

ChemMedChem

Supporting Information

Further Exploration of the Benzimidazole Scaffold as TRPC5 Inhibitors: Identification of 1-Alkyl-2-(pyrrolidin-1-yl)-1*H*-benzo[*d*]imidazoles as Potent and Selective Inhibitors

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Table of Contents:

| | |
|--|---|
| Table 1. PDSP Selectivity | 2 |
| ^1H and ^{13}C Spectra | 4 |

Supplemental Table 1. PDSP Selectivity of select compounds (Compounds tested at 10 μ M)

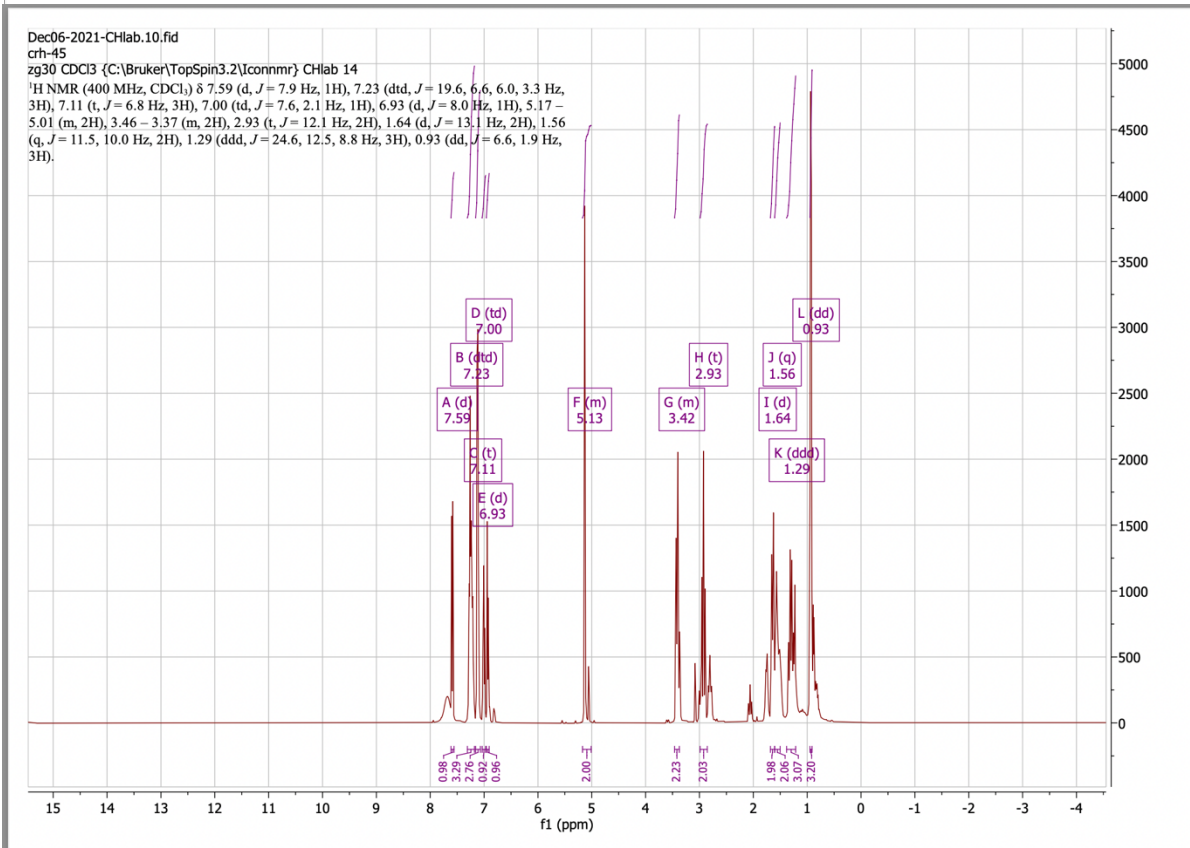
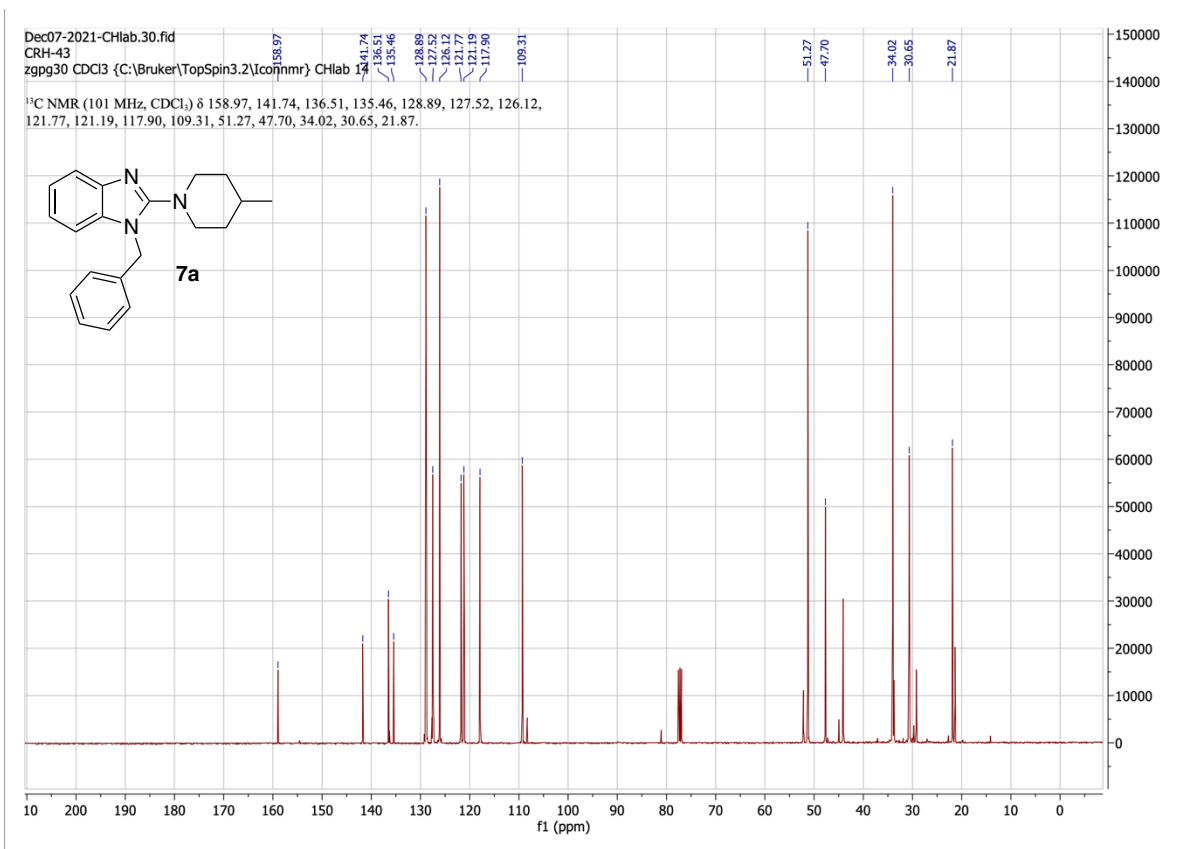
| 16f | | 9o | |
|-----------------|---------------|-----------------|---------------|
| Receptor | Mean % | Receptor | Mean % |
| 5-HT1A | 0.33 | 5-HT1A | -8.04 |
| 5-HT1B | -13.18 | 5-HT1B | -19.32 |
| 5-HT1D | -20.3 | 5-HT1D | -36.91 |
| 5-HT1E | 0.77 | 5-HT1E | -3.93 |
| 5-HT2A | 59.82 | 5-HT2A | 5.32 |
| 5-HT2B | 96.32 | | |
| Ki | 258.6 nM | 5-HT2B | 30.36 |
| 5-HT2C | 79.97 | 5-HT2C | 14.42 |
| 5-HT3 | -1.96 | 5-HT3 | -12.44 |
| 5-HT5A | 24.76 | 5-HT5A | -14.99 |
| 5-HT6 | 36.62 | 5-HT6 | 6.5 |
| 5-HT7A | 13.51 | 5-HT7A | -11.23 |
| Alpha1A | -2.69 | Alpha1A | -11.68 |
| Alpha1B | 16.13 | Alpha1B | -7.54 |
| Alpha1D | 10.22 | Alpha1D | -11.06 |
| Alpha2A | 90.23 | Alpha2A | 31.63 |
| Alpha2B | 82.96 | | |
| Ki | 676.7 nM | Alpha2B | 18.67 |
| Alpha2C | 84.82 | | |
| Ki | 434.3 nM | Alpha2C | 16.07 |
| Beta1 | 19.53 | Beta1 | -9.19 |
| Beta2 | -10.17 | Beta2 | 0 |

| | |
|------------|------------|
| BZP Rat | |
| Brain Site | 19.87 |
| D1 | 37.8 |
| D2 | 1.09 |
| D3 | 40.77 |
| D4 | 2.14 |
| D5 | 69.61 |
| Ki | 5,661.1 nM |
| DAT | 24.3 |
| DOR | -5.69 |
| GABAA | -5.57 |
| GABAA | -1.19 |
| H1 | 97.85 |
| Ki | 6.2 nM |
| H2 | 83.29 |
| H3 | -5.56 |
| H4 | -8.89 |
| KOR | 11.13 |
| M1 | -16.1 |
| M2 | 13.73 |
| M3 | -39.68 |
| M4 | -7.49 |
| M5 | 14.48 |
| MOR | 12.36 |
| NET | 21.91 |

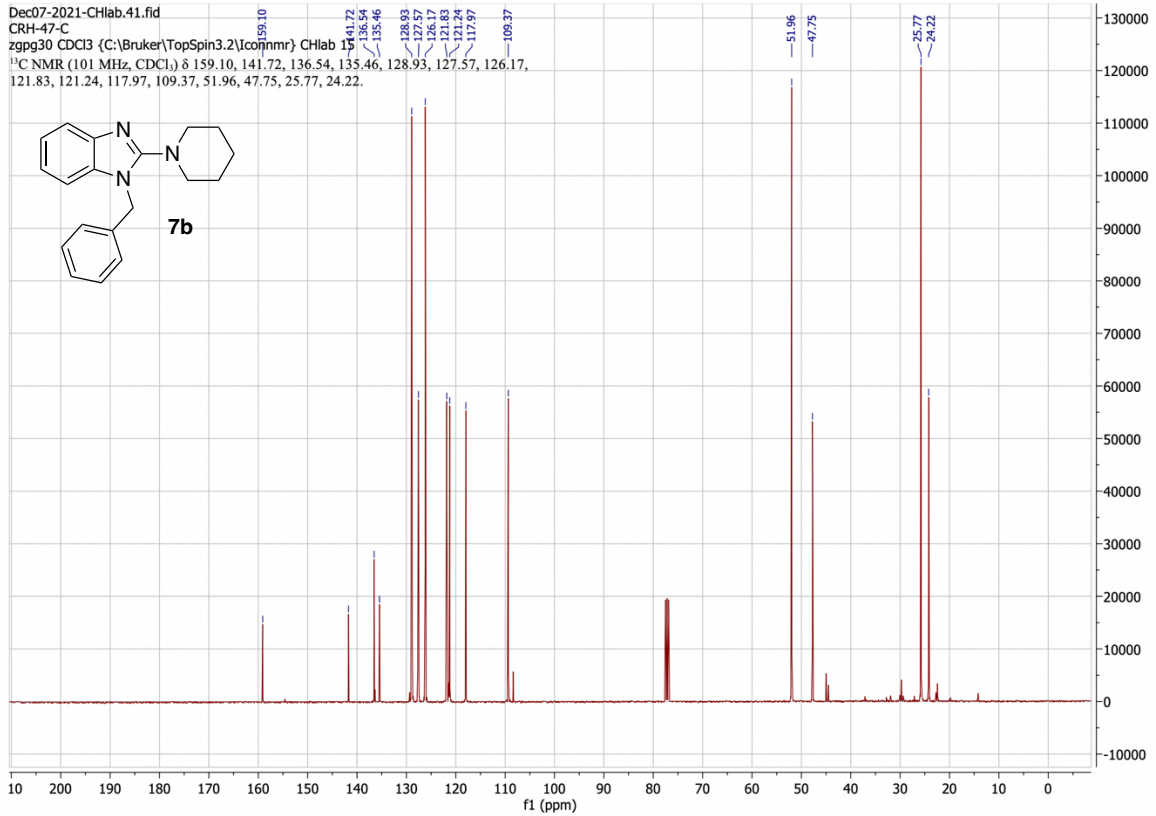
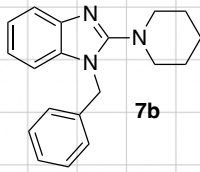
| | |
|------------|------------|
| BZP Rat | |
| Brain Site | 16.77 |
| D1 | 23.25 |
| D2 | -11.49 |
| D3 | 39.31 |
| D4 | -0.93 |
| D5 | 48.69 |
| DAT | 19.34 |
| DOR | -11.39 |
| GABAA | 13.14 |
| GABAA | 14.18 |
| H1 | 72.98 |
| Ki | 2,572.8 nM |
| H2 | 64.13 |
| H3 | 1.97 |
| H4 | -16.01 |
| KOR | -11.71 |
| M1 | -15.52 |
| M2 | 7.75 |
| M3 | -31.15 |
| M4 | -6.19 |
| M5 | 10.9 |
| MOR | -6.78 |
| NET | 39.4 |

| | | | |
|---------|--------|---------|---------|
| PBR | 49.22 | PBR | 76.69 |
| SERT | -8.27 | SERT | -16.85 |
| Sigma 1 | -18.76 | Sigma 1 | -19.5 |
| | | | 88.88 |
| Sigma 2 | 54 | Sigma 2 | 7,333.3 |
| | | Ki | nM |

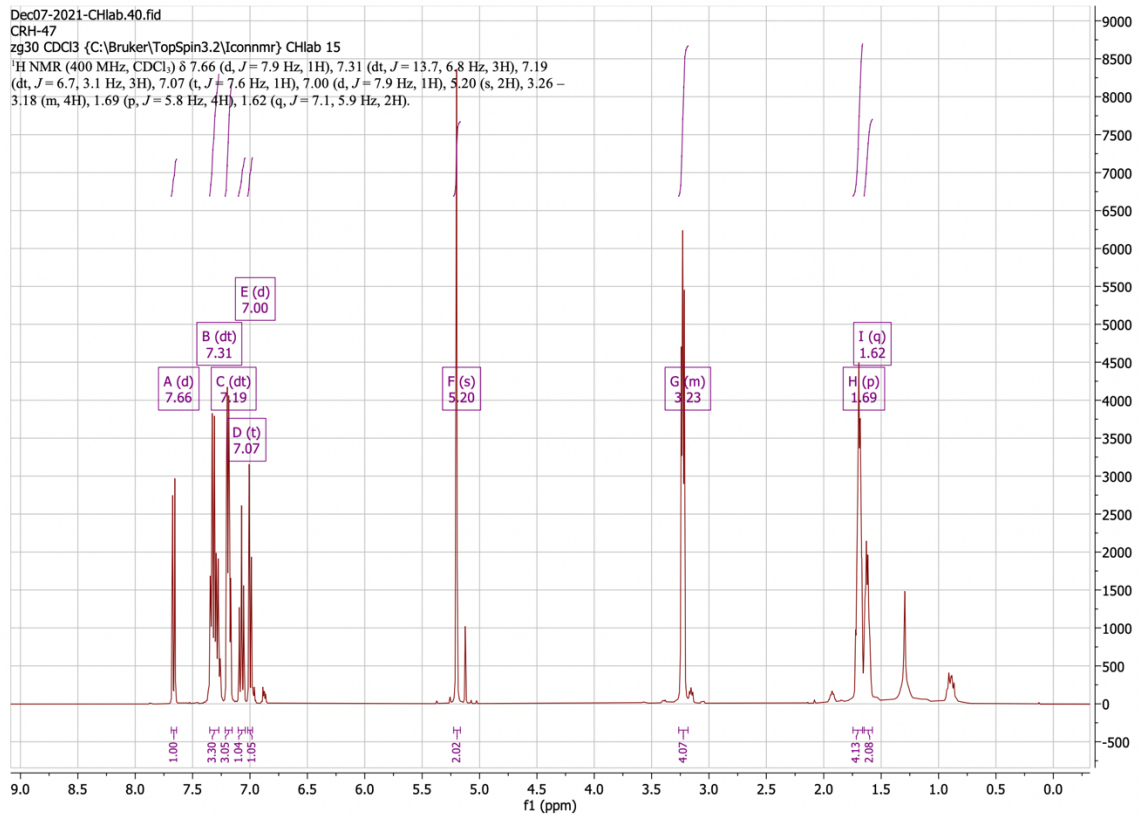
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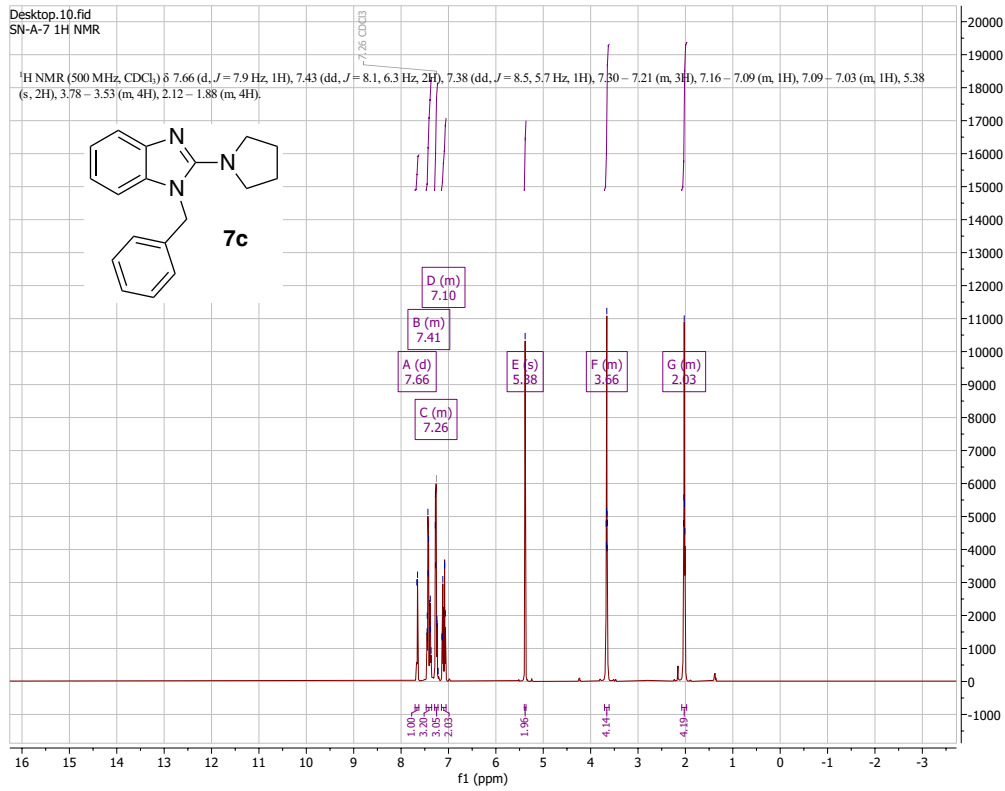
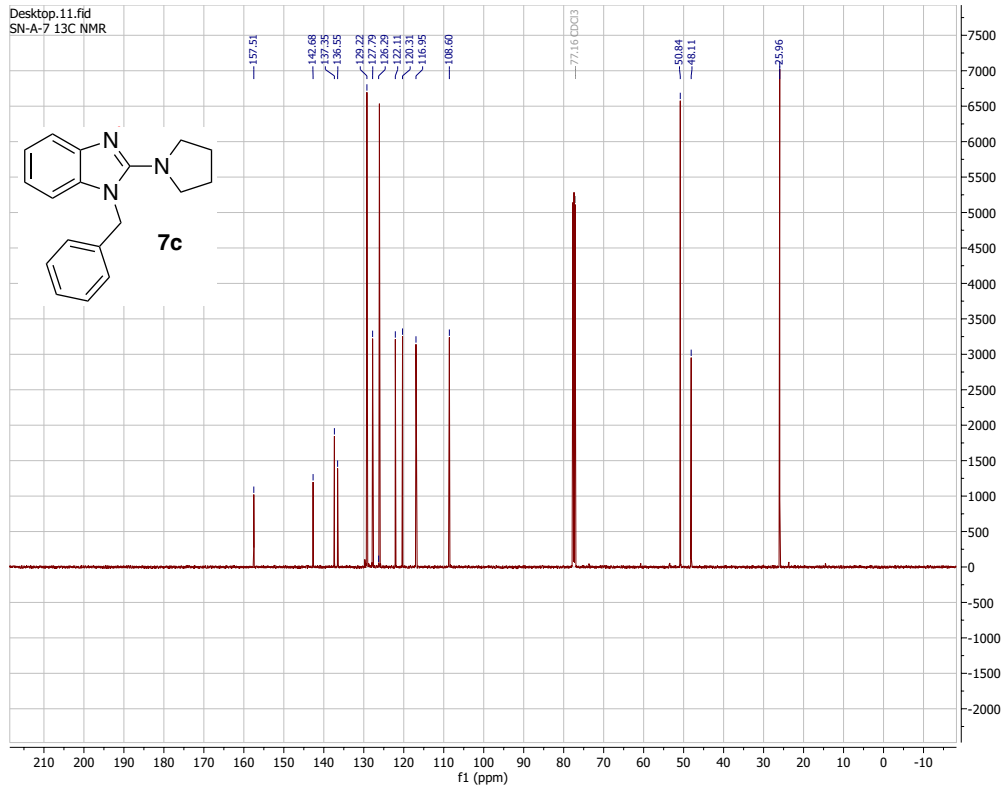


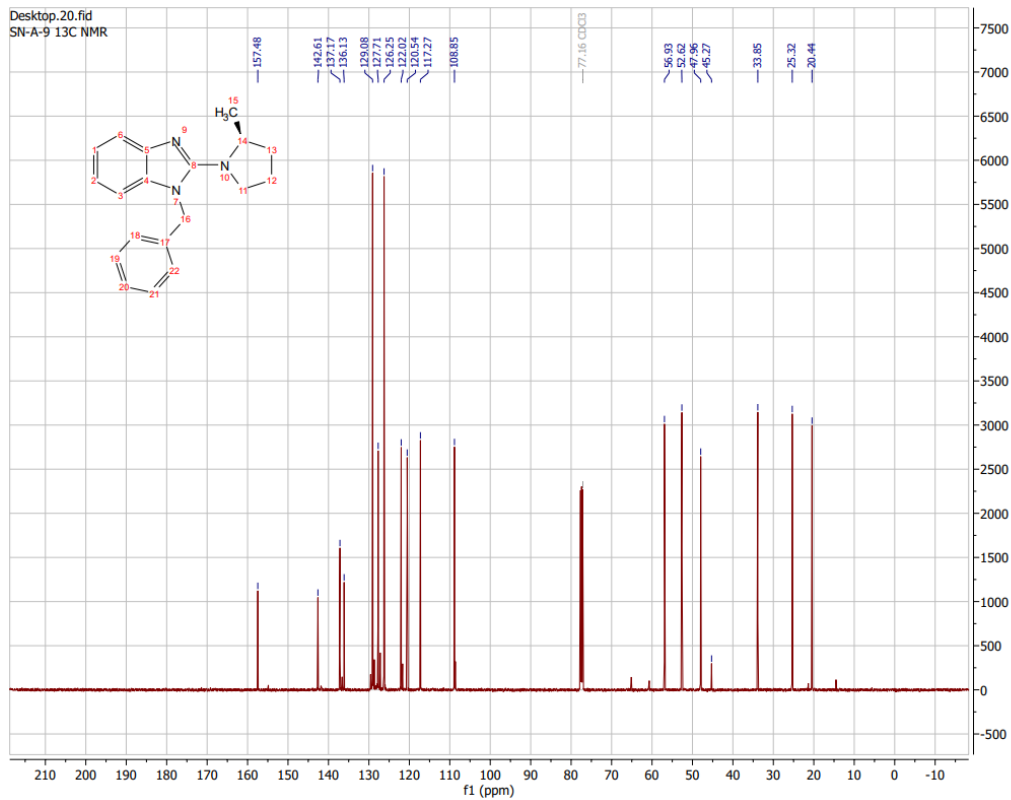
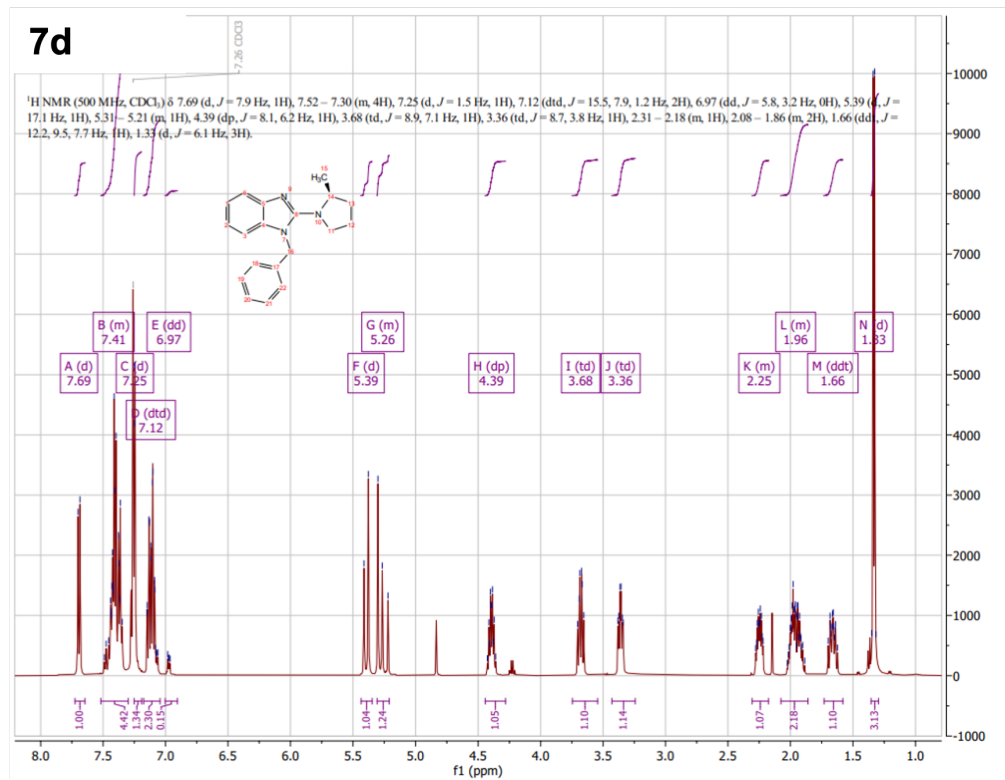
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 CRH-47-C
 zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 15
¹³C NMR (101 MHz, CDCl₃) δ 159.10, 141.72, 136.54, 135.46, 128.93, 127.57, 126.77, 126.83, 121.24, 117.97, 109.37, 51.96, 47.75, 25.77, 24.22.



Dec07-2021-CHlab.40.fid
 CRH-47
 zg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 15
¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 13.7, 6.8 Hz, 3H), 7.19 (dt, *J* = 6.7, 3.1 Hz, 3H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 5.20 (s, 2H), 3.26 – 3.18 (m, 4H), 1.69 (p, *J* = 5.8 Hz, 4H), 1.62 (q, *J* = 7.1, 5.9 Hz, 2H).

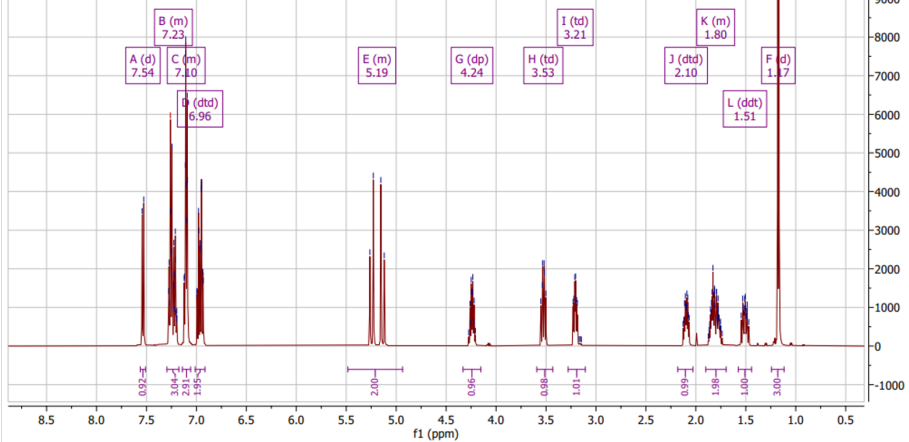
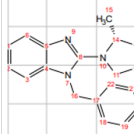




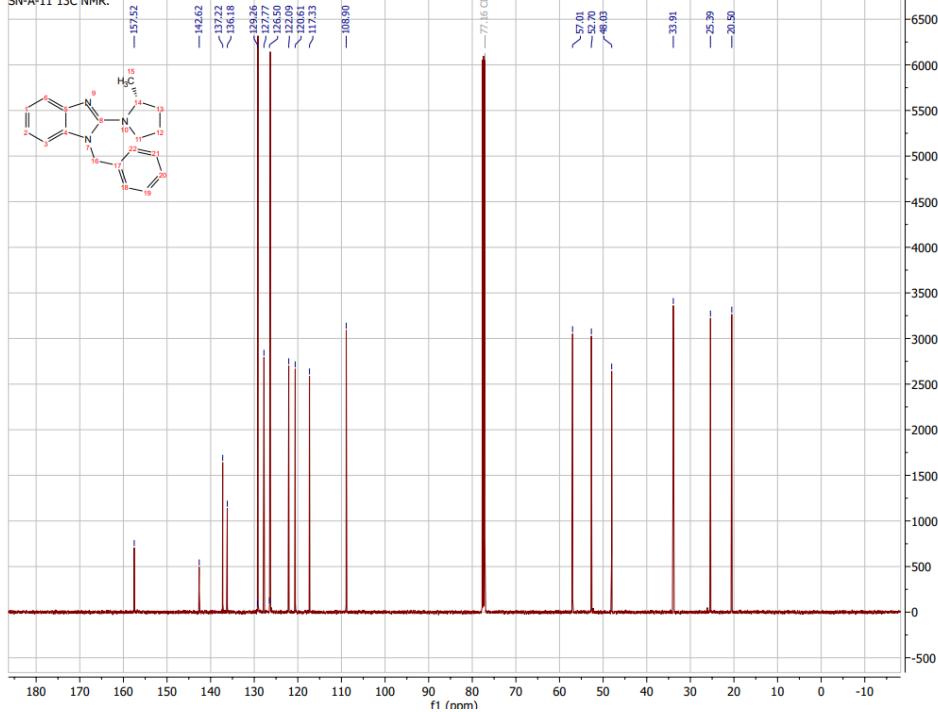


7e

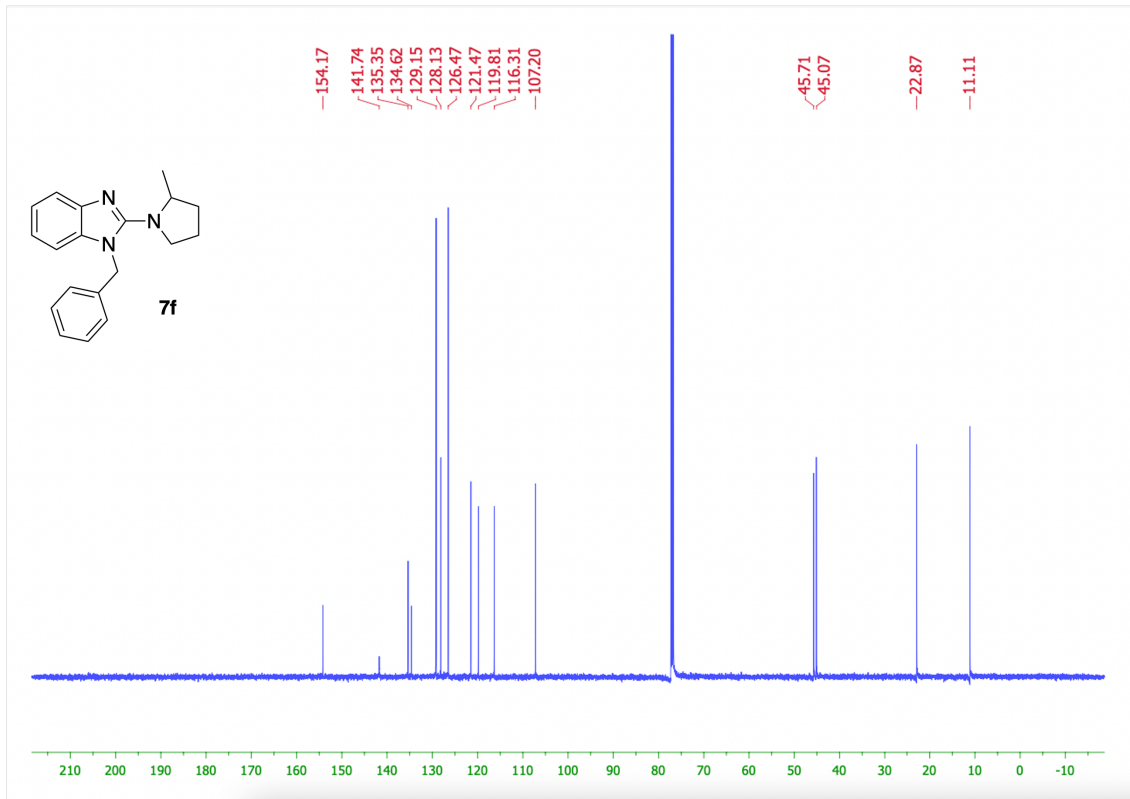
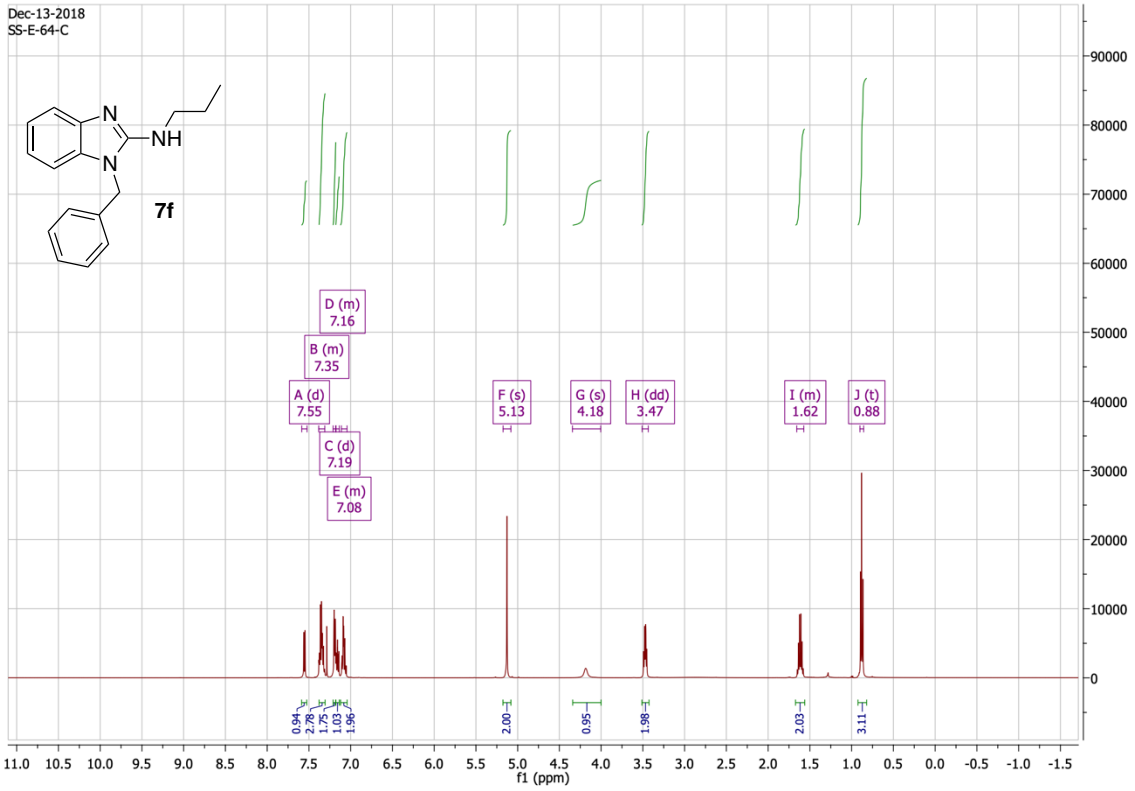
¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.29–7.18 (m, 3H), 7.14–7.06 (m, 3H), 6.96 (dtd, *J* = 15.1, 7.9, 1.3 Hz, 2H), 5.48–4.94 (m, 2H), 4.24 (dp, *J* = 8.5, 6.2 Hz, 1H), 3.53 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.21 (dd, *J* = 8.7, 3.8 Hz, 1H), 2.10 (dtd, *J* = 11.0, 6.8, 3.9 Hz, 1H), 1.90–1.70 (m, 2H), 1.51 (dtd, *J* = 12.3, 9.5, 7.7 Hz, 1H), 1.17 (d, *J* = 6.1 Hz, 3H).



