

## SUPPORTING INFORMATION

# Design, Synthesis, In Vitro and In Silico Studies of New Thiazolyldihydrazone-Piperazine Derivatives as Selective MAO-A Inhibitors

Begüm Nürpelin Sağlık <sup>1,2</sup>, Osman Cebeci <sup>1</sup>, Ulviye Acar Çevik <sup>1,2</sup>, Derya Osmaniye <sup>1,2\*</sup>, Serkan Levent <sup>1,2</sup>, Betül Kaya Çavuşođlu <sup>3</sup>, Sinem Ilgın <sup>4</sup>, Yusuf Özkay <sup>1,2</sup> and Zafer Asım Kaplancıklı <sup>1</sup>

<sup>1</sup> Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, 26470 Eskişehir, Turkey

<sup>2</sup> Doping and Narcotic Compounds Analysis Laboratory, Faculty of Pharmacy, Anadolu University, 26470 Eskişehir, Turkey

<sup>3</sup> Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Zonguldak Bülent Ecevit University, 67600 Zonguldak, Turkey

<sup>4</sup> Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Anadolu University, 26470 Eskişehir, Turkey

\* Correspondence: dosmaniye@anadolu.edu.tr; Tel.: +90-222-335-0580/3778

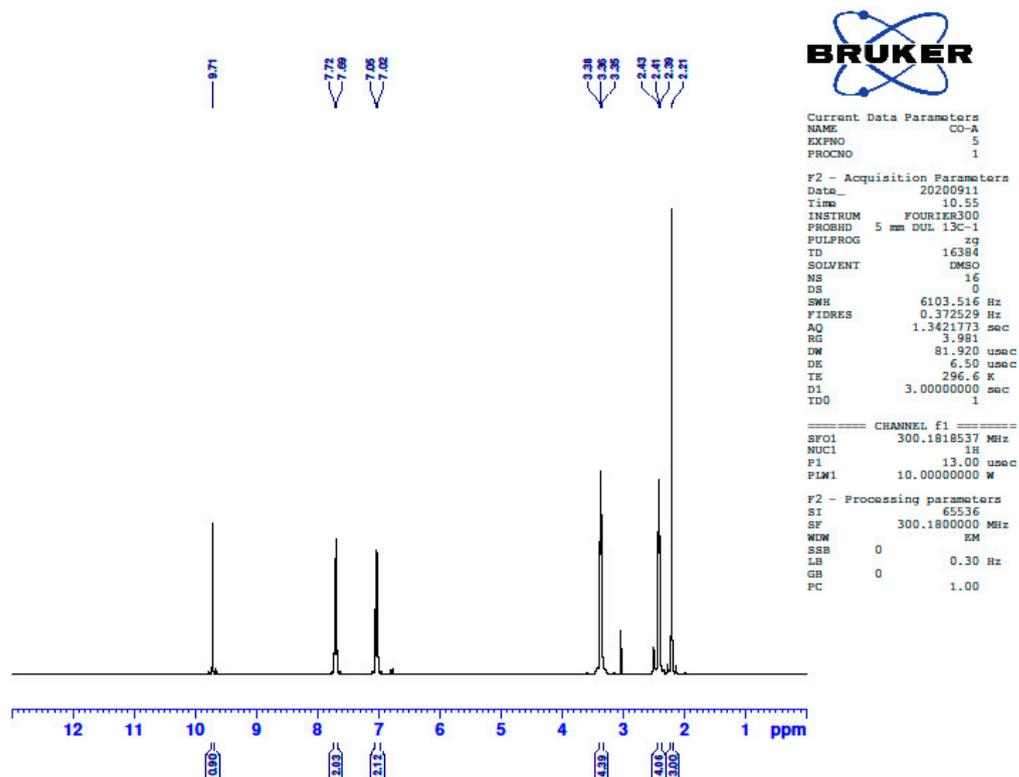


Figure S1. <sup>1</sup>H-NMR spectra of compound 1

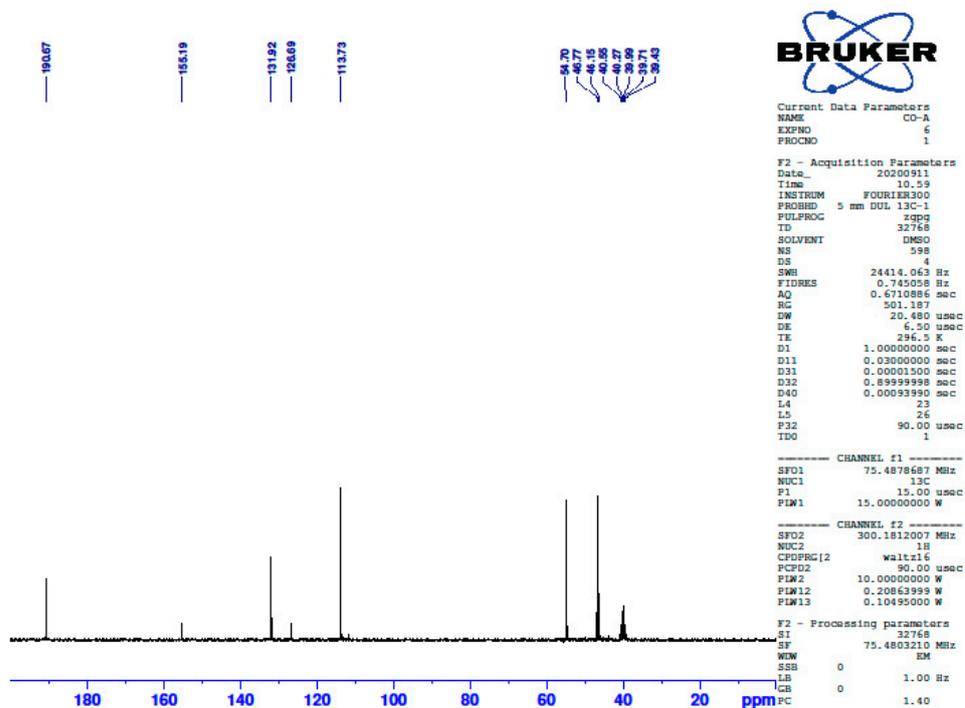


Figure S2. <sup>13</sup>C-NMR spectra of compound 1

Data File: C:\LabSolutions\Data\Analizi\Serkan\CO-B\_02.lcd

Elmt	Val	Min	Max	Use Adduct												
H	1	5	35	O	2	0	5	S	2	0	1	Ru	2	0	0	H
C	4	9	35	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): 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

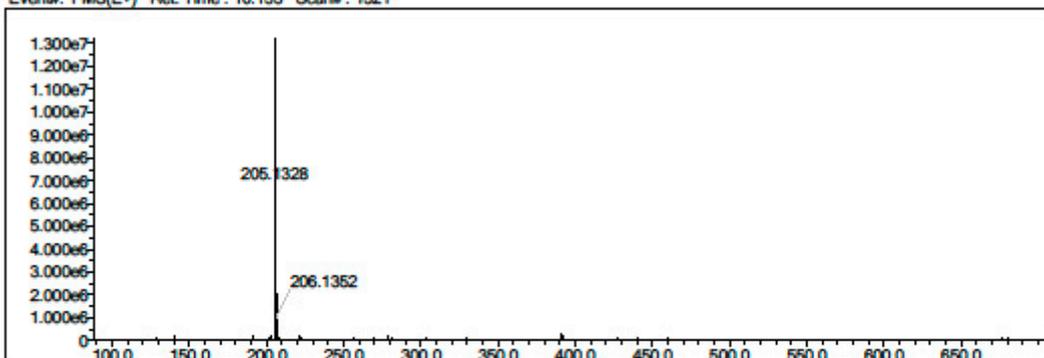
Electron Ions: both

Use MSn Info: yes

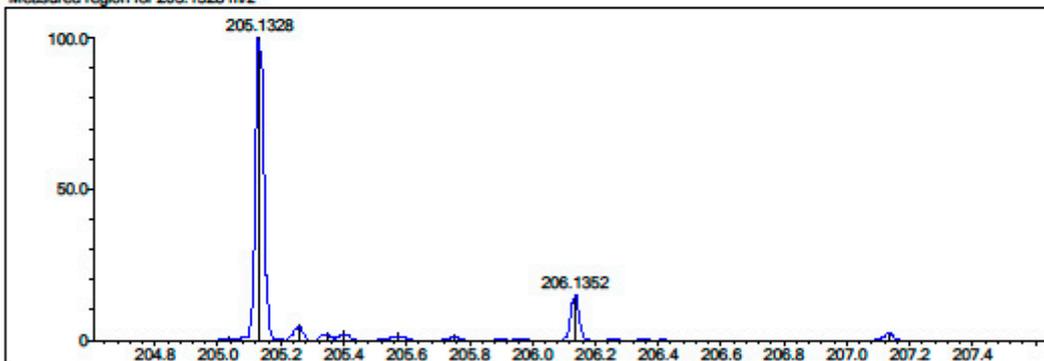
Isotope Res: 9000

Max Results: 100

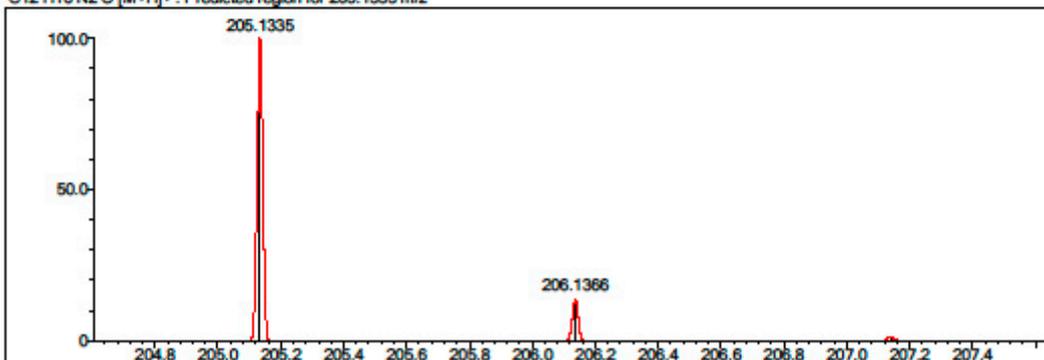
Event#: 1 MS(E+) Ret. Time : 10.133 Scan#: 1521



Measured region for 205.1328 m/z



C12 H16 N2 O [M+H]+ : Predicted region for 205.1335 m/z



Peak	Score	Formula (M)	Ion	Mass. m/z	Pred. m/z	Diff. (mDa)	Diff. (ppm)	Iso	DBE
1	67.98	C12 H16 N2 O	[M+H] <sup>+</sup>	205.1328	205.1335	-0.7	-3.41	72.34	6.0

Figure S3. HRMS spectra of compound 1

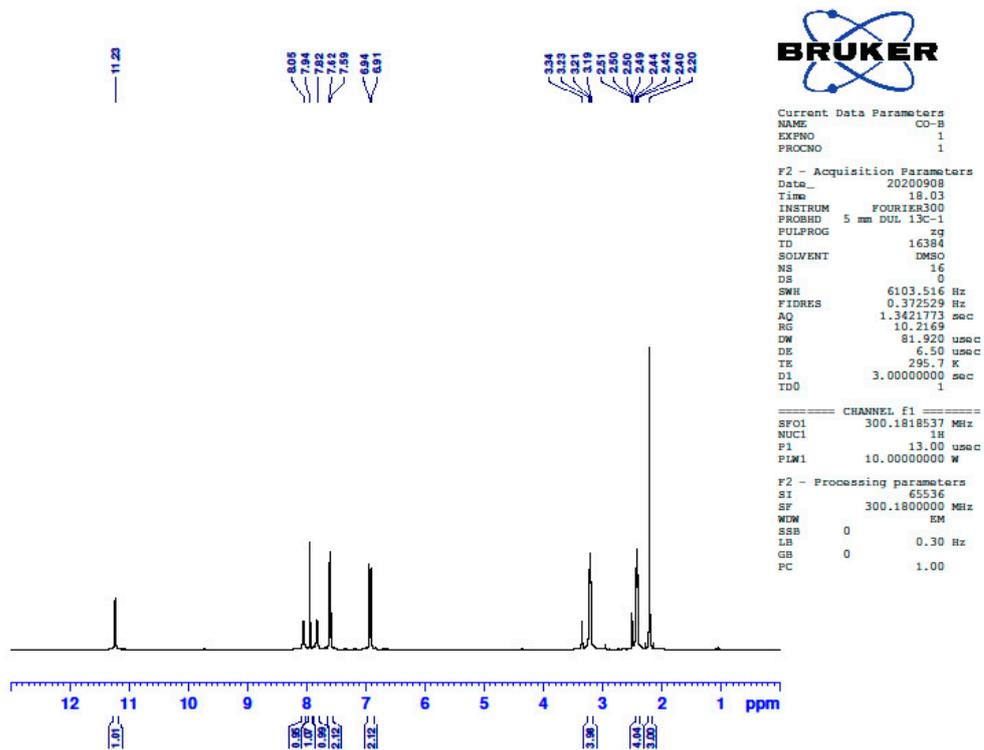


Figure S4. <sup>1</sup>H-NMR spectra of compound 2

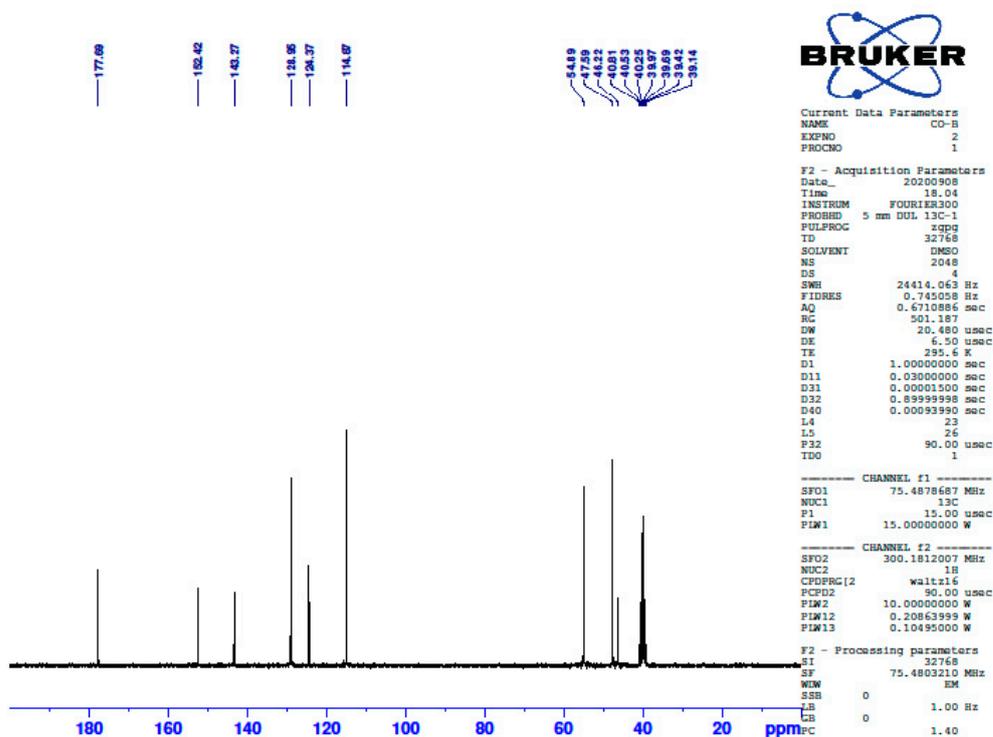


Figure S5. <sup>13</sup>C-NMR spectra of compound 2

Data File: C:\LabSolutions\Data\Analizi\Serkan\CO-A\_01.lcd

Elmt	Val	Min	Max	Use Adduct												
H	1	5	35	O	2	0	5	S	2	0	1	Ru	2	0	0	H
C	4	9	35	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): 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

