

Electronic Supplementary Information (ESI)

Synthesis of *N*-Isoindolinonyl Peptides via Pd-Catalyzed C(sp²)-H Olefination/activation and Their Conformational Studies

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1. NMR and Mass spectra of peptides and their respective Isoindolinone derivatives

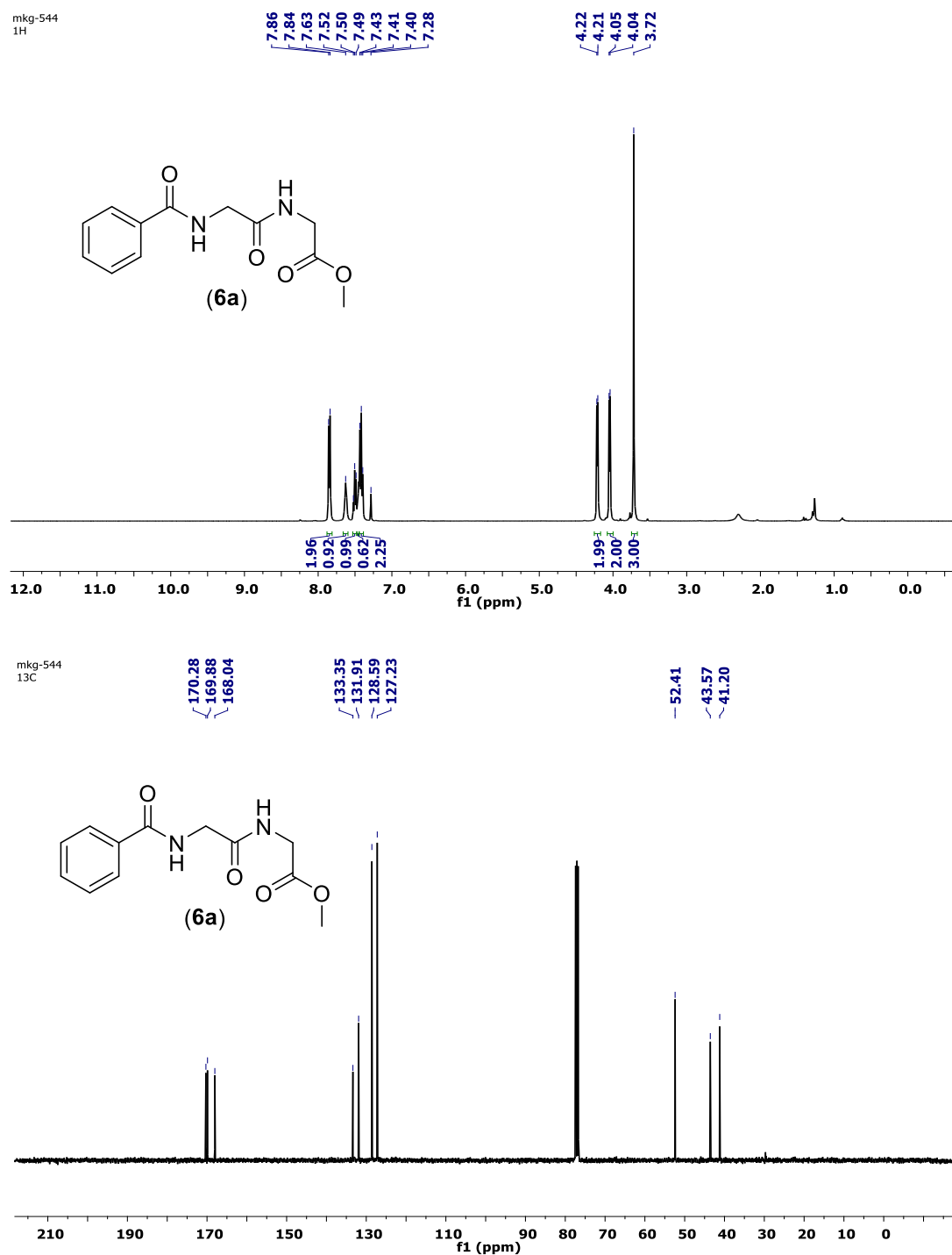


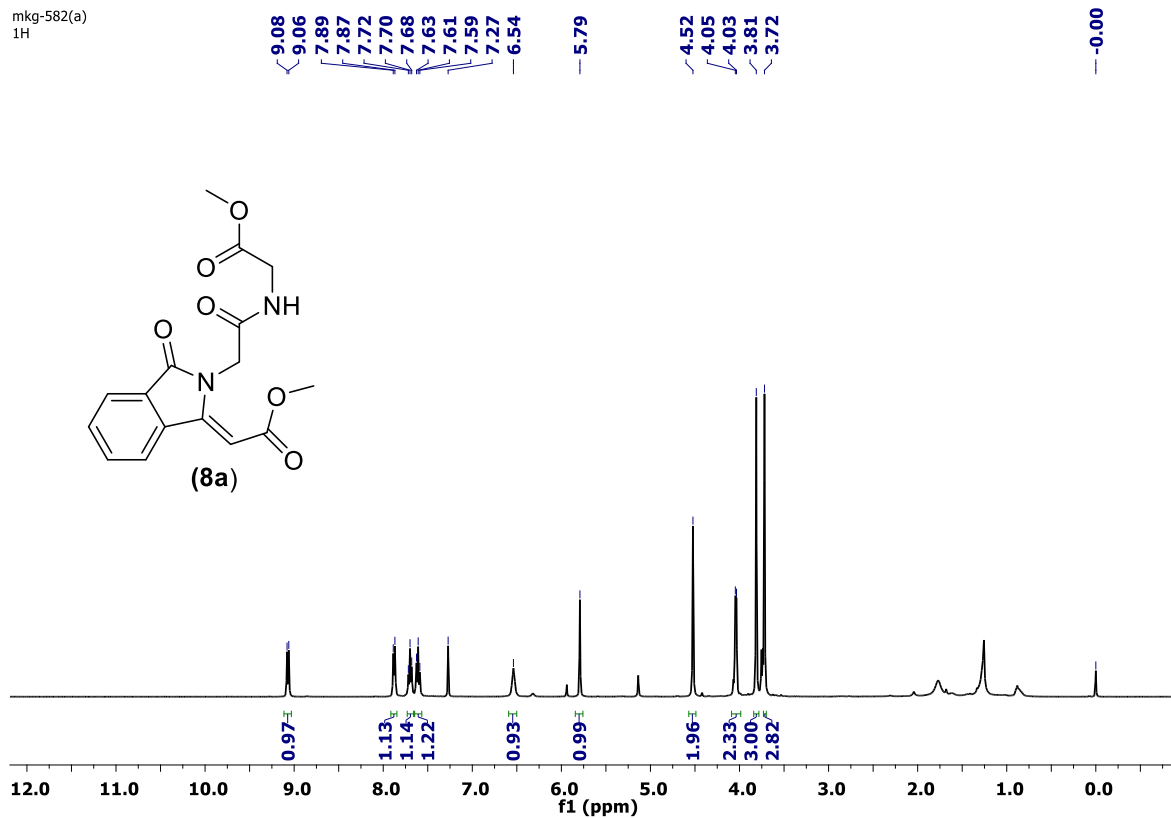
Figure. S1. ^1H , ^{13}C NMR spectra of **6a**

NKS_19122022_8 (0.054) Cu (0.05); Is (1.00,1.00) C12H15N2O4

1: TOF MS ASAP+
8.63e12



mkg-582(a)
1H



mkg-582(a)
13C

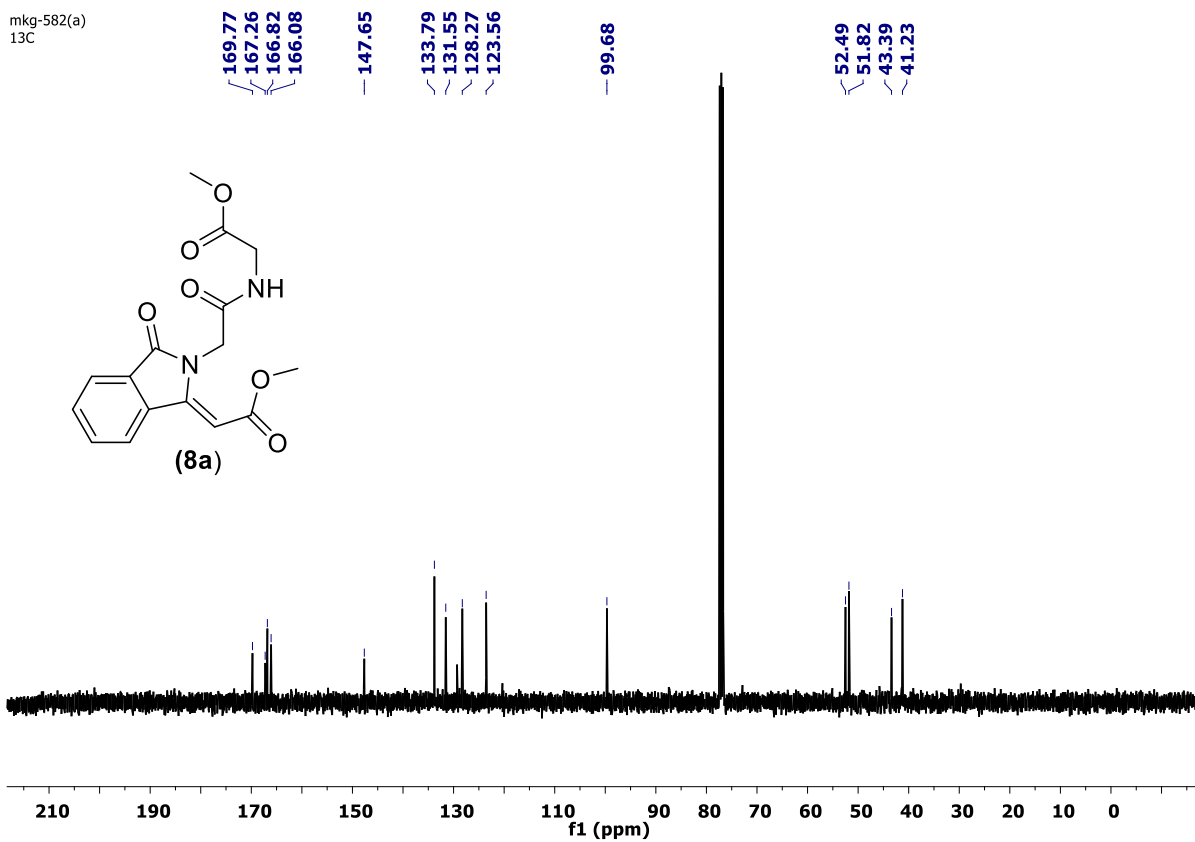


Figure. S3. ¹H, ¹³C NMR spectra of **8a**

MKG_1104_RE

12-Jan-2023
13:14:34

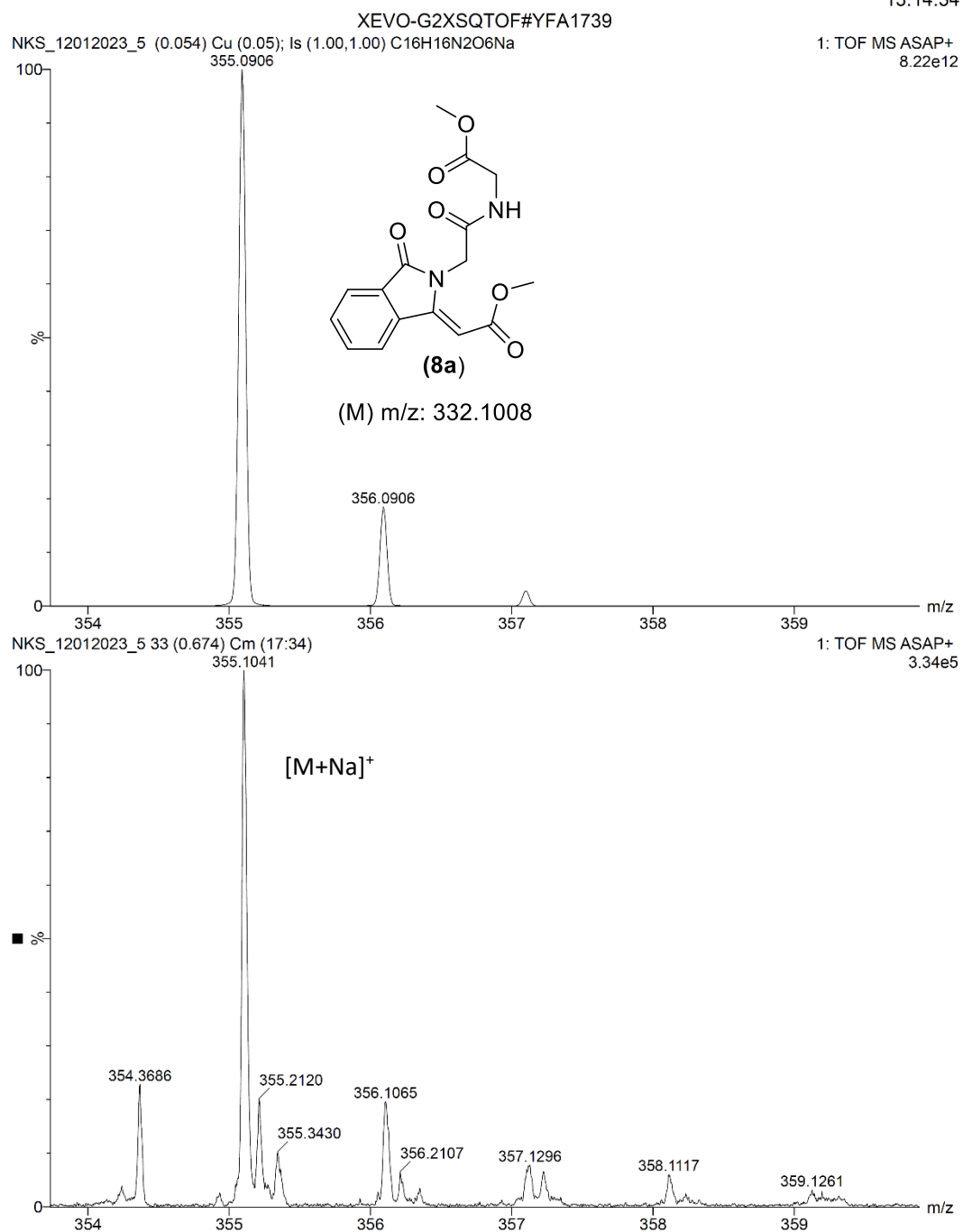


Figure. S4. ESI-HRMS spectra of indolinone **8a**

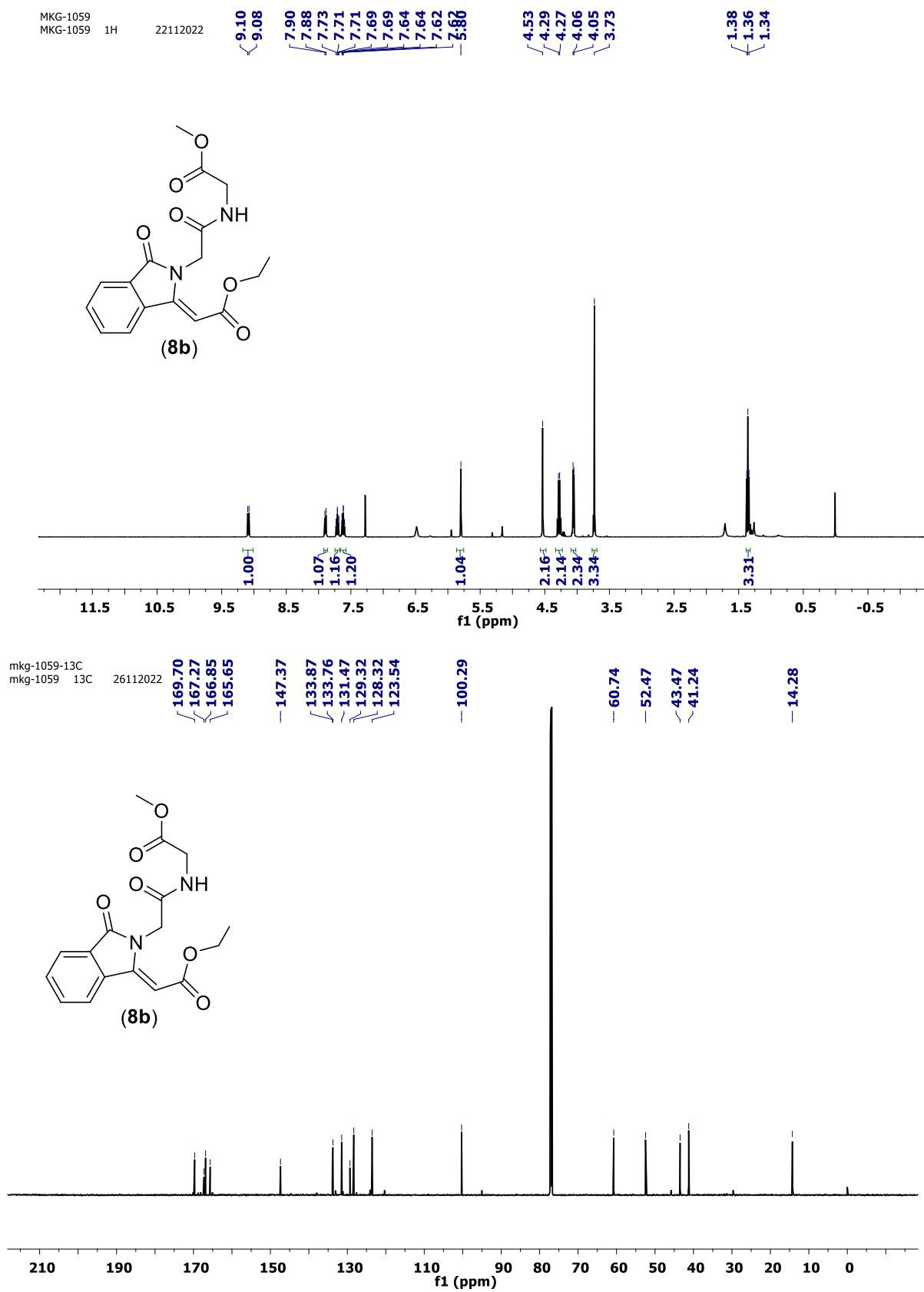


Figure. S5. ^1H , ^{13}C NMR spectra of **8b**

NKS_MKG_1059

19-Dec-2022
11:16:26

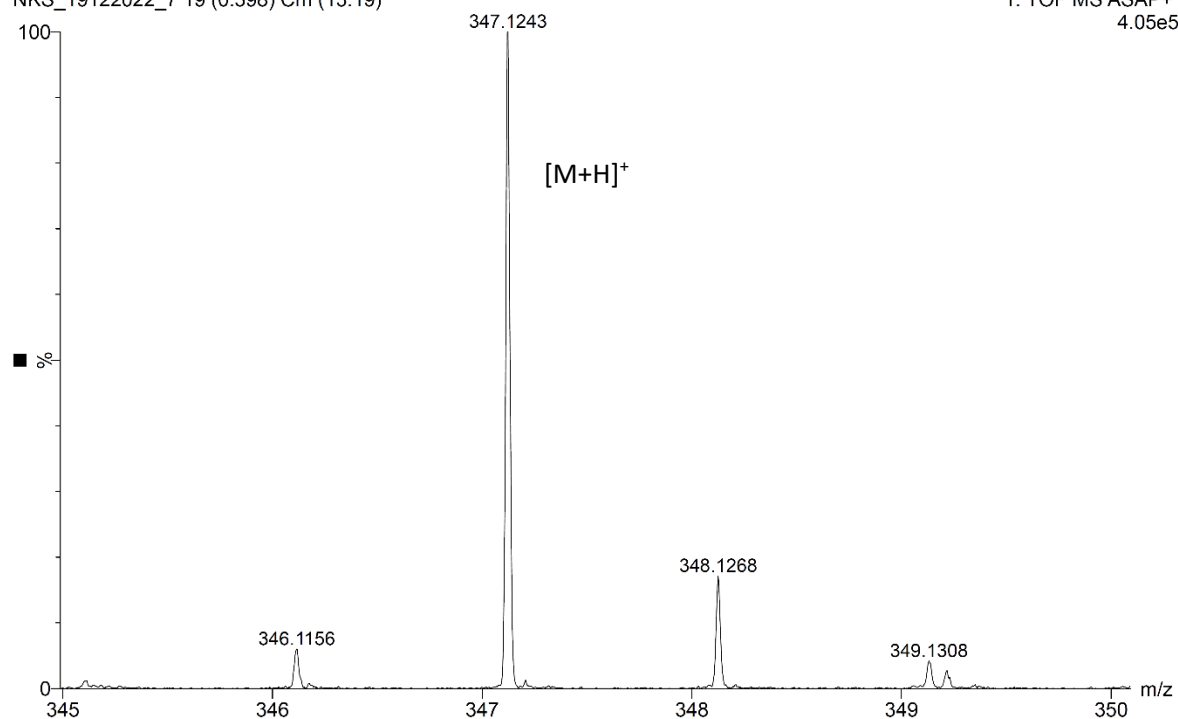
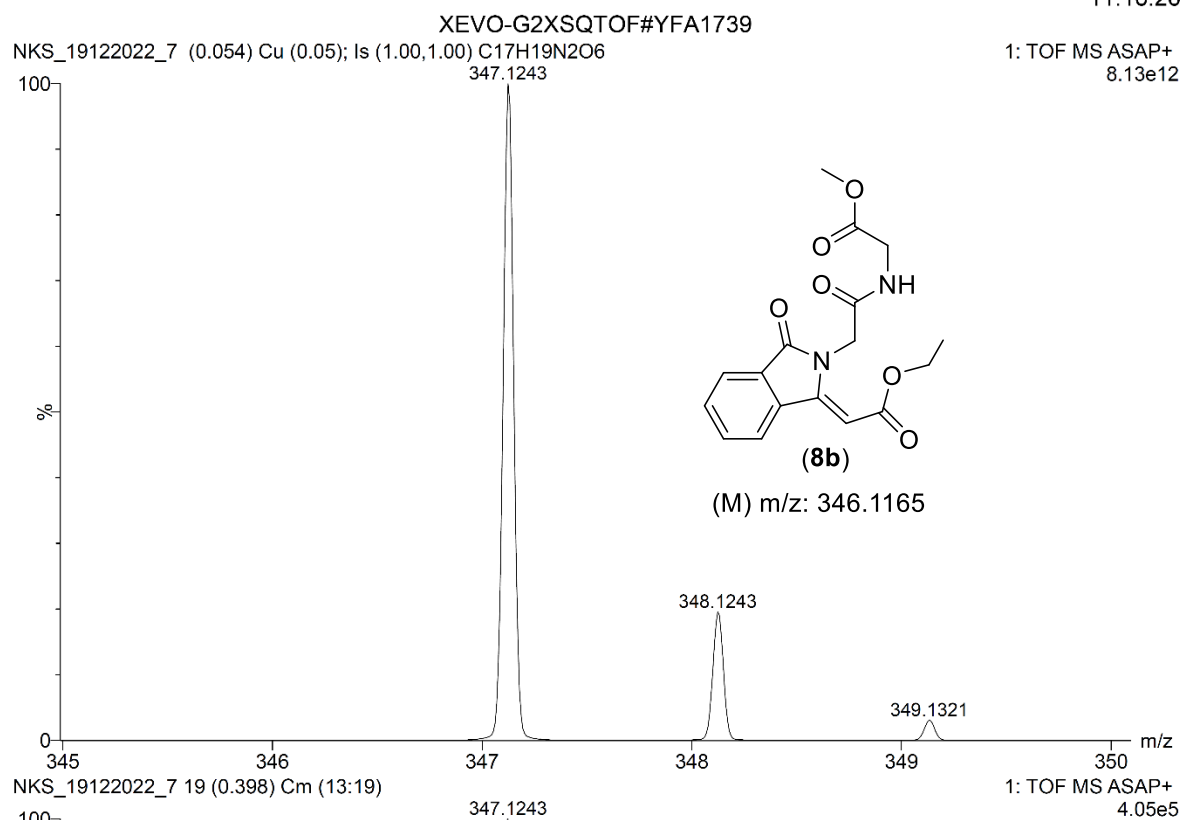


Figure. S6. ESI-HRMS spectra of **8b**

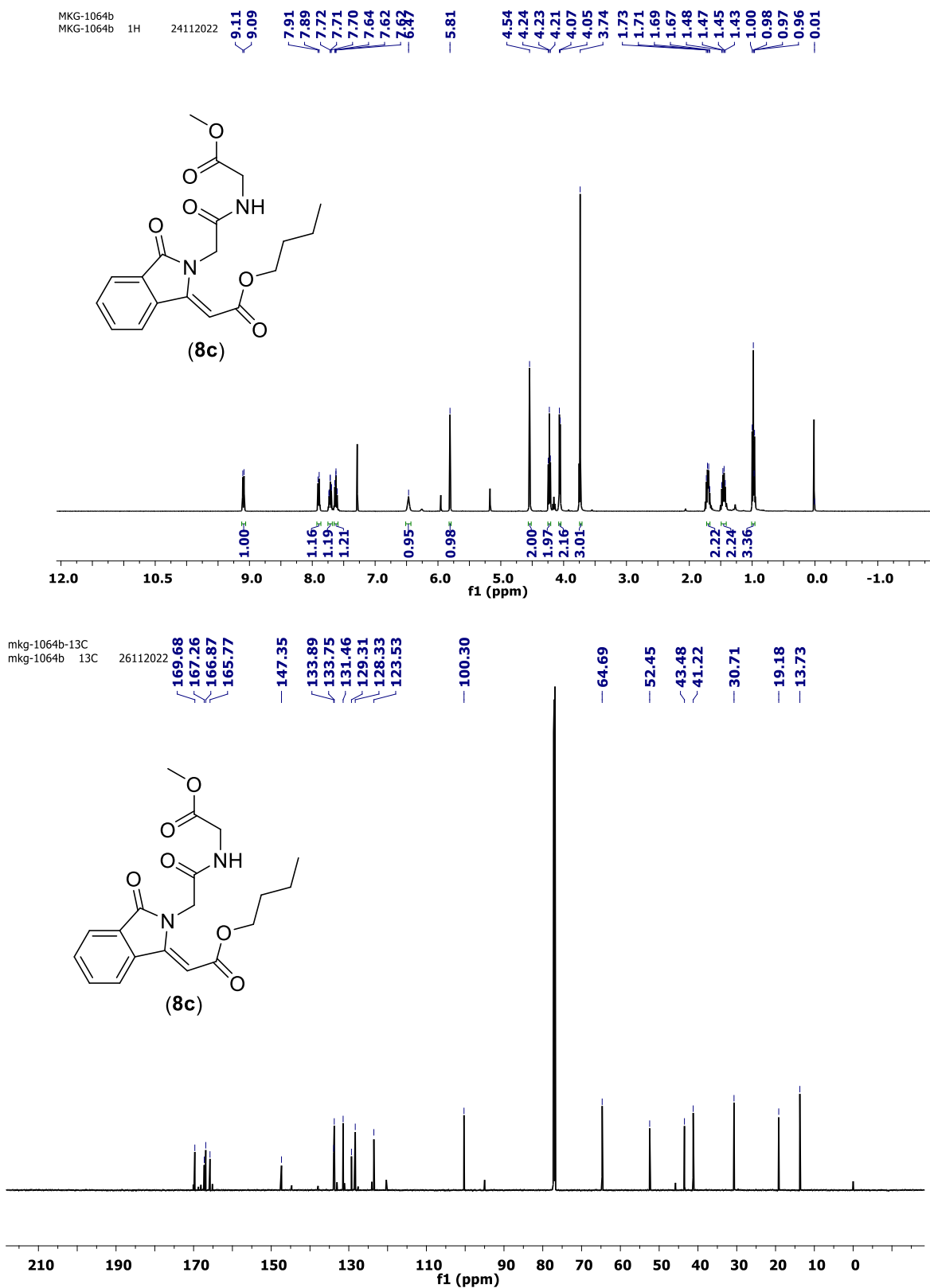


Figure. S7. ^1H , ^{13}C NMR spectra of **8c**

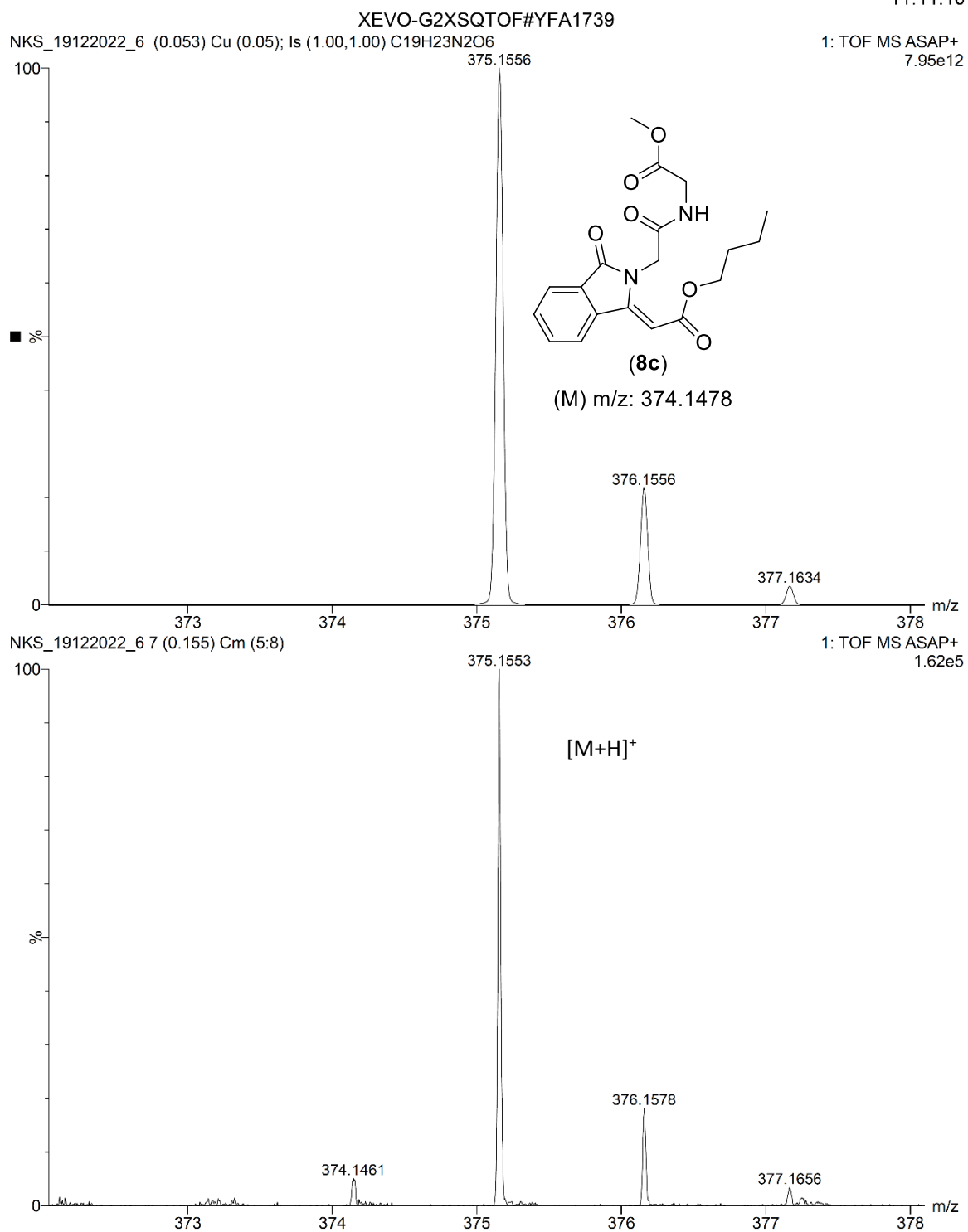


Figure. S8. ESI-HRMS spectra of **8c**

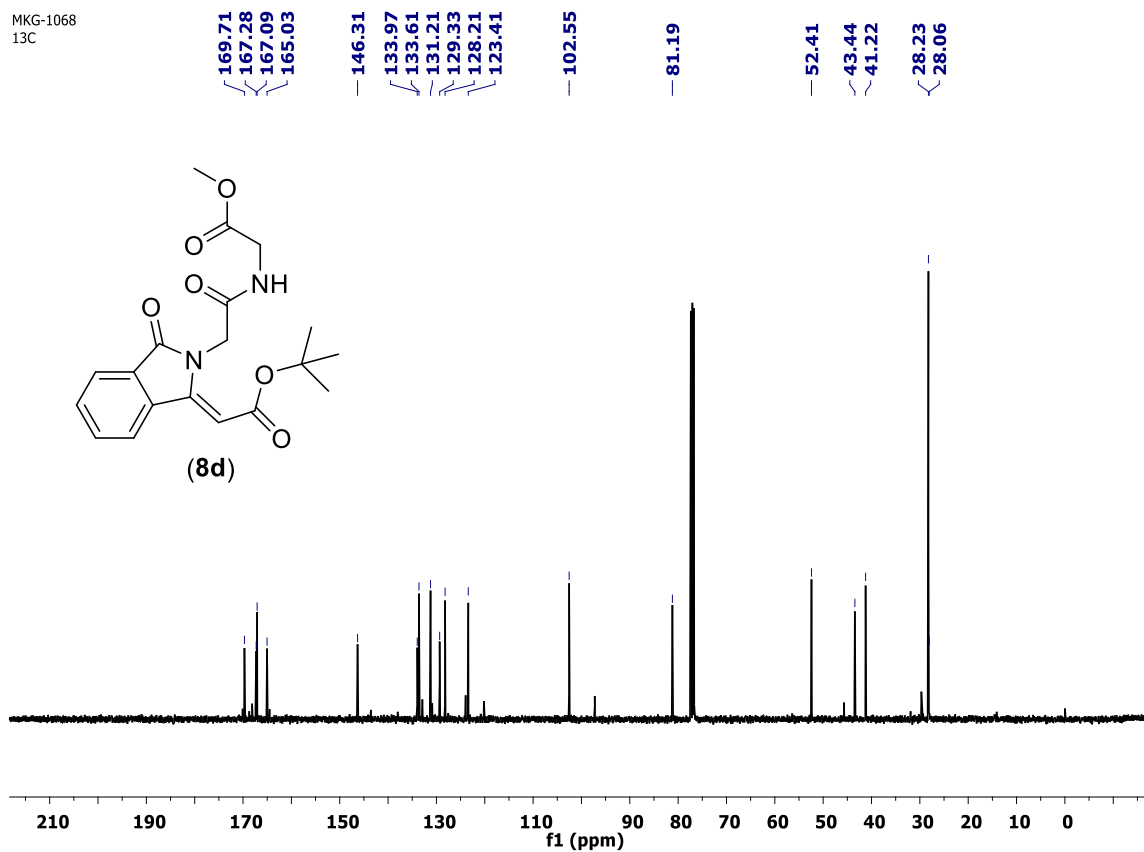
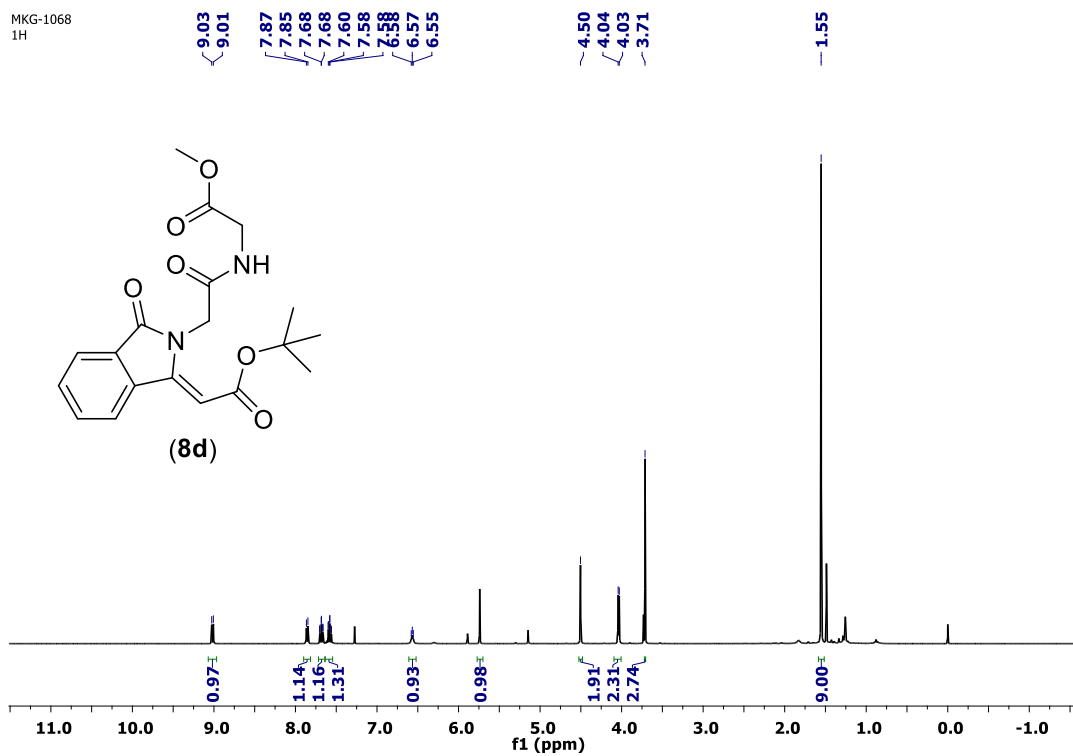


Figure. S9. ¹H, ¹³C NMR spectra of **8d**

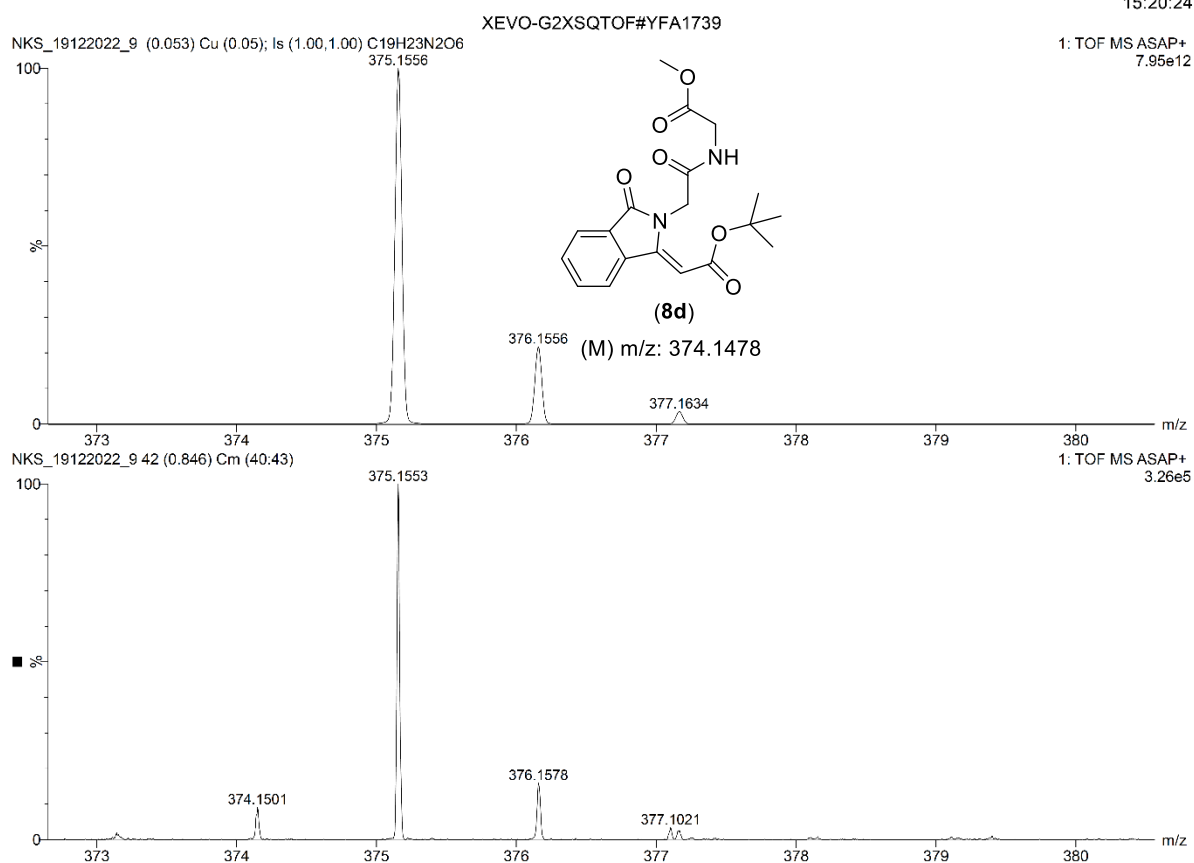
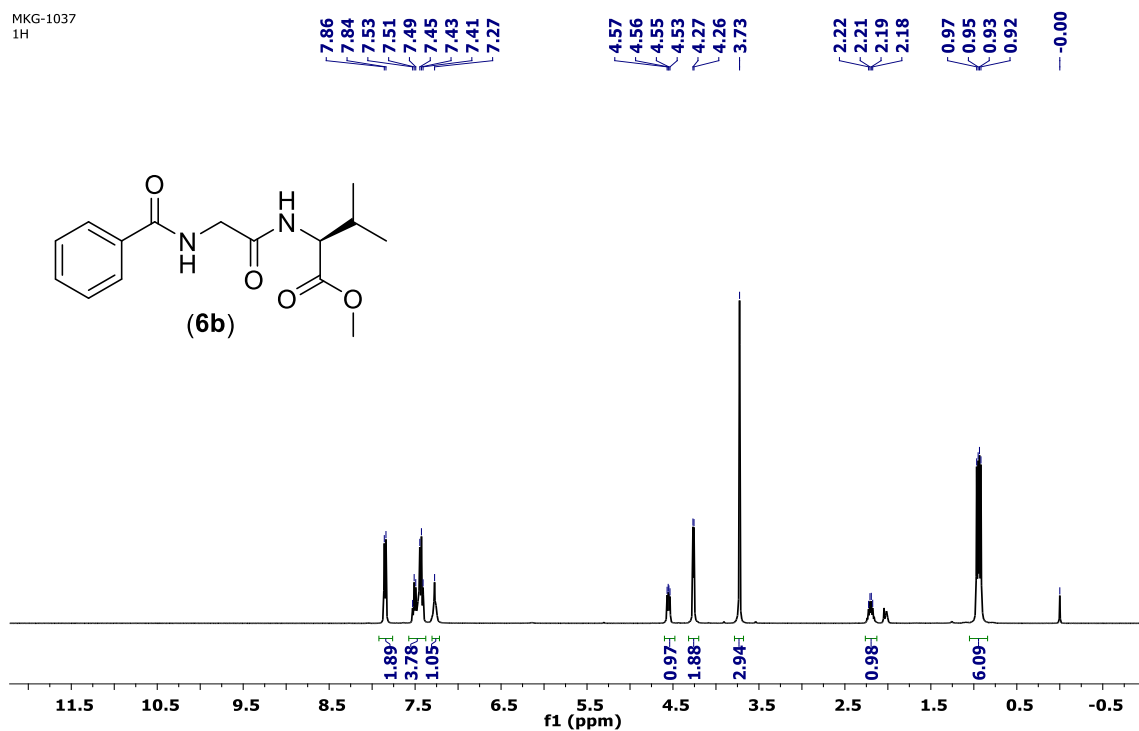


Figure. S10. ESI-HRMS spectra of **8d**

MKG-1037
1H



MKG-1037
13C

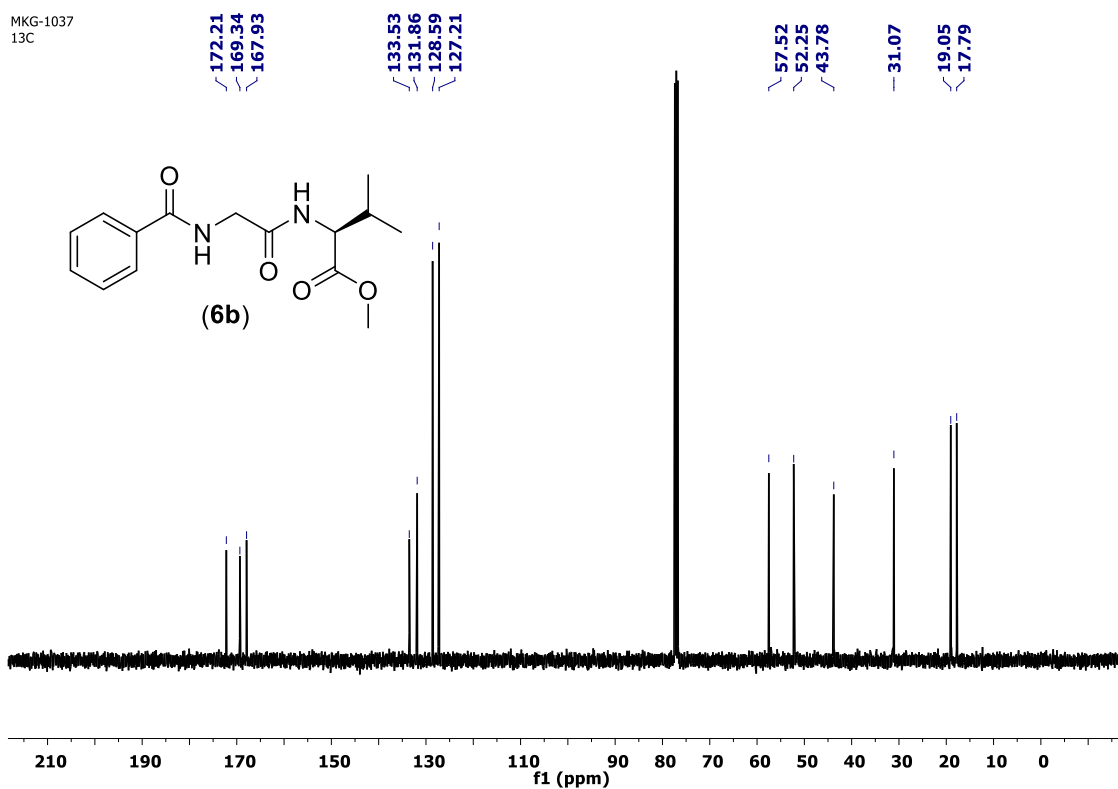


Figure. S11. ^1H , ^{13}C NMR spectra of **8**

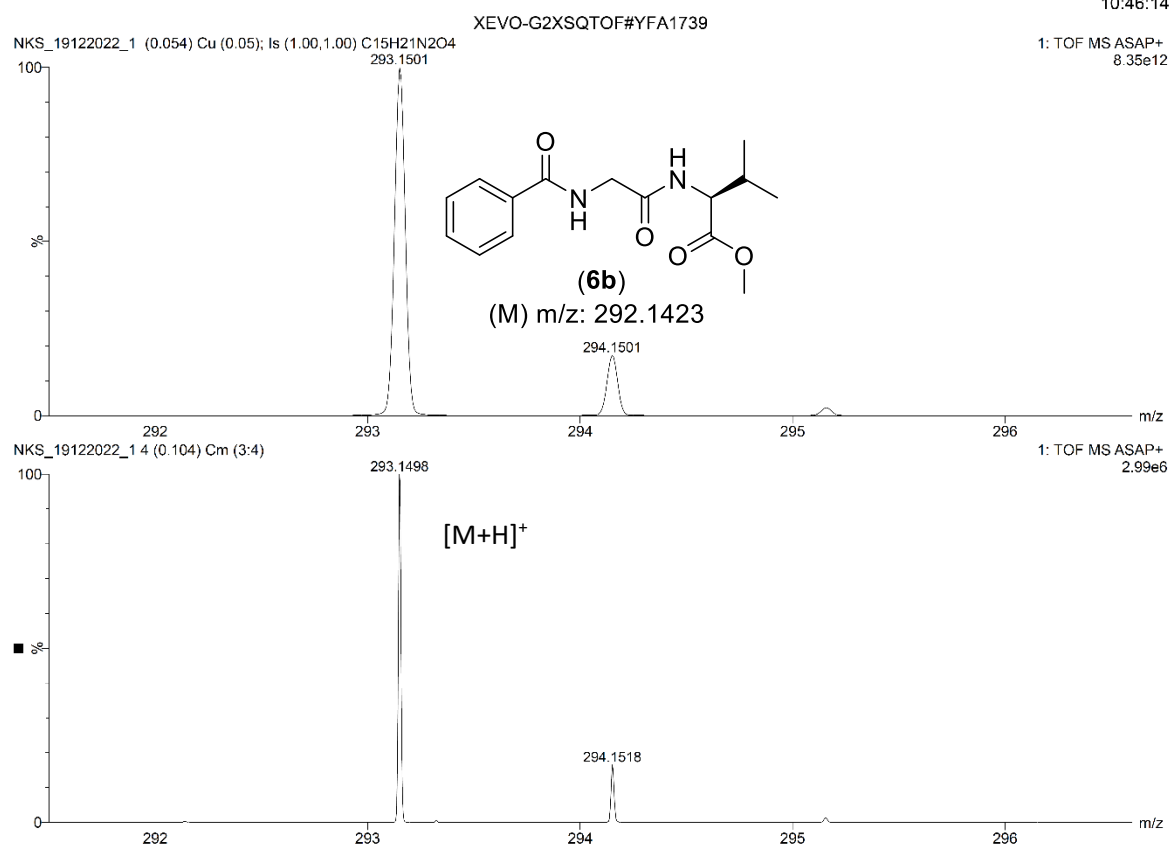


Figure. S12. ESI-HRMS spectra of **6b**

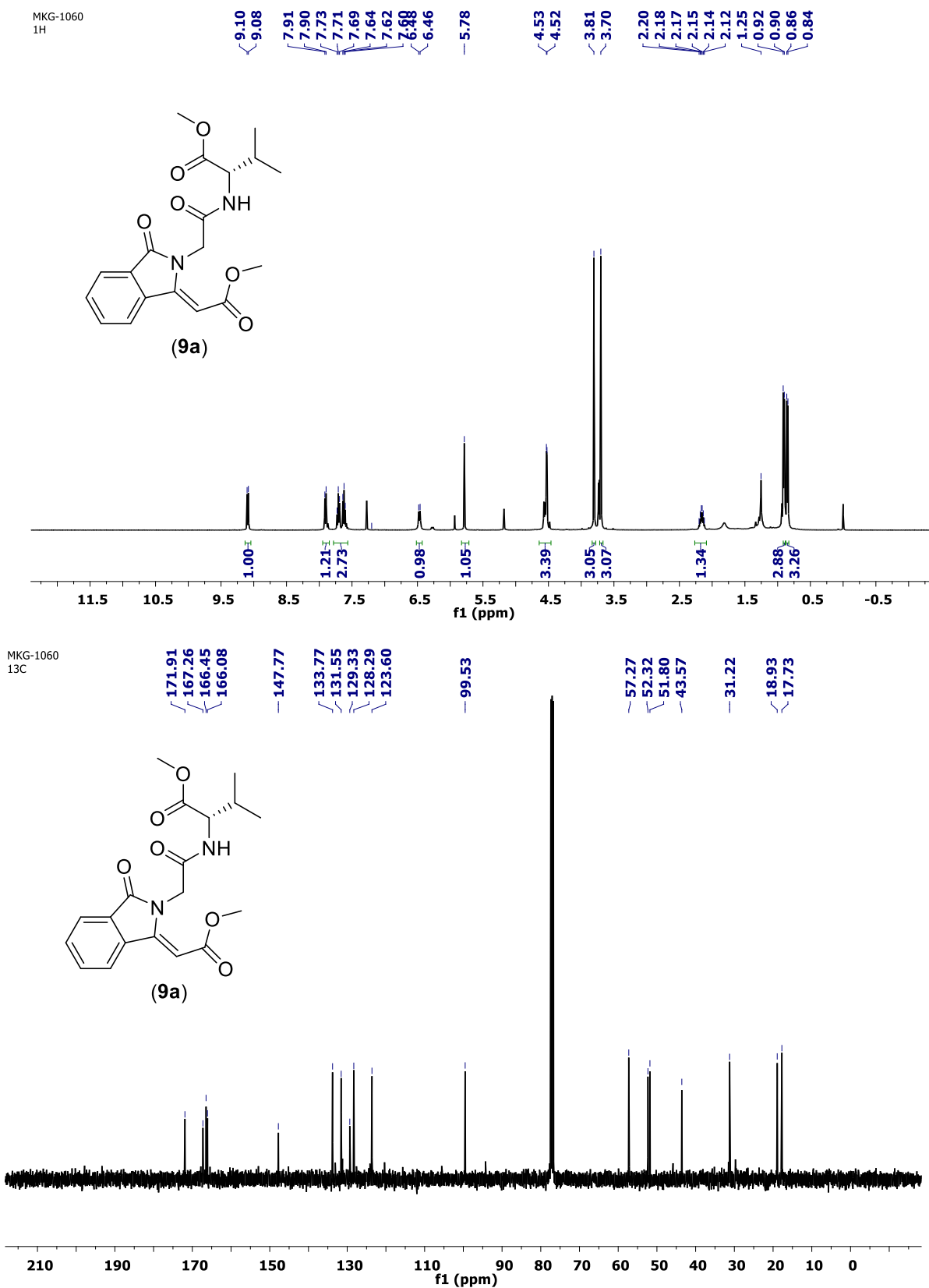


Figure. S13. ^1H , ^{13}C NMR spectra of 9a

NKS_MKG_1060

19-Dec-2022
10:49:40

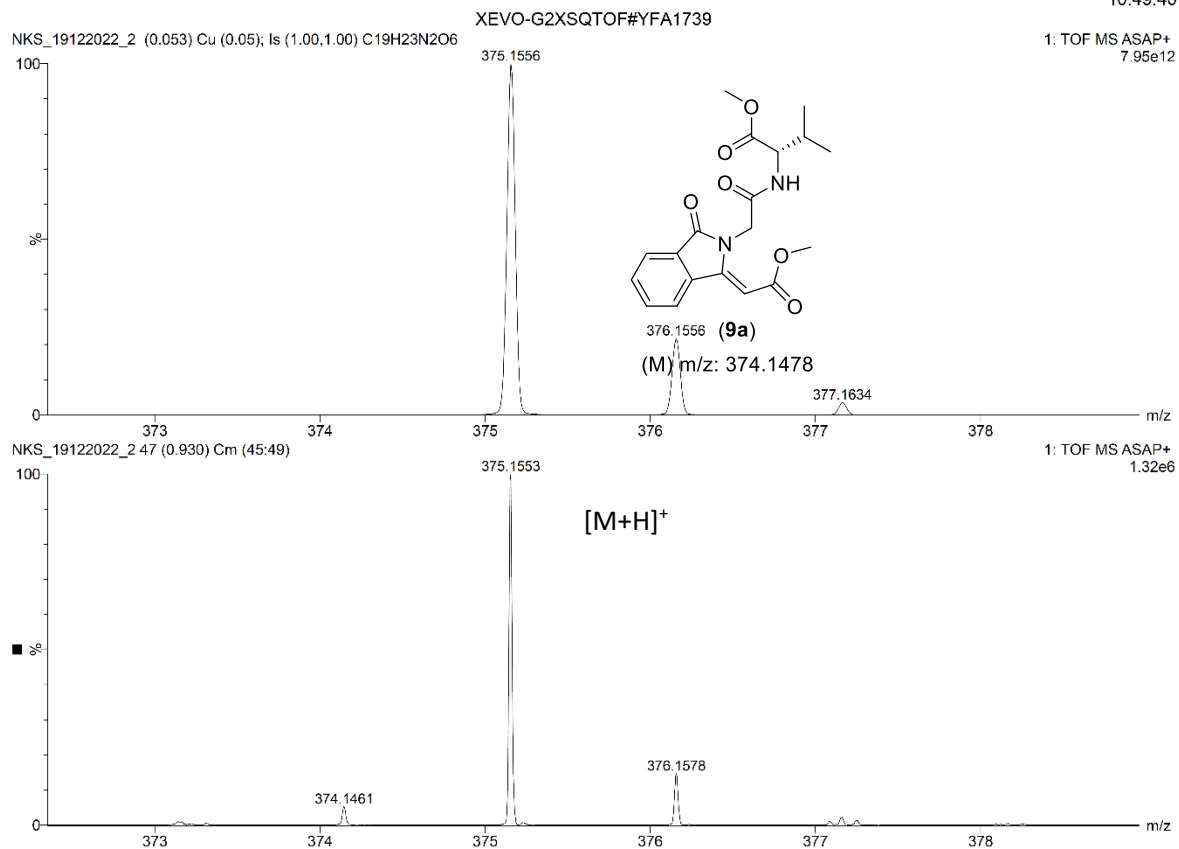
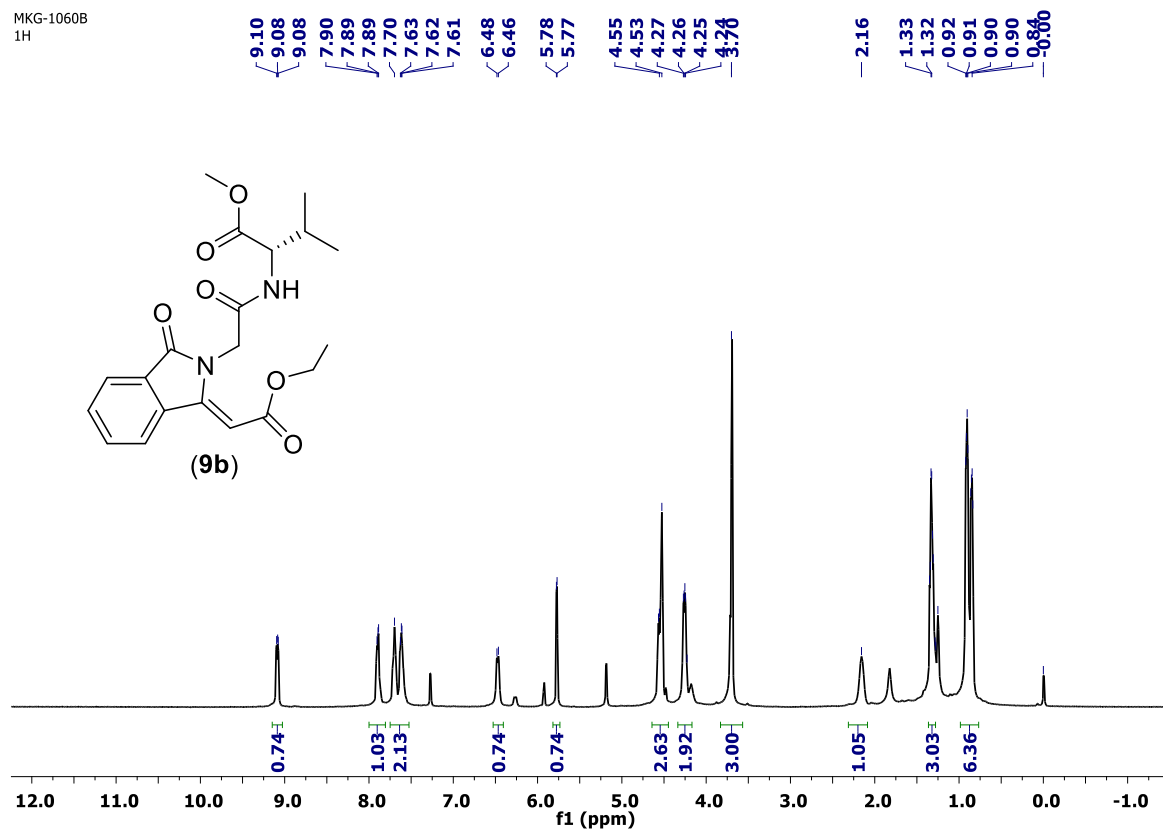


