Supplementary information

Novel potent and selective dual acetylcholinesterase inhibitors: N-substituted theobromine and theophylline derivatives

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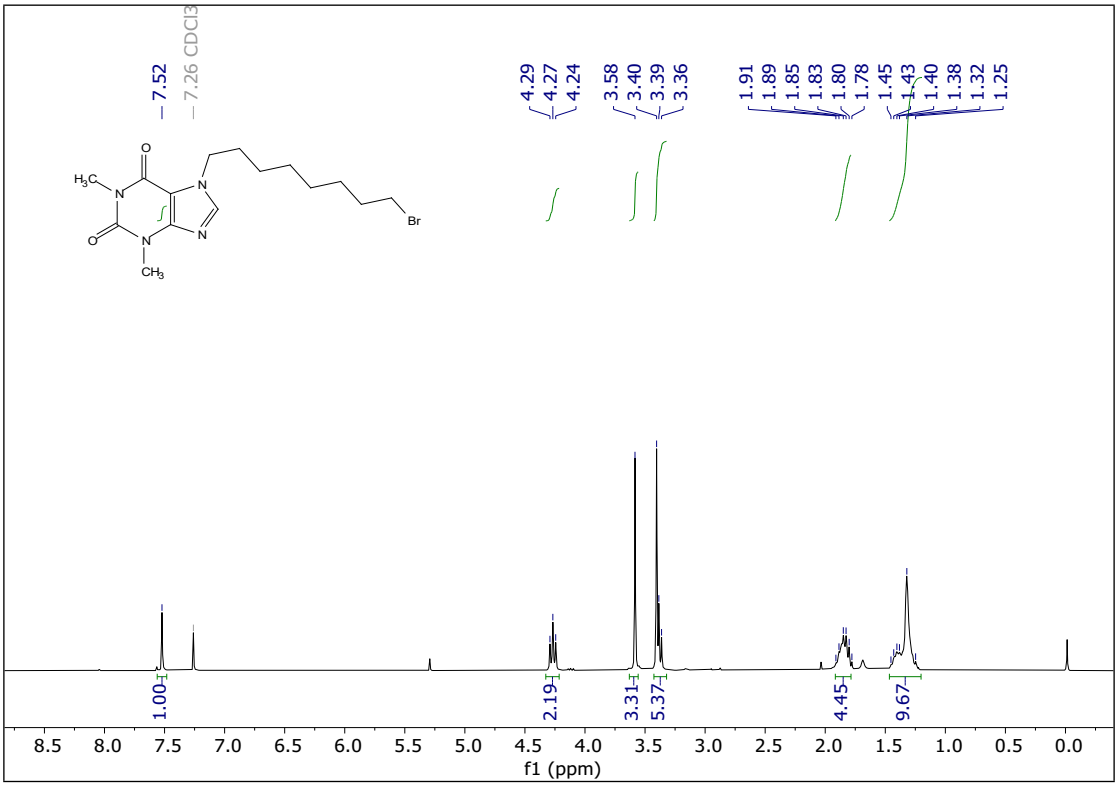
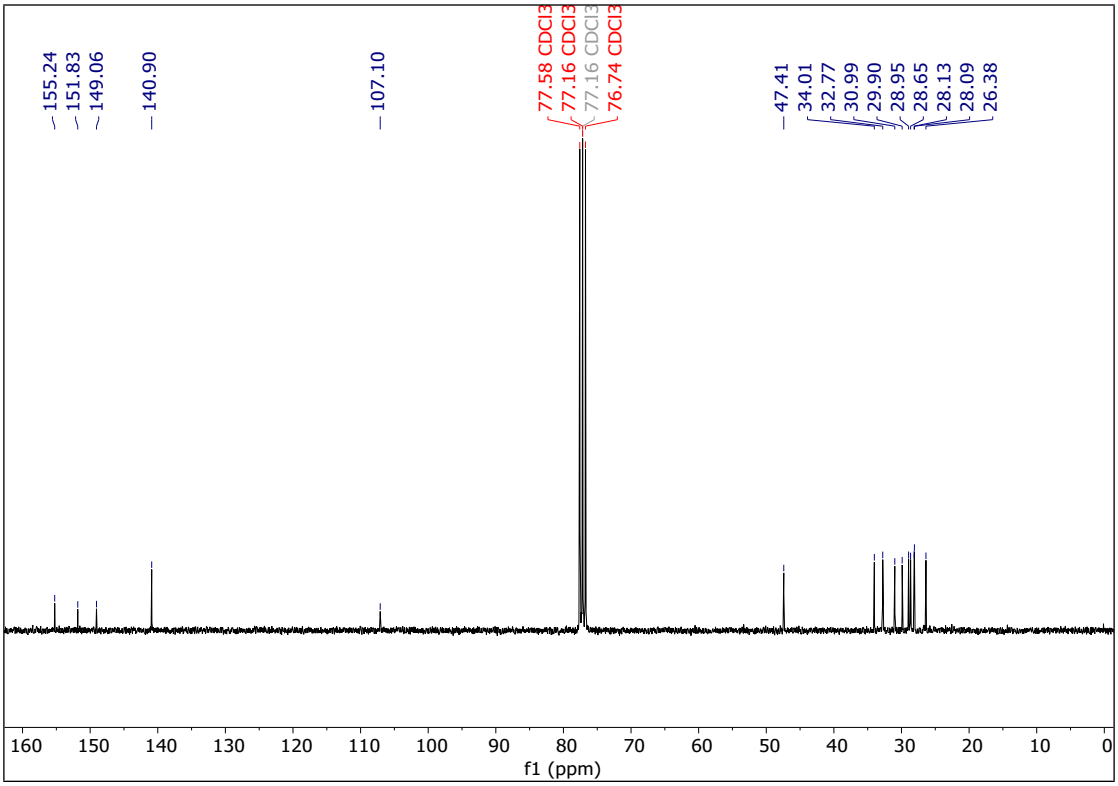
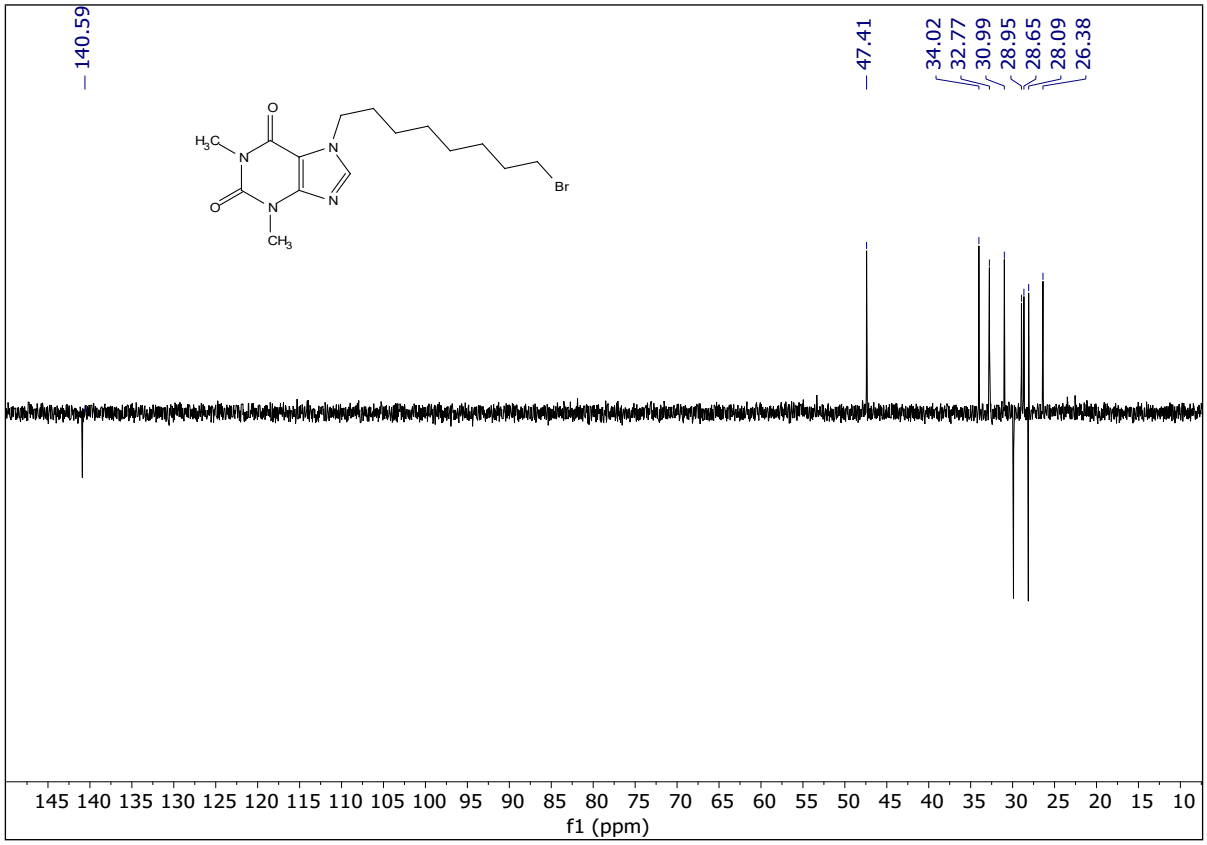
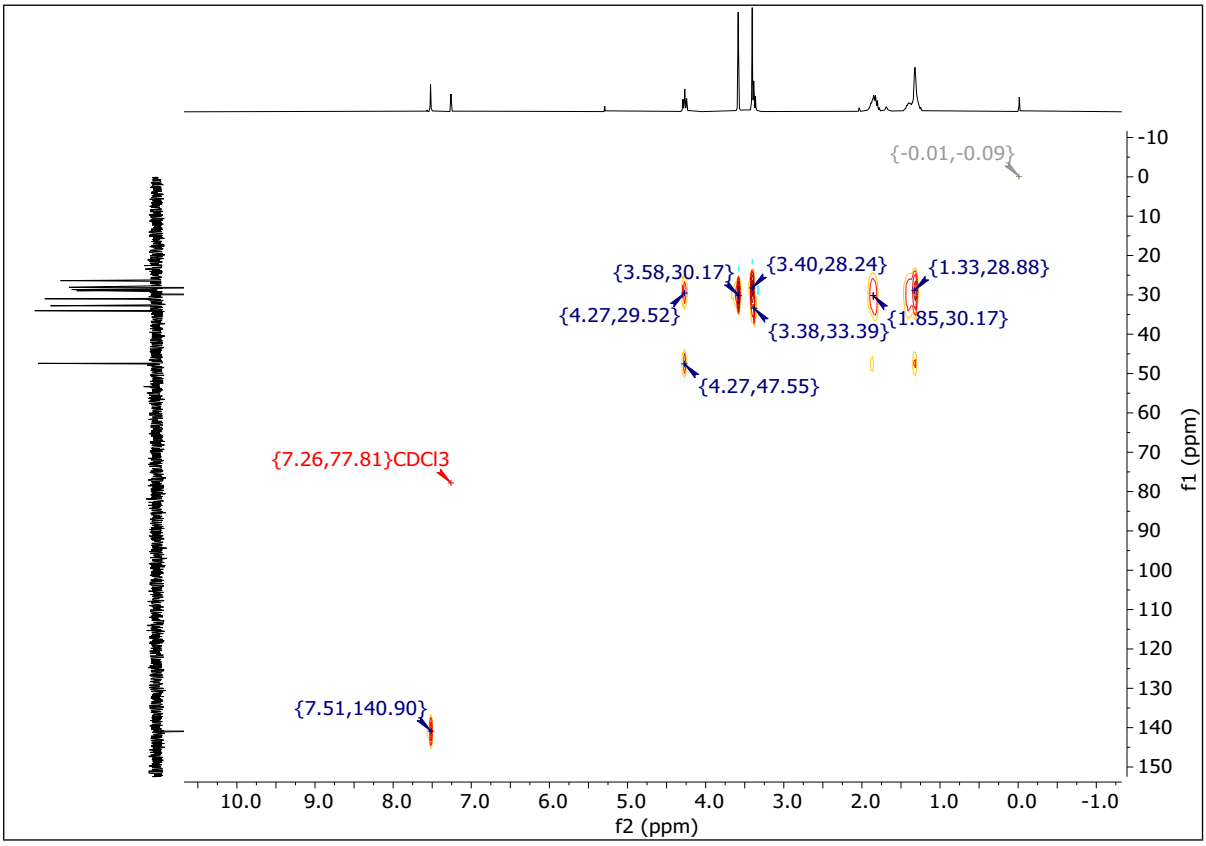
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **1e**



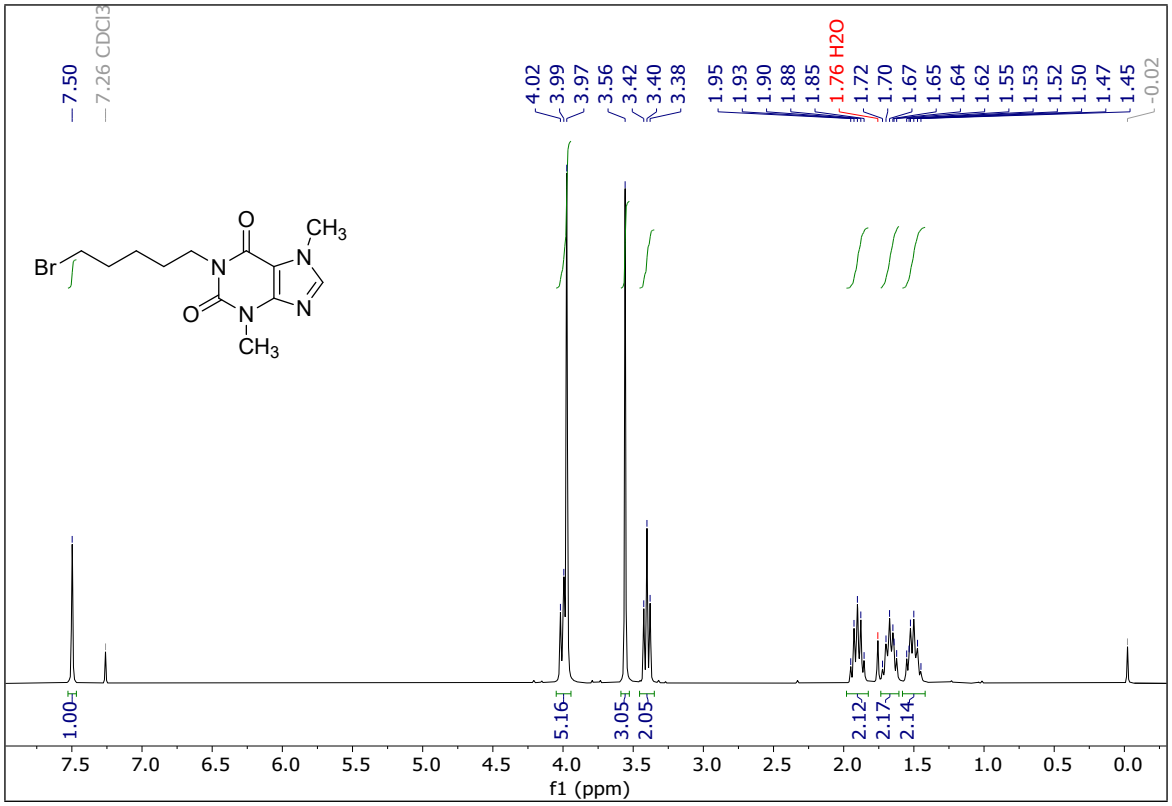


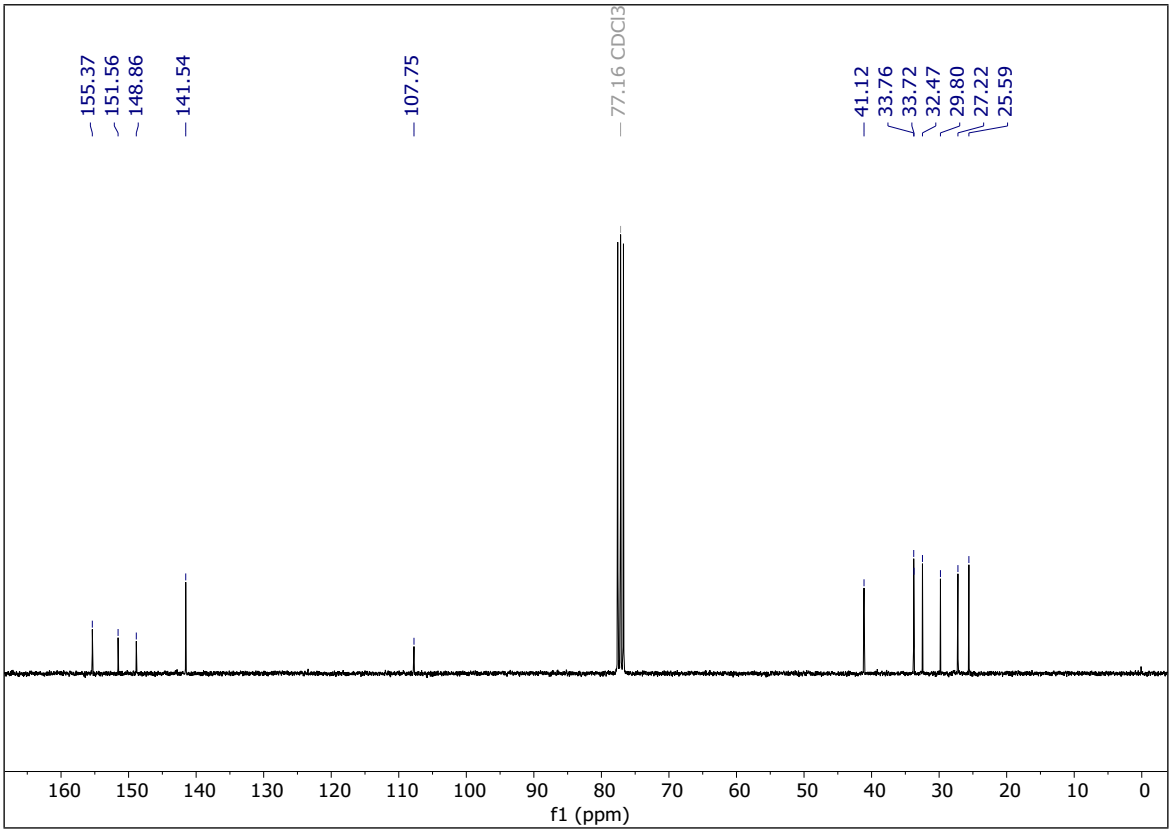
DEPT and HSQC spectra in $CDCl_3$ of **1e**



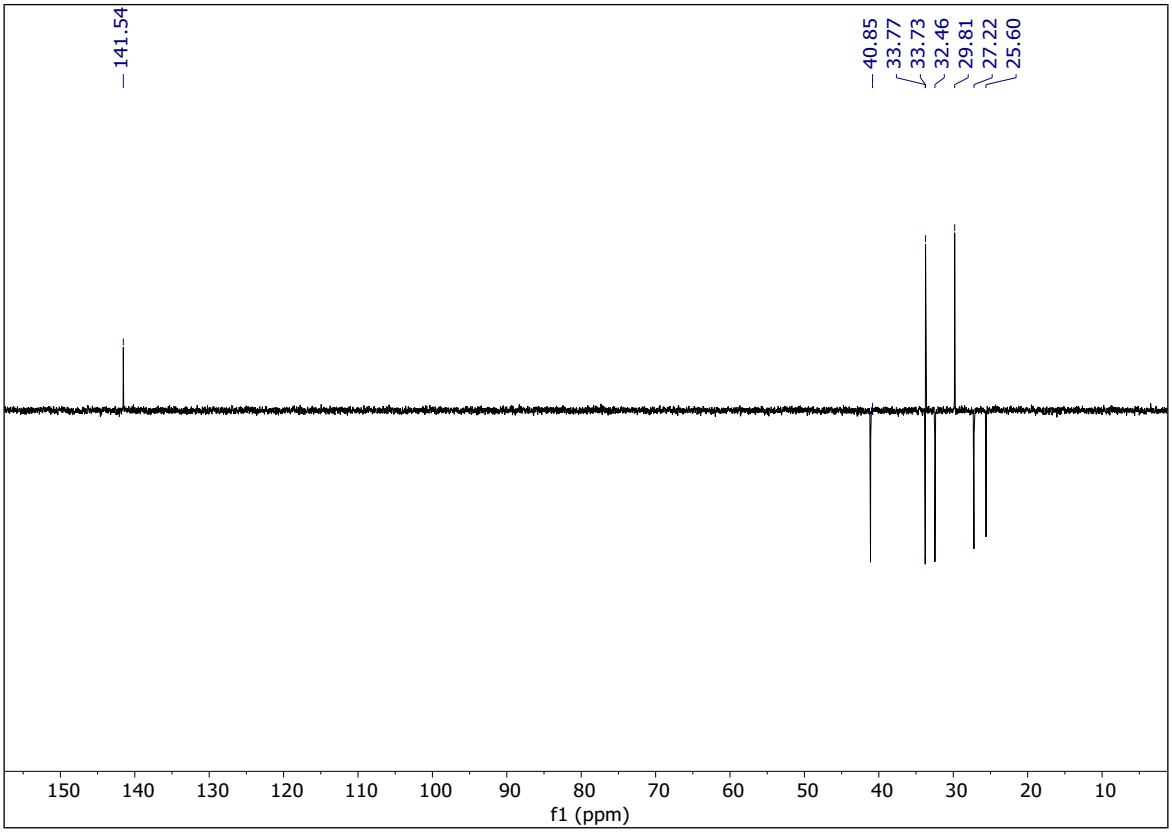


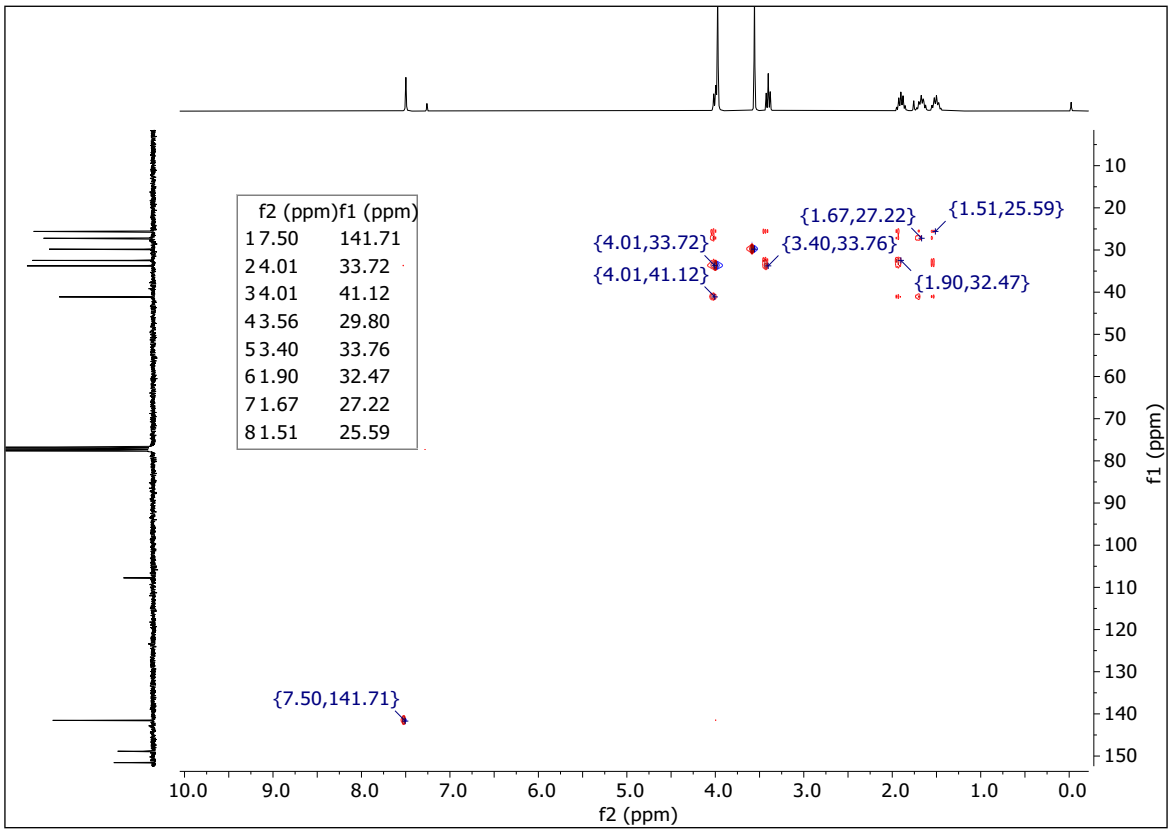
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **2b**





DEPT and HSQC spectra in $CDCl_3$ of **2b**





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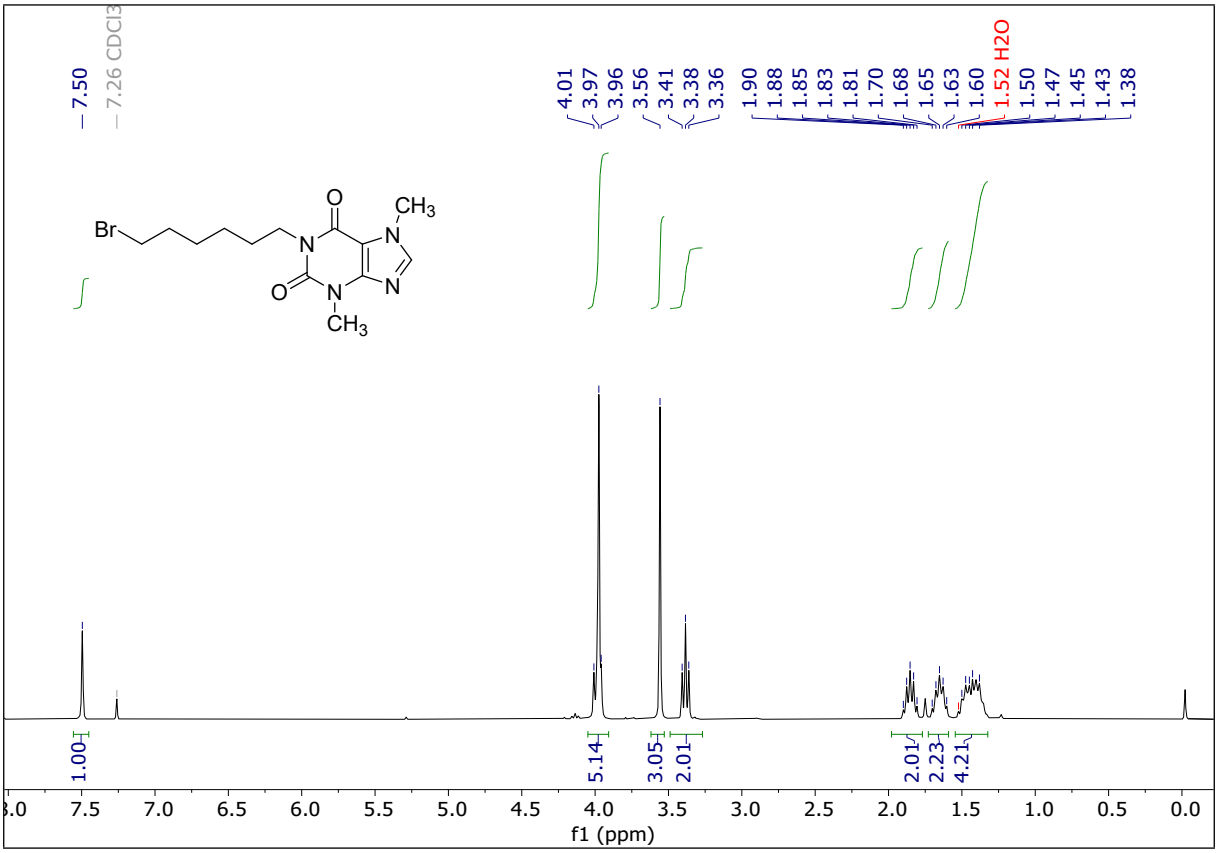
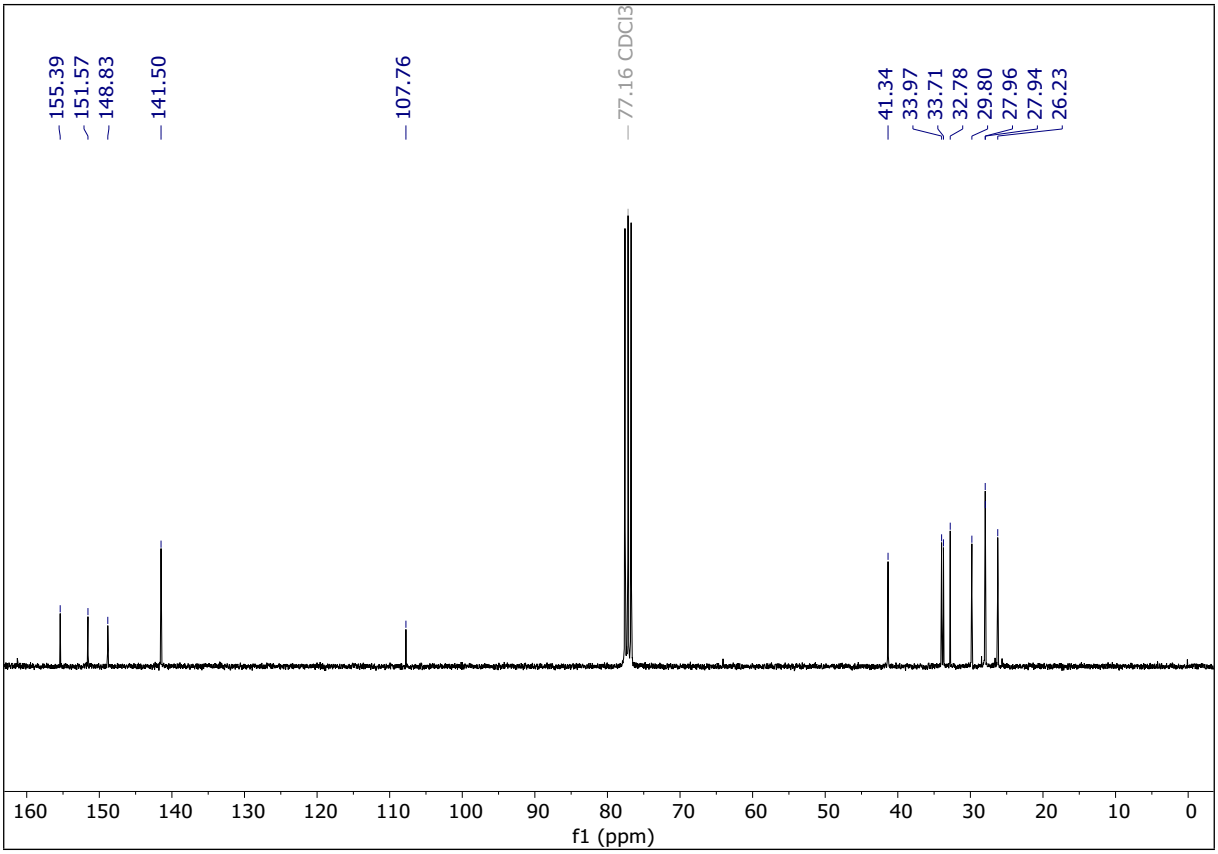
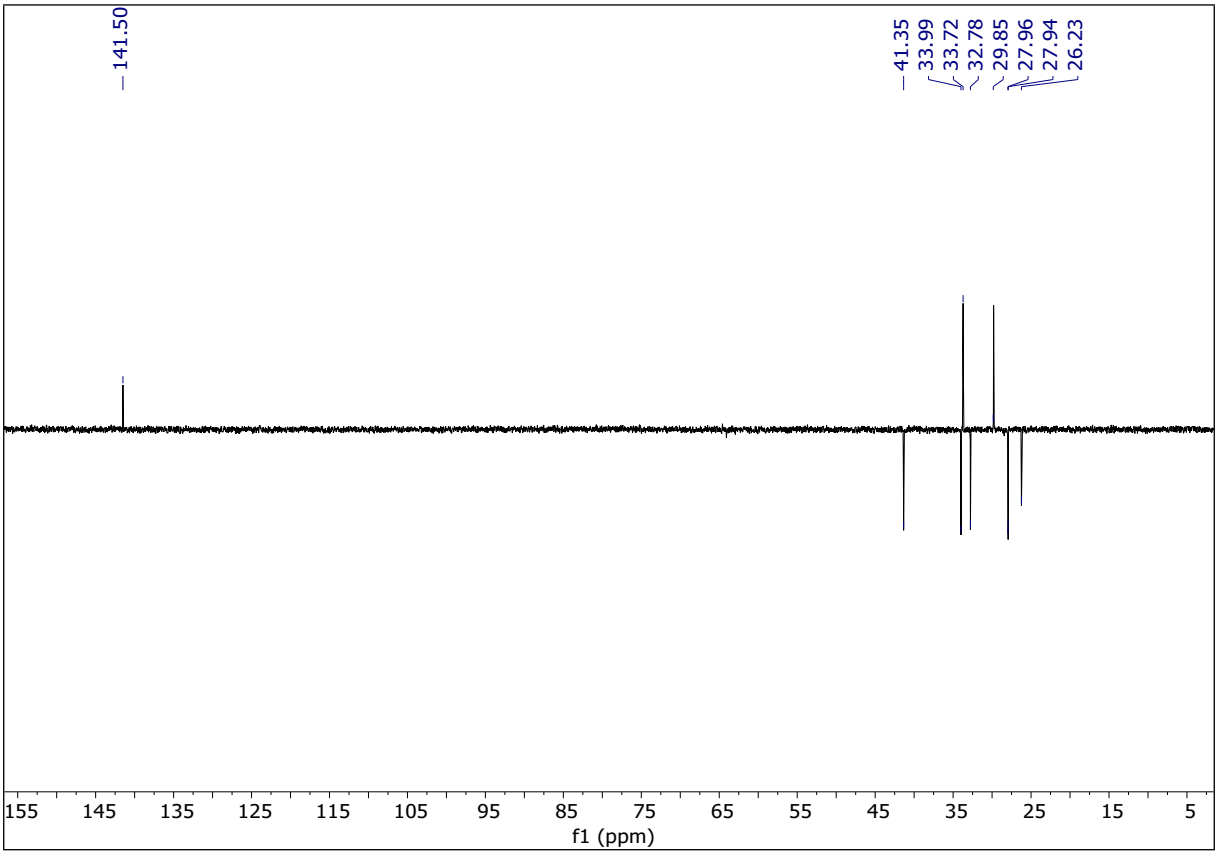
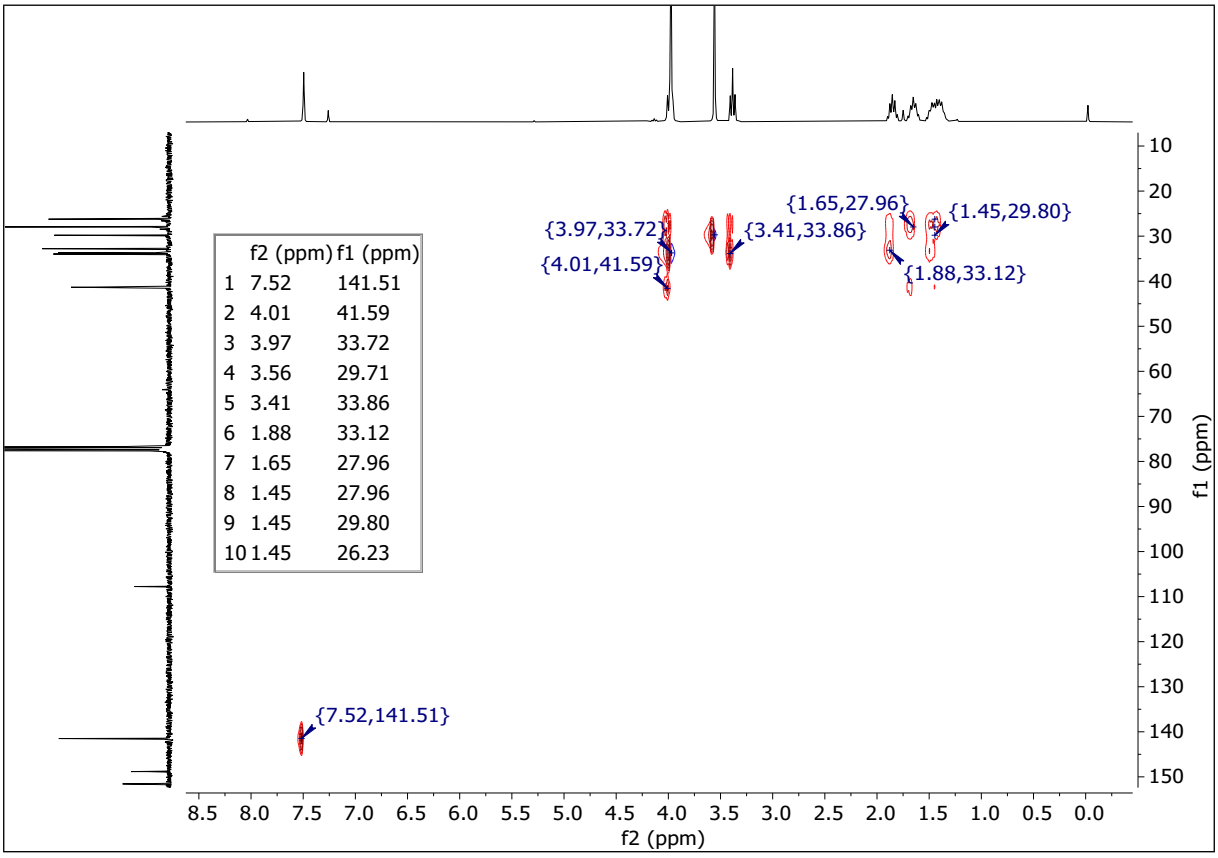


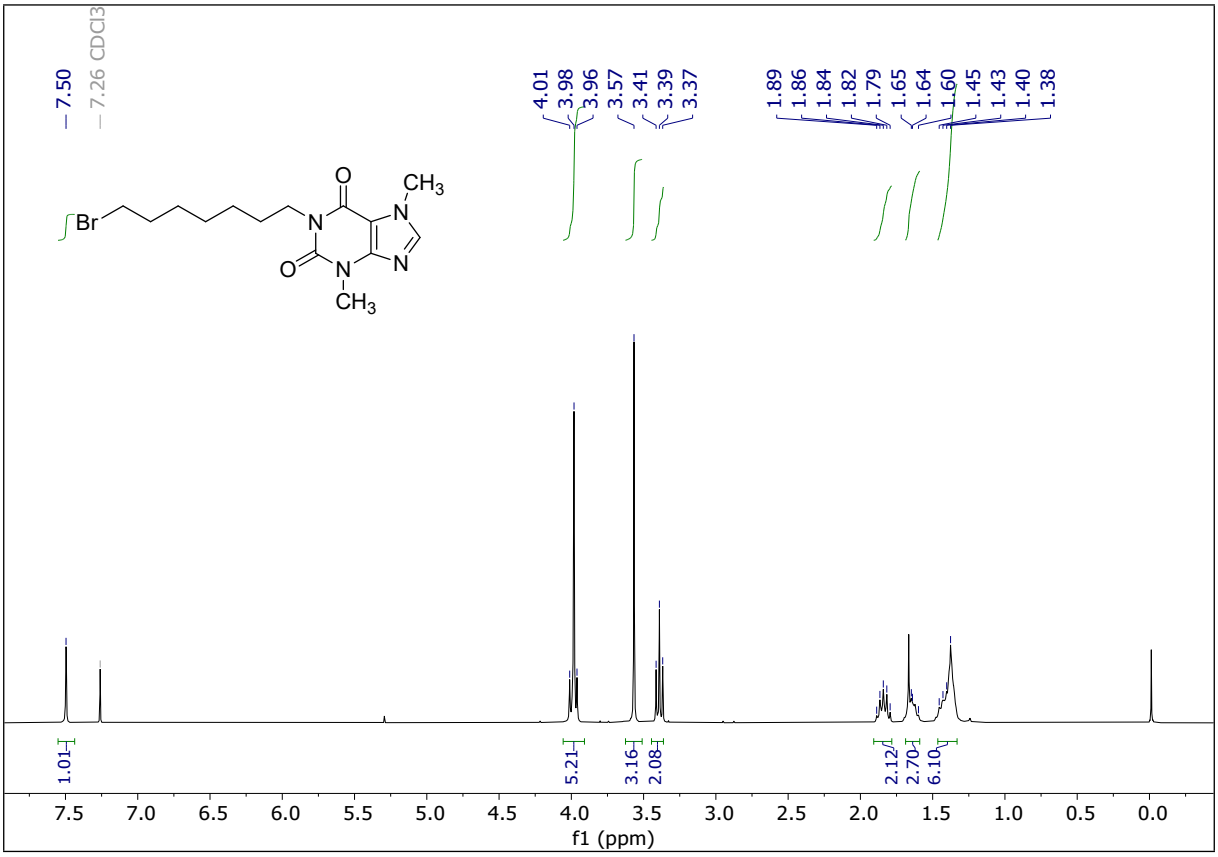


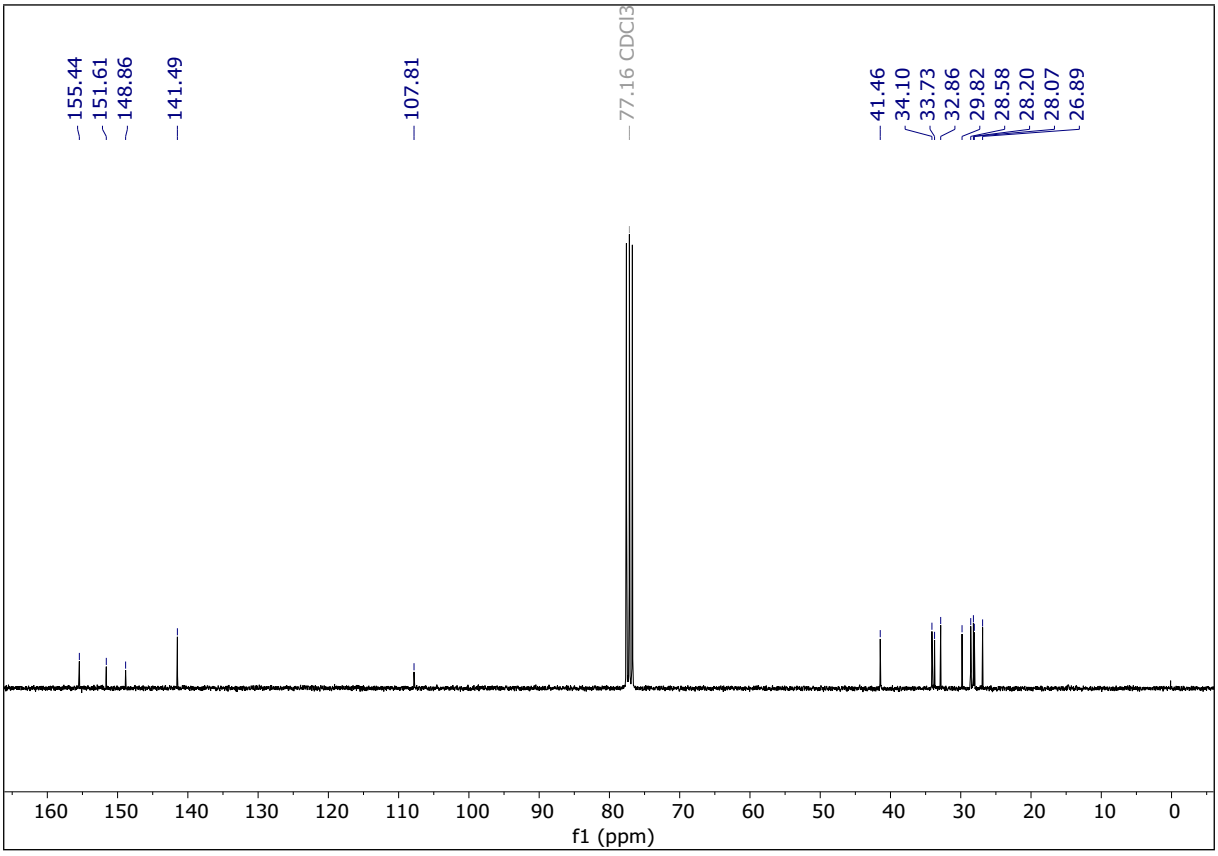
DEPT and HSQC spectra in $CDCl_3$ of **2c**



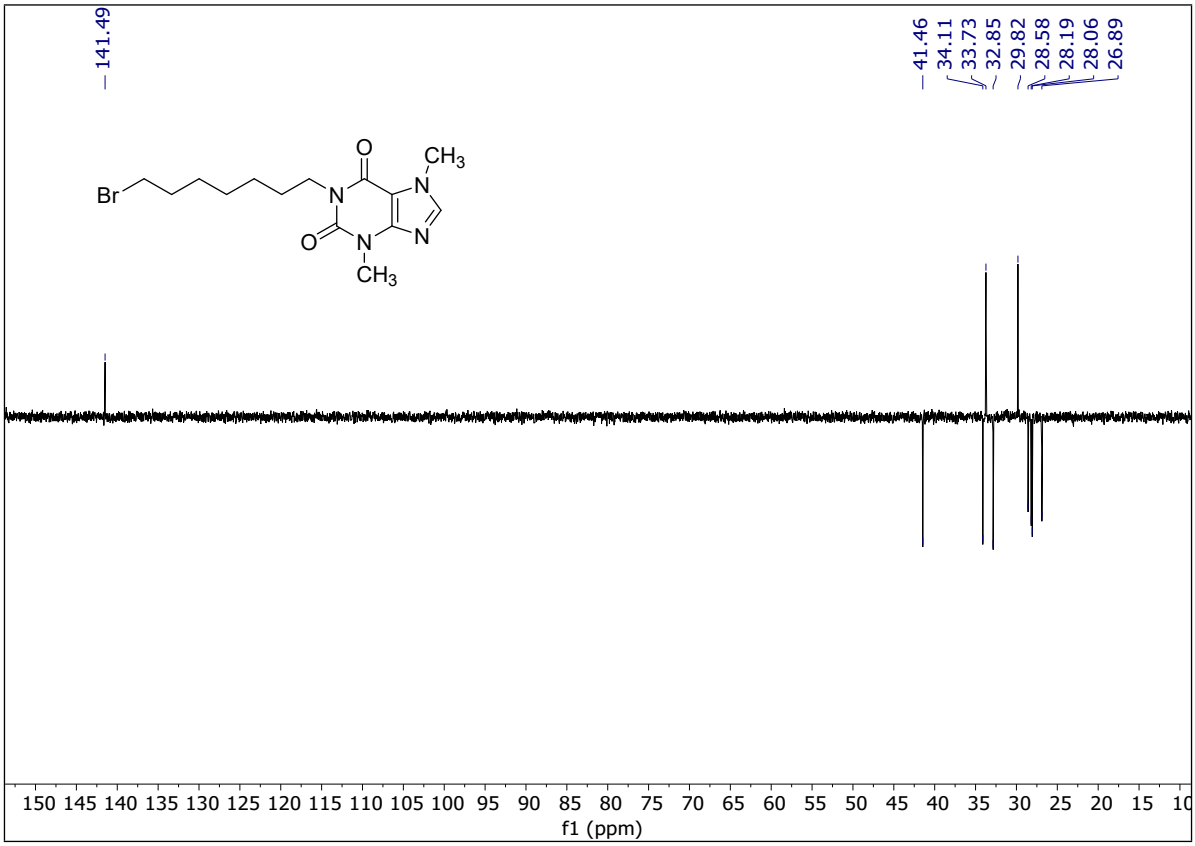


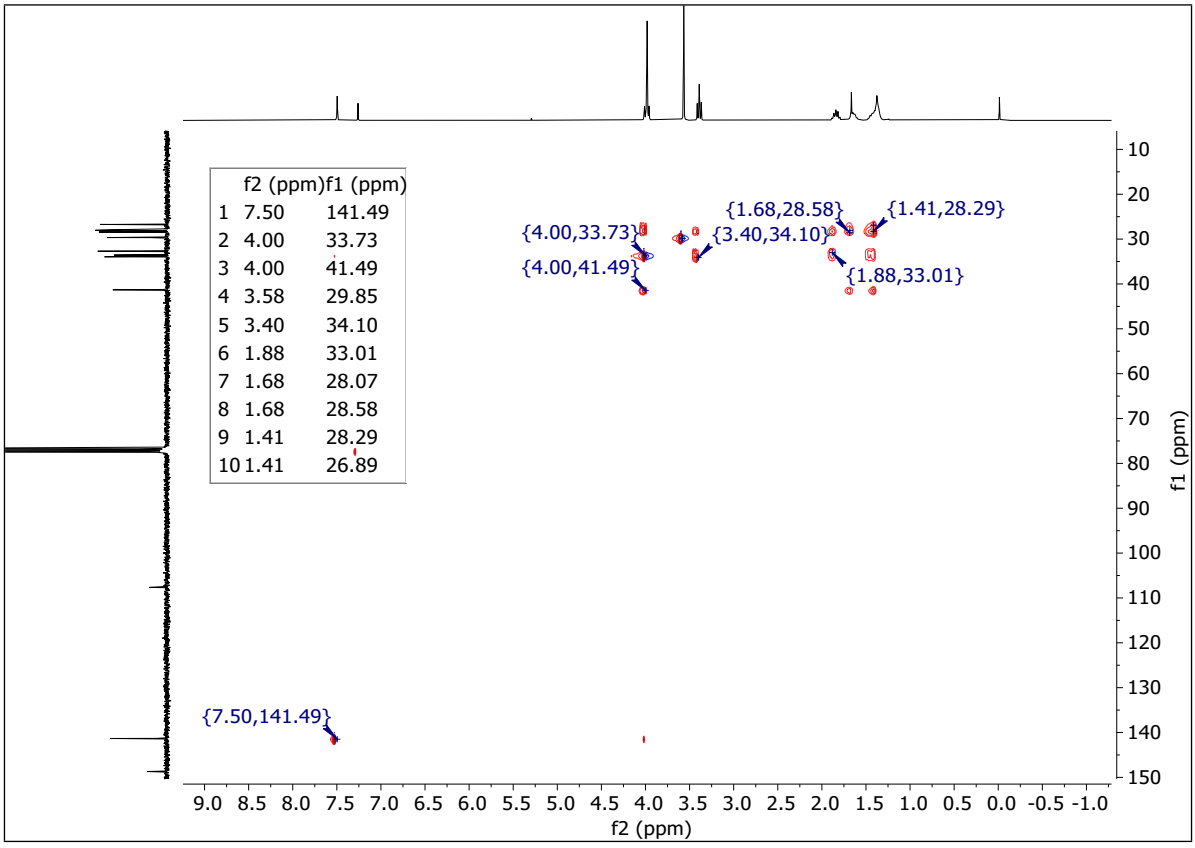
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **2d**



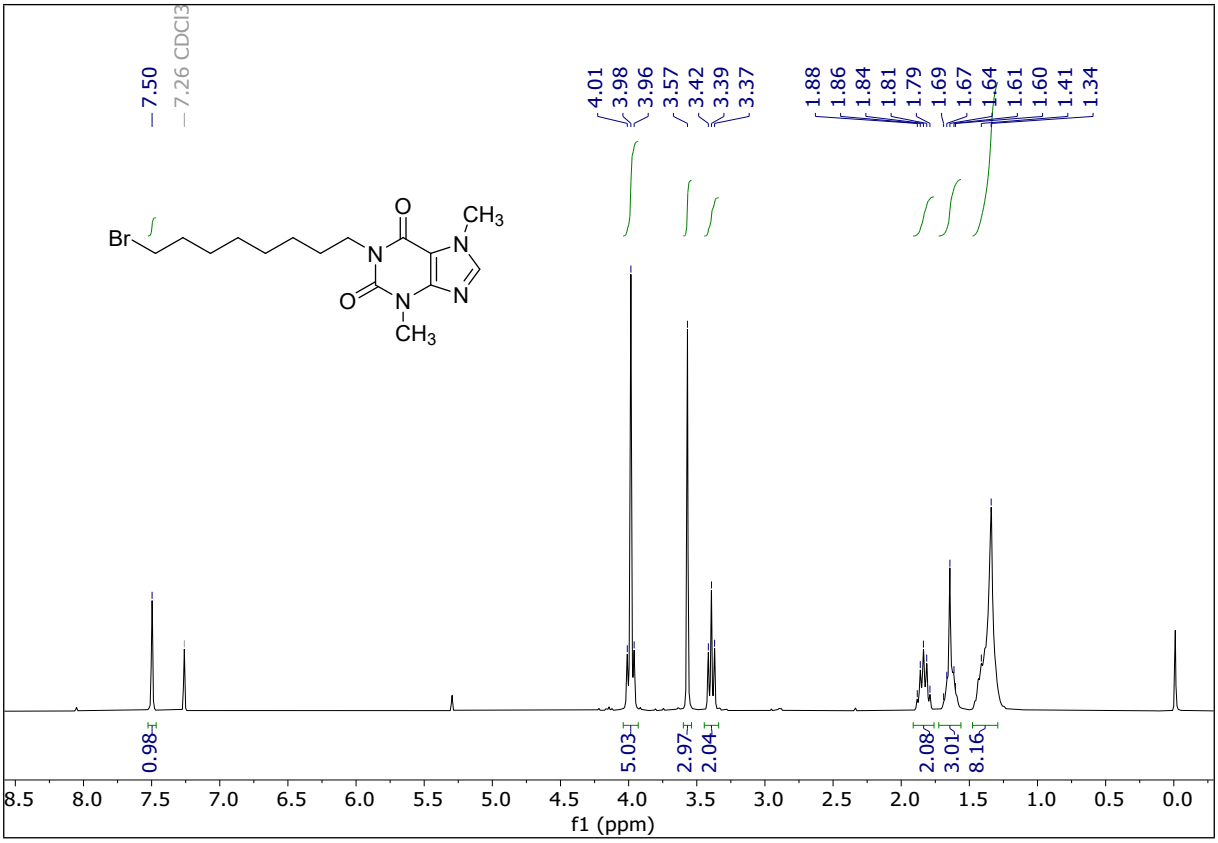


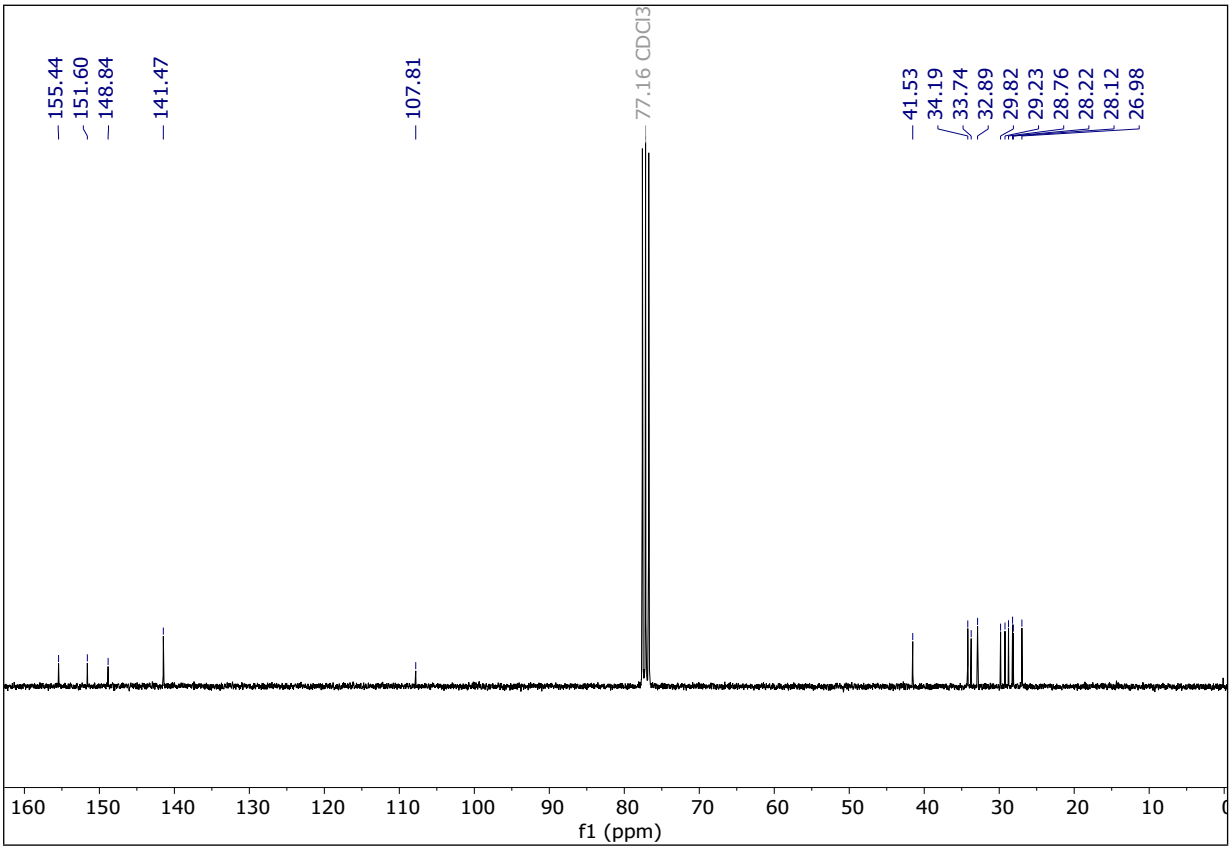
DEPT and HSQC spectra in $CDCl_3$ of **2d**



