SUPPORTING INFORMATION

Synthesis of Novel Benzothiazol Derivatives and Investigation of Their Enzyme Inhibitor Effects Against Alzheimer's Disease

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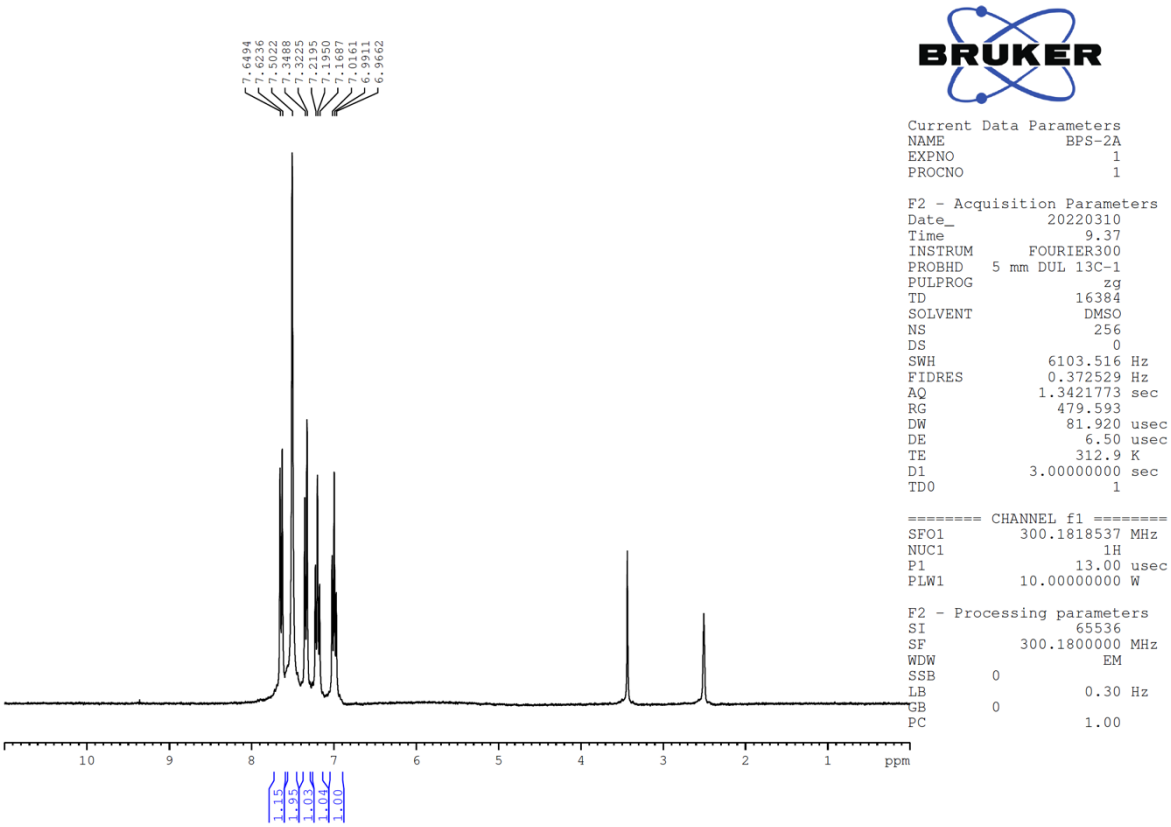

Figure S1. ^{1}H-NMR spectra of compounds **2a**

Formula Predictor Report - BPS-2A_226.lcd

Data File: C:\LabSolutions\Data\Analiz\derya\BPS-2A_226.lcd

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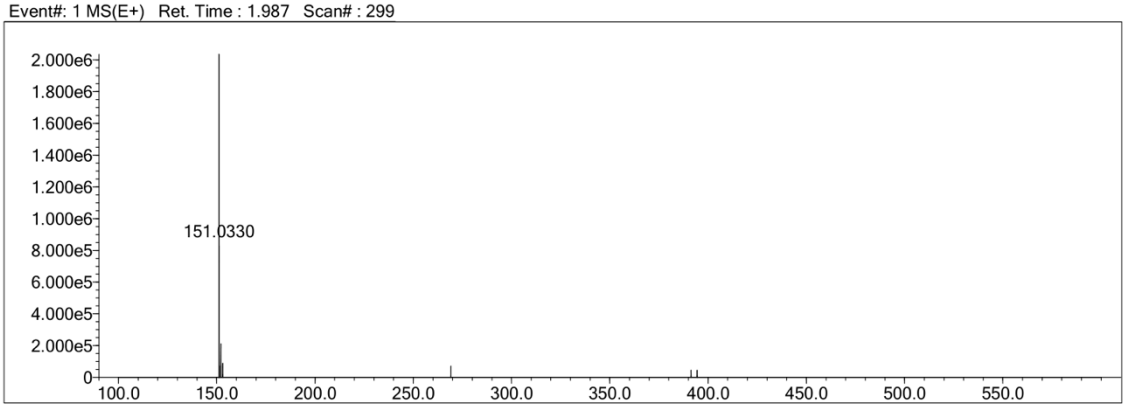
C	4	5	30	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	0	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

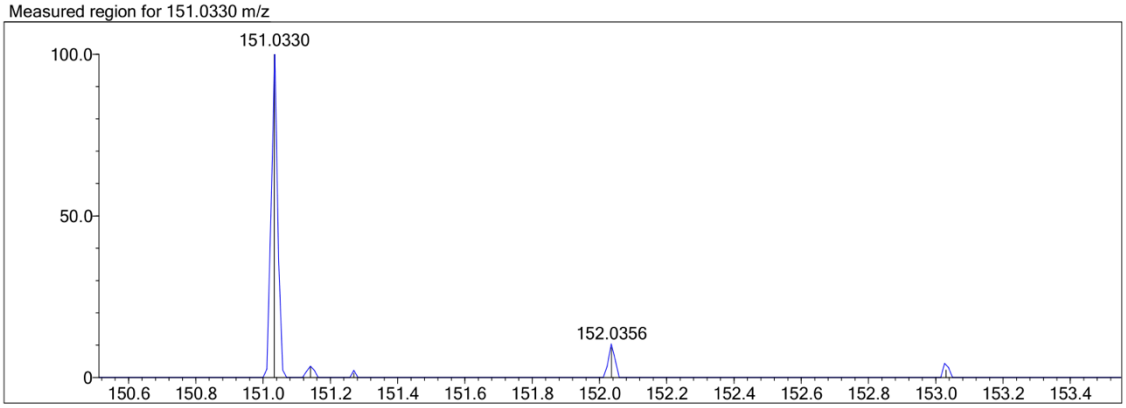
DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

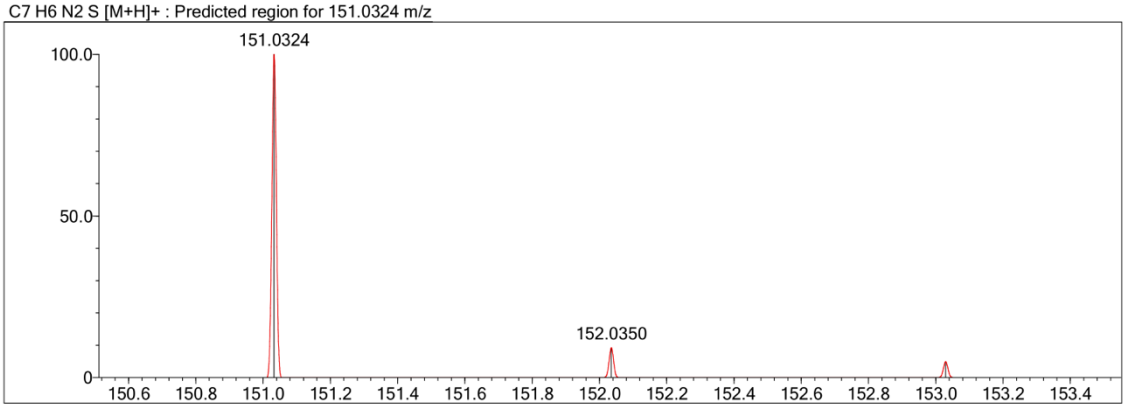
Event#: 1 MS(E+) Ret. Time : 1.987 Scan# : 299



Measured region for 151.0330 m/z



C7 H6 N2 S [M+H]+ : Predicted region for 151.0324 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	67.82	C7 H6 N2 S	[M+H]+	151.0330	151.0324	0.6	3.97	73.26	6.0

Figure S2. HRMS spectra of compounds **2a**

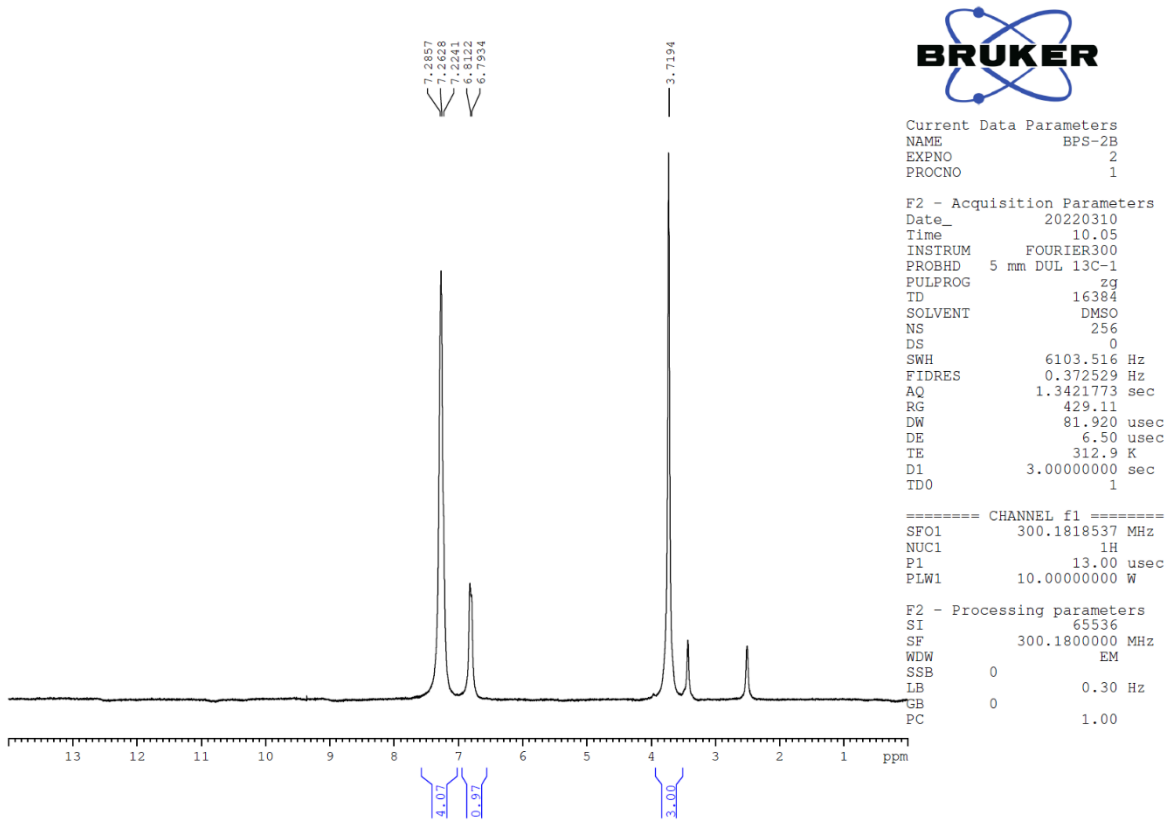


Figure S3. ^{1}H-NMR spectra of compounds **2b**

Formula Predictor Report - BPS-2B_227.lcd

Data File: C:\LabSolutions\Data\Analiz\derya\BPS-2B_227.lcd

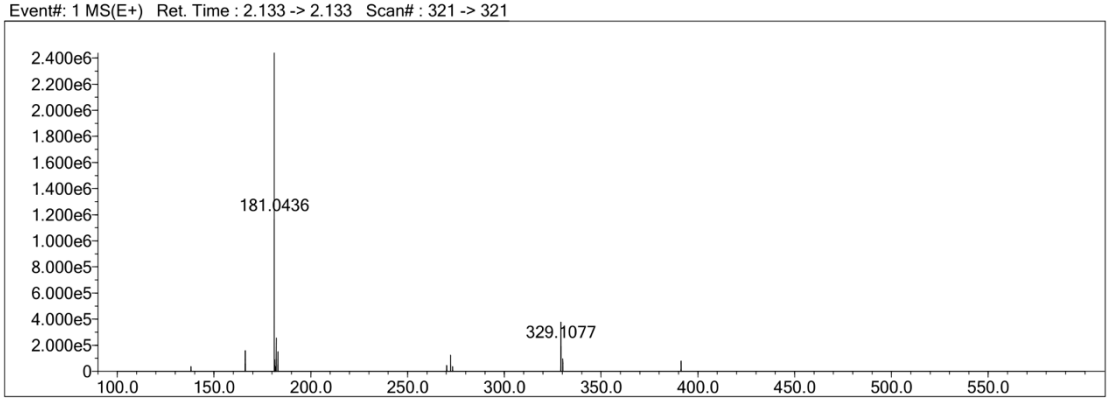
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	5	35	O	2	0	5	S	2	1	1	Ru	2	0	0	H
C	4	5	30	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	0	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

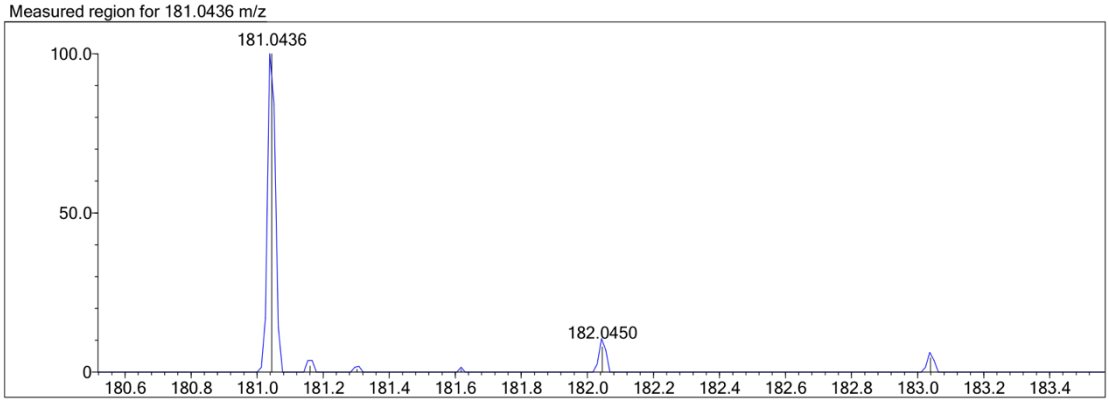
DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

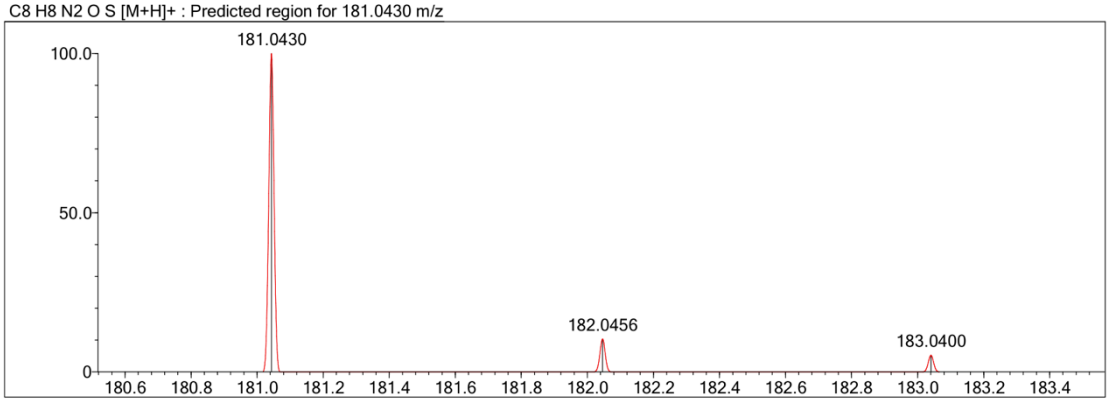
Event#: 1 MS(E+) Ret. Time : 2.133 -> 2.133 Scan# : 321 -> 321



Measured region for 181.0436 m/z



C8 H8 N2 O S [M+H]+ : Predicted region for 181.0430 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	79.33	C8 H8 N2 O S	[M+H]+	181.0436	181.0430	0.6	3.31	84.20	6.0

Figure S4. HRMS spectra of compounds **2b**

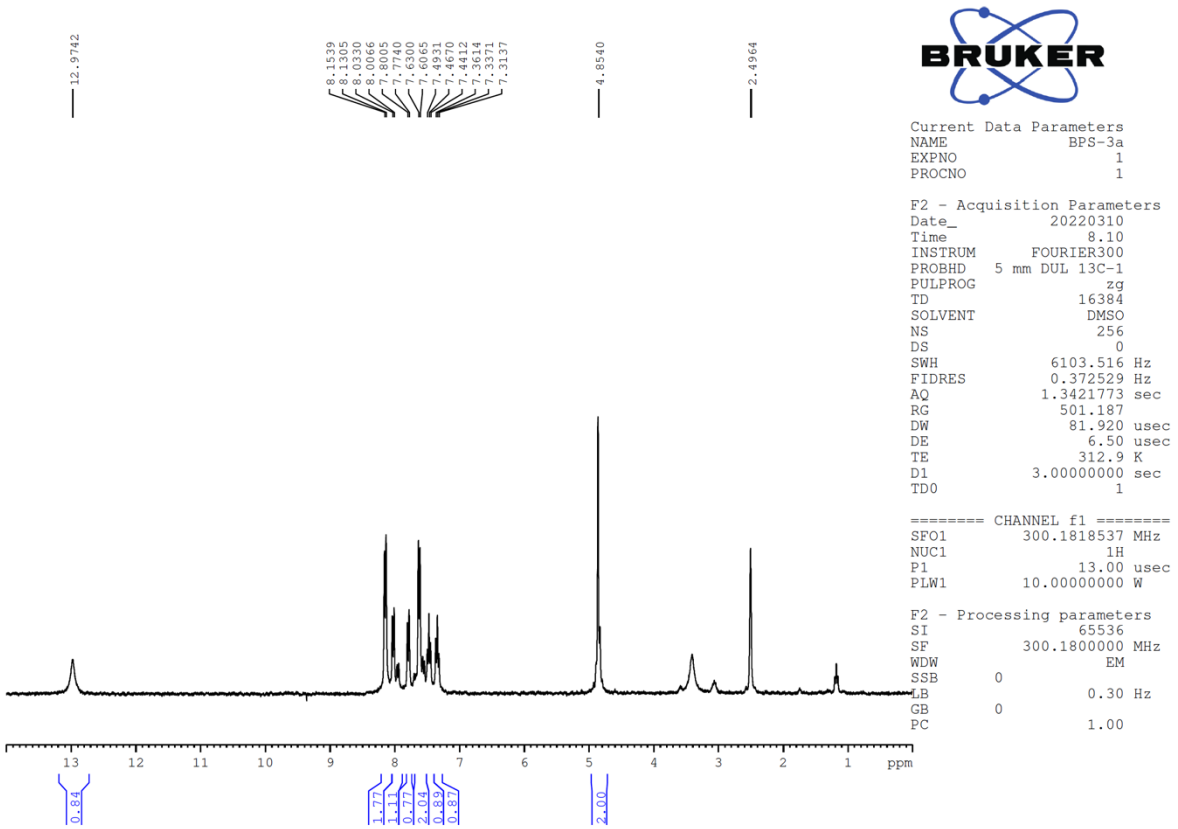


Figure S5. ^{1}H-NMR spectra of compounds **3a**

Formula Predictor Report - BPS-3A_229.lcd

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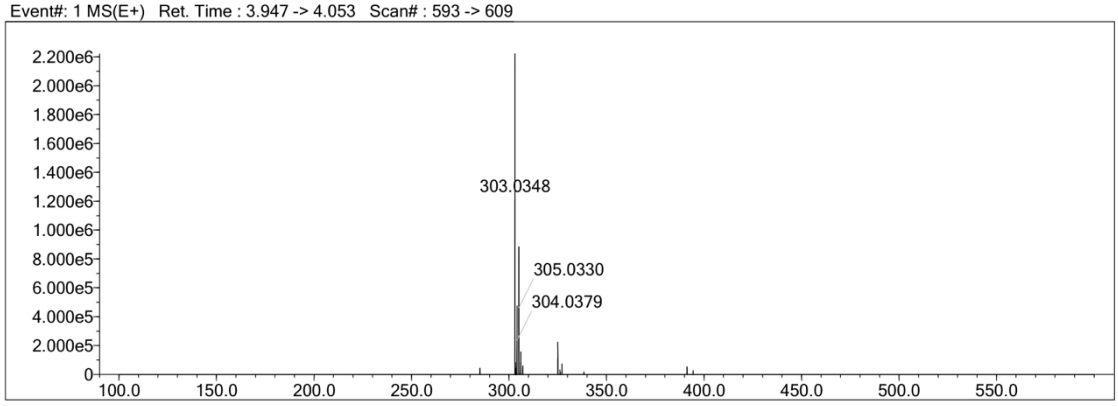
Data File: C:\LabSolutions\Data\Analiz\derya\BPS-3A_229.lcd

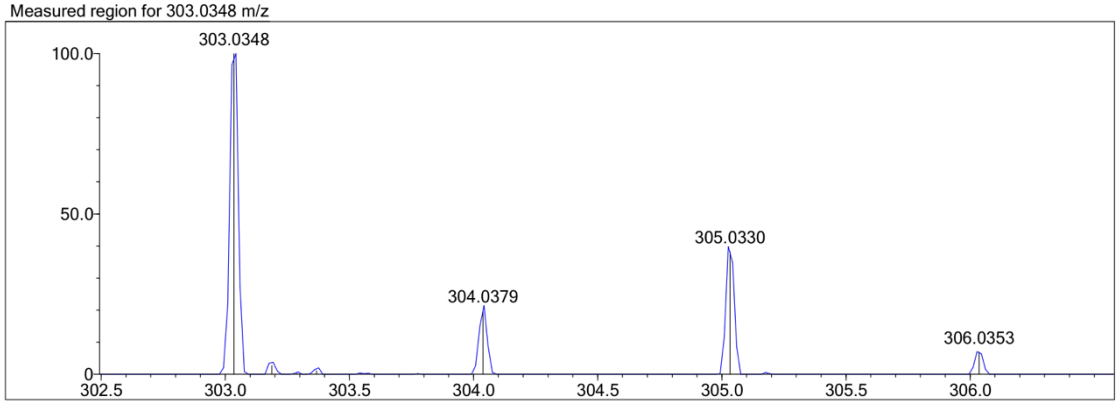
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	5	35	O	2	0	5	S	2	1	1	Ru	2	0	0	H
C	4	5	30	F	1	0	0	Cl	1	0	1	Pd	2	0	0	
N	3	0	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm):	5	DBE Range:	5.0 - 15.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	yes
Max Isotopes:	3	Isotope RI (%):	1.00	Isotope Res:	9000
MSn Iso RI (%):	10.00	MSn Logic Mode:	AND	Max Results:	500