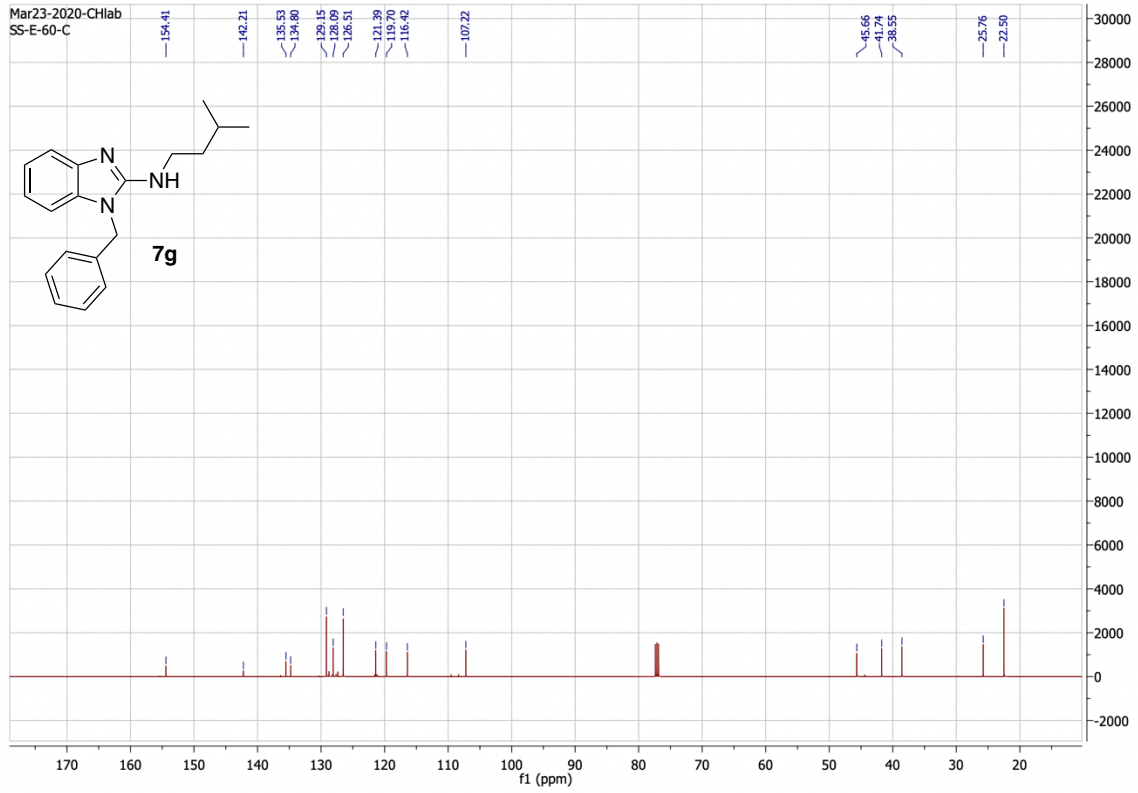
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SN-A-11 13C NMR.



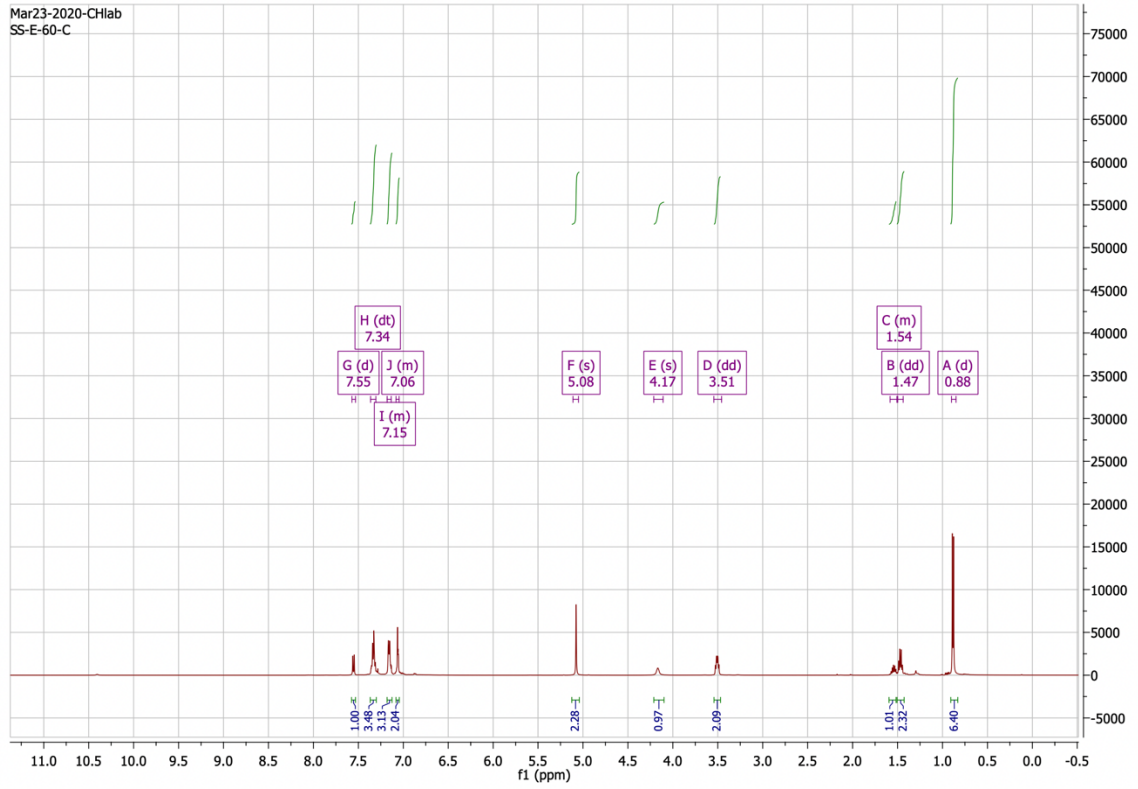
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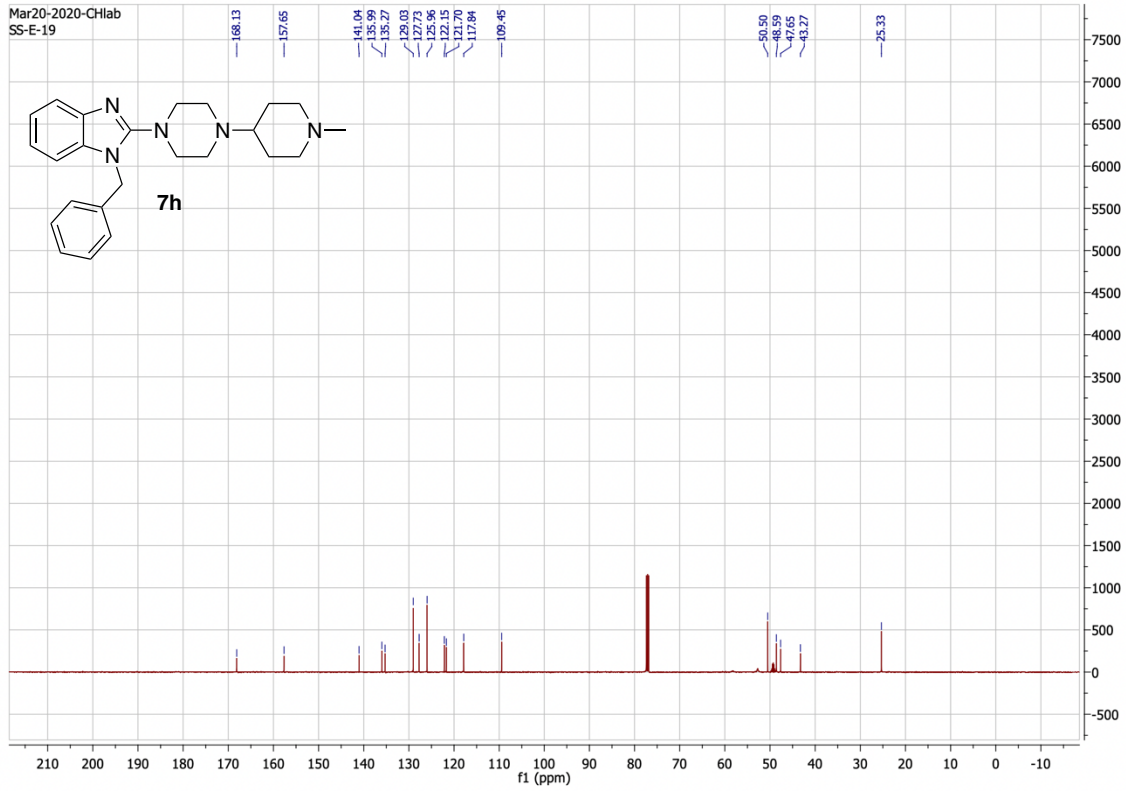
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SS-E-60-C



Mar23-2020-CHlab
SS-E-60-C

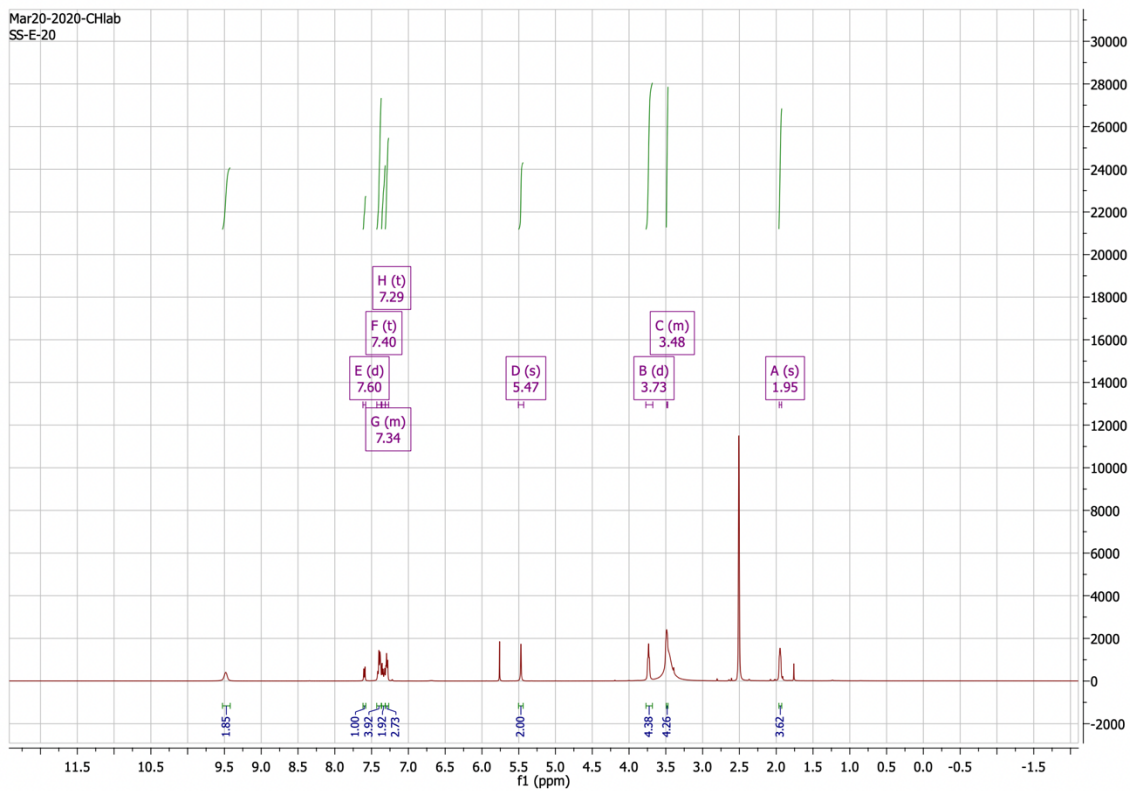
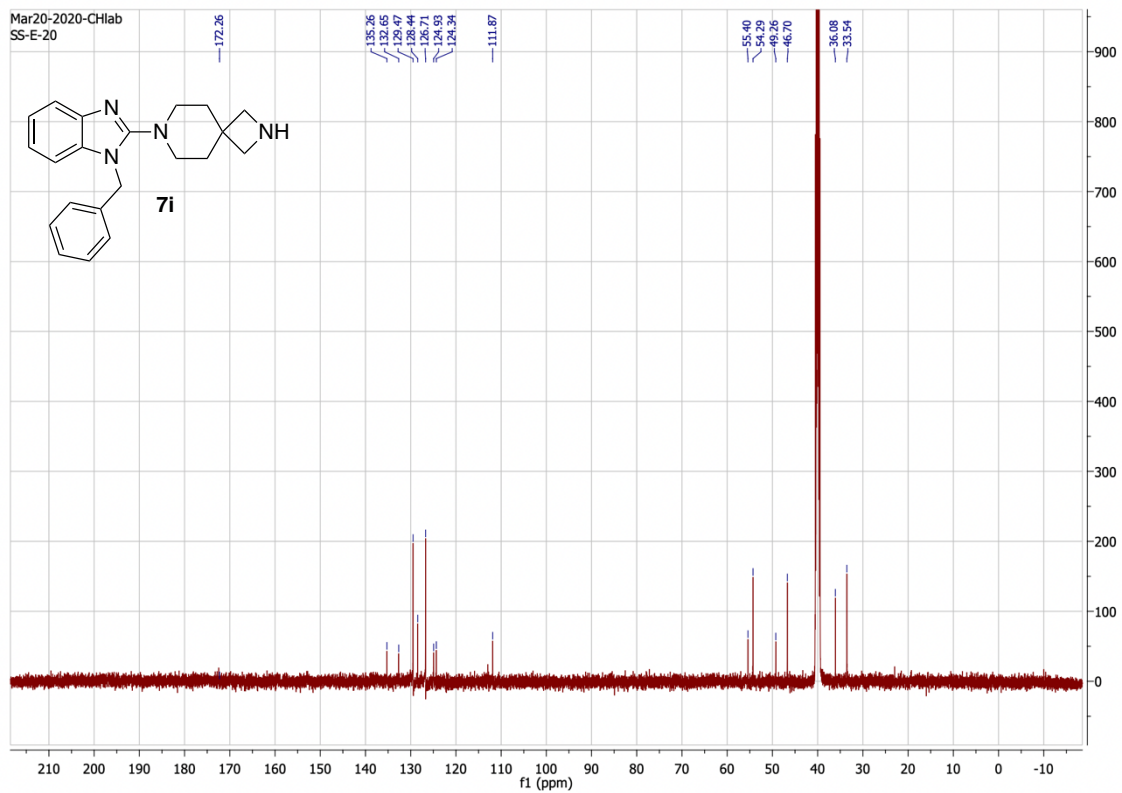


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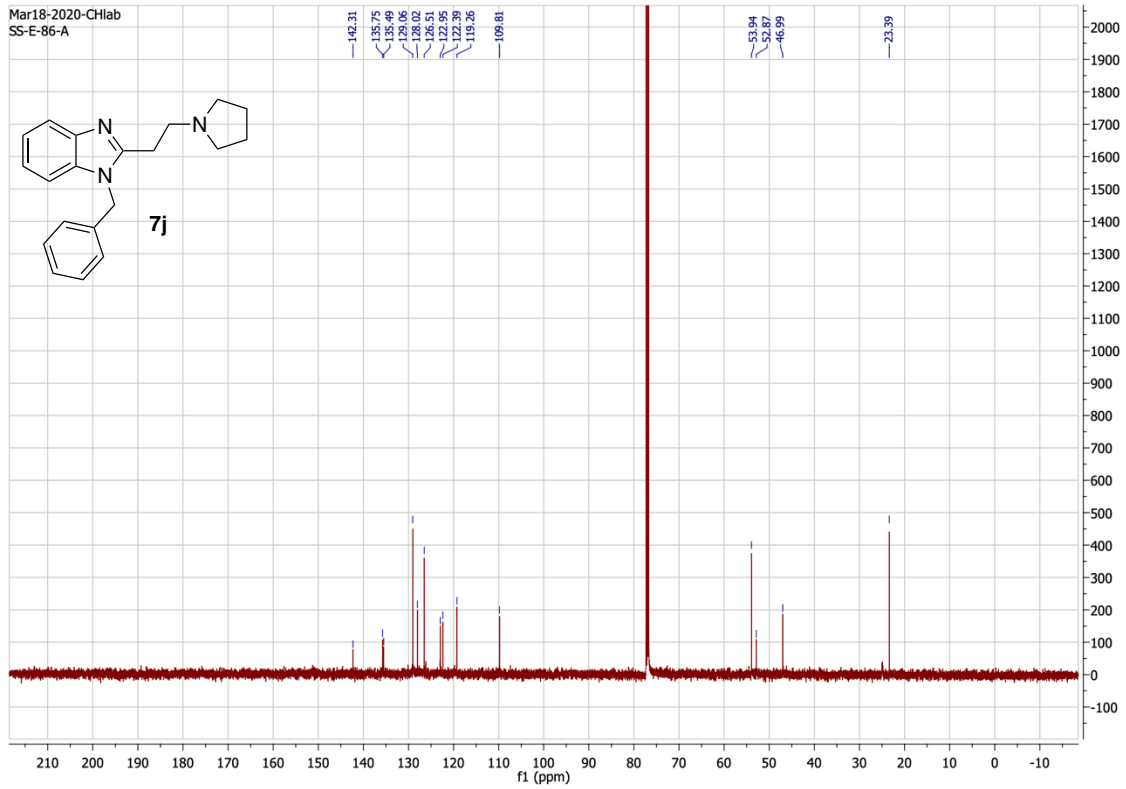
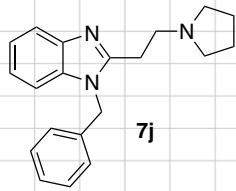


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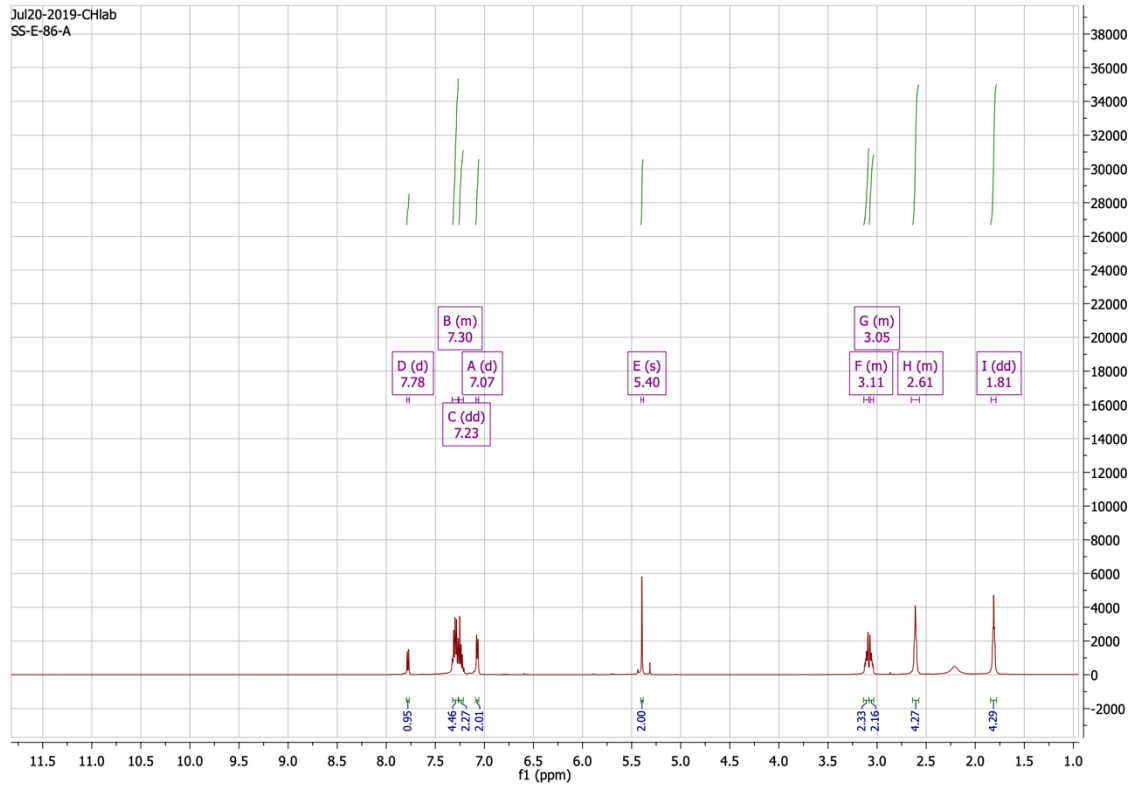


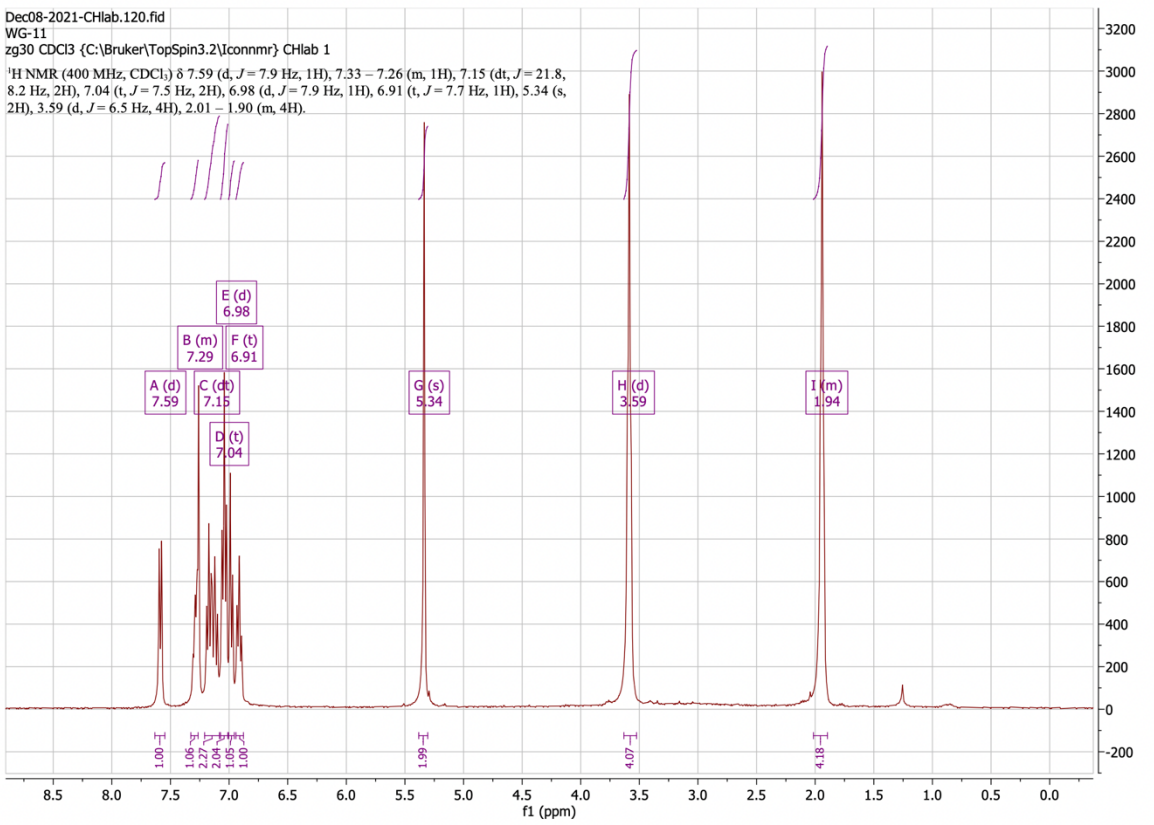
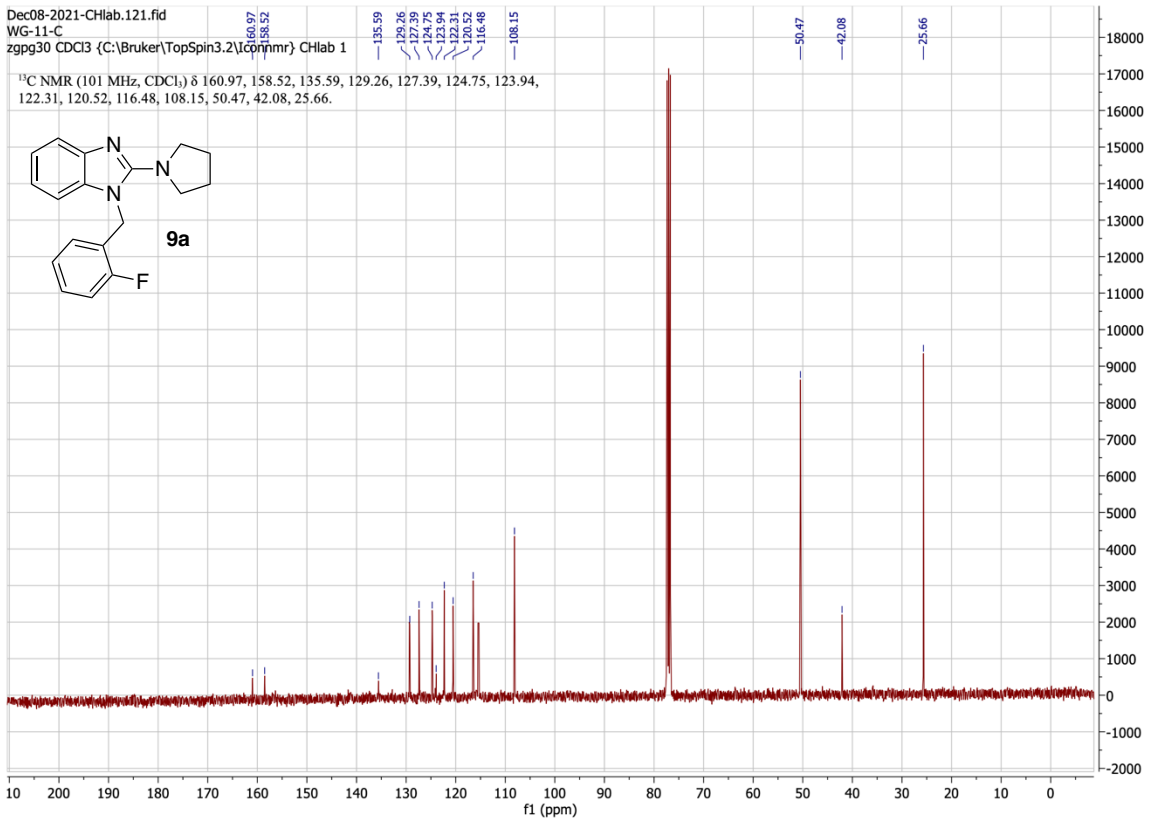


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SS-E-86-A



Jul20-2019-CHlab
SS-E-86-A



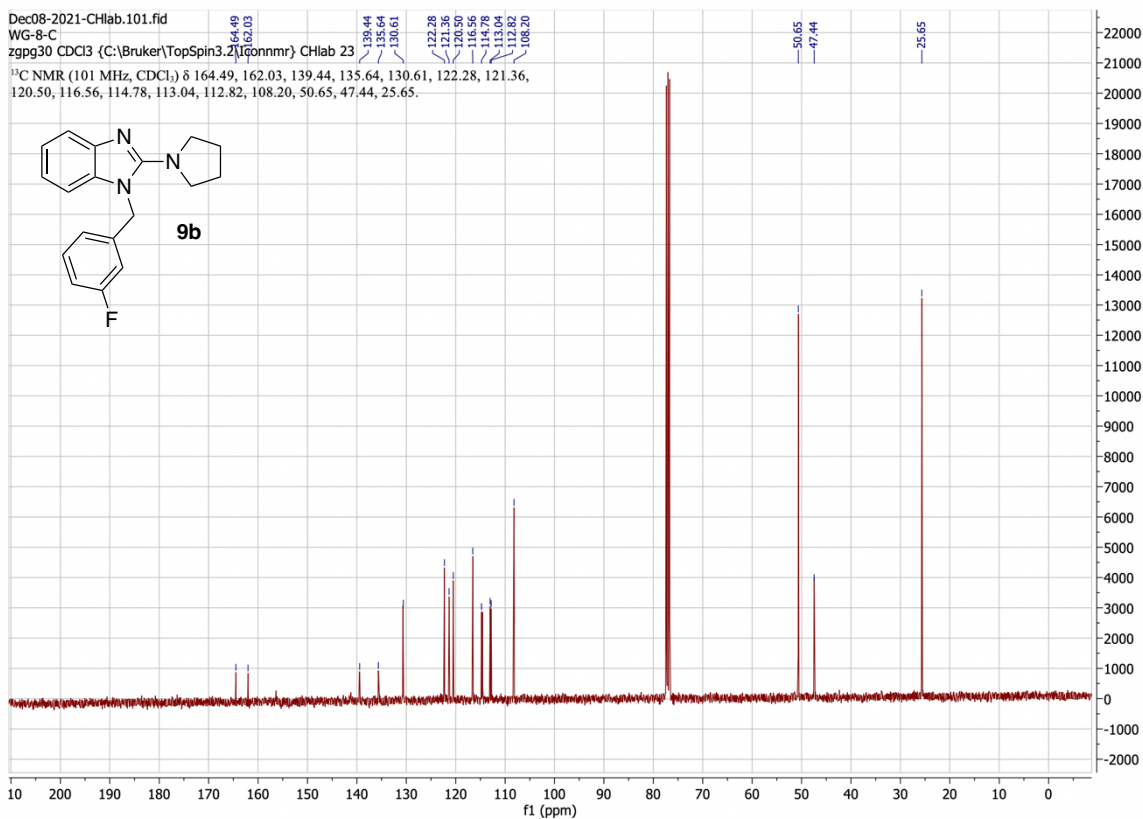
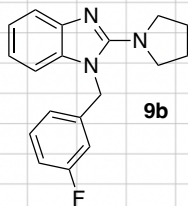


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WG-8-C

zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 23

¹³C NMR (101 MHz, CDCl₃) δ 164.49, 162.03, 139.44, 135.64, 130.61, 122.28, 121.36, 120.50, 116.56, 114.78, 113.04, 112.82, 108.20, 50.65, 47.44, 25.65.

