Supporting Information

Design, synthesis, *in-silico*, and *in-vitro* evaluation of pyrrol-2-yl-phenyl allylidene hydrazine carboximidamide derivatives as AChE/BACE 1 dual inhibitors

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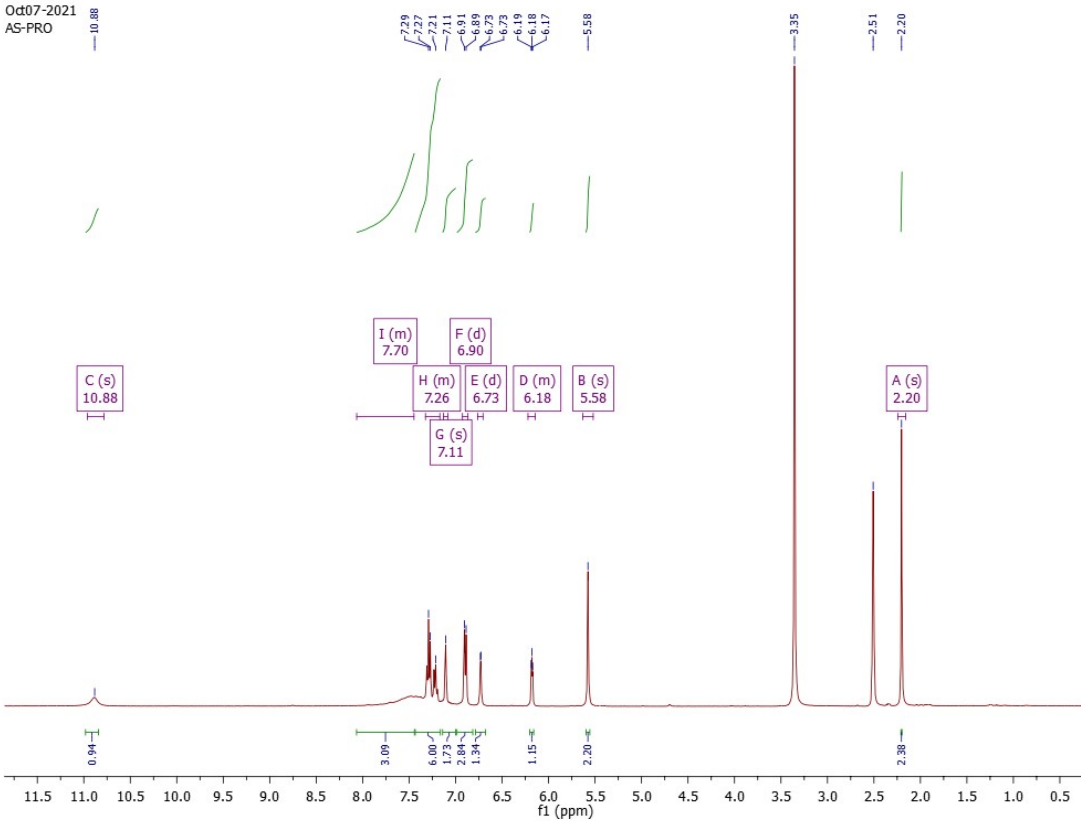
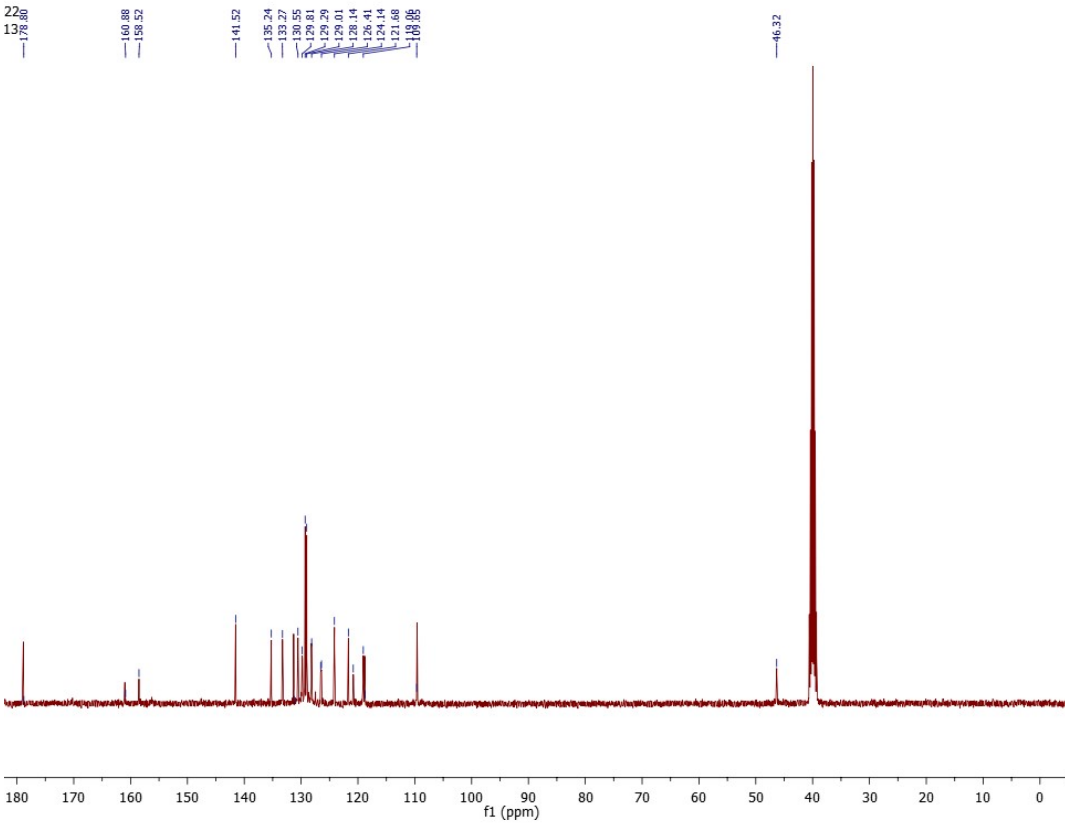
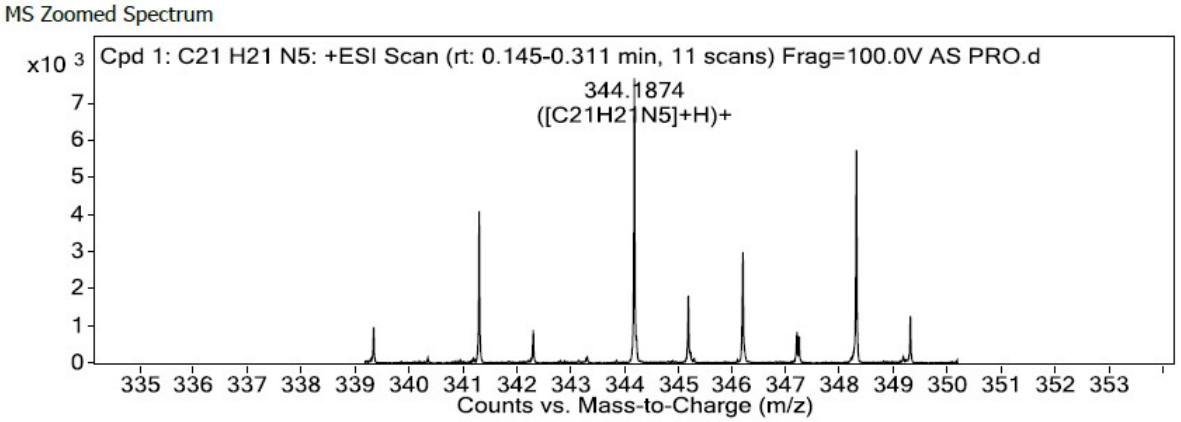
^{1}H NMR spectrum of compound **1a** in DMSO-d_6.



^{13}C NMR spectrum of compound **1a** in DMS

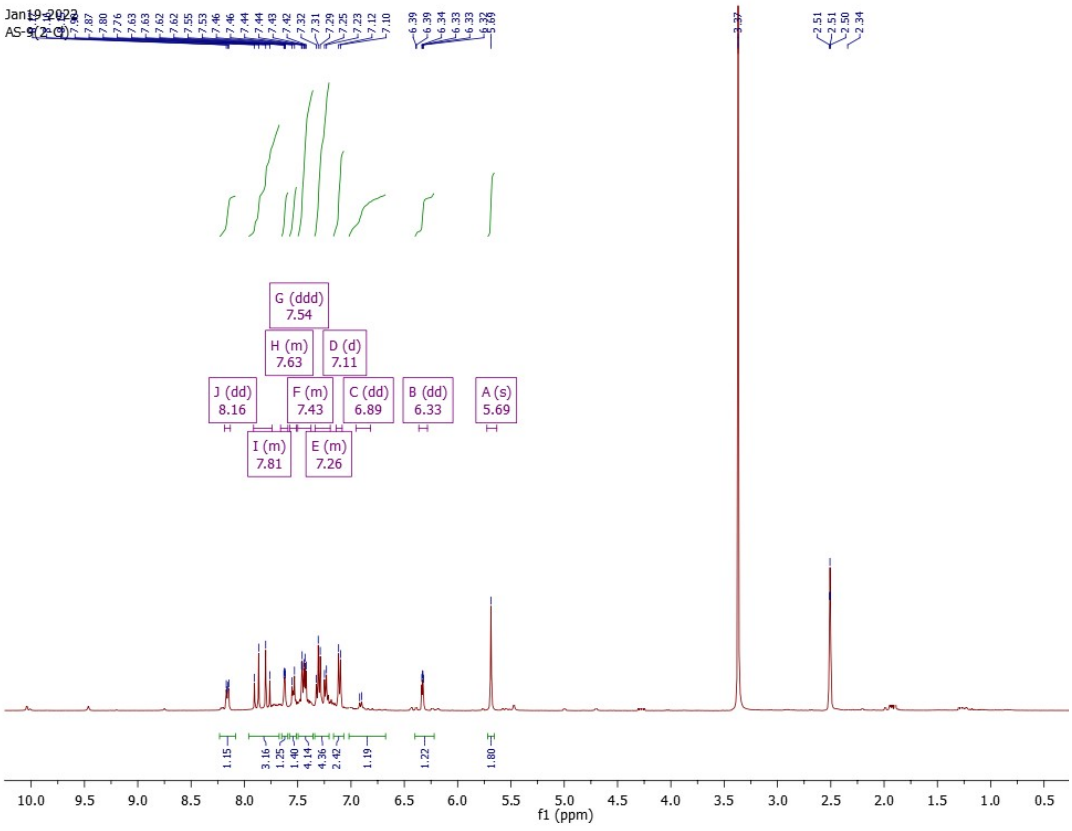


O-d_6

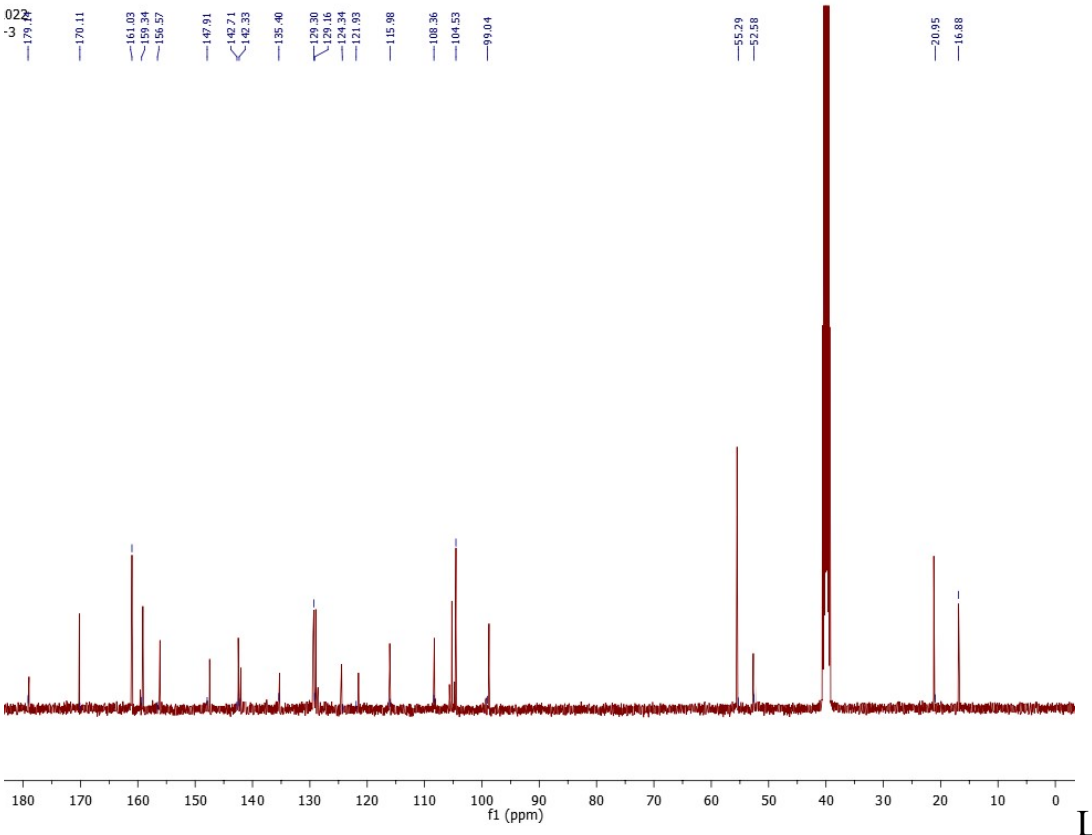


HRMS spectrum of compound **1a**.

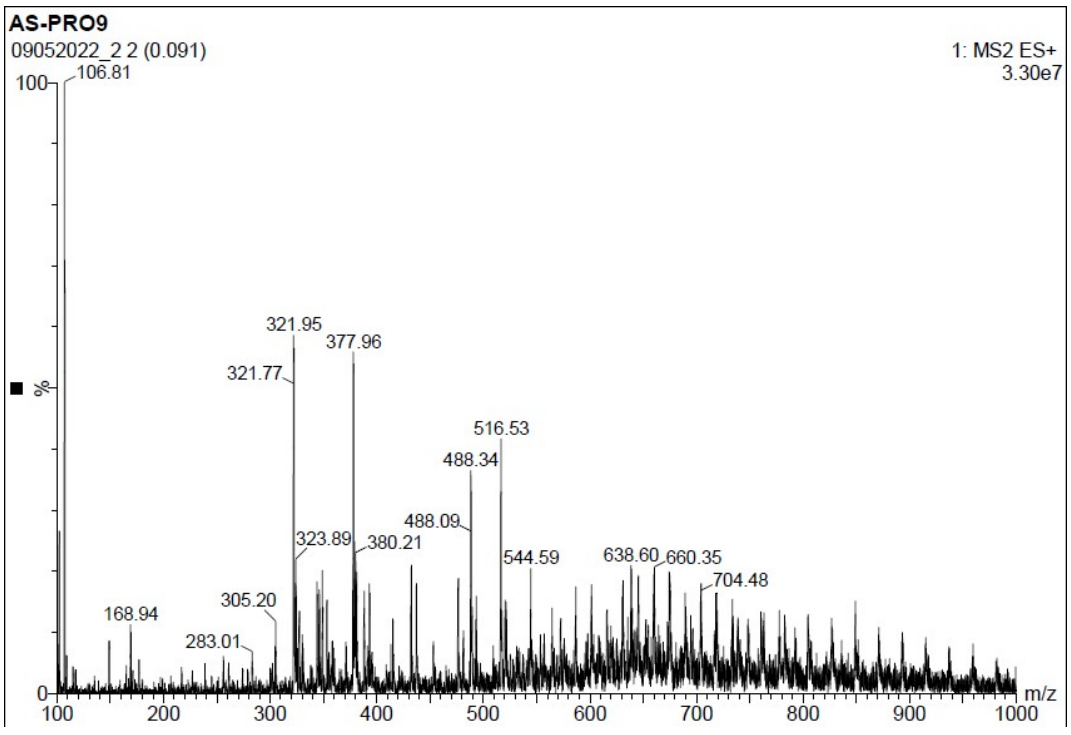
^{1}H NMR spectrum of compound **1b** in DMSO-d_6.



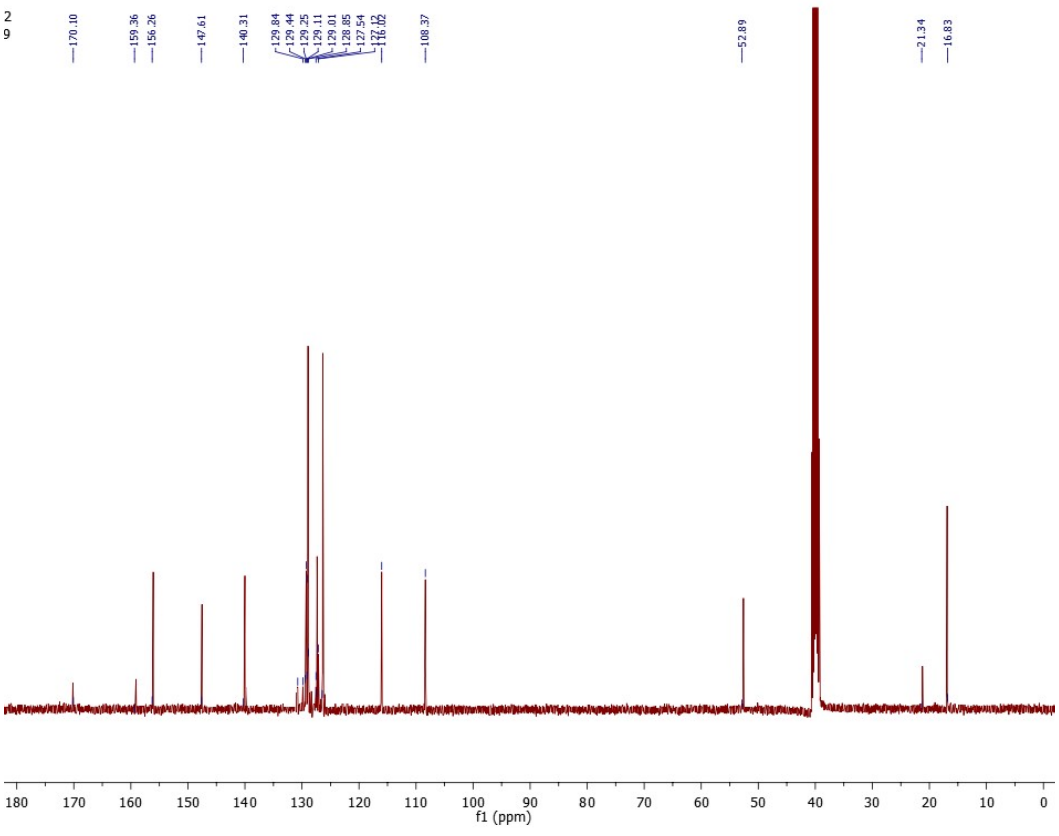
^{13}C NMR spectrum of compound **1b** in DMSO-d_6



LCMS/MS spectrum of compound **1b**.



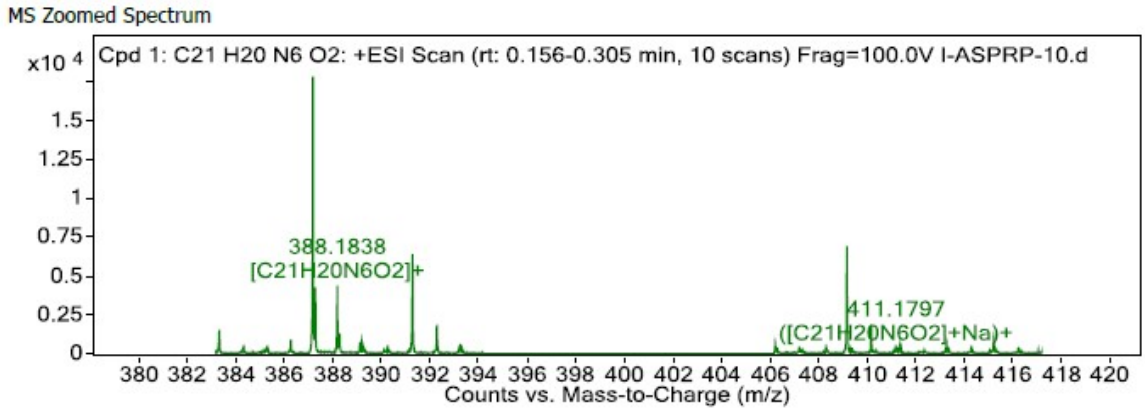
^{1}H NMR spectrum of compound **1c** in DMSO-d_6.



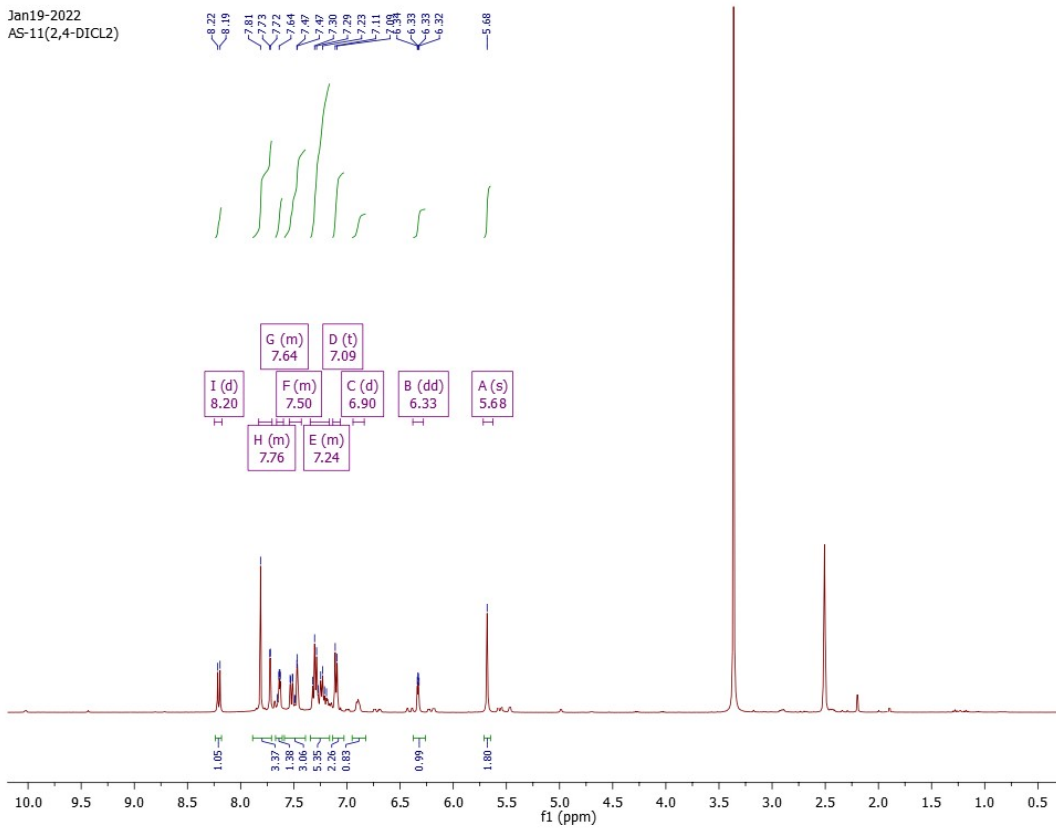
^{13}C NMR spectrum of compound **1c** in DMSO-d_6

HRMS spectru

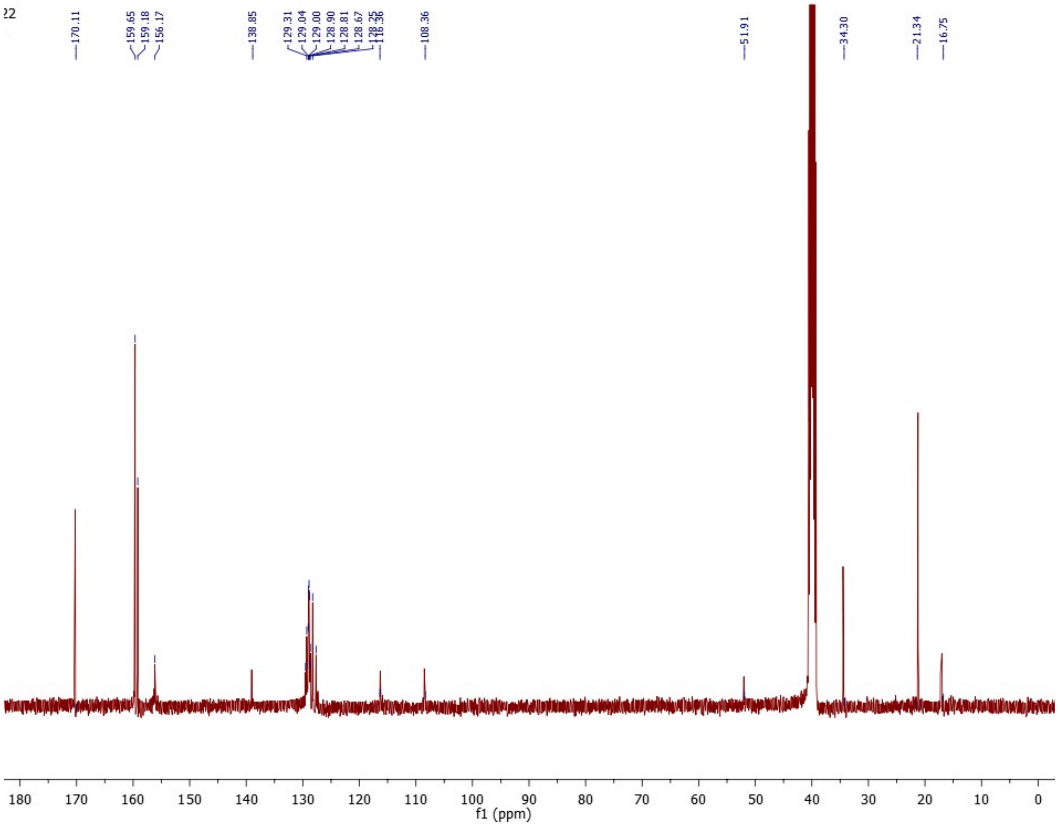
m of compound **1c**.

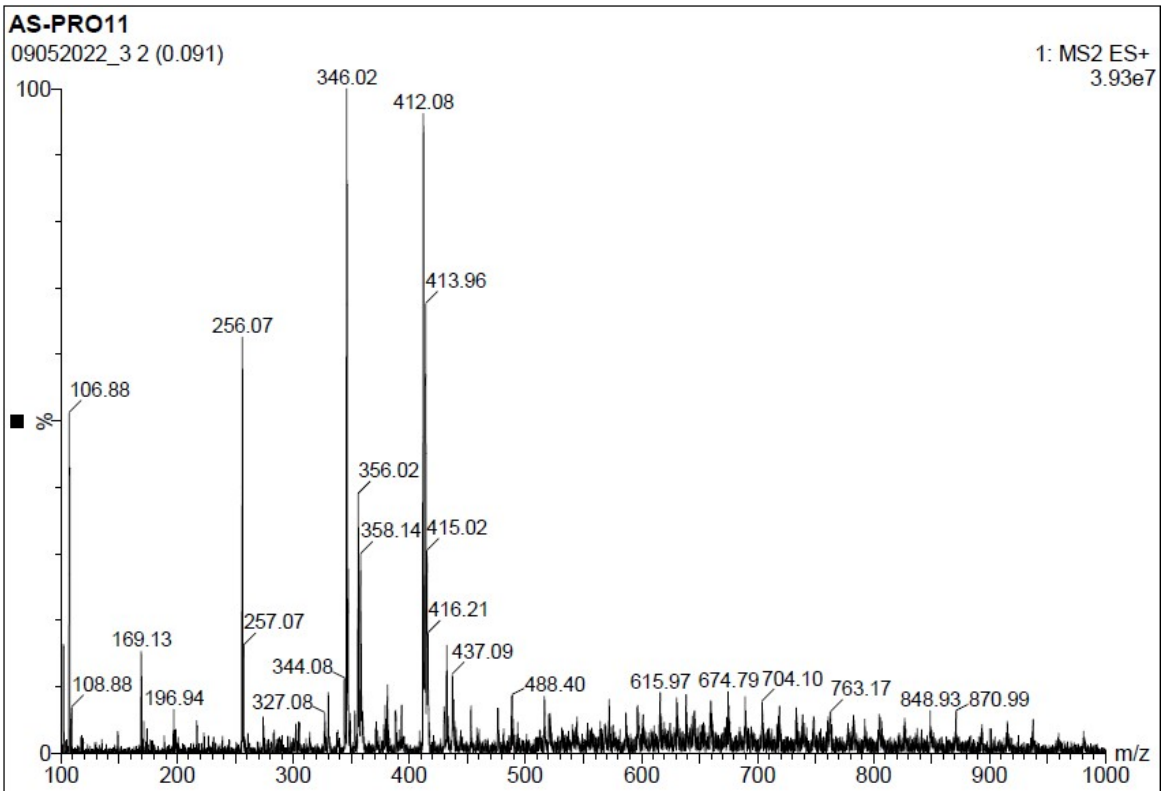


^{1}H NMR spectrum of compound **1d** in DMSO-d_6.



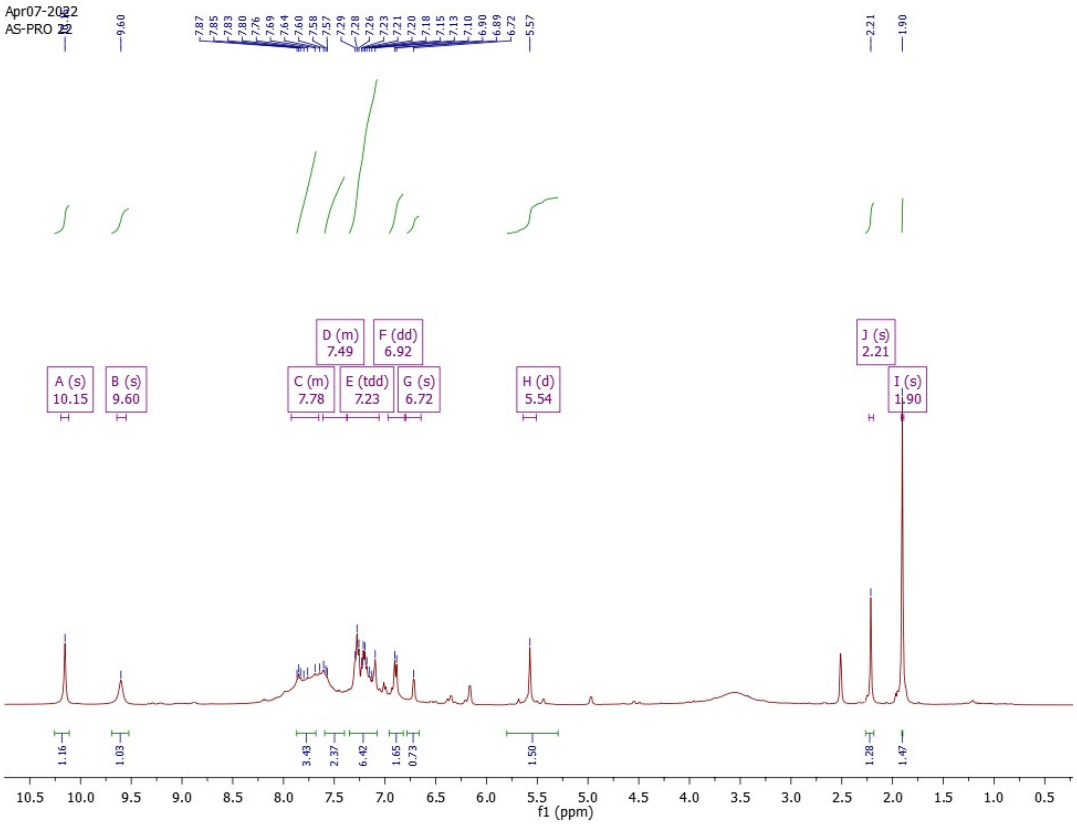
^{13}C NMR spectrum of compound **1d** in DMSO-d_6

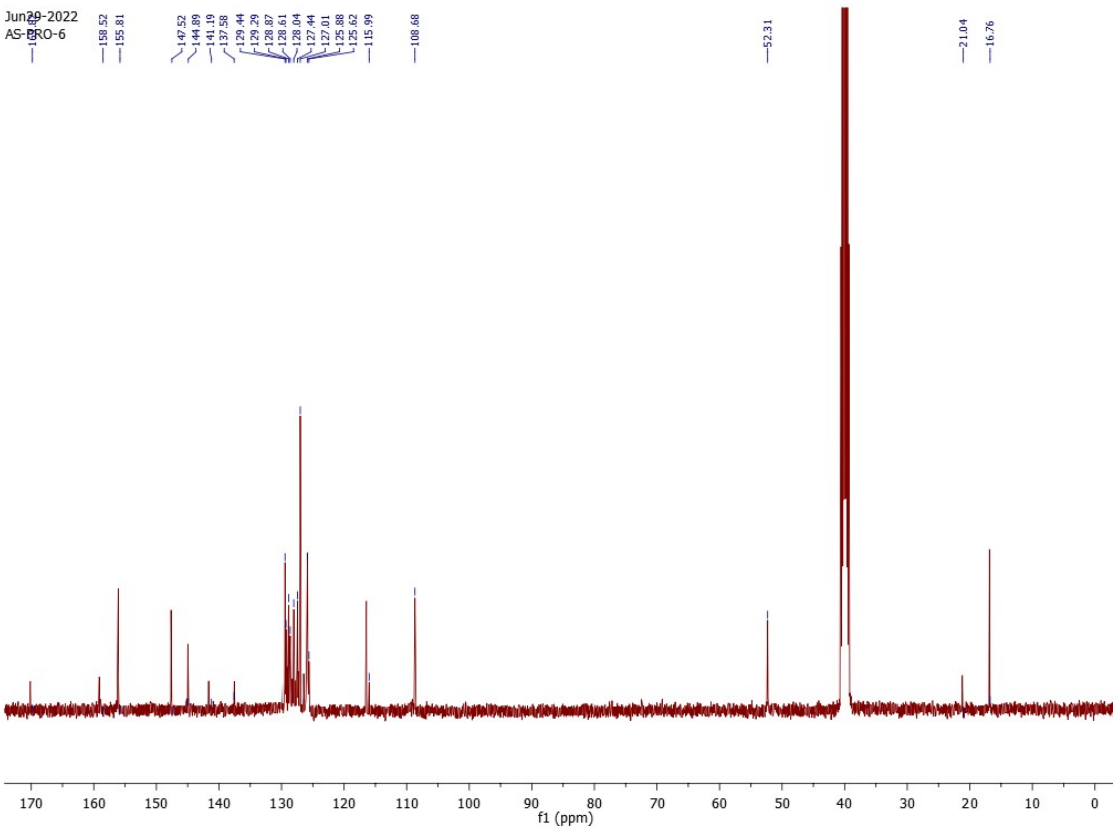




LCMS/MS spectrum of compound **1d**.