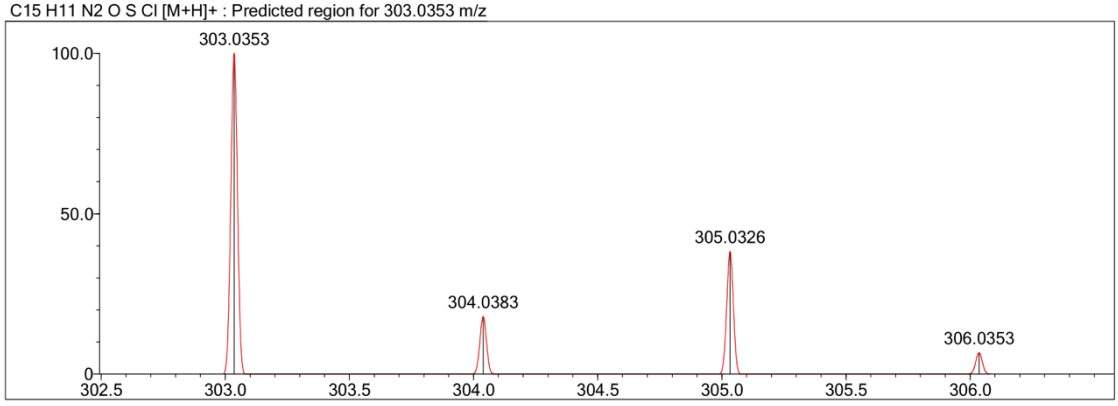
Event#: 1 MS(E+) Ret. Time : 3.947 -> 4.053 Scan# : 593 -> 609



Measured region for 303.0348 m/z



C15 H11 N2 O S Cl [M+H]+ : Predicted region for 303.0353 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.38	C15 H11 N2 O S Cl	[M+H]+	303.0348	303.0353	-0.5	-1.65	100.00	11.0

Figure S6. HRMS spectra of compounds **3a**

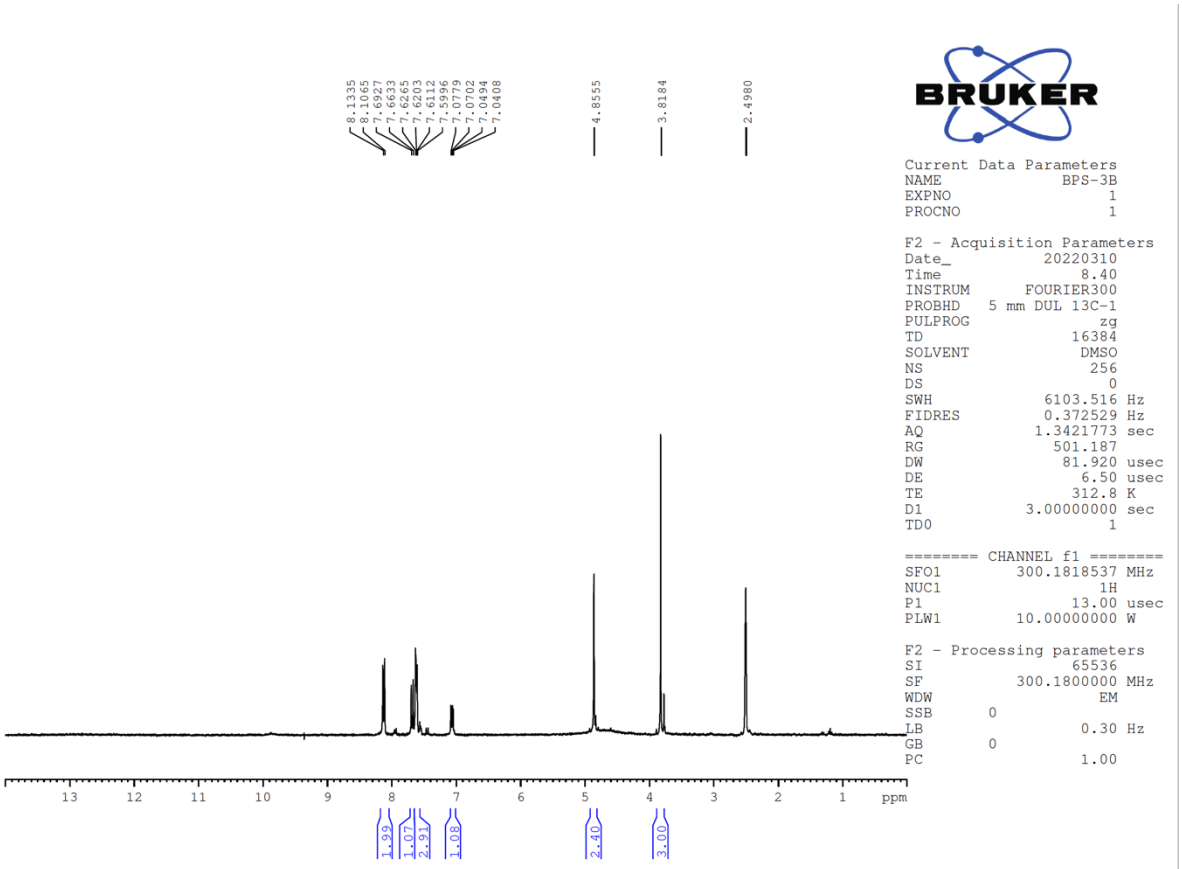


Figure S7. ^{1}H-NMR spectra of compounds **3b**

Formula Predictor Report - BPS-3B_228.lcd

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Data File: C:\LabSolutions\Data\Analiz\derya\BPS-3B_228.lcd

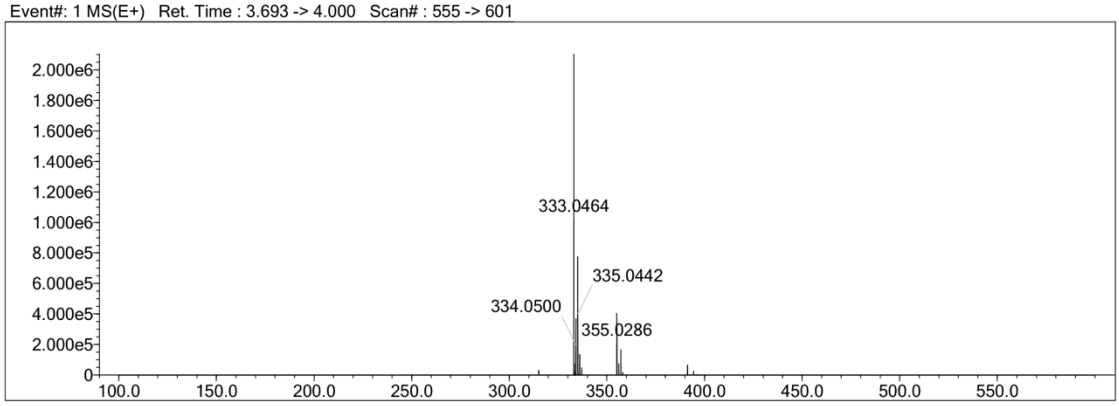
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	5	35	O	2	0	5	S	2	1	1	Ru	2	0	0	H
C	4	5	30	F	1	0	0	Cl	1	0	1	Pd	2	0	0	
N	3	0	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

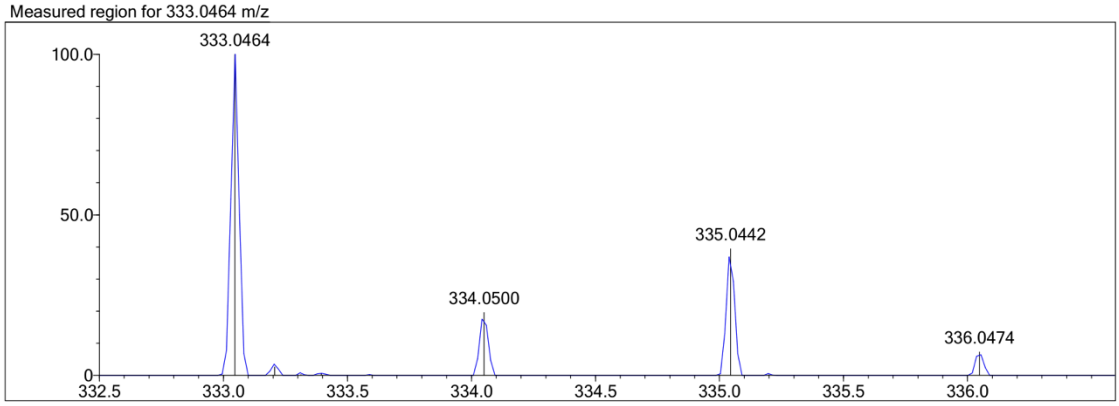
DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

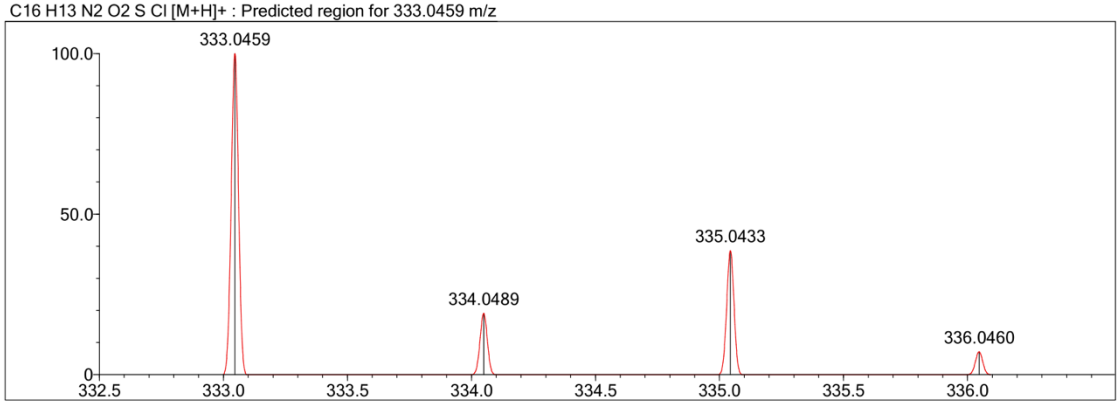
Event#: 1 MS(E+) Ret. Time : 3.693 -> 4.000 Scan# : 555 -> 601



Measured region for 333.0464 m/z



C16 H13 N2 O2 S Cl [M+H]+ : Predicted region for 333.0459 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	91.87	C16 H13 N2 O2 S Cl	[M+H]+	333.0464	333.0459	0.5	1.50	93.03	11.0

