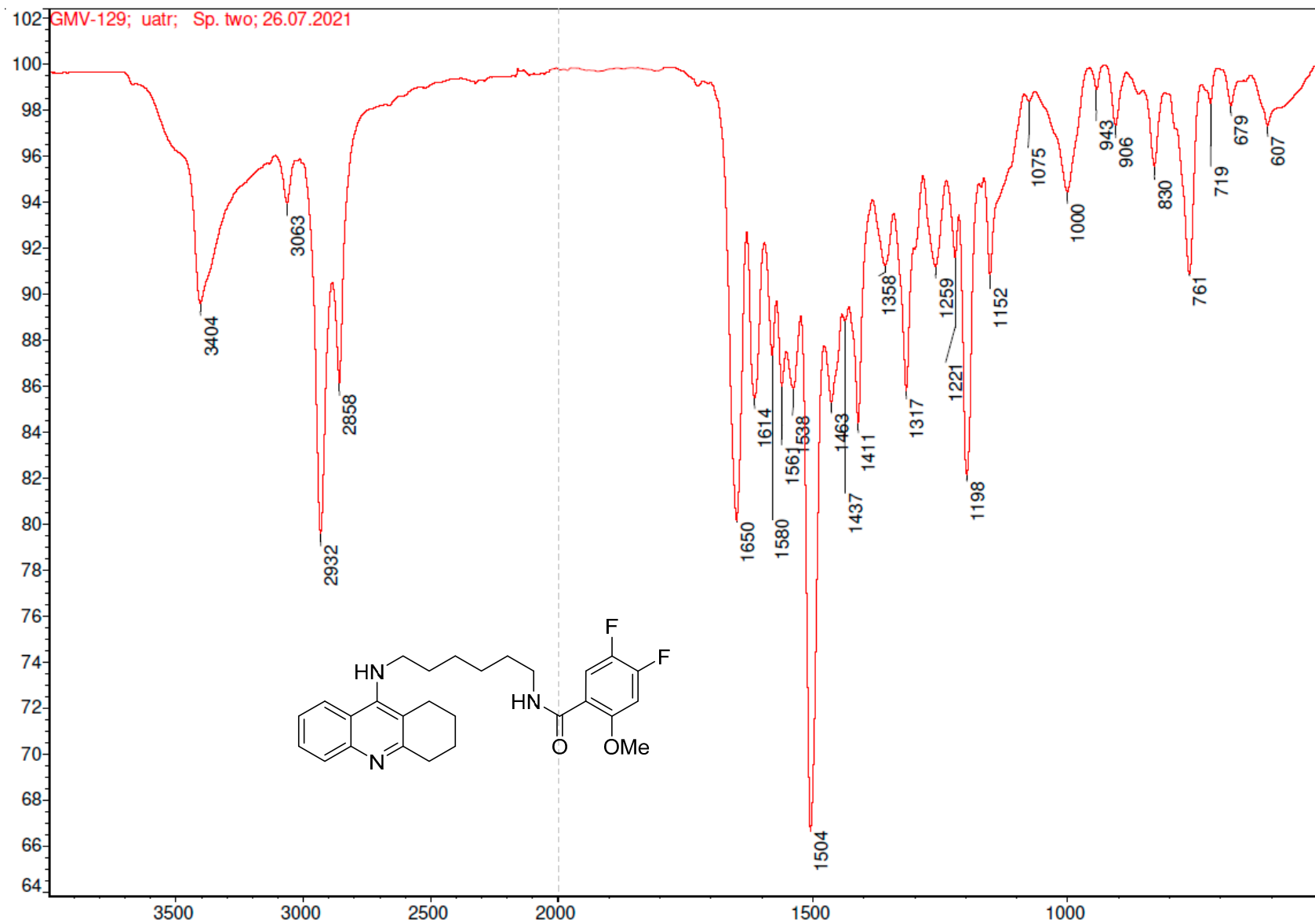


Figure S30. IR spectrum of compound 8b



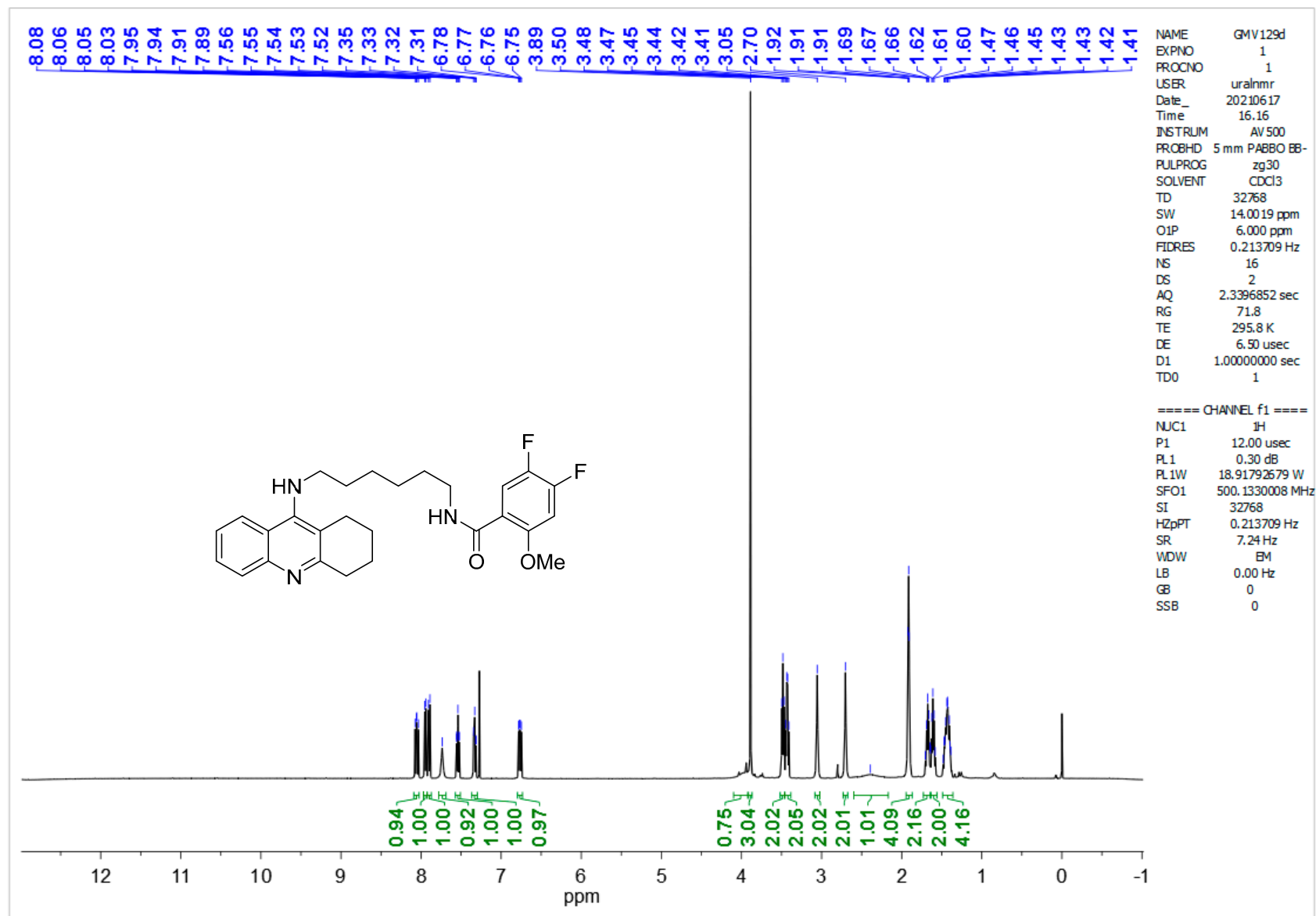


Figure S31. <sup>1</sup>H NMR spectrum of compound 8b

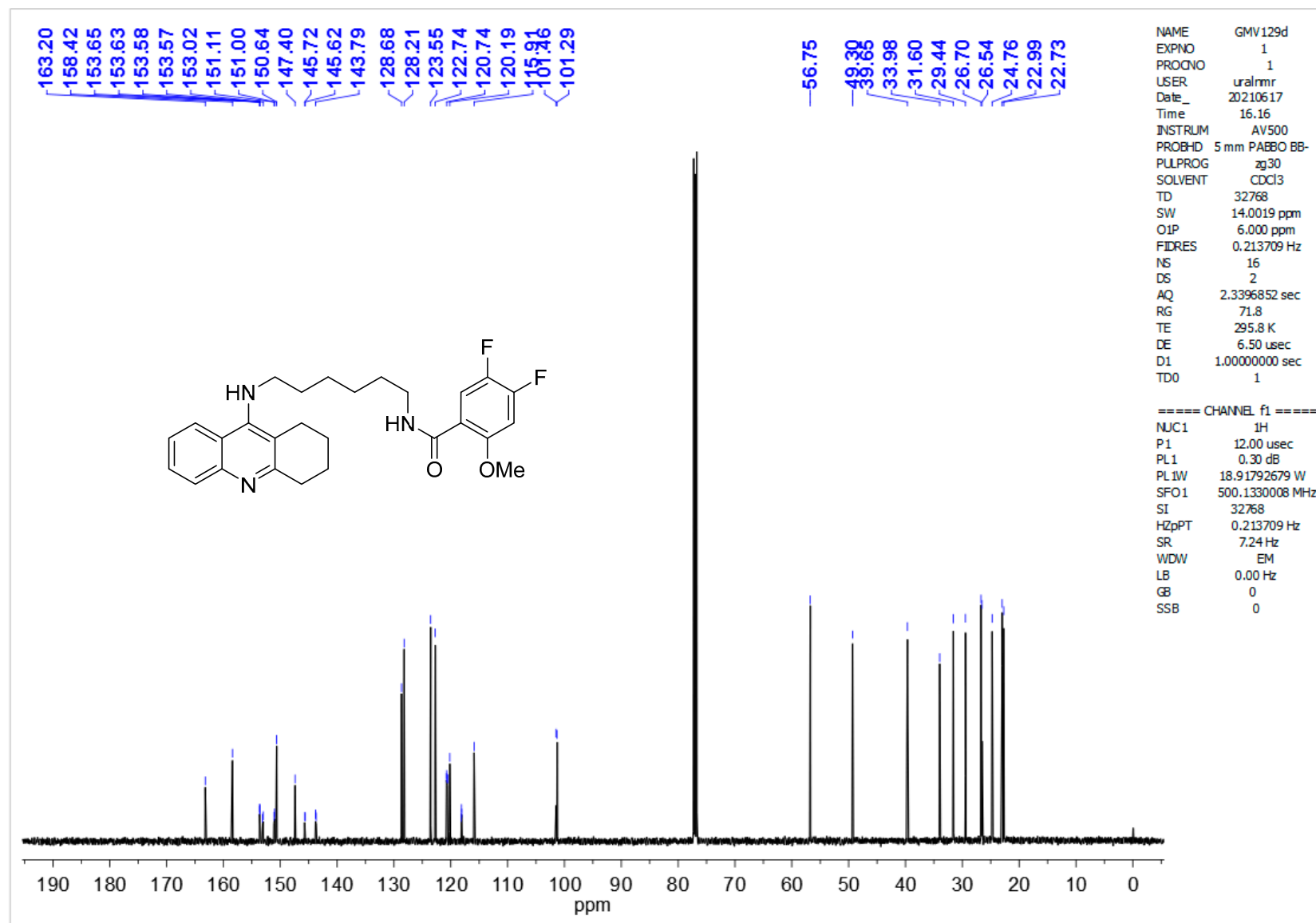
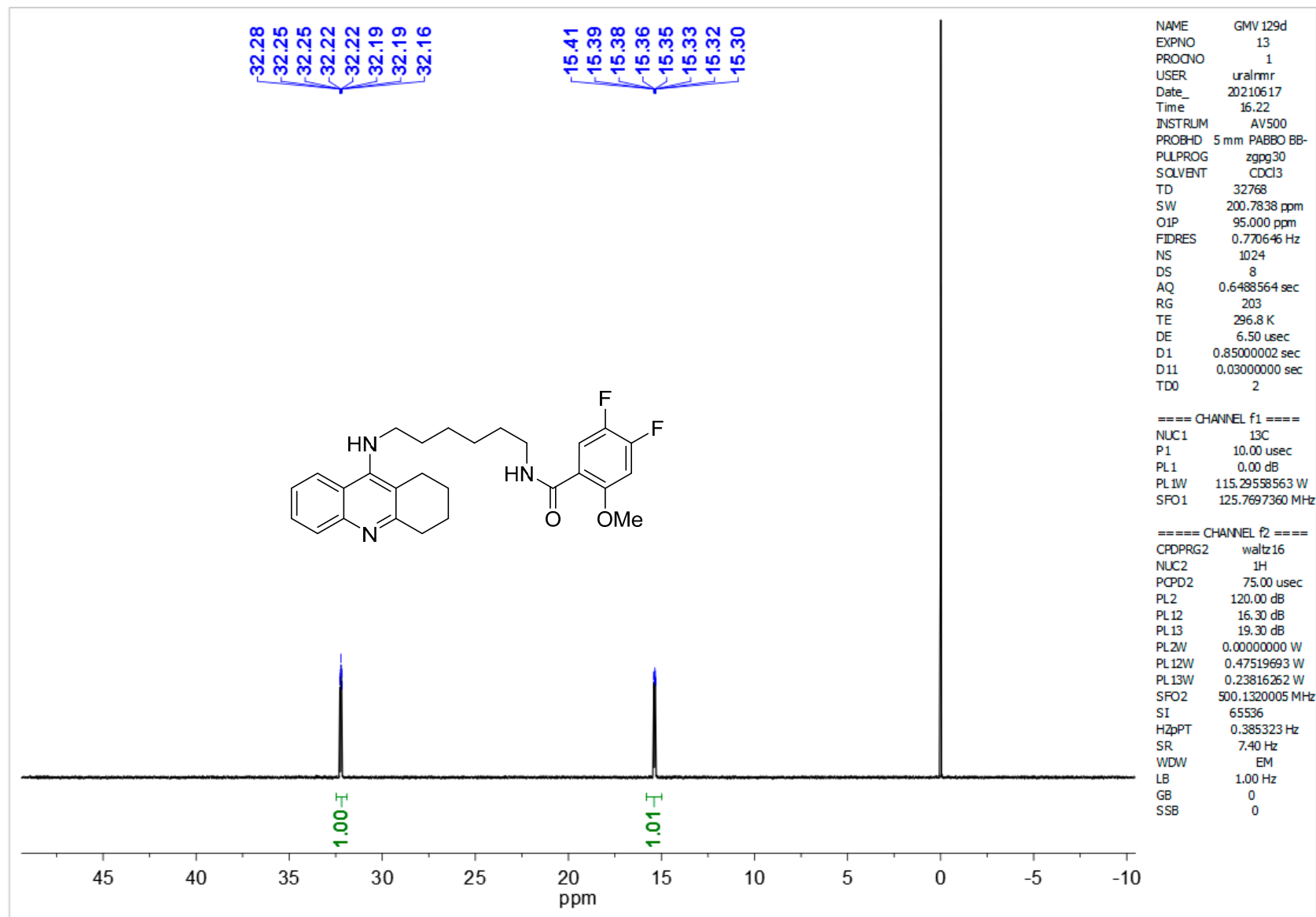


