Supplementary Information

Table of Content:

CHAPTER II DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF CHAETOCIN ANALOGUES 3

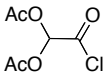
CHAPTER III STEREOCHEMISTRY OF ETP DESULFURISATION 34

CHAPTER IV TOWARDS THE DISCOVERY OF NOVEL EZH2 INHIBITORS 99

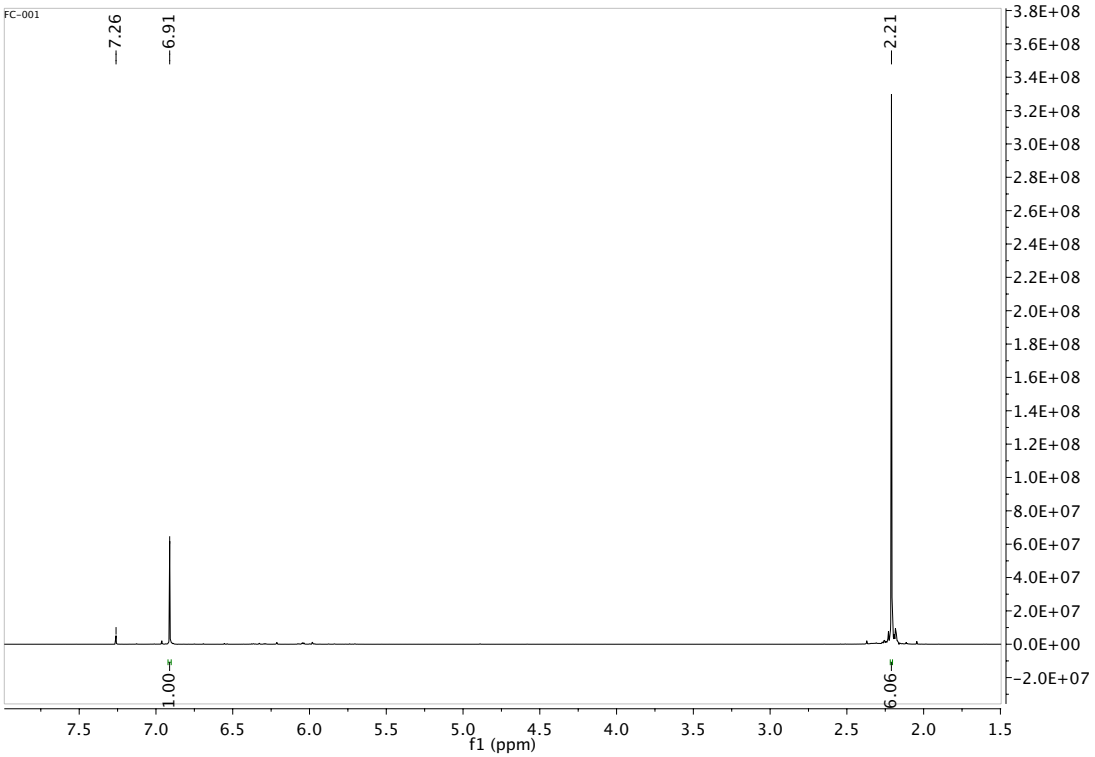
REFERENCES 158

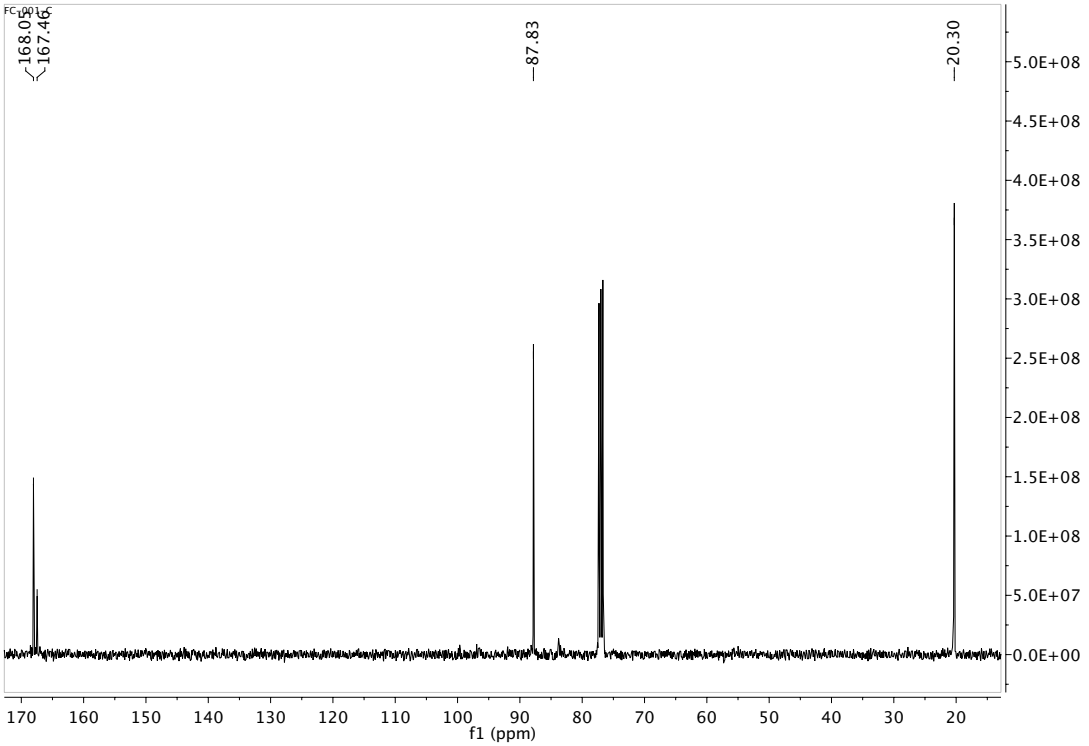
Chapter II Design, synthesis and biological evaluation of chaetocin analogues

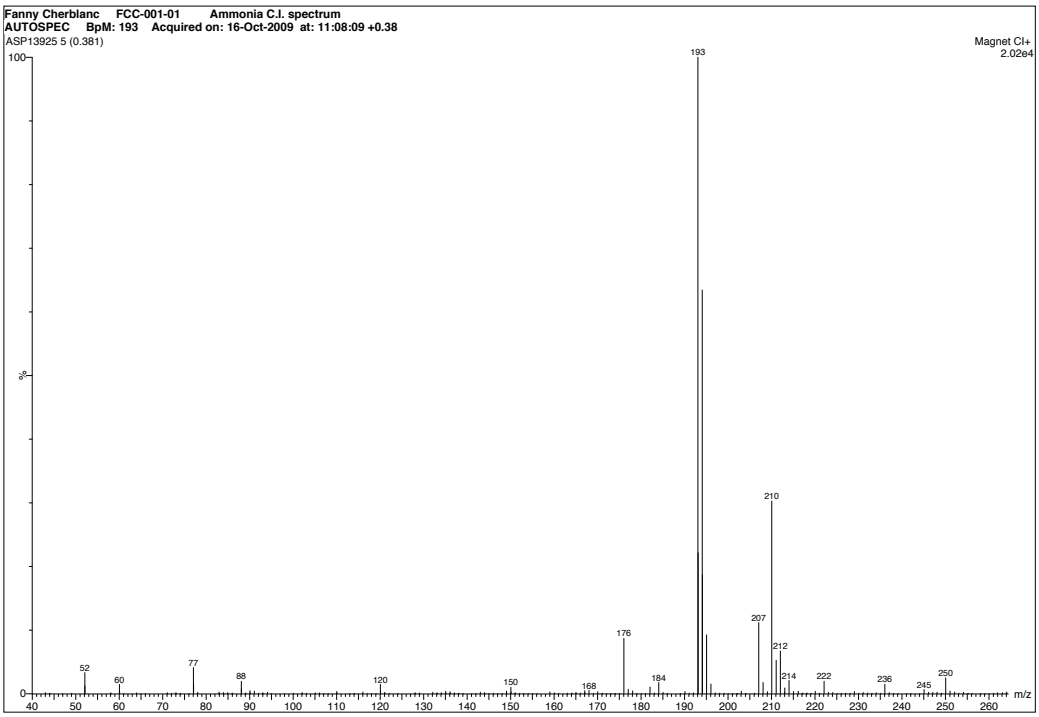
2-Chloro-2-oxoethane-1,1-diyl diacetate (7)[1]



Compound **7** was prepared as follows:[1] Glyoxylic acid (21.5 mL of a 75% w/w in water, 175.0 mmol), acetic anhydride (175.0 mL, 1.8 mol) and glacial acetic acid (40.0 mL, 0.7 mol) were mixed and heated under reflux for 3 h. The solvents were rotary evaporated and the remaining volatiles were removed as an azeotrope with toluene. The residual brown oil was dissolved in a mixture of CH_2Cl_2 (120 mL) and $SOCl_2$ (45 mL, 0.6 mol) and heated under reflux for 0.5 h. The mixture was rotary evaporated to afford acyl chloride **7** as a brown oil that was used in the next step without further purification (30.5 g, 89%): IR (neat) 1767, 1373, 1185, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 2.21 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 168.1 (2C), 167.5, 87.8, 20.3 (2C); MS (CI) *m/z* 195 $(M+H)^+$, 212 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_6H_{11}NO_5Cl$ 212.0326, found: 212.0331.




FC-001-C
168.05
167.46
87.83
20.30
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

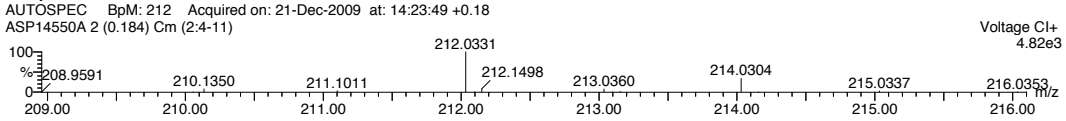

Fanny Cherblanc FCC-001-01 Ammonia C.I. spectrum
AUTOSPEC BpM: 193 Acquired on: 16-Oct-2009 at: 11:08:09 +0.38
ASP13925 5 (0.381)
Magnet CI+
2.02e4
100
%
0
193
210
207
212
176
52
60
77
88
120
150
168
184
214
222
236
245
250
40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

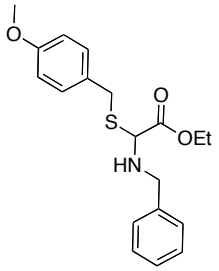
Monoisotopic Mass, Even Electron Ions
307 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-001-01
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ASP14550A 2 (0.184) Cm (2:4-11)

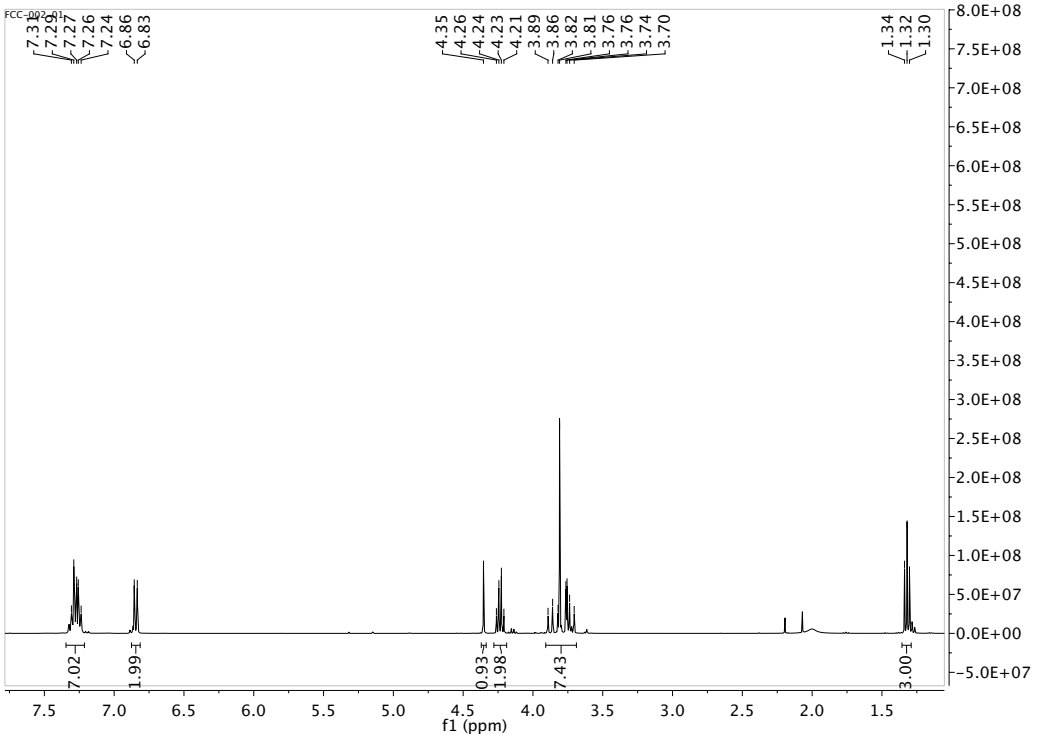


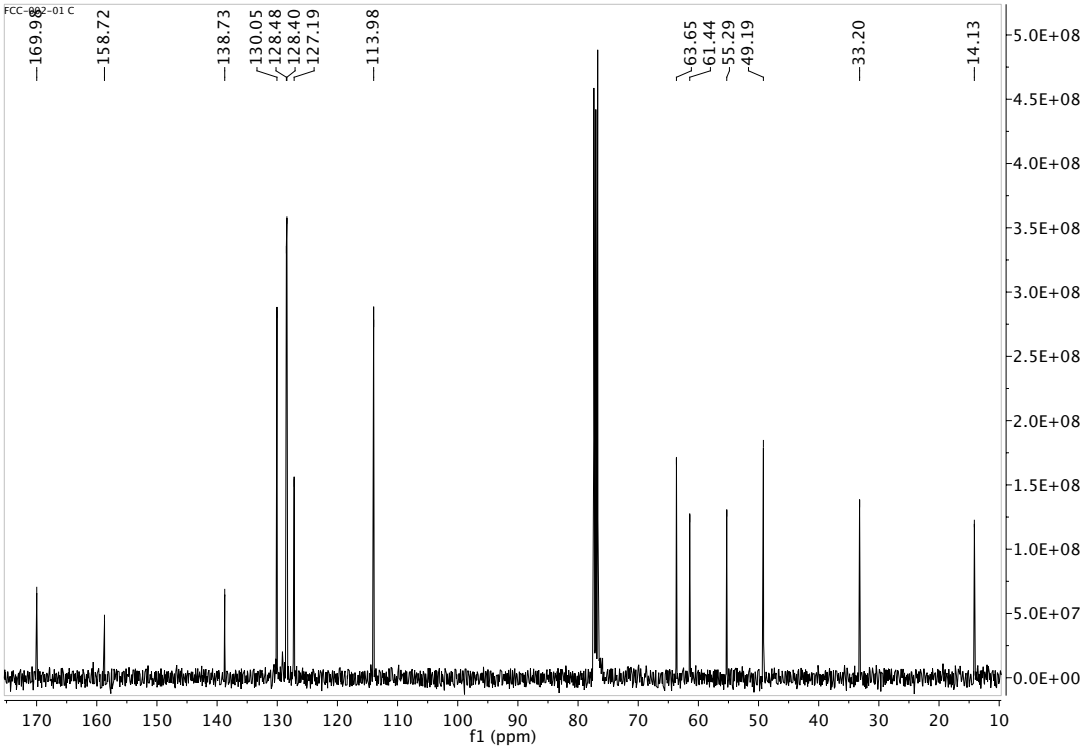
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Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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	212.0339	-0.8	-3.8	6.5	2	C7 H7 N5 O Cl
	212.0348	-1.7	-7.9	10.5	4	C12 H6 N O3
	212.0307	2.4	11.1	6.5	3	C7 H6 N3 O5

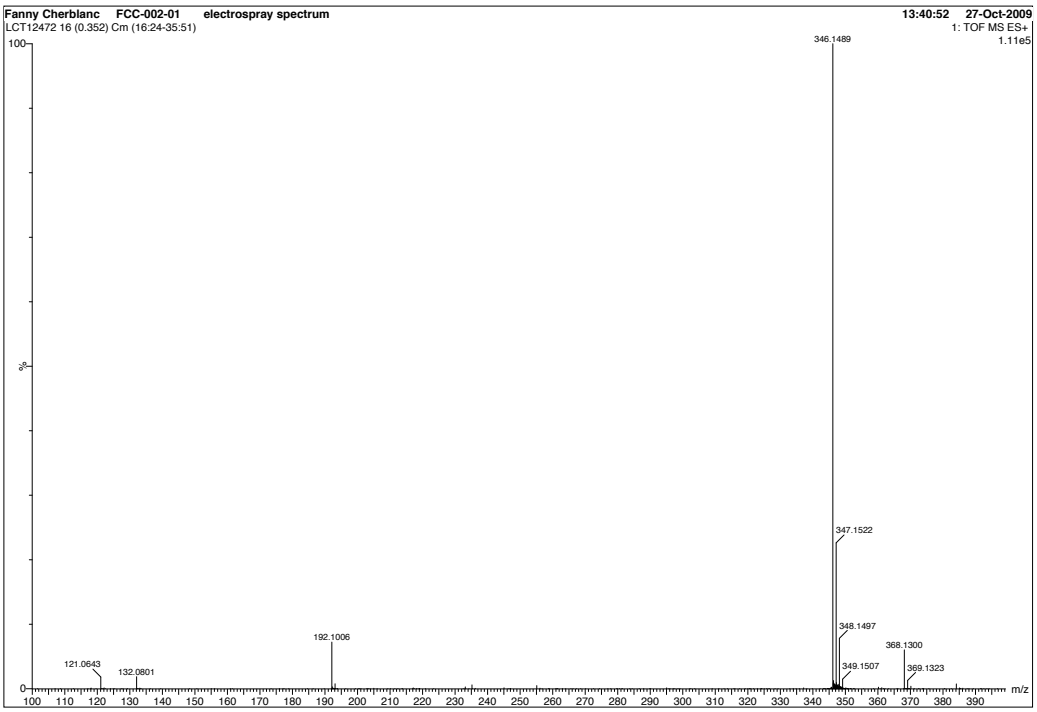
Ethyl 2-(benzylamino)-2-((4-methoxybenzyl)thio)acetate (9)[2]



Compound **9** was prepared as follows:[2] Benzylamine (13.8 mL, 126 mmol) was added to a solution of ethyl glyoxalate (25.0 mL of a 50% solution in toluene, 126 mmol) in toluene (200 mL). After 2 min, *p*-methoxybenzylmercaptan (17.5 mL, 126 mmol) was added and the resulting white solution was allowed to stir for 2.5 h at room temperature. The solvent was rotary evaporated and the resulting oil was purified by flash column chromatography (EtOAc : Hexanes, 1 : 2) to afford the title compound **9** as a yellow oil (21.2 g, 49%): IR (neat) 1729, 1611, 1511, 1243, 1172, 1032, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 7H), 6.84 (d, J = 8.8 Hz, 2H), 4.35 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 13.0 Hz, 1H), 3.81 (s, 3H), 3.76 (d, J = 3.2 Hz, 2H), 3.72 (d, J = 13.0 Hz, 1H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 169.9, 158.7, 138.7, 130.0 (3C), 128.5 (2C), 128.4 (2C), 127.2, 114.0 (2C), 63.6, 61.4, 55.3, 49.2, 33.2, 14.1; MS (ESI) *m/z* 346 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{19}H_{24}NO_3S$ 346.1477, found: 346.1489.


FCC-002-01
7.31
7.28
7.27
7.26
7.24
6.86
6.83
4.35
4.26
4.24
4.23
4.21
3.89
3.86
3.82
3.81
3.76
3.74
3.70
1.34
1.32
1.30
7.02
1.99
0.93
1.98
7.43
3.00
f1 (ppm)


FCC-002-01 C
169.98
158.72
138.73
130.05
128.48
128.40
127.19
113.98
63.65
61.44
55.29
49.19
33.20
14.13
f1 (ppm)

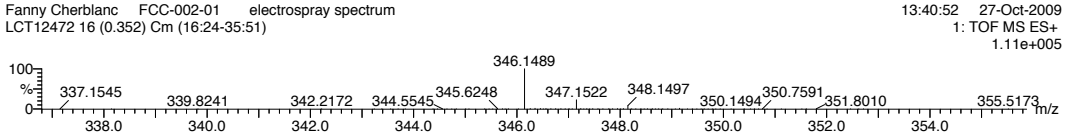


Elemental Composition Report

Single Mass Analysis

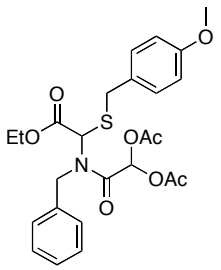
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
1225 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-16 S: 0-2

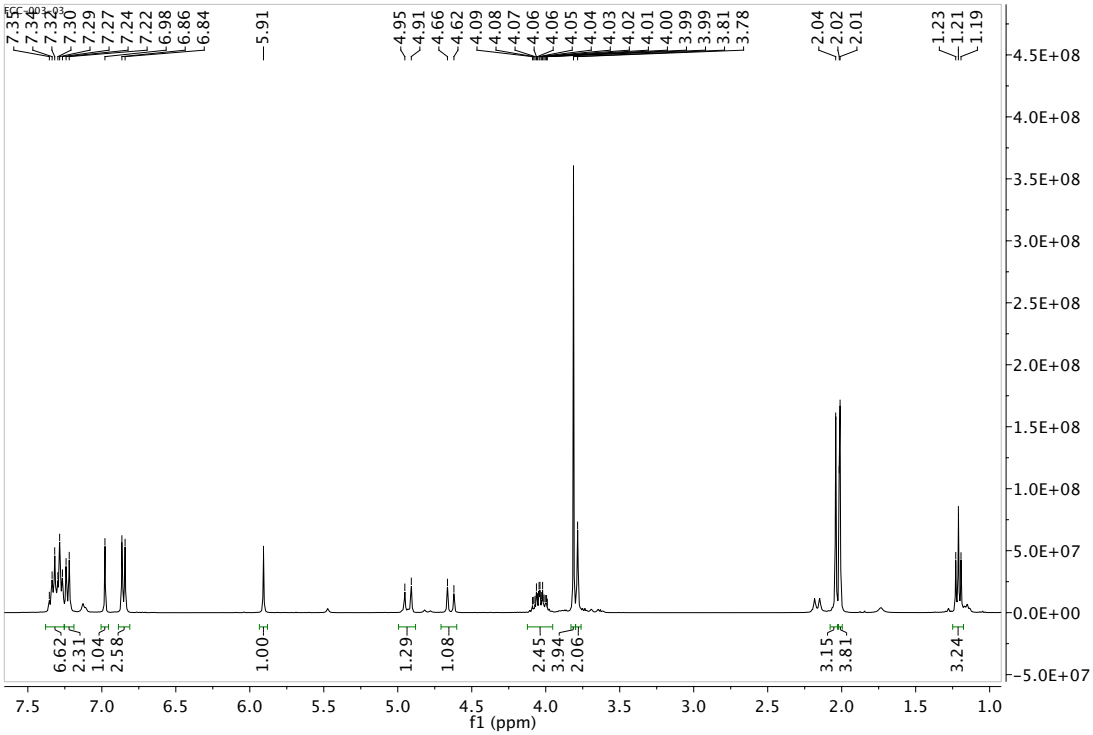


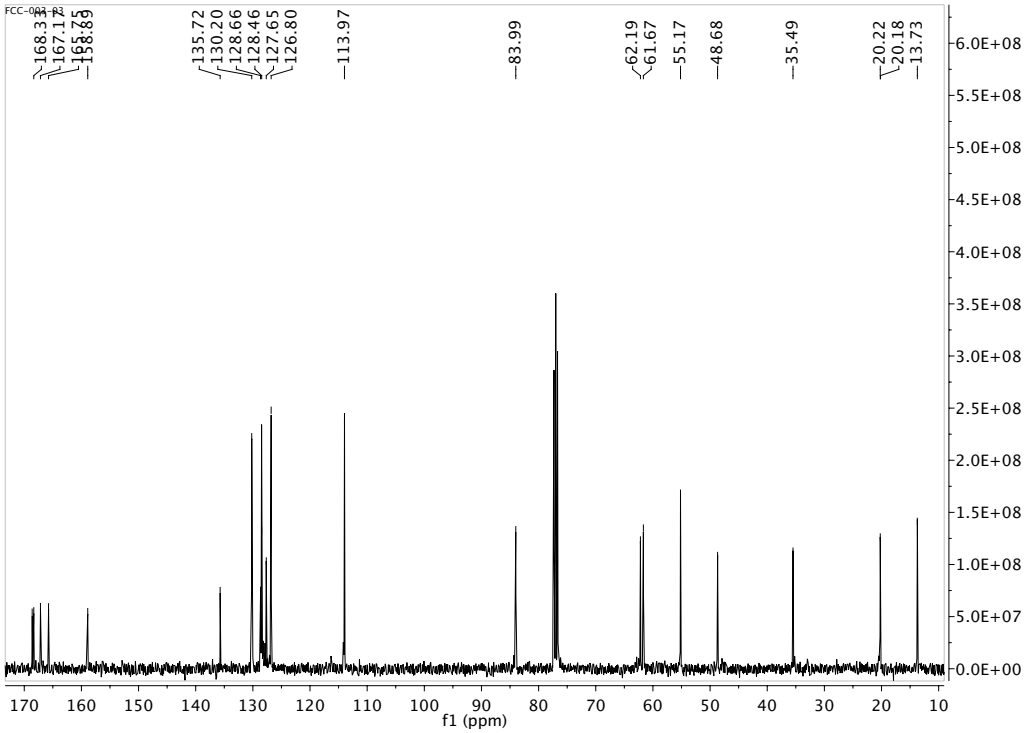
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
346.1489	346.1484	0.5	1.4	4.5	481.5	19.1	C12 H24 N7 O S2
	346.1477	1.2	3.5	8.5	462.4	0.0	C19 H24 N O3 S
	346.1502	-1.3	-3.8	4.5	486.7	24.3	C15 H24 N O8
	346.1475	1.4	4.0	5.5	487.3	24.9	C11 H20 N7 O6
	346.1470	1.9	5.5	-0.5	482.4	20.0	C11 H28 N3 O5 S2
	346.1509	-2.0	-5.8	0.5	480.3	17.9	C8 H24 N7 O6 S
	346.1511	-2.2	-6.4	3.5	480.3	17.9	C16 H28 N O3 S2
	346.1515	-2.6	-7.5	9.5	486.7	24.3	C16 H20 N5 O4
	346.1462	2.7	7.8	0.5	487.8	25.4	C10 H24 N3 O10
	346.1450	3.9	11.3	9.5	473.6	11.2	C15 H20 N7 O S
	346.1443	4.6	13.3	13.5	486.8	24.4	C22 H20 N O3
	346.1536	-4.7	-13.6	-0.5	477.4	15.0	C12 H28 N O8 S

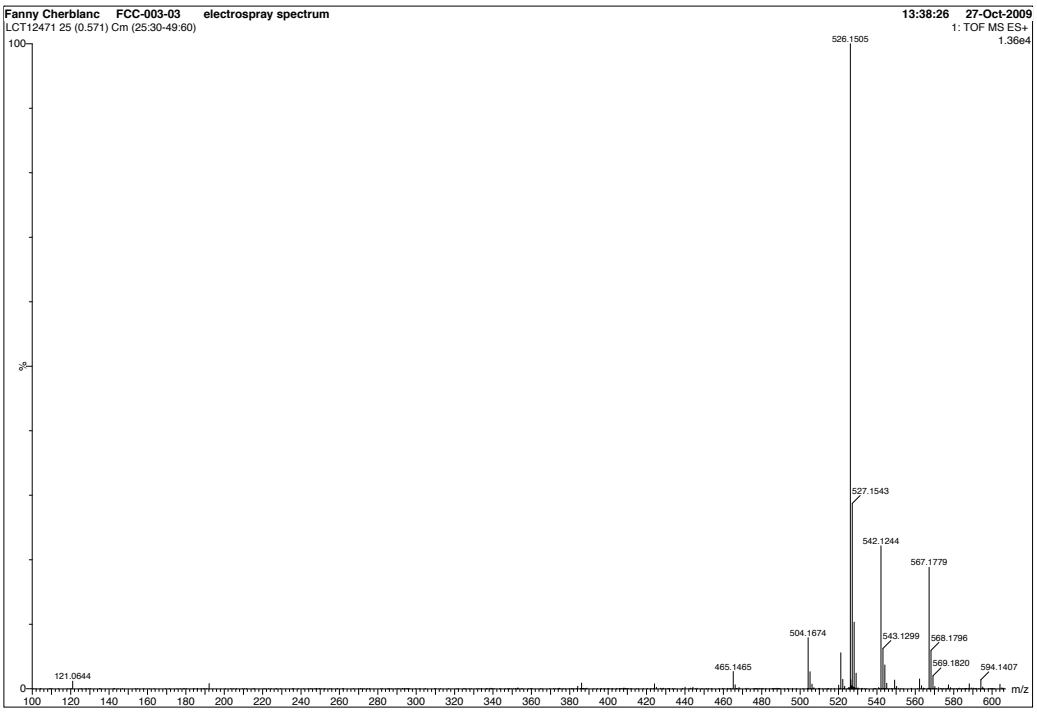
2-(Benzyl(2-ethoxy-1-((4-methoxybenzyl)thio)-2-oxoethyl)amino)-2-oxoethane-1,1-diyl diacetate (13)[3]



Compound **13** was prepared as follows:[3] Acyl chloride **7** (4.23 g, 21.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a biphasic mixture of amine **9** (7.52 g, 21.8 mmol) in CH_2Cl_2 (100 mL) and $NaHCO_3$ (1.83 g, 21.8 mmol) in water (50 mL) at room temperature. The resulting biphasic solution was allowed to stir vigorously for 3 h. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and rotary evaporated. Flash column chromatography (EtOAc : Hexanes, 1 : 2) afforded the title compound **13** as a colourless oil (8.31 g, 76%): IR (neat) 1770, 1743, 1684, 1513, 1246, 1192, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 7H), 6.98 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 5.91 (s, 1H), 4.93 (d, J = 17.6 Hz, 1H), 4.64 (d, J = 17.6 Hz, 1H), 4.09 – 3.99 (m, 2H), 3.81 (s, 3H), 3.78 (s, 2H), 2.04 (s, 3H), 2.02 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 168.6, 168.3, 167.1, 165.7, 158.9, 135.7, 130.2 (2C), 128.7, 128.5 (2C), 127.6, 126.8 (2C), 114.0 (2C), 84.0, 62.2, 61.7, 55.2, 48.7, 35.5, 20.4, 20.2, 13.7; MS (ESI) *m/z* 504 $(M+H)^+$, 526 $(M+Na)^+$; HRMS (ESI) *m/z* calc. for $C_{25}H_{30}NO_8S$ 504.1692, found: 504.1674.


FCC-003-03
7.35
7.34
7.32
7.30
7.29
7.27
7.24
7.22
6.98
6.86
6.84
5.91
4.95
4.91
4.66
4.62
4.09
4.08
4.07
4.06
4.06
4.05
4.04
4.03
4.02
4.01
4.00
3.99
3.99
3.81
3.78
2.04
2.02
2.01
1.23
1.21
1.19
6.62
2.31
1.04
2.58
1.00
1.29
1.08
2.45
3.94
2.06
3.15
3.81
3.24
f1 (ppm)


FCC-004-03
168.33
167.17
165.75
158.89
135.72
130.20
128.66
128.46
127.65
126.80
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62.19
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55.17
48.68
35.49
20.22
20.18
13.73
f1 (ppm)



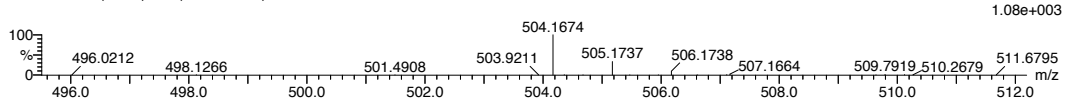
Elemental Composition Report

Single Mass Analysis

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

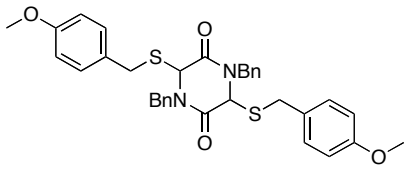
Monoisotopic Mass, Even Electron Ions
2154 formula(e) evaluated with 19 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-16 S: 0-2

Fanny Cherblanc FCC-003-03 electrospray spectrum
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13:38:26 27-Oct-2009
1: TOF MS ES+
1.08e+003

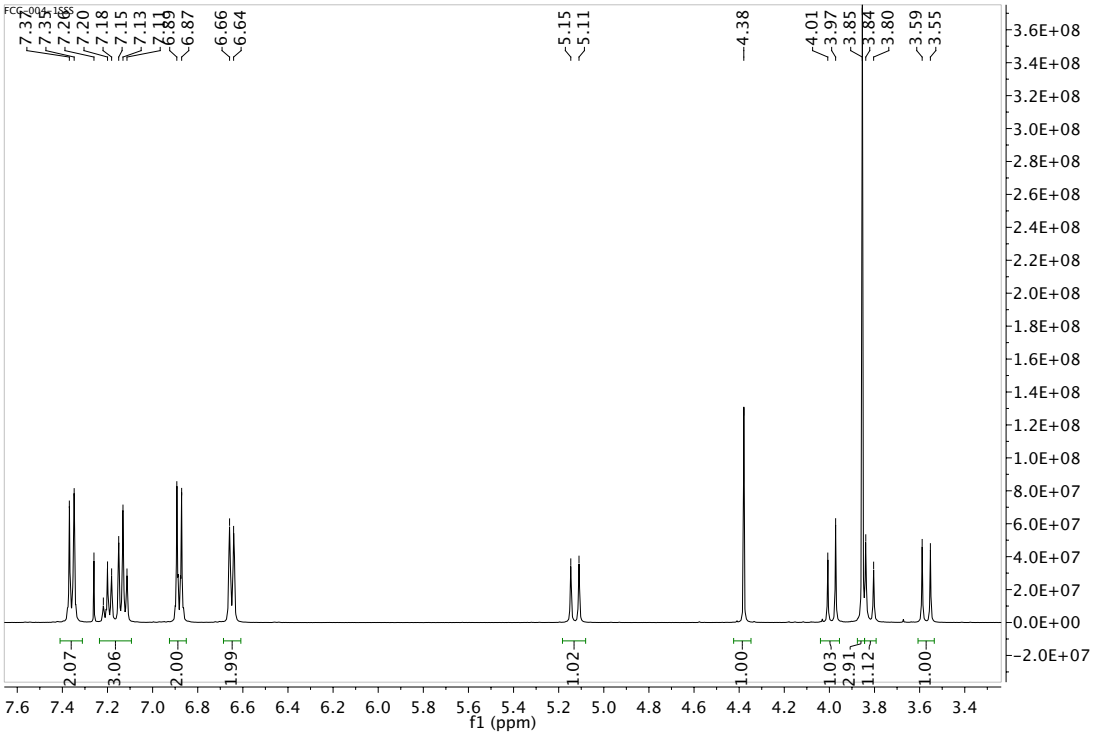


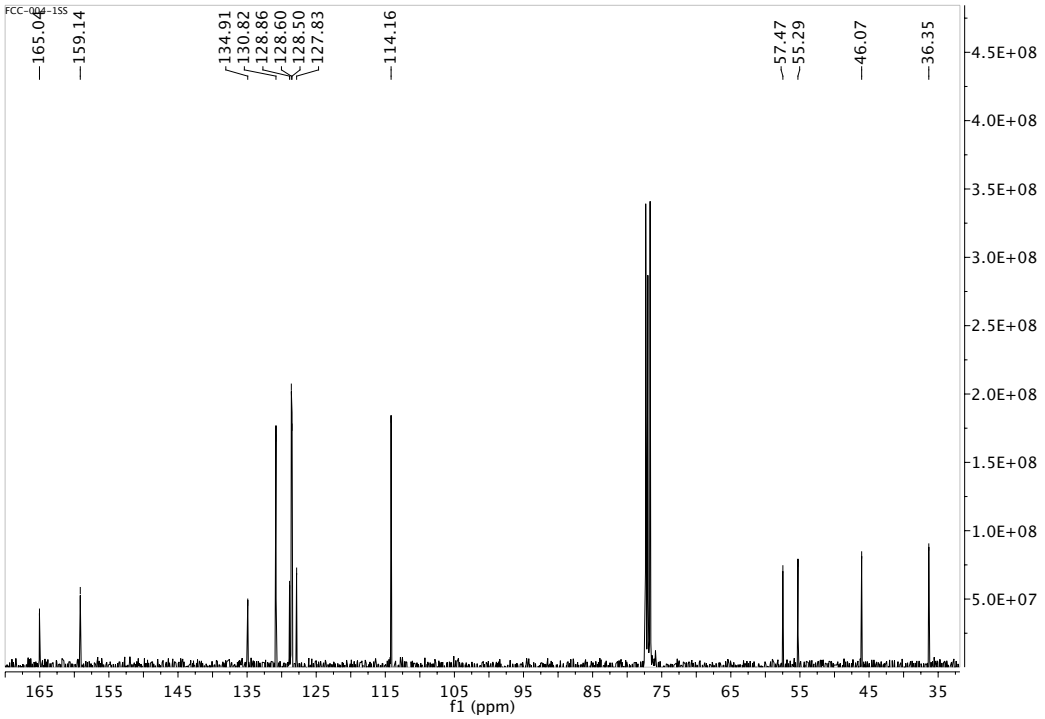
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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Maximum:		5.0	10.0	50.0			
504.1674	504.1672	0.2	0.4	21.5	20.4	1.6	C29 H22 N5 O4
	504.1677	-0.3	-0.6	3.5	25.6	6.8	C16 H30 N3 O15
	504.1667	0.7	1.4	15.5	27.6	8.8	C29 H30 N O3 S2
	504.1665	0.9	1.8	12.5	21.7	2.9	C21 H26 N7 O6 S
	504.1686	-1.2	-2.4	2.5	27.8	9.0	C17 H34 N3 O10 S2
	504.1658	1.6	3.2	16.5	20.0	1.2	C28 H26 N O8
	504.1690	-1.6	-3.2	8.5	25.3	6.5	C17 H26 N7 O11
	504.1692	-1.8	-3.6	11.5	21.1	2.3	C25 H30 N O8 S
	504.1652	2.2	4.4	7.5	23.7	4.8	C20 H30 N3 O10 S
	504.1699	-2.5	-5.0	7.5	27.3	8.5	C18 H30 N7 O6 S2
	504.1645	2.9	5.8	-1.5	29.7	10.8	C12 H34 N5 O12 S2
	504.1706	-3.2	-6.3	16.5	20.3	1.5	C26 H26 N5 O4 S
	504.1640	3.4	6.7	16.5	28.0	9.2	C25 H26 N7 O S2
	504.1711	-3.7	-7.3	-1.5	26.9	8.1	C13 H34 N3 O15 S
	504.1712	-3.8	-7.5	25.5	21.5	2.7	C34 H22 N3 O2
	504.1633	4.1	8.1	20.5	23.8	5.0	C32 H26 N O3 S
	504.1632	4.2	8.3	17.5	23.6	4.8	C24 H22 N7 O6
	504.1717	-4.3	-8.5	7.5	24.3	5.5	C21 H30 N O13
	504.1627	4.7	9.3	11.5	28.8	9.9	C24 H30 N3 O5 S2

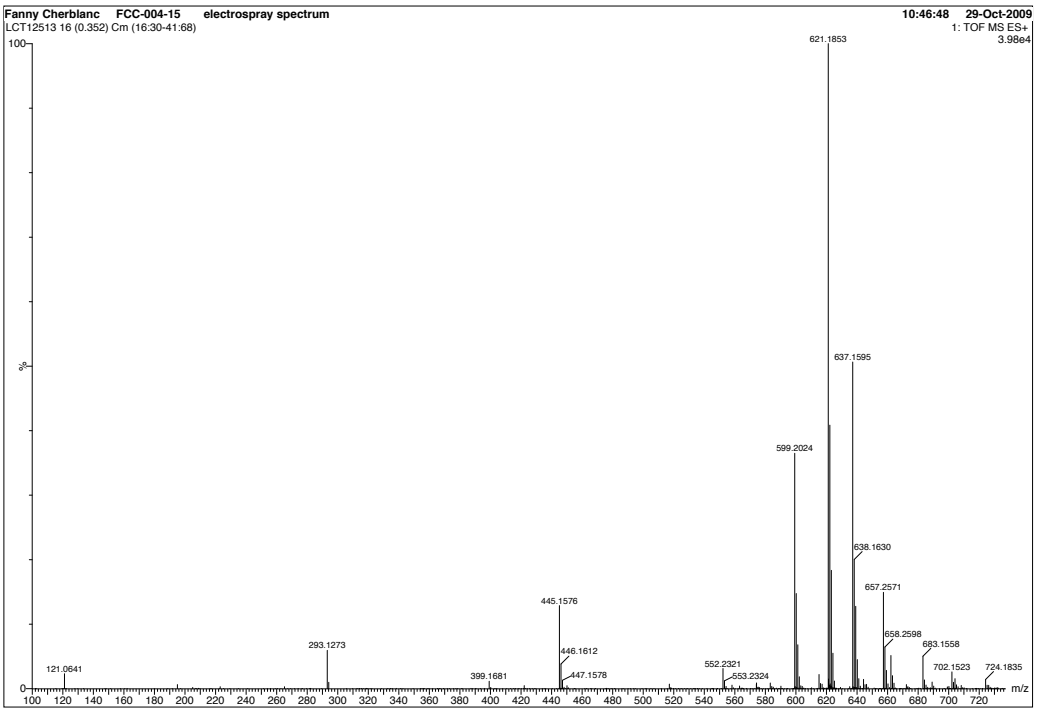
1,4-dibenzyl-3,6-bis((4-methoxybenzyl)thio)piperazine-2,5-dione (14)



Compound **14** was prepared as follows:[3,4] Benzylamine (1.3 mL, 11.7 mmol), followed by *p*-methoxybenzyl mercaptan (0.8 mL, 5.8 mmol) were added to a solution of ester **13** (2.00 g, 3.9 mmol) in MeCN (50 mL). The resulting mixture was allowed to stir for 2 min before adding TFA (85 μL, 1.1 mmol) and then heated at reflux for 20 h. The formed precipitate was recovered by filtration and rinsed with EtOAc to give the protected dithiodiketopiperazine **14** (1.02 g, 44%) as a white solid that was used in the next step without further purification: m.p. 172 – 174 ˚C; IR (neat) 1668, 1609, 1511, 1440, 1238, 1172, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 4H), 7.22 – 7.11 (m, 6H), 6.88 (d, *J* = 8.6 Hz, 4H), 6.65 (d, *J* = 7.2 Hz, 4H), 5.13 (d, *J* = 14.5 Hz, 2H), 4.39 (s, 2H), 3.99 (d, *J* = 14.0 Hz, 2H), 3.85 (s, 6H), 3.82 (d, *J* = 14.0 Hz, 2H), 3.57 (d, *J* = 14.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 165.1 (2C), 159.2 (2C), 134.9 (2C), 130.8 (4C), 128.9 (2C), 128.6 (4C), 128.5 (4C), 127.8 (2C), 114.2 (4C), 57.5 (2C), 55.3 (2C), 46.1 (2C), 36.4 (2C); MS (ESI) *m/z* 599 $(M+H)^+$, 621 $(M+Na)^+$; HRMS (ESI) *m/z* calc. for $C_{34}H_{35}N_2O_4S_2$ 599.2038, found: 599.2024.




FCC-004-15S
165.04
159.14
134.91
130.82
128.86
128.60
128.50
127.83
114.16
57.47
55.29
46.07
36.35
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
165 155 145 135 125 115 105 95 85 75 65 55 45 35
f1 (ppm)


Fanny Cherblanc FCC-004-15 electrospray spectrum
10:46:48 29-Oct-2009
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100
%
0
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658.2598
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445.1576
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m/z

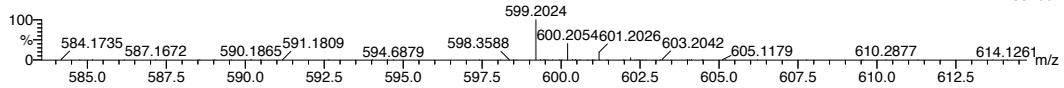
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
2710 formula(e) evaluated with 28 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-16 S: 0-2

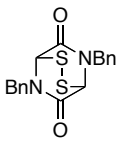
Fanny Cherblanc FCC-004-15 electrospray spectrum
LCT12513 16 (0.352) Cm (16:30-41:68)

10:46:48 29-Oct-2009
1: TOF MS ES+
1.45e+004



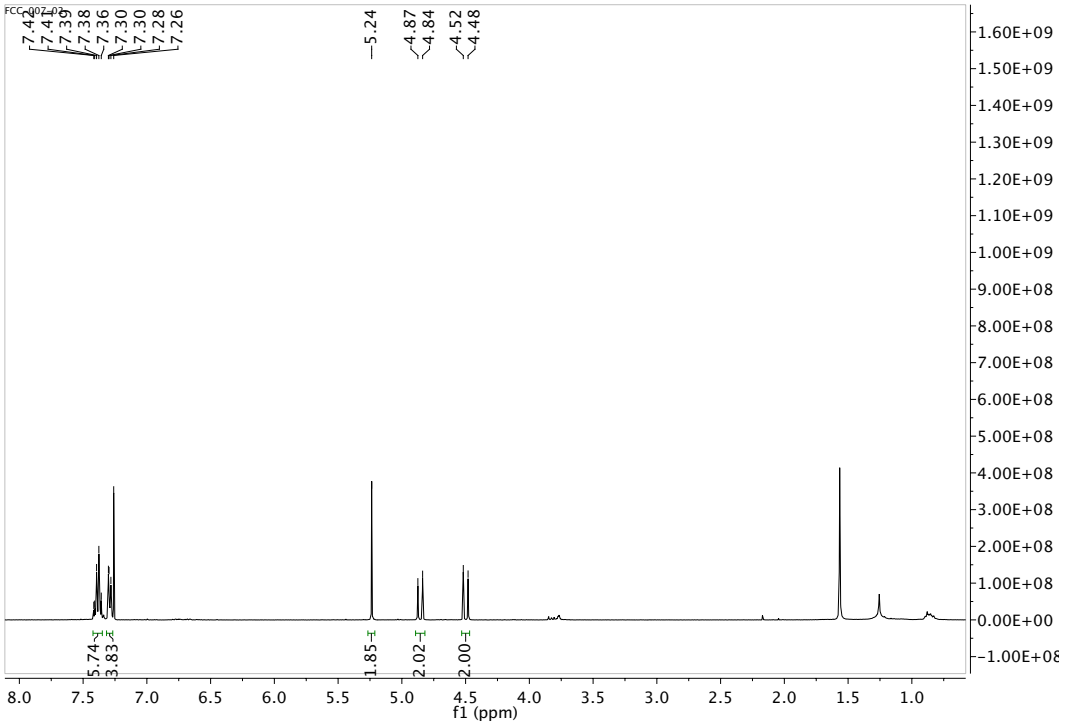
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Maximum:		5.0	10.0	50.0			
599.2024	599.2023	0.1	0.2	10.5	130.9	15.5	C25 H35 N4 O11 S
	599.2018	0.6	1.0	28.5	131.0	15.6	C38 H27 N6 S
	599.2030	-0.6	-1.0	19.5	140.7	25.3	C33 H31 N2 O9
	599.2017	0.7	1.2	1.5	131.0	15.6	C17 H39 N6 O13 S2
	599.2036	-1.2	-2.0	15.5	130.5	15.1	C26 H31 N8 O7 S
	599.2011	1.3	2.2	19.5	121.2	5.8	C30 H31 N8 O2 S2
	599.2011	1.3	2.2	32.5	140.6	25.2	C45 H27 O2
	599.2038	-1.4	-2.3	18.5	115.4	0.0	C34 H35 N2 O4 S2
	599.2010	1.4	2.3	5.5	132.0	16.6	C24 H39 O15 S
	599.2005	1.9	3.2	23.5	130.8	15.4	C37 H31 N2 O4 S
	599.2043	-1.9	-3.2	24.5	140.8	25.3	C34 H27 N6 O5
	599.2043	-1.9	-3.2	0.5	129.3	13.9	C21 H43 O15 S2
	599.2003	2.1	3.5	20.5	140.8	25.4	C29 H27 N8 O7
	599.2045	-2.1	-3.5	27.5	132.4	16.9	C42 H31 O2 S
	599.2048	-2.4	-4.0	6.5	142.0	26.5	C21 H35 N4 O16
	599.1998	2.6	4.3	14.5	123.4	7.9	C29 H35 N4 O6 S2
	599.2052	-2.8	-4.7	23.5	120.7	5.2	C35 H31 N6 S2
	599.2057	-3.3	-5.5	5.5	129.6	14.1	C22 H39 N4 O11 S2
	599.1989	3.5	5.8	15.5	141.0	25.6	C28 H31 N4 O11
	599.2061	-3.7	-6.2	11.5	141.9	26.4	C22 H31 N8 O12
	599.2063	-3.9	-6.5	14.5	132.7	17.3	C30 H35 N2 O9 S
	599.1985	3.9	6.5	9.5	126.4	10.9	C28 H39 O10 S2
	599.1984	4.0	6.7	33.5	140.7	25.3	C41 H23 N6
	599.1983	4.1	6.8	6.5	133.7	18.2	C20 H35 N6 O13 S
	599.2070	-4.6	-7.7	10.5	130.2	14.7	C23 H35 N8 O7 S2
	599.1978	4.6	7.7	24.5	131.8	16.3	C33 H27 N8 O2 S
	599.2070	-4.6	-7.7	23.5	140.8	25.4	C38 H31 O7
	599.1976	4.8	8.0	10.5	141.3	25.9	C27 H35 O15

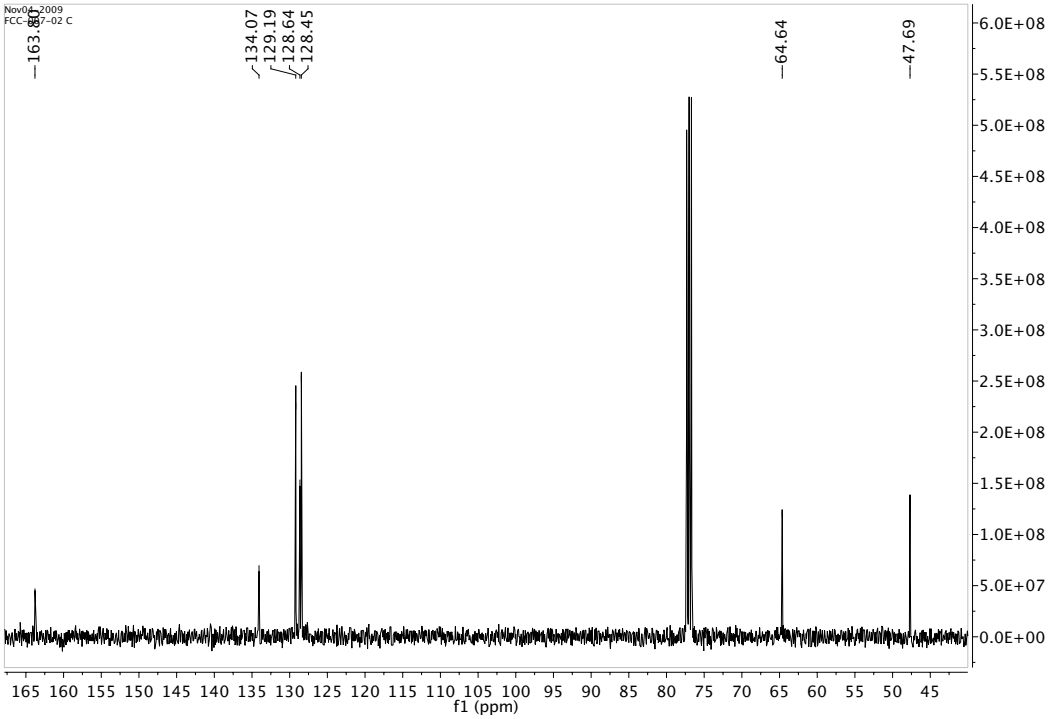
5,7-Dibenzyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (6)[3]

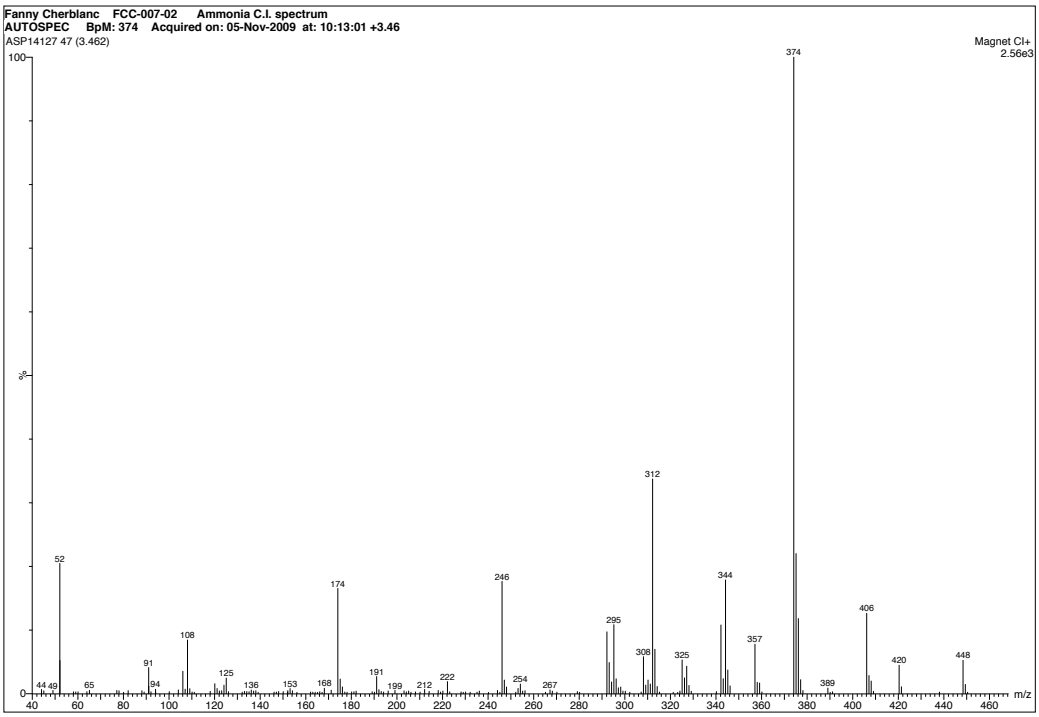


Compound **6** was prepared as follows:[3] BBr_3 (160 μL, 1.68 mmol) was added dropwise to a solution of diketopiperazine **14** (250 mg, 0.42 mmol) in CH_2Cl_2 (10 mL) at −78 ˚C. The solution was allowed to stir at this temperature for 45 min and then for 30 min at room temperature. After the addition of sat. aq. NH_4Cl (20 mL), the biphasic mixture was allowed to stir for 10 min and iodine was added portionwise until the red colour persisted. The resulting mixture was allowed to stir for 3 min, time after which solid sodium thiosulfate was added, until the colour of iodine disappeared. The mixture was allowed to stir for 10 min and then diluted with CH_2Cl_2 (10 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and rotary evaporated. Purification by column chromatography

(EtOAc : Hexanes, 1 : 3) furnished the title compound **6** as a white solid (110 mg, 74%): IR (neat) 1673, 1496, 1422, 1246, 1167, 730, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 10H), 5.24 (s, 2H), 4.86 (d, J = 14.8 Hz, 2H), 4.50 (d, J = 14.8 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 163.8 (2C), 134.1 (2C), 129.2 (4C), 128.7 (2C), 128.5 (4C), 64.7 (2C), 47.7 (2C); MS (CI) *m/z* 357 $(M+H)^+$, 374 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{18}H_{20}N_3O_2S_2$ 374.0997, found: 374.0996.



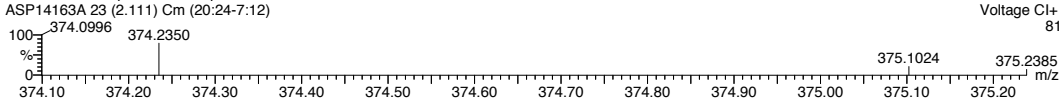

Nov04 2009
FCC-007-02 C
163.80
134.07
129.19
128.64
128.45
64.64
47.69
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45
f1 (ppm)


Fanny Cherblanc FCC-007-02 Ammonia C.I. spectrum
AUTOSPEC BpM: 374 Acquired on: 05-Nov-2009 at: 10:13:01 +3.46
ASP14127 47 (3.462)
Magnet CI+
2.56e3
100
%
0
374
312
52
174
246
344
406
295
357
108
308
325
420
448
91
125
136
153
168
191
199
212
222
254
267
389
44 49
65
94
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 35.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

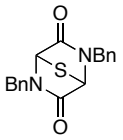
Monoisotopic Mass, Even Electron Ions
986 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-007-02
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ASP14163A 23 (2.111) Cm (20:24-7:12)
Voltage CI+ 81

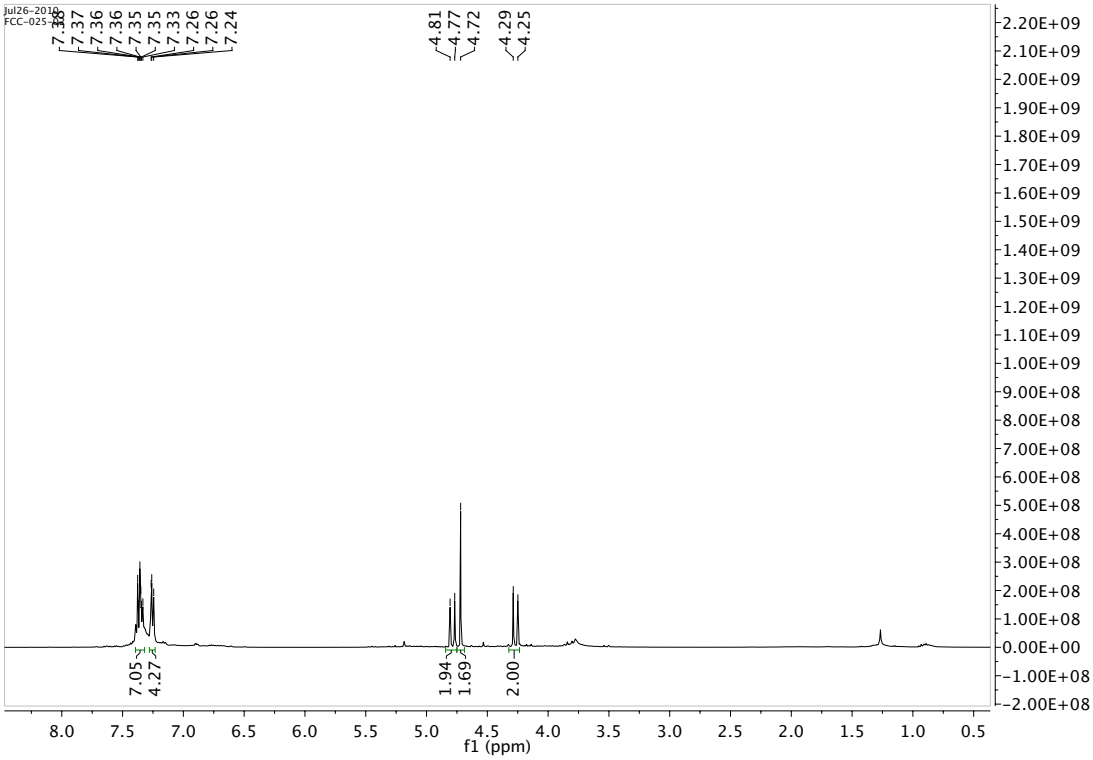


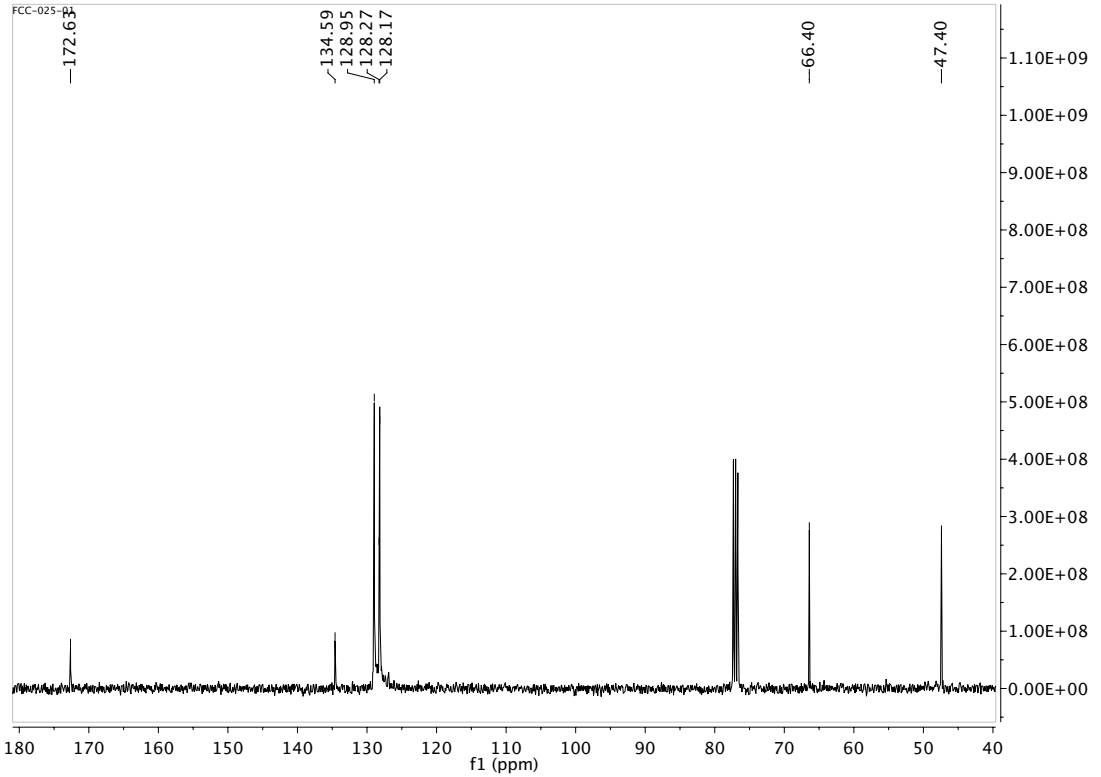
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Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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	374.1003	-0.7	-2.0	19.5	11	C26 H16 N S
	374.0988	0.8	2.1	11.5	1	C17 H16 N3 O7
	374.0982	1.4	3.8	2.5	7	C9 H20 N5 O9 S
	374.1022	-2.6	-6.9	6.5	5	C14 H20 N3 O7 S
	374.0970	2.6	7.0	24.5	10	C29 H12 N
	374.1028	-3.2	-8.7	15.5	2	C22 H16 N O5
	374.0963	3.3	8.8	15.5	6	C21 H16 N3 O2 S
	374.0957	3.9	10.5	6.5	8	C13 H20 N5 O4 S2
	374.1037	-4.1	-11.0	14.5	12	C23 H20 N S2
	374.1042	-4.6	-12.3	20.5	4	C23 H12 N5 O
	374.0948	4.8	12.8	7.5	3	C12 H16 N5 O9

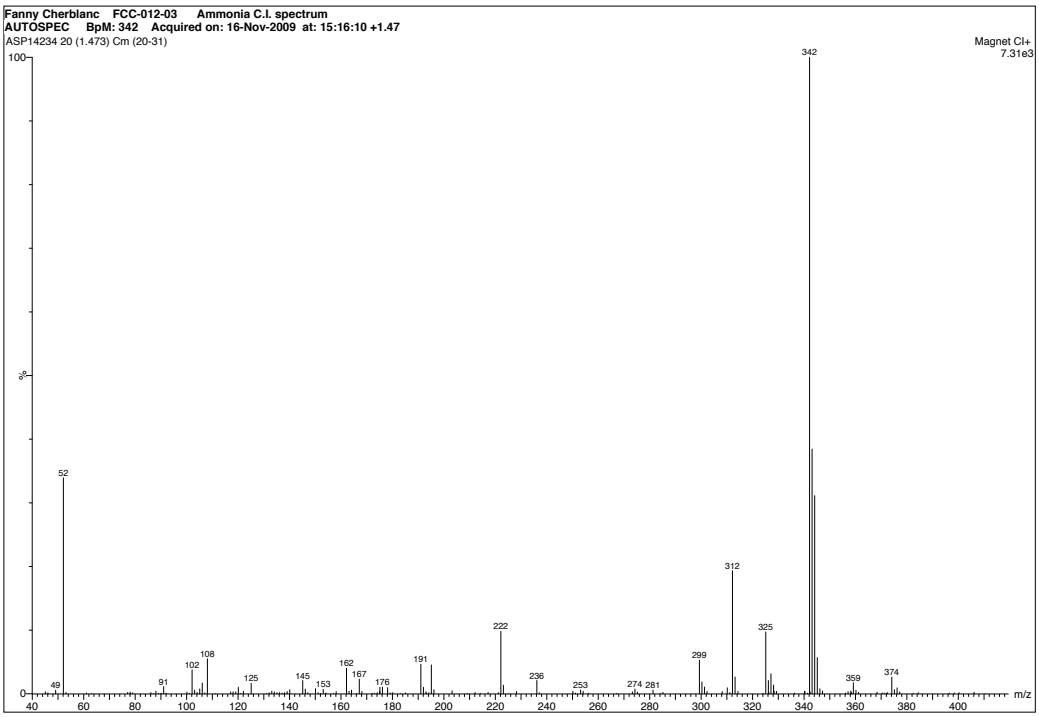
2,5-Dibenzyl-7-thia-2,5-diazabicyclo[2.2.1]heptane-3,6-dione (15)



Compound **15** was prepared as follows:[5] PPh_3 (40 mg, 0.15 mmol) was added to a solution of ETP **6** (50 mg, 0.14 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to stir for 16 h at room temperature. The solvent was then removed and column chromatography (CH_2Cl_2 : MeOH, 95 : 5) afforded the monosulfide derivative **15** (26.6 mg, 60%) as a white solid: m.p. 84 – 86 °C; IR (neat) 1699, 1357, 1190, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 10H), 4.79 (d, J = 15.2 Hz, 2H), 4.72 (s, 2H), 4.27 (d, J = 15.2 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 172.6 (2C), 134.6 (2C), 128.9 (4C), 128.3 (2C), 128.2 (4C), 66.4 (2C), 47.4 (2C); MS (CI) *m/z* 325 $(M+H)^+$, 342 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{18}H_{20}N_3O_2S$ 342.1276, found: 342.1275.


Jul26-2010
FCC-025-01
7.38
7.37
7.36
7.35
7.35
7.33
7.26
7.26
7.24
4.81
4.77
4.72
4.29
4.25
7.05
4.27
1.94
1.69
2.00
f1 (ppm)


FCC-025-01
172.63
134.59
128.95
128.27
128.17
66.40
47.40
f1 (ppm)

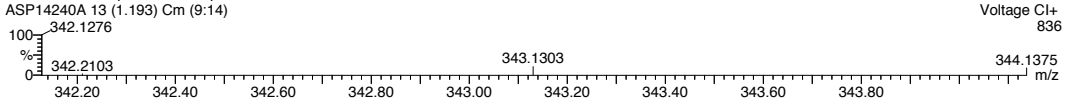


Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

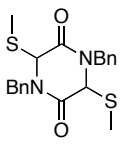
Monoisotopic Mass, Even Electron Ions
880 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-012-03
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ASP14240A 13 (1.193) Cm (9:14)
Voltage CI+
836



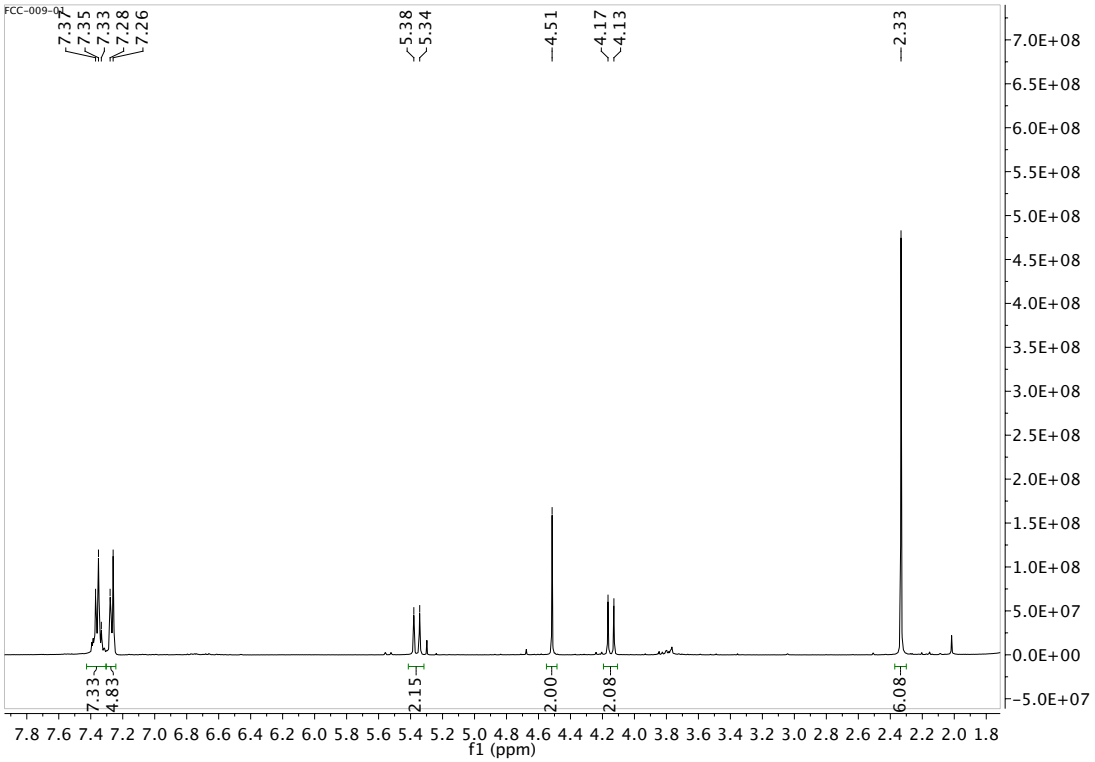
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Maximum:		5.0	10.0	35.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**Score**	**Formula**
342.1276	342.1276	0.0	-0.1	10.5	3	C18 H20 N3 O2 S
	342.1270	0.6	1.8	1.5	2	C10 H24 N5 O4 S2
	342.1283	-0.7	-2.0	19.5	8	C26 H16 N
	342.1261	1.5	4.4	2.5	9	C9 H20 N5 O9
	342.1301	-2.5	-7.4	6.5	7	C14 H20 N3 O7
	342.1243	3.3	9.8	15.5	6	C21 H16 N3 O2
	342.1310	-3.4	-9.9	5.5	1	C15 H24 N3 O2 S2
	342.1236	4.0	11.7	6.5	4	C13 H20 N5 O4 S
	342.1316	-4.0	-11.8	14.5	5	C23 H20 N S

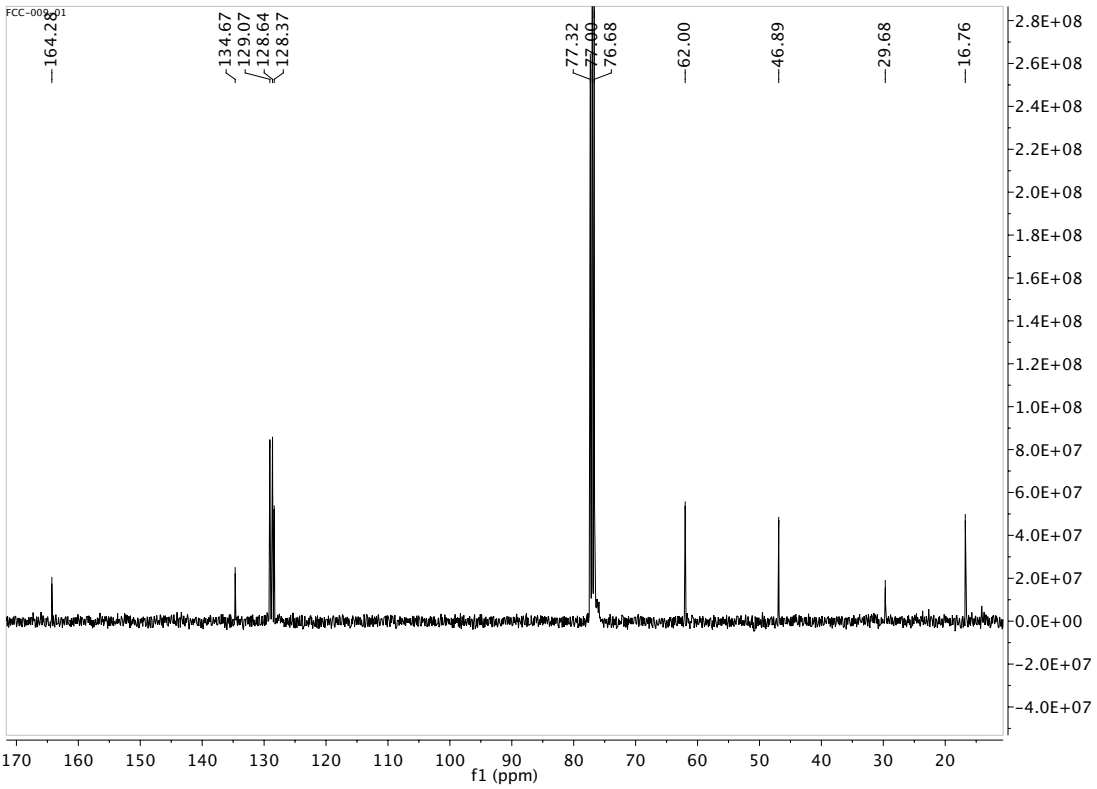
1,4-Dibenzyl-3,6-bis(methylthio)piperazine-2,5-dione (16)[3]

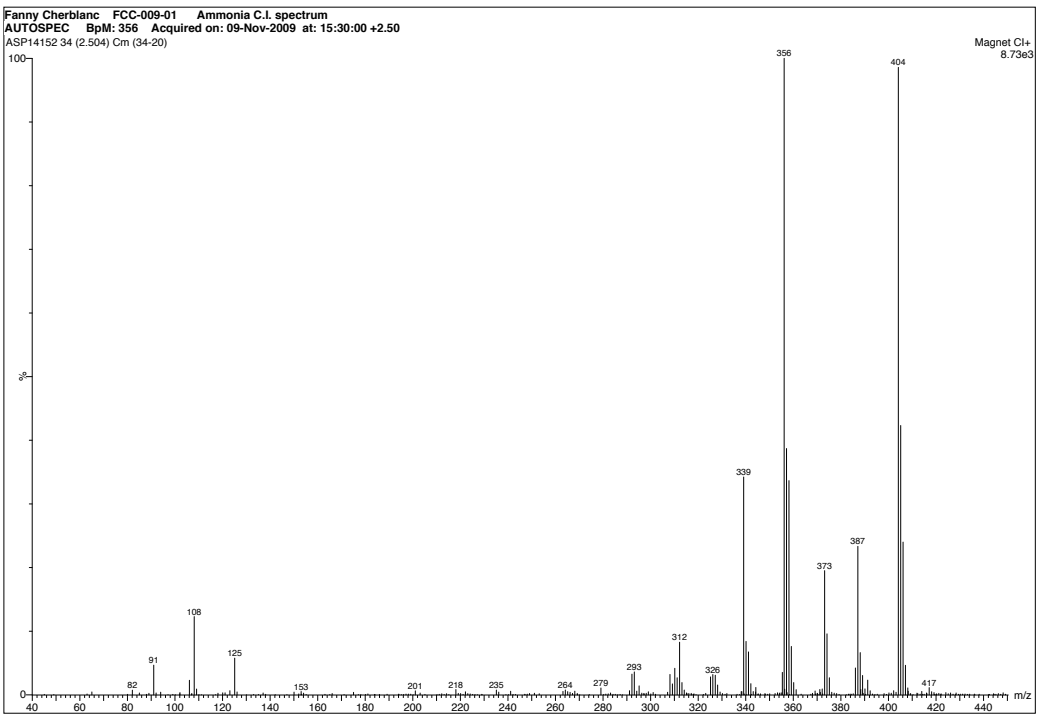


Compound **16** was prepared as follows:[5] $NaBH_4$ (9.4 mg, 0.24 mmol) was added to a solution of ETP **6** (11.2 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) and MeOH (1 mL) at 0 ˚C. The reaction mixture was allowed to stir for 0.5 h. MeI (2.0 mL, 32 mmol) was added

and the resulting mixture was allowed to stir for 16 h. The solution was then washed with 10% aq. HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL). The organic layers were combined, dried ($MgSO_4$) and rotary evaporated to afford methylthioether **16** as a brown oil (7.4 mg, 60%) that was used in the next step without further purification: IR (neat) 1667, 1429, 1241, 1168, 727, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 10H), 5.36 (d, *J* = 15.0 Hz, 2H), 4.51 (s, 2H), 4.14 (d, *J* = 15.0 Hz, 2H), 2.33 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 164.3 (2C), 134.7 (2C), 129.1 (4C), 128.7 (4C), 128.4 (2C), 62.0 (2C), 46.9 (2C), 16.7 (2C); MS (CI) *m/z* 387 $(M+H)^+$, 404 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{20}H_{26}N_3O_2S_2$ 404.1466, found: 404.1471.




