SUPPORTING INFORMATION

Discovery of a Series of Macrocycles as Potent Inhibitors of Leishmania Infantum

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CONTENTS

Table S1. *In vitro* potencies for inhibition of the growth of four kinetoplastid parasites by compounds **1-12**.[a]

	COMPOUNDS	1	2	3	4	5	6	7	8	9	10	11	12
EC$_{50}$	*T. b. brucei*	6.1 (2.0)	37 (24)	15 (10)	33 (0.2)	7.4 (3.0)	12 (11)	49 (15)	8.1 (0.1)	7.7 (0)	8.5 (0.8)	36 (19)	30 (1.4)
	T. b. rhodesiense	6.0 (1.4)	29 (26)	9.1 (4.6)	6.1 (0.9)	5.6 (2.4)	6.3 (2.4)	9.7 (1.4)	6.4 (0.1)	1.9 (0.1)	2.1 (0.4)	24 (10)	21 (13)
	T. cruzi	15 (4.7)	41 (26)	20 (18)	64 (0)	18 (14)	19 (11)	36 (5.6)	6.1 (2.1)	19 (11)	50 (15)	33 (7.9)	64 (0)
	L. infantum	33 (0.4)	31 (19)	1.8 (1.9)	38 (26)	17 (14)	12 (5.9)	16 (4.7)	8.2 (0.1)	6.6 (1.5)	2.1 (0.6)	38 (7.8)	7.1 (1.0)

[a] Mean values, with standard deviation in parenthesis, from 2 to 14 measurements.
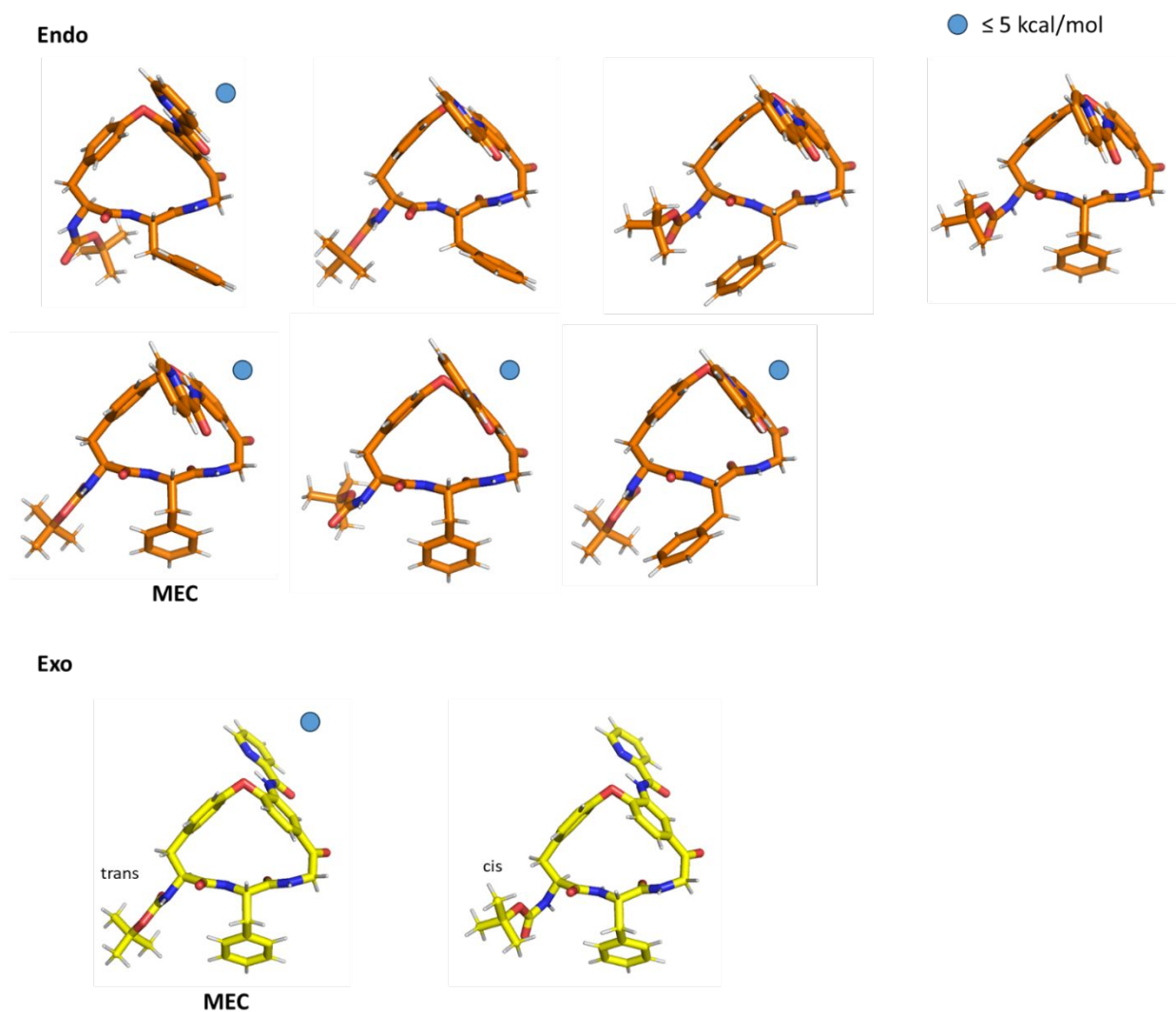
Figure S1. *Endo* and *exo* conformations for compound **3**, obtained using the Monte Carlo-QM protocol for conformational sampling. Minimum energy conformations (MECs) and all conformations within 5 kcal/mol of the MECs are shown.
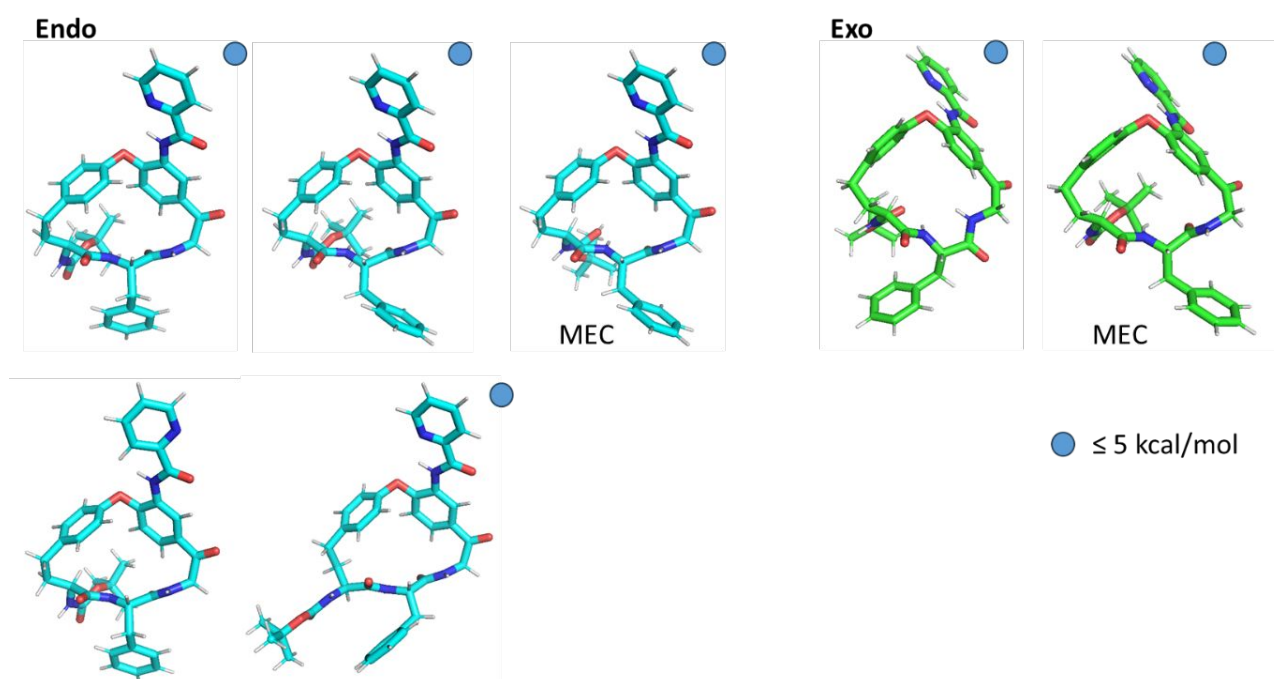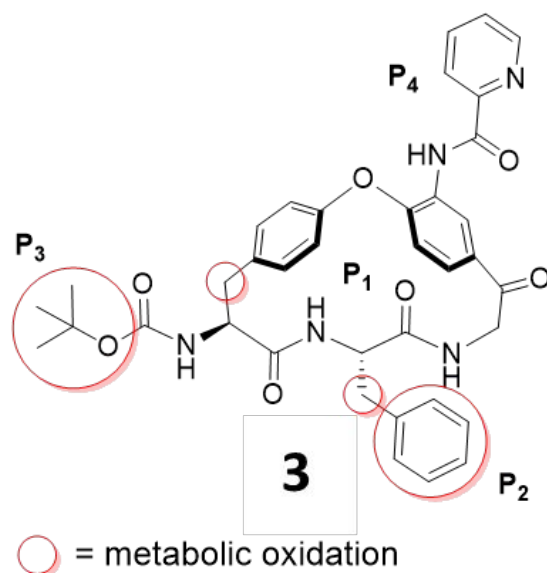
Figure S2. *Endo* and *exo* conformations for compound **5**, obtained using the Monte Carlo-QM protocol for conformational sampling. Minimum energy conformations (MECs) and all conformations within 5 kcal/mol of the MECs are shown.

Figure S3. Metabolically labile sites (indicated by red circles) observed for compound **3** after incubation with rat liver microsomes. Samples were collected at 5, 10, 20, 30 and 60 minutes.
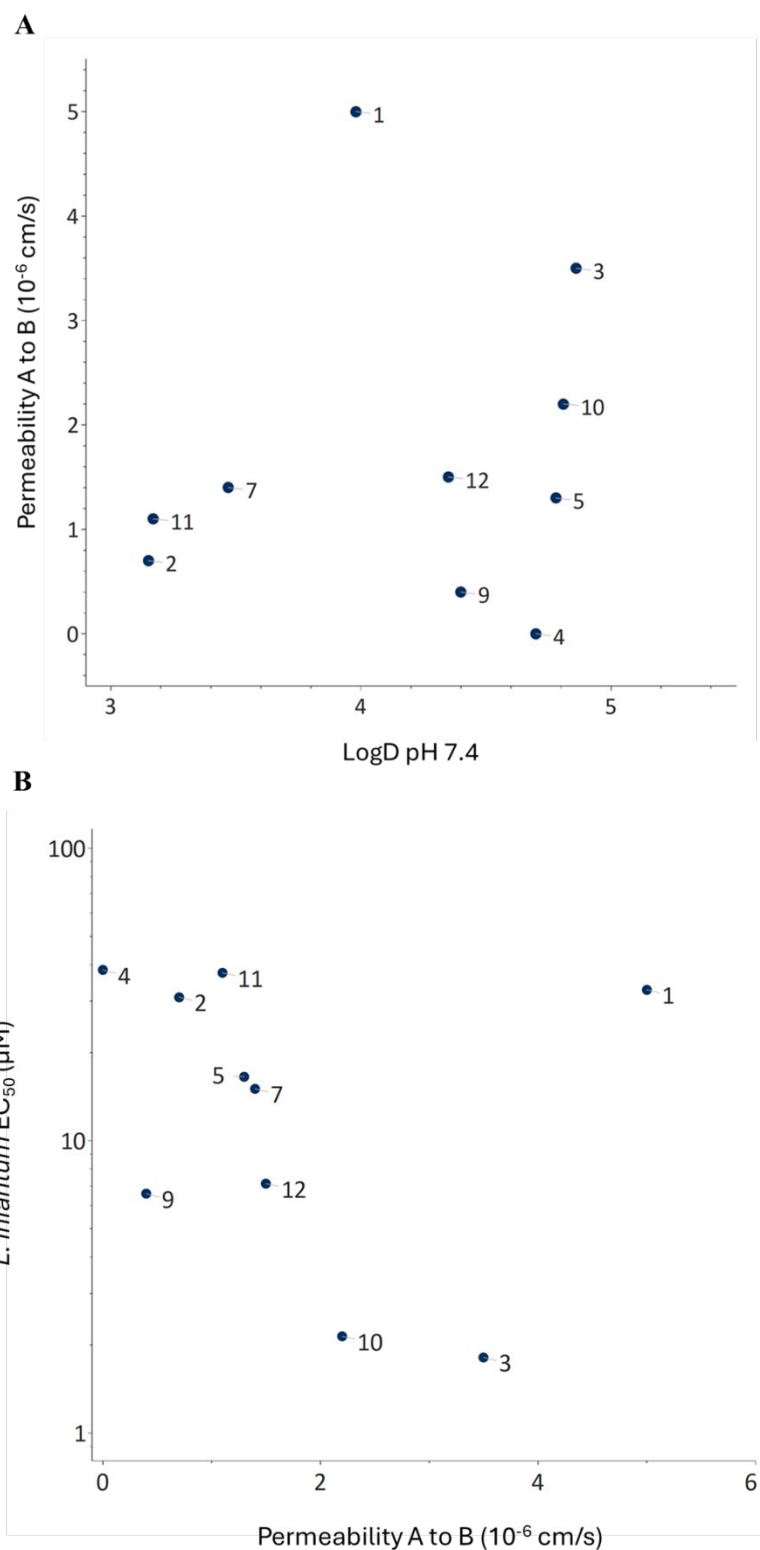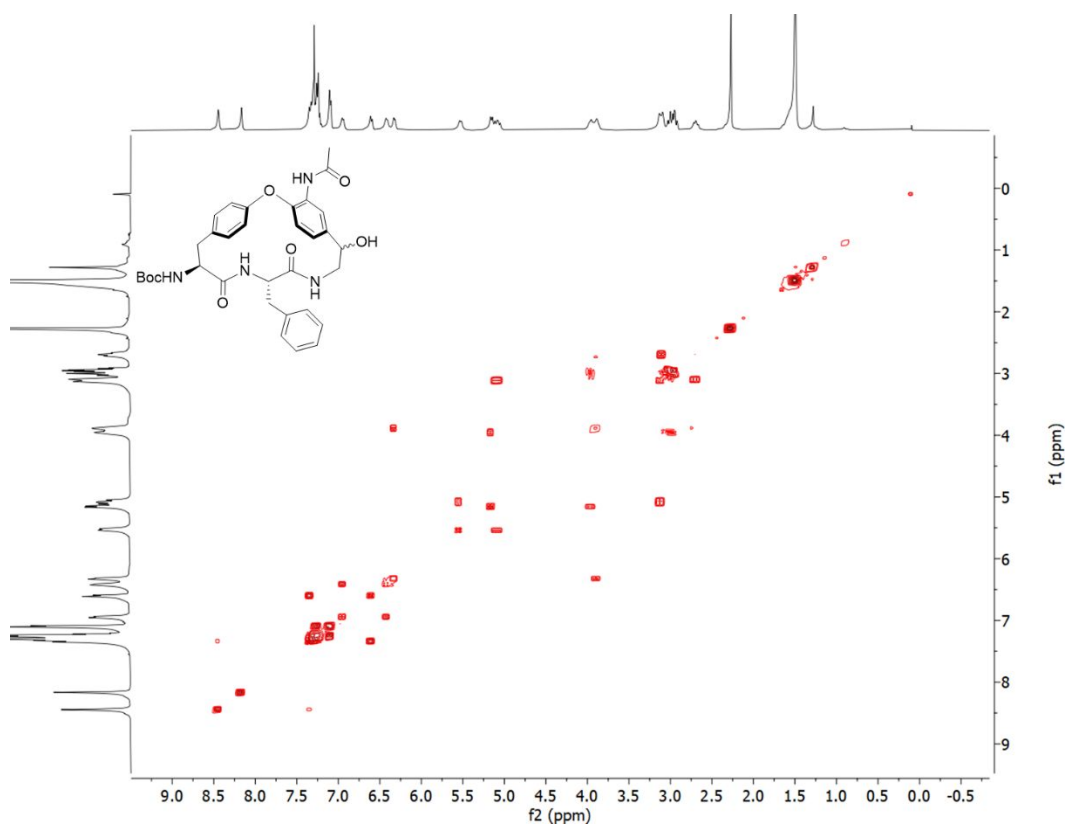
Figure S4. Correlations between **A)** the permeability across MDCK-MDR1 cell monolayers and LogD$_{7.4}$ and **B)** the potency for inhibition of the growth of *L. infantum* and the cell permeability for compounds **1-12**.

NMR SPECTRA
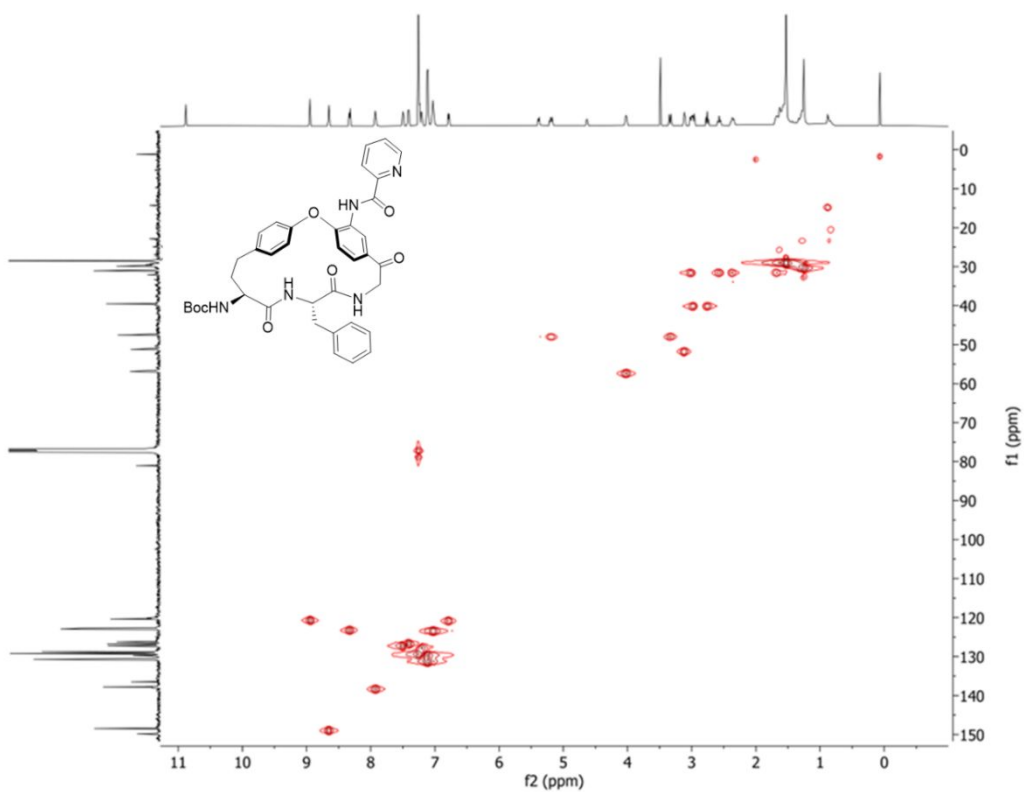
Compound 2: ^{1}H NMR (CDCl$_3$, 400 MHz)



Compound 2: ^{13}C NMR (CDCl$_3$, 100 MHz)

Compound 2: COSY NMR (CDCl₃)

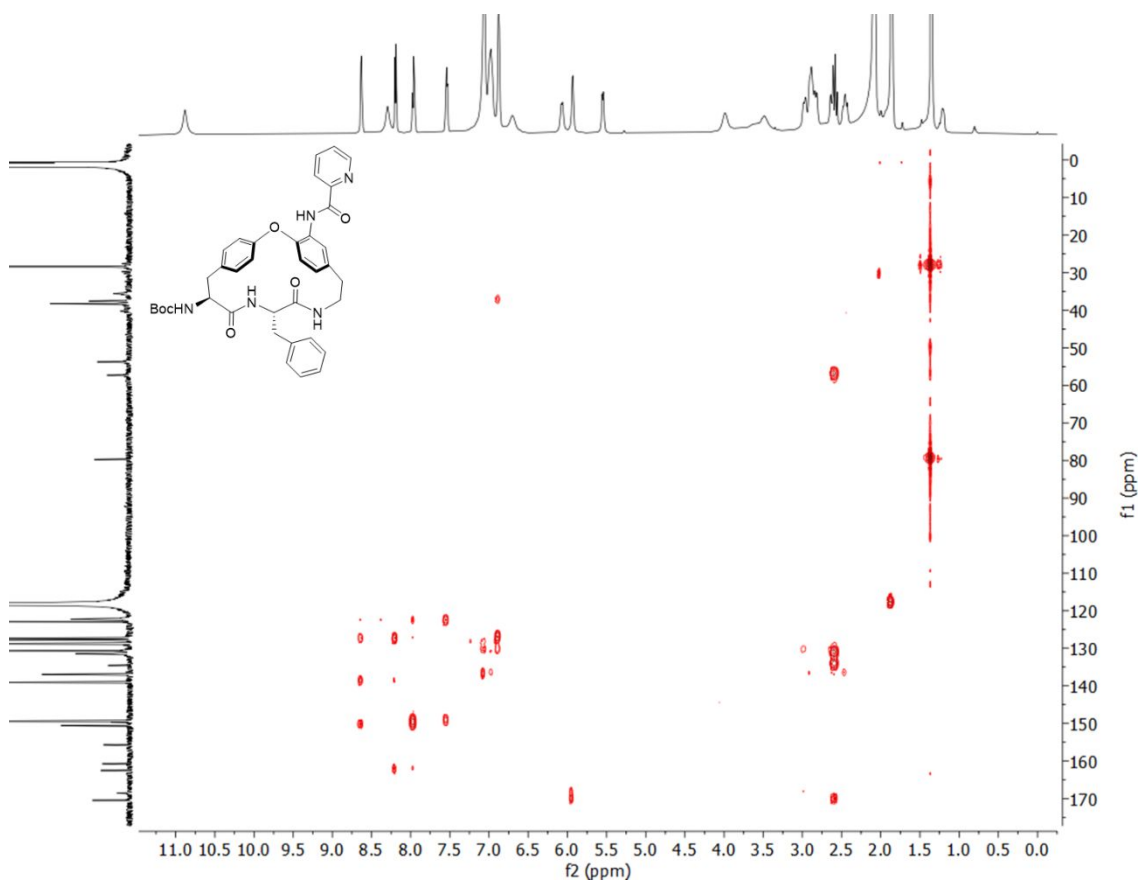**Compound 2: HSQC NMR (CDCl₃)**

Compound 2: HMBC NMR (CDCl₃)

