Double effect molecular switch leads to a novel potent negative allosteric modulator of metabotropic glutamate receptor 5

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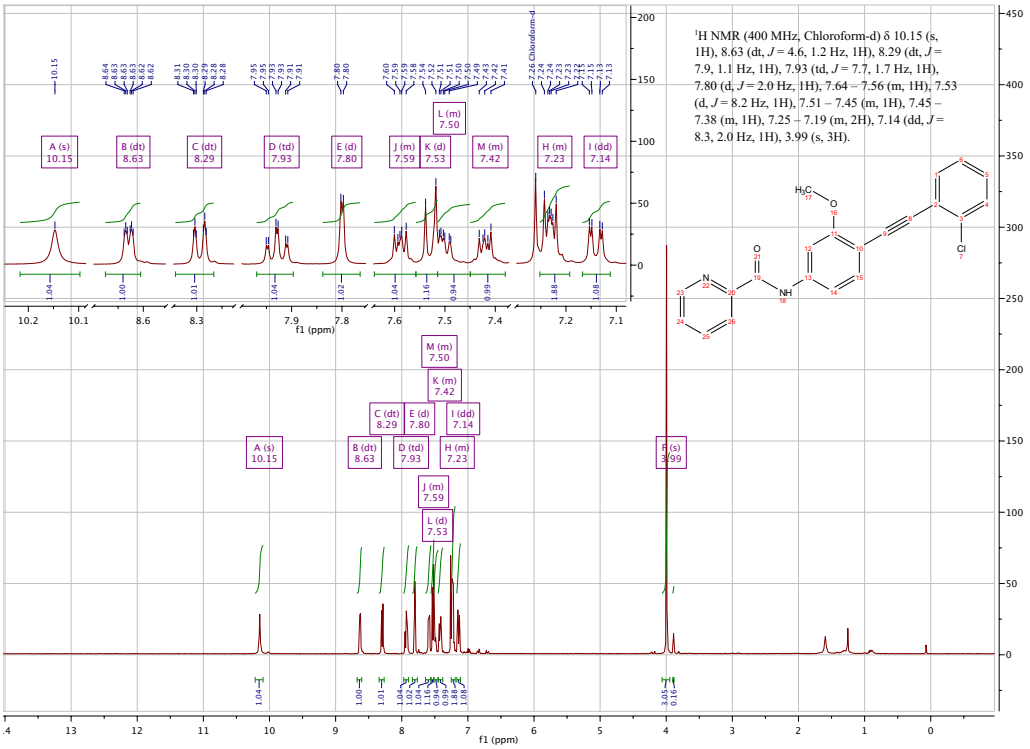
Supplementary Information

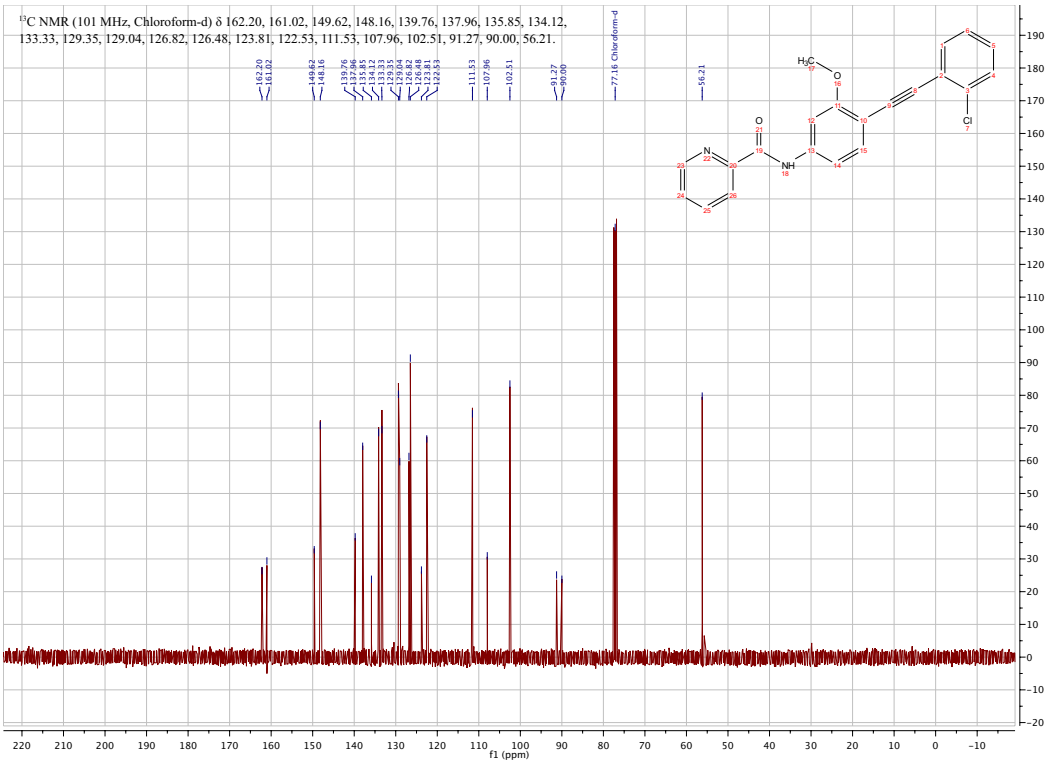
1. Nuclear Magnetic Resonance (NMR) spectra

1.1. Compound 16

1.1.1. ^{1}H-NMR (400 MHz, $CDCl_3$)