FCC-009-01
164.28
134.67
129.07
128.64
128.37
77.32
77.00
76.68
62.00
46.89
29.68
16.76
f1 (ppm)

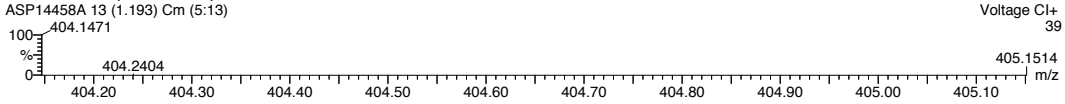

Fanny Cherblanc FCC-009-01 Ammonia C.I. spectrum
AUTOSPEC BpM: 356 Acquired on: 09-Nov-2009 at: 15:30:00 +2.50
ASP14152 34 (2.504) Cm (34-20)
Magnet CI+
8.73e3
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

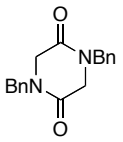
Monoisotopic Mass, Even Electron Ions
1087 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-026-01-B
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ASP14458A 13 (1.193) Cm (5:13) Voltage CI+ 39

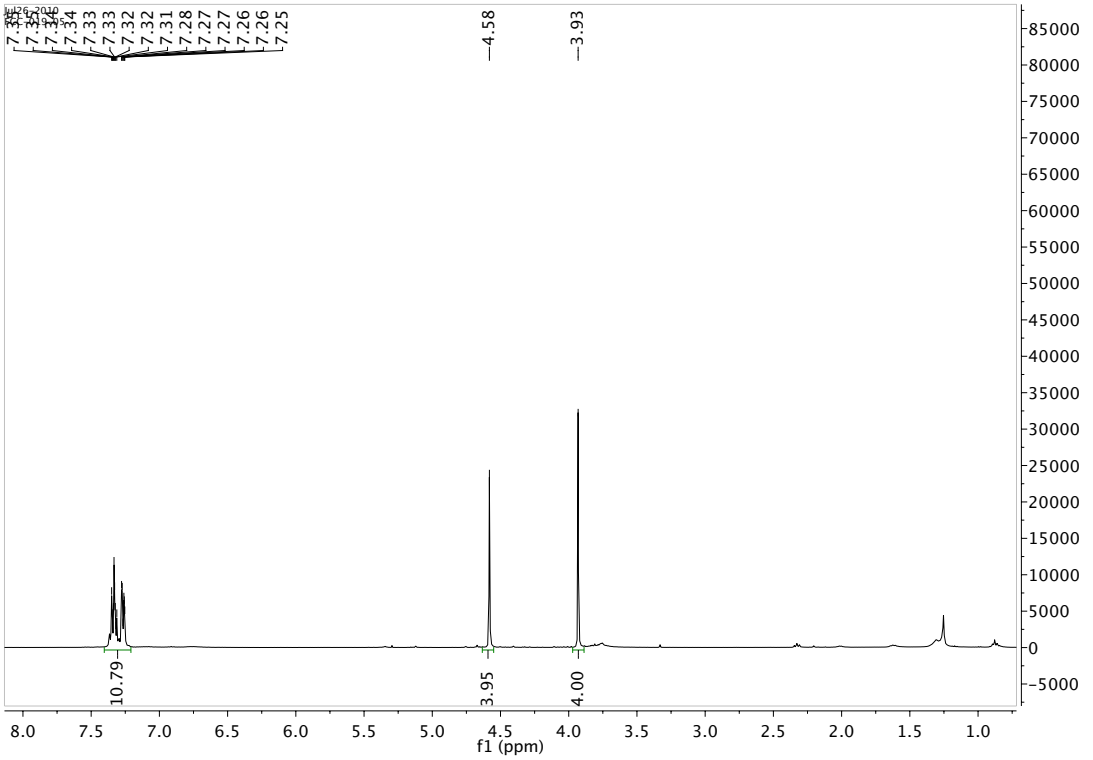


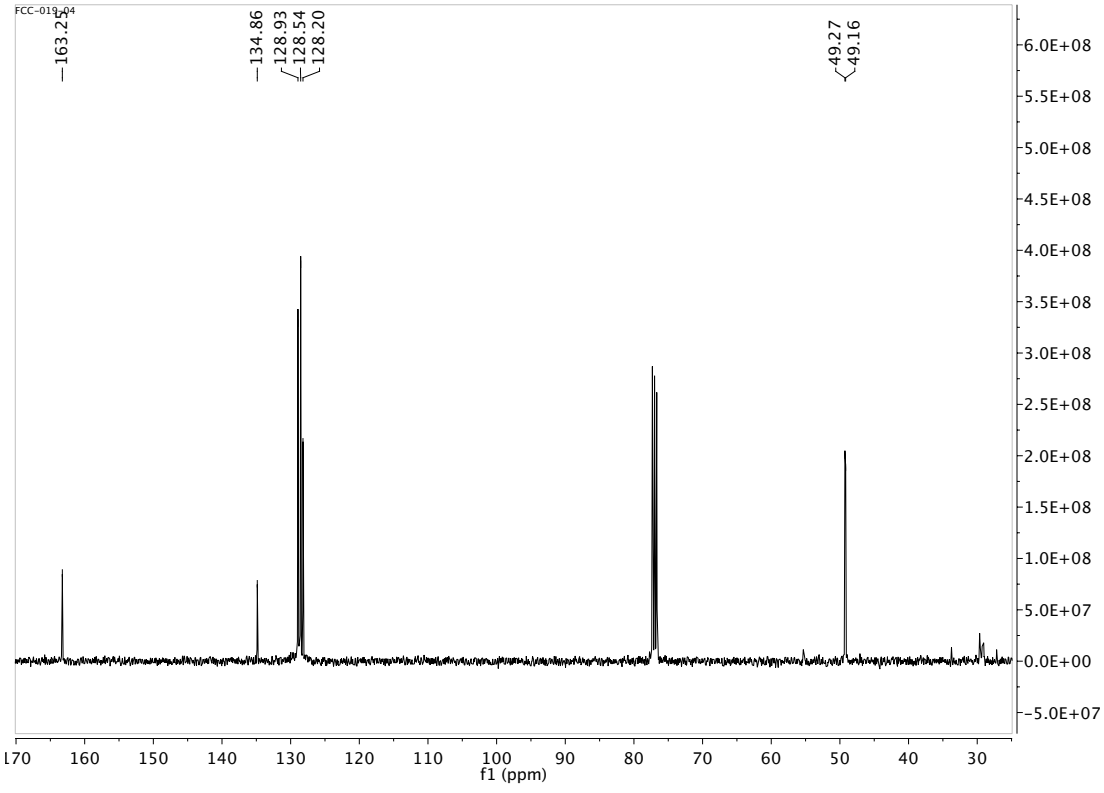
Minimum:				-1.5		
Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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	404.1466	0.5	1.1	9.5	9	C20 H26 N3 O2 S2
	404.1458	1.3	3.3	10.5	1	C19 H22 N3 O7
	404.1451	2.0	4.9	1.5	5	C11 H26 N5 O9 S
	404.1491	-2.0	-5.1	5.5	3	C16 H26 N3 O7 S
	404.1498	-2.7	-6.7	14.5	4	C24 H22 N O5
	404.1439	3.2	7.9	23.5	11	C31 H18 N
	404.1507	-3.6	-8.8	13.5	12	C25 H26 N S2
	404.1433	3.8	9.5	14.5	7	C23 H22 N3 O2 S
	404.1511	-4.0	-10.0	19.5	6	C25 H18 N5 O
	404.1426	4.5	11.1	5.5	8	C15 H26 N5 O4 S2
	404.1516	-4.5	-11.3	1.5	2	C12 H26 N3 O12

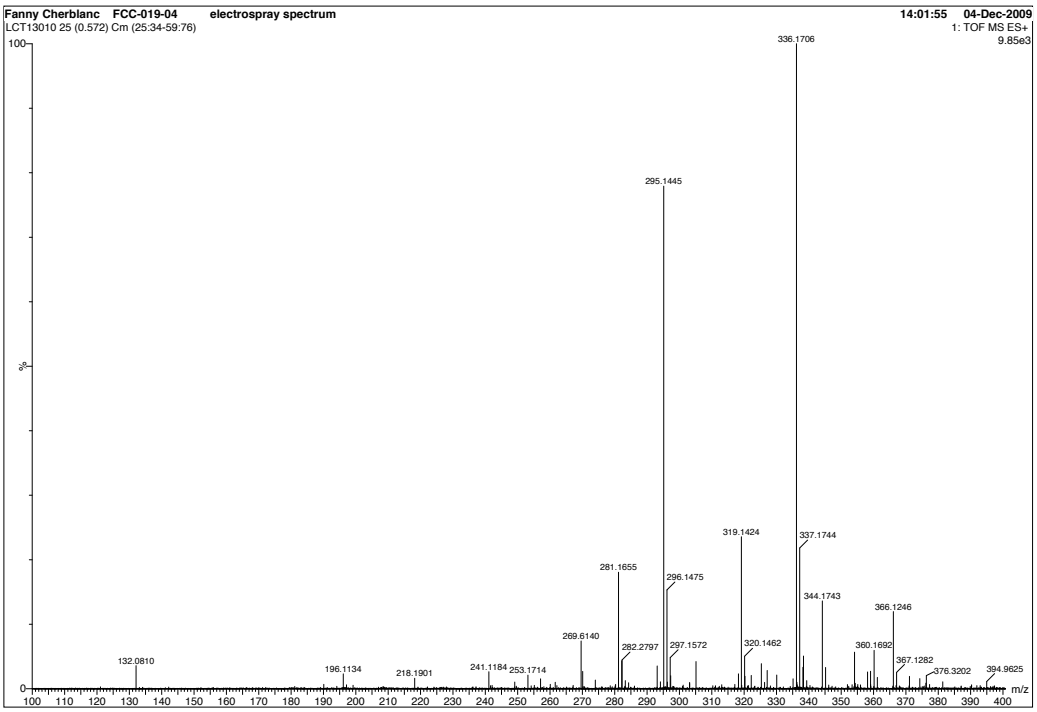
1,4-Dibenzylpiperazine-2,5-dione (18)[6]



Compound **18** was prepared as follows:[7] Nickel (II) chloride hexahydrate (267 mg, 1.12 mmol) was added to a solution of ETP **6** (40 mg, 0.11 mmol) in EtOH (5 mL). At 0 ˚C, a solution of $NaBH_4$ (127.5 mg, 3.37 mmol) in water (5 mL) was added dropwise to the reaction mixture which subsequently darkened. The mixture was allowed to stir at reflux for 16 h and was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$) and rotary evaporated. Column chromatography (CH_2Cl_2 : MeOH, 95 : 5) afforded the title compound **18** as a white solid (24.5 mg, 75%): IR (neat) 1648, 1483, 1333, 1254, 718, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 10H), 4.58 (s, 4H), 3.93 (s, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 163.2 (2C), 134.9 (2C), 128.9 (4C), 128.5 (4C), 128.2 (2C), 49.3 (2C), 49.2 (2C); MS (ESI) *m/z* 295 $(M+H)^+$, 336 $(M+MeCN+H)^+$; HRMS (ESI) *m/z* calc. for $C_{18}H_{19}N_2O_2$ 295.1447, found: 295.1445.


7.35
7.34
7.33
7.32
7.31
7.28
7.27
7.26
7.25
4.58
3.93
10.79
3.95
4.00
f1 (ppm)

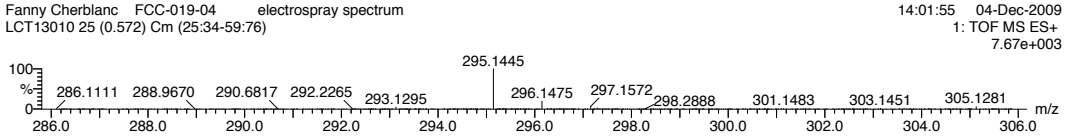

FCC-019_04
163.25
134.86
128.93
128.54
128.20
49.27
49.16
f1 (ppm)



Elemental Composition Report **Page 1**

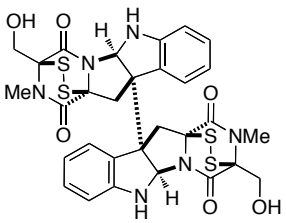
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
354 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
295.1445	295.1447	-0.2	-0.7	10.5	552.4	1.8	C18 H19 N2 O2
	295.1420	2.5	8.5	11.5	551.1	0.5	C14 H15 N8
	295.1478	-3.3	-11.2	2.5	554.5	3.9	C7 H19 N8 O5
	295.1406	3.9	13.2	6.5	553.2	2.5	C13 H19 N4 O4
	295.1487	-4.2	-14.2	14.5	552.9	2.2	C23 H19

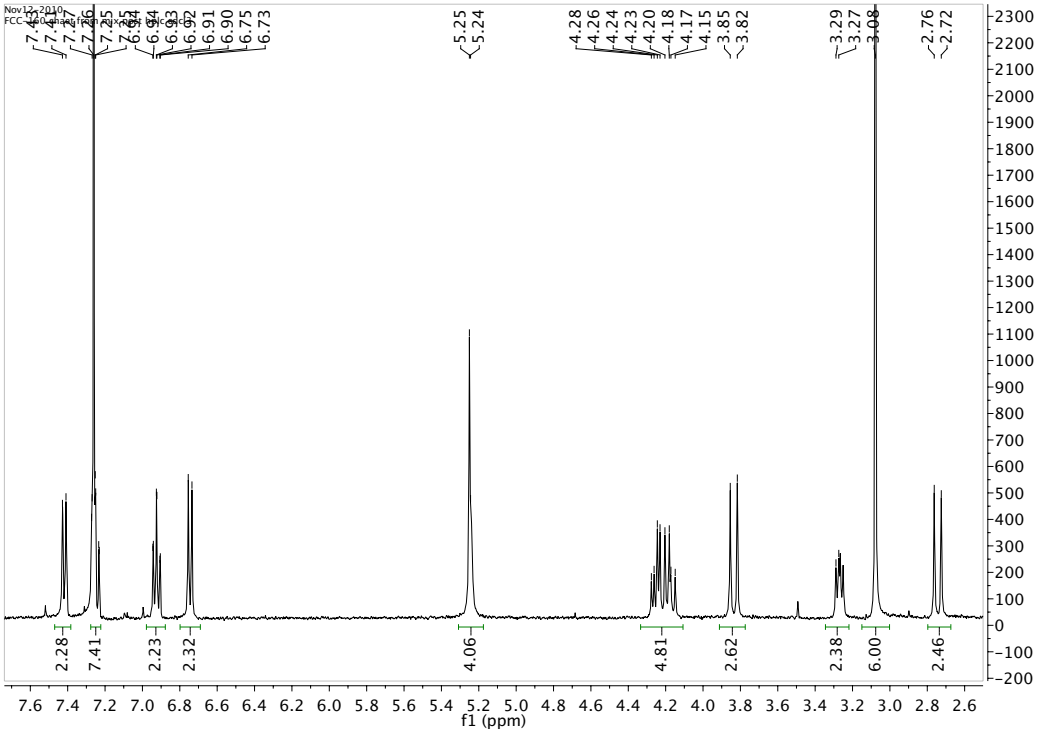
Chaetocin (1) Production[8]

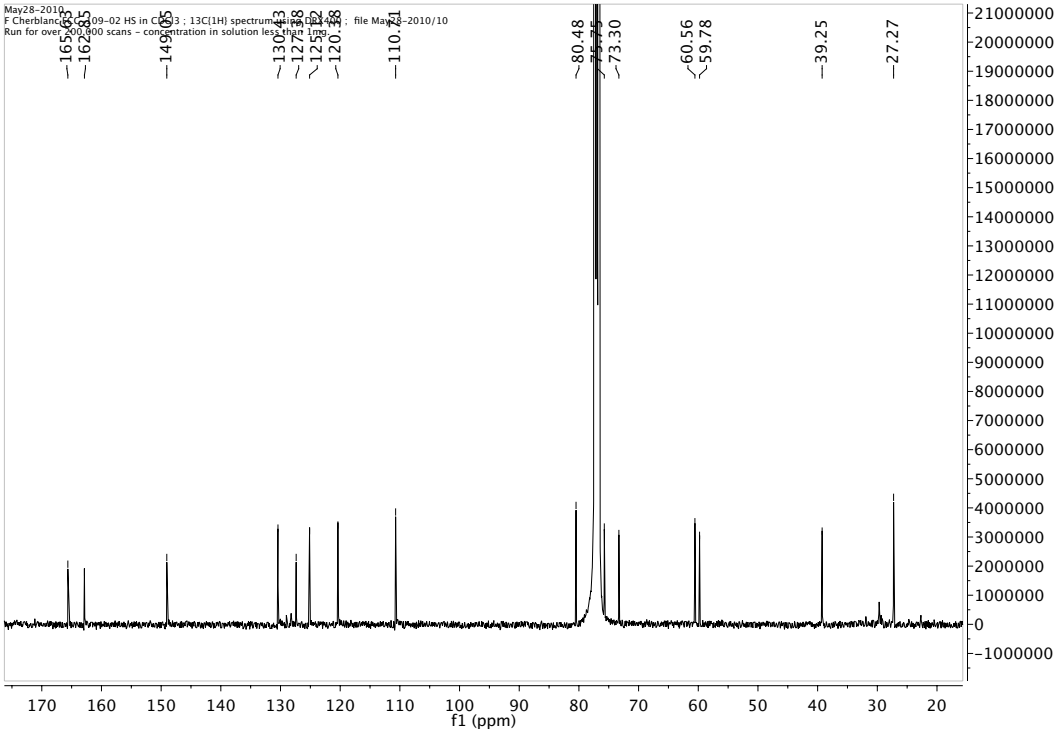


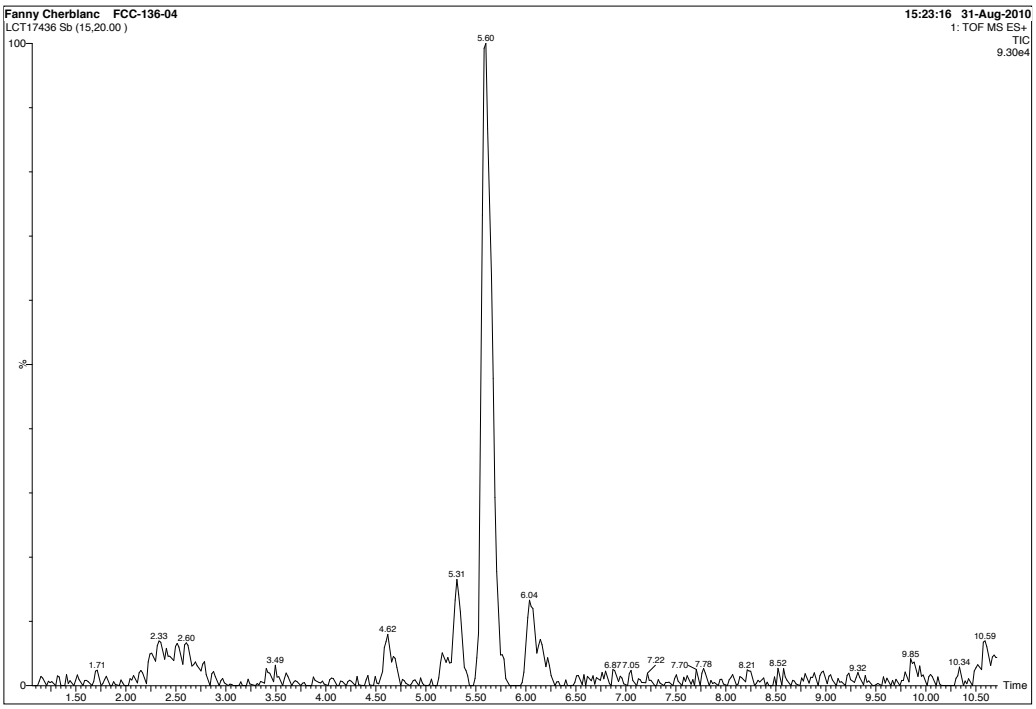
A conidial suspension of *Chaetomium virescens var. thielavioideum* was plated on solid complete media, containing 0.5% yeast extract (w/v), 1% vitamin

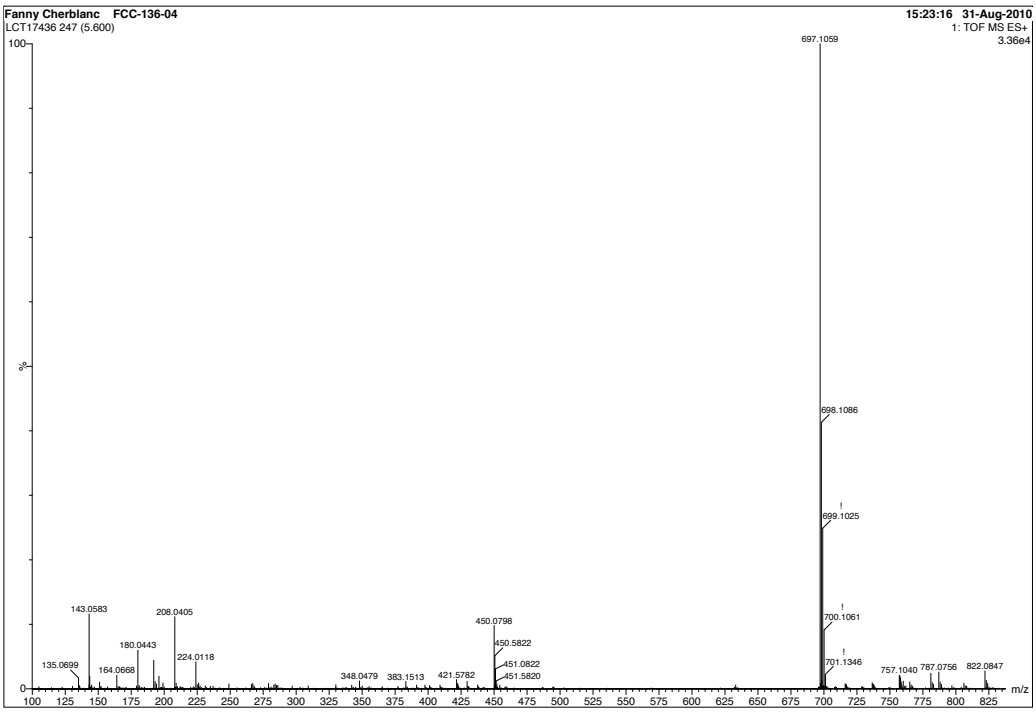
solution, 1% (w/v) glucose as carbon source and 5 mM ammonium tartrate as nitrogen source. The pH was adjusted to 6.5 with 10 M aq. NaOH. The plates were incubated during 5 days at 37 ˚C. A mycelia inoculum of *Chaetomium virescens var. thielavioideum* was prepared by dissecting agar surfaces of cultures grown on complete media and was inoculated into ten 1 L bottles half-filled with solid complete media.

After three weeks of incubation at room temperature, the culture media were extracted with CH_2Cl_2 (2 × 500 mL per bottle) for 24 h and 48 h with orbital shaking. The resulting mixtures were then filtered, dried over $MgSO_4$, and rotatory evaporated. The extracts were then purified by column chromatography (CH_2Cl_2 : MeOH, 98 : 2). The resulting solid was further purified by trituration in hexanes with sonication to afford 210 mg of chaetocin (**1**): $[\alpha]_D^{20}$ + 542 (*c* 0.82, $CHCl_3$); CD (MeOH) $\Delta\varepsilon^{20}$ (nm): +434 (237), 0 (263), –42 (272), 0 (284), +78 (304), +1 (350); IR (neat) 3383, 3336, 1670, 1066, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 7.5 Hz, 2H), 5.25 (s, 2H), 5.24 (br s, 2H), 4.25 (dd, *J* = 12.5, 6.0 Hz, 2H), 4.17 (dd, *J* = 12.5, 9.4 Hz, 2H), 3.83 (d, *J* = 15.0 Hz, 2H), 3.28 (dd, *J* = 9.4, 6.0 Hz, 2H), 3.08 (s, 6H), 2.74 (d, *J* = 15.0 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 165.6 (2C), 162.8 (2C), 149.1 (2C), 130.4 (2C), 127.4 (2C), 125.1 (2C), 120.4 (2C), 110.7 (2C), 80.5 (2C), 75.7 (2C), 73.3 (2C), 60.6 (2C), 59.8 (2C), 39.2 (2C), 27.3 (2C); LCMS: R_t = 5.62 min, MS (ESI) *m/z* 697 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{30}H_{29}N_6O_6S_4$ 697.1031, found: 697.1021.


Nov12-2010
7.48
7.47
7.47
7.46
7.25
6.94
6.94
6.93
6.92
6.91
6.90
6.75
6.73
5.25
5.24
4.28
4.26
4.24
4.23
4.20
4.18
4.17
4.15
3.85
3.82
3.29
3.27
3.08
2.76
2.72
2.28
7.41
2.23
2.32
4.06
4.81
2.62
2.38
6.00
2.46
f1 (ppm)


May28-2010
F Cherblanc 05-2009-02 HS in CDCl3 ; 13C{1H} spectrum using DEPT135 ; file May28-2010/10
Run for over 200,000 scans - concentration in solution less than 1mg
165.03
162.45
149.05
130.23
127.98
125.82
120.88
110.41
80.48
75.45
73.30
60.56
59.78
39.25
27.27
f1 (ppm)


Fanny Cherblanc FCC-136-04
15:23:16 31-Aug-2010
LCT17436 Sb (15,20.00)
1: TOF MS ES+
TIC
9.30e4
100
%
0
5.60
5.31
6.04
4.62
2.33
2.60
1.71
3.49
6.87
7.05
7.22
7.70
7.78
8.21
8.52
9.32
9.85
10.34
10.59
1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00 8.50 9.00 9.50 10.00 10.50
Time


Fanny Cherblanc FCC-136-04
15:23:16 31-Aug-2010
LCT17436 247 (5.600)
1: TOF MS ES+
3.36e4
100
%
0
697.1059
698.1086
699.1025
700.1061
701.1346
143.0583
208.0405
180.0443
224.0118
135.0699
164.0668
450.0798
450.5822
451.0822
451.5820
348.0479
383.1513
421.5782
757.1040
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822.0847
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m/z

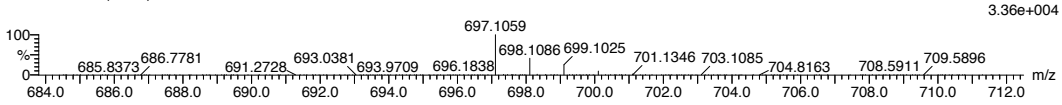
Single Mass Analysis

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

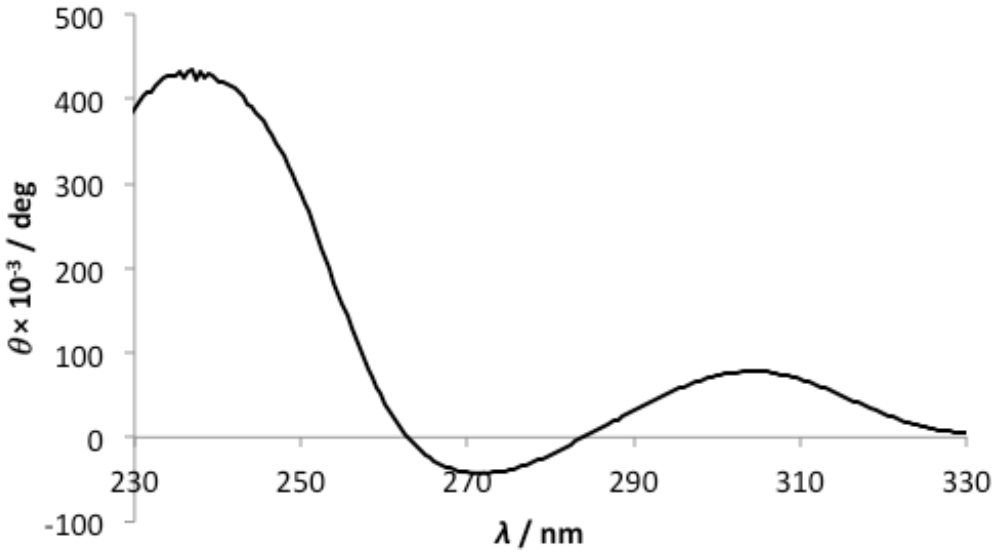
Monoisotopic Mass, Even Electron Ions
4128 formula(e) evaluated with 33 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 S: 0-4

Fanny Cherblanc FCC-136-04
LCT17436 247 (5.600)

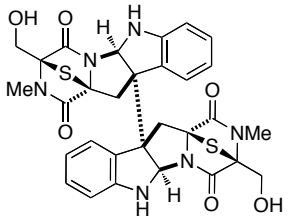
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1: TOF MS ES+
3.36e+004



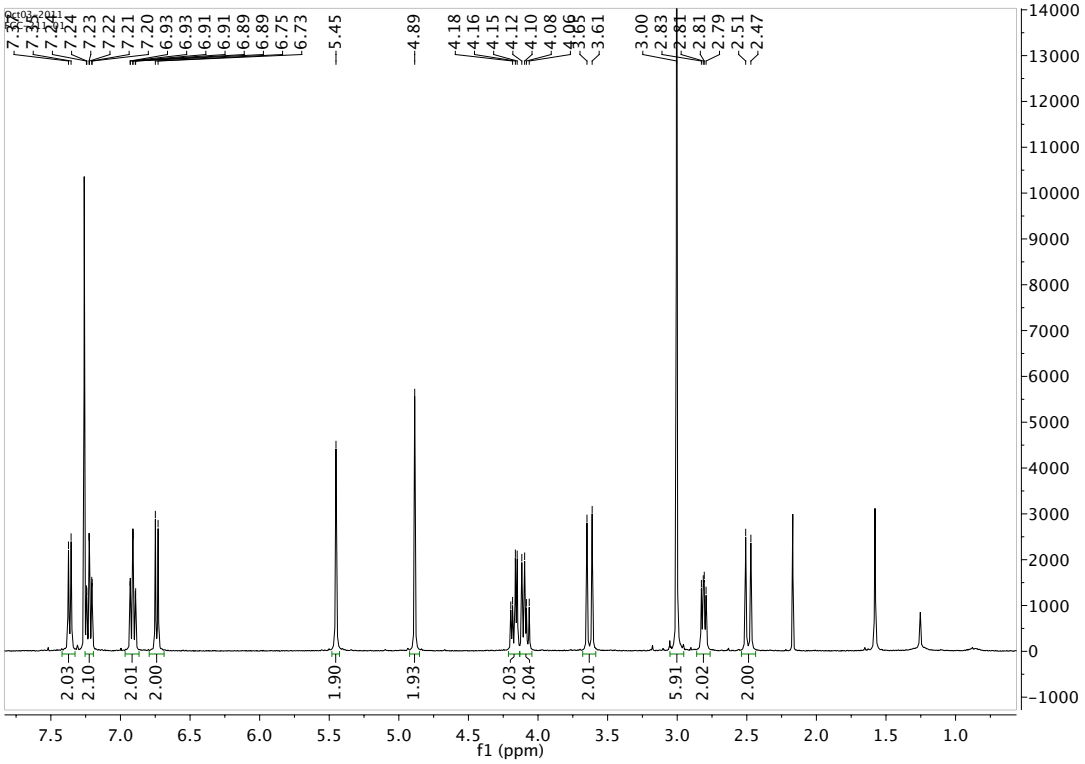
Minimum:				-1.5							
Maximum:		5.0	10.0	50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula				
697.1059	697.1058	0.1	0.1	18.5	316.7	2.3	C34	H33	O8	S4	
	697.1056	0.3	0.4	15.5	318.4	4.0	C26	H29	N6	O11	S3
	697.1063	-0.4	-0.6	24.5	322.4	8.0	C34	H25	N4	O9	S2
	697.1051	0.8	1.1	33.5	318.7	4.3	C39	H21	N8	S3	
	697.1051	0.8	1.1	46.5	329.1	14.7	C54	H17	S		
	697.1068	-0.9	-1.3	30.5	332.7	18.3	C34	H17	N8	O10	
	697.1069	-1.0	-1.4	33.5	327.8	13.4	C42	H21	N2	O7	S
	697.1049	1.0	1.4	43.5	332.7	18.3	C46	H13	N6	O3	
	697.1072	-1.3	-1.9	23.5	317.0	2.6	C35	H29	N4	O4	S4
	697.1044	1.5	2.2	37.5	324.2	9.8	C46	H21	N2	O2	S2
	697.1043	1.6	2.3	34.5	327.6	13.2	C38	H17	N8	O5	S
	697.1076	-1.7	-2.4	29.5	322.6	8.2	C35	H21	N8	O5	S2
	697.1076	-1.7	-2.4	42.5	332.8	18.4	C50	H17	O5		
	697.1078	-1.9	-2.7	32.5	321.0	6.6	C43	H25	N2	O2	S3
	697.1038	2.1	3.0	28.5	317.4	3.1	C38	H25	N4	O4	S3
	697.1036	2.3	3.3	38.5	332.5	18.1	C45	H17	N2	O7	
	697.1083	-2.4	-3.4	38.5	328.1	13.7	C43	H17	N6	O3	S
	697.1085	-2.6	-3.7	28.5	318.0	3.6	C36	H25	N8	S4	
	697.1085	-2.6	-3.7	41.5	326.0	11.6	C51	H21	S2		
	697.1031	2.8	4.0	19.5	315.3	0.9	C30	H29	N6	O6	S4
	697.1029	3.0	4.3	29.5	327.5	13.1	C37	H21	N4	O9	S
	697.1089	-3.0	-4.3	47.5	333.1	18.7	C51	H13	N4	O	
	697.1090	-3.1	-4.4	10.5	318.4	4.0	C23	H33	N6	O11	S4
	697.1025	3.4	4.9	23.5	316.3	1.9	C37	H29	O8	S3	
	697.1094	-3.5	-5.0	29.5	332.7	18.3	C38	H21	N2	O12	
	697.1023	3.6	5.2	20.5	323.0	8.6	C29	H25	N6	O11	S2
	697.1097	-3.8	-5.5	19.5	317.4	3.0	C31	H29	N4	O9	S3
	697.1018	4.1	5.9	38.5	323.6	9.2	C42	H17	N8	S2	
	697.1018	4.1	5.9	14.5	316.8	2.4	C29	H33	N2	O10	S4
	697.1101	-4.2	-6.0	25.5	328.2	13.8	C31	H21	N8	O10	S
	697.1103	-4.4	-6.3	28.5	323.2	8.8	C39	H25	N2	O7	S2
	697.1011	4.8	6.9	42.5	328.4	14.0	C49	H17	N2	O2	S
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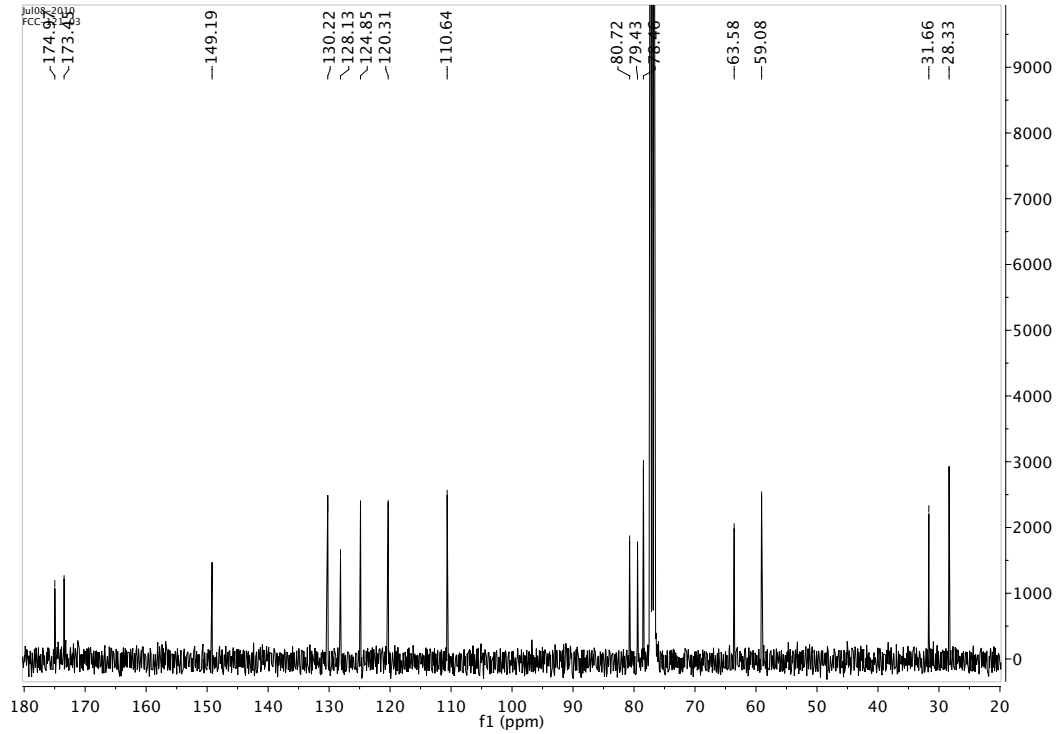


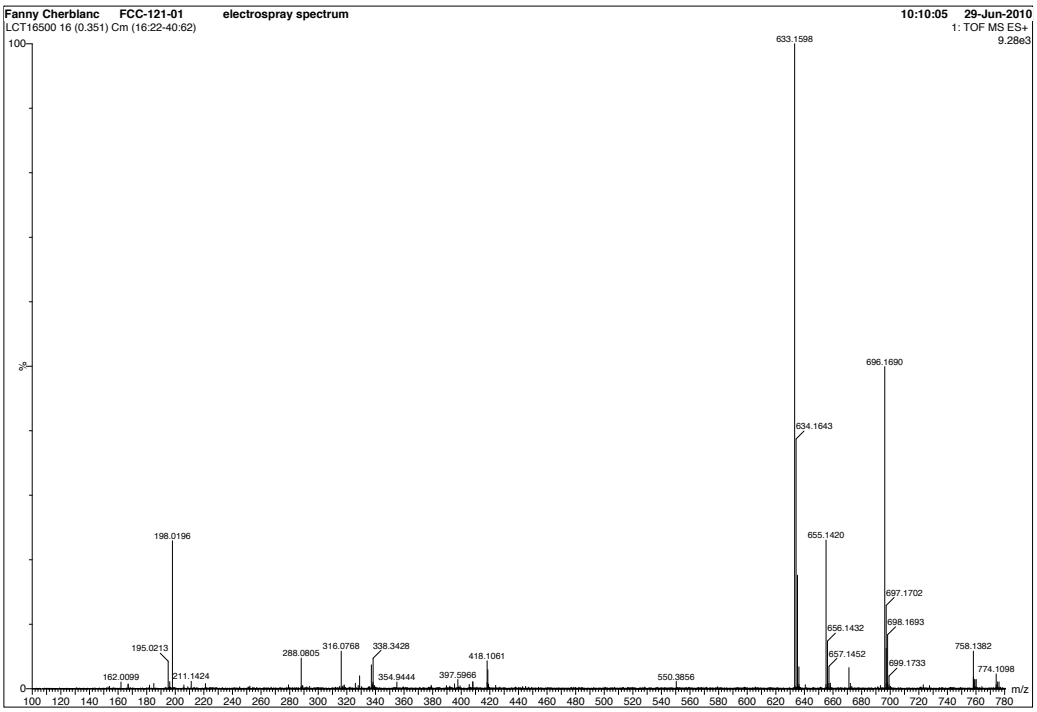
Chaetocin monosulfide derivative (3)[8]



Compound **3** was prepared as follows:[5] PPh_3 (28 mg, 0.11 mmol) was added to a solution of chaetocin (**1**, 20 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 2 h at room temperature. The solvent was rotatory evaporated and the resulting pink solid was purified by column chromatography (CH_2Cl_2 : EtOAc, 60 : 40) to afford monosulfide **3** (17 mg, 93 %) as a white solid: m.p. 210 – 212 ˚C (dec.); $[\alpha]_D^{20}$ + 484 (*c* 0.0039, $CHCl_3$); UV λ_{max} ($CHCl_3$) (A): 243.4 (0.49), 298 (0.21) nm; CD (MeOH) Δ_ε^{20} (nm): 0 (217), –43.7 (223.5), 0 (230), +184.9 (248.5), +59.5 (285), +81.6 (304), +0.8 (350); IR (neat) 3388, 2921, 1712, 1468, 1322, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.22 (td, *J* = 7.8, 0.7 Hz, 2H), 6.91 (td, *J* = 7.8, 0.7 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 2H), 5.46 (s, 2H), 4.89 (s, 2H), 4.17 (dd, *J* = 13.1, 5.2 Hz, 2H), 4.09 (dd, *J* = 13.1, 8.2 Hz, 2H), 3.63 (d, *J* = 14.9 Hz, 2H), 3.00 (s, 6H), 2.81 (dd, *J* = 8.2, 5.2 Hz, 2H), 2.49 (d, *J* = 14.9 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 174.9 (2C), 173.5 (2C), 149.2 (2C), 130.2 (2C), 128.1 (2C), 124.9 (2C), 120.3 (2C), 110.6 (2C), 80.7 (2C), 79.4 (2C), 78.5 (2C), 63.6 (2C), 59.1 (2C), 31.6 (2C), 28.3 (2C); LCMS: R_t = 4.77 min; MS (ESI) *m/z* 633 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{30}H_{29}N_6O_6S_2$ 633.1590 found: 633.1598.


Oct03_2011
7.32
7.31
7.24
7.23
7.22
7.21
7.20
6.93
6.91
6.89
6.75
6.73
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4.89
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4.16
4.15
4.12
4.10
4.08
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2.01
2.00
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1.93
2.03
2.04
2.01
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2.02
2.00
f1 (ppm)


Jul08_2010
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f1 (ppm)



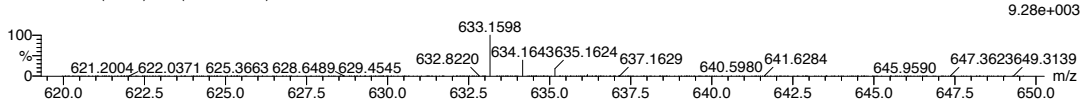
Elemental Composition Report

Single Mass Analysis

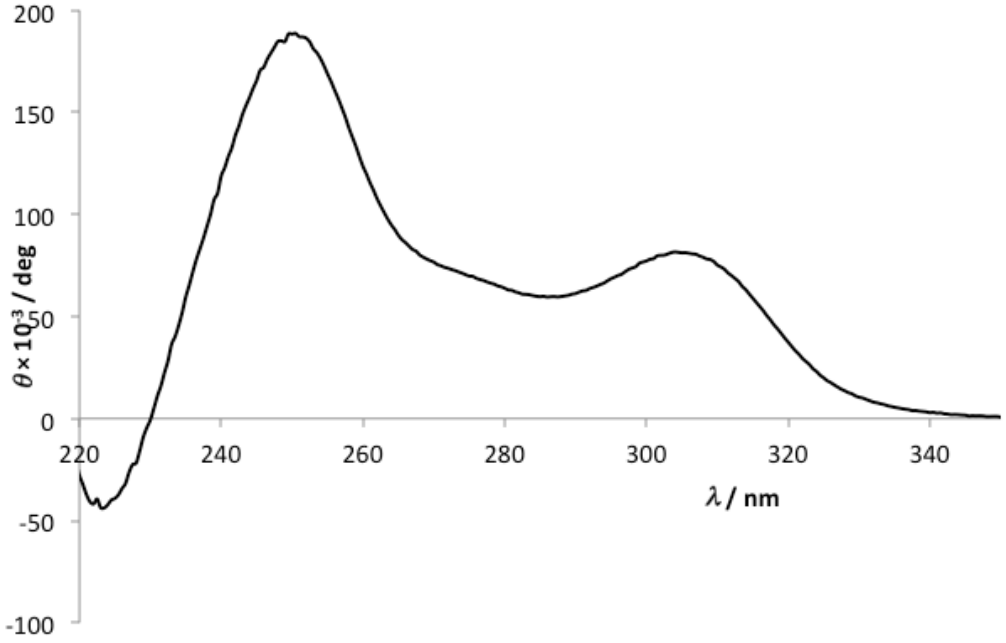
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
2343 formula(e) evaluated with 21 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 S: 0-2

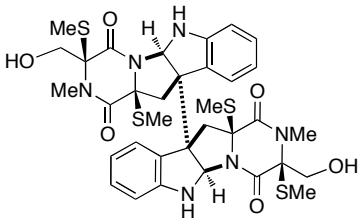
Fanny Cherblanc FCC-121-01 electrospray spectrum
10:10:05 29-Jun-2010
LCT16500 16 (0.351) Cm (16:22-40:62)
1: TOF MS ES+
9.28e+003



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
633.1598	633.1597	0.1	0.2	28.5	353.9	1.2	C38 H25 N4 O4 S
	633.1603	-0.5	-0.8	37.5	361.4	8.7	C46 H21 N2 O2
	633.1590	0.8	1.3	19.5	357.8	5.1	C30 H29 N6 O6 S2
	633.1610	-1.2	-1.9	33.5	354.7	2.0	C39 H21 N8 S
	633.1583	1.5	2.4	23.5	354.0	1.3	C37 H29 O8 S
	633.1581	1.7	2.7	20.5	360.8	8.1	C29 H25 N6 O11
	633.1615	-1.7	-2.7	15.5	354.3	1.6	C26 H29 N6 O11 S
	633.1617	-1.9	-3.0	18.5	357.0	4.3	C34 H33 O8 S2
	633.1577	2.1	3.3	14.5	358.4	5.7	C29 H33 N2 O10 S2
	633.1576	2.2	3.5	38.5	361.1	8.4	C42 H17 N8
	633.1622	-2.4	-3.8	24.5	360.7	8.0	C34 H25 N4 O9
	633.1630	-3.2	-5.1	23.5	358.0	5.3	C35 H29 N4 O4 S2
	633.1563	3.5	5.5	33.5	360.9	8.2	C41 H21 N4 O4
	633.1635	-3.7	-5.8	29.5	361.1	8.5	C35 H21 N8 O5
	633.1637	-3.9	-6.2	32.5	357.6	4.9	C43 H25 N2 O2 S
	633.1558	4.0	6.3	27.5	360.5	7.9	C41 H29 O3 S2
	633.1556	4.2	6.6	24.5	356.0	3.3	C33 H25 N6 O6 S
	633.1643	-4.5	-7.1	41.5	363.1	10.4	C51 H21
	633.1644	-4.6	-7.3	28.5	359.3	6.6	C36 H25 N8 S2
	633.1550	4.8	7.6	15.5	360.6	7.9	C25 H29 N8 O8 S2
	633.1549	4.9	7.7	28.5	360.9	8.2	C40 H25 O8

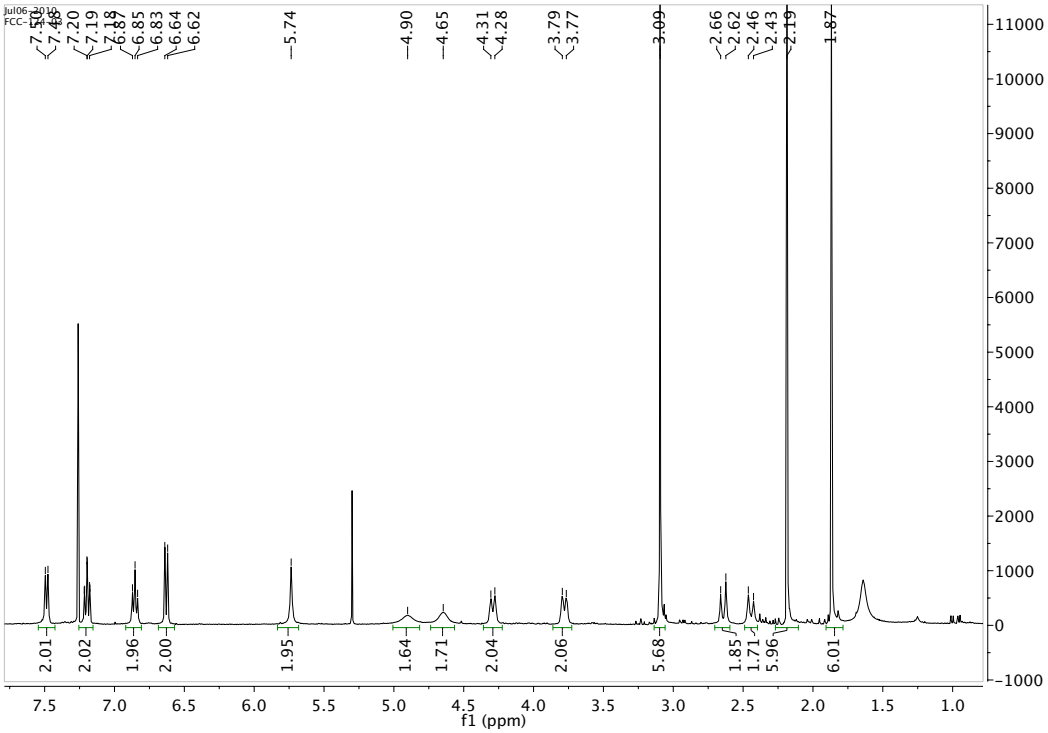


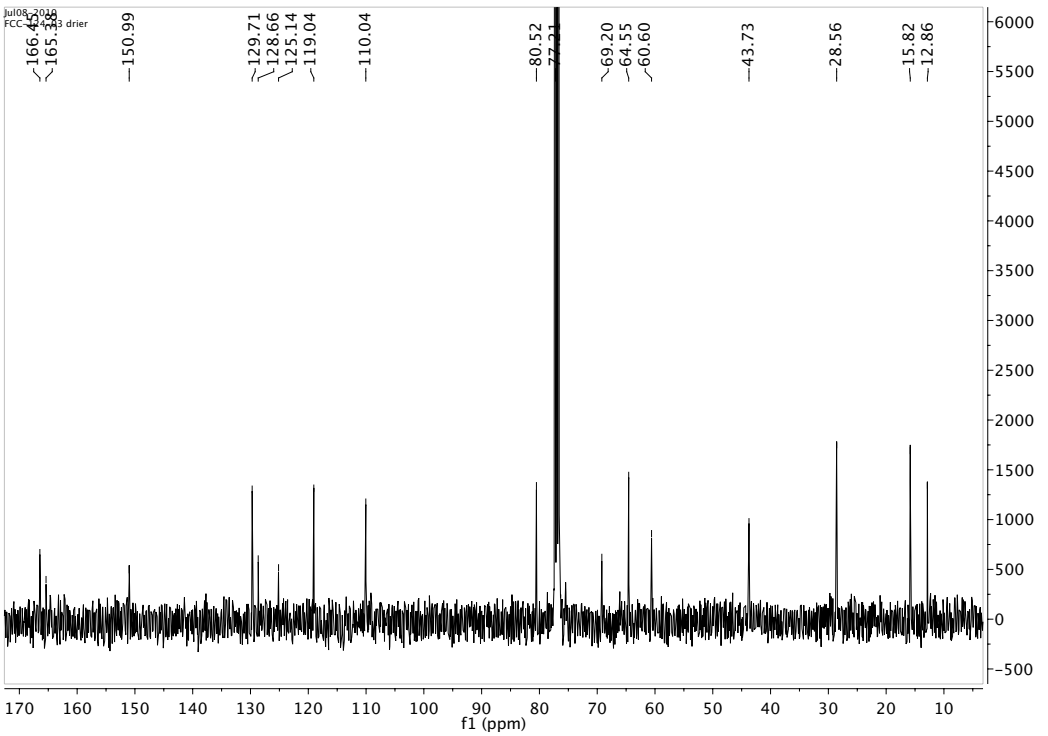
Chaetocin methylthioether derivative (4)[8]

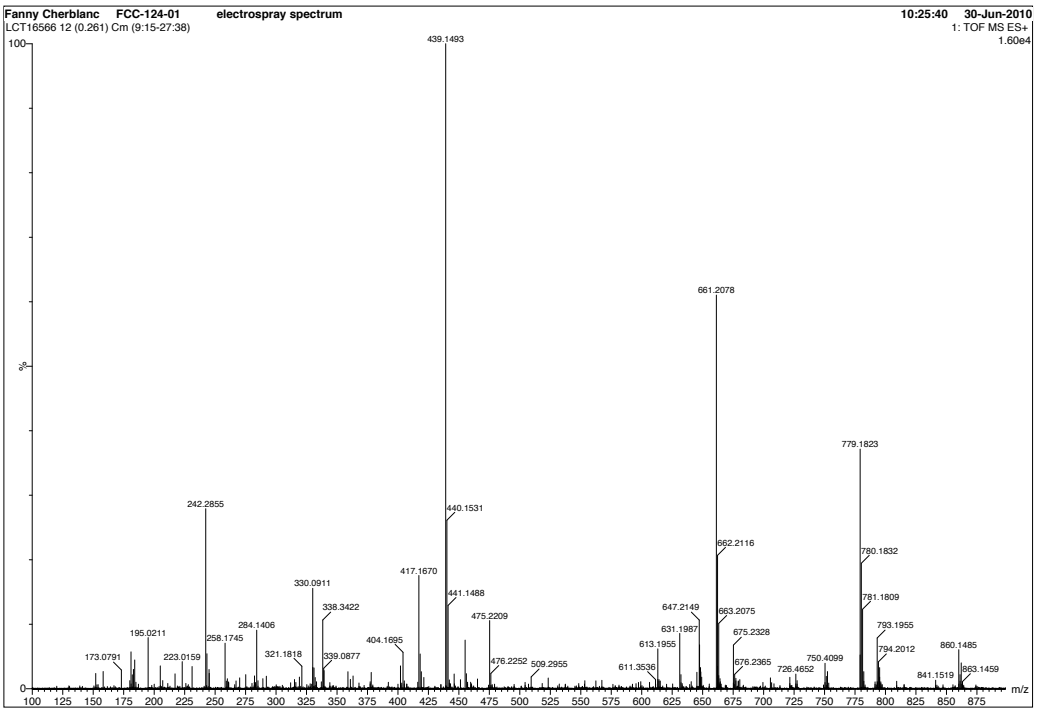


Compound **4** was prepared as follows:[5] $NaBH_4$ (16 mg, 0.42 mmol) was added to a solution of chaetocin (**1**, 20 mg, 0.03 mmol) in CH_2Cl_2 / MeOH (6 mL / 2 mL) at 0 ˚C. After 30 min, MeI (1 mL, excess) was added dropwise to the solution. It was allowed to stir for 16 h and then treated with 1 N aq. HCl (5 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried ($MgSO_4$), rotary evaporated and purified by column chromatography (CH_2Cl_2 : MeOH, 99 : 1) to afford the methylated compound **4** (10 mg, 47 %) as a white solid: m.p. 130 – 132 ˚C (dec.); $[\alpha]_D^{20}$ + 175 (*c* 0.002, $CHCl_3$); UV λ_{max} ($CHCl_3$) (A): 238.6 (1.07), 303.3 (0.44) nm, CD (MeOH) Δ_ε^{20} (nm): +180 (258), +53 (280), +126 (306), 0 (332); IR (neat) 3369, 2922, 2852, 1656, 1420, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.63 (d, *J* = 7.6 Hz, 2H), 5.73 (s, 2H), 4.90 (br s, 2H), 4.65 (br s, 2H), 4.29 (d, *J* = 10.7 Hz, 2H), 3.78 (d, *J* = 10.7 Hz, 2H), 3.09 (s, 6H), 2.64 (d, *J* = 15.2 Hz, 2H), 2.44 (d, *J* = 15.2 Hz, 2H), 2.19 (s, 6H), 1.87 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 166.5 (2C), 165.4 (2C), 150.9 (2C), 129.7 (2C), 128.7 (2C), 125.1

(2C), 119.1 (2C), 110.1 (2C), 80.5 (2C), 77.2 (2C), 69.2 (2C), 64.6 (2C), 60.6 (2C), 43.7 (2C), 28.6 (2C), 15.8 (2C), 12.8 (2C); LCMS: R_t = 5.58 min; MS (ESI) *m/z* 779 $(M+Na)^+$; HRMS (ESI) *m/z* calc. for $C_{34}H_{40}N_6O_6S_4Na$ 779.1790, found: 779.1777





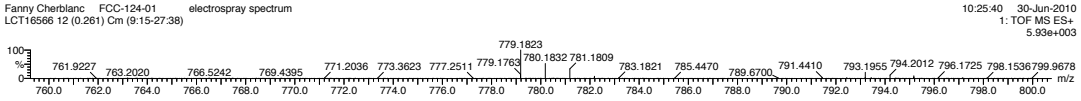


Elemental Composition Report

Single Mass Analysis

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
9171 formula(e) evaluated with 71 results within limits (all results (up to 1000) for each mass)
Elements Used:
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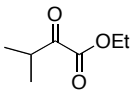

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Maximum:                5.0      10.0     50.0

Mass        Calc. Mass      mDa      PPM      DBE      i-FIT      i-FIT (Norm)  Formula

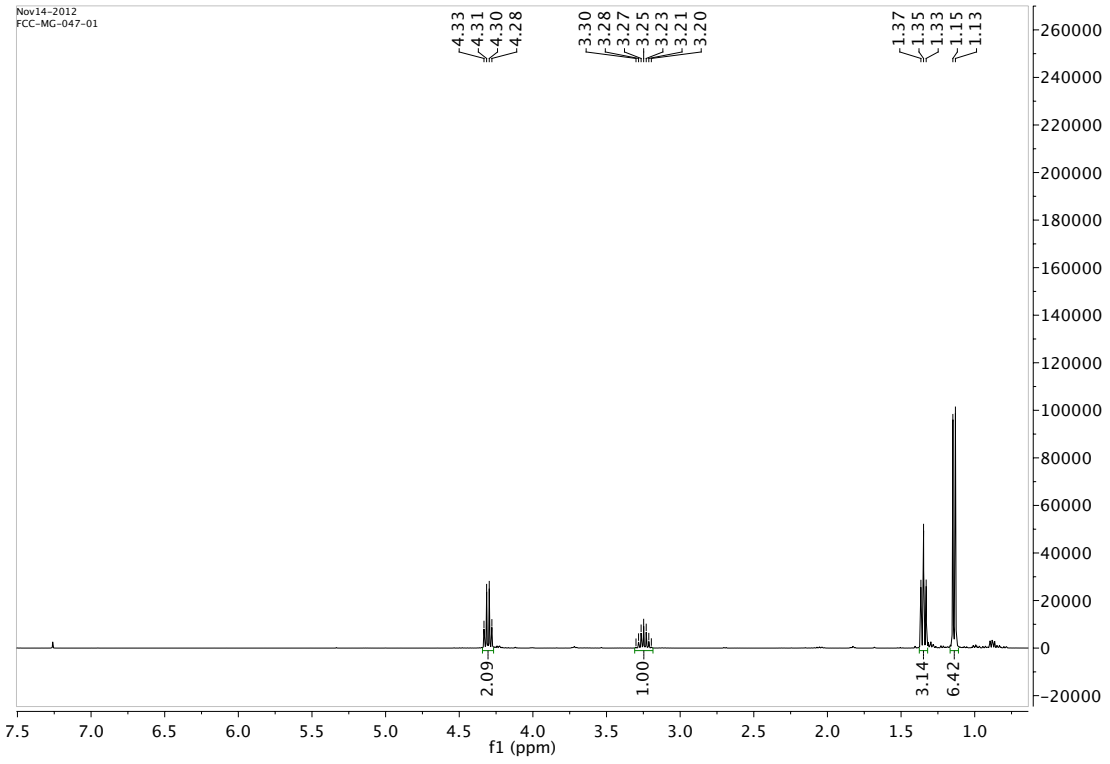
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            779.1849        -2.6     -3.3     8.5      406.4      5.3           C27  H44  N6  O11  Na  S4
            779.1850        -2.7     -3.5     31.5     415.3      14.1          C40  H27  N8  O10
            779.1796        2.7      3.5      26.5     403.4      2.3           C42  H36  N4  O4  Na  S3
            779.1794        2.9      3.7      36.5     414.2      13.1          C49  H28  N2  O7  Na
            779.1852        -2.9     -3.7     34.5     410.1      9.0           C48  H31  N2  O7  S
            779.1793        3.0      3.9      43.5     409.2      8.1           C55  H27  N2  O2  S
            779.1853        -3.0     -3.9     27.5     415.5      14.3          C42  H32  N2  O12  Na
            779.1854        -3.1     -4.0     24.5     407.2      6.0           C41  H39  N4  O4  S4
            779.1791        3.2      4.1      40.5     414.1      13.0          C47  H23  N8  O5
            779.1855        -3.2     -4.1     17.5     405.7      4.6           C35  H40  N4  O9  Na  S3
            779.1790        3.3      4.2      17.5     405.0      3.8           C34  H40  N6  O6  Na  S4
            779.1858        -3.5     -4.5     43.5     414.5      13.3          C56  H27  O5
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            779.1859        -3.6     -4.6     30.5     406.8      5.6           C41  H31  N8  O5  S2
            779.1787        3.6      4.6      34.5     405.3      4.2           C47  H31  N4  O4  S2
            779.1860        -3.7     -4.7     23.5     411.5      10.4          C35  H32  N8  O10  Na  S
            779.1861        -3.8     -4.9     33.5     407.9      6.7           C49  H35  N2  O2  S3
            779.1862        -3.9     -5.0     26.5     407.2      6.1           C43  H36  N2  O7  Na  S2
            779.1783        4.0      5.1      21.5     404.5      3.4           C41  H40  O8  Na  S3
            779.1782        4.1      5.3      28.5     407.5      6.4           C47  H39  O3  S4
            779.1865        -4.2     -5.4     39.5     410.6      9.4           C49  H27  N6  O3  S
            779.1781        4.2      5.4      18.5     406.7      5.6           C33  H36  N6  O11  Na  S2
            779.1780        4.3      5.5      25.5     404.2      3.0           C39  H35  N6  O6  S3
            779.1866        -4.3     -5.5     32.5     415.6      14.4          C43  H28  N6  O8  Na
            779.1867        -4.4     -5.6     42.5     409.6      8.4           C57  H31  S2
            779.1868        -4.5     -5.8     35.5     410.8      9.6           C51  H32  O5  Na  S
            779.1868        -4.5     -5.8     29.5     408.3      7.1           C42  H35  N8  S4
            779.1778        4.5      5.8      35.5     414.2      13.1          C46  H27  N4  O9
            779.1777        4.6      5.9      12.5     406.6      5.5           C33  H44  N2  O10  Na  S4
            779.1869        -4.6     -5.9     22.5     406.2      5.1           C36  H36  N8  O5  Na  S3
            779.1776        4.7      6.0      36.5     405.6      4.4           C46  H28  N8  Na  S2
            779.1870        -4.7     -6.0     25.5     409.1      8.0           C44  H40  N2  O2  Na  S4
            779.1776        4.7      6.0      49.5     413.9      12.8          C61  H24  Na
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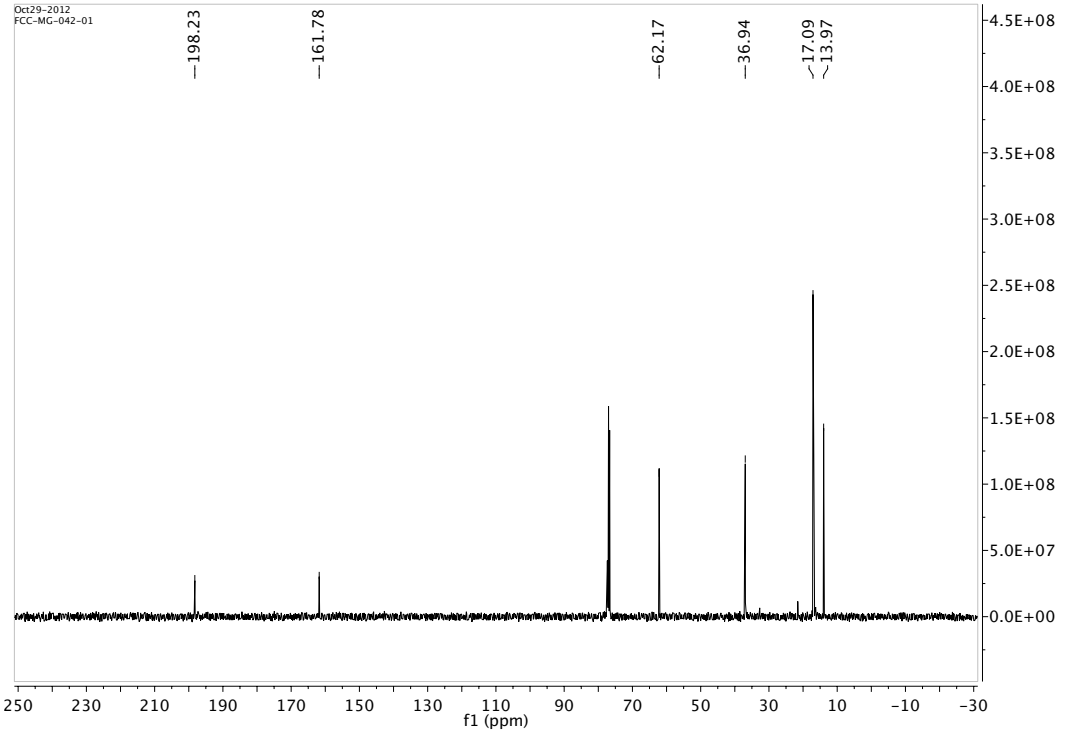
Chapter III Stereochemistry of ETP desulfurisation

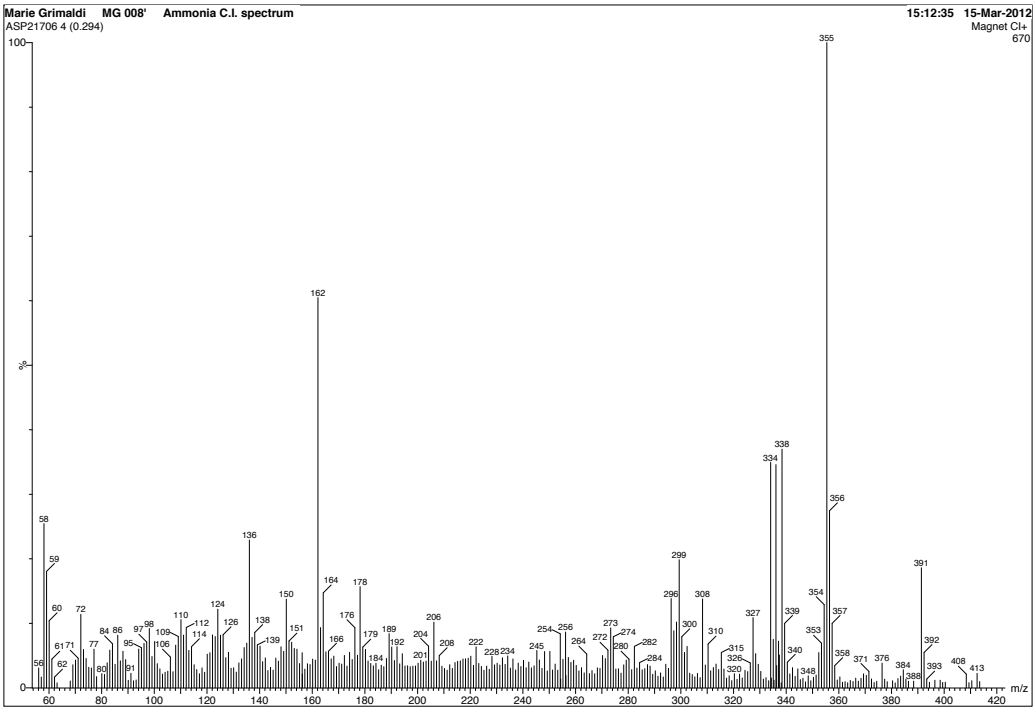
Ethyl 3-methyl-2-oxobutanoate (40)[9]



Compound **40** was prepared as follows:[9] Isopropyl magnesium chloride (2 M in THF, 50 mL, 100 mmol) was added dropwise to a solution of diethyl oxalate (6.8 mL, 50 mmol) in dry THF (50 mL) at −78 ˚C. The solution was allowed to stir at −78 ˚C for 1 h, then poured into a allowed to stir suspension of ice (40 g), Et_2O (50 mL) and conc. aq. HCl (3.6 mL). The mixture was extracted with Et_2O (3 × 50 mL). The organic layer was washed with water, dried ($MgSO_4$), filtered through celite and rotatory evaporated to afford the title compound **40** as a yellow oil (3.310 g, 46%) that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.31 (q, J = 7.2 Hz, 2H), 3.25 (sept, J = 6.8 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 6.8 Hz, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 198.2, 161.8, 62.2, 36.9, 17.1 (2C), 14.0; MS (CI) *m/z* 162 ($M+NH_4^+$); HRMS (CI) *m/z* calc. for $C_7H_{16}NO_3$ 162.1130, found: 162.1128.




Oct29-2012
FCC-MG-042-01
198.23
161.78
62.17
36.94
17.09
13.97
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
250 230 210 190 170 150 130 110 90 70 50 30 10 -10 -30
f1 (ppm)


Marie Grimaldi MG 008' Ammonia C.I. spectrum
15:12:35 15-Mar-2012
ASP21706 4 (0.294)
Magnet CI+
670
100
%
0
m/z
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420

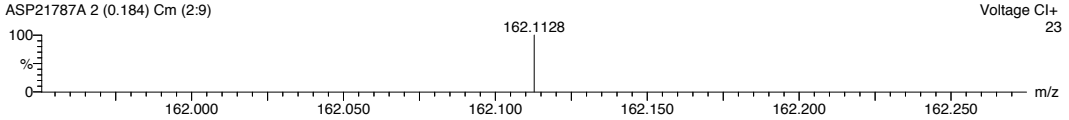
Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
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Selected filters: None

Monoisotopic Mass, Even Electron Ions
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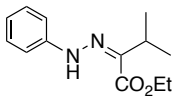
Marie Grimaldi MG 008'
ASP21787A 2 (0.184) Cm (2:9)

14:28:26 22-Mar-2012
Voltage CI+
23

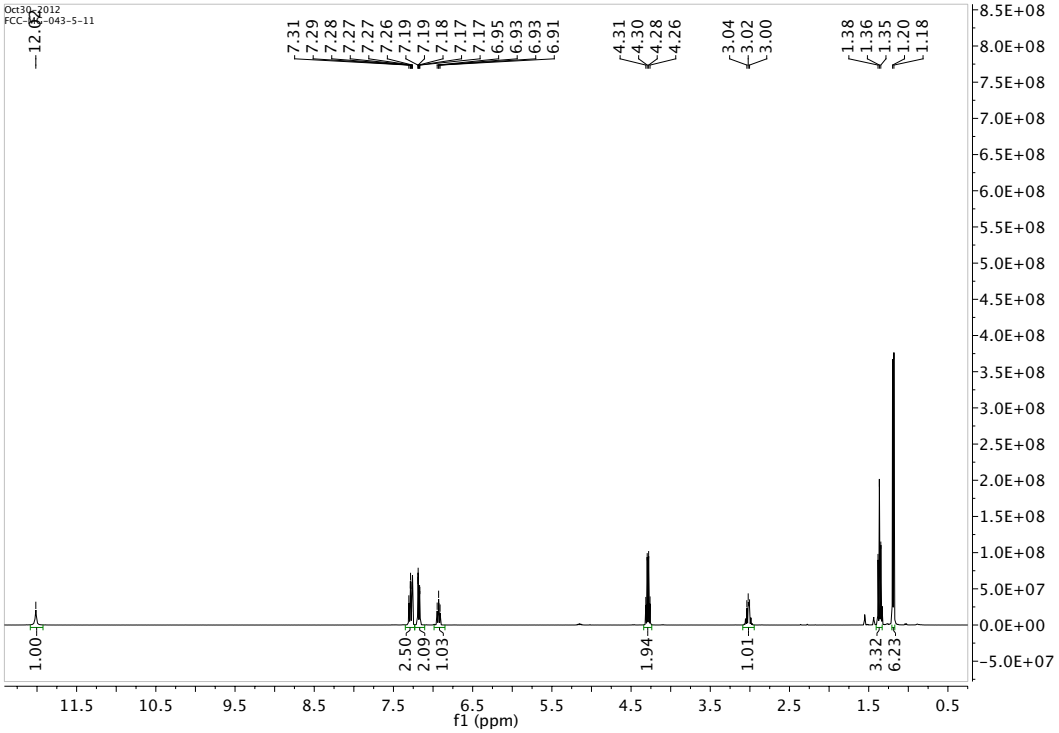


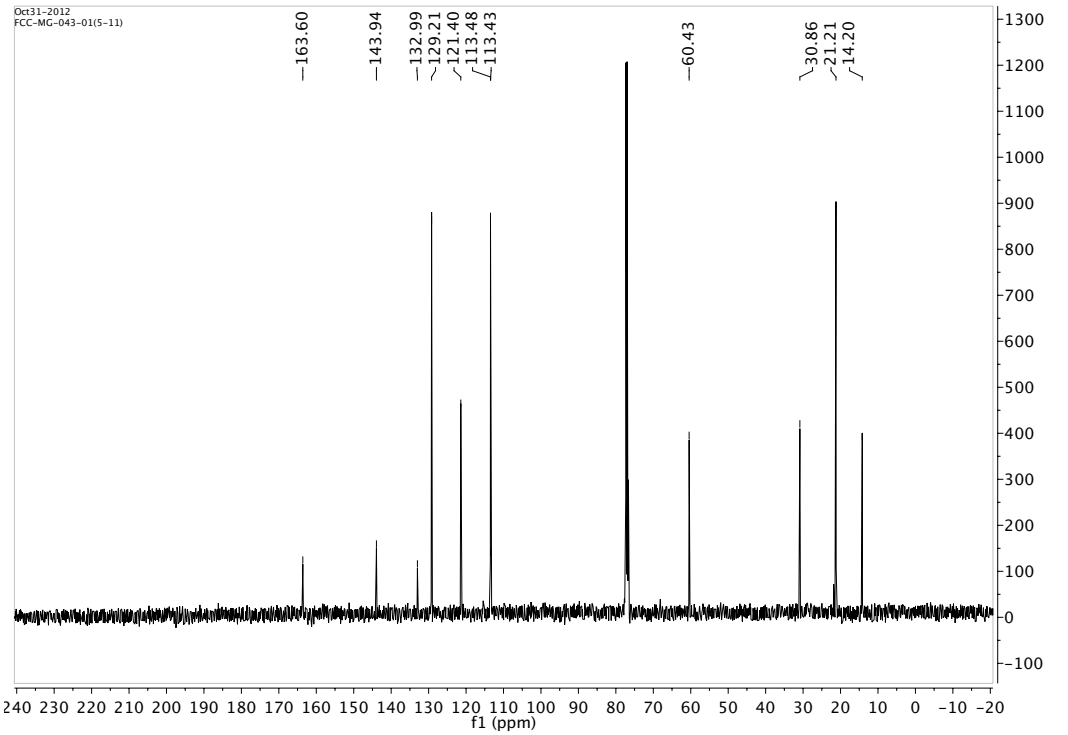
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Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
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	162.1103	2.5	15.4	1.5	5546025.5	C3 H12 N7 O

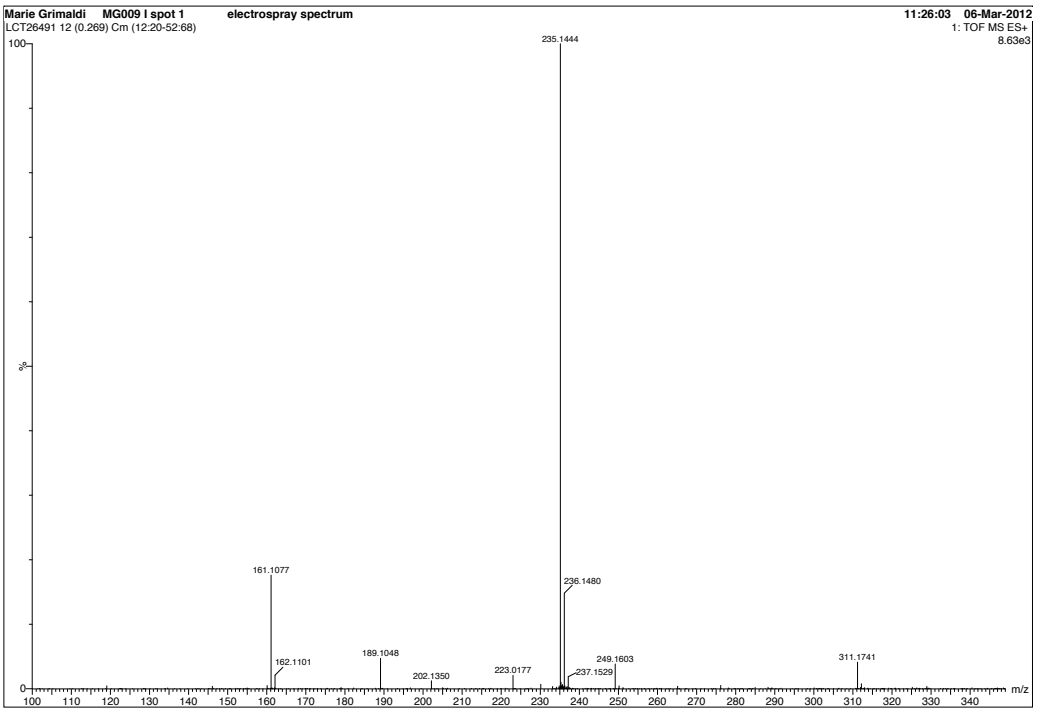
(*Z*)-Ethyl 3-methyl-2-(2-phenylhydrazono)butanoate (41)[9]



Compound **41** was prepared as follows:[9] A solution of keto-ester **40** (3.25 g, 22.6 mmol) and phenylhydrazine (3.4 mL, 33.9 mmol) in toluene was heated at 60 ˚C for 1 h under N_2. The solvent was rotatory evaporated and the crude product was purified by column chromatography (EtOAc : Hexanes, 5 : 95) to afford hydrazone **41** as a yellow oil (4.11 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (br s, 1H), 7.26 – 7.32 (m, 2H), 7.19 – 7.21 (m, 2H), 6.93 – 6.97 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.02 (sept, *J* = 6.8 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 143.9, 133.0, 129.2 (2C), 121.4, 113.5 (2C), 60.4, 30.9, 21.2 (2C), 14.2; MS (ESI) *m/z* 235 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{13}H_{19}N_2O_2$ 235.1447, found 235.1444.


