molecules

MDPI

Supplementary Materials

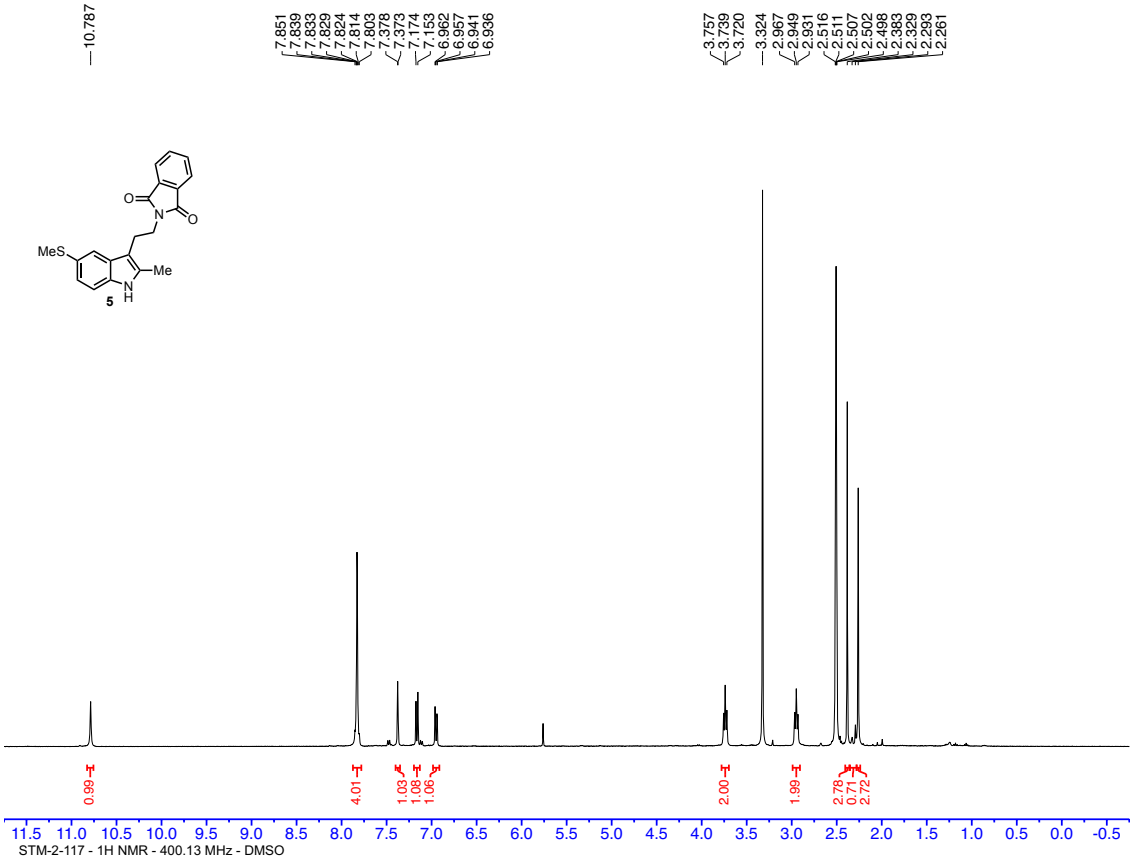
N1-Benzyl Tryptamine Pan-SHIP1/2 Inhibitors: Synthesis and Preliminary Biological Evaluation as Anti-Tumor Agents

Sandra Fernandes [1], Shea T. Meyer [2], Jigisha P. Shah [2], Arijit A. Adhikari [2], William G. Kerr [1] and John D. Chisholm [2,*]

[1] Department of Microbiology & Immunology, SUNY Upstate Medical University, Syracuse, NY 13210, USA
[2] Department of Chemistry, Syracuse University, Syracuse, NY 13244, USA
* Correspondence: jdchisho@syr.edu