Figure S8. HRMS spectra of compounds **3b**

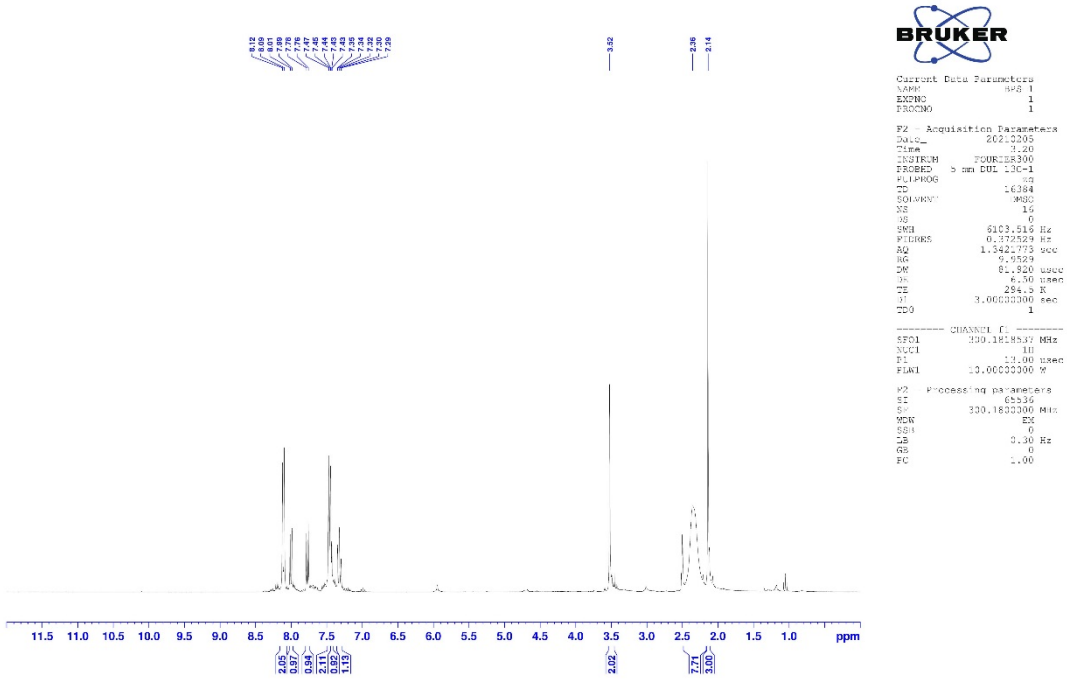


Figure S9. [1]H-NMR spectra of compounds **4a**

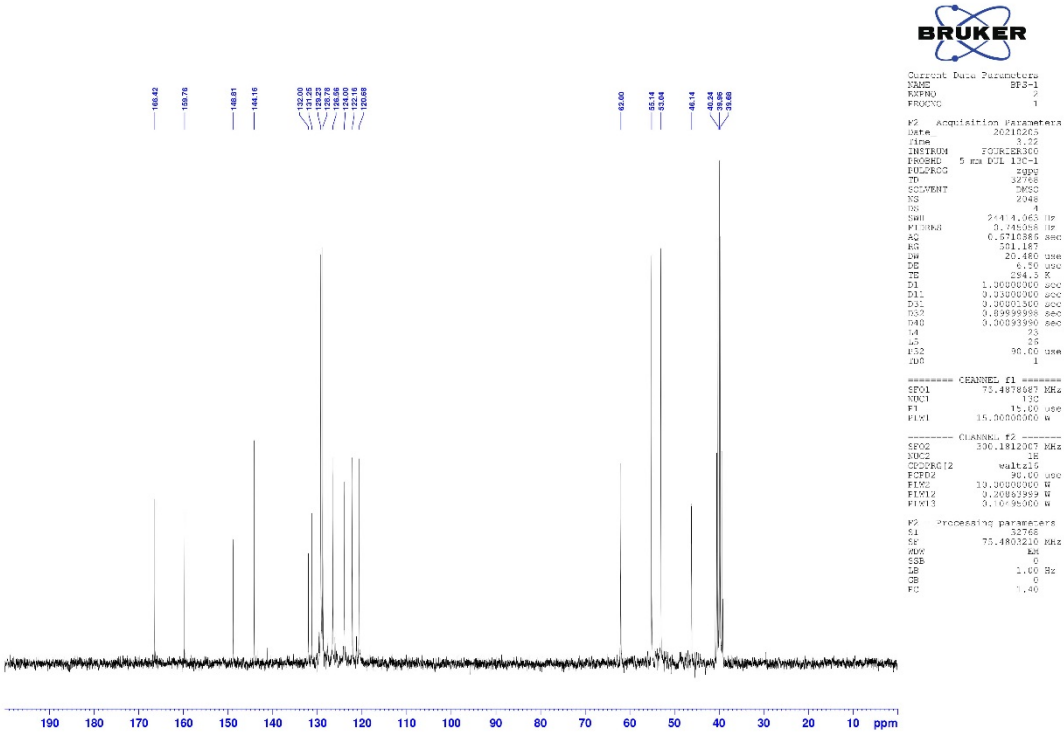


Figure S10. [13]C-NMR spectra of compounds **4a**

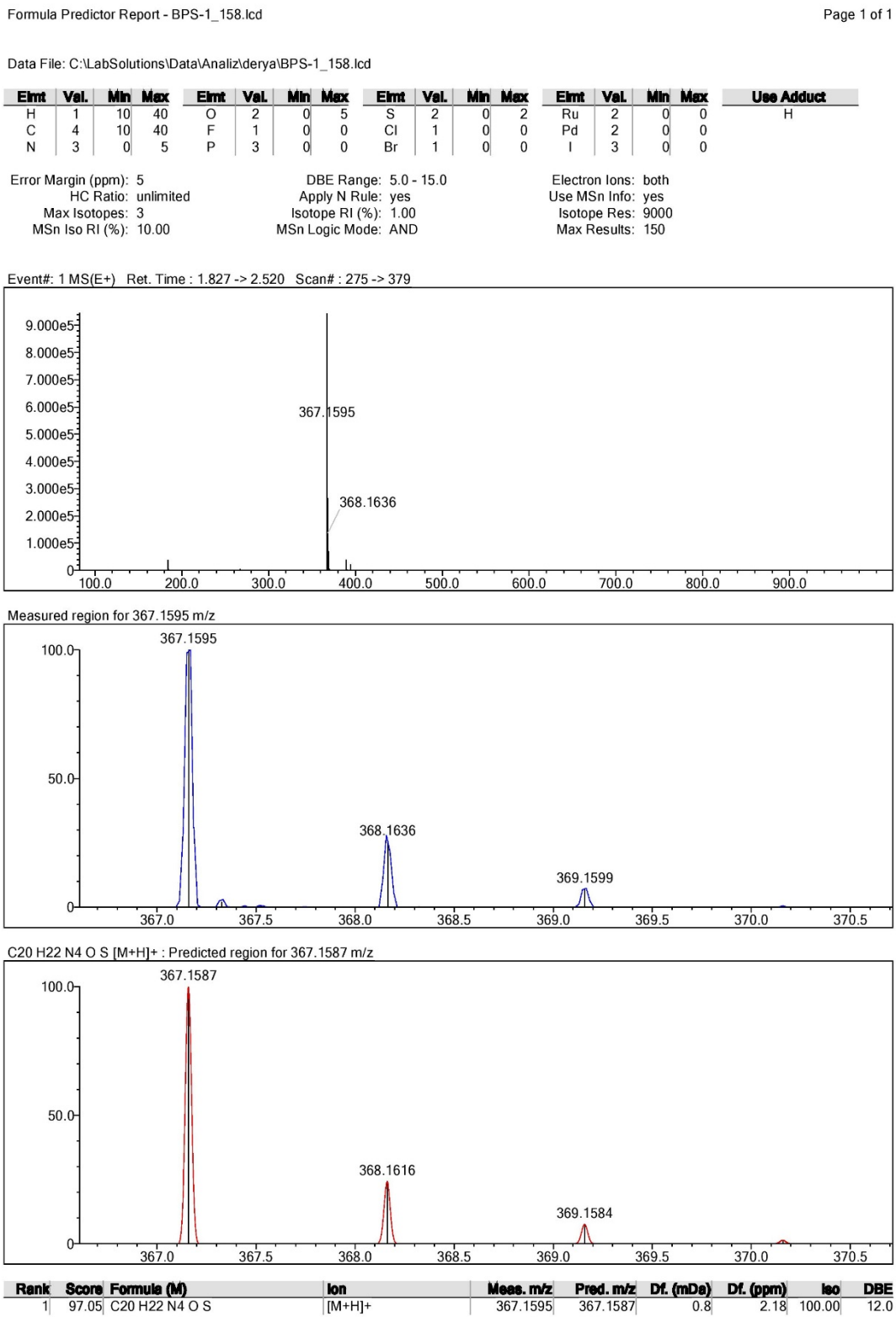


Figure S11. HRMS spectra of compounds **4a**

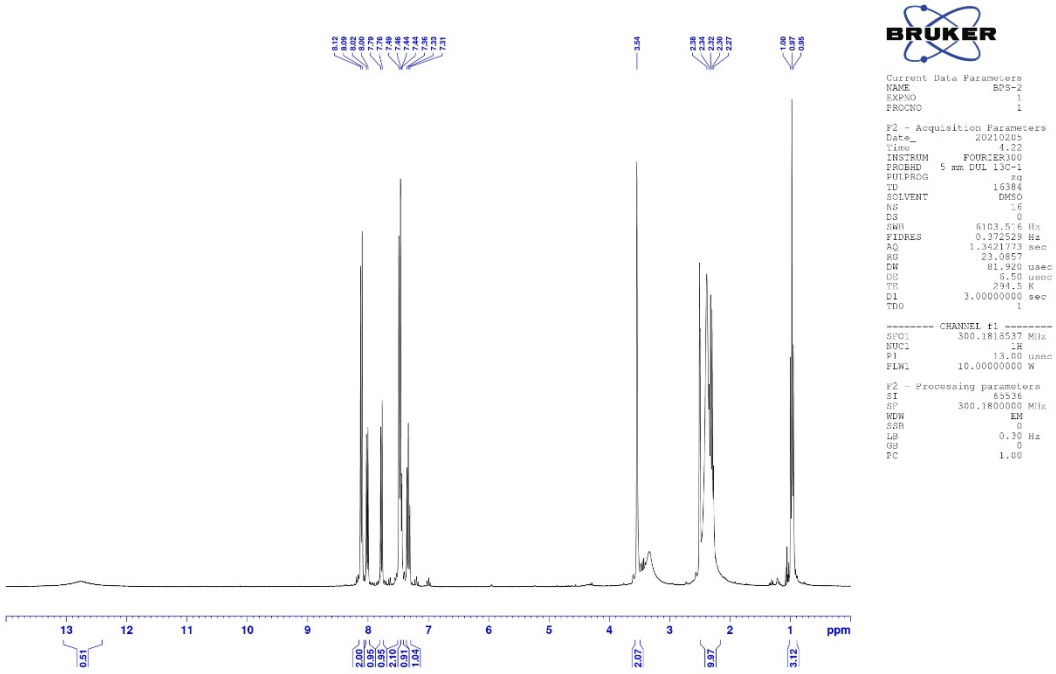


Figure S12. [1]H-NMR spectra of compounds **4b**

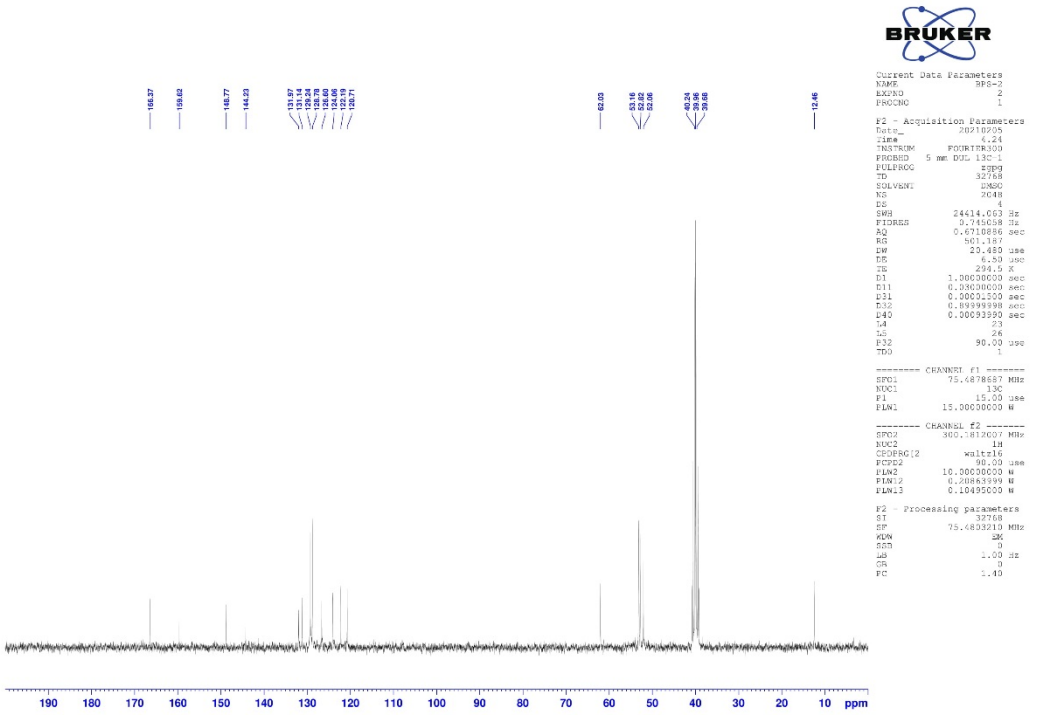


Figure S13. [13]C-NMR spectra of compounds **4b**

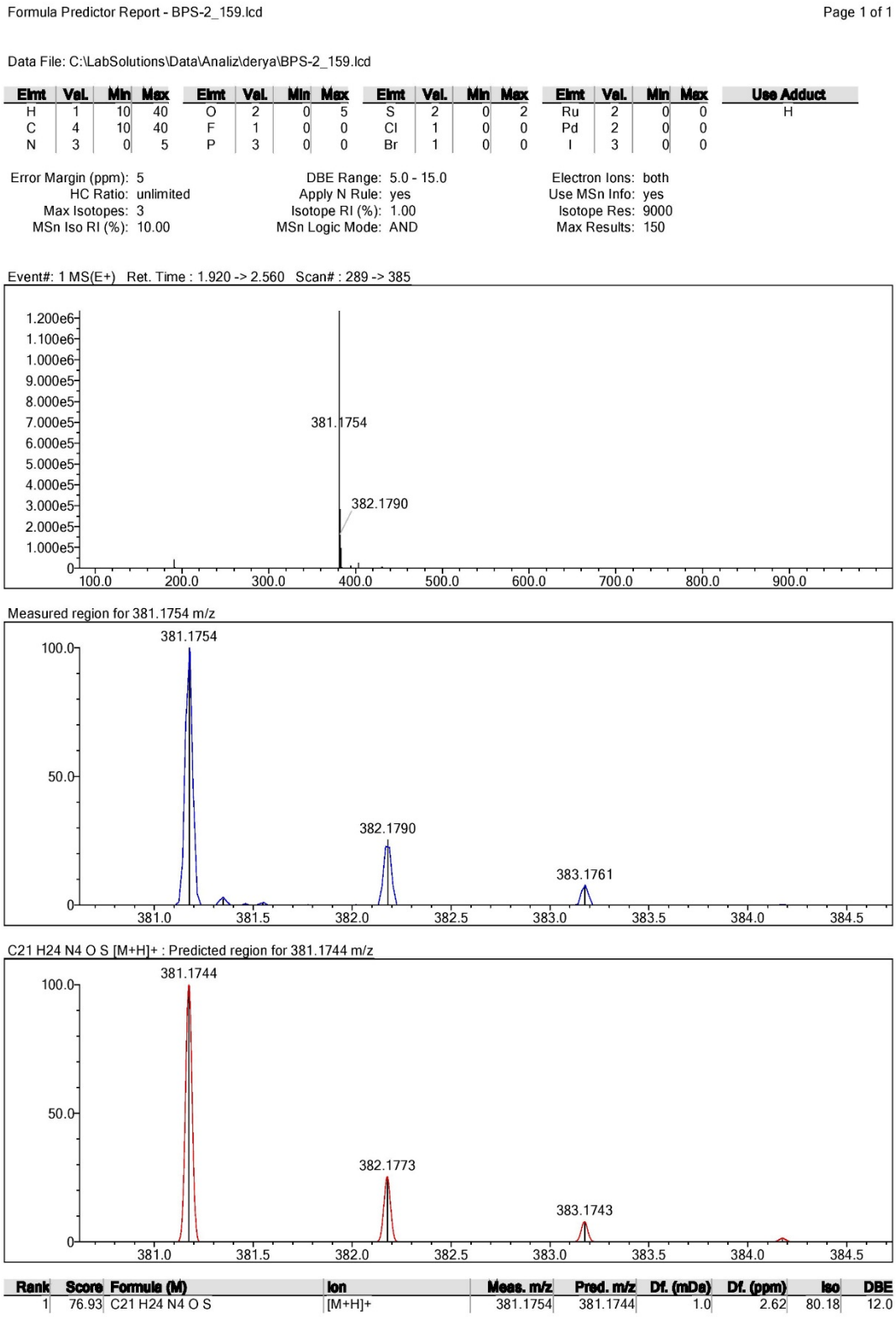


Figure S14. HRMS spectra of compounds **4b**

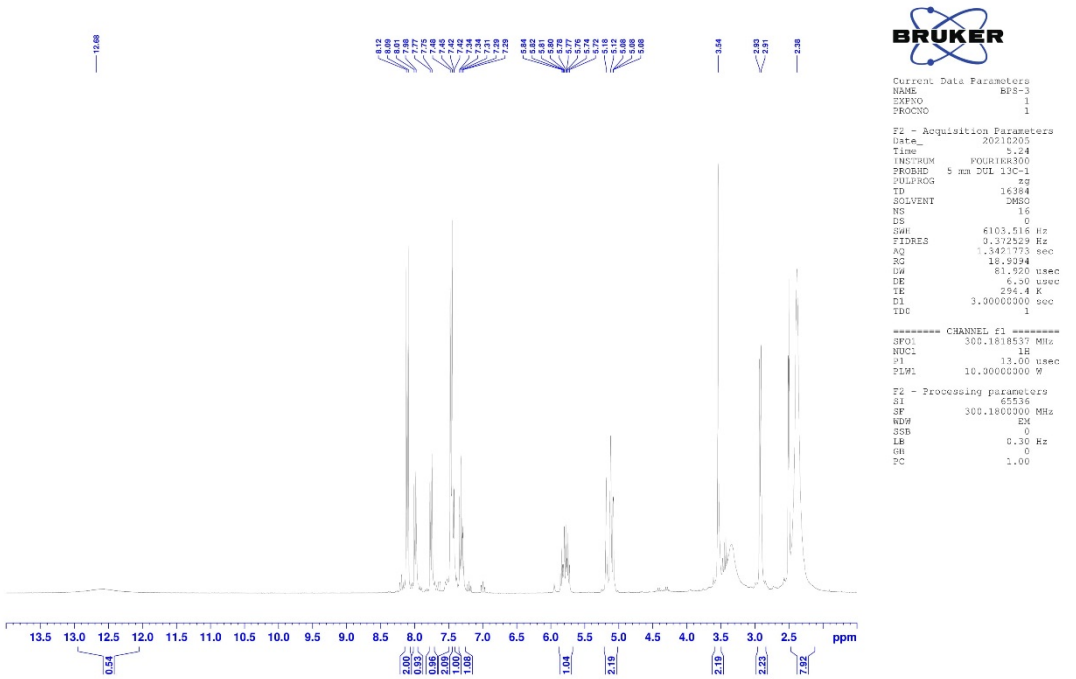


Figure S15. [1]H-NMR spectra of compounds **4c**

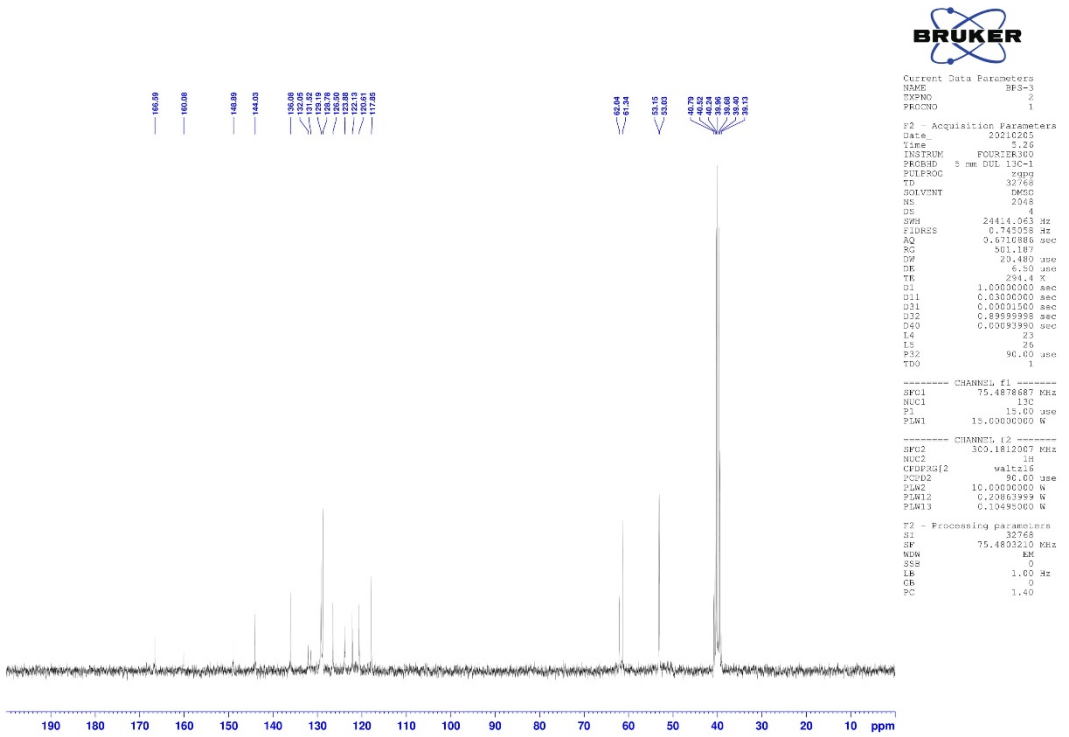


Figure S16. [13]C-NMR spectra of compounds **4c**

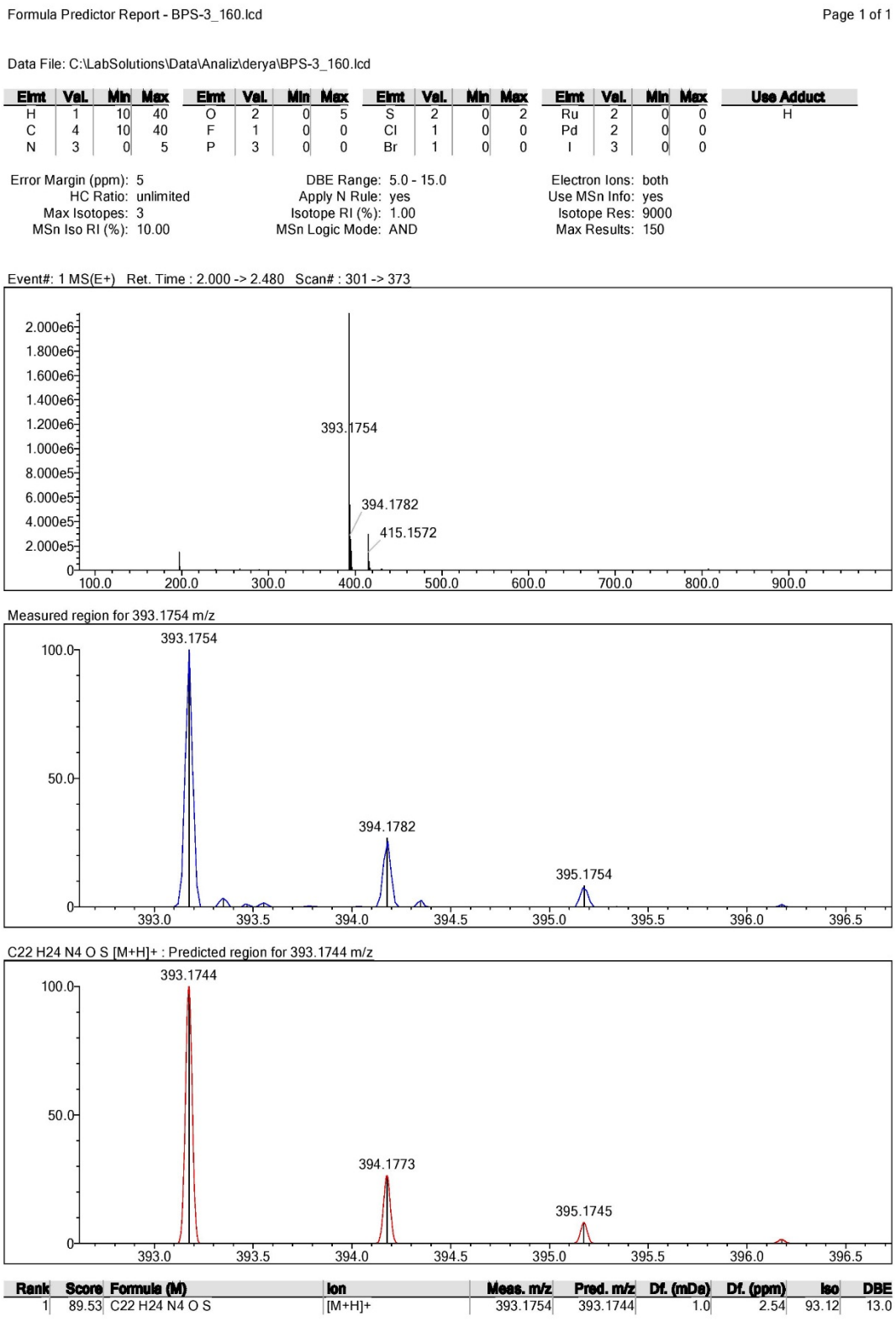


Figure S17. HRMS spectra of compounds **4c**

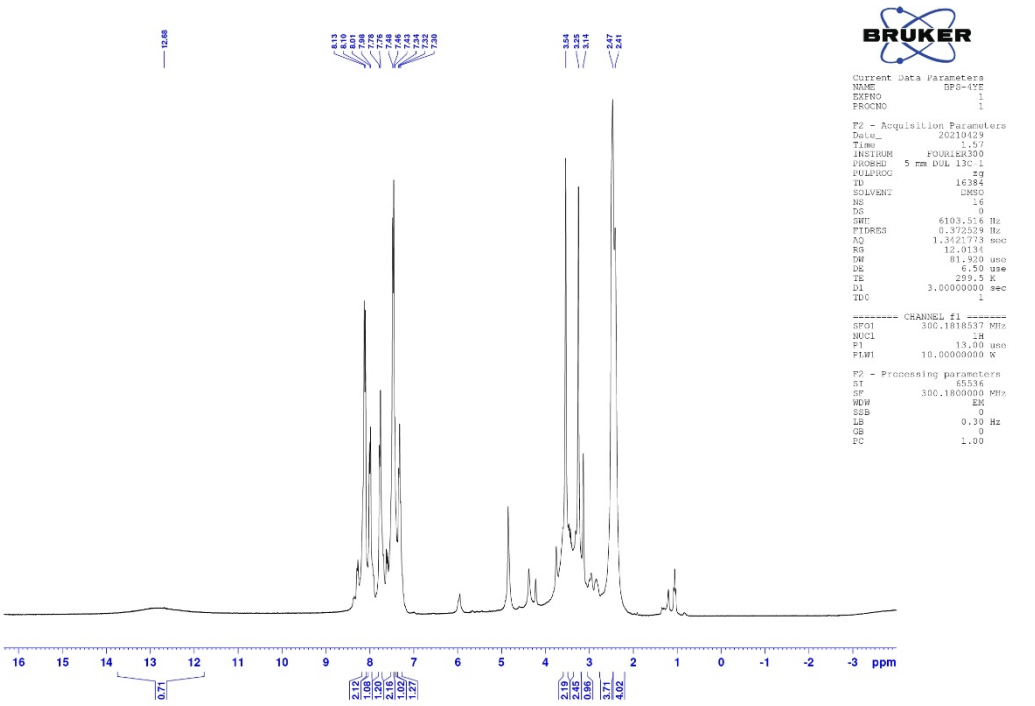


Figure S18. [1]H-NMR spectra of compounds **4d**

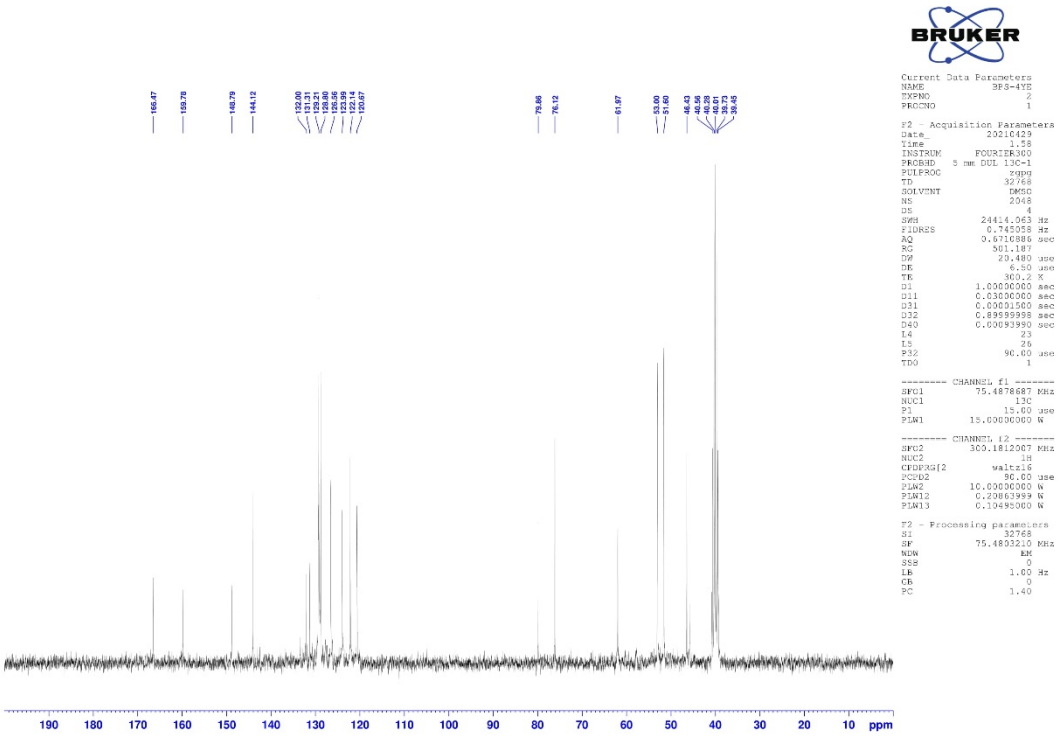


Figure S19. [13]C-NMR spectra of compounds **4d**

Formula Predictor Report - BPS-4_161.lcd

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Data File: C:\LabSolutions\Data\Analiz\derya\BPS-4_161.lcd

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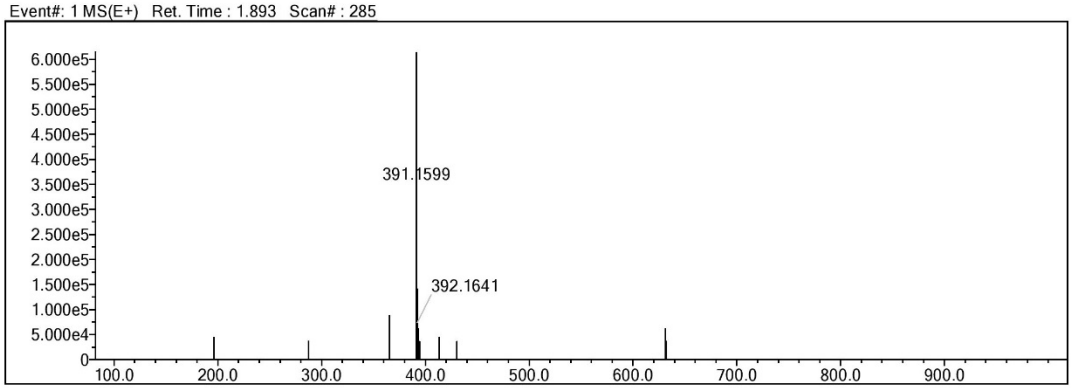
C	4	10	40	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	1	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

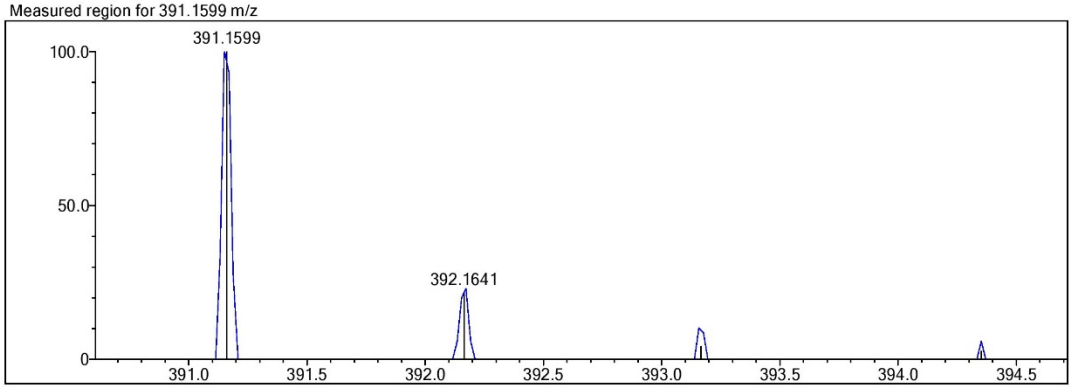
DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 150