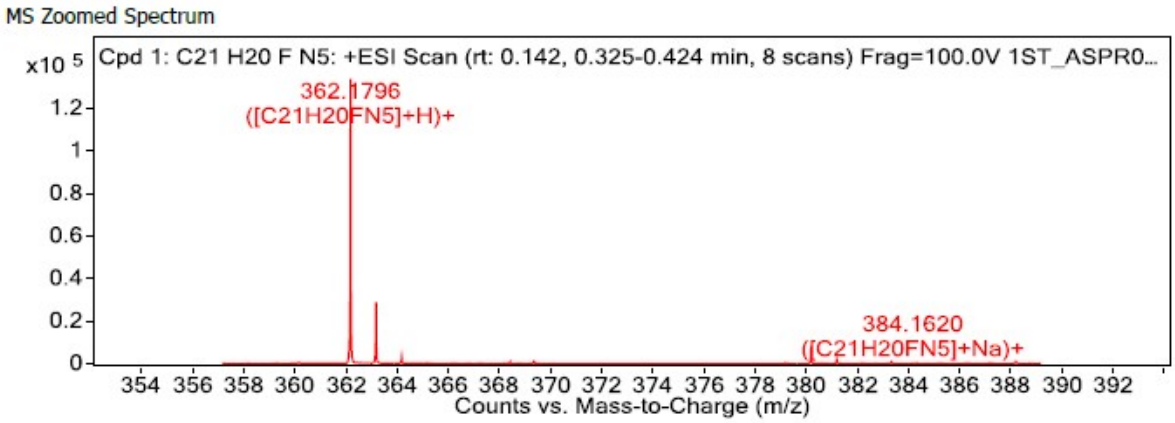
^{1}H NMR spectrum of compound **1e** in DMSO-d_6.



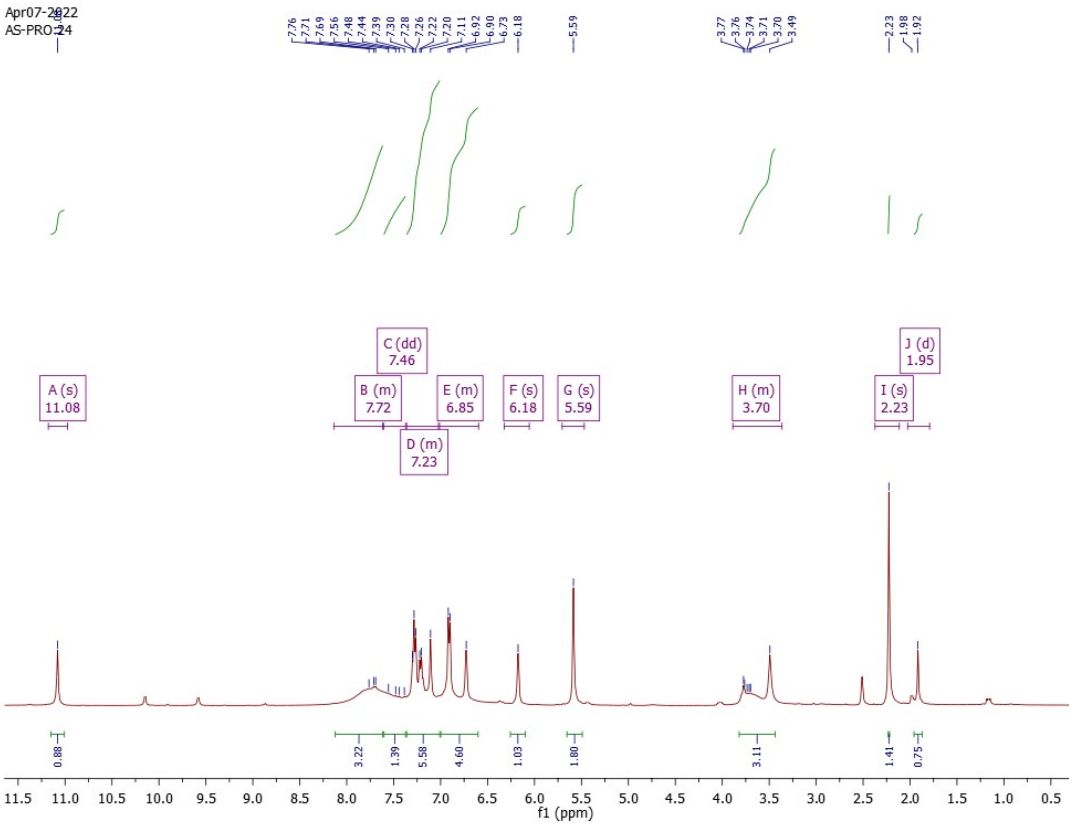


^{13}C NMR spectrum of compound **1e** in DMSO-d_6

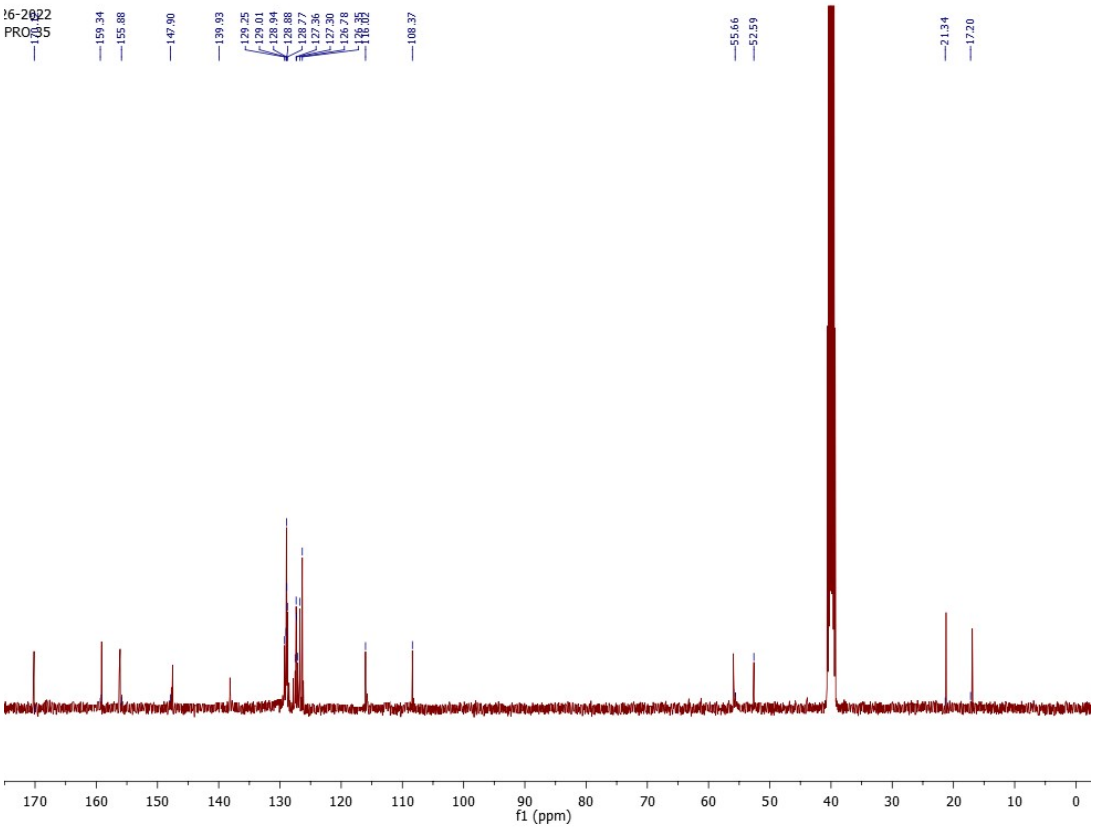
HRMS spectrum of compound **1e**.



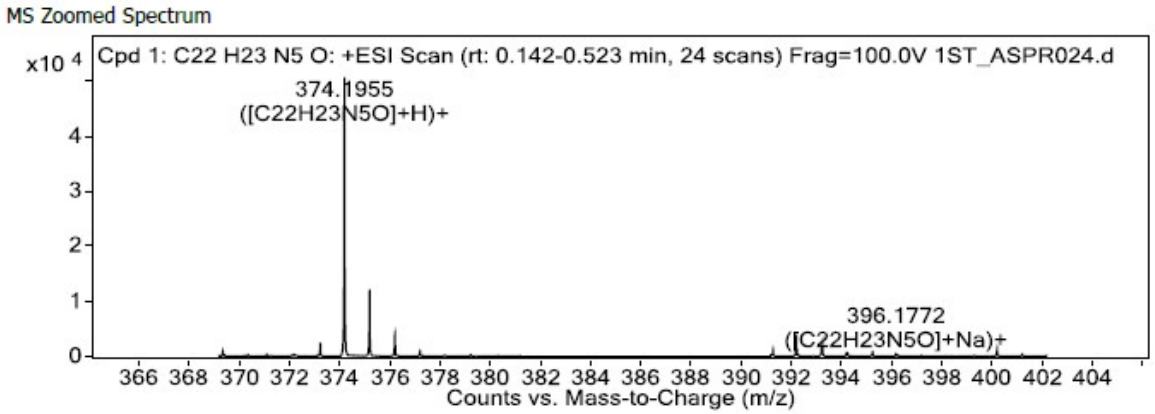
^{1}H NMR spectrum of compound **1f** in DMSO-d_6.



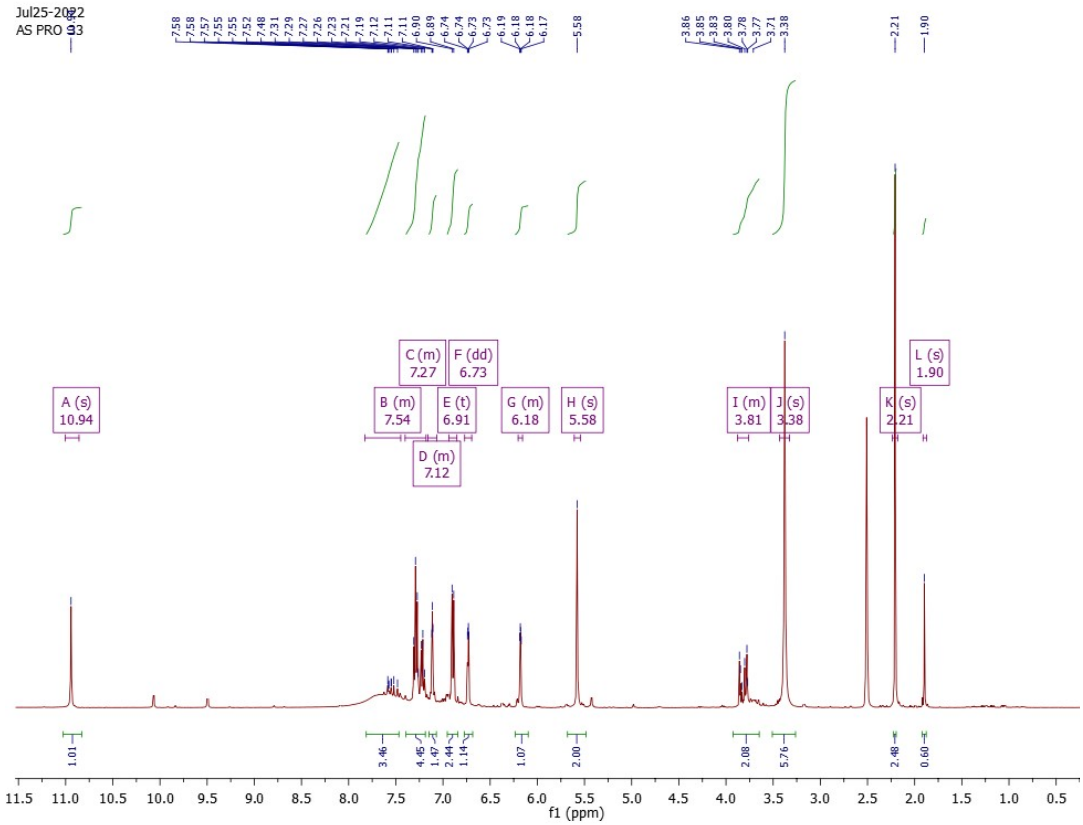
^{13}C NMR spectrum of compound **1f** in DMSO-d_6

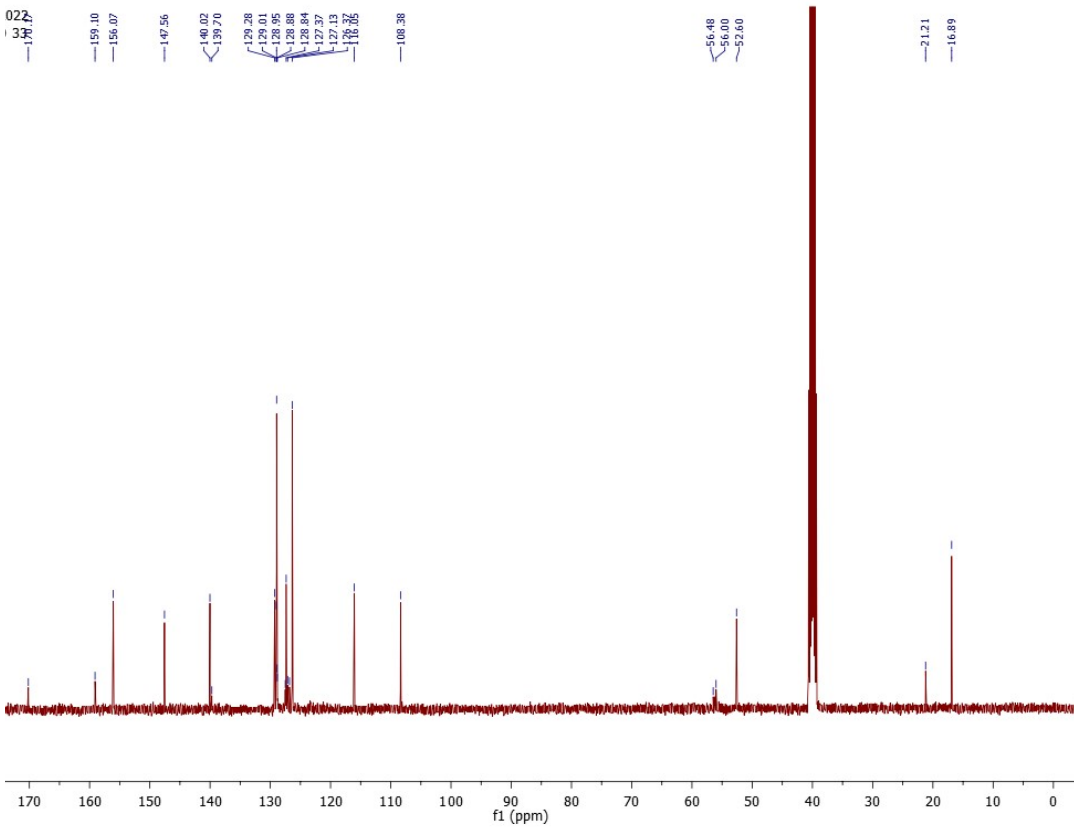


HRMS spectrum of compound **1f**.

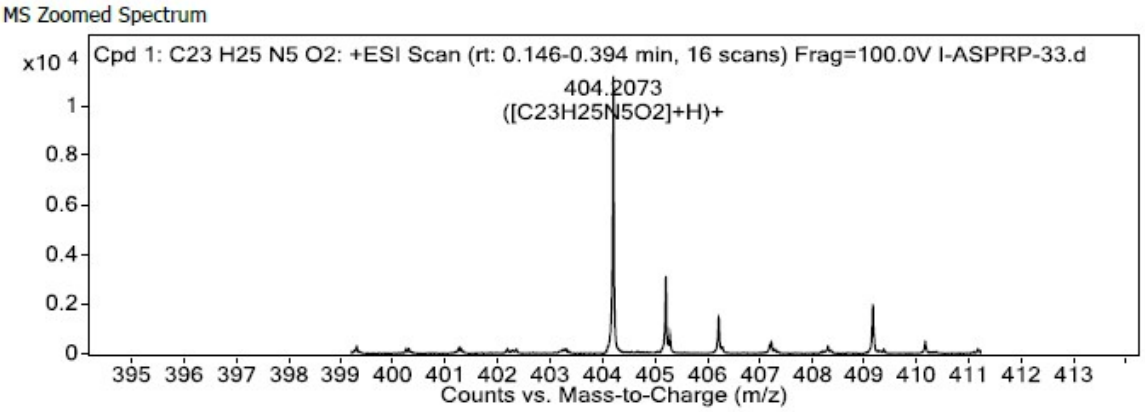


^{1}H NMR spectrum of compound **1g** in DMSO-d_6.



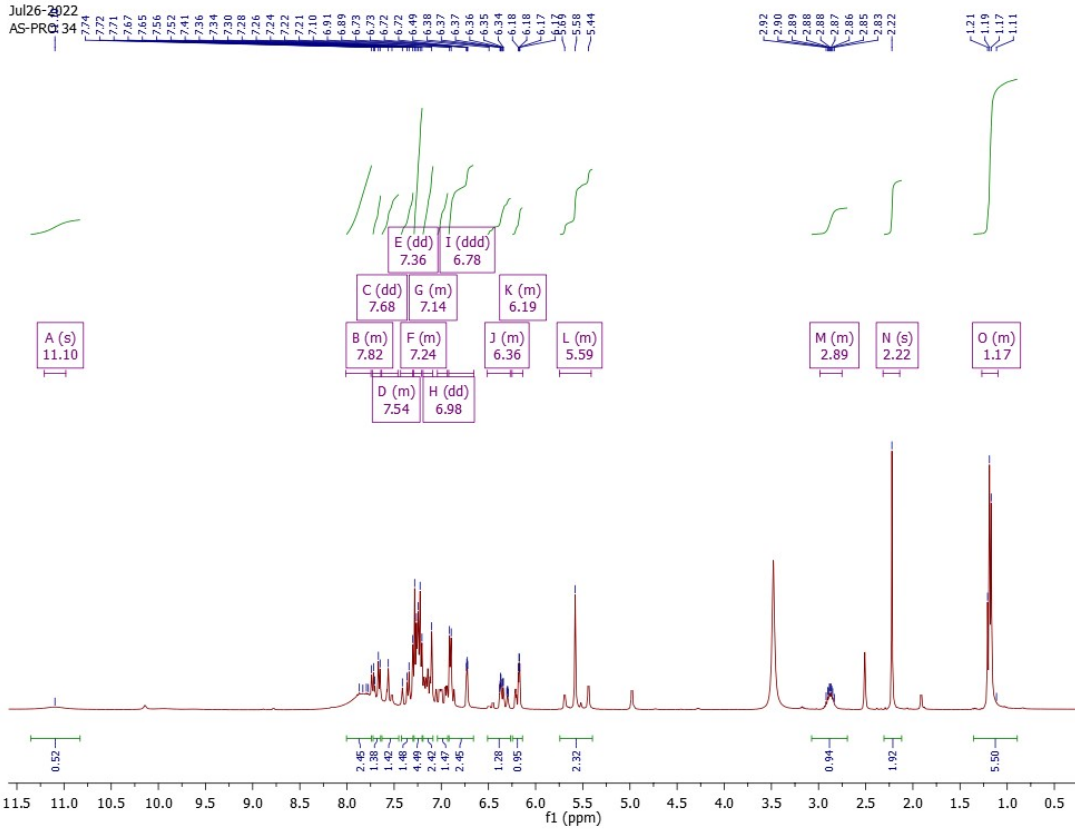


^{13}C NMR spectrum of compound **1g** in DMSO-d_6.

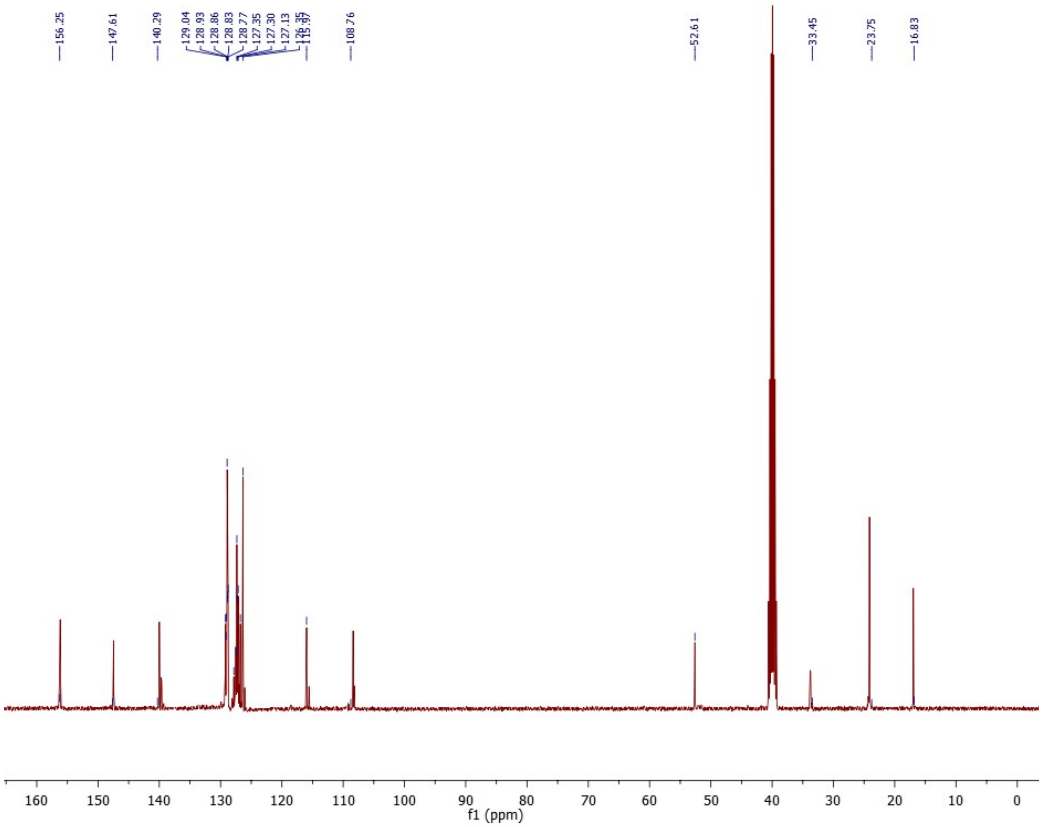


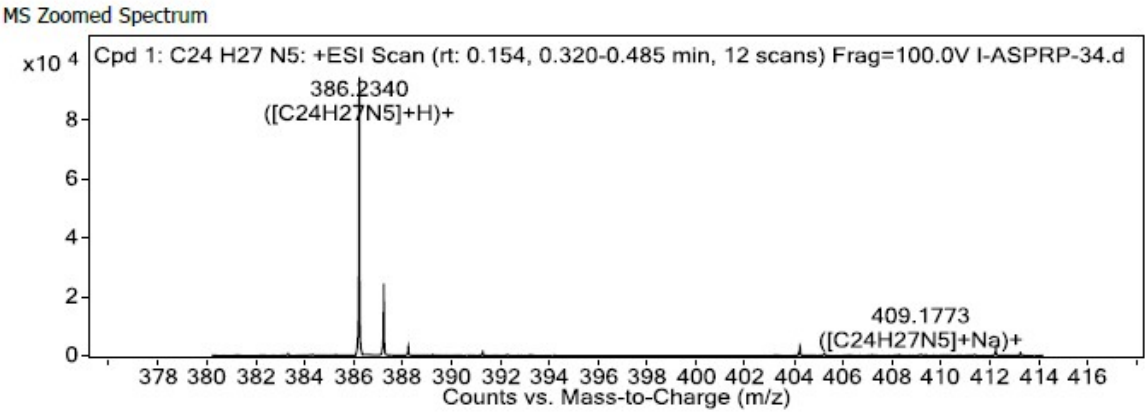
HRMS spectrum of compound **1g**.

^{1}H NMR spectrum of compound **1h** in DMSO-d_6.



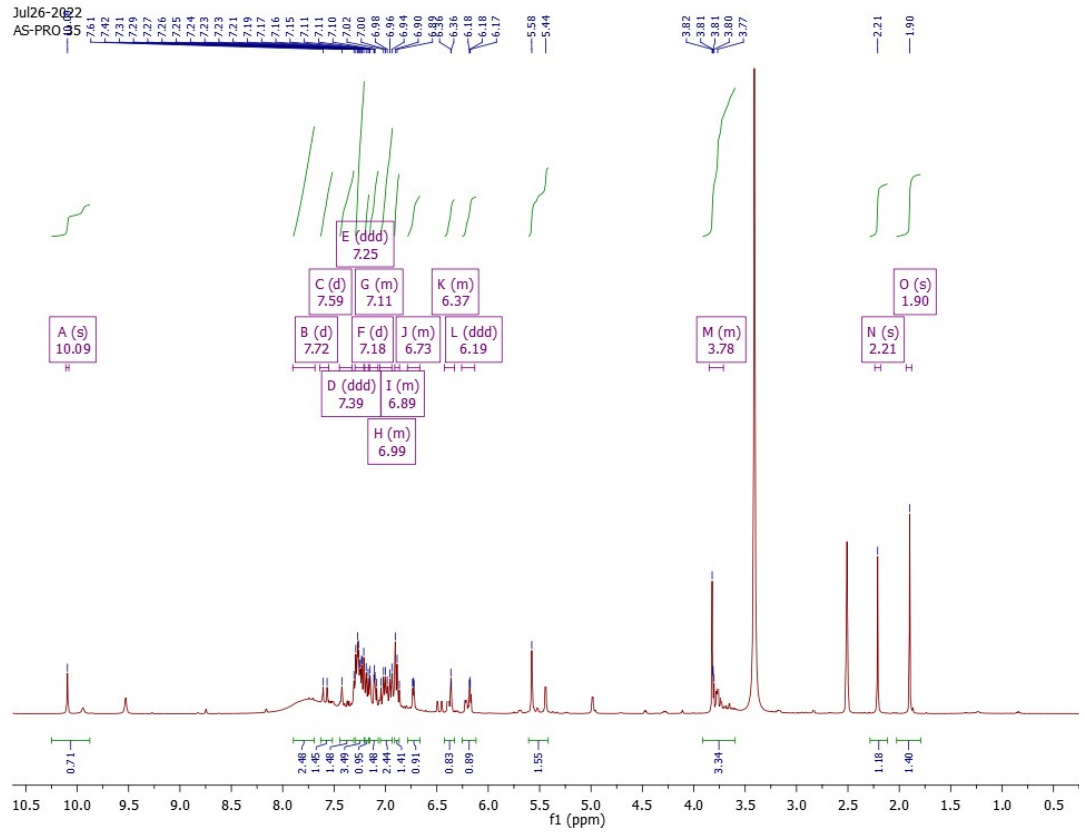
^{13}C NMR spectrum of compound **1h** in DMSO-d_6.

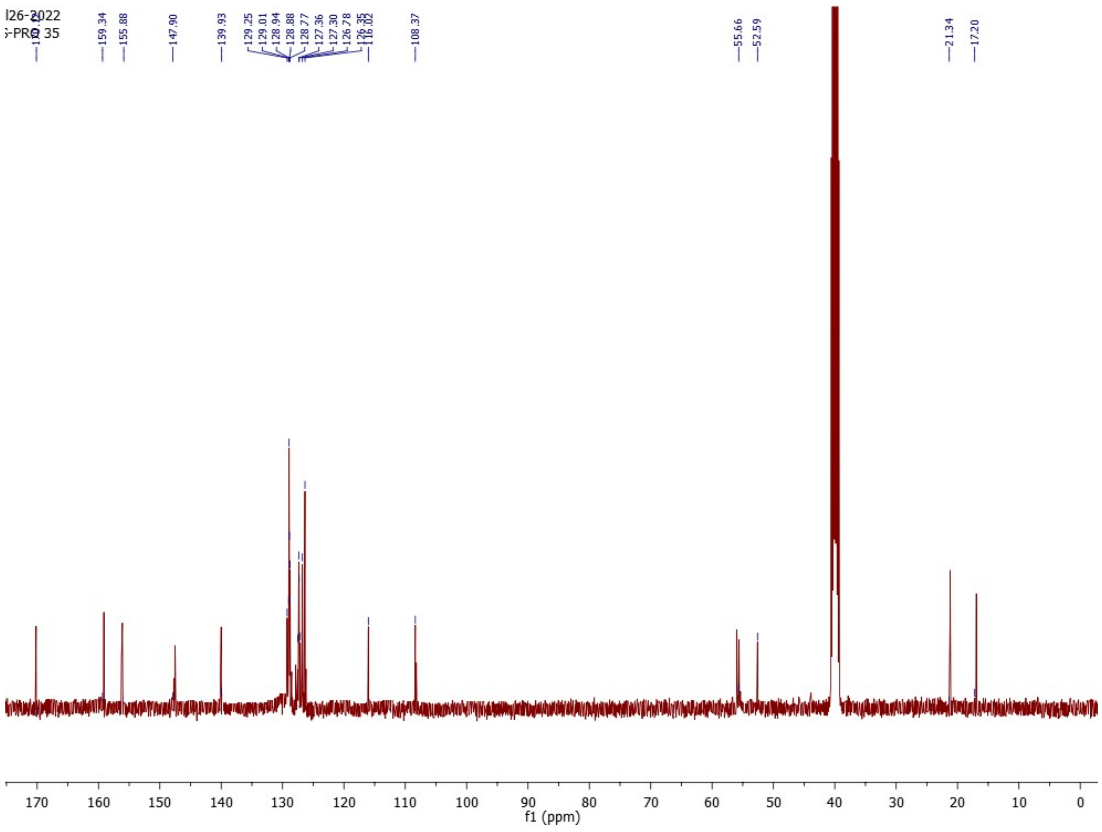




HRMS spectrum of compound **1h**.

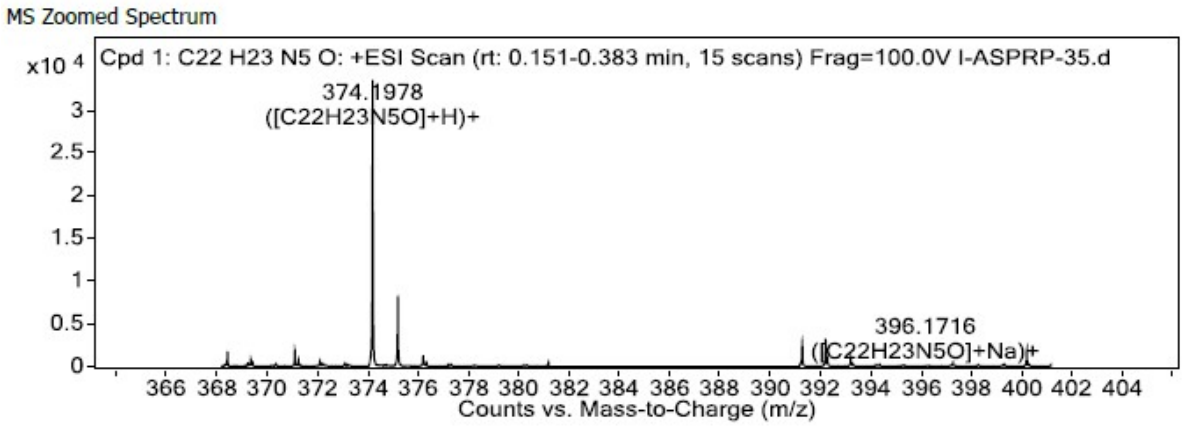
^{1}H NMR spectrum of compound **1i** in DMSO-d_6.