Contents

Table of Contents	S1
NMR Spectra	S2-S24
Tables of Predicted Pharmacodynamic data	S25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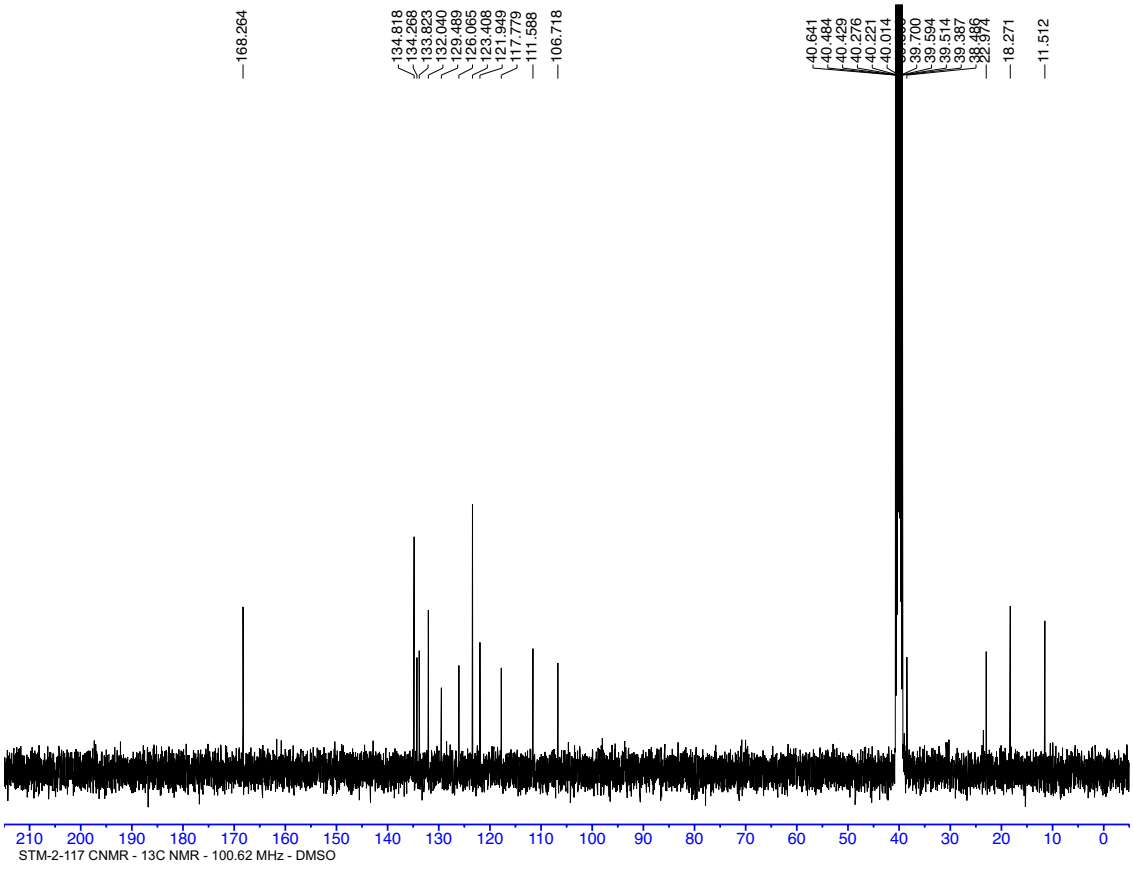
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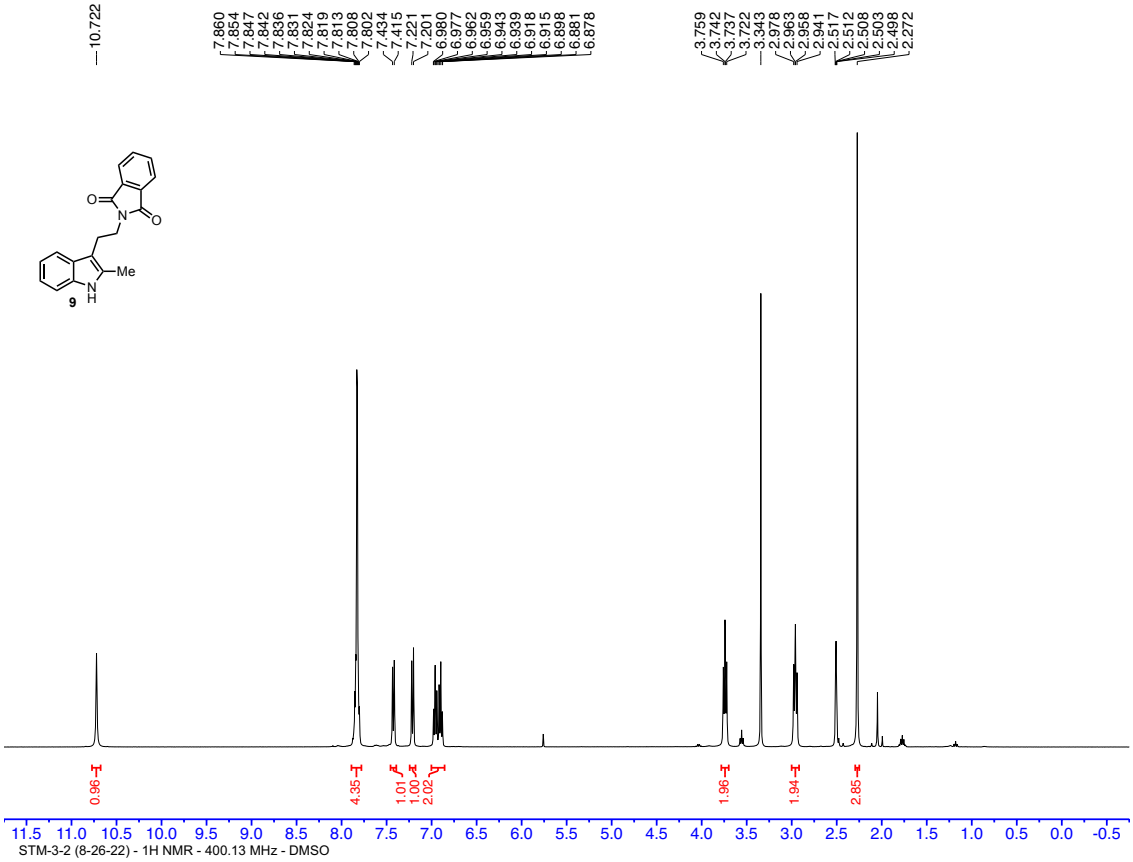
STM-2-117 CNMR - 13C NMR - 100.62 MHz - DMSO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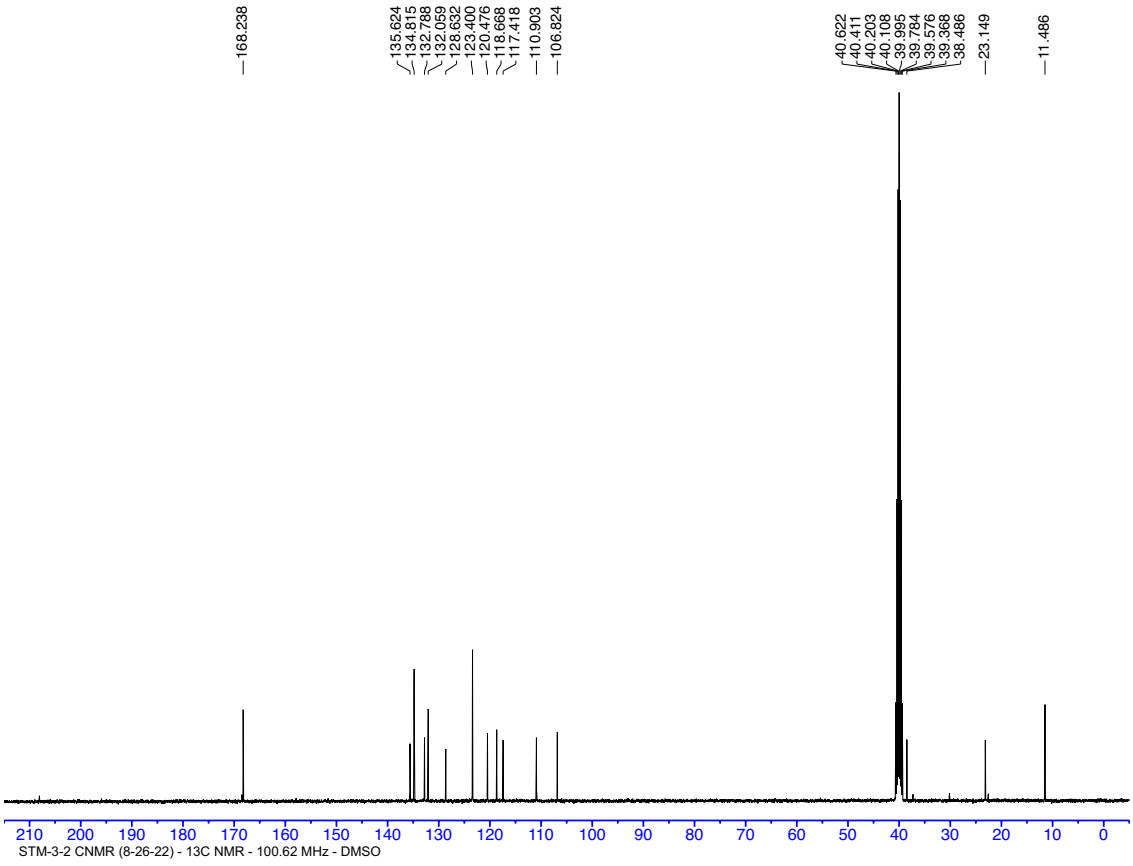
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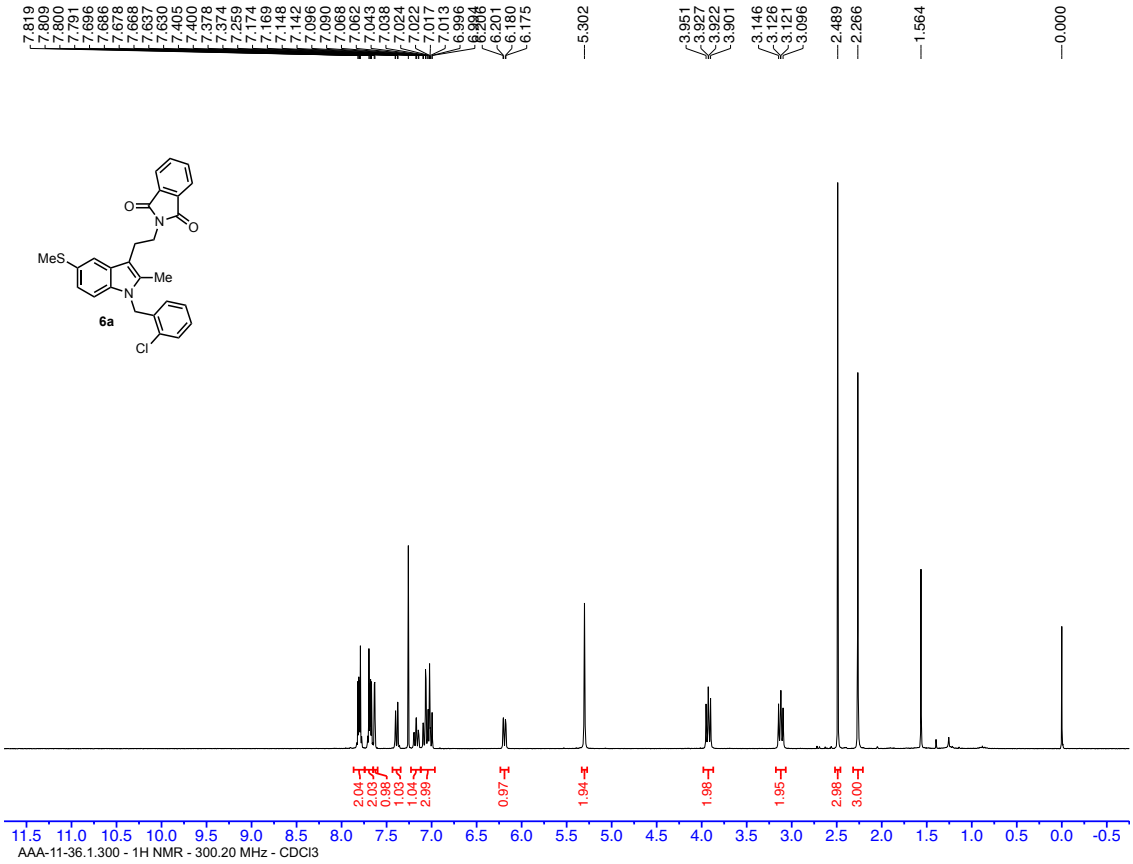
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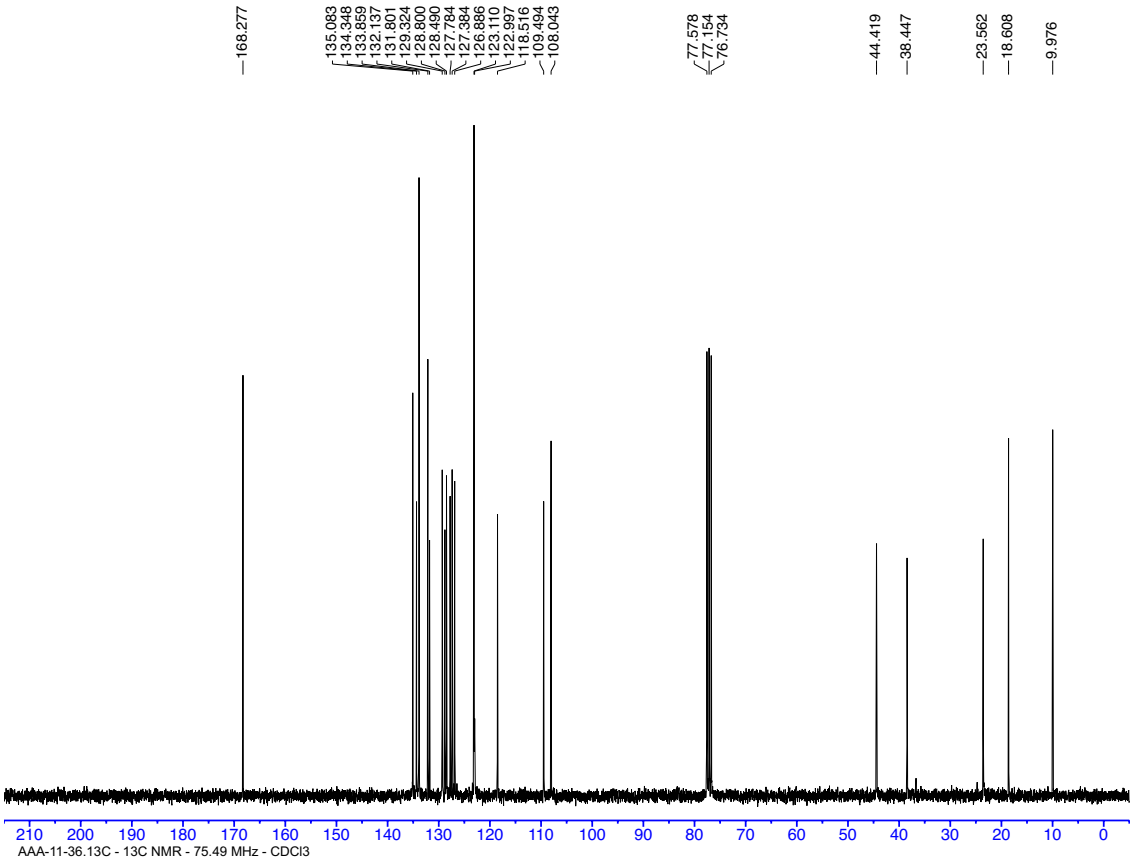
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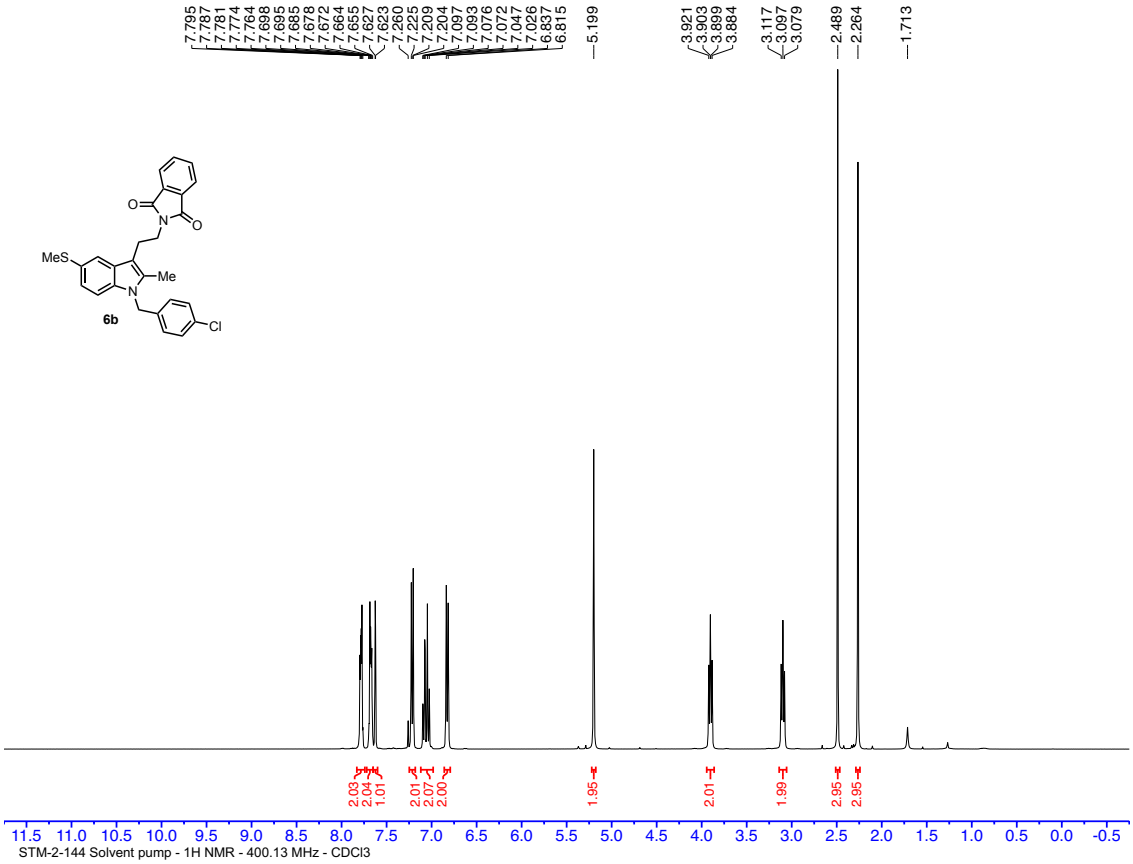
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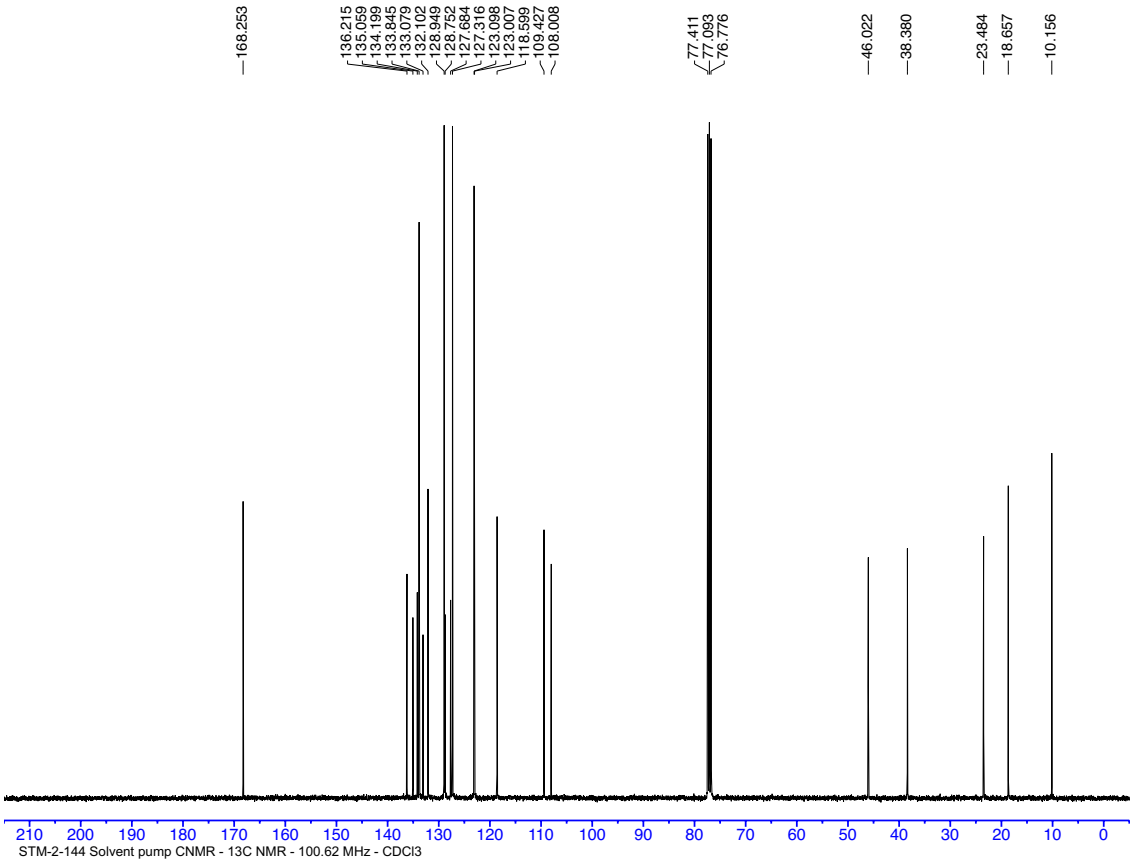
STM-2-144 Solvent pump - 1H NMR - 400.13 MHz - CDCl3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23.484
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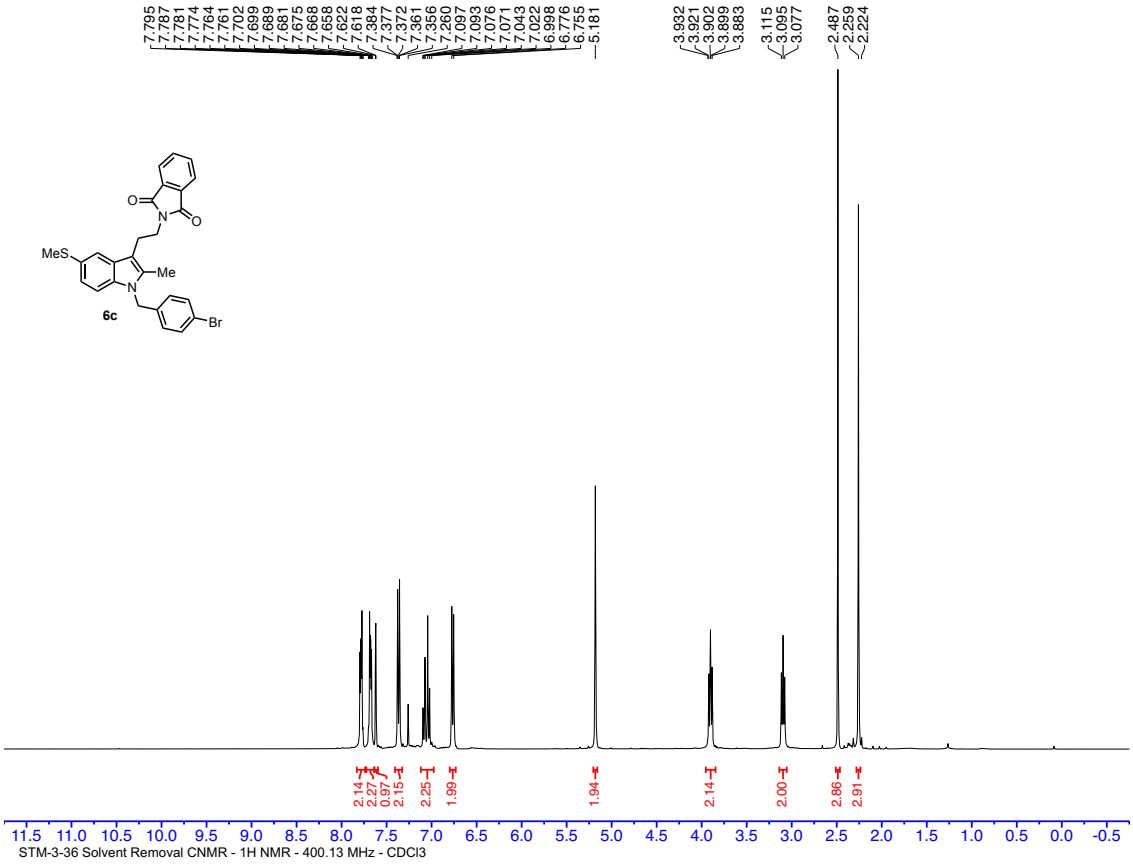
STM-2-144 Solvent pump CNMR - 13C NMR - 100.62 MHz - CDCl3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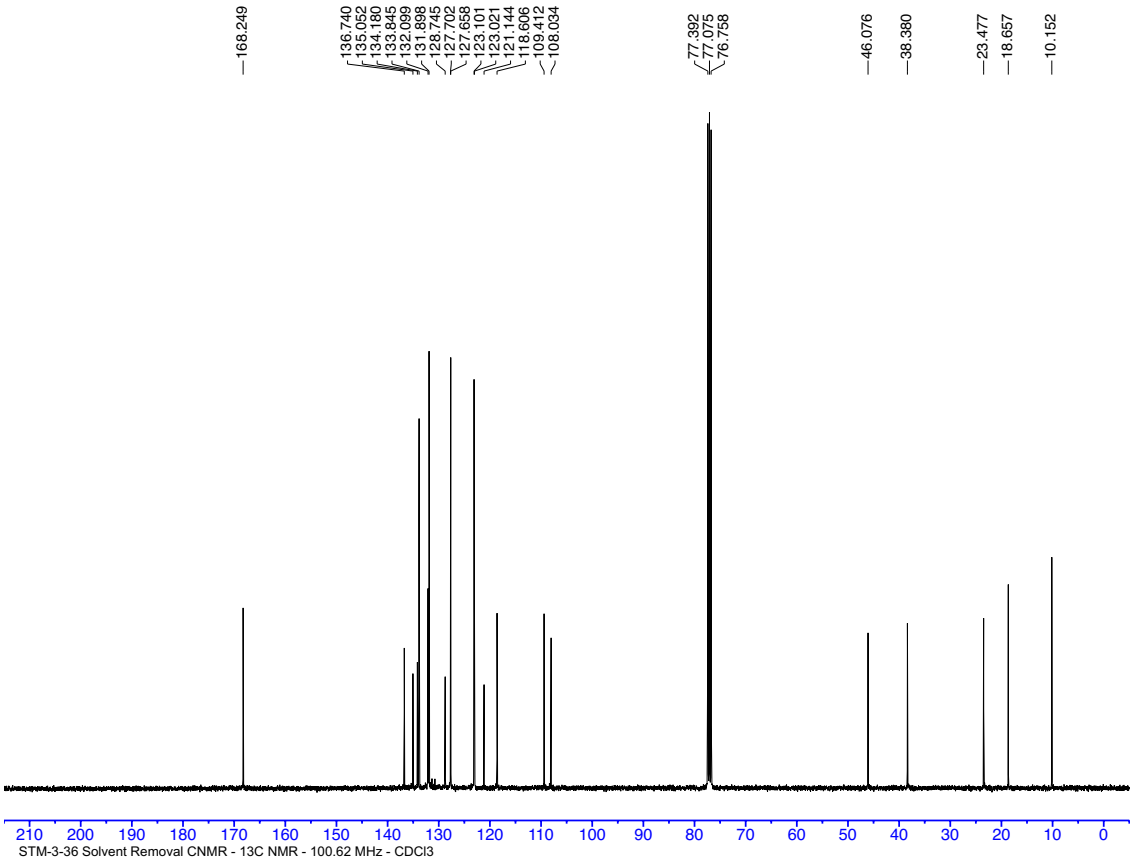
STM-3-36 Solvent Removal CNMR - 1H NMR - 400.13 MHz - CDCl3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121.144
118.606
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77.392
77.075
76.758
46.076
38.380
23.477
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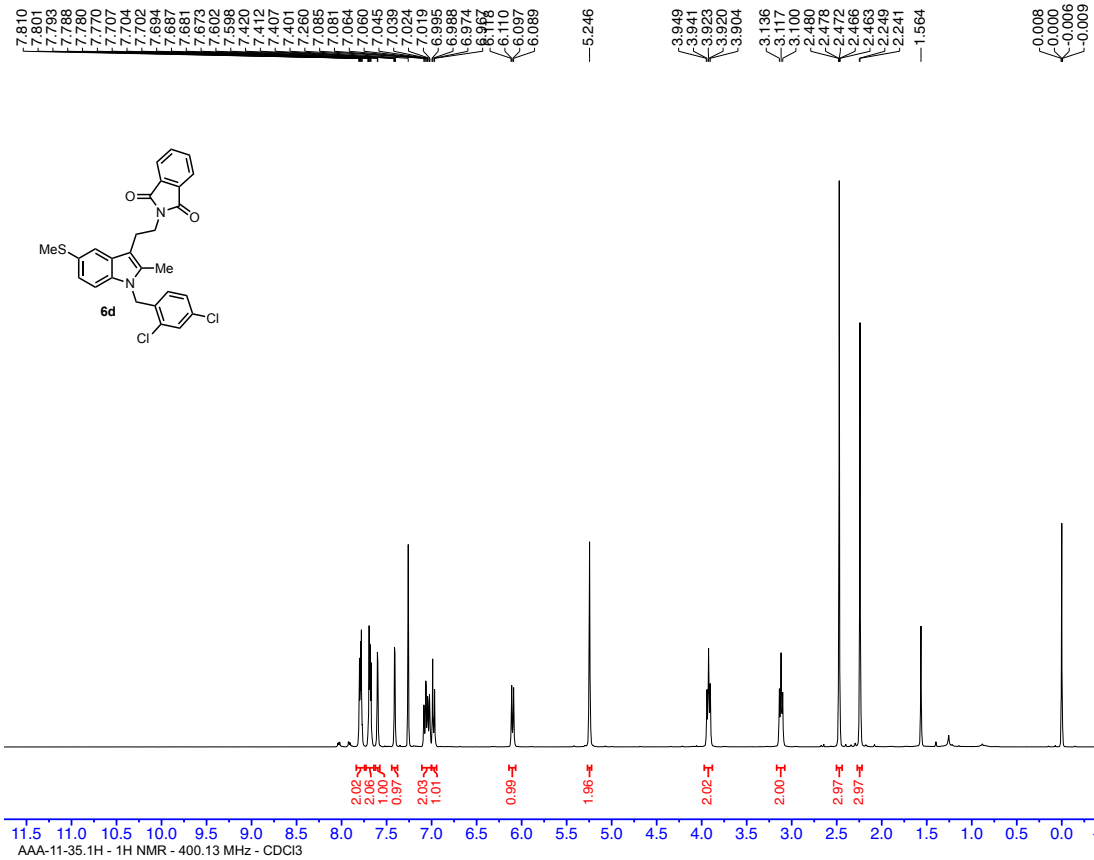
STM-3-36 Solvent Removal CNMR - 13C NMR - 100.62 MHz - CDCl3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-0.009
MeS
Me
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O
N
O
6d
Cl
Cl
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2.06
1.00
0.97
2.03
1.01
0.99
1.96
2.02
2.00
2.97
2.97
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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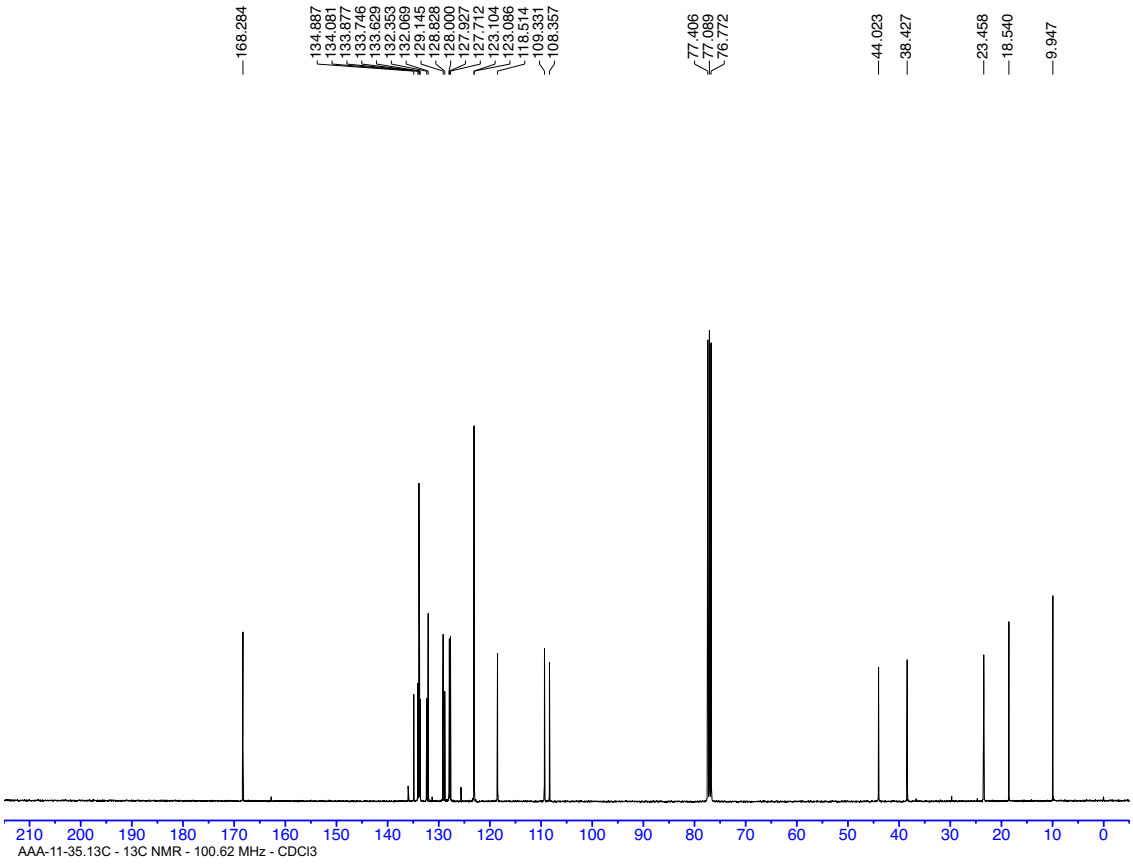
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127.927
