Pharmacophore-based virtual screening, synthesis, biological evaluation, and molecular docking study of novel pyrrolizines bearing urea/thiourea moieties with potential anticancer and CDK inhibitory activities

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Chemical structures of the compound library

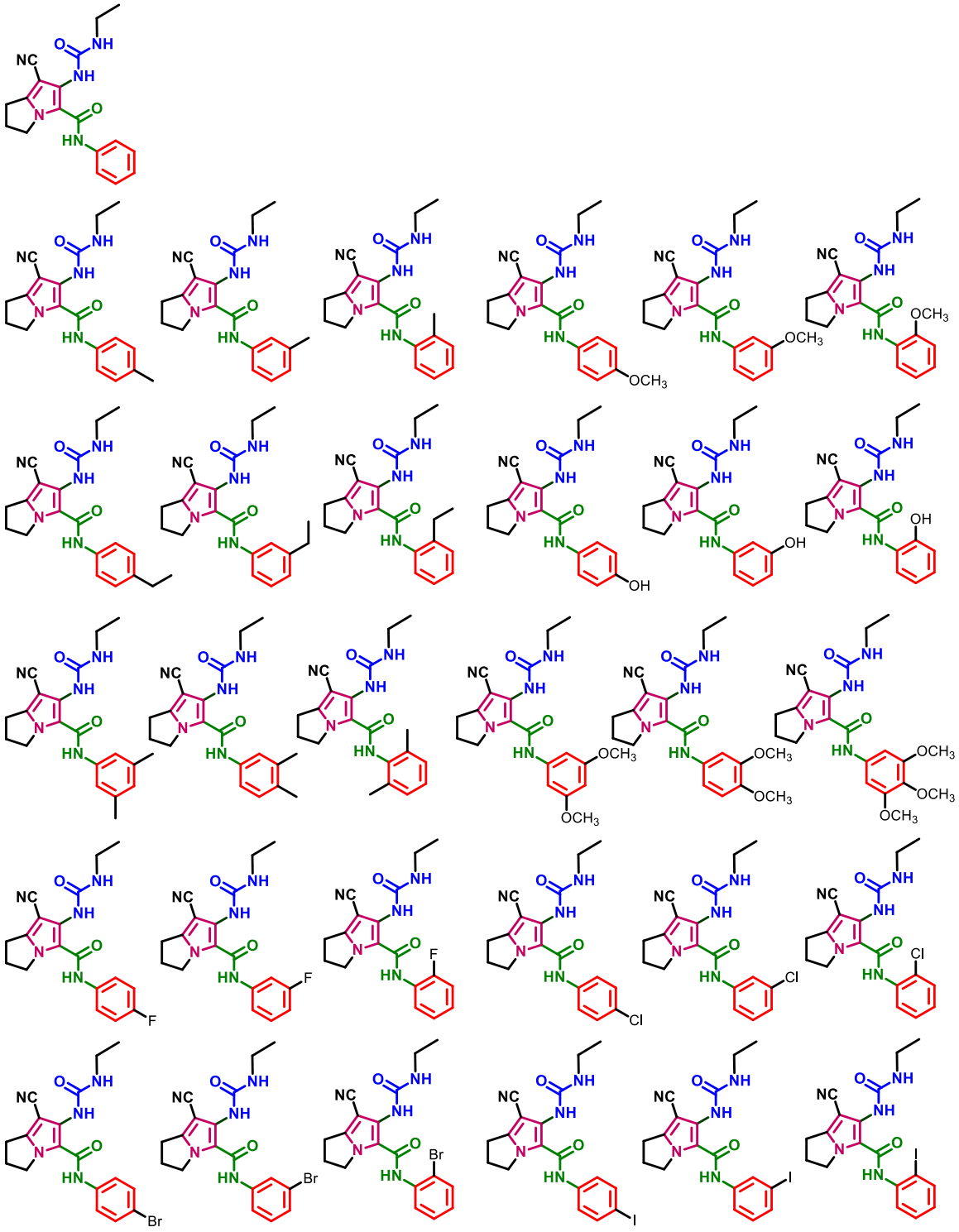


Figure S1. Chemical structure of compound 1-31 (Etiso)

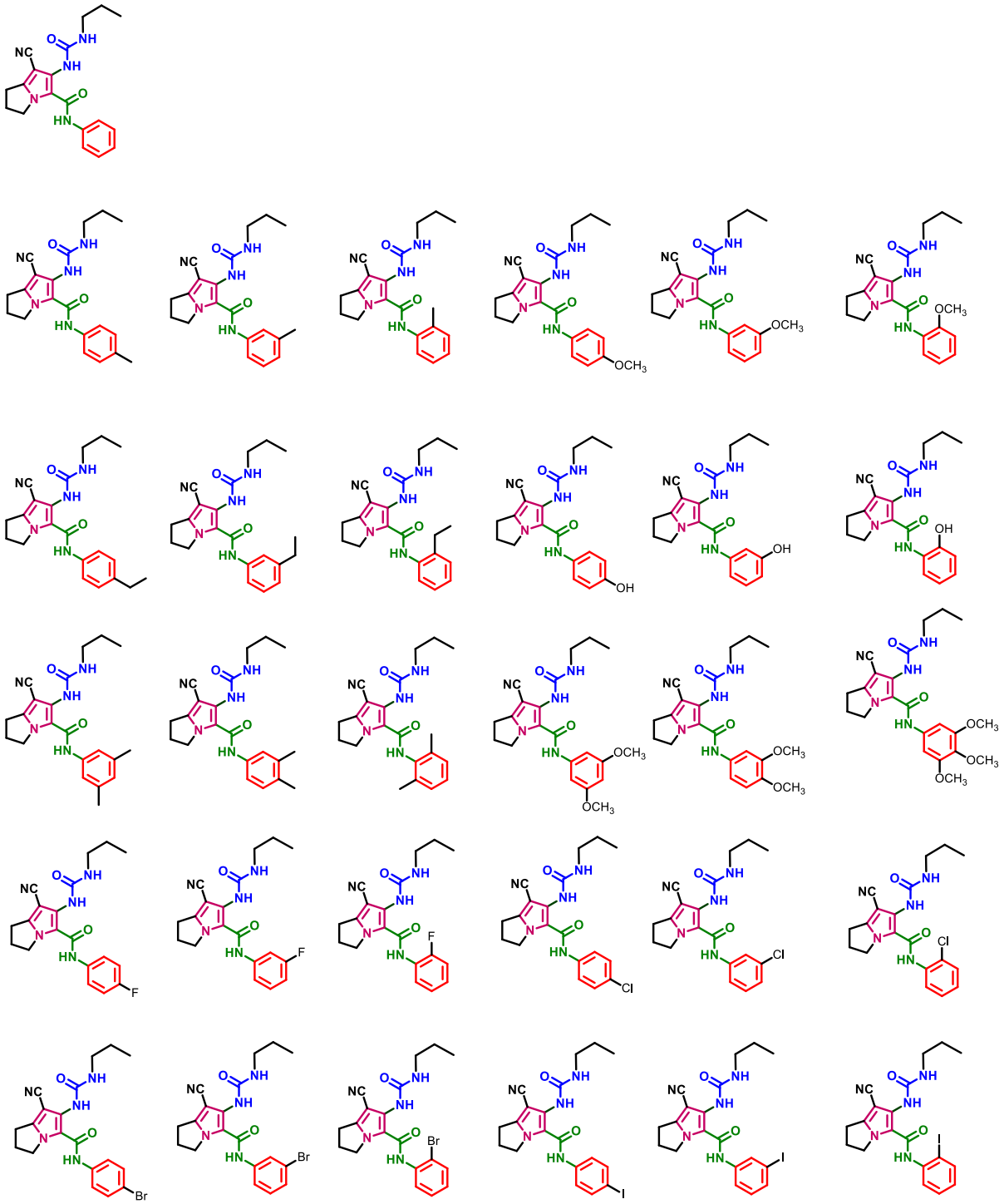


Figure S2. Chemical structure of compound 32-62 (Propyliso)

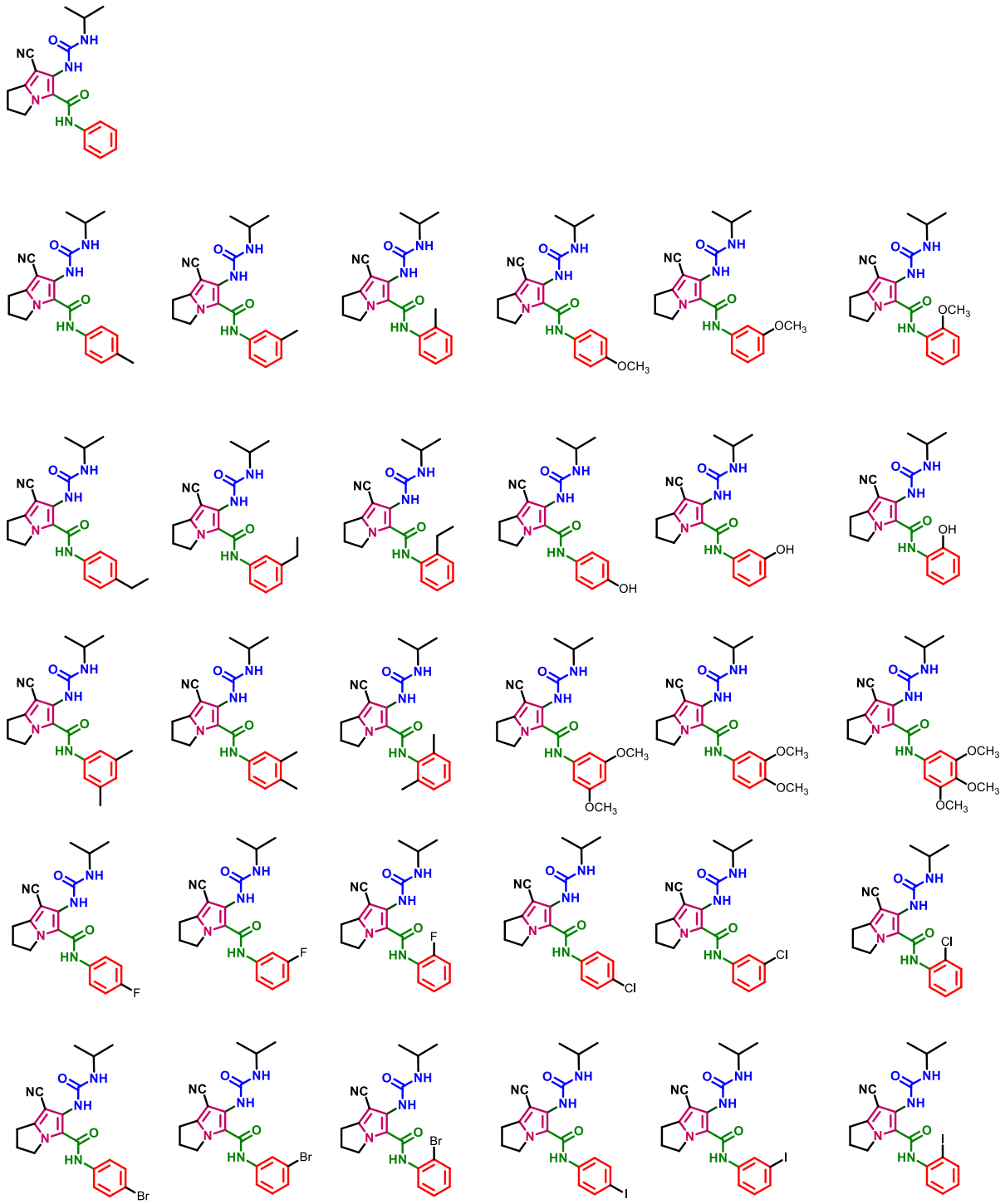


Figure S3. **Chemical structure of compound 63-93 (Isopropyliso)**

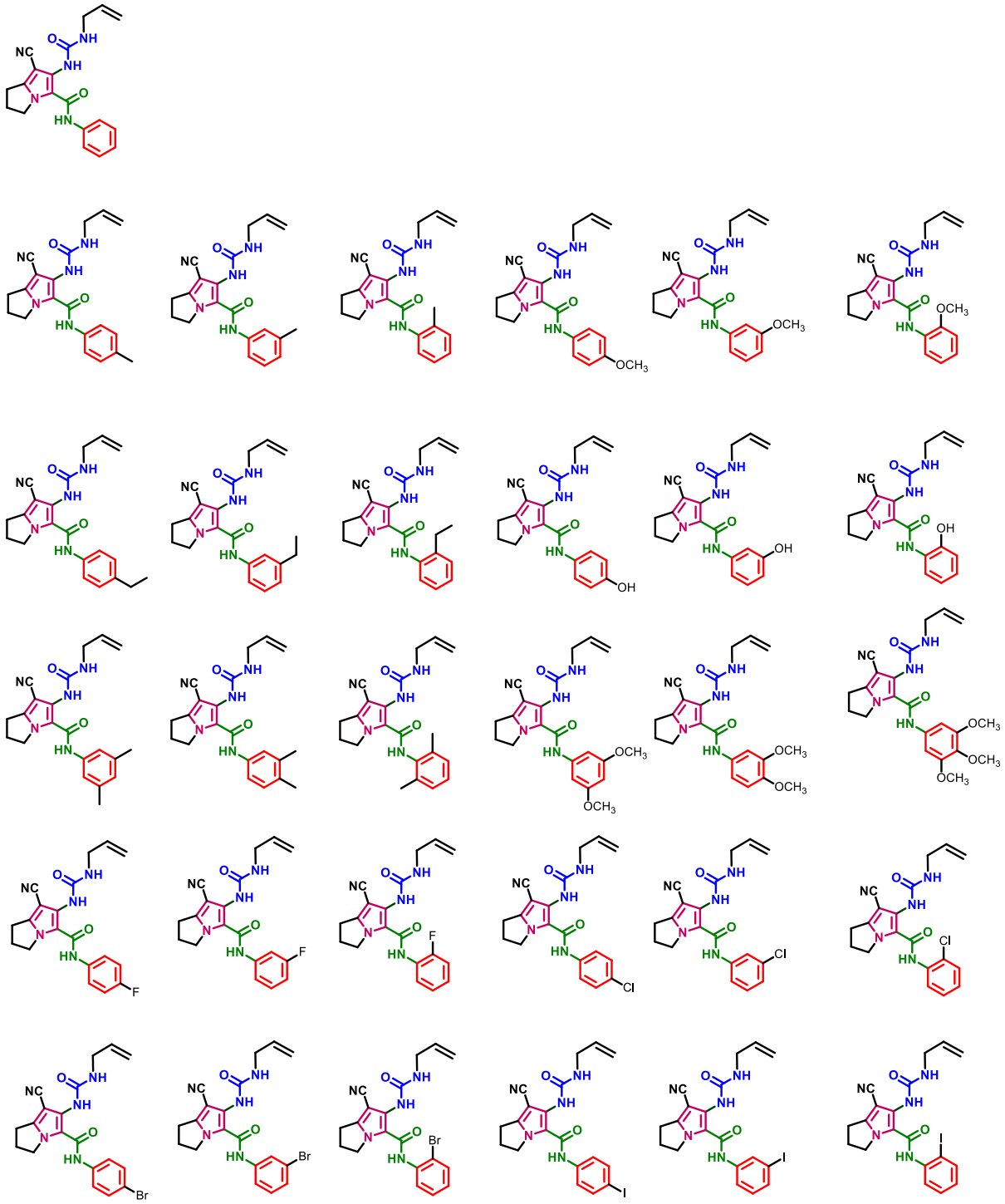
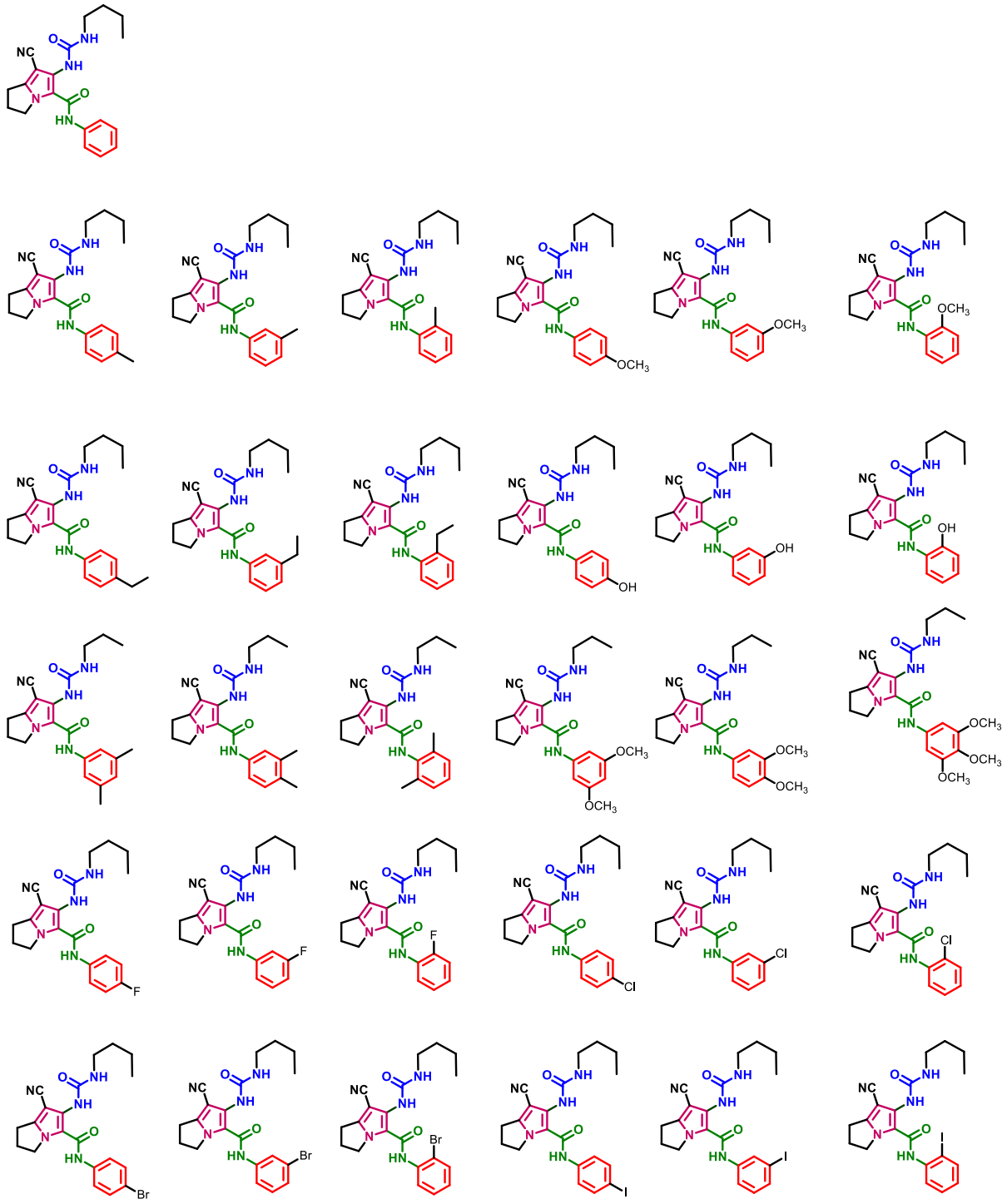


Figure S4. Chemical structure of compound 94-124 (allyliso)



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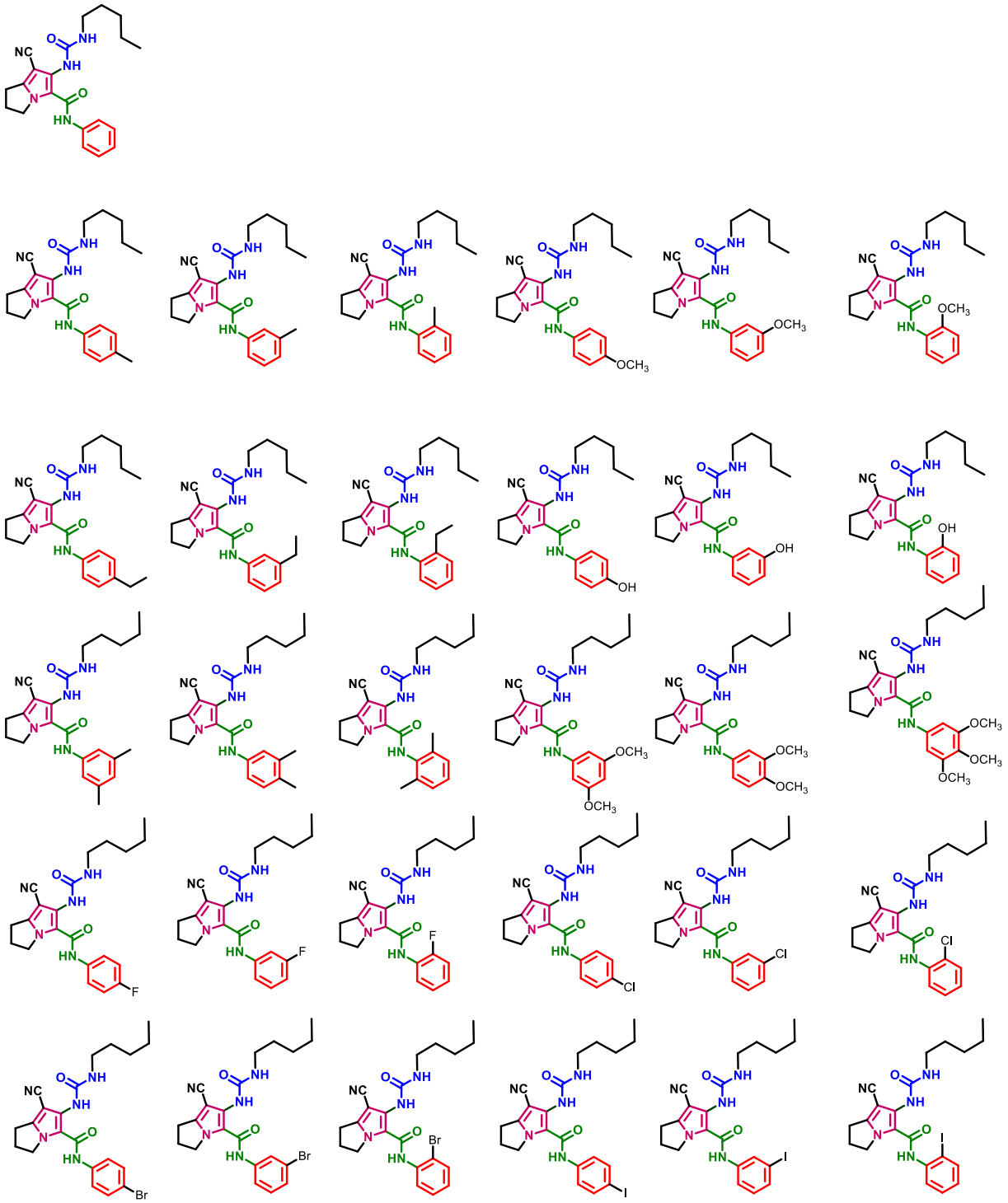


Figure S6. Chemical structure of compound 156-186 (pentyliso)

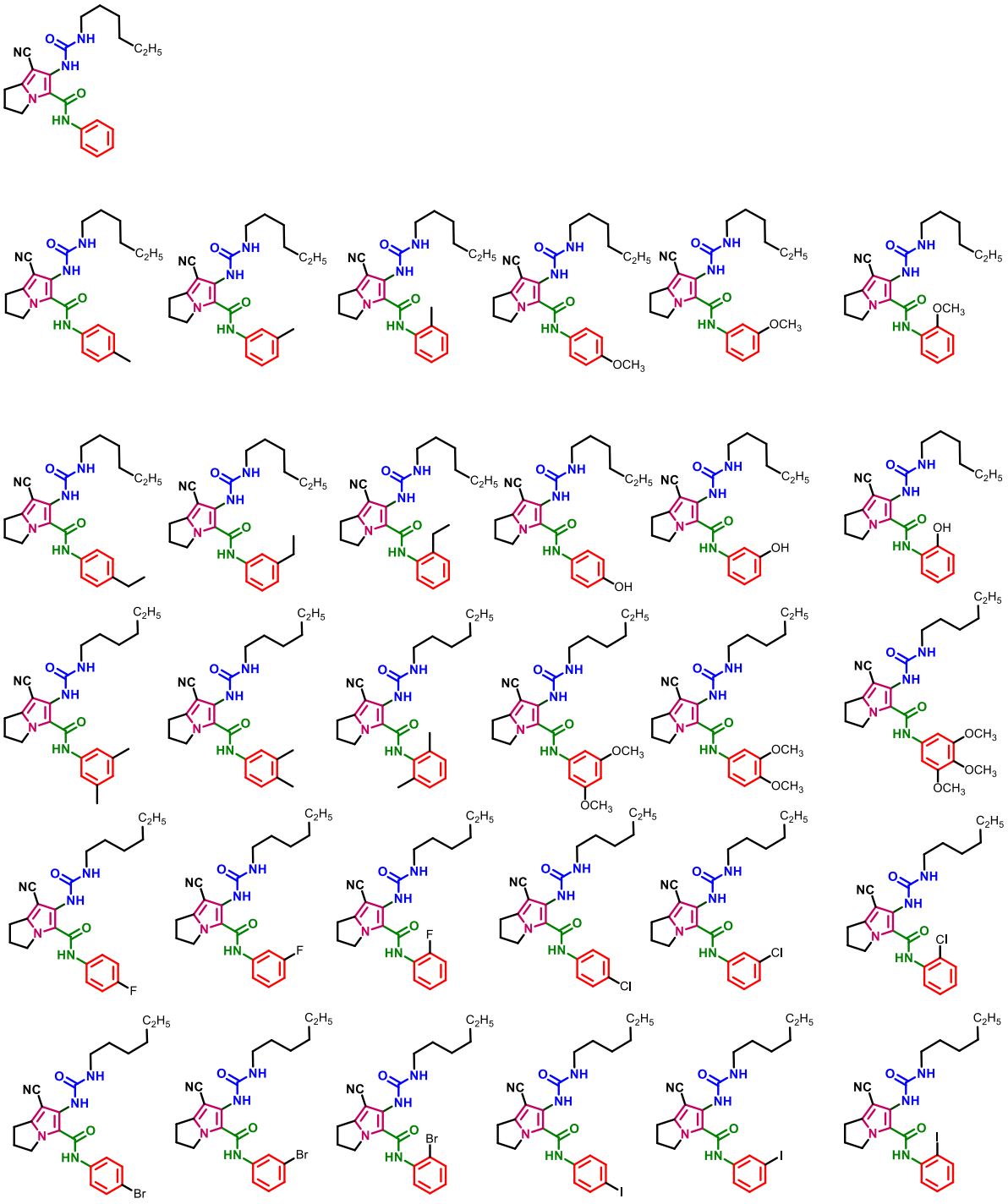


Figure S7. Chemical structure of compound 187-217 (hexyliso)

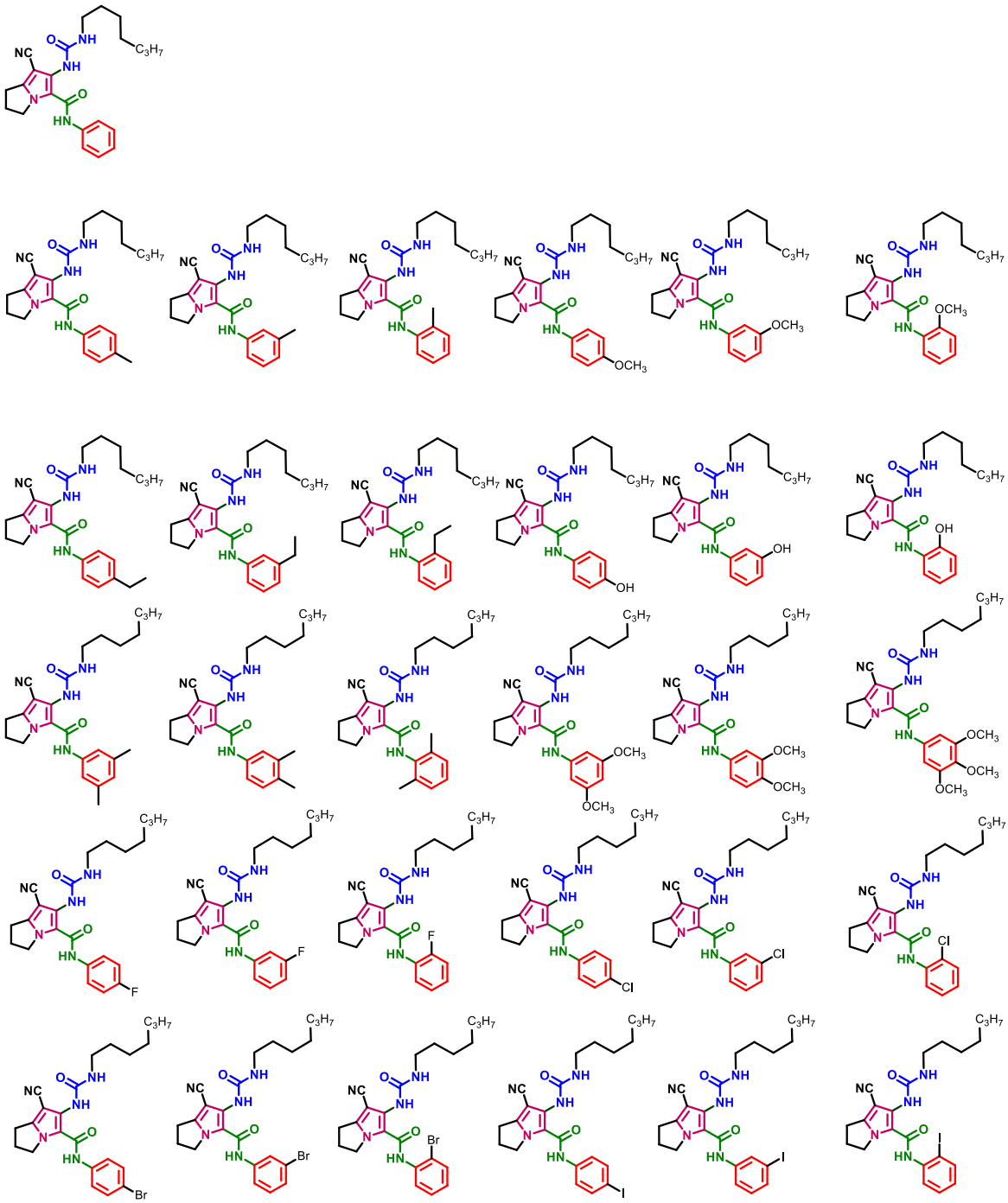


Figure S8. Chemical structure of compound 218-248 (heptyliso)

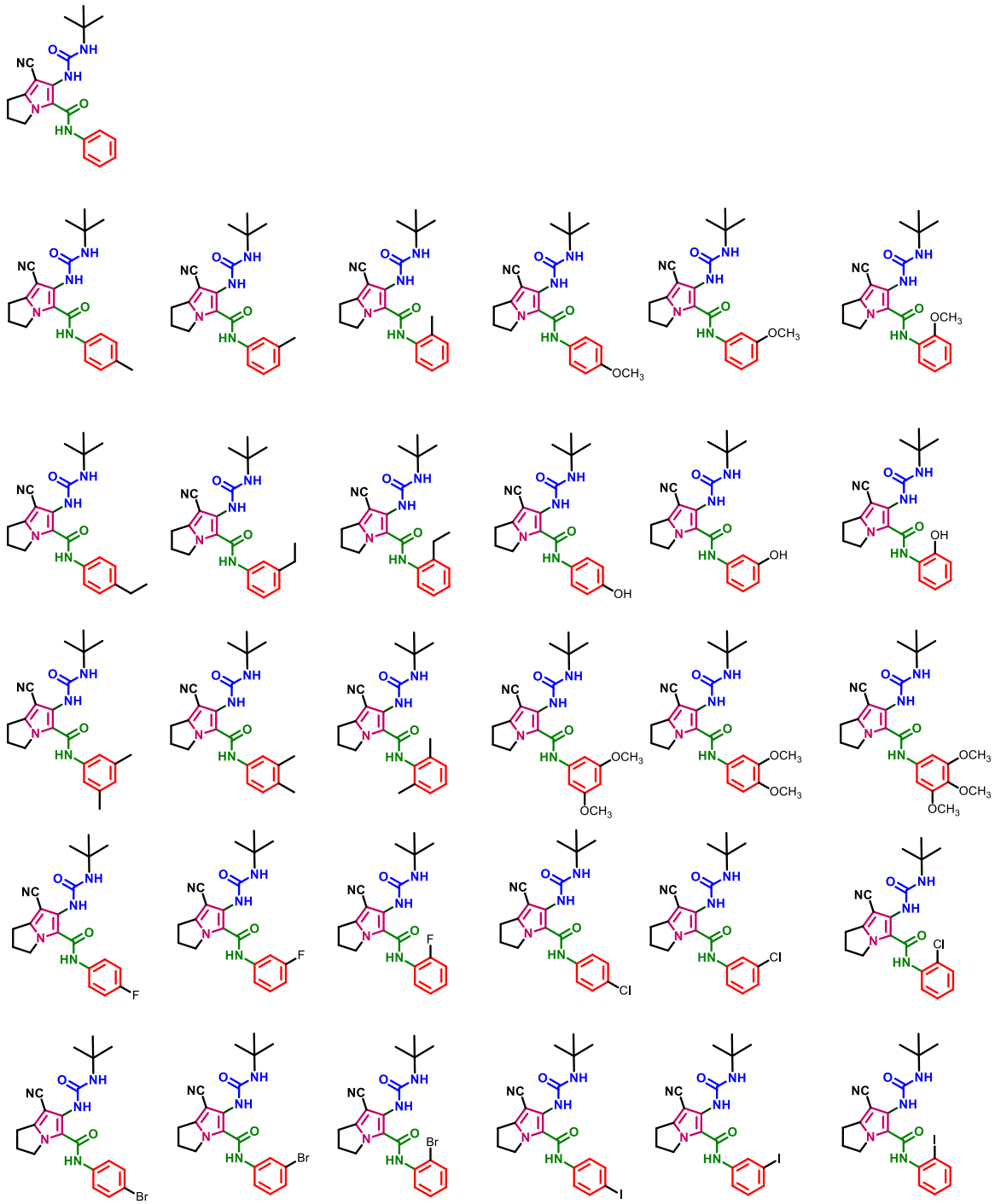
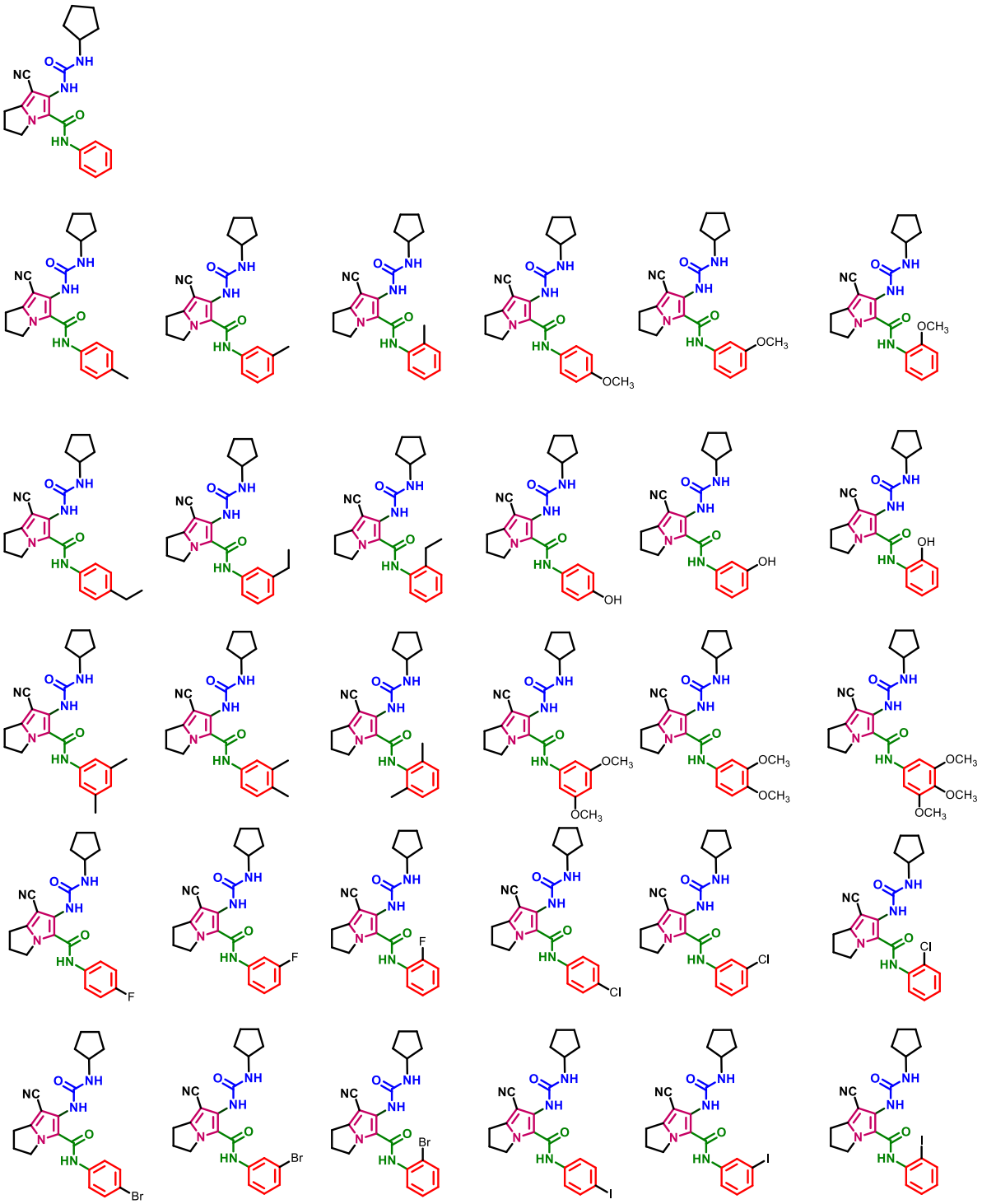


Figure S9. Chemical structure of compound 249-279 (tertbutyl)



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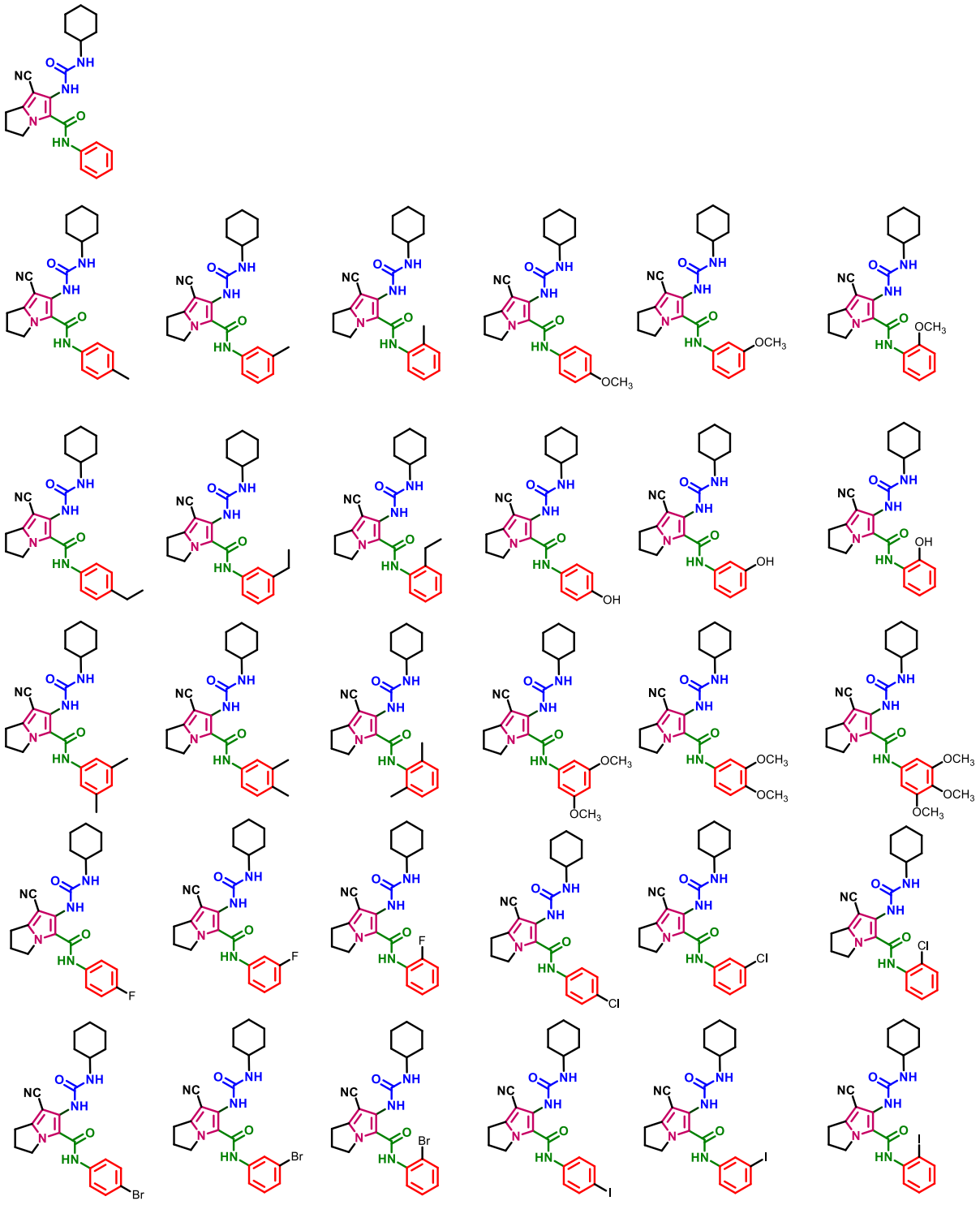

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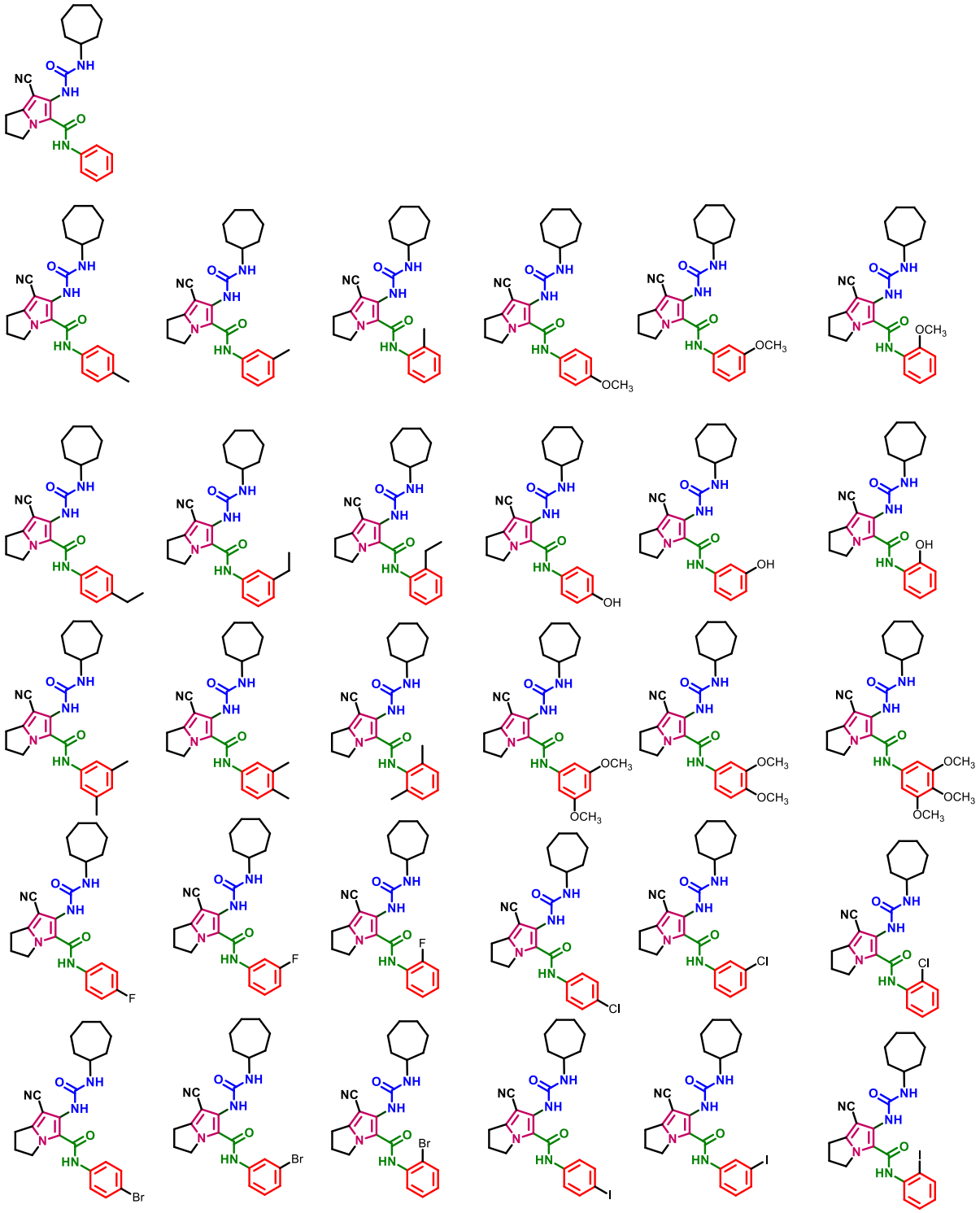


Figure S12. **Chemical structure of compound 342-372 (cycloheptyl)**

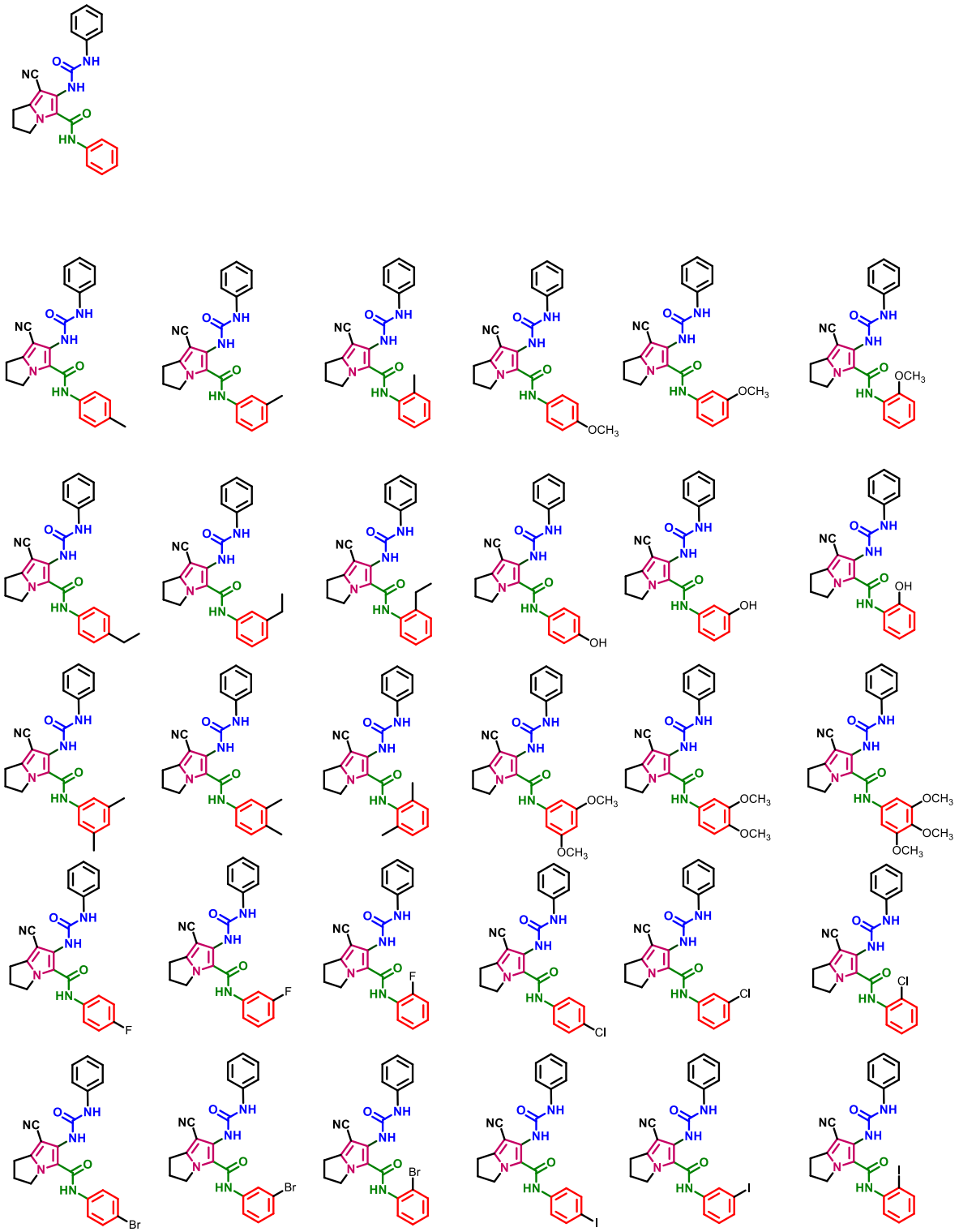


Figure S13. **Chemical structure of compound 373-403 (phenyliso)**

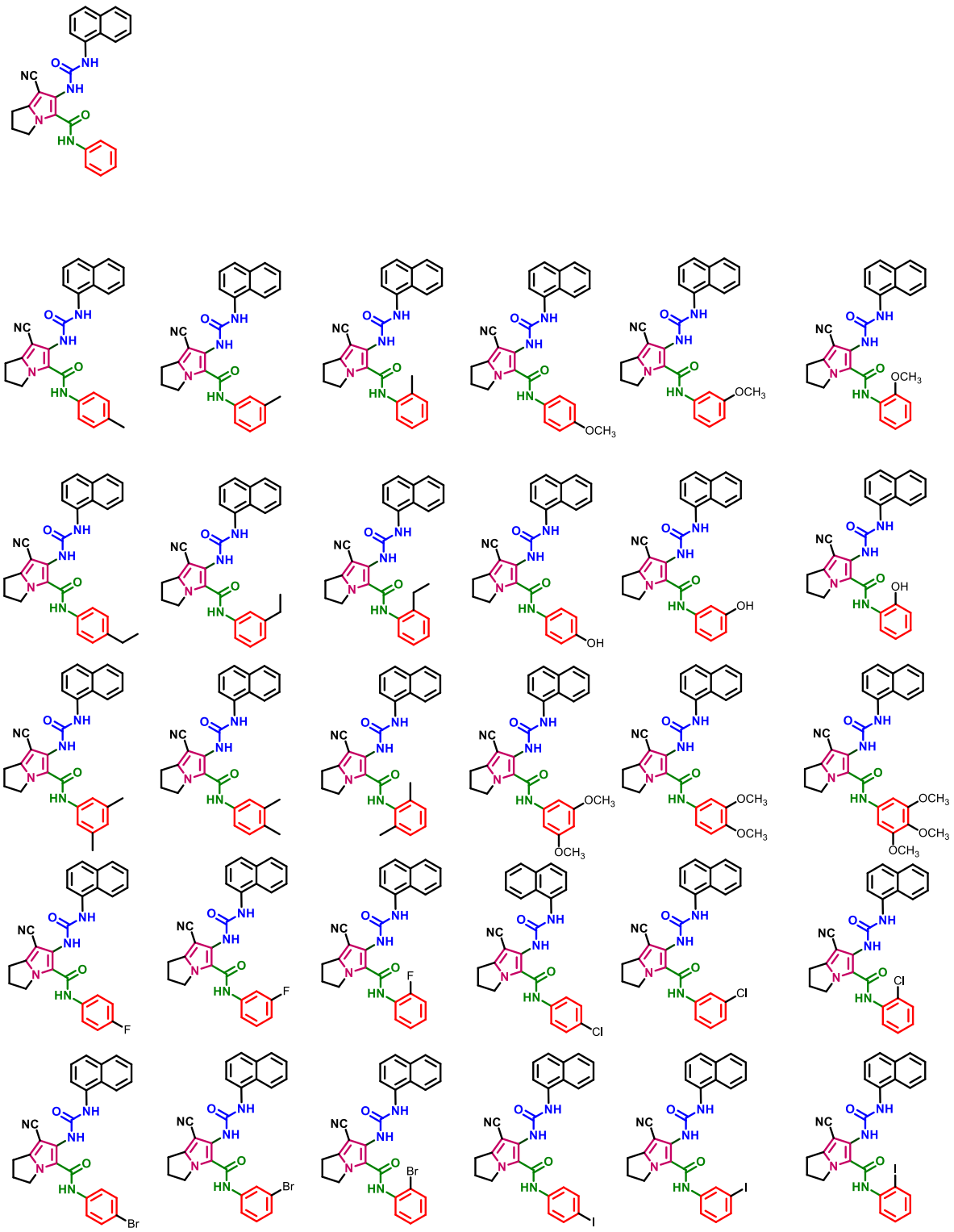


Figure S14. Chemical structure of compound 404-434 (1naphthyliso)

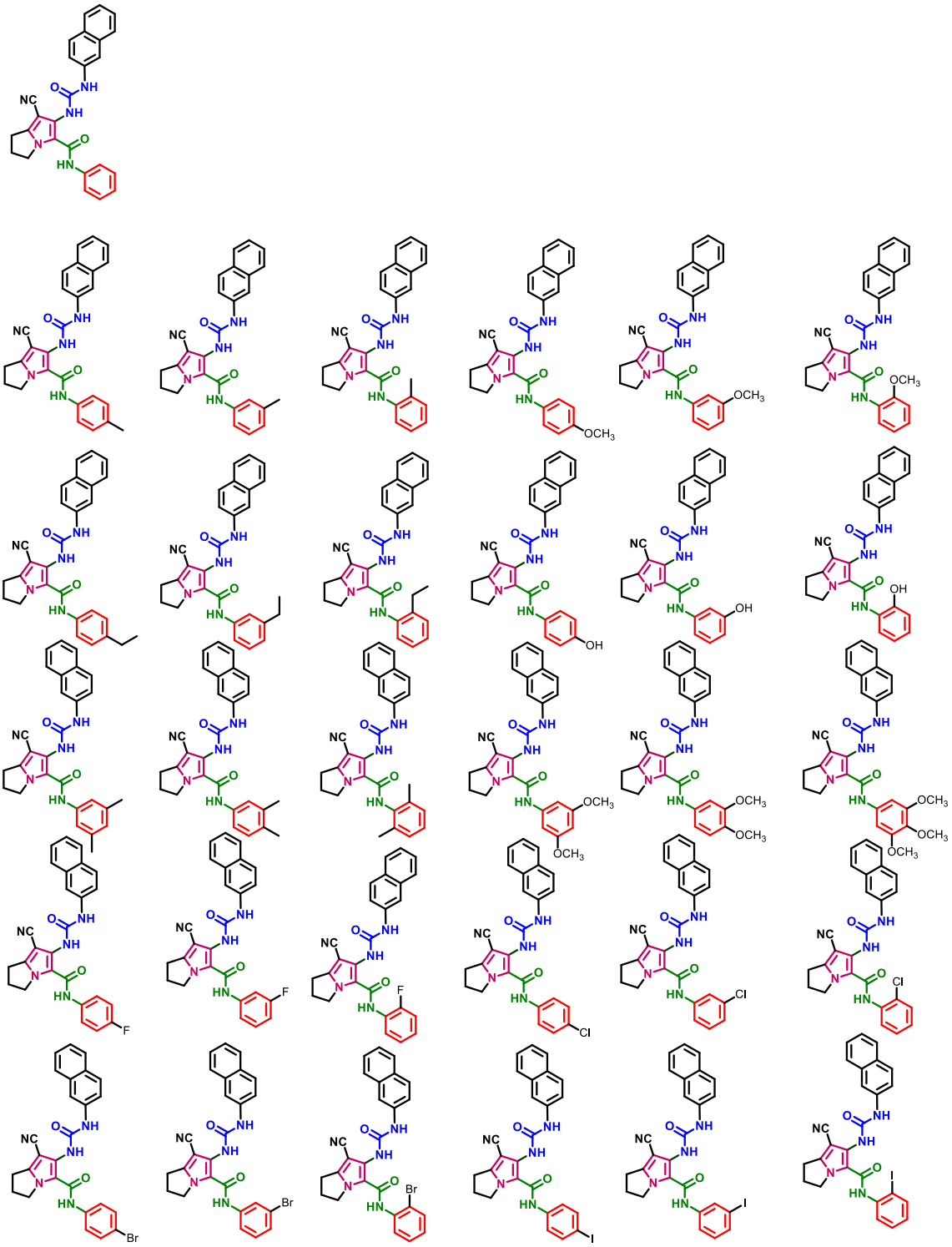


Figure S15. Chemical structure of compound 435-465 (2naphthyliso)

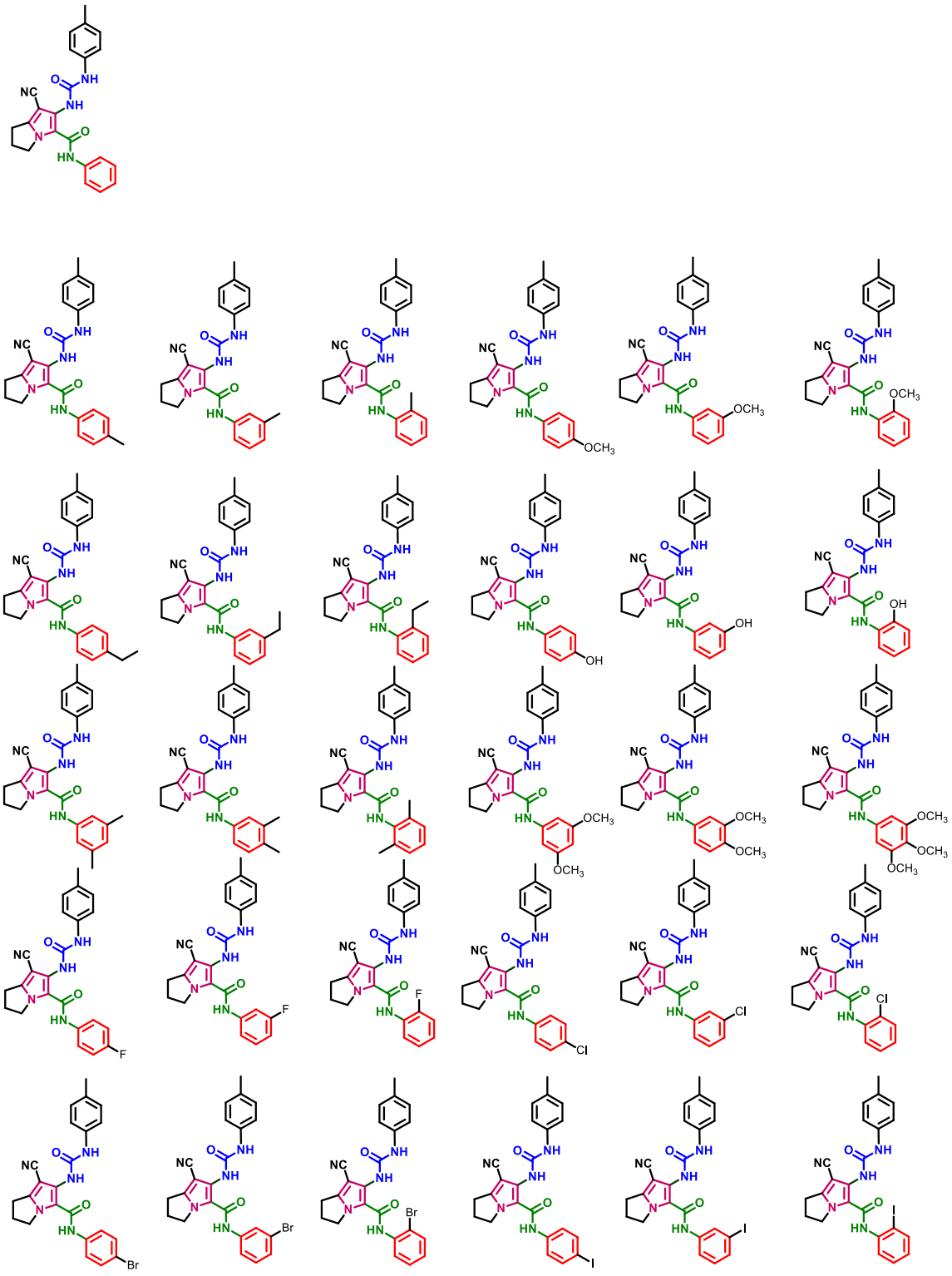


Figure S16. Chemical structure of compound 466-496 (4methylphenyliso)

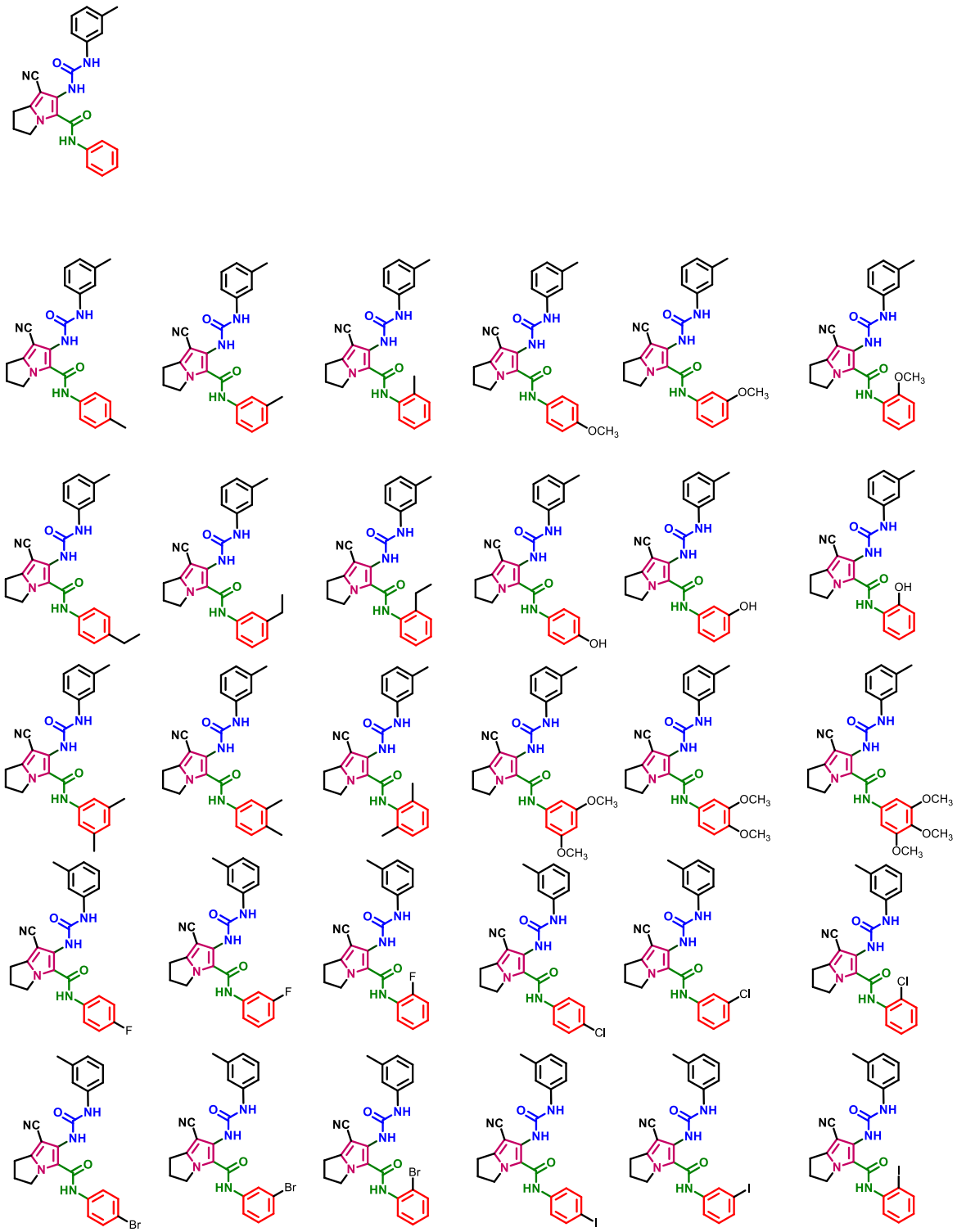


Figure S17. Chemical structure of compound 497-527 (3methylphenyliso)

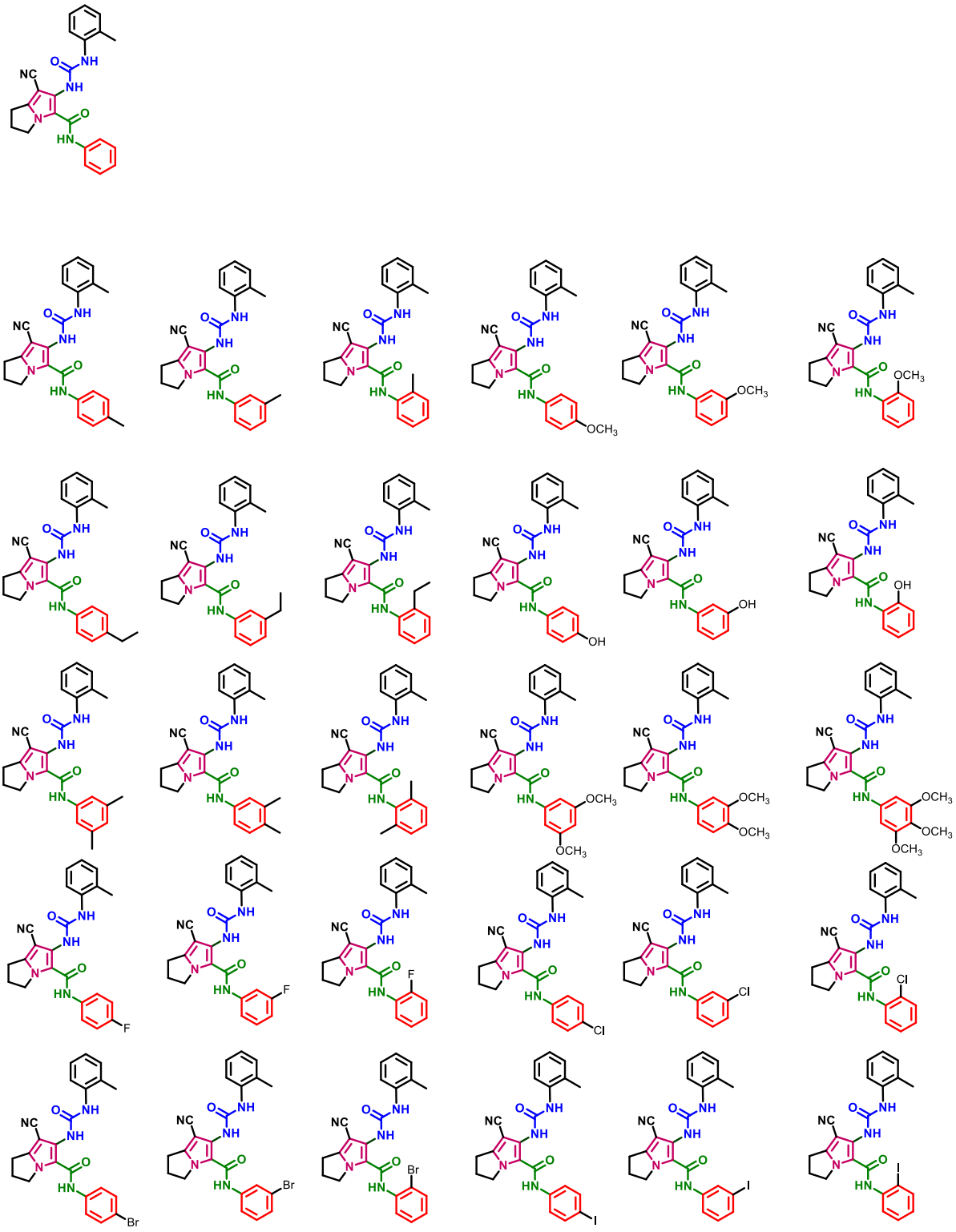


Figure S18. Chemical structure of compound 528-558 (2methylphenyliso)

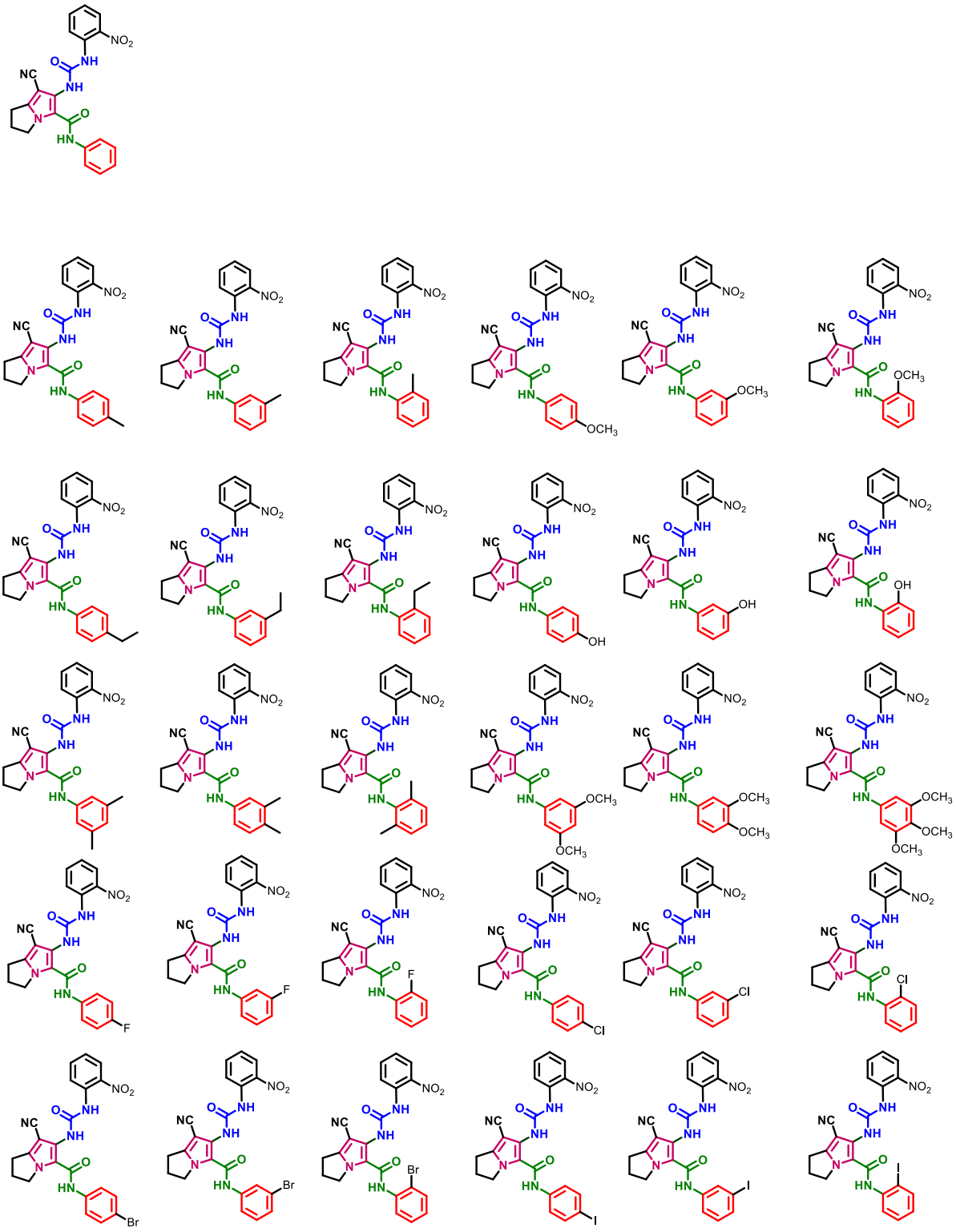


Figure S19. Chemical structure of compound 559-589 (2nitrophenyliso)