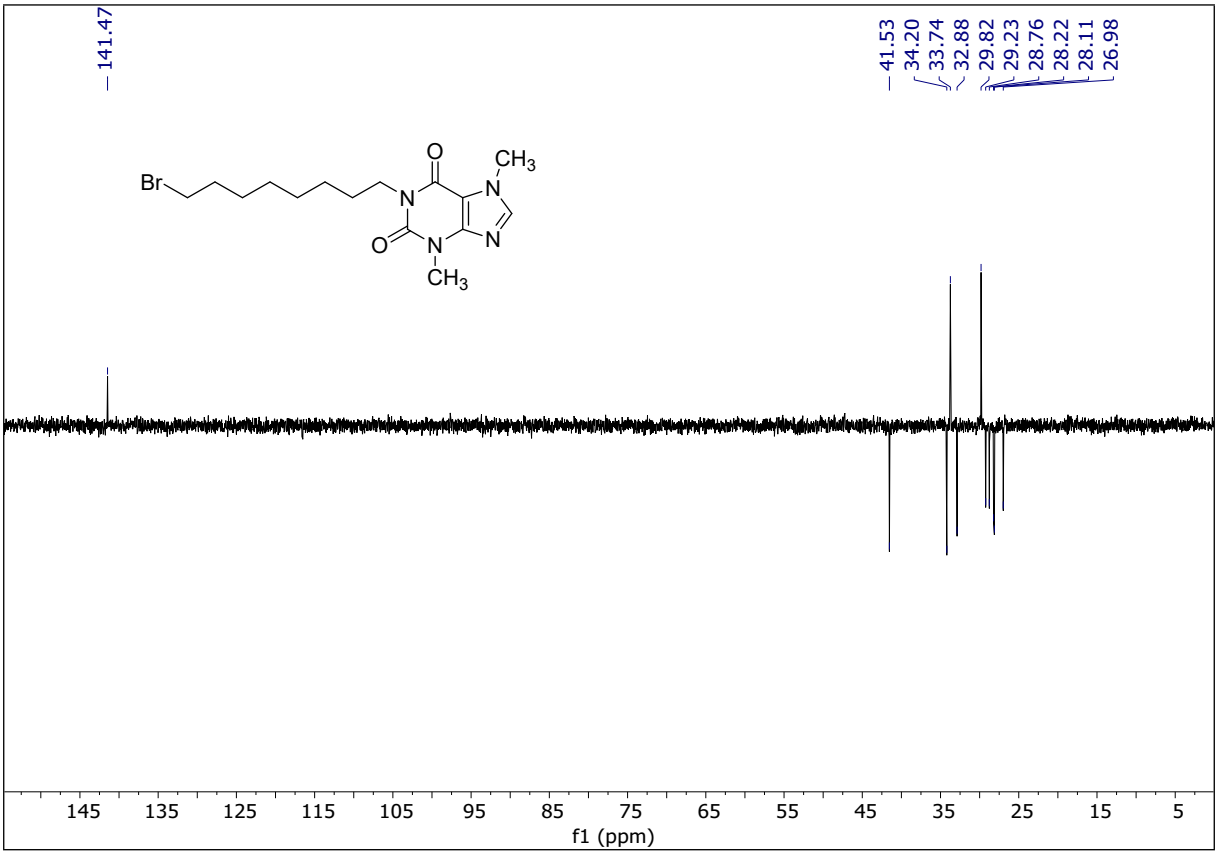


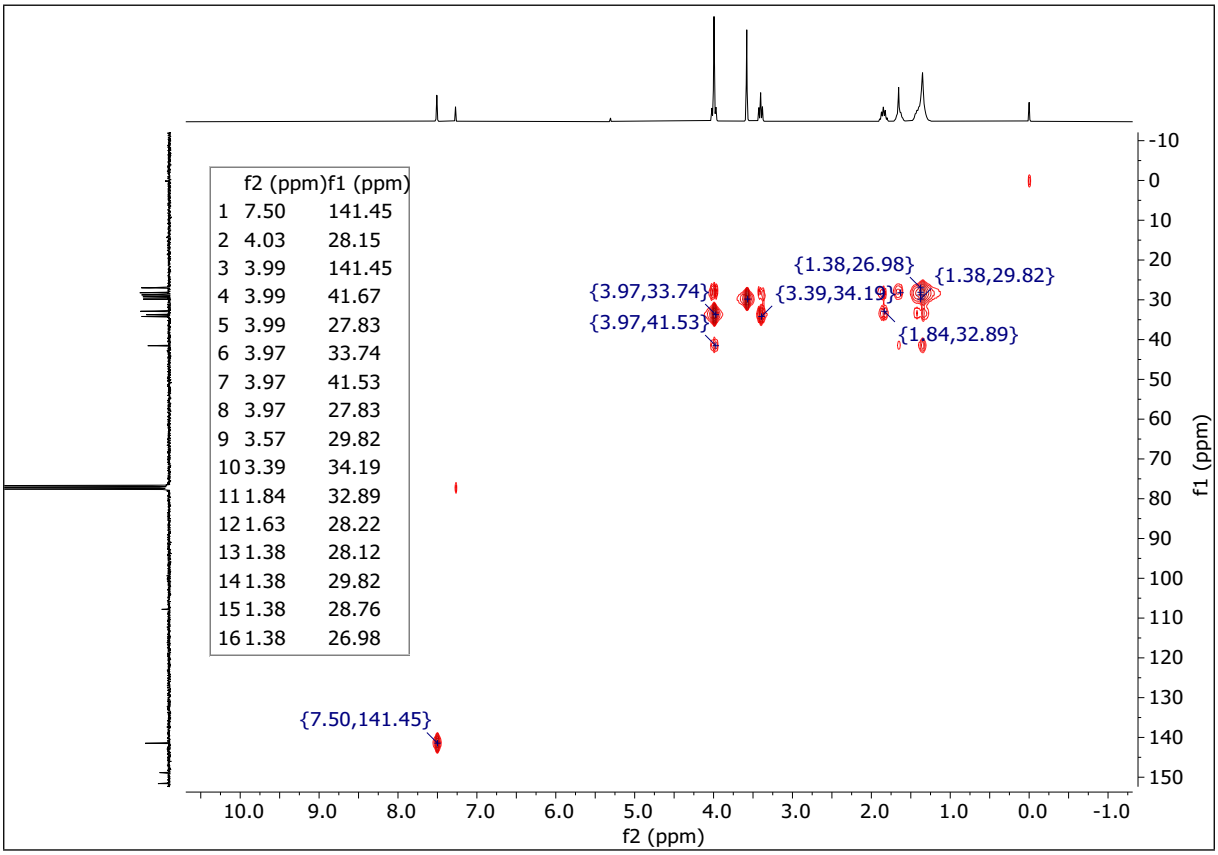
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **2e**





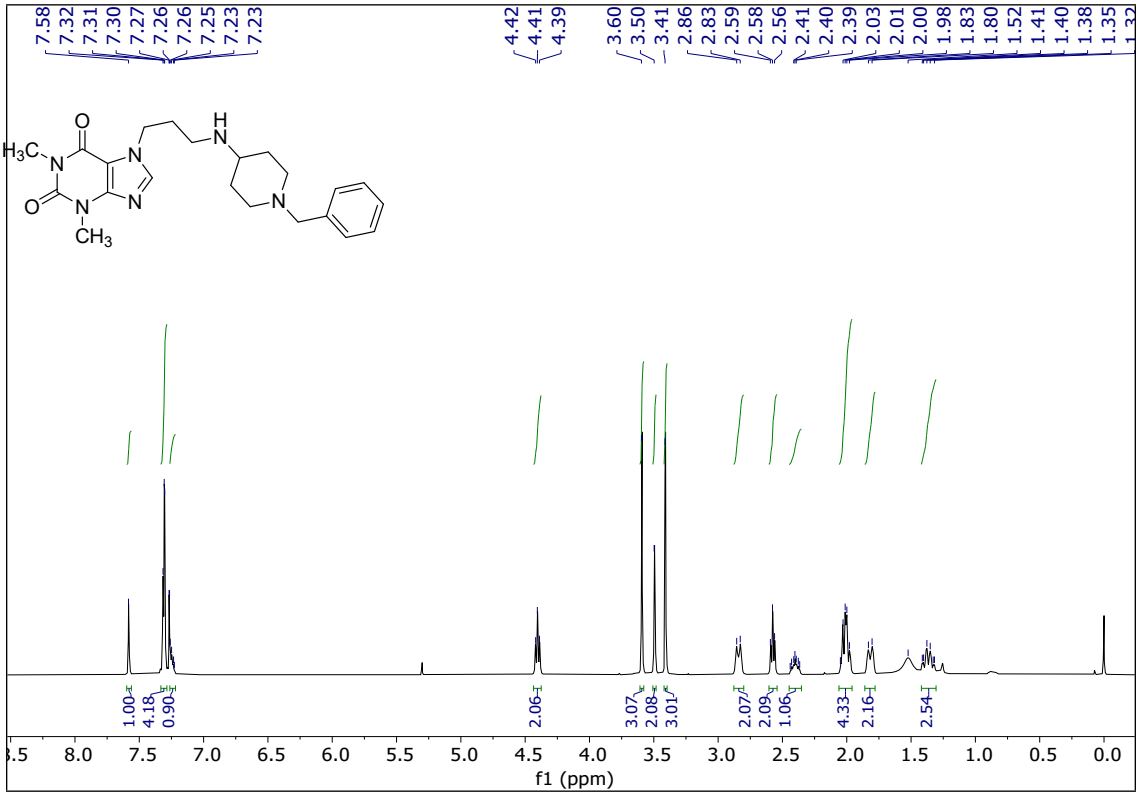
DEPT and HSQC spectra in $CDCl_3$ of **2e**

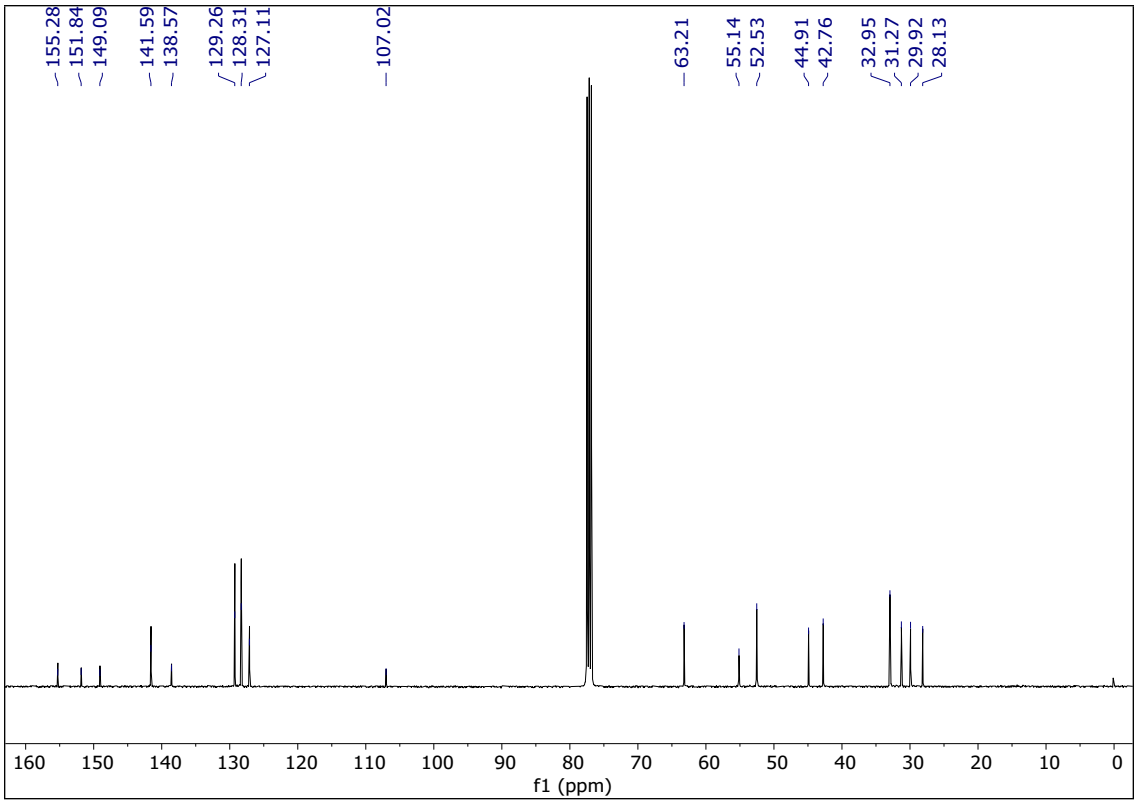




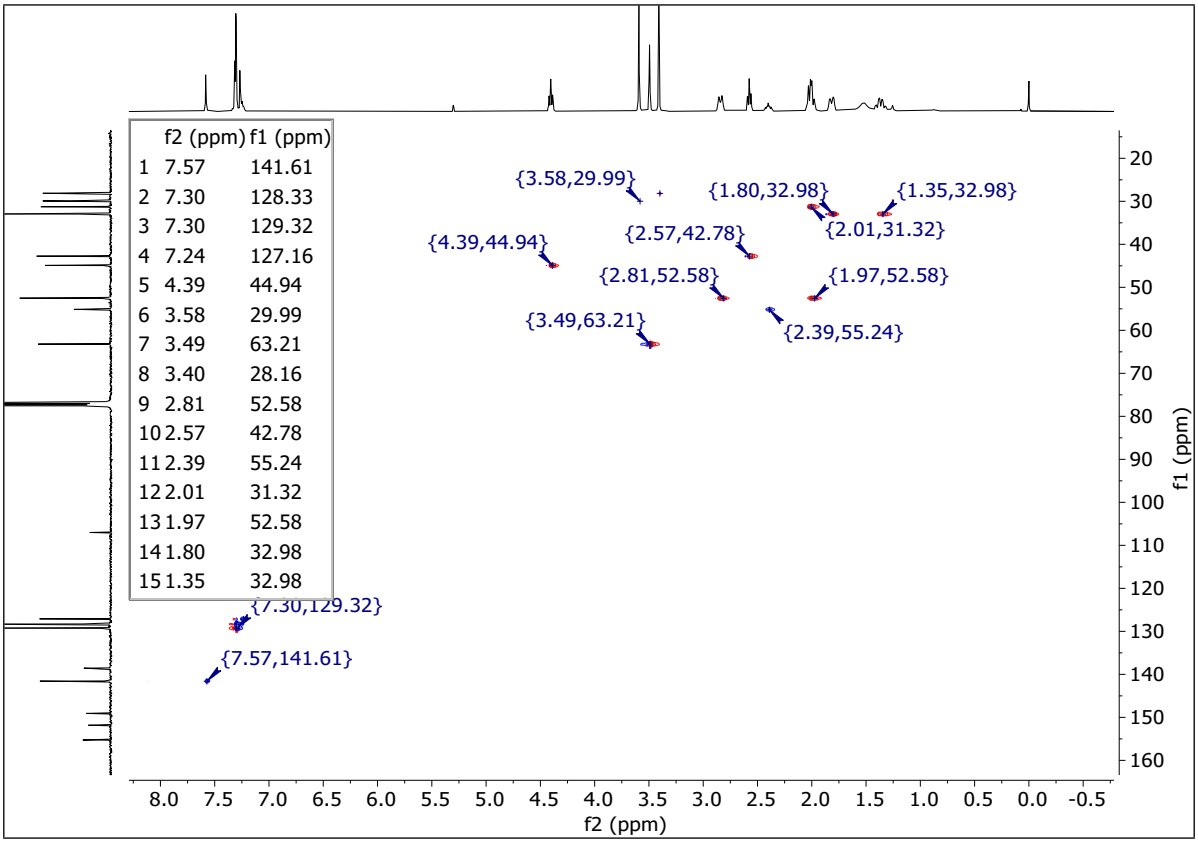
NMR Spectra of Methylxanthine Derivatives

^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **3**





HSQC spectra in $CDCl_3$ of **3**



HRMS (ESI-TOF) of **3**

Qualitative Compound Report

Data File	2048_BBP_4_01.d	**Sample Name**	BBP_4
Sample Type	Sample	**Position**	Vial 28
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/21/2022 10:26:17 AM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

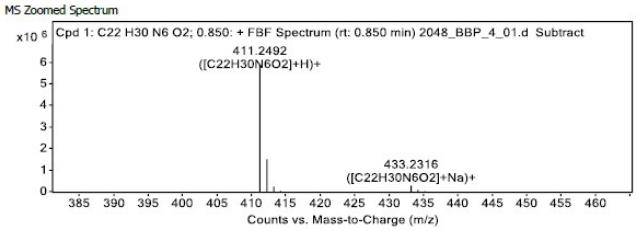
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/21/2022 10:26:17 AM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

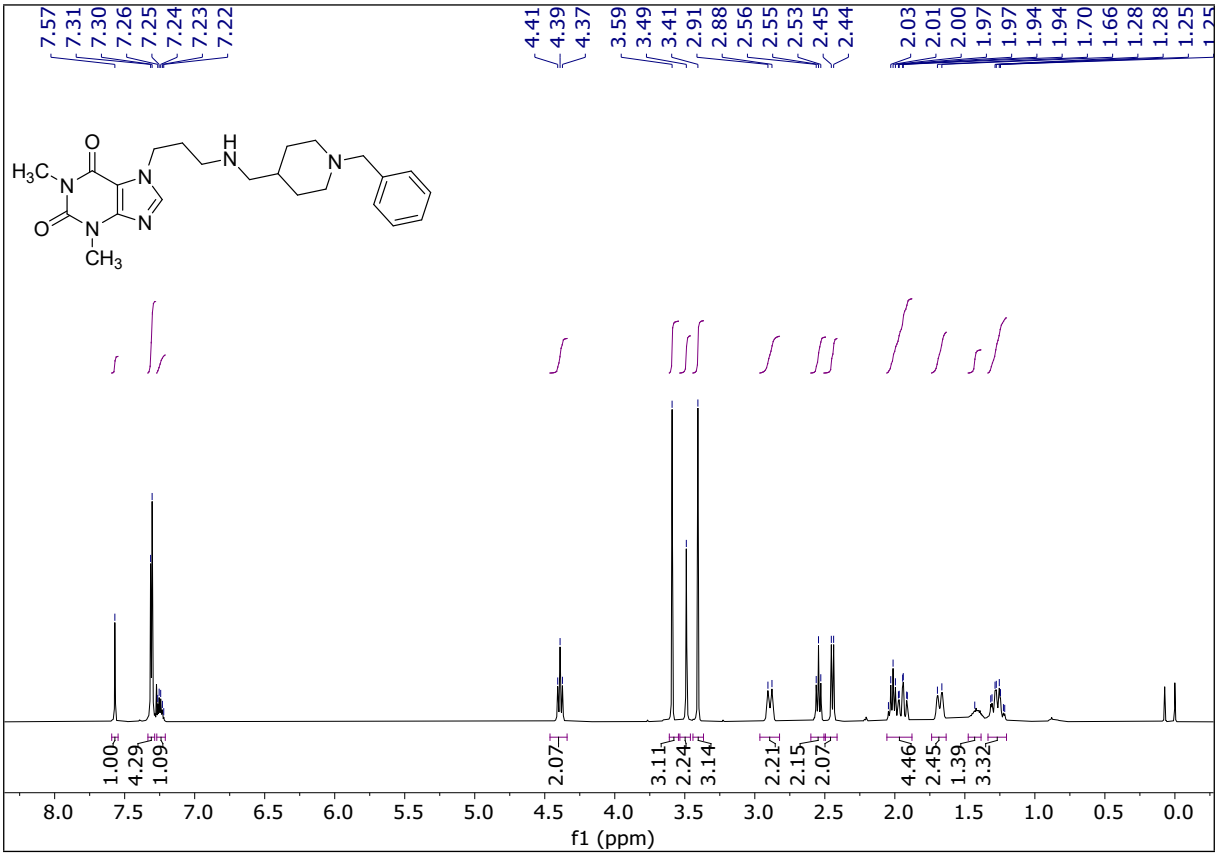
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C22 H30 N6 O2; 0.850	0.85	410.2422	283104	C22 H30 N6 O2	410.243	-2.07	1

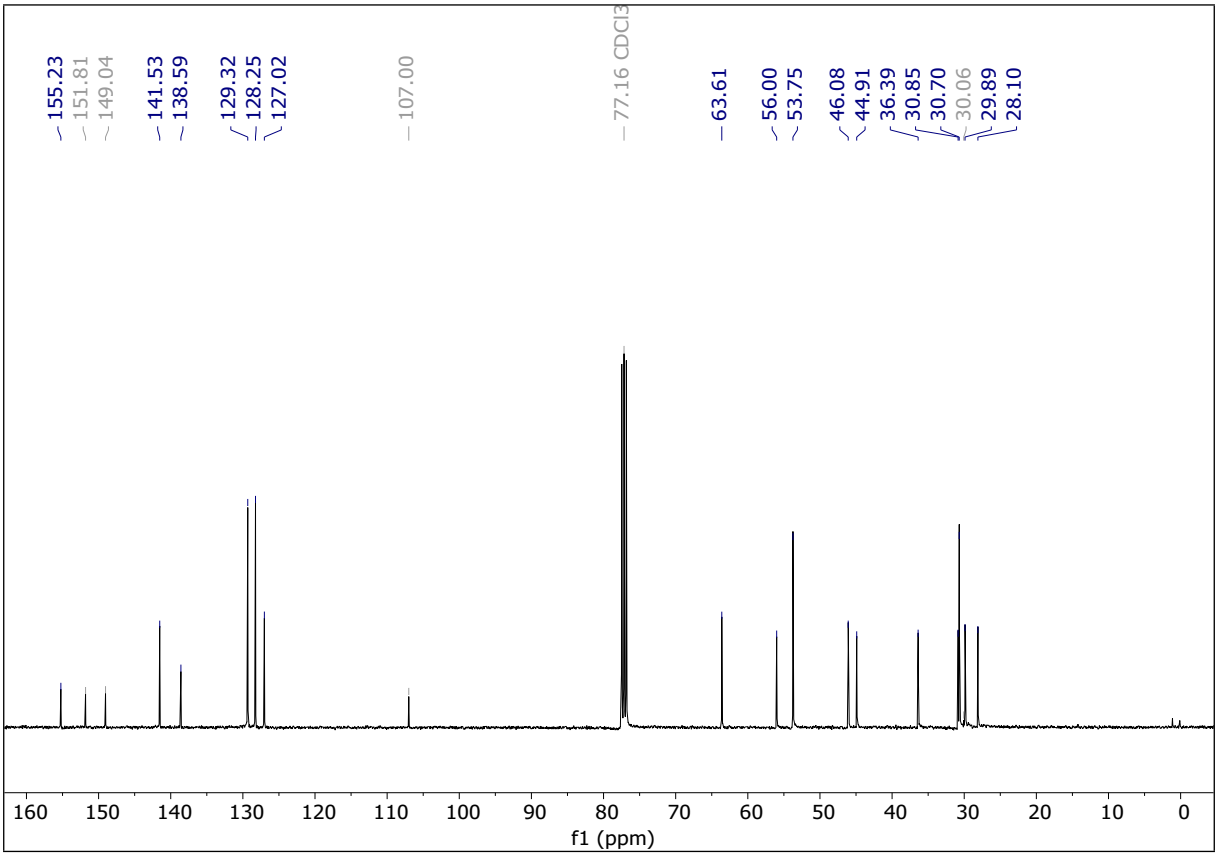
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C22 H30 N6 O2; 0.850	433.2316	0.85	Find by Formula	410.2422

MS Zoomed Spectrum

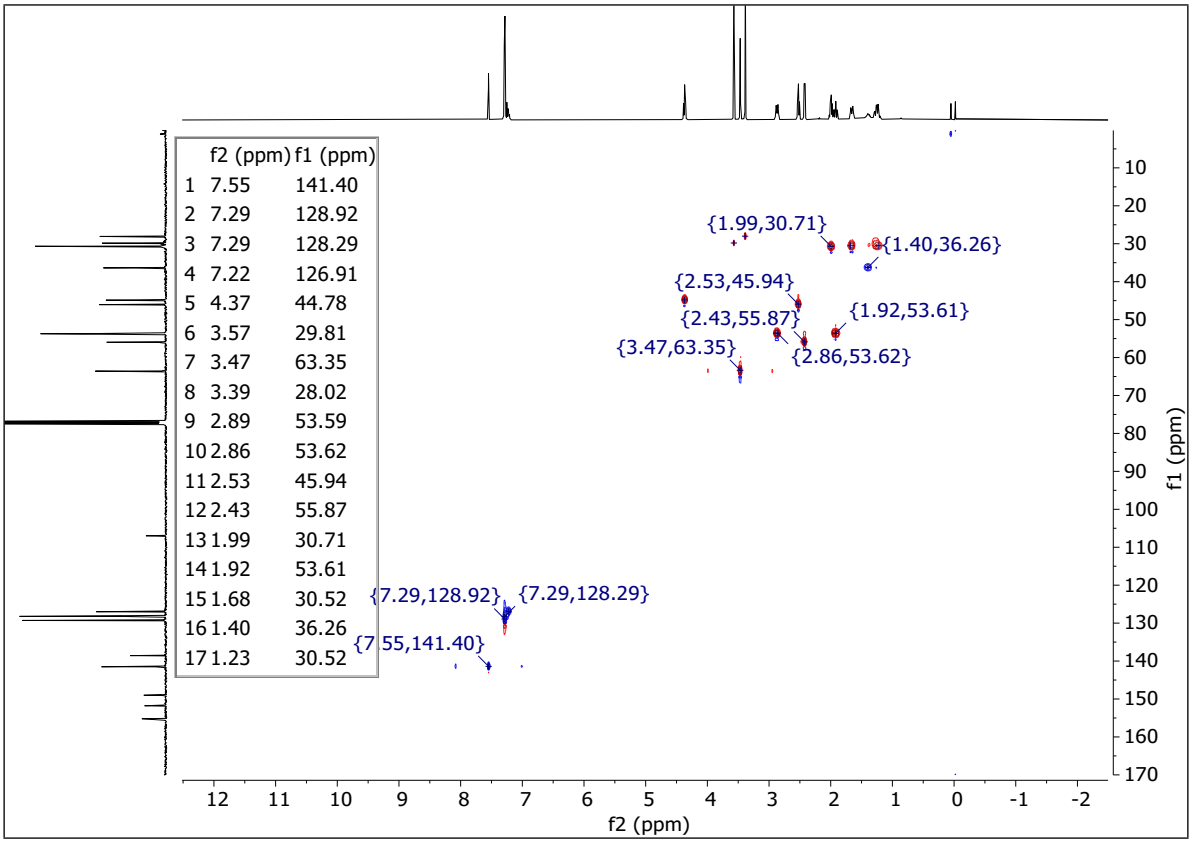


^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **4**





HSQC spectra in $CDCl_3$ of **4**



HRMS (ESI-TOF) of **4**

Qualitative Compound Report

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IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

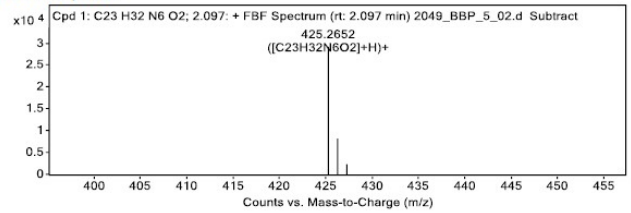
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 1:23:55 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

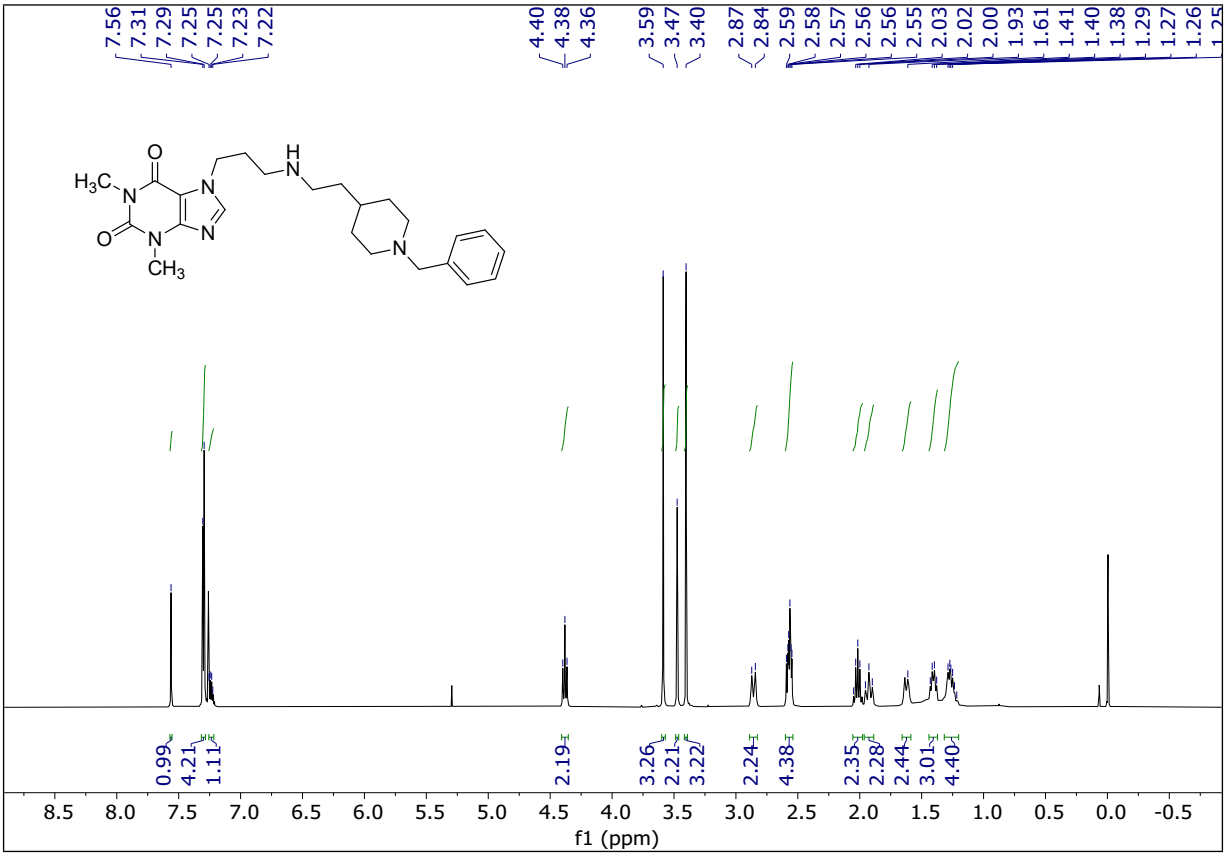
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C23 H32 N6 O2; 2.097	2.097	424.2588	29181	C23 H32 N6 O2	424.2587	0.35	1

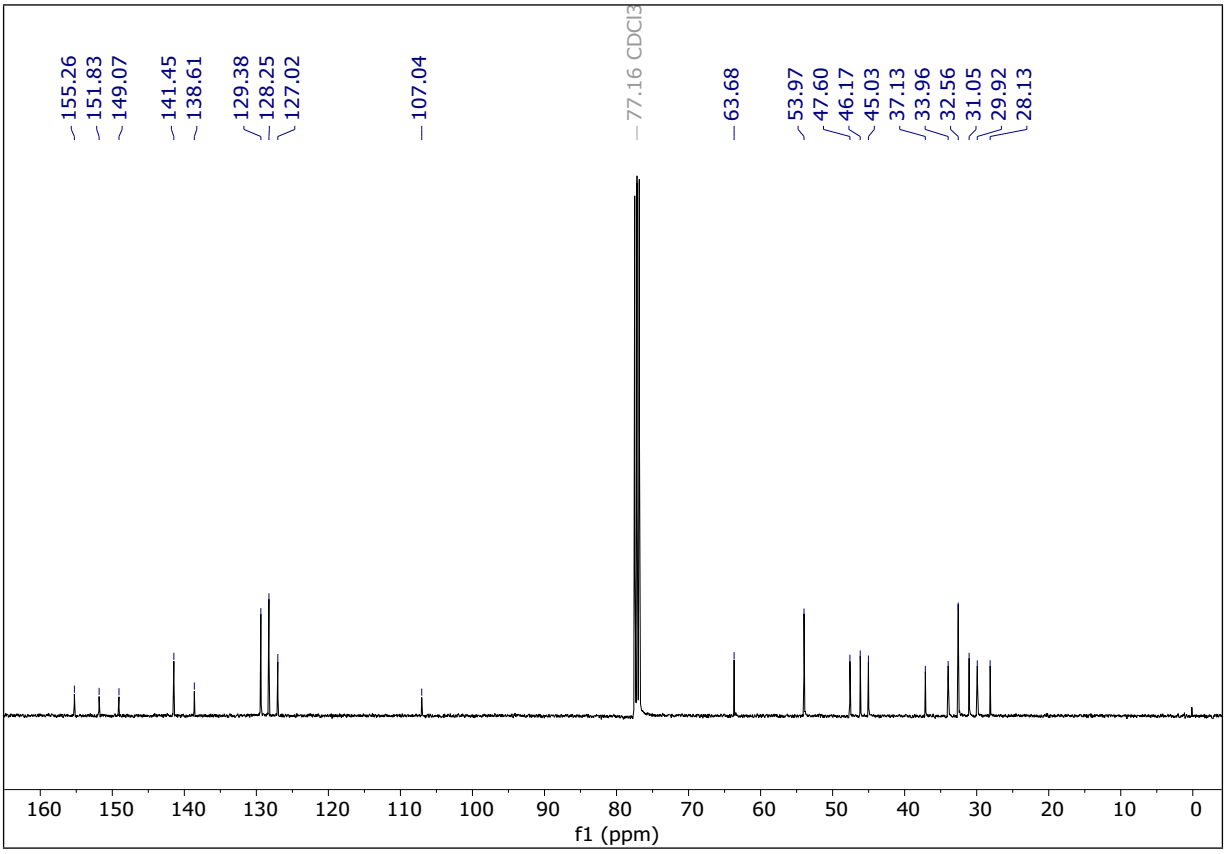
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C23 H32 N6 O2; 2.097	425.2652	2.097	Find by Formula	424.2588

MS Zoomed Spectrum

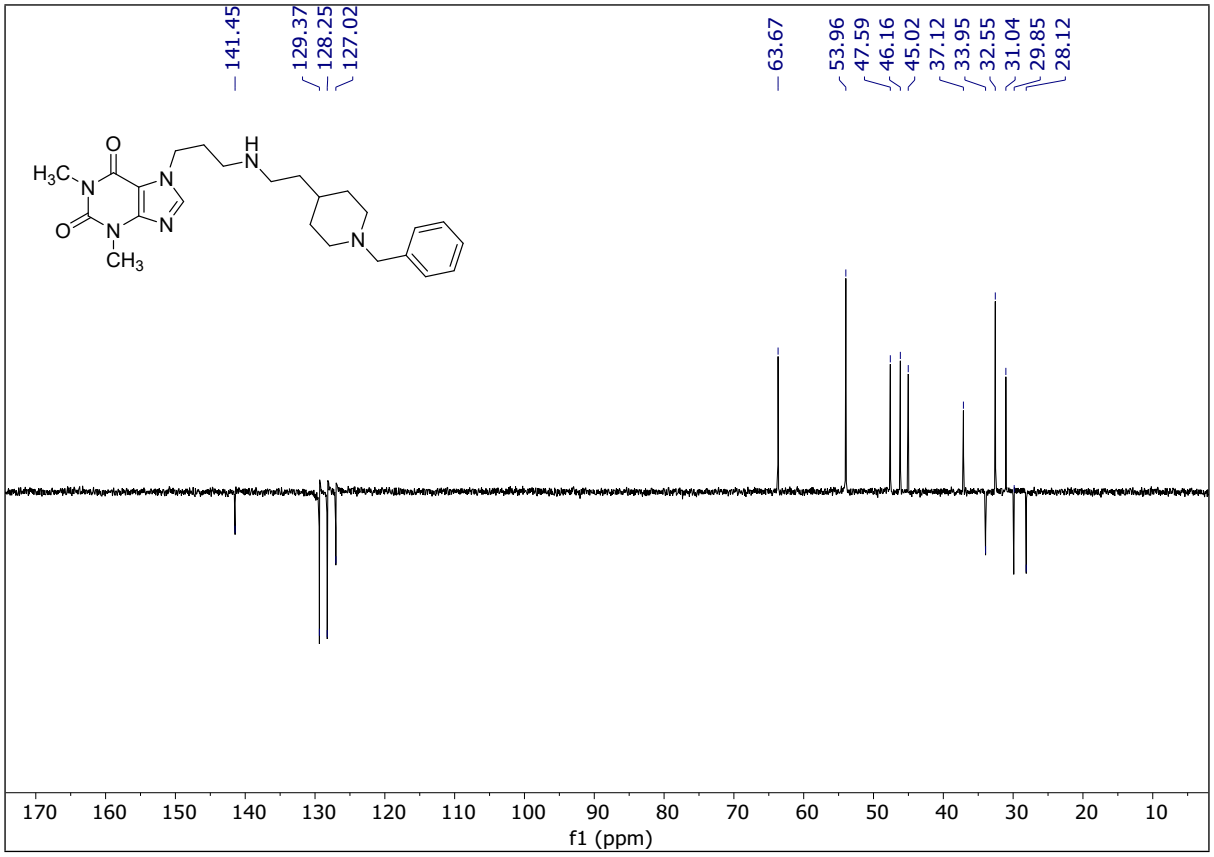


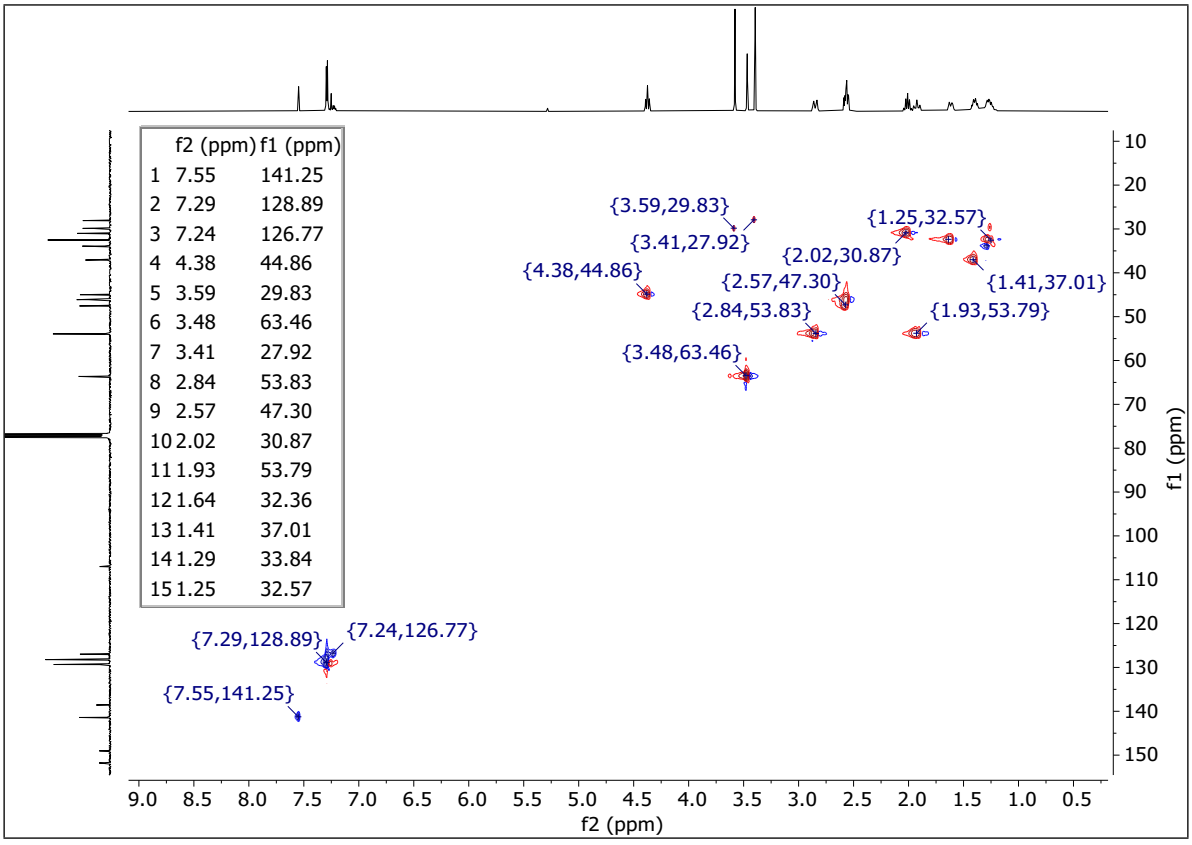
^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **5**



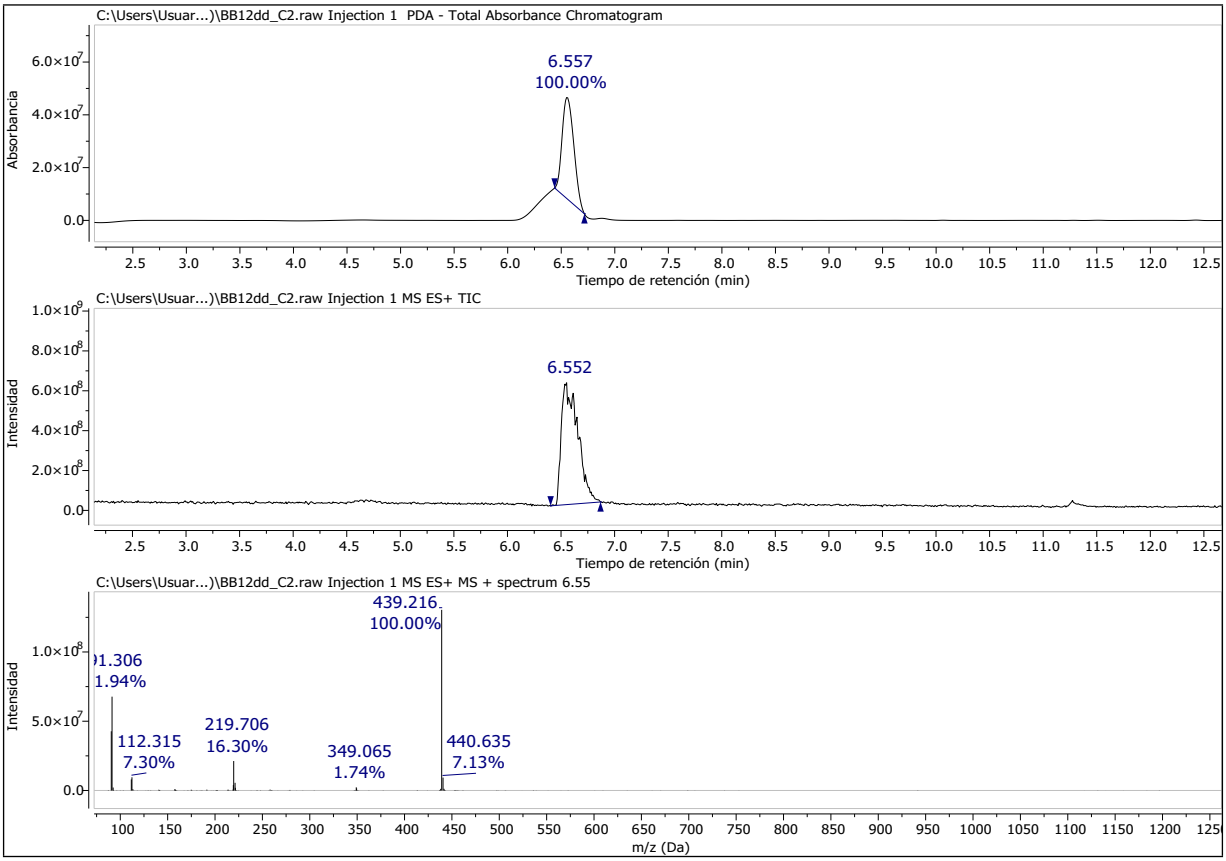


DEPT and HSQC spectra in $CDCl_3$ of **5**

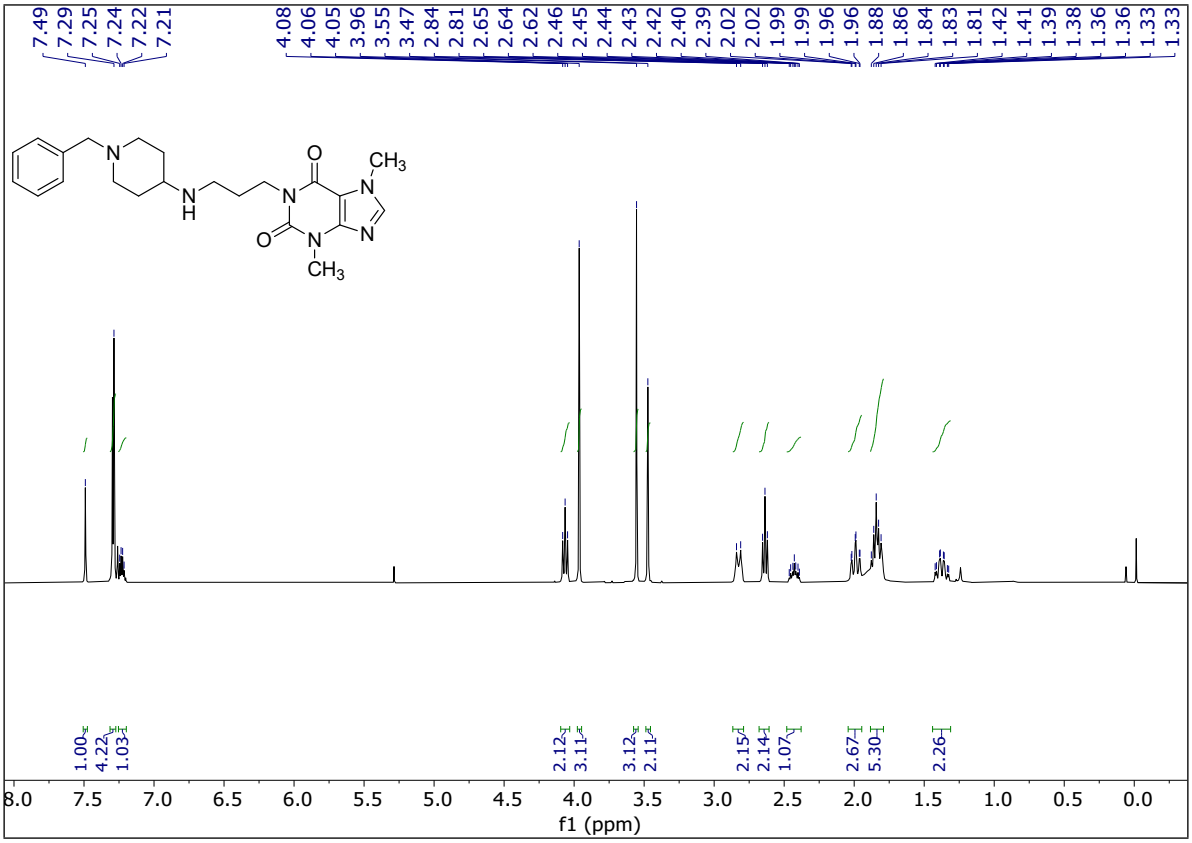


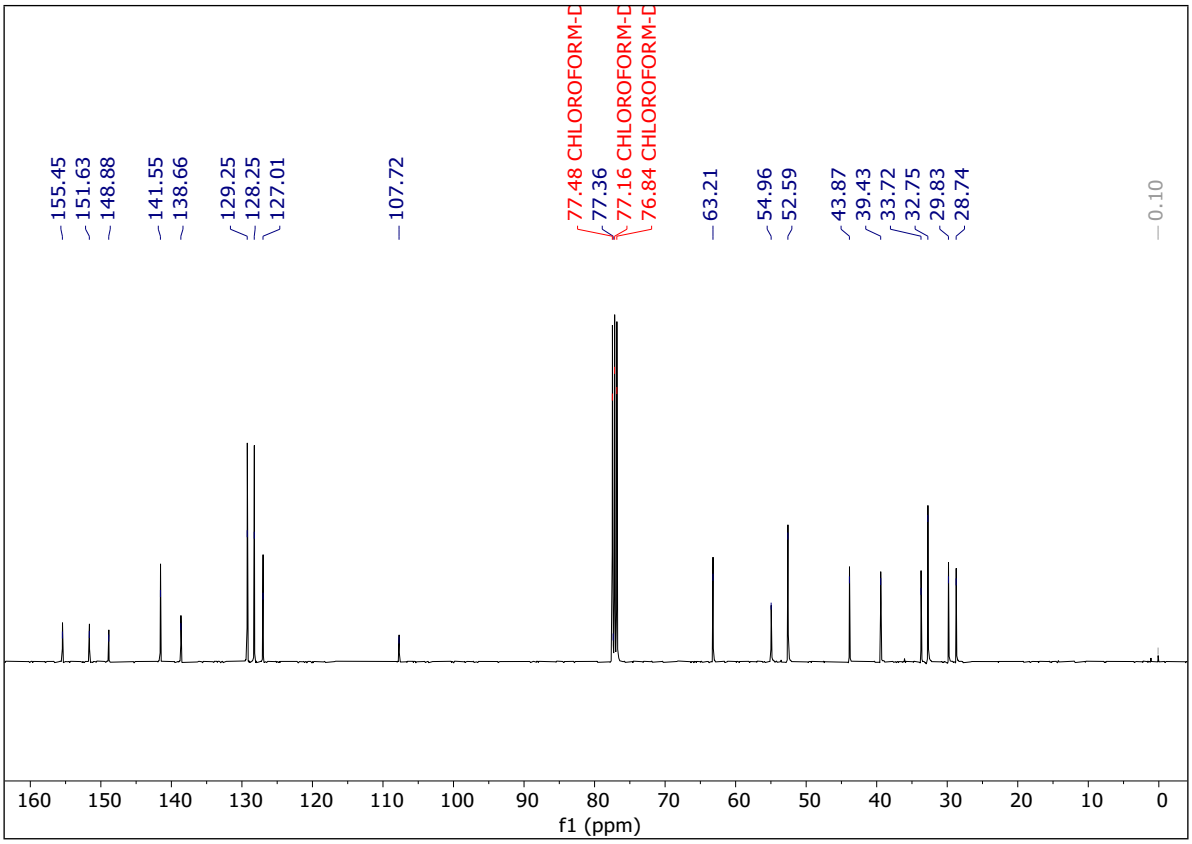


HPLC-UV/MS of **5**

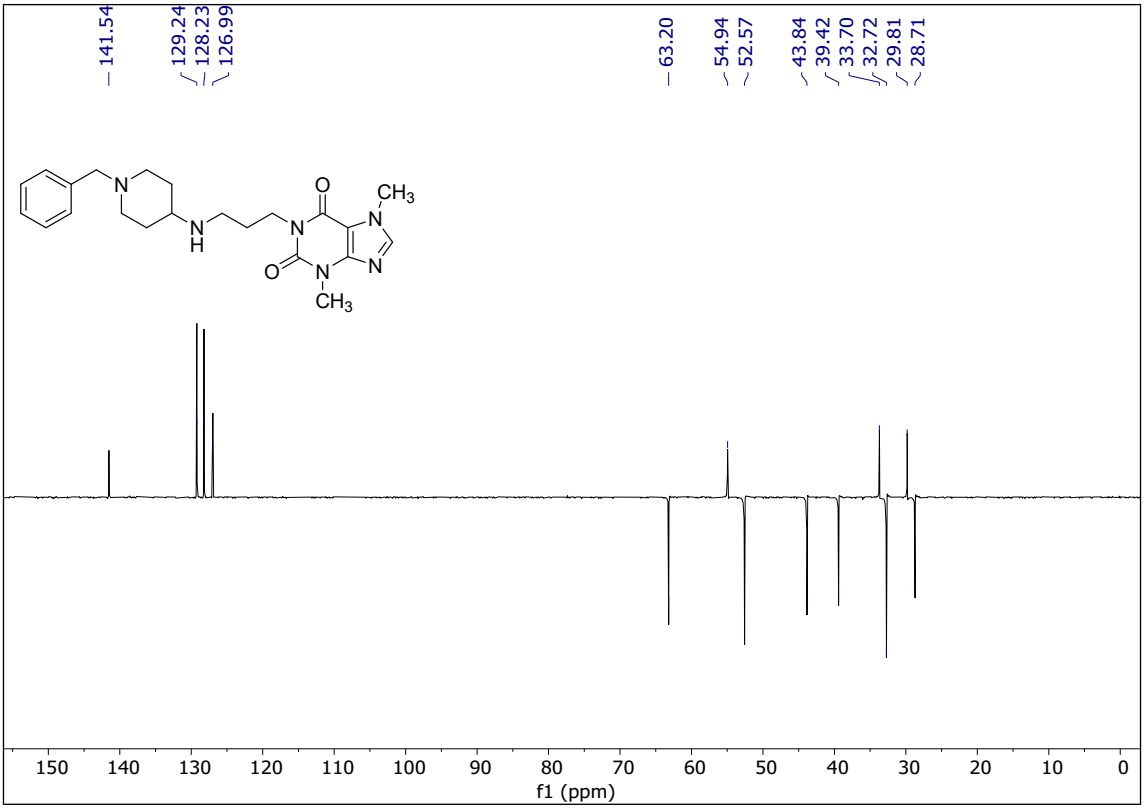


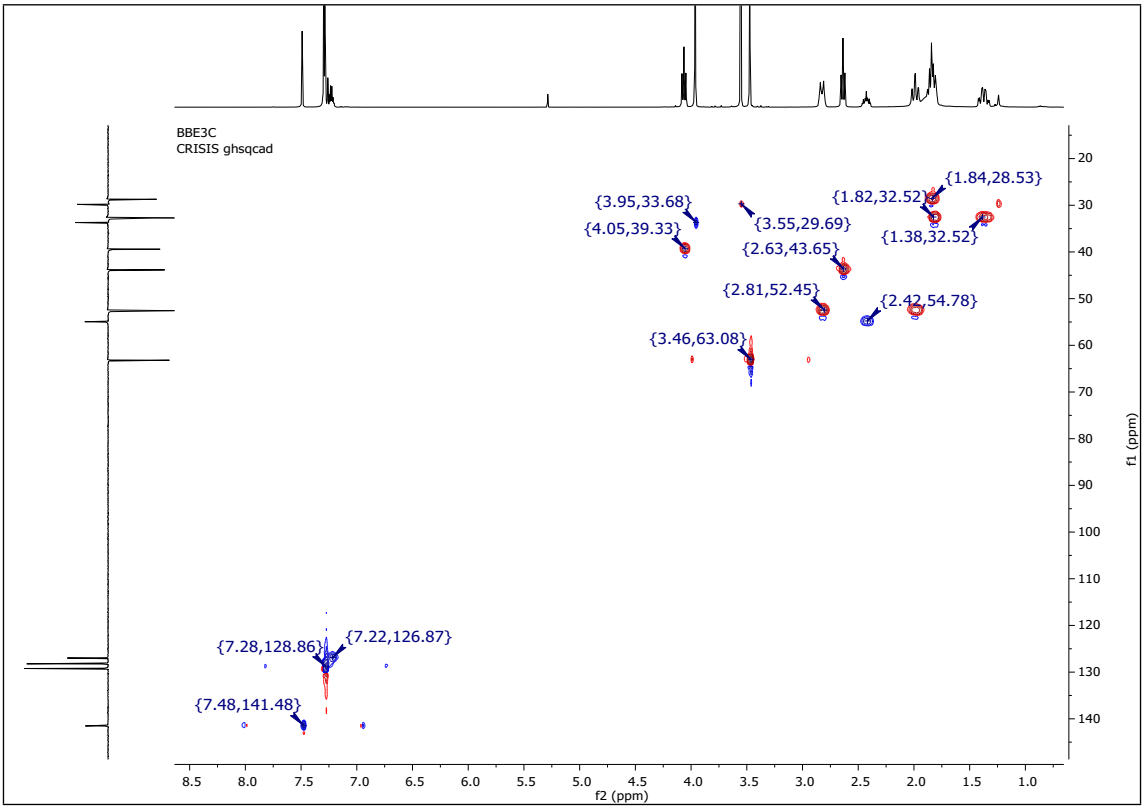
^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **6**





DEPT and HSQC spectra in $CDCl_3$ of **6**





Qualitative Compound Report

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IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

Sample Group Info.			
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/21/2022 10:04:34 AM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C22 H30 N6 O2; 0.475	0.475	410.2437	420581	C22 H30 N6 O2	410.243	1.75	1