Compound 3: ¹H NMR (CDCl₃, 600 MHz)
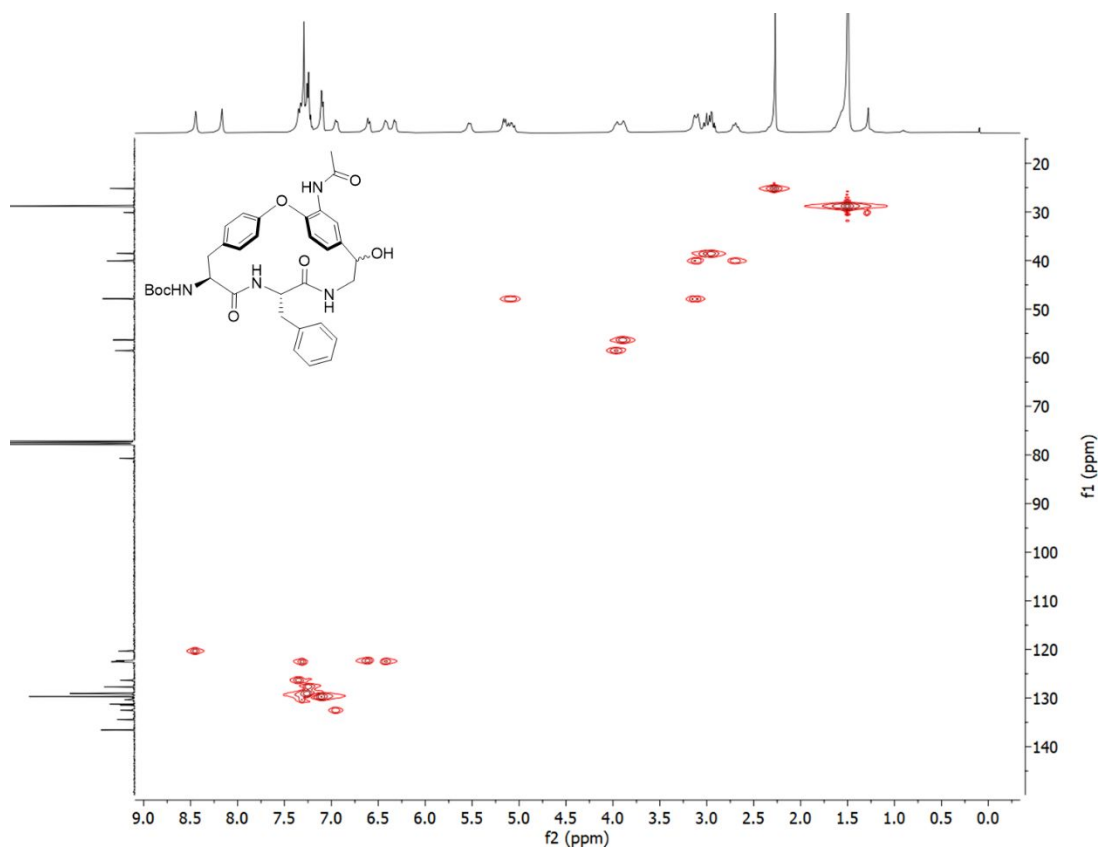
Compound 3: ^{13}C NMR (CDCl$_3$, 150 MHz)
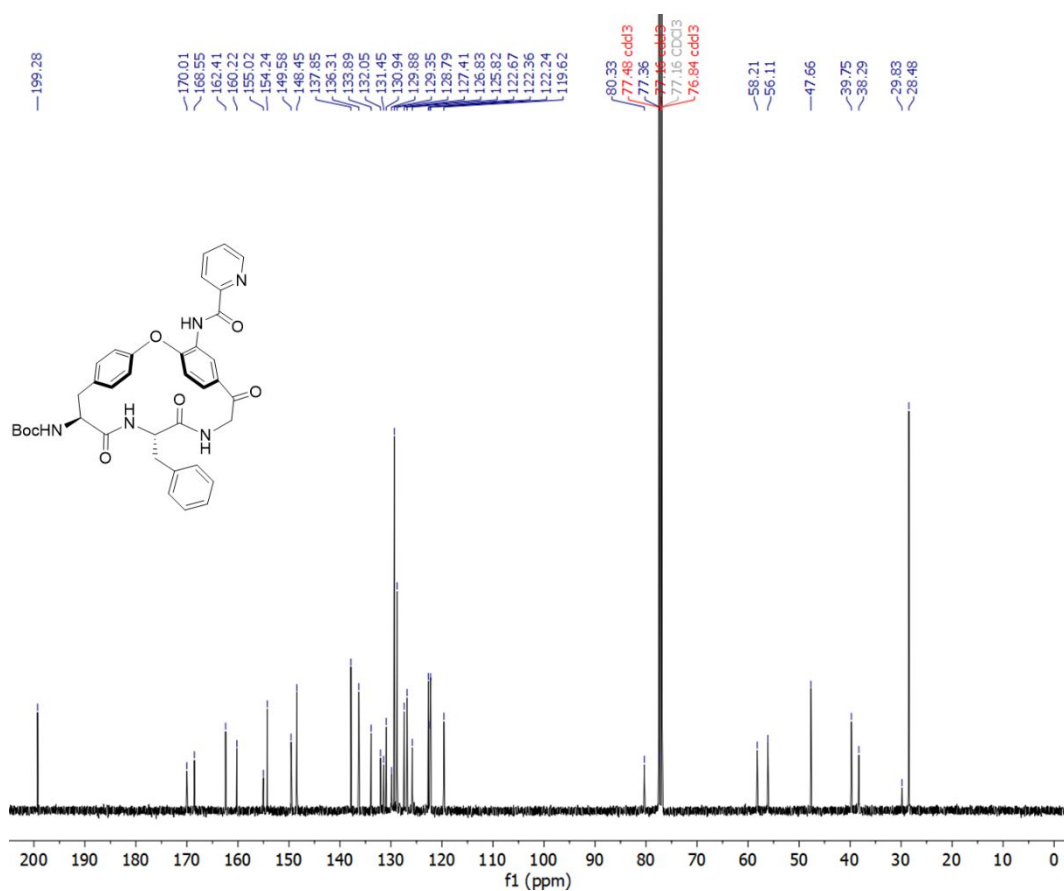
Compound 3: COSY NMR (CDCl$_3$)
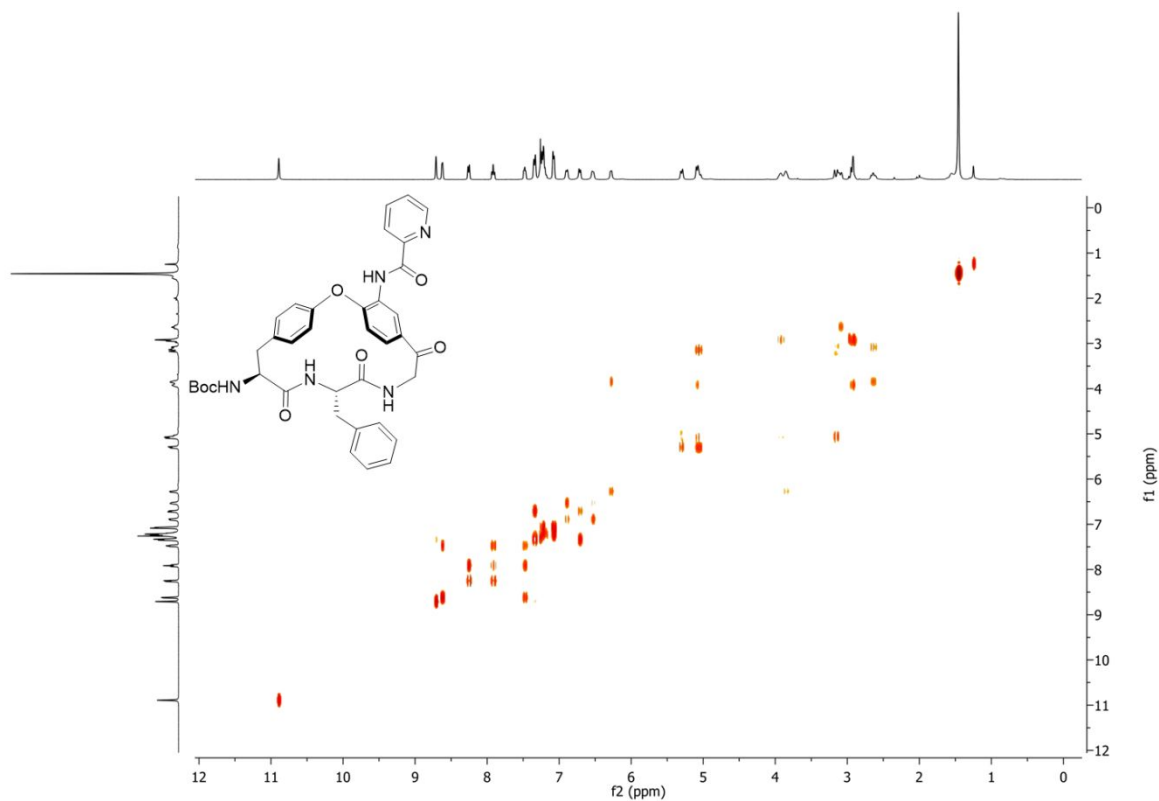
Compound 3: HSQC NMR (CDCl₃)
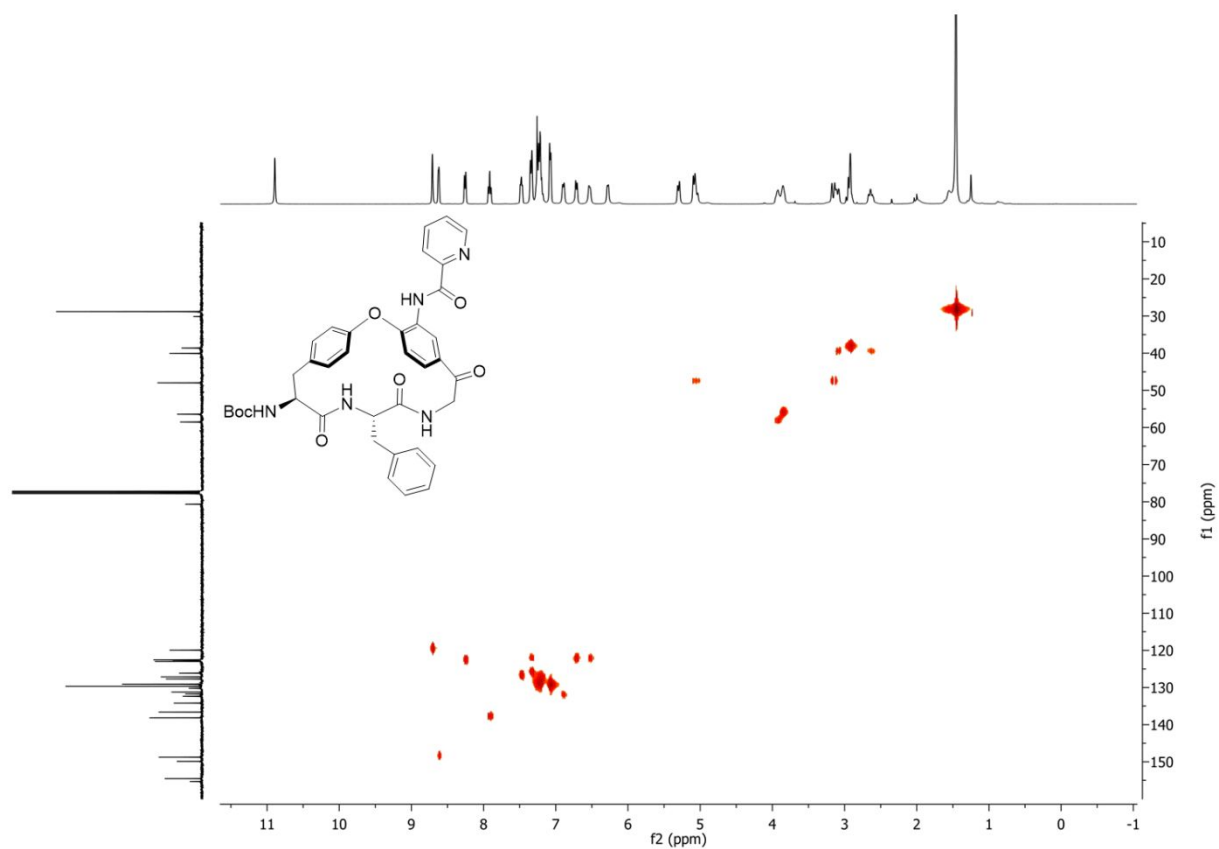
Compound 3: HMBC NMR (CDCl₃)
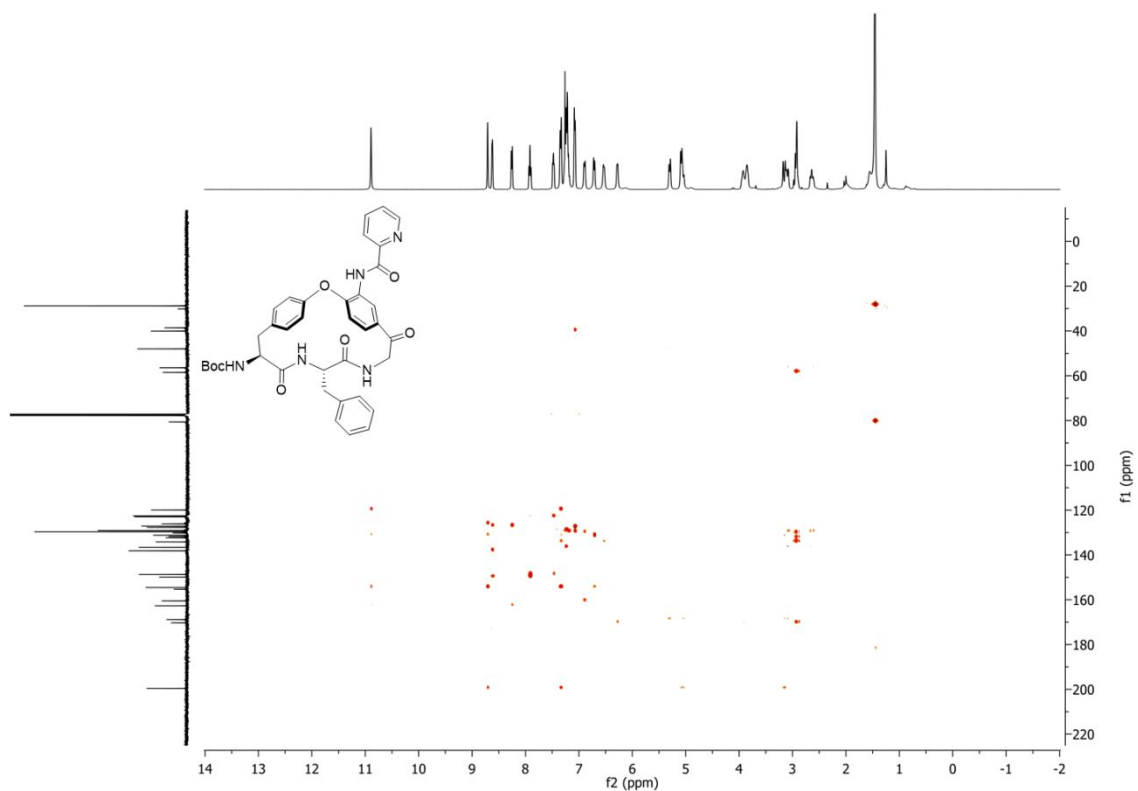
Compound 4: ^{1}H NMR (CD$_3$CN, 500 MHz)
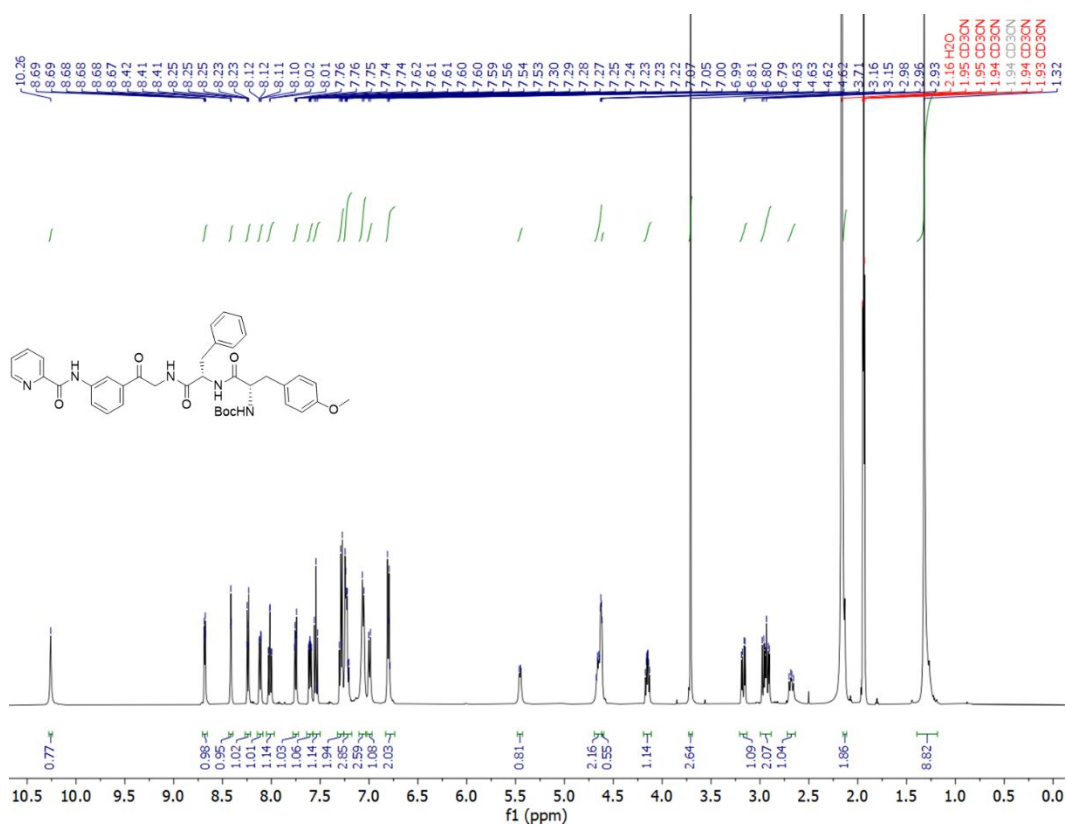
Compound 4: ^{13}C NMR (CD$_3$CN, 125 MHz)
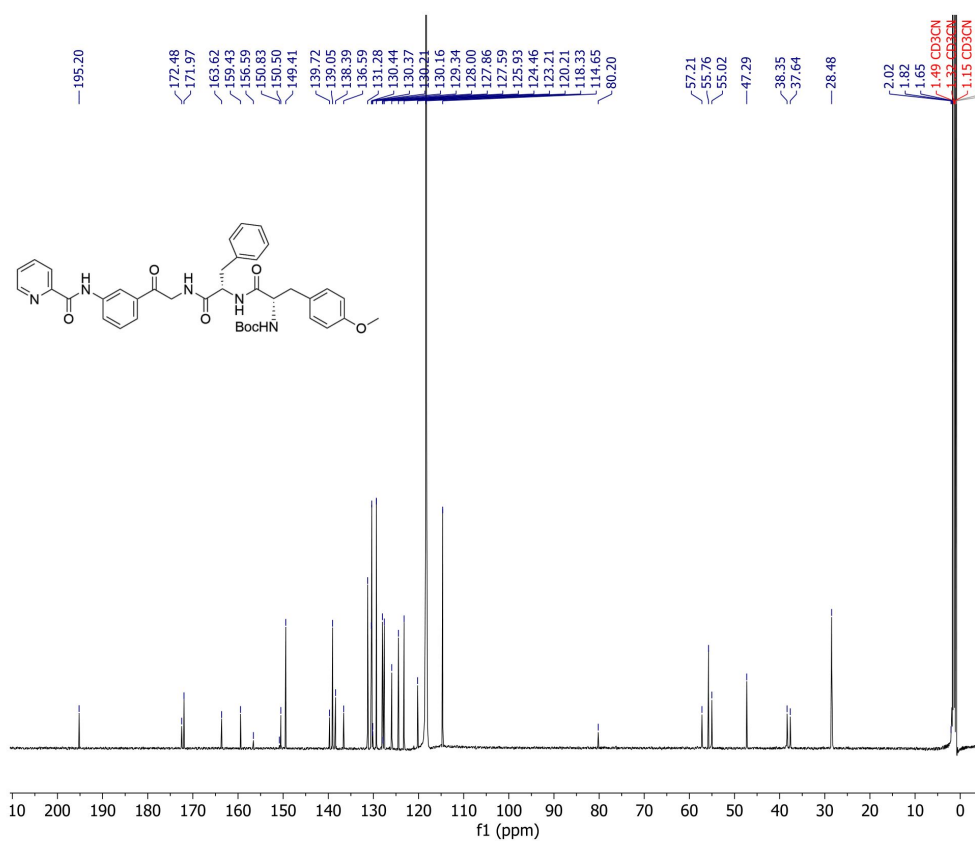
Compound 4: COSY NMR (CD₃CN)
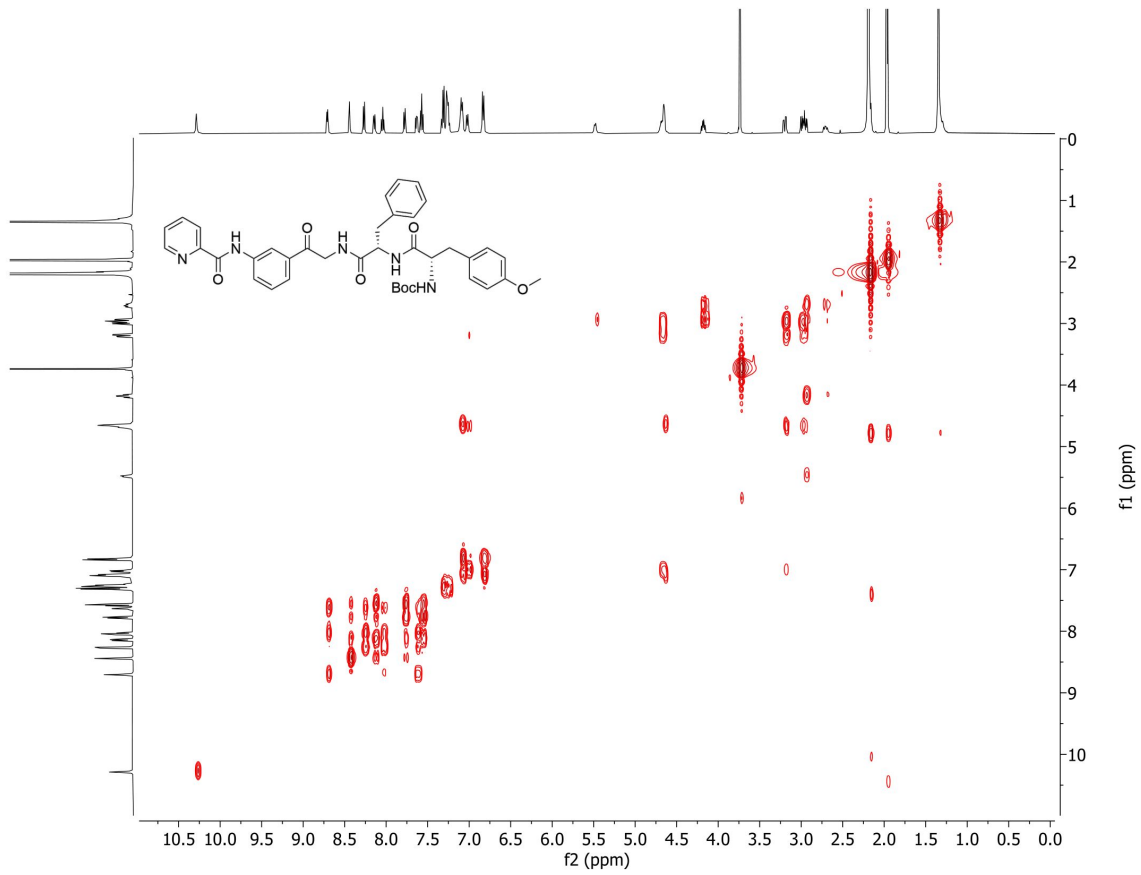
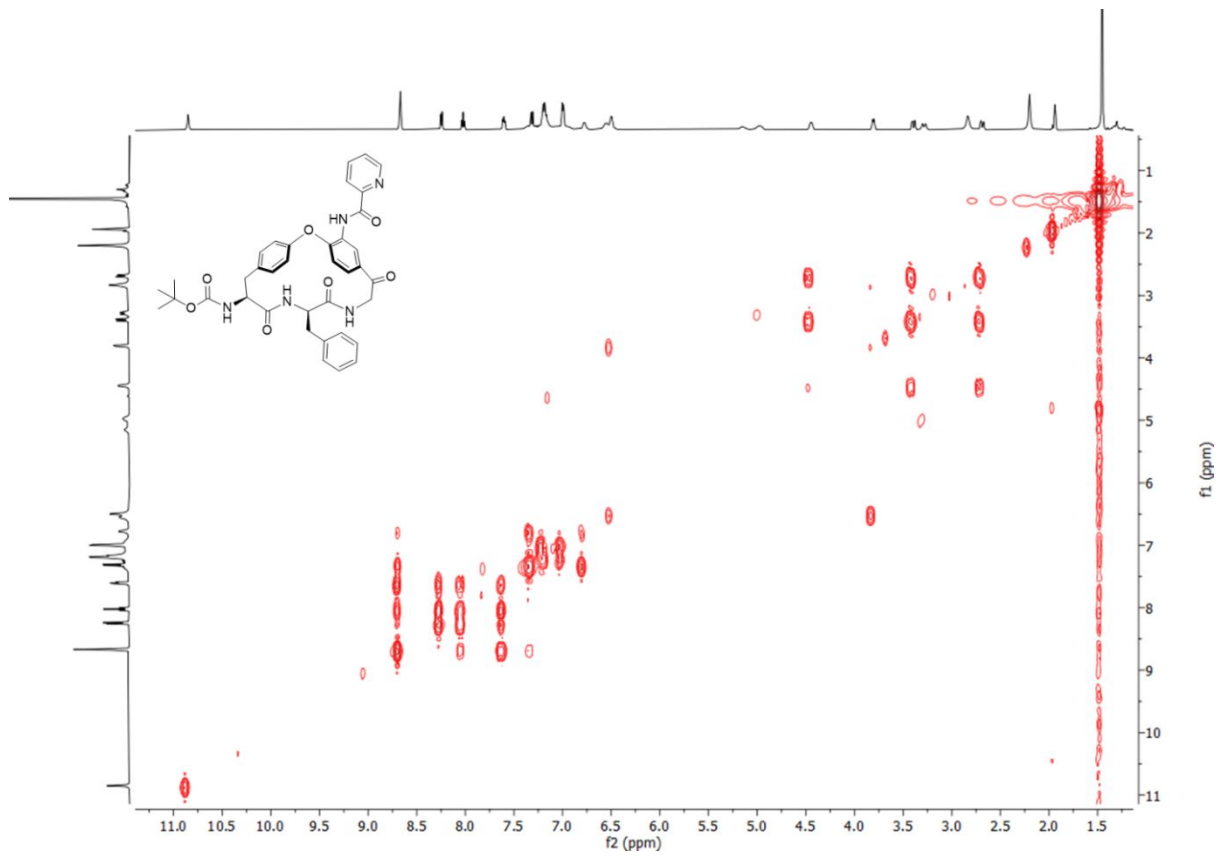## Compound 4: HSQC NMR (CD₃CN)
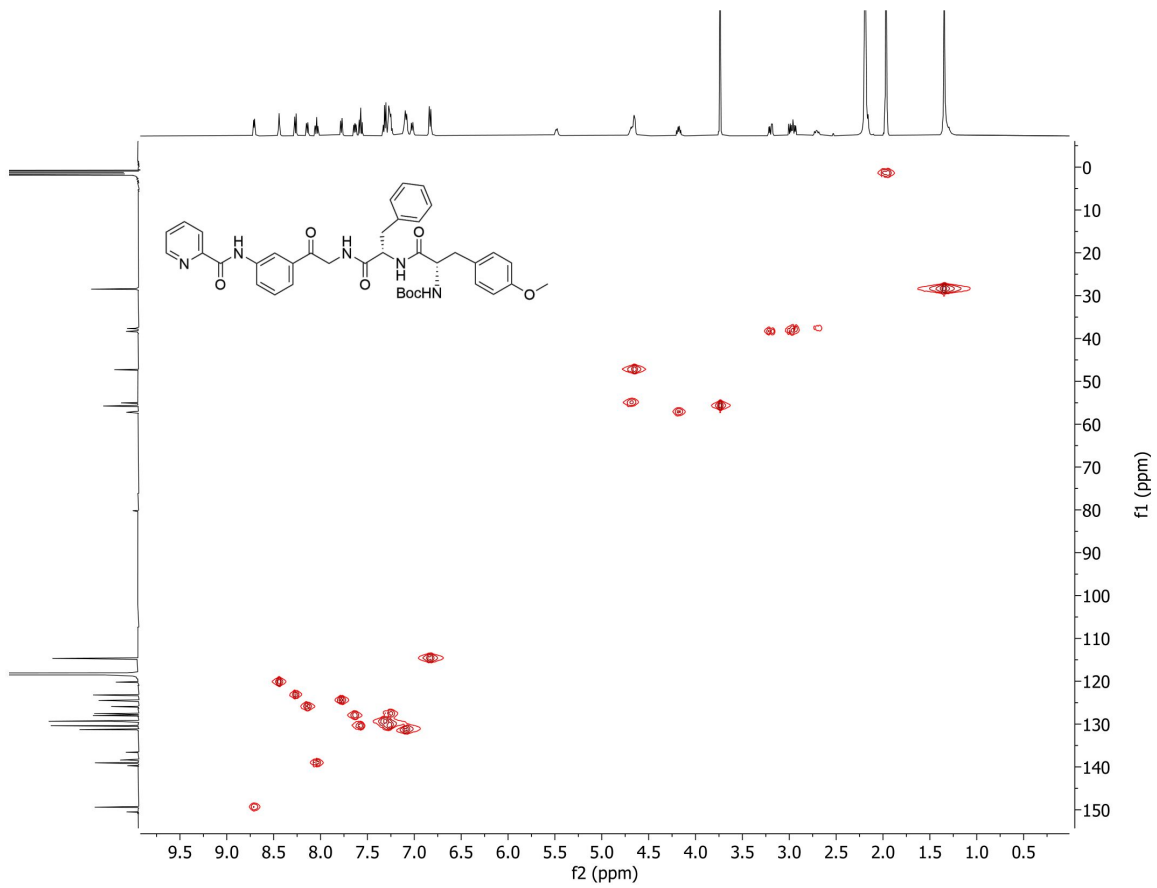
Compound 4: HMBC NMR (CD₃CN)
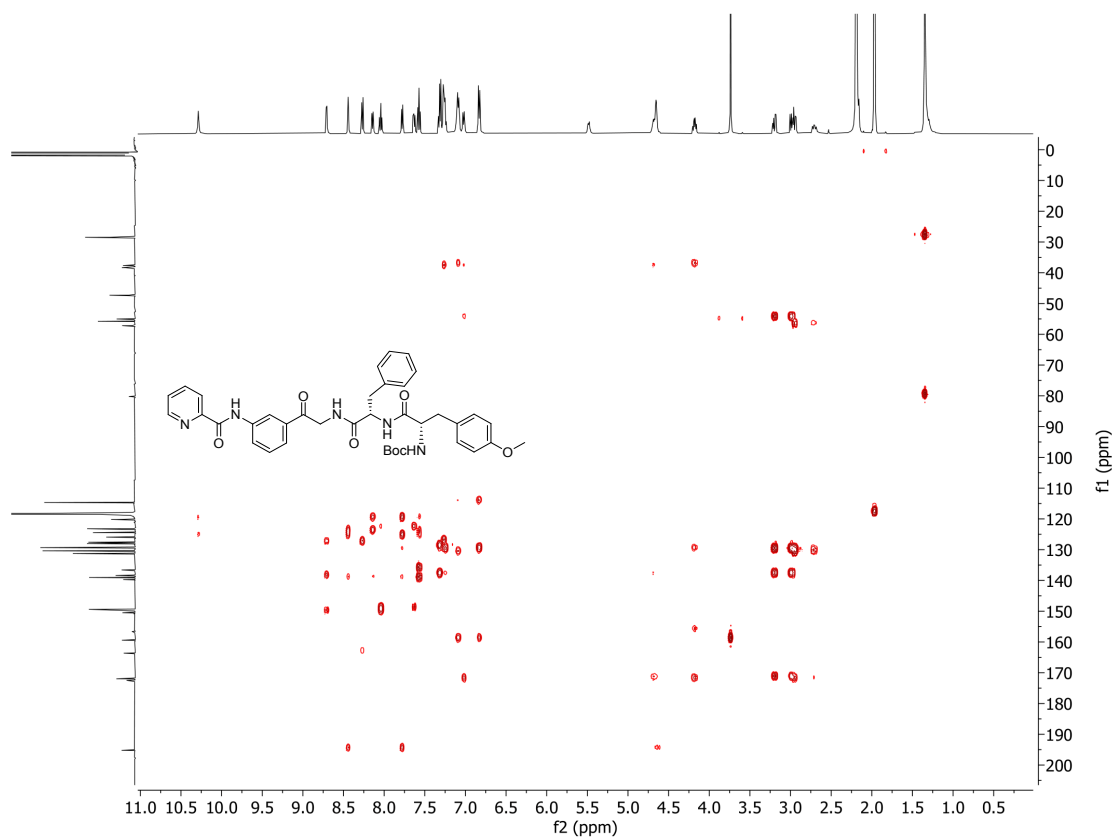
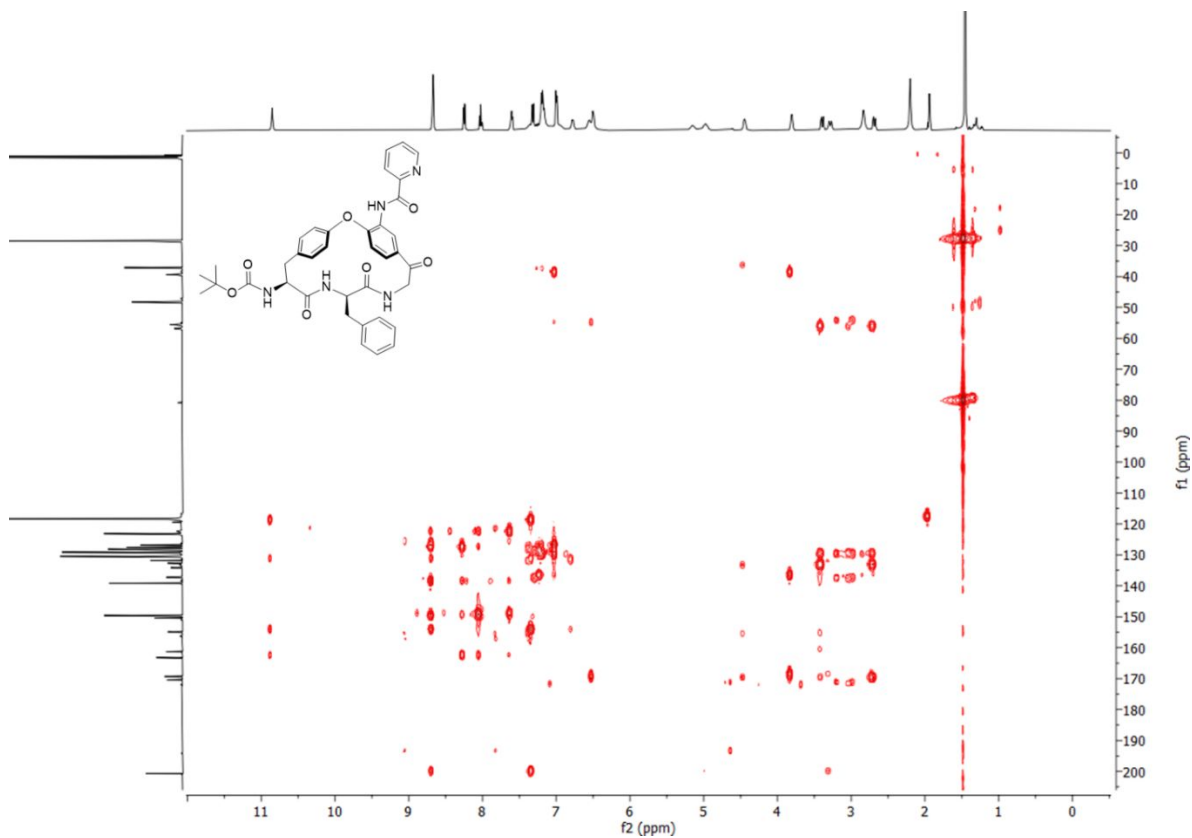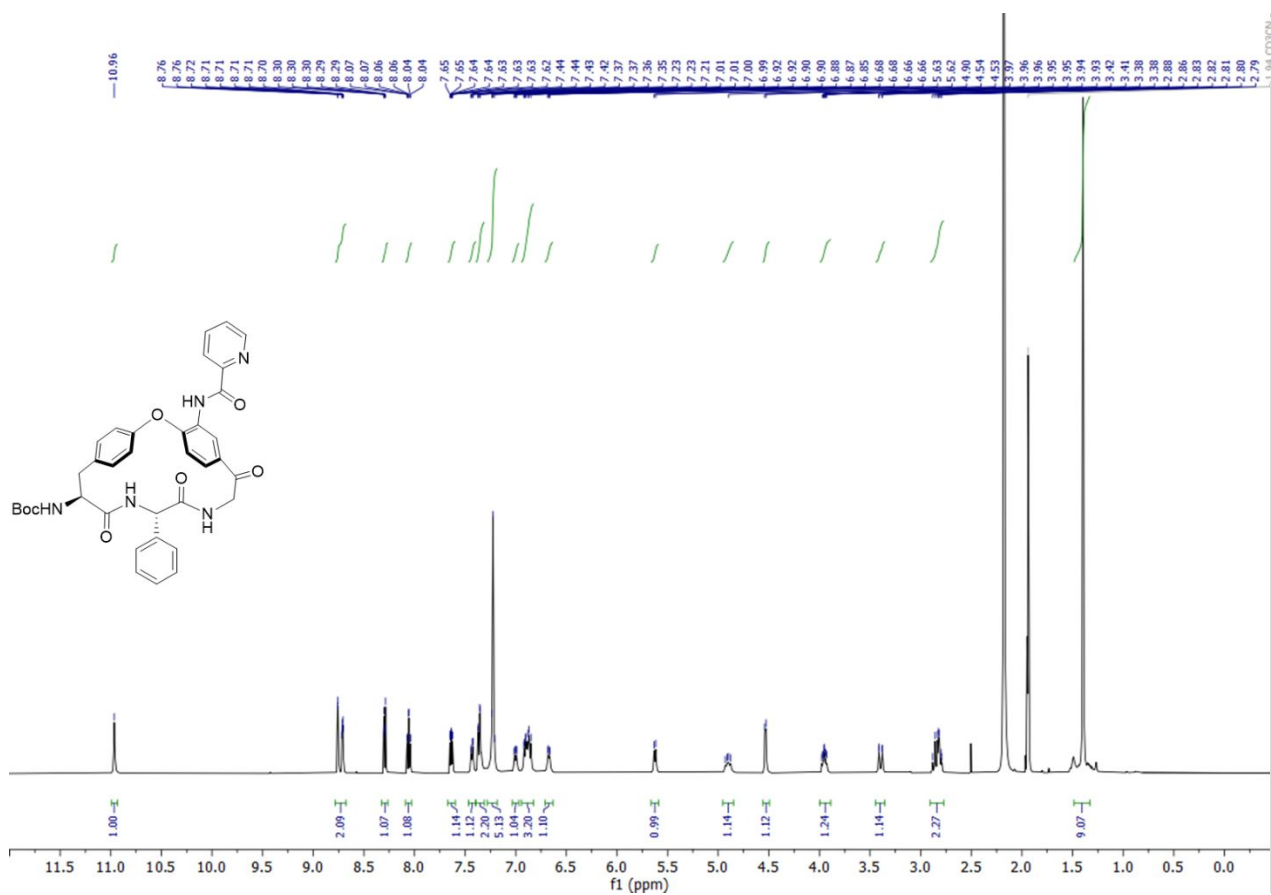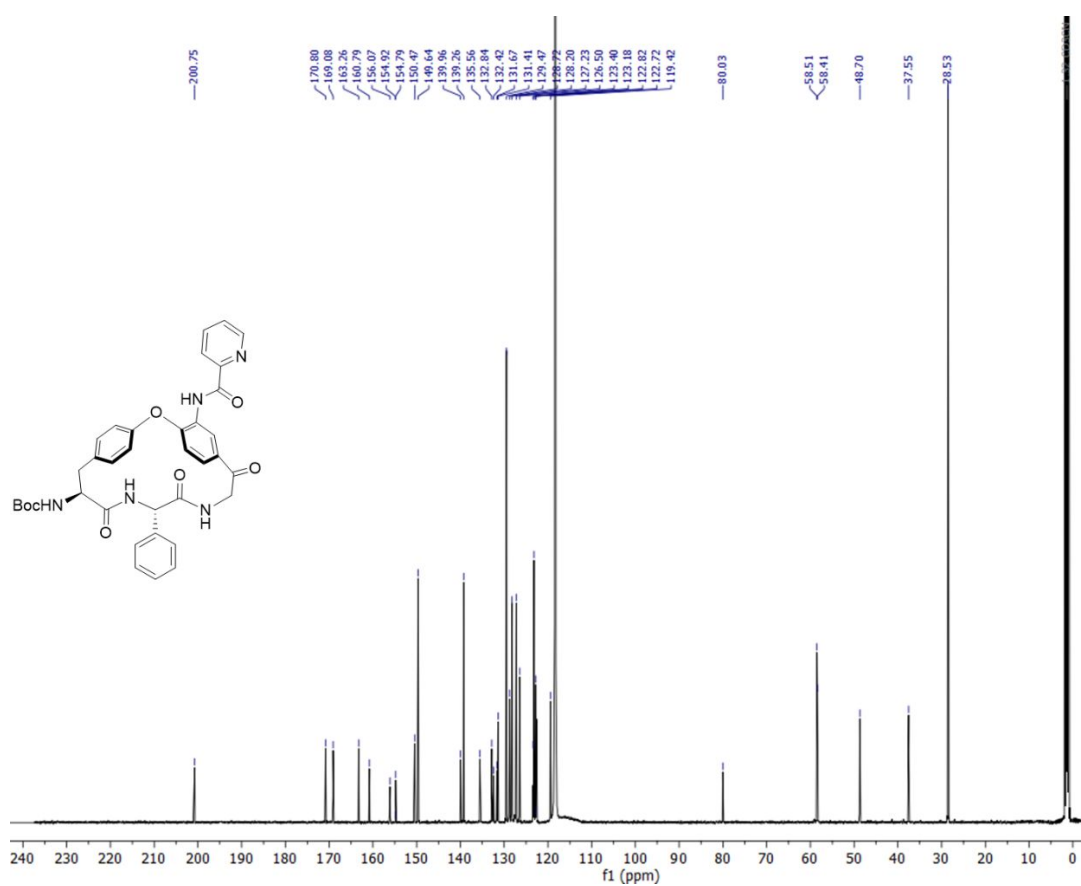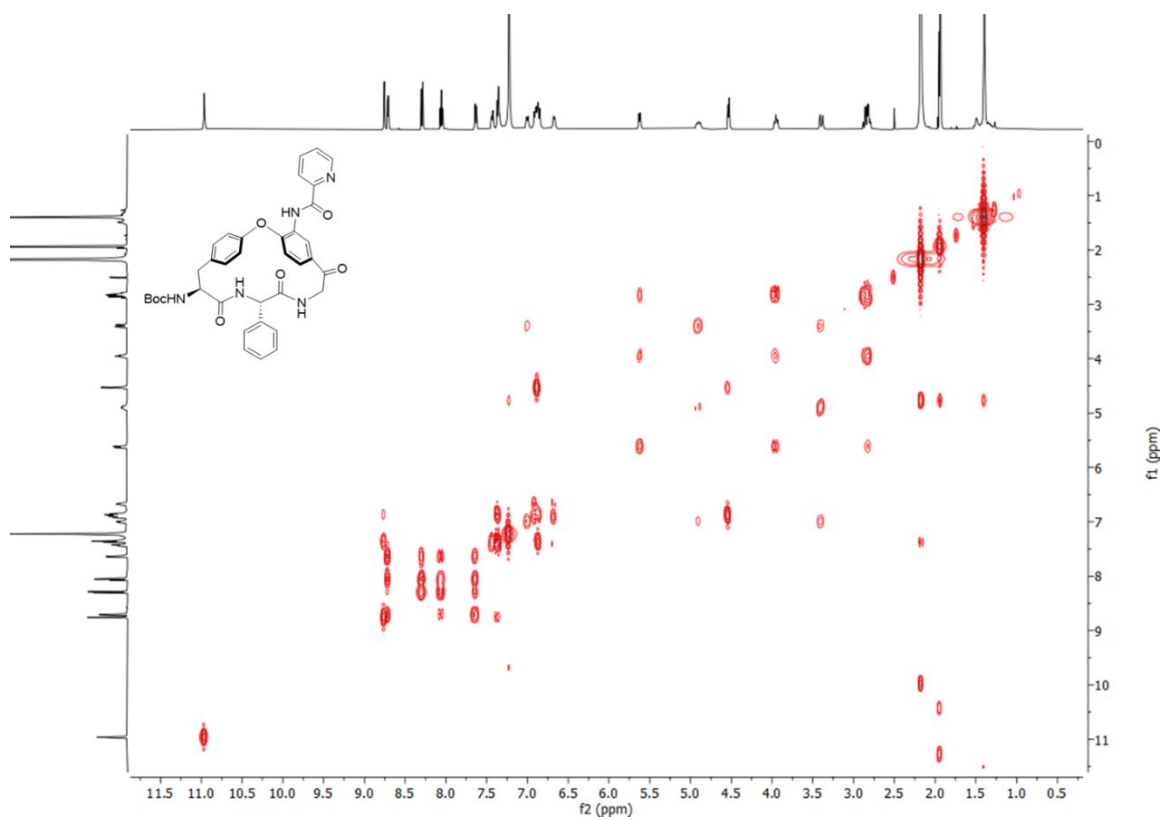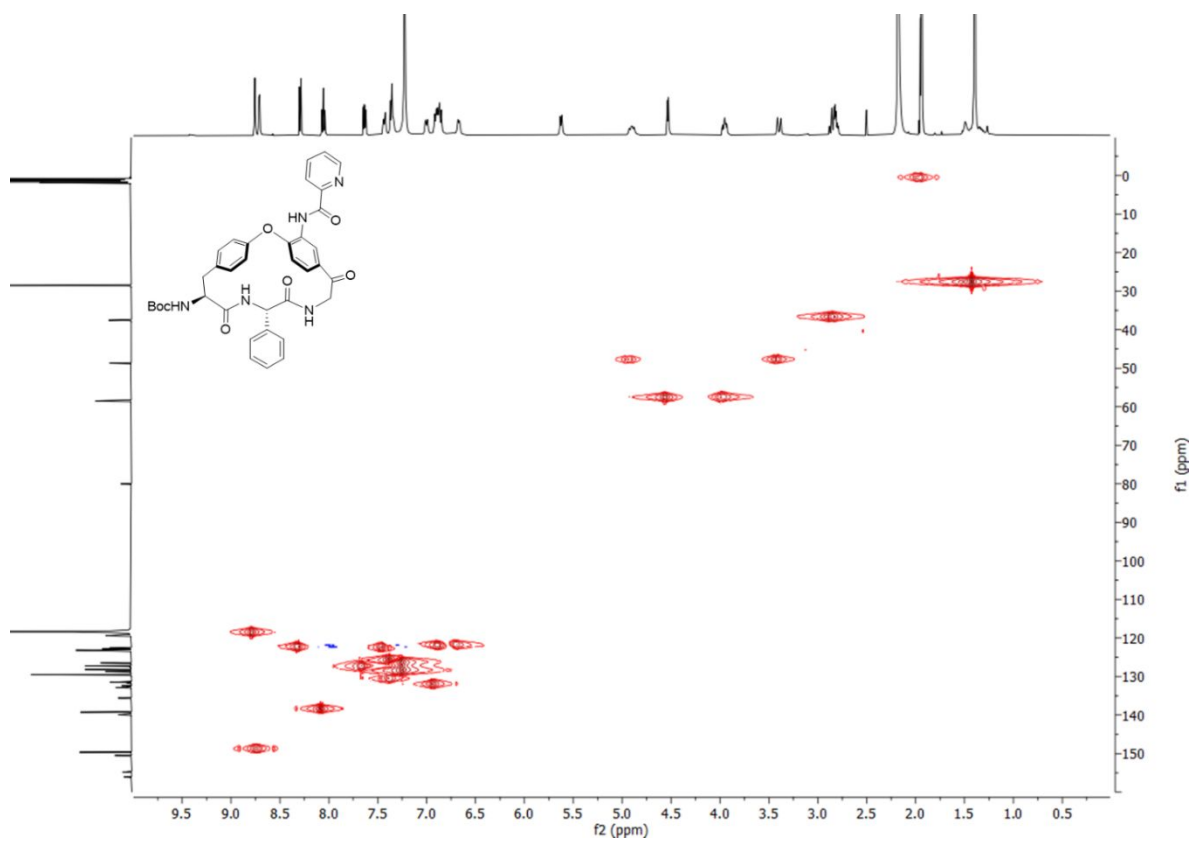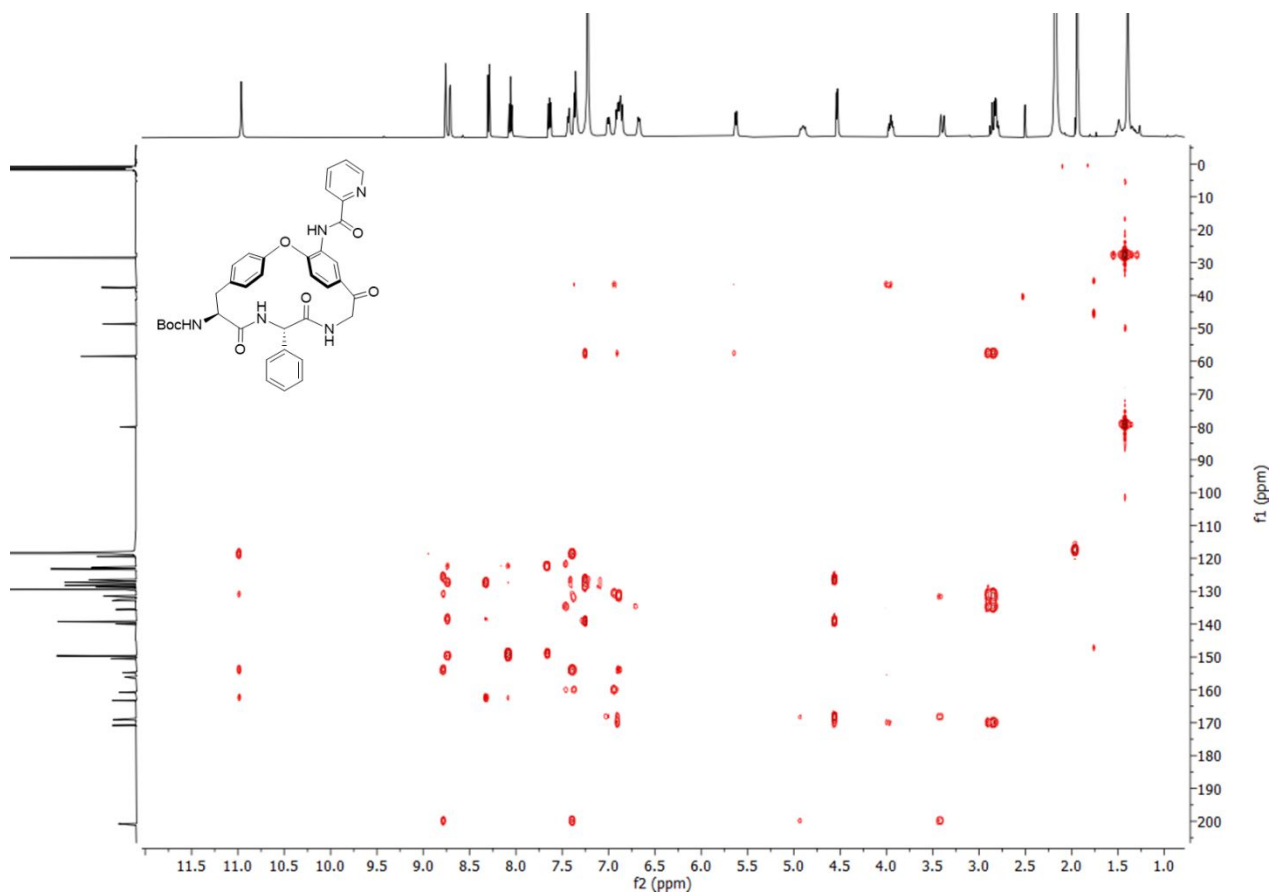