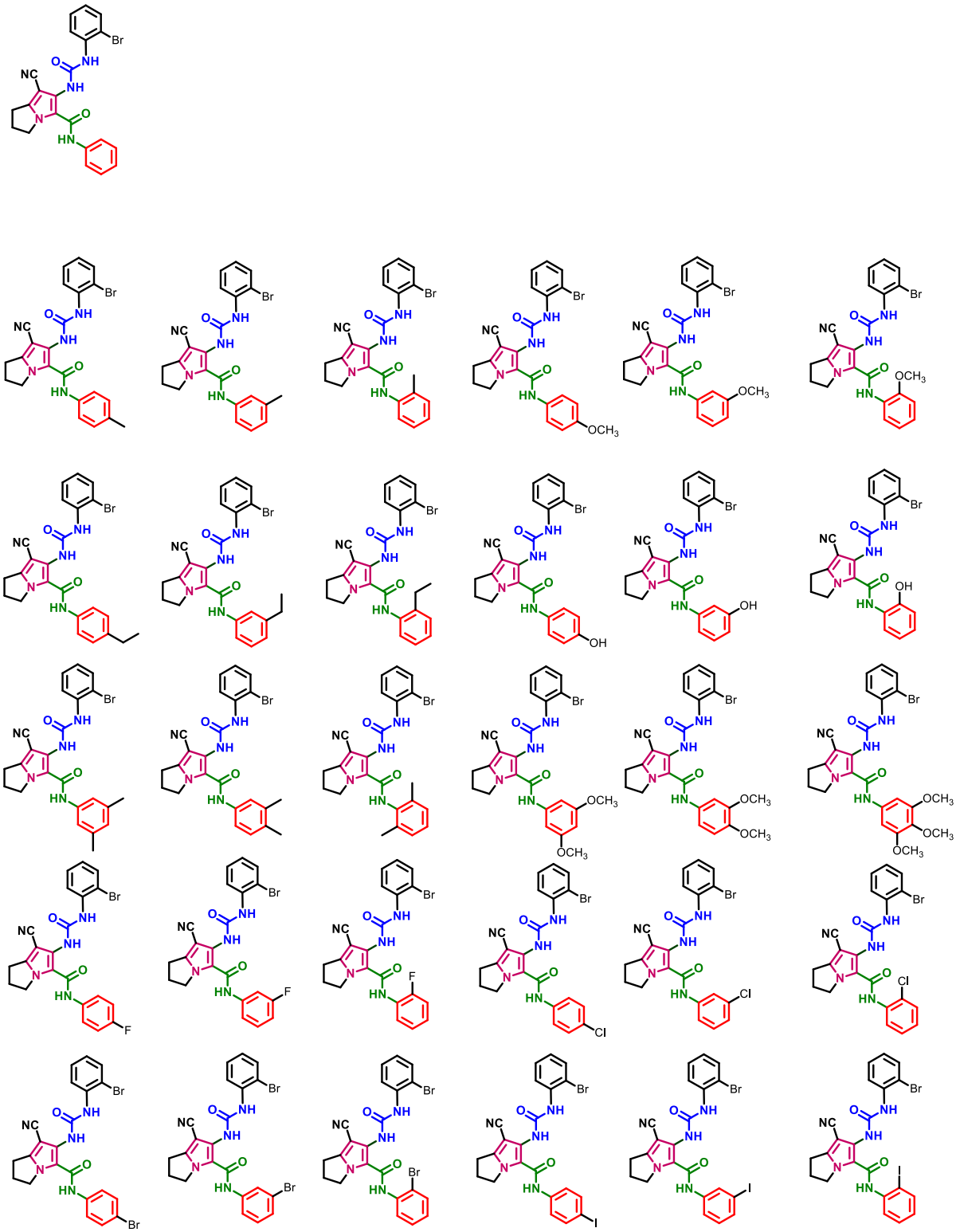


Figure S20. Chemical structure of compound 590-620 (2bromophenyliso)

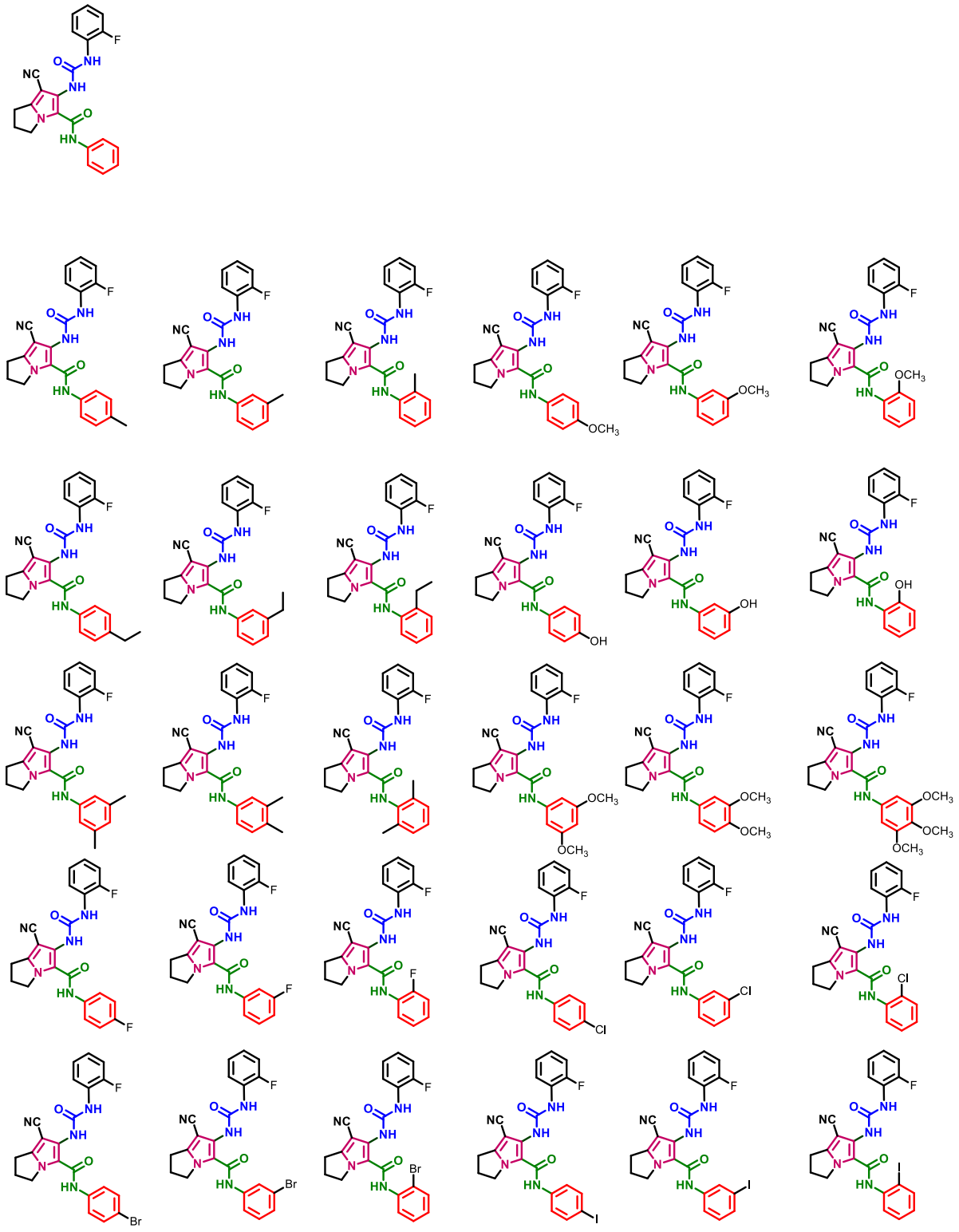


Figure S21. Chemical structure of compound 621-651 (2fluorophenyliso)

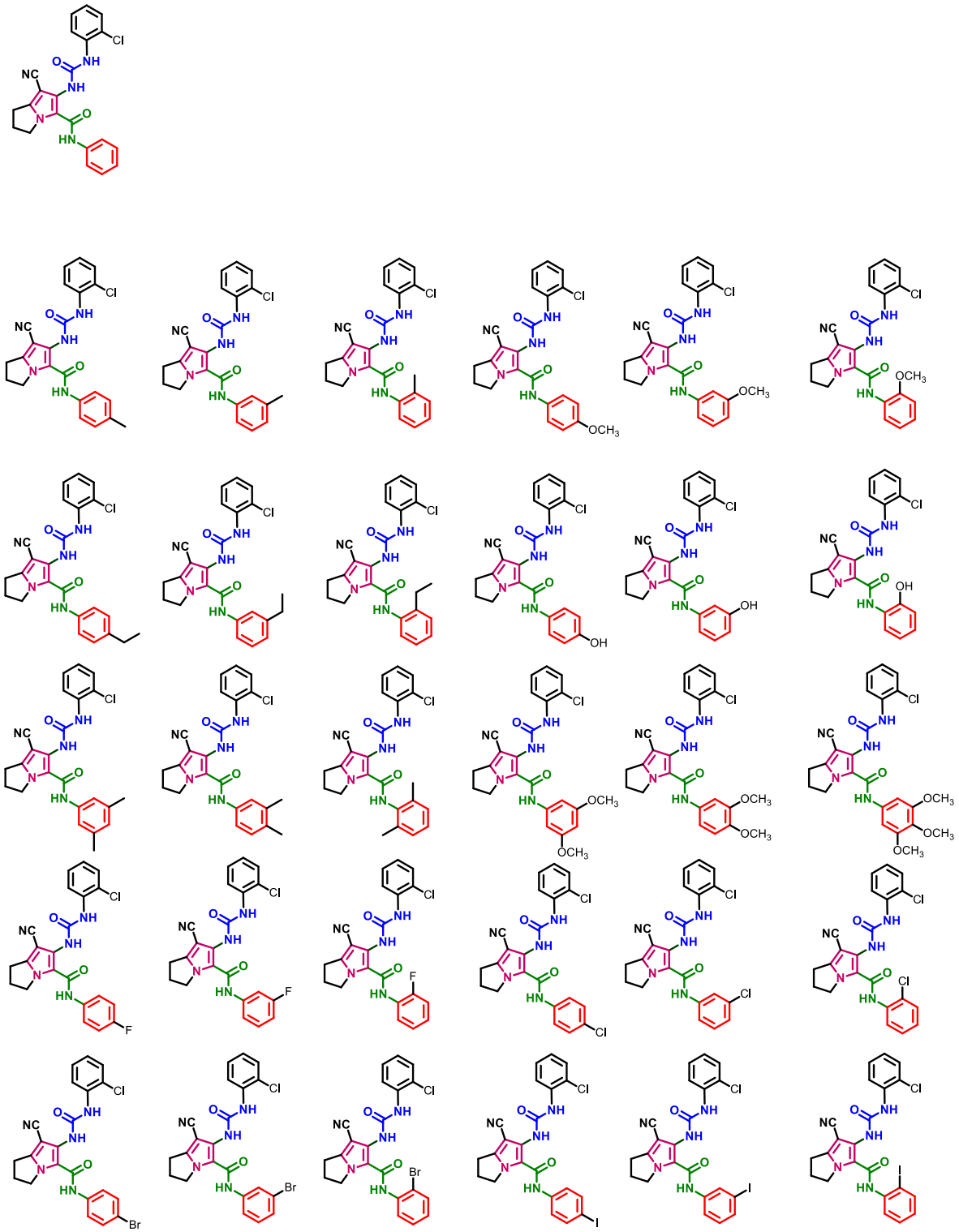


Figure S22. **Chemical structure of compound 652-682 (2chlorophenyliso)**

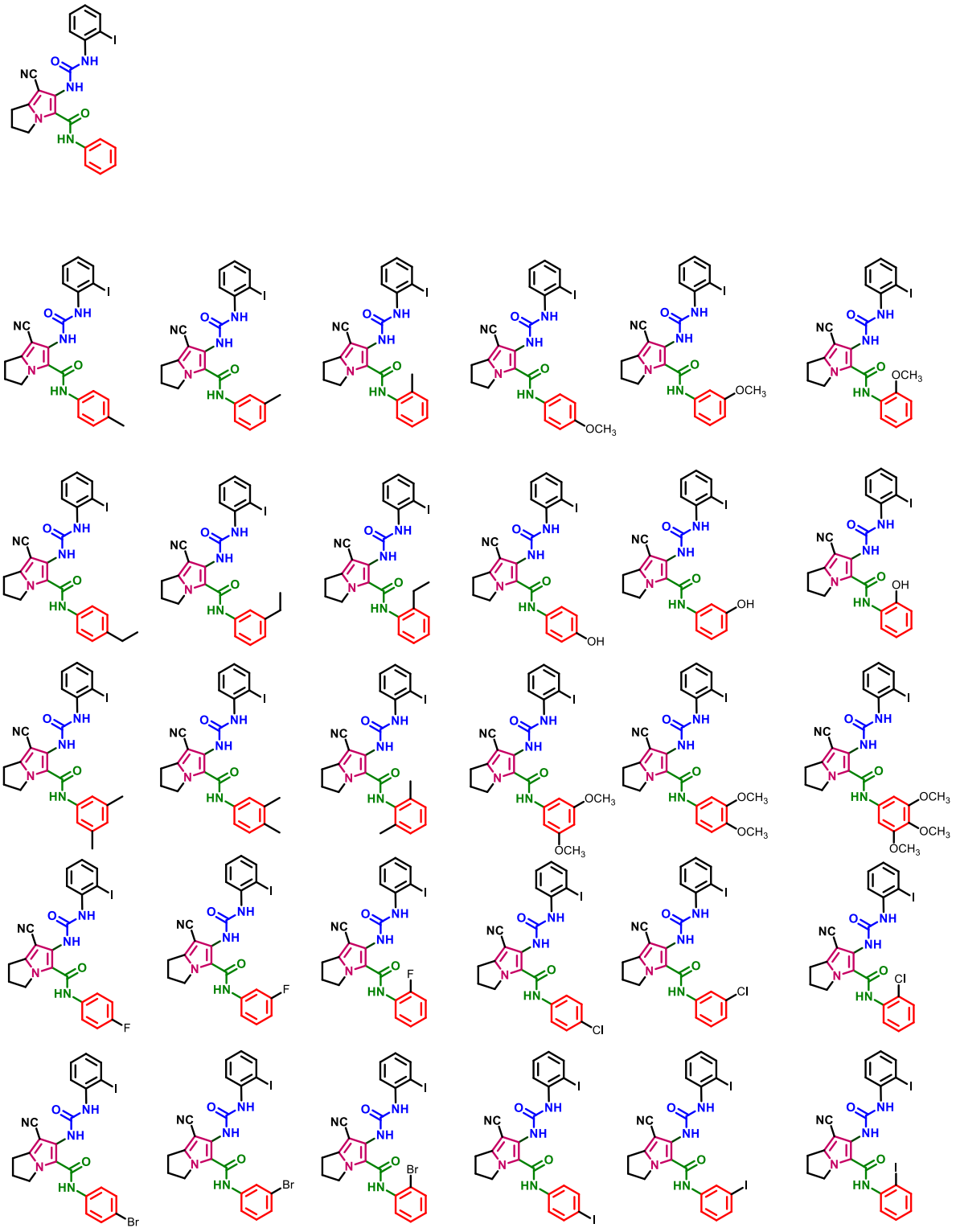


Figure S23. Chemical structure of compound 683-713 (2iodophenyliso)

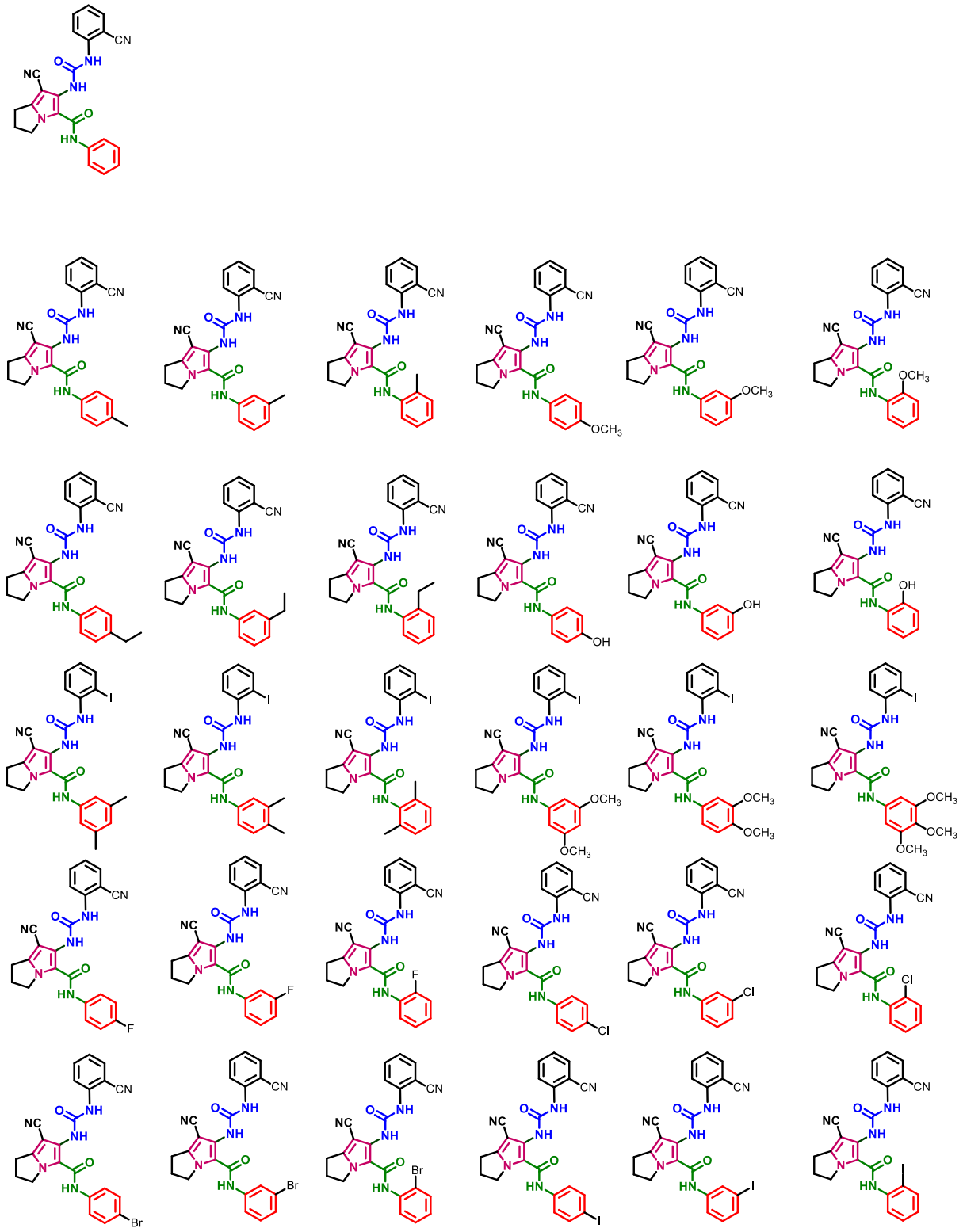


Figure S24. Chemical structure of compound 714-744 (2cyanophenyliso)

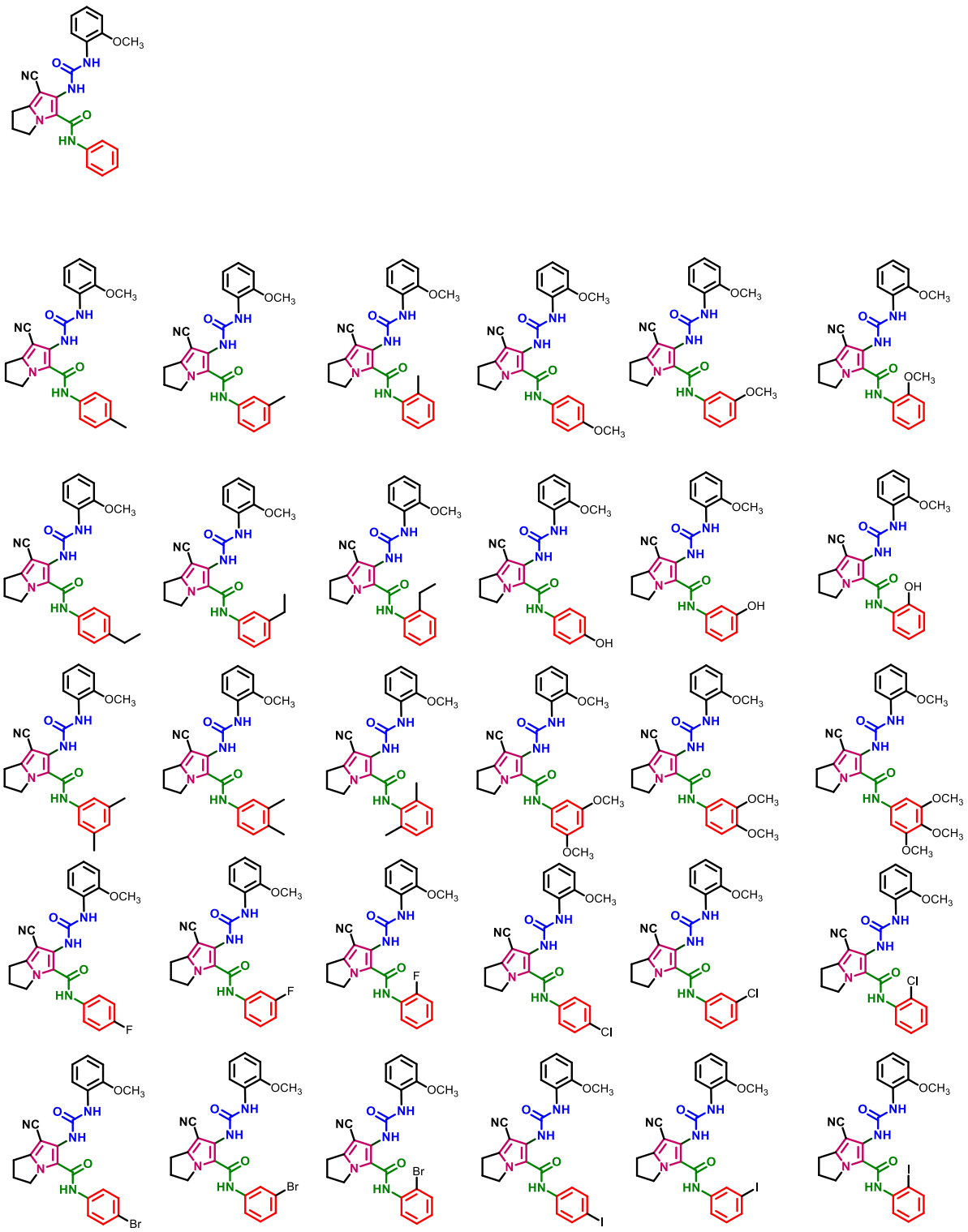


Figure S25. Chemical structure of compound 745-775 (2methoxyphenyliso)

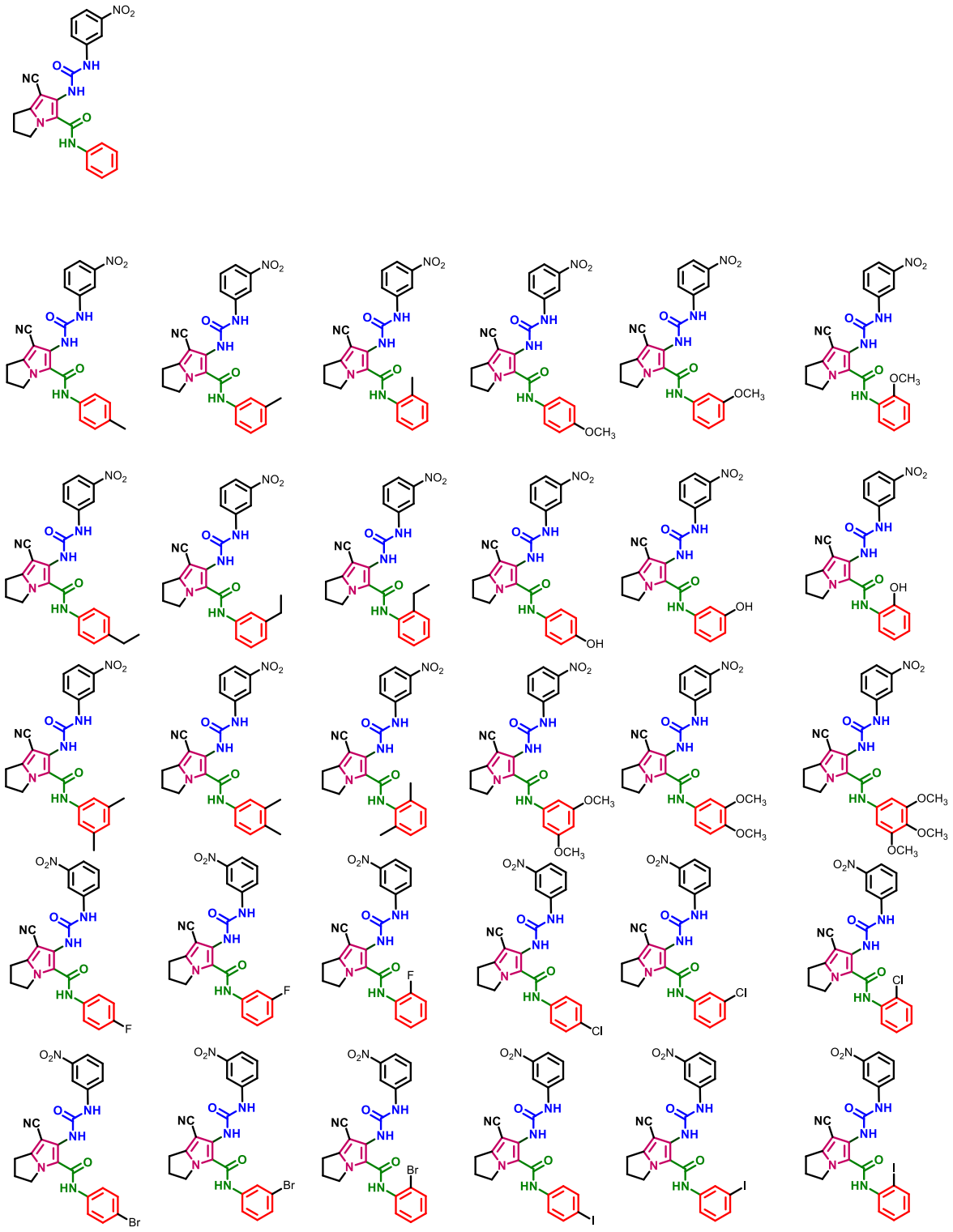


Figure S26. Chemical structure of compound 776-806 (3nitrophenyliso)

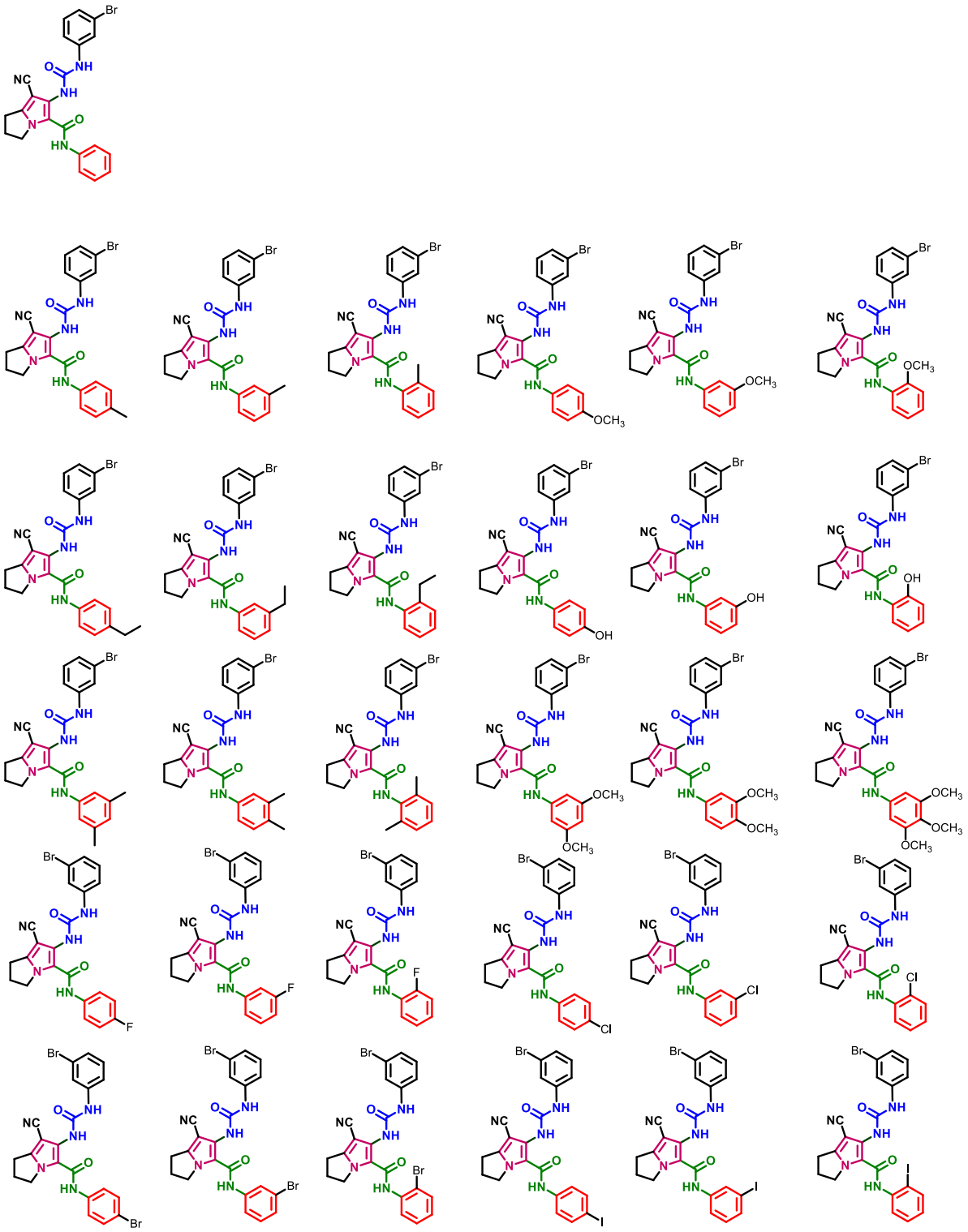


Figure S27. Chemical structure of compound 807-837 (3bromophenyliso)

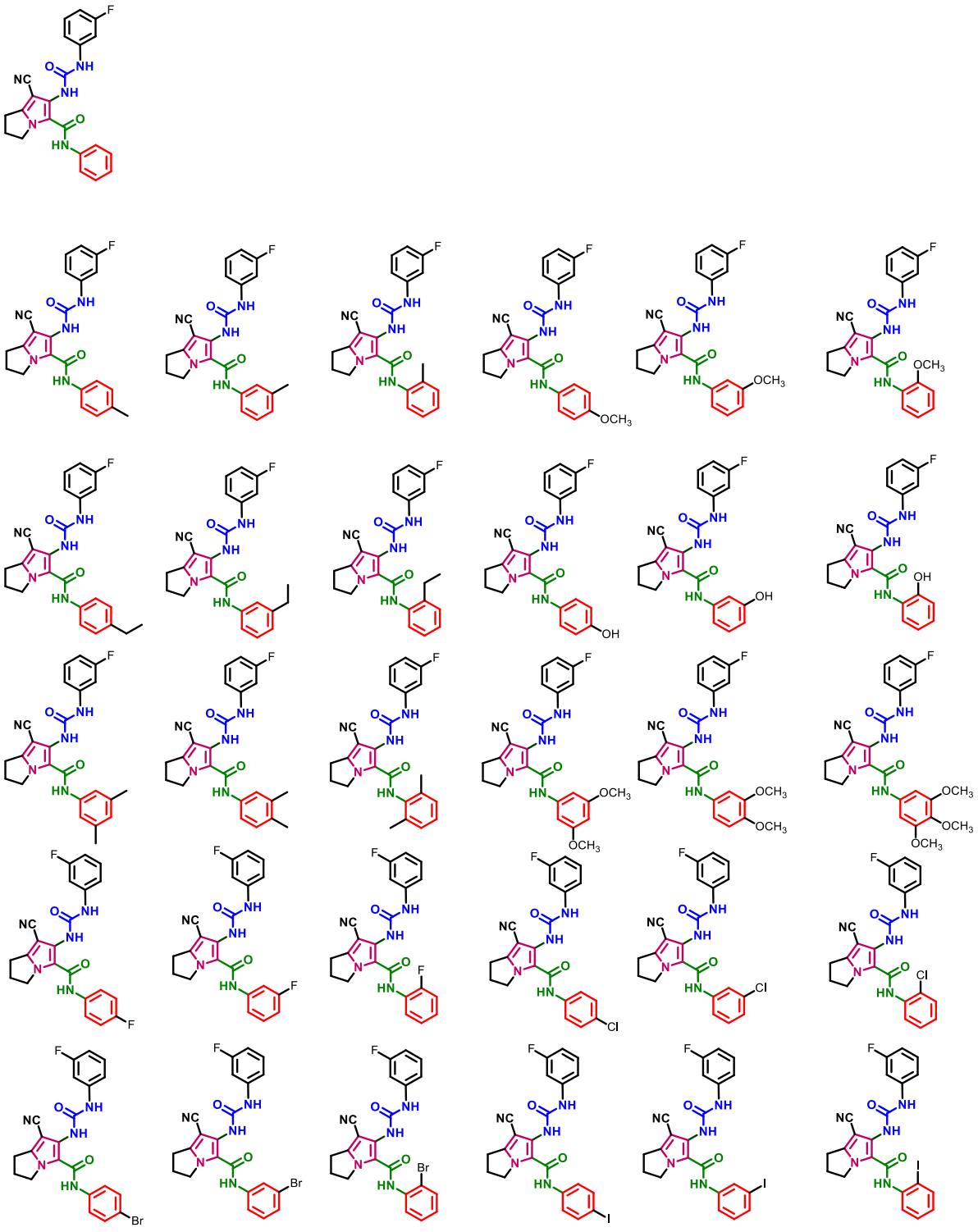


Figure S28. Chemical structure of compound 838-868 (3fluorophenyliso)

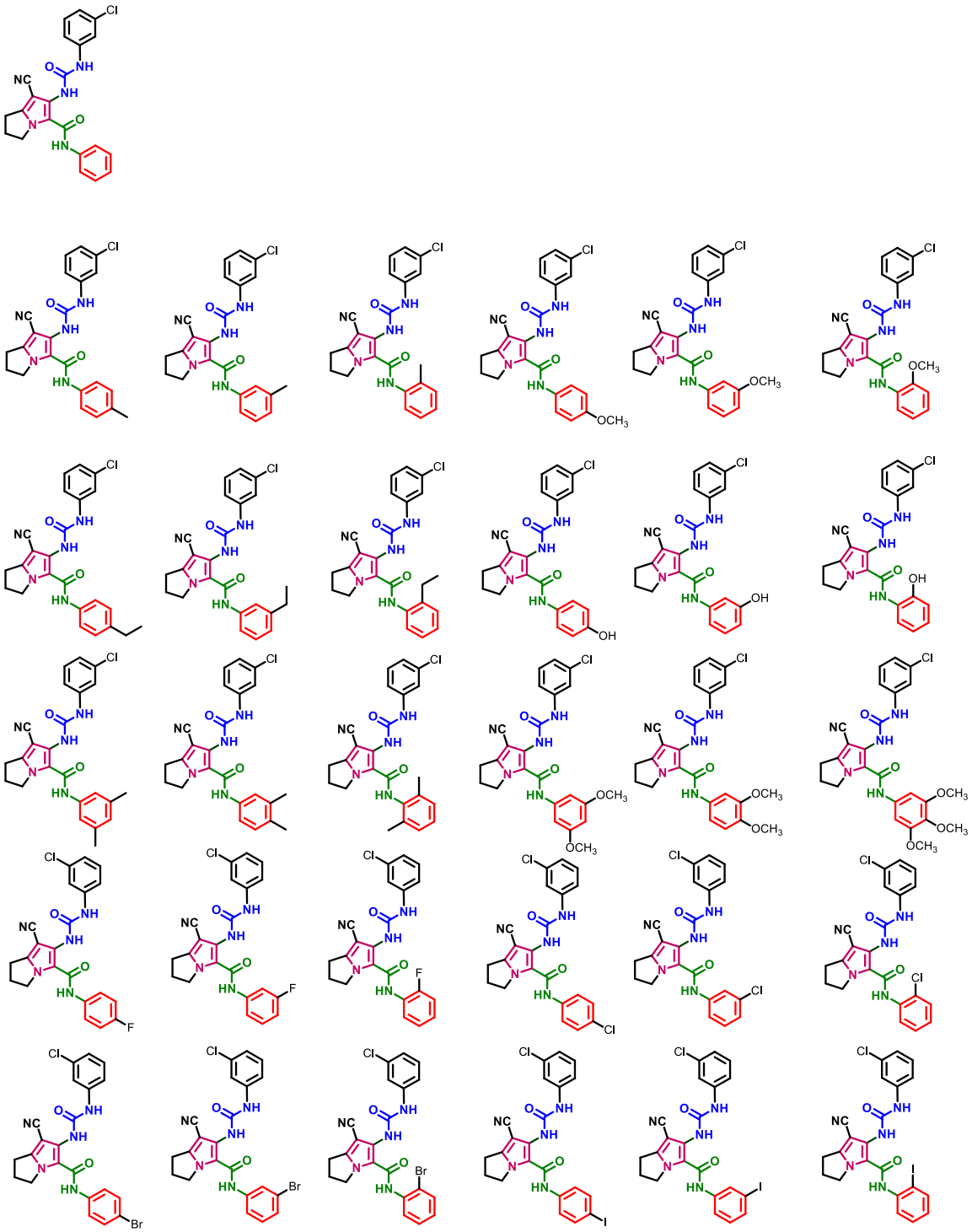


Figure S29. Chemical structure of compound 869-899 (3chlorophenyliso)

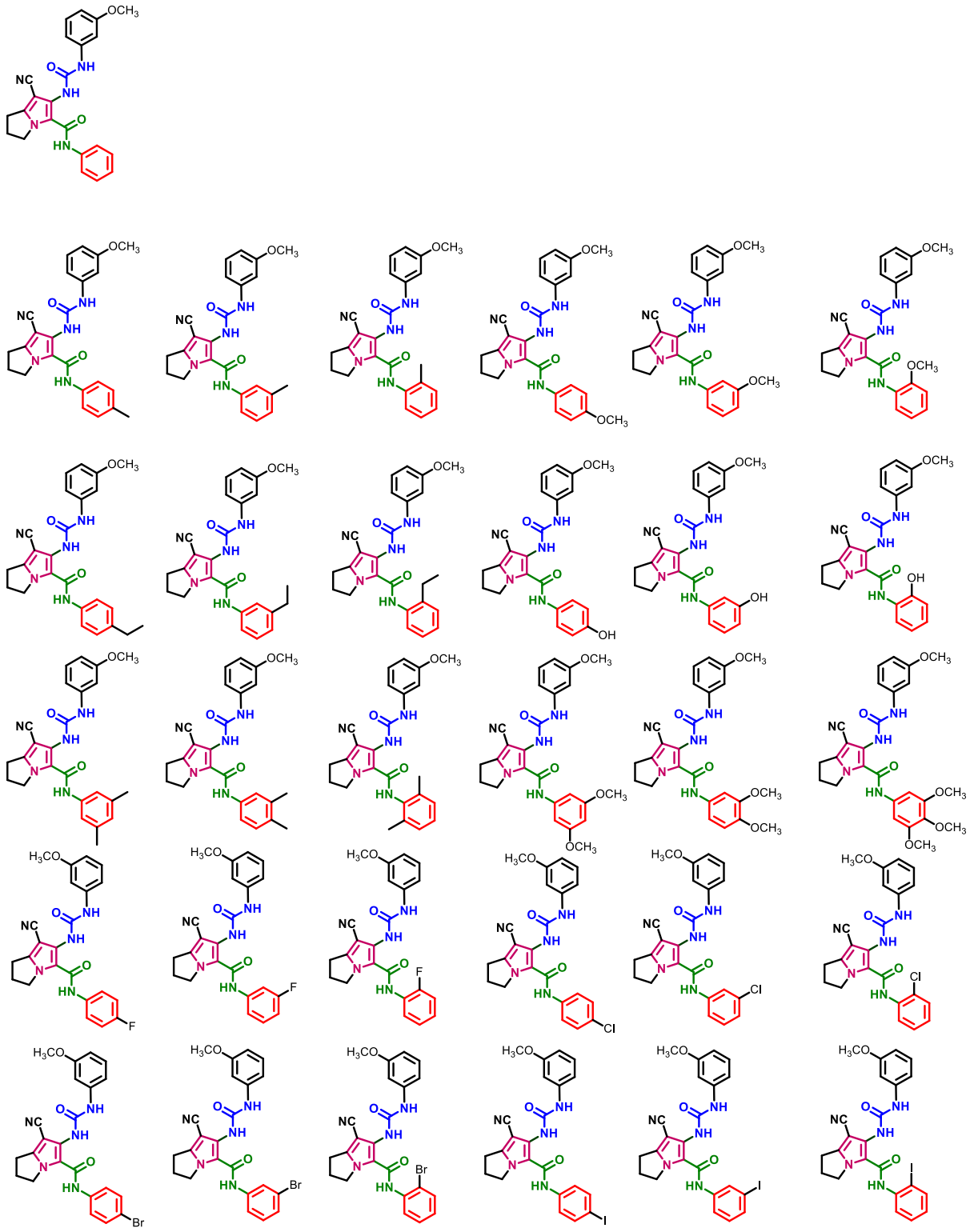


Figure S30. Chemical structure of compound 900-930 (3methoxyphenyliso)

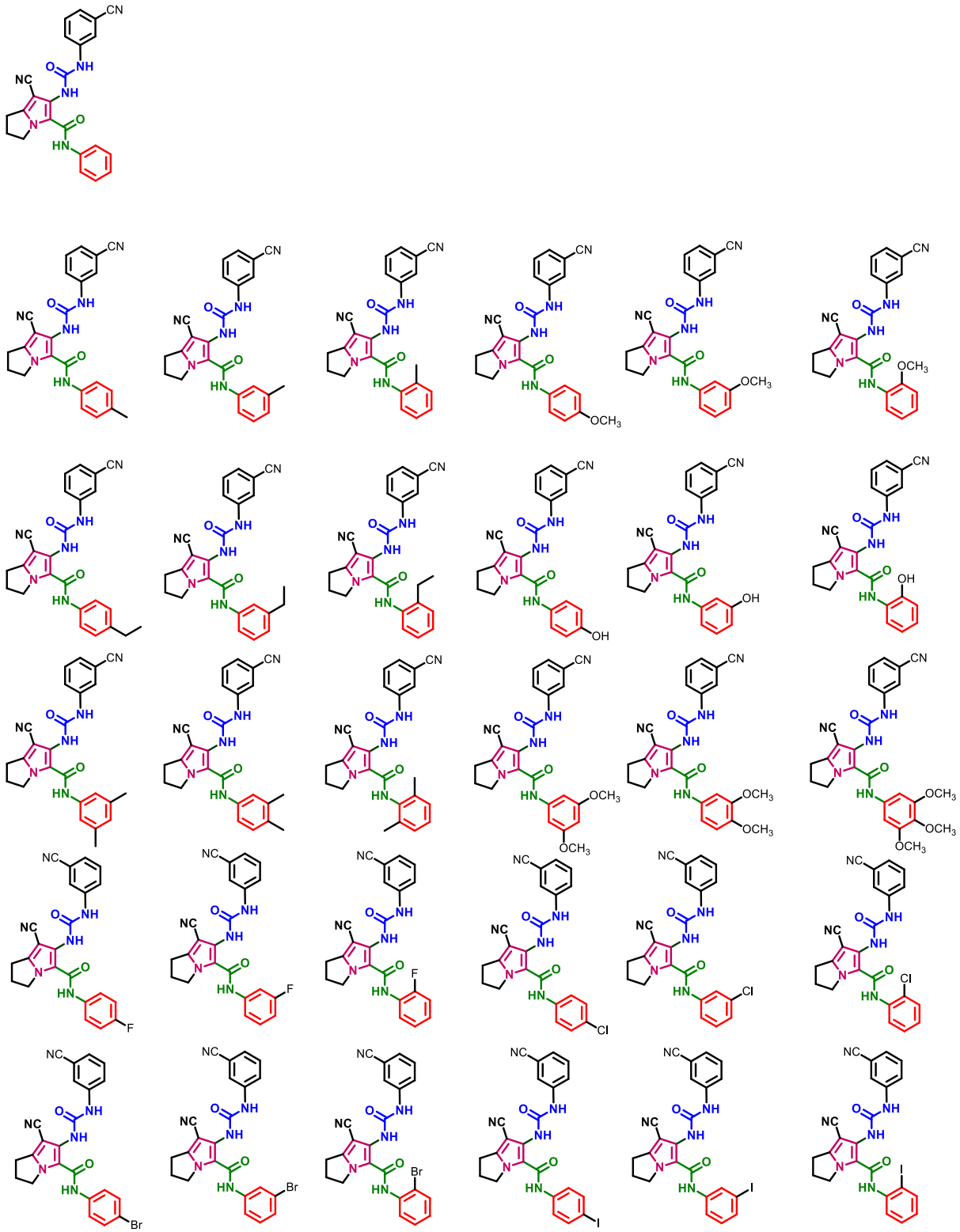


Figure S31. Chemical structure of compound 931-961 (3cyanophenyliso)

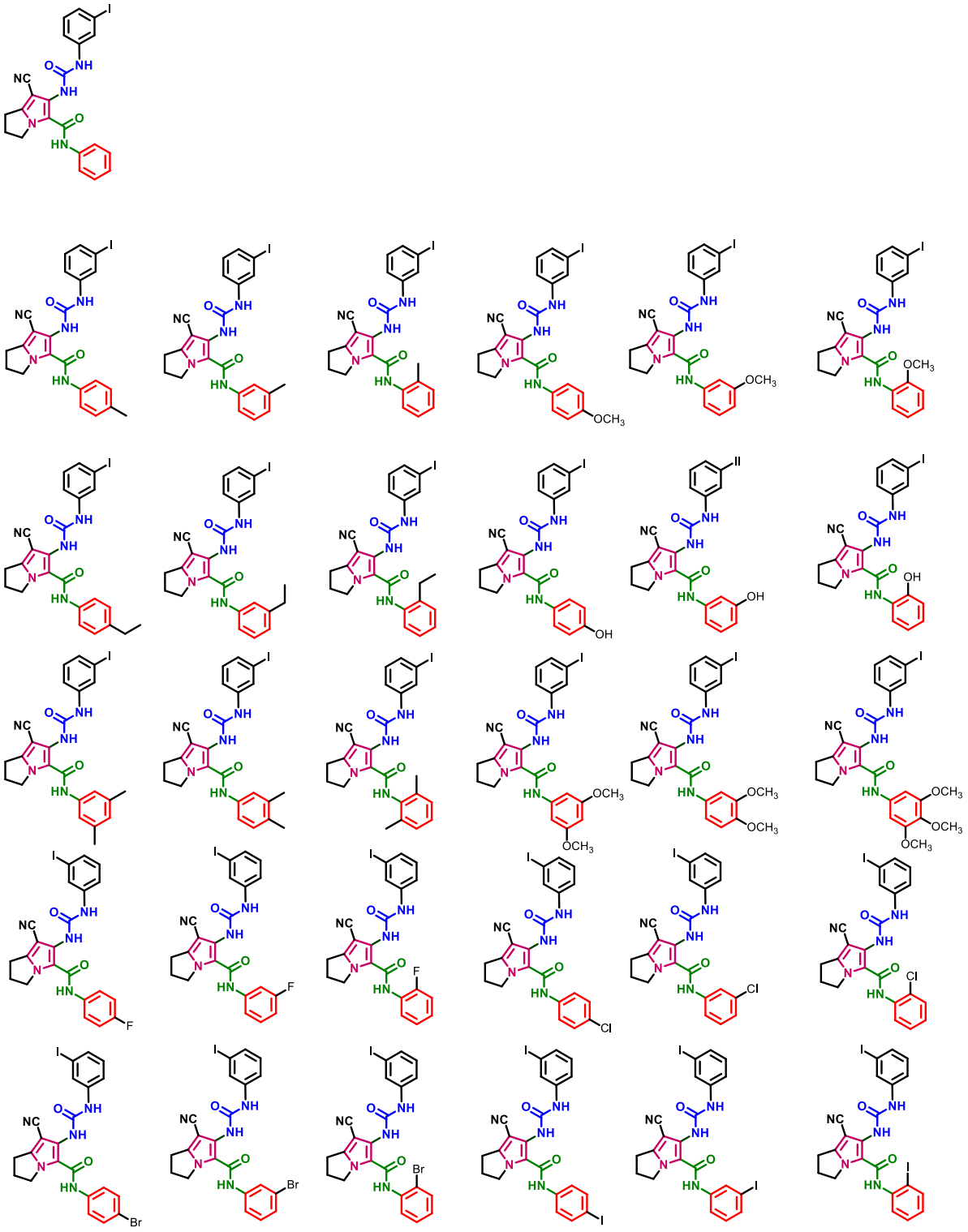


Figure S32. Chemical structure of compound 962-992 (3iodophenyliso)

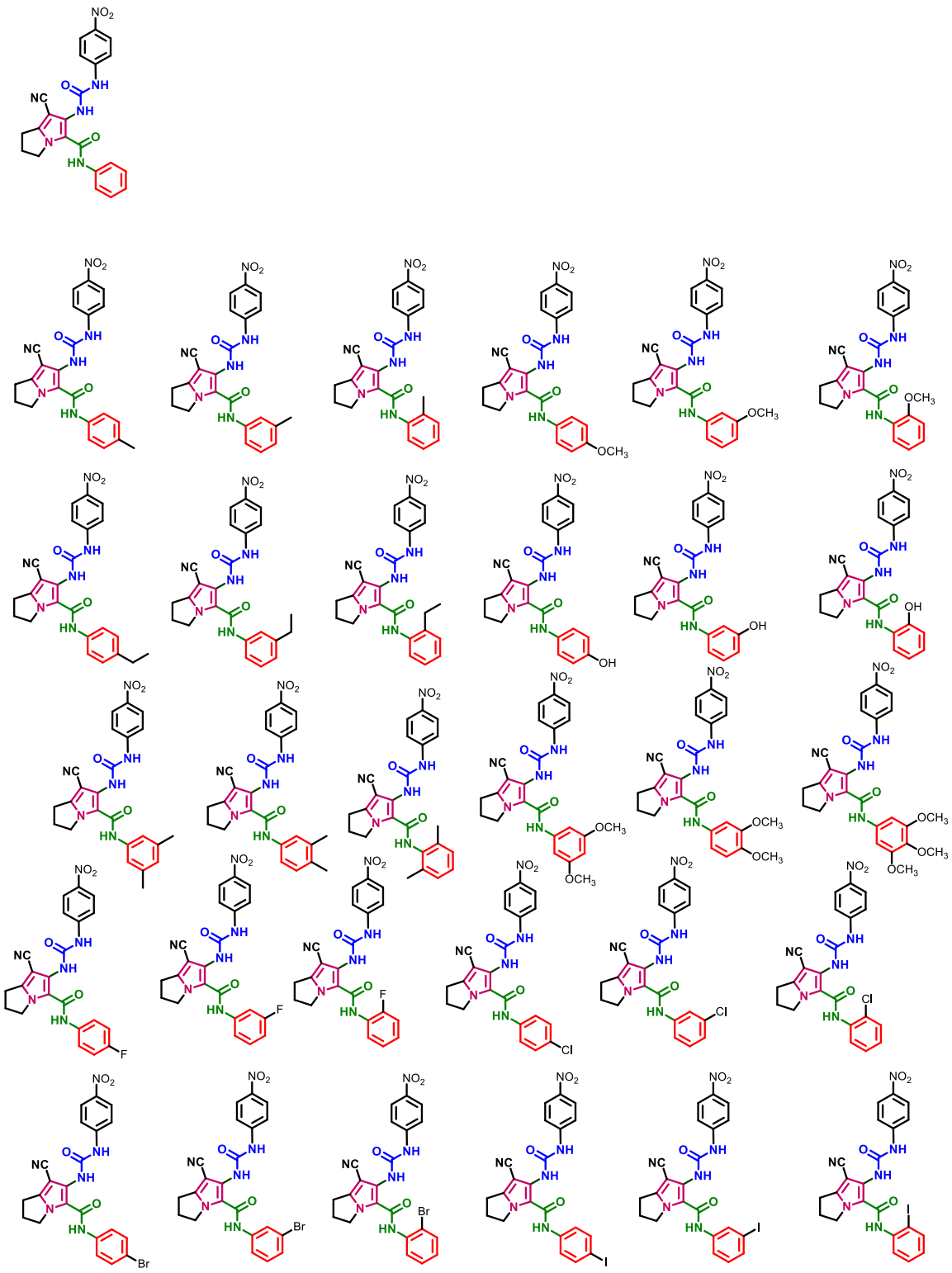


Figure S33. Chemical structure of compound 993-1023 (4nitrophenyliso)

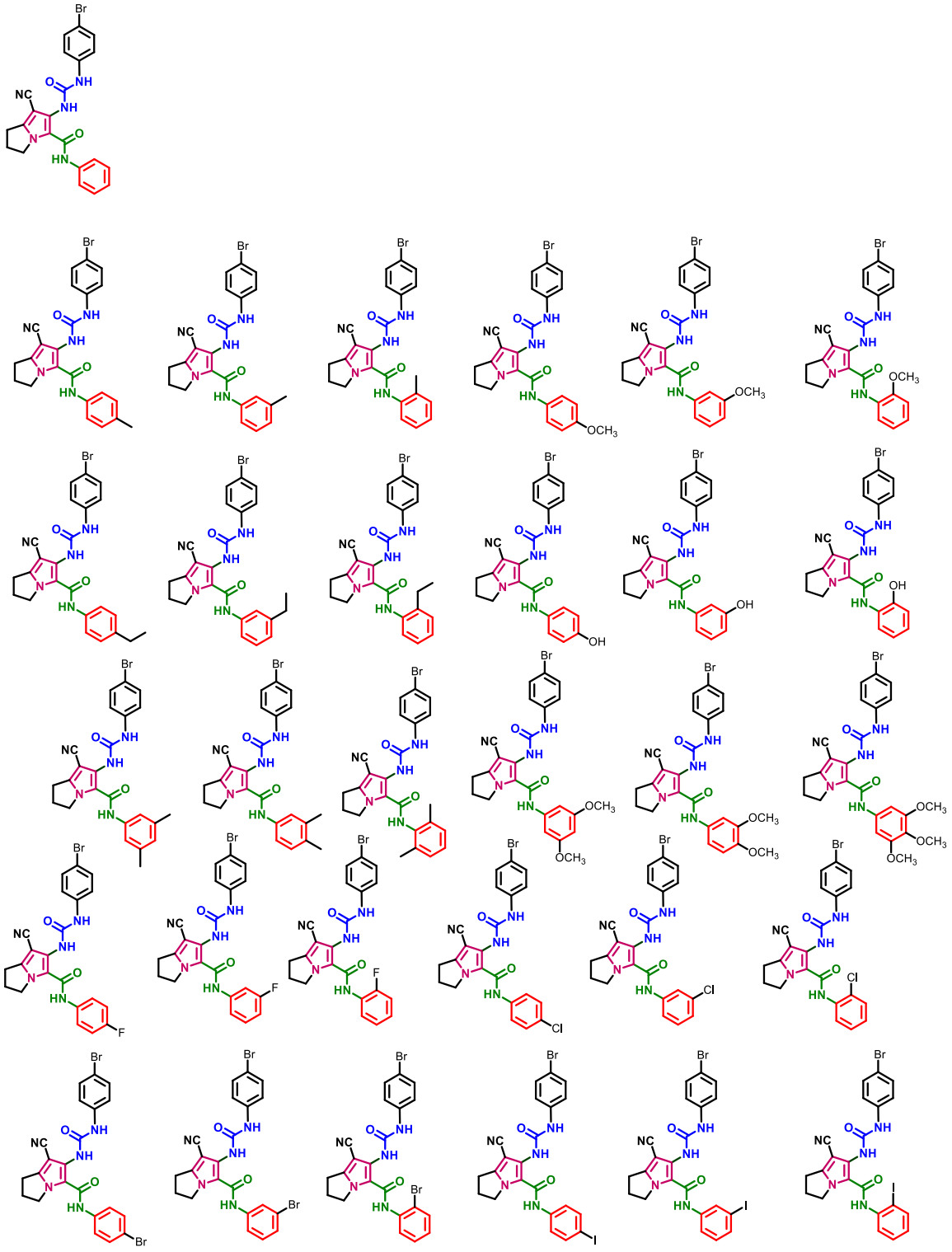


Figure S34. Chemical structure of compound 1024-1054 (4bromophenyliso)

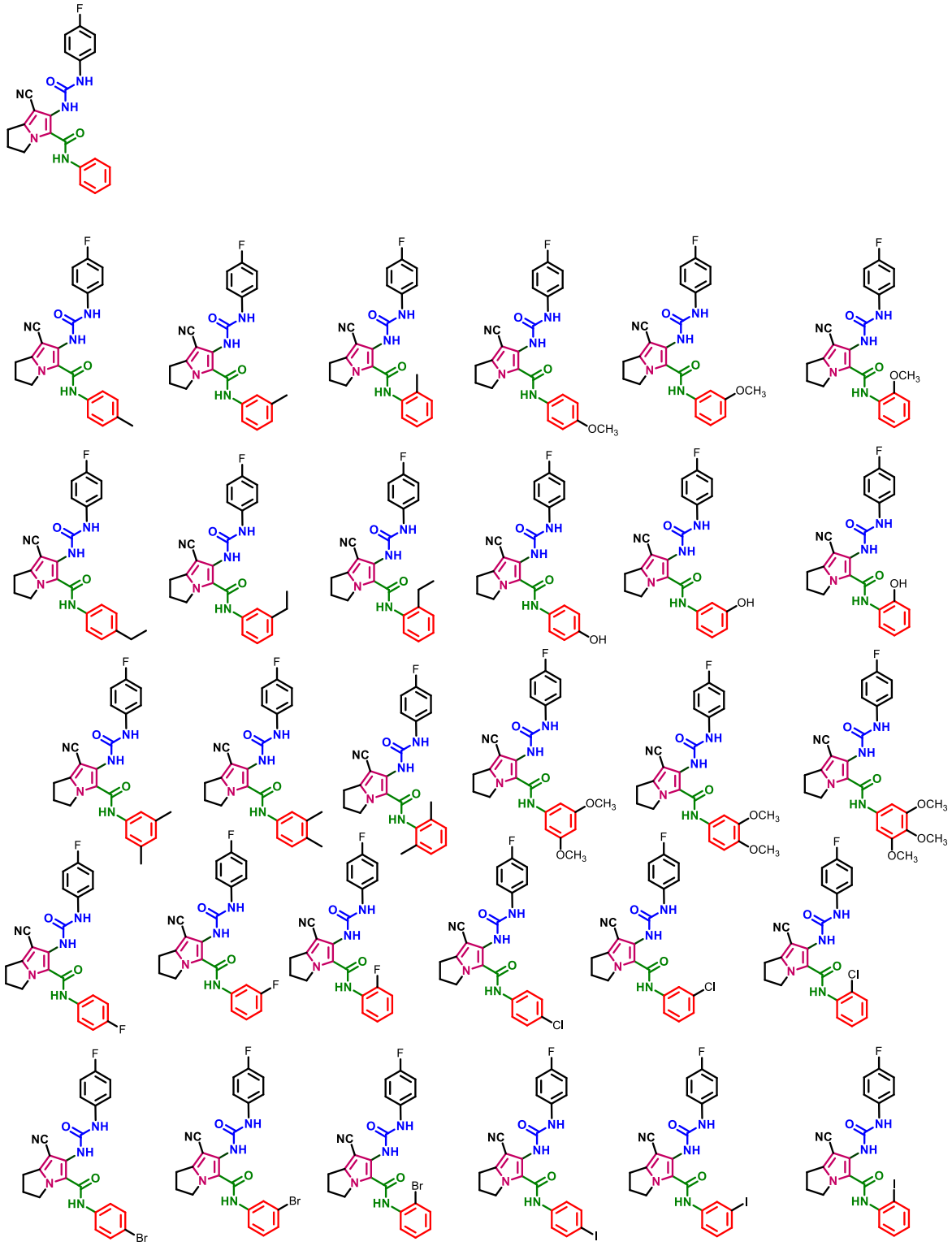


Figure S35. Chemical structure of compound 1055-1085 (4fluorophenyliso)

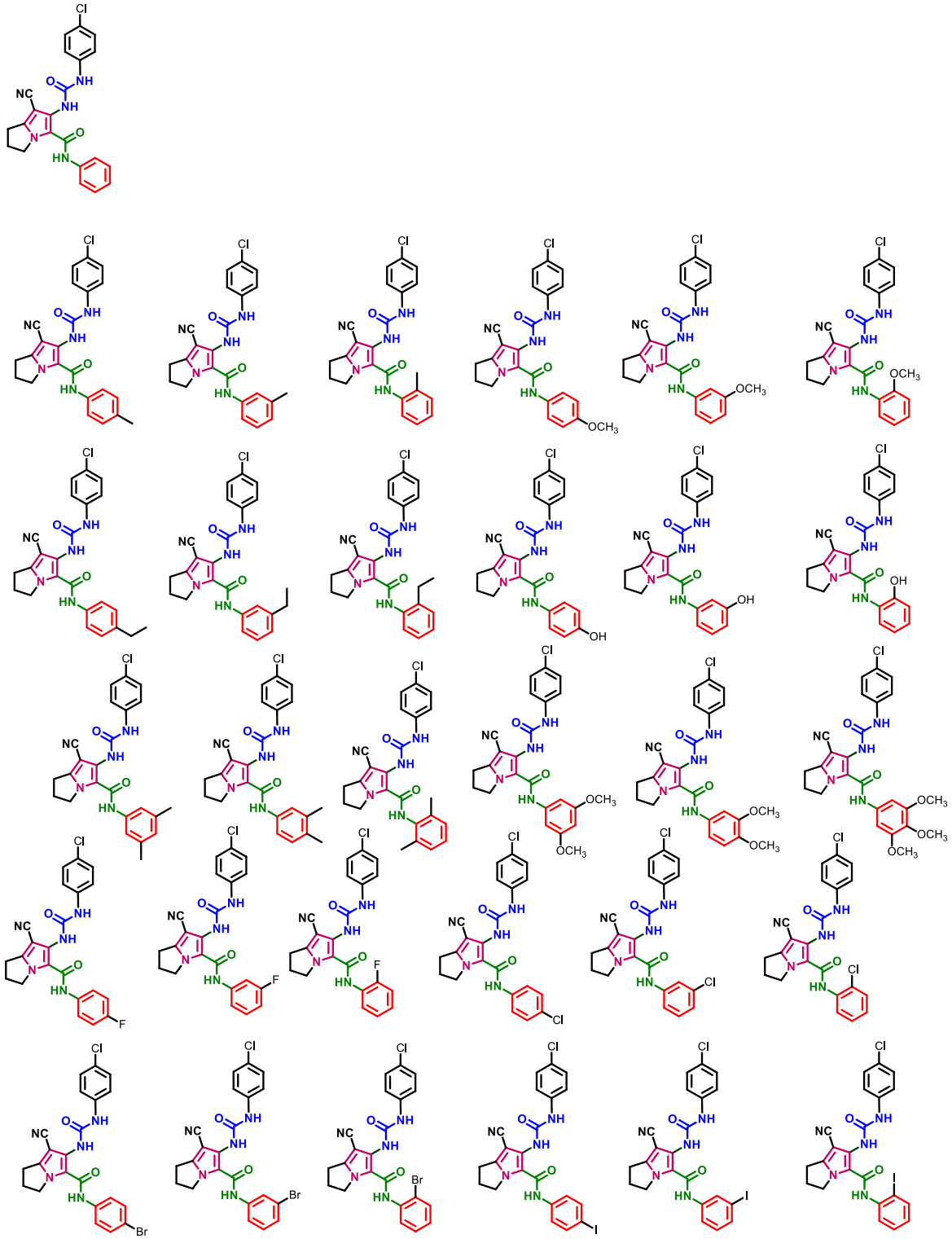


Figure S36. Chemical structure of compound 1086-1116 (4chlorophenyliso)

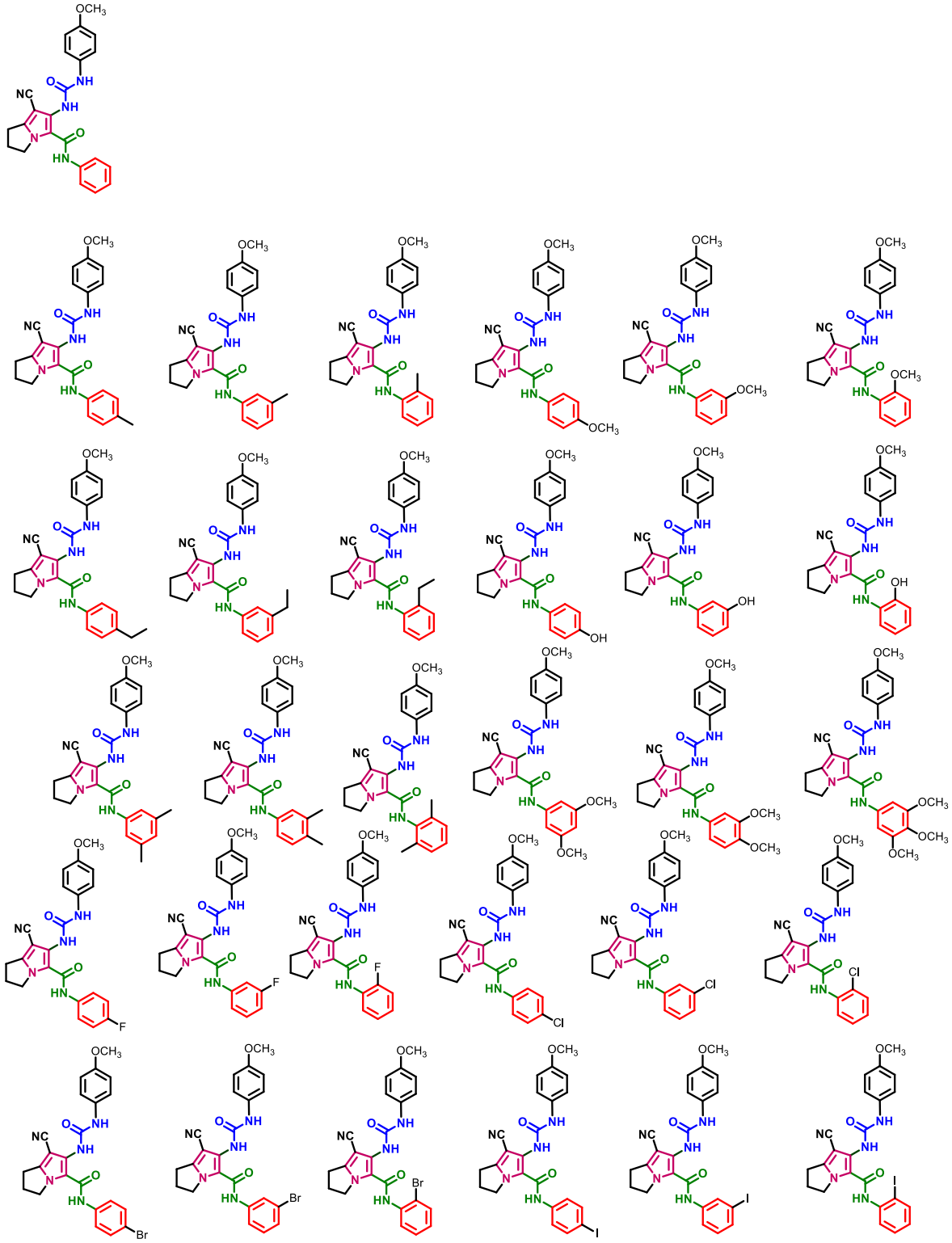


Figure S37. Chemical structure of compound 1117-1147 (4methoxyphenyliso)

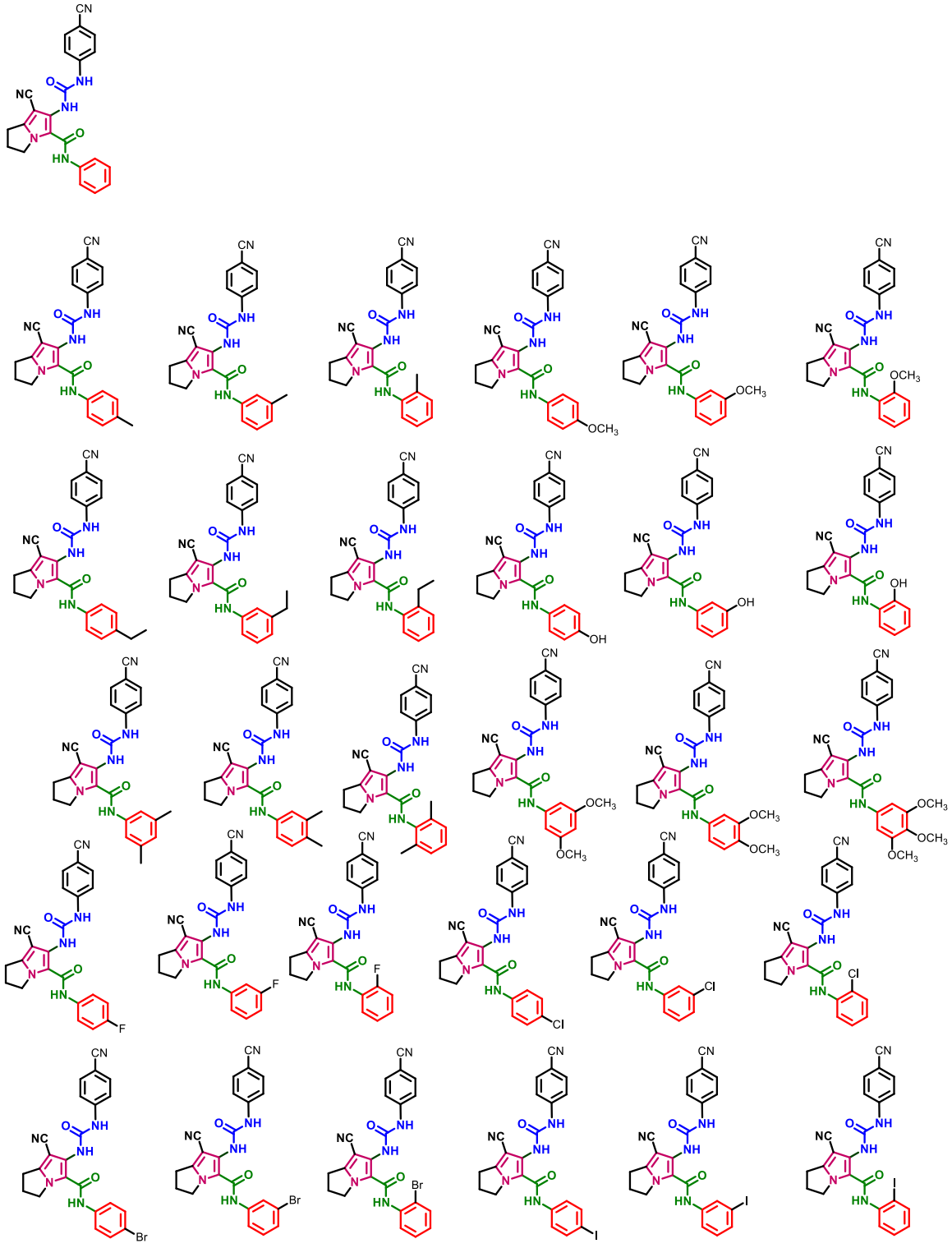


Figure S38. Chemical structure of compound 1148-1178 (4cyanohenyliso)

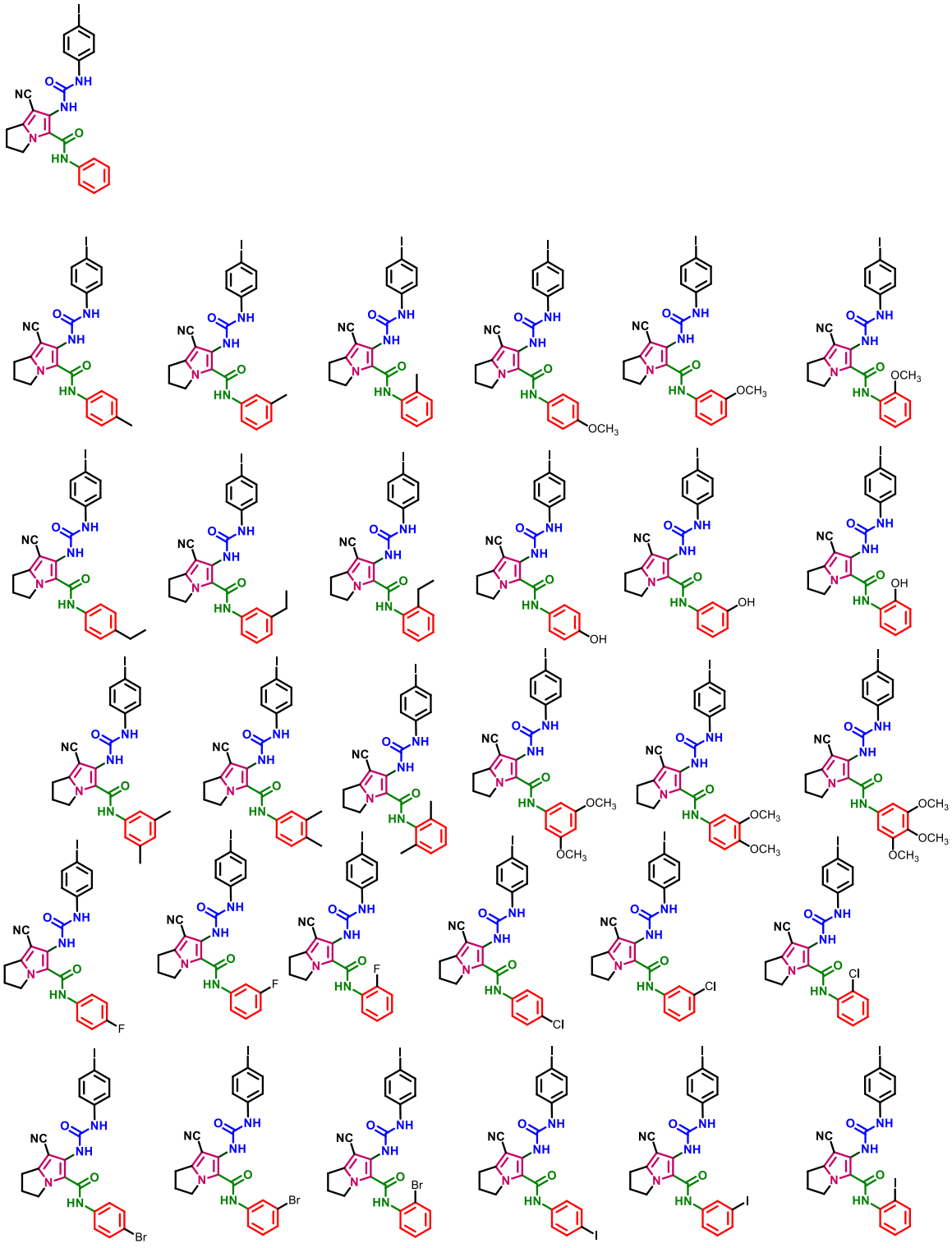


Figure S39. Chemical structure of compound 1179-1209 (4iodophenyliso)