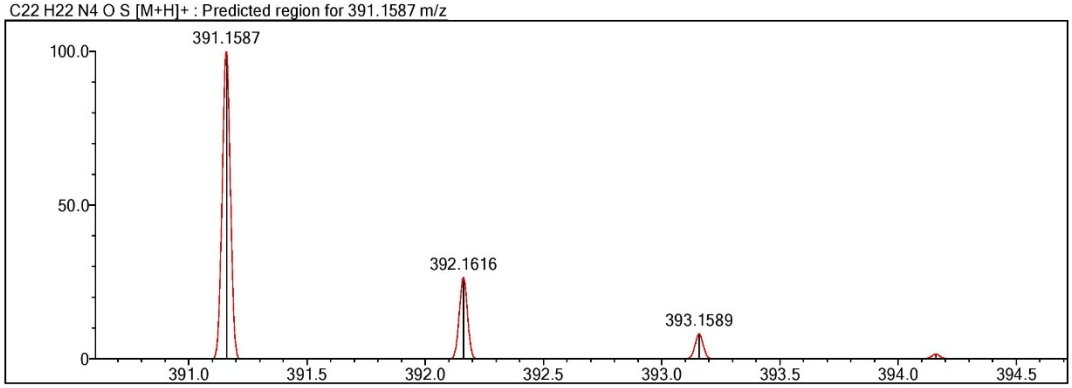
Event#: 1 MS(E+) Ret. Time : 1.893 Scan# : 285



Measured region for 391.1599 m/z



C22 H22 N4 O S [M+H]+ : Predicted region for 391.1587 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	62.15	C22 H22 N4 O S	[M+H]+	391.1599	391.1587	1.2	3.07	65.54	14.0

Figure S20. HRMS spectra of compounds **4d**

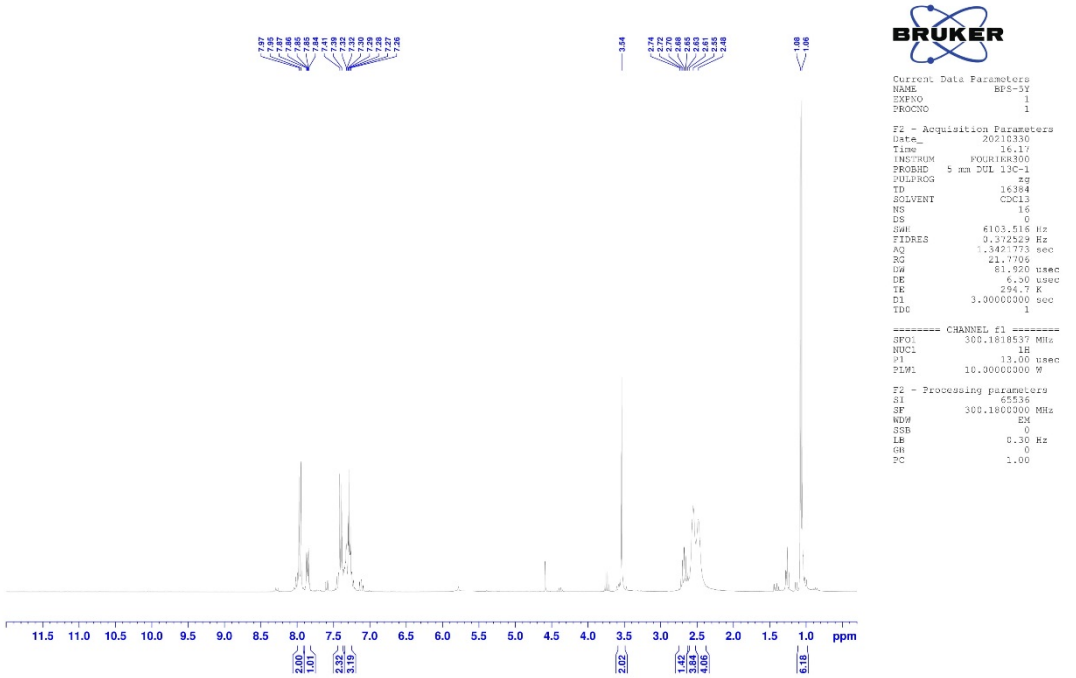


Figure S21. [1]H-NMR spectra of compounds **4e**

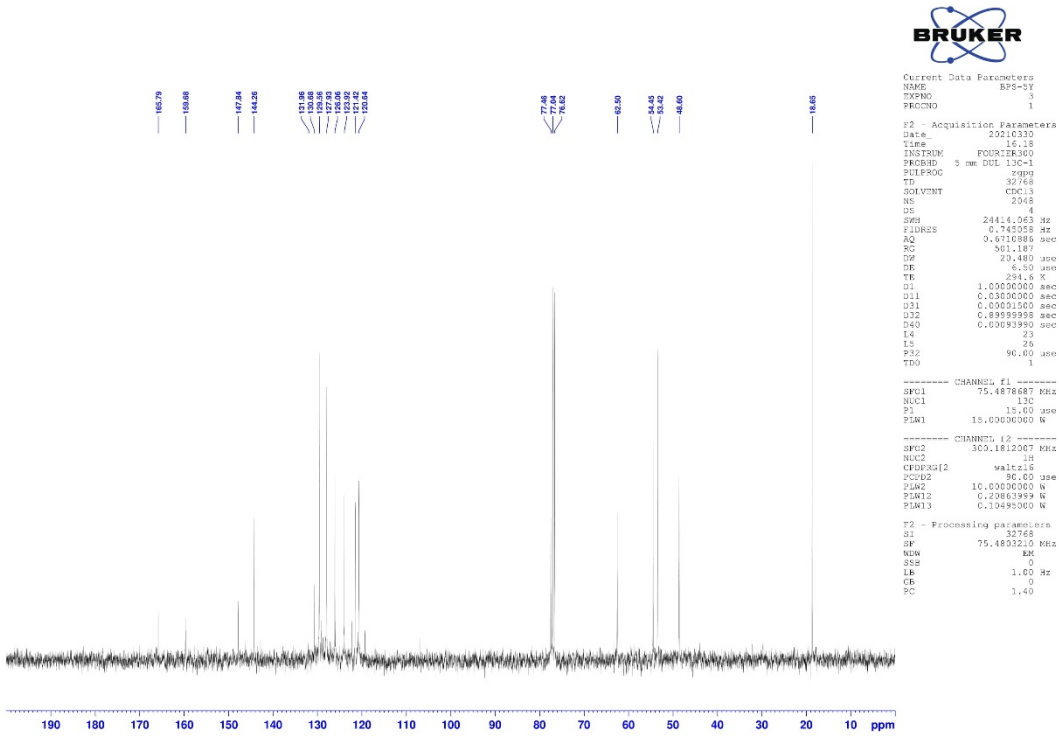


Figure S22. [13]C-NMR spectra of compounds **4e**

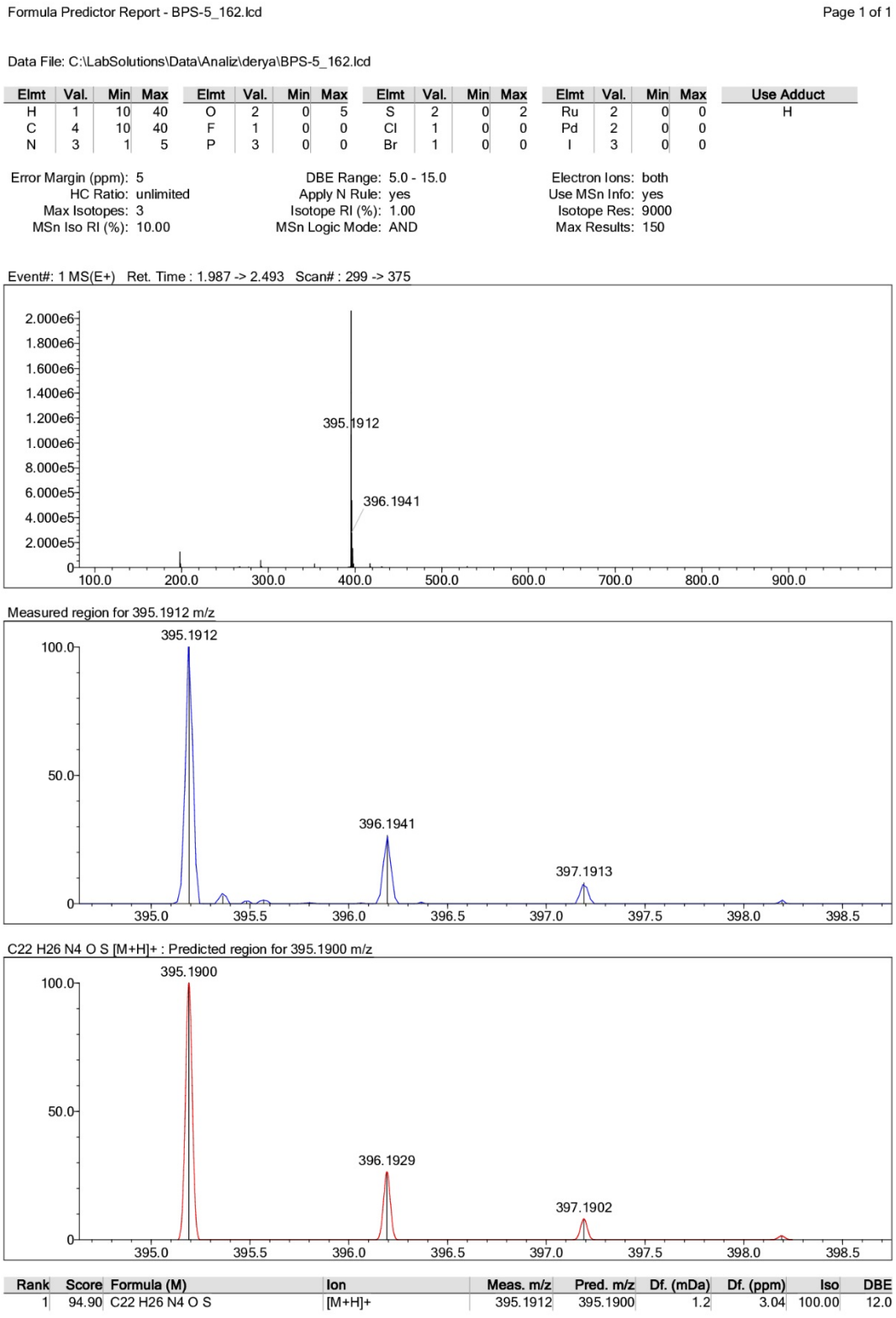


Figure S23. HRMS spectra of compounds **4e**

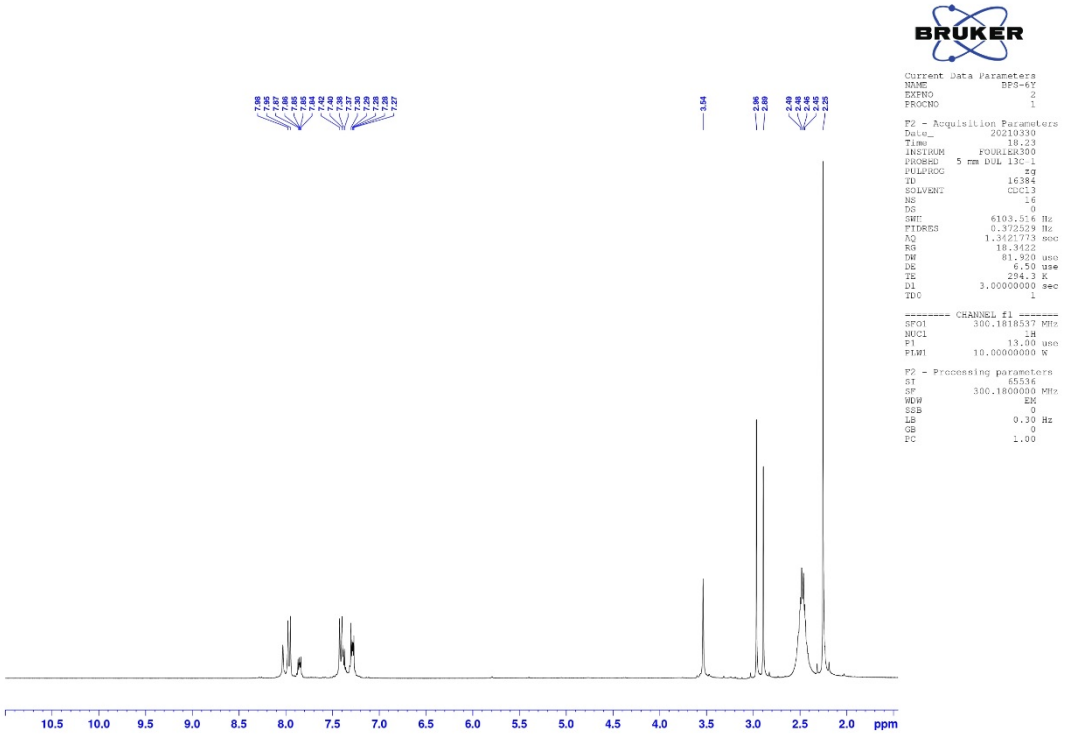


Figure S24. [1]H-NMR spectra of compounds **4f**

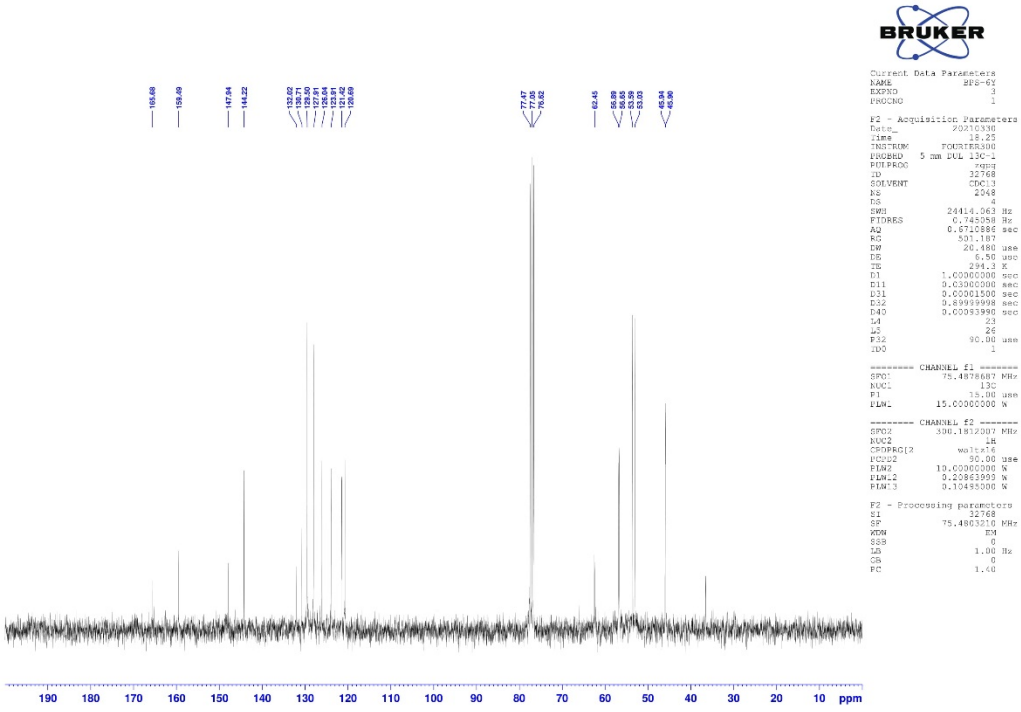


Figure S25. [13]C-NMR spectra of compounds **4f**

Formula Predictor Report - BPS-6_163.lcd

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Data File: C:\LabSolutions\Data\Analiz\derya\BPS-6_163.lcd

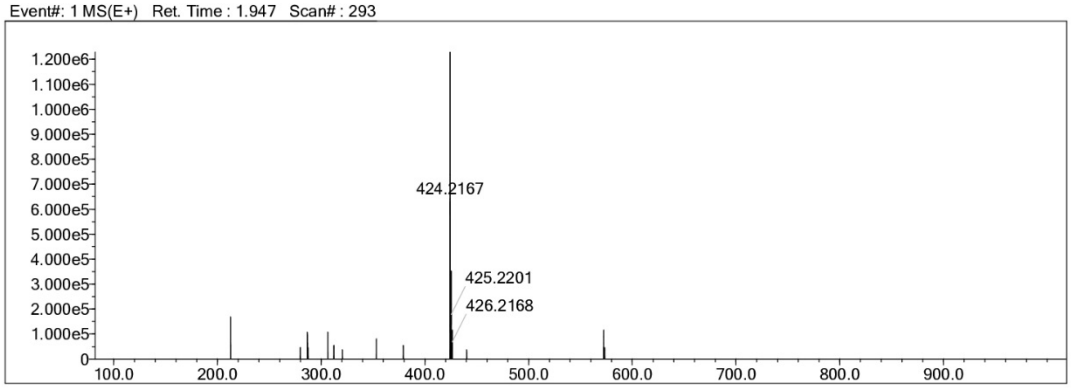
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	10	40	O	2	0	5	S	2	0	2	Ru	2	0	0	H
C	4	10	40	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	2	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

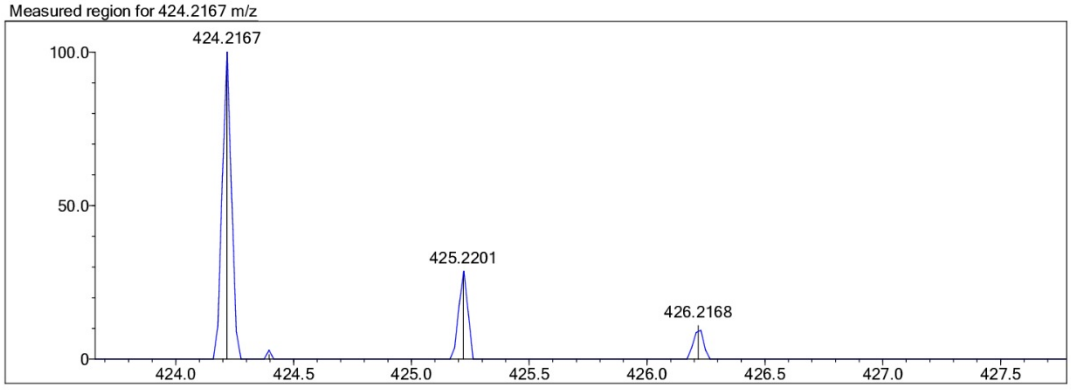
DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 150

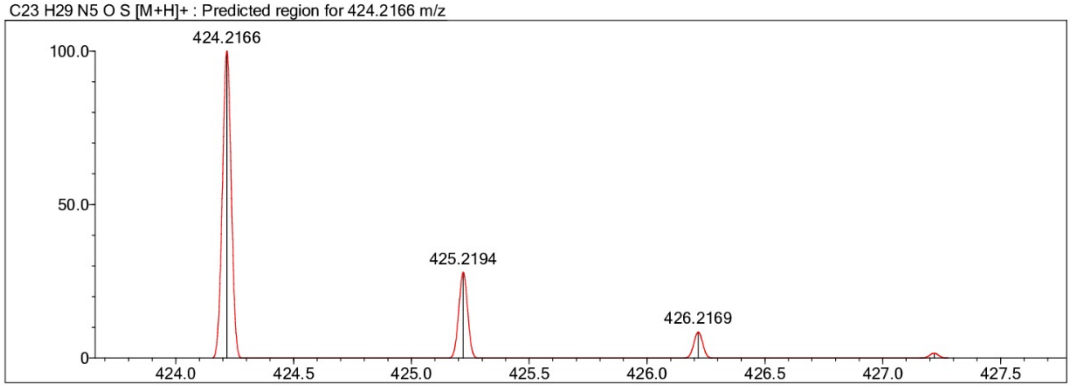
Event#: 1 MS(E+) Ret. Time : 1.947 Scan# : 293



Measured region for 424.2167 m/z



C23 H29 N5 O S [M+H]+ : Predicted region for 424.2166 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.87	C23 H29 N5 O S	[M+H]+	424.2167	424.2166	0.1	0.24	98.87	12.0