Compound 5: ¹H NMR (CDCl₃, 600 MHz)

Compound 5: ¹³C NMR (CDCl₃, 150 MHz)
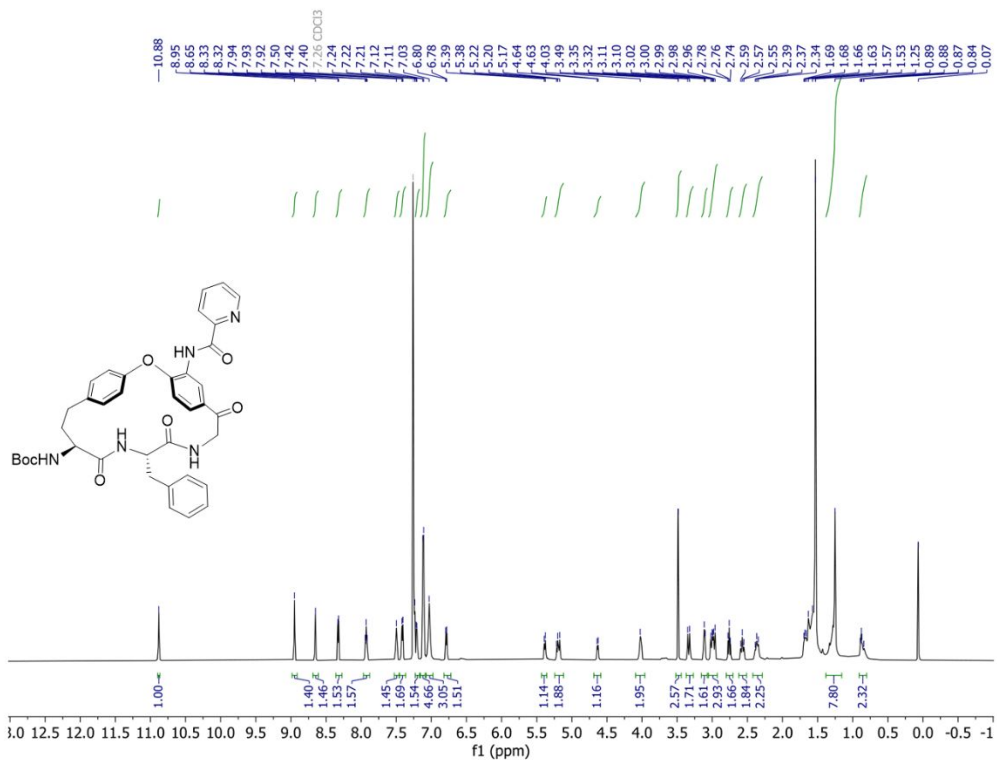
Compound 5: ^{13}C NMR (CDCl$_3$, 150 MHz)