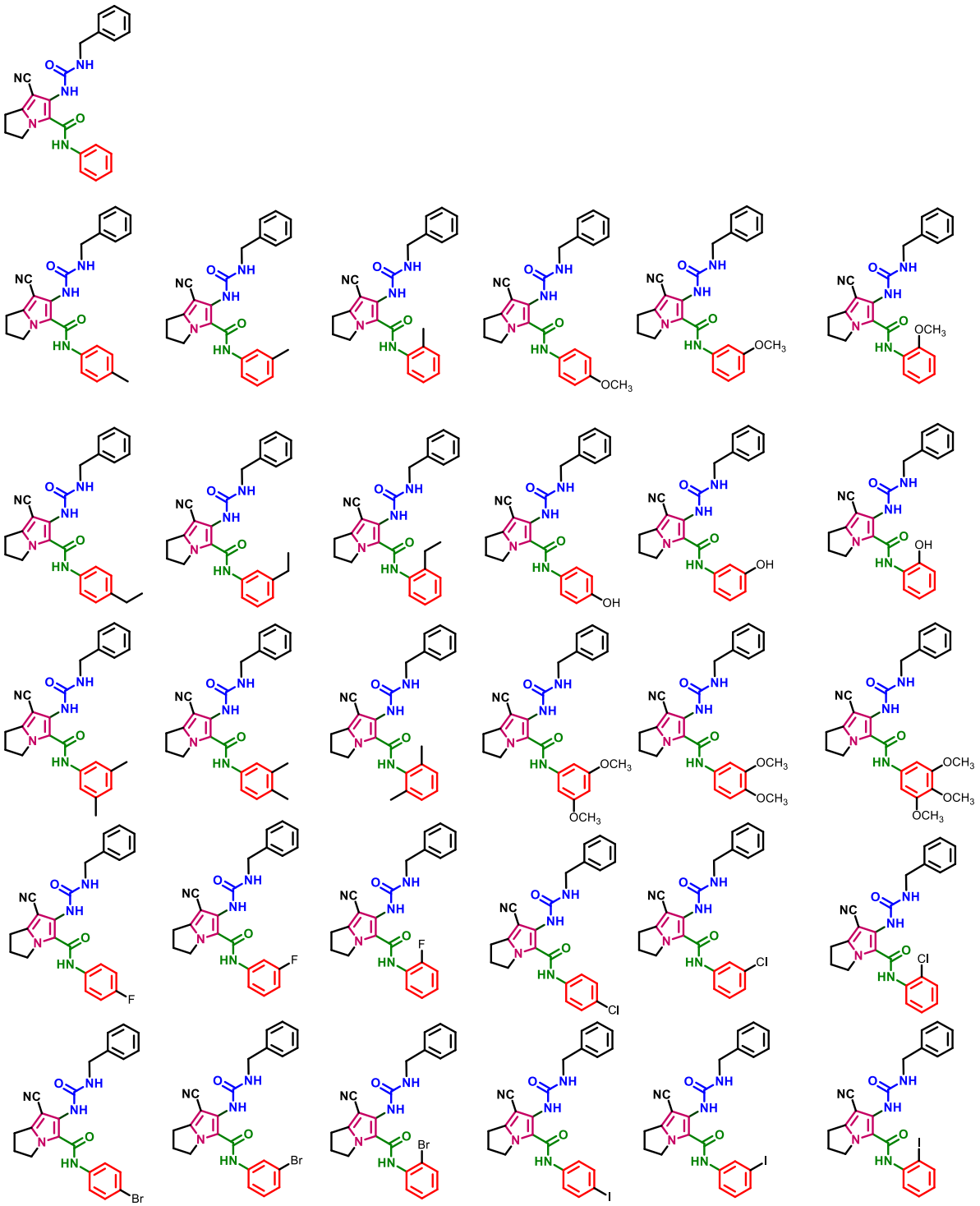


Figure S40. **Chemical structure of compound 1210-1240 (benzyliso)**

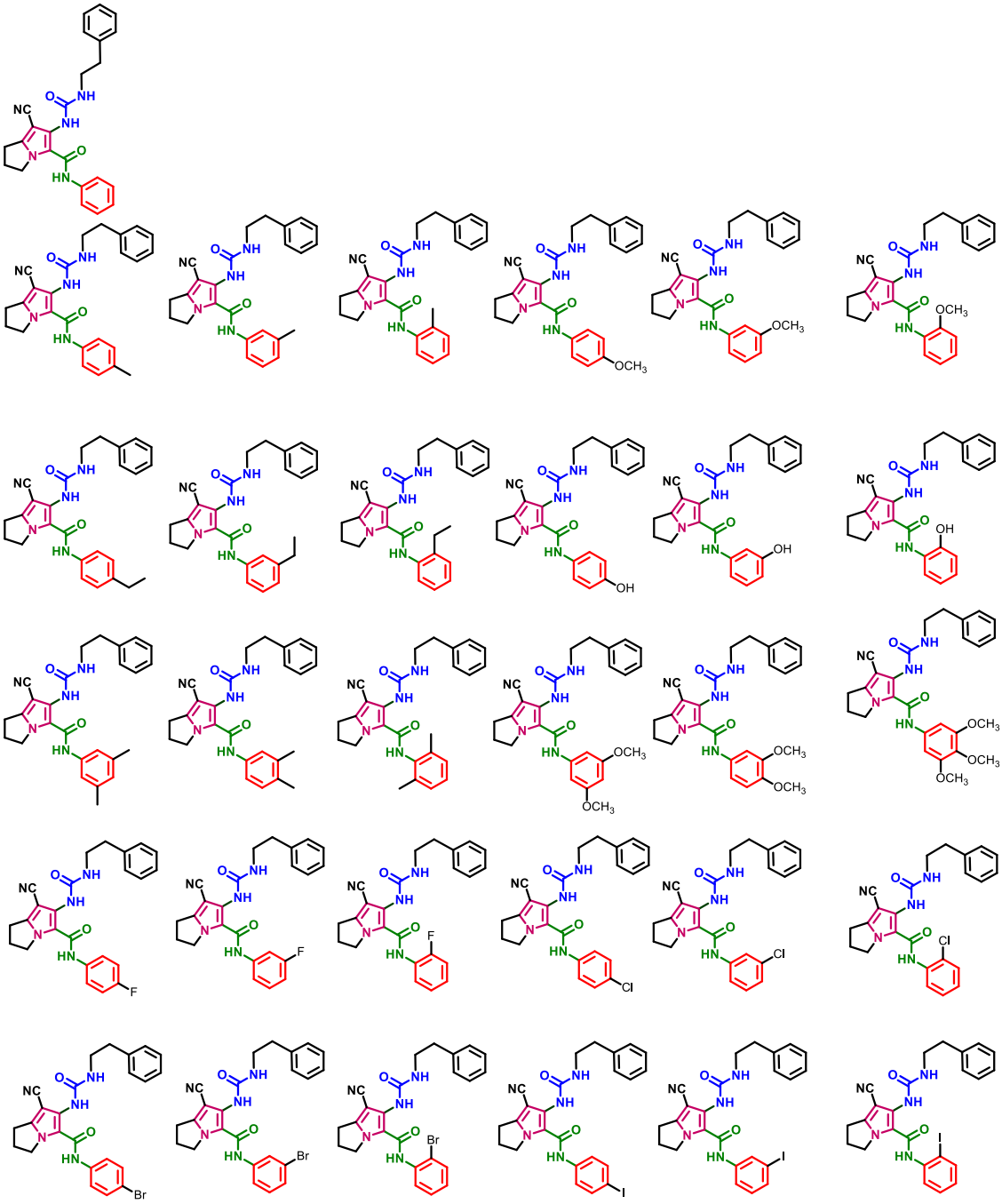


Figure S41. Chemical structure of compound 1241-1271 (phenylethyl)

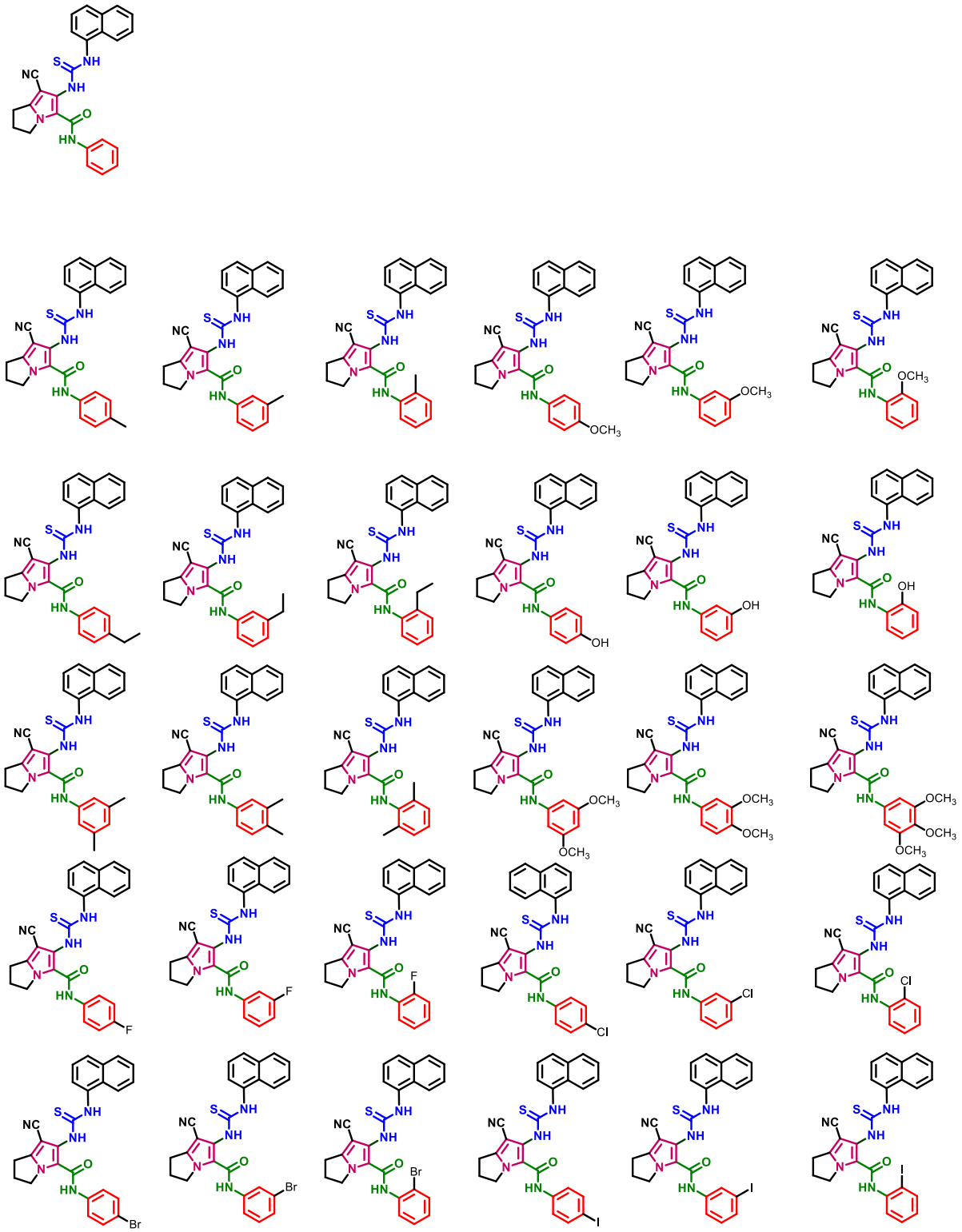
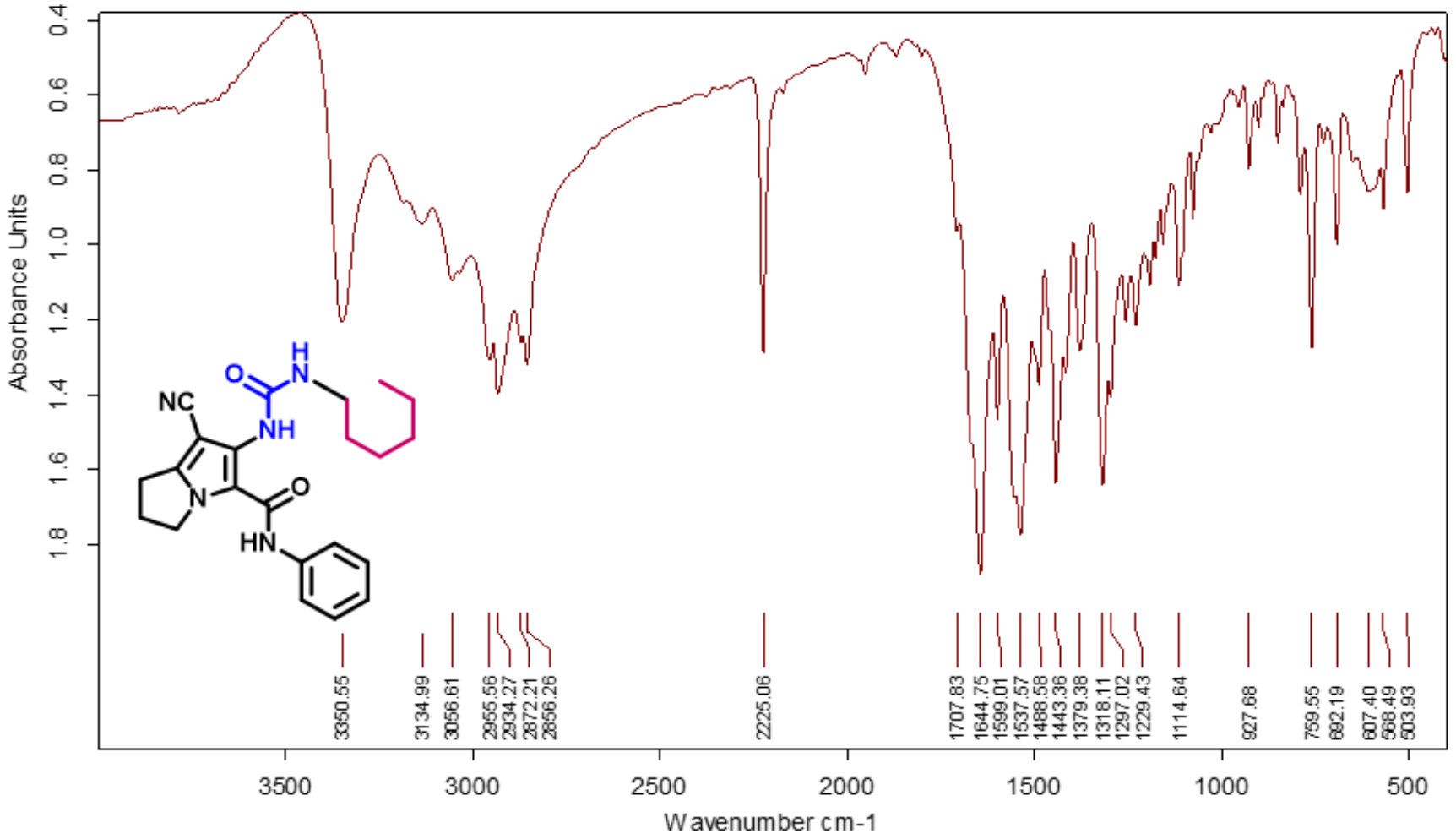


Figure S42. Chemical structure of compound 1272-1302 (phenylethyl)

IR Spectra

Infrared spectra (IR) were done using BRUKER TENSOR 37 spectrophotometer and absorption were expressed in wave number (cm^{-1}) using KBr Disk.

Figure S43. IR spectrum of compound **16a**



C:\Program Files\OPUS_65\MEAS\Protein.247	Protein	AquaSpec	31/01/2018

Figure S44. IR spectrum of compound **16b**

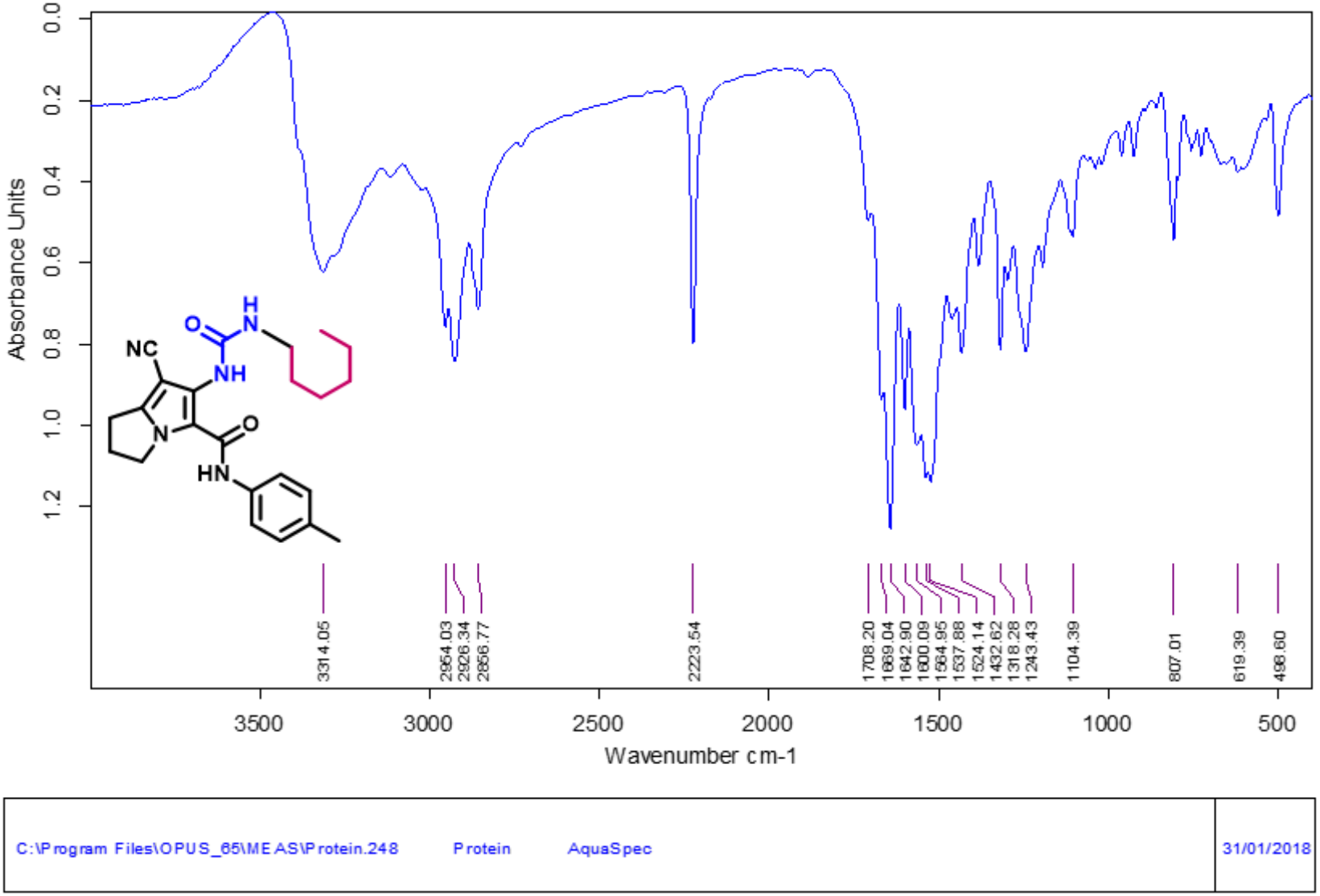


Figure S45. IR spectrum of compound 16c

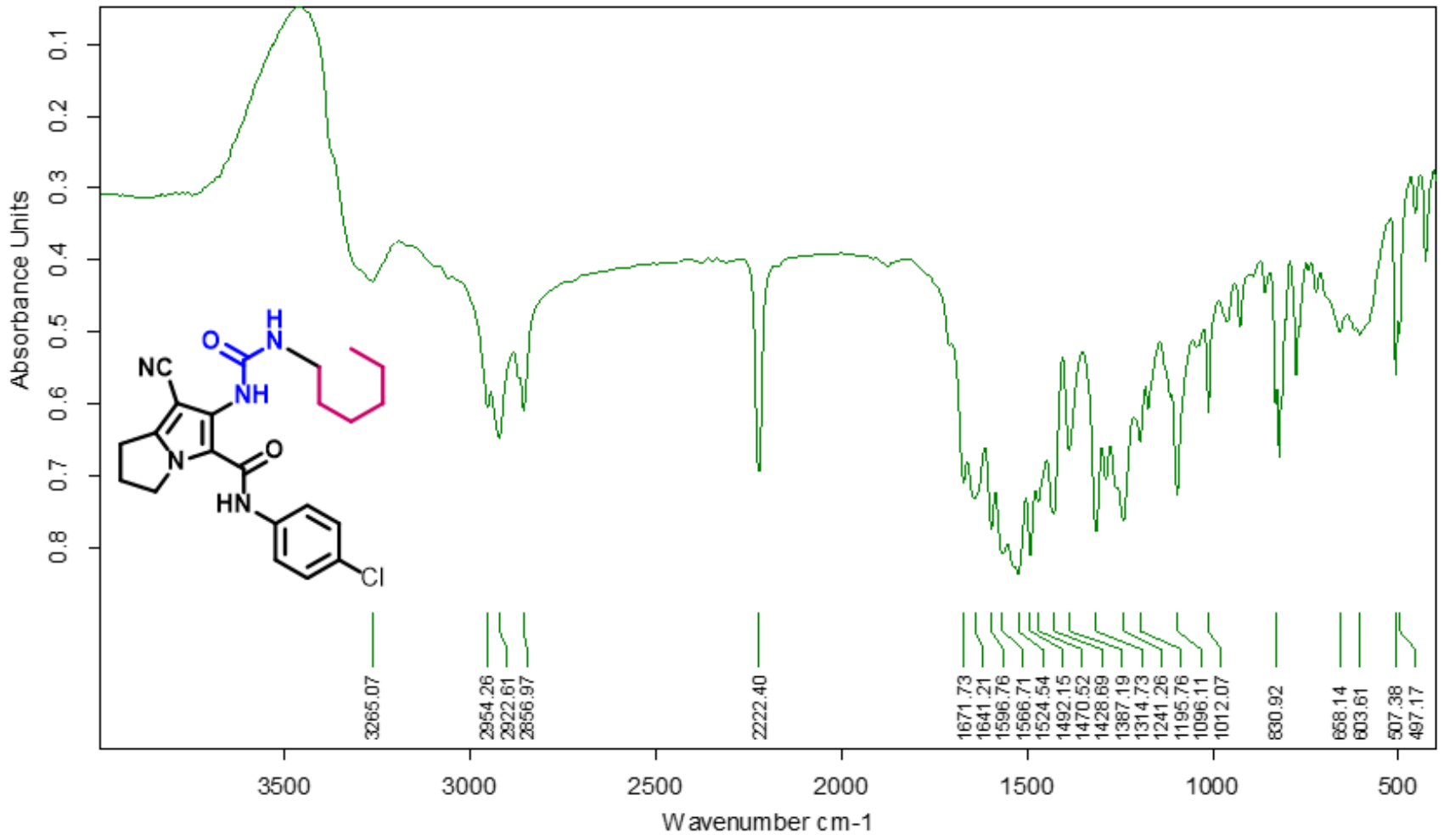


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Figure S46. IR spectrum of compound **17a**

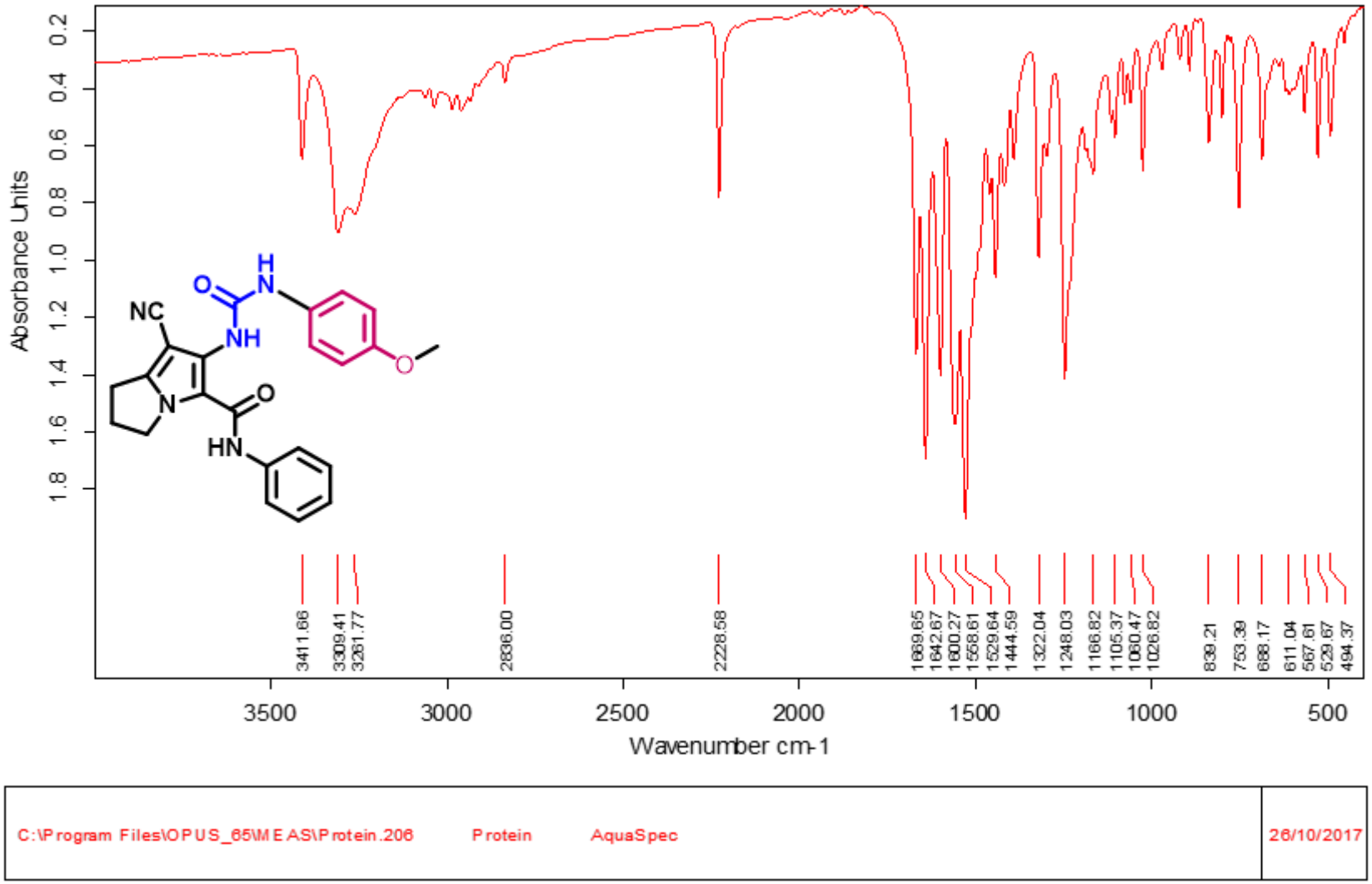

Figure S47. IR spectrum of compound 17b

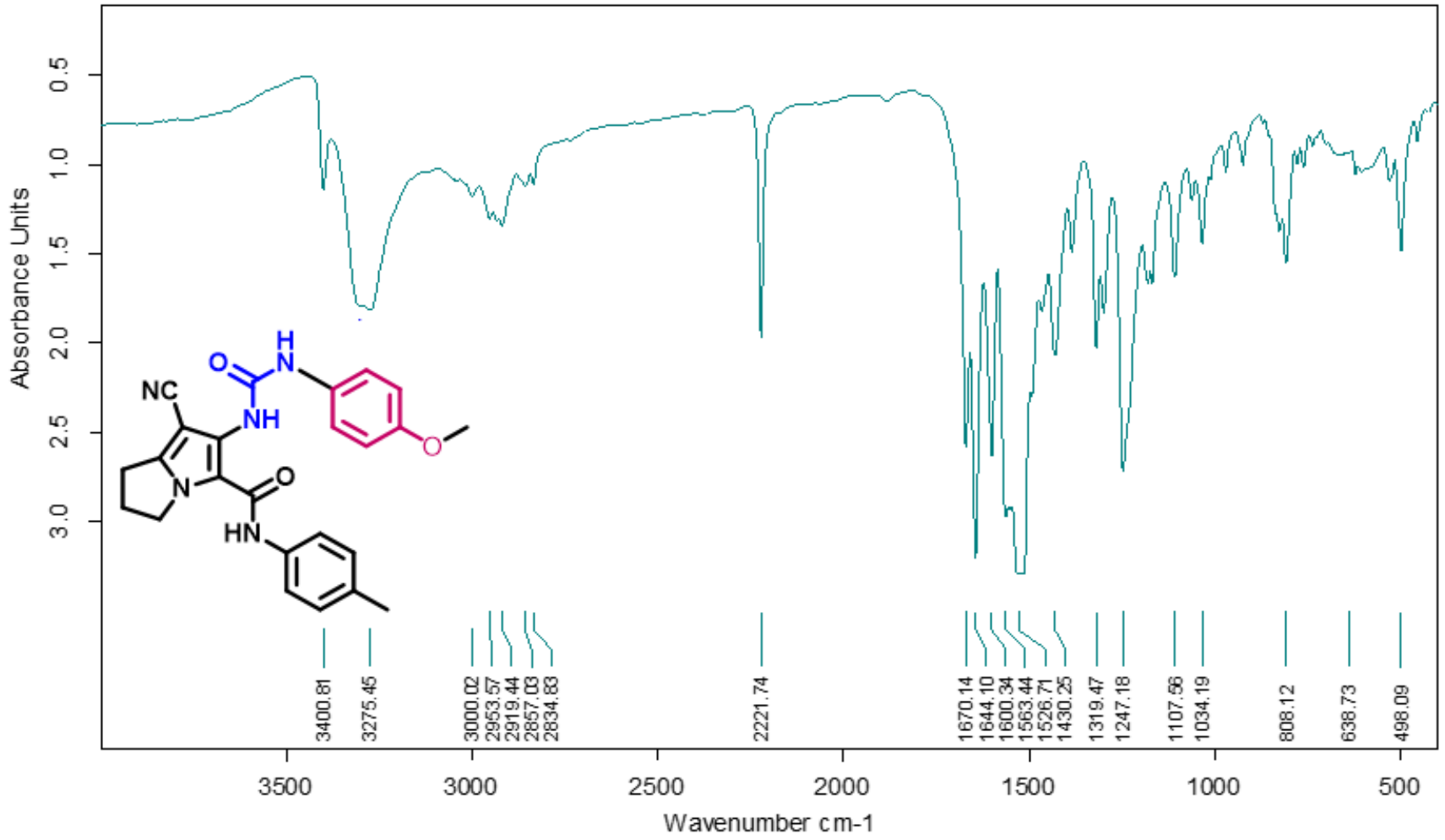

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Figure S48. IR spectrum of compound 17c

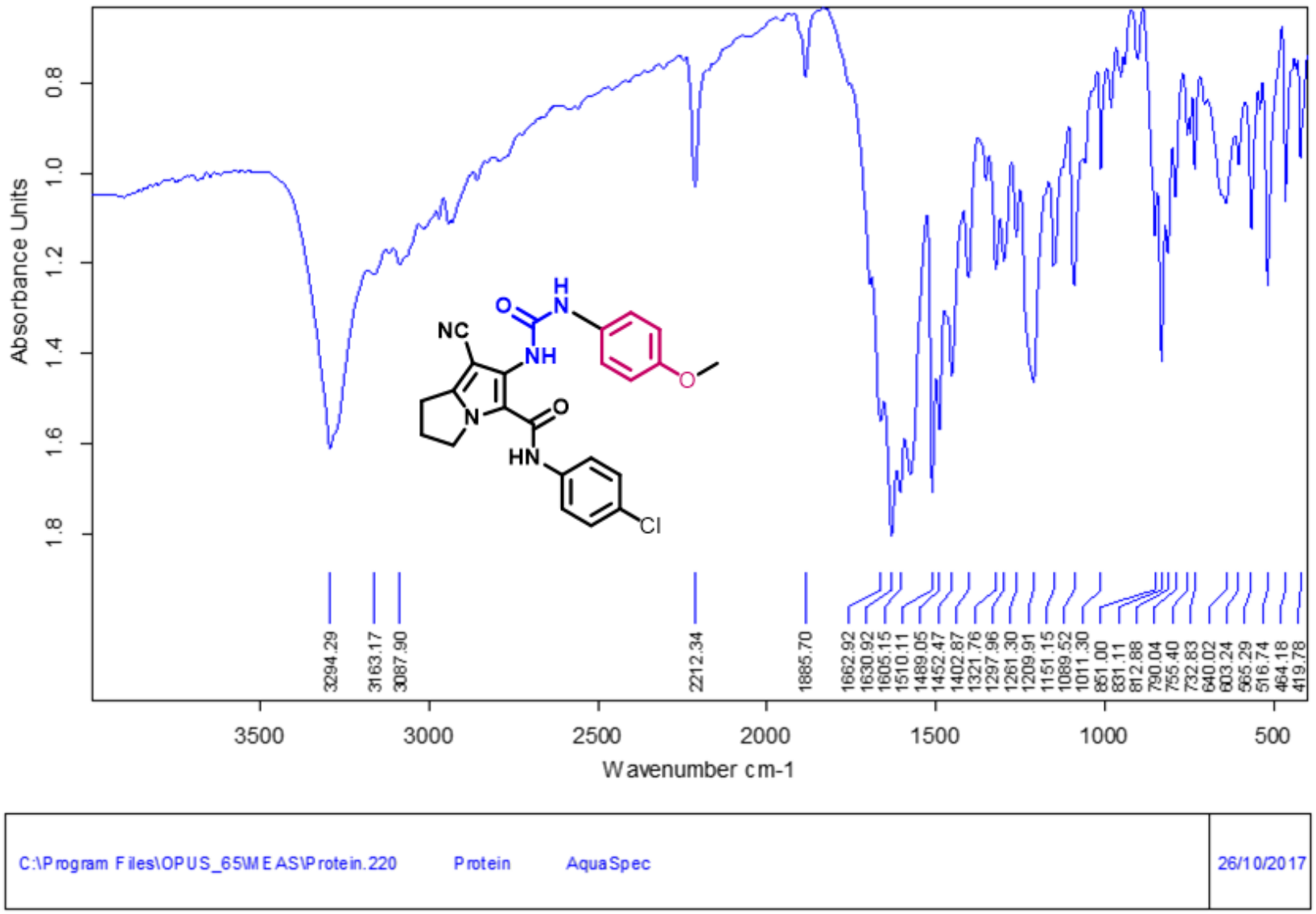

Figure S49. **IR spectrum of compound 18a**

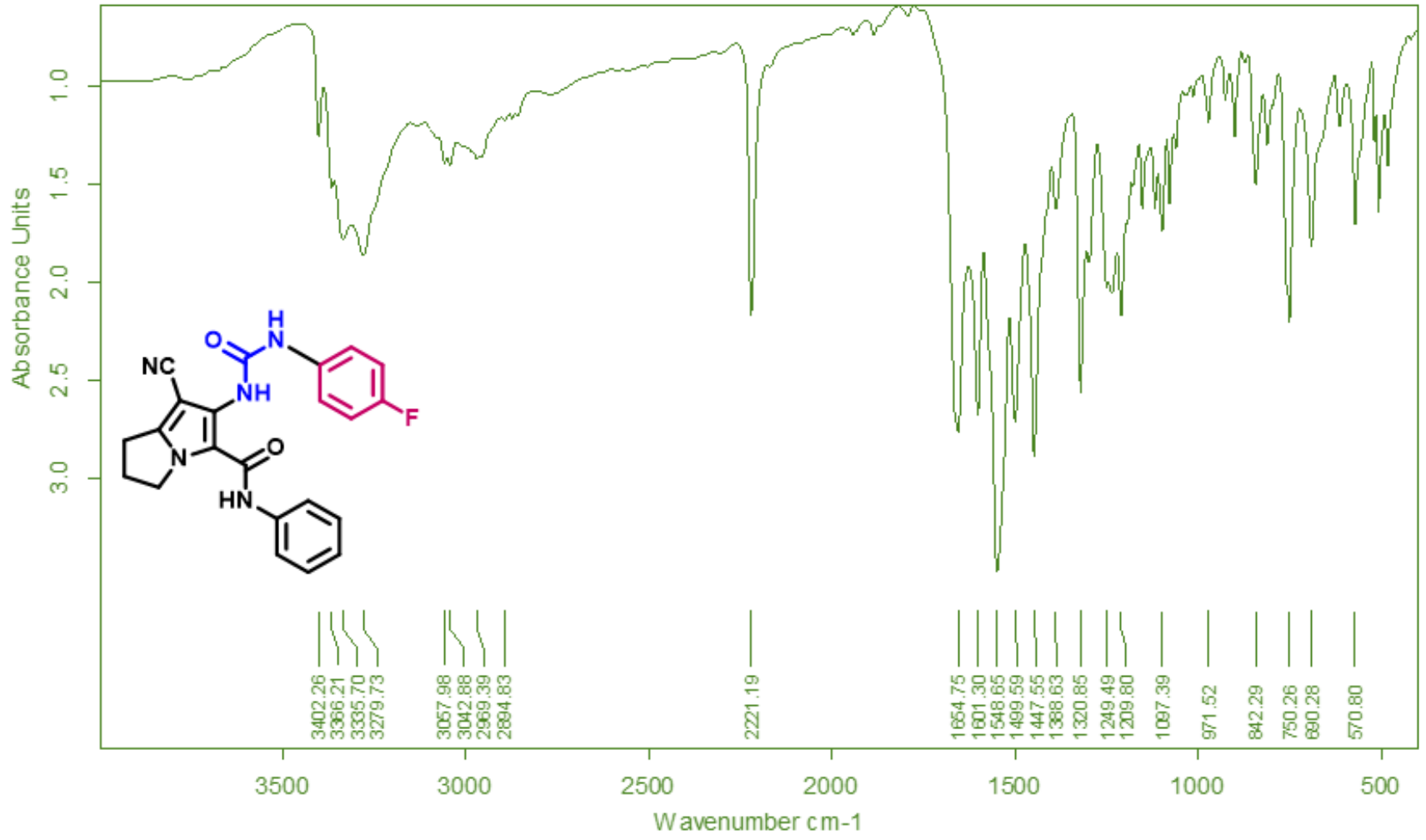

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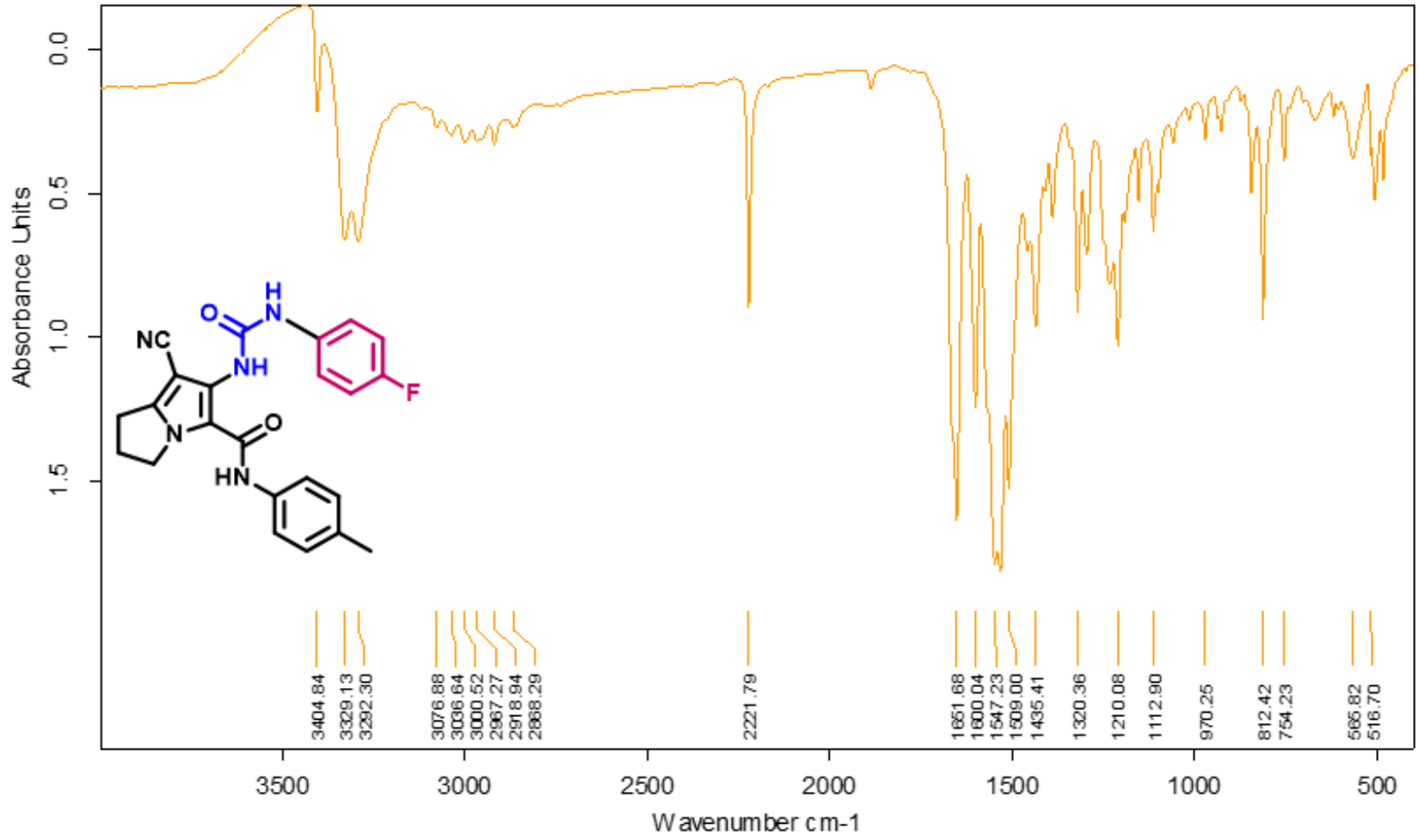
Figure S50. IR spectrum of compound **18b**



C:\Program Files\OPUS_65\MEAS\Protein.252	Protein	AquaSpec	31/01/2018

Figure S51. IR spectrum of compound 18c

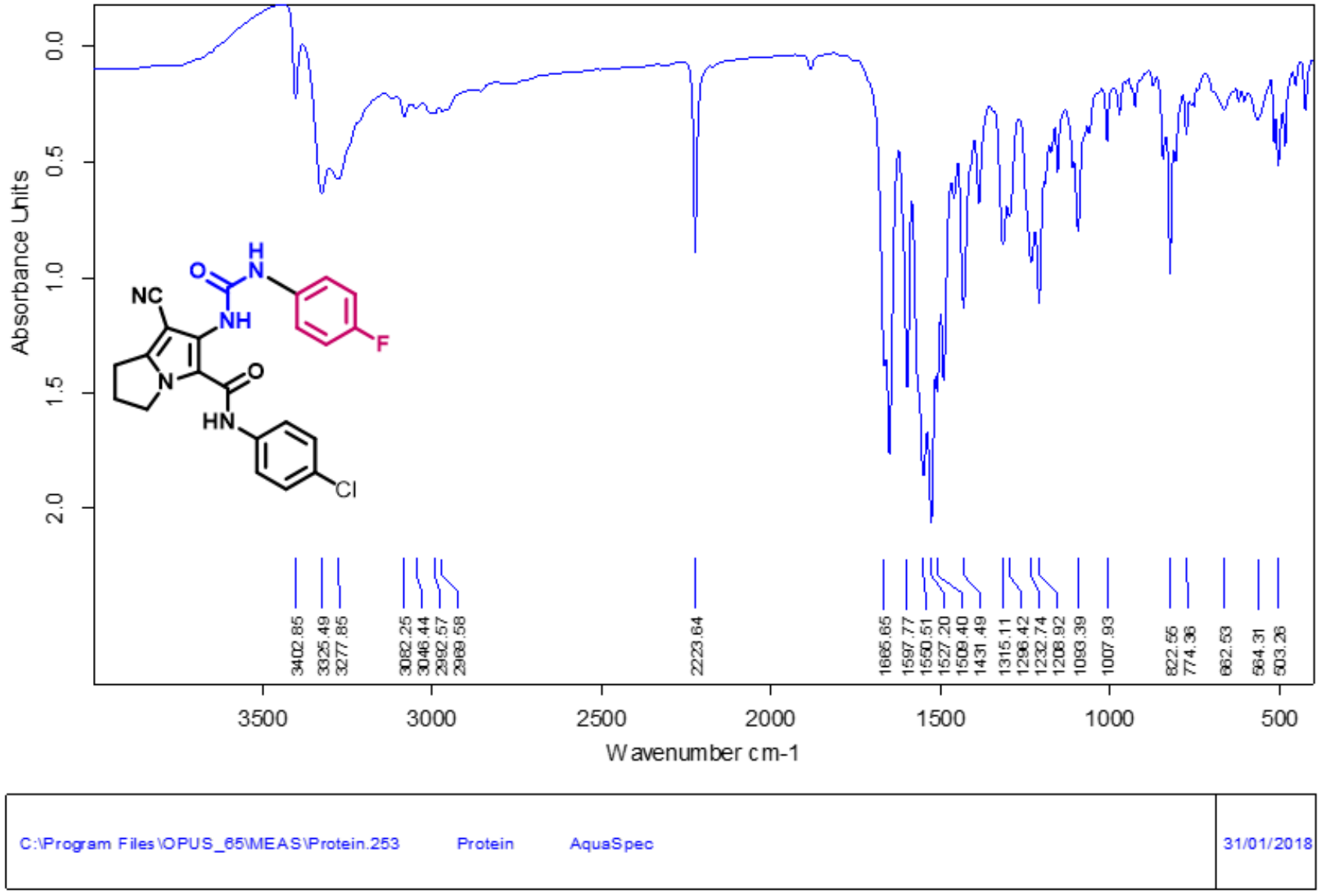


Figure S52. IR spectrum of compound **19a**

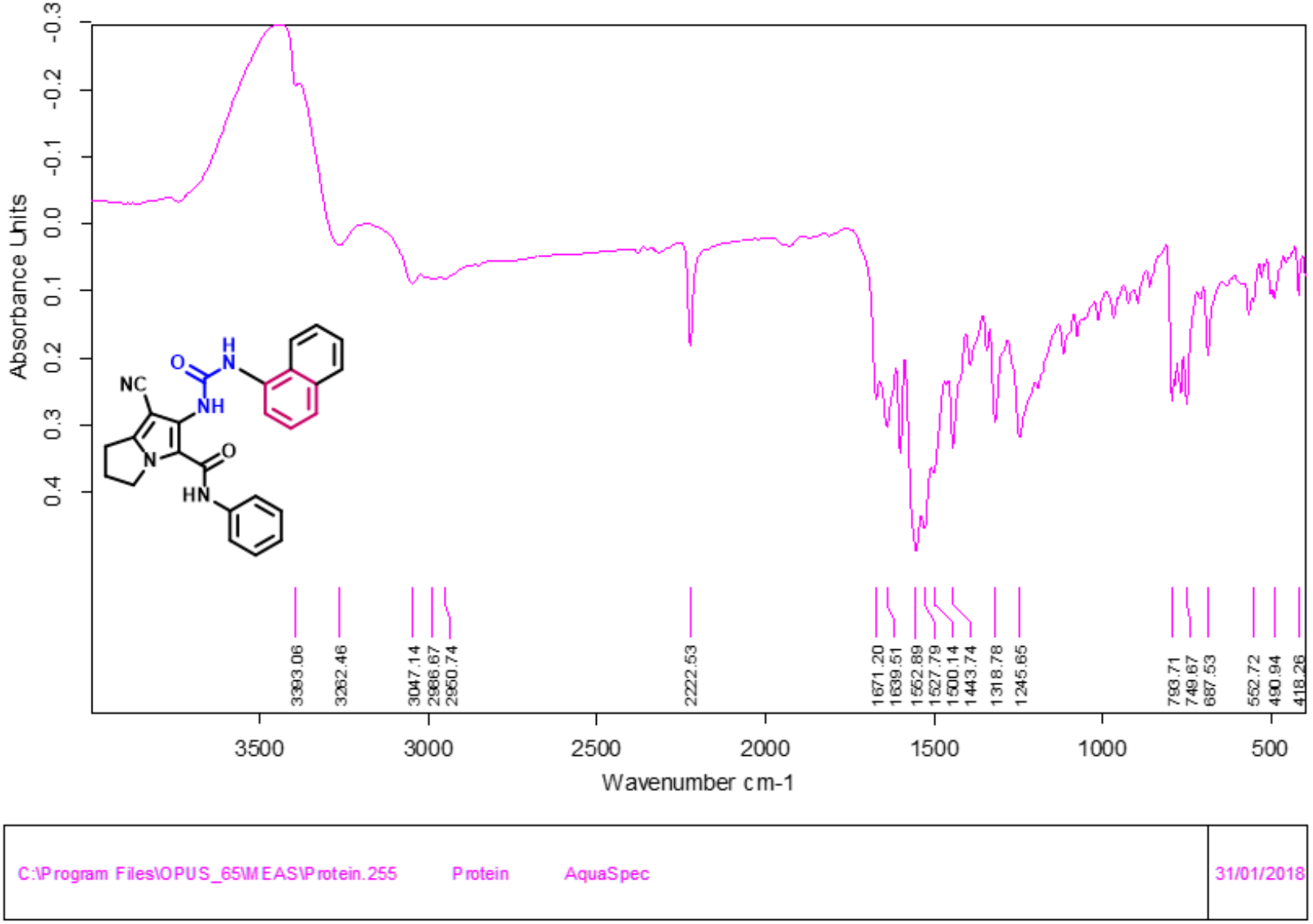


Figure S53. IR spectrum of compound **19b**

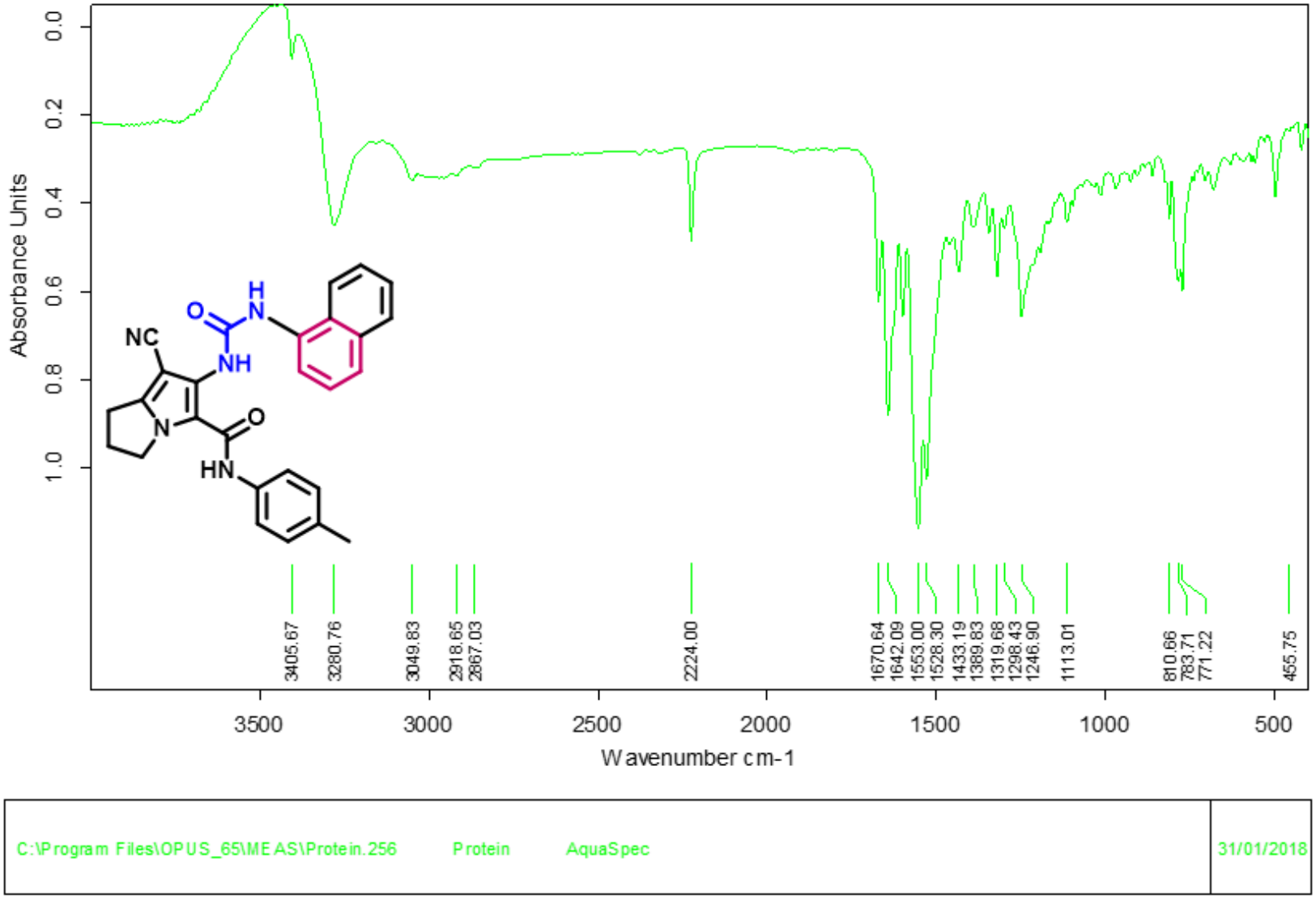


Figure S54. IR spectrum of compound 19c

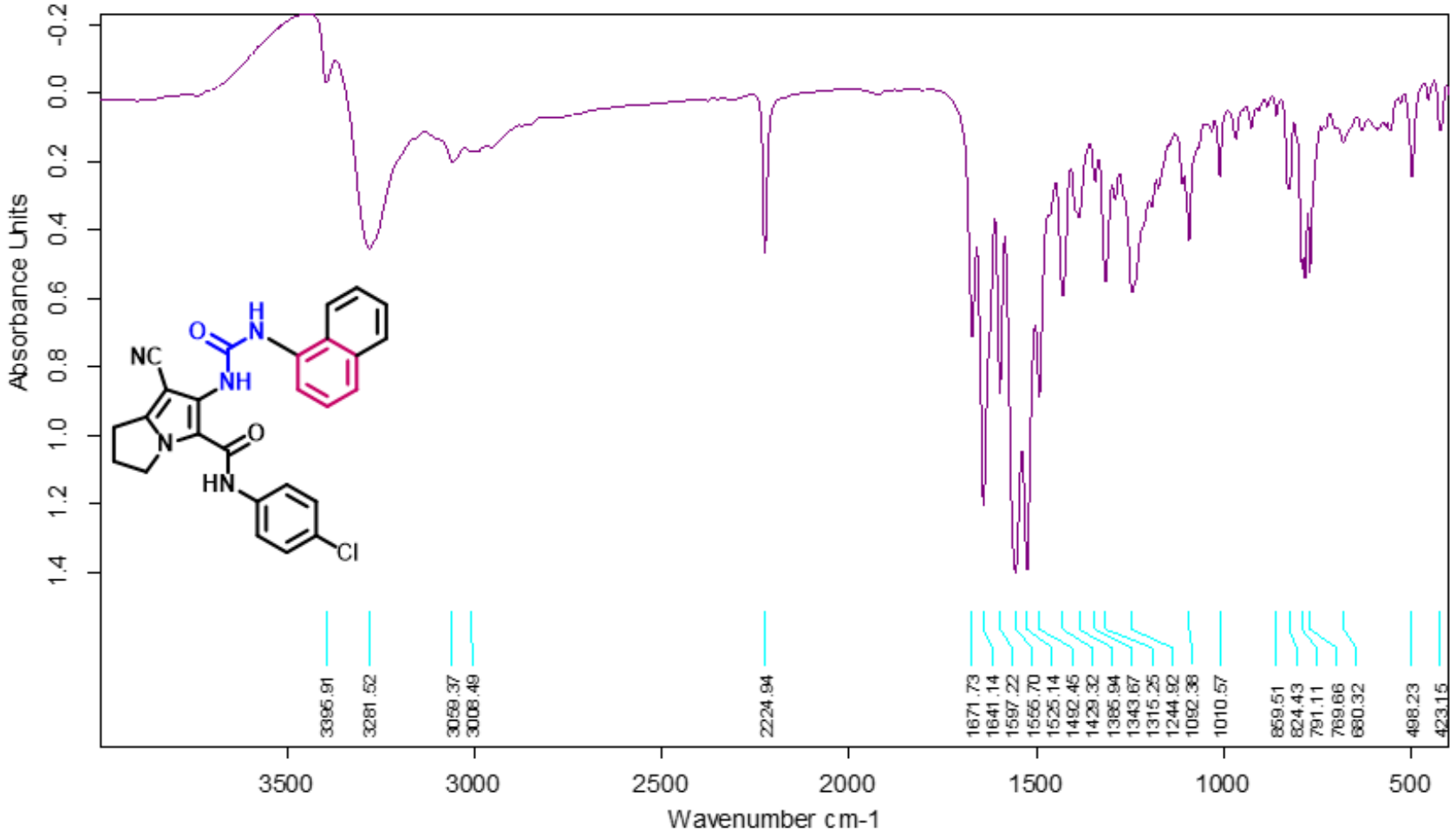
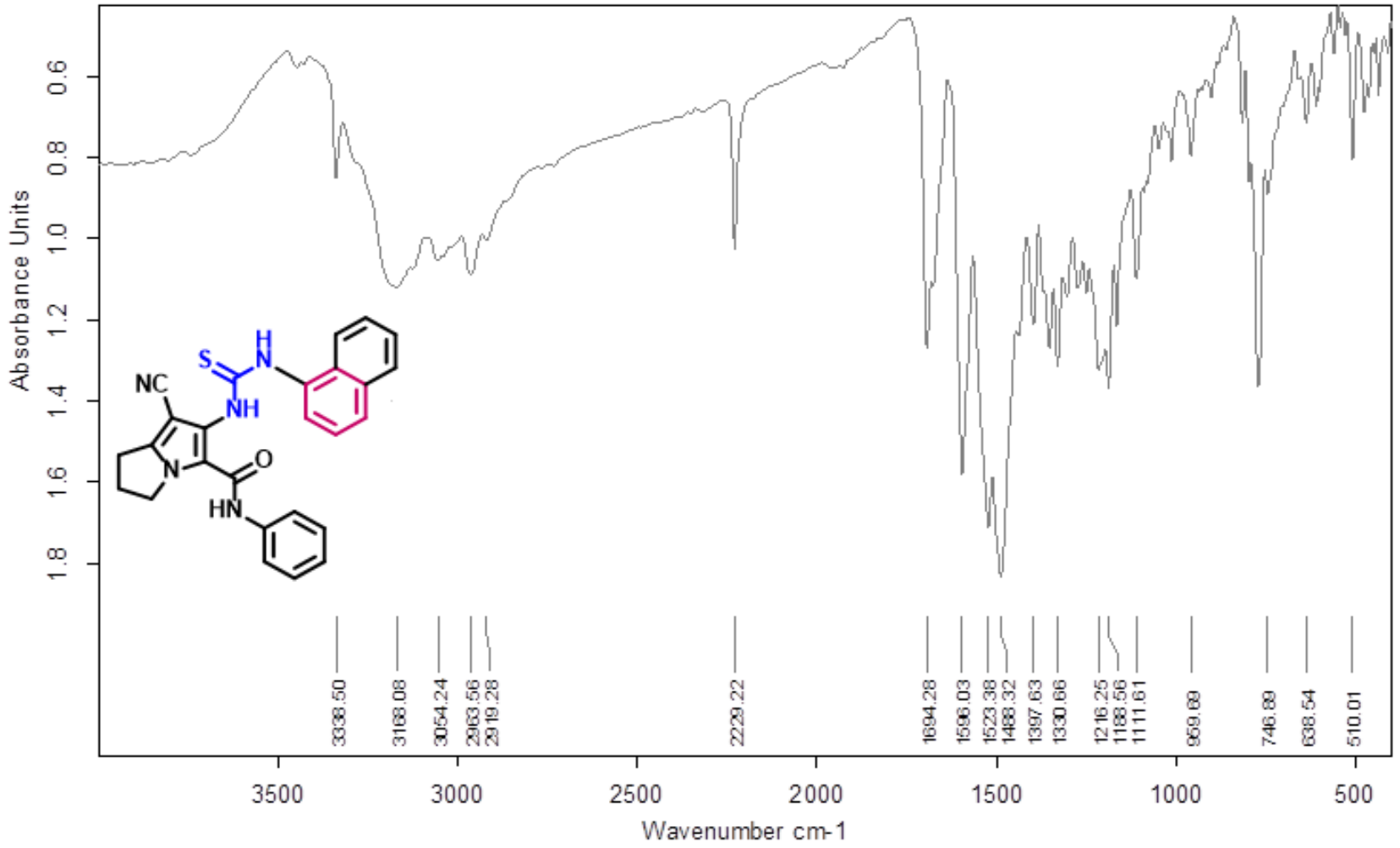
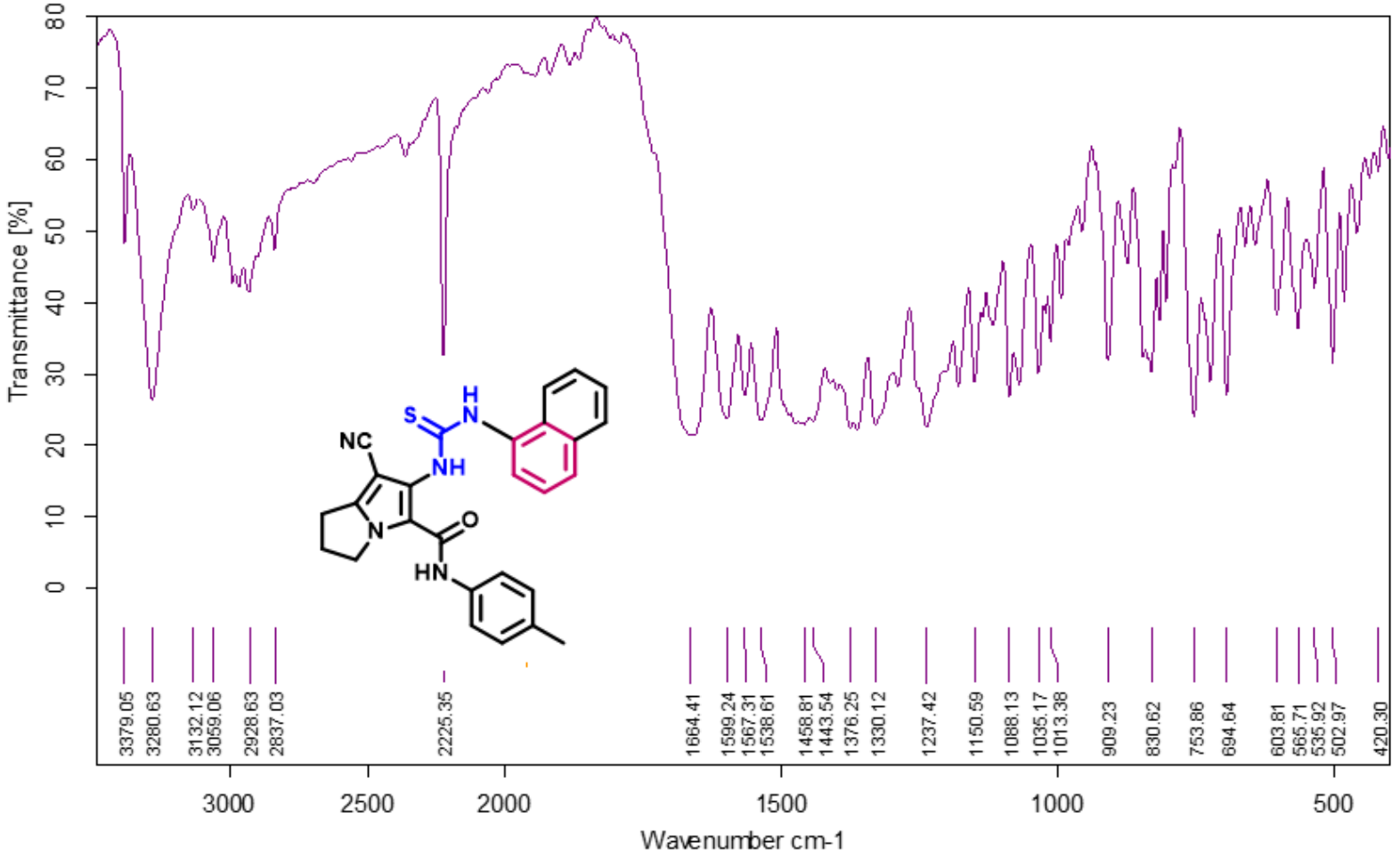


Figure S55. IR spectrum of compound **20a**



C:\Program Files\OPUS_65\MEAS\Protein.260	Protein	AquaSpec	31/01/2018

Figure S56. IR spectrum of compound **20b**



C:\Program Files\OPUS_65\MEAS\MLT.128 MLT Instrument type and / or accessory

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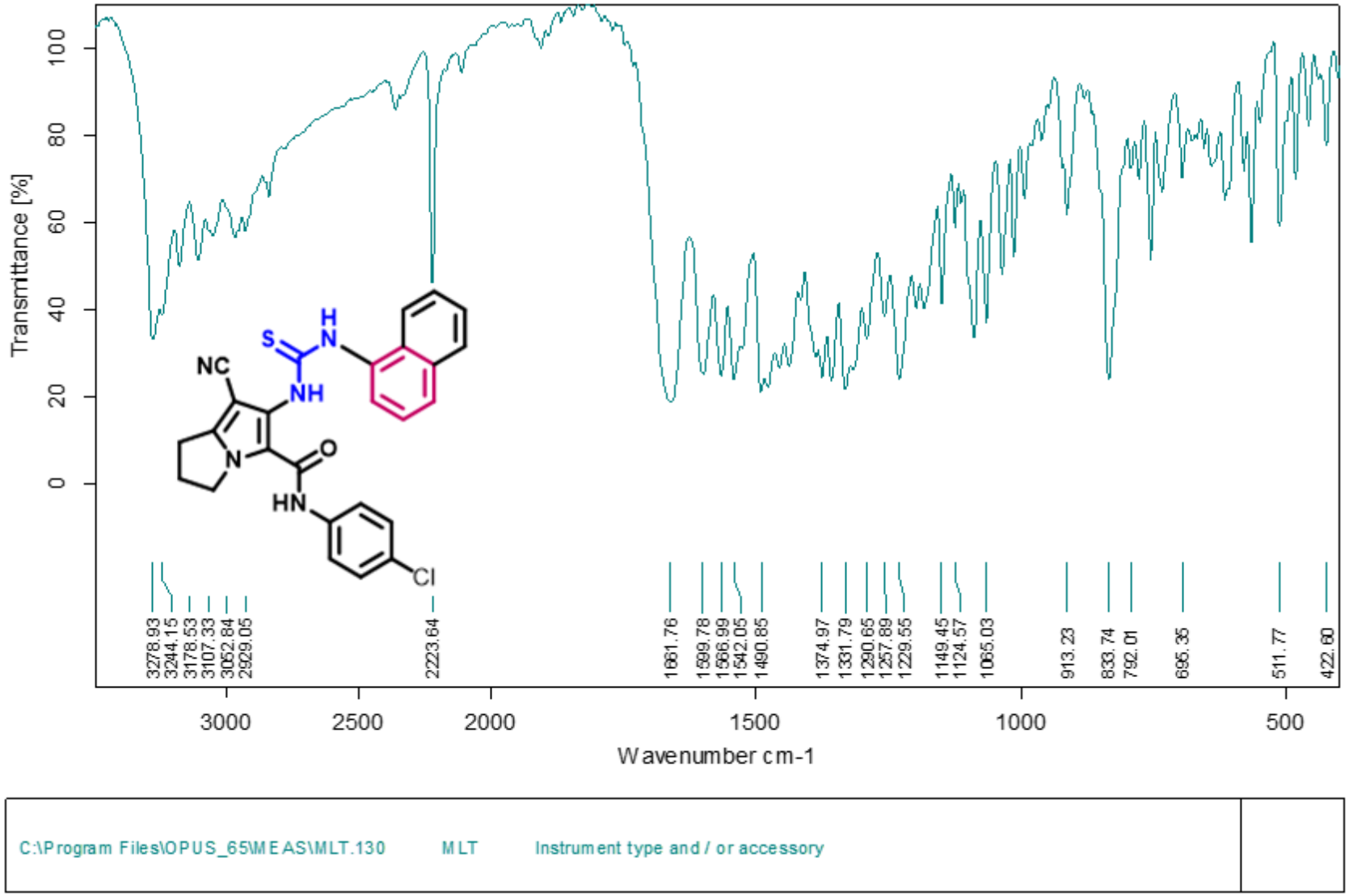
Figure S57. **IR spectrum of compound 20c**



^{1}H-NMR, ^{13}C-NMR and DEPT C^{135} Spectra

^{1}H-NMR spectra were recorded on a BRUKER AVANCE III spectrometer (at the faculty of pharmacy, Umm Al-Qura University) at 500 MHz in the specified solvent, chemical shifts were reported on the δ (ppm) scale and were related to that of the solvent and *J* values are given in Hz. ^{13}C NMR and DEPT C^{135} spectra were obtained on a BRUKER AVANCE III at 125 MHz (at the faculty of pharmacy, Umm Al-Qura University).