Figure. S14. ESI-HRMS spectra of **9a**

MKG-1060B
1H



MKG-1060B
13C

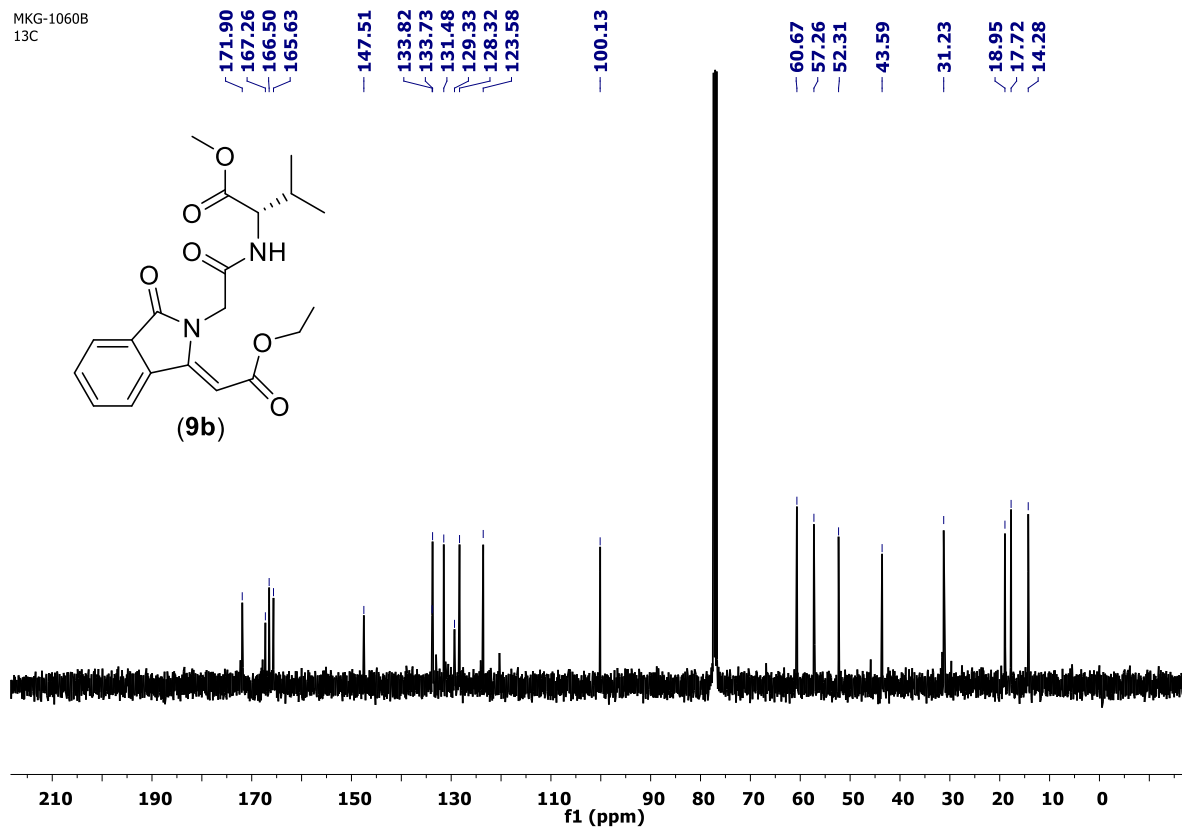


Figure. S15. ¹H, ¹³C NMR spectra of **9b**

NKS_MKG_1060_B

19-Dec-2022
10:58:52

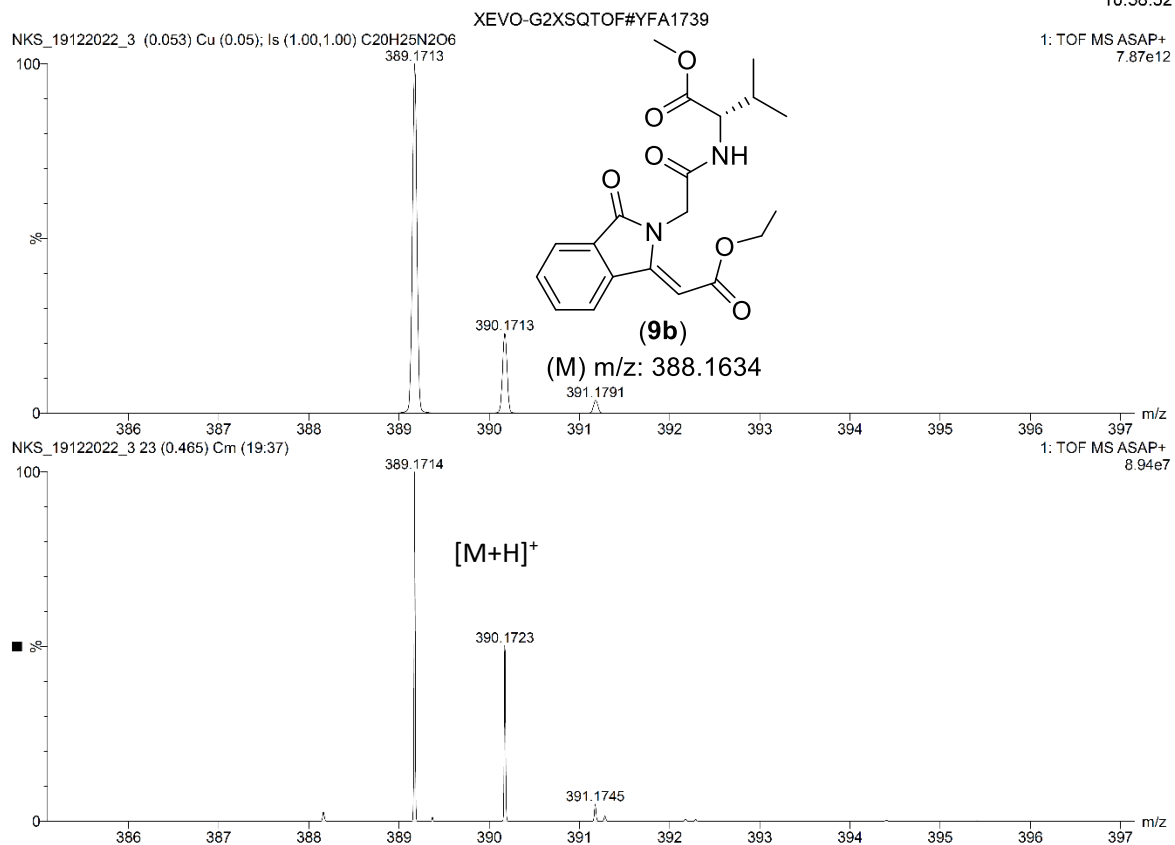


Figure. S16. ESI-HRMS spectra of **9b**

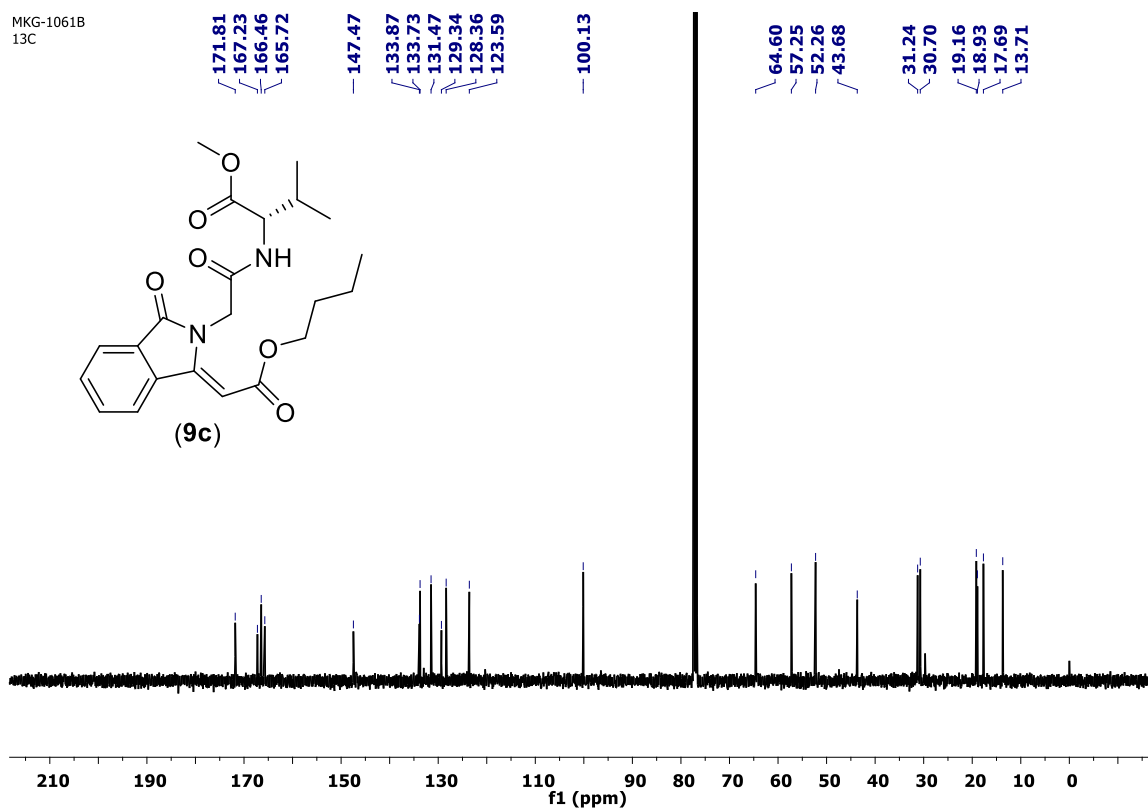
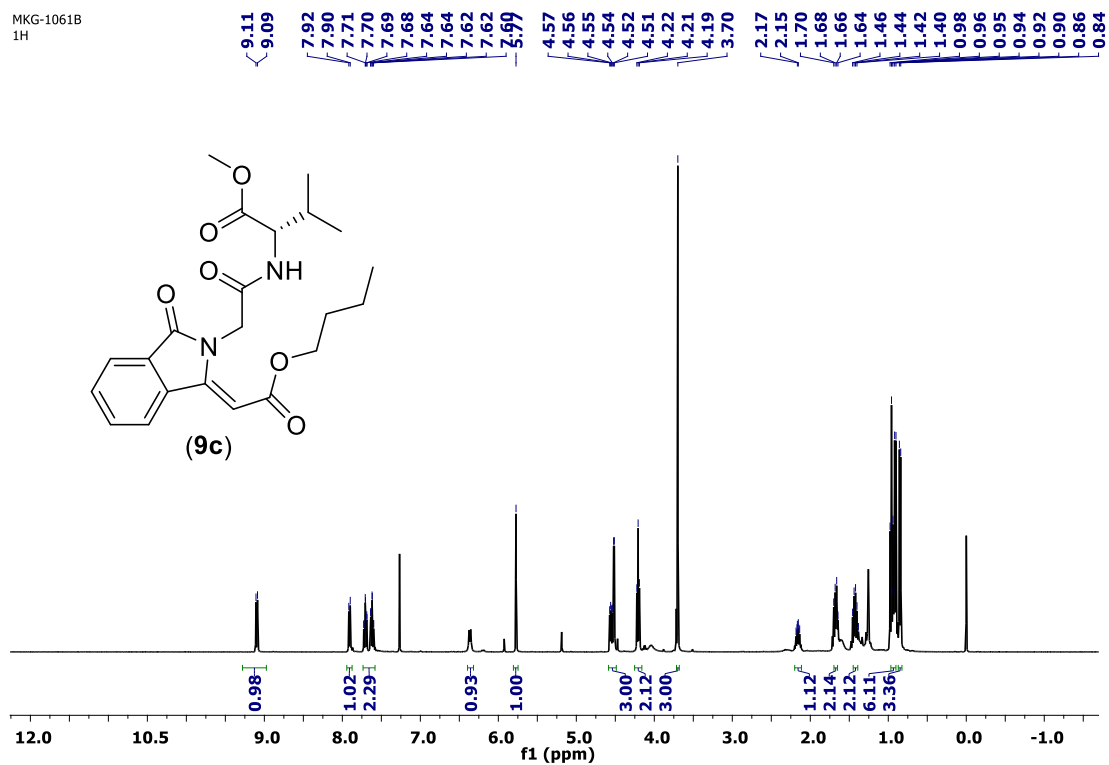


Figure. S17. ^1H , ^{13}C NMR spectra of **9c**

NKS_MKG_1061_B

19-Dec-2022
11:02:53

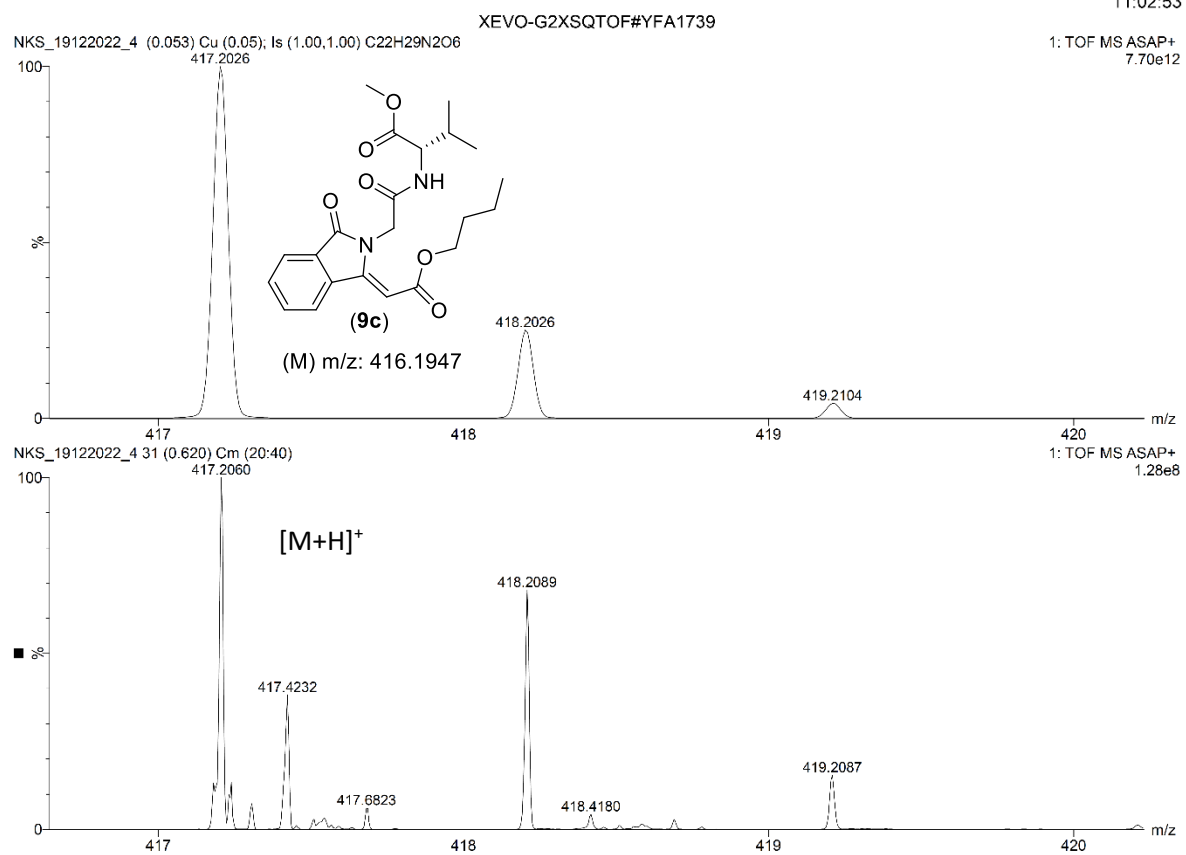


Figure. S18. ESI-HRMS spectra of **9c**

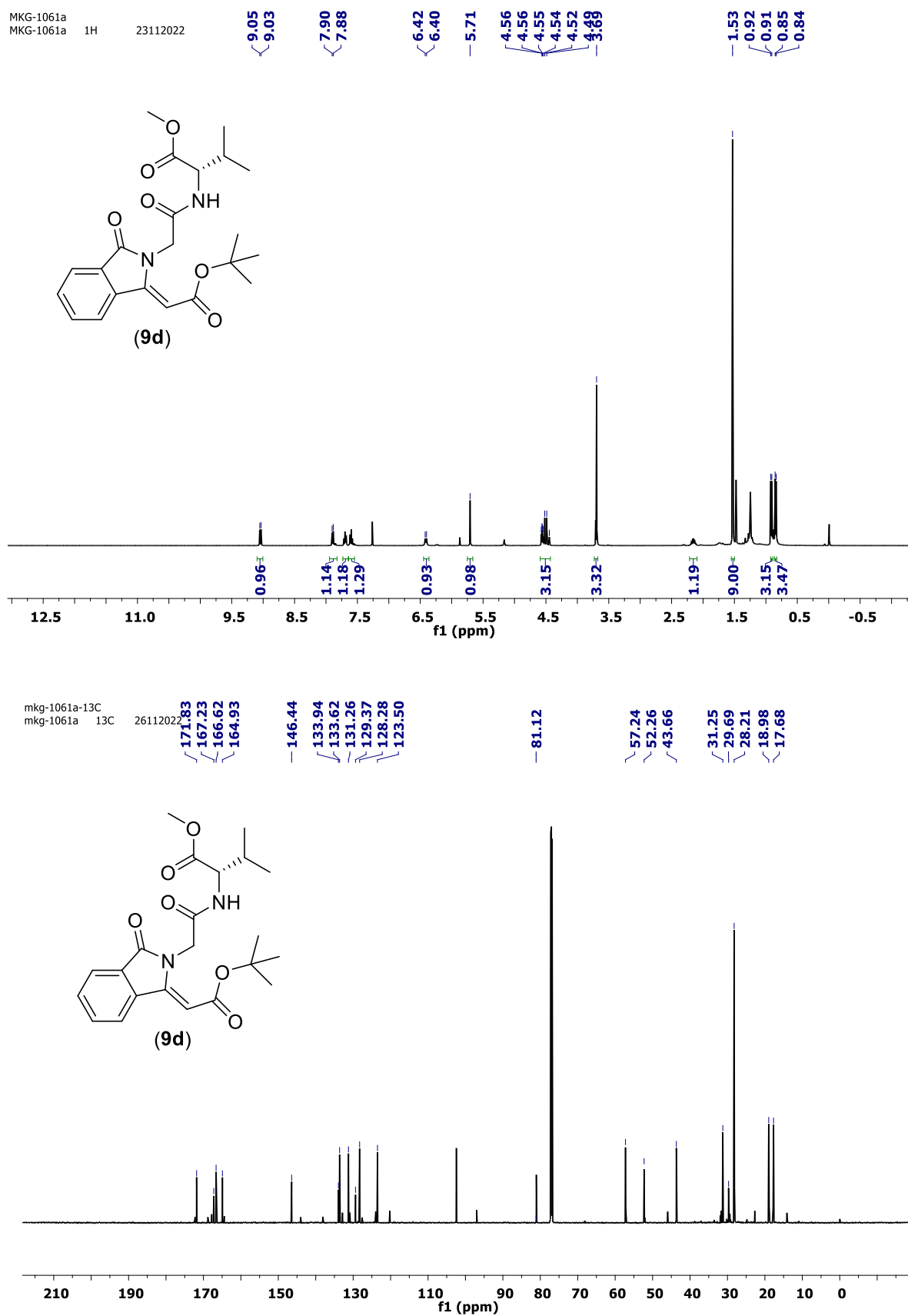
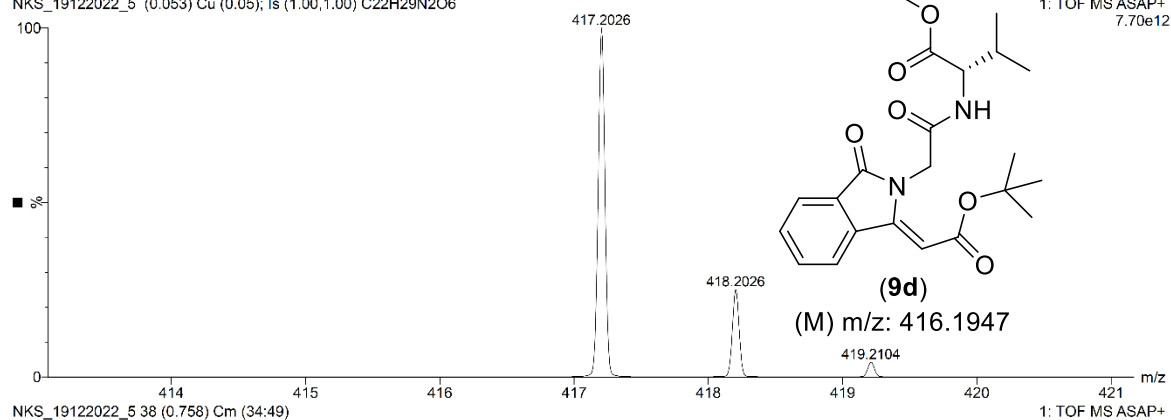


Figure. S19. ^1H , ^{13}C NMR spectra of 9d

NKS_MKG_1061_A

19-Dec-2022
11:07:34

XEVO-G2XSQTOF#YFA1739
NKS_19122022_5 (0.053) Cu (0.05); Is (1.00,1.00) C₂₂H₂₉N₂O₆



NKS_19122022_5 38 (0.758) Cm (34:49)

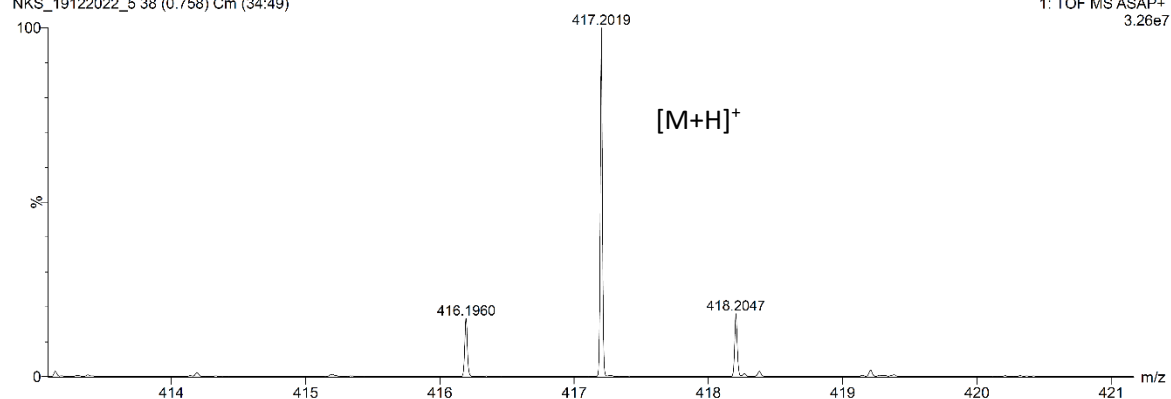


Figure. S20. ESI-HRMS spectra of **9d**

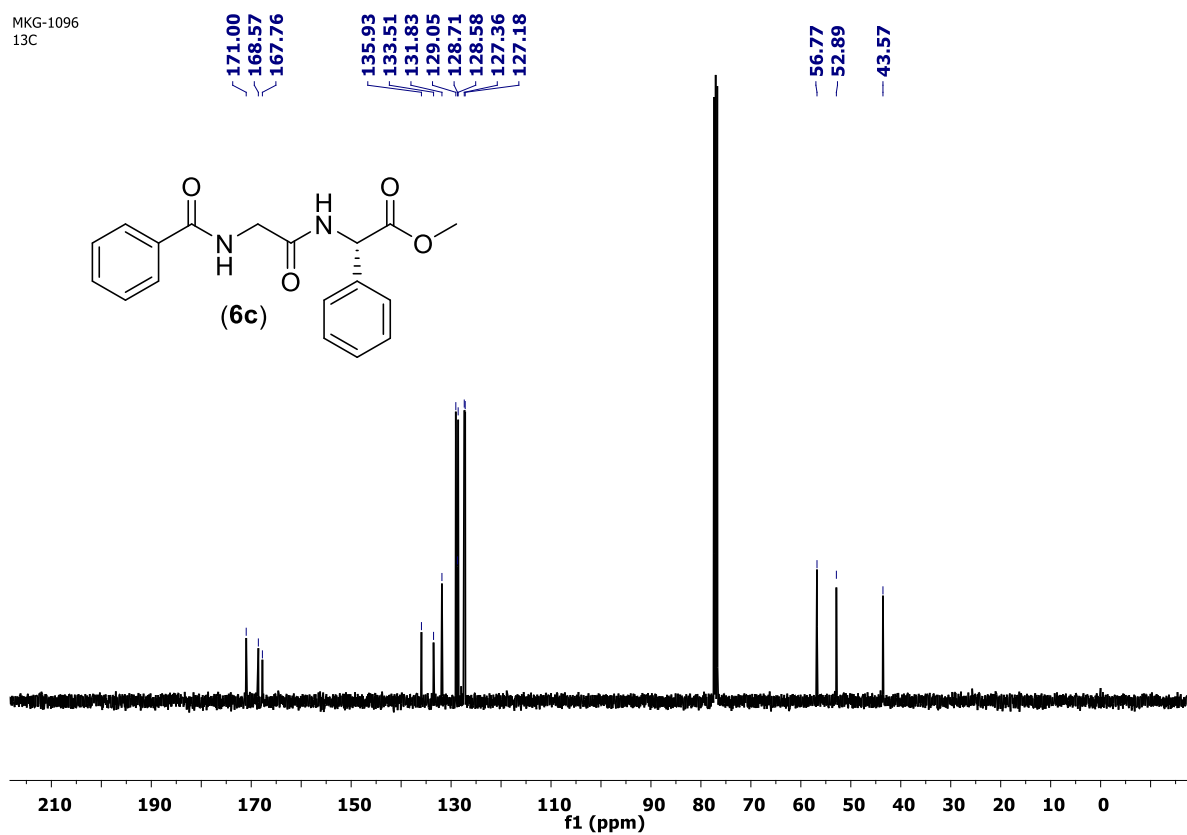
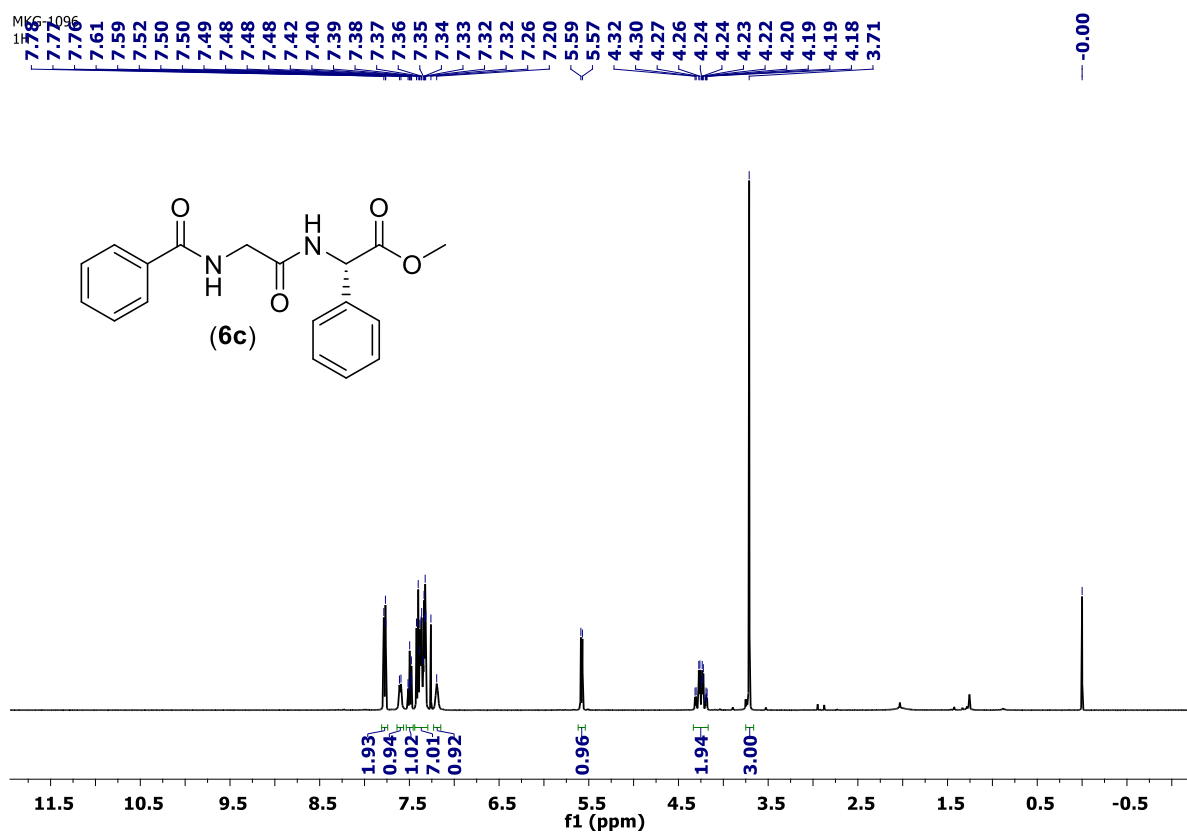


Figure. S21. ^1H , ^{13}C NMR spectra of **6c**

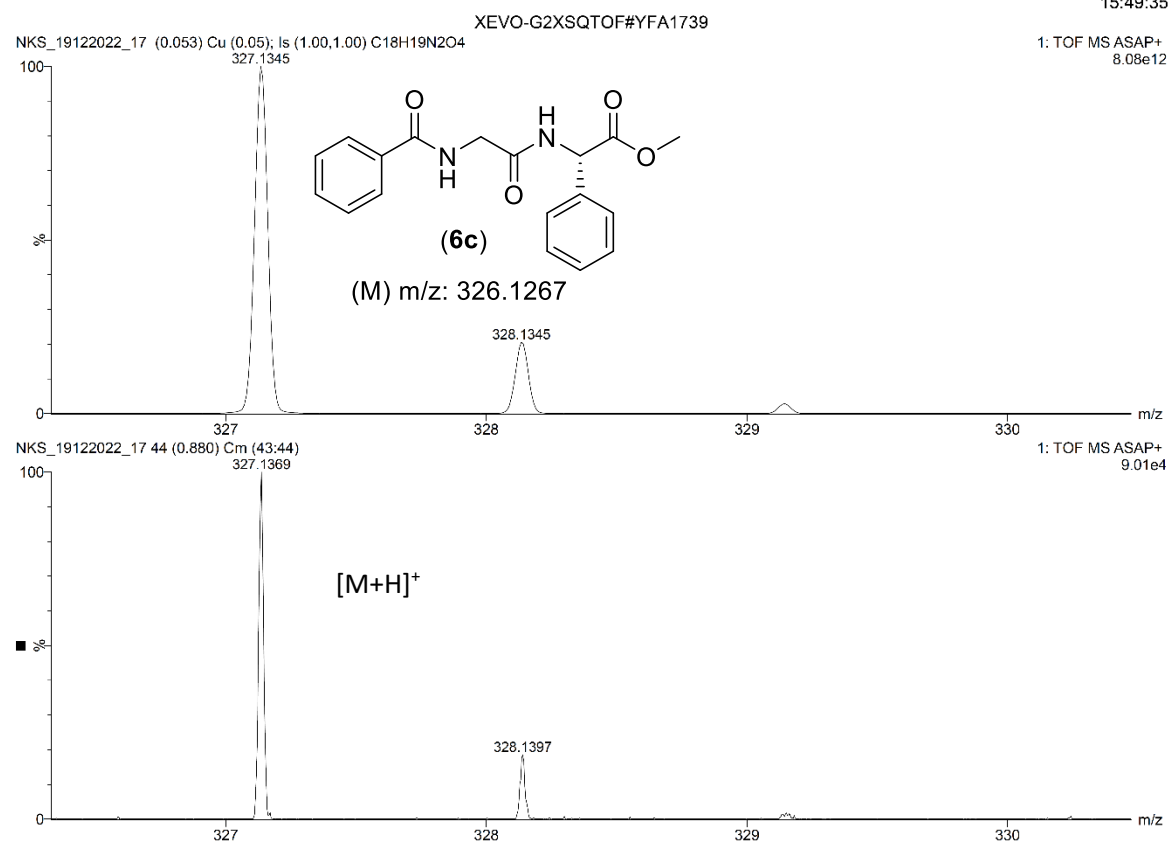


Figure. S22. ESI-HRMS spectra of **6c**

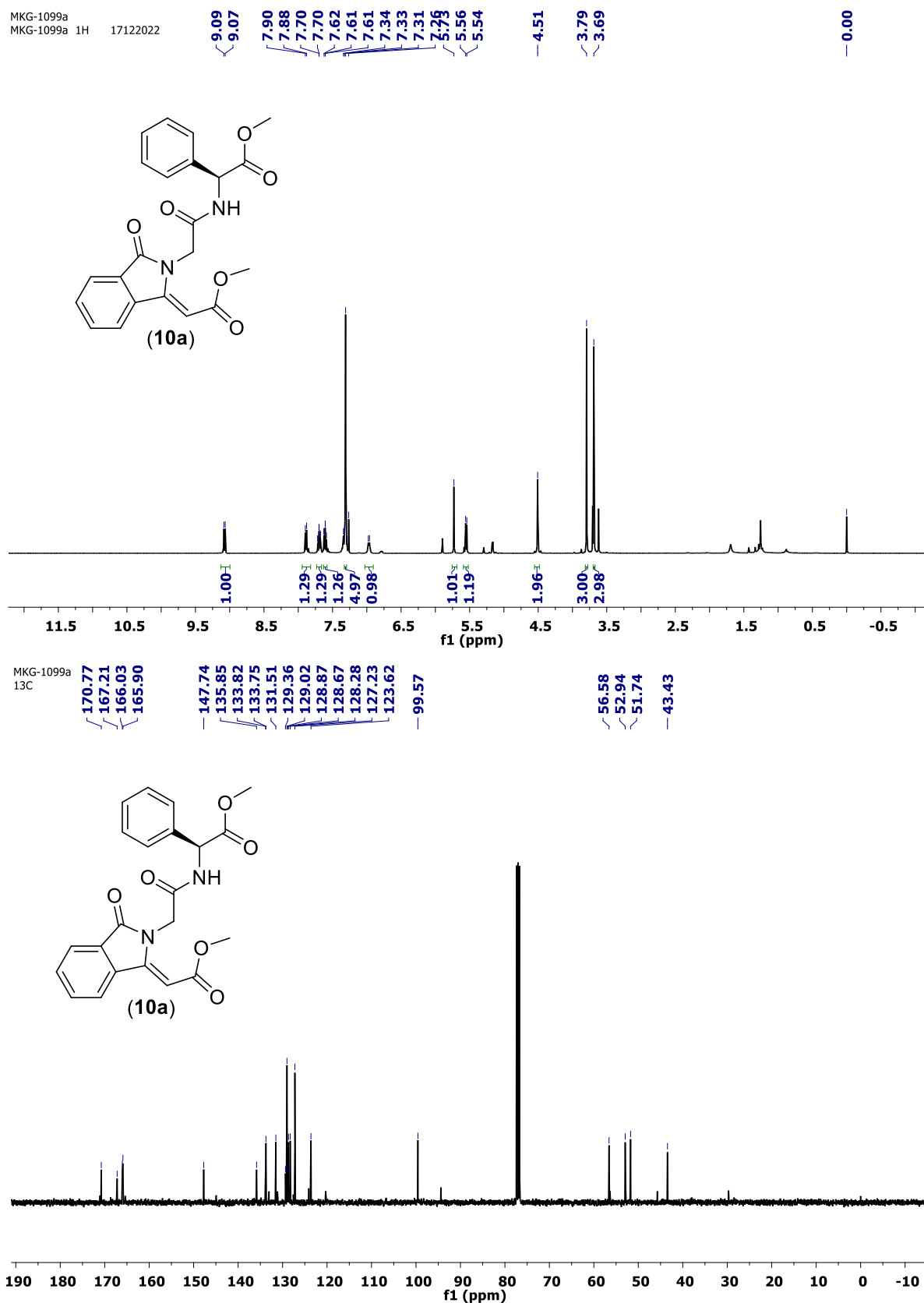


Figure. S23. ^1H , ^{13}C NMR spectra of 10a

NKS_MKG_1099_A

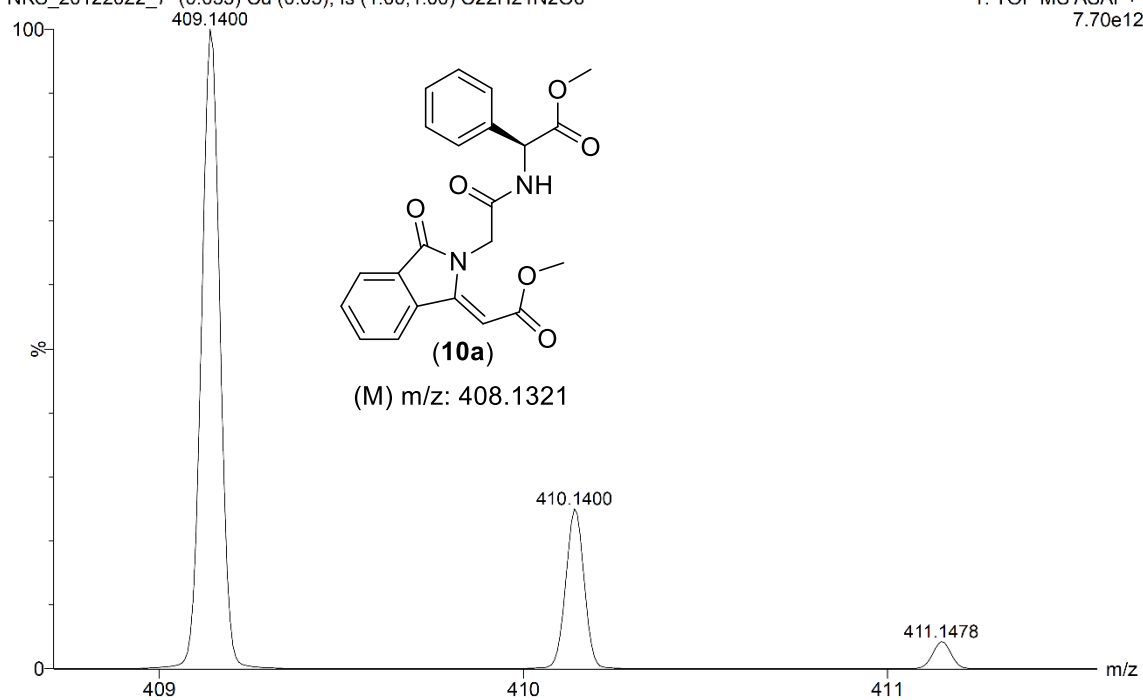
20-Dec-2022

11:08:54

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NKS_20122022_7 (0.053) Cu (0.05); Is (1.00,1.00) C₂₂H₂₁N₂O₆

1: TOF MS ASAP+
7.70e12



NKS_20122022_7 6 (0.138) Cm (3:7)

1: TOF MS ASAP+
5.22e7

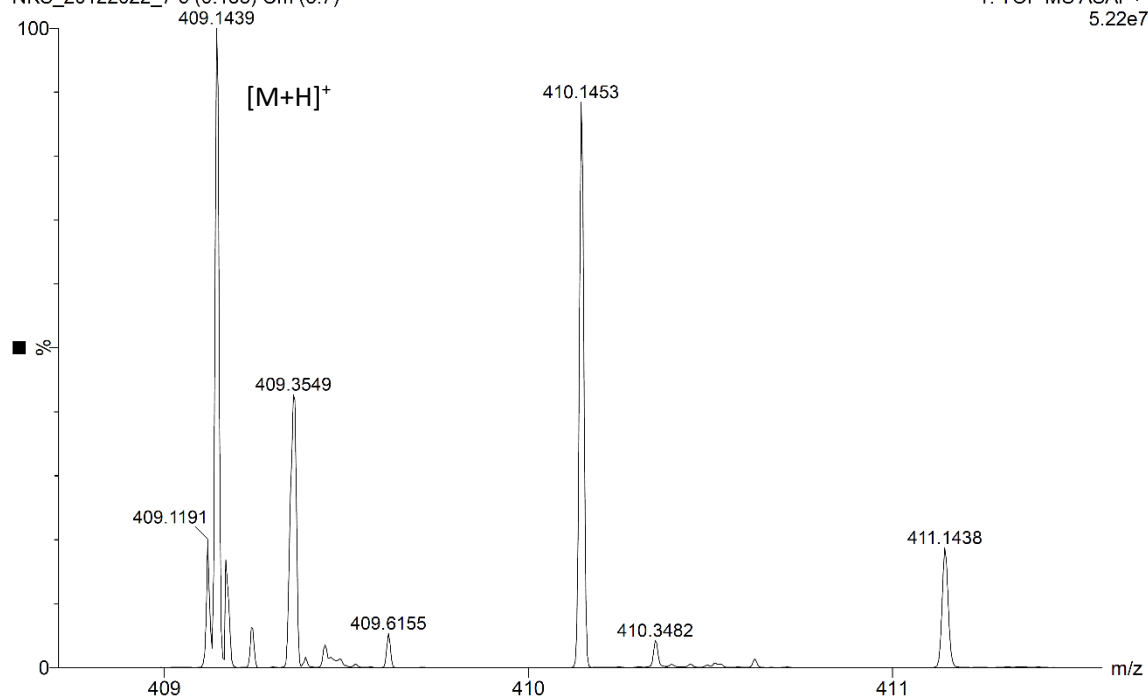


Figure. S24. ESI-HRMS spectra of **10a**

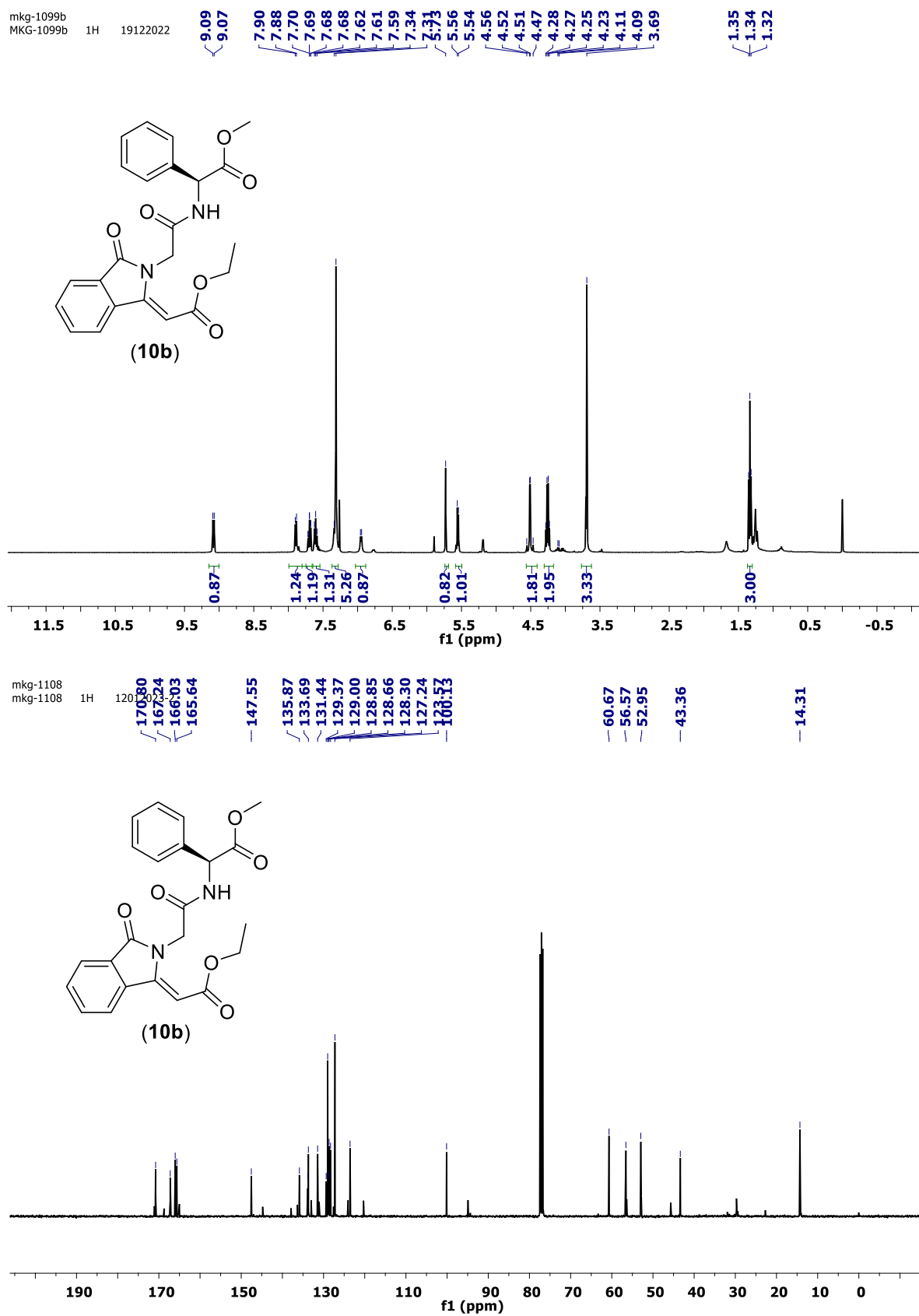


Figure. S25. ^1H , ^{13}C NMR spectra of **10b**

NKS_MKG_1099_B

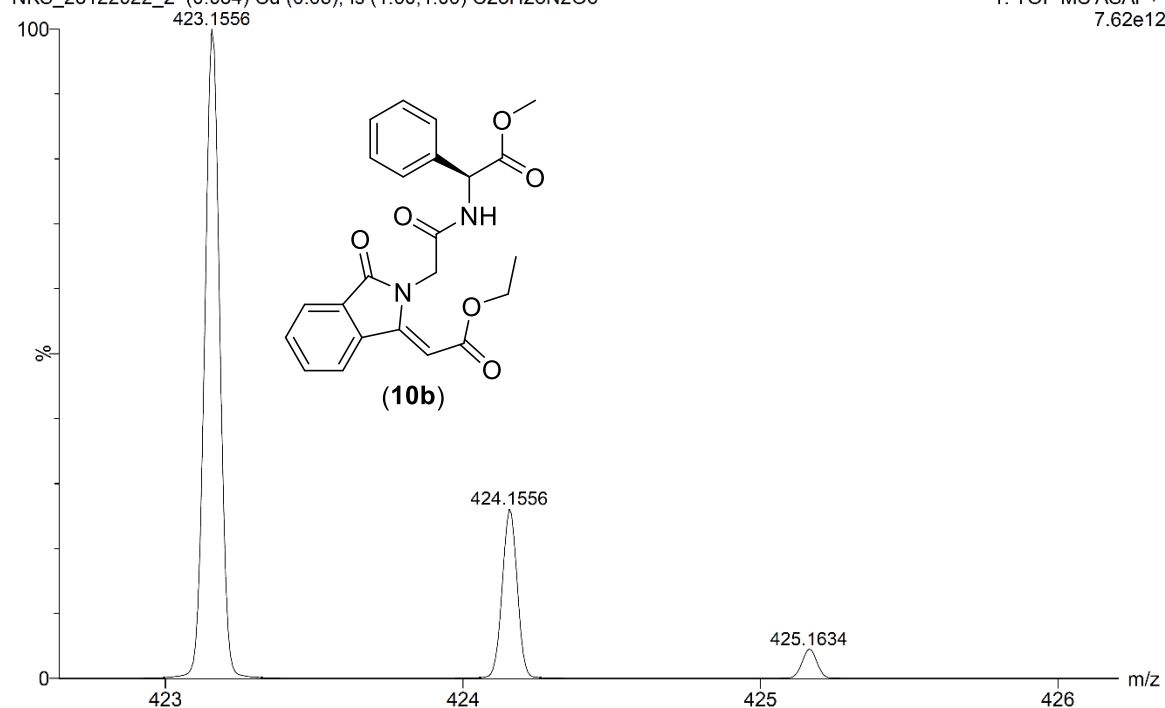
23-Dec-2022

10:48:23

XEVO-G2XSQTOF#YFA1739

NKS_23122022_2 (0.054) Cu (0.05); Is (1.00,1.00) C₂₃H₂₃N₂O₆

1: TOF MS ASAP+
7.62e12



NKS_23122022_2 38 (0.759) Cm (38)

1: TOF MS ASAP+
9.73e6

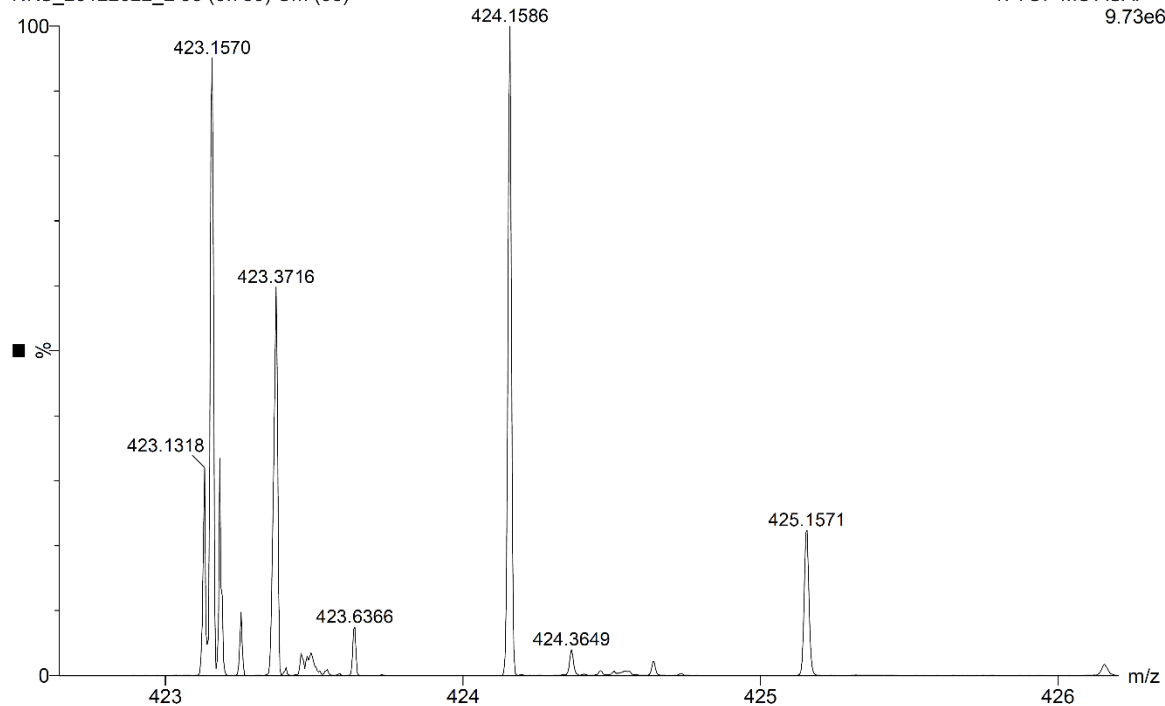
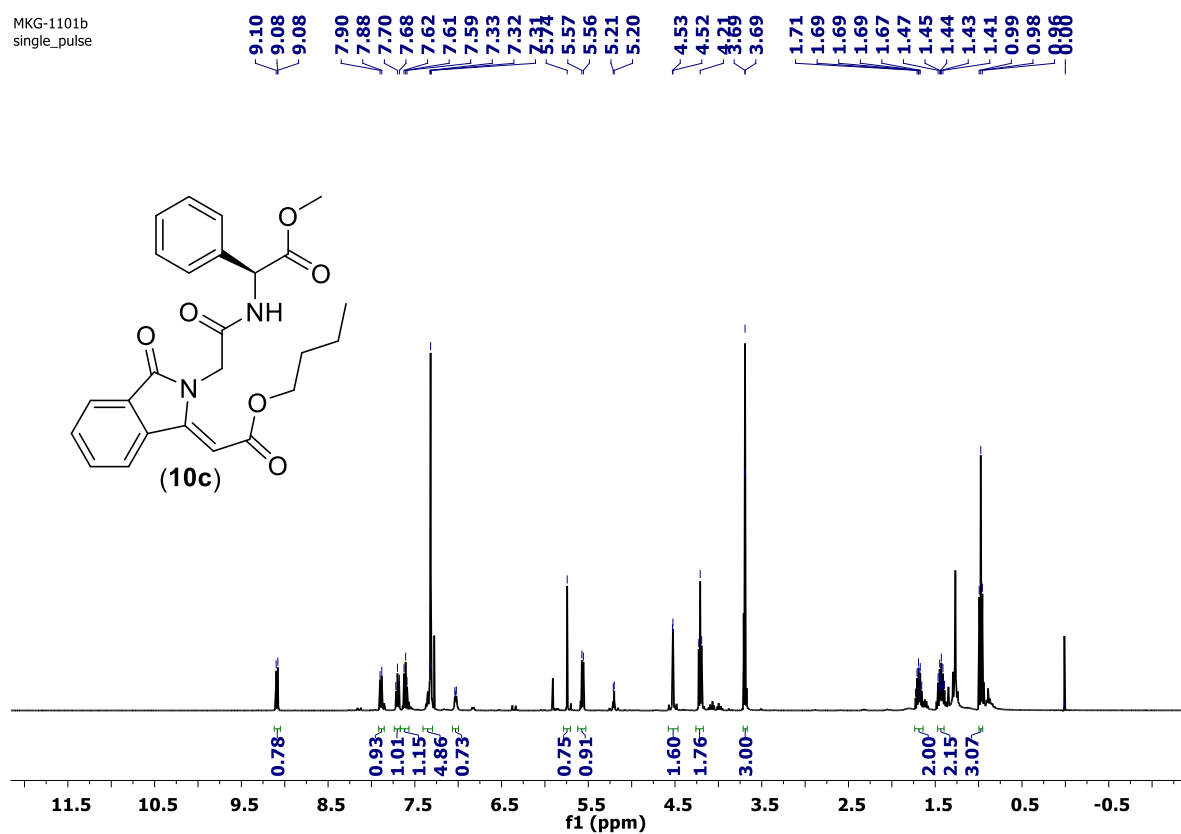


Figure. S26. ESI-HRMS spectra of **10b**

MKG-1101b
single_pulse



MKG-1101b
single pulse decoupled gated NMR

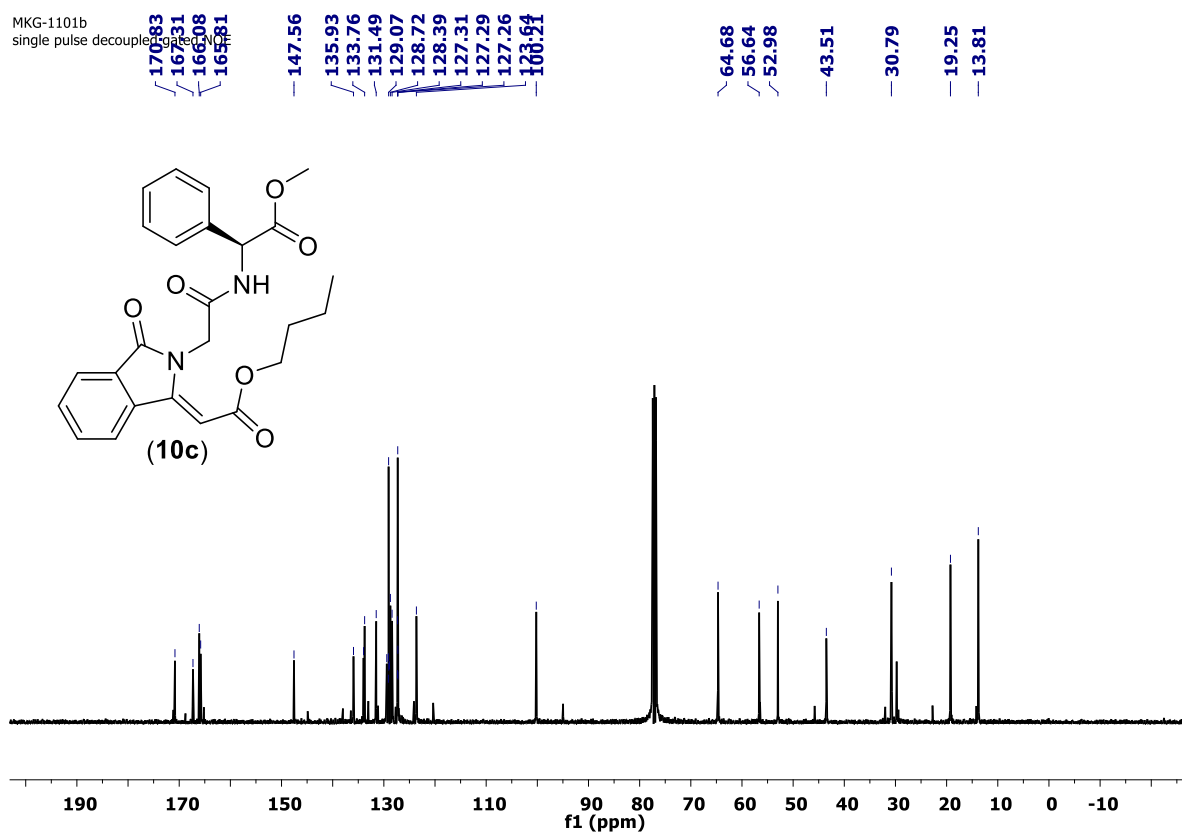


Figure. S27. ^1H , ^{13}C NMR spectra of **10c**

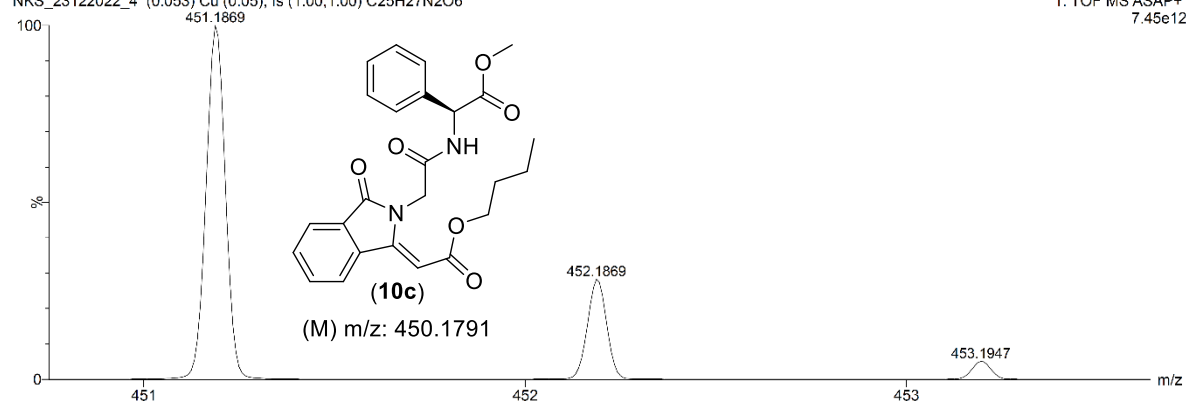
NKS_MKG_1101_A

23-Dec-2022
10:55:07

XEVO-G2XSQTOF#YFA1739

NKS_23122022_4 (0.053) Cu (0.05); Is (1.00,1.00) C₂₅H₂₇N₂O₆

1: TOF MS ASAP+
7.45e12



NKS_23122022_4 15 (0.310) Cm (15:16)