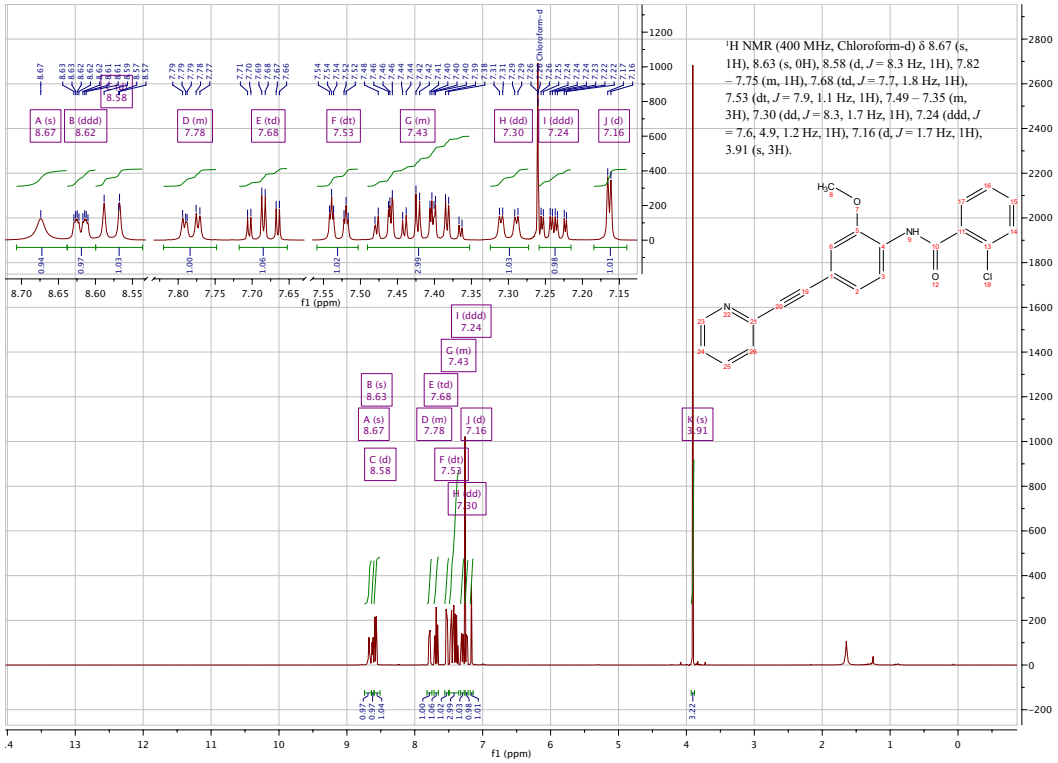


1.1.2. ^{13}C-NMR (101 MHz, $CDCl_3$)

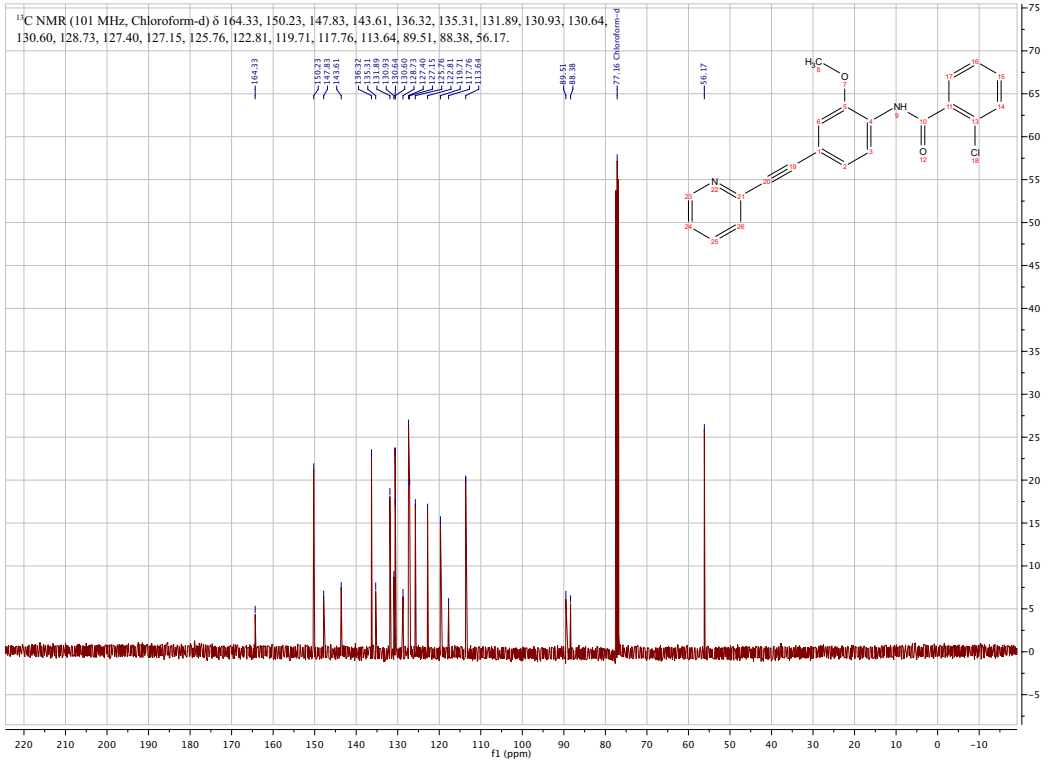


1.2. Compound 17

1.2.1. ^{1}H-NMR (400 MHz, $CDCl_3$)