Figure S58. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16a**

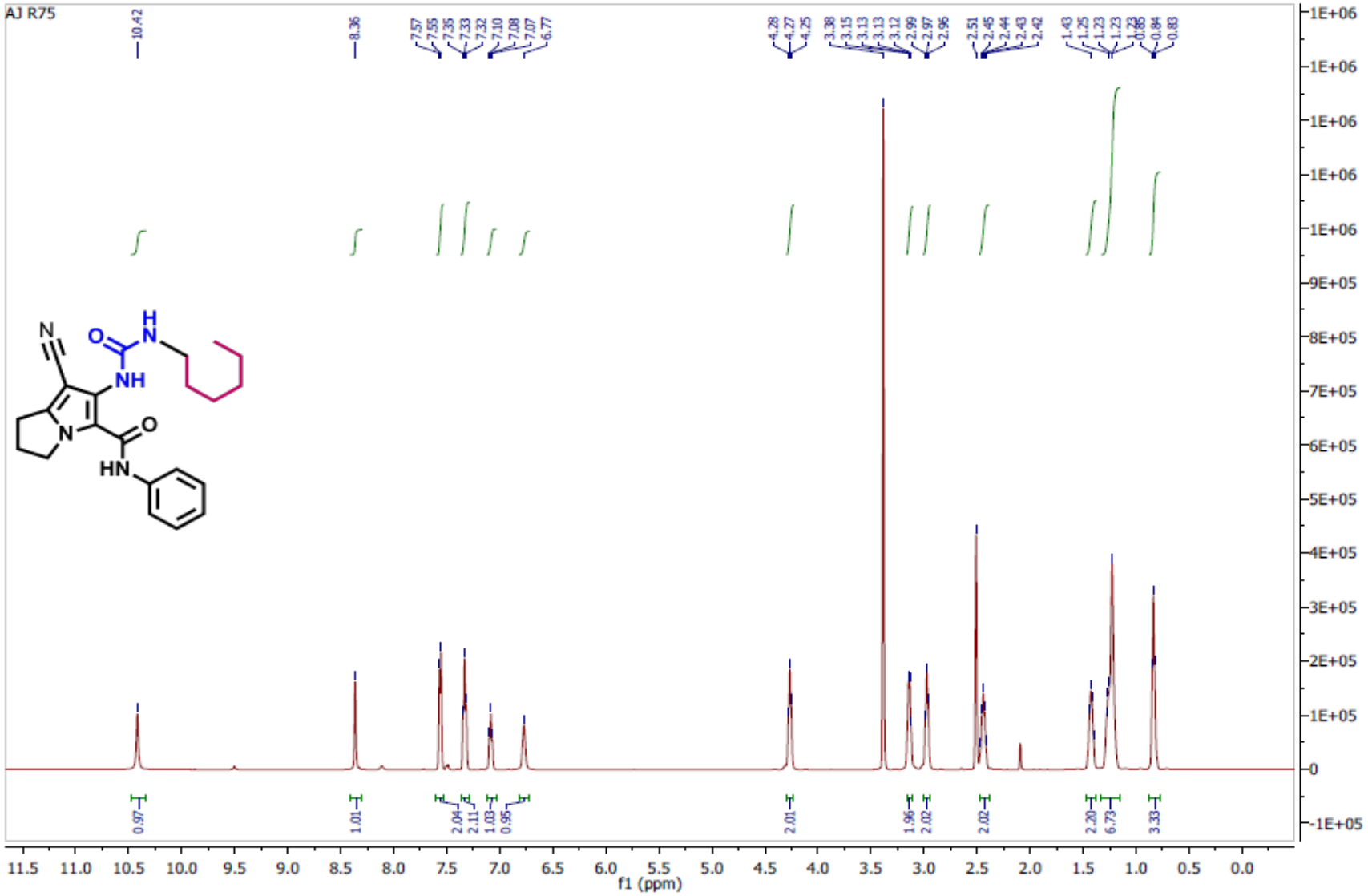


Figure S59. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16a (zoom on aliphatic Hs)

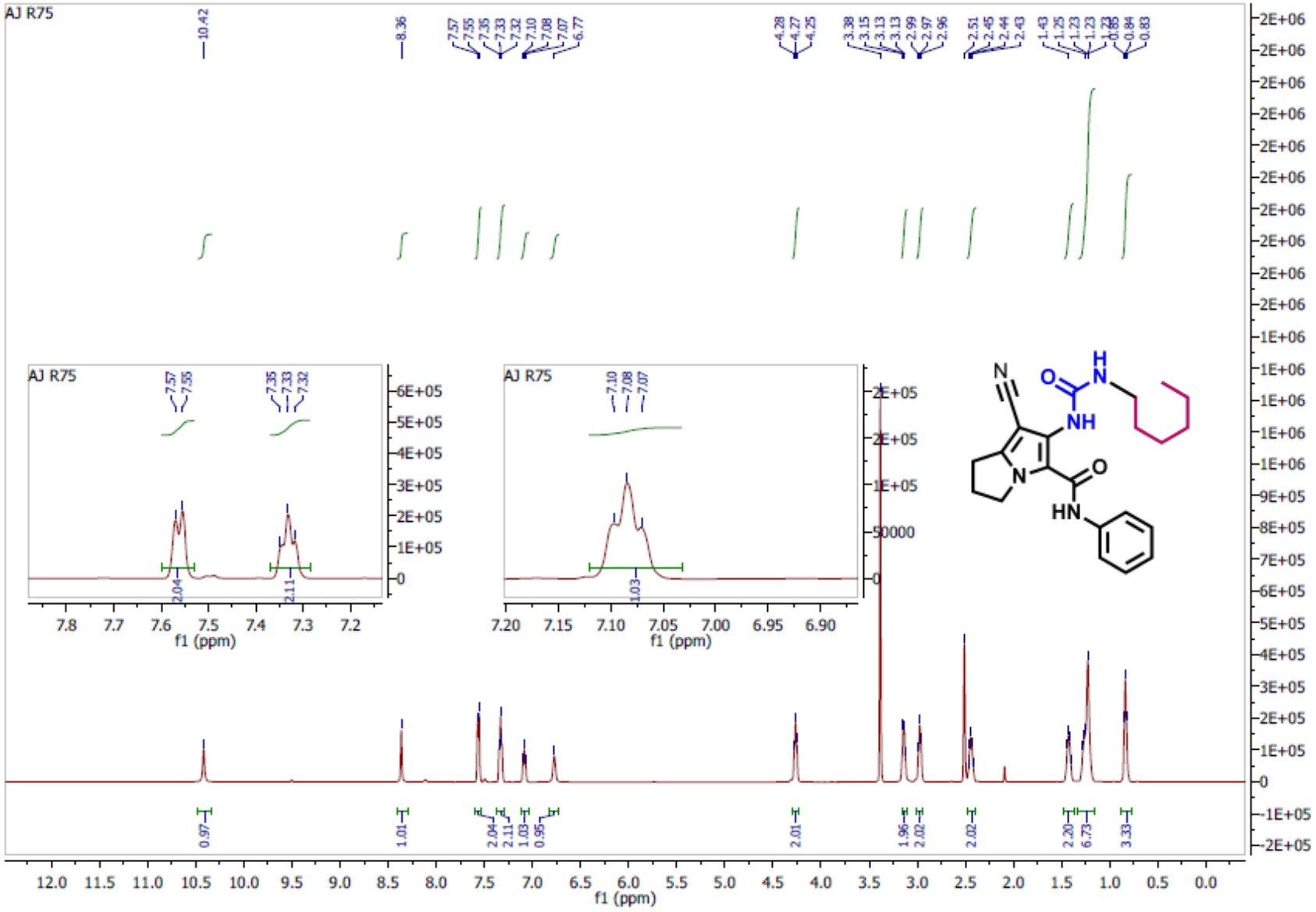


Figure S60. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16a (zoom on aliphatic Hs)

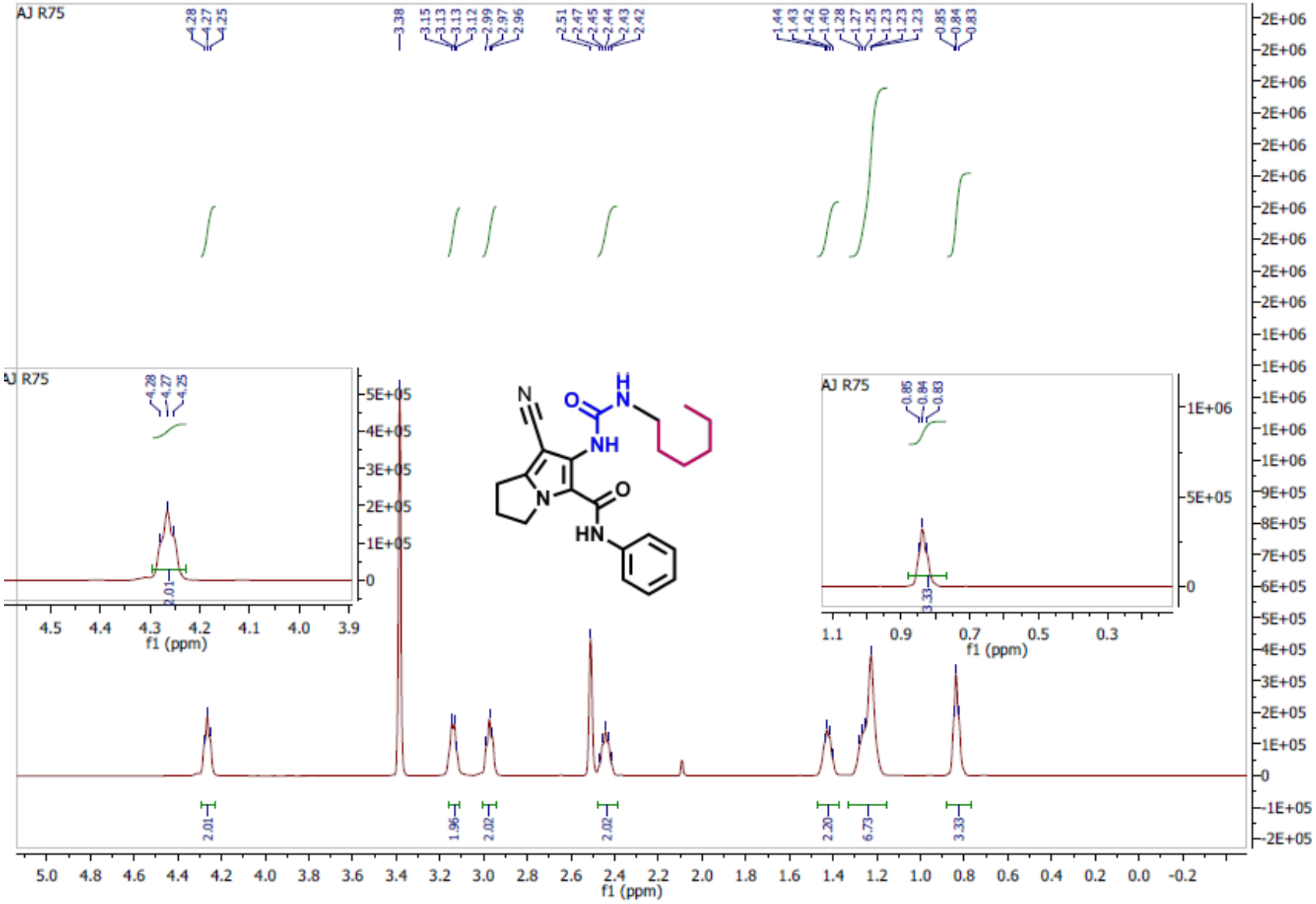


Figure S61. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16a (zoom on aliphatic Hs)

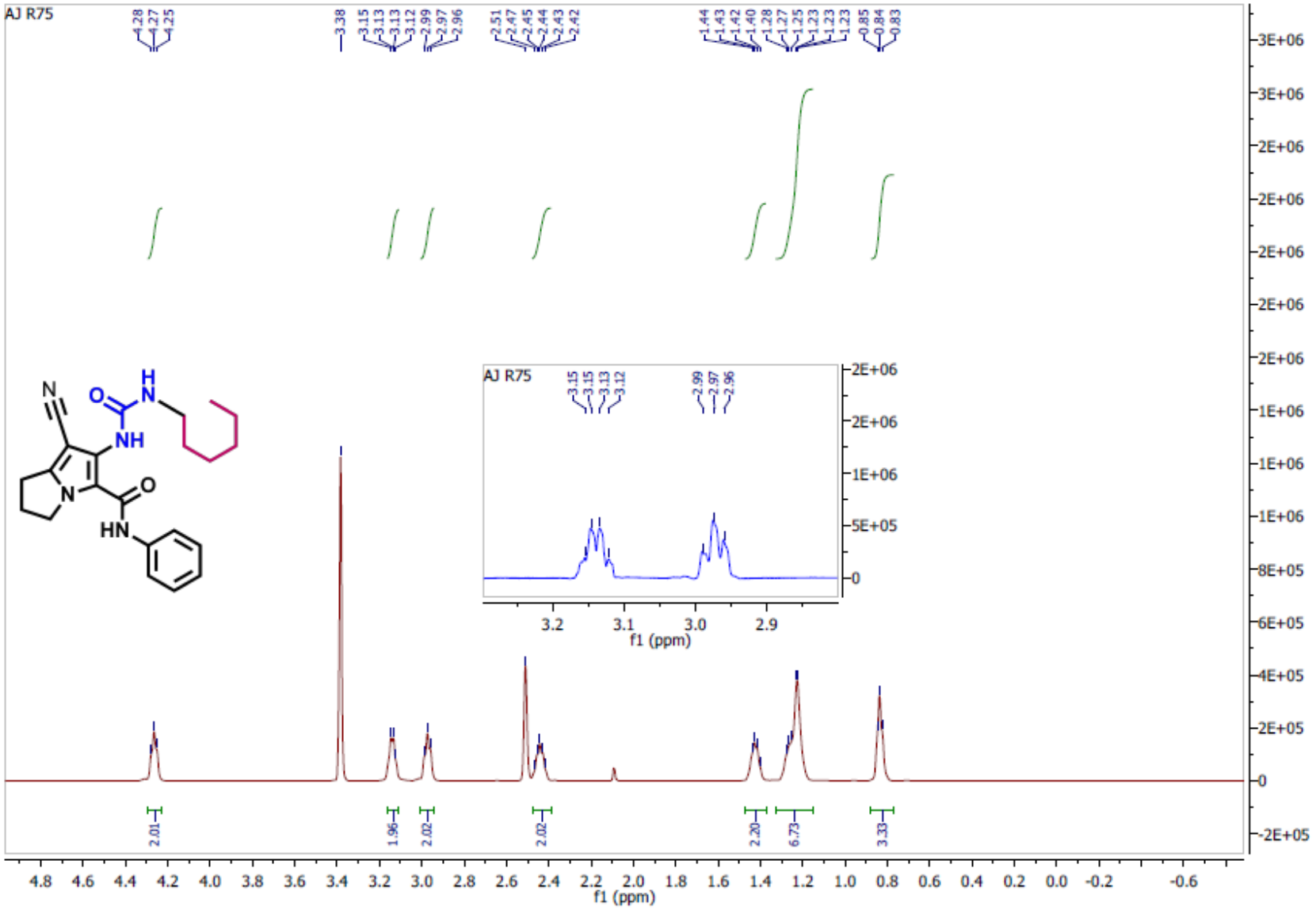


Figure S62. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16a (zoom on NHs & aromatic Hs)

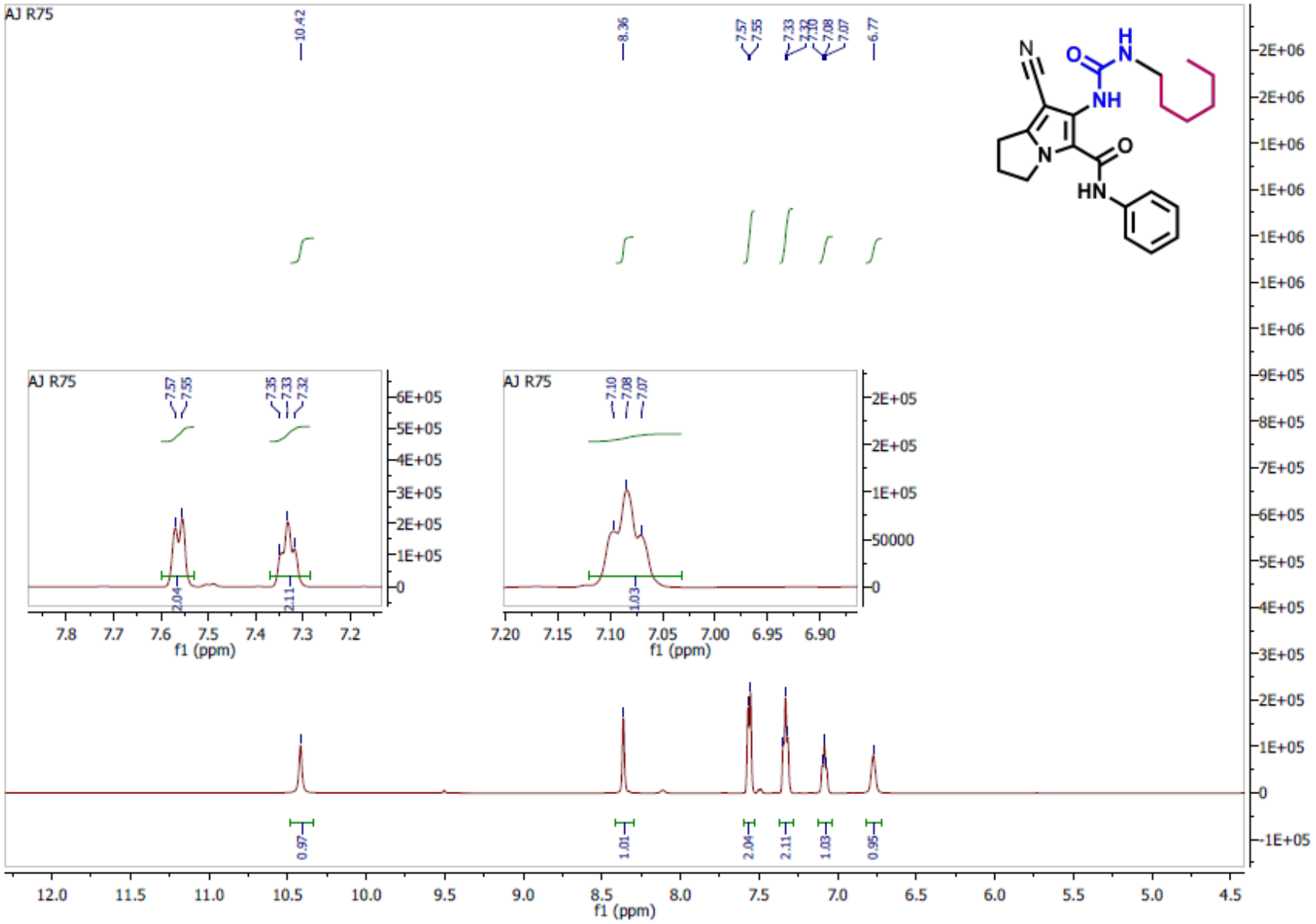


Figure S63. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **16a**

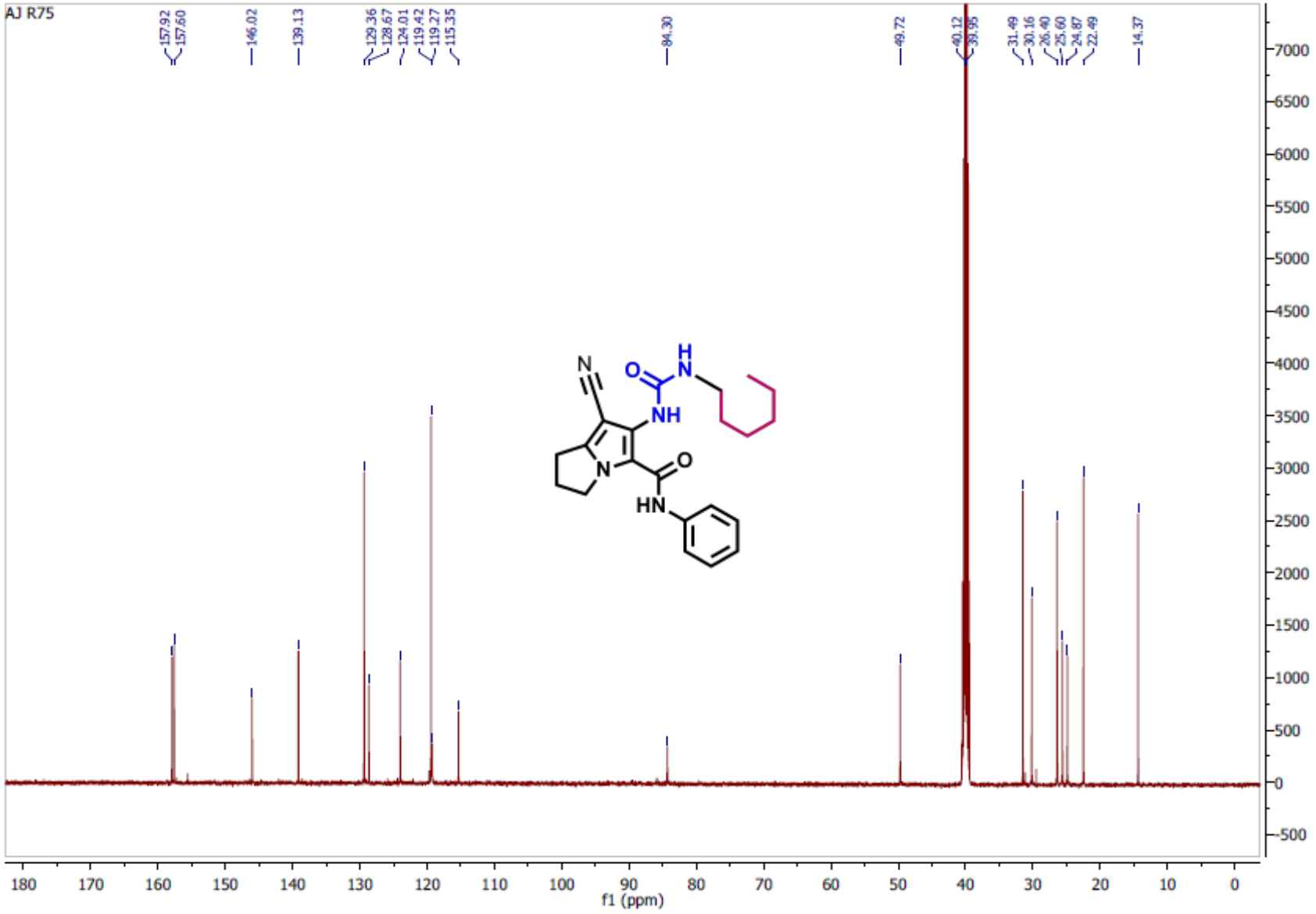


Figure S64. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 16a (zoom on aliphatic Cs)

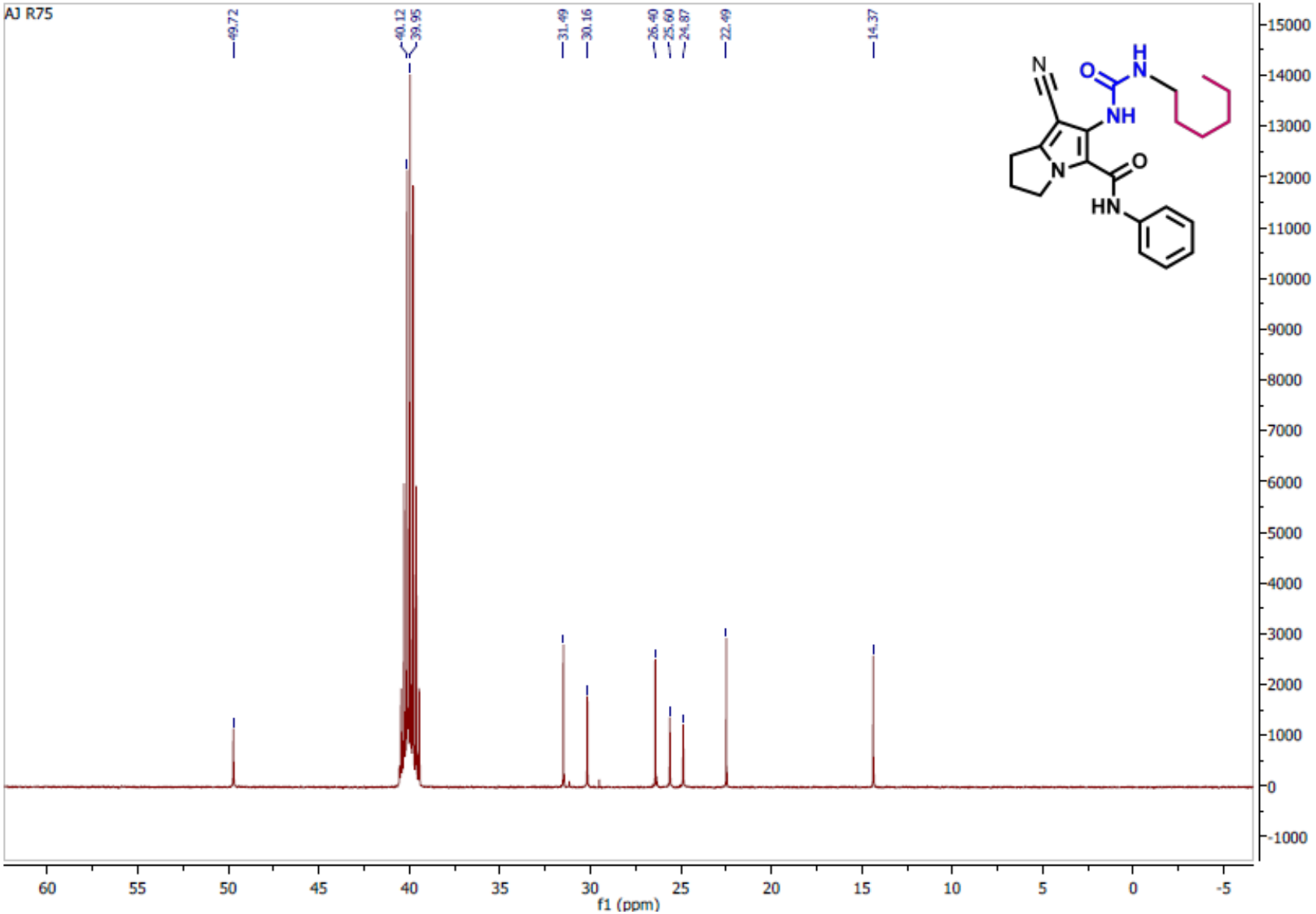


Figure S65. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **16a** (zoom on aromatic Cs)

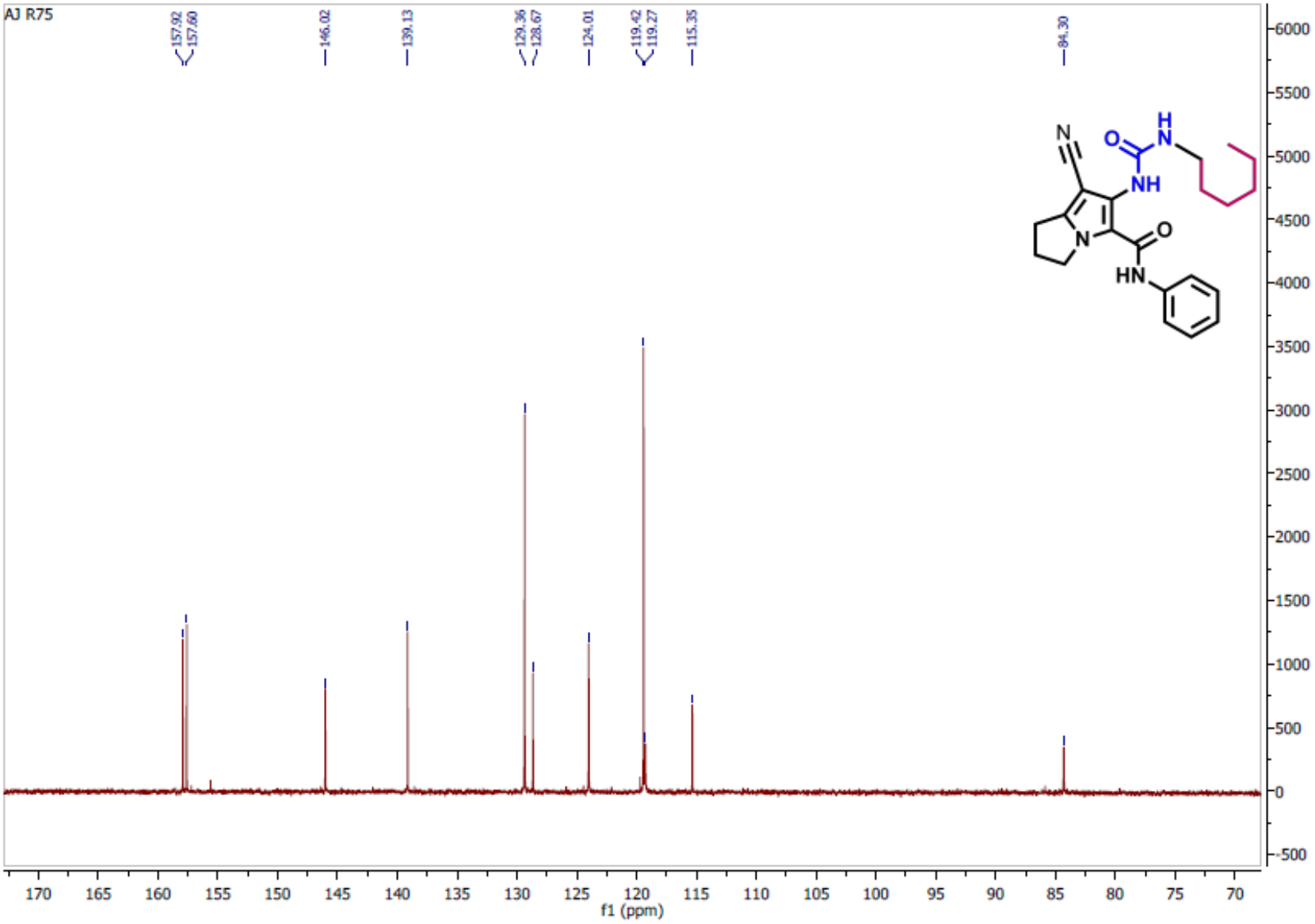


Figure S66. **DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 16a.**

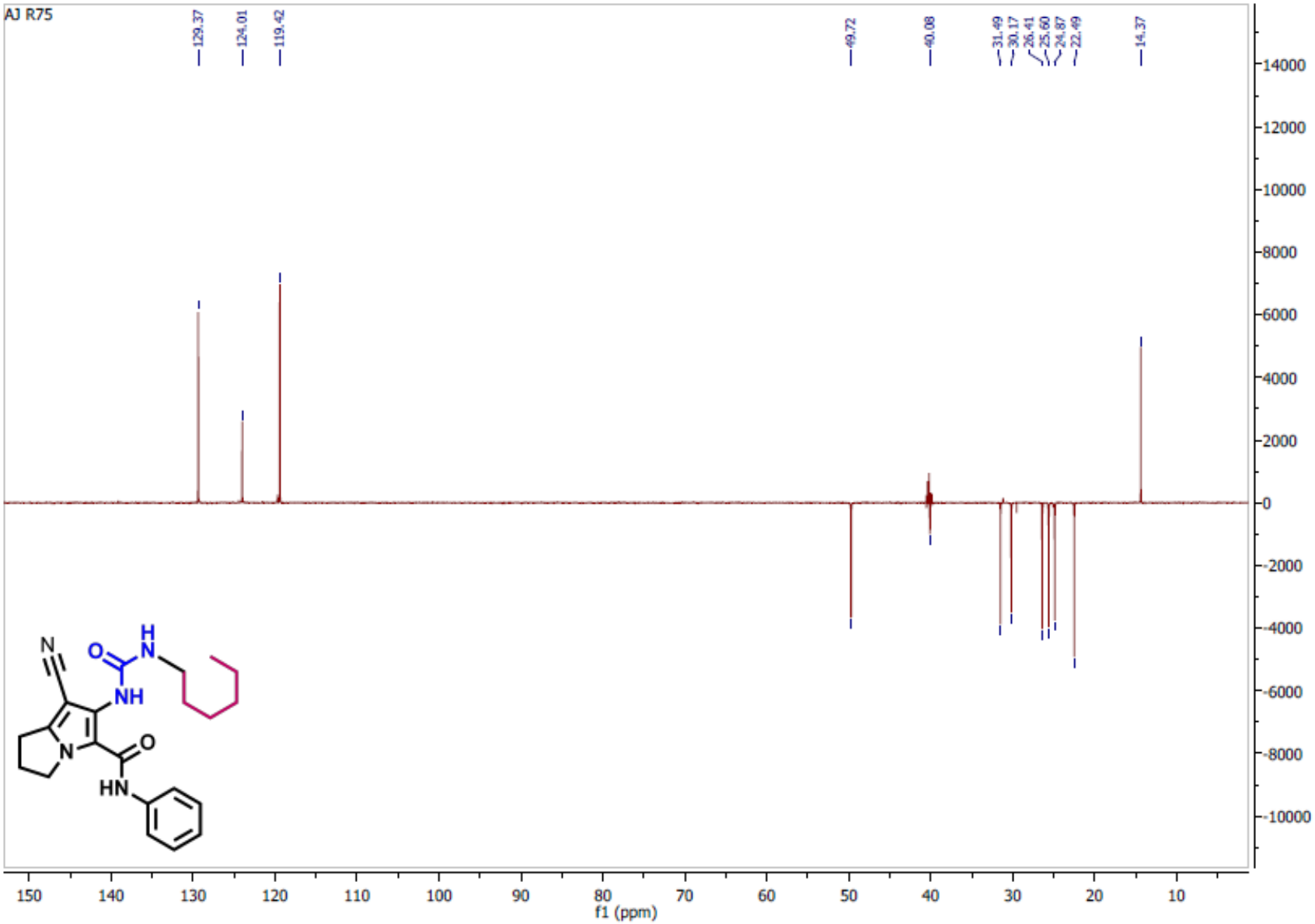


Figure S67. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16b**.

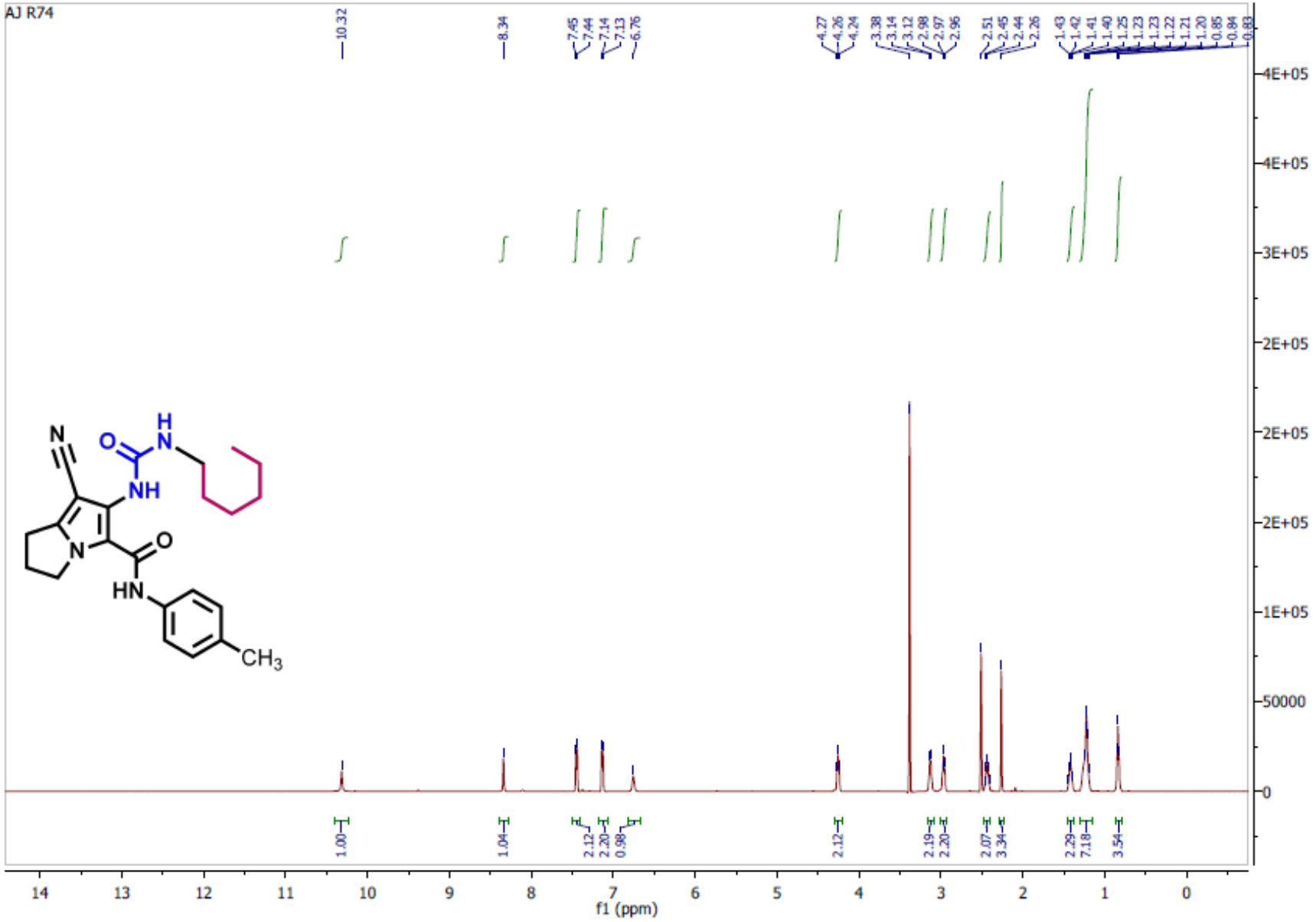


Figure S68. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16b (zoom on aliphatic Hs).

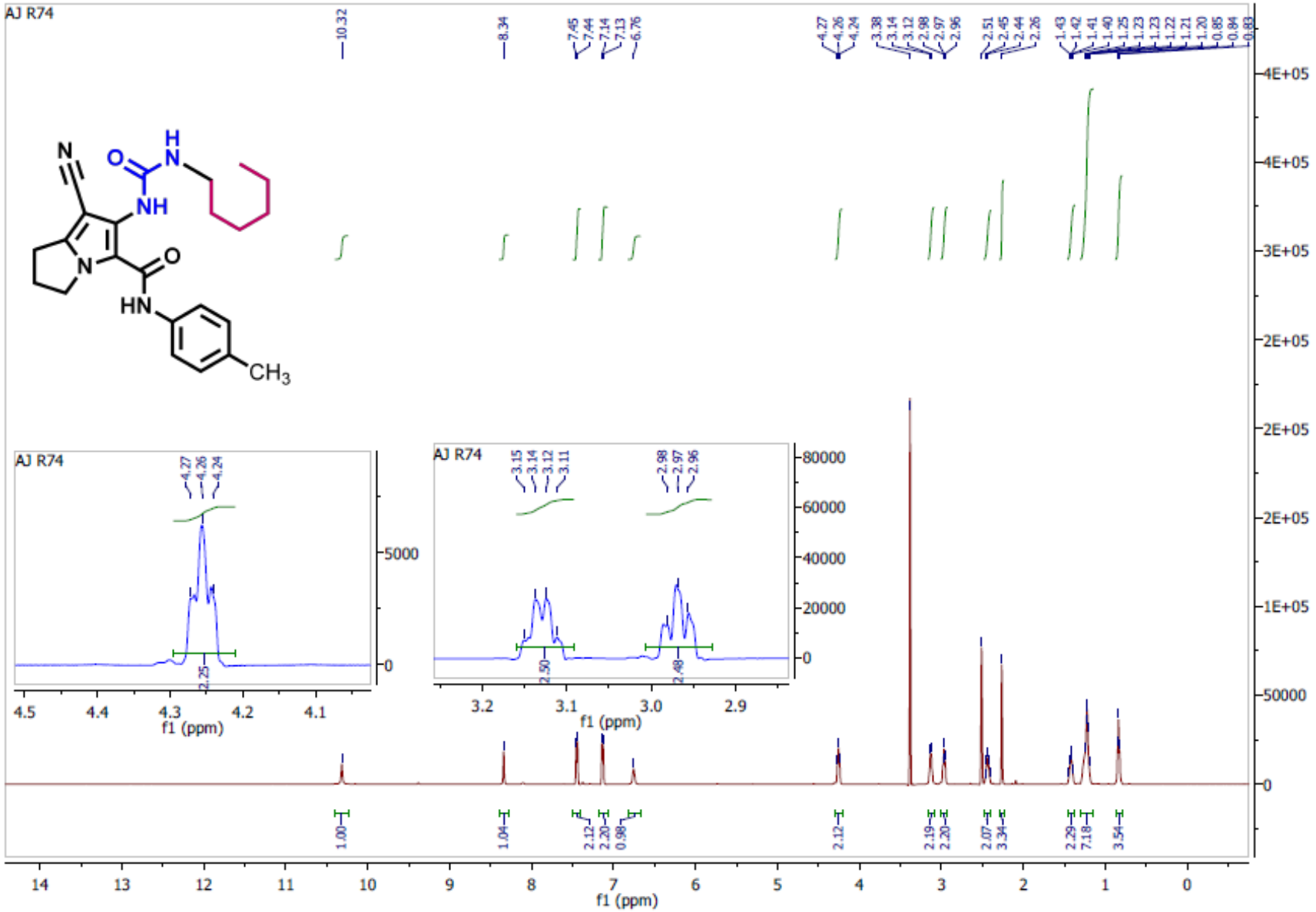


Figure S69. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16b** (**zoom on aliphatic Hs**).

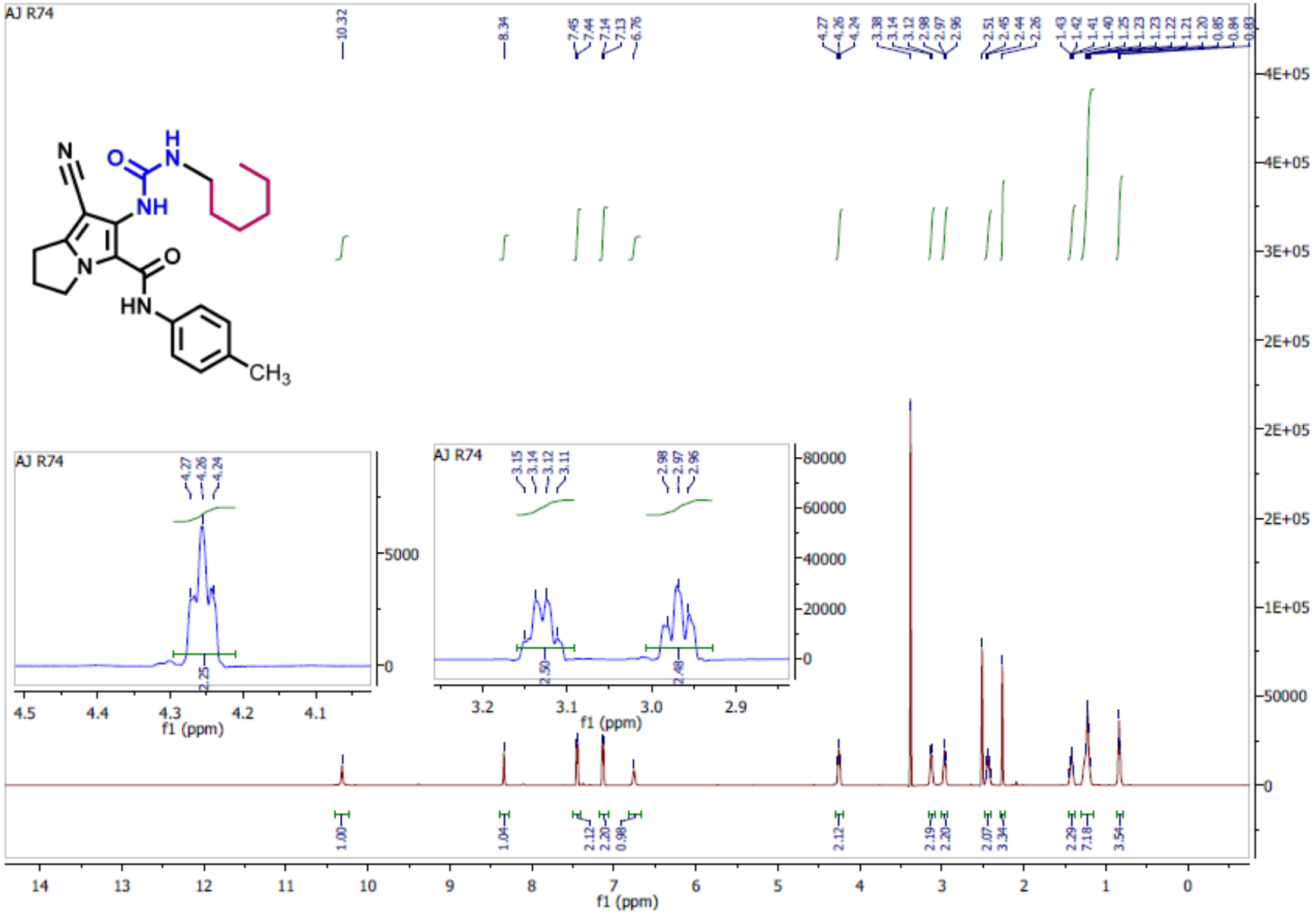


Figure S70. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16b** (**zoom on aromatic Hs**).

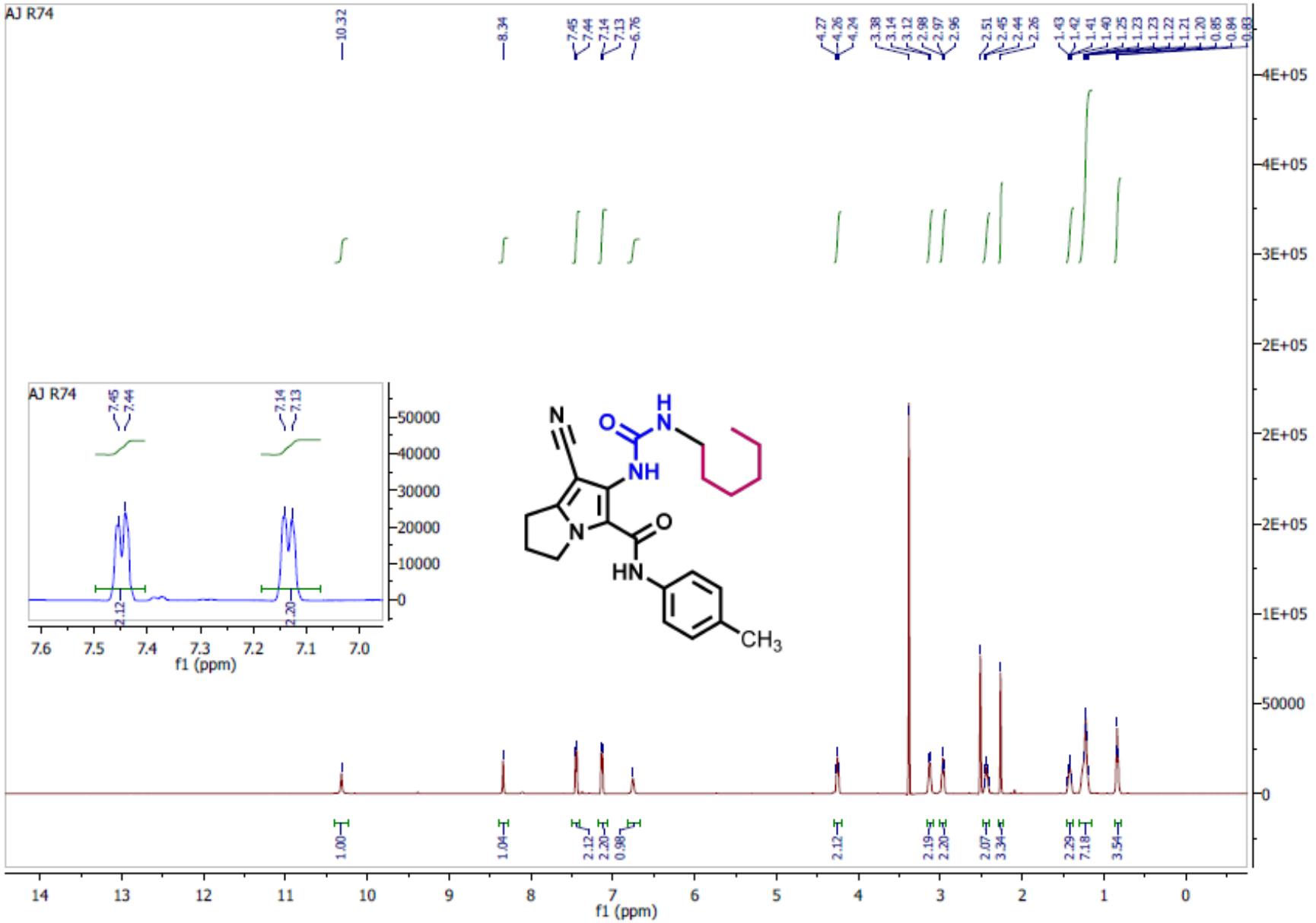


Figure S71. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **16b**.

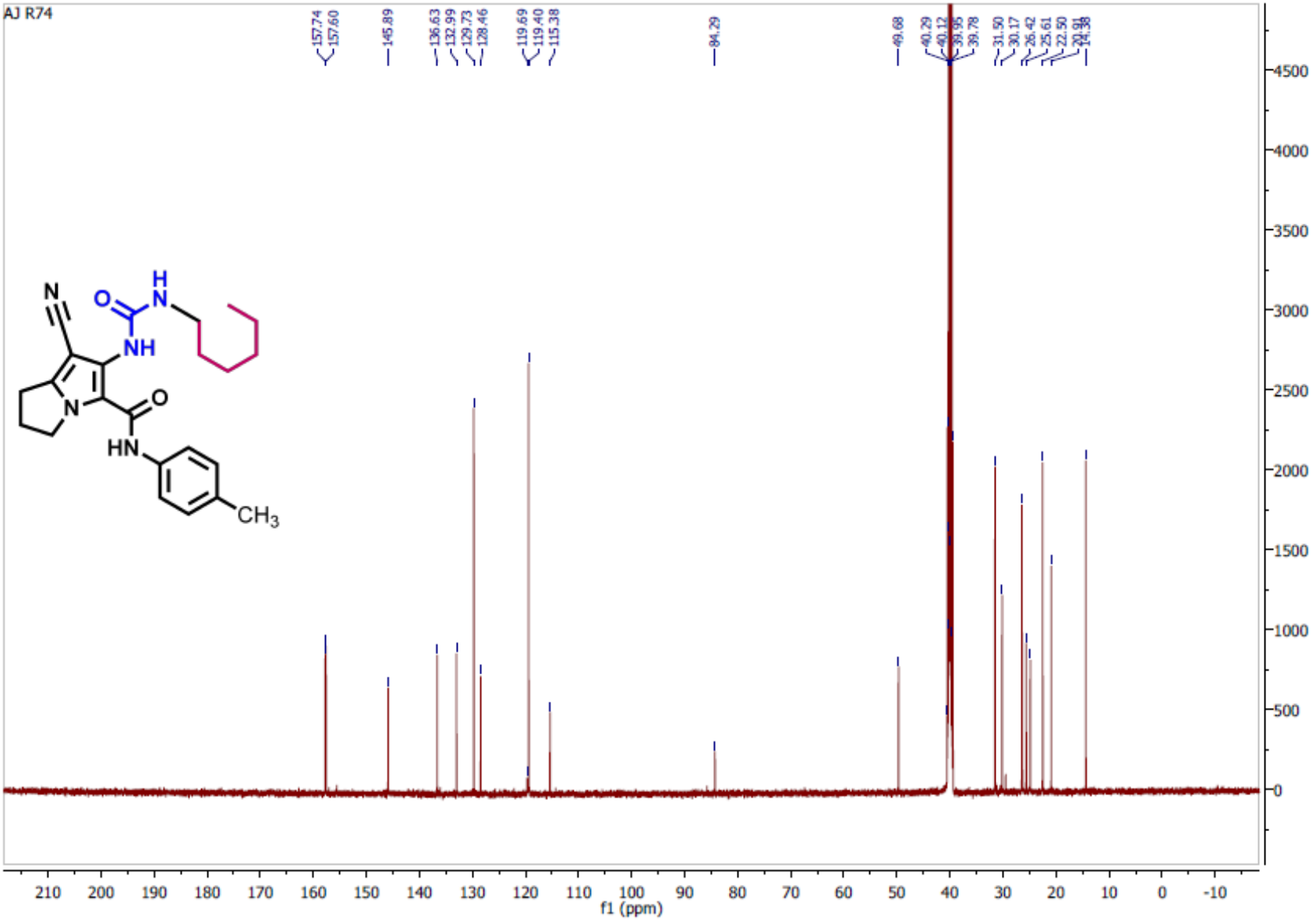


Figure S72. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **16b** (**zoom on aliphatic Cs**).

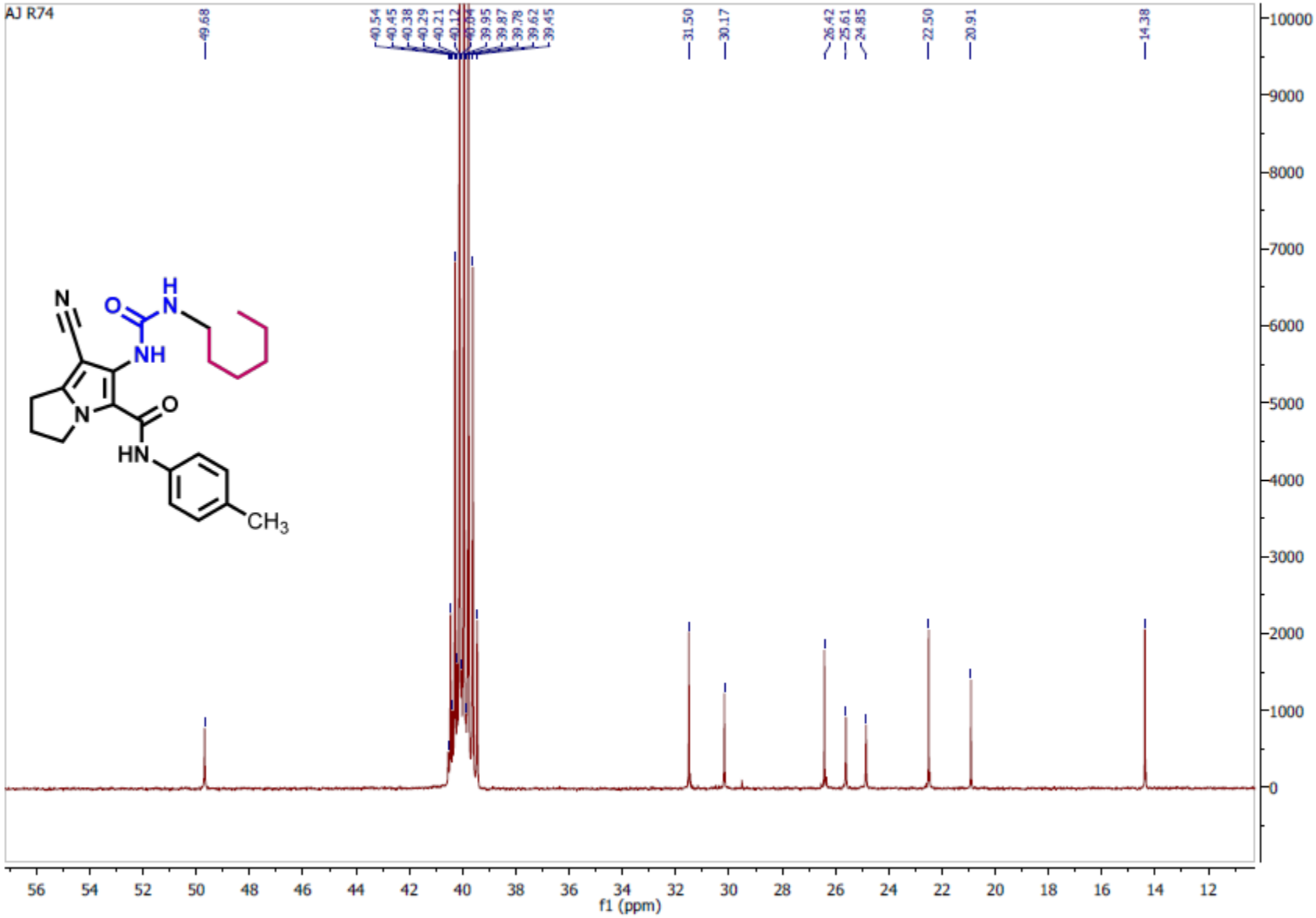


Figure S73. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **16b** (**zoom on aromatic Cs**).

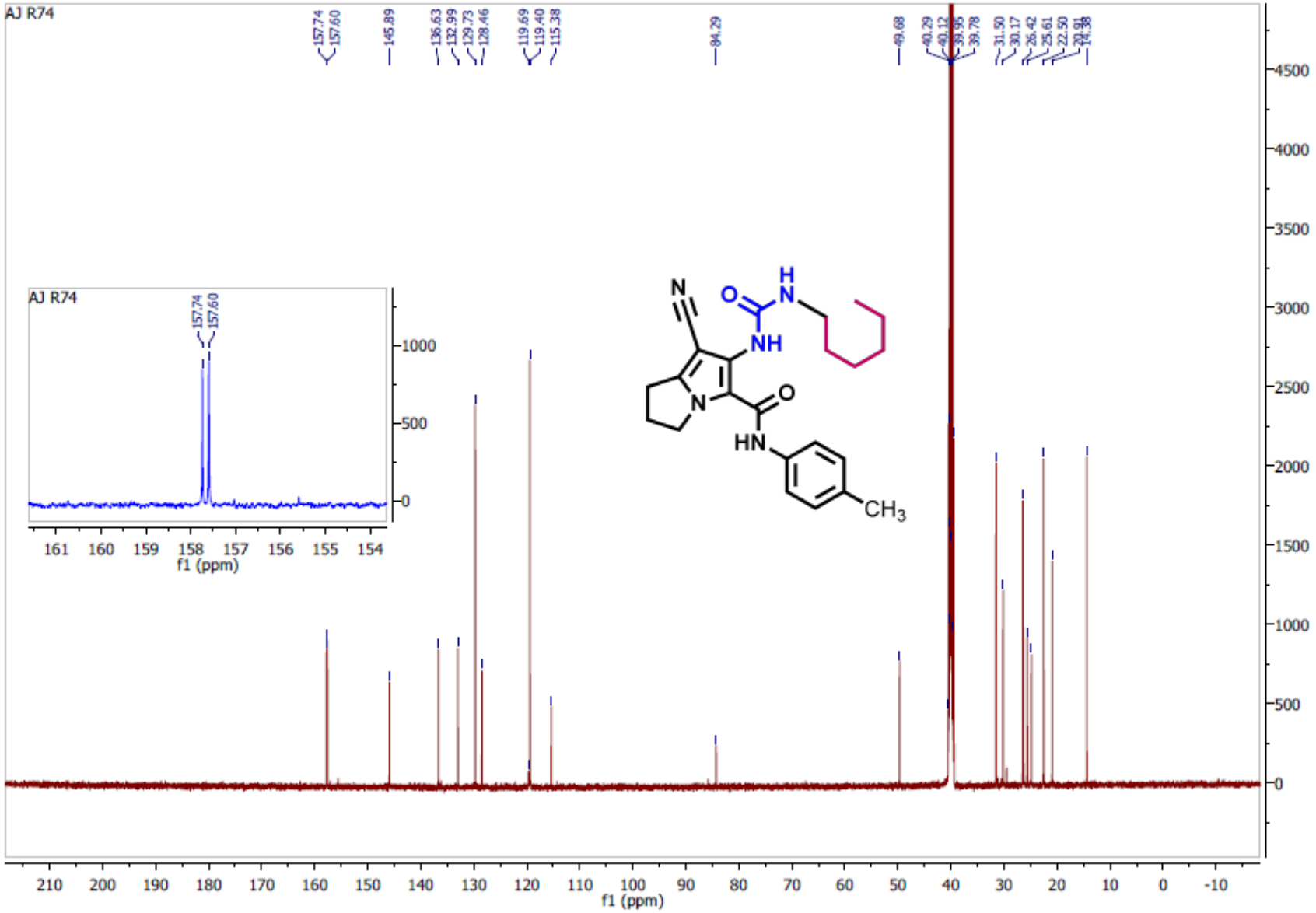


Figure S74. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound **16b**.

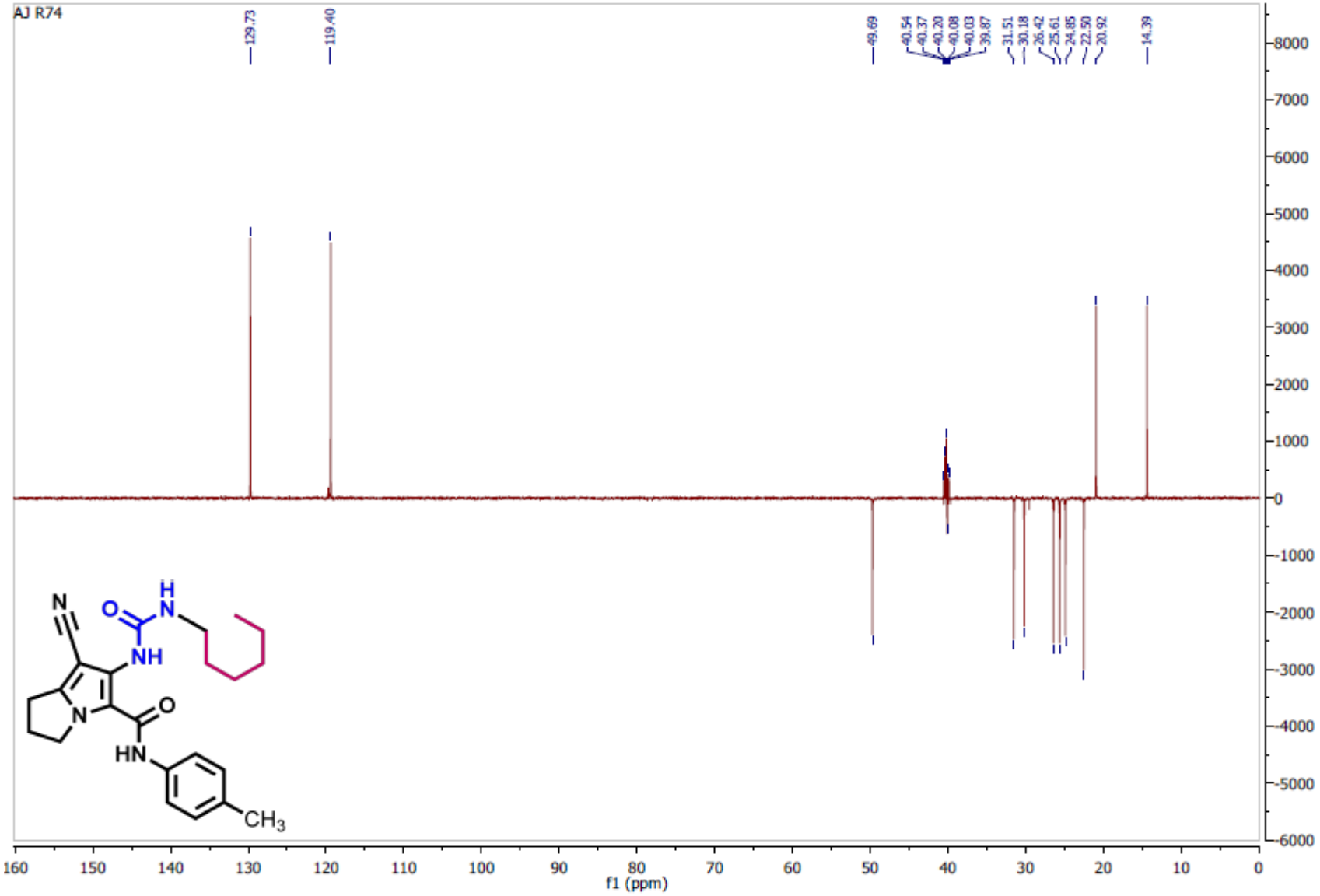


Figure S75. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 16b (zoom on aliphatic Cs).

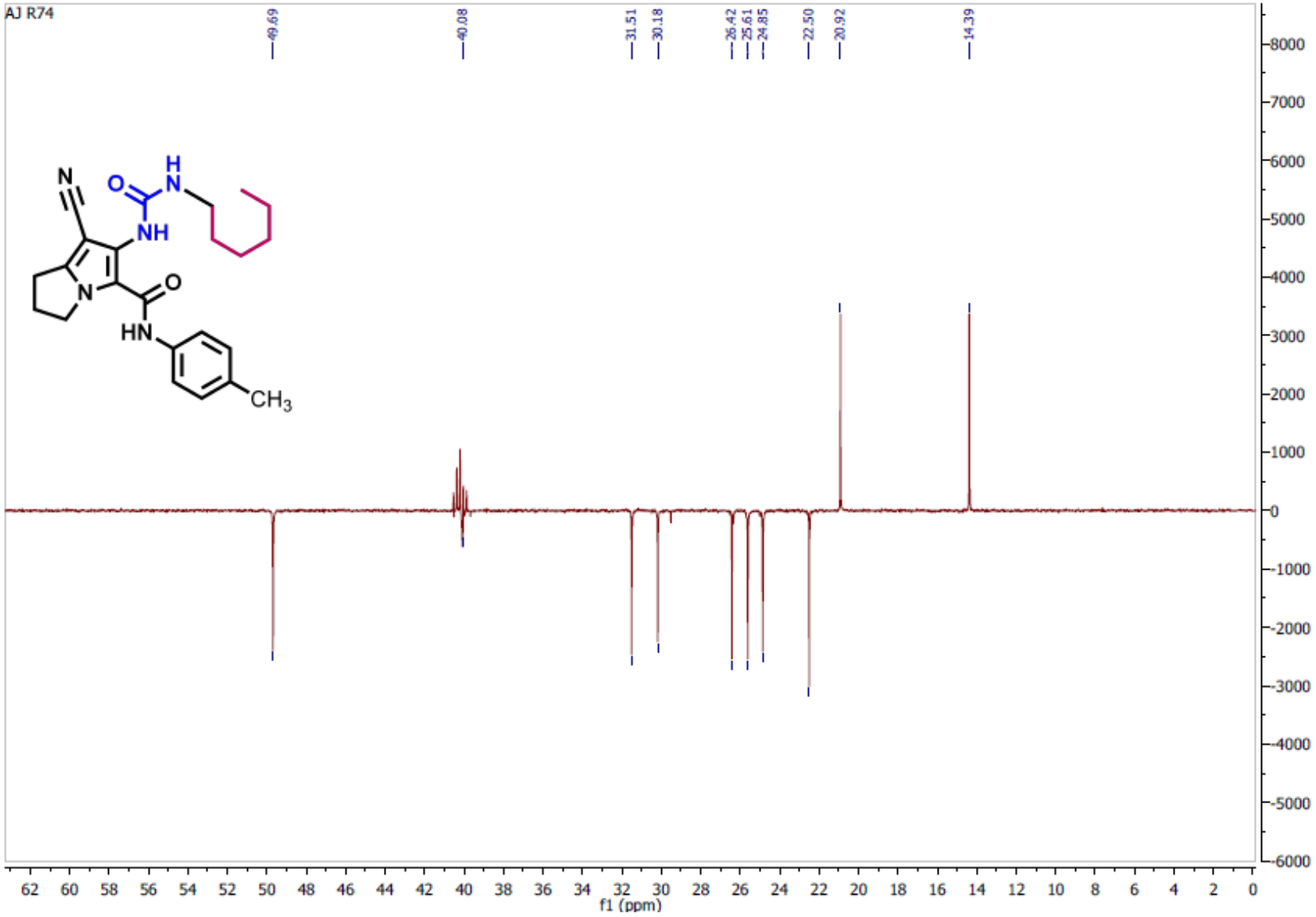


Figure S76. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 16b (zoom on aliphatic Cs).

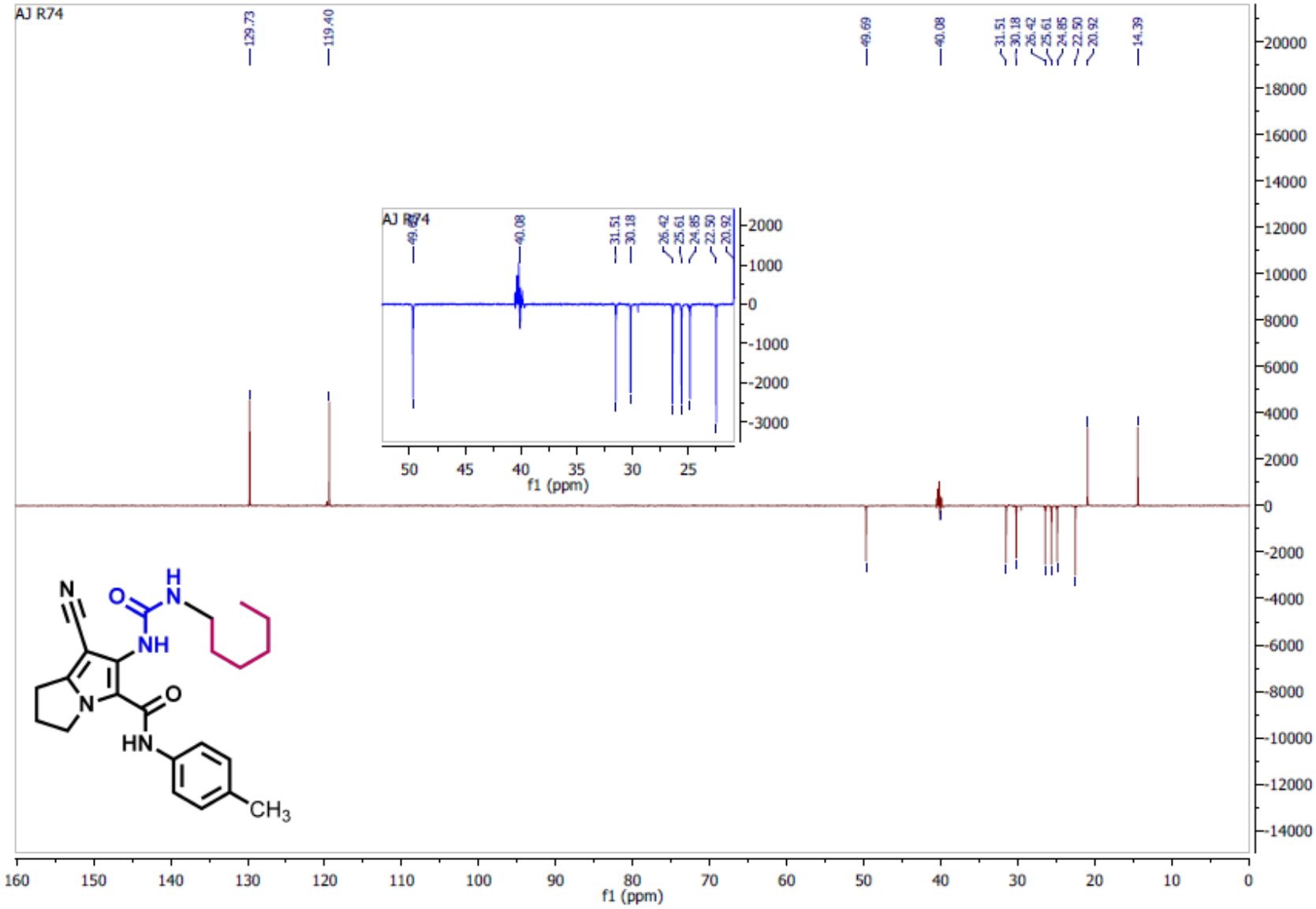


Figure S77. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16c**.

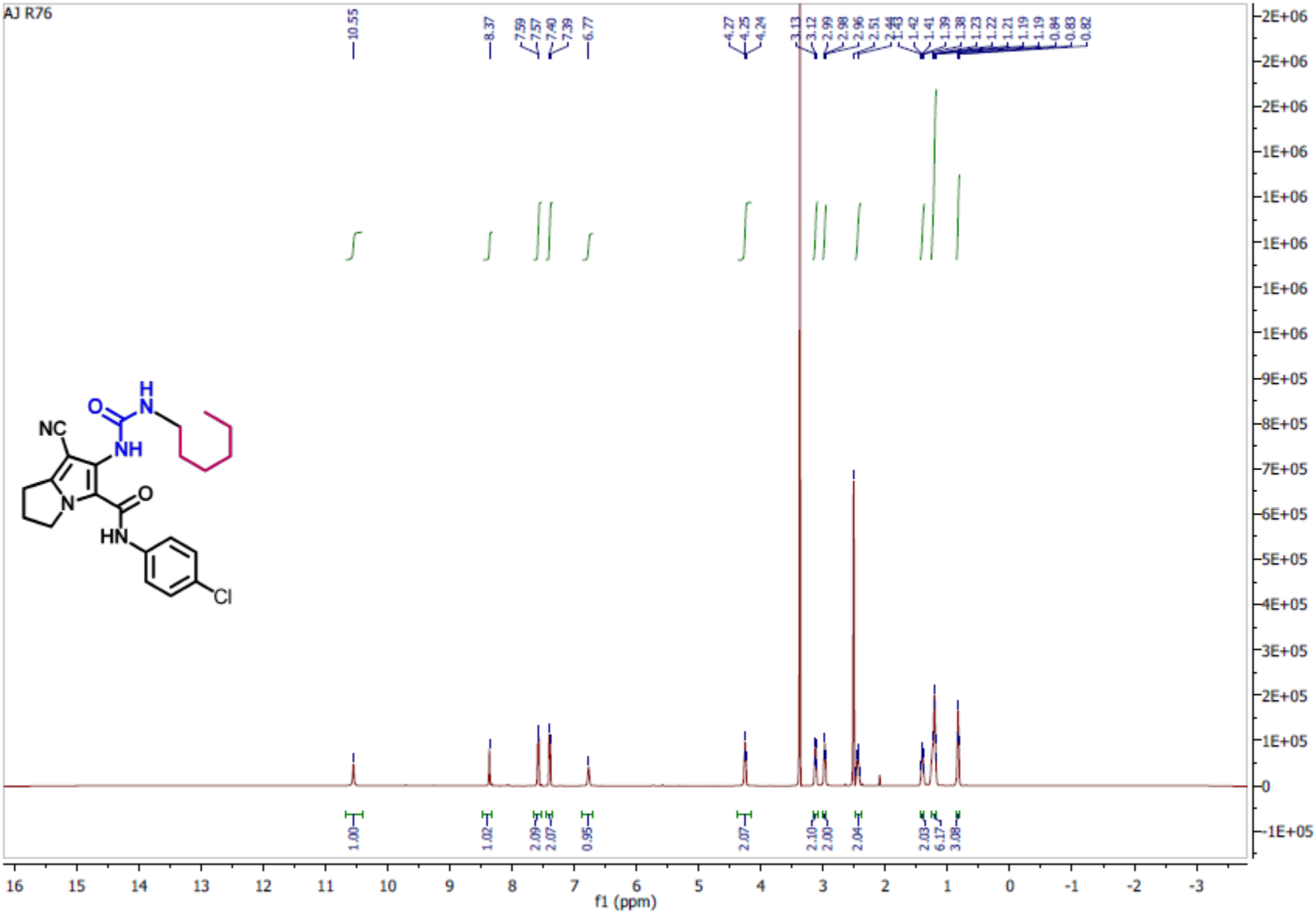


Figure S78. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16c (zoom on aliphatic Hs).