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123.104
123.086
118.514
109.331
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77.406
77.089
76.772
44.023
38.427
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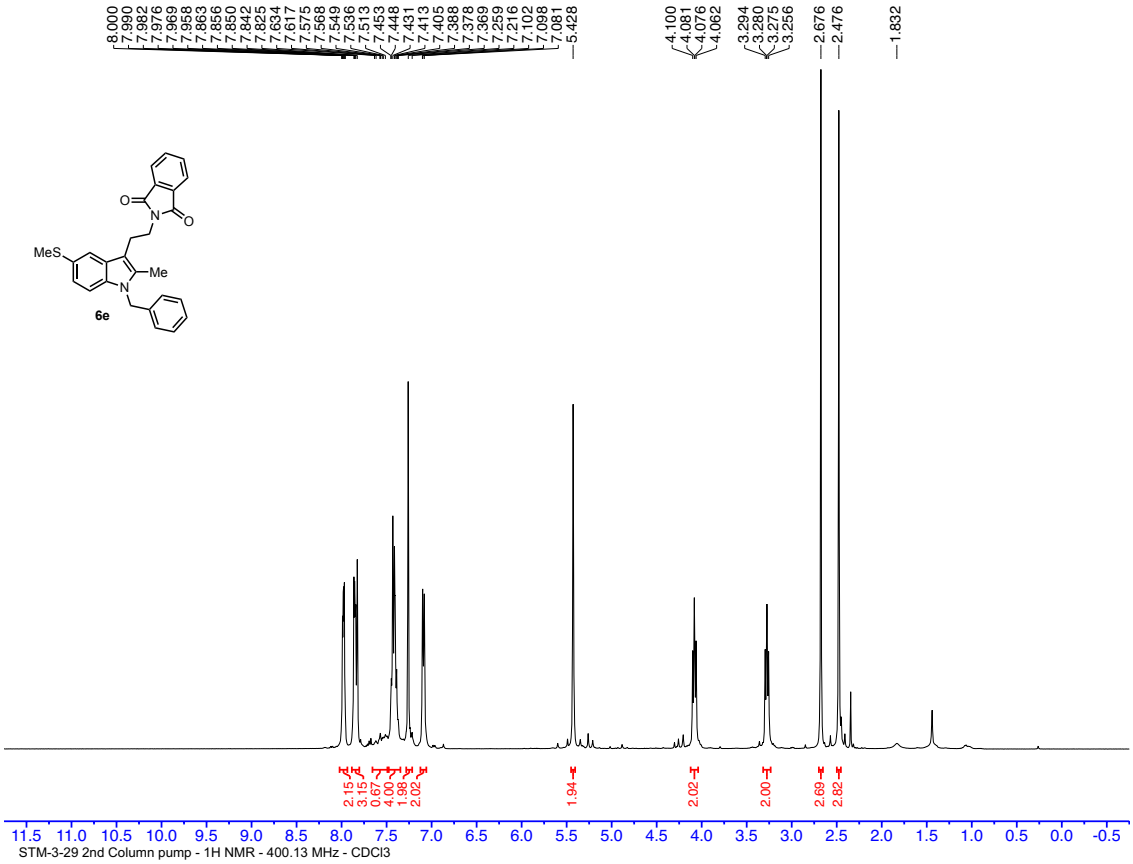
AAA-11-35.13C - 13C NMR - 100.62 MHz - CDCl3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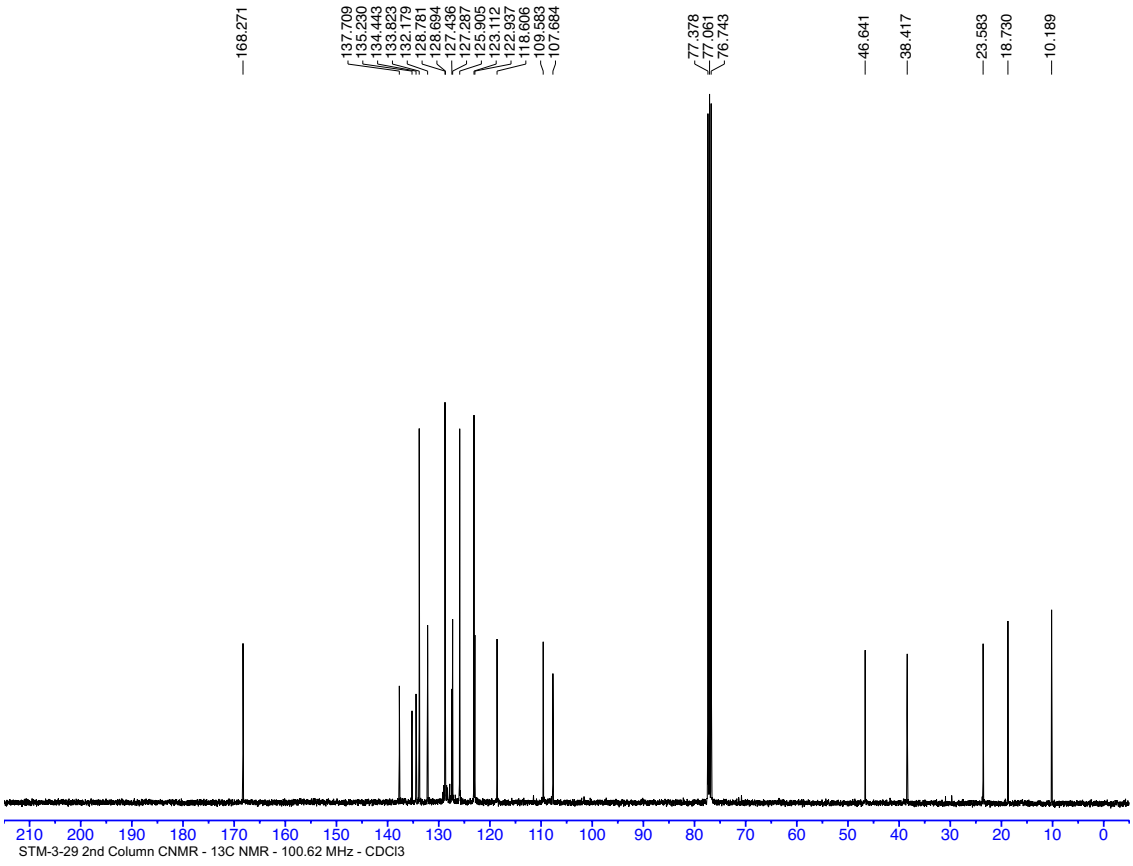
STM-3-29 2nd Column pump - 1H NMR - 400.13 MHz - CDCl3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46.641
38.417
23.583
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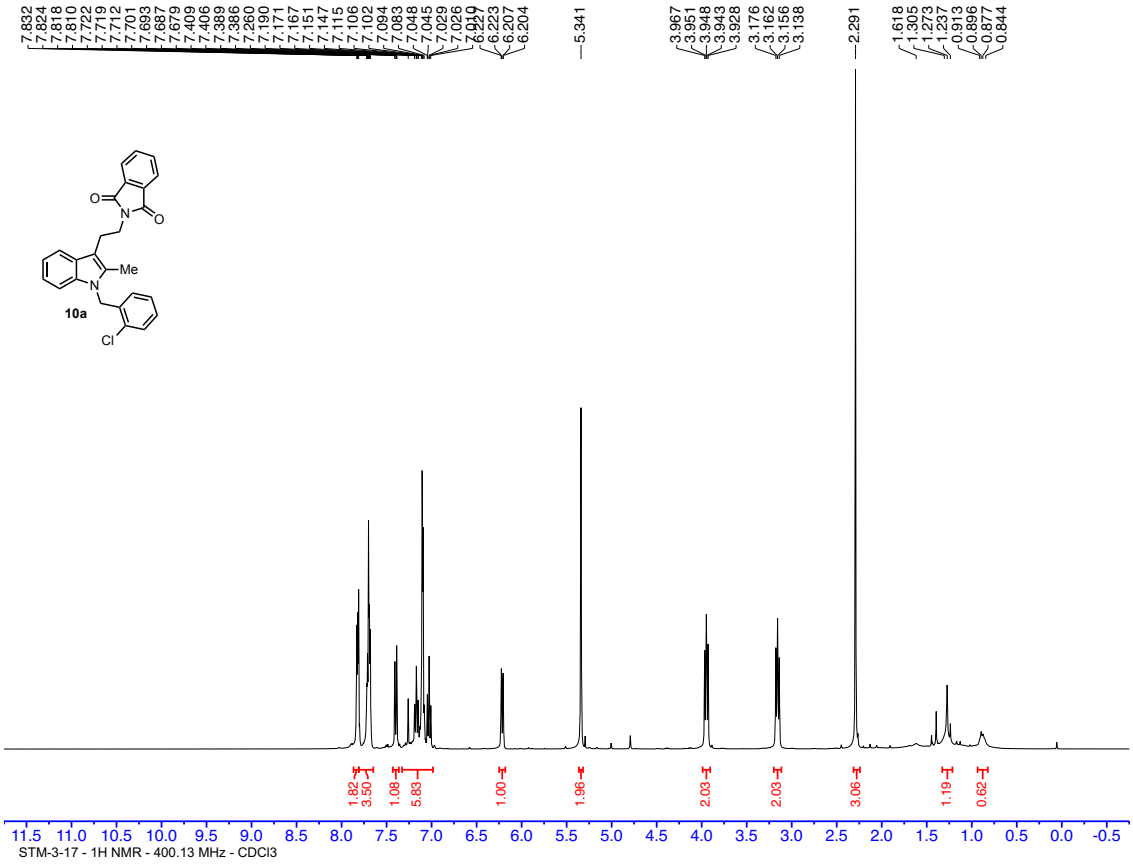
STM-3-29 2nd Column CNMR - 13C NMR - 100.62 MHz - CDCl3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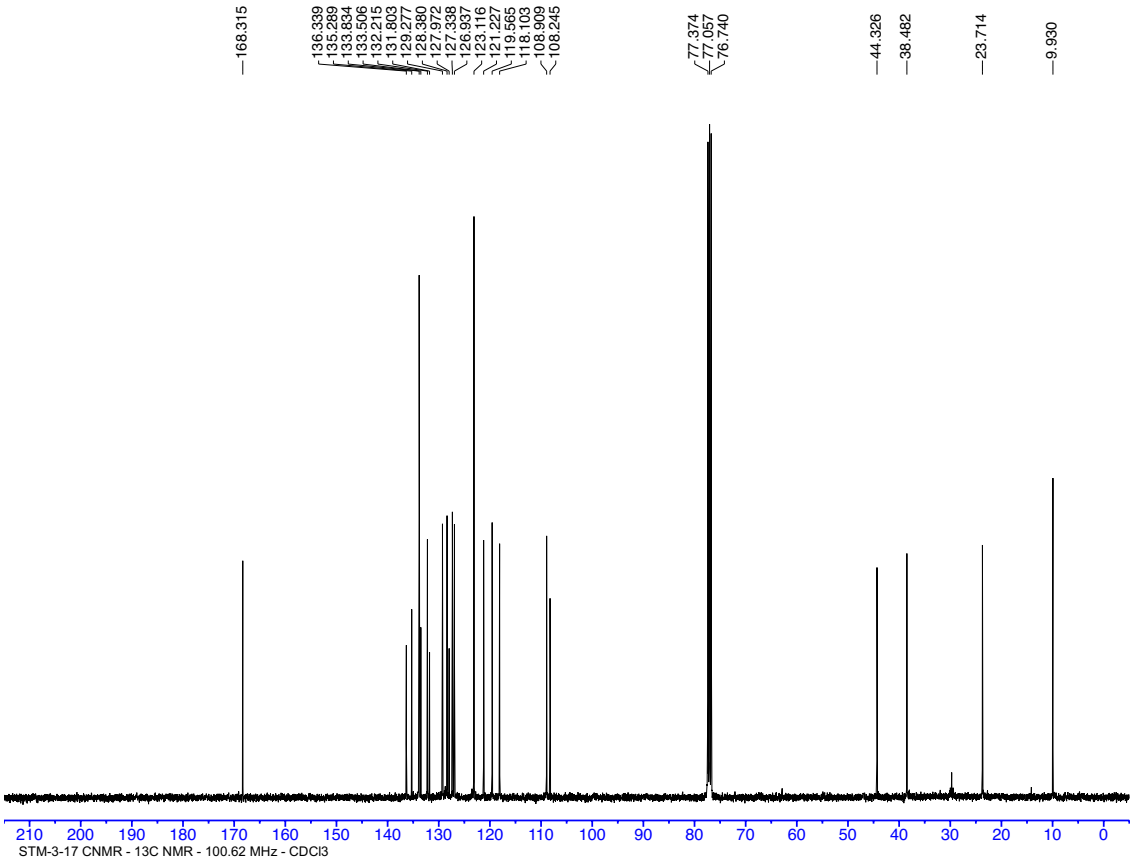
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-17 - 1H NMR - 400.13 MHz - CDCl3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119.565
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108.909
108.245
77.374
77.057
76.740
44.326
38.482
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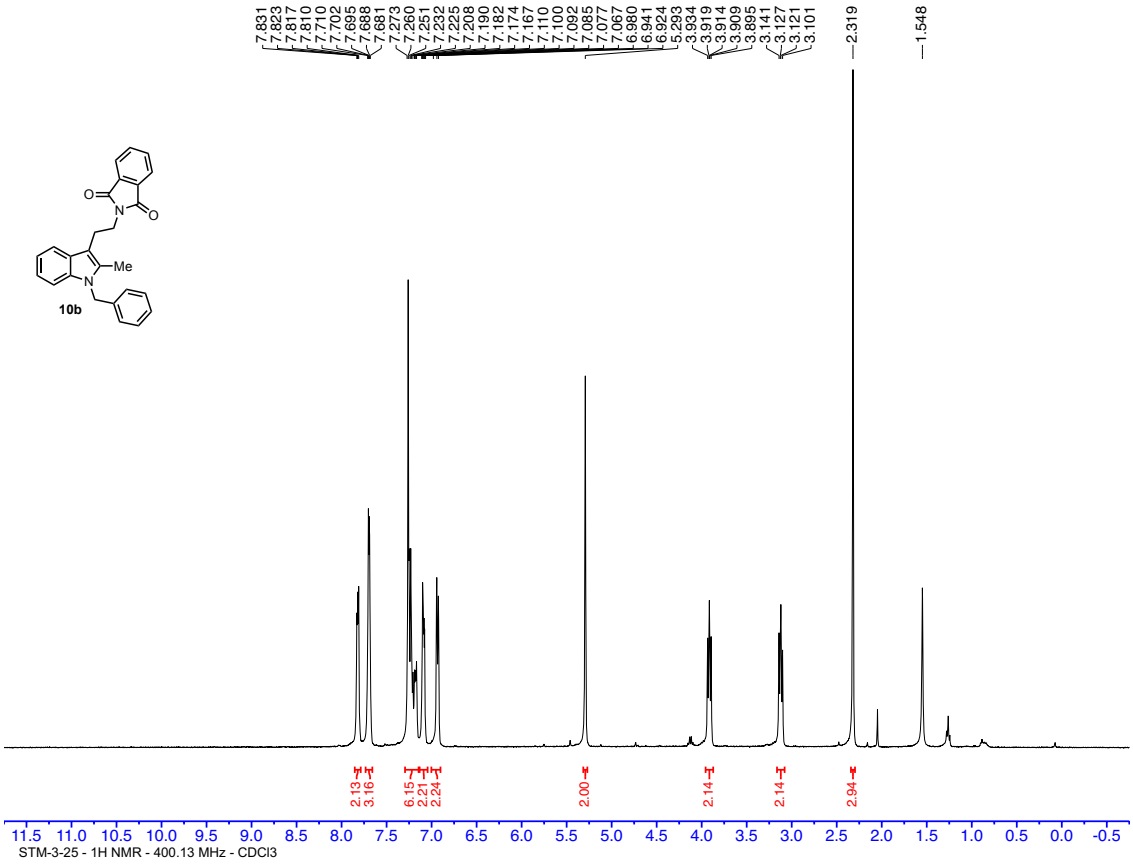
STM-3-17 CNMR - 13C NMR - 100.62 MHz - CDCl3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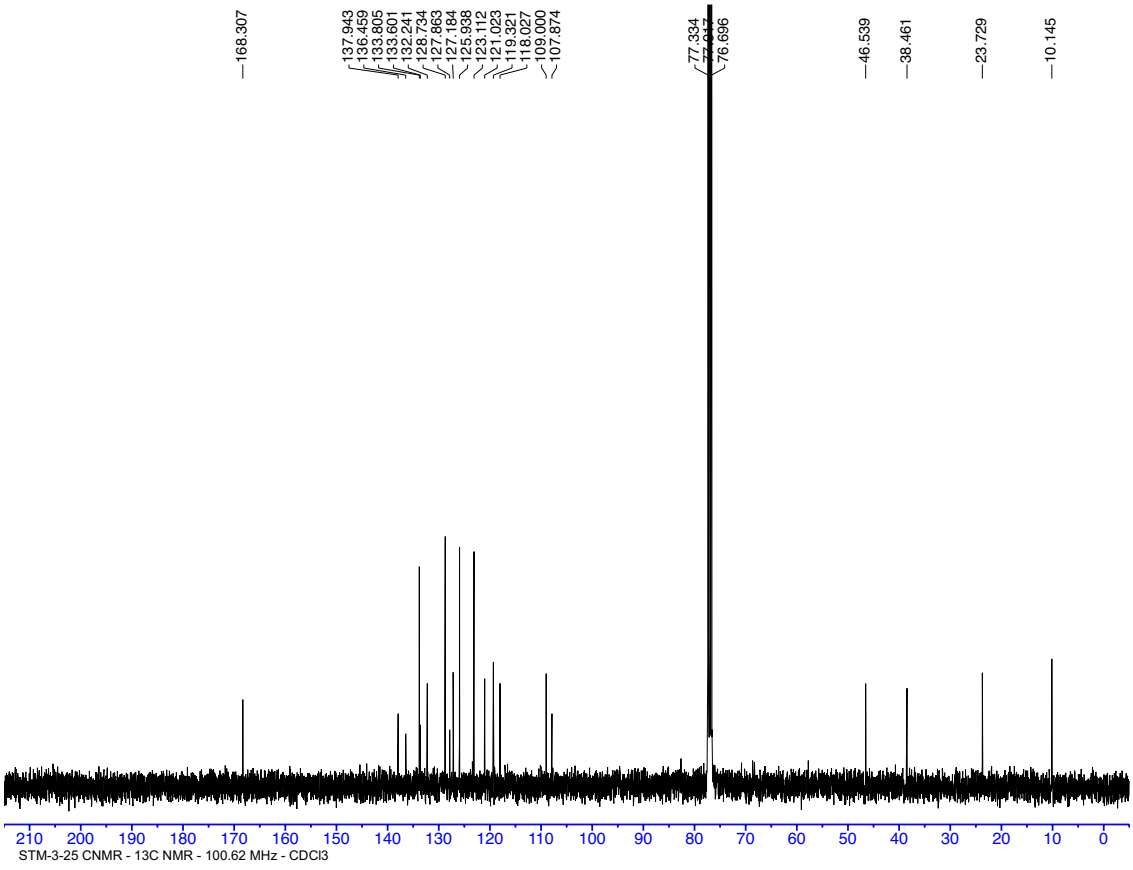
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-25 - 1H NMR - 400.13 MHz - CDCl3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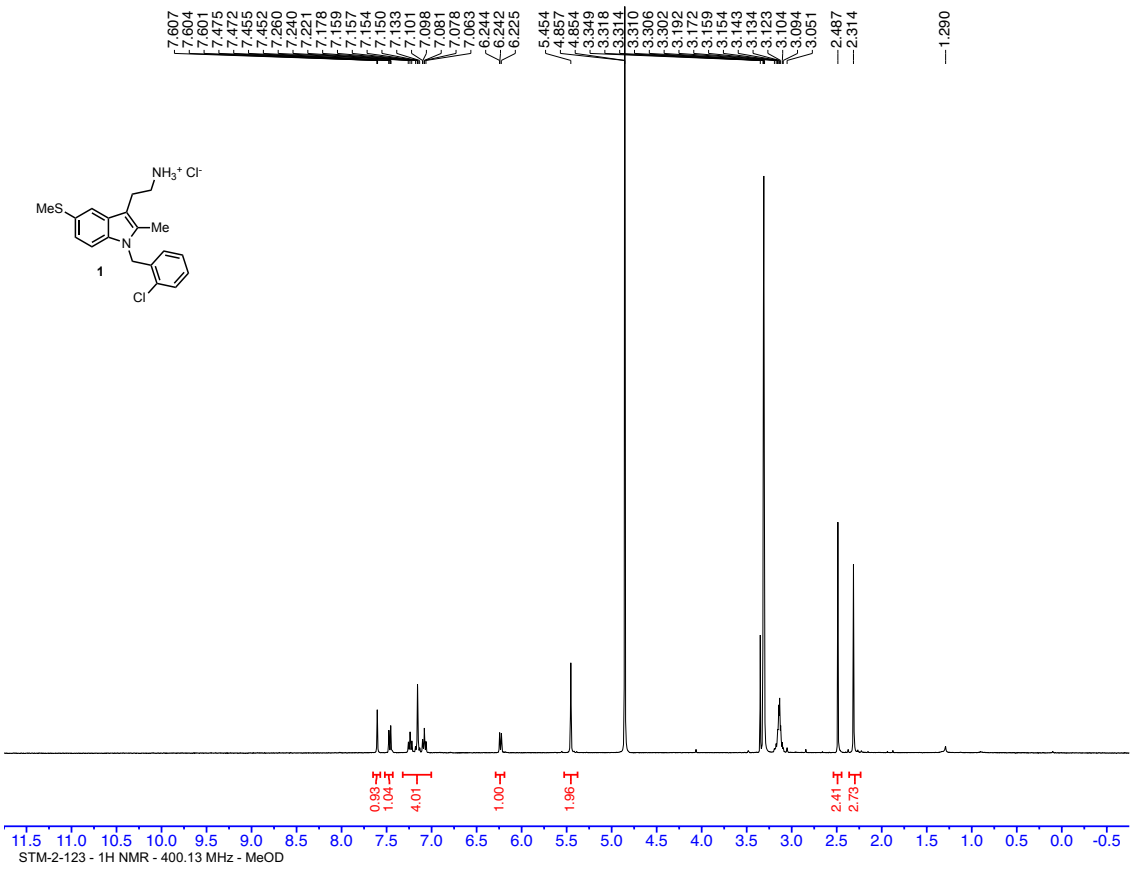
STM-3-25 CNMR - 13C NMR - 100.62 MHz - CDCl3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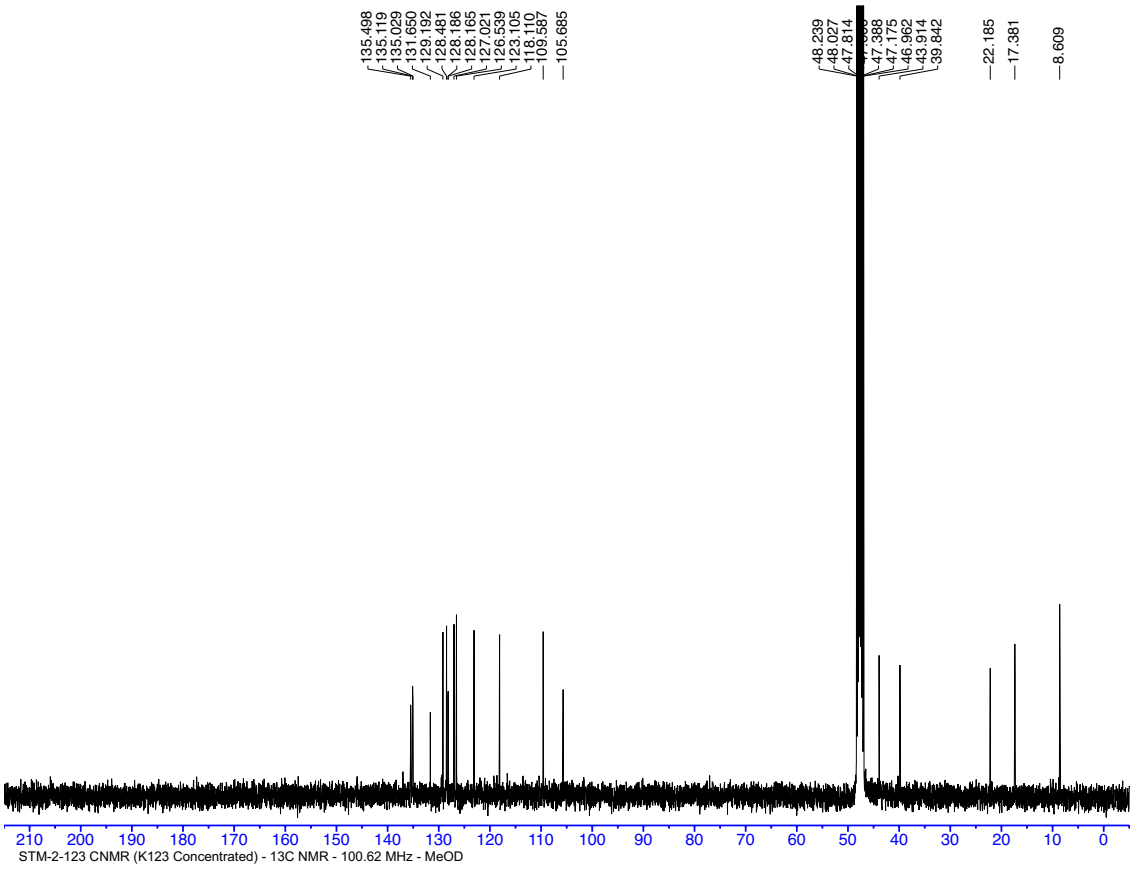
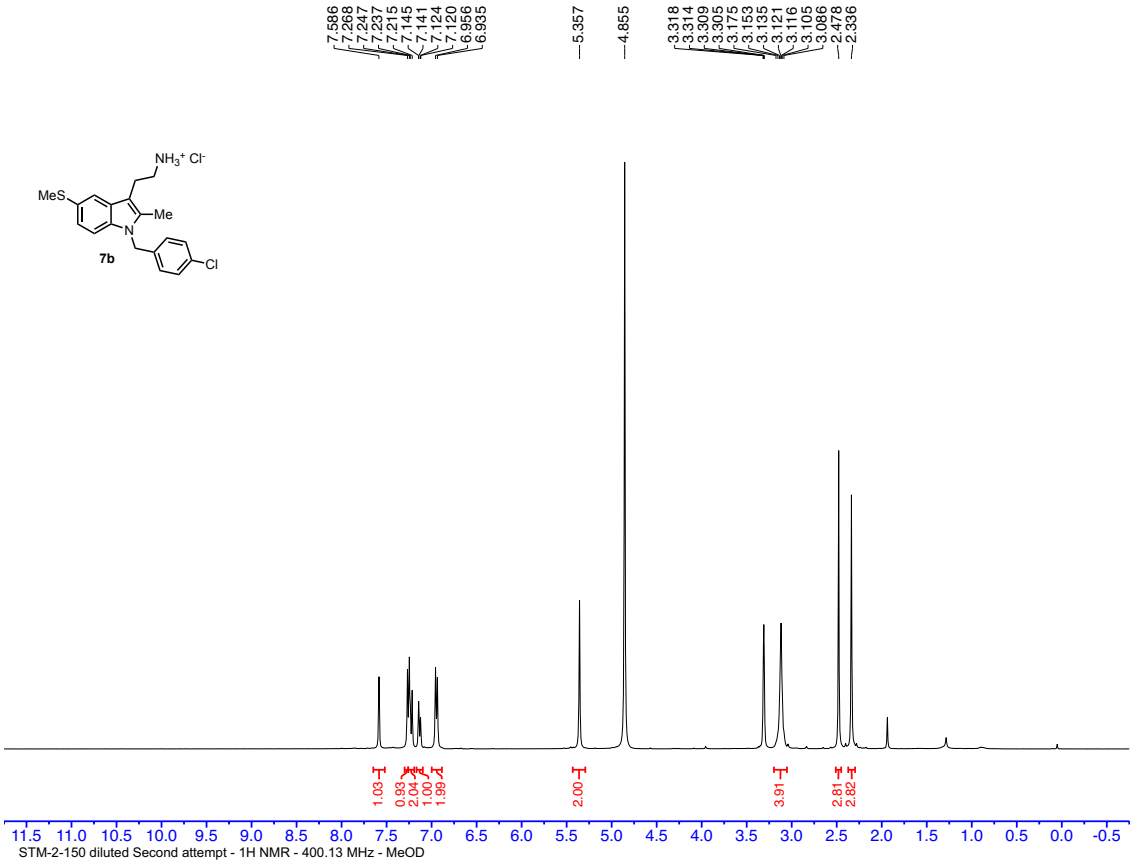
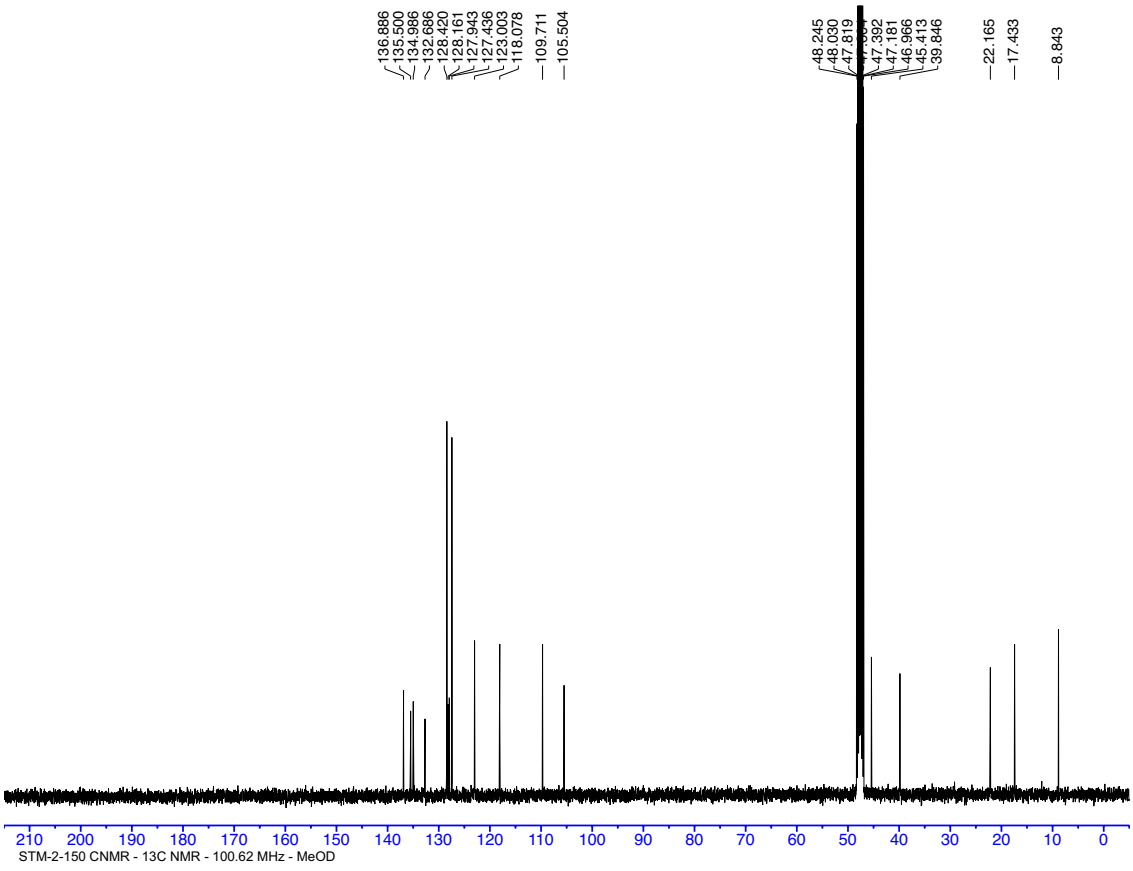
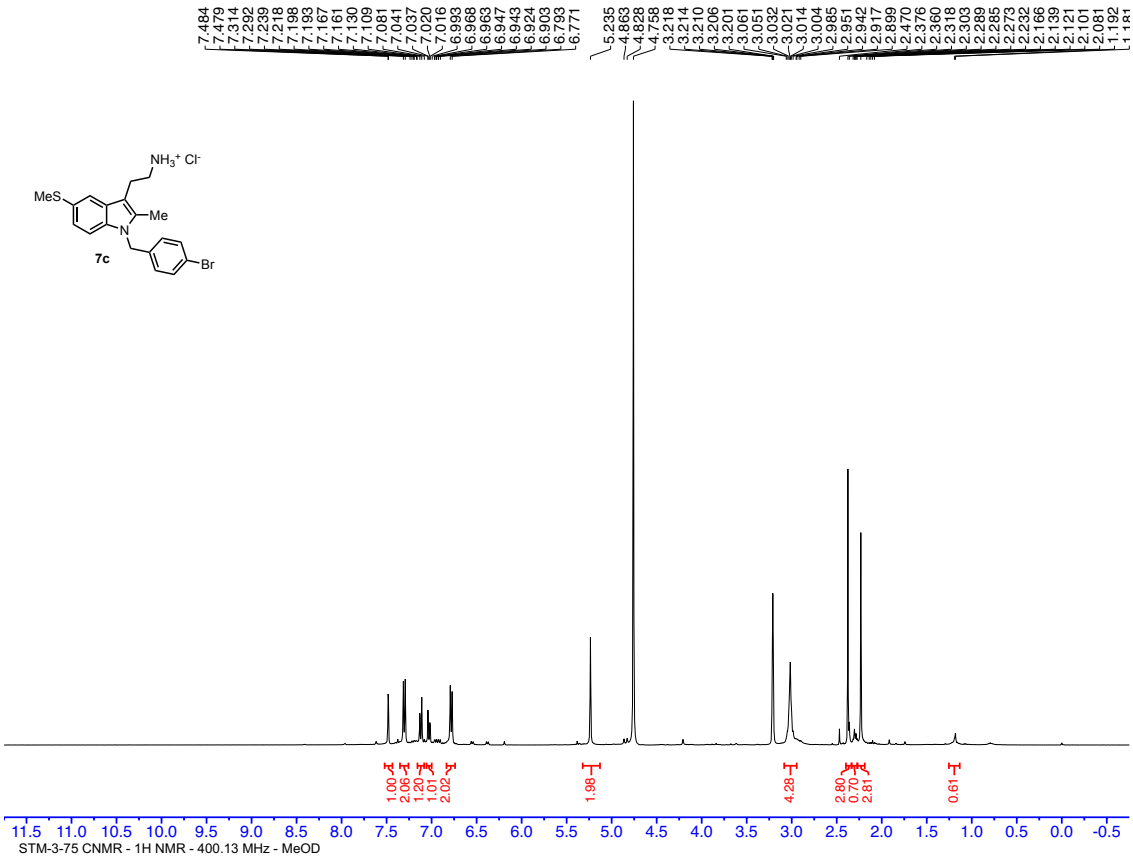
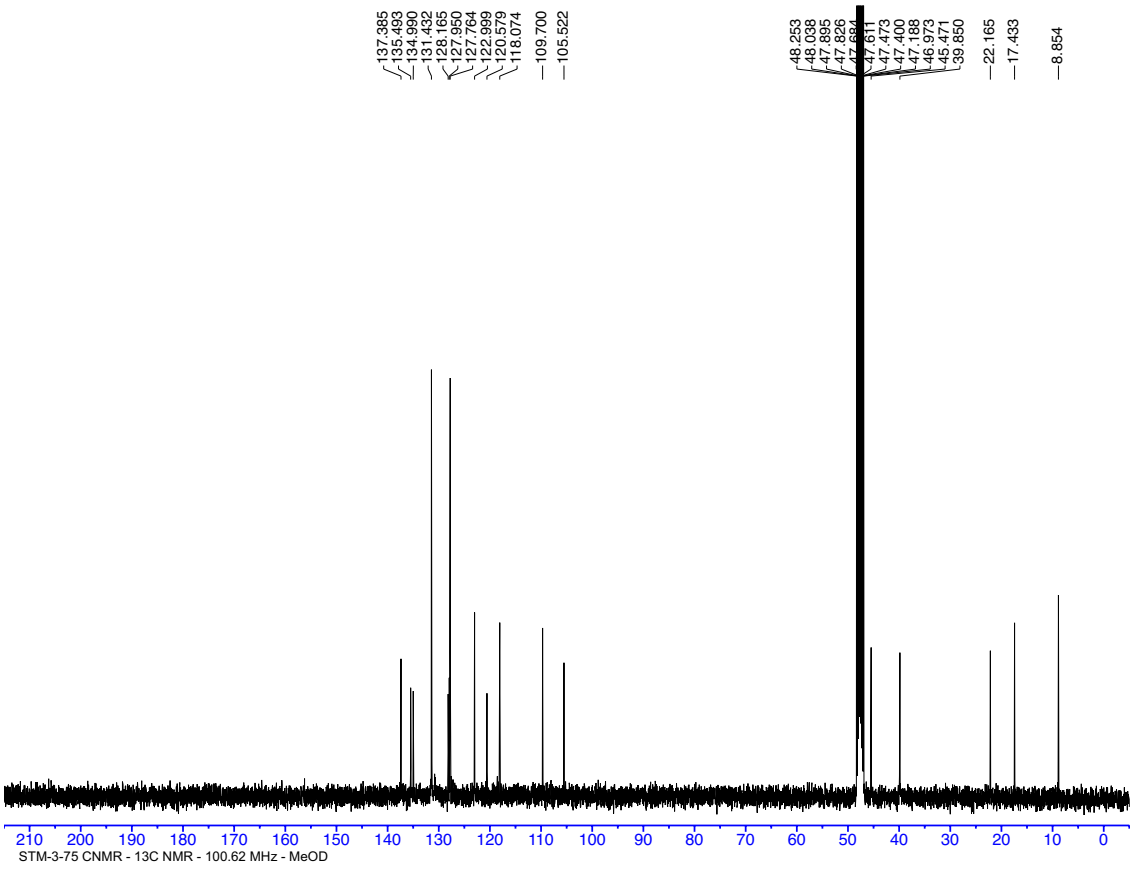
3.172
3.159
3.154
3.143
3.134
3.123
3.104
3.094
3.051
2.487
2.314
1.290
NH3+ Cl-
MeS
Me
N
1
Cl
0.93
1.04
4.01
1.00
1.96
2.41
2.73
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-2-123 - 1H NMR - 400.13 MHz - MeOD