Figure S33.  $^{13}\text{C}$  NMR spectrum of compound **8b**



**Figure S34.**  $^{19}\text{F}$  NMR spectrum of compound **8b**

# Compound Spectrum SmartFormula Report

## Analysis Info

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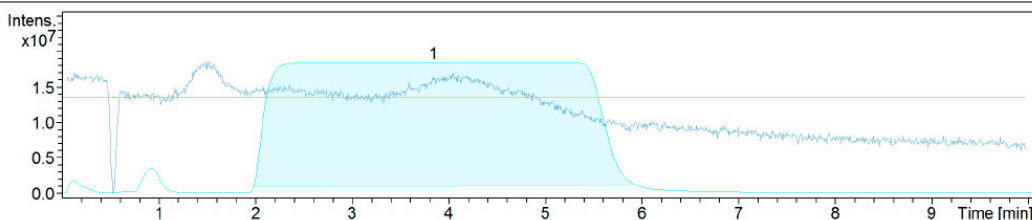
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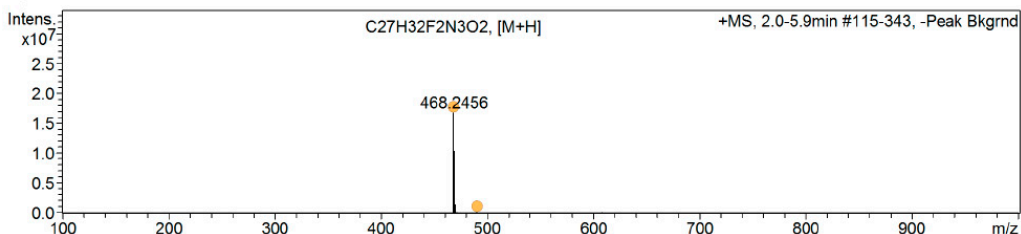
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Scan End	1300 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



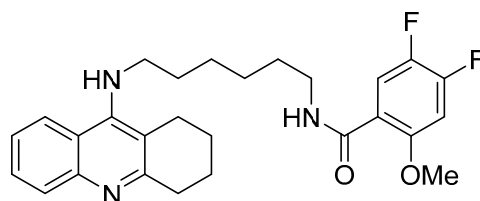
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## Cmpd 1, 3.8 min



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
468.2456	1	C27H32F2N3O2	468.2457	0.3	181.3	1	100.00	12.5	even	ok
	2	C21H34N5O7	468.2453	-0.6	213.4	2	6.39	7.5	even	ok
	3	C18H35FN5O8	468.2464	1.8	232.1	3	0.85	3.5	even	ok
	4	C15H27FN15O2	468.2451	-1.1	232.4	4	0.99	9.5	even	ok
	5	C12H28F2N15O3	468.2462	1.4	251.0	5	0.14	5.5	even	ok
	6	C11H32F2N11O7	468.2449	-1.5	264.2	6	0.03	0.5	even	ok
	1	C17H32FN9NaO4	468.2453	-0.5	231.5	1	100.00	5.5	even	ok
	2	C14H33F2N9NaO5	468.2465	2.0	250.1	2	10.94	1.5	even	ok
490.2261	1	C15H26FN15NaO2	490.2270	2.0	39.2	1	100.00	9.5	even	ok
	1	C11H31F2N11NaO7	490.2268	1.6	70.2	1	100.00	0.5	even	ok

## +MS, 6.1-6.5min #352-377



GMV-129.25F-C.6122\_EP\_22\_01\_1072.d

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Figure S35. HRMS spectrum of compound 8b