Oct30-2012
FCC-MG-043-5-11
12.05
7.31
7.29
7.28
7.27
7.27
7.26
7.19
7.19
7.18
7.17
7.17
6.95
6.93
6.93
6.91
4.31
4.30
4.28
4.26
3.04
3.02
3.00
1.38
1.36
1.35
1.20
1.18
1.00
2.50
2.09
1.03
1.94
1.01
3.32
6.23
f1 (ppm)


Oct31-2012
FCC-MG-043-01(5-11)
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132.99
129.21
121.40
113.48
113.43
60.43
30.86
21.21
14.20
f1 (ppm)

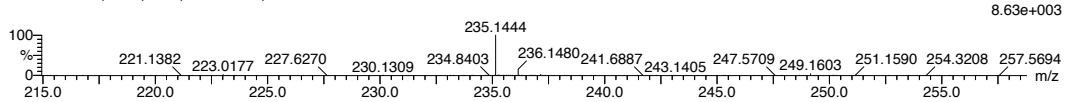


Elemental Composition Report **Page 1**

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

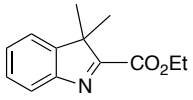
Monoisotopic Mass, Even Electron Ions
283 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-12

Marie Grimaldi MG009 I spot 1 electrospray spectrum
LCT26491 12 (0.269) Cm (12:20-52:68)
11:26:03 06-Mar-2012
1: TOF MS ES+
8.63e+003



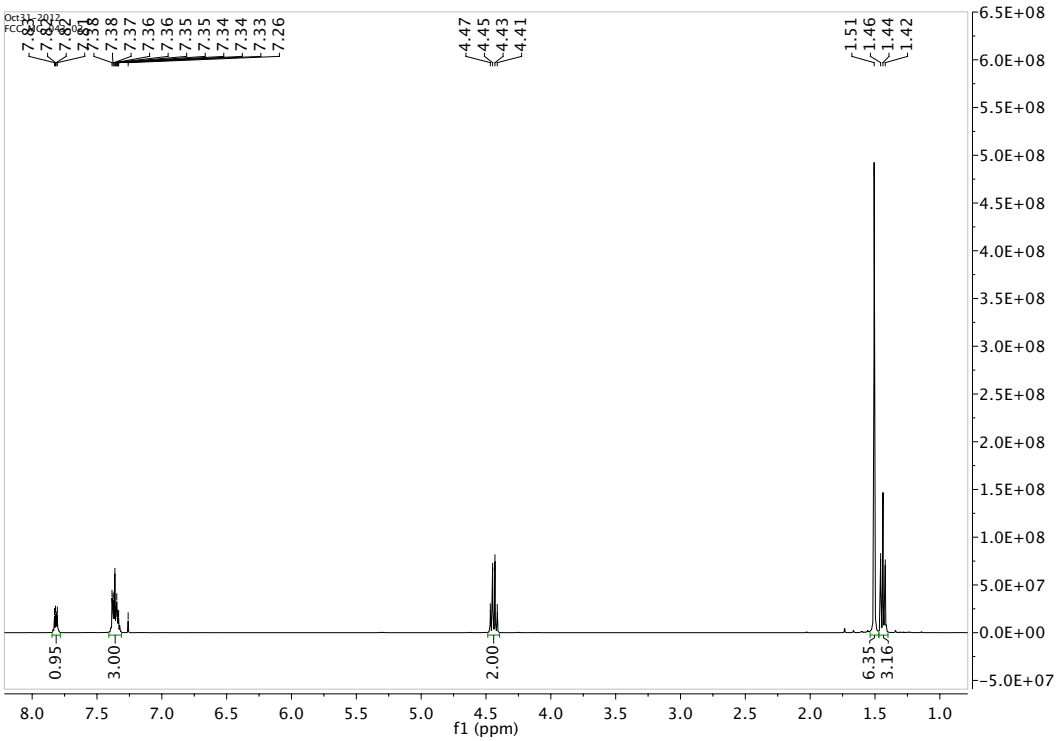
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Maximum:		6.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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	235.1420	2.4	10.2	6.5	155.9	5.5	C9 H15 N8
	235.1406	3.8	16.2	1.5	156.9	6.5	C8 H19 N4 O4
	235.1487	-4.3	-18.3	9.5	157.4	7.1	C18 H19

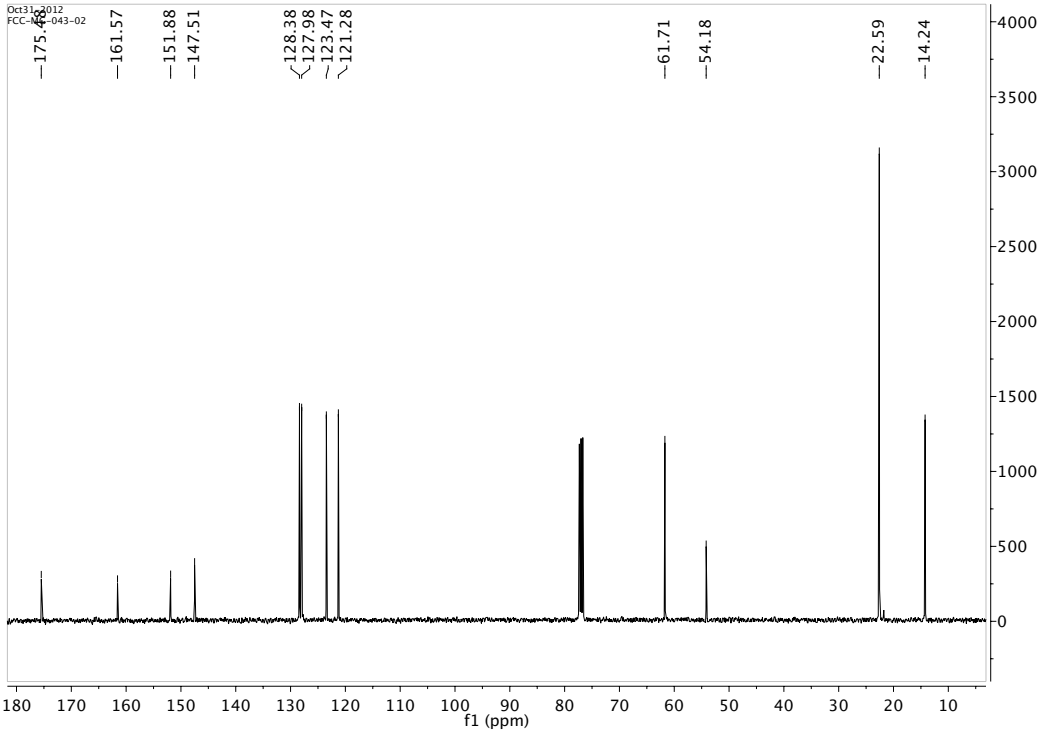
Ethyl 3,3-dimethyl-3*H*-indole-2-carboxylate (39)[9]

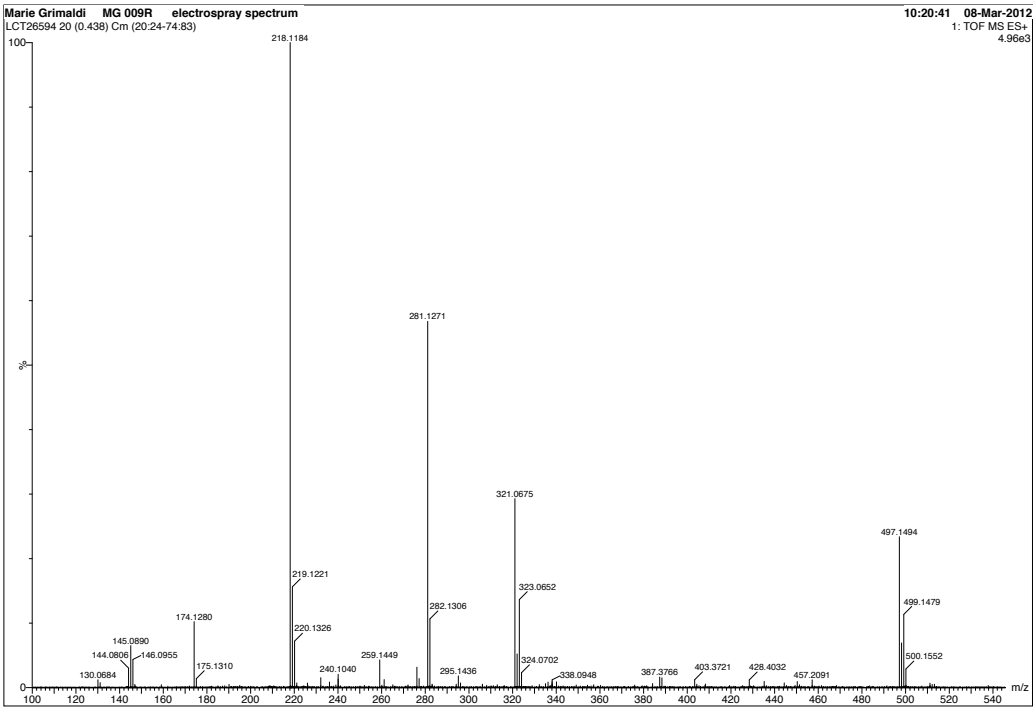


Compound **39** was prepared as follows:[9] A solution of 34% HCl in EtOH was prepared by adding acetyl chloride to EtOH at 0 ˚C. Hydrazone ester **41** (4.11 g, 17.6 mmol) was added to the ethanolic HCl (150 mL) and the mixture was heated to reflux for 10 min. The solvent was then rotatory evaporated to afford a residue that

was taken up in Et_2O (100 mL) and treated with 5% aq. Na_2CO_3. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with water until neutral, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc : Hexanes, 1 : 9) afforded indolenine **39** (2.57 g, 67%) as light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 1H), 7.33 – 7.38 (m, 3H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.51 (s, 6H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 161.6, 151.9, 147.5, 128.4, 128.0, 123.5, 121.3, 61.7, 54.2, 22.6 (2C), 14.2; MS (ESI) *m/z* 218 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{13}H_{16}NO_2$ 218.1181, found 218.1184.




Oct31-2012
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161.57
151.88
147.51
128.38
127.98
123.47
121.28
61.71
54.18
22.59
14.24
4000
3500
3000
2500
2000
1500
1000
500
0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Marie Grimaldi MG 009R electrospray spectrum
10:20:41 08-Mar-2012
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100
%
0
218.1184
281.1271
321.0675
497.1494
219.1221
323.0652
499.1479
282.1306
174.1280
220.1326
145.0890
144.0806
146.0955
259.1449
175.1310
240.1040
295.1436
324.0702
338.0948
387.3766
403.3721
428.4032
457.2091
500.1552
130.0684
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m/z

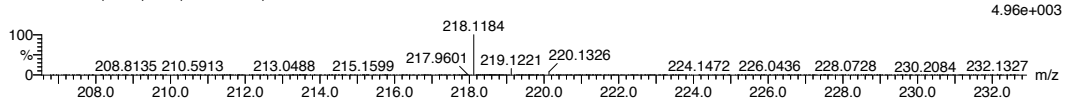
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 6.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
236 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-12

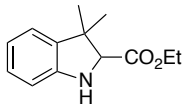
Marie Grimaldi MG 009R electrospray spectrum
LCT26594 20 (0.438) Cm (20:24-74:83)

10:20:41 08-Mar-2012
1: TOF MS ES+
4.96e+003

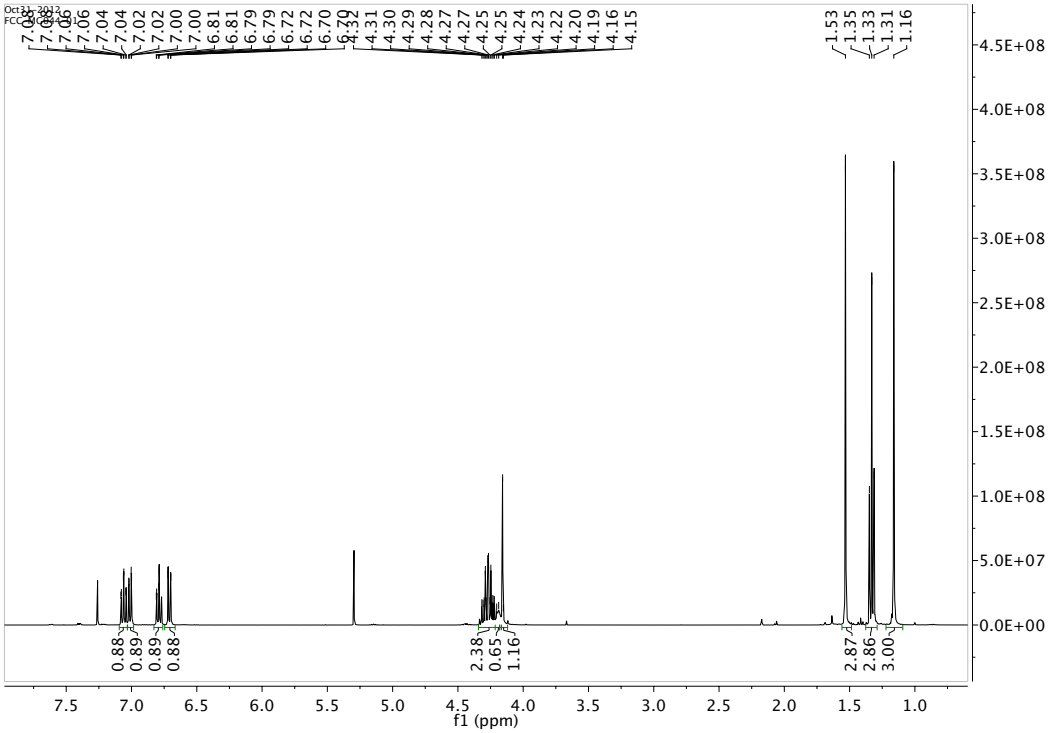


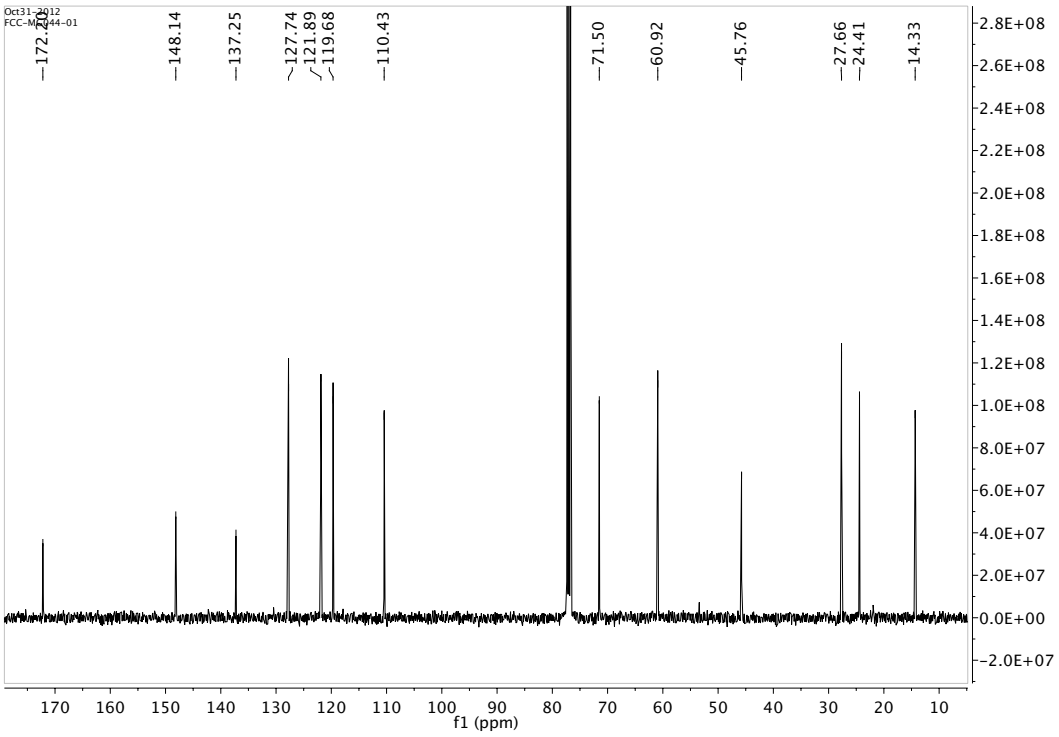
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Maximum:		6.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
218.1184	218.1181	0.3	1.4	6.5	410.7	1.3	C13 H16 N O2
	218.1213	-2.9	-13.3	-1.5	410.8	1.4	C2 H16 N7 O5
	218.1154	3.0	13.8	7.5	410.8	1.4	C9 H12 N7
	218.1141	4.3	19.7	2.5	410.9	1.4	C8 H16 N3 O4

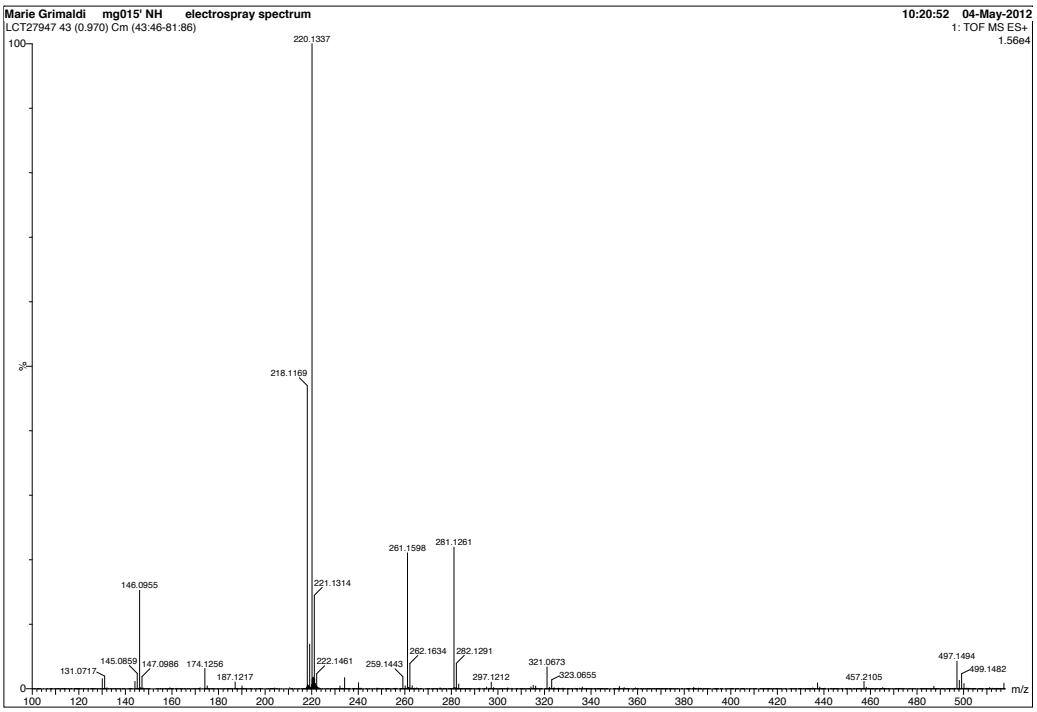
Ethyl 3,3-dimethylindoline-2-carboxylate (42)[9]



Compound **42** was prepared as follows:[10] To a solution of indolenine **39** (615 mg, 2.83 mmol) in 12 mL of MeOH and 2.5 mL of AcOH was added sodium cyanoborohydride (232 mg, 3.69 mmol). The reaction mixture was allowed to stir at room temperature for 18 h, time after which the reaction was quenched by addition of 12 N aq. HCl (0.5 mL). Removal of the solvent under reduced pressure gave a residue which was treated with 5% aq. Na_2CO_3 (15 mL) and the resulting solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give indoline **42** a colourless oil (640 mg, 98%) that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (td, *J* = 7.8, 1.3 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.79 (td, *J* = 7.3, 0.9 Hz, 1H), 6.71 (*app*-d, *J* = 7.9 Hz, 1H), 4.32 – 4.22 (m, 2H), 4.19 (br s, 1H), 4.16 (s, 1H), 1.53 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 148.1, 137.2, 127.7, 121.9, 119.7, 110.4, 71.5, 60.9, 45.8, 27.7, 24.4, 14.3; MS (ESI) *m/z* 220 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{13}H_{18}NO_2$ 220.1338, found: 220.1337.


Oct31-2012
FCC-MP044-01
7.08
7.06
7.04
7.02
7.00
6.81
6.79
6.72
6.70
4.32
4.31
4.30
4.29
4.28
4.27
4.25
4.24
4.23
4.22
4.20
4.19
4.16
4.15
1.53
1.35
1.33
1.31
1.16
0.88
0.89
0.89
0.88
2.38
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1.16
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3.00
f1 (ppm)

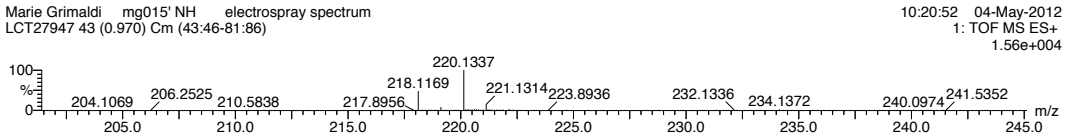

Oct31-2012
FCC-MP044-01
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137.25
127.74
121.89
119.68
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71.50
60.92
45.76
27.66
24.41
14.33
f1 (ppm)



Elemental Composition Report **Page 1**

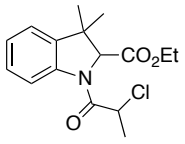
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
244 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-12



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
220.1337	220.1338	-0.1	-0.5	5.5	296.4	0.0	C13 H18 N O2
	220.1311	2.6	11.8	6.5	302.6	6.2	C9 H14 N7
	220.1297	4.0	18.2	1.5	305.1	8.7	C8 H18 N3 O4

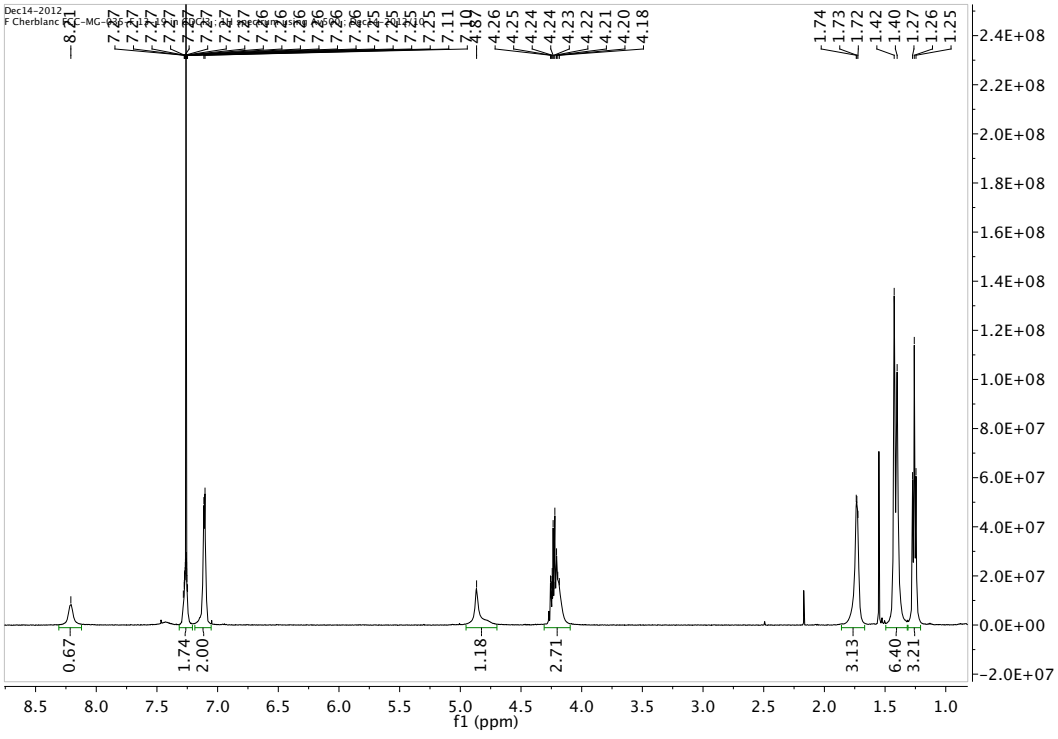
Ethyl 1-(2-chloropropanoyl)-3,3-dimethylindoline-2-carboxylate (43)

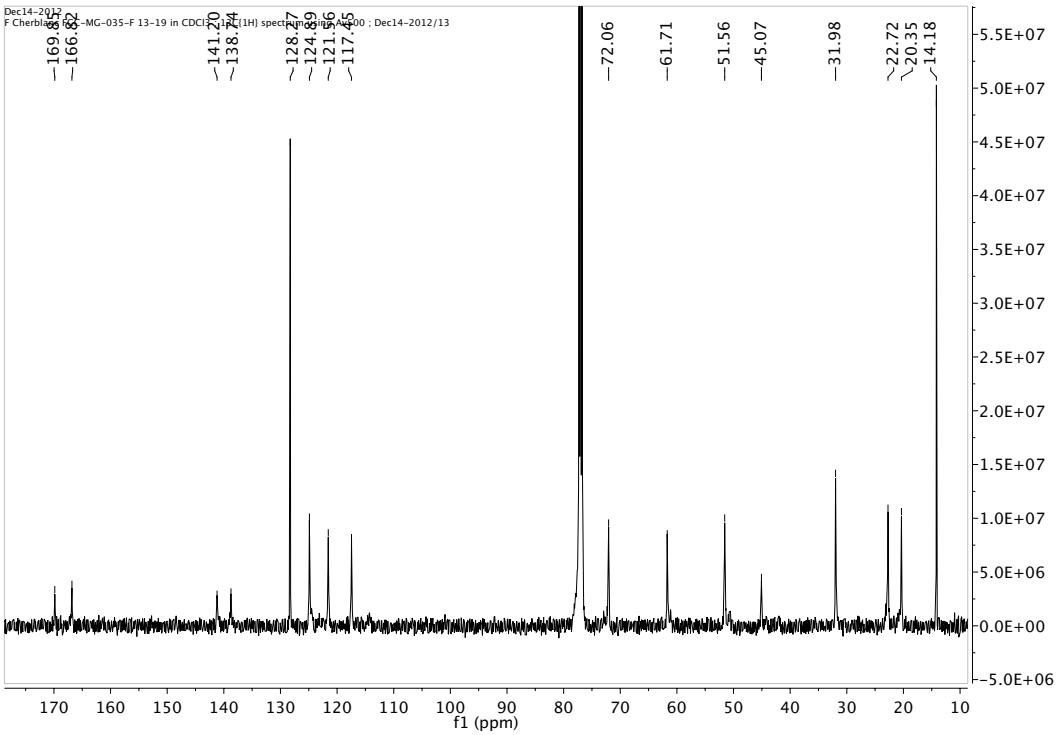


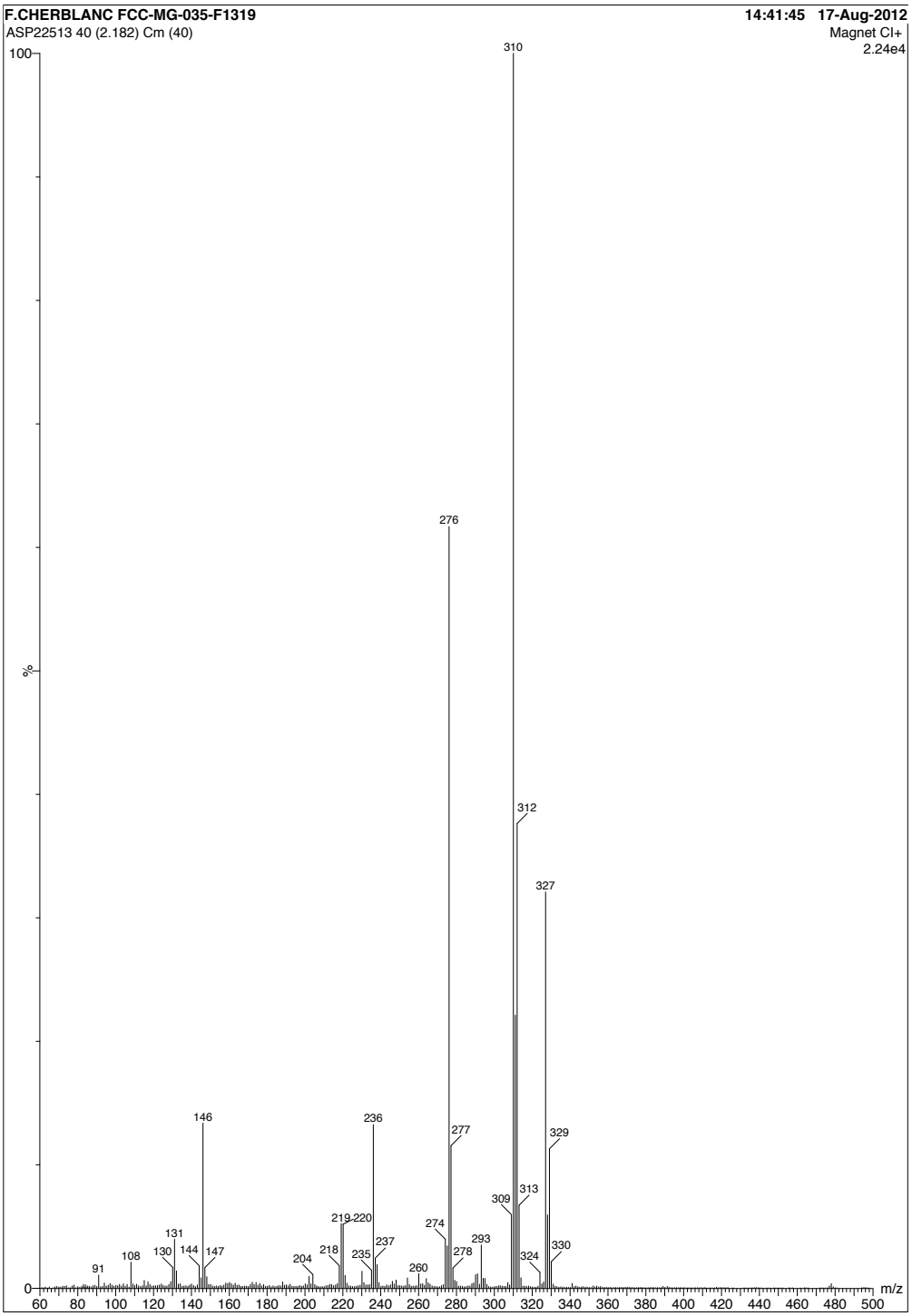
Compound **43** was prepared as follows:[11] 2-Chloropropionyl chloride (0.35 mL, 3.56 mmol) was added dropwise to a solution of triethylamine (0.46 mL, 3.29 mmol) and indoline **42** (600 mg, 2.70 mmol) in chloroform (50 mL) at 0 ˚C. The mixture was allowed to warm to room temperature and stir for a further 4 h. After that time, the

reaction mixture was poured into ice-water, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and rotatory evaporated. The residue was purified by column chromatography (Hexanes : EtOAc, 95 : 5) to afford the title compound **43** as two diastereoisomers as colourless oil (combined mass 731 mg, 87%): IR (neat) 2972, 1747, 1673, 1598, 1483, 1409, 1199, 752 cm^{-1}; Diastereoisomer 1: ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.28 – 7.24 (m, 1H), 7.10 – 7.08 (m, 2H), 4.86 (s, 1H), 4.26 – 4.11 (m, 3H), 1.73 (br d, *J* = 6.4 Hz, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.1, 141.2, 138.7, 128.3, 124.9, 121.6, 117.5, 72.0, 61.7, 51.6, 45.1, 32.0, 22.7, 20.3, 14.2; MS (CI) *m/z* 310 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{16}H_{21}NO_3Cl$ 310.1210, found: 310.1213; Diastereoisomer 2: ^1H NMR (500 MHz, DMSO) δ 8.05 (br d, *J* = 7.8 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.10 (br t, *J* = 7.5 Hz, 1H), 5.09 (br s, 1H), 5.02 (br q, *J* = 6.2 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.78 (br d, *J* = 6.2 Hz, 3H), 1.33 (br s, 3H), 1.31 (br s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.2, 166.8, 141.4, 139.6, 127.6, 124.6, 122.1, 116.7, 71.0, 60.9, 51.5, 44.6, 31.2, 21.8, 21.2, 13.9; MS (CI) *m/z* 310 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{16}H_{21}NO_3Cl$ 310.1210, found: 310.1215.

Diastereoisomer 1:

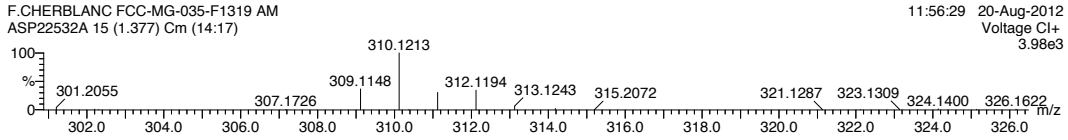



Dec14-2012
F Cherblanc MG-035-F 13-19 in CDCl3 1H{1H} spectrum
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141.20
138.74
128.27
124.89
121.56
117.45
72.06
61.71
51.56
45.07
31.98
22.72
20.35
14.18
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F.CHERBLANC FCC-MG-035-F1319
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ASP22513 40 (2.182) Cm (40)
Magnet CI+
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100
%
0
310
276
312
327
146
236
277
329
309
313
219
220
274
131
237
293
330
108
130
144
147
218
235
278
324
91
204
260
m/z
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500

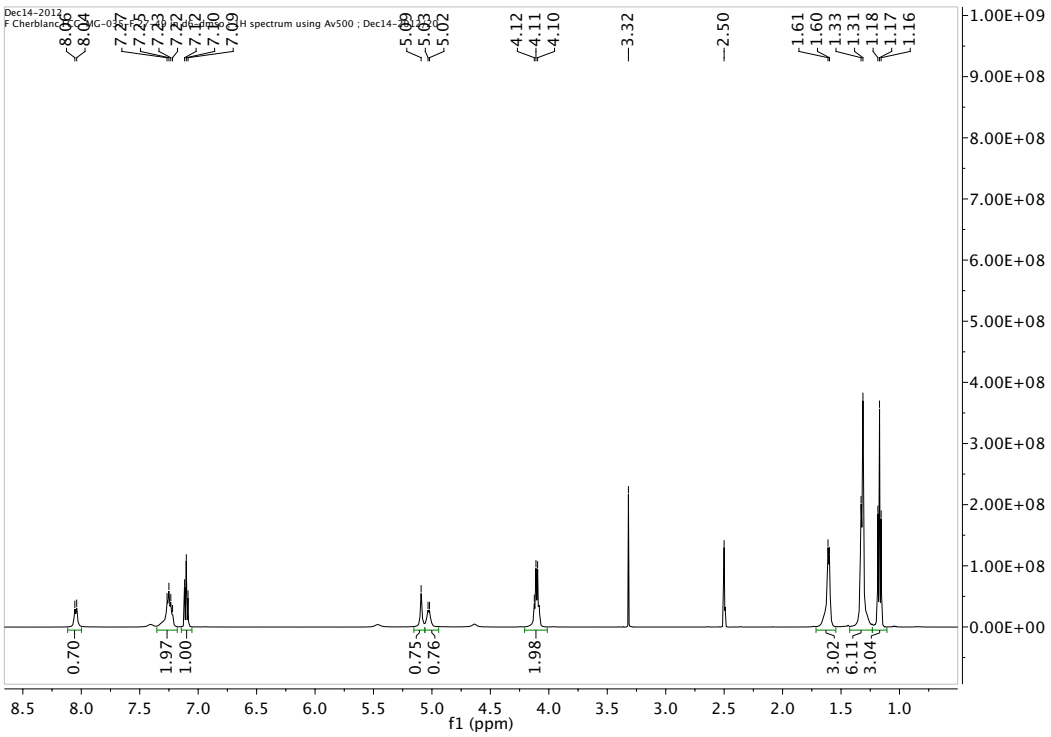
Single Mass Analysis (displaying only valid results)
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Selected filters: None

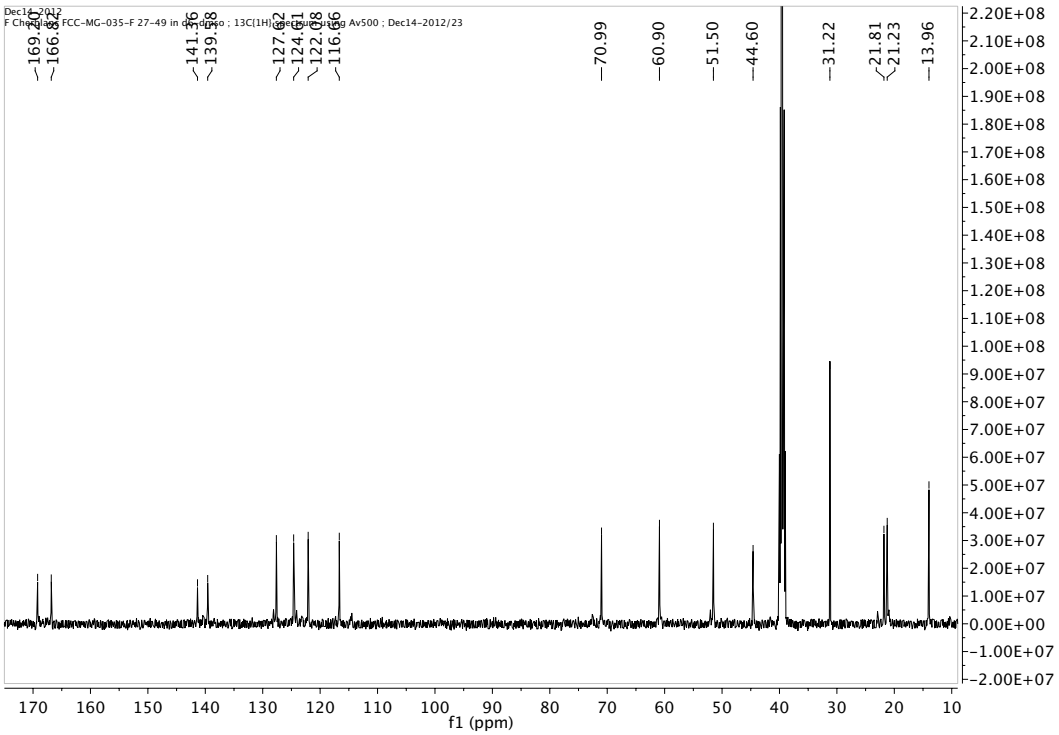
Monoisotopic Mass, Odd and Even Electron Ions
179 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 16-16 H: 0-1000 N: 0-10 O: 0-10 Cl: 1-1 I: 0-2

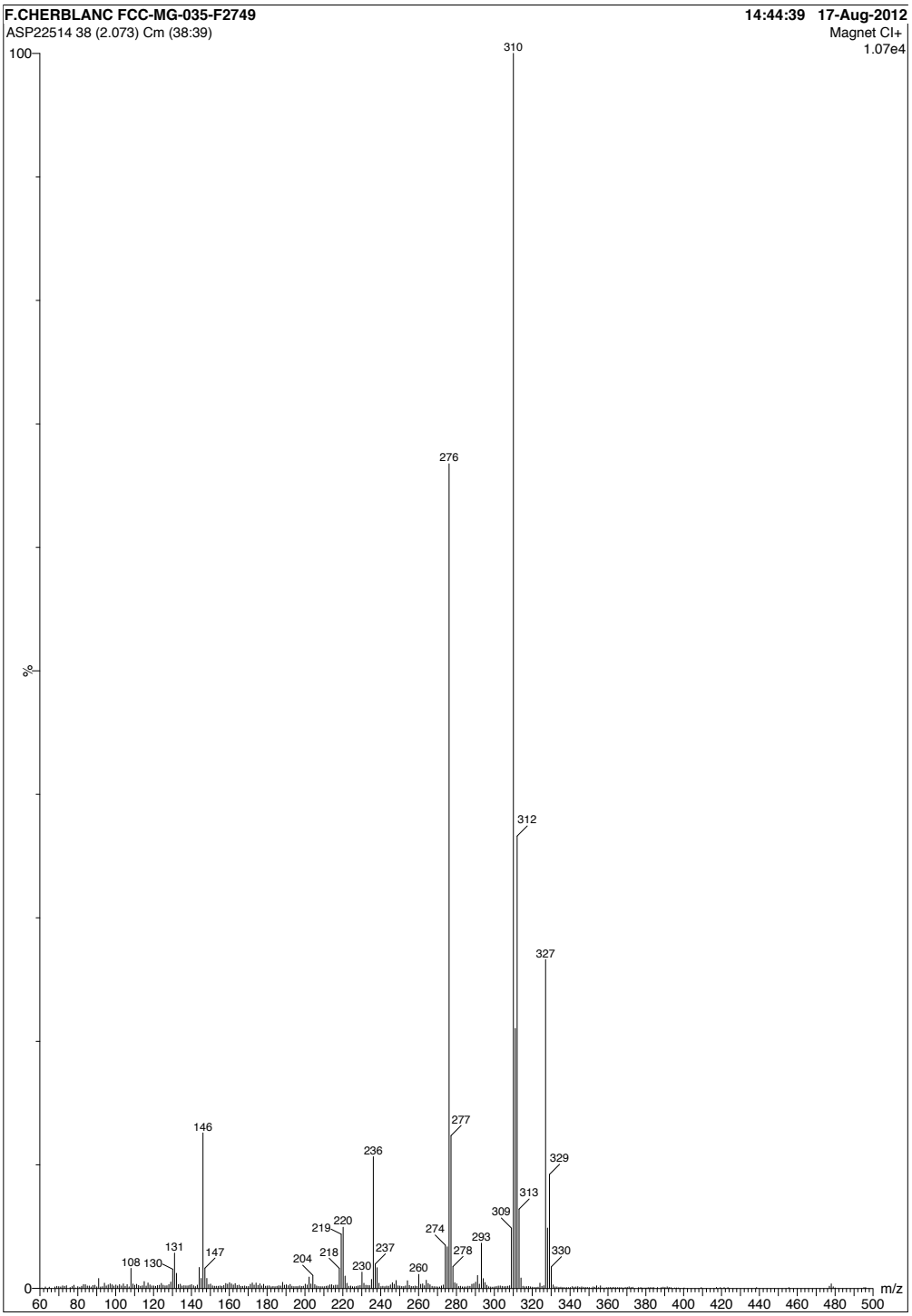


Minimum:				-1.5		
Maximum:		7.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
310.1213	310.1210	0.3	1.0	6.5	82.1	C16 H21 N O3 Cl

Diastereoisomer 2:




Dec14-2012
F Chem Data FCC-MG-035-F 27-49 in CDCl3 ; 13C{1H} decoupled ; Bug Av500 ; Dec14-2012/23
169.40
166.86
141.76
139.88
127.62
124.61
122.08
116.66
70.99
60.90
51.50
44.60
31.22
21.81
21.23
13.96
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1.90E+08
1.80E+08
1.70E+08
1.60E+08
1.50E+08
1.40E+08
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1.10E+08
1.00E+08
9.00E+07
8.00E+07
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5.00E+07
4.00E+07
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2.00E+07
1.00E+07
0.00E+00
-1.00E+07
-2.00E+07
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20
10
f1 (ppm)

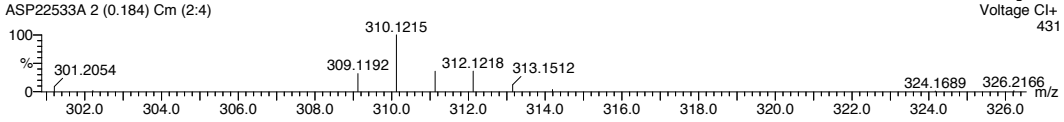

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14:44:39 17-Aug-2012
ASP22514 38 (2.073) Cm (38:39)
Magnet CI+
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%
0
m/z
310
276
312
327
277
146
236
329
313
309
219
220
274
293
131
147
237
278
108
130
218
204
230
260
330
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
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Selected filters: None

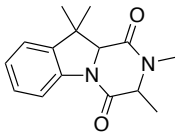
Monoisotopic Mass, Odd and Even Electron Ions
179 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
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ASP22533A 2 (0.184) Cm (2:4)
11:58:29 20-Aug-2012
Voltage CI+
431

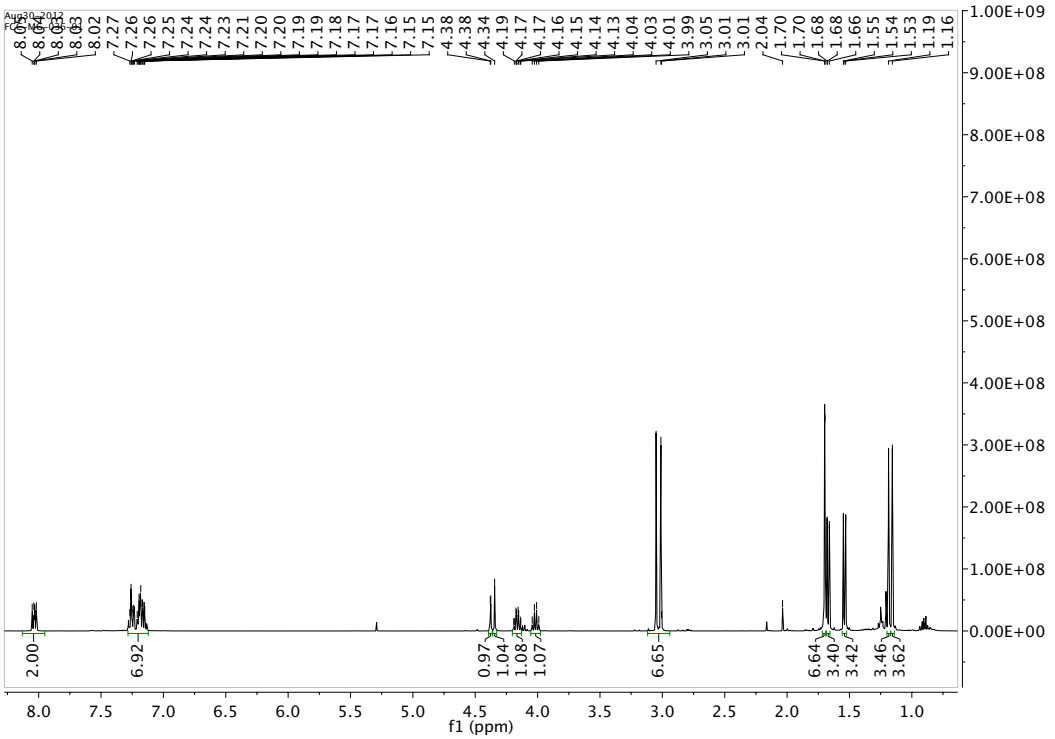


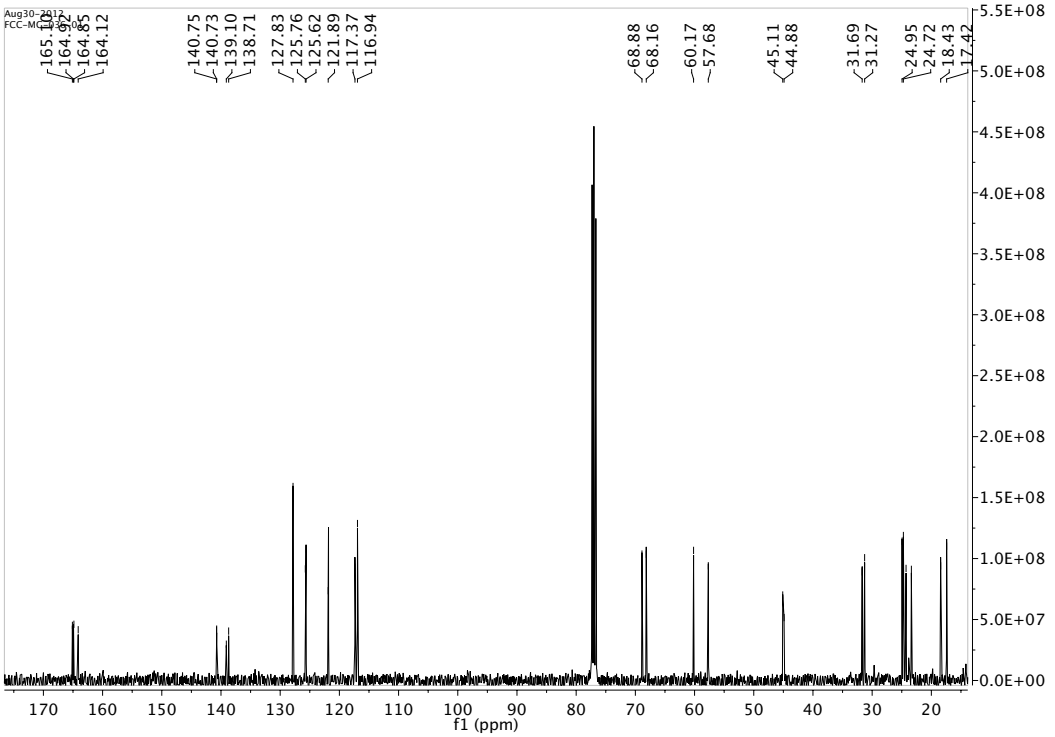
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2,3,10,10-tetramethyl-2,3,10,10a-tetrahydropyrazino[1,2-*a*]indole-1,4-dione (44)



Compound **44** was prepared as follows:[11] Potassium carbonate (218 mg, 1.7 mmol) and an excess of methylamine (5.5 mL of a 2M solution in THF, 11.0 mmol) were added to a solution of acylated indoline **43** (340 mg, 1.1 mmol) in MeCN (10 mL) in a sealed tube. After refluxing for 18 h, the reaction mixture was filtered, concentrated and the residue was purified by column chromatography (Hexanes : EtOAc, 1 : 1) to afford the title compound **44** as a mixture of non-separable diastereoisomers as a colorless oil (190 mg, 67%): IR (neat) 2969, 1666, 1602, 1483, 1426, 1402, 1290, 755 cm^{-1}; Diastereoisomer 1 (*cis)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (*app*-d, *J* = 7.6 Hz, 1H), 7.28 – 7.13 (m, 3H), 4.38 (d, *J* = 1.6 Hz, 1H), 4.16 (dq, *J* = 7.1, 1.6 Hz, 1H), 3.05 (s, 3H), 1.70 (s, 3H), 1.67 (d, *J* = 7.1 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.8, 140.4, 138.8, 127.5, 125.4, 121.6, 116.9, 68.5, 57.3, 44.5, 30.9, 24.0, 23.1, 18.0; Diastereoisomer 2 (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (*app*-d, *J* = 7.8 Hz, 1H), 7.28 – 7.13 (m, 3H), 4.34 (s, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 3.01 (s, 3H), 1.70 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.8, 140.8, 138.7, 127.9, 125.6, 121.9, 116.9, 68.2, 60.2, 45.1, 31.7, 24.9, 24.3, 17.4; MS (ESI) m/z 259 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{15}H_{19}N_2O_2$ 259.1447, found: 259.1462.


f1 (ppm)


f1 (ppm)

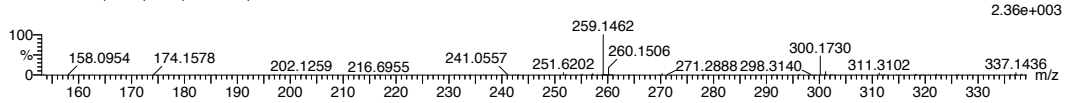
Elemental Composition Report **Page 1**

Single Mass Analysis
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Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
214 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
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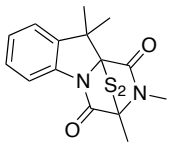
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LCT28751A 8 (0.254) Cm (8:9-24:30)

15:53:48 28-Aug-2012
1: TOF MS ES+
2.36e+003



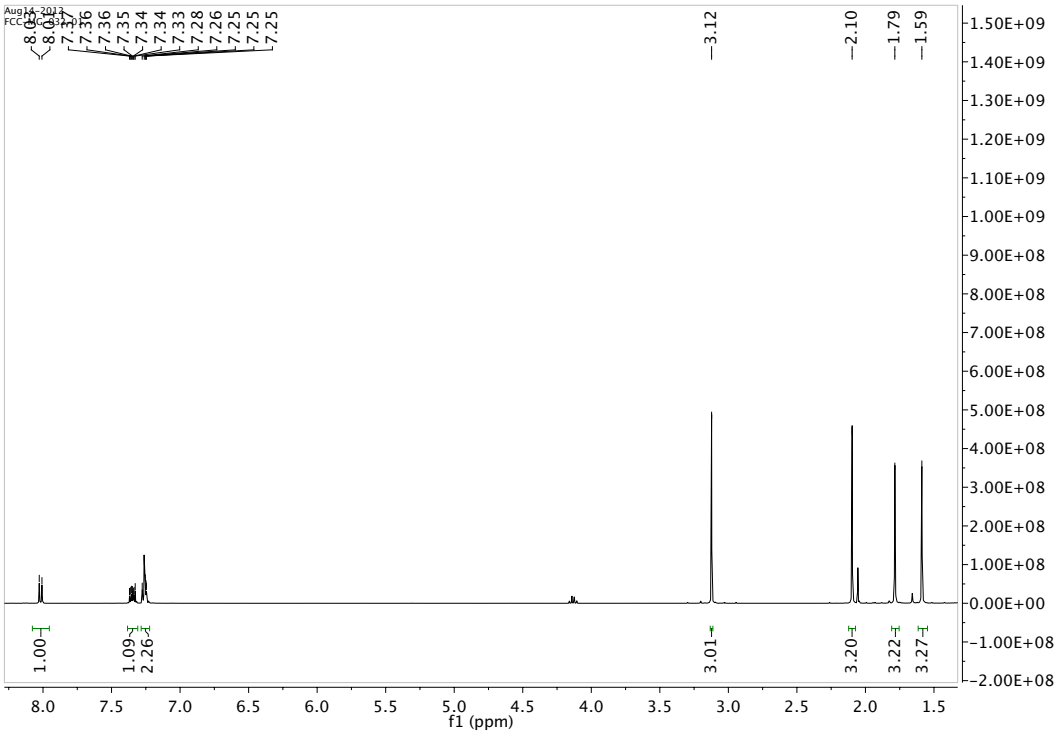
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Maximum:		5.0	10.0	50.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
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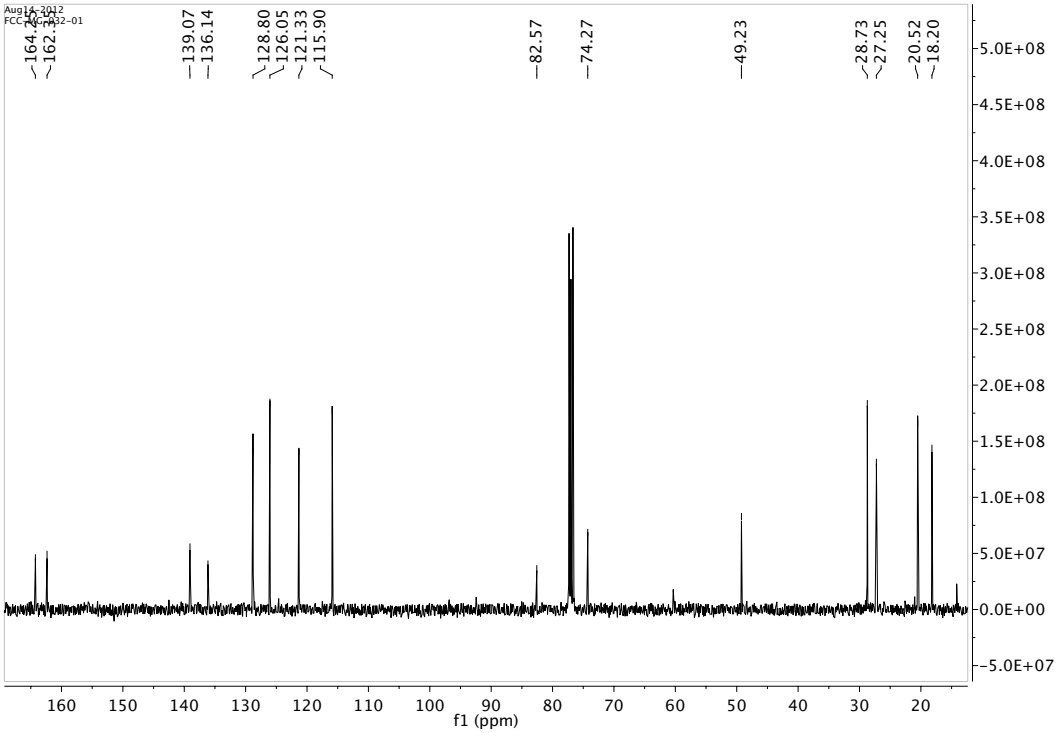
2,3,10,10-Tetramethyl-2,3-dihydro-1*H*-3,10a-epithiopyrazino[1,2-*a*]indole-1,4(10*H*)-dione 11-sulfide – ((±)-25)[12]

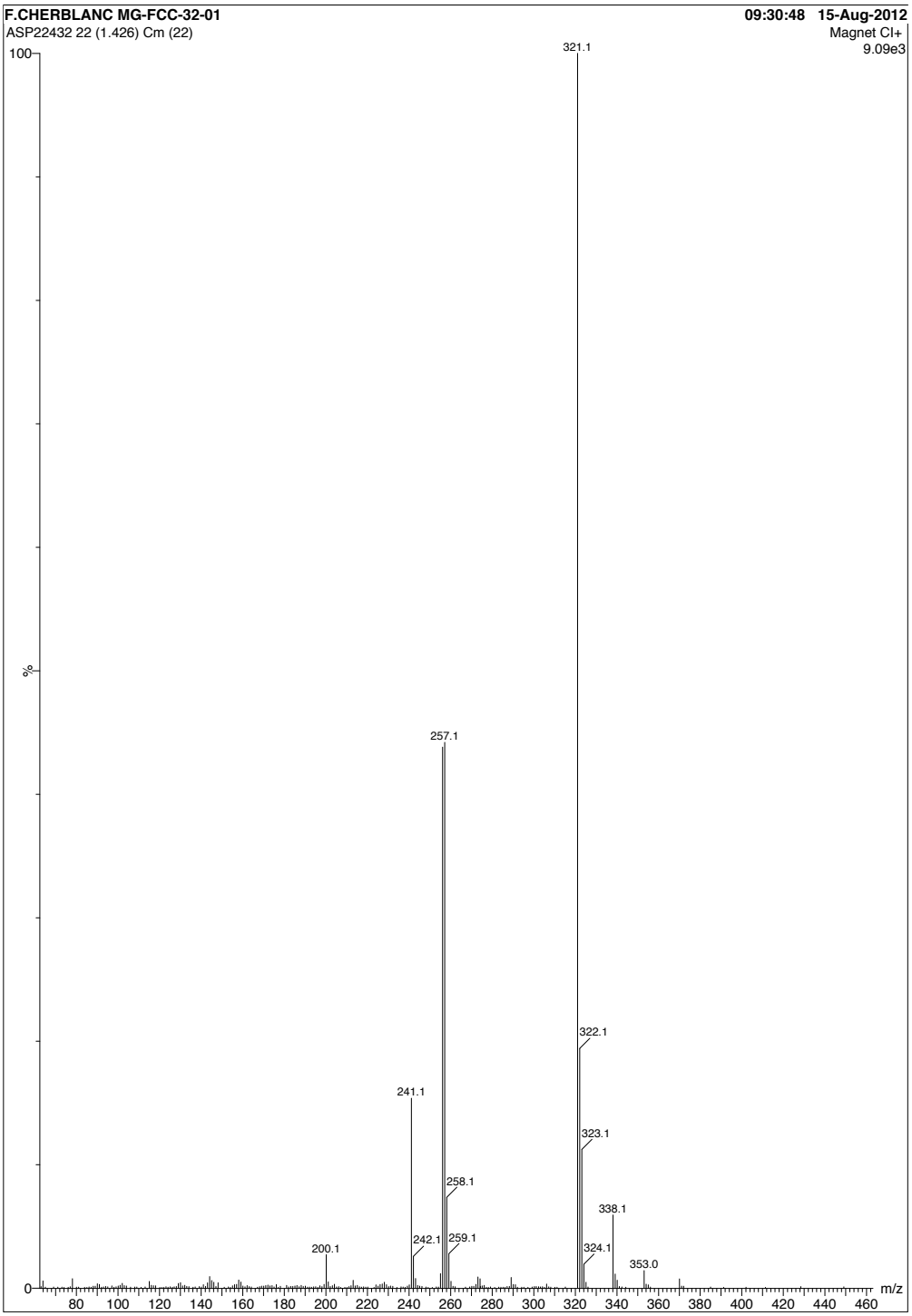


Compound **25** was prepared as follows:[13,14] NaHMDS (6.4 mL of a 0.6 M solution in PhMe, 3.84 mmol) was added dropwise to a solution of elemental sulfur (328 mg, 10.24 mmol) in dry THF (40 mL) at room temperature. The solution was allowed to stir for 1 min, time after which diketopiperazine **44** (330 mg, 1.28 mmol) in THF (6 mL) was added dropwise. The solution was allowed to stir for 1 min and additional NaHDMS (4.3 mL of a 0.6 M solution in PhMe, 2.56 mmol) was added. The resulting orange / light brown mixture was allowed to stir for 30 min at room temperature. The solution was then quenched with aq. sat. NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a dark green residue which was taken up in a degassed mixture of THF – EtOH (1:1, 26 mL) and cooled to 0 ˚C. Sodium borohydride (1.210 g, 32 mmol) was then added in small portions and the resulting mixture was allowed to warm up to room temperature and to stir for 45 min. The solution was subsequently cooled to 0 ˚C and quenched by addition of aq. sat. NH_4Cl. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were then treated with an aqueous solution of KI_3 (1.4 M), until the dark purple colour persisted. The mixture was allowed to stir for 10 min and quenched with 5% aq. $Na_2S_2O_3$ solution until

disappearance of the dark purple colour. The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (Hexanes : EtOAc, 90 : 10) to afford the racemic title compound **25** as a yellow solid (100 mg, 24%) which was recrystallised from CH_2Cl_2 to afford white crystals: m.p. 104 – 106 °C; IR (neat) 1690, 1460, 1357, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.28 – 7.25 (m, 2H), 3.12 (s, 3H), 2.10 (s, 3H), 1.79 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 162.4, 139.1, 136.1, 128.8, 126.1, 121.3, 115.9, 82.6, 74.3, 49.2, 28.7, 27.3, 20.5, 18.2; MS (CI) *m/z* 321 $(M+H)^+$, 257 $(M–S_2+H)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{17}N_2O_2S_2$ 321.0731, found: 321.0745. The obtained enantiomers could be separated by chiral HPLC (OD+ semiprep column, Hexane : Isopropanol, 1 : 1). First peak: $[\alpha]_D^{20}$ −335 (*c* 2.00, $CHCl_3$), Second peak: $[\alpha]_D^{20}$ +394 (*c* 2.05, $CHCl_3$).




Aug 14 2012
FCC_AG_332-01
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162.33
139.07
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121.33
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20.52
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4.0E+08
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2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

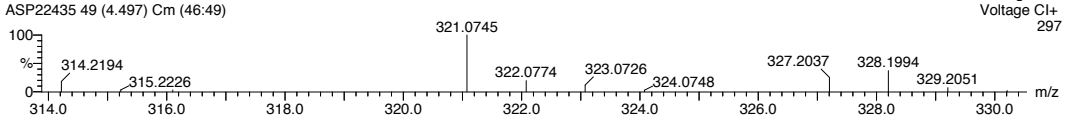

F.CHERBLANC MG-FCC-32-01
09:30:48 15-Aug-2012
ASP22432 22 (1.426) Cm (22)
Magnet CI+
9.09e3
100
%
0
321.1
257.1
322.1
241.1
323.1
258.1
338.1
200.1
242.1
259.1
324.1
353.0
m/z
80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

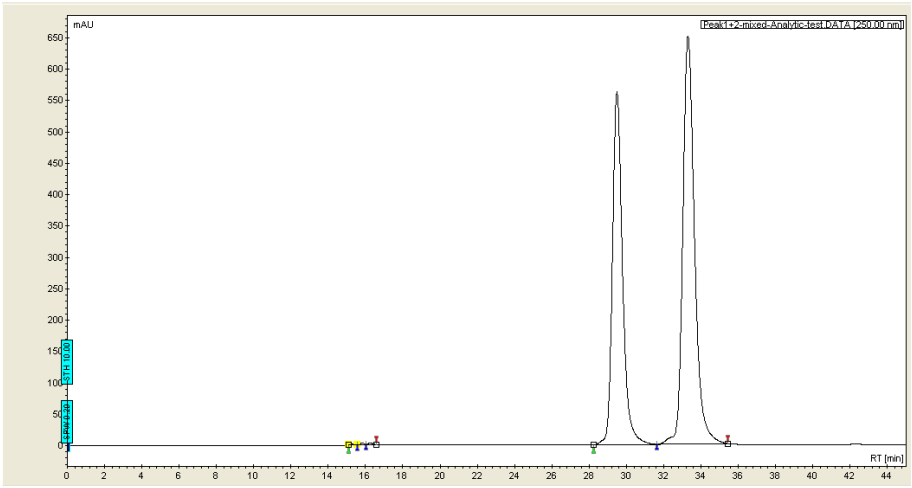
Monoisotopic Mass, Odd and Even Electron Ions
274 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
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F.CHERBLANC MG-FCC-32-01 AM M+H
ASP22435 49 (4.497) Cm (46:49)
09:46:52 15-Aug-2012
Voltage CI+
297

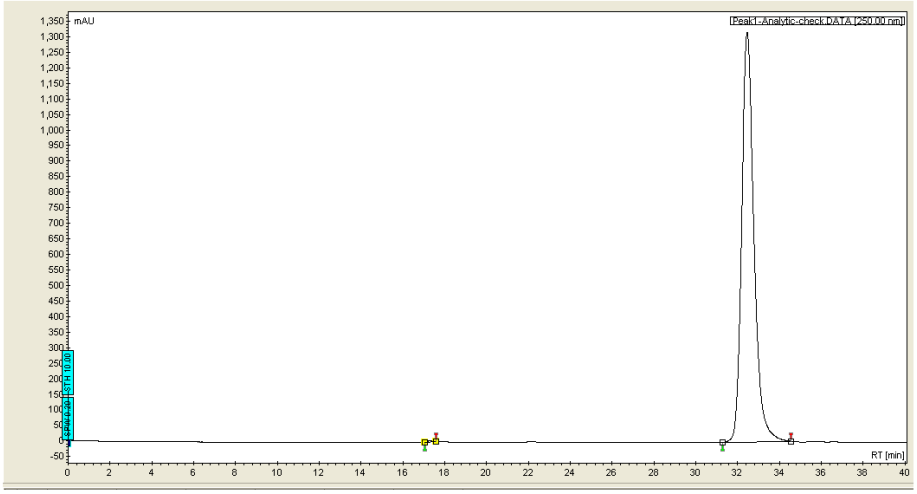


Minimum:				-1.5		
Maximum:		7.0	10.0	50.0		
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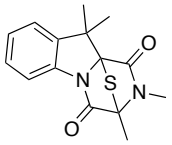
Gliotoxin analogue racemic (Hexane – Isopropanol, 50:50)



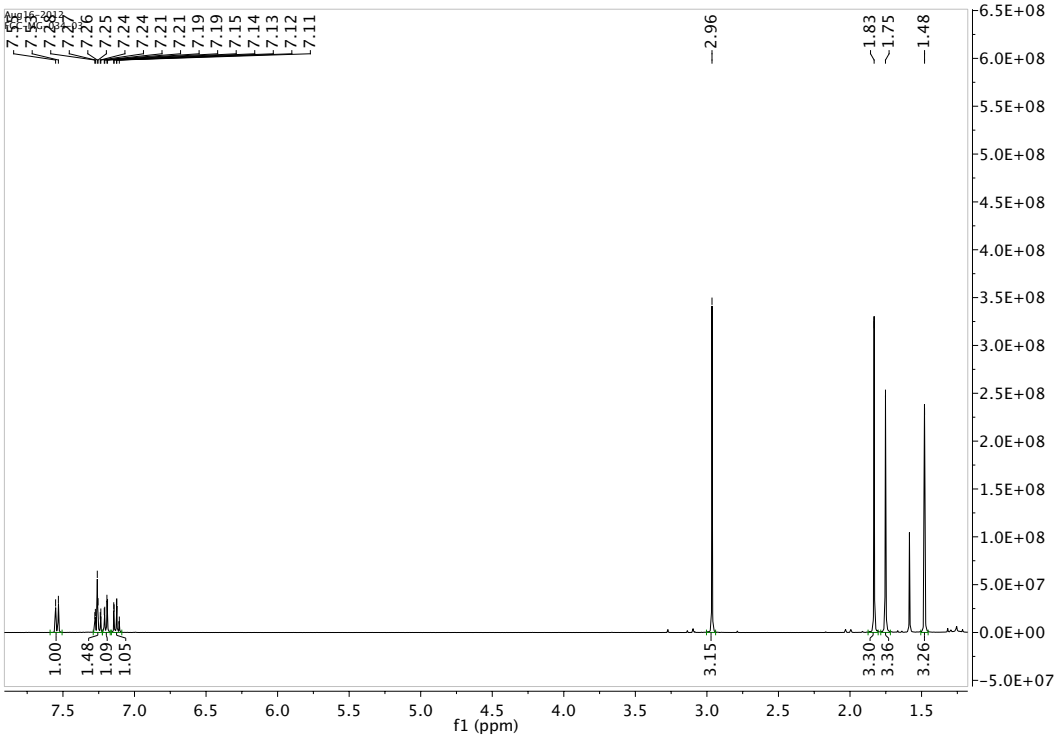
Gliotoxin analogue first enantiomer separated (Hexane – Isopropanol, 50:50)

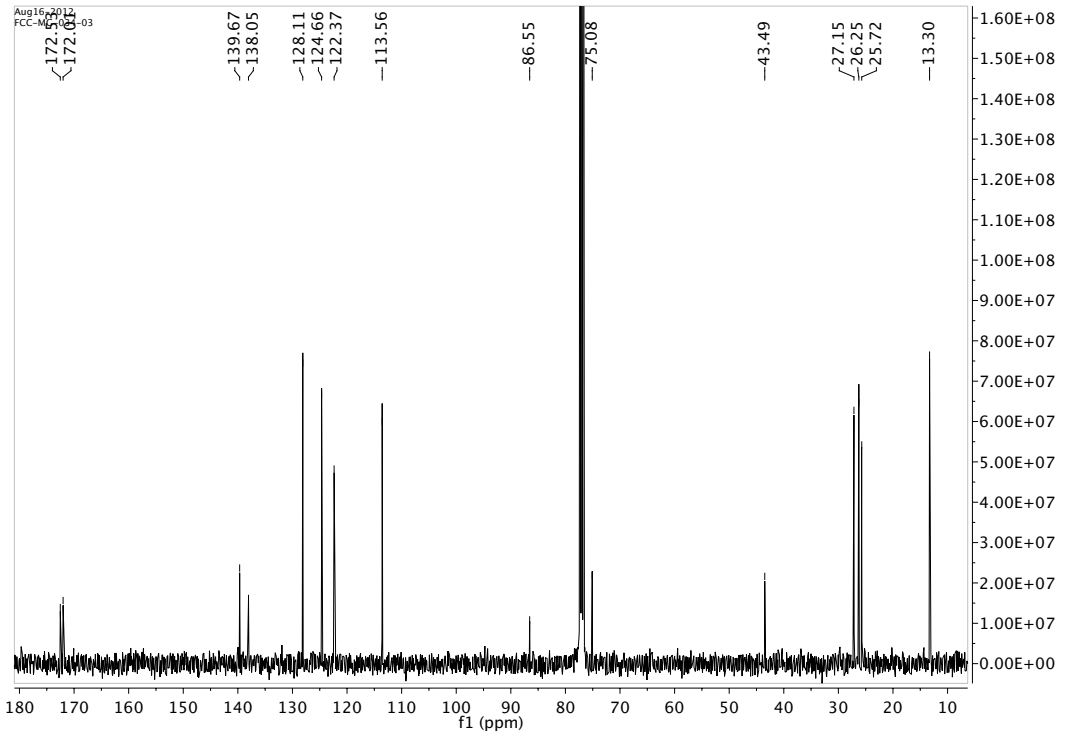


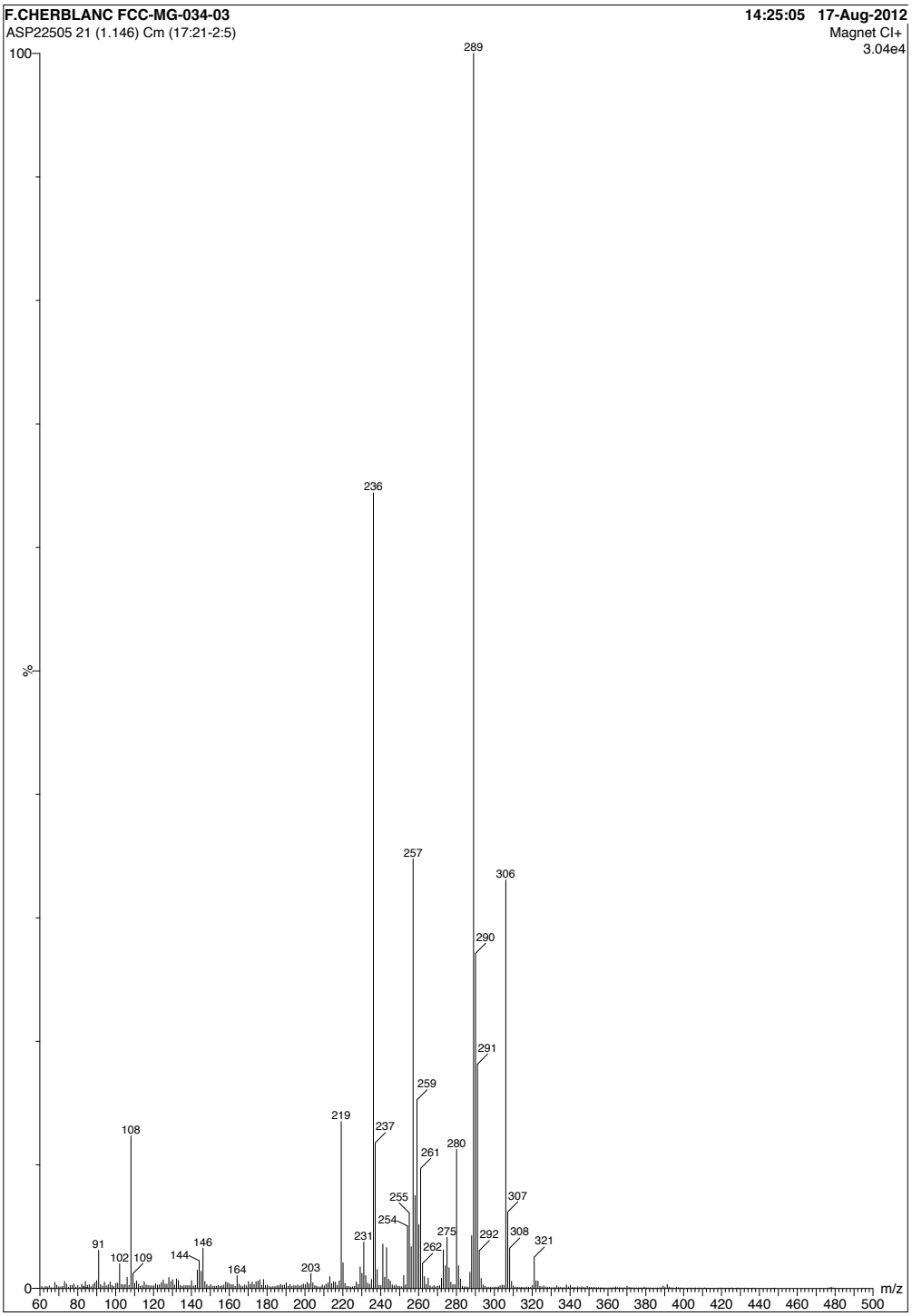
2,3,10,10-Tetramethyl-2,3-dihydro-1*H*-3,10a-epithiopyrazino[1,2-*a*]indole-1,4(10*H*)-dione - ((±)-26)[12]



To a solution of ETP **25** (33 mg, 0.10 mmol) in dioxane (8 mL) was added PPh_3 (33 mg, 0.16 mmol) and the resulting mixture was allowed to stir overnight at room temperature. The solvent was then removed under reduced pressure and the pink residue was purified by column chromatography (Hexanes : EtOAc, 100 : 0 to 95 : 5) to afford the racemic title compound **26** as colourless oil (19 mg, 64%), which was recrystallised from CH_2Cl_2 to give a white solid: m.p. 58 – 60 ˚C; IR (neat) 1720, 1456, 1387, 1288, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (*app*-d, *J* = 7.8 Hz, 1H), 7.25 (td, *J* = 7.8, 1.0 Hz, 1H), 7.20 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.13 (td, *J* = 7.8, 1.0 Hz, 1H), 2.96 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.0, 139.7, 138.1, 128.1, 124.7, 122.4, 113.6, 86.6, 75.1, 43.5, 27.2, 26.3, 25.7, 13.3; MS (CI) *m/z* 289 $(M+H)^+$, 306 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{17}N_2O_2S$ 289.1011, found: 289.1026. The obtained enantiomers could be separated by chiral HPLC (OD+ semiprep column, Hexane : Isopropanol, 90 : 10): First peak: $[\alpha]_D^{20}$ –47.5 (*c* 1.12, CH_2Cl_2), Second peak $[\alpha]_D^{20}$ +34.4 (*c* 1.12, CH_2Cl_2).


Aug16,2012
FCC-MC-02-03
7.27
7.26
7.25
7.24
7.24
7.21
7.21
7.19
7.19
7.15
7.14
7.13
7.12
7.11
2.96
1.83
1.75
1.48
1.00
1.48
1.09
1.05
3.15
3.30
3.36
3.26
f1 (ppm)


Aug16,2012
FCC-MC-02-03
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172.02
139.67
138.05
128.11
124.66
122.37
113.56
86.55
75.08
43.49
27.15
26.25
25.72
13.30
f1 (ppm)


F.CHERBLANC FCC-MG-034-03
14:25:05 17-Aug-2012
ASP22505 21 (1.146) Cm (17:21-2:5)
Magnet CI+
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100
%
0
289
236
257
306
290
291
259
219
237
108
280
261
255
307
254
231
275
292
308
321
91
102
109
144
146
164
203
262
m/z
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500

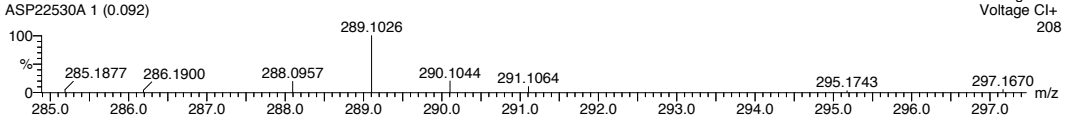
Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Odd and Even Electron Ions
486 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
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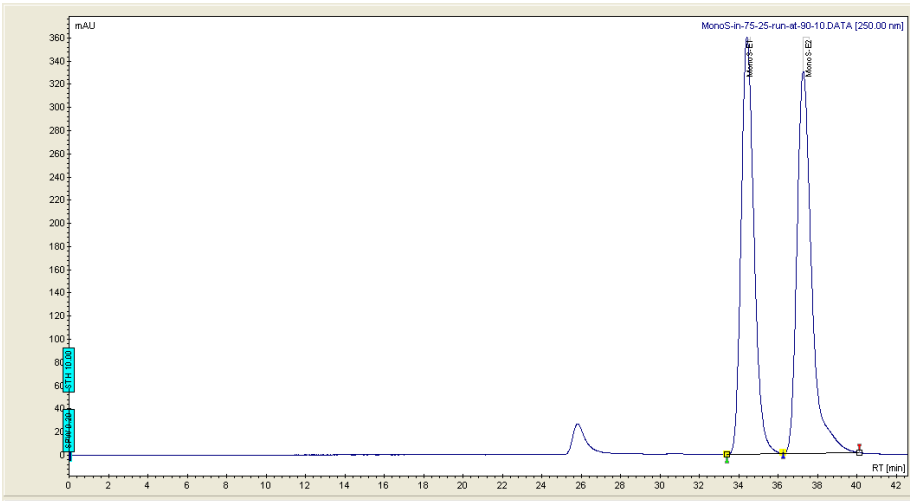
F.CHERBLANC FCC-MG-034-03 AM
ASP22530A 1 (0.092)

11:51:09 20-Aug-2012
Voltage CI+
208



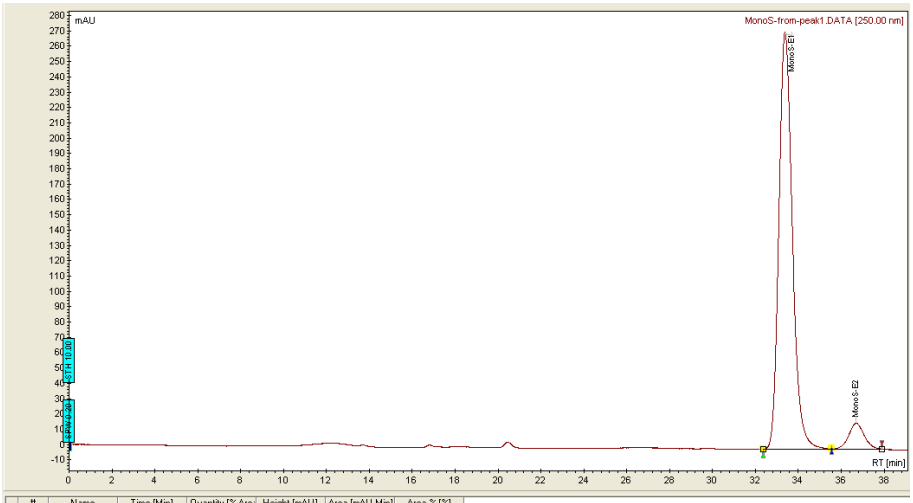
Minimum:				-1.5		
Maximum:		7.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
289.1026	289.1011	1.5	5.2	8.5	1.5	C15 H17 N2 O2 S

Monosulfide from racemic Gliotoxin analogue (Hexane – Isopropanol, 90:10)



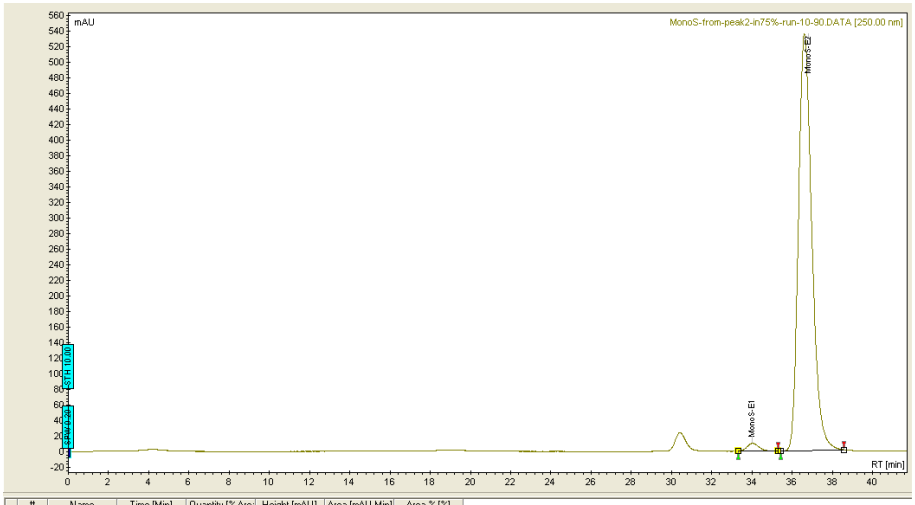
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	MonoS-E1	34.411	48.80	359.7	272.0	48.800
2	MonoS-E2	37.277	51.20	329.5	285.4	51.200
Total			100.00	689.2	557.4	100.000

Monosulfide from first enantiomer of Gliotoxin analogue (Hexane – Isopropanol, 90:10)



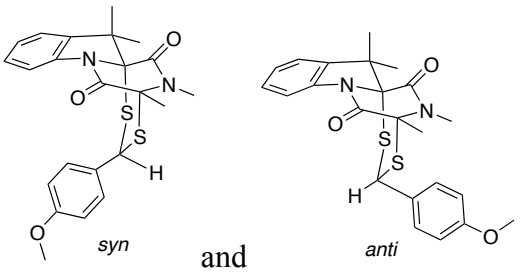
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	MonoS-E1	33.371	93.35	272.1	197.5	93.347
2	MonoS-E2	36.704	6.65	16.7	14.1	6.653
Total			100.00	288.8	211.6	100.000

Monosulfide from second enantiomer of Gliotoxin analogue (Hexane – Isopropanol, 90:10)



#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	MonoS-E1	34.024	1.60	9.9	6.7	1.604
2	MonoS-E2	36.611	98.40	534.8	412.7	98.396
Total			100.00	544.7	419.4	100.000

2-(4-methoxyphenyl)-4,11,11,13-tetramethyl-4*H*-4,11a-(epiminomethano)[1,3,5]dithiazepino[5,4-*a*]indole-5,12(11*H*)-dione (47)



and

From ETP **25**: $NaBH_4$ (4.5 mg, 0.117 mmol) was added to a solution of racemic ETP **25** (15.0 mg, 0.047 mmol) in degassed MeOH : THF (1:1, 5 mL) at 0 °C. Once complete (monitored by TLC), a few drops of 0.1 N aq. HCl were added and the solvent was removed under reduced pressure. The residue was taken up with CH_2Cl_2 (5 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue obtained was dried under vacuum and then dissolved in dry CH_2Cl_2 (5 mL). *p*-anisaldehyde (7 µL, 0.056 mmol) and boron trifluoride etherate (9 µL, 0.073 mmol) were added and the reaction was allowed to stir for 16 h under N_2. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (Hexanes : EtOAc, 80 : 20) to afford the title compound as a mixture of diastereoisomers as a colorless oil (Diastereoisomer 1: only traces observed by TLC and LCMS of the crude but not isolated; Diastereoisomer 2: 9 mg, 43%;). Diastereoisomer 2: IR (neat) 1682, 1606, 1511, 1483, 1372, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.28 (*app*-d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 4.2 Hz, 2H), 6.80 (*app*-d, *J* = 8.8 Hz, 2H), 5.10 (s, 1H), 3.76 (s, 3H), 3.27 (s, 3H), 1.98 (s, 3H), 1.72 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 162.2, 160.4, 139.5, 137.5, 130.6 (2C), 128.4, 126.8, 125.9, 121.5, 117.4, 114.2 (2C), 82.1, 68.8, 55.3, 52.0, 49.2, 28.0, 27.6, 22.3, 21.8; A NOESY experiment showed a correlation between the signal at 5.1 ppm (CH of the thioacetal carbon) and the signal at 3.27 ppm (CH_3 on the nitrogen atom of the ETP ring) thus suggesting that this diastereoisomer is the *syn*. MS (ES) *m/z* 441 $(M+H)^+$; HRMS (ES) *m/z* calc. for $C_{23}H_{25}N_2O_3S_2$ 441.1307, found: 441.1316.