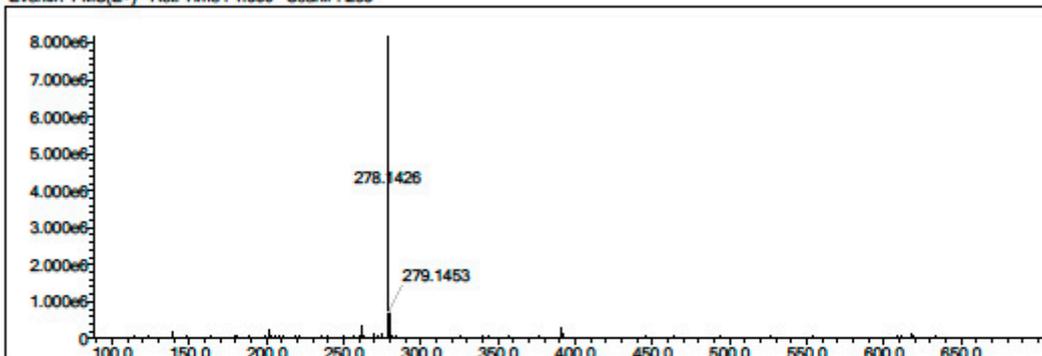
Electron Ions: both

Use MSn Info: yes

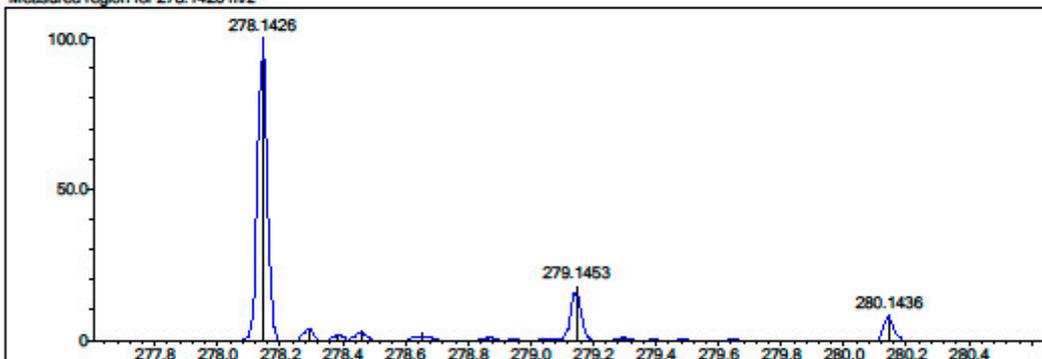
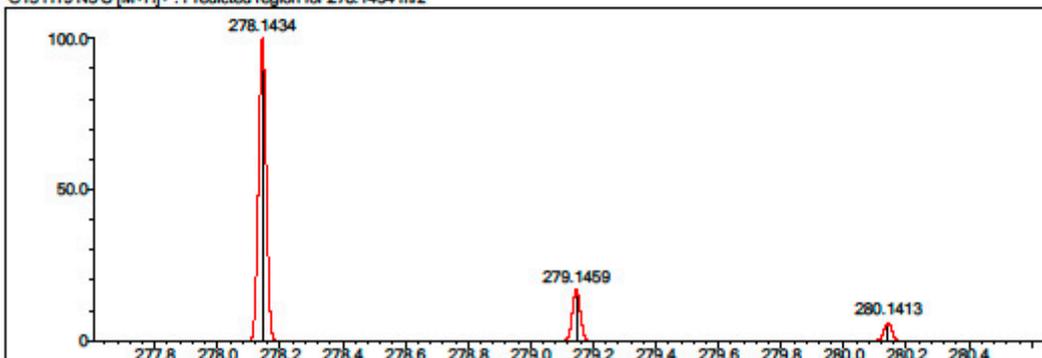
Isotope Res: 9000

Max Results: 100

Event#: 1 MS(E+) Ret. Time : 1.560 Scan#: 235



Measured region for 278.1426 m/z

C13 H19 N5 S [M+H]<sup>+</sup> : Predicted region for 278.1434 m/z

Peak	Score	Formula (M)	Ion	Mass. m/z	Pred. m/z	Diff. (mDa)	Diff. (ppm)	Iso	DBE
1	78.43	C13 H19 N5 S	[M+H] <sup>+</sup>	278.1426	278.1434	-0.8	-2.88	82.30	7.0

Figure S6. HRMS spectra of compound 2

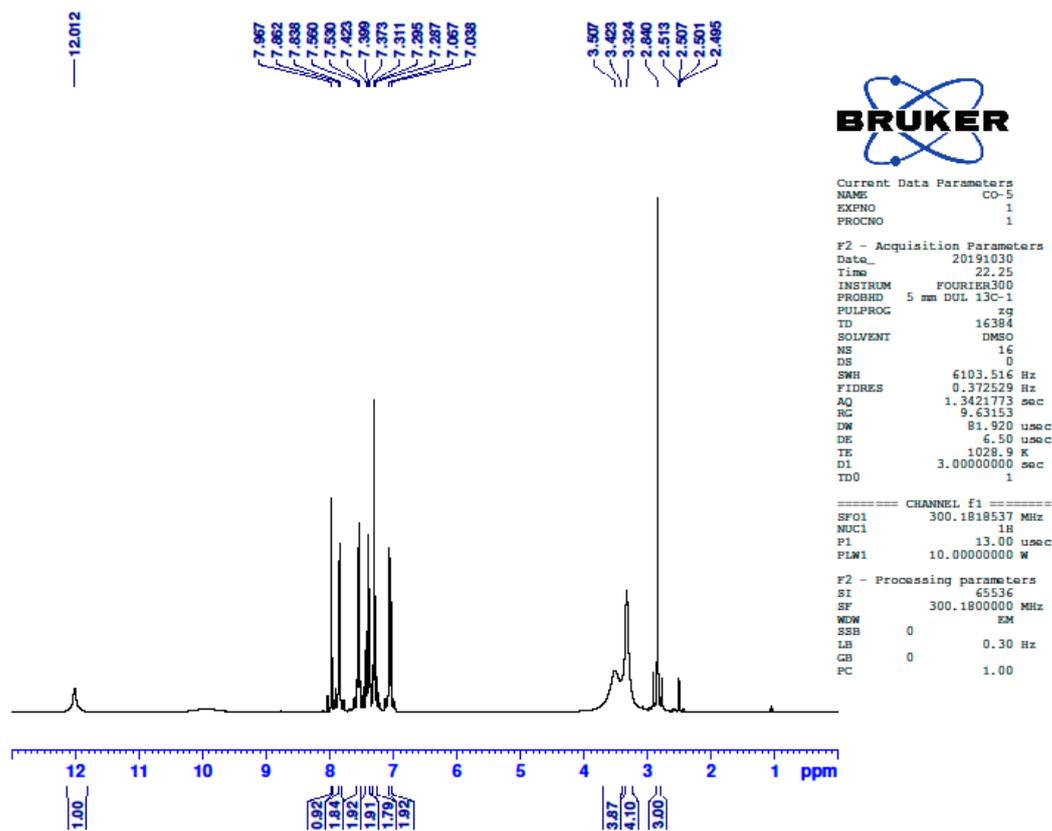


Figure S7. <sup>1</sup>H-NMR spectra of compound 3a

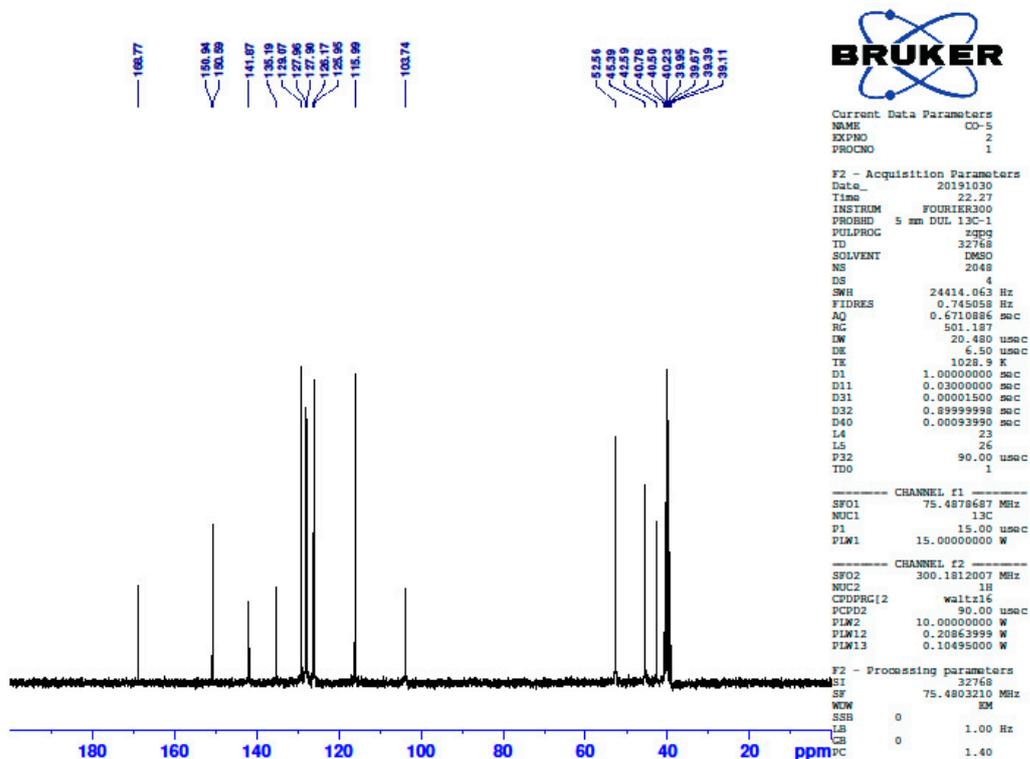


Figure S8. <sup>13</sup>C-NMR spectra of compound 3a

Data File: C:\LabSolutions\Data\Analiz\iderya\CO-5\_5.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	1	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

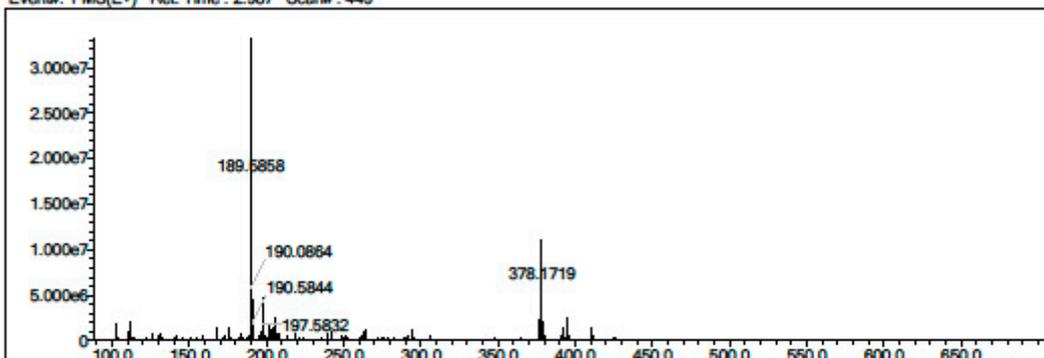
Electron Ions: both

Use MSn Info: yes

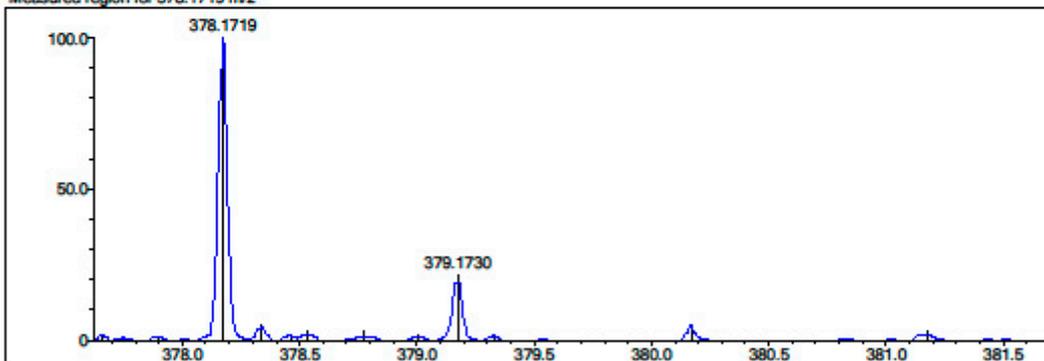
Isotope Res: 9000

Max Results: 100

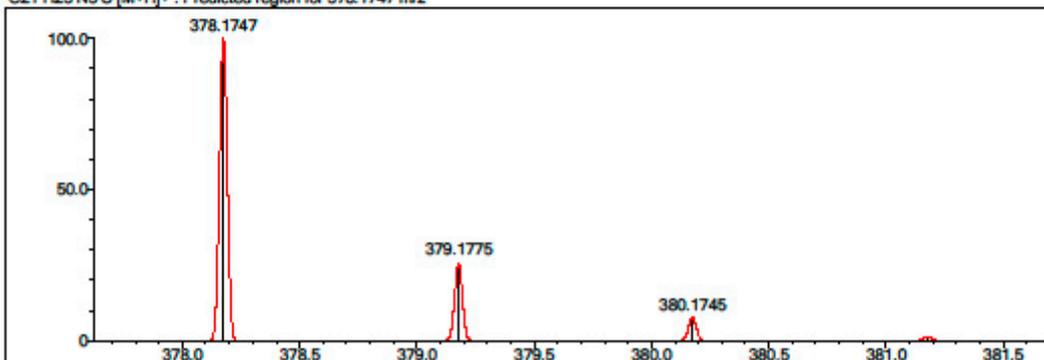
Event#: 1 MS(E+) Ret. Time : 2.987 Scan#: 449



Measured region for 378.1719 m/z



C21 H23 N5 S [M+H]<sup>+</sup> : Predicted region for 378.1747 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	44.59	C21 H23 N5 S	[M+H] <sup>+</sup>	378.1719	378.1747	-2.8	-7.40	67.56	13.0