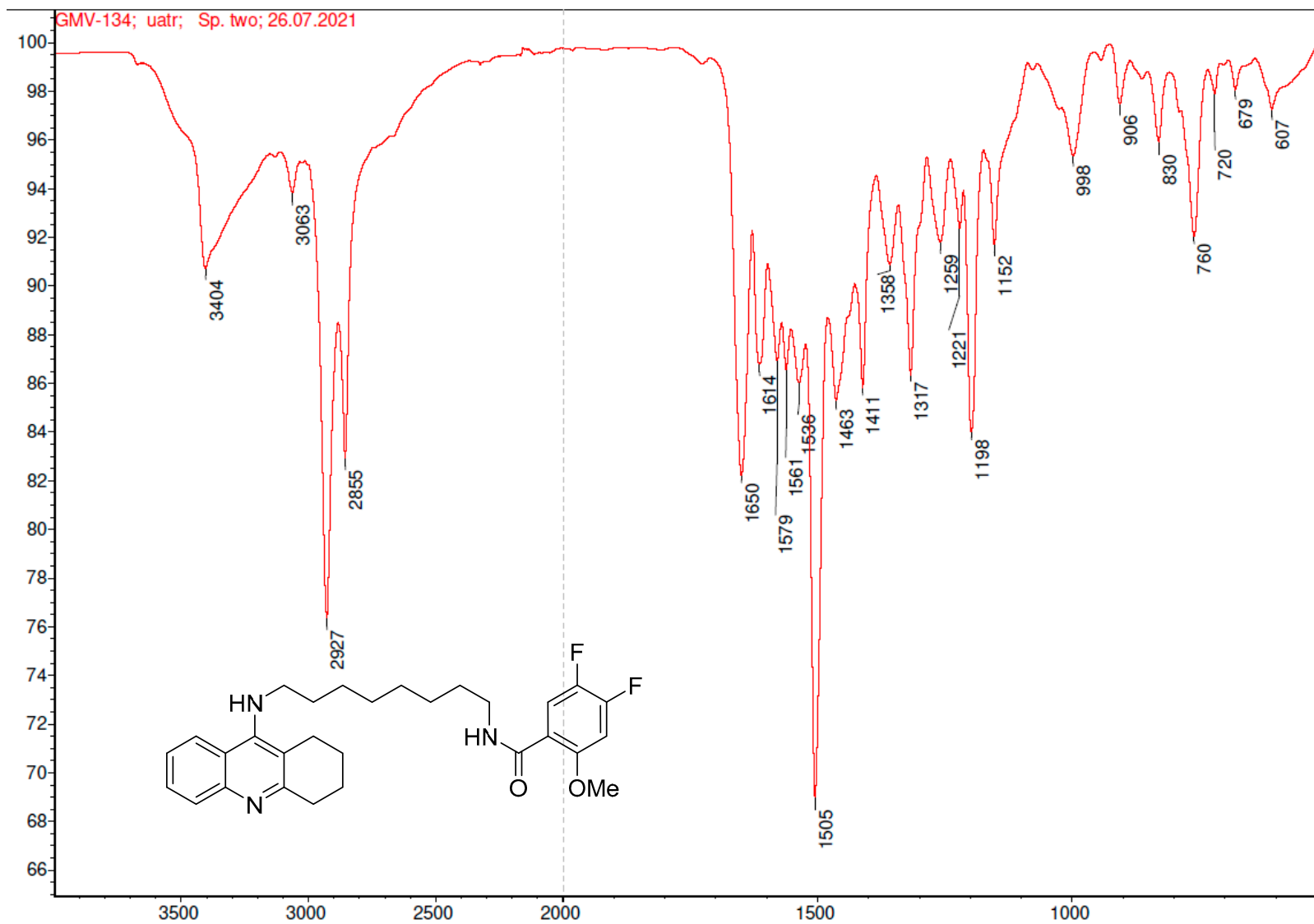


Figure S36. IR spectrum of compound 8c

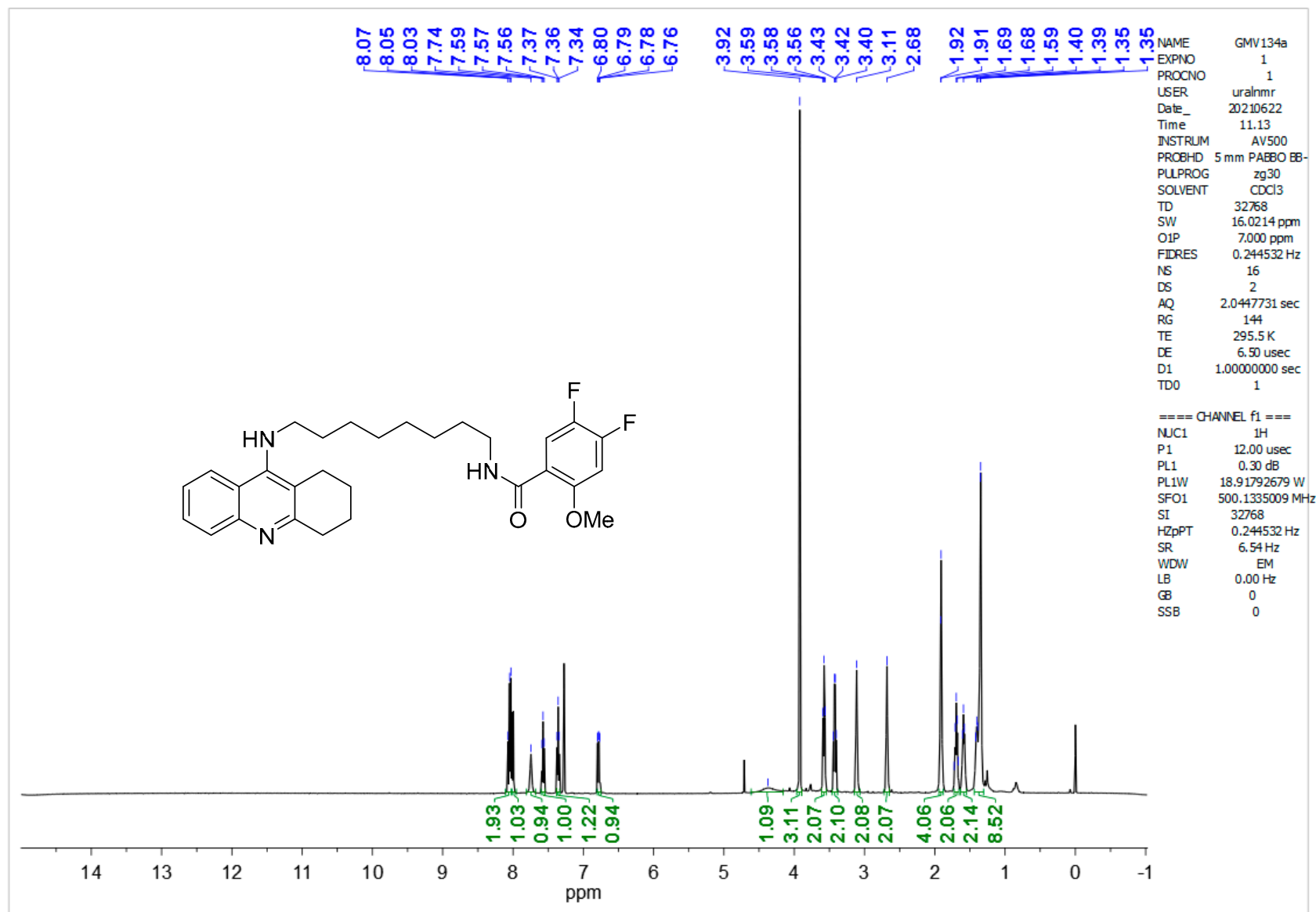


Figure S37. <sup>1</sup>H NMR spectrum of compound 8c

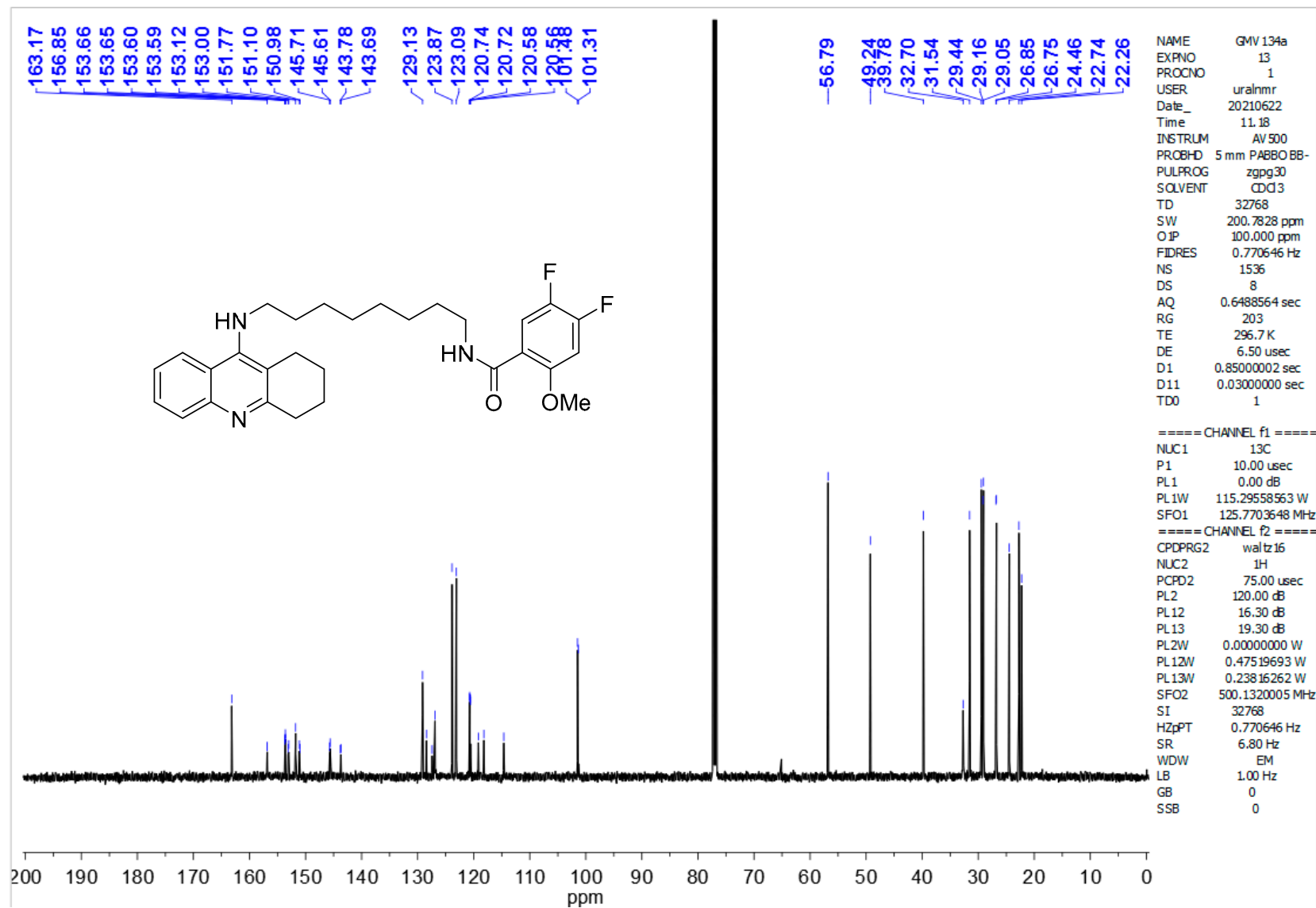


Figure S38. <sup>13</sup>C NMR spectrum of compound 8c

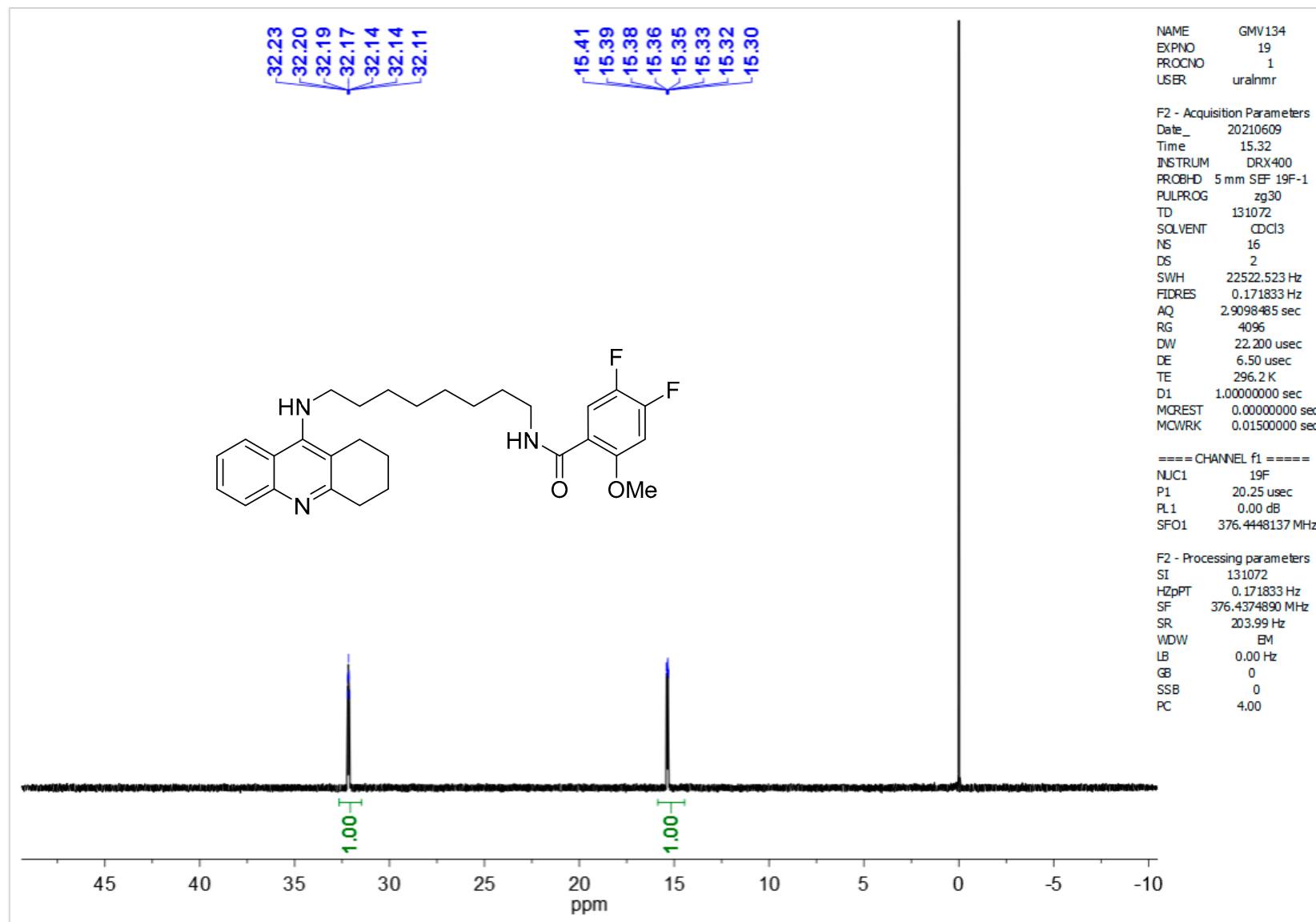


Figure S39. <sup>19</sup>F NMR spectrum of compound 8c



# Compound Spectrum SmartFormula Report

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Sample Name

Instrument maXis impact

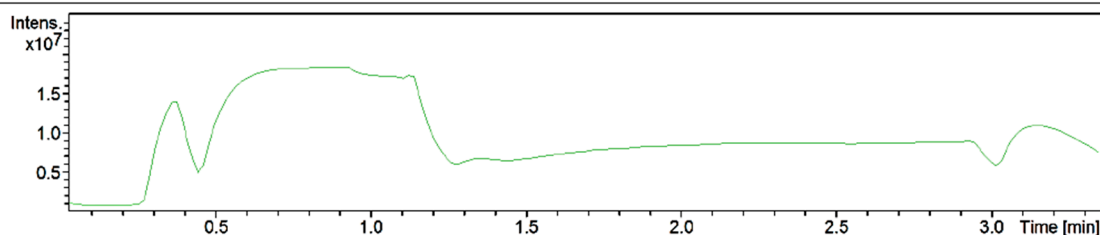
Comment

2/09/2022: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2\*e4): 102.13 (NEt3); 132.91 (\*2-PrOH); 391.28&413.26 (DOP); 86.10, 113.13, 140.07, 149.02, 158.96, 167.03, 187.07, 194.10, 203.14, 207.17, 209.19, 214.25, 217.10, 223.21, 227.23, 237.22, 245.19, 249.22, 251.24, 255.27, 259.20, 263.23, 265.25, 273.22, 279.16, 291.27, 293.28, 304.30, 307.30, 321.31, 326.38, 332.33, 335.33, 349.35, 413.27, 1259.95, 1307.08, 1559.93: background (prev. analyzed samples and impurities); 188.09 (#6216); 588.32 (#6218); 404.23 (#6219); 376.20 (#6220); 440.21 (#6221)

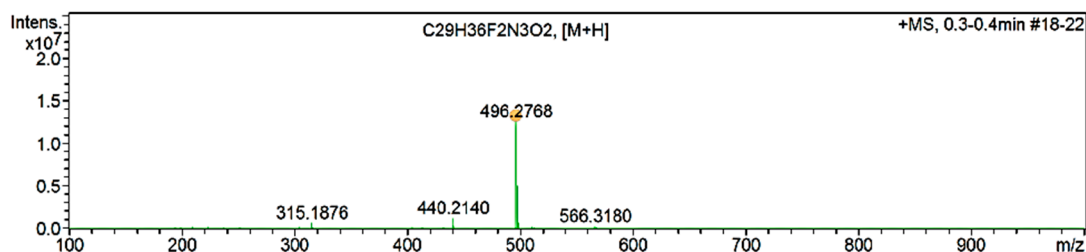
## Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

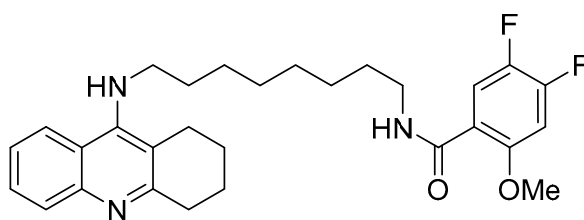
1819696.00172



## +MS, 0.3-0.4min #18-22



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
496.2768	1	C32H35FN3O	496.2759	-1.9	21.6	1	100.00	16.5	even	ok
	2	C29H36F2N3O2	496.2770	0.4	42.7	2	64.33	12.5	even	ok



GMV-134.22i-C.EP180.6223\_23i1045.d

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Figure S40. HRMS spectrum of compound 8c