Compound Label	*m/z*	RT	Algorithm	Mass
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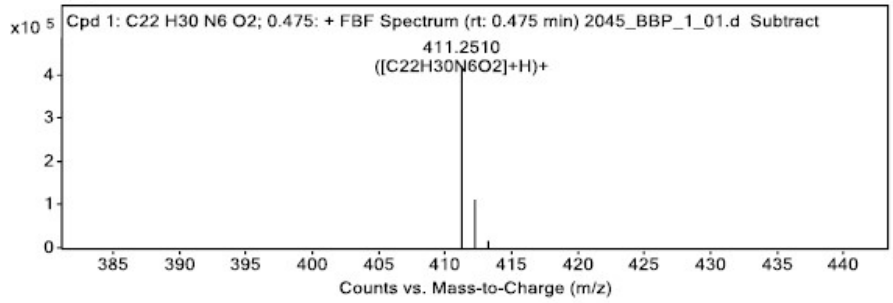
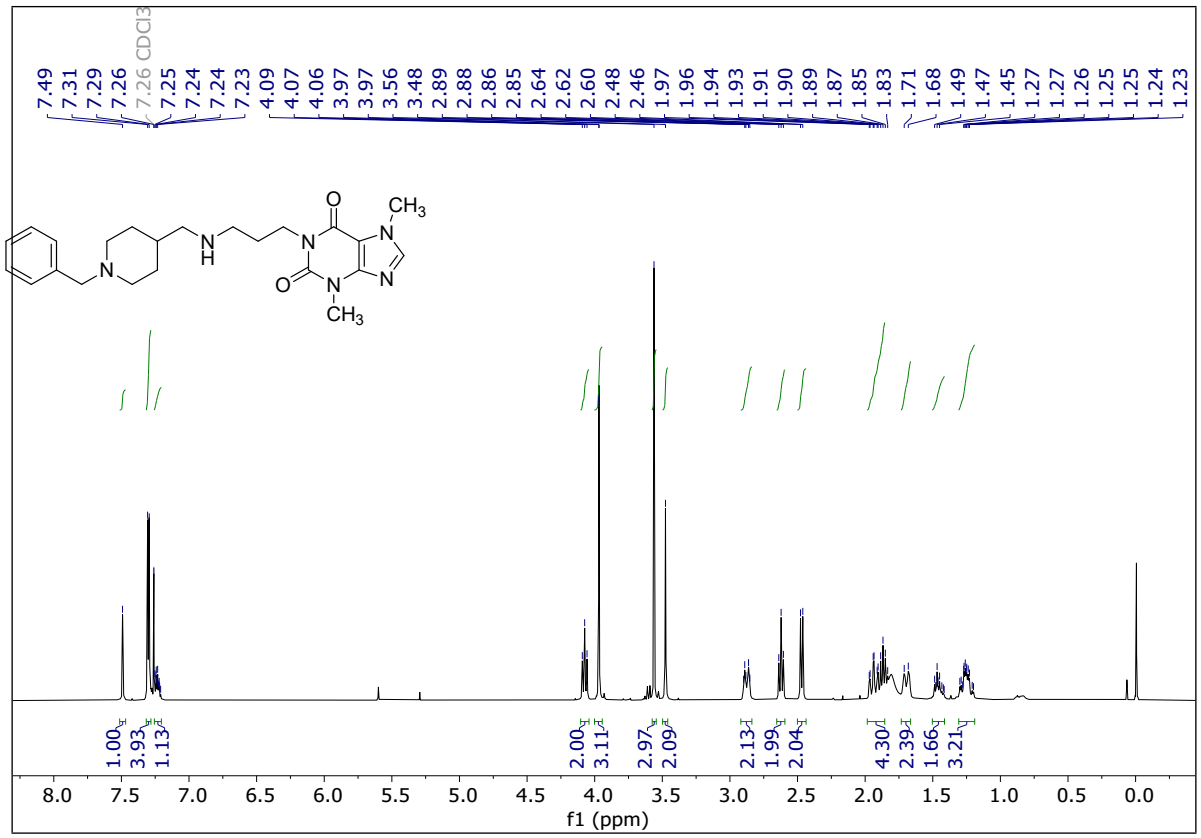
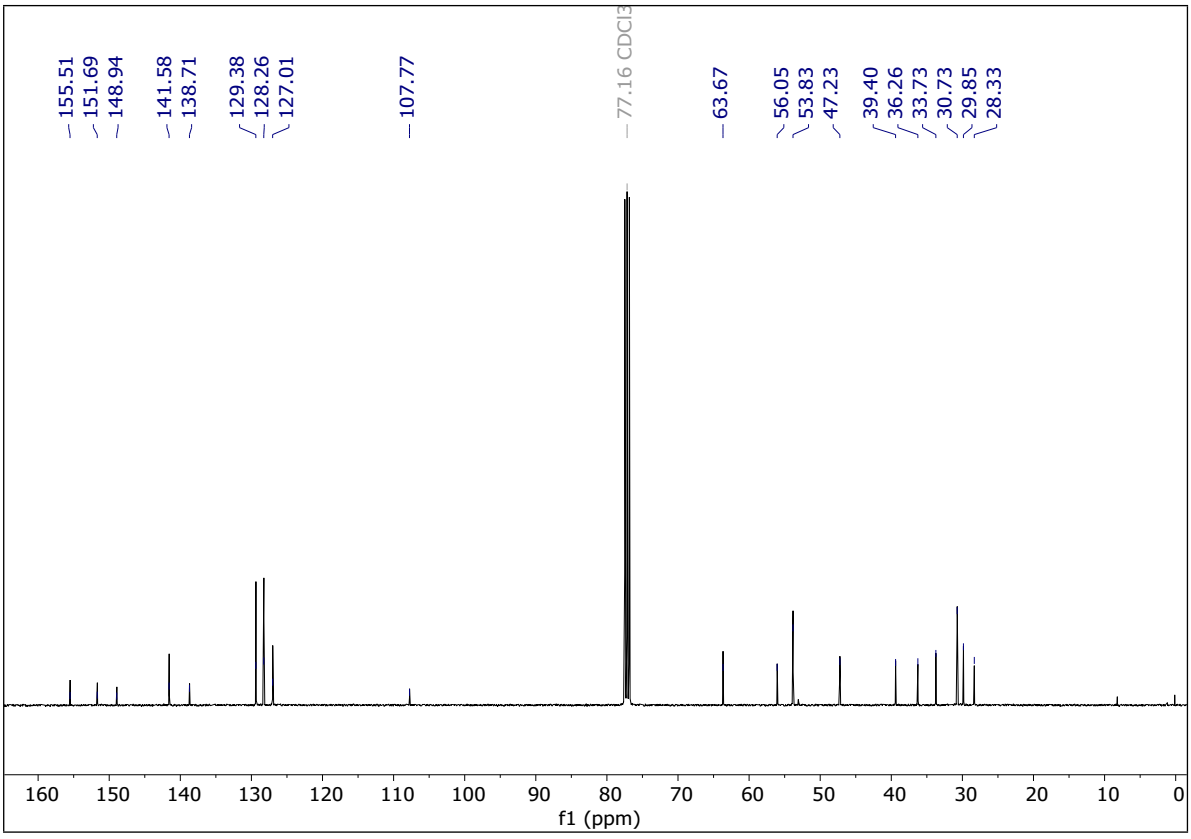
MS Zoomed Spectrum

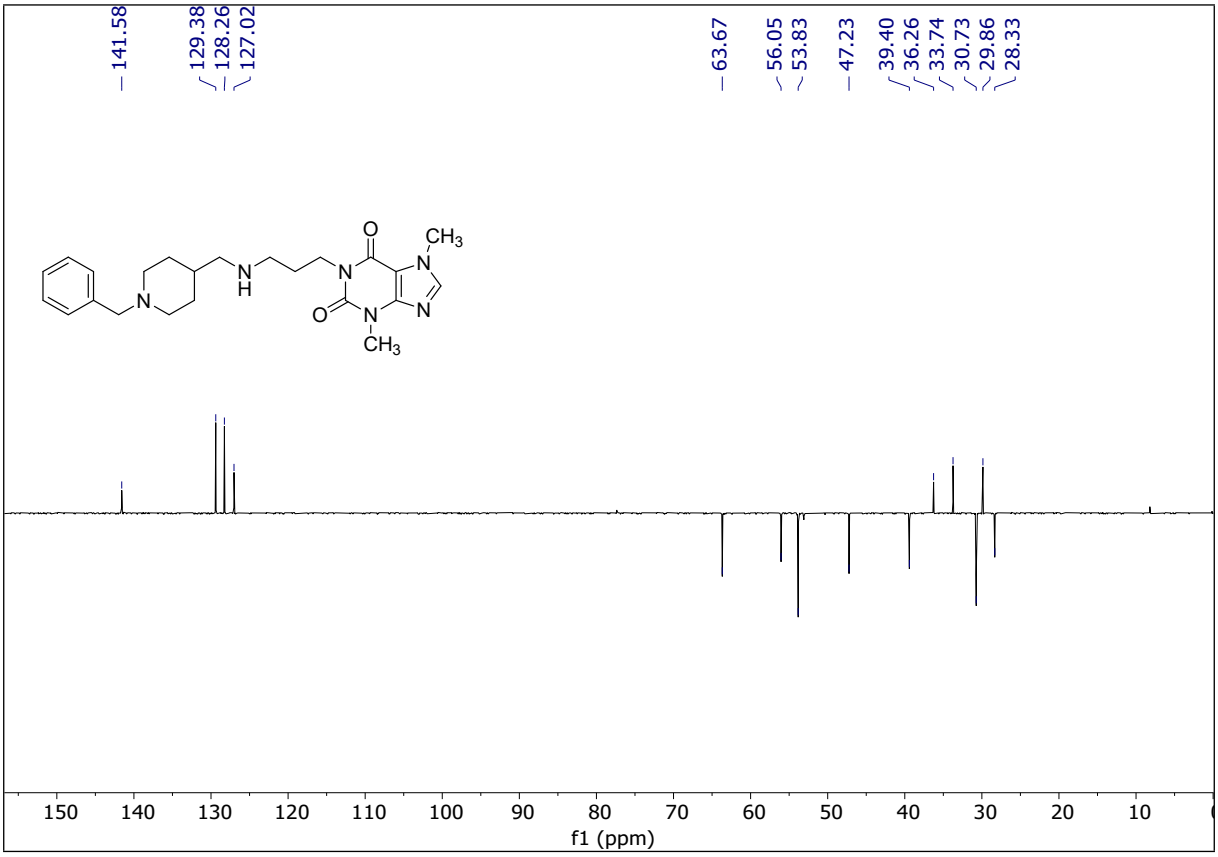


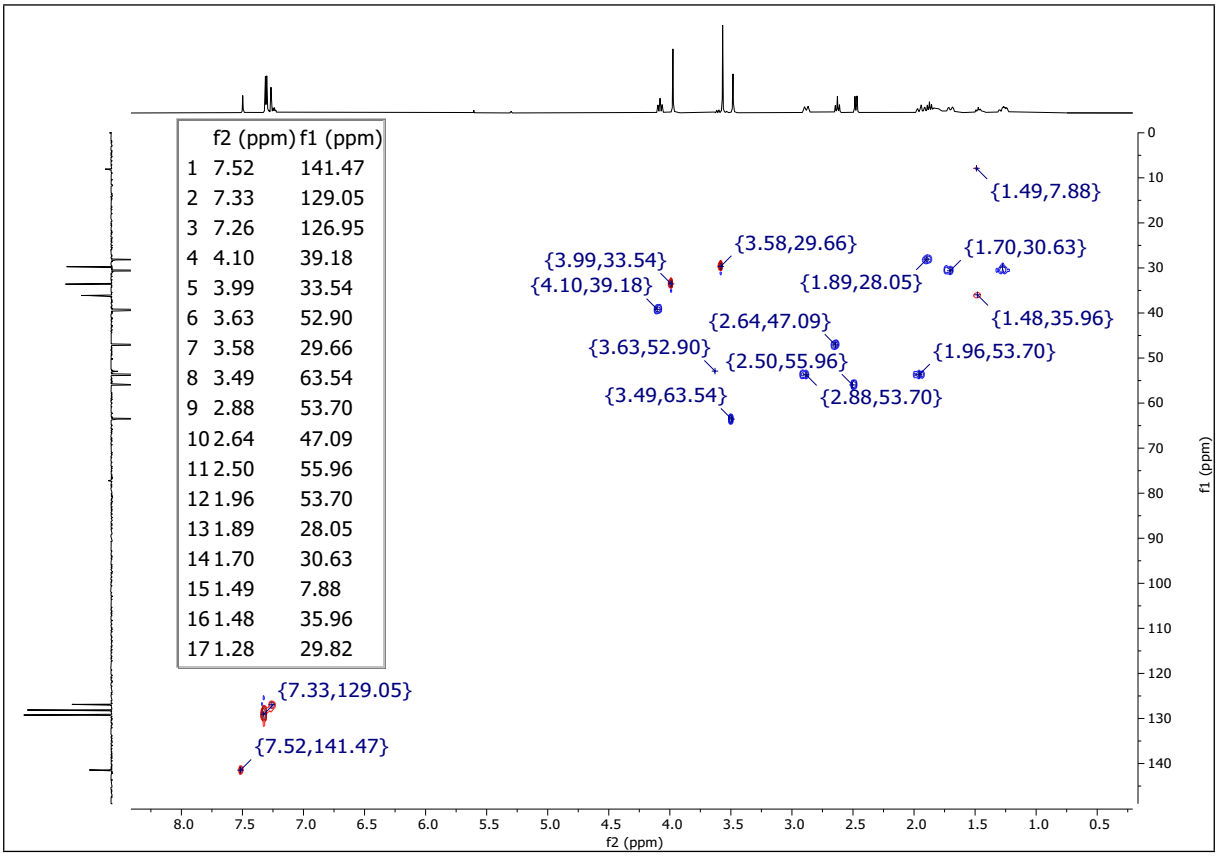
^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **7**



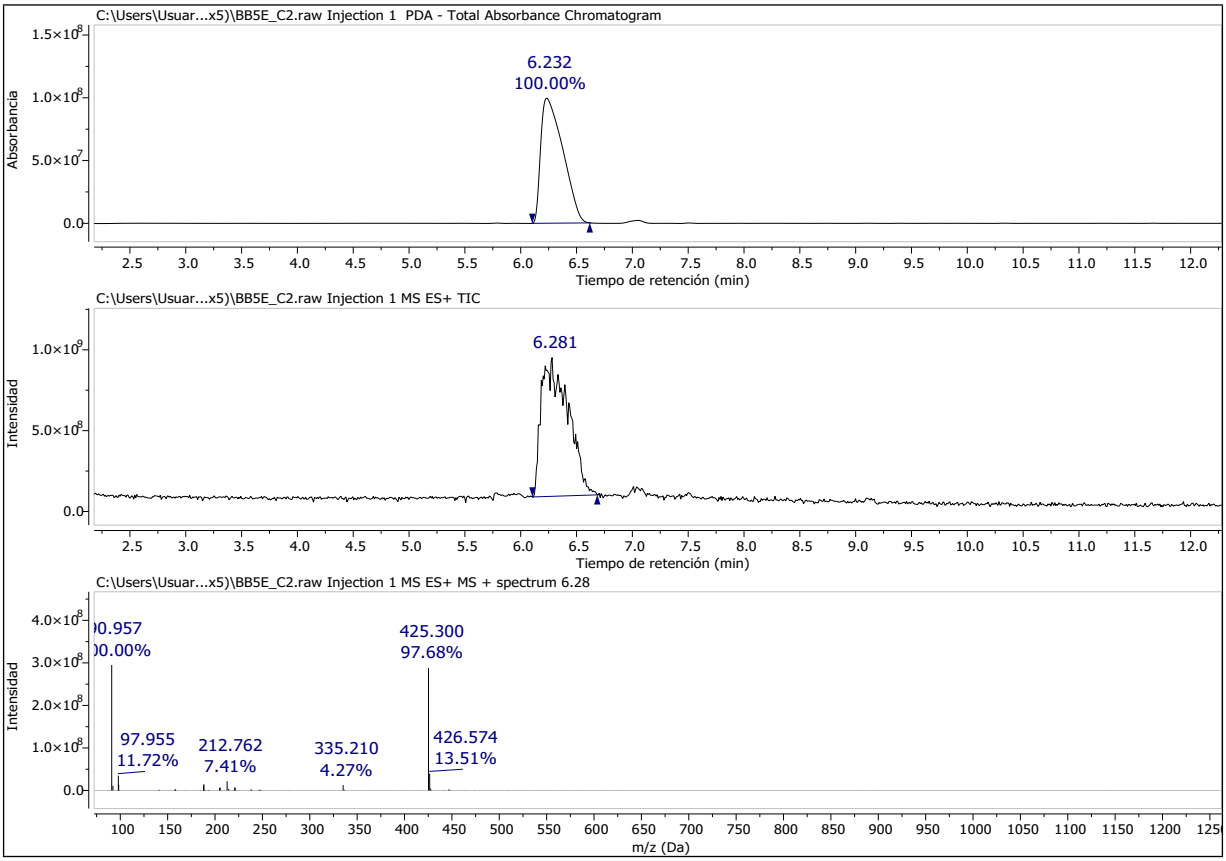


DEPT and HSQC spectra in $CDCl_3$ of **7**

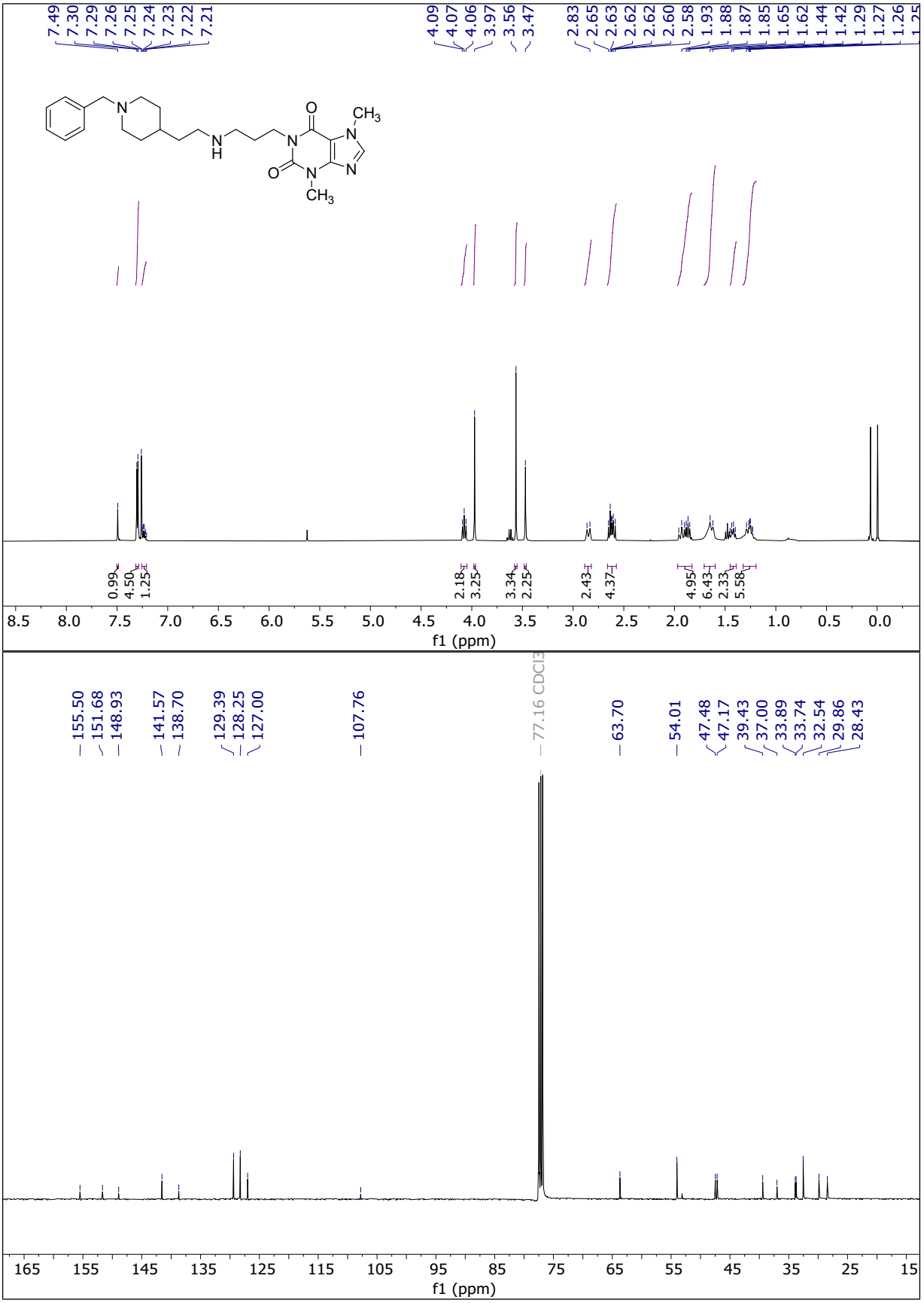




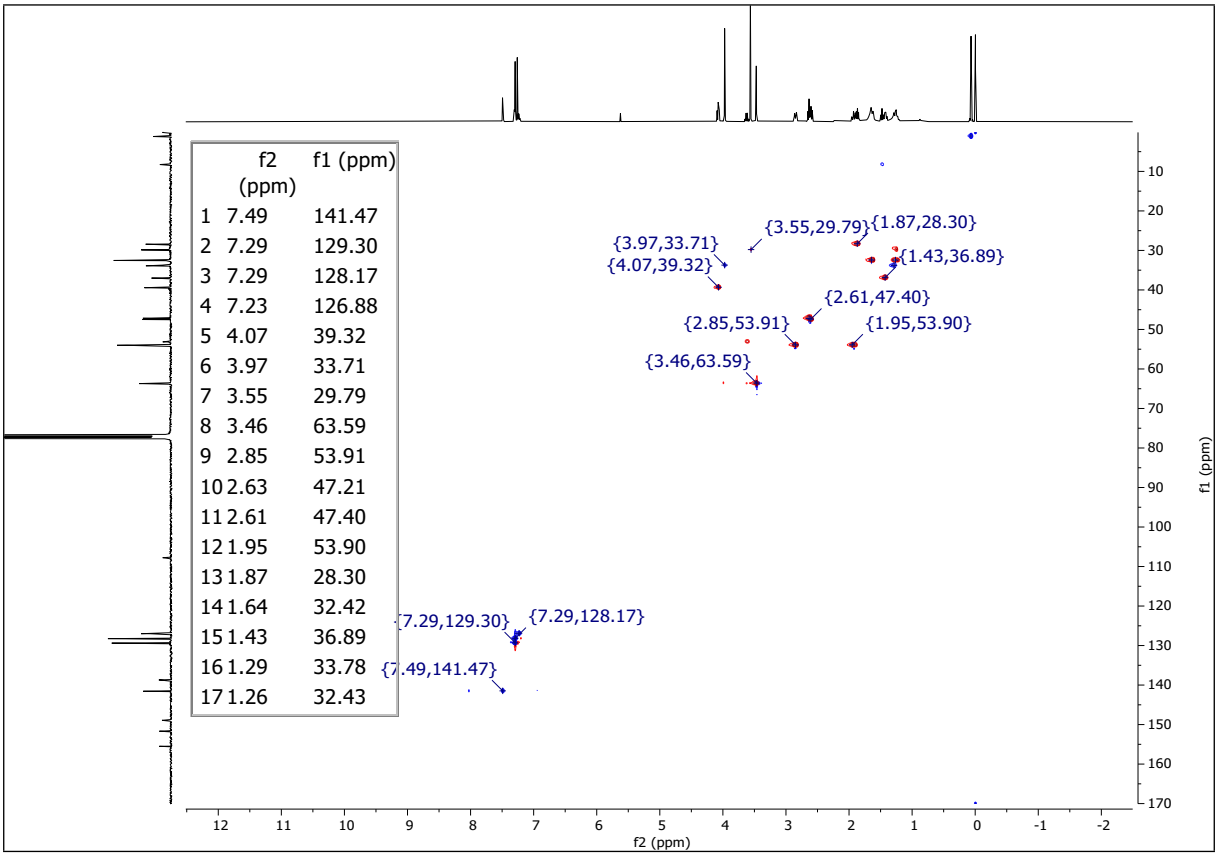
HPLC-UV/MS of **7**



^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in $CDCl_3$ of **8**

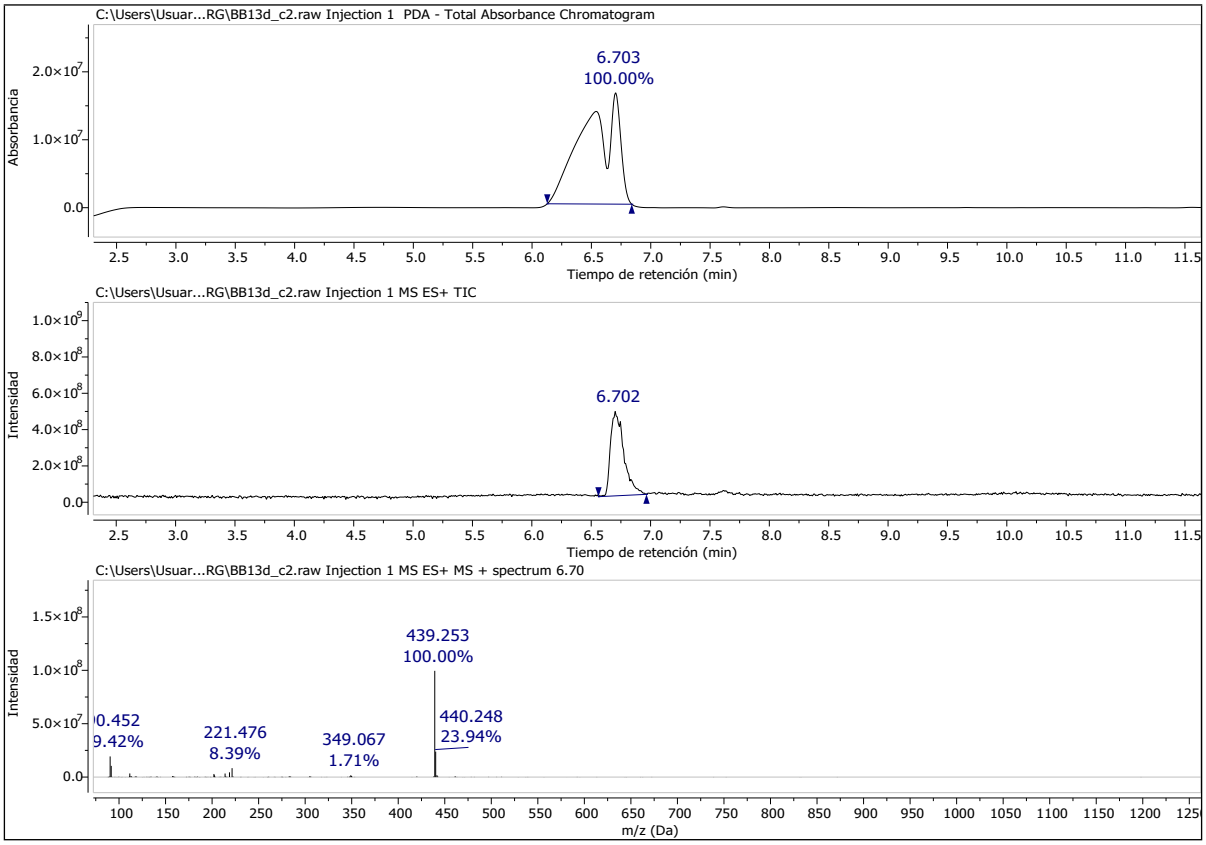


DEPT and HSQC spectra in $CDCl_3$ of **8**

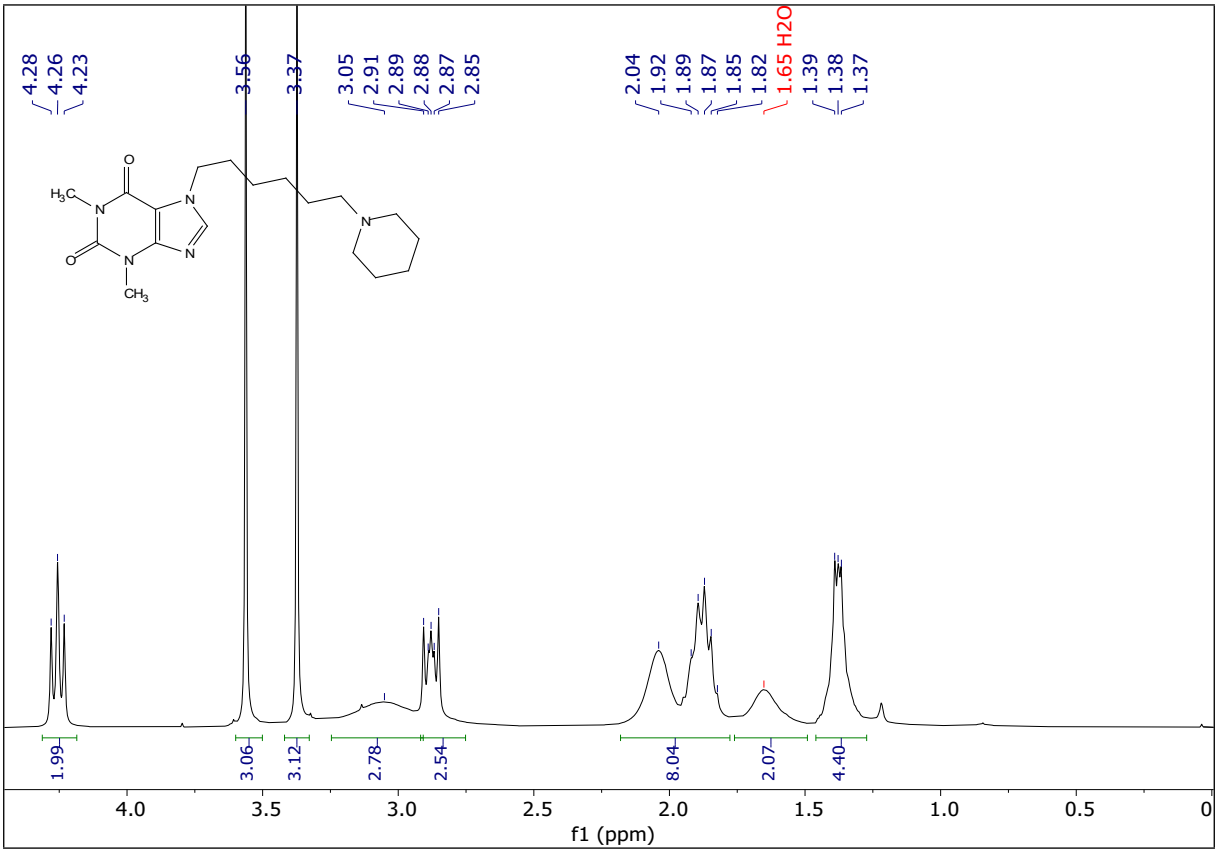


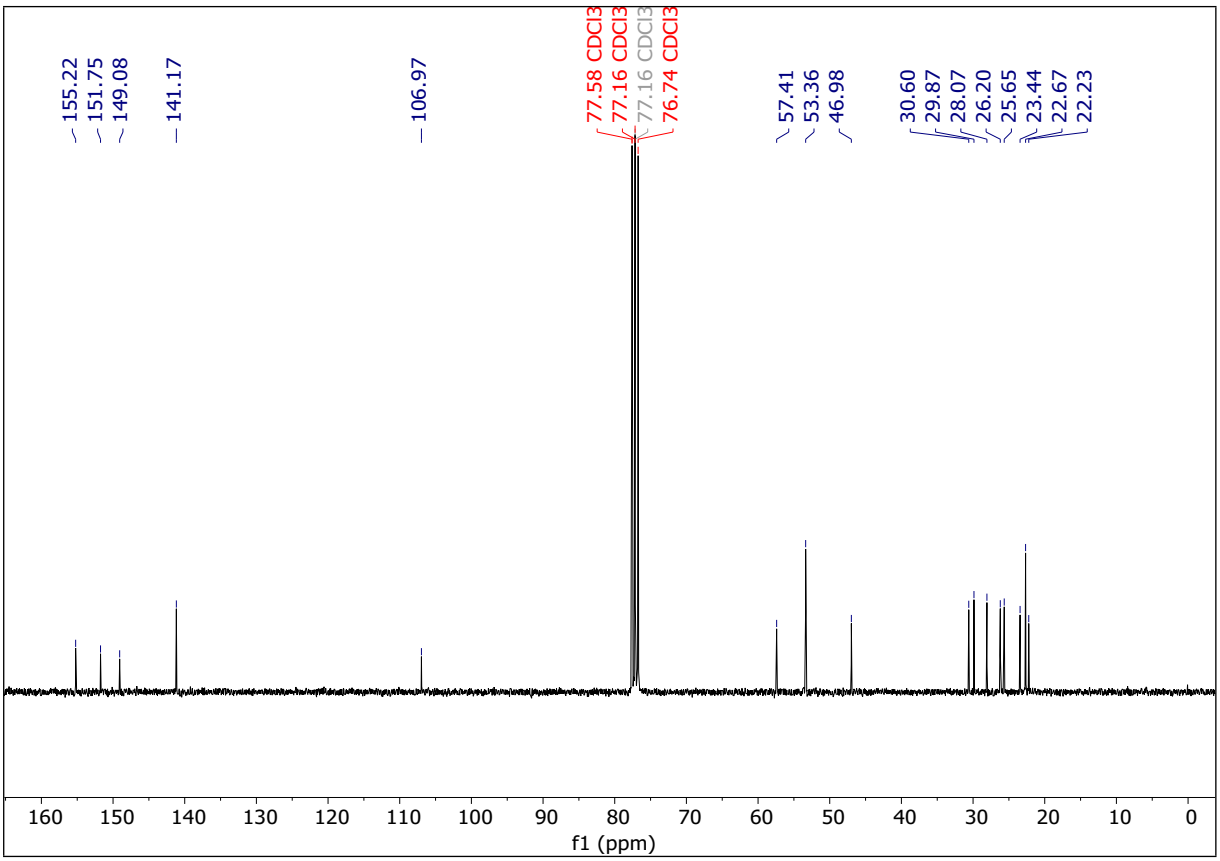
	f2 (ppm)	f1 (ppm)
1	7.49	141.47
2	7.29	129.30
3	7.29	128.17
4	7.23	126.88
5	4.07	39.32
6	3.97	33.71
7	3.55	29.79
8	3.46	63.59
9	2.85	53.91
10	2.63	47.21
11	2.61	47.40
12	1.95	53.90
13	1.87	28.30
14	1.64	32.42
15	1.43	36.89
16	1.29	33.78
17	1.26	32.43

HPLC-UV/MS of **8**

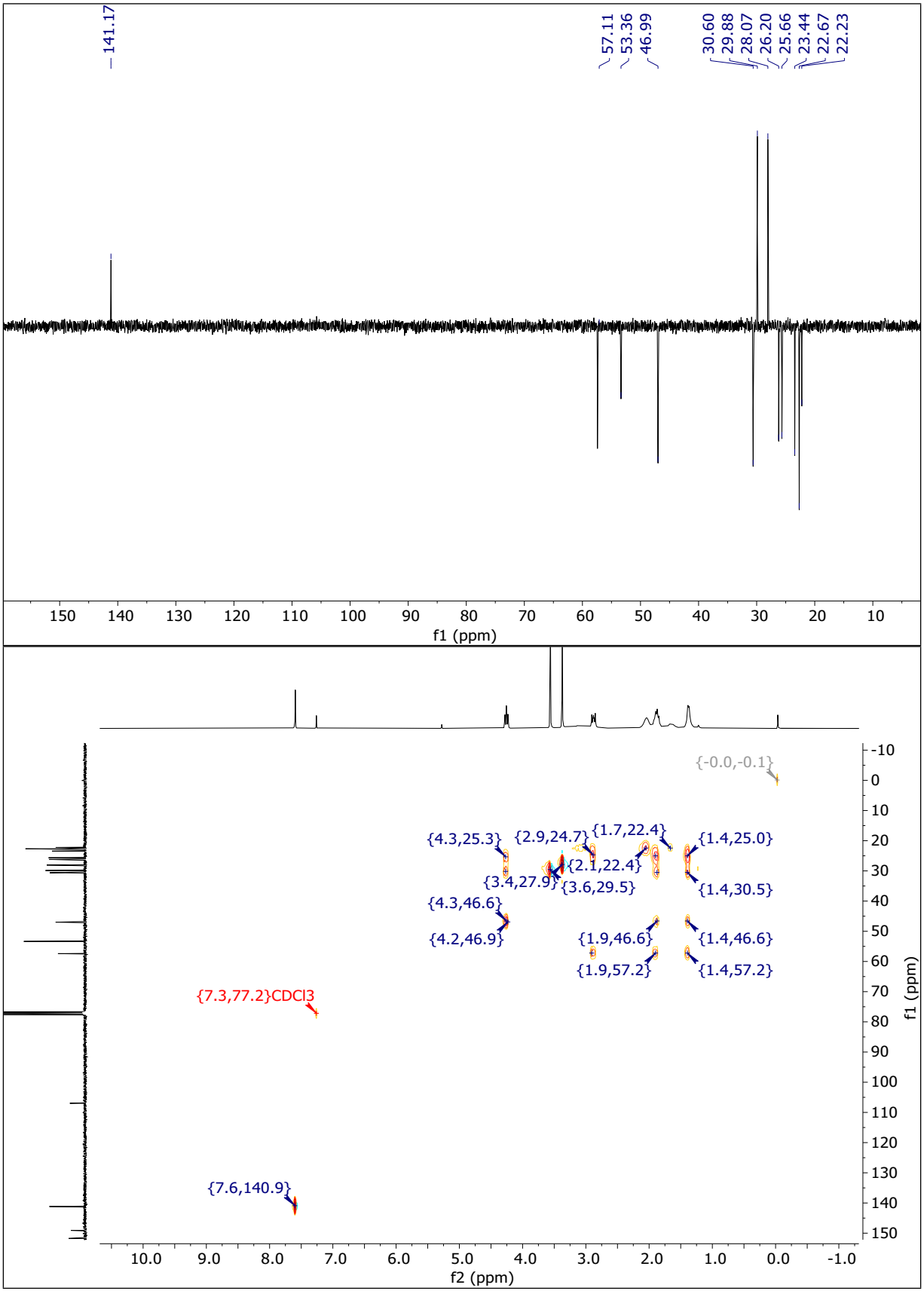


^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **9**





DEPT and HSQC spectra in $CDCl_3$ of **9**



HRMS (ESI-TOF) of **9**

Qualitative Compound Report

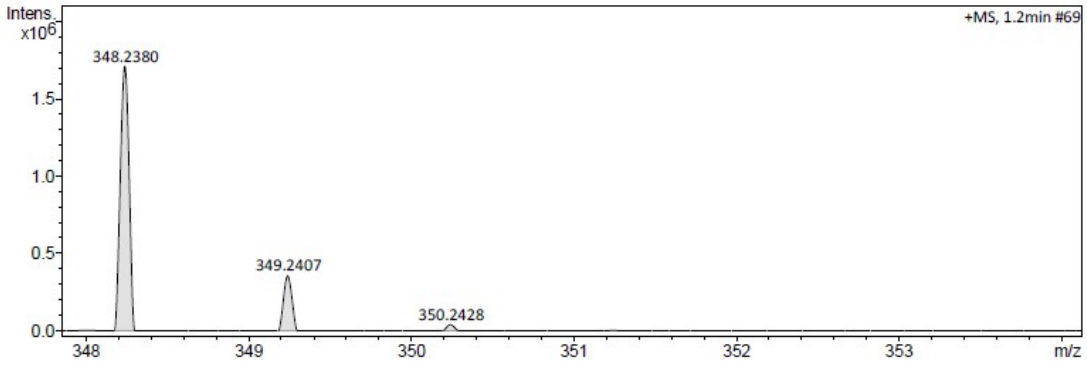
Analysis Info

Acquisition Date 12/27/2023 2:37:34 PM

Analysis Name	D:\Data\ggc\23-122610_P1-F-8_01_8413.d		
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122610	Instrument	micrOTOF-Q II
Comment	T6P Sv: MeOH + HCOOH Brunella Biscussi		

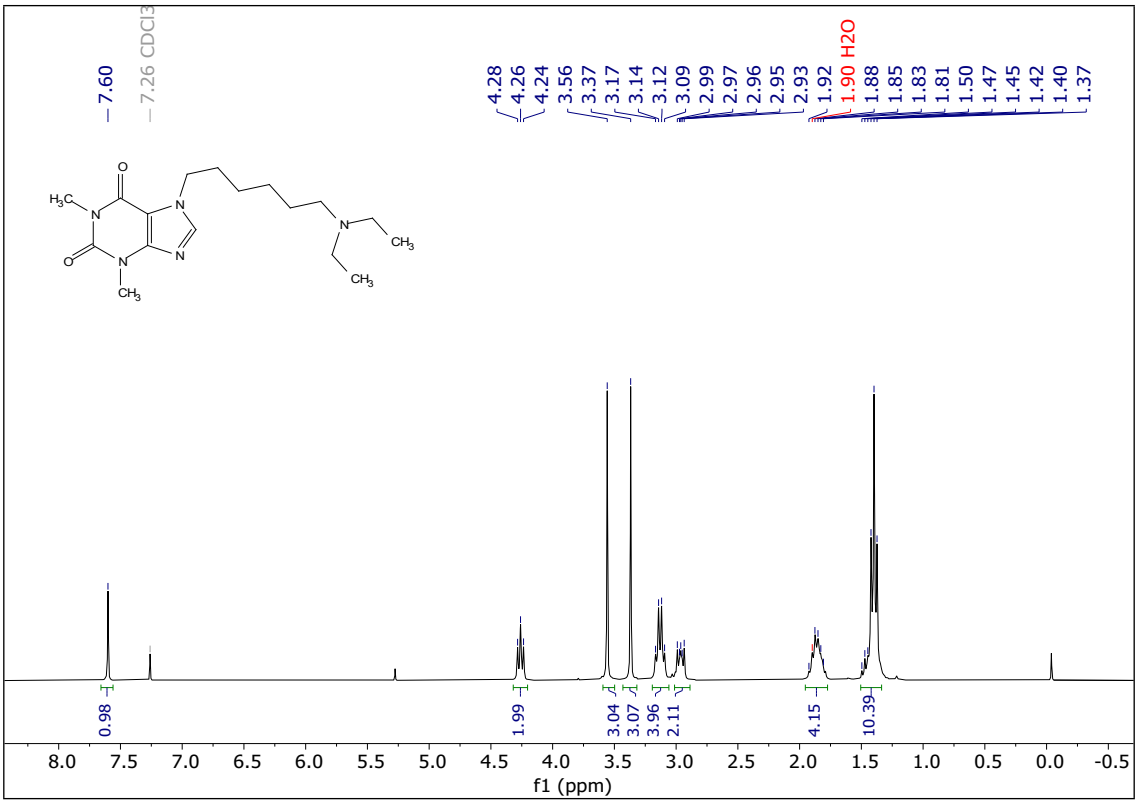
Acquisition Parameter

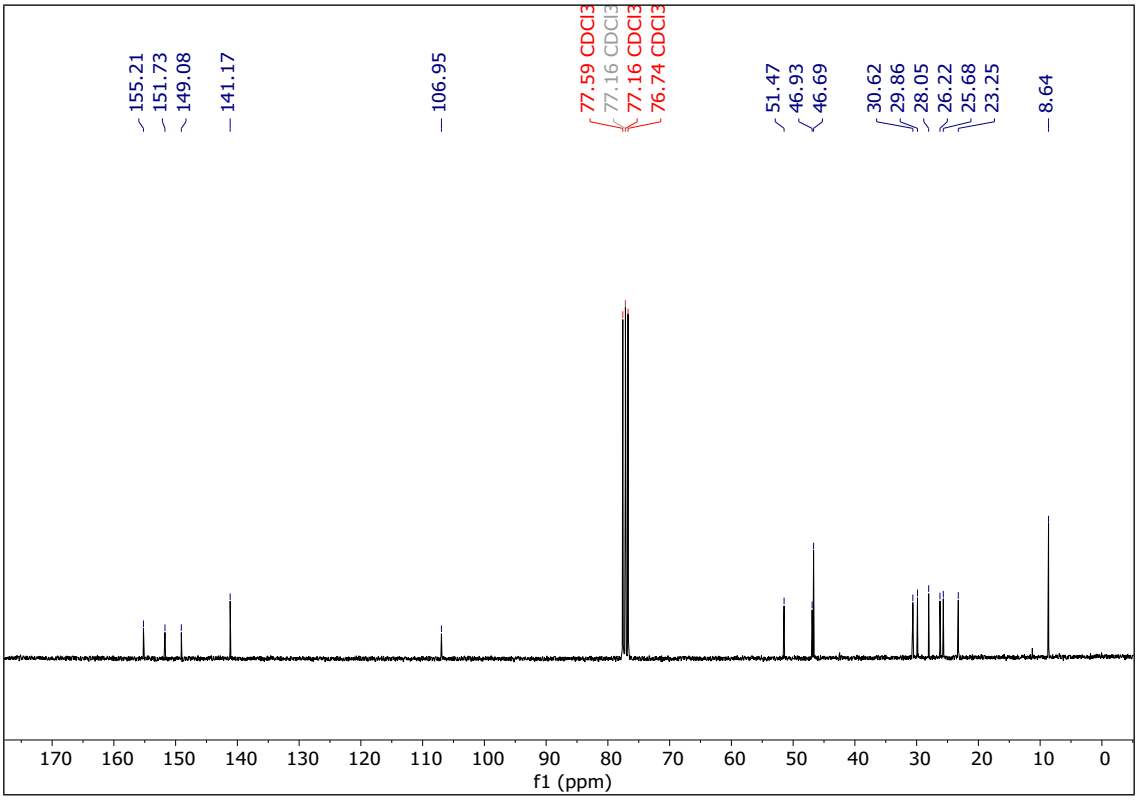
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



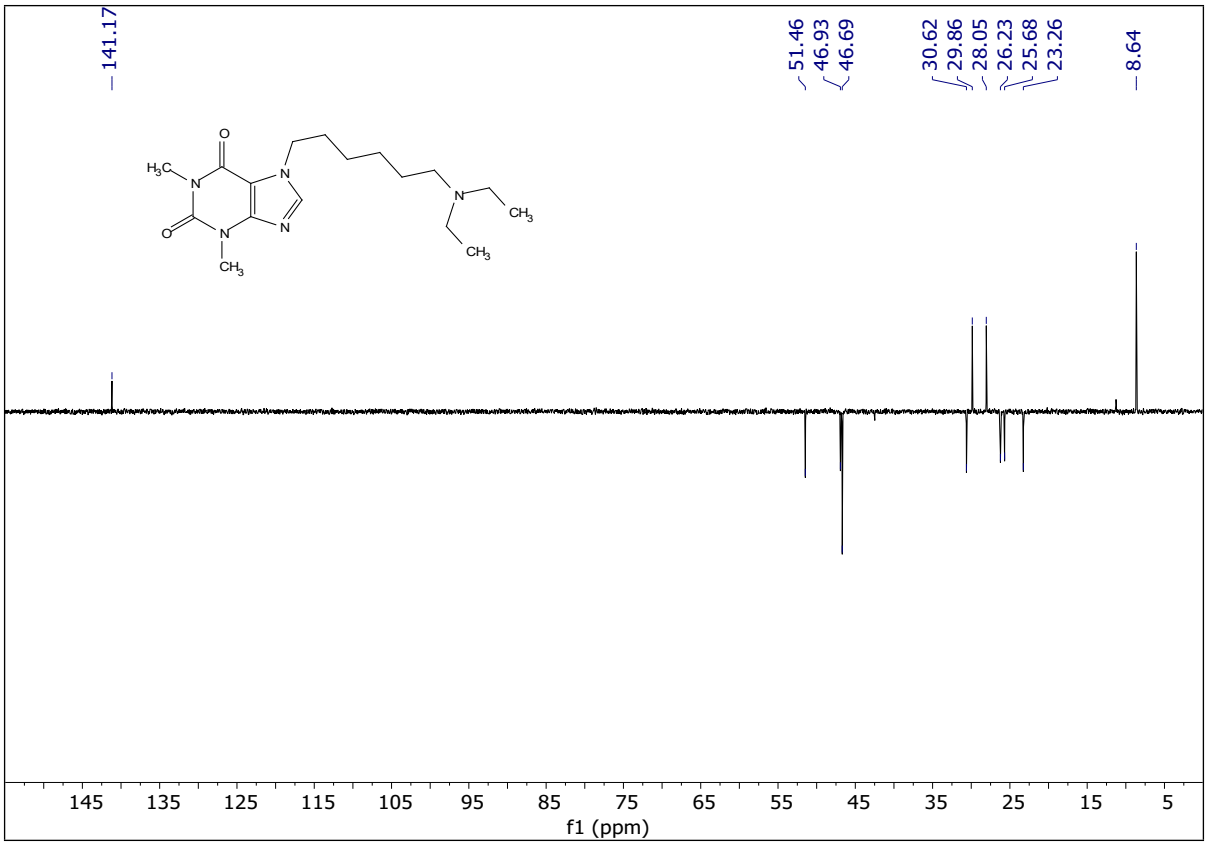
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
348.2380	1	C18H30N5O2	348.2394	4.1	6.4	1	51.71	6.5	even	ok

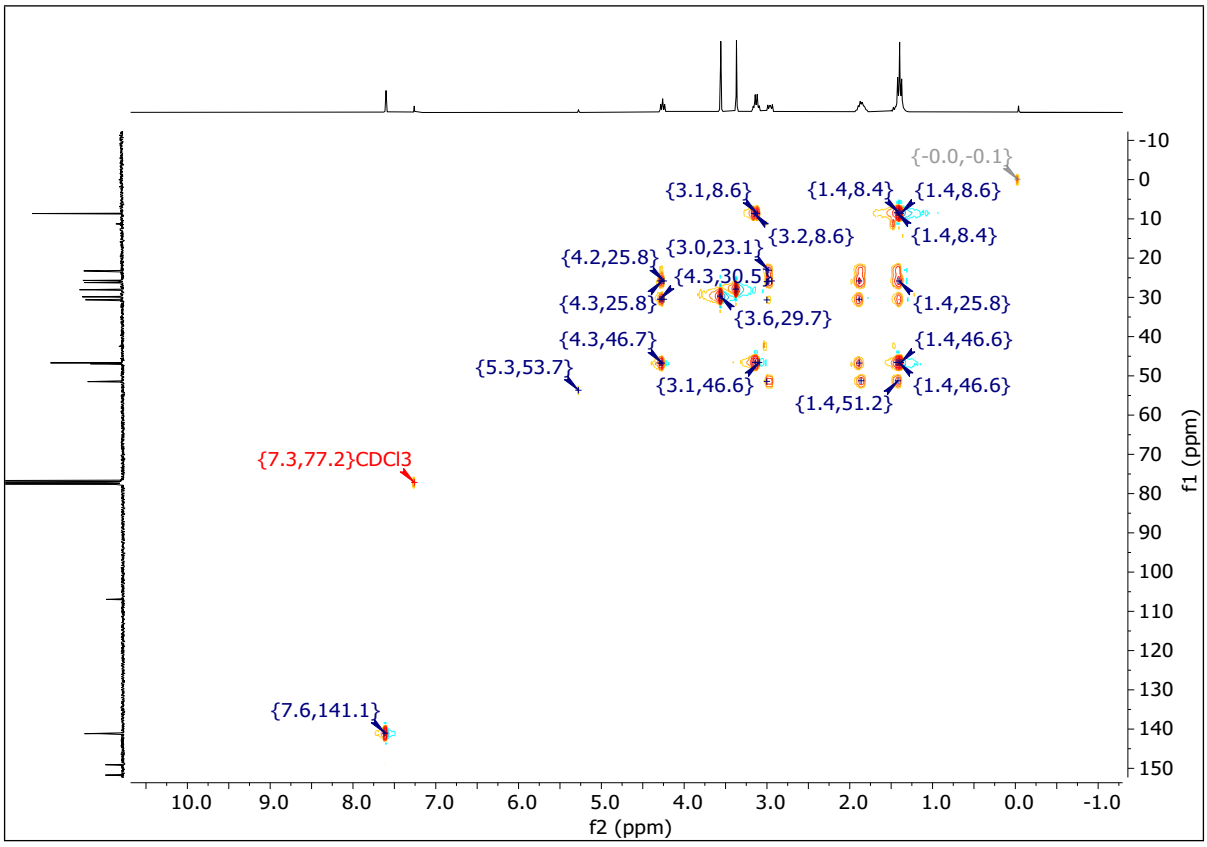
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **10**





DEPT and HSQC spectra in $CDCl_3$ of **10**





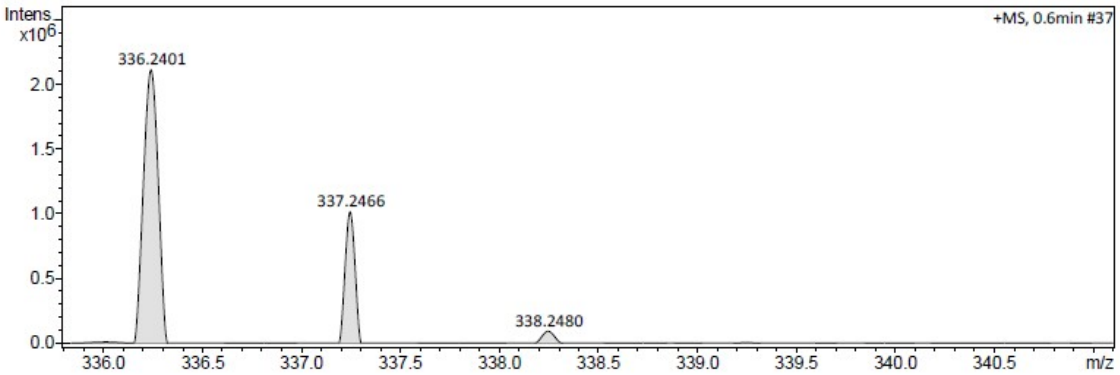
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122611_P1-F-9_01_8414.d	Acquisition Date	12/27/2023 2:42:42 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122611	Instrument	micrOTOF-Q II
Comment	T6D Sv: MeOH + HCOOH Brunella Biscussi		

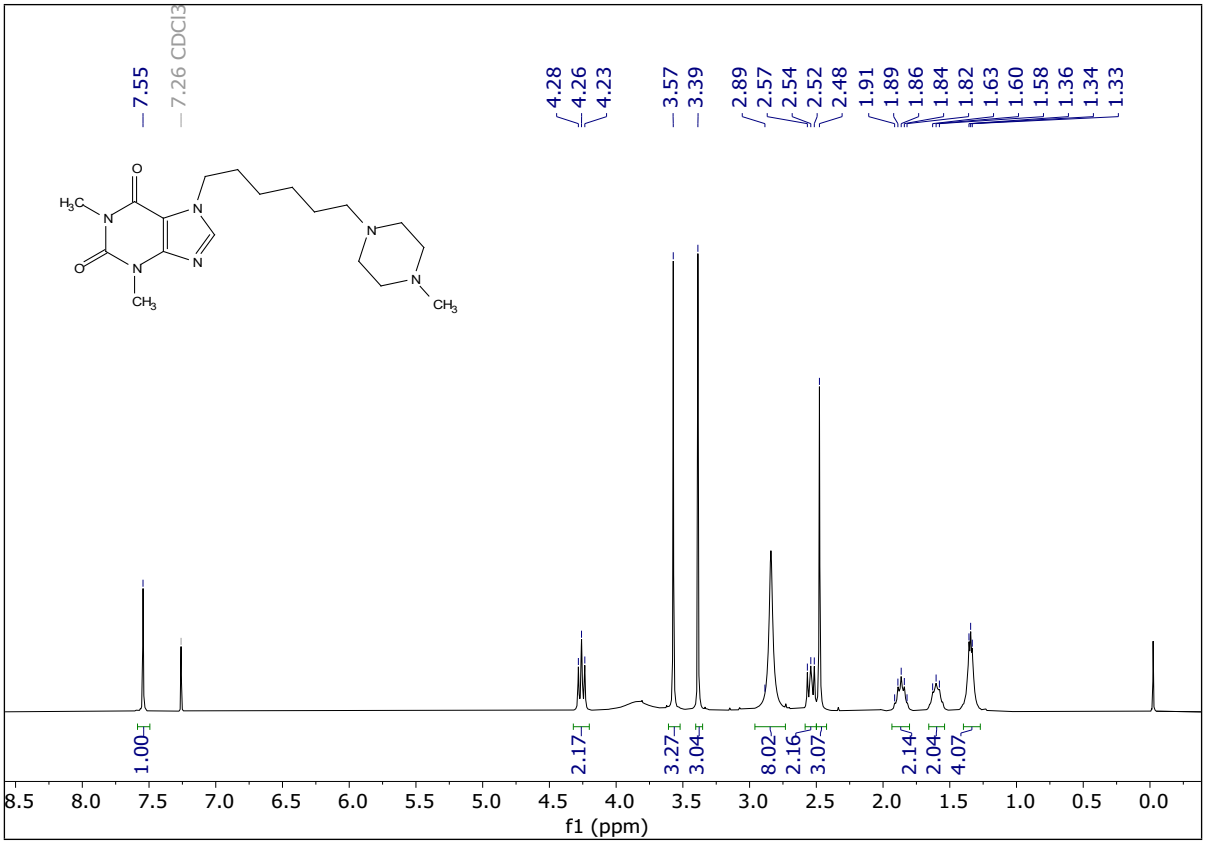
Acquisition Parameter

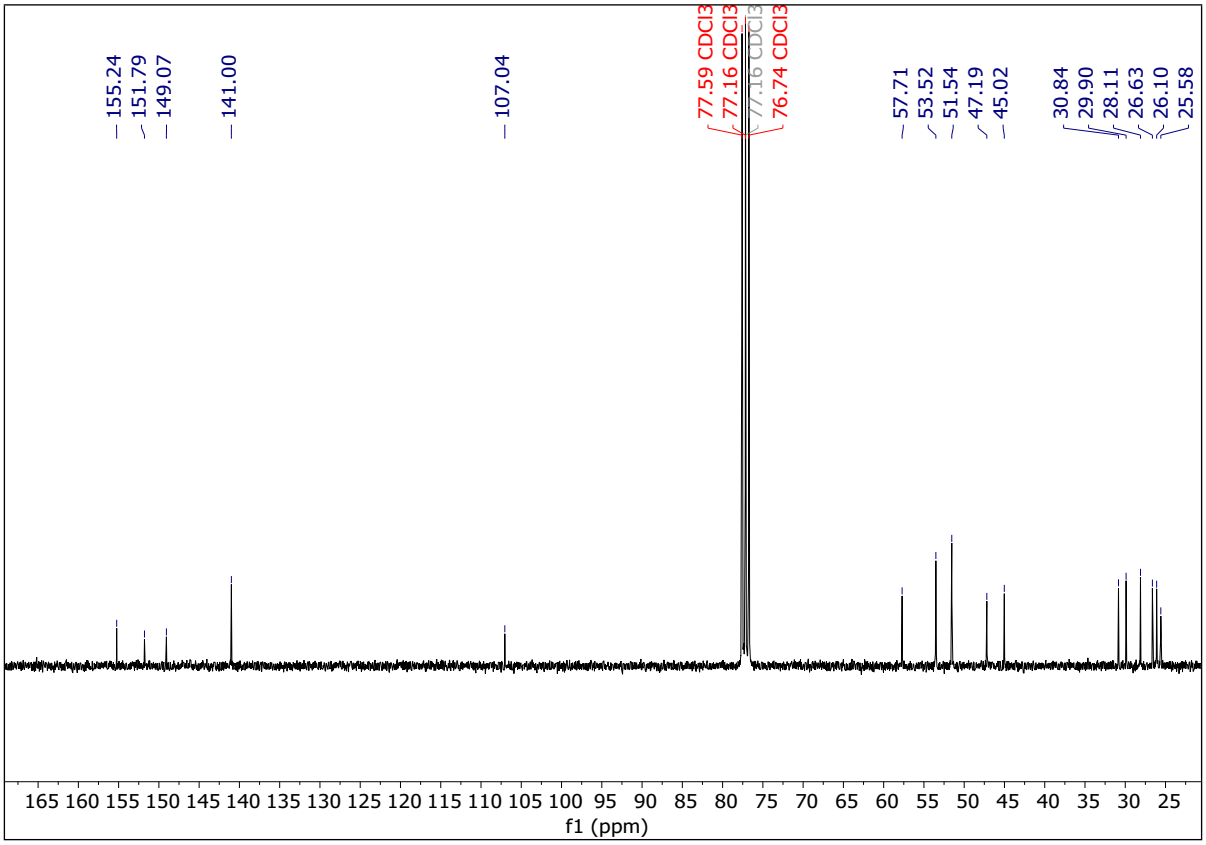
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