Figure S9. HRMS spectra of compound 3a

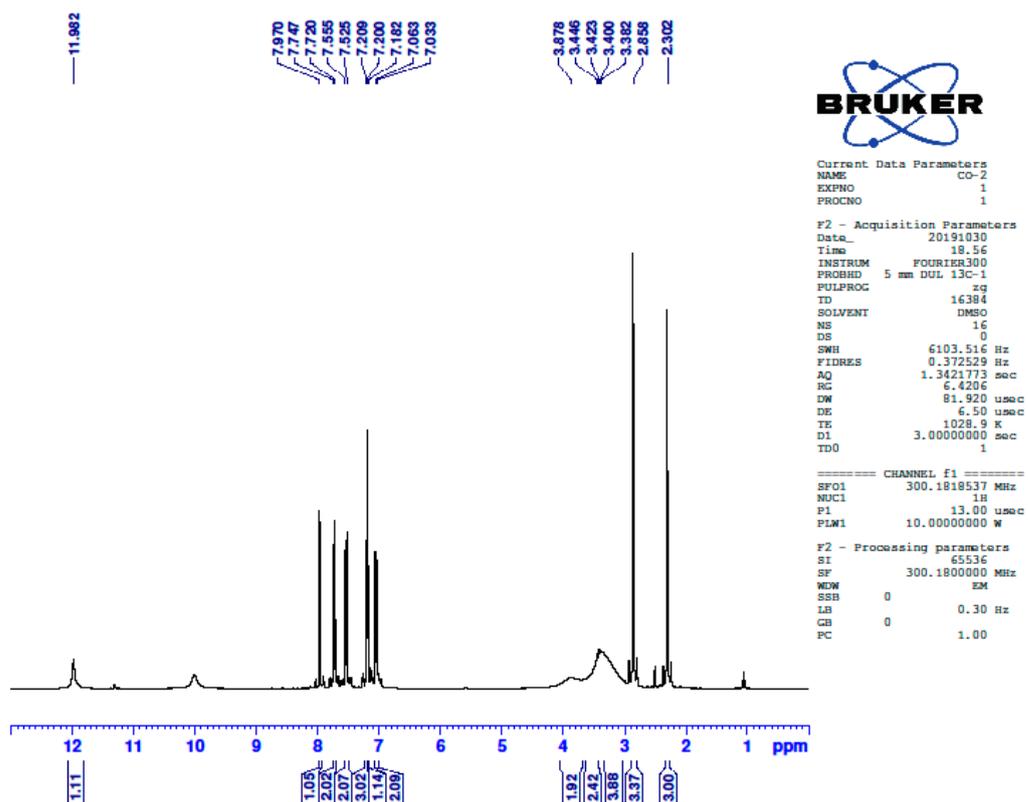


Figure S10.  $^1\text{H}$ -NMR spectra of compound 3b

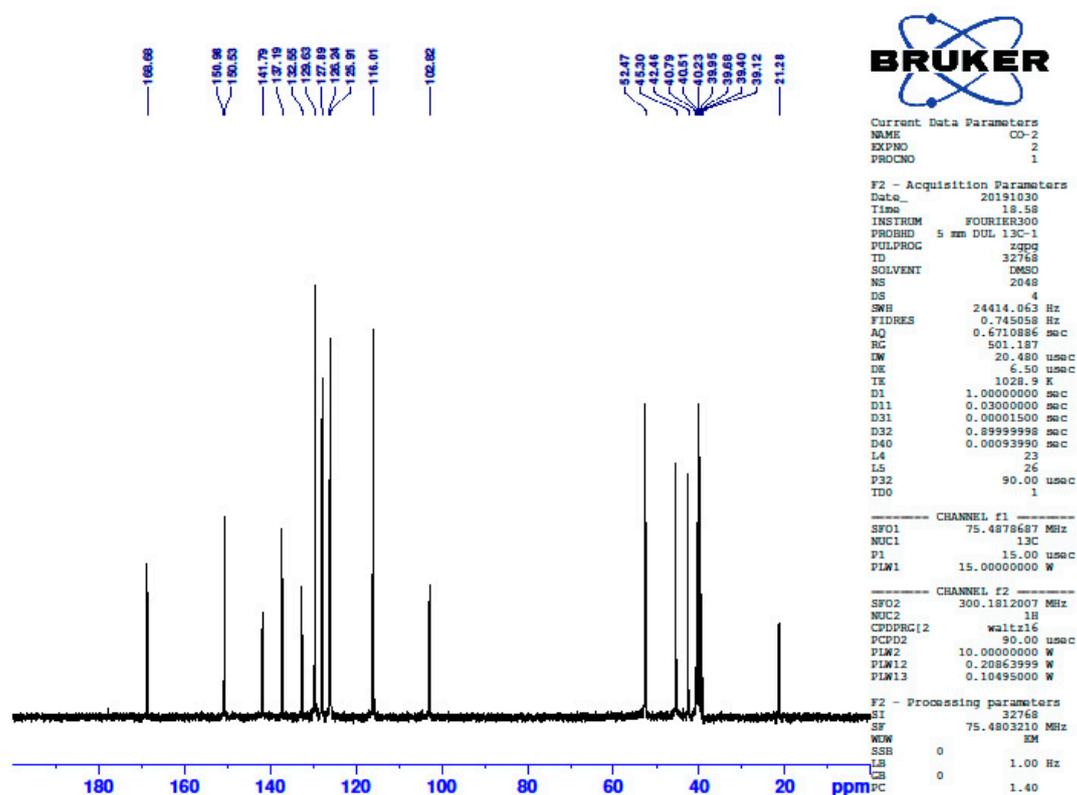


Figure S11.  $^{13}\text{C}$ -NMR spectra of compound 3b

Data File: C:\LabSolutions\Data\Analiz\deriv\CO-2\_2.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	1	S	2	1	1	Pu	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

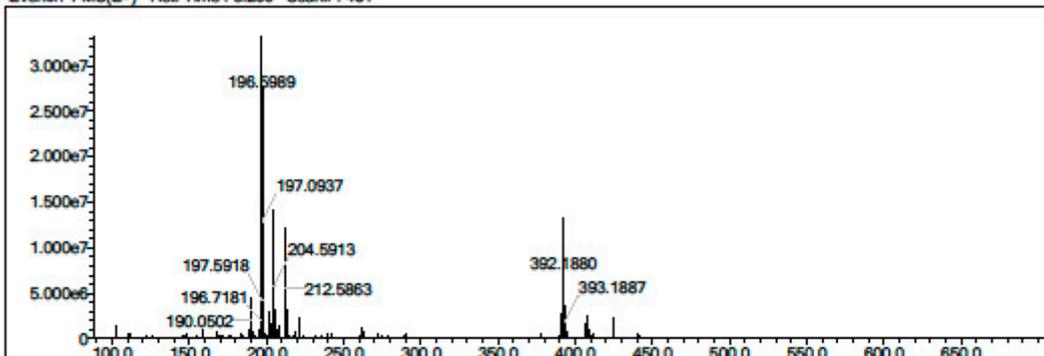
Electron Ions: both

Use MSn Info: yes

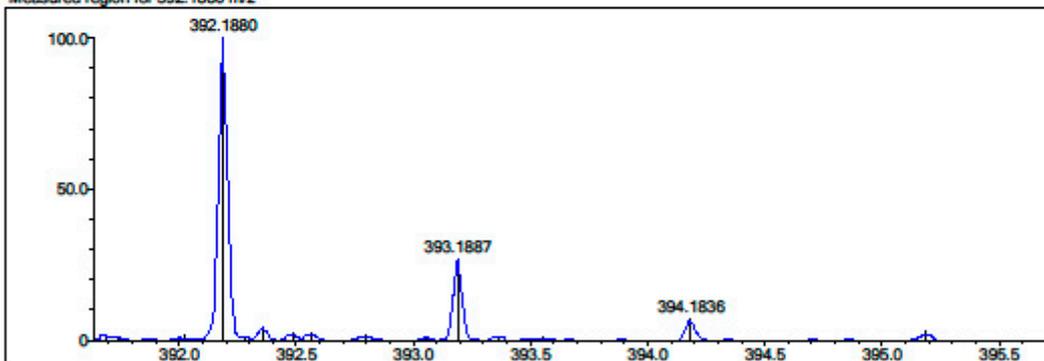
Isotope Res: 9000

Max Results: 100

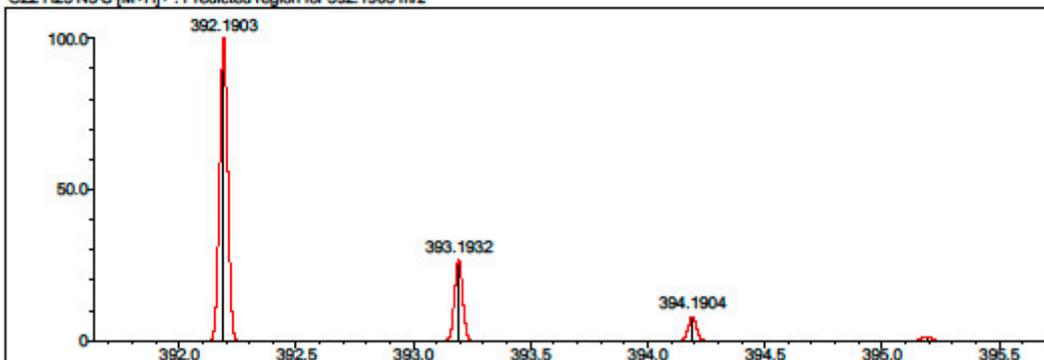
Event#: 1 MS(E+) Ret. Time : 3.200 Scan#: 481



Measured region for 392.1880 m/z



C22 H25 N5 S [M+H]<sup>+</sup> : Predicted region for 392.1903 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	54.22	C22 H25 N5 S	[M+H] <sup>+</sup>	392.1880	392.1903	-2.3	-5.86	66.61	13.0

Figure S12. HRMS spectra of compound 3b

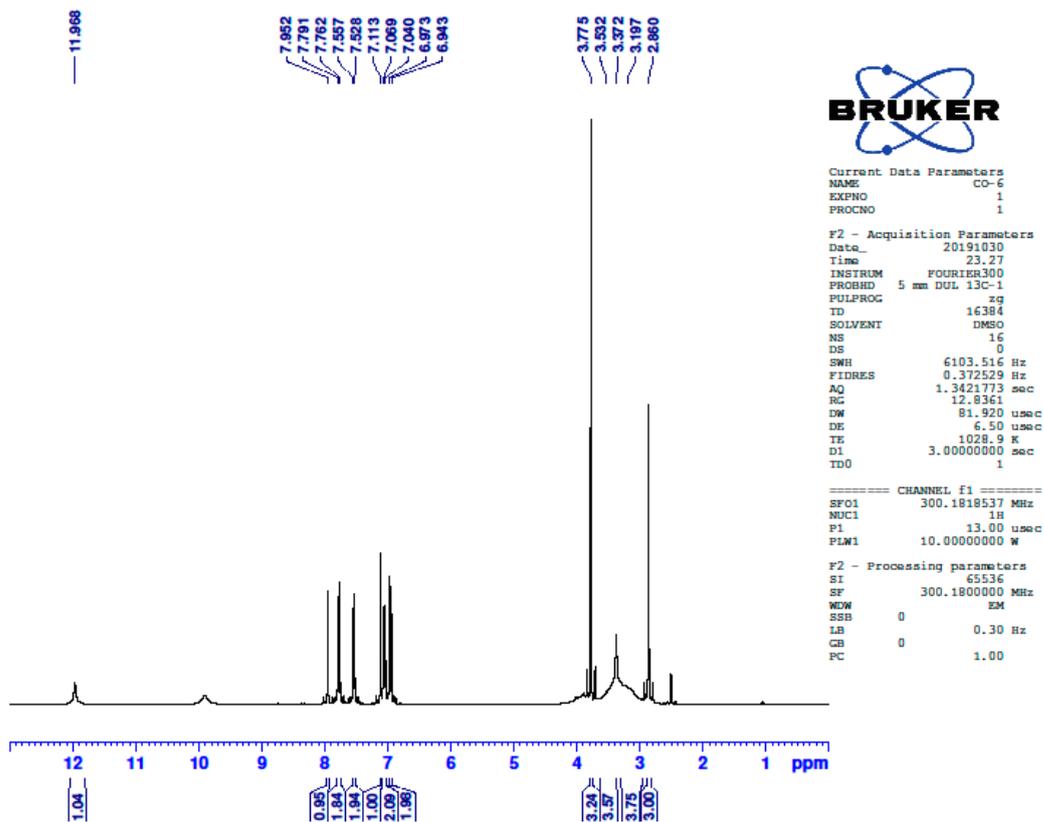


Figure S13.  $^1\text{H}$ -NMR spectra of compound 3c

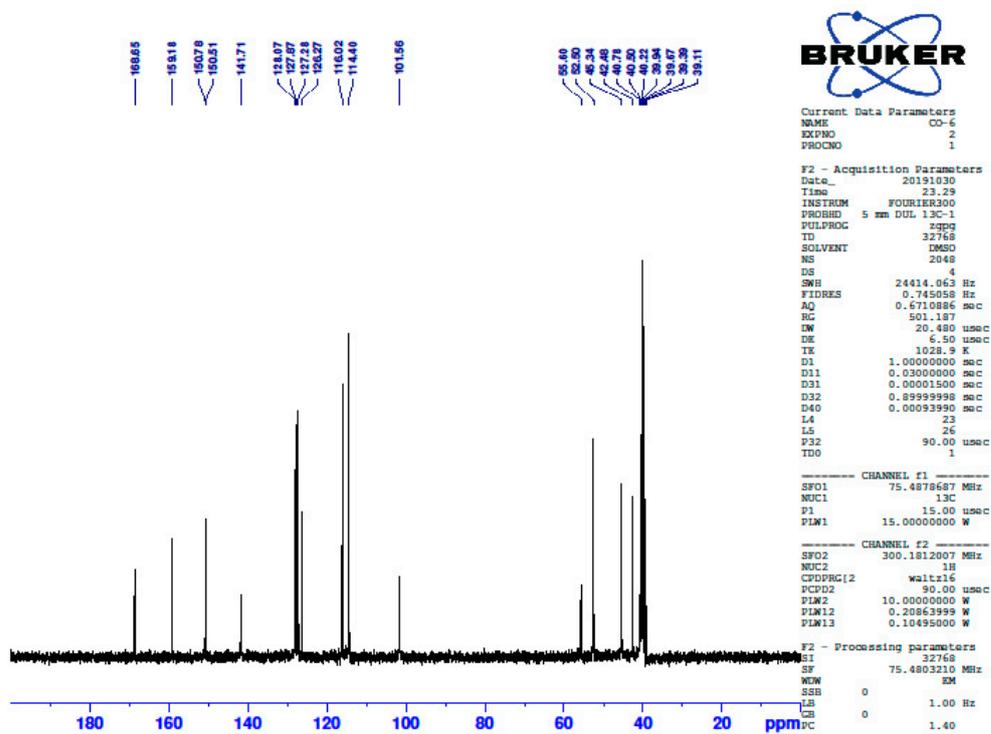


Figure S14.  $^{13}\text{C}$ -NMR spectra of compound 3c

Data File: C:\LabSolutions\Data\Analiz\ideryal\CO-6\_6.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	1	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

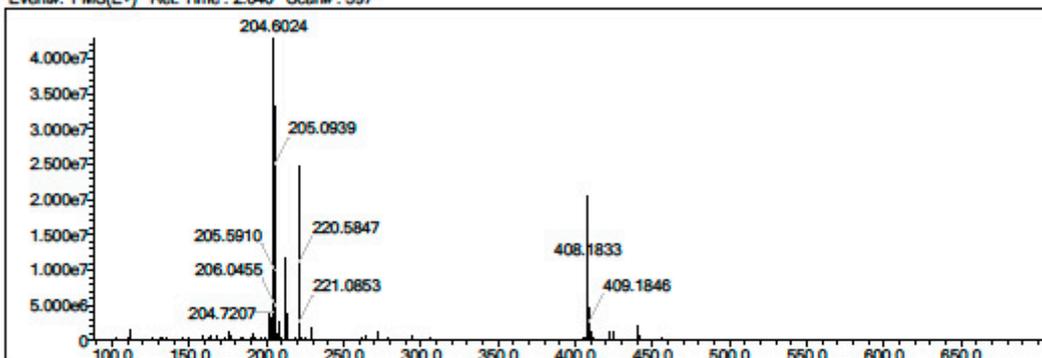
Electron Ions: both

Use MSn Info: yes

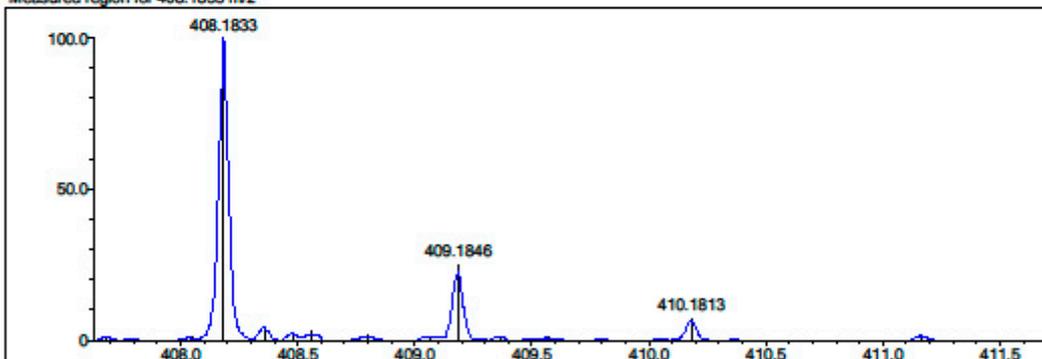
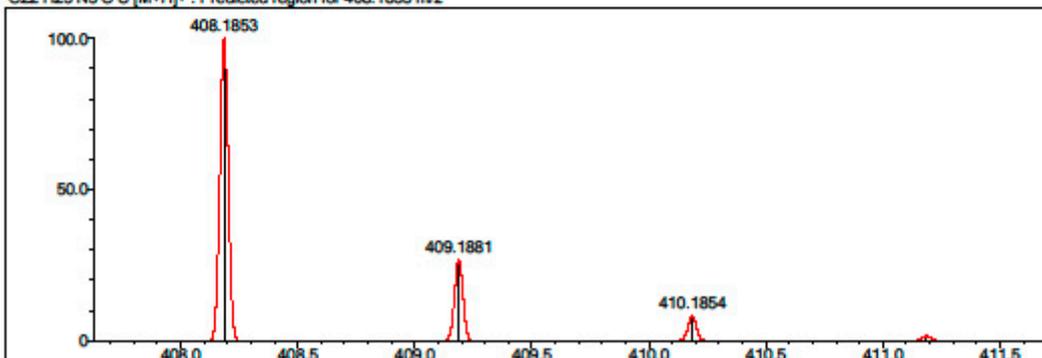
Isotope Res: 9000