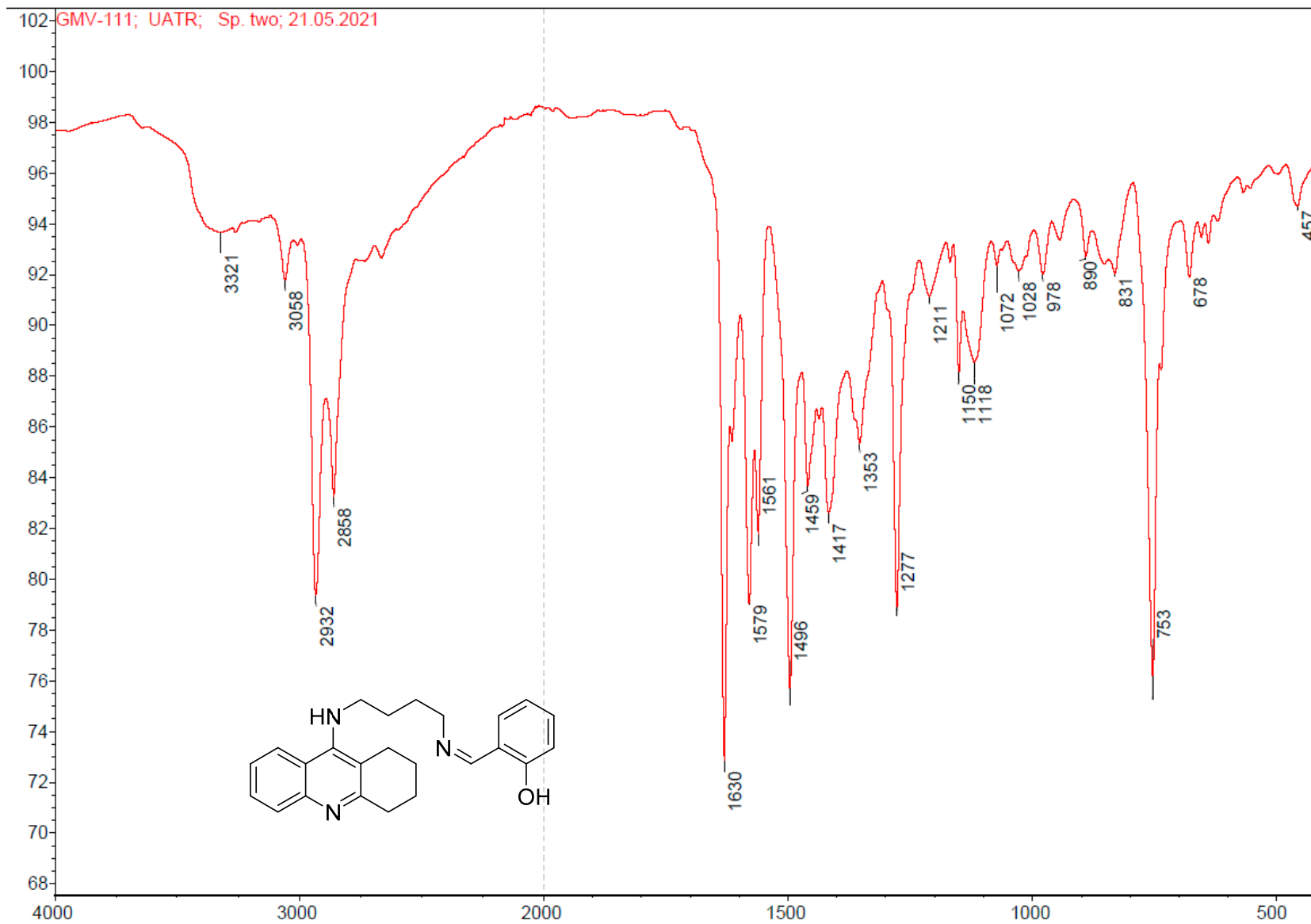


Figure S41. IR spectrum of compound 10a

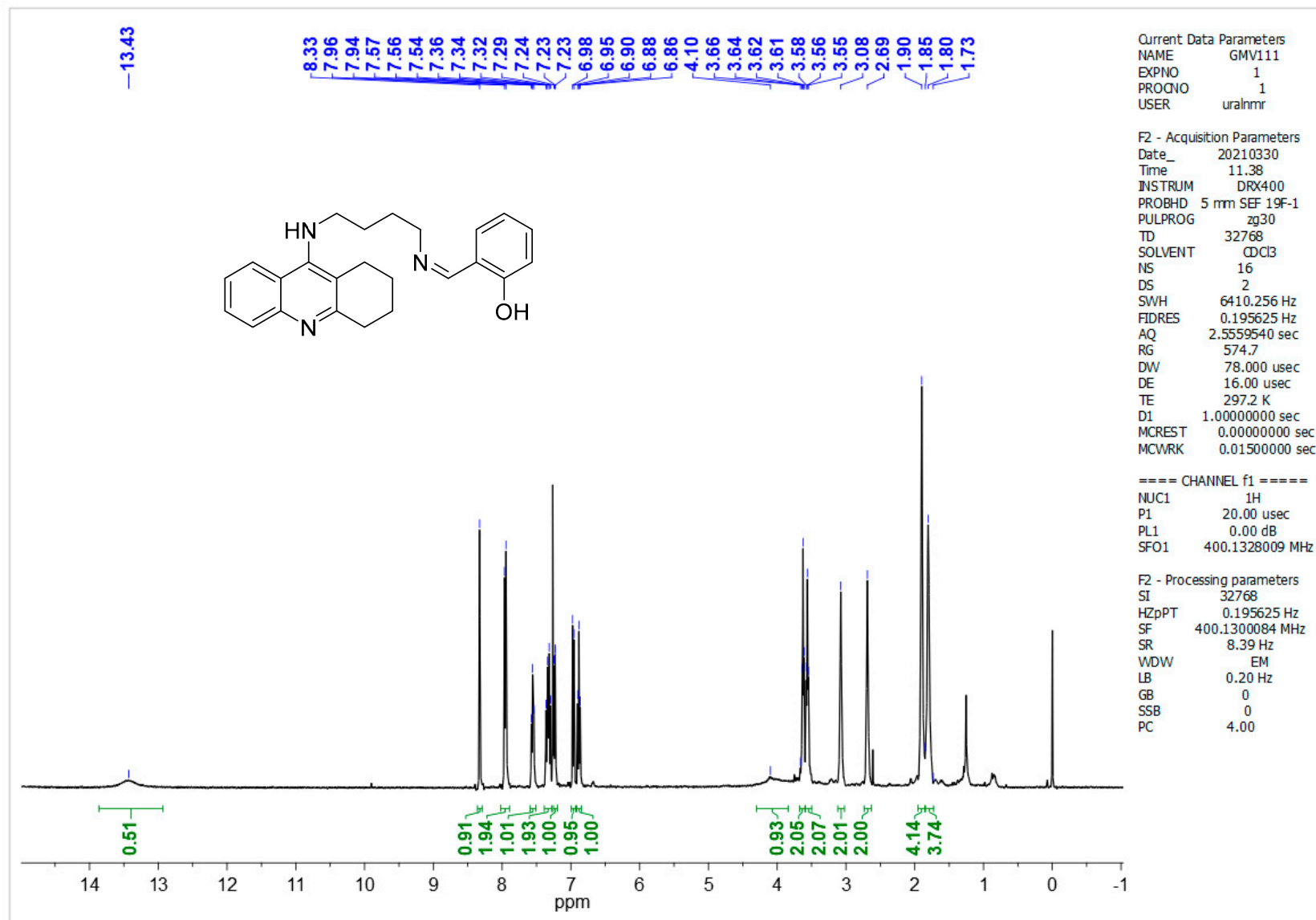


Figure S42. <sup>1</sup>H NMR spectrum of compound 10a

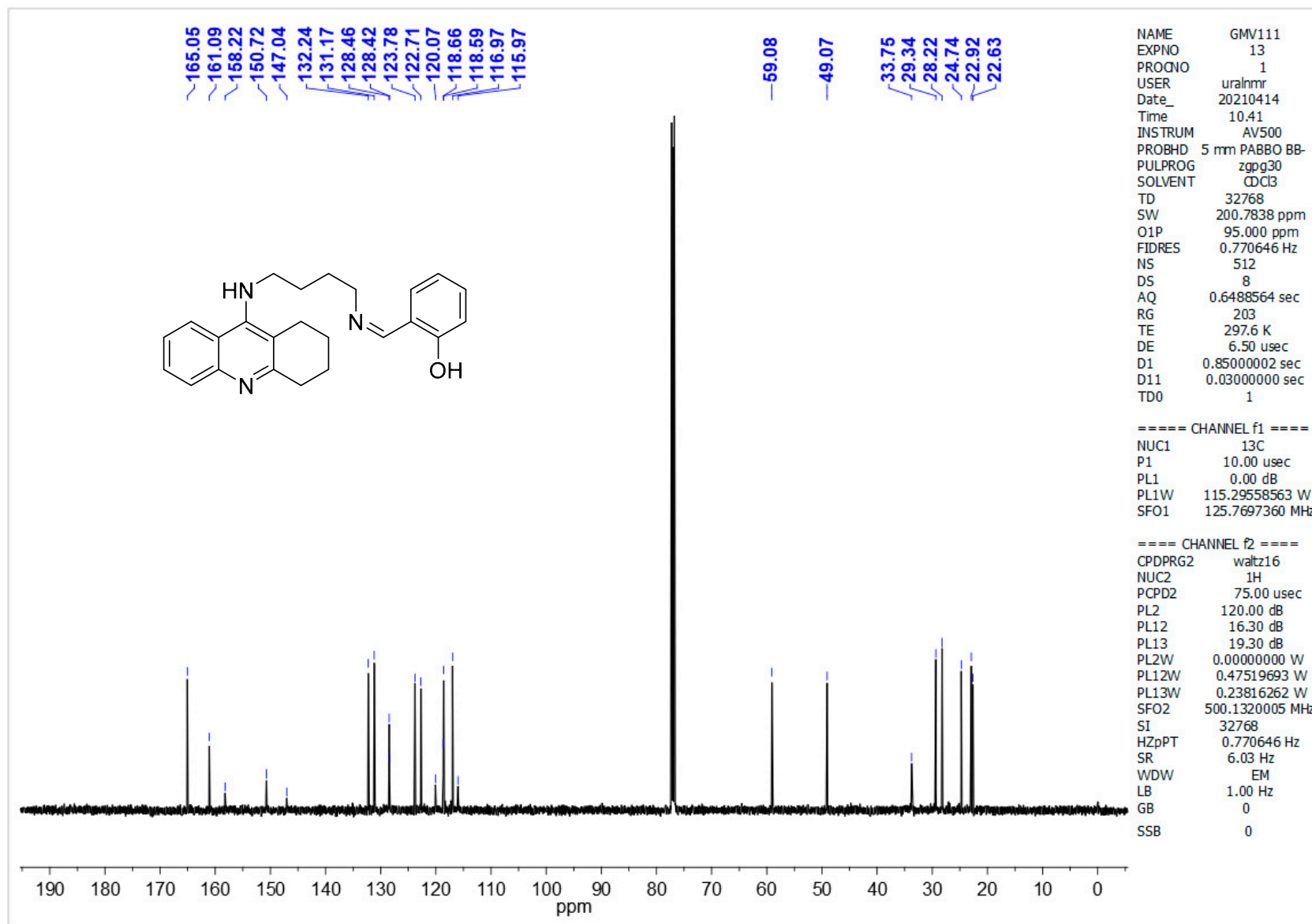


Figure S43.  $^{13}\text{C}$  NMR spectrum of compound 10a

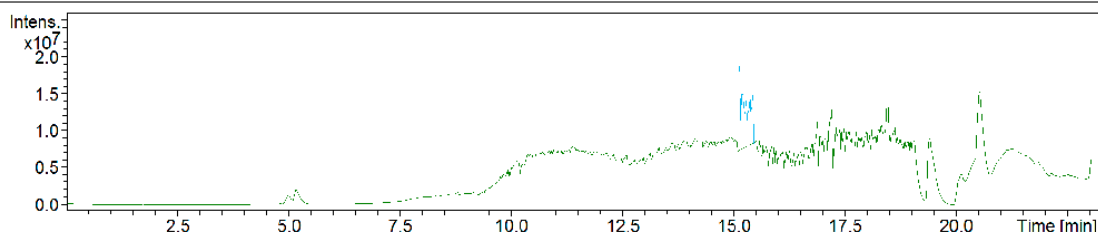
# Compound Spectrum SmartFormula Report

## Analysis Info

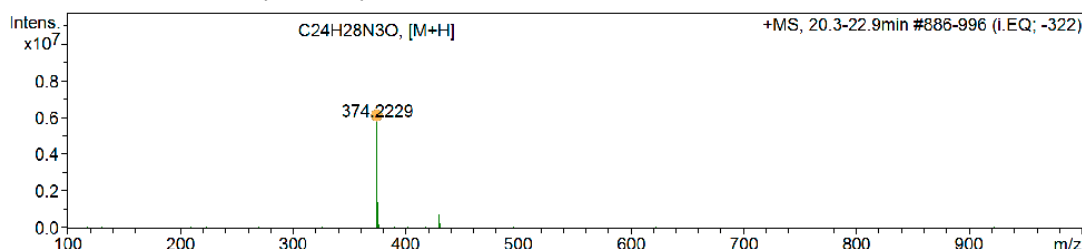
Acquisition Date 4/26/2021 4:17:07 PM  
 Analysis Name D:\Data\ING21\GMV-111.22D-C1.6-ESIPOS-180.5875-26D1615.d  
 Method EP180\_50-2200\_TunePosStd-UA13\_1f3002f200hrf50ie3lm1 Operator admin  
 Sample Name 00ce3crf300-800tt60-120pps6x0.75\_fstnpc.m Instrument maXis impact 1819696.00172  
 Comment 26/04/2021: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2e4): 102.13 (NEt3); 132.91 (2-PrOH); 391.28 (DOP); 79.0, 86.10, 111.09, 157.03 (DMSO); 129.05, 132.91, 144.98, 140.02, 161.08, 165.13, 175.10, 183.17, 194.12, 199.12, 209.19, 214.25, 223.21, 227.24, 237.24, 249.22, 251.24, 251.24, 255.27, 277.25, 293.28, 299.19, 304.30, 307.30, 344.19, 407.10, 430.17, 707.12, 1007.10, 1307.08, 1557.95: background (prev. analyzed samples and impurities); 339.12 (#5451); 446.28 (#5721); 390.22 (#5874); 430.29 (#5876); 419.25 (#5878); 402.25 (#5876)

## Acquisition Parameter

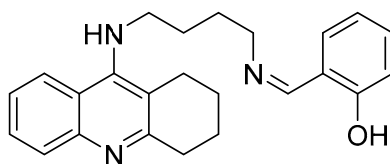
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 20.3-22.9min #886-996 (i.EQ; -322)



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
374.2229	1	C24H28N3O	374.2227	-0.7	14.4	1	100.00	12.5	even	ok



GMV-111.22D-C1.6-ESIPOS-180.5875-26D1615.d

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Figure S44. HRMS spectrum of compound 10a