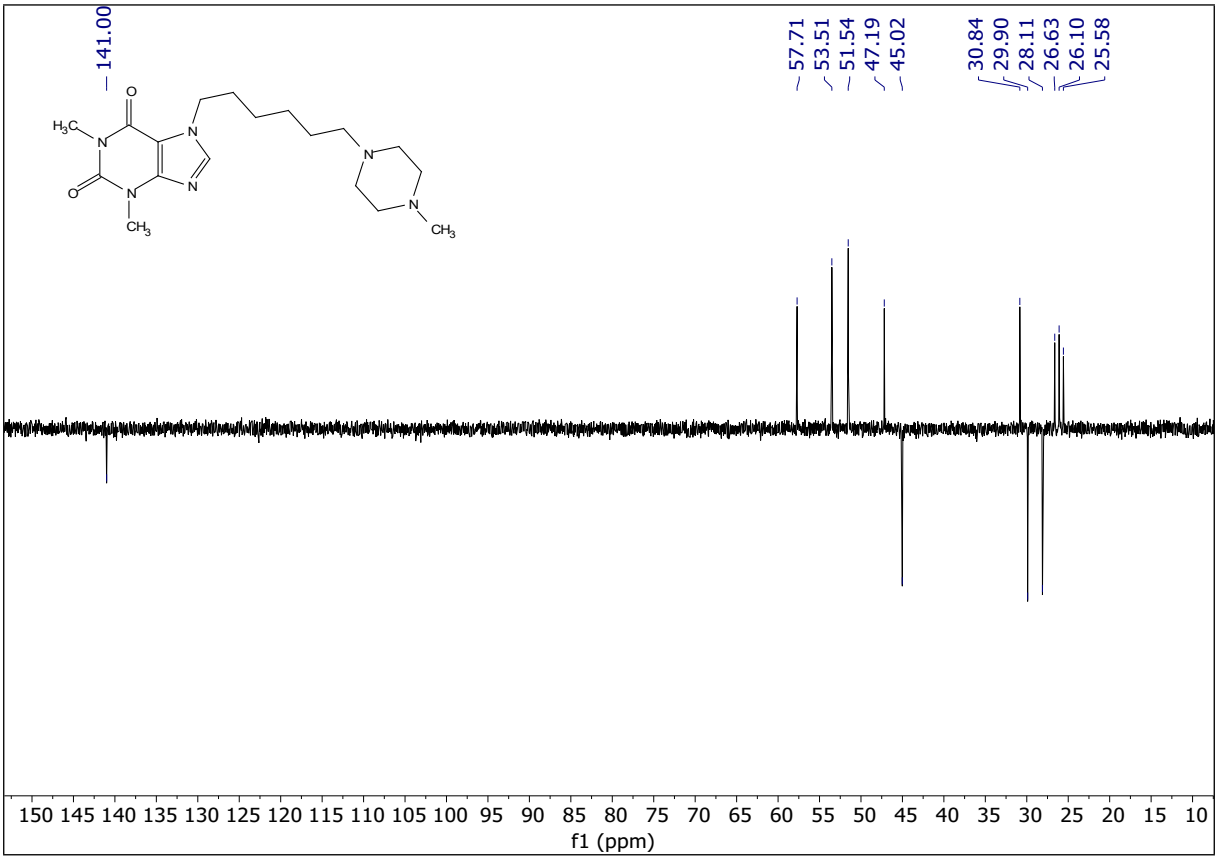
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
336.2401	1	C17H30N5O2	336.2394	-2.0	158.5	1	100.00	5.5	even	ok

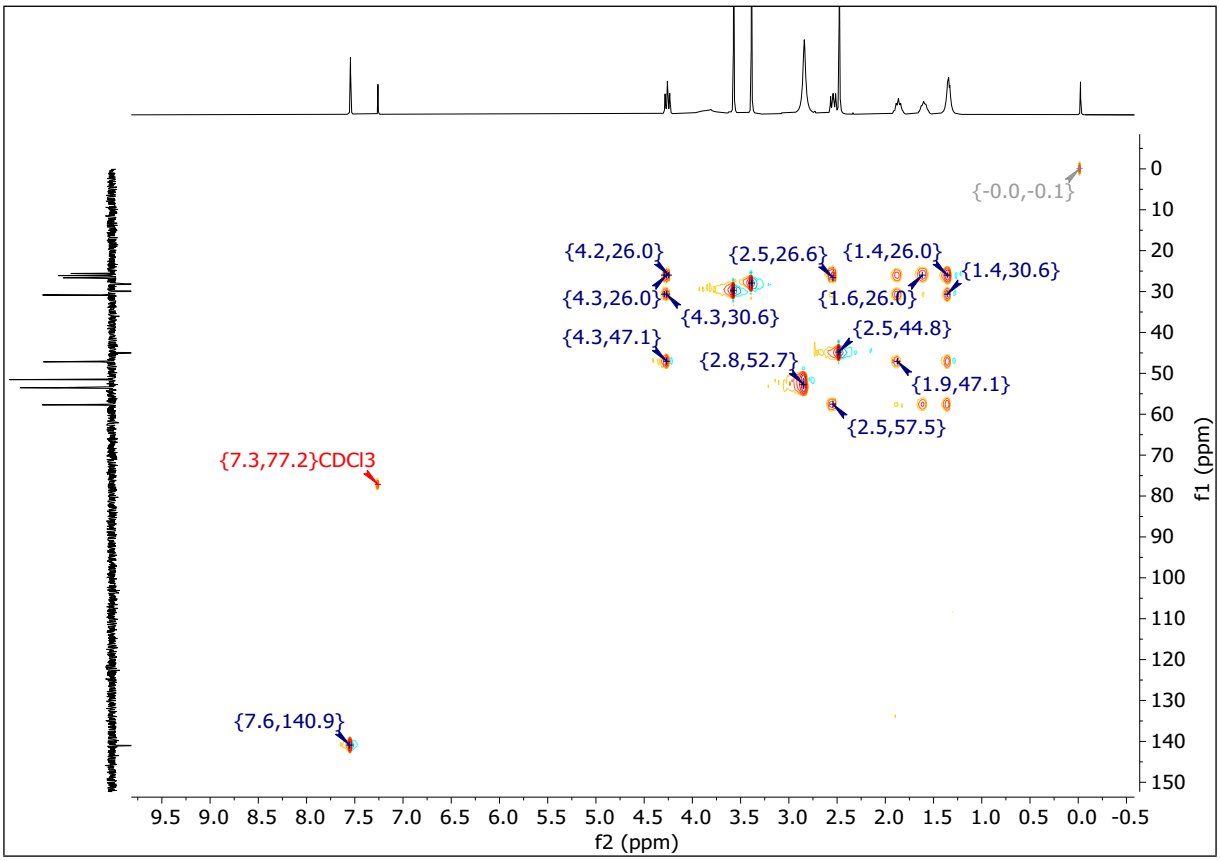
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **11**





DEPT and HSQC spectra in $CDCl_3$ of **11**





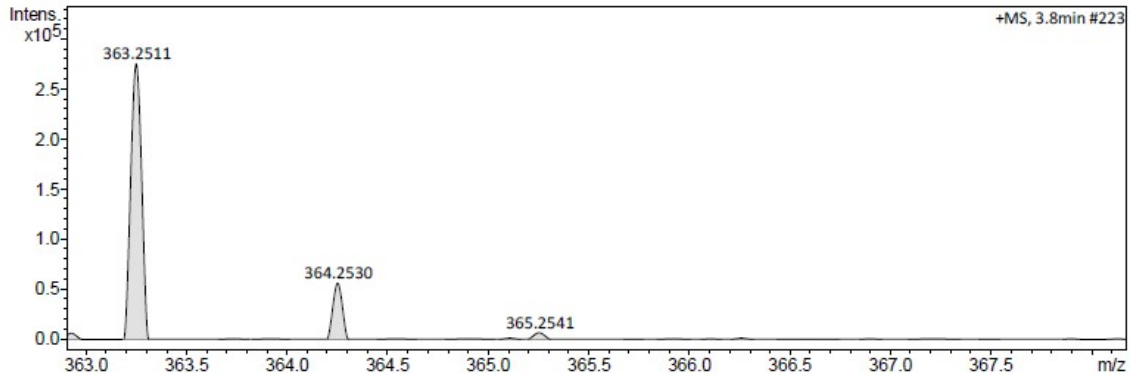
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122612_P1-C-1_01_8437.d	Acquisition Date	12/28/2023 1:18:54 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122612	Instrument	micrOTOF-Q II
Comment	T6MP Sv: MeOH + HCOOH Brunella Biscussi		

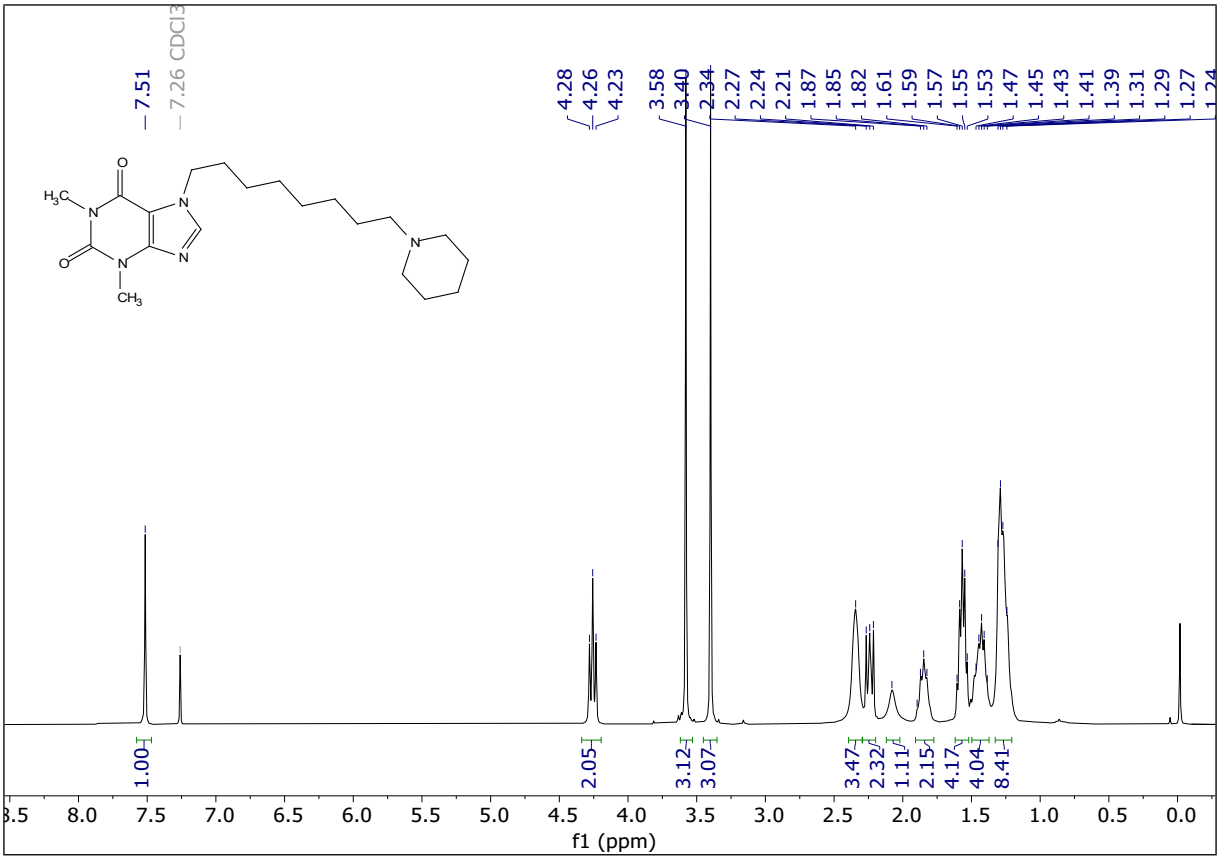
Acquisition Parameter

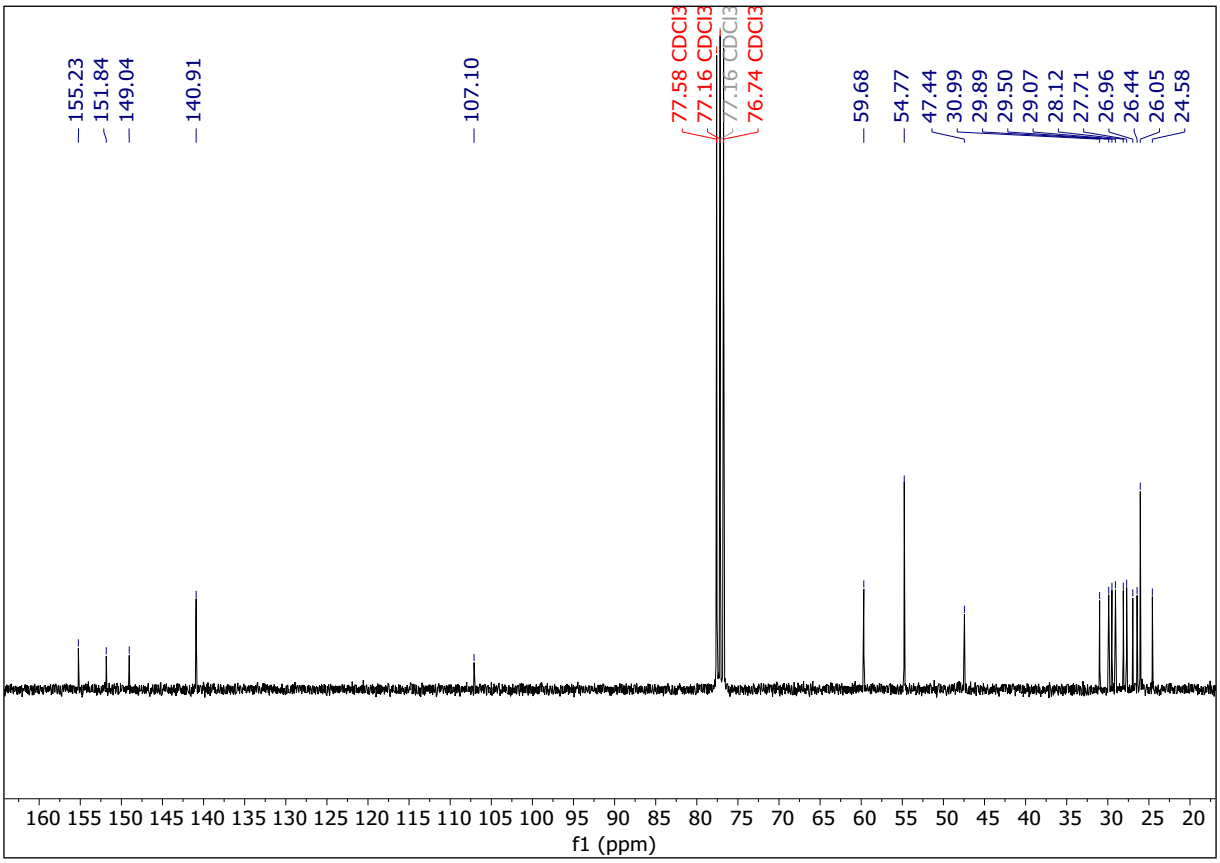
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



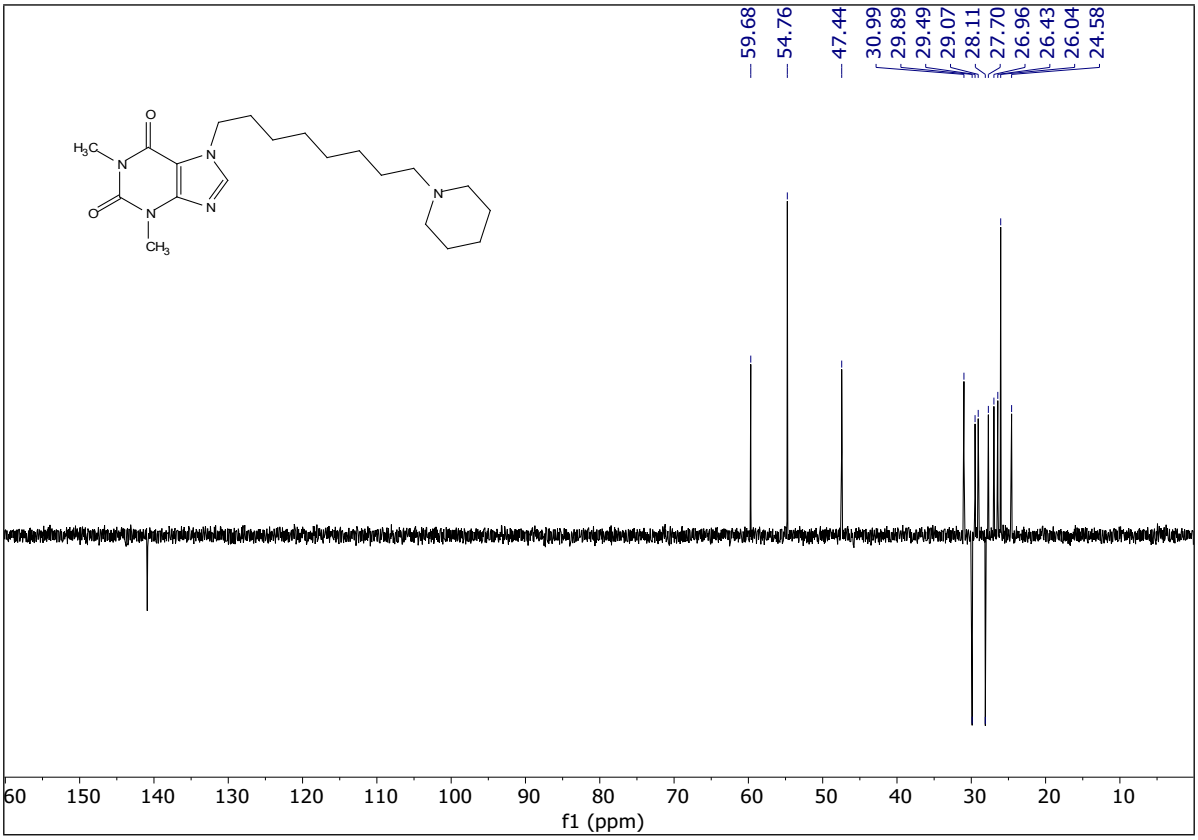
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
363.2511	1	C18H31N6O2	363.2503	-2.1	10.2	1	100.00	6.5	even	ok

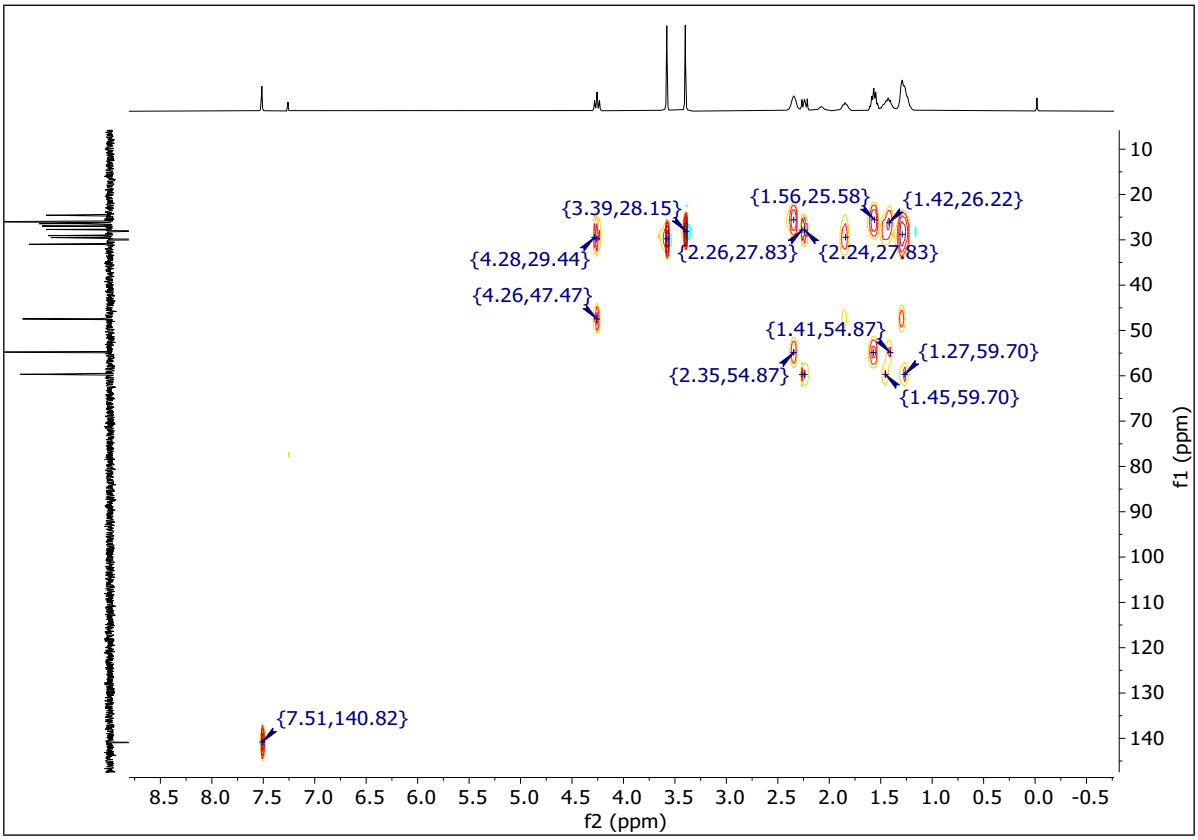
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **12**





DEPT and HSQC spectra in $CDCl_3$ of **12**





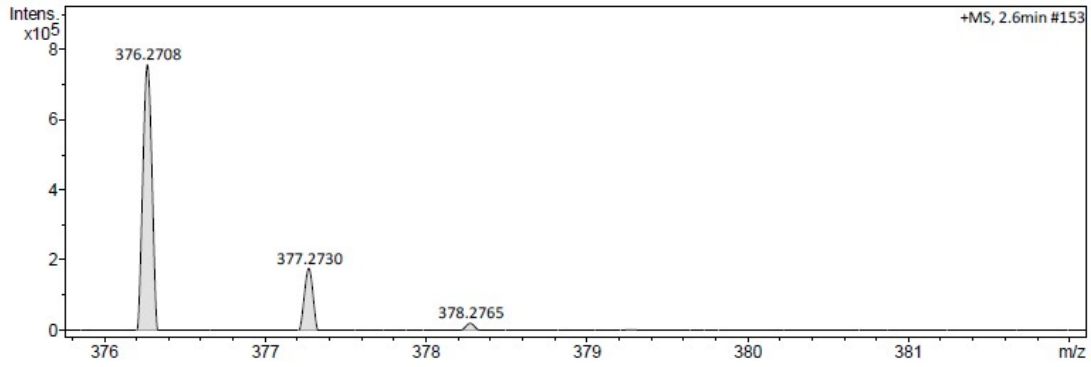
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122617_P1-B-5_01_8442.d	Acquisition Date	12/28/2023 1:44:32 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122617	Instrument	micrOTOF-Q II
Comment	T8P Sv: MeOH + HCOOH Brunella Biscussi		

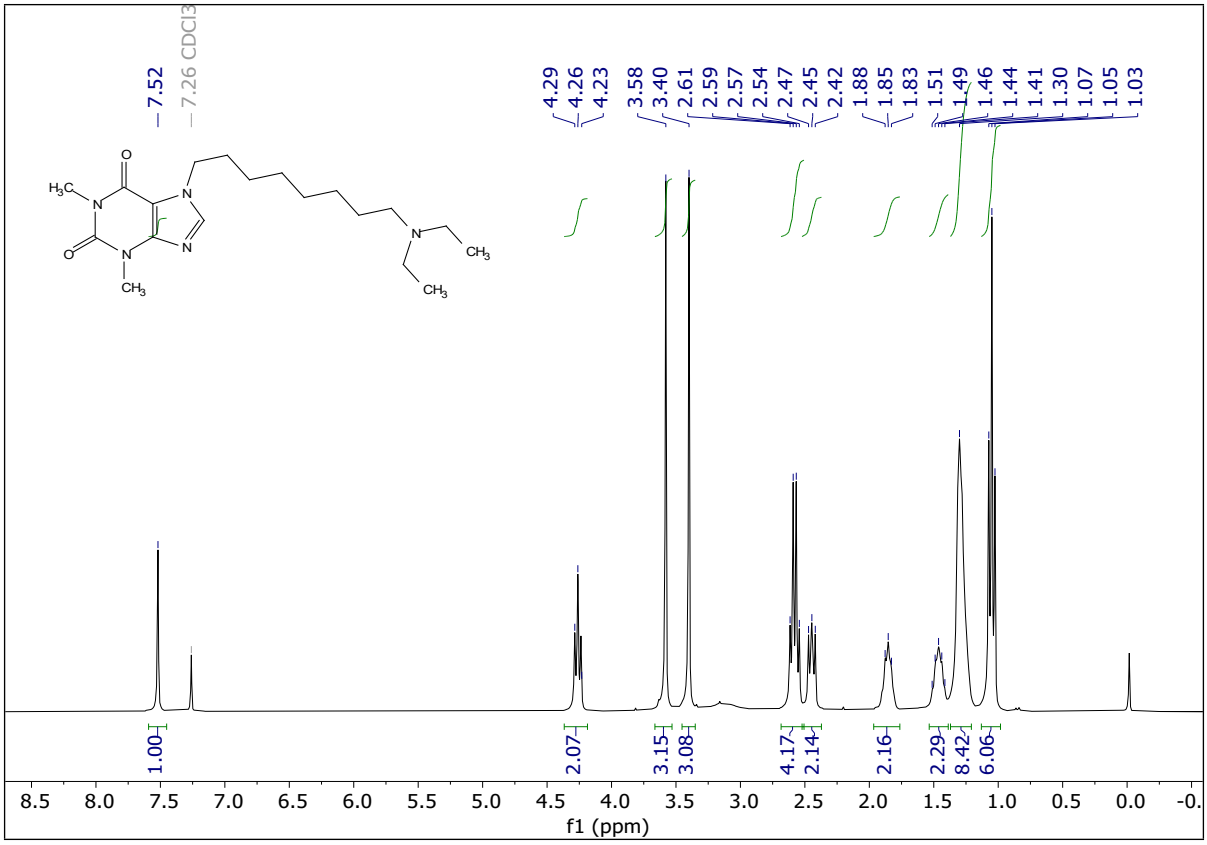
Acquisition Parameter

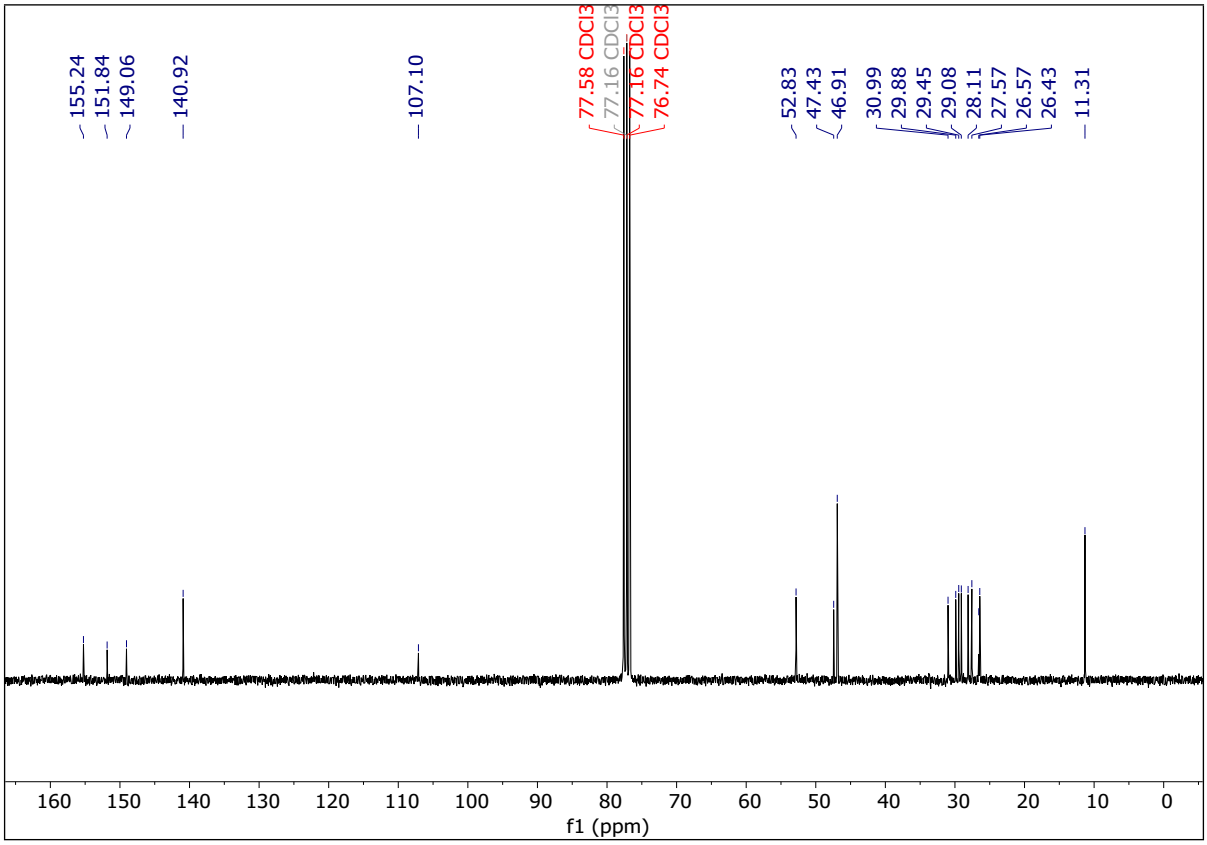
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



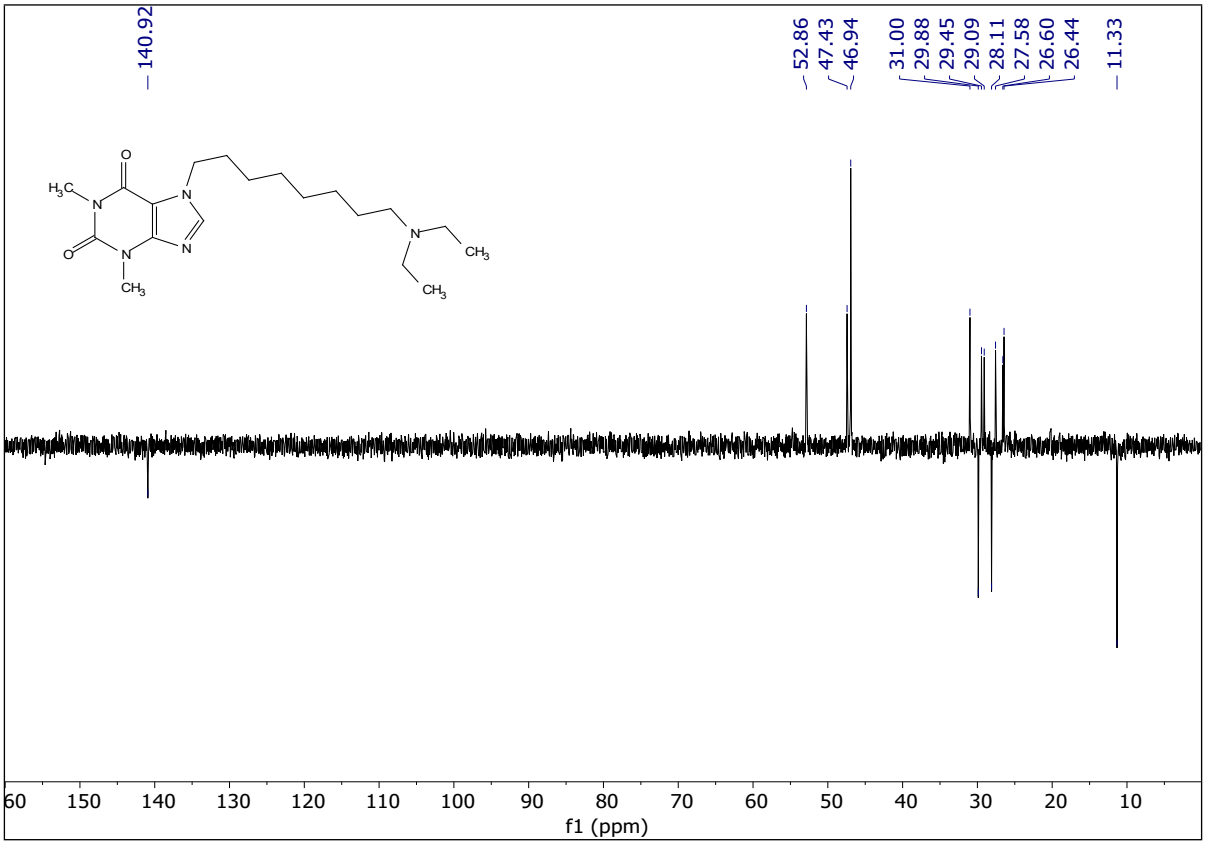
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
376.2708	1	C20H34N5O2	376.2707	-0.3	4.4	2	100.00	6.5	even	ok

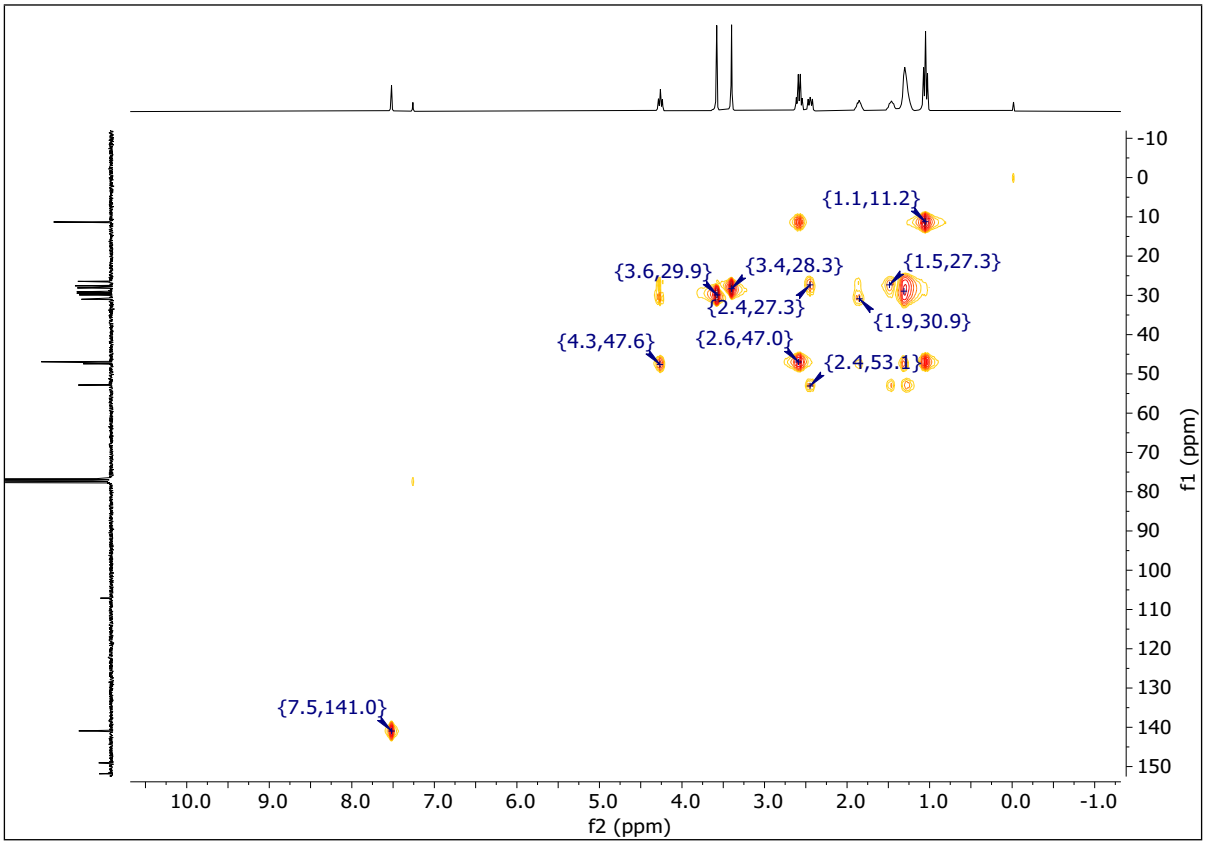
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **13**





DEPT and HSQC spectra in $CDCl_3$ of **13**





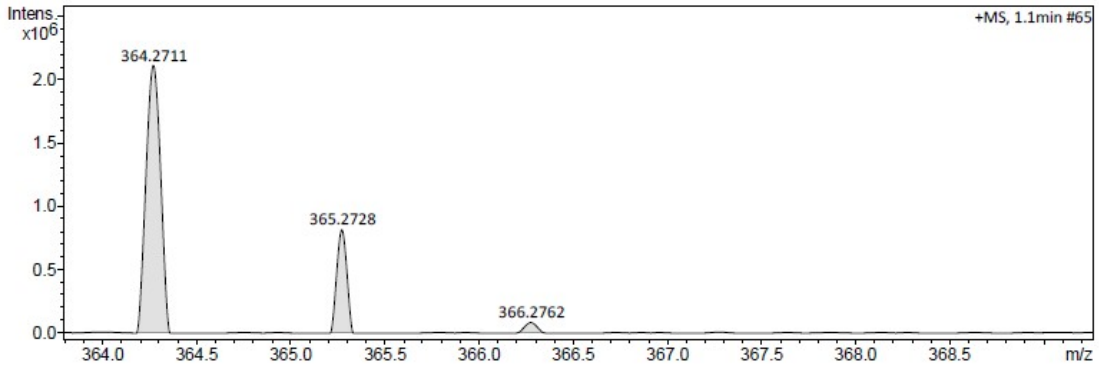
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122618_P1-B-6_01_8443.d	Acquisition Date	12/28/2023 1:49:41 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122618	Instrument	micrOTOF-Q II
Comment	T8D Sv: MeOH + HCOOH Brunella Biscussi		

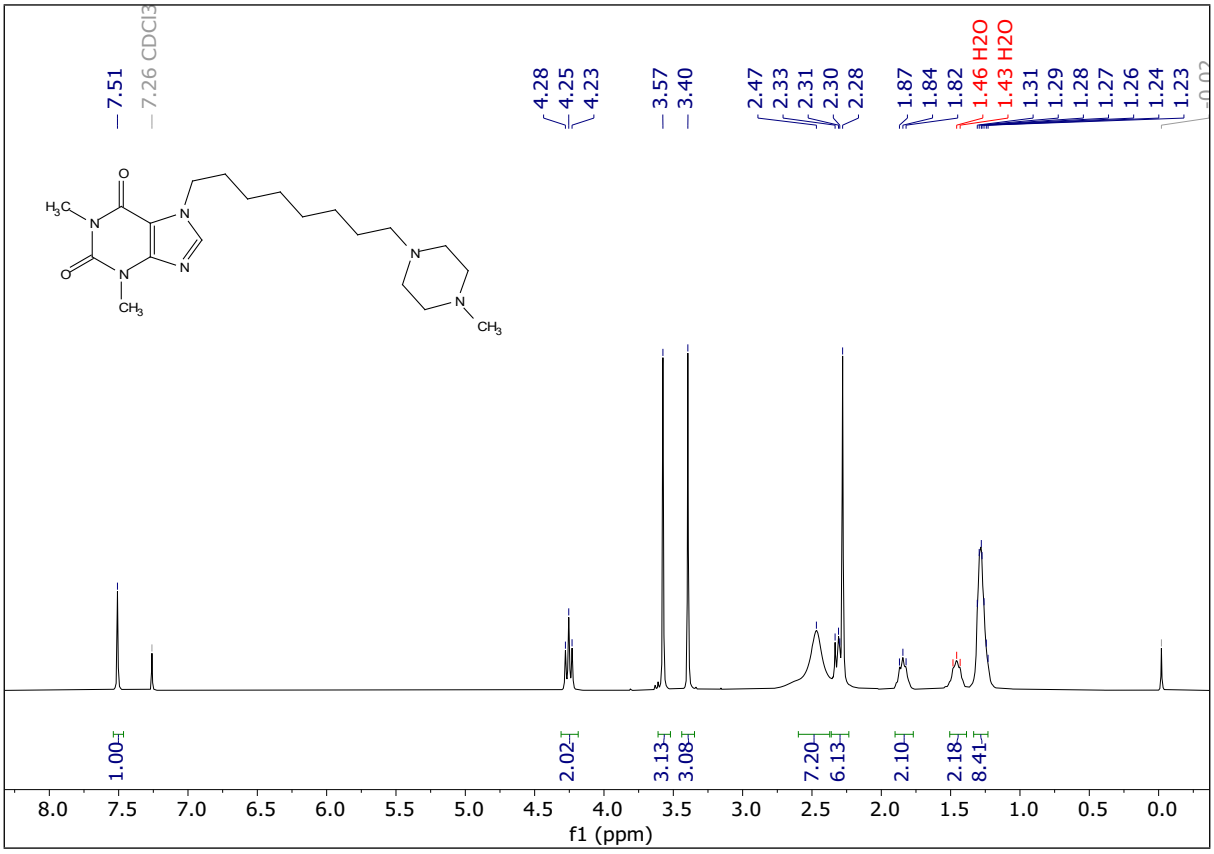
Acquisition Parameter

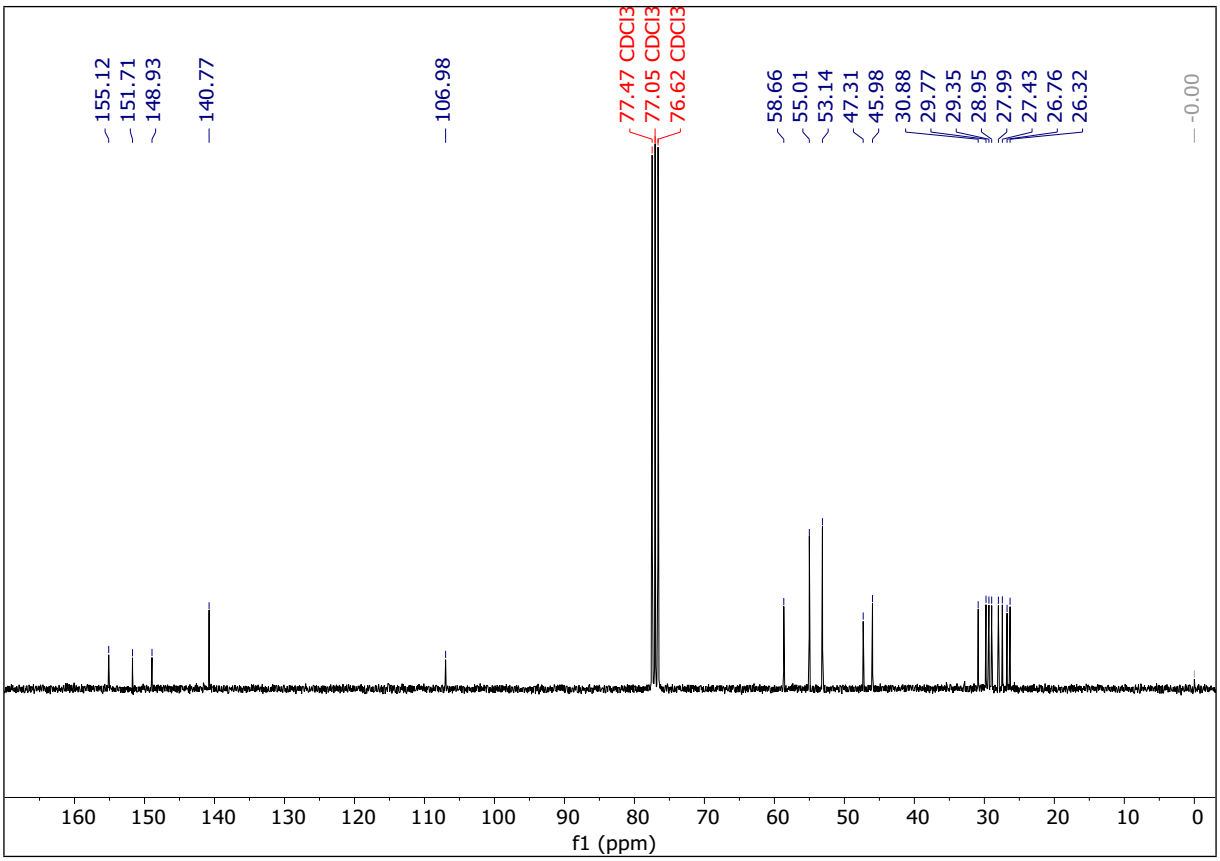
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



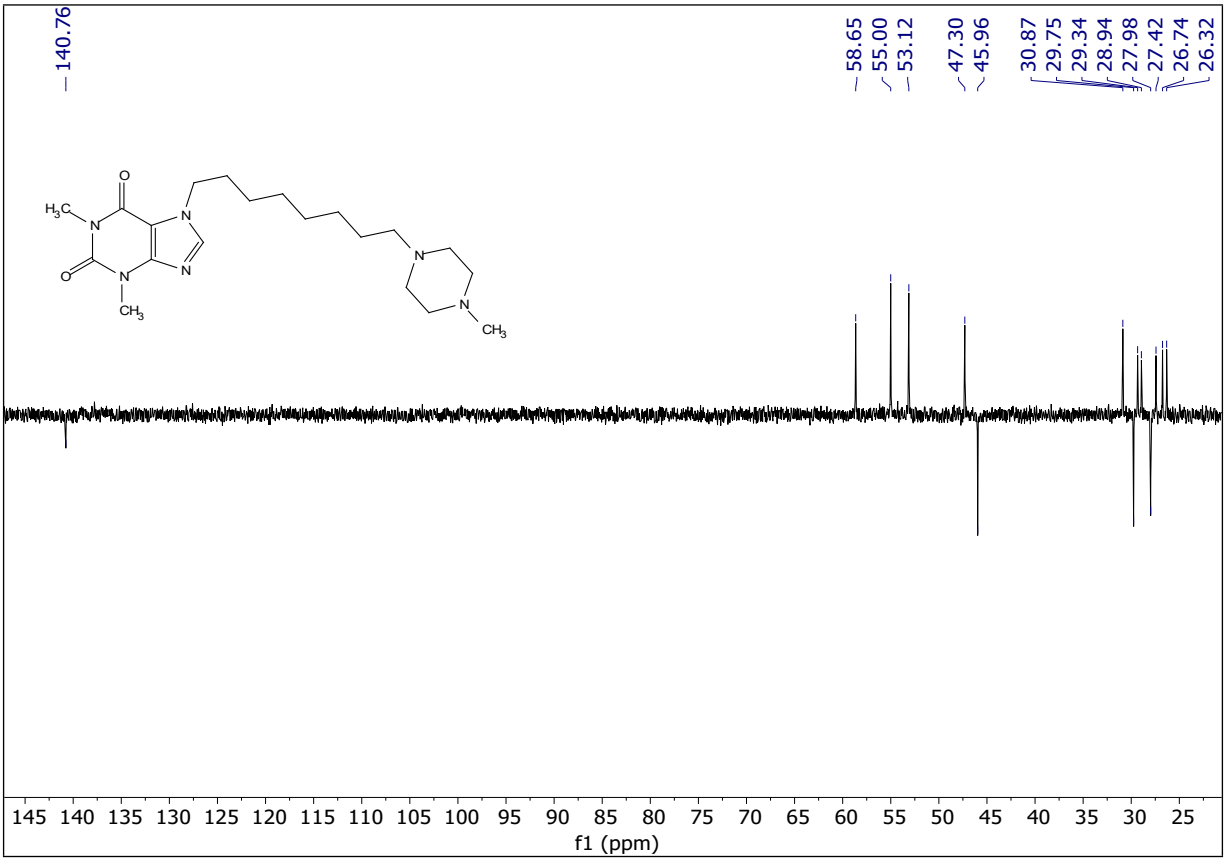
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
364.2711	1	C19H34N5O2	364.2707	-1.0	90.9	2	100.00	5.5	even	ok

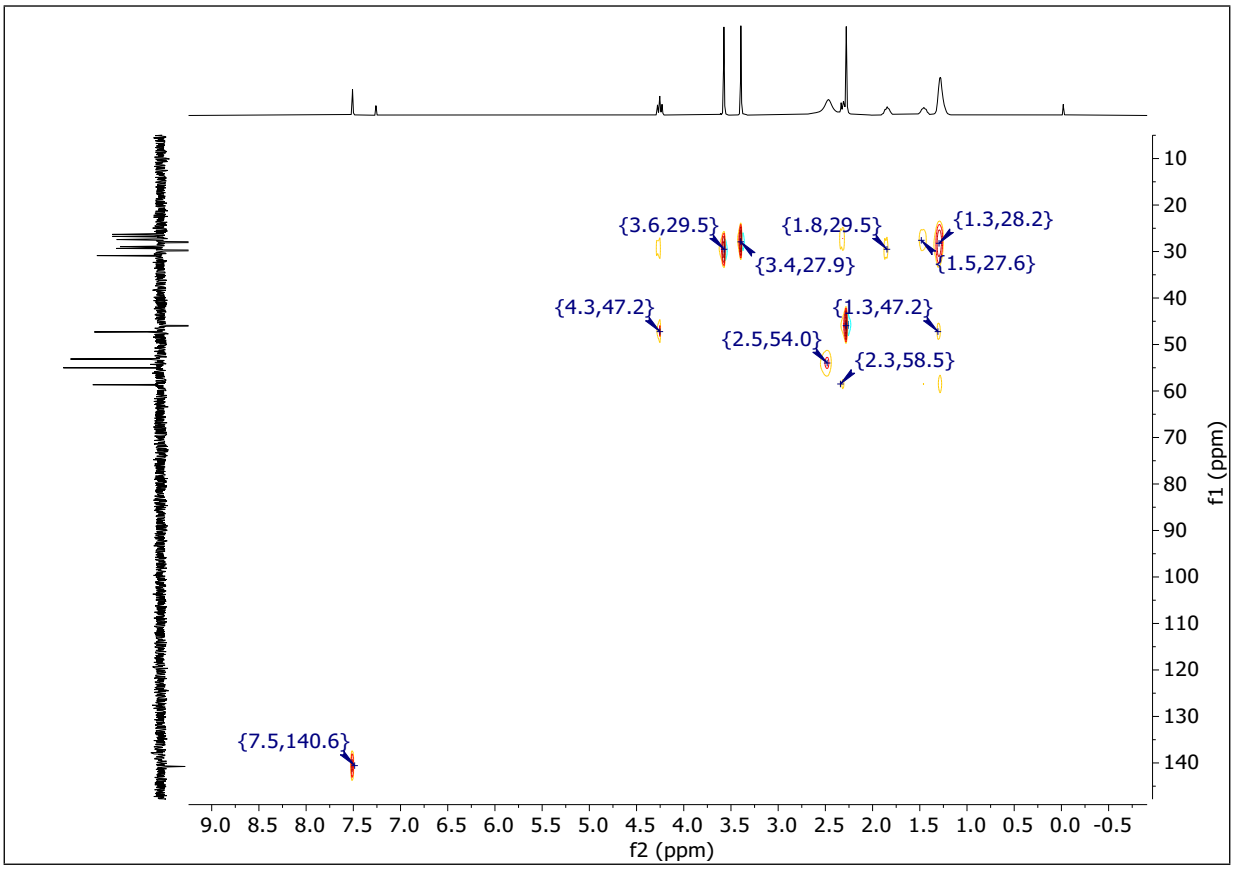
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **14**





DEPT and HSQC spectra in $CDCl_3$ of **14**





HRMS (ESI-TOF) of **14**

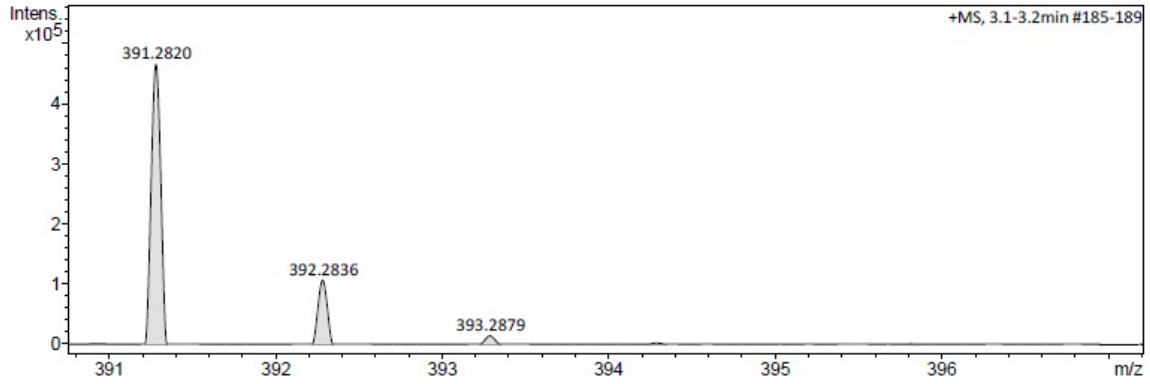
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122619_P1-B-7_01_8444.d	Acquisition Date	12/28/2023 1:54:50 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122619	Instrument	micrOTOF-Q II
Comment	T8MP Sv: MeOH + HCOOH Brunella Biscussi		

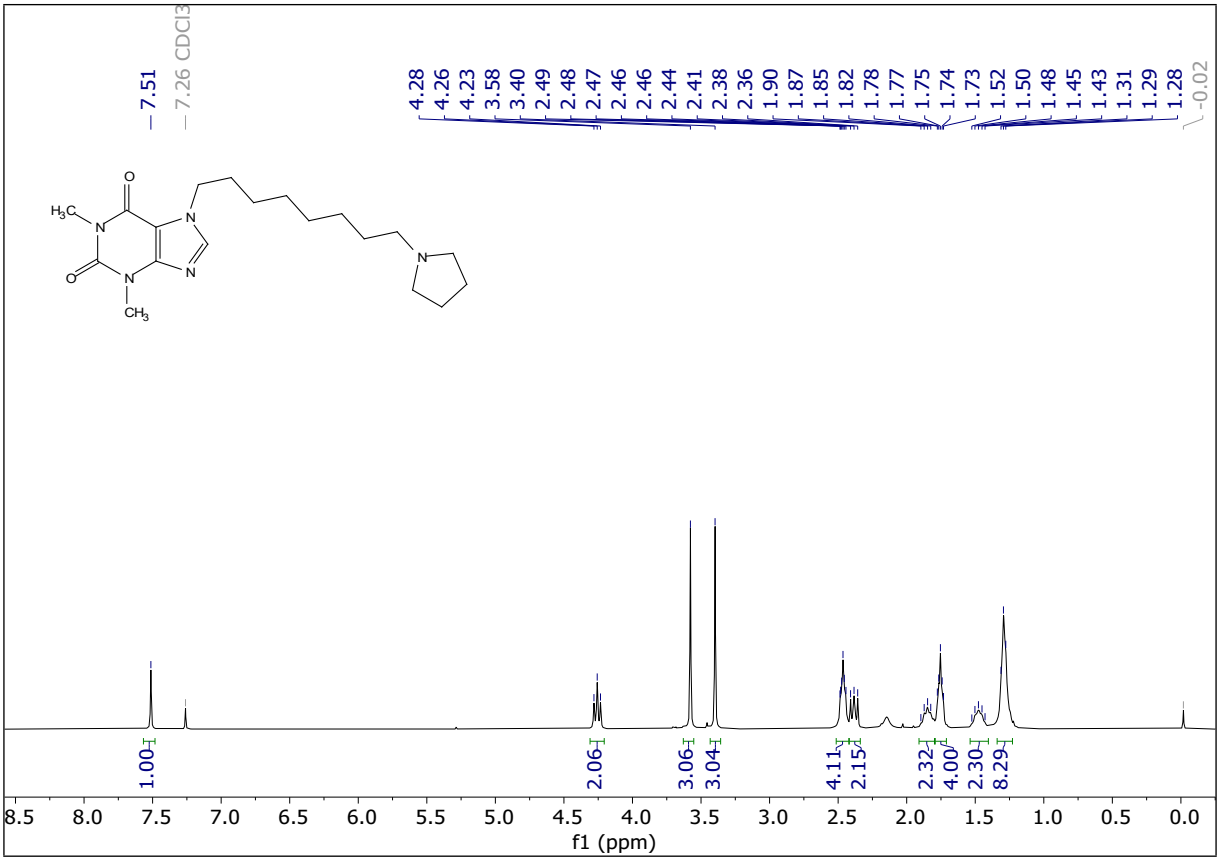
Acquisition Parameter

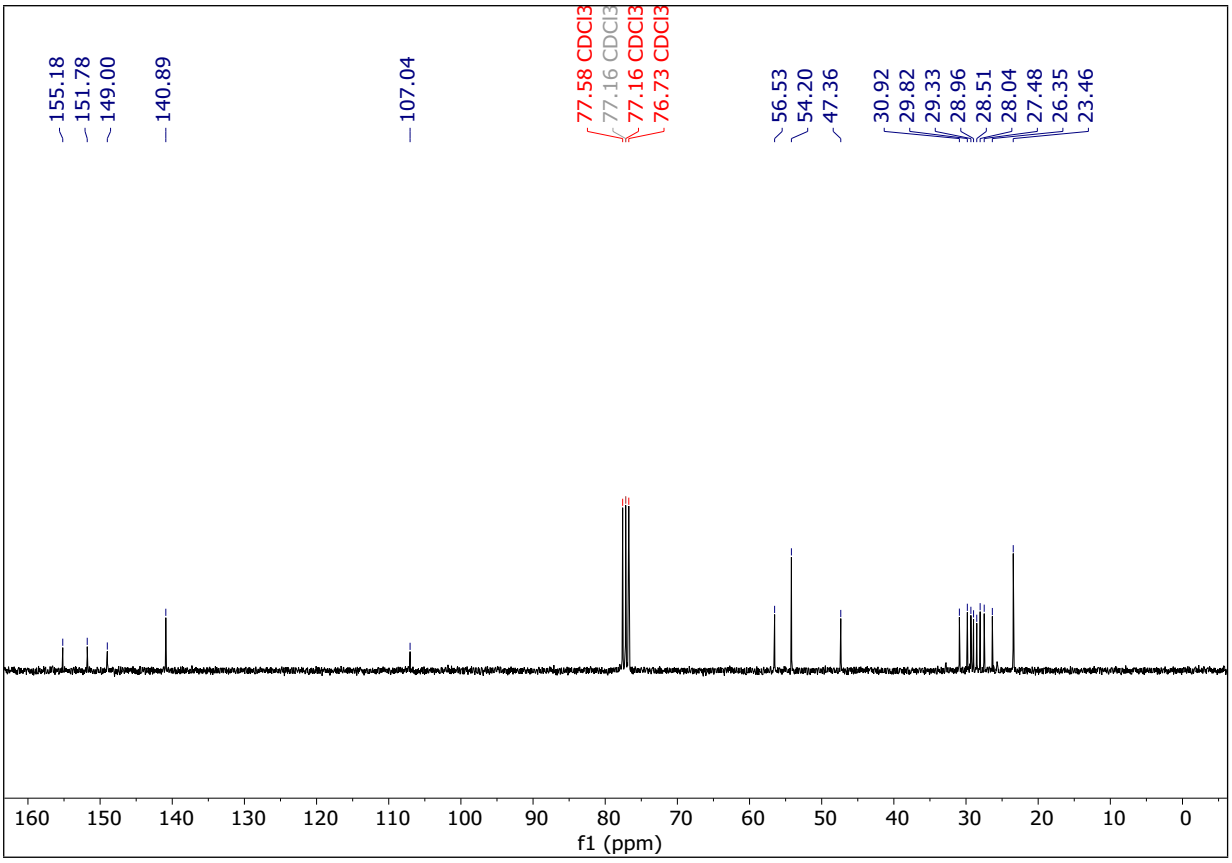
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