1: TOF MS ASAP+
9.60e5

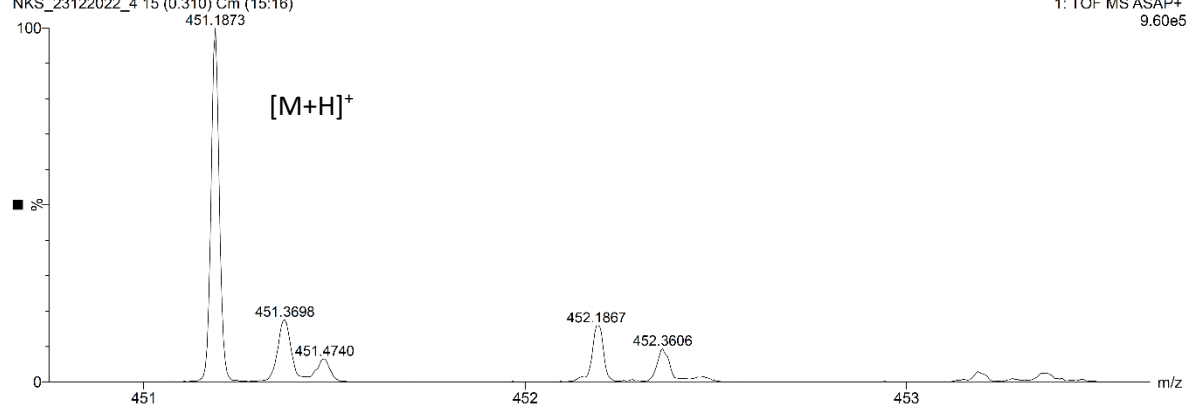
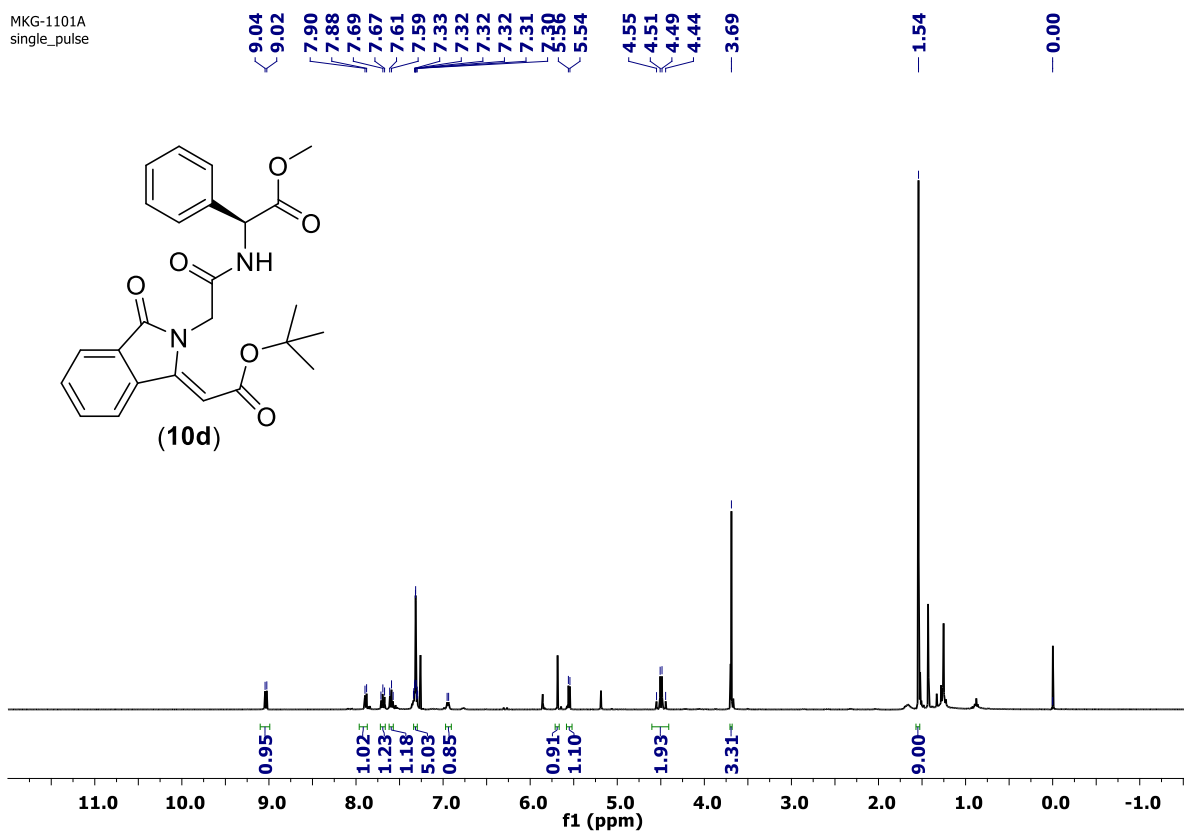


Figure. S28. ESI-HRMS spectra of **10c**

MKG-1101A
single_pulse



MKG-1101A
single pulse decoupled

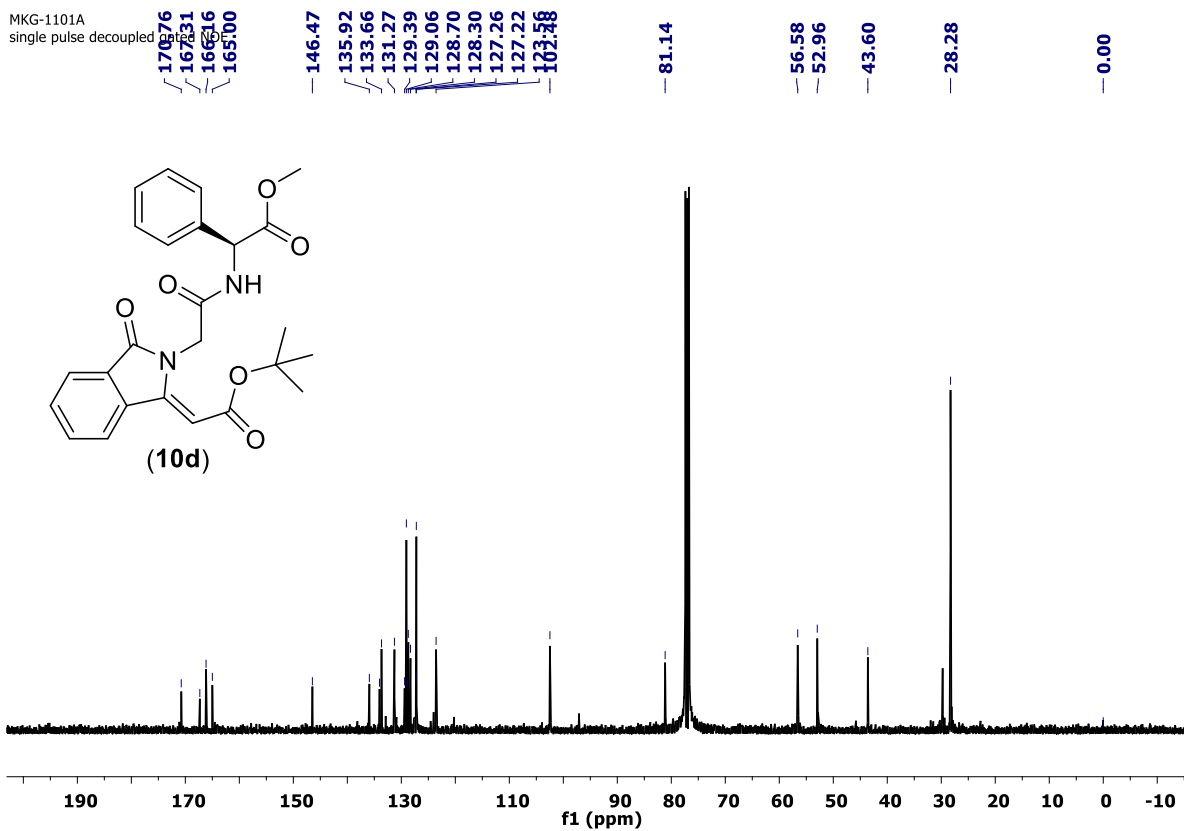


Figure. S29. ^1H , ^{13}C NMR spectra of indolinone **10d**

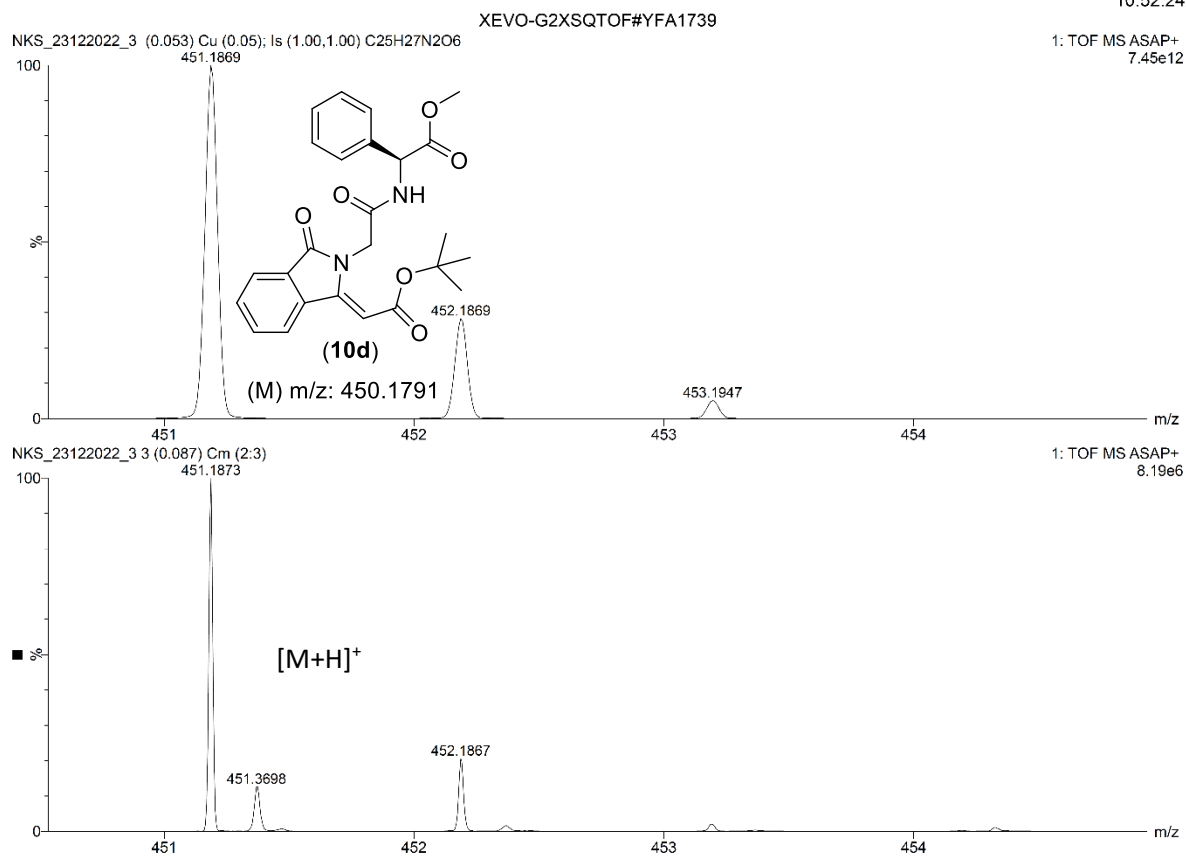


Figure. S30. ESI-HRMS spectra of indolinone **10d**

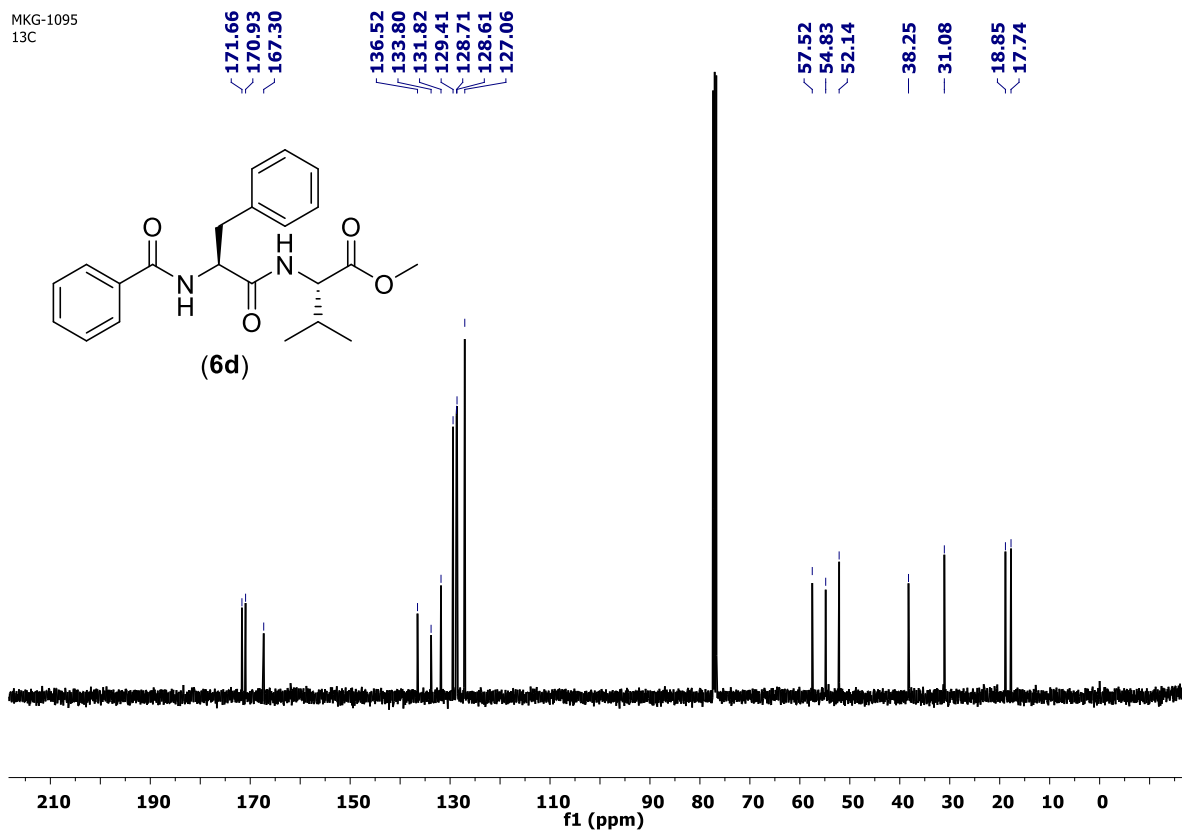
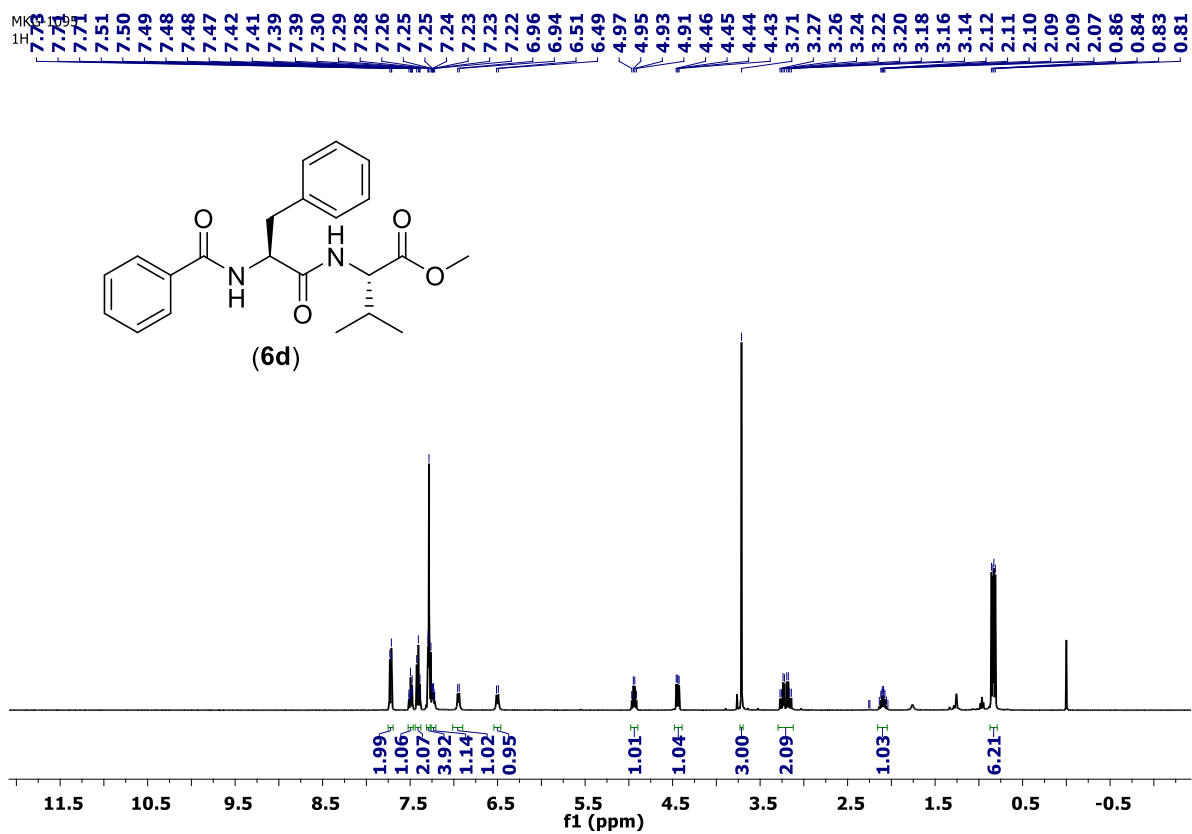
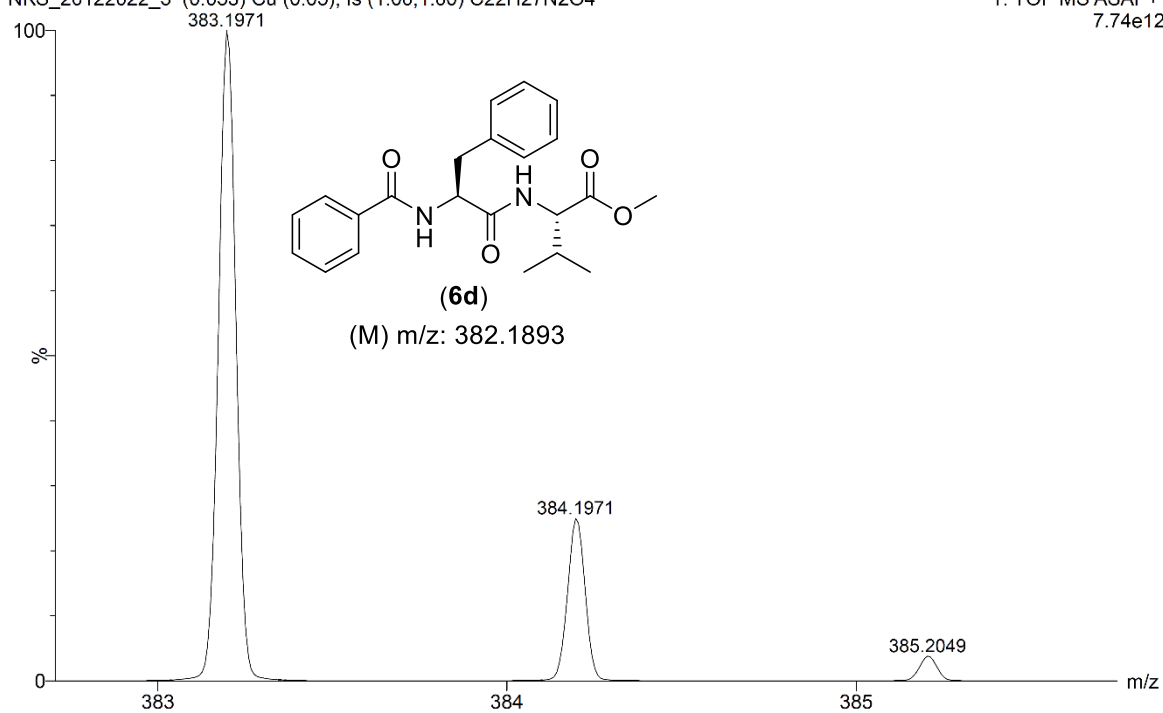


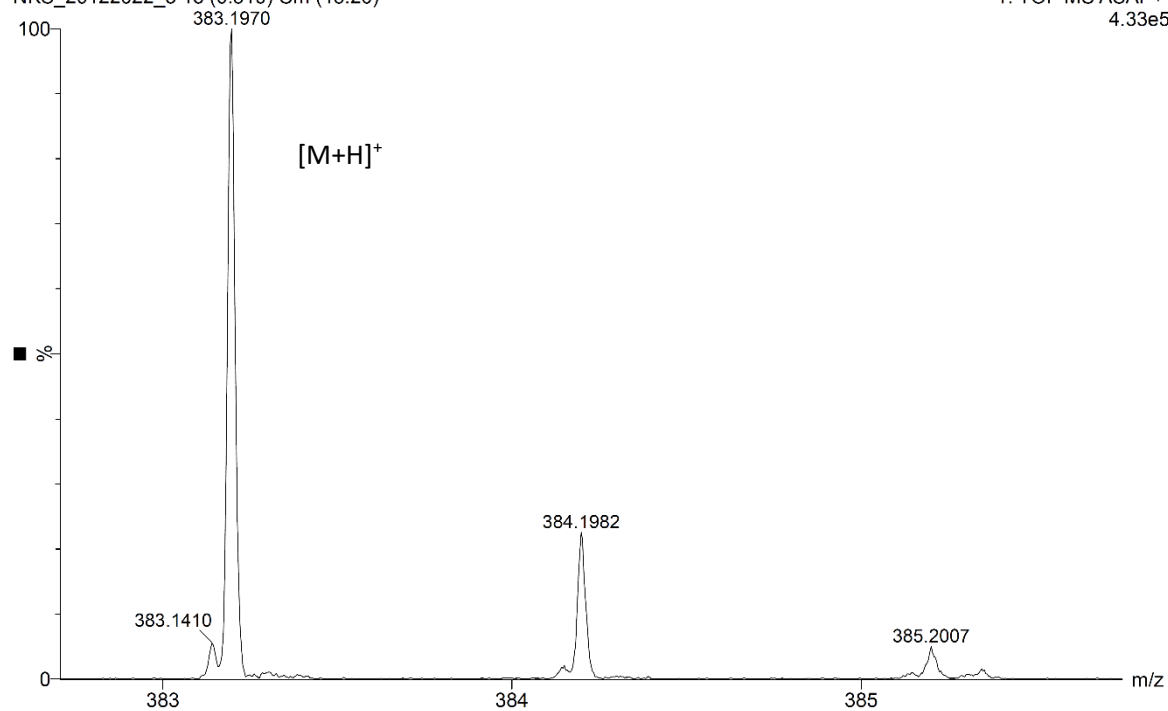
Figure. S31. ¹H, ¹³C NMR spectra of 6d

XEVO-G2XSQTOF#YFA1739

NKS_20122022_3 (0.053) Cu (0.05); ls (1.00,1.00) C22H27N2O4

1: TOF MS ASAP+
7.74e12

NKS_20122022_3 15 (0.310) Cm (15:20)

1: TOF MS ASAP+
4.33e5**Figure. S32.** ESI-HRMS spectra of **6d**

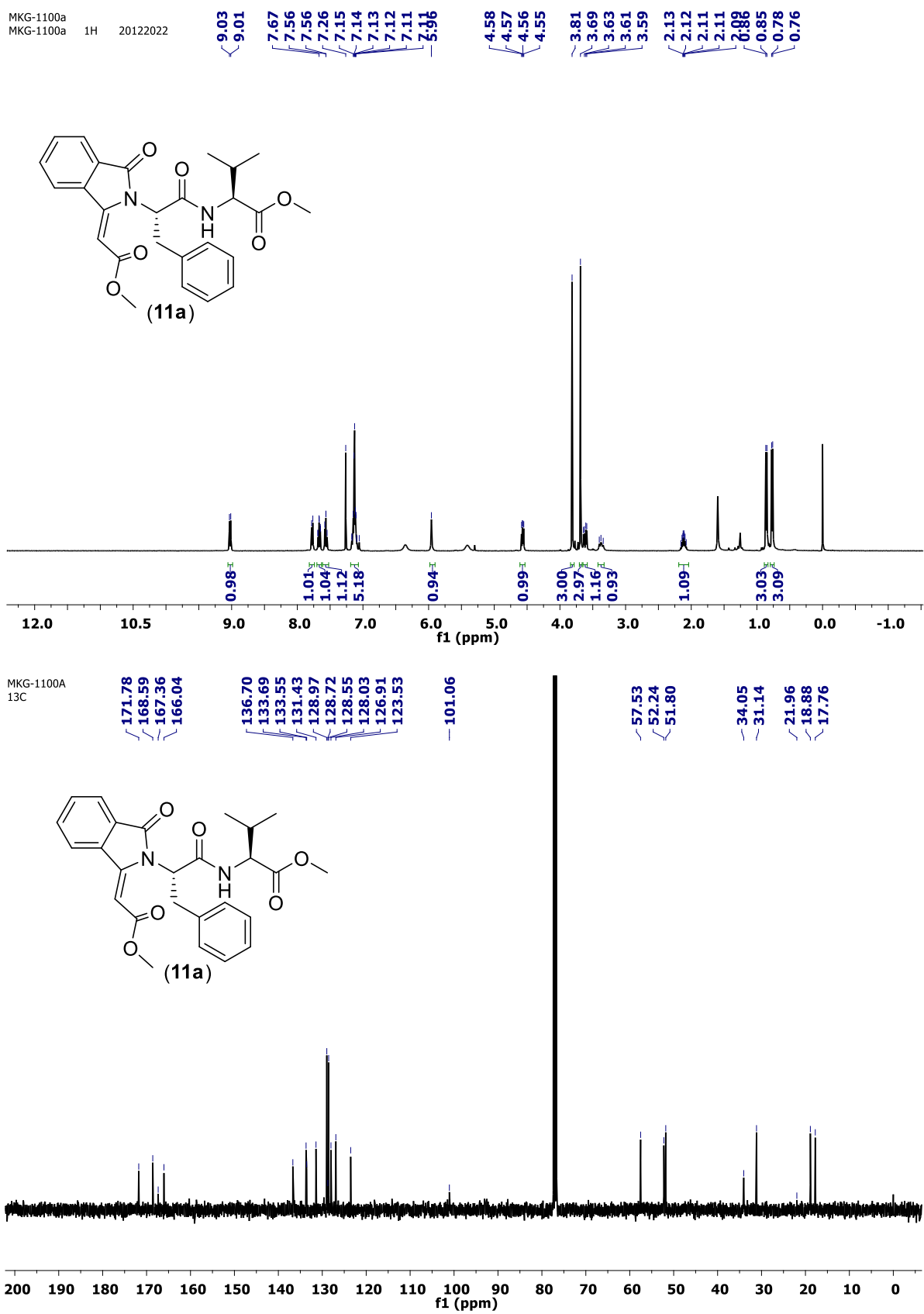


Figure. S33. ^1H , ^{13}C NMR spectra of **11a**

NKS_MKG_1100_A

23-Dec-2022
10:57:33

XEVO-G2XSQTOF#YFA1739

NKS_23122022_5 (0.053) Cu (0.05); Is (1.00,1.00) C₂₆H₂₈N₂O₆

1: TOF MS ASAP+
7.37e12

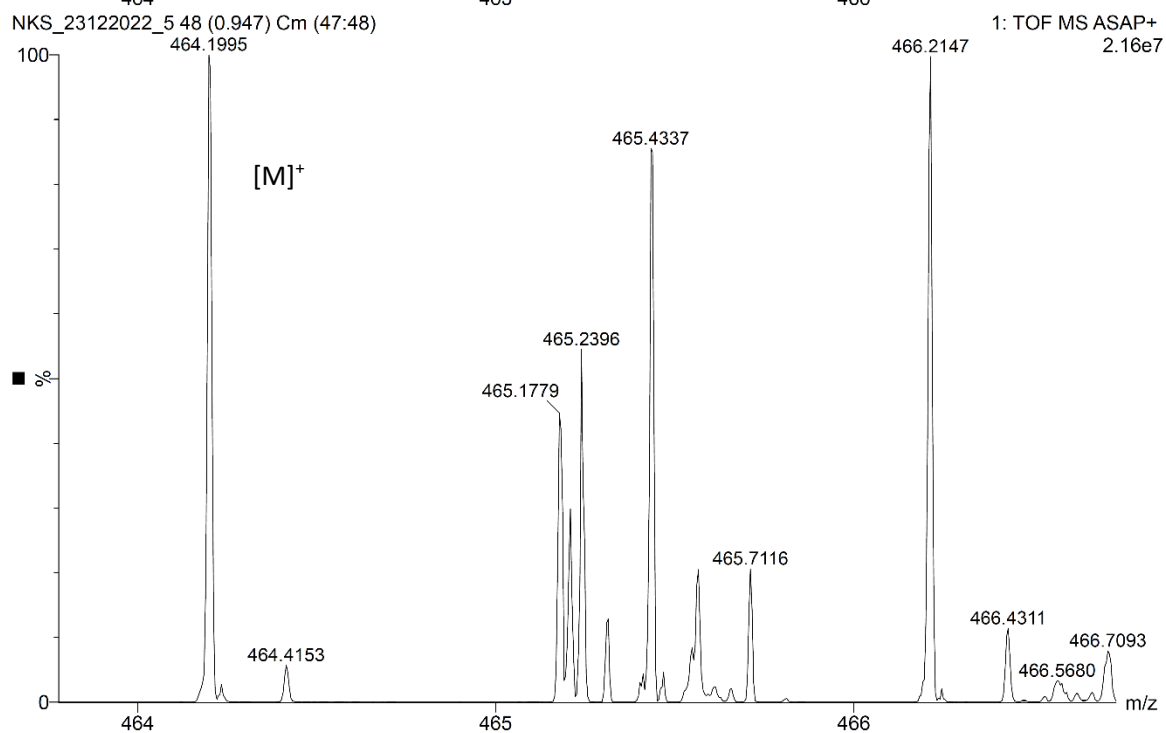
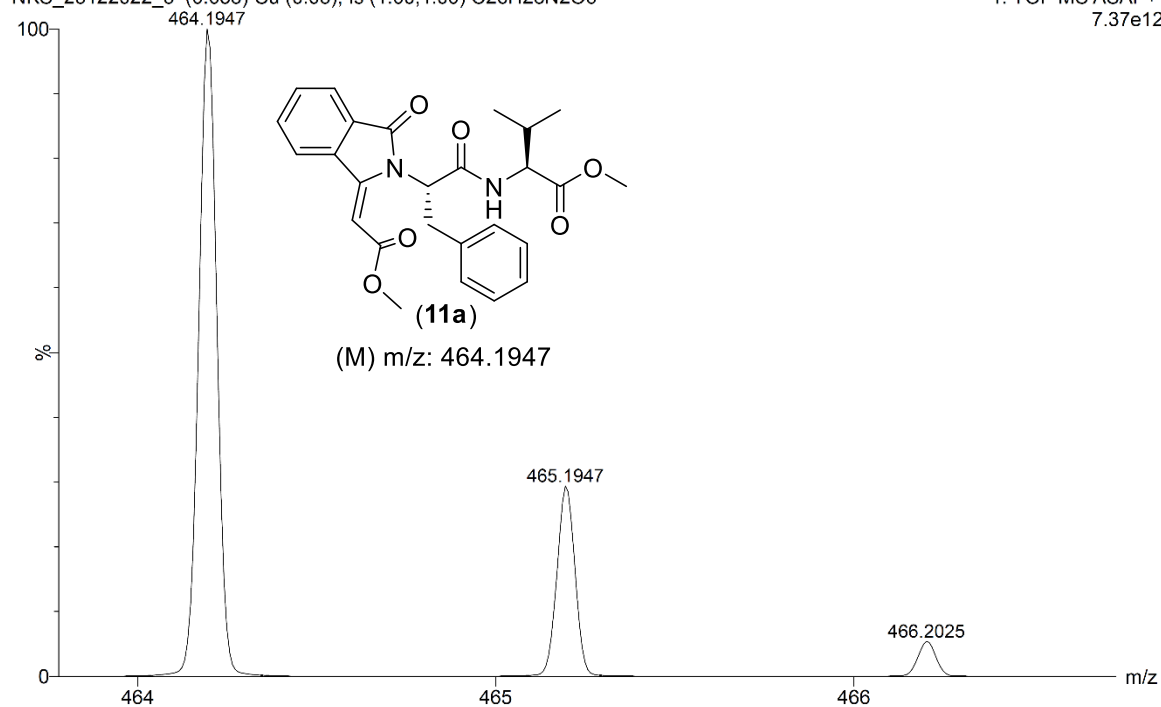


Figure. S34. ESI-HRMS spectra of **11a**

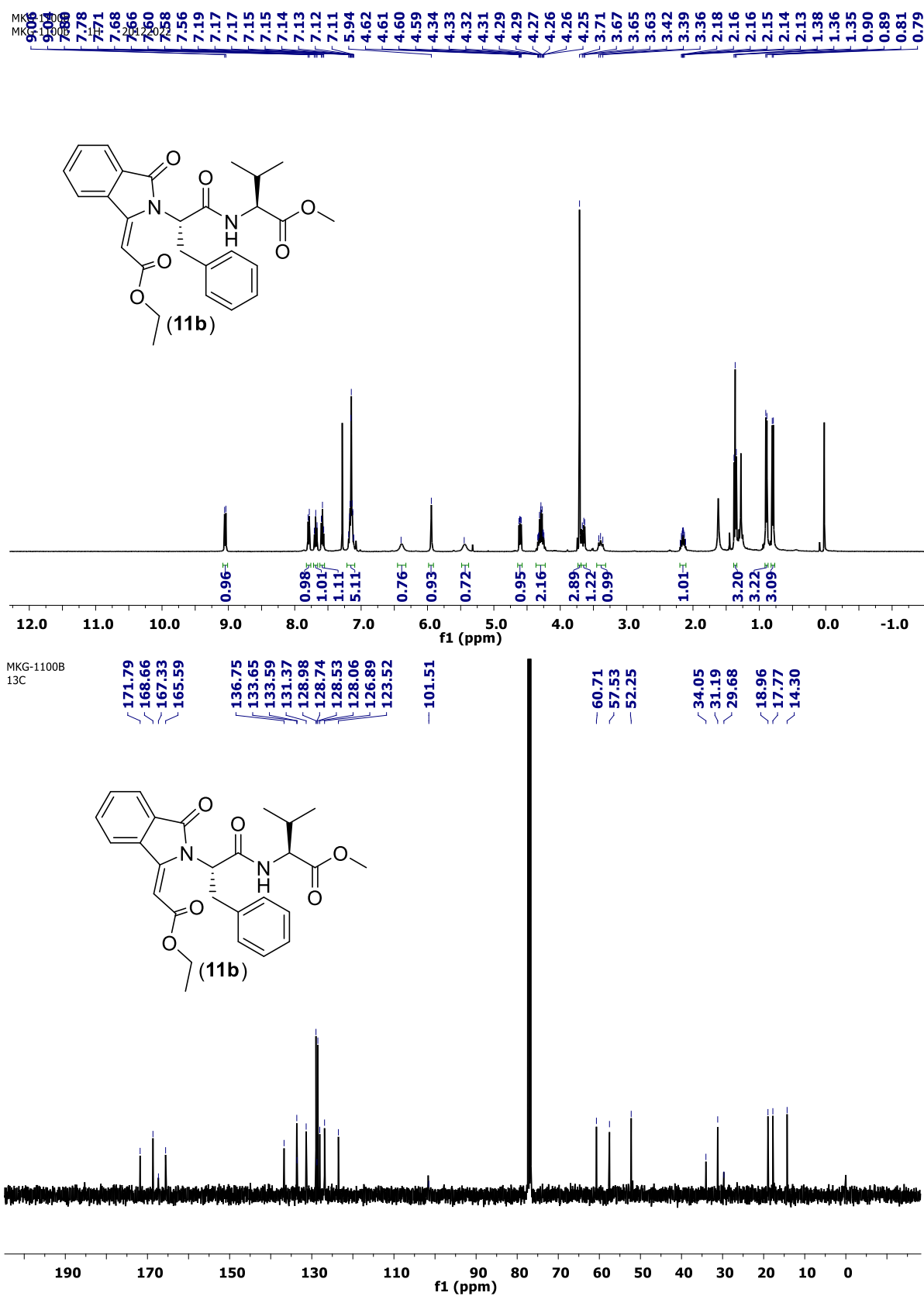


Figure. S35. ^1H , ^{13}C NMR spectra of **11b**

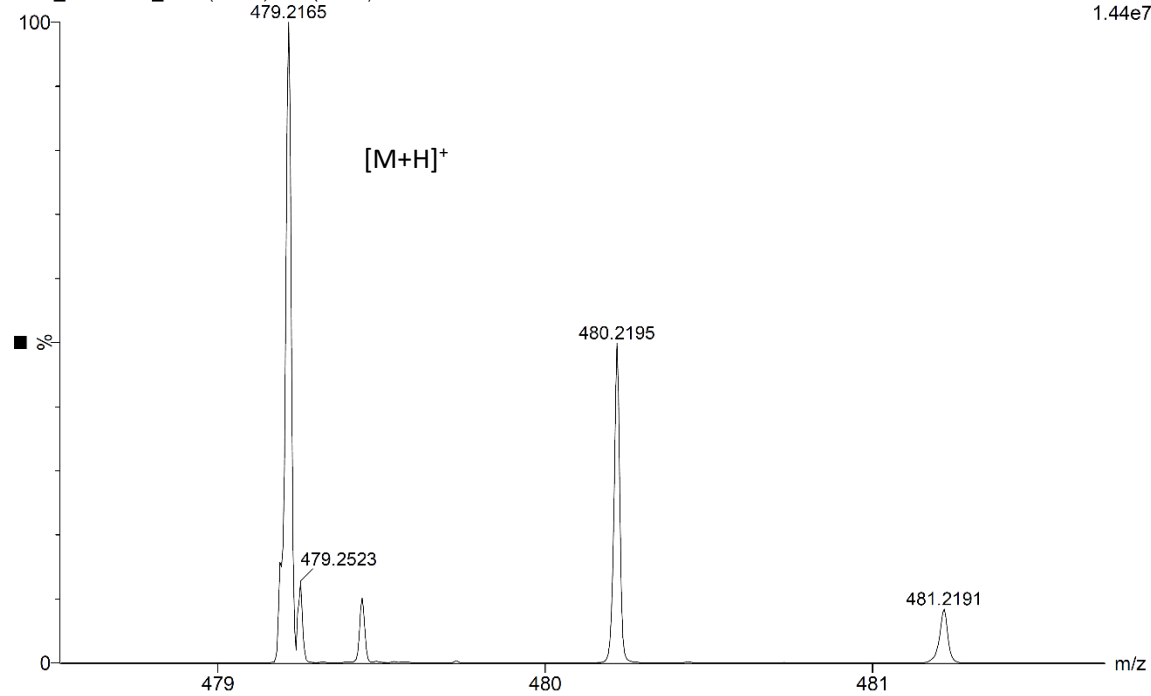
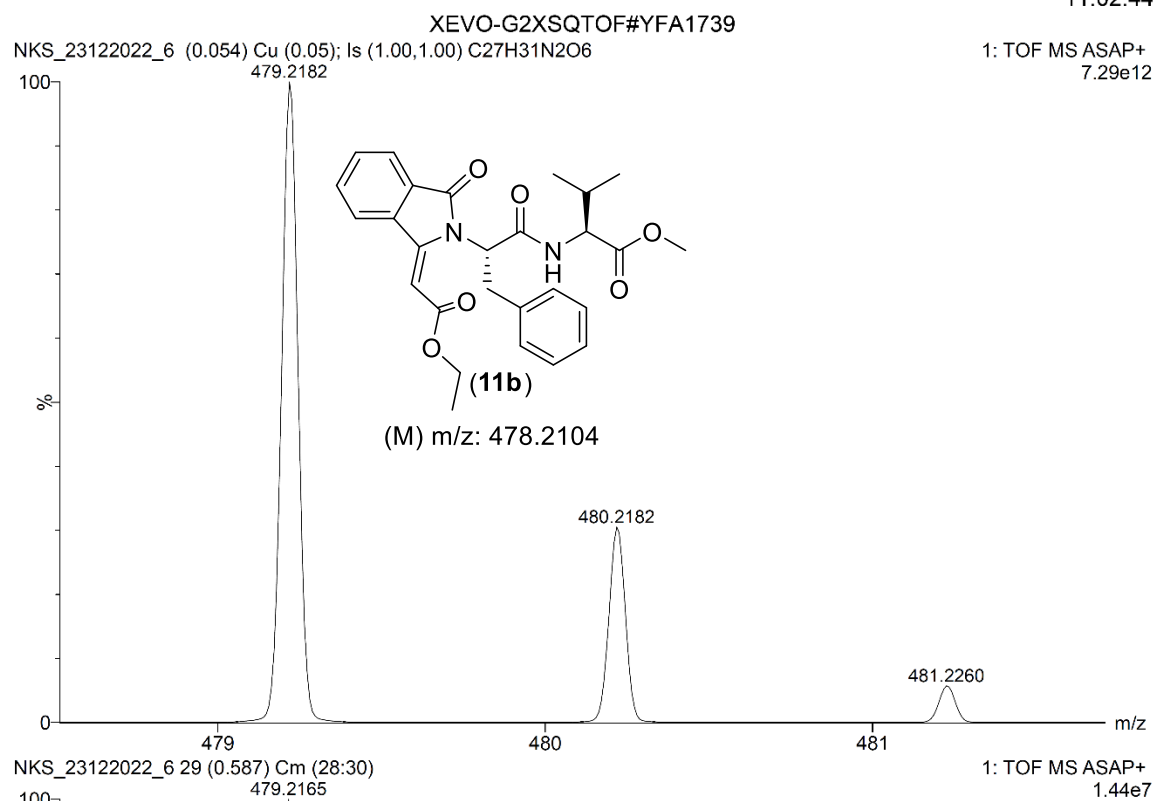


Figure. S36. ESI-HRMS spectra of **11b**

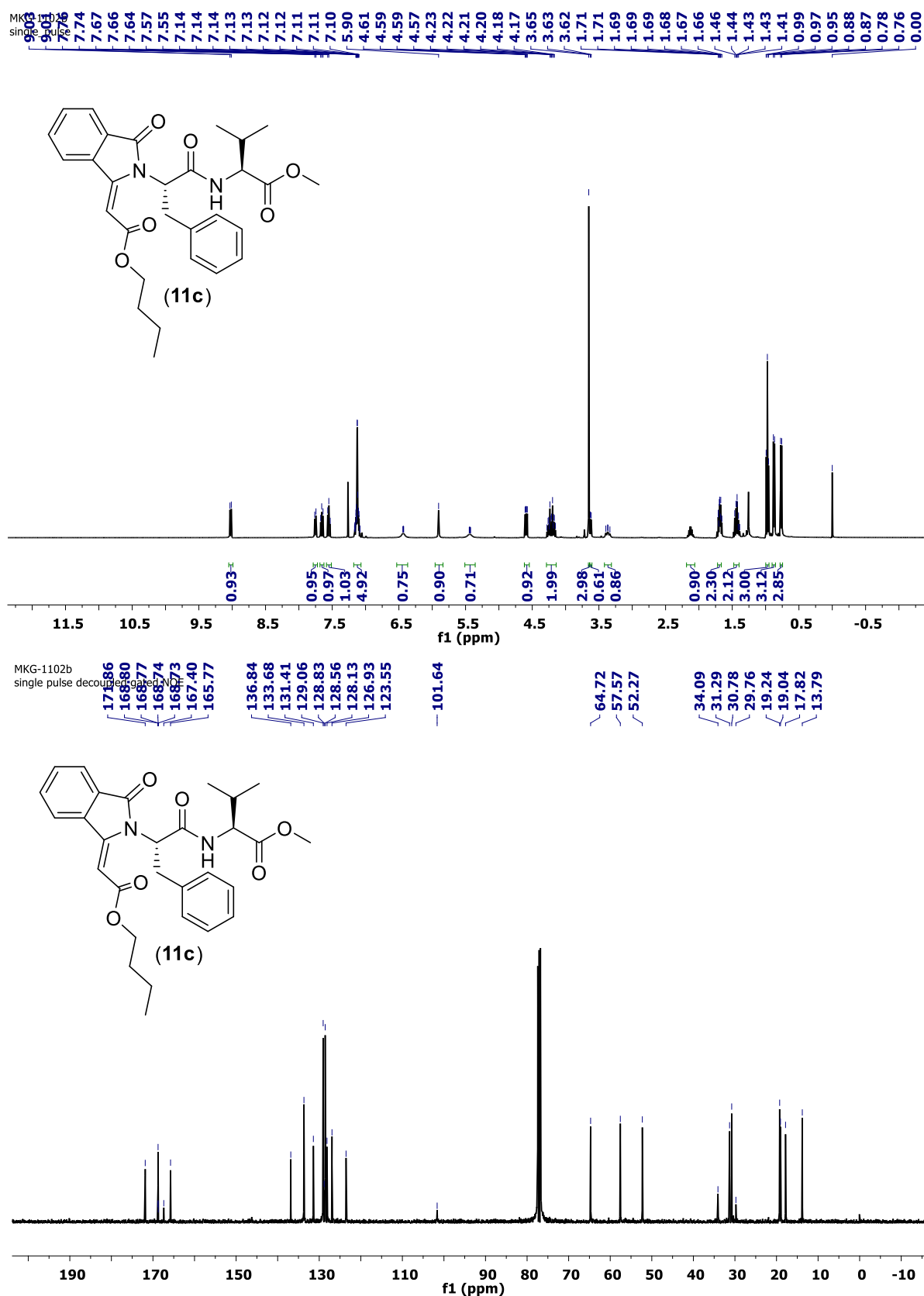


Figure. S37. ¹H, ¹³C NMR spectra of **11c**

NKS_MKG_1102_A

23-Dec-2022
11:11:01

XEVO-G2XSQTOF#YFA1739

NKS_23122022_8 (0.054) Cu (0.05); Is (1.00,1.00) C₂₉H₃₅N₂O₆

1: TOF MS ASAP+
7.13e12

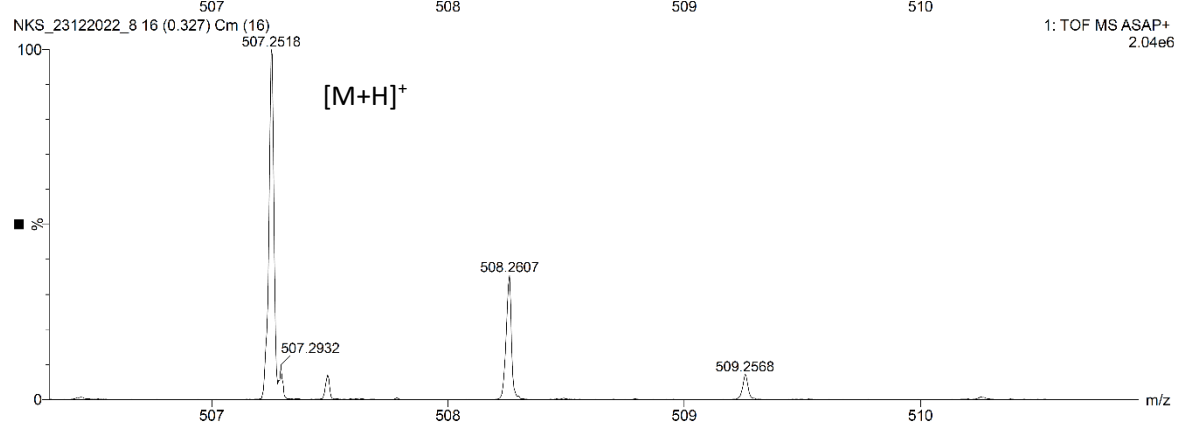
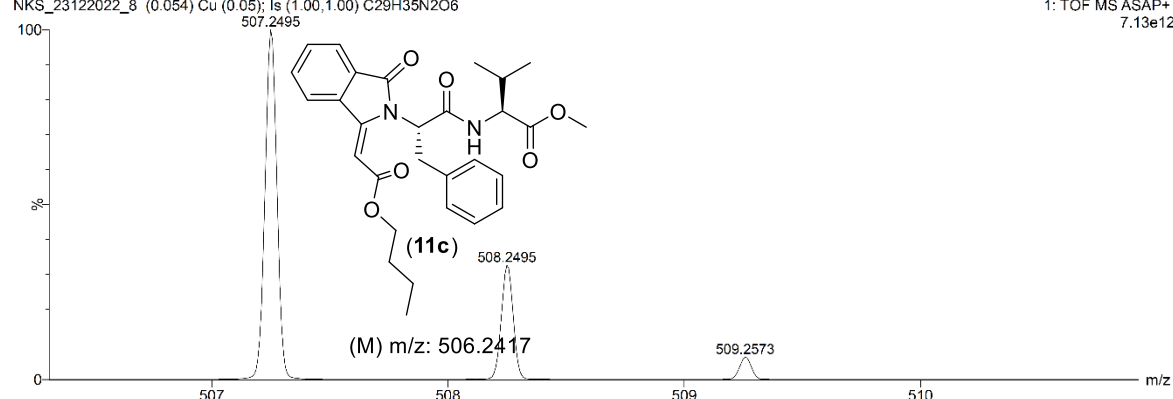


Figure. S38. ESI-HRMS spectra of **11c**

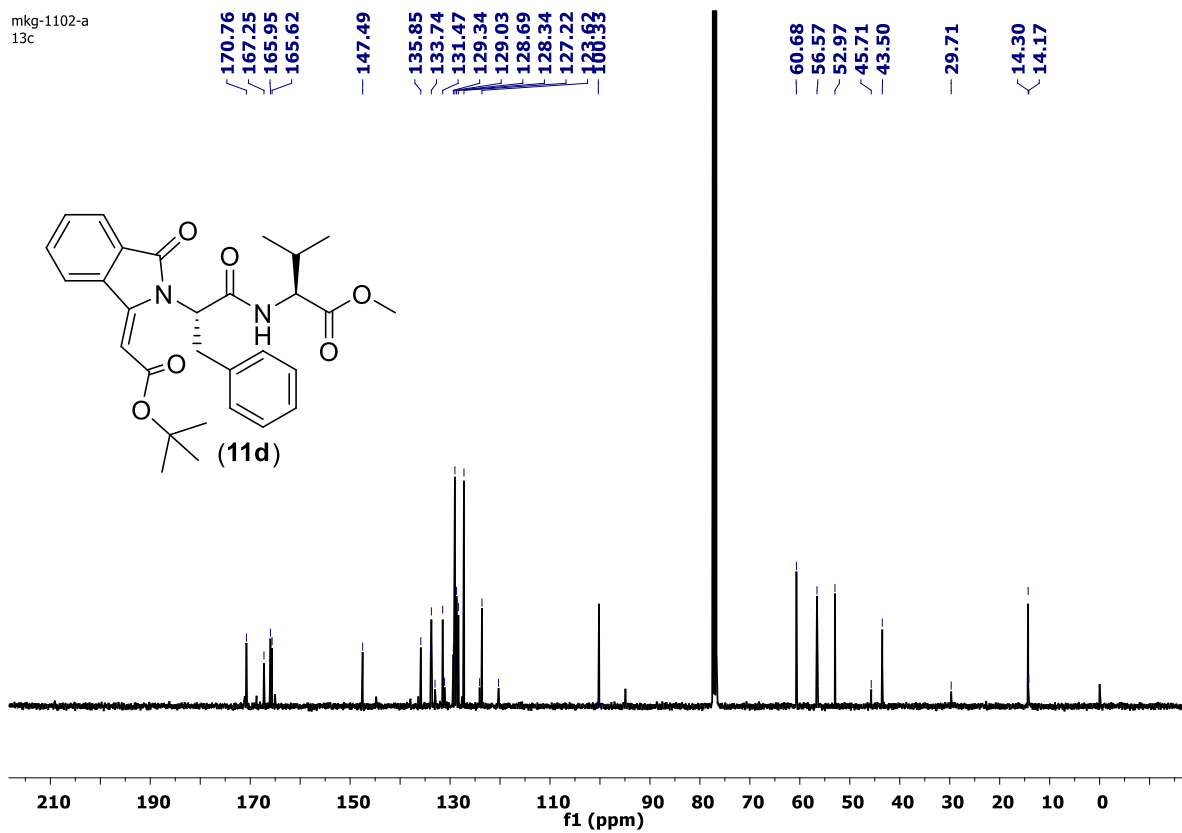
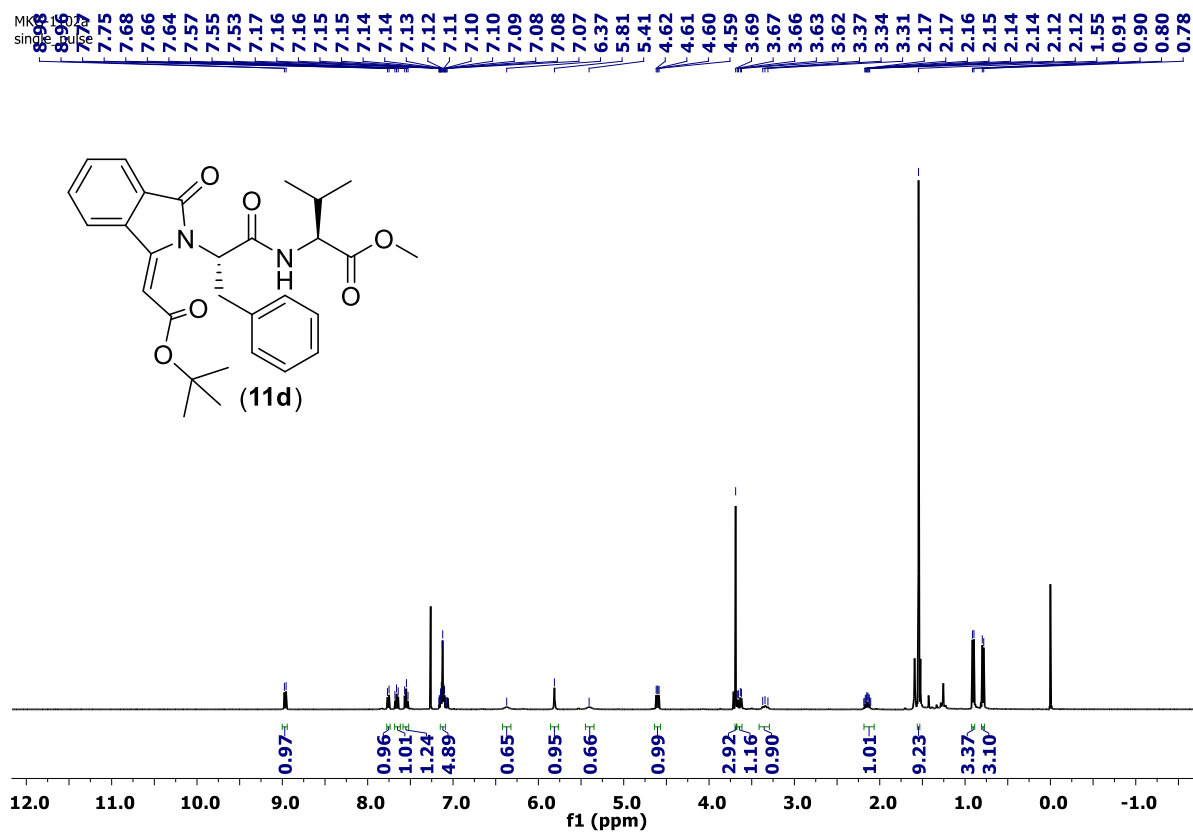


Figure. S39. ¹H, ¹³C NMR spectra of **11d**

NKS_MKG_1102_B

23-Dec-2022
11:05:20

XEVO-G2XSQTOF#YFA1739

NKS_23122022_7 (0.054) Is (1.00,1.00) C₂₉H₃₅N₂O₆

1: TOF MS ASAP+
7.13e12

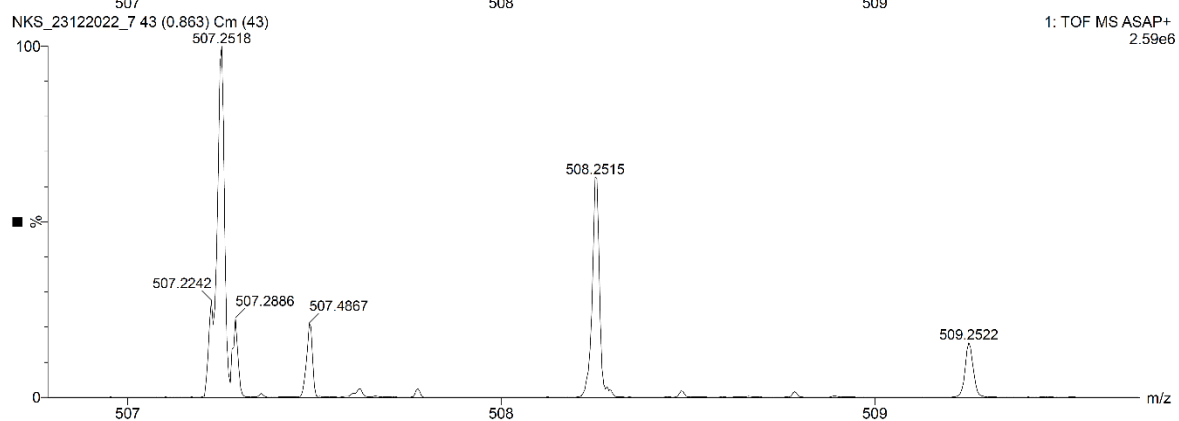
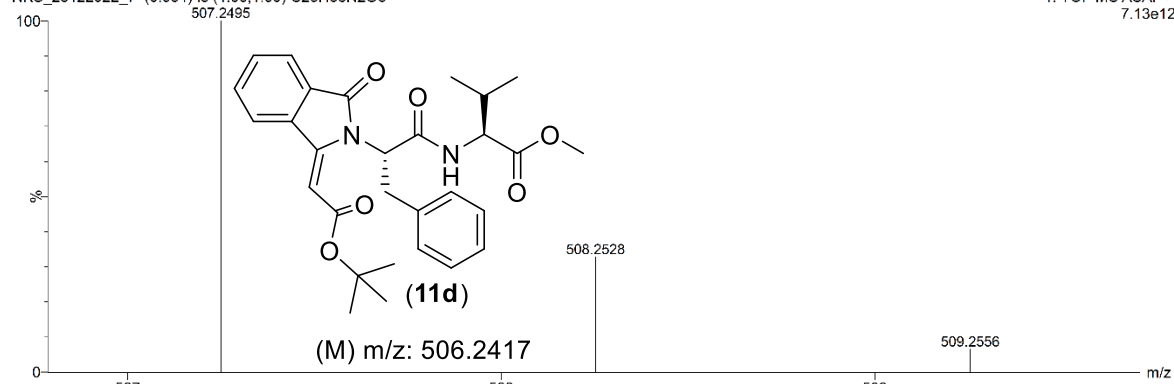