Figure S26. HRMS spectra of compounds **4f**

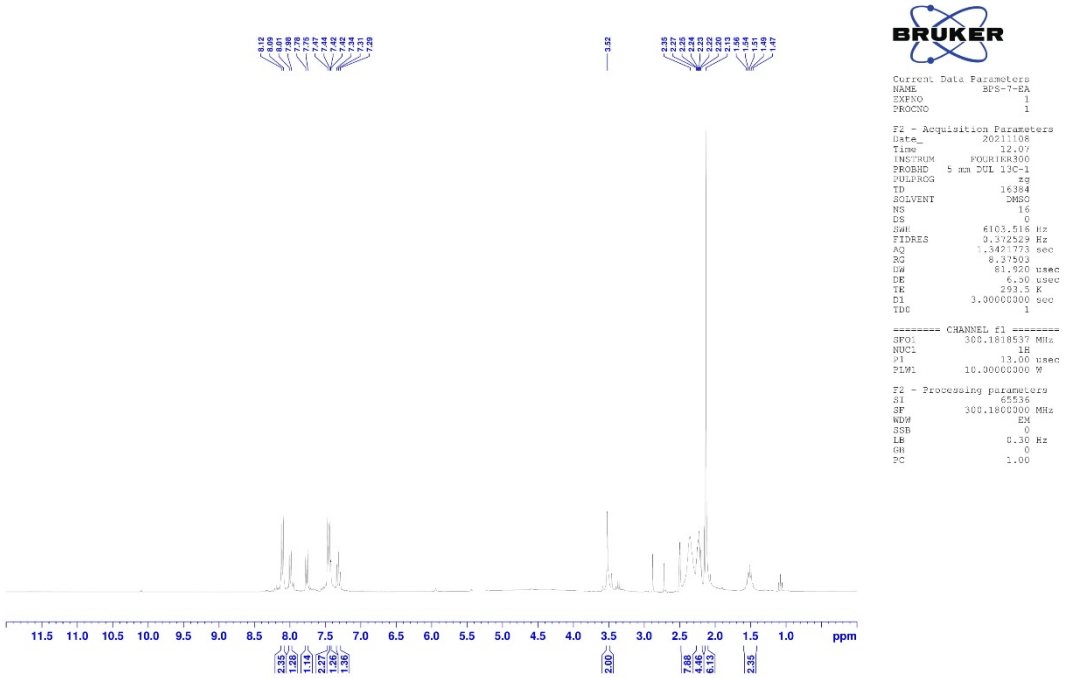


Figure S27. [1]H-NMR spectra of compounds **4g**

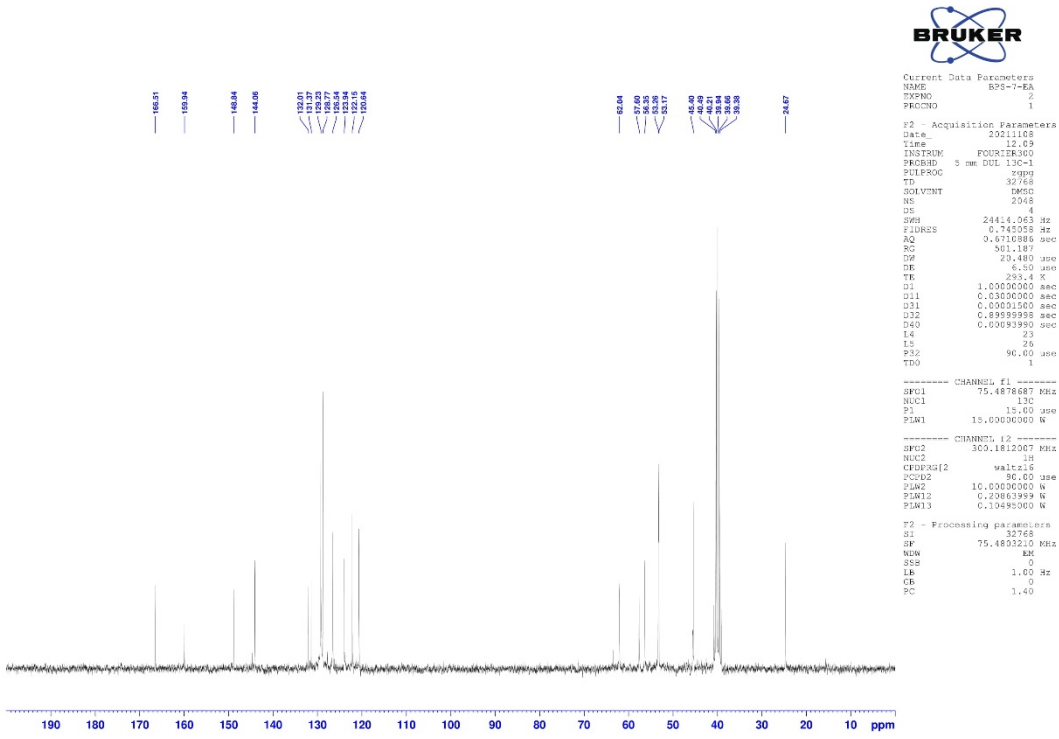


Figure S28. [13]C-NMR spectra of compounds **4g**

Formula Predictor Report - BPS-7_164.lcd

Page 1 of 1

Data File: C:\LabSolutions\Data\Analiz\derya\BPS-7_164.lcd

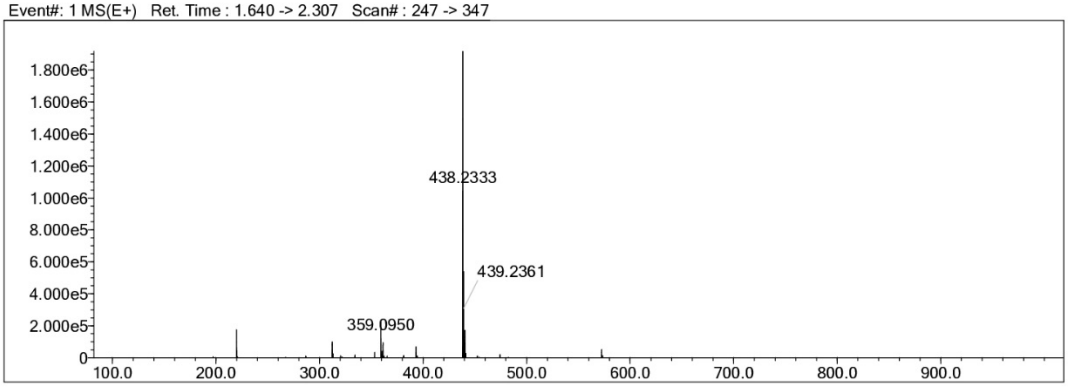
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	10	40	O	2	0	5	S	2	0	2	Ru	2	0	0	H
C	4	10	40	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	2	5	P	3	0	0	Br	1	0	0	I	3	0	0	

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

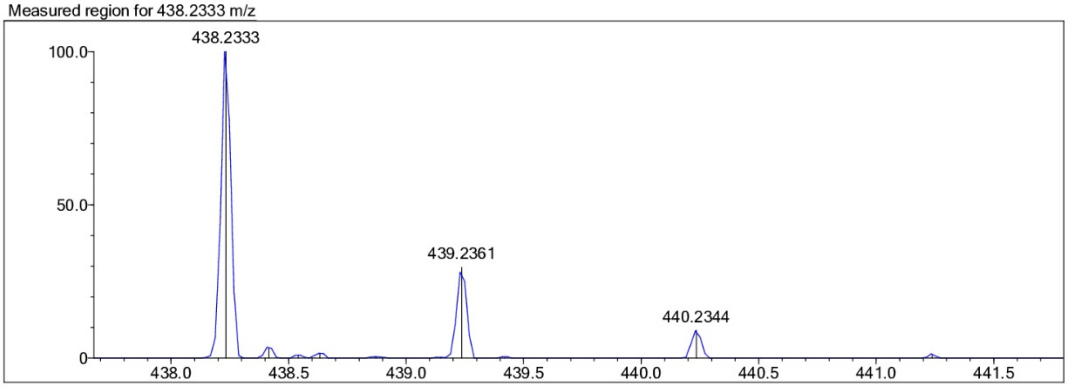
DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 150

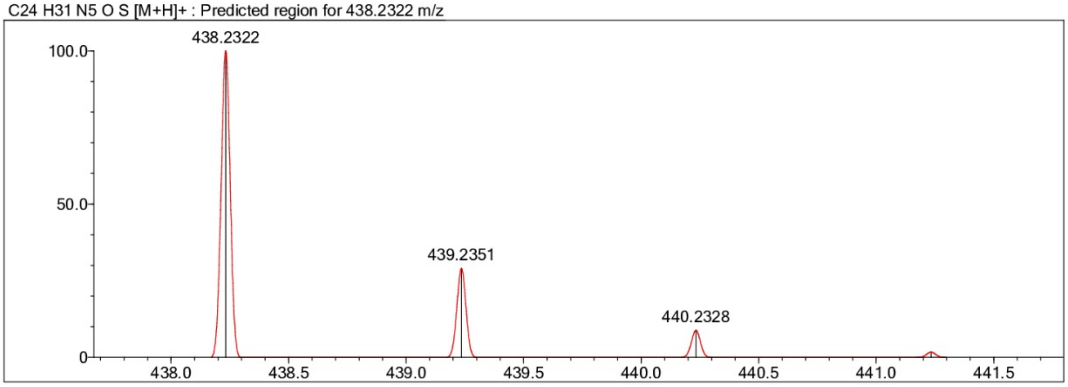
Event#: 1 MS(E+) Ret. Time : 1.640 -> 2.307 Scan# : 247 -> 347



Measured region for 438.2333 m/z



C24 H31 N5 O S [M+H]+ : Predicted region for 438.2322 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	91.64	C24 H31 N5 O S	[M+H]+	438.2333	438.2322	1.1	2.51	95.23	12.0