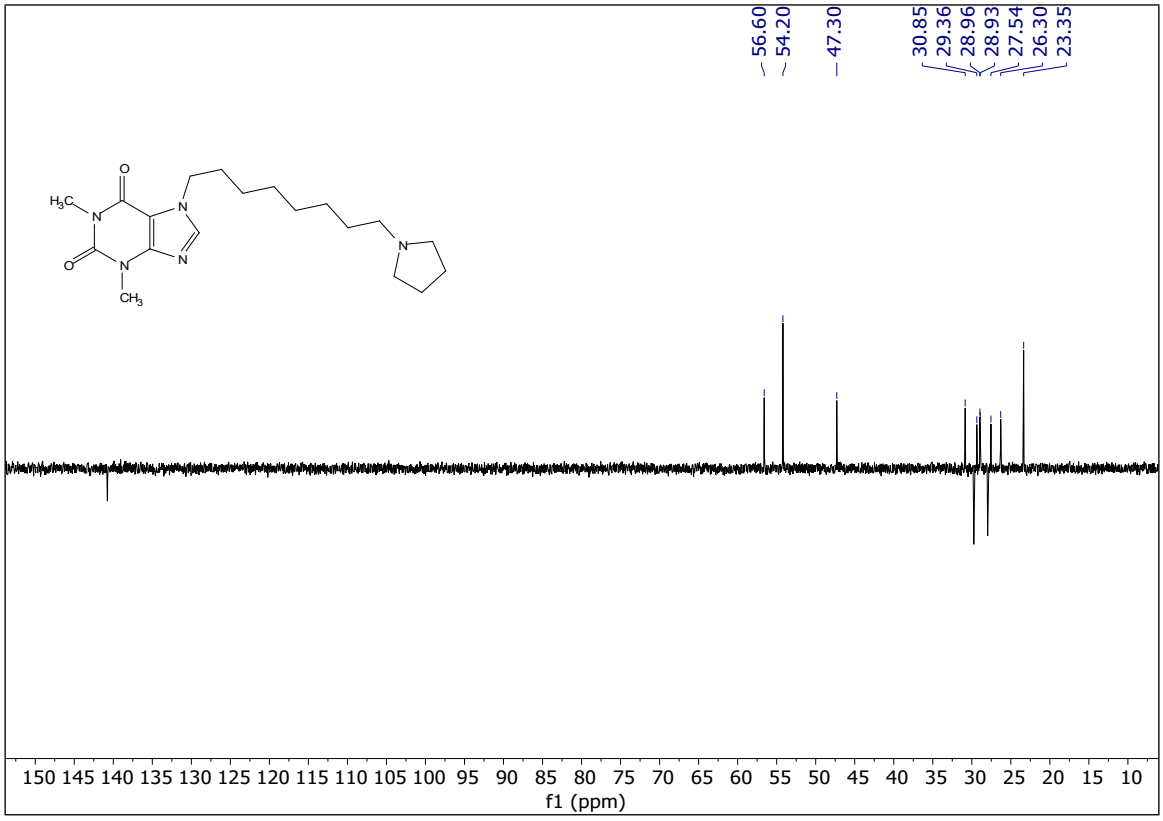
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
391.2820	1	C20H35N6O2	391.2816	-1.1	8.4	1	100.00	6.5	even	ok

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **15**





DEPT spectra in $CDCl_3$ of **15**



HRMS (ESI-TOF) of **15**

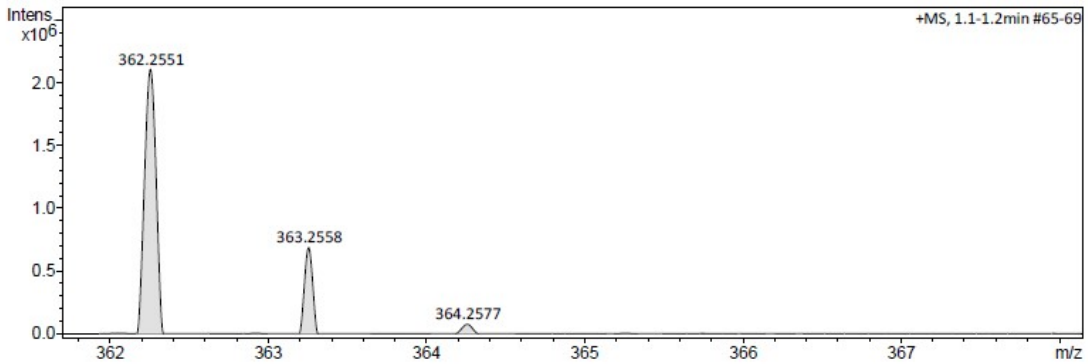
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122616_P1-B-4_01_8441.d	Acquisition Date	12/28/2023 1:39:25 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122616	Instrument	micrOTOF-Q II
Comment	T8PIRR Sv: MeOH + HCOOH Brunella Biscussi		

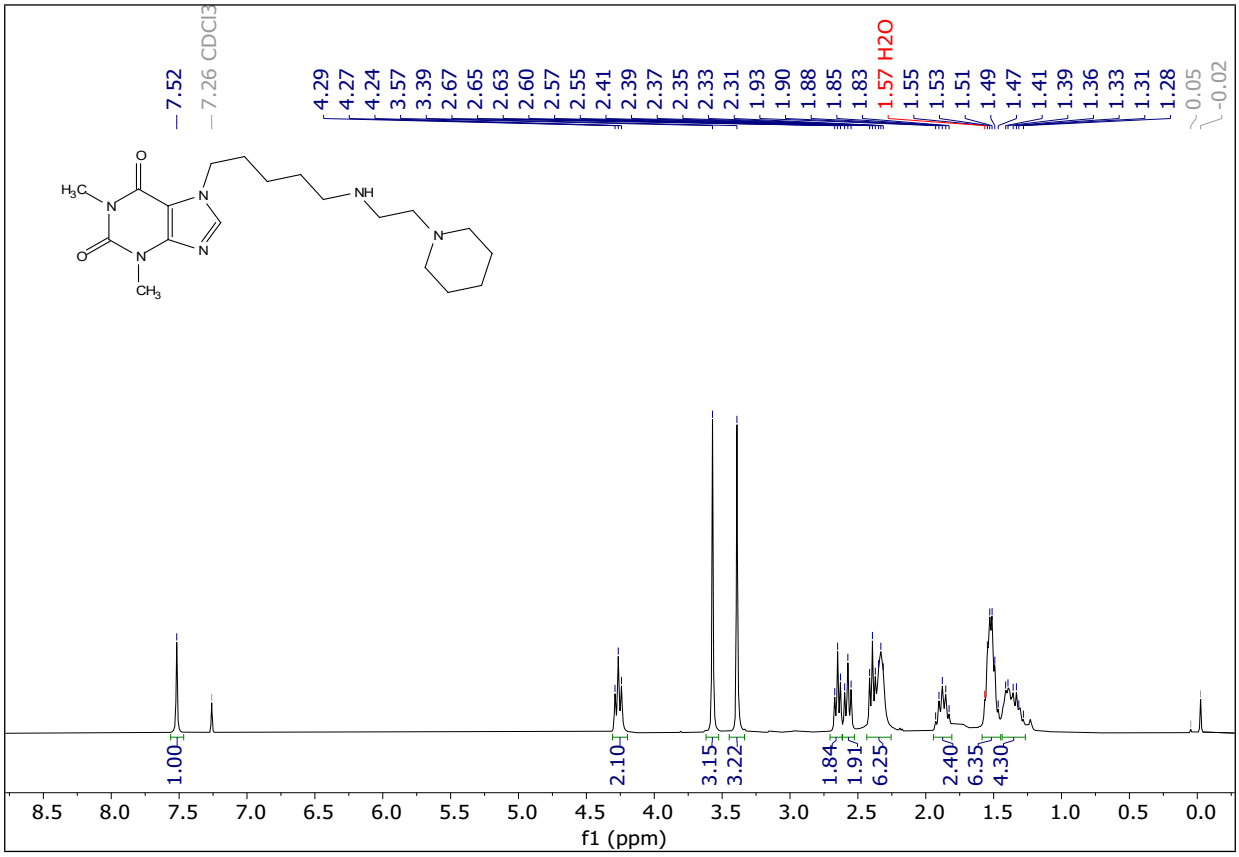
Acquisition Parameter

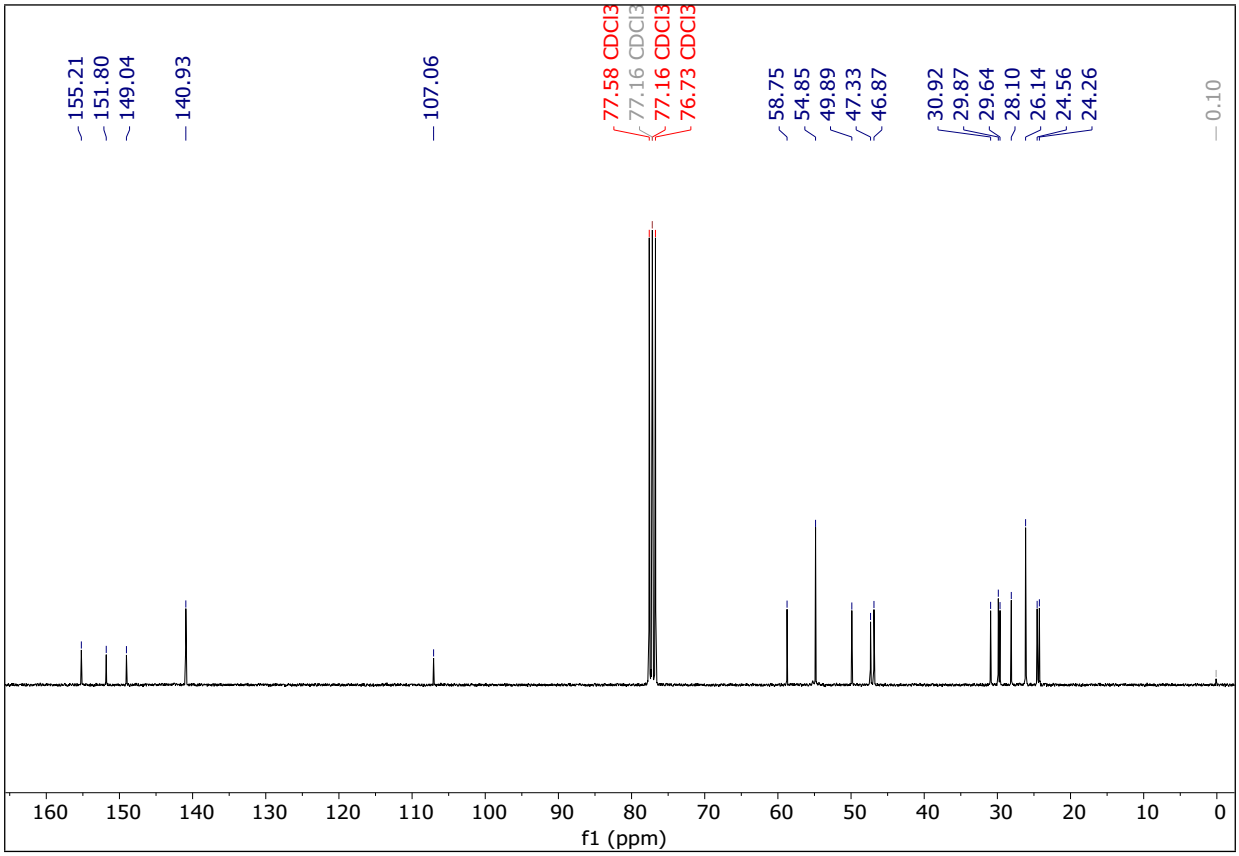
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



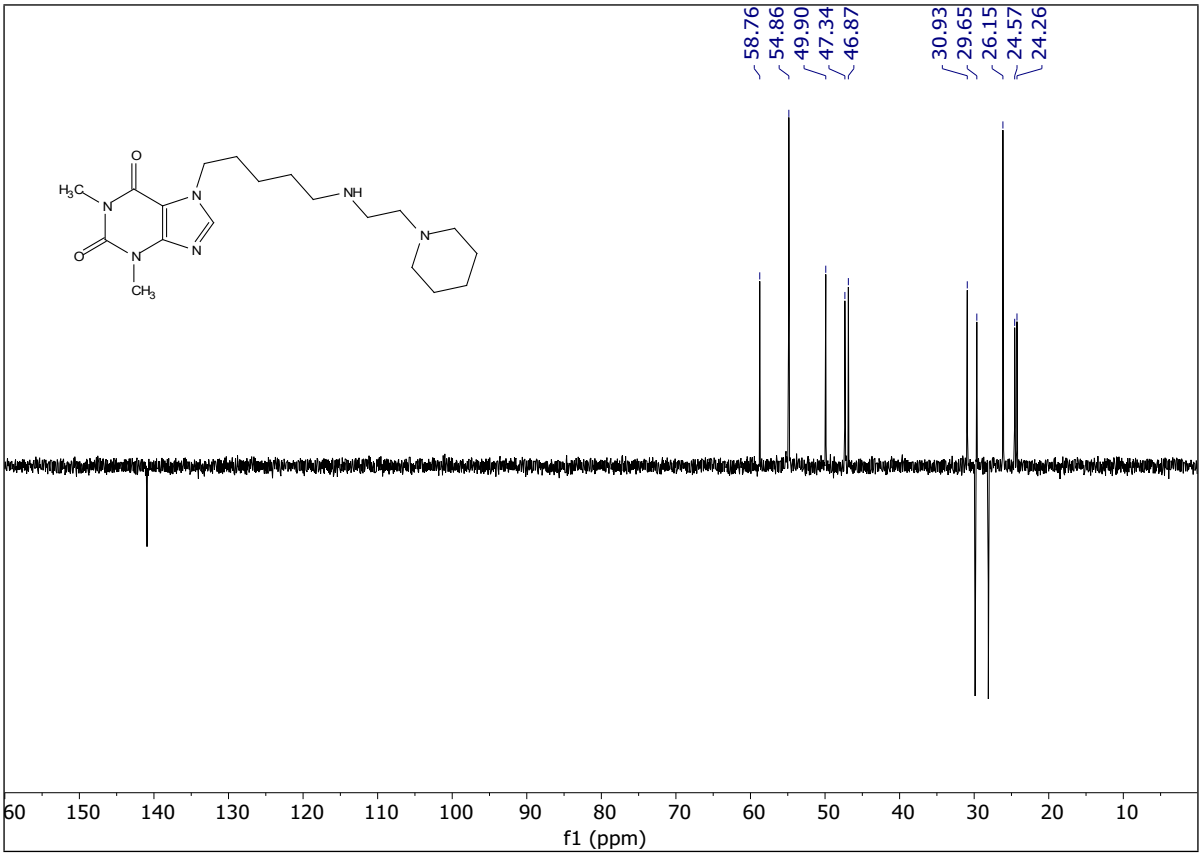
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
362.2551	1	C19H32N5O2	362.2551	-0.2	57.0	2	100.00	6.5	even	ok

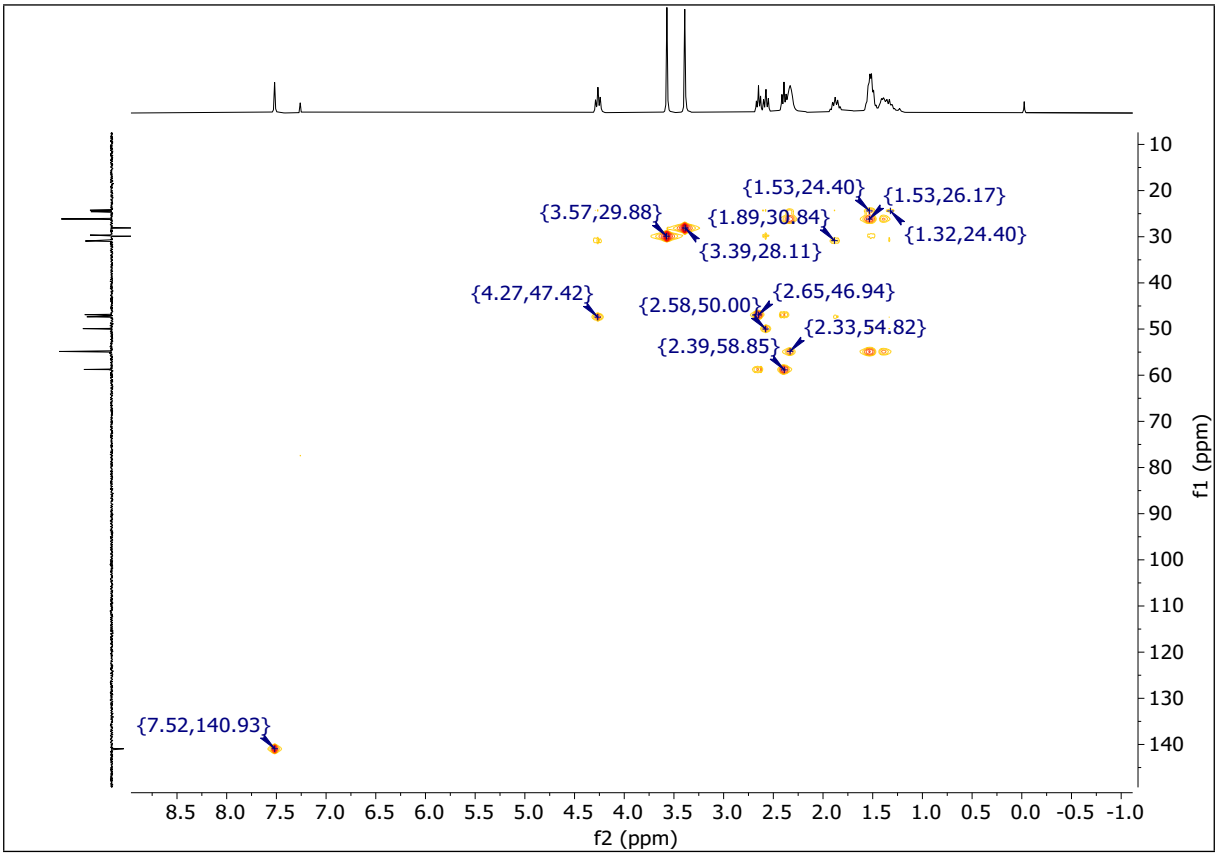
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **16**





DEPT and HSQC spectra in $CDCl_3$ of **16**





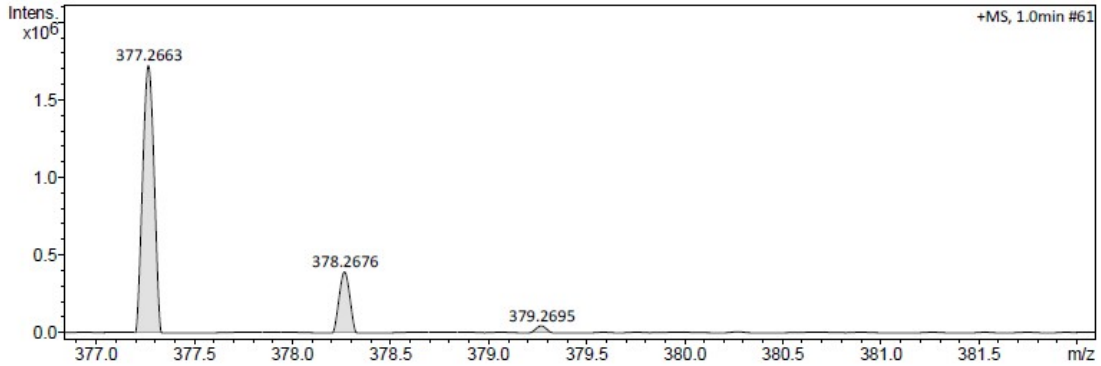
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122608_P1-F-6_01_8411.d	Acquisition Date	12/27/2023 2:27:22 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122608	Instrument	micrOTOF-Q II
Comment	T5-2PP Sv: MeOH + HCOOH Brunella Biscussi		

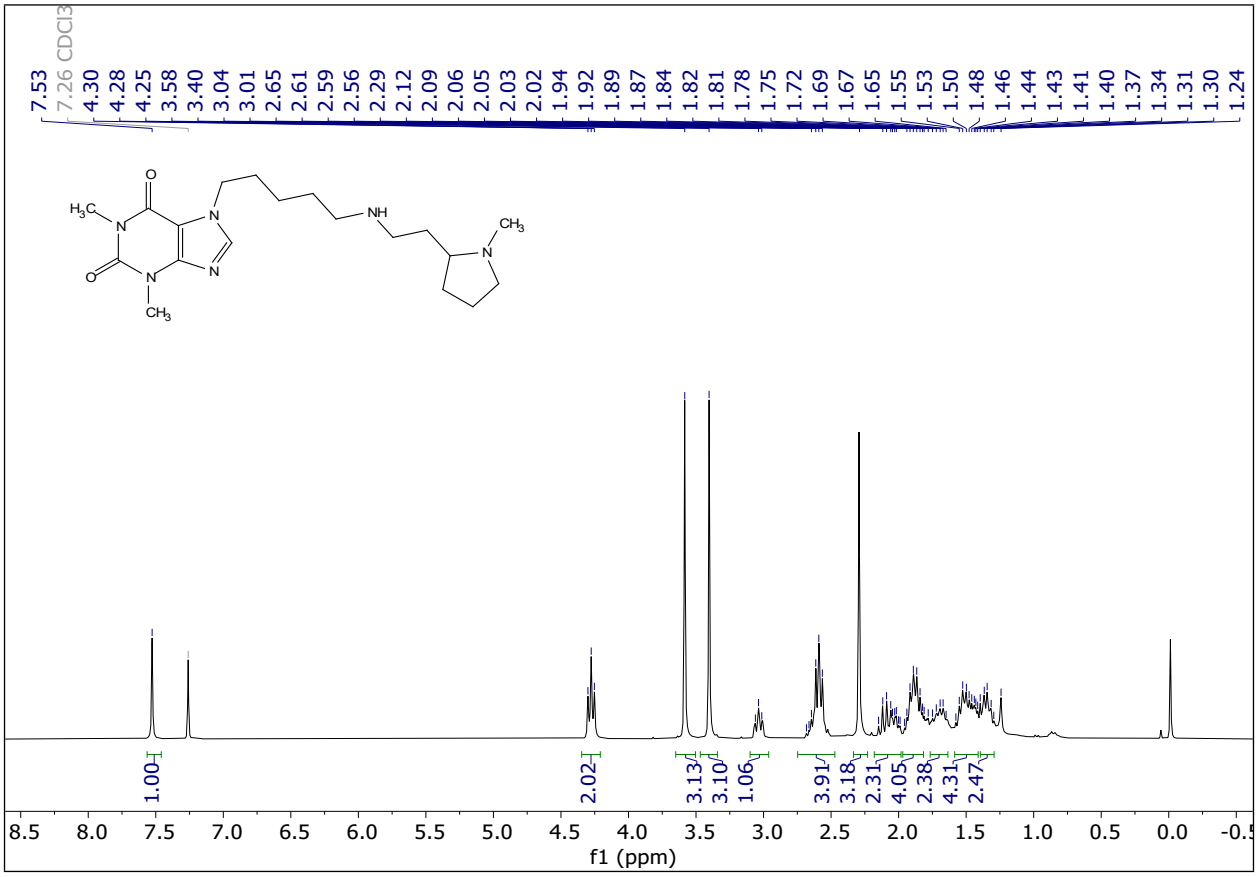
Acquisition Parameter

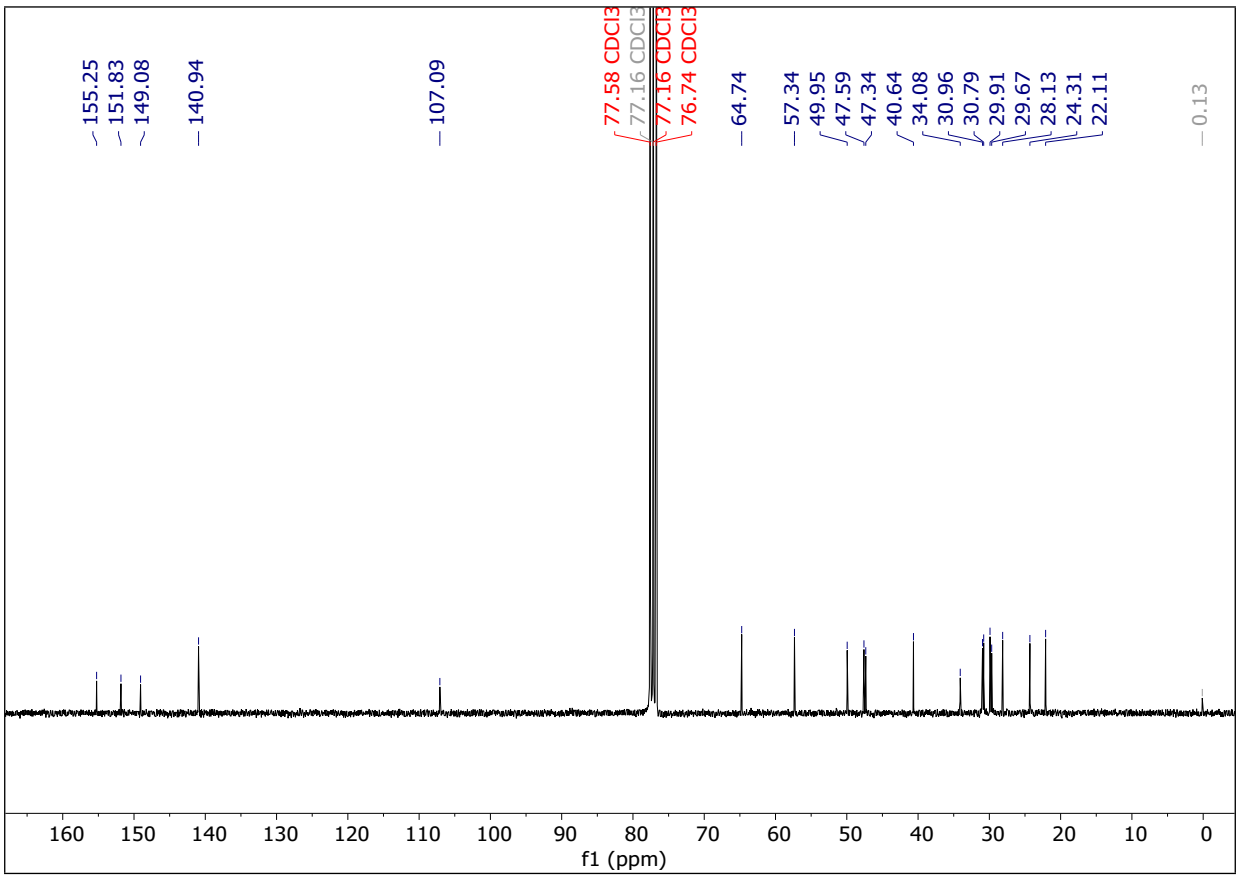
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



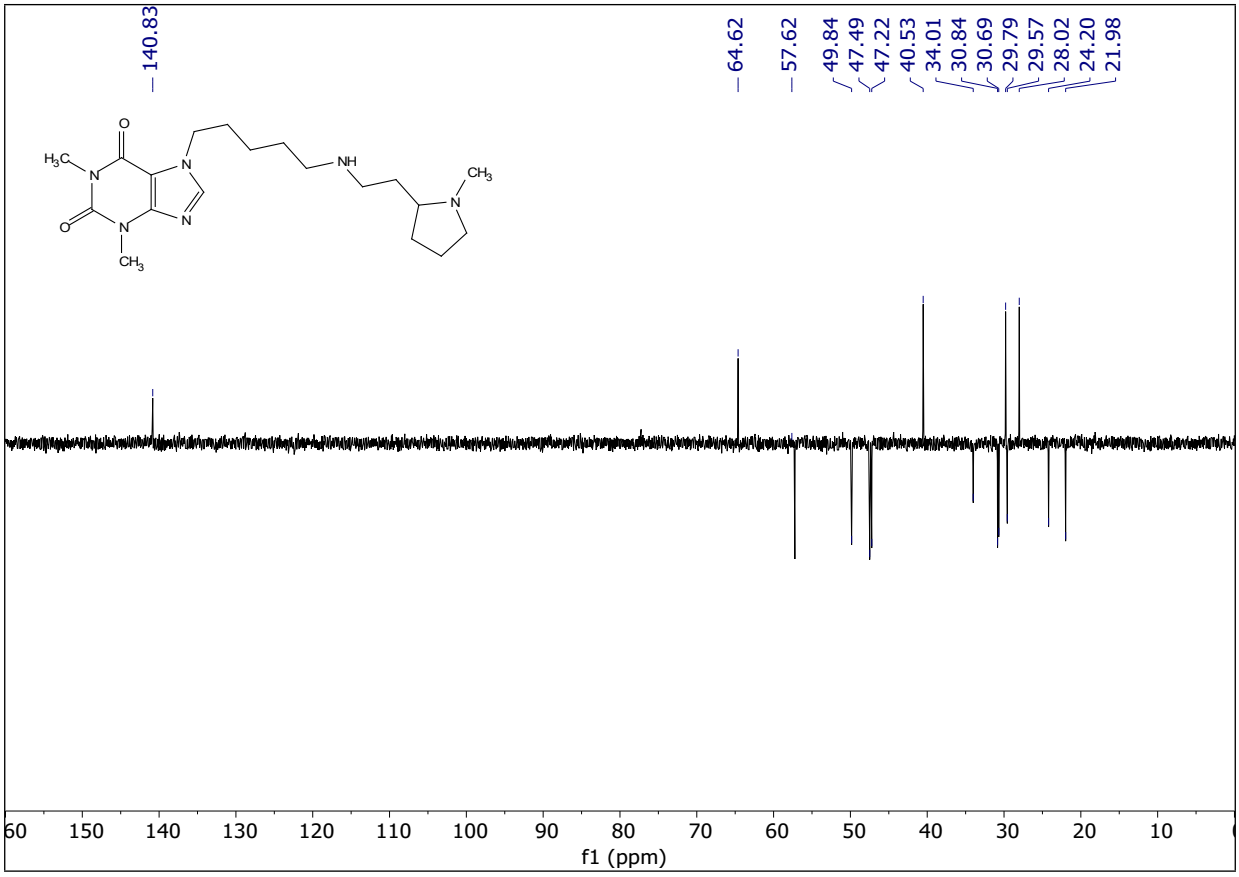
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
377.2663	1	C19H33N6O2	377.2660	-0.8	4.2	1	100.00	6.5	even	ok

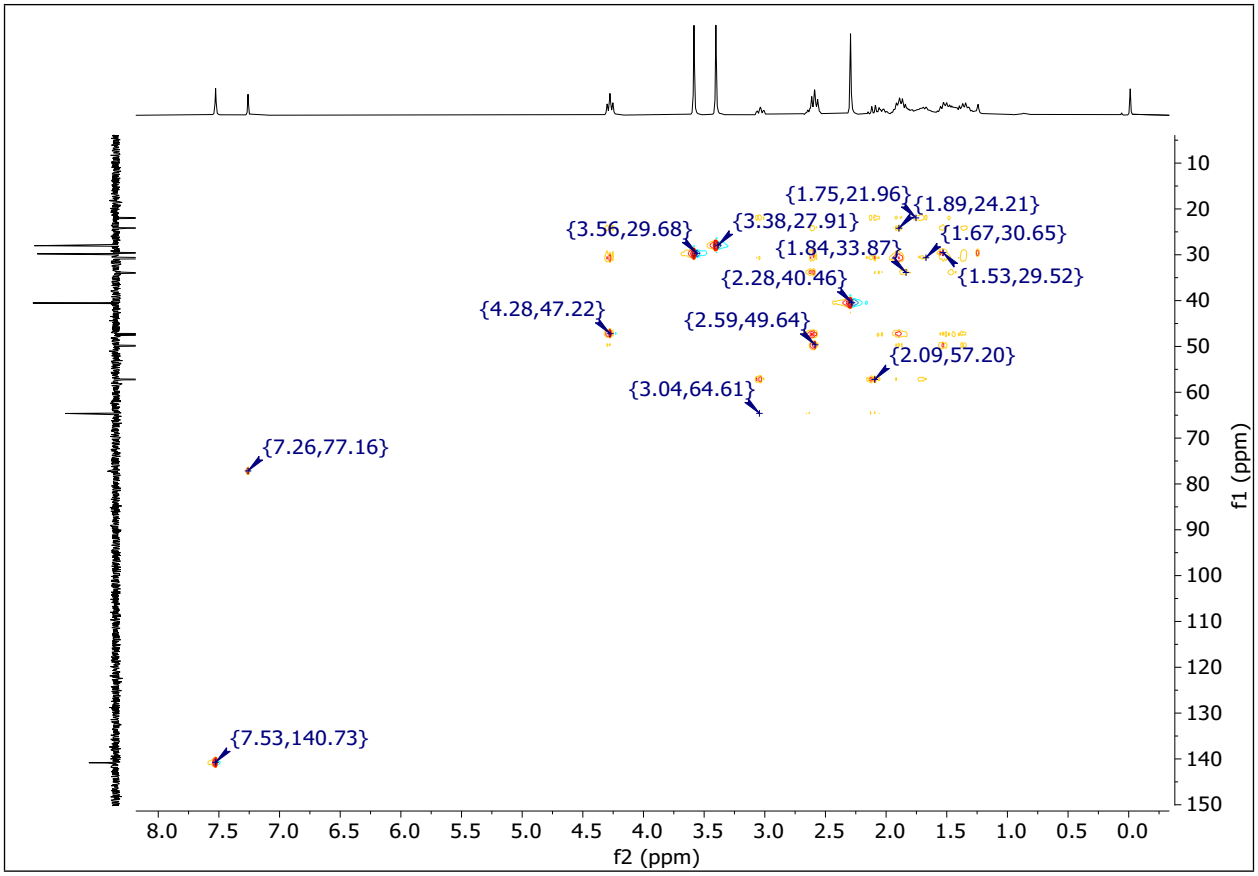
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **17**





DEPT and HSQC spectra in $CDCl_3$ of **17**





HRMS (ESI-TOF) of **17**

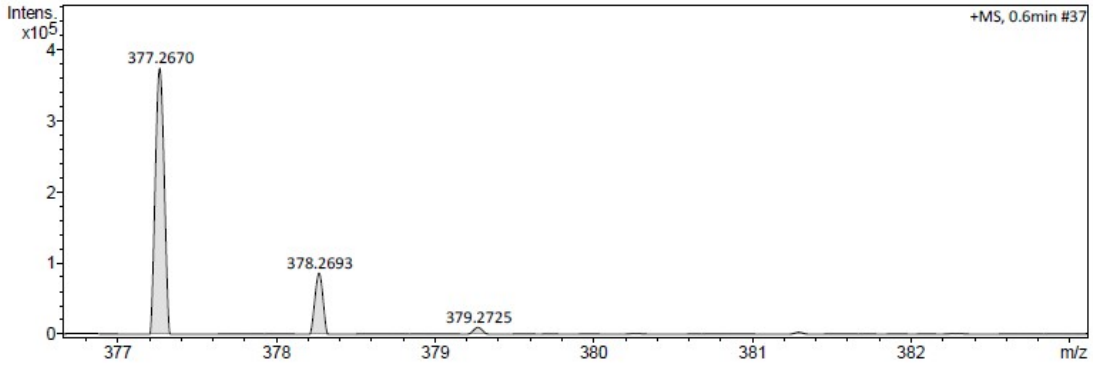
Qualitative Compound Report

Analysis Info

Analysis Name	D:\Data\ggc\23-122609_P1-F-7_01_8412.d	Acquisition Date	12/27/2023 2:32:30 PM
Method	lc_qtof_directospos.m	Operator	ELB
Sample Name	23-122609	Instrument	micrOTOF-Q II
Comment	T5-2MP Sv: MeOH + HCOOH Brunella Biscussi		

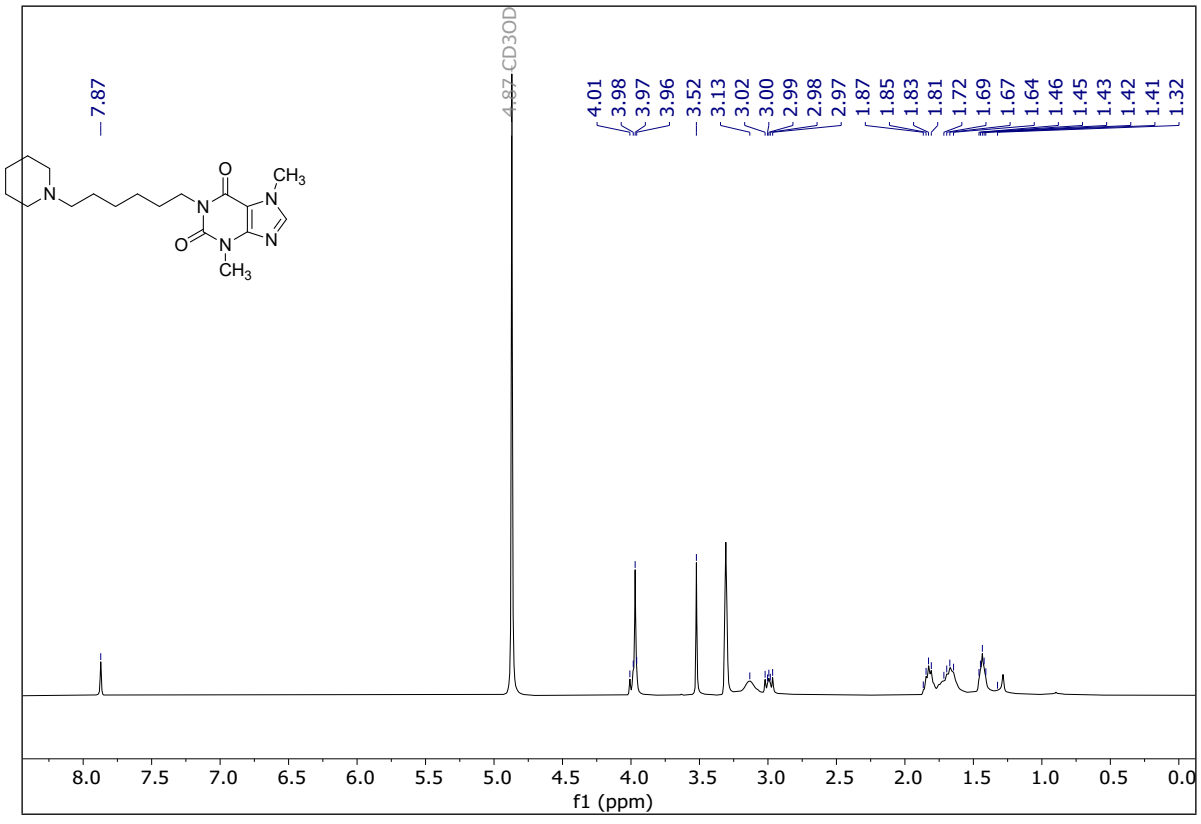
Acquisition Parameter

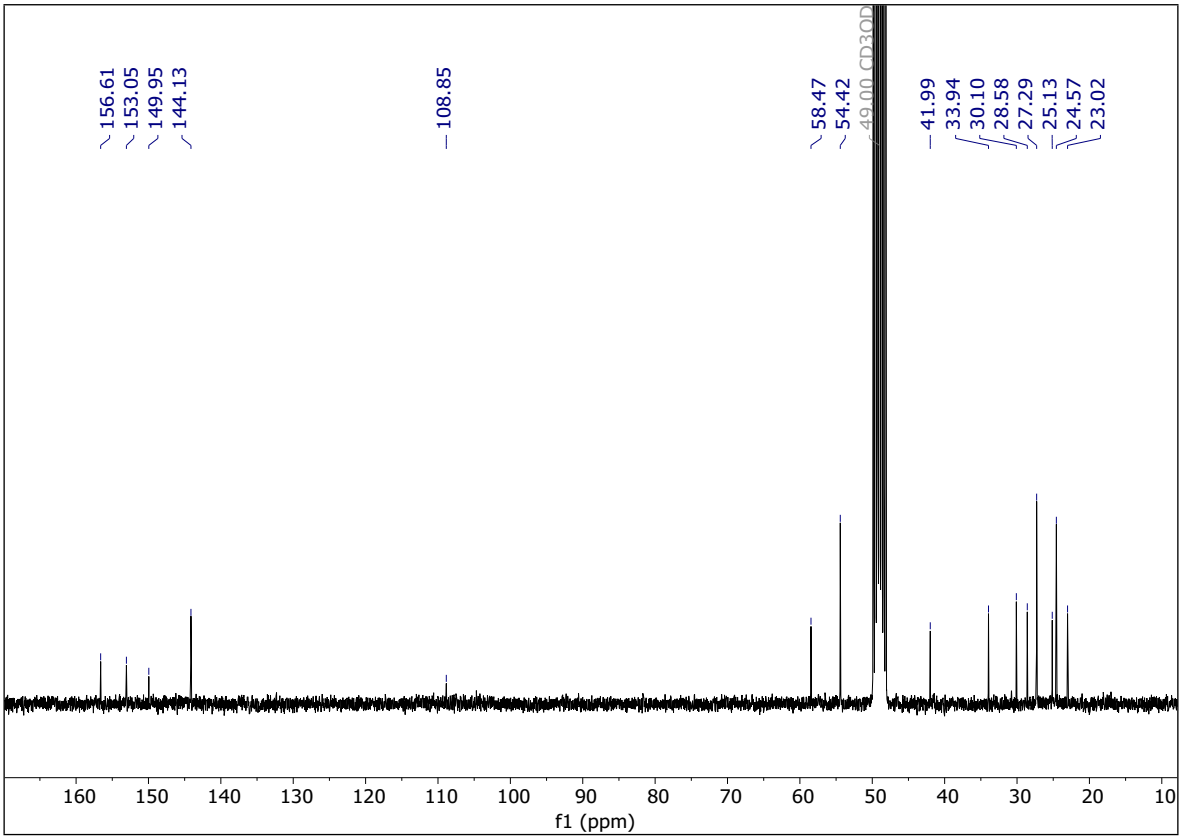
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	70 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



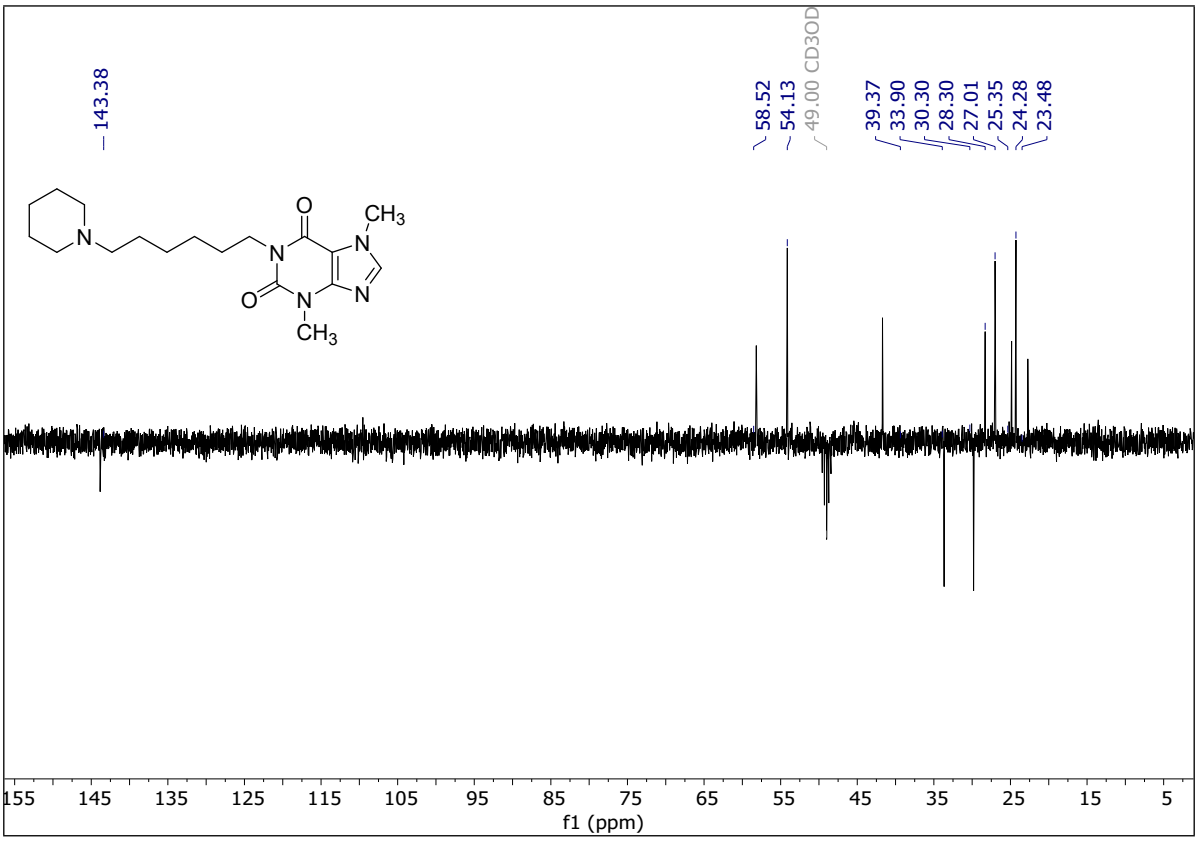
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
377.2670	1	C19H33N6O2	377.2660	-2.8	2.8	1	100.00	6.5	even	ok

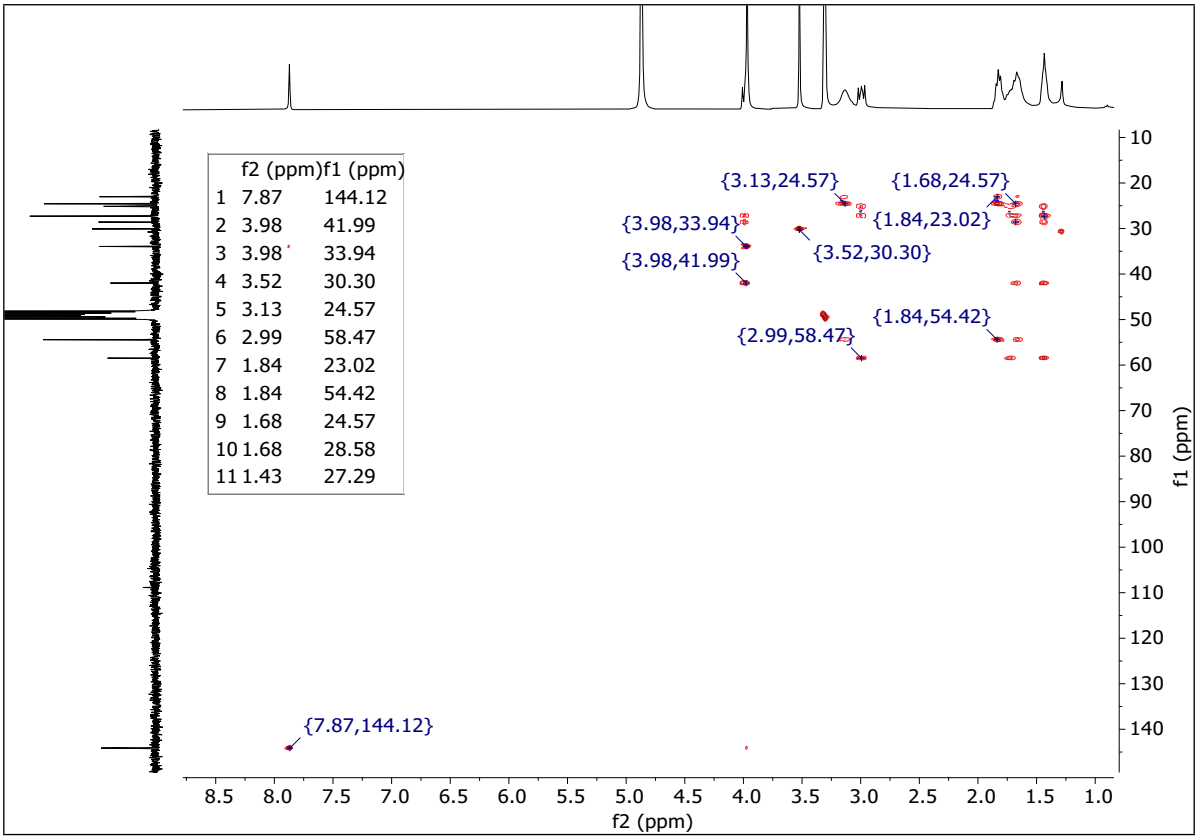
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in MeOD of **18**





DEPT and HSQC spectra in MeOD of **18**




f2 (ppm) f1 (ppm)
1 7.87 144.12
2 3.98 41.99
3 3.98 33.94
4 3.52 30.30
5 3.13 24.57
6 2.99 58.47
7 1.84 23.02
8 1.84 54.42
9 1.68 24.57
10 1.68 28.58
11 1.43 27.29
{3.13,24.57}
{1.68,24.57}
{3.98,33.94}
{1.84,23.02}
{3.52,30.30}
{3.98,41.99}
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{7.87,144.12}
f2 (ppm)
f1 (ppm)

Qualitative Compound Report

Data File	2033_BBA_12_01.d	**Sample Name**	BBA_12
Sample Type	Sample	**Position**	Vial 12
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 2:09:24 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

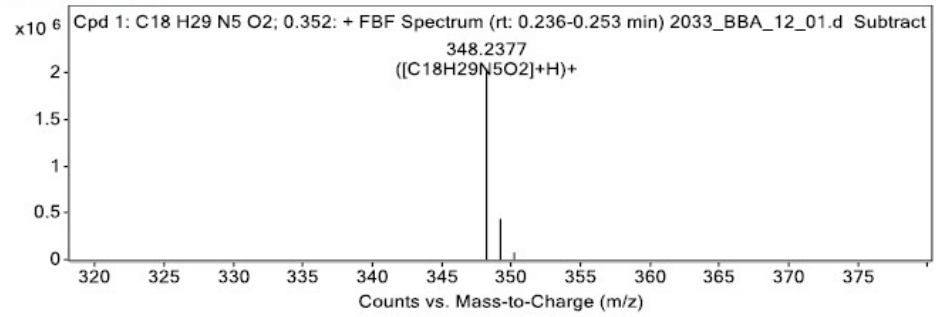
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 2:09:24 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

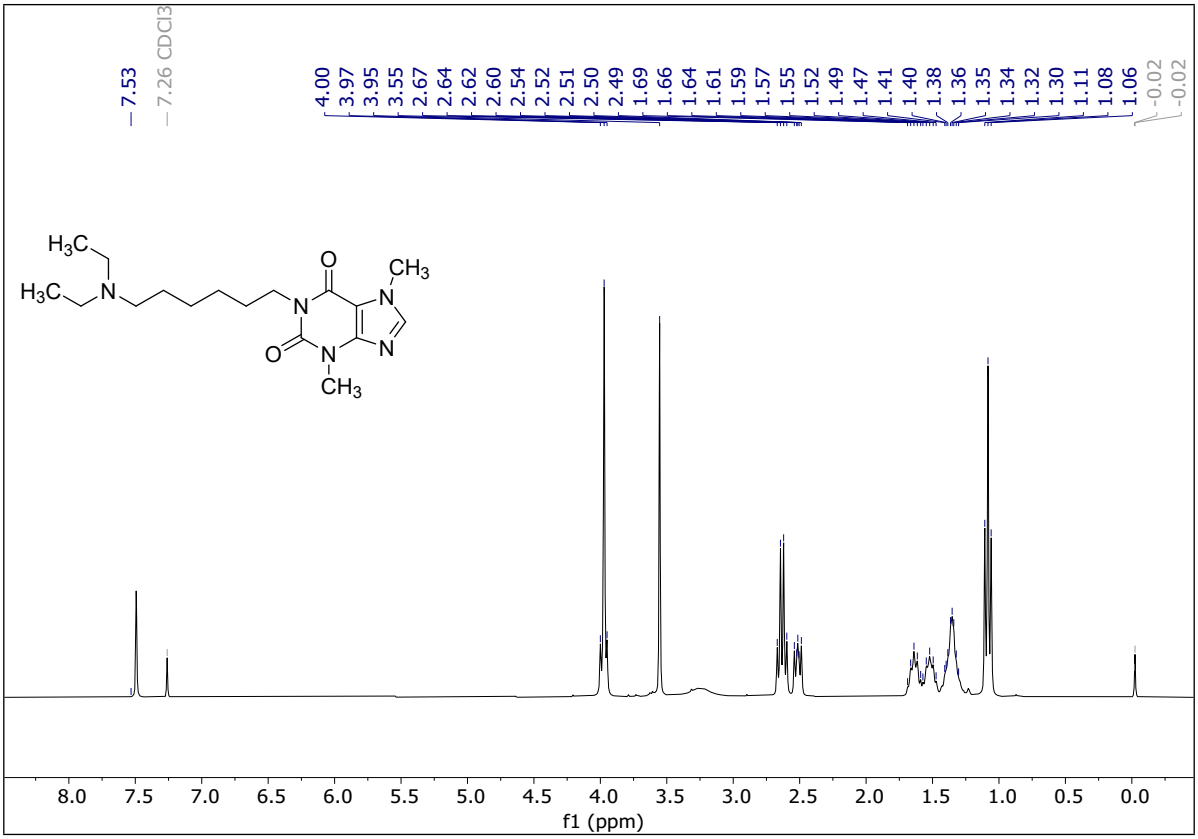
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C18 H29 N5 O2; 0.352	0.352	347.2308	2037270	C18 H29 N5 O2	347.2321	-3.95	1

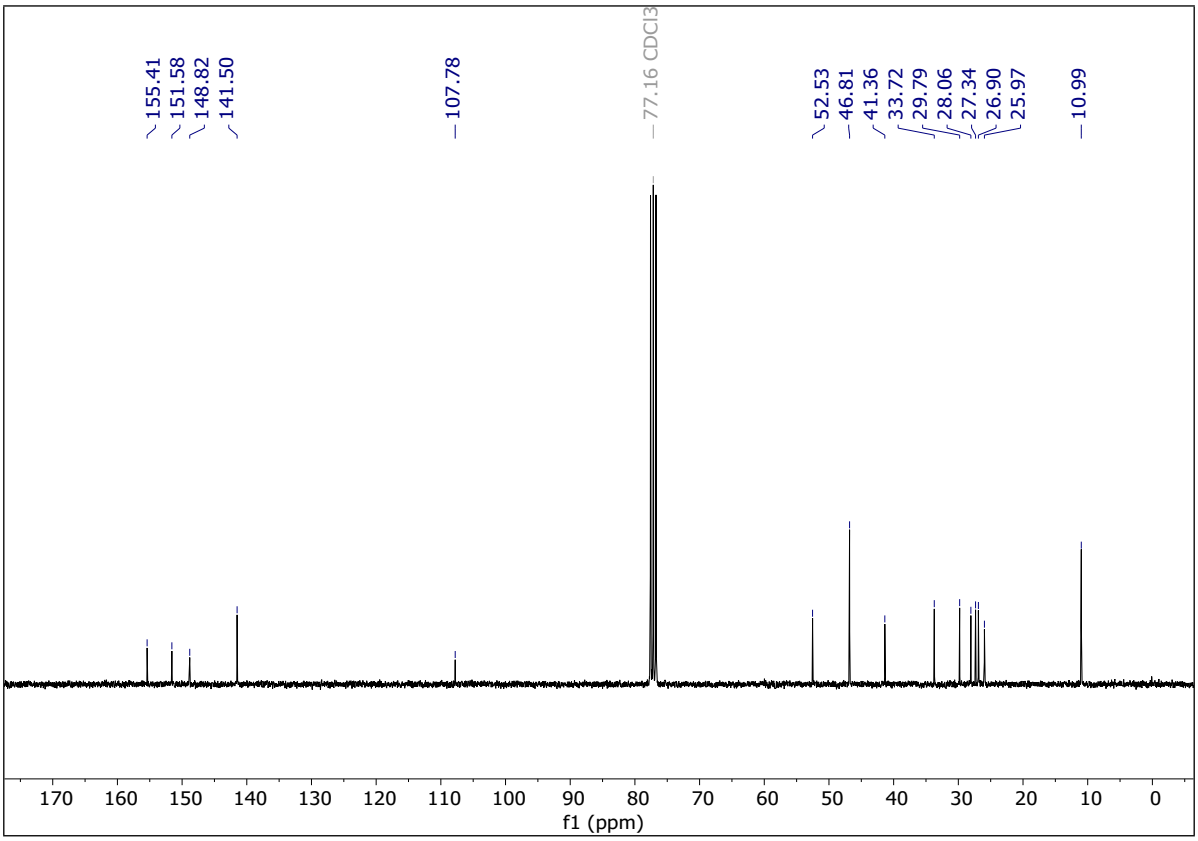
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C18 H29 N5 O2; 0.352	348.2377	0.352	Find by Formula	347.2308