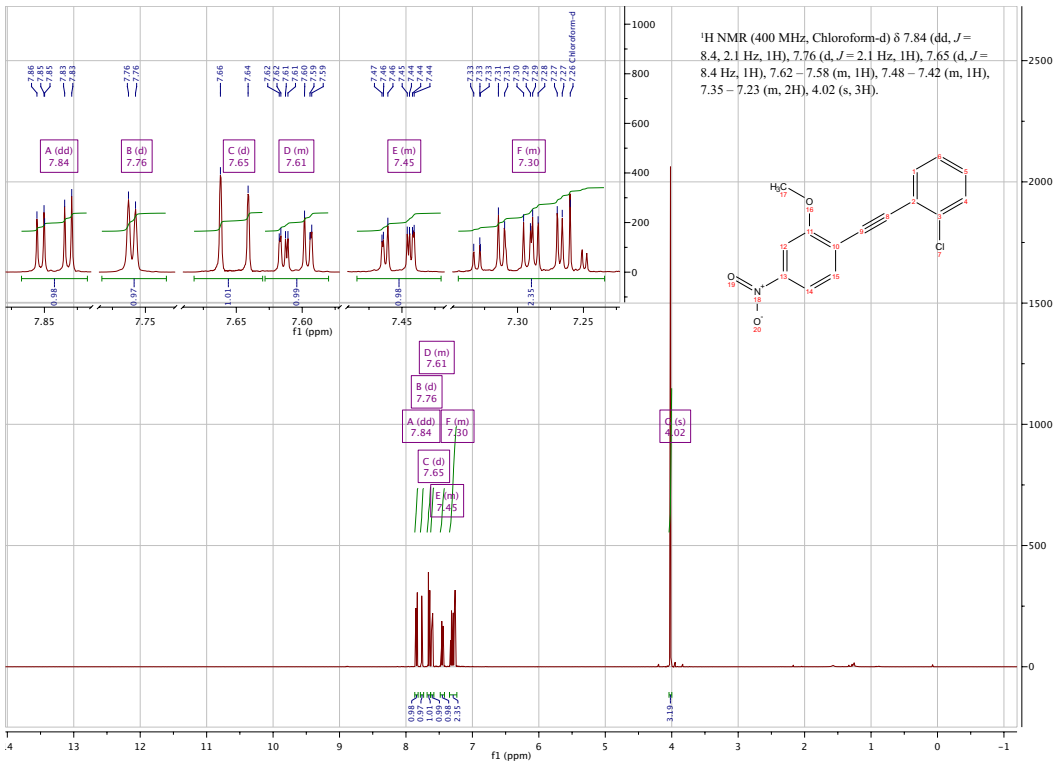


1.2.2. ^{13}C-NMR (101 MHz, $CDCl_3$)

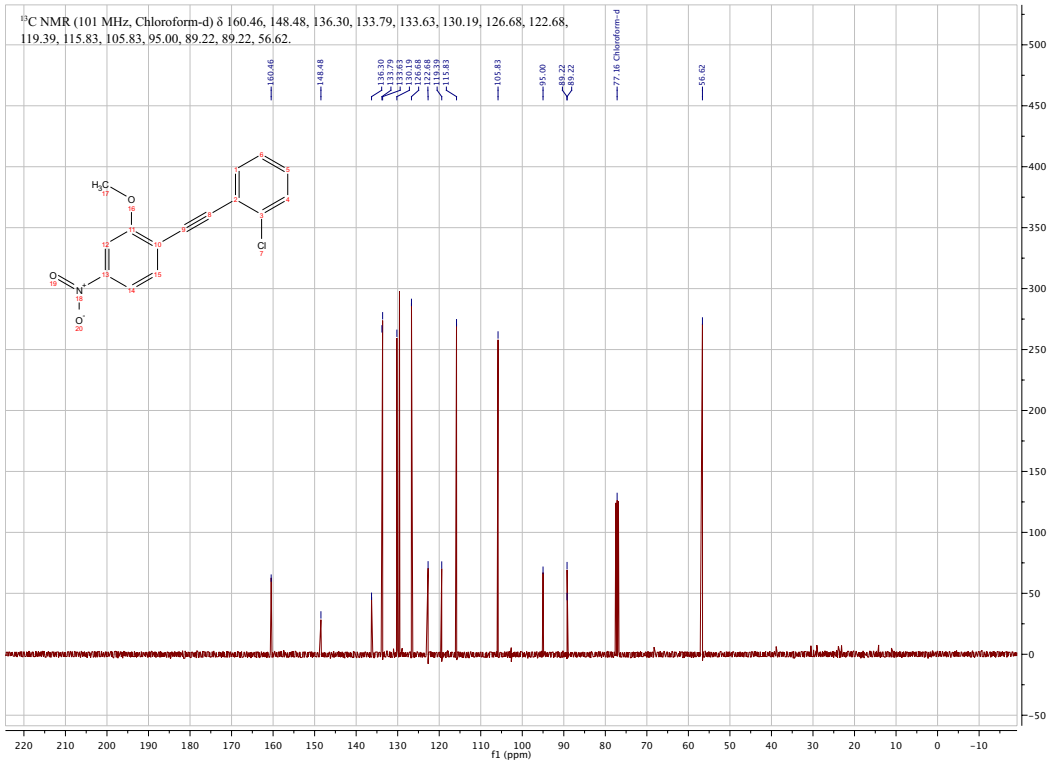


1.3. Compound 20

1.3.1. ^{1}H-NMR (400 MHz, $CDCl_3$)