Figure. S40. ESI-HRMS spectra of **11d**

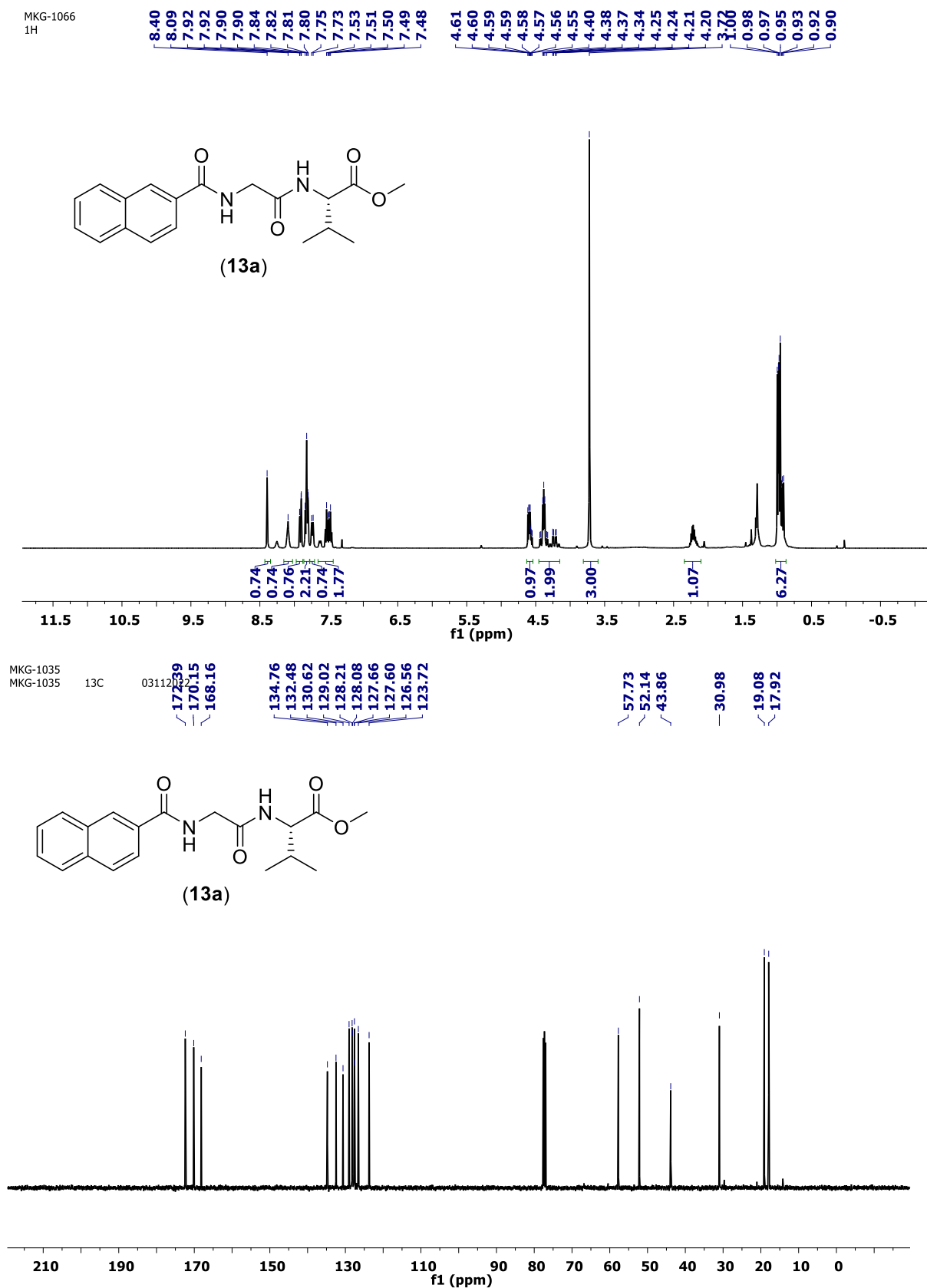


Figure. S41. ^1H , ^{13}C NMR spectra of **13a**

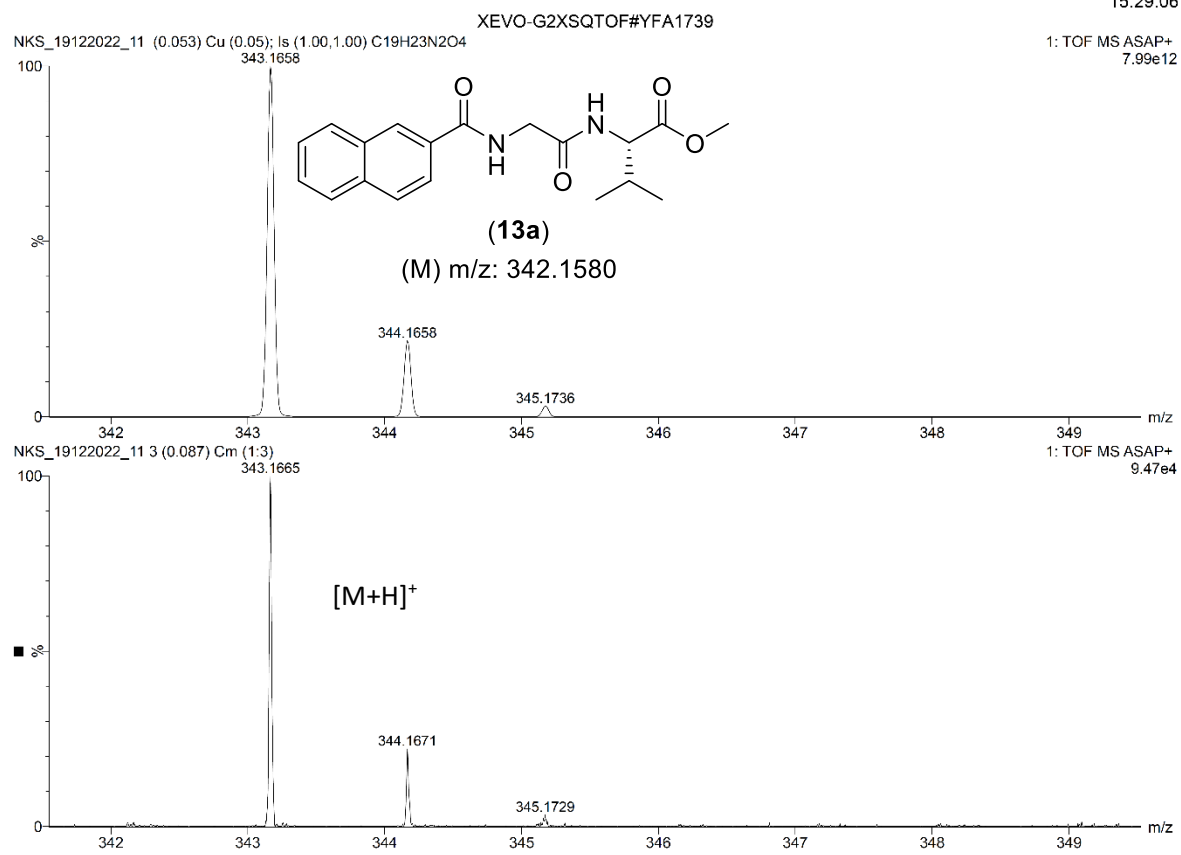


Figure. S42. ESI-HRMS spectra of **13a**

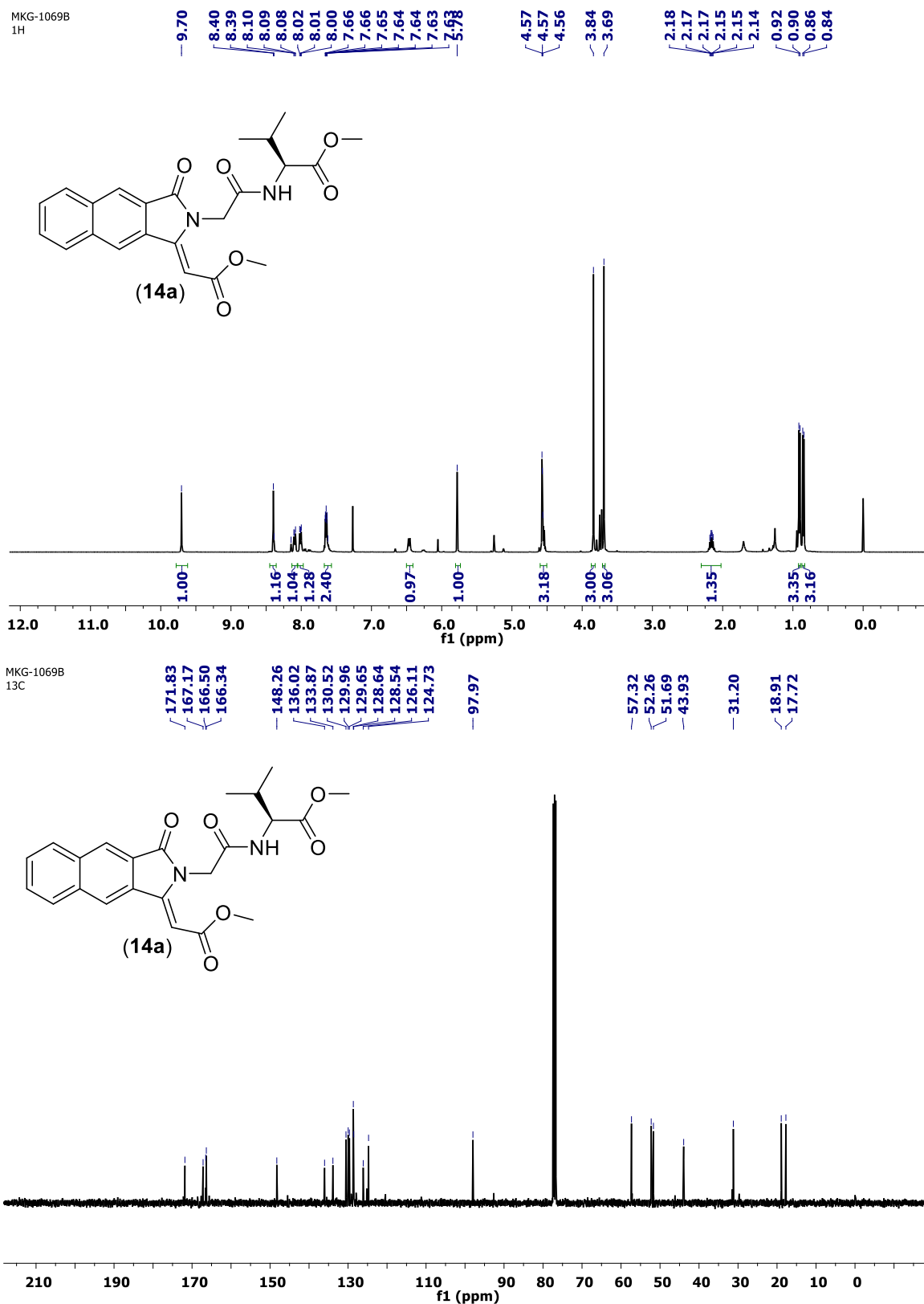
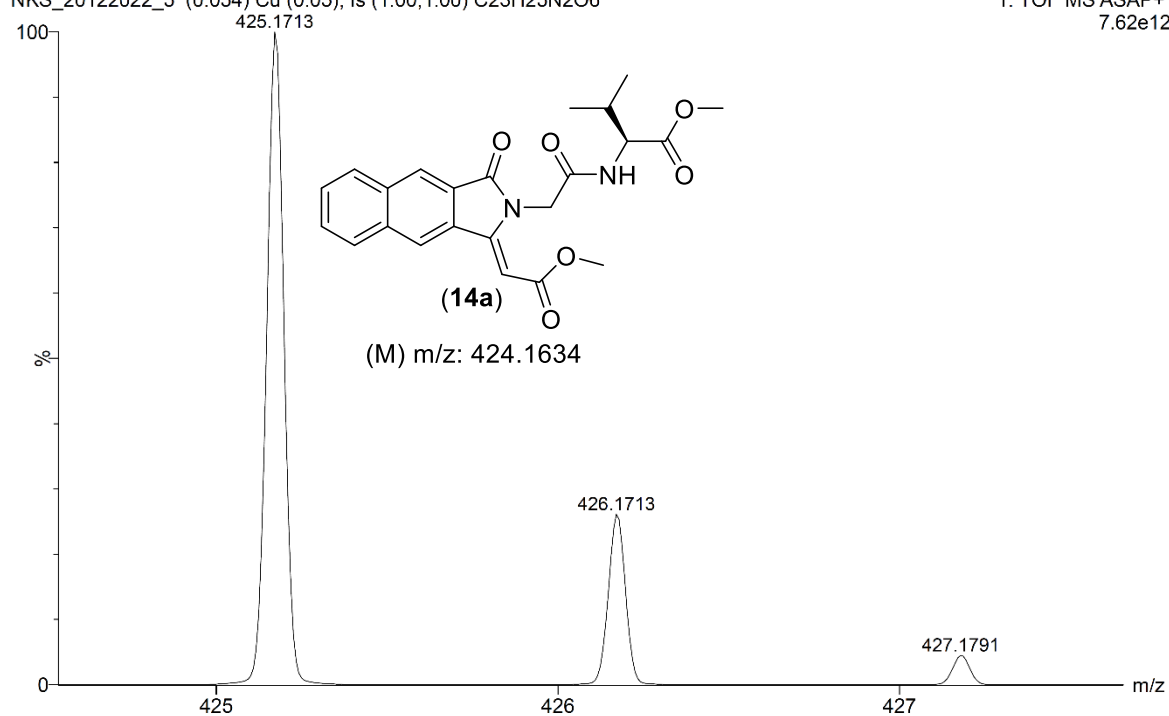
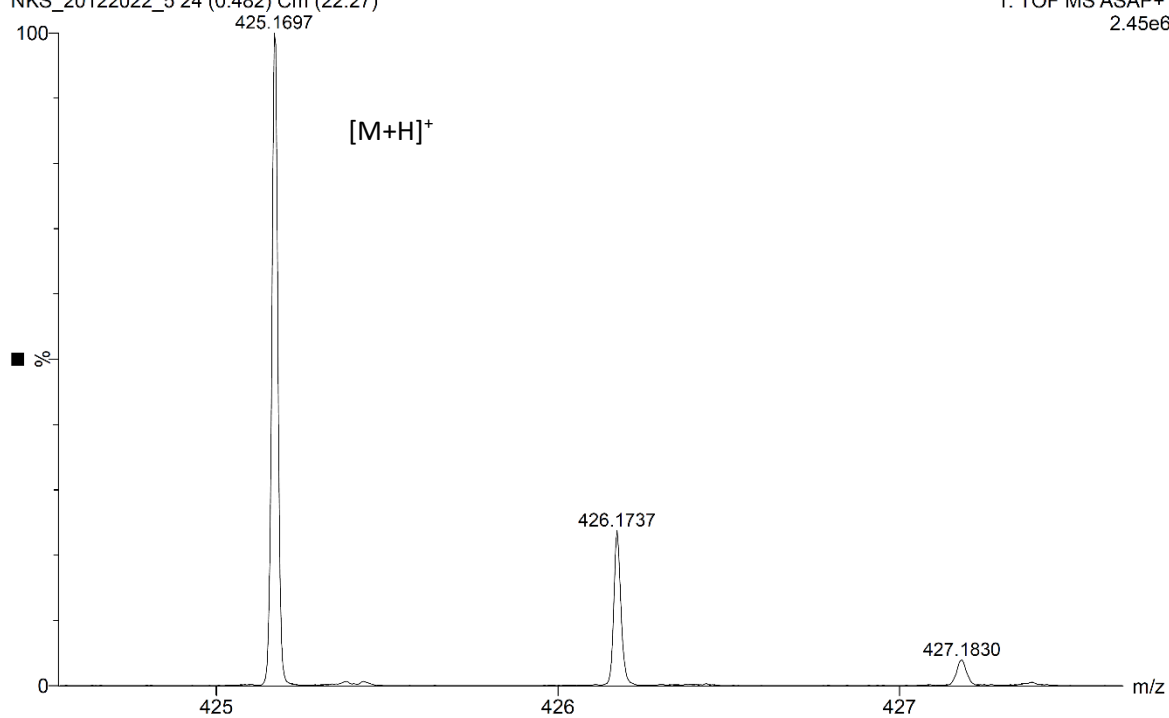


Figure.S43. ^1H , ^{13}C NMR spectra of 14a

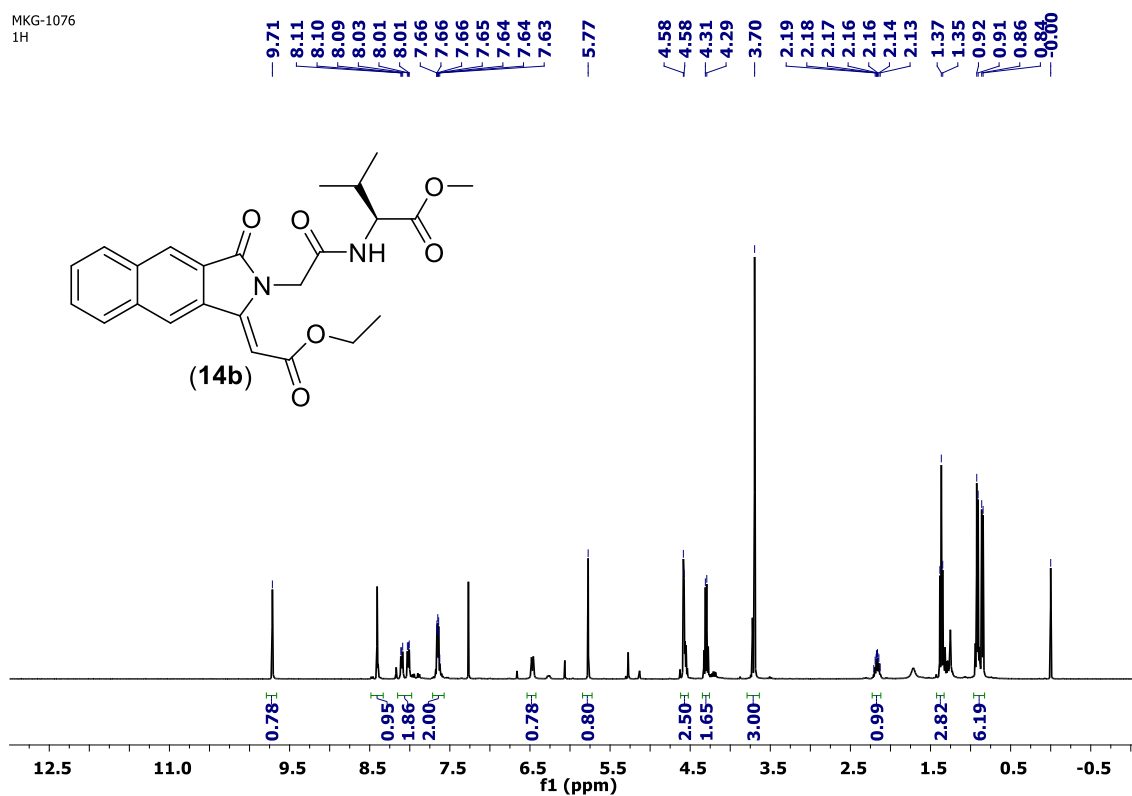
XEVO-G2XSQTOF#YFA1739

NKS_20122022_5 (0.054) Cu (0.05); Is (1.00,1.00) C₂₃H₂₅N₂O₆1: TOF MS ASAP+
7.62e12

NKS_20122022_5 24 (0.482) Cm (22:27)

1: TOF MS ASAP+
2.45e6**Figure. S44.** ESI-HRMS spectra of **14a**

MKG-1076
1H



MKG-1076
MKG-1076 13C

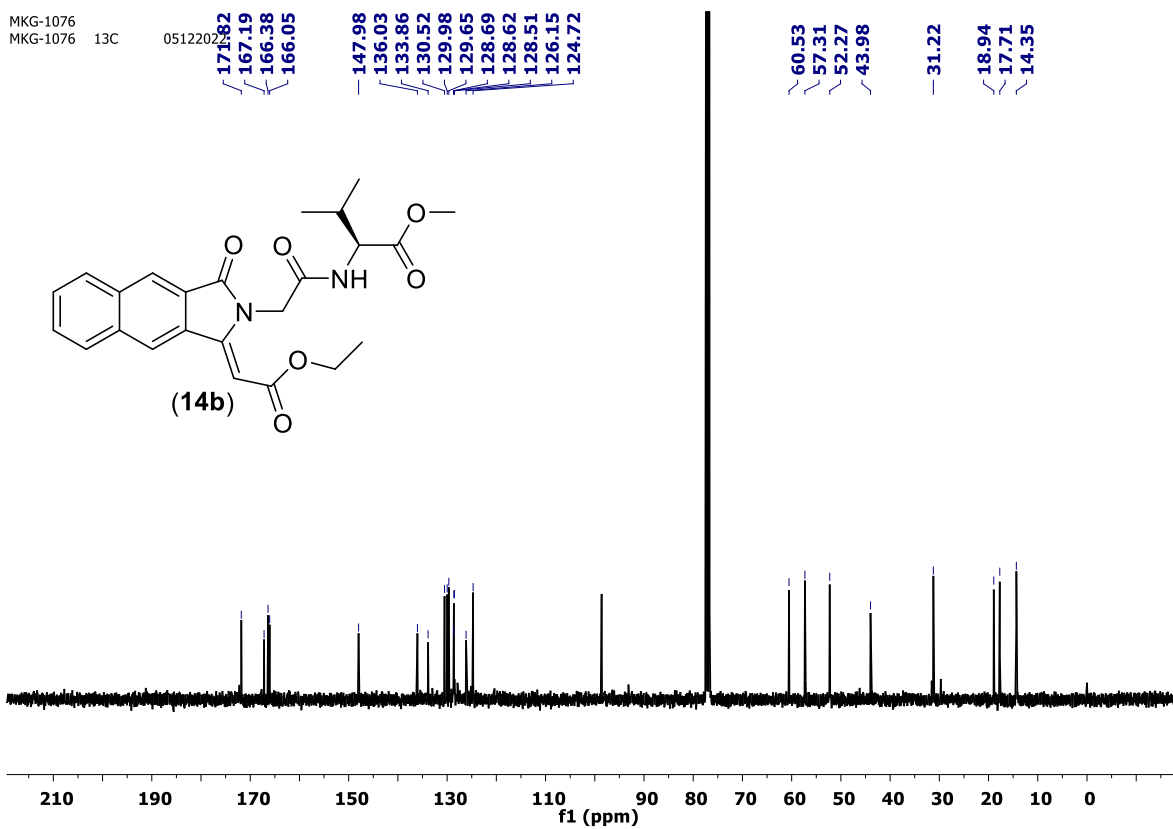


Figure. S45. ^1H , ^{13}C NMR spectra of **14b**

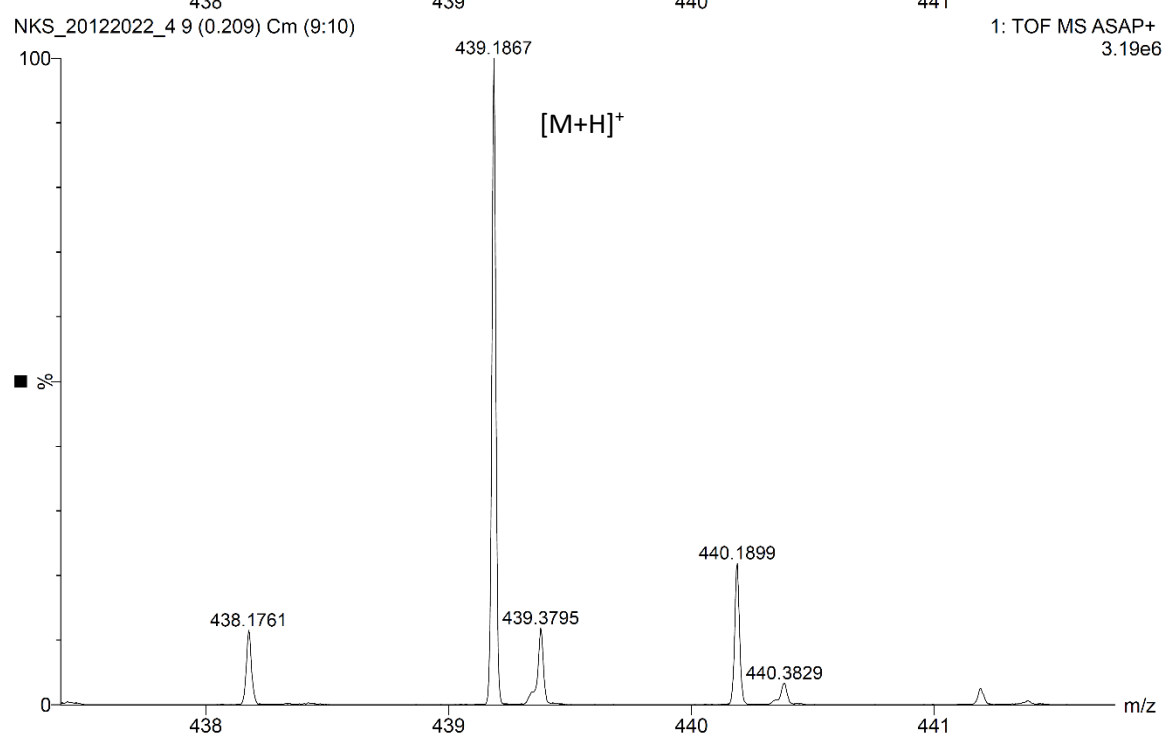
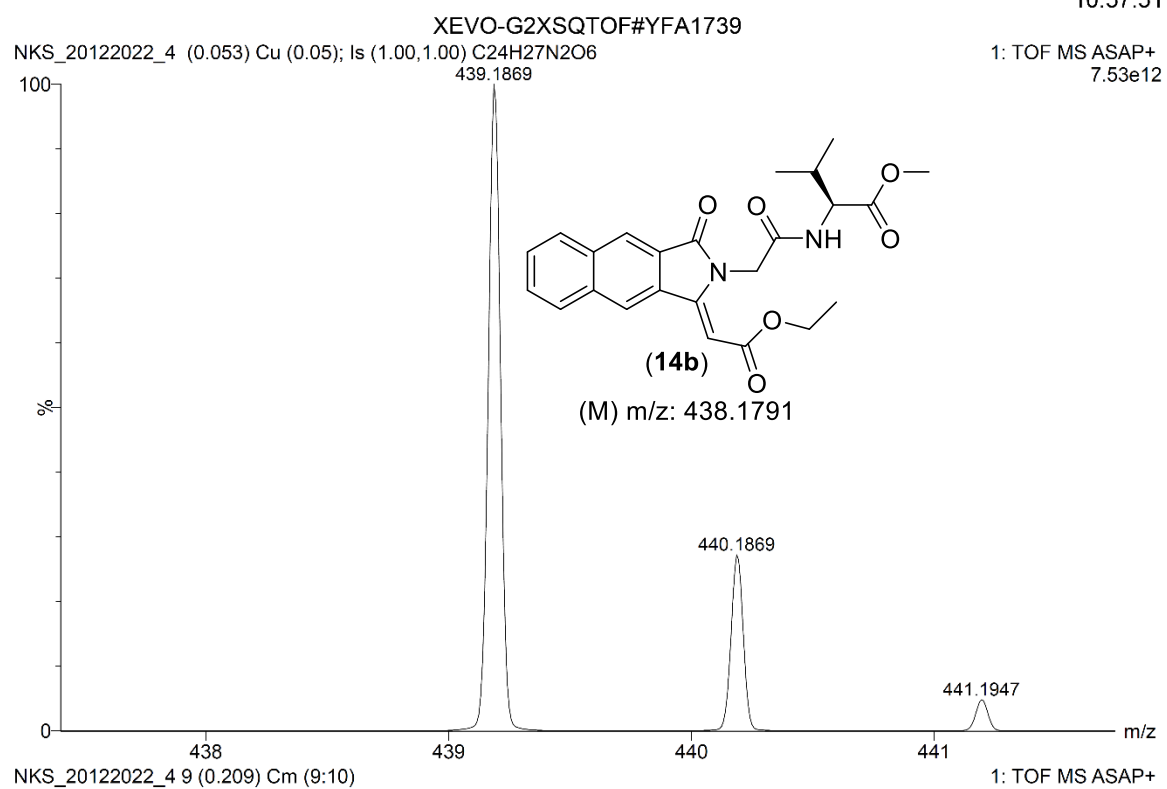
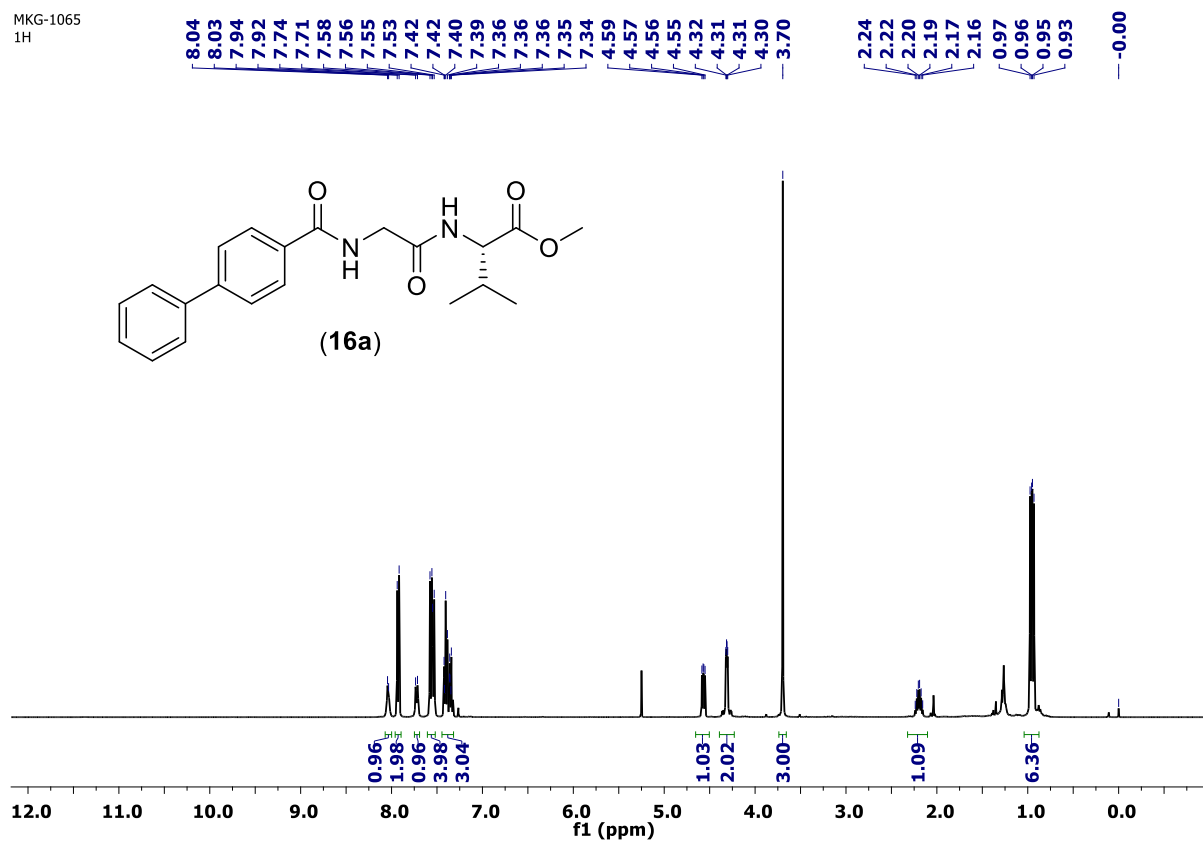


Figure. S46. ESI-HRMS spectra of **14b**

MKG-1065
1H



MKG-1065
13C

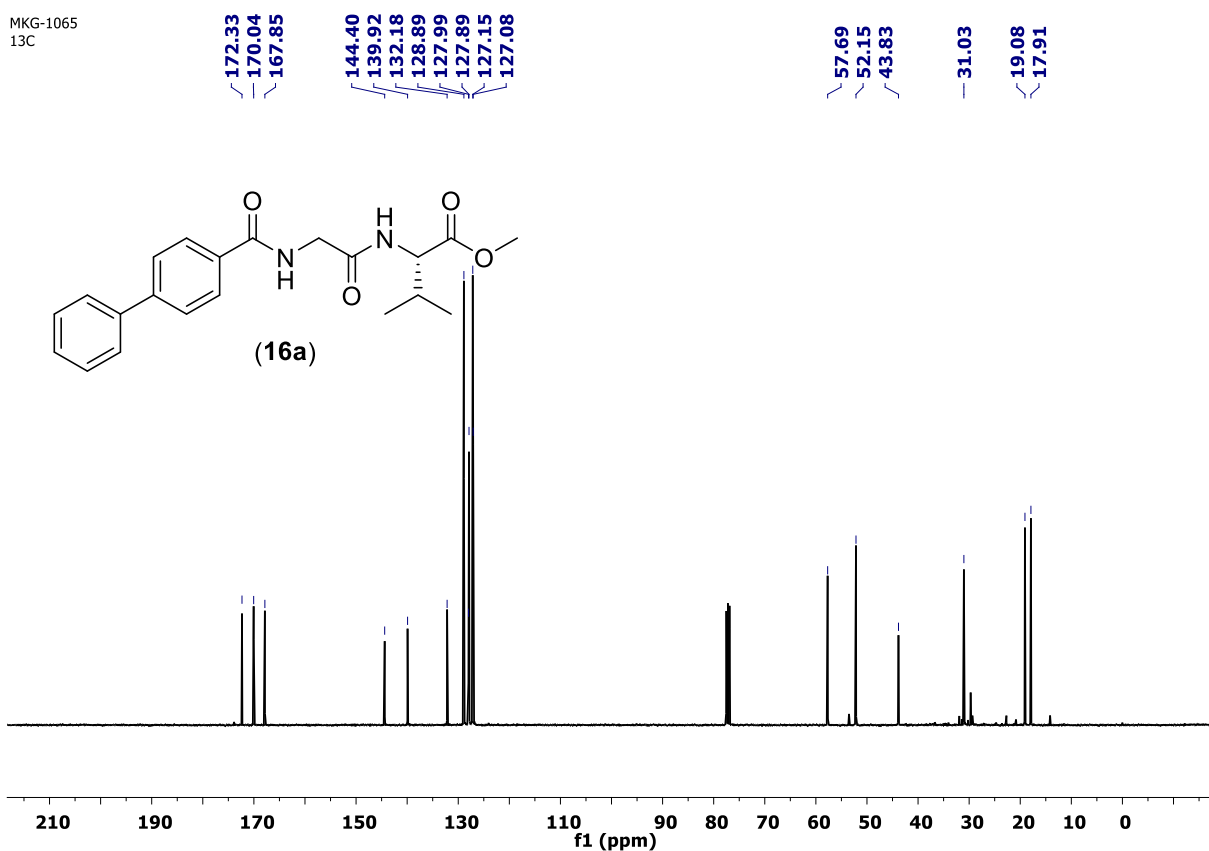


Figure. S47. ¹H, ¹³C NMR spectra of 16a

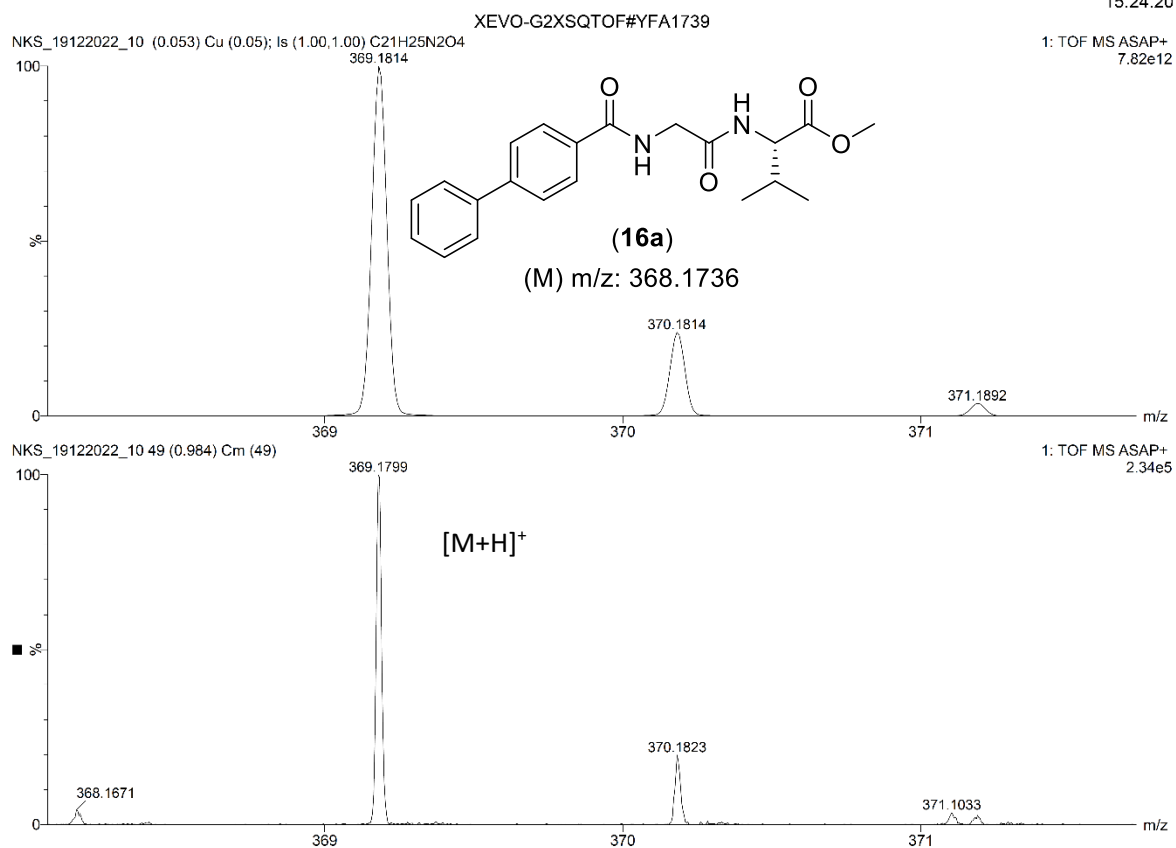


Figure. S48. ESI-HRMS spectra of **16a**

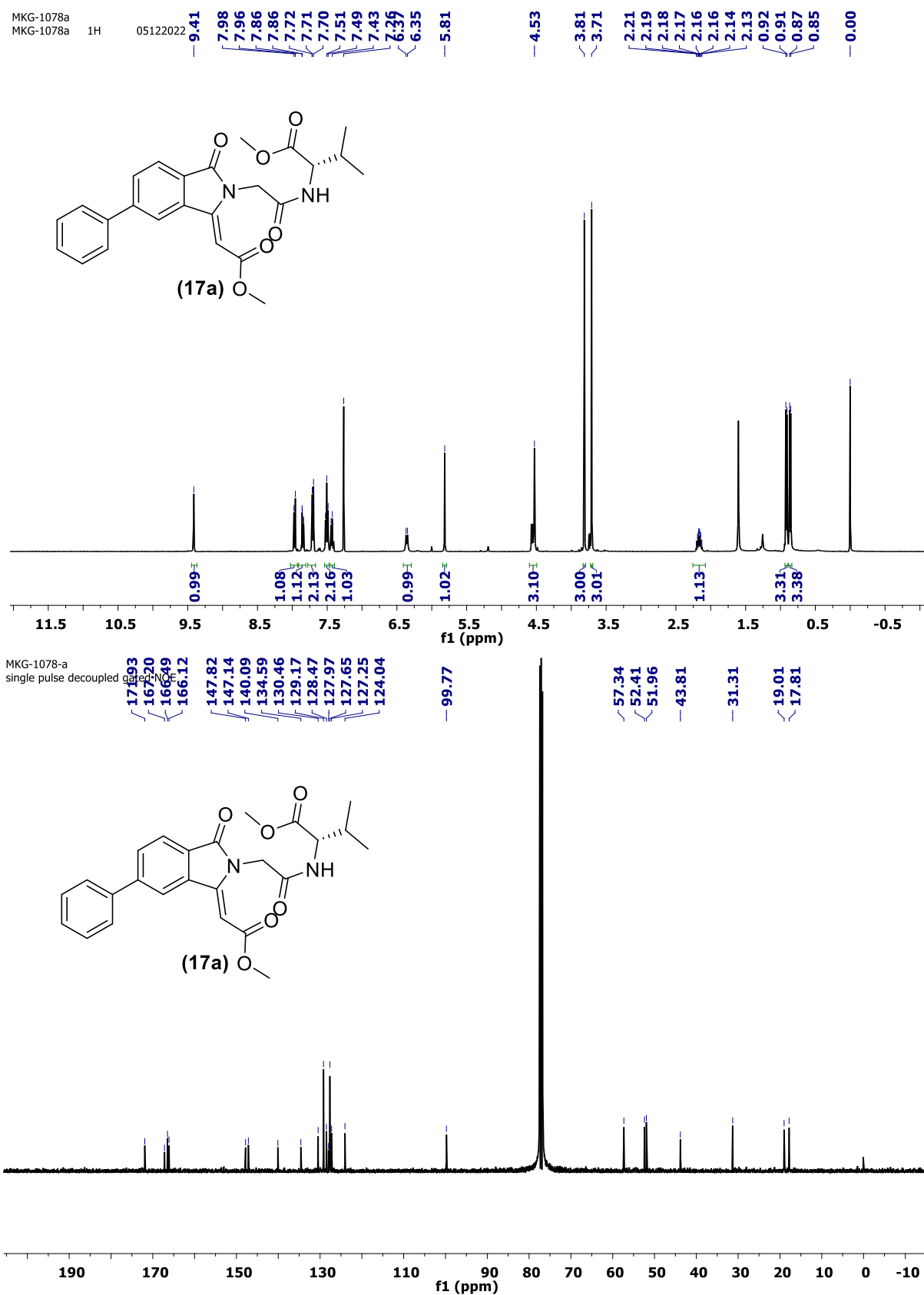


Figure. S49. ¹H, ¹³C NMR spectra of 17a

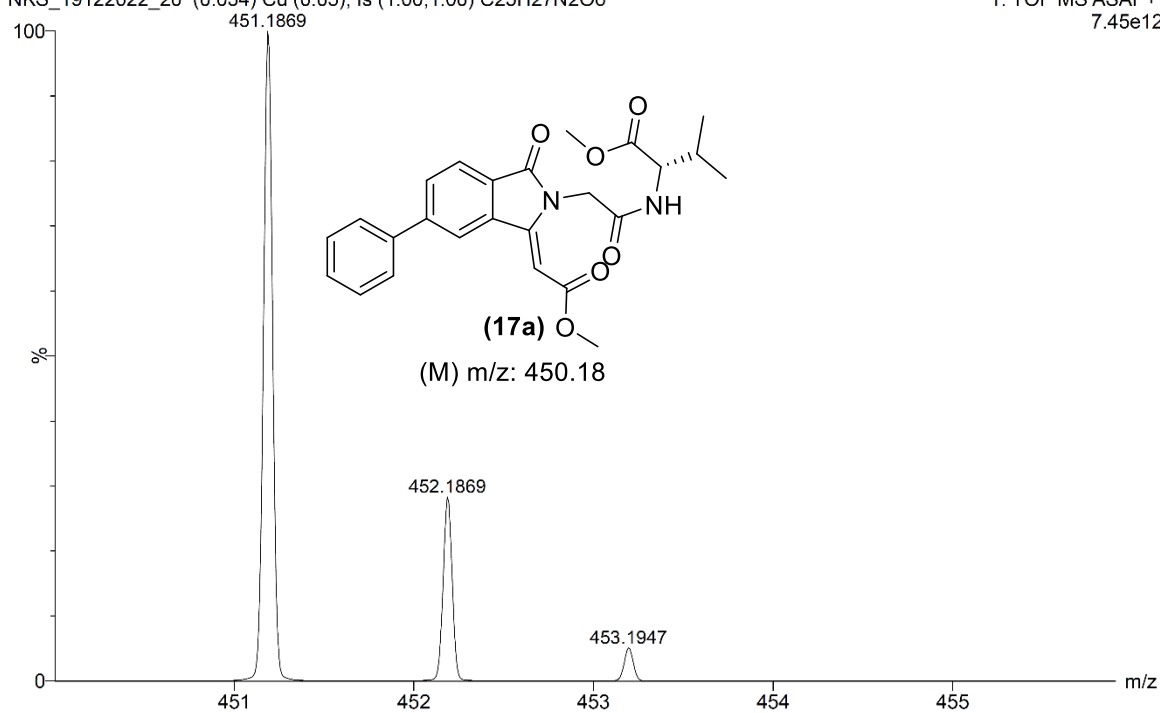
NKS_MKG_1078_A

19-Dec-2022
16:00:43

XEVO-G2XSQTOF#YFA1739

NKS_19122022_20 (0.054) Cu (0.05); Is (1.00,1.00) C₂₅H₂₇N₂O₆

1: TOF MS ASAP+
7.45e12



NKS_19122022_20 11 (0.242) Cm (9:11)
451.1873

1: TOF MS ASAP+
1.56e6

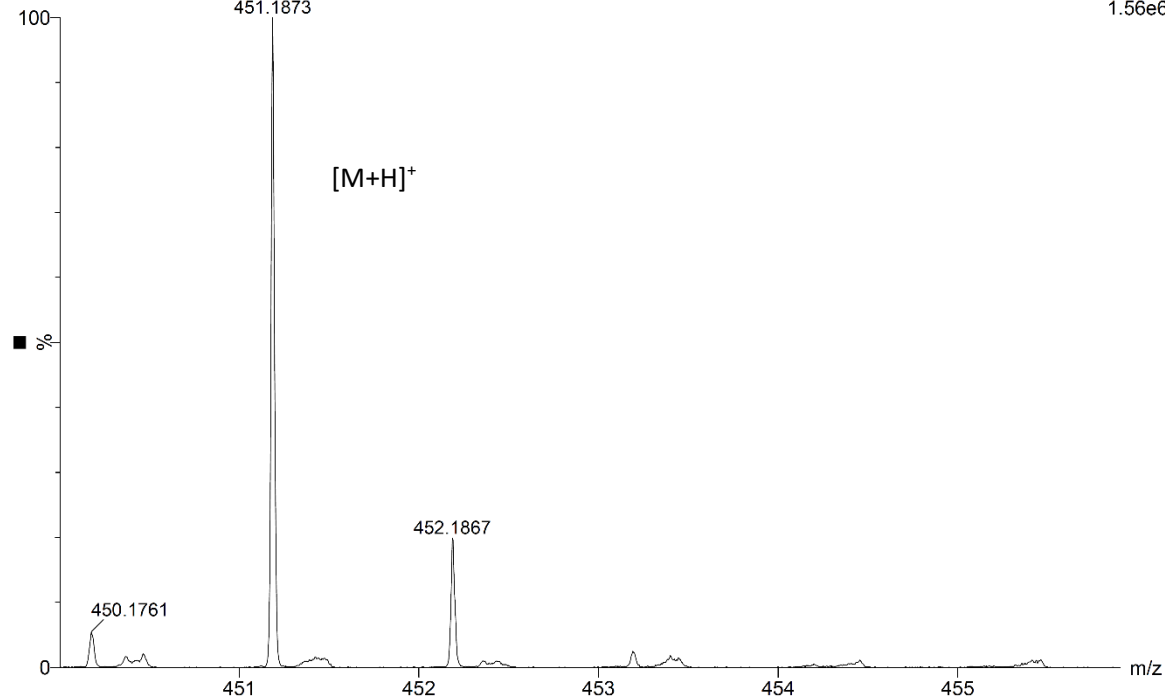
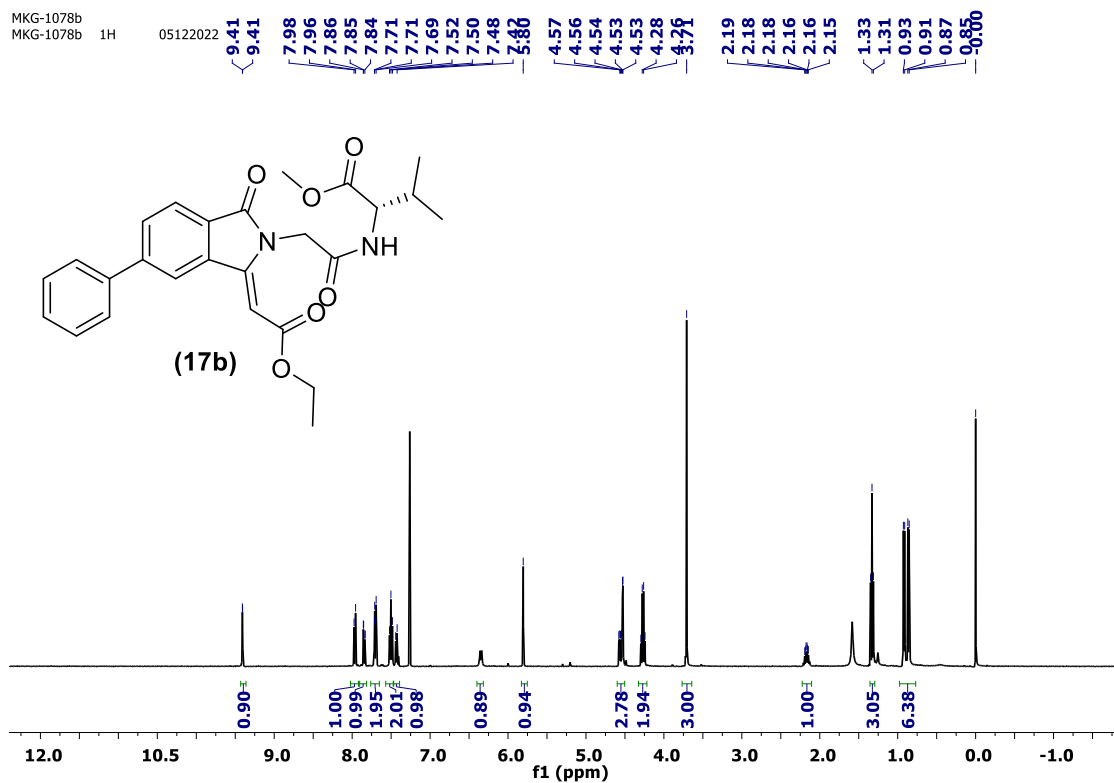


Figure. S50. ESI-HRMS spectra of **17a**

MKG-1078b
MKG-1078b 1H

05122022



MKG-1078-B
single pulse decoupled gated

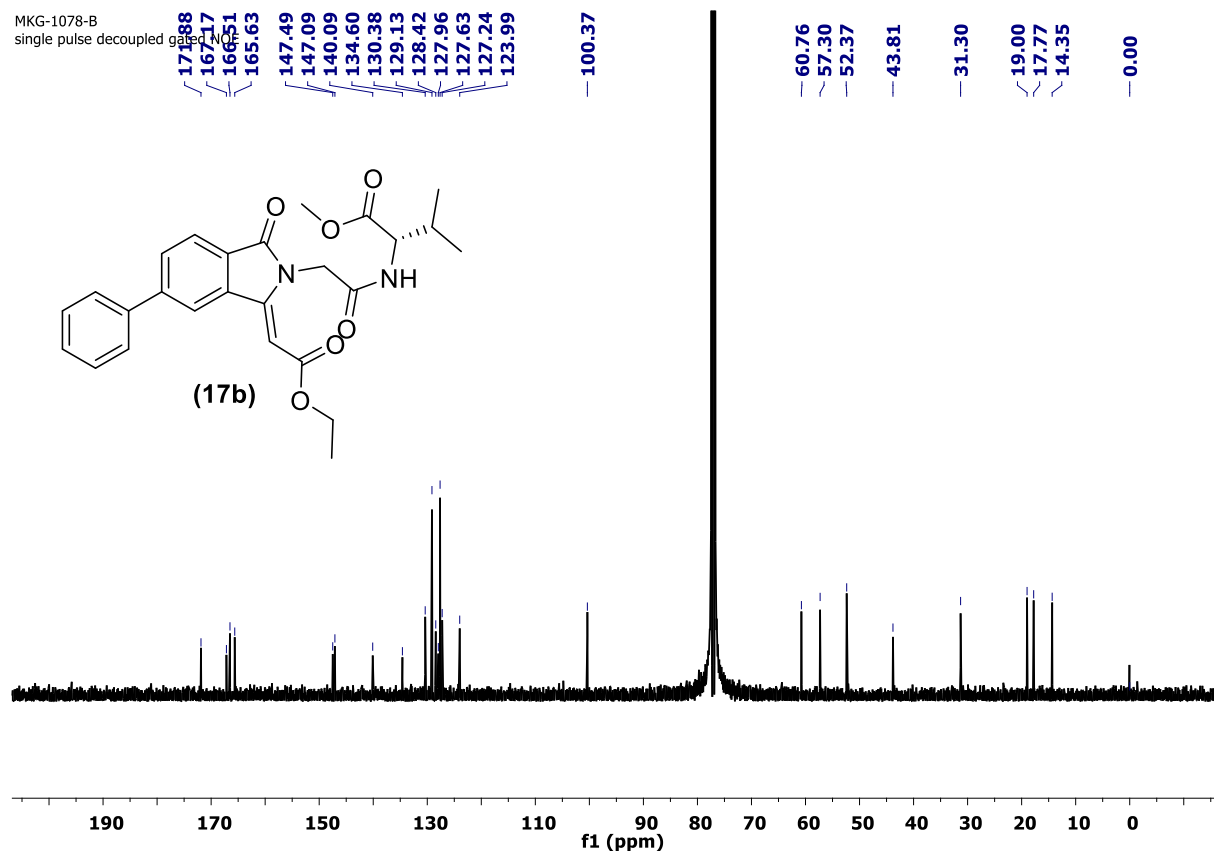


Figure. S51. ¹H, ¹³C NMR spectra of **17b**

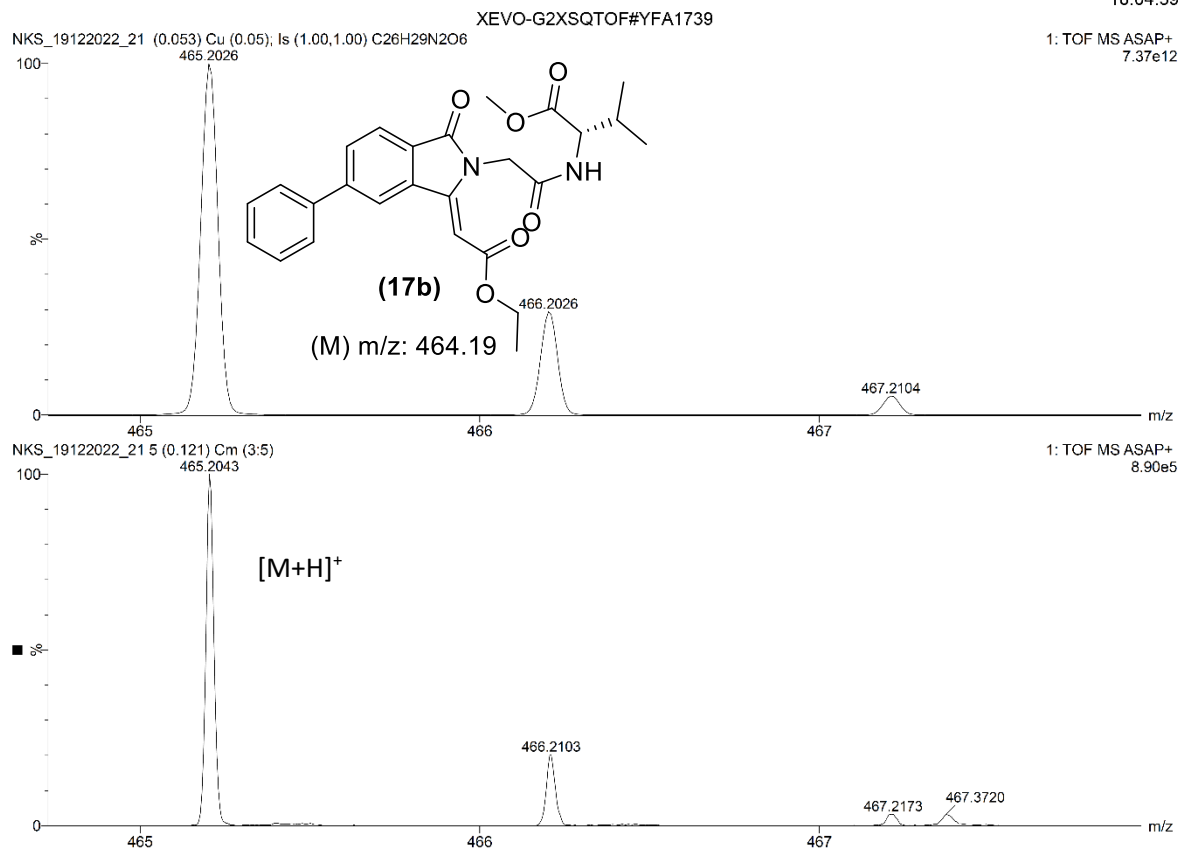


Figure. S52. ESI-HRMS spectra of benzamide **17b**

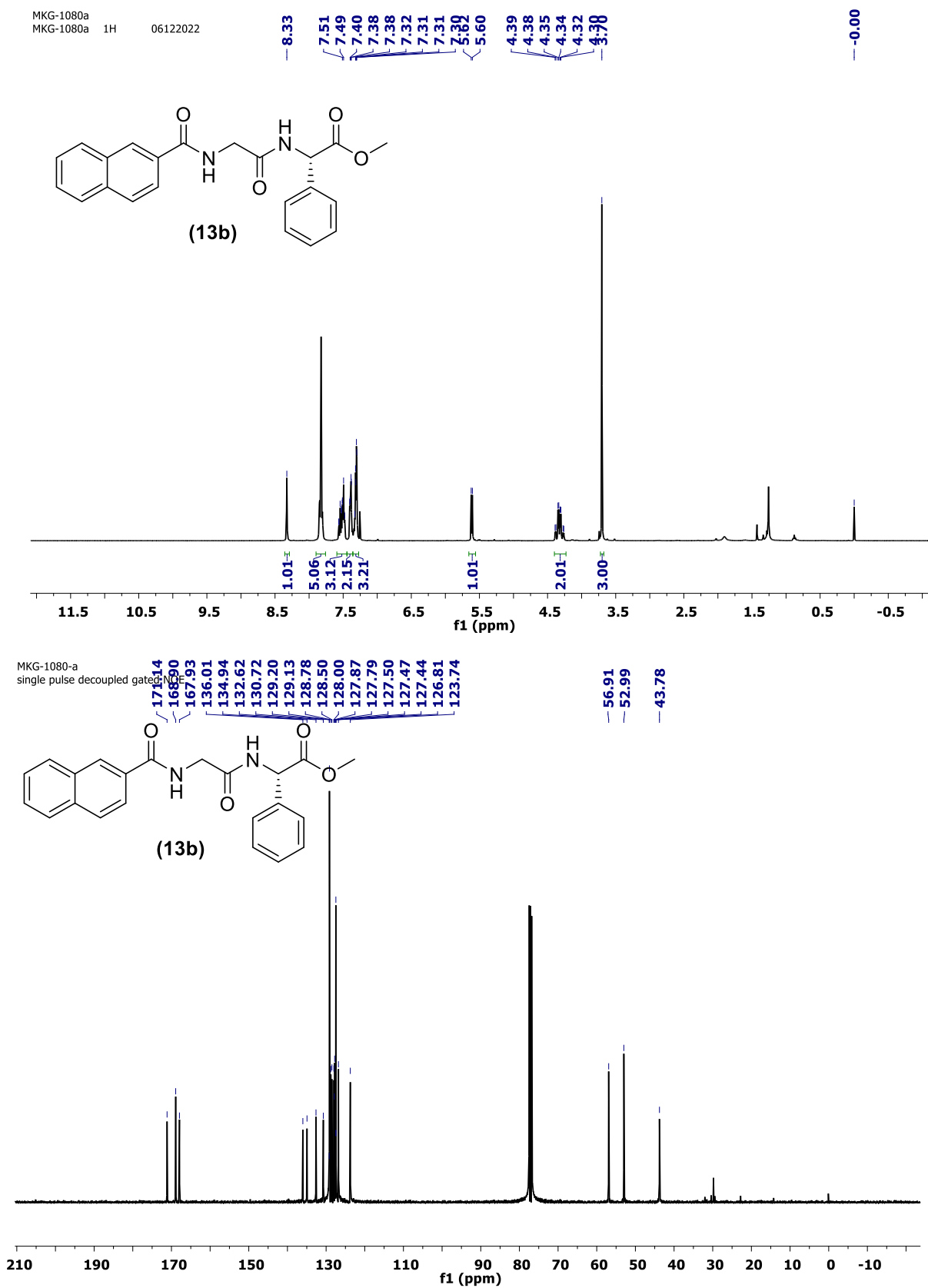


Figure. S53. ¹H, ¹³C NMR spectra of 13b

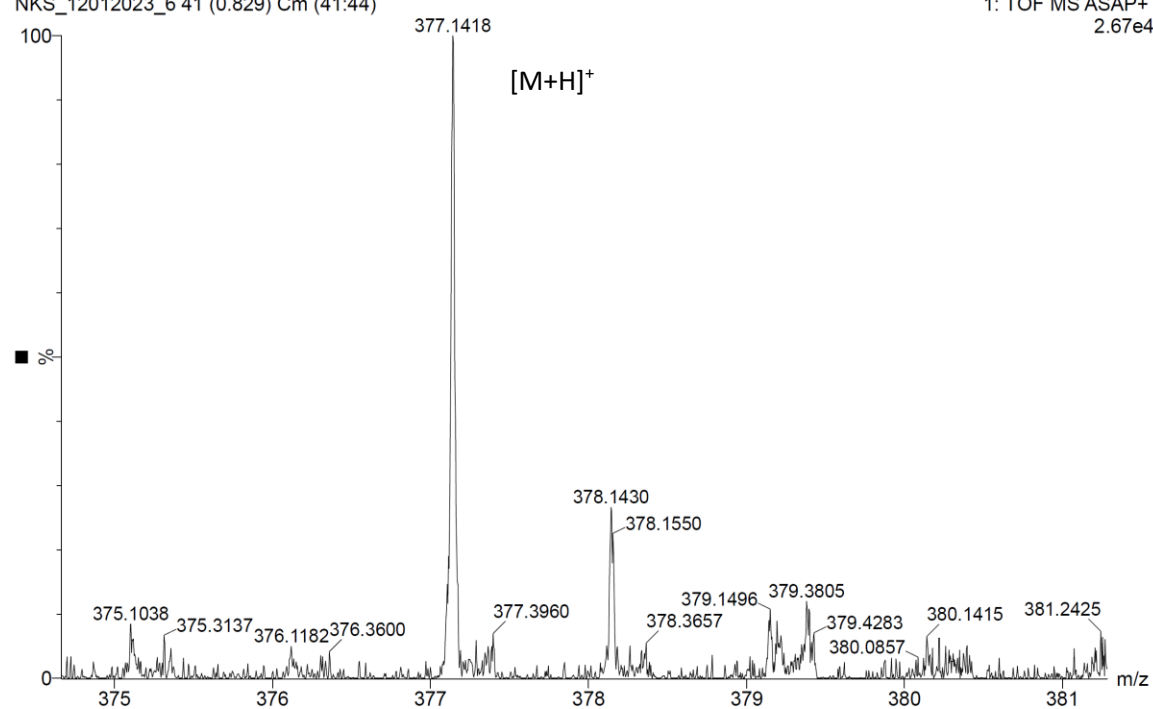
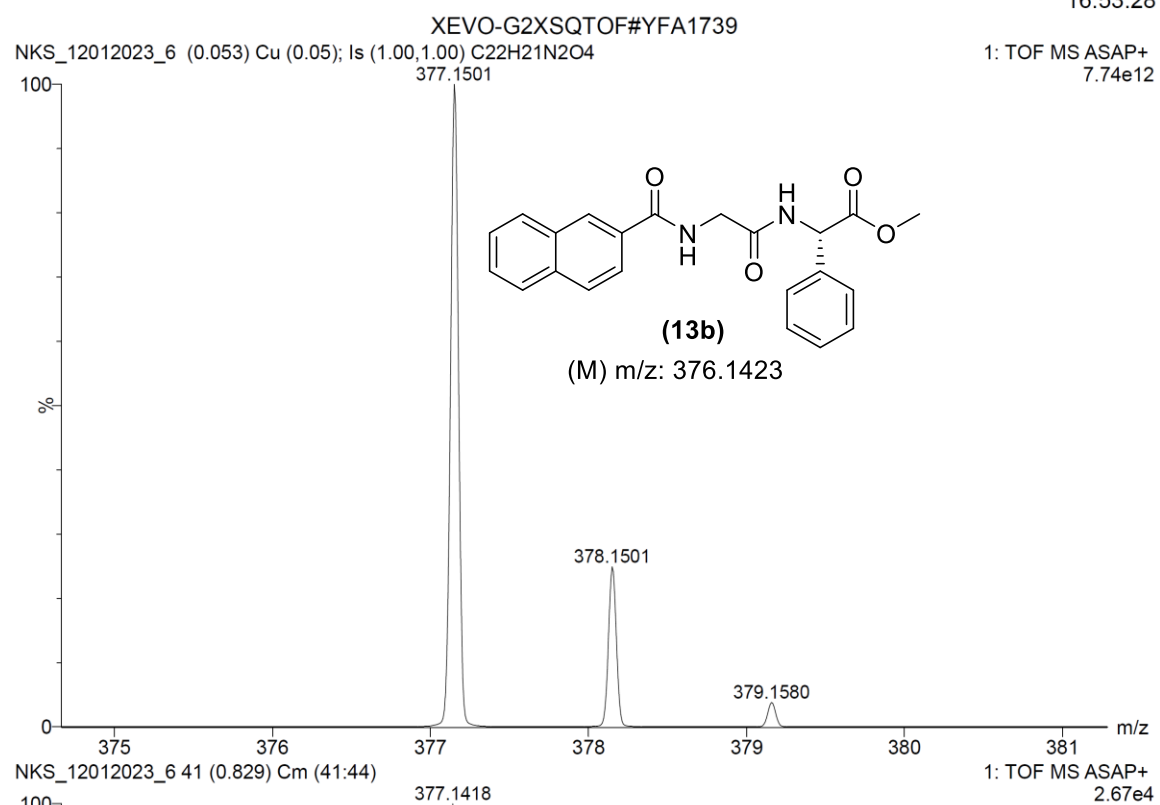