MS Zoomed Spectrum

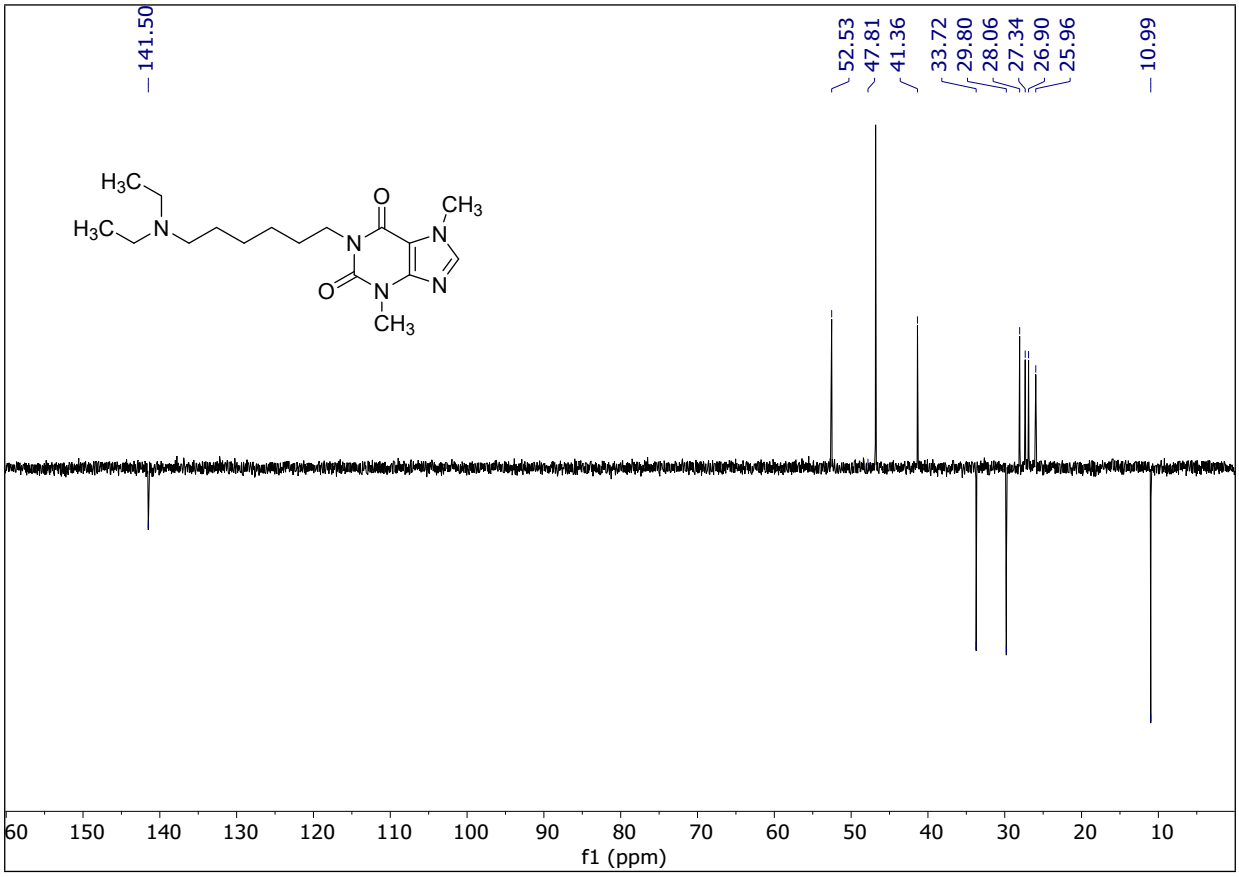


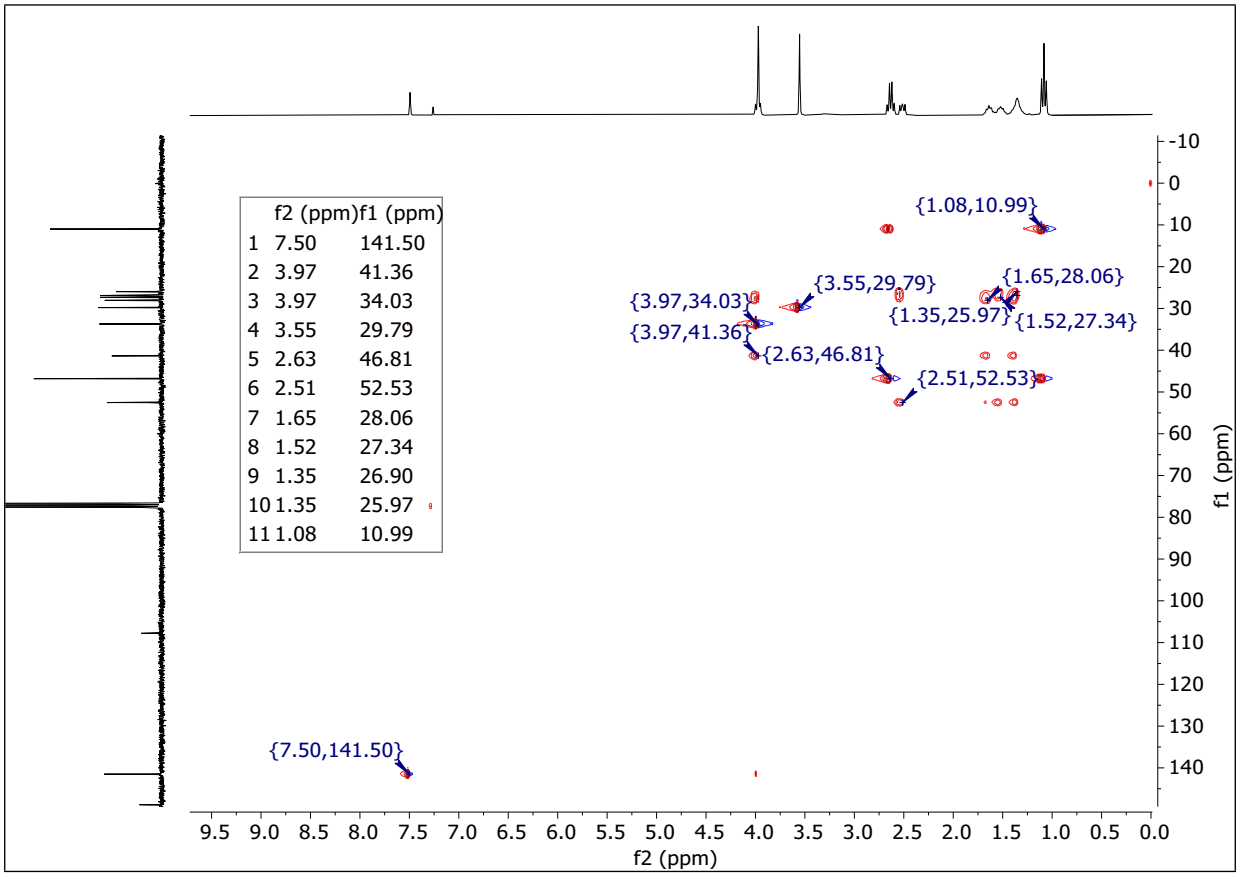
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **19**





DEPT and HSQC spectra in $CDCl_3$ of **19**





Qualitative Compound Report

Data File	2034_BBA_13_01.d	**Sample Name**	BBA_13
Sample Type	Sample	**Position**	Vial 13
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 2:16:39 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

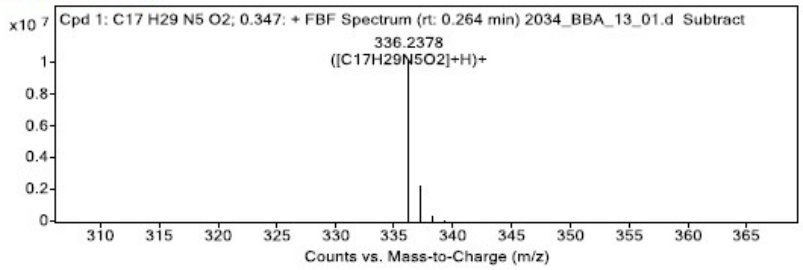
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 2:16:39 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Versio**	2.723
Tune Mass Range	1700		

Compound Table

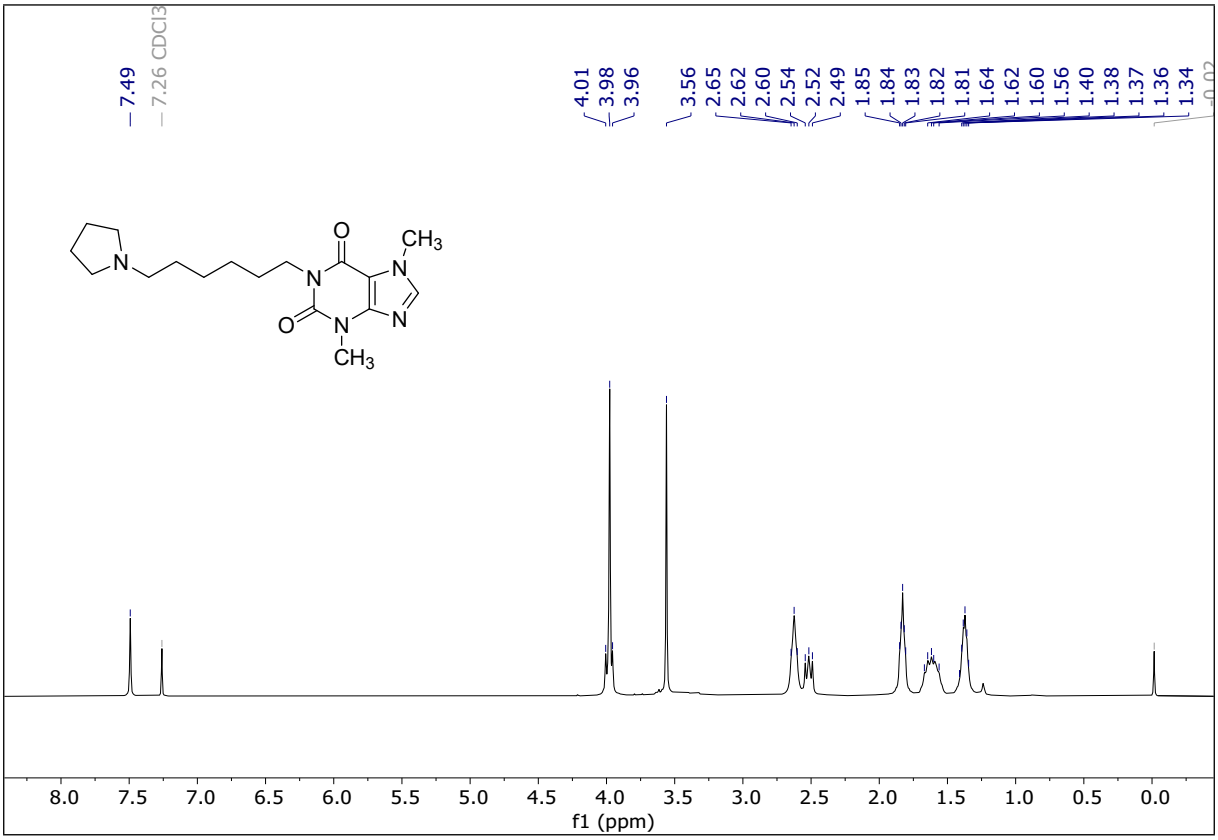
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C17 H29 N5 O2; 0.347	0.347	335.2306	10149366	C17 H29 N5 O2	335.2321	-4.58	1

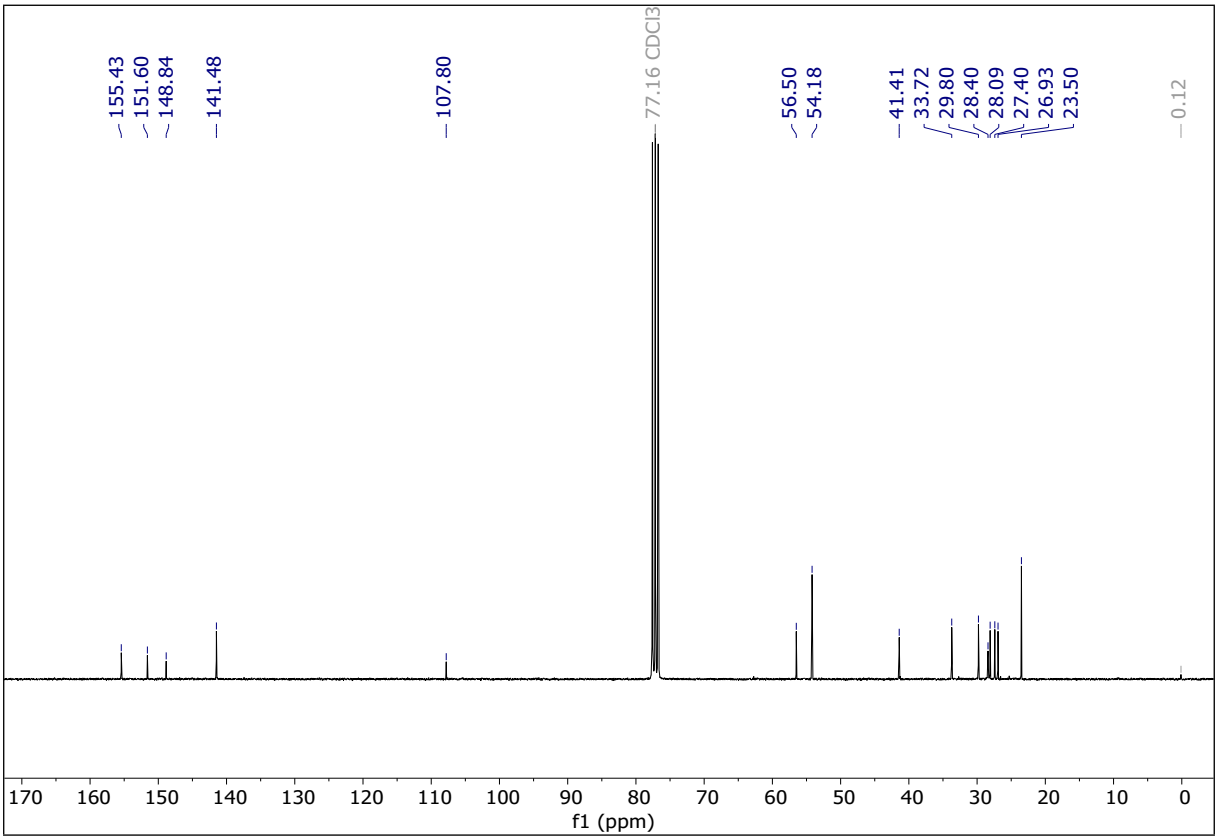
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C17 H29 N5 O2; 0.347	336.2378	0.347	Find by Formula	335.2306

MS Zoomed Spectrum

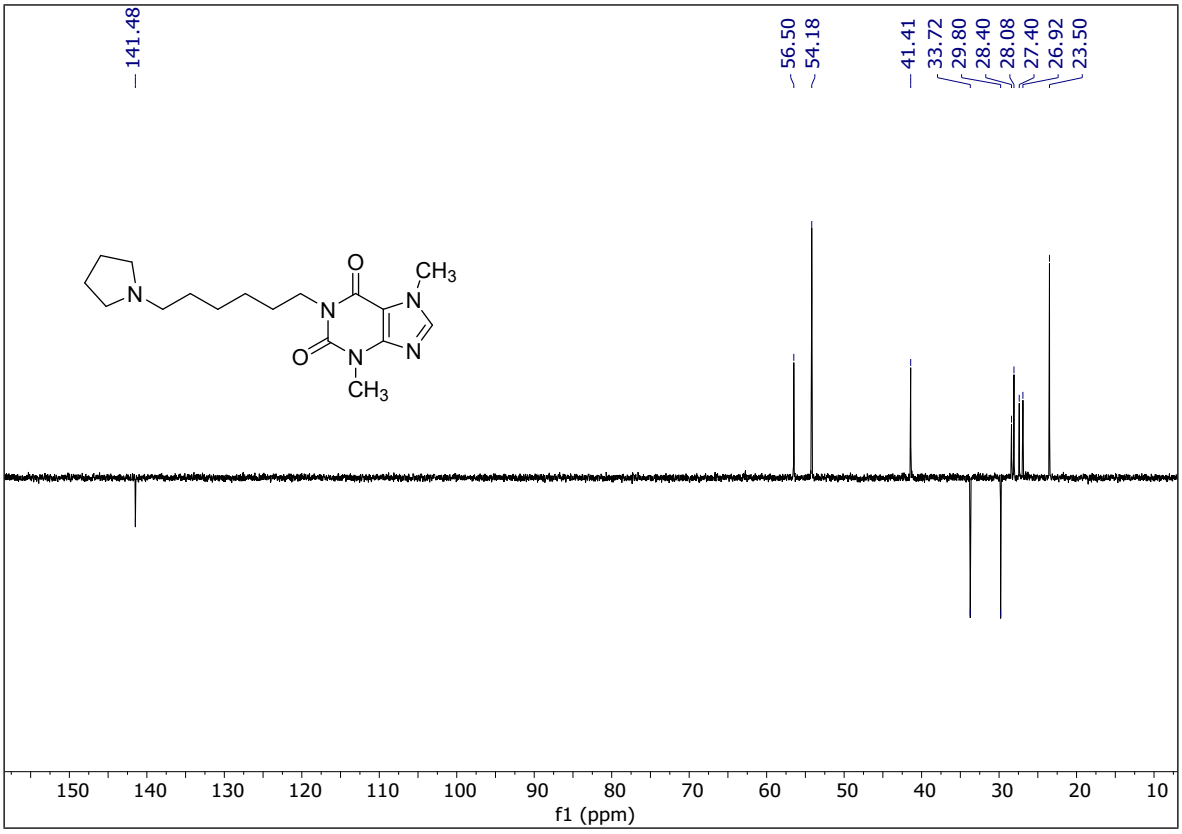


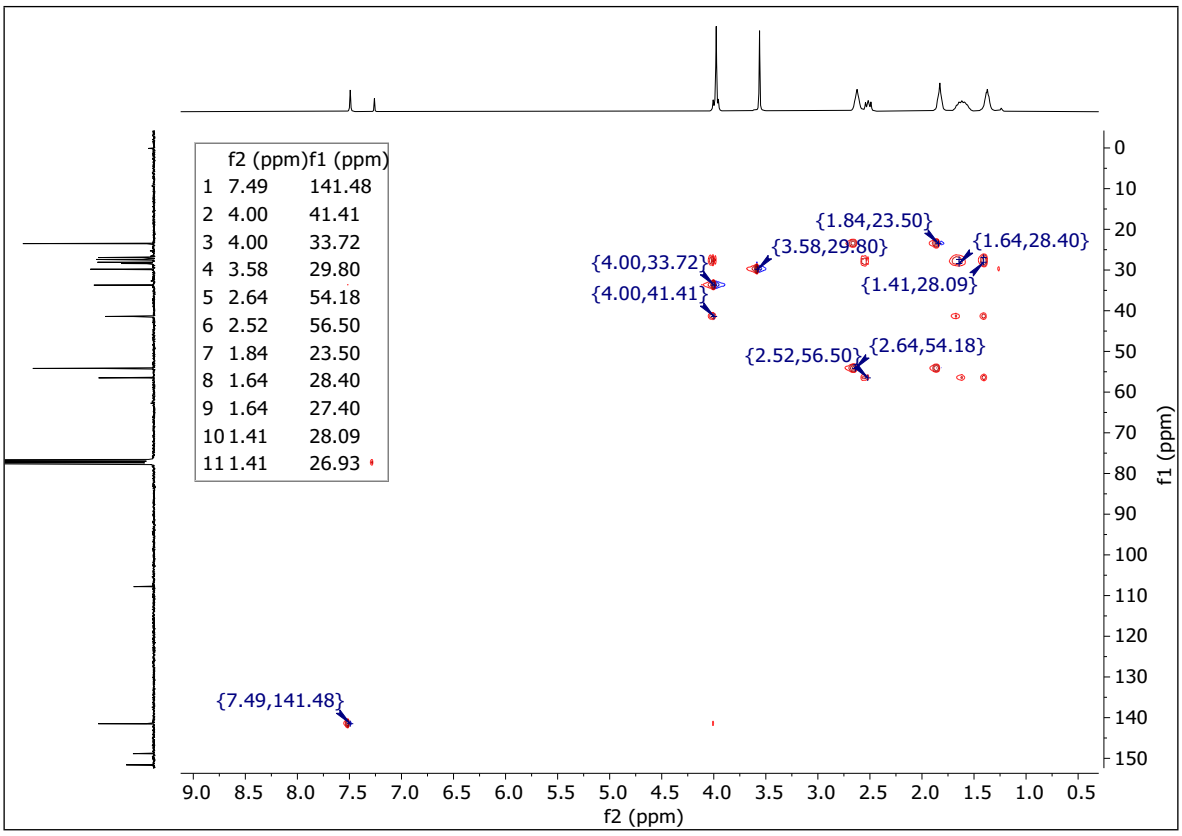
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in **20**





DEPT and HSQC spectra in $CDCl_3$ of **20**





Qualitative Compound Report

Data File	2032_BBA_11_01.d	**Sample Name**	BBA_11
Sample Type	Sample	**Position**	Vial 11
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 2:02:14 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

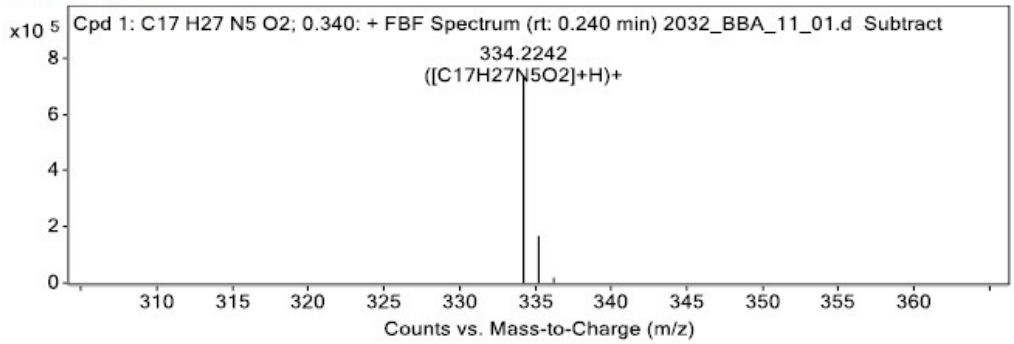
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 2:02:14 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

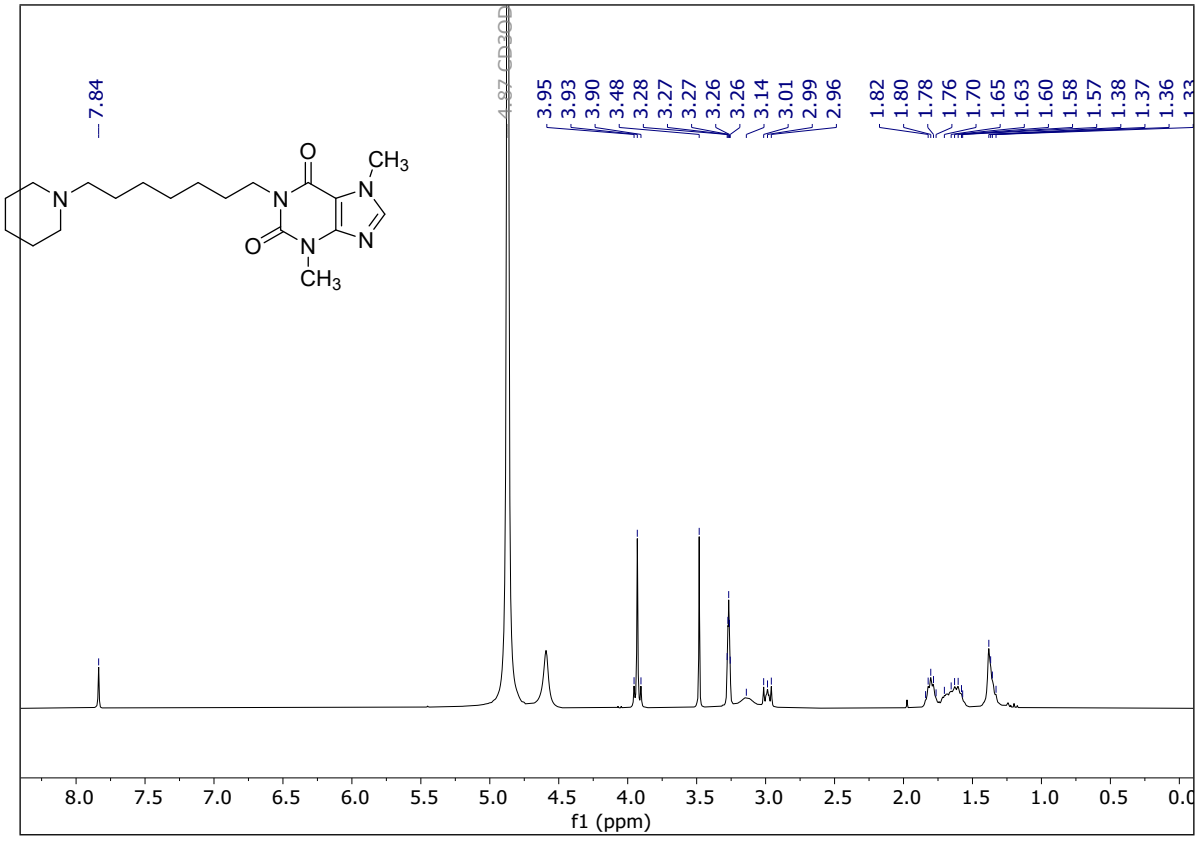
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C17 H27 N5 O2; 0.340	0.34	333.2169	738387	C17 H27 N5 O2	333.2165	1.26	1

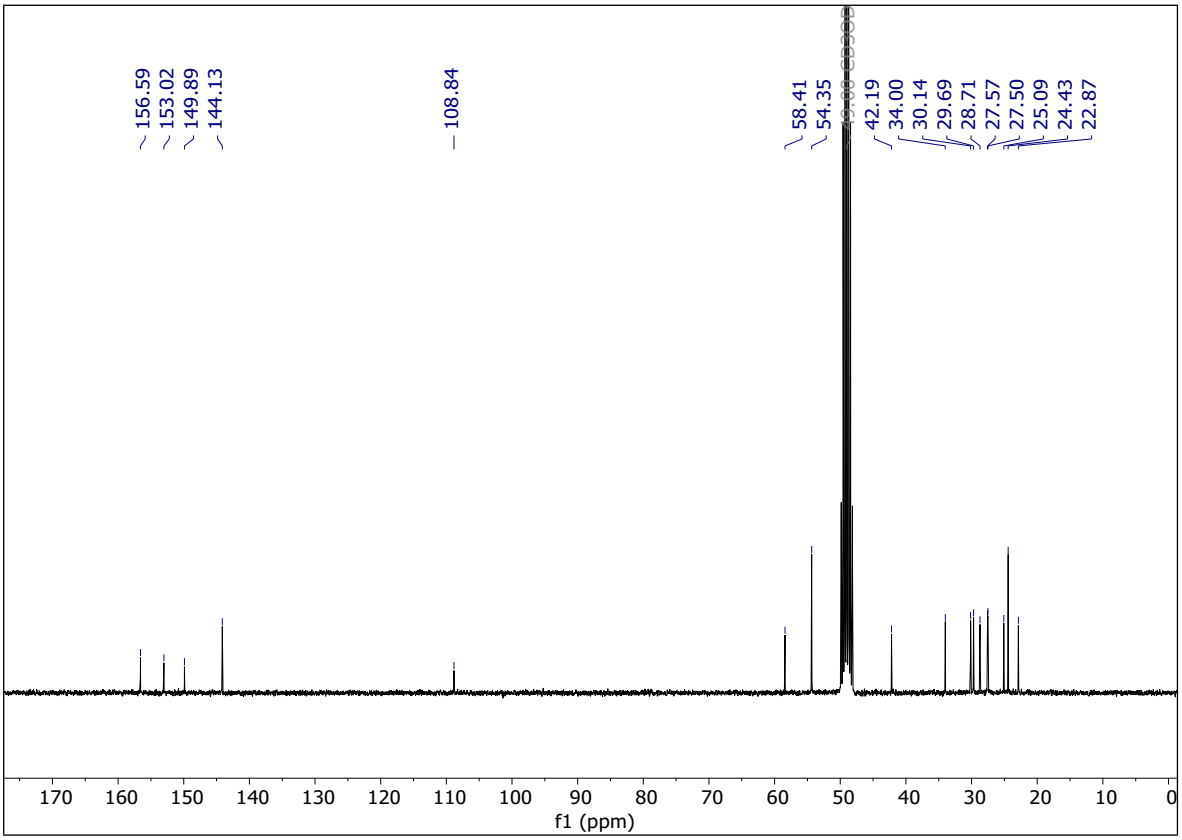
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C17 H27 N5 O2; 0.340	334.2242	0.34	Find by Formula	333.2169

MS Zoomed Spectrum

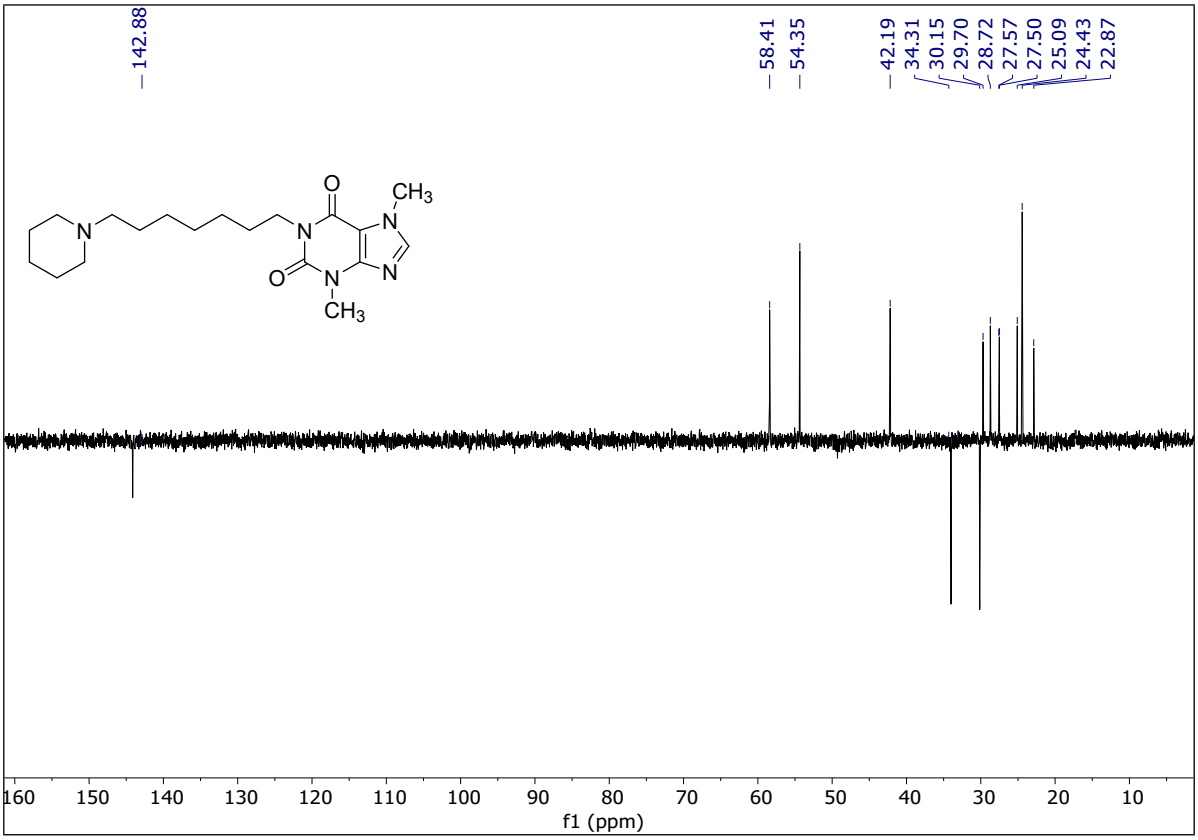


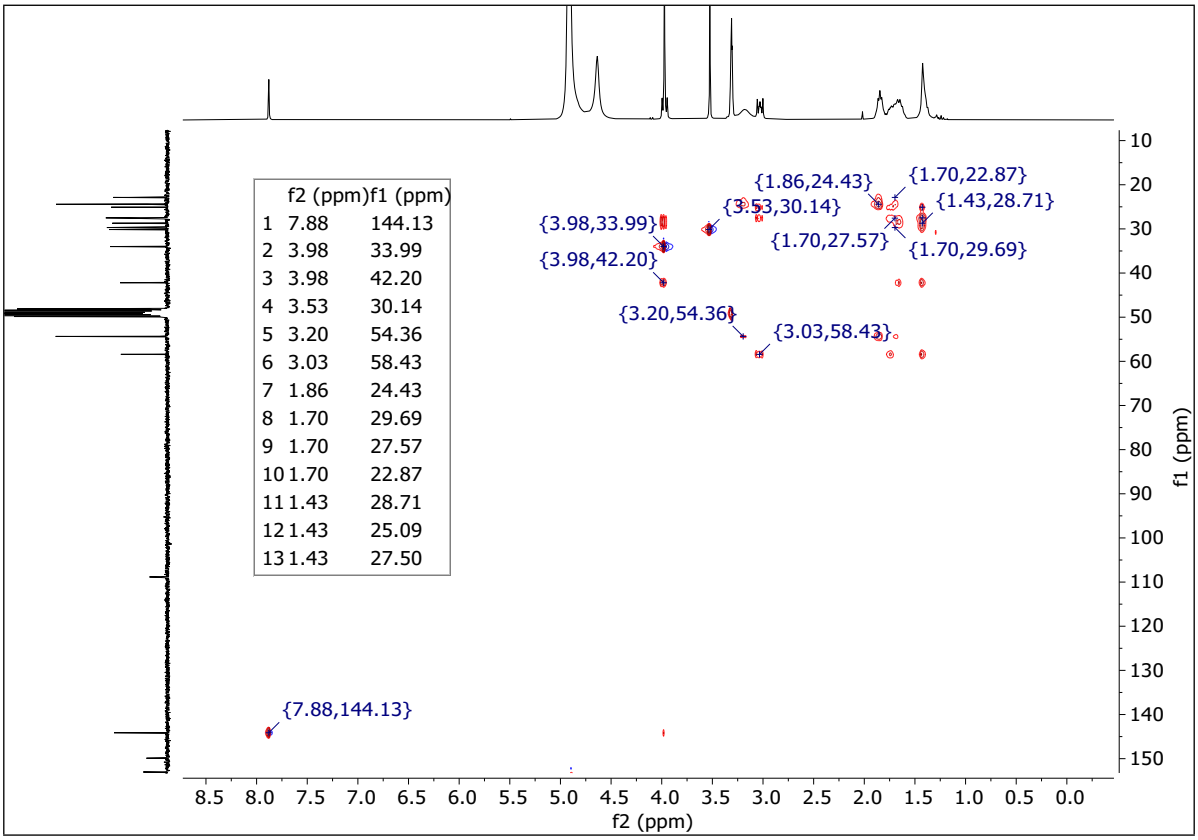
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in MeOD of **21**





DEPT and HSQC spectra in MeOD of **21**





	f2 (ppm)	f1 (ppm)
1	7.88	144.13
2	3.98	33.99
3	3.98	42.20
4	3.53	30.14
5	3.20	54.36
6	3.03	58.43
7	1.86	24.43
8	1.70	29.69
9	1.70	27.57
10	1.70	22.87
11	1.43	28.71
12	1.43	25.09
13	1.43	27.50

Qualitative Compound Report

Data File	2029_BBA_8_01.d	**Sample Name**	BBA_8
Sample Type	Sample	**Position**	Vial 8
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 1:40:29 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

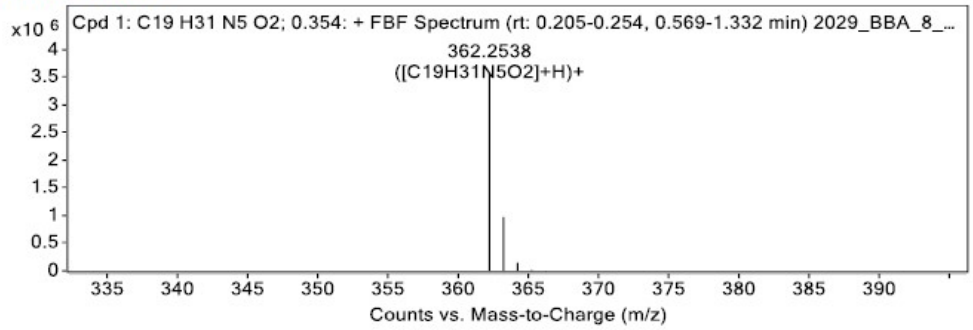
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 1:40:29 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

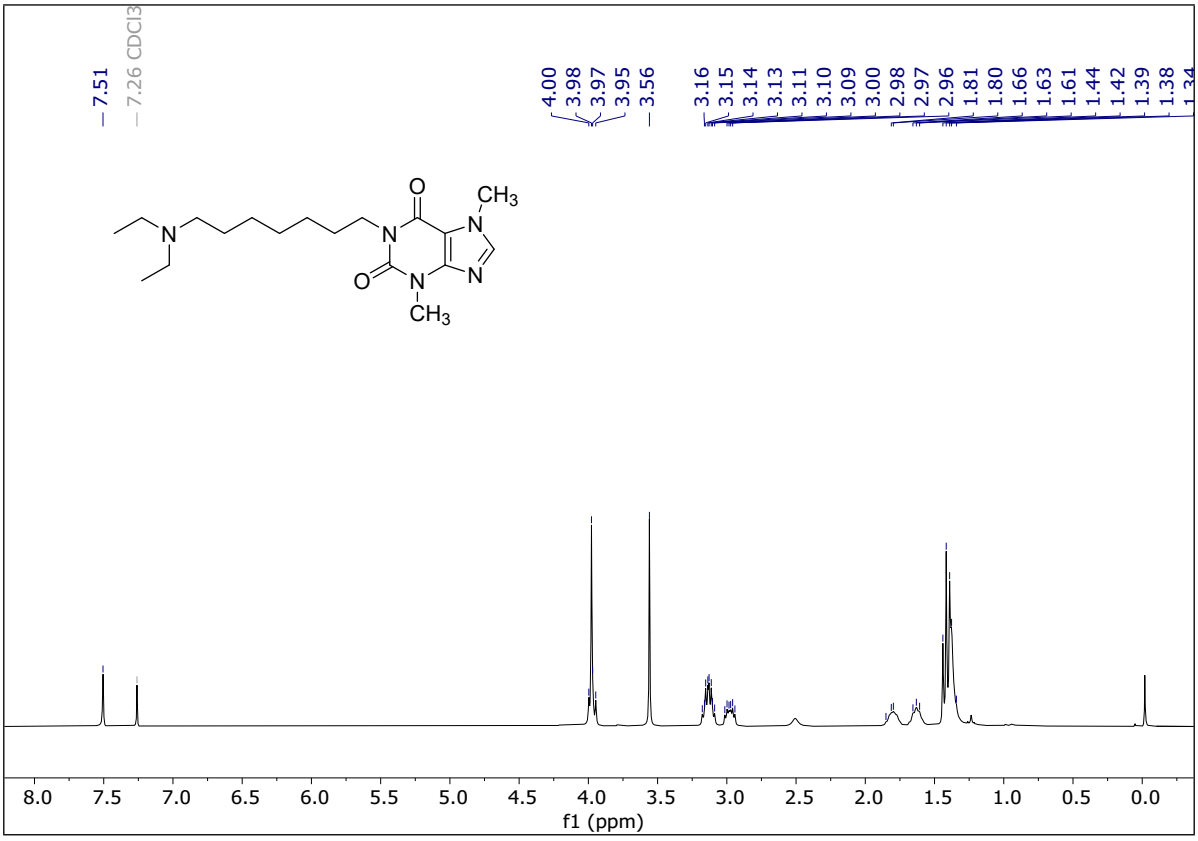
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C19 H31 N5 O2; 0.354	0.354	361.2464	3576911	C19 H31 N5 O2	361.2478	-3.9	1

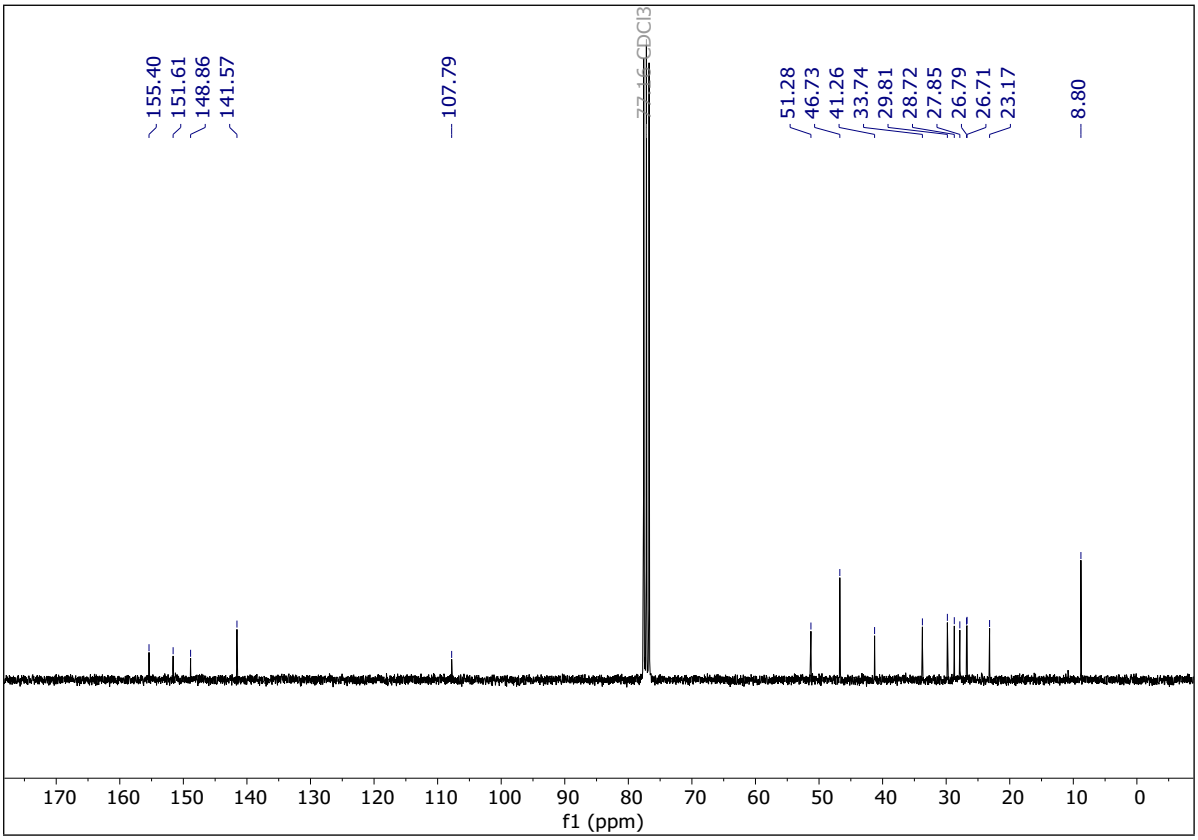
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C19 H31 N5 O2; 0.354	362.2538	0.354	Find by Formula	361.2464

MS Zoomed Spectrum

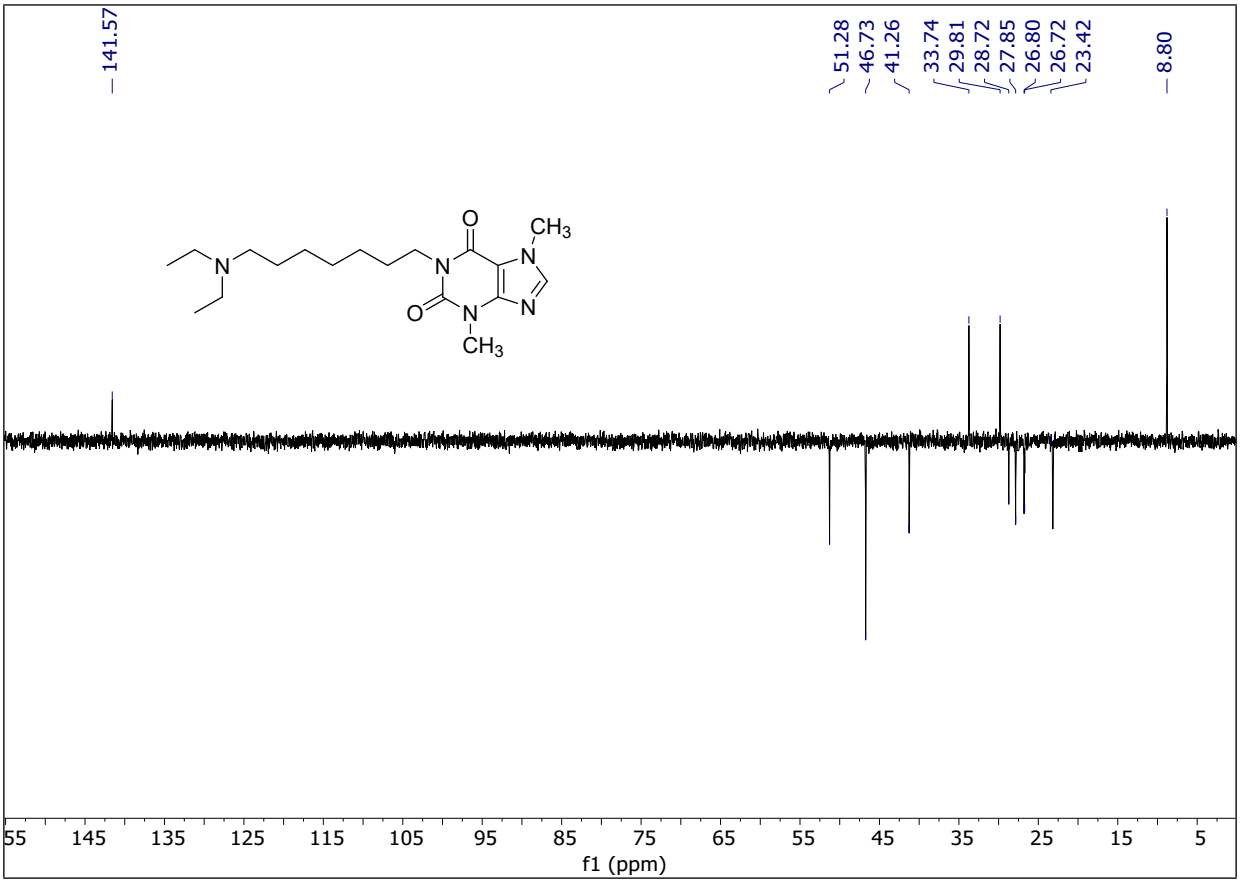


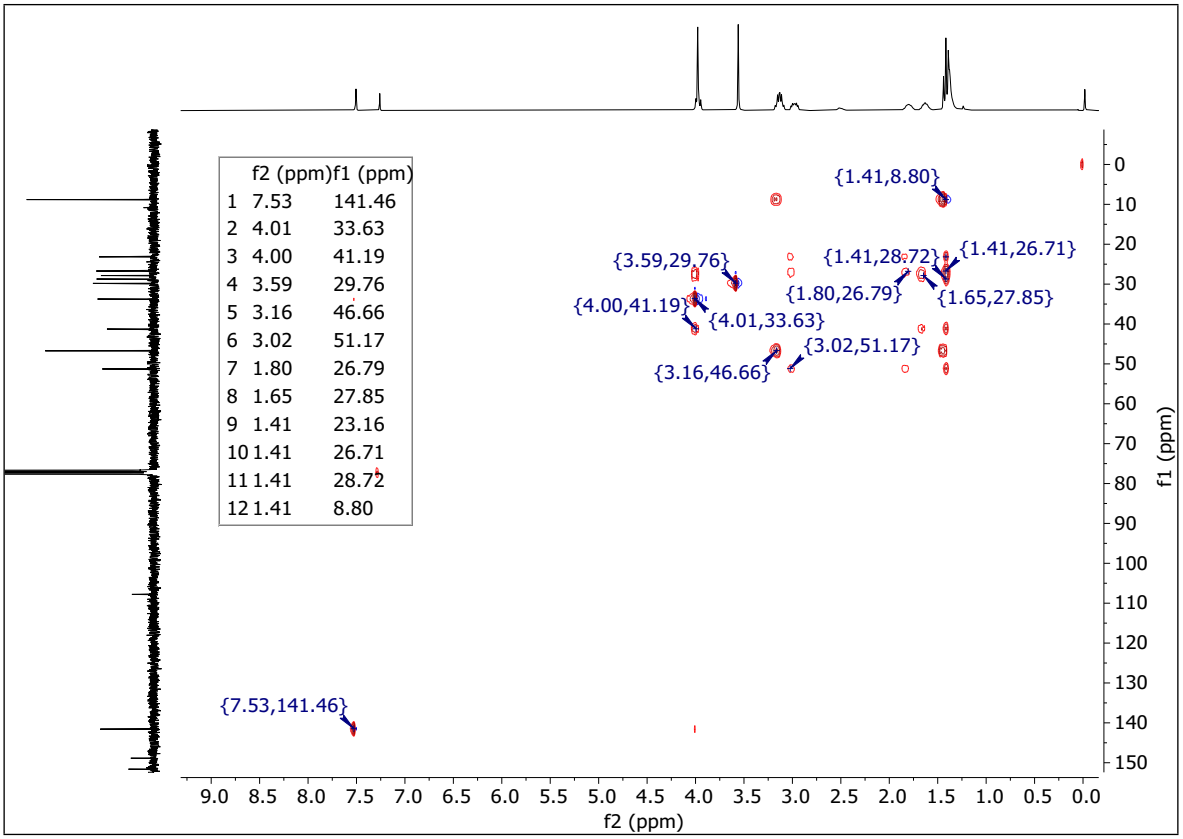
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **22**





DEPT and HSQC spectra in $CDCl_3$ of **22**





Qualitative Compound Report

Data File	2030_BBA_9_02.d	**Sample Name**	BBA_9
Sample Type	Sample	**Position**	Vial 5
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/22/2022 1:02:07 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

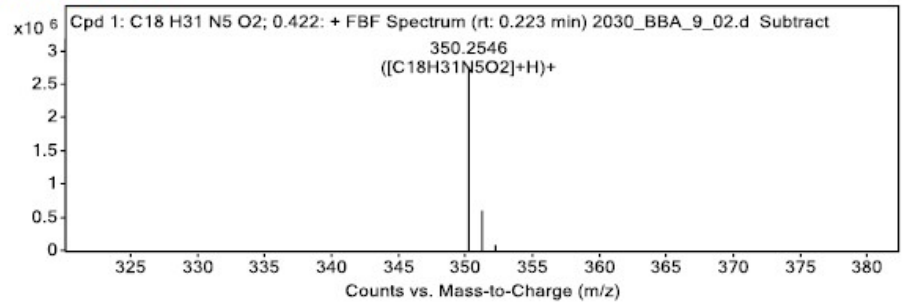
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 1:02:07 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

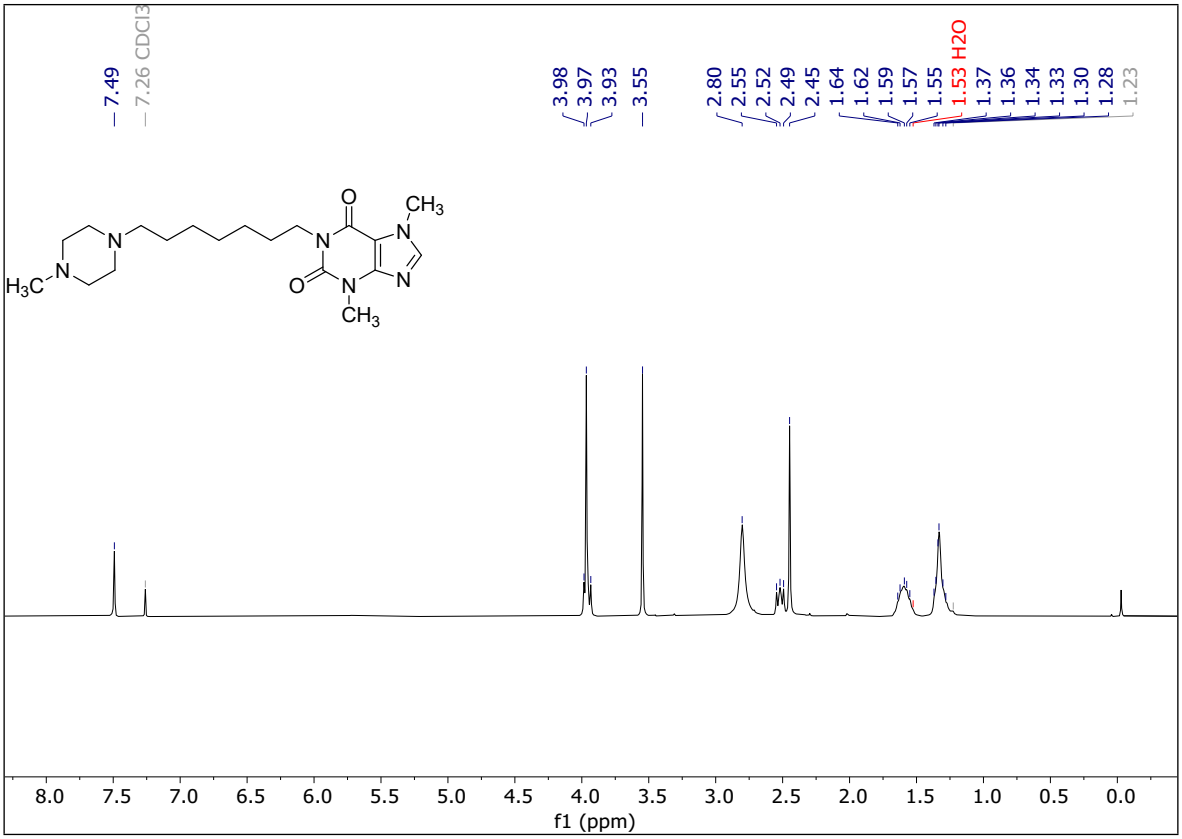
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C18 H31 N5 O2; 0.422	0.422	349.2476	2753006	C18 H31 N5 O2	349.2478	-0.48	1

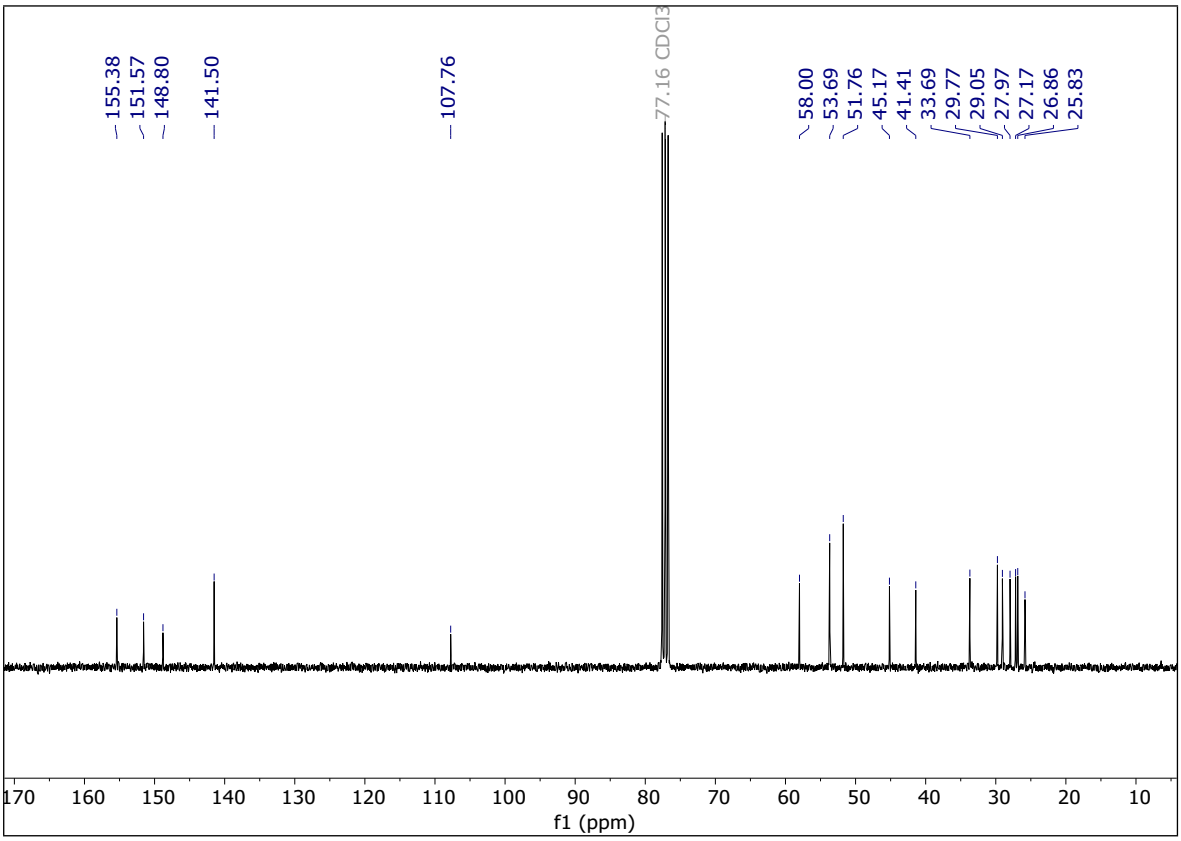
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C18 H31 N5 O2; 0.422	350.2546	0.422	Find by Formula	349.2476