Compound 5: COSY NMR (CDCl₃)
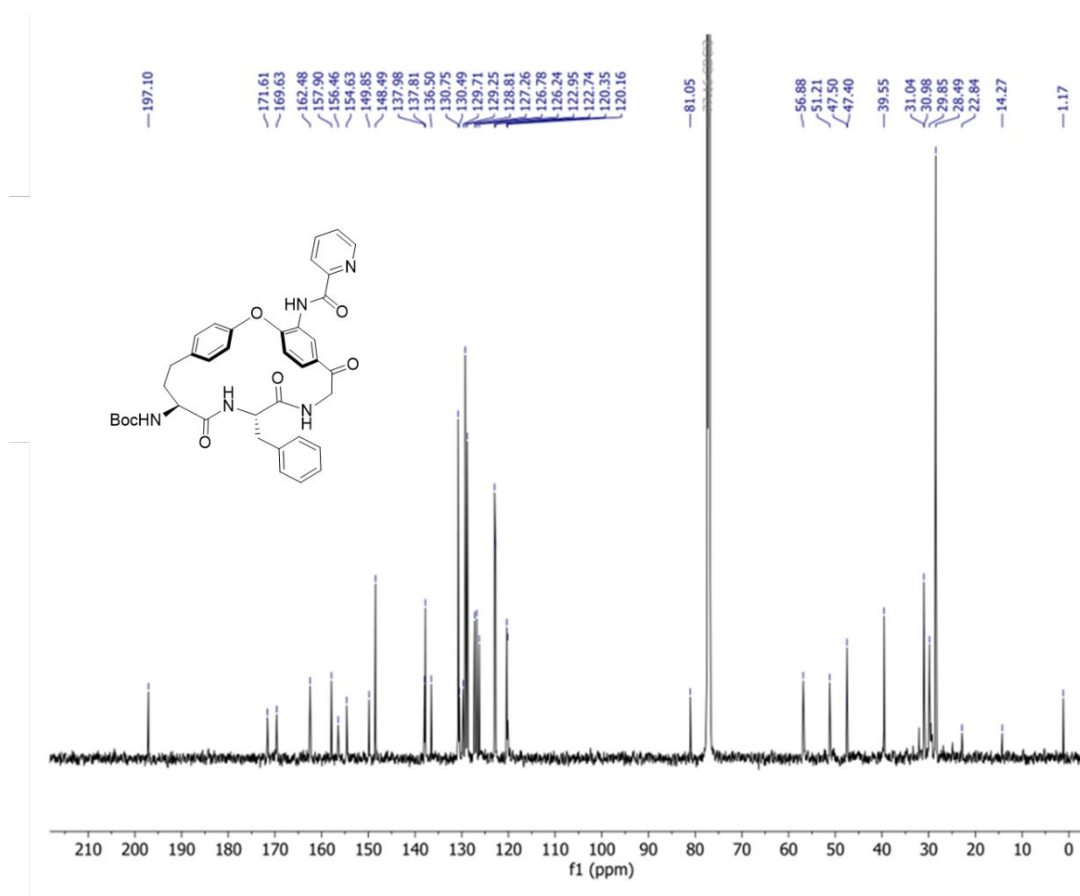
Compound 5: COSY NMR (CDCl$_3$)
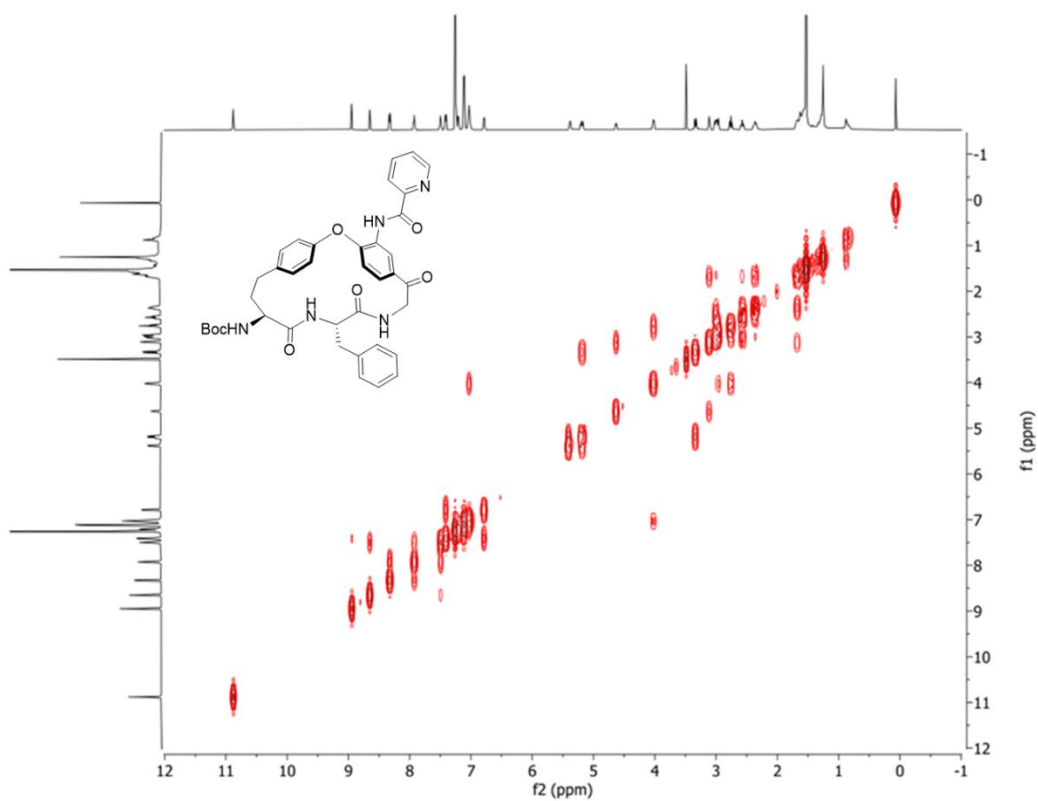
Compound 5: HSQC NMR (CDCl₃)

Compound 5: HMBC NMR (CDCl₃)

Compound 6: ¹H NMR (CD₃CN, 400 MHz)

Compound 6: ¹³C NMR (CD₃CN, 125 MHz)
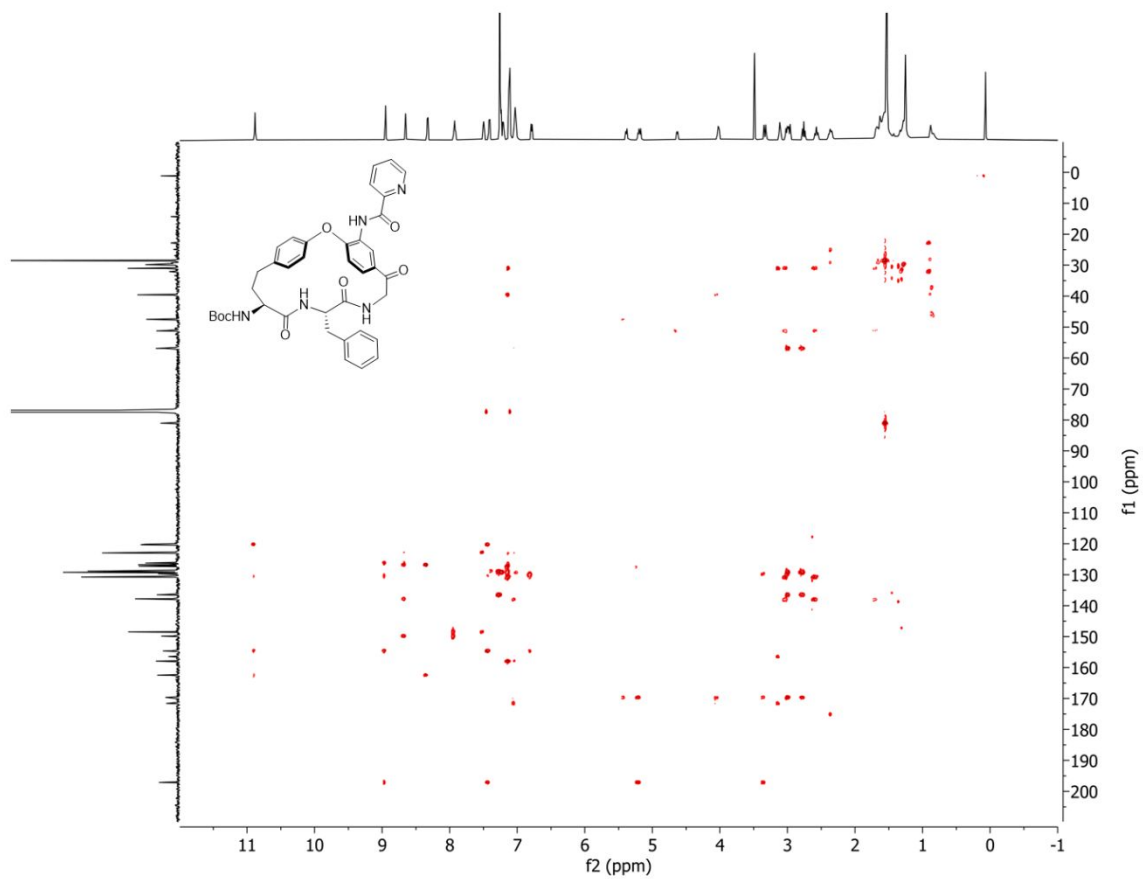
Compound 6: COSY NMR (CD₃CN)
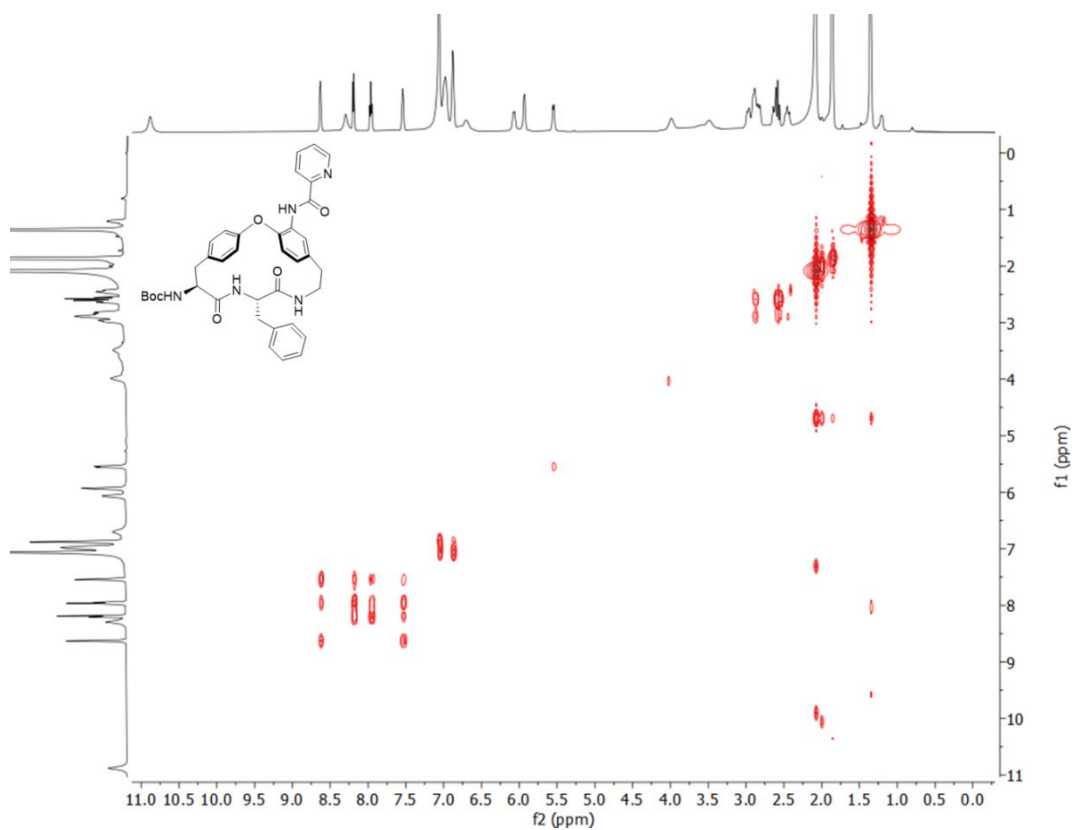
Compound 6: HSQC NMR (CD₃CN)
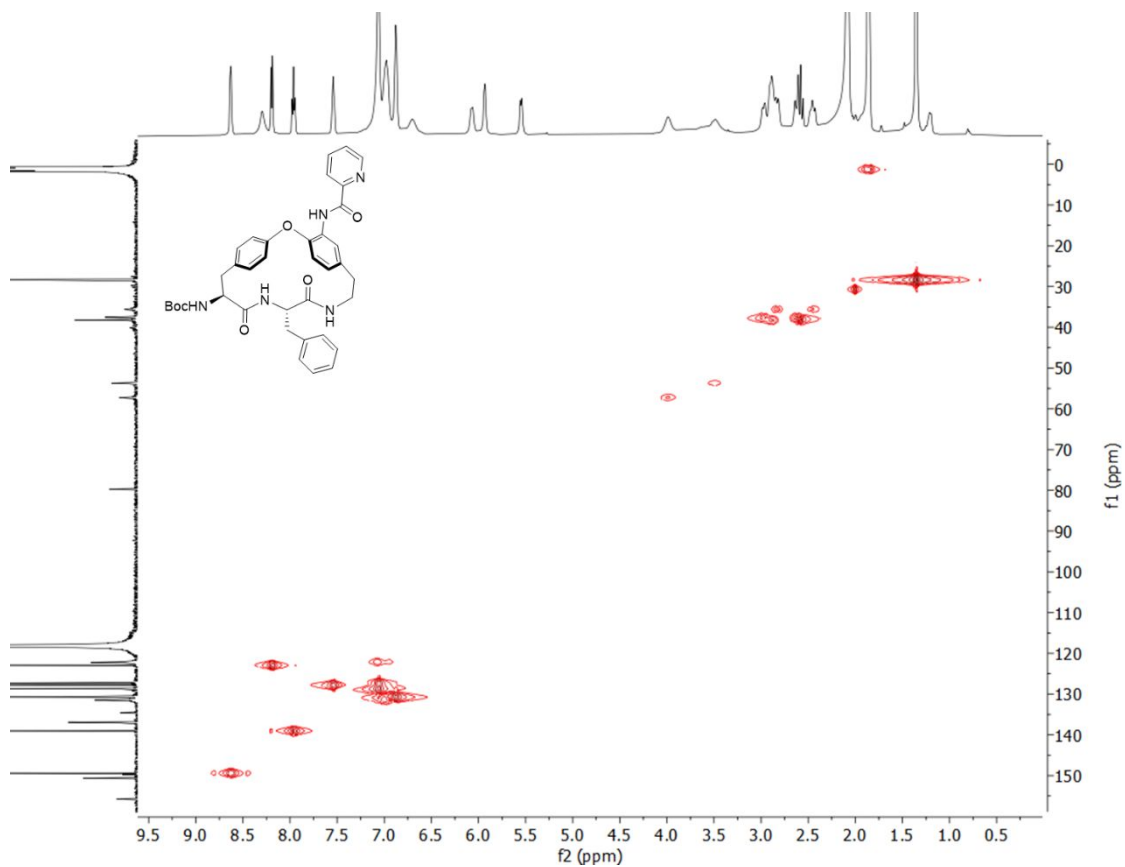
Compound 6: HMBC NMR (CD₃CN)