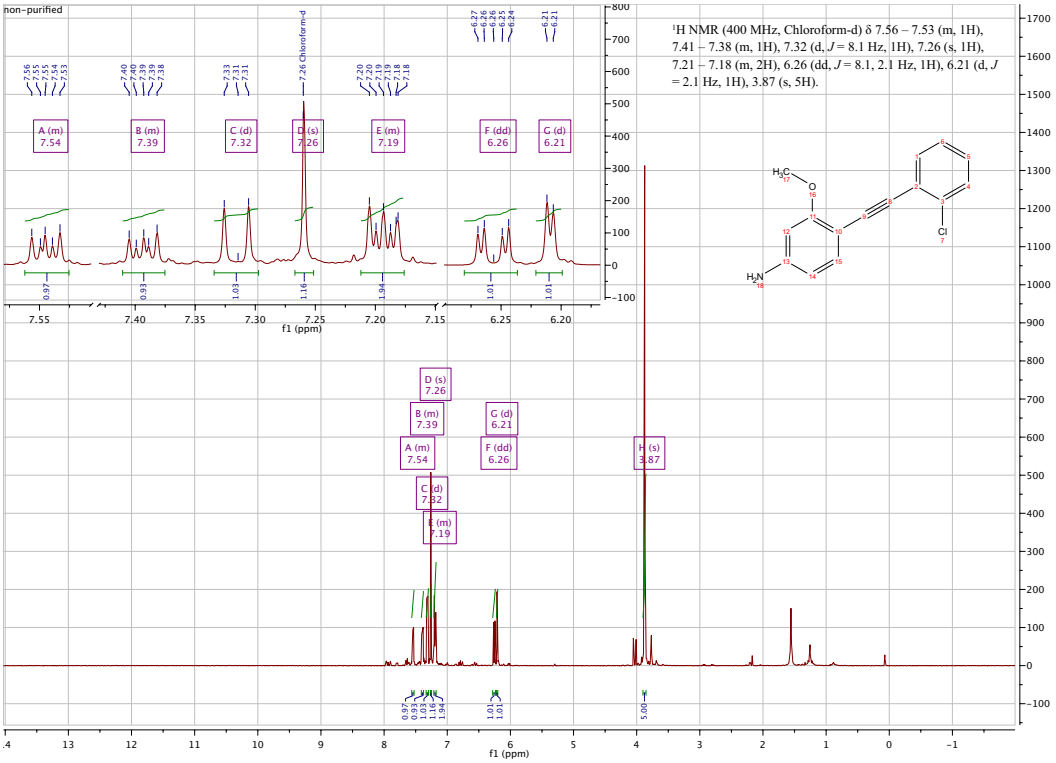


1.3.2. ^{13}C-NMR (101 MHz, $CDCl_3$)



1.4. Compound 21

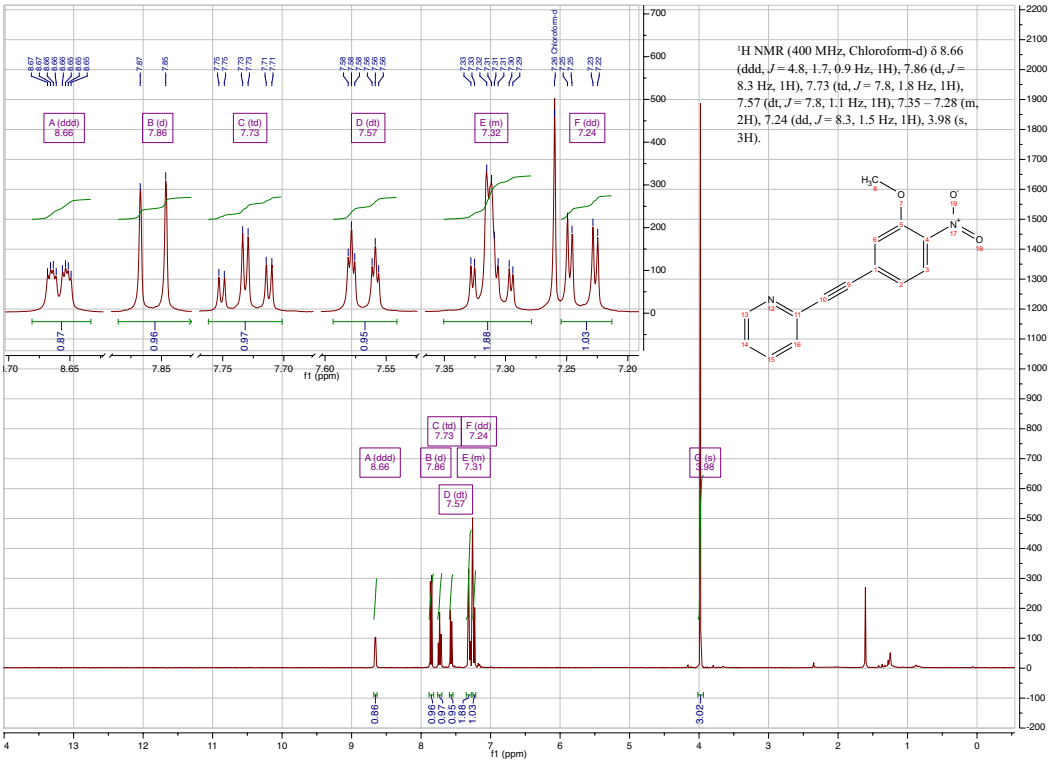
1.4.1. ^{1}H-NMR (400 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 – 7.53 (m, 1H), 7.41 – 7.38 (m, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.21 – 7.18 (m, 2H), 6.26 (dd, J = 8.1, 2.1 Hz, 1H), 6.21 (d, J = 2.1 Hz, 1H), 3.87 (s, 5H).