MS Zoomed Spectrum

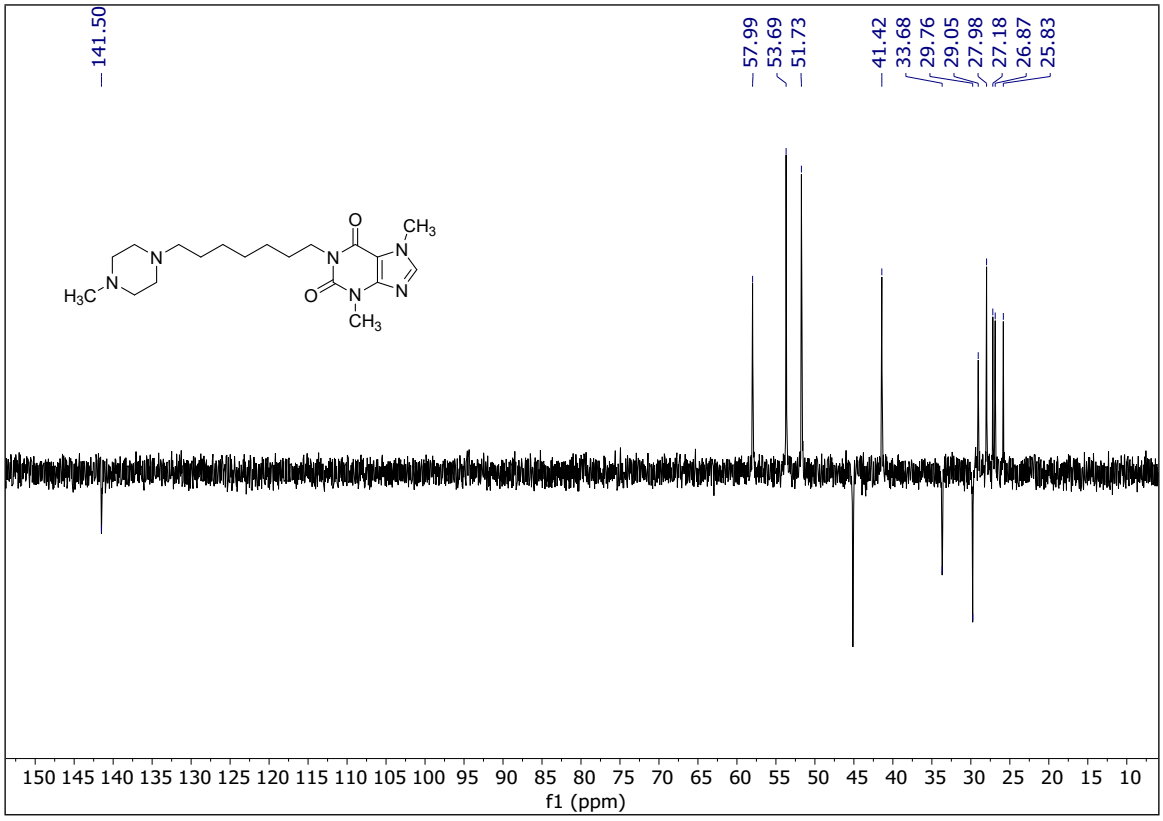


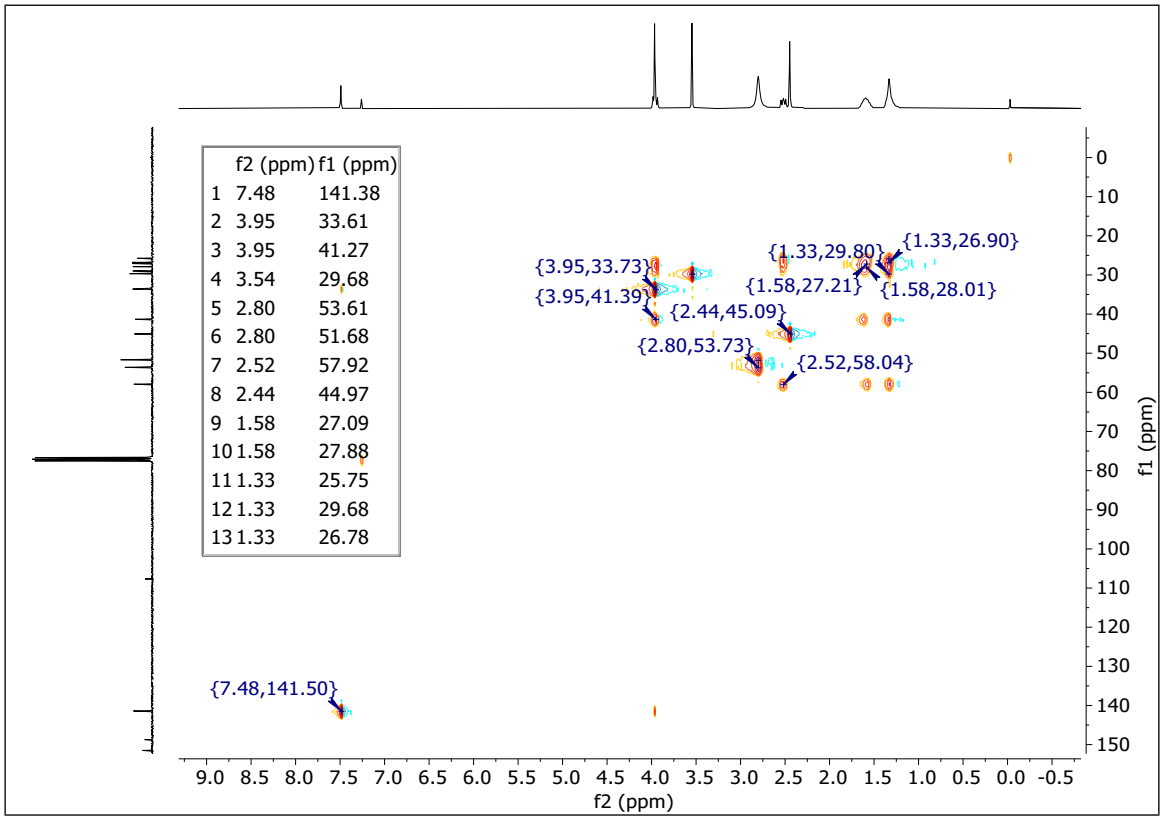
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **23**





DEPT and HSQC spectra in $CDCl_3$ of **23**





Qualitative Compound Report

Data File	2031_BBA_10_01.d	**Sample Name**	BBA_10
Sample Type	Sample	**Position**	Vial 10
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 1:55:01 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

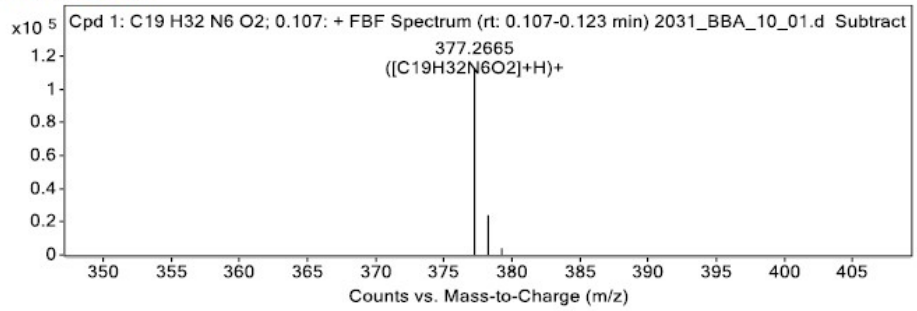
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 1:55:01 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

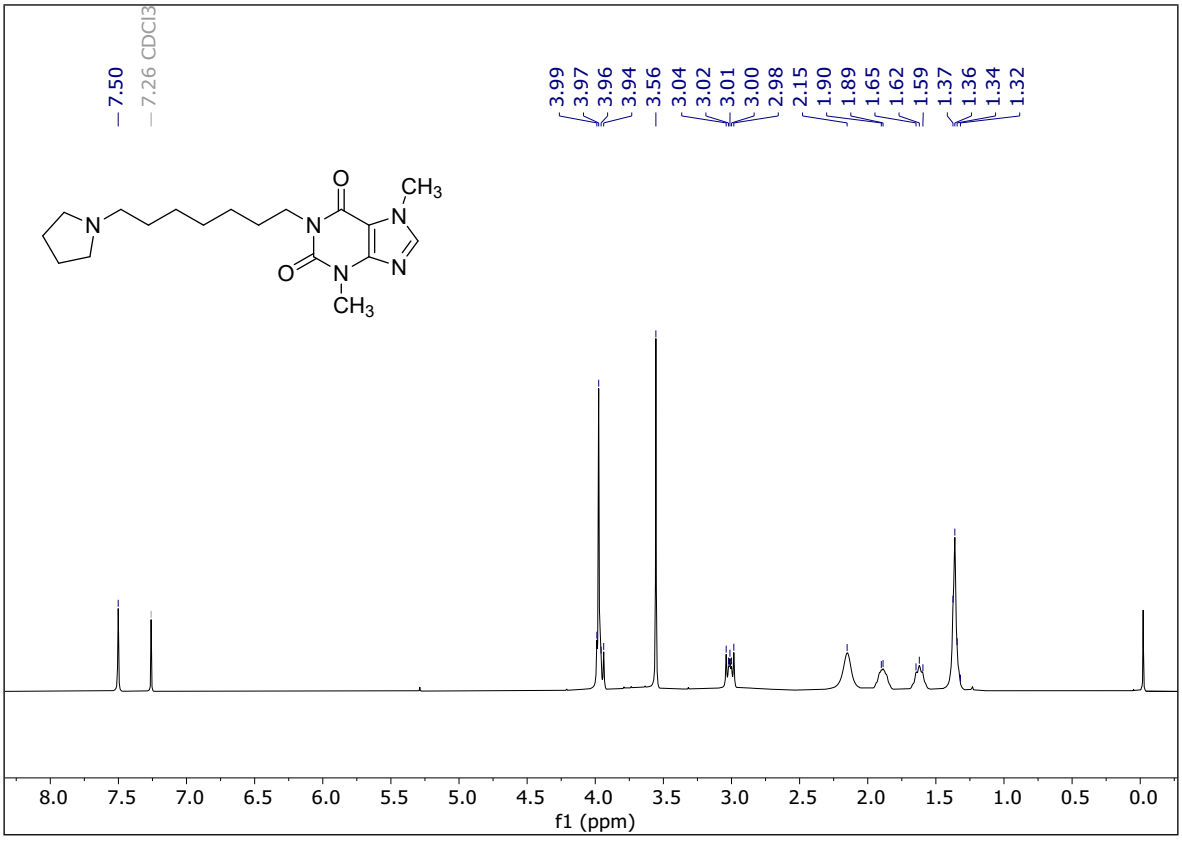
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C19 H32 N6 O2; 0.107	0.107	376.2588	113039	C19 H32 N6 O2	376.2587	0.46	1

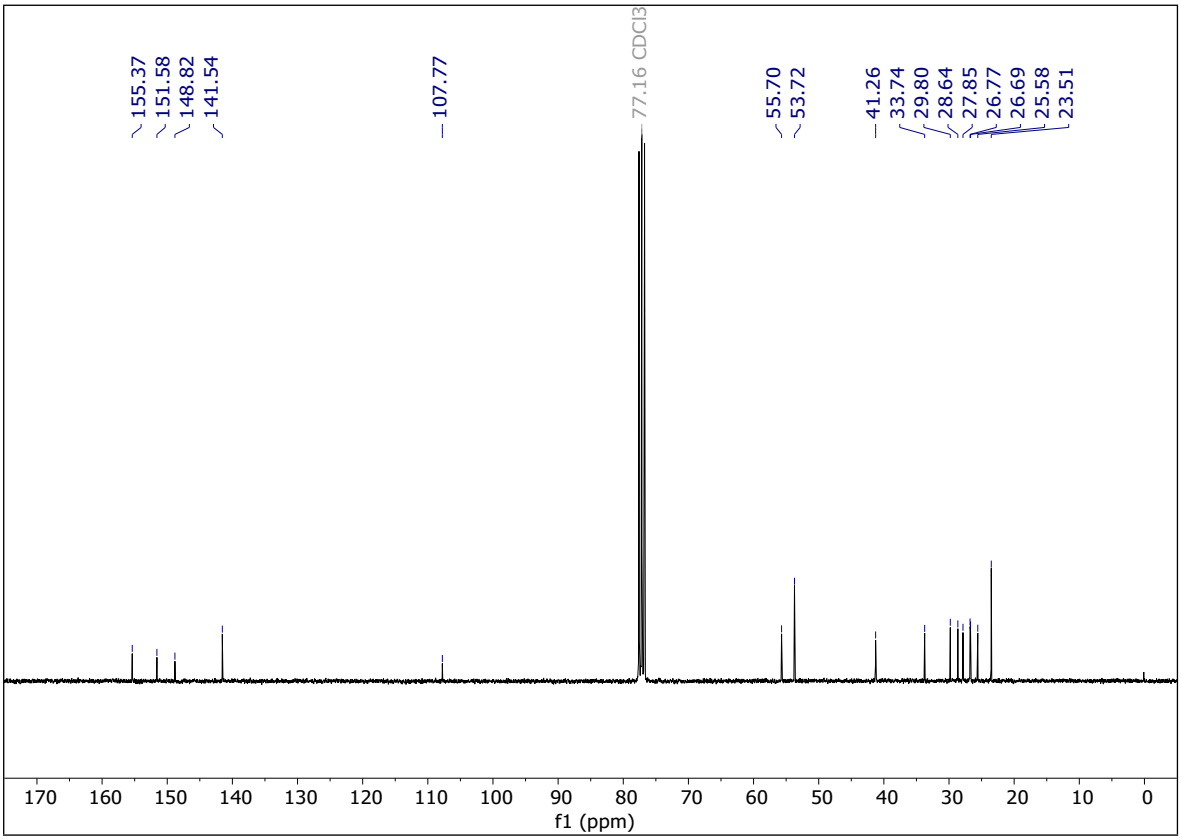
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C19 H32 N6 O2; 0.107	377.2665	0.107	Find by Formula	376.2588

MS Zoomed Spectrum

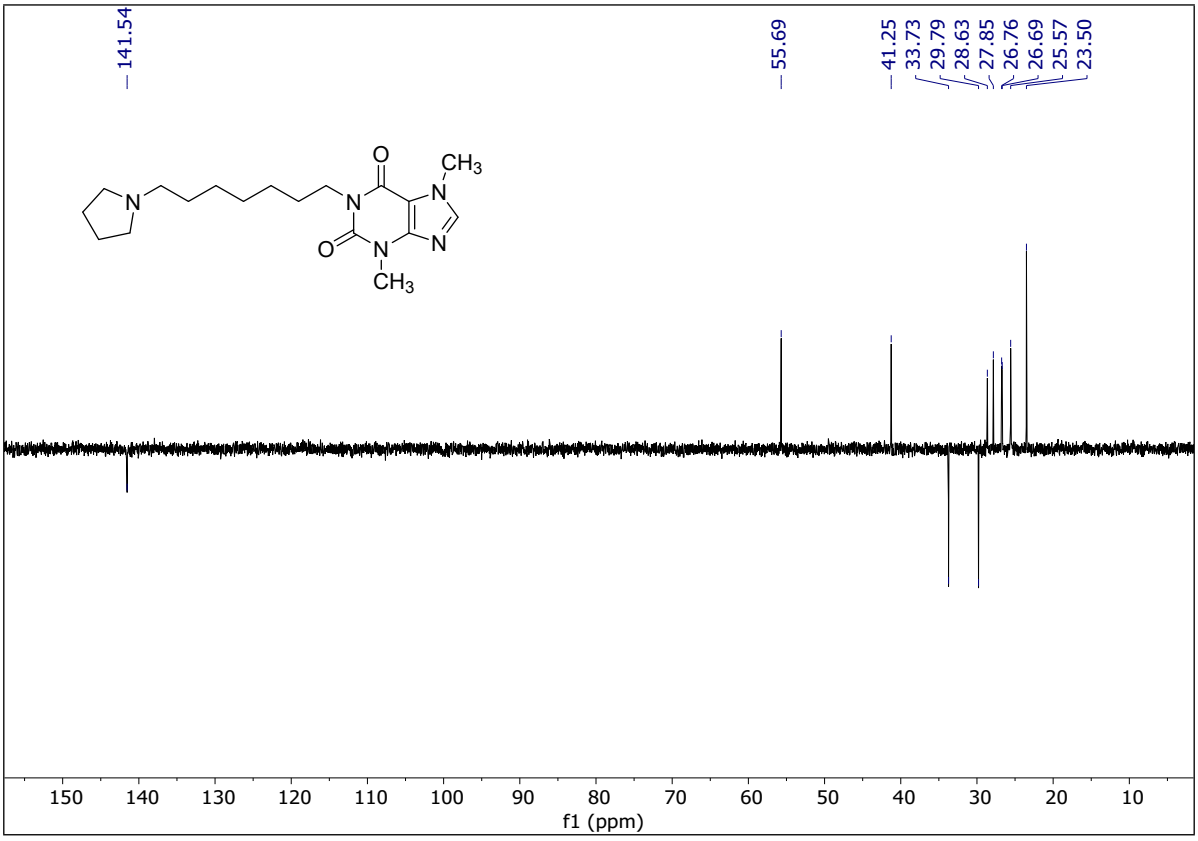


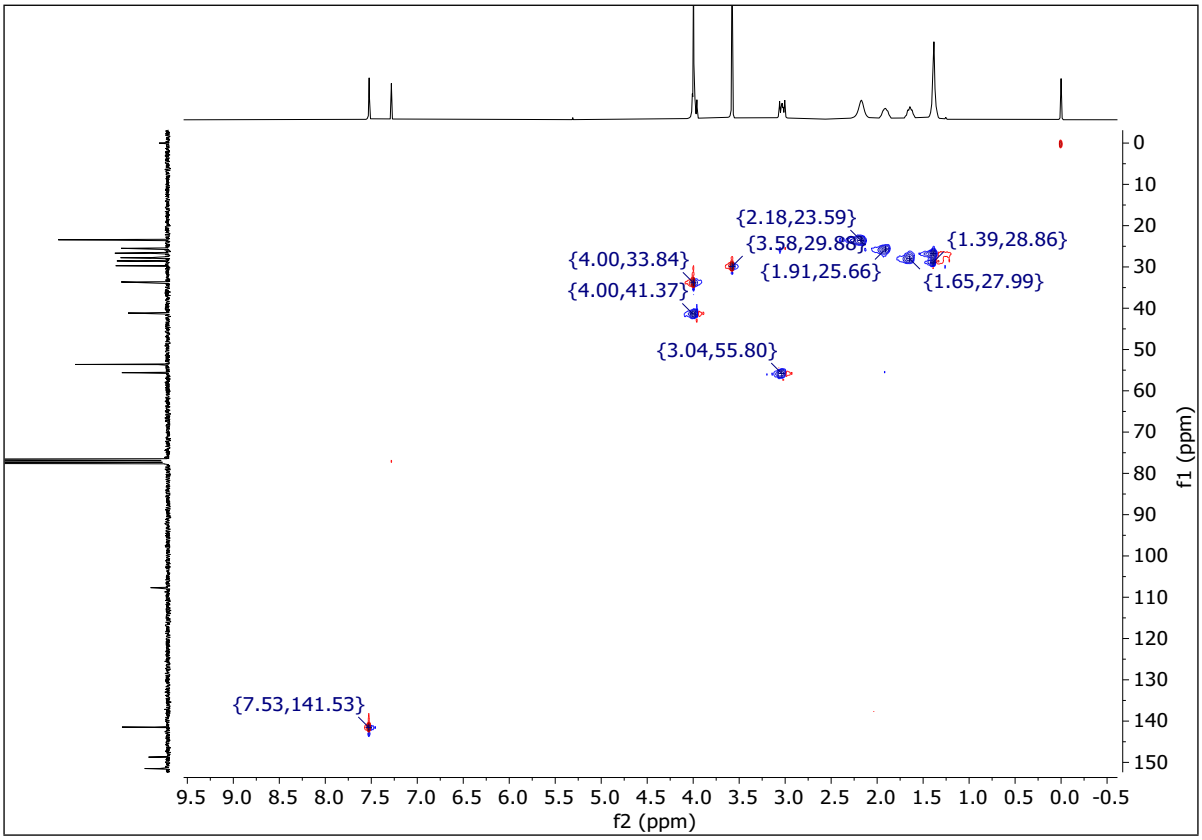
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **24**





DEPT and HSQC spectra in $CDCl_3$ of **24**





Qualitative Compound Report

Data File	2028_BBA_7_01.d	**Sample Name**	BBA_7
Sample Type	Sample	**Position**	Vial 7
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 1:33:15 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

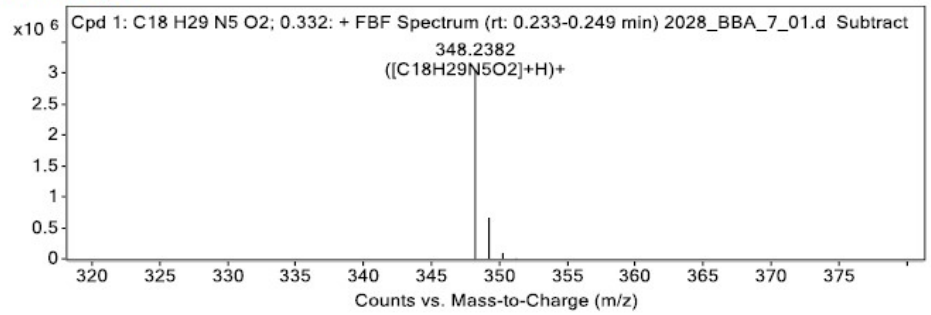
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 1:33:15 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

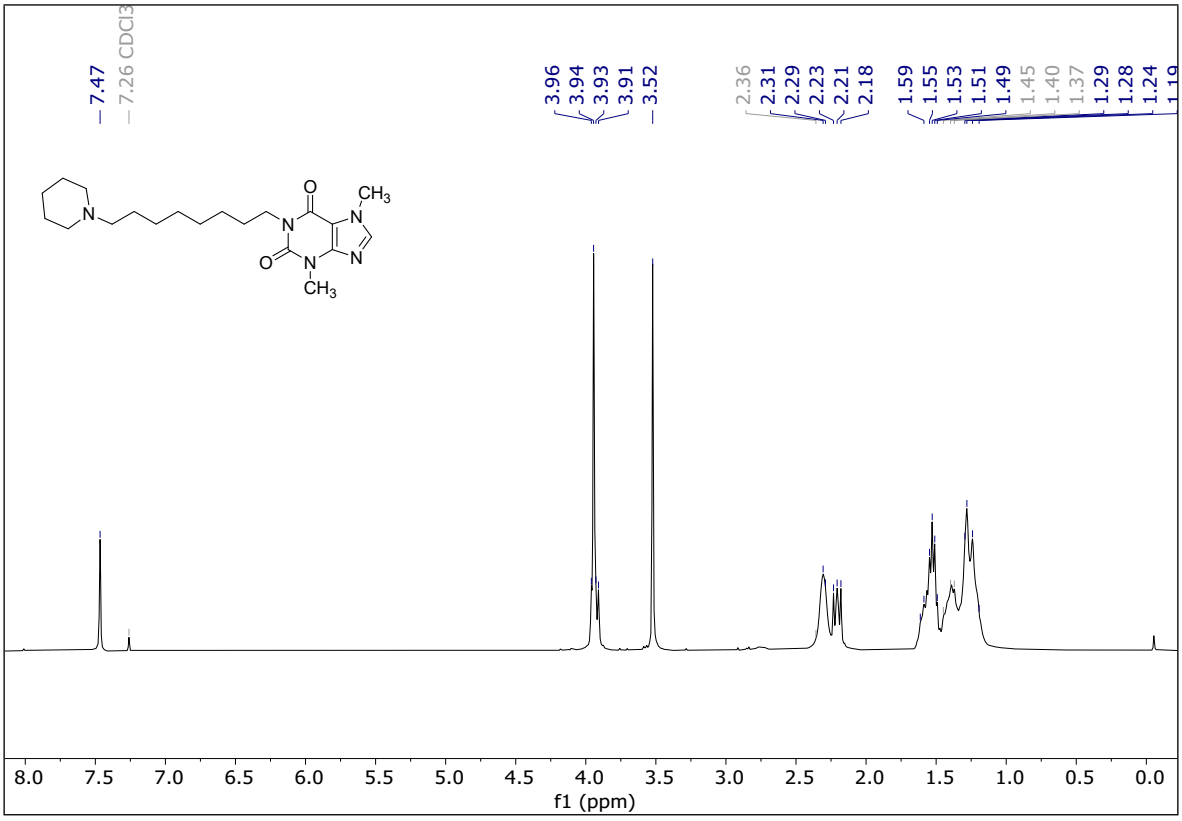
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C18 H29 N5 O2; 0.332	0.332	347.2311	3050682	C18 H29 N5 O2	347.2321	-2.88	1

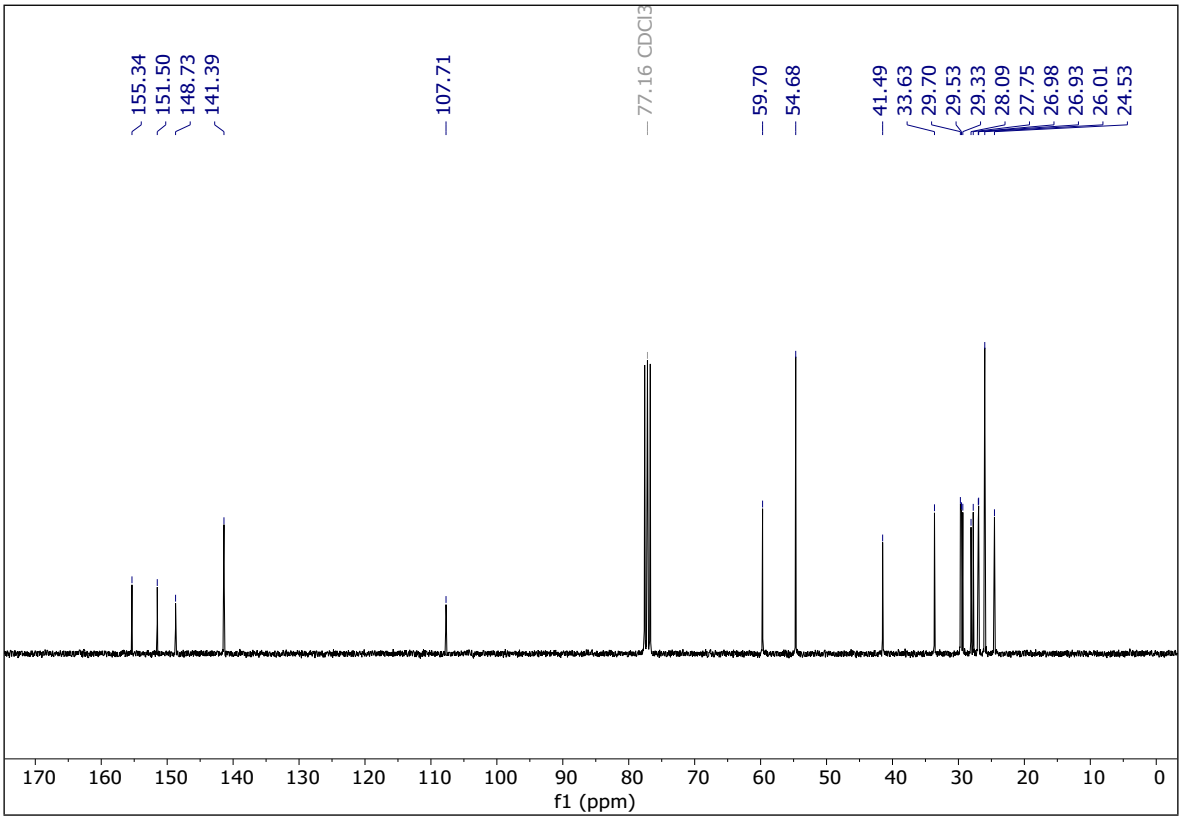
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C18 H29 N5 O2; 0.332	348.2382	0.332	Find by Formula	347.2311

MS Zoomed Spectrum

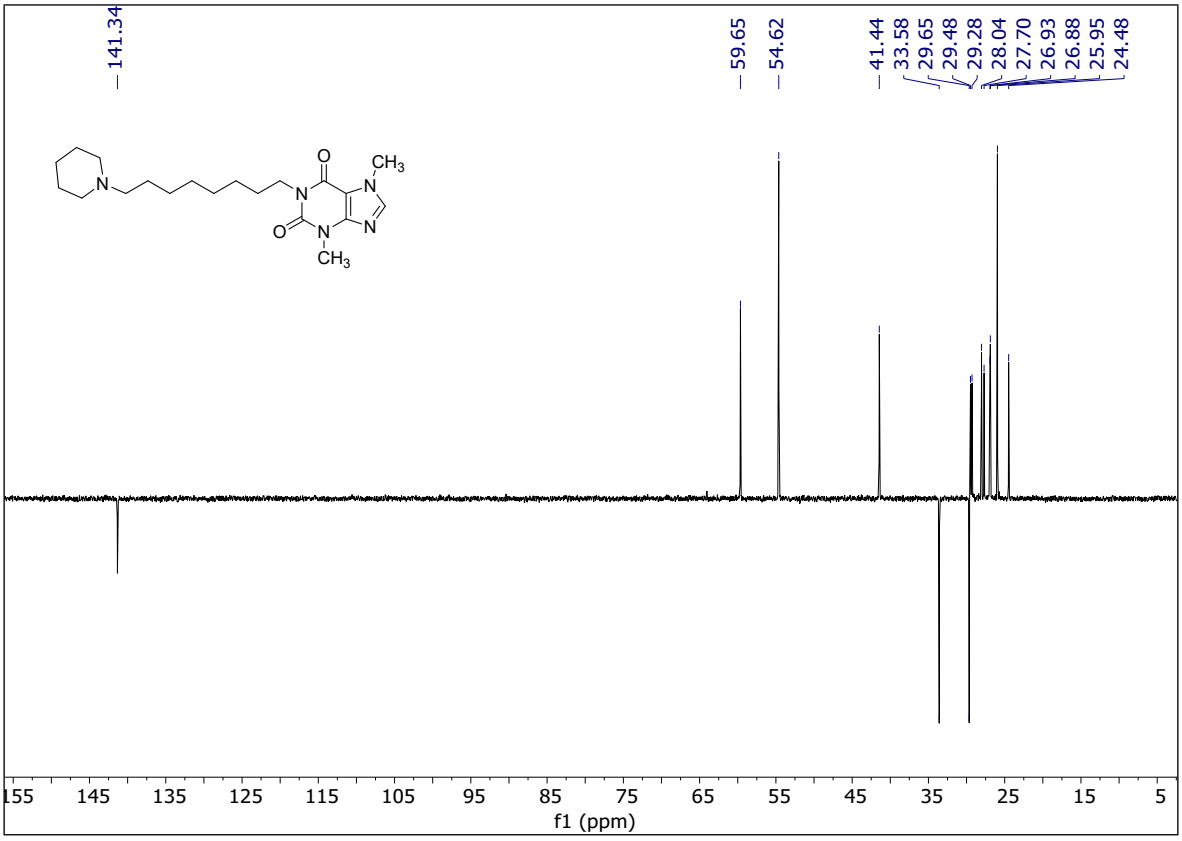


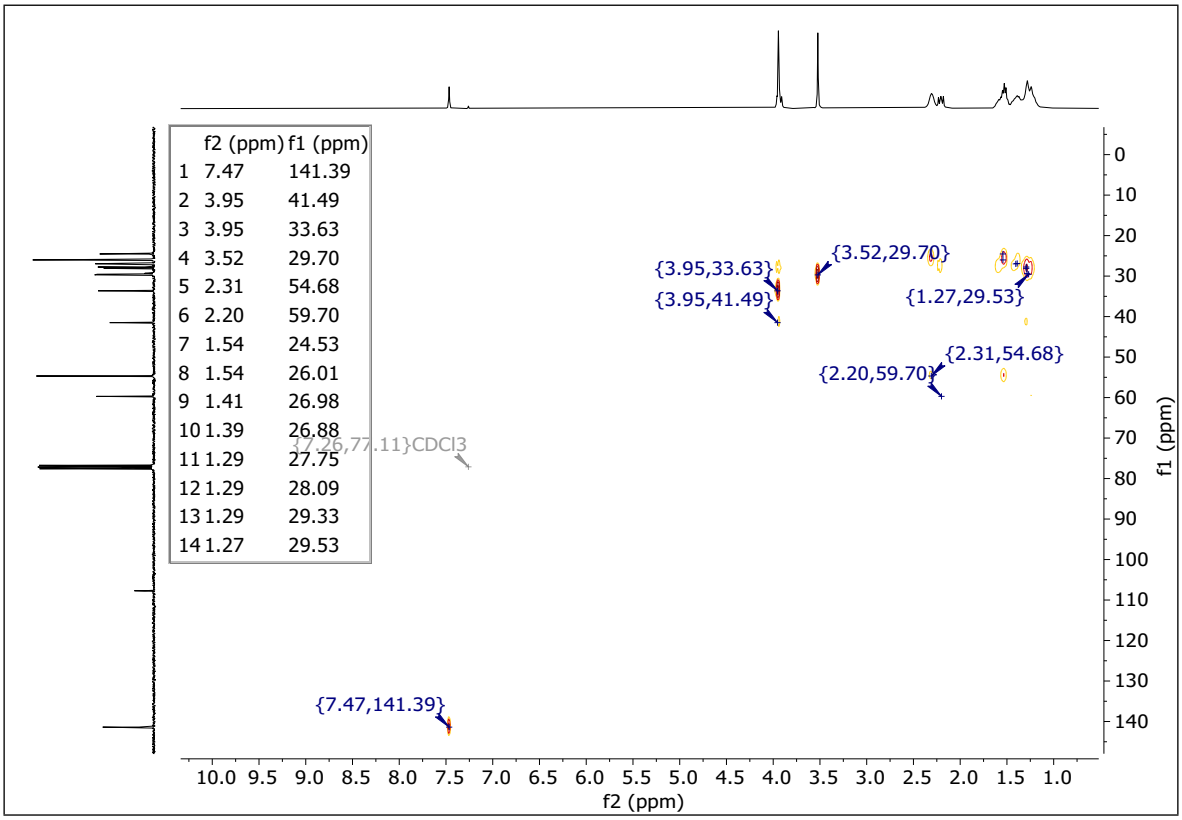
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **25**





DEPT and HSQC spectra in $CDCl_3$ of **25**





Qualitative Compound Report

Data File	2026_BBA_5_01.d	**Sample Name**	BBA_5
Sample Type	Sample	**Position**	Vial 5
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 1:18:46 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

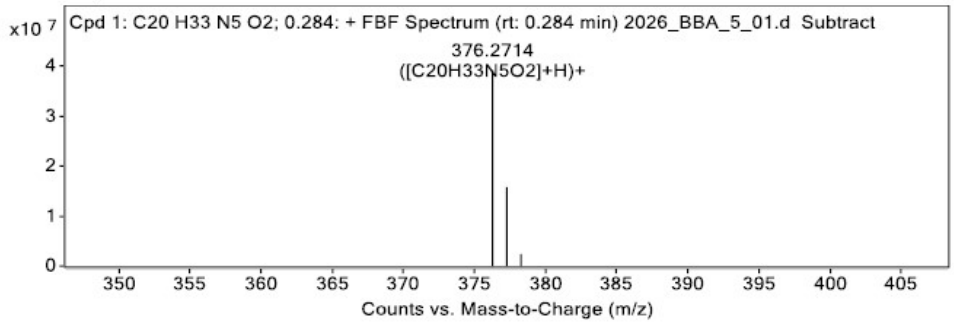
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 1:18:46 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

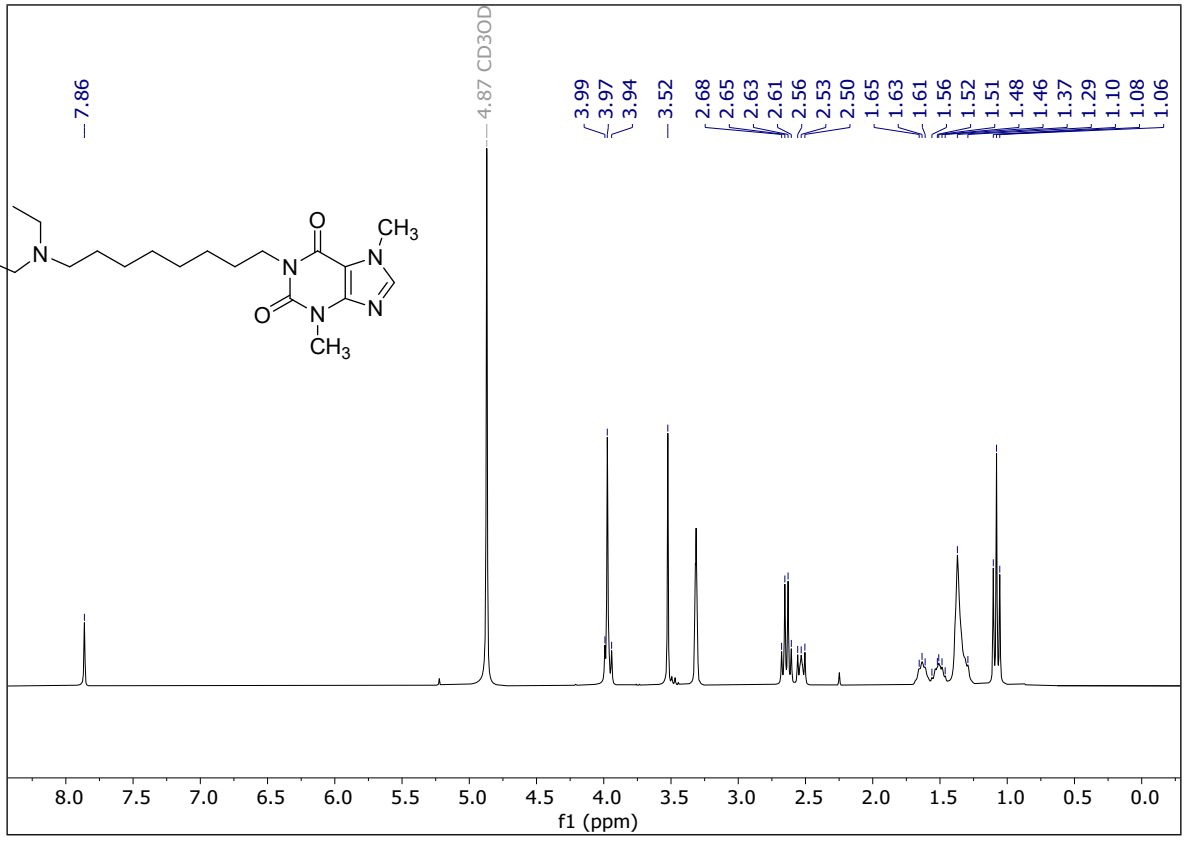
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C20 H33 N5 O2; 0.284	0.284	375.2635	39219620	C20 H33 N5 O2	375.2634	0.18	1

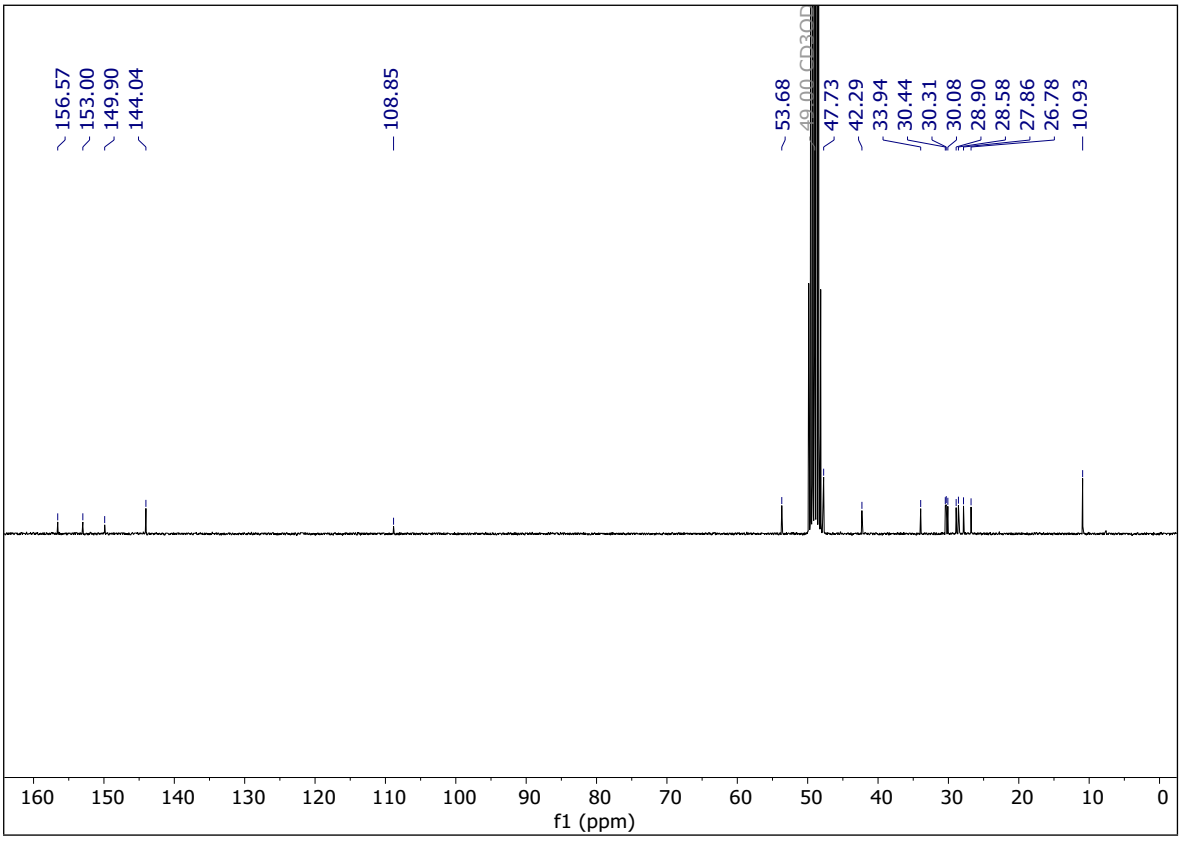
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C20 H33 N5 O2; 0.284	376.2714	0.284	Find by Formula	375.2635

MS Zoomed Spectrum

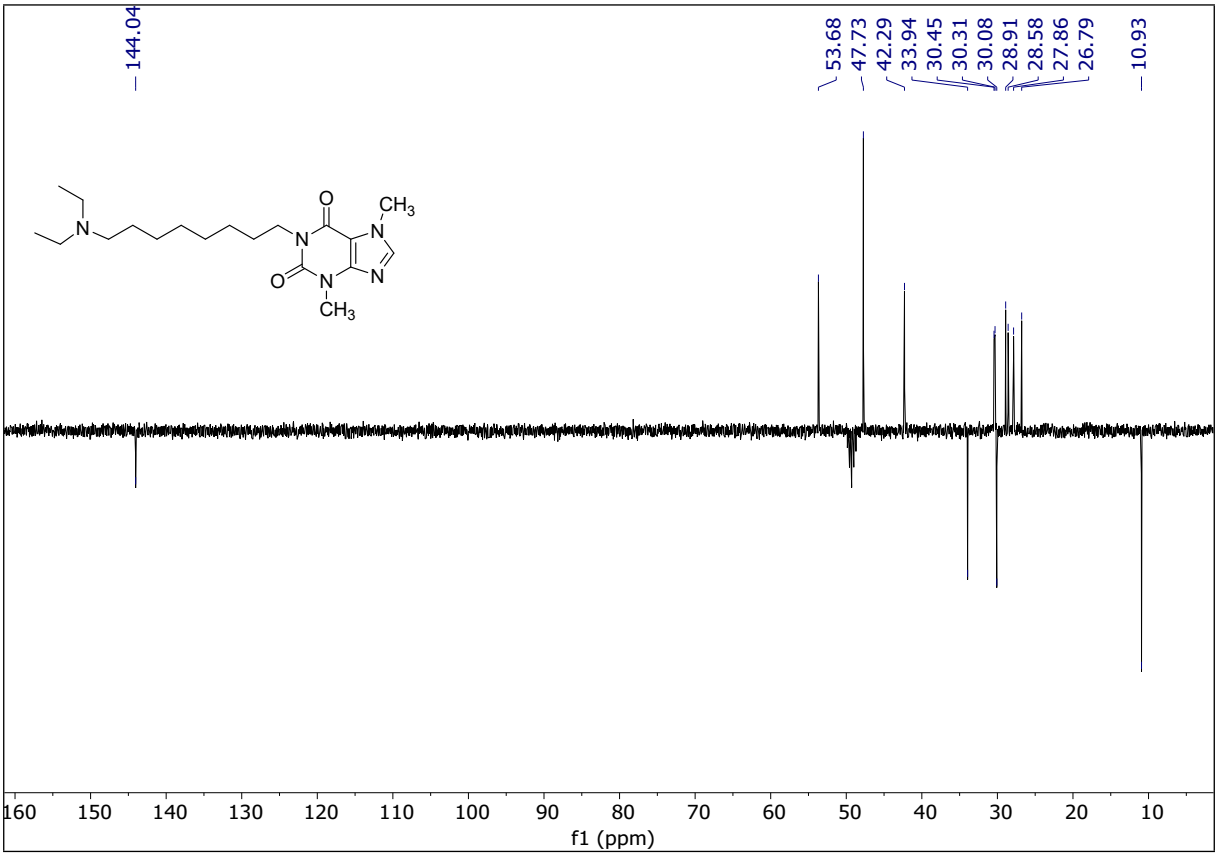


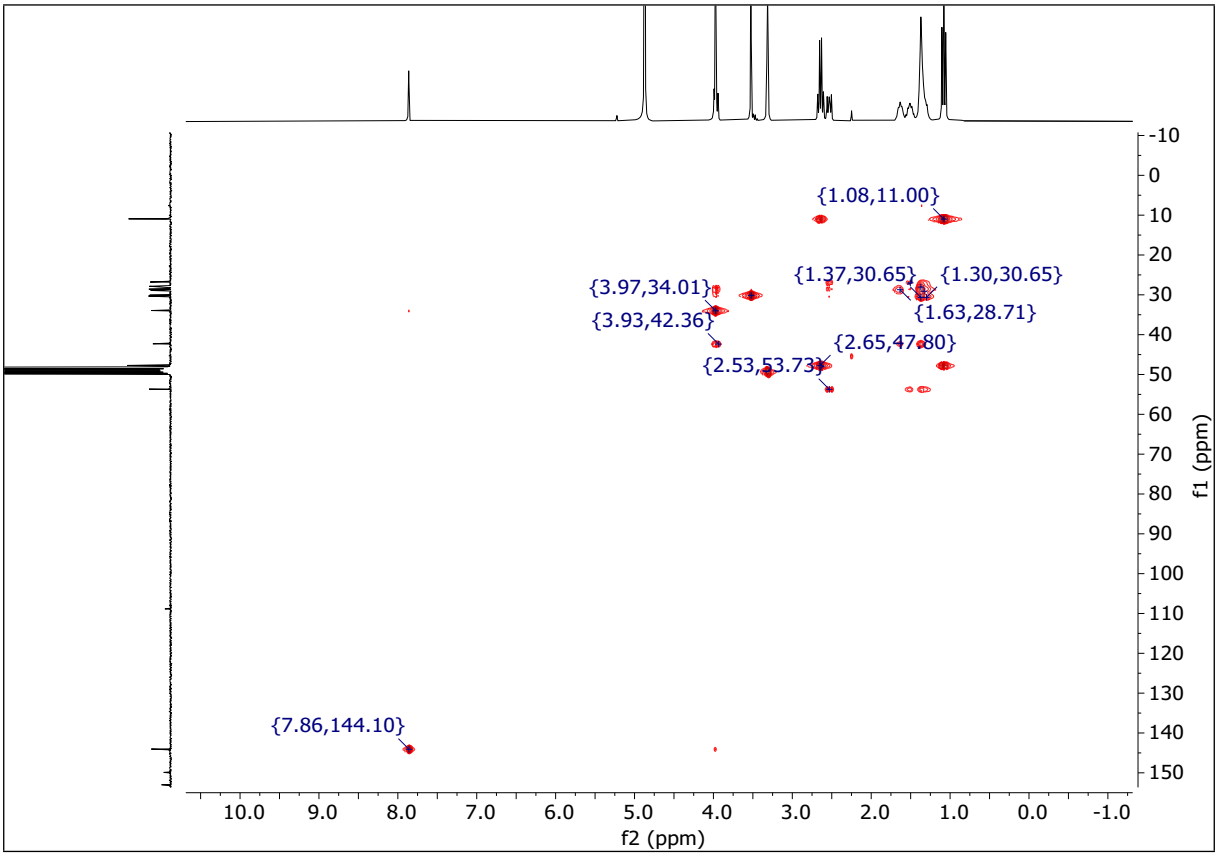
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in MeOD of **26**





DEPT and HSQC spectra in MeOD of **26**





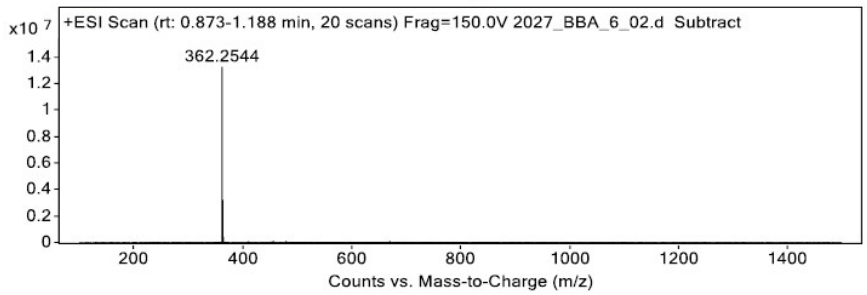
Qualitative Analysis Report

Data Filename	2027_BBA_6_02.d	**Sample Name**	BBA_6
Sample Type	Sample	**Position**	Vial 4
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/22/2022 12:54:48 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

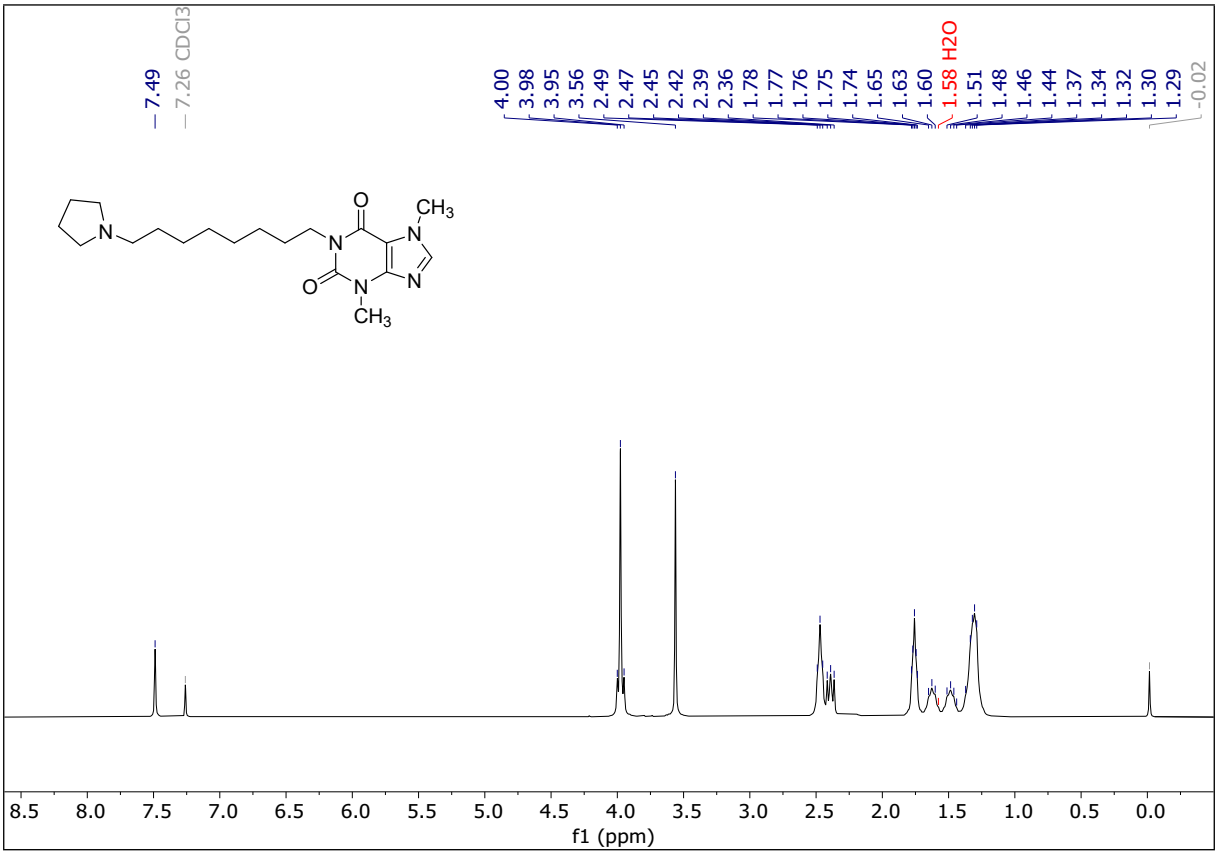
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 12:54:48 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

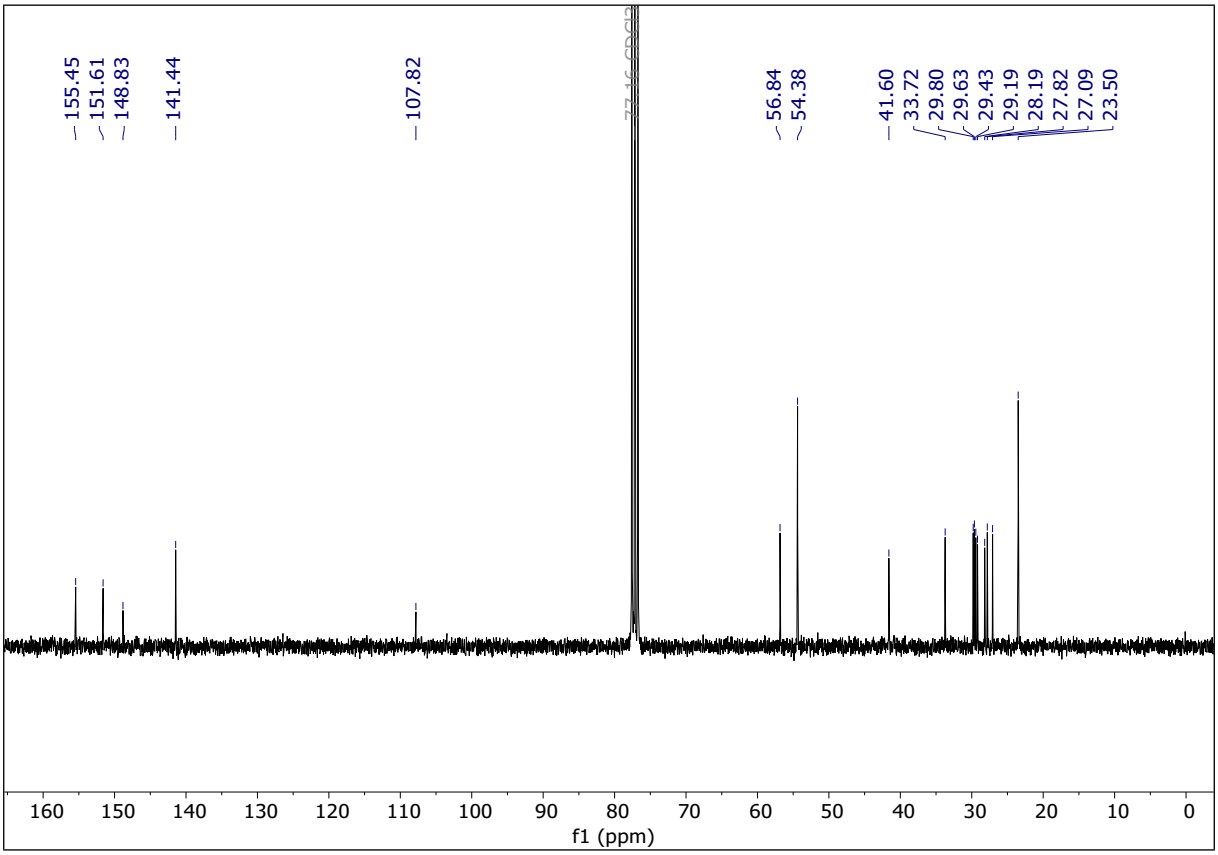
Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
150	0	ESI

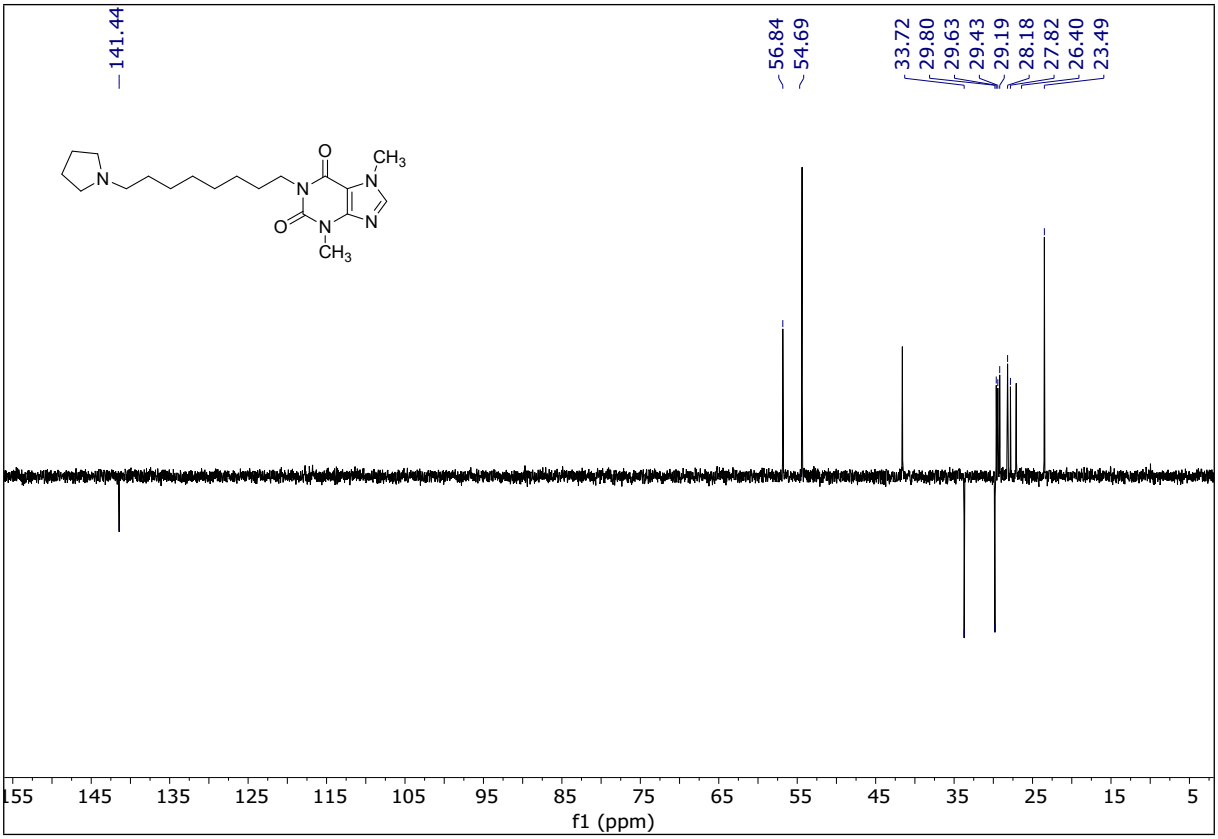


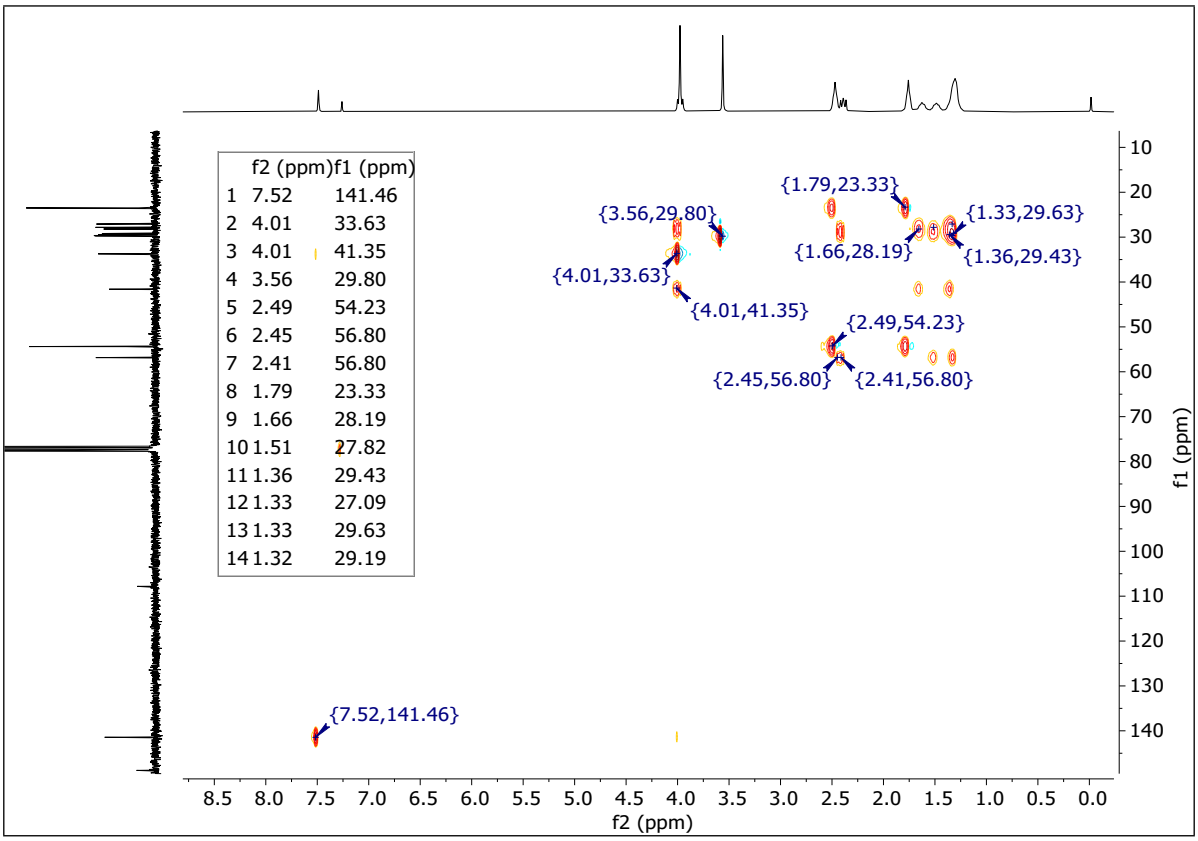
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ of **27**