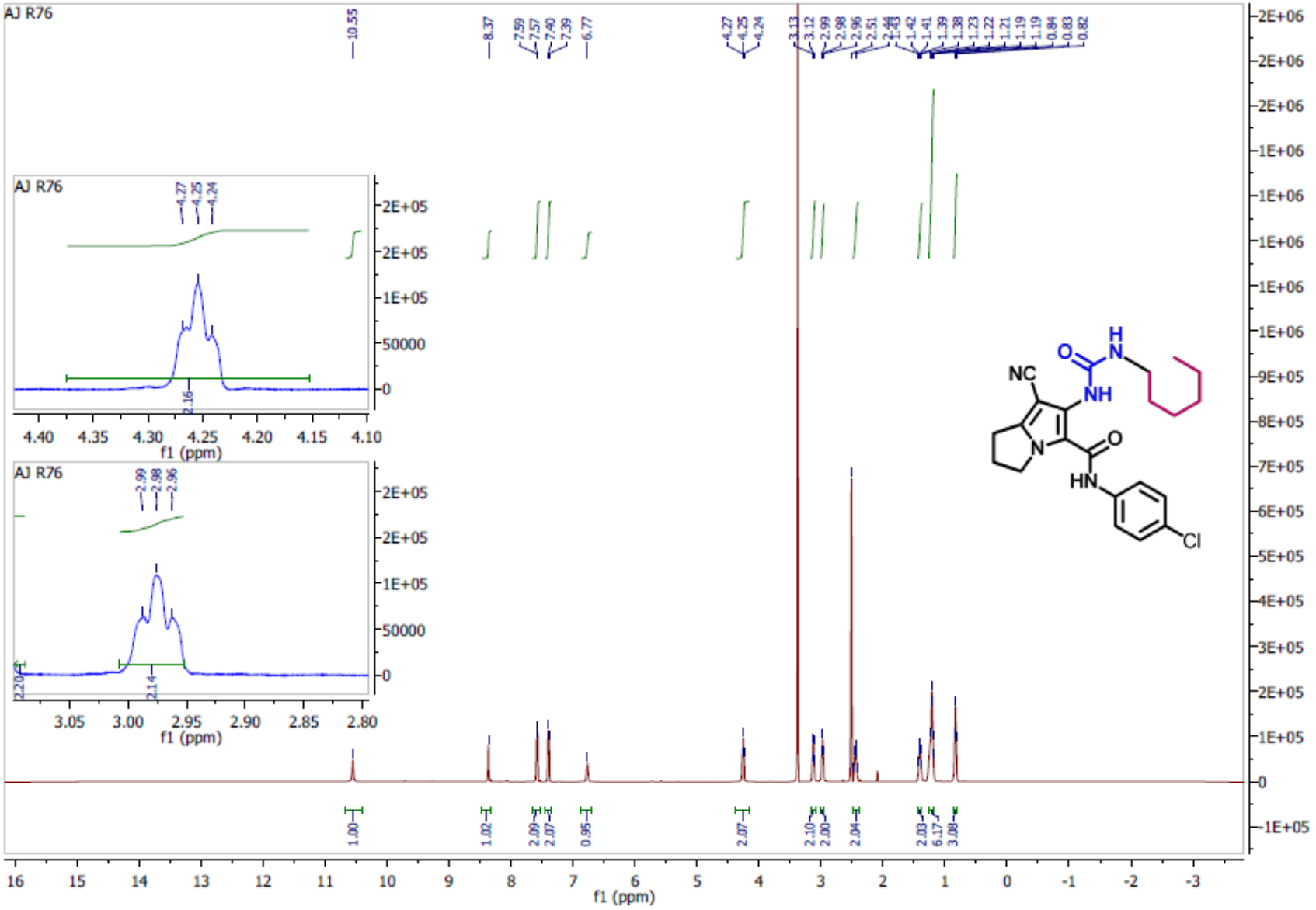


Figure S79. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16c** (**zoom on aliphatic Hs**).

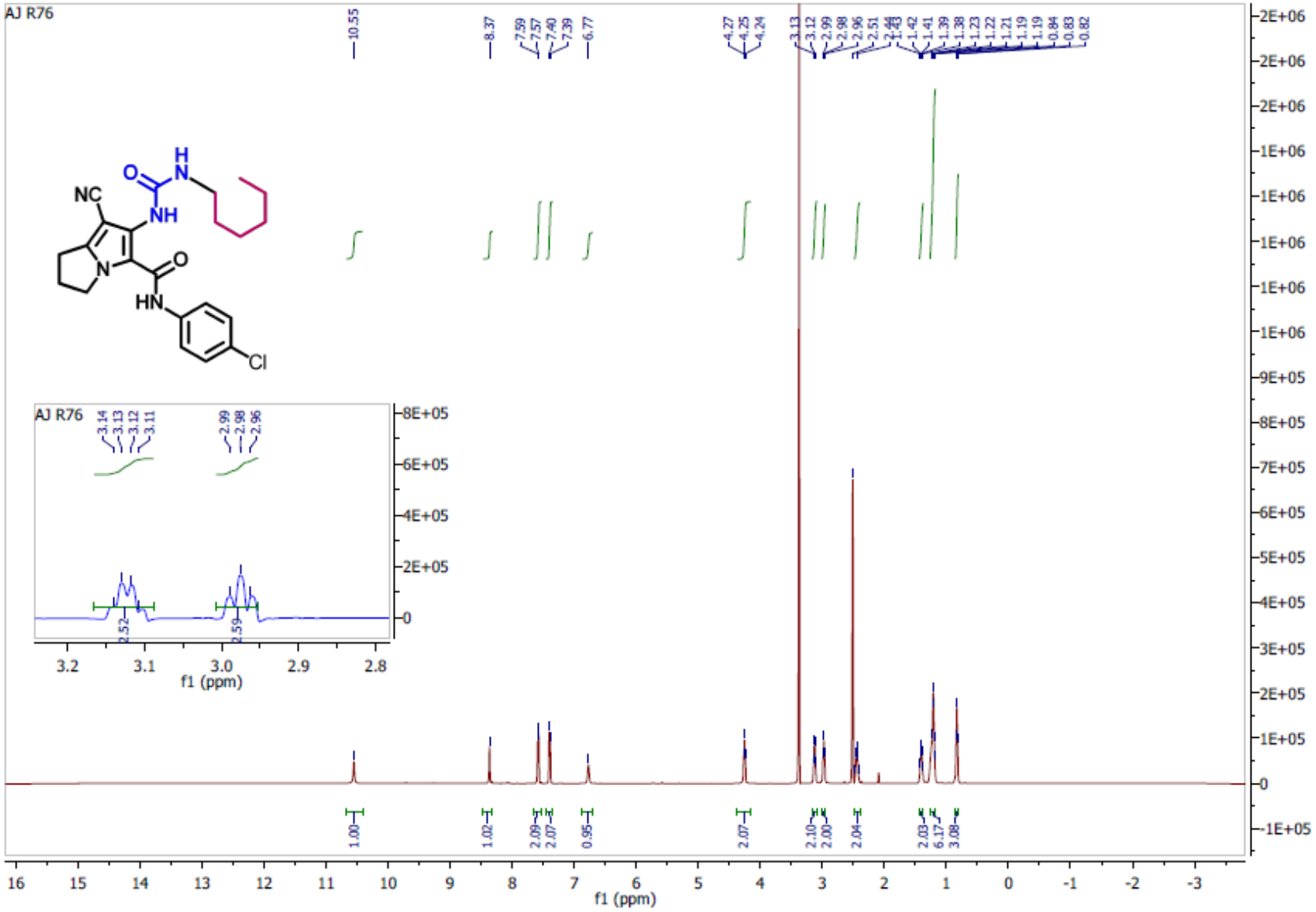


Figure S80. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 16c (zoom on aliphatic/aromatic Hs).

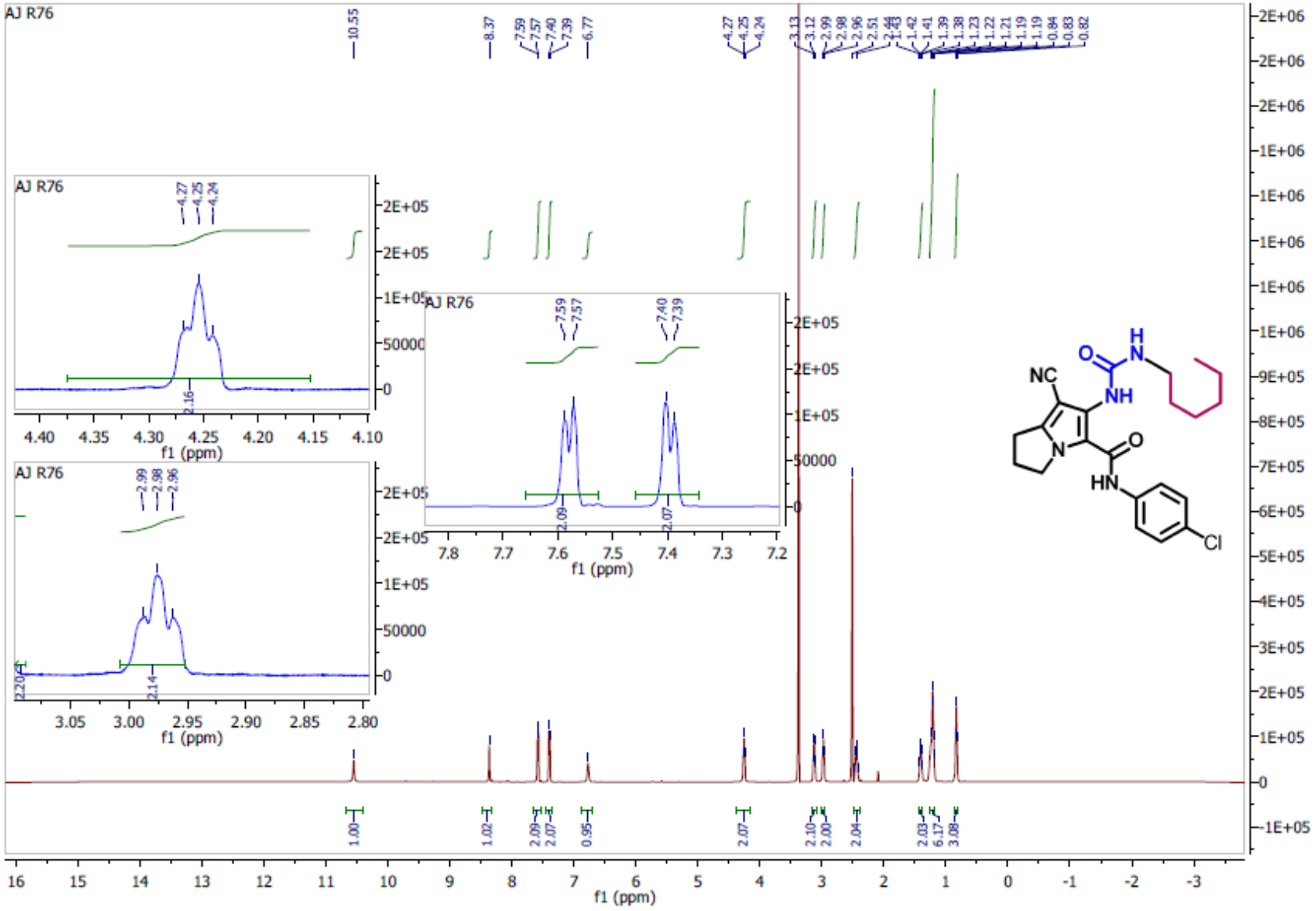


Figure S81. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 16c.

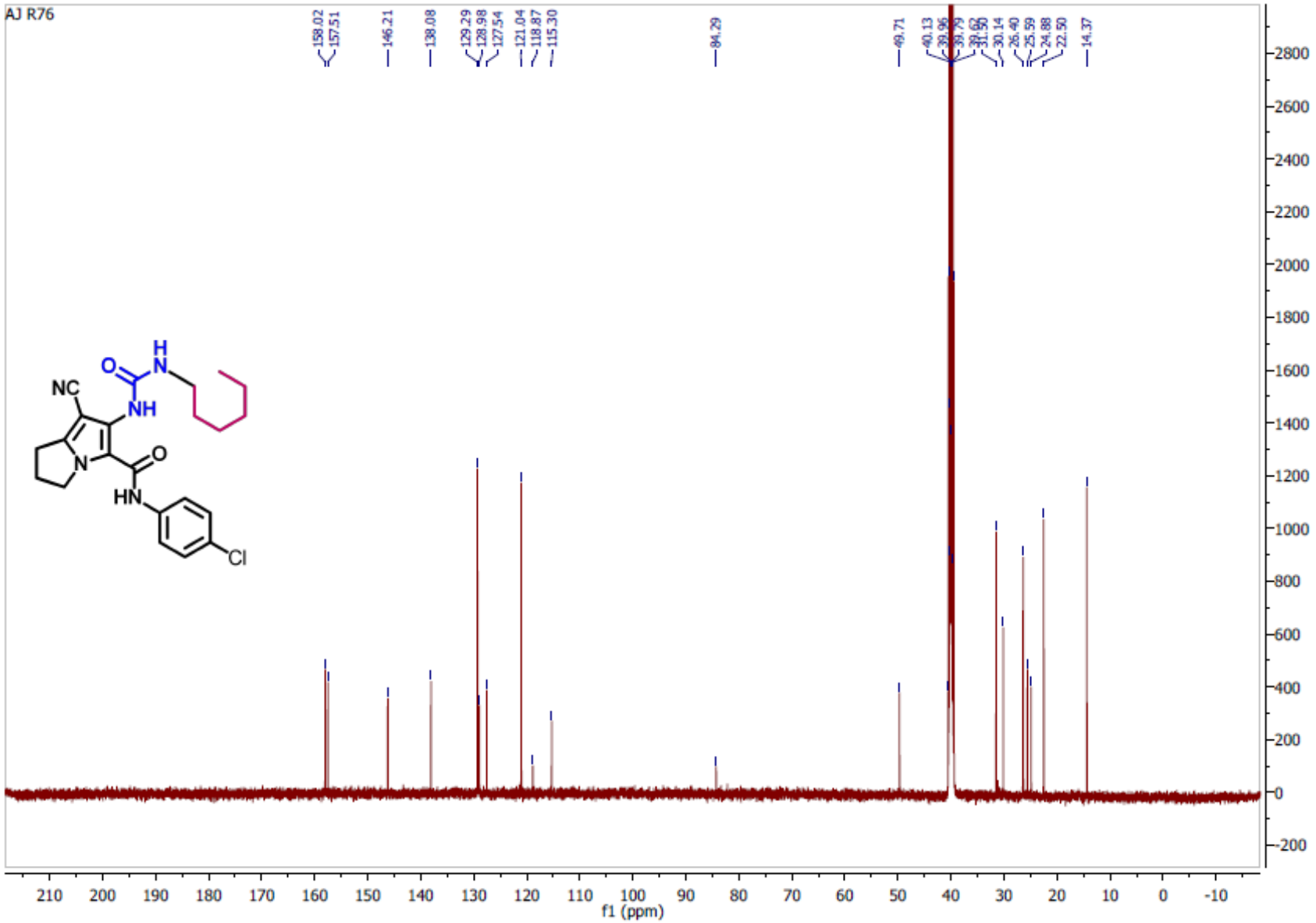


Figure S82. **^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 16c (zoom on aliphatic/aromatic Cs).**

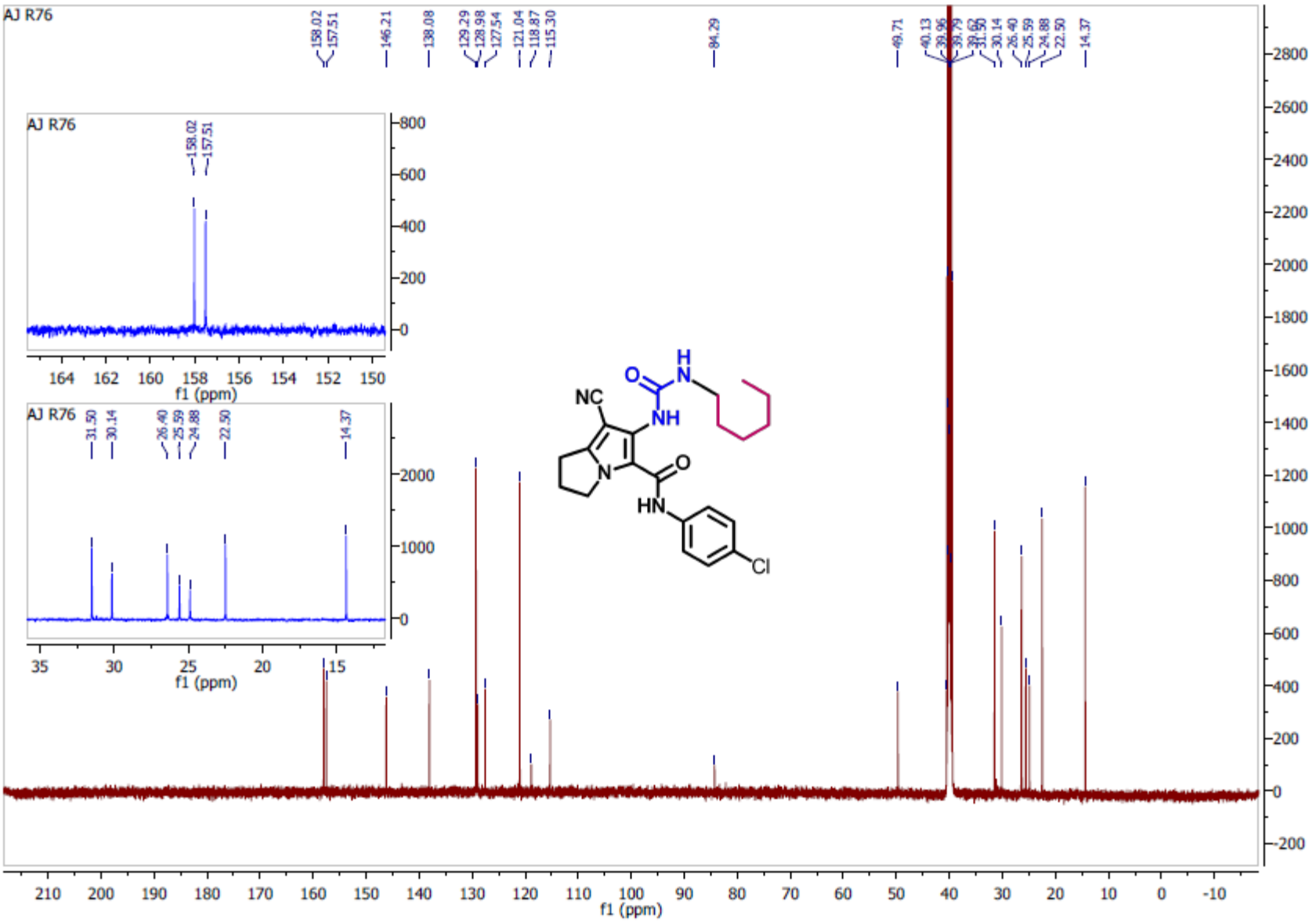


Figure S83. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 16c.

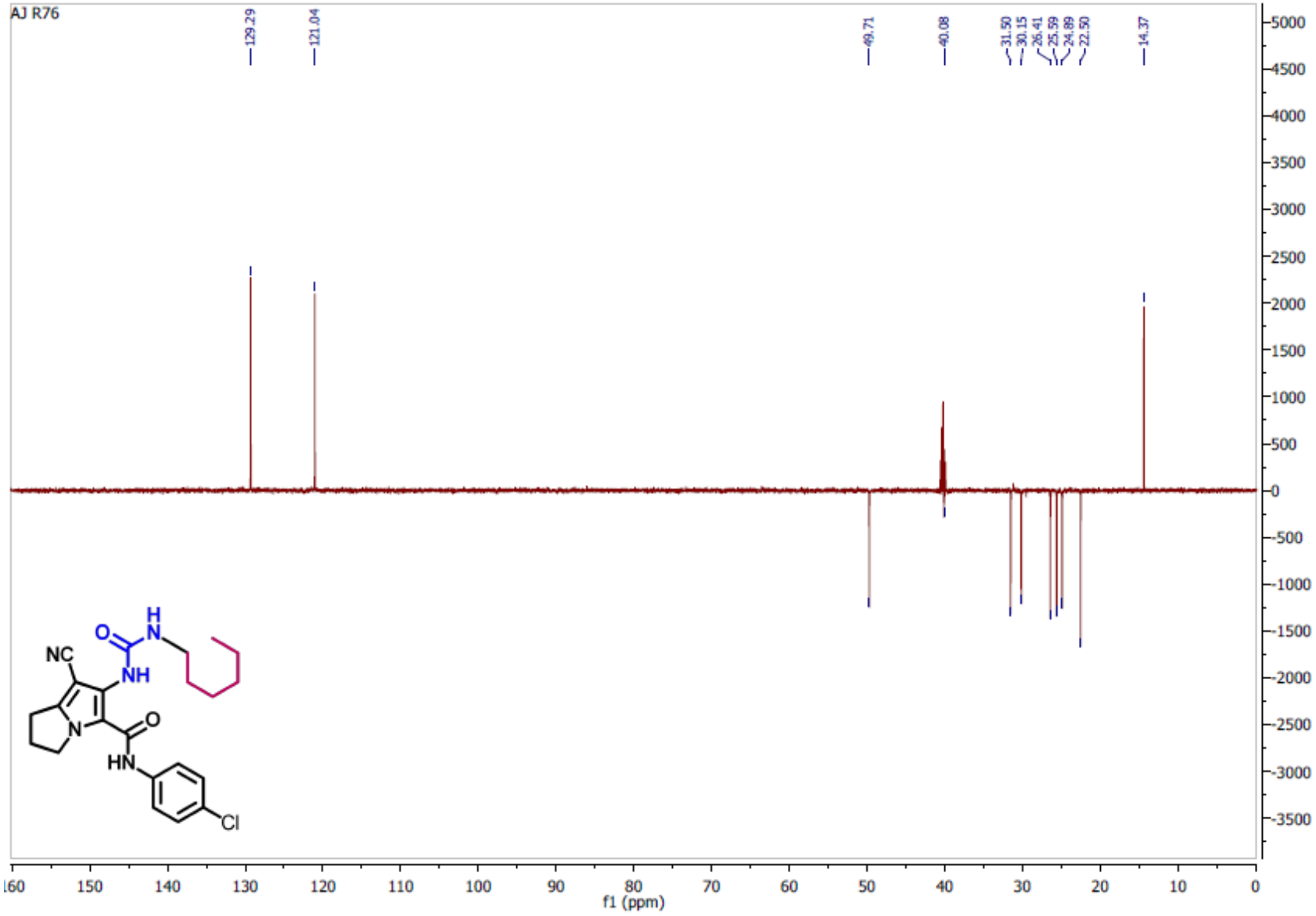


Figure S84. ^{1}**H-NMR (DMSO, 500 MHz,** δ **ppm) spectrum of compound 17a.**

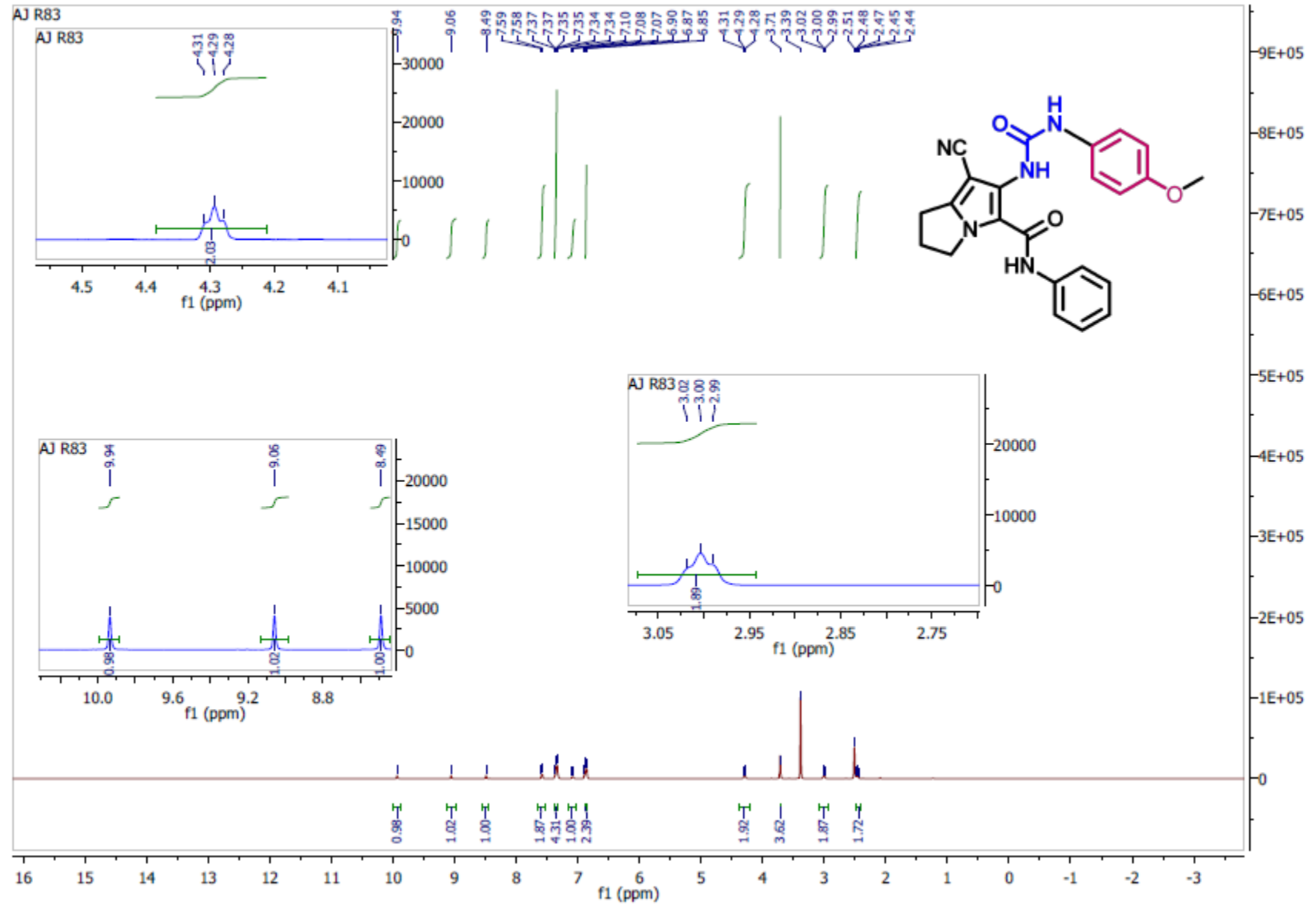


Figure S85. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 17a.

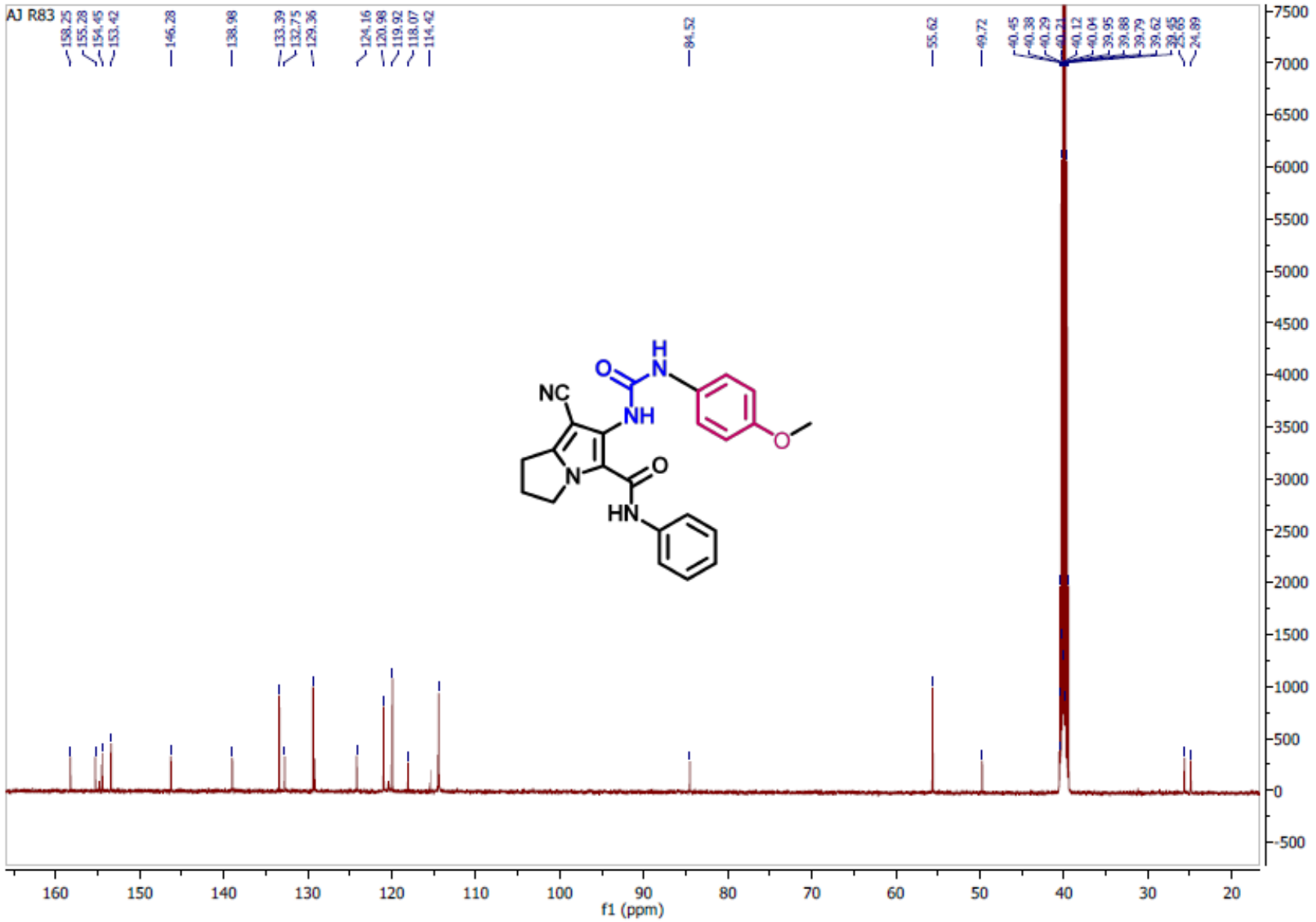


Figure S86. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 17a.

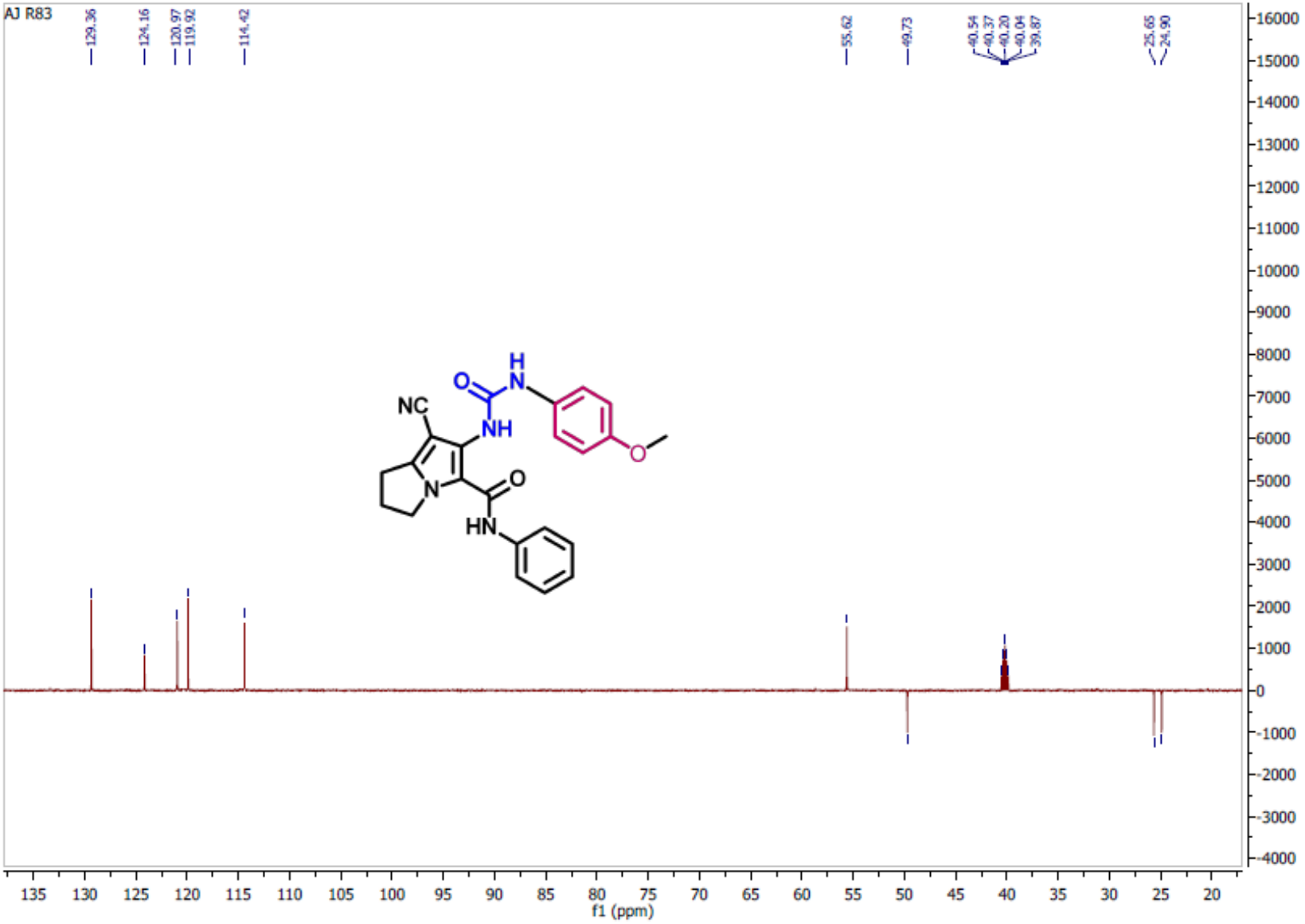


Figure S87. ^{1}**H-NMR (DMSO, 500 MHz,** δ **ppm) spectrum of compound 17b**

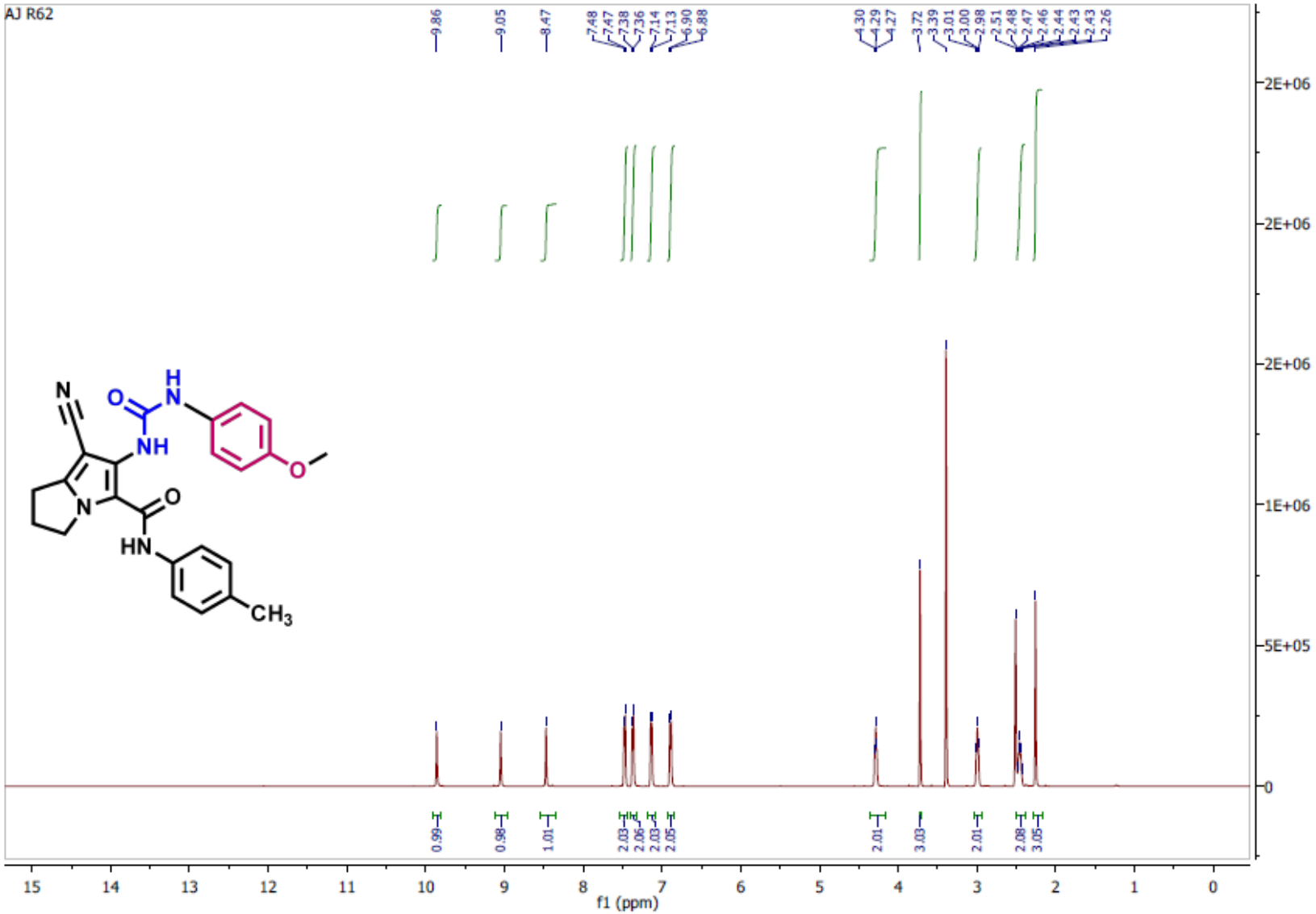


Figure S88. ^{1}**H-NMR (DMSO, 500 MHz,** δ **ppm) spectrum of compound 17b (zoom on aliphatic Hs).**

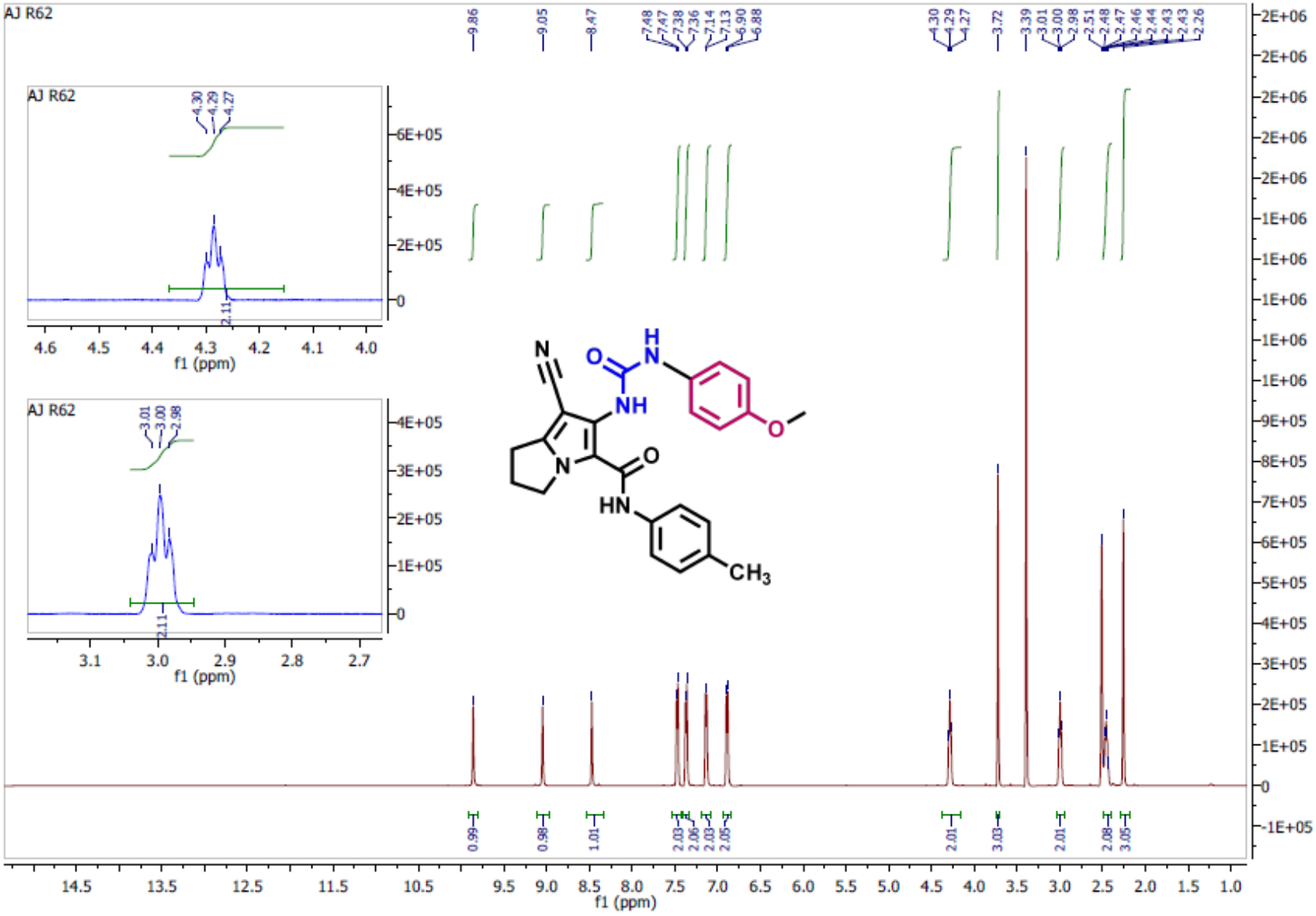


Figure S89. ^{1}**H-NMR (DMSO, 500 MHz,** δ **ppm) spectrum of compound 17b (zoom on aliphatic/aromatic Hs).**

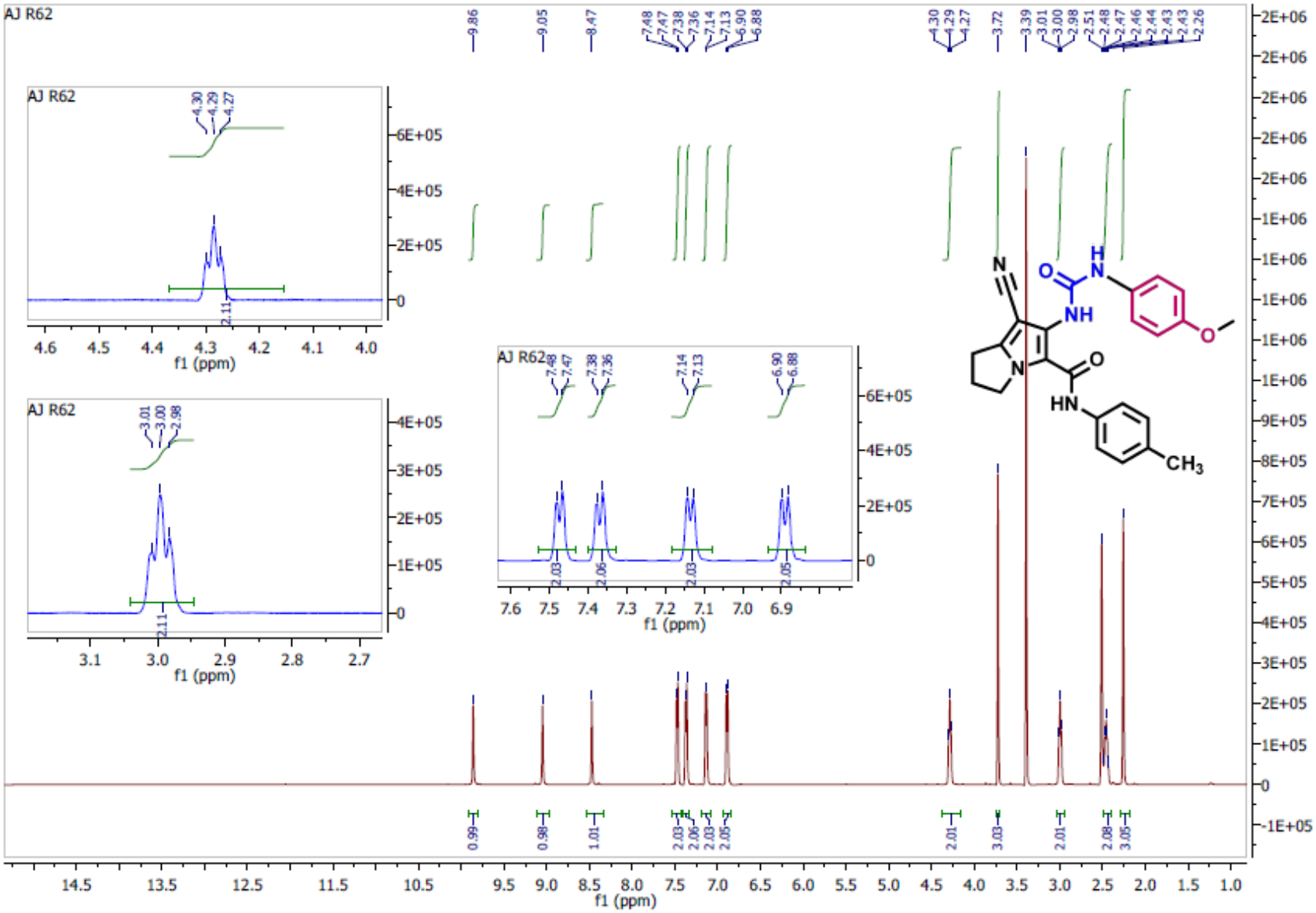


Figure S90. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 17b.

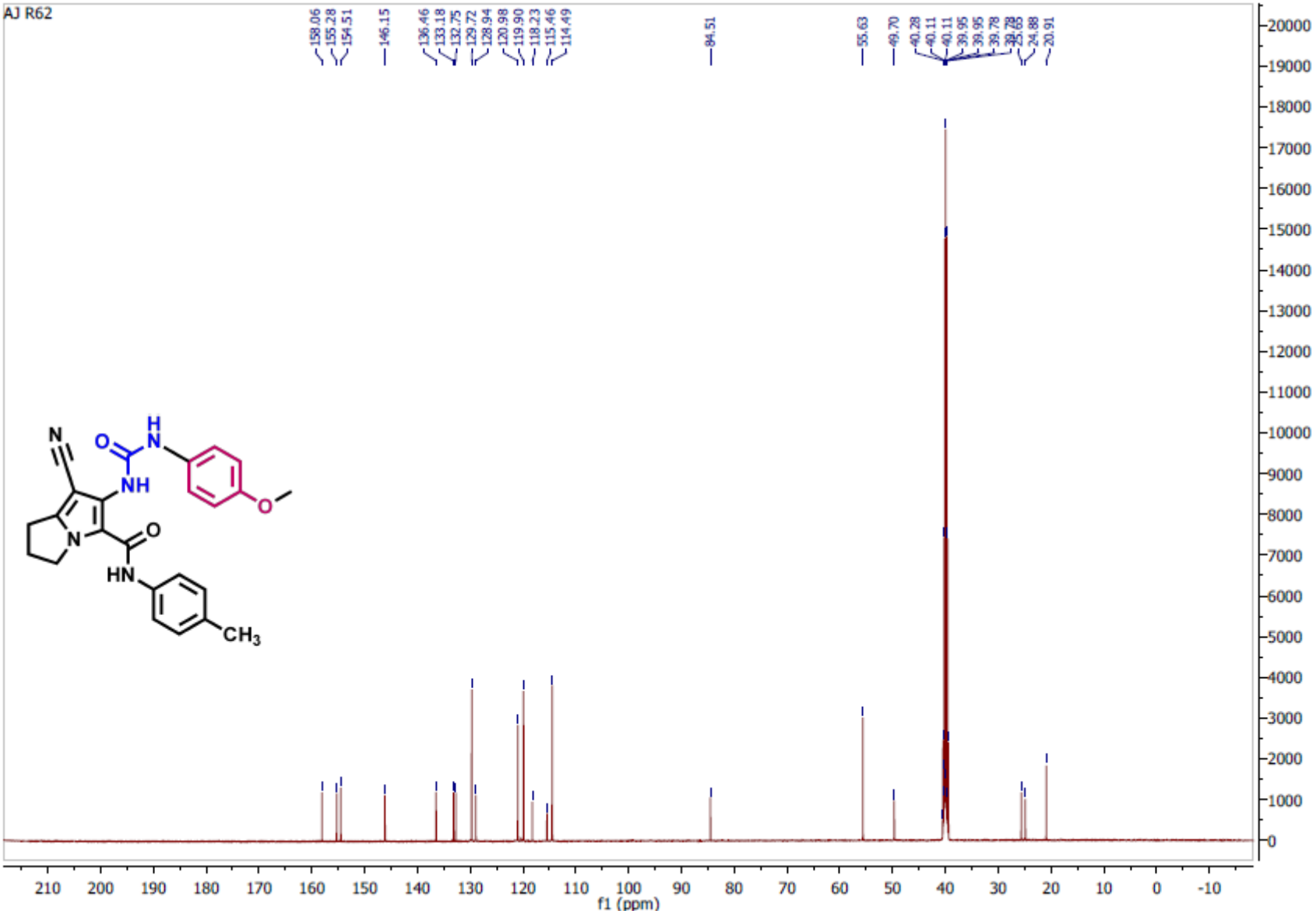


Figure S91. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 17b.

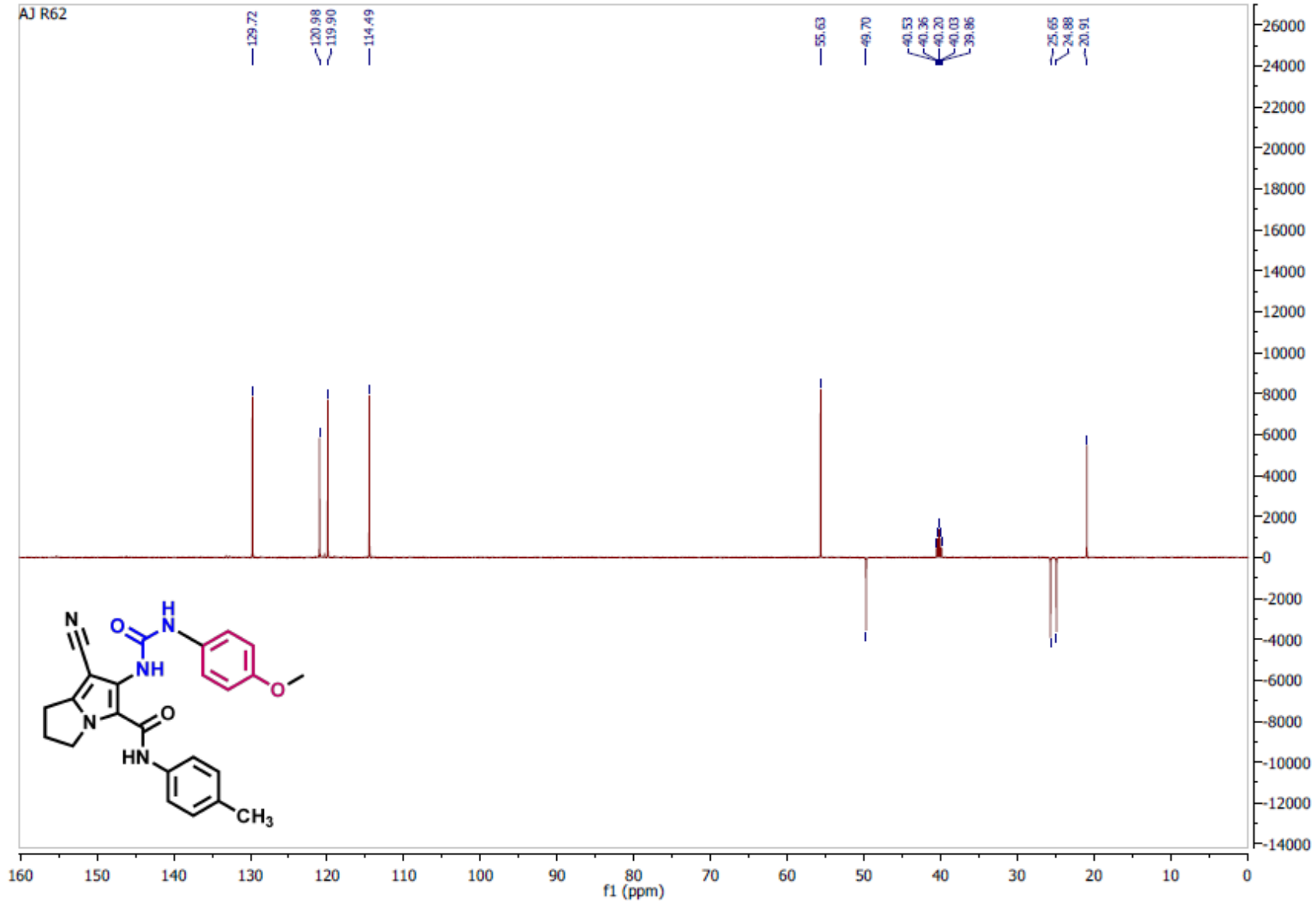


Figure S92. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **18a**

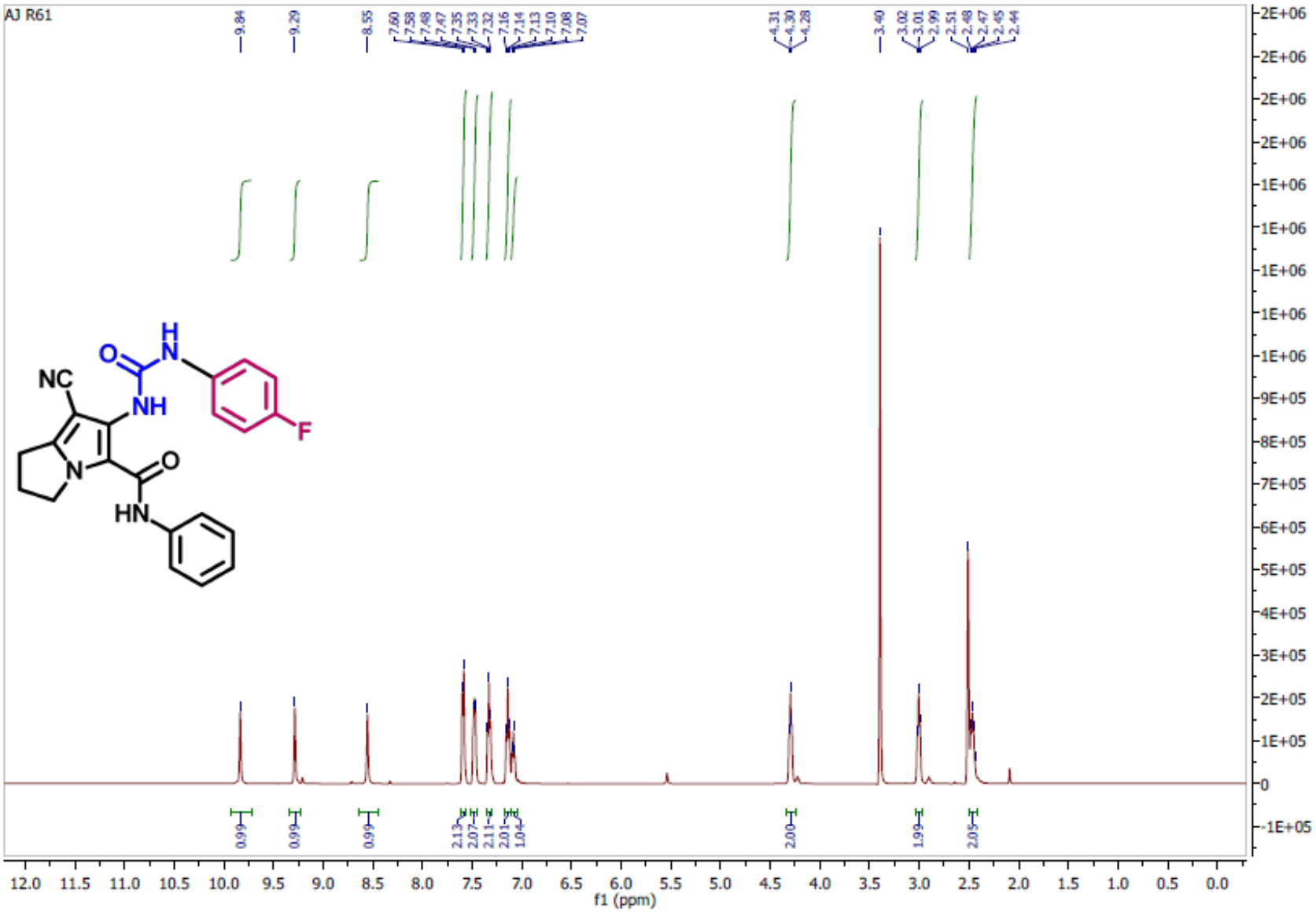


Figure S93. ^{1}**H-NMR (DMSO, 500 MHz,** δ **ppm) spectrum of compound 18a (ZOOM on aliphatic Hs)**

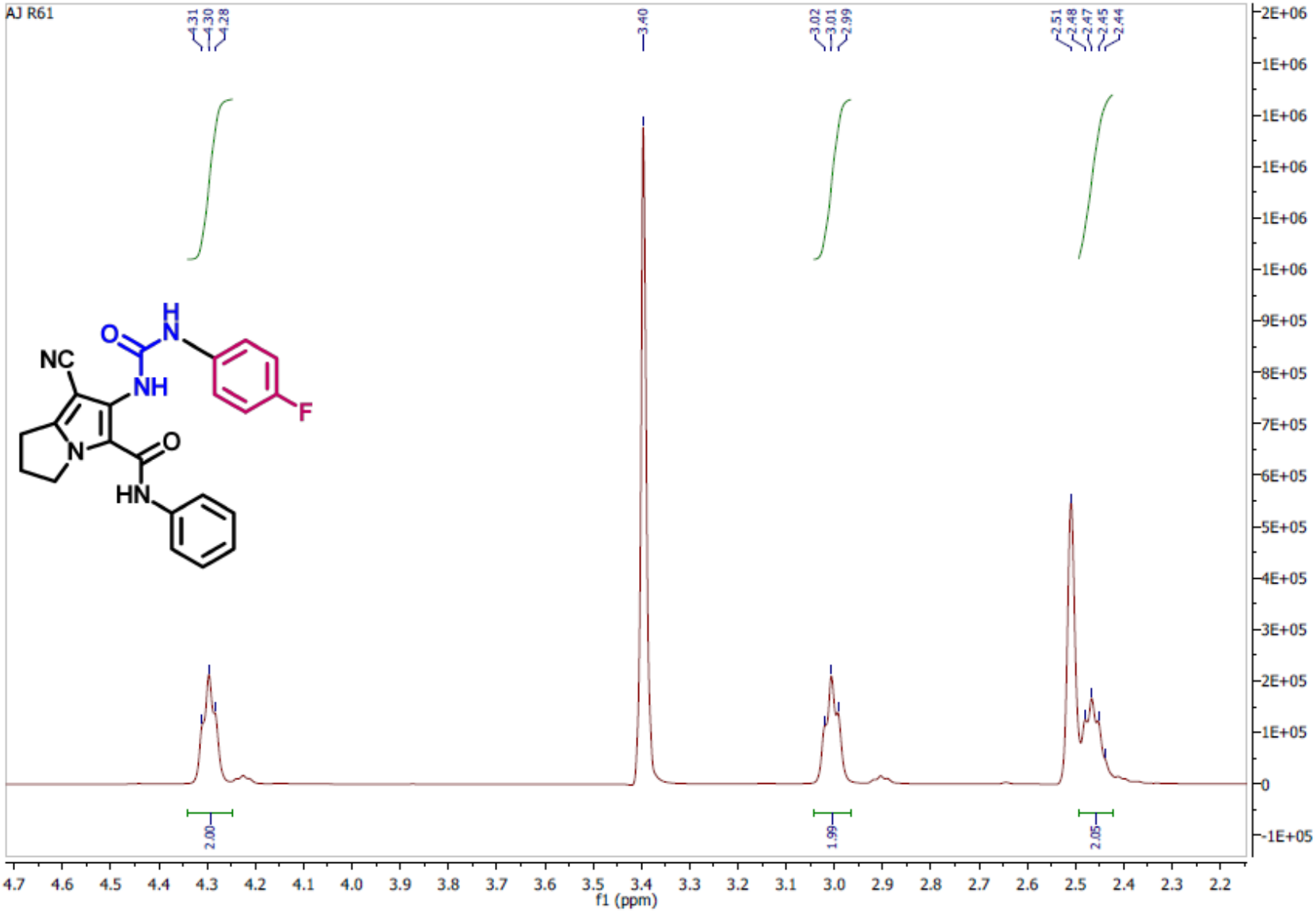

AJ R61
4.31
4.30
4.28
3.40
3.02
3.01
2.99
2.51
2.48
2.47
2.45
2.44
NC
NH
O
N
H
F
N
O
HN
2.00
1.99
2.05
f1 (ppm)

Figure S94. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 18a (ZOOM on NHs & aromatic Hs)

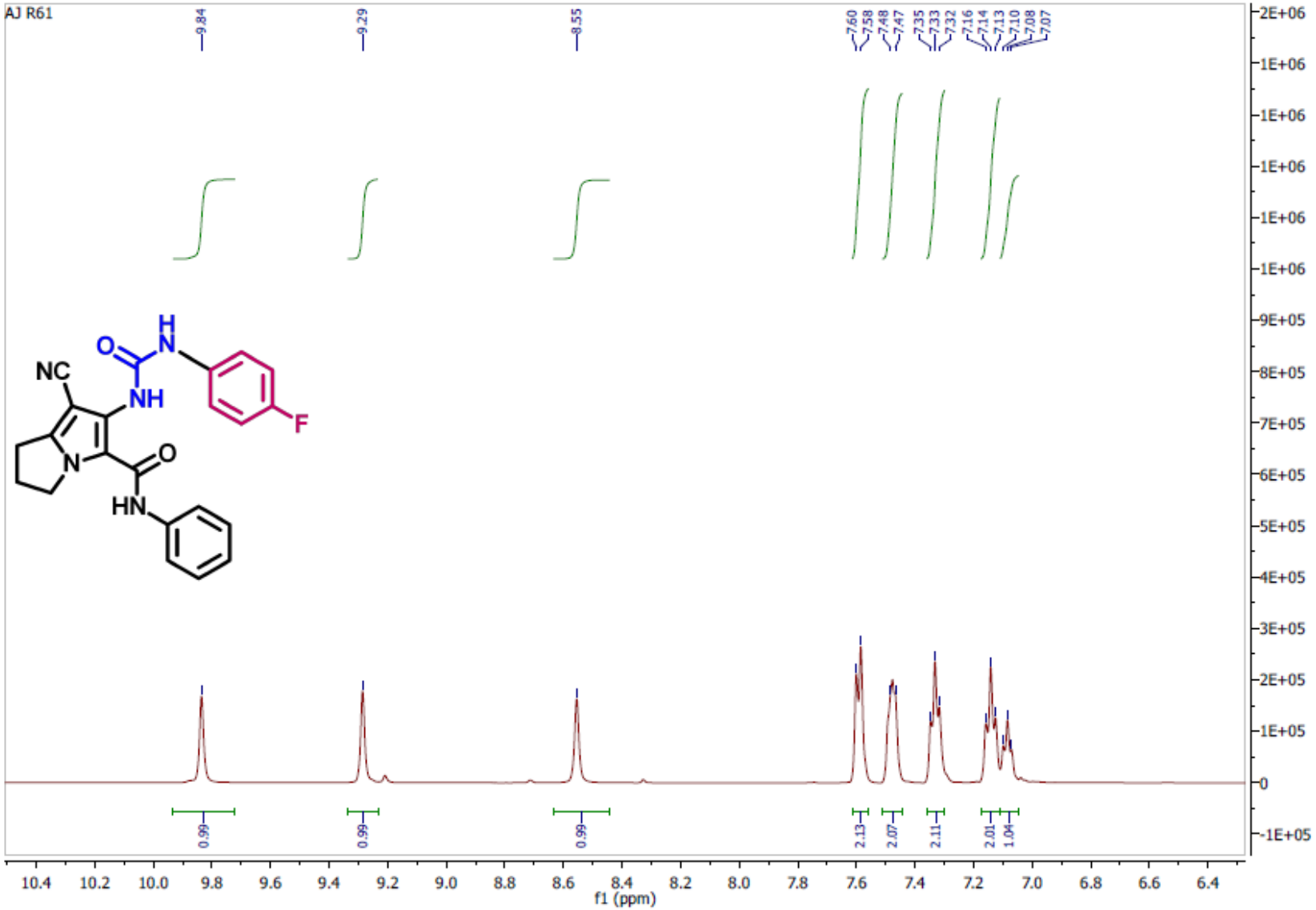


Figure S95. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **16a** (**ZOOM on aromatic Hs**)

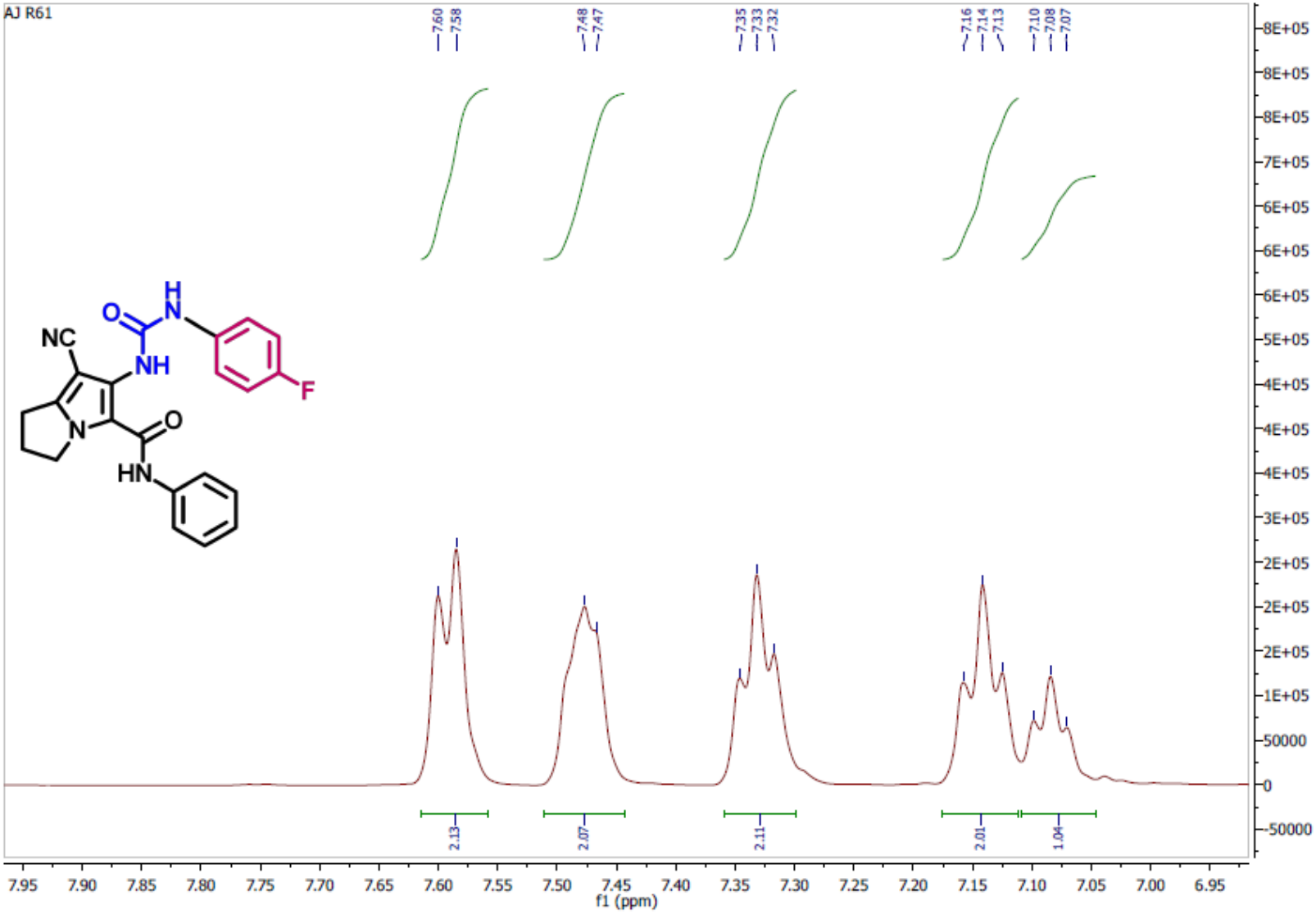


Figure S96. **^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18a**

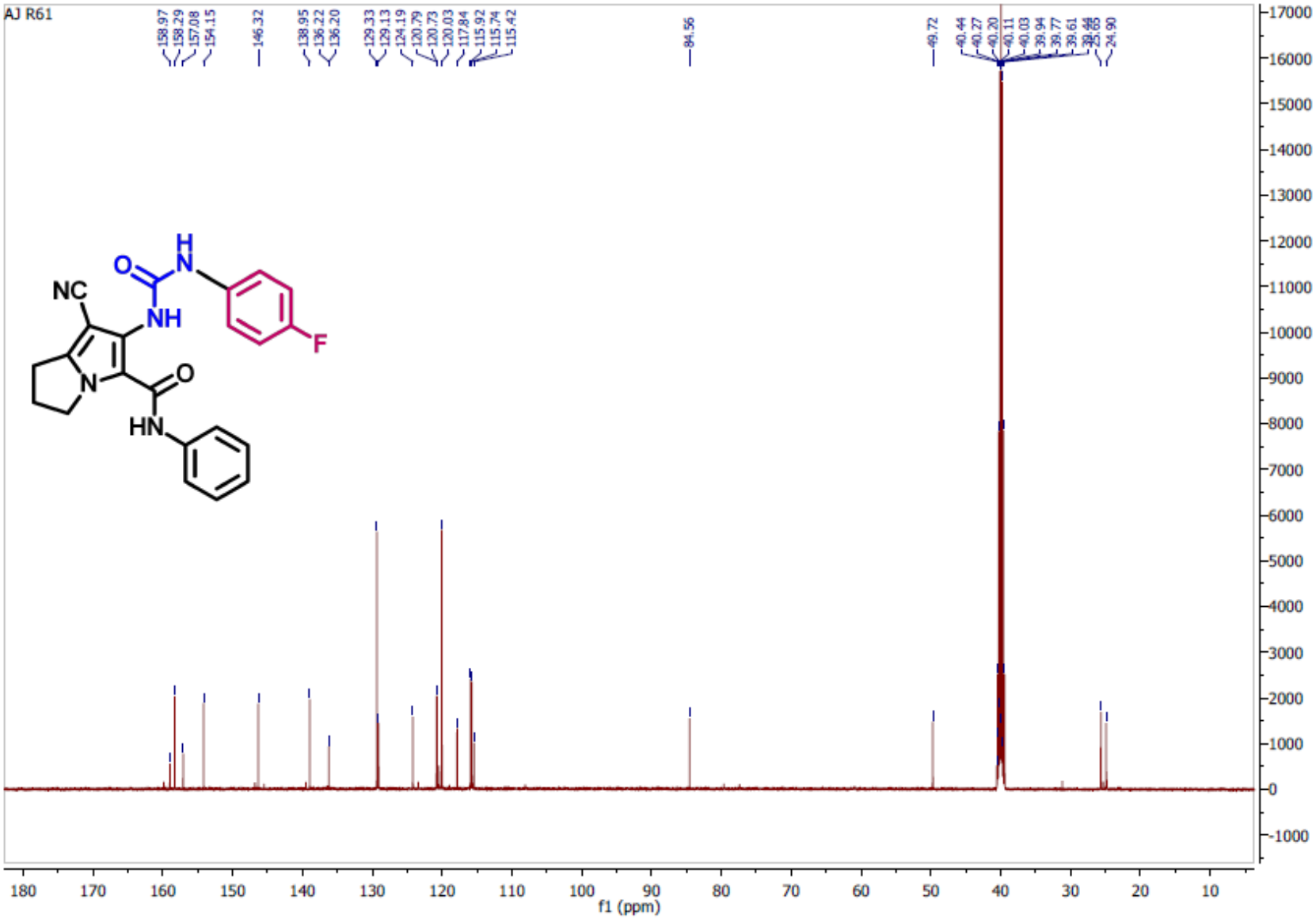

AJ R61
158.97
158.29
157.08
154.15
146.32
138.95
136.22
136.20
129.33
129.13
124.19
120.79
120.73
120.03
117.84
115.92
115.74
115.42
84.56
49.72
40.44
40.27
40.20
40.11
40.03
39.94
39.77
39.61
25.65
24.90
NC
O
H
N
NH
F
N
O
HN
f1 (ppm)