Max Results: 100

Event#: 1 MS(E+) Ret. Time : 2.640 Scan#: 397



Measured region for 408.1833 m/z

C22 H25 N5 O S [M+H]<sup>+</sup> : Predicted region for 408.1853 m/z

Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	58.93	C22 H25 N5 O S	[M+H] <sup>+</sup>	408.1833	408.1853	-2.0	-4.90	63.08	13.0

Figure S15. HRMS spectra of compound 3c



Data File: C:\LabSolutions\Data\Analiz\idery\CO-7\_7.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	1	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

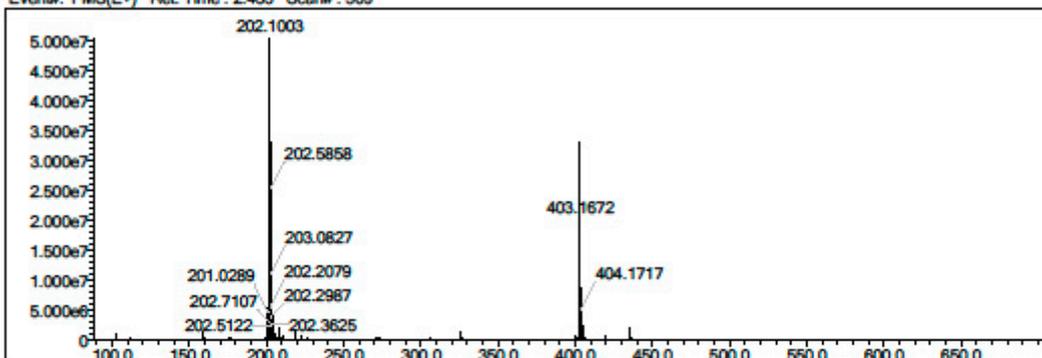
Electron Ions: both

Use MSn Info: yes

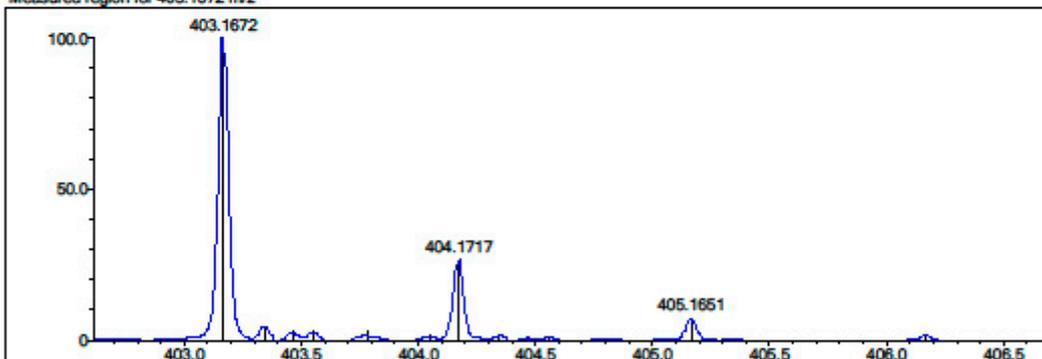
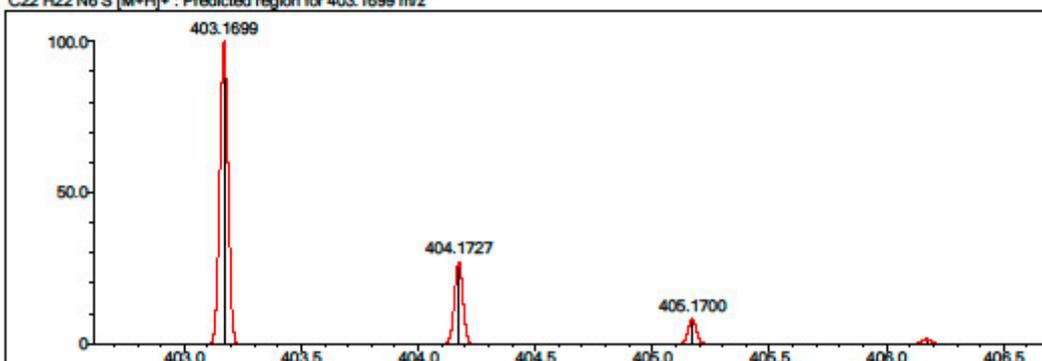
Isotope Res: 9000

Max Results: 100

Event#: 1 MS(E+) Ret. Time: 2.453 Scan#: 369



Measured region for 403.1672 m/z

C22 H22 N6 S [M+H]<sup>+</sup>: Predicted region for 403.1699 m/z

Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	60.74	C22 H22 N6 S	[M+H] <sup>+</sup>	403.1672	403.1699	-2.7	-6.70	83.21	15.0

Figure S18. HRMS spectra of compound 3d

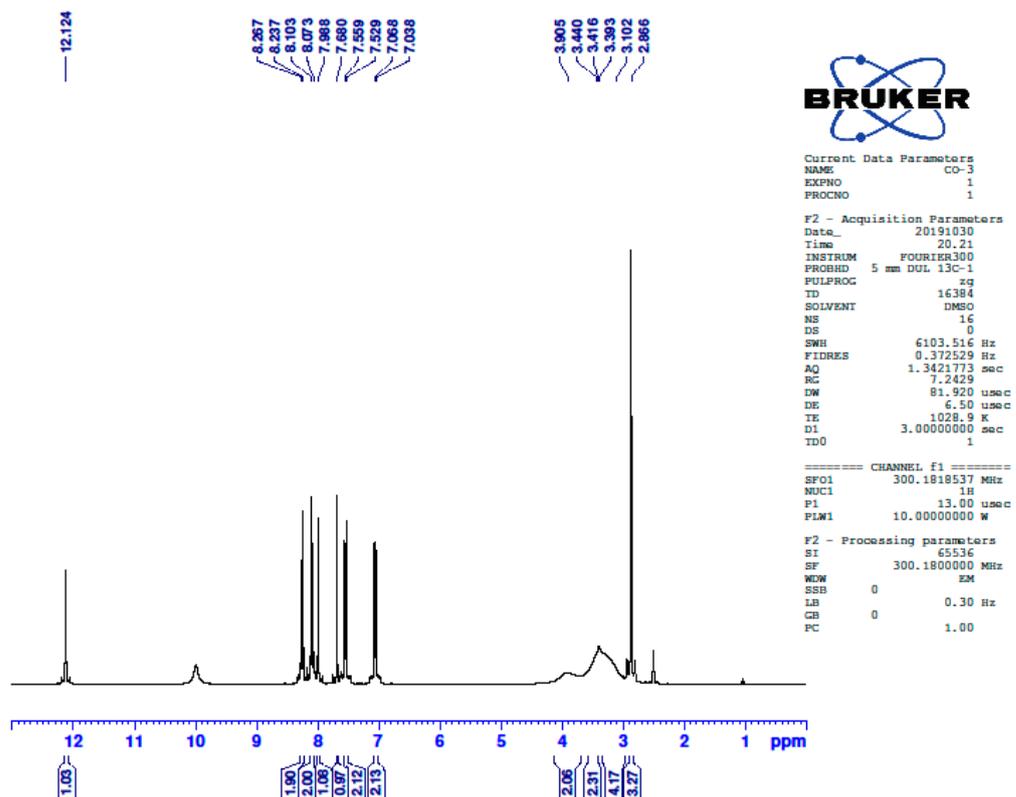


Figure S19.  $^1\text{H}$ -NMR spectra of compound 3e

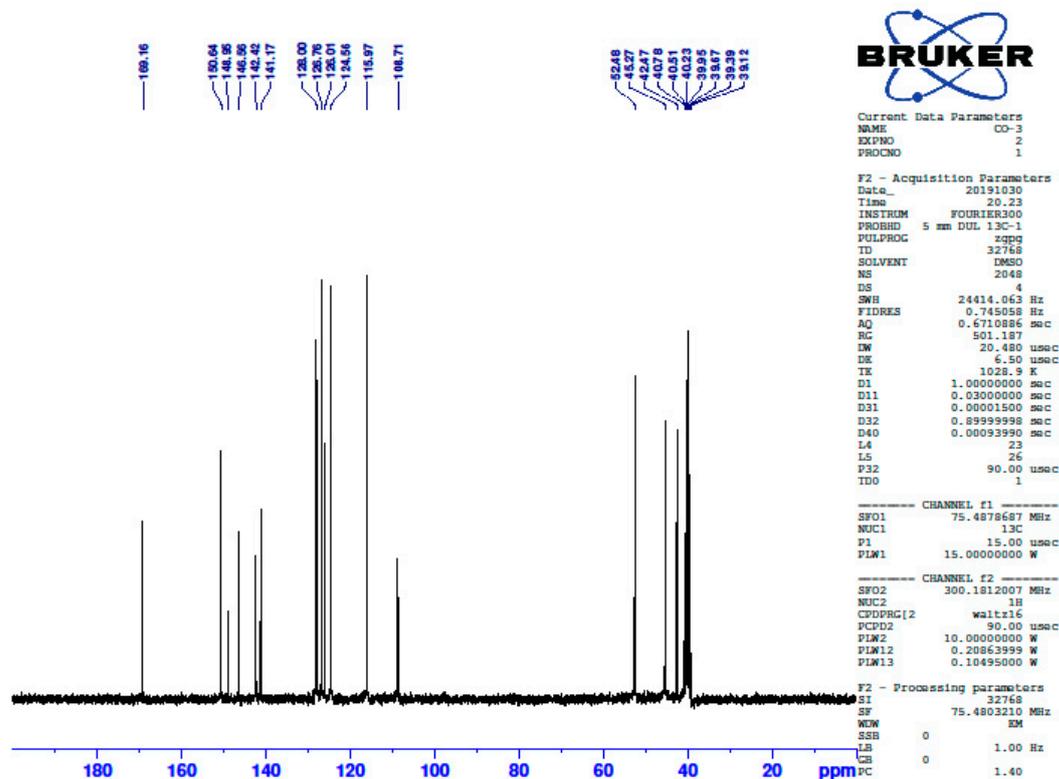


Figure S20.  $^{13}\text{C}$ -NMR spectra of compound 3e

Data File: C:\LabSolutions\Data\Analiz\deriv\CO-3\_3.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

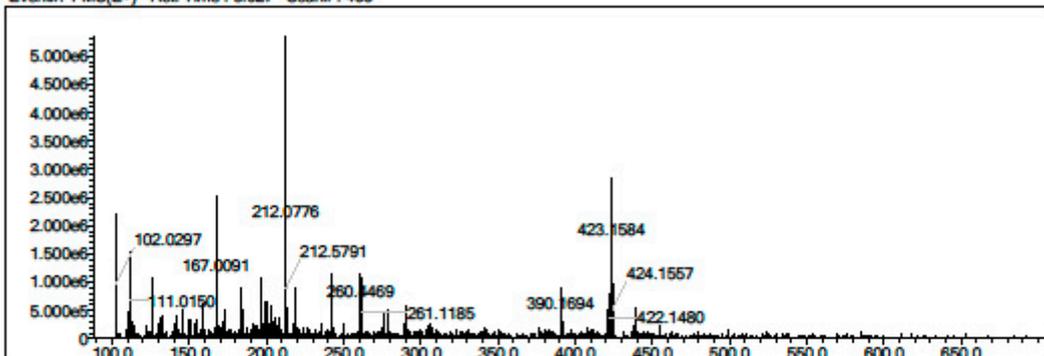
Electron Ions: both

Use MSn Info: yes

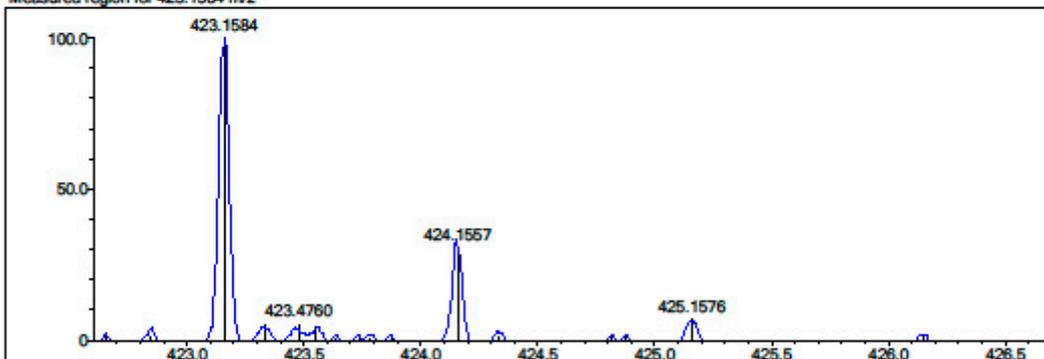
Isotope Res: 9000

Max Results: 100

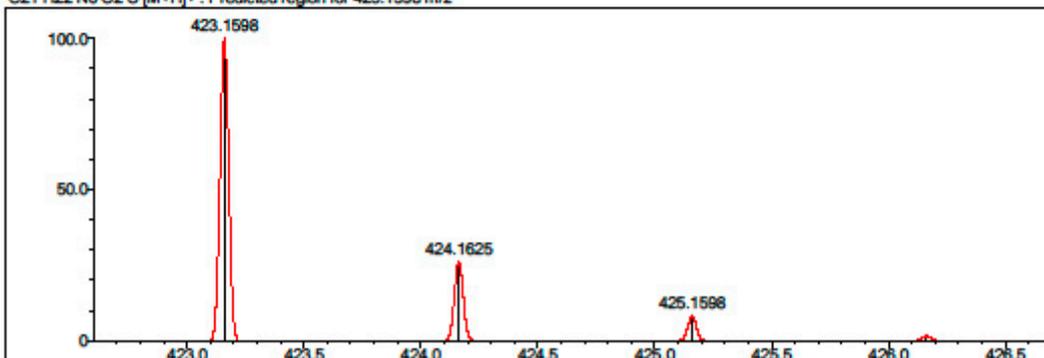
Event#: 1 MS(E+) Ret. Time : 3.027 Scan#: 455



Measured region for 423.1584 m/z



C21 H22 N6 O2 S [M+H]<sup>+</sup> : Predicted region for 423.1598 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	71.93	C21 H22 N6 O2 S	[M+H] <sup>+</sup>	423.1584	423.1598	-1.4	-3.31	76.34	14.0