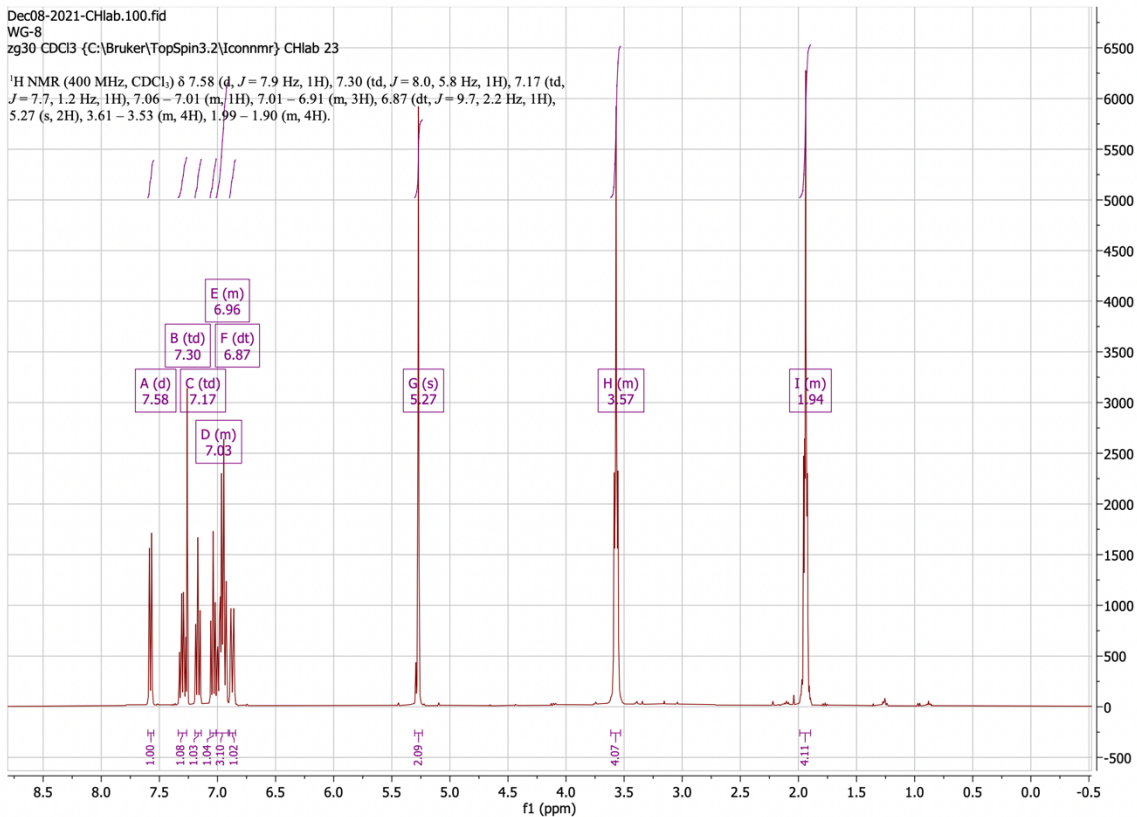


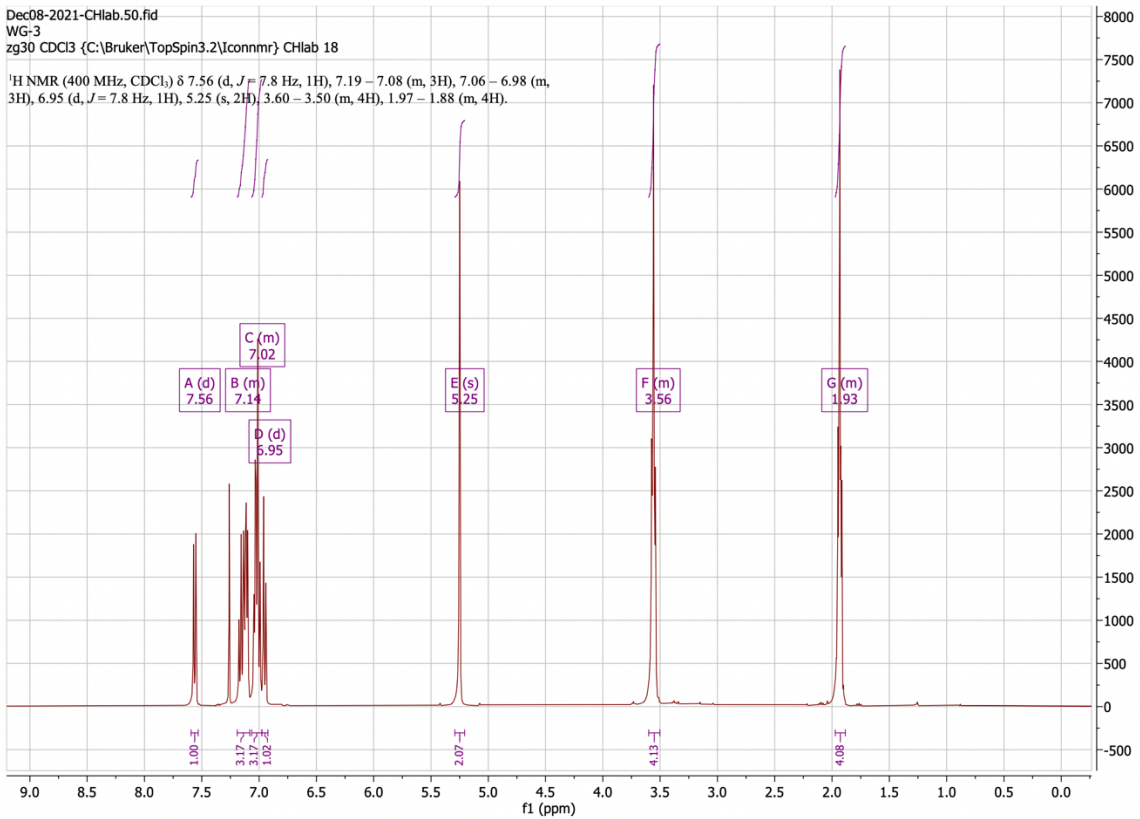
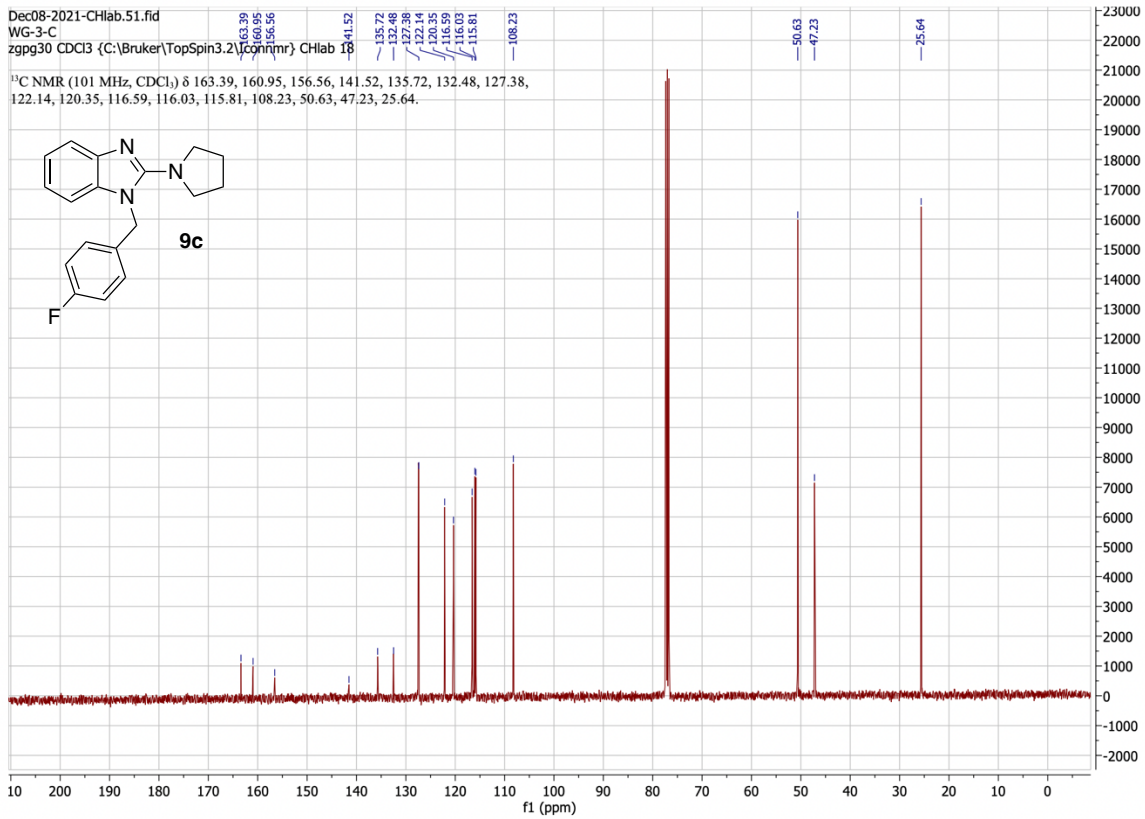
Dec08-2021-CHlab.100.fid

WG-8

zg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 23

¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.30 (td, *J* = 8.0, 5.8 Hz, 1H), 7.17 (td, *J* = 7.7, 1.2 Hz, 1H), 7.06 – 7.01 (m, 1H), 7.01 – 6.91 (m, 3H), 6.87 (dt, *J* = 9.7, 2.2 Hz, 1H), 5.27 (s, 2H), 3.61 – 3.53 (m, 4H), 1.99 – 1.90 (m, 4H).



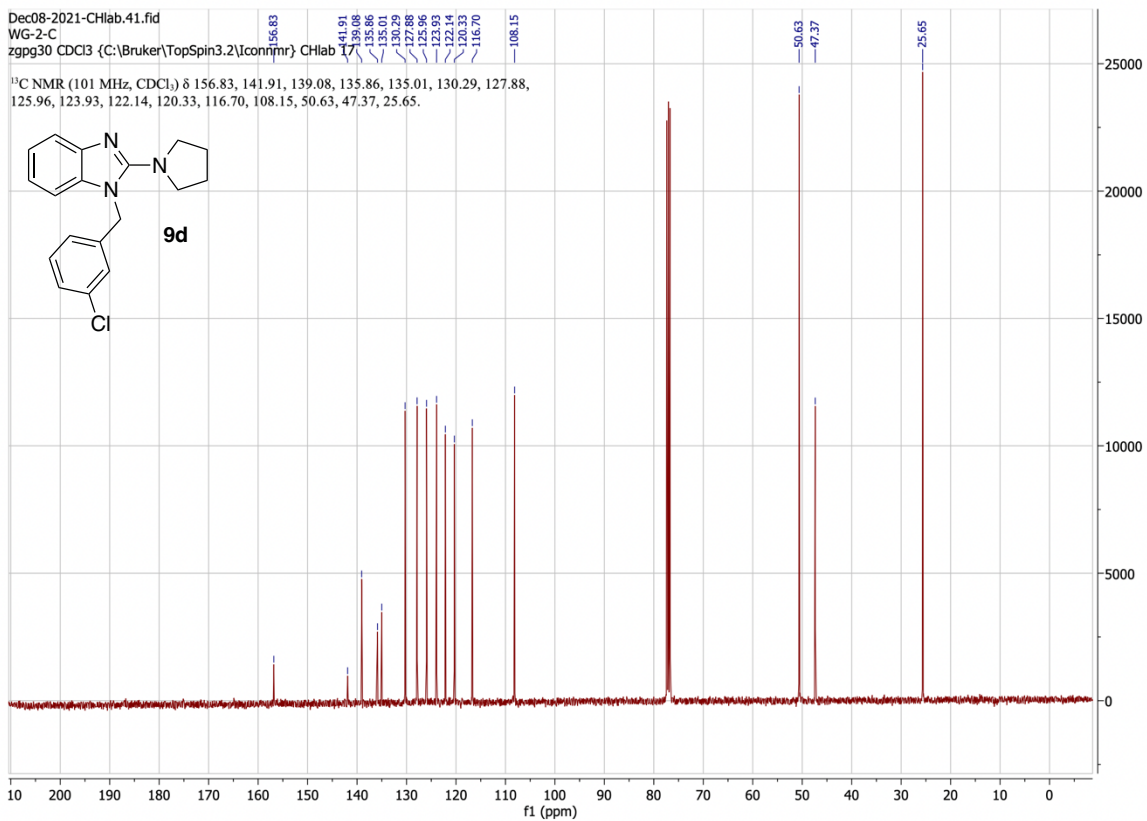
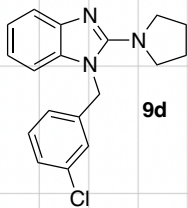


Dec08-2021-CHlab.41.fid

WG-2-C

zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 17

¹³C NMR (101 MHz, CDCl₃) δ 156.83, 141.91, 139.08, 135.86, 135.86, 135.86, 130.29, 127.88, 125.96, 123.93, 122.14, 120.33, 116.70, 108.15, 50.63, 47.37, 25.65.

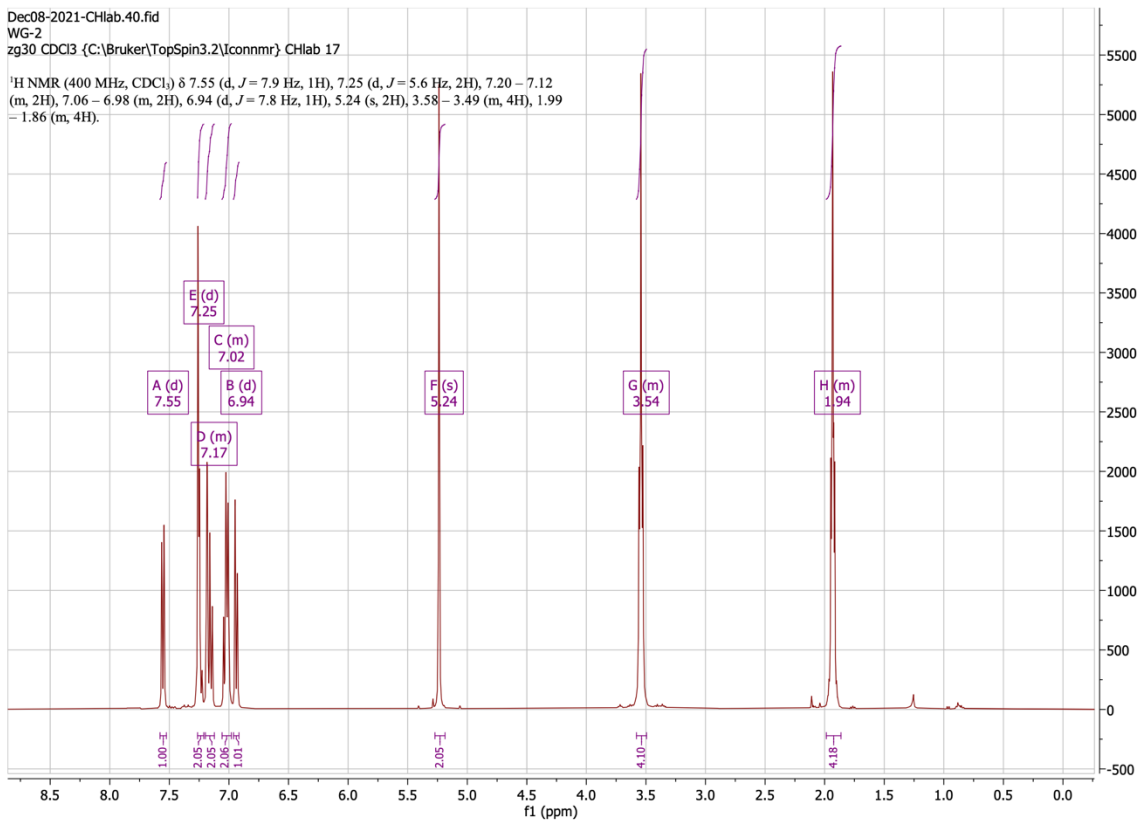


Dec08-2021-CHlab.40.fid

WG-2

zg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 17

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 2H), 7.20 – 7.12 (m, 2H), 7.06 – 6.98 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 2H), 3.58 – 3.49 (m, 4H), 1.99 – 1.86 (m, 4H).

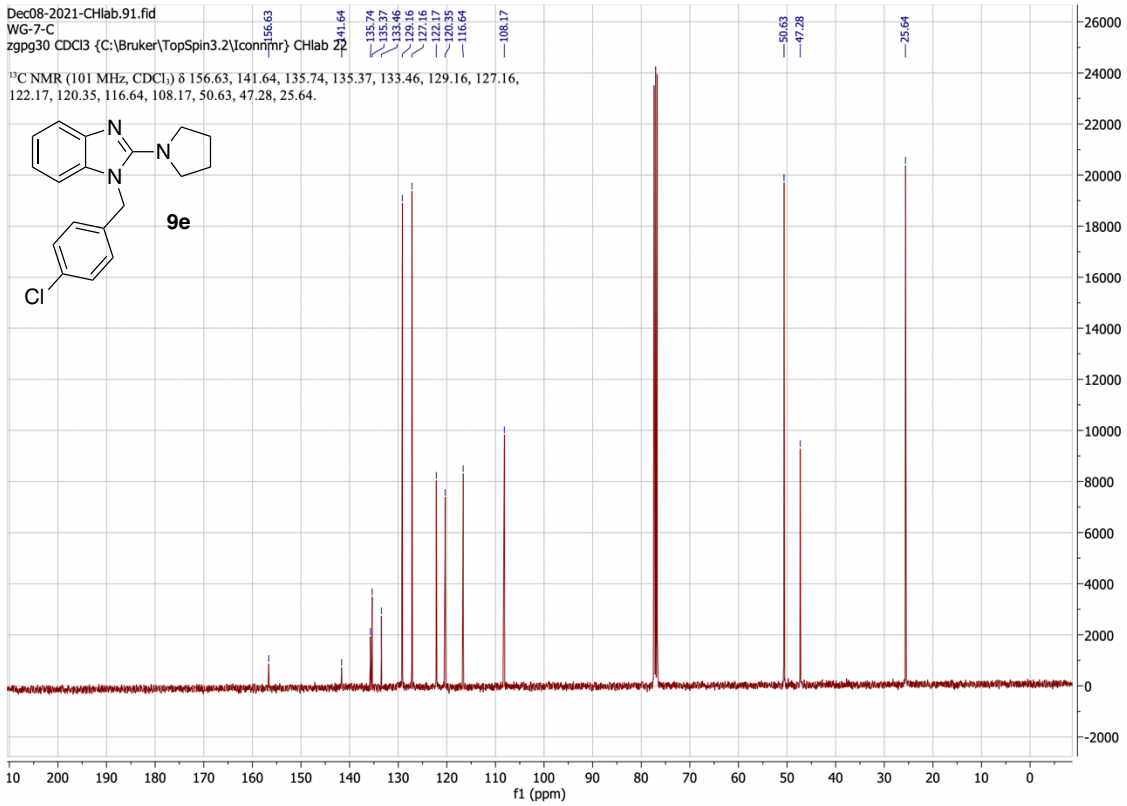
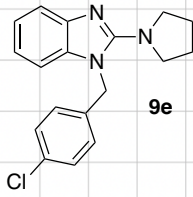


Dec08-2021-CHlab.91.fid

WG-7-C

zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\Iconnmr} CHlab 22

^{13}C NMR (101 MHz, CDCl_3) δ 156.63, 141.64, 135.74, 135.37, 133.46, 129.16, 127.16, 122.17, 120.35, 116.64, 108.17, 50.63, 47.28, 25.64.

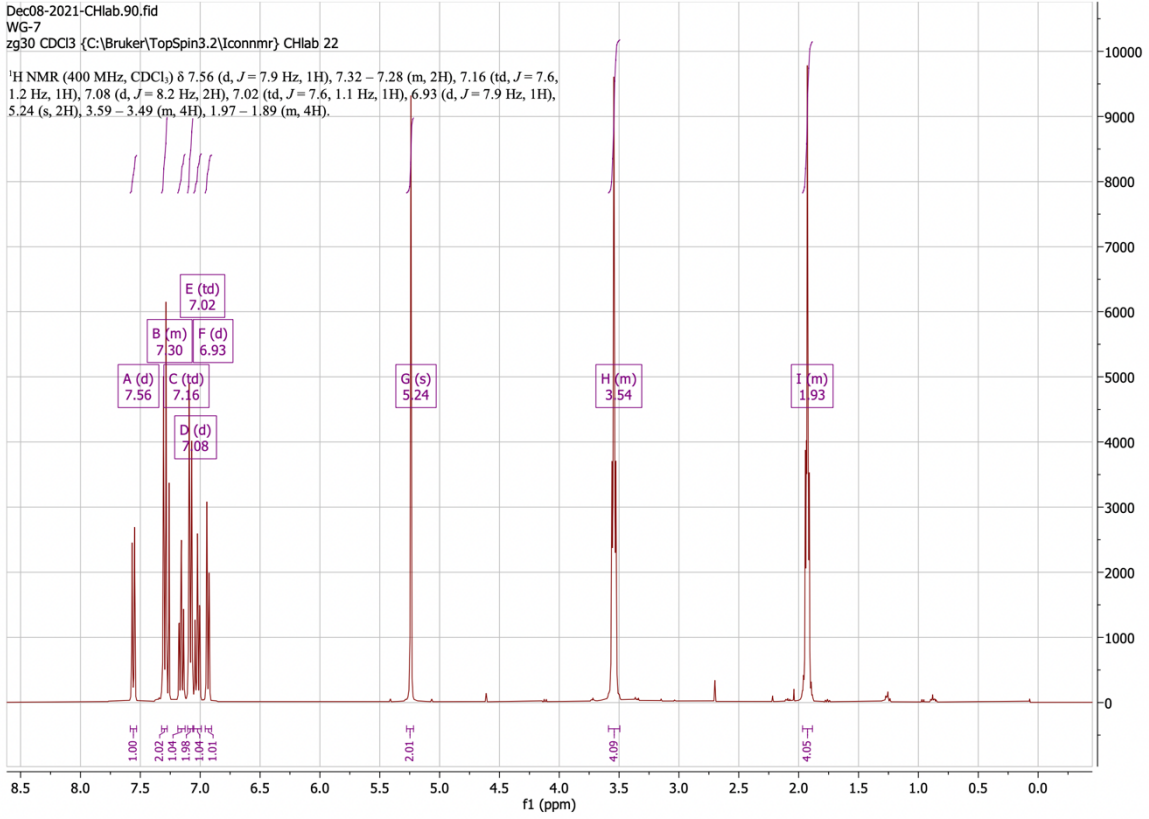


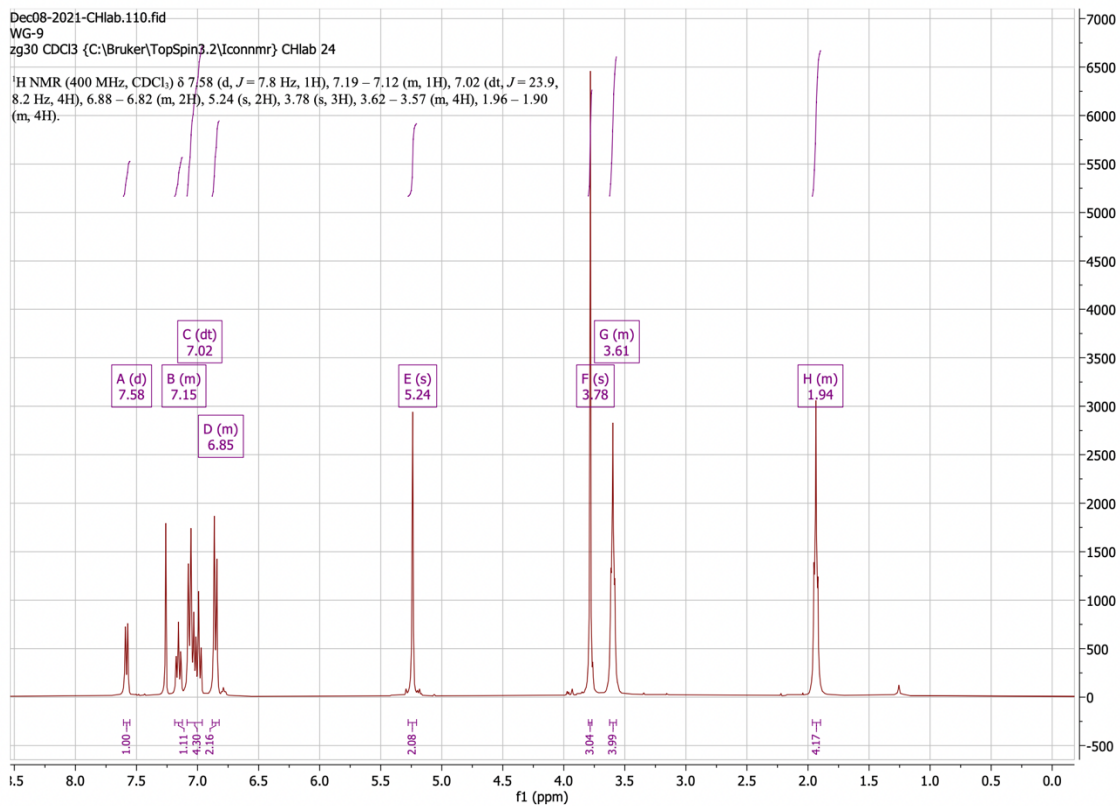
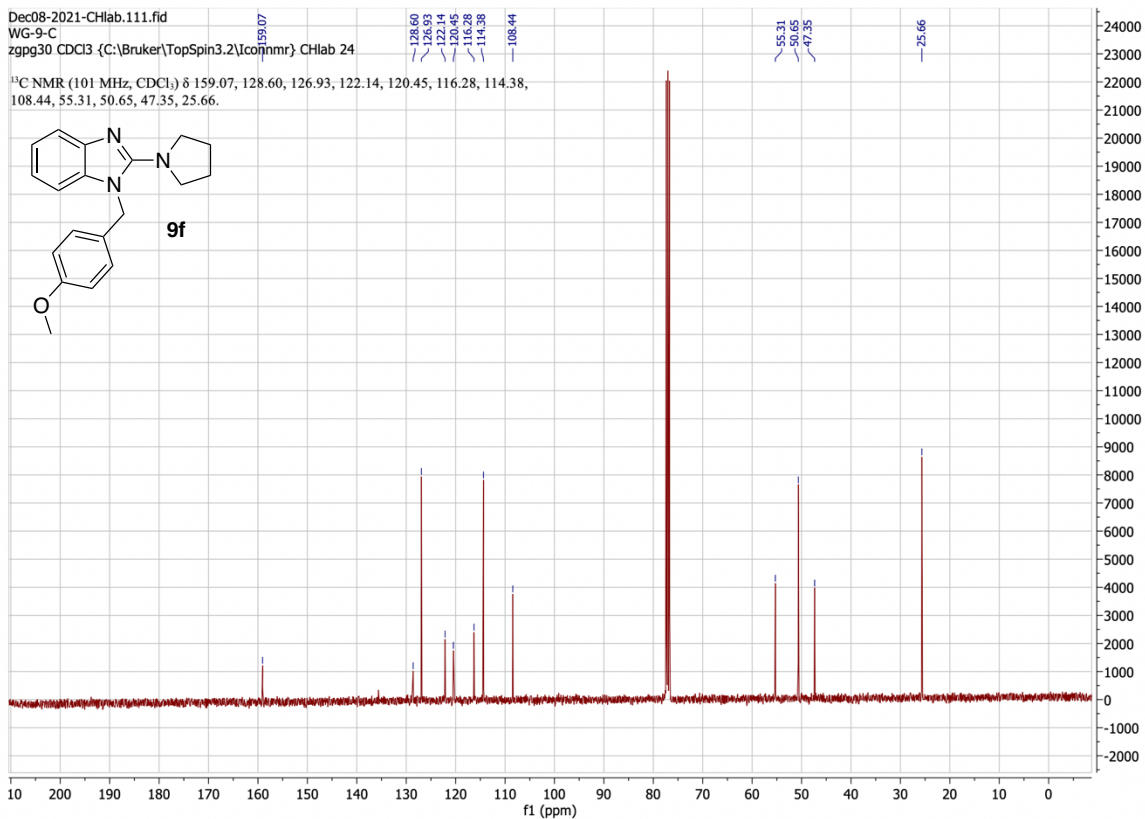
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WG-7

zg30 CDCl3 {C:\Bruker\TopSpin3.2\Iconnmr} CHlab 22

^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, $J = 7.9$ Hz, 1H), 7.32 – 7.28 (m, 2H), 7.16 (td, $J = 7.6$, 1.2 Hz, 1H), 7.08 (d, $J = 8.2$ Hz, 2H), 7.02 (td, $J = 7.6$, 1.1 Hz, 1H), 6.93 (d, $J = 7.9$ Hz, 1H), 5.24 (s, 2H), 3.59 – 3.49 (m, 4H), 1.97 – 1.89 (m, 4H).



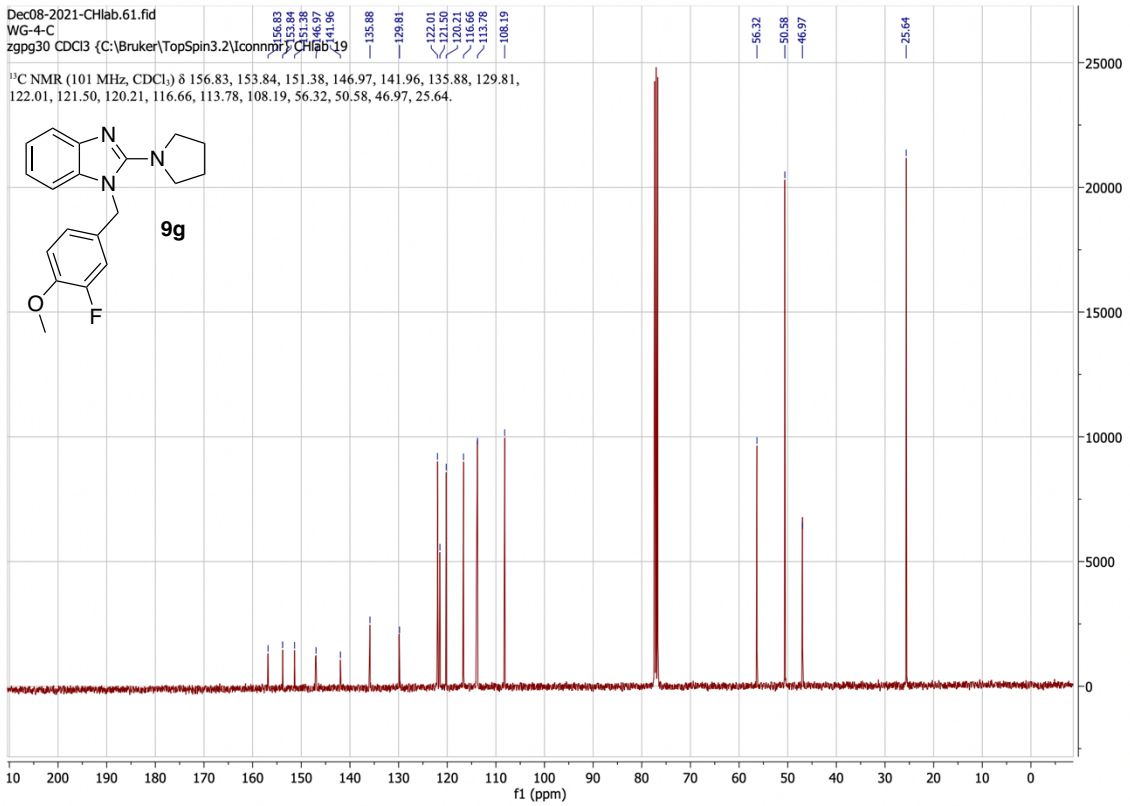
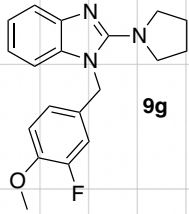


Dec08-2021-CHlab.61.fid

WG-4-C

zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\Iconmmr\CHlab\19

¹³C NMR (101 MHz, CDCl₃) δ 156.83, 153.84, 151.38, 146.97, 141.96, 135.88, 129.81, 122.01, 121.50, 120.21, 116.66, 113.78, 108.19, 56.32, 50.58, 46.97, 25.64.