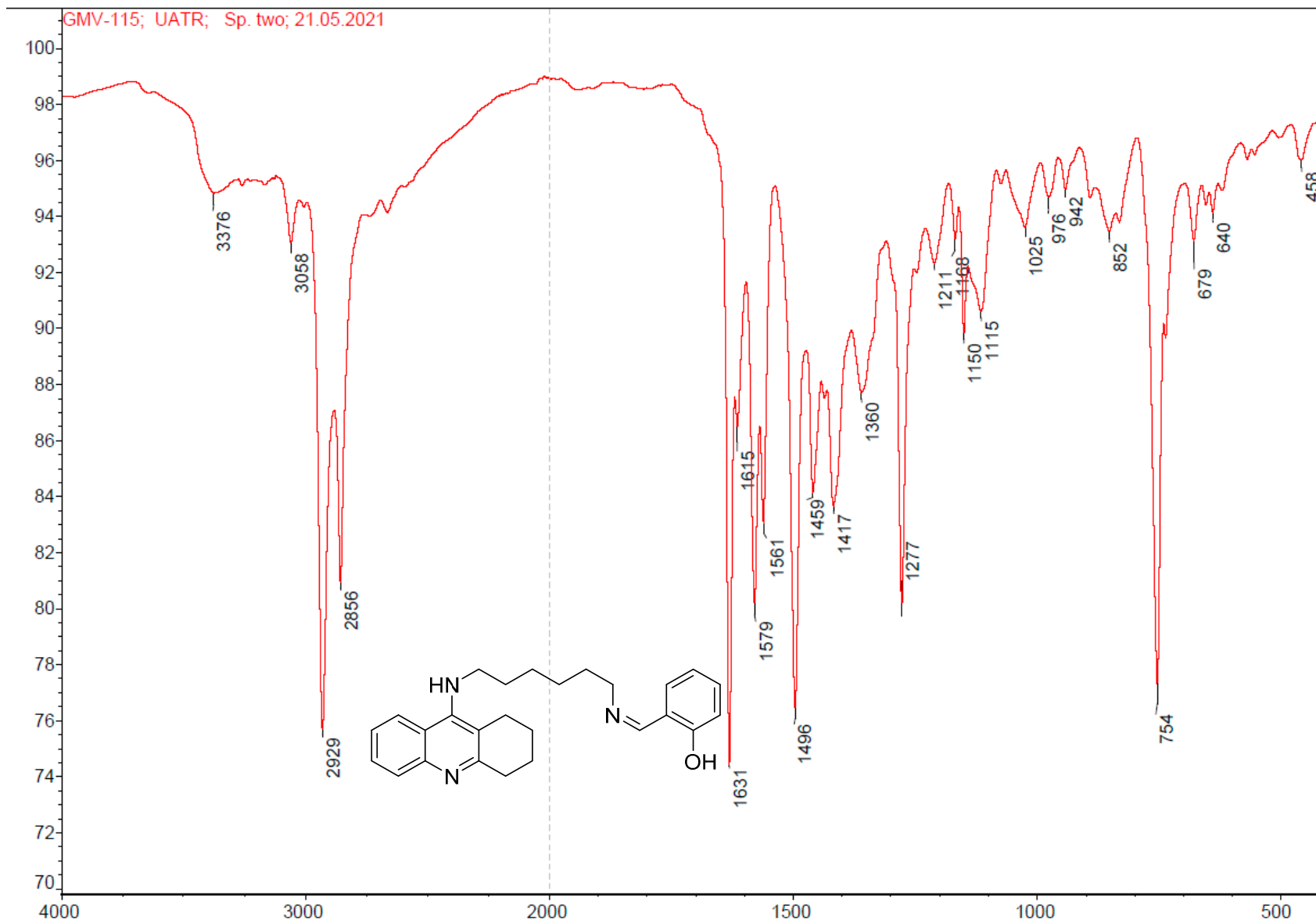


Figure S45. IR spectrum of compound 10b

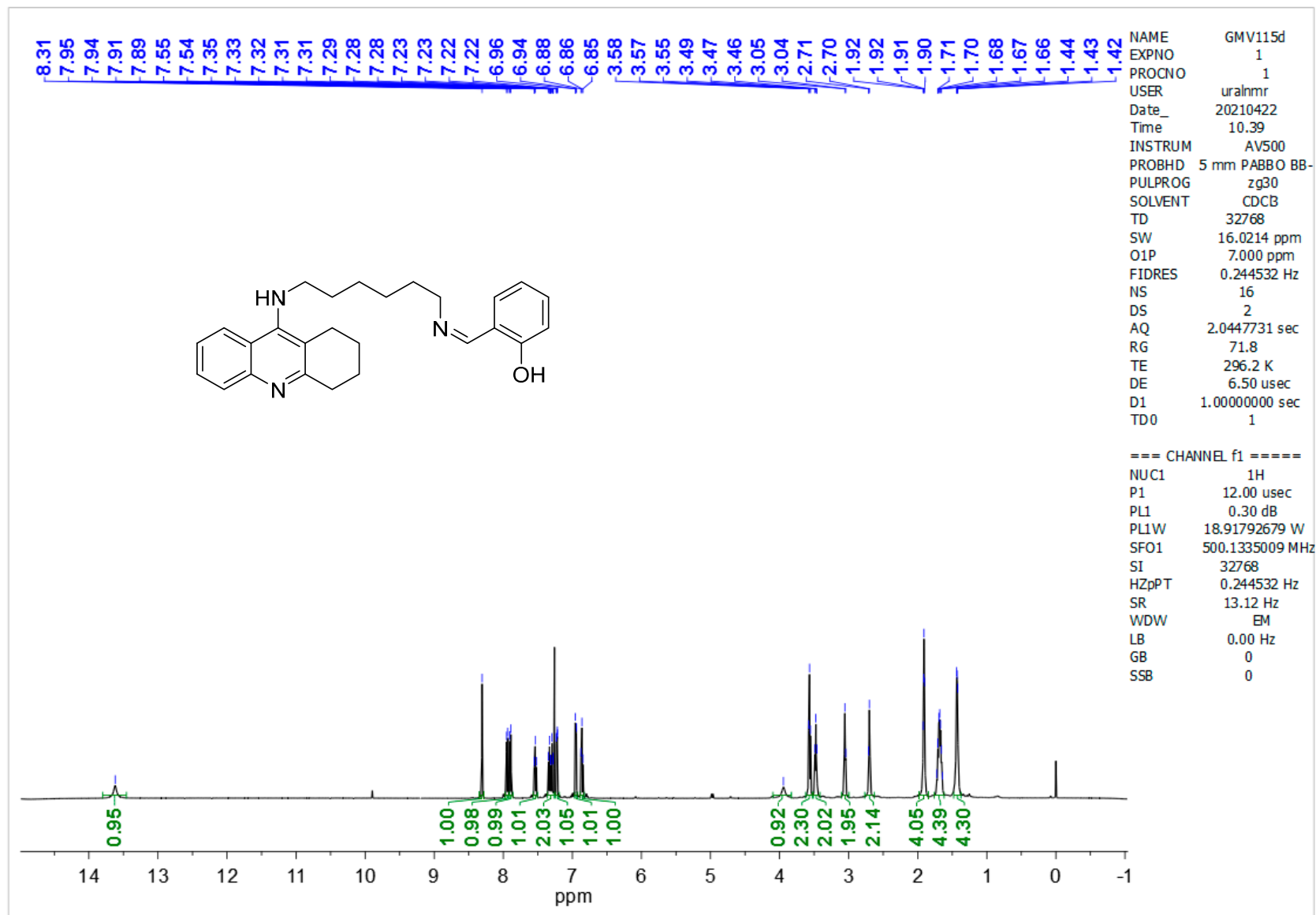


Figure S46. <sup>1</sup>H NMR spectrum of compound 10b

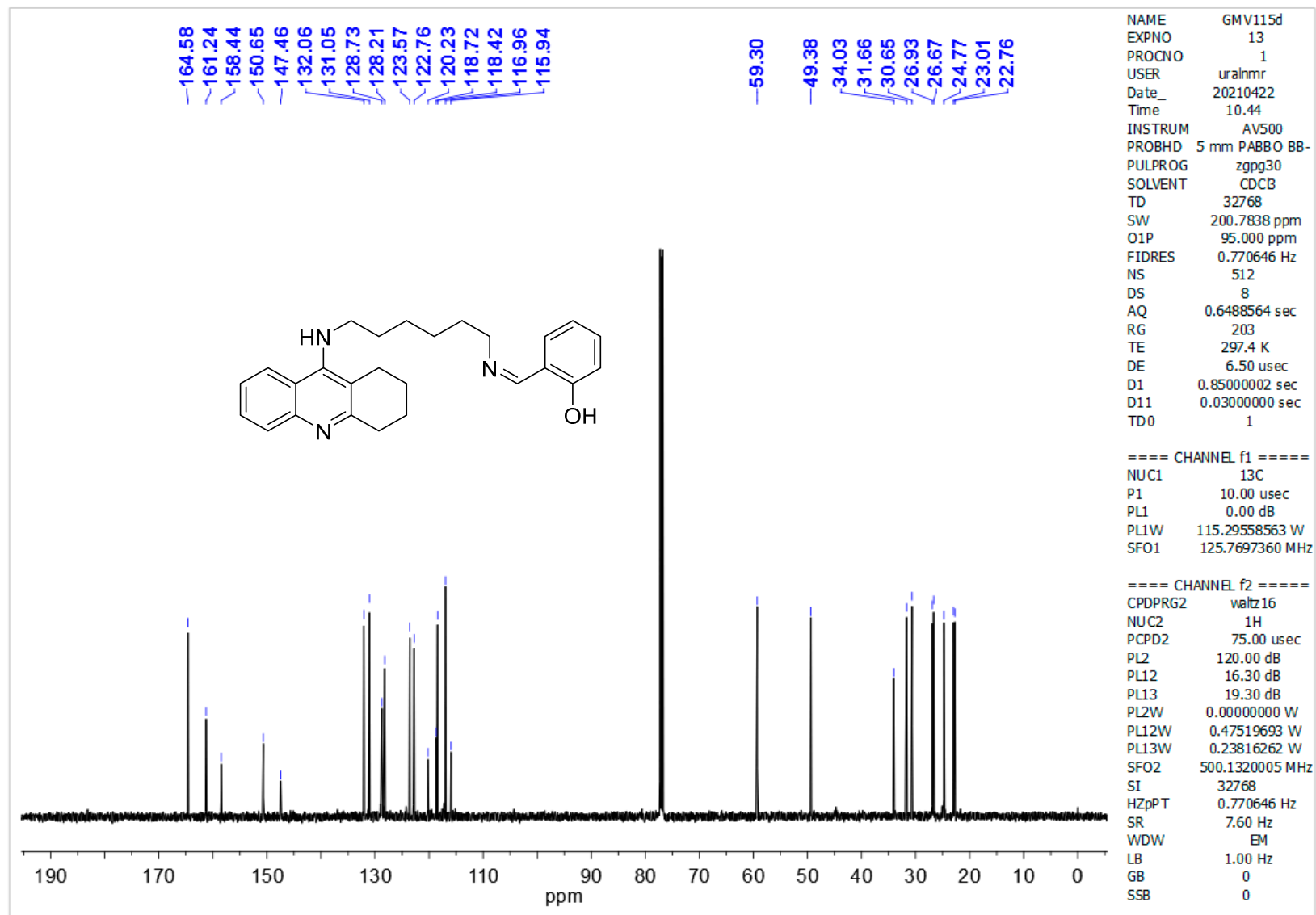


Figure S47. <sup>13</sup>C NMR spectrum of compound 10b



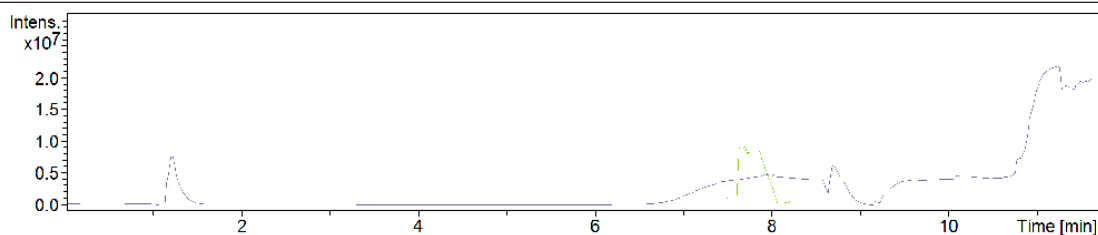
# Compound Spectrum SmartFormula Report

## Analysis Info

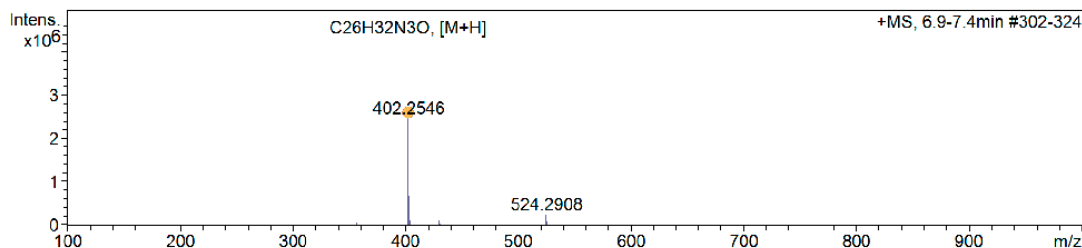
Analysis Name D:\Data\ING21\GMV-115.22D-C1.6-ESIPOS-180.5876-26D1540.d  
 Method EP180\_50-2200\_TunePosStd-UA13\_1f3002f200hrf50ie3lm1 Operator admin  
 Sample Name Instrument maXis impact 1819696.00172  
 Comment 26/04/2021: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2e4): 102.13 (NEt3); 132.91 (2-PrOH); 391.28 (DOP); 79.0, 86.10, 111.09, 157.03 (DMSO); 129.05, 132.91, 144.98, 140.02, 161.08, 165.13, 175.10, 183.17, 194.12, 199.12, 209.19, 214.25, 223.21, 227.24, 237.24, 249.22, 251.24, 251.24, 255.27, 277.25, 293.28, 299.19, 304.30, 307.30, 344.19, 407.10, 430.17, 707.12, 1007.10, 1307.08, 1557.95: background (prev. analyzed samples and impurities); 339.12 (#5451); 446.28 (#5721); 390.22 (#5874); 430.29 (#5876); 419.25 (#5878)

## Acquisition Parameter

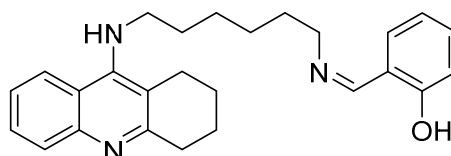
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 6.9-7.4min #302-324



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
402.2546	1	C26H32N3O	402.2540	-1.6	13.4	1	100.00	12.5	even	ok



GMV-115.22D-C1.6-ESIPOS-180.5876-26D1540.d

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Figure S48. HMRS spectrum of compound 10b