Figure. S54. ESI-HRMS spectra of **13b**

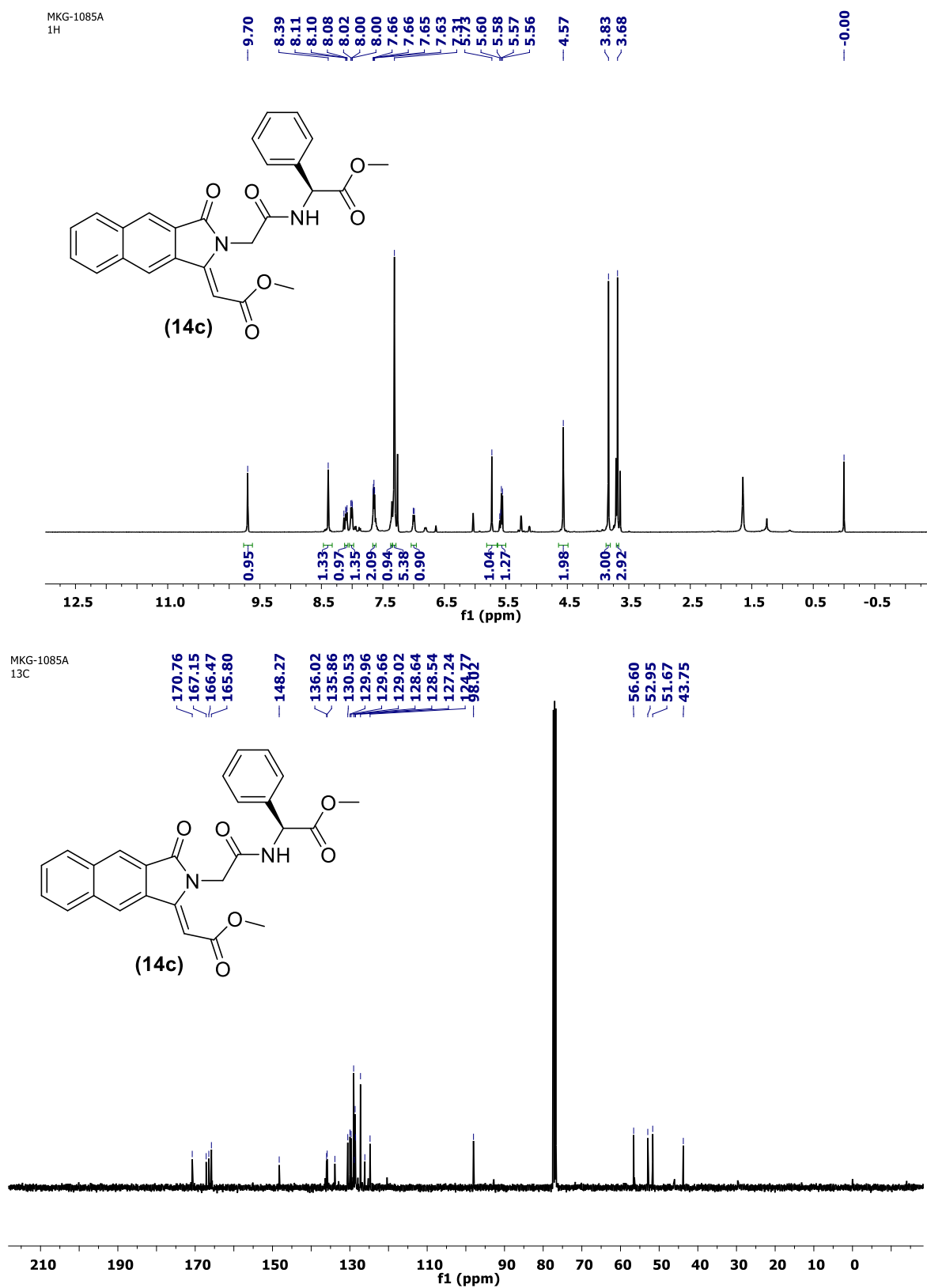


Figure. S55. ¹H, ¹³C NMR spectra of 14

NKS_MKG_1085_A

20-Dec-2022
10:51:05

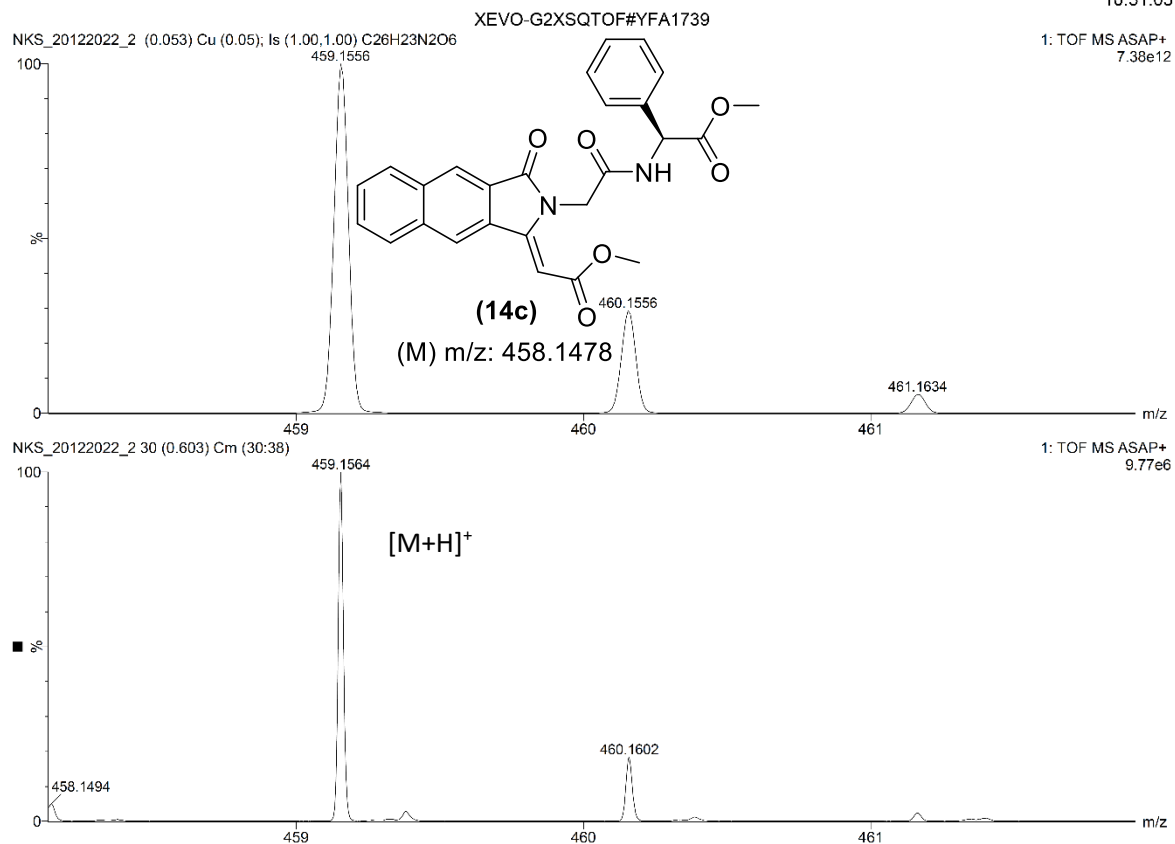


Figure. S56. ESI-HRMS spectra of **14c**

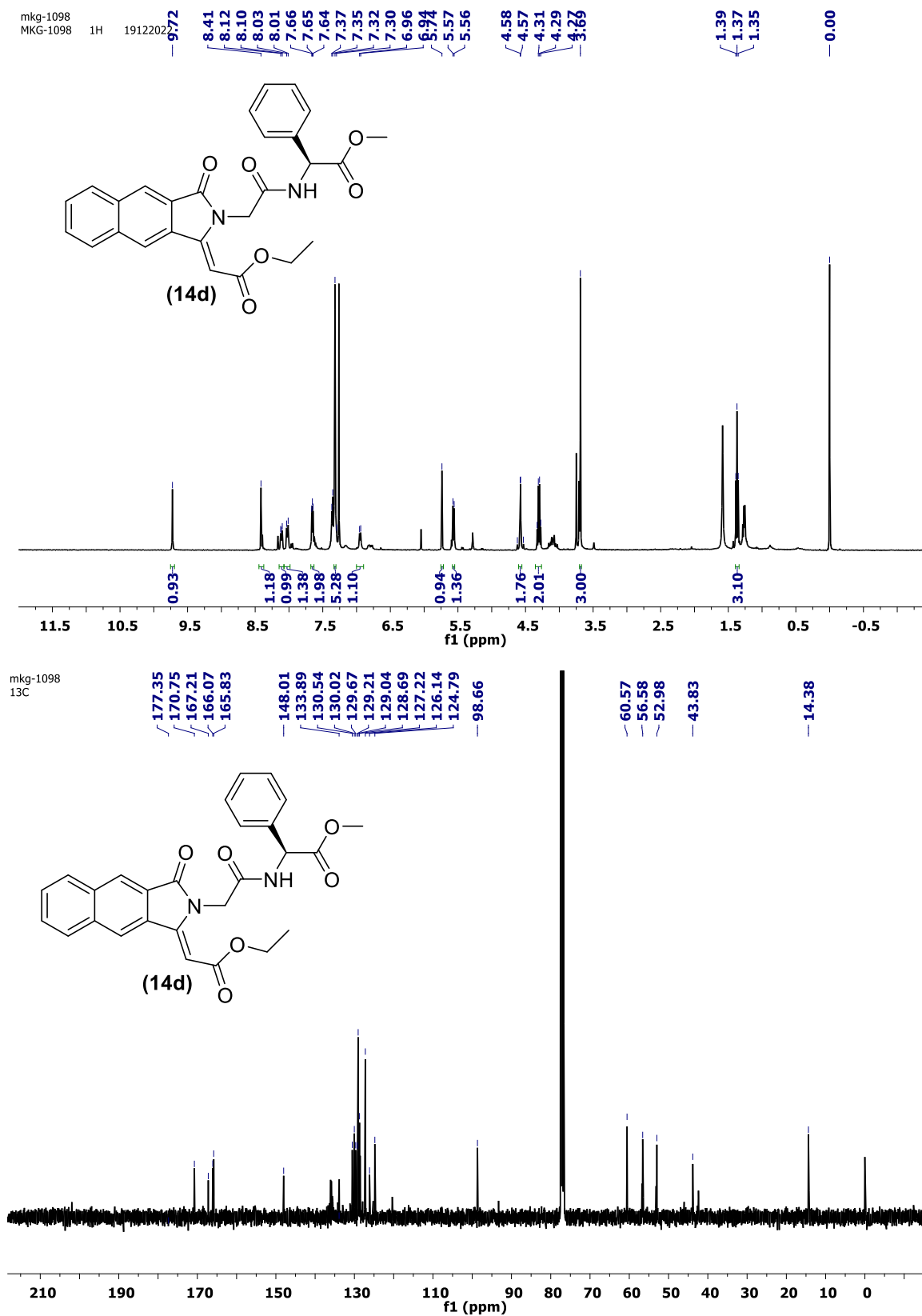


Figure. S57. ¹H, ¹³C NMR spectra of **14d**

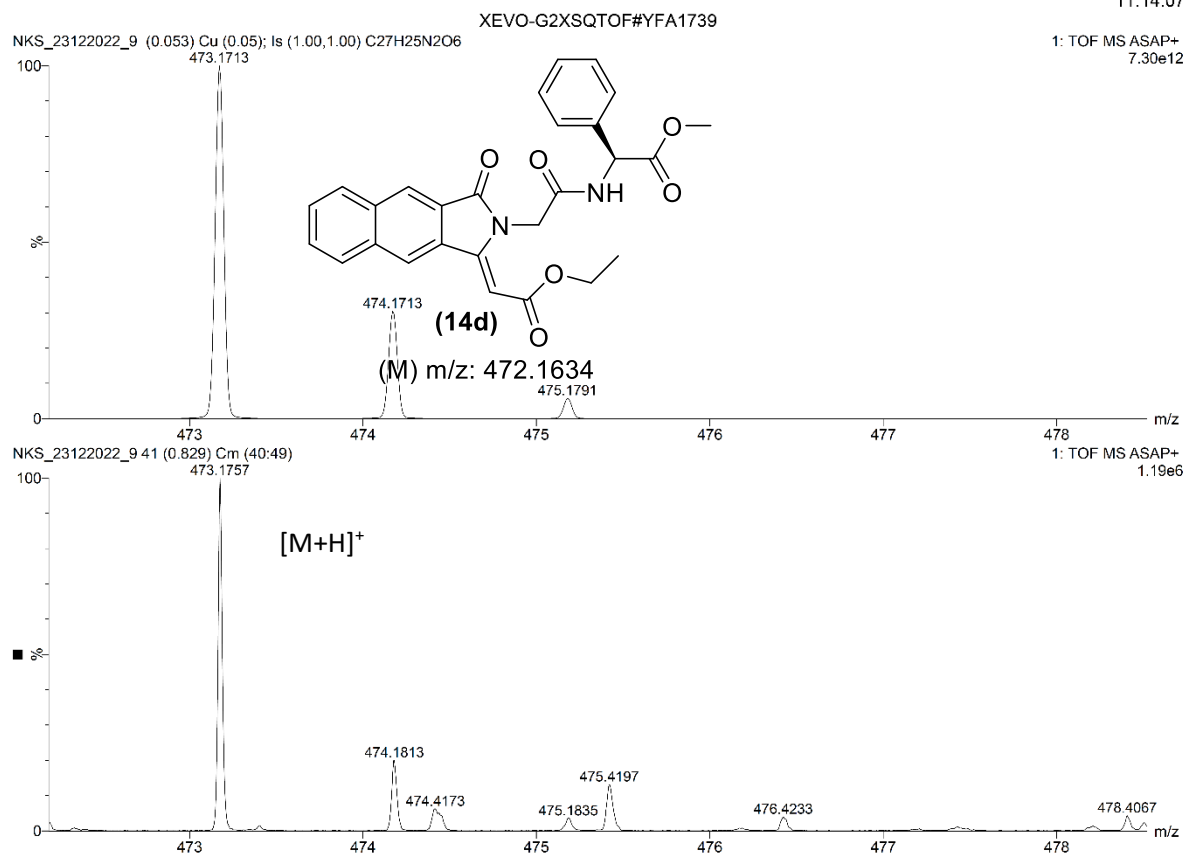


Figure. S58. ESI-HRMS spectra of **14d**

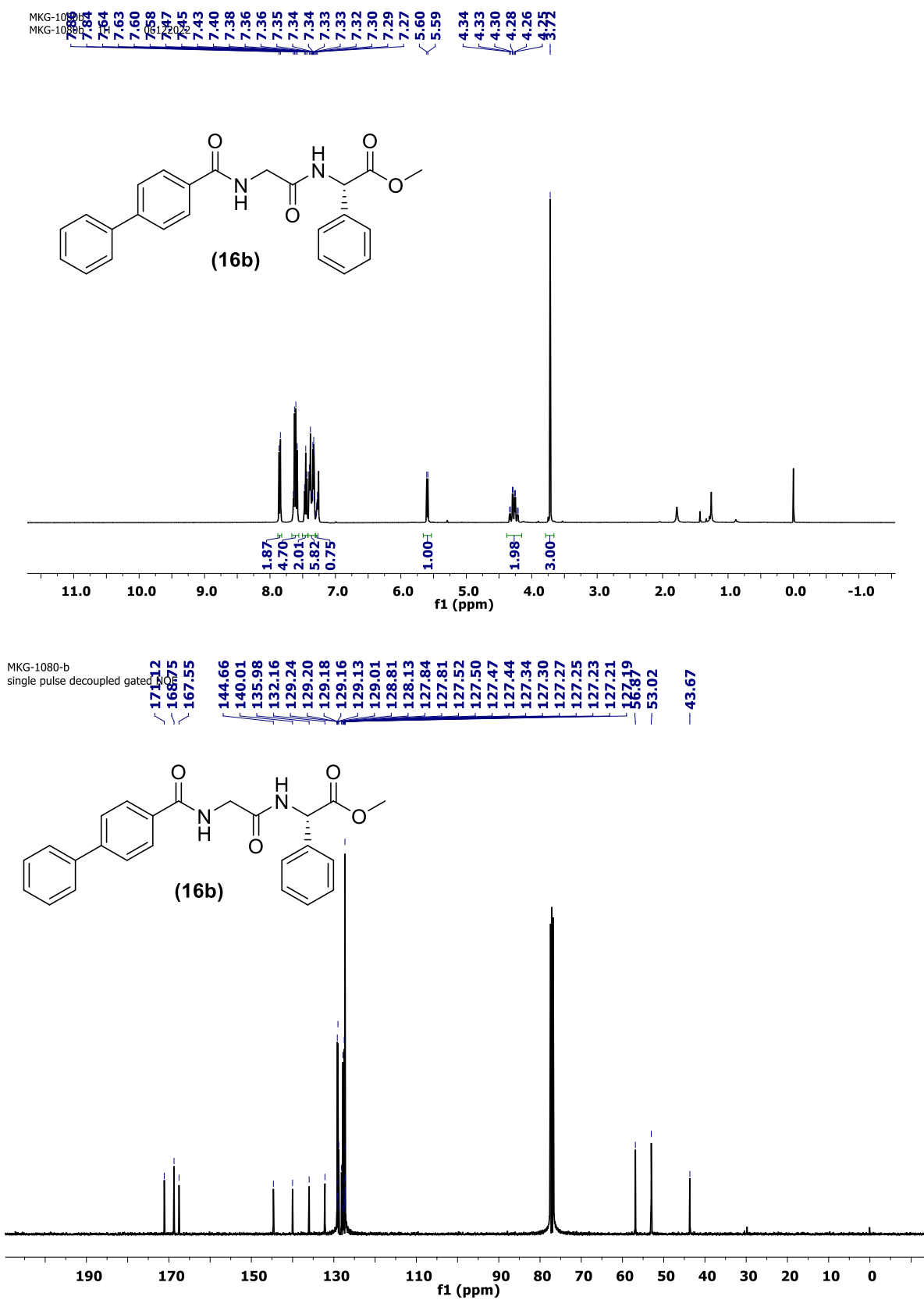


Figure. S59. ^1H , ^{13}C NMR spectra of **16b**

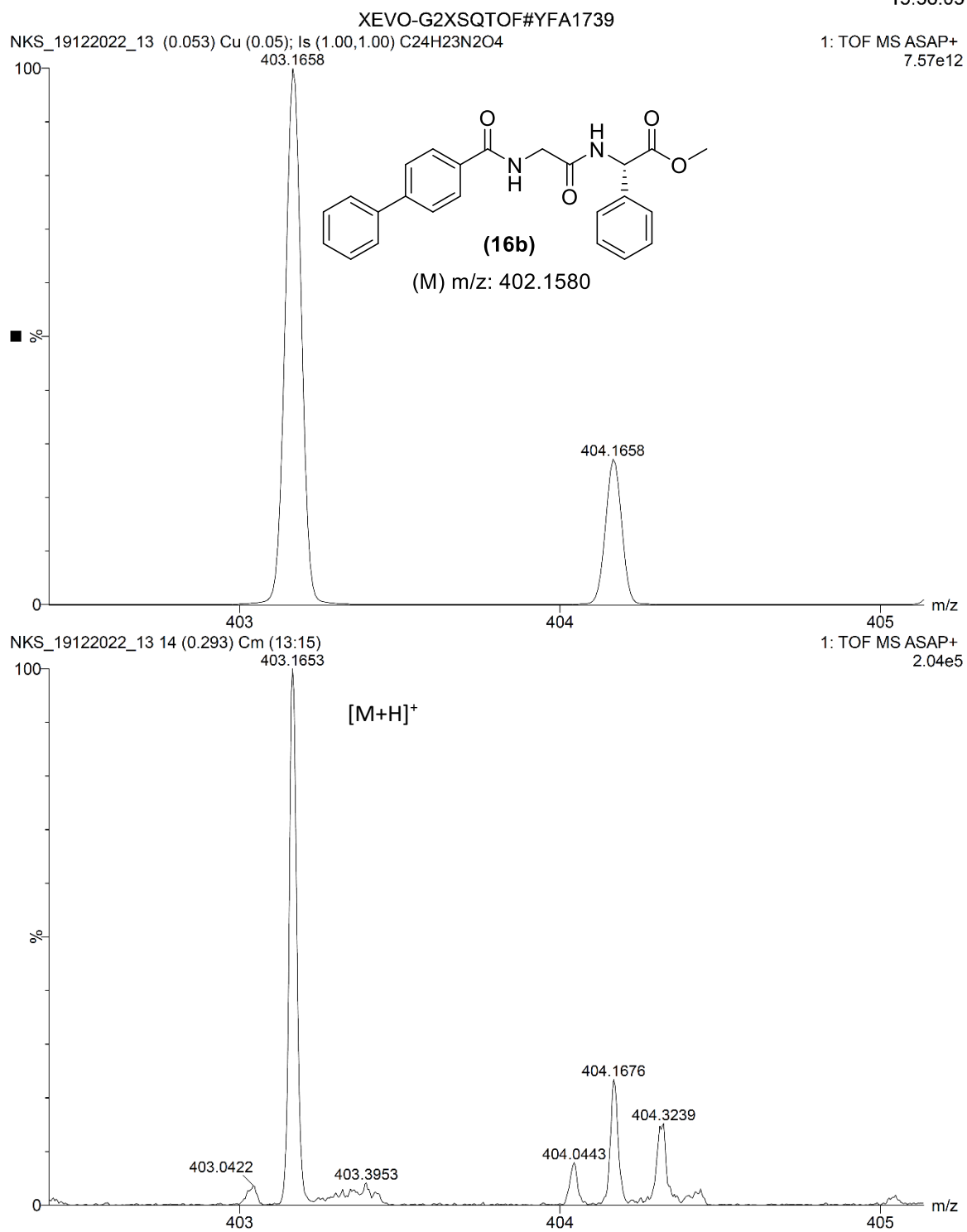
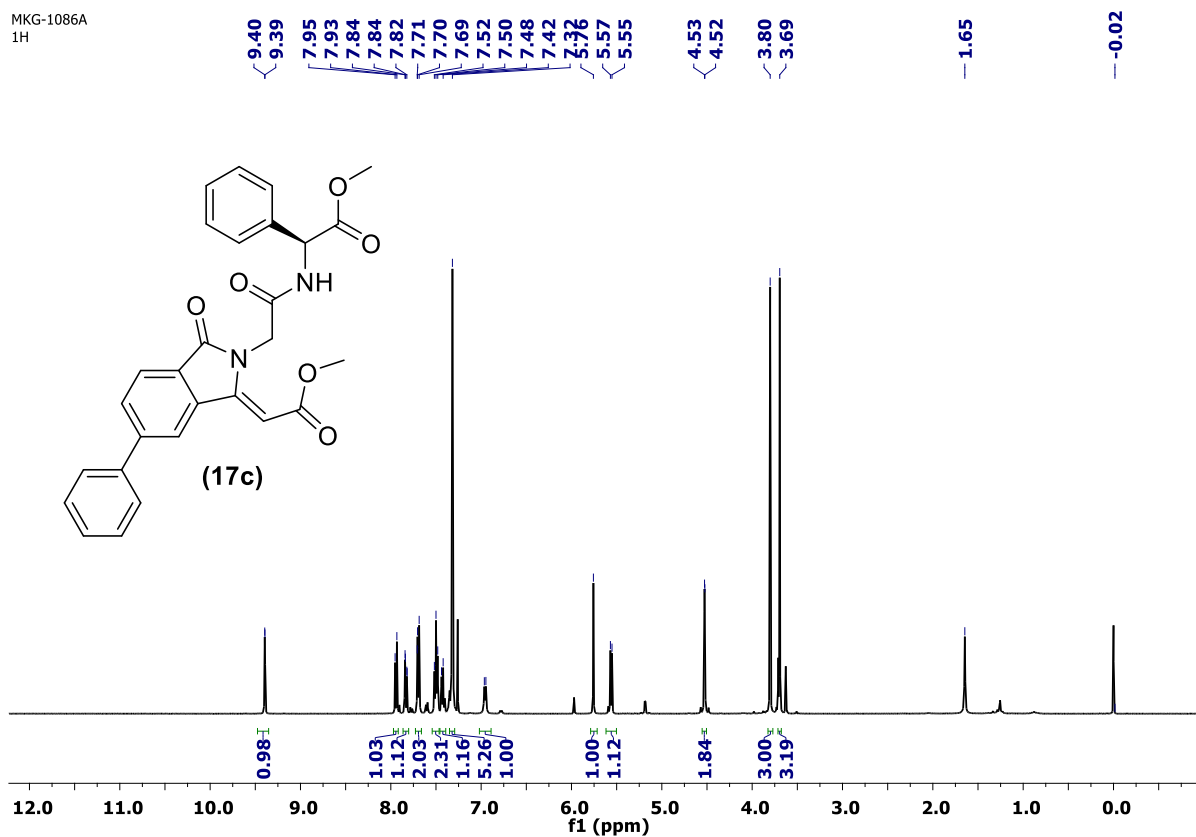


Figure. S60. ESI-HRMS spectra of **16b**

MKG-1086A
1H



MKG-1086A
13C

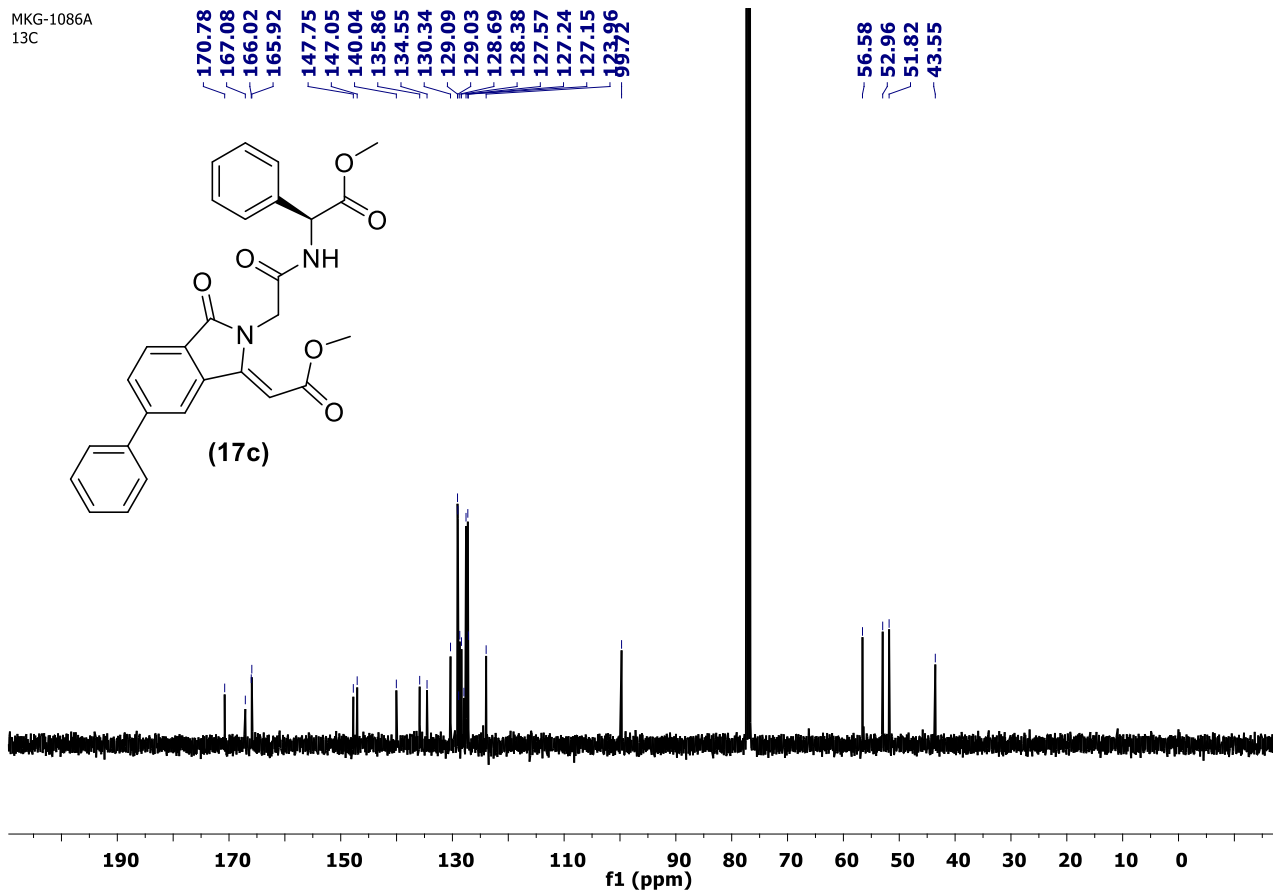


Figure. S61. ¹H, ¹³C NMR spectra of 17c

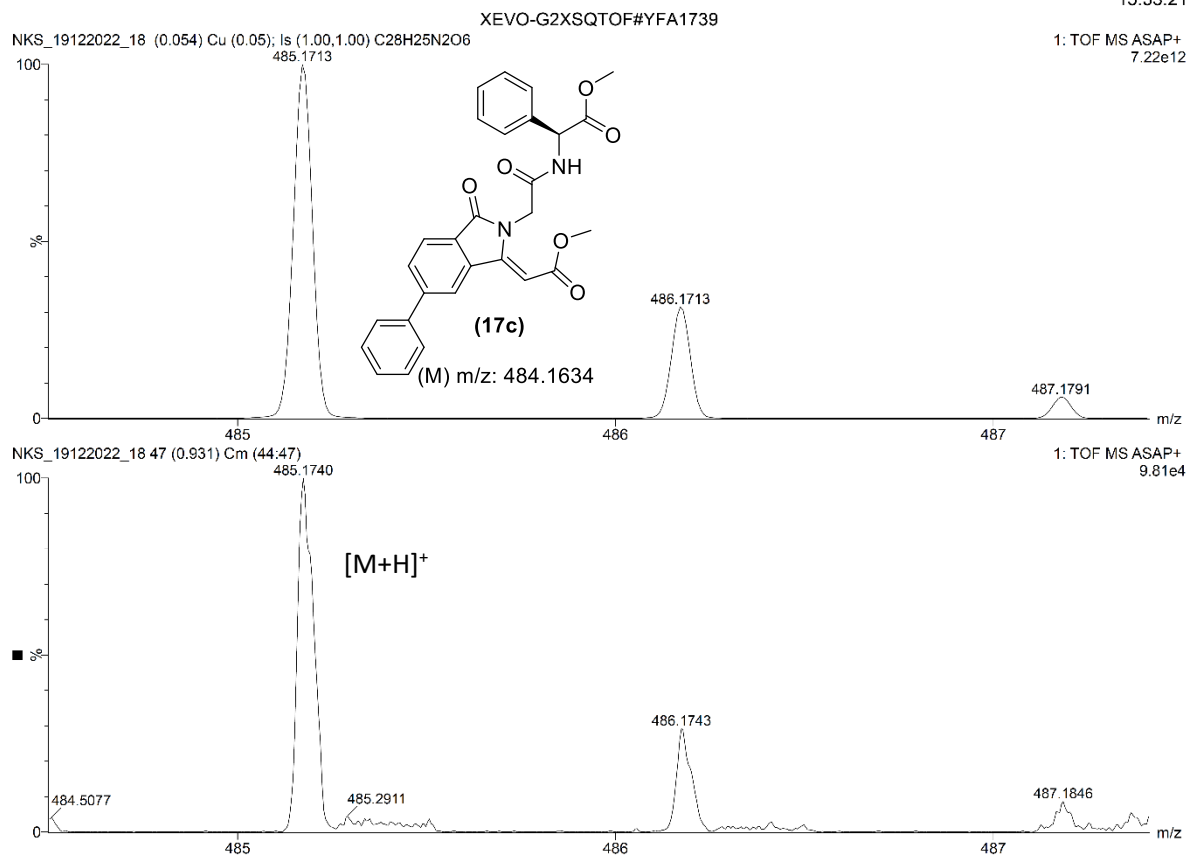


Figure. S62. ESI-HRMS spectra of 17c

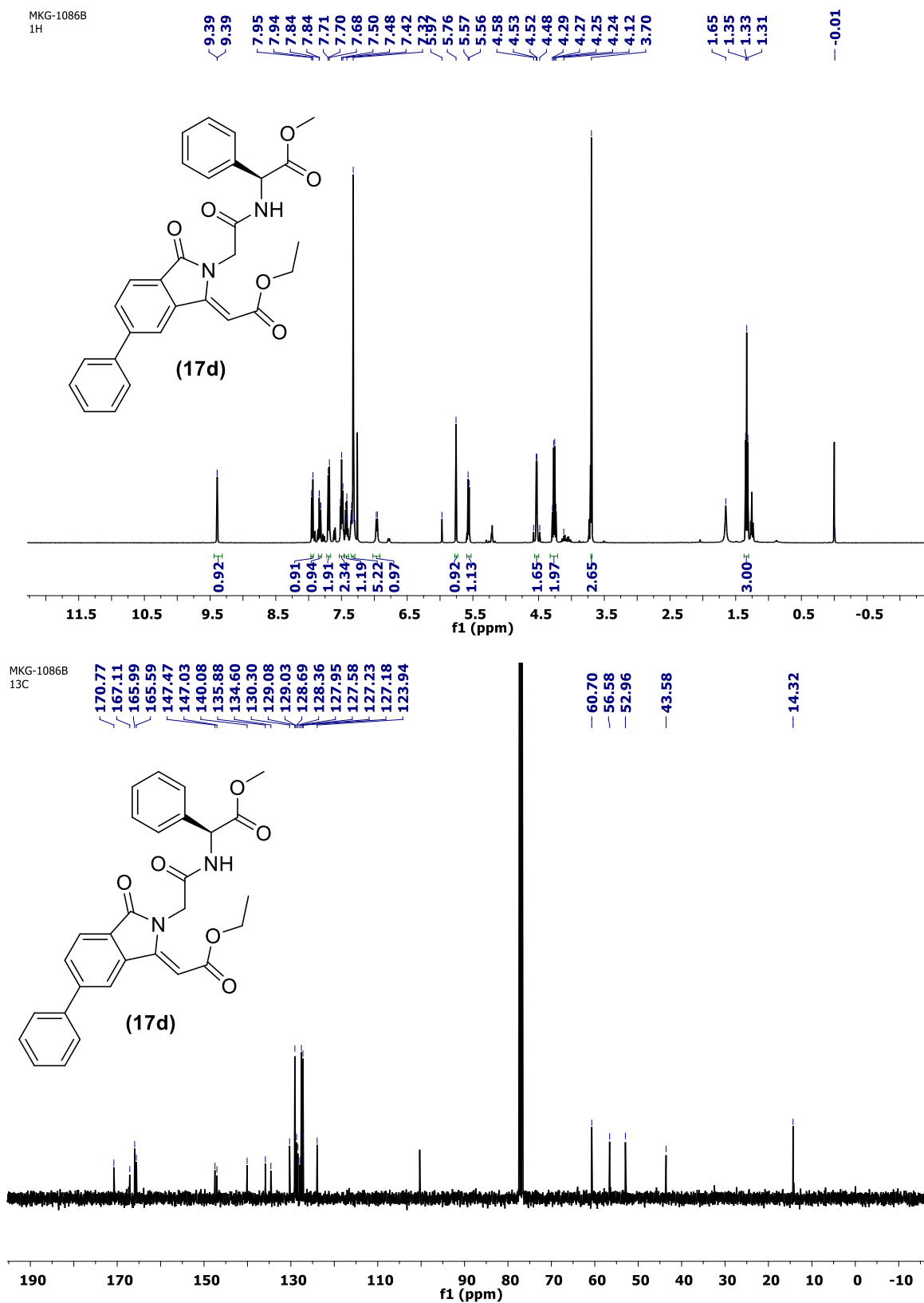


Figure. S63. ^1H , ^{13}C NMR spectra of 17d

NKS_MKG_1086_B

19-Dec-2022
15:57:42

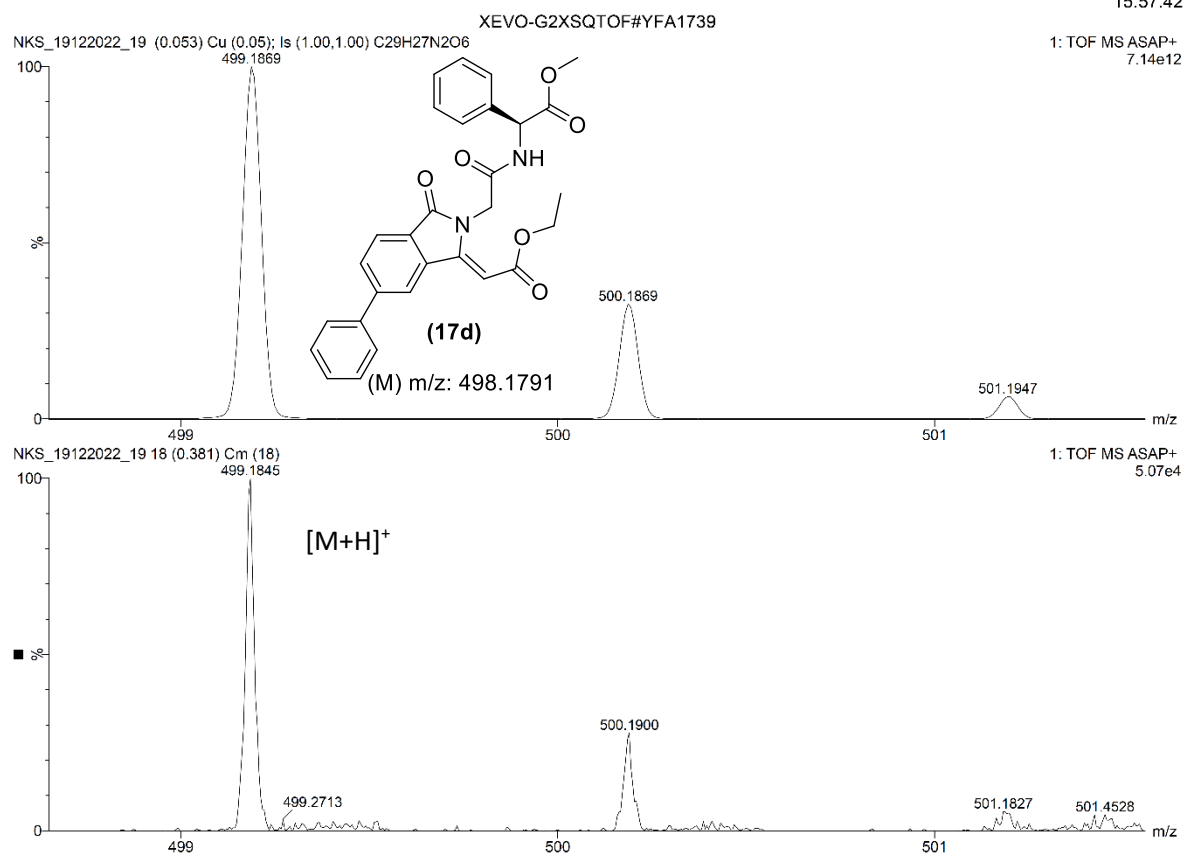


Figure. S64. ESI-HRMS spectra of **17d**

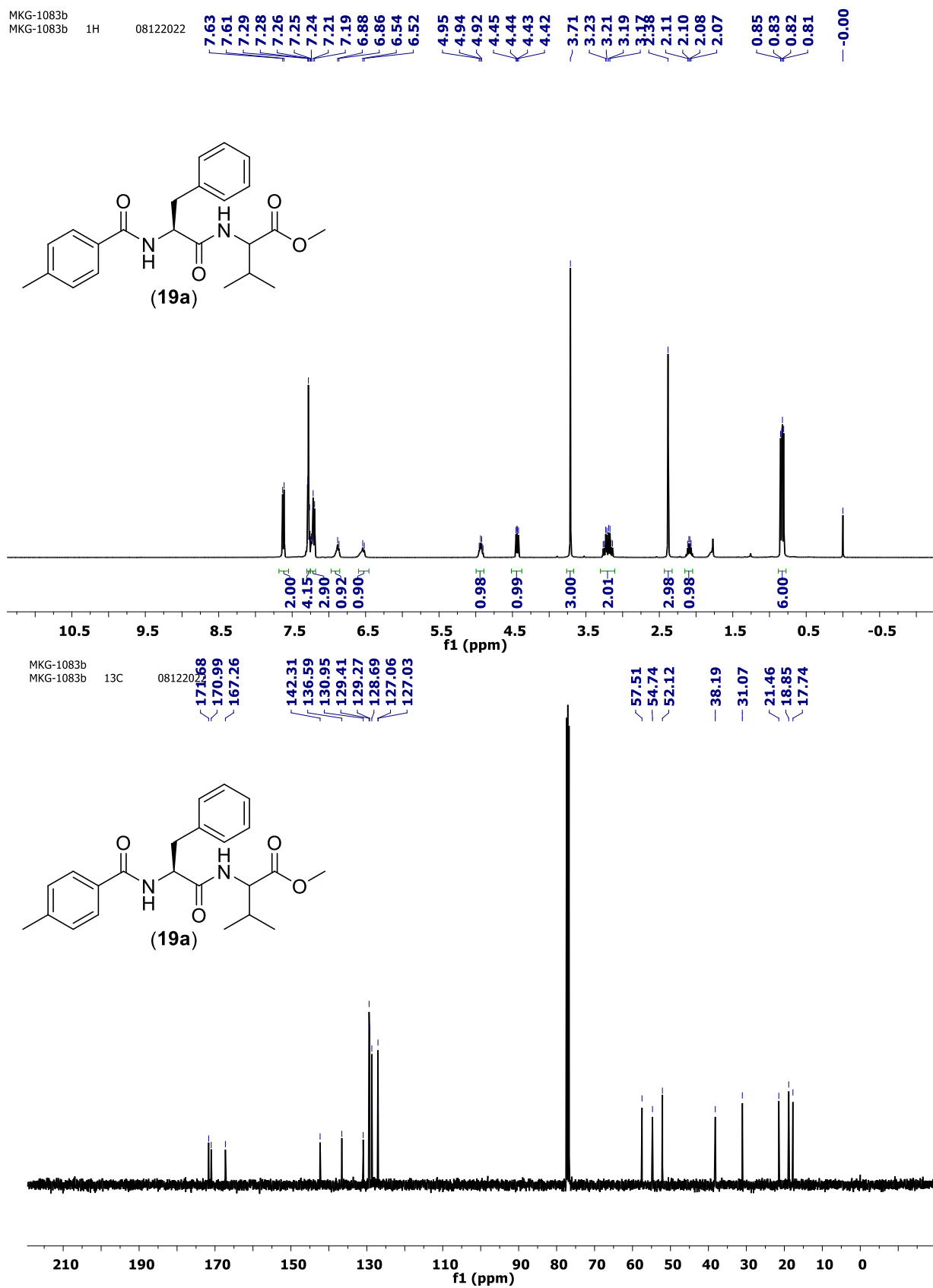


Figure. S65. ^1H , ^{13}C NMR spectra of 19a

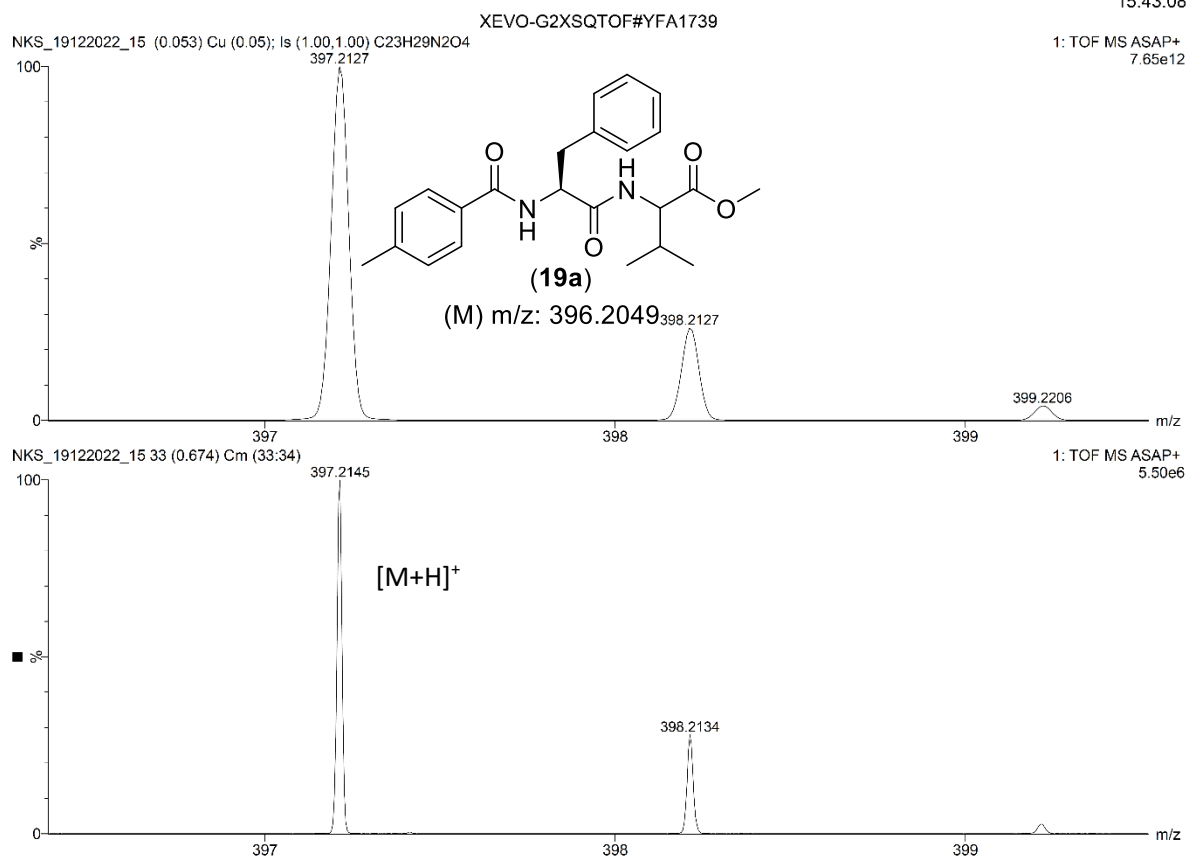


Figure. S66. ESI-HRMS spectra of **19a**

NKS_MKG_1103_A

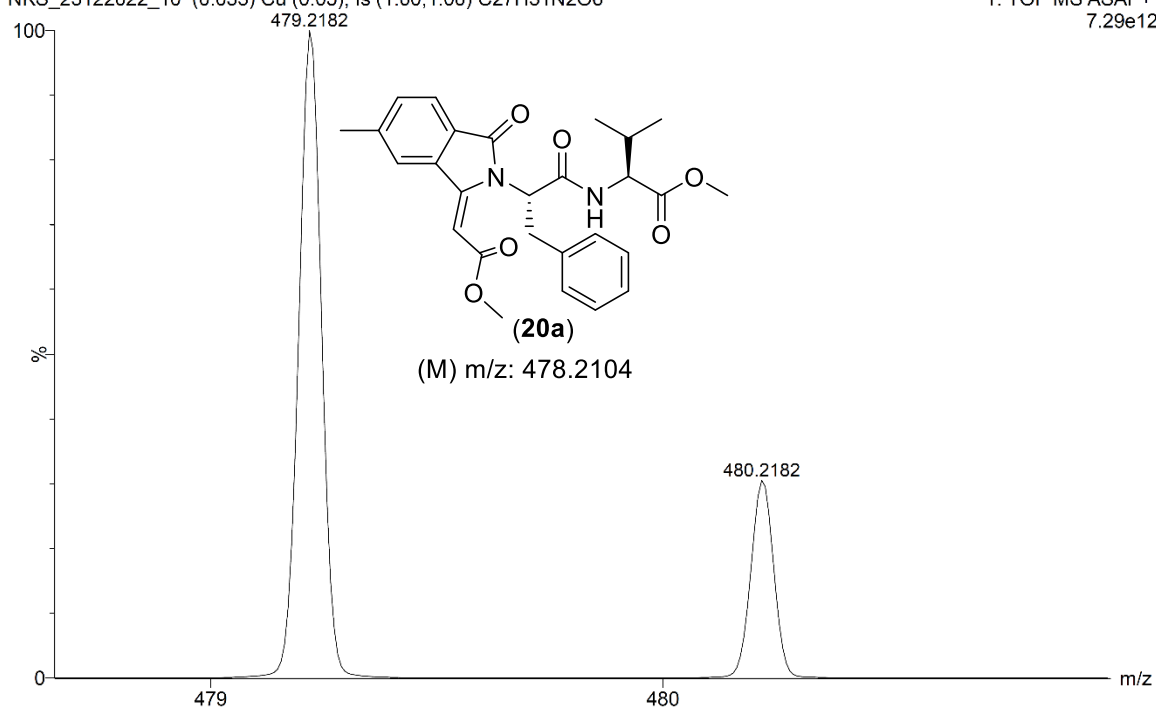
23-Dec-2022

11:18:03

XEVO-G2XSQTOF#YFA1739

NKS_23122022_10 (0.053) Cu (0.05); Is (1.00,1.00) C₂₇H₃₁N₂O₆

1: TOF MS ASAP+
7.29e12



NKS_23122022_10 43 (0.863) Cm (43)