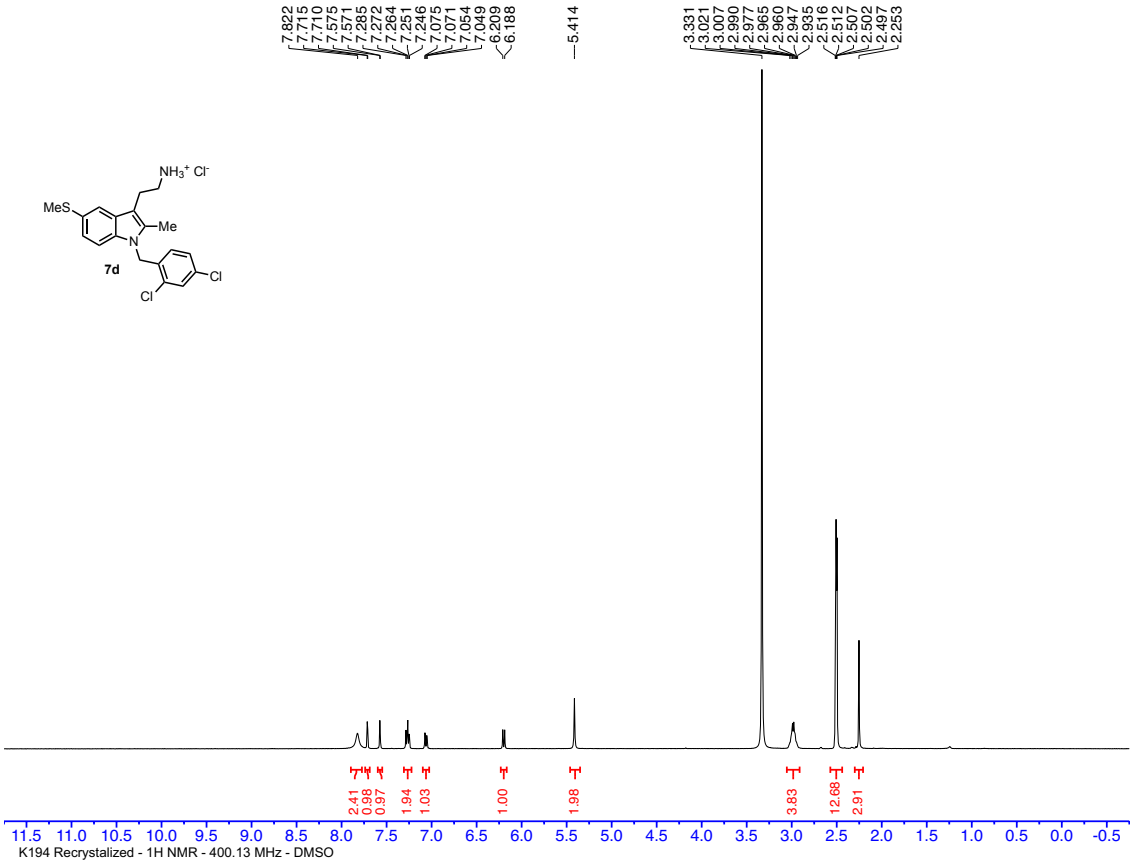

135.498
135.119
135.029
131.650
129.192
128.481
128.186
128.165
127.021
126.539
123.105
118.110
109.587
105.685
48.239
48.027
47.814
47.388
47.175
46.962
43.914
39.842
22.185
17.381
8.609
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-2-123 CNMR (K123 Concentrated) - 13C NMR - 100.62 MHz - MeOD