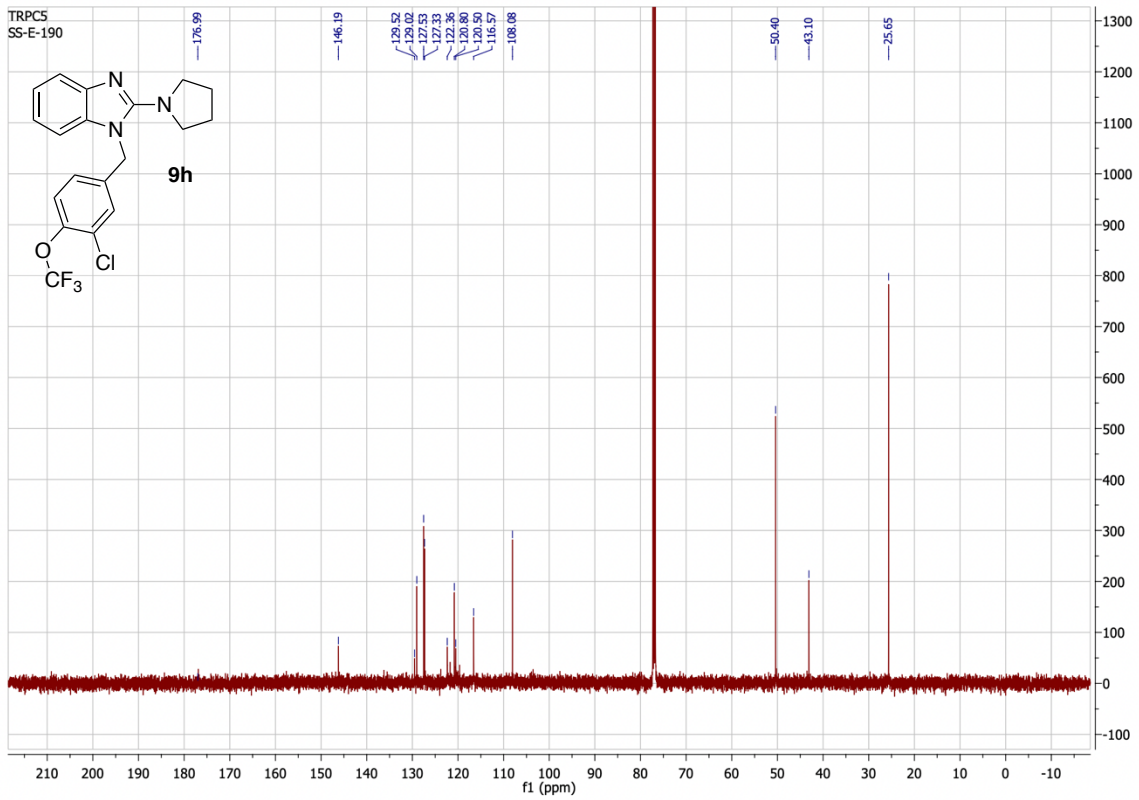
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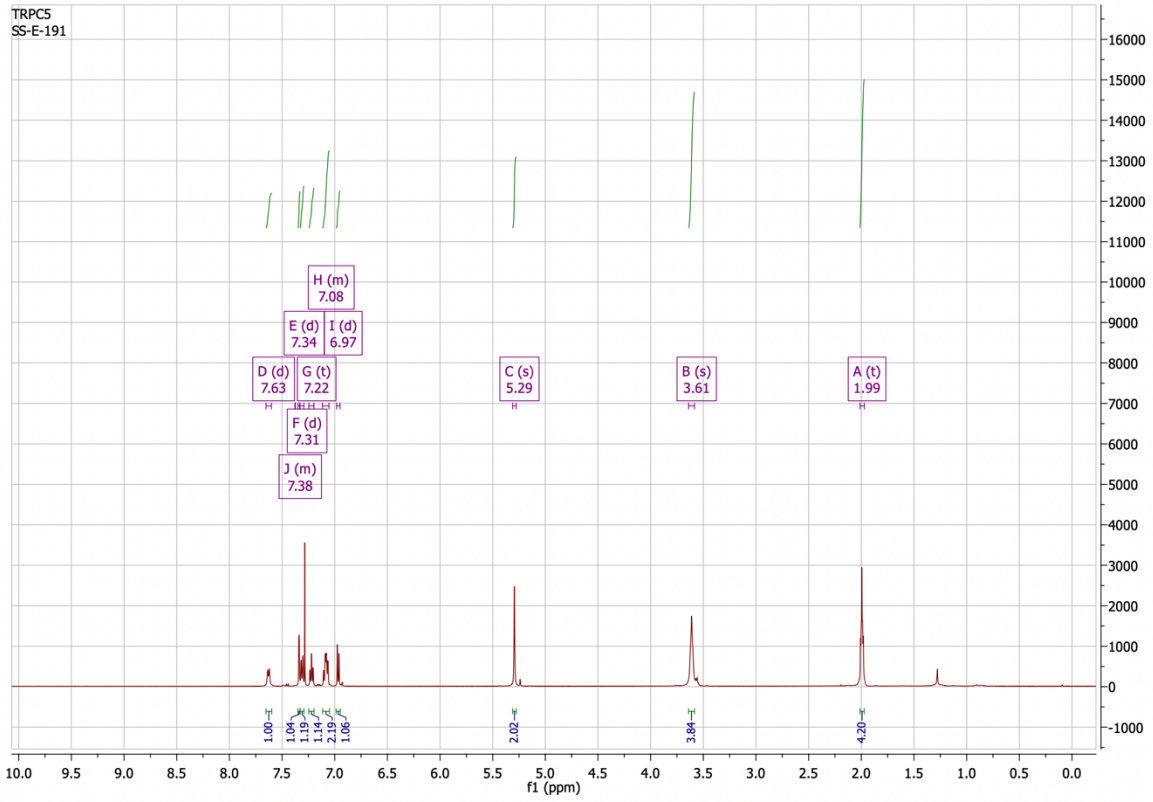
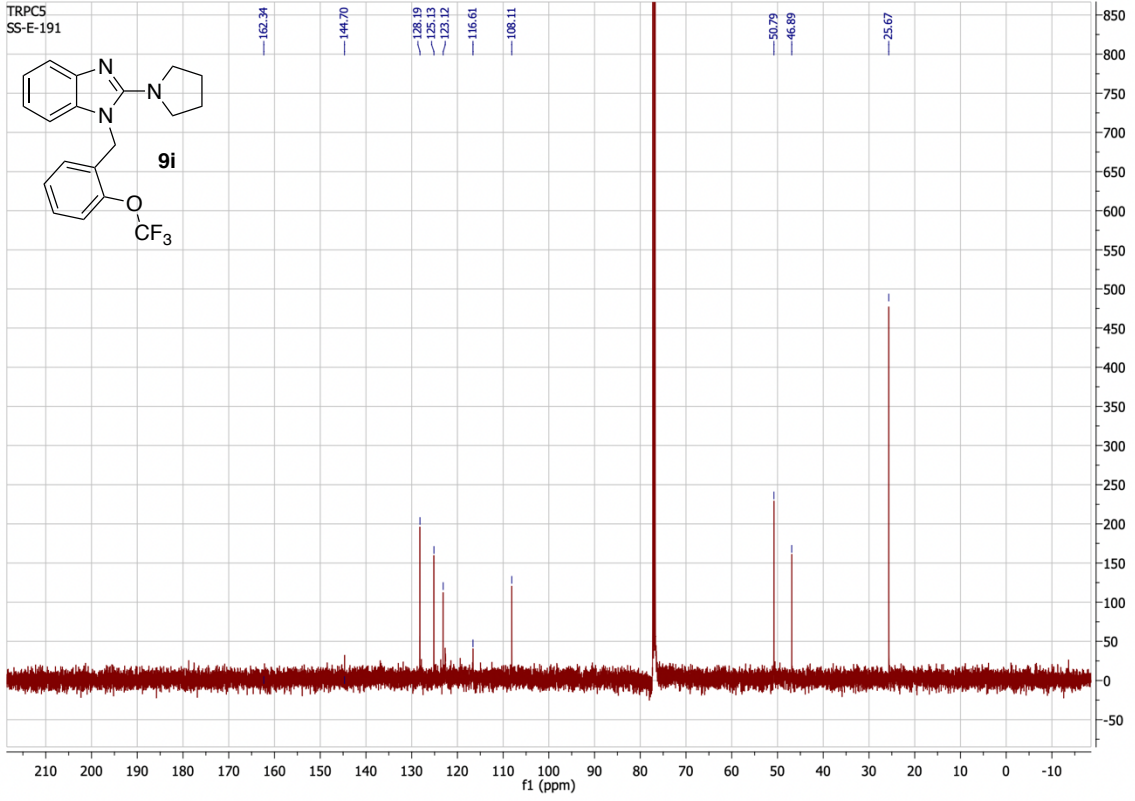
WG-4

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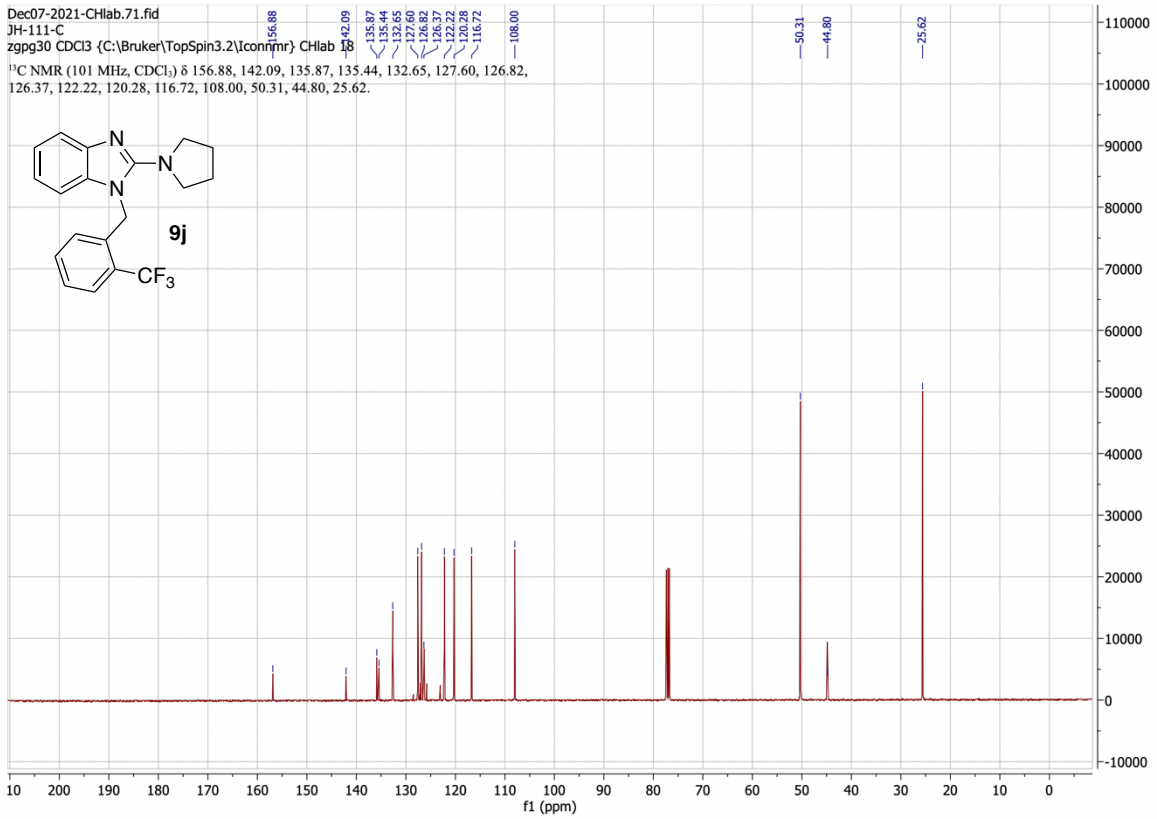
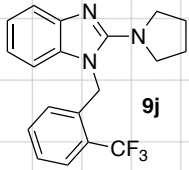
¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.15 (td, *J* = 7.6, 1.3 Hz, 1H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 6.97 – 6.79 (m, 4H), 5.19 (s, 2H), 3.86 (s, 3H), 3.59 – 3.51 (m, 4H), 1.97 – 1.89 (m, 4H).



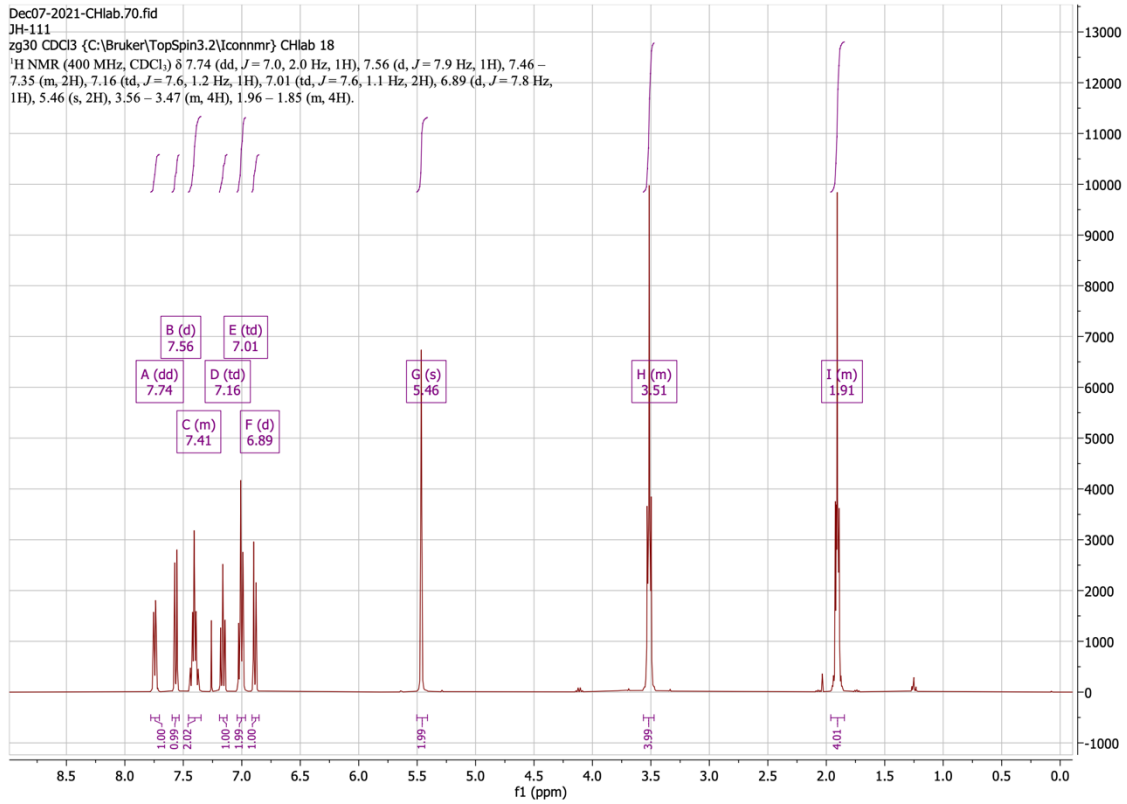


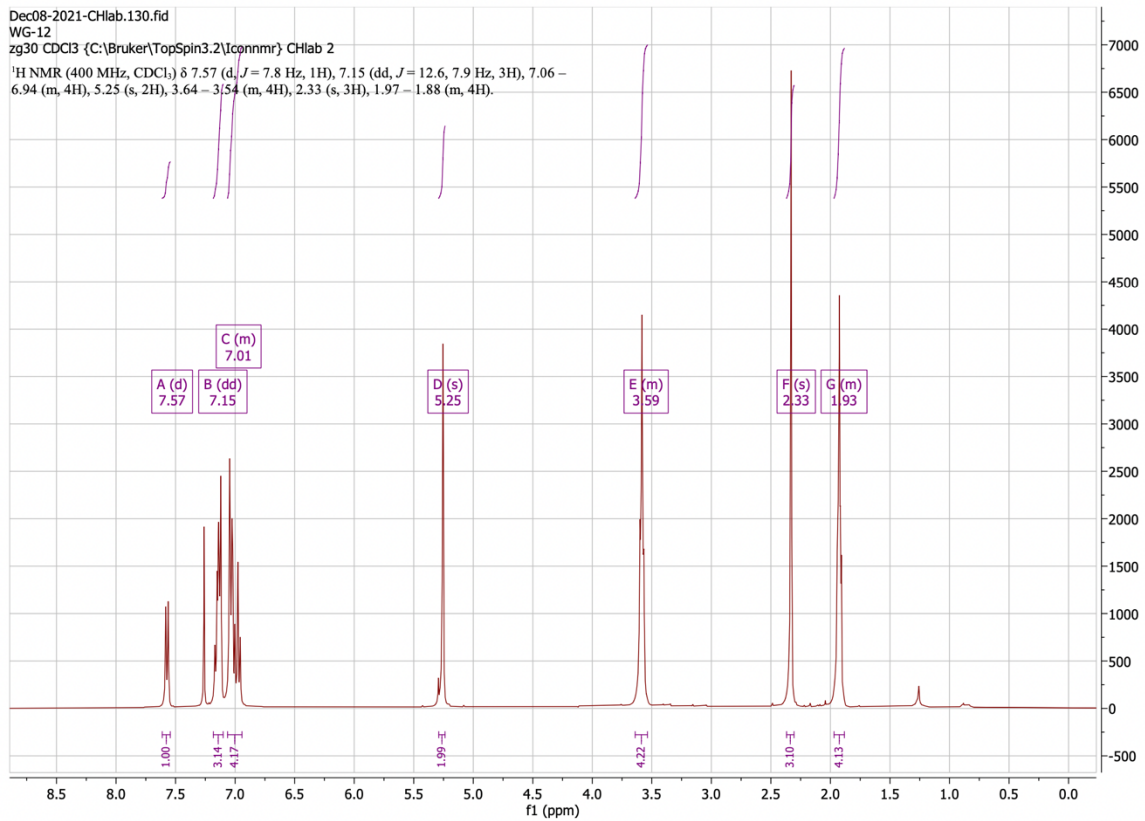
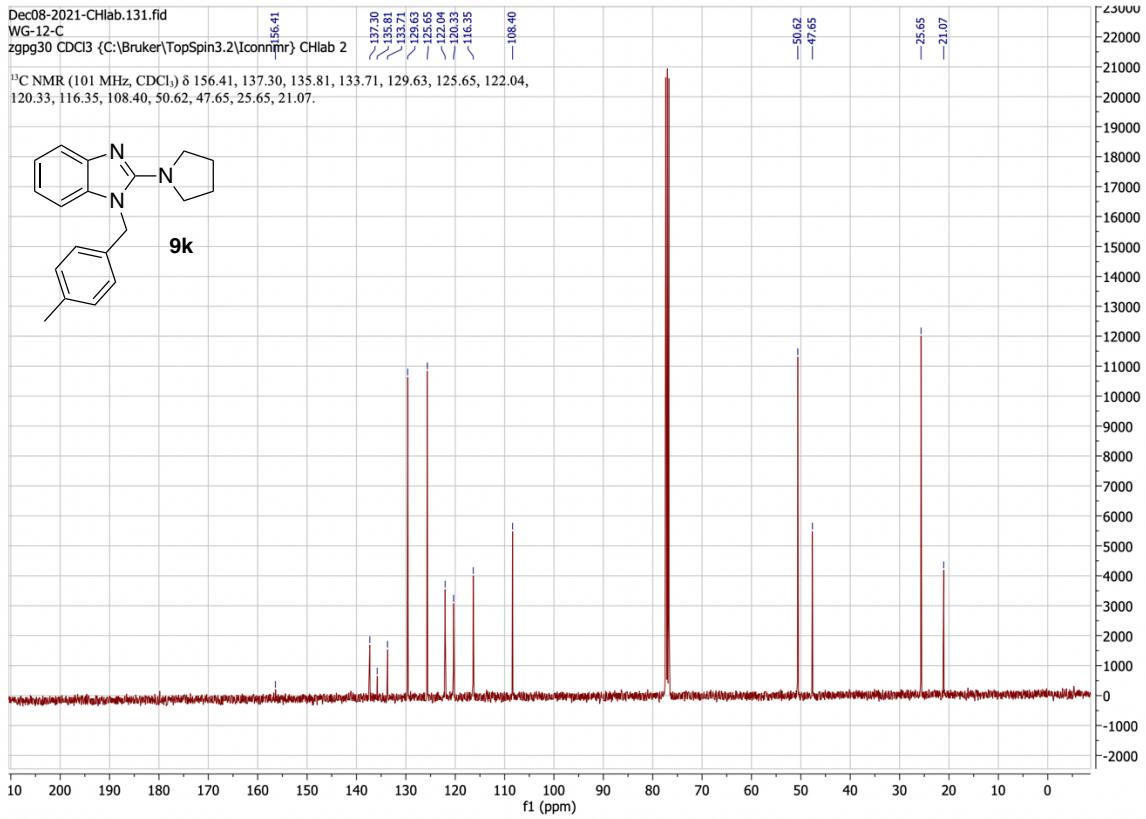


Dec07-2021-CHlab.71.fid
 JH-111-C
 zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\Iconnmr} CHlab 18
¹³C NMR (101 MHz, CDCl₃) δ 156.88, 142.09, 135.87, 135.44, 132.65, 127.60, 126.82, 126.37, 122.22, 120.28, 116.72, 108.00, 50.31, 44.80, 25.62.

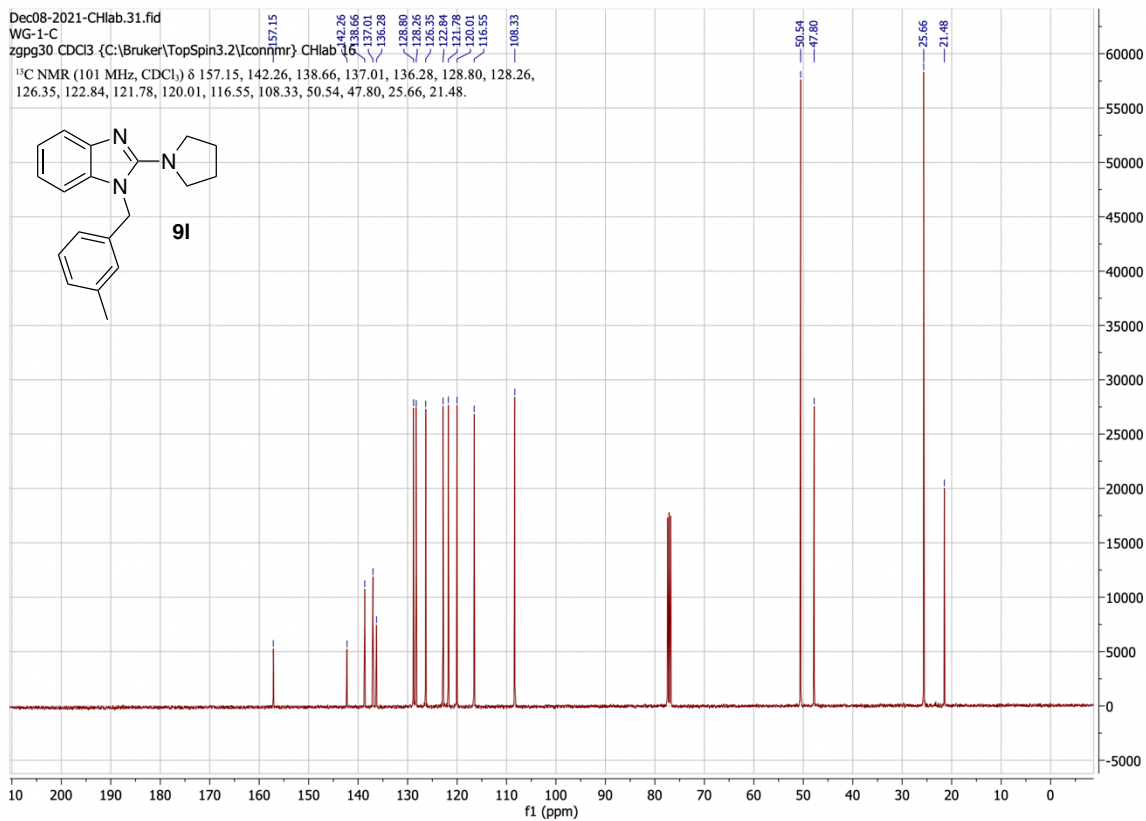
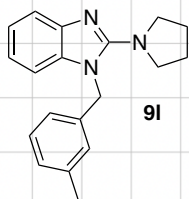


Dec07-2021-CHlab.70.fid
 JH-111
 zg30 CDCl3 {C:\Bruker\TopSpin3.2\Iconnmr} CHlab 18
¹H NMR (400 MHz, CDCl₃) δ 7.74 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.35 (m, 2H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 (td, *J* = 7.6, 1.1 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.46 (s, 2H), 3.56 – 3.47 (m, 4H), 1.96 – 1.85 (m, 4H).

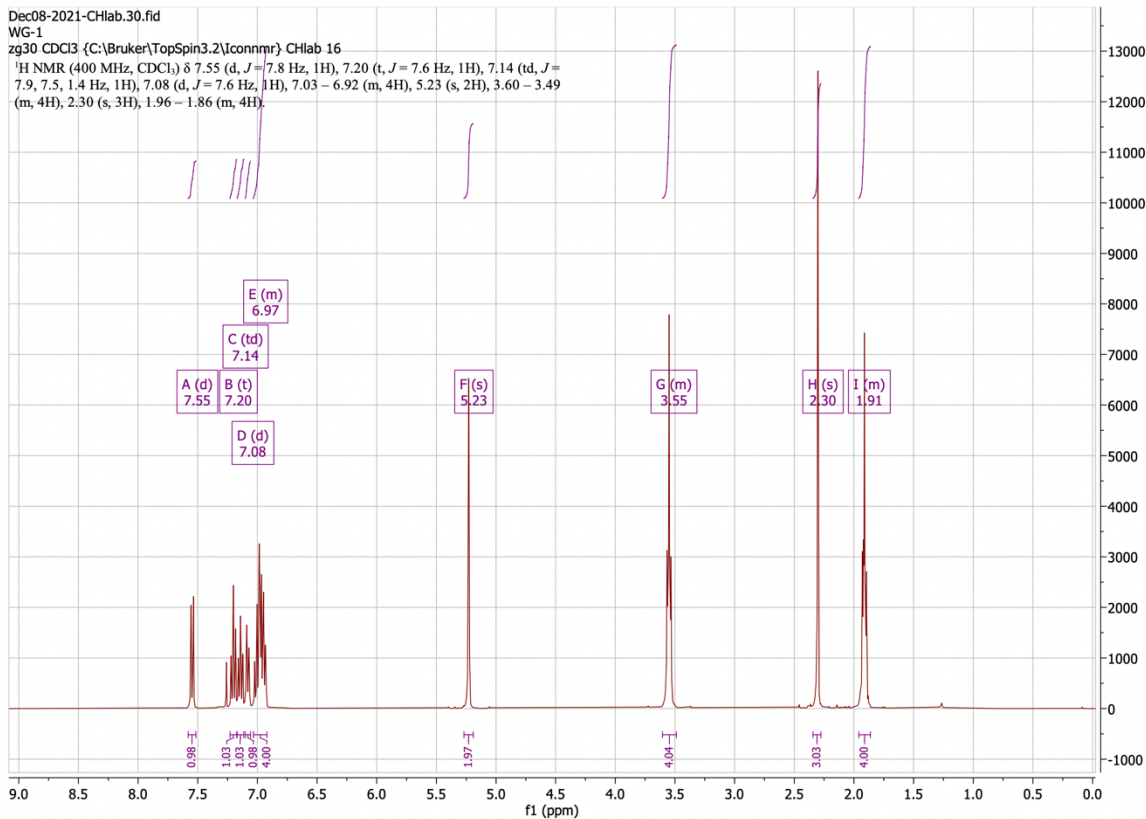


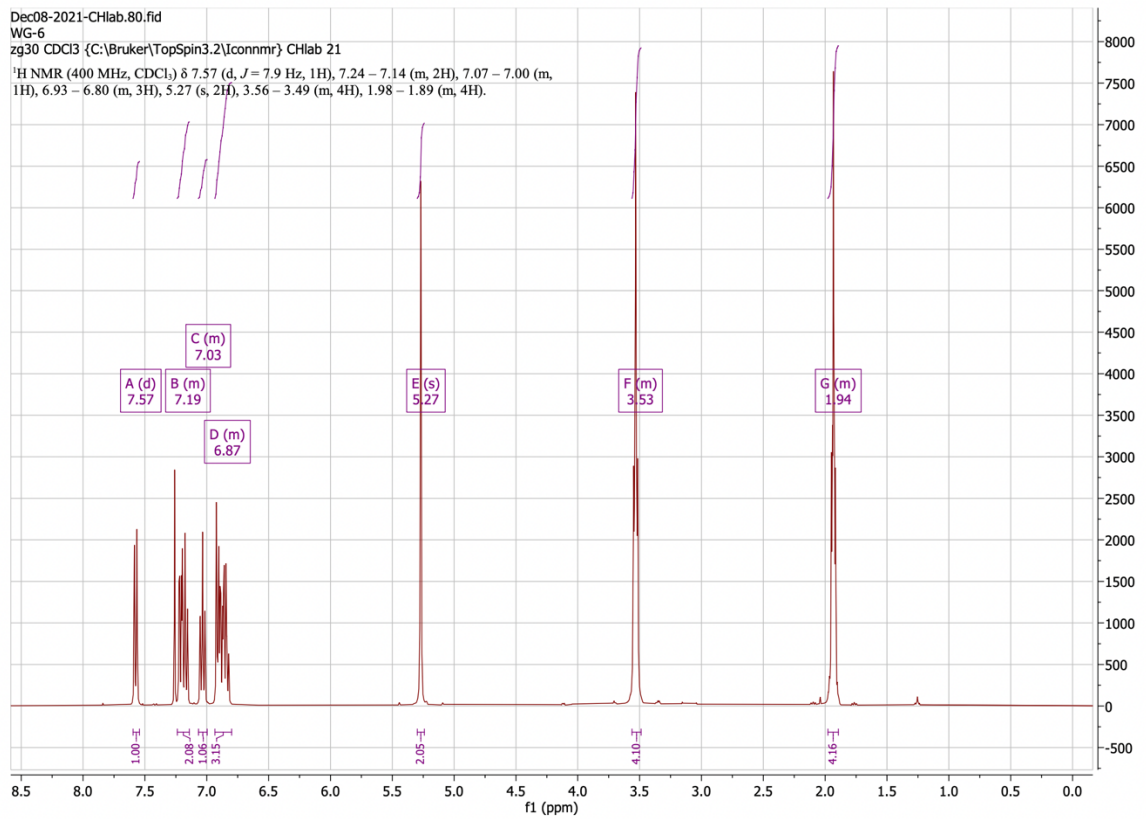
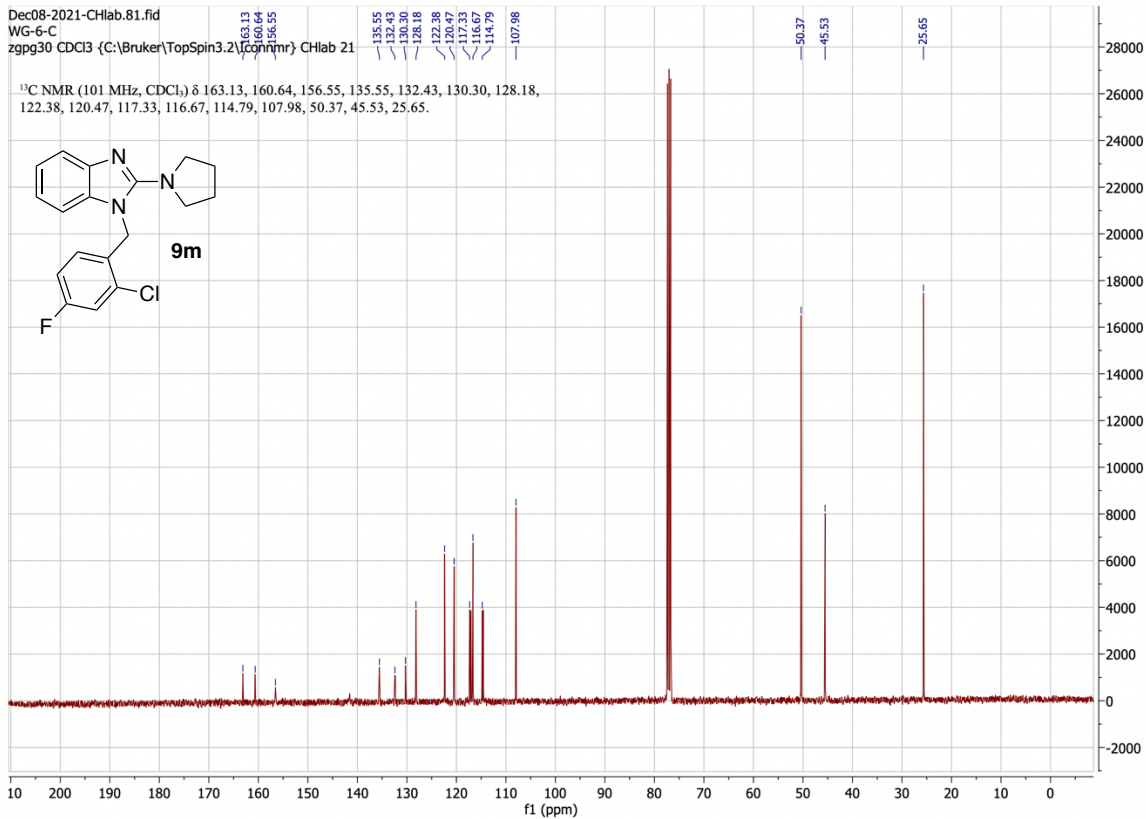


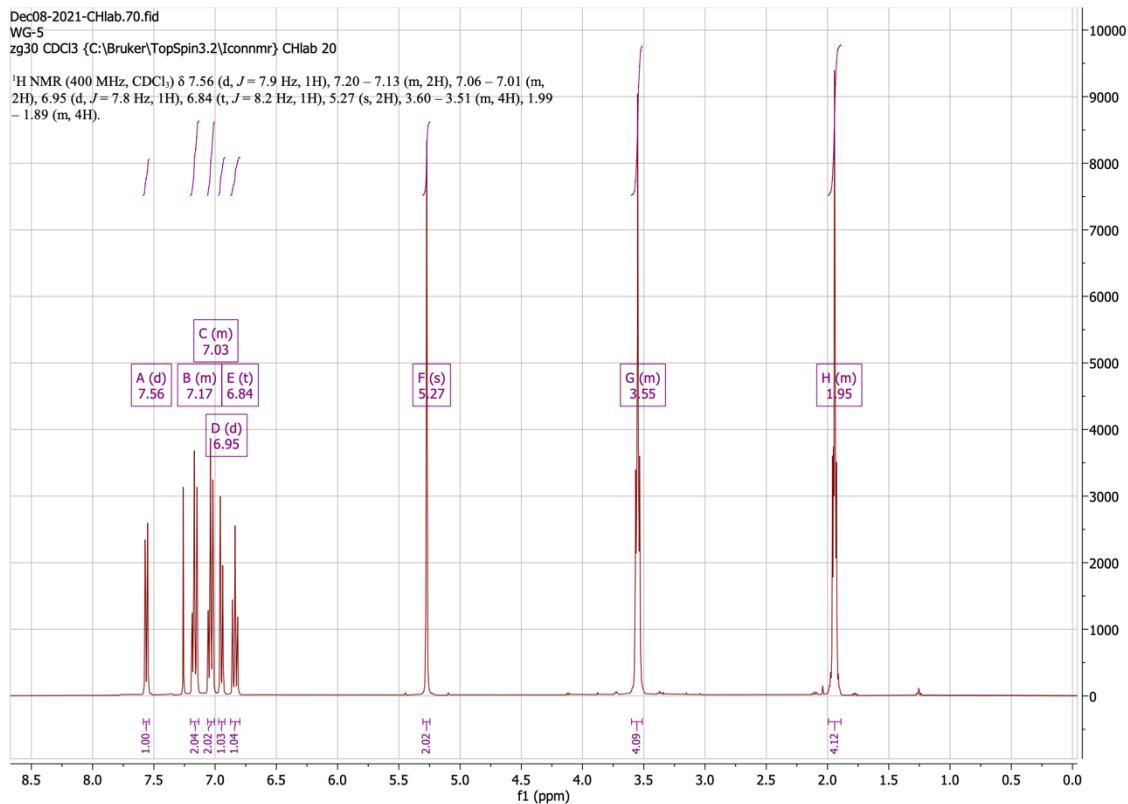
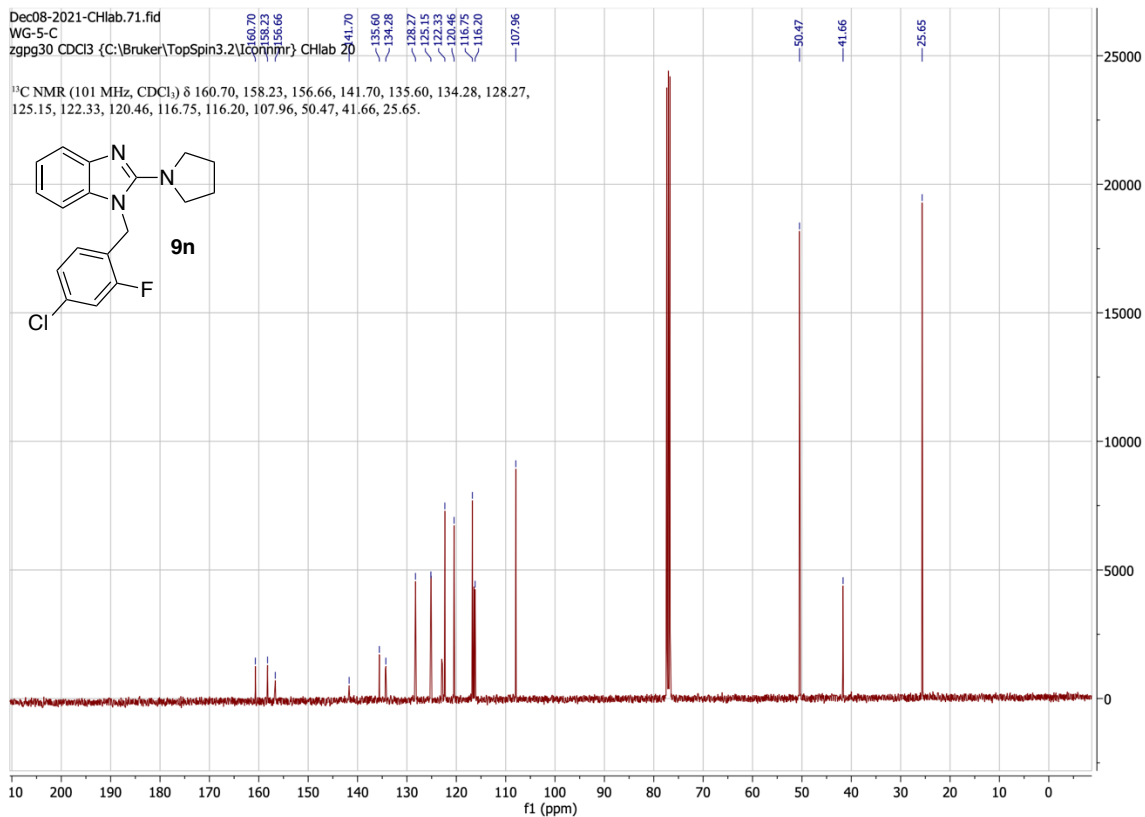
Dec08-2021-CHlab.31.fid
 WG-1-C
 zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\iconmr} CHlab 16
¹³C NMR (101 MHz, CDCl₃) δ 157.15, 142.26, 138.66, 137.01, 136.28, 128.80, 128.55, 122.84, 121.78, 120.01, 116.55, 108.33, 50.54, 47.80, 25.66, 21.48.