Figure S97. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **18a** (**ZOOM on aliphatic Cs**)

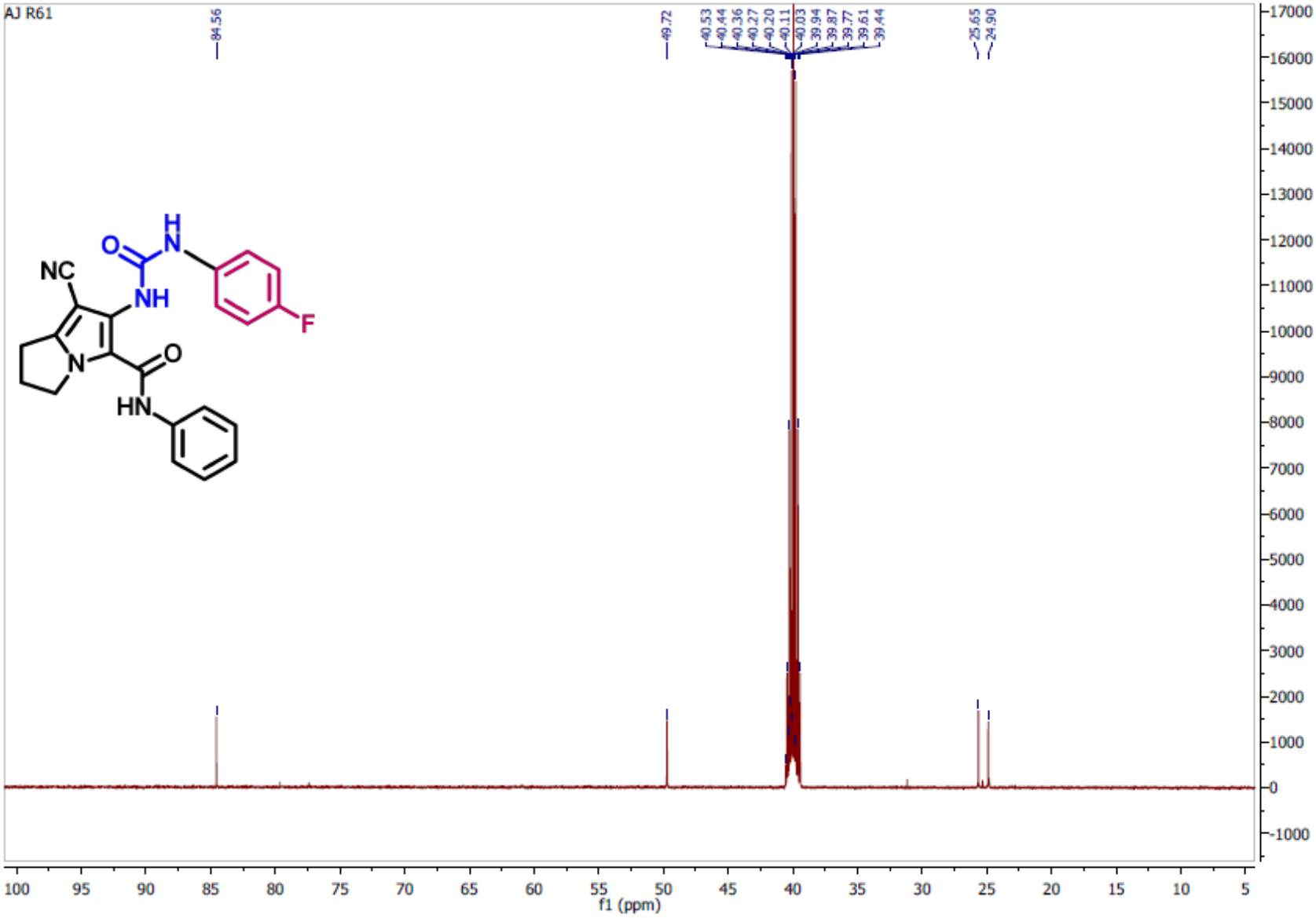


Figure S98. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **18a** (**ZOOM on aromatic Cs**)

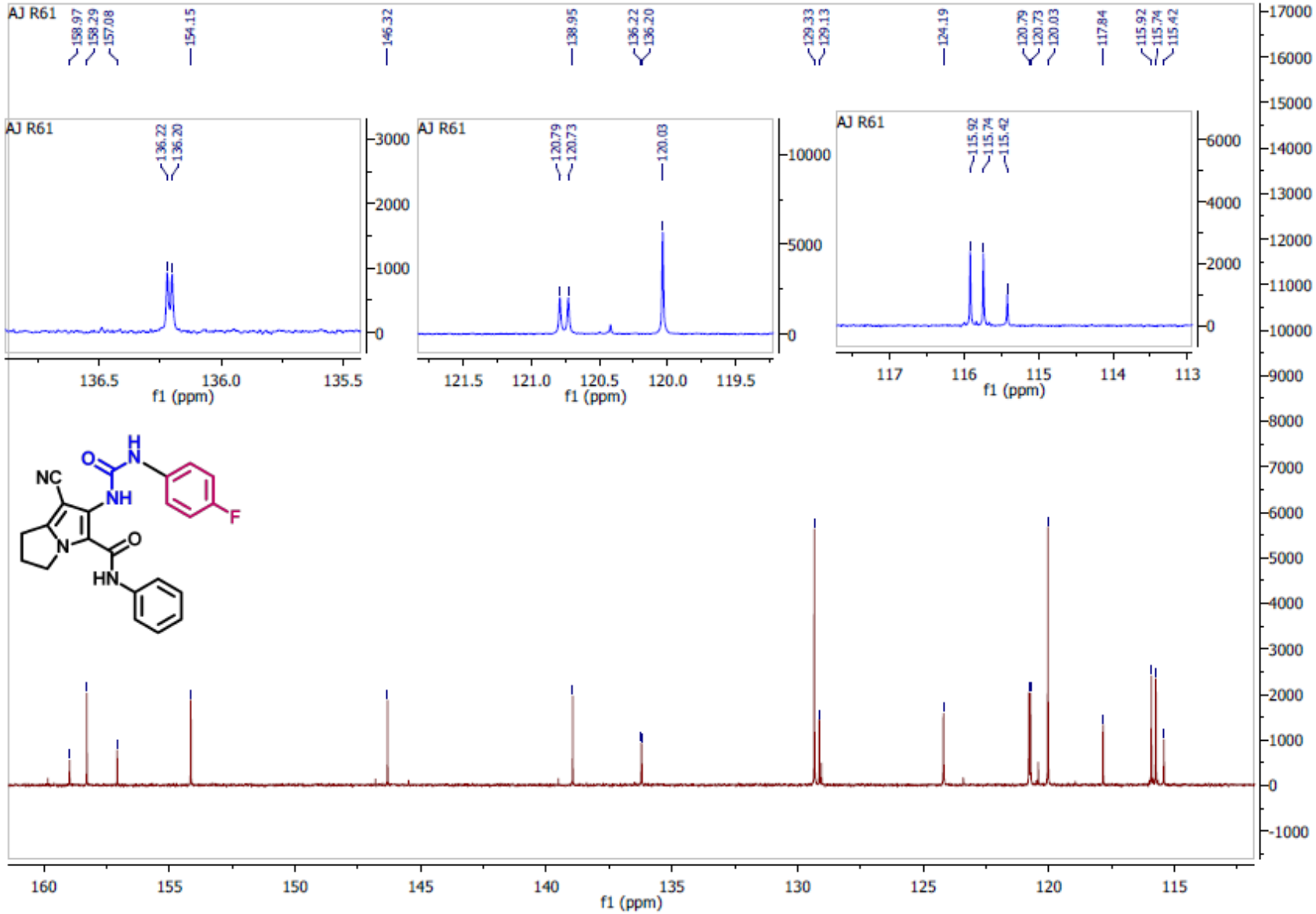


Figure S99. **DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 18a.**

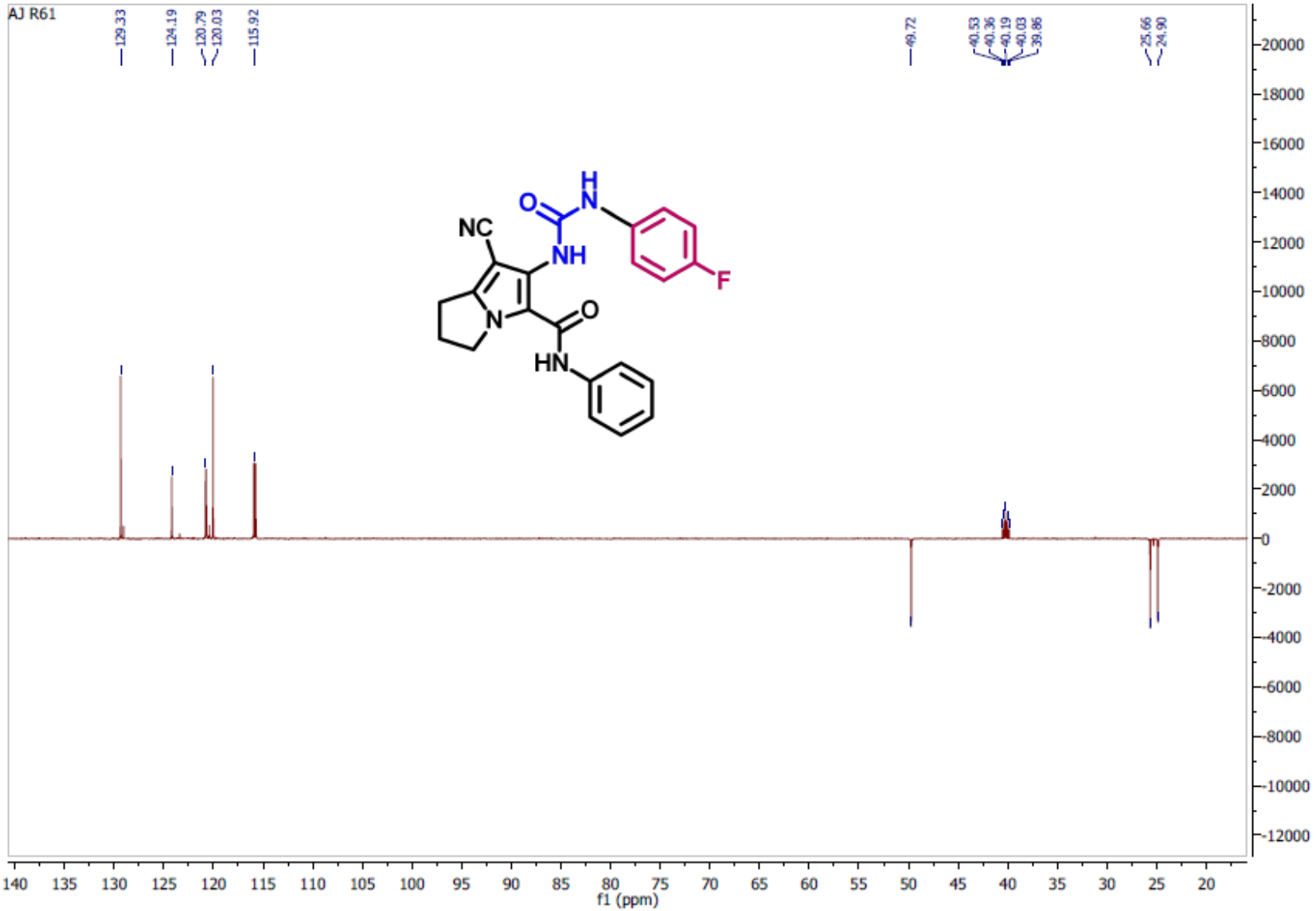


Figure S100. DEPT C^{135} spectrum of compound **18a** (zoom, aliphatic CH_2 groups)

Figure S101. DEPT C^{135} spectrum of compound **18a** (zoom, aromatic CH groups)

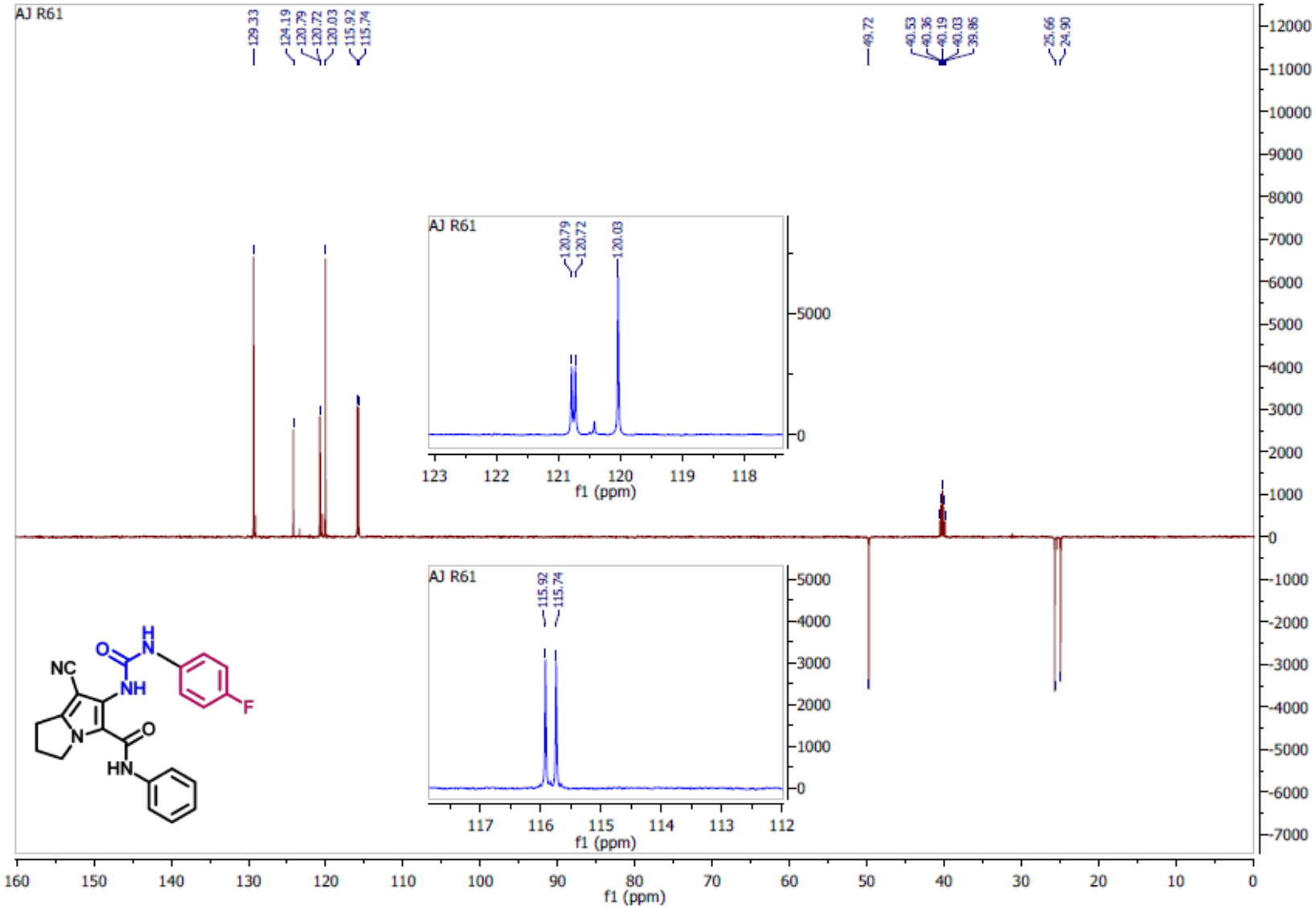


Figure S102. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **18b**

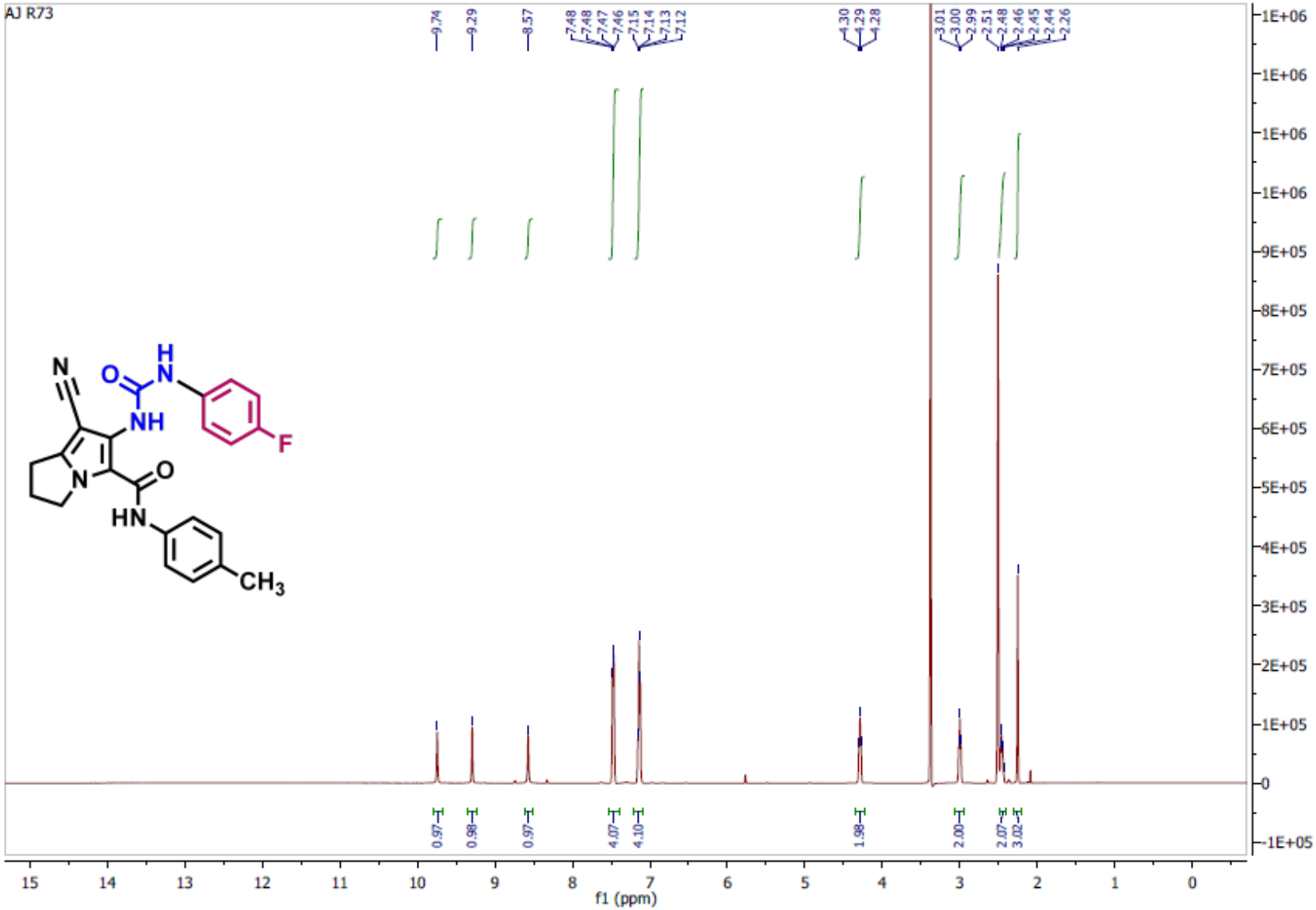


Figure S103. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 18b (zoom on aliphatic/aromatic Hs)

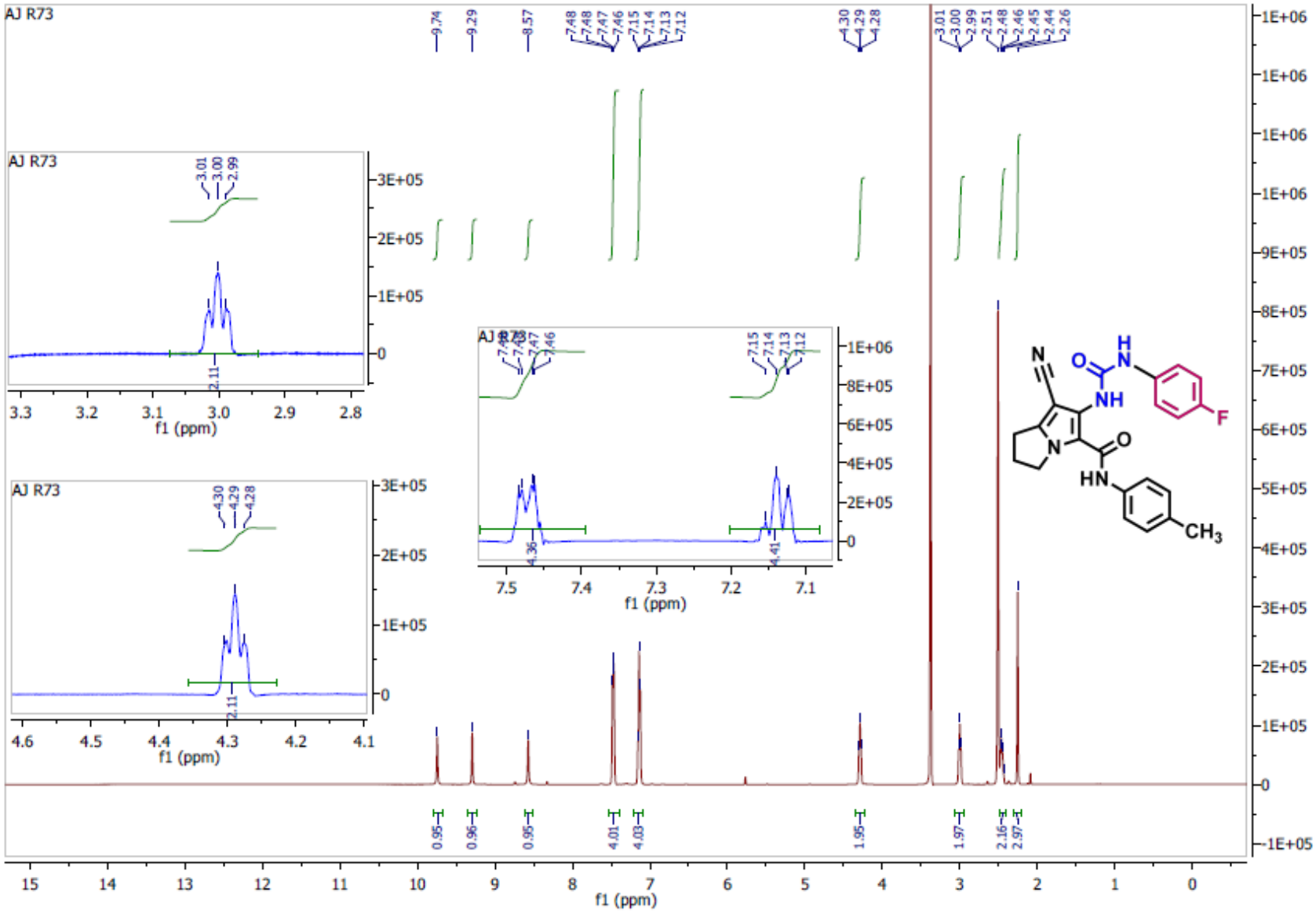


Figure S104. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **18b**

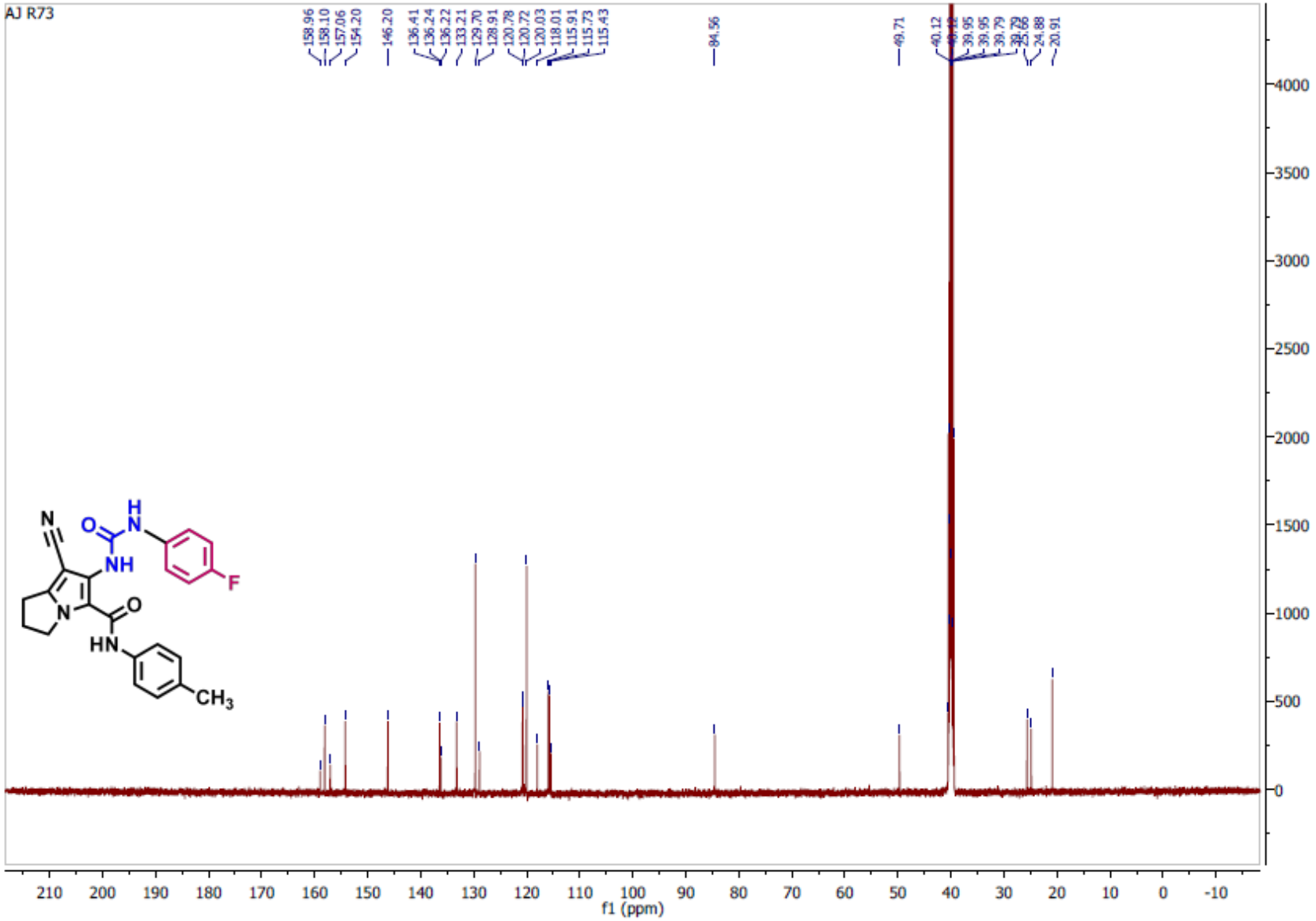


Figure S105. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18b (zoom on aliphatic Cs)

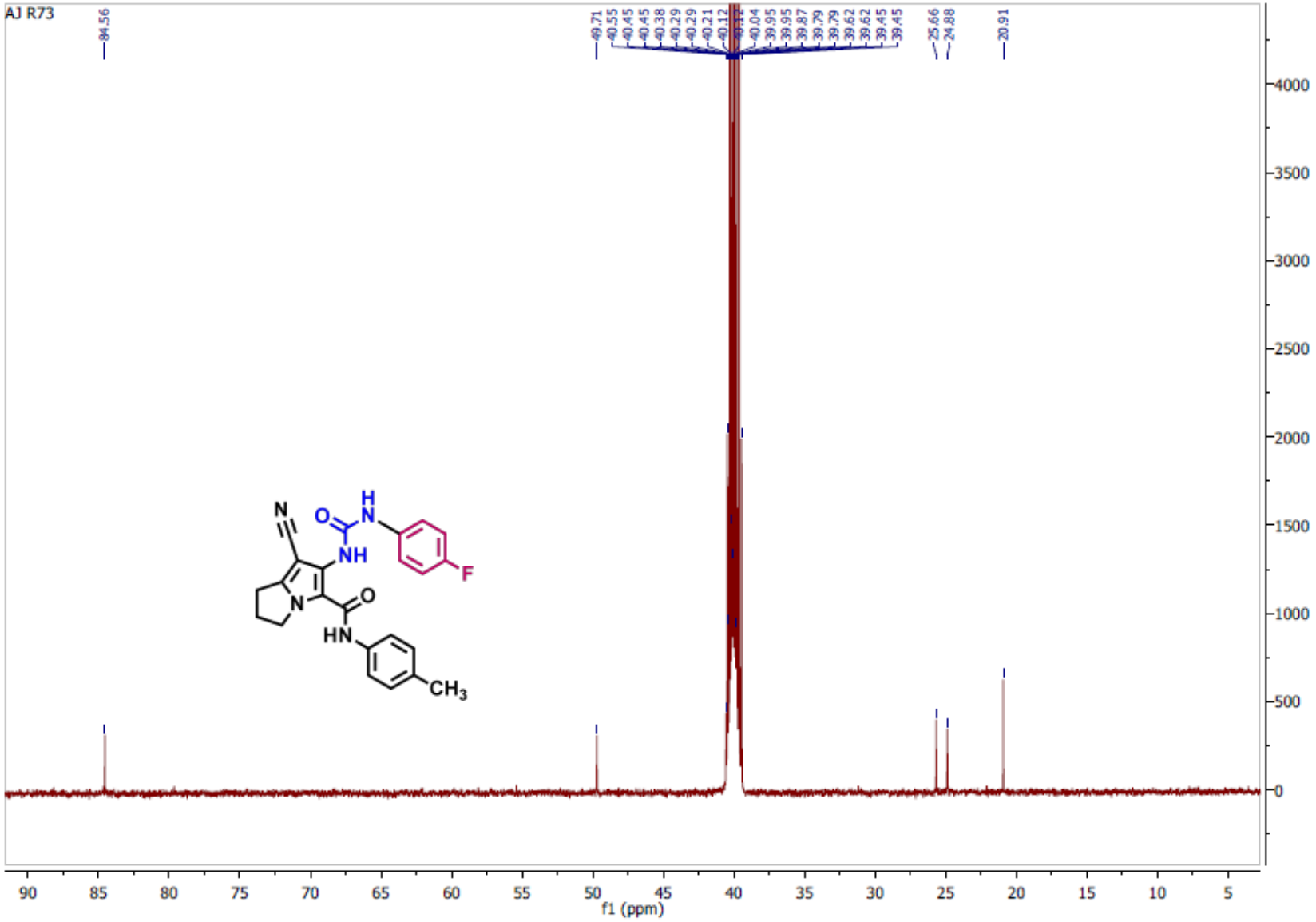


Figure S106. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18b (zoom on aromatic Cs)

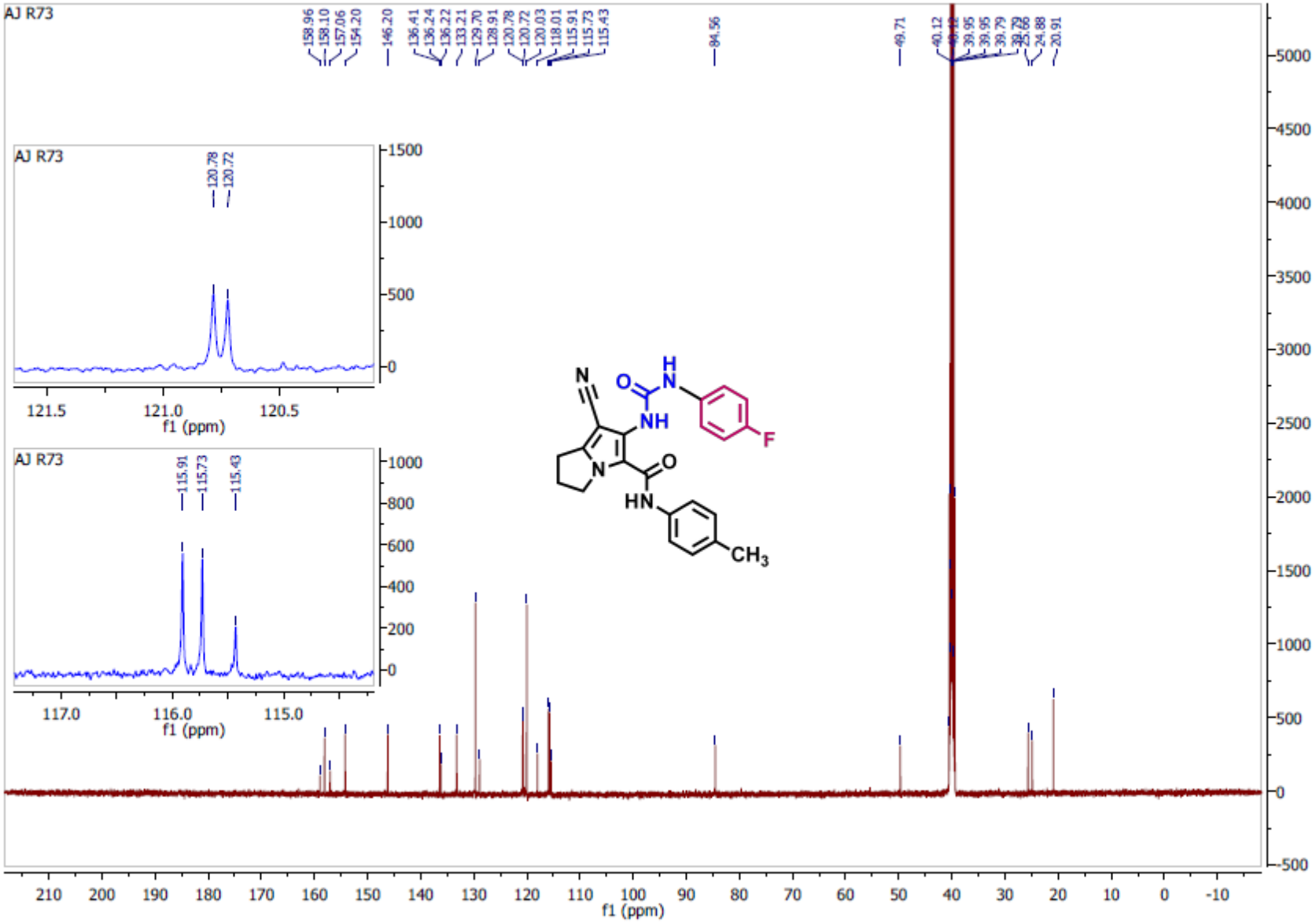


Figure S107. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18b (zoom on aromatic Cs)

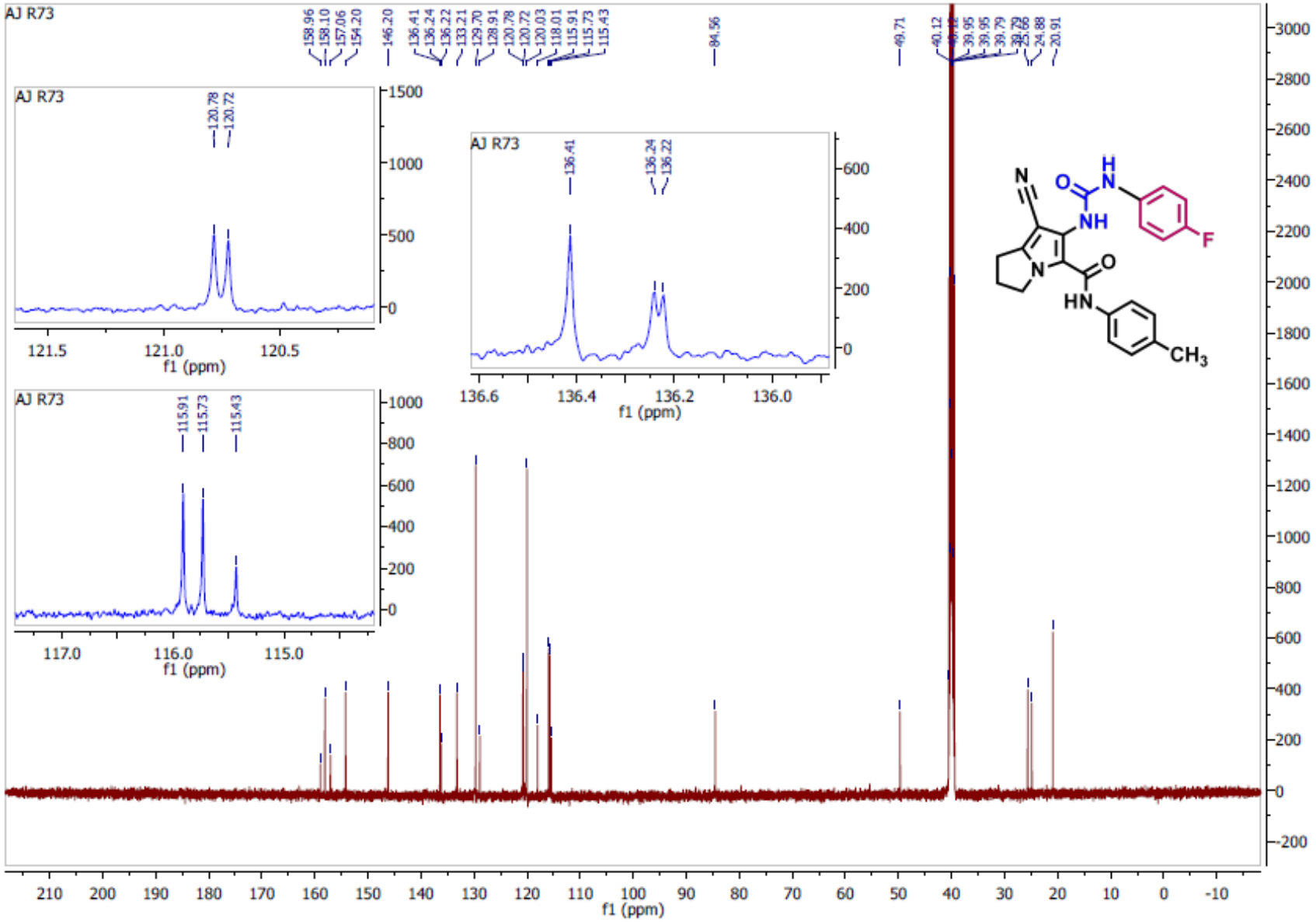


Figure S108. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound **18b**.

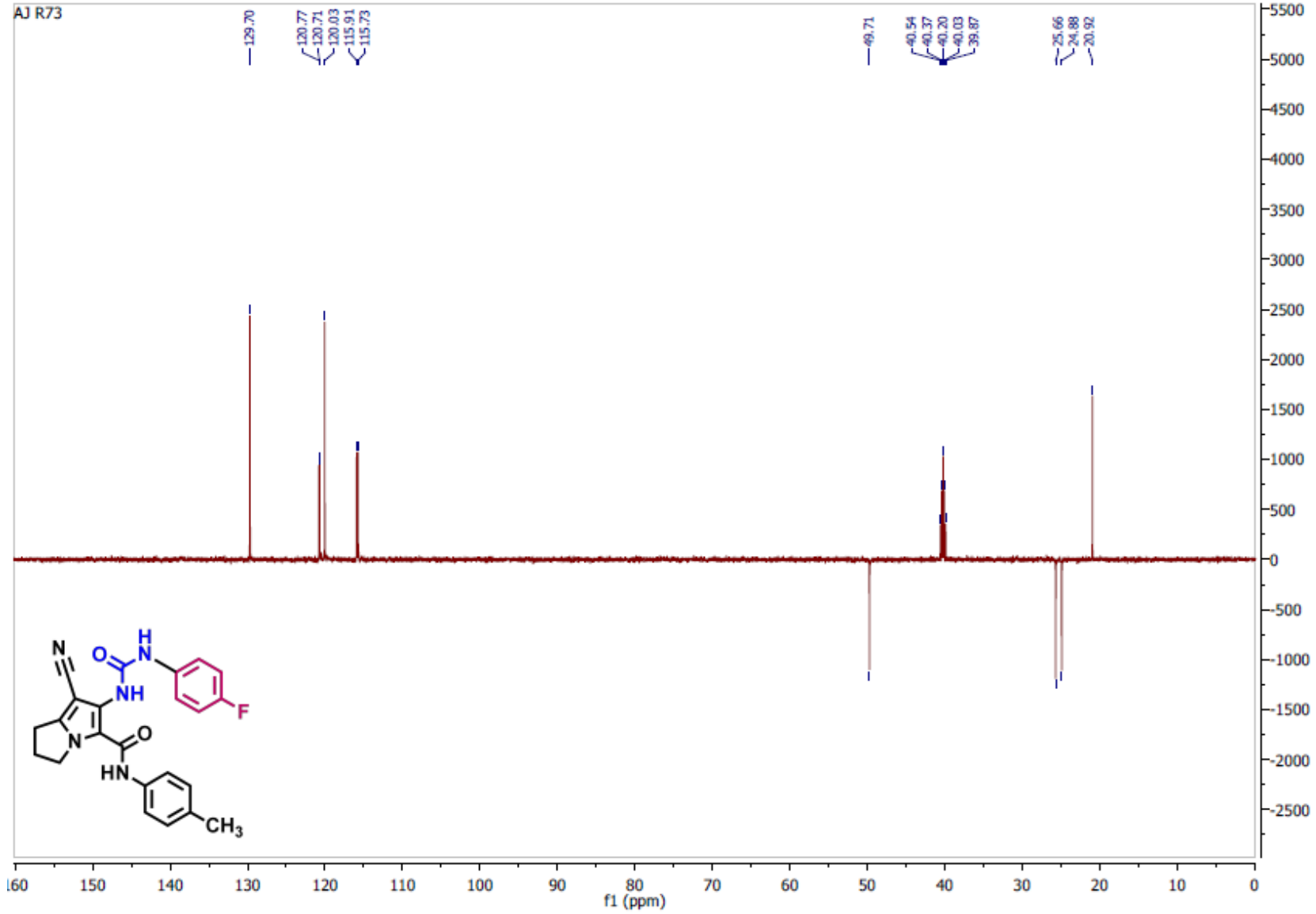


Figure S109. DEPT C^{135} spectrum of compound **18b** (zoom on aromatic Cs)

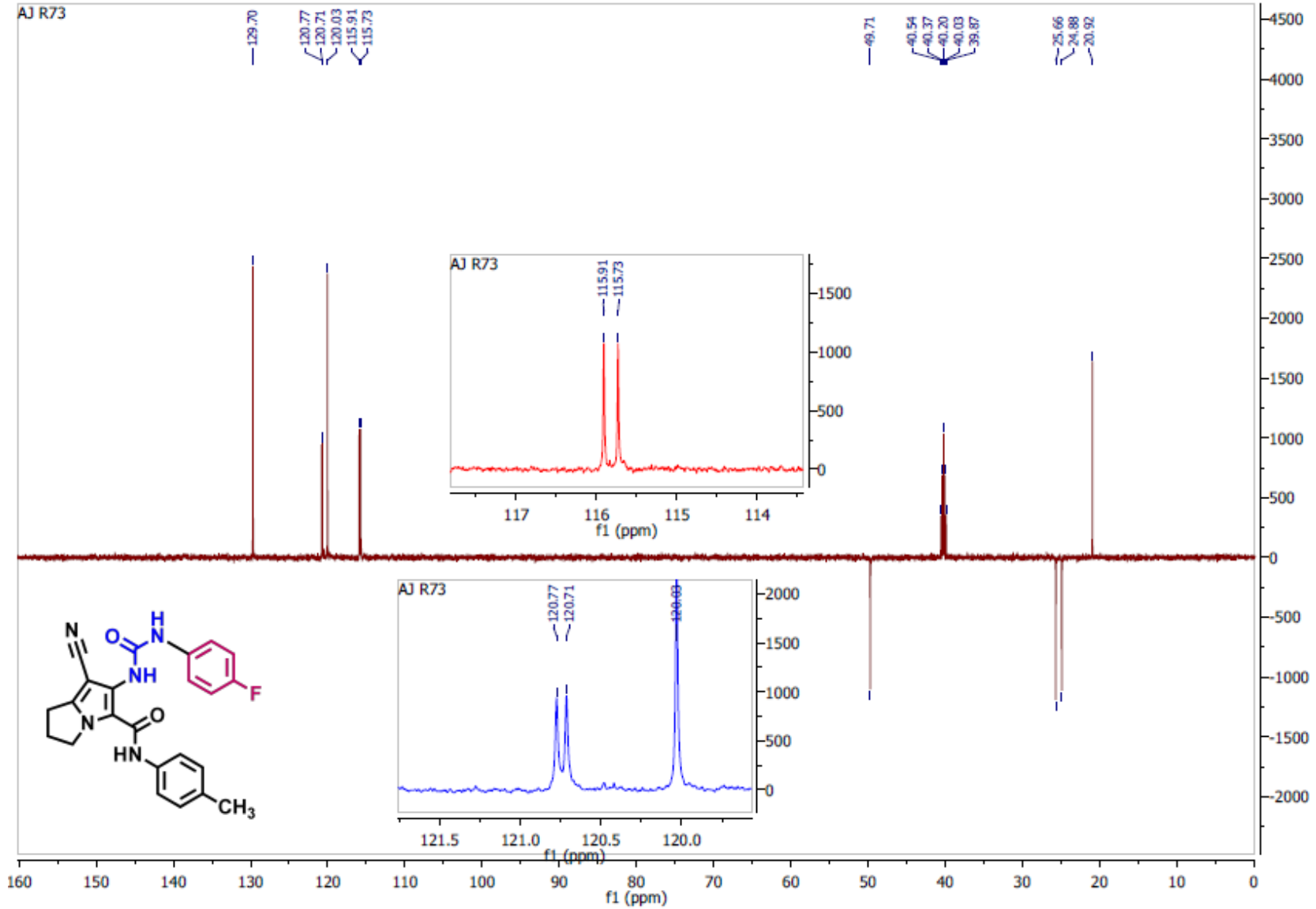


Figure S110. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound **18c.**

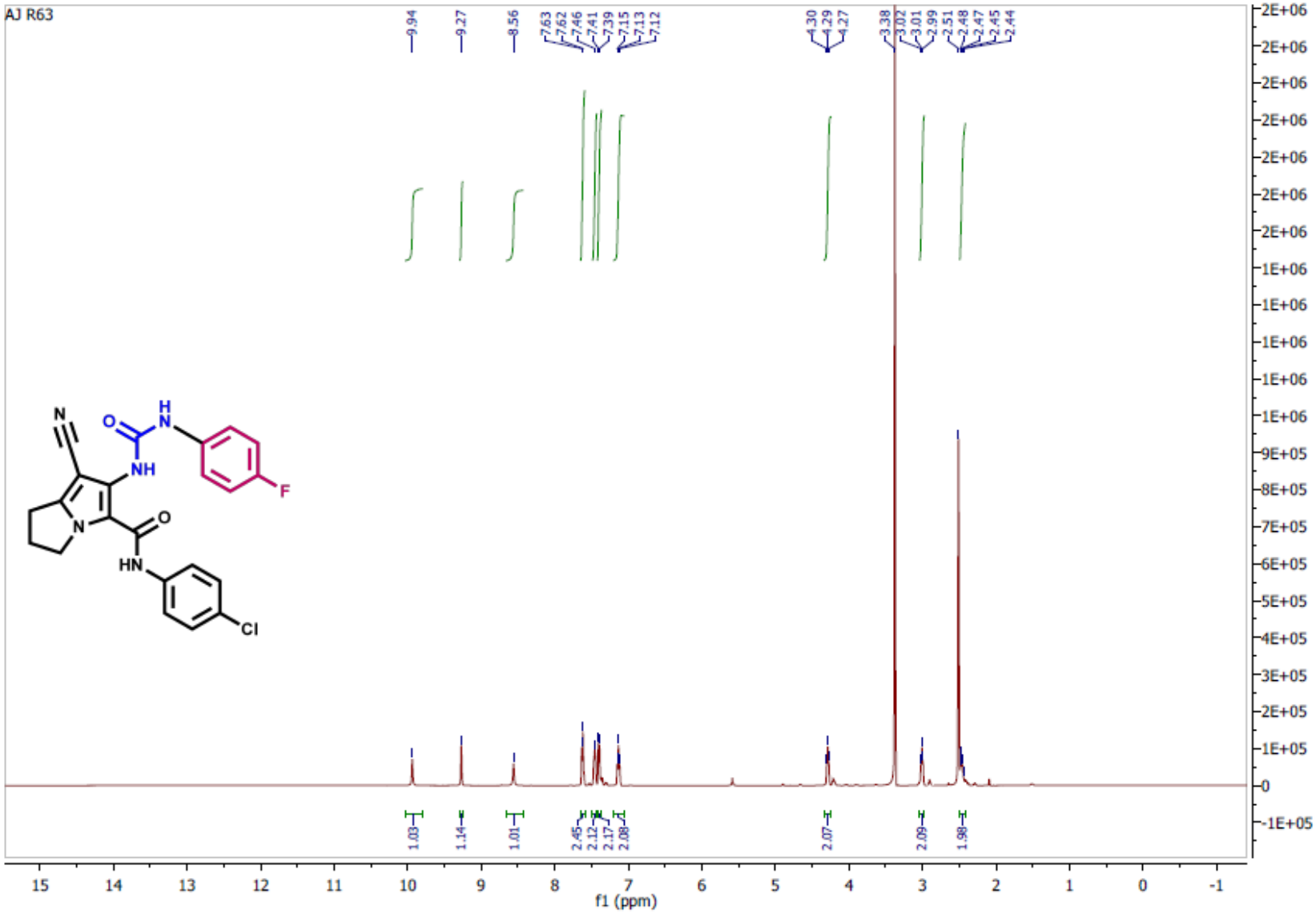


Figure S111. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 18c (zoom on aromatic Hs)

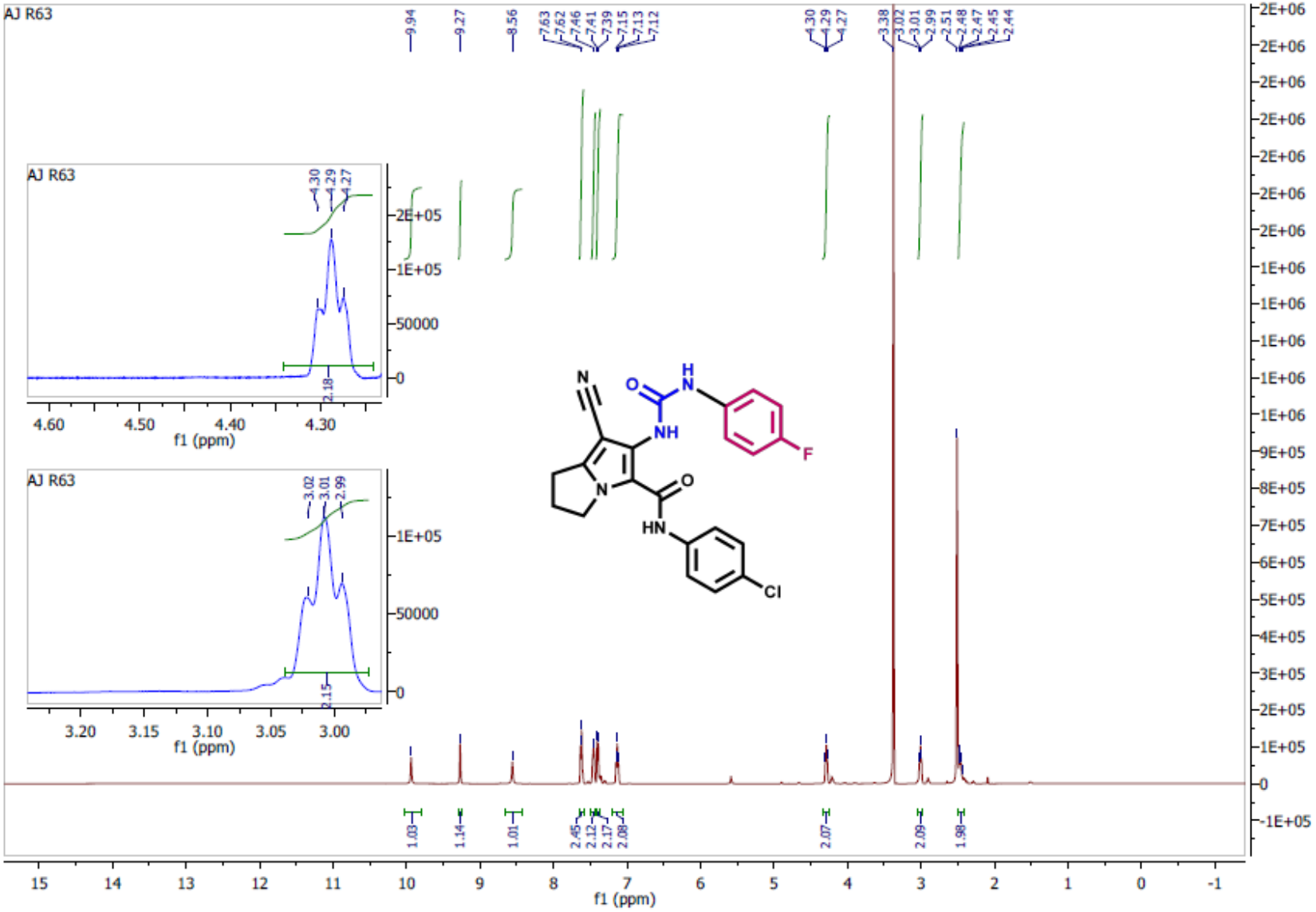


Figure S112. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 18c (zoom on aliphatic/aromatic Hs)

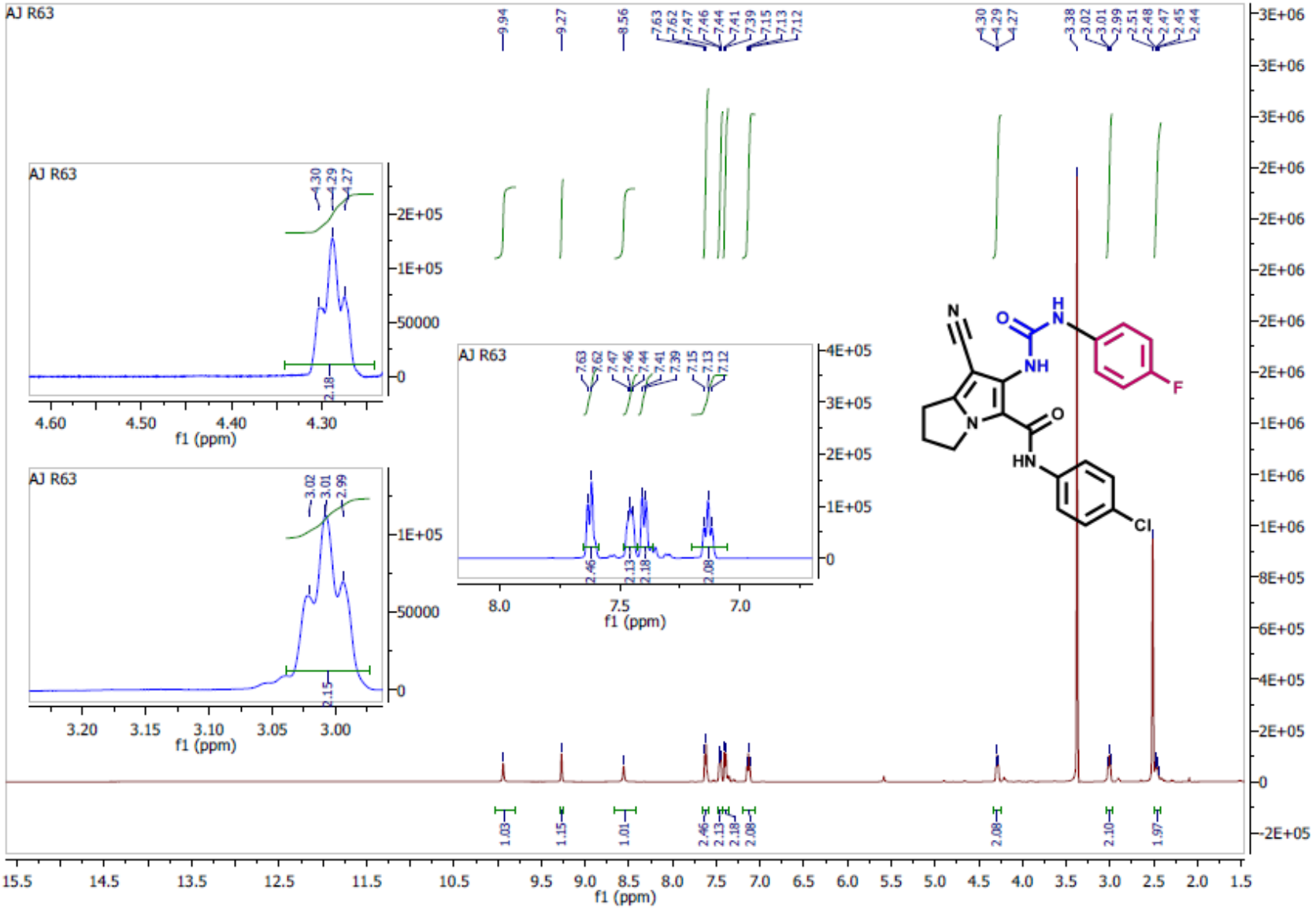


Figure S113. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **18c**

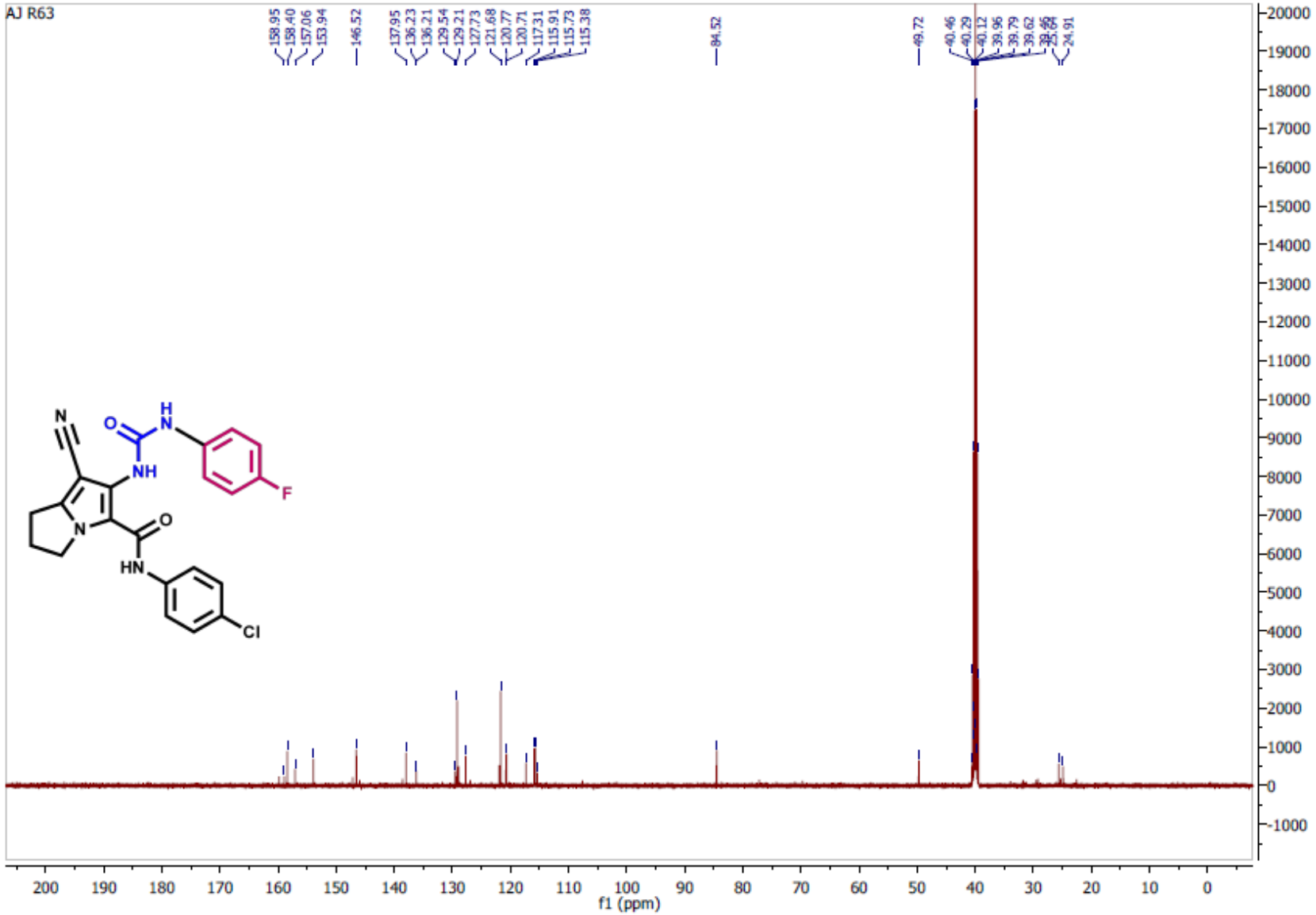


Figure S114. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18c (zoom on aromatic C-F Cs)

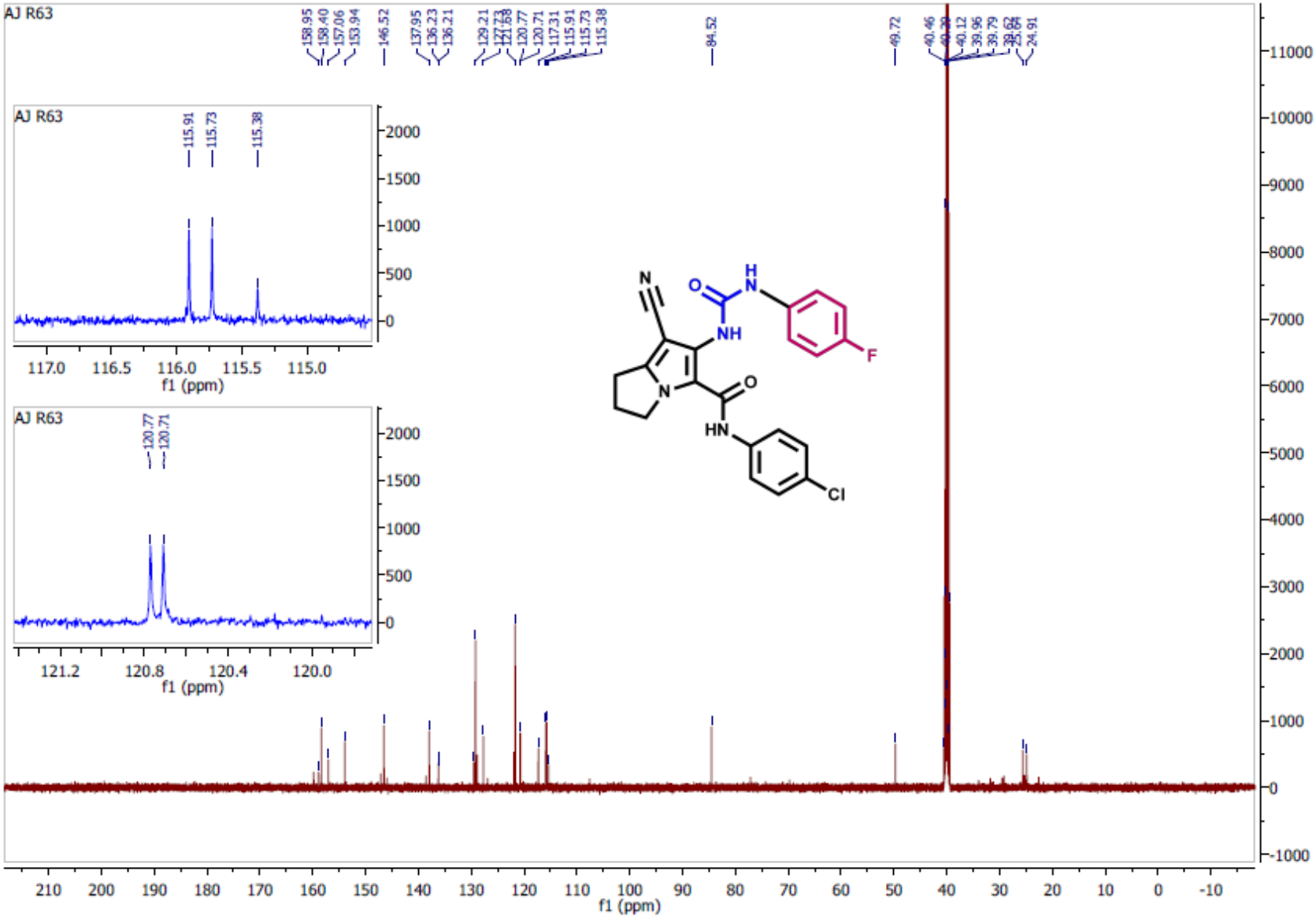


Figure S115. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18c (zoom on aromatic C-F Cs)

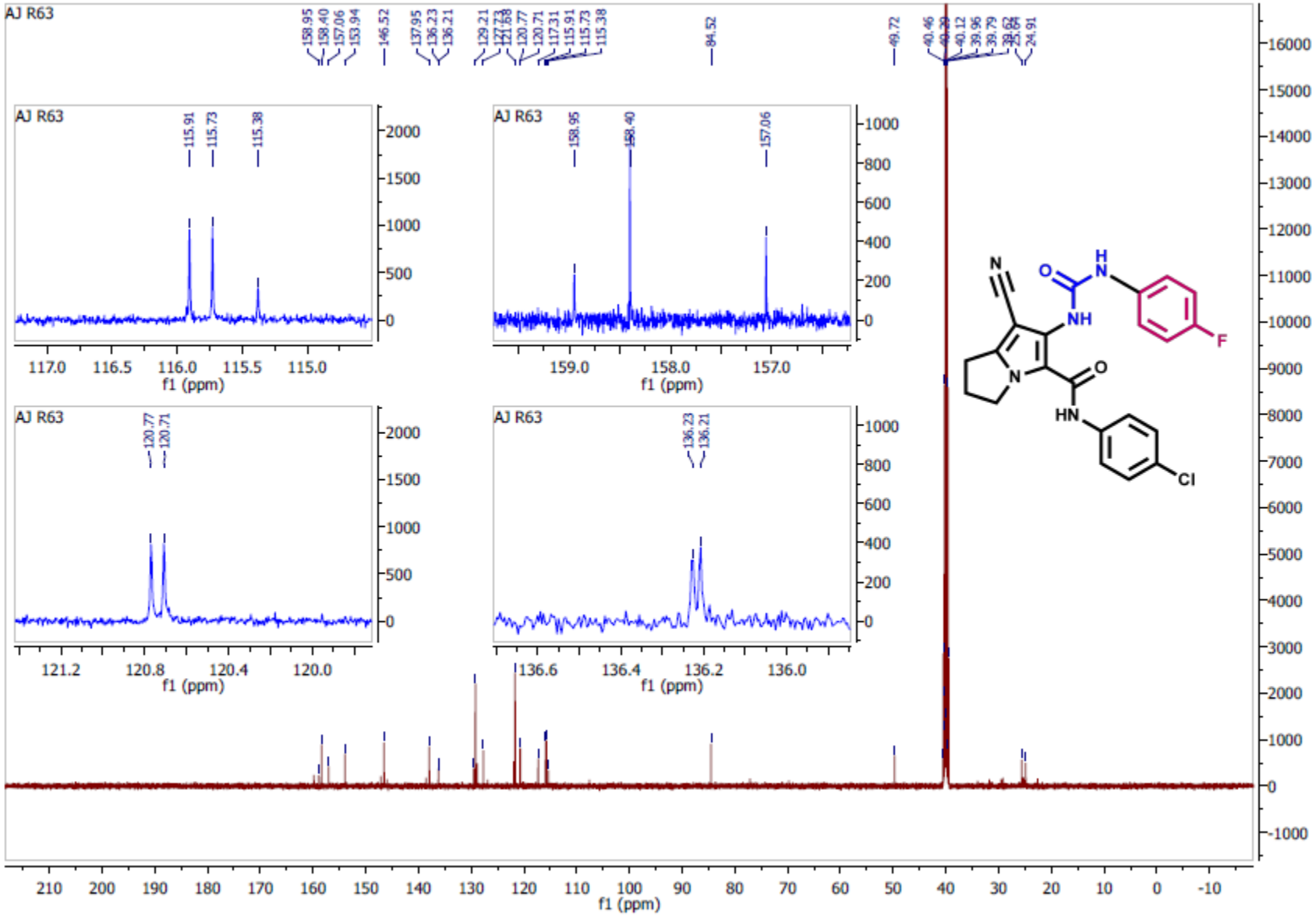


Figure S116. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound **18c**

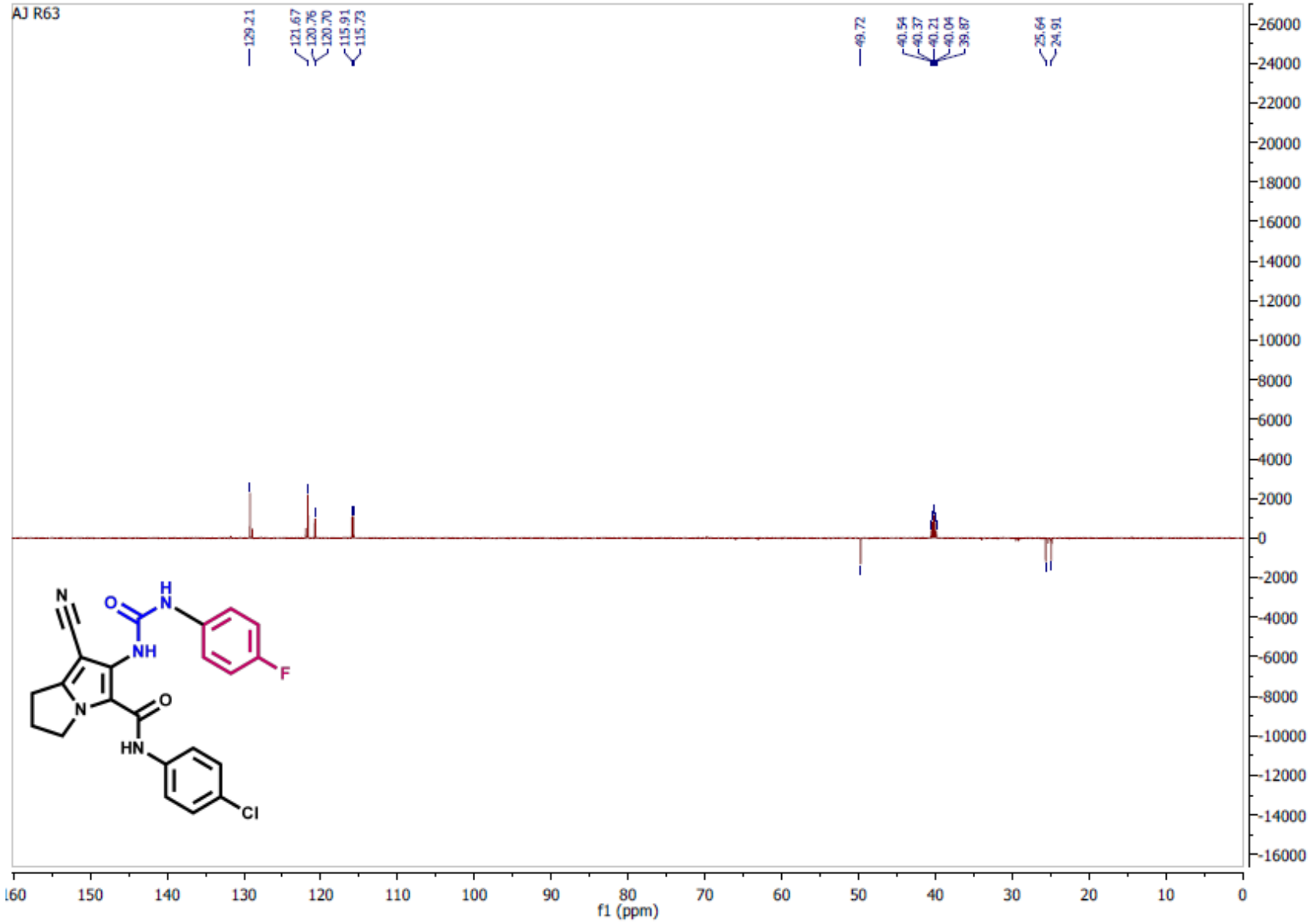


Figure S117. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound 18c (zoom on aromatic C-F Cs)