The 2 enantiomers could be observed by chiral HPLC (OD+ analytical column, Hexane : Isopropanol, 98 : 2, 1 mL/min) around 60 min and 100 min. The reaction was repeated on a single enantiomer of ETP **25** (first peak by HPLC separation) and the product was also obtained as mixture of diastereoisomers (13% of diastereoisomer

2, and 6% of diastereoisomer 1). Diastereoisomer 2 was obtained as a single enantiomer eluting with a comparable retention time as the first peak of the racemic (around 70 min). $[\alpha]_D^{20}$ −66 (*c* 0.20, $CHCl_3$)

From monosulfide (**26**):

The trithiane derivative of *p*-anysaldehyde **48** was prepared as follows:[15,16] A mixture of Na_2S (390 mg, 5 mmol) and $SiCl_4$ (1.15 mL, 10 mmol) in MeCN (7.5 mL) was allowed to stir for 15 min. After that time, *p*-anysaldehyde (304 μL, 2.5 mmol) was added and the mixture was allowed to stir for 16 h at room temperature. Ice-cold water (50 mL) was then added and the resulting mixture was extracted with EtOAc (2 × 100 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The solid obtained was recrystallised from acetic acid to afford the trithiane derivative of *p*-anysaldehyde **48** as a pink solid (41 mg, 4%).

In DMSO, only the Beta conformer was observed[17]: ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.36 (d, *J* = 8.7 Hz, 3 × 2H), 6.96 (d, *J* = 8.7 Hz, 3 × 2H), 5.68 (s, 3 × 1H), 3.75 (s, 3 × 3H); ^{13}C NMR (100 MHz, DMSO) δ 159.4 (3 × 1C), 130.2 (3 × 1C), 129.1 (3 × 2C), 114.4 (3 × 2C), 56.4 (3 × 1C), 55.2 (3 × 1C); In $CDCl_3$, alpha/beta ratio[17] varied as a function of the temperature (1:10 at 25 ˚C versus 1:5 at 40 ˚C). Alpha conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2 × 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2 × 2H), 5.69 (s, 1H), 5.40 (s, 2 × 1H), 3.86 (s, 3H), 3.80 (s, 2 × 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 160.0 (2 × 1C), 130.4 (2 × 1C), 130.3, 130.1 (2 × 1C), 129.2 (2 × 2C), 114.4 (2 × 2C), 114.3 (1 × 2C), 55.4, 55.3 (2 × 1C), 52.8, 51.2 (2 × 1C); MS (CI) *m/z* 153 $(1/3M+H)^+$; HRMS (CI) *m/z* calc. for C_8H_9OS 153.0369, found: 153.0422.

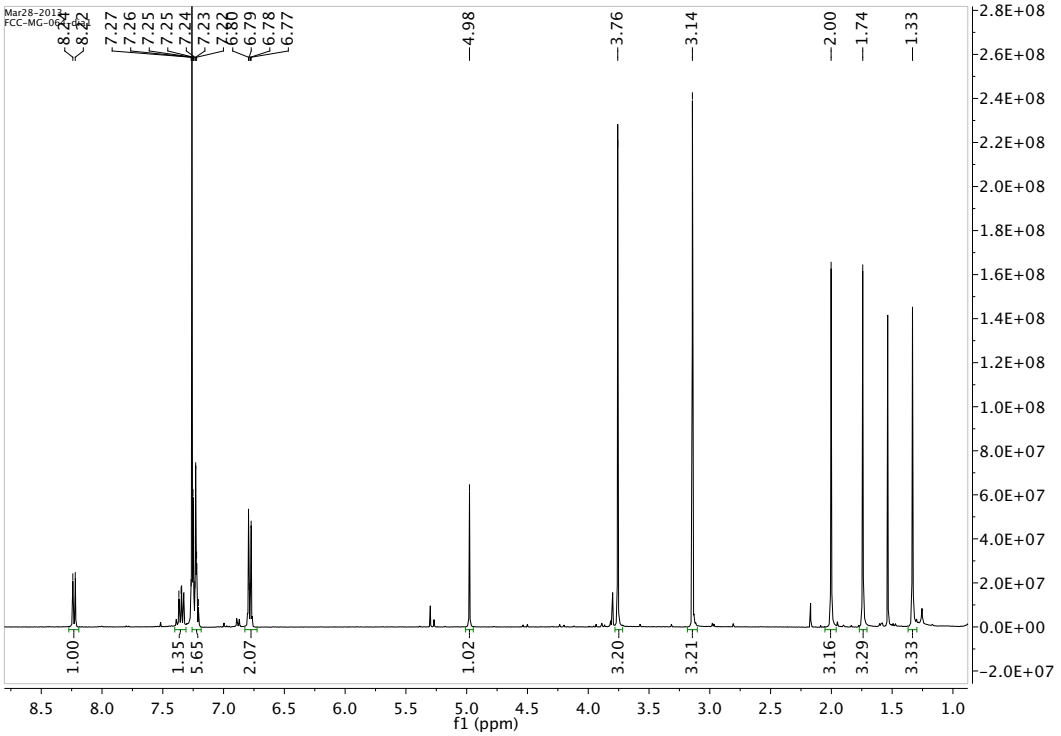
A solution of the racemic monosulfide **26** (21 mg, 0.073 mmol) in CH_2Cl_2 (10 mL) was treated with the trithiane derivative of *p*-anysaldehyde **48** (17 mg, 0.036 mmol) and boron trifluoride etherate (15 μL, 0.117 mmol). The mixture was allowed to stir at 40 ˚C for 5 h and then additional boron trifluoride etherate (2 × 30 μL, 0.234 mmol) was added. The mixture was subsequently absorbed on silica gel and purified by column chromatography (Hexanes : EtOAc, 85 : 15) and title compound **47** was obtained as a mixture of two diastereoisomers as colourless oils (56% of diastereoisomer 1 and 25% of diastereoisomer 2, 7:3): Diastereoisomer 1: IR (neat) 1682, 1606, 1510, 1481, 1459, 1372, 1254 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23

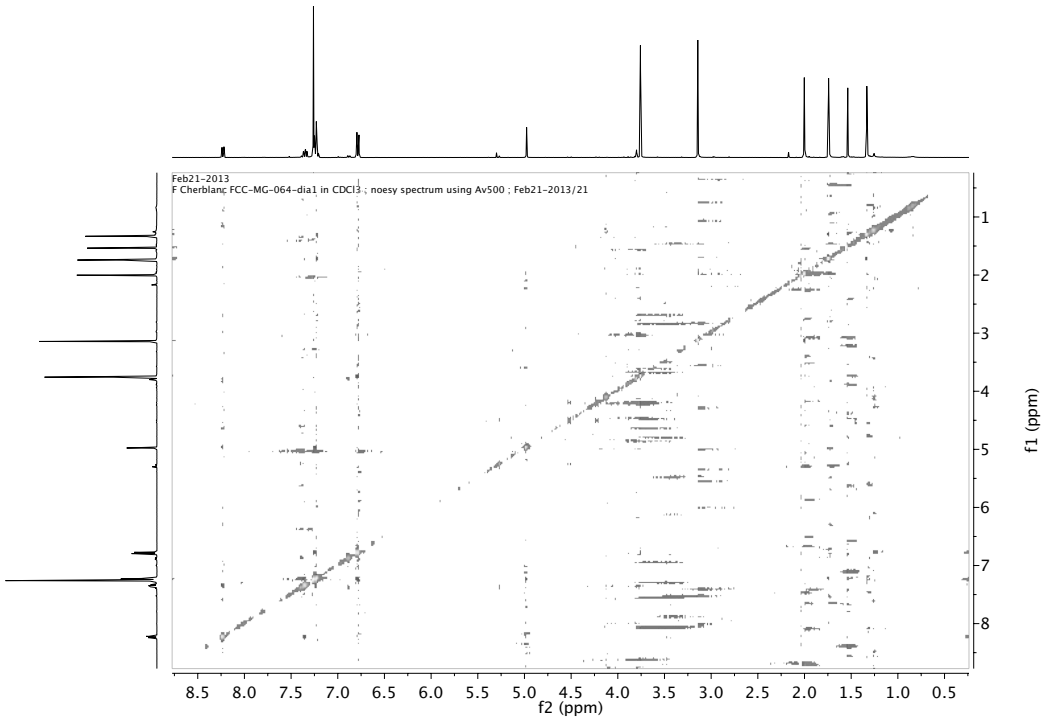
(d, *J* = 8.0 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.24 (*app*-d, *J* = 8.7 Hz, 2H), 7.27 – 7.21 (m 2H), 6.78 (*app*-d, *J* = 8.7 Hz, 2H), 4.98 (s, 1H), 3.76 (s, 3H), 3.14 (s, 3H), 2.00 (s, 3H), 1.74 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 161.7, 160.4, 140.0, 136.6, 130.6 (2C), 128.2, 126.7, 126.5, 122.2, 116.8, 114.2 (2C), 77.8, 71.3, 55.3, 51.6, 50.4, 28.5, 27.6, 22.7, 19.5; A NOESY experiment did not show any correlation between the signal at 5.1 ppm (CH of the thioacetal carbon) and the signal at 3.37 ppm (CH_3 on the nitrogen atom of the ETP ring) thus suggesting that this diastereoisomer is the *trans*. MS (ES) *m/z* 441 $(M+H)^+$; HRMS (ES) *m/z* calc. for $C_{23}H_{25}N_2O_3S_2$ 441.1307, found: 441.1308;

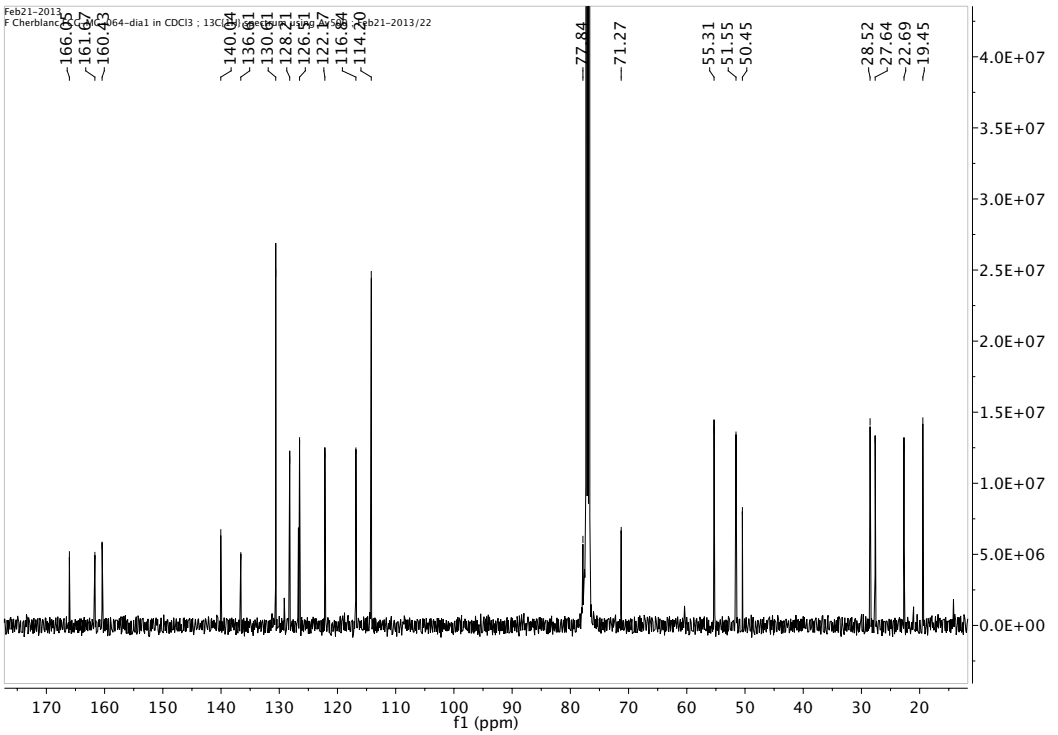
Diastereoisomer 2 matched the data of the compound obtained by reaction of the ETP **25** (IR, ^{1}H, ^{13}C, HSQC and NOESY). MS (ES) *m/z* 441 $(M+H)^+$; HRMS (ES) *m/z* calc. for $C_{23}H_{25}N_2O_3S_2$ 441.1307, found: 441.1318; The two enantiomers could be observed by chiral HPLC (OD+ analytical column, Hexane : Isopropanol, 98 : 2, 1 mL/min) at 52 min and 80 min.

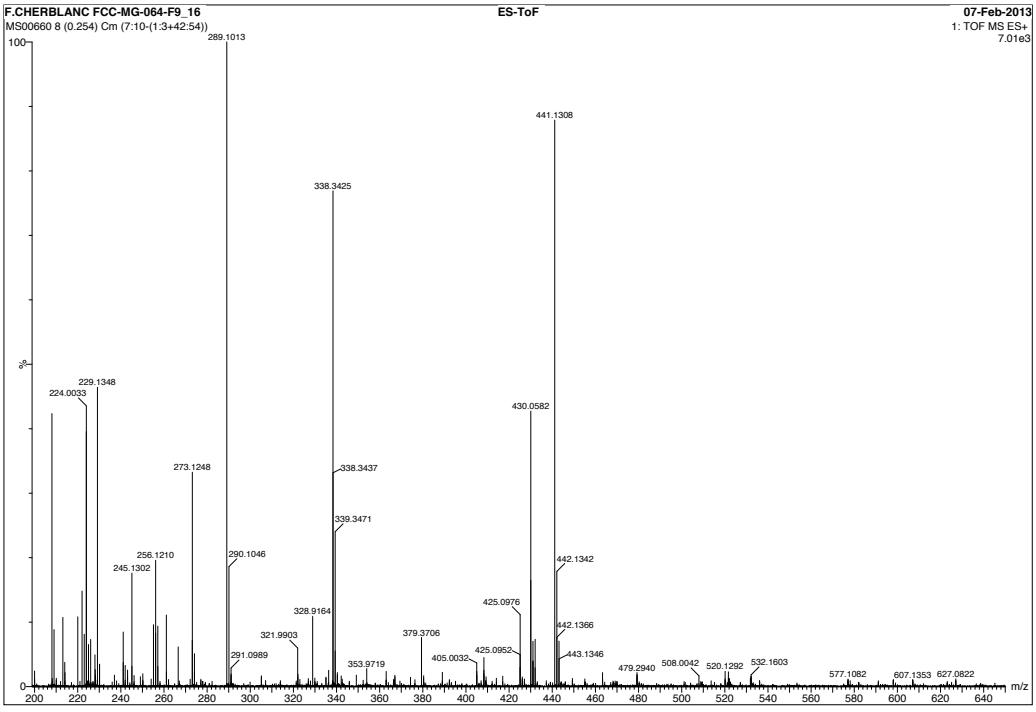
The reaction was repeated on a single enantiomer of monosulfide **26** (first peak by HPLC separation) and diastereoisomer 2 was obtained as a single enantiomer $[\alpha]_D^{20}$ –40 (*c* 0.20, $CHCl_3$) eluting with the comparable retention time as the first peak of the racemic (around 70 min), and importantly with the same retention time as the thioacetal obtained from ETP **25** (as confirmed by spiking).

Diastereoisomer 1 (*trans*)






Feb21-2013
166.03
161.67
160.43
140.04
136.61
130.61
128.21
126.51
122.17
116.84
114.20
77.84
71.27
55.31
51.55
50.45
28.52
27.64
22.69
19.45
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


F.CHERBLANC FCC-MG-064-F9_16
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07-Feb-2013
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%
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338.3437
273.1248
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256.1210
290.1046
245.1302
442.1342
425.0976
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442.1366
321.9903
379.3706
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425.0952
405.0032
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479.2940
508.0042
520.1292
532.1603
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627.0822
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m/z

Elemental Composition Report **Page 1**

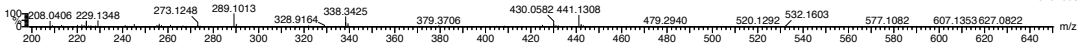
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1428 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 23-23 H: 5-200 N: 0-15 O: 0-15 Na: 0-1 S: 0-2

F.CHERBLANC FCC-MG-064-F9_16
MS00660 8 (0.254) Cm (7:10-(1:3+42:54))

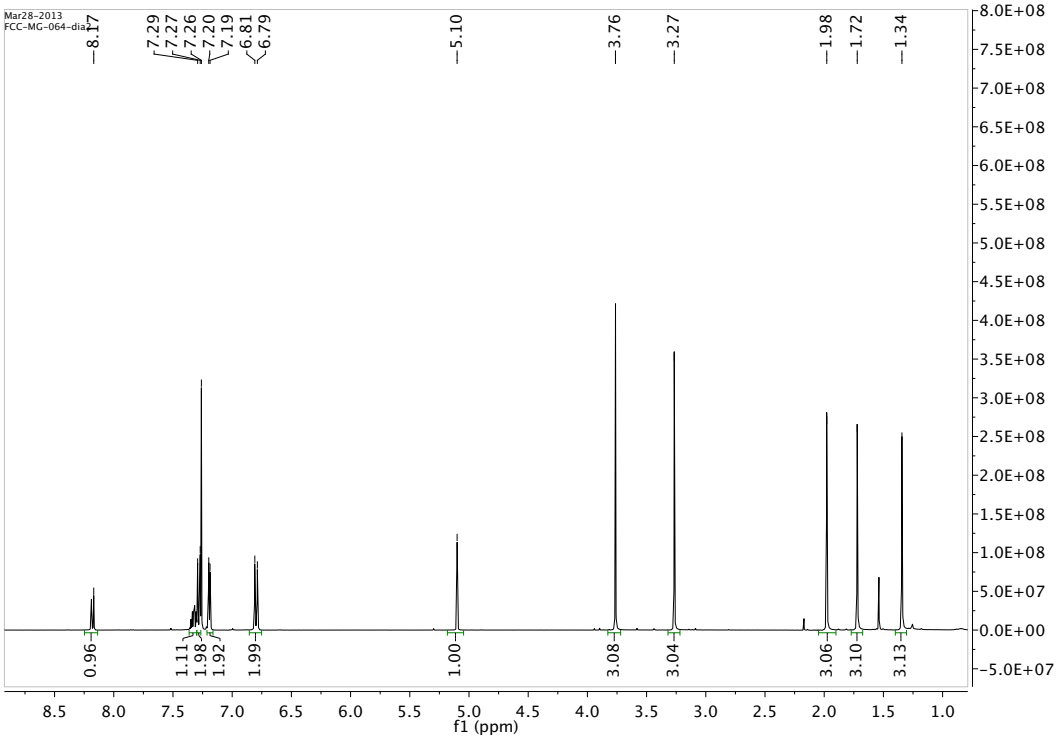
ES-ToF

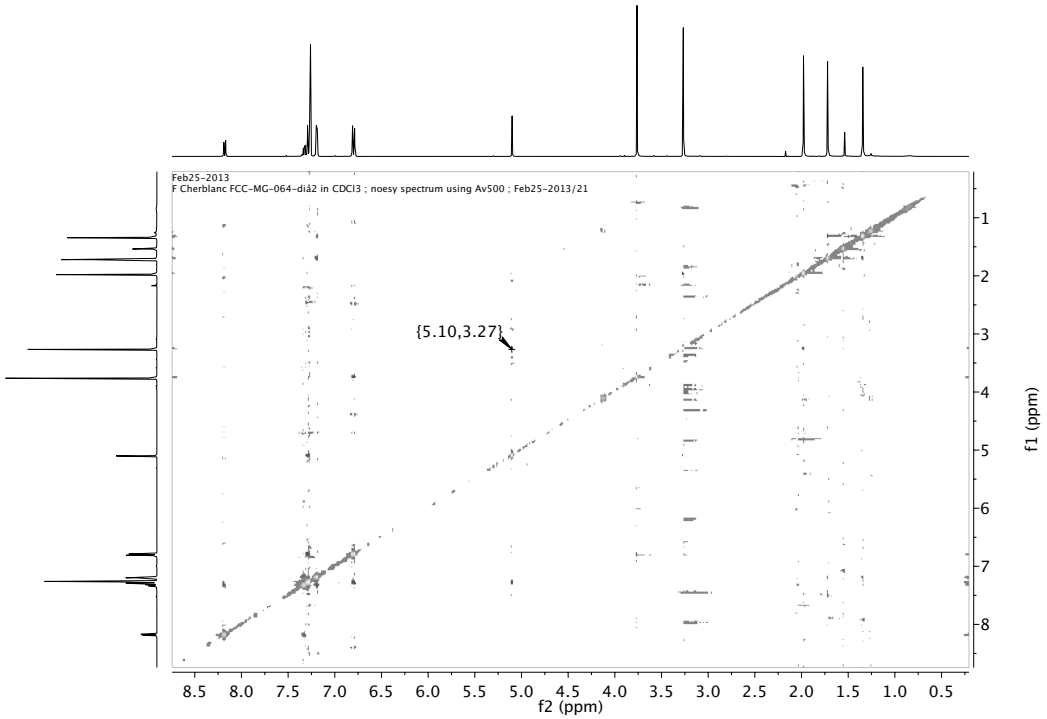
07-Feb-2013
1: TOF MS ES+
7.01e+003

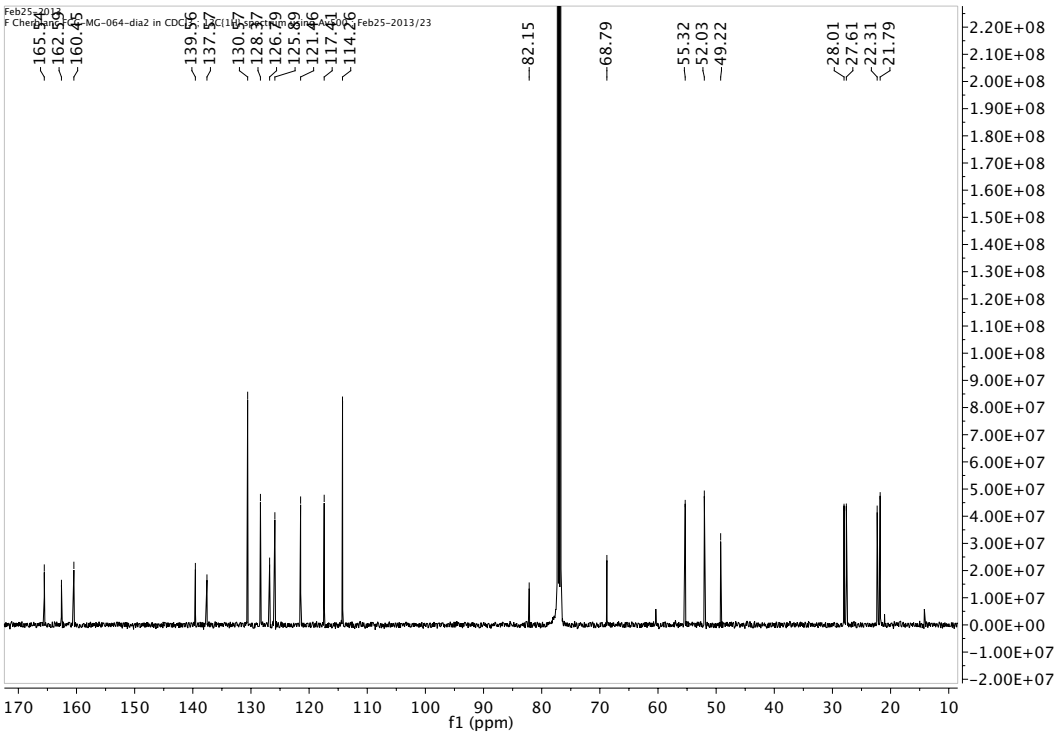


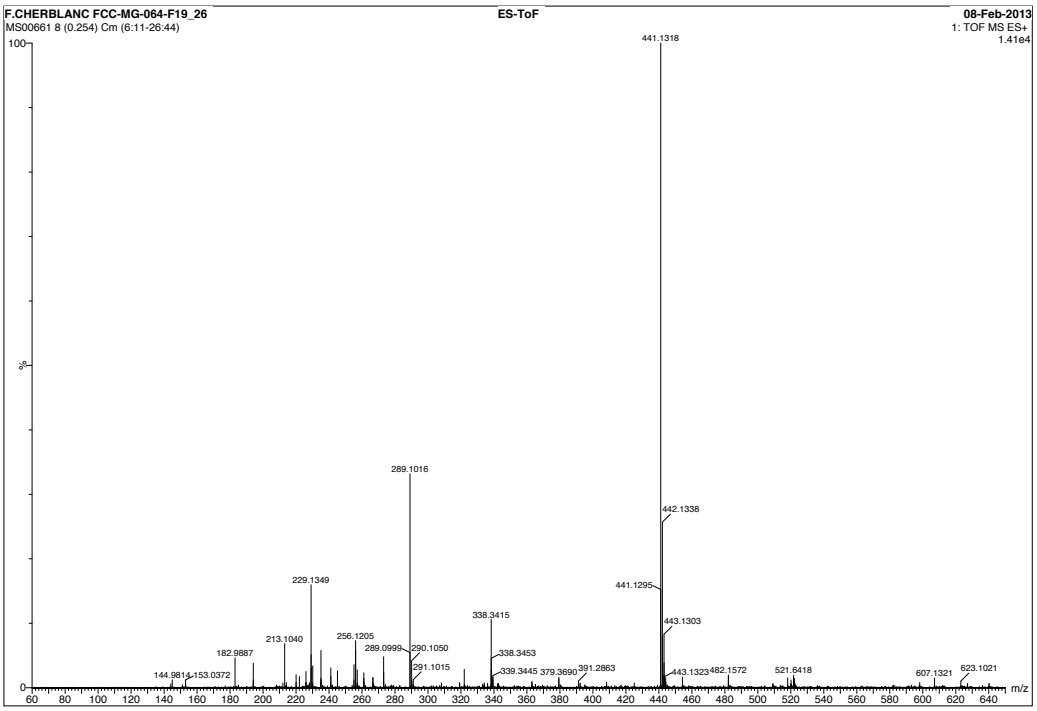
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
441.1308	441.1307	0.1	0.2	12.5	354.9	0.7	C23 H25 N2 O3 S2
	441.1311	-0.3	-0.7	18.5	354.8	0.7	C23 H17 N6 O4

Diastereoisomer 2 (*cis*)




Feb25-2013
F Cherblanc FCC-MG-064-dia2 in CDCl3 ; noesy spectrum using Av500 ; Feb25-2013/21
{5.10,3.27}
f2 (ppm)
f1 (ppm)

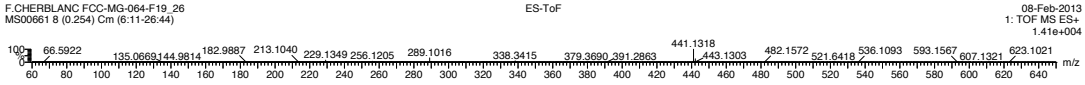

Feb25-2013
F Cherblanc FCC-MG-064-dia2 in CDCl3 ; nAChR spectrum using Av500 ; Feb25-2013/23
165.43
162.59
160.45
139.56
137.67
130.77
128.57
126.79
125.99
121.46
117.41
114.26
82.15
68.79
55.32
52.03
49.22
28.01
27.61
22.31
21.79
f1 (ppm)



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

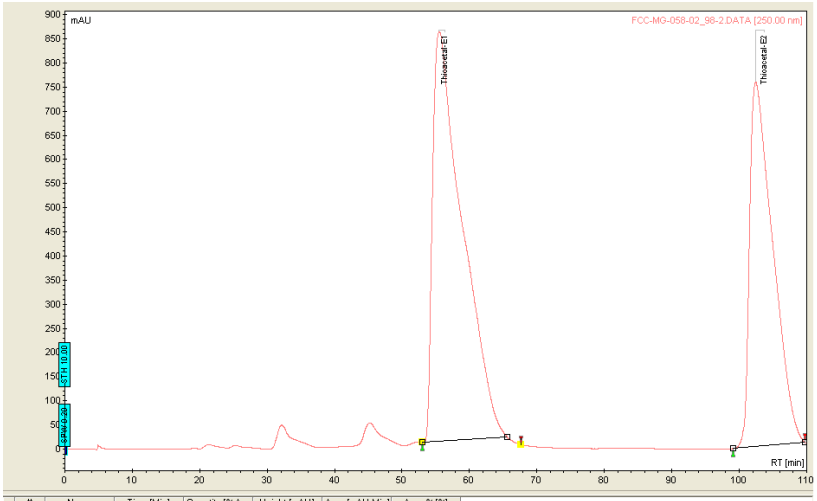
Monoisotopic Mass, Even Electron Ions
1428 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 23-23 H: 5-200 N: 0-15 O: 0-15 Na: 0-1 S: 0-2



Minimum:				-1.5								
Maximum:		5.0	10.0	50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula					
441.1318	441.1311	0.7	1.6	18.5	497.5	0.3	C23	H17	N6	O4		
	441.1307	1.1	2.5	12.5	498.8	1.6	C23	H25	N2	O3	S2	
	441.1361	-4.3	-9.7	14.5	500.6	3.3	C23	H22	N4	O2	Na	S

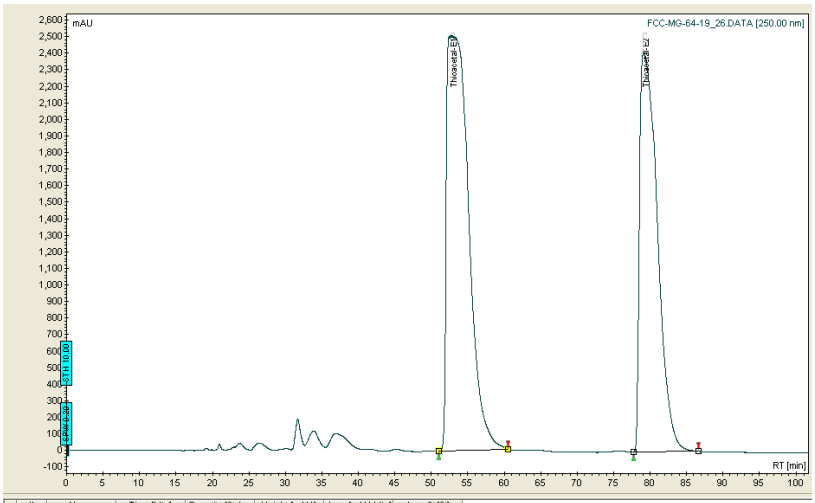
HPLC Traces *(Traces obtained on ODH column)*

Thioacetal from Gliotoxin analogue racemic (Hexane – Isopropanol, 98:2)



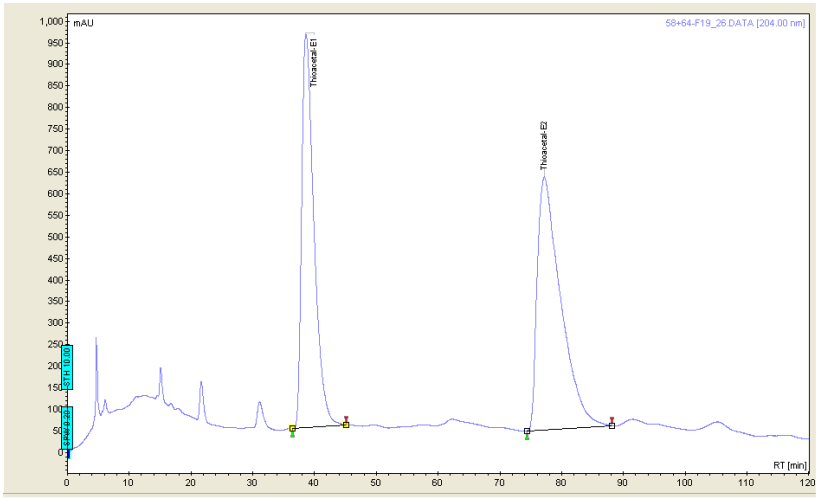
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Thioacetal-E1	55.473	58.84	848.4	4302.6	58.837
2	Thioacetal-E2	102.430	41.16	755.6	3010.2	41.163
Total			100.00	1604.1	7312.8	100.000

Thioacetal from Monosulfide racemic, diastereoisomer 2



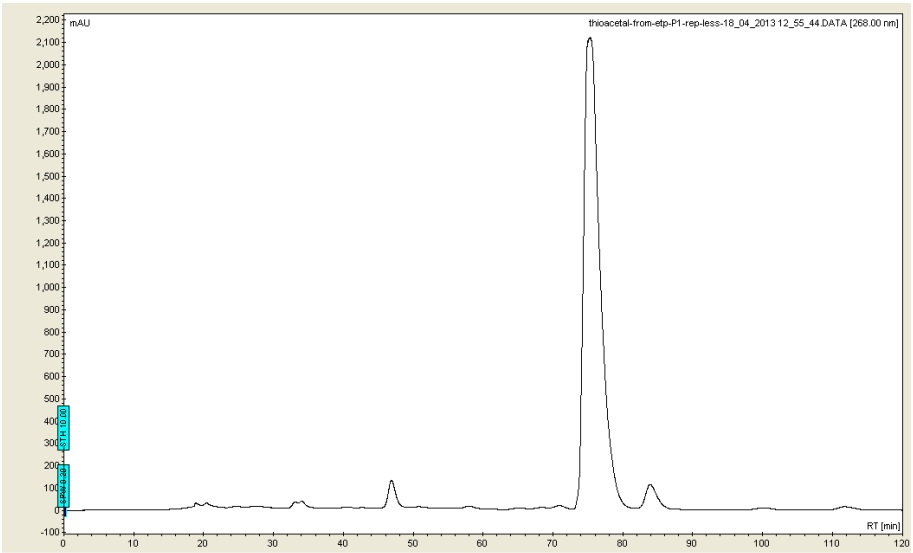
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Thioacetal-E1	52.661	56.28	2506.3	8774.2	56.279
2	Thioacetal-E2	79.065	43.72	2413.9	6816.3	43.721
Total			100.00	4920.2	15590.4	100.000

Mix Thioacetal from Gliotoxin analogue racemic and thioacetal from Monosulfide racemic, diastereoisomer 2.

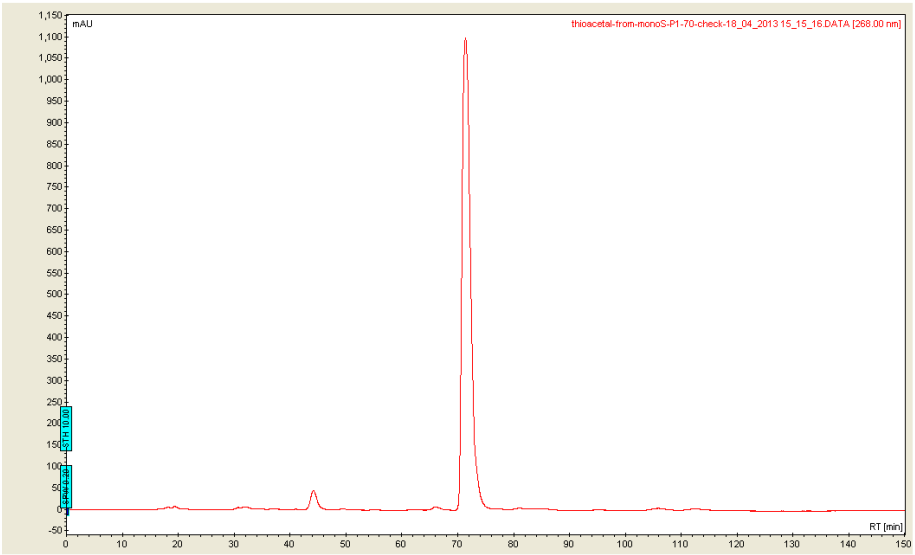


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Thioacetal-E1	38.560	44.98	911.4	2105.4	44.984
2	Thioacetal-E2	77.212	55.02	586.2	2575.0	55.016
Total			100.00	1497.6	4680.4	100.000

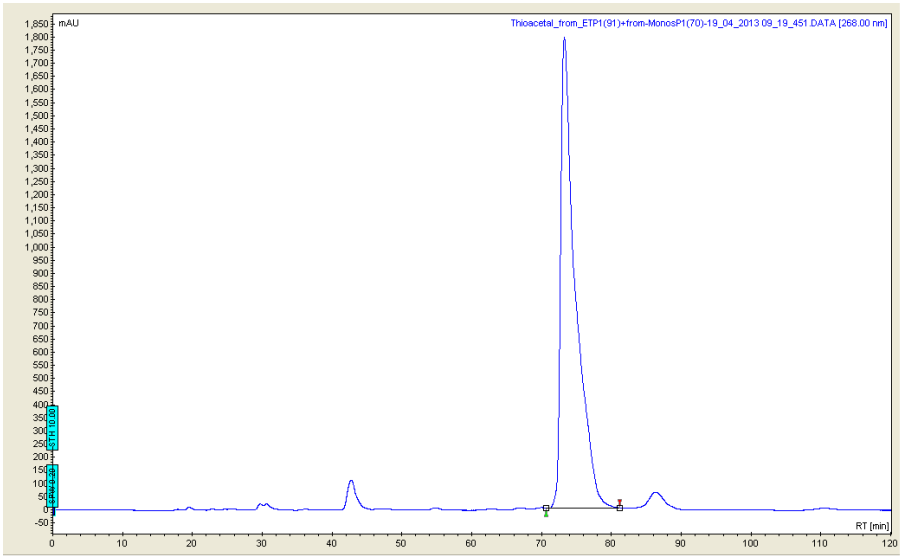
Thioacetal from Gliotoxin analogue first enantiomer



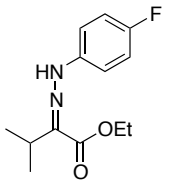
Thioacetal from Monosulfide of gliotoxin analogue first enantiomer



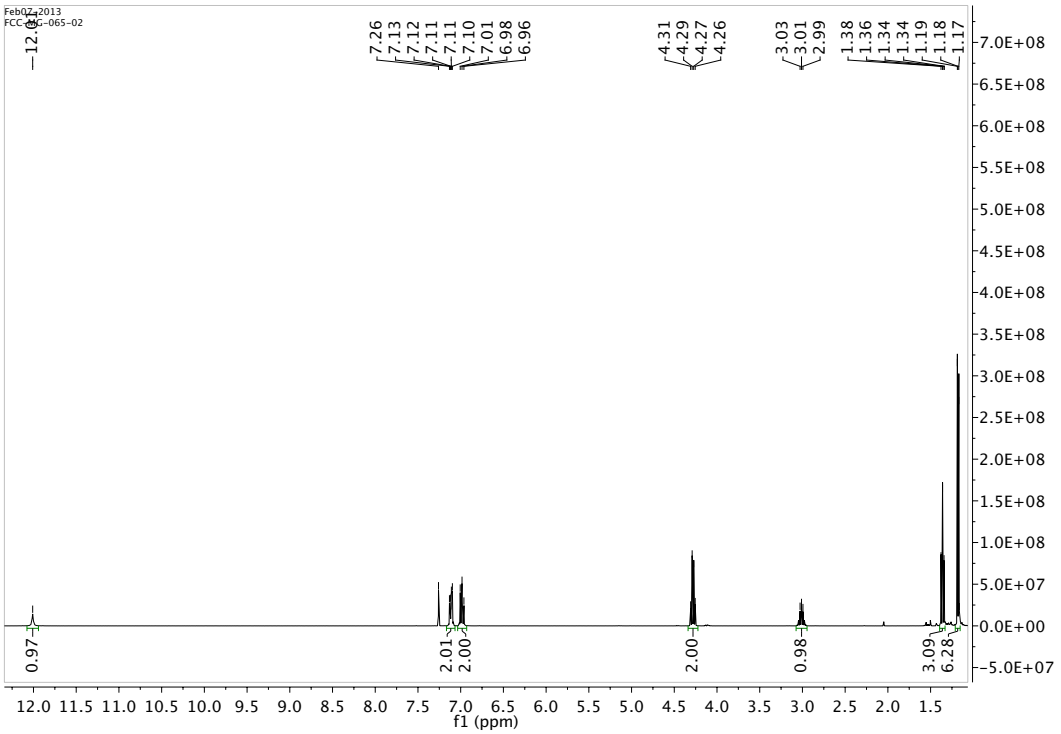
Mix Thioacetal from Gliotoxin analogue first enantiomer + Thioacetal from Monosulfide of gliotoxin analogue first enantiomer (dia2)

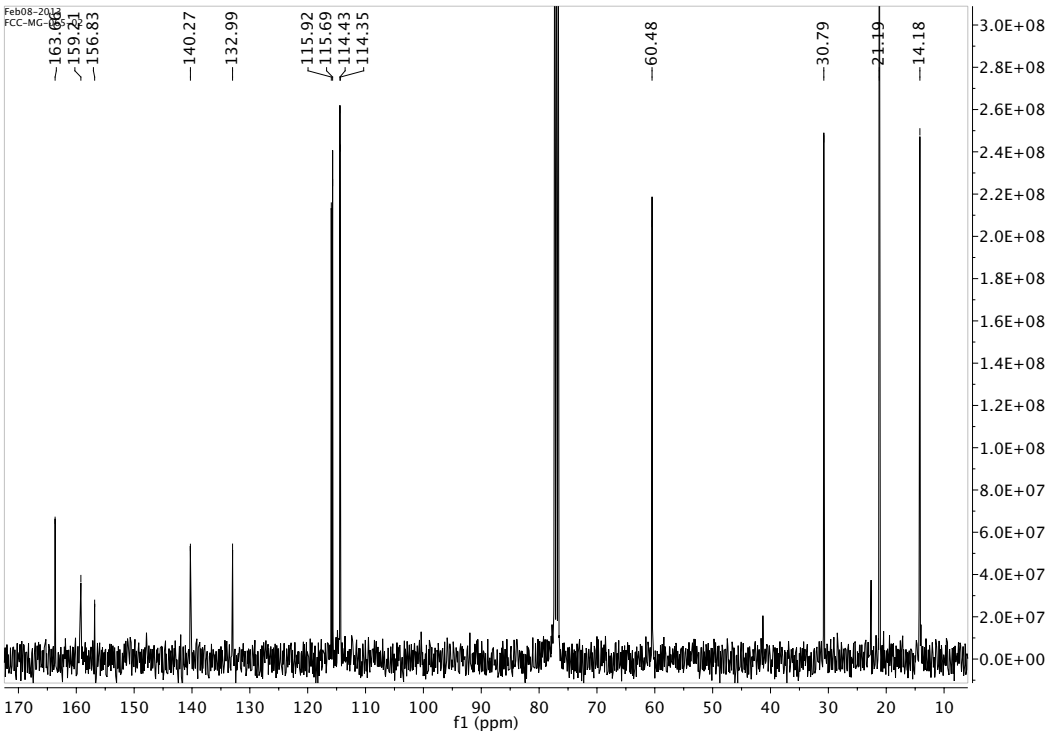


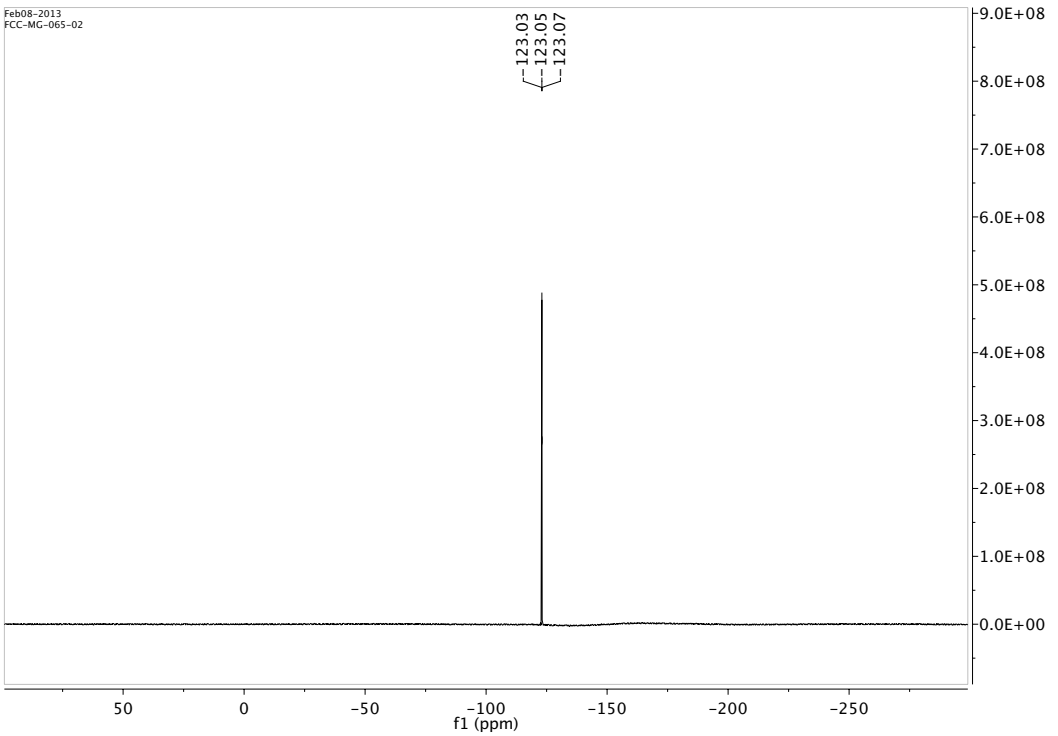
Ethyl 2-(2-(4-fluorophenyl)hydrazono)-3-methylbutanoate (51)

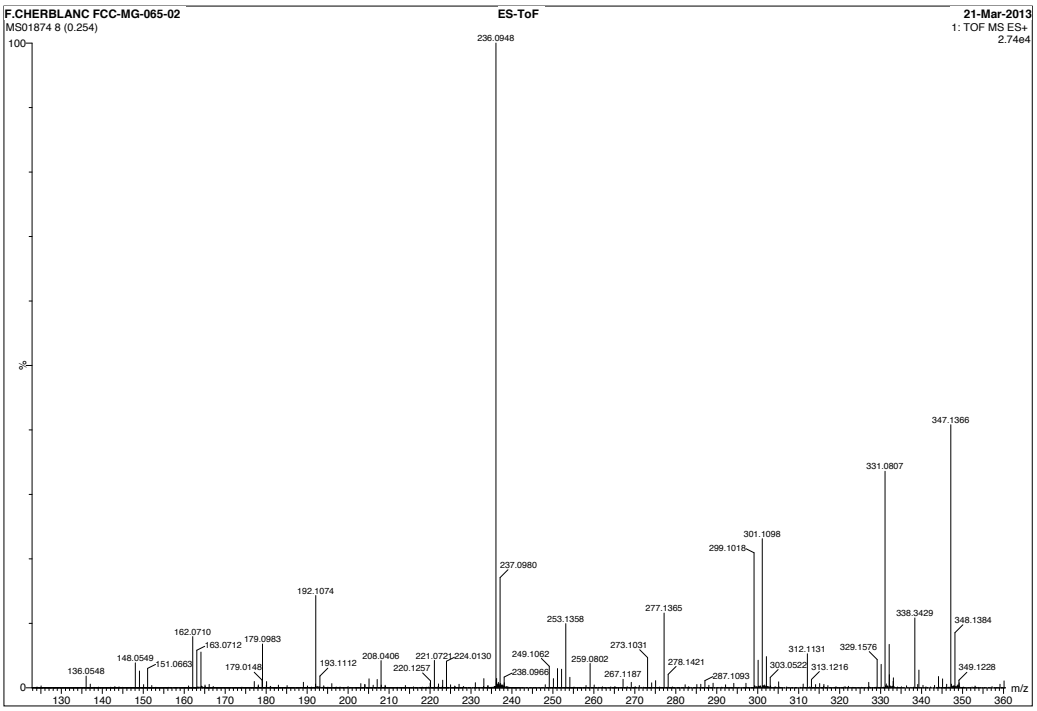


Compound **51** was prepared as follows:[9] Keto-ester **40** (2.000 g, 13.87 mmol) was added to a solution of the hydrochloride salt of 4-fluorophenylhydrazine (3.384 g, 20.81 mmol) and triethylamine (2.9 mL, 20.81 mmol) in toluene and the resulting mixture was heated at 60 ˚C for 1 h. The solvent was rotatory evaporated and the crude product purified by column chromatography (EtOAc : Hexanes, 5 : 95) to afford hydrazone **51** as a yellow oil (3.250 g, 93%): IR (neat) 1727, 1683, 1551, 1510, 1205, 1155 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.01 (br s, 1H), 7.13 – 7.10 (m, 2H), 7.01 – 6.96 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.01 (sept, *J* = 6.8 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 158.0 (d, *J* = 237 Hz, 1C), 140.3, 133.0, 115.8 (d, *J* = 22 Hz, 2C), 114.4 (d, *J* = 8 Hz, 2C), 60.5, 30.8, 21.2 (2C), 14.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ −123.05; MS (ESI) *m/z* 253 ($M+H^+$), 236; HRMS (ESI) *m/z* calc. for $C_{13}H_{18}FN_2O_2$ 253.1352, found 253.1358.




Feb08-2013
FCC-MG-065-02
163.65
159.21
156.83
140.27
132.99
115.92
115.69
114.43
114.35
60.48
30.79
21.19
14.18
f1 (ppm)

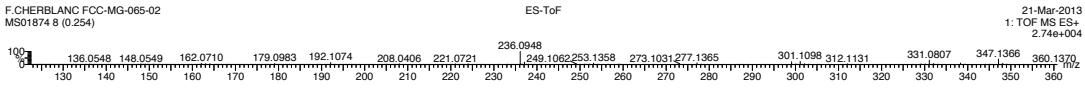

Feb08-2013
FCC-MG-065-02
123.03
123.05
123.07
f1 (ppm)



Elemental Composition Report **Page 1**

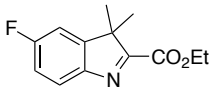
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
246 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 13-13 H: 2-200 N: 0-15 O: 0-15 Na: 0-1 F: 1-1



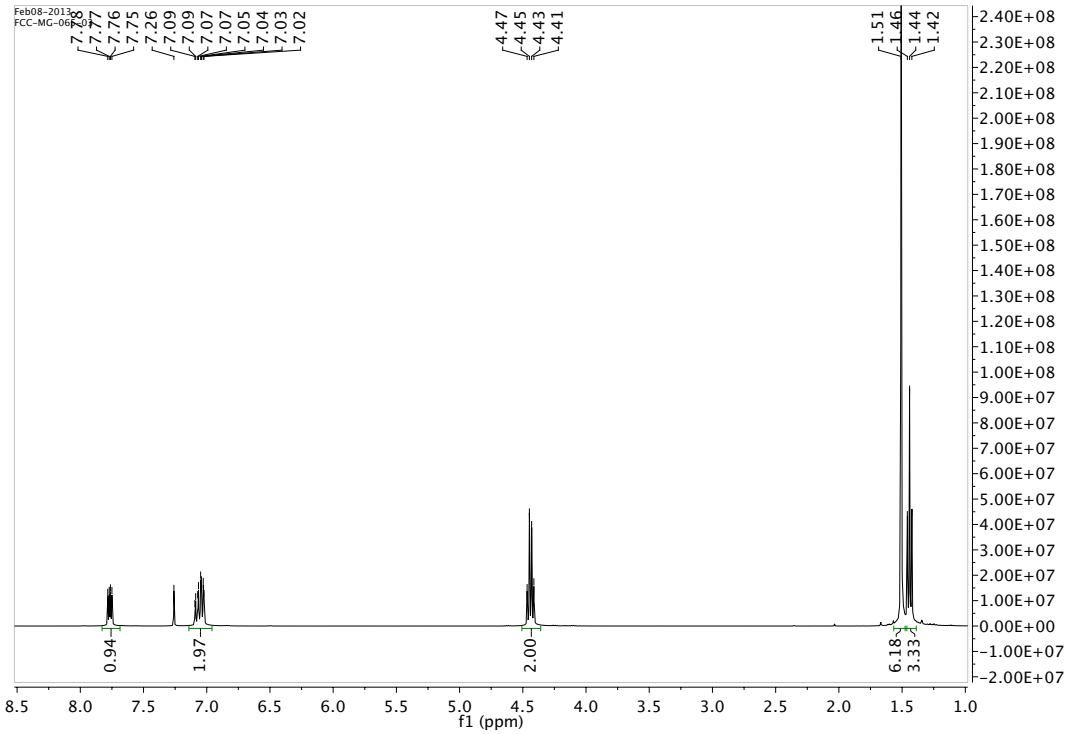
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
253.1358	253.1352	0.6	2.4	5.5	147.0	0.0	C13 H18 N2 O2 F

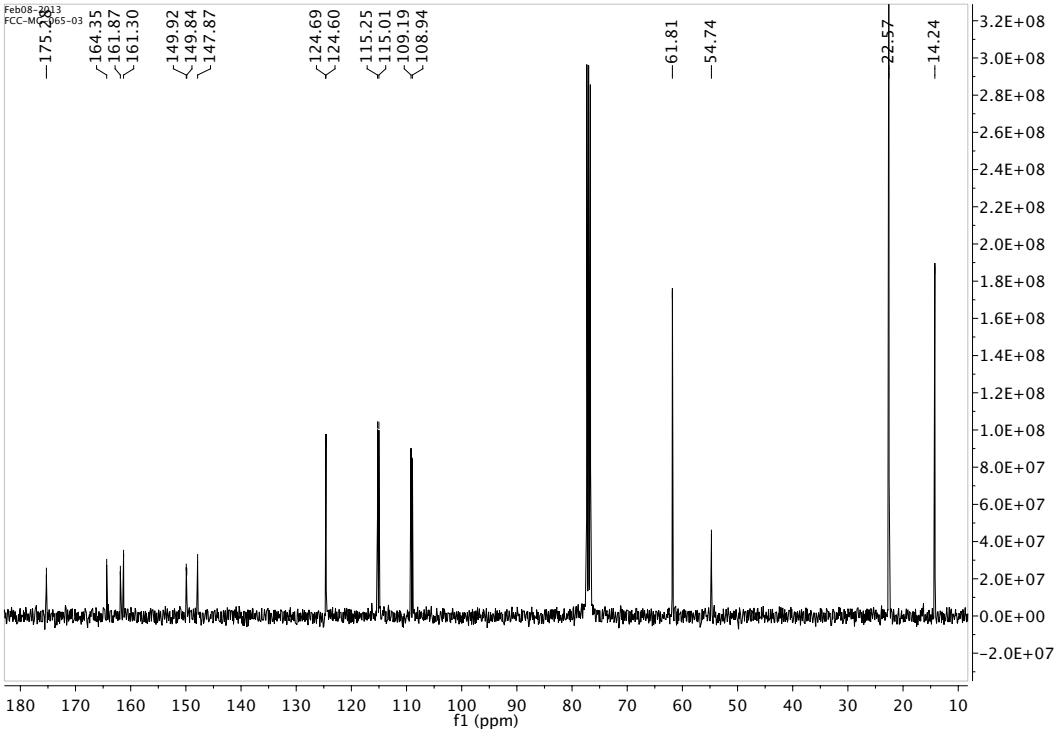
Ethyl 5-fluoro-3,3-dimethyl-3*H*-indole-2-carboxylate (52)

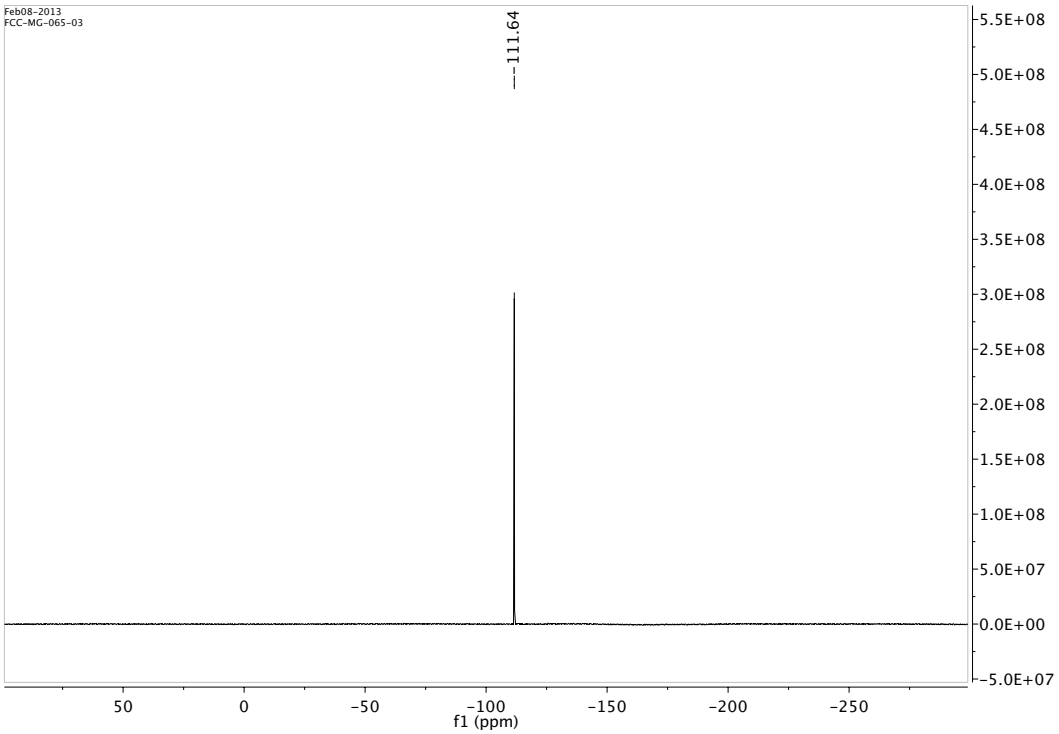


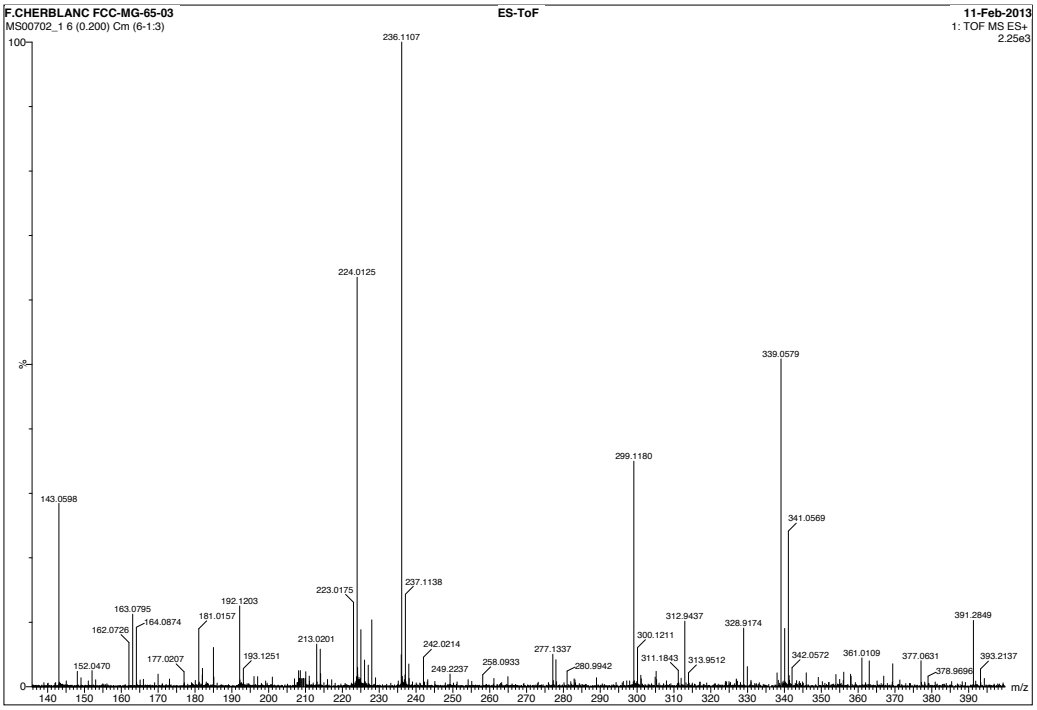
Compound **52** was prepared as follows:[9] A solution of 34% HCl in EtOH was prepared by adding acetyl chloride to EtOH at 0 ˚C. Hydrazone ester **51** (3.250 g, 12.88 mmol) was added to the ethanolic HCl (150 mL) and the mixture was heated to reflux for 10 min. The solvent was then rotatory evaporated to afford a residue that was taken up in Et_2O (100 mL) and treated with 5% aq. Na_2CO_3. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with water until neutral, dried ($MgSO_4$) and

rotatory evaporated. Purification by column chromatography (EtOAc : Hexanes, 1 : 9) afforded indolenine **52** (1.662 g, 55%) as a pale pink solid: m.p. 90 – 92 ˚C; IR (neat) 1710, 1595, 1543, 1461, 1305, 1198, 1093, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 8.4, 4.7 (J_{H-F}) Hz, 1H), 7.09 – 7.02 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.51 (s, 6H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 163.1 (d, J = 250.3 Hz, 1C), 161.3, 149.9 (d, J = 8.6 Hz, 1C) , 147.9, 124.6 (d, J = 9.7 Hz, 1C), 115.1 (d, J = 24.0 Hz, 1C), 109.1 (d, J = 24.9 Hz, 1C), 61.8, 54.7, 22.6 (2C), 14.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ −111.64; MS (ESI) *m/z* 236 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{13}H_{15}FNO_2$ 236.1087, found 236.1107.




Feb08-2013
FCC-MG-065-03
175.20
164.35
161.87
161.30
149.92
149.84
147.87
124.69
124.60
115.25
115.01
109.19
108.94
61.81
54.74
22.57
14.24
f1 (ppm)

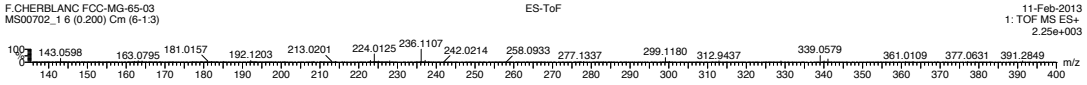

Feb08-2013
FCC-MG-065-03
111.64
f1 (ppm)



Elemental Composition Report **Page 1**

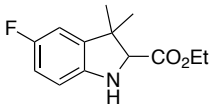
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
183 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 13-13 H: 5-200 N: 0-10 O: 0-10 F: 1-1 Na: 0-1



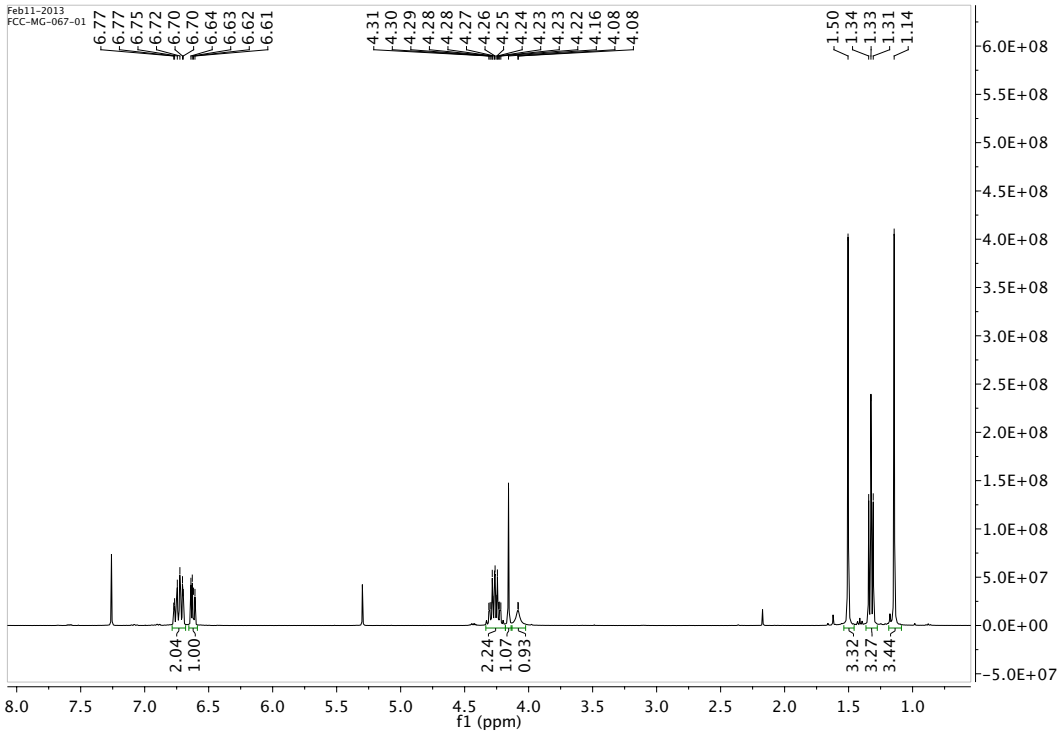
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
236.1107	236.1087	2.0	8.5	6.5	176.5	0.0	C13 H15 N O2 F

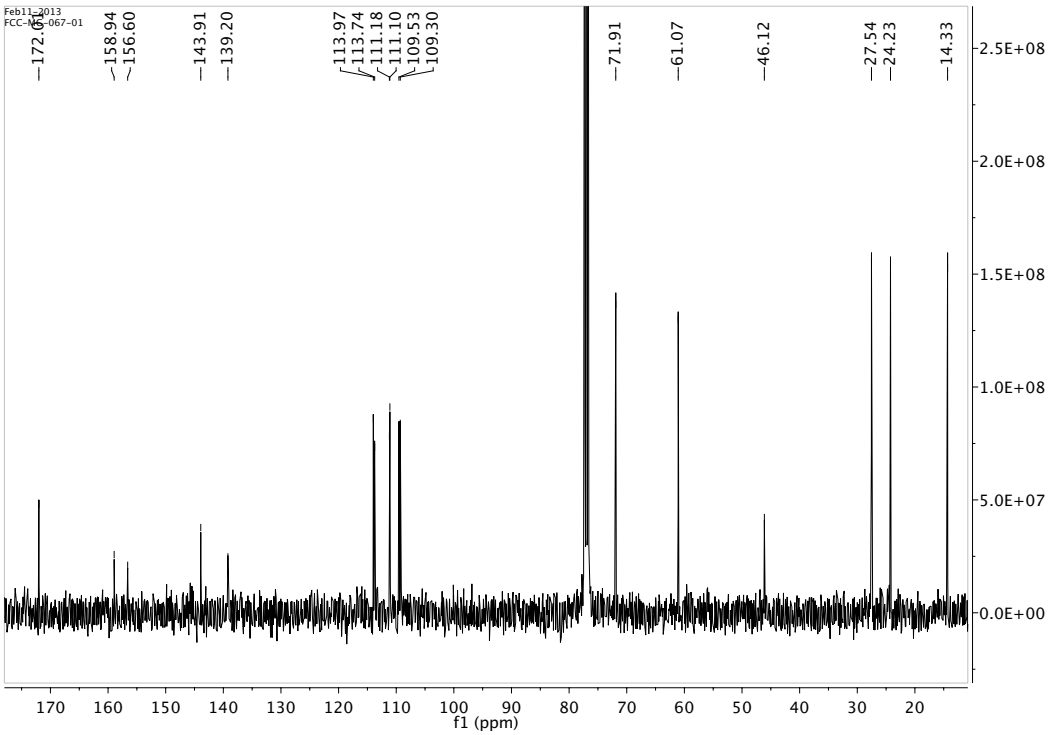
Ethyl 5-fluoro-3,3-dimethylindoline-2-carboxylate (53)

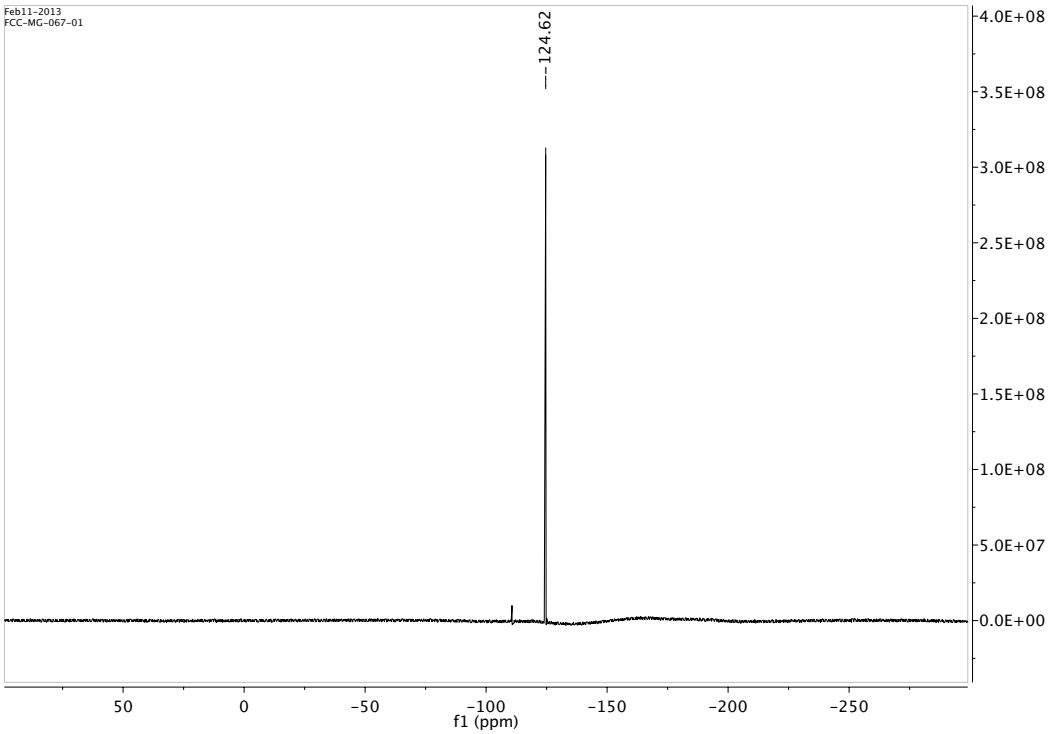


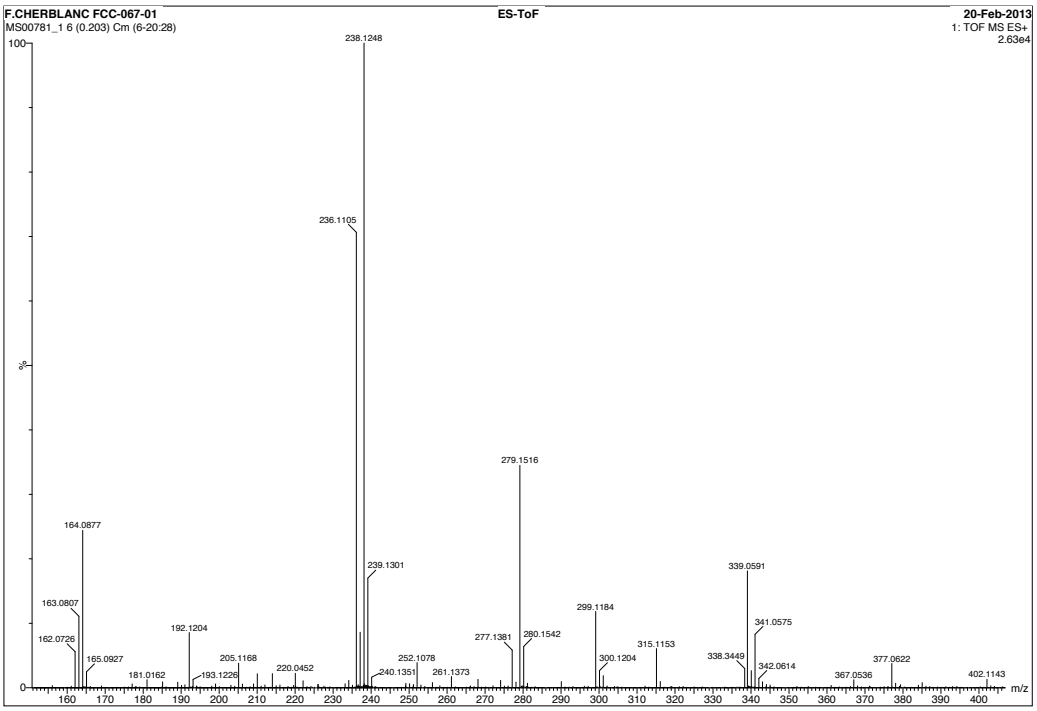
Compound **53** was prepared as follows:[10] To a solution of indolenine **52** (1.445 g, 6.14 mmol) in 28 mL of MeOH and 7 mL of AcOH was added sodium cyanoborohydride (502 mg, 7.98 mmol). The reaction mixture was allowed to stir at room temperature for 18 h. 12 N aq. HCl (2 mL) was then added. The solvent was rotatory evaporated and the obtained residue which was taken up in 5% aq. Na_2CO_3 (50 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and rotatory evaporated to afford title compound **53** as a yellow oil (1.721 g, quant.) that was used in the next step without further

purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.70 (m, 2H), 6.62 (dd, J = 8.3, 4.3 ($J_{H\text{-}F}$) Hz, 1H), 4.31 – 4.22 (m, 2H), 4.16 (s, 1H), 4.08 (br s, 1H), 1.50 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 157.8 (d, J = 234.5 Hz, 1C), 143.9, 139.2 (d, J = 8.2 Hz, 1C), 113.8 (d, J = 23.7 Hz, 1C), 111.1 (d, J = 8.7 Hz, 1C), 109.4 (d, J = 24.1 Hz, 1C), 71.9, 61.1, 46.1, 27.5, 24.2, 14.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ −124.62; MS (ESI) *m/z* 238 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{13}H_{17}FNO_2$ 238.1243, found: 238.1248.