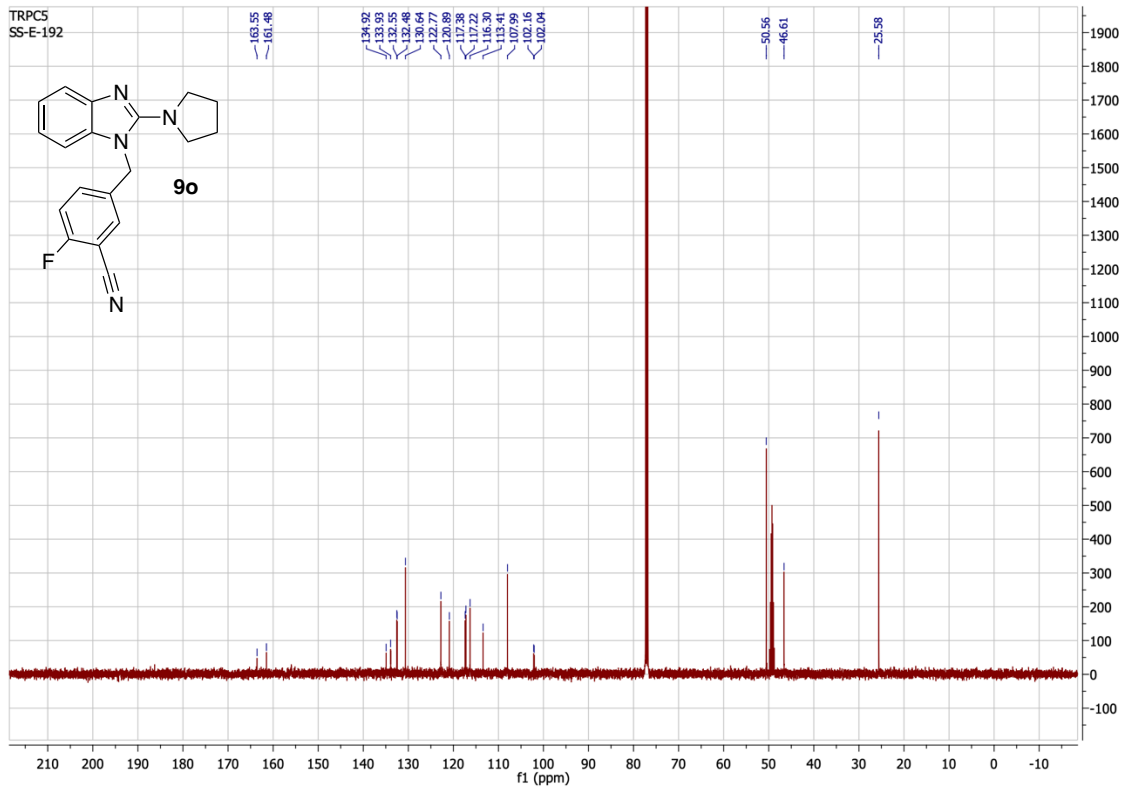


Dec08-2021-CHlab.30.fid
 WG-1
 zg30 CDCl3 {C:\Bruker\TopSpin3.2\iconmr} CHlab 16
¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.14 (td, *J* = 7.9, 7.5, 1.4 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 – 6.92 (m, 4H), 5.23 (s, 2H), 3.60 – 3.49 (m, 4H), 2.30 (s, 3H), 1.96 – 1.86 (m, 4H).







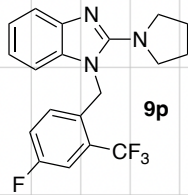


Dec07-2021-CHlab.81.fid

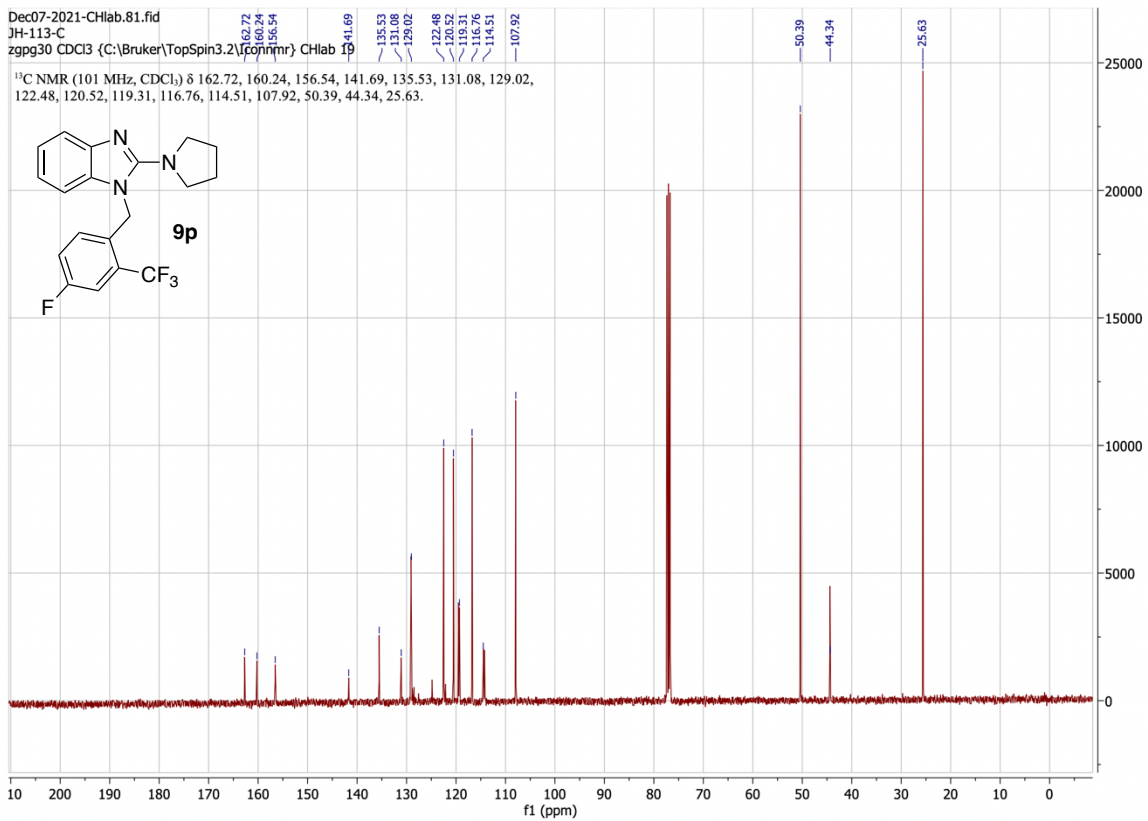
JH-113-C

zgpg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 19

¹³C NMR (101 MHz, CDCl₃) δ 162.72, 160.24, 156.54, 141.69, 135.53, 131.08, 129.02, 122.48, 120.52, 119.31, 116.76, 114.51, 107.92, 50.39, 44.34, 25.63.



9p

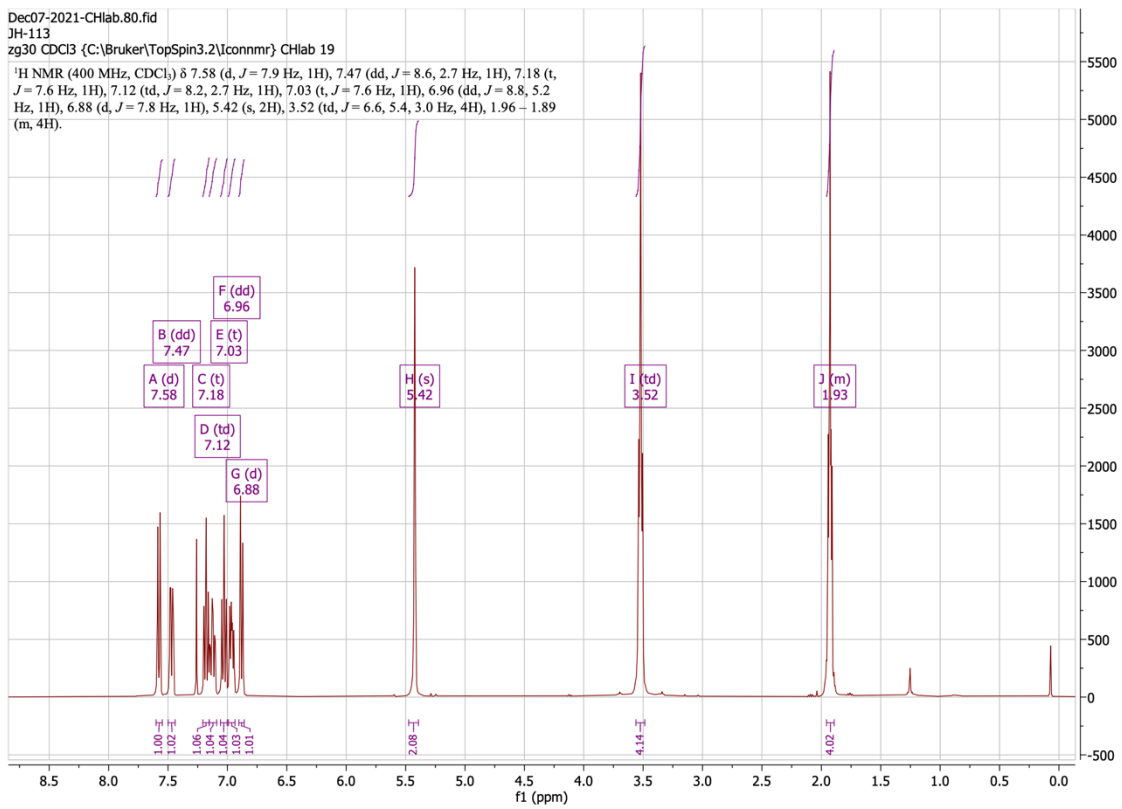


Dec07-2021-CHlab.80.fid

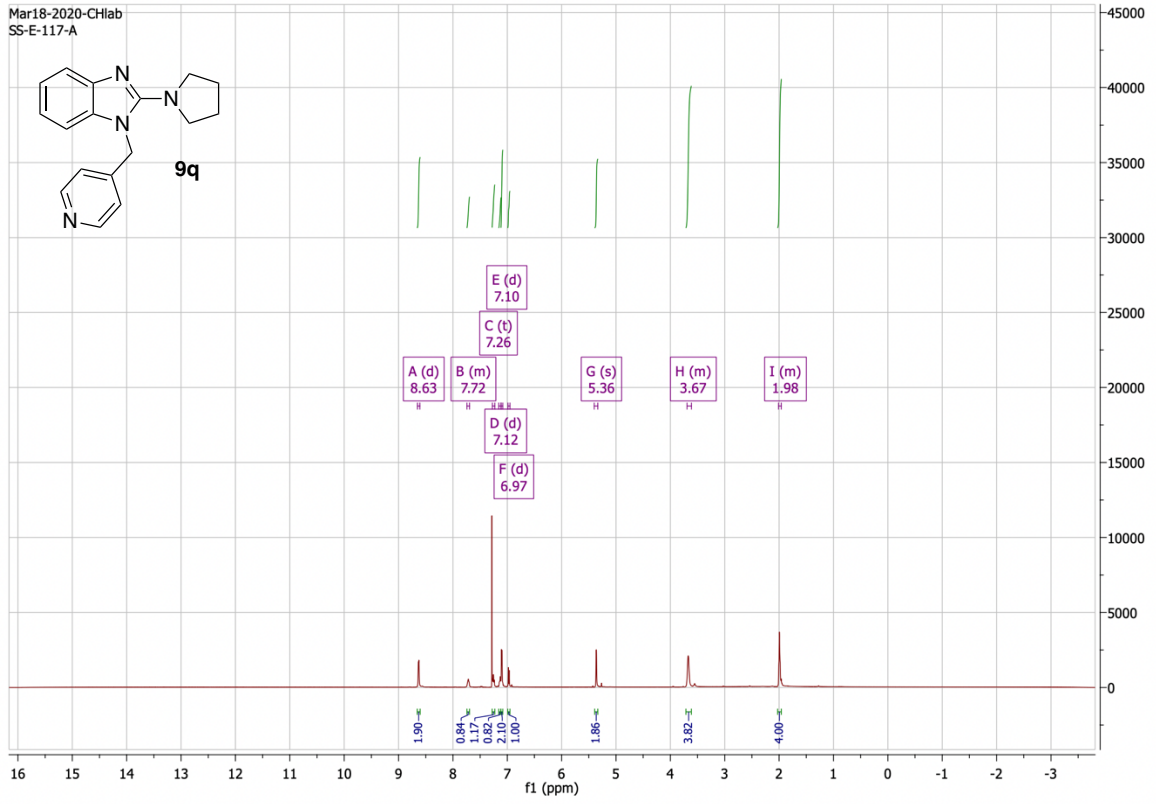
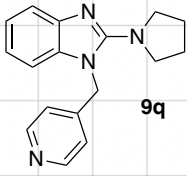
JH-113

zg30 CDCl3 {C:\Bruker\TopSpin3.2\iconnmr} CHlab 19

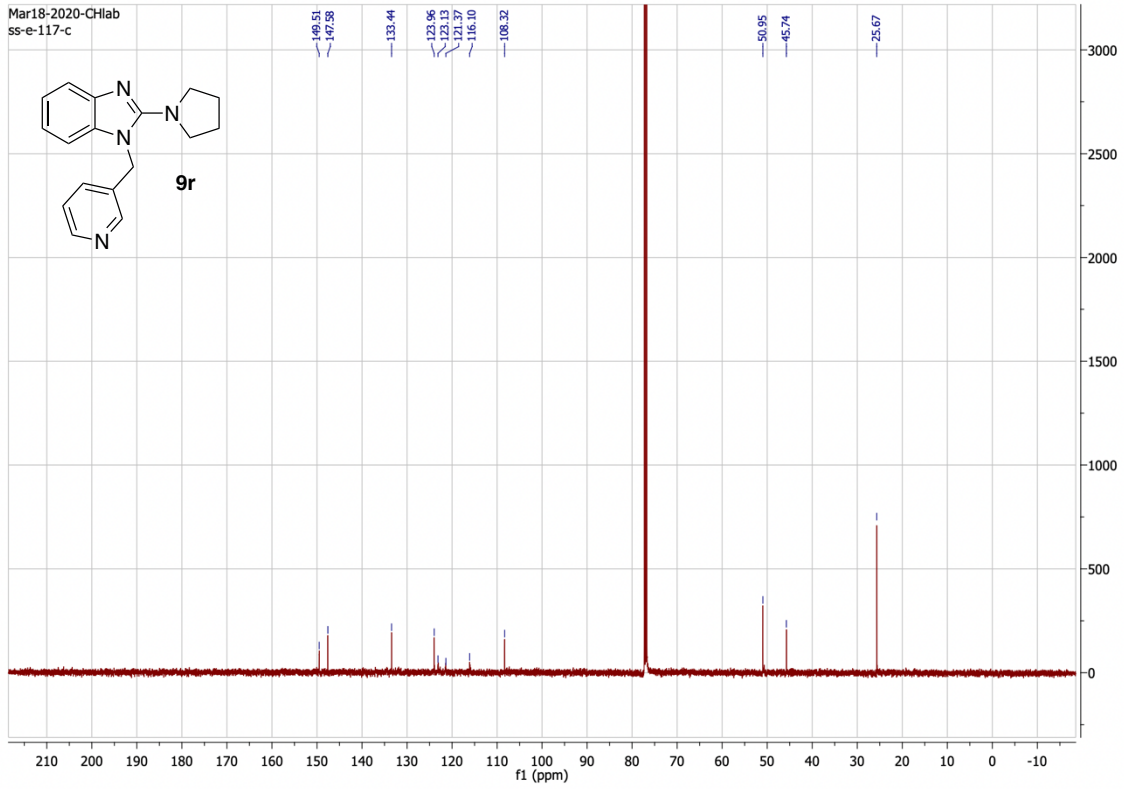
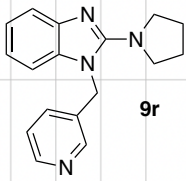
¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.12 (td, *J* = 8.2, 2.7 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 8.8, 5.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.42 (s, 2H), 3.52 (td, *J* = 6.6, 5.4, 3.0 Hz, 4H), 1.96 – 1.89 (m, 4H).



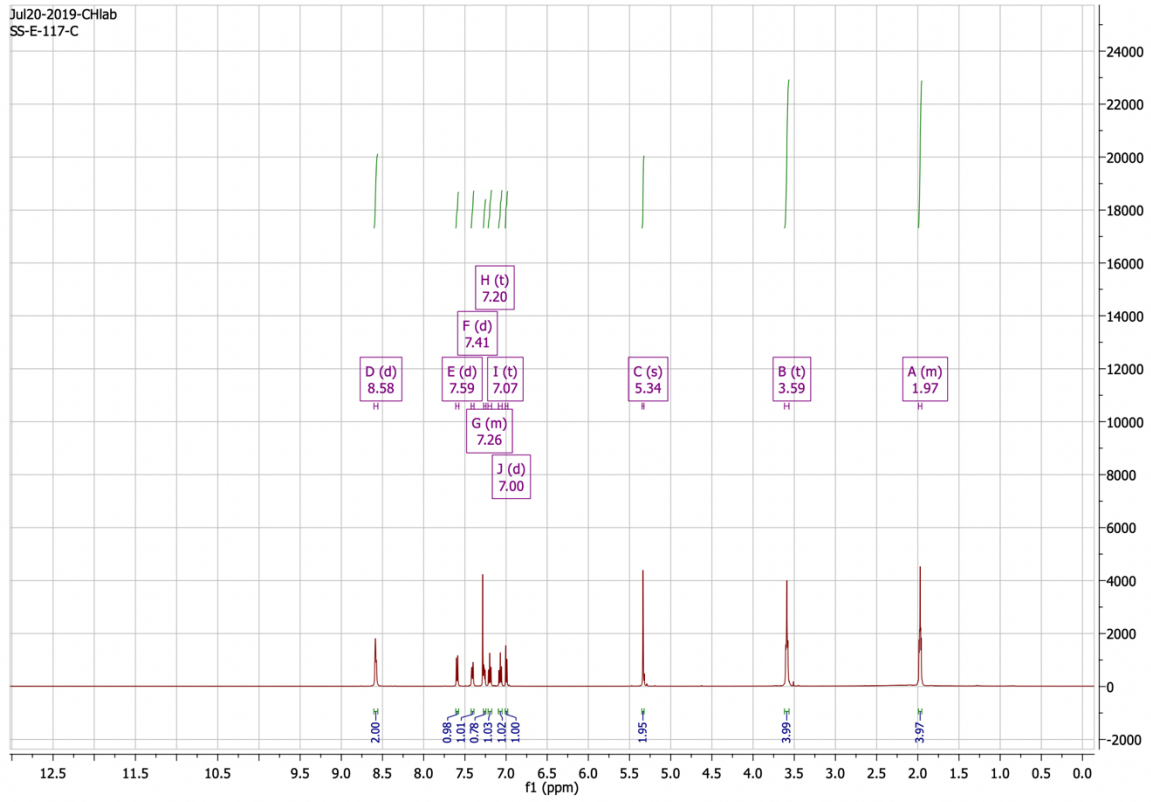
Mar18-2020-CHlab
SS-E-117-A



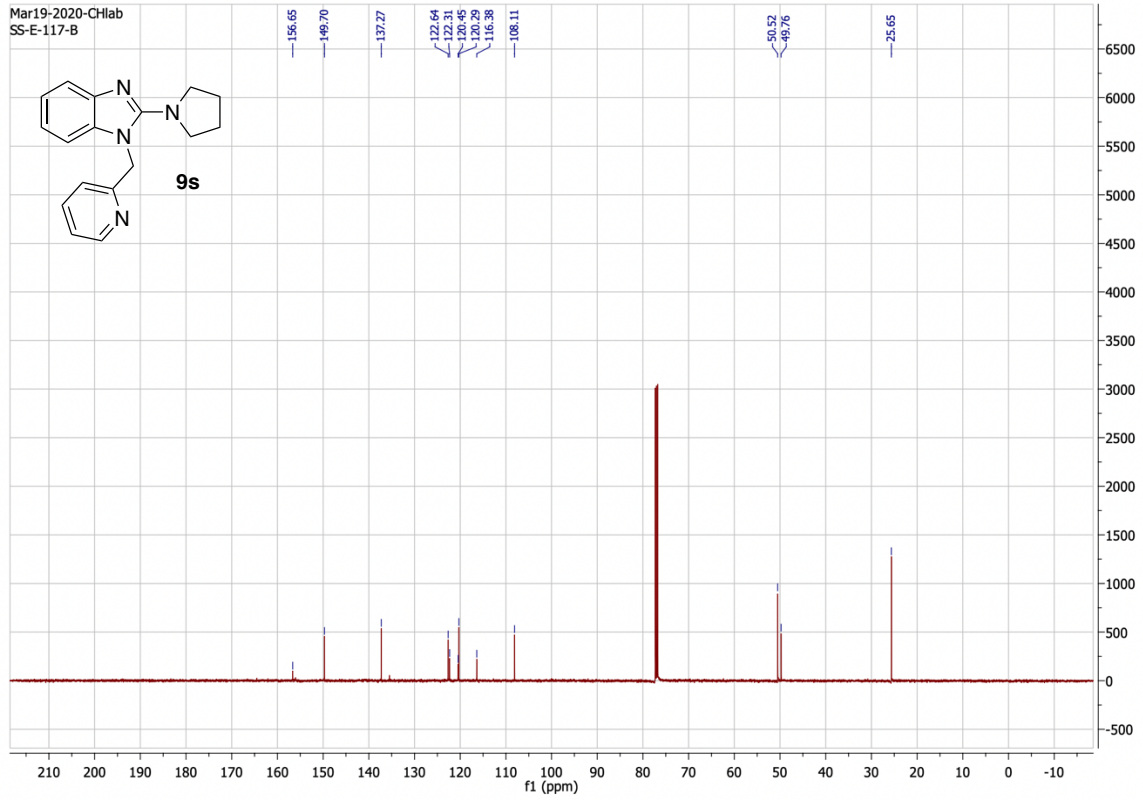
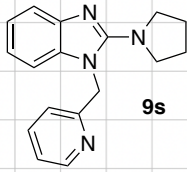
Mar18-2020-CHlab
ss-e-117-c



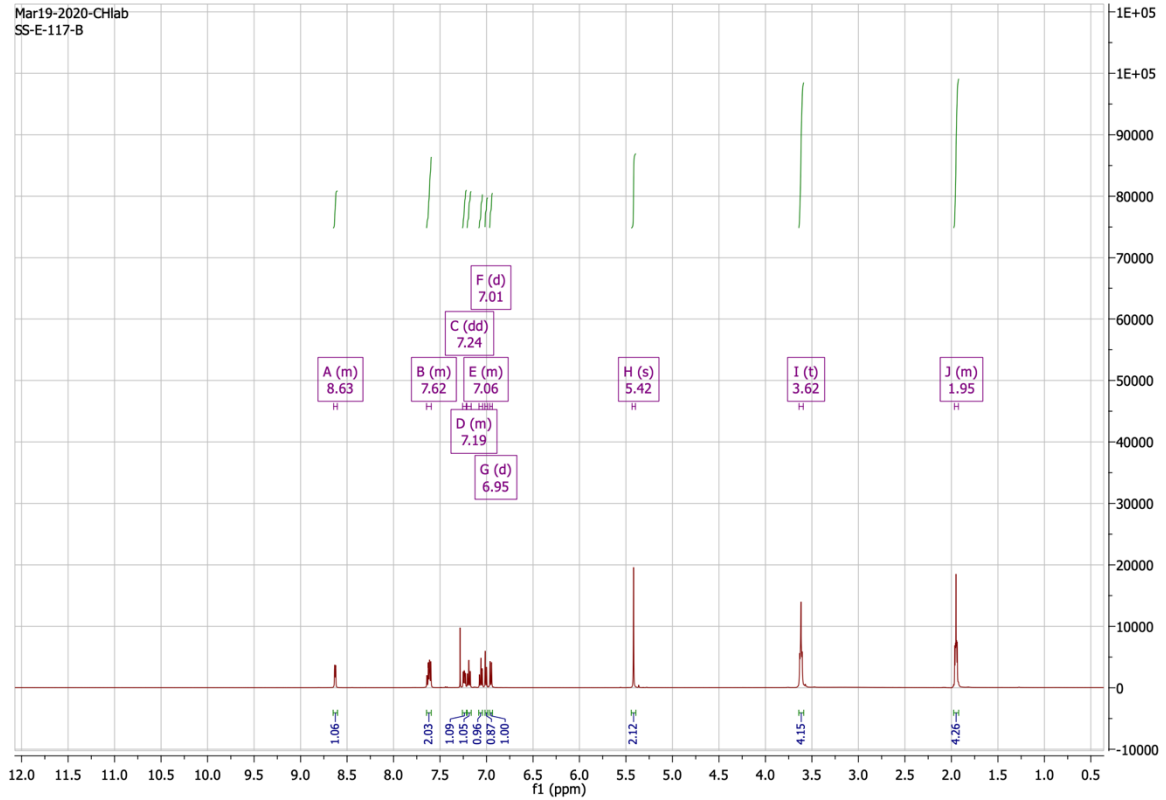
Jul20-2019-CHlab
SS-E-117-C



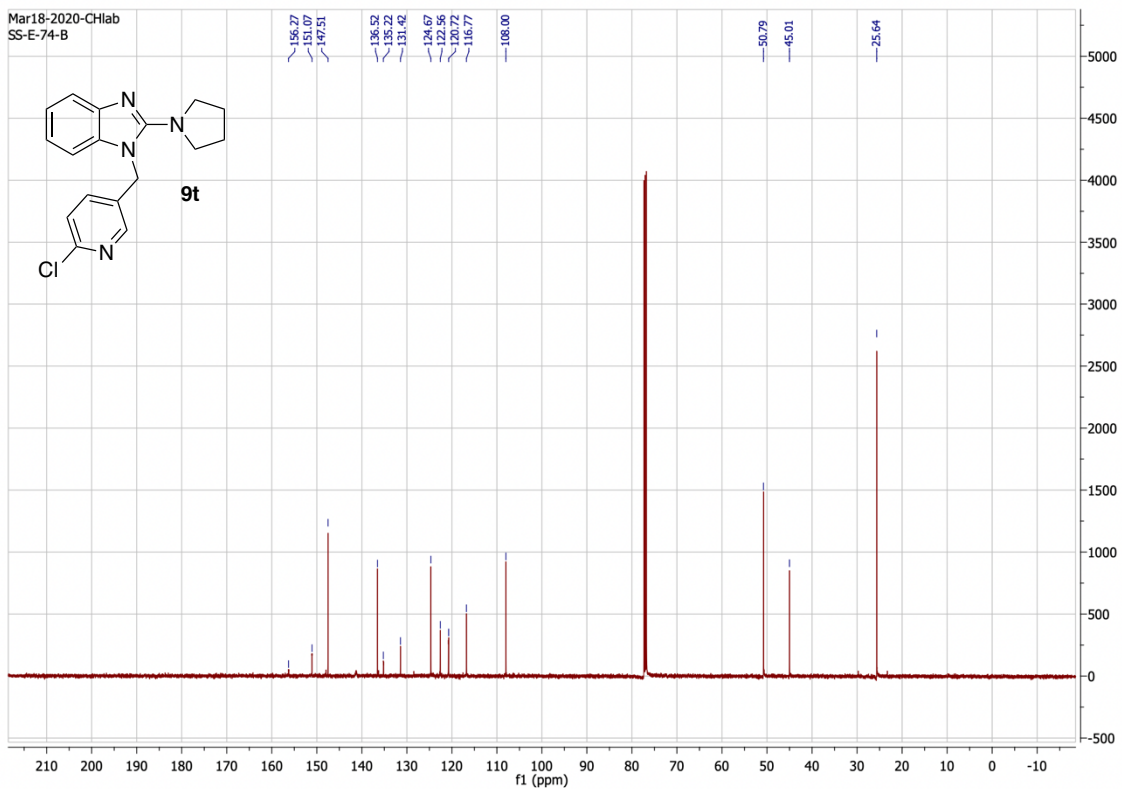
Mar19-2020-CHlab
SS-E-117-B



Mar19-2020-CHlab
SS-E-117-B



Mar18-2020-CHlab
SS-E-74-B

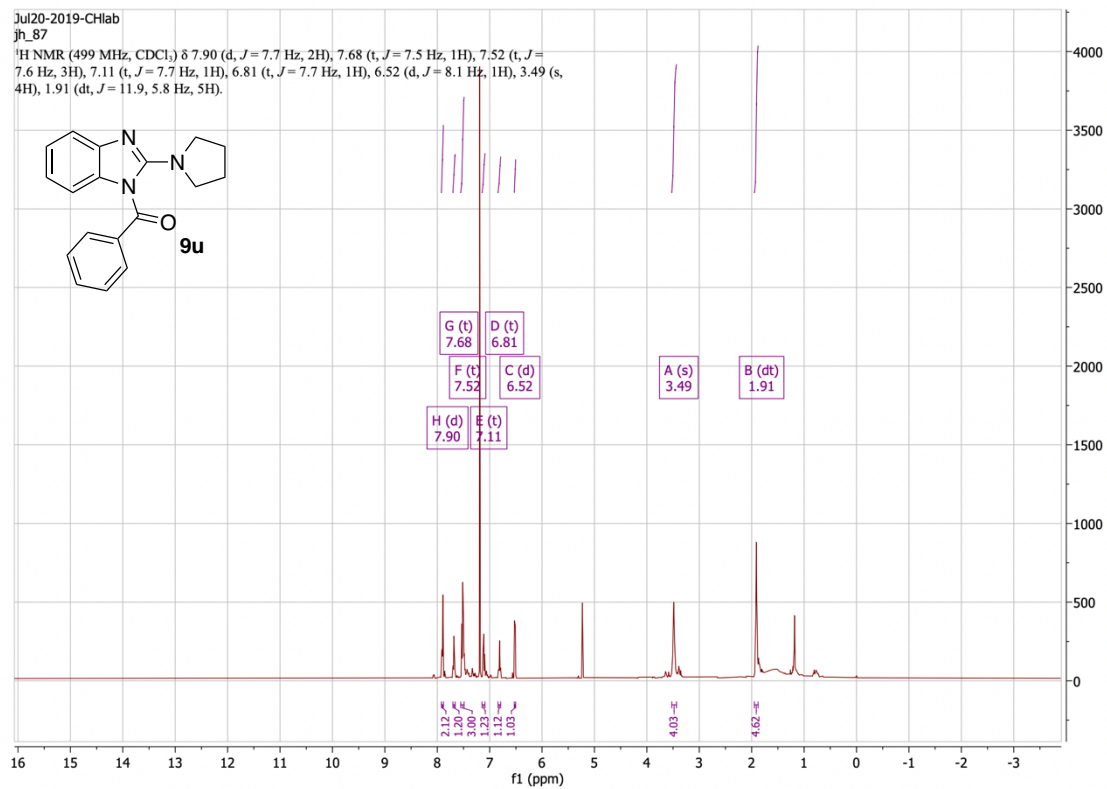
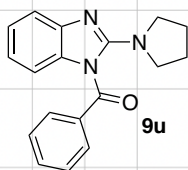


Mar18-2020-CHlab
SS-E-74-B



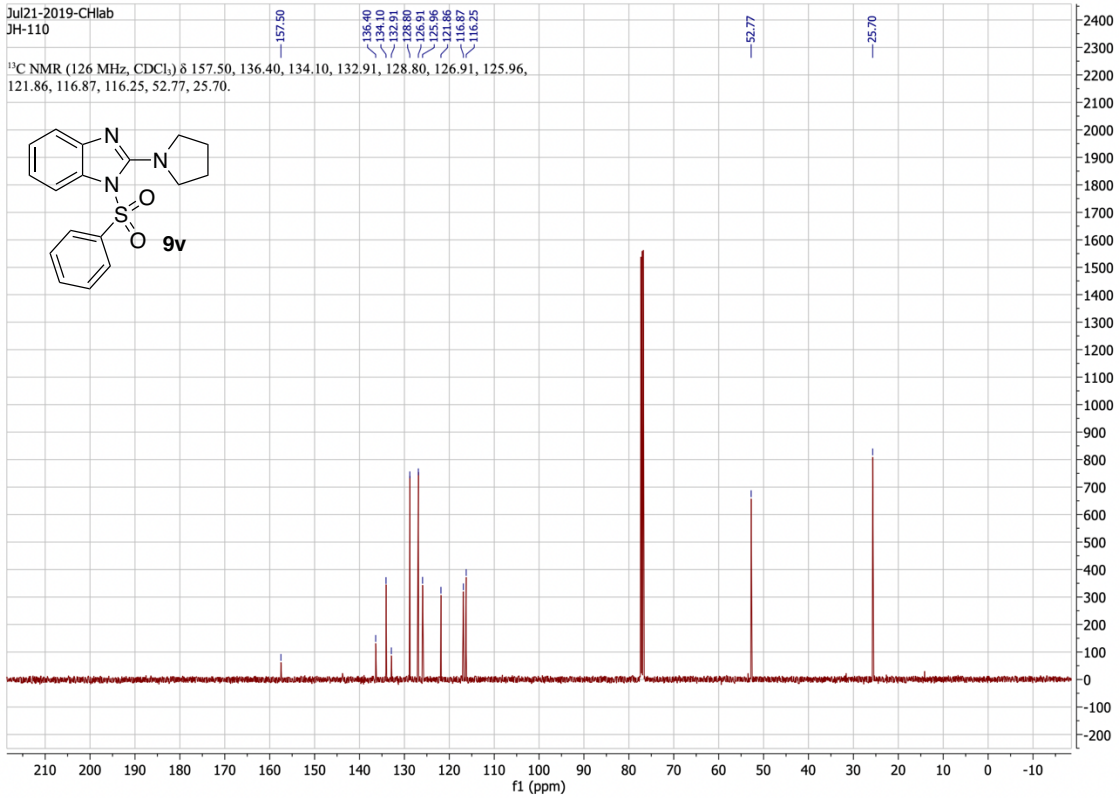
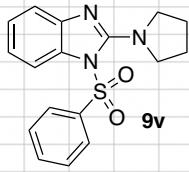
Jul20-2019-CHlab
jh_87

¹H NMR (499 MHz, CDCl₃) δ 7.90 (d, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 3H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 3.49 (s, 4H), 1.91 (dt, *J* = 11.9, 5.8 Hz, 5H).