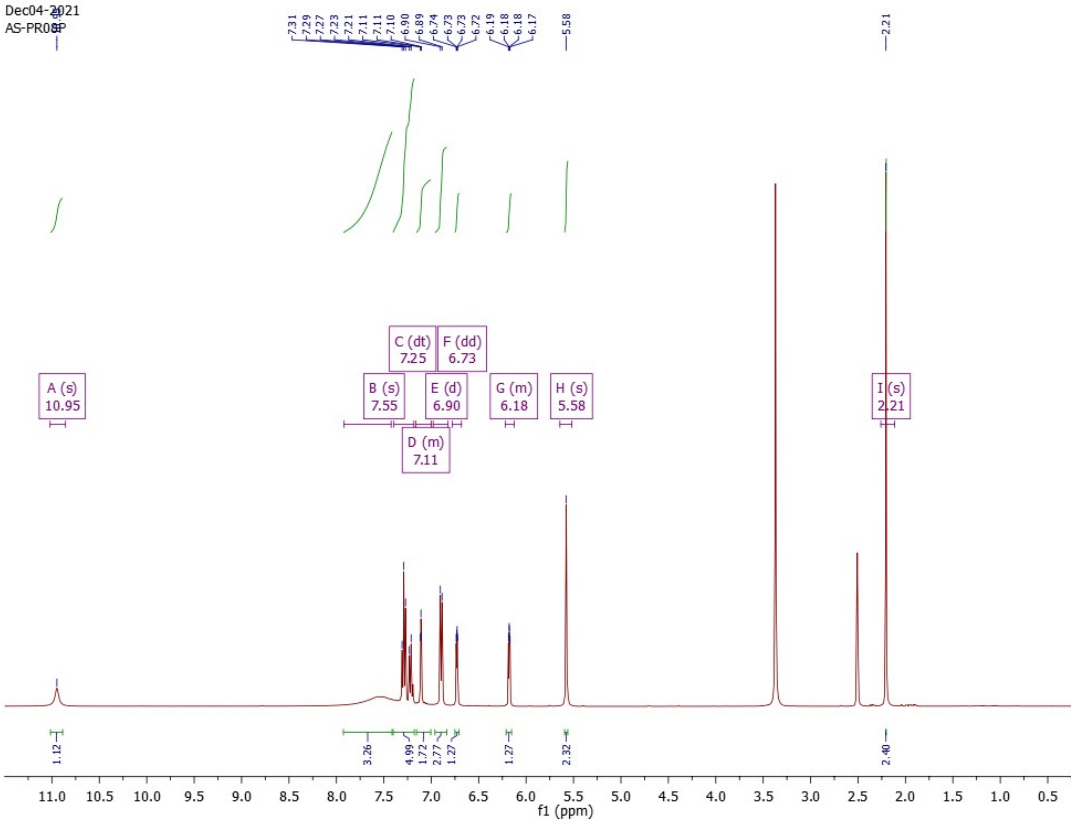


^{13}C NMR spectrum of compound **1i** in DMSO-d_6.

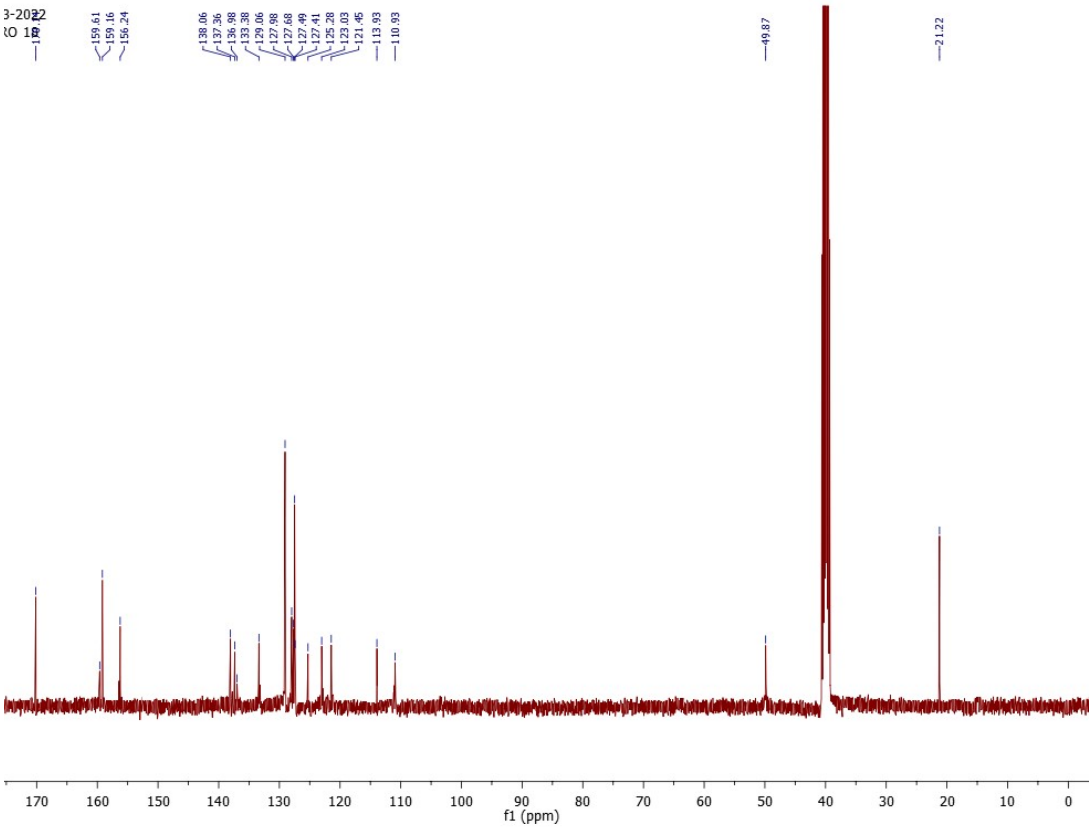
HRMS spectrum of compound **1i**.



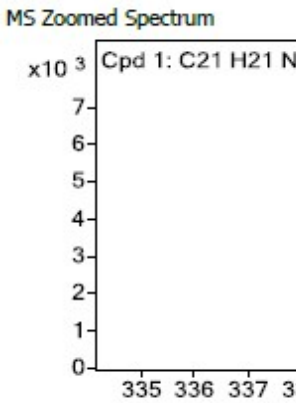
^{1}H NMR spectrum of compound **1j** in DMSO-d_6.

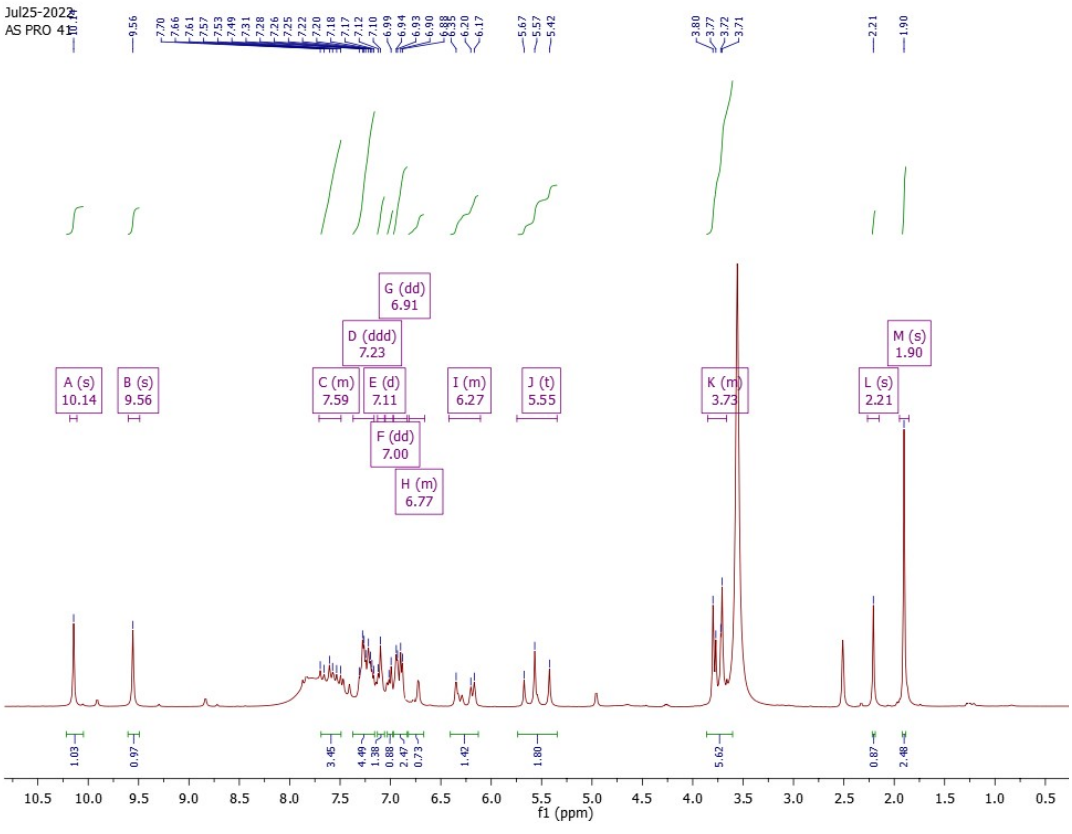


^{13}C NMR spectrum of compound **1j** in DMSO-d_6



HRMS spectrum of compound **1j**.

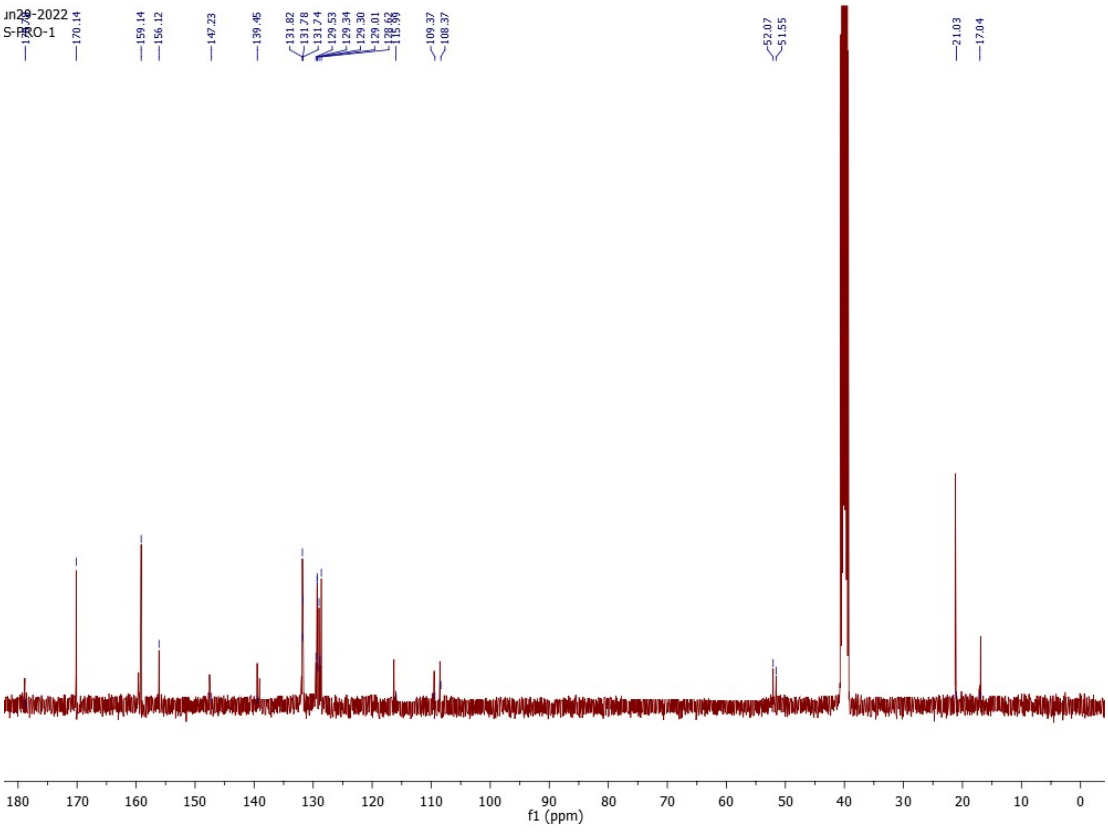


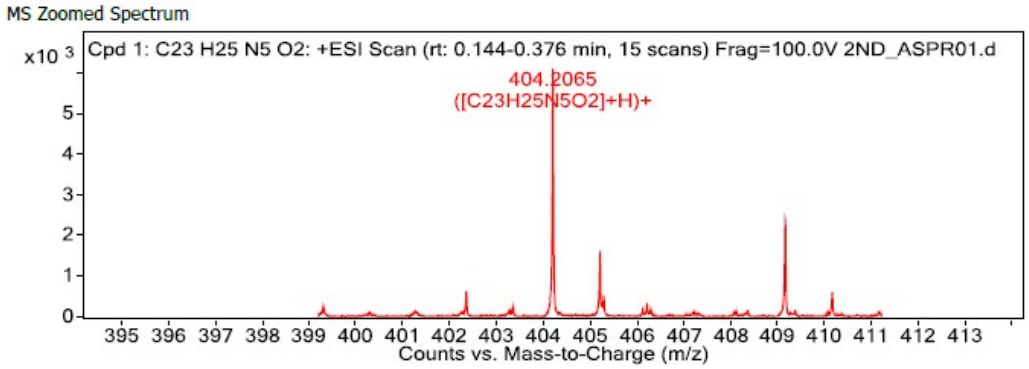


^{1}H NMR spectrum of

compound **2a** in DMSO-d_6.

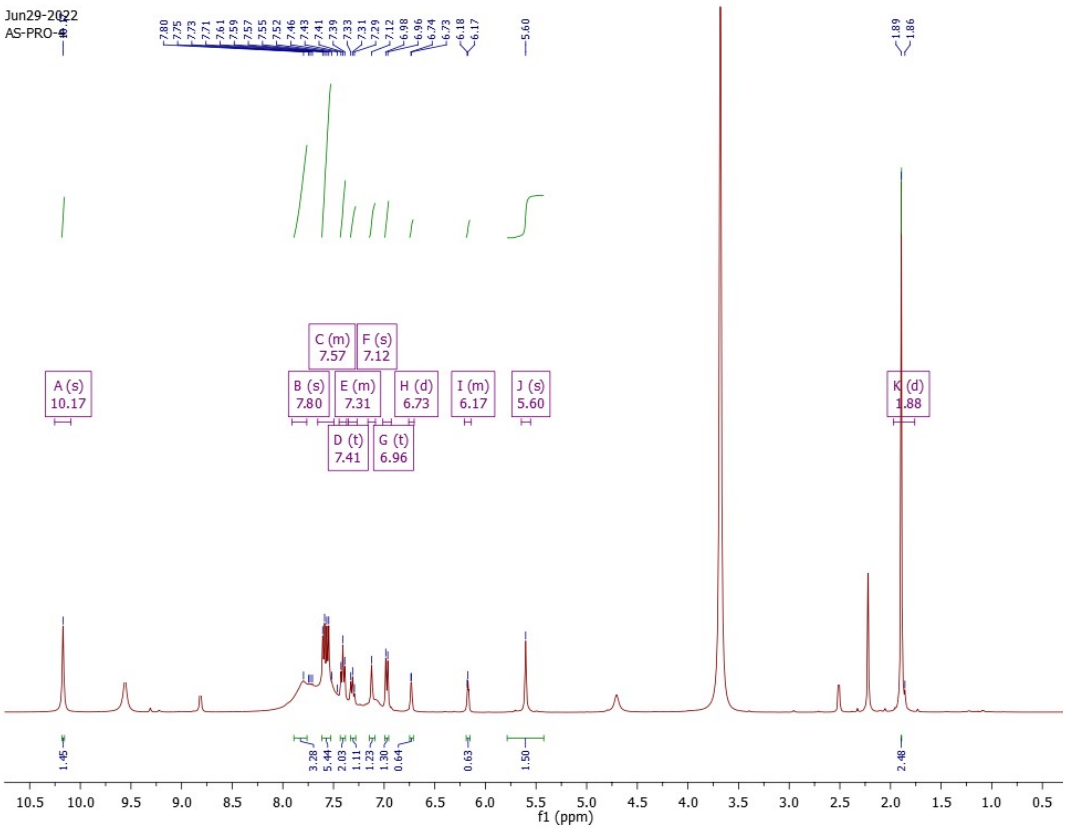
^{13}C NMR spectrum of compound **2a** in DMSO-d_6.

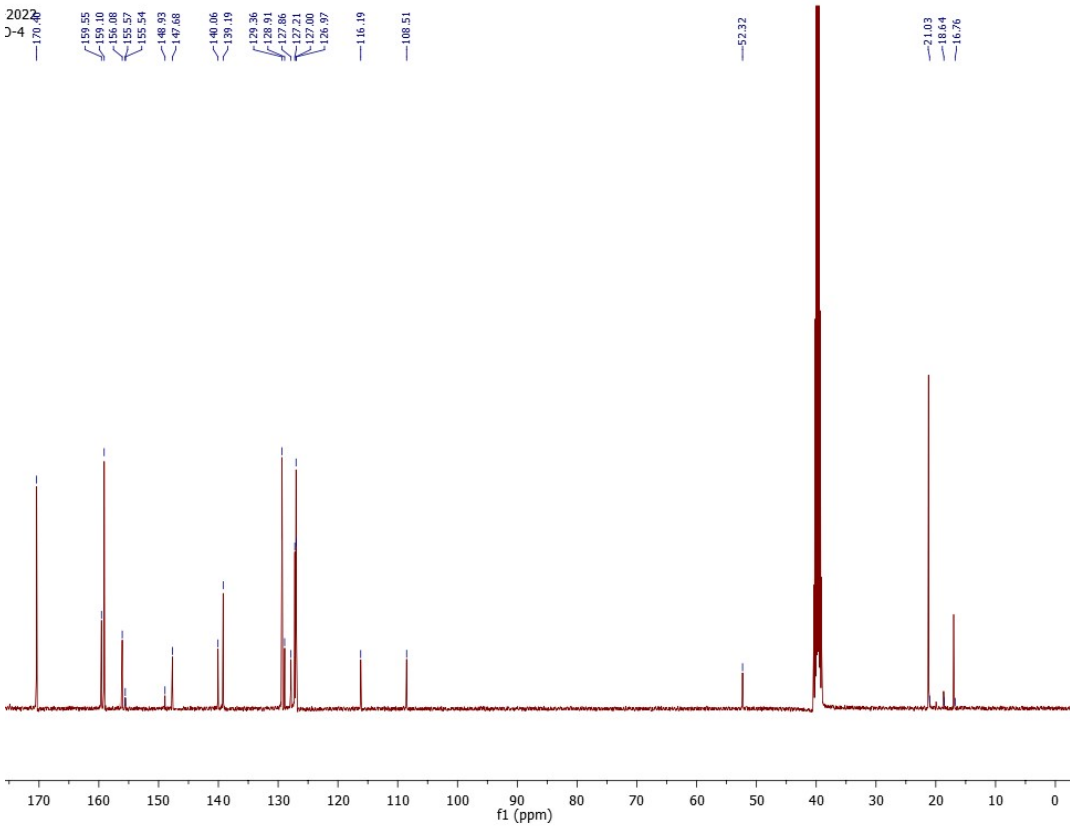




HRMS spectrum of compound **2a**.

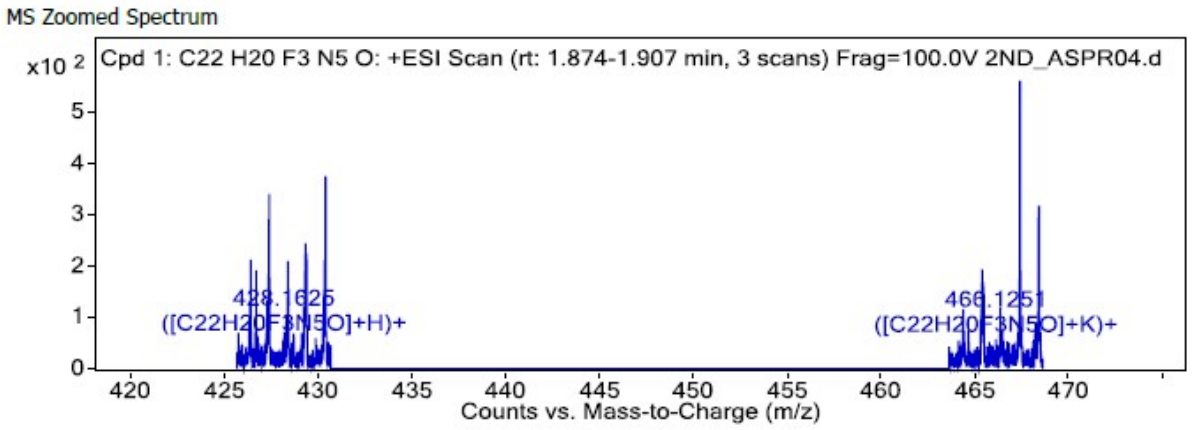
^{1}H NMR spectrum of compound **2b** in DMSO-d_6.



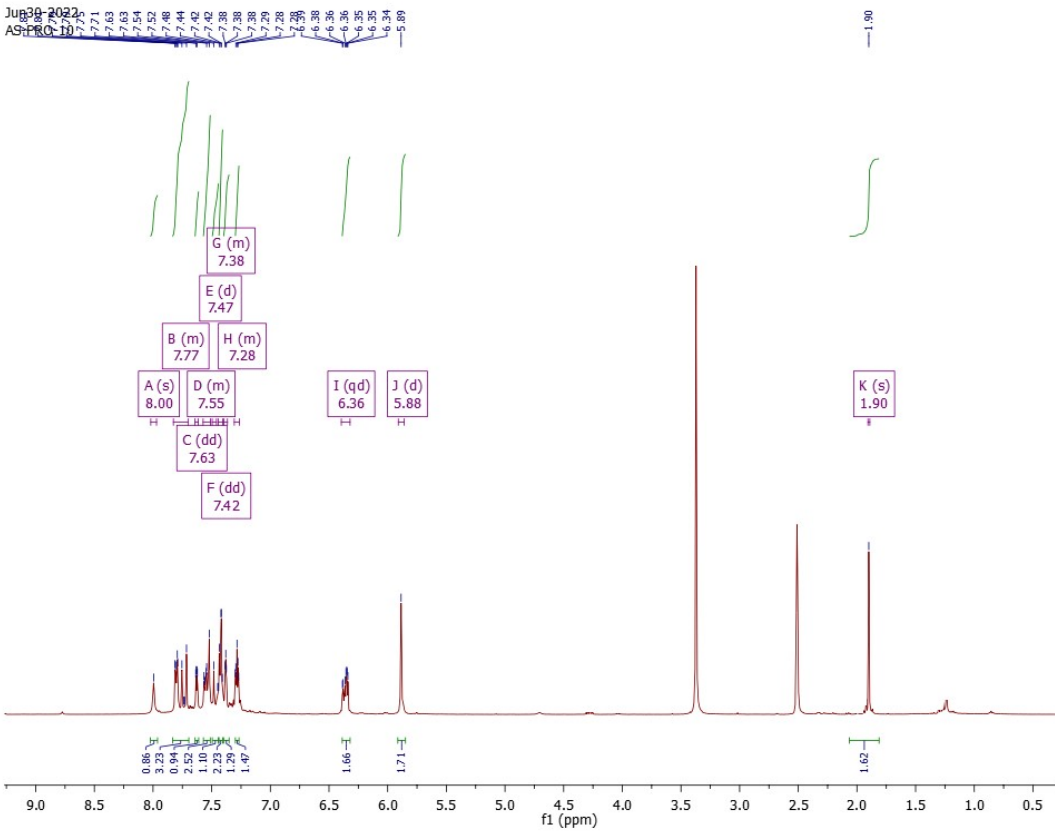


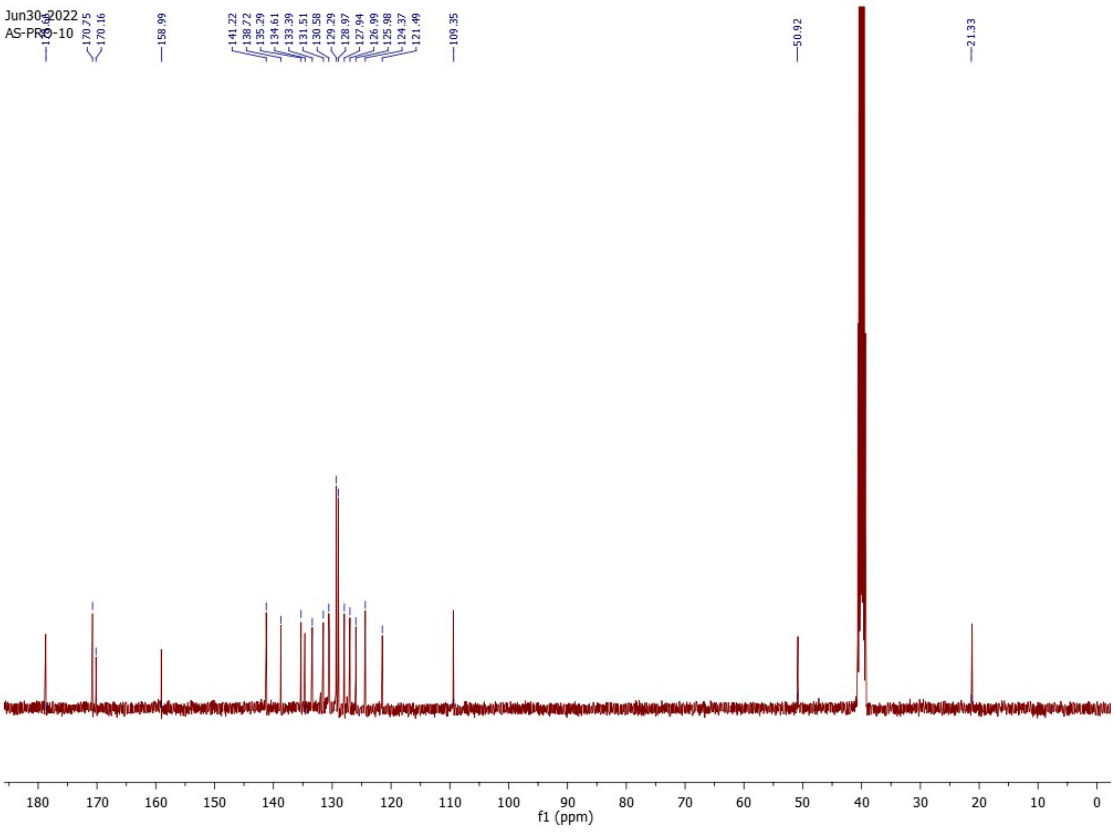
^{13}C NMR spectrum of compound **2b** in DMSO-d_6.

HRMS spectrum of compound **2b**.

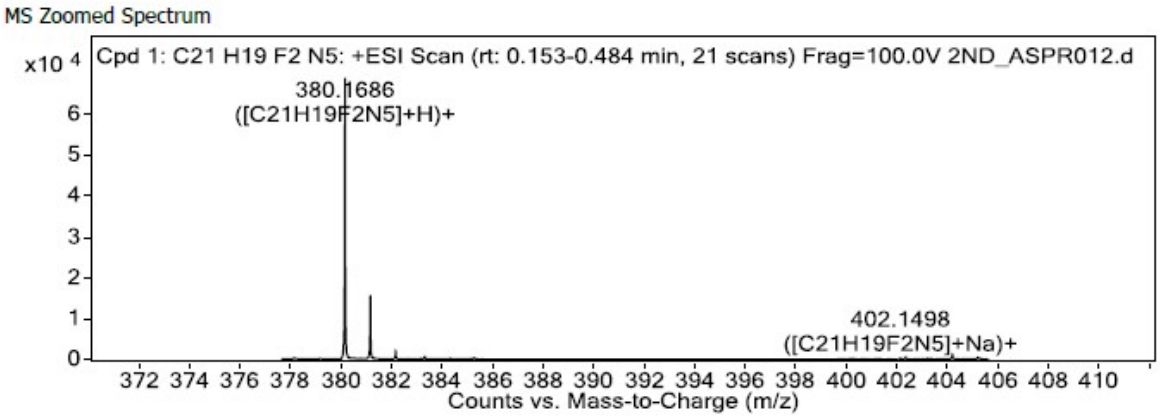


^{1}H NMR spectrum of compound **2d** in DMSO-d_6.



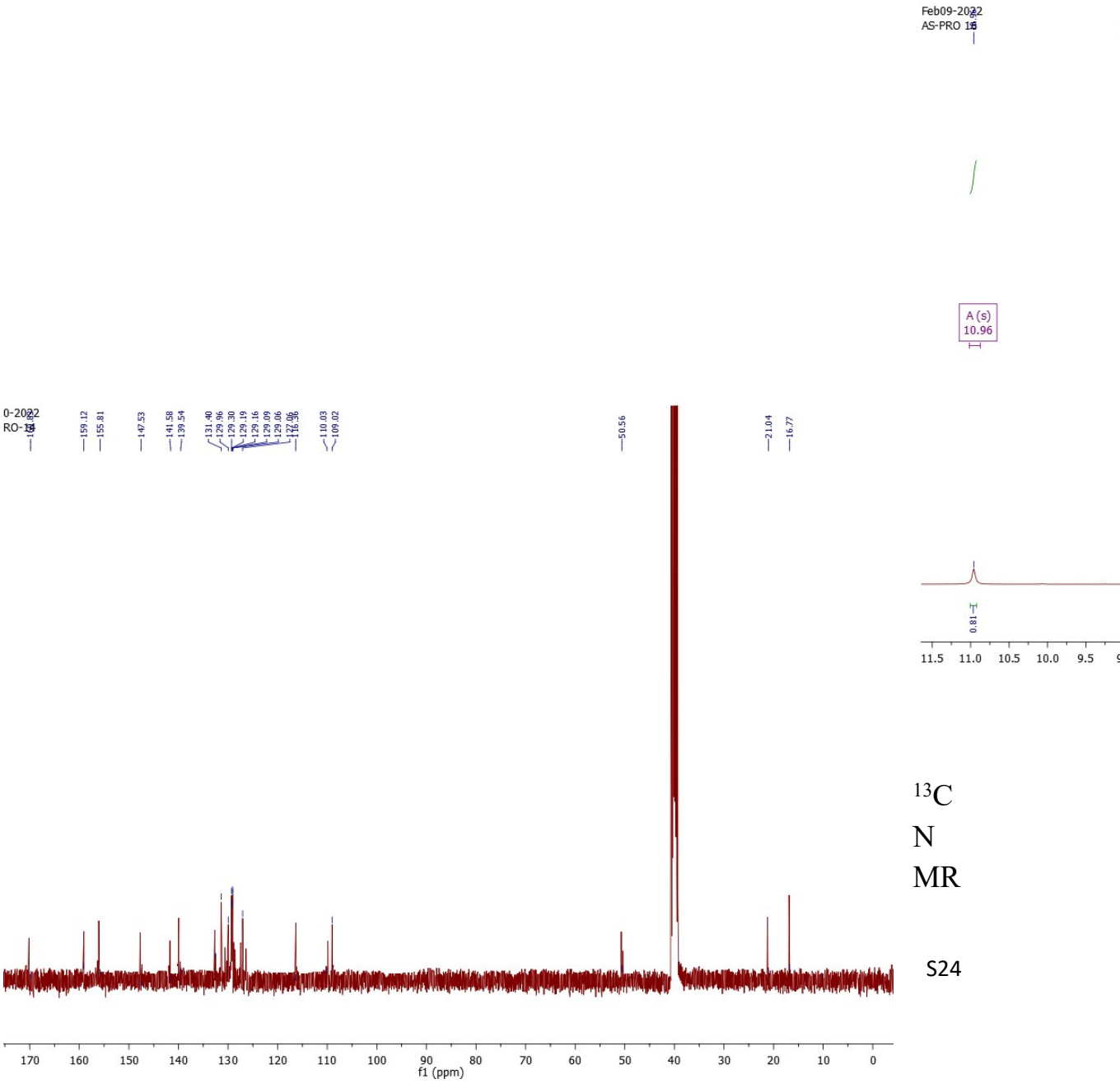


^{13}C NMR spectrum of compound **2d** in DMSO-d_6.



HRMS spectrum of compound **2d**.