Feb11-2013
FCC-MG-067-01
172.65
158.94
156.60
143.91
139.20
113.97
113.74
111.18
111.10
109.53
109.30
71.91
61.07
46.12
27.54
24.23
14.33
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

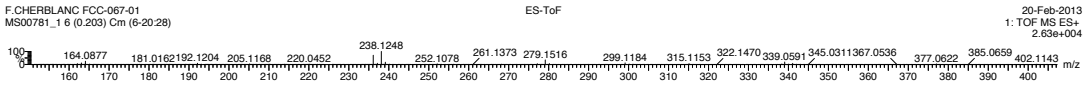

Feb11-2013
FCC-MG-067-01
124.62
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
50 0 -50 -100 -150 -200 -250
f1 (ppm)



Elemental Composition Report **Page 1**

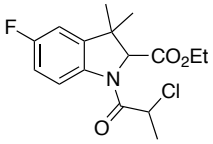
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
185 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 13-13 H: 5-200 N: 0-10 O: 0-10 F: 1-2



Minimum:			-1.5				
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
238.1248	238.1243	0.5	2.1	5.5	308.0	0.0	C13 H17 N O2 F

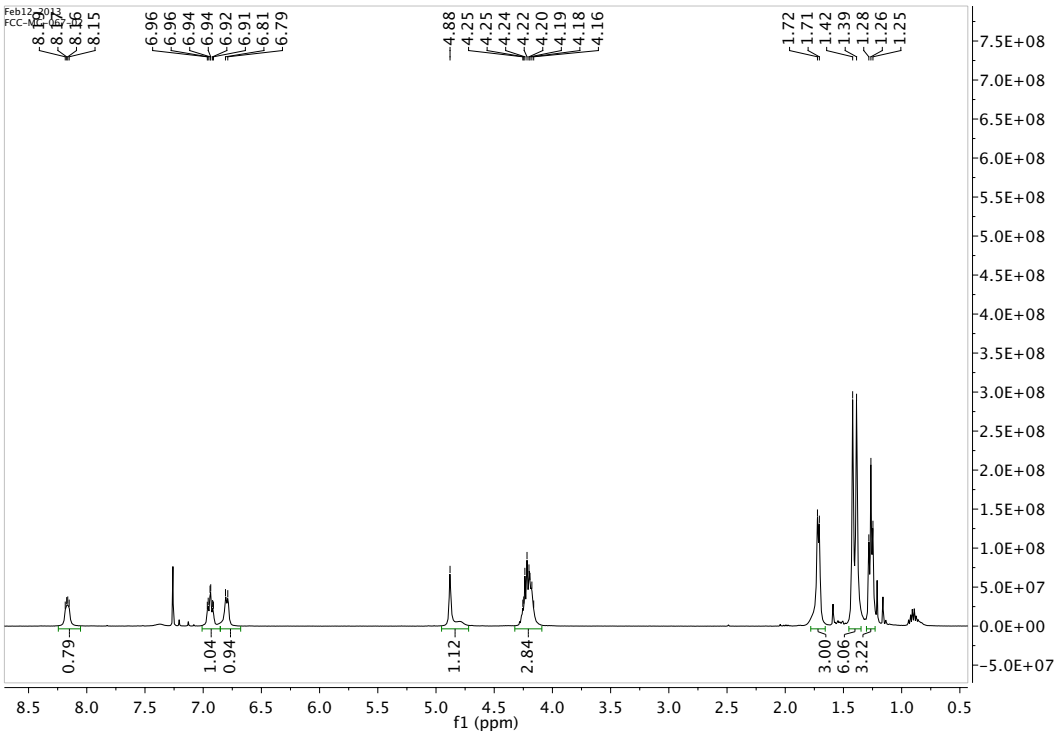
Ethyl 1-(2-chloropropanoyl)-5-fluoro-3,3-dimethylindoline-2-carboxylate (54)

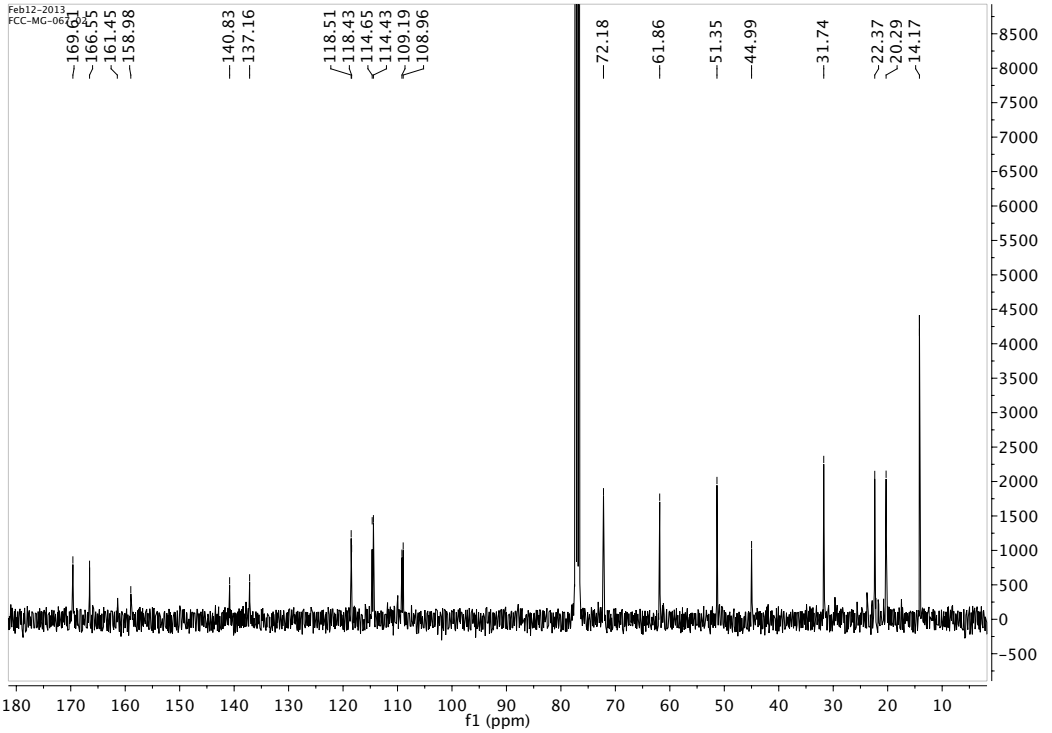


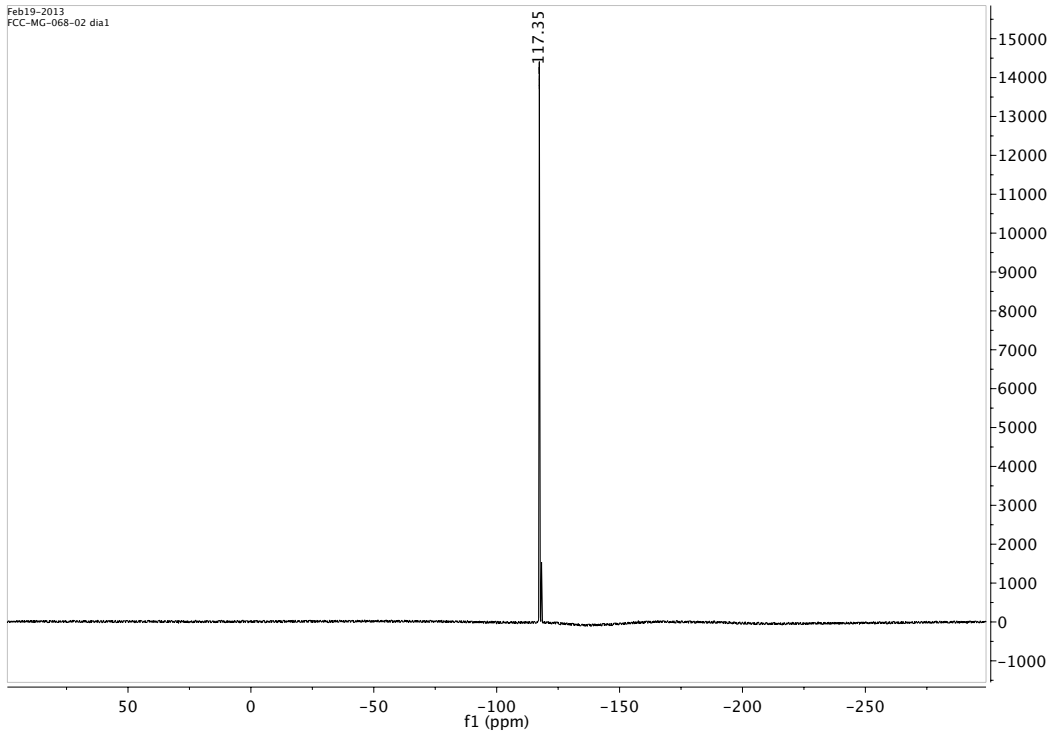
Compound **54** was prepared as follows:[11] 2-Chloropropionyl chloride (0.774 mL, 7.98 mmol) was added dropwise to a solution of triethylamine (1.027 mL, 7.37 mmol) and crude indoline **53** (1.721 g, 6.14 mmol) in chloroform (100 mL) at 0 ˚C. The mixture was allowed to warm to room temperature and stir for a further 4 h. After that time, the reaction mixture was poured into ice-water, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and rotatory evaporated. The residue was purified by column chromatography

(Hexanes : EtOAc, 95 : 5) to afford the title compound **54** as two diastereoisomers as colourless oils (combined mass 1.862 g, 92% over 2 steps): Diastereoisomer 1: IR (neat) 1741, 1674, 1487,1400, 1259, 1199, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 6.94 (td, *J* = 9.0, 2.9 Hz, 1H), 6.80 (br d, *J* = 7.2 Hz, 1H), 4.88 (s, 1H), 4.26 – 4.18 (m, 3H), 1.71 (br d, *J* = 6.1 Hz, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.6, 160.2 (d, *J* = 248.6 Hz, 1C), 140.9 (d, *J* = 4.8 Hz, 1C), 137.2, 118.5 (d, *J* = 7.7 Hz, 1C), 114.5 (d, *J* = 23.3 Hz, 1C), 109.0 (d, *J* = 22,8 Hz, 1C), 72.2, 61.9, 51.3, 45.0, 31.7, 22.4, 20.3, 14.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.35; MS (ESI) *m/z* 328 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{16}H_{20}FNO_3Cl$ 328.1116, found: 328.1118; Diastereoisomer 2: IR (neat) 1740, 1665, 1485,1399, 1257, 1196, 1167 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 6.94 (td, *J* =8.7, 2.5 Hz, 1H), 6.81 (br s, 1H), 4.75 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.76 (br d, *J* = 4.5 Hz, 3H), 1.38 (br s, 6H), 1.24 (br unresolved t, 3H); ^{13}C NMR (100 MHz, DMSO) δ 168.8, 166.8, 160.1 (d, *J* = 240.6 Hz, 1C), 141.4, 137.4, 118.8, 114.4 (d, *J* = 24.2 Hz, 1C), 109.1, 73.3, 61.7, 51.3, 44.8, 31.5, 21.8, 21.1, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.27; MS (ESI) *m/z* 328 ($M+H^+$); HRMS (ESI) *m/z* calc. for $C_{16}H_{20}FNO_3Cl$ 328.1116, found: 328.1117.

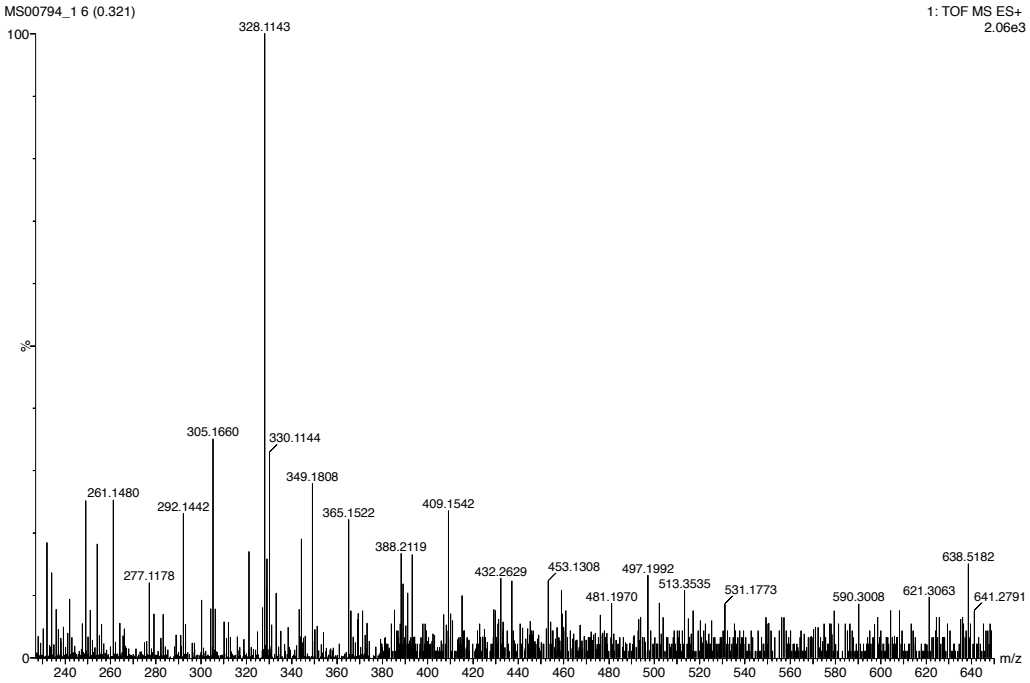
Diastereoisomer 1:




Feb12-2013
FCC-MG-068-02
169.61
166.55
161.45
158.98
140.83
137.16
118.51
118.43
114.65
114.43
109.19
108.96
72.18
61.86
51.35
44.99
31.74
22.37
20.29
14.17
f1 (ppm)


Feb19-2013
FCC-MG-068-02 dia1
117.35
f1 (ppm)

F.CHERBLANC FCC-067-02



Elemental Composition Report

Single Mass Analysis

Tolerance = 25.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

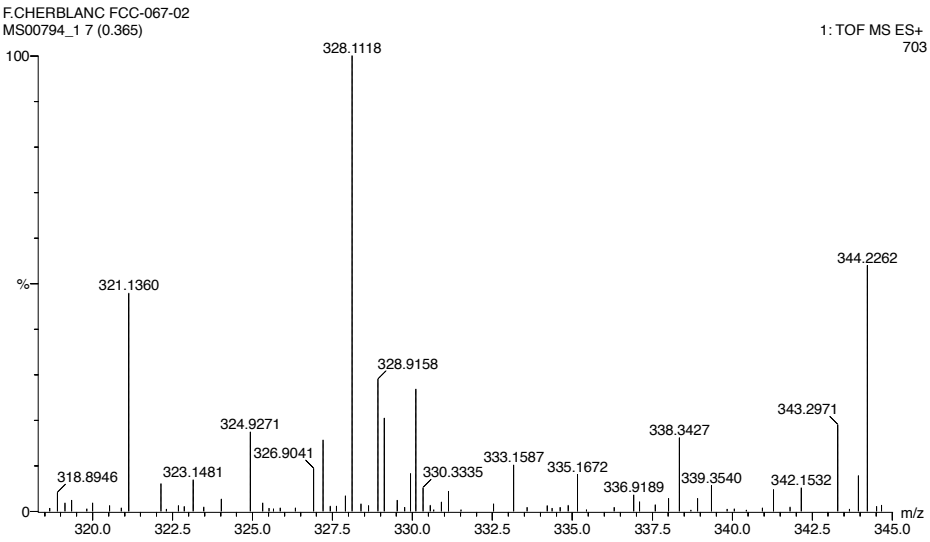
Monoisotopic Mass, Even Electron Ions

457 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

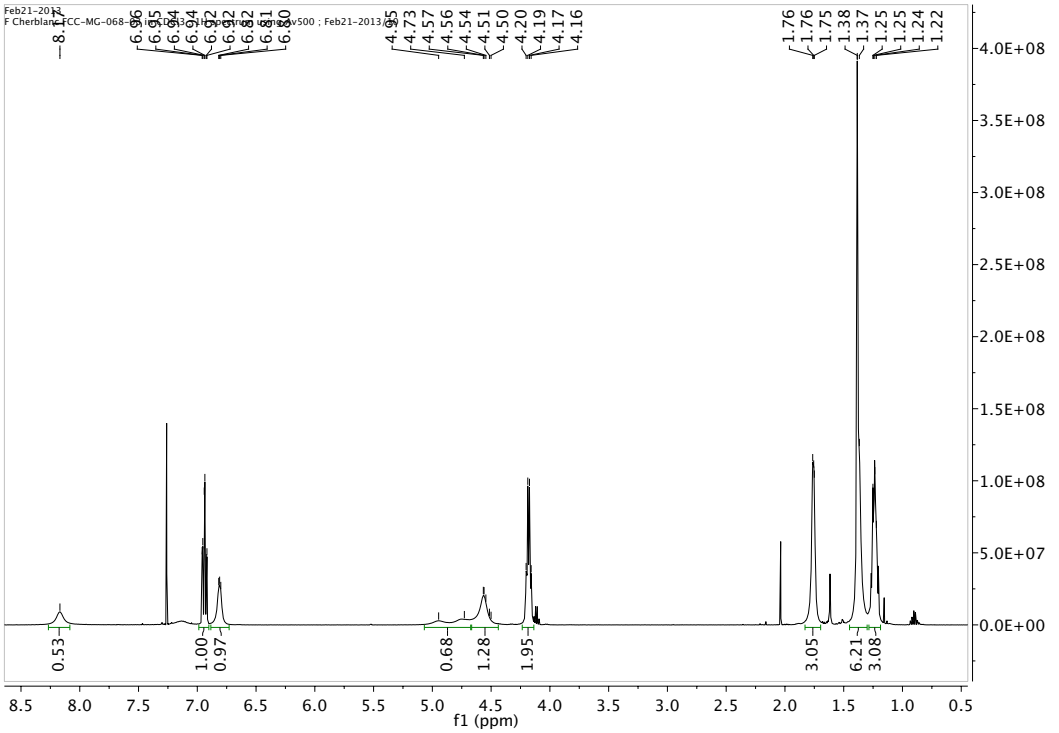
C: 16-16 H: 0-300 N: 0-10 O: 0-10 Na: 0-1 Cl: 1-1 F: 0-1

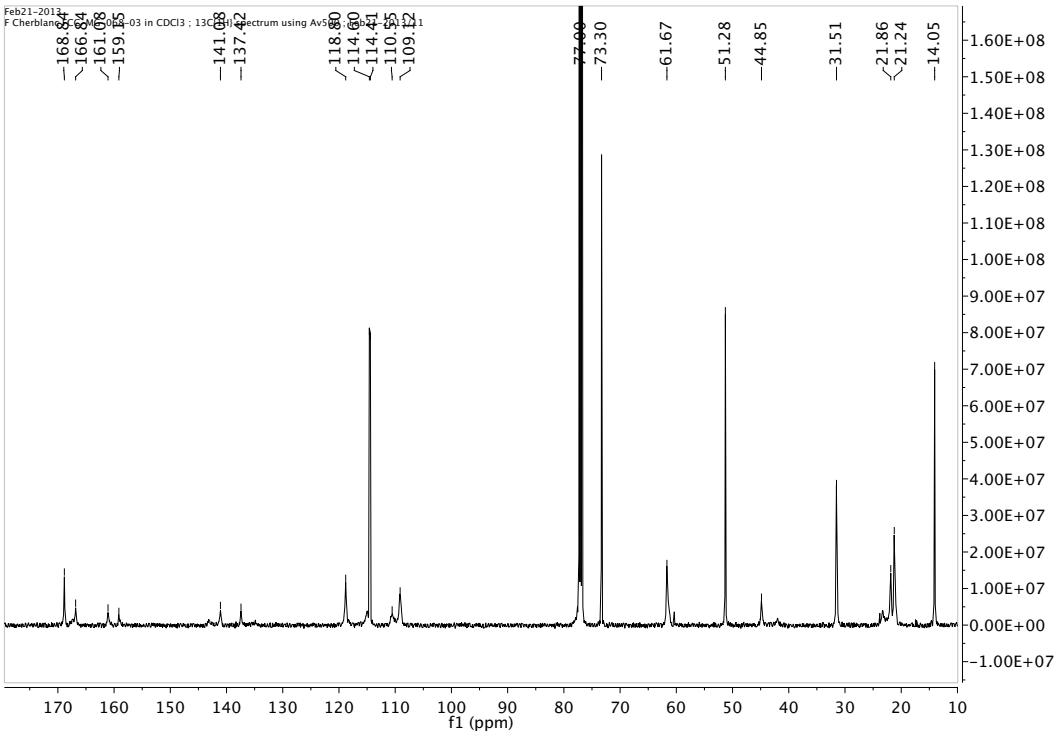
F.CHERBLANC FCC-067-02

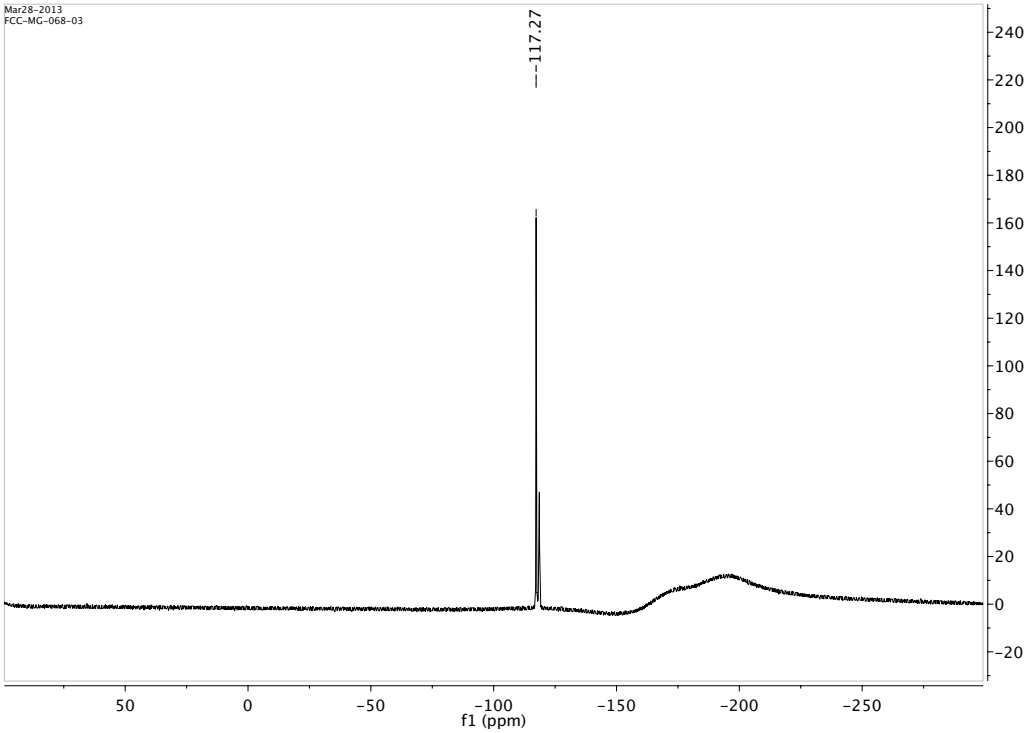


Minimum:				-1.5		
Maximum:		5.0	25.0	50.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
328.1118	328.1116	0.2	0.6	6.5	6.5	C16 H20 N O3 Cl F
	328.1193	-7.5	-22.9	7.5	6.9	C16 H20 N3 O Na Cl

Diastereoisomer 2:







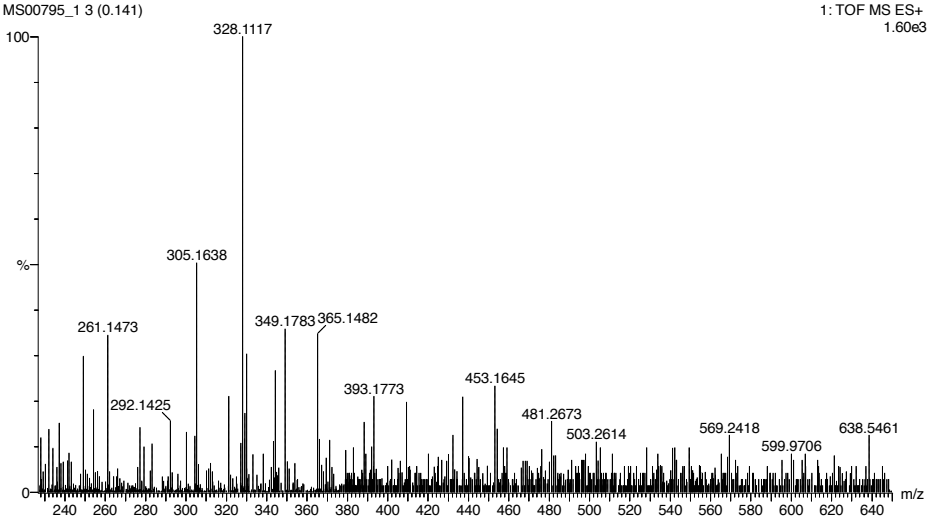
Elemental Composition Report

Single Mass Analysis

Tolerance = 25.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

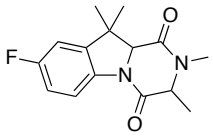
Monoisotopic Mass, Even Electron Ions
457 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 16-16 H: 0-300 N: 0-10 O: 0-10 F: 0-1 Na: 0-1 Cl: 1-1

F.CHERBLANC FCC-067-03
MS00795_1 3 (0.141)



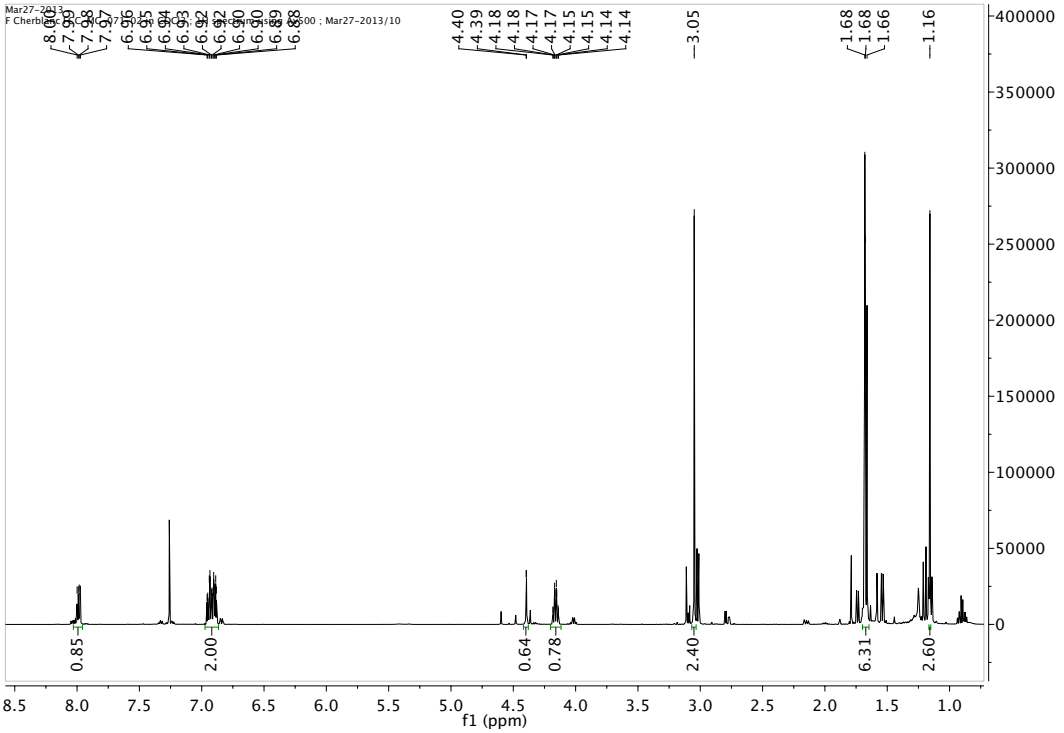
Minimum:				-1.5		
Maximum:		5.0	25.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
328.1117	328.1116	0.1	0.3	6.5	3.1	C16 H20 N O3 F Cl
	328.1193	-7.6	-23.2	7.5	7.0	C16 H20 N3 O Na Cl

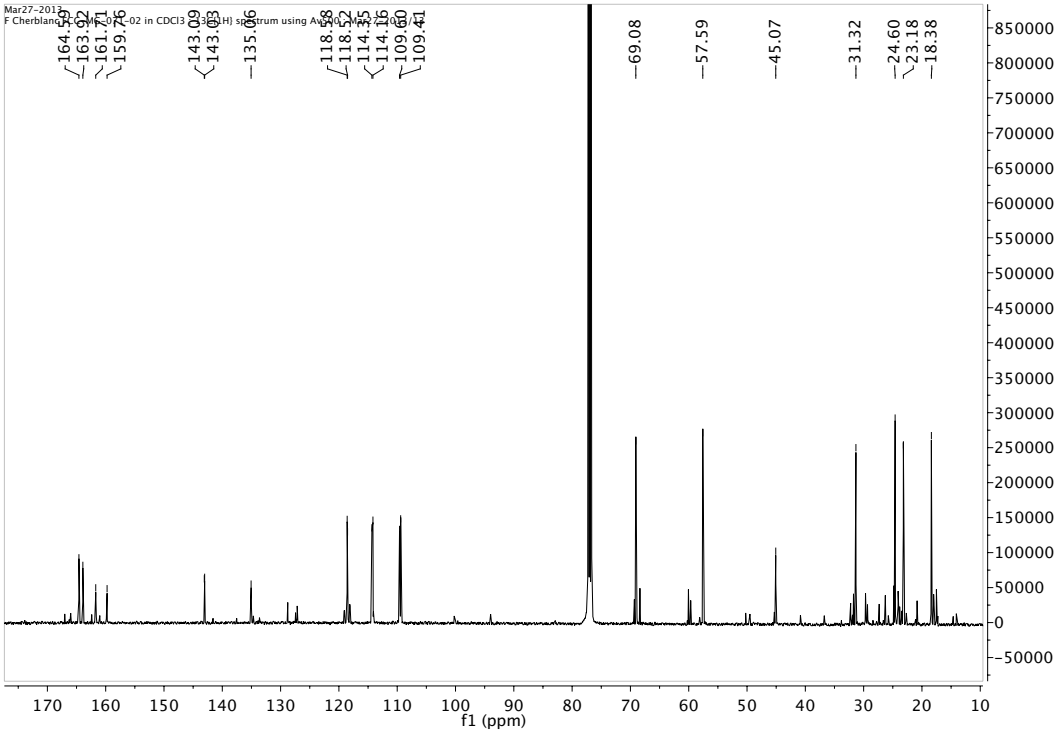
8-Fluoro-2,3,10,10-tetramethyl-2,3,10,10a-tetrahydropyrazino[1,2-*a*]indole-1,4-dione (55)

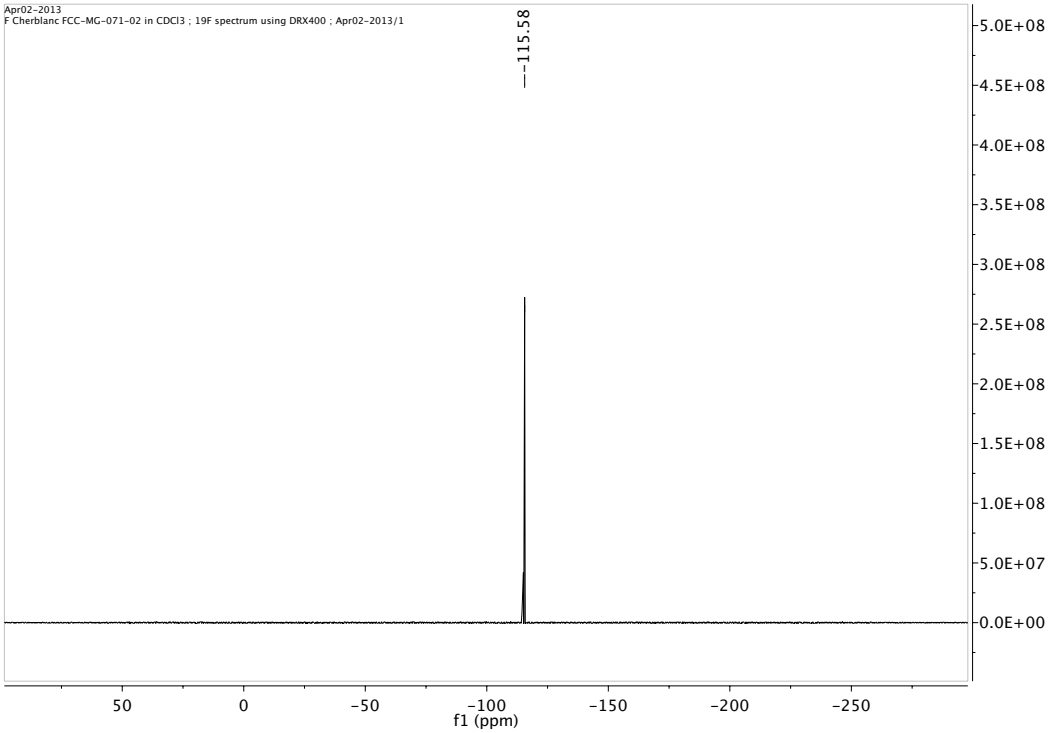


Compound **55** was prepared as follows:[11] Potassium carbonate (1.209 mg, 9.1 mmol) and an excess of methylamine (31 mL of a 2M solution in THF, 61.0 mmol) were added to a solution of acylated indoline **54** (2.000 g, 6.1 mmol) in MeCN (20 mL) in a sealed tube. After refluxing for 18 h, the reaction mixture was filtered, concentrated and the residue was purified by column chromatography (Hexanes : EtOAc, 1 : 1) to afford the title compound **55** as a mixture of non-separable diastereoisomers as a colorless oil (1.554 g, 92%): IR (neat) 1665, 1611, 1482, 1418, 1400 cm^{-1}; Diastereoisomer 1 (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.6, 4.7 (J_{H-F}) Hz, 1H), 6.94 (*app*-td, J = 8.7 (J_{H-F} and J_{H-H}), 2.7 Hz, 1H), 6.89 (dd, J = 8.1 (J_{H-F}), 2.6 Hz, 1H), 4.40 (d, J = 1.7 Hz, 1H, *cis coupling*, confirmed by NOESY), 4.17 (qd, J = 6.7, 1.7 Hz, 1H, *cis coupling*, confirmed by NOESY), 3.05 (s, 3H), 1.68 (s, 3H), 1.67 (d, J = 6.7 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.9, 160.7 (d, J = 244.4 Hz, 1C), 143.0 (d, J = 7.8 Hz, 1C), 135.0, 118.5 (d, J = 8.8 Hz, 1C), 114.2 (d, J = 22.7 Hz, 1C), 109.5 (d, J = 23.8 Hz, 1C), 69.1, 57.6, 45.1, 31.3, 24.6, 23.2, 18.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −115.58; Diastereoisomer 2 (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.7, 4.7 (J_{H-F}) Hz, 1H), 6.94 (*app*-td, J = 8.8 (J_{H-F} and J_{H-H}), 2.5 Hz, 1H), 6.89 (dd, J = 8.1 (J_{H-F}), 2.7 Hz, 1H), 4.36 (s, 1H), 4.01 (q, J = 7.0 Hz, 1H), 3.01 (s, 3H), 1.68 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 164.6, 160.6 (d, J = 244.3 Hz, 1C), 143.0 (d, J = 7.4 Hz, 1C), 134.7, 118.1 (d, J = 8.7 Hz, 1C), 114.3 (d, J = 23.4 Hz, 1C), 109.4 (d, J = 23.4 Hz, 1C), 68.3, 60.0, 45.3, 31.7, 24.8, 24.1, 17.5; MS (ESI) m/z 277 ($M+H^+$), 225, 214, 206; HRMS (ESI) *m/z* calc. for $C_{15}H_{18}FN_2O_2$ 277.1352, found: 277.1359.

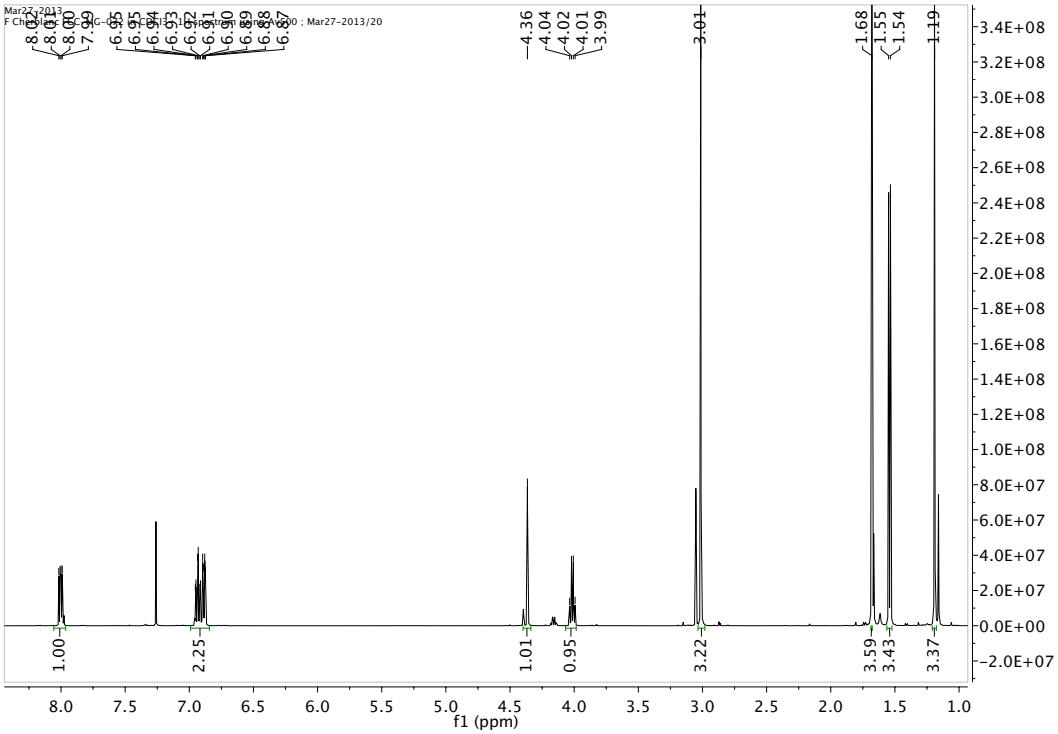
Diastereoisomer 1 (*cis*, major):

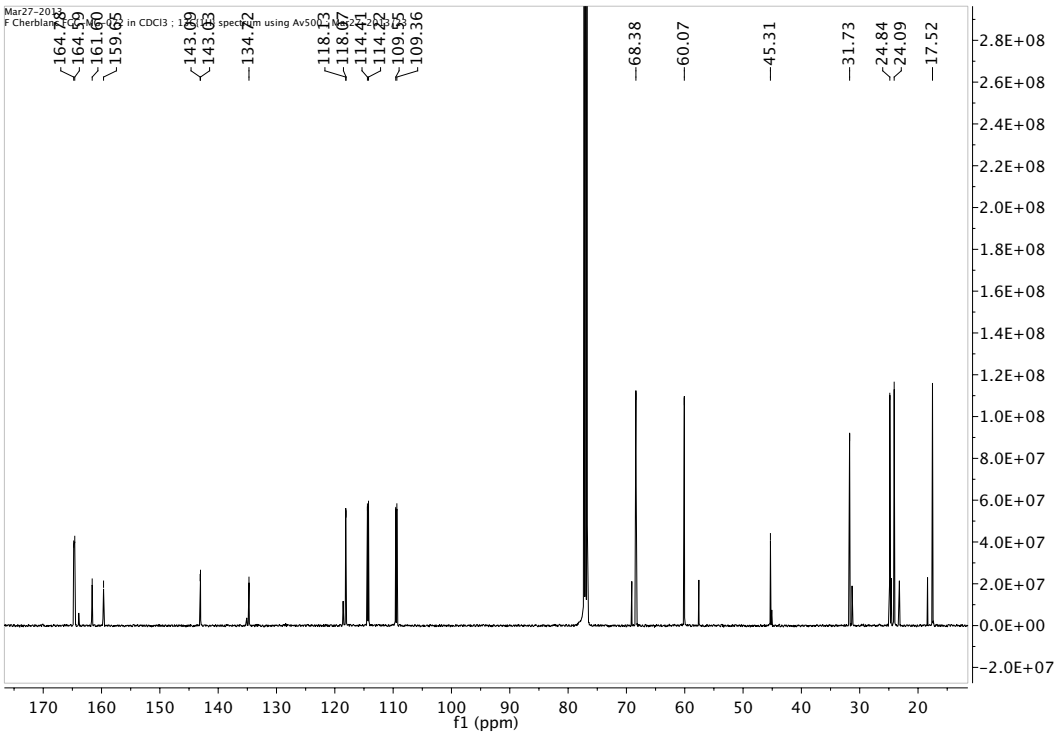

8.00
7.99
7.98
7.97
6.96
6.95
6.94
6.93
6.92
6.92
6.90
6.90
6.89
6.88
4.40
4.39
4.18
4.18
4.17
4.17
4.15
4.15
4.14
4.14
3.05
1.68
1.68
1.66
1.16
0.85
2.00
0.64
0.78
2.40
6.31
2.60
f1 (ppm)

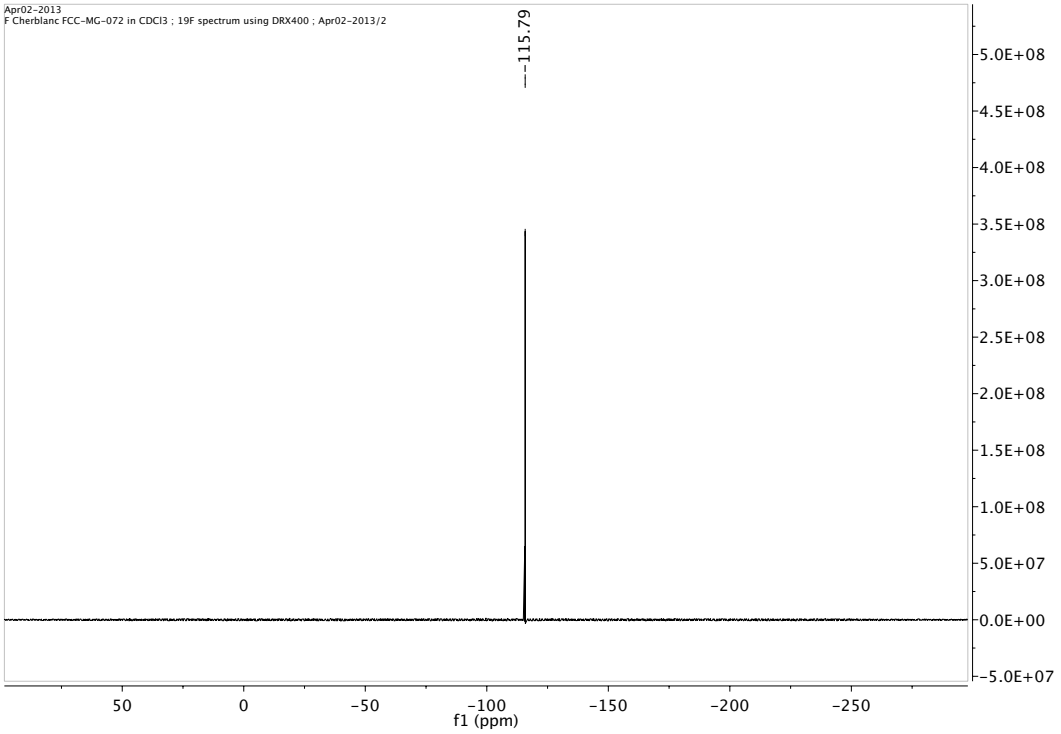

164.59
163.92
161.71
159.76
143.09
143.03
135.06
118.58
118.52
114.35
114.16
109.60
109.41
69.08
57.59
45.07
31.32
24.60
23.18
18.38
f1 (ppm)

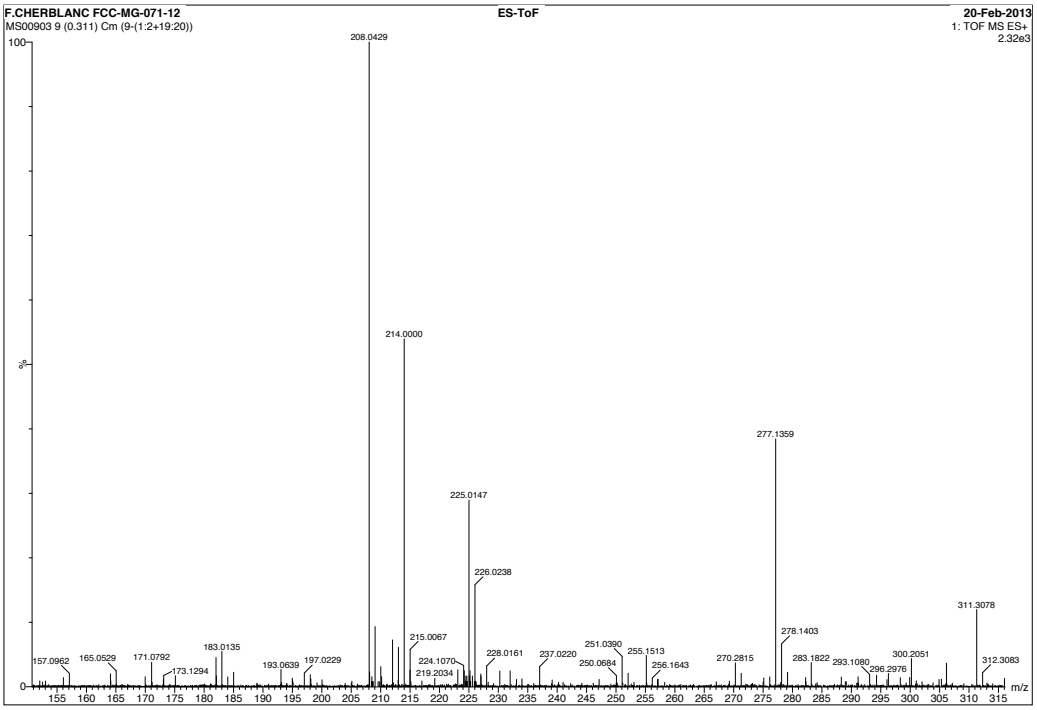


Diastereoisomer 2 (*trans*, major)




Mar27-2013
F Cherblanc FCC-MG-072 in CDCl3 ; 13C{1H} spectrum using Av500 ; Mar27-2013/2
164.78
164.59
161.60
159.65
143.09
143.03
134.72
118.13
118.07
114.41
114.22
109.55
109.36
68.38
60.07
45.31
31.73
24.84
24.09
17.52
f1 (ppm)


Apr02-2013
F Cherblanc FCC-MG-072 in CDCl3 ; 19F spectrum using DRX400 ; Apr02-2013/2
-115.79
f1 (ppm)

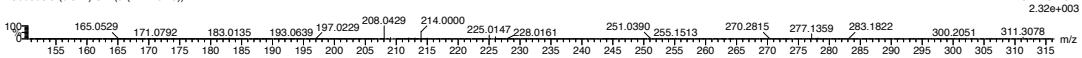


Elemental Composition Report **Page 1**

Single Mass Analysis
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Element prediction: Off
Number of isotope peaks used for i-FIT = 3

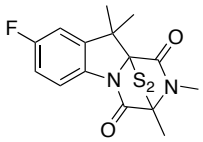
Monoisotopic Mass, Even Electron Ions
584 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 15-15 H: 5-200 B: 0-1 N: 0-10 O: 0-10 F: 1-1 S: 0-2

F.CHERBLANC FCC-MG-071-12
MS00903 9 (0.311) Cm (9-(1:2+19:20))
ES-ToF
20-Feb-2013
1: TOF MS ES+
2.32e+003



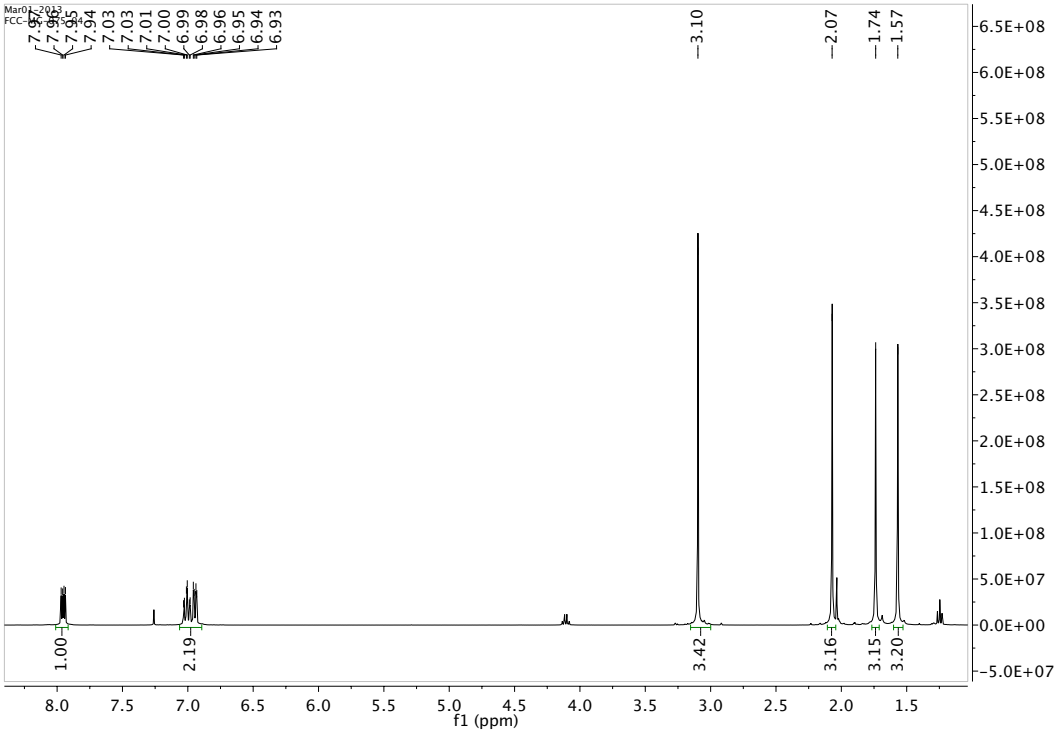
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
277.1359	277.1352	0.7	2.5	7.5	108.2	0.0	C15 H18 N2 O2 F

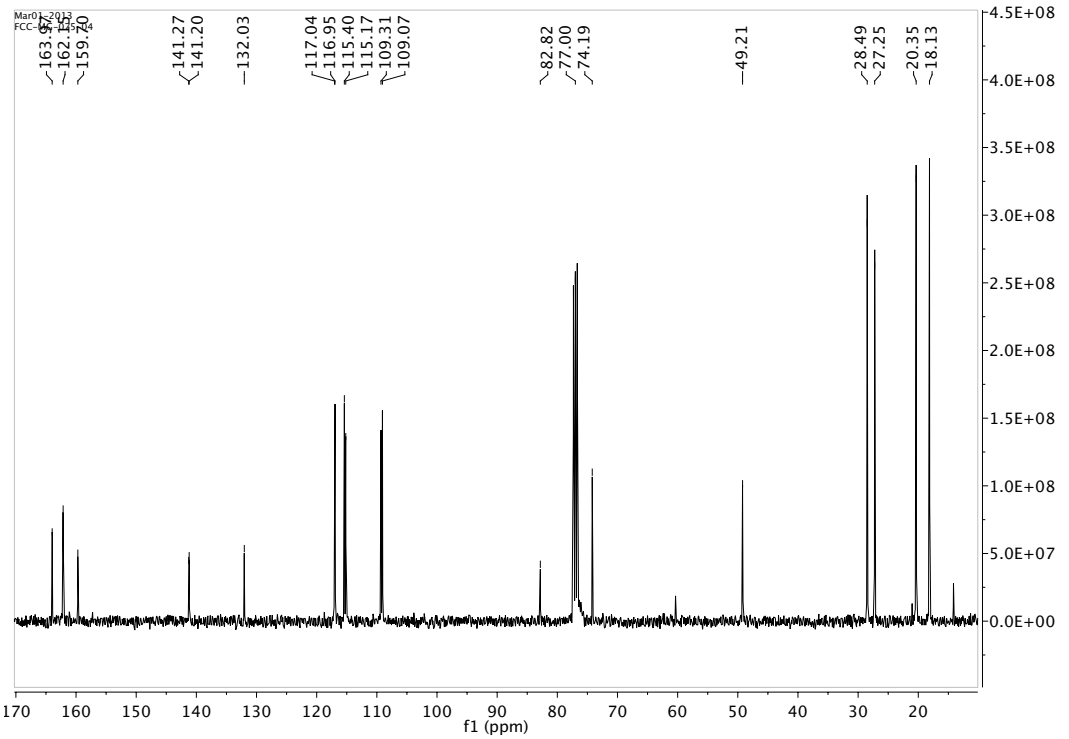
8-Fluoro-2,3,10,10-tetramethyl-2,3-dihydro-1*H*-3,10a-epithiopyrazino[1,2-*a*]indole-1,4(10*H*)-dione 11-sulfide (49)

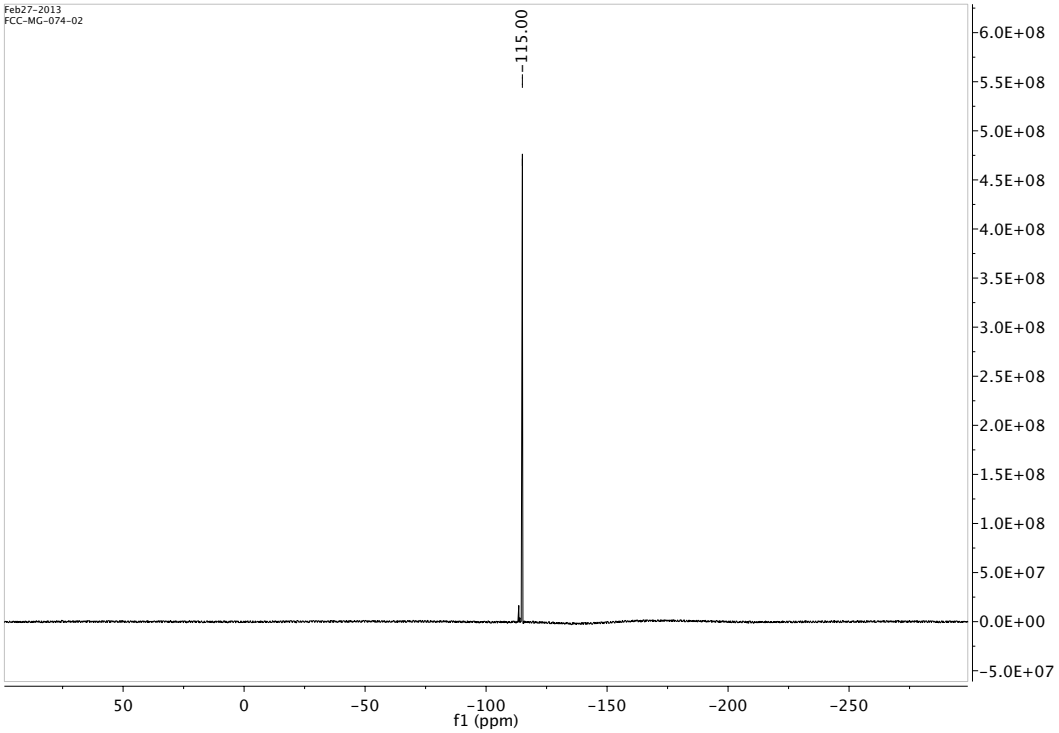


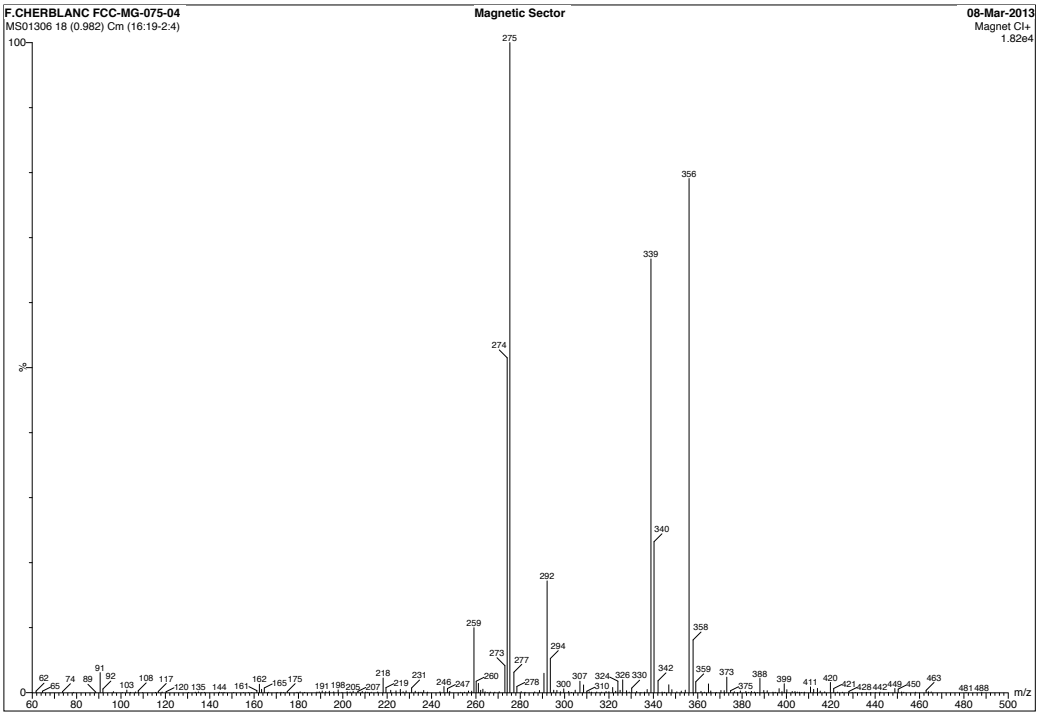
Compound **49** was prepared as follows:[13,14] NaHMDS (9.2 mL of a 0.6 M solution in PhMe, 5.48 mmol) was added dropwise to a solution of elemental sulfur (468 mg, 14.62 mmol) in dry THF (73 mL) at room temperature. The solution was allowed to stir for 1 min, time after which diketopiperazine **55** (500 mg, 1.83 mmol) in THF (9 mL) was added dropwise. The solution was allowed to stir for 1 min and additional NaHDMS (6.1 mL of a 0.6 M solution in PhMe, 3.66 mmol) was added. The resulting

orange / light brown mixture was allowed to stir for 30 min at room temperature. The solution was then quenched with aq. sat. NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a dark green residue which was taken up in a degassed mixture of THF – EtOH (1:1, 36 mL) and cooled to 0 ˚C. Sodium borohydride (1.730 g, 45.70 mmol) was then added in small portions and the resulting mixture was allowed to warm up to room temperature and to stir for 45 min. After that time, the solution was cooled to 0 ˚C and quenched by addition of aq. sat. NH_4Cl. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were then treated with an aqueous solution of KI_3 (1.4 M), until the dark purple colour persisted. The mixture was allowed to stir for 10 min and quenched with 5% aq. $Na_2S_2O_3$ solution until disappearance of the dark purple colour. The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and rotatory evaporated. The residue was purified by column chromatography (Hexanes : EtOAc, 90 : 10) to afford the racemic title compound **49** as a yellow solid (262 mg, 42%) which was recrystalised from CH_2Cl_2 to afford yellow crystals: m.p. 138 – 140 ˚C; IR (neat) 1686, 1486, 1357, 1316, 1259, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.8, 4.5 ($J_{H\text{-}F}$) Hz, 1H), 7.01 (*app*-td, J = 8.8 ($J_{H\text{-}F}$ and $J_{H\text{-}H}$), 2.6 Hz, 1H), 6.95 (dd, J = 7.9 ($J_{H\text{-}F}$), 2.6 Hz, 1H), 3.10 (s, 3H), 2.07 (s, 3H), 1.74 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.2, 161.0 (d, J = 247.2 Hz, 1C), 141.2 (d, J = 7.7 Hz, 1C), 132.03, 117.0 (d, J = 9.4 Hz, 1C), 115.3 (d, J = 23.5 Hz, 1C), 109.1 (d, J = 24.7 Hz, 1C), 82.8, 74.2, 49.2, 28.5, 27.3, 20.4, 18.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ −115.00; MS (CI) *m/z* 356 $(M+NH_4)^+$, 339 $(M+H)^+$, 275 $(M\text{-}S_2+H)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{16}FN_2O_2S_2$ 339.0637, found: 339.0631. The two enantiomers could be separated by chiral HPLC (OD+ semiprep column, Hexane : Isopropanol, 1 : 1): First peak: $[\alpha]_D^{20}$ −419 (*c* 1.05, $CHCl_3$), Second peak $[\alpha]_D^{20}$ +300 (*c* 1.05, $CHCl_3$).


7.95
7.94
7.03
7.01
7.00
6.99
6.98
6.96
6.95
6.94
6.93
3.10
2.07
1.74
1.57
1.00
2.19
3.42
3.16
3.15
3.20
f1 (ppm)


163.97
162.15
159.70
141.27
141.20
132.03
117.04
116.95
115.40
115.17
109.31
109.07
82.82
77.00
74.19
49.21
28.49
27.25
20.35
18.13
f1 (ppm)


Feb27-2013
FCC-MG-074-02
-115.00
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
50
0
-50
-100
-150
-200
-250
f1 (ppm)

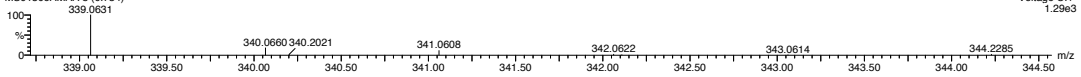

F.CHERBLANC FCC-MG-075-04
MS01306 18 (0.982) Cm (16:19-2:4)
Magnetic Sector
08-Mar-2013
Magnet CI+
1.82e4
100
%
0
275
274
356
339
340
292
259
358
273
294
277
m/z
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

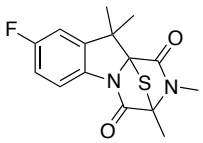
Monoisotopic Mass, Odd and Even Electron Ions
213 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 15-15 H: 0-500 N: 0-10 O: 0-10 S: 2-3 F: 1-1

F.CHERBLANC FCC-MG-075-04 AM +H
MS01306AMAA 8 (0.734)
Magnetic Sector
08-Mar-2013
Voltage CI+
1.29e3

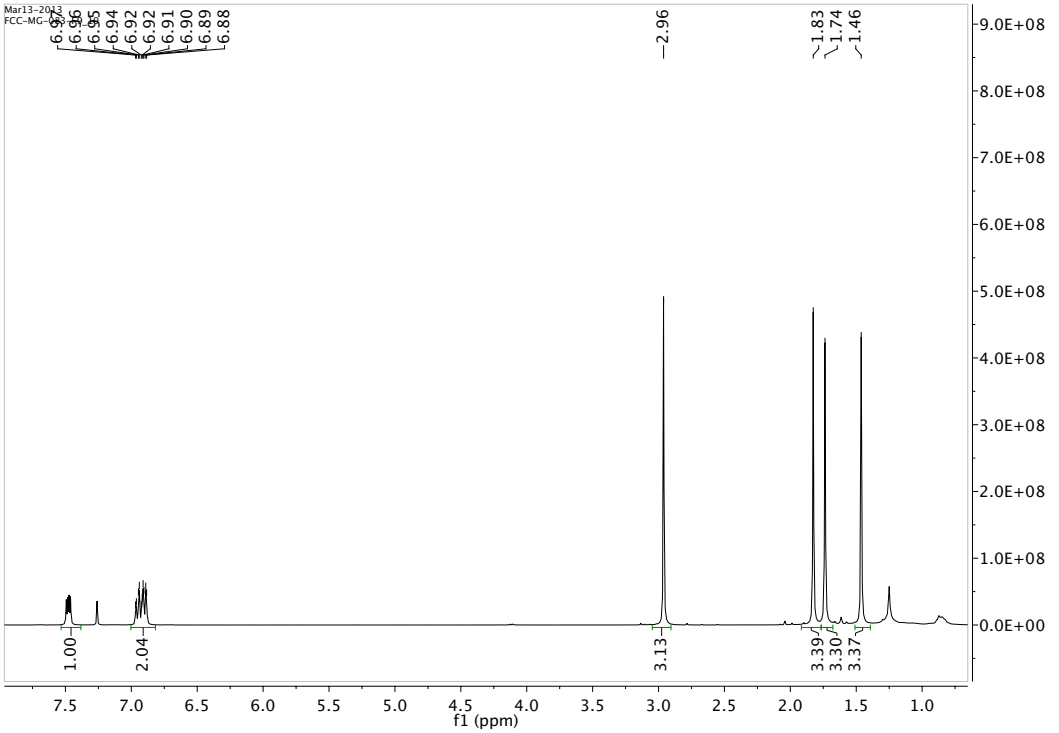


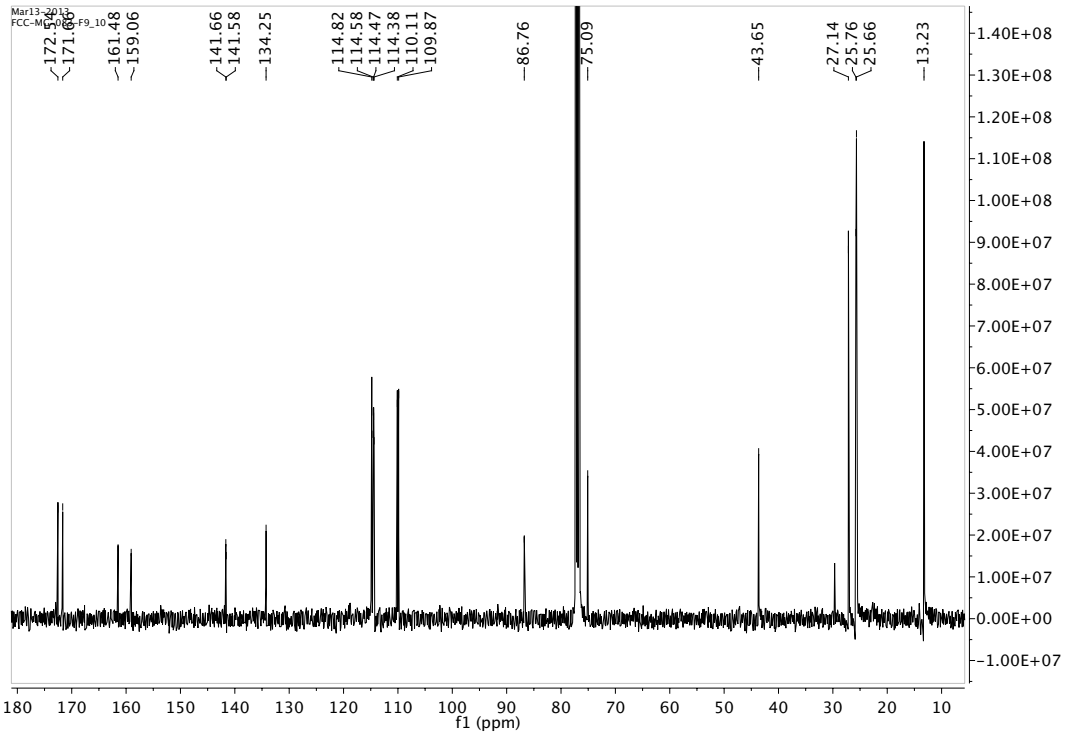
Minimum:				-1.5		
Maximum:		7.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
339.0631	339.0637	-0.6	-1.8	8.5	0.7	C15 H16 N2 O2 S2 F

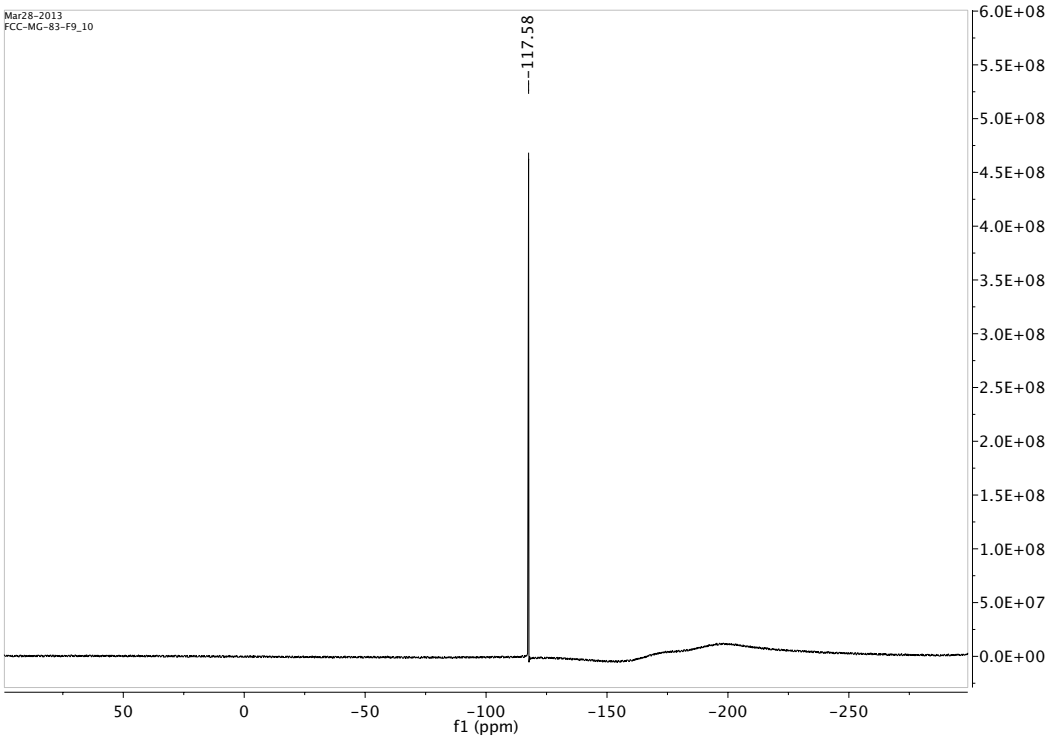
8-Fluoro-2,3,10,10-tetramethyl-2,3-dihydro-1*H*-3,10a-epithiopyrazino[1,2-*a*]indole-1,4(10*H*)-dione (50)

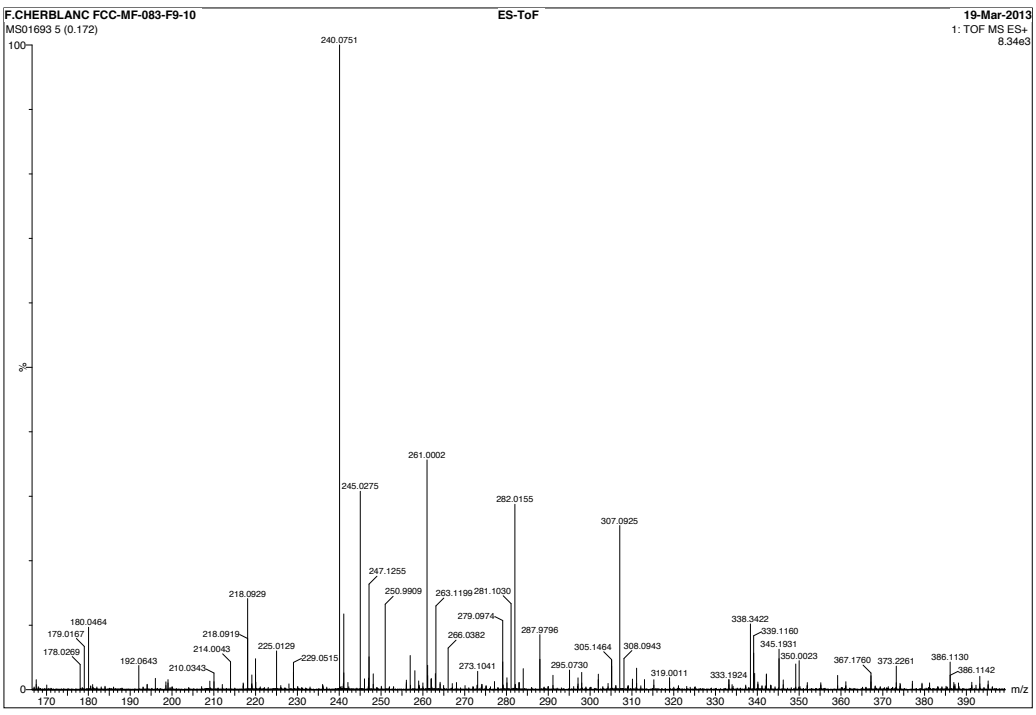


Compound **50** was prepared as follows:[5] PPh_3 (187 mg, 0.71 mmol) was added to a solution of F-ETP **49** (100 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was allowed to stir for 1 h at room temperature. The solvent was rotatory evaporated and the orange residue was purified by column chromatography (Hexanes : EtOAc, 97 : 3 to 93 : 7) to afford the title compound **50** as a white solid (45.5 mg, 50%): m.p. 126 – 128 °C; IR (neat) 1720, 1487, 1301, 1259, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 8.6, 4.5 ($J_{H\text{-}F}$) Hz, 1H), 6.94 (*app*-td, J = 8.6 ($J_{H\text{-}F}$ and $J_{H\text{-}H}$), 2.5 Hz, 1H), 6.90 (dd, J = 8.1 ($J_{H\text{-}F}$), 2.5 Hz, 1H), 2.96 (s, 3H), 1.83 (s, 3H), 1.74 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 160.3 (d, J = 242.3 Hz, 1C), 141.6 (d, J = 8.0 Hz, 1C), 134.3, 114.7 (d, J = 24.5 Hz, 1C), 114.4 (d, J = 9.7 Hz, 1C), 110.0 (d, J = 24.1 Hz, 1C), 86.8, 75.1, 43.7, 27.1, 25.8, 25.7, 13.2; MS (ESI) *m/z* 307 $(M+H)^+$, 240; HRMS (ESI) *m/z* calc. for $C_{15}H_{16}FN_2O_2S$ 307.0917, found: 307.0925. The obtained enantiomers could be separated by chiral HPLC (OD+ semiprep column, Hexane : Isopropanol, 90 : 10). First peak: $[\alpha]_D^{20}$ −32.2 (*c* 1.01, $CHCl_3$), Second peak $[\alpha]_D^{20}$ +30.7 (*c* 1.03, $CHCl_3$).


Mar13-2013
FCC-MG-02
6.96
6.95
6.94
6.92
6.92
6.91
6.90
6.89
6.88
2.96
1.83
1.74
1.46
1.00
2.04
3.13
3.39
3.30
3.37
f1 (ppm)


Mar13-2013
FCC-MG-02-F9_10
172.27
171.65
161.48
159.06
141.66
141.58
134.25
114.82
114.58
114.47
114.38
110.11
109.87
86.76
75.09
43.65
27.14
25.76
25.66
13.23
f1 (ppm)


Mar28-2013
FCC-MG-83-F9_10
-117.58
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
50
0
-50
-100
-150
-200
-250
f1 (ppm)

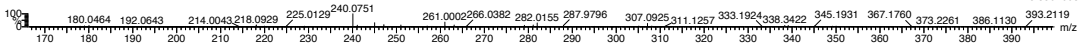

F.CHERBLANC FCC-MF-083-F9-10
ES-ToF
19-Mar-2013
MS01693 5 (0.172)
1: TOF MS ES+
8.34e3
100
%
0
240.0751
261.0002
245.0275
282.0155
307.0925
247.1255
250.9909
263.1199
281.1030
218.0929
279.0974
180.0464
179.0167
218.0919
225.0129
214.0043
178.0269
192.0643
210.0343
229.0515
266.0382
273.1041
287.9796
295.0730
305.1464
308.0943
319.0011
333.1924
338.3422
339.1160
345.1931
350.0023
367.1760
373.2261
386.1130
386.1142
170
180
190
200
210
220
230
240
250
260
270
280
290
300
310
320
330
340
350
360
370
380
390
m/z

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
863 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
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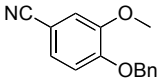
F.CHERBLANC FCC-MF-083-F9-10 ES-ToF 19-Mar-2013
MS01693 5 (0.172) 1: TOF MS ES+
8.35e+003



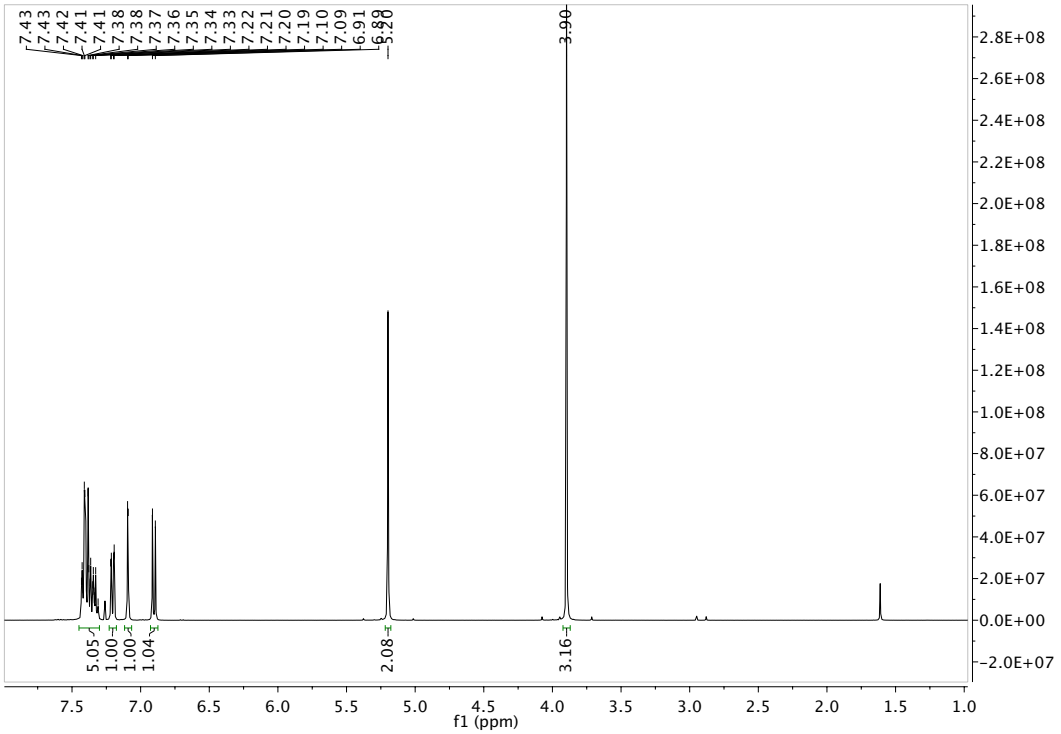
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
307.0925	307.0917	0.8	2.6	8.5	327.5	0.0	C15 H16 N2 O2 F S

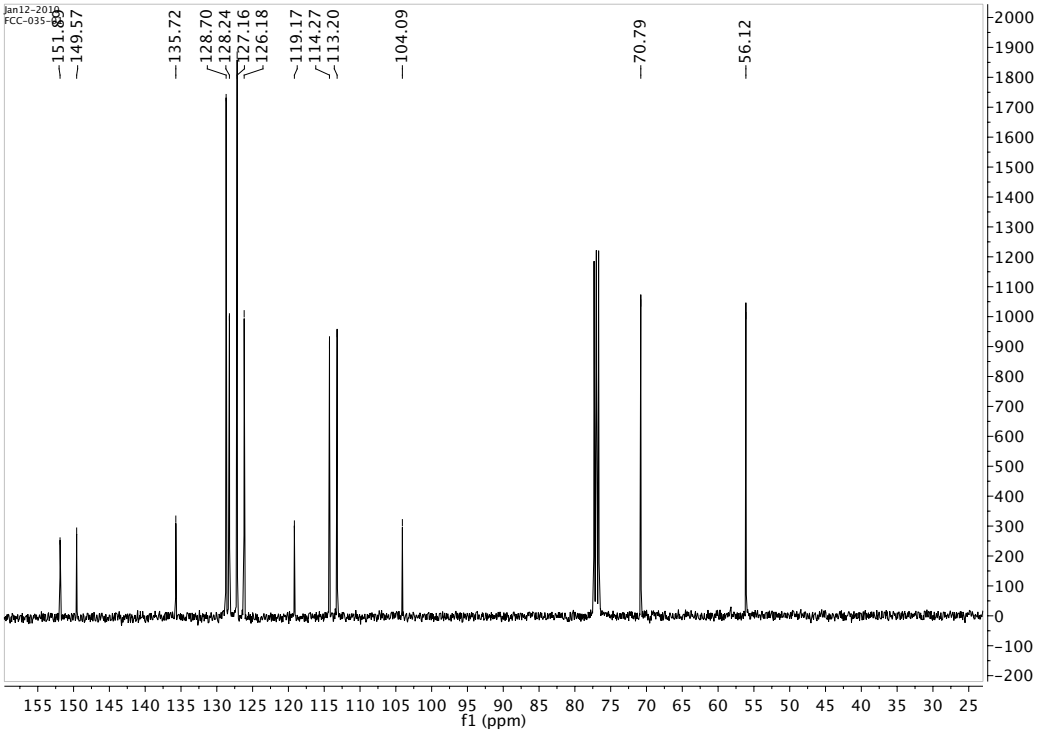
Chapter IV Towards the discovery of novel EZH2 inhibitors

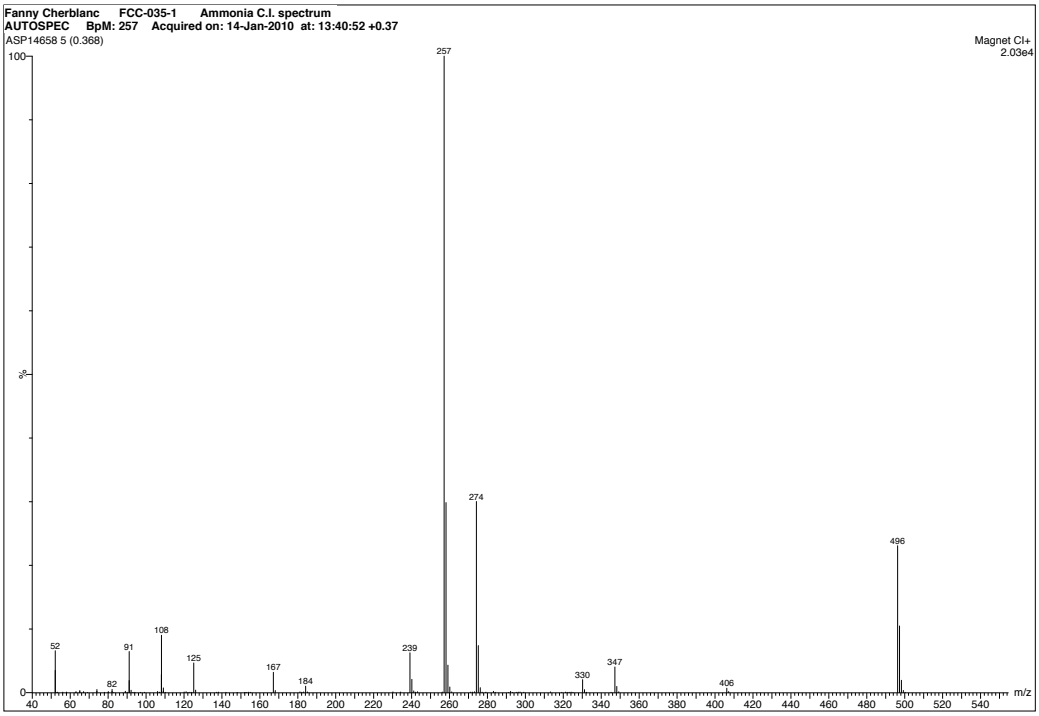
4-Benzyloxy-3-methoxybenzonitrile (58)[18]

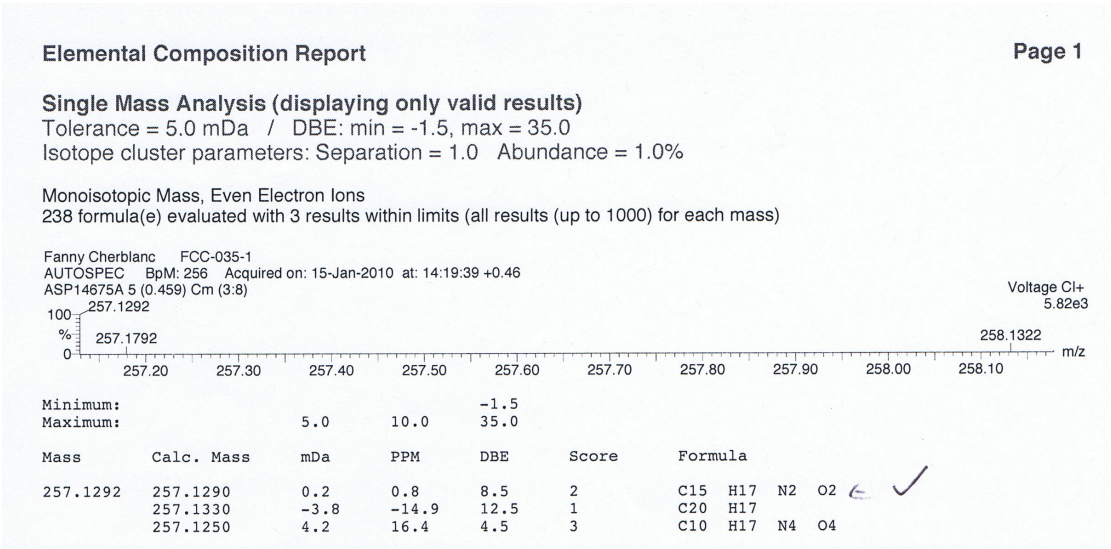


Compound **58** was prepared as follows:[18] To an ice-cooled solution of 4-hydroxy-3-methoxybenzonitrile (**57**, 5.00 g, 33.5 mmol) in DMF (60 mL) were slowly added K_2CO_3 (6.95 g, 50.3 mmol) followed by benzylbromide (4.4 mL, 36.8 mmol). The solution was allowed to stir overnight at room temperature. Sat. aq. NaCl (100 mL) was then added and the resulting precipitate was filtered, washed with water and dried under vacuum to afford the title compound **58** as a white solid (7.74 g, 96%) that was used in the next step without further purification: IR (neat) 2223, 1595, 1512, 1267, 1241, 1132, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 7.21 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.20 (s, 2H), 3.90 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 151.9, 149.6, 135.7, 128.7 (2C), 128.2, 127.2 (2C), 126.2, 119.2, 114.3, 113.2, 104.1, 70.8, 56.1; MS (CI) *m/z* 257 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{17}N_2O_2$ 257.1290, found: 257.1292.