Figure S21. HRMS spectra of compound 3e

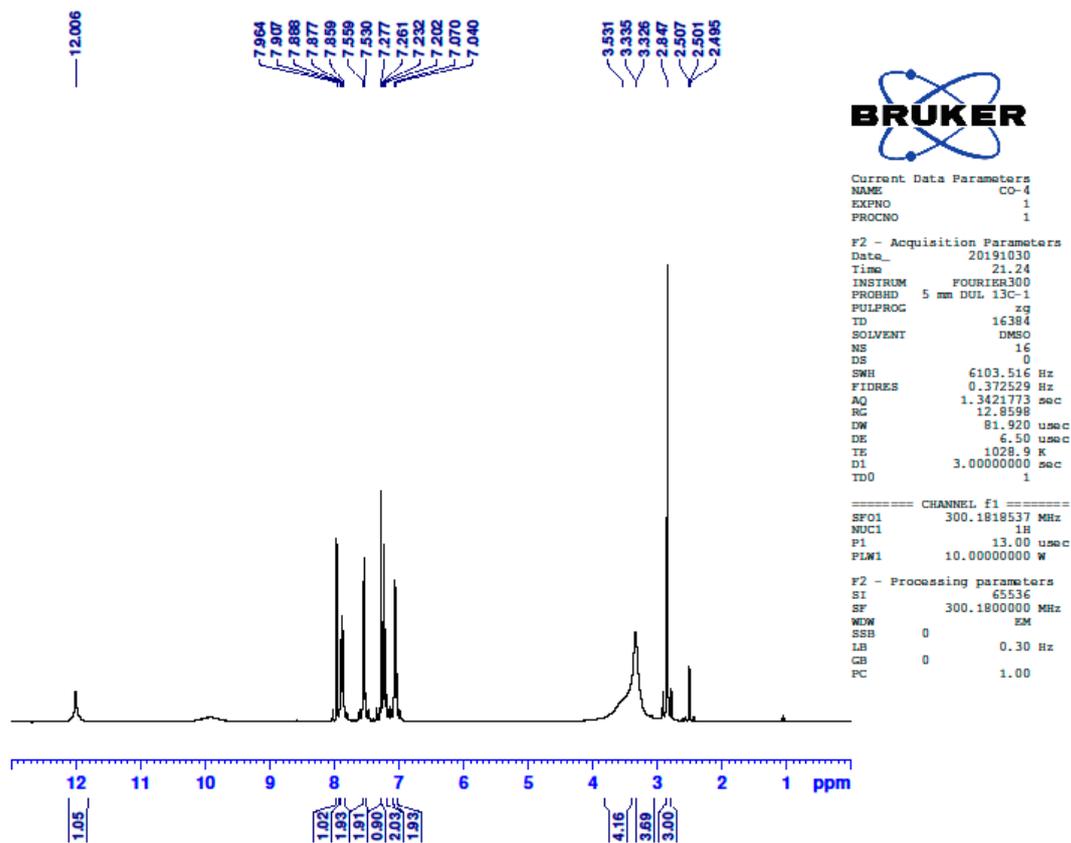


Figure S22.  $^1\text{H}$ -NMR spectra of compound 3f

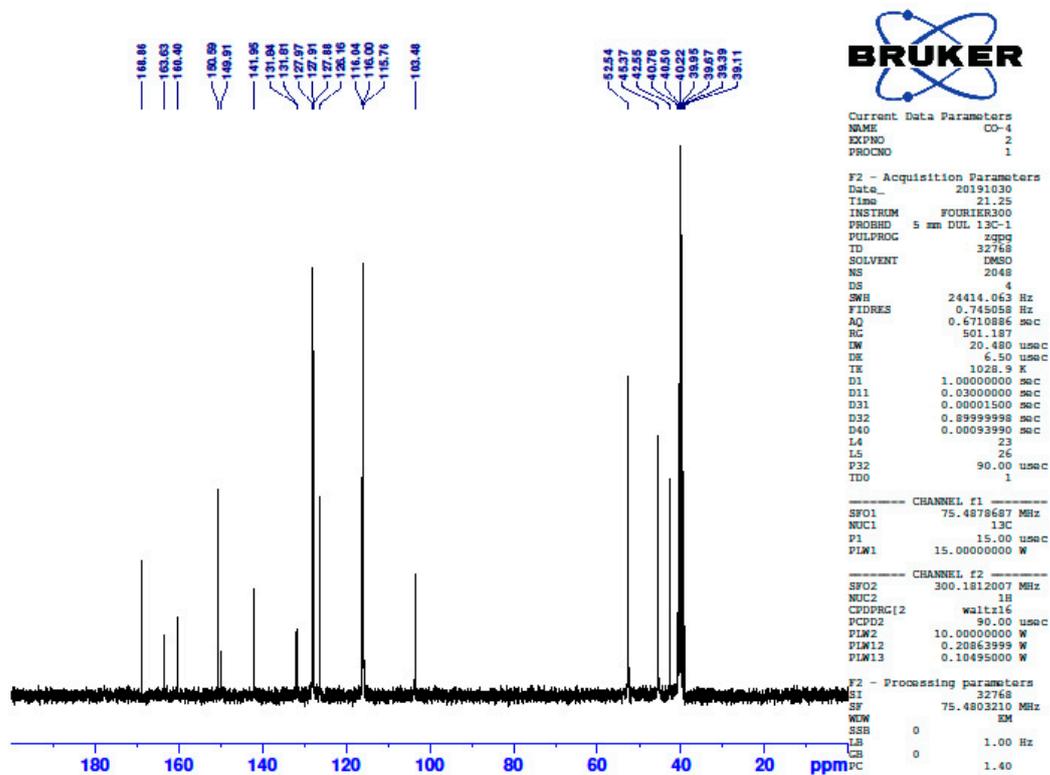


Figure S23.  $^{13}\text{C}$ -NMR spectra of compound 3f

Data File: C:\LabSolutions\Data\Analizidery\CO-4\_4.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	1	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

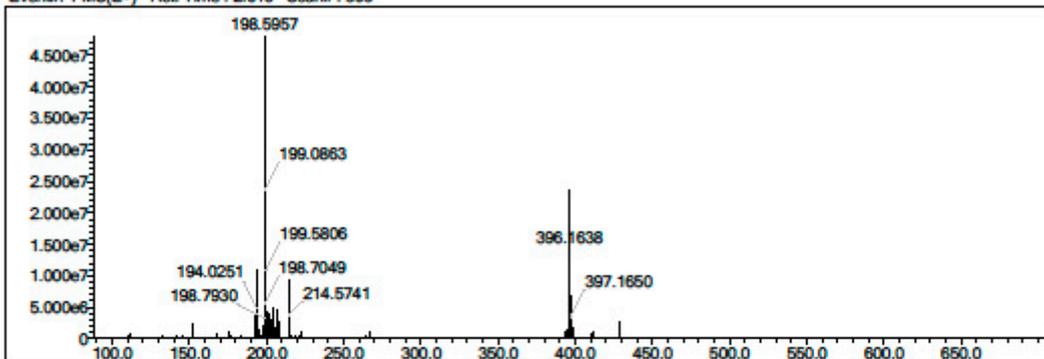
Electron Ions: both

Use MSn Info: yes

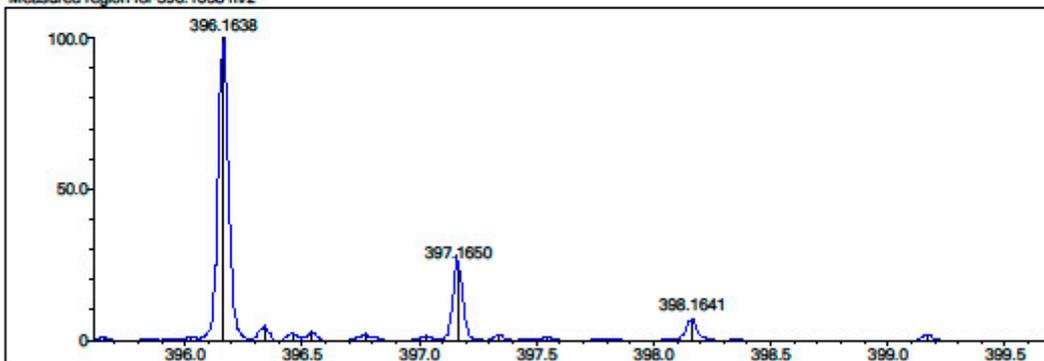
Isotope Res: 9000

Max Results: 100

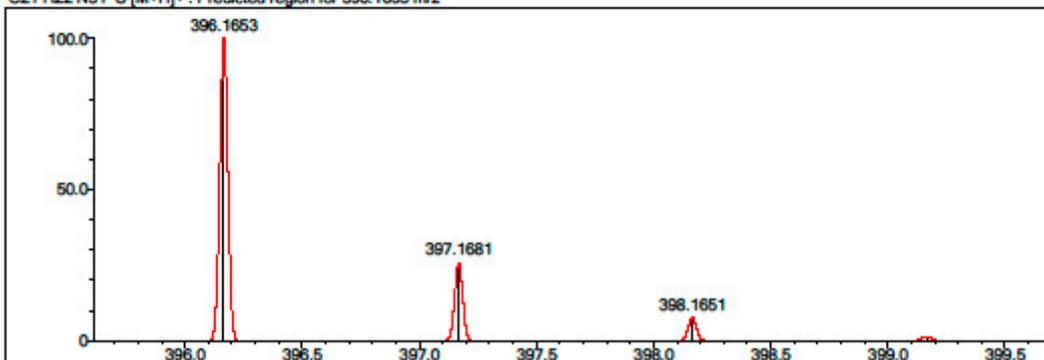
Event#: 1 MS(E+) Ret. Time: 2.613 Scan#: 393



Measured region for 396.1638 m/z



C21 H22 N5 F S [M+H]+ : Predicted region for 396.1653 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	91.60	C21 H22 N5 F S	[M+H] <sup>+</sup>	396.1638	396.1653	-1.5	-3.79	98.47	13.0

Figure S24. HRMS spectra of compound 3f

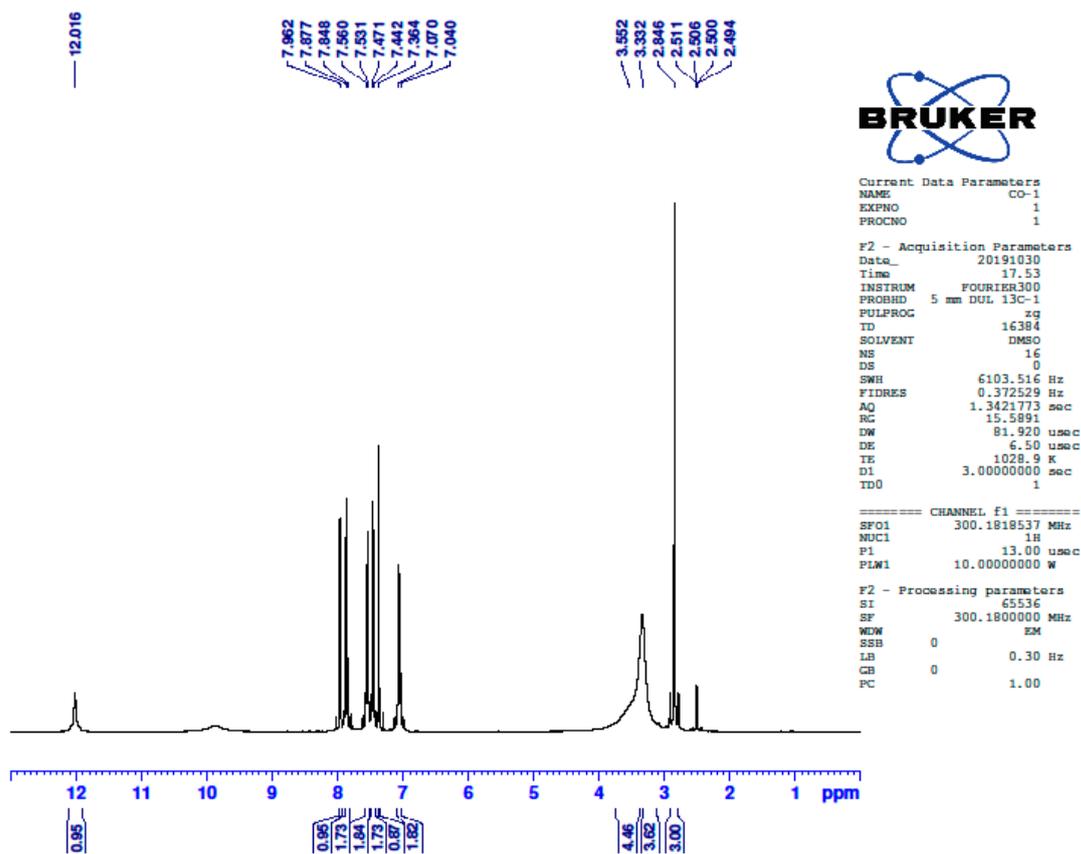


Figure S25.  $^1\text{H}$ -NMR spectra of compound 3g

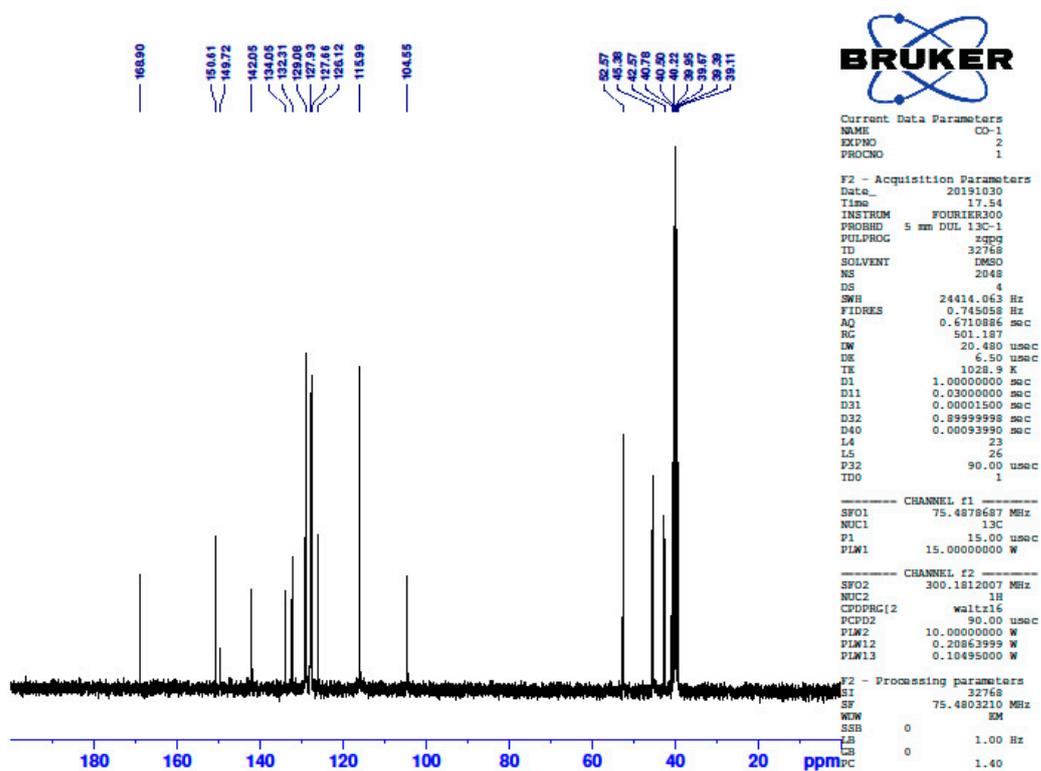


Figure S26.  $^{13}\text{C}$ -NMR spectra of compound 3g

Data File: C:\LabSolutions\Data\Analizidery\CO-1\_1.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	1	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