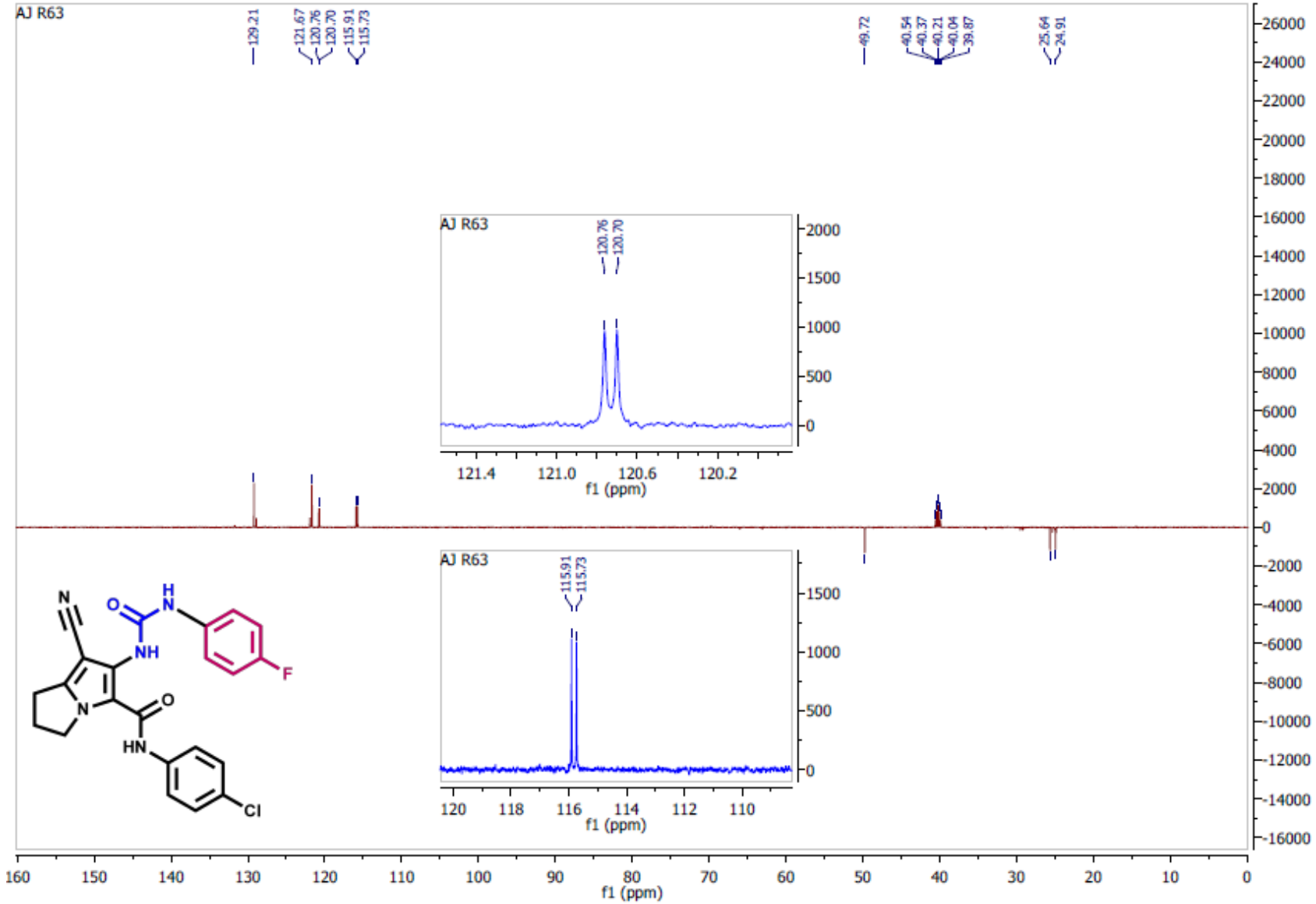


Figure S118. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 19c

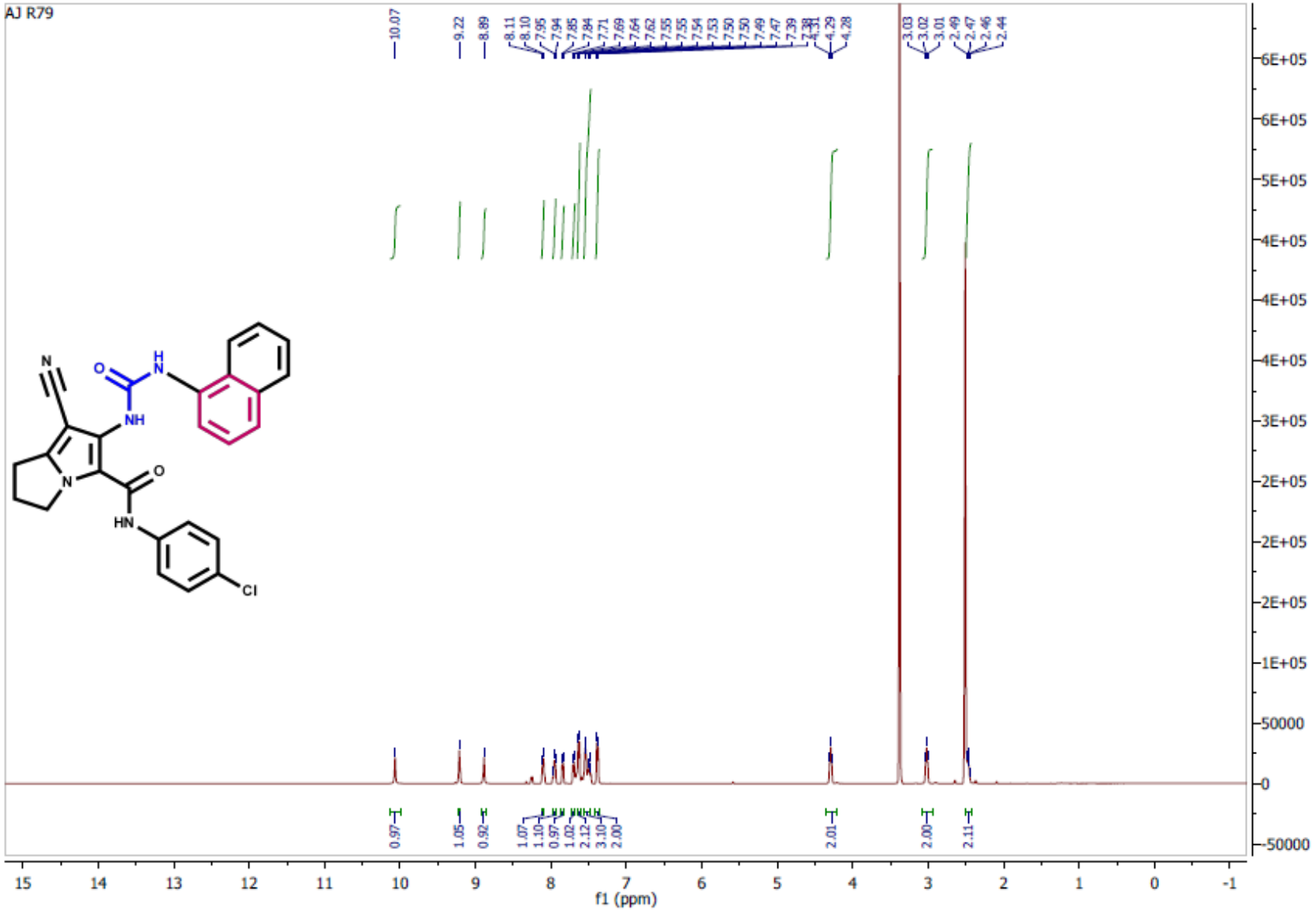


Figure S119. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 19c (zoom on aliphatic Hs)

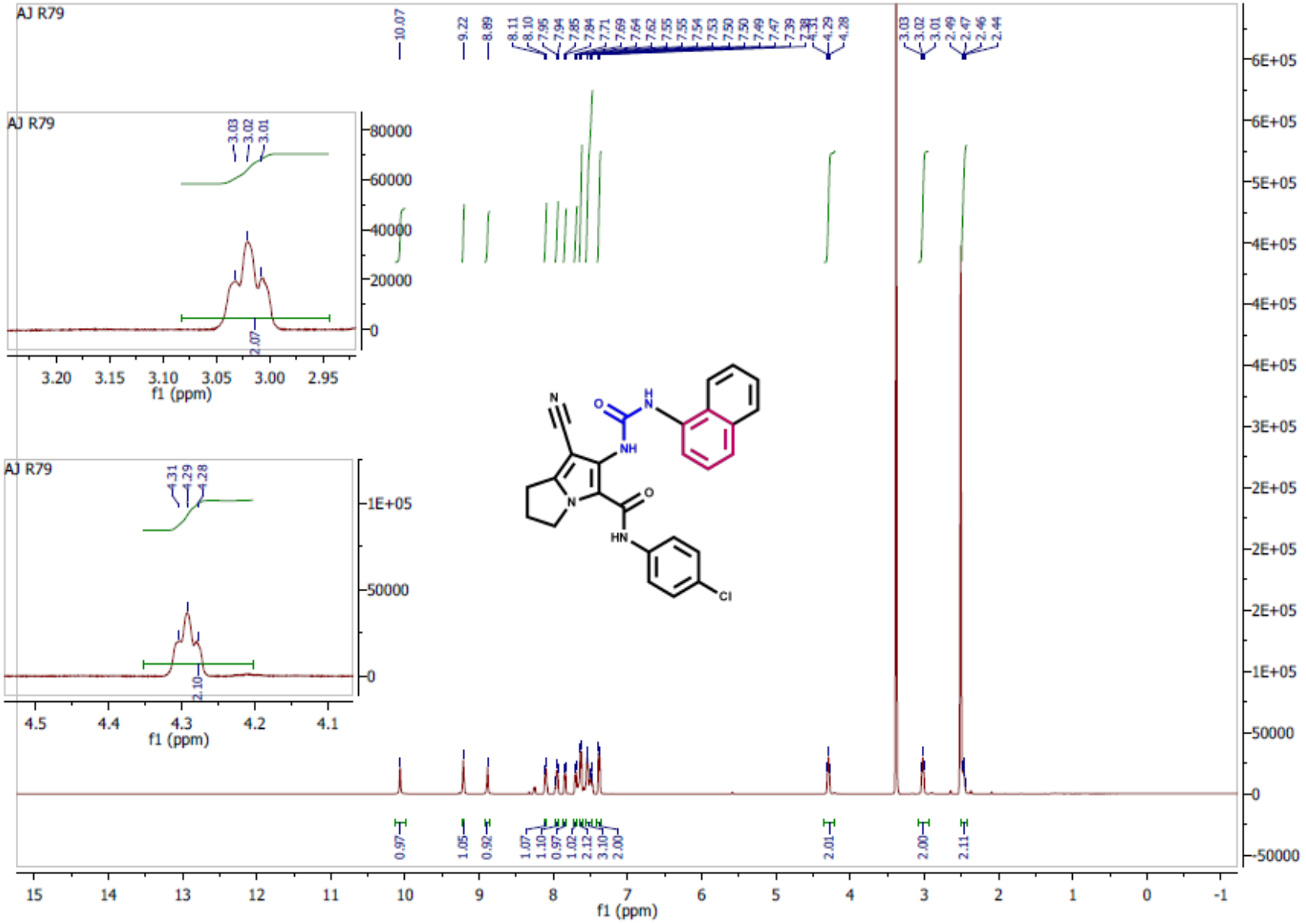


Figure S120. ^{1}H-NMR (DMSO, 500 MHz, δ ppm) spectrum of compound 19c (zoom on aromatic Hs)

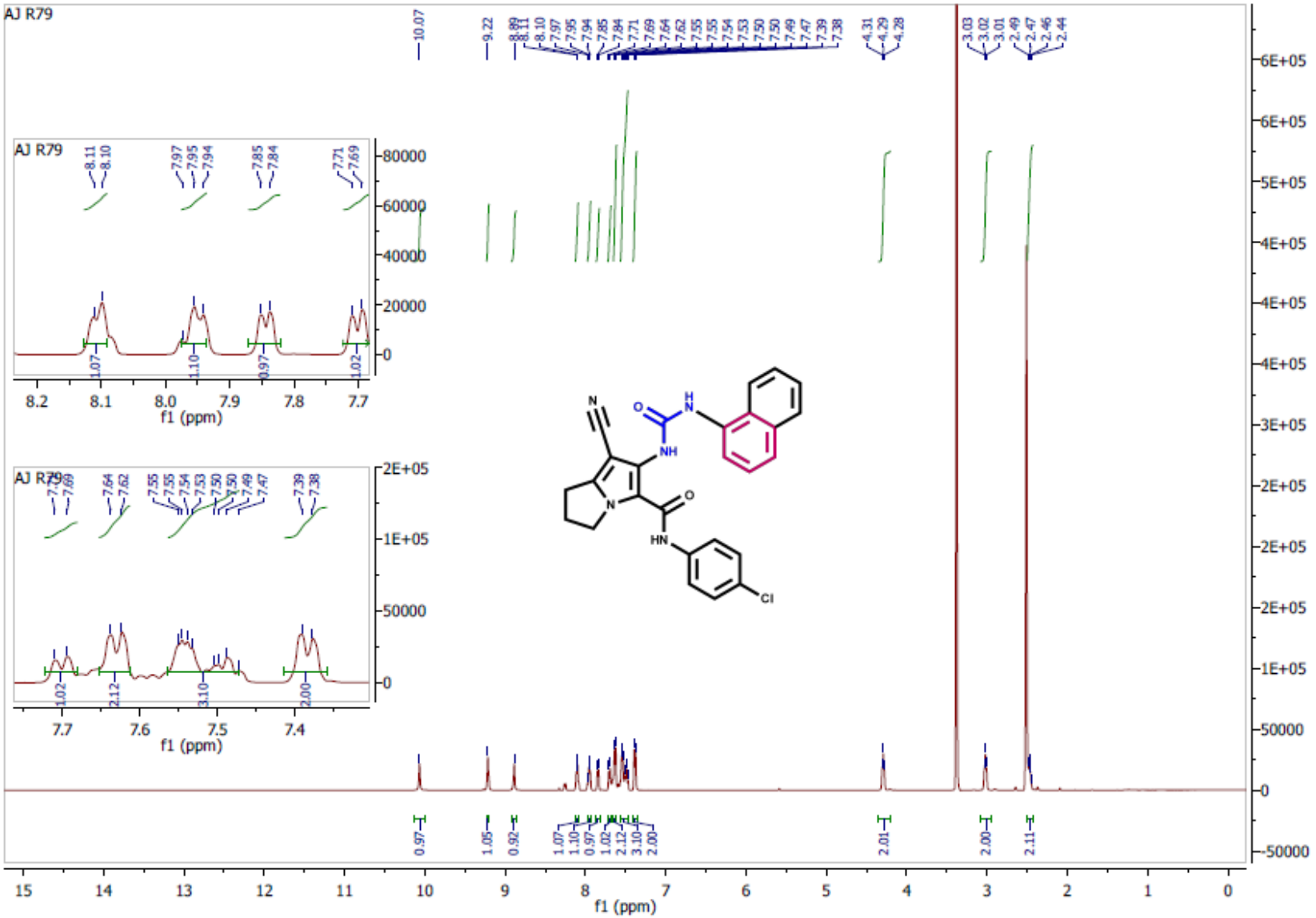


Figure S121. ^{13}C-NMR (DMSO, 125 MHz, δ ppm) spectrum of compound **19c**

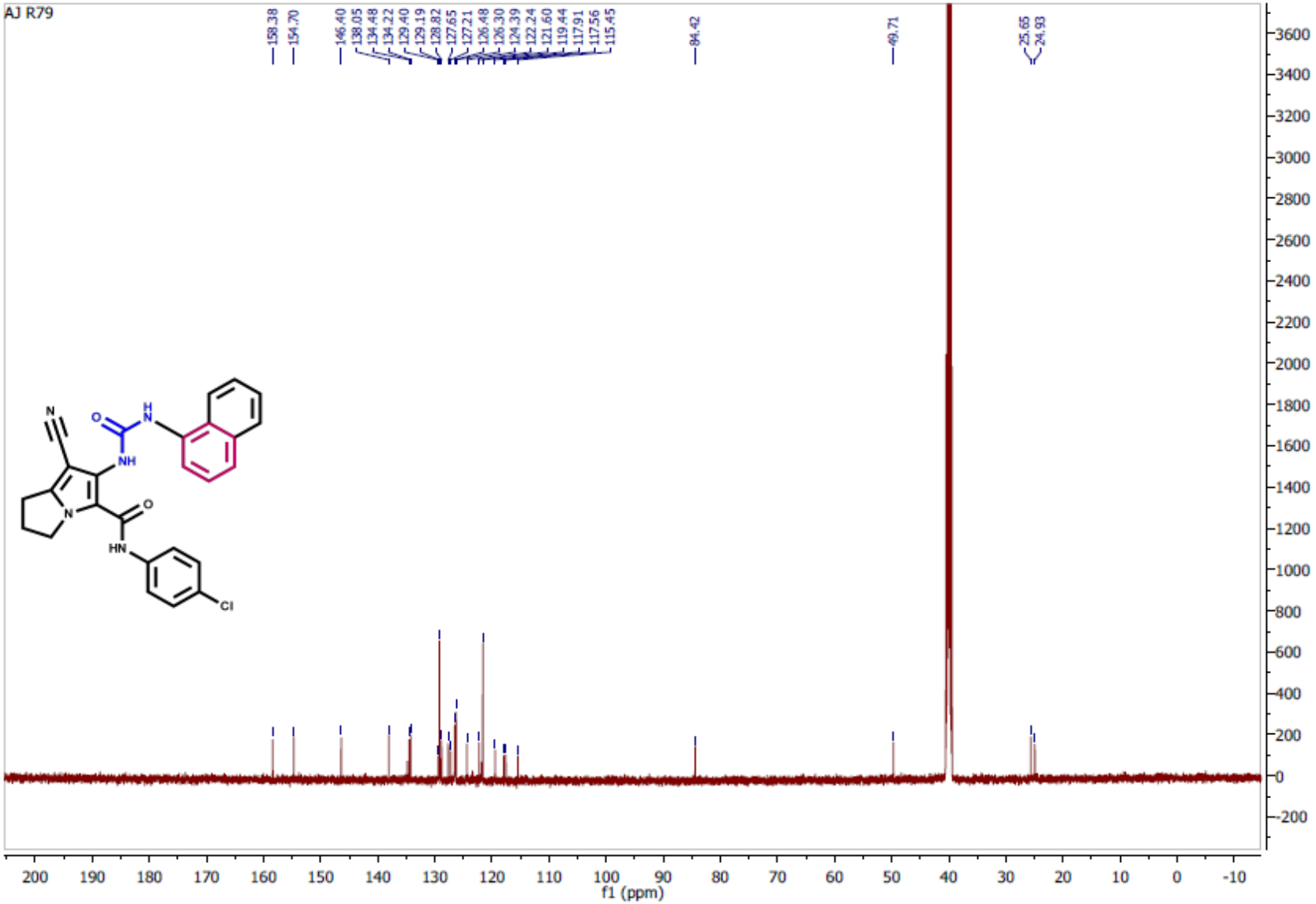
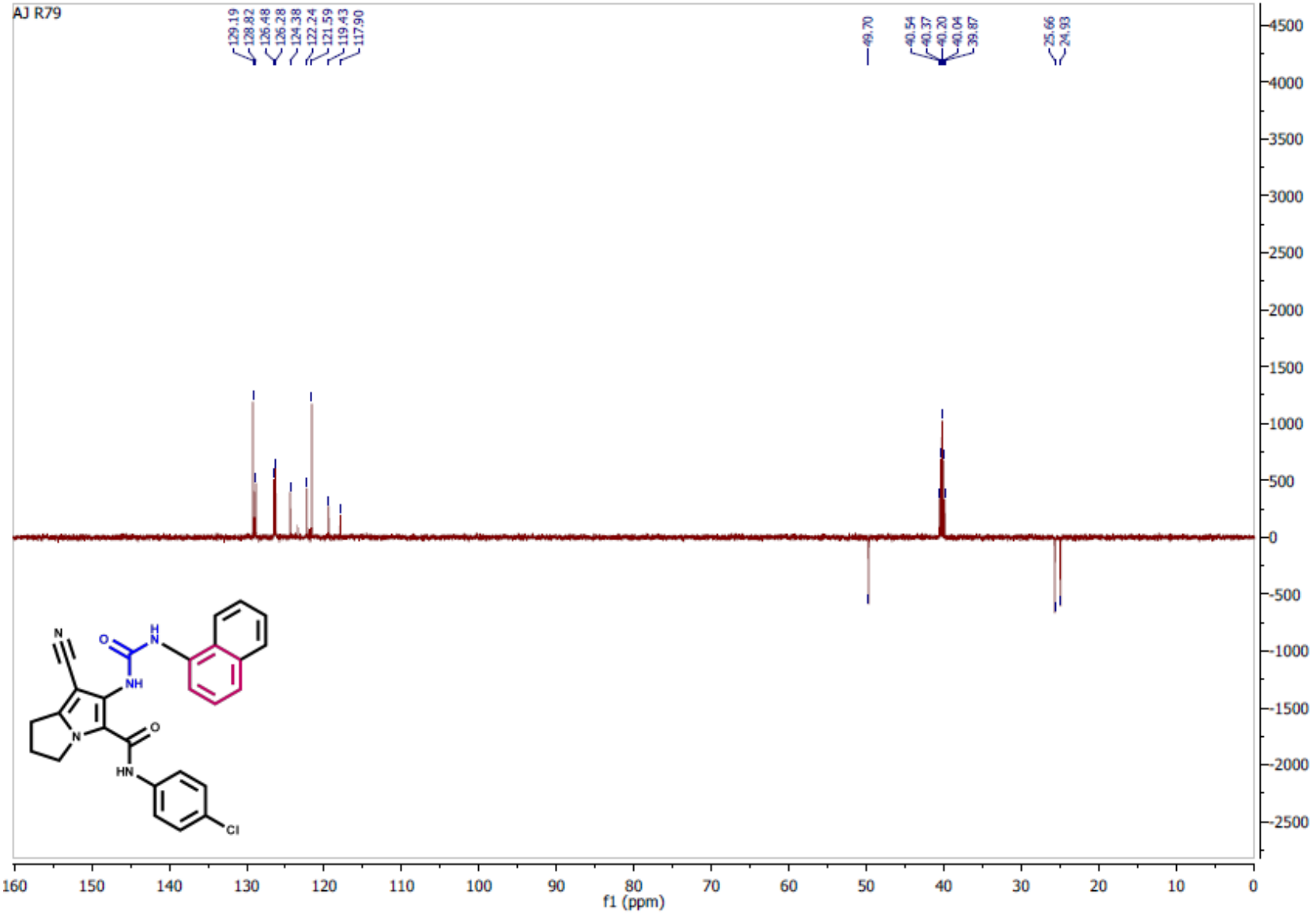
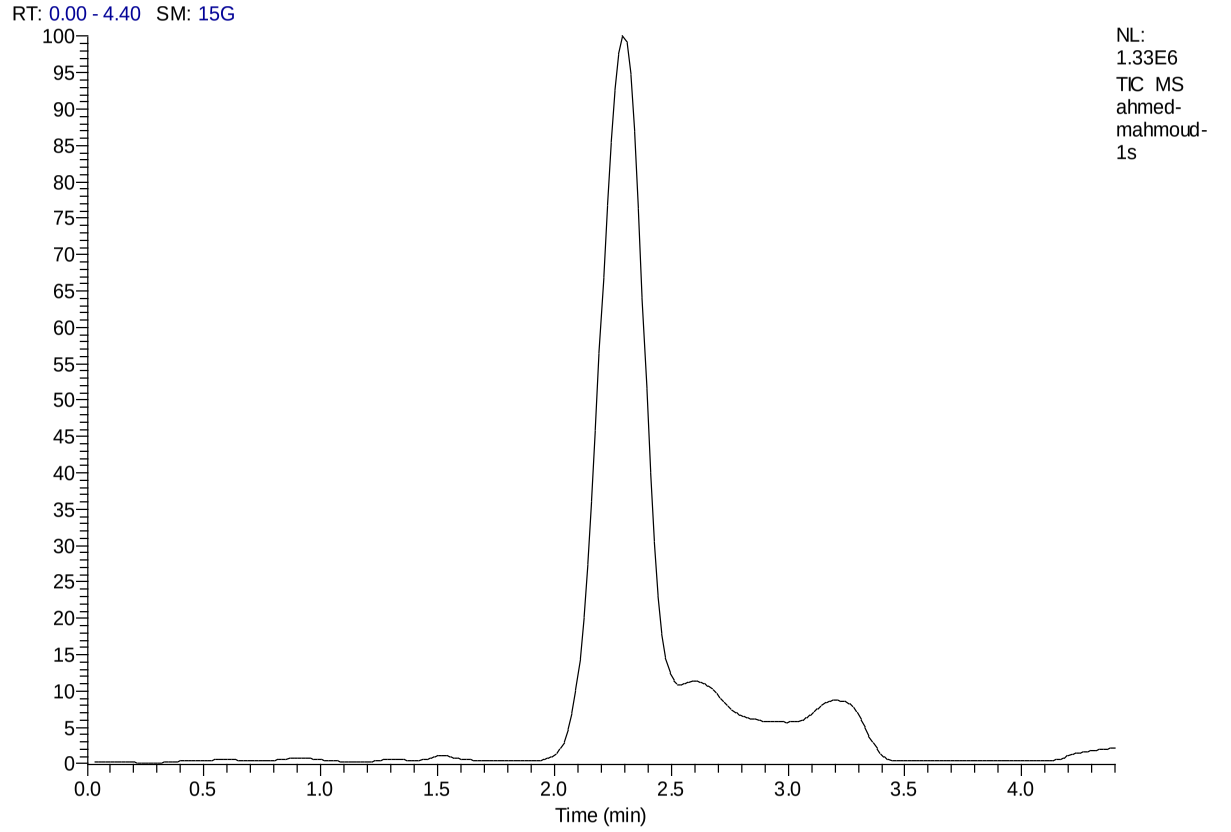


Figure S122. DEPT C^{135} (DMSO, 125 MHz, δ ppm) of compound **19c**



Mass Spectra

Mass spectra were recorded on Shimadzu GCMS QP5050A spectrometer, at 70 eV (EI) at the regional center for mycology and biotechnology, Al-Azhar University.



ahmed-mahmoud-1s #135 RT: 2.28 AV: 1 SB: 2 4.40 , 4.40 NL: 3.90E5
T: {0,0} + c EI Full ms [40.00-1000.00]

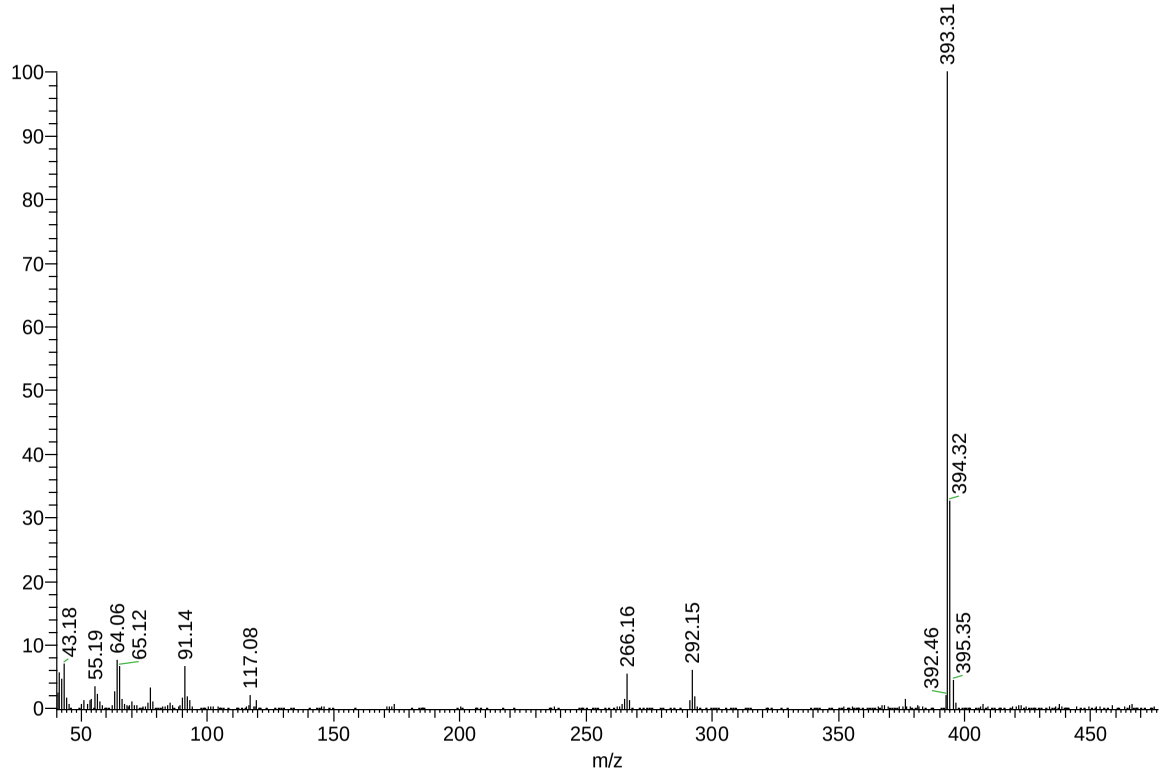
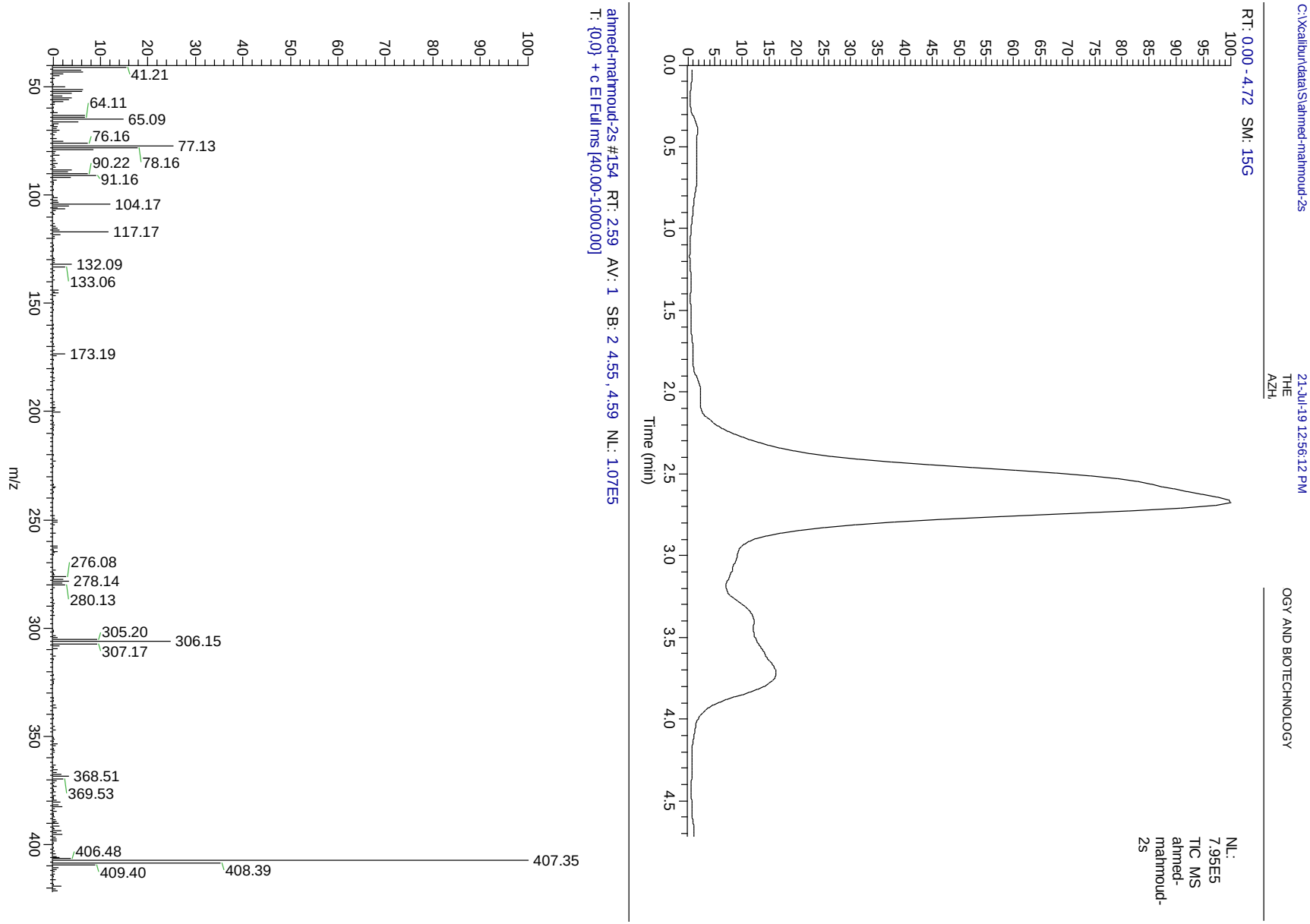


Figure S123. Mass spectrum of compound 16a

Figure S124. **Mass spectrum of compound 16b**



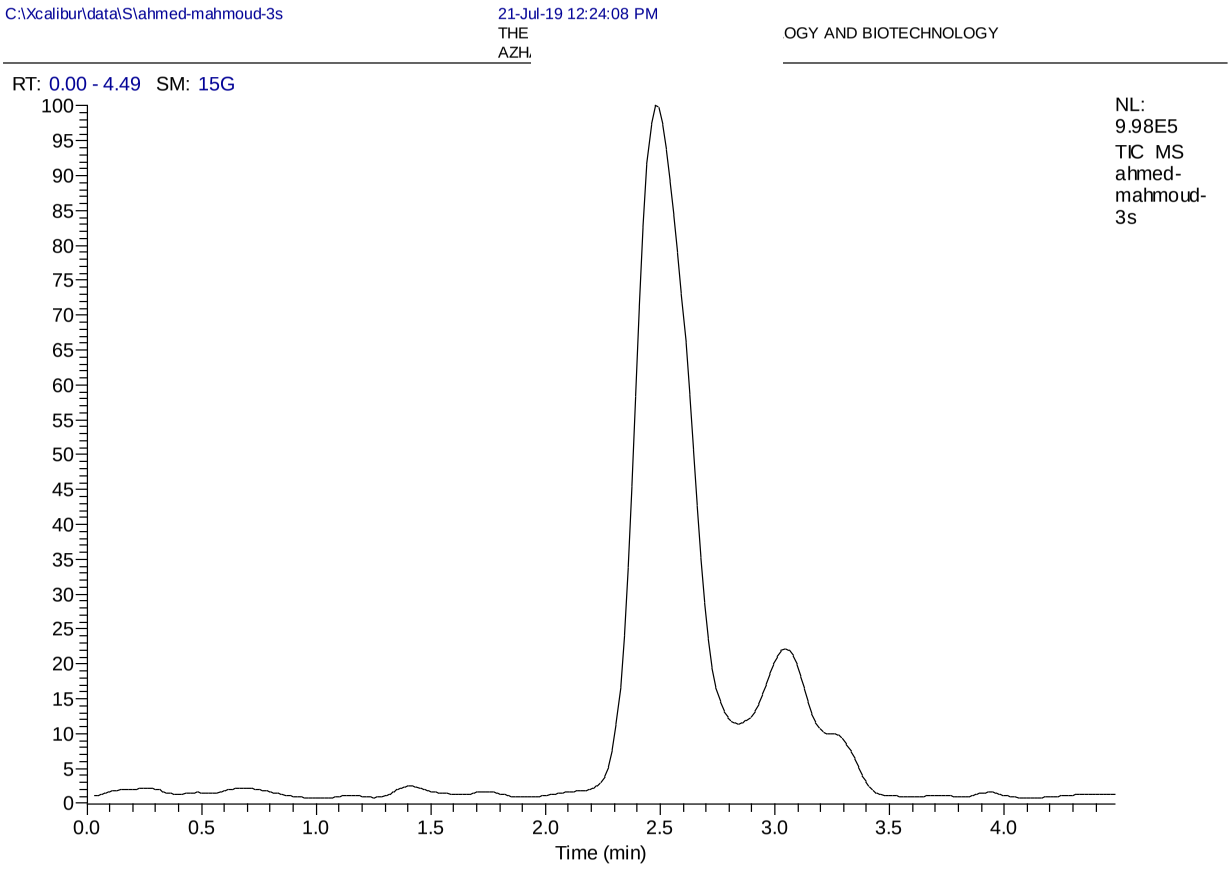
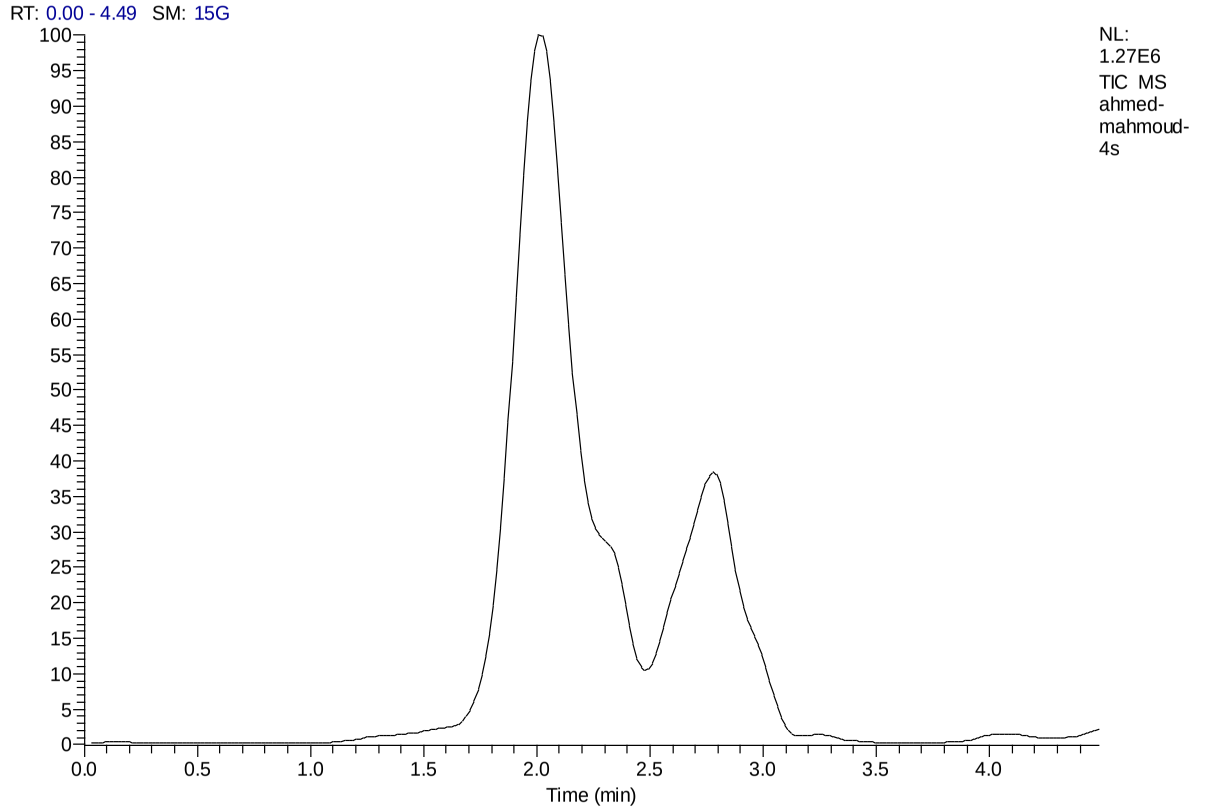


Figure S125. Mass spectrum of compound **16c**



ahmed-mahmoud-4s #165 RT: 2.78 AV: 1 SB: 2 4.49 , 4.49 NL: 5.53E4
T: {0,0} + c EI Full ms [40.00-1000.00]

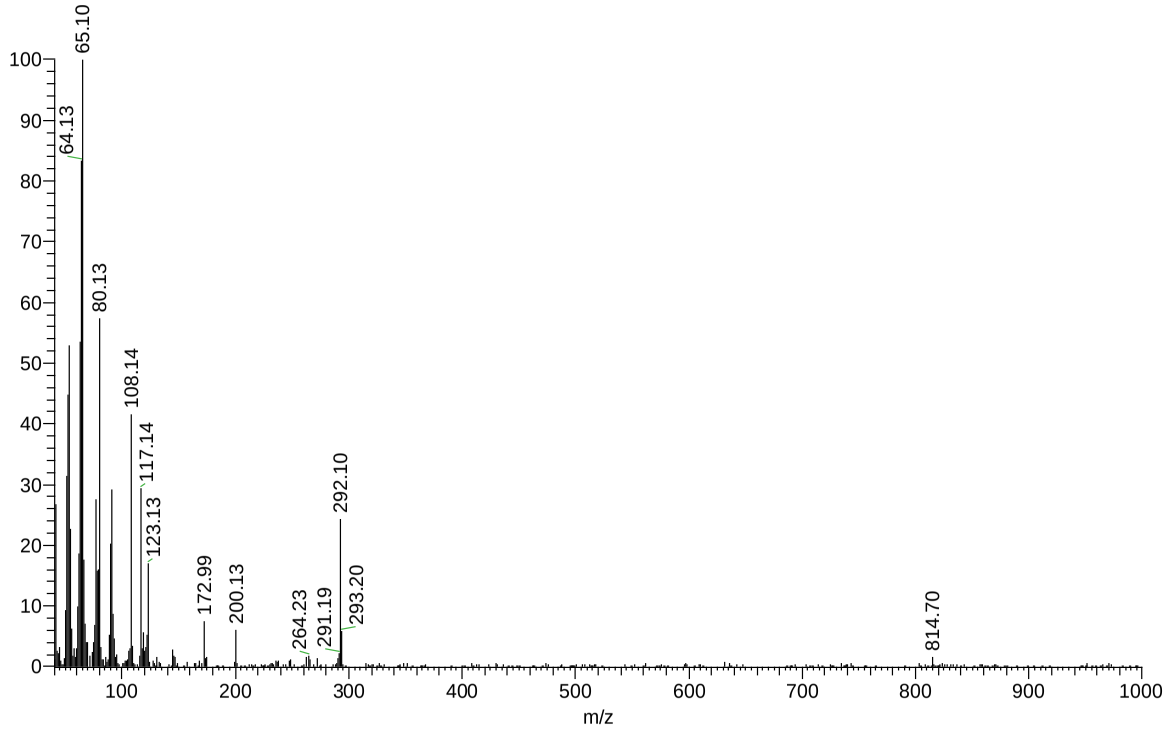


Figure S126. Mass spectrum of compound 17a

Figure S127. **Mass spectrum of compound 17b**

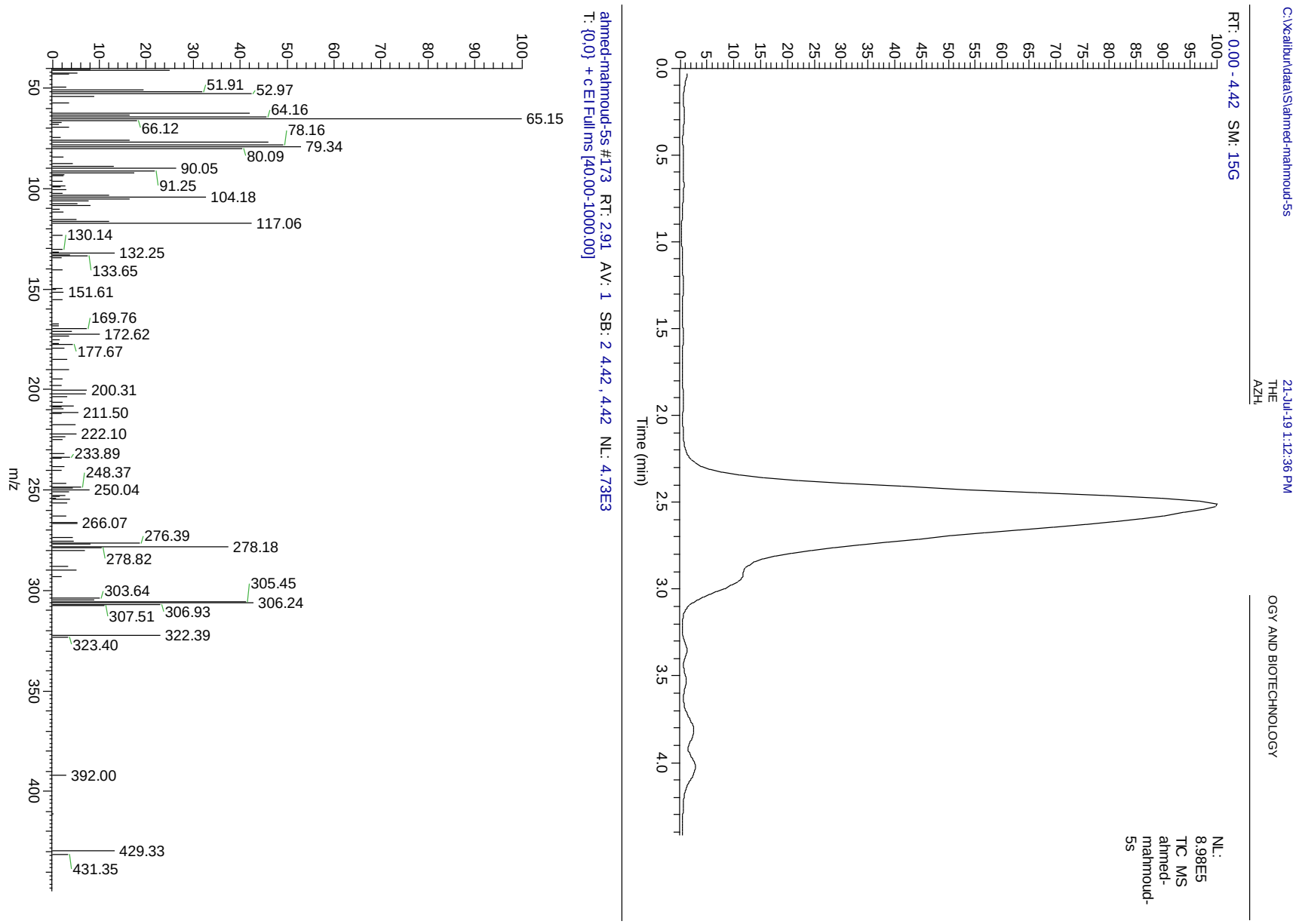


Figure S128. **Mass spectrum of compound 17c**

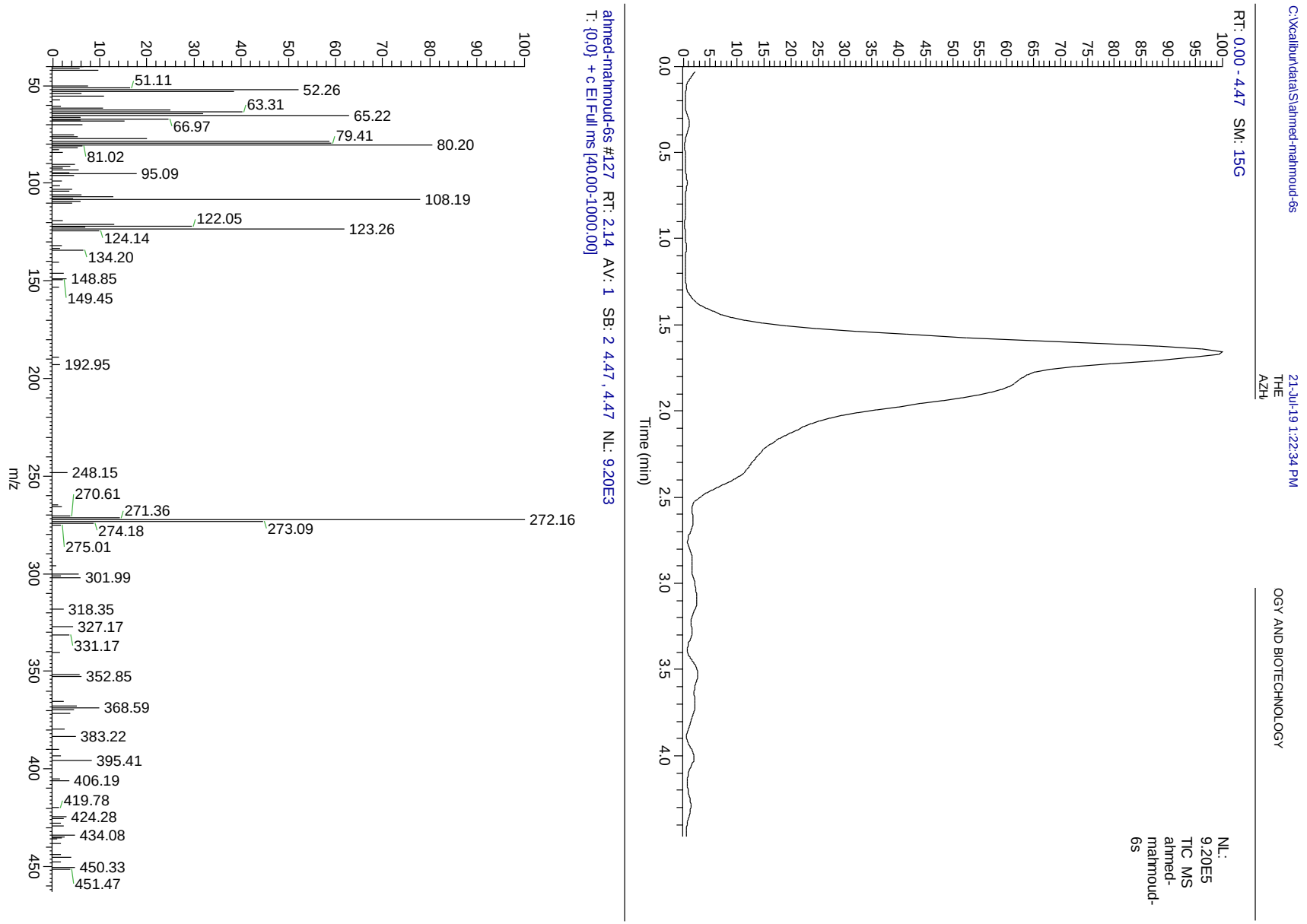


Figure S129. **Mass spectrum of compound 18a**

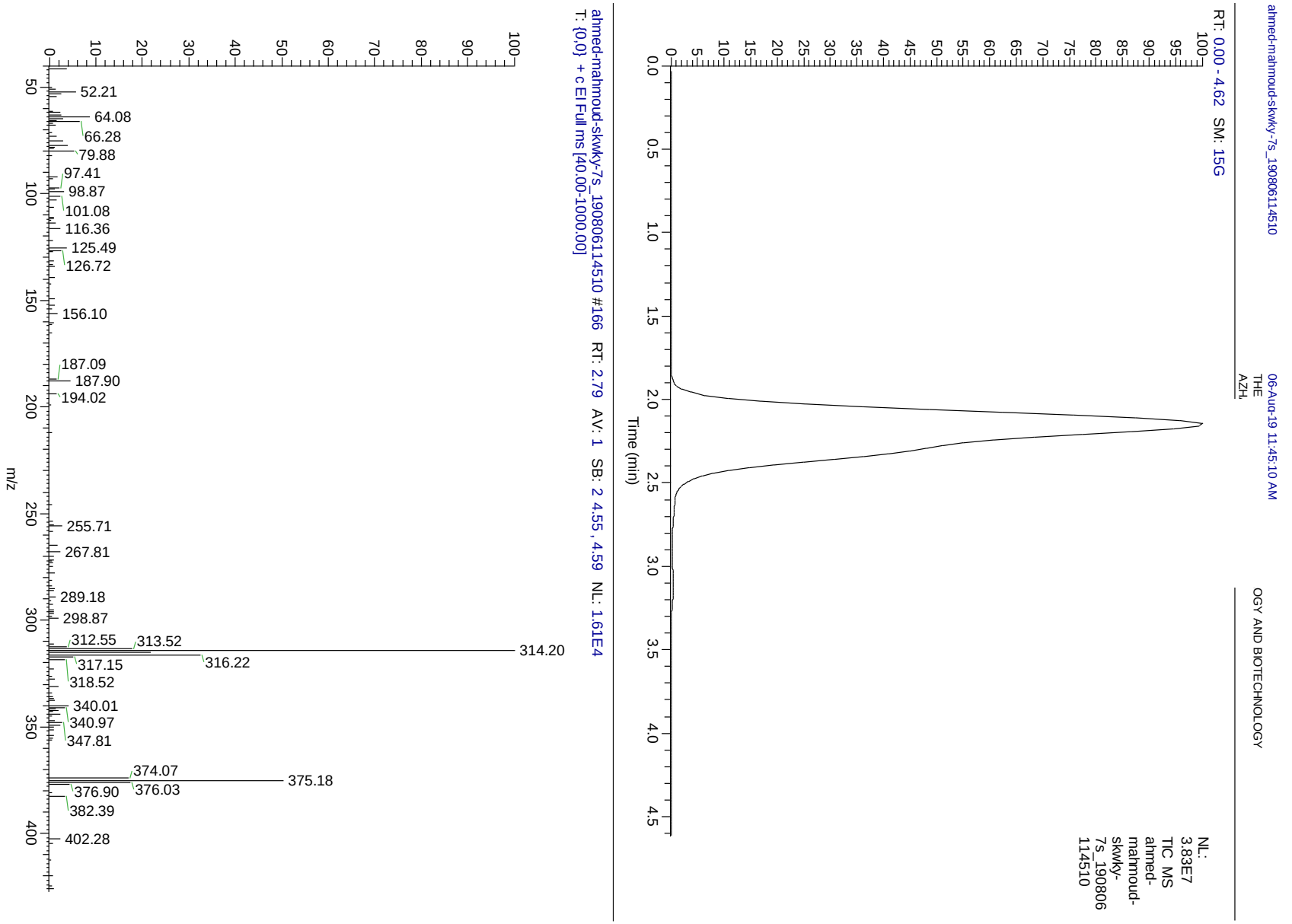


Figure S130. **Mass spectrum of compound 18b**

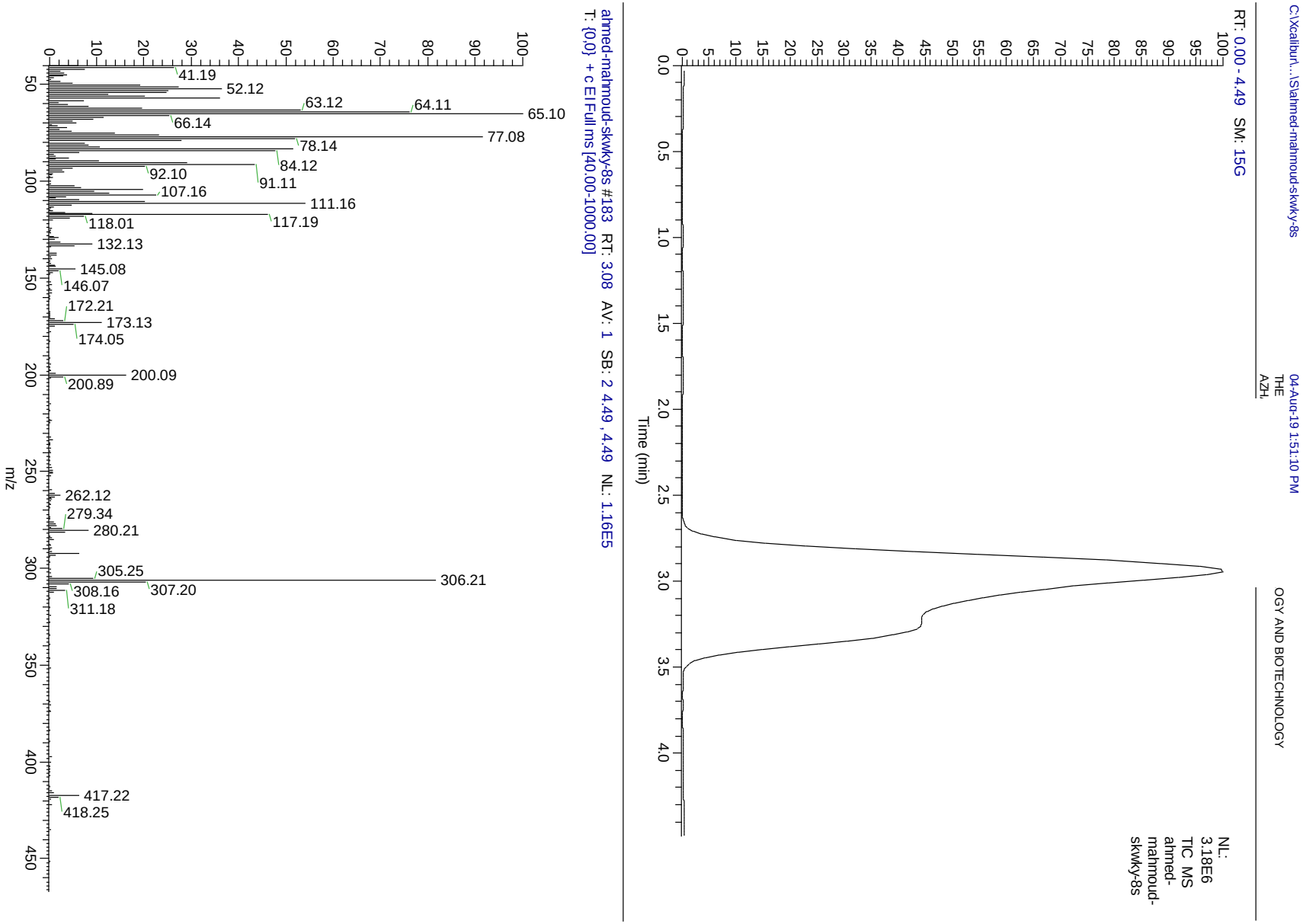


Figure S131. **Mass spectrum of compound 18c**

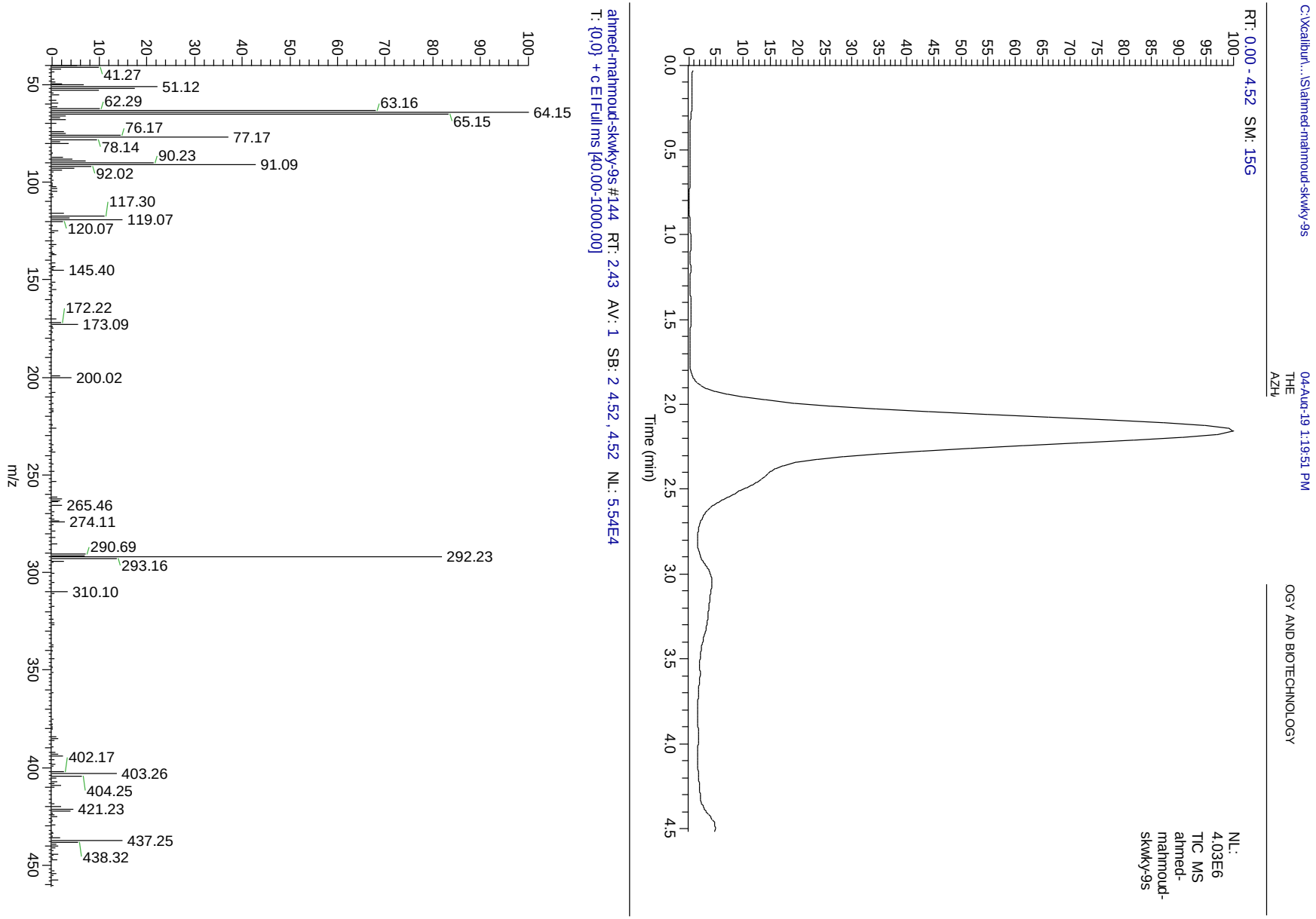


Figure S132. **Mass spectrum of compound 19a**

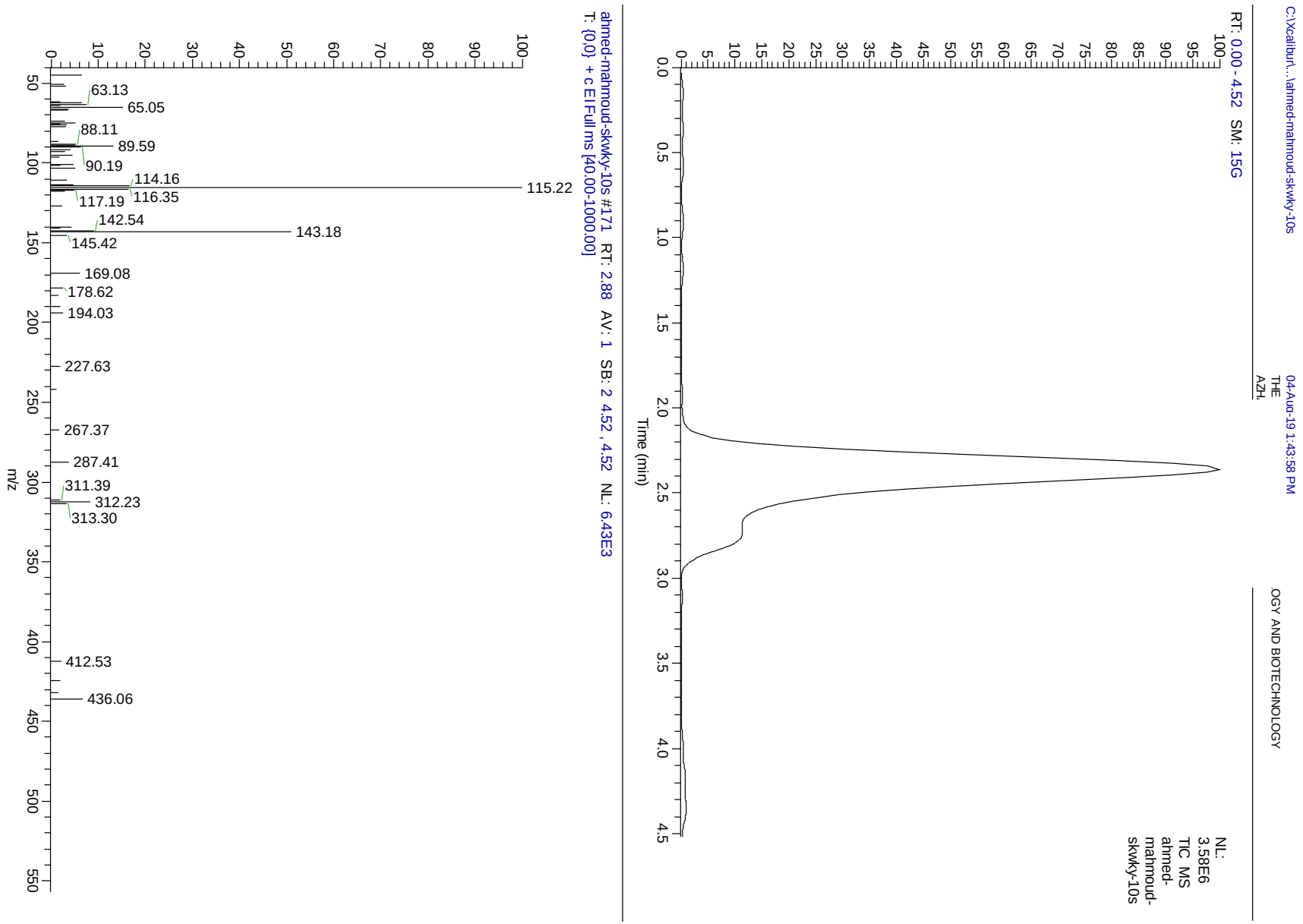
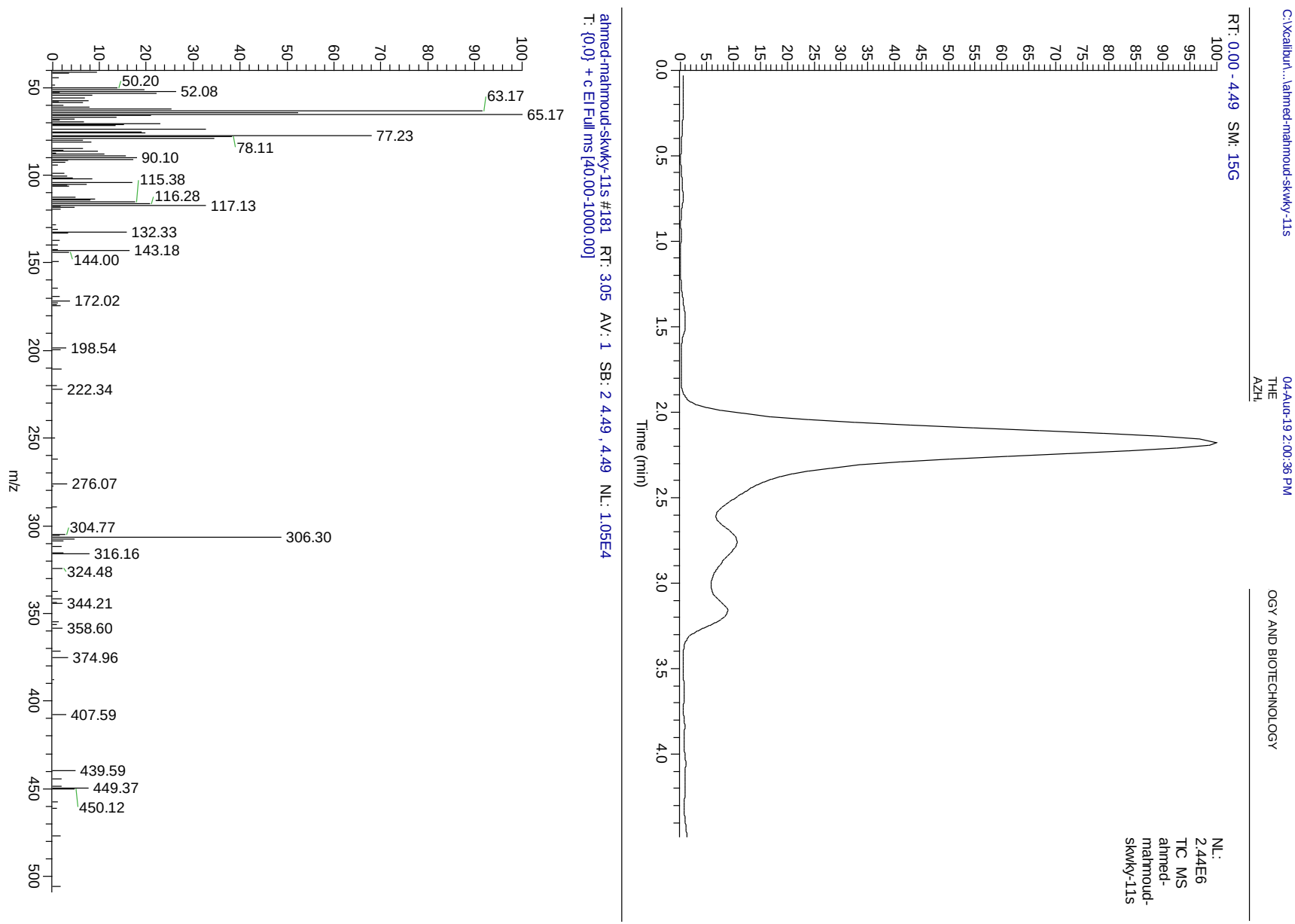
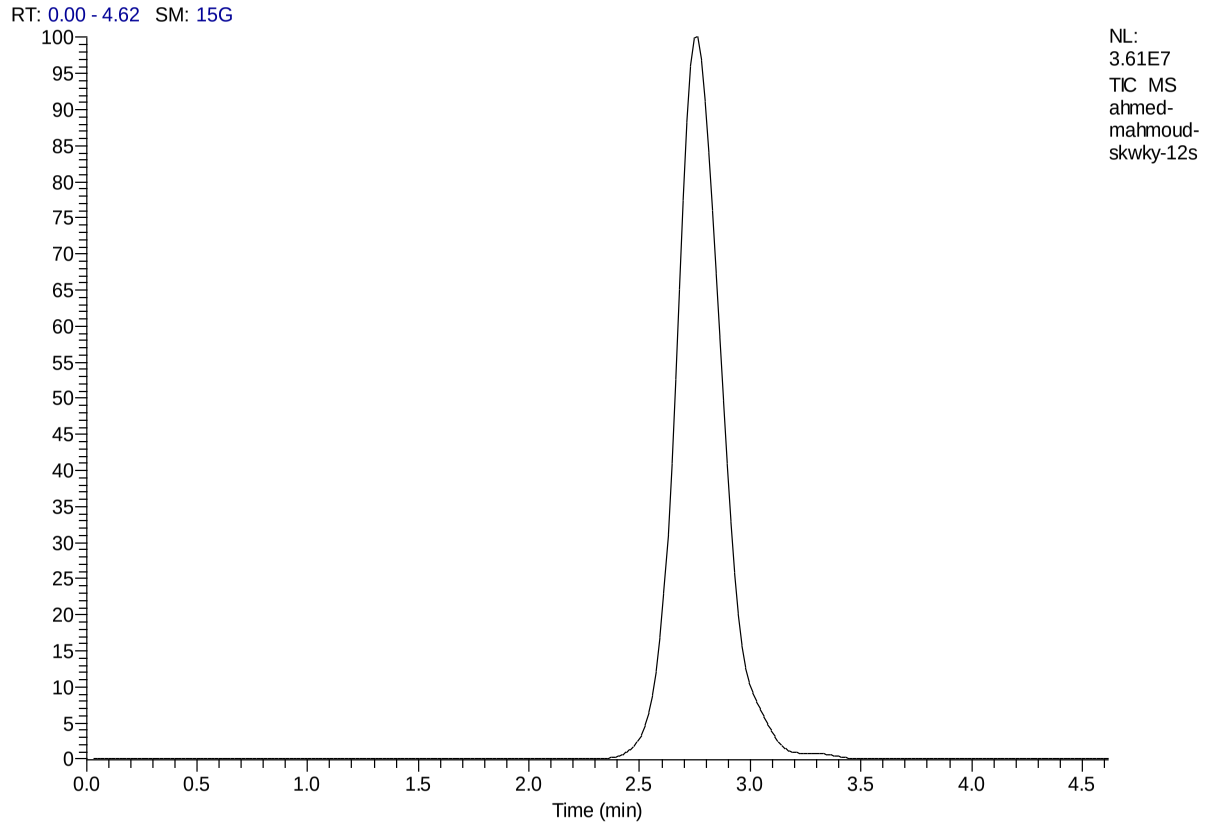


Figure S133. **Mass spectrum of compound 19b**





ahmed-mahmoud-skwky-12s #192 RT: 3.23 AV: 1 SB: 2 4.55 , 4.59 NL: 3.26E4
T: {0,0} + c EI Full ms [40.00-1000.00]