Jan12-2010
FCC-035-1
151.89
149.57
135.72
128.70
128.24
127.16
126.18
119.17
114.27
113.20
104.09
70.79
56.12
f1 (ppm)


Fanny Cherblanc FCC-035-1 Ammonia C.I. spectrum
AUTOSPEC BpM: 257 Acquired on: 14-Jan-2010 at: 13:40:52 +0.37
ASP14658 5 (0.368)
Magnet CI+
2.03e4
257
274
496
108
52
91
125
167
184
239
330
347
406
82
%
m/z



Elemental Composition Report Page 1

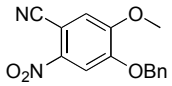
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
238 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)

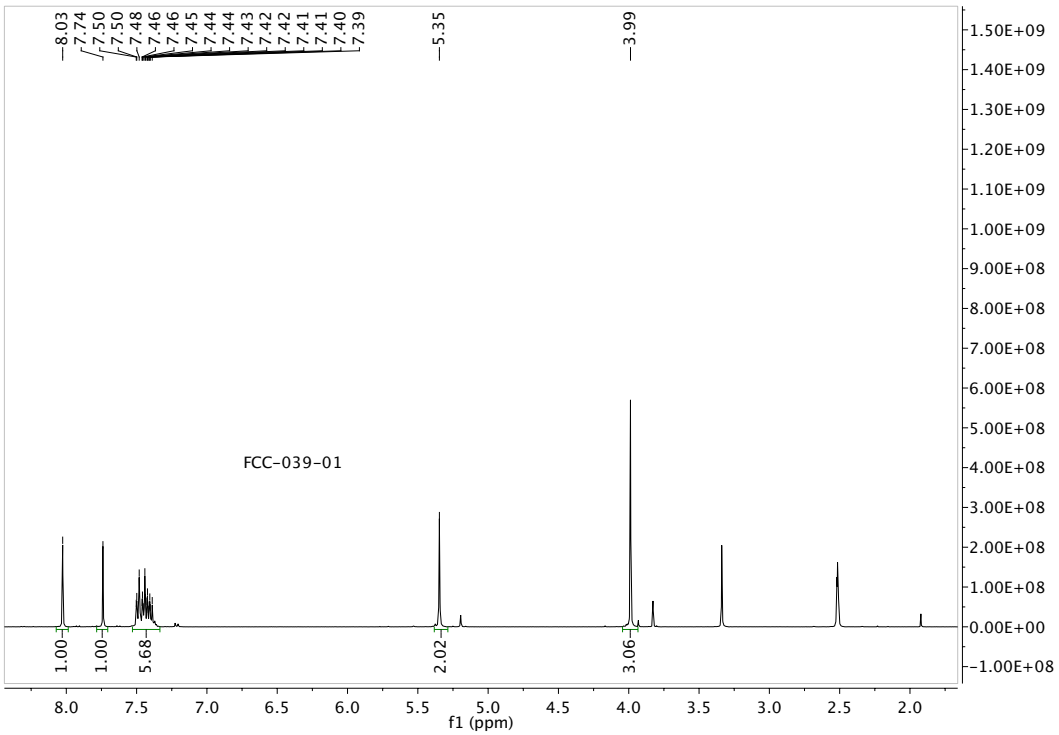
Fanny Cherblanc FCC-035-1
AUTOSPEC BpM: 256 Acquired on: 15-Jan-2010 at: 14:19:39 +0.46
ASP14675A 5 (0.459) Cm (3:8)
Voltage CI+ 5.82e3

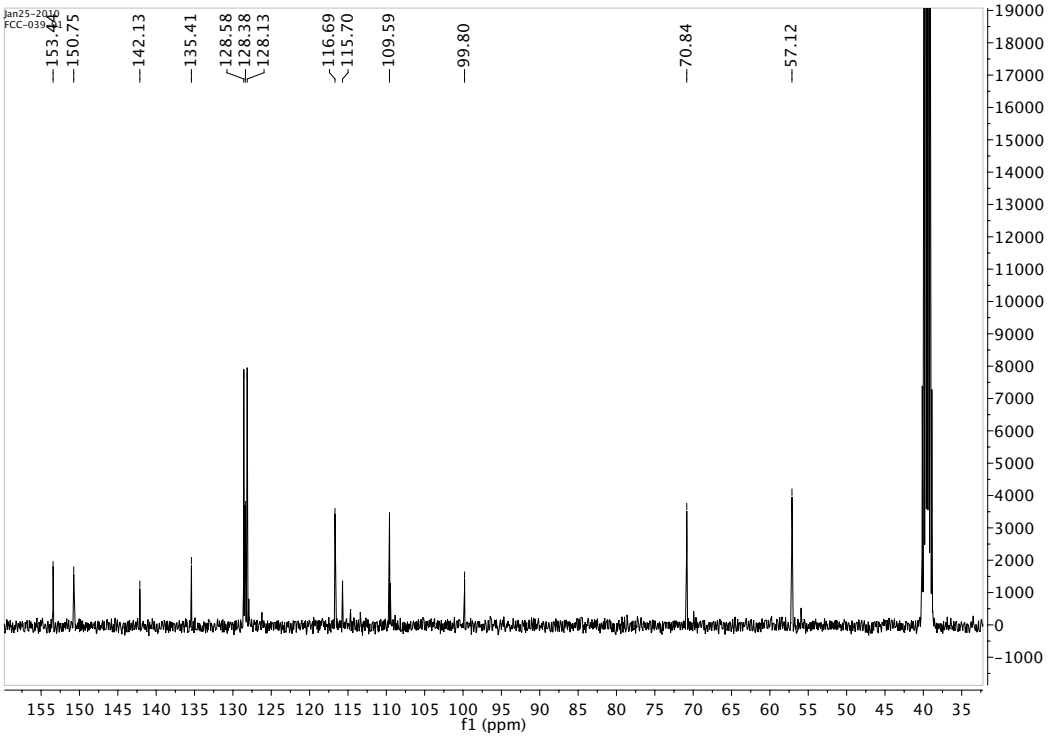
Minimum:				-1.5		
Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
257.1292	257.1290	0.2	0.8	8.5	2	C15 H17 N2 O2
	257.1330	-3.8	-14.9	12.5	1	C20 H17
	257.1250	4.2	16.4	4.5	3	C10 H17 N4 O4

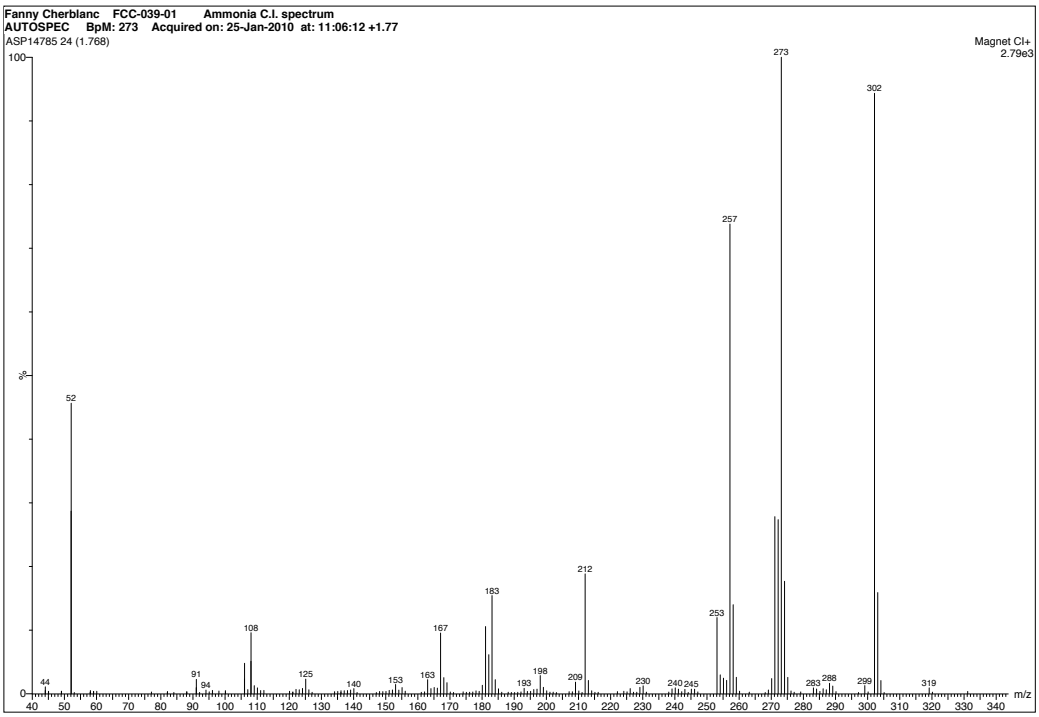
4-Benzyloxy-5-methoxy-2-nitrobenzonitrile (59)



Compound **59** was prepared as follows:[18] Benzonitrile **58** (7.00 g, 29.3 mmol) was dissolved in acetic anhydride (70 mL) and cooled to 0 ˚C. Nitric acid (4.9 mL of 69 wt.% solution in water, 76.7 mmol) was added slowly and the reaction was allowed to stir overnight at room temperature. The mixture was then poured into ice-water and the resulting precipitate was filtered, washed with water and dried under vacuum to afford the title compound **59** (8.04 g, 96%) as a white solid that was used in the next step without further purification: m.p. 128 – 130 ˚C; IR (neat) 2228, 1572, 1533, 1517, 1336, 1288, 1223, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.46 – 7.37 (m, 5H), 7.21 (s, 1H), 5.27 (s, 2H), 4.01 (s, 3H); ^{13}C (100 MHz, DMSO) δ 153.4, 150.8, 142.1, 135.4, 128.6 (2C), 128.4, 128.1 (2C), 116.7, 115.7, 109.6, 99.8, 70.8, 57.1; MS (CI) *m/z* 302 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{16}N_3O_4$ 302.1141, found: 303.1141.


8.03
7.74
7.50
7.50
7.48
7.46
7.46
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
5.35
3.99
FCC-039-01
1.00
1.00
5.68
2.02
3.06
f1 (ppm)

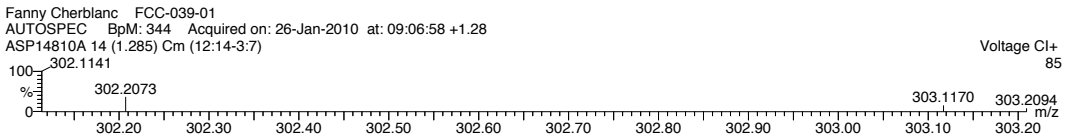

Jan25-2010
FCC-039-13
153.44
150.75
142.13
135.41
128.58
128.38
128.13
116.69
115.70
109.59
99.80
70.84
57.12
f1 (ppm)



Elemental Composition Report **Page 1**

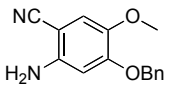
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Tolerance = 5.0 mDa / DBE: min = -1.5, max = 35.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
283 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)



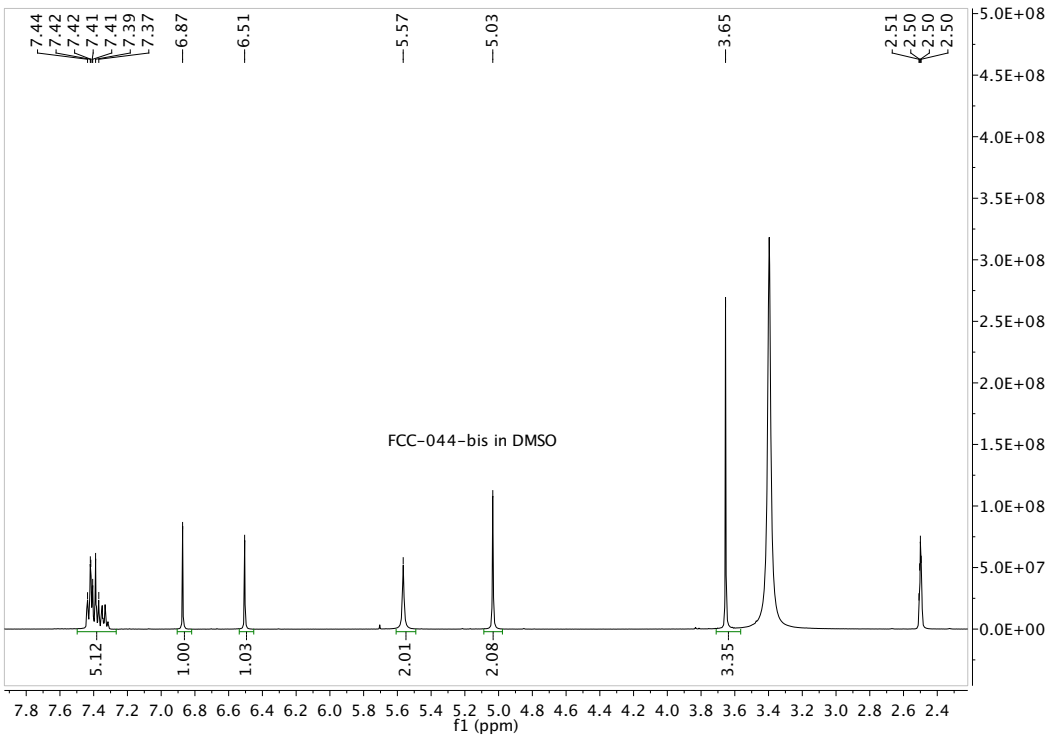
Minimum:				-1.5		
Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
302.1141	302.1141	0.0	0.1	9.5	2	C15 H16 N3 O4
	302.1181	-4.0	-13.3	13.5	3	C20 H16 N O2
	302.1101	4.0	13.4	5.5	1	C10 H16 N5 O6

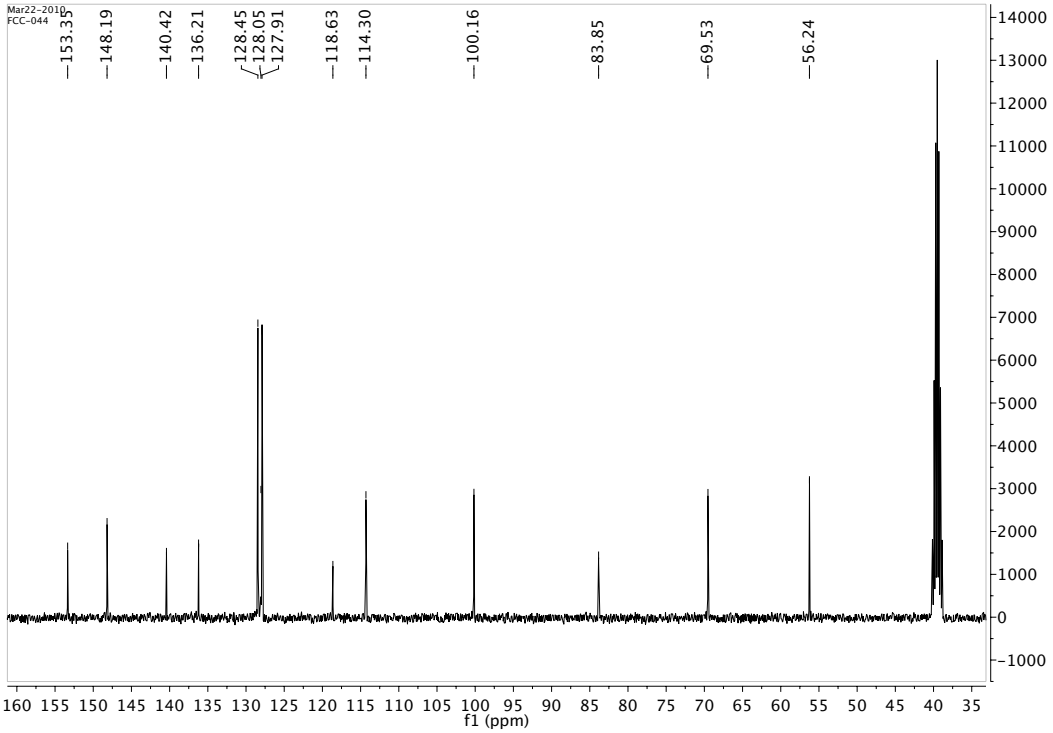
2-Amino-4-benzyloxy-2-methoxybenzonitrile (60)[18]

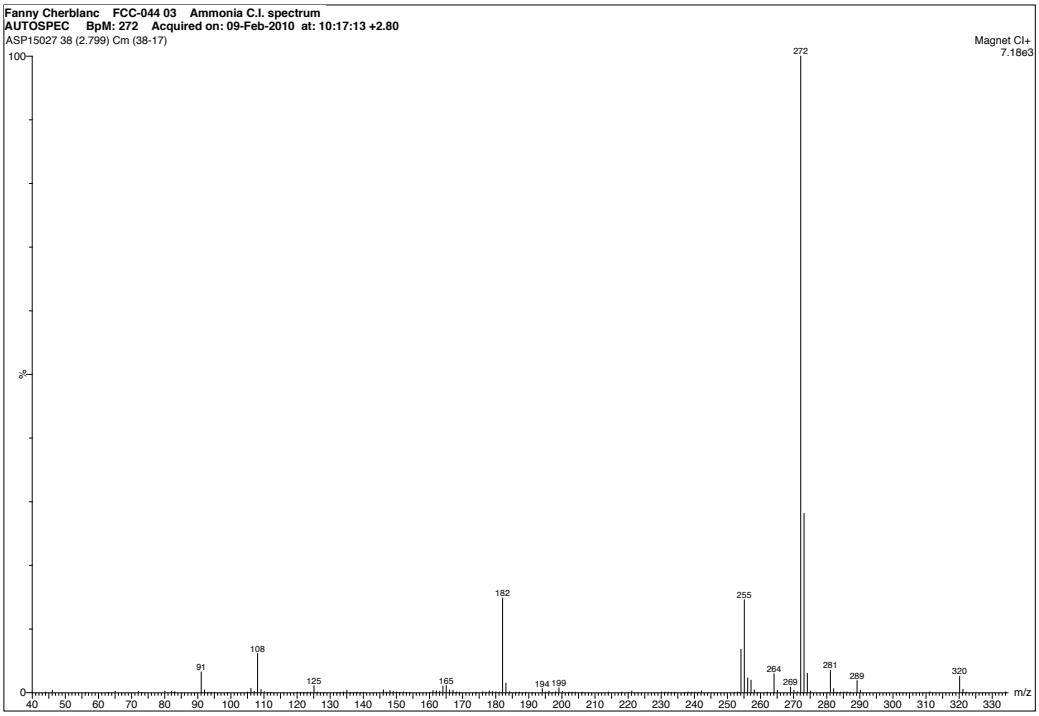


Compound **60** was prepared as follows:[19] To a solution of nitrobenzonitrile **59** (100 mg, 0.35 mmol) in CH_2Cl_2 (3 mL), tetrabutylammonium chloride monohydrate (68 mg, 0.24 mmol) was added, followed by the slow addition of a solution of sodium dithionite (367 mg, 2.11 mmol) in water (3 mL). The mixture was allowed to stir

overnight at room temperature and then basified with 2 N aq. NaOH at 0 ˚C. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). A precipitate was obtained upon treatment of the combined organic layers with 1M HCl in Et_2O. The white solid was filtered and dissolved in water. The aqueous layer was basified with 2N NaOH and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to yield the title compound **60** (87 mg, 97%) as a white solid: IR (neat) 3440, 3352, 3243, 2205, 1641, 1620, 1505, 1239, 1119, 985 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 7.44 – 7.37 (m, 5H), 6.87 (s, 1H), 6.51 (s, 1H), 5.57 (s, 2H), 5.03 (s, 2H), 3.65 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 153.4, 148.2, 140.4, 136.2, 128.5 (2C), 128.1, 127.9 (2C), 116.6, 114.3, 100.1, 83.9, 69.5, 56.2; MS (CI) *m/z* 272 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{15}H_{18}N_3O_2$ 272.1399, found: 272.1402.




Mar22-2010
FCC-044
153.35
148.19
140.42
136.21
128.45
128.05
127.91
118.63
114.30
100.16
83.85
69.53
56.24
f1 (ppm)

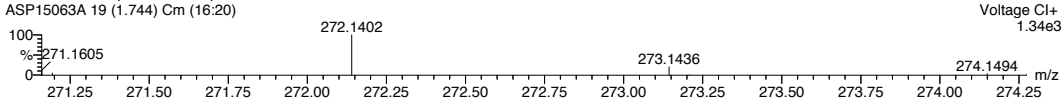

Fanny Cherblanc FCC-044 03 Ammonia C.I. spectrum
AUTOSPEC BpM: 272 Acquired on: 09-Feb-2010 at: 10:17:13 +2.80
ASP15027 38 (2.799) Cm (38-17)
Magnet CI+
7.18e3
%
m/z
272
182
255
108
91
125
165
194 199
264
269
281
289
320

Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 35.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

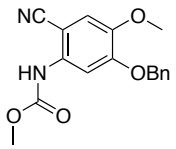
Monoisotopic Mass, Odd and Even Electron Ions
250 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-044 03
AUTOSPEC BpM: 256 Acquired on: 11-Feb-2010 at: 11:51:40 +1.74
ASP15063A 19 (1.744) Cm (16:20)
Voltage CI+ 1.34e3

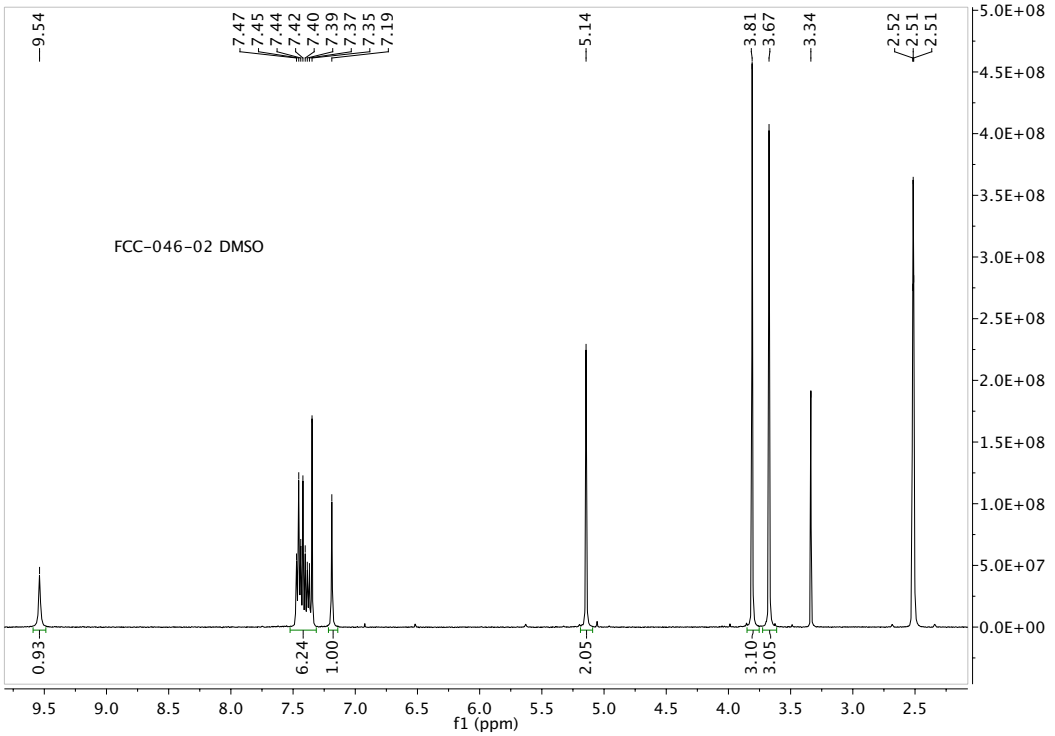


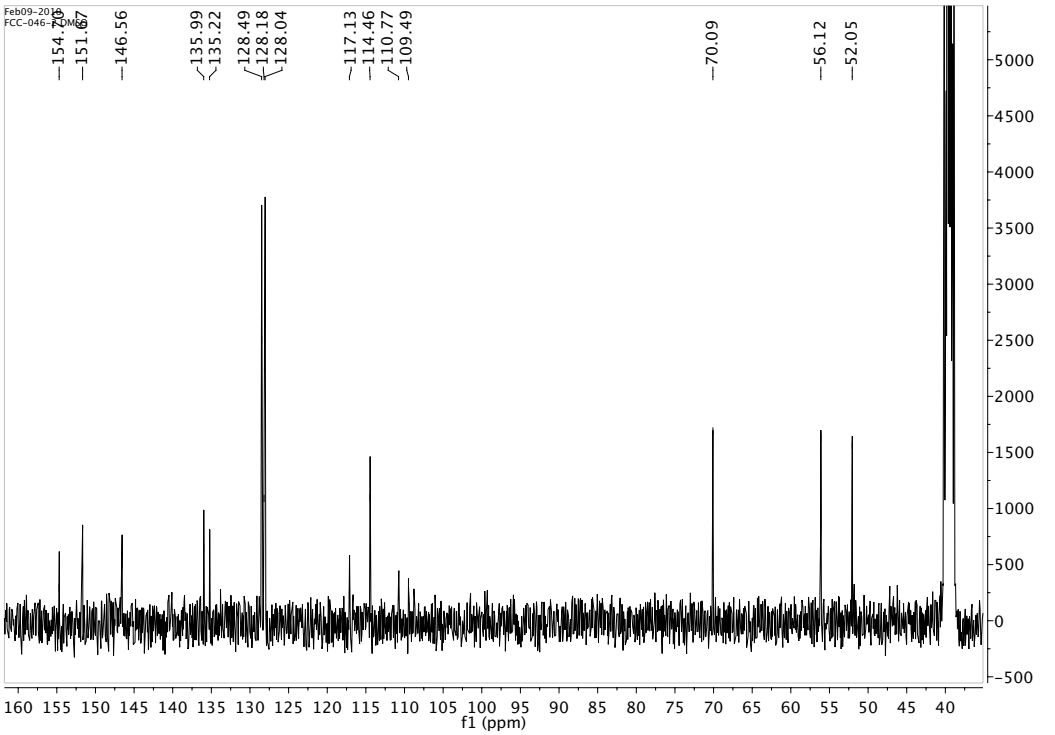
Minimum:				-1.5		
Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
272.1402	272.1399	0.3	1.1	8.5	2	C15 H18 N3 O2
	272.1412	-1.0	-3.8	8.0	1	C17 H20 O3
	272.1386	1.6	6.0	9.0	4	C13 H16 N6 O
	272.1372	3.0	10.9	4.0	5	C12 H20 N2 O5
	272.1439	-3.7	-13.7	12.5	3	C20 H18 N
	272.1444	-4.2	-15.6	0.0	7	C6 H20 N6 O6
	272.1359	4.3	15.9	4.5	6	C10 H18 N5 O4

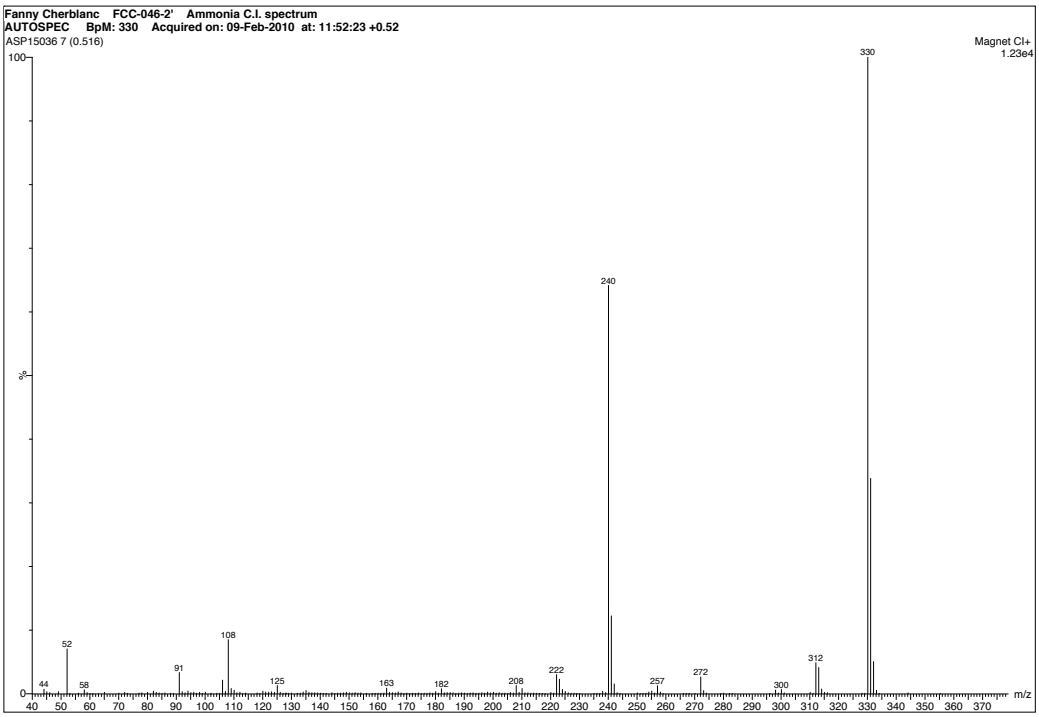
Methyl (5-(benzyloxy)-2-cyano-4-methoxyphenyl)carbamate (61)



Compound **61** was prepared as follows:[18] To a solution of aniline **60** (50 mg, 0.19 mmol) and DIEA (137 μL, 0.79 mmol) in DMA – CH_2Cl_2 (1 mL : 0.5 mL) at 0 ˚C was added methyl chloroformate (23 μL, 0.29 mmol). The mixture was allowed to stir overnight at room temperature. Water (5 mL) was then added and the resulting precipitate was recovered and dried under vacuum to afford the title compound **61** (47 mg, 79%) as a yellow solid that was used in the next step without further purification: IR (neat) 3329, 2223, 1716, 1595, 1510 1220, 1128, 996 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.55 (br s, 1H), 7.47 – 7.37 (m, 5H), 7.35 (s, 1H), 7.19 (s, 1H), 5.14 (s, 2H), 3.80 (s, 3H), 3.67 (s, 3H); ^{13}C (100 MHz, DMSO) δ 154.7, 151.7, 146.6, 136.0, 135.2, 128.5 (2C), 128.2, 128.0 (2C), 117.1, 114.5, 110.8, 109.5, 70.1, 56.1, 52.1; MS (CI) *m/z* 330 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{17}H_{20}N_3O_4$ 330.1454, found: 330.1462.


9.54
7.47
7.45
7.44
7.42
7.40
7.39
7.37
7.35
7.19
5.14
3.81
3.67
3.34
2.52
2.51
2.51
FCC-046-02 DMSO
0.93
6.24
1.00
2.05
3.10
3.05
f1 (ppm)


Feb09-2016
FCC-046-FCM66
154.70
151.67
146.56
135.99
135.22
128.49
128.18
128.04
117.13
114.46
110.77
109.49
70.09
56.12
52.05
f1 (ppm)

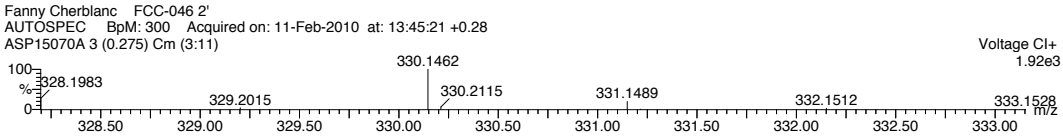


Elemental Composition Report

Single Mass Analysis (displaying only valid results)

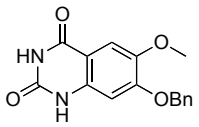
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 35.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
313 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)

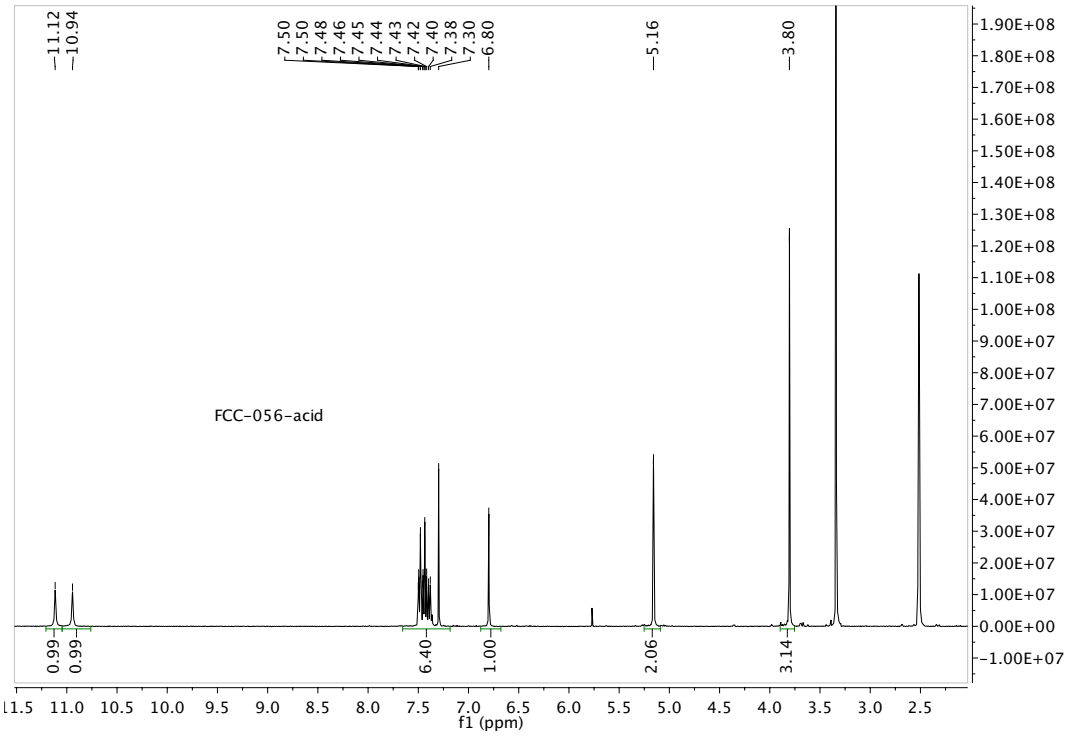


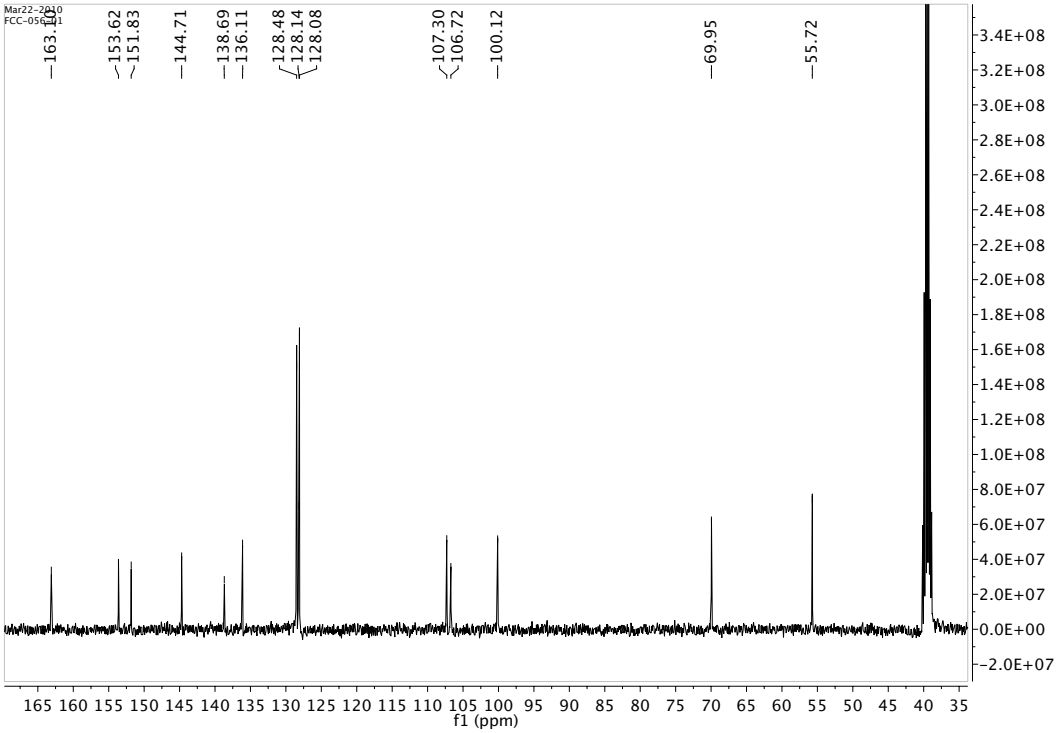
Minimum:				-1.5		
Maximum:		5.0	10.0	35.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**Score**	**Formula**
330.1462	330.1467	-0.5	-1.6	9.0	3	C19 H22 O5
	330.1454	0.8	2.5	9.5	2	C17 H20 N3 O4
	330.1481	-1.9	-5.6	14.0	6	C20 H18 N4 O
	330.1440	2.2	6.5	10.0	1	C15 H18 N6 O3
	330.1494	-3.2	-9.7	13.5	7	C22 H20 N O2
	330.1427	3.5	10.6	5.0	4	C14 H22 N2 O7
	330.1499	-3.7	-11.2	1.0	8	C8 H22 N6 O8
	330.1414	4.8	14.7	5.5	5	C12 H20 N5 O6

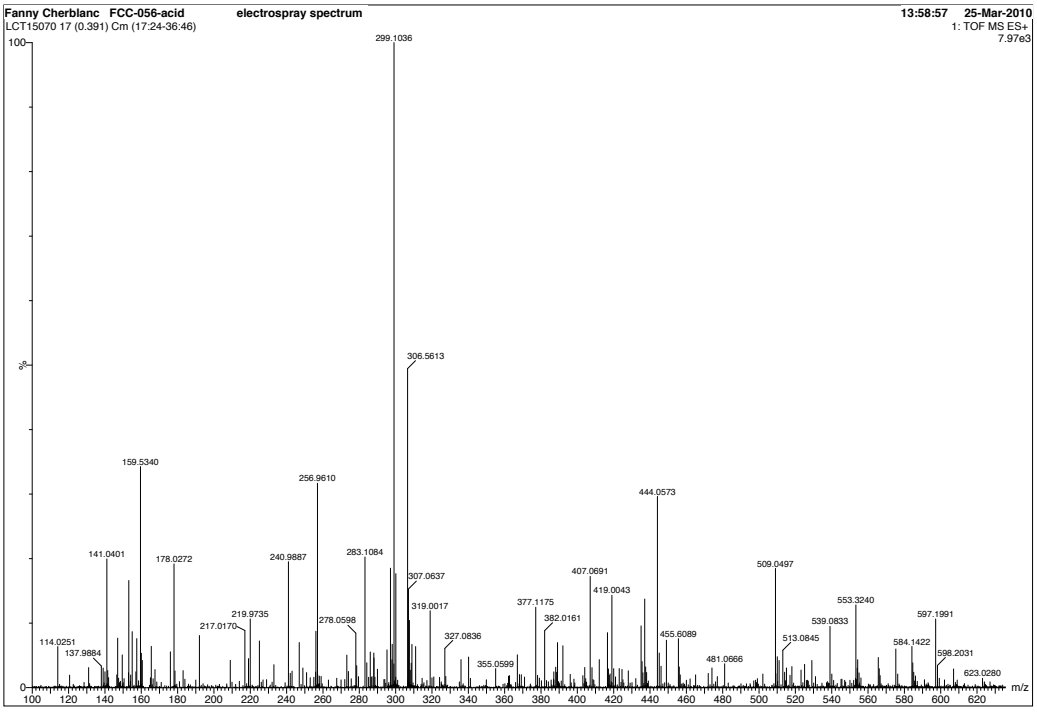
7-(Benzyloxy)-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (62)[18]



Compound **62** was prepared as follows:[18] Carbamate **61** (1.088 g, 3.5 mmol) was added to a solution of H_2O_2 (10 mL of 35 wt.% solution in water, 110 mmol) and NaOH (1.28 g, 32 mmol) in ethanol (50 mL) and the resulting mixture was allowed to stir for 4 h under reflux. Water (70 mL) was added and the solution was allowed to cool to room temperature and then acidified with 1 N aq. HCl. The resulting precipitate was recovered, washed with water and dried under vacuum to afford the title compound **62** (609 mg, 64%) as a white solid that was used in the next step without further purification: IR (neat) 1718, 1649, 1618, 1512, 1267, 1107, 838 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 11.12 (s, 1H), 10.94 (s, 1H), 7.50 – 7.38 (m, 5H), 7.30 (s, 1H), 6.80 (s, 1H), 5.16 (s, 2H), 3.80 (s, 3H); ^{13}C (100 MHz, DMSO) δ 163.1, 153.6, 151.8, 144.7, 138.7, 136.1, 128.5 (2C), 128.1, 128.0 (2C), 107.3, 106.7, 100.1, 70.0, 55.7; MS (ESI) *m/z* 299 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{16}H_{15}N_2O_4$ 299.1032, found: 299.1036.




Mar22-2010
FCC-056-acid
163.10
153.62
151.83
144.71
138.69
136.11
128.48
128.14
128.08
107.30
106.72
100.12
69.95
55.72
3.4E+08
3.2E+08
3.0E+08
2.8E+08
2.6E+08
2.4E+08
2.2E+08
2.0E+08
1.8E+08
1.6E+08
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
-2.0E+07
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35
f1 (ppm)

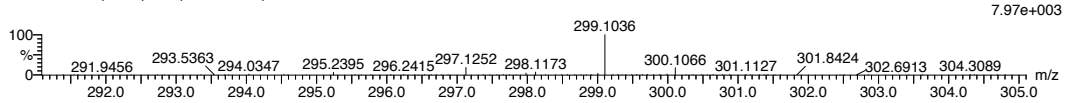

Fanny Cherblanc FCC-056-acid electrospray spectrum
13:58:57 25-Mar-2010
LCT15070 17 (0.391) Cm (17:24-36:46)
1: TOF MS ES+
7.97e3
100
%
0
299.1036
306.5613
159.5340
256.9610
444.0573
141.0401
178.0272
240.9887
283.1084
307.0637
407.0691
419.0043
509.0497
319.0017
377.1175
553.3240
219.9735
217.0170
278.0598
382.0161
539.0833
597.1991
327.0836
455.6089
513.0845
584.1422
114.0251
137.9884
355.0599
481.0666
598.2031
623.0280
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 7.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

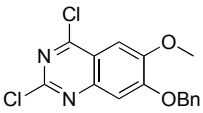
Monoisotopic Mass, Even Electron Ions
363 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC-056-acid electrospray spectrum 13:58:57 25-Mar-2010
LCT15070 17 (0.391) Cm (17:24-36:46) 1: TOF MS ES+
7.97e+003

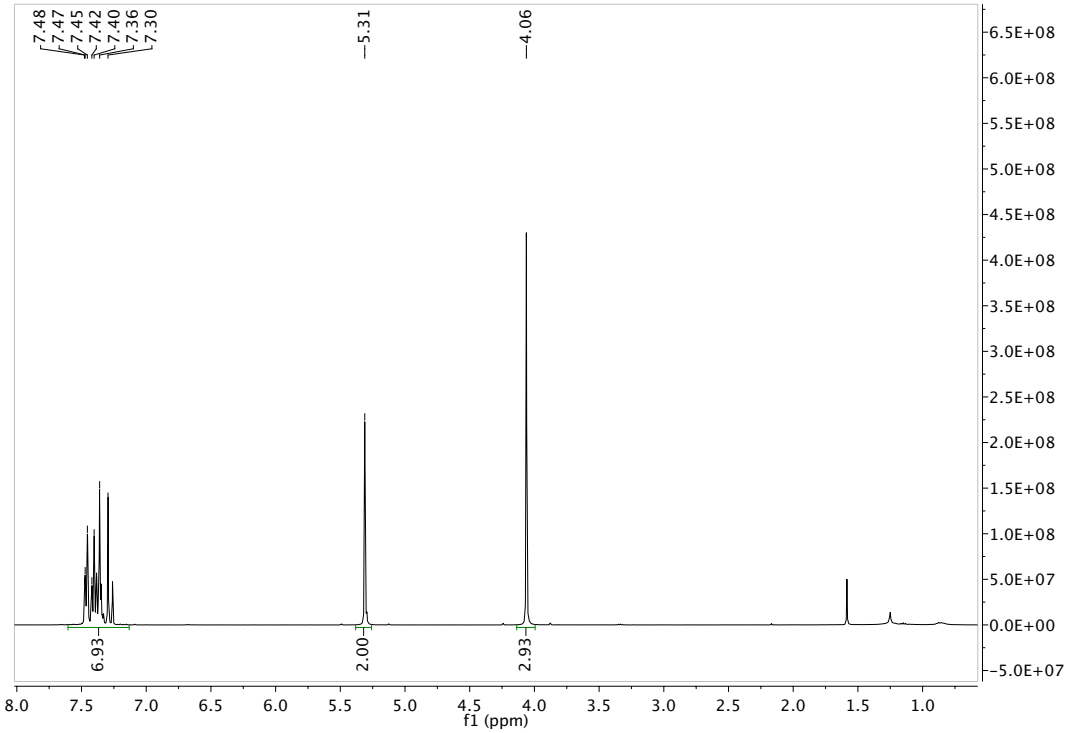


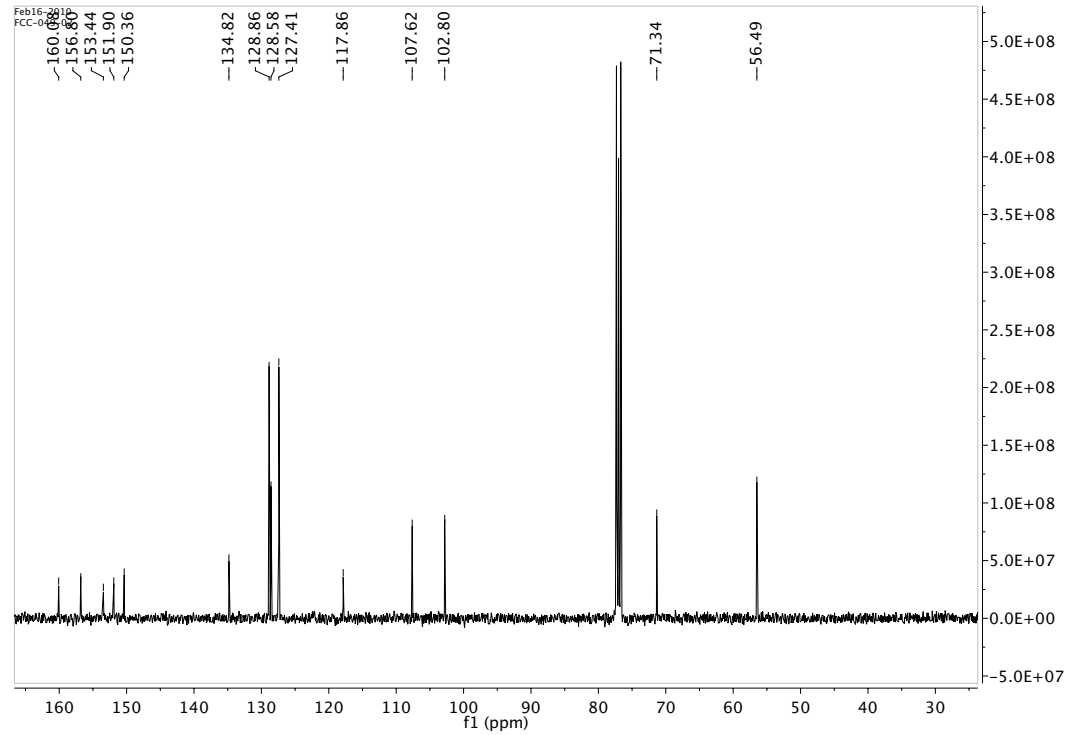
Minimum:				-1.5			
Maximum:		7.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
299.1036	299.1032	0.4	1.3	10.5	189.7	3.1	C16 H15 N2 O4
	299.1045	-0.9	-3.0	15.5	187.6	0.9	C17 H11 N6
	299.1064	-2.8	-9.4	2.5	192.4	5.8	C5 H15 N8 O7
	299.1005	3.1	10.4	11.5	187.3	0.7	C12 H11 N8 O2
	299.1072	-3.6	-12.0	14.5	191.4	4.8	C21 H15 O2
	299.0992	4.4	14.7	6.5	190.7	4.0	C11 H15 N4 O6
	299.1091	-5.5	-18.4	1.5	192.4	5.7	C9 H19 N2 O9
	299.0978	5.8	19.4	1.5	193.1	6.4	C10 H19 O10
	299.1104	-6.8	-22.7	6.5	190.6	3.9	C10 H15 N6 O5

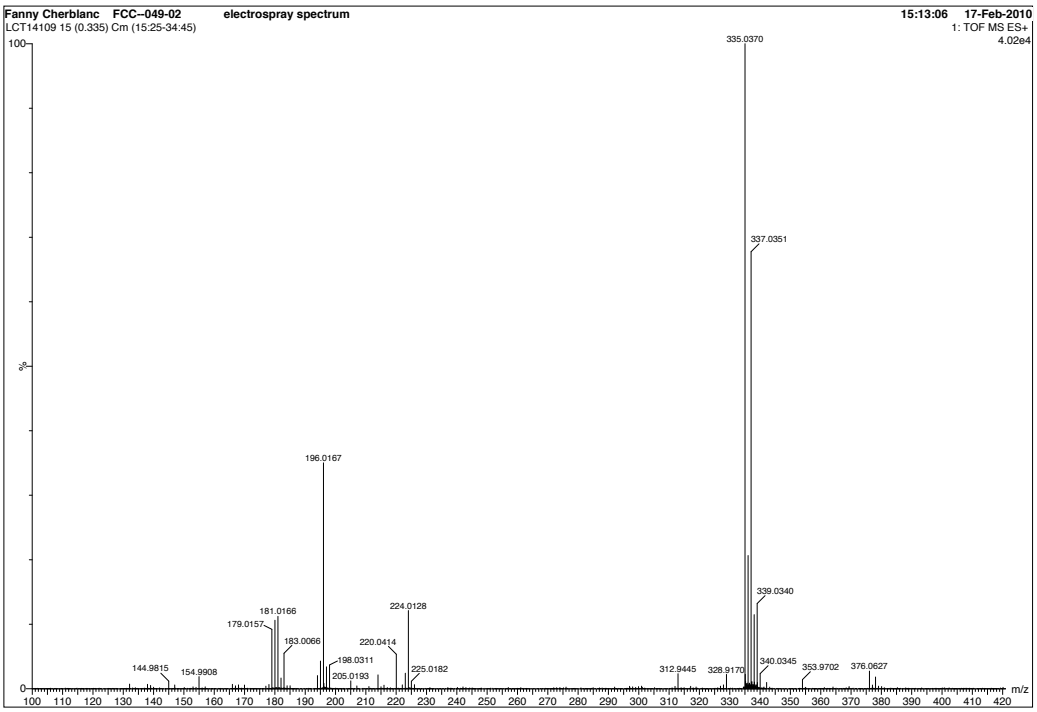
7-(Benzyloxy)-2,4-dichloro-6-methoxyquinazoline (63)[18]



Compound **63** was prepared as follows:[18] A mixture of quinazolinedione **62** (282.2 mg, 0.95 mmol), *N,N*-diethylaniline (166 μL, 1.04 mmol) and $POCl_3$ (2 mL) was allowed to stir under reflux for 3 h and then rotary evaporated. Sat. aq. $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with chloroform (2 × 10 mL). The combined organic layer was dried ($MgSO_4$), rotary evaporated and purified by column chromatography (EtOAc : Hexanes, 2 : 8) to afford the title compound **63** (248.4 mg, 78%) as a colourless oil: IR (neat) 1611, 1547, 1500, 1424, 1237, 1149, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.35 (m, 5H), 7.36 (s, 1H), 7.30 (s, 1H), 5.31 (s, 2H), 4.06 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 160.1, 156.8, 153.4, 151.9, 150.4, 134.8, 128.9 (2C), 128.6, 127.4 (2C), 117.9, 107.6, 102.8, 71.3, 56.5; MS (ESI) *m/z* 335 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{16}H_{13}N_2O_2Cl_2$ 335.0354, found: 335.0370.


7.48
7.47
7.45
7.42
7.40
7.36
7.30
5.31
4.06
6.93
2.00
2.93
f1 (ppm)


160.08
156.80
153.44
151.90
150.36
134.82
128.86
128.58
127.41
117.86
107.62
102.80
71.34
56.49
f1 (ppm)



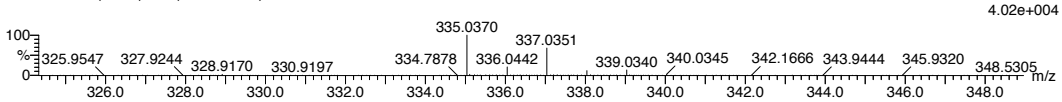
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: On (Carbon range ± 5) (Set 0 < Cl < 9, 0< Br < 9 and 0 < S < 7 for enhanced filtering)
Number of isotope peaks used for i-FIT = 5

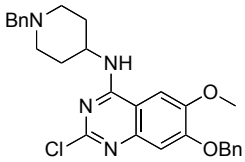
Monoisotopic Mass, Even Electron Ions
1047 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 Cl: 0-2

Fanny Cherblanc FCC--049-02 electrospray spectrum
LCT14109 15 (0.335) Cm (15:25-34:45)
15:13:06 17-Feb-2010
1: TOF MS ES+
4.02e+004

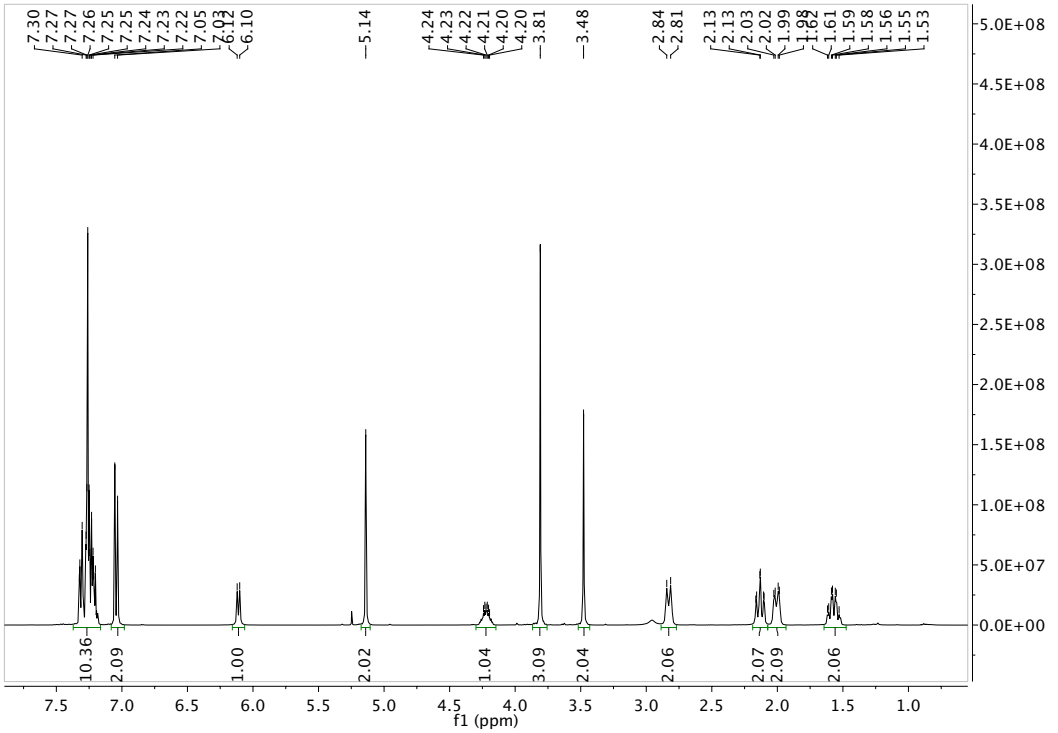


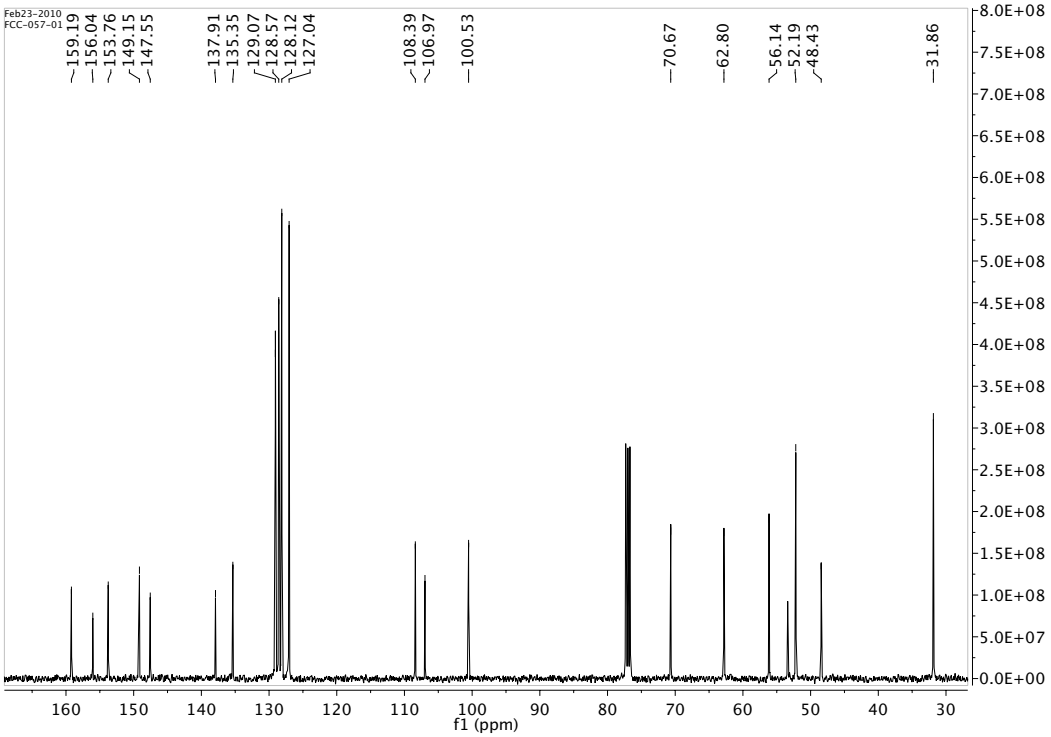
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
335.0370	335.0354	1.6	4.8	10.5	543.5	0.0	C16 H13 N2 O2 Cl2
	335.0394	-2.4	-7.2	14.5	547.4	4.0	C21 H13 Cl2
	335.0327	4.3	12.8	11.5	547.8	4.4	C12 H9 N8 Cl2

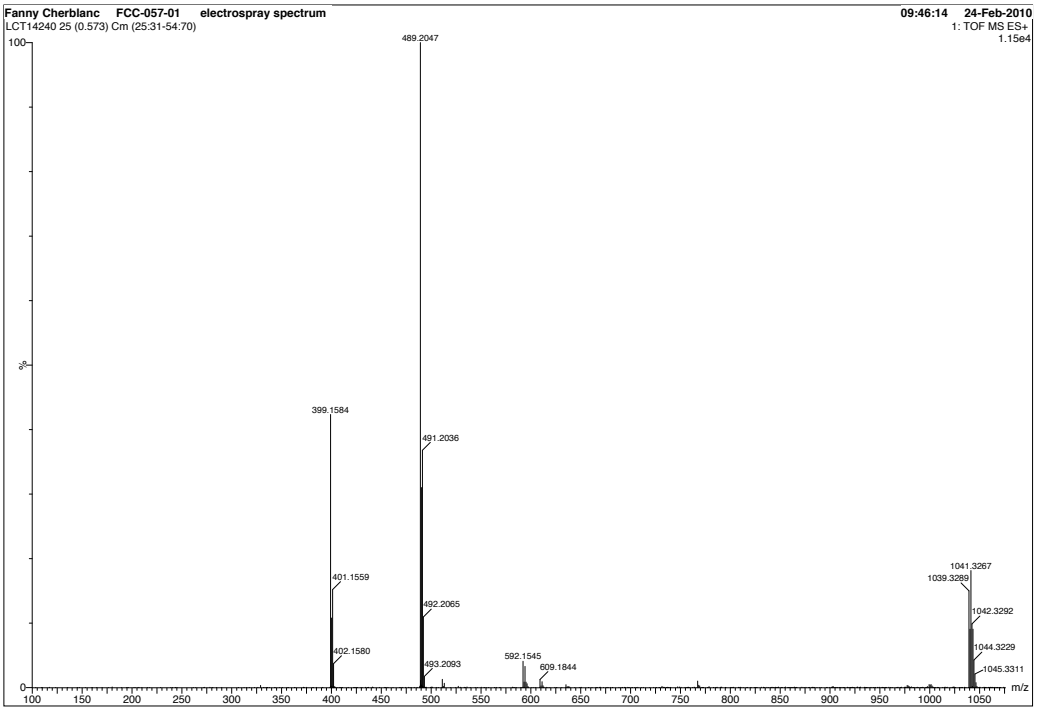
7-(Benzyloxy)-N-(1-benzylpiperidin-4-yl)-2-chloro-6-methoxy-quinazolin-4-amine (65)



Compound **65** was prepared as follows:[18] A mixture of dichloroquinazoline **63** (265 mg, 0.79 mmol), 4-amino-1-benzylpiperidine (**64**, 484 μL, 2.37 mmol) and DIEA (206 μL, 1.18 mmol) in THF (2 mL) was allowed to stir overnight at room temperature. The solution was then rotary evaporated and purified by column chromatography (MeOH : CH_2Cl_2, 5 : 95) to afford the title compound **65** (285 mg, 74%) as a white solid: m.p. 108 – 110 ˚C; IR (neat) 1584, 1514, 1452, 1260, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 10H), 7.05 (s, 1H), 7.03 (s, 1H), 6.11 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 2H), 4.24 – 4.20 (m, 1H), 3.81 (s, 3H), 3.48 (s, 2H), 2.83 (br *app*-d, *J* = 12.0 Hz, 2H), 2.13 (br *app*-td, *J* = 12.0, 1.5 Hz, 2H), 2.01 (br *app*-d, *J* = 12.0 Hz, 2H), 1.57 (qd, *J* = 12.0, 3.6 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 156.0, 153.8, 149.1, 147.6, 137.9, 135.3, 129.1 (2C), 128.6 (2C), 128.1 (3C), 127.0 (3C), 108.4, 107.0, 100.5, 70.7, 62.8, 56.1, 52.1 (2C), 48.4, 31.9 (2C); MS (ESI) *m/z* 489 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{28}H_{30}N_4O_2Cl$ 489.2057, found: 489.2047.




Feb23-2010
FCC-057-01
159.19
156.04
153.76
149.15
147.55
137.91
135.35
129.07
128.57
128.12
127.04
108.39
106.97
100.53
70.67
62.80
56.14
52.19
48.43
31.86
f1 (ppm)


Fanny Cherblanc FCC-057-01 electrospray spectrum
09:46:14 24-Feb-2010
LCT14240 25 (0.573) Cm (25:31-54:70)
1: TOF MS ES+
1.15e4
489.2047
399.1584
491.2036
401.1559
492.2065
402.1580
493.2093
592.1545
609.1844
1041.3267
1039.3289
1042.3292
1044.3229
1045.3311
%
m/z

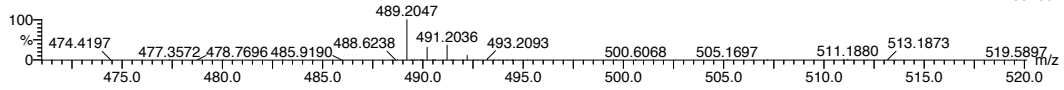
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
1182 formula(e) evaluated with 13 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 Cl: 0-1

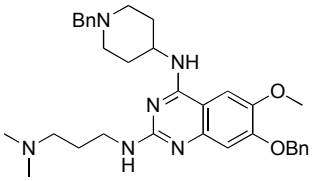
Fanny Cherblanc FCC-057-01 electrospray spectrum
LCT14240 25 (0.573) Cm (25:31-54:70)

09:46:14 24-Feb-2010
1: TOF MS ES+
1.15e+004



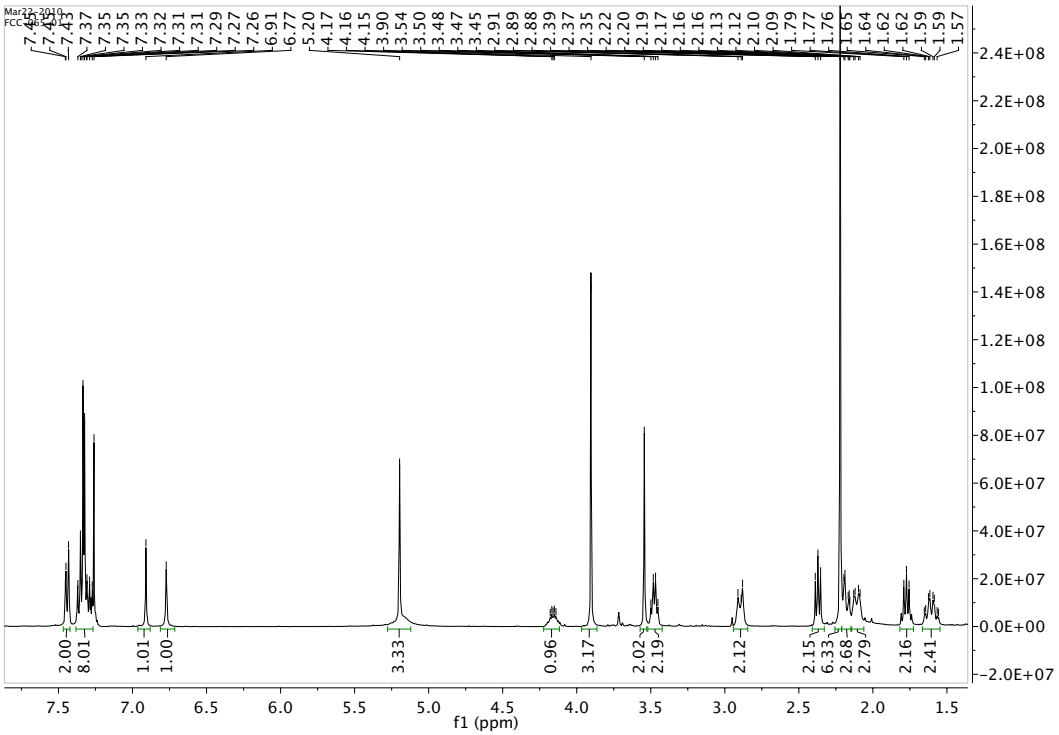
Minimum:				-1.5							
Maximum:		5.0	10.0	50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula				
489.2047	489.2044	0.3	0.6	10.5	80.4	0.1	C27	H34	O6	Cl	
	489.2039	0.8	1.6	20.5	112.0	31.7	C29	H25	N6	O2	
	489.2057	-1.0	-2.0	15.5	82.8	2.5	C28	H30	N4	O2	Cl
	489.2057	-1.0	-2.0	7.5	111.5	31.2	C17	H29	N8	O9	
	489.2036	1.1	2.2	-1.5	99.0	18.7	C11	H34	N8	O11	Cl
	489.2066	-1.9	-3.9	19.5	112.4	32.1	C33	H29	O4		
	489.2026	2.1	4.3	15.5	112.0	31.7	C28	H29	N2	O6	
	489.2076	-2.9	-5.9	2.5	95.5	15.2	C16	H34	N6	O9	Cl
	489.2017	3.0	6.1	11.5	88.4	8.1	C23	H30	N6	O4	Cl
	489.2079	-3.2	-6.5	24.5	112.5	32.2	C34	H25	N4		
	489.2084	-3.7	-7.6	6.5	111.9	31.6	C21	H33	N2	O11	
	489.2004	4.3	8.8	6.5	92.4	12.1	C22	H34	N2	O8	Cl
	489.1999	4.8	9.8	16.5	111.7	31.4	C24	H25	N8	O4	

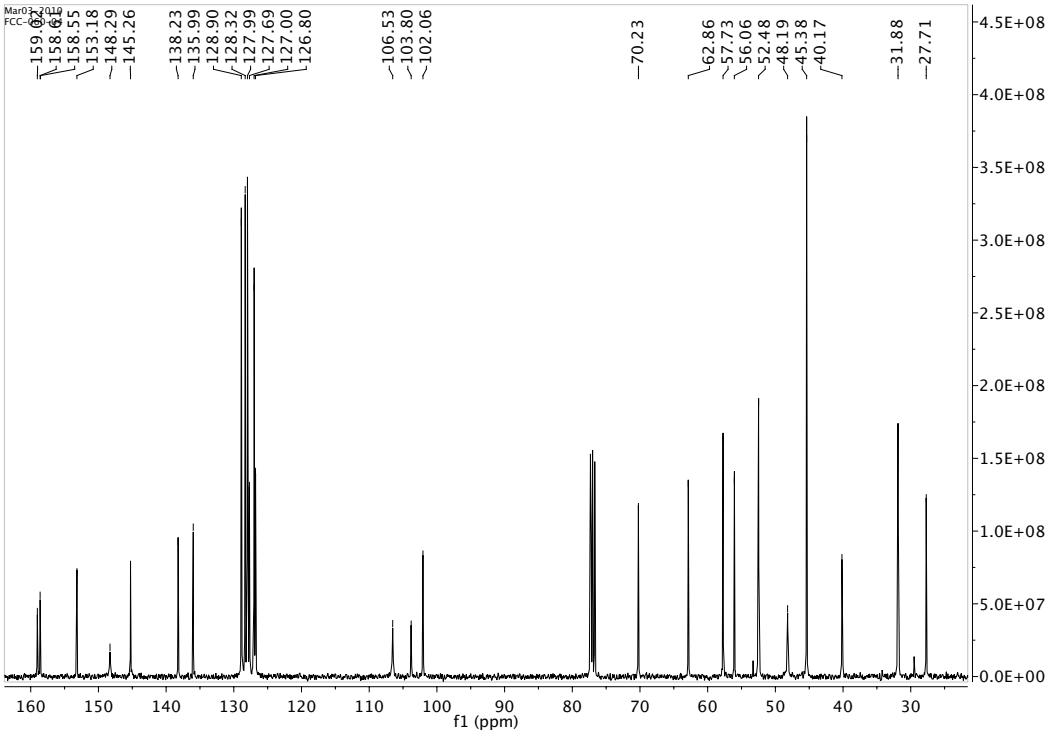
7-(Benzyloxy)-N^4-(1-benzylpiperidin-4-yl)-N^2-(3-(dimethylamino)propyl)-6-methoxyquinazoline-2,4-diamine (67)

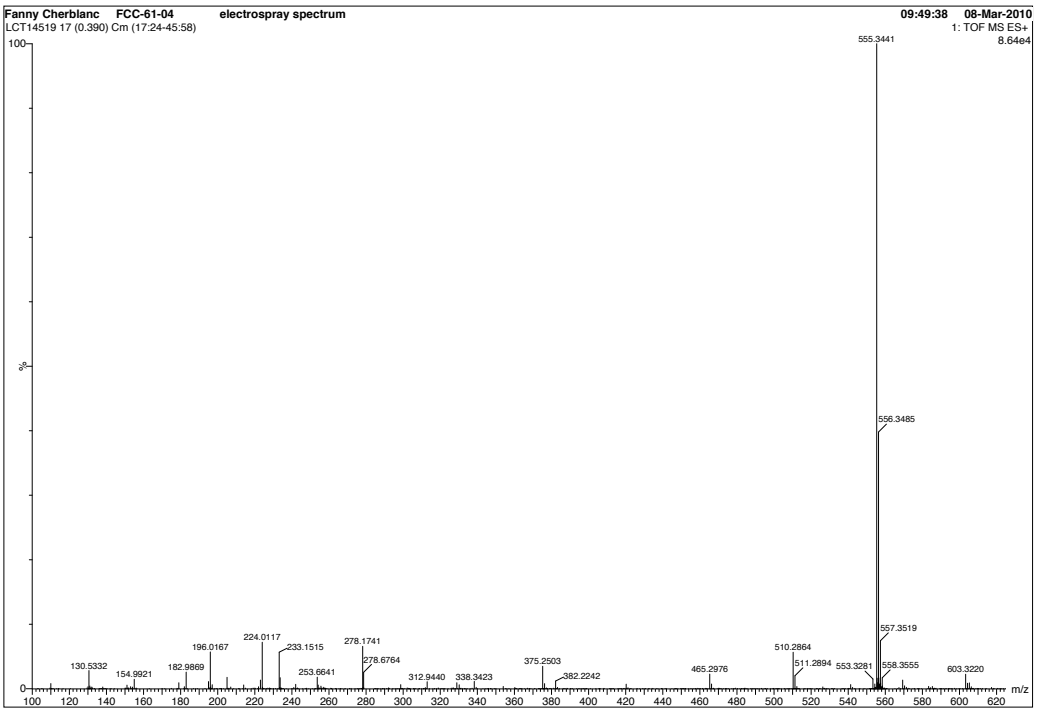


Compound **67** was prepared as follows:[18] A mixture of chloroquinazoline **65** (367 mg, 0.75 mmol), *N,N*-dimethyl-1,3-propanediamine (**66**, 189 μL, 1.50 mmol) and 4 M HCl in dioxane (375 μL, 1.50 mmol) in isopropanol (4 mL) was allowed to stir for 20 minutes at 160 ˚C in a microwave reactor. The solution was then diluted with 10 mL of CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), rotary evaporated and purified by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH, 95 : 5) to afford the title compound **67** (124 mg, 30%) as an orange oil: IR (neat) 1581, 1505, 1450, 1249, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 10H), 6.91 (s, 1H), 6.77 (s, 1H), 5.20 (br s, 2H+1H), 4.18 – 4.14 (m, 1H), 3.90 (s, 3H), 3.54 (s, 2H), 3.48 (*app*-q, J = 6.9 Hz, 2H), 2.86 (br *app*-d, J = 12.0 Hz, 2H), 2.37 (t, J = 6.9 Hz, 2H), 2.22 (s, 6H), 2.19 (br *app*-td, J = 12.0, 2.6 Hz, 2H), 2.06 (br *app*-dd, J = 12.0, 4.4 Hz, 2H), 1.77 (quint, J = 6.9 Hz, 2H), 1.60 (qd, J = 12.0, 4.4 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.0, 158.6, 153.2, 148.3, 145.3, 138.2, 136.0,

128.9 (2C), 128.3 (2C), 128.0 (2C), 127.7, 127.0 (2C), 126.8, 106.5, 103.8, 102.1, 70.2, 62.9, 57.7, 56.1, 52.5 (2C), 48.2, 45.4 (2C), 40.2, 31.9 (2C), 27.7; MS (ESI) *m/z* 555 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{33}H_{43}N_6O_2$ 555.3448, found: 555.3441.