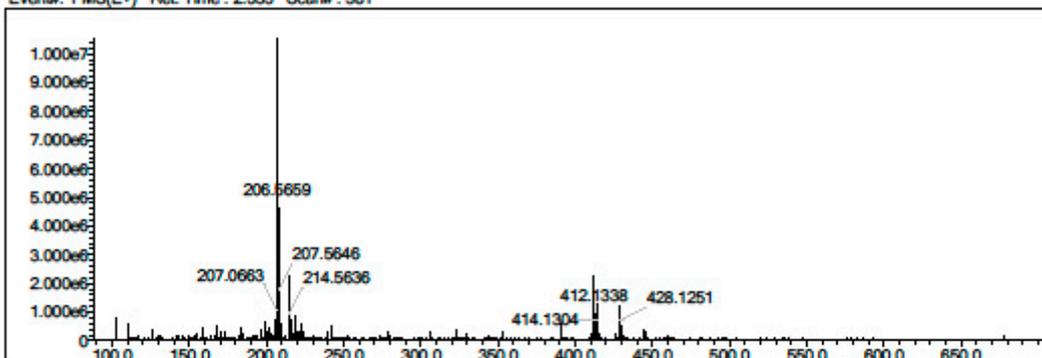
Electron Ions: both

Use MSn Info: yes

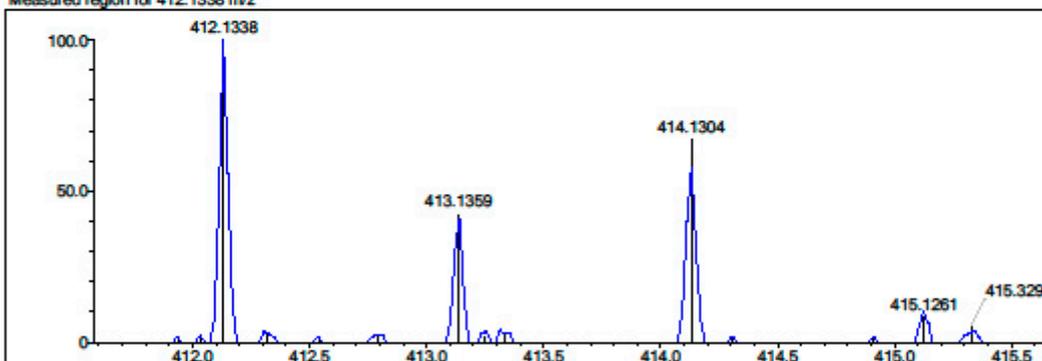
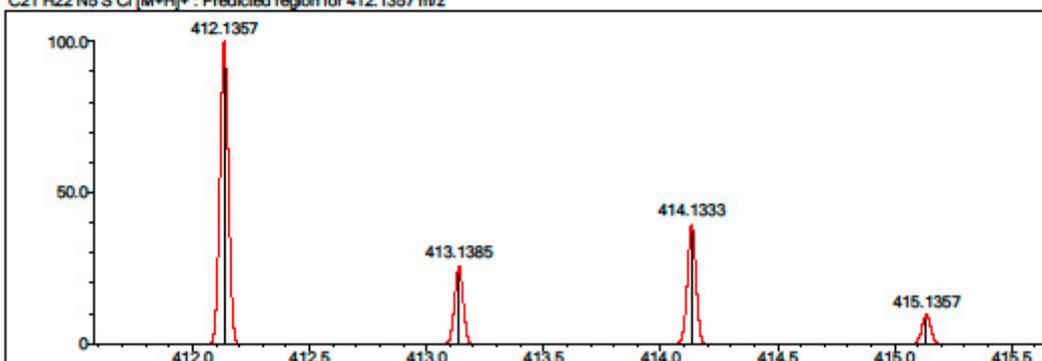
Isotope Res: 9000

Max Results: 100

Event#: 1 MS(E+) Ret. Time: 2.533 Scan#: 381



Measured region for 412.1338 m/z

C21 H22 N5 S Cl [M+H]<sup>+</sup>: Predicted region for 412.1357 m/z

Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	39.31	C21 H22 N5 S Cl	[M+H] <sup>+</sup>	412.1338	412.1357	-1.9	-4.61	43.21	13.0

Figure S27. HRMS spectra of compound 3g

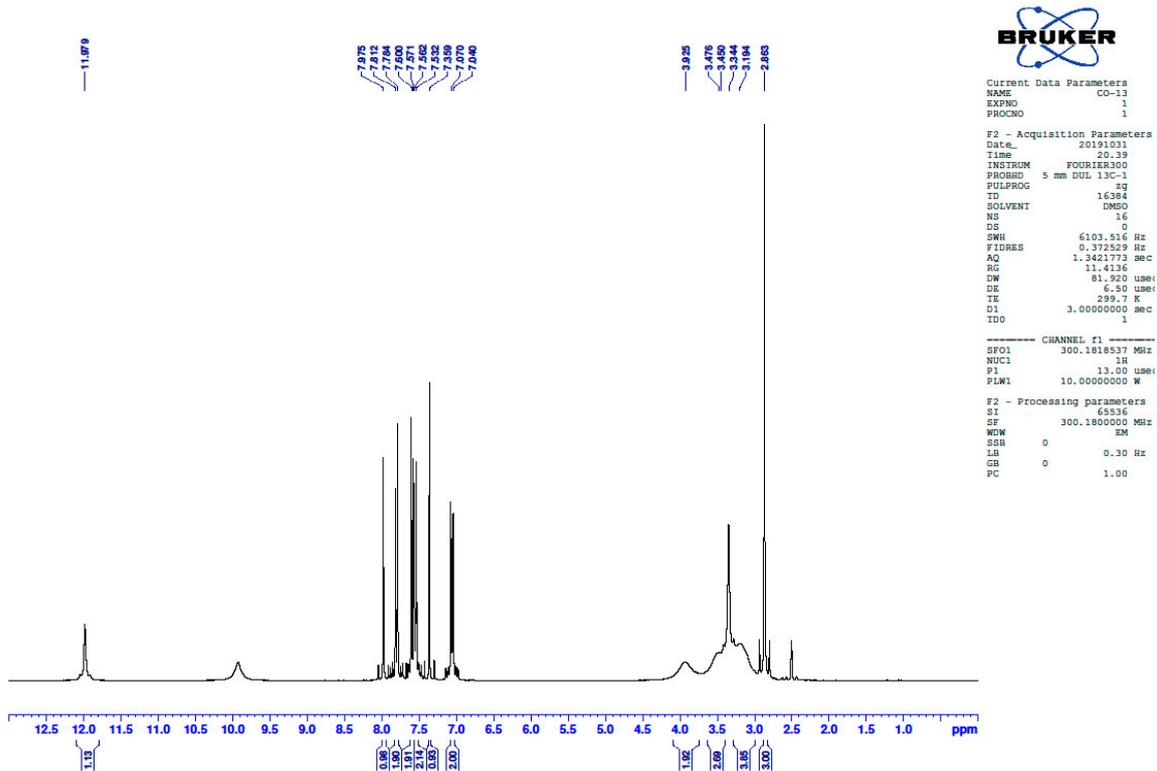


Figure S28.  $^1\text{H}$ -NMR spectra of compound **3h**

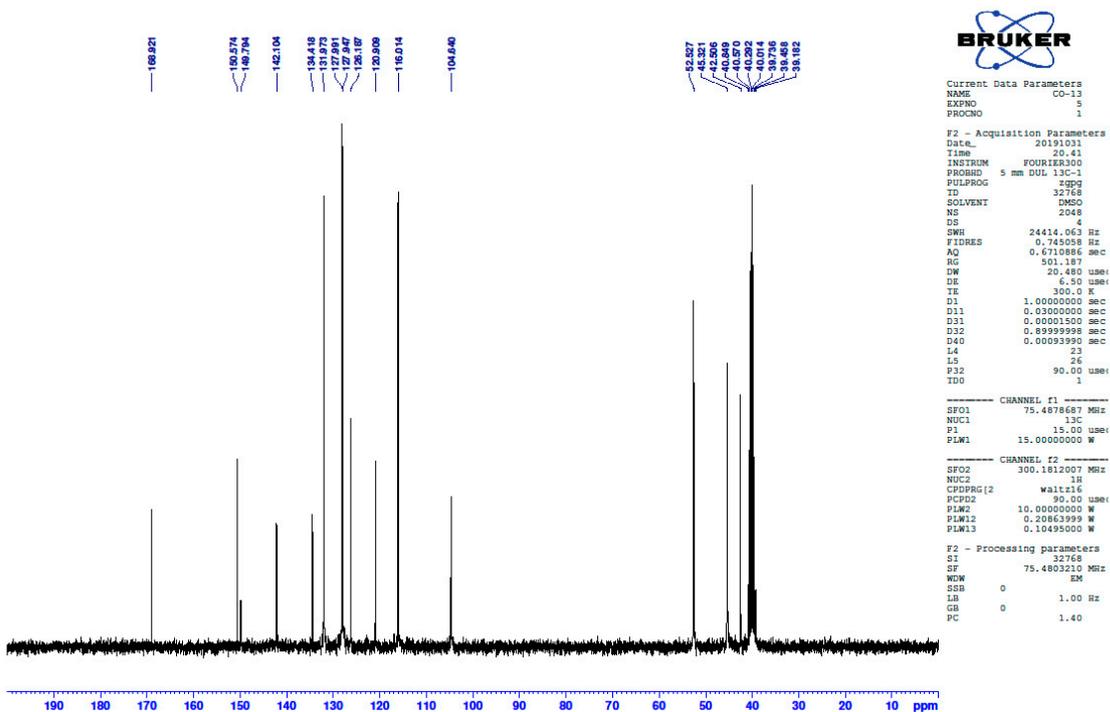


Figure S29.  $^{13}\text{C}$ -NMR spectra of compound **3h**

Data File: C:\LabSolutions\Data\Analiz\deriv\CO-13\_12.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	1	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 20

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

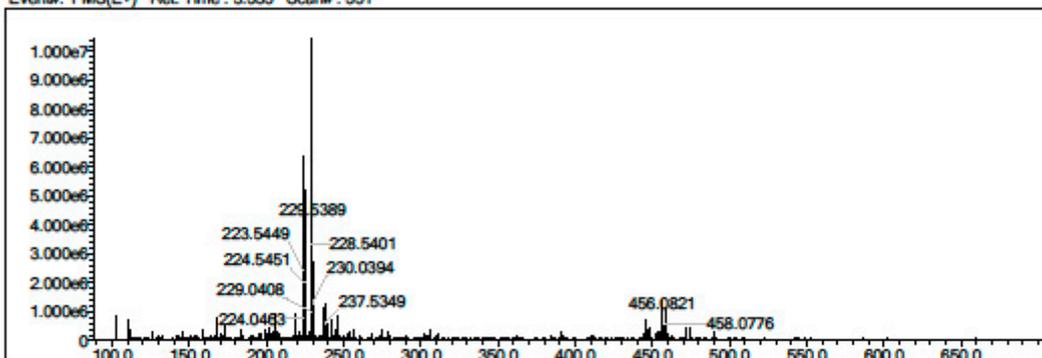
Electron Ions: both

Use MSn Info: yes

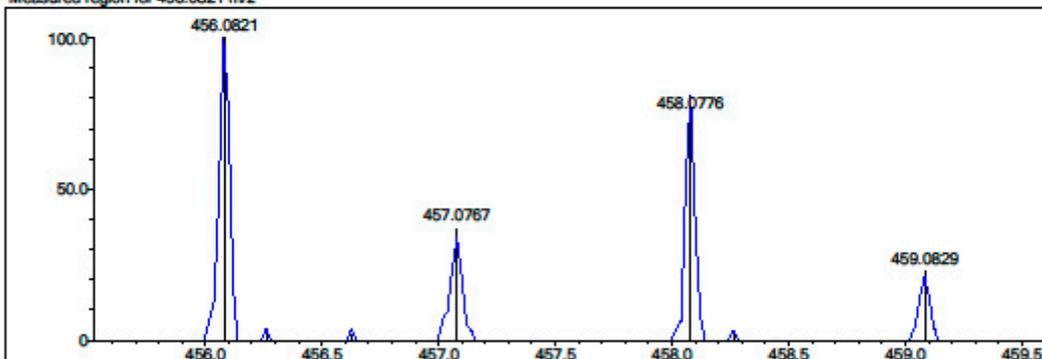
Isotope Res: 9000

Max Results: 100

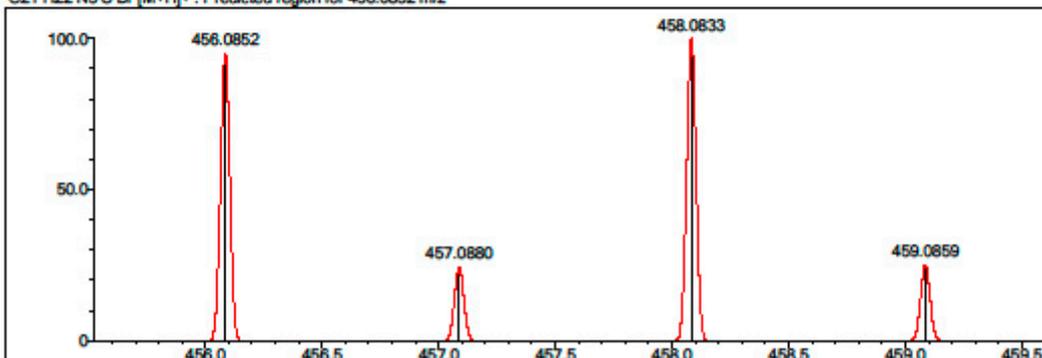
Event#: 1 MS(E+) Ret. Time : 3.533 Scan#: 531



Measured region for 456.0821 m/z



C21 H22 N5 S Br [M+H]<sup>+</sup> : Predicted region for 456.0852 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	31.82	C21 H22 N5 S Br	[M+H] <sup>+</sup>	456.0821	456.0852	-3.1	-6.80	44.20	13.0

Figure S30. HRMS spectra of compound 3h



Data File: C:\LabSolutions\Data\Analiz\deriv\CO-12\_11.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 20

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

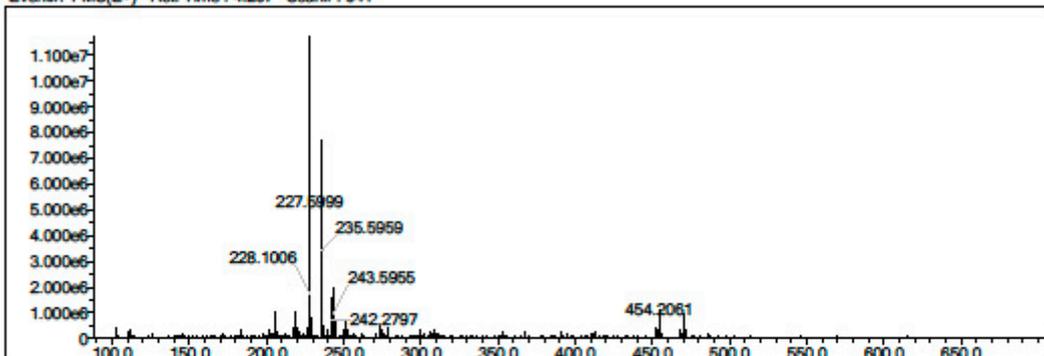
Electron Ions: both

Use MSn Info: yes

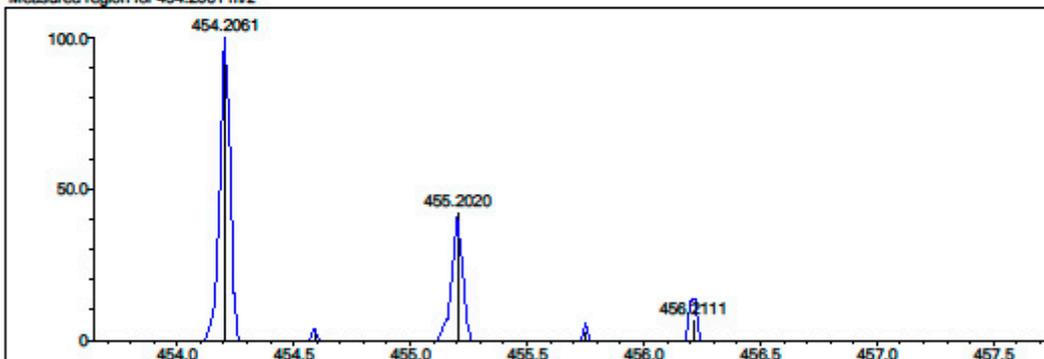
Isotope Res: 9000

Max Results: 100

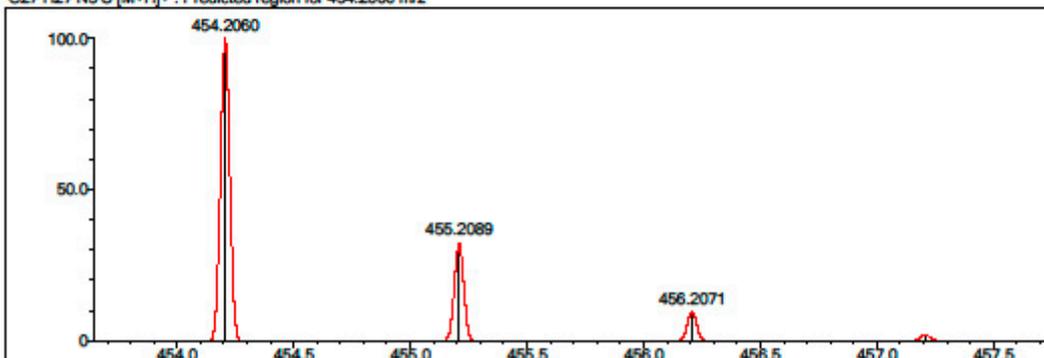
Event#: 1 MS(E+) Ret. Time: 4.267 Scan#: 641