Figure S29. HRMS spectra of compounds **4g**

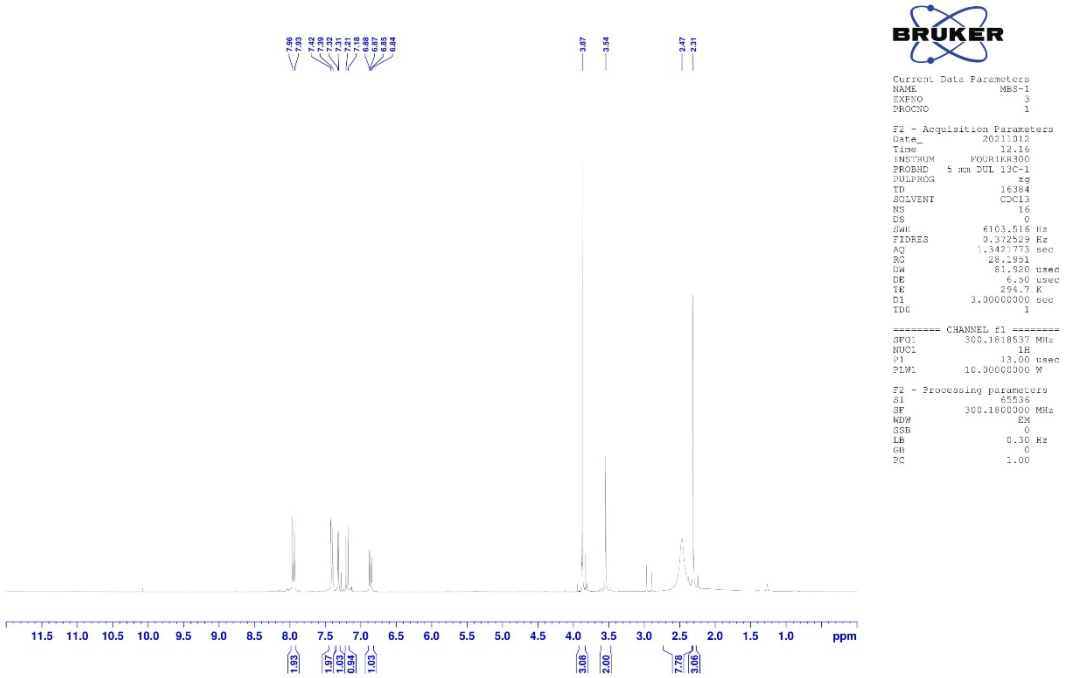


Figure S30. [1]H-NMR spectra of compounds **4h**

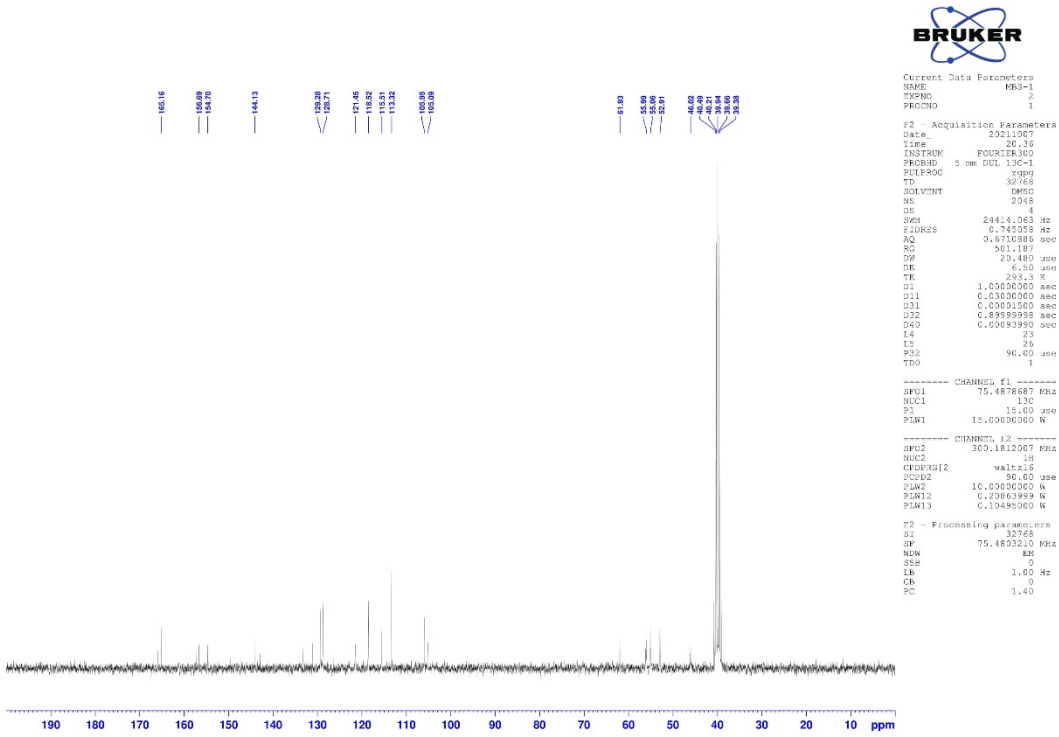


Figure S31. [13]C-NMR spectra of compounds **4h**

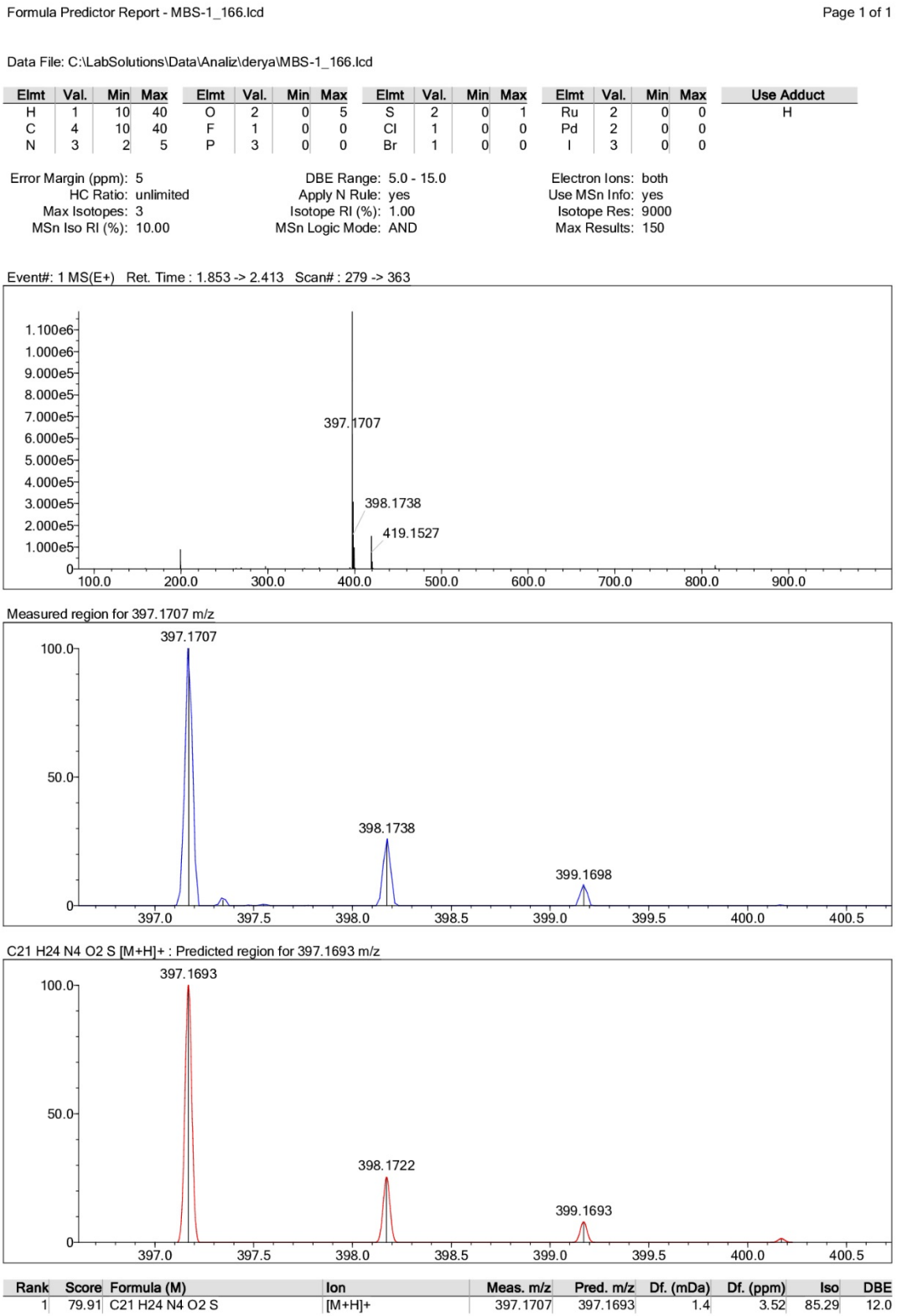


Figure S32. HRMS spectra of compounds **4h**

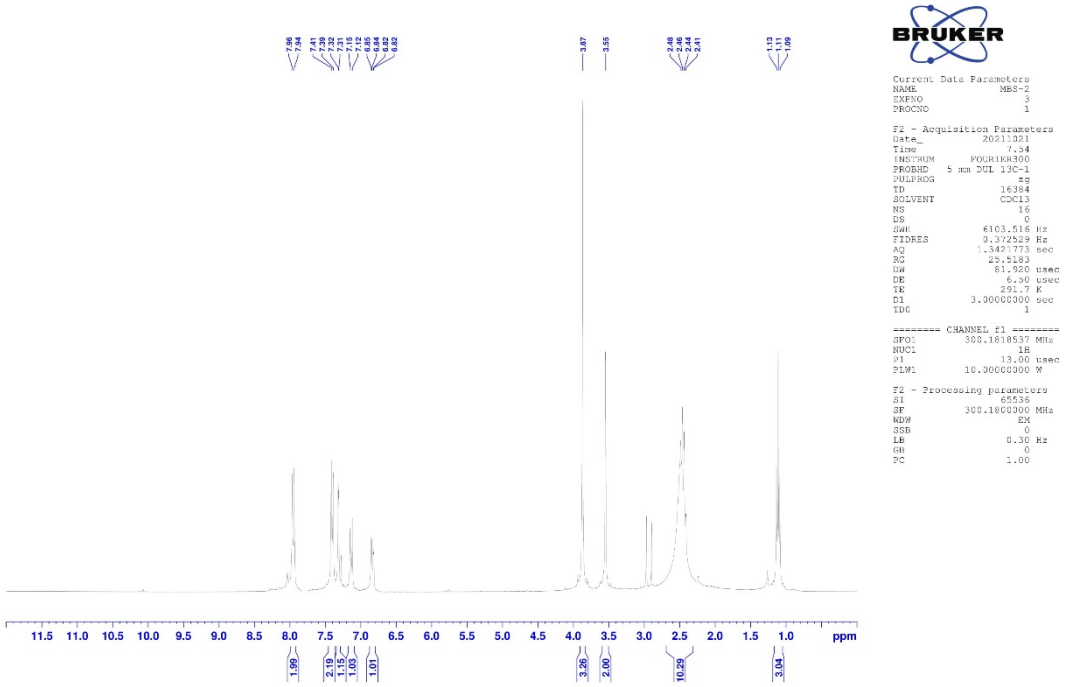


Figure S33. [1]H-NMR spectra of compounds **4i**

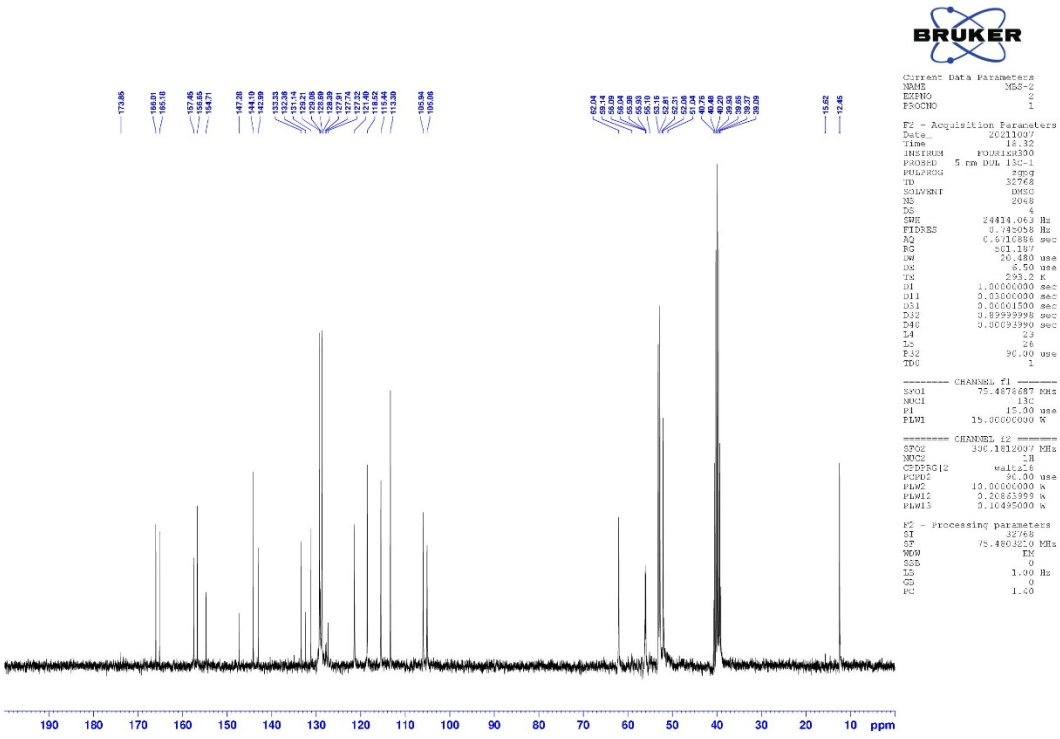


Figure S34. [13]C-NMR spectra of compounds **4i**

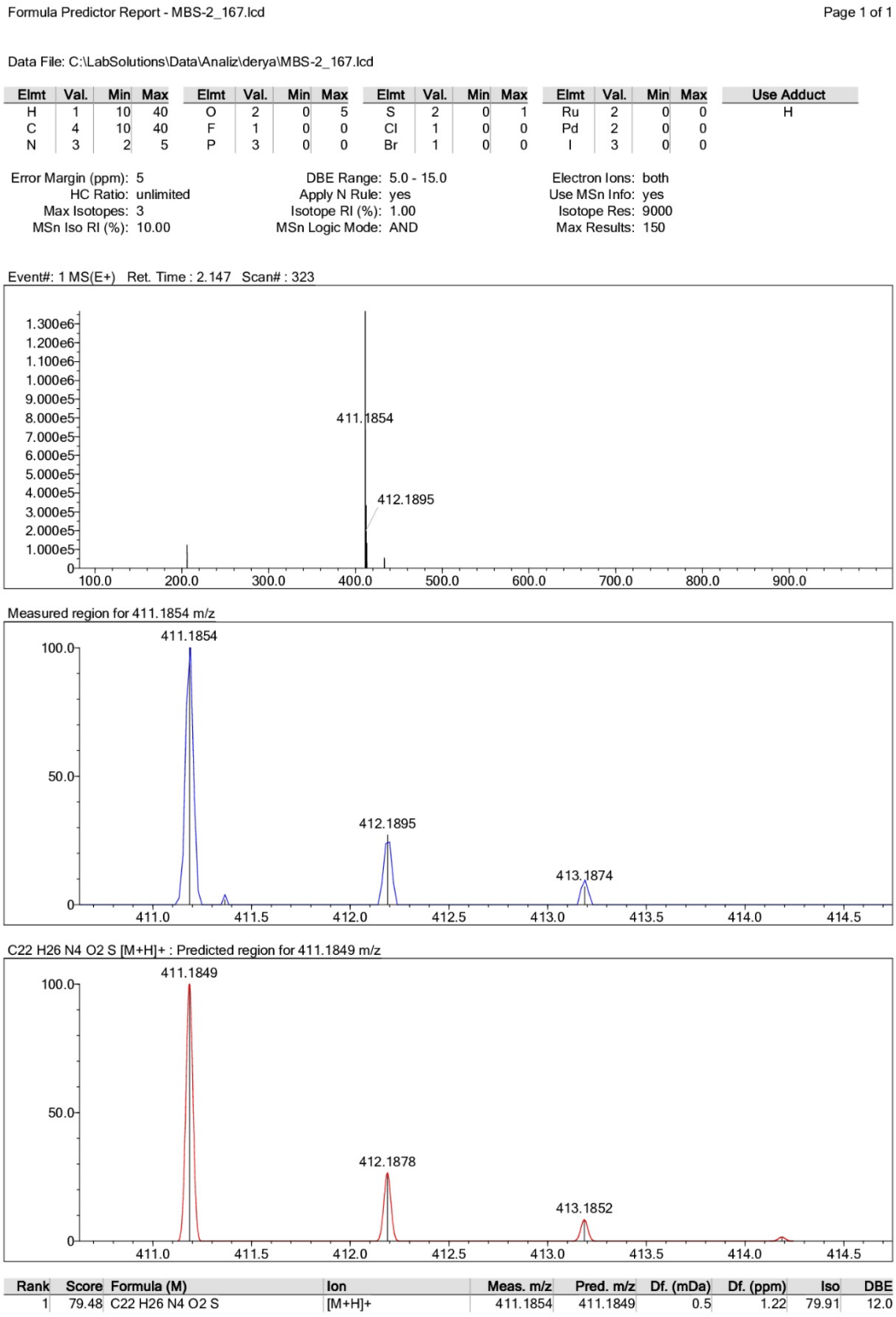


Figure S35. HRMS spectra of compounds **4i**

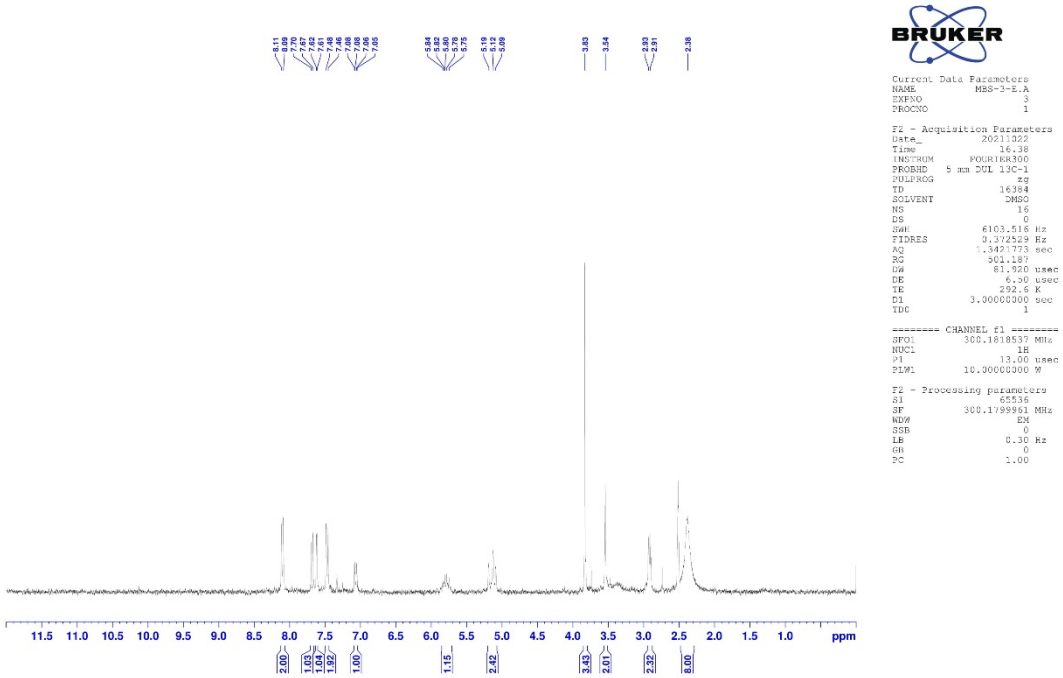


Figure S36. [1]H-NMR spectra of compounds **4j**

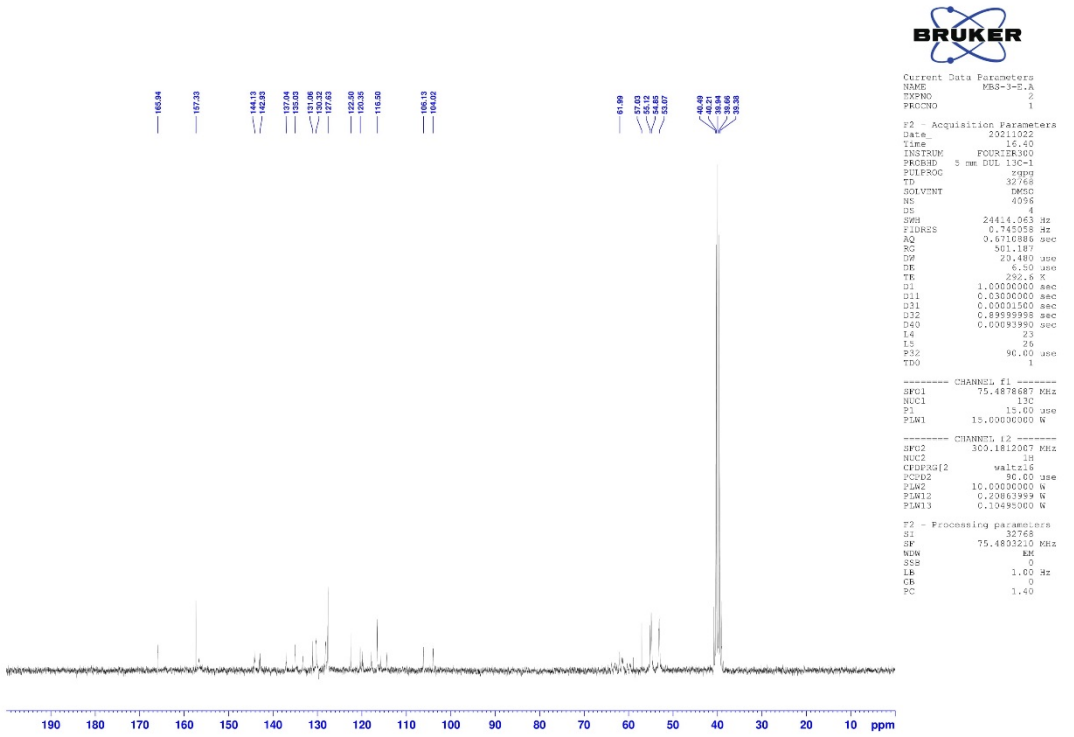


Figure S37. [13]C-NMR spectra of compounds **4j**

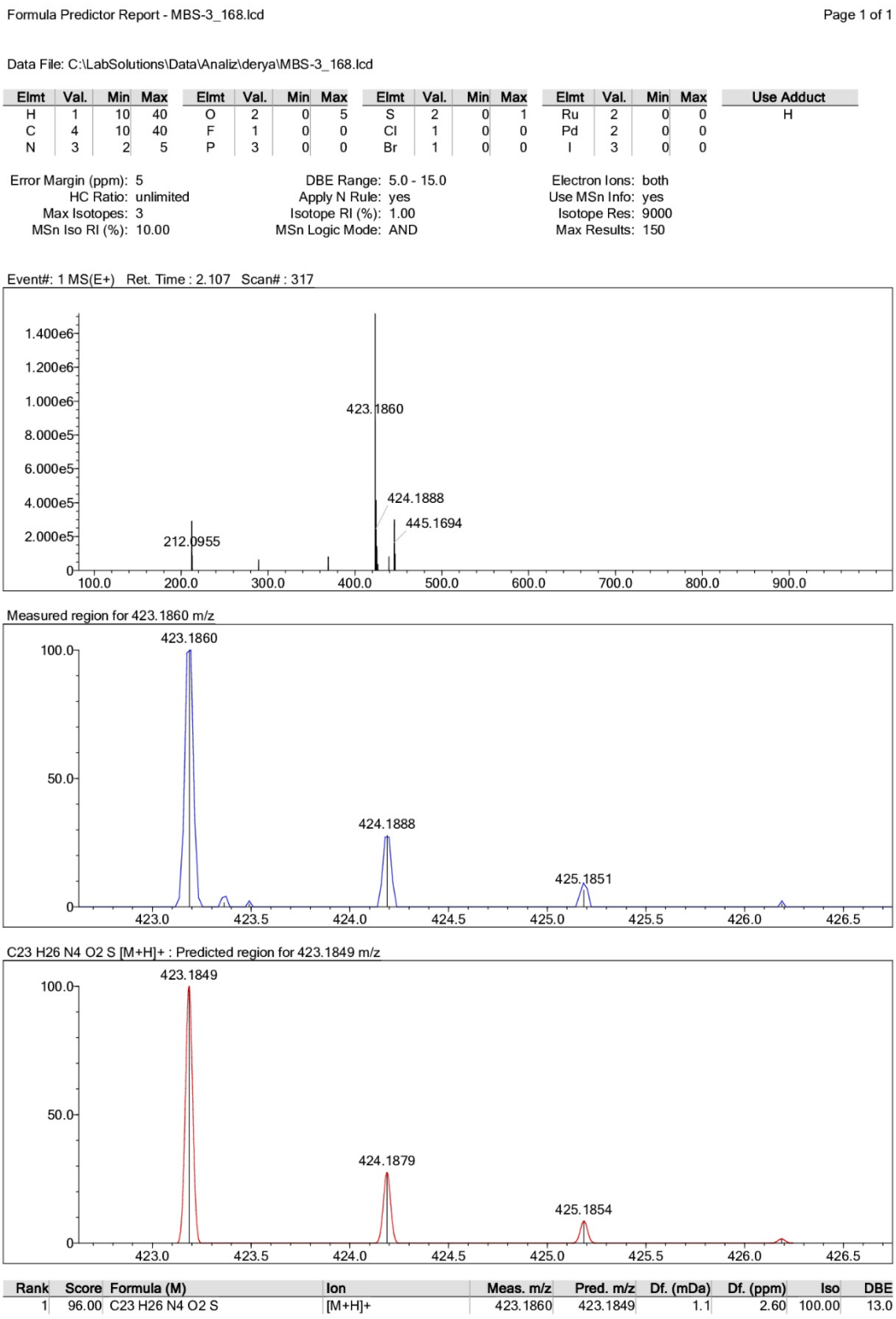


Figure S38. HRMS spectra of compounds **4j**

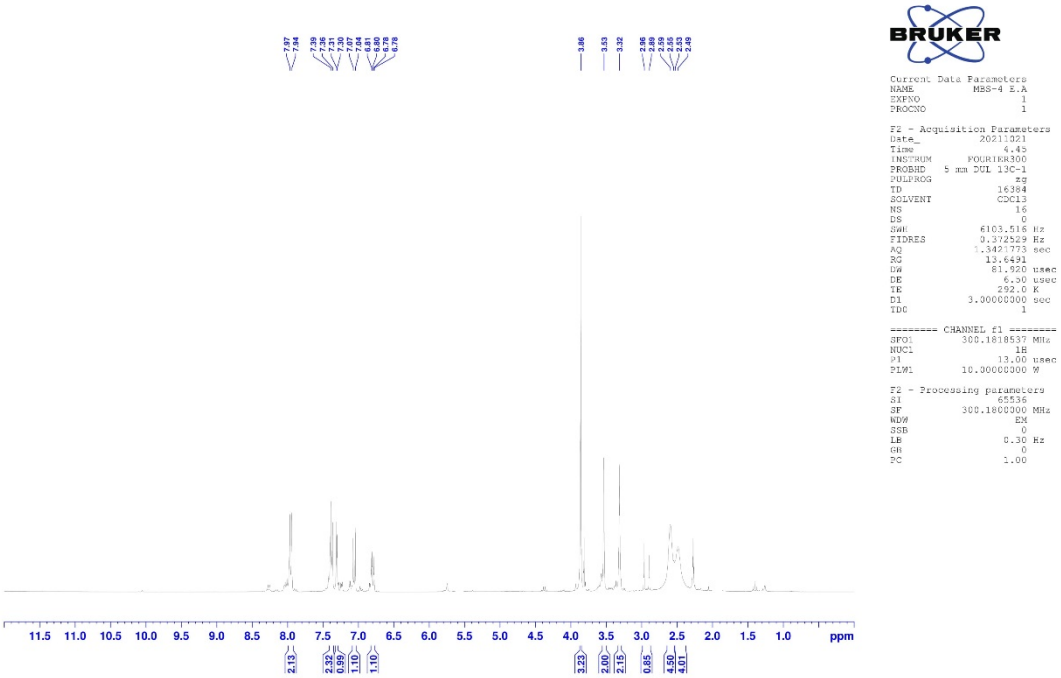


Figure S39. [1]H-NMR spectra of compounds **4k**

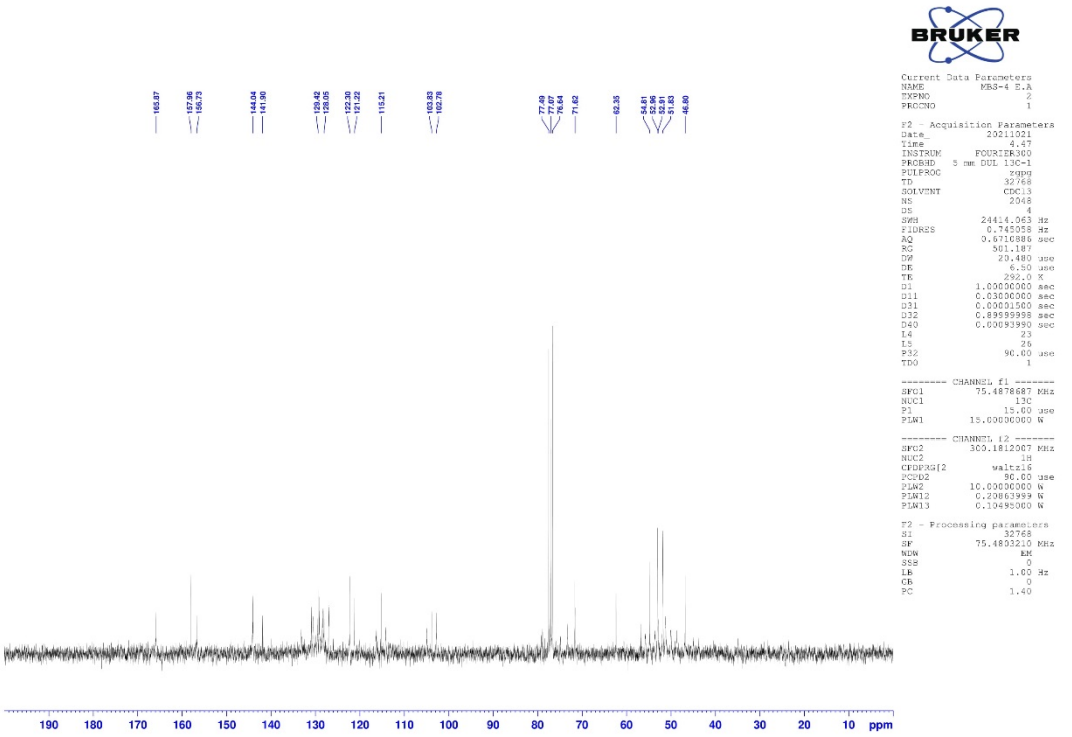


Figure S40. [13]C-NMR spectra of compounds **4k**

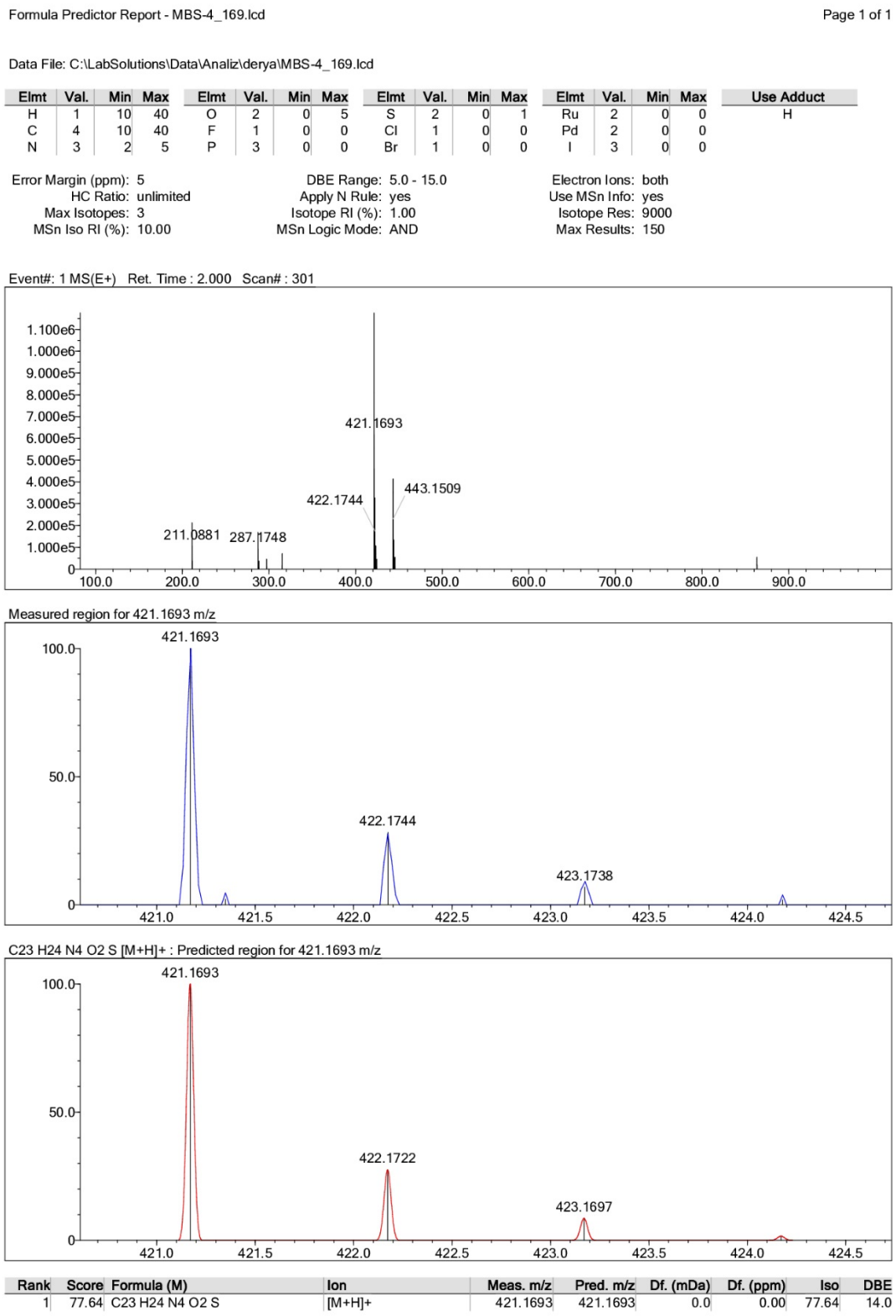