1.4. Compound 24

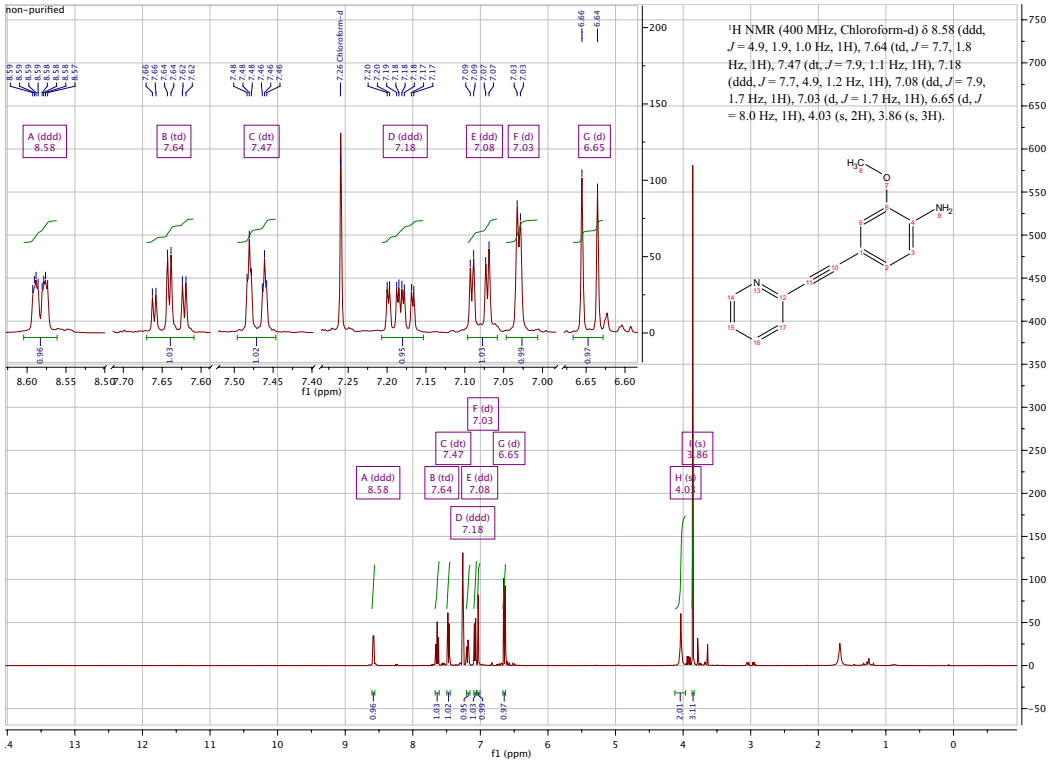
1.4.1. ^{1}H-NMR (400 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, Chloroform-d) δ 8.66 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.57 (dt, J = 7.8, 1.1 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.24 (dd, J = 8.3, 1.5 Hz, 1H), 3.98 (s, 3H).

1.5. Compound 25

1.5.1. ^{1}H-NMR (400 MHz, $CDCl_3$)



2. High Performance Liquid Chromatography Coupled to Photodiode Array (HPLC/PDA)

2.1. Compound 16

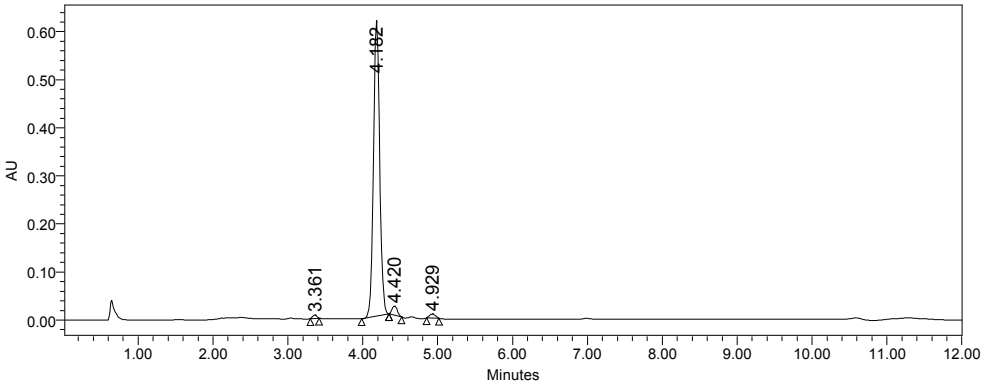
Empower software

Multi Sample Summary

Reported by User: System Project Name: mGlu

SAMPLE INFORMATION

Sample Name:	Compund 16	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	12/19/2013 7:41:54 PM
Vial:	58	Acq. Method Set:	XGS RC_MT 1
Injection #:	1	Date Processed:	3/6/2014 3:00:45 PM
Injection Volume:	5.00 ul	Processing Method:	xgs_254
Run Time:	12.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:	XGS	Proc. Chnl. Descr.:	PDA 254.0 nm



	RT	Area	% Area	Height
1	3.361	26425	0.71	6893
2	4.182	3571148	95.40	611254
3	4.420	98646	2.64	19064
4	4.929	47209	1.26	8423

2.2. Compound 17

Empower software

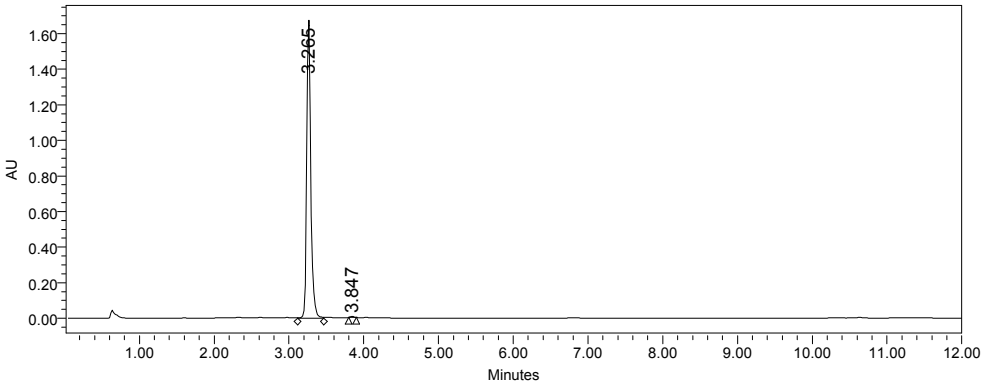
Multi Sample Summary

Reported by User: System

Project Name: mGlu

SAMPLE INFORMATION

Sample Name:	Compund 17	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	12/19/2013 2:59:20 PM
Vial:	36	Acq. Method Set:	XGS RC_MT 1
Injection #:	1	Date Processed:	3/6/2014 3:06:45 PM
Injection Volume:	5.00 ul	Processing Method:	xgs_254
Run Time:	12.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:	XGS	Proc. Chnl. Descr.:	PDA 254.0 nm