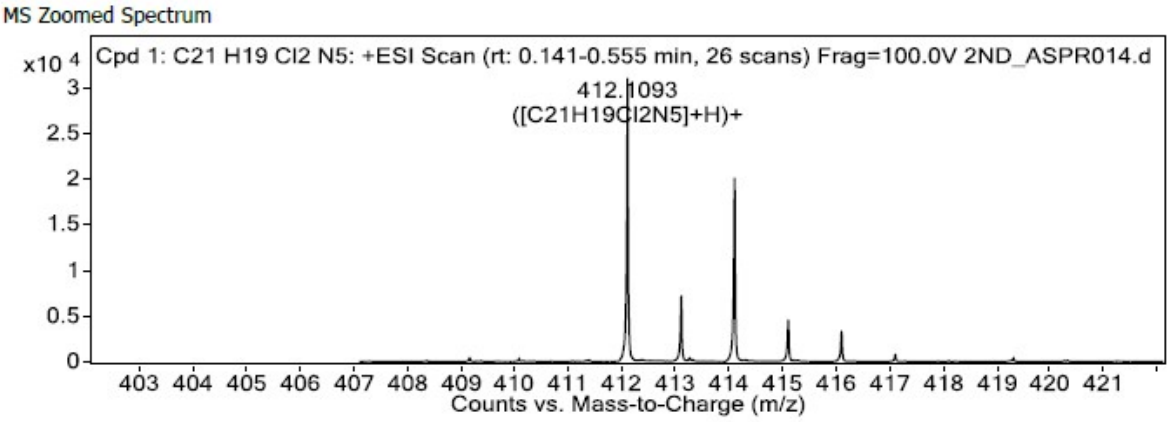
^{1}H NMR spectrum of compound **2e** in DMSO-d_6.



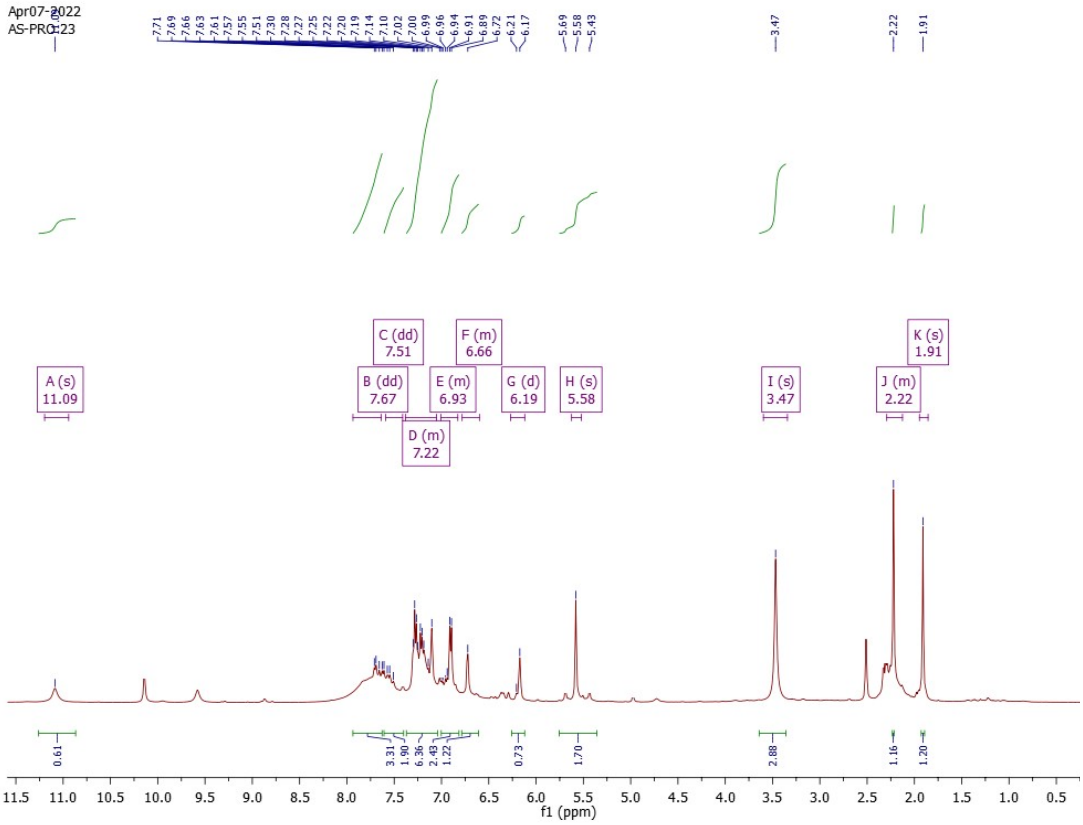
^{13}C NMR

spectrum of compound **2e** in DMSO-d_6.

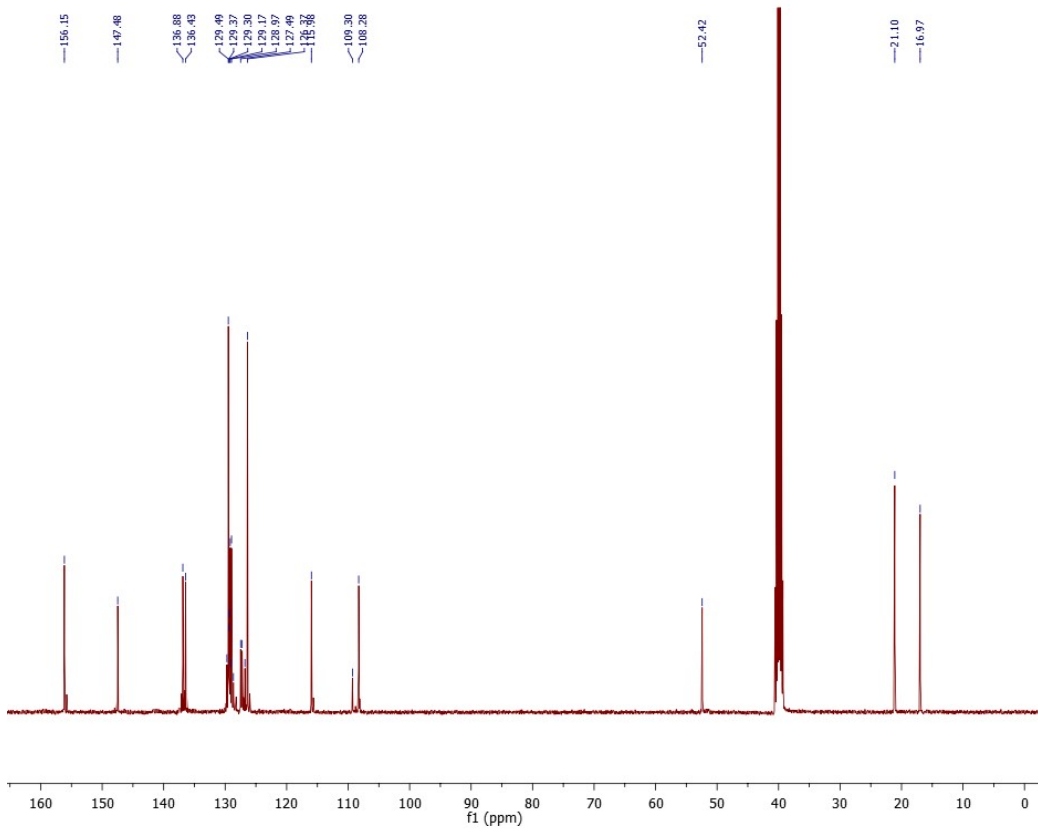
HRMS spectrum of compound **2e**.



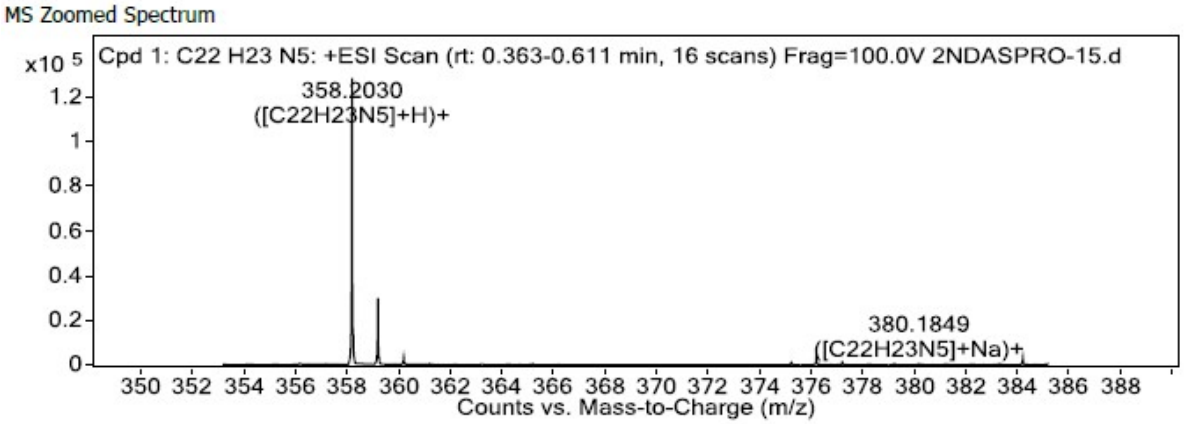
^{1}H NMR spectrum of compound **2f** in DMSO-d_6.



^{13}C

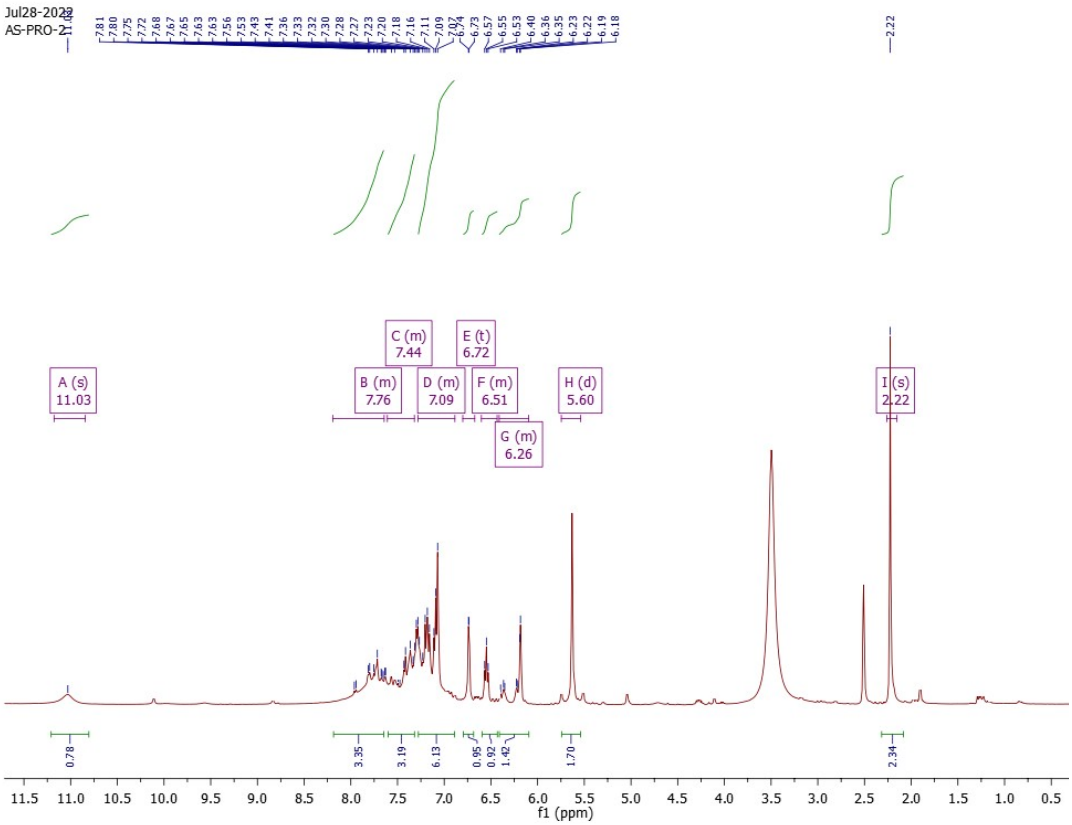


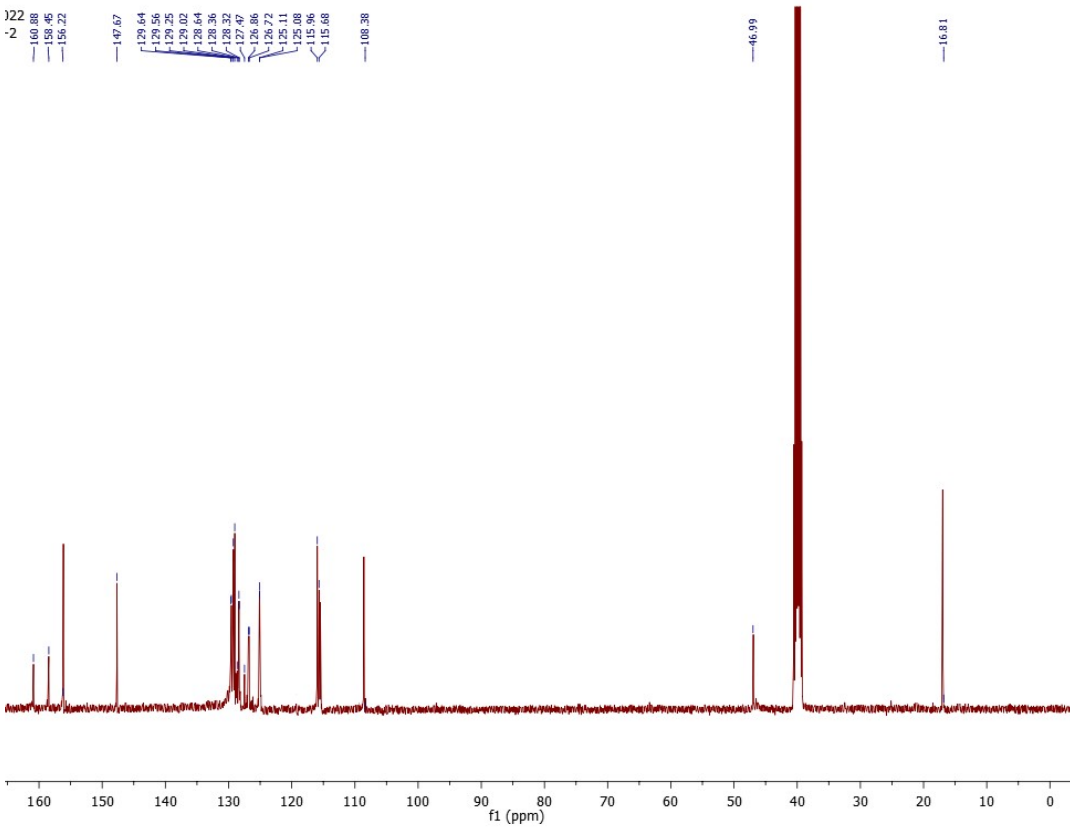
NMR spectrum of compound **2f** in DMSO-d_6.



HRMS spectrum of compound **2f**.

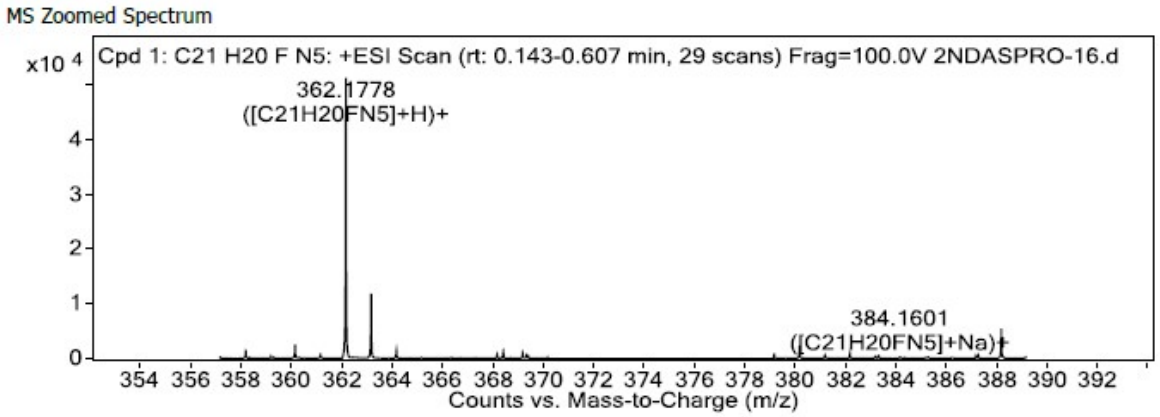
^1H NMR spectrum of compound **2g** in DMSO-d_6.



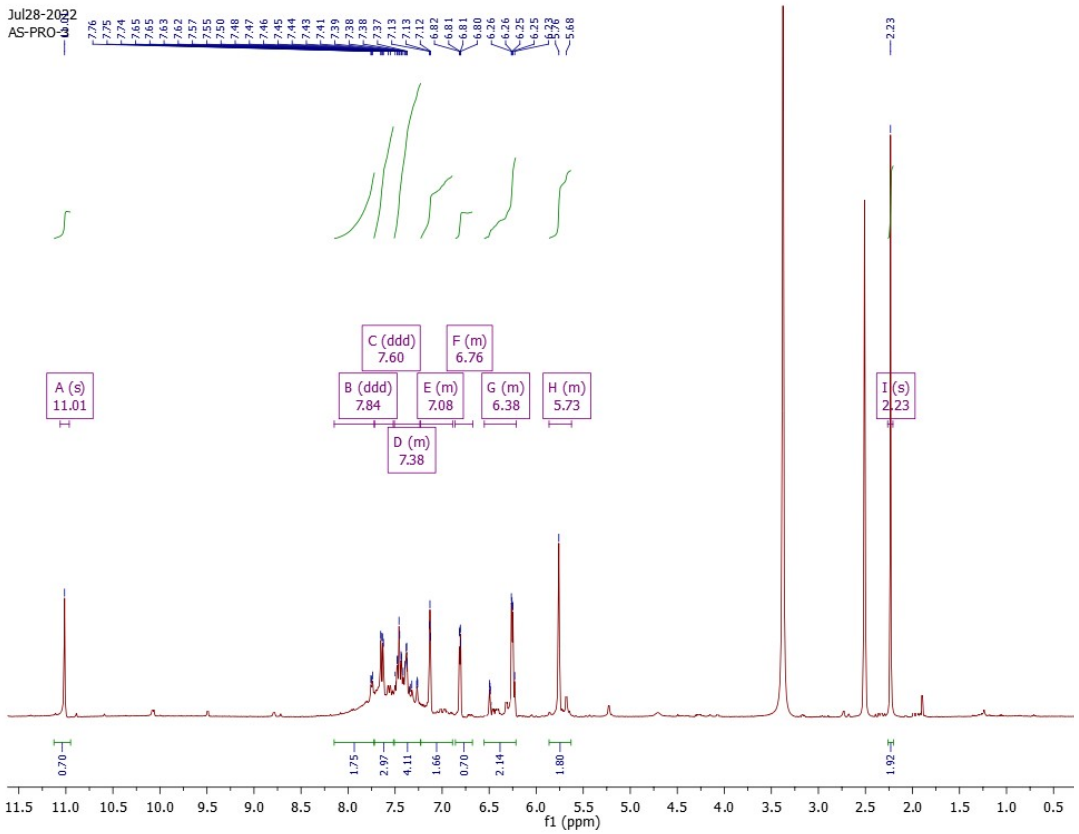


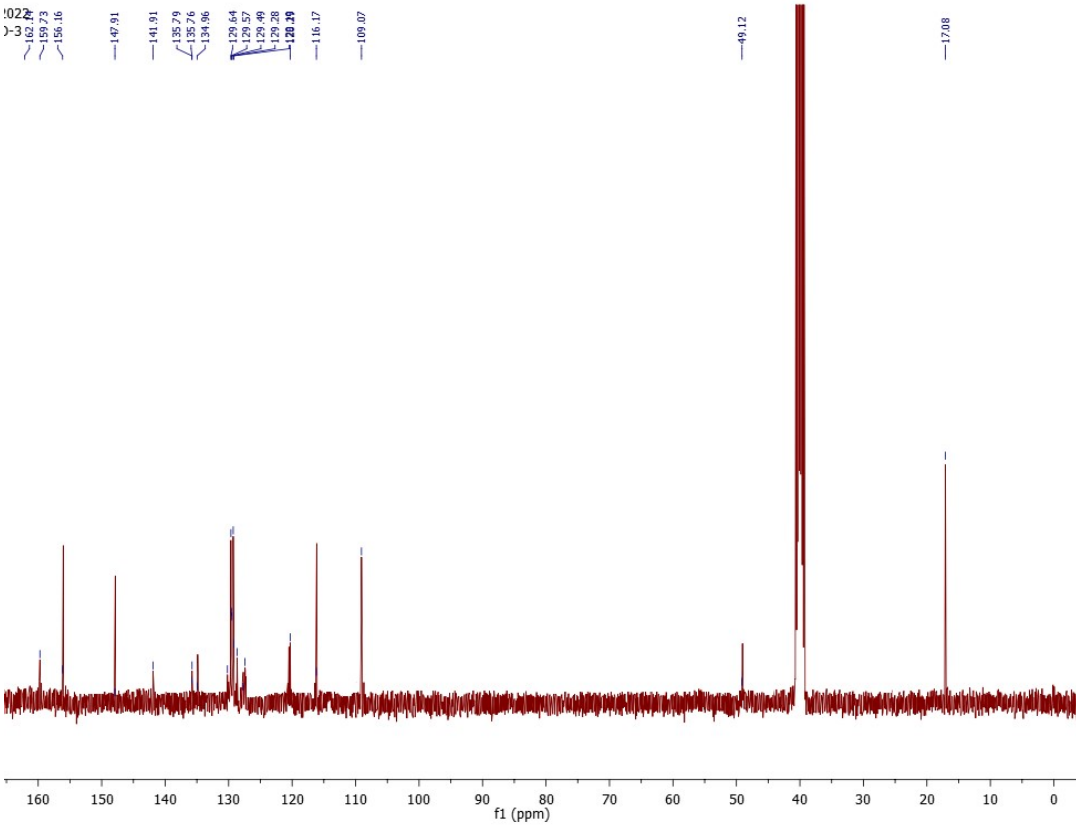
^{13}C NMR spectrum of compound **2g** in DMSO-d_6.

HRMS spectrum of compound **2g**.

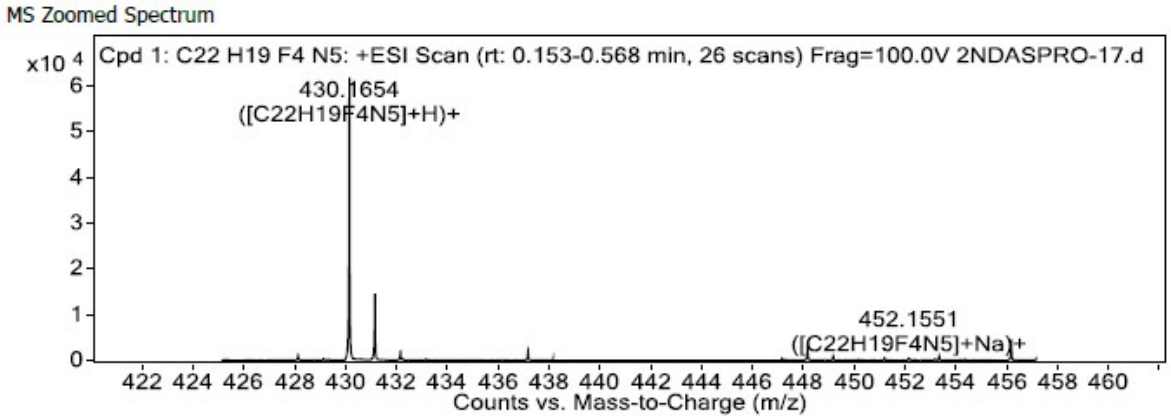


^{1}H NMR spectrum of compound **2h** in DMSO-d_6.



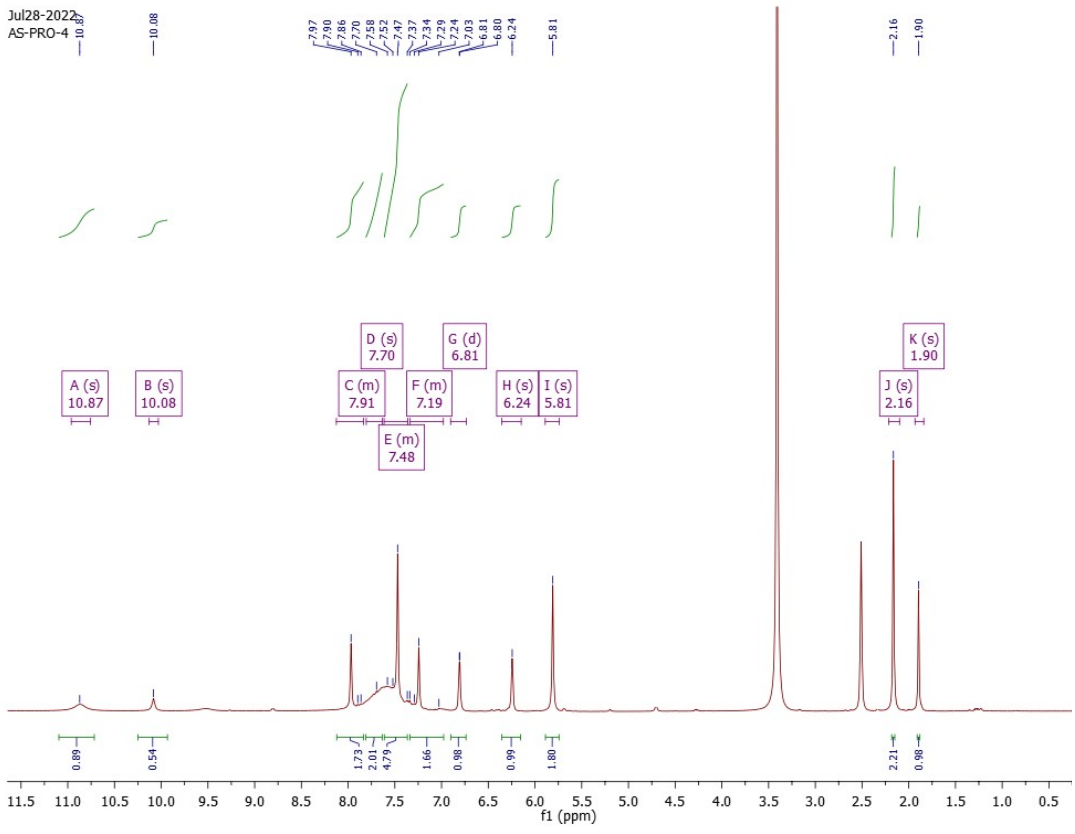


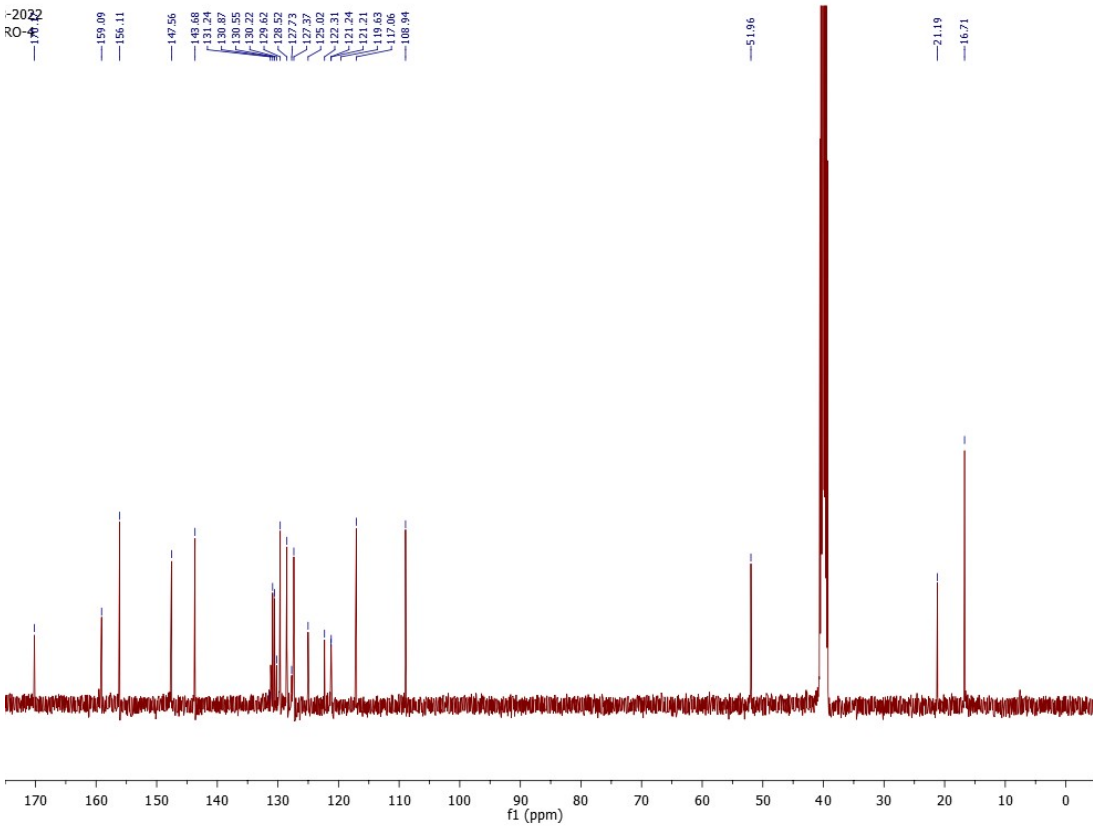
^{13}C NMR spectrum of compound **2h** in DMSO-d_6.



HRMS spectrum of compound **2h**.

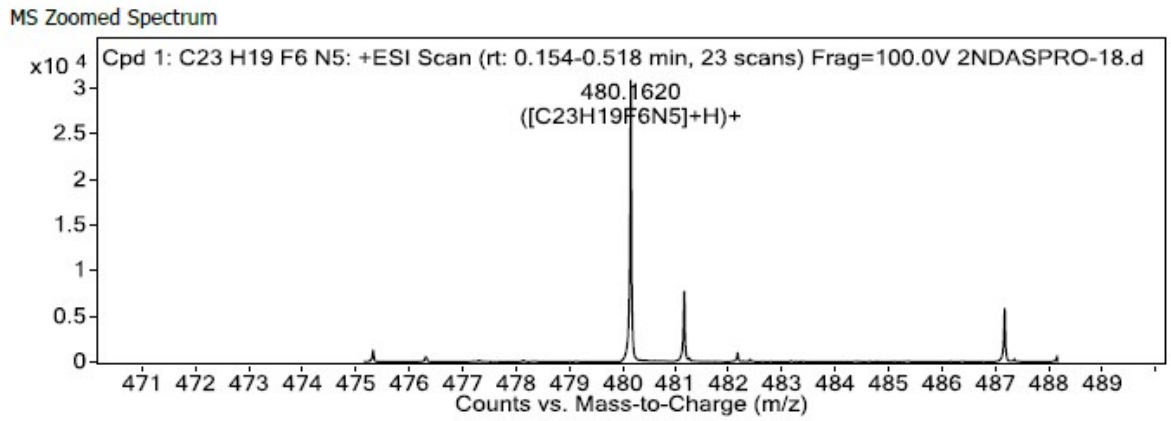
^{1}H NMR spectrum of compound **2i** in DMSO-d_6.