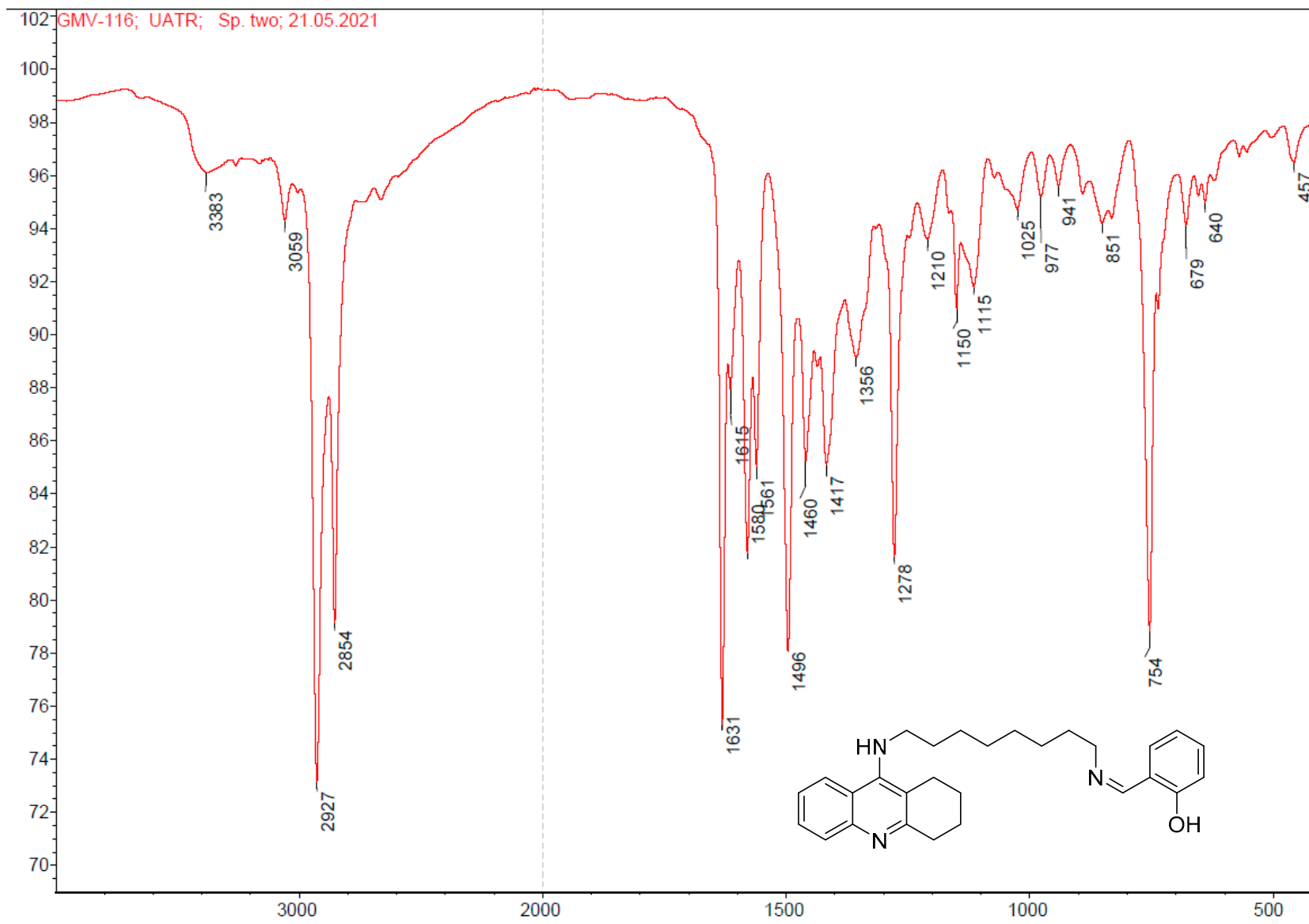


Figure S49. IR spectrum of compound 10c

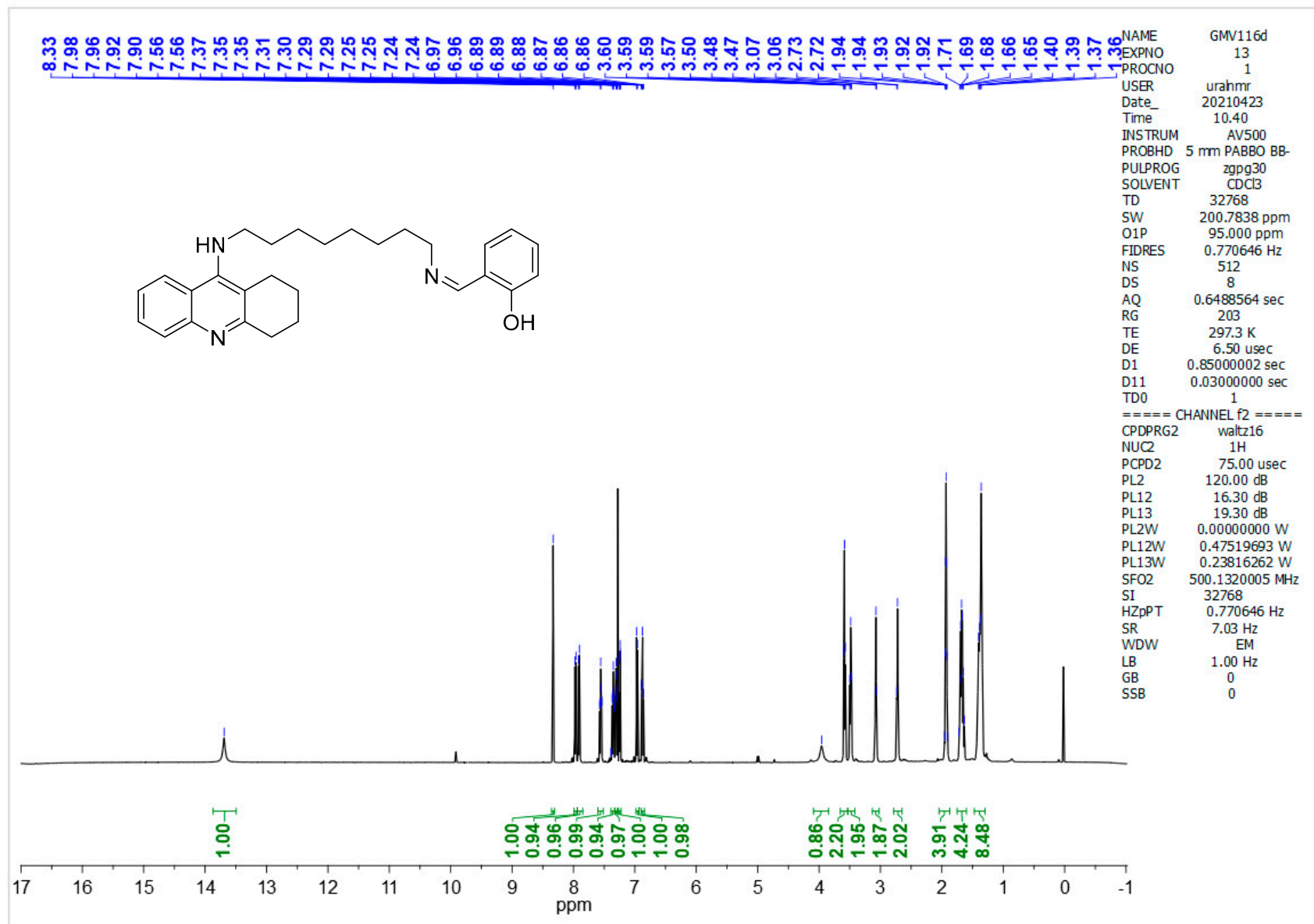


Figure S50. <sup>1</sup>H NMR spectrum of compound 10c

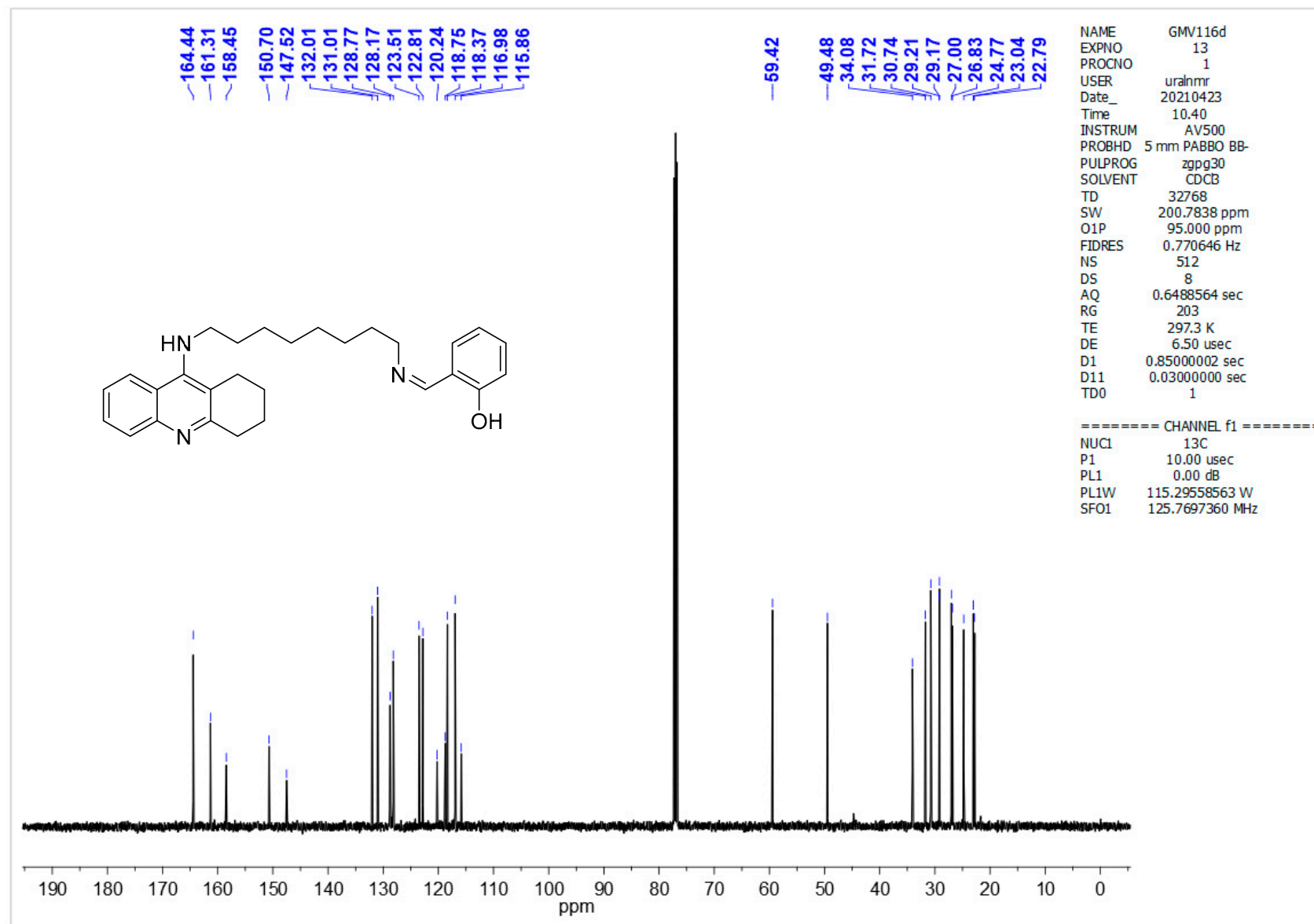


Figure S51. <sup>13</sup>C NMR spectrum of compound 10c

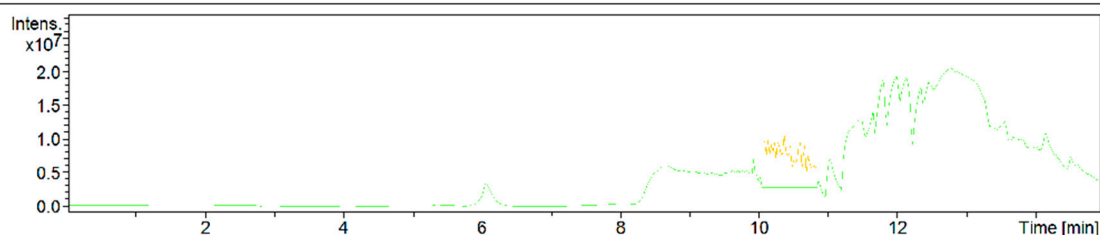
# Compound Spectrum SmartFormula Report

## Analysis Info

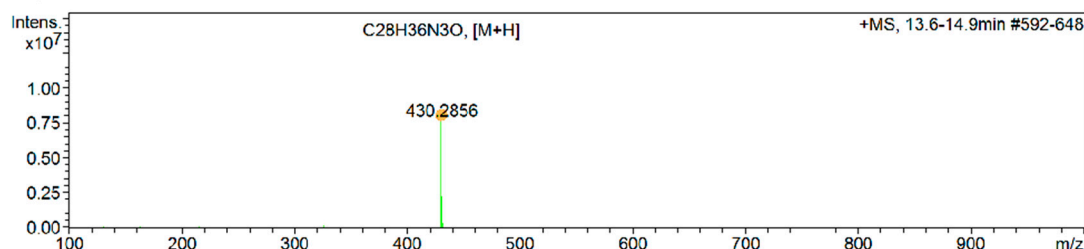
Acquisition Date 4/26/2021 2:59:56 PM  
 Analysis Name D:\Data\ING21\GMV-116.22D-C1.6-ESIPOS-180.5877-26D1500.d  
 Method EP180\_50-2200\_TunePosStd-UA13\_1f3002f200hfr50ie3lm1 Operator admin  
 Sample Name 00ce3crf300-800tt60-120pps6x0.75\_fsthpc.m Instrument maXis impact 1819696.00172  
 Comment 26/04/2021: +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89 (G1969-85000; +/-299.981 HPC); other intense peaks (>2e4): 102.13 (NEt3); 132.91 (2-PrOH); 391.28 (DOP); 79.0, 86.10, 111.09, 157.03 (DMSO); 129.05, 132.91, 144.98, 140.02, 161.08, 165.13, 175.10, 183.17, 194.12, 199.12, 209.19, 214.25, 223.21, 227.24, 237.24, 249.22, 251.24, 251.24, 255.27, 277.25, 293.28, 299.19, 304.30, 307.30, 344.19, 407.10, 430.17, 707.12, 1007.10, 1307.08, 1557.95: background (prev. analyzed samples and impurities); 339.12 (#5451); 446.28 (#5721); 309.02/311.02 (#5899); 155.08 (#5898); 231.11 (#5901); 321.14 (#5990); 367.19 (#5873); 390.22 (#5874)

## Acquisition Parameter

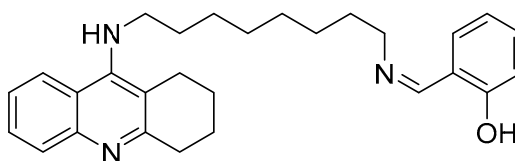
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



## +MS, 13.6-14.9min #592-648



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup> Conf	N-Rule
430.2856	1	C28H36N3O	430.2853	-0.8	14.3	1	100.00	12.5	even	ok



GMV-116.22D-C1.6-ESIPOS-180.5877-26D1500.d

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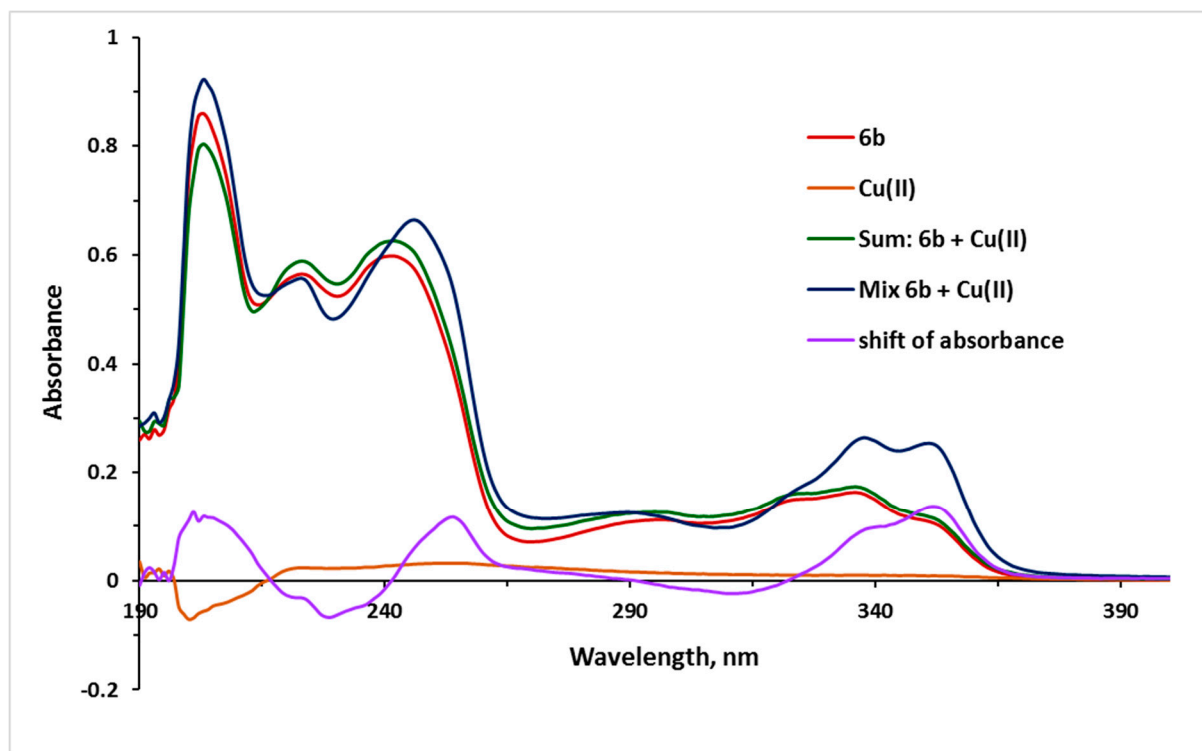
Page 1 of 1