Jul21-2019-CHlab
JH-110

^{13}C NMR (126 MHz, CDCl_3) δ 157.50, 136.40, 134.10, 132.91, 128.80, 126.91, 125.96, 121.86, 116.87, 116.25, 52.77, 25.70.

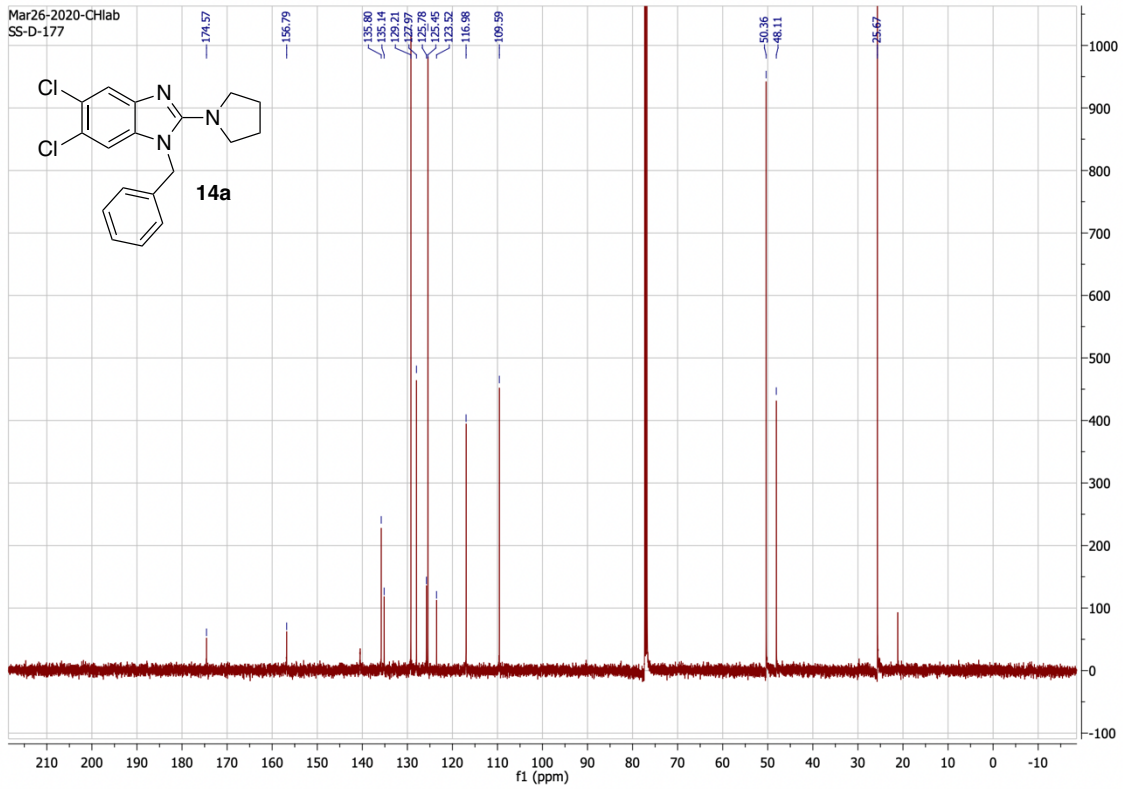


Jul21-2019-CHlab
JH-110

^1H NMR (499 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 1H), 7.60 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.24 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.19 (td, $J = 7.6, 1.2$ Hz, 1H), 7.10 (td, $J = 7.7, 1.4$ Hz, 1H), 3.75 (td, $J = 6.7, 5.4, 3.0$ Hz, 4H), 2.02 - 1.97 (m, 4H).



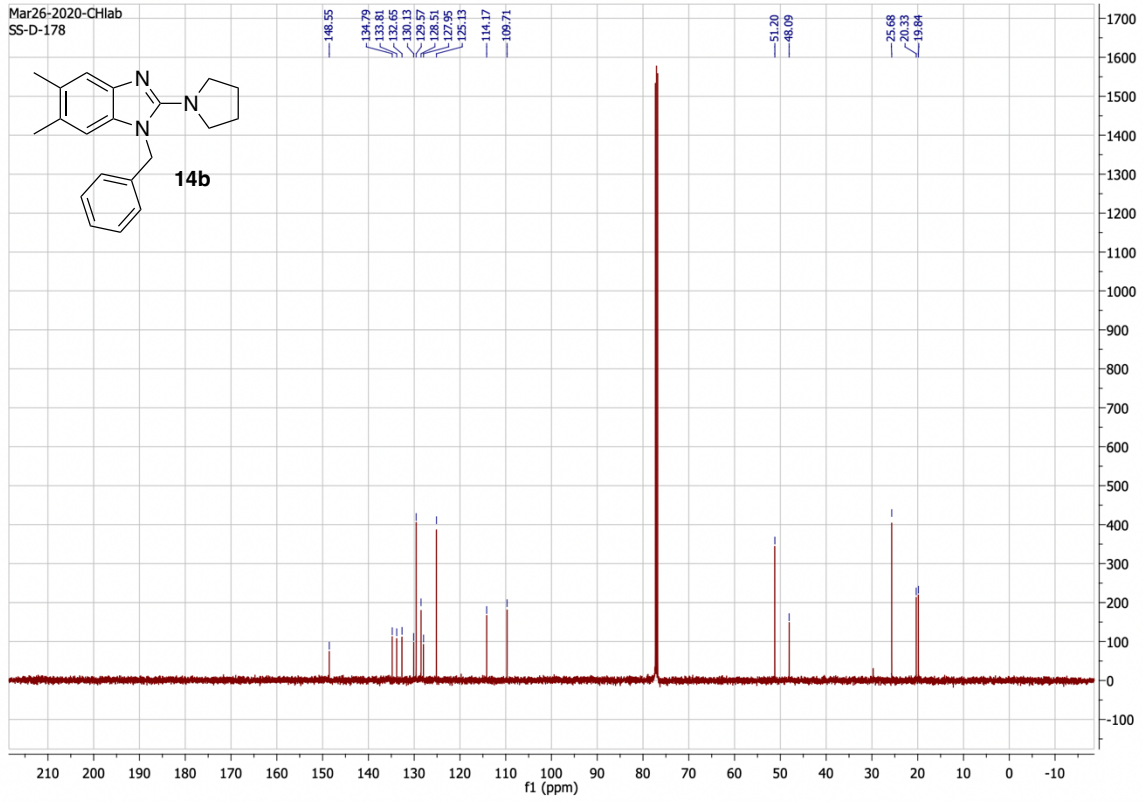
Mar26-2020-CHlab
SS-D-177



Mar26-2020-CHlab
SS-D-177

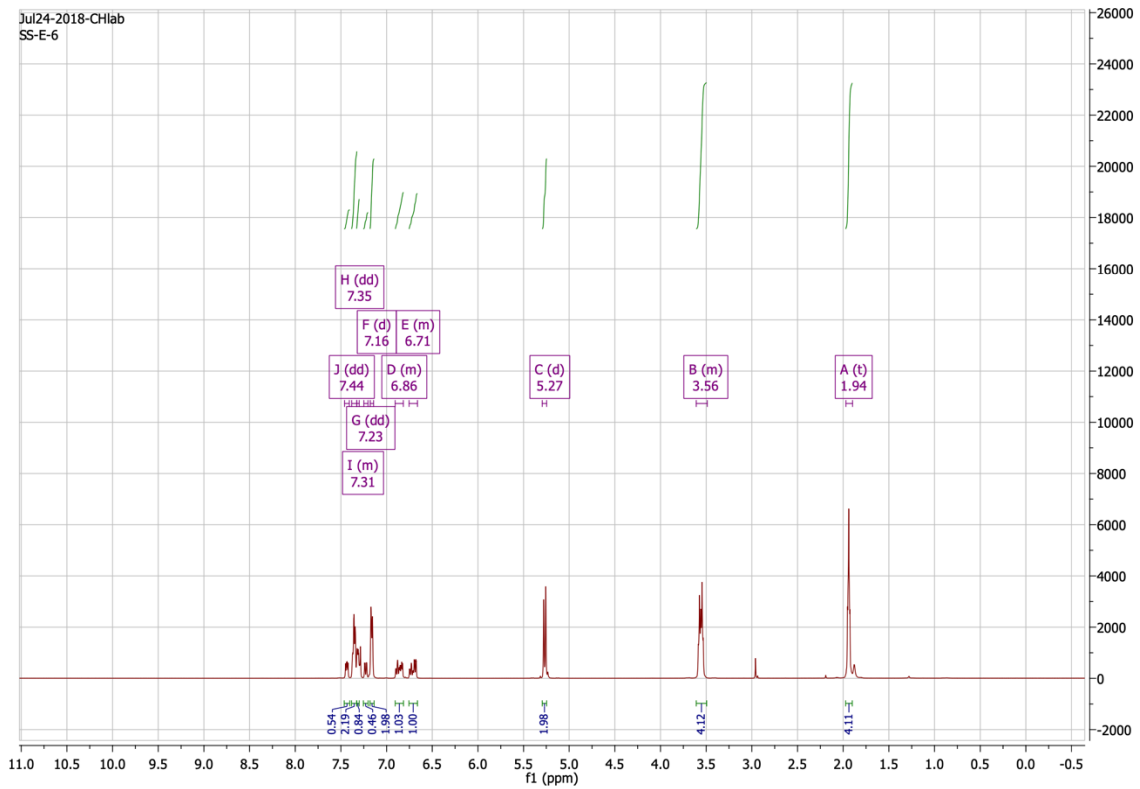
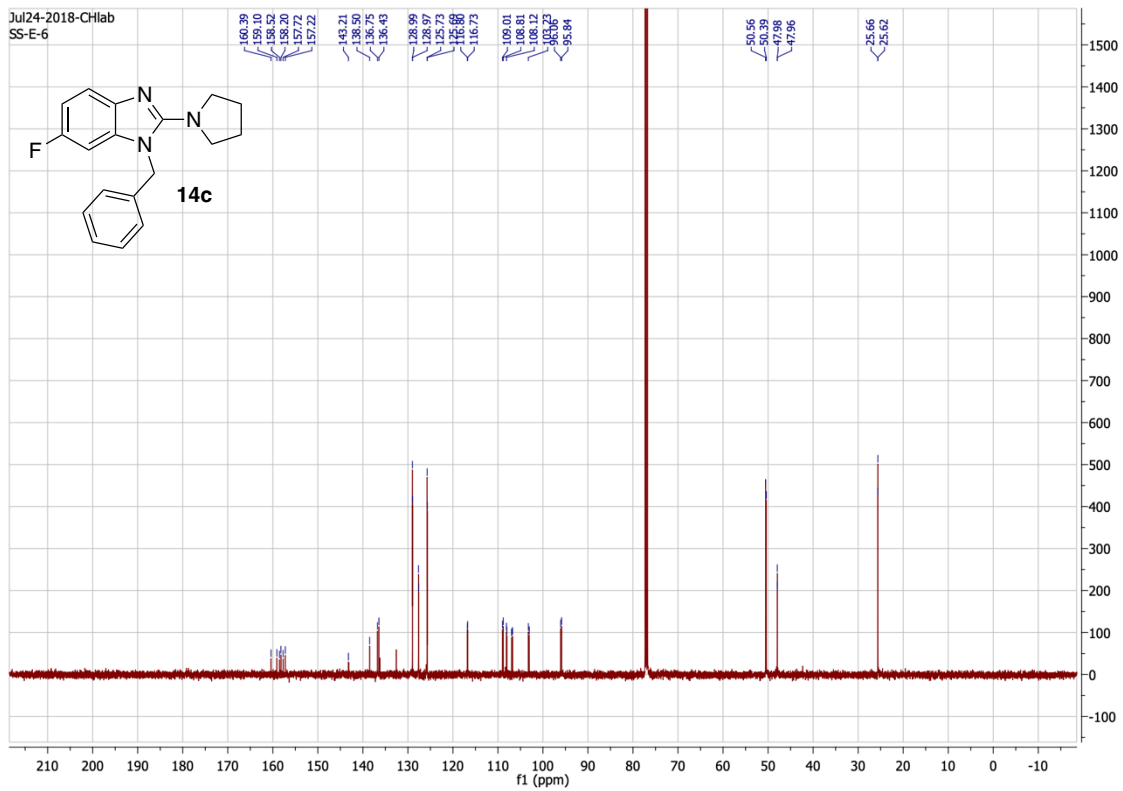


Mar26-2020-CHlab
SS-D-178

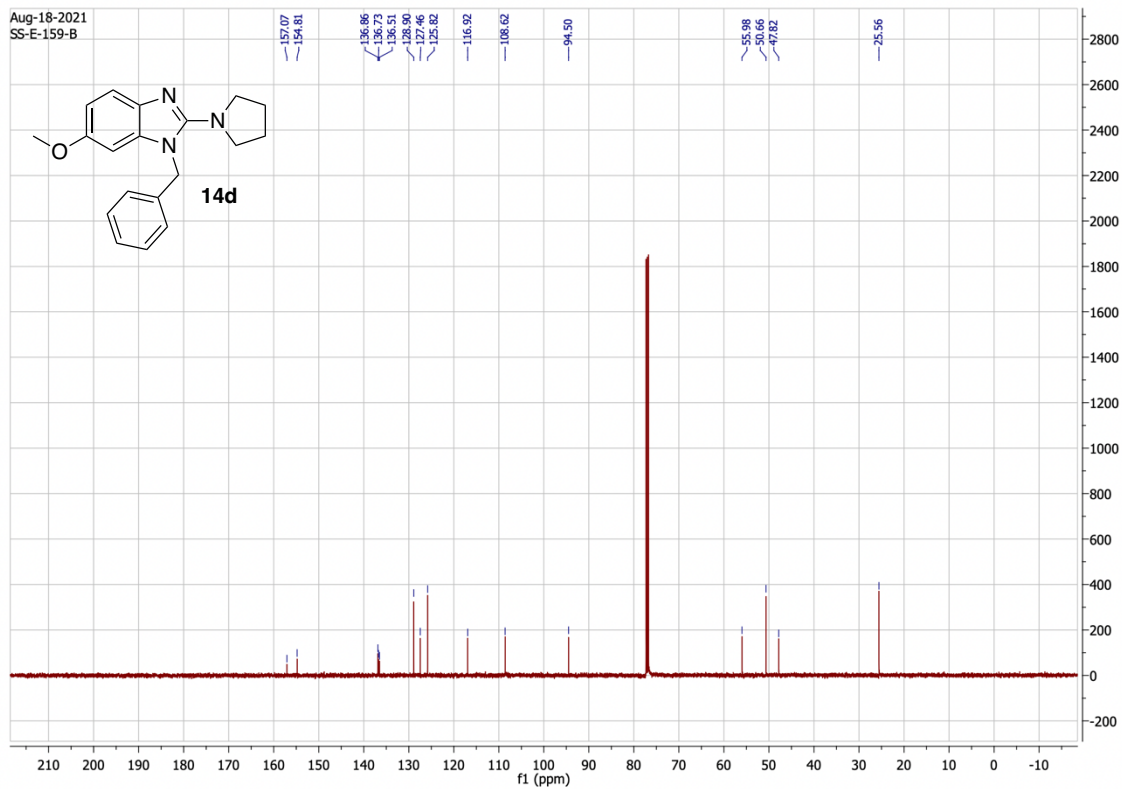


Mar26-2020-CHlab
SS-D-178

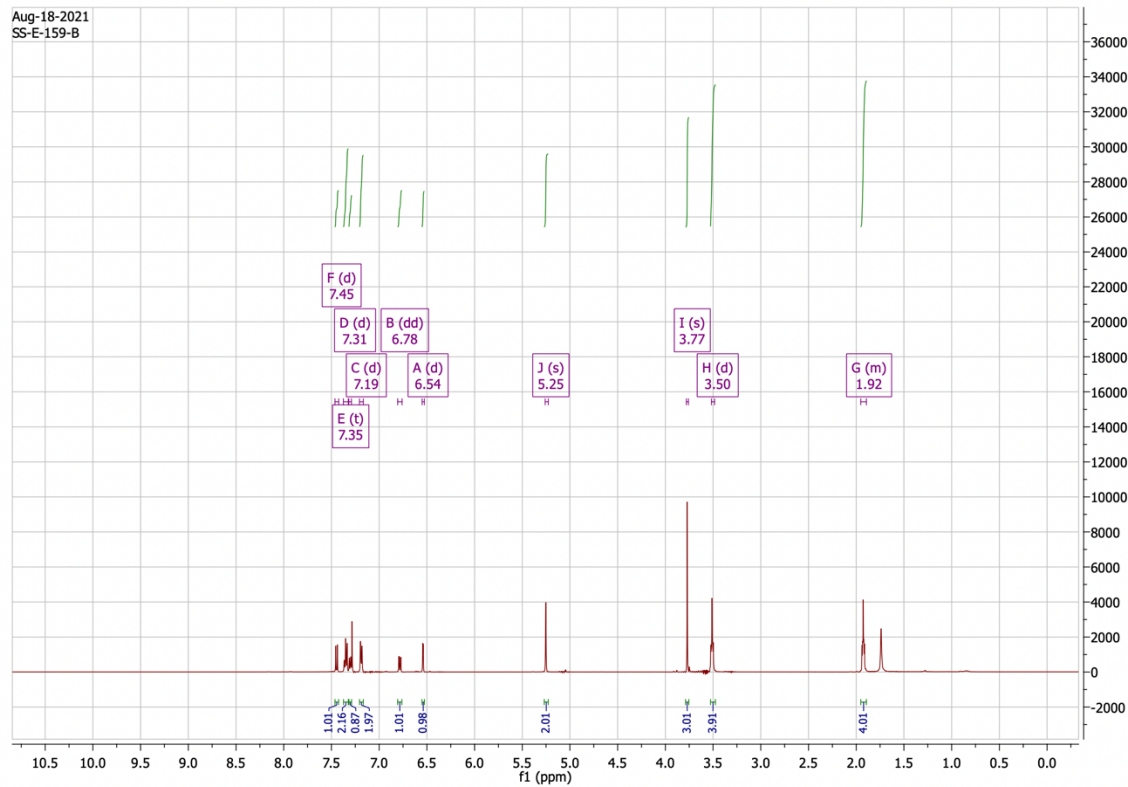


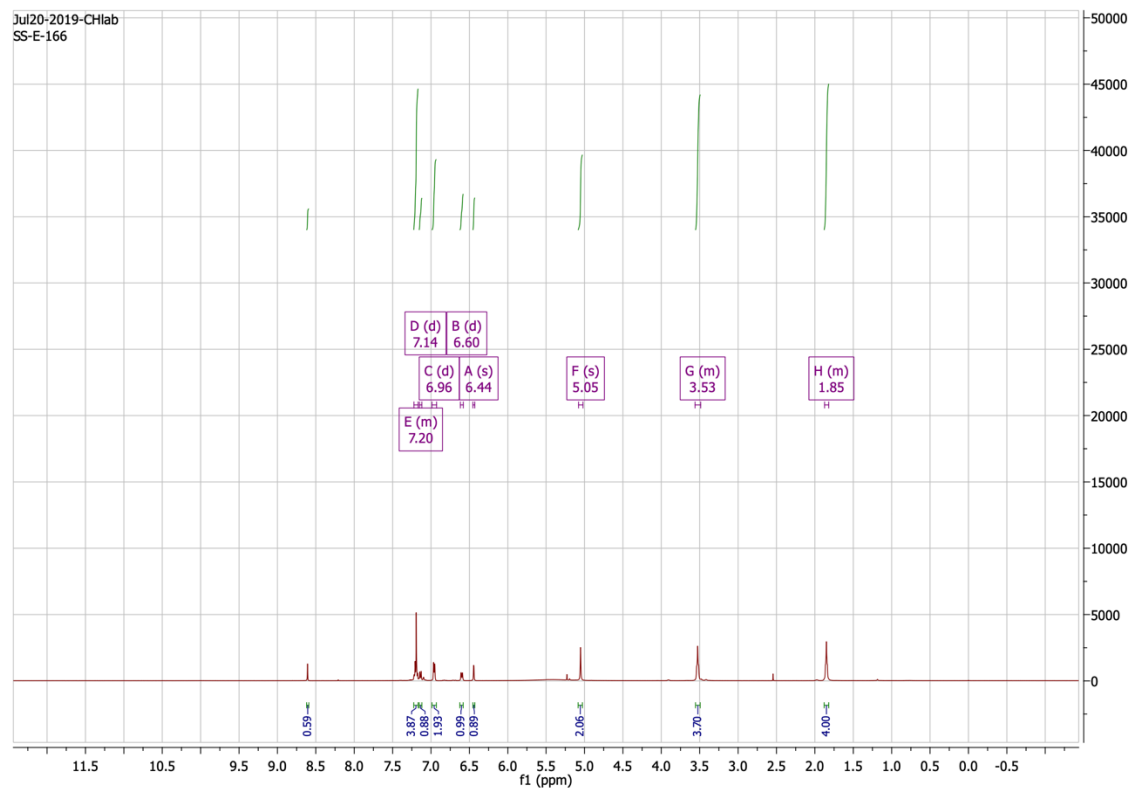
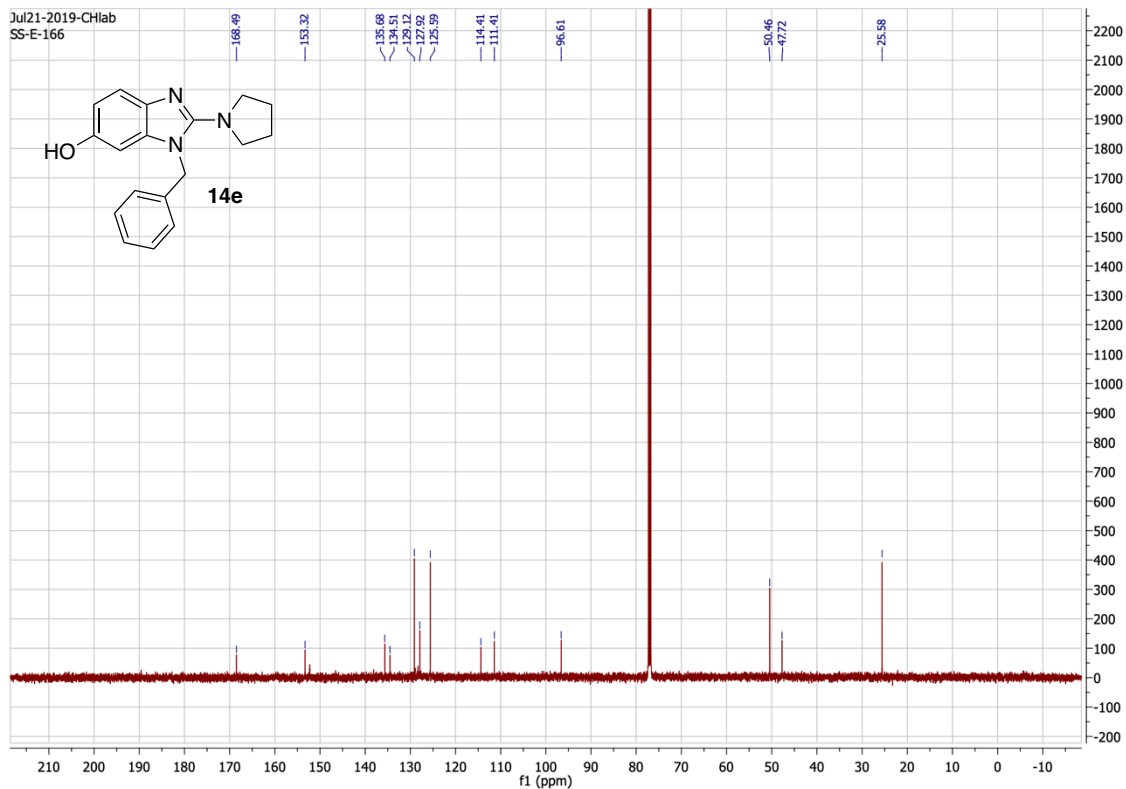