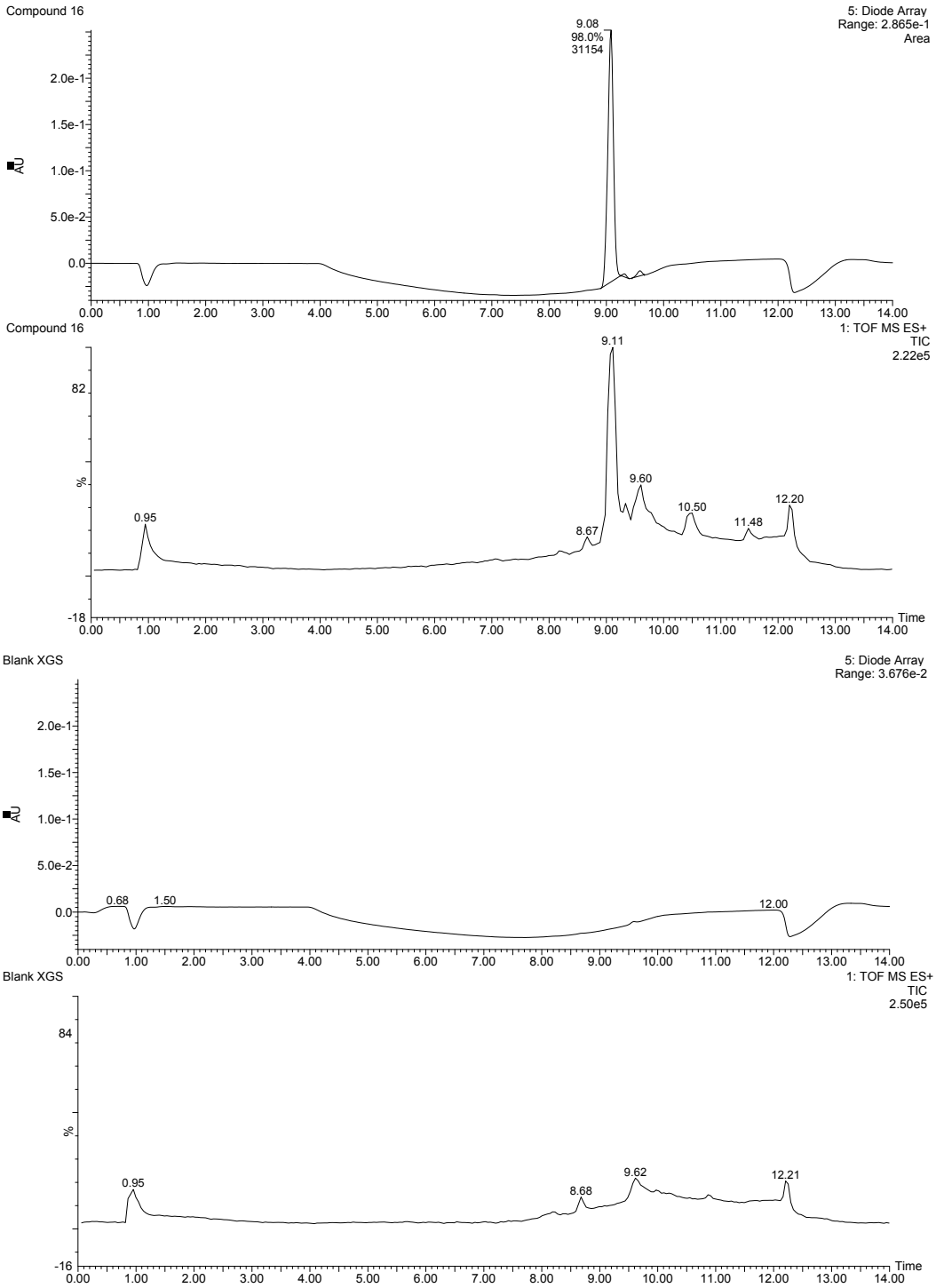


	RT	Area	% Area	Height
1	3.265	6336952	99.66	1579560
2	3.847	21508	0.34	6304

3. Liquid Chromatography coupled to Mass Spectrum (HPLC/MS)

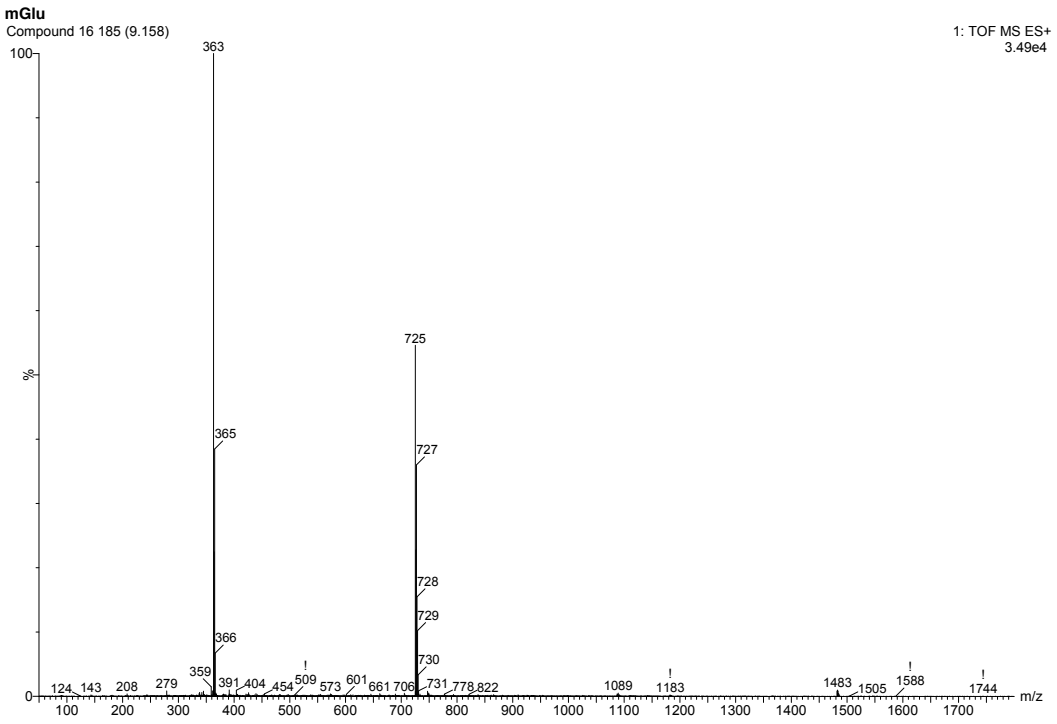
3.1. Compound 16

3.1.1. UV-Vis absorbance chromatogram and TIC chromatogram



Compound 16			
RT	**Height**	**Area**	**% Area**
9.083	271822	31153.928	97.5%
9.317	3284	247.251	0.8%
9.583	5605	548.625	1.7%

3.1.2. TOF Mass Spectrum