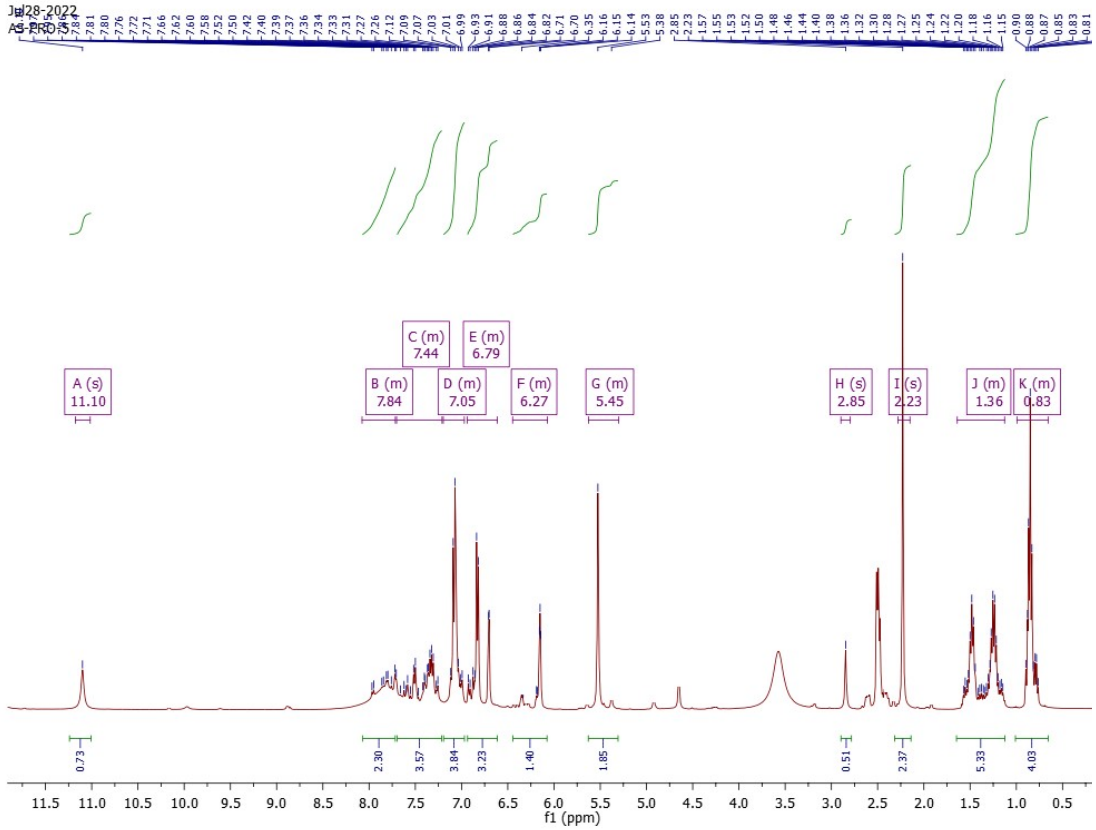


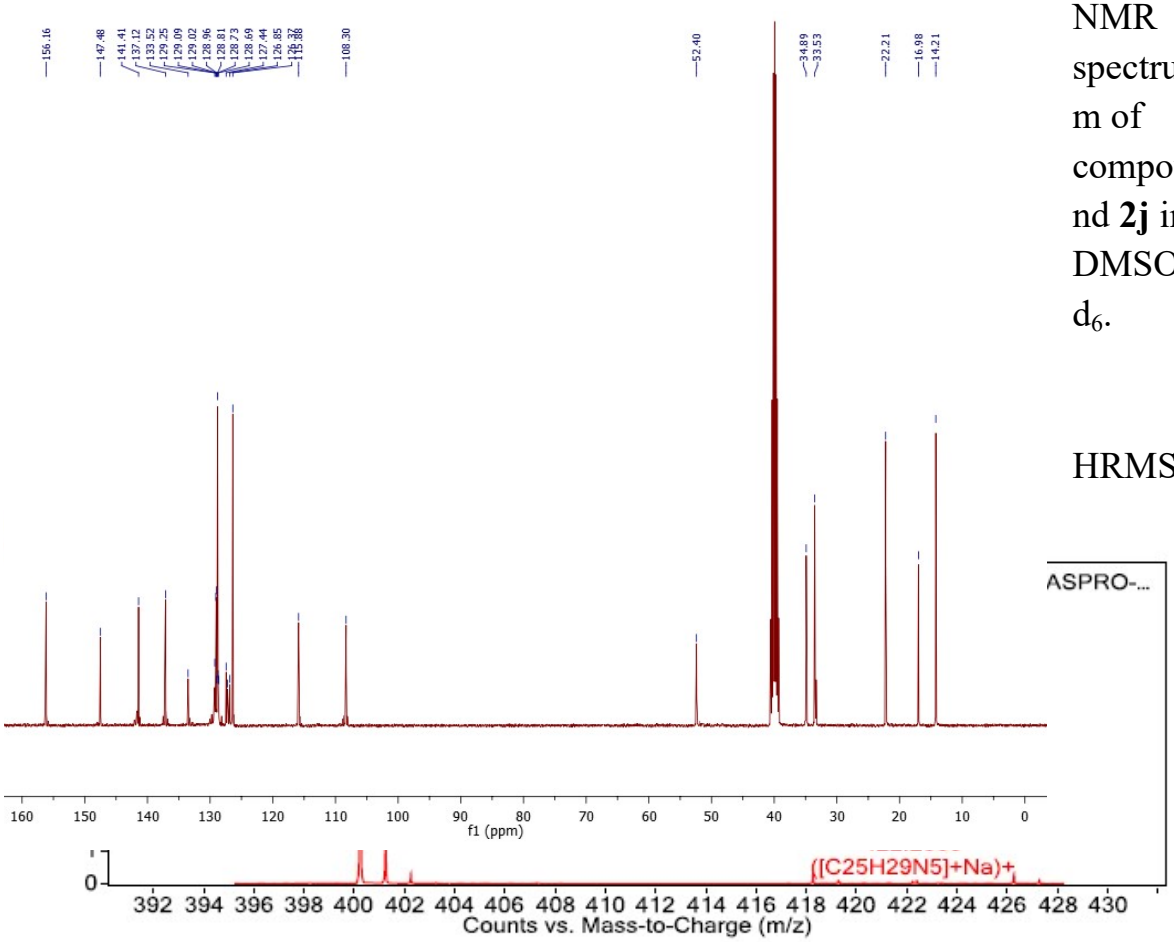
^{13}C NMR spectrum of compound **2i** in DMSO-d_6.

HRMS spectrum of compound **2i**.



^{1}H NMR spectrum of compound **2j** in DMSO-d_6.

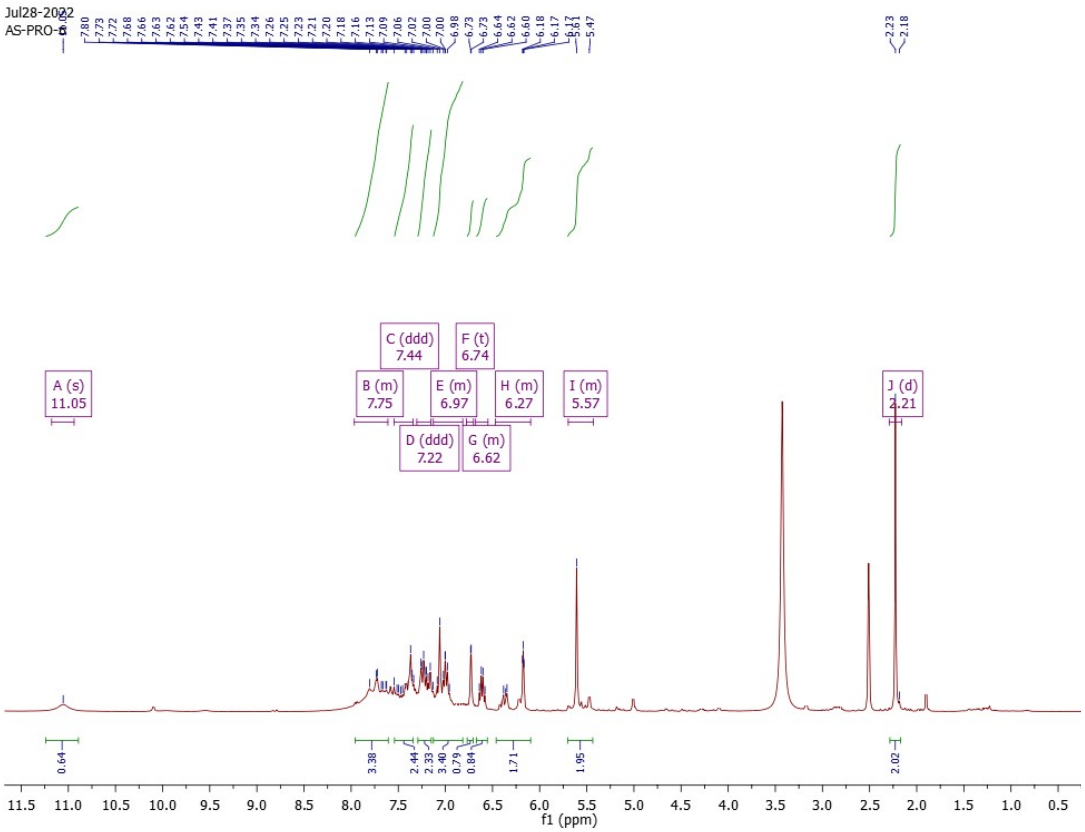


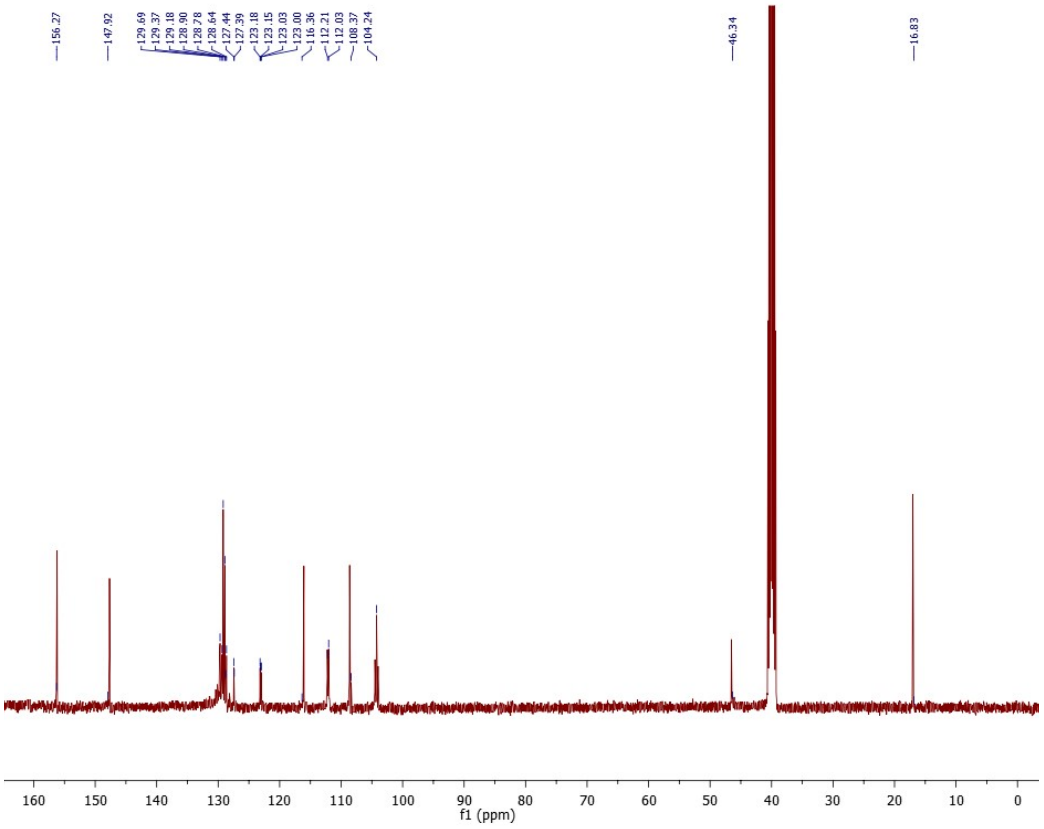


^{13}C NMR spectrum of compound **2j** in DMSO-d_6.

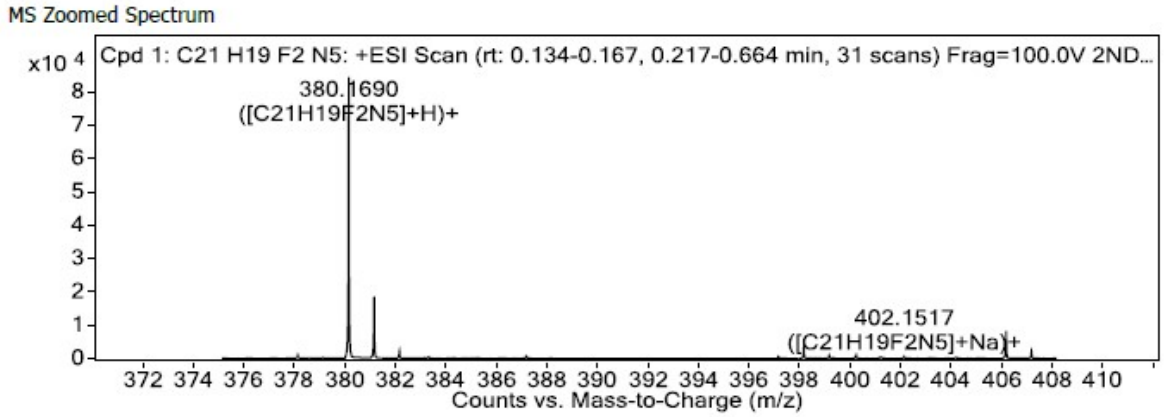
HRMS spectrum of compound **2j**.

^{1}H NMR spectrum of compound **2k** in DMSO-d_6.



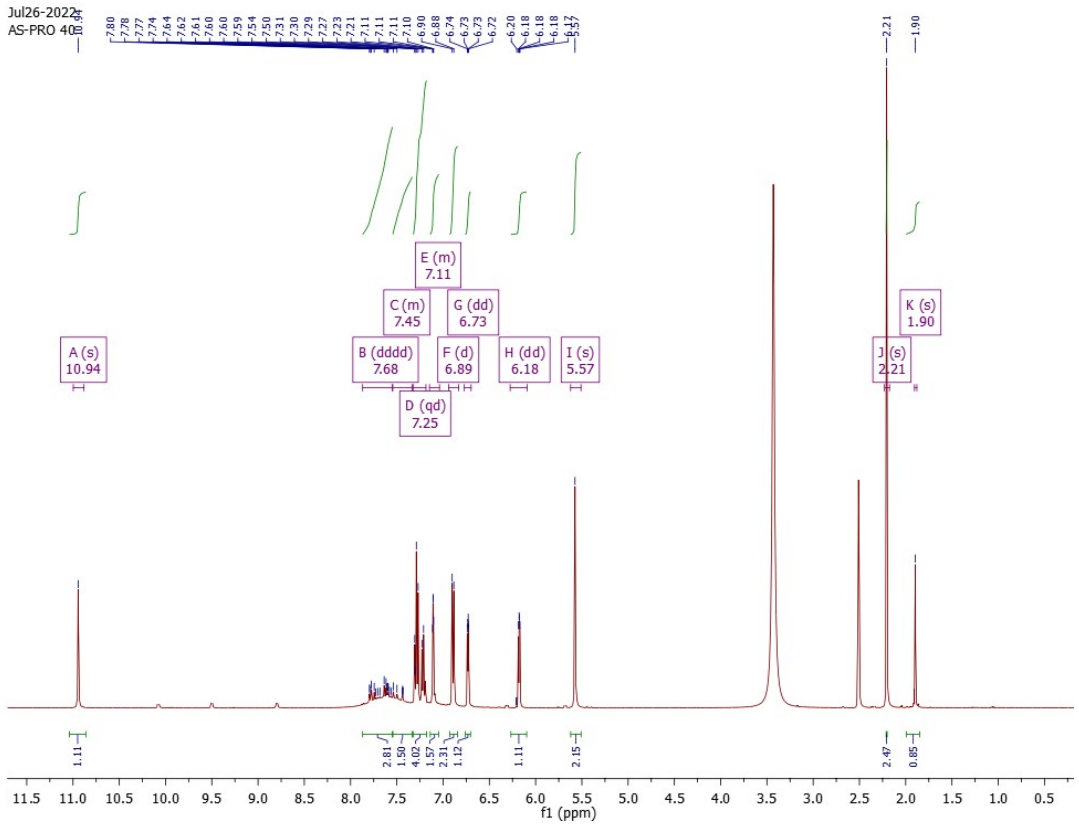


^{13}C NMR spectrum of compound **2k** in DMSO-d_6.

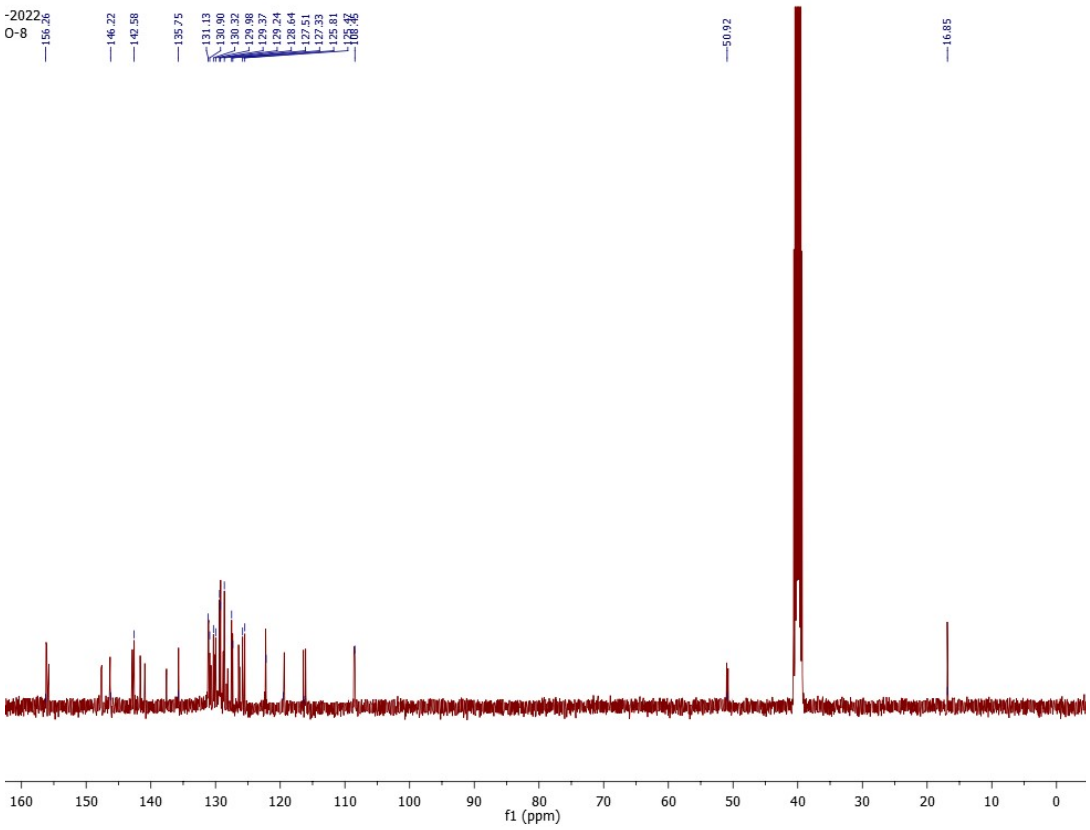


HRMS spectrum of compound **2k**.

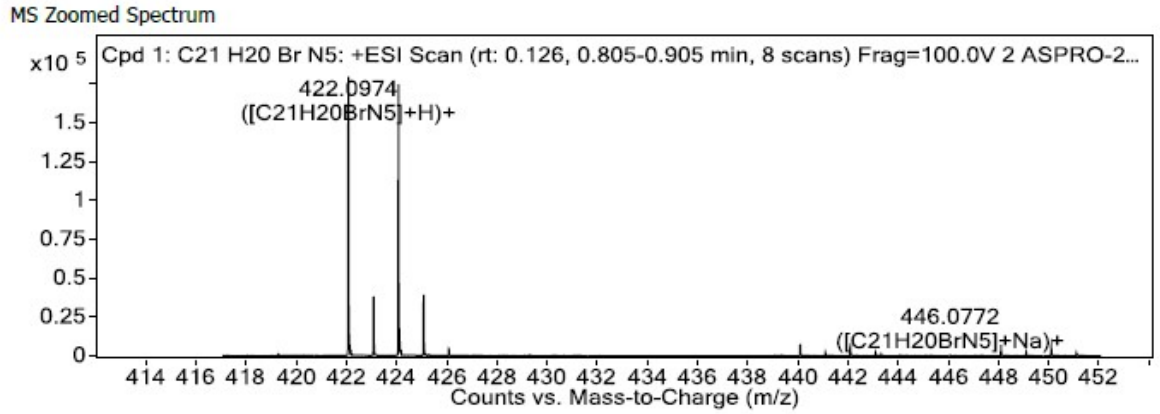
^{1}H NMR spectrum of compound **2m** in DMSO-d_6.



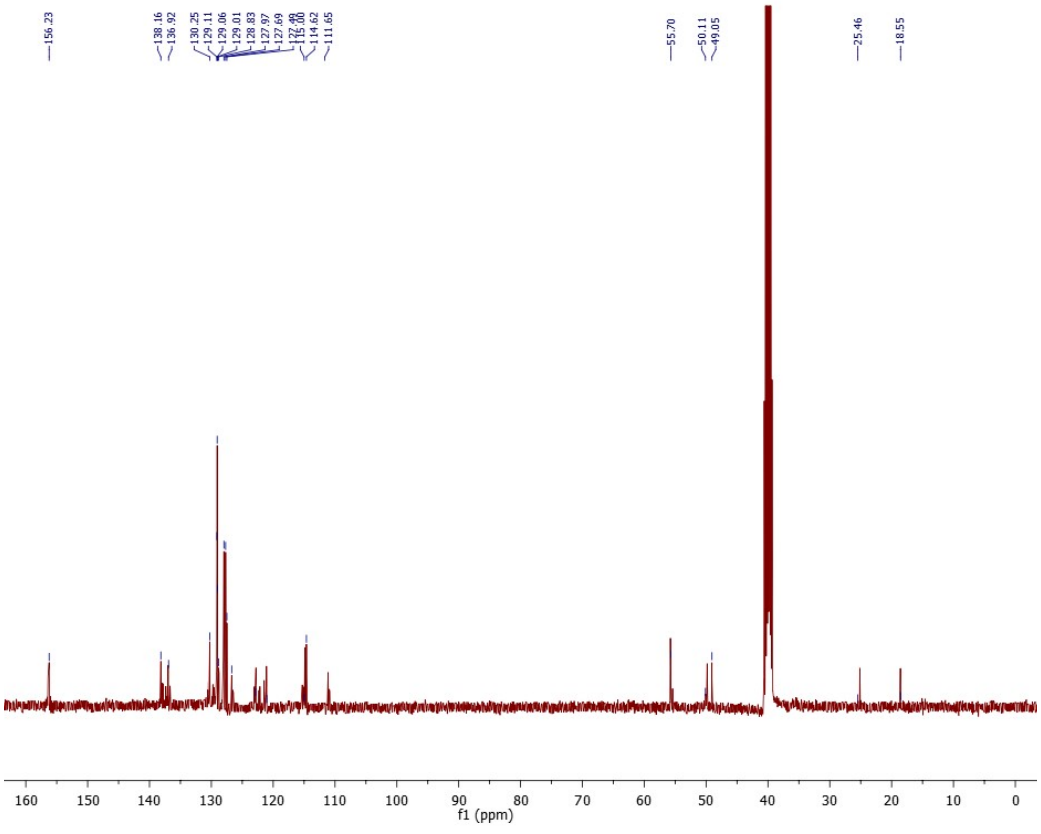
^{13}C NMR spectrum of compound **2m** in DMSO-d_6.



HRMS spectrum of compound **2m**.

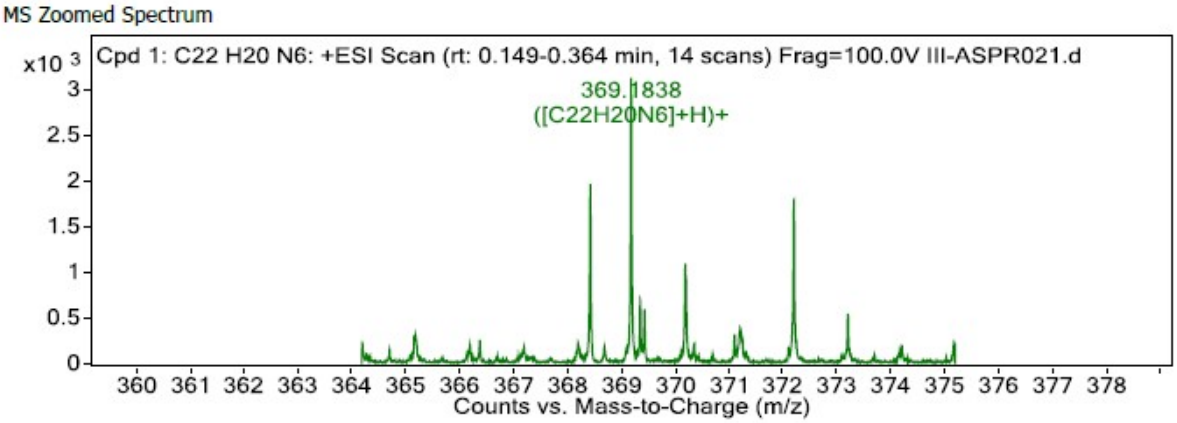


^{1}H NMR spectrum of compound **2o** in DMSO-d_6.



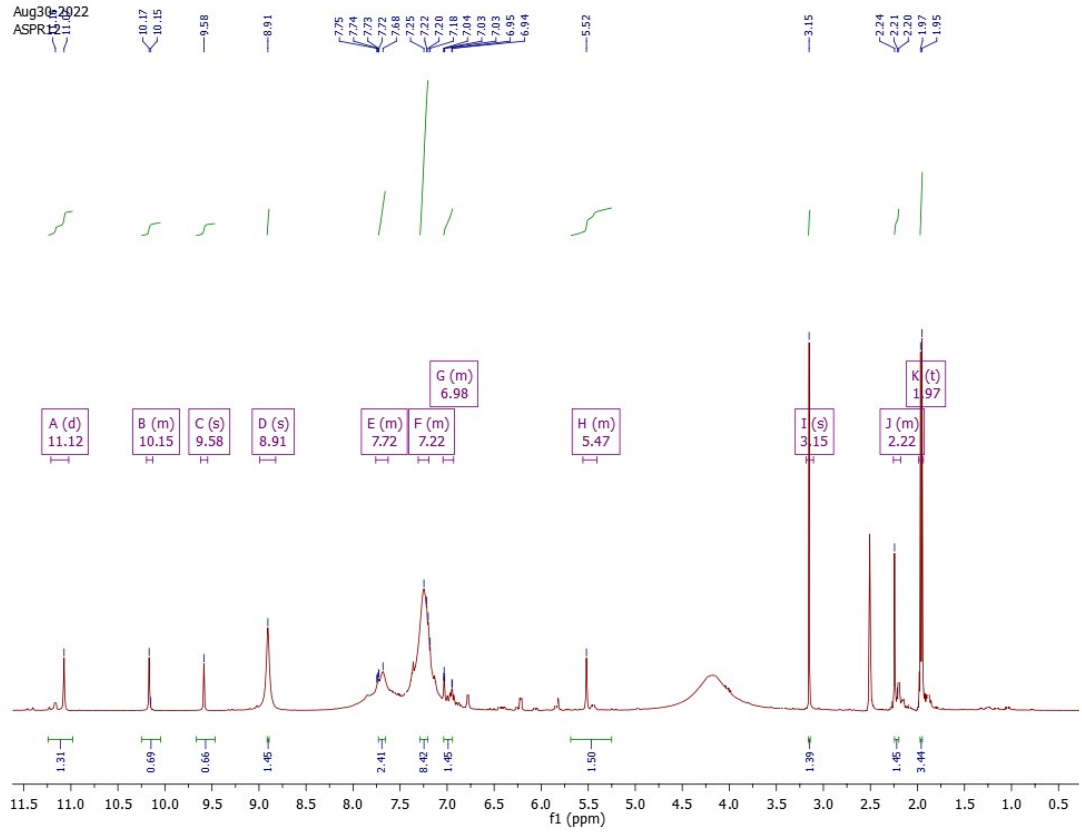
^{13}C NMR spectrum of compound **2o** in

DMSO-d_6.

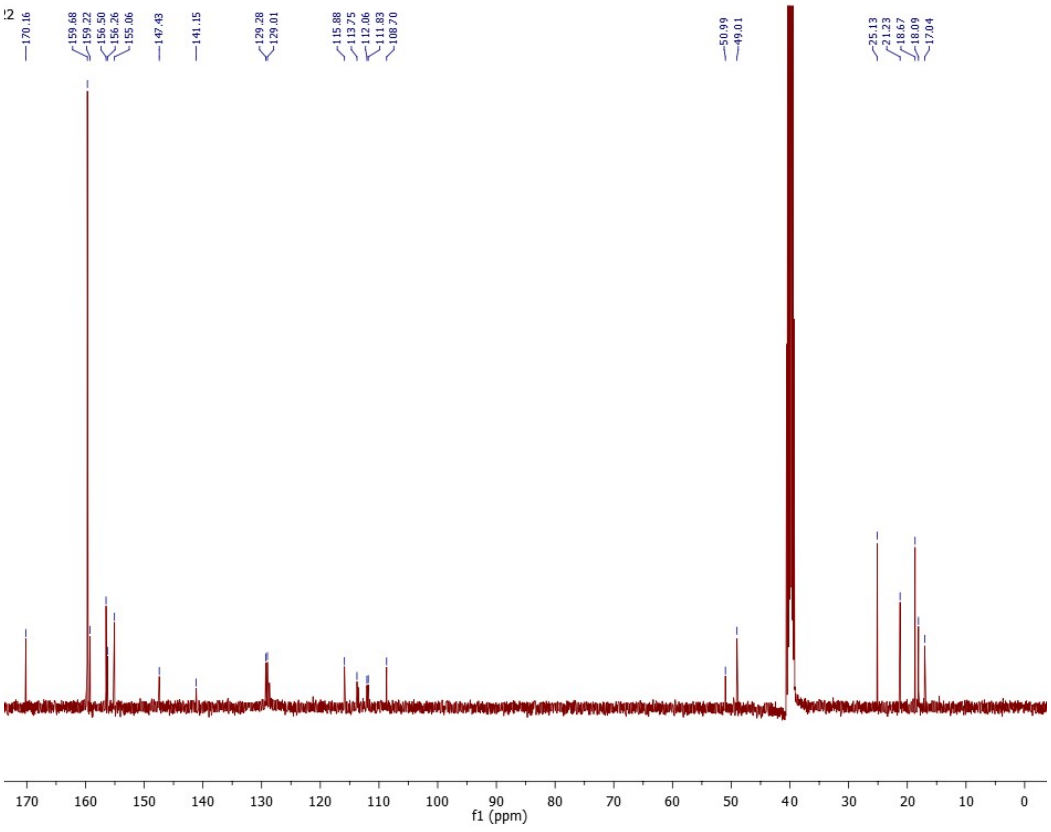


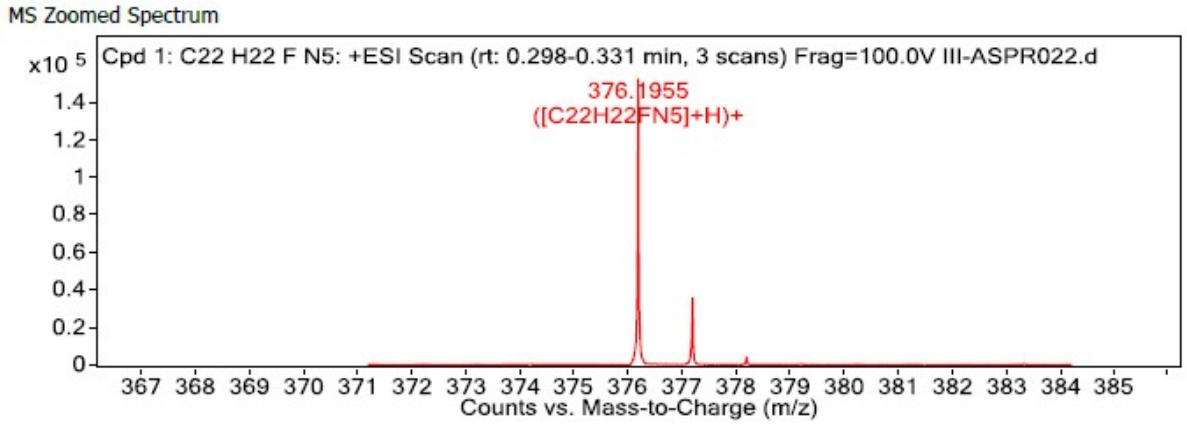
HRMS spectrum of compound **2o**.

^{1}H NMR spectrum of compound **2p** in DMSO-d_6.