Figure S41. HRMS spectra of compounds **4k**

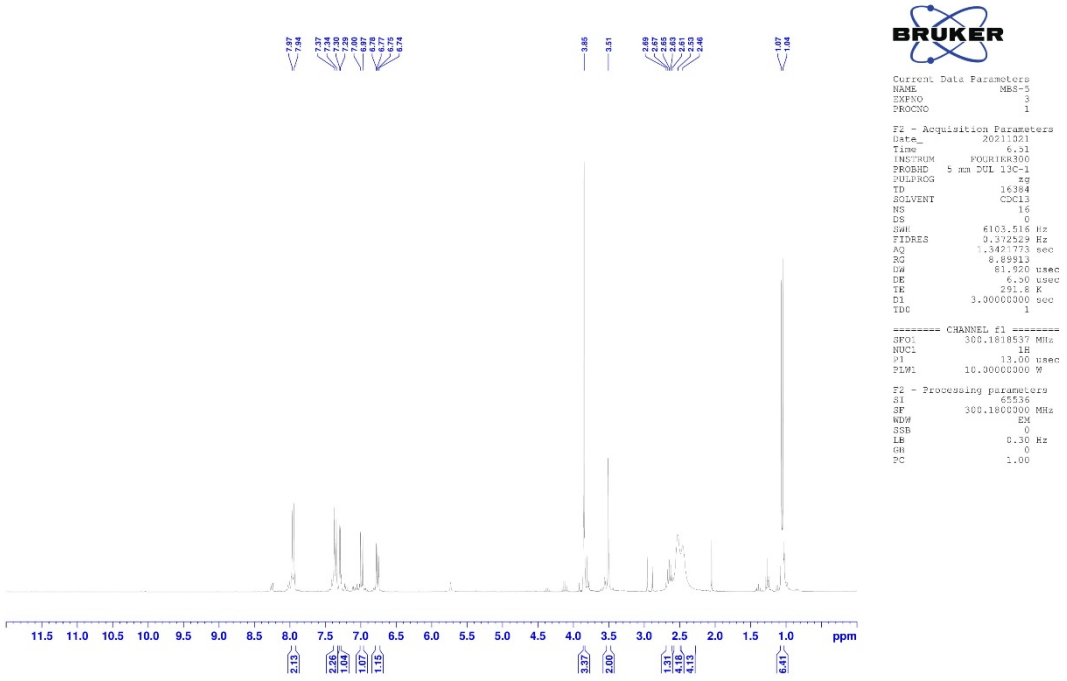


Figure S42. [1]H-NMR spectra of compounds **4l**

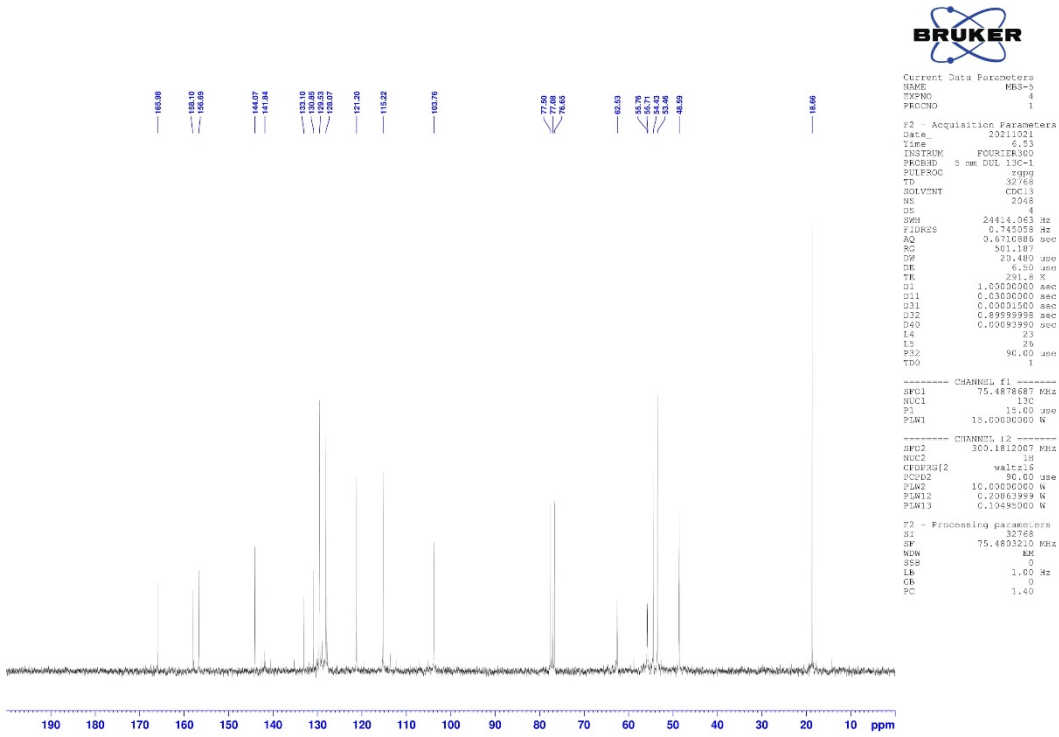


Figure S43. [13]C-NMR spectra of compounds **4l**

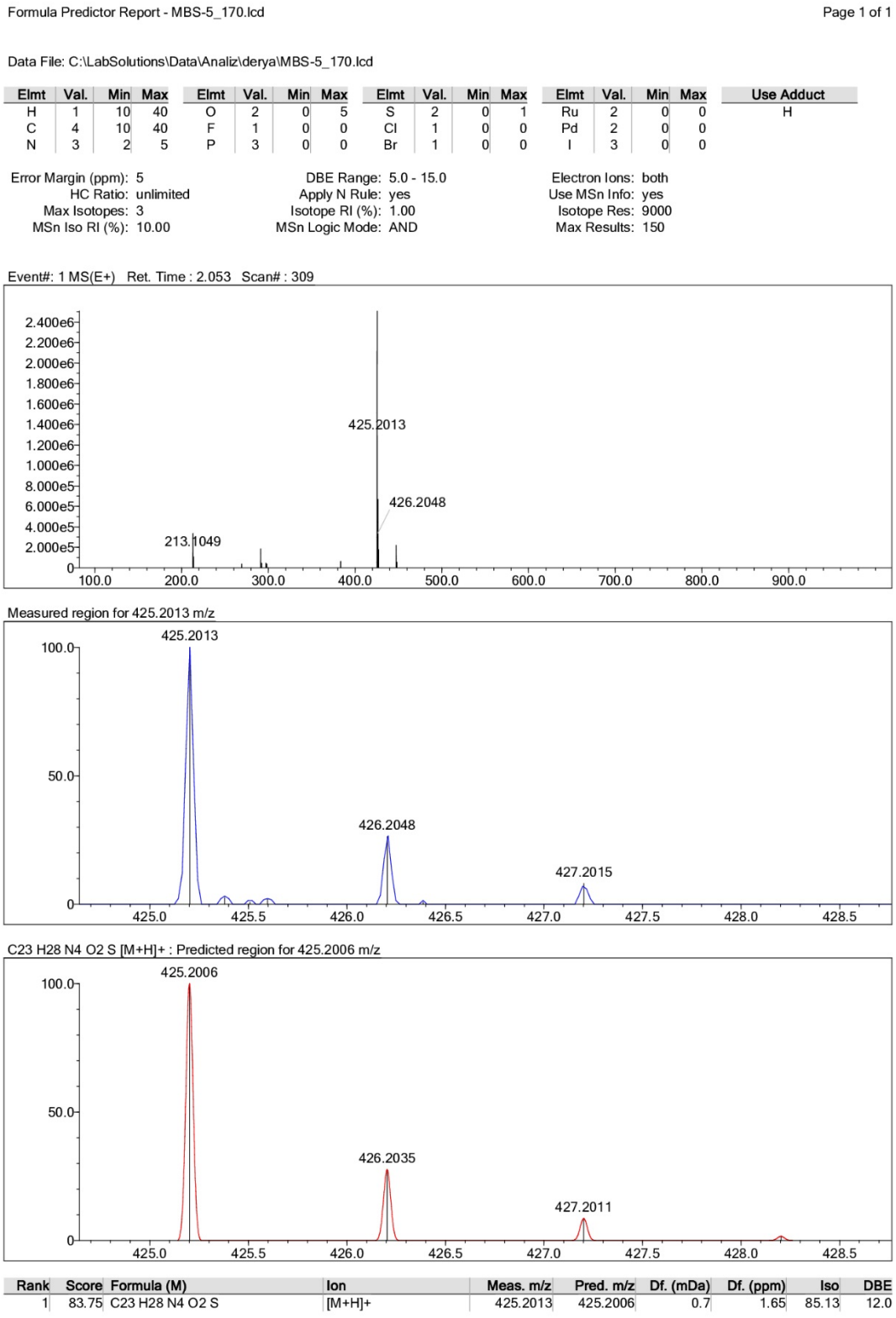


Figure S44. HRMS spectra of compounds **4l**

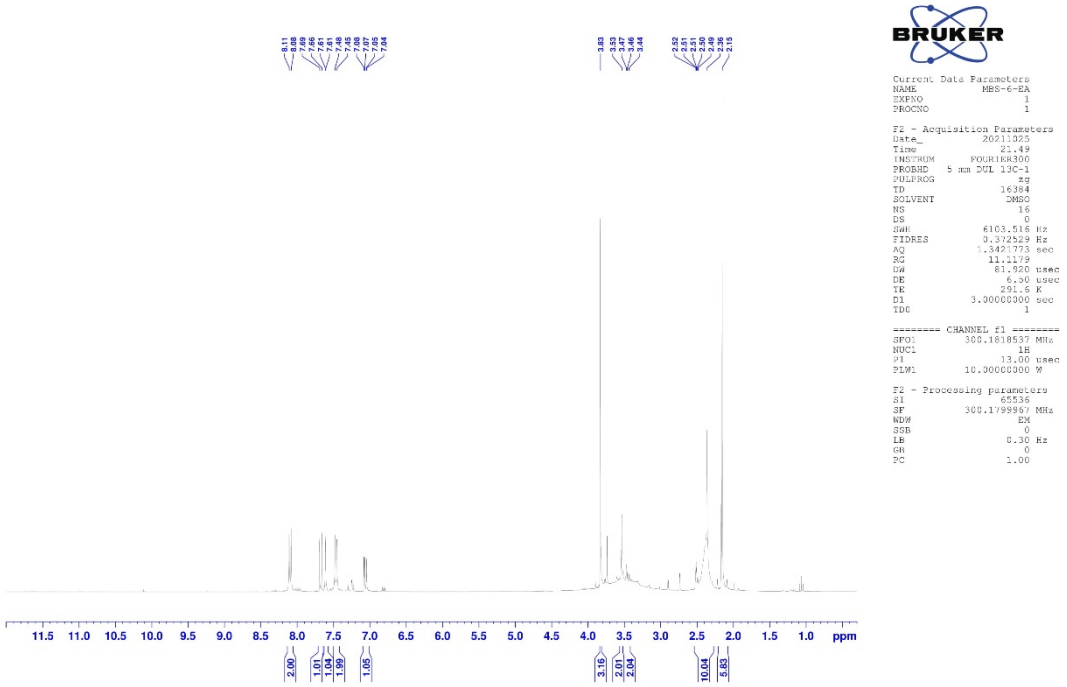


Figure S45. [1]H-NMR spectra of compounds **4m**

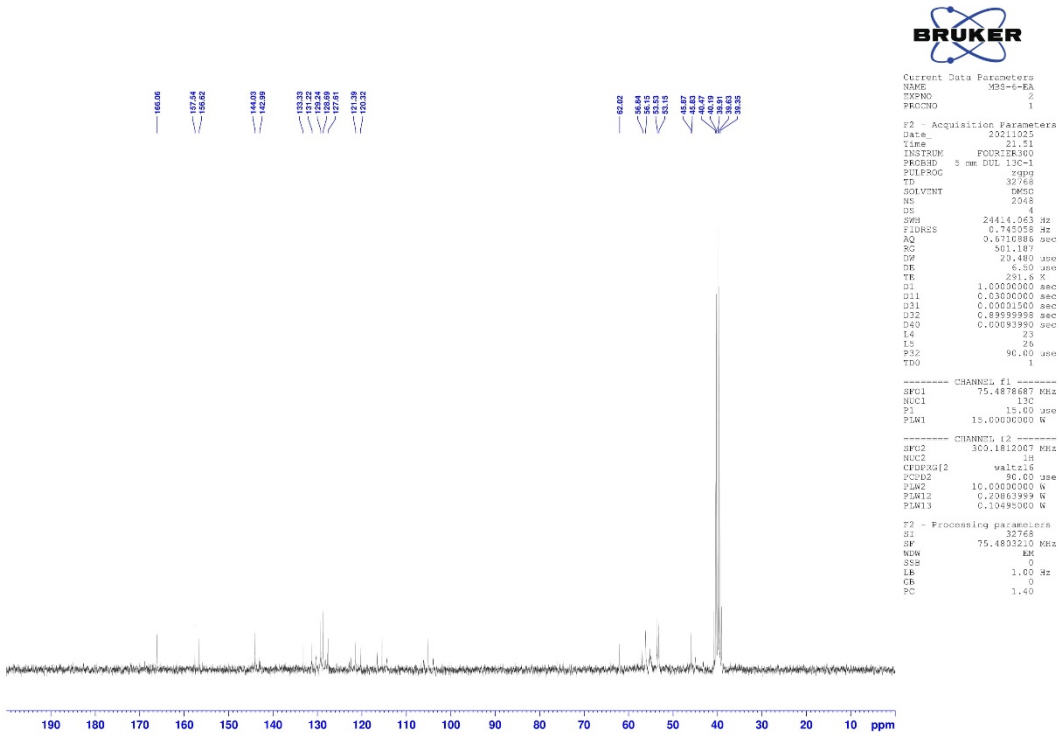


Figure S46. [13]C-NMR spectra of compounds **4m**

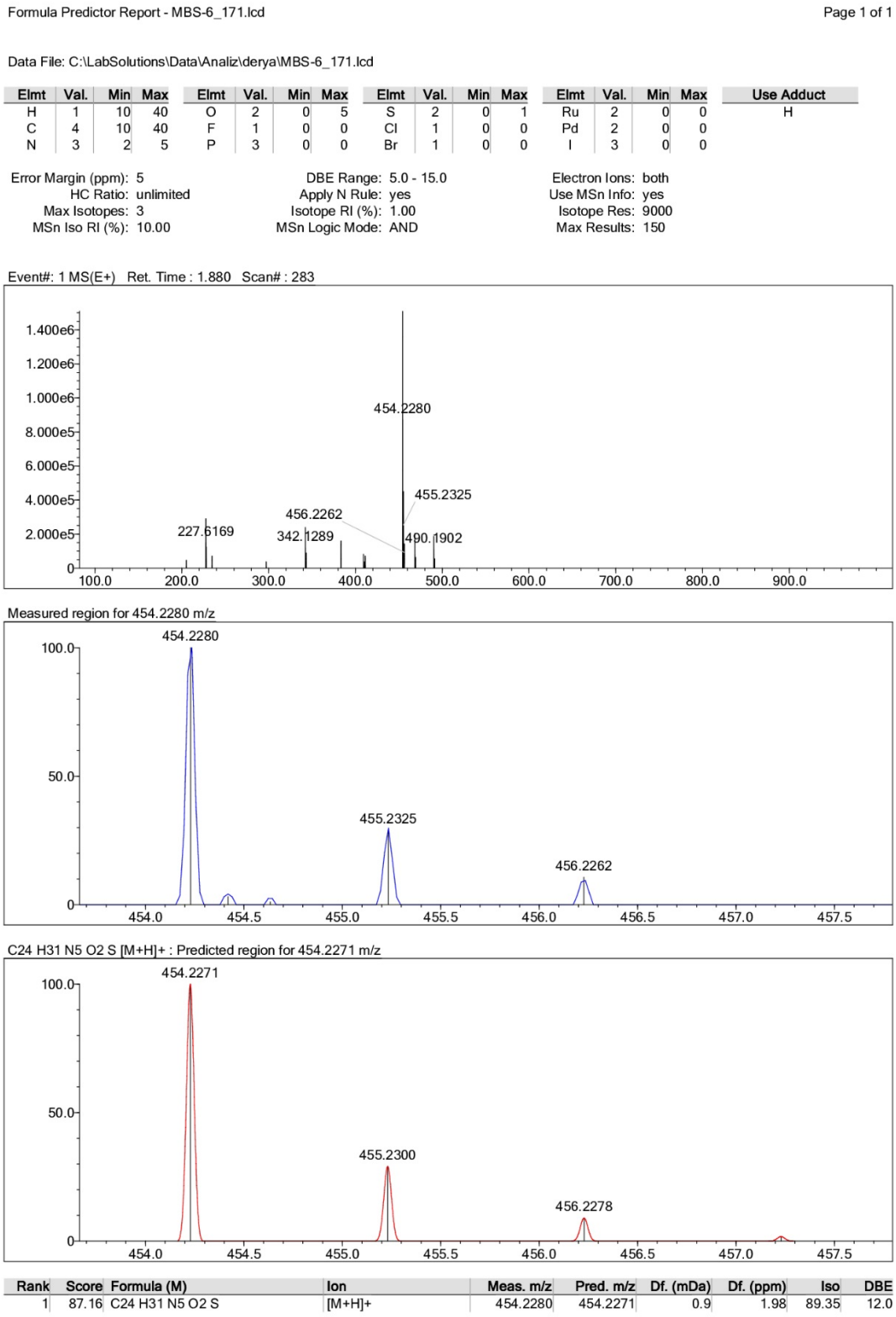


Figure S47. HRMS spectra of compounds **4m**

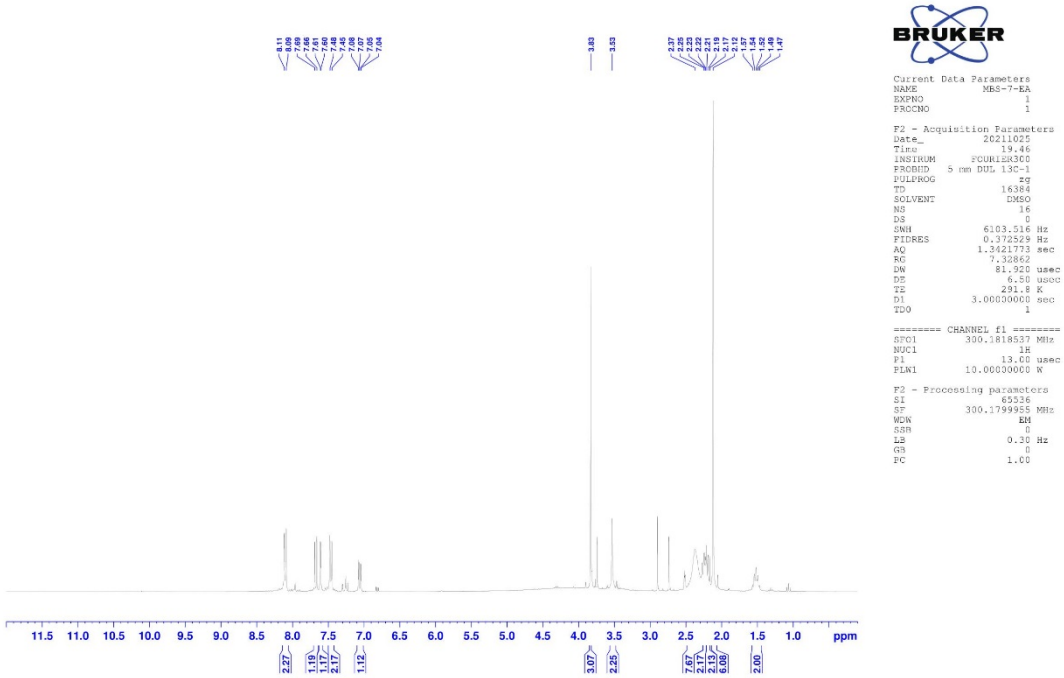


Figure S48. [1]H-NMR spectra of compounds **4n**

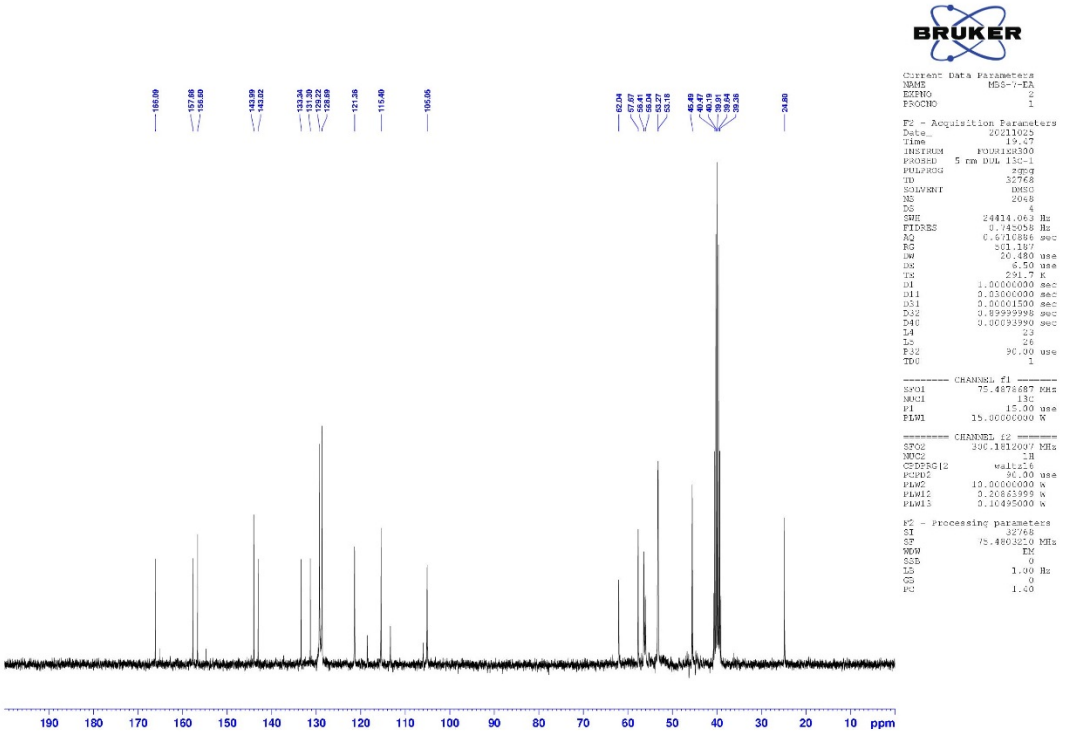


Figure S49. [13]C-NMR spectra of compounds **4n**

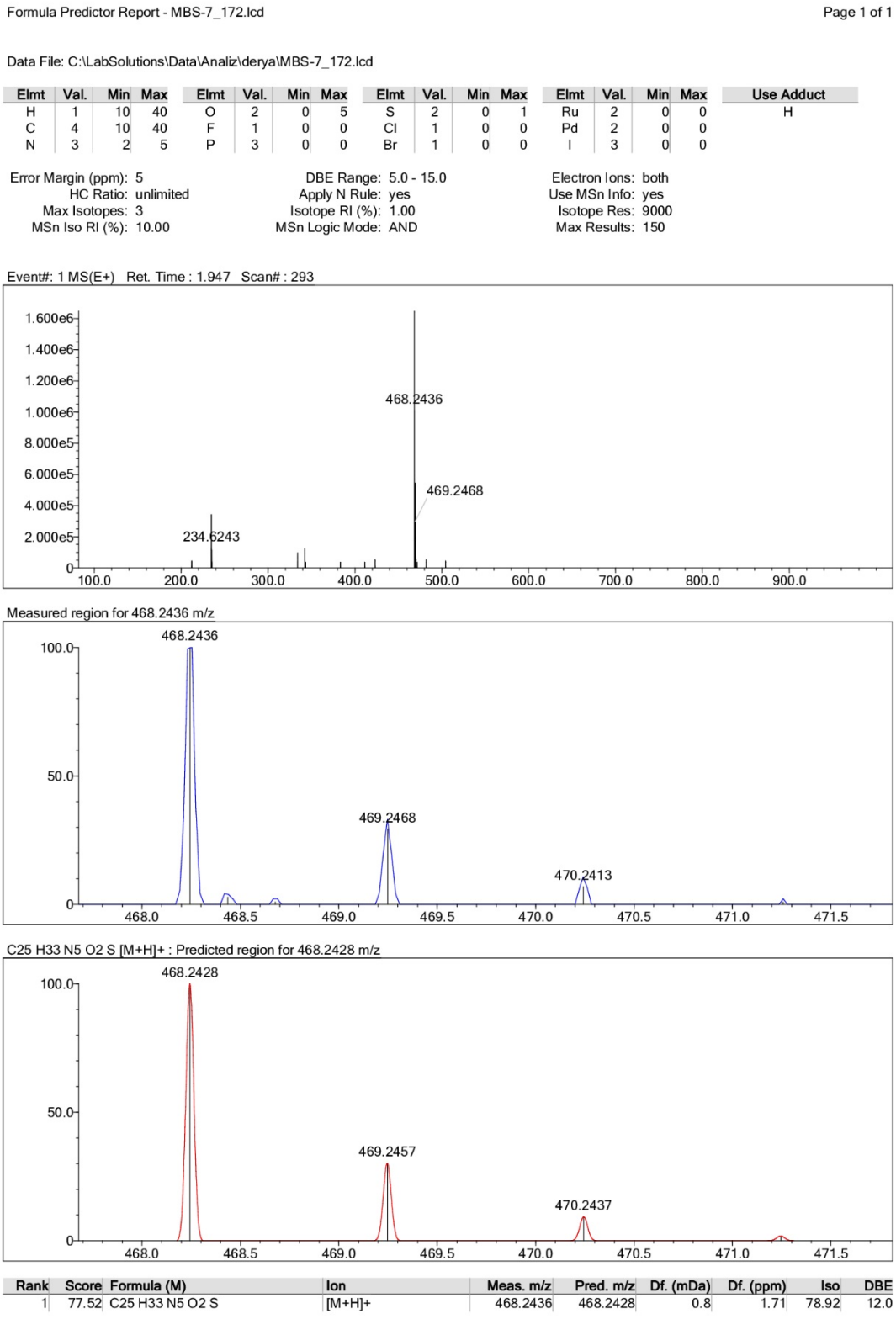


Figure S50. HRMS spectra of compounds **4n**

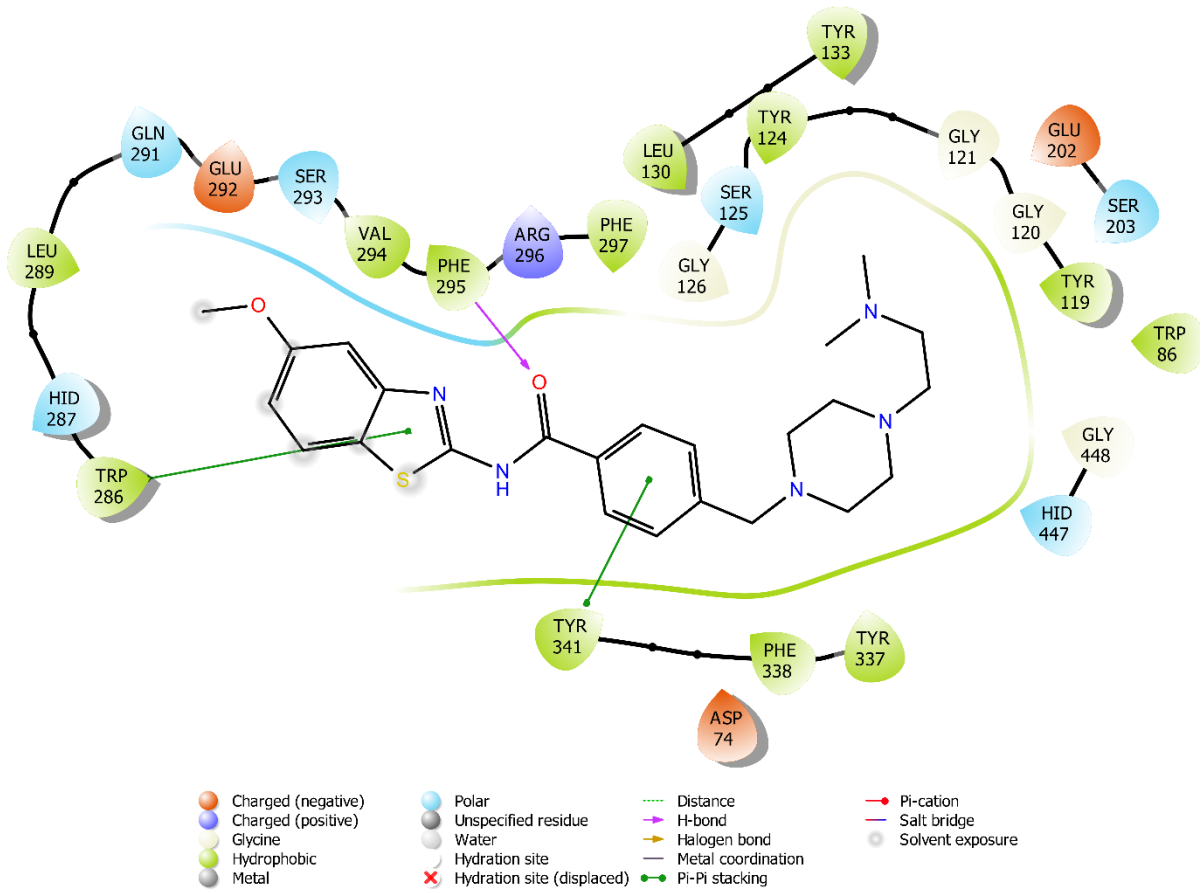


Figure S51. 2D interaction of compound **4m** at binding region (PBDID: 4EY7).

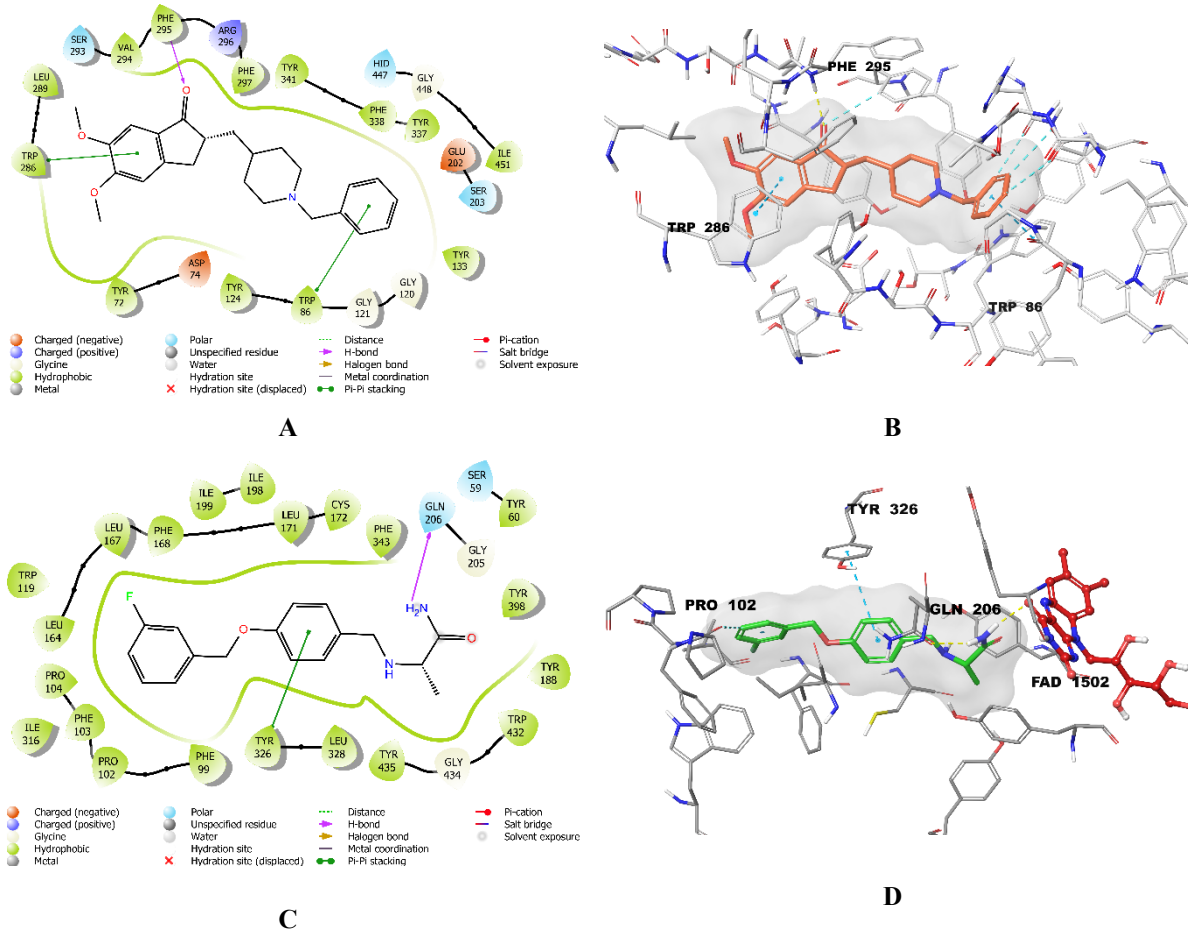
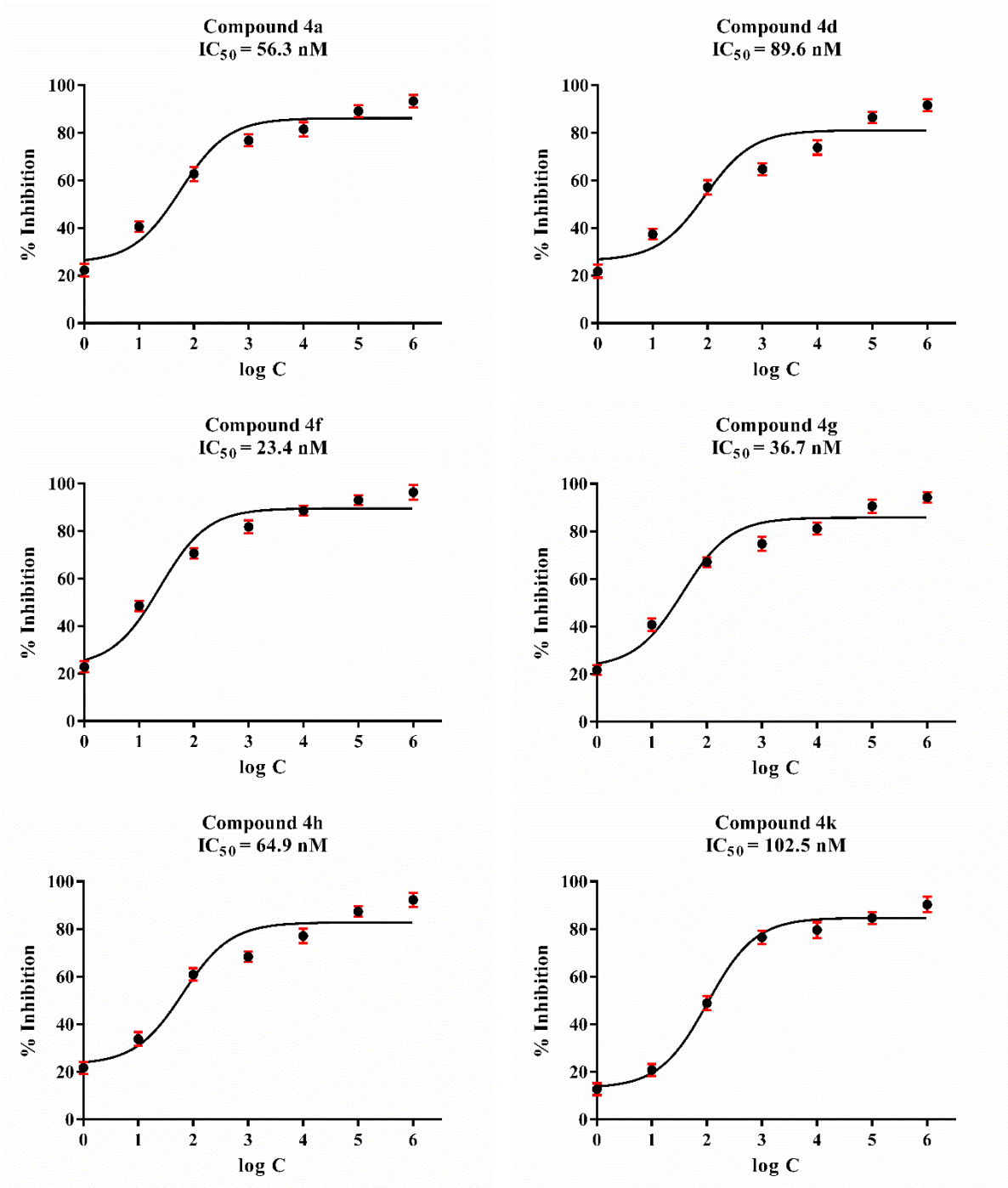