DEPT and HSQC spectra in $CDCl_3$ of **27**





Qualitative Compound Report

Data File	2025_BBA_4_01.d	**Sample Name**	BBA_4
Sample Type	Sample	**Position**	Vial 4
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_new.m	**Acquired Time**	12/20/2022 1:11:36 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

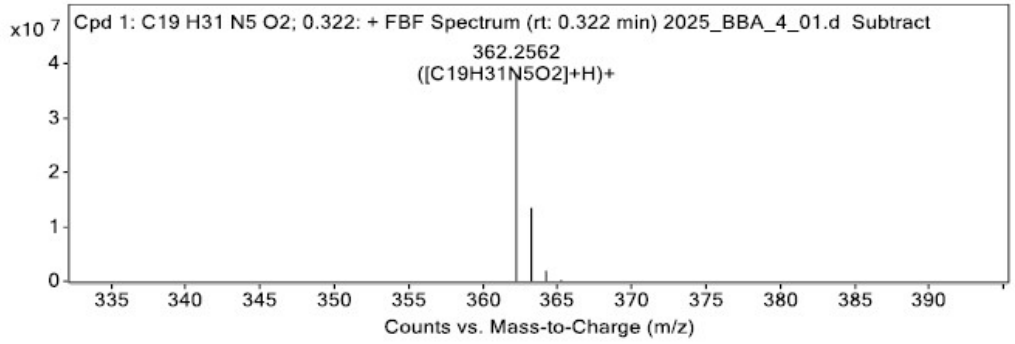
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/20/2022 1:11:36 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

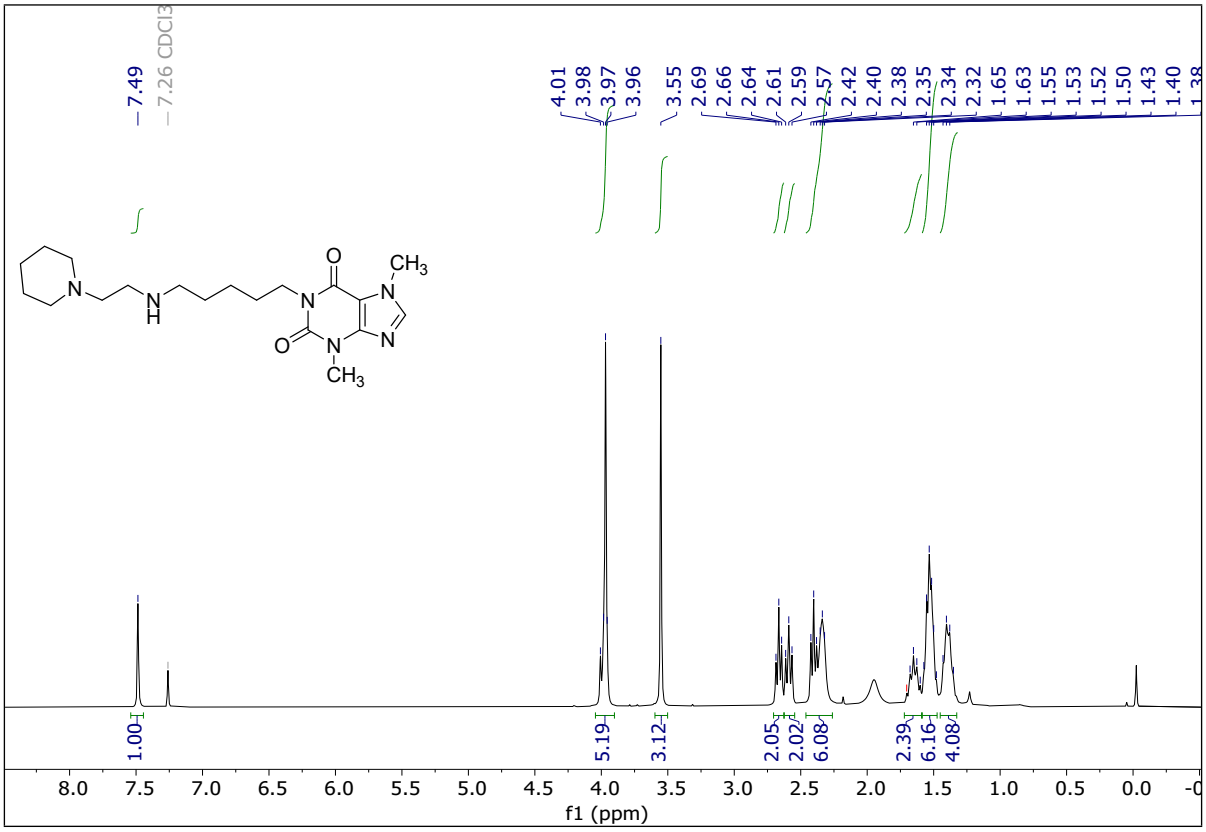
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C19 H31 N5 O2; 0.322	0.322	361.2485	37944788	C19 H31 N5 O2	361.2478	0.01	1

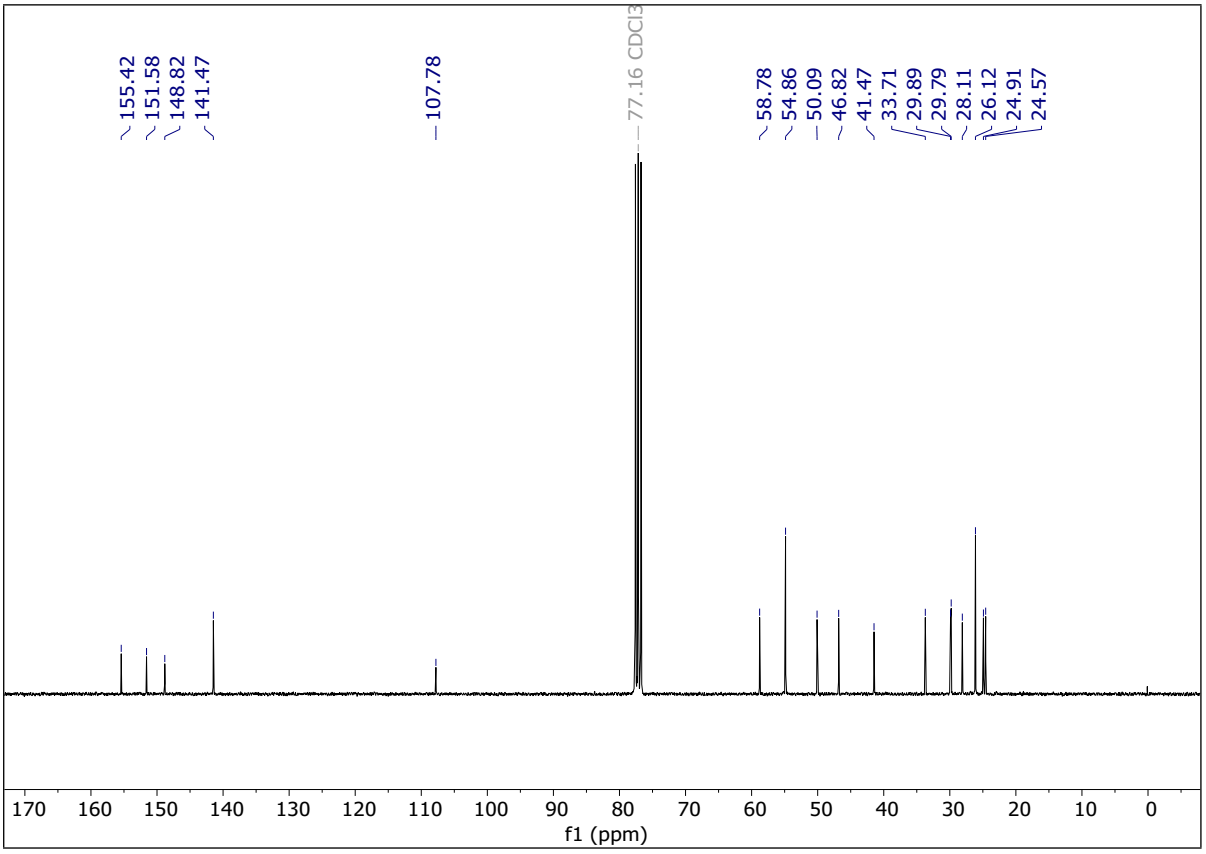
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C19 H31 N5 O2; 0.322	362.2562	0.322	Find by Formula	361.2485

MS Zoomed Spectrum

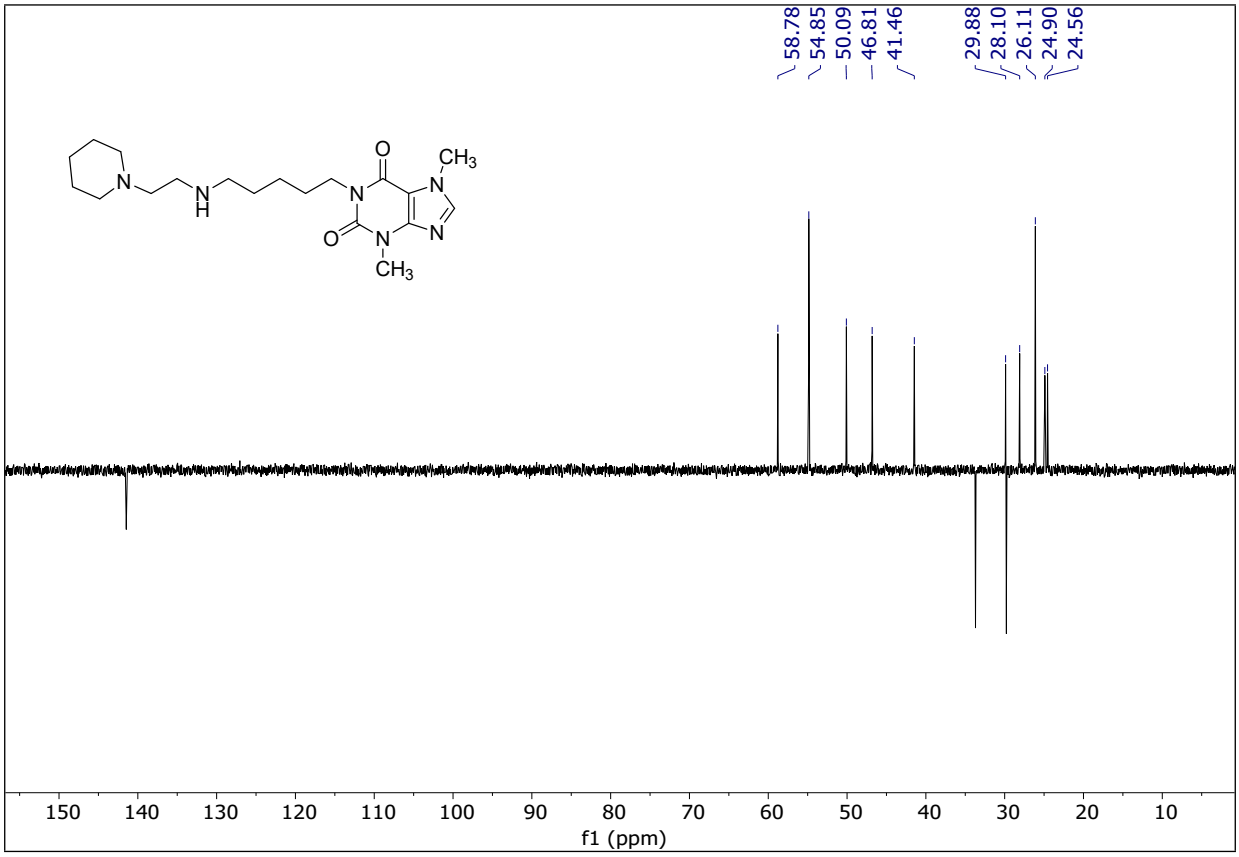


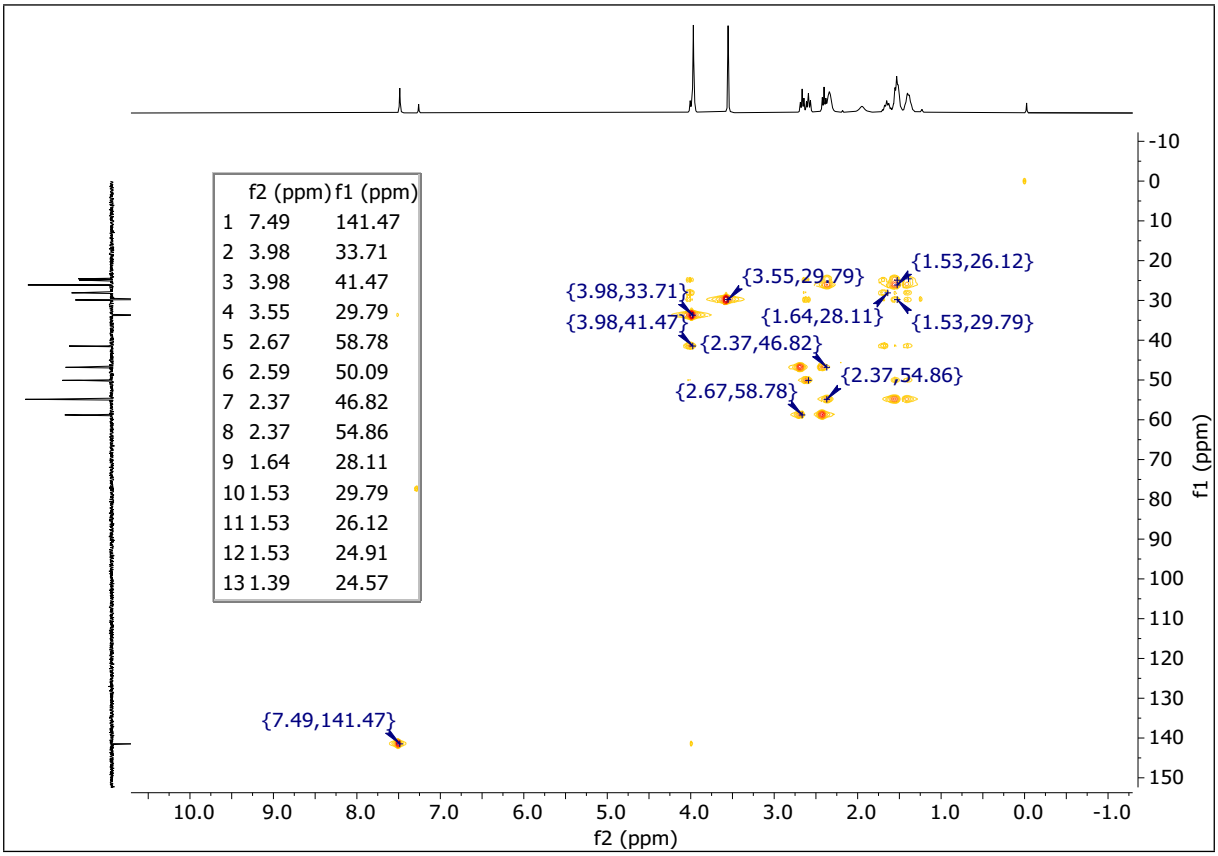
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDl_3 of **28**





DEPT and HSQC spectra in $CDCl_3$ of **28**





	f2 (ppm)	f1 (ppm)
1	7.49	141.47
2	3.98	33.71
3	3.98	41.47
4	3.55	29.79
5	2.67	58.78
6	2.59	50.09
7	2.37	46.82
8	2.37	54.86
9	1.64	28.11
10	1.53	29.79
11	1.53	26.12
12	1.53	24.91
13	1.39	24.57

Qualitative Compound Report

Data File	2023_BBA_2_02.d	**Sample Name**	BBA_2
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/22/2022 12:40:21 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

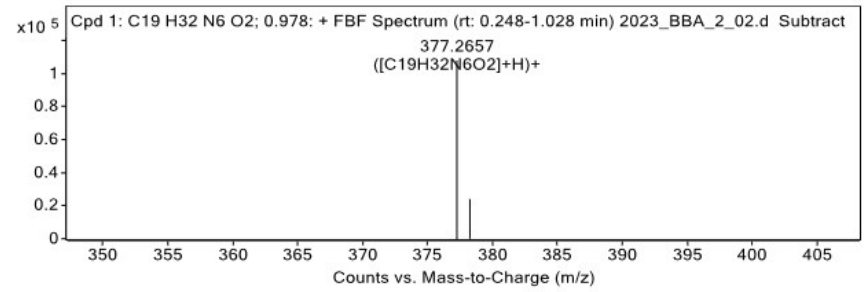
Sample Group Info.			
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 12:40:21 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

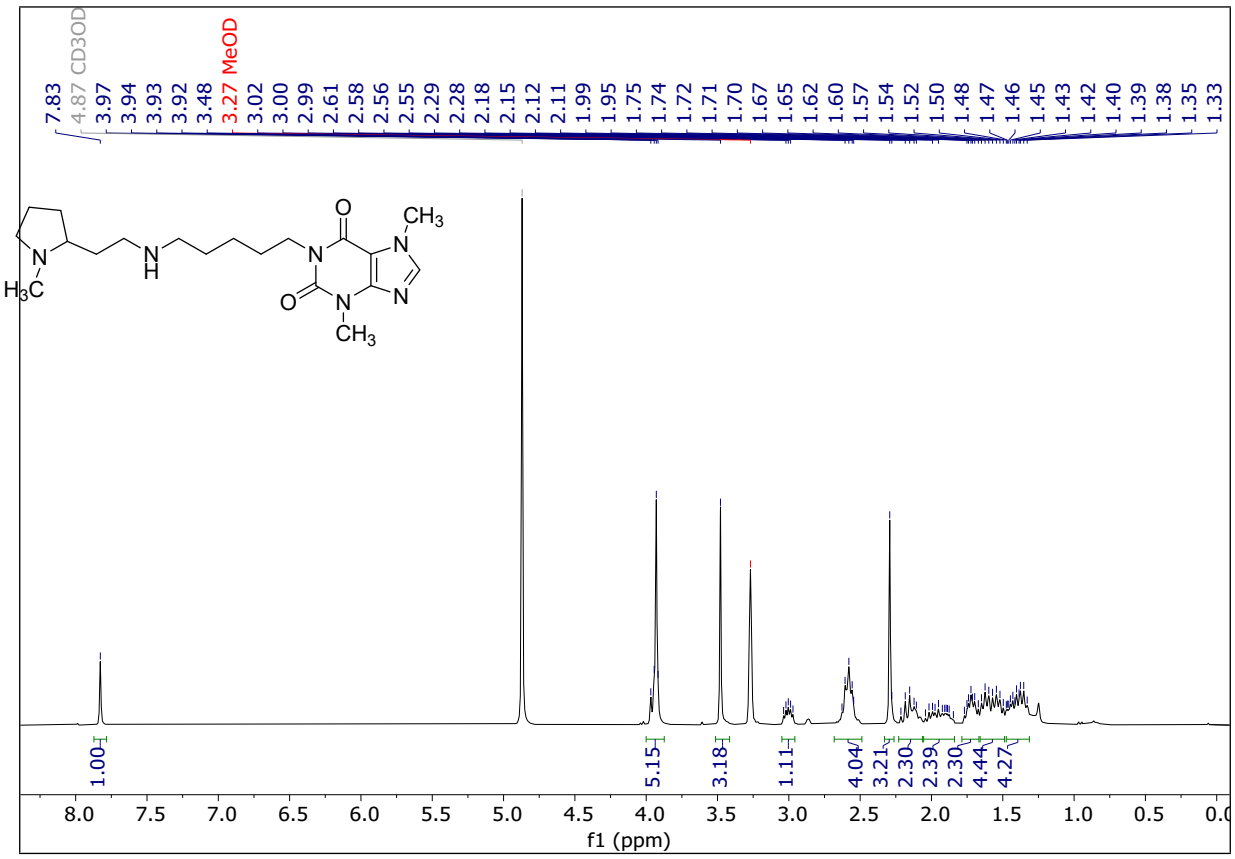
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C19 H32 N6 O2; 0.978	0.978	376.2584	107805	C19 H32 N6 O2	376.2587	-0.79	1

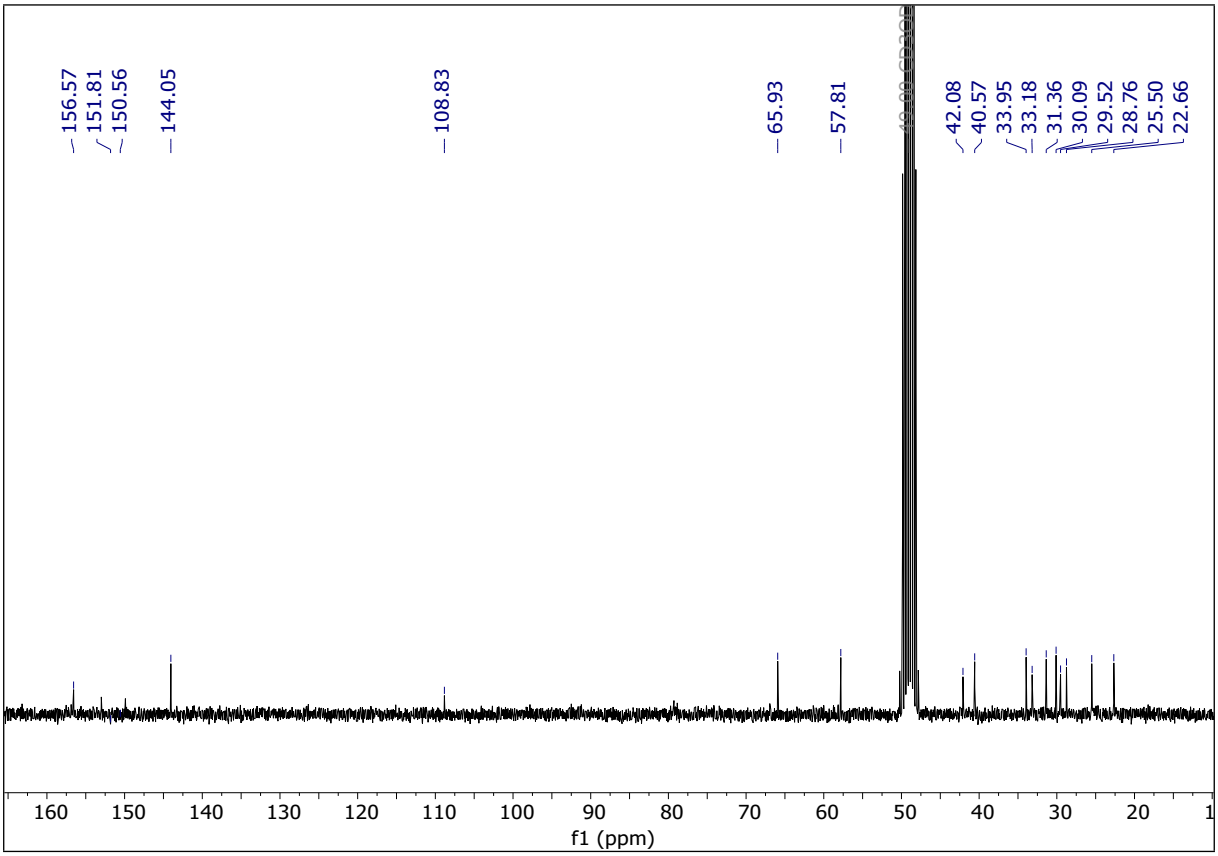
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C19 H32 N6 O2; 0.978	377.2657	0.978	Find by Formula	376.2584

MS Zoomed Spectrum

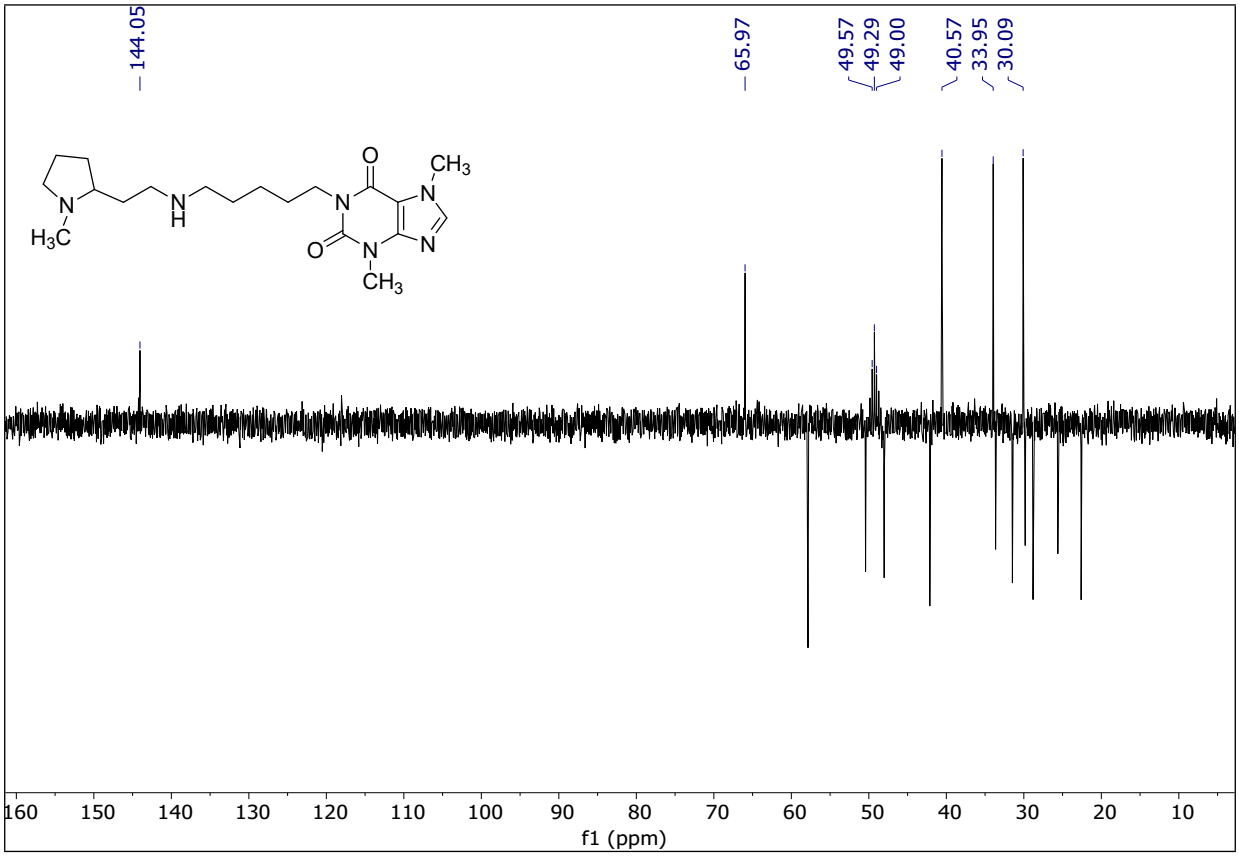


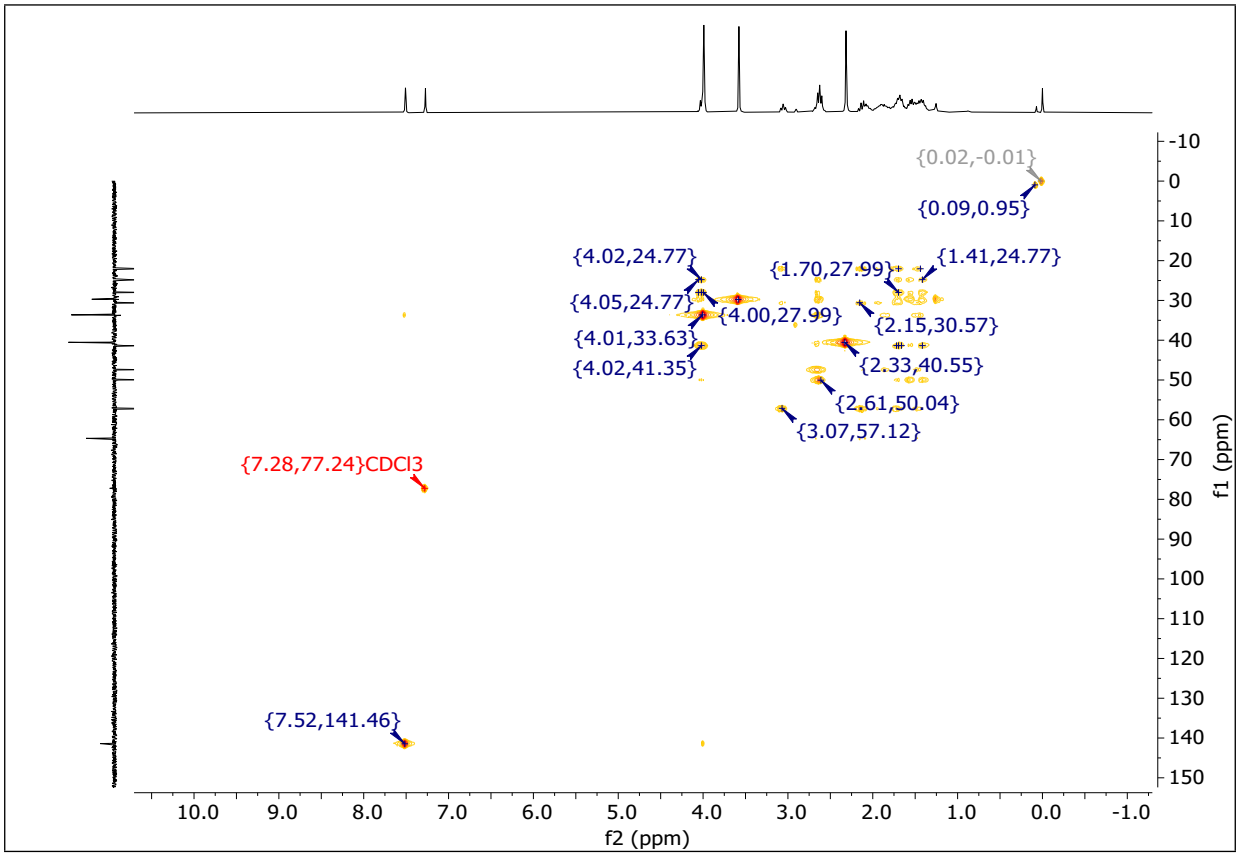
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in MeOD of **29**





DEPT and HSQC spectra in $CDCl_3$ of **29**





Qualitative Compound Report

Data File	2024_BBA_3_02.d	**Sample Name**	BBA_3
Sample Type	Sample	**Position**	Vial 3
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/22/2022 12:47:32 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

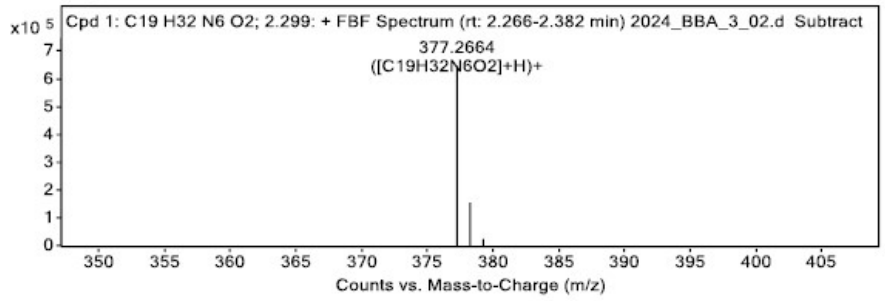
Sample Group		**Info.**	
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 12:47:32 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

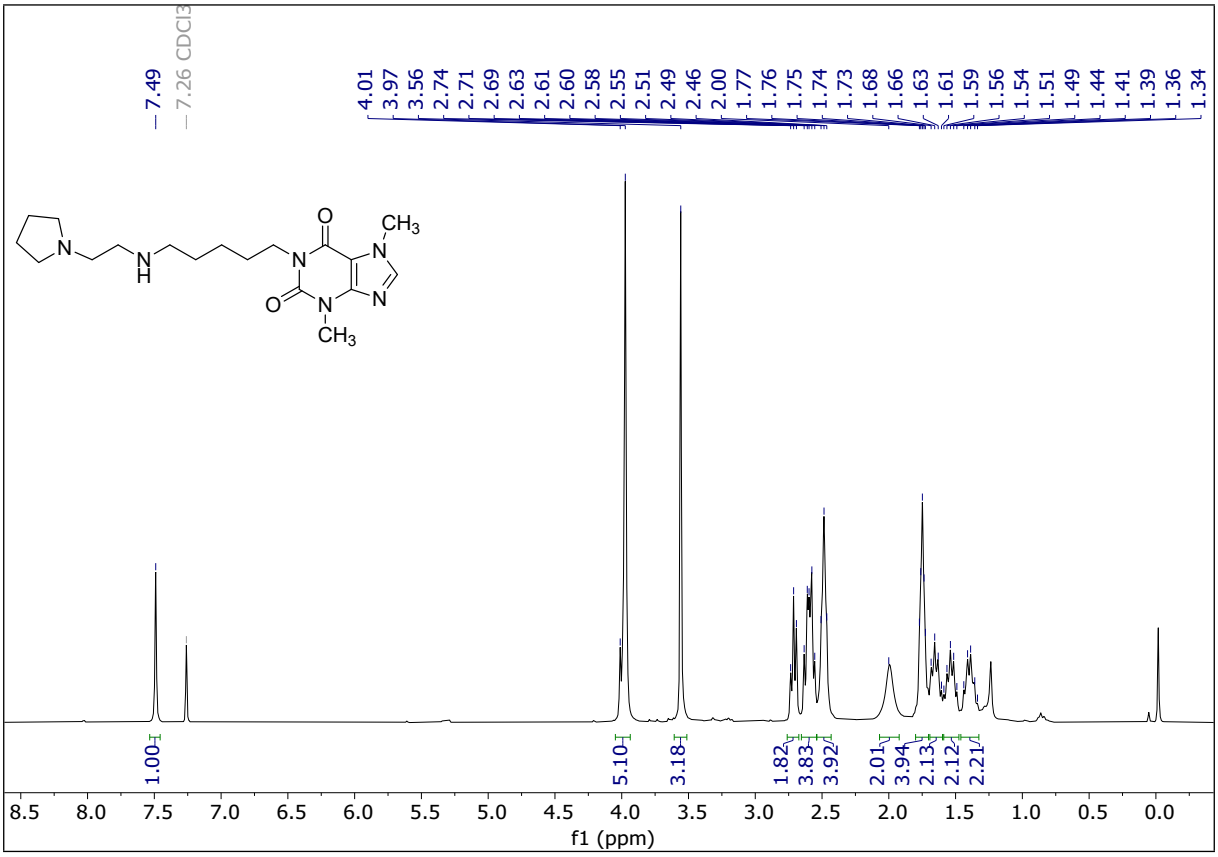
Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C19 H32 N6 O2; 2.299	2.299	376.259	645896	C19 H32 N6 O2	376.2587	0.87	1

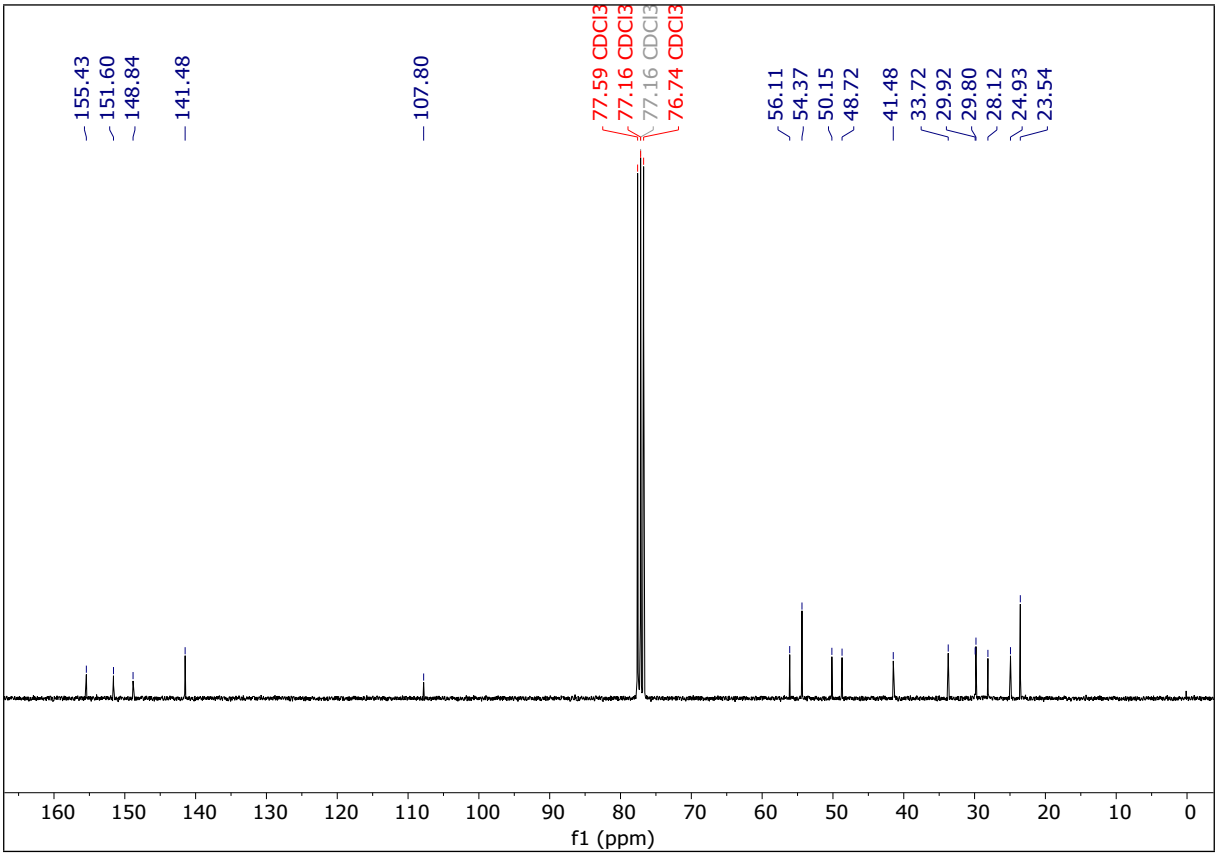
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C19 H32 N6 O2; 2.299	377.2664	2.299	Find by Formula	376.259

MS Zoomed Spectrum

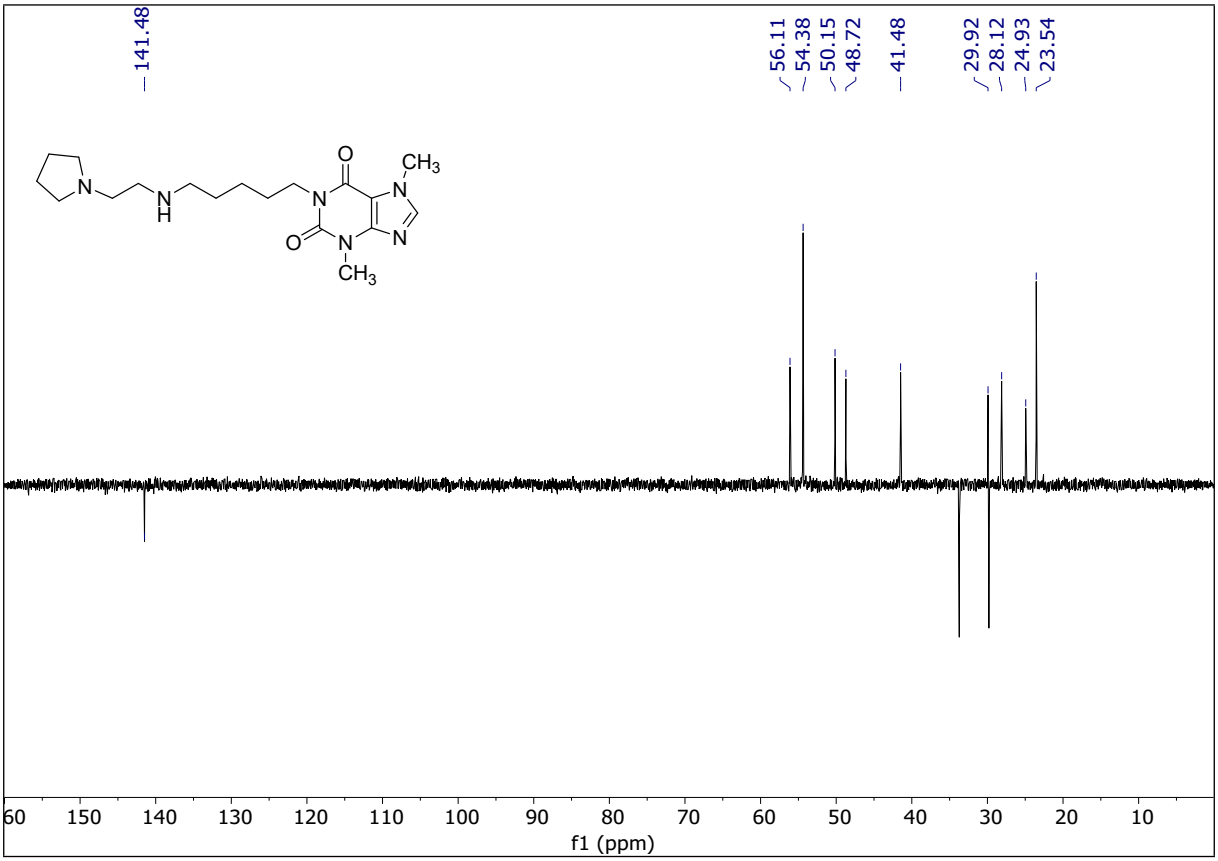


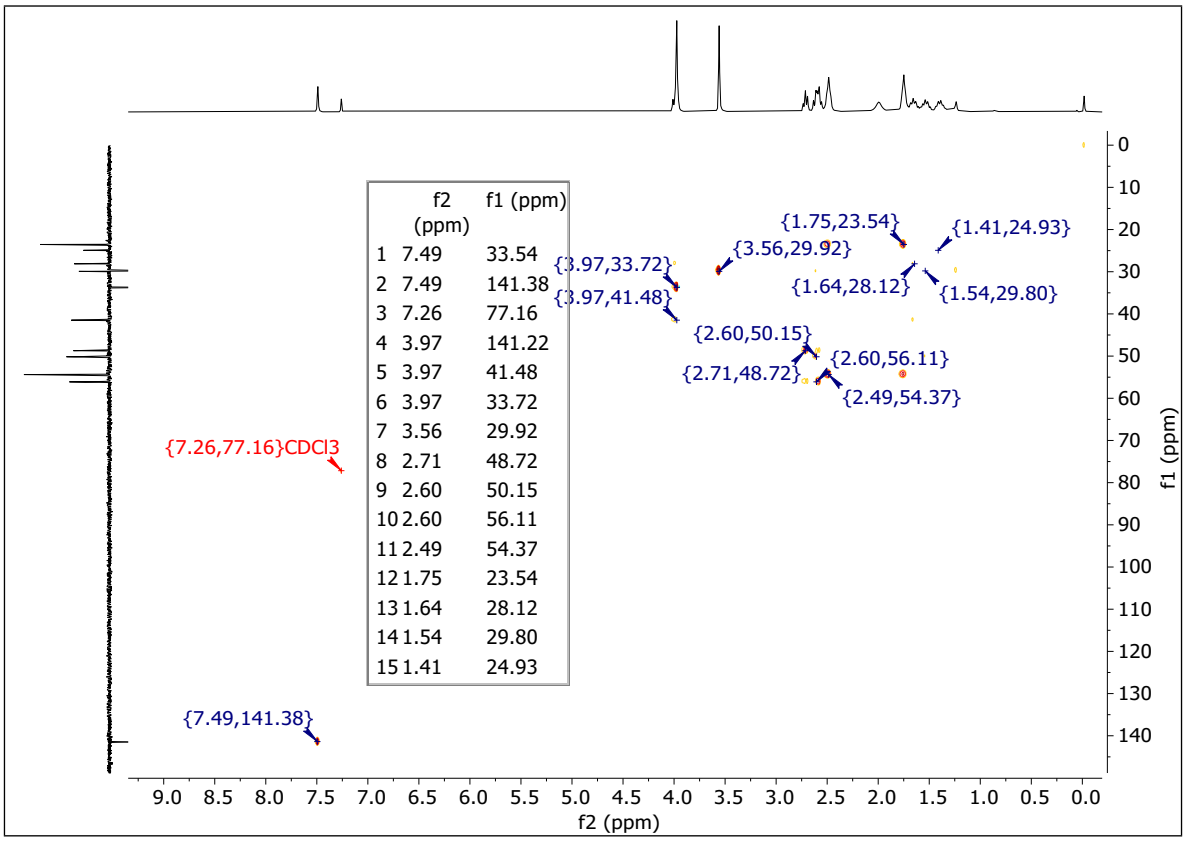
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDl_3 of **30**





DEPT and HSQC spectra in $CDCl_3$ of **30**





Qualitative Compound Report

Data File	2022_BBA_1_02.d	**Sample Name**	BBA_1
Sample Type	Sample	**Position**	Vial 1
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI_ACN_75_pos_UNICO CANAL A1.m	**Acquired Time**	12/22/2022 12:33:09 PM (UTC+01:00)
IRM Calibration Status	Success	**DA Method**	DefaultMPS.m
Comment			

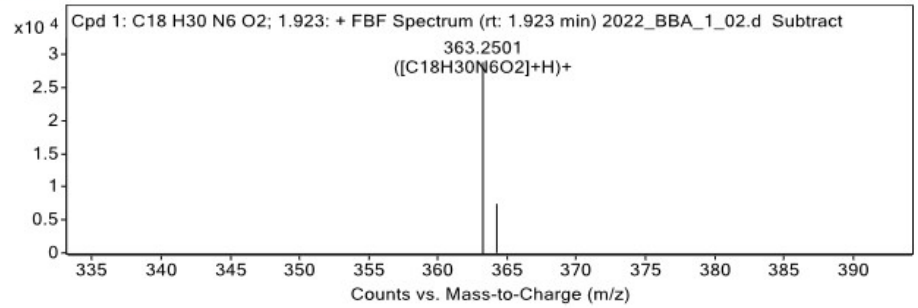
Sample Group Info.			
User	BRUNELLA BISCUSSI	**Stream Name**	LC 1
Acquisition Time (Local)	12/22/2022 12:33:09 PM (UTC+01:00)	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1)
QTOF Driver Version	8.00.00	**QTOF Firmware Version**	2.723
Tune Mass Range Max.	1700		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C18 H30 N6 O2; 1.923	1.923	362.2427	28818	C18 H30 N6 O2	362.243	-0.8	1

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C18 H30 N6 O2; 1.923	363.2501	1.923	Find by Formula	362.2427

MS Zoomed Spectrum



Molecular Docking

Table 1. Electrostatic (coul), van der Waals (vdW), and hydrogen bond (h-bond) energies of protein-ligand complex (Kcal/mol) and calculated per-residue distances.

Donepezil

	coul	vdW	h-bond	distance (Å)
TYR72	-1.374	-1.881	0	2.748
ASP74	-25.178	-0.82	0	4.107
THR83	-0.095	-0.235	0	5.135
TRP86	-0.292	-4.769	0	2.647
GLY121	1.331	-1.527	0	2.958
GLY122	0.457	-0.317	0	5.097
TYR124	-1.29	-2.546	0	2.346
SER125	-0.791	-0.406	0	4.027
TYR133	-0.161	-0.509	0	2.901
GLU202	0.51	-1.02	0	2.381
SER203	1.807	-0.171	0	3.208
TRP286	0.955	-5.594	0	3.001
SER293	-0.762	-0.986	0	2.41
VAL294	0.106	-1.599	0	2.843
PHE295	-1.569	-1.263	-1.0	2.031
PHE296	10.305	-0.939	0	3.433
PHE297	0.454	-1.972	0	2.119
TYR337	-1.6	-1.515	0	2.327
PHE338	-1.258	-4.285	0	2.444
TYR341	-1.313	-7.101	0	2.664
HIS447	-3.421	-3.093	0	2.073

	Compd 21				**Compd 32**			
	coul	**vdW**	**h-bond**	**distance (Å)**	**coul**	**vdW**	**h-bond**	**distance (Å)**
TYR72	-1.591	-1.469	0	2.204	-0.754	-0.82	0	3.344
ASP74	-21.231	-0.979	0	3.881	-24.206	-0.763	0	4.101
THR83	-0.631	-0.26	0	4.255	-0.674	-0.283	0	4.267
TRP86	-2.807	-5.15	0	2.186	-2.802	-5.654	0	2.385
GLY121	1.96	-1.656	0	2.174	1.832	-1.358	0	2.444
GLY122	0.421	-0.25	0	3.842	0.36	-0.216	0	4.689
TYR124	-0.687	-2.275	0	2.753	-0.557	-2.009	0	2.669
SER125	-1.285	-0.341	0	4.330	-1.28	-0.284	0	4.364
TYR133	-0.457	-0.562	0	3.015	-0.436	-0.373	0	3.467
GLU202	-0.23	-1.333	0	2.476	-0.162	-1.081	0	2.645
SER203	0.021	-0.792	0	2.836	0.069	-0.498	0	3.202
TRP286	0.024	-6.529	0	2.765	0.871	-5.592	0	2.801
SER293	-0.299	-1.199	0	2.625	-0.423	-1.857	0	2.242
VAL294	-0.42	-2.105	0	2.015	0.615	-2.401	0	2.001

PHE295	-1.558	-1.143	-1	1.987	-0.721	-1.915	-0.485	2.204
PHE296	8.979	-0.855	0	3.256	9.378	-2.558	0	1.542
PHE297	0.338	-1.537	0	2.470	0.263	-2.039	0	2.181
TYR337	-0.983	0	-3.326	2.371	-1.108	-2.343	0	2.209
PHE338	-0.396	-3.161	0	2.641	-0.479	-2.895	0	2.235
TYR341	-0.242	-8.333	0	2.681	-1.11	-6.173	0	2.497
HIS447	-4.159	-2.231	0	2.258	-4.099	-2.35	0	2.124

	Compd 28				**Compd 16**			
	coul	**vdW**	**h-bond**	**distance (Å)**	**coul**	**vdW**	**h-bond**	**distance (Å)**
TYR72	-1.805	-1.427	0	2.233	-1.392	-1.880	0	2.095
ASP74	-27.573	-1.124	-0.406	2.043	-30.648	-1.978	0	2.009
THR83	-0.793	-0.728	0	3.231	-0.537	-0.727	0	3.552
TRP86	-2.158	-6.09	0	2.568	-0.716	-4.637	0	2.13
GLY121	1.877	-1.22	0	2.501	1.348	-0.972	0	2.654
GLY122	0.261	-0.218	0	4.642	0.189	-0.222	0	4.968
TYR124	-0.552	-2.99	0	2.460	-0.676	-3.046	0	1.701
SER125	-1.365	-0.345	0	4.190	-1.188	-1.048	0	2.713
TYR133	-0.269	-0.249	0	3.811	-0.145	-0.074	0	5.447
GLU202	-0.311	-0.812	0	3.048	0.018	-0.112	0	5.334
SER203	-0.061	-0.382	0	3.765	0.105	-0.103	0	5.997
TRP286	0	-6.317	0	2.642	-0.055	-5.719	0	2.775
SER293	-0.362	-1.177	0	2.666	-0.058	-1.034	0	2.501
VAL294	-0.302	-2.101	0	2.067	-0.085	-2.063	0	2.285
PHE295	-1.144	-1.248	-0.758	2.197	0.065	-1.648	-0.380	2.198
PHE296	8.949	-0.844	0	3.520	9.547	-0.921	0	3.628
PHE297	0.398	-1.575	0	2.165	0.513	-1.970	0	2.161
TYR337	-1.317	-3.248	0	2.640	-0.474	-3.883	0	2.469
PHE338	-0.392	-2.311	0	2.497	-0.349	-3.780	0	2.139
TYR341	-0.976	-7.891	-0.071	2.394	-1.035	-8.119	0	2.338
HIS447	-3.649	-2.31	0	2.343	-2.622	-1.217	0	2.009

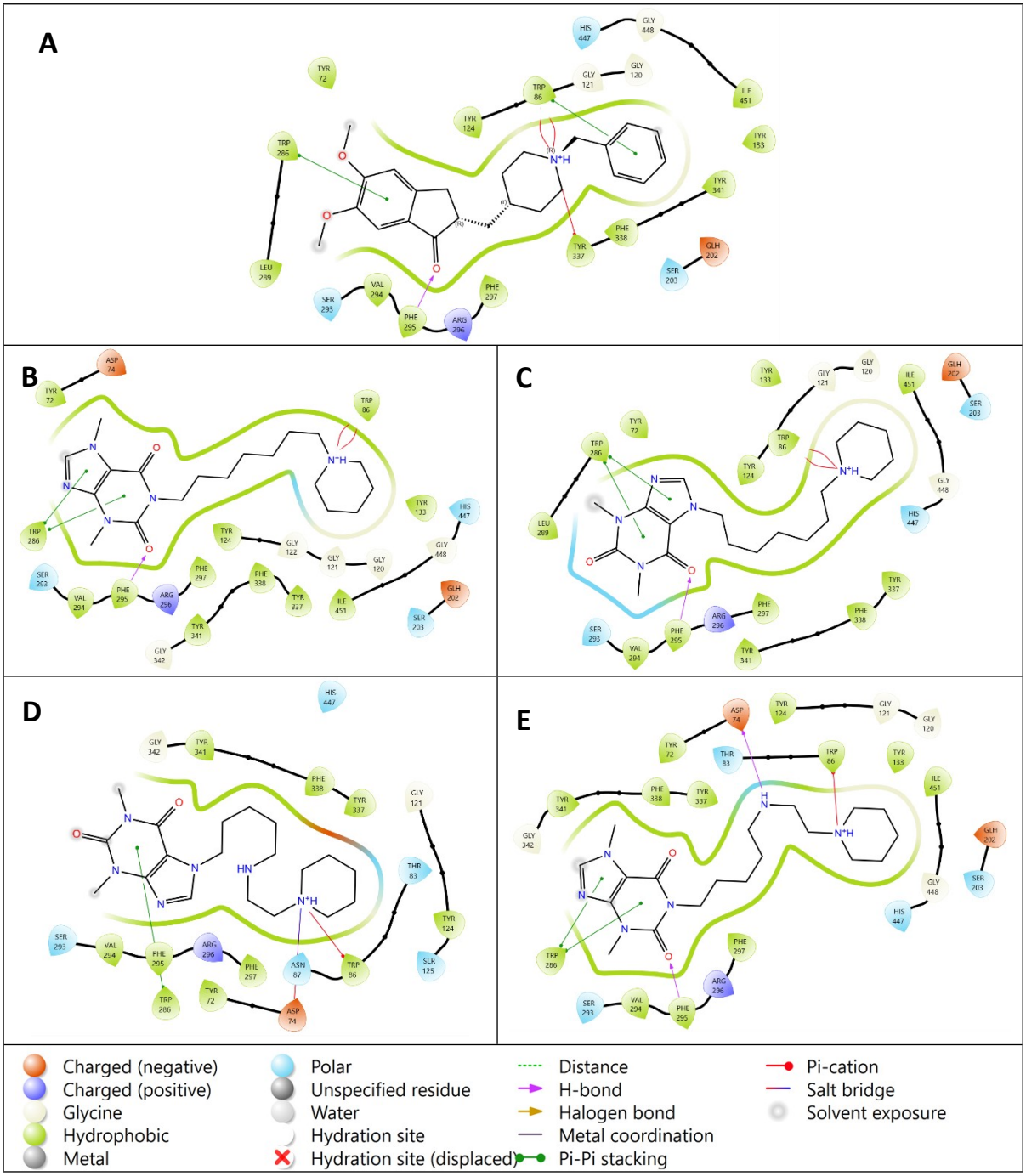


Figure S1. 2D representation of best docking poses and protein–ligand interactions of donepezil (A), compd **21** (B), compd **32** (C), compd **16** (D)and compd **28** (E).

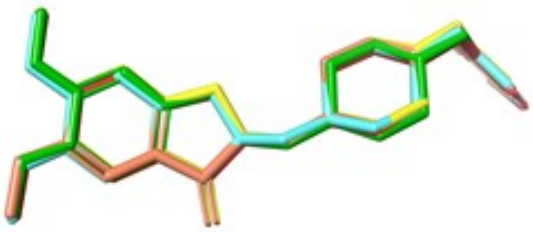


Fig. S2. Docking validation, a comparison of the redocked binding mode and the co-crystallized pose (green) of donepezil.