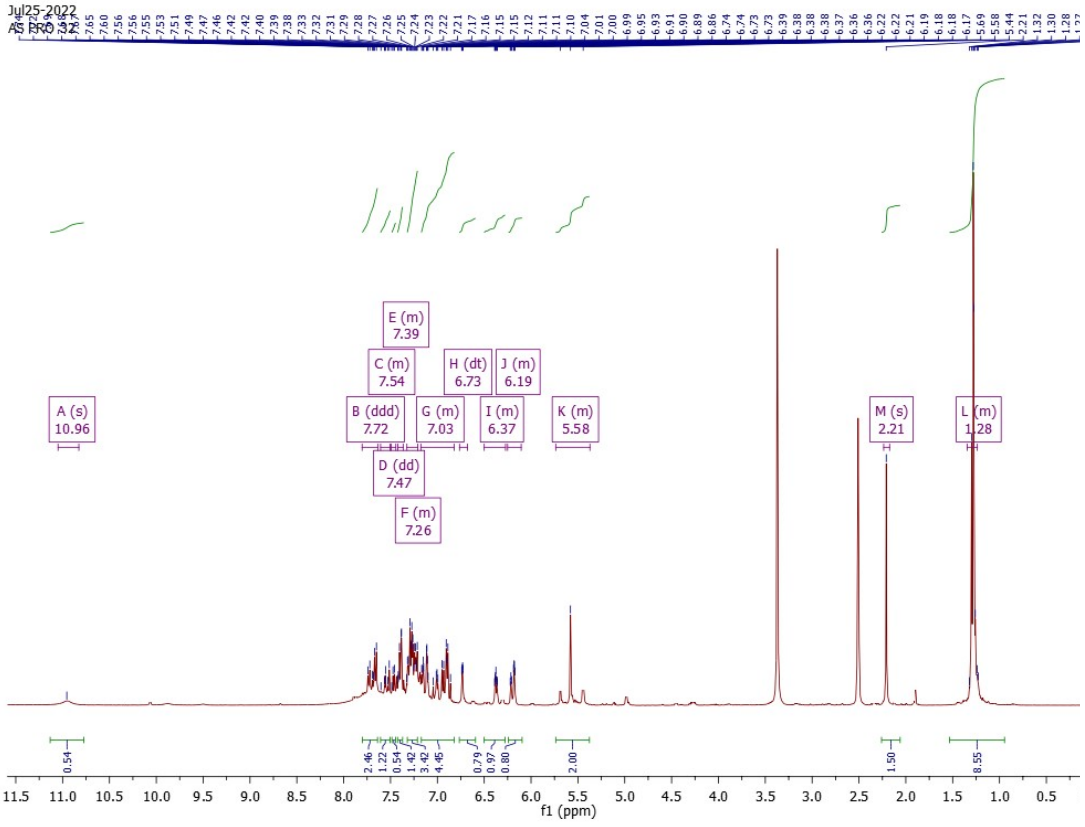


^{13}C NMR spectrum of compound **2p** in DMSO-d_6.



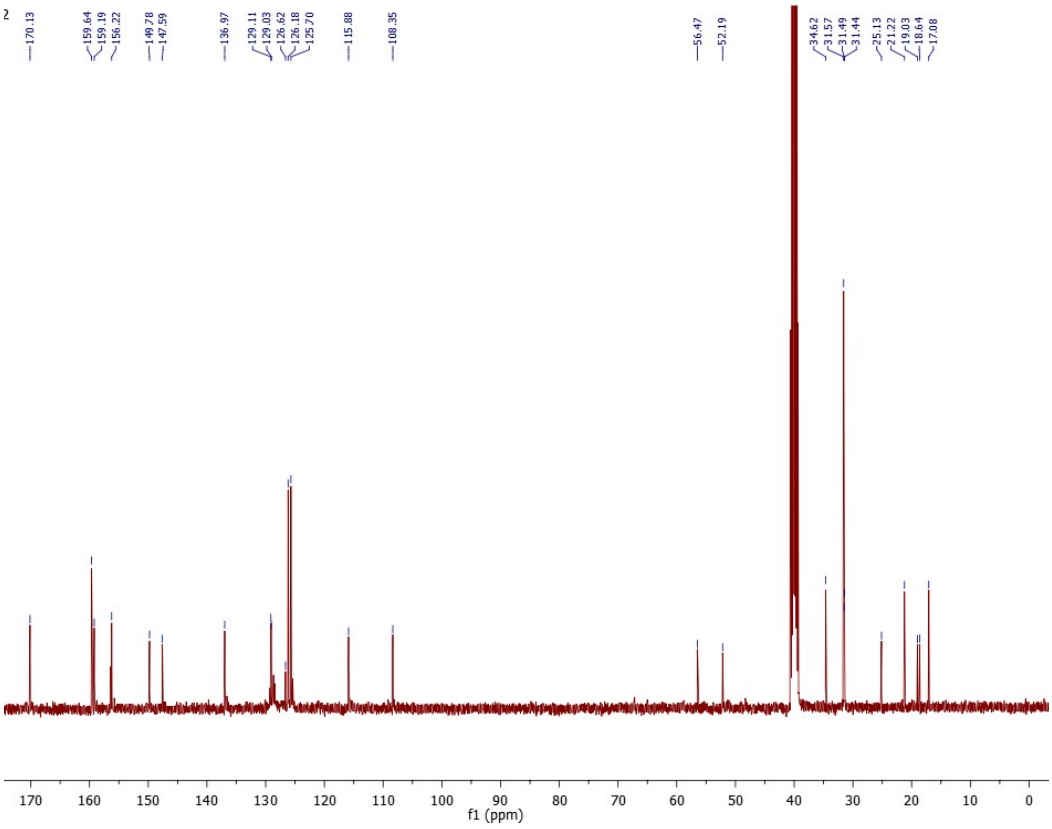


HRMS spectrum of compound **2p**.

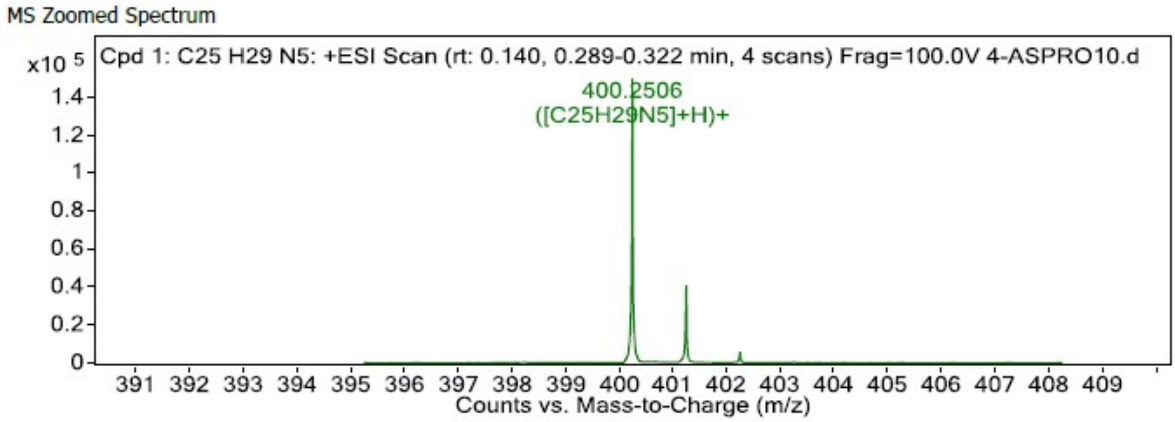


^{1}H NMR spectrum of compound **2q** in DMSO-d_6.

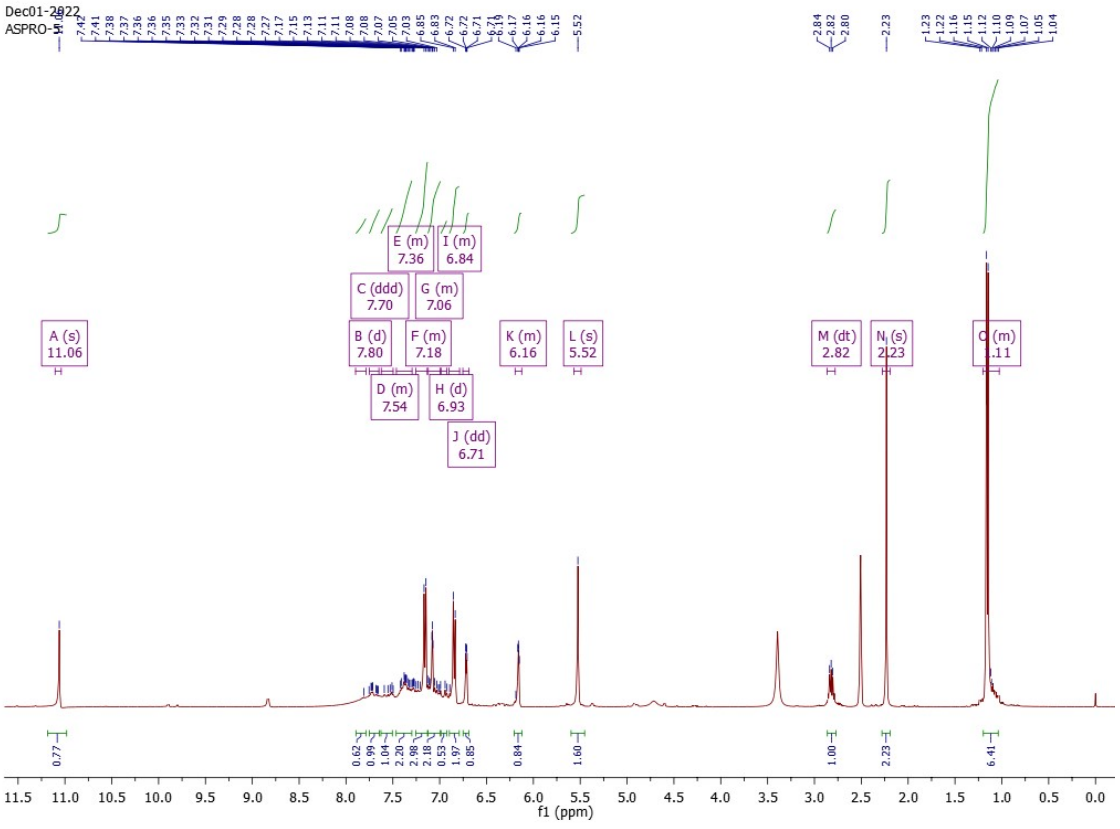
^{13}C NMR spectrum of compound **2q** in DMSO-d_6.

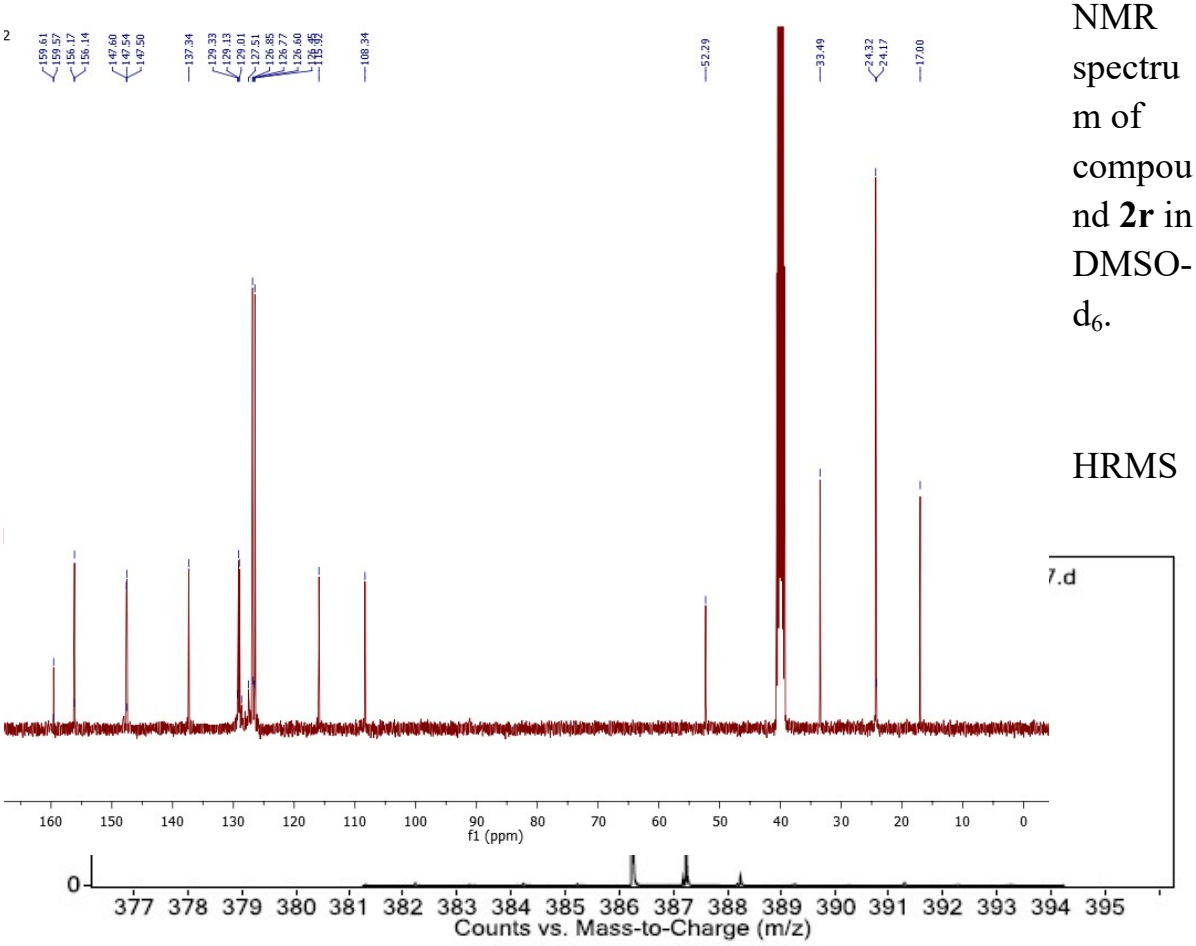


HRMS spectrum of compound **2q**.



^{1}H NMR spectrum of compound **2r** in DMSO-d_6.

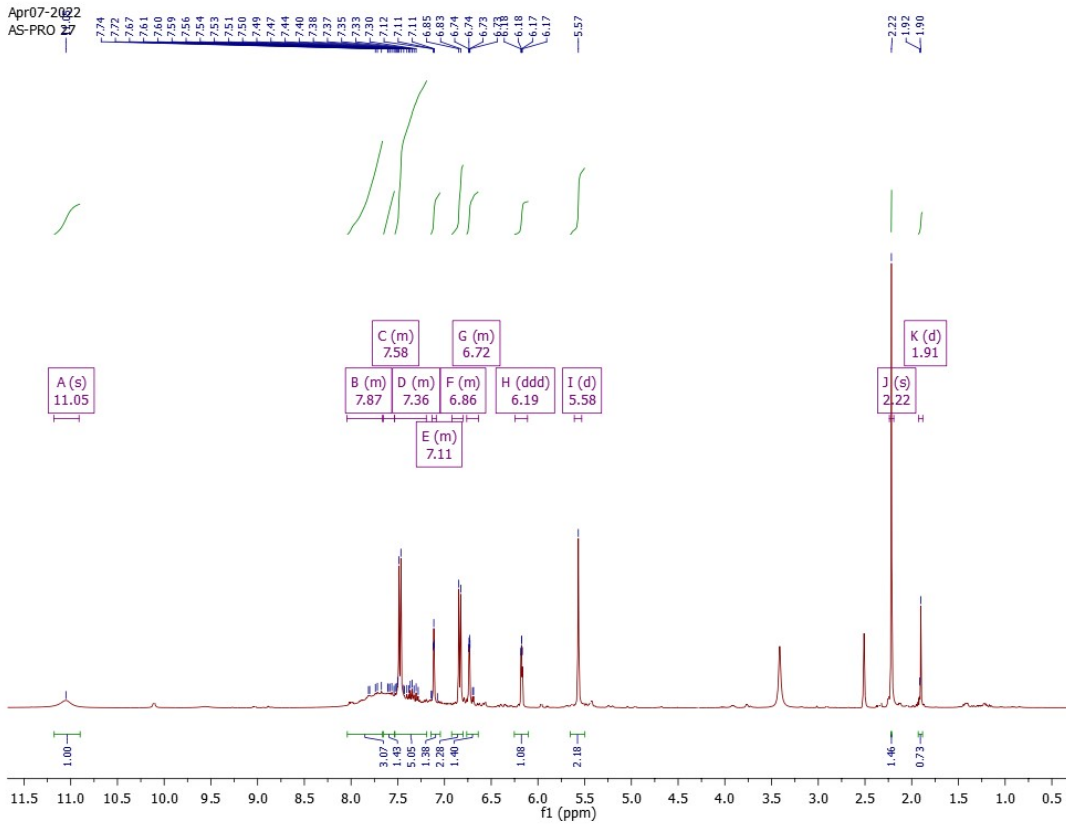


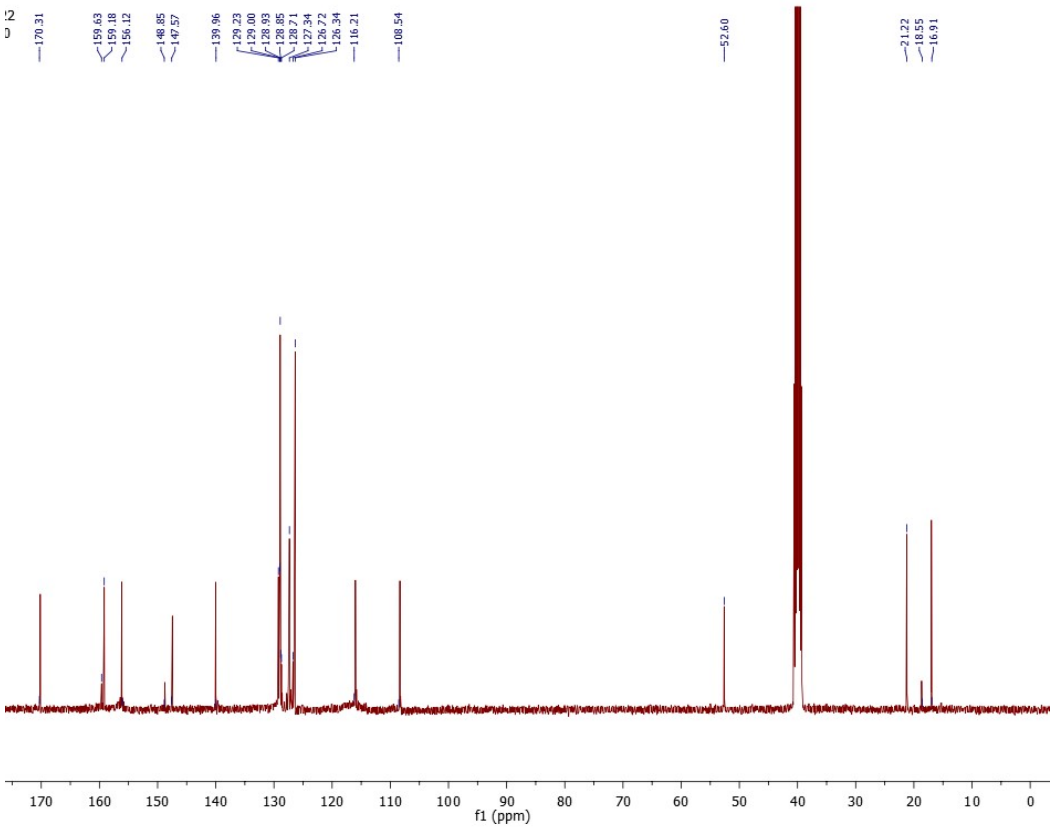


^{13}C NMR spectrum of compound **2r** in DMSO-d_6.

HRMS spectrum of compound **2r**.

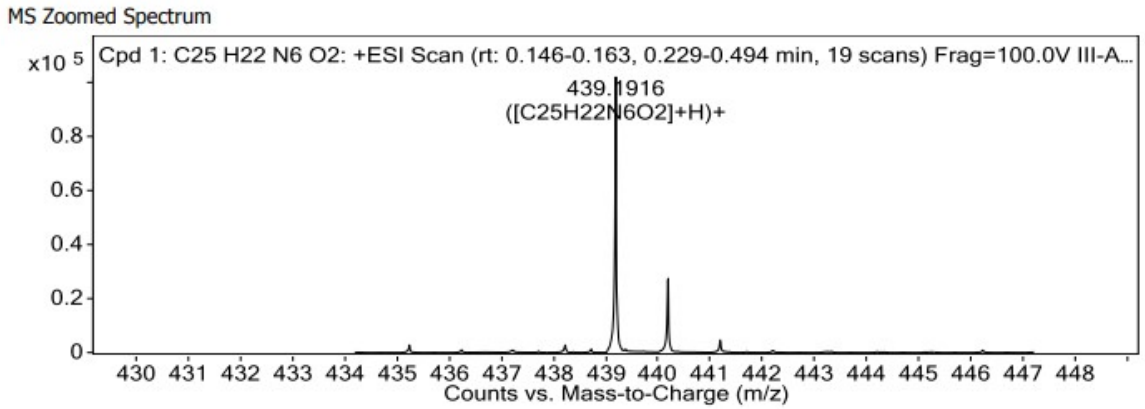
^{1}H NMR spectrum of compound **3a** in DMSO-d_6.



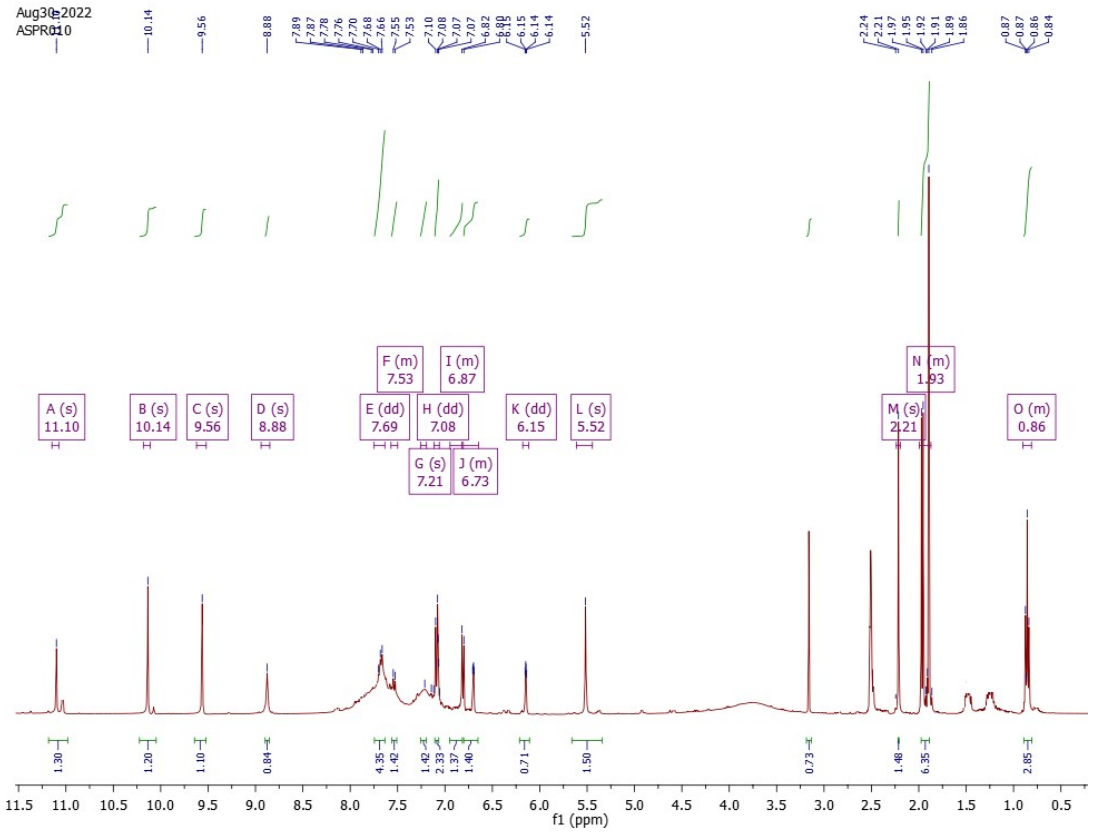


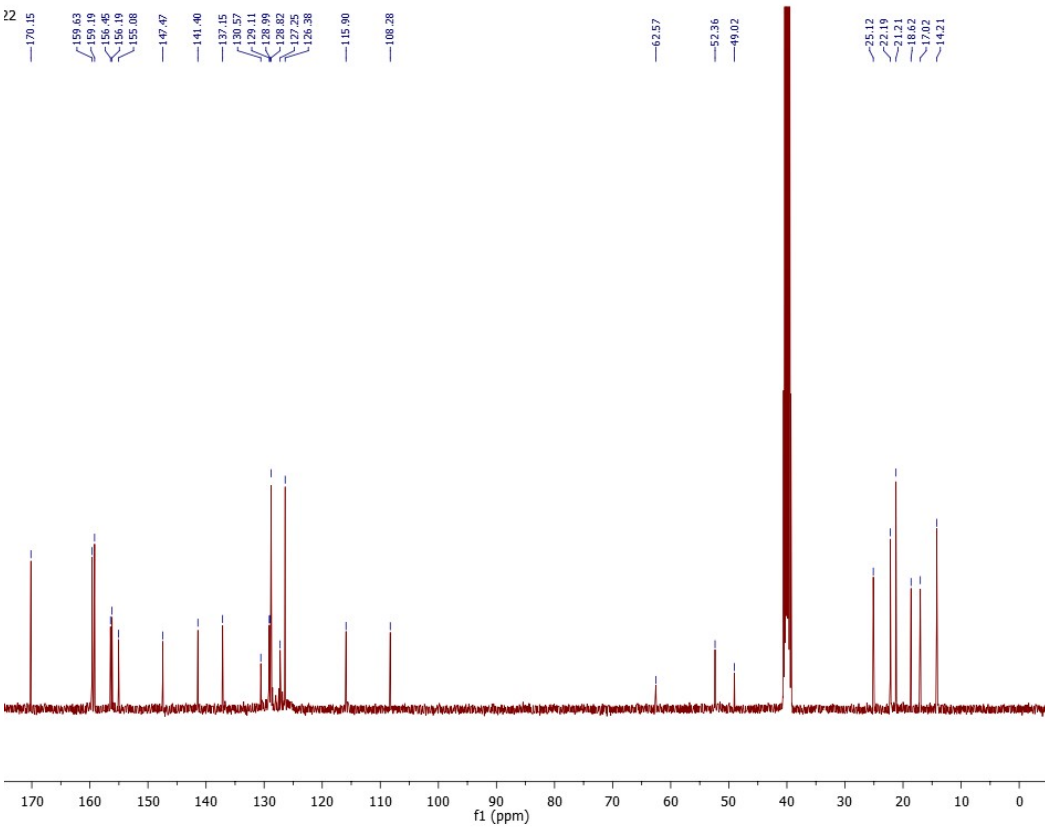
^{13}C NMR spectrum of compound **3a** in DMSO-d_6.

HRMS spectrum of compound **3a**.



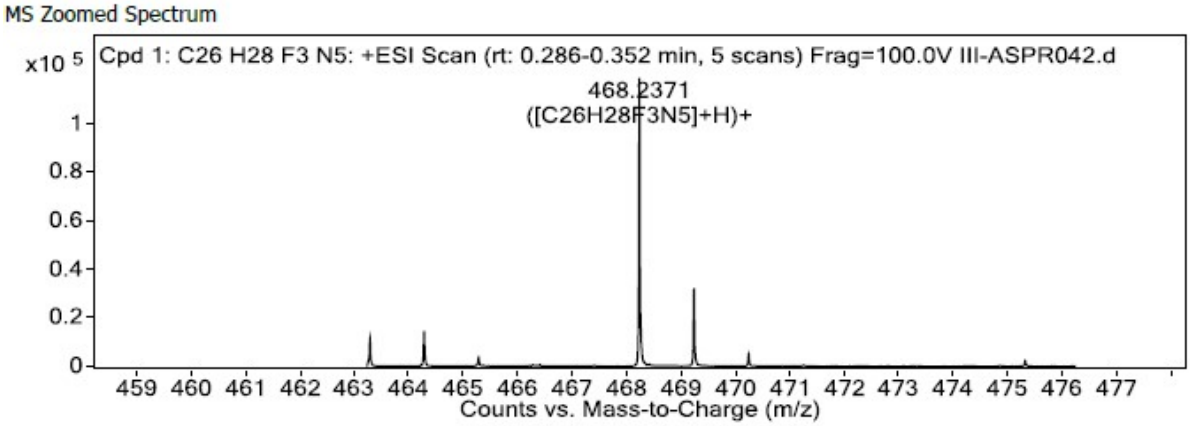
^{1}H NMR spectrum of compound **3b** in DMSO-d_6.



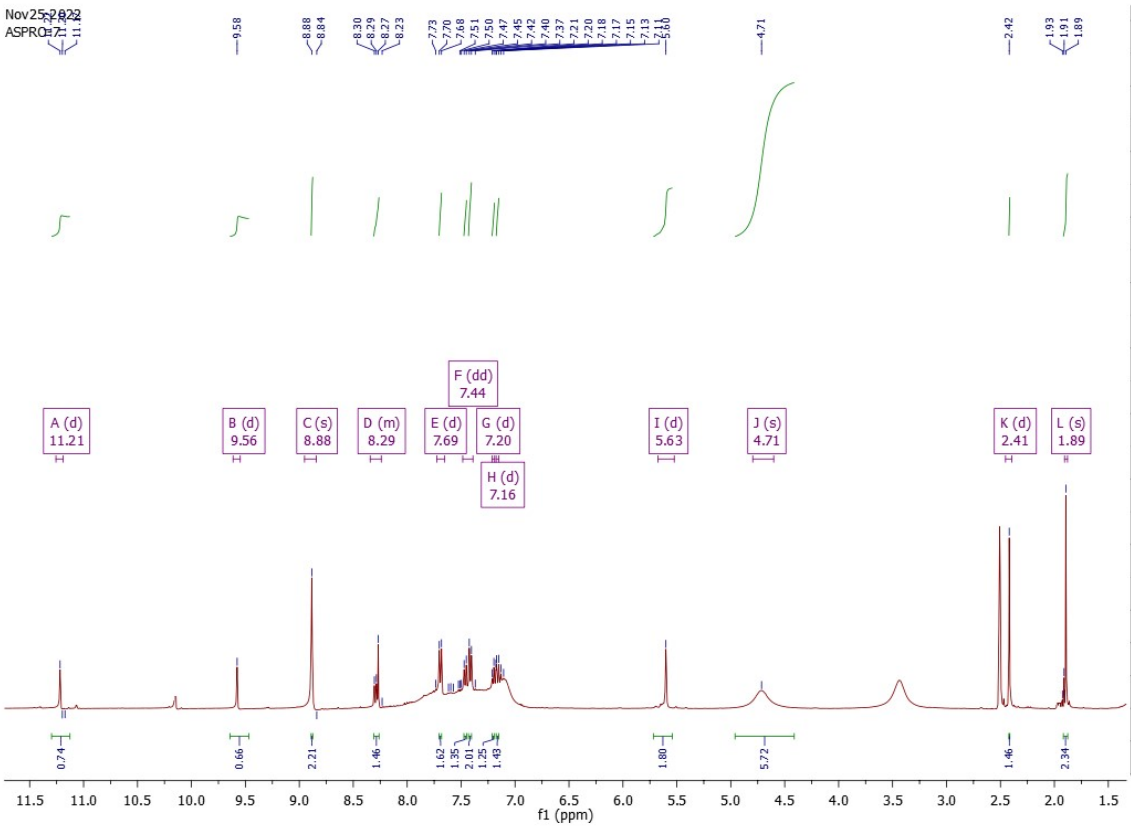


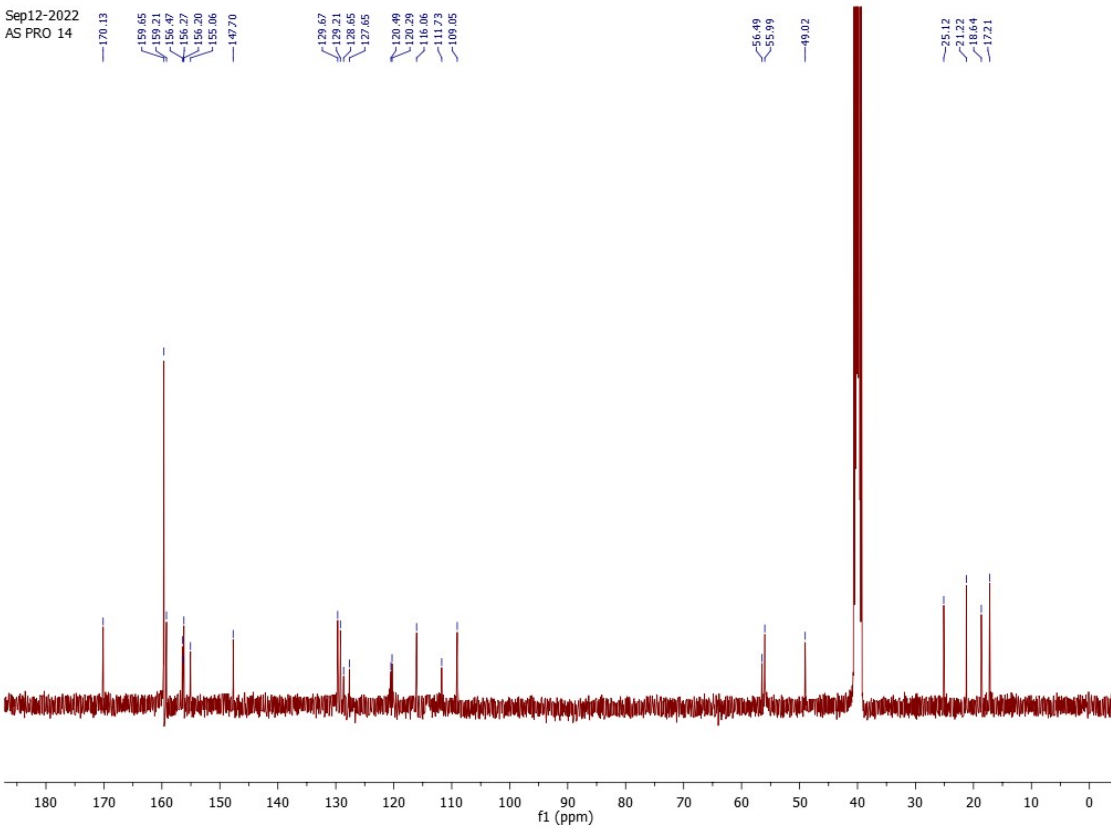
^{13}C NMR spectrum of compound **3b** in DMSO-d_6.