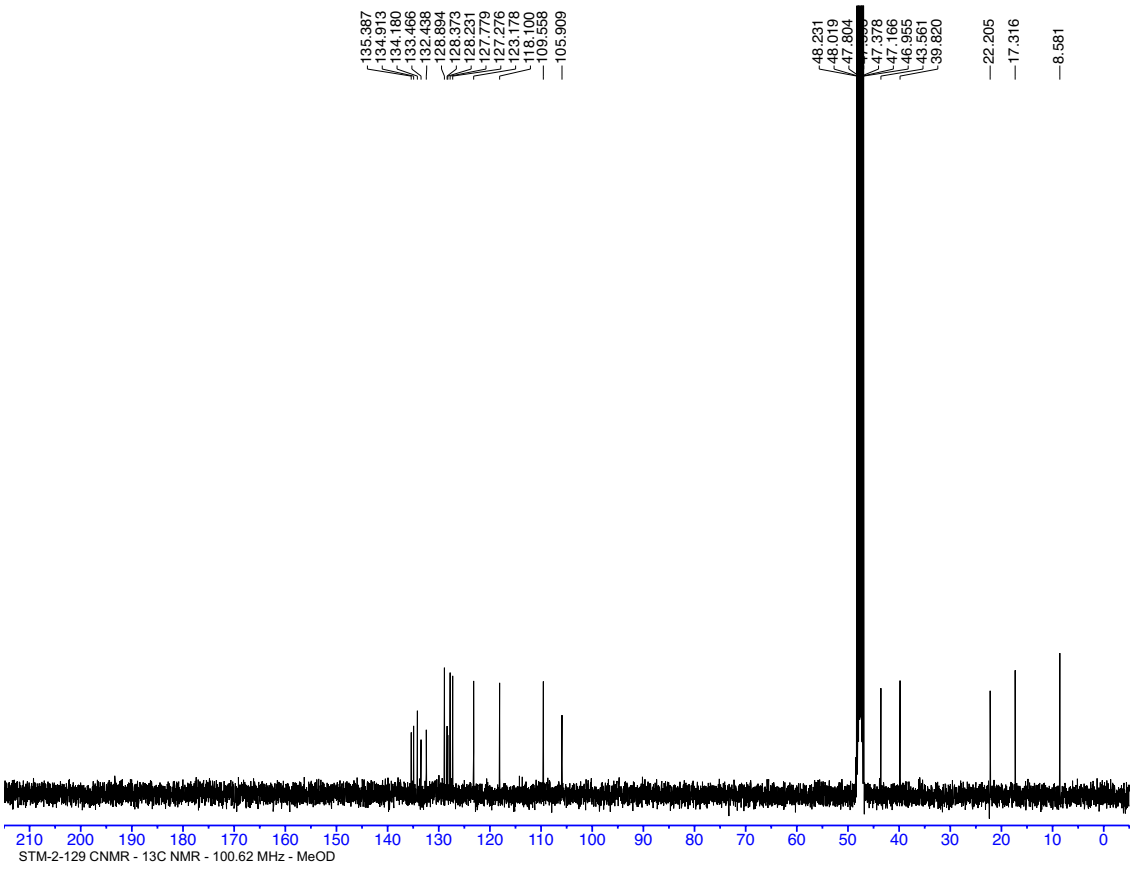

7.586
7.268
7.247
7.237
7.215
7.145
7.141
7.124
7.120
6.956
6.935
5.357
4.855
3.318
3.314
3.309
3.305
3.175
3.153
3.135
3.121
3.116
3.105
3.086
2.478
2.336
NH3+ Cl-
MeS
Me
N
Cl
7b
1.03
0.93
2.04
1.00
1.99
2.00
3.91
2.81
2.82
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-2-150 diluted Second attempt - 1H NMR - 400.13 MHz - MeOD

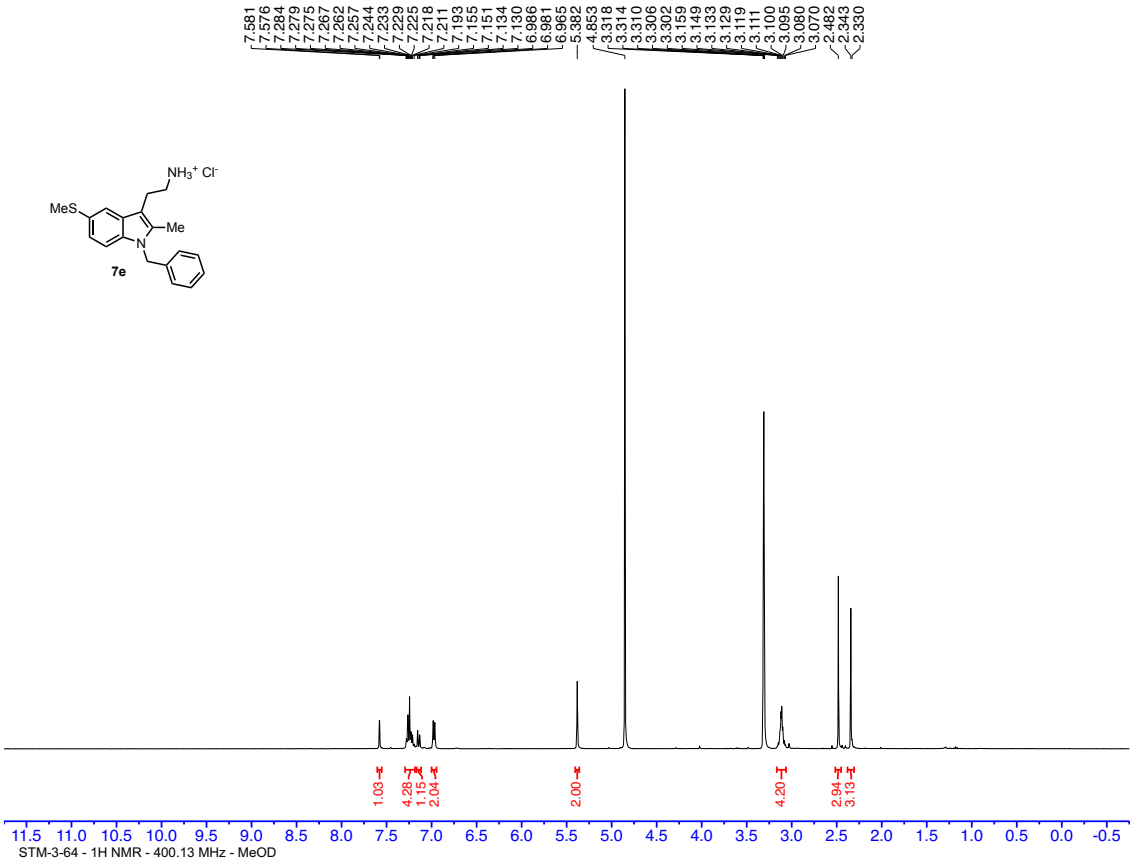

136.886
135.500
134.986
132.686
128.420
128.161
127.943
127.436
123.003
118.078
109.711
105.504
48.245
48.030
47.819
47.392
47.181
46.966
45.413
39.846
22.165
17.433
8.843
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-2-150 CNMR - 13C NMR - 100.62 MHz - MeOD

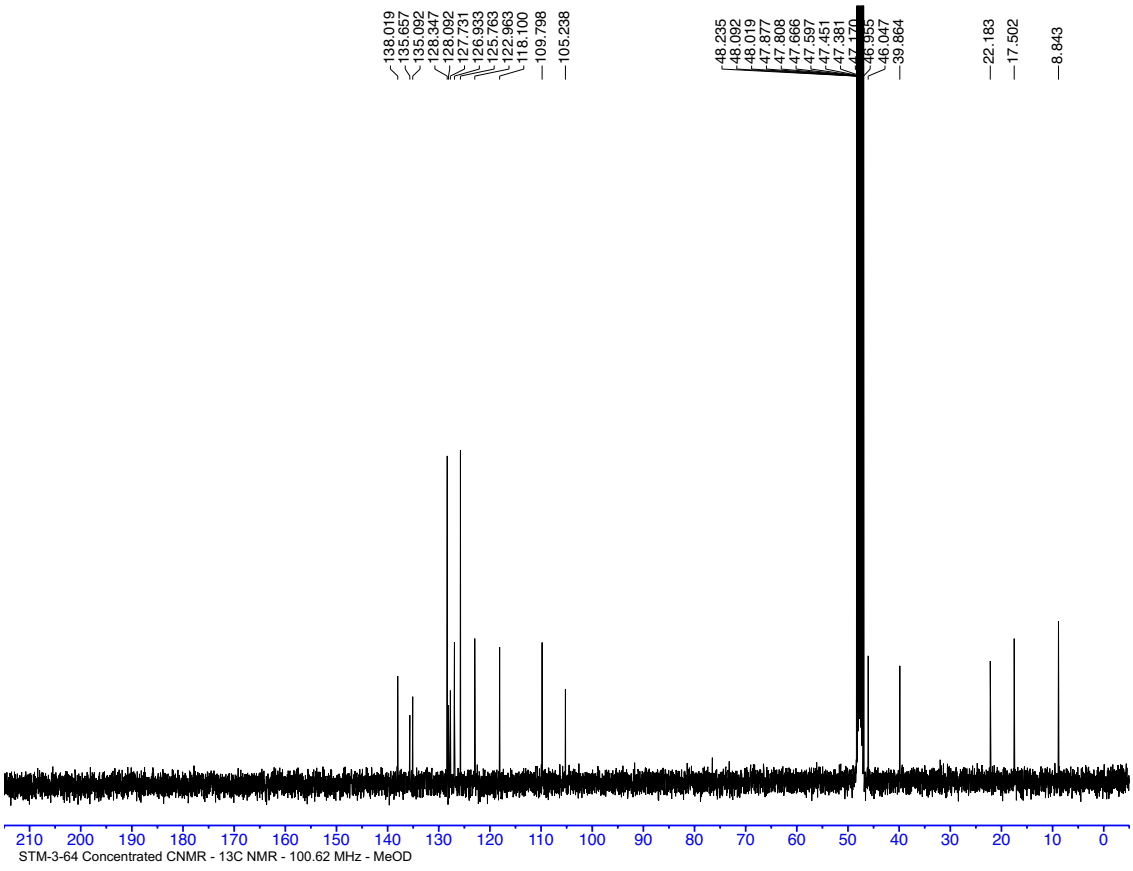

7.484
7.479
7.314
7.292
7.239
7.218
7.198
7.193
7.167
7.161
7.130
7.109
7.081
7.041
7.037
7.020
7.016
6.993
6.968
6.963
6.947
6.943
6.924
6.903
6.793
6.771
5.235
4.863
4.828
4.758
3.218
3.214
3.210
3.206
3.201
3.061
3.051
3.032
3.021
3.014
3.004
2.985
2.951
2.942
2.917
2.899
2.470
2.376
2.360
2.318
2.303
2.289
2.285
2.273
2.232
2.166
2.139
2.121
2.101
2.081
1.192
NH3+ Cl-
MeS
Me
N
Br
7c
1.00
2.06
1.20
1.01
2.02
1.98
4.28
2.80
0.70
2.81
0.61
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-75 CNMR - 1H NMR - 400.13 MHz - MeOD

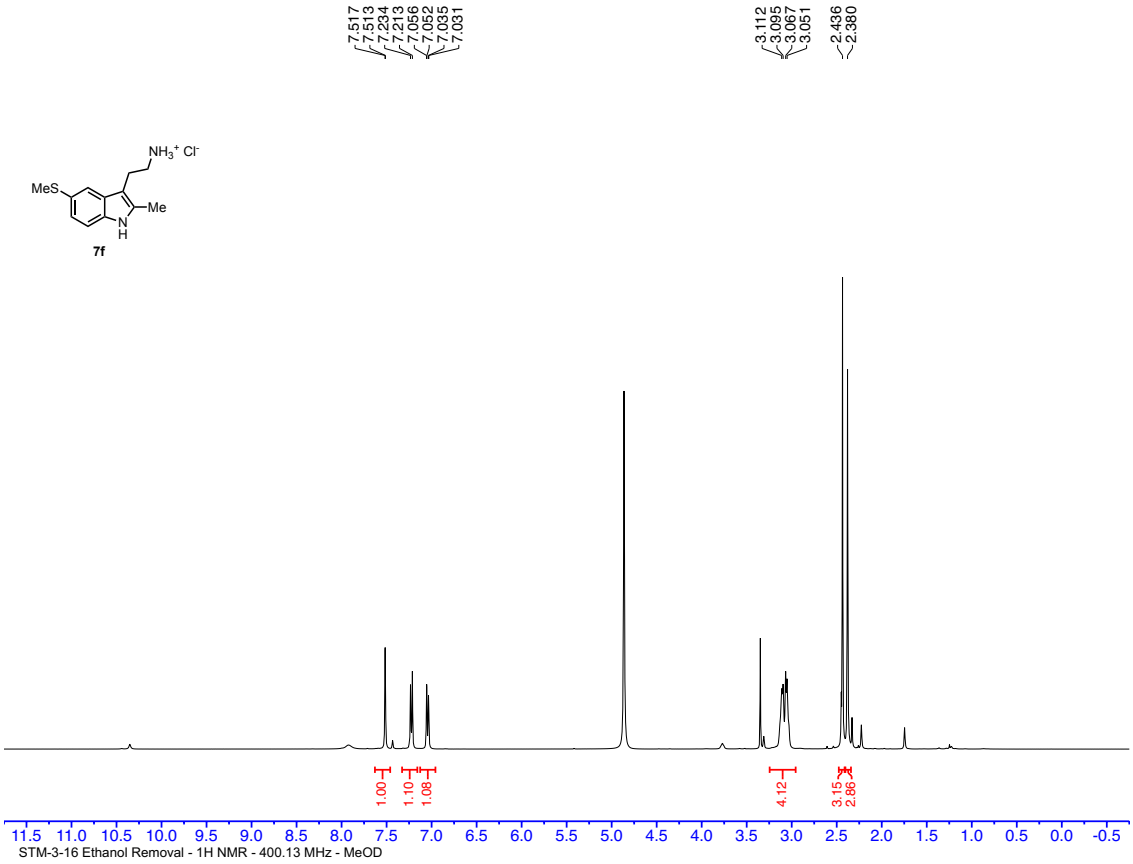

137.385
135.493
134.990
131.432
128.165
127.950
127.764
122.999
120.579
118.074
109.700
105.522
48.253
48.038
47.895
47.826
47.684
47.611
47.473
47.400
47.188
46.973
45.471
39.850
22.165
17.433
8.854
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-75 CNMR - 13C NMR - 100.62 MHz - MeOD

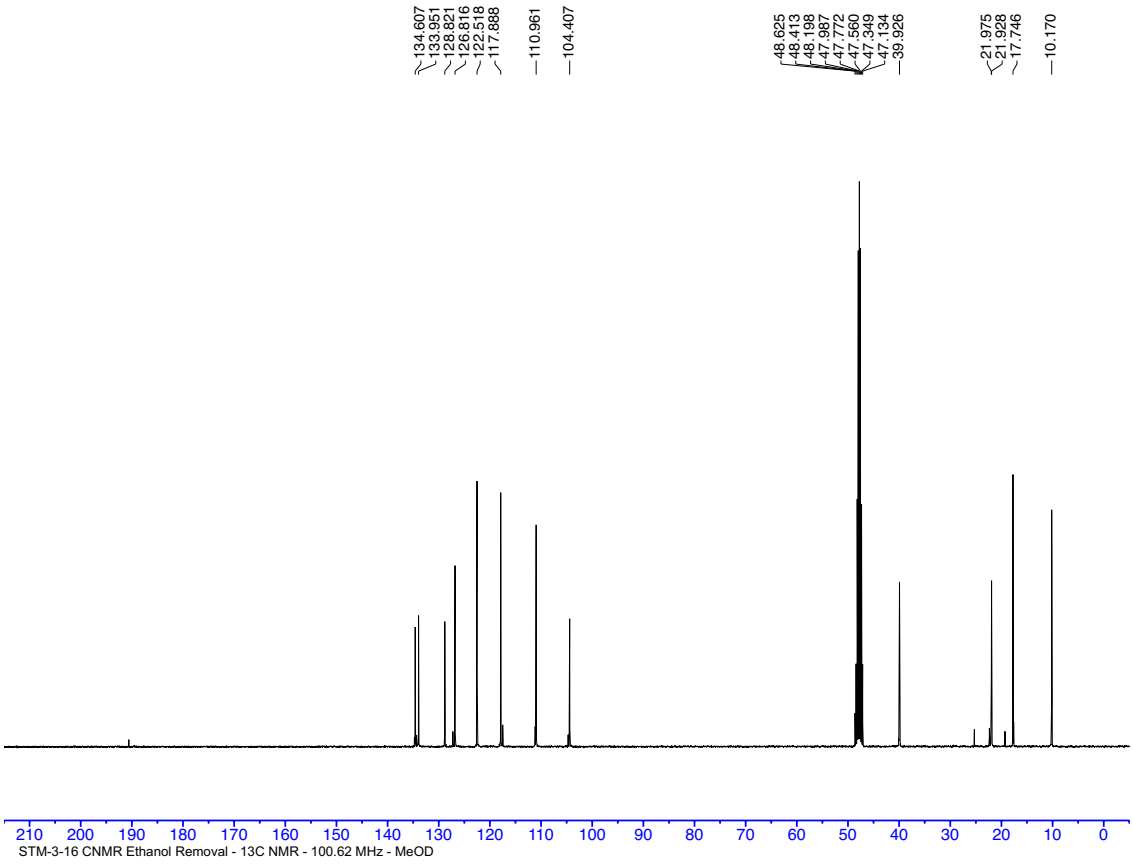

7.822
7.715
7.710
7.575
7.571
7.285
7.272
7.264
7.251
7.246
7.075
7.071
7.054
7.049
6.209
6.188
5.414
3.331
3.021
3.007
2.990
2.977
2.965
2.960
2.947
2.935
2.516
2.512
2.507
2.502
2.497
2.253
NH3+ Cl-
MeS
Me
N
7d
Cl
Cl
2.41
0.99
0.97
1.94
1.03
1.00
1.98
3.83
12.68
2.91
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
K194 Recrystalized - 1H NMR - 400.13 MHz - DMSO

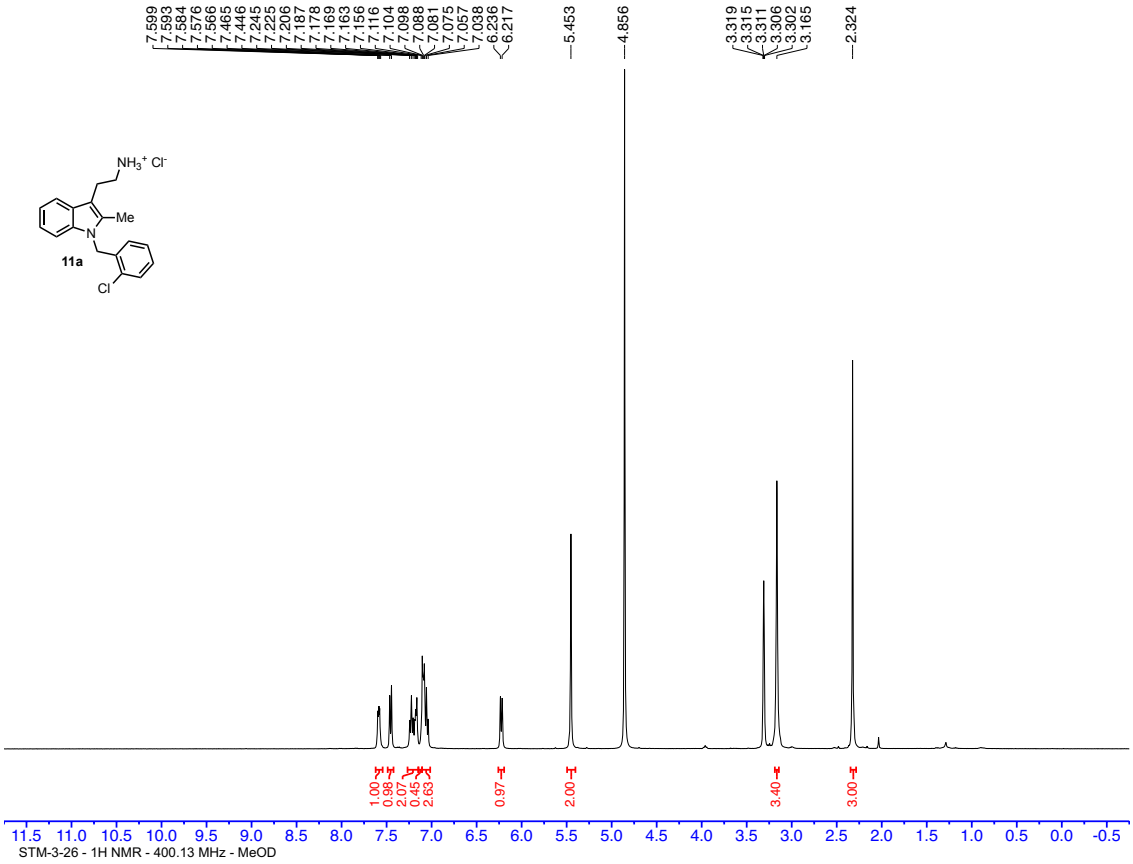

135.387
134.913
134.180
133.466
132.438
128.894
128.373
128.231
127.779
127.276
123.178
118.100
109.558
105.909
48.231
48.019
47.804
47.378
47.166
46.955
43.561
39.820
22.205
17.316
8.581
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-2-129 CNMR - 13C NMR - 100.62 MHz - MeOD