1: TOF MS ASAP+
6.78e6

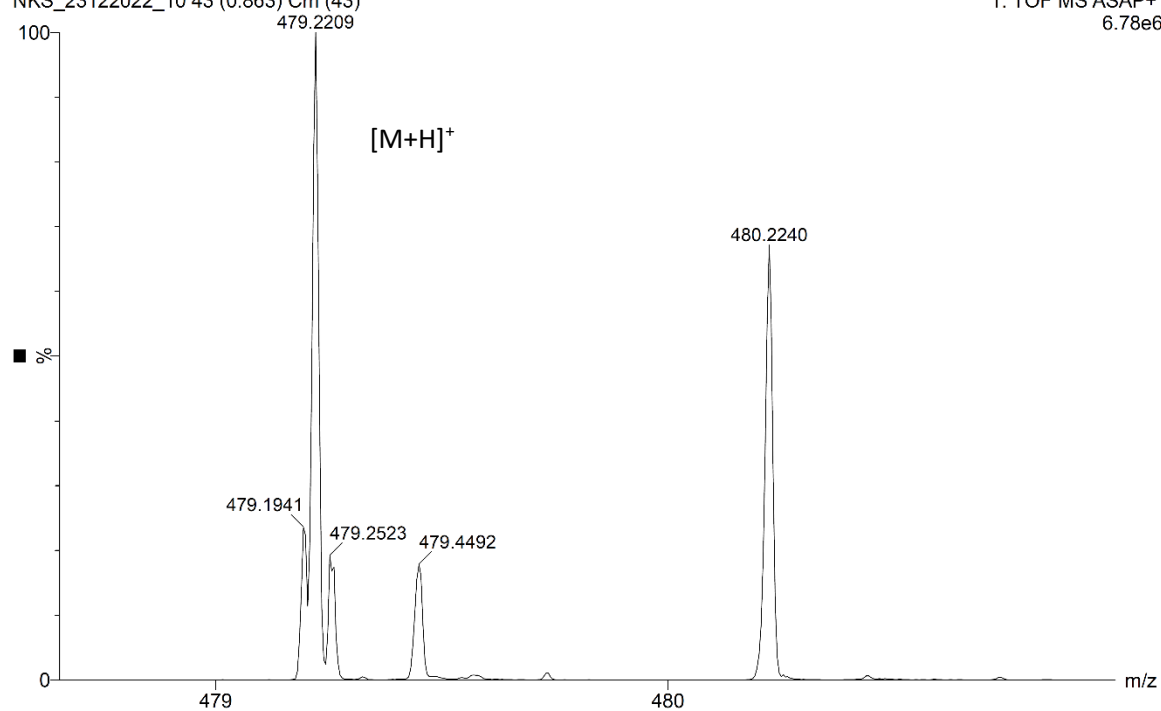


Figure. S68. ESI-HRMS spectra of **20a**

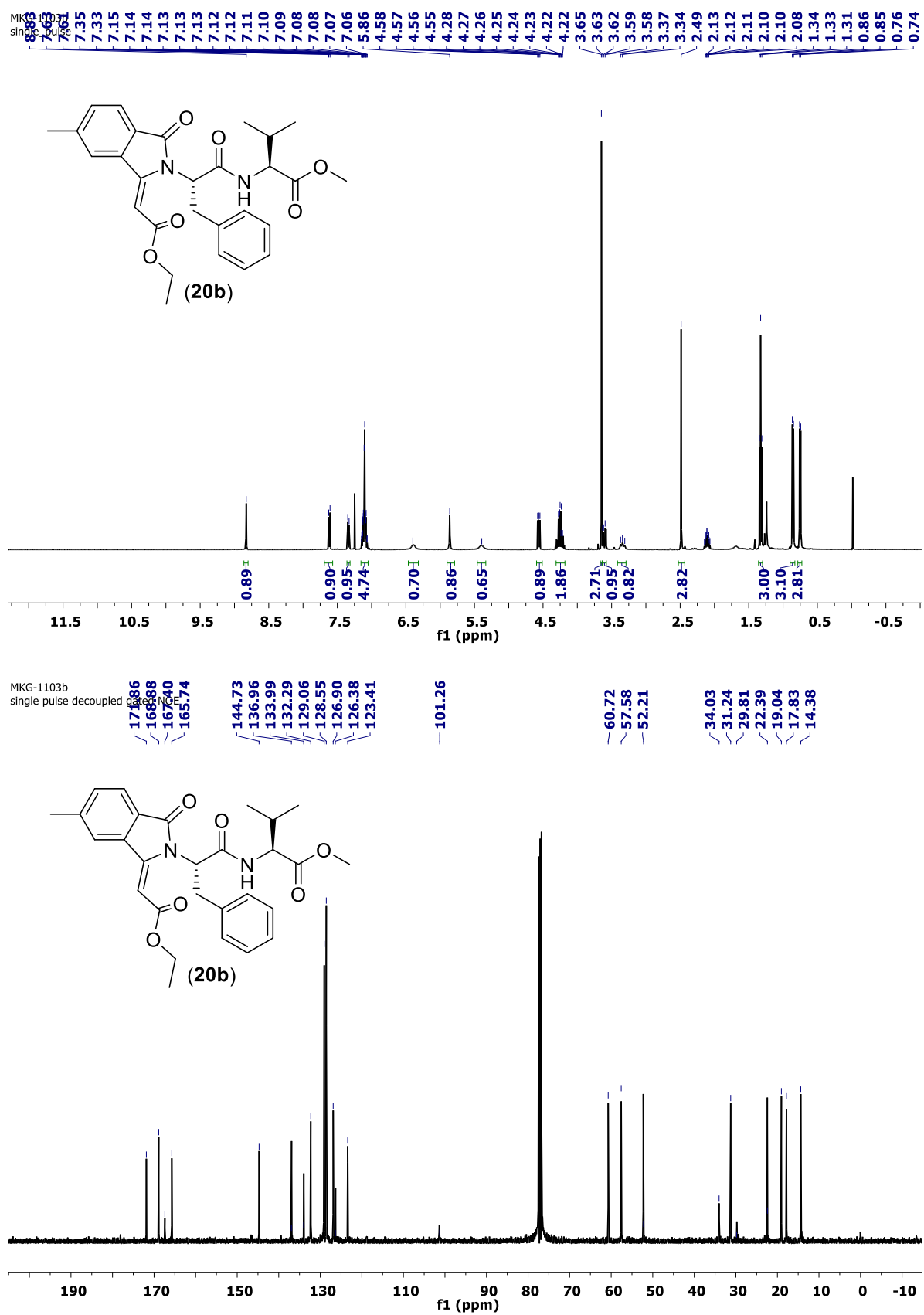


Figure. S69. ^1H , ^{13}C NMR spectra of **20b**

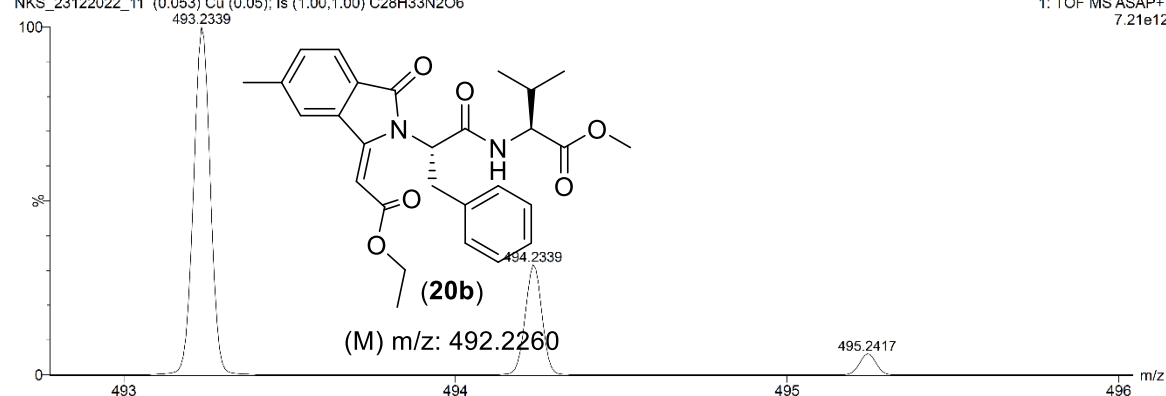
NKS_MKG_1103_B

23-Dec-2022
11:20:38

XEVO-G2XSQTOF#YFA1739

NKS_23122022_11 (0.053) Cu (0.05); Is (1.00,1.00) C₂₈H₃₃N₂O₆

1: TOF MS ASAP+
7.21e12



NKS_23122022_11 35 (0.708) Cm (35:36)

1: TOF MS ASAP+
1.06e7

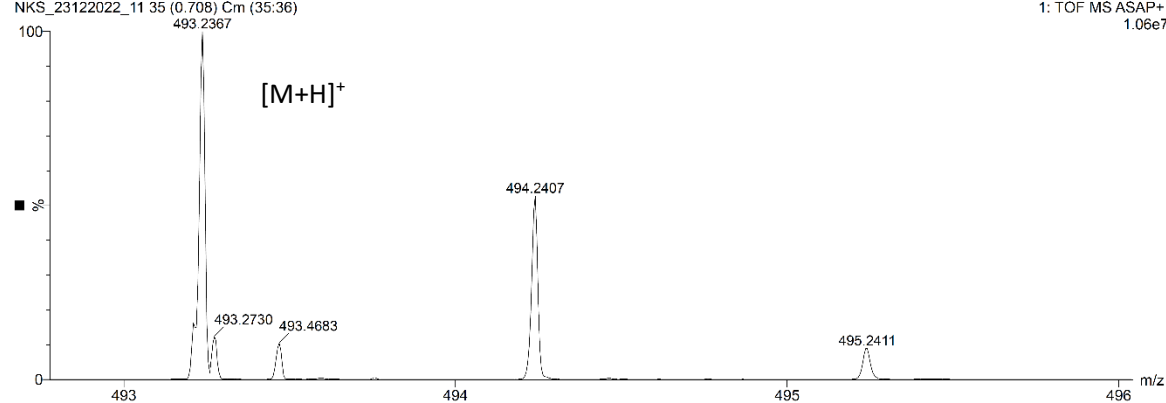


Figure. S70. ESI-HRMS spectra of **20b**

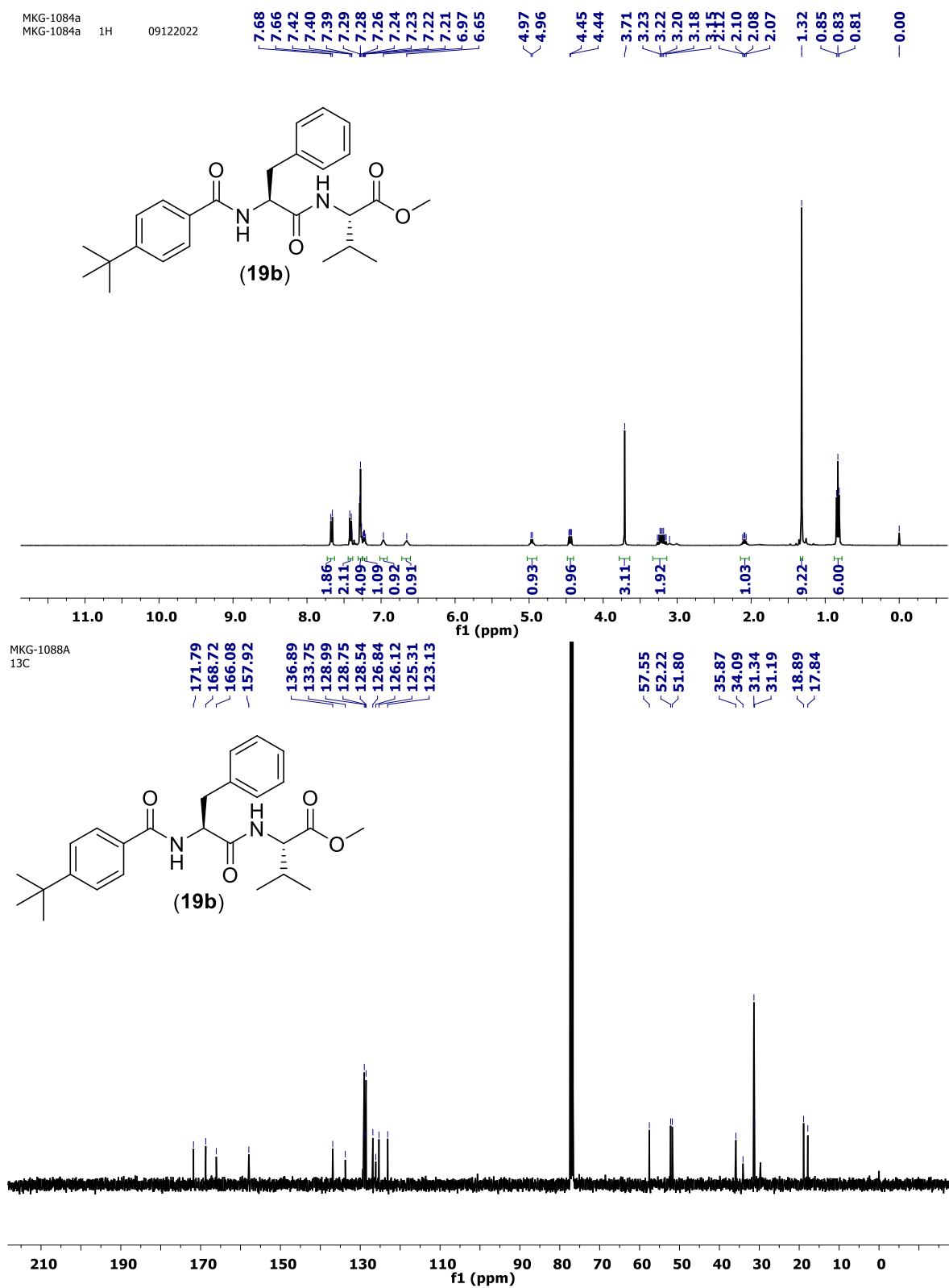


Figure. S71. ^1H , ^{13}C NMR spectra of **19b**

MKG_1084_A

12-Jan-2023
12:54:20

XEVO-G2XSQTOF#YFA1739

NKS_12012023_2 (0.053) Cu (0.05); Is (1.00,1.00) C₂₆H₃₅N₂O₄

1: TOF MS ASAP+
7.40e12

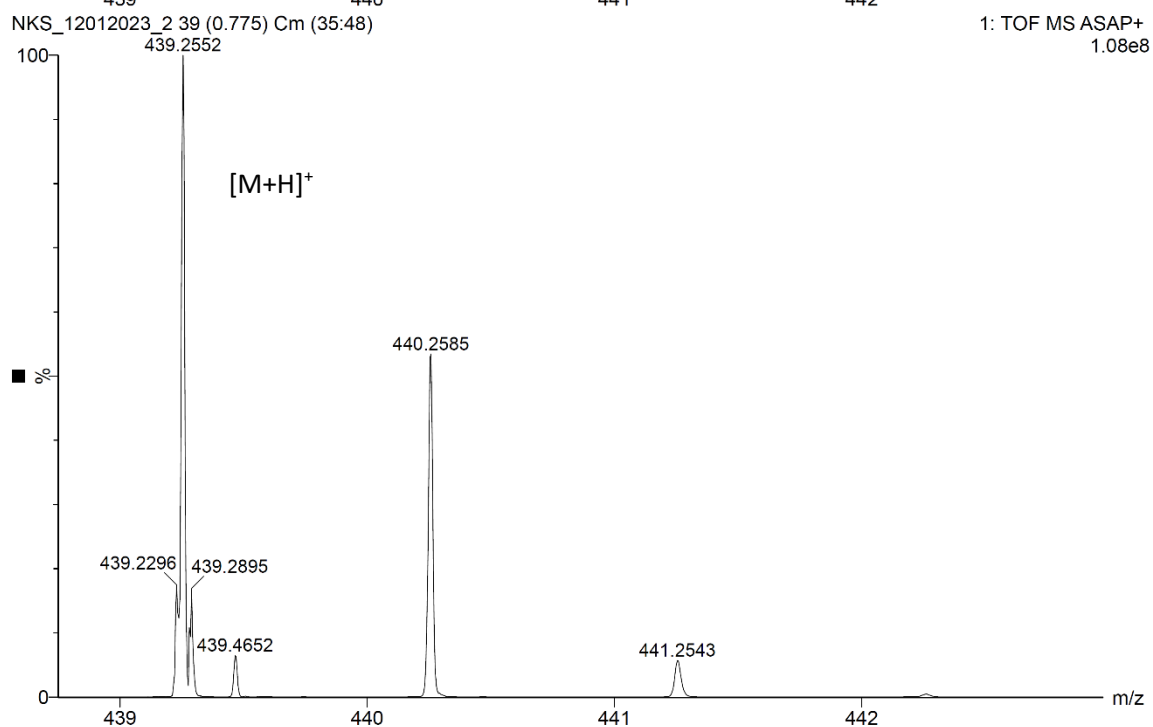
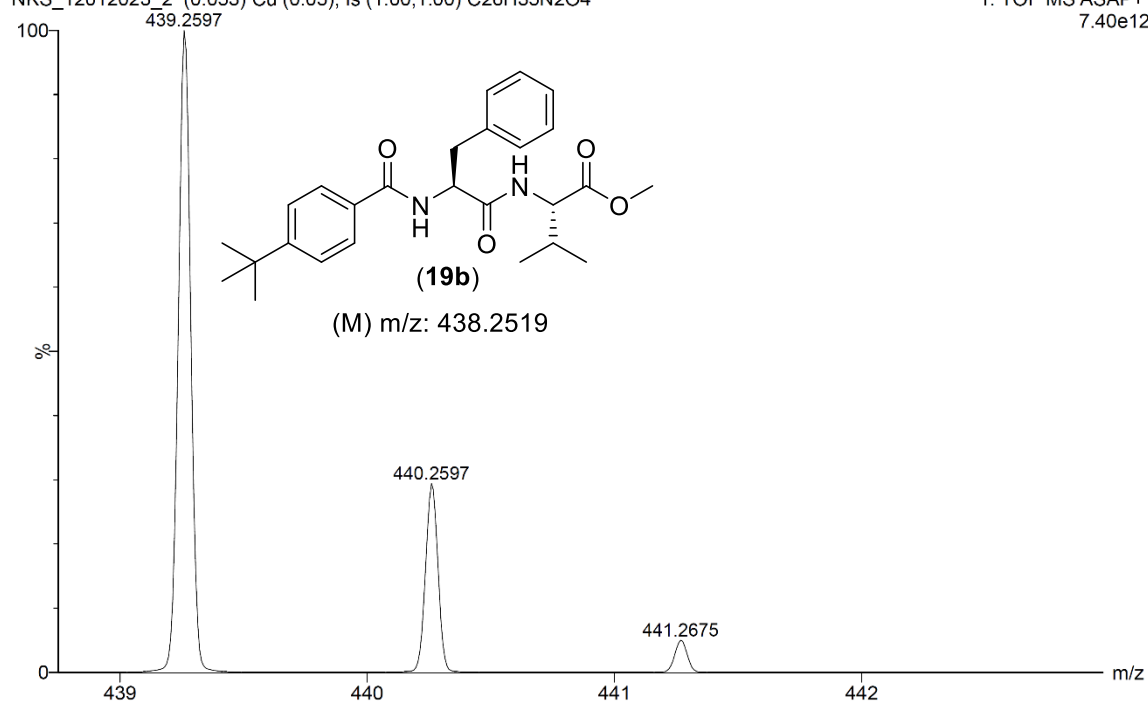
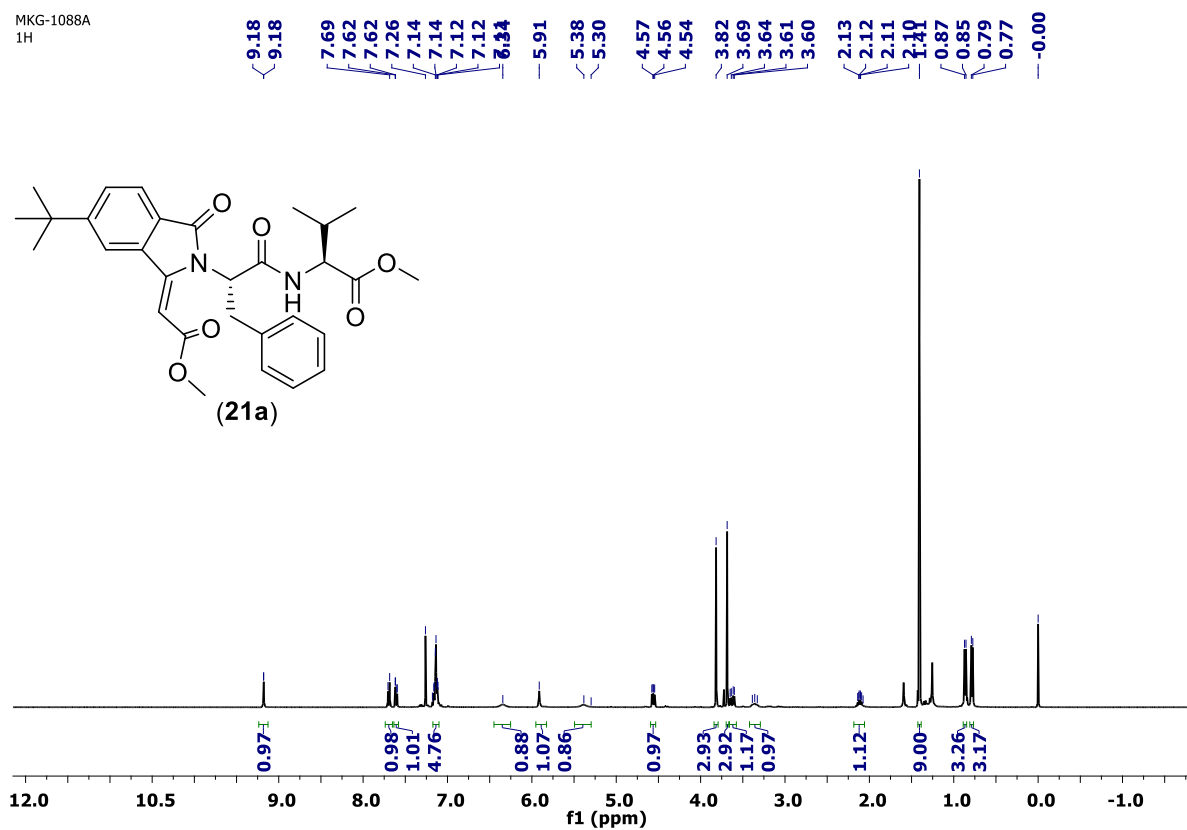


Figure. S72. ESI-HRMS spectra of **19b**

MKG-1088A
1H



MKG-1088A
13C

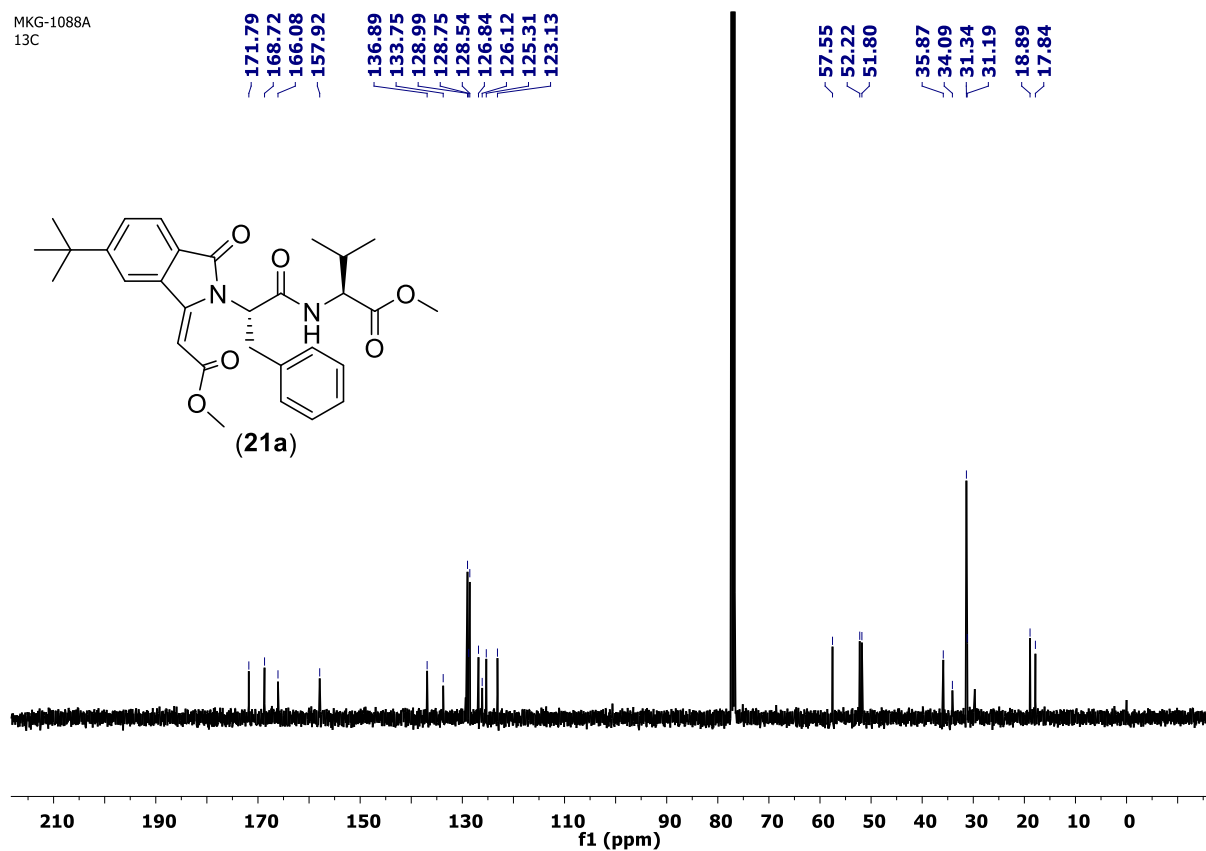


Figure. S73. ¹H, ¹³C NMR spectra of 21a

NKS_MKG_1088_A

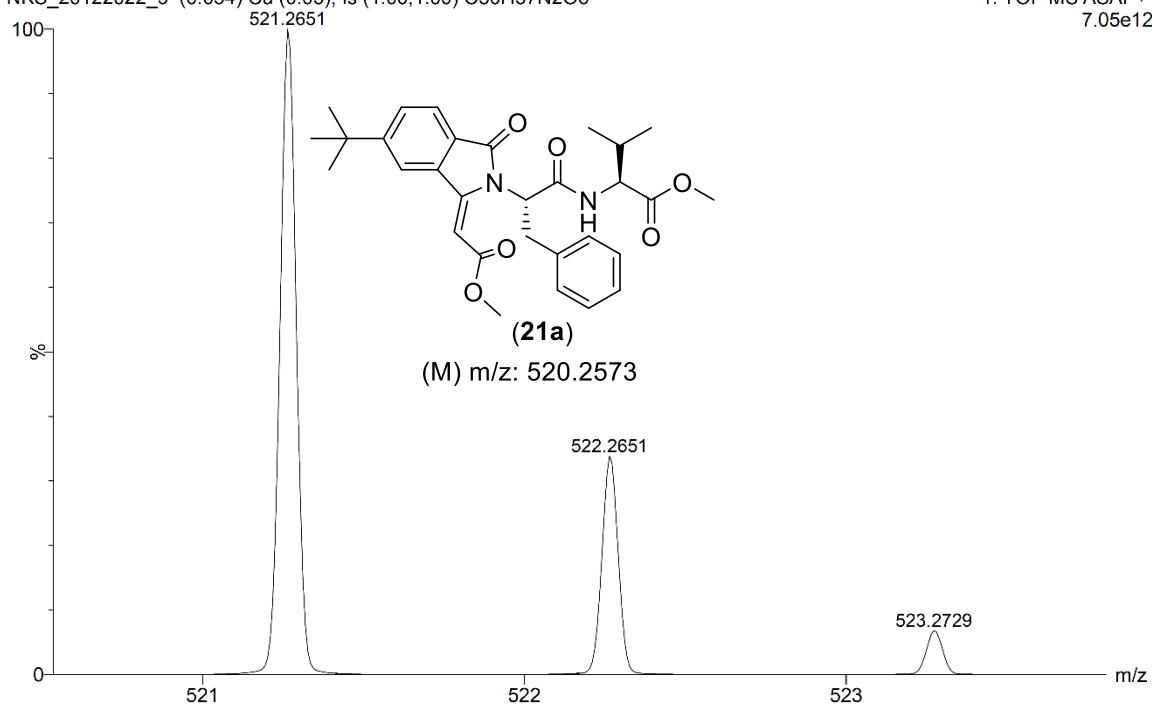
20-Dec-2022

11:14:15

XEVO-G2XSQTOF#YFA1739

NKS_20122022_9 (0.054) Cu (0.05); Is (1.00,1.00) C₃₀H₃₇N₂O₆

1: TOF MS ASAP+
7.05e12



NKS_20122022_9 25 (0.519) Cm (25)

1: TOF MS ASAP+
3.38e6

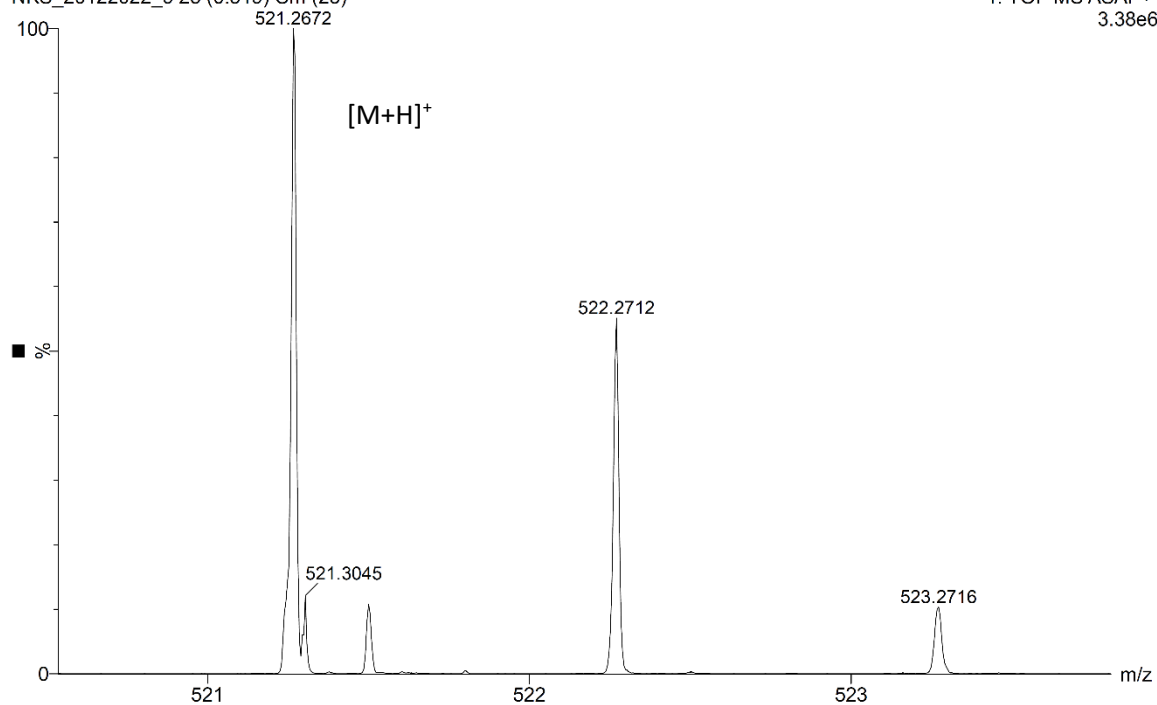


Figure. S74. ESI-HRMS spectra of **21a**

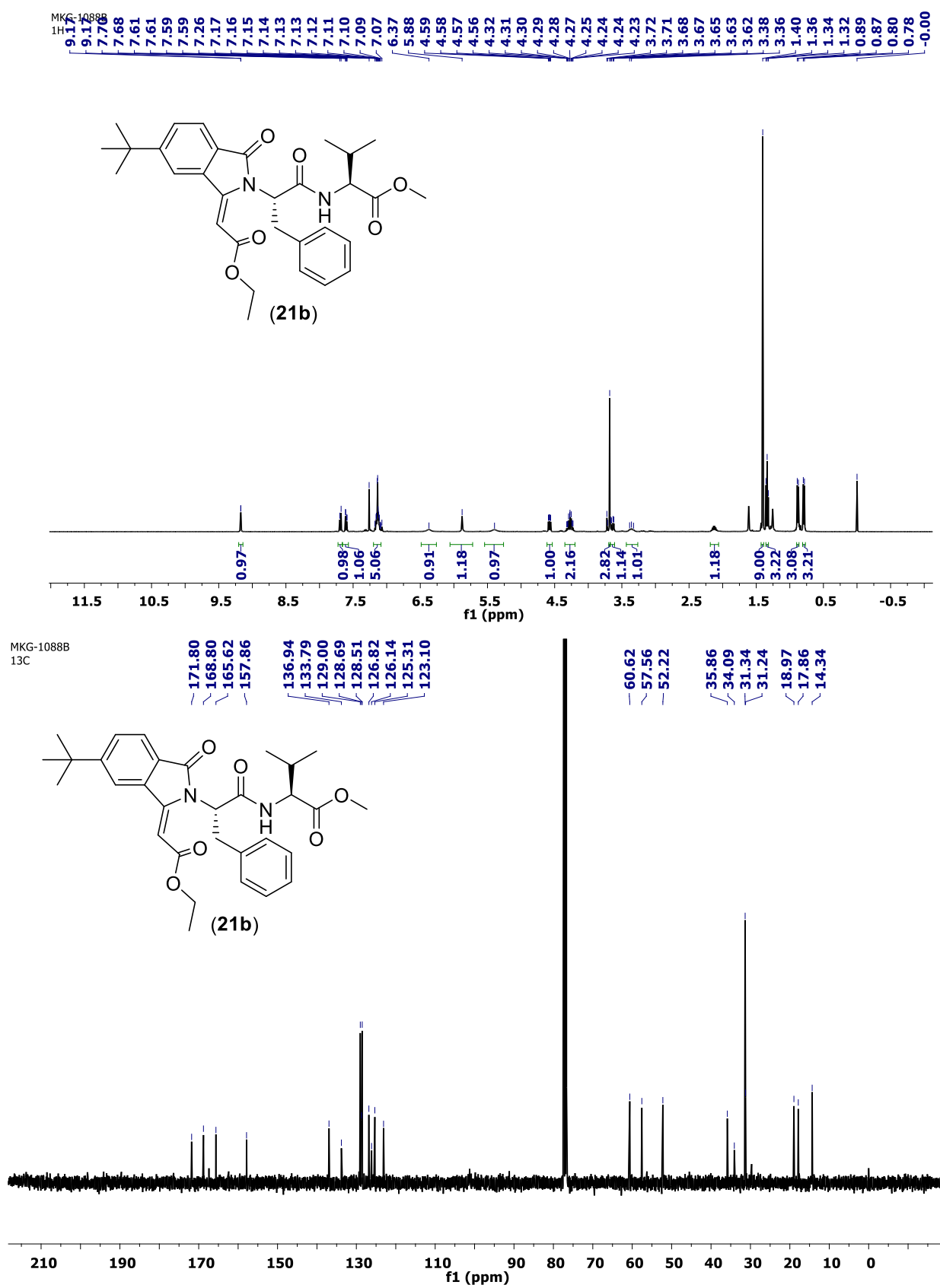


Figure. S73. ^1H , ^{13}C NMR spectra of **21b**

MKG_10888_B

12-Jan-2023
16:58:59

XEVO-G2XSQTOF#YFA1739
NKS_12012023_7 (0.054) Cu (0.05); Is (1.00,1.00) C₃₁H₃₈N₂O₆

1: TOF MS ASAP+
6.98e12

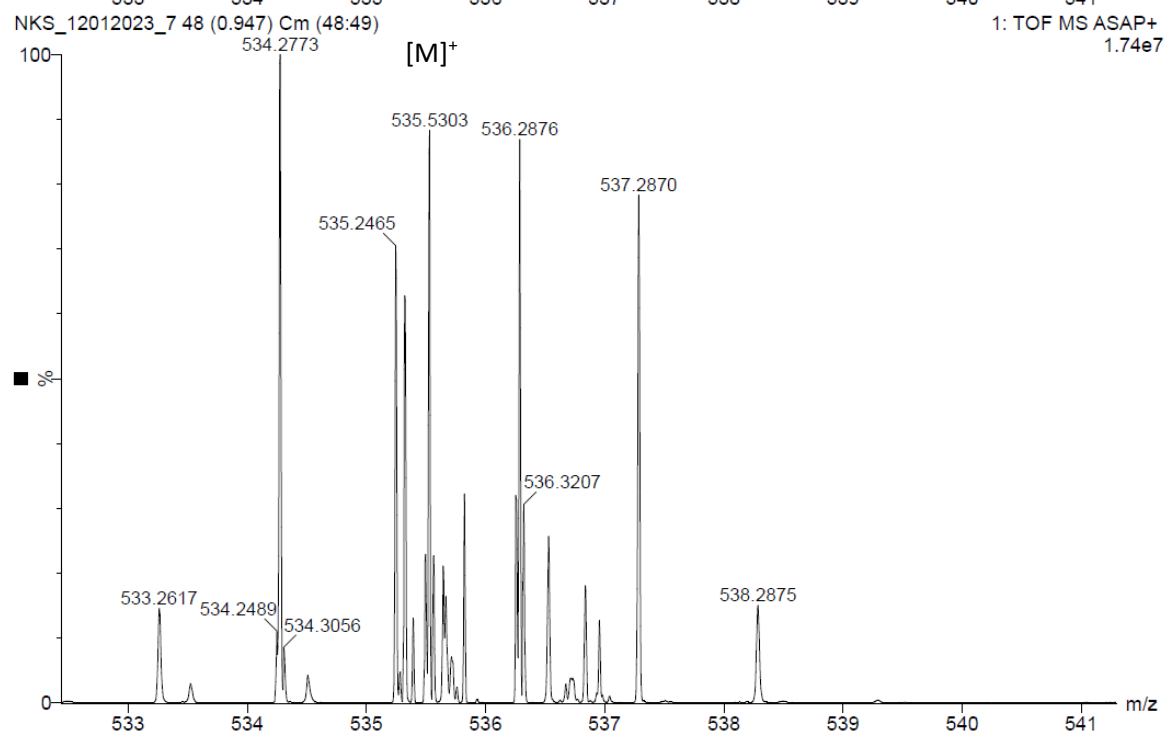
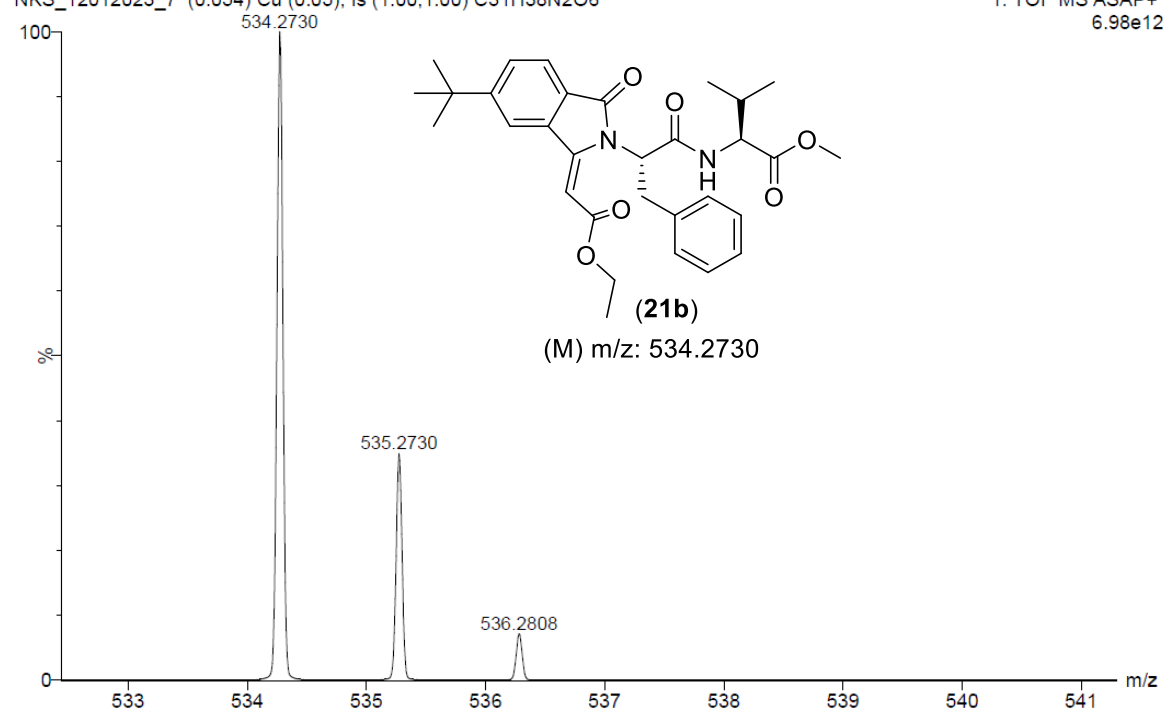
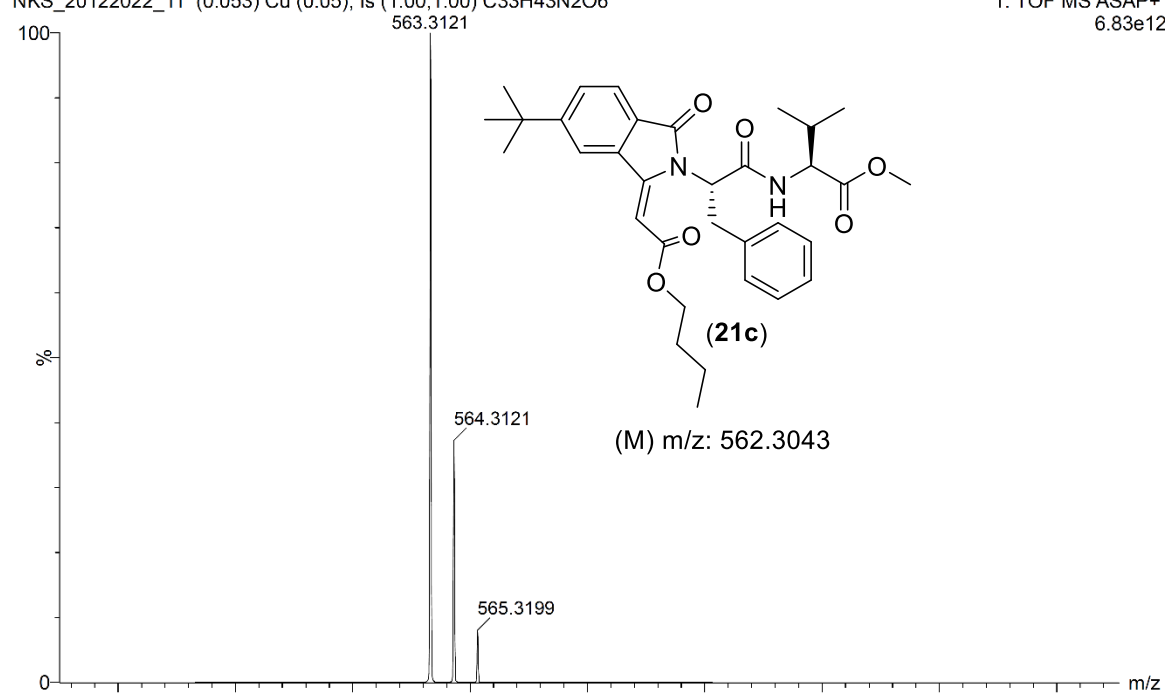
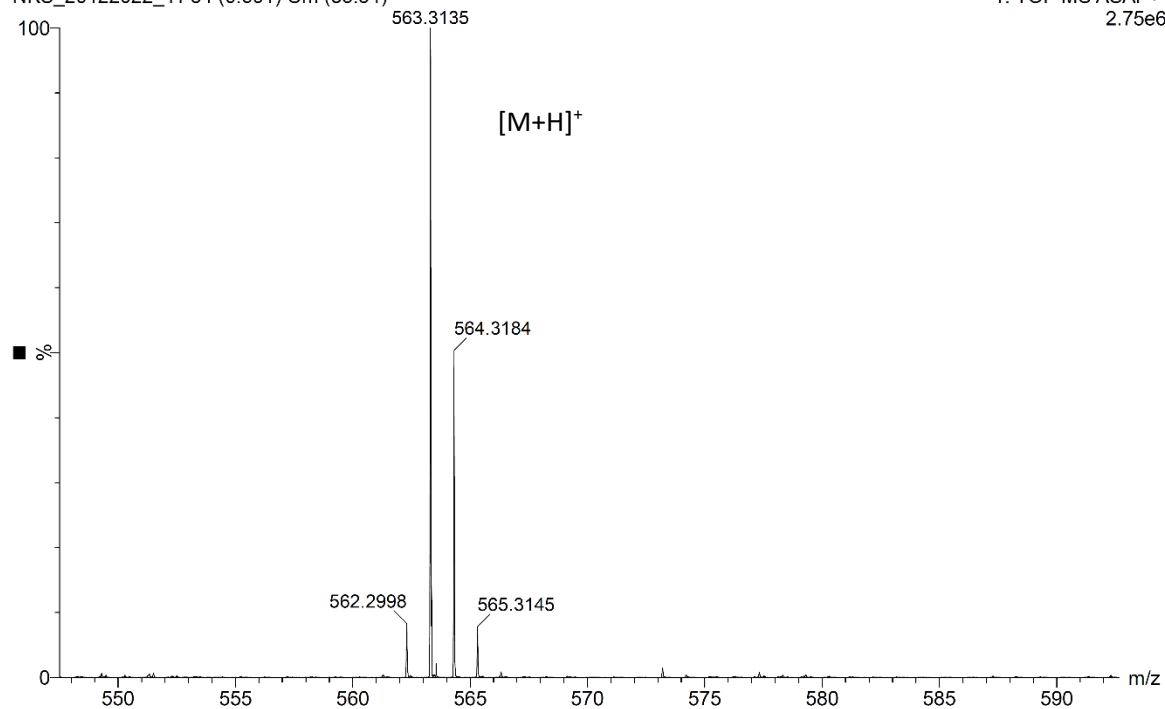


Figure. S74. ESI-HRMS spectra of **21b**

XEVO-G2XSQTOF#YFA1739

NKS_20122022_11 (0.053) Cu (0.05); Is (1.00,1.00) C₃₃H₄₃N₂O₆1: TOF MS ASAP+
6.83e12

NKS_20122022_11 34 (0.691) Cm (33:34)

1: TOF MS ASAP+
2.75e6**Figure. S75.** ESI-HRMS spectra of **21c**

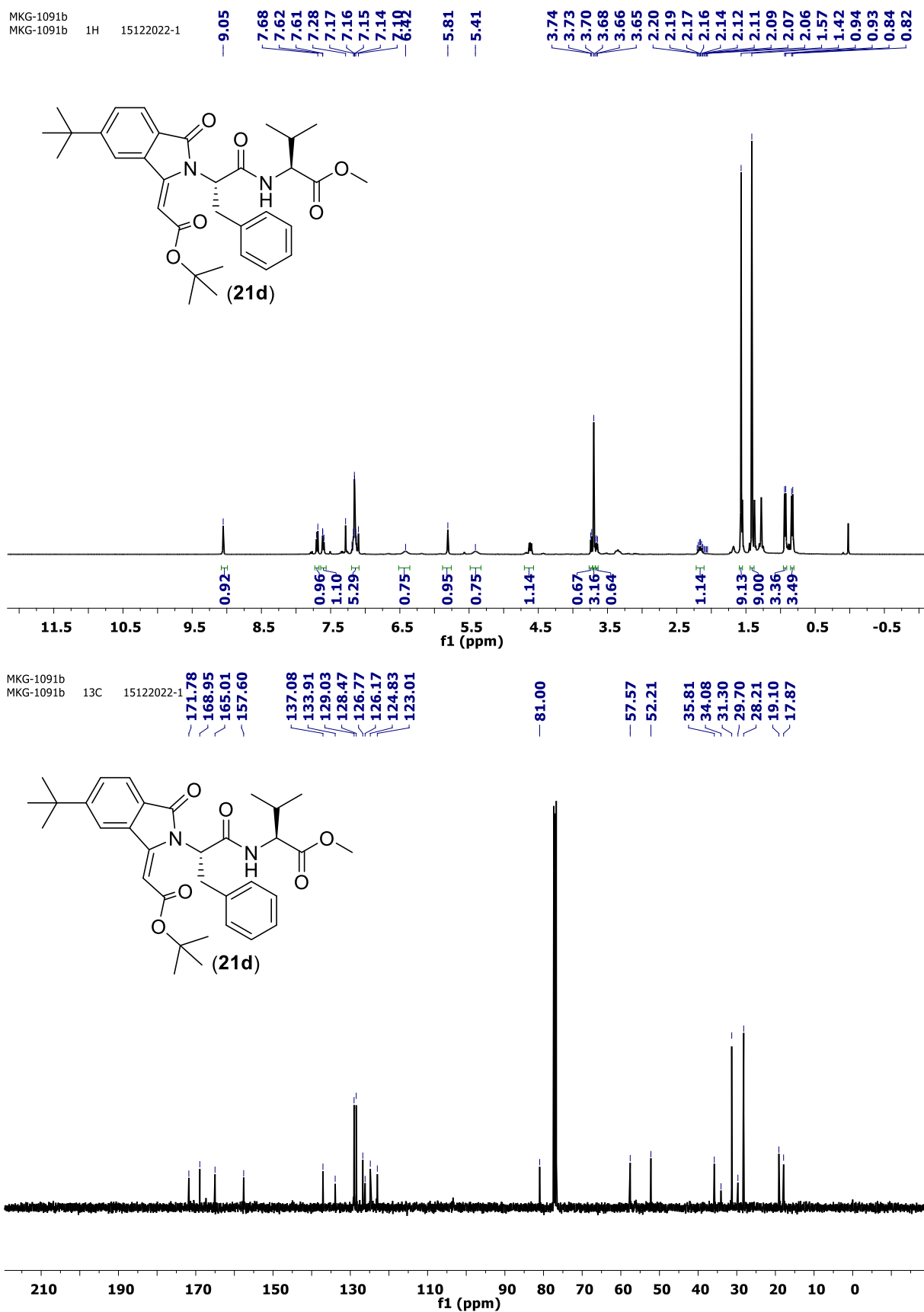


Figure. S76. ^1H , ^{13}C NMR spectra of 21d

MKG_1091_B

12-Jan-2023
12:59:31

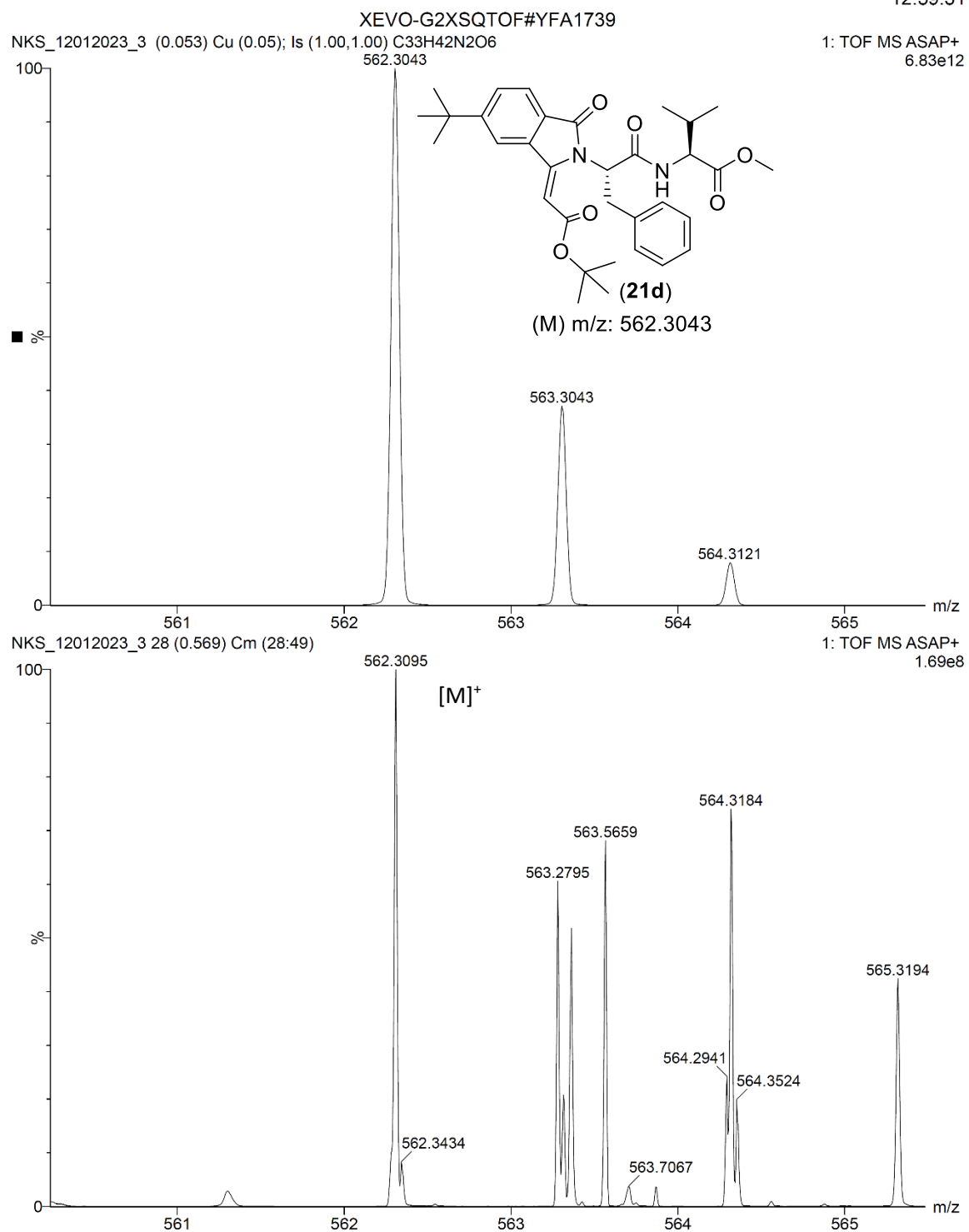


Figure. S77. ESI-HRMS spectra of 21d

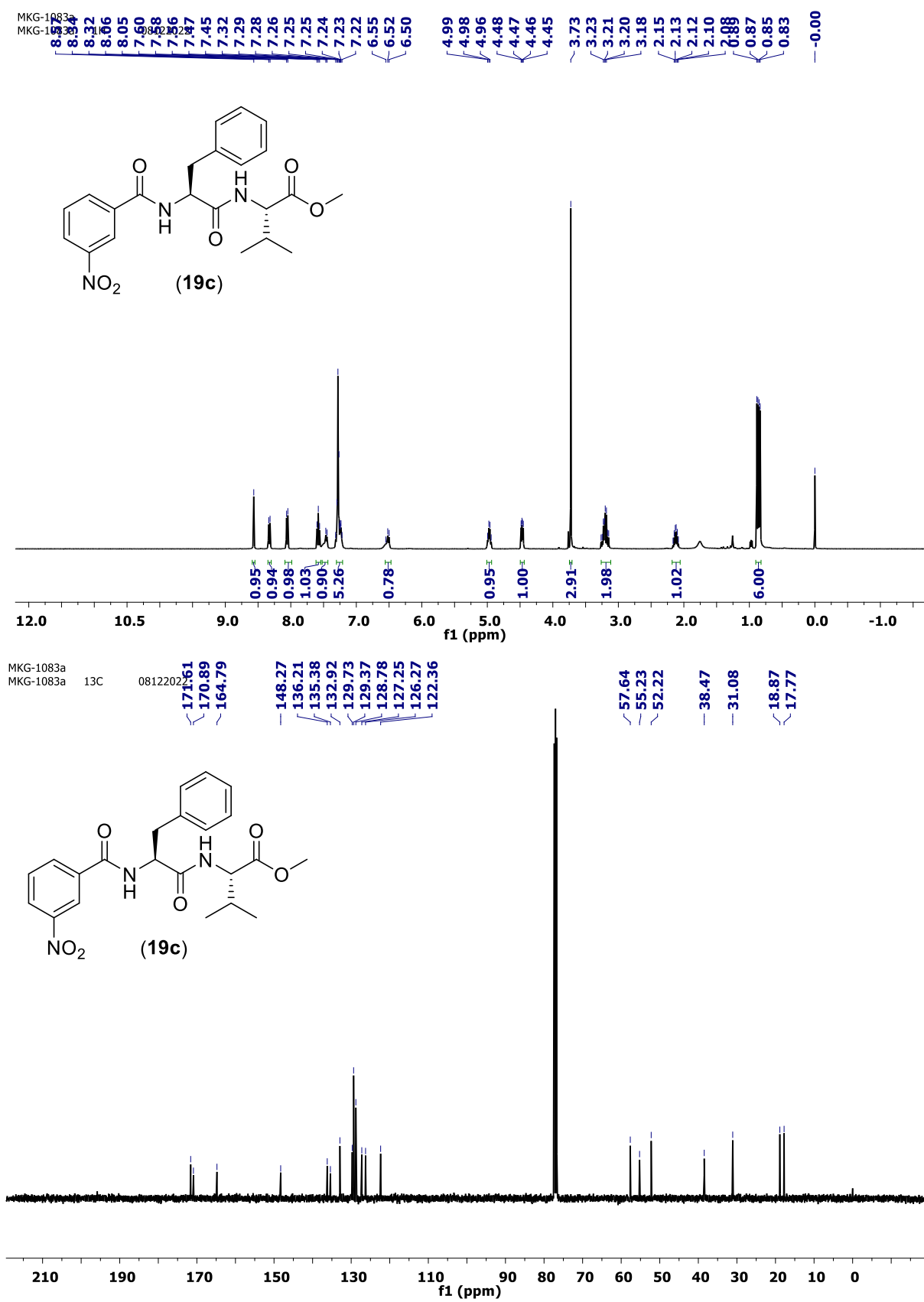


Figure. S78. ¹H, ¹³C NMR spectra of spectra of **19c**

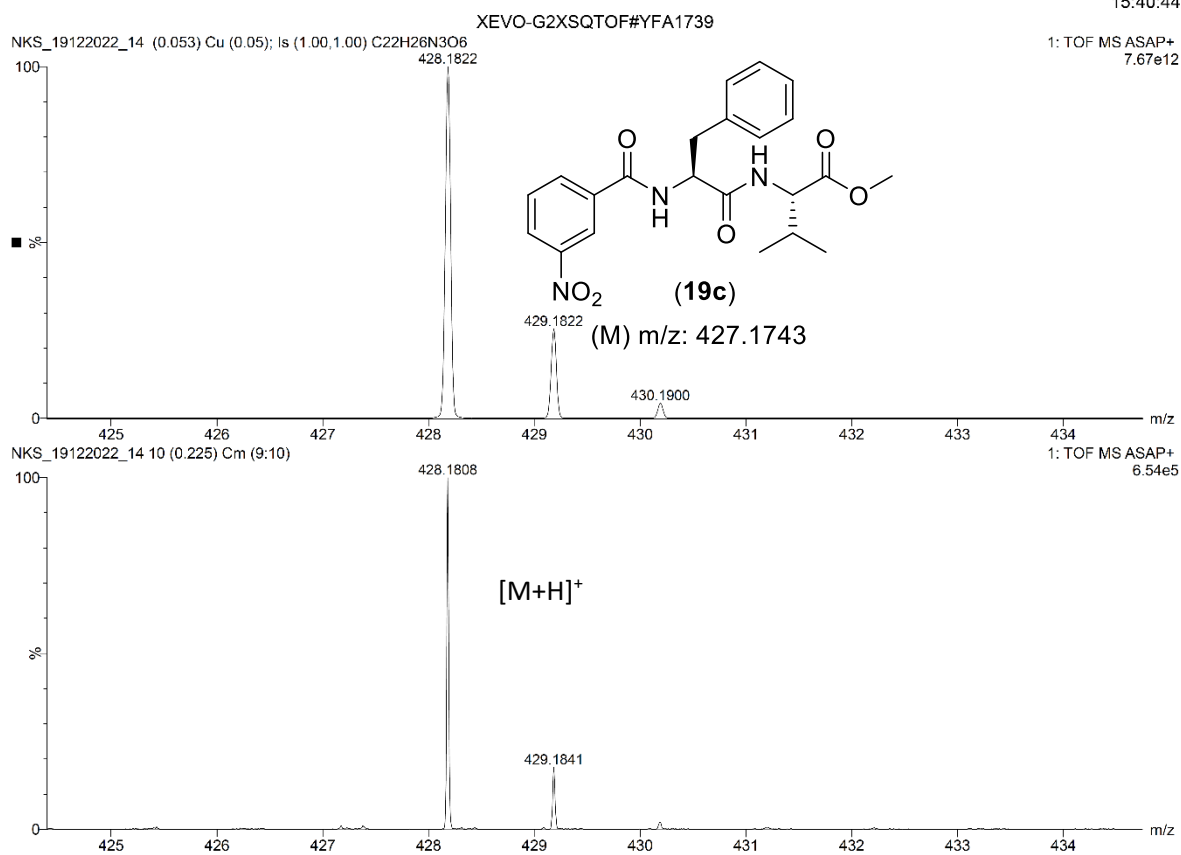


Figure. S79. ESI-HRMS spectra of **19c**

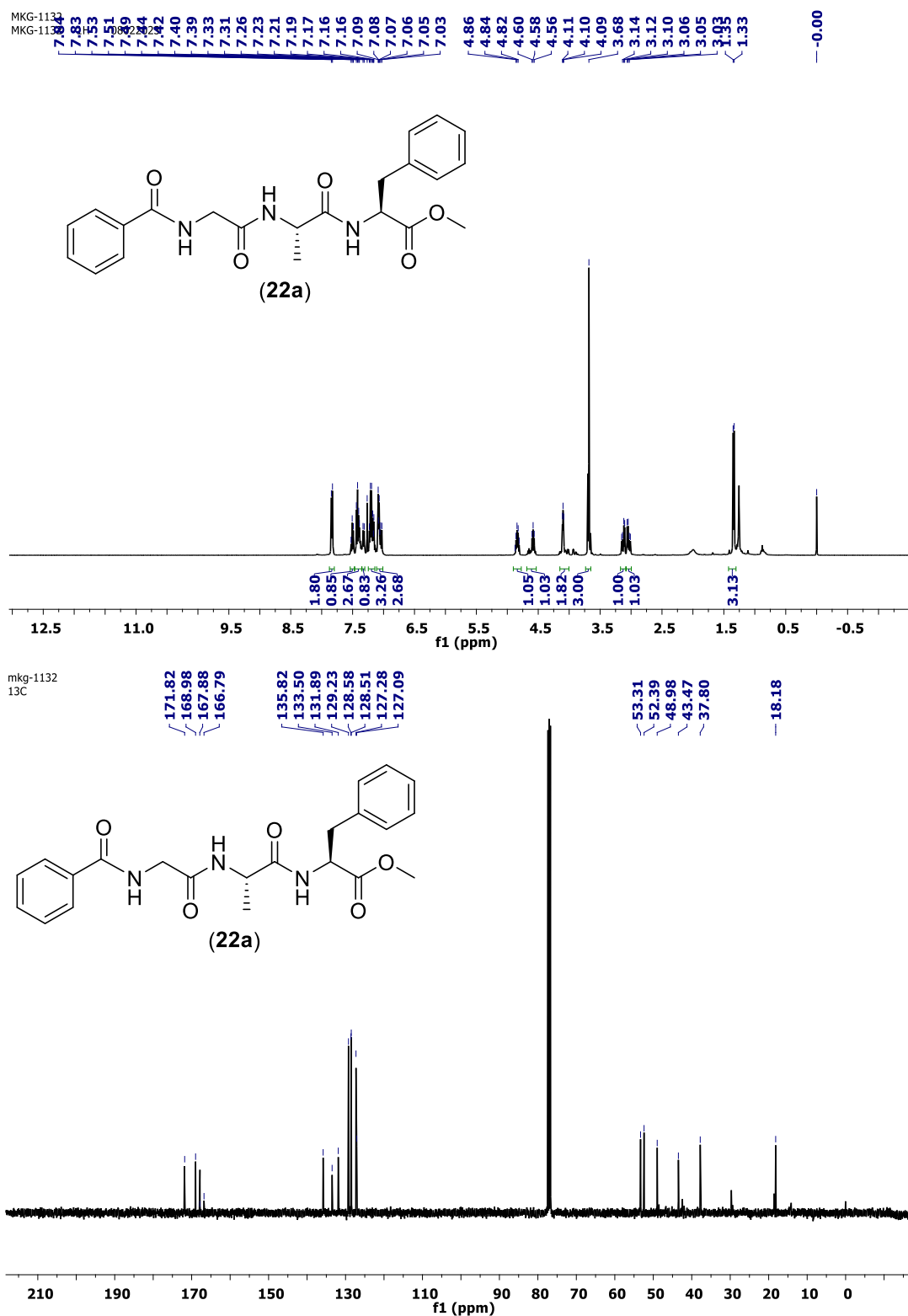


Figure. S80. ^1H , ^{13}C NMR spectra of 22a

NKS_mkg_1132

10-Feb-2023

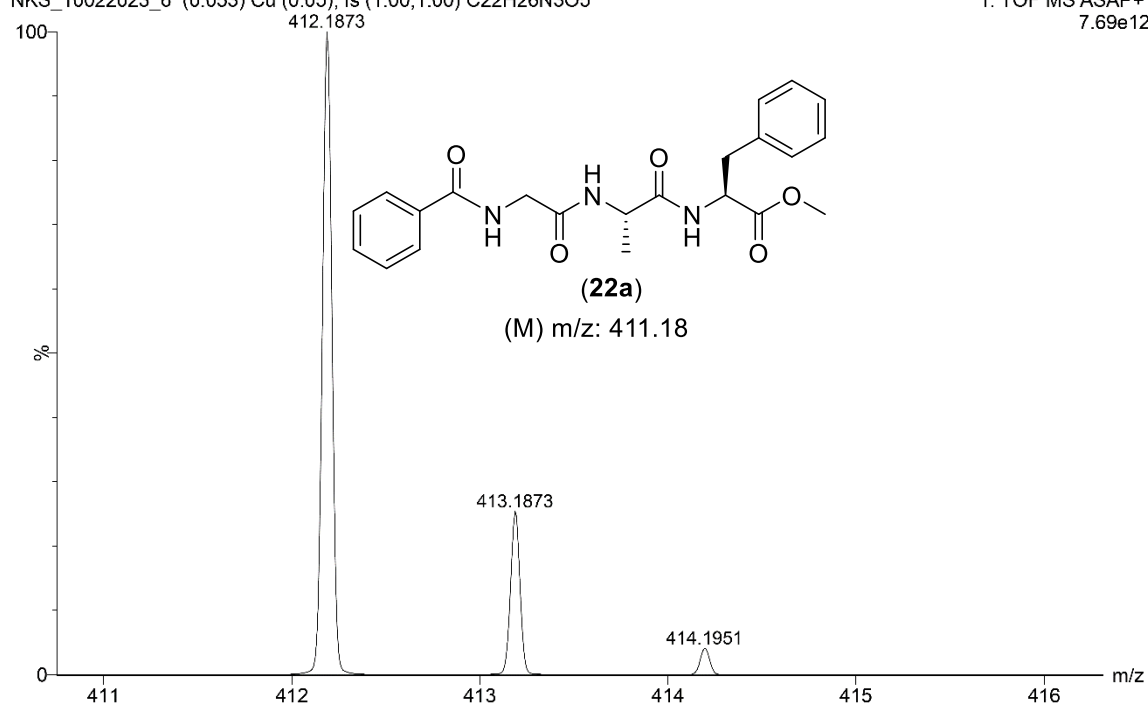
15:17:17

XEVO-G2XSQTOF#YFA1739

NKS_10022023_6 (0.053) Cu (0.05); Is (1.00,1.00) C₂₂H₂₆N₃O₅

1: TOF MS ASAP+

7.69e12



NKS_10022023_6 30 (0.603) Cm (27.32)