Measured region for 454.2061 m/z



C27 H27 N5 S [M+H]<sup>+</sup> : Predicted region for 454.2060 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	67.25	C27 H27 N5 S	[M+H] <sup>+</sup>	454.2061	454.2060	0.1	0.22	67.25	17.0

Figure S33. HRMS spectra of compound 3i

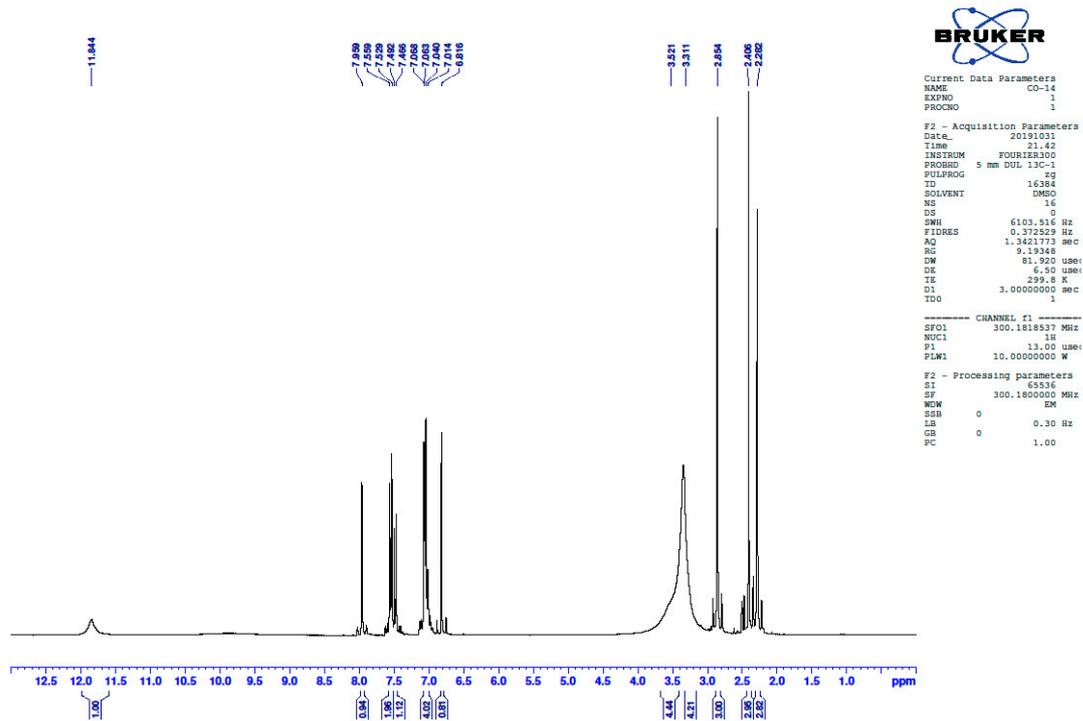


Figure S34. <sup>1</sup>H-NMR spectra of compound 3j

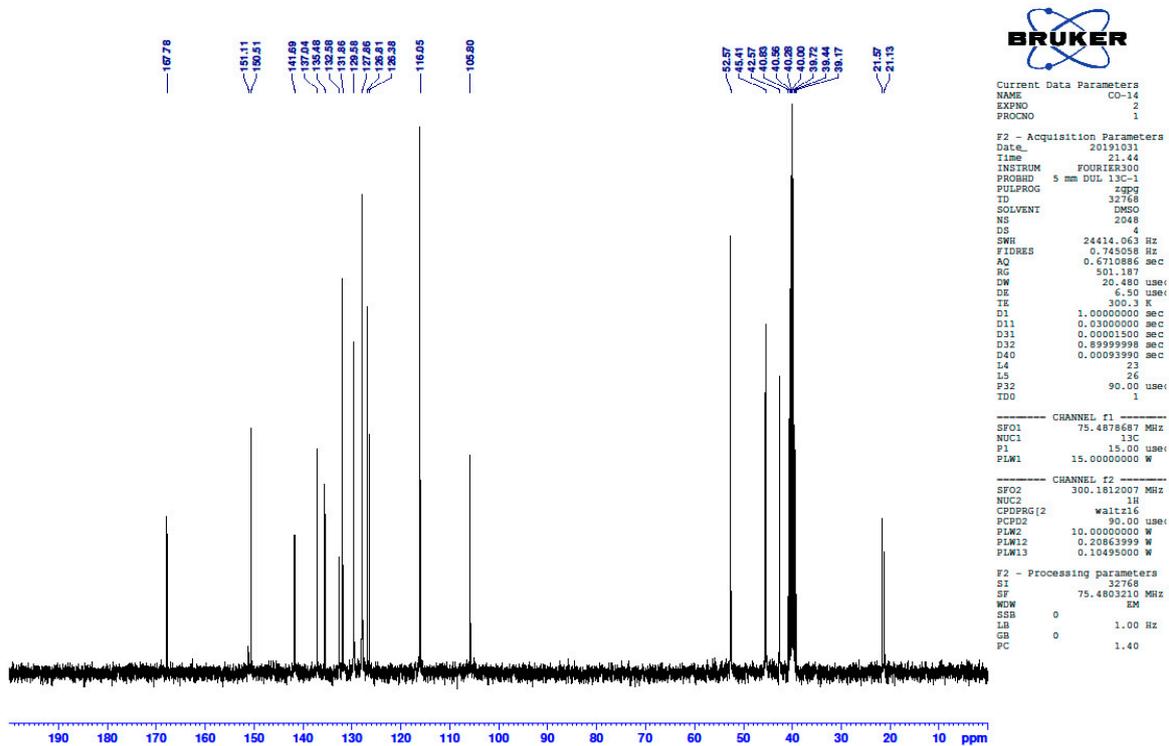


Figure S35. <sup>13</sup>C-NMR spectra of compound 3j

Data File: C:\LabSolutions\Data\Analizidery\CO-14\_13.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	1	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 20

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

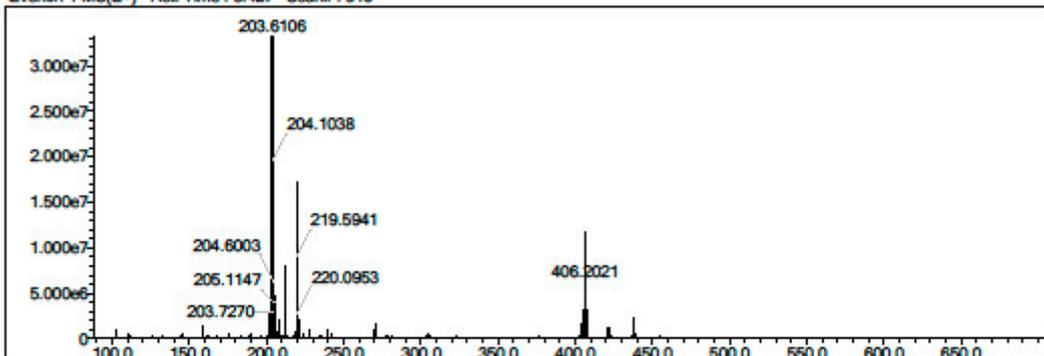
Electron Ions: both

Use MSn Info: yes

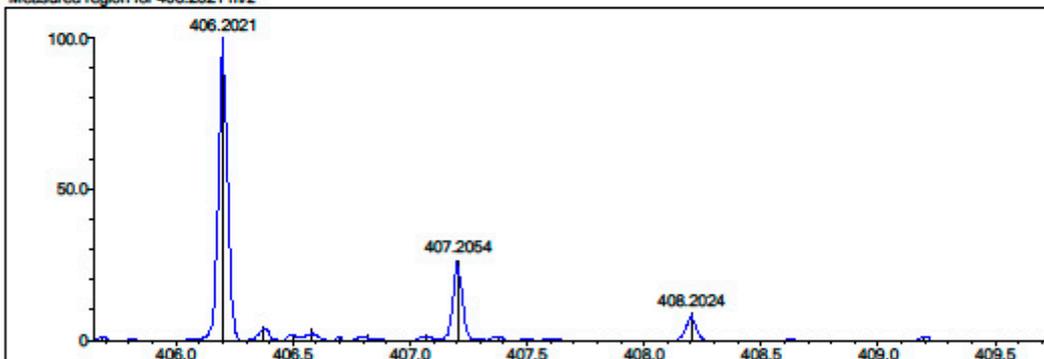
Isotope Res: 9000

Max Results: 100

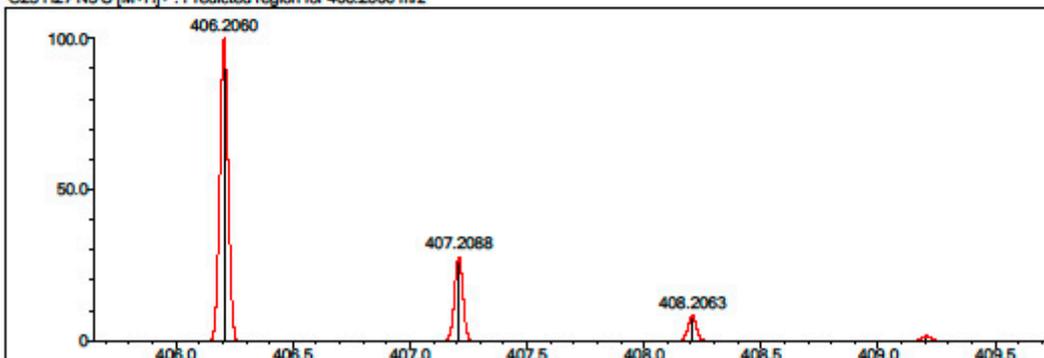
Event#: 1 MS(E+) Ret. Time: 3.427 Scan#: 515



Measured region for 406.2021 m/z



C23 H27 N5 S [M+H]<sup>+</sup> : Predicted region for 406.2060 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	23.71	C23 H27 N5 S	[M+H] <sup>+</sup>	406.2021	406.2060	-3.9	-9.60	53.89	13.0

Figure S36. HRMS spectra of compound 3j

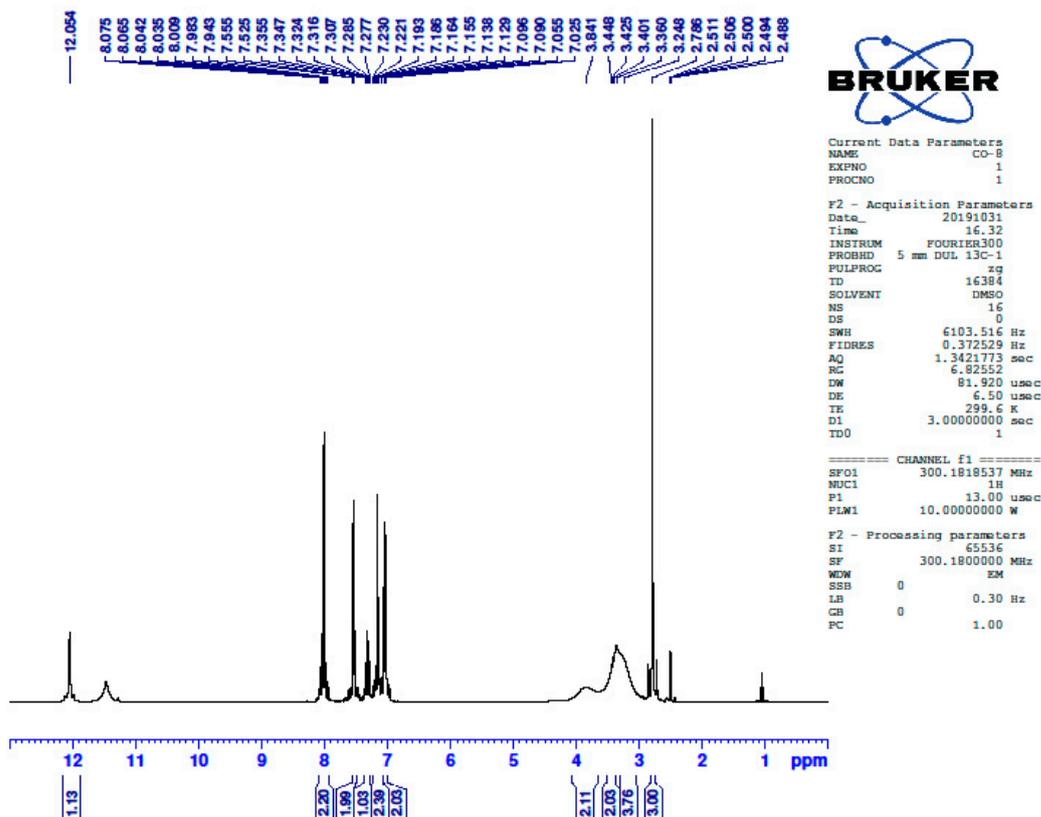


Figure S37. <sup>1</sup>H-NMR spectra of compound 3k

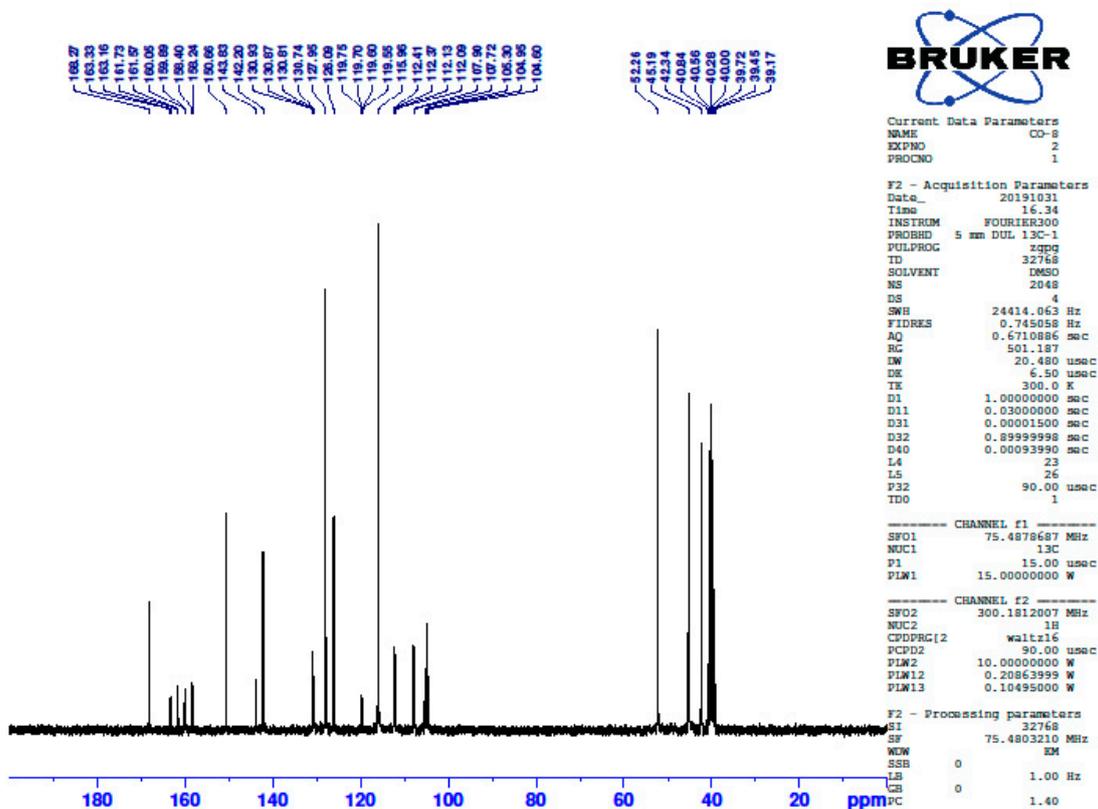


Figure S38. <sup>13</sup>C-NMR spectra of compound 3k

Data File: C:\LabSolutions\Data\Analiz\deriv\CO-8\_8.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Ru	2	0	0	H
C	4	21	35	F	1	1	2	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 25