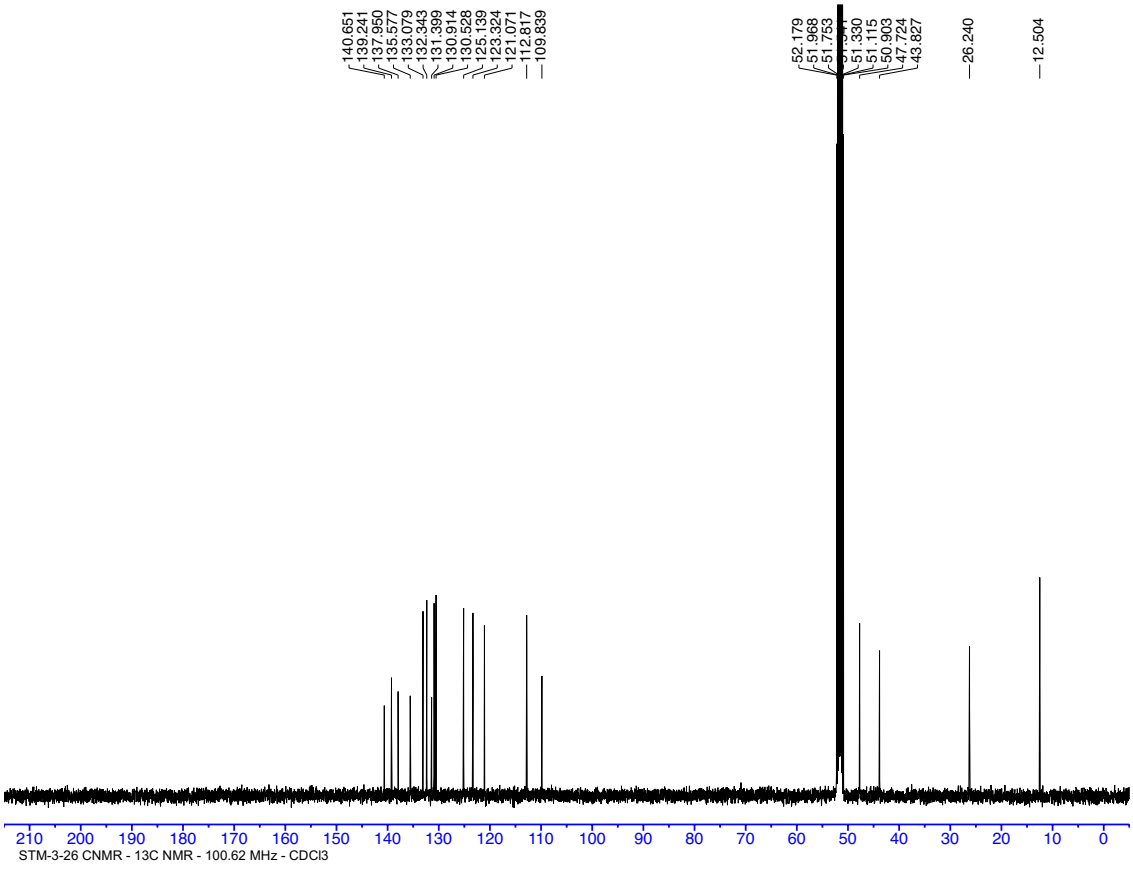

7.581
7.576
7.284
7.279
7.275
7.267
7.262
7.257
7.244
7.233
7.229
7.225
7.218
7.211
7.193
7.155
7.151
7.134
7.130
6.986
6.981
6.965
5.382
4.853
3.318
3.314
3.310
3.306
3.302
3.159
3.149
3.133
3.129
3.119
3.111
3.100
3.095
3.080
3.070
2.462
2.343
2.330
NH3+ Cl-
MeS
Me
N
7e
1.03
4.28
1.15
2.04
2.00
4.20
2.94
3.13
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-64 - 1H NMR - 400.13 MHz - MeOD

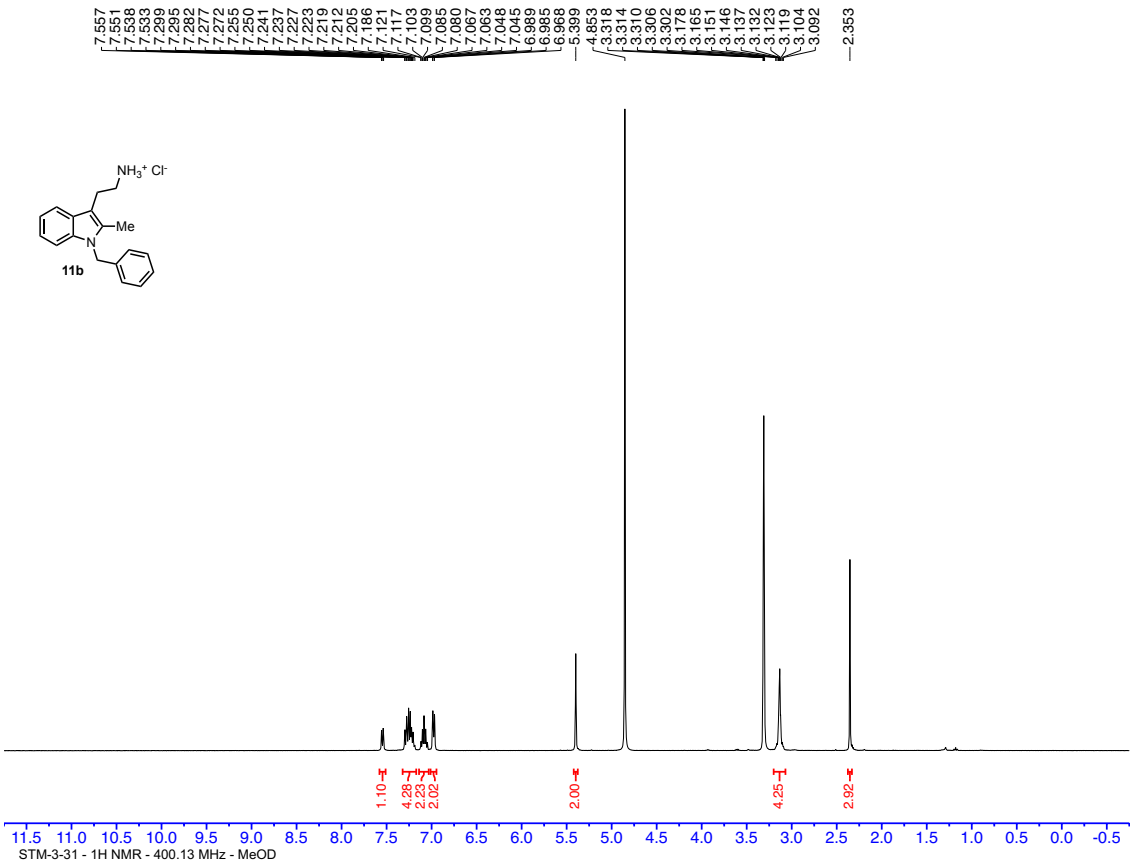

138.019
135.657
135.092
128.347
128.092
127.731
126.933
125.763
122.963
118.100
109.798
105.238
48.235
48.092
48.019
47.877
47.808
47.666
47.597
47.451
47.381
47.170
46.955
46.047
39.864
22.183
17.502
8.843
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-64 Concentrated CNMR - 13C NMR - 100.62 MHz - MeOD

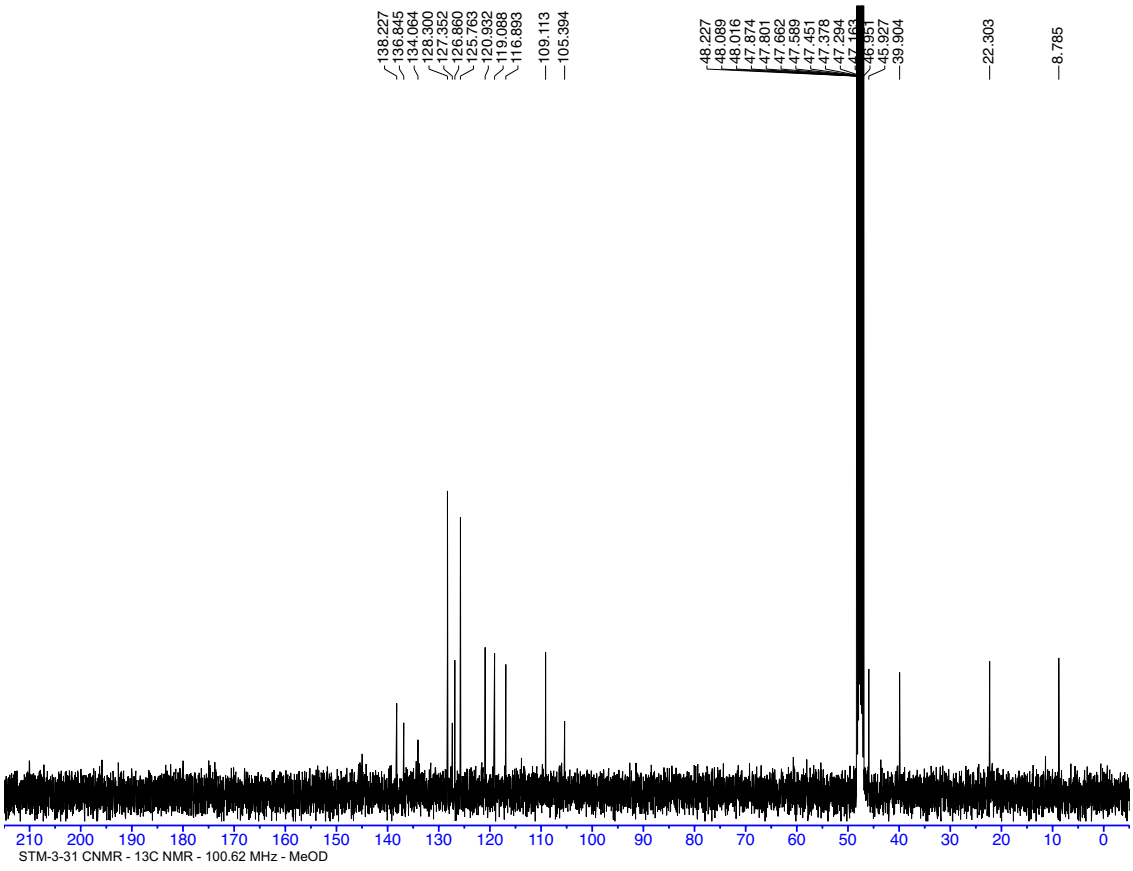

7.517
7.513
7.234
7.213
7.056
7.052
7.035
7.031
3.112
3.095
3.067
3.051
2.436
2.380
NH3+ Cl-
MeS
Me
N
H
7f
1.00
1.10
1.08
4.12
3.15
2.86
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-16 Ethanol Removal - 1H NMR - 400.13 MHz - MeOD

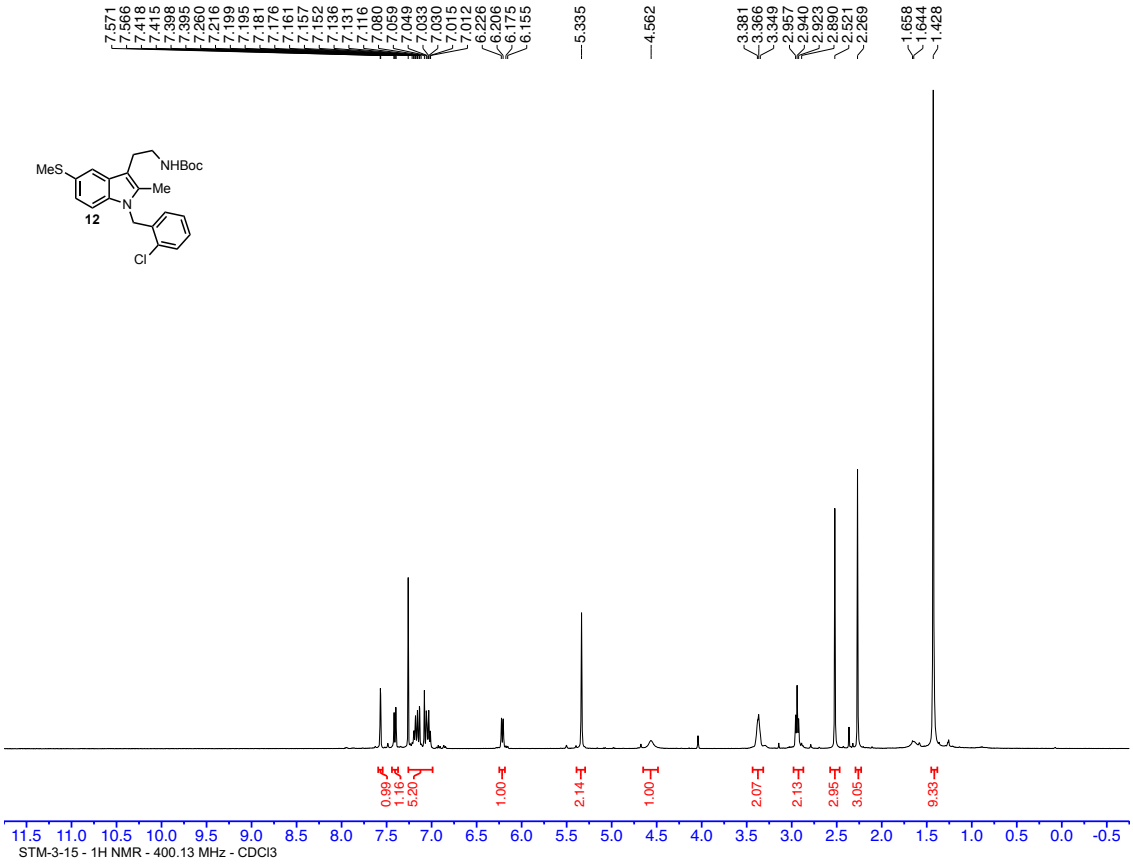

134.607
133.951
128.821
126.816
122.518
117.888
110.961
104.407
48.625
48.413
48.198
47.987
47.772
47.560
47.349
47.134
39.926
21.975
21.928
17.746
10.170
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-16 CNMR Ethanol Removal - 13C NMR - 100.62 MHz - MeOD

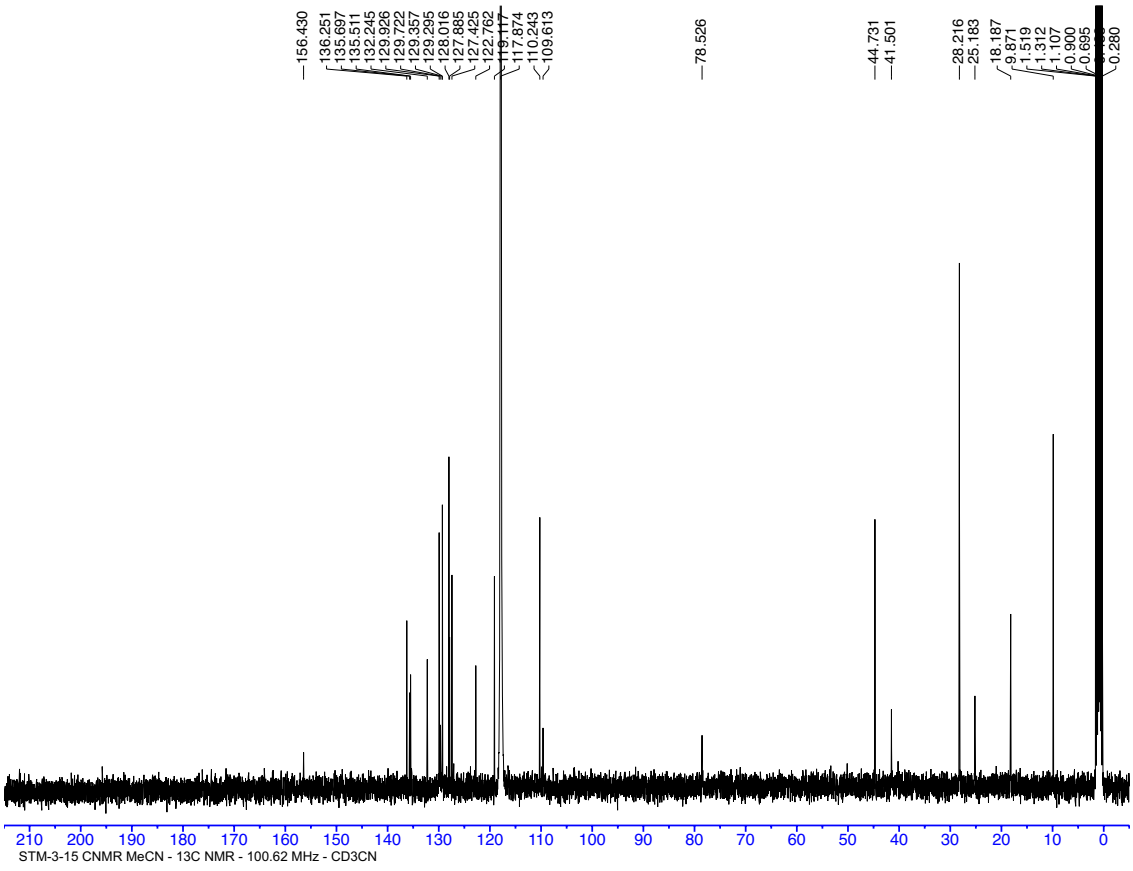

7.599
7.593
7.584
7.576
7.566
7.465
7.446
7.245
7.225
7.206
7.187
7.178
7.169
7.163
7.156
7.116
7.104
7.098
7.088
7.081
7.075
7.057
7.038
6.236
6.217
5.453
4.856
3.319
3.315
3.311
3.306
3.302
3.165
2.324
NH3+ Cl-
Me
N
11a
Cl
1.00
0.98
2.07
0.45
2.63
0.97
2.00
3.40
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-26 - 1H NMR - 400.13 MHz - MeOD