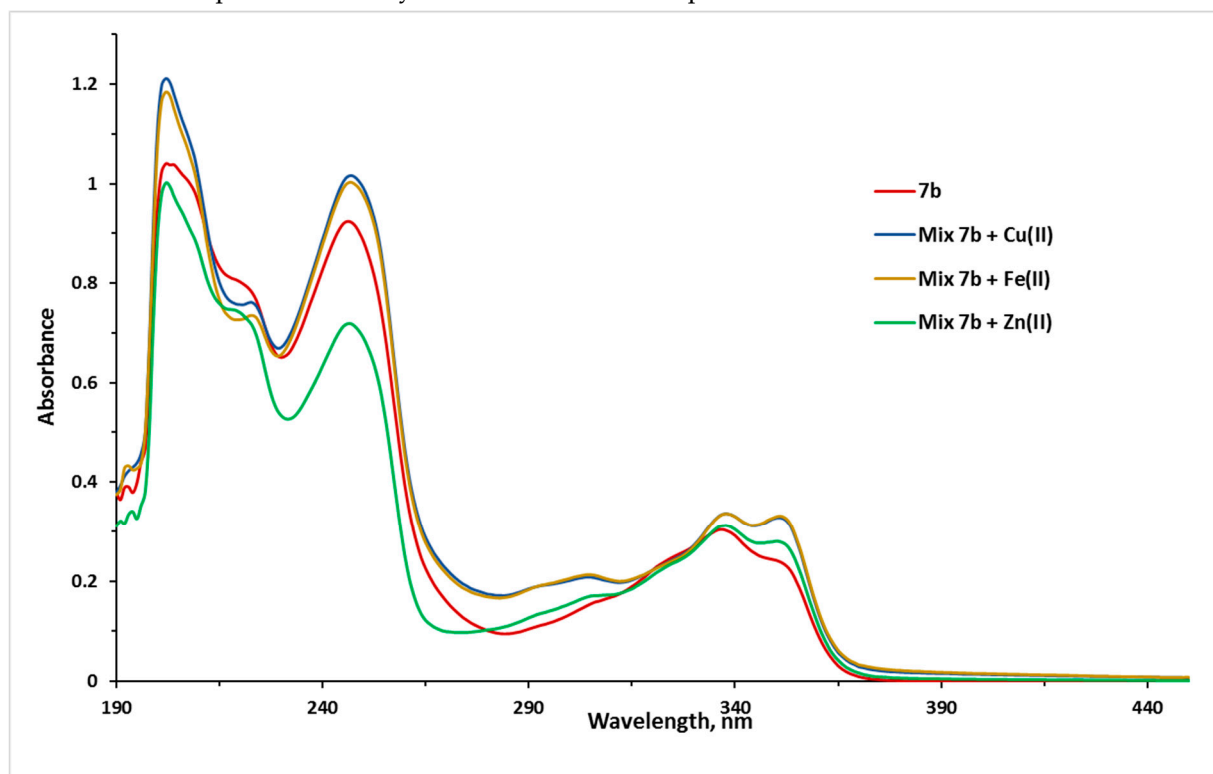
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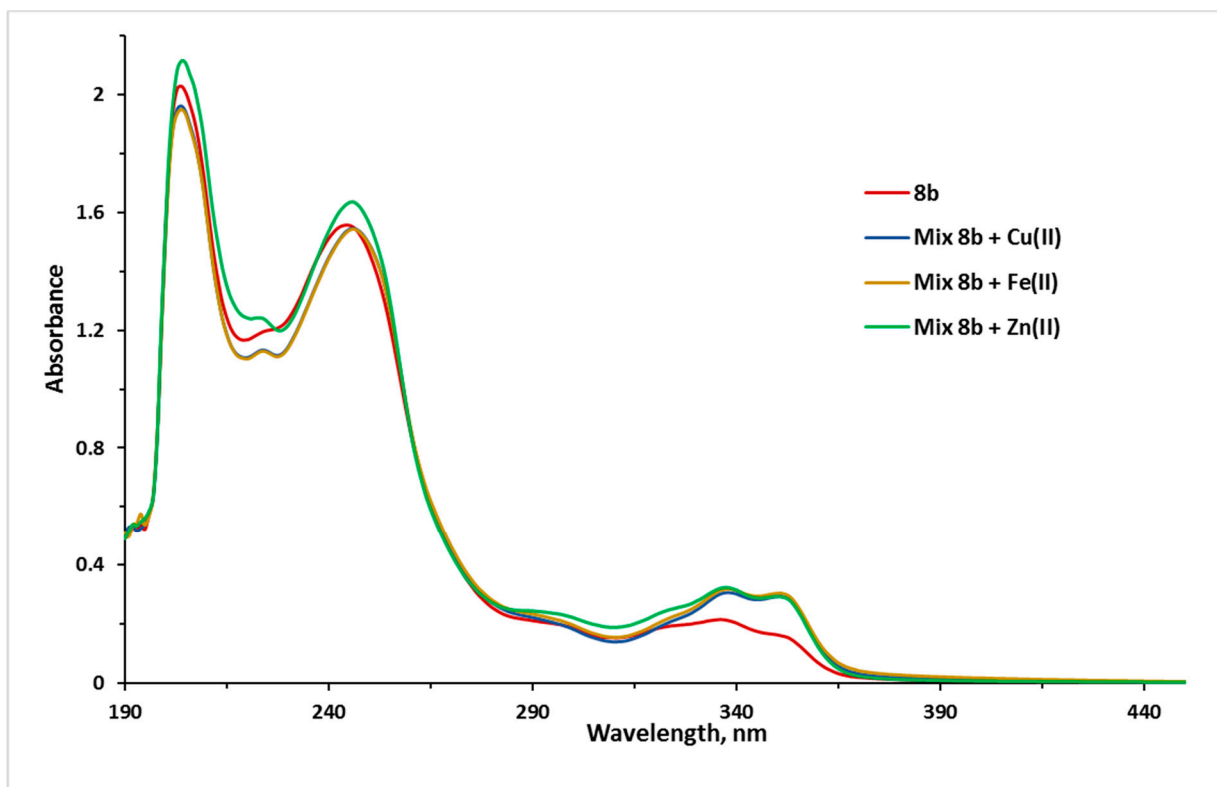
Figure S52. HRMS spectrum of compound 10c



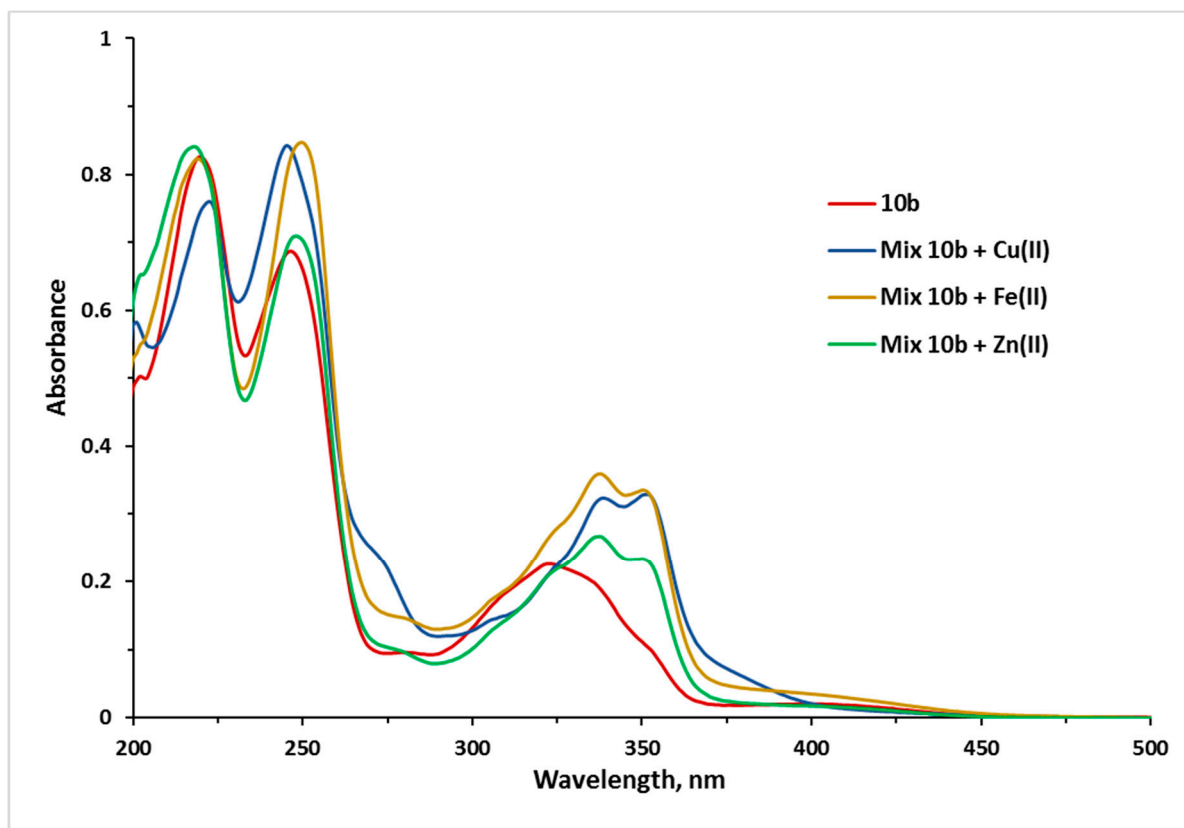
**Figure S53.** Absorption spectra of: compound **6b**,  $\text{Cu}^{2+}$  ions solution, a sum of **6b** and  $\text{Cu}^{2+}$ , their mixture, and the shift of the spectra caused by the formation of a complex.



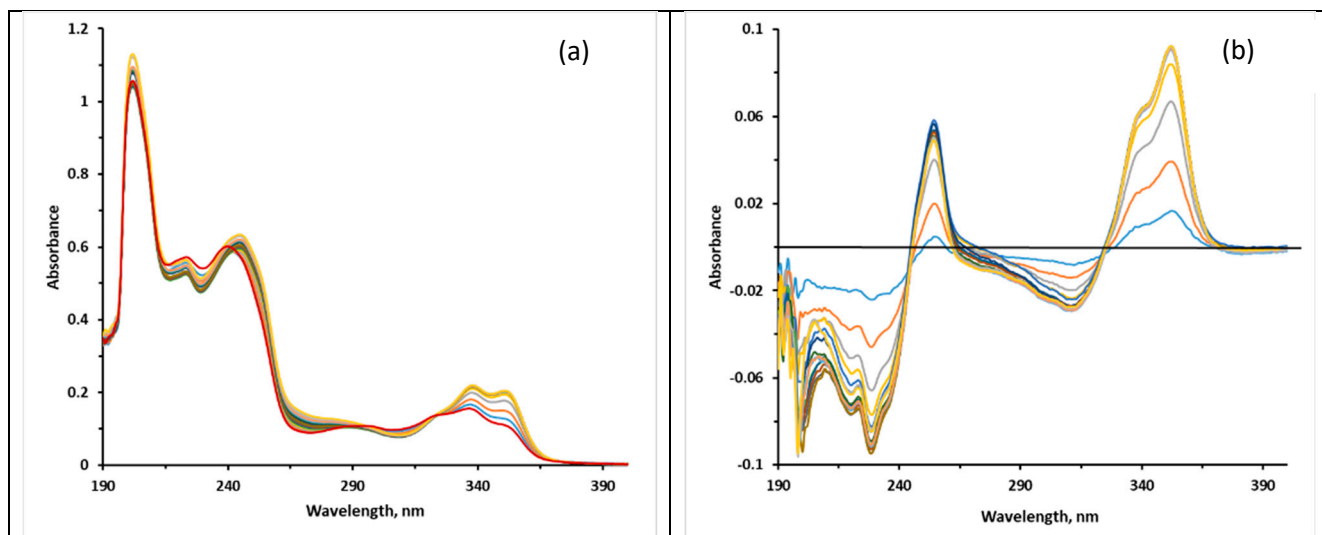
**Figure S54.** UV spectra of compound **7b** and mixture of **7b** with  $\text{Cu(II)}$ ,  $\text{Fe(II)}$  and  $\text{Zn(II)}$  ions.



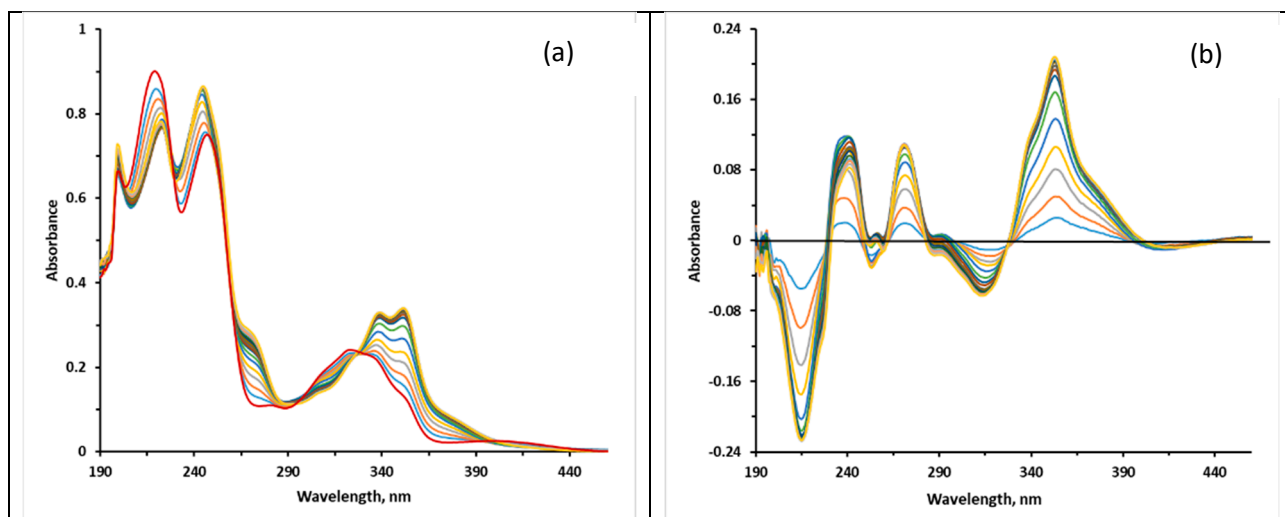
**Figure S55.** UV spectra of compound **8b** and mixture of **8b** with Cu(II), Fe(II) and Zn(II) ions.