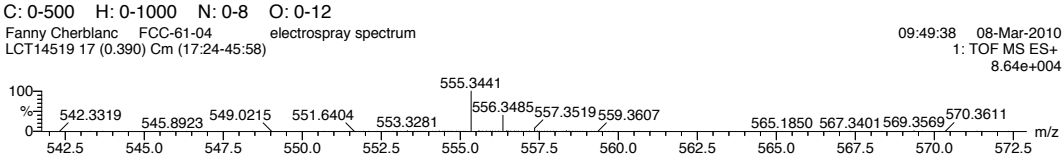


Elemental Composition Report

Single Mass Analysis

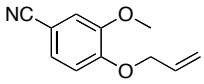
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
719 formula(e) evaluated with 11 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

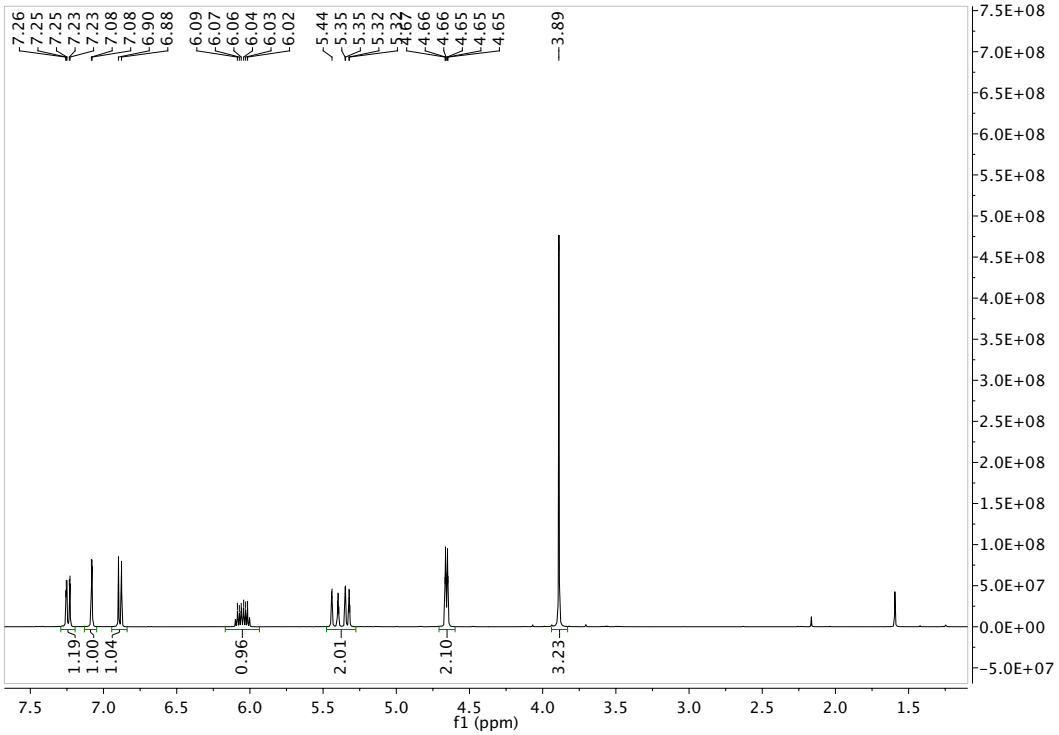


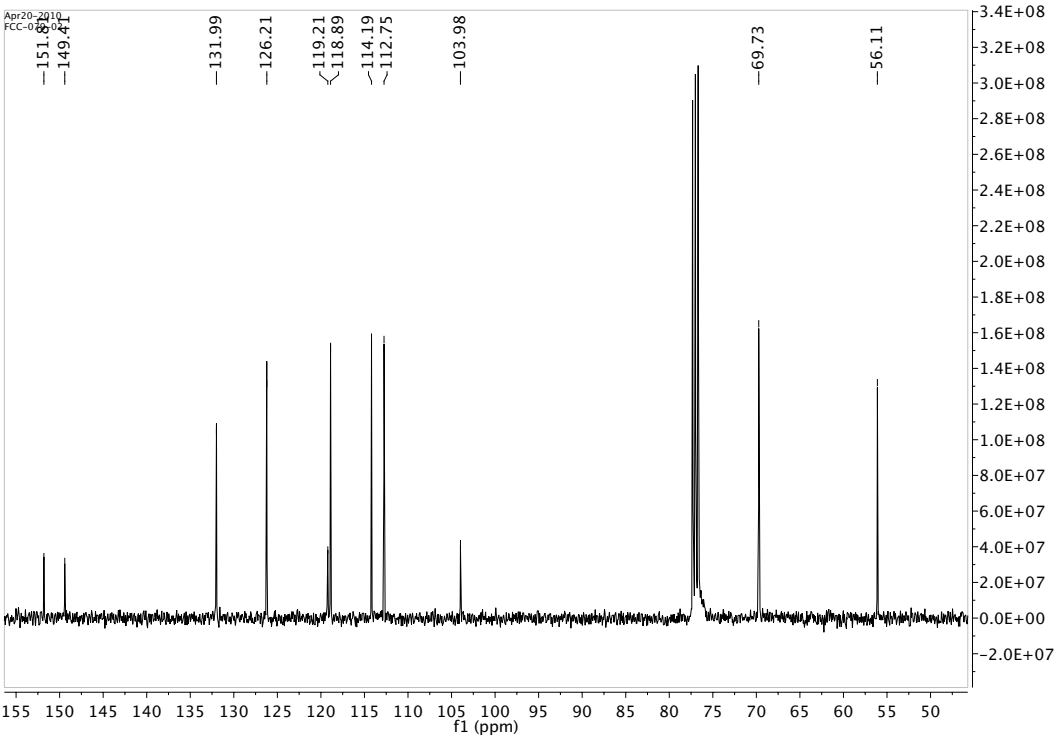
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Maximum:		7.0	10.0	50.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
555.3441	555.3434	0.7	1.3	10.5	426.4	1.1	C32	H47	N2	O6
	555.3448	-0.7	-1.3	15.5	425.9	0.7	C33	H43	N6	O2
	555.3466	-2.5	-4.5	2.5	436.9	11.6	C21	H47	N8	O9
	555.3474	-3.3	-5.9	14.5	427.2	2.0	C37	H47	O4	
	555.3407	3.4	6.1	11.5	431.4	6.2	C28	H43	N8	O4
	555.3394	4.7	8.5	6.5	432.9	7.6	C27	H47	N4	O8
	555.3488	-4.7	-8.5	19.5	429.2	4.0	C38	H43	N4	
	555.3493	-5.2	-9.4	1.5	434.3	9.0	C25	H51	N2	O11
	555.3381	6.0	10.8	1.5	434.4	9.2	C26	H51	O12	
	555.3506	-6.5	-11.7	6.5	433.6	8.3	C26	H47	N6	O7
	555.3375	6.6	11.9	19.5	431.4	6.1	C39	H43	N2	O

4-Allyloxy-3-methoxybenzonitrile (70)

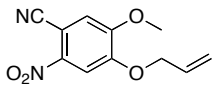


Compound **70** was prepared as follows:[18] To an ice-cooled solution of benzonitrile **57** (2.00 g, 13.4 mmol) in acetone (150 mL) were slowly added K_2CO_3 (2.22 g, 16.1 mmol), followed by allyl bromide (2.32 mL, 26.8 mmol). The solution was refluxed for 3 h, time after which it was quenched with water (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and rotary evaporated to afford the title compound **70** (2.33 g, 92%) as a white solid that was used in the next step without further purification: m.p. 48 – 50 ˚C; IR (neat) 2223, 1595, 1512, 1241, 1135, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.10 – 6.00 (m, 1H), 5.42 (*app*-dq, *J* = 17.4, 1.3 Hz, 1H), 5.36 (*app*-dq, *J* = 10.4, 1.3 Hz, 1H), 4.66 (*app*-dt, *J* = 5.4, 1.3 Hz, 2H), 3.89 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 151.9, 149.5, 132.0, 126.3, 119.3, 118.9, 114.2, 112.8, 104.0, 69.8, 56.2; MS (CI) *m/z* 207 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{11}H_{15}N_2O_2$ 207.1134, found: 207.1133.

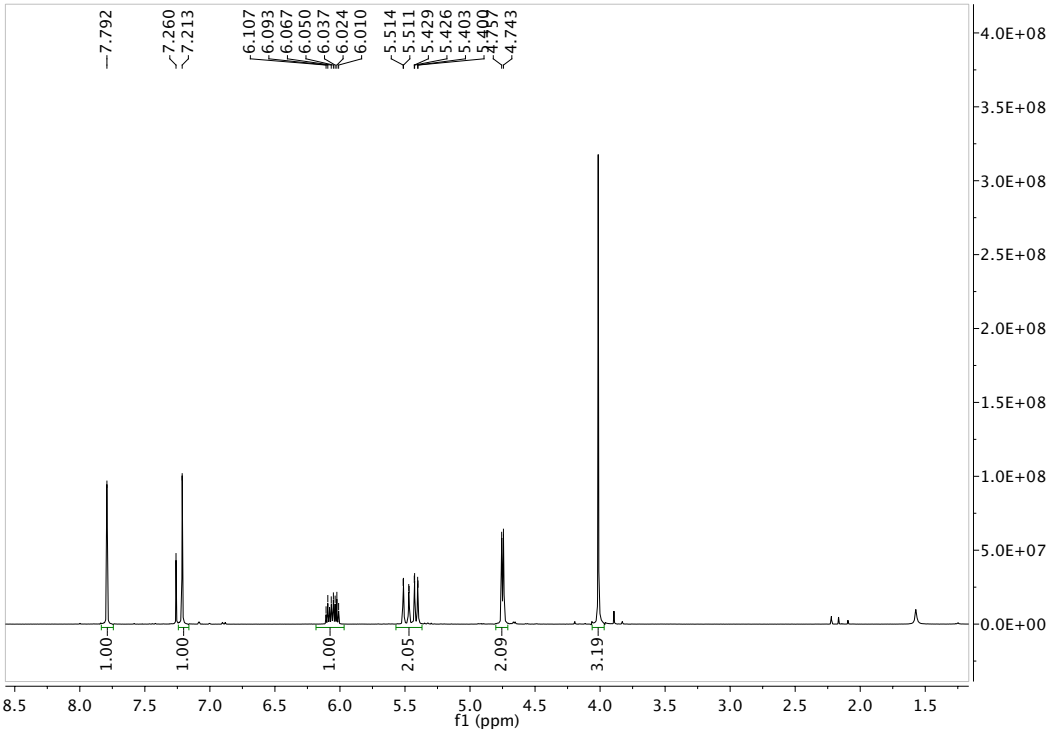


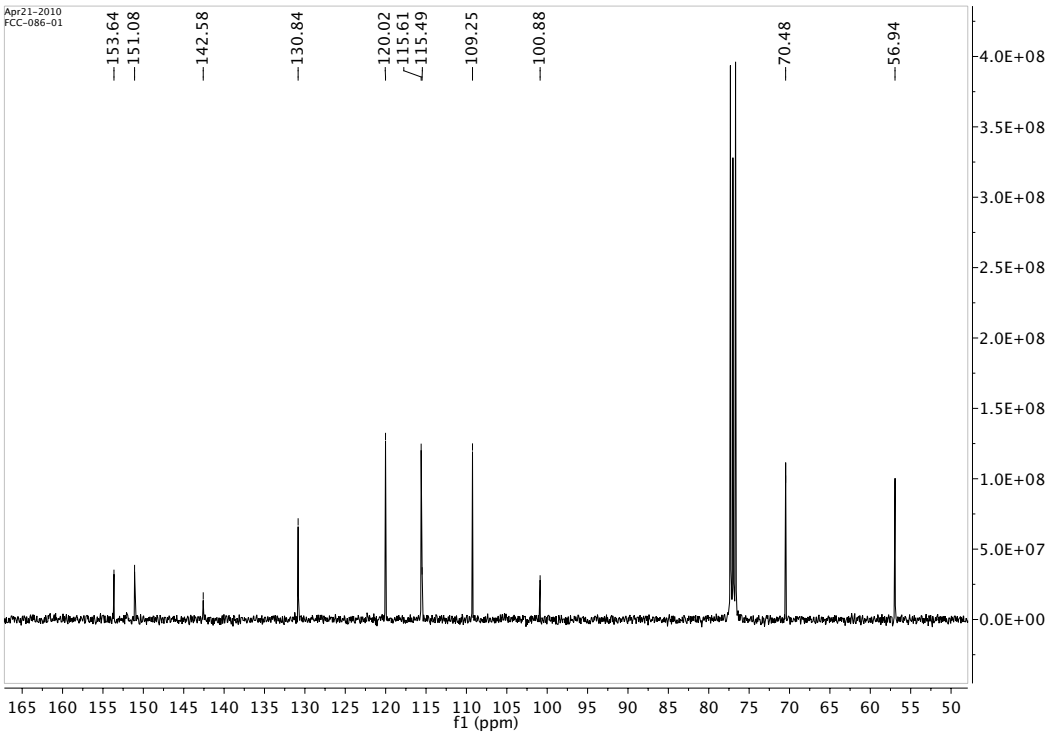


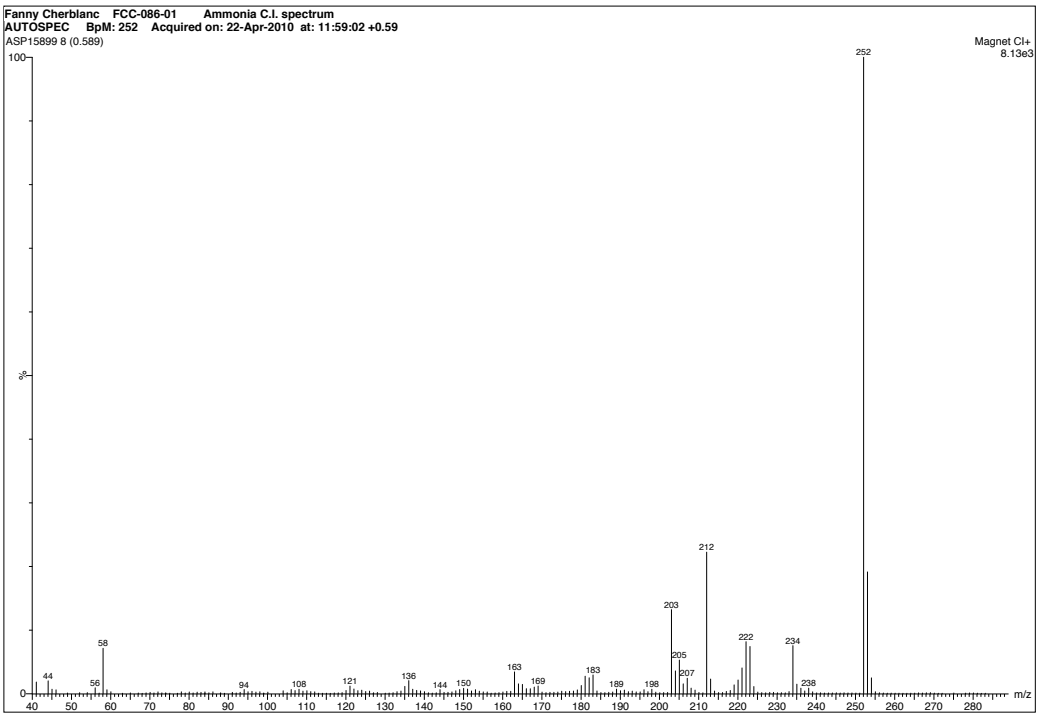
4-Allylyloxy-5-methoxy-2-nitrobenzonitrile (71)



Compound **71** was prepared as follows:[18] Nitric acid (1.4 mL of 69 wt% solution in water, 21.14 mmol) was slowly added to a solution of benzonitrile **70** (2.00 g, 10.57 mmol) in acetic anhydride (50 mL) at 0 ˚C. The reaction was allowed to stir for 1 h at room temperature, time after which the mixture was poured into ice-water and the resulting precipitate was filtered, washed with water and dried under vacuum to afford the title compound **71** (2.216 g, 89%) as a pale yellow solid that was used in the next step without further purification: m.p. 156 – 158 ˚C; IR (neat) 2224, 1572, 1507, 1334, 1224, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.21 (s, 1H), 6.11 – 6.01 (m, 1H), 5.49 (*app*-dq, *J* = 17.2, 1.2 Hz, 1H), 5.41 (*app*-dq, *J* = 10.4, 1.2 Hz, 1H), 4.75 (*app*-dt, *J* = 5.6, 1.2 Hz, 2H), 4.01 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 153.6, 151.1, 142.6, 130.8, 120.0, 115.6, 115.5, 109.2, 100.9, 70.5, 56.9; MS (CI) *m/z* 252 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{11}H_{14}N_3O_4$ 252.0984, found: 252.0982.


7.792
7.260
7.213
6.107
6.093
6.067
6.050
6.037
6.024
6.010
5.514
5.511
5.429
5.426
5.403
5.400
4.757
4.743
1.00
1.00
1.00
2.05
2.09
3.19
f1 (ppm)

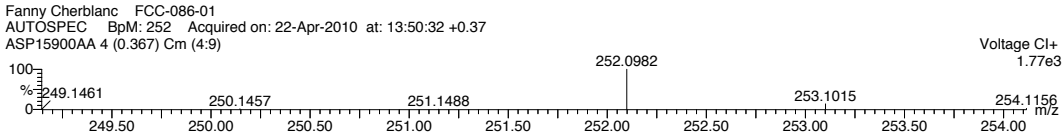

Apr21-2010
FCC-086-01
153.64
151.08
142.58
130.84
120.02
115.61
115.49
109.25
100.88
70.48
56.94
f1 (ppm)



Elemental Composition Report **Page 1**

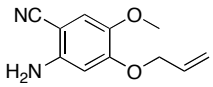
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Even Electron Ions
230 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)



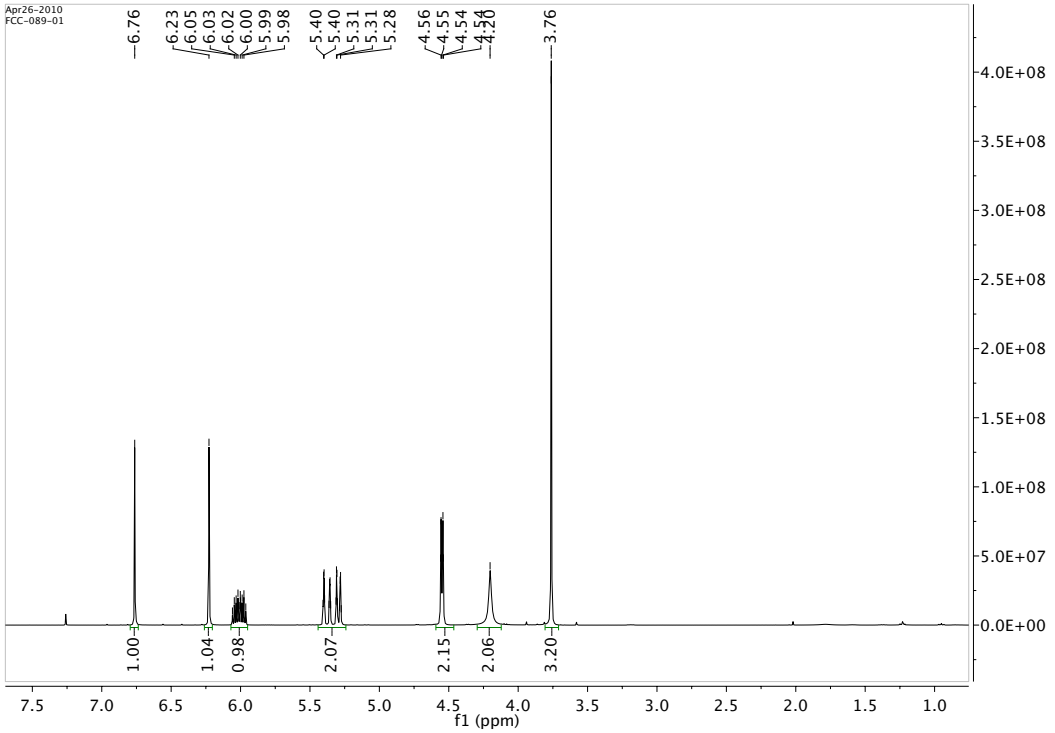
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Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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	252.0944	3.8	15.0	2.5	2	C6 H14 N5 O6
	252.1025	-4.3	-16.9	10.5	3	C16 H14 N O2

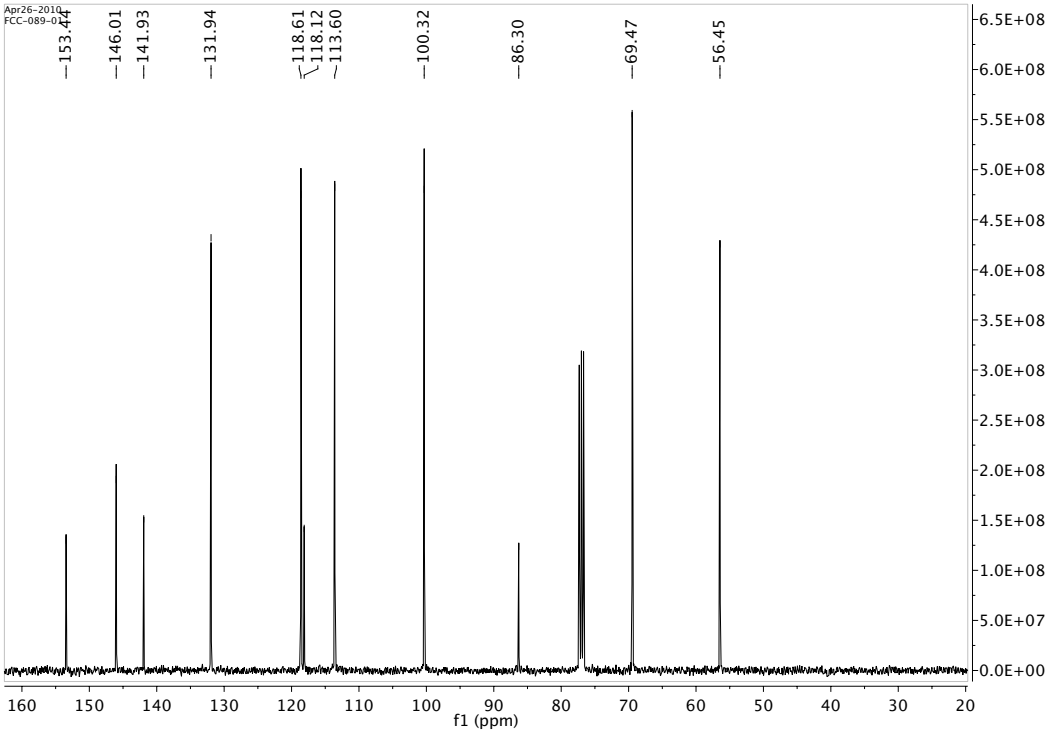
2-Amino-4-allyloxy-2-methoxybenzonitrile (72)

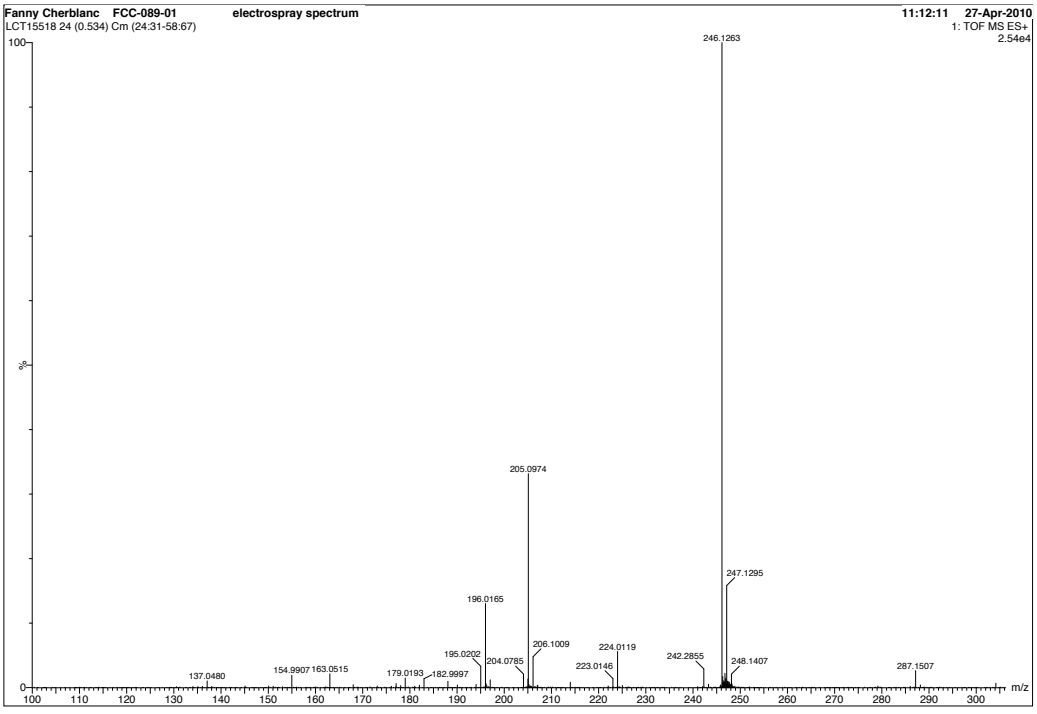


Compound **72** was prepared as follows:[19] To a solution of nitrobenzonitrile **71** (2.21 g, 9.39 mmol) in CH_2Cl_2 (50 mL) was added tetrabutylammonium bromide (2.1 g, 6.57 mmol), followed by the slow addition of a solution of sodium dithionite (9.8 g, 56.3 mmol) in water (50 mL). The mixture was allowed to stir for 3 h at room temperature

and then basified with 2 N aq. NaOH at 0 ˚C. The organic layer was recovered and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). A precipitate was obtained upon treatment of the combined organic layer with 1M HCl in Et_2O. The white solid was filtered and dissolved in water. The aqueous layer was basified with 2N NaOH and extracted with EtOAc (2 × 100 mL). The organic layer was dried ($MgSO_4$) and rotary evaporated to give the title compound **72** (1.32 g, 69%) as a white solid that was used in the next step without further purification: m.p. 50 – 52 ˚C; IR (neat) 3438, 3355, 3248, 2200, 1646, 1507, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.23 (s, 1H), 6.06 – 5.96 (m, 1H), 5.37 (*app*-dq, *J* = 17.2, 1.5 Hz, 1H), 5.29 (*app*-dq, *J* = 10.4, 1.5 Hz, 1H), 4.55 (*app*-dt, *J* = 5.6, 1.5 Hz, 2H), 4.20 (br s, 2H), 3.76 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 153.4, 146.0, 141.9, 131.9, 118.6, 118.1, 113.6, 100.3, 86.3, 69.5, 56.4; MS (ESI) *m/z* 205 $(M+H)^+$, 246 $(M+MeCN+H)^+$; HRMS (ESI) *m/z* calc. for $C_{11}H_{13}N_2O_2$ 205.0977 found: 205.0974.




Apr26-2010
FCC-089-01
153.44
146.01
141.93
131.94
118.61
118.12
113.60
100.32
86.30
69.47
56.45
6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

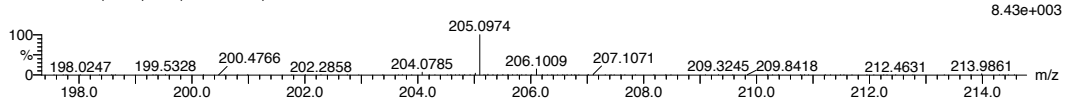

Fanny Cherblanc FCC-089-01 electrospray spectrum
11:12:11 27-Apr-2010
LCT15518 24 (0.534) Cm (24:31-58:67)
1: TOF MS ES+
2.54e4
100
%
0
246.1263
205.0974
247.1295
196.0165
206.1009
224.0119
195.0202
204.0785
242.2855
248.1407
223.0146
287.1507
137.0480
154.9907
163.0515
179.0193
182.9997
100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 7.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

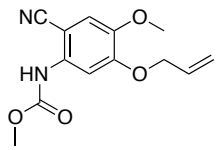
Monoisotopic Mass, Even Electron Ions
197 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC-089-01 electrospray spectrum 11:12:11 27-Apr-2010
LCT15518 24 (0.534) Cm (24:31-58:67) 1: TOF MS ES+
8.43e+003

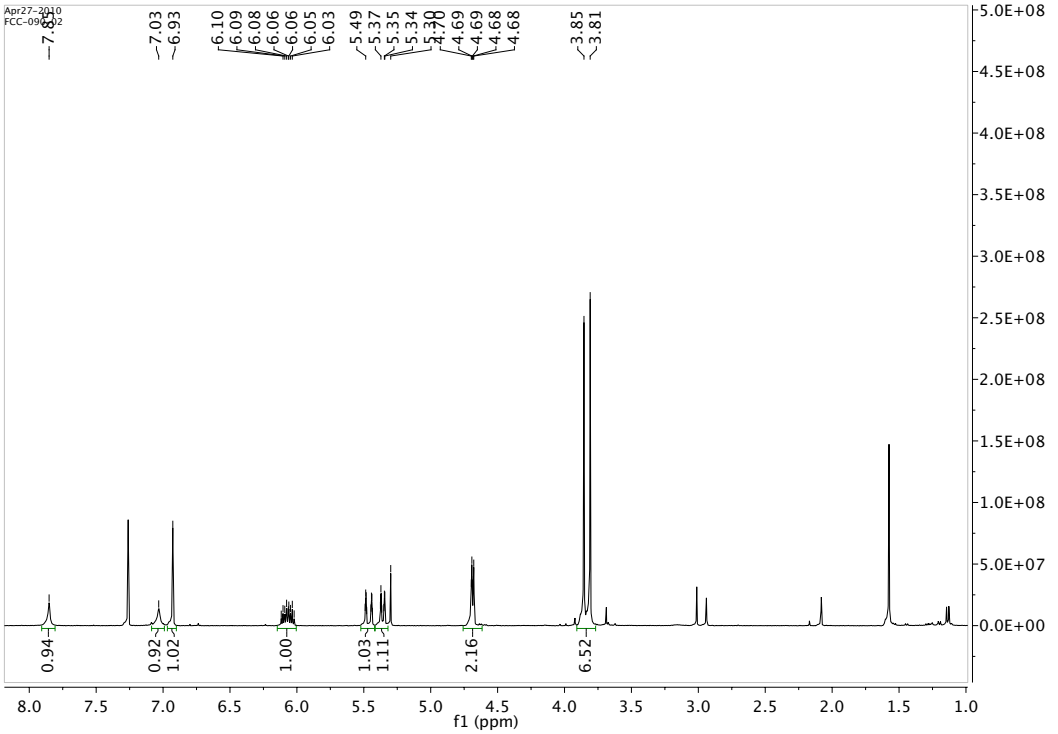


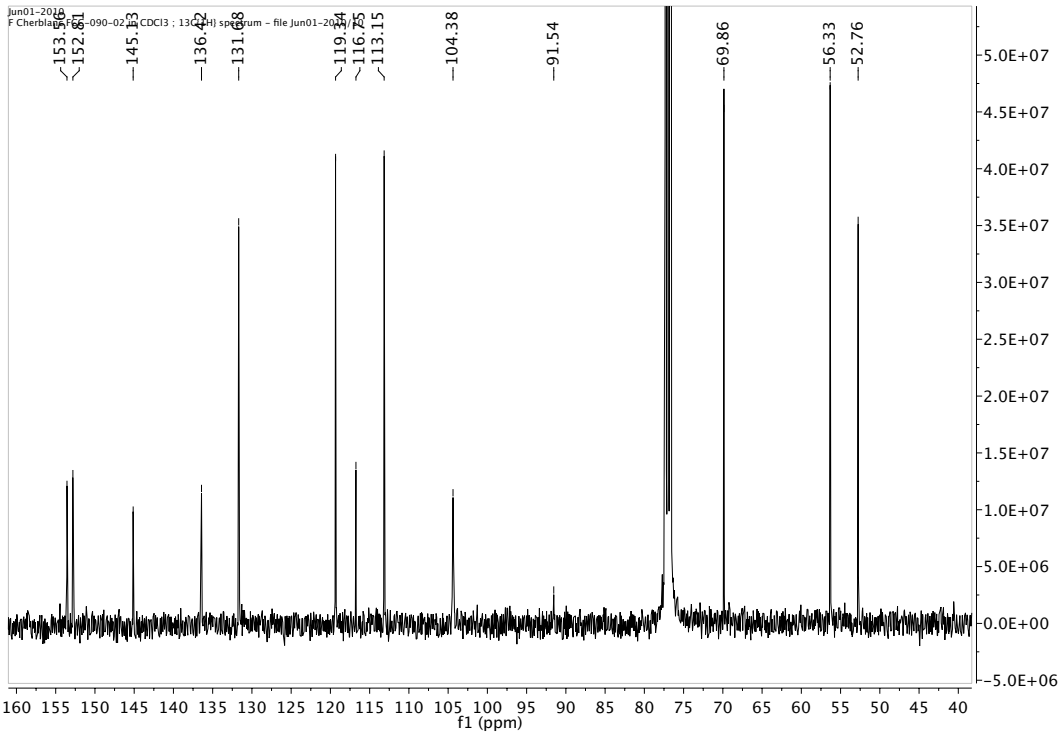
Minimum:				-1.5			
Maximum:		7.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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	205.0950	2.4	11.7	7.5	184.8	3.0	C7 H9 N8
	205.1009	-3.5	-17.1	-1.5	193.7	11.9	H13 N8 O5
	205.0937	3.7	18.0	2.5	187.0	5.2	C6 H13 N4 O4
	205.1017	-4.3	-21.0	10.5	184.0	2.2	C16 H13

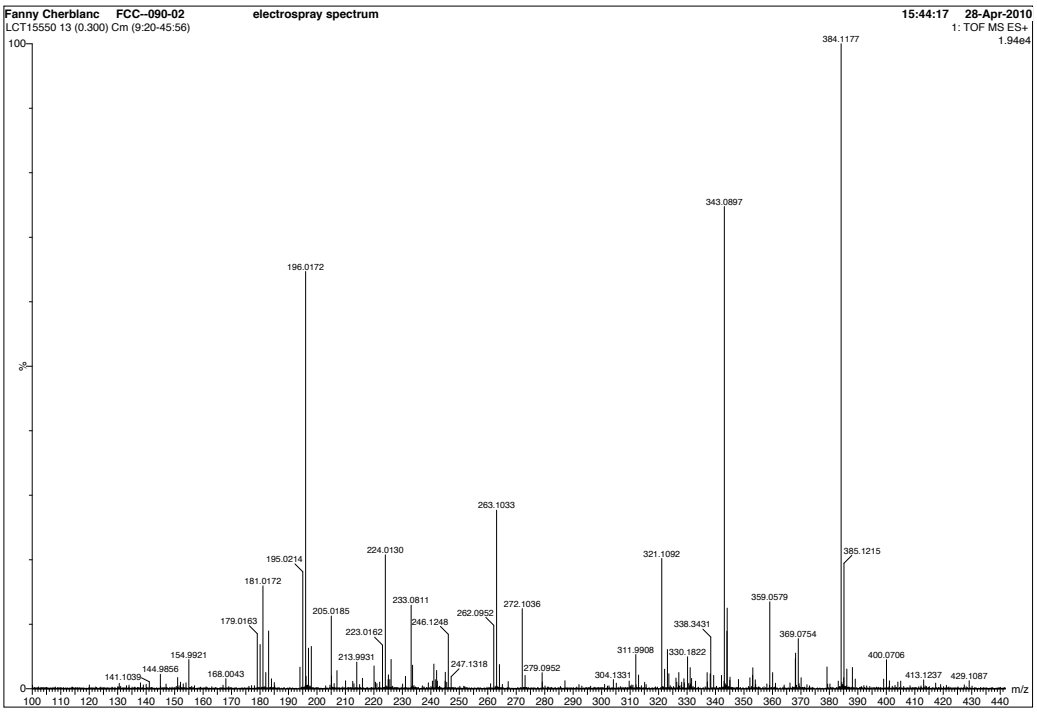
Methyl (5-(allyloxy)-2-cyano-4-methoxyphenyl)carbamate (73)



Compound **73** was prepared as follows:[18] To a solution of aniline **72** (1.382 g, 6.77 mmol) and DIEA (4.7 mL, 27.1 mmol) in DMA – CH_2Cl_2 (10 mL : 5 mL) at 0 ˚C was added methyl chloroformate (784 μL, 10.15 mmol). The mixture was allowed to stir overnight at room temperature. Water (30 mL) was added and the resulting precipitate was recovered, washed with water and dried under vacuum. It was re-dissolved in CH_2Cl_2 and washed with 1M aq. HCl, then with brine, dried ($MgSO_4$) and rotary evaporated to afford the title compound **73** (1.415 g, 80%) as a white solid that was used in the next step without further purification: IR (neat) 2223, 1734, 1600, 1524, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.03 (br s, 1H), 6.93 (s, 1H), 6.12 – 6.02 (m, 1H), 5.46 (*app*-dq, *J* = 17.2, 1.3 Hz, 1H), 5.36 (*app*-dq, *J* = 10.4, 1.3 Hz, 1H), 4.69 (*app*-dt, *J* = 5.4, 1.3 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 153.6, 152.8, 145.1, 136.4, 131.7, 119.3, 116.7, 113.1, 104.4, 91.5, 69.9, 56.3, 52.8; MS (ESI) *m/z* 263 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{13}H_{15}N_2O_4$ 263.1032 found: 263.1033.


Apr27-2010
FCC-090-02
7.85
7.03
6.93
6.10
6.09
6.08
6.06
6.06
6.05
6.03
5.49
5.37
5.35
5.34
5.30
4.70
4.69
4.68
4.68
3.85
3.81
0.94
0.92
1.02
1.00
1.03
1.11
2.16
6.52
f1 (ppm)

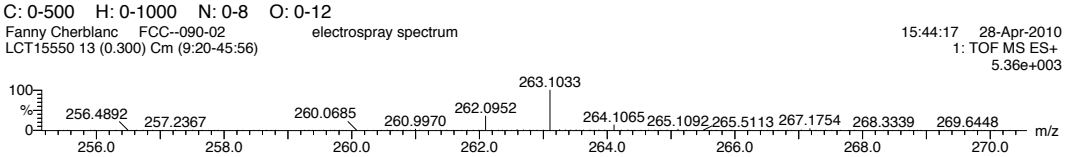

Jun01-2010
153.46
152.61
145.03
136.22
131.08
119.24
116.75
113.15
104.38
91.54
69.86
56.33
52.76
f1 (ppm)



Elemental Composition Report **Page 1**

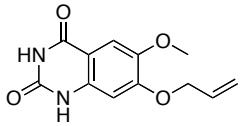
Single Mass Analysis
Tolerance = 7.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
296 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12



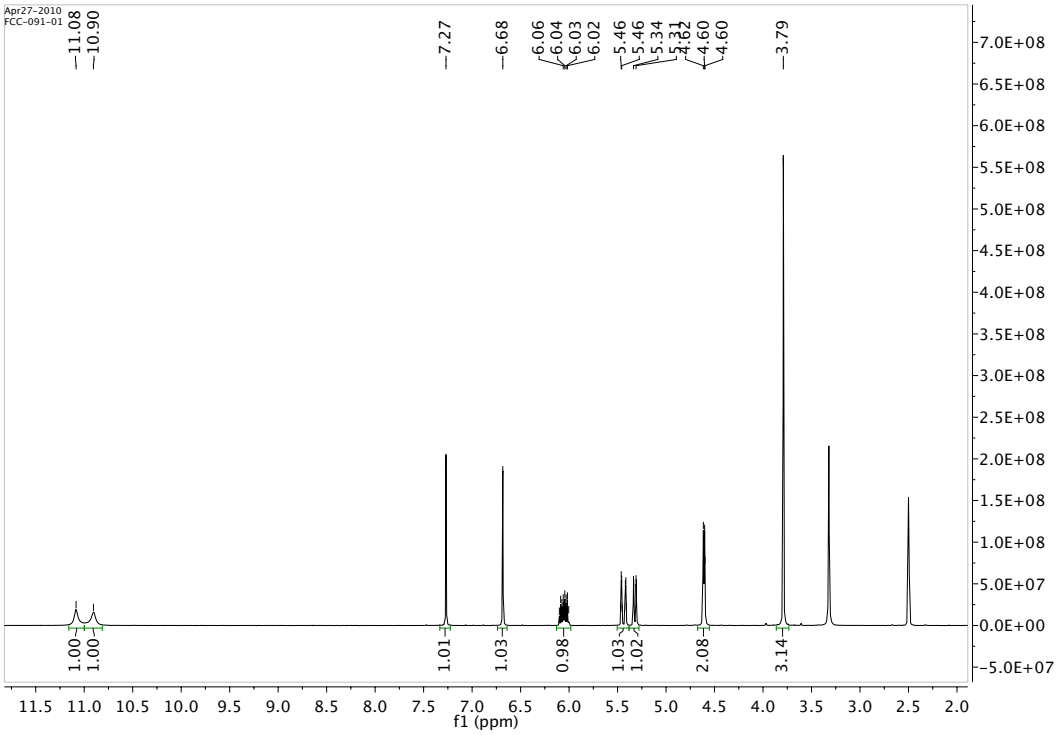
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Maximum:		7.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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	263.1045	-1.2	-4.6	12.5	265.4	1.6	C14 H11 N6
	263.1005	2.8	10.6	8.5	265.6	1.8	C9 H11 N8 O2
	263.1064	-3.1	-11.8	-0.5	273.5	9.7	C2 H15 N8 O7
	263.1072	-3.9	-14.8	11.5	268.6	4.8	C18 H15 O2
	263.0992	4.1	15.6	3.5	266.7	2.9	C8 H15 N4 O6
	263.0978	5.5	20.9	-1.5	269.3	5.5	C7 H19 O10
	263.1091	-5.8	-22.0	-1.5	269.4	5.6	C6 H19 N2 O9

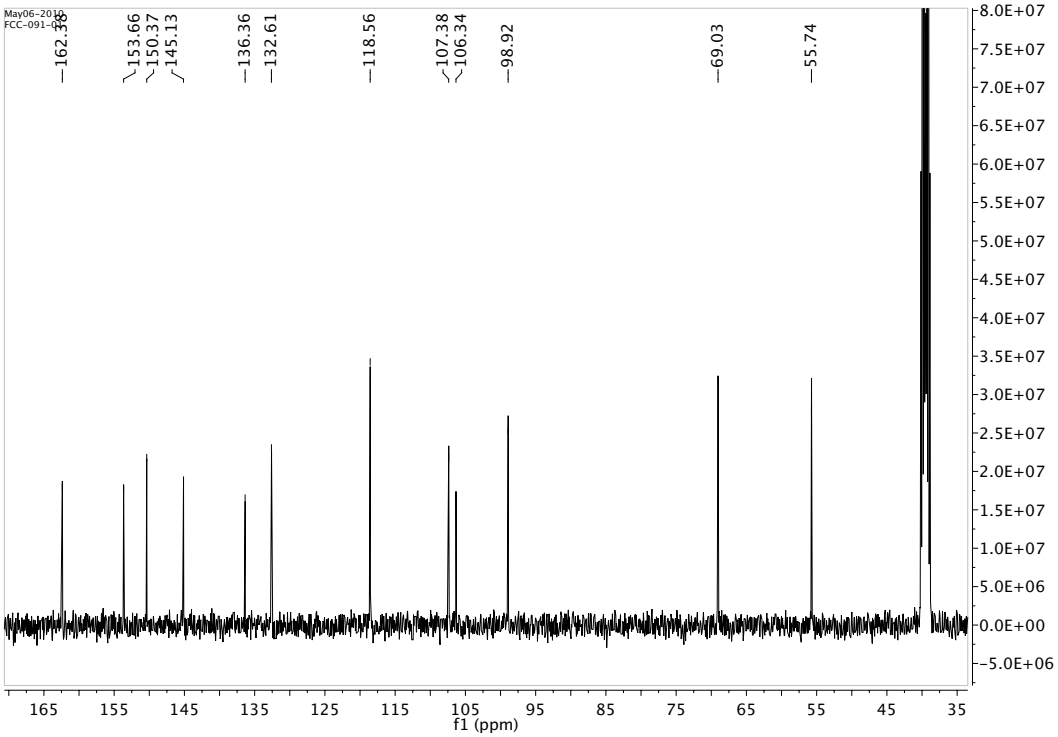
7-(Allyloxy)-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (74)

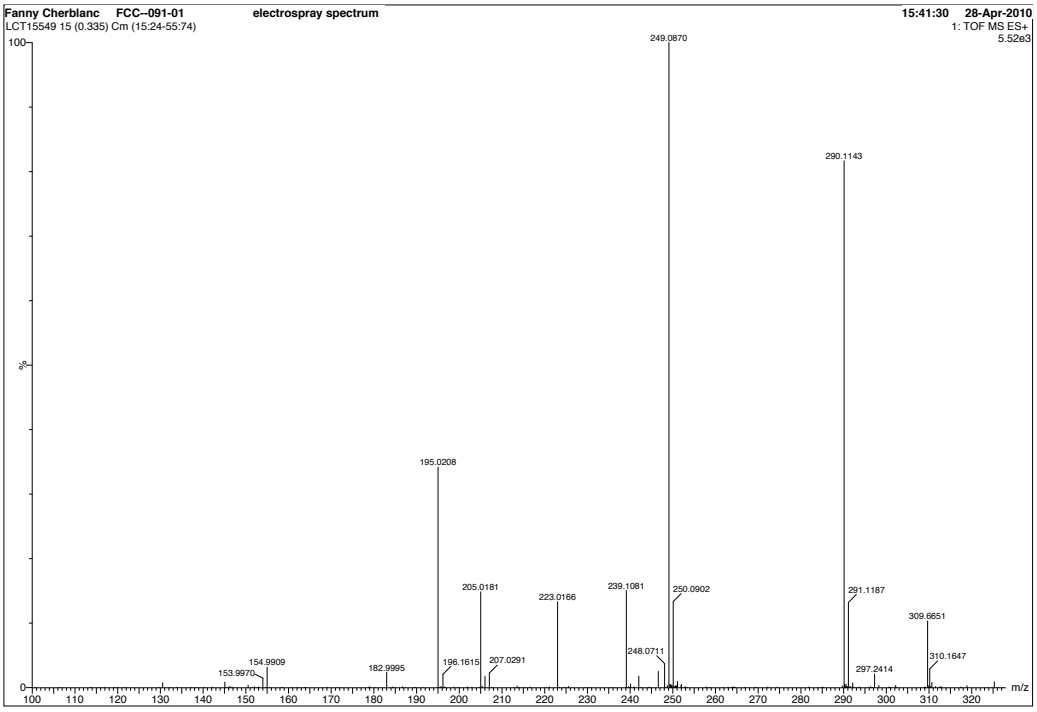


Compound **74** was prepared as follows:[18] Carbamate **73** (1.415 g, 5.4 mmol) was added to a solution of H_2O_2 (10 mL of 35 wt% solution in water, 110 mmol) and

NaOH (2.13 g, 54 mmol) in ethanol (100 mL) and the resulting mixture was allowed to stir for 4 h under reflux. Water (100 mL) was added and the solution was allowed to cool to room temperature, then acidified with 1 N aq. HCl. The resulting precipitate was recovered, washed with water and dried to afford the title compound **74** (932 mg, 69%) as a white solid that was used in the next step without further purification: m.p. 202 – 204 ˚C; IR (neat) 1709, 1649, 1621, 1267, 1206 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 11.08 (br s, 1H), 10.90 (br s, 1H), 7.27 (s, 1H), 6.68 (s, 1H), 6.10 – 6.00 (m, 1H), 5.44 (*app*-dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (*app*-dq, *J* = 10.4, 1.5 Hz, 1H), 4.60 (*app*-dt, *J* = 5.4, 1.5 Hz, 2H), 3.79 (s, 3H); ^{13}C (100 MHz, DMSO) δ 162.4, 153.7, 150.4, 145.1, 136.4, 132.6, 118.6, 107.4, 106.3, 98.9, 69.0, 55.7; MS (ESI) *m/z* 249 $(M+H)^+$, 290 $(M+MeCN+H)^+$; HRMS (ESI) *m/z* calc. for $C_{12}H_{13}N_2O_4$ 249.0875, found: 249.0870.




May06-2010
FCC-091-01
162.38
153.66
150.37
145.13
136.36
132.61
118.56
107.38
106.34
98.92
69.03
55.74
f1 (ppm)

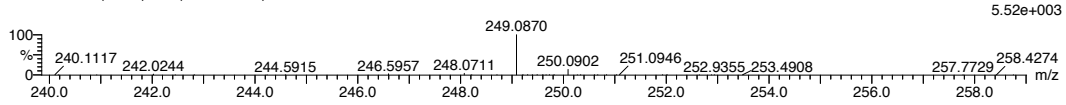

Fanny Cherblanc FCC--091-01 electrospray spectrum
15:41:30 28-Apr-2010
LCT15549 15 (0.335) Cm (15:24-55:74)
1: TOF MS ES+
5.52e3
249.0870
290.1143
195.0208
205.0181
223.0166
239.1081
250.0902
291.1187
309.6651
310.1647
248.0711
154.9909
153.9970
182.9995
196.1615
207.0291
297.2414
%
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 7.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

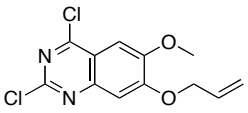
Monoisotopic Mass, Even Electron Ions
271 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC--091-01 electrospray spectrum 15:41:30 28-Apr-2010
LCT15549 15 (0.335) Cm (15:24-55:74) 1: TOF MS ES+
5.52e+003

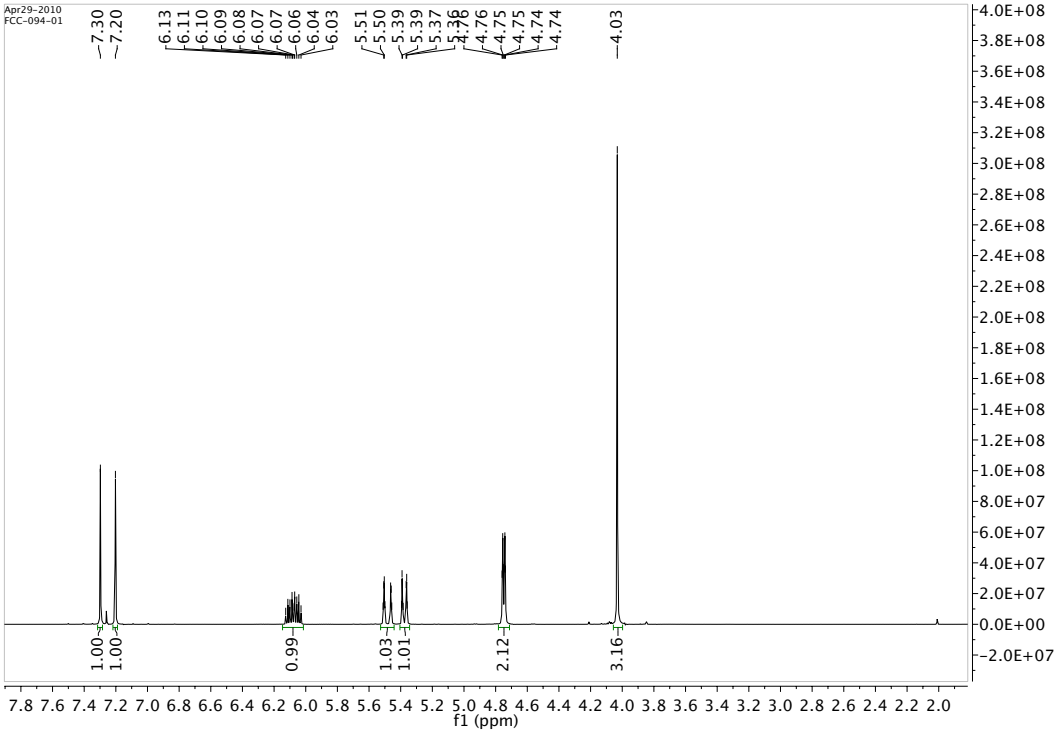


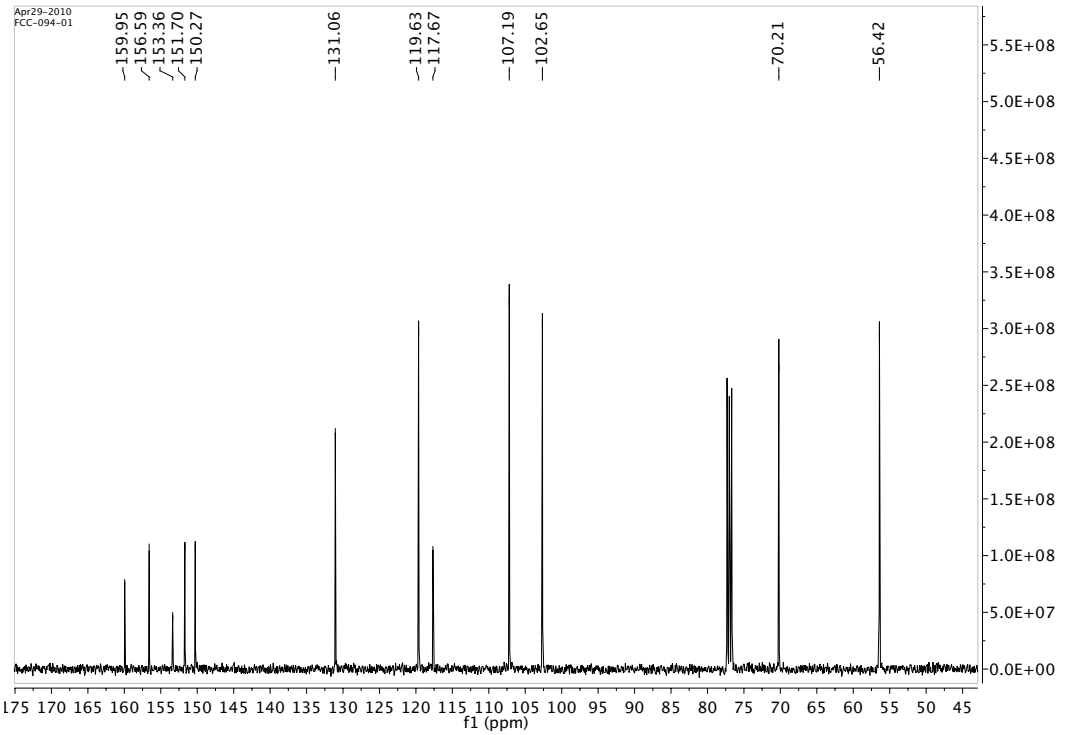
Minimum:				-1.5			
Maximum:		7.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
249.0870	249.0875	-0.5	-2.0	7.5	106.9	2.6	C12 H13 N2 O4
	249.0889	-1.9	-7.6	12.5	106.1	1.8	C13 H9 N6
	249.0848	2.2	8.8	8.5	104.6	0.3	C8 H9 N8 O2
	249.0835	3.5	14.1	3.5	109.5	5.3	C7 H13 N4 O6
	249.0907	-3.7	-14.9	-0.5	115.7	11.4	C H13 N8 O7
	249.0916	-4.6	-18.5	11.5	110.7	6.4	C17 H13 O2
	249.0822	4.8	19.3	-1.5	112.5	8.2	C6 H17 O10
	249.0934	-6.4	-25.7	-1.5	112.9	8.6	C5 H17 N2 O9

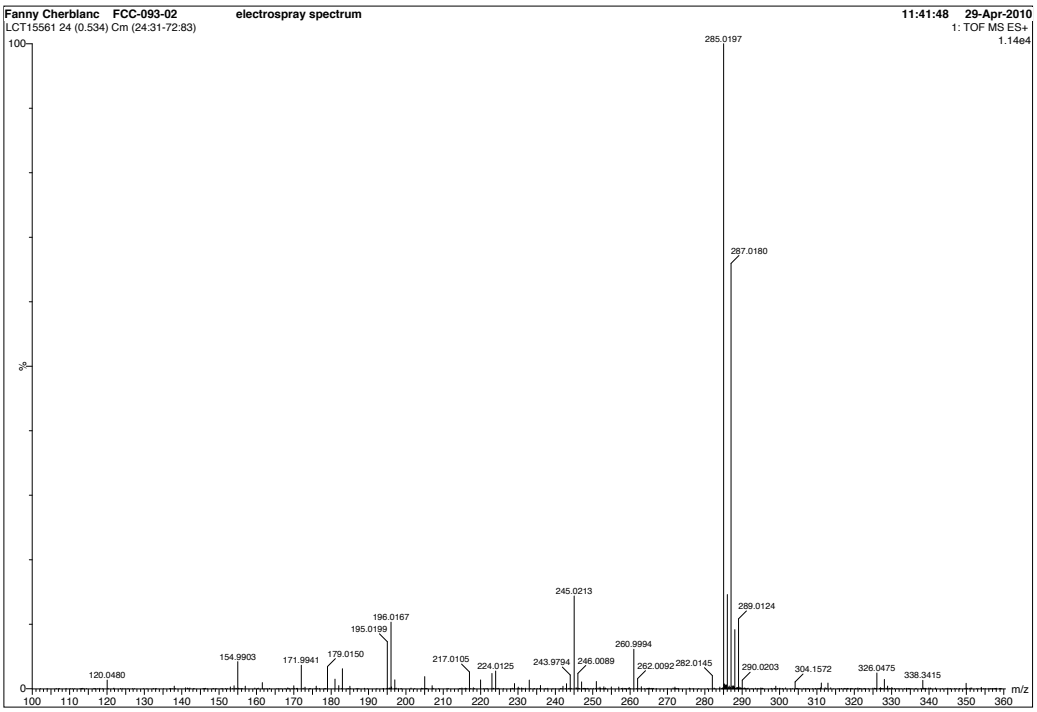
7-(Allyloxy)-2,4-dichloro-6-methoxyquinazoline (69)



Compound **69** was prepared as follows:[18] A mixture of quinazolinedione **74** (920 mg, 3.69 mmol), *N,N*-diethylaniline (649 μL, 4.07 mmol) and $POCl_3$ (20 mL) was allowed to stir under reflux for 1.5 h. The solution was slowly poured into a sat. aq. $NaHCO_3$ at 0 ˚C. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and purified by column chromatography (EtOAc : Hexanes, 3 : 7) to afford the title compound **69** (908 mg, 86%) as a white solid: m.p. 92 – 94 ˚C; IR (neat) 1614, 1549, 1500, 1415, 1237, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.20 (s, 1H), 6.13 – 6.03 (m, 1H), 5.52 (*app*-dq, *J* = 17.2, 1.2 Hz, 1H), 5.37 (*app*-dq, *J* = 10.4, 1.2 Hz, 1H), 4.75 (*app*-dt, *J* = 5.6, 1.2 Hz, 2H), 4.03 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.9, 156.6, 153.4, 151.7, 150.3, 131.1, 119.6, 117.7, 107.2, 102.6, 70.2, 56.4; MS (ESI) *m/z* 285 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{12}H_{11}N_2O_2Cl_2$ 285.0198, found: 285.0197.


Apr29-2010
FCC-094-01
7.30
7.20
6.13
6.11
6.10
6.09
6.08
6.07
6.07
6.06
6.04
6.03
5.51
5.50
5.39
5.39
5.37
4.76
4.75
4.75
4.74
4.74
4.03
1.00
1.00
0.99
1.03
1.01
2.12
3.16
f1 (ppm)

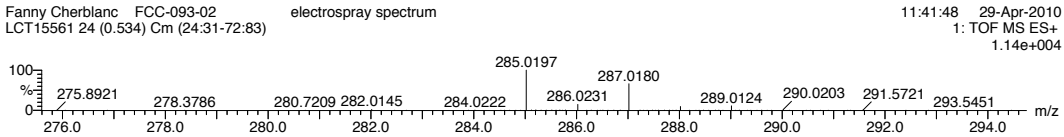

Apr29-2010
FCC-094-01
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156.59
153.36
151.70
150.27
131.06
119.63
117.67
107.19
102.65
70.21
56.42
f1 (ppm)



Elemental Composition Report **Page 1**

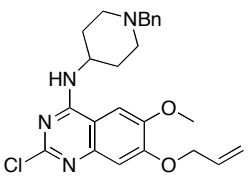
Single Mass Analysis
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Element prediction: On (Carbon range ± 5) (Set 0 < Cl < 9, 0< Br < 9 and 0 < S < 7 for enhanced filtering)
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
800 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 Cl: 0-2

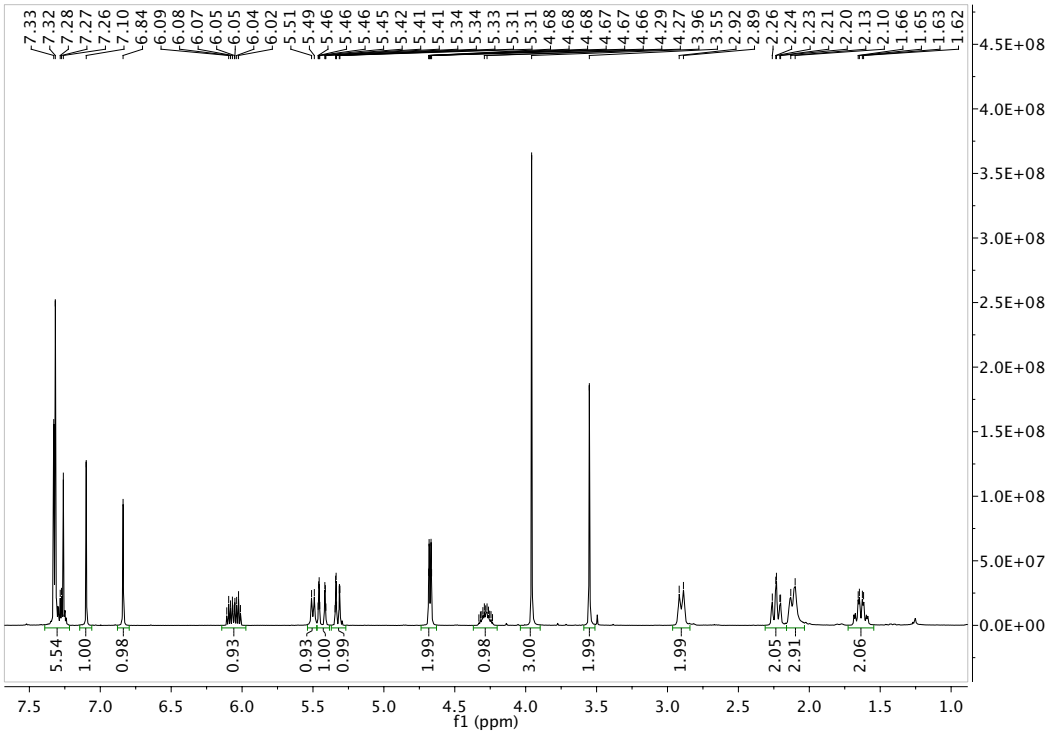


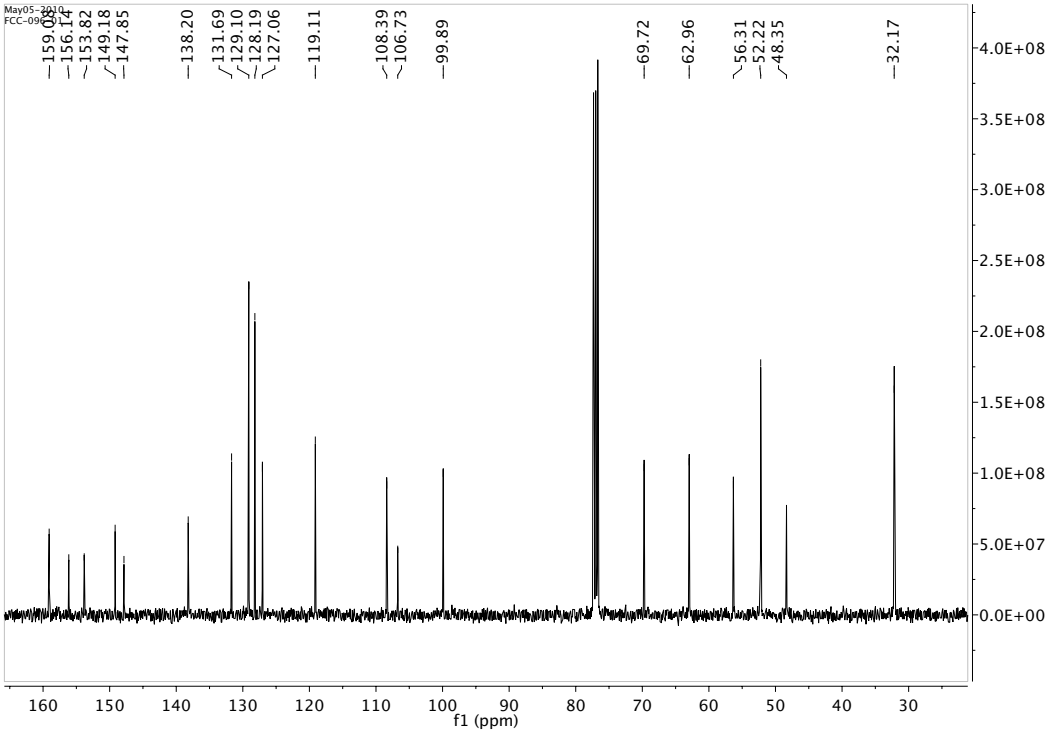
Minimum:				-1.5			
Maximum:		7.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
285.0197	285.0198	-0.1	-0.4	7.5	235.3	0.0	C12 H11 N2 O2 Cl2
	285.0171	2.6	9.1	8.5	244.1	8.8	C8 H7 N8 Cl2
	285.0157	4.0	14.0	3.5	248.1	12.8	C7 H11 N4 O4 Cl2
	285.0238	-4.1	-14.4	11.5	247.5	12.2	C17 H11 Cl2

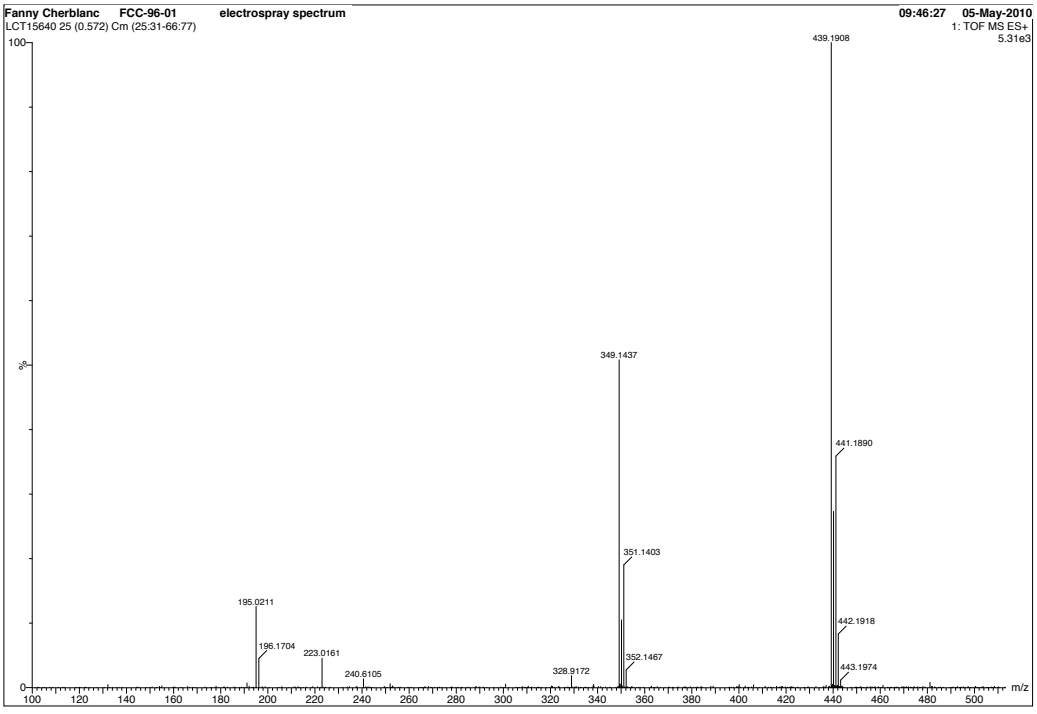
7-(Allyloxy)-*N*-(1-benzylpiperidin-4-yl)-2-chloro-6-methoxy-quinazolin-4-amine (75)



Compound **75** was prepared as follows:[18] A mixture of dichloroquinazoline **69** (102 mg, 0.36 mmol), 4-amino-1-benzylpiperidine (**64**, 214 μL, 1.07 mmol) and DIEA (92 μL, 0.536 mmol) in THF (2 mL) was allowed to stir for 8 h at room temperature. The solution was then rotary evaporated and purified by column chromatography (MeOH : CH_2Cl_2, 4 : 96) to afford the title compound **75** (133.5 mg, 85%) as a white solid: m.p. 90 – 92 ˚C; IR (neat) 3313, 1584, 1510, 1452, 1253, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 5H), 7.10 (s, 1H), 6.84 (s, 1H), 6.11 – 6.01 (m, 1H), 5.50 (d, *J* = 7.8 Hz, 1H), 5.44 (*app*-dq, *J* = 17.3, 1.2 Hz, 1H), 5.32 (*app*-dq, *J* = 10.5, 1.2 Hz, 1H), 4.67 (*app*-dt, *J* = 5.4, 1.2 Hz, 2H), 4.33 – 4.23 (m, 1H), 3.96 (s, 3H), 3.55 (s, 2H), 2.90 (br *app*-d, *J* = 12.0 Hz, 2H), 2.23 (*app*-dt, *J* = 12.0, 1.5 Hz, 2H), 2.12 (br *app*-d, *J* = 12.0 Hz, 2H), 1.64 (*app*-dq, *J* = 12.0, 3.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.1, 156.1, 153.8, 149.2, 147.8, 138.2, 131.7, 129.1 (2C), 128.2 (2C), 127.1, 119.1, 108.4, 106.7, 99.9, 69.7, 62.9, 56.3, 52.2 (2C), 48.3, 32.2 (2C); MS (ESI) *m/z* 439 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{24}H_{28}N_4O_2Cl$ 439.1901, found: 439.1908.




May05-2010
FCC-09-01
159.04
156.14
153.82
149.18
147.85
138.20
131.69
129.10
128.19
127.06
119.11
108.39
106.73
99.89
69.72
62.96
56.31
52.22
48.35
32.17
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)


Fanny Cherblanc FCC-96-01 electrospray spectrum
09:46:27 05-May-2010
LCT15640 25 (0.572) Cm (25:31-66:77)
1: TOF MS ES+
5.31e3
100
%
0
439.1908
349.1437
441.1890
351.1403
195.0211
442.1918
196.1704
223.0161
352.1467
240.6105
328.9172
443.1974
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m/z

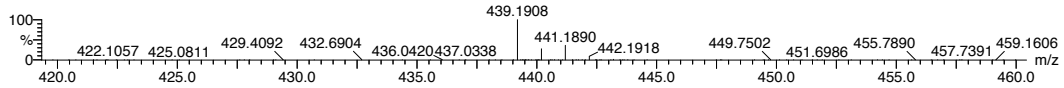
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 7.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
1047 formula(e) evaluated with 18 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 Cl: 0-1

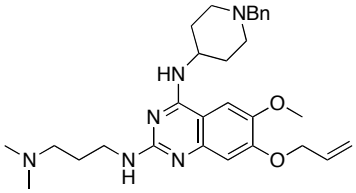
Fanny Cherblanc FCC-96-01 electrospray spectrum
LCT15640 25 (0.572) Cm (25:31-66:77)

09:46:27 05-May-2010
1: TOF MS ES+
5.31e+003



Minimum:				-1.5							
Maximum:		7.0	10.0	50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula				
439.1908	439.1909	-0.1	-0.2	16.5	146.5	25.1	C29	H27	O4		
	439.1901	0.7	1.6	4.5	145.4	24.0	C13	H27	N8	O9	
	439.1901	0.7	1.6	12.5	122.1	0.8	C24	H28	N4	O2	Cl
	439.1919	-1.1	-2.5	-0.5	131.0	9.7	C12	H32	N6	O9	Cl
	439.1923	-1.5	-3.4	21.5	146.6	25.2	C30	H23	N4		
	439.1928	-2.0	-4.6	3.5	145.8	24.5	C17	H31	N2	O11	
	439.1887	2.1	4.8	7.5	122.1	0.7	C23	H32	O6	Cl	
	439.1882	2.6	5.9	17.5	146.0	24.6	C25	H23	N6	O2	
	439.1941	-3.3	-7.5	16.5	128.7	7.3	C29	H28	N2	Cl	
	439.1941	-3.3	-7.5	8.5	145.8	24.4	C18	H27	N6	O7	
	439.1946	-3.8	-8.7	-1.5	131.0	9.6	C16	H36	O11	Cl	
	439.1869	3.9	8.9	12.5	146.1	24.7	C24	H27	N2	O6	
	439.1861	4.7	10.7	8.5	124.5	3.1	C19	H28	N6	O4	Cl
	439.1960	-5.2	-11.8	3.5	128.8	7.4	C17	H32	N4	O7	Cl
	439.1968	-6.0	-13.7	7.5	146.3	24.9	C22	H31	O9		
	439.1847	6.1	13.9	3.5	128.8	7.4	C18	H32	N2	O8	Cl
	439.1973	-6.5	-14.8	8.5	126.2	4.8	C18	H28	N8	O3	Cl
	439.1842	6.6	15.0	13.5	145.7	24.3	C20	H23	N8	O4	

7-(allyloxy)-N^4-(1-benzylpiperidin-4-yl)-N^2-(3-(dimethylamino)propyl)-6-methoxyquinazoline-2,4-diamine (76)



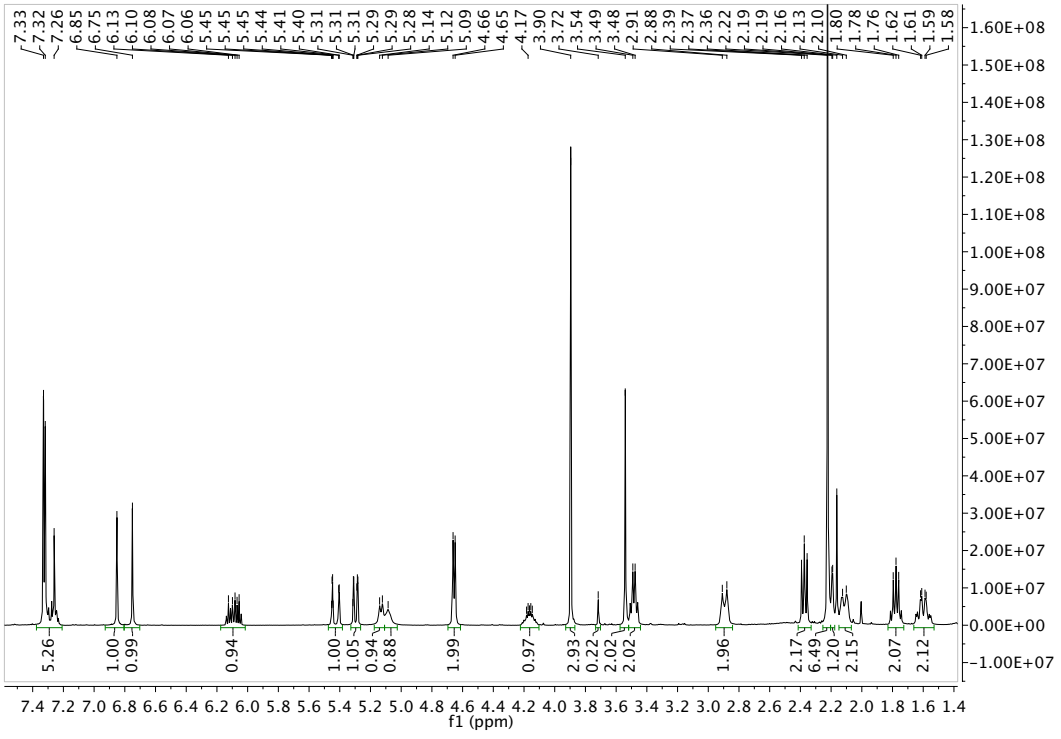
Procedure 1:[18]

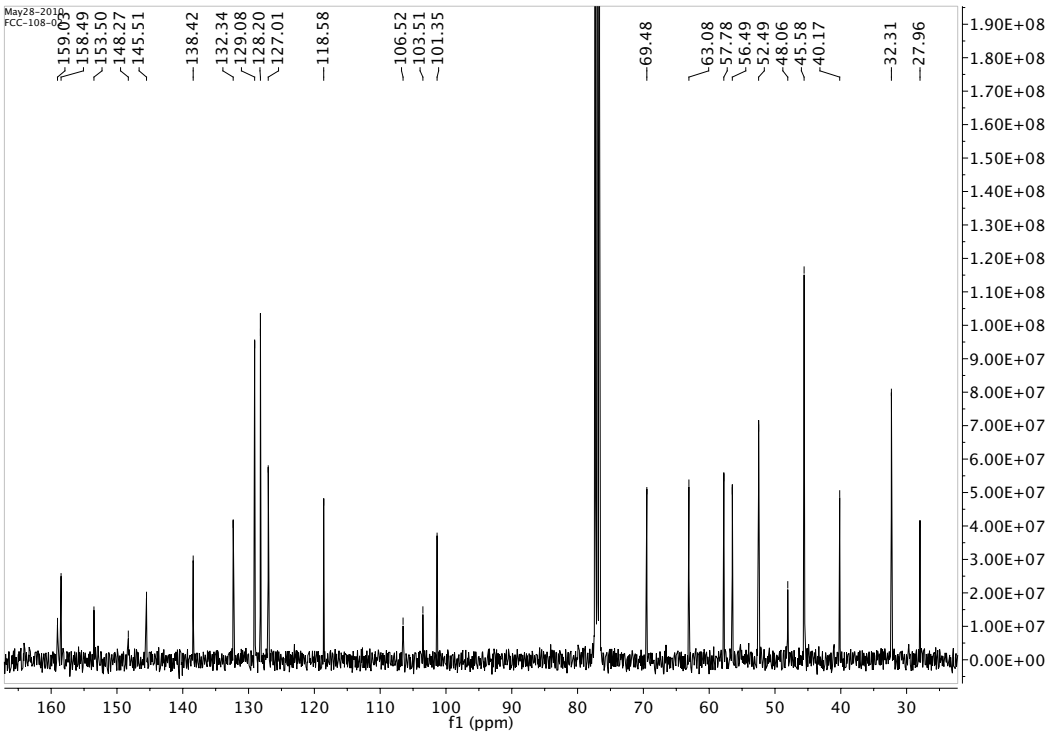
A mixture of chloroquinazoline **75** (478 mg, 1.09 mmol) and *N,N*-dimethyl-1,3-propanediamine (**66**, 1.5 mL, 11.4 mmol) in MeCN (1.5 mL) was allowed to stir for 3 days at reflux. The solution was then diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), rotary evaporated and purified by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH; 9 : 1) to afford the title compound **75** (426 mg, 77%).

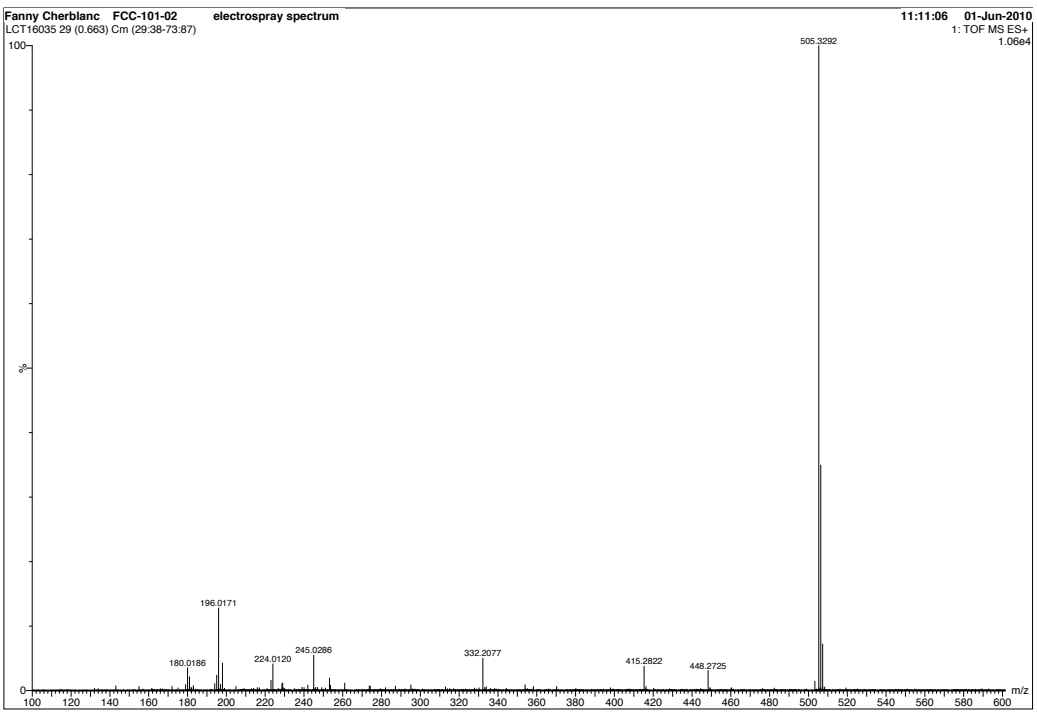
Procedure 2

Chloroquinazoline **75** (528 mg, 1.2 mmol) was refluxed in *N,N*-dimethyl-1,3-propanediamine (**66**, 10 mL, excess) for 16 h. The crude reaction mixture was then purified by column chromatography (CH_2Cl_2 : MeOH, 95 : 5, with 1% NH_3 aq. solution) to afford the title compound **76** (274 mg, 45%).

Compound **76** was obtained as a light yellow solid: m.p. 56 – 58 ˚C; IR (neat) 1579, 1498, 1454, 1246, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 6.85 (s, 1H), 6.75 (s, 1H), 6.15 – 6.06 (m, 1H), 5.43 (*app*-dq, *J* = 17.3, 1.2 Hz, 1H), 5.31 (*app*-dq, *J* = 10.5, 1.2 Hz, 1H), 5.13 (br d, *J* = 7.1 Hz, 1H), 5.09 (br s, 1H), 4.65 (*app*-dt, *J* = 5.4, 1.2 Hz, 2H), 4.22 – 4.12 (m, 1H), 3.90 (s, 3H), 3.54 (s, 2H), 3.48 (*app*-q, *J* = 7.0 Hz, 2H), 2.89 (br *app*-d, *J* = 12.0 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.22 (s, 6H), 2.19 (br *app*-td, *J* = 12.0, 2.1 Hz, 2H), 2.11 (br *app*-dd, *J* = 12.0, 3.2 Hz, 2H), 1.78 (quint, *J* = 7.0 Hz, 2H), 1.60 (*app*-dq, *J* = 12.0, 3.2 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.0, 158.5, 153.5, 148.3, 145.5, 138.4, 132.3, 129.1 (2C), 128.2 (2C), 127.0, 118.6, 106.5, 103.5, 101.3, 69.5, 63.1, 57.8, 56.5, 52.5 (2C), 48.1, 45.6 (2C), 40.2, 32.3 (2C), 27.9; MS (ESI) *m/z* 505 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{29}H_{41}N_6O_2$ 505.3291, found: 505.3292.