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

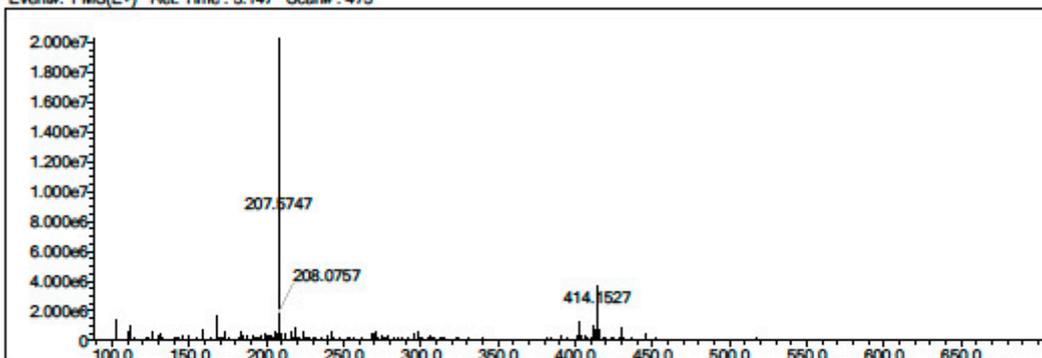
Electron Ions: both

Use MSn Info: yes

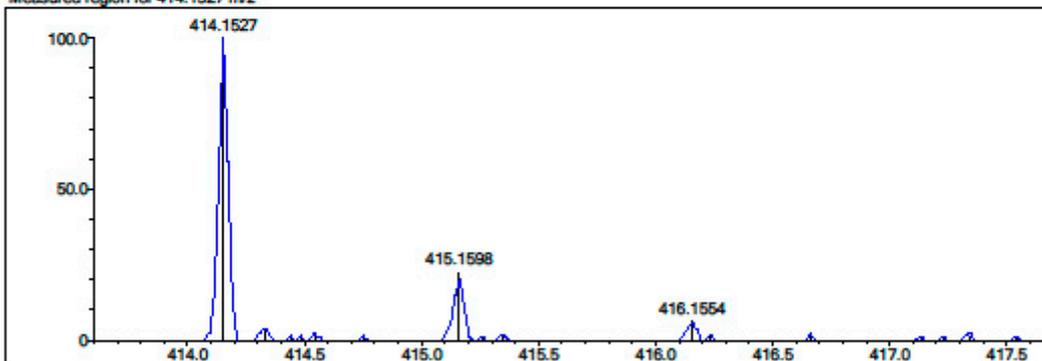
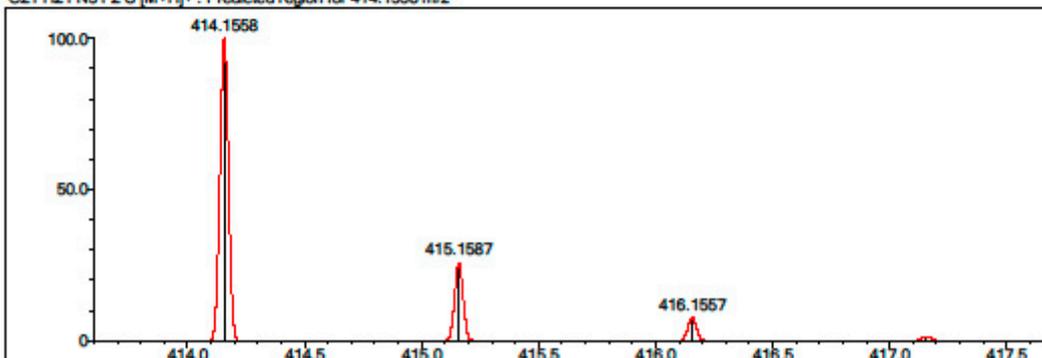
Isotope Res: 9000

Max Results: 100

Event#: 1 MS(E+) Ret. Time : 3.147 Scan#: 473



Measured region for 414.1527 m/z

C21 H21 N5 F2 S [M+H]<sup>+</sup> : Predicted region for 414.1558 m/z

Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	42.54	C21 H21 N5 F2 S	[M+H] <sup>+</sup>	414.1527	414.1558	-3.1	-7.49	65.36	13.0

Figure S39. HRMS spectra of compound 3k

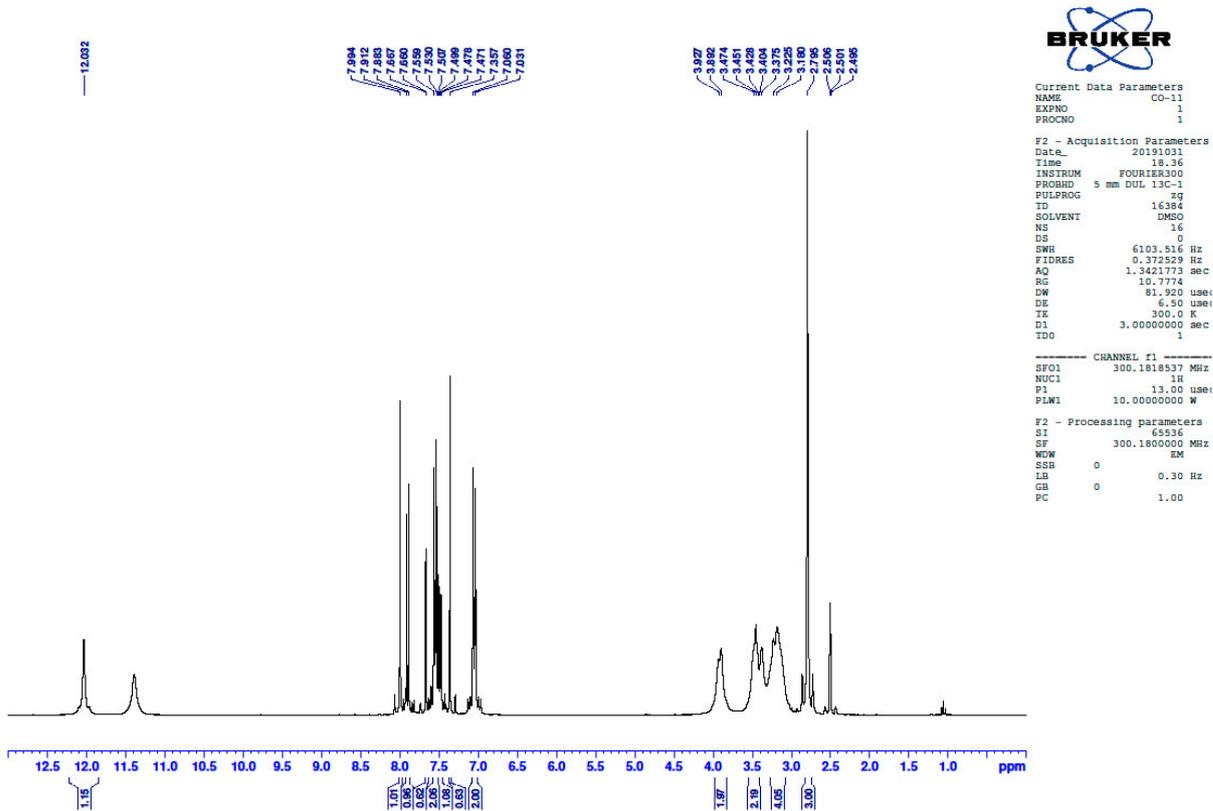


Figure S40. <sup>1</sup>H-NMR spectra of compound 31

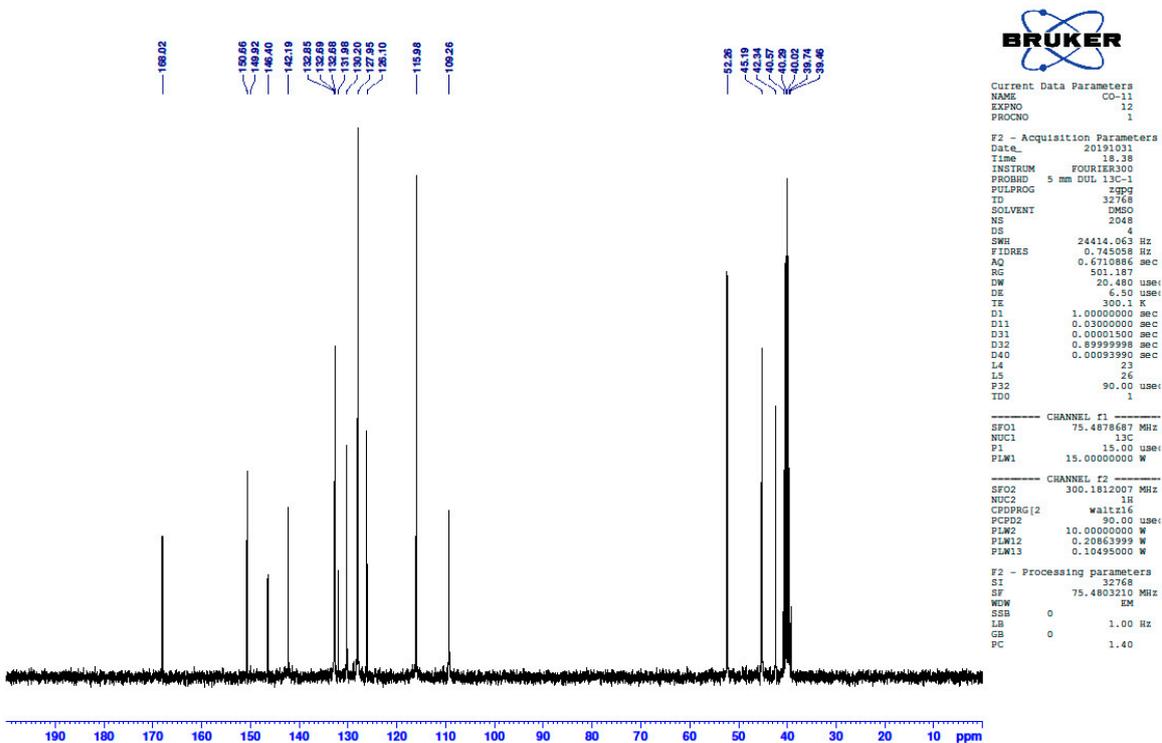


Figure S41. <sup>13</sup>C-NMR spectra of compound 31

Data File: C:\LabSolutions\Data\Analiz\deriv\CO-11\_10.lcd

Elmt	Val.	Min	Max	Use Adduct												
H	1	0	40	O	2	0	2	S	2	1	1	Pu	2	0	0	H
C	4	21	35	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	5	6	P	3	0	0	Br	1	0	1	I	3	0	0	

Error Margin (ppm): 20

HC Ratio: unlimited

Max Isotopes: 3

MSn Iso RI (%): 10.00

DBE Range: 10.0 - 20.0

Apply N Rule: yes

Isotope RI (%): 1.00

MSn Logic Mode: AND

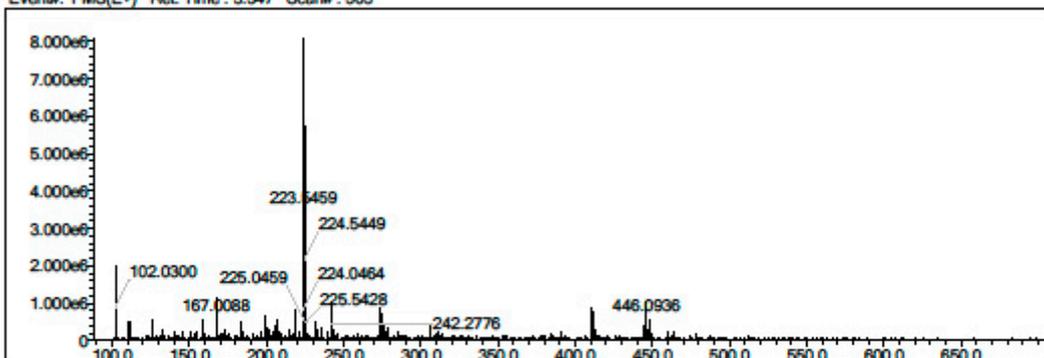
Electron Ions: both

Use MSn Info: yes

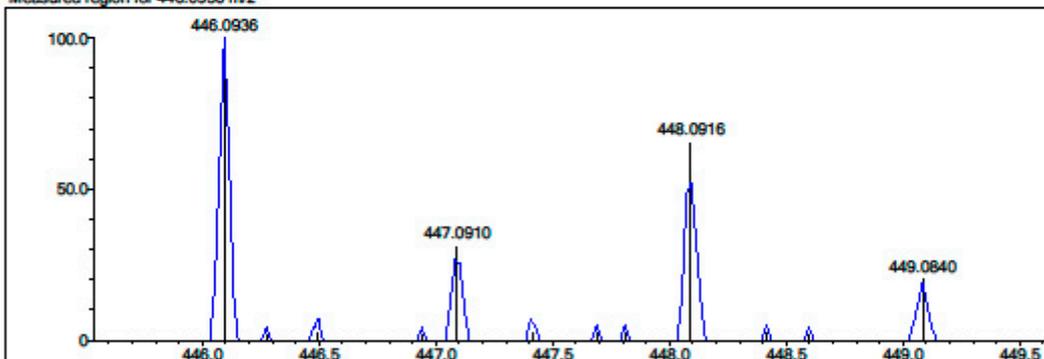
Isotope Res: 9000

Max Results: 100

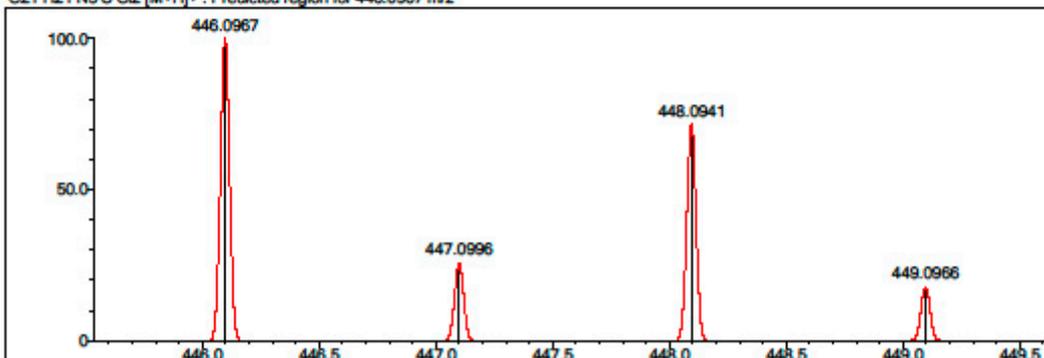
Event#: 1 MS(E+) Ret. Time : 3.347 Scan#: 503



Measured region for 446.0936 m/z



C21 H21 N5 S Cl2 [M+H]<sup>+</sup> : Predicted region for 446.0967 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	29.48	C21 H21 N5 S Cl2	[M+H] <sup>+</sup>	446.0936	446.0967	-3.1	-6.95	41.81	13.0

Figure S42. HRMS spectra of compound 31