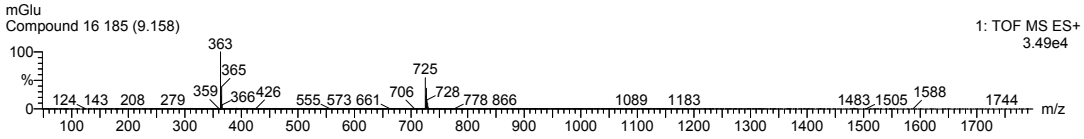


3.1.3. Elemental Composition Analysis

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

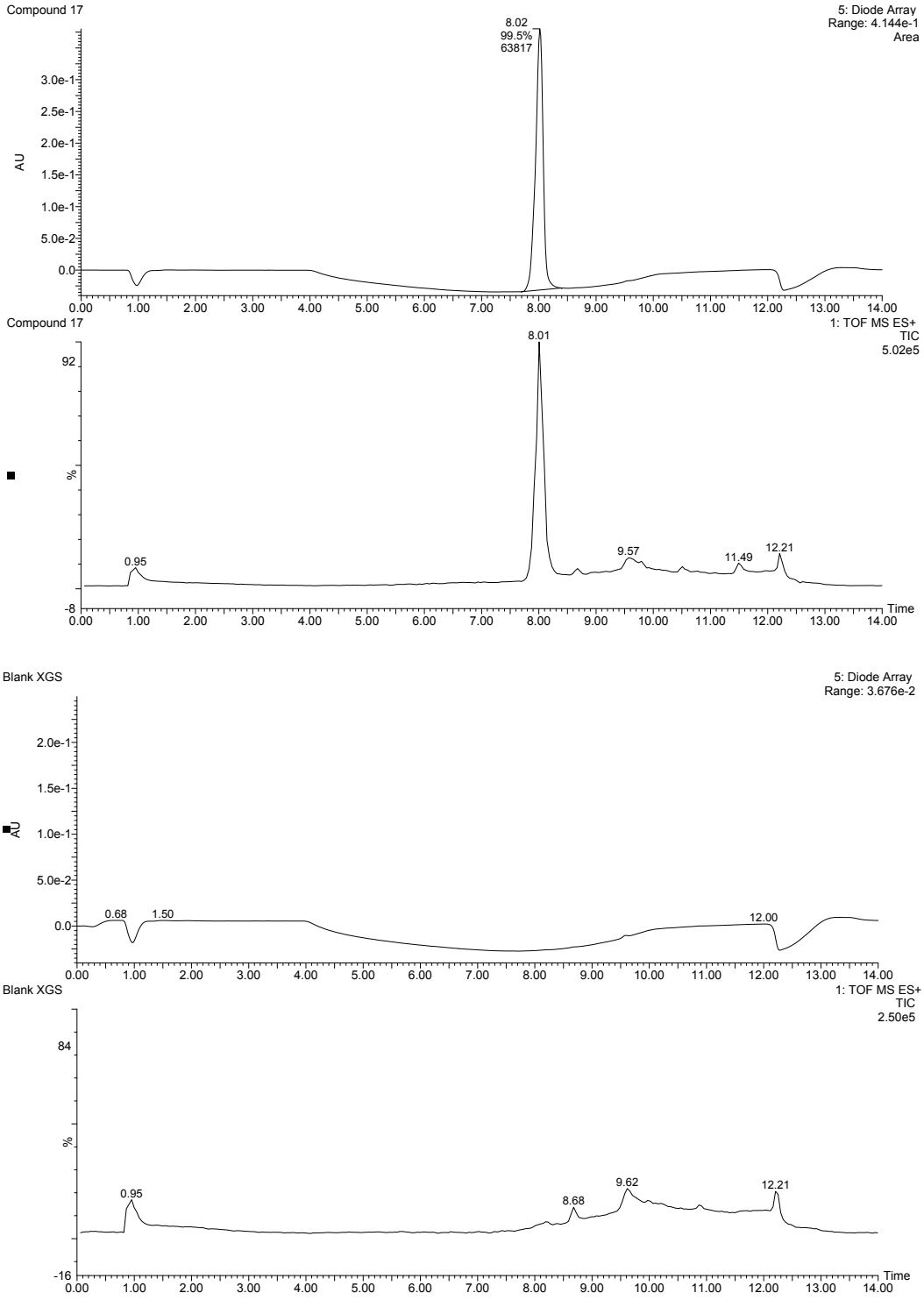
Monoisotopic Mass, Even Electron Ions
111 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-25 H: 15-20 N: 0-5 O: 0-5 Cl: 0-5



Minimum:		5.0	10.0	-1.5		
Maximum:				50.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
363.0897	363.0900	-0.3	-0.8	14.5	76.1	C21 H16 N2 O2 Cl