1: TOF MS ASAP+

4.19e7

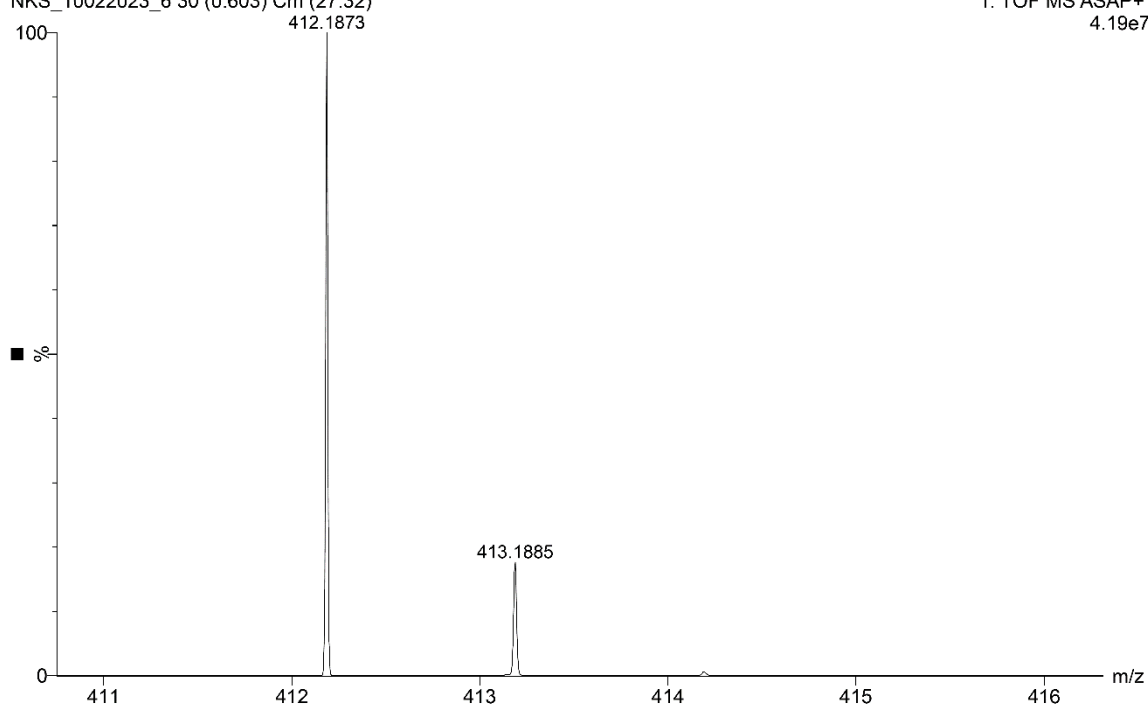


Figure. S81. ESI-HRMS spectra of **22a**

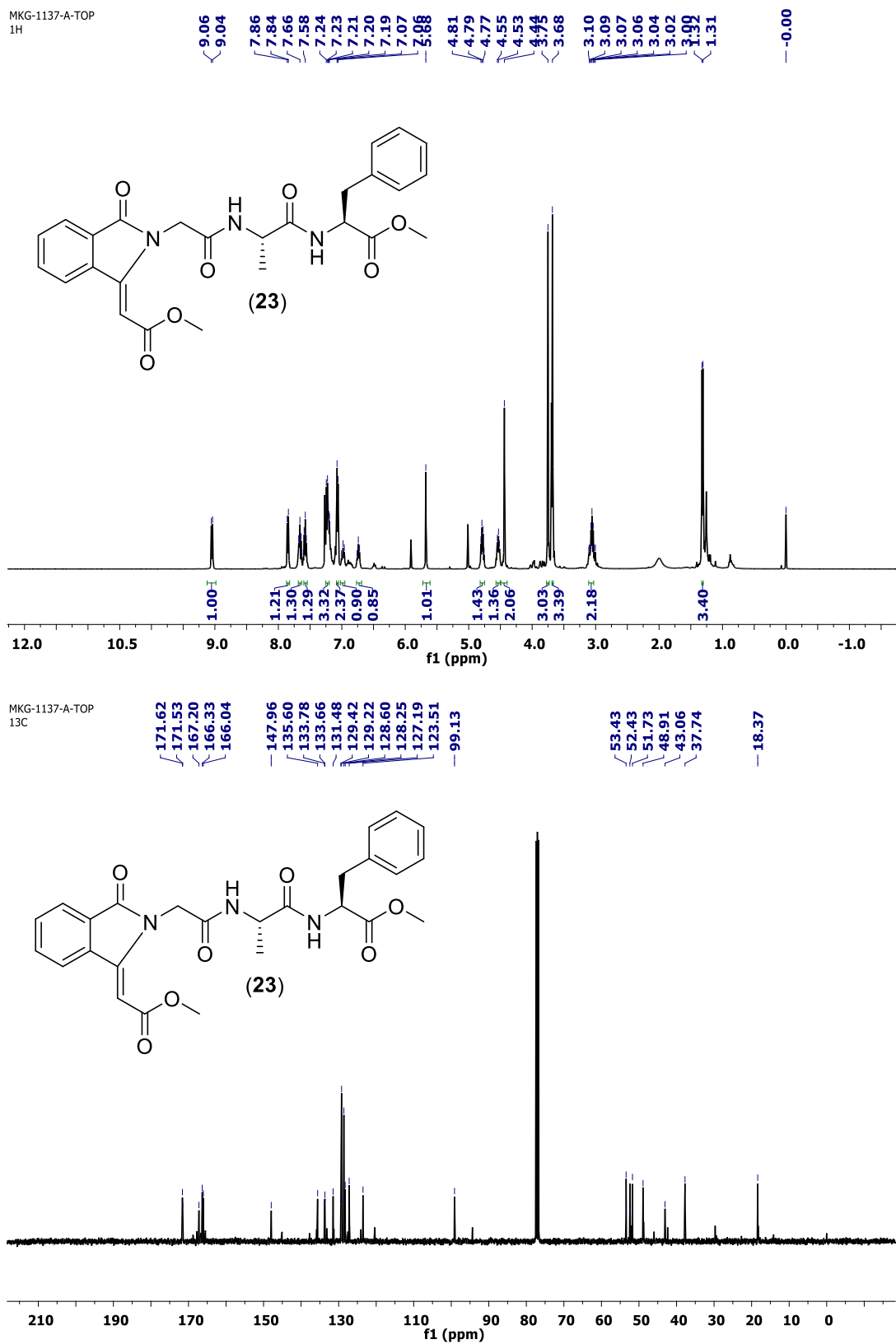


Figure. S82. ^1H , ^{13}C NMR spectra of 23

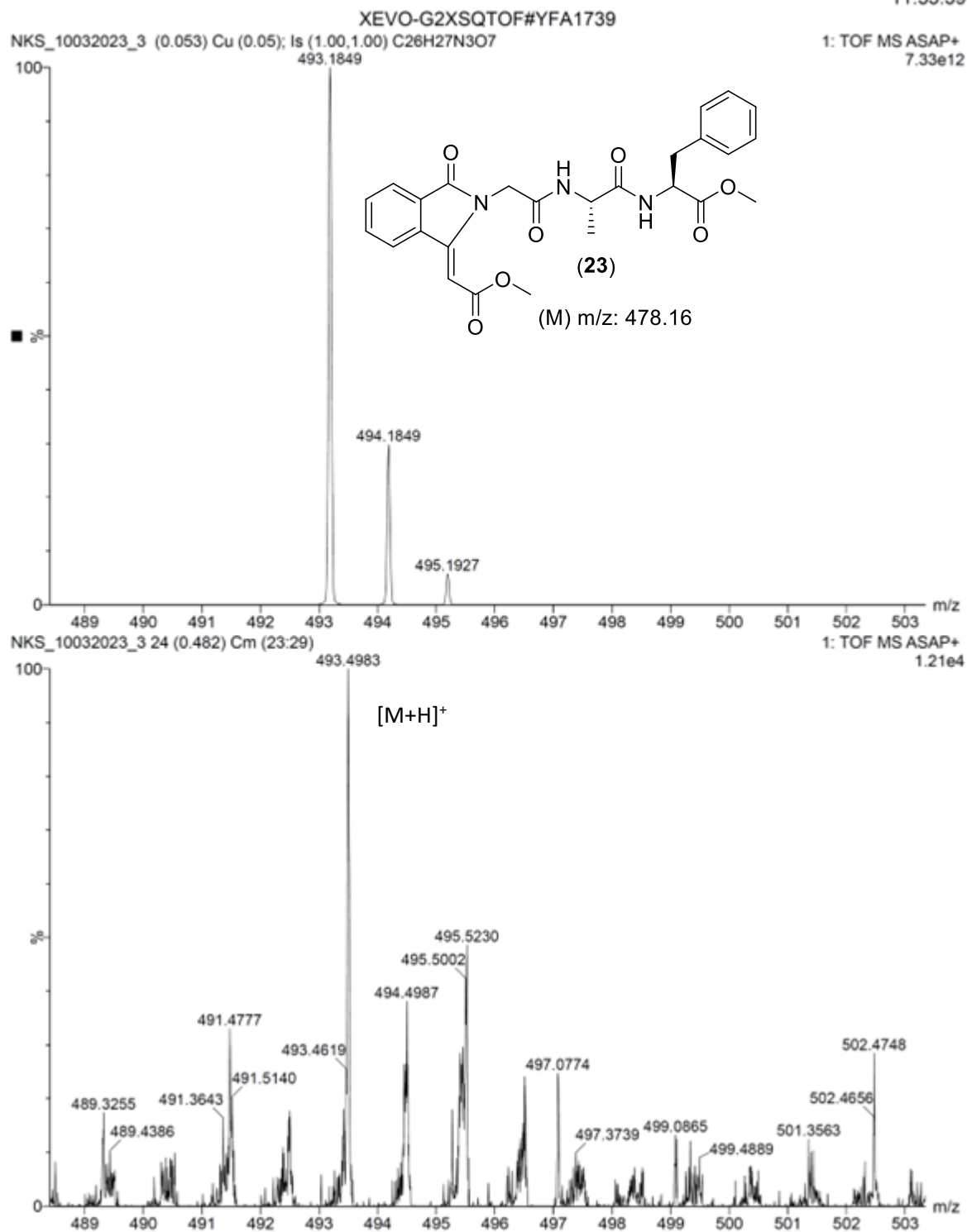


Figure. S83. ESI-HRMS spectra of 23

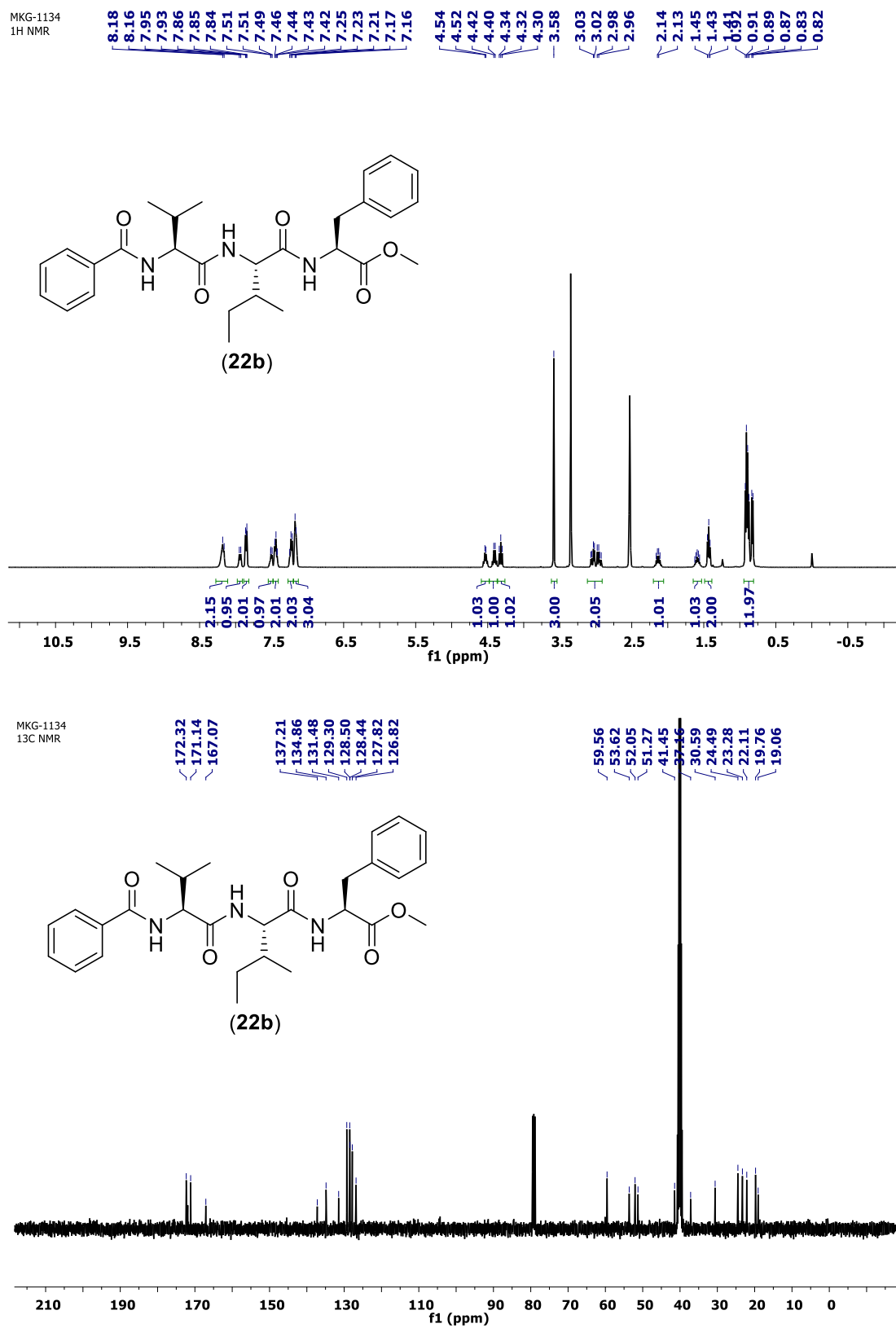


Figure. S84. ^1H , ^{13}C NMR spectra of **22b** in DMSO d_6 .

NKS_MKG_1134

10-Feb-2023
15:20:58

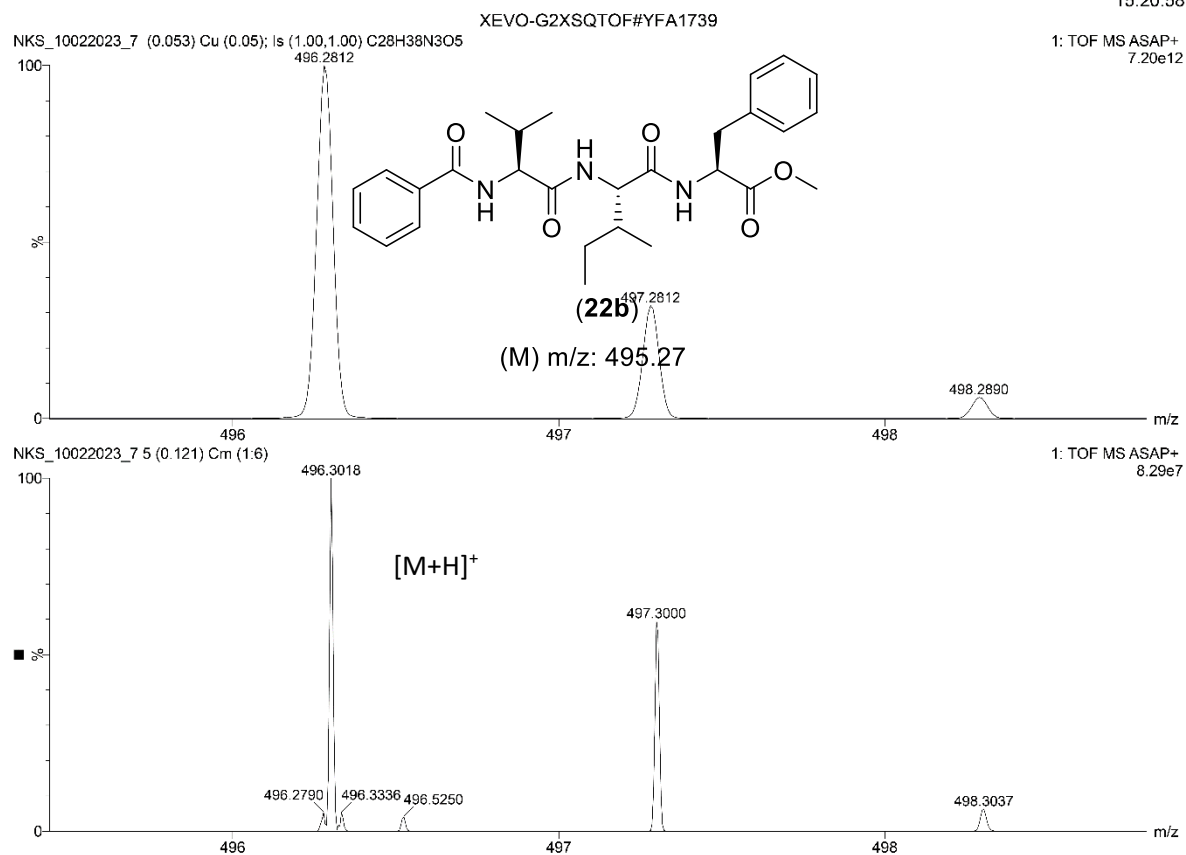


Figure. S85. ESI-HRMS spectra of **22b**

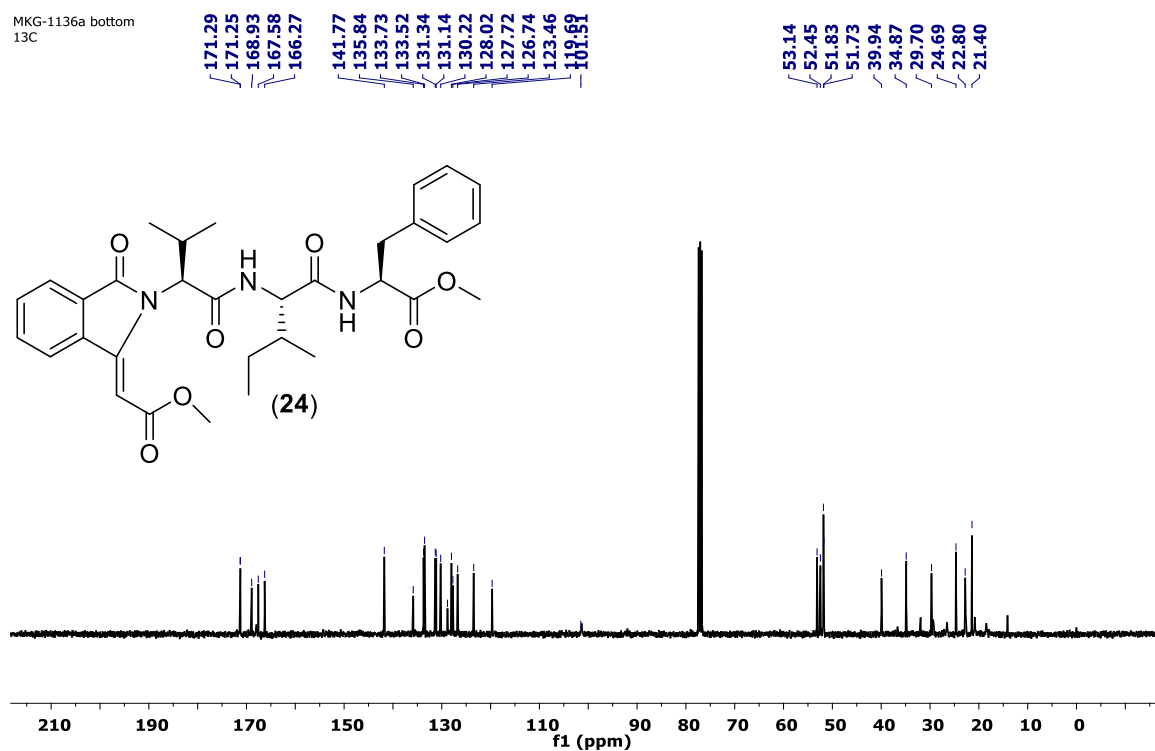
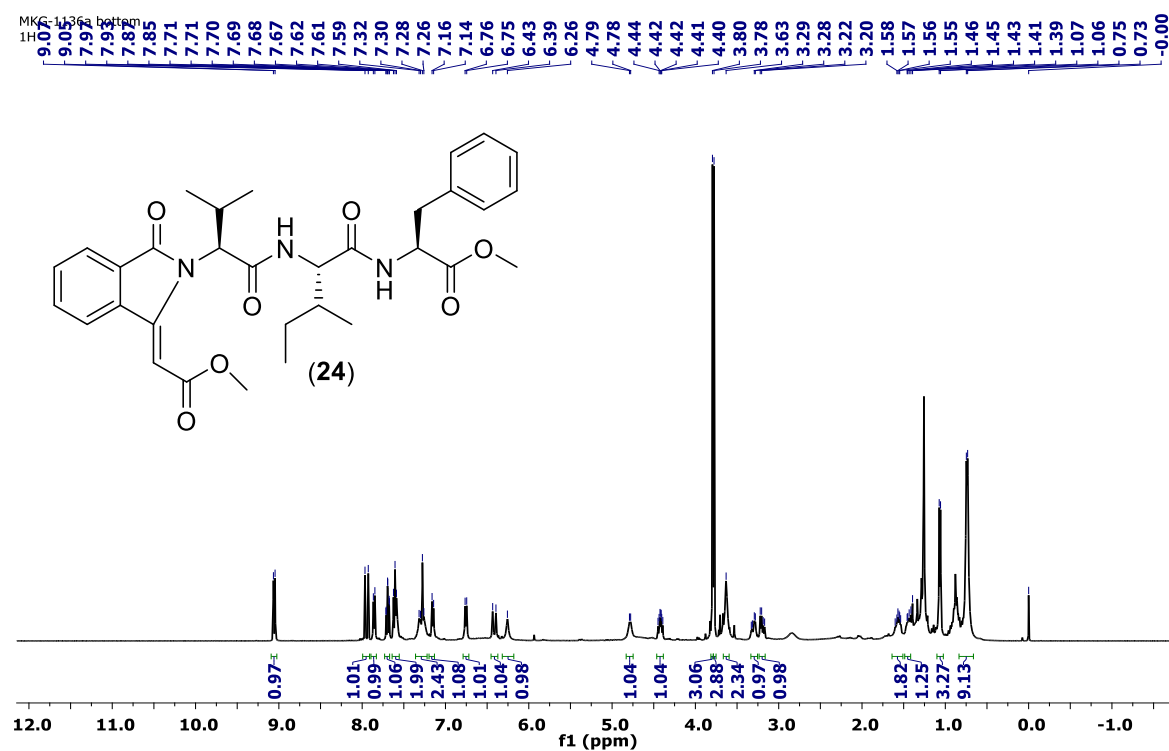


Figure. S86. ESI-HRMS spectra of **24**

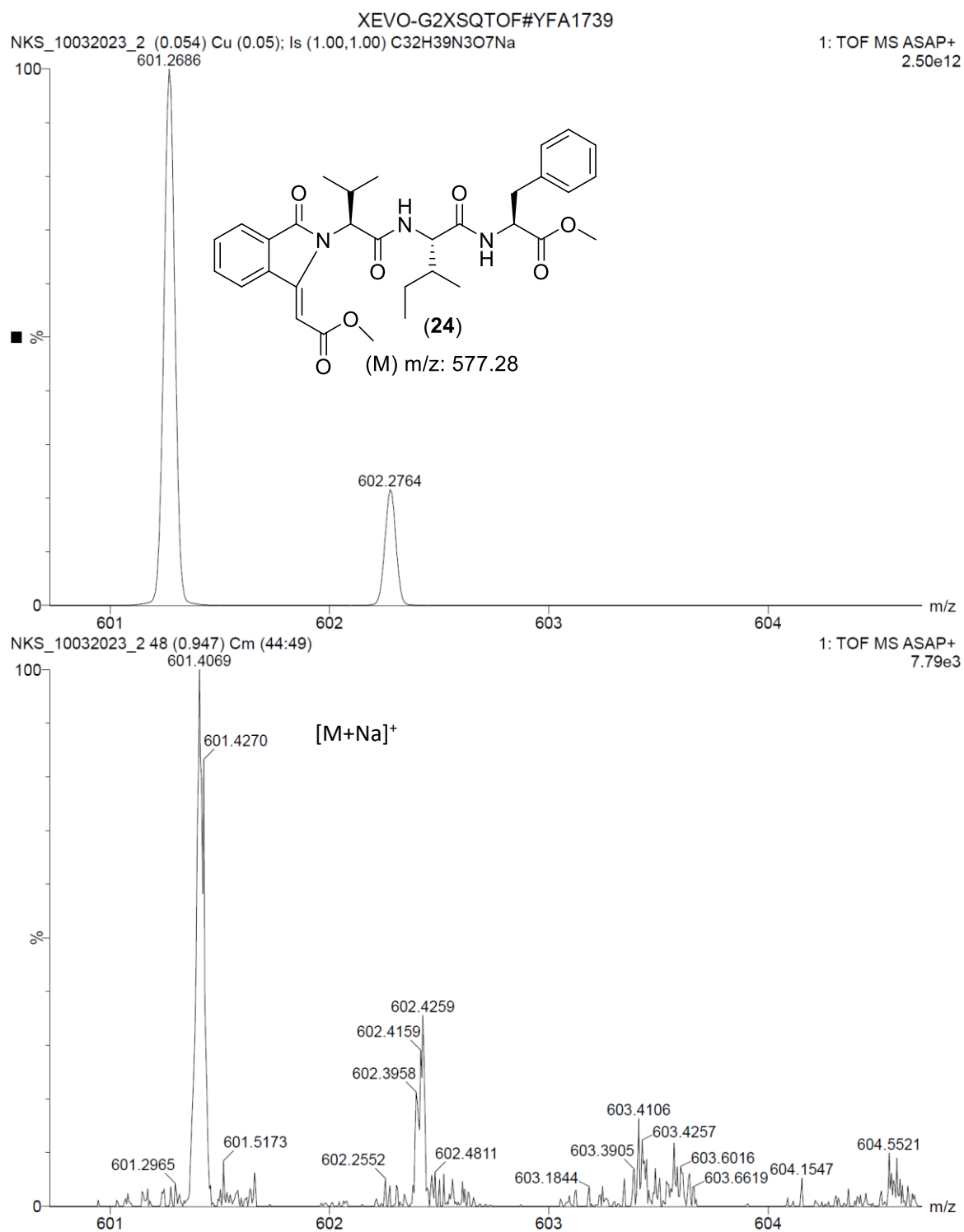


Figure. S87. ESI-HRMS spectra of 24

2. 2D Spectra of Peptides

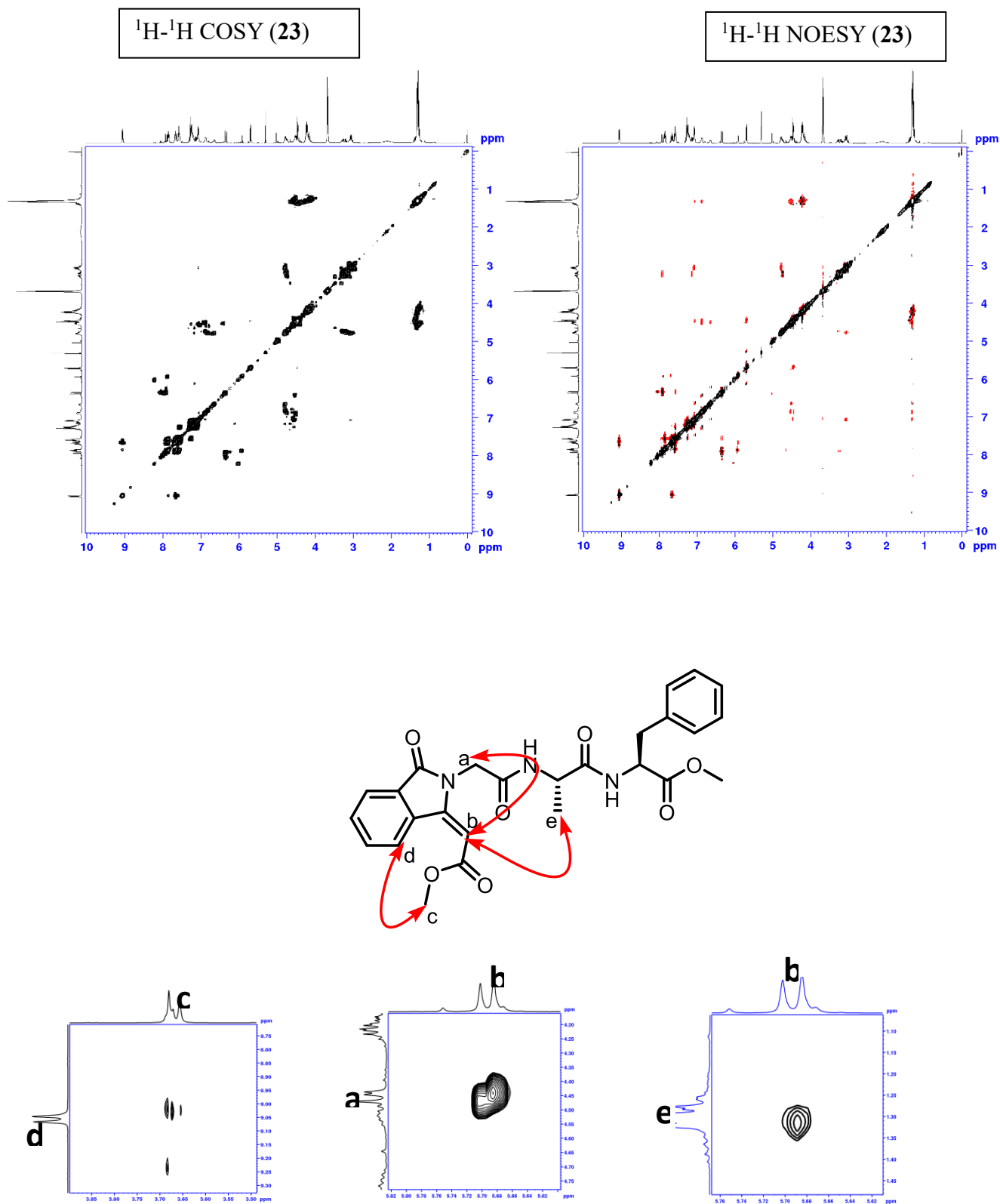
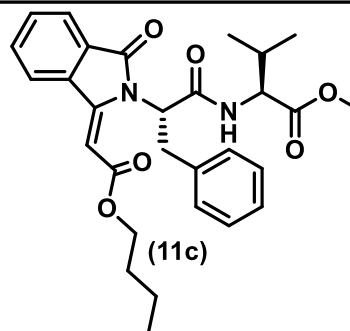
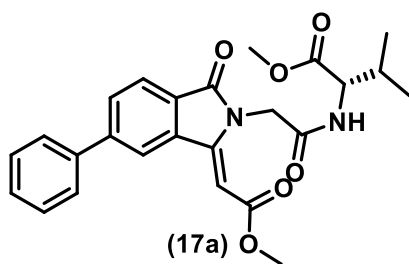
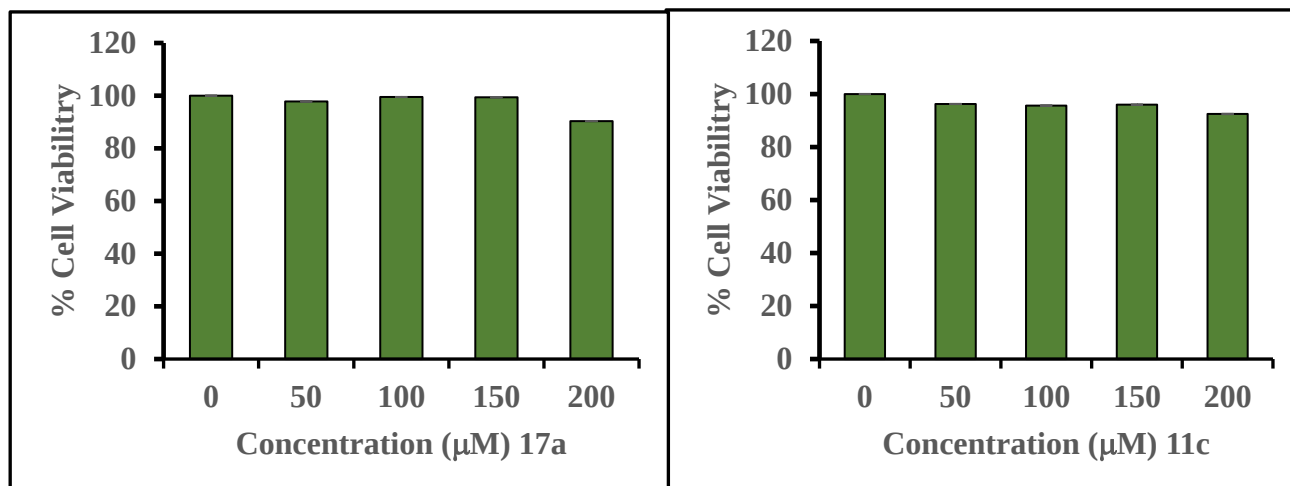
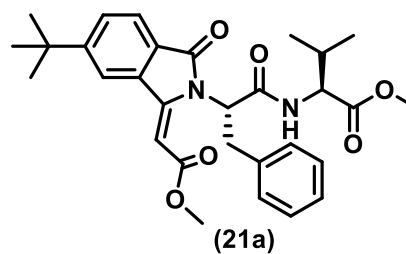
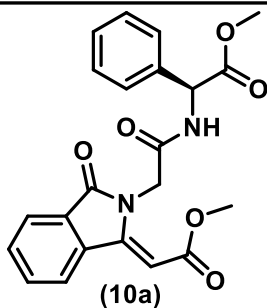
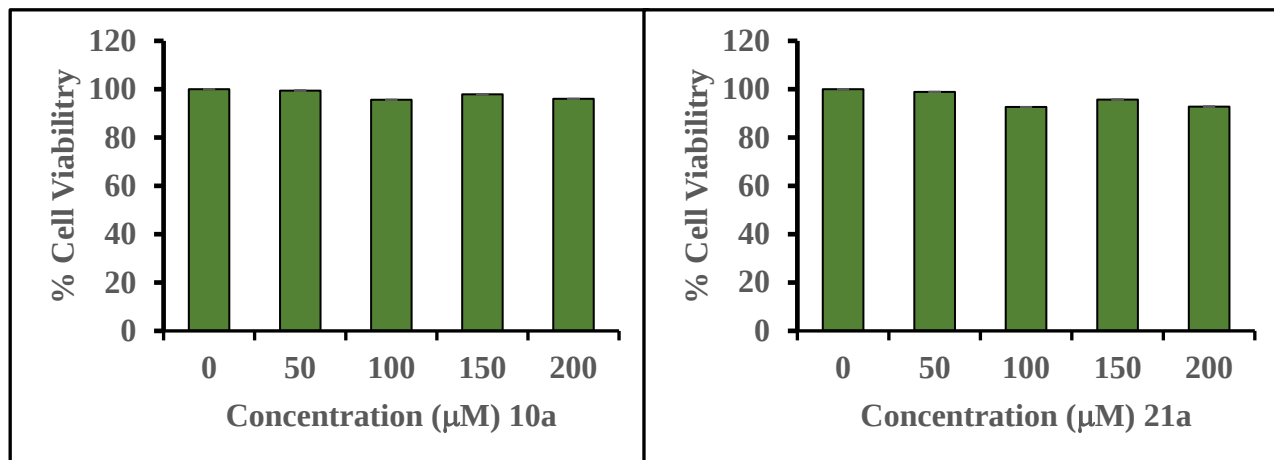
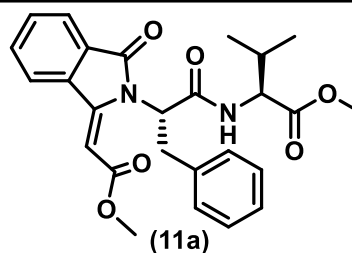
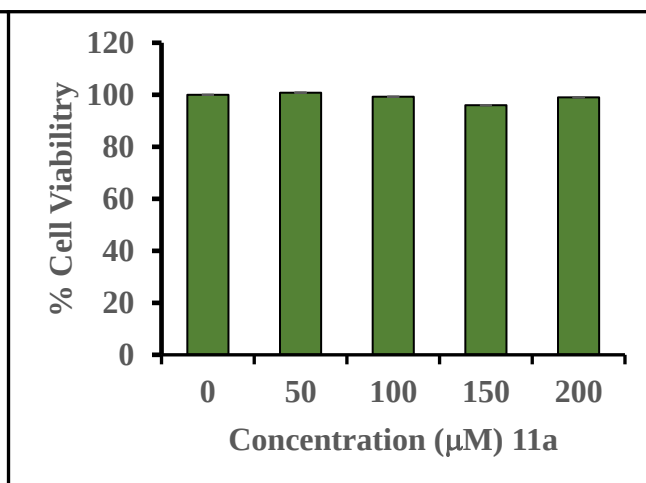
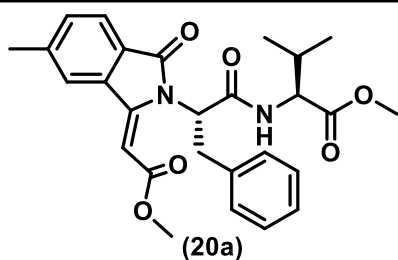
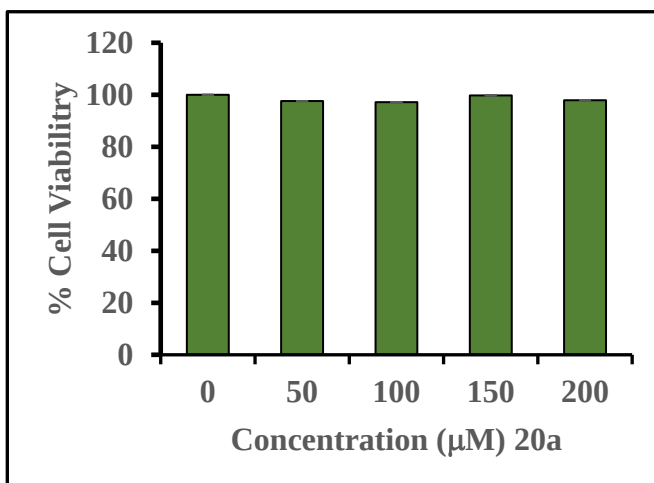
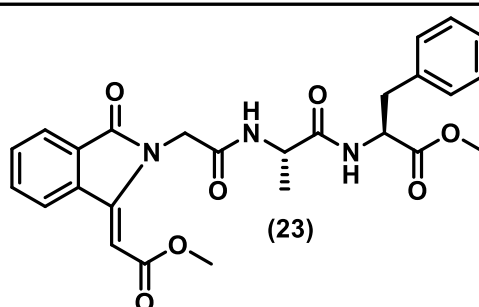
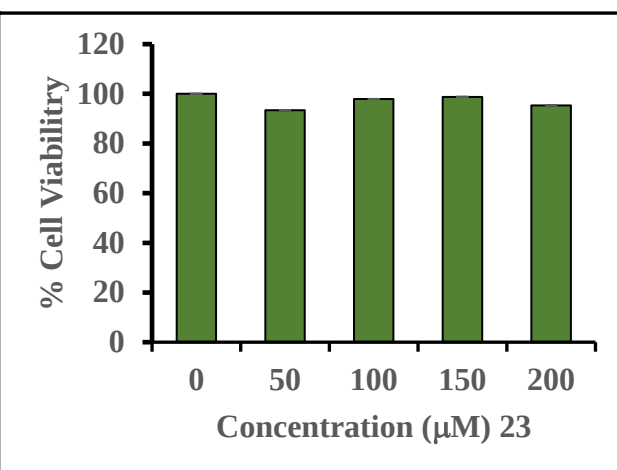
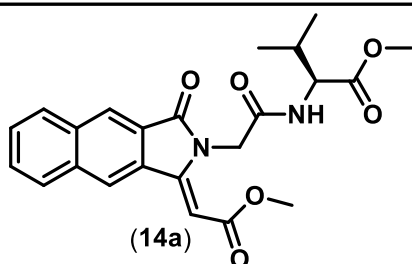
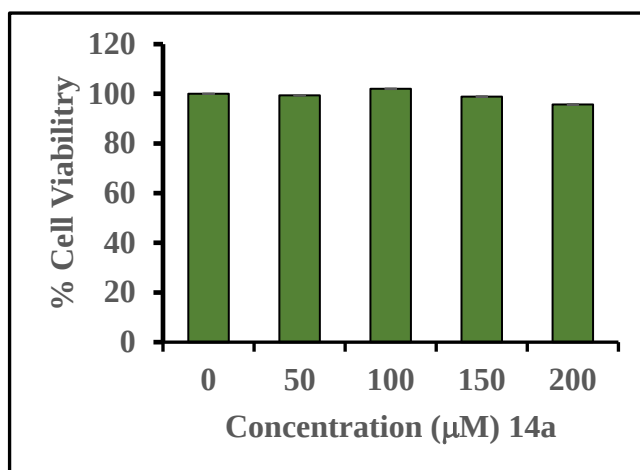


Figure. S88. 2D ^1H - ^1H NOESY Spectra of tetrapeptide isoindolinone(23)

3. Cell proliferation

4.





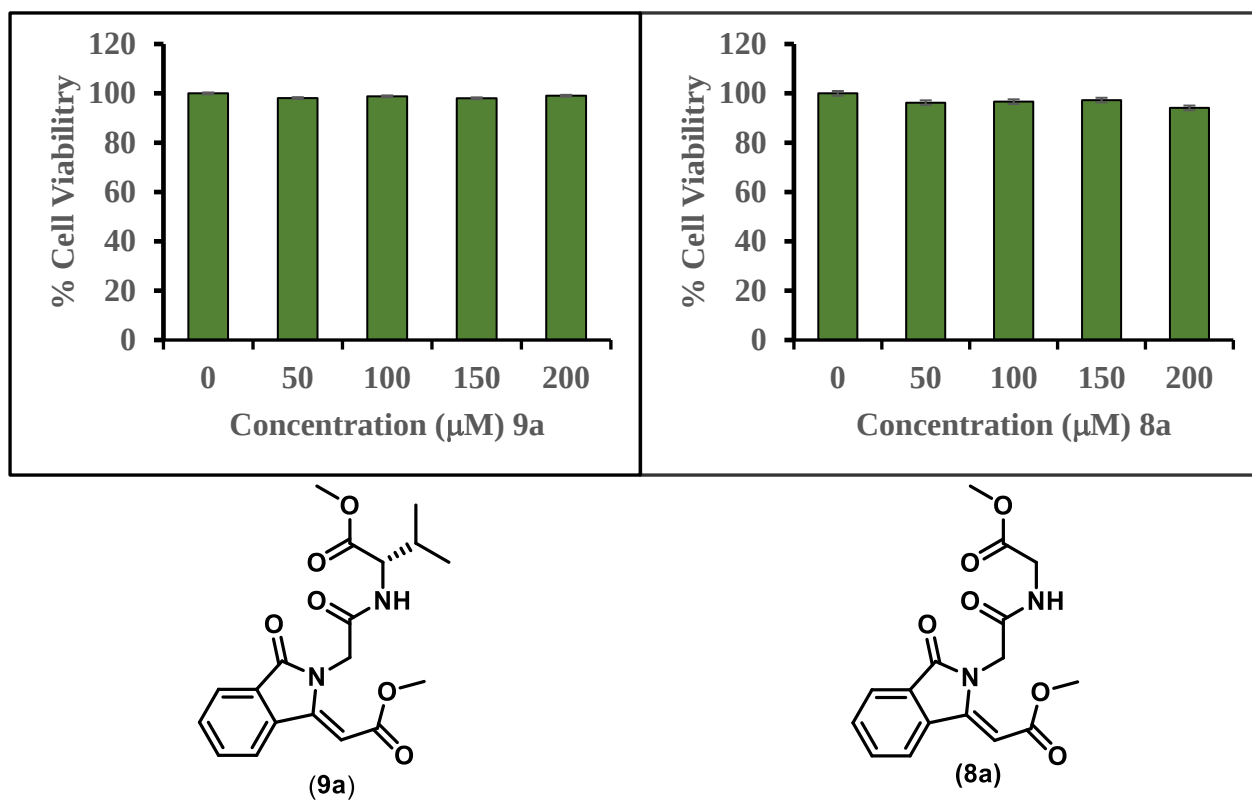
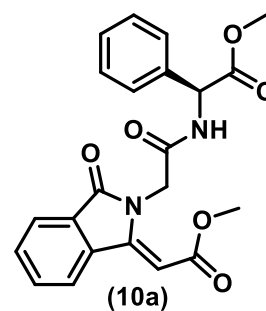
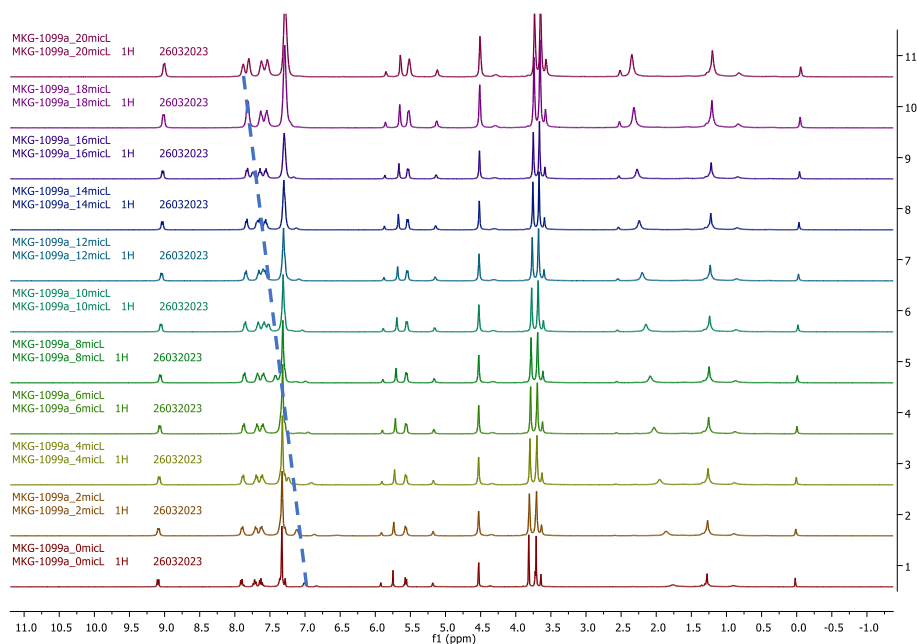
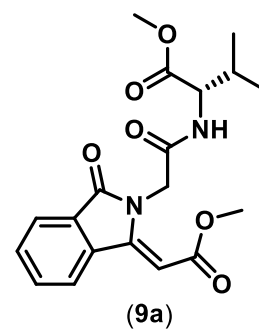
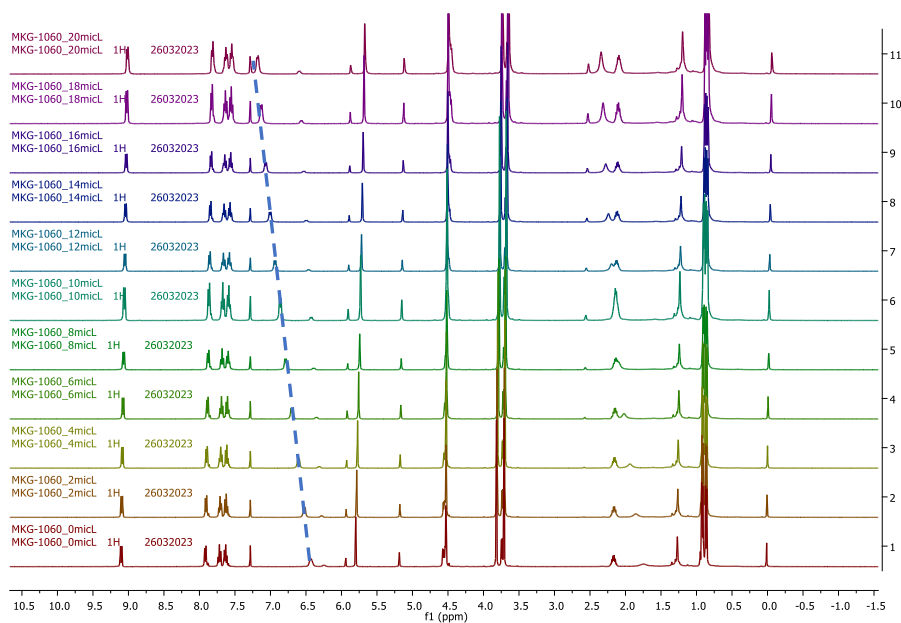
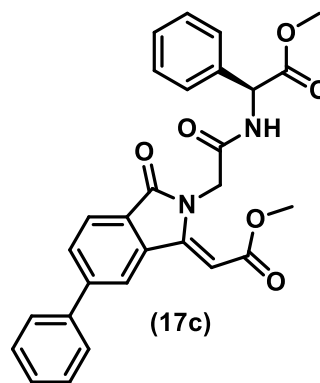
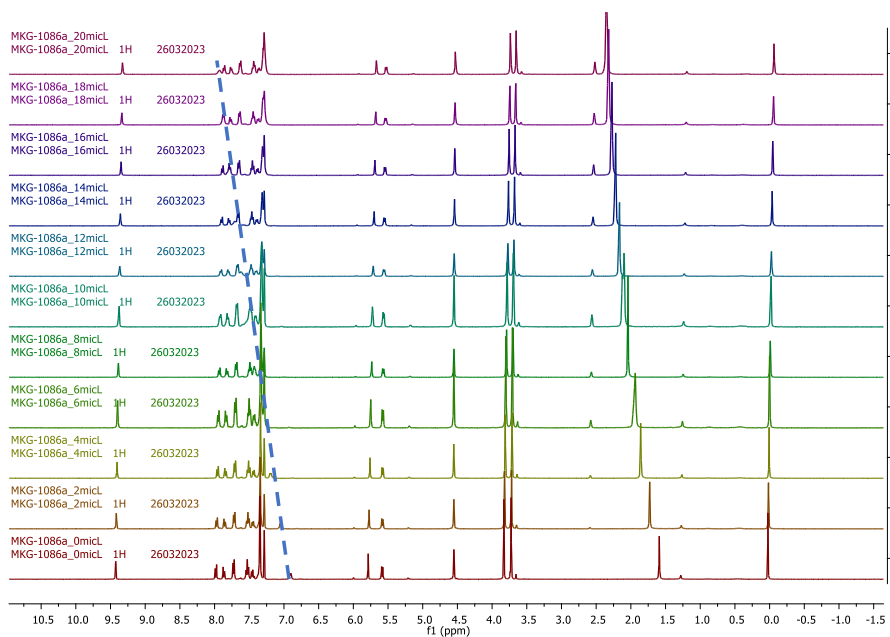
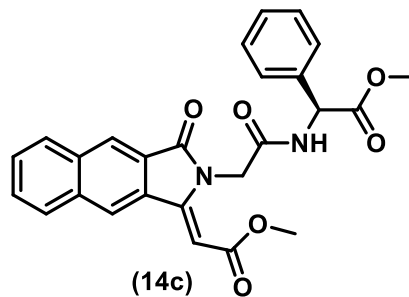
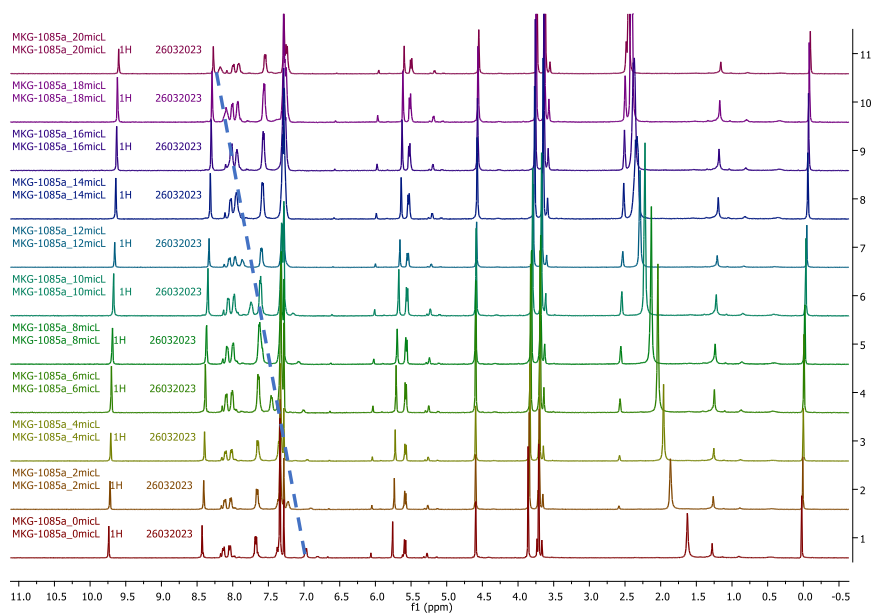
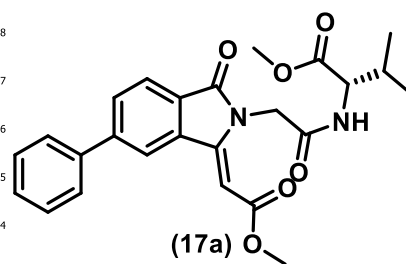
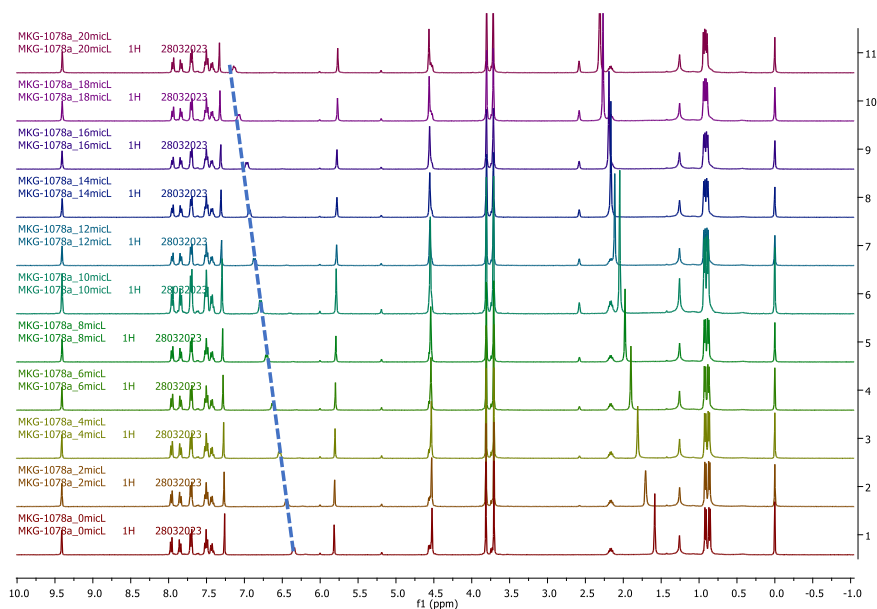
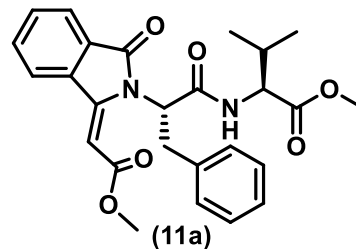
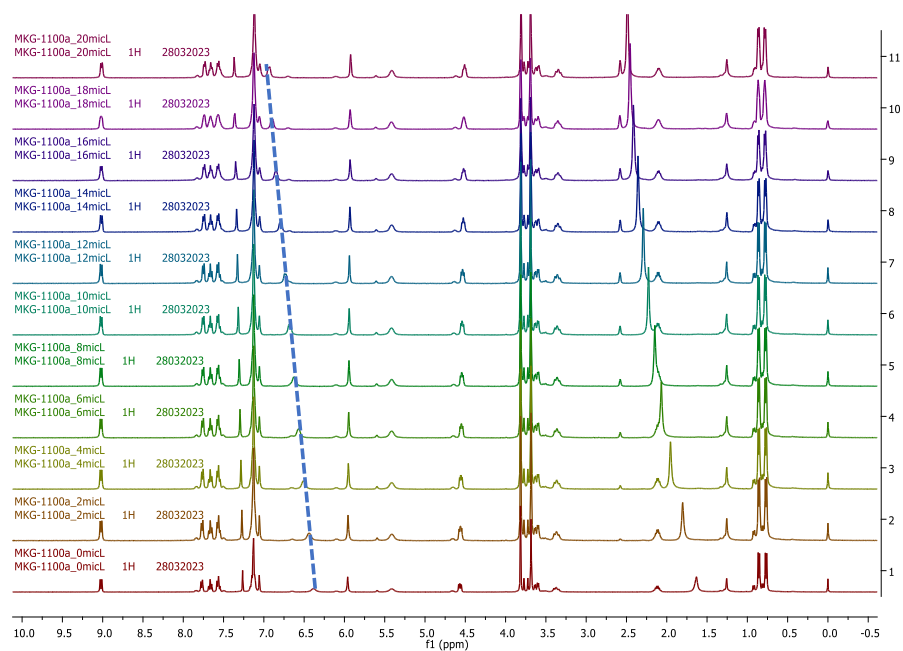