Aug-18-2021
SS-E-159-B

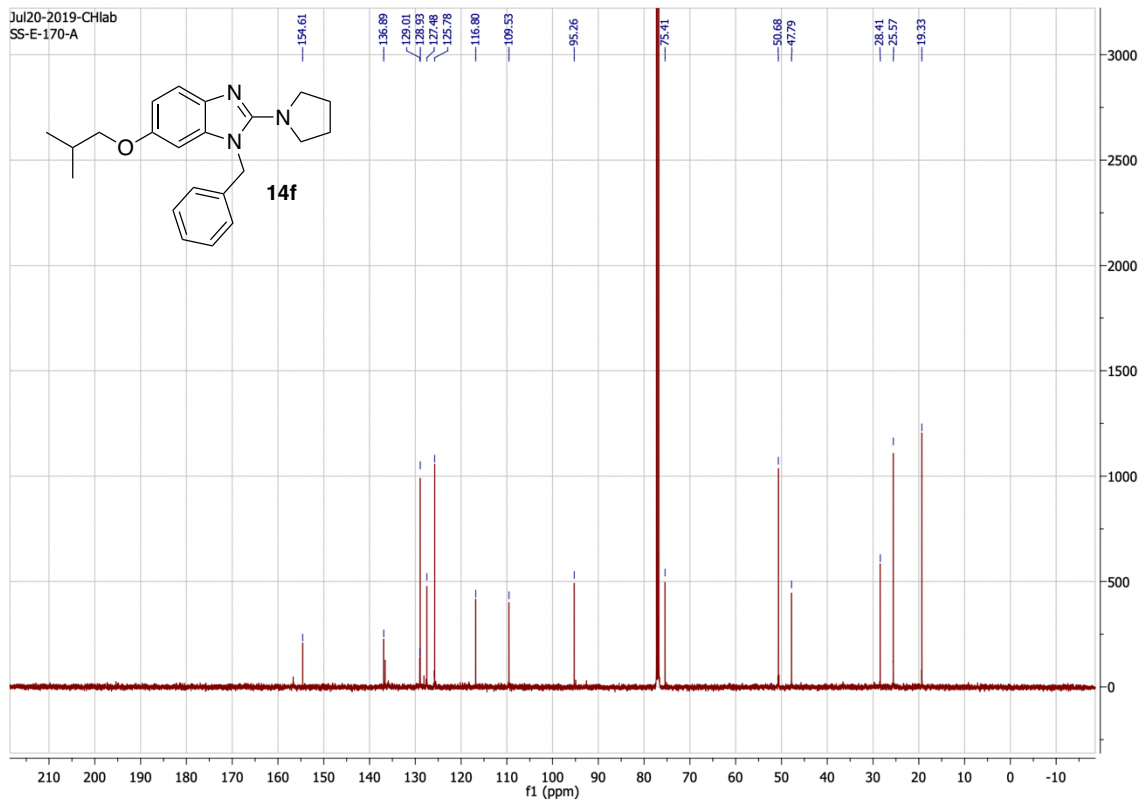


Aug-18-2021
SS-E-159-B

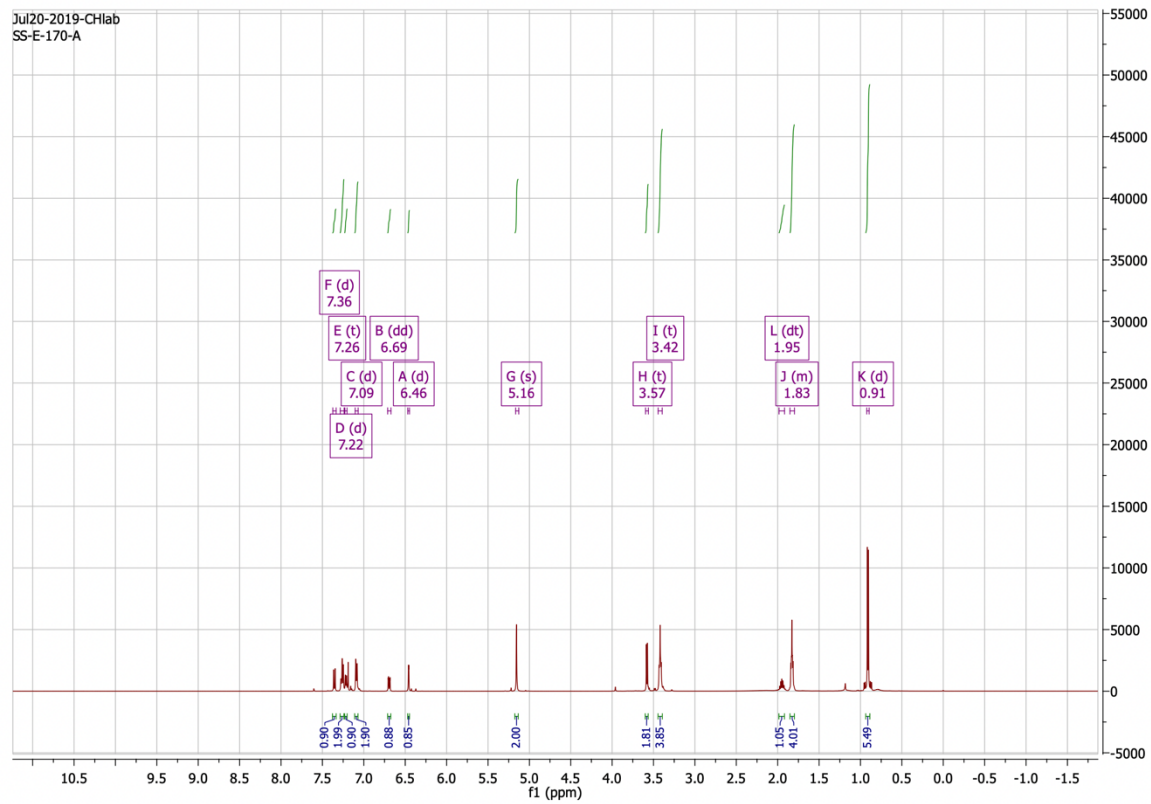




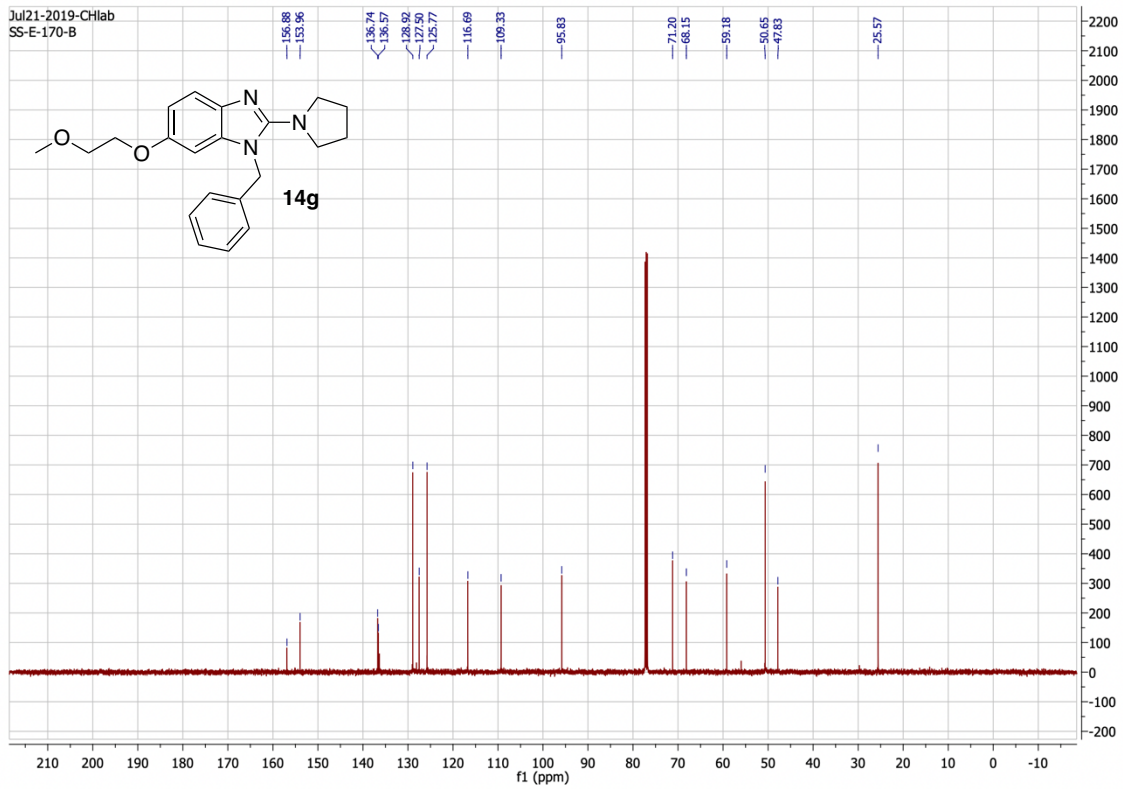
Jul20-2019-CHlab
SS-E-170-A



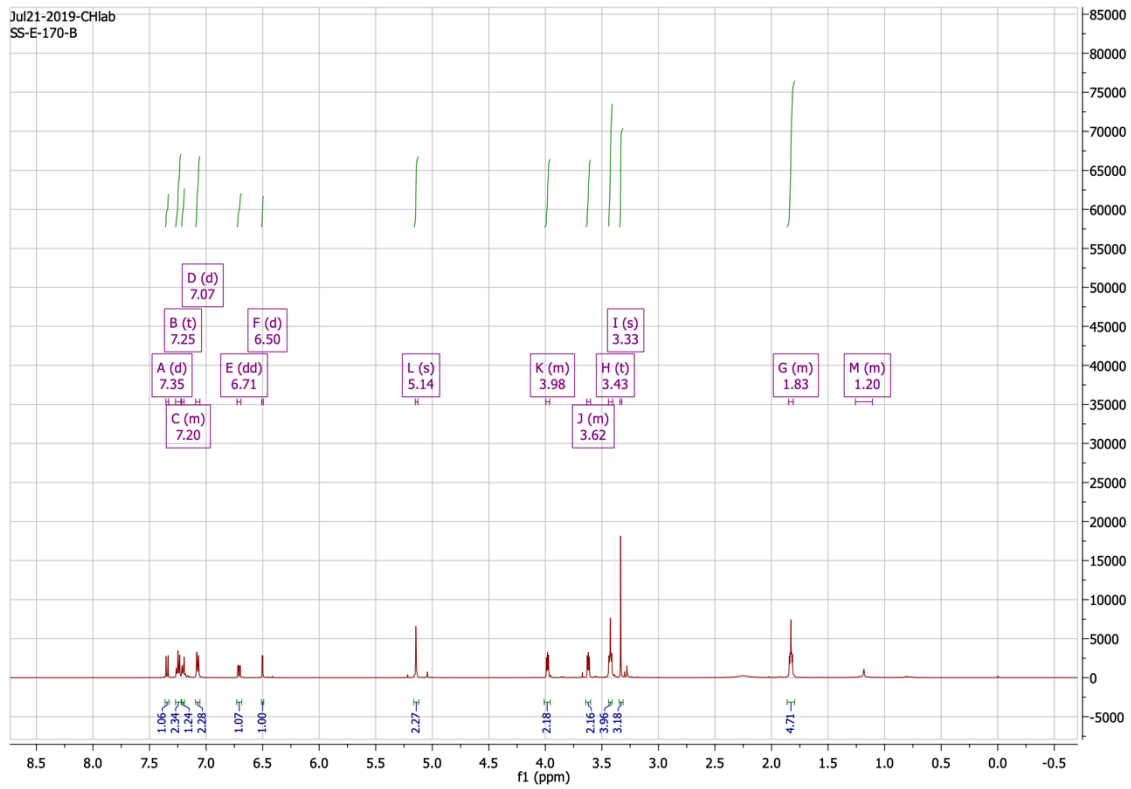
Jul20-2019-CHlab
SS-E-170-A



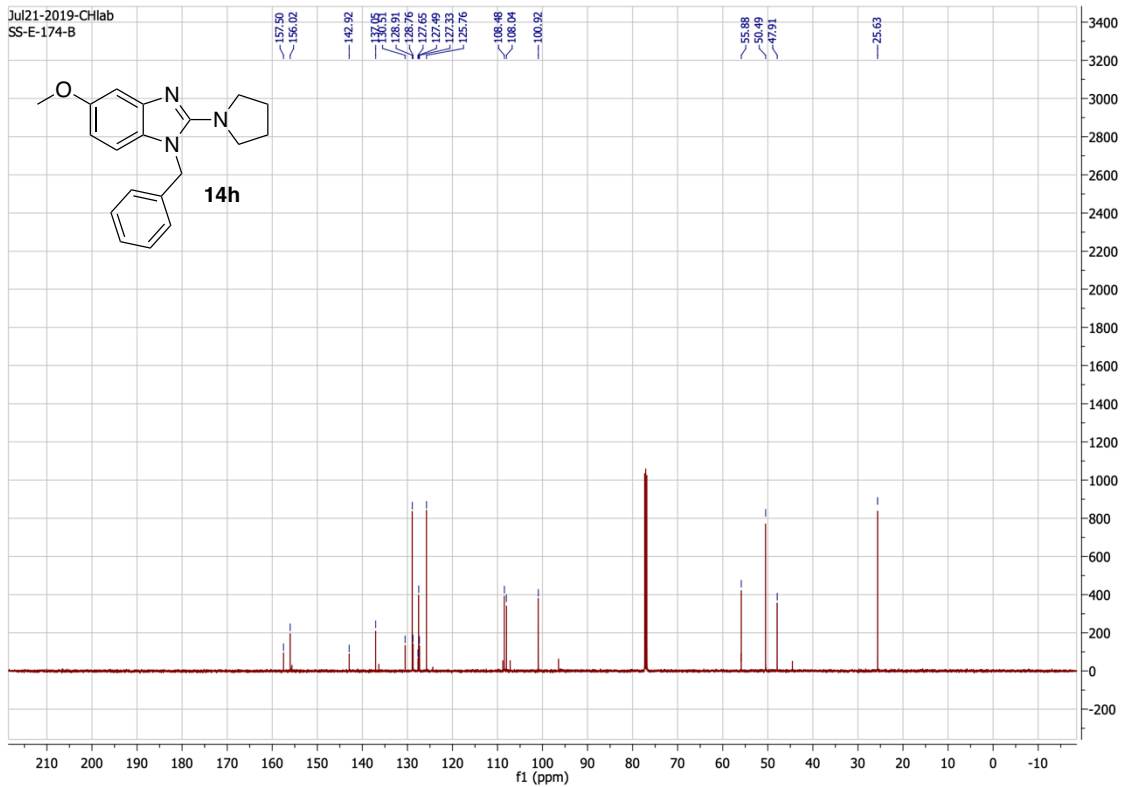
Jul21-2019-CHlab
SS-E-170-B



Jul21-2019-CHlab
SS-E-170-B



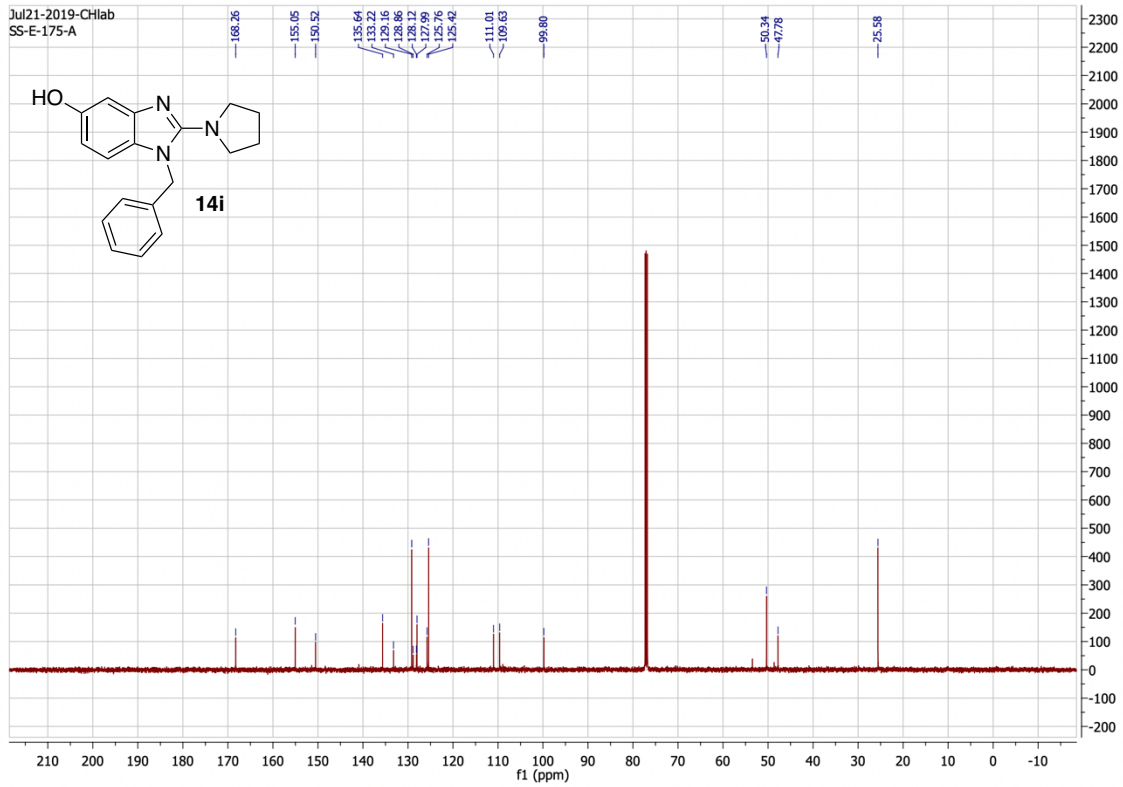
Jul21-2019-CHlab
SS-E-174-B



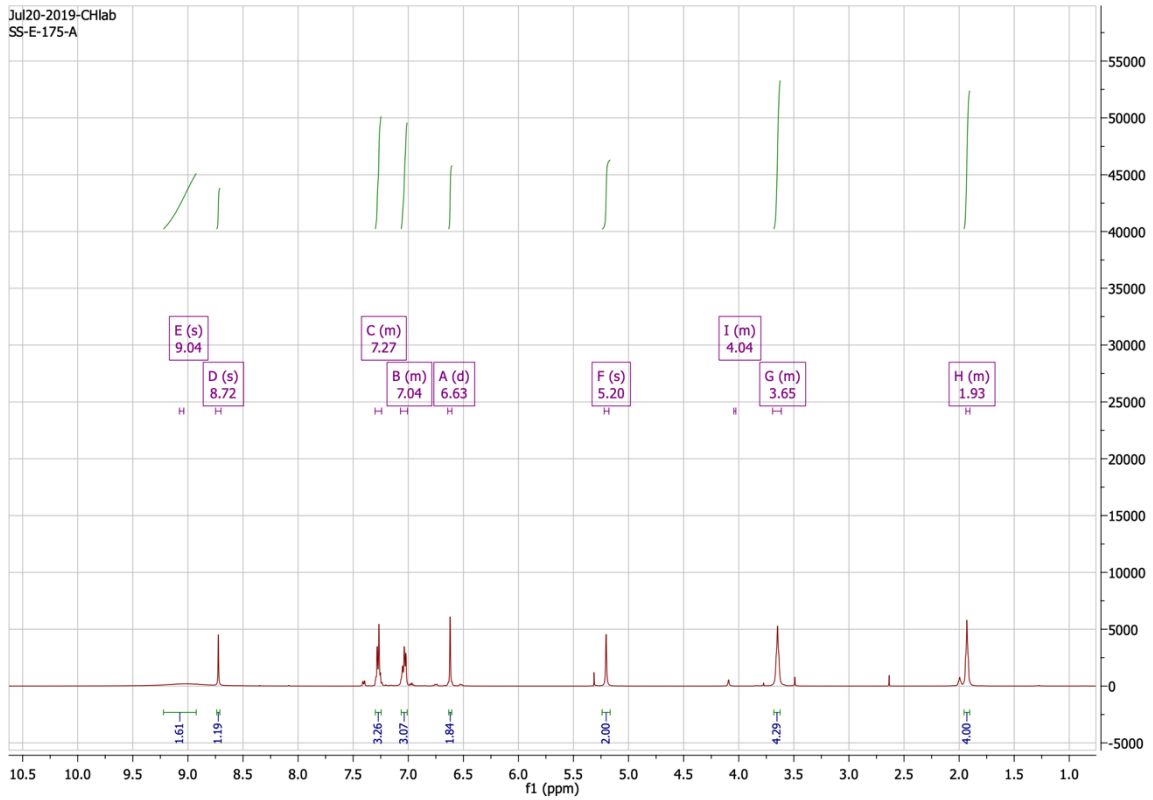
Jul21-2019-CHlab
SS-E-174-B



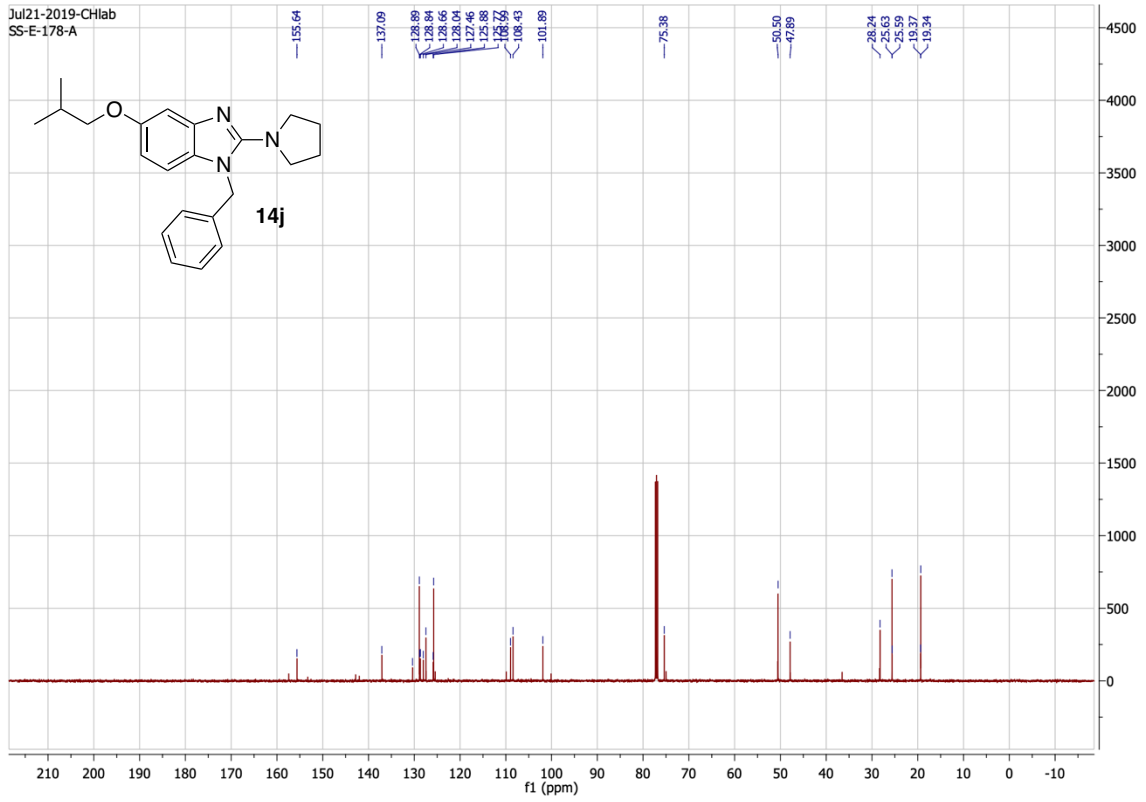
Jul21-2019-CHlab
SS-E-175-A



Jul20-2019-CHlab
SS-E-175-A

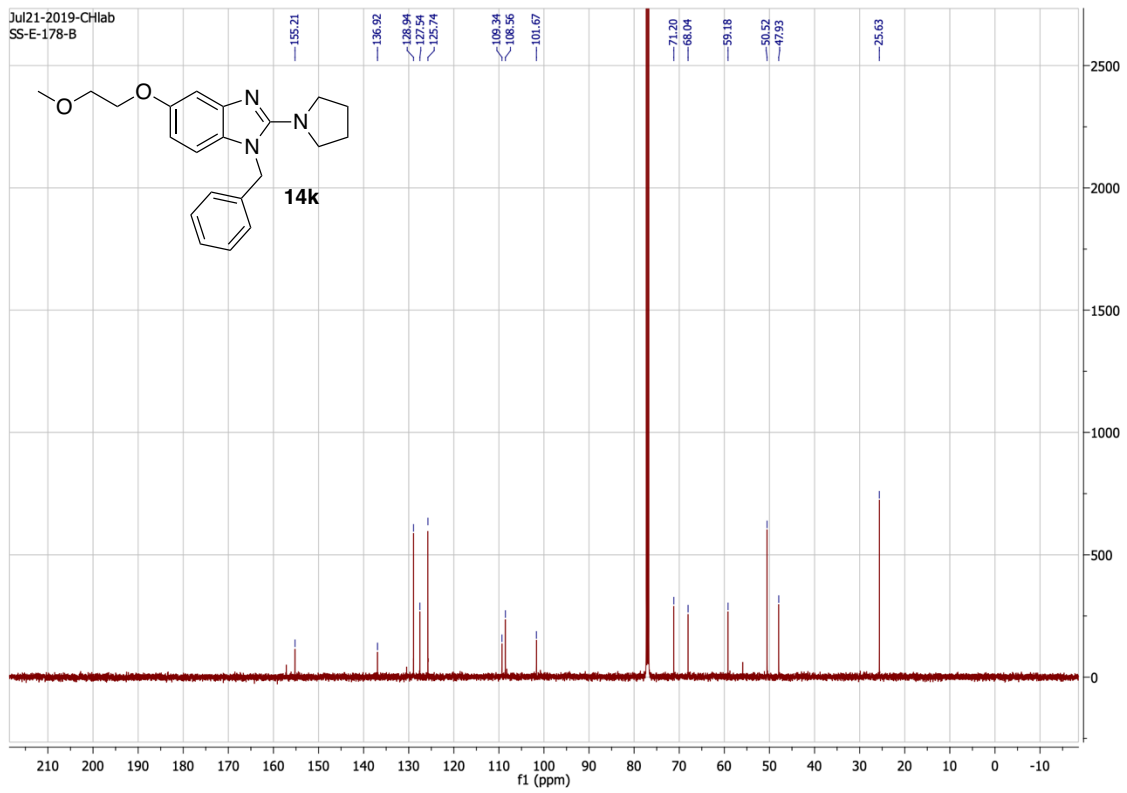


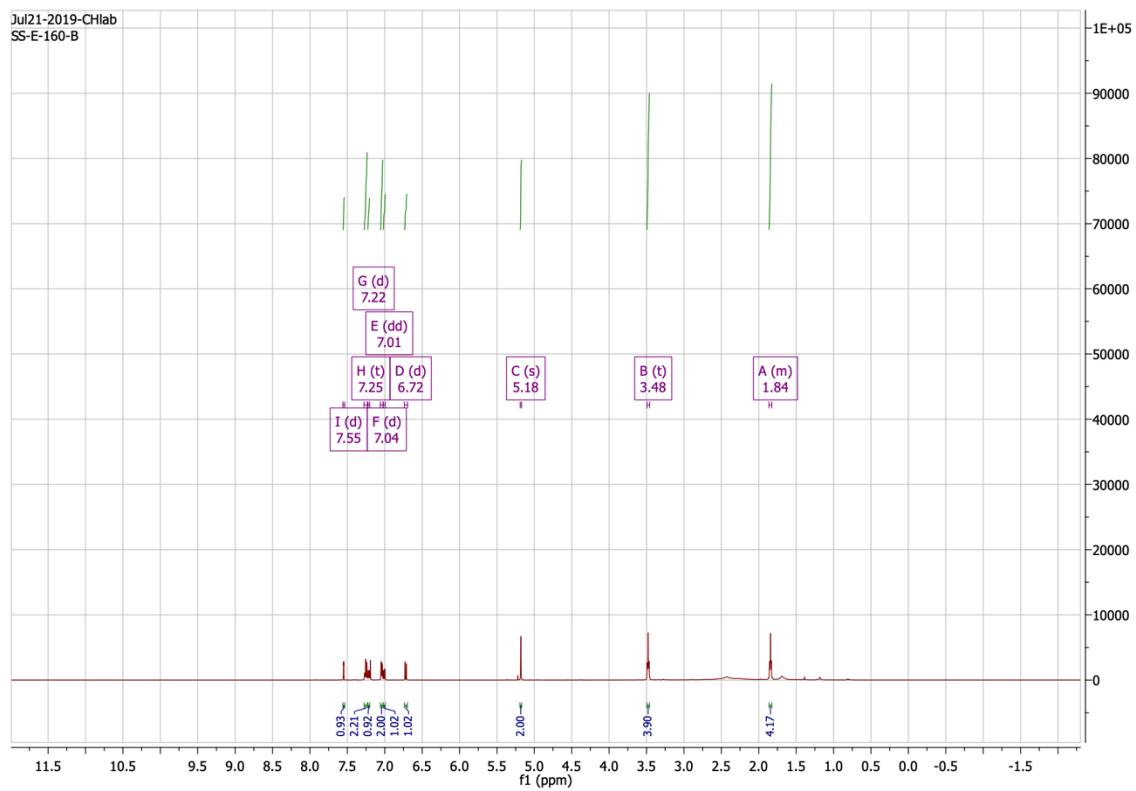
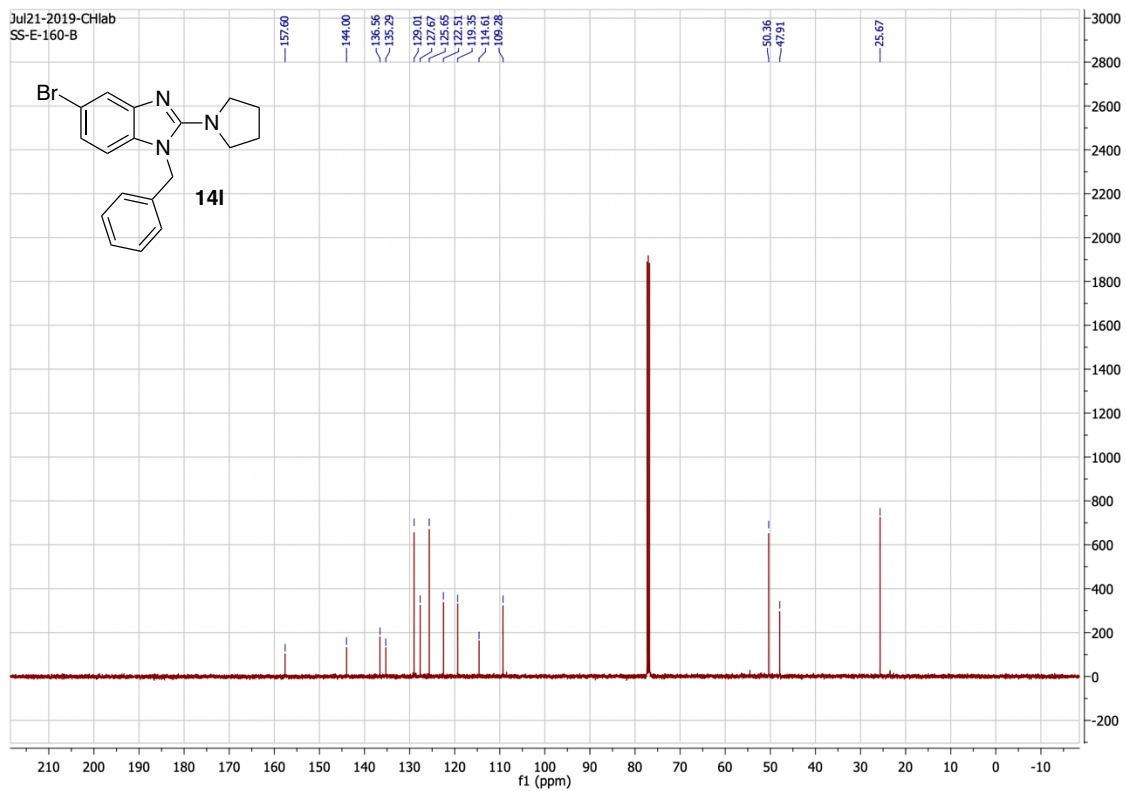
Jul21-2019-CHlab
SS-E-178-A



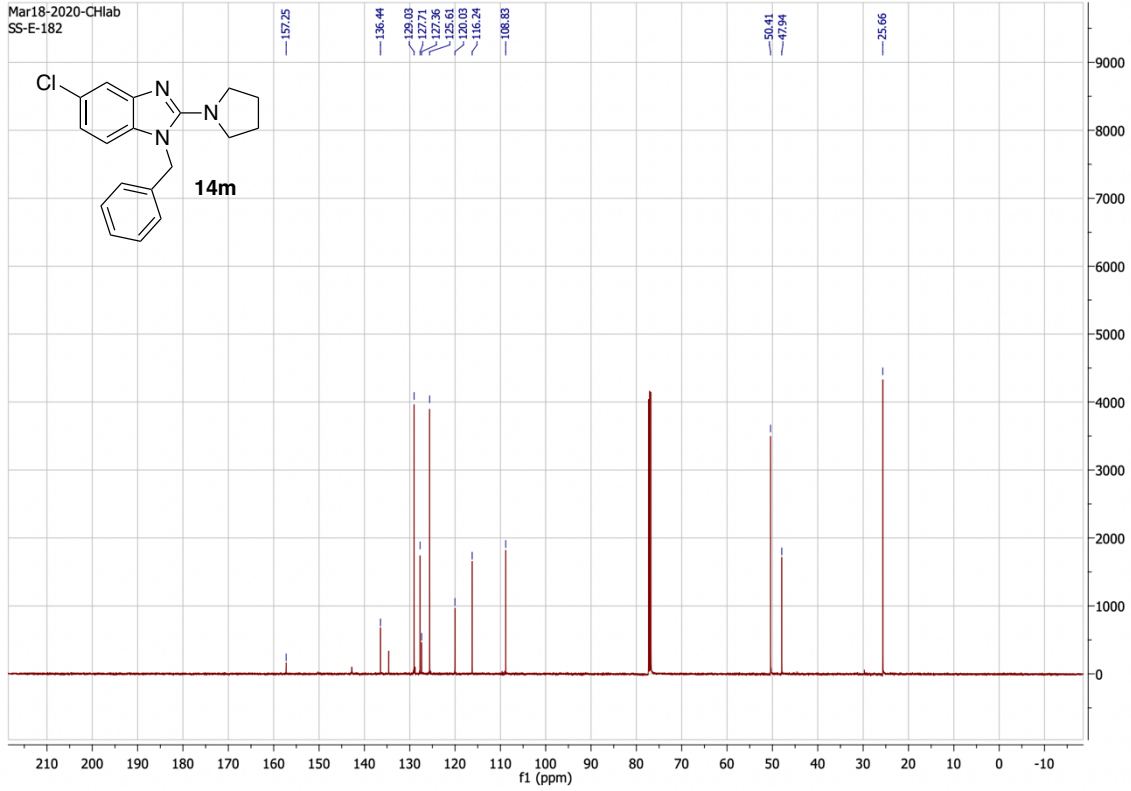
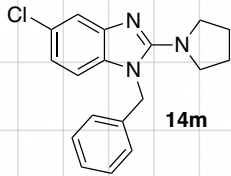
Jul21-2019-CHlab
SS-E-178-A



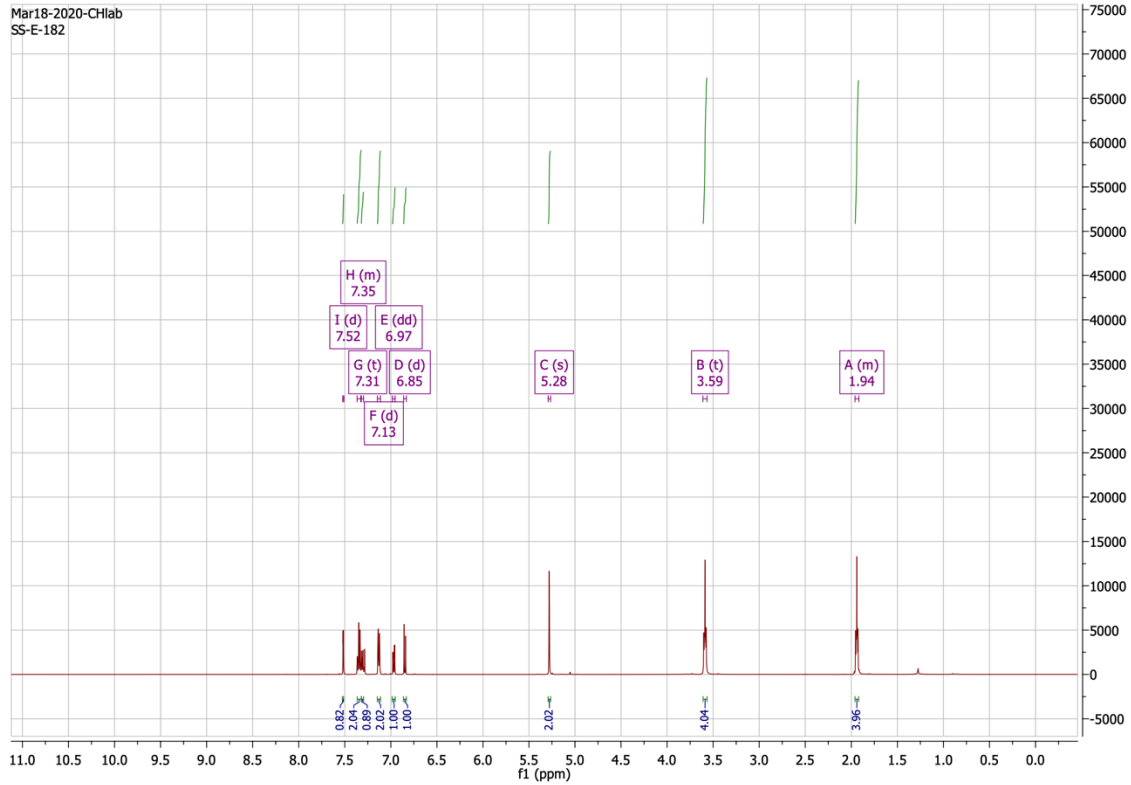




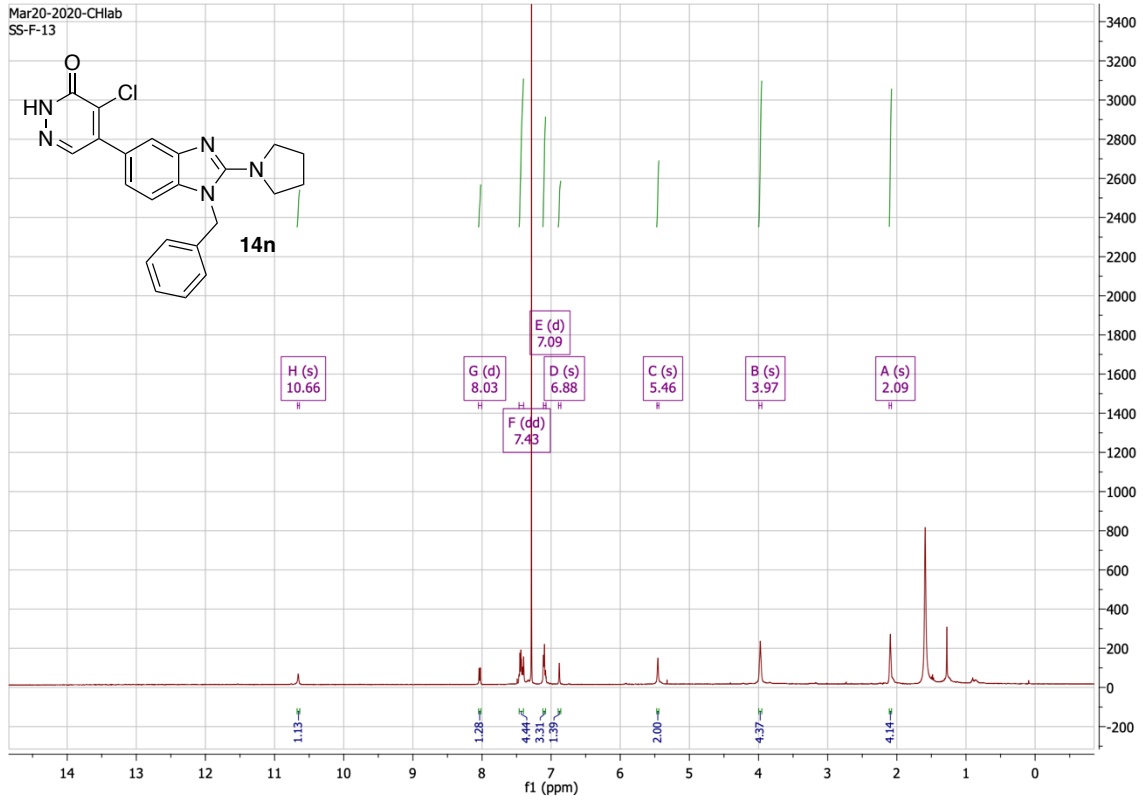
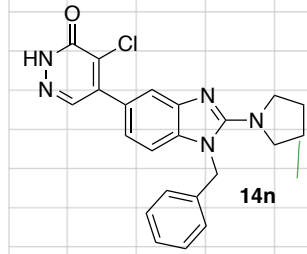
Mar18-2020-CHlab
SS-E-182