Compound 7: ¹H NMR (CD₃CN, 500 MHz)
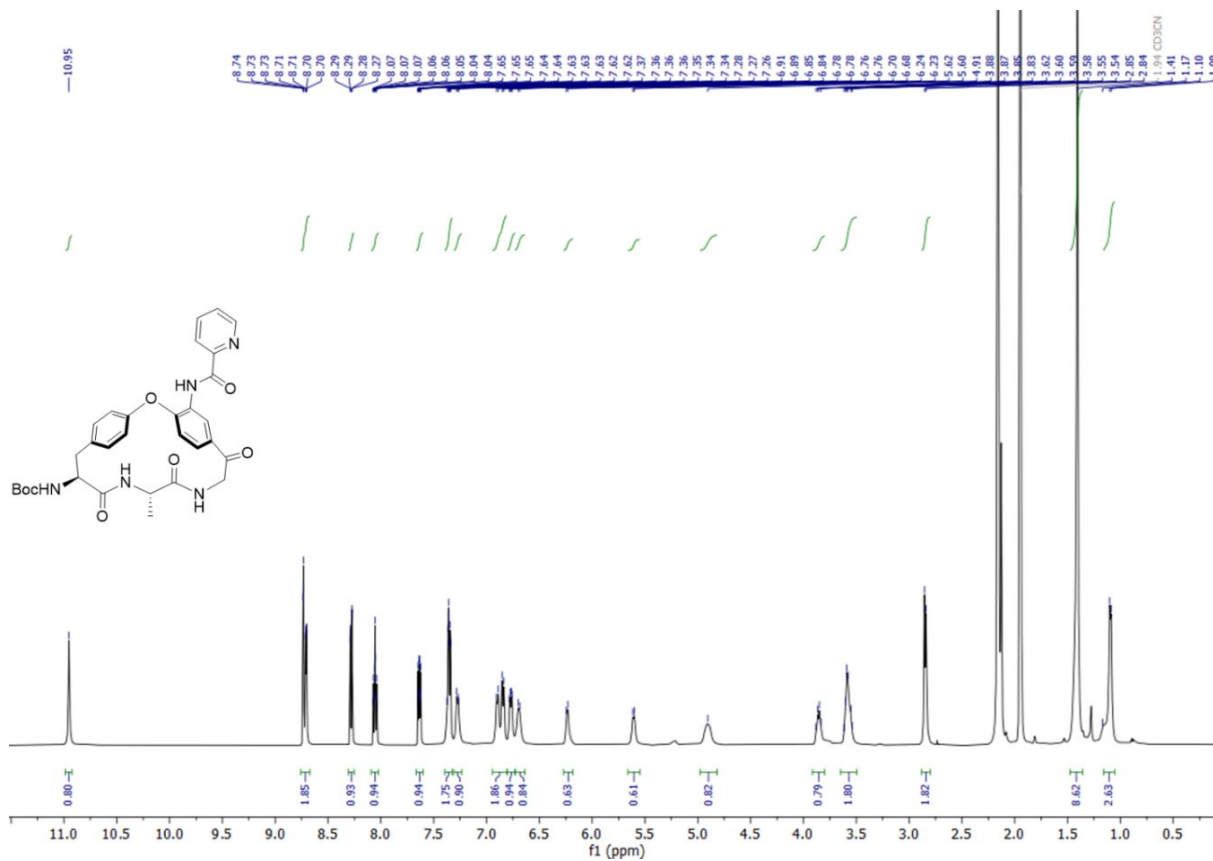
Compound 7: ^{13}C NMR (CD$_3$CN, 125 MHz)
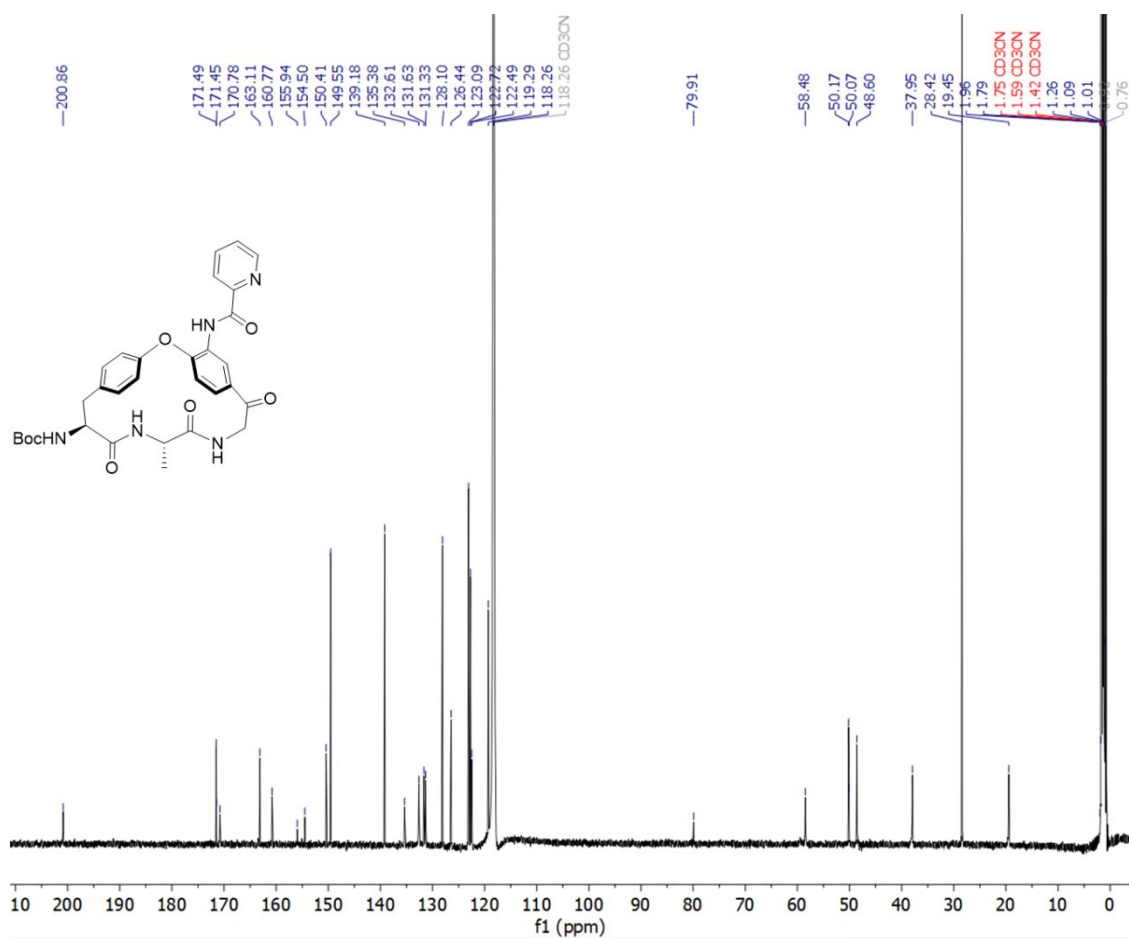
Compound 7: COSY NMR (CD$_3$CN)
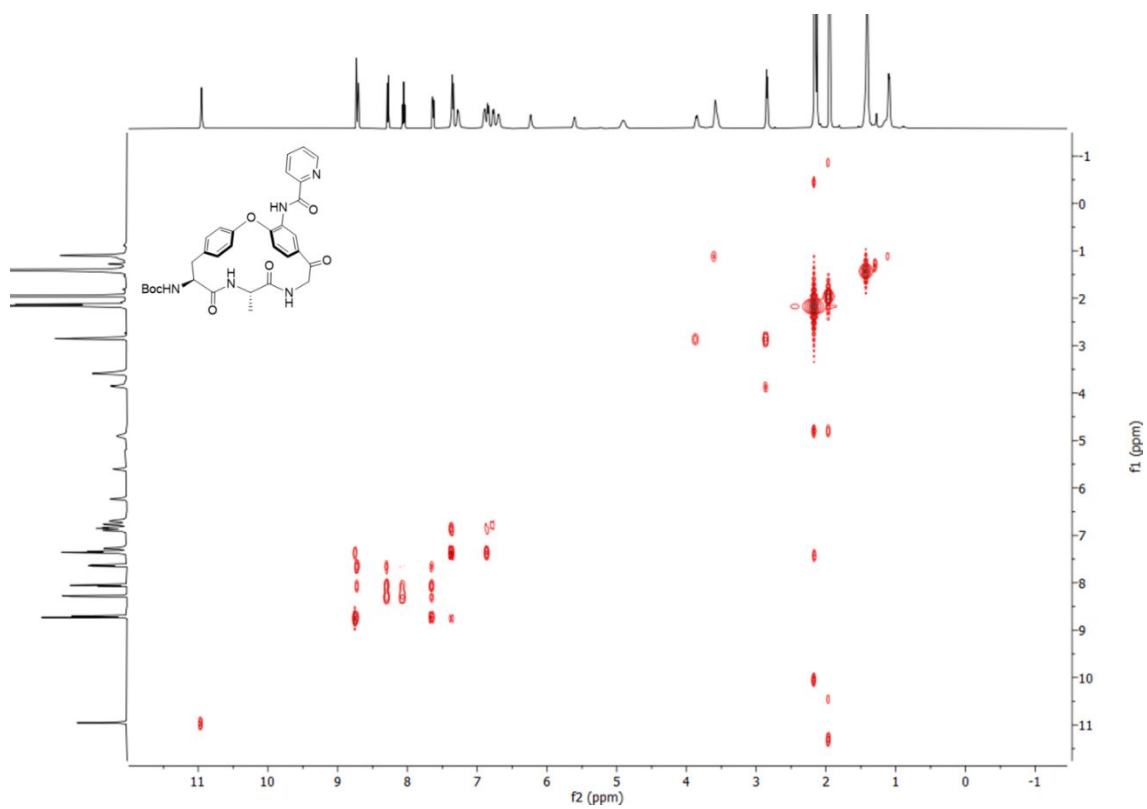
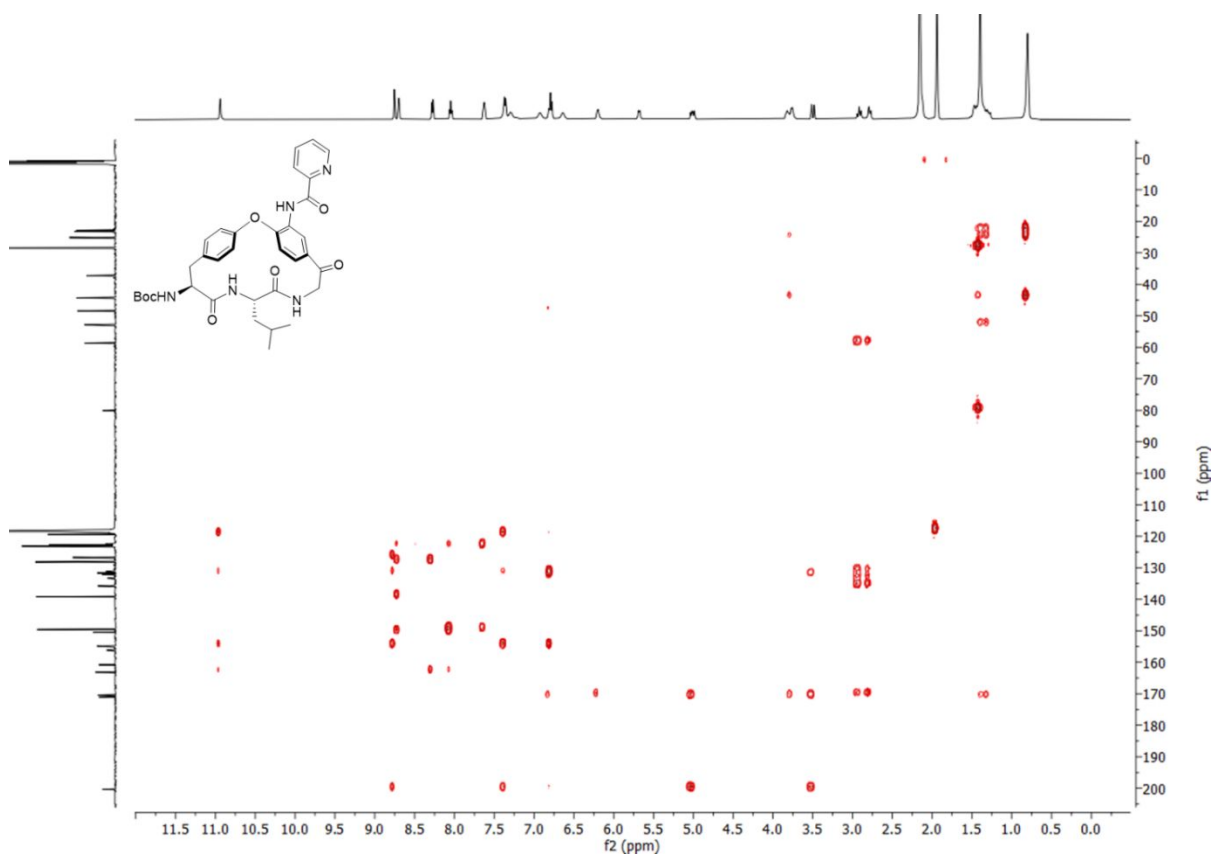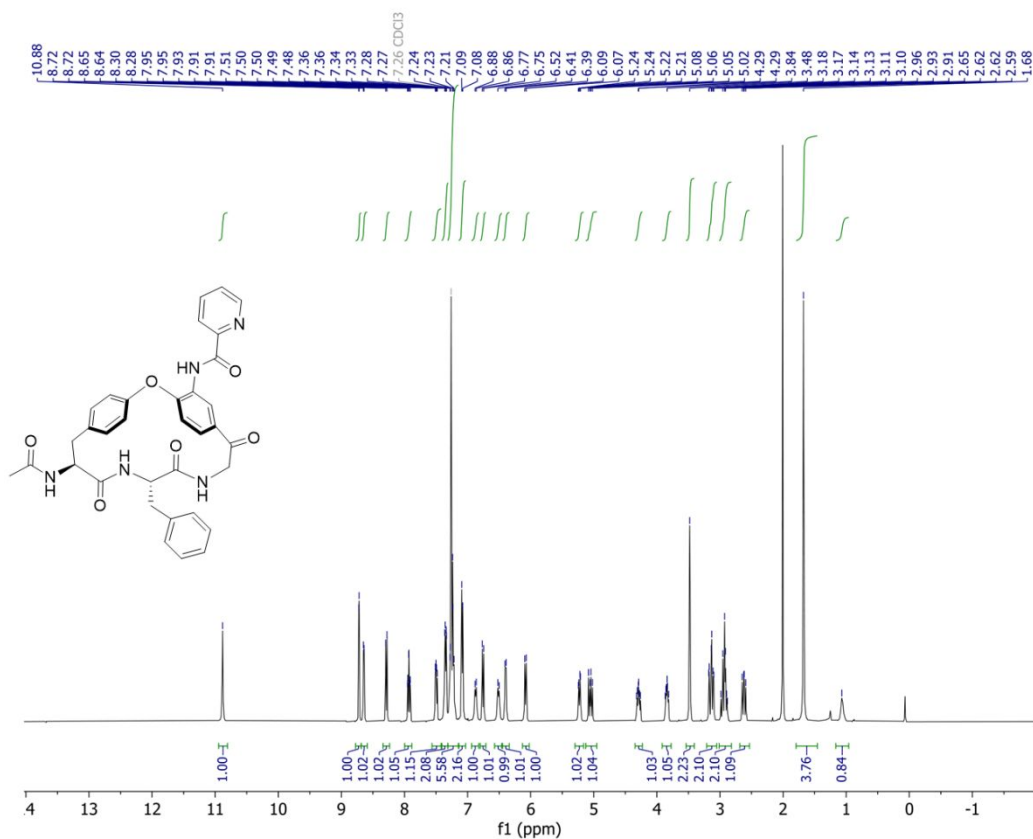**Compound 7: HSQC NMR (CD₃CN)**
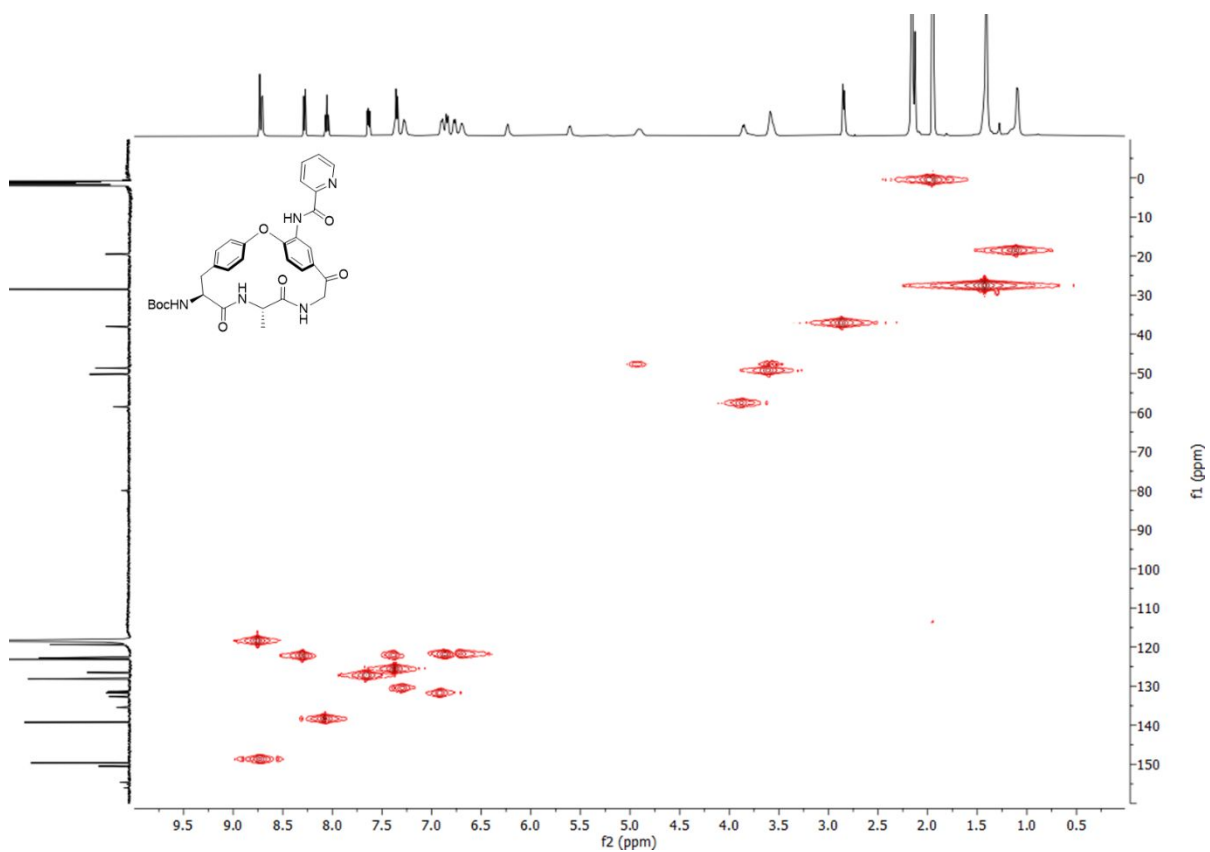
Compound 7: HMBC NMR (CD₃CN)
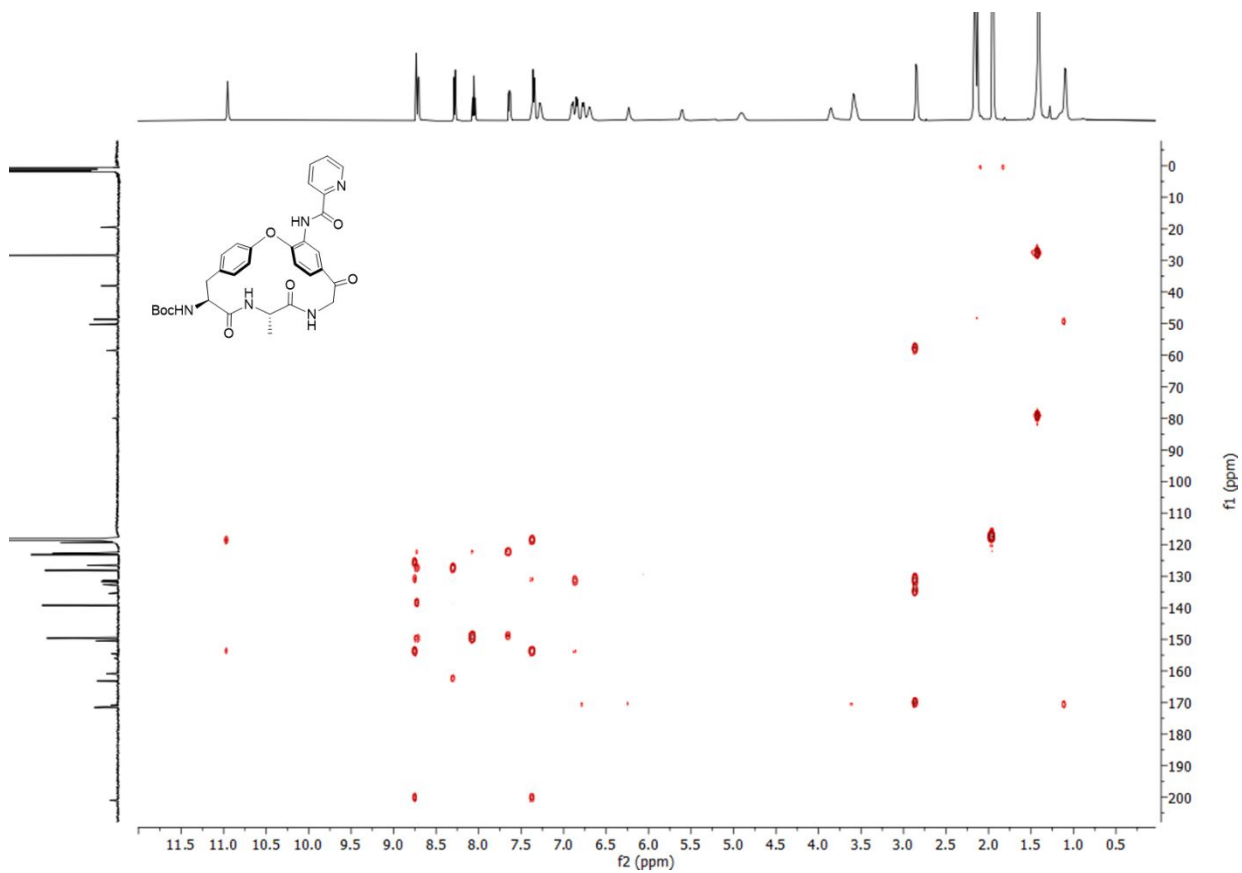
Compound 8: ¹H NMR (CD₃CN, 500 MHz)
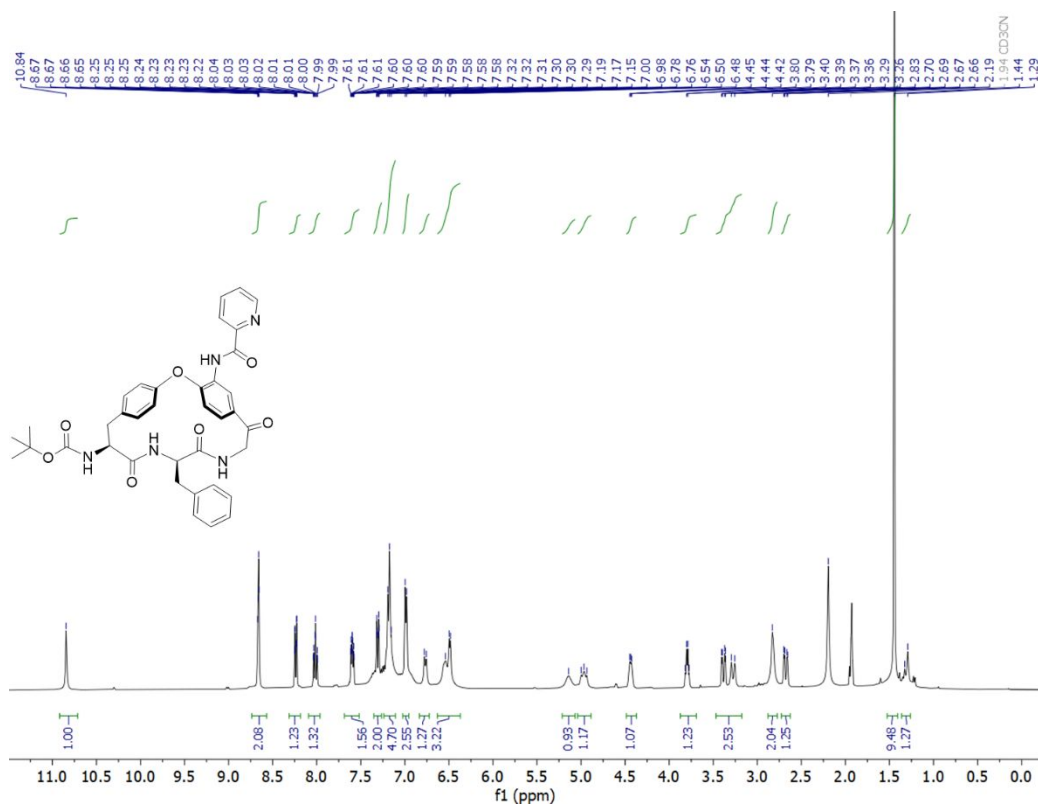
Compound 8: ¹³C NMR (CD₃CN, 125 MHz)
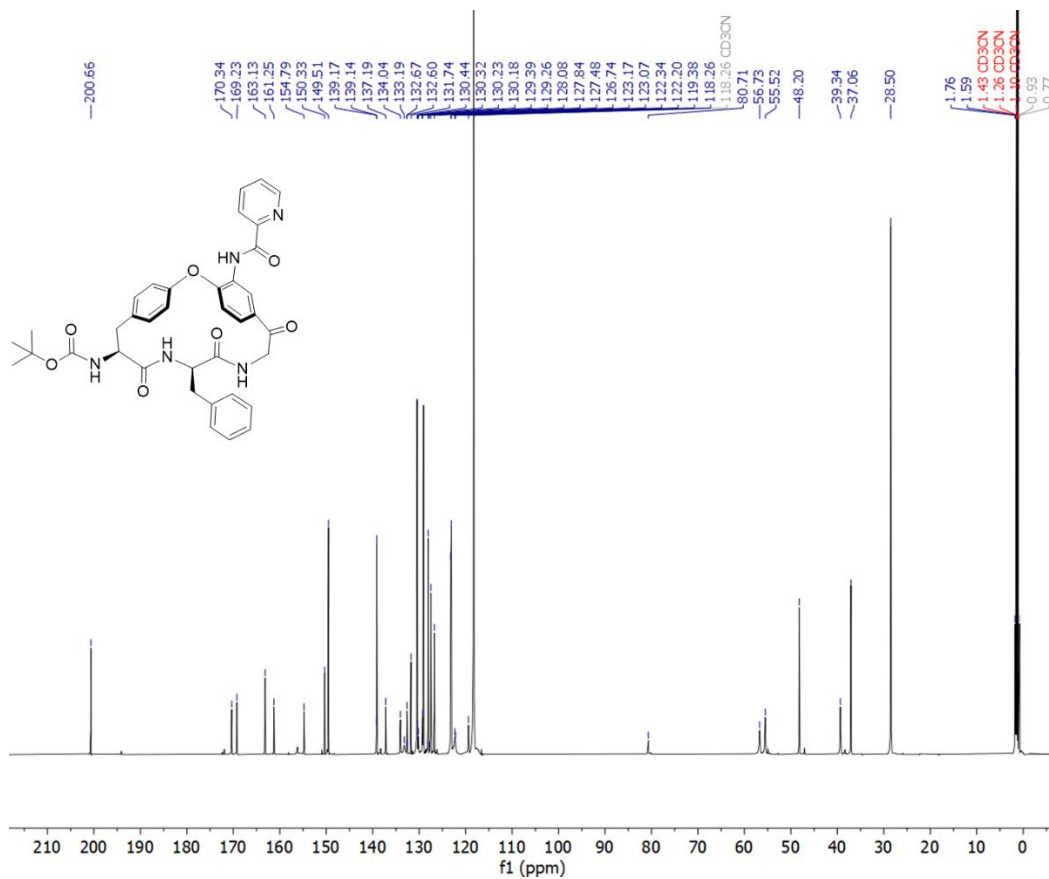
Compound 8: COSY NMR (CD₃CN)

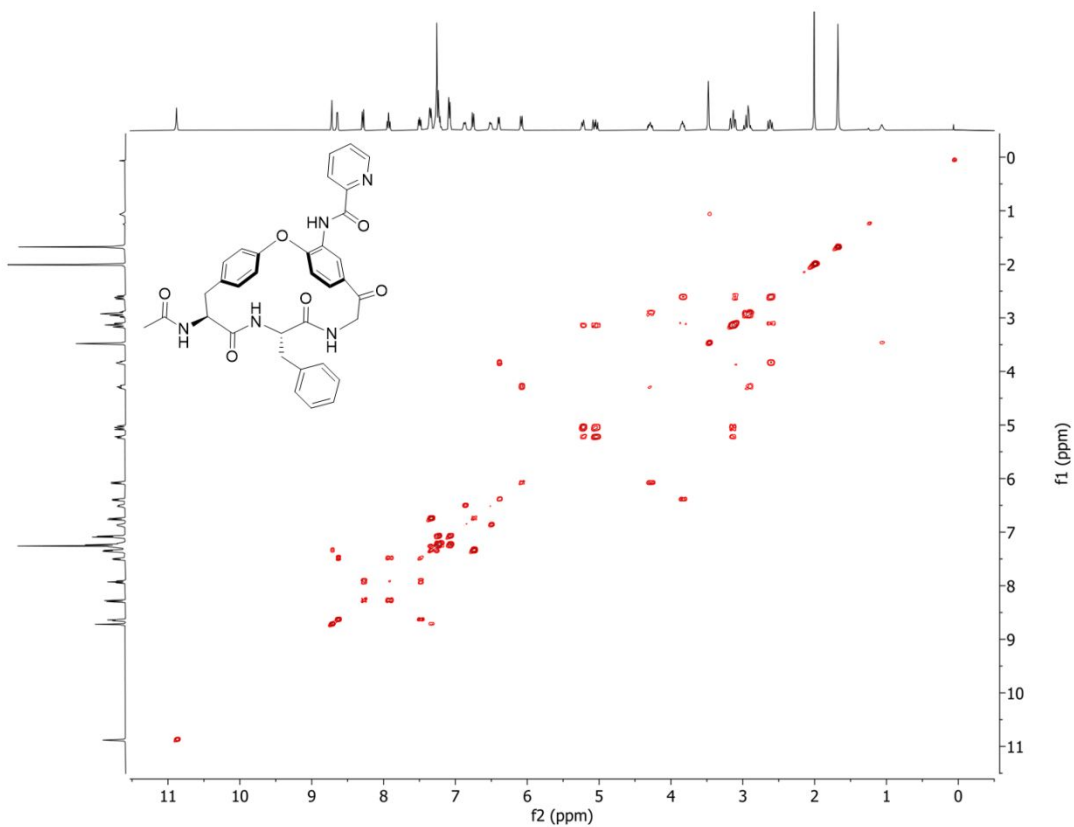**Compound 8: HSQC NMR (CD₃CN)**
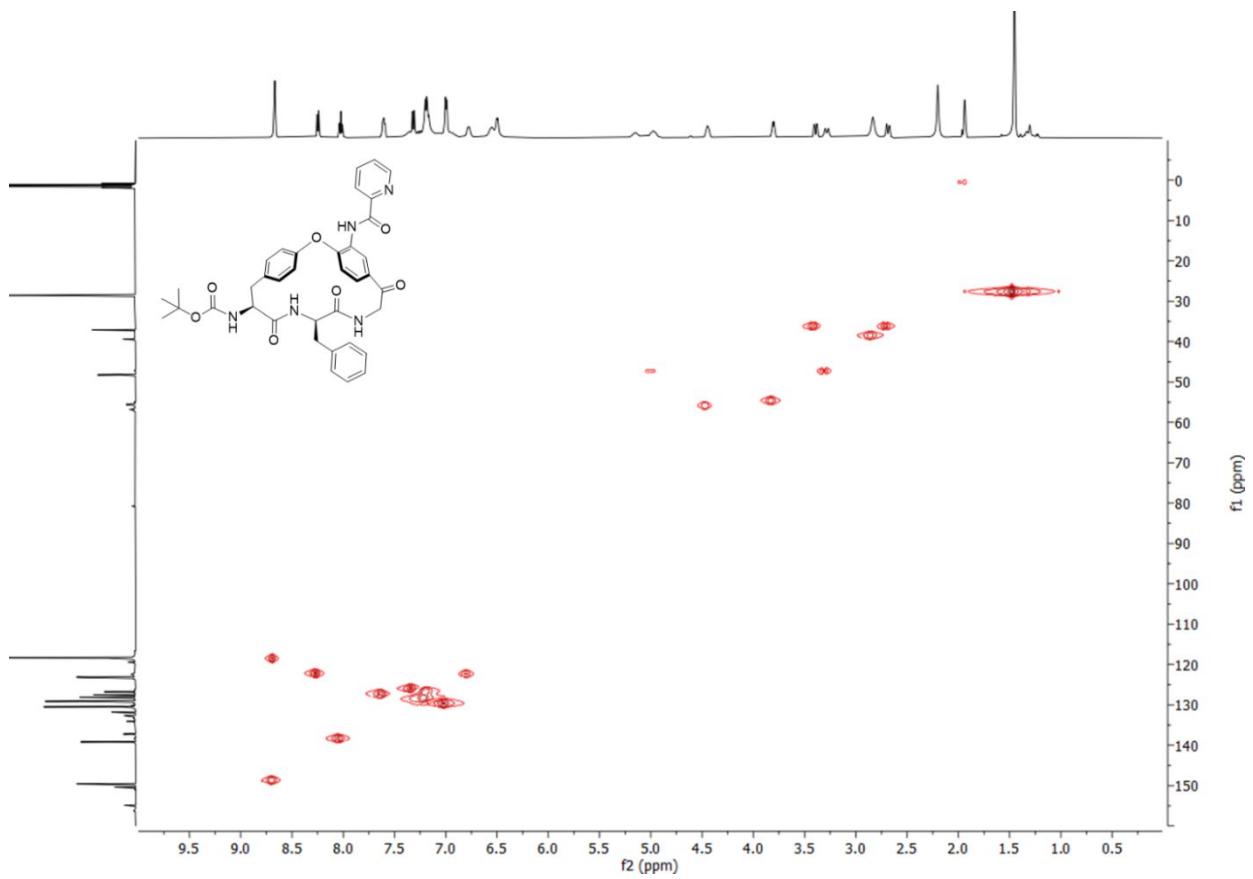
Compound 8: HMBC NMR (CD₃CN)

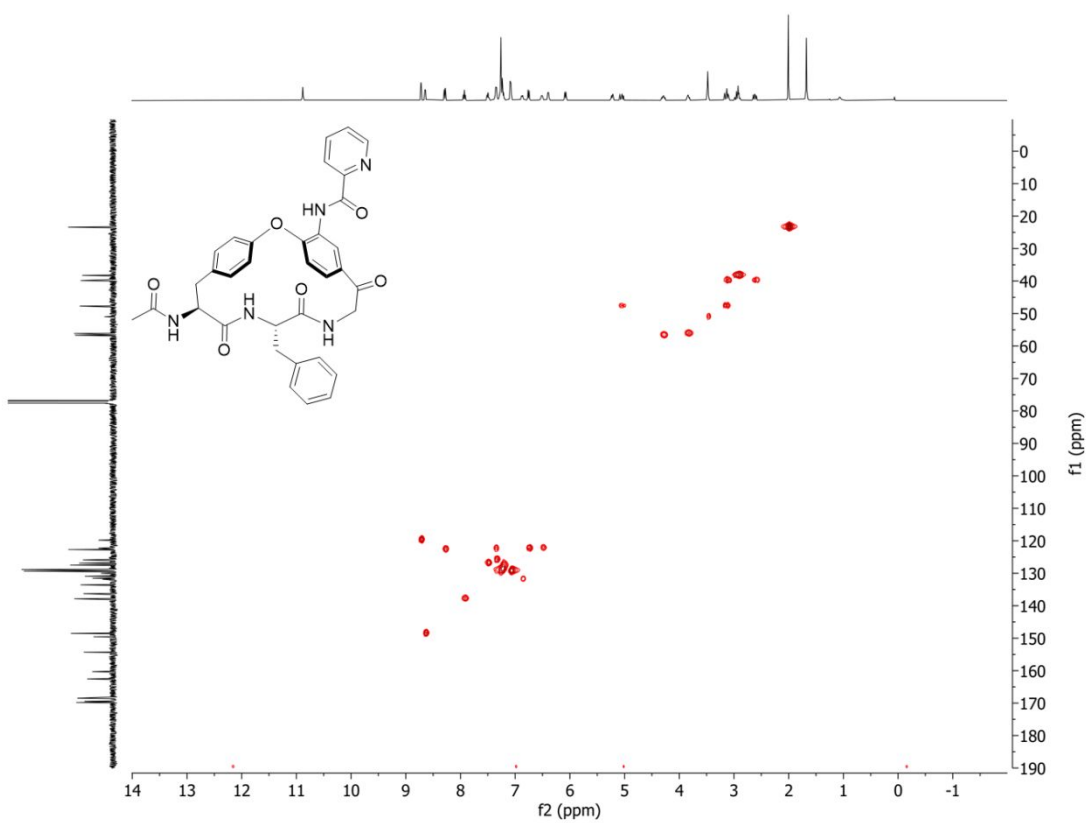**Compound 9: ¹H NMR (CD₃CN, 500 MHz)**

Compound 9: ^{13}C NMR (CD$_3$CN, 125 MHz)