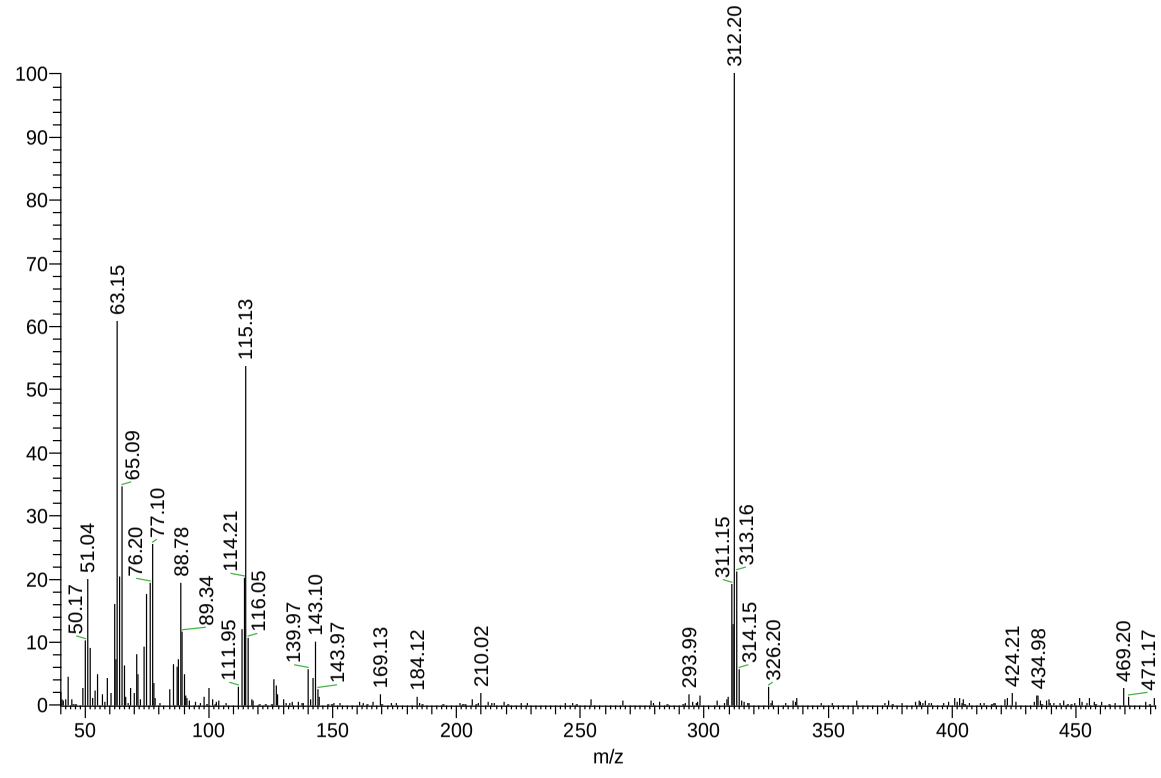


Figure S134. Mass spectrum of compound 19c

Figure S135. **Mass spectrum of compound 20a**

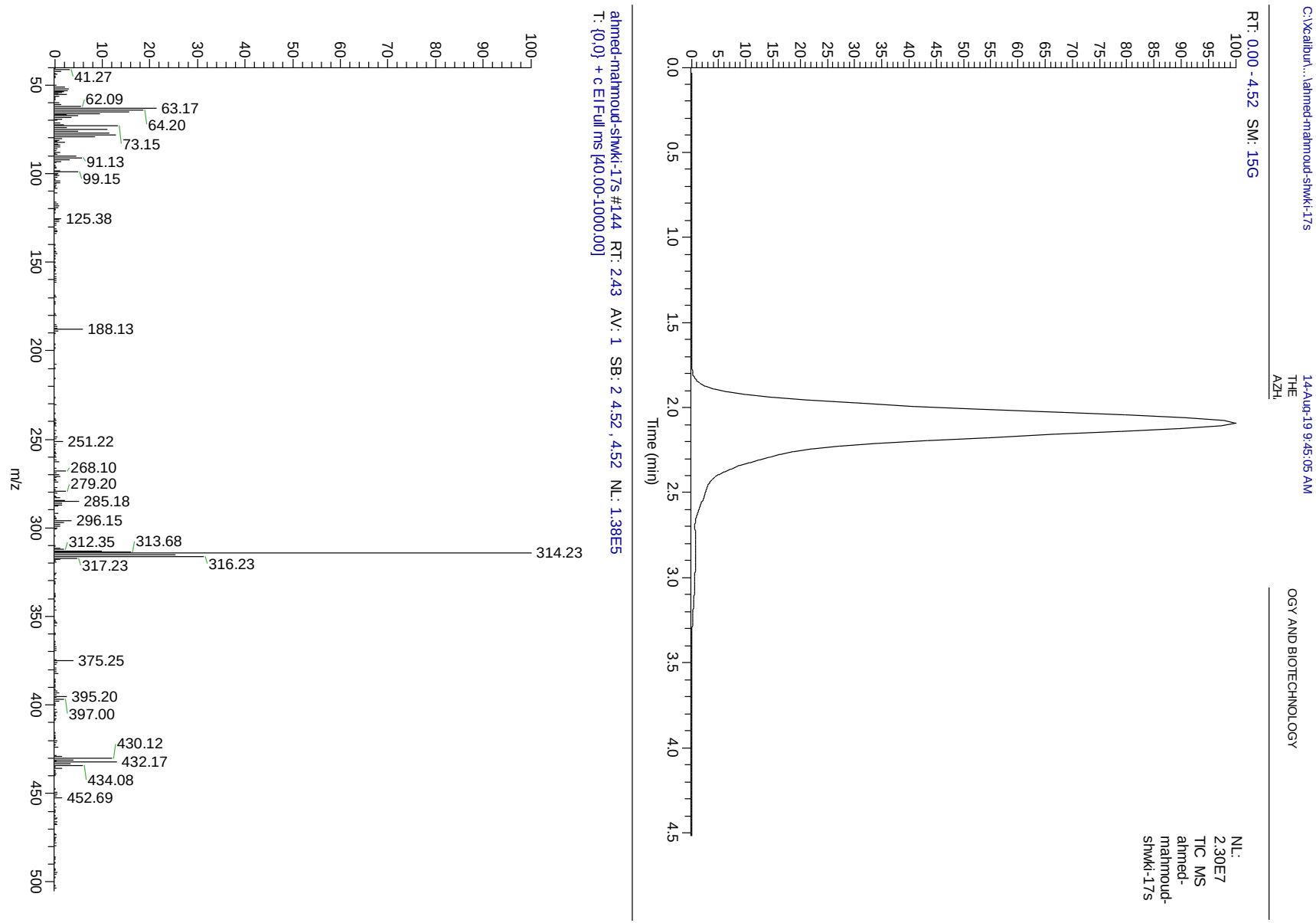


Figure S136. **Mass spectrum of compound 20b**

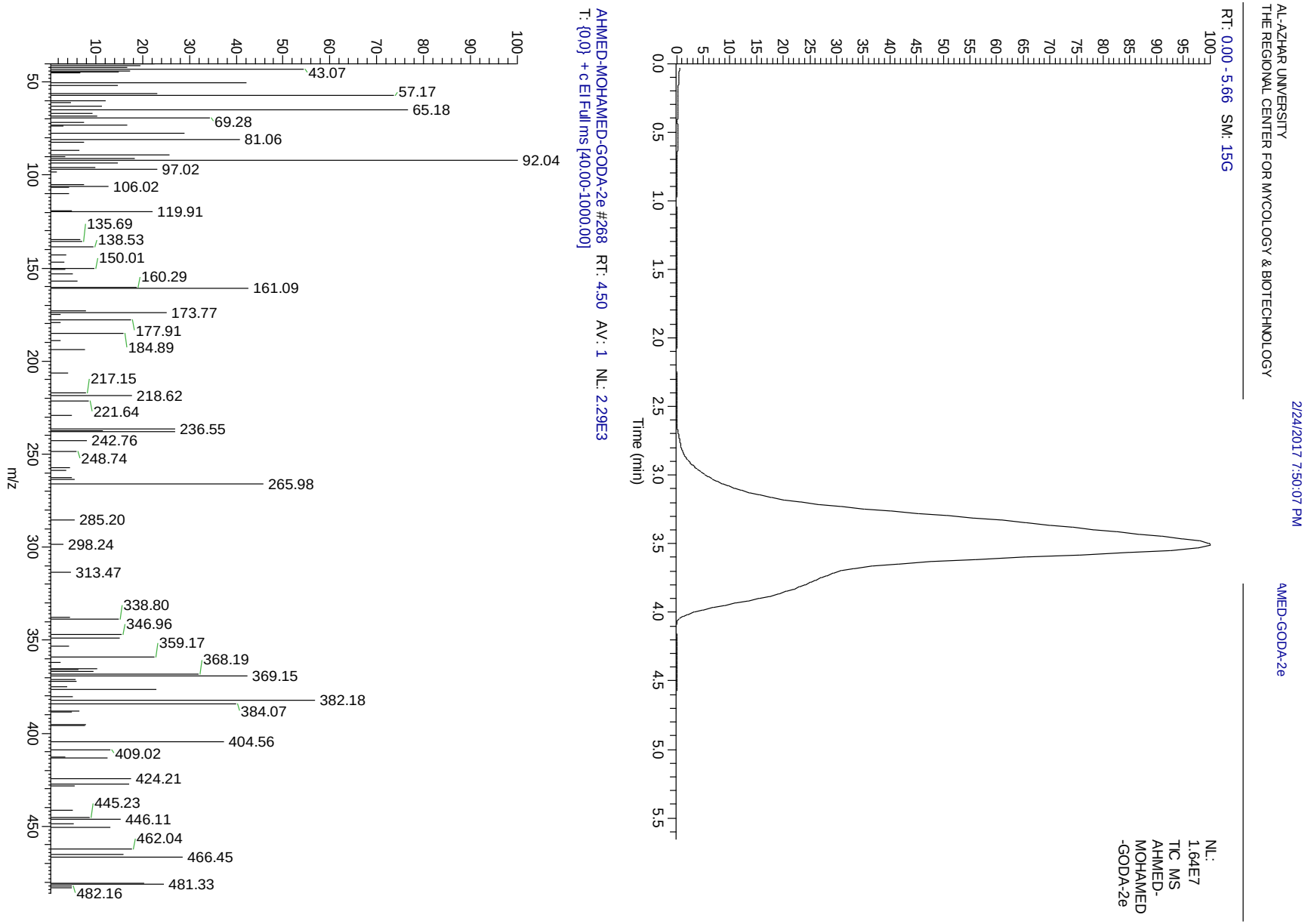
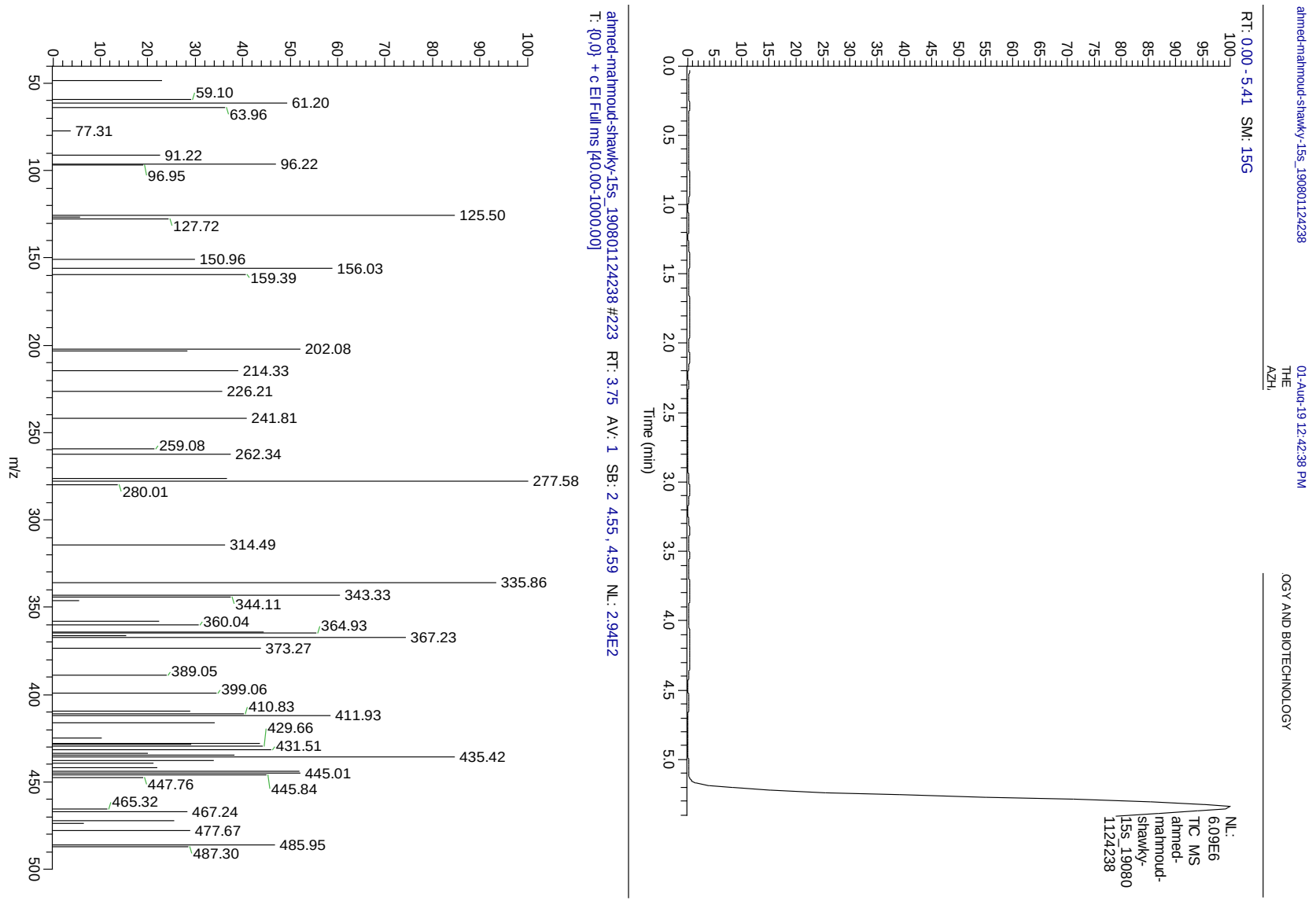


Figure S137. Mass spectrum of compound **20b**



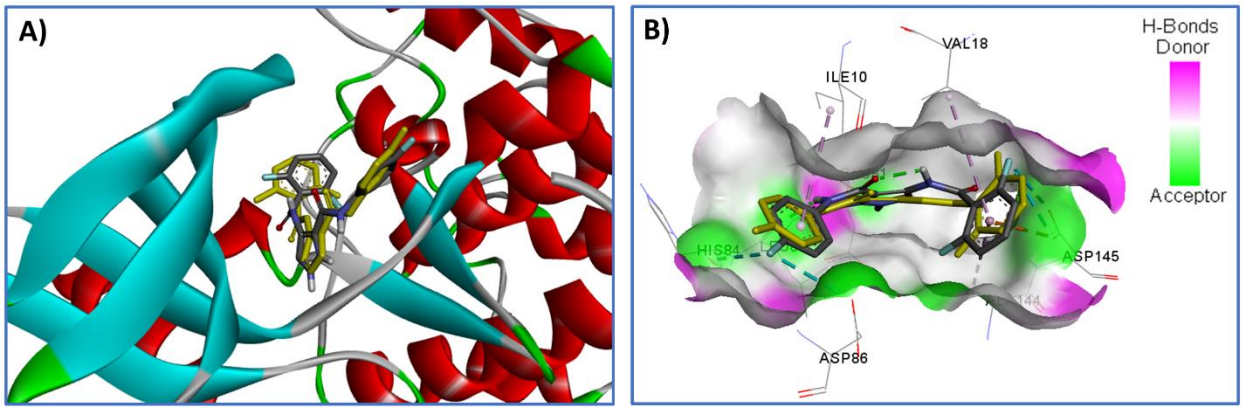


Figure S138. Binding modes/interactions of re-docked/bound LZ9 (compound **3**) into CDK-2 (pdb 2VTP): A) 3D binding mode of re-docked LZ9 (shown as sticks colored by element) into CDK-2 overlaid with the native ligand, LZ9 shown as yellow sticks; B) 3D binding mode of re-docked LZ9 (shown as sticks colored by element) overlaid with the native ligand (shown as yellow sticks) into CDK-2, the native ligand LZ9 shown as yellow sticks, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity.

Table S1. Docking results of the new compounds into CDK-2 (pdb: 2VTP).

Ligand	ΔG_b [a]	K_i [b]	HBs [c]	Atoms in H-bonding		Length [d] (Å)
				In ligand	In protein	
16a	-8.92	288.31 nM	4	CN	Thr14	2.17
				Urea NH	Lys33	1.95
				Urea NH	Asp145	1.78
				Urea NH	Asp145	1.97
16b	-8.73	398.11 nM	3	Urea NH	Asp86	2.04
				Urea NH	Gln131	2.13
				CONH	Asp145	2.10
16c	-8.60	500.18 nM	4	CN	Lys129	2.84
				CN	Gln131	2.36
				Urea NH	Asn132	2.36
				Urea NH	Asp145	1.84
17a	-9.84	60.97 nM	3	CN	Thr14	2.10
				Urea CO	Lys33	1.75
				Urea NH	Asp145	2.05
17b	-9.65	85.09 nM	2	Urea CO	Leu83	1.92
				CONH	Gln131	2.24
17c	-9.48	111.80 nM	2	CN	Leu83	2.09
				Urea NH	Asp86	2.06
18a	-8.89	301.92 nM	2	CN	Leu83	1.91
				Urea NH	Leu83	2.06
18c	-9.54	101.92 nM	3	Urea NH	Leu83	2.27
				CN	Leu83	2.19
				CONH	Gln131	2.15
19b	-10.41	23.47 nM	3	CN	Leu83	2.17
				Urea NH	Asp86	2.08
				CONH	Gln131	2.81
19c	-10.67	15.06 nM	2	Urea CO	Lys33	2.34
				Urea NH	Asp145	2.04
20b	-10.10	39.21 nM	4	CN	Leu83	2.05
				Thiourea S	Leu83	2.86
				Thiourea NH	Asp86	3.06
				CONH	Gln131	2.39
20c	-9.76	70.64 nM	2	Urea NH	Asp86	2.09
				CONH	Gln131	1.96

[a] *Binding free energy (kcal/mol);*
[b] *Inhibition constant (n/μM)*
[c] *HBs, number of hydrogen bonds*
[d] *length in angstrom (Å)*

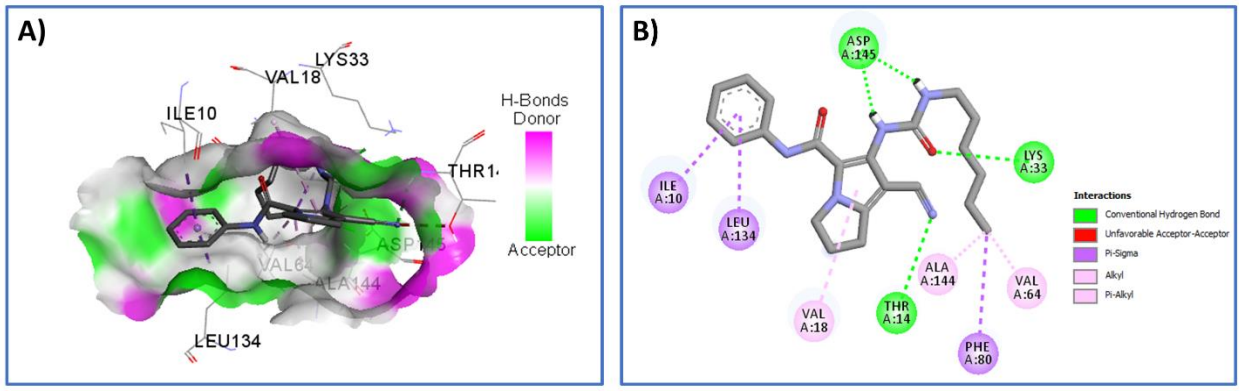


Figure S139. Binding modes/interactions of compound **16a** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **16a** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **16a** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

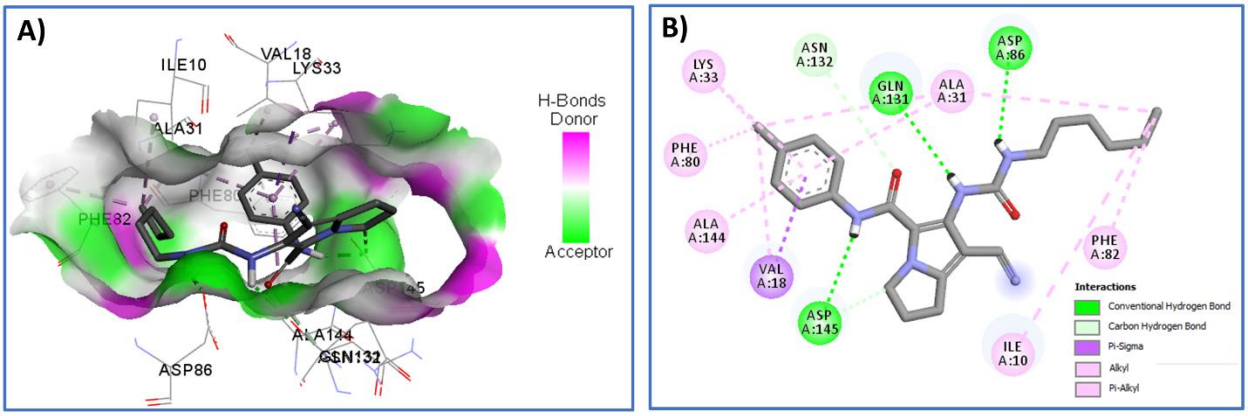


Figure S140. Binding modes/interactions of compound **16b** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **16b** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **16b** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

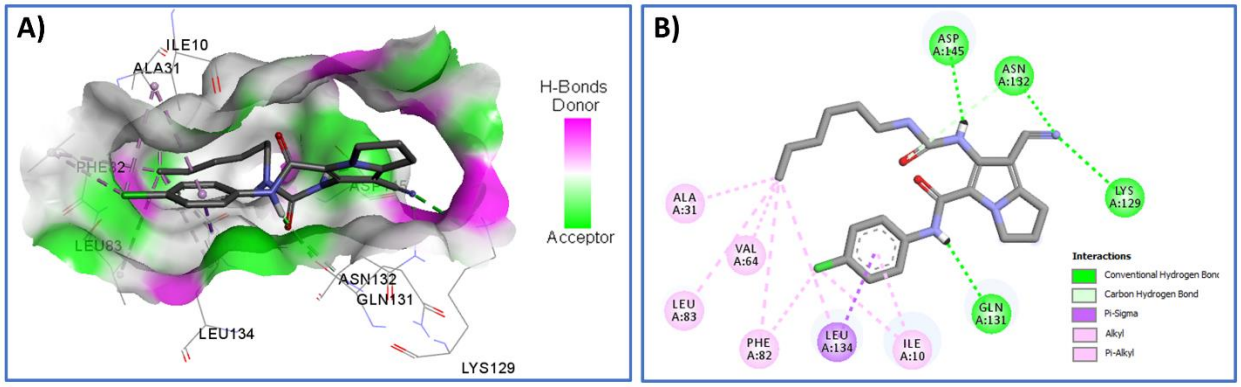


Figure S141. Binding modes/interactions of compound **16c** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **16c** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **16c** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

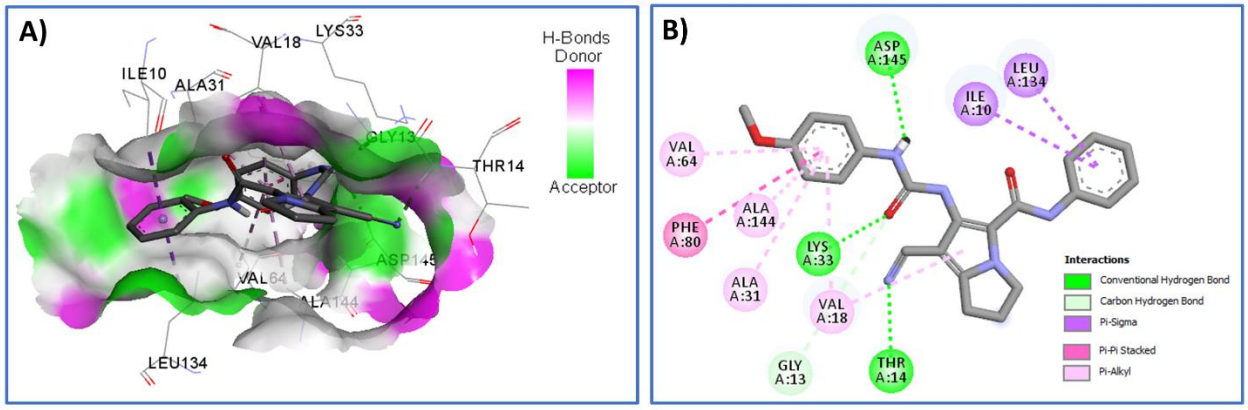


Figure S142. Binding modes/interactions of compound **17a** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **17a** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **17a** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

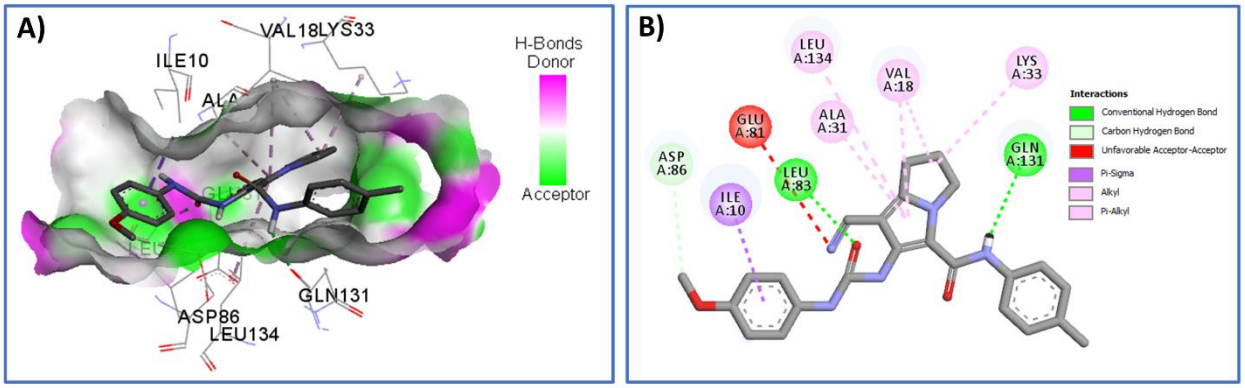


Figure S143. Binding modes/interactions of compound **17b** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **17b** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **17b** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

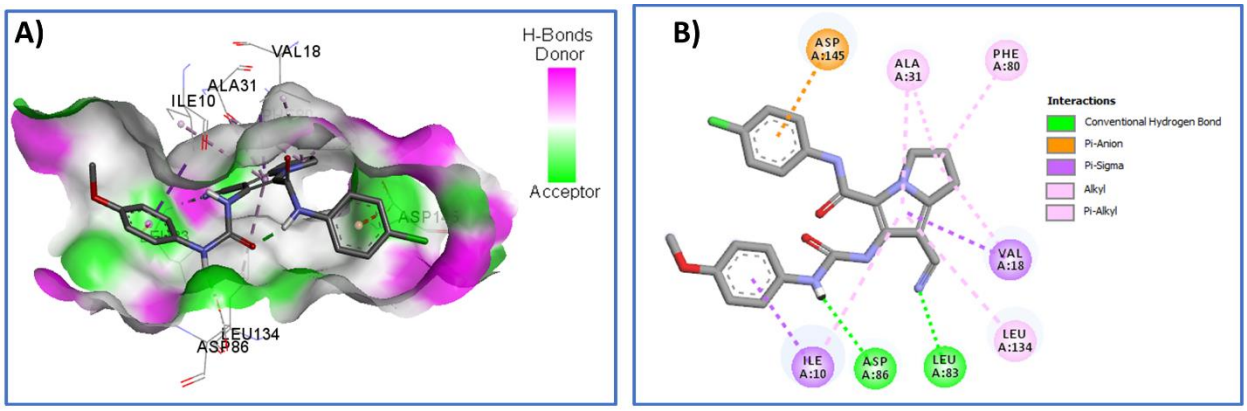


Figure S144. Binding modes/interactions of compound **17c** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **17c** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **17c** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

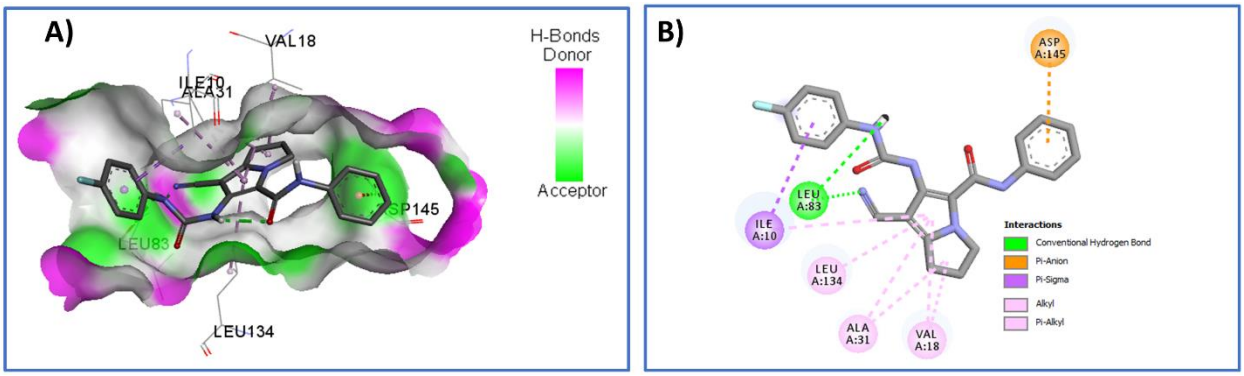


Figure S145. Binding modes/interactions of compound **18a** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **18a** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **18a** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

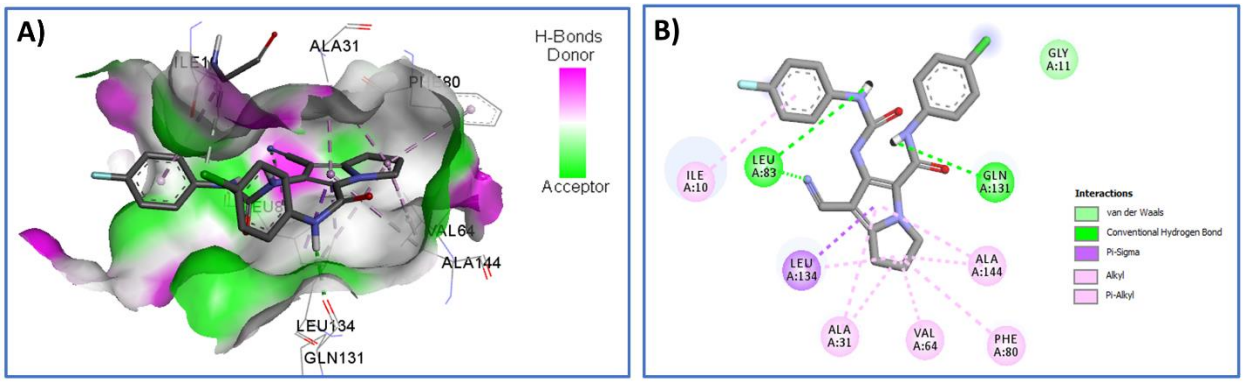


Figure S146. Binding modes/interactions of compound **18c** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **18c** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **18c** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

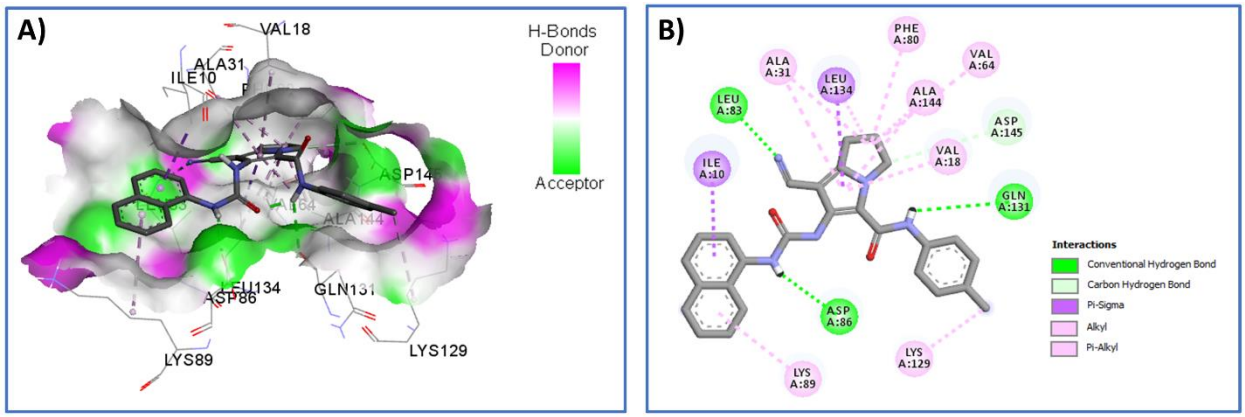


Figure S147. Binding modes/interactions of compound **19b** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **19b** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **19b** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

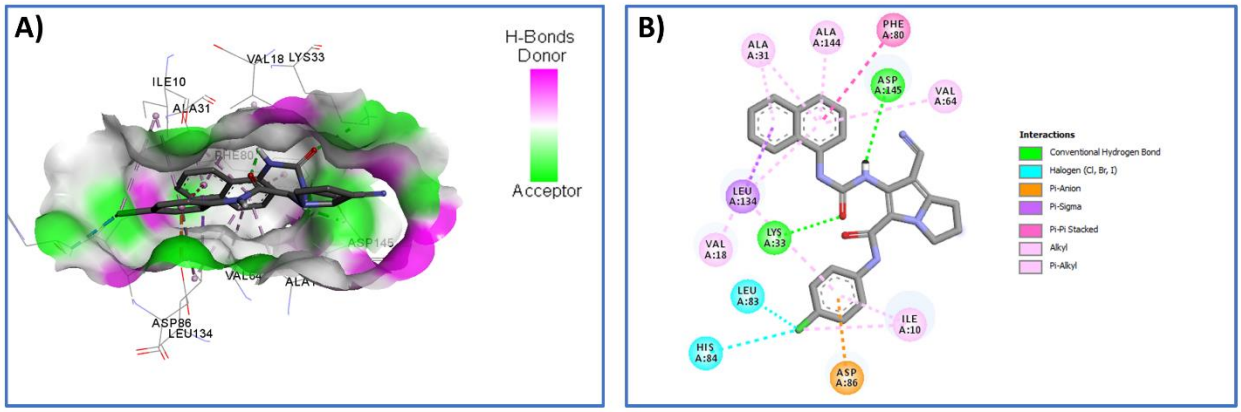


Figure S148. Binding modes/interactions of compound **19c** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **19c** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **19c** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

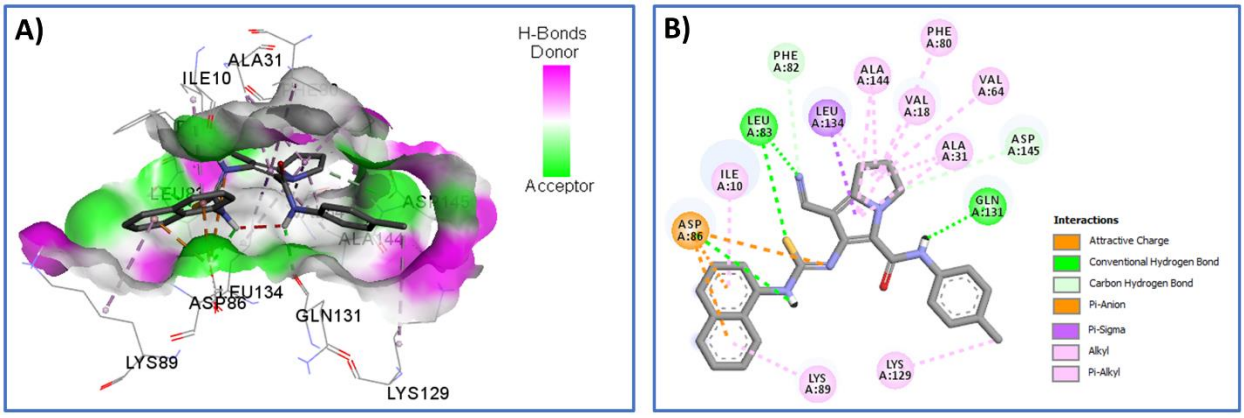


Figure S149. Binding modes/interactions of compound **20b** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **20b** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **20b** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

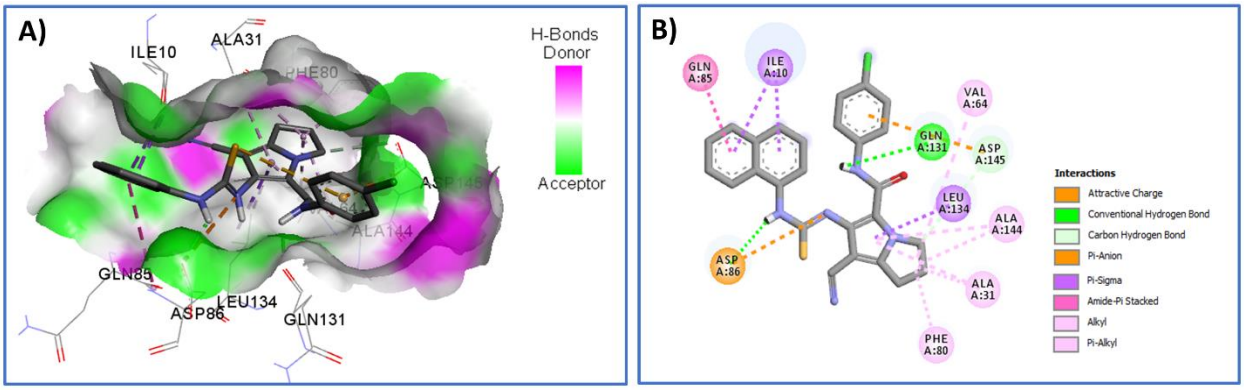


Figure S150. Binding modes/interactions of compound **20c** into CDK-2 (pdb: 2VTP): A) 3D binding mode of compound **20c** into the active site of CDK-2, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity; B) 3D binding mode of compound **20c** into CDK-2 showing different types of hydrogen bonding and hydrophobic interactions.

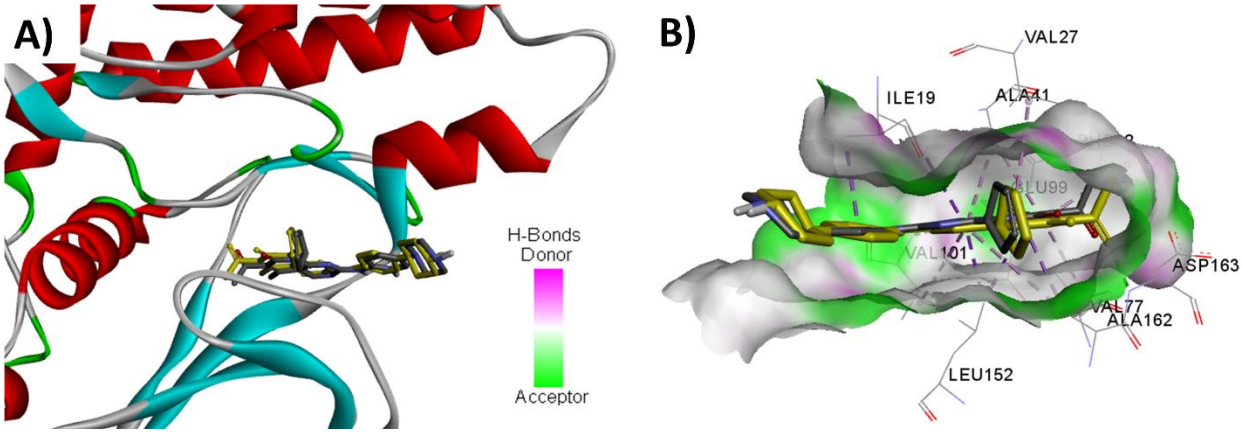


Figure S151. Binding modes/interactions of re-docked/bound palbociclib into CDK-6 (pdb 2EUF): A) 3D binding mode of re-docked palbociclib (shown as sticks colored by element) into CDK-6 overlaid with the native ligand (shown as yellow sticks); B) 3D binding mode of re-docked palbociclib (shown as sticks colored by element) overlaid with the native ligand (shown as yellow sticks) into CDK-6, the native ligand palbociclib shown as yellow sticks, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity.

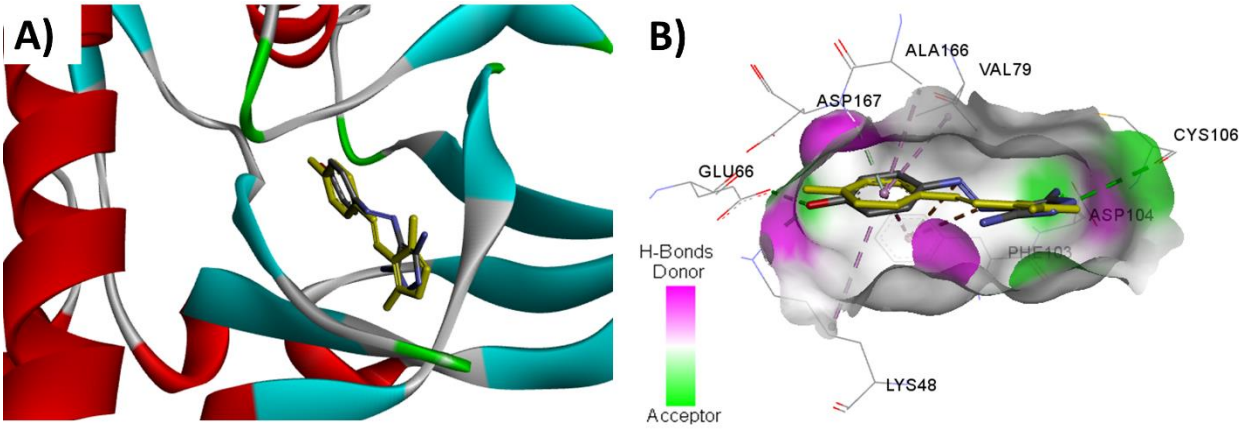


Figure S152. Binding modes/interactions of re-docked/bound palbociclib into CDK-9 (pdb 3TNH): A) 3D binding mode of re-docked CAN508 (shown as sticks colored by element) into CDK-9 overlaid with the native ligand (shown as yellow sticks); B) 3D binding mode of re-docked CAN508 (shown as sticks colored by element) overlaid with the native ligand (shown as yellow sticks) into CDK-9, the native ligand CAN508 shown as yellow sticks, receptor shown as hydrogen-bond surface, hydrogen atoms were omitted for clarity
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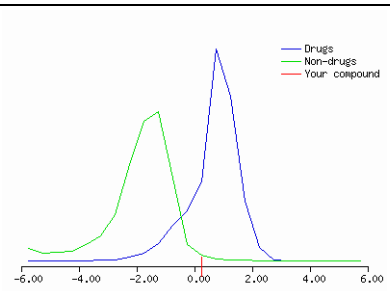
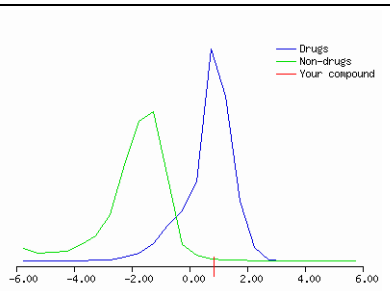
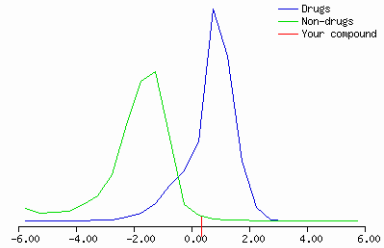
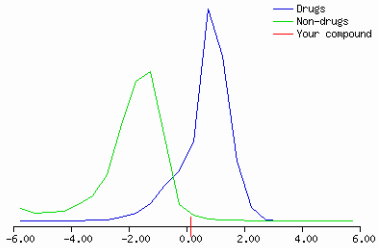
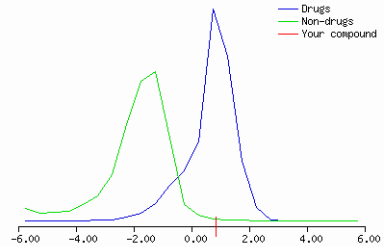
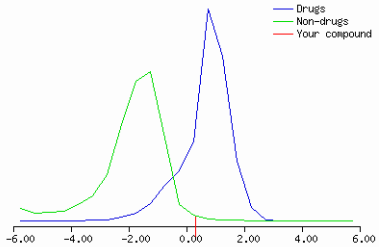
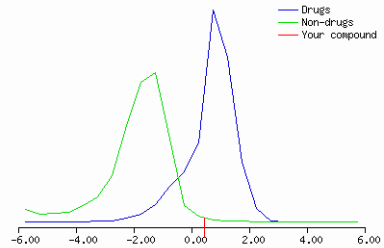
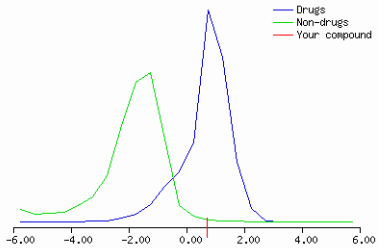
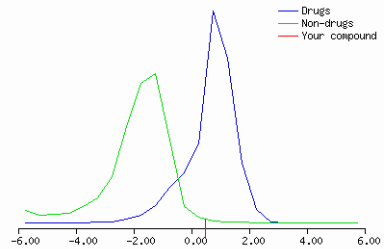
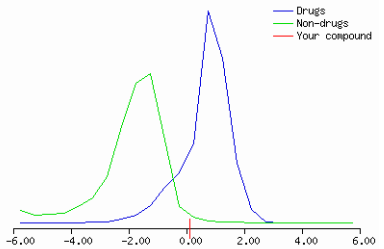
Table S2. **DLS figures and scores of compounds 9 and 16-20a-c.**

Comp.		DLS	Comp.		DLS
16a		0.24	**18c**		0.86
16b		0.35	**19a**		0.14
16c		0.84	**19b**		0.30
17a		0.45	**19c**		0.71
17b		0.48	**20a**		0.11

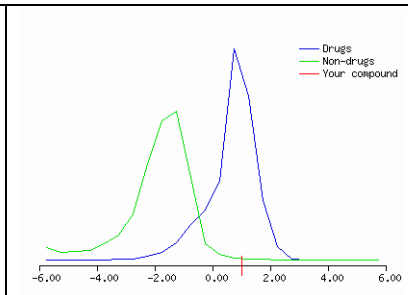
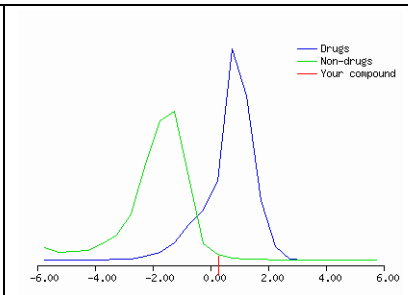
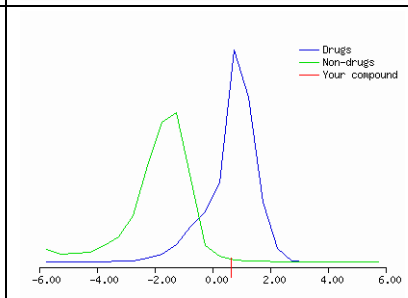
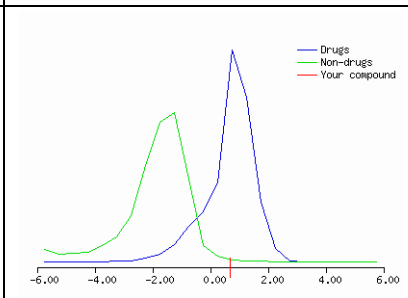
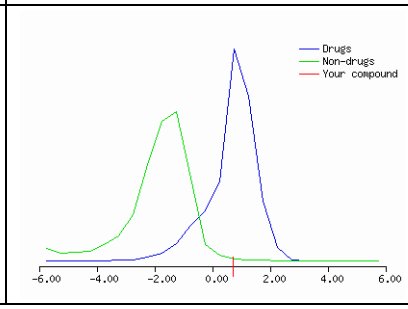
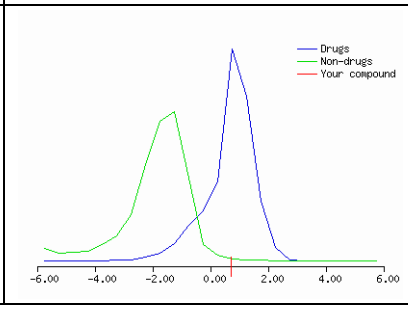
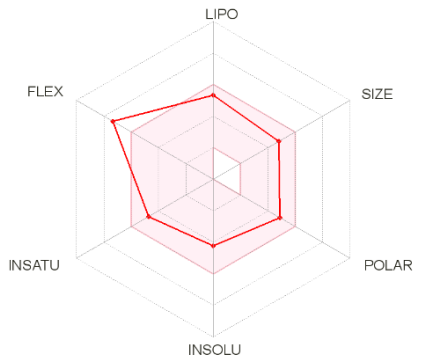
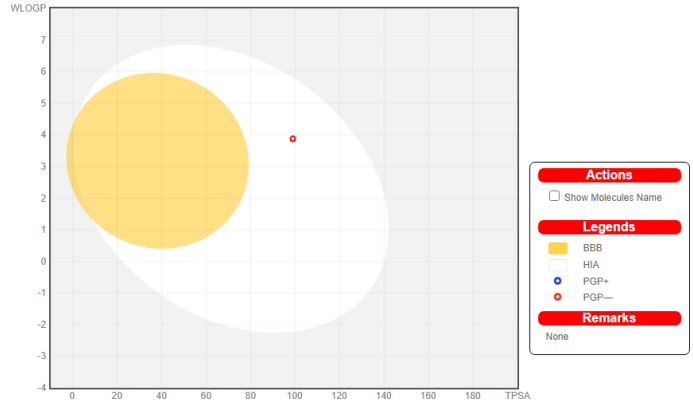
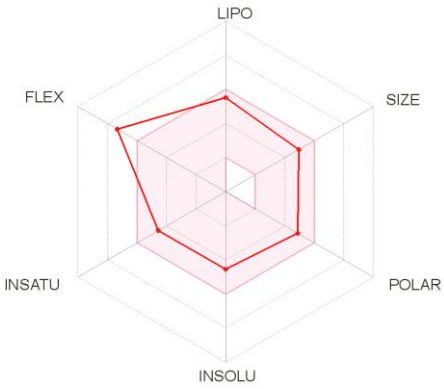
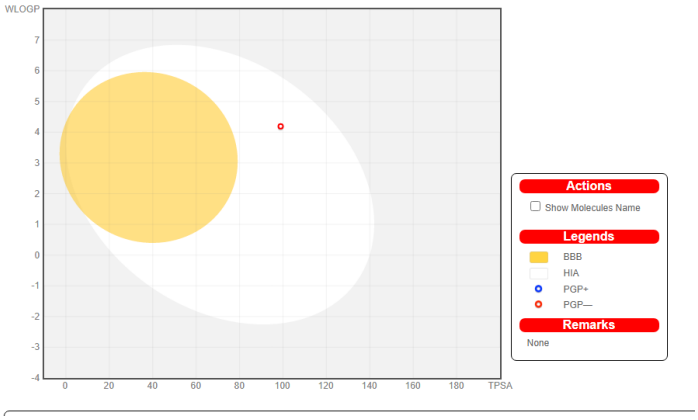
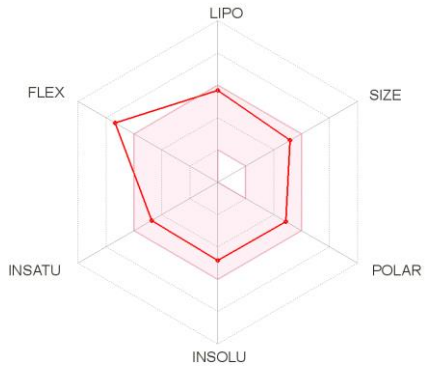
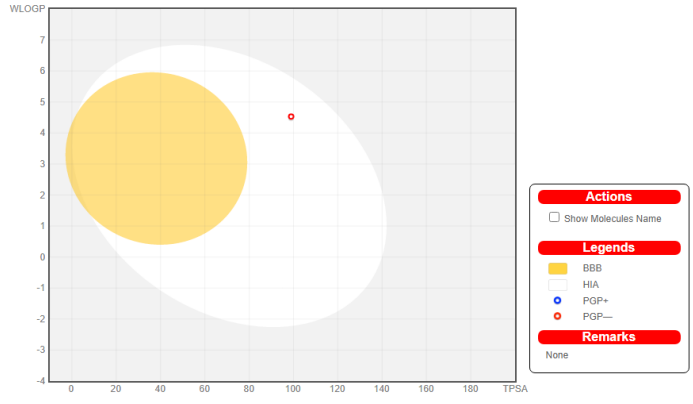
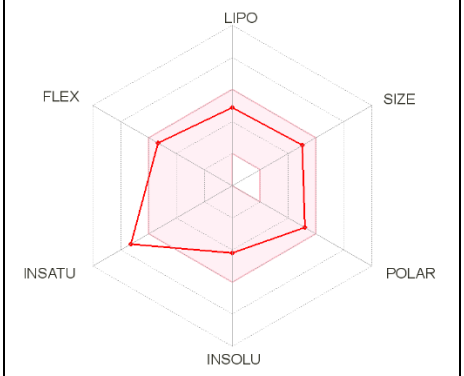
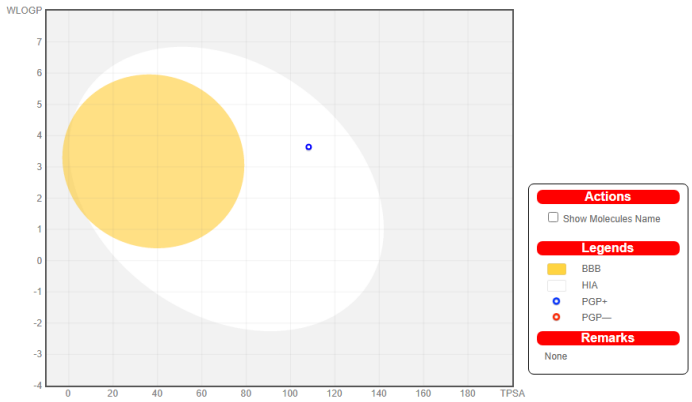
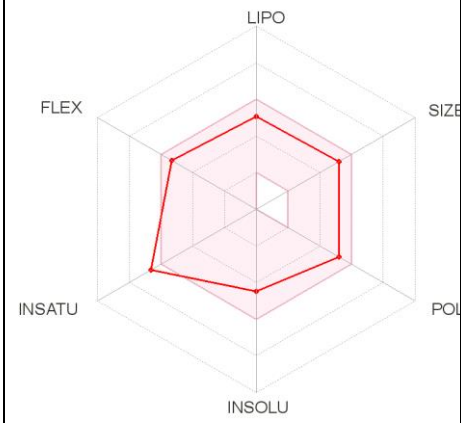
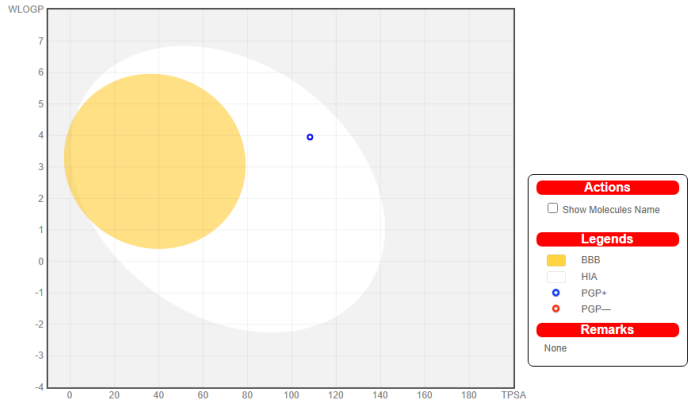
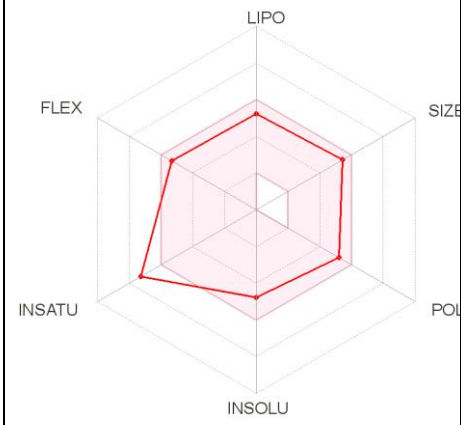
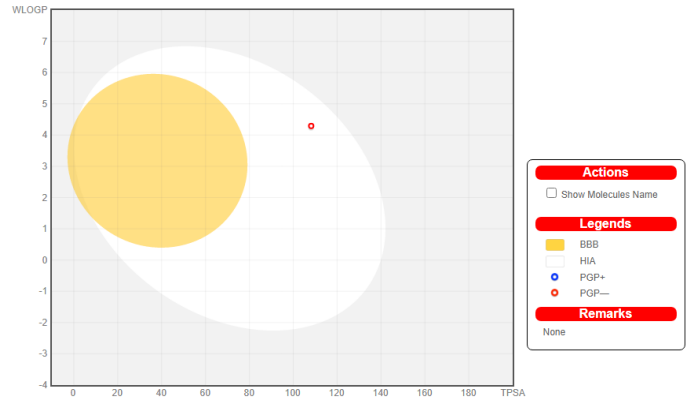
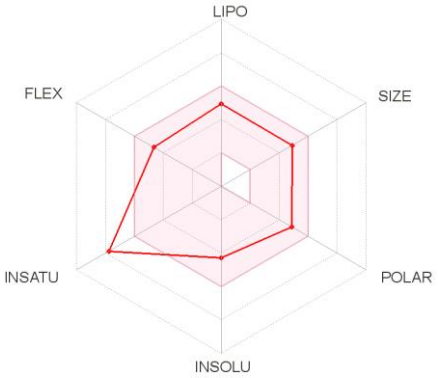
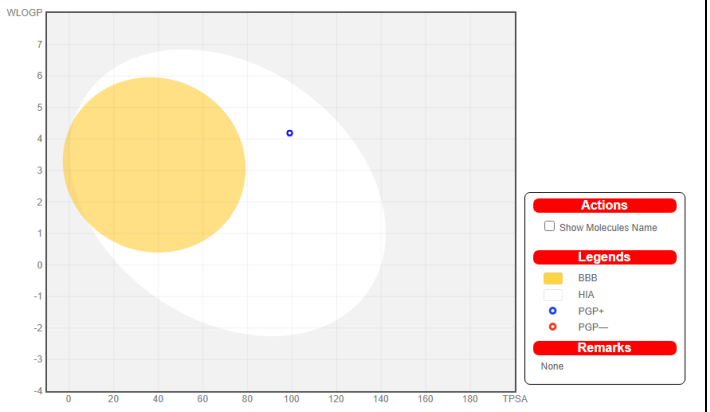
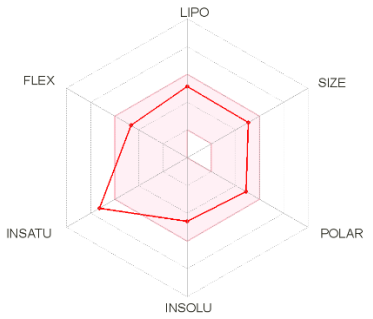
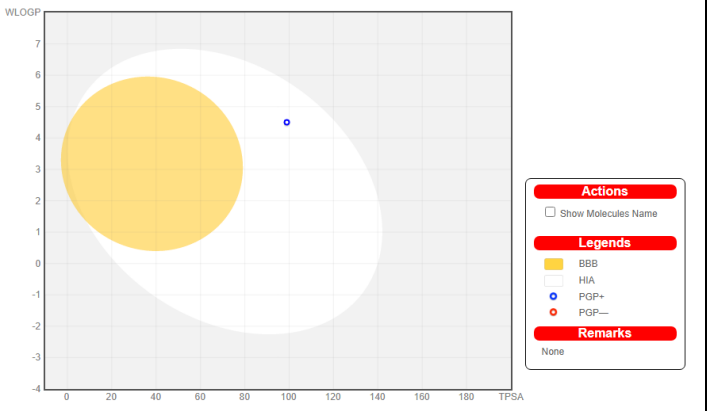
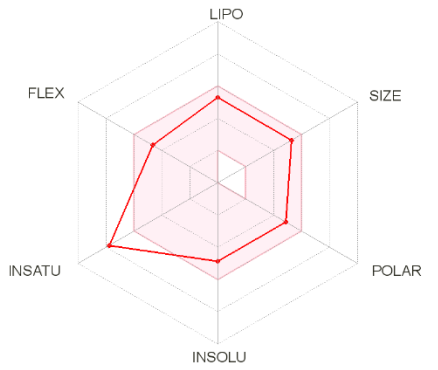
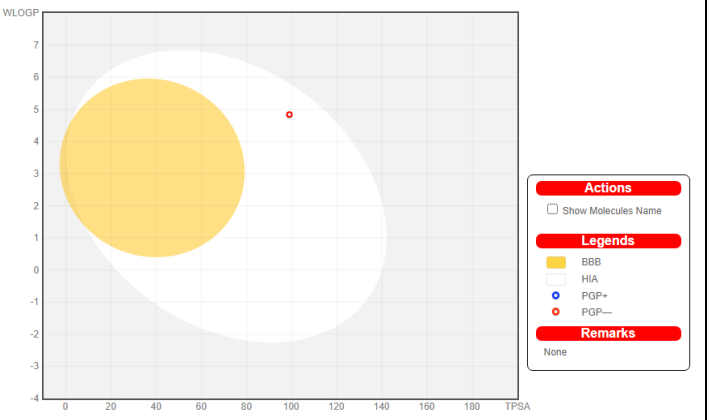
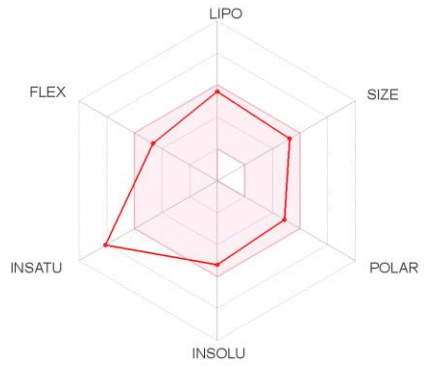
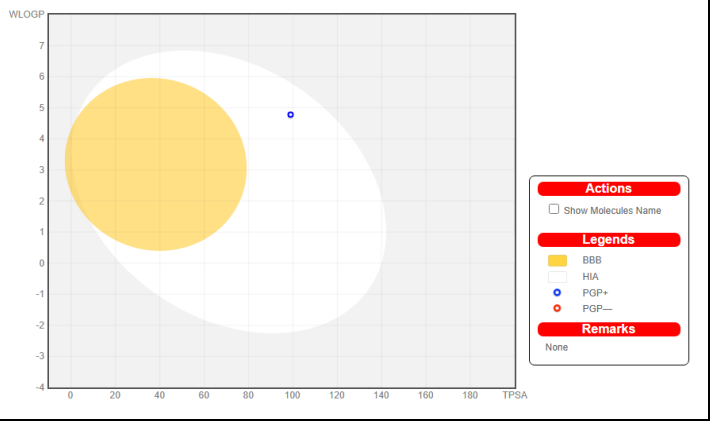
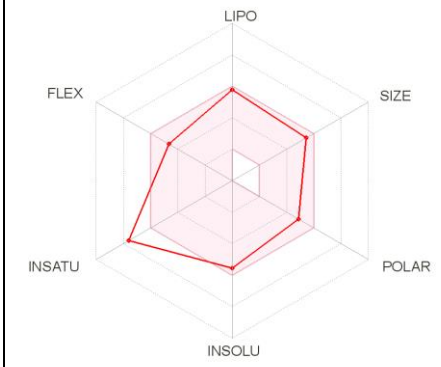
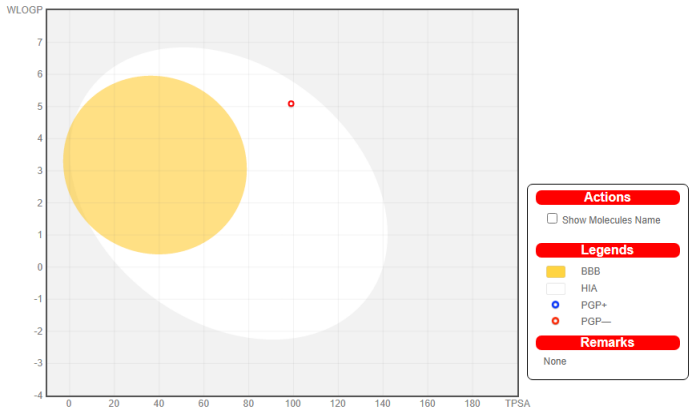
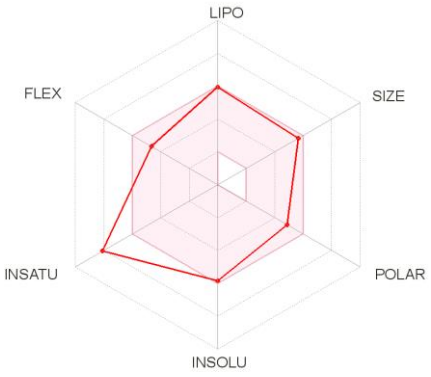
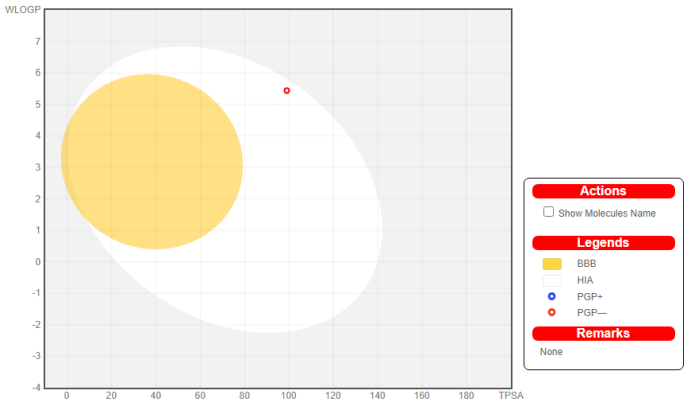
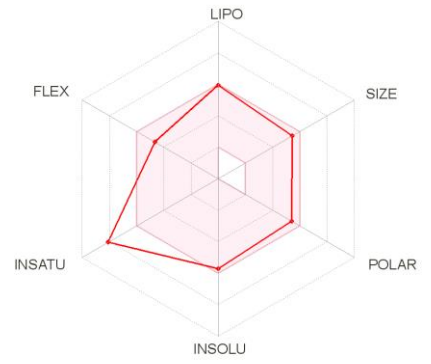
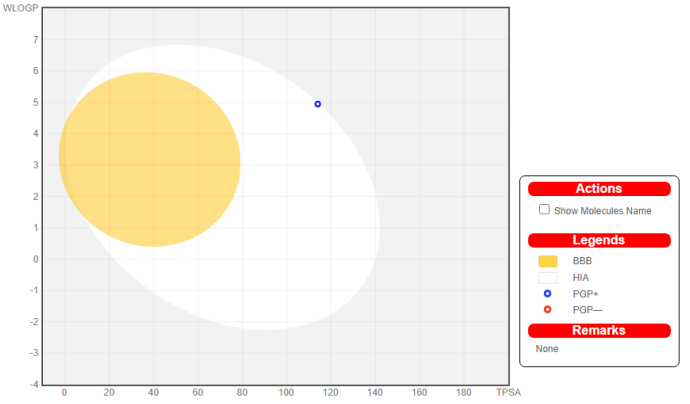
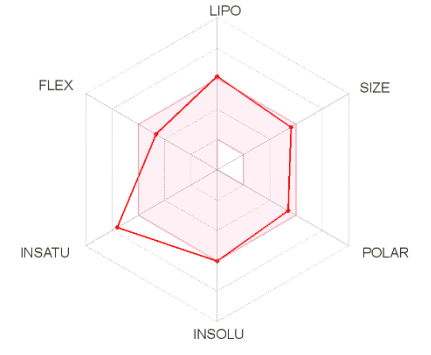
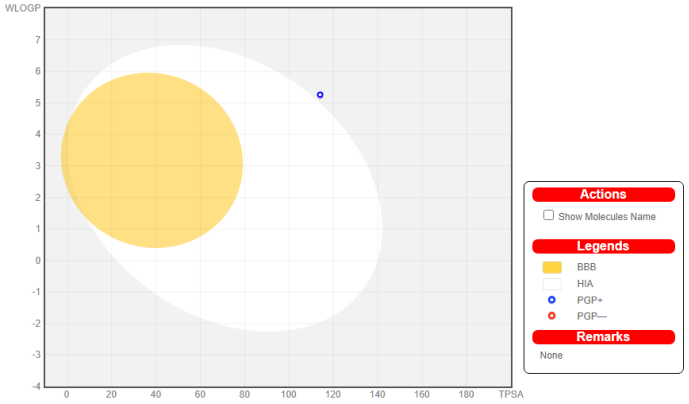
17c		1.01	**20b**		0.28
18a		0.65	**20c**		0.69
18b		0.71	**9**		0.71

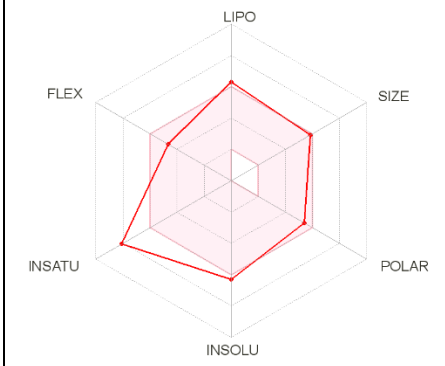
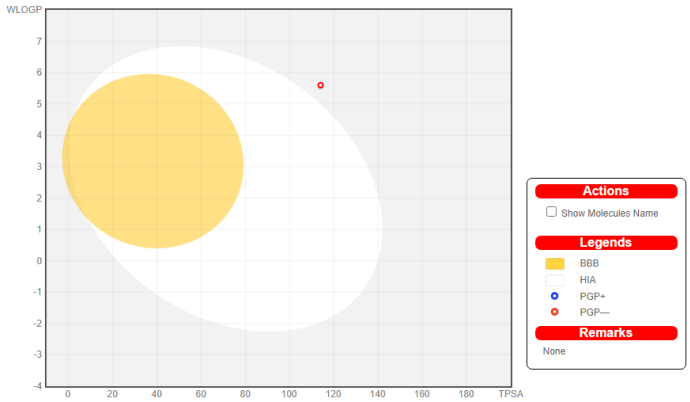
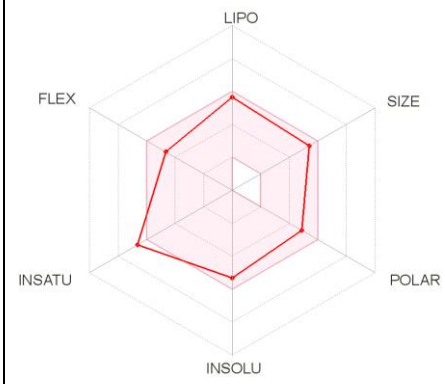
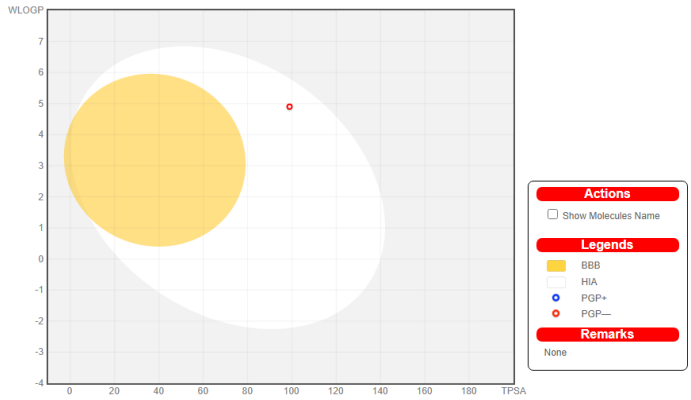
Table S3. The suitable physicochemical space for oral bioavailability and Boiled-Egg models of compounds 9 and 16-20a-c.

Comp.	Physicochemical space	Boiled-Egg model
16a		
16b		
16c		

17a	 LIPO SIZE POLAR INSOLU INSATU FLEX	 WLOGP TPSA Actions Show Molecules Name Legends BBB HIA PGP+ PGP— Remarks None
17b	 LIPO SIZE POL INSOLU INSATU FLEX	 WLOGP TPSA Actions Show Molecules Name Legends BBB HIA PGP+ PGP— Remarks None
17c	 LIPO SIZE POL INSOLU INSATU FLEX	 WLOGP TPSA Actions Show Molecules Name Legends BBB HIA PGP+ PGP— Remarks None

18a		
18b		
18c		
19a		

19b		
19c		
20a		
20b		

20c		
9		

The suitable physicochemical space figures and BOILED-Egg's models were calculated using SwissADME (http://www.swissadme.ch/)

The colored zone is the suitable physicochemical space for oral bioavailability

- LIPO (lipophilicity) -0.7 to +5.0
- SIZE (MW), 150g/mol to 500g/mol
- POLAR (polarity): 20 Å² < TPSA < 130 Å².
- INSOLU (insolubility): 0< Log S (ESOL) < 6
- INSATU (insaturaion): 0.25 < Fraction Csp3 < 1
- Flex (flexibility): 0 < Num. rotatable bonds < 9

BOILED-Egg's models

- Points located in BOILED-Egg's yolk are molecules predicted to passively permeate through the blood-brain barrier (BBB).
- Points located in BOILED-Egg's white are molecules predicted to passively absorbed by the GIT.
- Blue dots are for molecules predicted to be effluated from the CNS by P-glycoprotein.
- Red dots are for molecules predicted not to be effluated from the CNS by P-glycoprotein.