HRMS spectrum of compound **3b**.



^{1}H NMR spectrum of compound **3c** in DMSO-d_6.

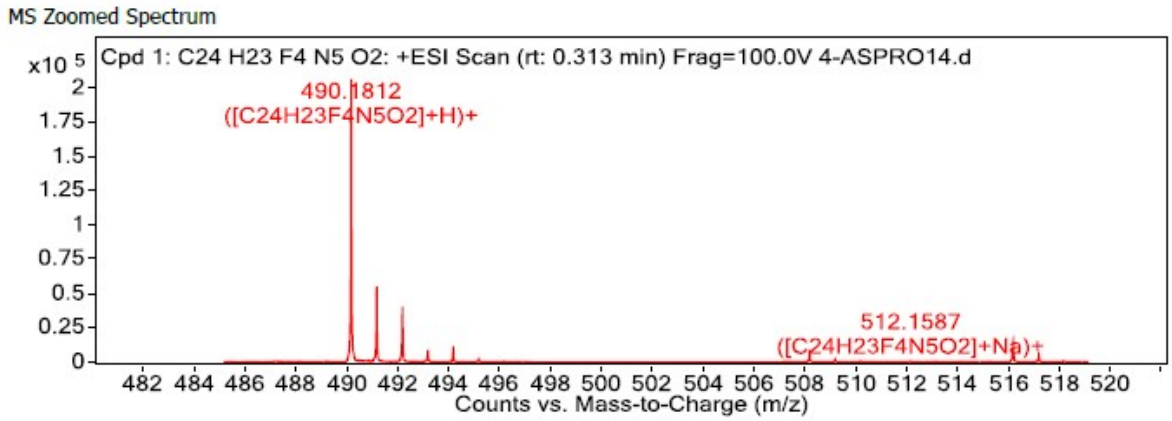


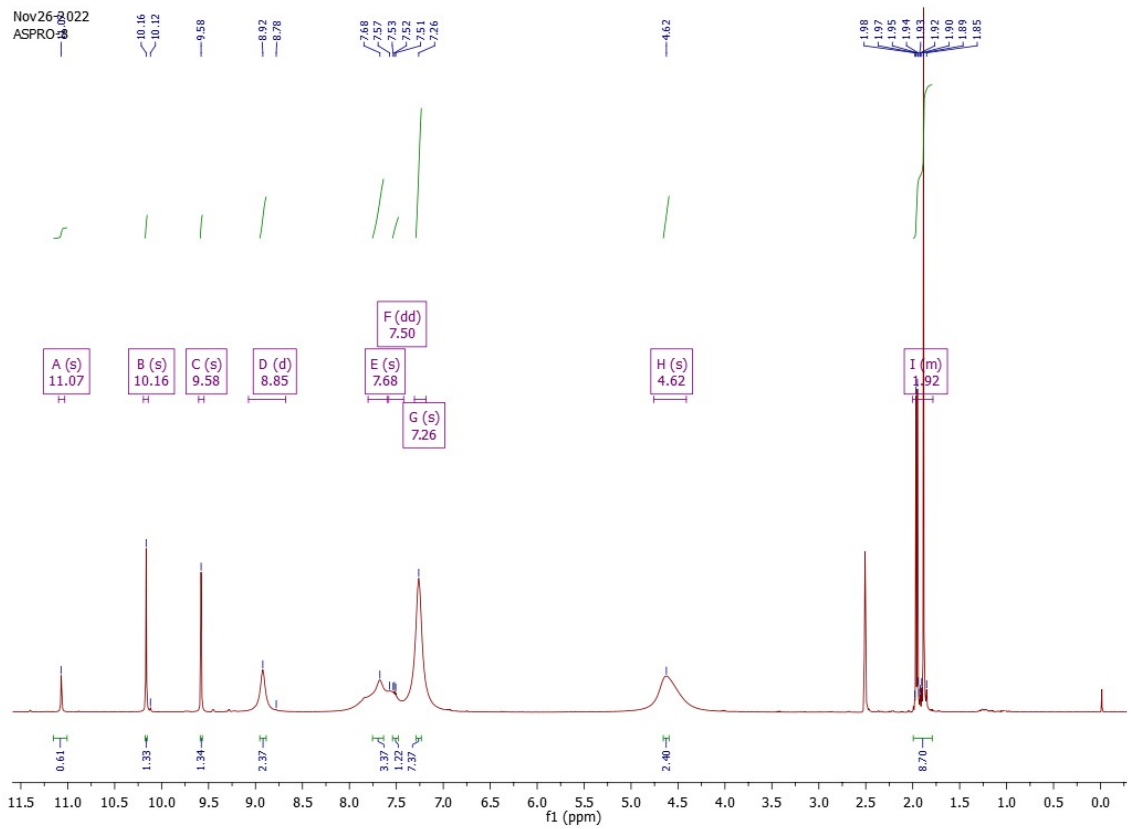


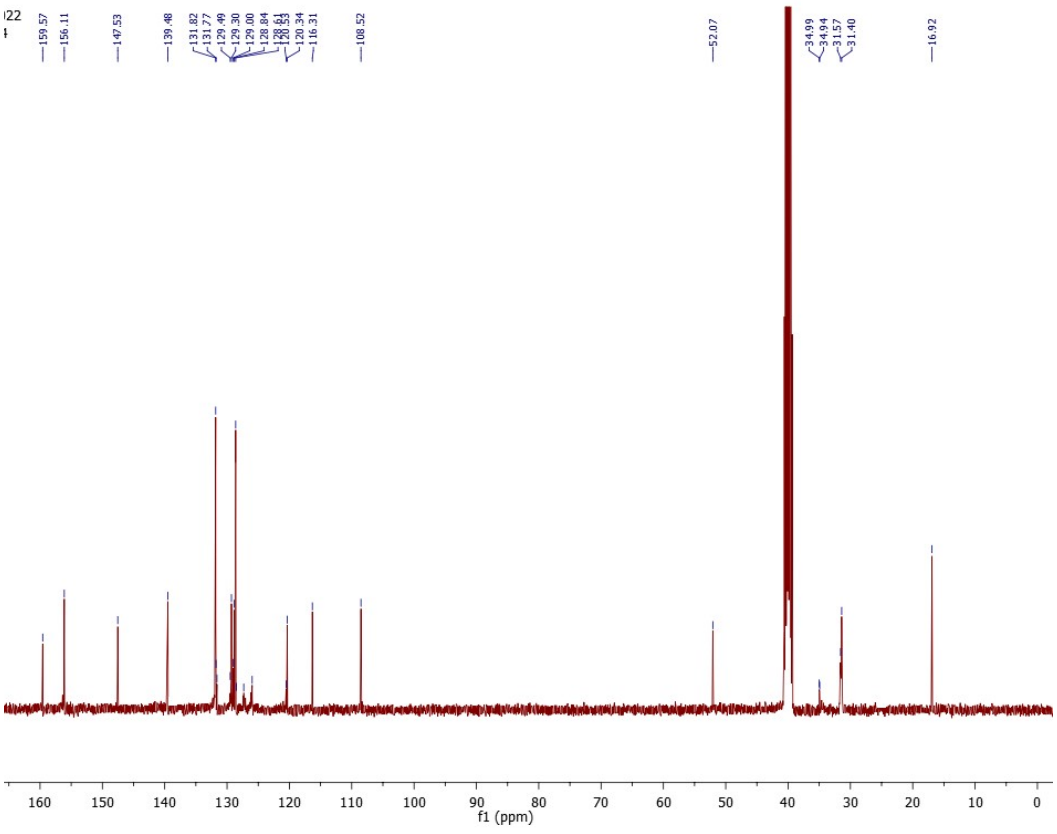
^{13}C NMR spectrum of compound **3c** in DMSO-d_6.

HRMS spectrum of compound **3c**.

^{1}H NMR spectrum of compound **3d** in DMSO-d_6.

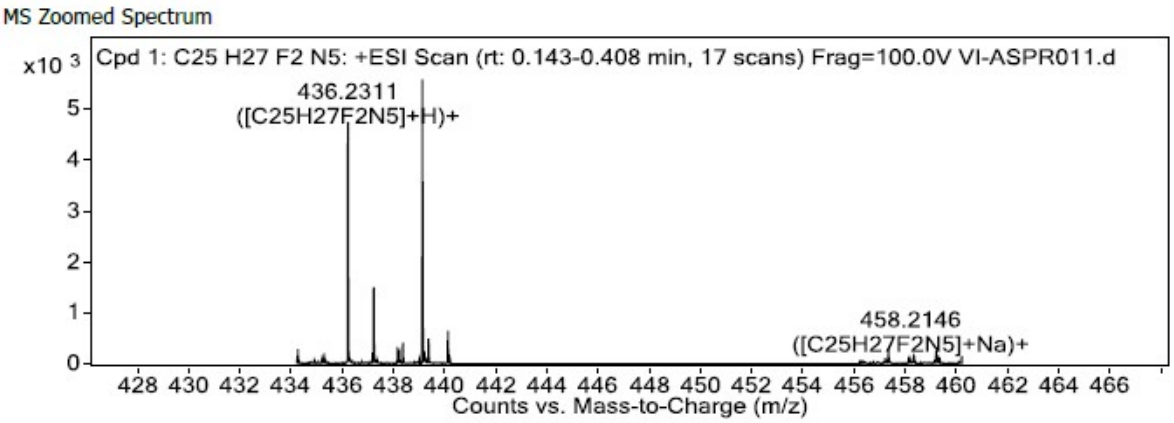




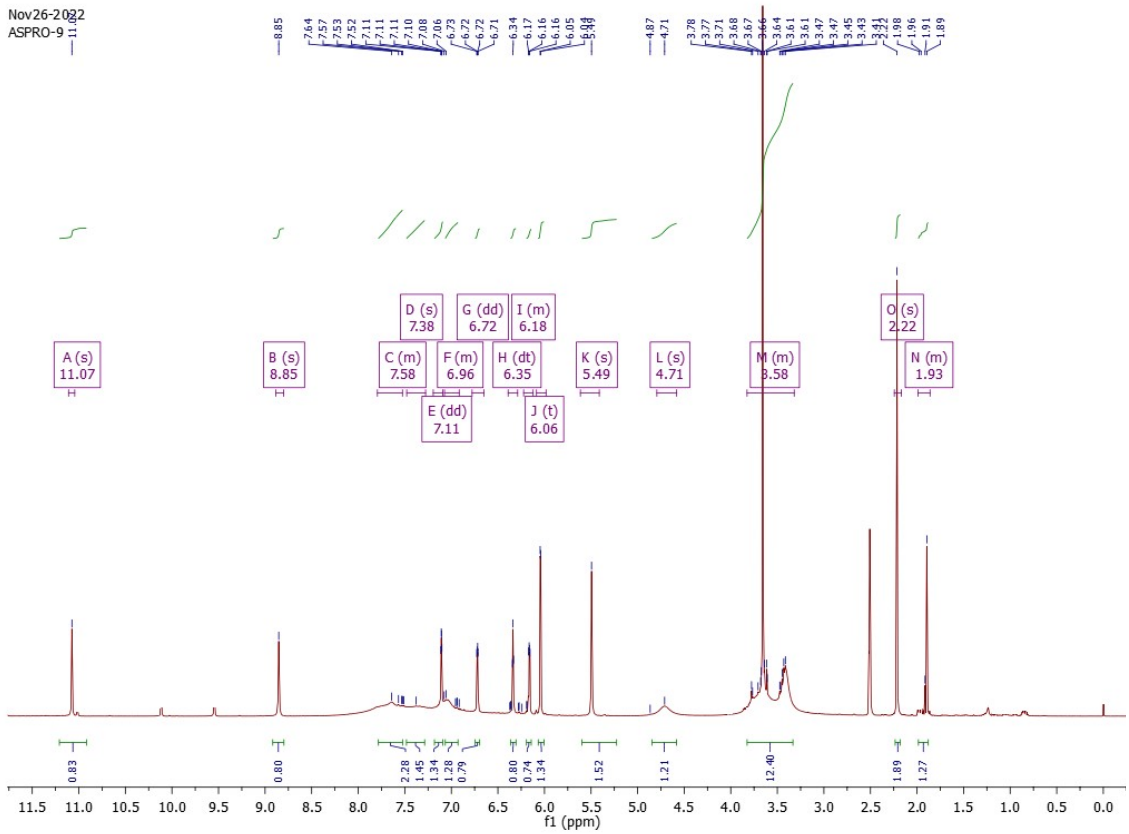


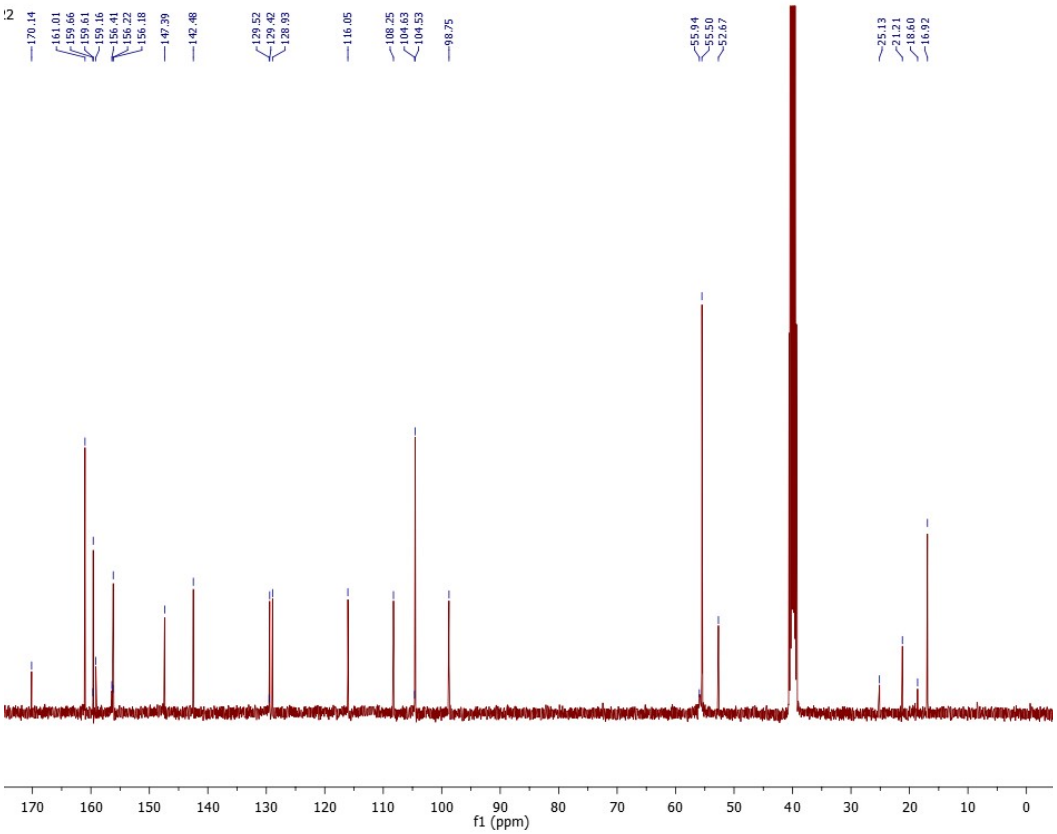
^{13}C NMR spectrum of compound **3d** in DMSO-d_6.

HRMS spectrum of compound **3d**.



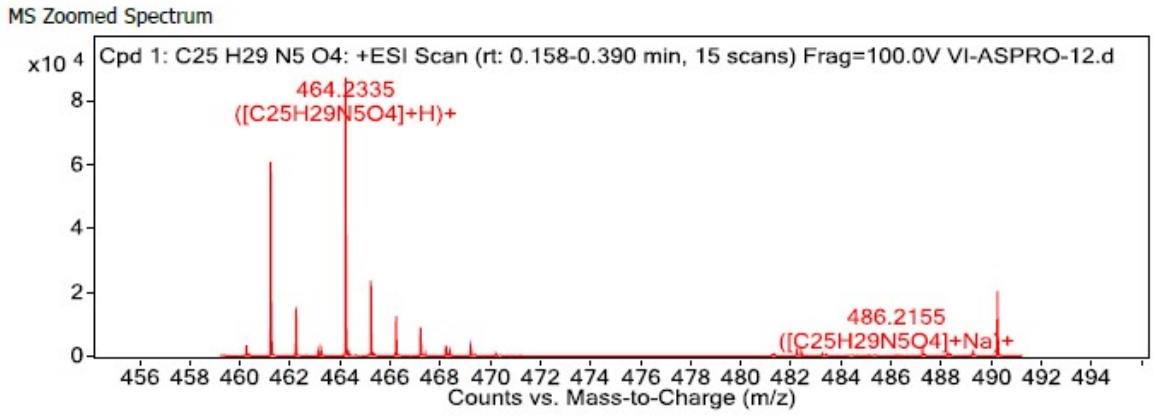
^{1}H NMR spectrum of compound **3e** in DMSO-d_6.



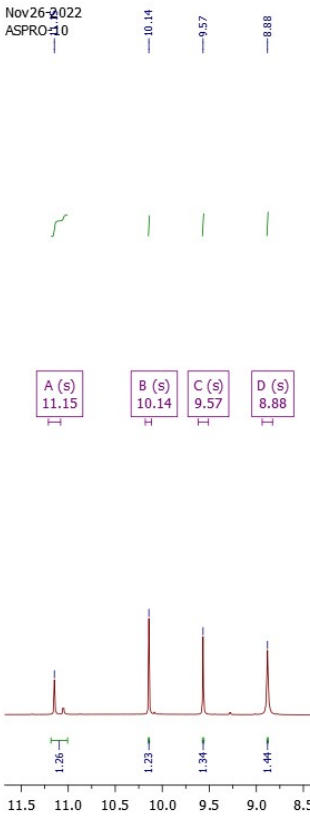


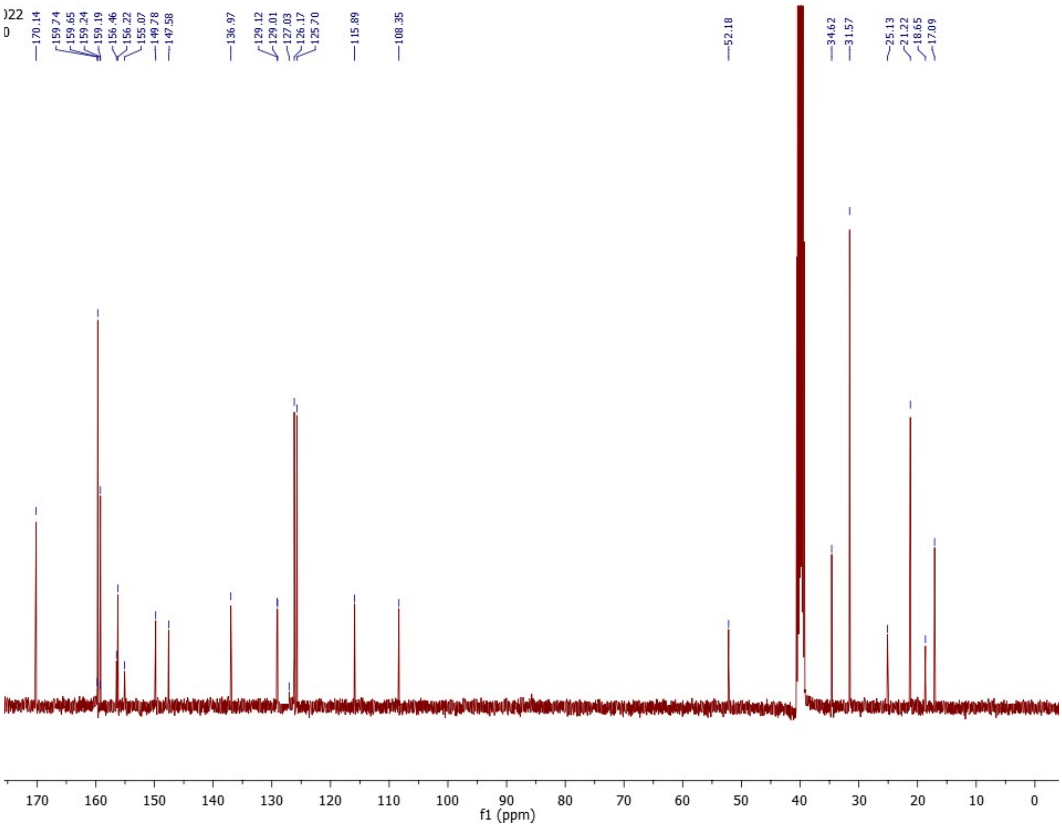
^{13}C NMR spectrum of compound **3e** in DMSO-d_6.

HRMS spectrum of compound **3e**.

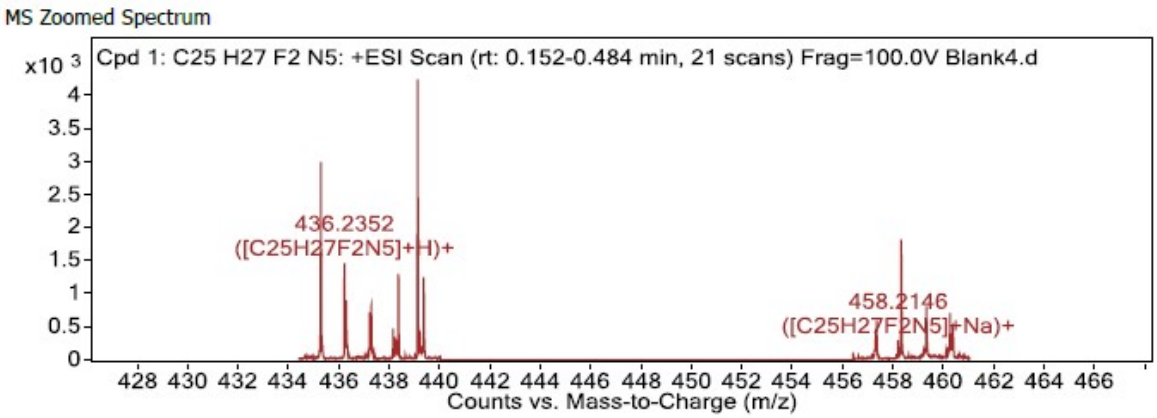


^{1}H NMR spectrum of compound **3f** in DMSO-d_6.



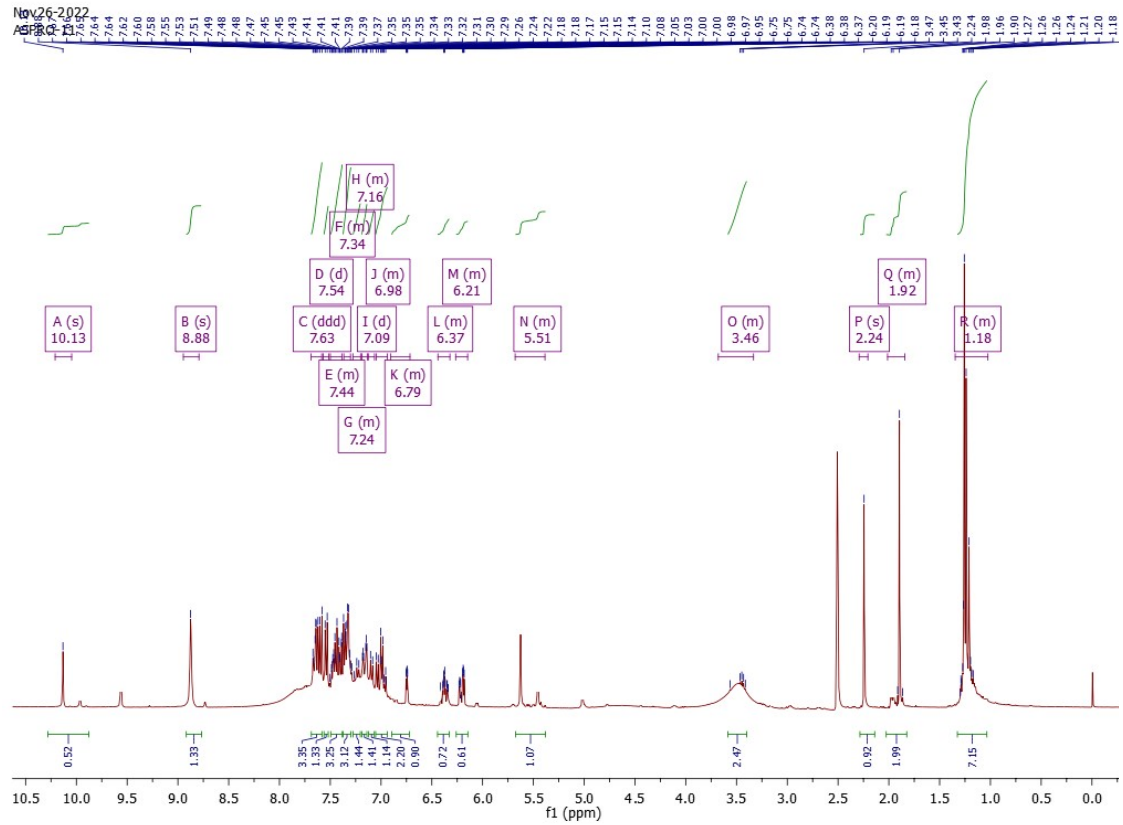


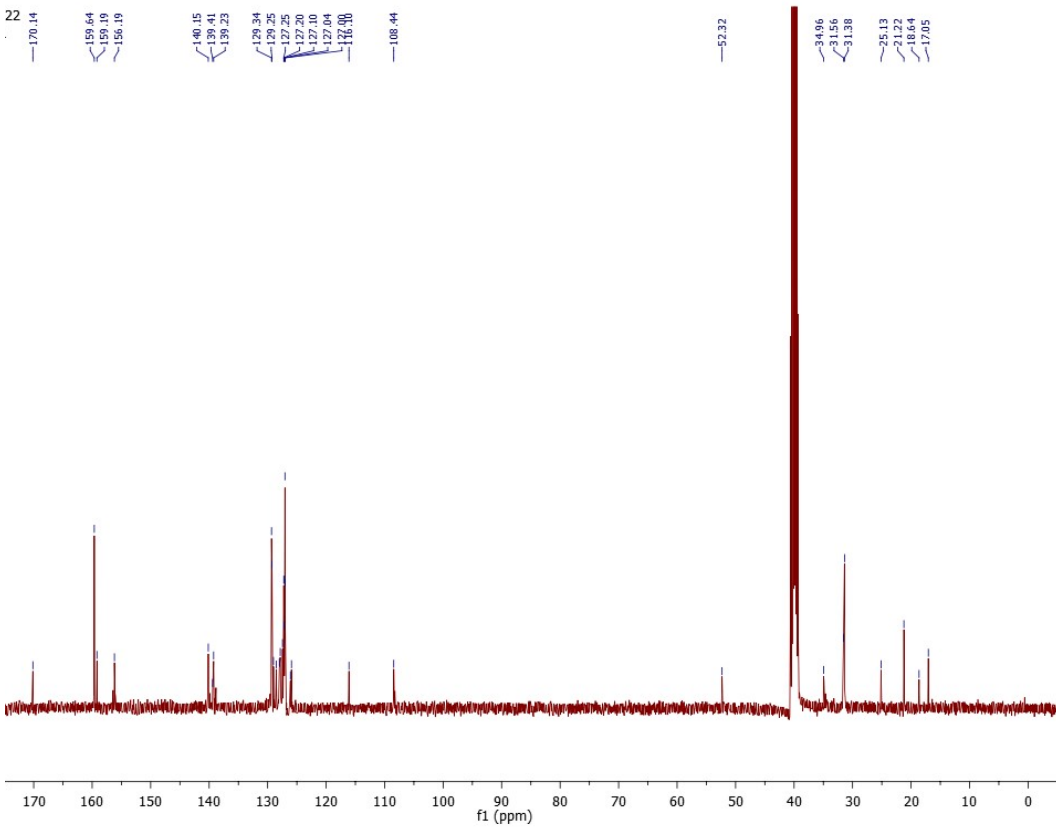
^{13}C NMR spectrum of compound **3f** in DMSO-d_6.



HRMS spectrum of compound **3f**.

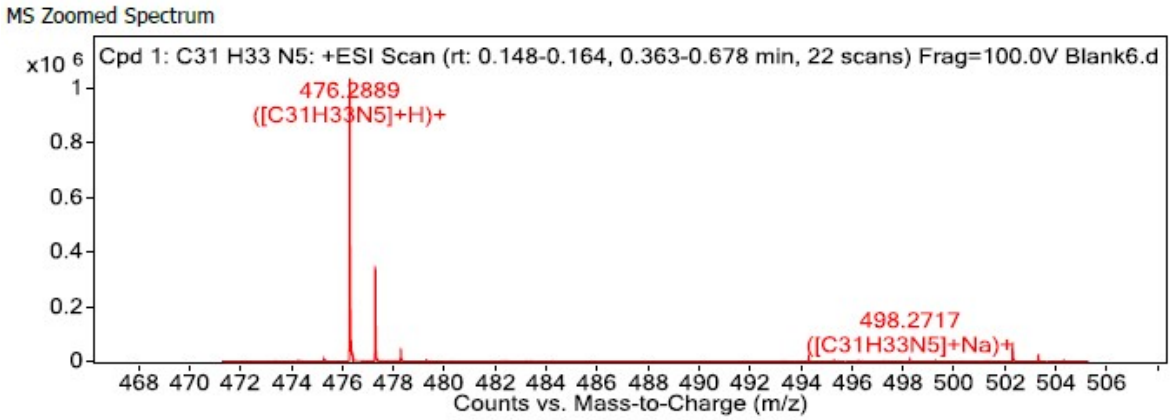
^{1}H NMR spectrum of compound **3g** in DMSO-d_6.



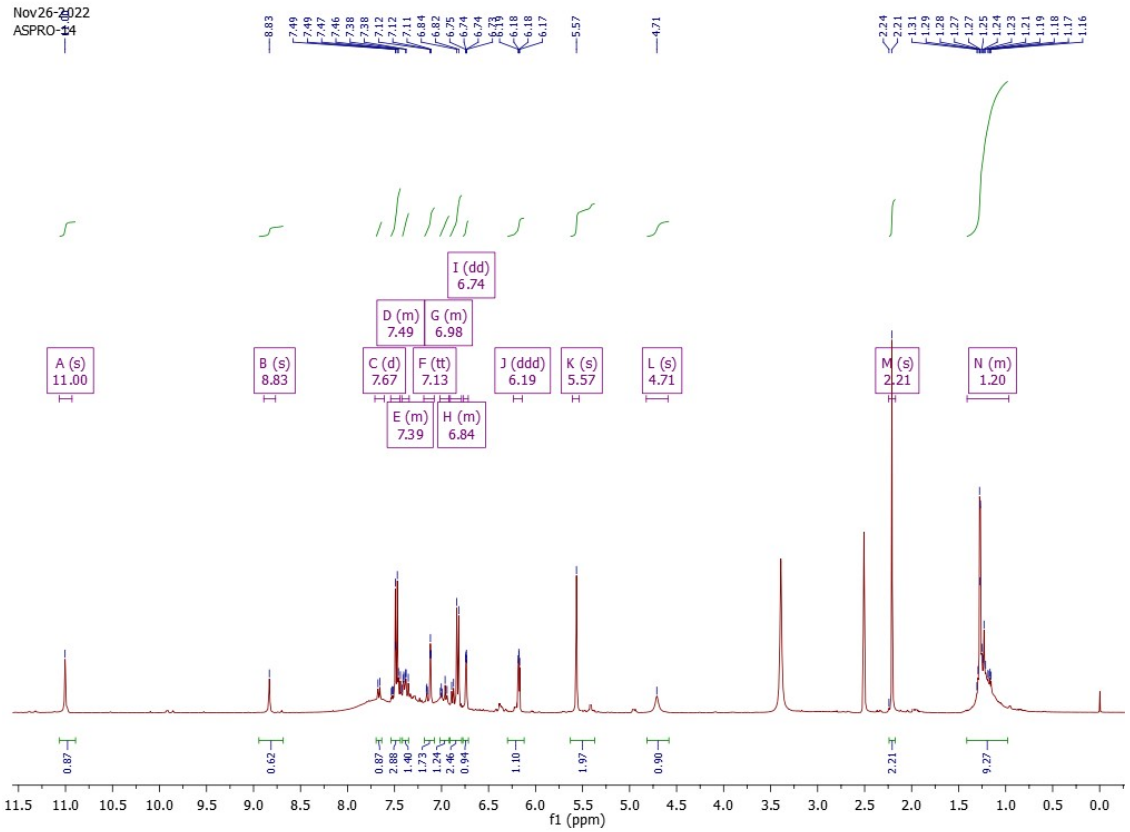


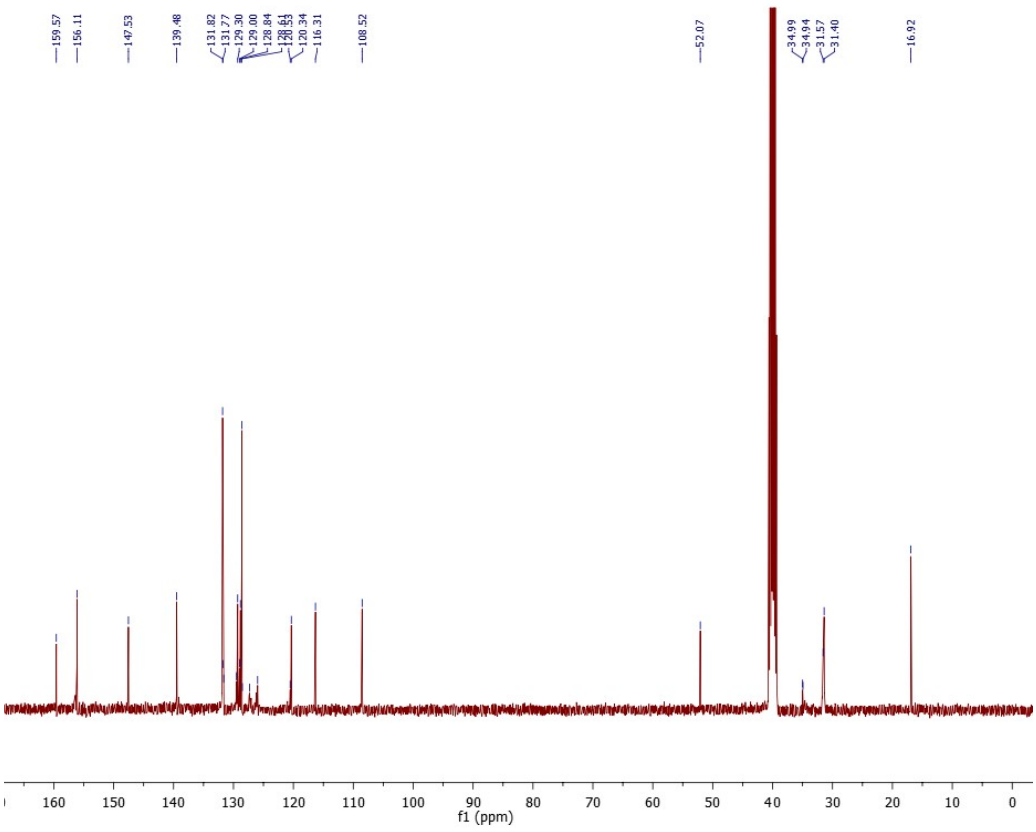
^{13}C NMR spectrum of compound **3g** in DMSO-d_6.