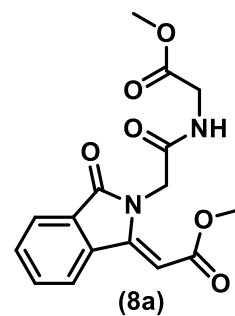
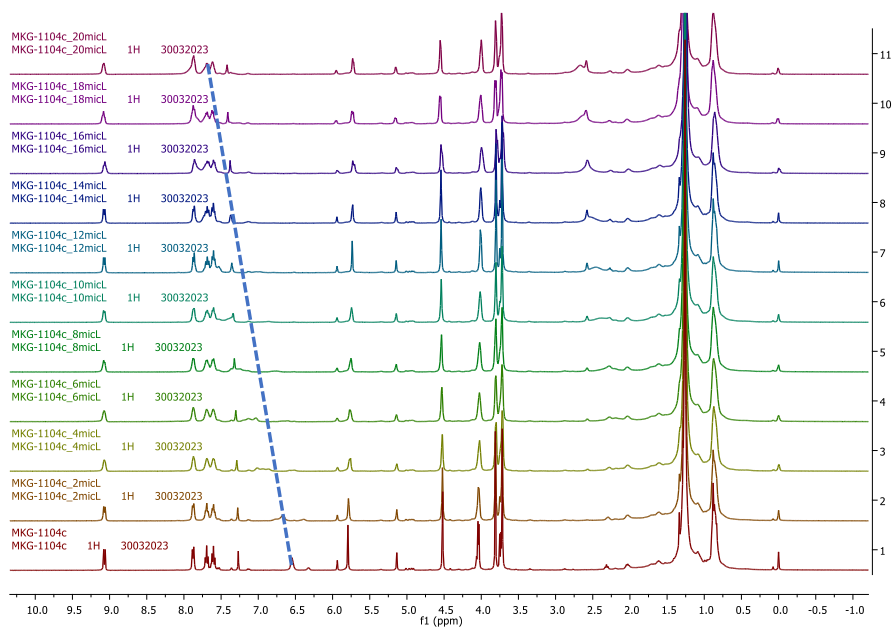
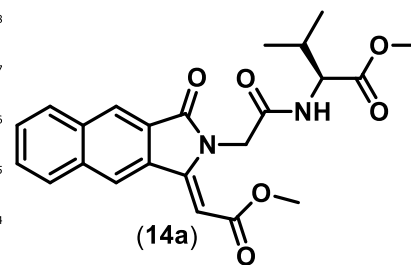
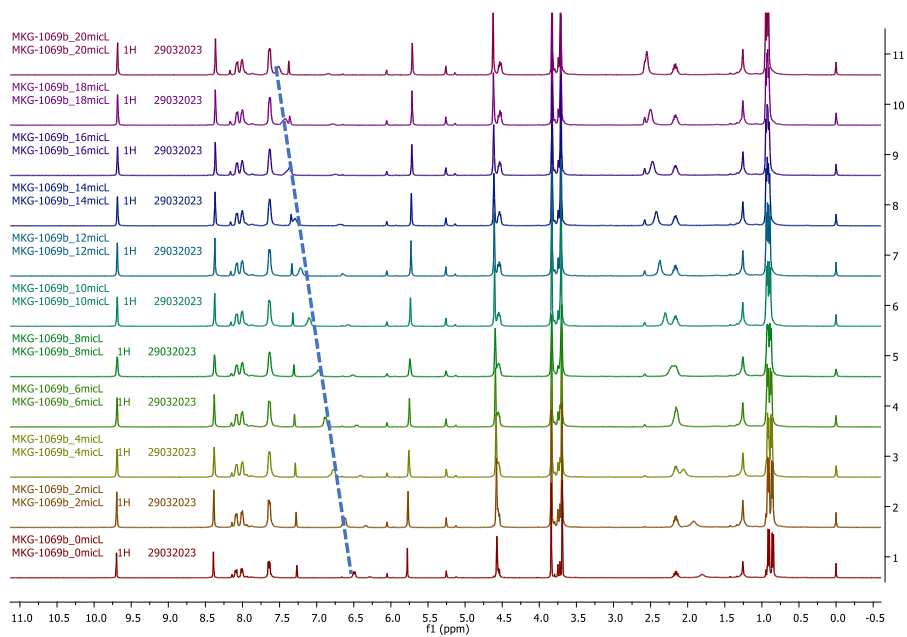
Figure. S89 Cell proliferation data of peptides.

5. DMSO d6 Titration of peptides









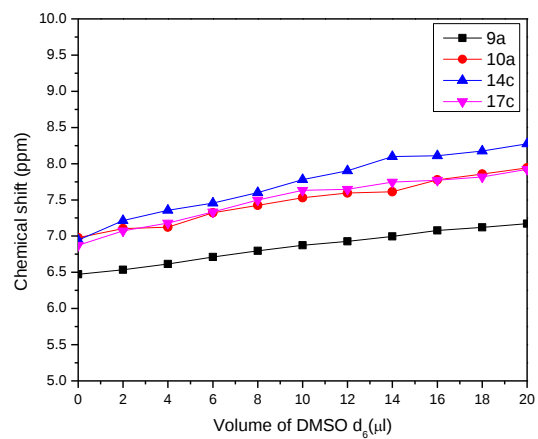
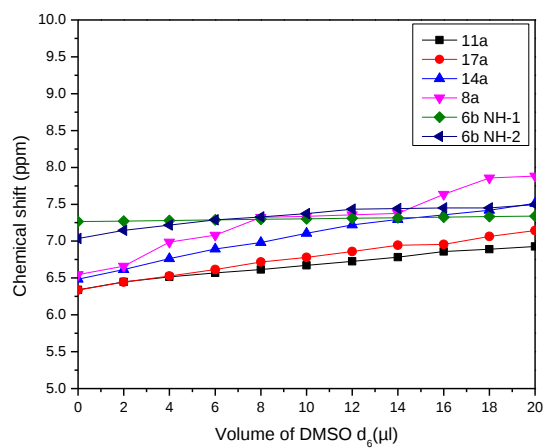
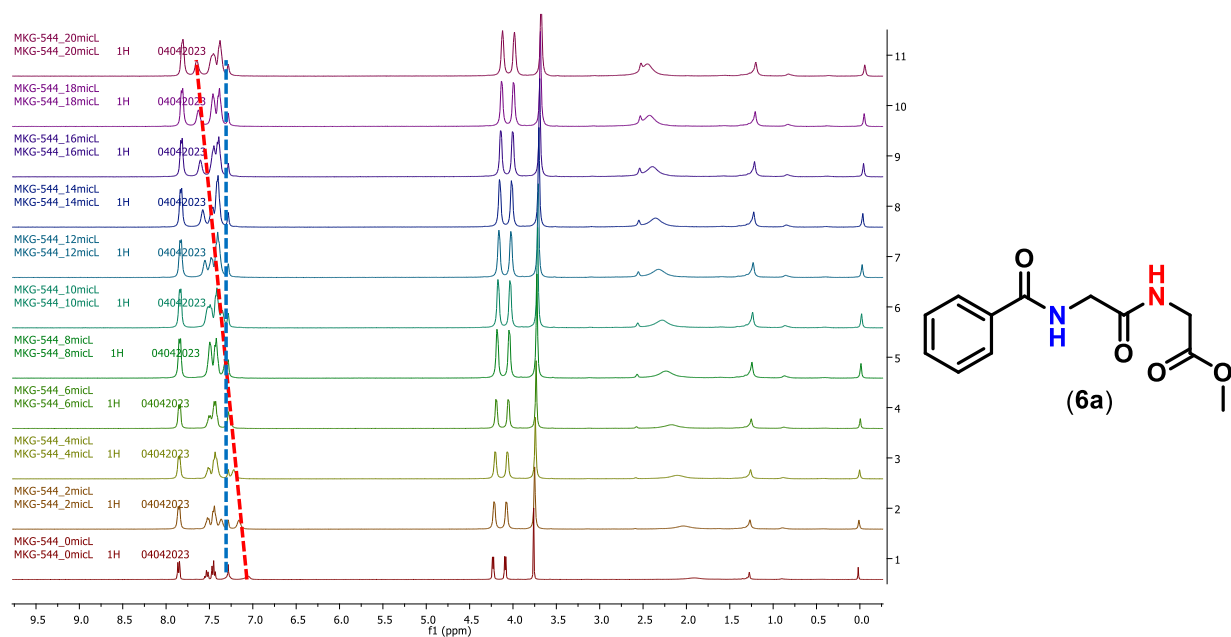
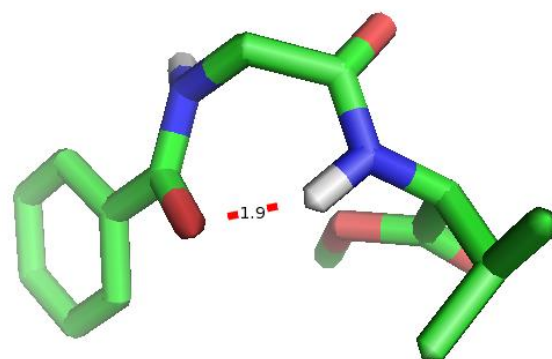
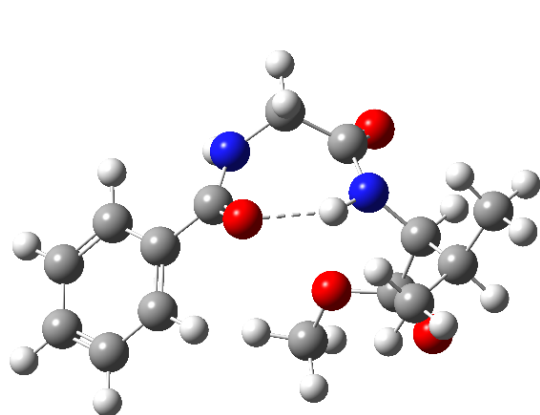


Figure. S90 DMSO- d_6 titration of peptides.

6. GMMX Energy Plot and conformation



Control 6b (N-H...O: 1.9Å)
 $\angle$ N-H-O: 149°)

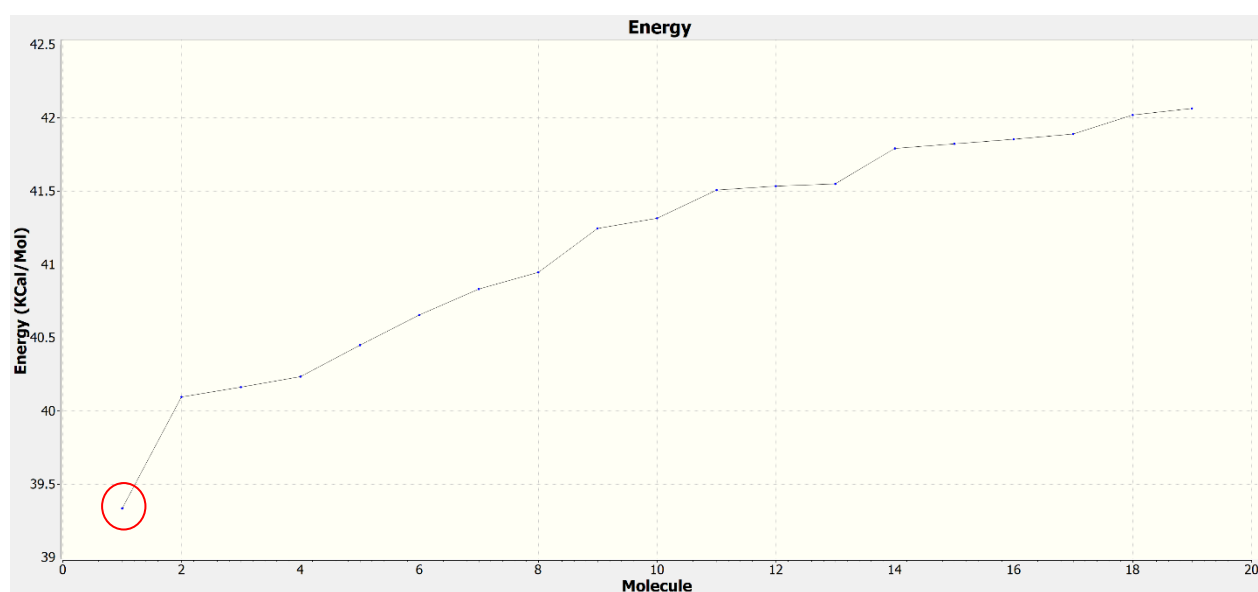


Figure. S91 GMMX results peptide **6b**: Energy Plot and conformation of lowest energy conformer

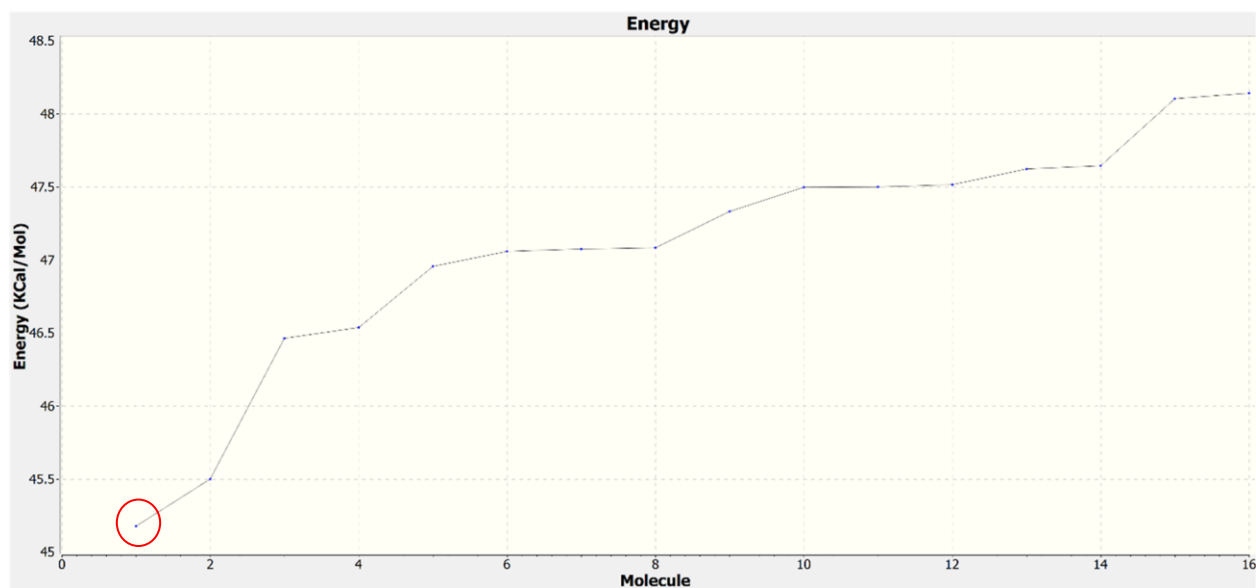
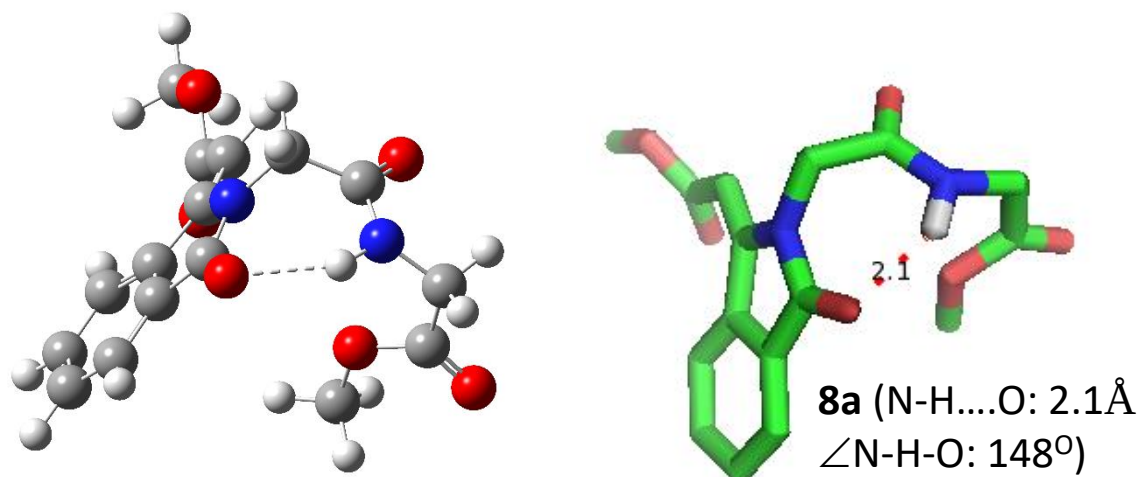


Figure. S92 GMMX results peptide **8a**: Energy Plot and conformation of lowest energy conformer

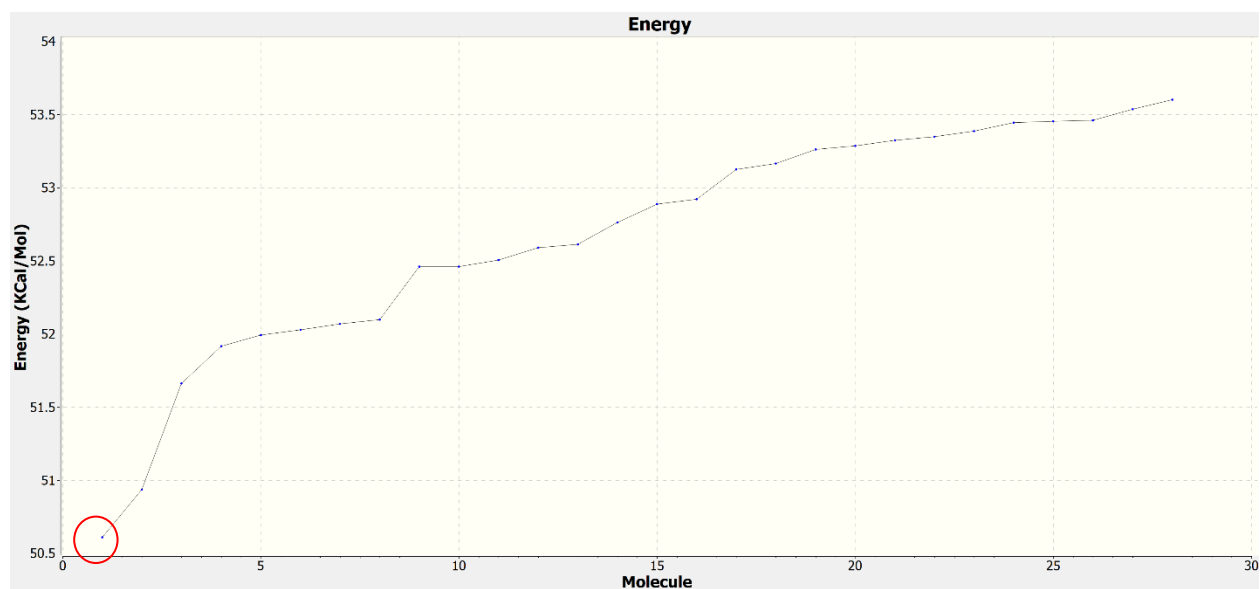
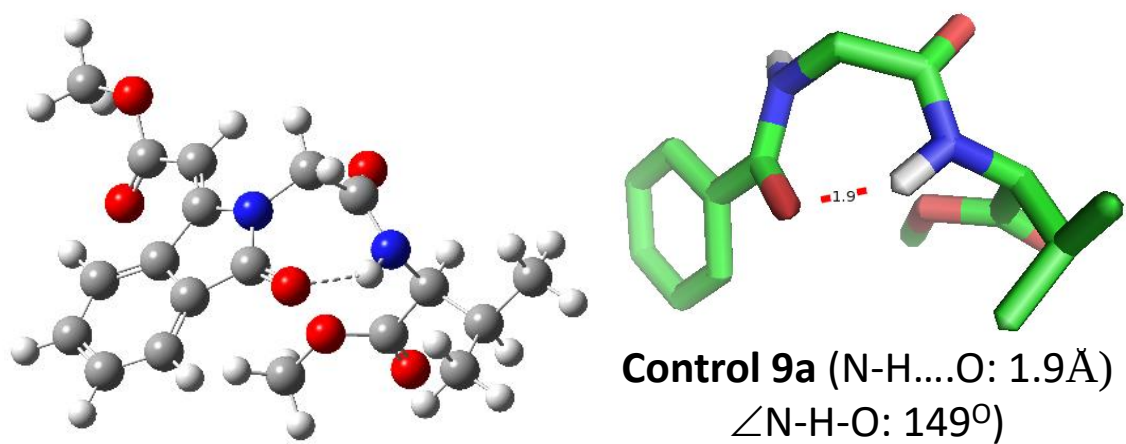


Figure. S93 GMMX results peptide **9a**: Energy Plot and conformation of lowest energy conformer

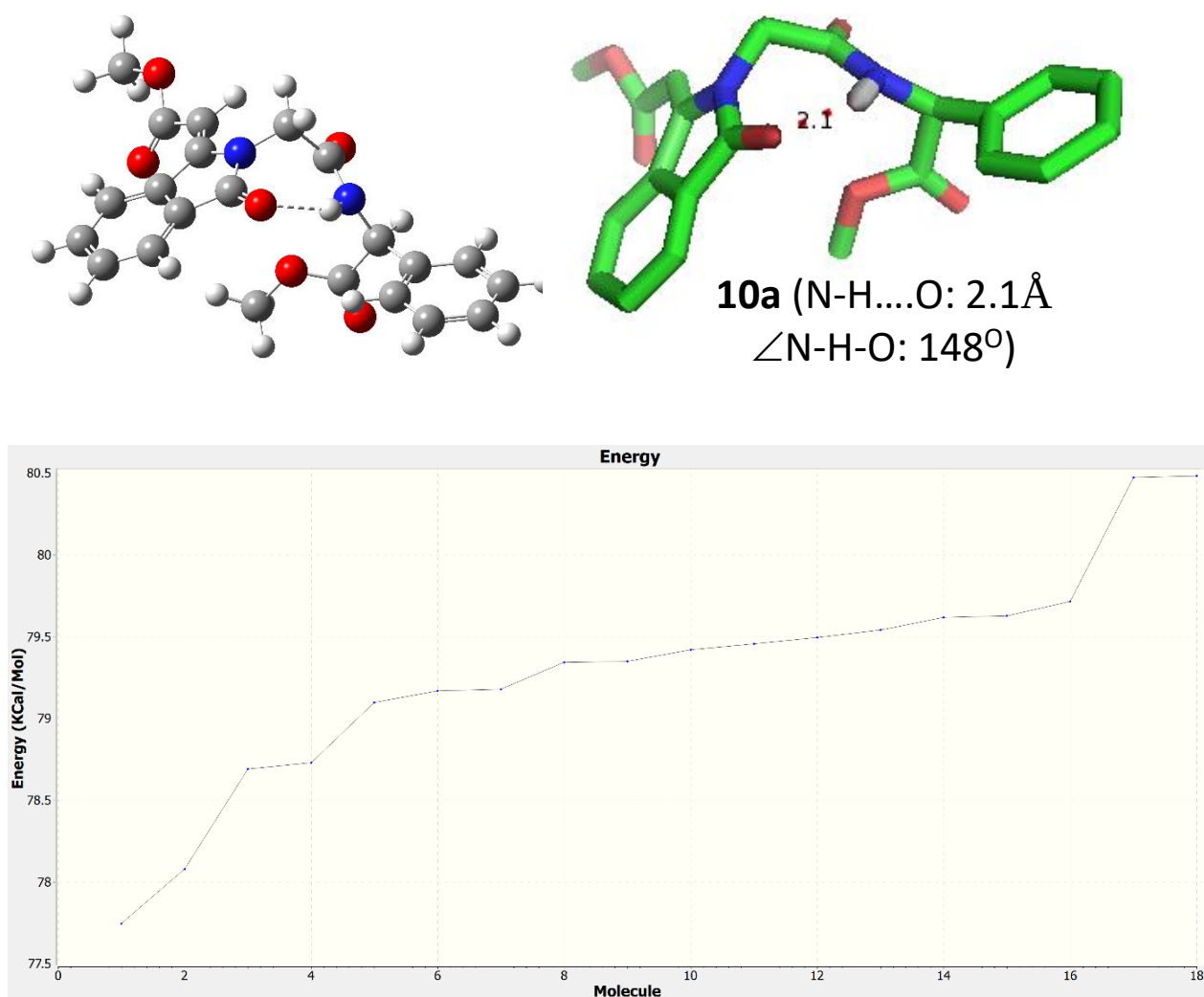
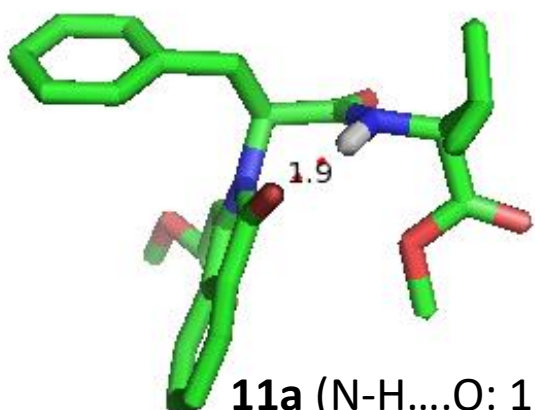
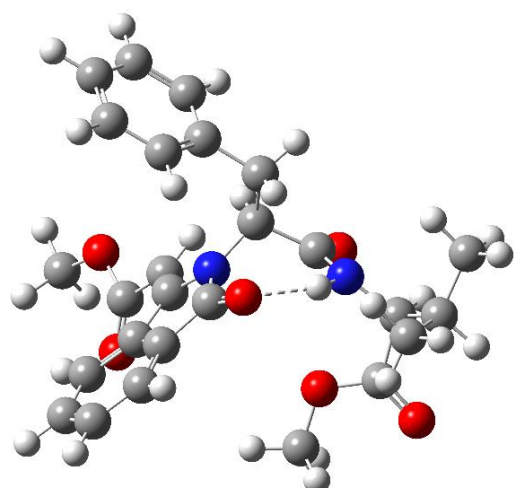


Figure. S94 GMMX results peptide **10a**: Energy Plot and conformation of lowest energy conformer



11a (N-H...O: 1.9Å
 $\angle$ N-H-O: 153°)

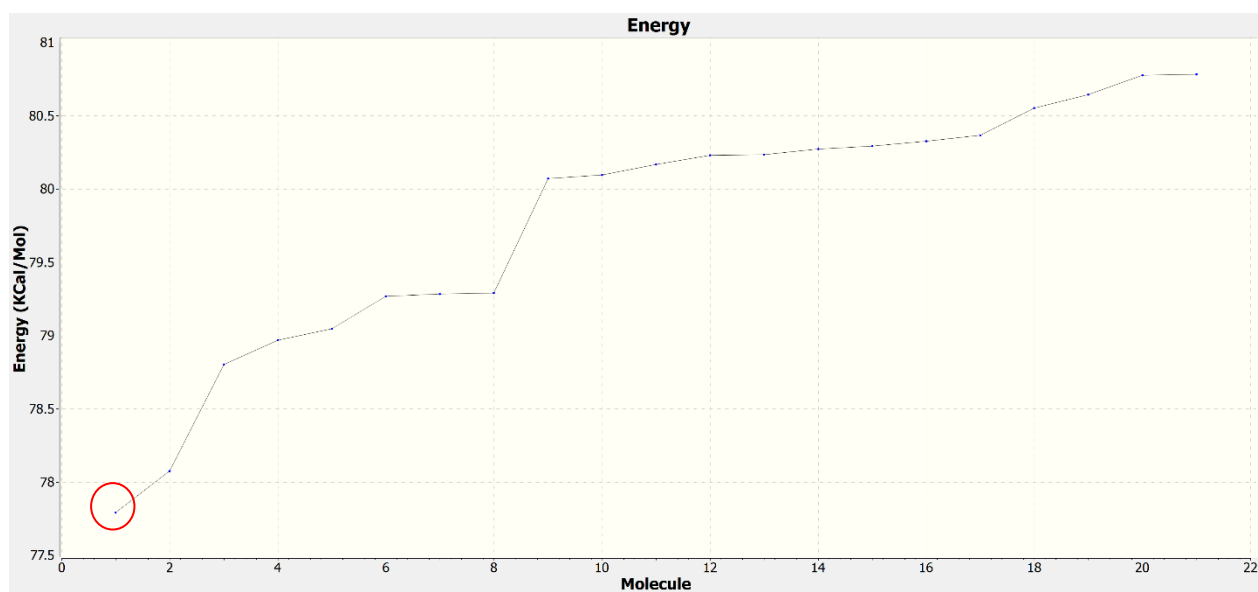


Figure. S95 GMMX results peptide **11a**: Energy Plot and conformation of lowest energy conformer

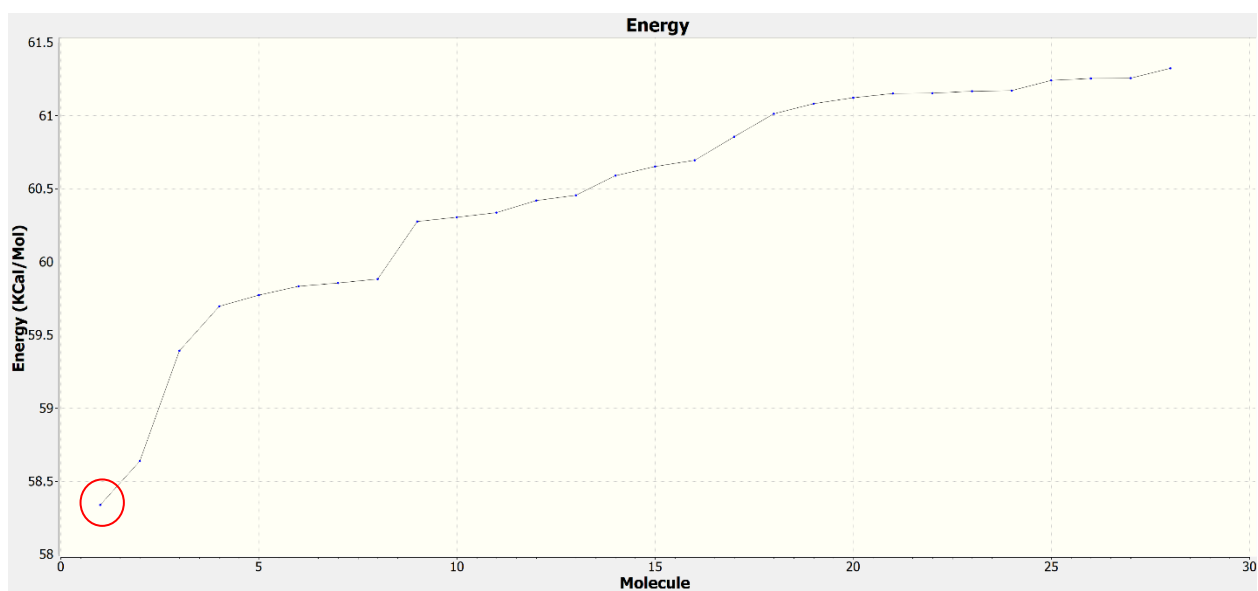
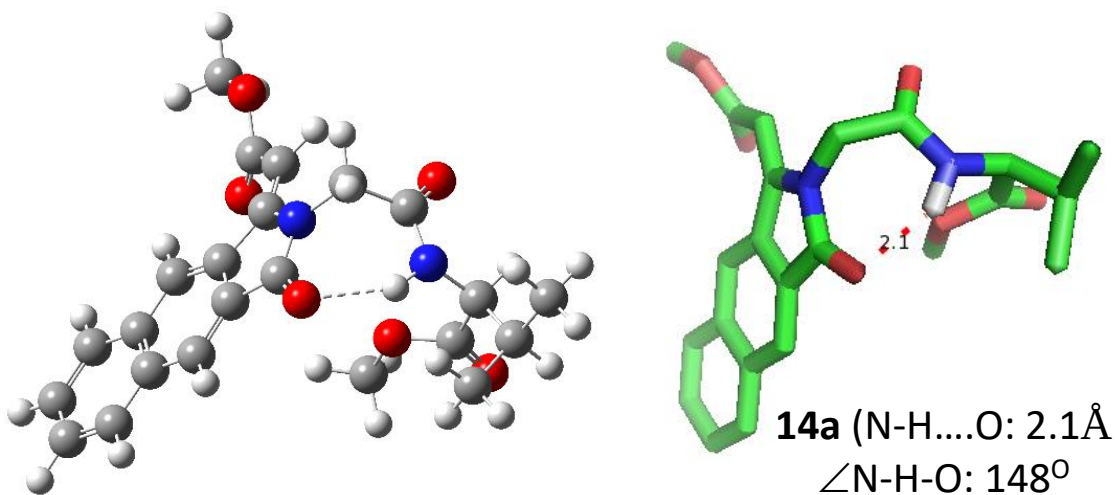


Figure. S96 GMMX results peptide **14a**: Energy Plot and conformation of lowest energy conformer

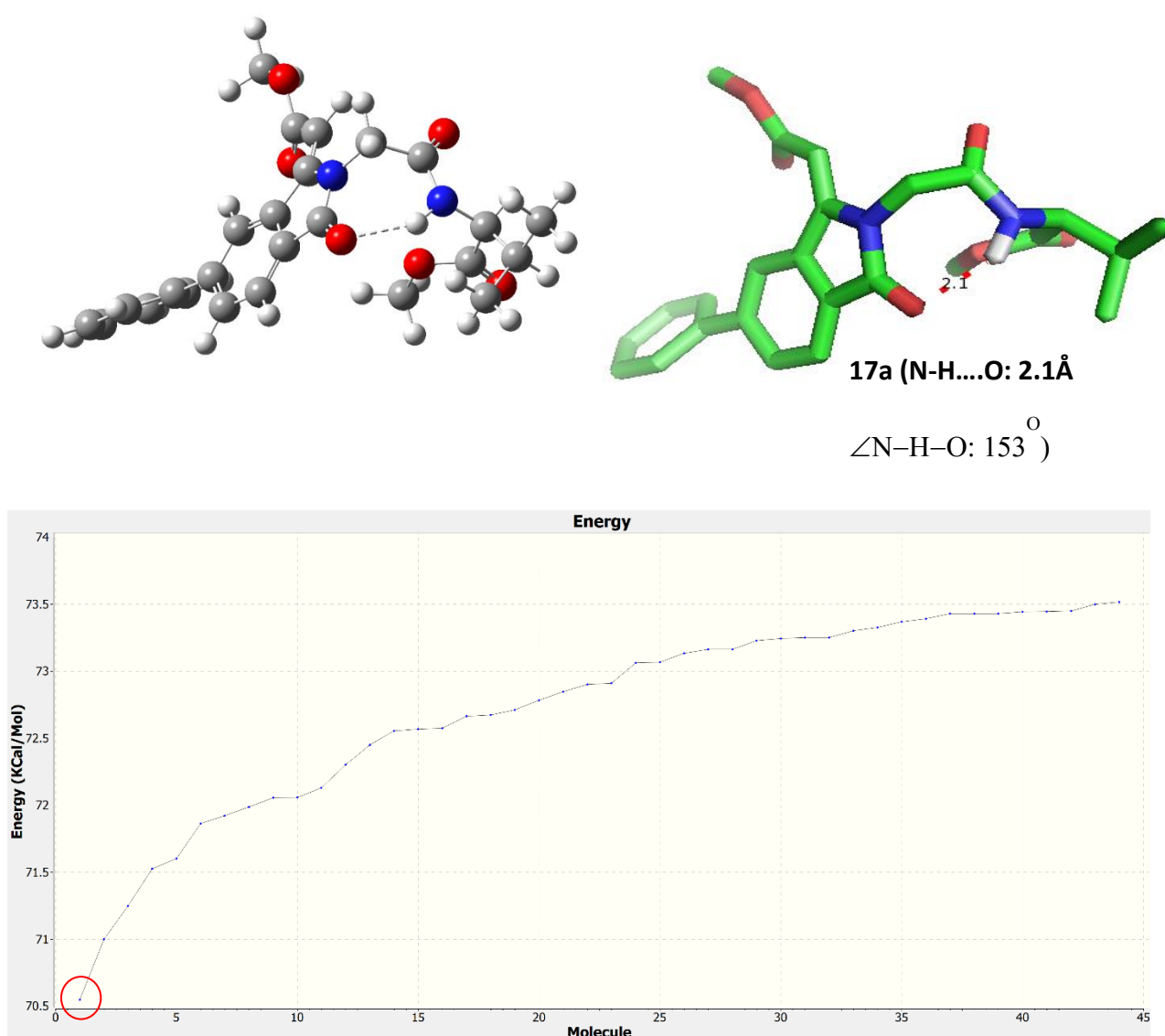


Figure. S97 GMMX results peptide **17a**: Energy Plot and conformation of lowest energy conformer

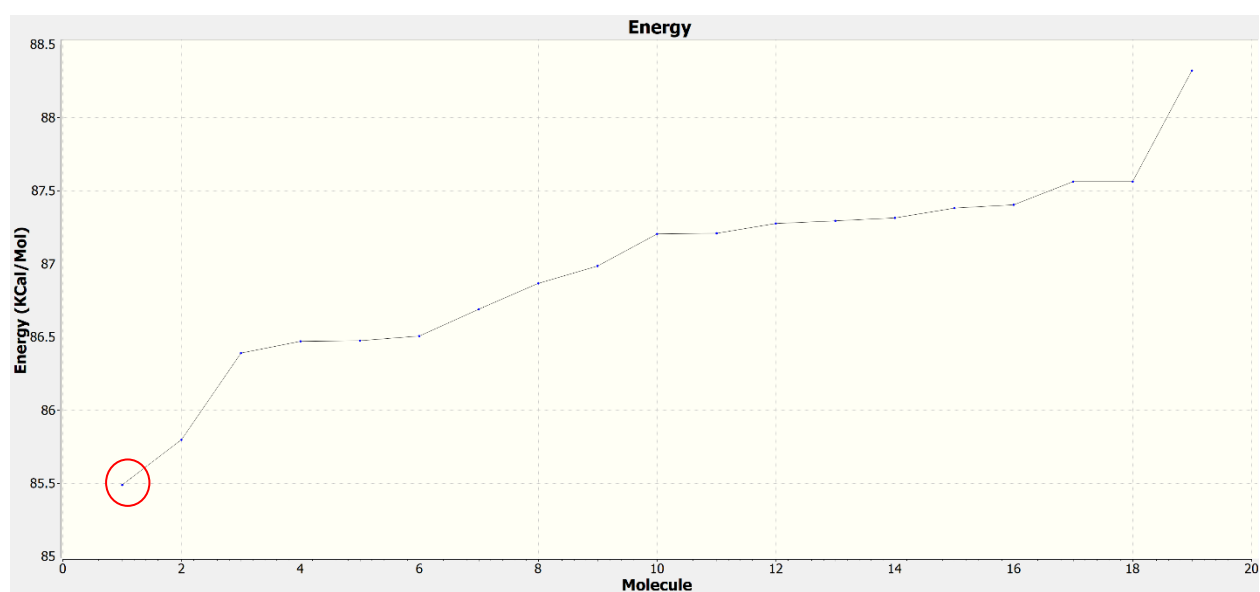
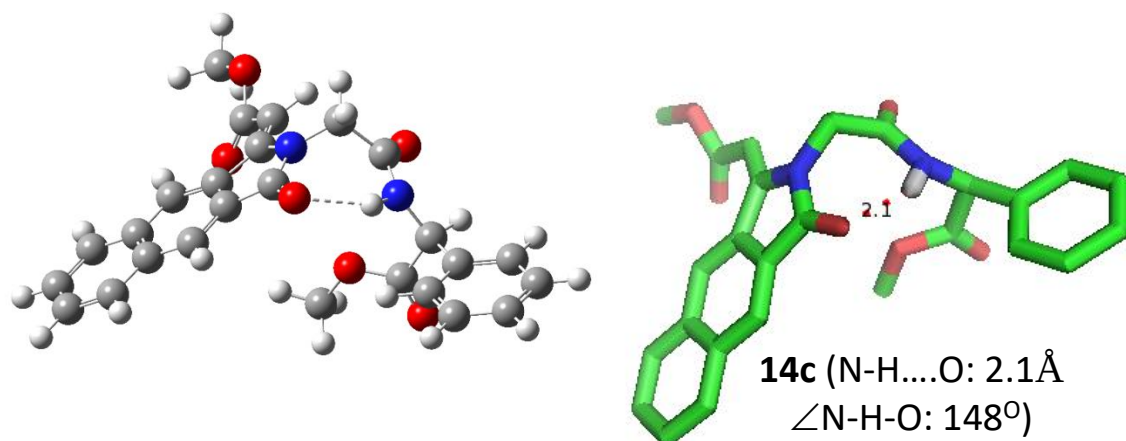


Figure. S98 GMMX results peptide **14c**: Energy Plot and conformation of lowest energy conformer

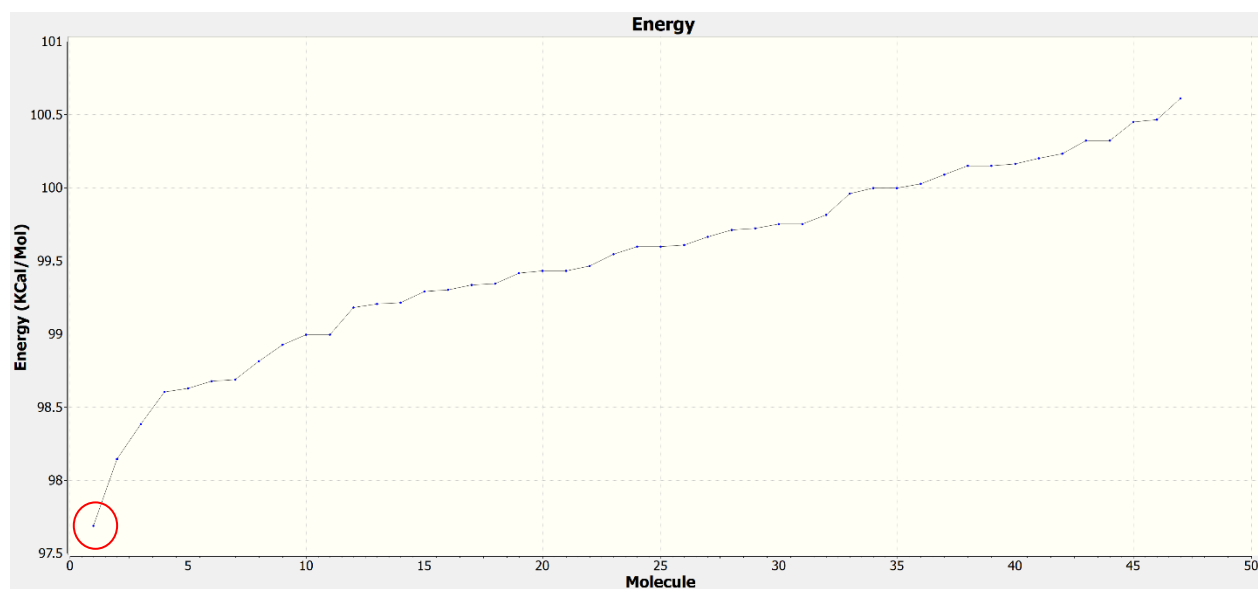
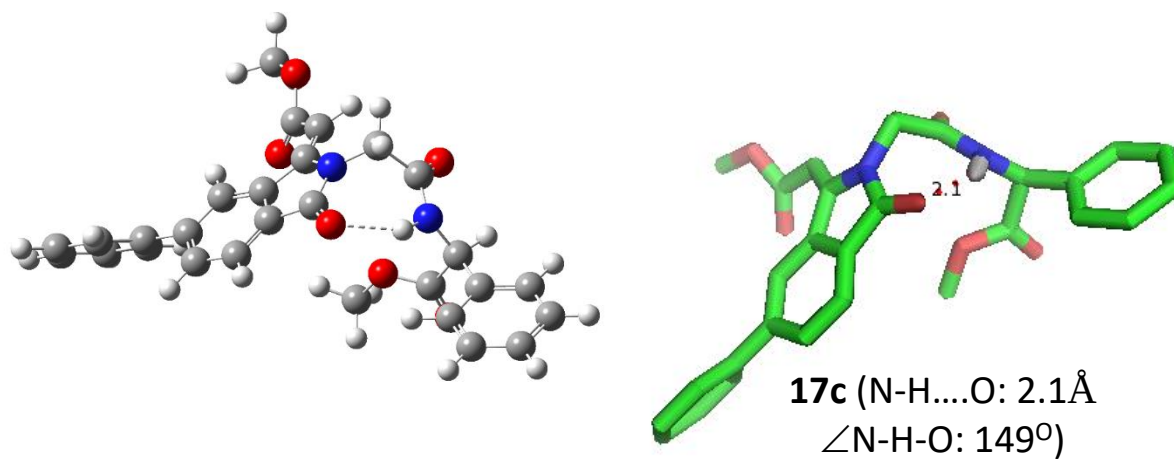


Figure. S99 GMMX results peptide **17c**: Energy Plot and conformation of lowest energy conformer

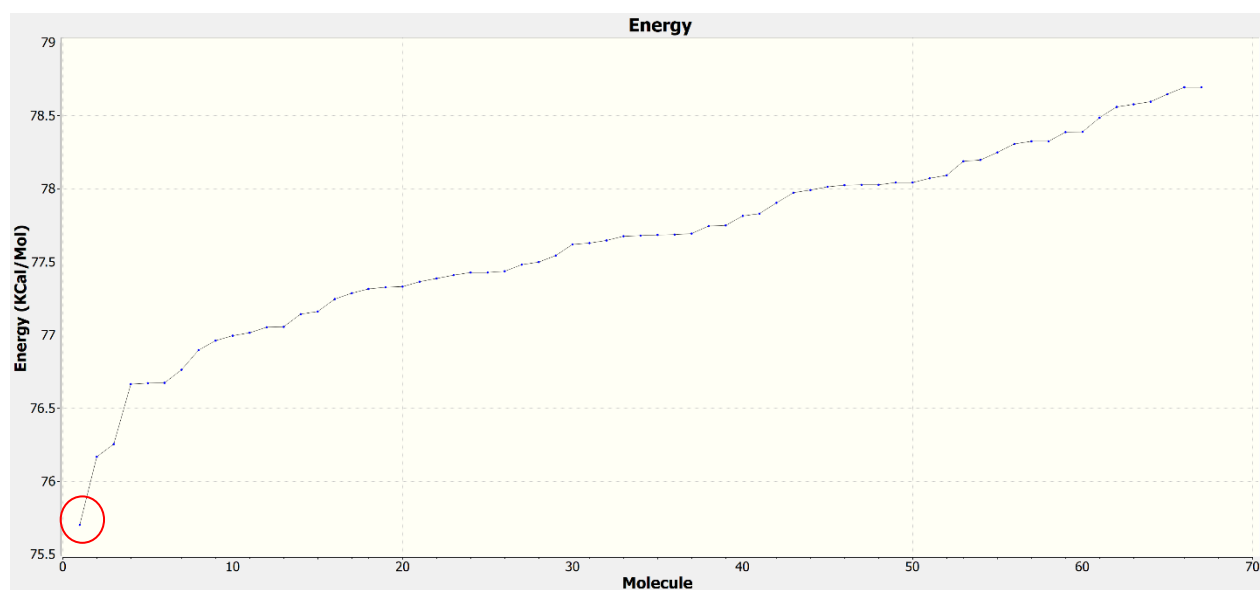
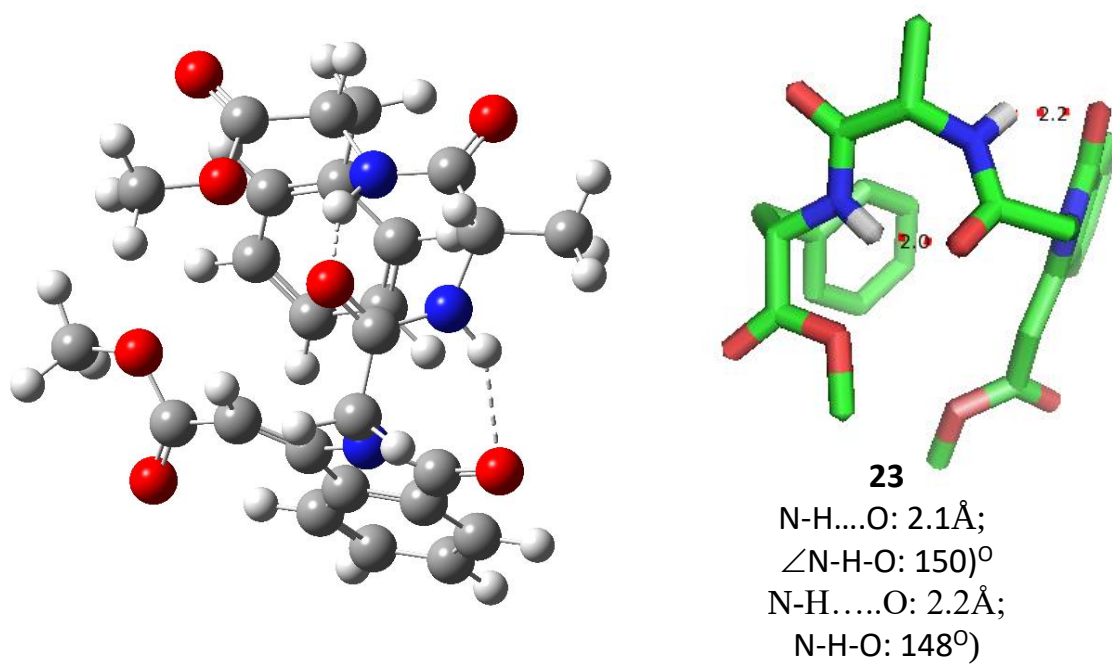
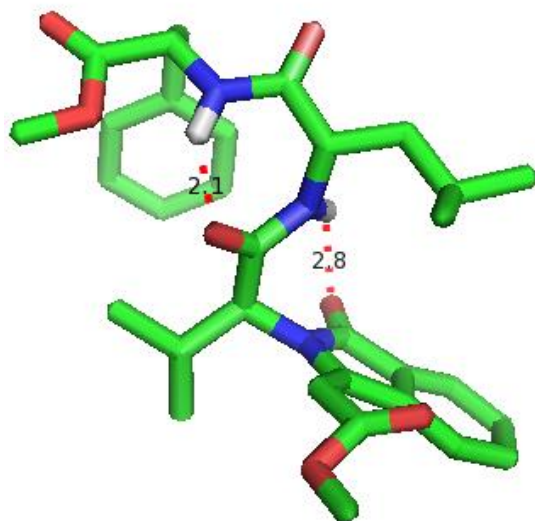
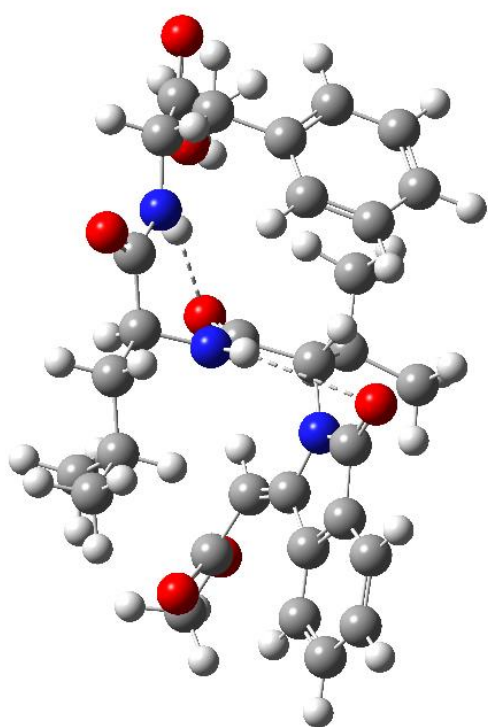


Figure. S100 GMMX results peptide **23**: Energy Plot and conformation of lowest energy conformer



24 (N-H...O: 2.1Å;
 $\angle$ N-H-O: 147°)
 N-H...O: 2.8Å ;
 $\angle$ N-H-O: 136°

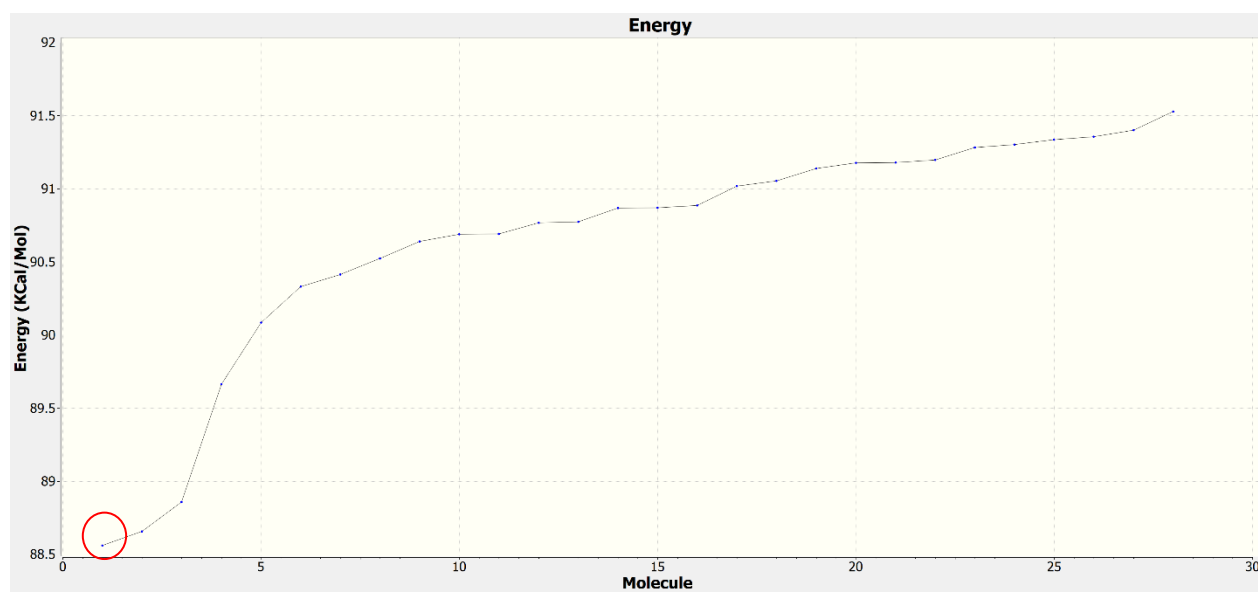


Figure. S101 GMMX results peptide **24**: Energy Plot and conformation of lowest energy conformer