Figure S52. The 2D (A) and 3D (B) interacting modes of donepezil (colored with orange) in the active region the AChE (PDB ID: 4EY7). The 2D (C) and 3D (D) interacting modes of safinamide (colored with green) in the active region the MAO-B (PDB ID: 2V5Z).


Compound 4a
IC50 = 56.3 nM
Compound 4d
IC50 = 89.6 nM
Compound 4f
IC50 = 23.4 nM
Compound 4g
IC50 = 36.7 nM
Compound 4h
IC50 = 64.9 nM
Compound 4k
IC50 = 102.5 nM
% Inhibition
log C

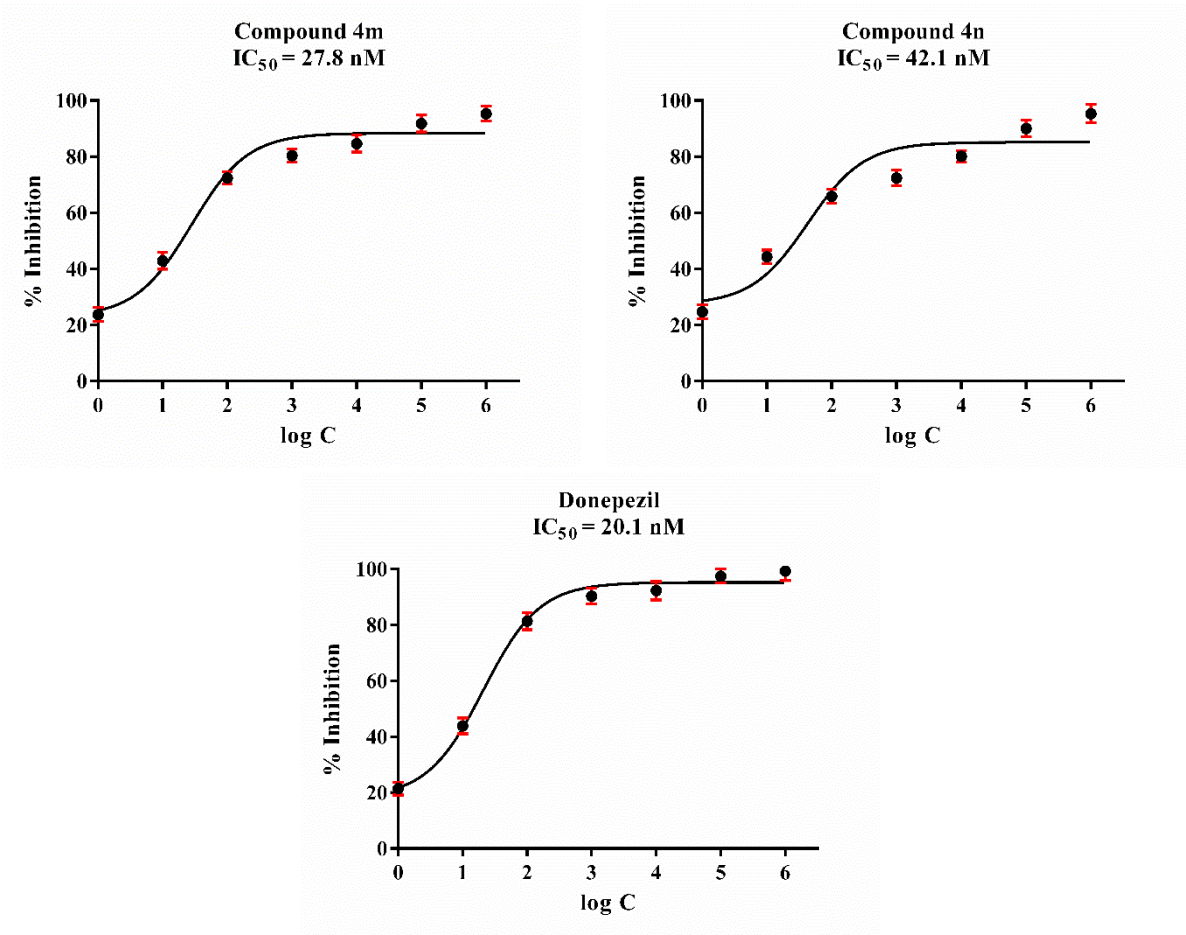
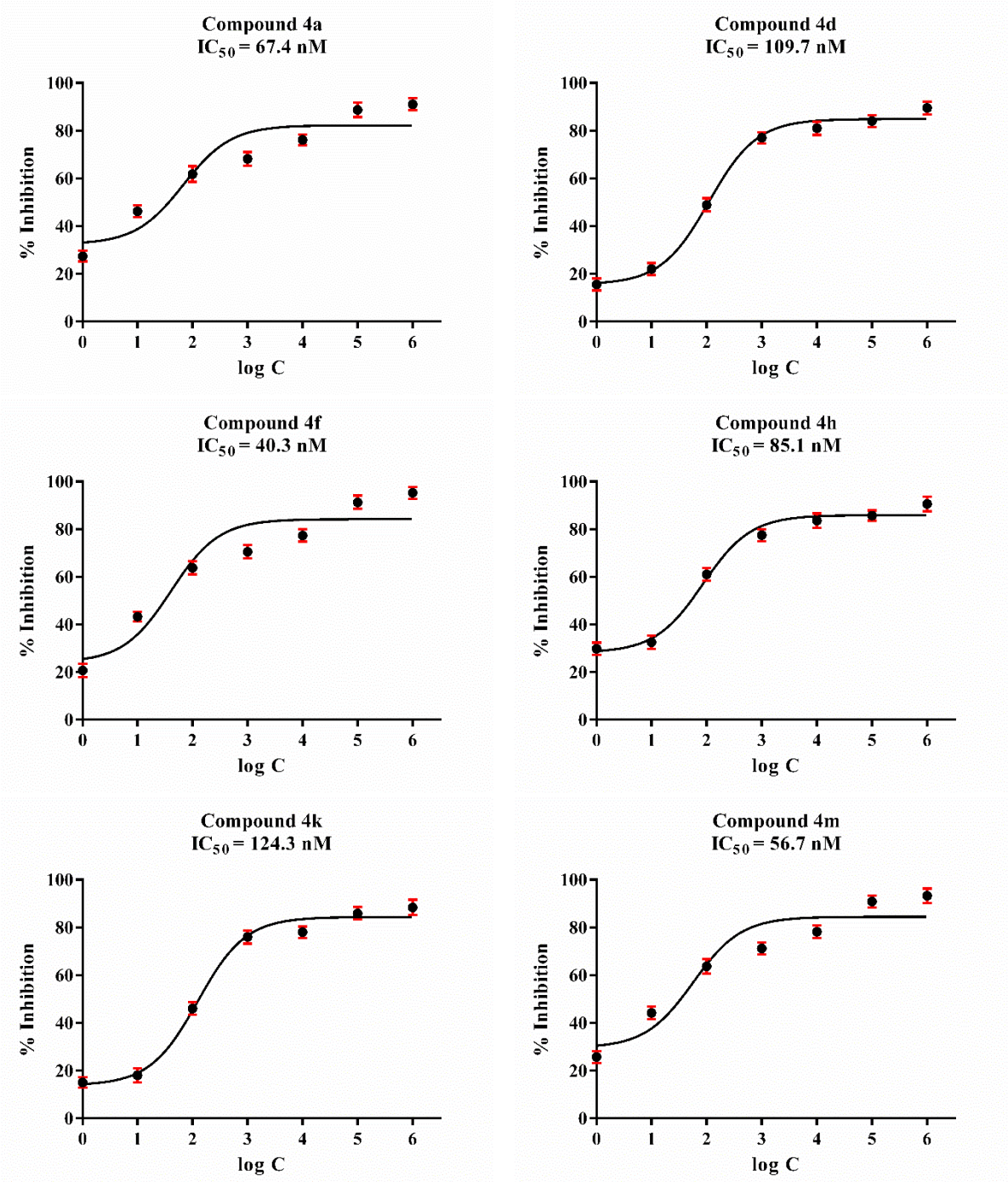


Figure S53. The IC_{50} graphs of compounds **4a**, **4d**, **4f**, **4g**, **4h**, **4k**, **4m**, **4n** and donepezil on AChE enzyme (The graphs are formed using GraphPad Prism Version 6 via regression analyses).


Compound 4a
IC50 = 67.4 nM
Compound 4d
IC50 = 109.7 nM
Compound 4f
IC50 = 40.3 nM
Compound 4h
IC50 = 85.1 nM
Compound 4k
IC50 = 124.3 nM
Compound 4m
IC50 = 56.7 nM
% Inhibition
log C

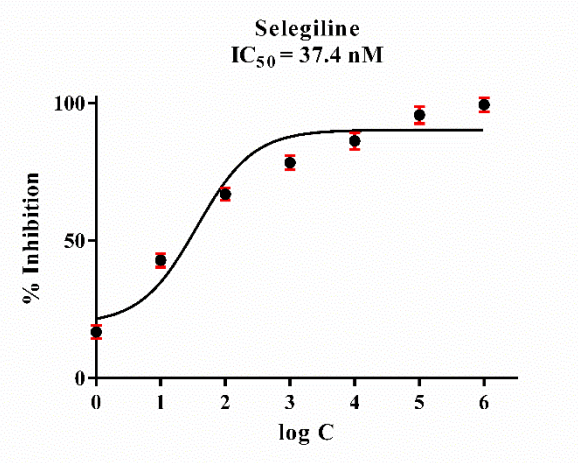


Figure S54. The IC_{50} graphs of compounds **4a**, **4d**, **4f**, **4h**, **4k**, **4m** and selegiline on MAO-B enzyme (The graphs are formed using GraphPad Prism Version 6 via regression analyses).