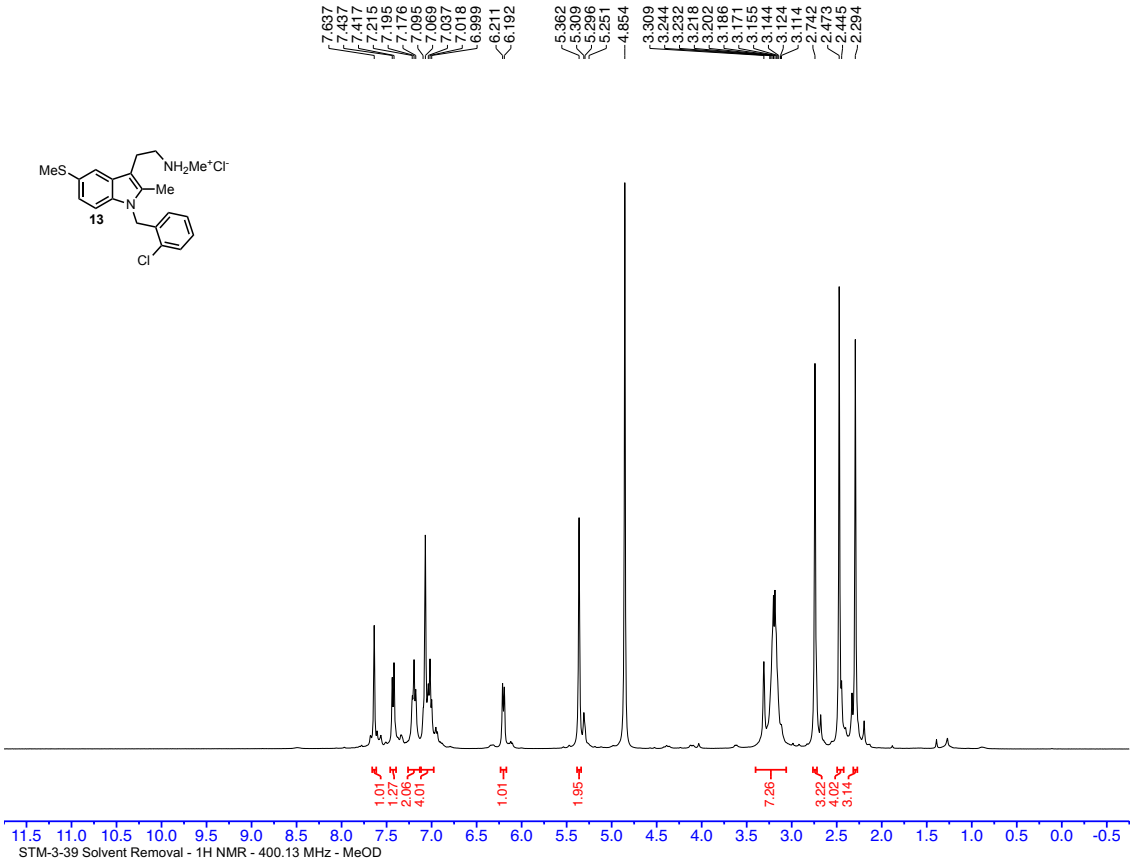

140.651
139.241
137.950
135.577
133.079
132.343
131.399
130.914
130.528
125.139
123.324
121.071
112.817
109.839
52.179
51.968
51.753
51.330
51.115
50.903
47.724
43.827
26.240
12.504
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-26 CNMR - 13C NMR - 100.62 MHz - CDCl3

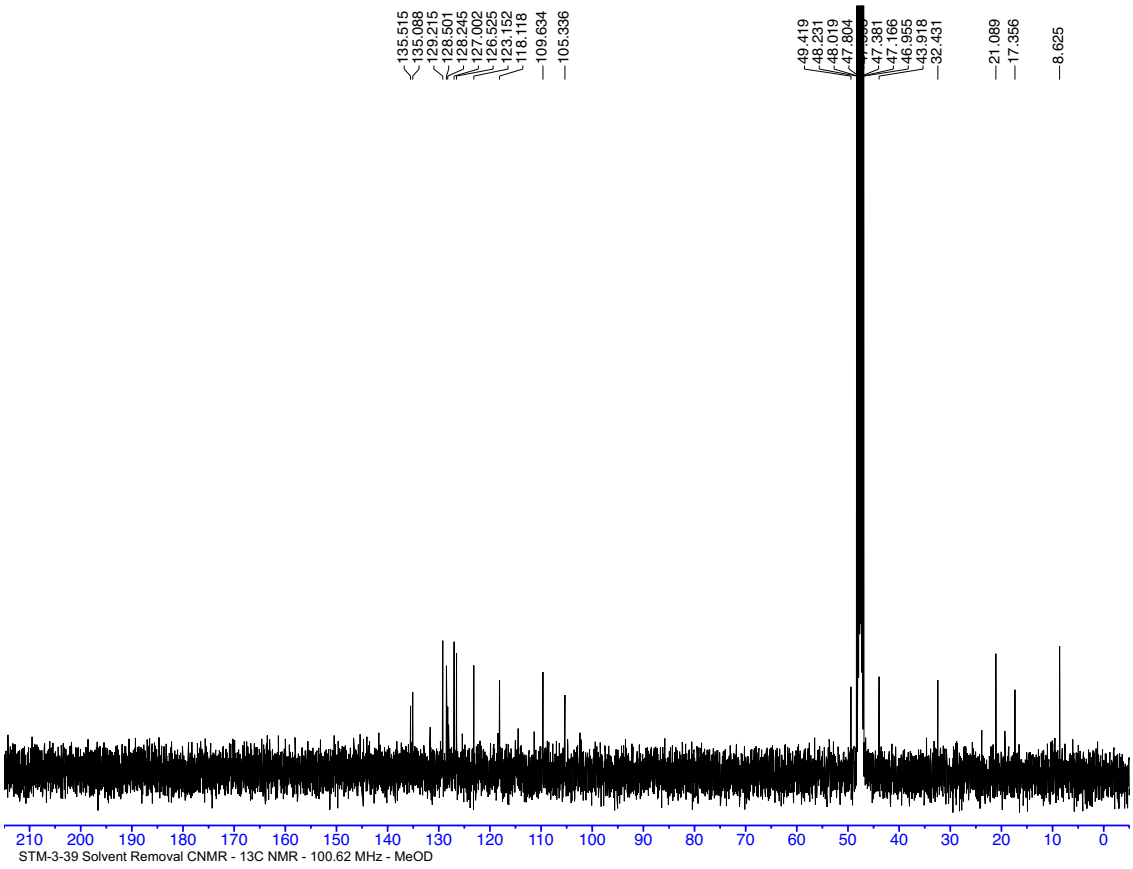

7.557
7.551
7.538
7.533
7.299
7.295
7.282
7.277
7.272
7.255
7.250
7.241
7.237
7.227
7.223
7.219
7.212
7.205
7.186
7.121
7.117
7.103
7.099
7.085
7.080
7.067
7.063
7.048
7.045
6.989
6.985
6.968
5.399
4.853
3.318
3.314
3.310
3.306
3.302
3.178
3.165
3.151
3.146
3.137
3.132
3.123
3.119
3.104
3.092
2.353
NH3+ Cl-
Me
N
11b
1.10
4.28
2.23
2.02
2.00
4.25
2.92
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-31 - 1H NMR - 400.13 MHz - MeOD

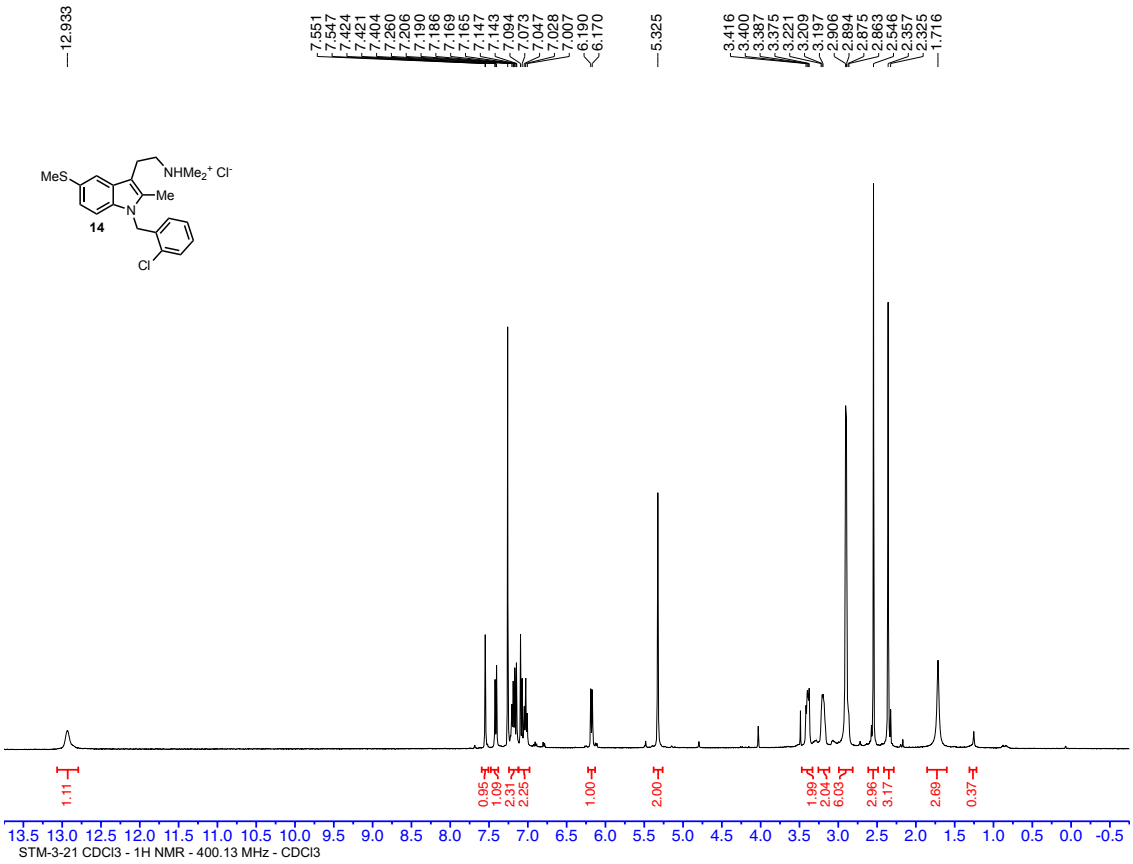

138.227
136.845
134.064
128.300
127.352
126.860
125.763
120.932
119.088
116.893
109.113
105.394
48.227
48.089
48.016
47.874
47.801
47.662
47.589
47.451
47.378
47.294
47.163
46.951
45.927
39.904
22.303
8.785
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-31 CNMR - 13C NMR - 100.62 MHz - MeOD

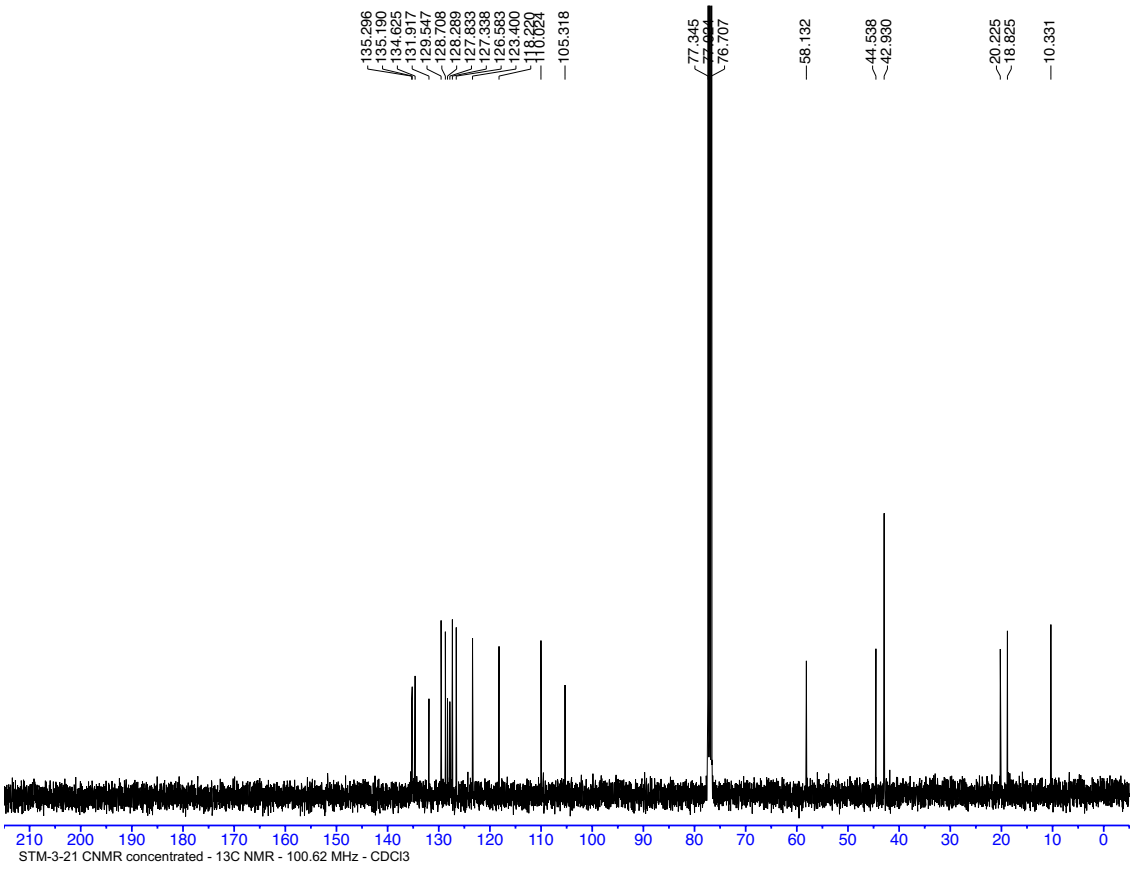

7.571
7.566
7.418
7.415
7.398
7.395
7.260
7.216
7.199
7.195
7.181
7.176
7.161
7.157
7.152
7.136
7.131
7.116
7.080
7.059
7.049
7.033
7.030
7.015
7.012
6.226
6.206
6.175
6.155
5.335
4.562
3.381
3.366
3.349
2.957
2.940
2.923
2.890
2.521
2.269
1.658
1.644
1.428
MeS
NHBoc
Me
N
12
Cl
0.99
1.16
5.20
1.00
2.14
1.00
2.07
2.13
2.95
3.05
9.33
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-15 - 1H NMR - 400.13 MHz - CDCl3


156.430
136.251
135.697
135.511
132.245
129.926
129.722
129.357
129.295
128.016
127.885
127.425
122.762
119.117
117.874
110.243
109.613
78.526
44.731
41.501
28.216
25.183
18.187
9.871
1.519
1.312
1.107
0.900
0.695
0.280
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-15 CNMR MeCN - 13C NMR - 100.62 MHz - CD3CN


7.637
7.437
7.417
7.215
7.195
7.176
7.095
7.069
7.037
7.018
6.999
6.211
6.192
5.362
5.309
5.296
5.251
4.854
3.309
3.244
3.232
3.218
3.202
3.186
3.171
3.155
3.144
3.124
3.114
2.742
2.473
2.445
2.294
MeS
NH2Me+Cl-
Me
N
13
Cl
1.01
1.27
2.06
4.01
1.01
1.95
7.26
3.22
4.02
3.14
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-39 Solvent Removal - 1H NMR - 400.13 MHz - MeOD


135.515
135.088
129.215
128.501
128.245
127.002
126.525
123.152
118.118
109.634
105.336
49.419
48.231
48.019
47.804
47.381
47.166
46.955
43.918
32.431
21.089
17.356
8.625
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-39 Solvent Removal CNMR - 13C NMR - 100.62 MHz - MeOD