HRMS spectrum of compound **3g**.

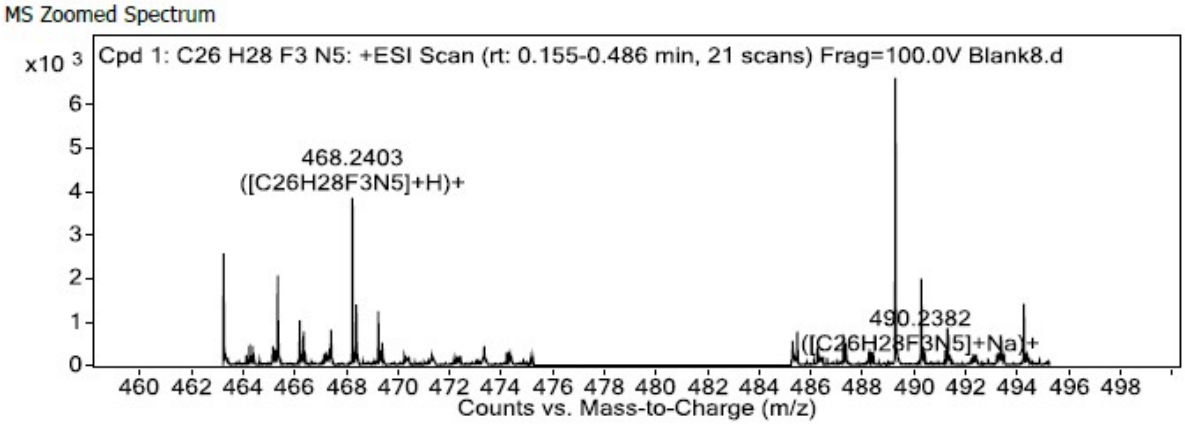


^{1}H NMR spectrum of compound **3h** in DMSO-d_6.



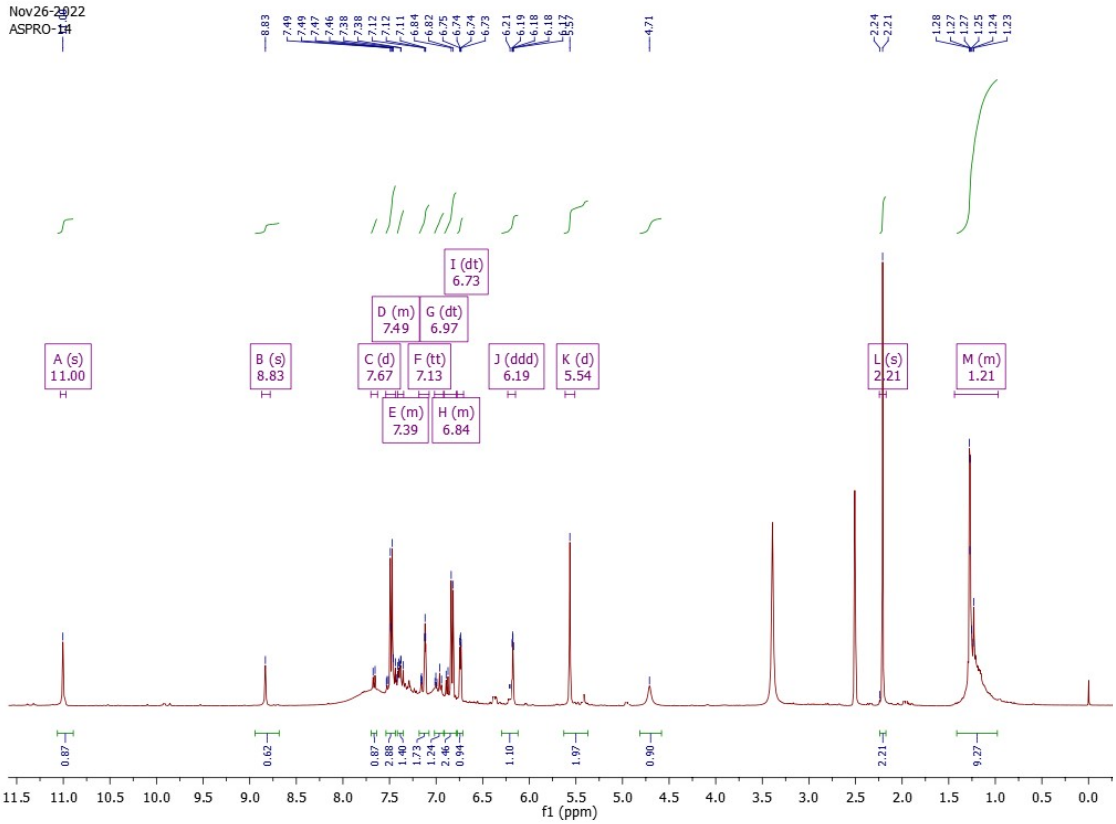


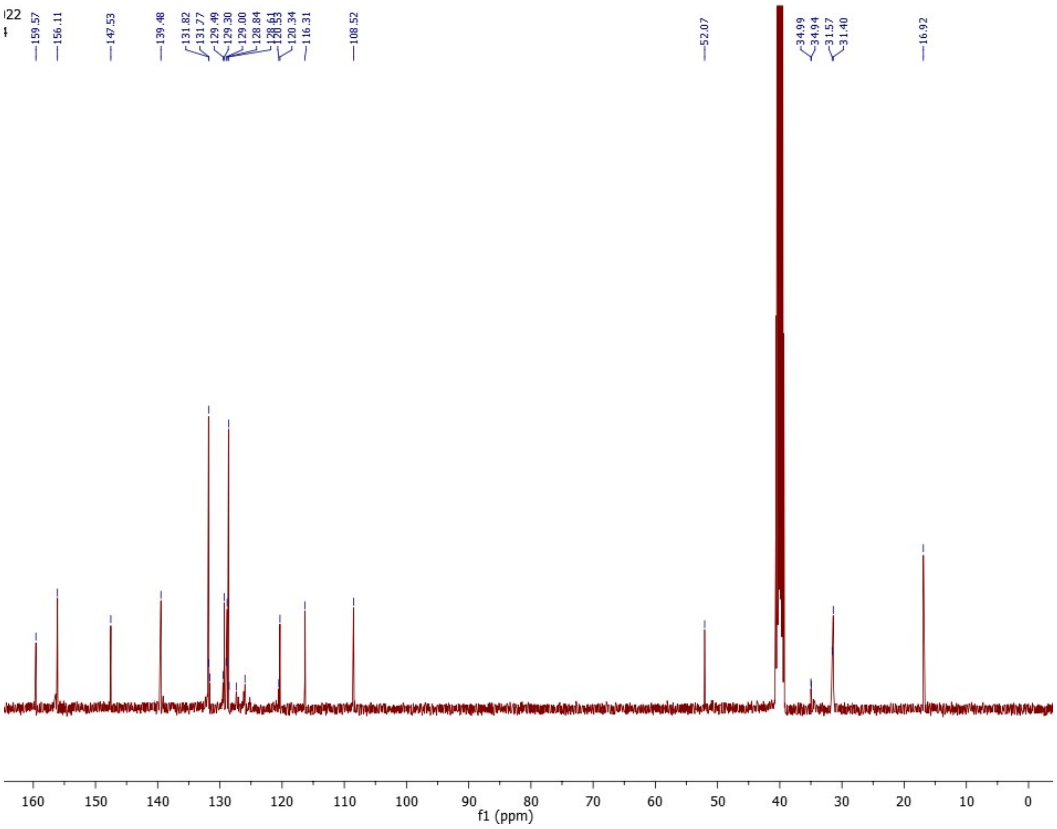
^{13}C NMR spectrum of compound **3h** in DMSO-d_6.



HRMS spectrum of compound **3h**.

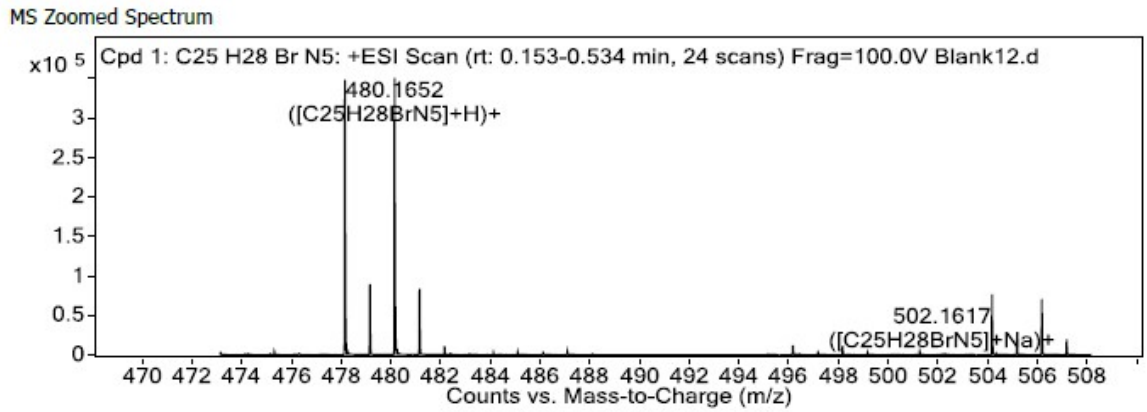
^{1}H NMR spectrum of compound **3i** in DMSO-d_6.



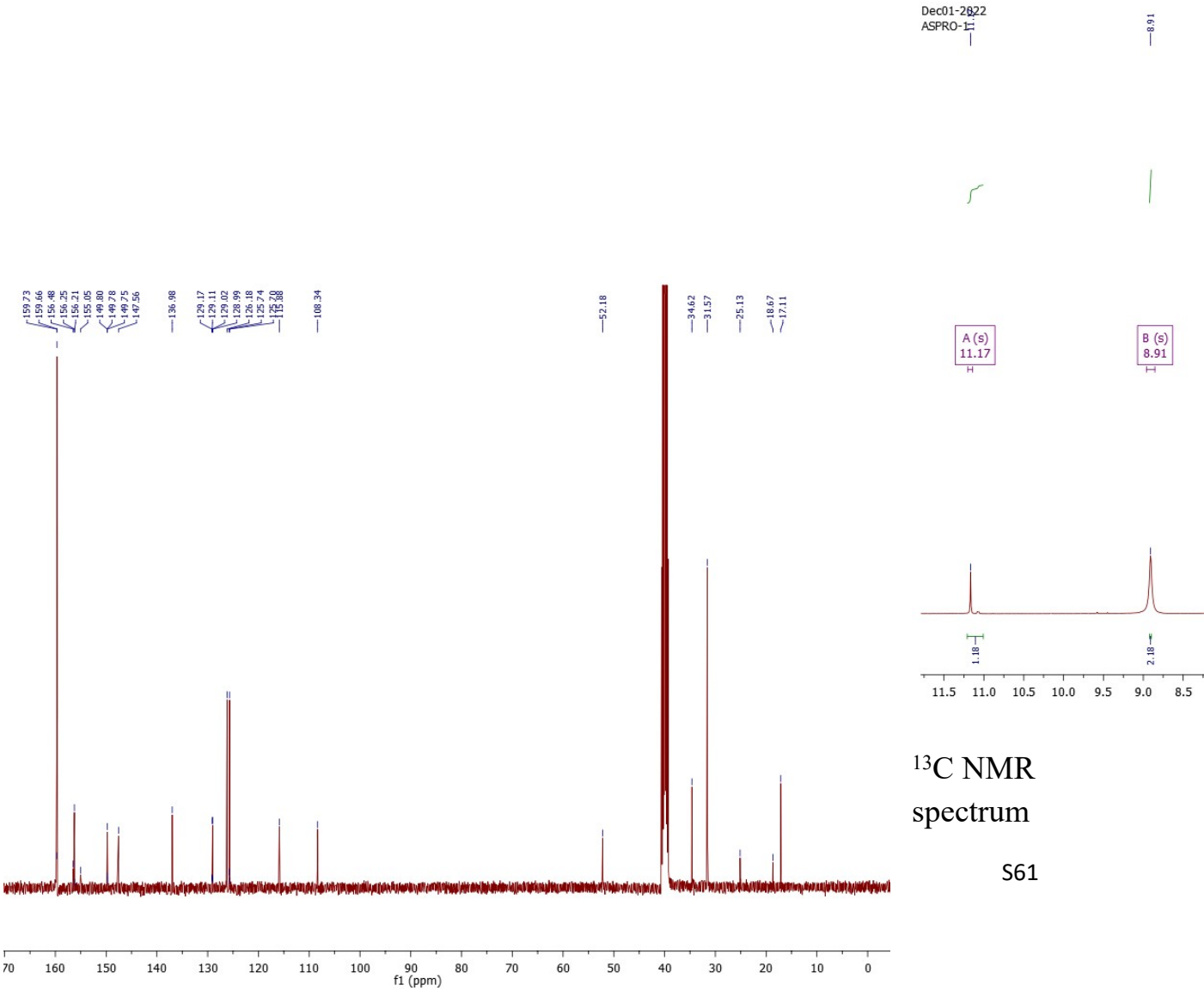


^{13}C NMR spectrum of compound **3i** in DMSO-d_6.

HRMS spectrum of compound **3i**.

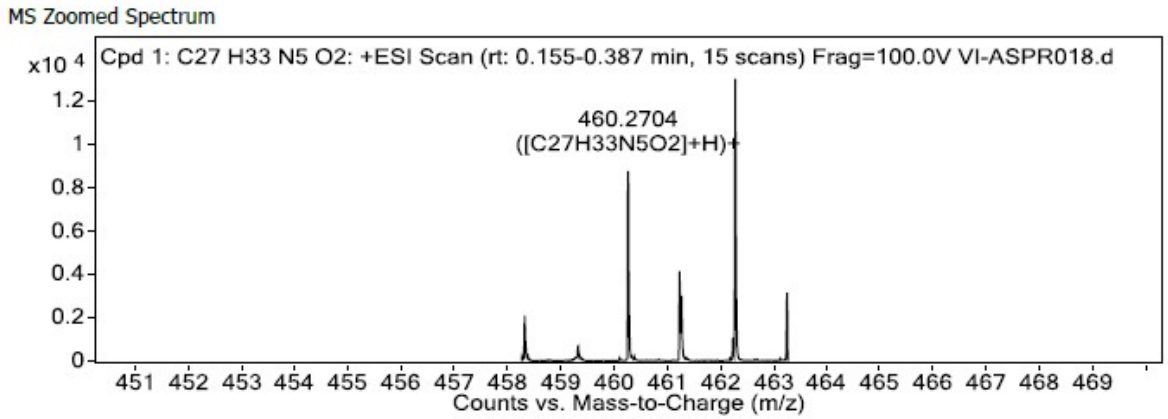


^{1}H NMR spectrum of compound **3j** in DMSO-d_6.



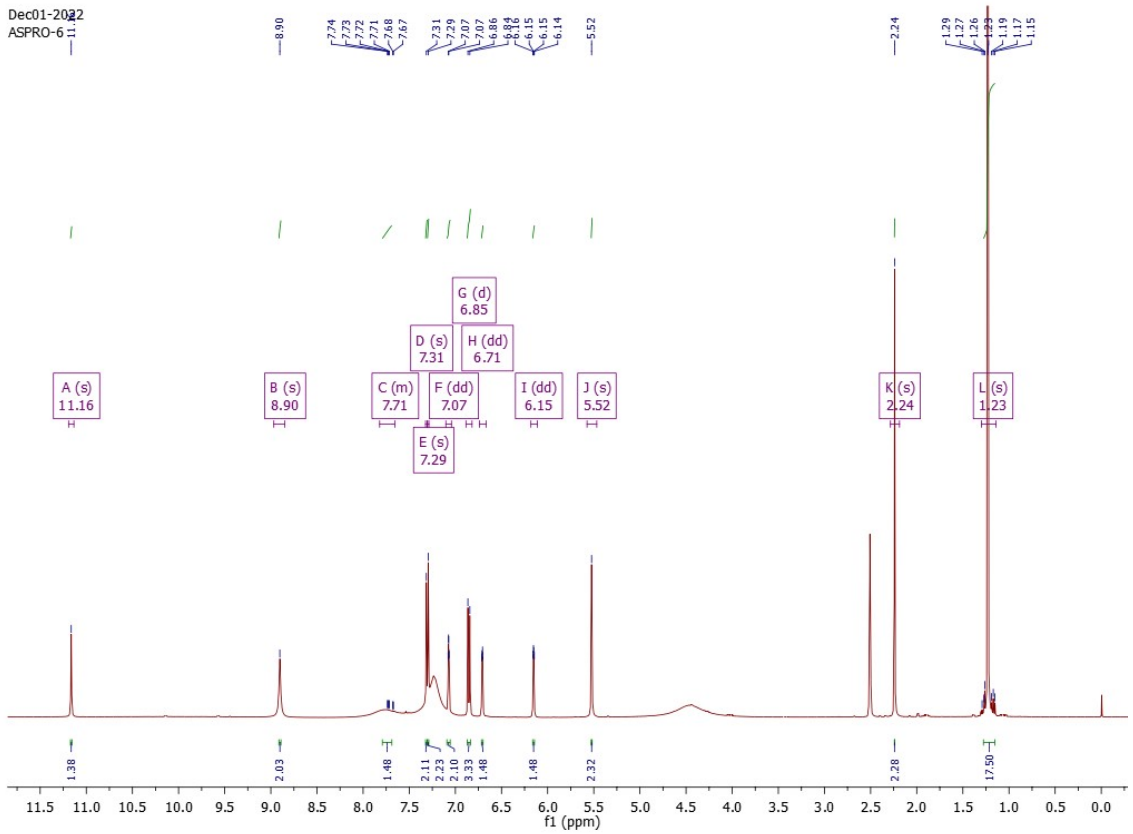
^{13}C NMR spectrum

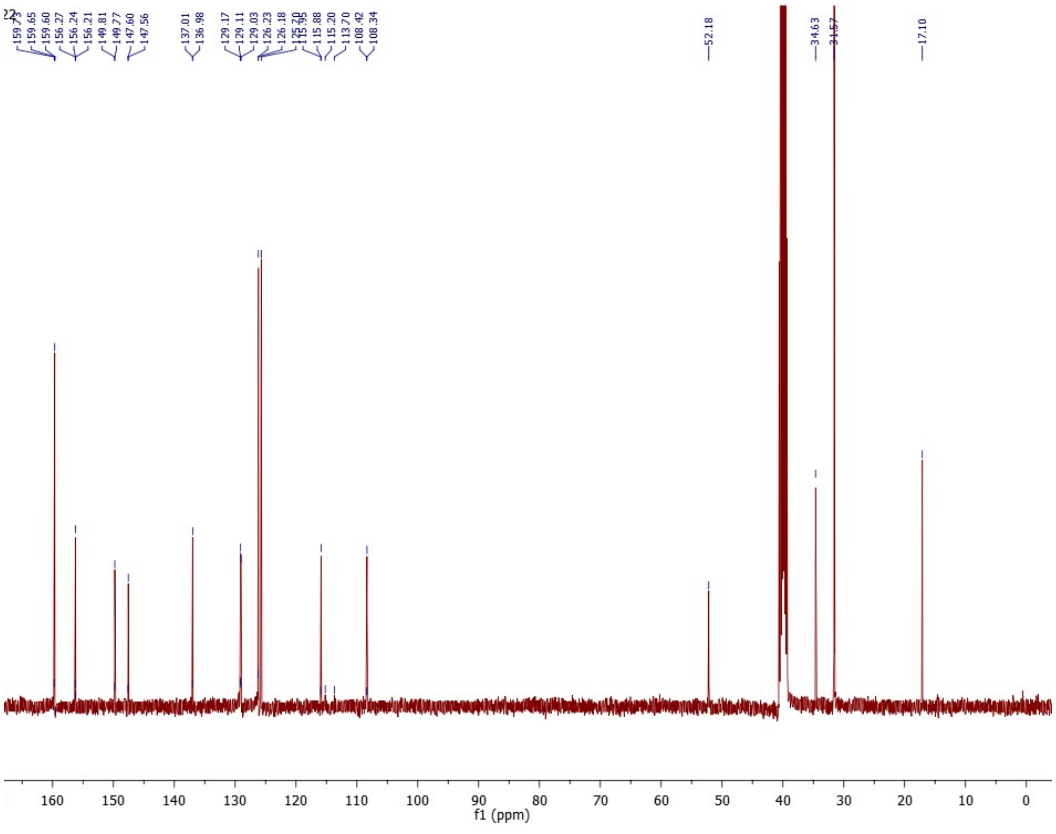
of compound **3j** in DMSO-d_6.



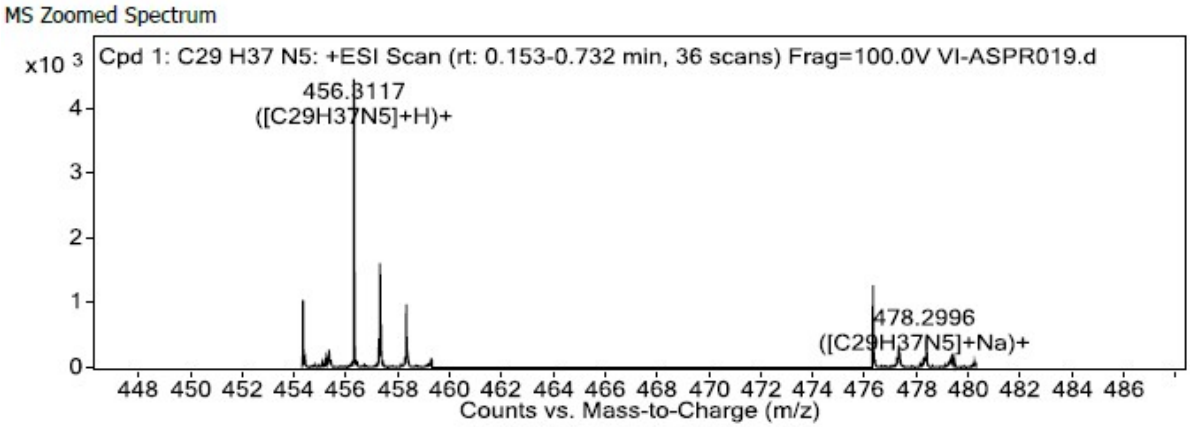
HRMS spectrum of compound **3j**.

^{1}H NMR spectrum of compound **3k** in DMSO-d_6.





^{13}C NMR spectrum of compound **3k** in DMSO-d_6.



HRMS spectrum of compound **3k**.

Table 1. Interactions of the representative compounds in the active site of BACE 1 (6UWP)

Compounds	Glide score	Hydrogen Bonds Interacting residues and bonding	Hydrophobic Interactions

	(Kcal/mol)	distance	
1c	-9.35	Asp32 (1.85Å), Asp228 (2.49 Å), Thr231 (2.44 Å), Asn233 (2.48 Å), Ser325 (1.59 Å)	Tyr71 (π-π stacked, 3.42 Å), Gln73 (π-π stacked, 2.54 Å), Thr231 (π-π stacked,1.79 Å), Thr232 (π-π stacked, 2.34 Å)
1d	-8.22	Asp228 (1.80Å)	Asp228 (salt bridge, 2.79Å)
1j	-8.03	Asp32 (2.43Å and 1.89Å), Asp228 (2.14 Å), Tyr198 (1.65 Å), Ser35 (1.45Å)	Tyr71 (π-π stacked, 4.02Å), Trp76 (π-π stacked, 2.80Å), Ile126 (π-π stacked, 5.49 Å), Ile226 (π-π stacked, 3.25 Å), Val332 (π-π stacked, 2.58 Å)
2c	-8.58	Asp32 (1.99Å and 1.89Å), Asp228 (1.94 Å), Phe108 (1.65 Å), Ser10 (2.64 Å), Thr232 (1.32 Å), Gly230 (1.24 Å), Gly13 (1.84 Å)	Tyr71 (π-π stacked, 2.22 Å), Gln12 (halogen bond, 1.59 Å), Ser229 (halogen bond, 2.34 Å), Thr231 (halogen bond, 1.57 Å)
2h	-7.94	Asp32 (1.96Å and 1.75Å), Asp228 (2.31 Å), Thr232 (1.35 Å), Phe108 (1.88 Å)	Thr231 (π-π stacked, 1.54 Å), Gly11 (π-π stacked, 2.11 Å), Ser10 (π-π stacked, 2.55 Å), Ile110 (π-π stacked, 2.36 Å)
2j	-8.64	Asp32 (2.40Å), Asp228 (2.11 and 1.75 Å)	Tyr71 (π-π stacked, 5.28 Å), Arg128 (pi- cation, 3.26 Å), Asp228 (salt bridge, 2.71Å)
2k	-7.69	Asp32 (2.16 and 1.88Å), Asp228 (1.71Å)	Tyr71 (π-π stacked, 3.99 Å)
2l	-6.22	Asp32 (1.74 and 1.90Å)	Asp228 (salt bridge, 4.99 Å), Asp32 (salt bridge, 2.76Å)
2m	-7.34	Ile126 (2.15Å), Asn37 (1.89Å), Trp76 (2.54Å)	Gln73 (halogen bond, 3.25Å), Tyr71 (π-π stacked, 3.35 Å)
2n	-8.13	Trp76 (2.71Å), Asn37 (1.88Å)	-
3e	-9.87	Asp32 (1.57 and 2.50Å), Asp228 (2.25Å), Gly230	Tyr71 (π-π stacked, 2.34 Å)

		(1.34 Å), Arg235 (1.25 Å), Thr72 (1.58 Å), Thr71 (2.31 Å), Lys107 (1.75 Å),	
3k	-9.35	Asp32 (1.77 and 2.12Å)	Asp228 (salt bridge, 4.81Å), Asp32 (salt bridge, 2.93Å)

Table 2. Interactions of the representative compounds in the active site of AChE (4EY7)

Compounds	Glide score (Kcal/mol)	Hydrogen Bonds Interacting residues and bonding distance	Hydrophobic Interactions
1a	-10.07	Ser203 (1.87Å)	Phe338 (π-π stacked, 5.05 Å)
1c	-11.47	His447 (1.64 and 2.12Å), Asp74 (1.85Å), Gly121 (1.75Å), Ser125 (1.35Å), Val73 (1.38Å), Asn87 (2.15Å), Pro88 (1.68Å),	Tyr124 (π-π stacked, 4.27 Å), His447 (π-π stacked, 4.21 Å), Tyr337 (π-π stacked, 3.85 Å), Trp86 (π-π stacked, 2.75 Å)
1d	-10.12	His447 (2.38Å)	Trp86 (π-cation, 3.12 Å), Phe338 (π-π stacked, 5.47 Å), His447 (π-π stacked, 5.01 Å), Tyr341 (π-π stacked, 3.98 Å),
1j	-12.26	Asp74 (2.22Å), Tyr341 (1.74Å), His447 (2.14Å), Gly121 (1.22Å), Tyr133 (2.35Å),	Gly120 (π-π stacked, 3.68Å), Leu130 (π-π stacked, 3.97 Å), Glu202 (π-π stacked, 2.82 Å), Trp86 (π-π stacked, 1.89 Å), His447 (π-π stacked, 2.48 Å)
2c	-11.31	Ser203 (2.80Å), His447 (2.14 and 2.12Å), Gly121 (1.36Å), Phe338 (1.59Å)	Tyr124 (π-π stacked, 3.65 Å), Ser125 (π-π stacked, 2.31Å), Trp86 (π-π stacked, 3.43 Å), Tyr 337 (π-π stacked, 1.45 Å), Tyr337 (halogen bond, 1.45 Å), Phe338 (π-π stacked, 1.35 Å)
2h	-12.59	Ser125 (2.15 and 2.12Å), Gly120 (1.36 and 2.36Å),	Trp86 (π-π stacked, 3.42 Å), Tyr341 (π-π stacked, 2.37 Å),

		Trp86 (1.37Å), Gly121 (2.68Å), Asp74 (1.39Å), Tyr341 (3.49Å), Gly448 (1.29Å)	Tyr337 (π-π stacked, 1.39 Å), Phe338 (π-π stacked, 2.49 Å), Gly448 (π-π stacked, 2.31 Å), His447 (halogen bond, 2.24Å),
2j	-6.29	Glu202 (2.07Å)	Phe338 (π-π stacked, 4.37 Å), Tyr124 (π-π stacked, 5.41 Å)
2k	-12.54	-	Trp86 (π-π stacked, 5.00 and 5.23 Å), Phe338 (π-π stacked, 3.97Å), Tyr341 (π-π stacked, 4.93 Å), Trp286 (π-π stacked, 4.21 Å)
2l	-10.15	Glu202 (1.91 and 2.08Å), Phe295 (2.21Å)	Tyr124 (π-π stacked, 5.40 Å), Tyr337 (π-π stacked, 3.90Å), Glu202 (salt bridge, 3.02Å)
2m	-10.04	His447 (2.08Å)	Phe338 (π-π stacked, 4.87 Å), Tyr124 (π-π stacked, 5.47Å), Tyr72 (halogen bond, 3.39 Å), Asp74 (halogen bond, 2.84Å)
2n	-9.99	Glu202 (2.20Å)	Tyr124 (π-π stacked, 5.43 and 5.45Å), Tyr341 (π-π stacked, 3.85Å),
2p	-10.14	Glu202 (2.16Å), His447 (2.22Å)	Tyr124 (π-π stacked, 5.49Å), His447 (π-π stacked, 5.27Å), Phe338 (π-π stacked, 4.32Å), Tyr341 (π-π stacked, 3.91Å)
2q	-9.08	Glu202 (2.00 and 1.77Å)	His447 (π-π stacked, 5.25Å), Tyr124 (π-π stacked, 5.40Å), Tyr341 (π-π stacked, 3.75Å)
3e	-11.47	Tyr341 (2.04Å), Phe295 (2.25Å), Val294 (1.65Å), Ser293 (2.38Å), Arg296 (1.28Å), Tyr337 (1.49Å), His447 (2.04 and 1.77Å), Trp86 and 1.54Å)	Trp86 (π-π stacked, 3.23 and 2.31Å), Trp286 (π-π stacked, 4.46Å), Phe297 (π-π stacked, 1.83Å)

3k	-12.73	Asp74 (2.03Å)	Tyr337 (π-π stacked, 5.48Å), Asp74 (salt bridge, 2.95Å)