May28-2010
FCC-108-03
159.03
158.49
153.50
148.27
145.51
138.42
132.34
129.08
128.20
127.01
118.58
106.52
103.51
101.35
69.48
63.08
57.78
56.49
52.49
48.06
45.58
40.17
32.31
27.96
f1 (ppm)

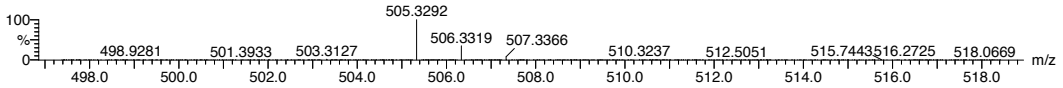

Fanny Cherblanc FCC-101-02 electrospray spectrum
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505.3292
196.0171
180.0186
224.0120
245.0286
332.2077
415.2822
448.2725
%
m/z

Elemental Composition Report **Page 1**

Single Mass Analysis
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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

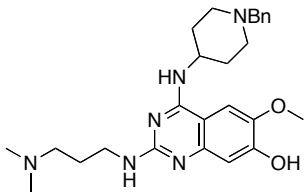
Monoisotopic Mass, Even Electron Ions
647 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC-101-02 electrospray spectrum 11:11:06 01-Jun-2010
LCT16035 29 (0.663) Cm (29:38-73:87) 1: TOF MS ES+
1.06e+004

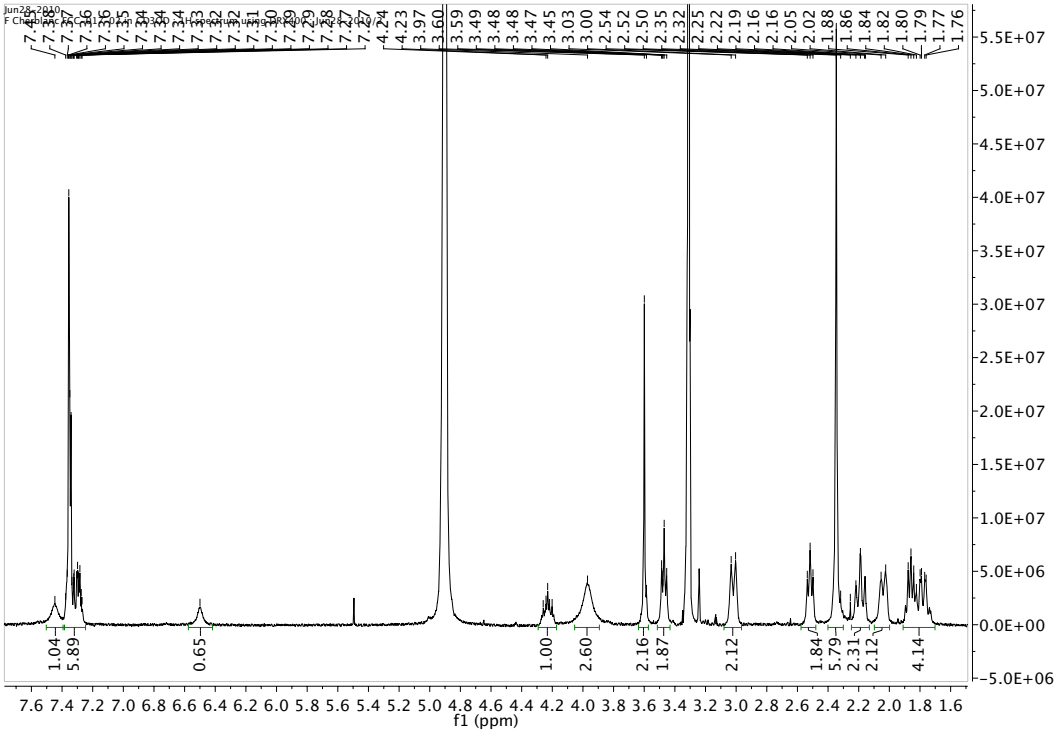


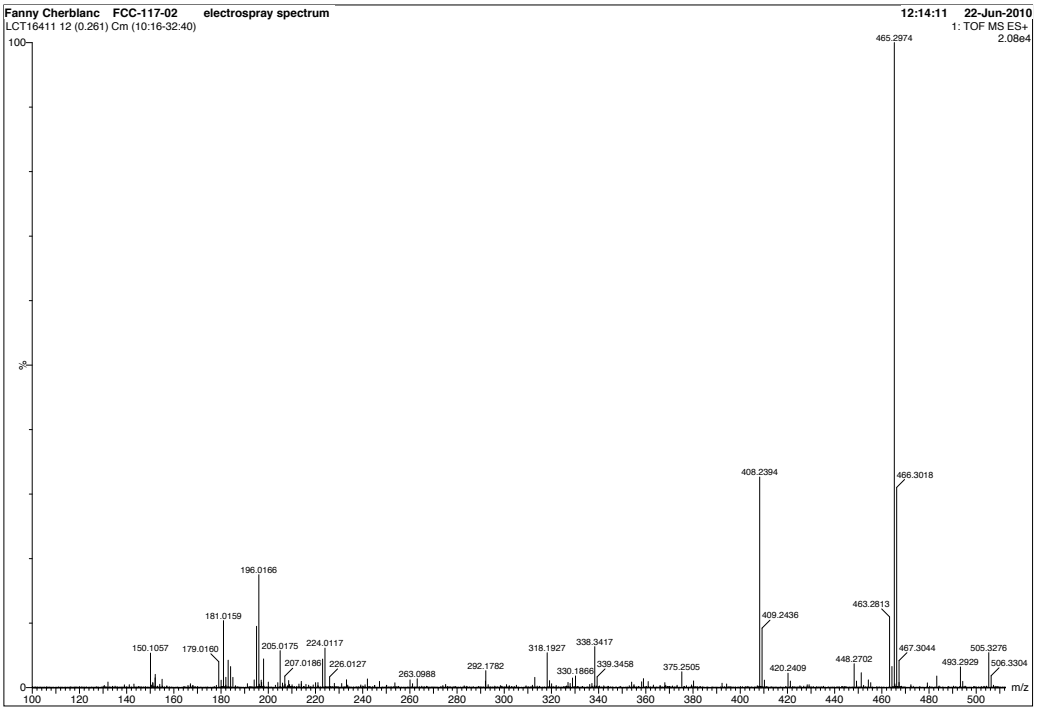
Minimum:				-1.5							
Maximum:		5.0	10.0	50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula				
505.3292	505.3291	0.1	0.2	12.5	590.6	1.4	C29	H41	N6	O2	
	505.3278	1.4	2.8	7.5	591.6	2.4	C28	H45	N2	O6	
	505.3310	-1.8	-3.6	-0.5	590.7	1.5	C17	H45	N8	O9	
	505.3318	-2.6	-5.1	11.5	592.5	3.3	C33	H45	O4		
	505.3331	-3.9	-7.7	16.5	591.9	2.7	C34	H41	N4		
	505.3251	4.1	8.1	8.5	590.5	1.3	C24	H41	N8	O4	
	505.3336	-4.4	-8.7	-1.5	592.0	2.8	C21	H49	N2	O11	

4-(1-benzylpiperidin-4-ylamino)-2-(3-(dimethylamino)propylamino)-6-methoxyquinazolin-7-ol (68)



Compound **68** was prepared as follows:[20] $Pd(PPh_3)_4$ (34 mg, 0.029 mmol) was added to a solution of allyl protected quinazoline **76** (294 mg, 0.580 mmol) in MeOH (50 mL). After 5 min, K_2CO_3 (400 mg, 2.900 mmol) was added and the solution was allowed to stir for 4 h at 50 ˚C. The solvent was rotatory evaporated to afford a brown oil which was subsequently treated with 1 N aq. HCl (50 mL). The solution was then basified with 2 N aq. NaOH and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were then combined, dried ($MgSO_4$) and rotary evaporated to afford the title compound **68** (crude, 286 mg). The obtained product was too polar to be purified by column chromatography and was thus used directly in the next step without further purification: ^{1}H NMR (400 MHz, MeOD) δ 7.45 (br s, 1H), 7.36 – 7.27 (m, 5H), 6.50 (br s, 1H), 4.26 – 4.20 (m, 1H), 3.98 (br s, 3H), 3.60 (s, 2H), 3.48 (br t, *J* = 7.0 Hz, 2H), 3.01 (br *app*-d, *J* = 12.0 Hz, 2H), 2.51 (*app*-t, *J* = 7.0 Hz, 2H), 2.34 (s, 6H), 2.19 (br *app*-dt, *J* = 12.0, 1.8 Hz, 2H), 2.03 (br *app*-d, *J* = 12.0 Hz, 2H), 1.85 (quint, *J* = 7.0 Hz, 2H), 1.78 (*app*-qd, *J* = 12.0, 3.3 Hz, 2H); MS (ESI) *m/z* 465 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{26}H_{37}N_6O_2$ 465.2978 found: 465.2974.


f1 (ppm)

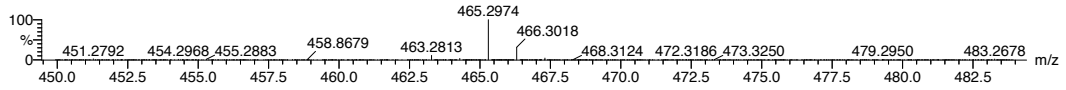

Fanny Cherblanc FCC-117-02 electrospray spectrum
12:14:11 22-Jun-2010
LCT16411 12 (0.261) Cm (10:16-32:40)
1: TOF MS ES+
2.08e4
m/z

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

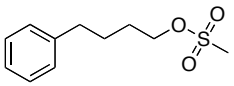
Monoisotopic Mass, Even Electron Ions
592 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC-117-02 electrospray spectrum 12:14:11 22-Jun-2010
LCT16411 12 (0.261) Cm (10:16-32:40) 1: TOF MS ES+
2.08e+004

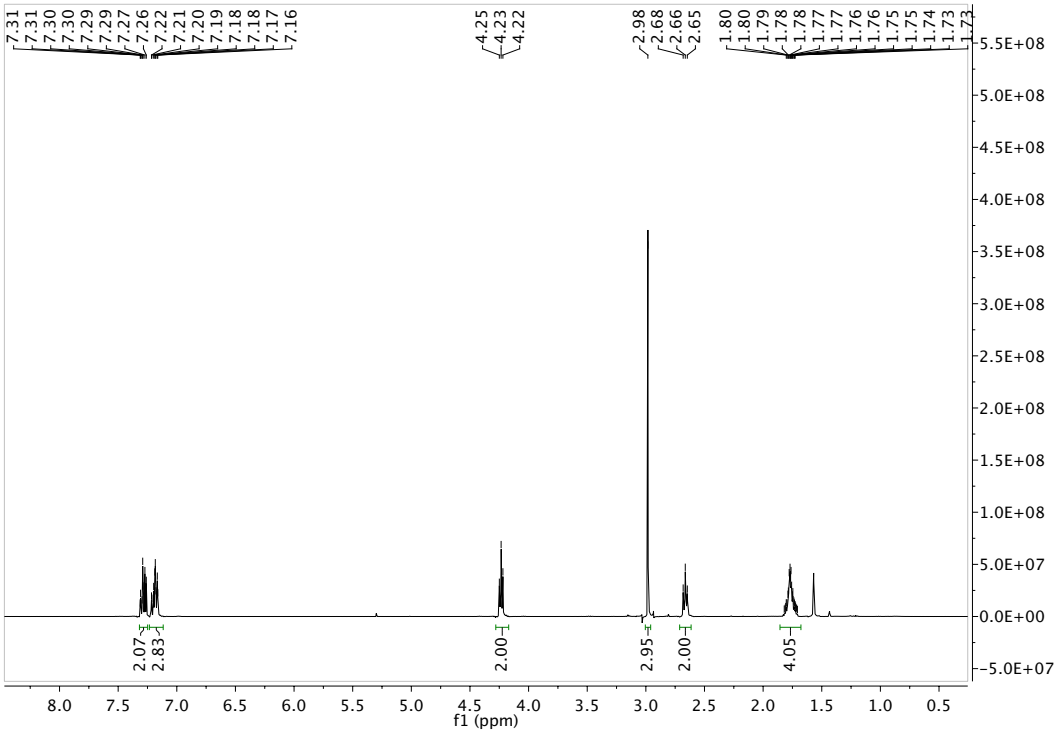


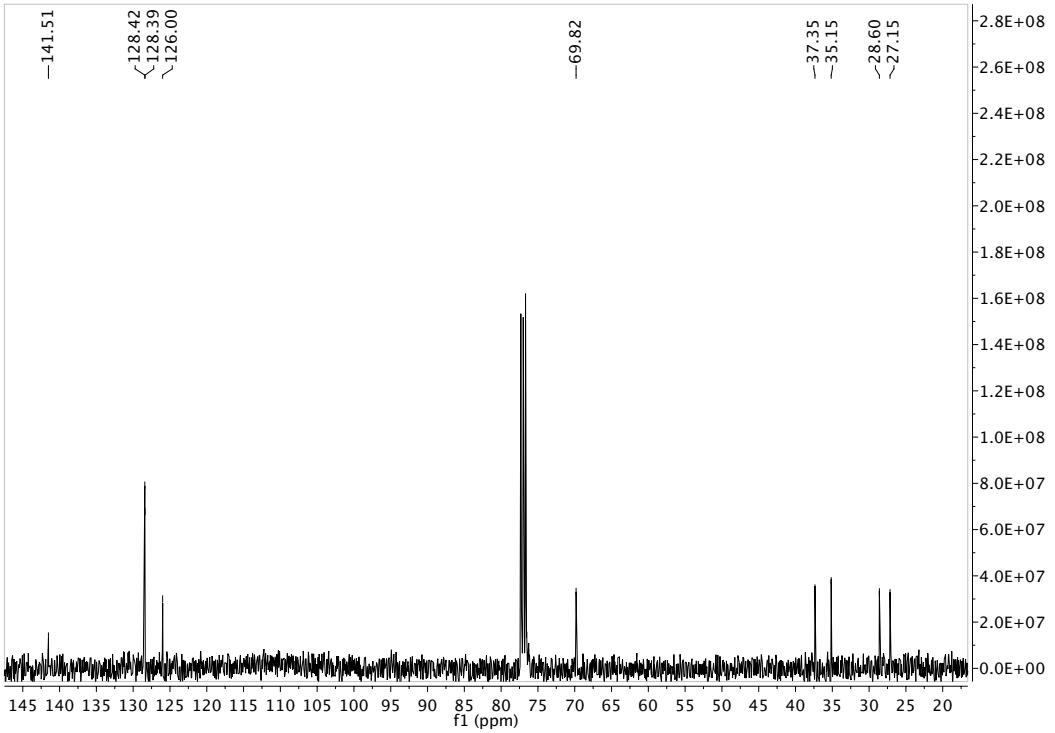
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
465.2974	465.2978	-0.4	-0.9	11.5	709.3	1.5	C26 H37 N6 O2
	465.2965	0.9	1.9	6.5	709.0	1.2	C25 H41 N2 O6
	465.2997	-2.3	-4.9	-1.5	709.9	2.2	C14 H41 N8 O9
	465.3005	-3.1	-6.7	10.5	709.5	1.7	C30 H41 O4
	465.2938	3.6	7.7	7.5	710.6	2.8	C21 H37 N8 O4
	465.3018	-4.4	-9.5	15.5	710.4	2.6	C31 H37 N4
	465.2924	5.0	10.7	2.5	710.8	3.1	C20 H41 N4 O8

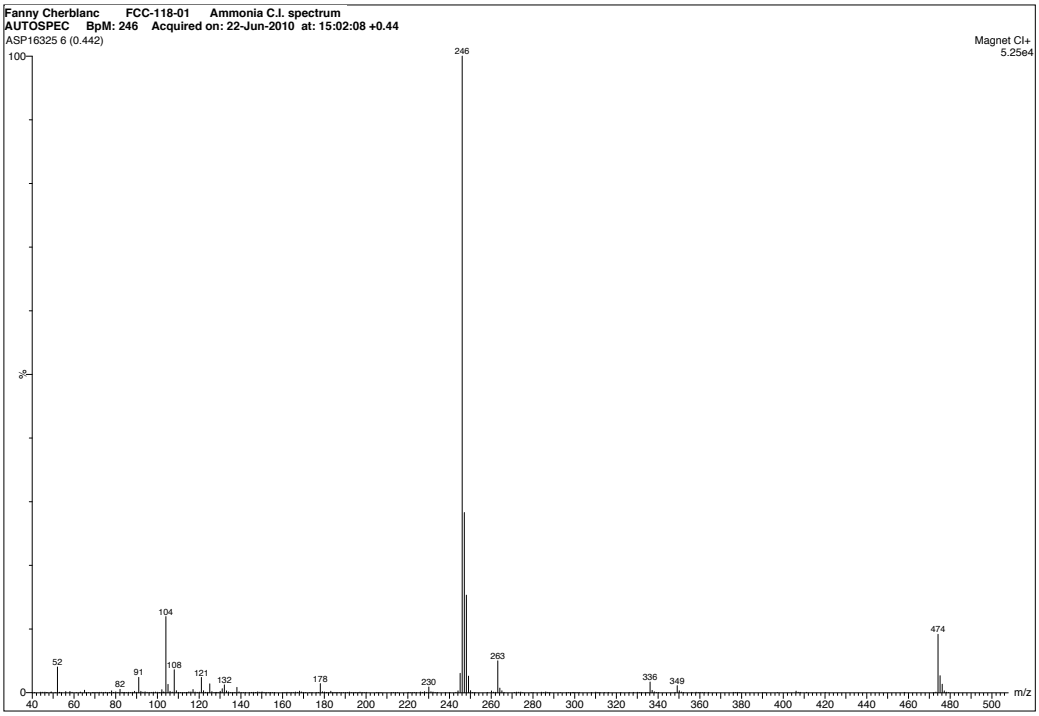
4-phenylbutyl methane sulfonate (77)[21]



To a solution of 4-phenylbutan-1-ol (**78**, 200 μL, 1.35 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C, was added Et_3N (282 μL, 2.03 mmol), followed by methanesulfonyl chloride (109 μL, 1.41 mmol). The resulting mixture was allowed to stir for 2 h and allowed to warm to room temperature. Sat. aq. NH_4Cl (5 mL) was added and the organic layer was rotatory evaporated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to afford the title compound **77** as a colourless oil (299 mg, 97%) that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 4.23 (t, *J* = 6.2 Hz, 2H), 2.98 (s, 3H), 2.66 (t, *J* = 6.7 Hz, 2H), 1.82 – 1.71 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 141.5, 128.4 (2C), 128.4 (2C), 126.0, 69.8, 37.3, 35.1, 28.6, 27.1; MS (CI) *m/z* 246 $(M+NH_4)^+$; HRMS (CI) *m/z* calc. for $C_{11}H_{20}NO_3S$ 246.1164, found: 246.1152.



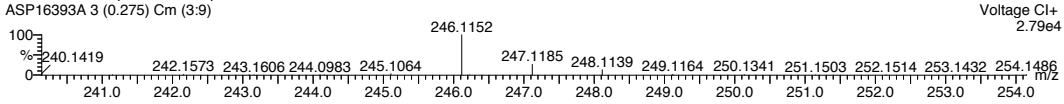

141.51
128.42
128.39
126.00
69.82
37.35
35.15
28.60
27.15
2.8E+08
2.6E+08
2.4E+08
2.2E+08
2.0E+08
1.8E+08
1.6E+08
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)


Fanny Cherblanc FCC-118-01 Ammonia C.I. spectrum
AUTOSPEC BpM: 246 Acquired on: 22-Jun-2010 at: 15:02:08 +0.44
ASP16325 6 (0.442)
Magnet CI+
5.25e4
100
%
0
246
104
52
91
82
108
121
132
178
230
263
336
349
474
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500
m/z

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 35.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

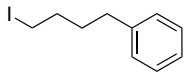
Monoisotopic Mass, Even Electron Ions
612 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)

Fanny Cherblanc FCC-118-01
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ASP16393A 3 (0.275) Cm (3:9)
Voltage CI+ 2.79e4

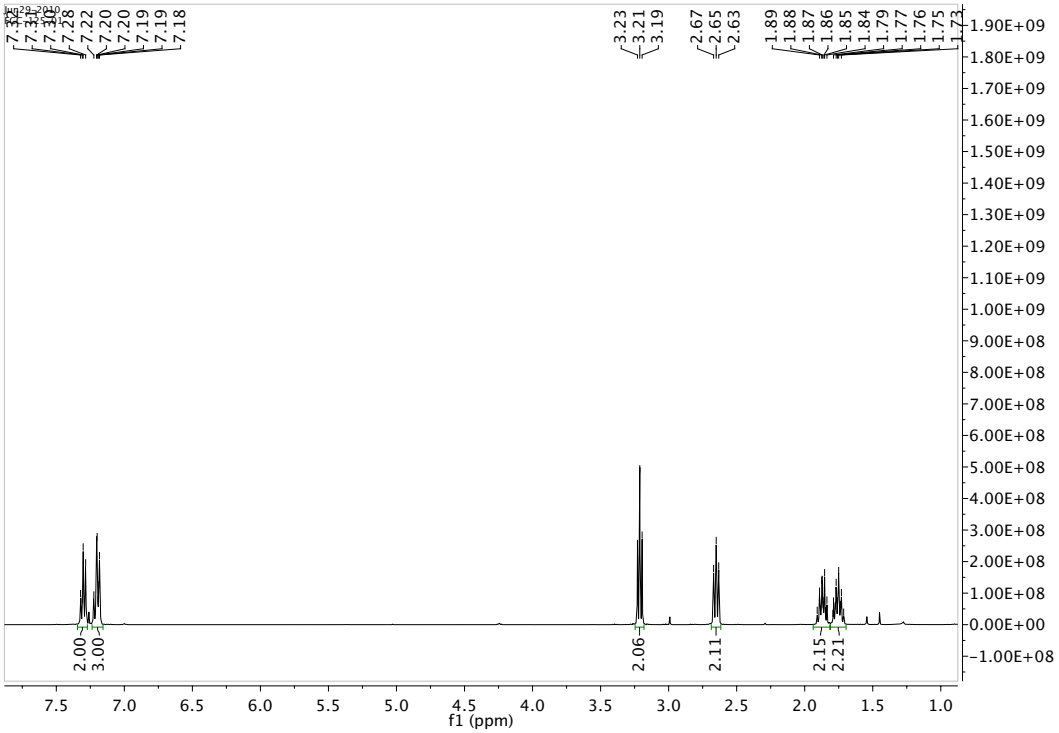


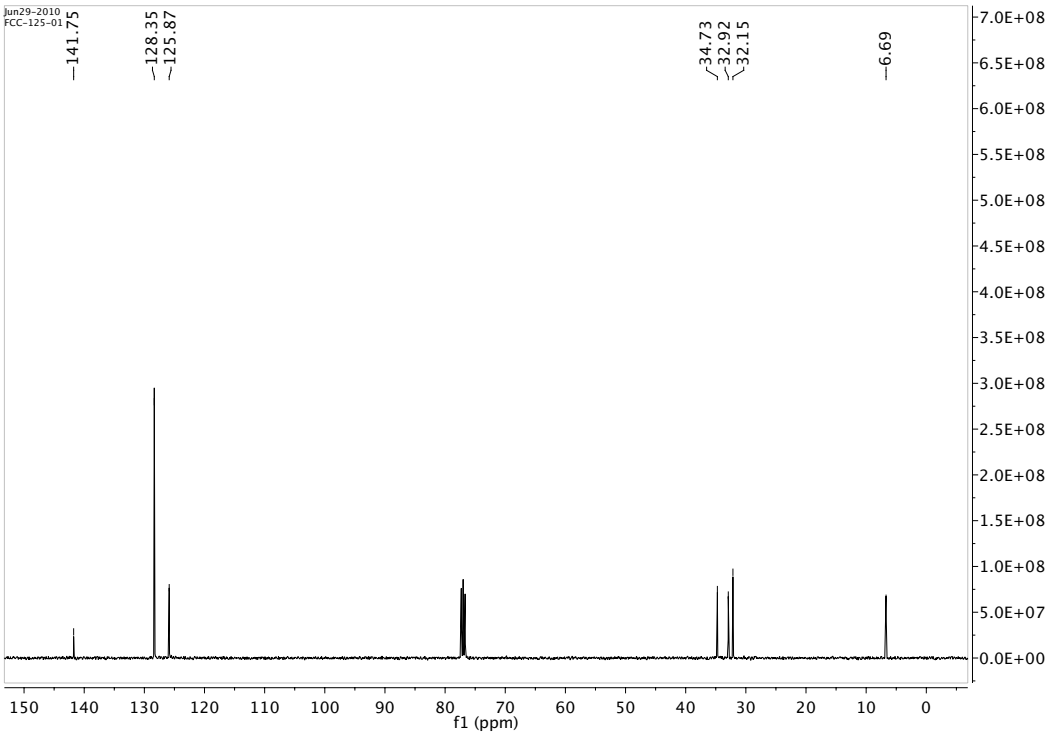
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Maximum:		5.0	10.0	35.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
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	246.1164	-1.2	-4.8	2.5	1	C11 H20 N O3 S
	246.1137	1.5	6.1	3.5	3	C7 H16 N7 O S
	246.1171	-1.9	-7.6	-1.5	4	C4 H20 N7 O S2
	246.1130	2.2	8.9	7.5	2	C14 H16 N O3
	246.1124	2.8	11.5	-1.5	6	C6 H20 N3 O5 S
	246.1189	-3.7	-15.0	-1.5	7	C7 H20 N O8
	246.1103	4.9	19.8	8.5	5	C10 H12 N7 O

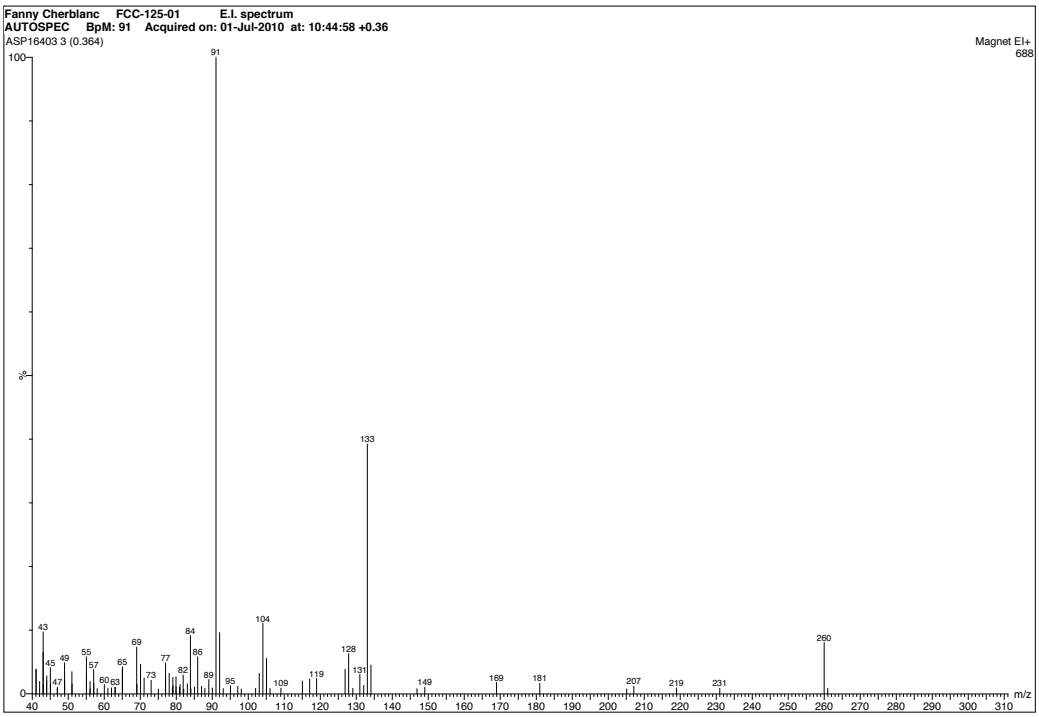
(4-Iodobutyl)benzene (79)[22]



Compound **79** was prepared as follows:[22] To a solution of NaI (284 mg, 1.927 mmol) in acetone (3 mL) was added sulfonate **77** (100 mg, 0.438 mmol). The resulting mixture was allowed to stir at room temperature for 16 h and then rotary evaporated. The residue was taken up in water (20 mL) and extracted with Et_2O (2 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to afford the title compound **79** as a yellow oil that was used in the next step without further purification (103 mg, 90%). IR (neat) 1604, 1495, 1452, 1206, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 3.21 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.79 – 1.71 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 141.8, 128.4 (4C), 125.9, 34.7, 32.9, 32.1, 6.7; MS (EI) *m/z* 260 (M^+); HRMS (EI) *m/z* calc. for $C_{10}H_{13}I$ 260.0062, found: 260.0054.


Jun29-2010
7.28
7.22
7.20
7.20
7.19
7.19
7.18
3.23
3.21
3.19
2.67
2.65
2.63
1.89
1.88
1.87
1.86
1.85
1.84
1.79
1.77
1.76
1.75
1.73
2.00
3.00
2.06
2.11
2.15
2.21
f1 (ppm)


Jun29-2010
FCC-125-01
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128.35
125.87
34.73
32.92
32.15
6.69
f1 (ppm)

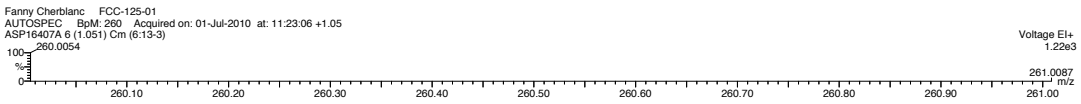


Elemental Composition Report

Single Mass Analysis (displaying only valid results)

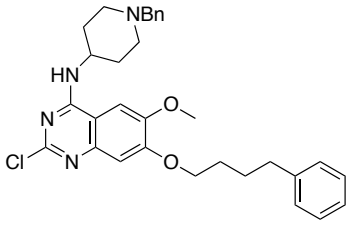
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Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd Electron Ions
366 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)

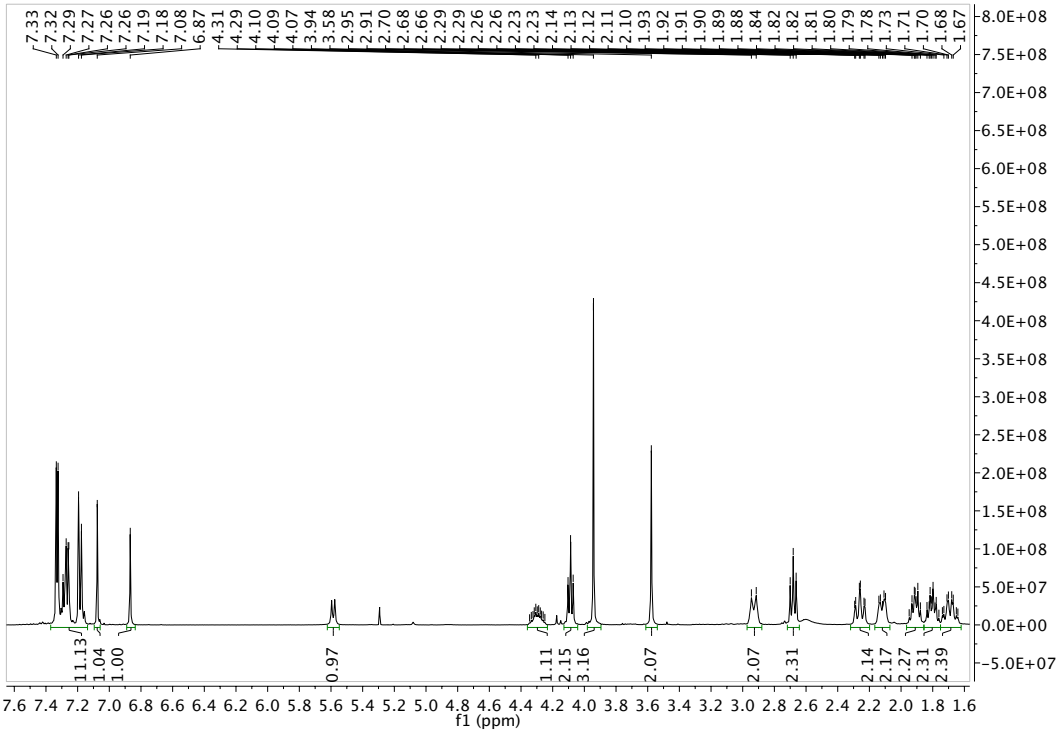


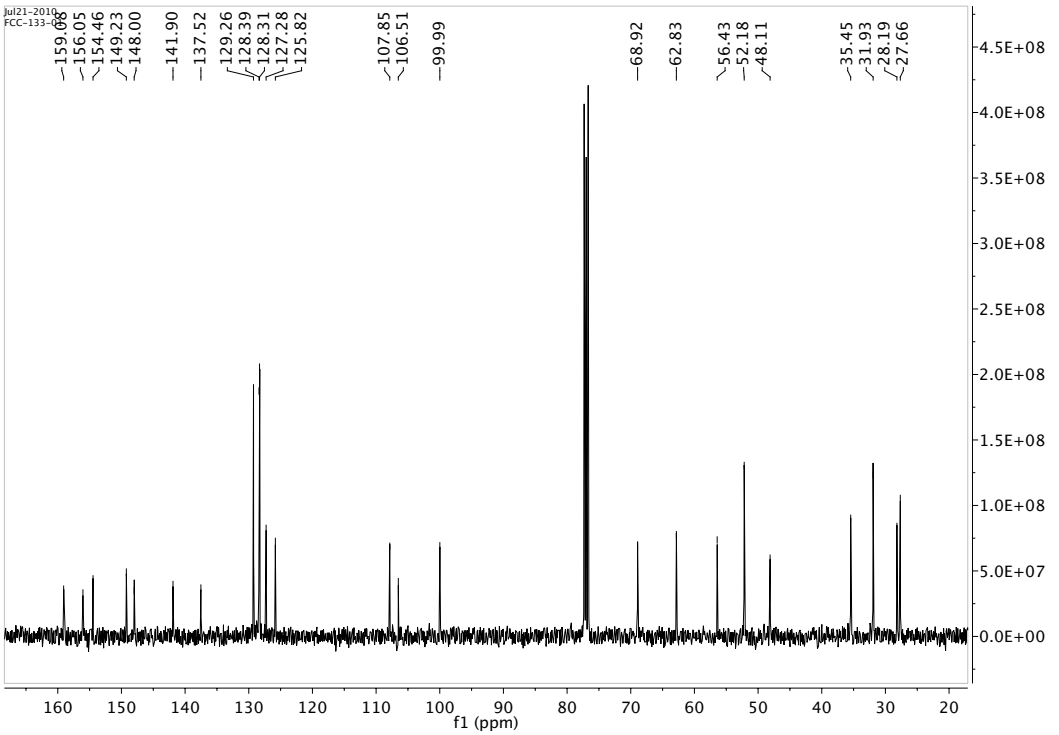
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Maximum:		5.0	10.0	35.0		
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	260.0043	1.1	4.4	12.0	2	C7 N8 O4
	260.0069	-1.5	-5.9	11.0	3	C11 H4 N2 O6
	260.0029	2.5	9.6	7.0	4	C6 H4 N4 O8
	260.0083	-2.9	-11.1	16.0	6	C12 N6 O2
	260.0022	3.2	12.4	0.0	5	C5 H13 N2 O2 I
	260.0016	3.8	14.7	2.0	7	C5 H8 O12
	260.0011	4.3	16.7	20.0	9	C18 N2 O
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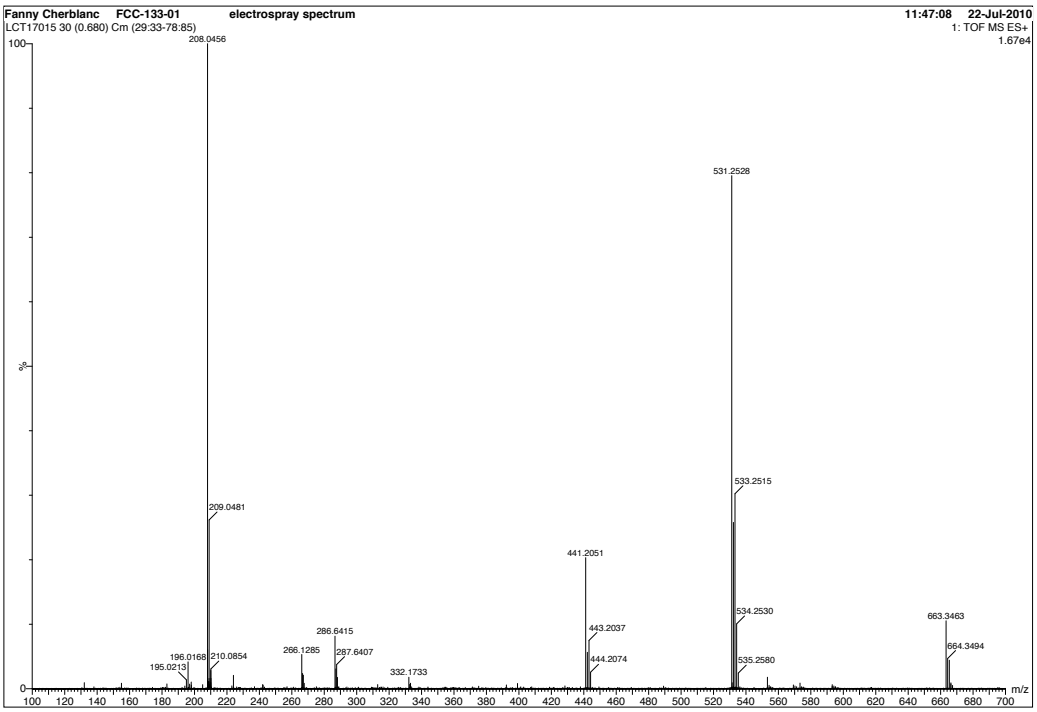
***N*-(1-benzylpiperidin-4-yl)-2-chloro-6-methoxy-7-(4-phenylbutoxy)quinazolin-4-amine (81)**



TBAB (4 mg, 0.013 mmol) and K_2CO_3 (26 mg, 0.187 mmol) were added to a solution of phenol **80** (50 mg, 0.125 mmol) in acetone (5 mL). Methane sulfonate **77** (34 mg, 0.138 mmol) was then added and the mixture was allowed to stir overnight under reflux. NaI (18.7 mg, 0.125 mmol) was then added and the reaction was allowed to stir under reflux for an extra 20 h. After this time, the mixture was filtered, washed with CH_2Cl_2 and rotary evaporated. Purified by column chromatography (CH_2Cl_2 : MeOH, 95 : 5) afforded the title compound **81** as a colourless oil (30 mg, 45%): IR (neat) 1621, 1581, 1508, 1439, 1250, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 10H), 7.08 (s, 1H), 6.87 (s, 1H), 5.59 (d, *J* = 7.9 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.94 (s, 3H), 3.58 (s, 2H), 2.93 (br *app*-d, *J* = 12.0 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.26 (*app*-dt, *J* = 12.0, 1.5 Hz, 2H), 2.12 (br *app*-d, *J* = 12.0 Hz, 2H), 1.95 – 1.88 (m, 2H), 1.84 – 1.76 (m, 2H), 1.69 (*app*-dq, *J* = 12.0, 3.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.1, 156.0, 154.5, 149.2, 147.9, 141.9, 137.5, 129.2 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 127.3, 125.8, 107.8, 106.5, 99.9, 68.9, 62.8, 56.4, 52.2 (2C), 48.1, 35.4, 31.9 (2C), 28.2, 27.7; MS (ESI) *m/z* 531 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{31}H_{36}N_4O_2Cl$ 531.2527 found: 531.2528.


7.33
7.32
7.29
7.27
7.26
7.26
7.19
7.18
7.08
6.87
4.31
4.29
4.10
4.09
4.07
3.94
3.58
2.95
2.91
2.70
2.68
2.66
2.29
2.29
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2.26
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2.23
2.14
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2.11
2.10
1.93
1.92
1.91
1.90
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1.68
1.67
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1.00
0.97
1.11
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3.16
2.07
2.07
2.31
2.14
2.17
2.27
2.31
2.39
f1 (ppm)


Jul21-2010
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f1 (ppm)

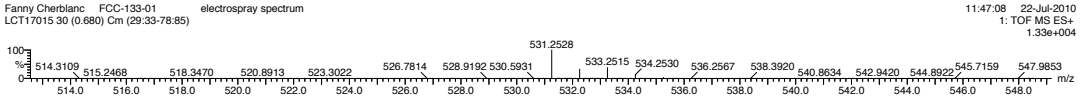


Elemental Composition Report

Single Mass Analysis

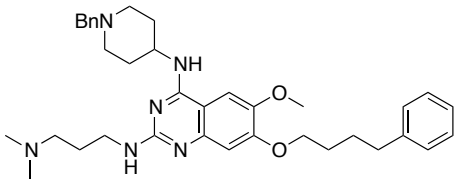
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
1306 formula(e) evaluated with 14 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12 Cl: 0-1



Minimum:				-1.5								
Maximum:		5.0	10.0	50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula					
531.2528	531.2527	0.1	0.2	15.5	604.8	1.5	C31	H36	N4	O2	Cl	
	531.2527	0.1	0.2	7.5	628.3	24.9	C20	H35	N8	O9		
	531.2535	-0.7	-1.3	19.5	629.2	25.9	C36	H35	O4			
	531.2513	1.5	2.8	10.5	603.6	0.3	C30	H40	O6	Cl		
	531.2545	-1.7	-3.2	2.5	611.7	8.3	C19	H40	N6	O9	Cl	
	531.2508	2.0	3.8	20.5	628.8	25.5	C32	H31	N6	O2		
	531.2549	-2.1	-4.0	24.5	629.4	26.0	C37	H31	N4			
	531.2505	2.3	4.3	-1.5	615.0	11.7	C14	H40	N8	O11	Cl	
	531.2554	-2.6	-4.9	6.5	628.8	25.4	C24	H39	N2	O11		
	531.2495	3.3	6.2	15.5	628.8	25.5	C31	H35	N2	O6		
	531.2567	-3.9	-7.3	19.5	610.6	7.3	C36	H36	N2	Cl		
	531.2567	-3.9	-7.3	11.5	628.8	25.4	C25	H35	N6	O7		
	531.2487	4.1	7.7	11.5	607.8	4.5	C26	H36	N6	O4	Cl	
	531.2572	-4.4	-8.3	1.5	612.0	8.7	C23	H44	O11	Cl		

N^4-(1-benzylpiperidin-4-yl)-N^2-(3-(dimethylamino)propyl)-6-methoxy-7-(4-phenylbutoxy)quinazoline-2,4-diamine (56)



Procedure 1 : From phenol **68** (with Cs_2CO_3 in DMF)

Crude phenol **68 (**50 mg, 0.11 mmol) was dissolved in degassed DMF (2 mL). Cs_2CO_3 (52 mg, 0.16 mmol) was added followed by methane sulfonate **77** (27 mg, 0.12 mmol). The resulting solution was allowed to stir at room temperature for 16 h then heated to 80 ˚C for 1 h. The mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with water (3 × 20 mL), dried ($MgSO_4$) and rotary evaporated. Purification by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH, 95 : 5) afforded the title compound **56** (1.2 mg, 2%).

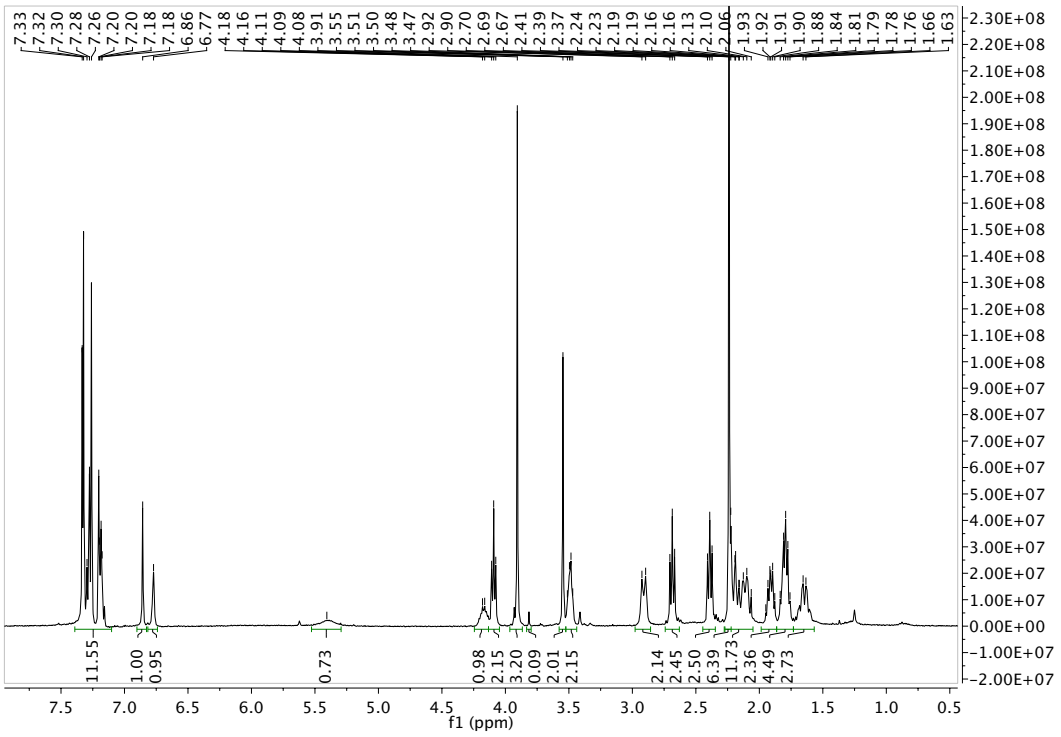
Procedure 2 : From phenol **68** (with *t*BuOK in acetone)

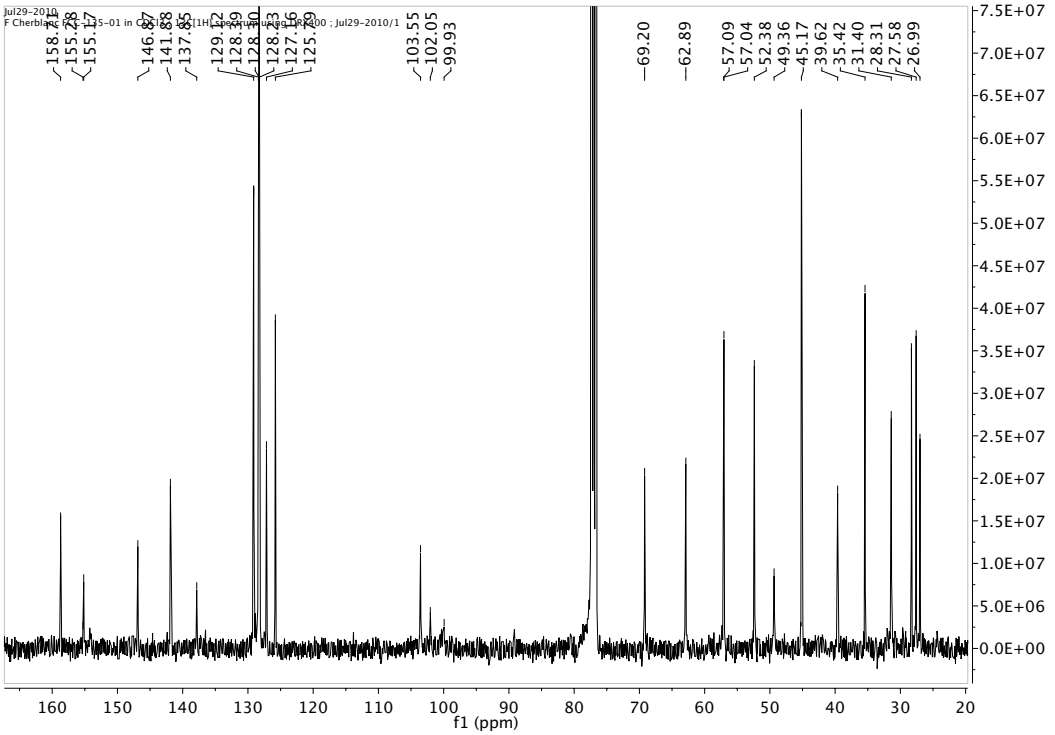
To a solution of crude phenol **68** (35 mg, 0.075 mmol) in acetone (3 mL) was added *t*BuOK (8.5 mg, 0.075 mmol) and methane sulfonate **77** (17.1 mg, 0.075 mmol) and the resulting solution was allowed to stir at 40 ˚C for 16 h. The mixture was then diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (3 × 20 mL), dried ($MgSO_4$) and rotary evaporated. Purification by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH, 95 : 5) afforded the title compound **56** (4 mg, 9%).

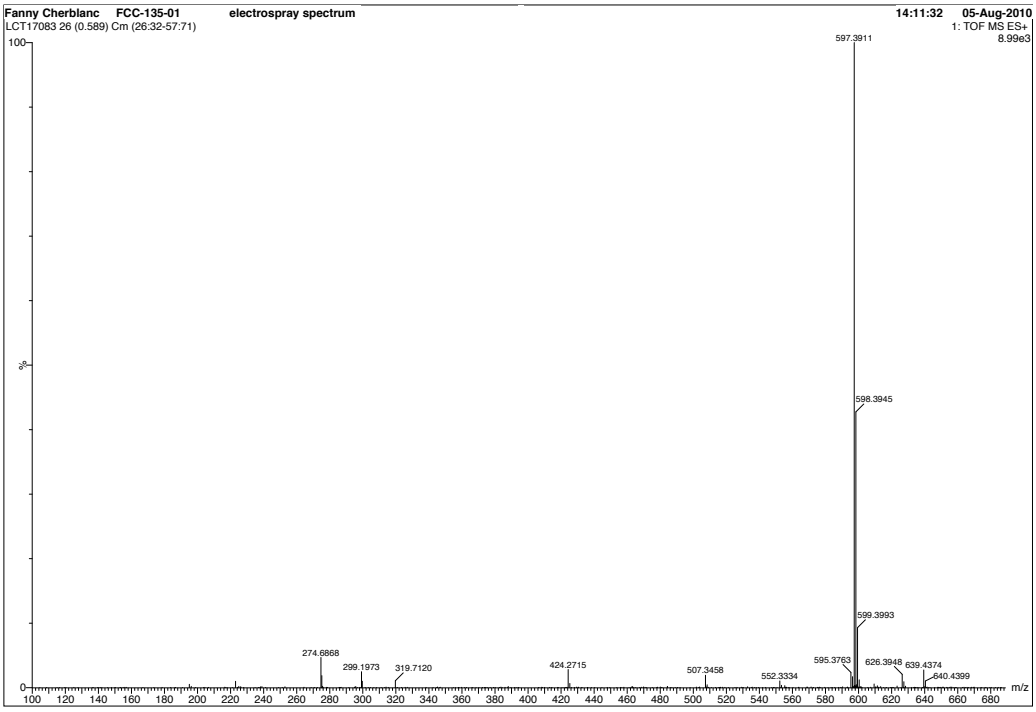
Procedure 3: From chloroquinazoline (**81**)

N,N-dimethyl-1,3-propanediamine (**66**, 36 μL, 0.280 mmol) was added to a solution of chloroquinazoline **81** (30 mg, 0.056 mmol) in toluene (2 mL). The resulting mixture was heated under reflux for 16 h, then diluted with CH_2Cl_2 (3 mL) and then washed with sat. aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and purified by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH, 90 : 10) to afford the title compound **56** (12 mg, 36%).

Compound **56** was obtained as a colourless oil: IR (neat) 2154, 1645, 1608, 1585, 1514, 1455, 1274 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 10H), 6.86 (s, 1H), 6.77 (br s, 1H), 5.41 (br s, 1H), 4.18 – 4.08 (m, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.91 (s, 3H), 3.55 (s, 2H), 3.51 – 3.47 (m, 2H), 2.91 (br *app*-d, *J* = 12.0 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.24 (s, 6H), 2.19 (*app*-dt, *J* = 12.0, 1.5 Hz, 2H), 2.12 (br *app*-d, *J* = 12.0 Hz, 2H), 1.95 – 1.88 (m, 2H), 1.84 – 1.76 (m, 4H), 1.64 (*app*-dq, *J* = 12.0, 3.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 158.7, 155.3, 155.2, 146.9 (2C), 141.9, 137.9, 129.1 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 127.1, 125.8, 103.5, 102.1, 99.9, 69.2, 62.9, 57.1, 57.0, 52.4 (2C), 49.4, 45.2 (2C), 39.6, 35.4 (2C), 31.4, 28.3, 27.6, 27.0; MS (ESI) *m/z* 597 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{36}H_{49}N_6O_2$ 597.3917 found: 597.3911.




Jul29-2010
F Cherblanc FCC-135-01 in CDCl3 {1H}13C Inverse gated decoupling 256 scans 298.200 ; Jul29-2010/1
158.71
155.28
155.17
146.87
141.88
137.65
129.12
128.39
128.30
128.23
127.76
125.89
103.55
102.05
99.93
69.20
62.89
57.09
57.04
52.38
49.36
45.17
39.62
35.42
31.40
28.31
27.58
26.99
7.5E+07
7.0E+07
6.5E+07
6.0E+07
5.5E+07
5.0E+07
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4.0E+07
3.5E+07
3.0E+07
2.5E+07
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f1 (ppm)

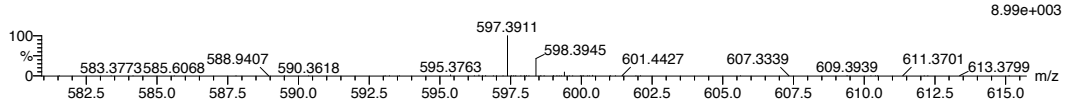

Fanny Cherblanc FCC-135-01 electrospray spectrum
14:11:32 05-Aug-2010
LCT17083 26 (0.589) Cm (26:32-57:71)
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100
%
0
597.3911
598.3945
599.3993
274.6868
299.1973
319.7120
424.2715
507.3458
552.3334
595.3763
626.3948
639.4374
640.4399
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680
m/z

Elemental Composition Report **Page 1**

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

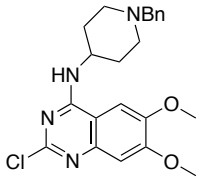
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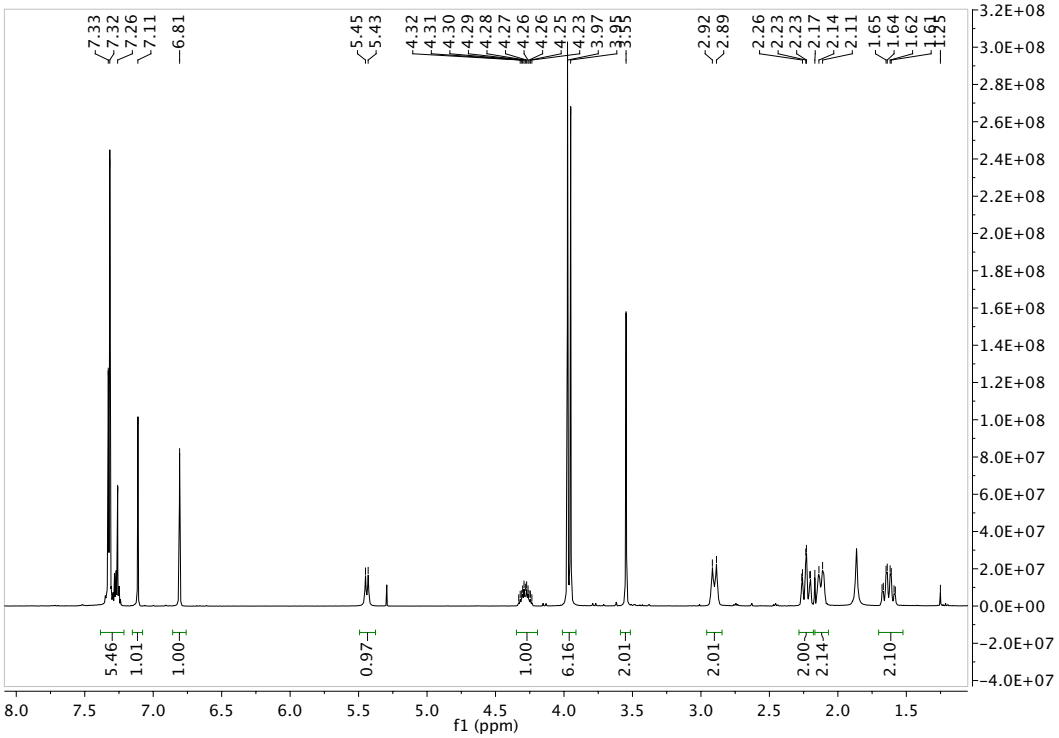


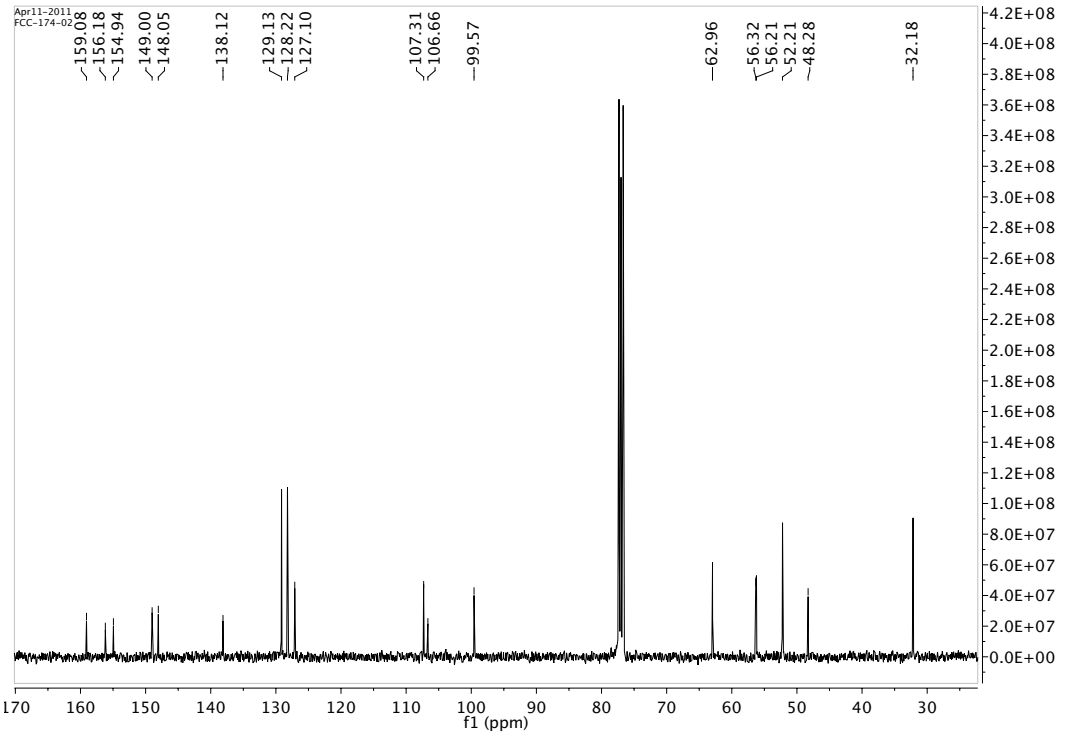
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Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
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	597.3904	0.7	1.2	10.5	116.4	3.1	C35	H53	N2	O6
	597.3936	-2.5	-4.2	2.5	125.9	12.6	C24	H53	N8	O9
	597.3944	-3.3	-5.5	14.5	120.1	6.8	C40	H53	O4	
	597.3877	3.4	5.7	11.5	120.2	6.9	C31	H49	N8	O4
	597.3957	-4.6	-7.7	19.5	121.2	7.9	C41	H49	N4	
	597.3863	4.8	8.0	6.5	122.5	9.1	C30	H53	N4	O8

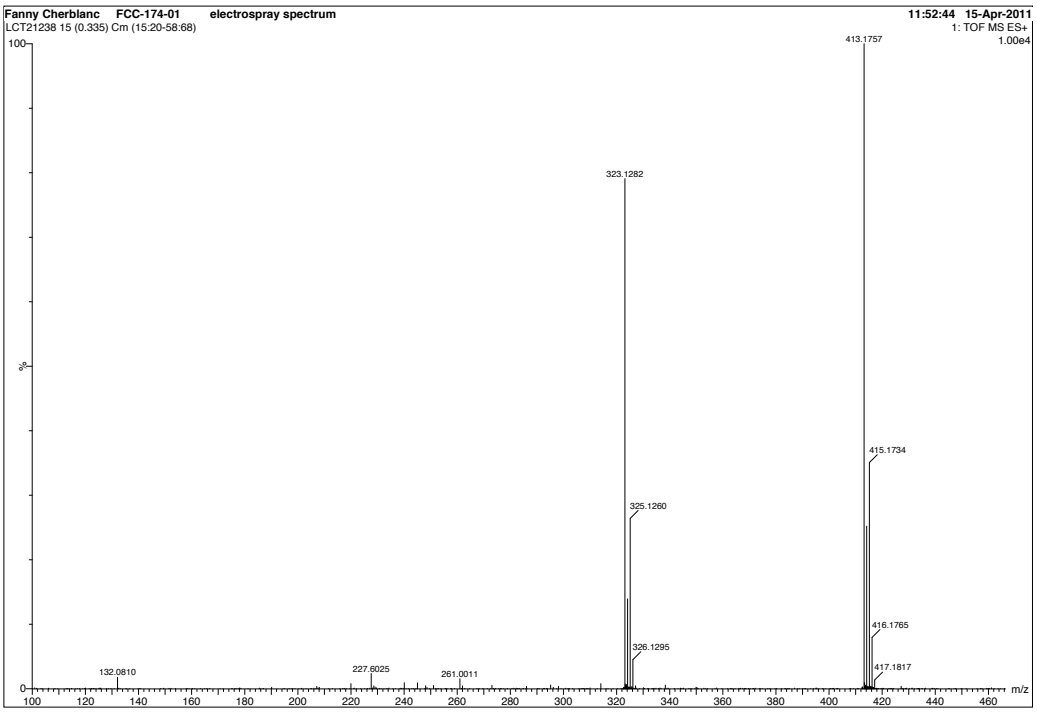
N-(1-benzylpiperidin-4-yl)-2-chloro-6,7-dimethoxyquinazolin-4-amine (84)[18]



Compound **84** was prepared as follows:[18] A mixture of dichloroquinazoline **83** (300 mg, 1.15 mmol), 4-amino-1-benzylpiperidine (**64**, 0.700 mL, 3.45 mmol) and DIEA (0.300 mL, 1.72 mmol) in THF (5 mL) was allowed to stir at room temperature for 16 h. The solution was concentrated and purified by column chromatography (MeOH : CH_2Cl_2, 10 : 90) to afford the title compound **84** (478 mg, quant.) as a white solid: m.p. 116 – 118 ˚C; IR (neat) 2936, 1739, 1579, 1508, 1454, 1428, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 5H), 7.11 (s, 1H), 6.81 (s, 1H), 5.44 (d, *J* = 7.8 Hz, 1H), 4.33 – 4.23 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.55 (s, 2H), 2.90 (br *app*-d, *J* = 12.0 Hz, 2H), 2.23 (br *app*-td, *J* = 12.0, 1.6 Hz, 2H), 2.12 (br *app*-d, *J* = 12.0 Hz, 2H), 1.63 (br *app*-qd, *J* = 12.0, 3.6 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.1, 156.2, 154.9, 149.0, 148.1, 138.1, 129.1 (2C), 128.2 (2C), 127.1, 107.3, 106.7, 99.6, 62.9, 56.3, 56.2, 52.2 (2C), 48.3, 32.2 (2C); MS (ESI) *m/z* 413 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{22}H_{26}N_4O_2Cl$ 413.1744 found: 413.1757.


7.33
7.32
7.26
7.11
6.81
5.45
5.43
4.32
4.31
4.30
4.29
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4.27
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4.26
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3.97
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2.17
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2.11
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1.64
1.62
1.61
1.25
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1.00
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2.01
2.00
2.14
2.10
f1 (ppm)


Apr11-2011
FCC-174-02
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f1 (ppm)

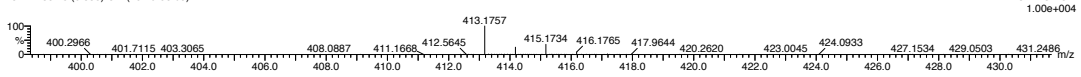


Elemental Composition Report

Single Mass Analysis

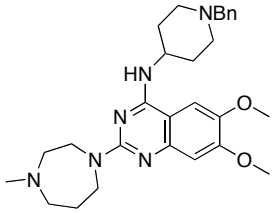
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Monoisotopic Mass, Even Electron Ions
1290 formula(e) evaluated with 13 results within limits (all results (up to 1000) for each mass)
Elements Used:
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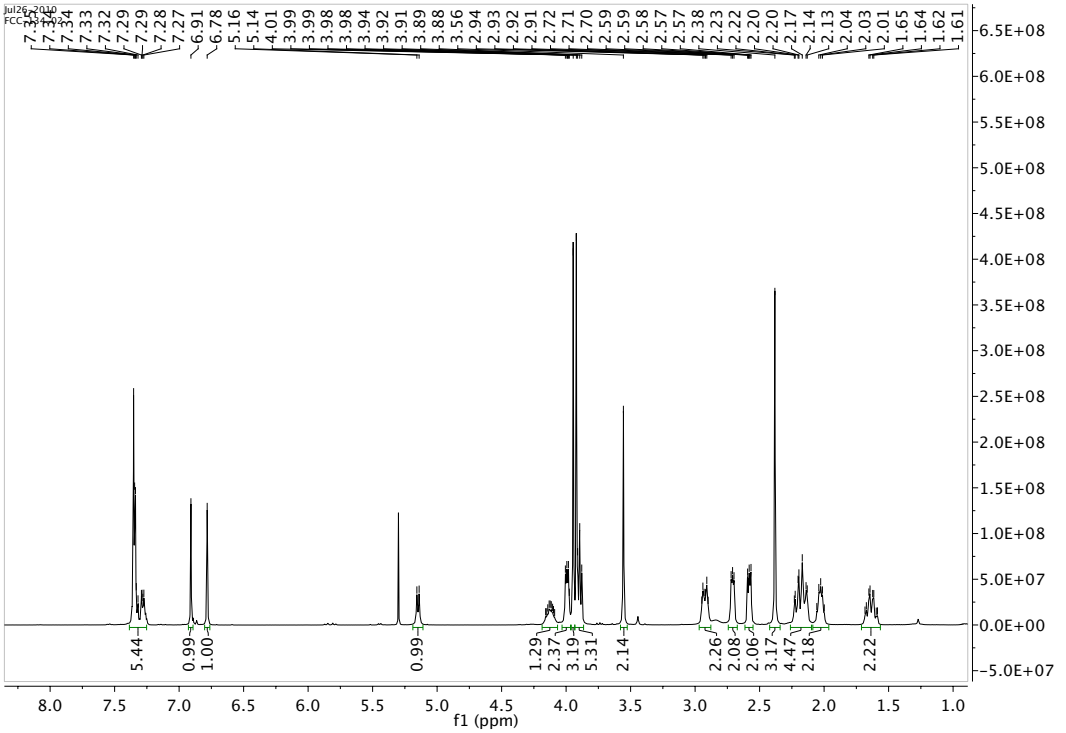


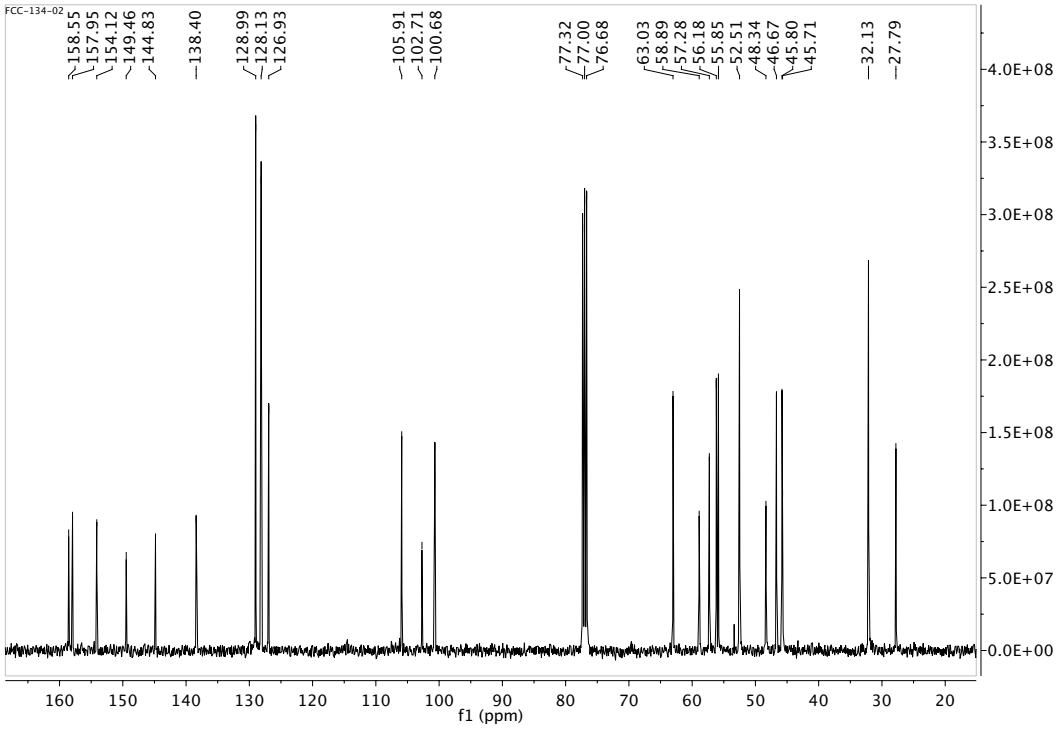
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	413.1763	-0.6	-1.5	-1.5	244.2	13.8	C10	H30	N6	O9	Cl
	413.1766	-0.9	-2.2	20.5	260.6	30.1	C28	H21	N4		
	413.1744	1.3	3.1	3.5	259.5	29.0	C11	H25	N8	O9	
	413.1744	1.3	3.1	11.5	231.5	1.1	C22	H26	N4	O2	Cl
	413.1771	-1.4	-3.4	2.5	259.8	29.3	C15	H29	N2	O11	
	413.1731	2.6	6.3	-1.5	259.6	29.2	C10	H29	N4	O13	
	413.1731	2.6	6.3	6.5	230.9	0.4	C21	H30	O6	Cl	
	413.1785	-2.8	-6.8	15.5	239.5	9.0	C27	H26	N2	Cl	
	413.1785	-2.8	-6.8	7.5	259.8	29.3	C16	H25	N6	O7	
	413.1726	3.1	7.5	16.5	260.0	29.6	C23	H21	N6	O2	
	413.1713	4.4	10.6	11.5	260.0	29.6	C22	H25	N2	O6	
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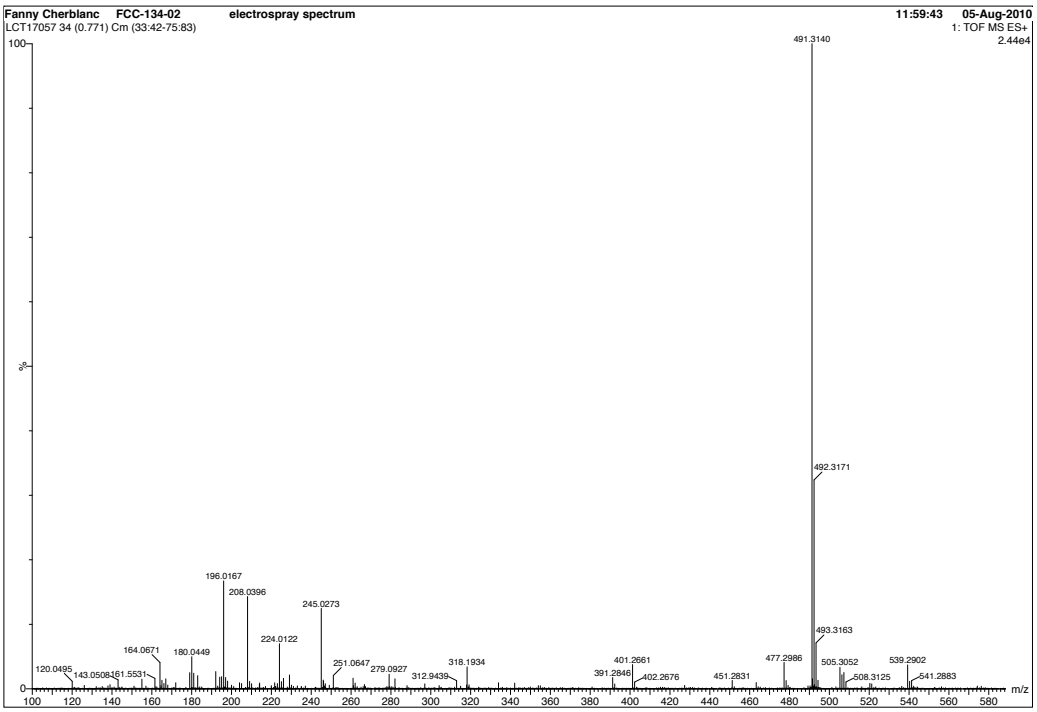
***N*-(1-benzylpiperidin-4-yl)-6,7-dimethoxy-2-(4-methyl-1,4-diazepan-1-yl)quinazolin-4-amine) (2, BIX-01294)[18,23]**



Compound **2** was prepared as follows:[18] 1-Methyl-1,4-diazepane (**85**, 150 μL, 1.210 mmol) was added to a solution of chloroquinazoline **84** (100 mg, 0.242 mmol) in toluene (2 mL). The reaction mixture was allowed to stir under reflux for 16 h, diluted with CH_2Cl_2 (3 mL) and washed with sat. aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and purified by column chromatography (CH_2Cl_2 : 7M NH_3 in MeOH, 90 : 10) to afford the title compound **2** as a yellow oil (75 mg, 63%): IR (neat) 1573, 1493, 1423, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 6.91 (s, 1H), 6.78 (s, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.16 – 4.09 (m, 1H), 4.01 – 3.98 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.56 (s, 2H), 2.92 (br *app*-d, *J* = 12.0 Hz, 2H), 2.72 – 2.70 (m, 2H), 2.59 – 2.57 (m, 2H), 2.38 (s, 3H), 2.23 – 2.13 (m, 4H), 2.06 – 2.00 (m, 2H), 1.63 (br *app*-qd, *J* = 12.0, 3.6 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 158.6, 157.9, 154.1, 149.5, 144.8, 138.4, 128.9 (2C), 128.1 (2C), 126.9, 105.9, 102.7, 100.7, 63.0, 58.9, 57.3, 56.2, 55.8, 52.5 (2C), 48.3, 46.7, 45.8, 45.7, 32.1 (2C), 27.8; MS (ESI) *m/z* 491 $(M+H)^+$; HRMS (ESI) *m/z* calc. for $C_{28}H_{39}N_6O_2$ 491.3134 found: 491.3140.


Jul26-2016
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f1 (ppm)


FCC-134-02
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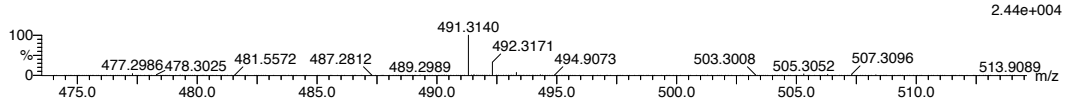
Elemental Composition Report

Single Mass Analysis

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Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
629 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-8 O: 0-12

Fanny Cherblanc FCC-134-02 electrospray spectrum 11:59:43 05-Aug-2010
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2.44e+004



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	491.3153	-1.3	-2.6	-0.5	340.7	7.5	C16 H43 N8 O9
	491.3121	1.9	3.9	7.5	333.7	0.4	C27 H43 N2 O6
	491.3161	-2.1	-4.3	11.5	335.2	1.9	C32 H43 O4
	491.3175	-3.5	-7.1	16.5	337.9	4.7	C33 H39 N4
	491.3180	-4.0	-8.1	-1.5	339.7	6.4	C20 H47 N2 O11
	491.3094	4.6	9.4	8.5	337.4	4.1	C23 H39 N8 O4

References

(1) Rewcastle, G. W.; Sutherland, H. S.; Weir, C. A.; Blackburn, A. G.; Denny, W. A. *Tetrahedron Lett.* **2005**, *46*, 8719-8721.

(2) Hilton, S. T.; Motherwell, W. B.; Selwood, D. L. *Synlett* **2004**, 2609-2611.

(3) Cook, K. M.; Hilton, S. T.; Mecinovic, J.; Motherwell, W. B.; Figg, W. D.; Schofield, C. J. *J. Biol. Chem.* **2009**, *284*, 26831-26838.

(4) Aliev, A. E.; Hilton, S. T.; Motherwell, W. B.; Selwood, D. L. *Tetrahedron Lett.* **2006**, *47*, 2387-2390.

(5) Chai, C. L. L.; Elix, J. A.; Huleatt, P. B.; Waring, P. *Bioorg. Med. Chem.* **2004**, *12*, 5991-5995.

(6) Jiang, H.; Newcombe, N.; Sutton, P.; Lin, Q. H.; Mullbacher, A.; Waring, P. *Aust. J. Chem.* **1993**, *46*, 1743-1754.

(7) Truce, W. E.; Perry, F. M. *J. Org. Chem.* **1965**, *30*, 1316-1317.

(8) Saito, T.; Suzuki, Y.; Koyama, K.; Natori, S.; Iitaka, Y.; Kinoshita, T. *Chem. Pharm. Bull.* **1988**, *36*, 1942-1956.

(9) Rose, C.; Vargas, F.; Bourgeat, P.; Schwartz, J.-C.; Bishop, P. B.; Bambal, R. B.; Ganellin, C. R.; Leblond, B.; Moore, A. N. J.; Chan, S.; Lihua, Z. Tripeptidylpeptidase inhibitors. WO9635805 (A2), November, 14, 1996.

(10) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511-1516.

(11) Zhao, H.; He, X.; Thurkauf, A.; Hoffman, D.; Kieltyka, A.; Brodbeck, R.; Primus, R.; Wasley, J. W. F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3111-3115.

(12) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, *41*, 3433-3438.

(13) Nicolaou, K. C.; Giguere, D.; Totokotsopoulos, S.; Sun, Y. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 728-732.

(14) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320-17332.

(15) Takikawa, Y.; Shimada, K.; Makabe, T.; Takizawa, S. *Chem. Lett.* **1983**, *12*, 1503-1506.

(16) Salama, T. A.; El-Ahl, A.-A. S.; Elmorsy, S. S.; Khalil, A.-G. M.; Ismail, M. A. *Tetrahedron Lett.* **2009**, *50*, 5933-5936.

(17) Jerumanis, S.; Lalancette, J. M. *Can. J. Chem.* **1964**, *42*, 1928-1935.

(18) Liu, F.; Chen, X.; Allali-Hassani, A.; Quinn, A. M.; Wasney, G. A.; Dong, A.; Barsyte, D.; Kozieradzki, I.; Senisterra, G.; Chau, I.; Siarheyeva, A.; Kireev, D. B.; Jadhav, A.; Herold, J. M.; Frye, S. V.; Arrowsmith, C. H.; Brown, P. J.; Simeonov, A.; Vedadi, M.; Jin, J. *J. Med. Chem.* **2009**, *52*, 7950-7953.

(19) Jung, F. H.; Pasquet, G.; Van der Brempt, C. L.; Lohmann, J.-J. M.; Warin, N.; Renaud, F.; Germain, H.; De Savi, C.; Roberts, N.; Johnson, T.; Dousson, C.; Hill, G. B.; Mortlock, A. A.; Heron, N.; Wilkinson, R. W.; Wedge, S. R.; Heaton, S. P.; Odedra, R.; Keen, N. J.; Green, S.; Brown, E.; Thompson, K.; Brightwell, S. *J. Med. Chem.* **2006**, *49*, 955-970.

(20) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2002**, *68*, 1146-1149.

(21) Romeiro, L. A. S.; da Silva Ferreira, M.; da Silva, L. L.; Castro, H. C.; Miranda, A. L. P.; Silva, C. L. M.; Noël, F.; Nascimento, J. B.; Araújo, C. V.; Tibiriçá, E.; Barreiro, E. J.; Fraga, C. A. M. *Eur. J. Med. Chem.* **2011**, *46*, 3000-3012.

(22) R. Dennison, P.; Gibson, A.; I. Gray, A.; L. Patrick, G. *J. Chem. Soc. Perk. Trans. 1* **1997**, *0*, 721-728.

(23) Liu, F.; Chen, X.; Allali-Hassani, A.; Quinn, A. M.; Wigle, T. J.; Wasney, G. A.; Dong, A. P.; Senisterra, G.; Chau, I.; Siarheyeva, A.; Norris, J. L.; Kireev, D. B.; Jadhav, A.; Herold, J. M.; Janzen, W. P.; Arrowsmith, C. H.; Frye, S. V.; Brown, P. J.; Simeonov, A.; Vedadi, M.; Jin, J. A. *J. Med. Chem.* **2010**, *53*, 5844-5857.