12.933
7.551
7.547
7.424
7.421
7.404
7.260
7.206
7.190
7.186
7.169
7.165
7.147
7.143
7.094
7.073
7.047
7.028
7.007
6.190
6.170
5.325
3.416
3.400
3.387
3.375
3.221
3.209
3.197
2.906
2.894
2.875
2.863
2.546
2.357
2.325
1.716
MeS
NHMe2+ Cl-
Me
N
14
Cl
1.11
0.95
1.09
2.31
2.25
1.00
2.00
1.99
2.04
6.03
2.96
3.17
2.69
0.37
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-21 CDCl3 - 1H NMR - 400.13 MHz - CDCl3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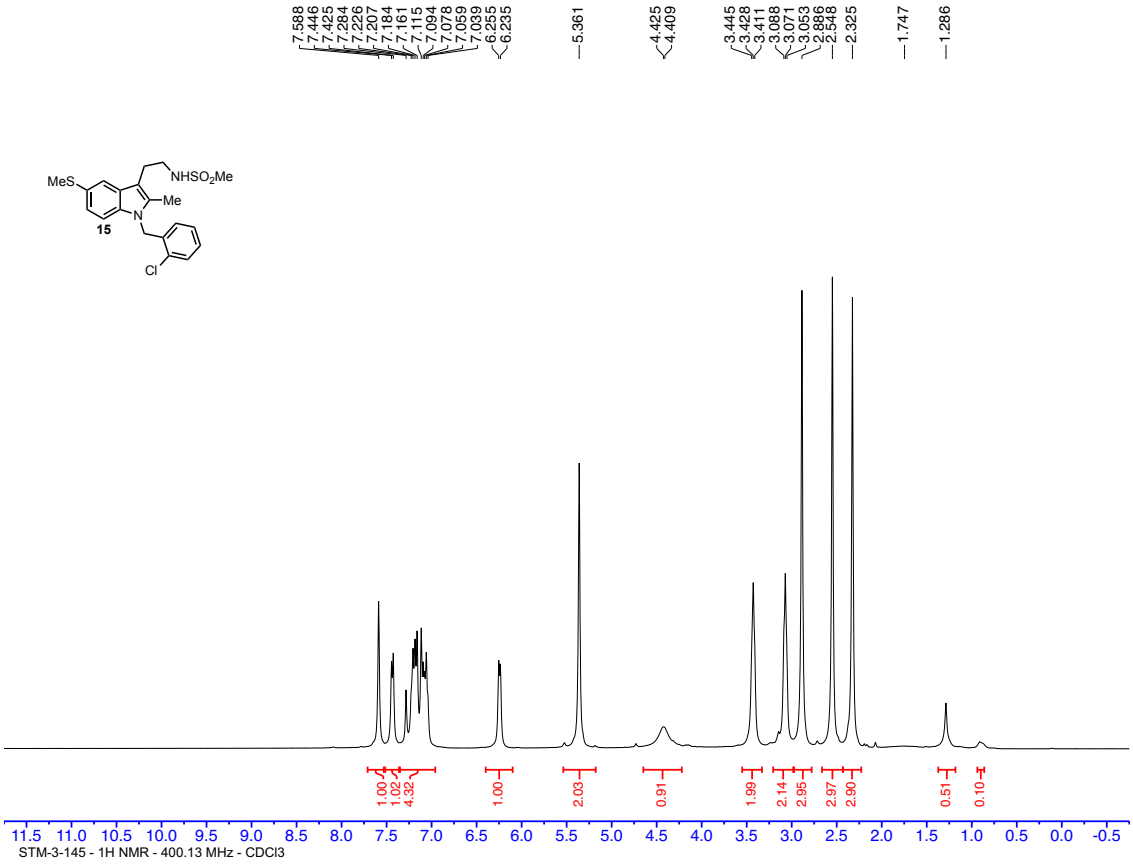
110.024
105.318
77.345
77.094
76.707
58.132
44.538
42.930
20.225
18.825
10.331
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-3-21 CNMR concentrated - 13C NMR - 100.62 MHz - CDCl3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7.094
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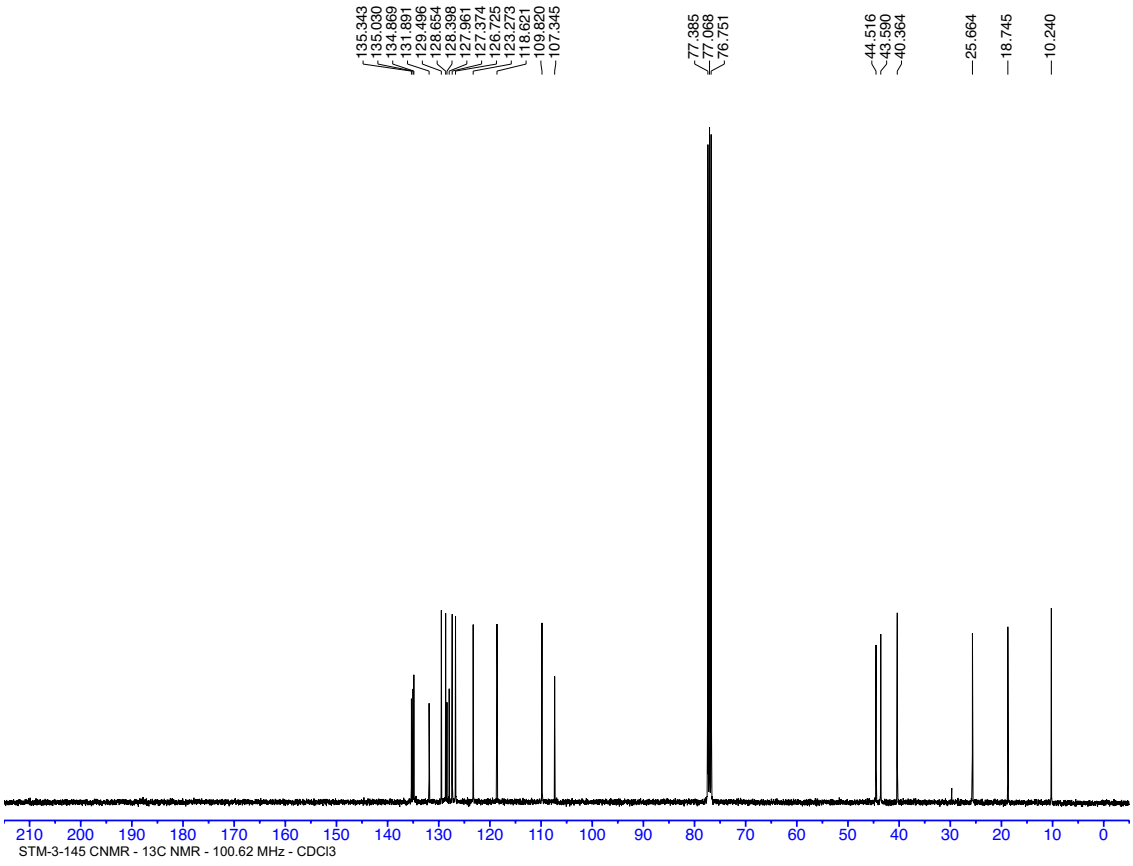
7.059
7.039
6.255
6.235
5.361
4.425
4.409
3.445
3.428
3.411
3.088
3.071
3.053
2.886
2.548
2.325
1.747
1.286
MeS
NHSO2Me
Me
N
15
Cl
1.00
1.02
4.32
1.00
2.03
0.91
1.99
2.14
2.95
2.97
2.90
0.51
0.10
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-3-145 - 1H NMR - 400.13 MHz - CDCl3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109.820
107.345
77.385
77.068
76.751
44.516
43.590
40.364
25.664
18.745
10.240
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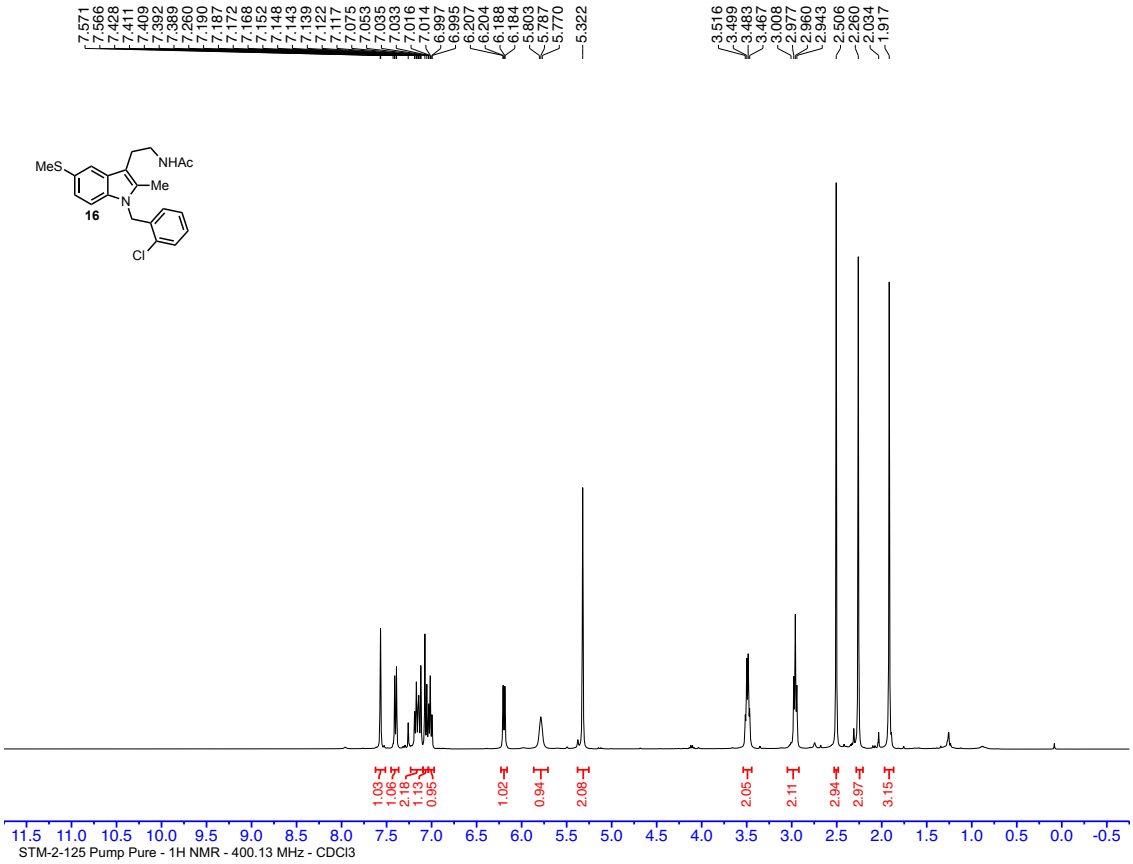
STM-3-145 CNMR - 13C NMR - 100.62 MHz - CDCl3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7.152
7.148
7.143
7.139
7.122
7.117
7.075
7.053
7.035
7.033
7.016
7.014
6.997
6.995
6.207
6.204
6.188
6.184
5.803
5.787
5.770
5.322
3.516
3.499
3.483
3.467
3.008
2.977
2.960
2.943
2.506
2.260
2.034
1.917
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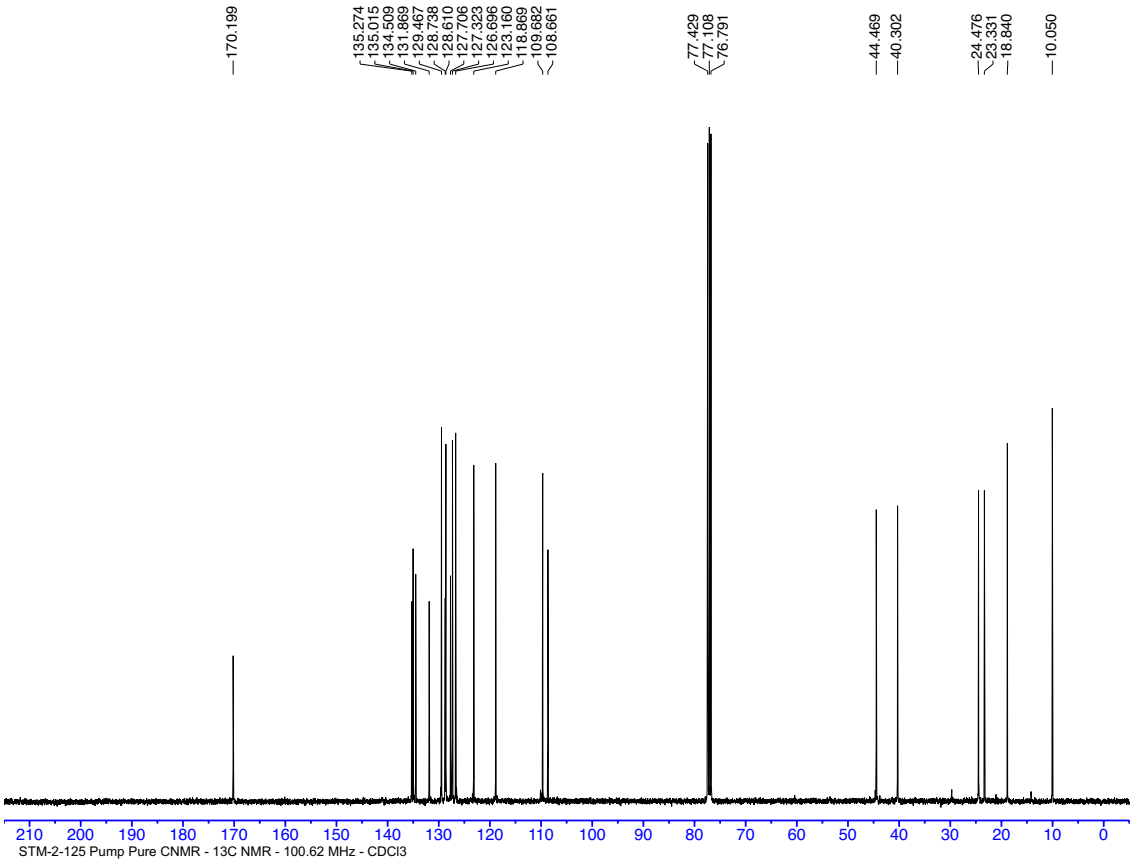
NHAc
Me
N
16
Cl
1.03
1.06
2.18
1.13
0.95
1.02
0.94
2.08
2.05
2.11
2.94
2.97
3.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
STM-2-125 Pump Pure - 1H NMR - 400.13 MHz - CDCl3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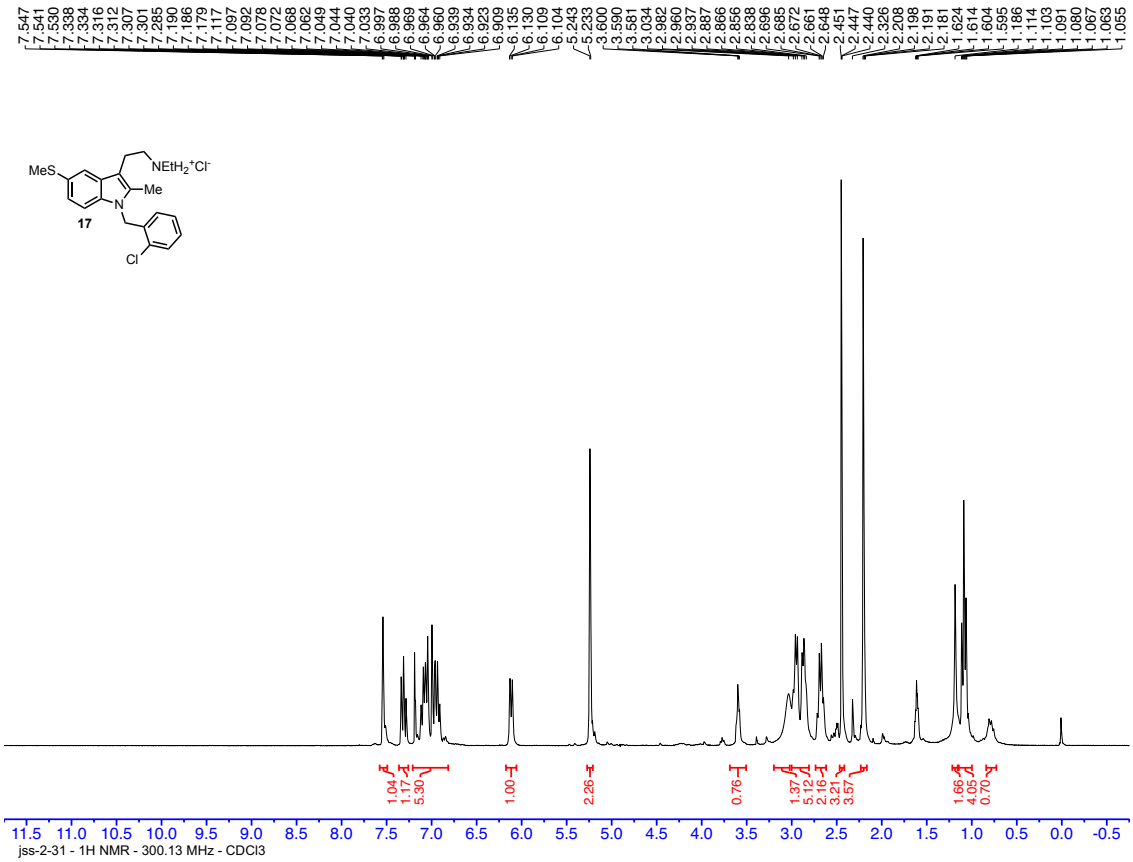
135.015
134.509
131.869
129.467
128.738
128.610
127.706
127.323
126.696
123.160
118.869
109.682
108.661
77.429
77.108
76.791
44.469
40.302
24.476
23.331
18.840
10.050
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
STM-2-125 Pump Pure CNMR - 13C NMR - 100.62 MHz - CDCl3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Me
N
17
Cl
jss-2-31 - 1H NMR - 300.13 MHz - CDCl3

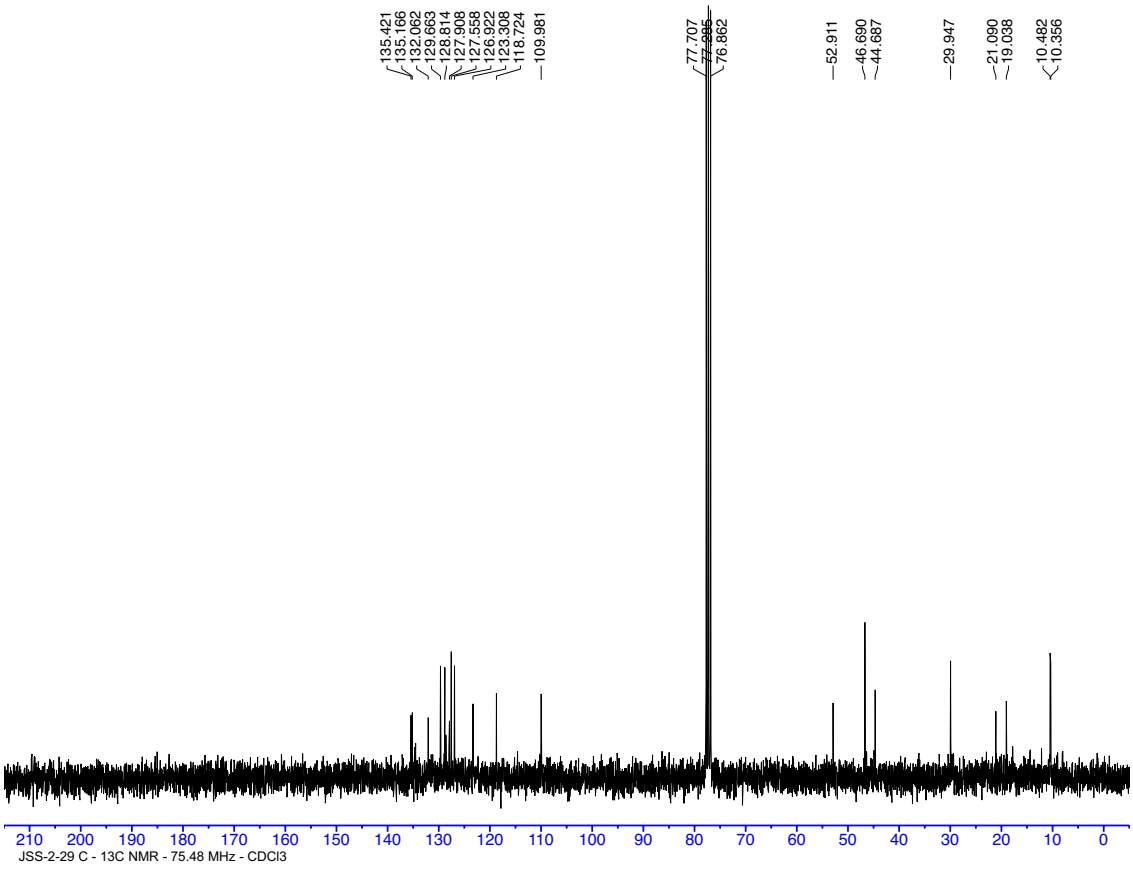
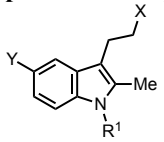

JSS-2-29 C - 13C NMR - 75.48 MHz - CDCl3

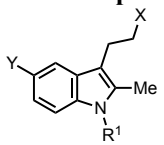
Table S1. Predicted Physiochemical Properties and Lipophilicity for the Tested Tryptamines[a]



Entry	Cmpd	R^1	X	Y	MW	CLogP[b]	TPSA	Molar Refractivity	Number of Rotatable Bonds	H Bond Acceptors	H Bond Donors
1	**1**	2-chlorobenzyl	$NH_3^+ Cl^-$	SMe	344.9	4.11	56.25	101.86	5	1	1
2	**7b**	4-chlorobenzyl	$NH_3^+ Cl^-$	SMe	344.9	4.11	56.25	101.86	5	1	1
3	**7c**	4-bromobenzyl	$NH_3^+ Cl^-$	SMe	389.35	4.23	56.25	104.55	5	1	1
4	**7d**	2,4-dichlorobenzyl	$NH_3^+ Cl^-$	SMe	379.35	4.60	56.25	106.87	5	1	1
5	**7e**	benzyl	$NH_3^+ Cl^-$	SMe	310.46	2.10	56.25	96.85	5	1	1
6	**7f**	H	$NH_3^+ Cl^-$	SMe	220.33	3.62	67.11	67.47	3	1	2
7	**11a**	benzyl	$NH_3^+ Cl^-$	H	264.36	3.12	30.95	85.13	4	1	1
8	**11b**	2-chlorobenzyl	$NH_3^+ Cl^-$	H	298.81	3.62	30.95	90.14	4	1	1
9	**13**	2-chlorobenzyl	$MeNH_2^+ Cl^-$	SMe	358.93	4.34	42.26	106.77	6	1	1
10	**14**	2-chlorobenzyl	$Me_2NH^+ Cl^-$	SMe	372.95	4.56	33.47	111.67	6	1	0
11	**15**	2-chlorobenzyl	$NHSO_2Me$	SMe	422.99	3.27	84.78	115.73	7	3	1
12	**16**	2-chlorobenzyl	NHAc	SMe	386.94	4.01	59.33	111.77	7	1	1
13	**17**	2-chlorobenzyl	$EtNH_2^+ Cl^-$	SMe	372.95	4.56	42.26	111.57	7	1	1

[a]Calculated using SwissADME.[1] [b]CLogP calculated for the free amine using the MLOGP method[2, 3] with SwissADME.[1]

Table S2. Predicted Pharmacokinetic Properties for the Tested Tryptamines[a]



Entry	Cmpd	R^1	X	Y	ESOL Log S	ESOL Solubility class	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	log Kp (cm/s)
1	**1**	2-chlorobenzyl	$NH_3^+ Cl^-$	SMe	-4.93	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	-5.24
2	**7b**	4-chlorobenzyl	$NH_3^+ Cl^-$	SMe	-4.93	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	-5.24
3	**7c**	4-bromobenzyl	$NH_3^+ Cl^-$	SMe	-5.25	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	-5.47
4	**7d**	2,4-dichlorobenzyl	$NH_3^+ Cl^-$	SMe	-5.52	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	-5.01
5	**7e**	benzyl	$NH_3^+ Cl^-$	SMe	-4.35	Moderately soluble	High	Yes	Yes	Yes	Yes	No	-5.47
6	**7f**	H	$NH_3^+ Cl^-$	SMe	-2.89	Soluble	High	Yes	No	Yes	No	No	-6.03
7	**11a**	benzyl	$NH_3^+ Cl^-$	H	-3.86	Soluble	High	Yes	Yes	Yes	Yes	No	-5.56
8	**11b**	2-chlorobenzyl	$NH_3^+ Cl^-$	H	-4.44	Moderately soluble	High	Yes	Yes	Yes	Yes	No	-5.33
9	**13**	2-chlorobenzyl	$MeNH_2^+ Cl^-$	SMe	-5.26	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	-4.96
10	**14**	2-chlorobenzyl	$Me_2NH^+ Cl^-$	SMe	-5.62	Moderately soluble	High	Yes	No	Yes	Yes	Yes	-4.72
11	**15**	2-chlorobenzyl	$NHSO_2Me$	SMe	-5.25	Moderately soluble	High	No	No	Yes	Yes	Yes	-5.69
12	**16**	2-chlorobenzyl	NHAc	SMe	-5.17	Moderately soluble	High	Yes	No	Yes	Yes	Yes	-5.32
13	**17**	2-chlorobenzyl	$EtNH_2^+ Cl^-$	SMe	-5.49	Moderately soluble	High	Yes	Yes	Yes	Yes	No	-4.79

[a]Calculated using SwissADME.[1]

References

1. Daina, A.; Michielin, O.; Zoete, V.; Michielin, O.; Michielin, O. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* **2017,** *7*, 42717. doi:10.1038/srep42717
2. Moriguchi, I.; Hirono, S.; Nakagome, I.; Hirano, H. Comparison of reliability of log P values for drugs calculated by several methods. *Chem. Pharm. Bull.* **1994,** *42*, 976. doi:10.1248/cpb.42.976
3. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997,** *23*, 3-25. doi:10.1016/s0169-409x(00)00129-0