## Compound 9: COSY NMR (CD$_3$CN)

Compound 9: HSQC NMR (CD₃CN)

Compound 9: HMBC NMR (CD₃CN)

Compound 10: ^{1}H NMR (CD$_3$CN, 500 MHz)

Compound 10: ^{13}C NMR (CD$_3$CN, 125 MHz)

Compound 10: COSY NMR (CD₃CN)
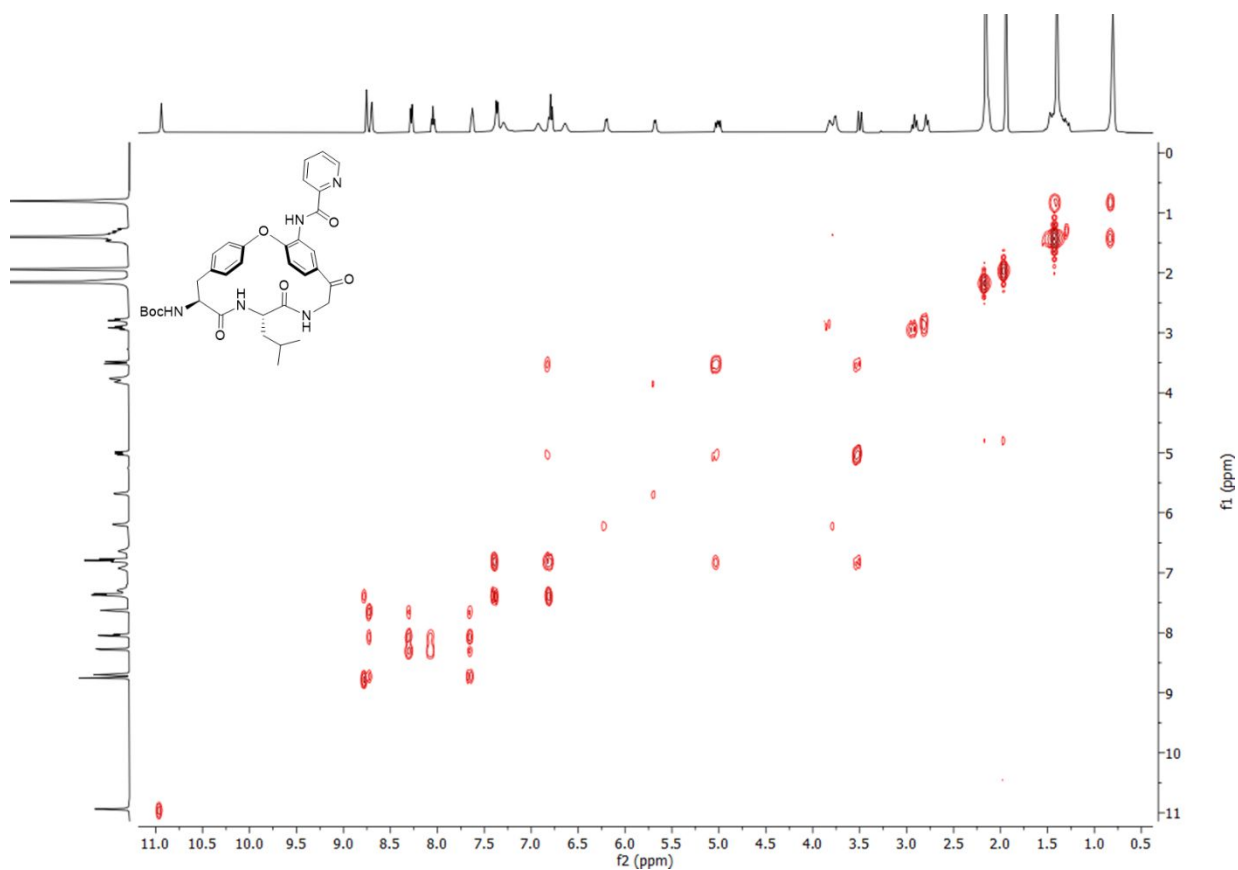
Compound 10: HSQC NMR (CD₃CN)
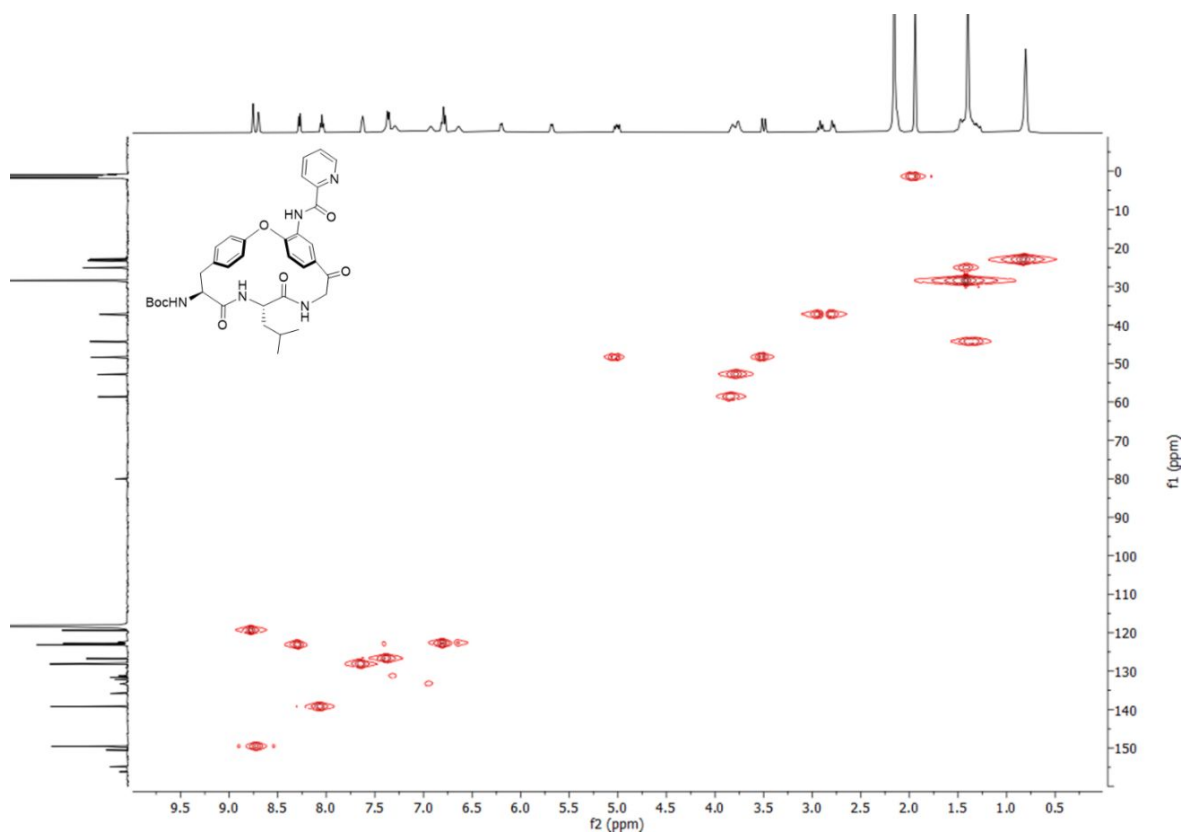
Compound 10: HMBC NMR (CD₃CN)

Compound 11: ¹H NMR (CDCl₃, 400 MHz)

Compound 11: ^{13}C NMR (CDCl$_3$, 100 MHz)
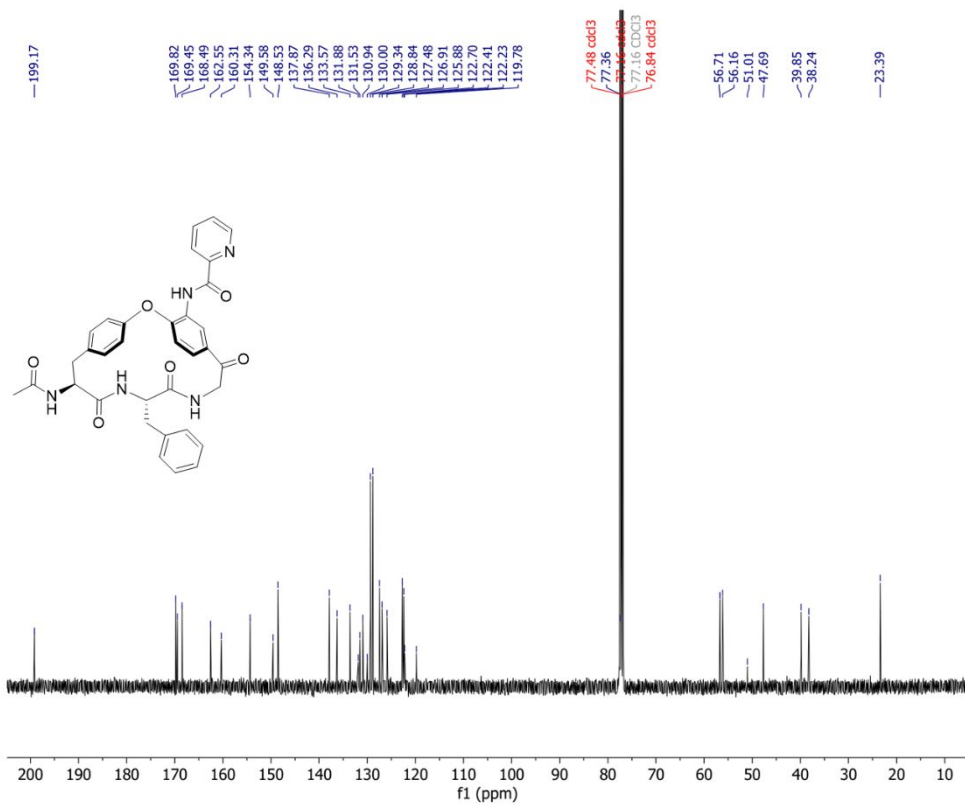
Compound 11: COSY NMR (CDCl$_3$)

Compound 11: HSQC (CDCl₃)

Compound 11: HMBC NMR (CDCl₃)
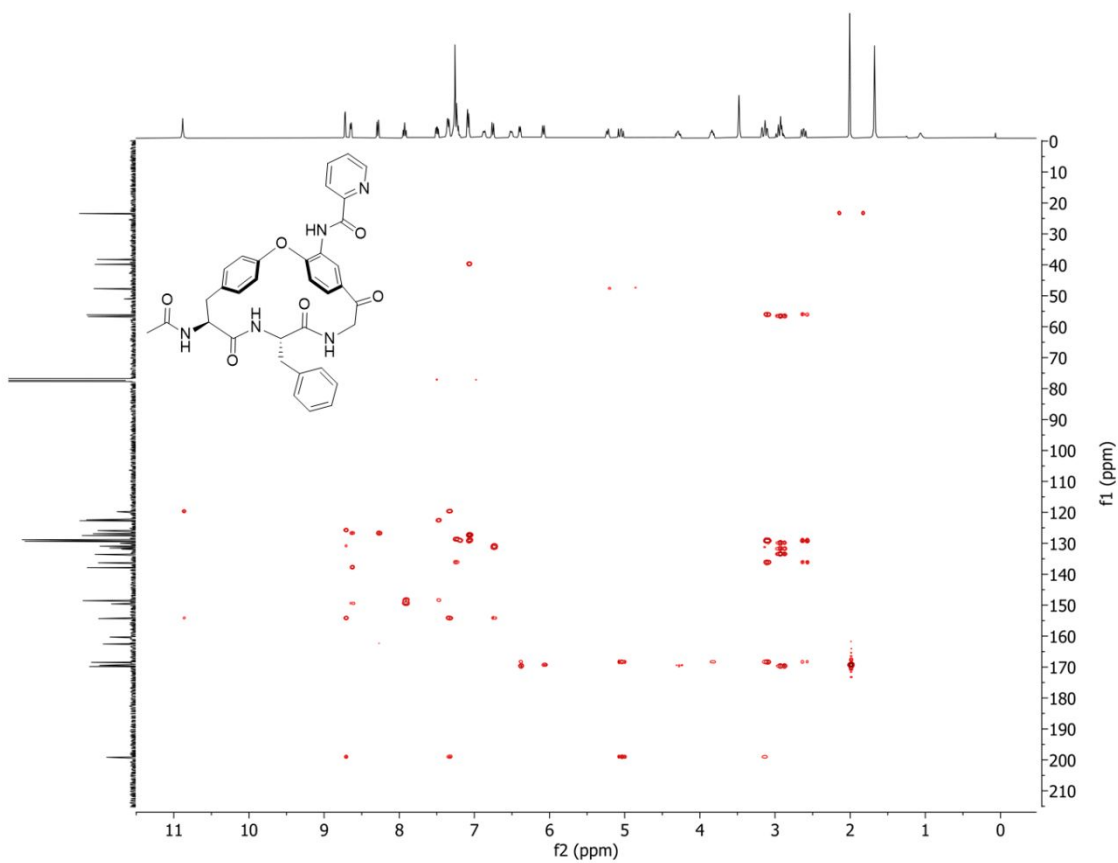
Compound 12: ^{1}H NMR (CD$_3$CN, 400 MHz)
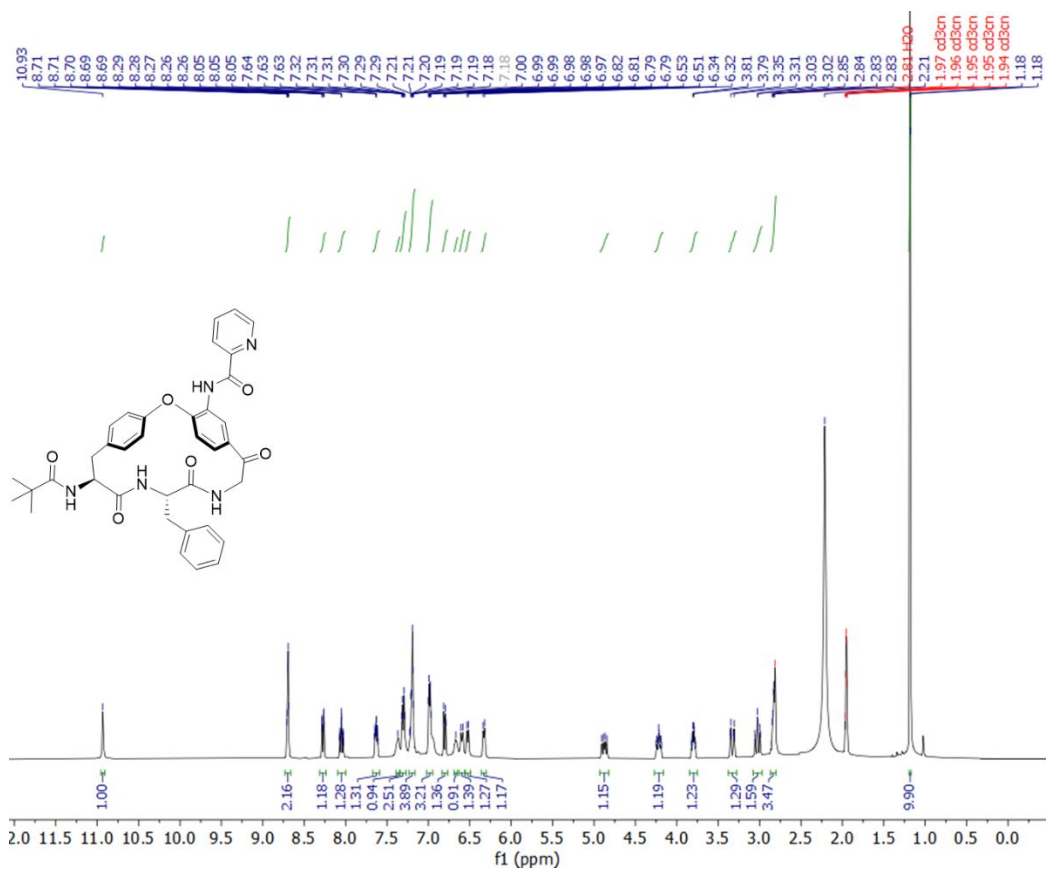
Compound 12: ^{13}C NMR (CD$_3$CN, 500 MHz)
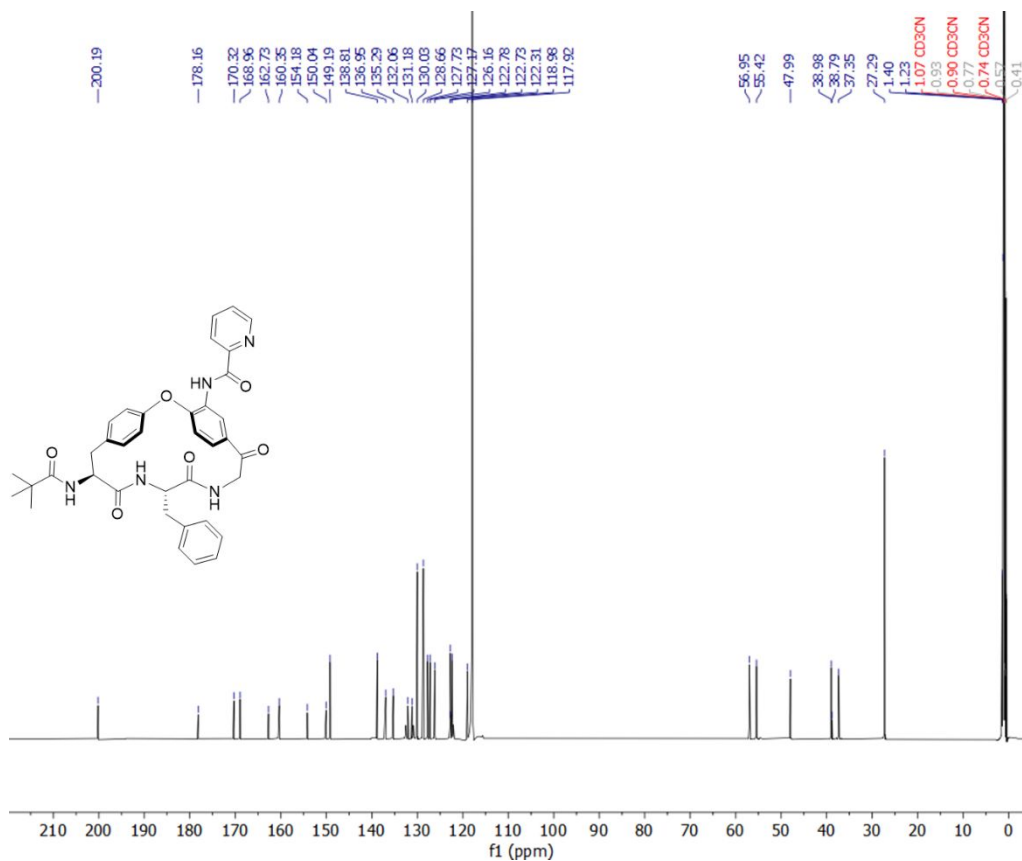
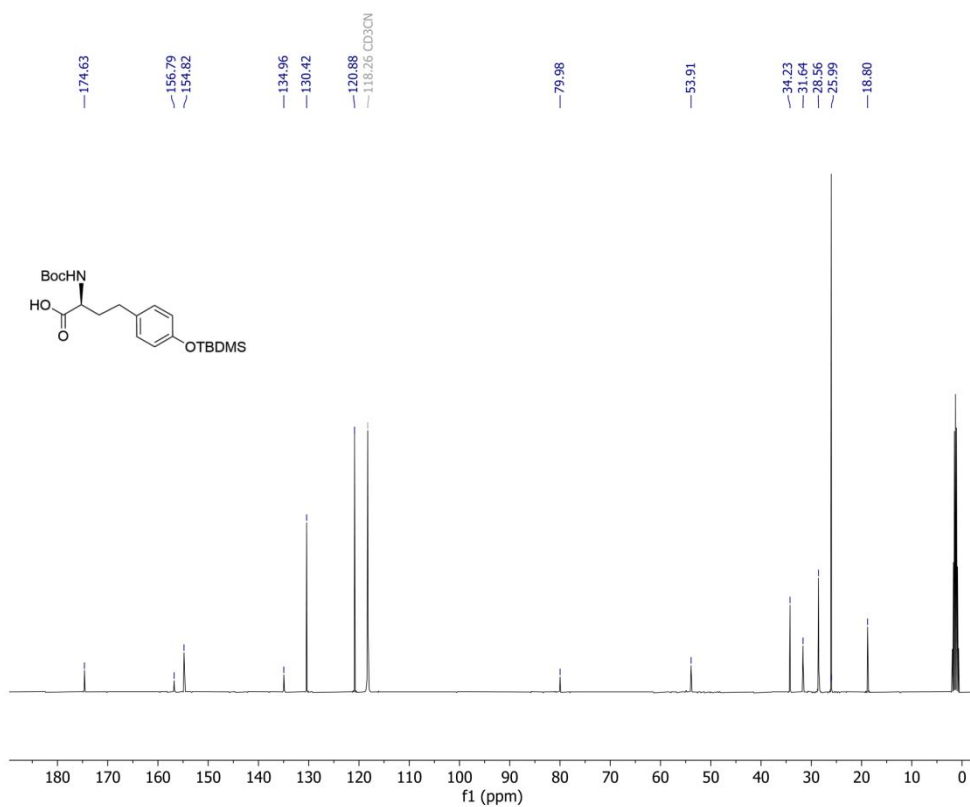**Compound 12: COSY (CD₃CN)**
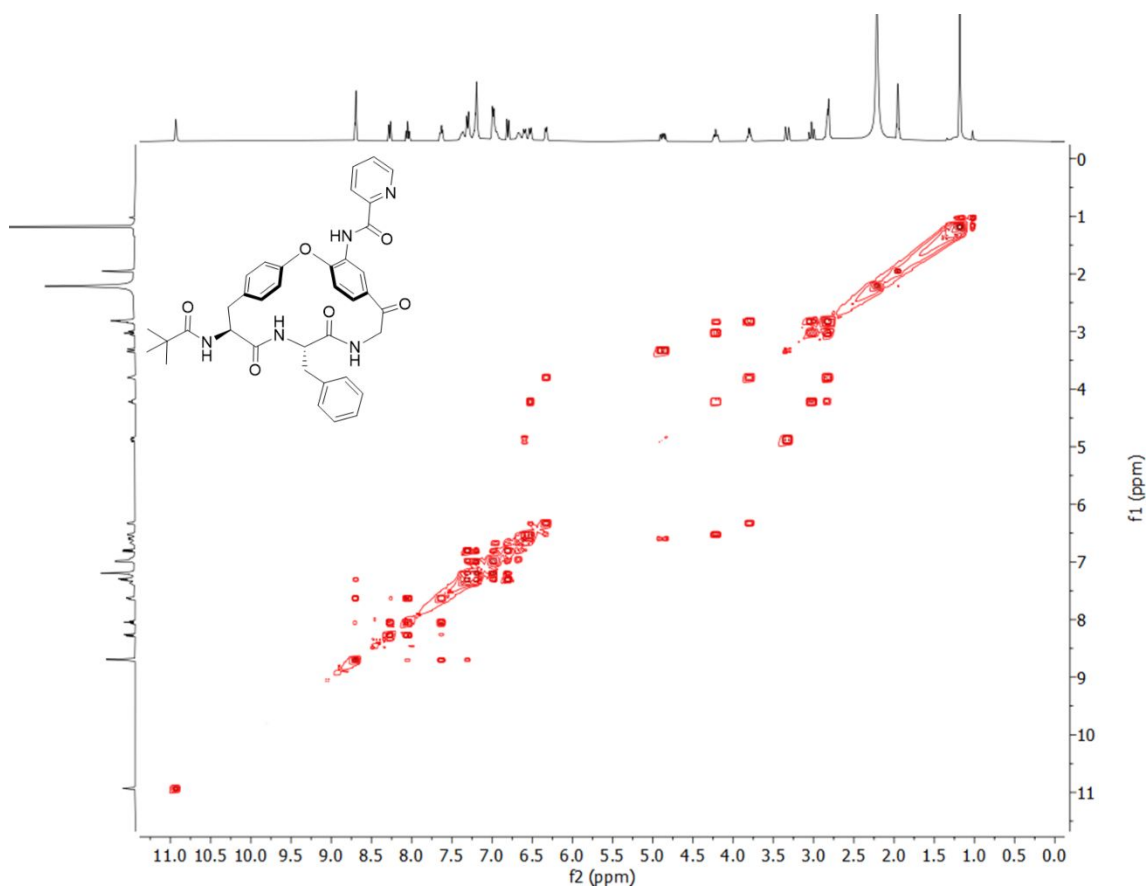
Compound 12: HSQC (CD₃CN)
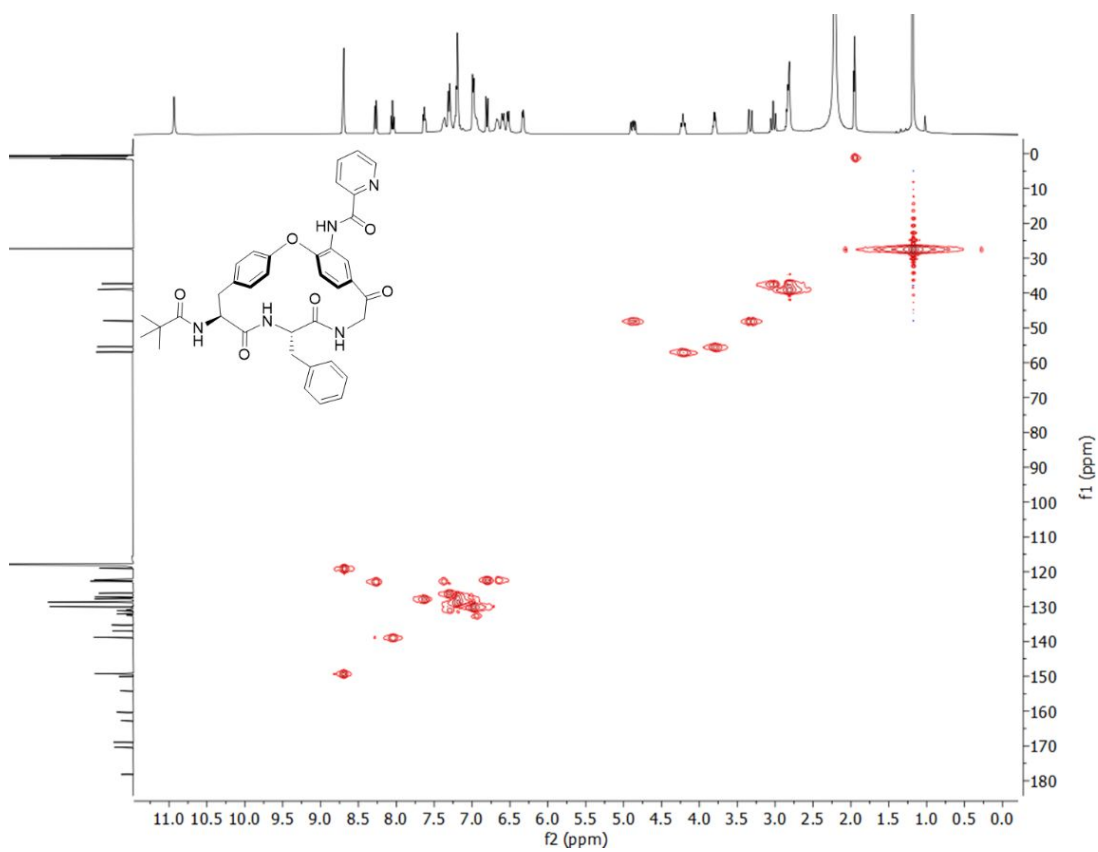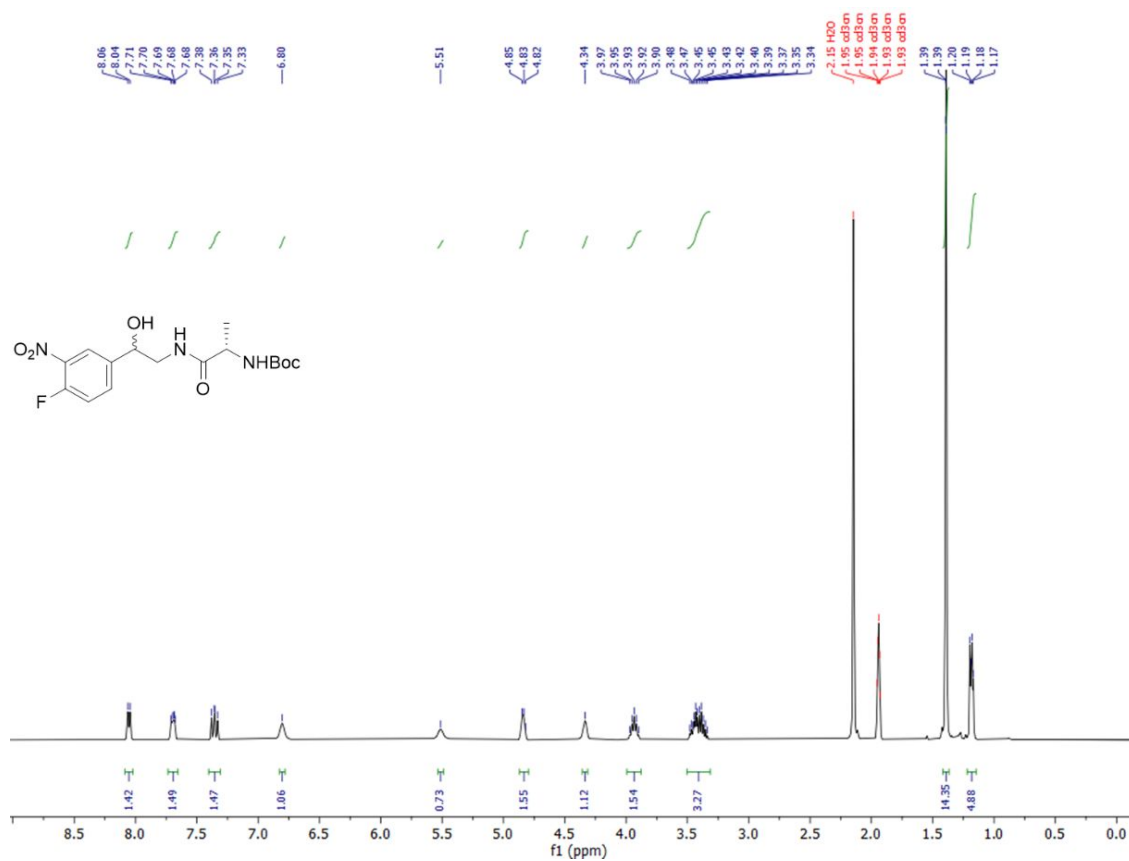
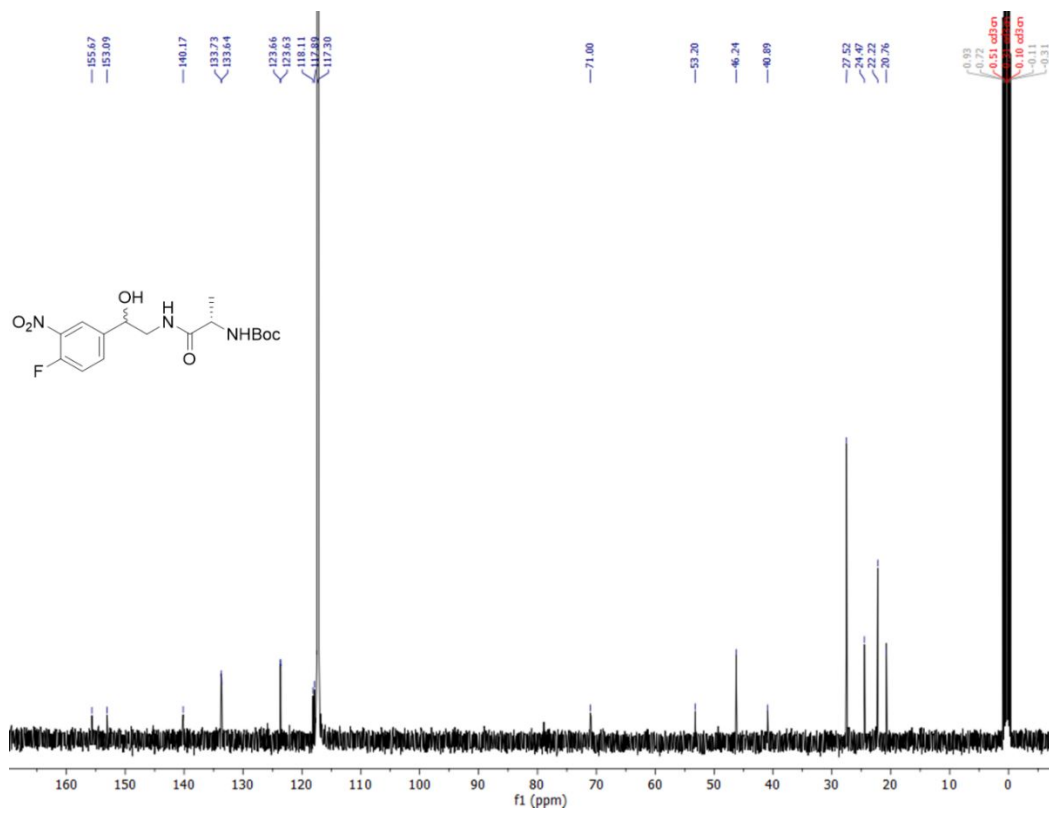# Compound 12: HMBC (CD₃CN)
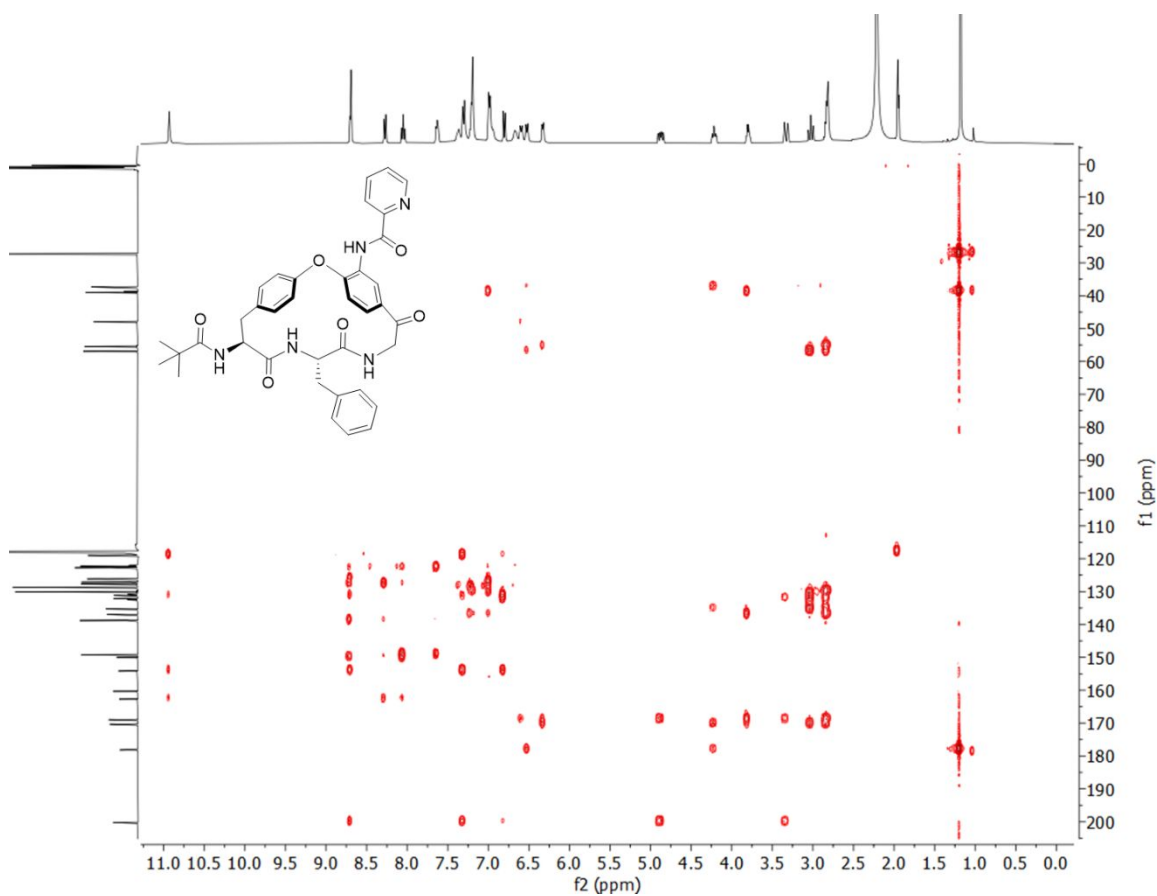
Compound 15: ¹H NMR (CD₃CN, 400 MHz)
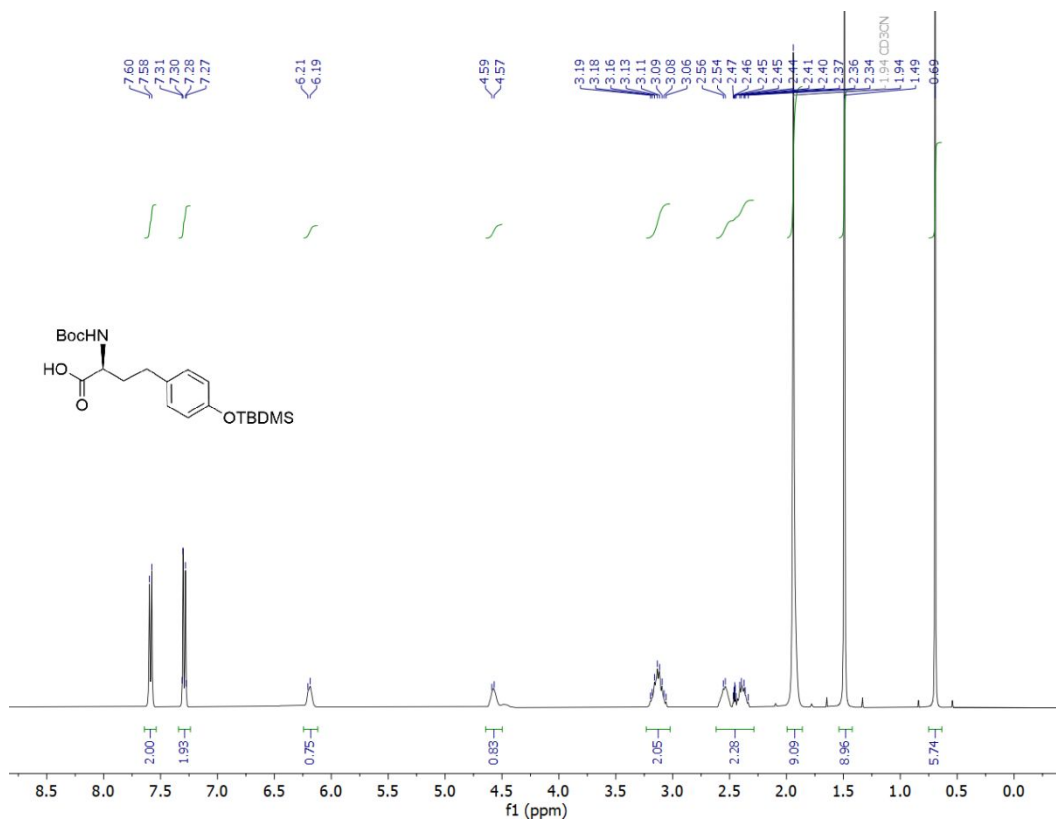
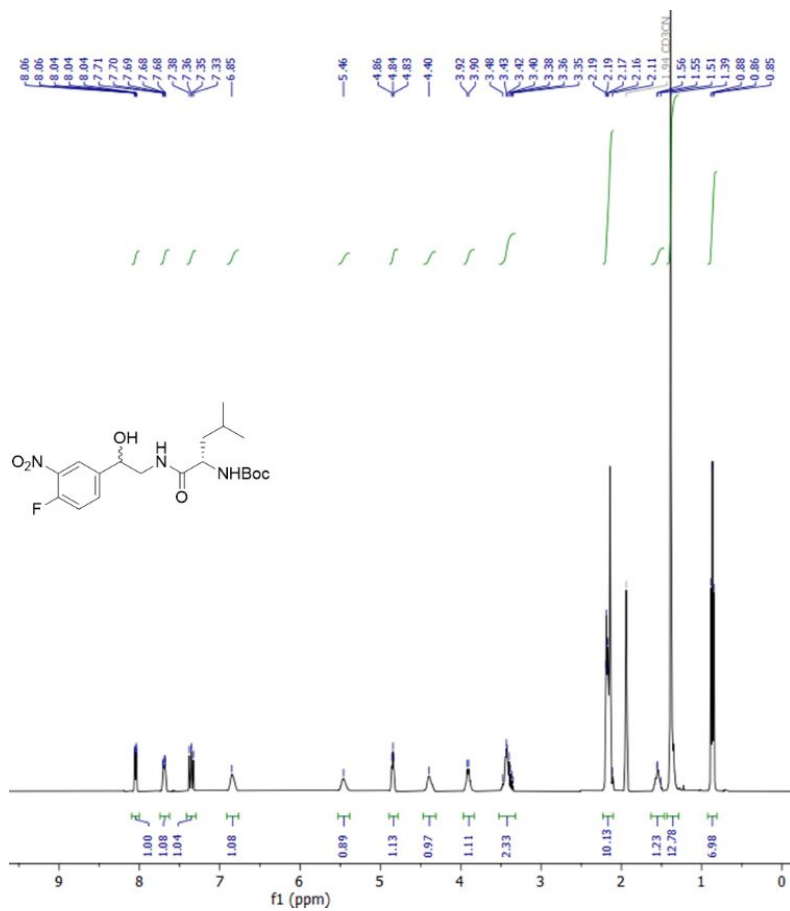**Compound 15: ^{13}C NMR (CD$_3$CN, 100 MHz)**