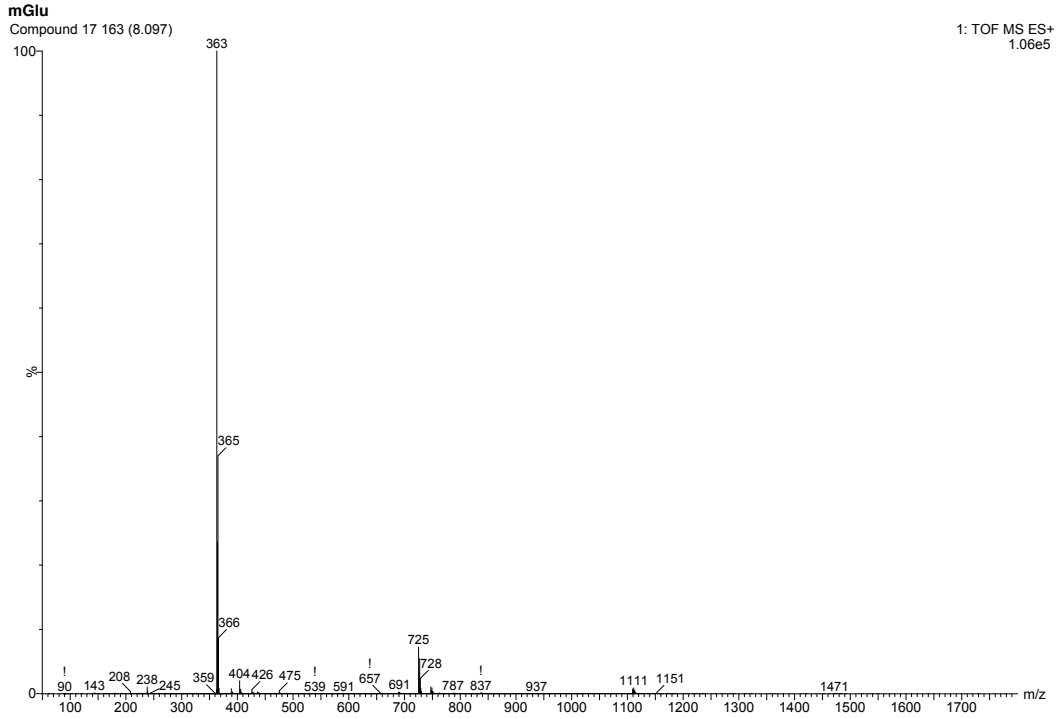
3.1. Compound 17

3.1.1. UV-Vis absorbance chromatogram and TIC chromatogram



Compound 17			
RT	**Height**	**Area**	**% Area**
8.017	411373	63816.559	100%

3.1.2. TOF Mass Spectrum

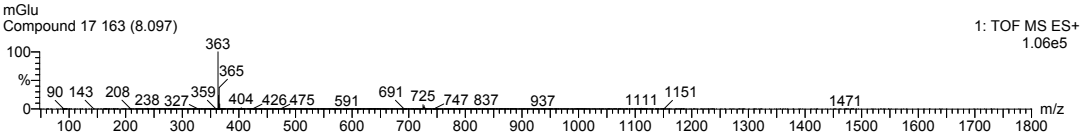


3.1.3. Elemental Composition Analysis

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
111 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-25 H: 15-20 N: 0-5 O: 0-5 Cl: 0-5



Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
363.0906	363.0900	0.6	1.7	14.5	61.0	C21 H16 N2 O2 Cl

4. Elemental Composition by High Resolution Mass Spectroscopy (HRMS)

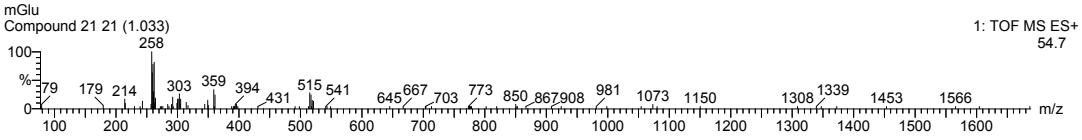
4.1. Compound 21

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 10-20 H: 10-20 N: 0-5 O: 0-5 Cl: 1-1

mGlu
Compound 21 21 (1.033)



Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
258.0685	258.0686	-0.1	-0.4	9.5	14.0	C15 H13 N O Cl

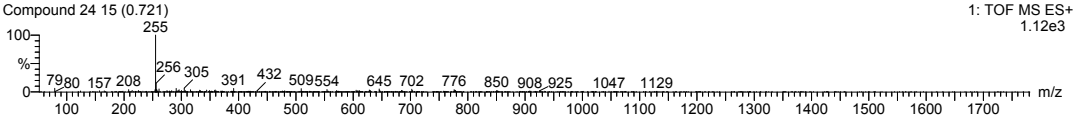
4.2. Compound 24

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-3 O: 0-3 Cl: 0-1

mGlu
Compound 24 15 (0.721)



Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
255.0769	255.0770	-0.1	-0.4	10.5	1.2	C14 H11 N2 O3

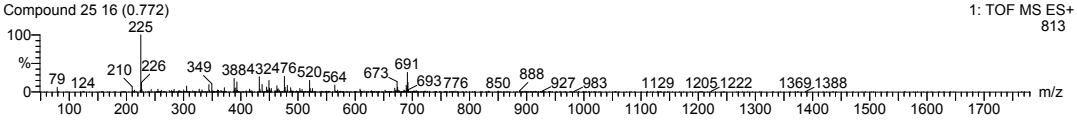
4.3. Compound 25

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-3 O: 0-3 Cl: 0-1

mGlu
Compound 25 16 (0.772)



Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
225.1027	225.1028	-0.1	-0.4	9.5	8.8	C14 H13 N2 O