Mar18-2020-CHlab
SS-E-182

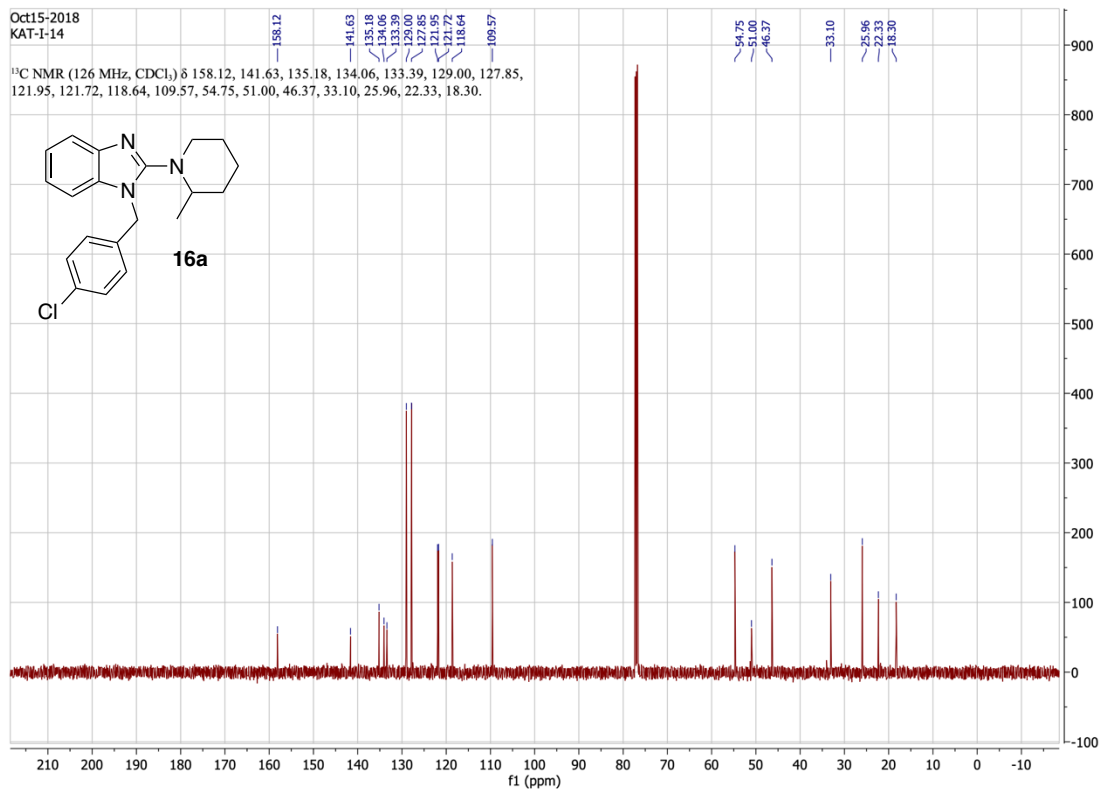
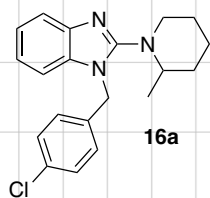


Mar20-2020-CHlab
SS-F-13



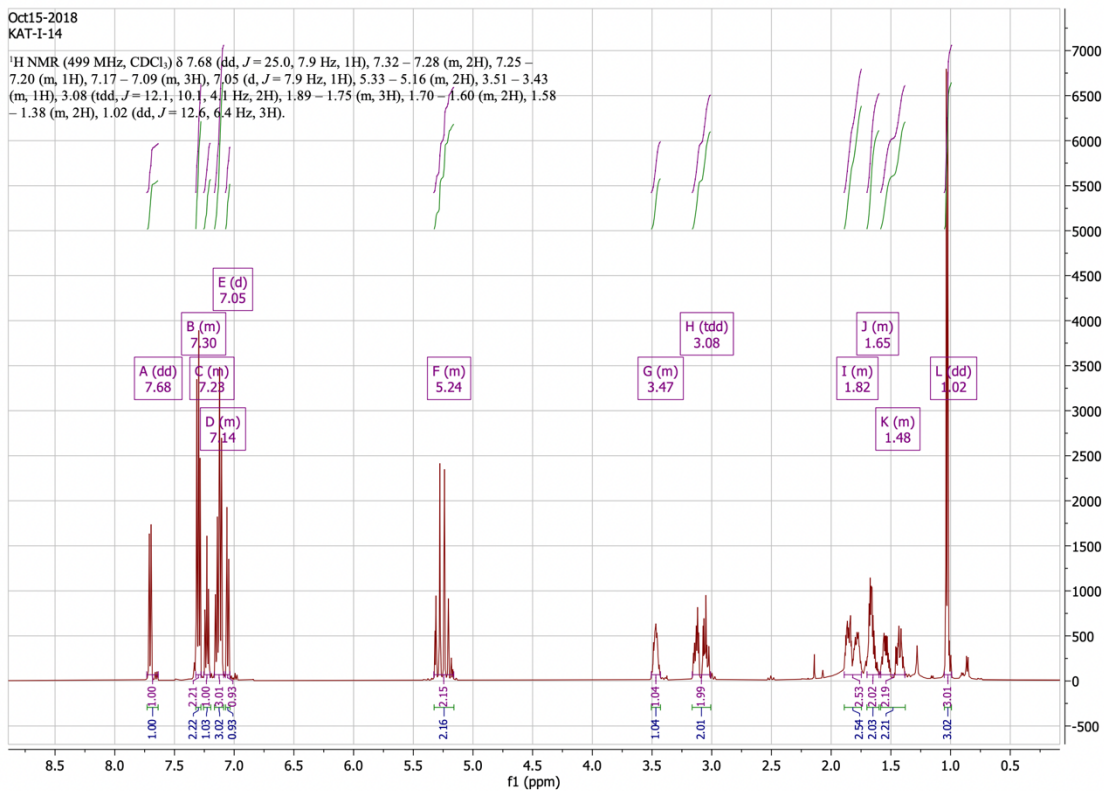
Oct15-2018
KAT-I-14

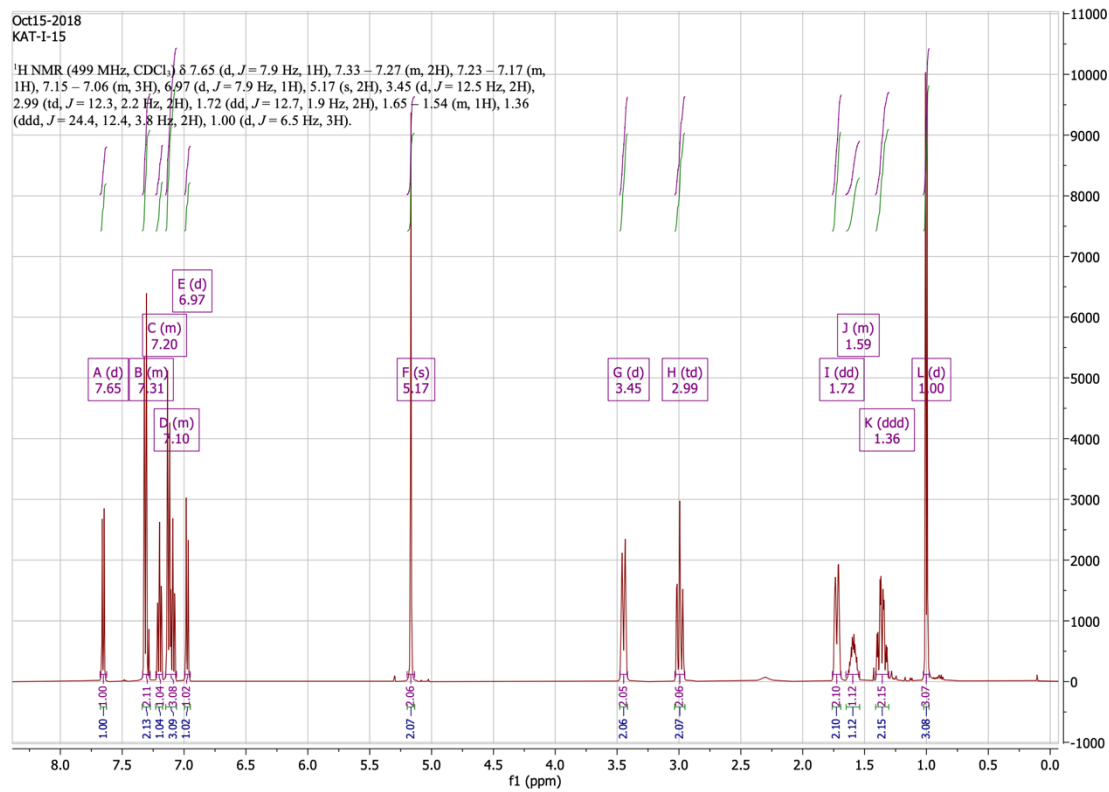
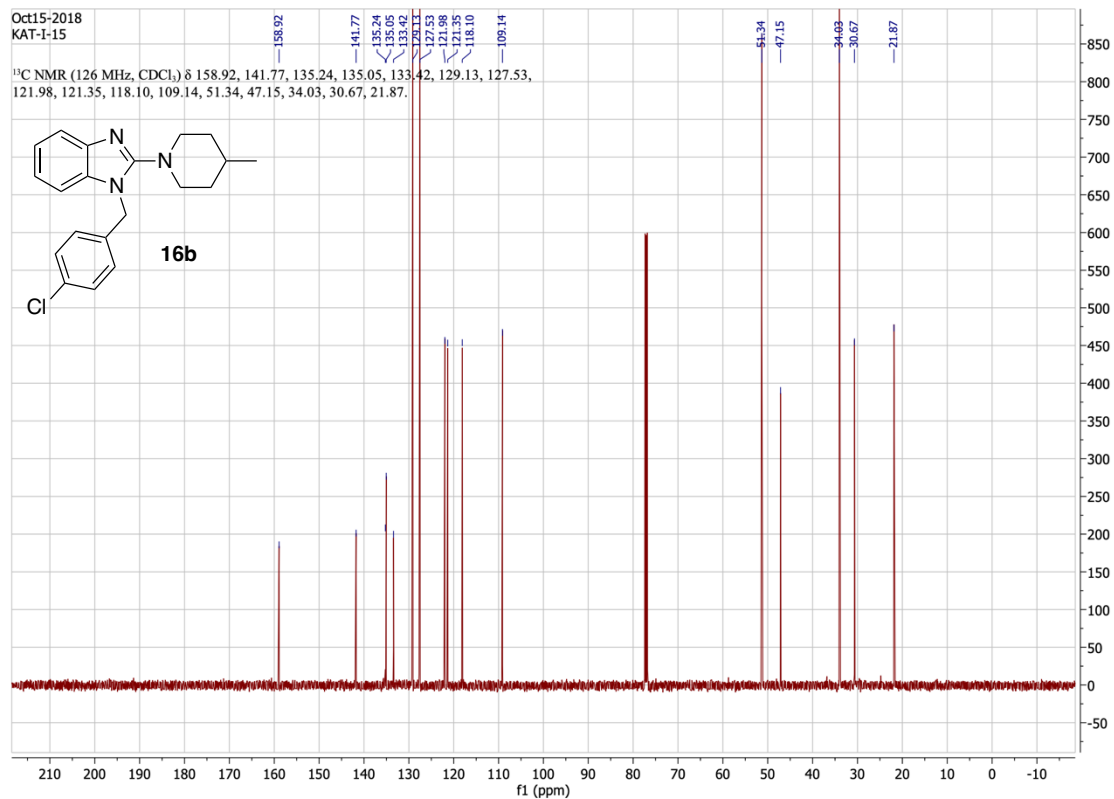
^{13}C NMR (126 MHz, CDCl_3) δ 158.12, 141.63, 135.18, 134.06, 133.39, 129.00, 127.85, 121.95, 121.72, 118.64, 109.57, 54.75, 51.00, 46.37, 33.10, 25.96, 22.33, 18.30.

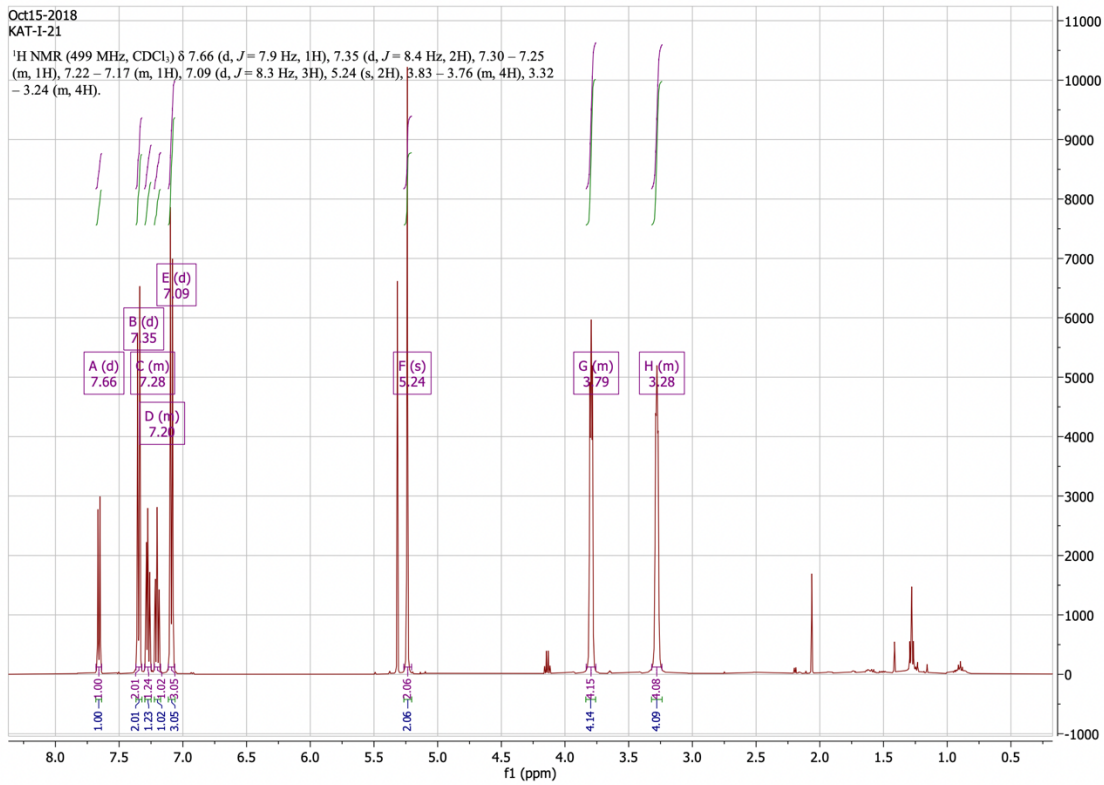
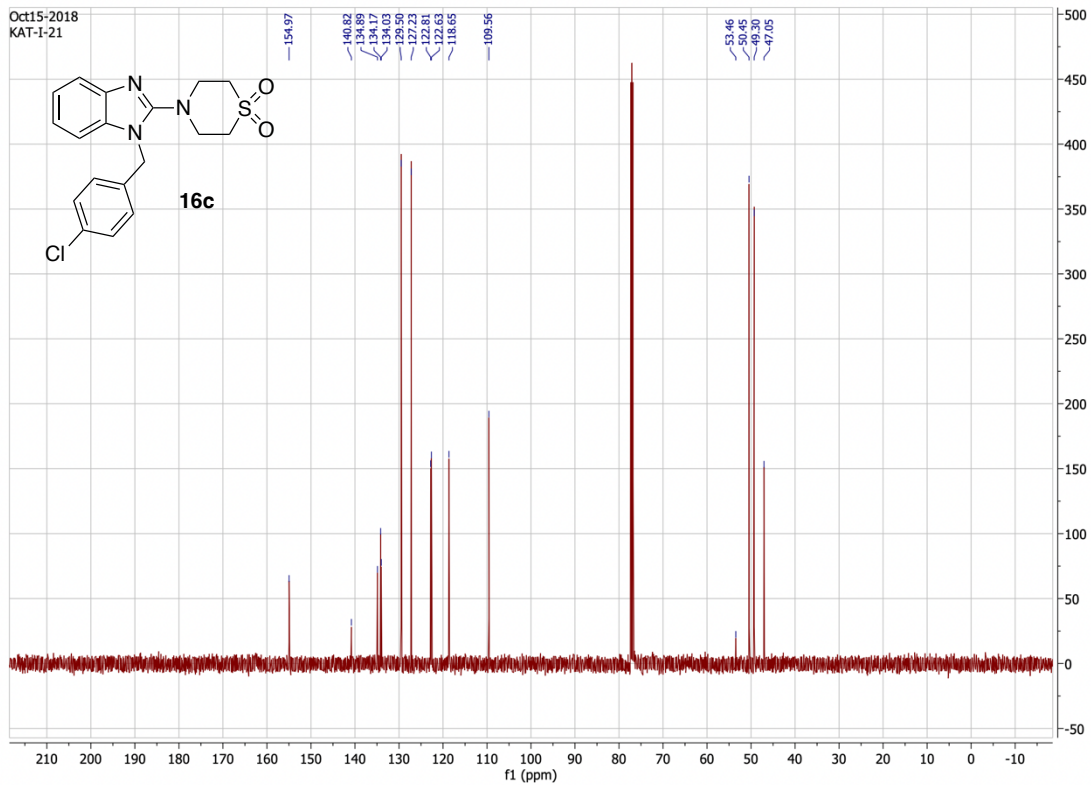


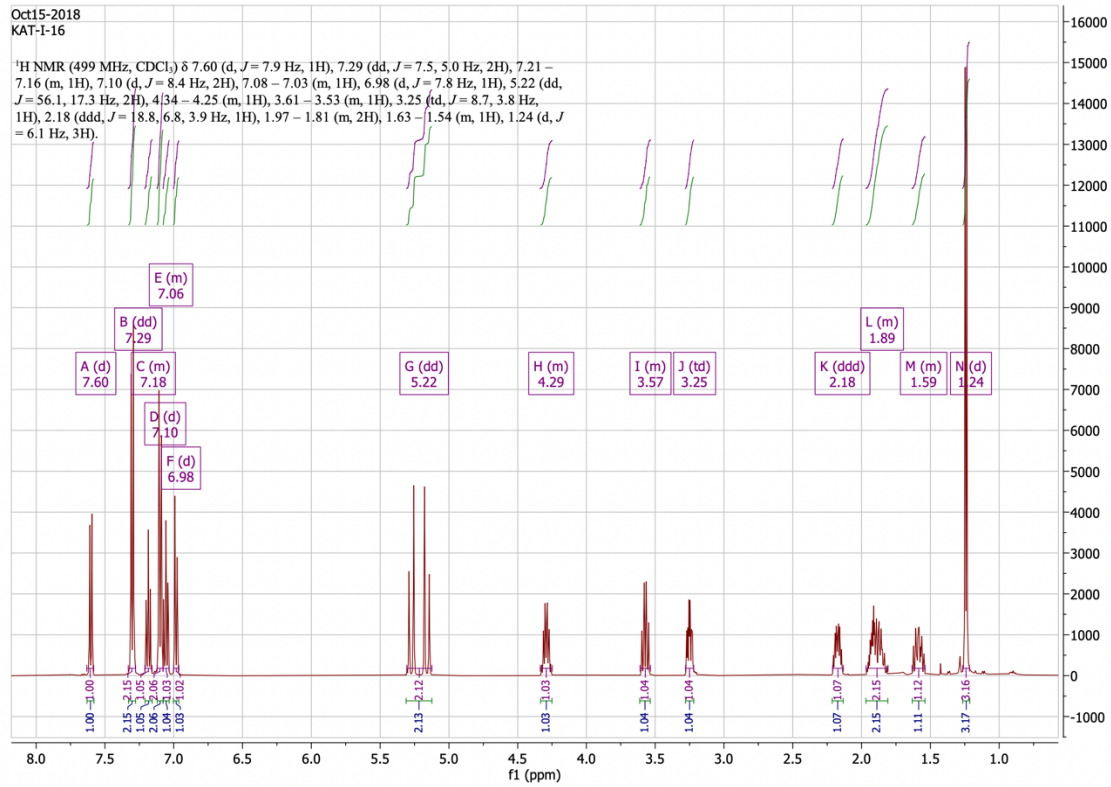
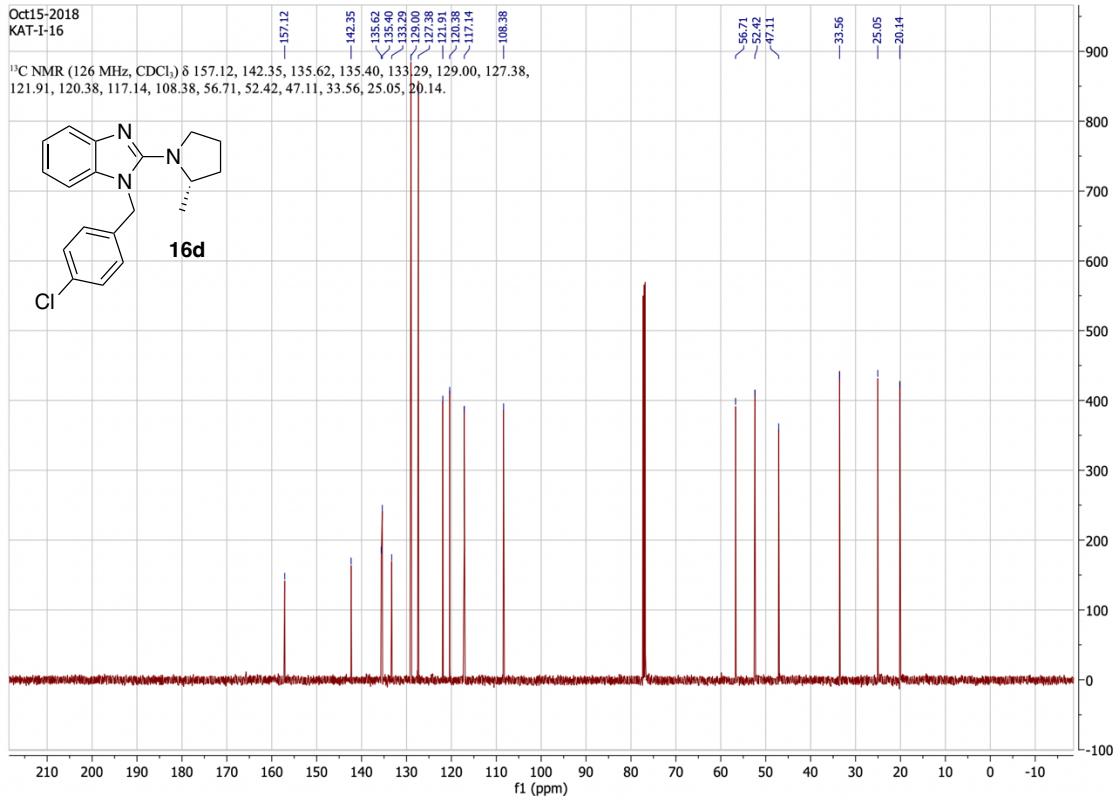
Oct15-2018
KAT-I-14

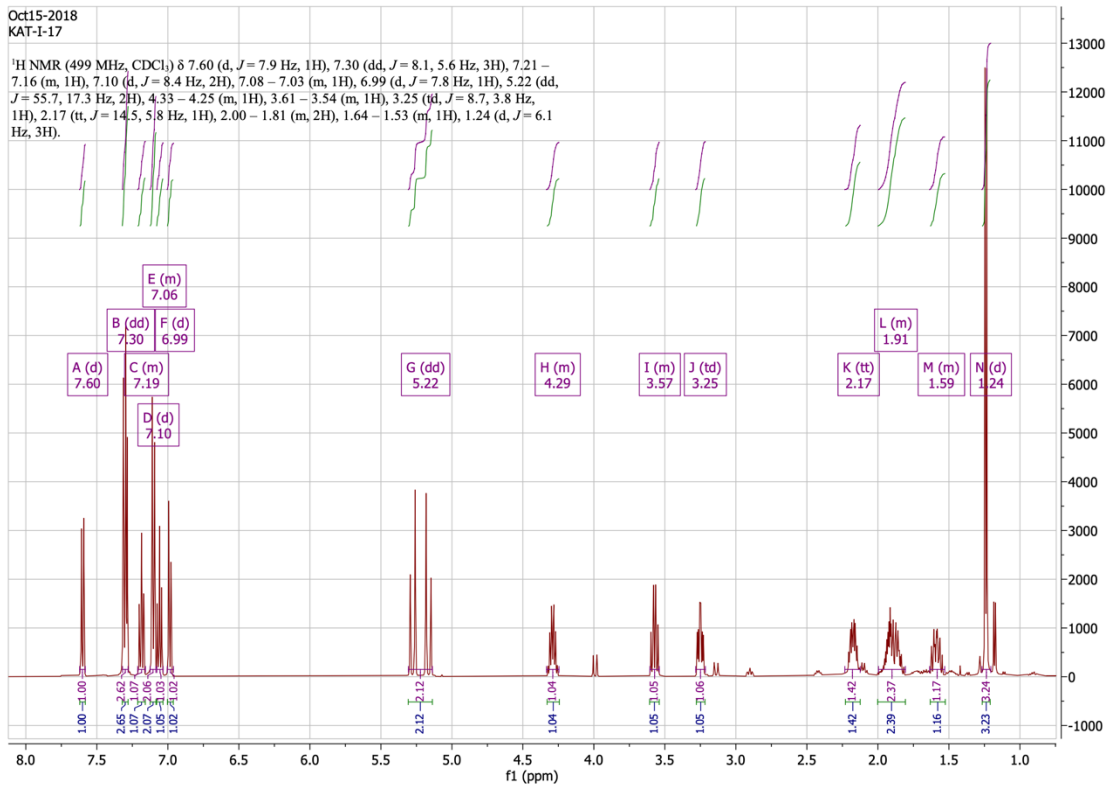
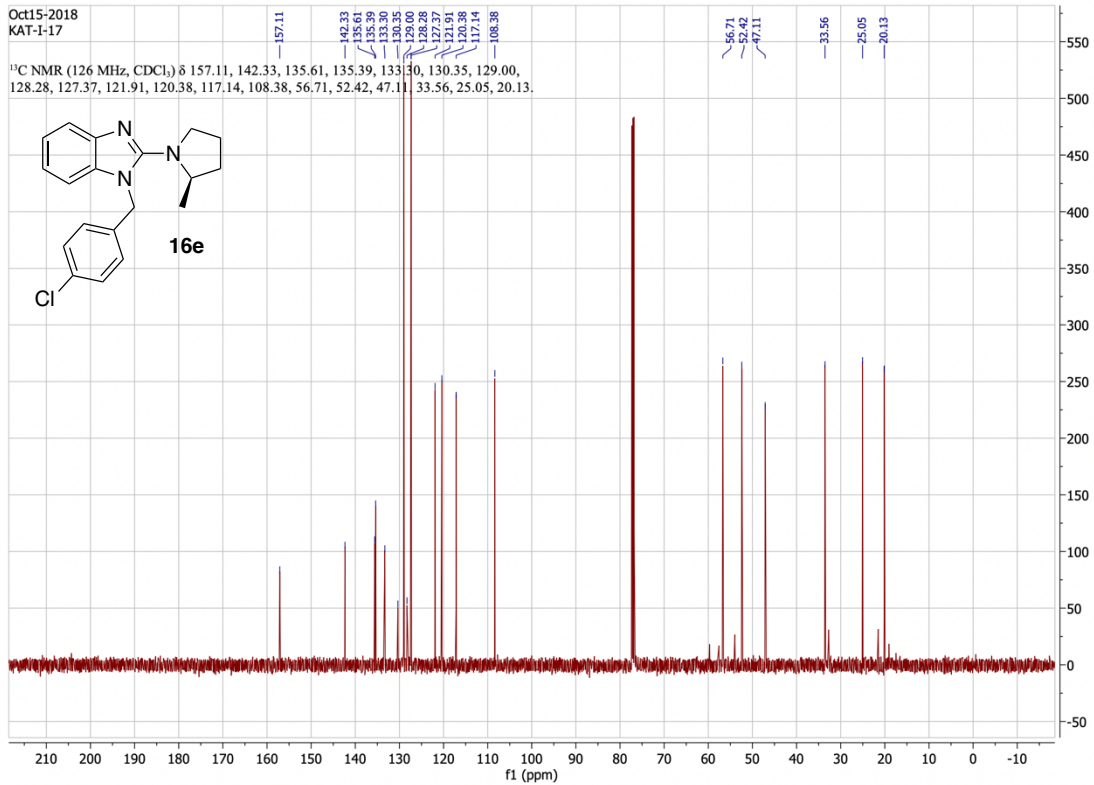
^1H NMR (499 MHz, CDCl_3) δ 7.68 (dd, $J = 25.0, 7.9$ Hz, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.17 – 7.09 (m, 3H), 7.05 (d, $J = 7.9$ Hz, 1H), 5.33 – 5.16 (m, 2H), 3.51 – 3.43 (m, 1H), 3.08 (tdd, $J = 12.1, 10.1, 4.1$ Hz, 2H), 1.89 – 1.75 (m, 3H), 1.70 – 1.60 (m, 2H), 1.58 – 1.38 (m, 2H), 1.02 (dd, $J = 12.6, 6.4$ Hz, 3H).



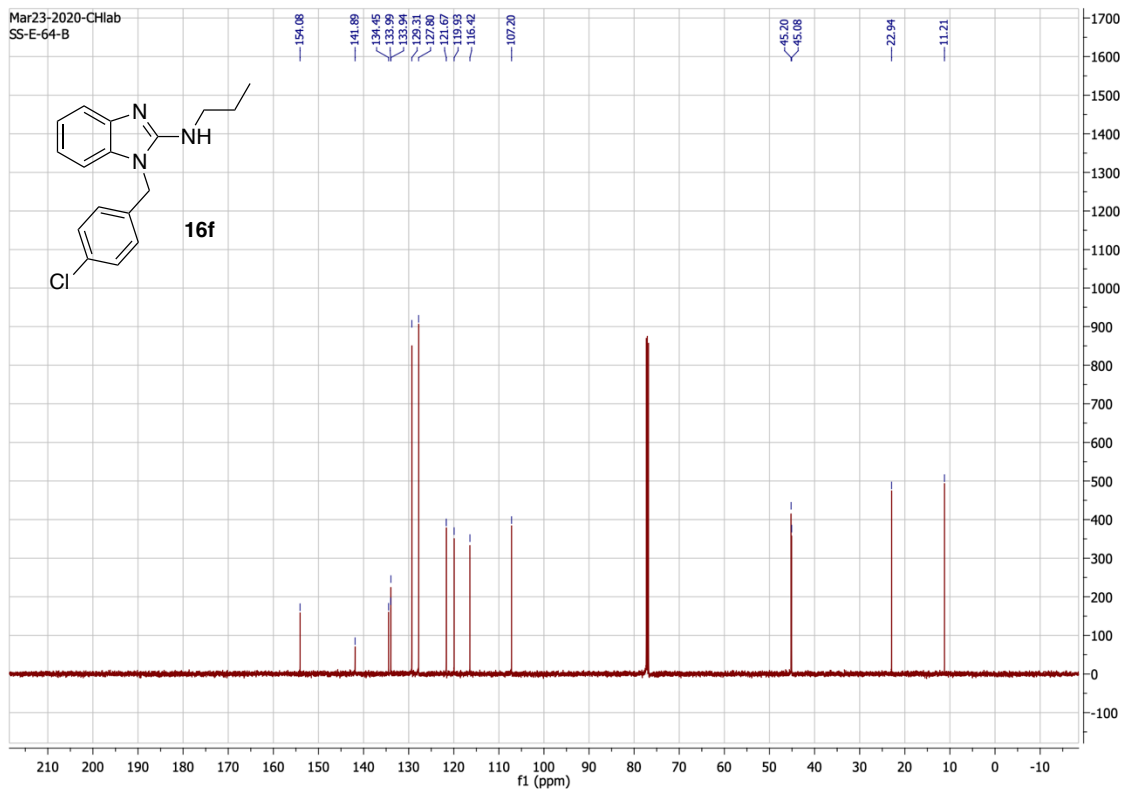








Mar23-2020-CHlab
SS-E-64-B



Mar23-2020-CHlab
SS-E-64-B