Compound 16: ^{1}H NMR (CD$_3$CN, 400 MHz)
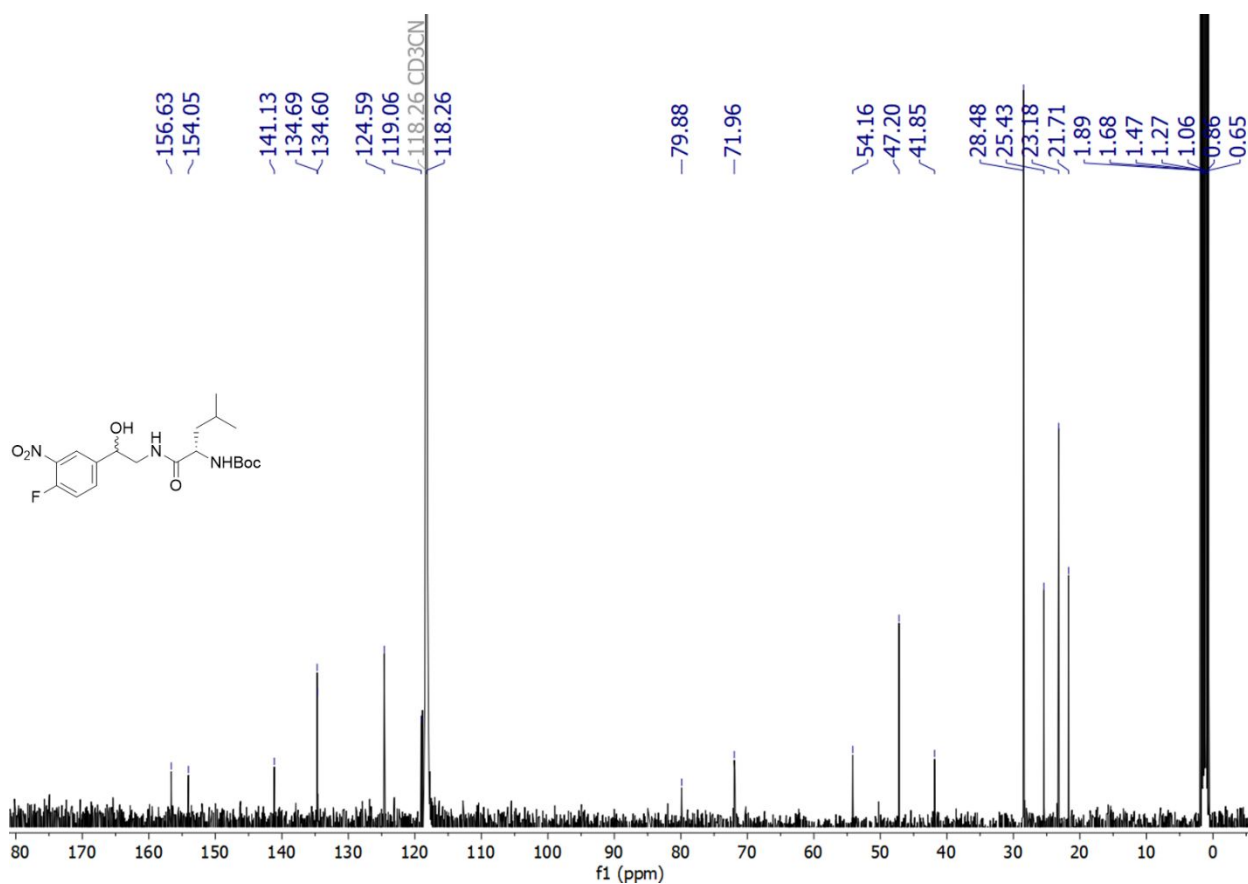
Compound 16: ^{13}C NMR (CD$_3$CN, 100 MHz)

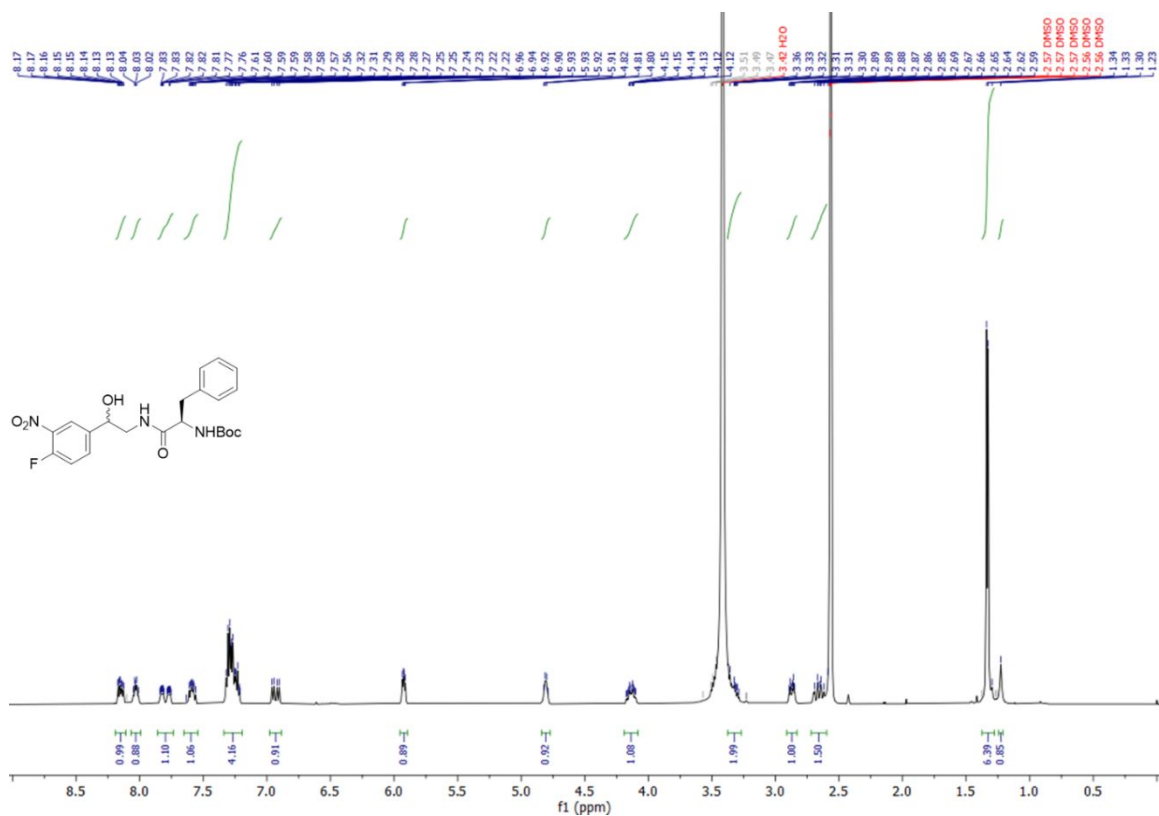**Compound 17: ^{1}H NMR (CD$_3$CN, 400 MHz)**
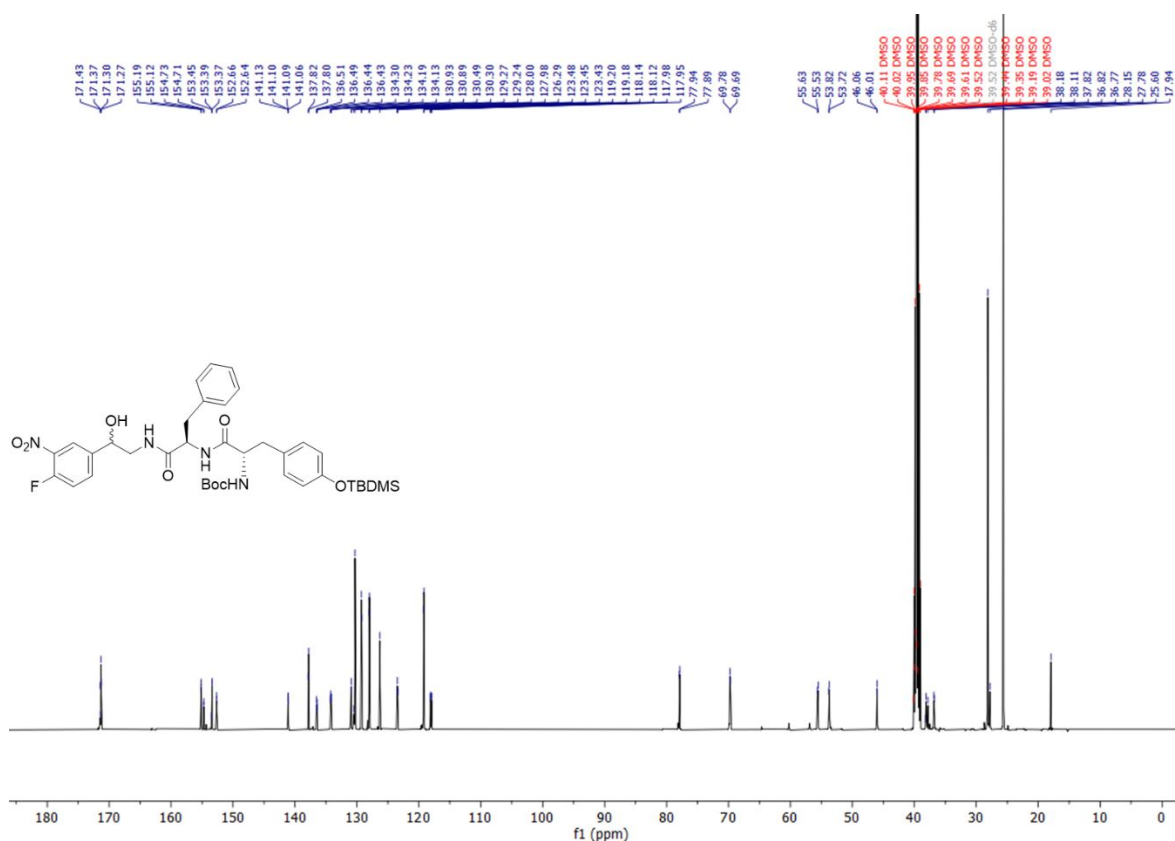
Compound 17: ¹³C NMR (CD₃CN, 100 MHz)

Compound 19: ¹H NMR (DMSO-d₆, 500 MHz)