**Figure S56.** UV spectra of compound **10b** and mixture of **10b** with Cu(II), Fe(II) and Zn(II) ions.

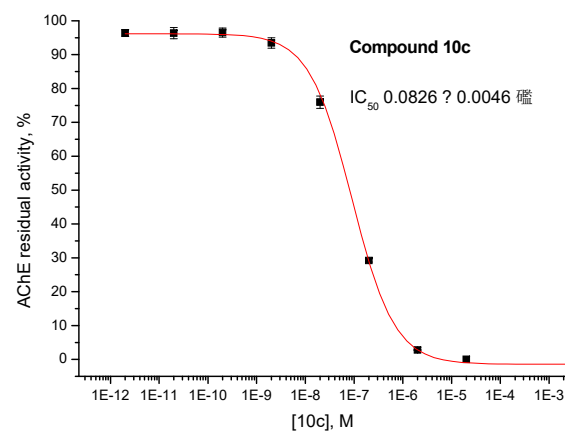
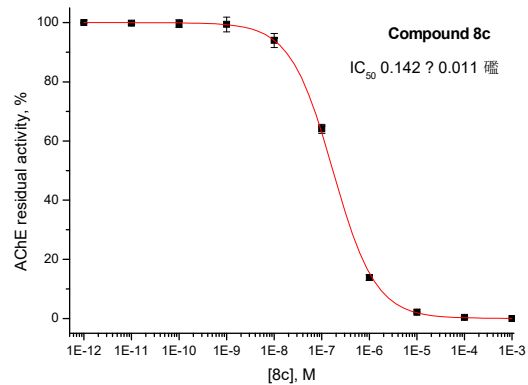
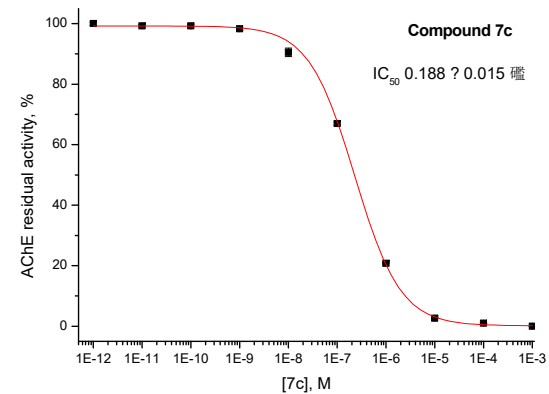
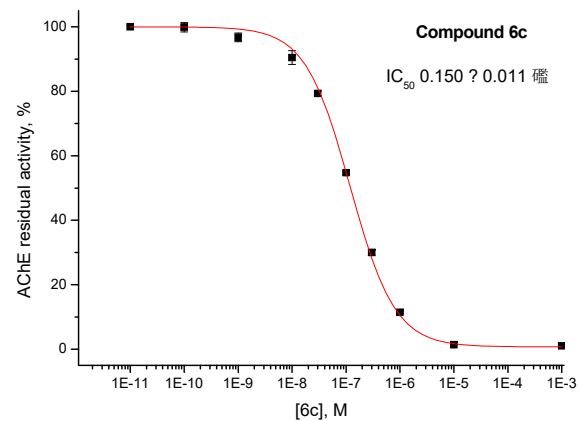
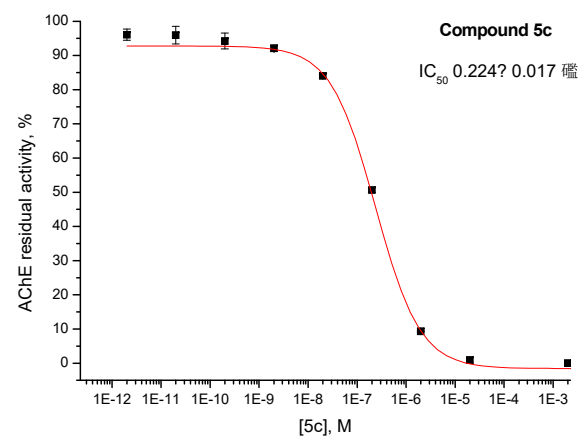


**Figure S57.** (a) UV absorption spectra of **6b** (20  $\mu\text{M}$ ) in ethanol after addition of increasing concentrations of  $\text{CuCl}_2$  (2-34  $\mu\text{M}$ ). (b) the differential spectra due to **6b**- $\text{Cu}^{2+}$  complex formation obtained by numerical subtraction from the spectra of the mixture of the spectra of the  $\text{Cu}^{2+}$  alone and **6b** alone at the corresponding concentrations.

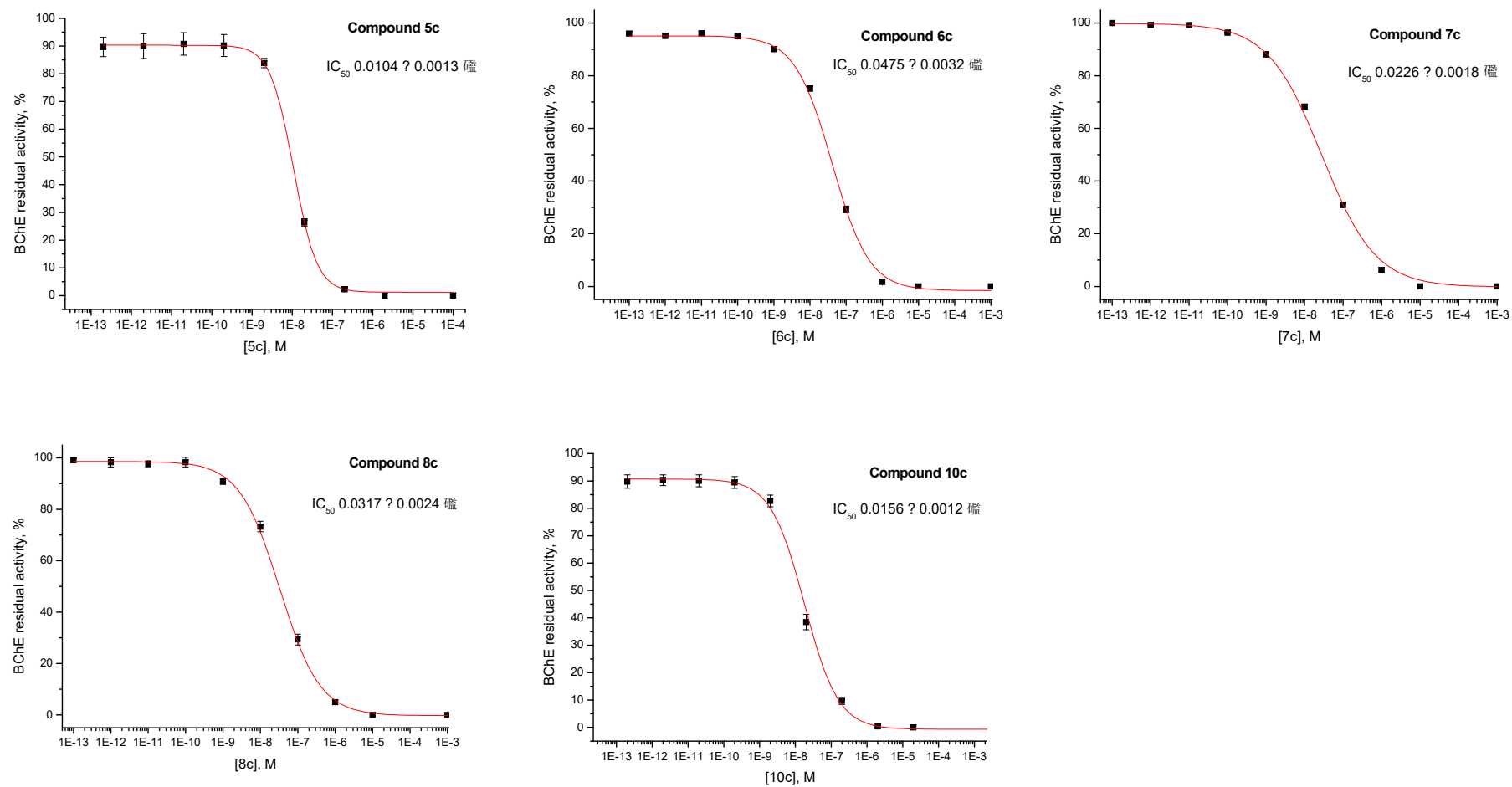


**Figure S58.** (a) UV absorption spectra of **10b** (20  $\mu\text{M}$ ) in ethanol after addition of increasing concentrations of  $\text{CuCl}_2$  (2-34  $\mu\text{M}$ ). (b) the differential spectra due to **10b**- $\text{Cu}^{2+}$  complex formation obtained by numerical subtraction from the spectra of the mixture of the spectra of the  $\text{Cu}^{2+}$  alone and **10b** alone at the corresponding concentrations.

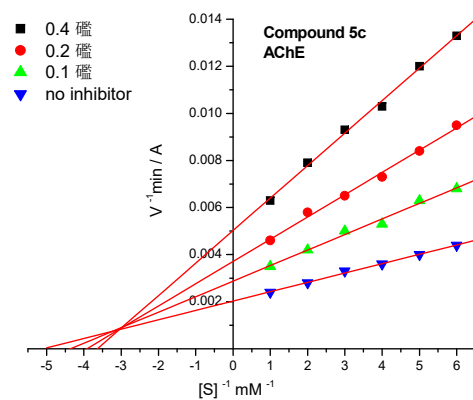




**Figure S59.** IC<sub>50</sub> values for AChE inhibition by compounds 5c, 6c, 7c, 8c and 10c (Mean ± SEM, n = 3)

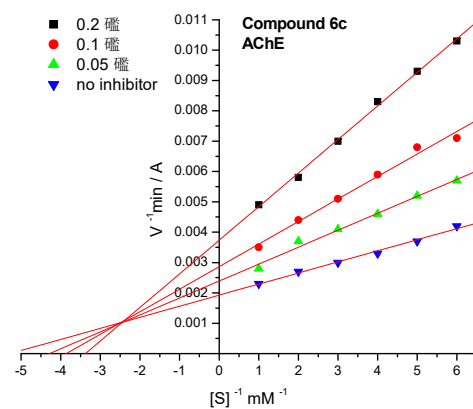


**Figure S60.**  $IC_{50}$  values for BChE inhibition by compounds 5c,6c,7c,8c and 10c (Mean  $\pm$  SEM, n = 3)



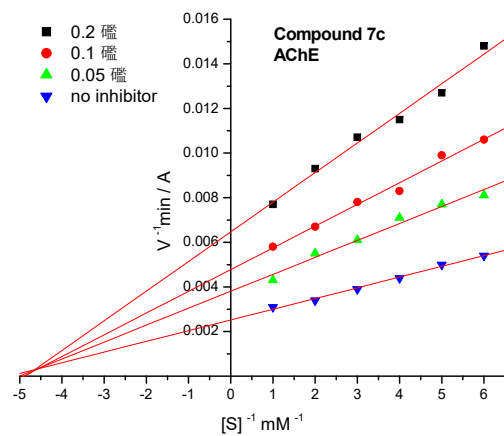
$$K_i = 0.152 \pm 0.012 \mu\text{M}$$

$$K_i' = 0.263 \pm 0.018 \mu\text{M}$$



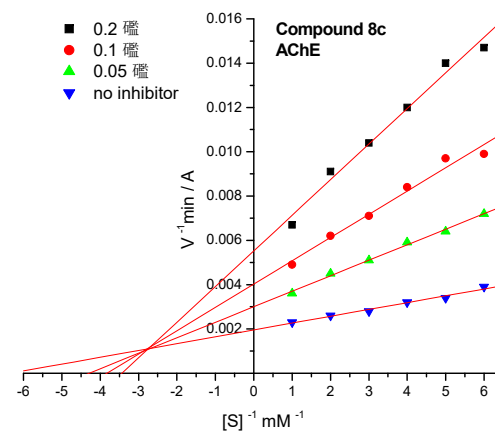
$$K_i = 0.104 \pm 0.004 \mu\text{M}$$

$$K_i' = 0.213 \pm 0.012 \mu\text{M}$$



$$K_i = 0.125 \pm 0.003 \mu\text{M}$$

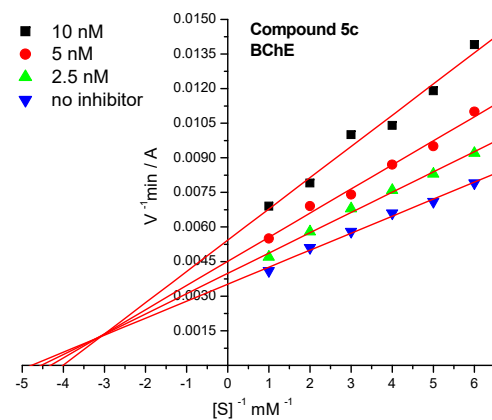
$$K_i' = 0.134 \pm 0.009 \mu\text{M}$$



$$K_i = 0.0536 \pm 0.0025 \mu\text{M}$$

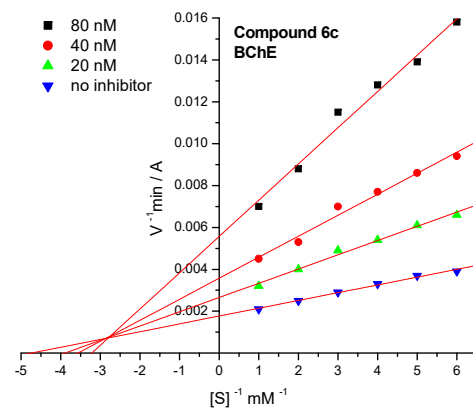
$$K_i' = 0.0998 \pm 0.0058 \mu\text{M}$$

**Figure S61.** Lineweaver-Burk double-reciprocal plots of steady state inhibition of AChE by compounds 5c,6c,7c,8c. Each plot indicates mixed-type inhibition.



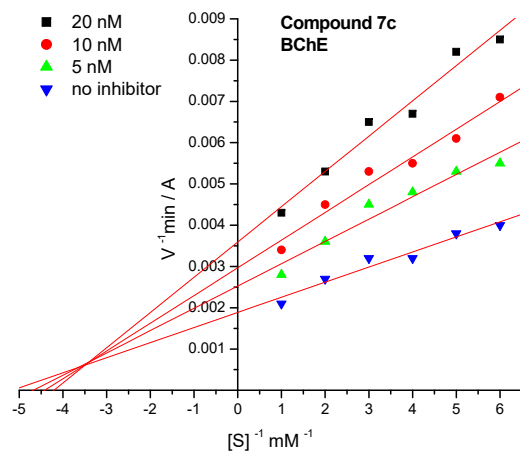
$$K_i = 0.0106 \pm 0.0007 \mu\text{M}$$

$$K_i' = 0.0171 \pm 0.0013 \mu\text{M}$$



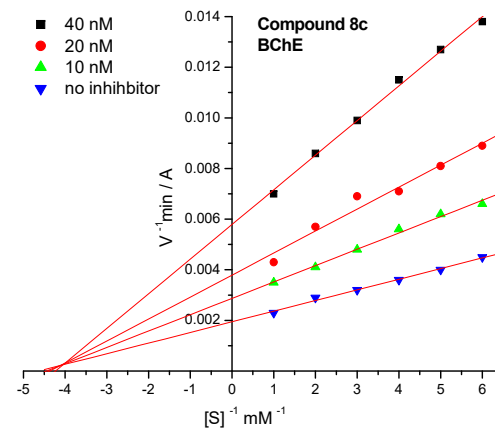
$$K_i = 0.0188 \pm 0.0011 \mu\text{M}$$

$$K_i' = 0.0314 \pm 0.0025 \mu\text{M}$$



$$K_i = 0.0173 \pm 0.0006 \mu\text{M}$$

$$K_i' = 0.0243 \pm 0.0001 \mu\text{M}$$



$$K_i = 0.0177 \pm 0.0007 \mu\text{M}$$

$$K_i' = 0.0187 \pm 0.0013 \mu\text{M}$$

**Figure S62.** Lineweaver-Burk double-reciprocal plots of steady state inhibition of BChE by compounds 5c,6c,7c,8c. Each plot indicates mixed-type inhibition.

**Table S1.** pKa values and charges of the investigated compounds.

Compound	Tacrine N	Spacer N	Ar-OH	Charge of the Molecule
<b>5a</b>	7.5	-	8.3	+1
<b>6a</b>	7.5	-	-	+1
<b>7a</b>	7.5	-	7.3	+1
<b>10a</b>	7.5	8.4	9	+2