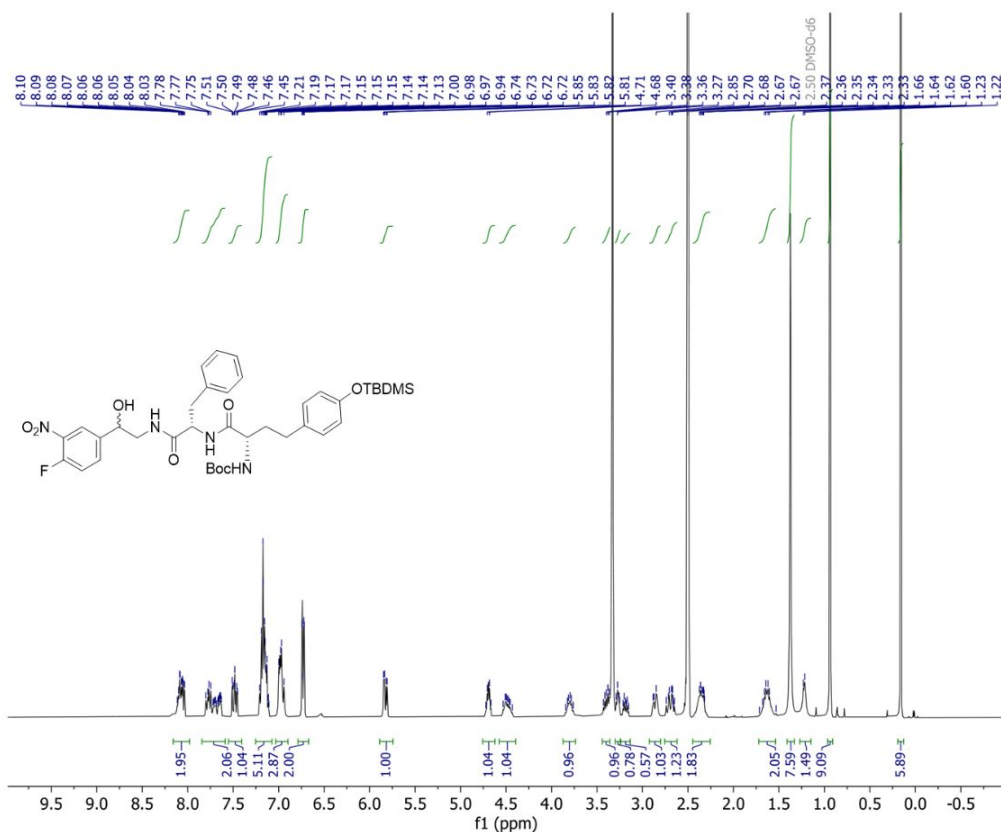**Compound 19: ^{13}C NMR (DMSO-d$_6$, 125 MHz)**

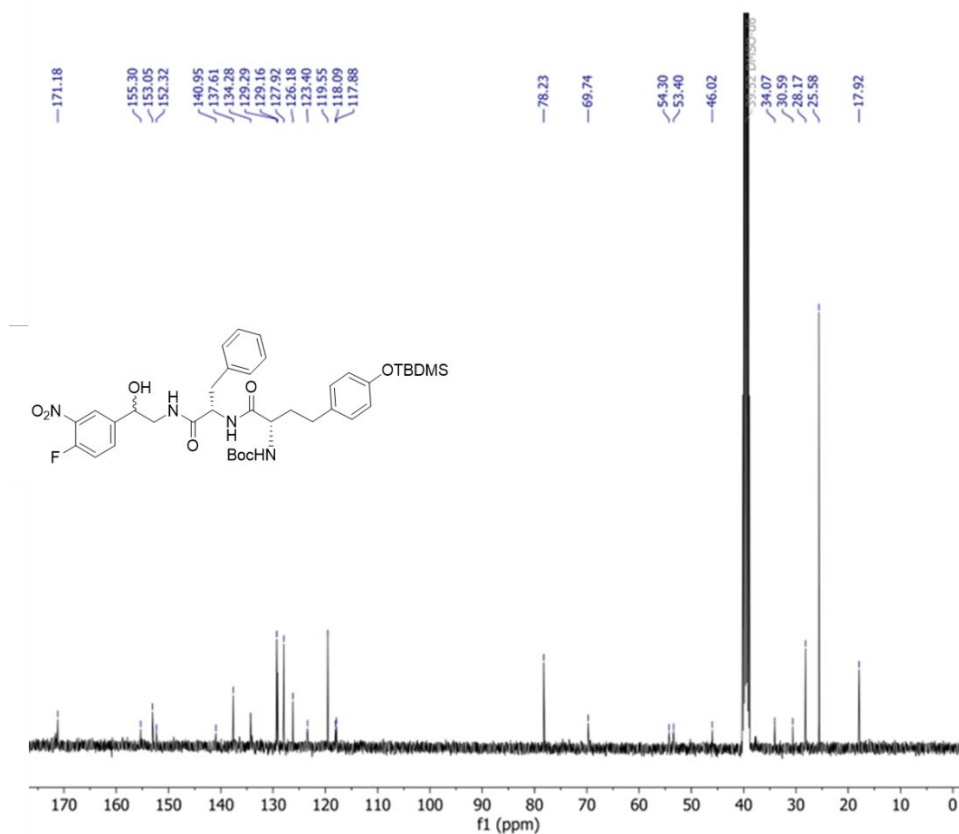**Compound 24: ^{1}H NMR (DMSO-d$_6$, 500 MHz)**

Compound 24: ^{13}C NMR (DMSO-d$_6$, 125 MHz)

Compound 26: ^{1}H NMR (DMSO-d$_6$, 400 Hz)
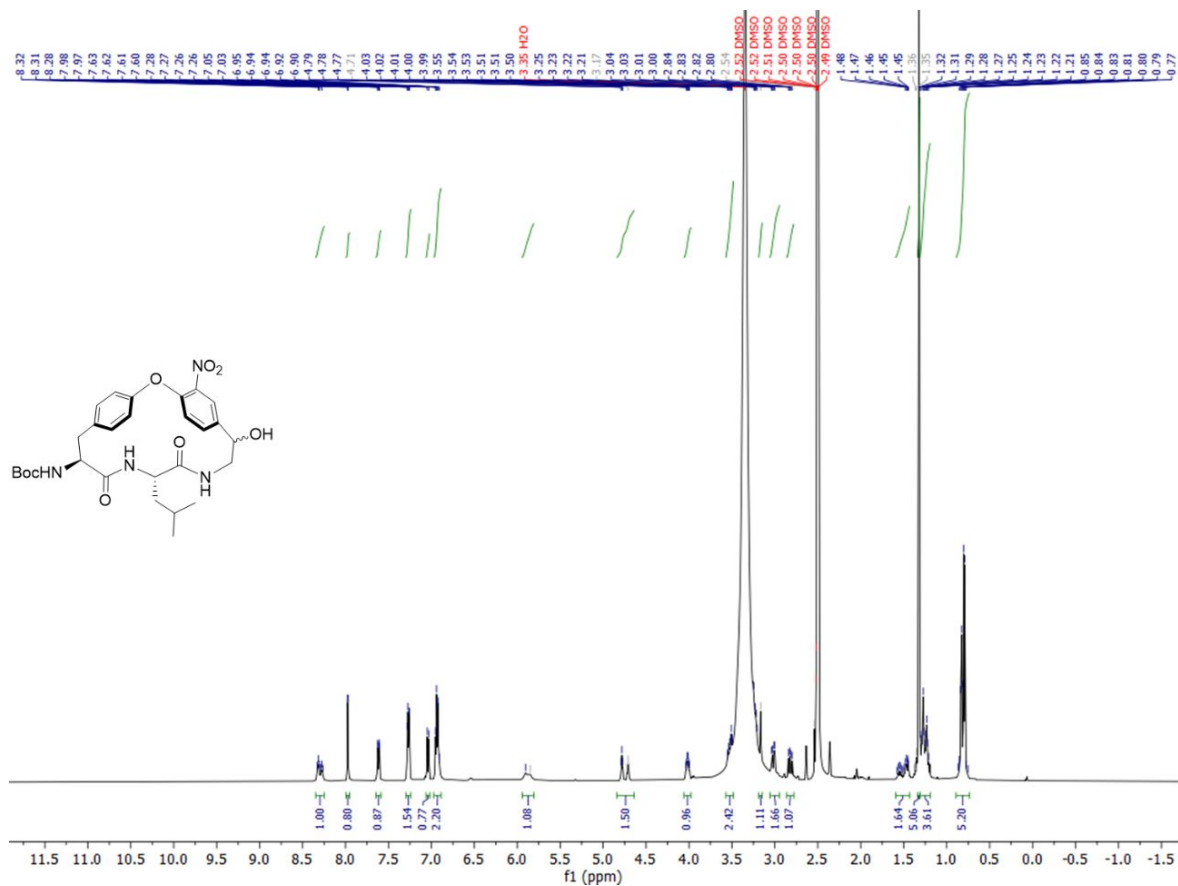
Compound 26: ^{13}C NMR (DMSO-d$_6$, 100 MHz)

Compound 27: ^{1}H NMR (DMSO-d$_6$, 400 MHz)
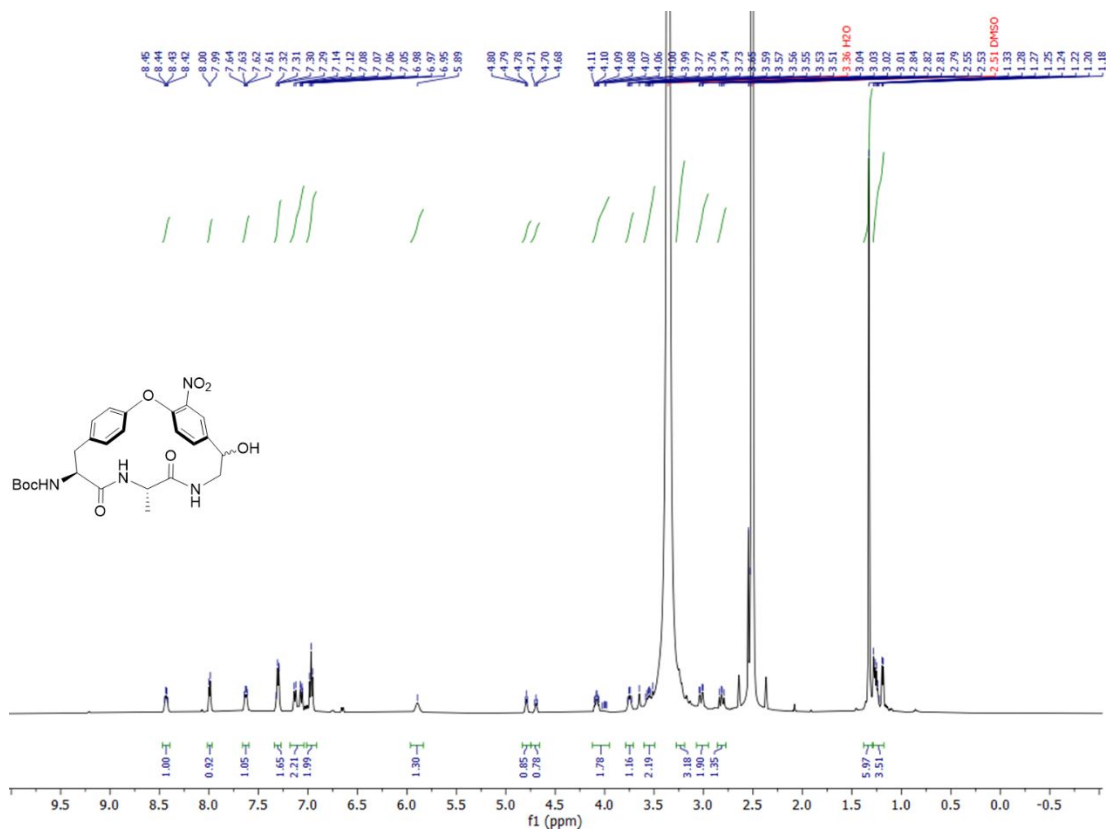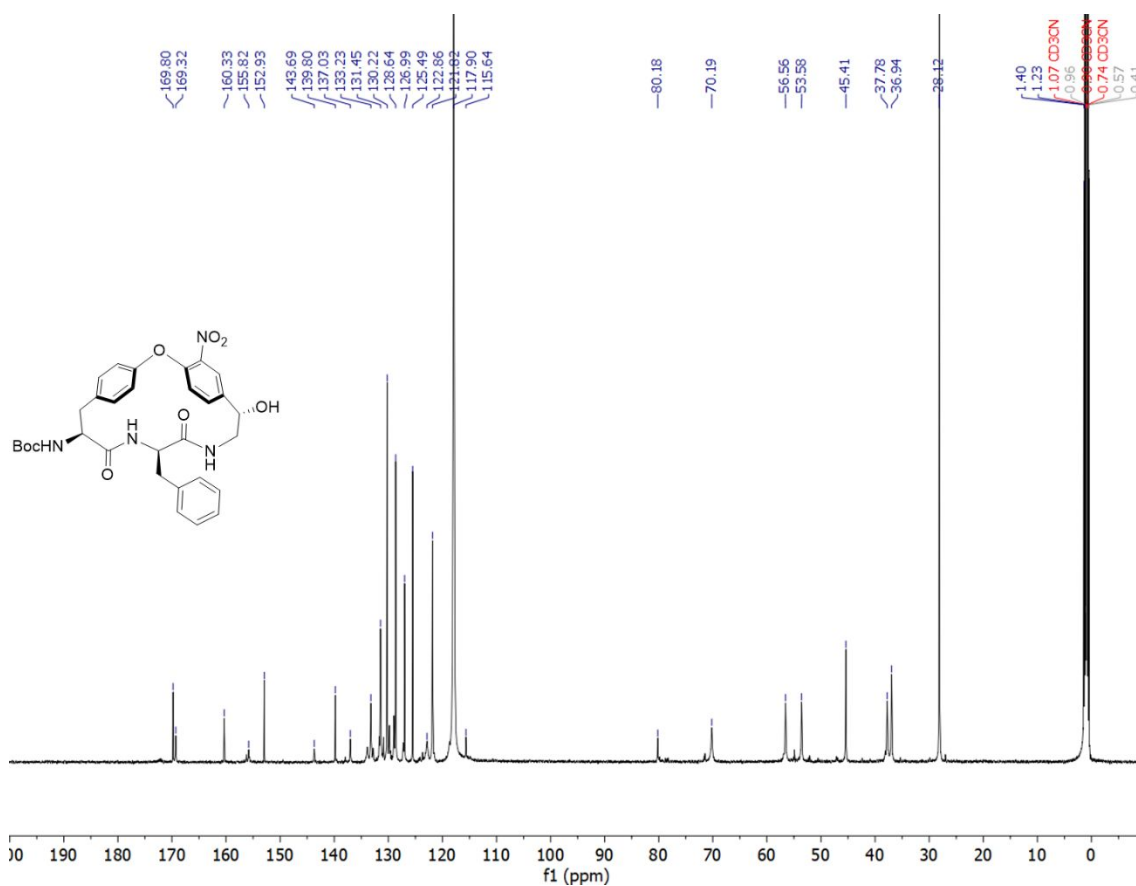
Compound 27: ^{13}C NMR (DMSO-d$_6$, 100 MHz)
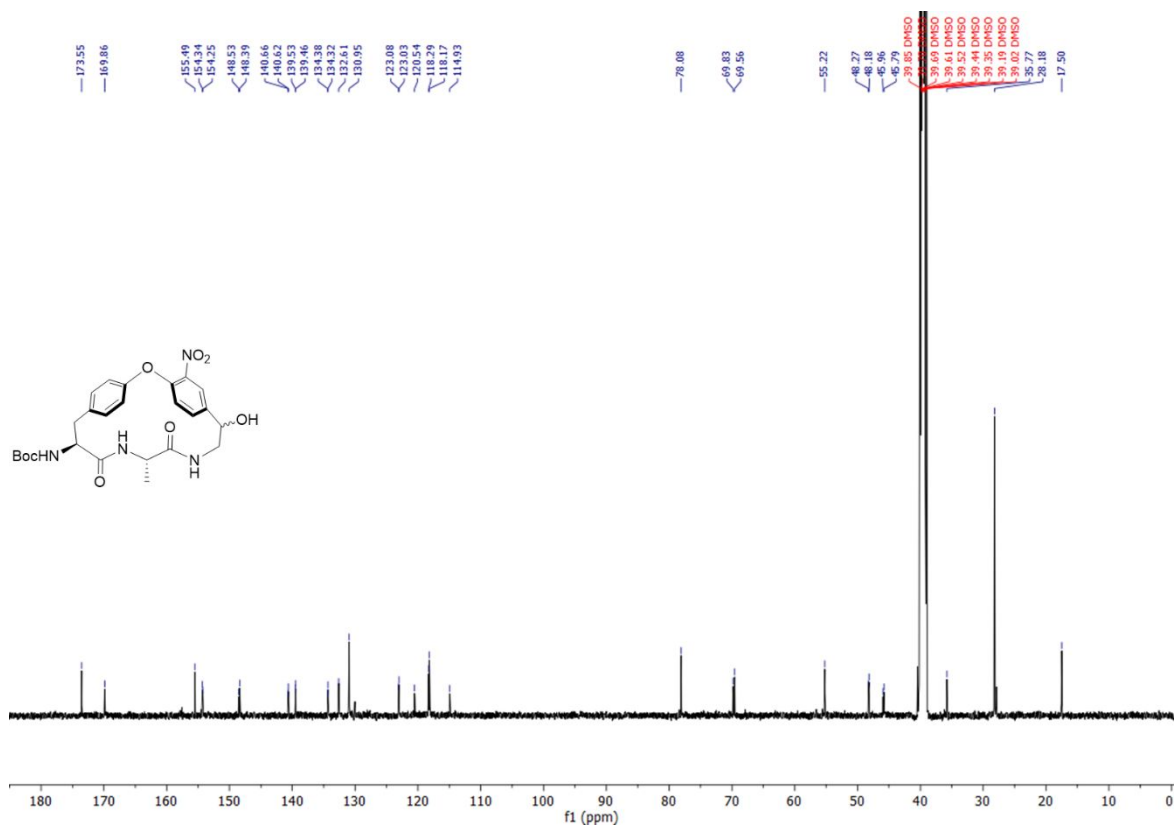
Compound 28: ^{1}H NMR (DMSO-d$_6$, 500 MHz)

Compound 28: ^{13}C NMR (DMSO-d$_6$, 125 MHz)

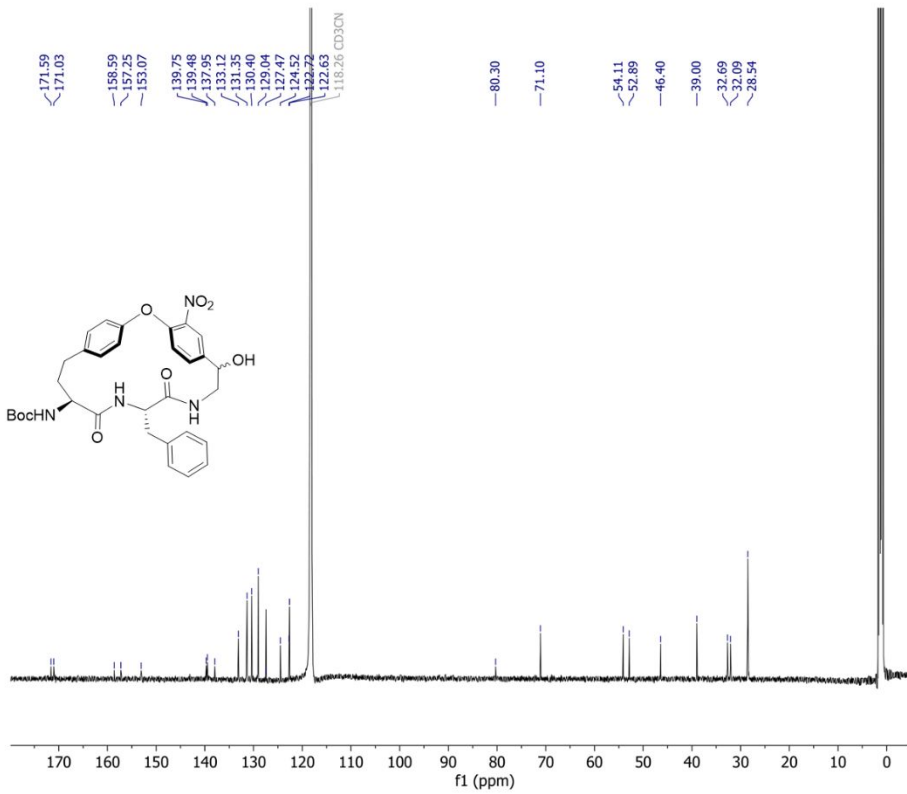**Compound 30: ^{1}H NMR (DMSO-d$_6$, 500 MHz)**

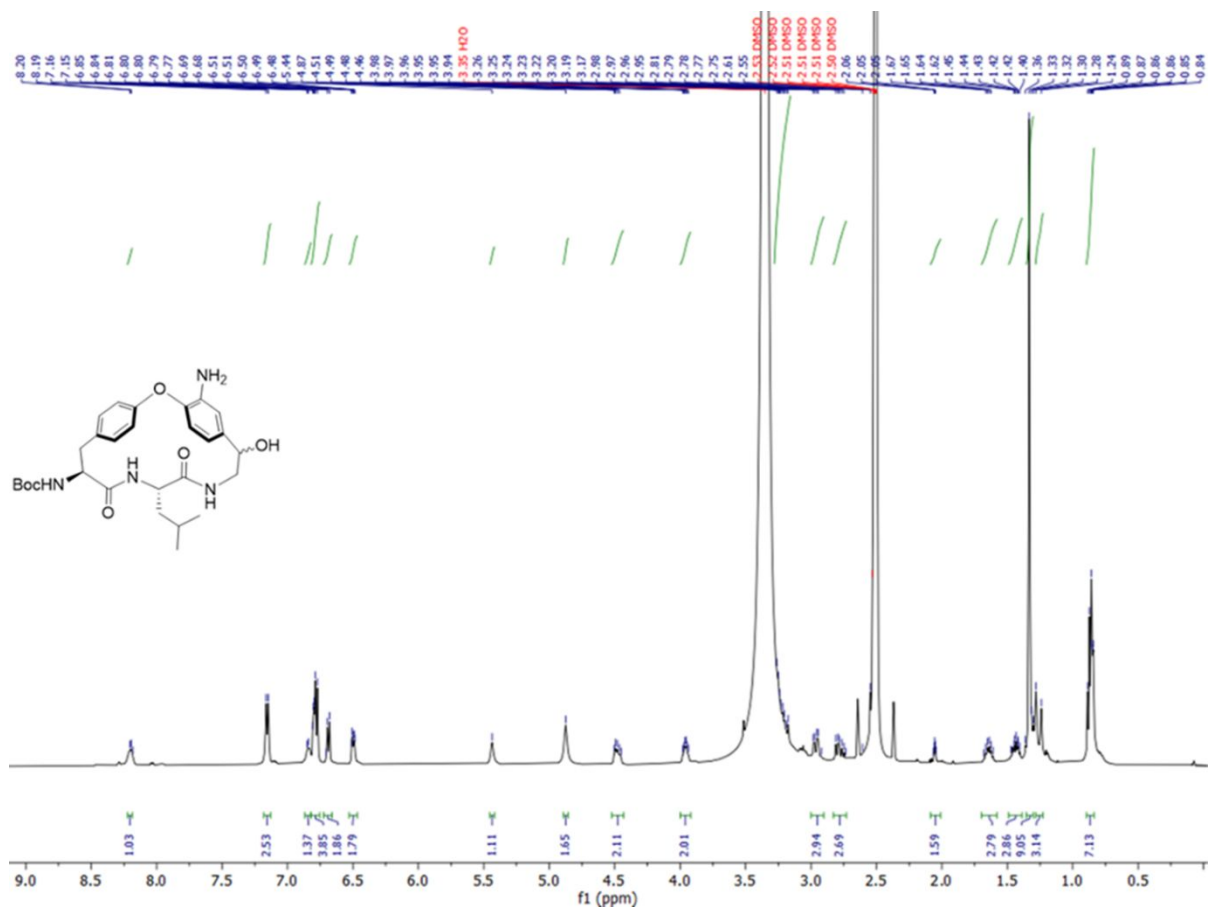**Compound 30: ¹³C NMR (DMSO-d₆, 125 MHz)**
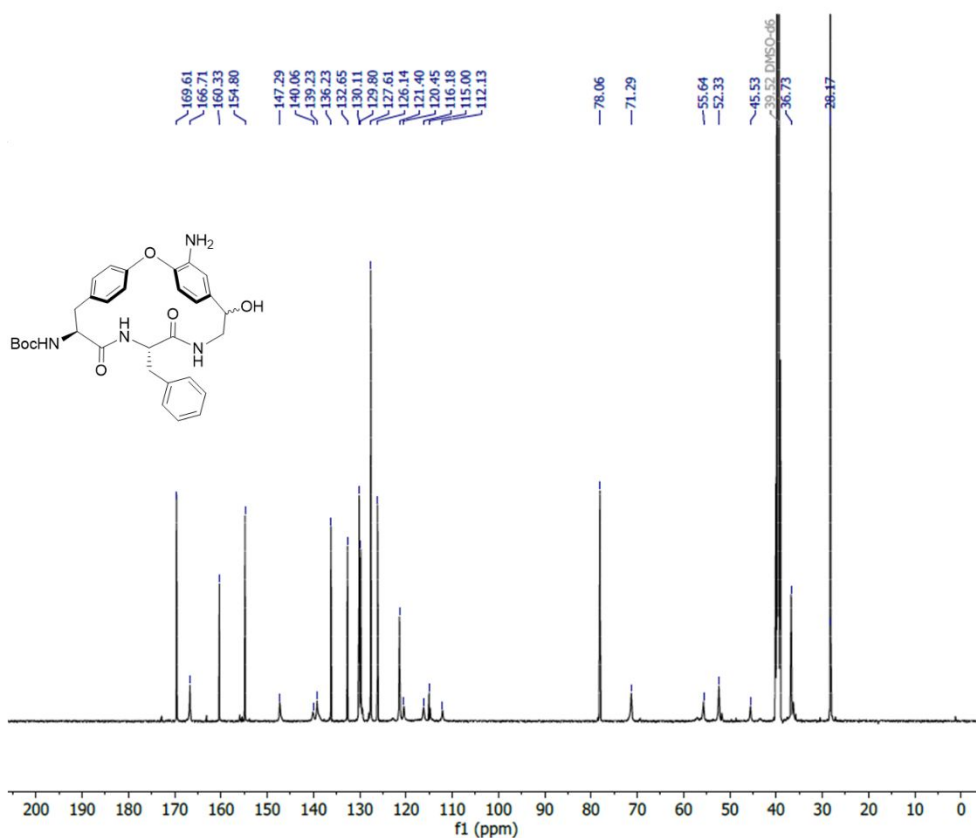

Compound 32: ¹H NMR (CD₃CN, 500 MHz)
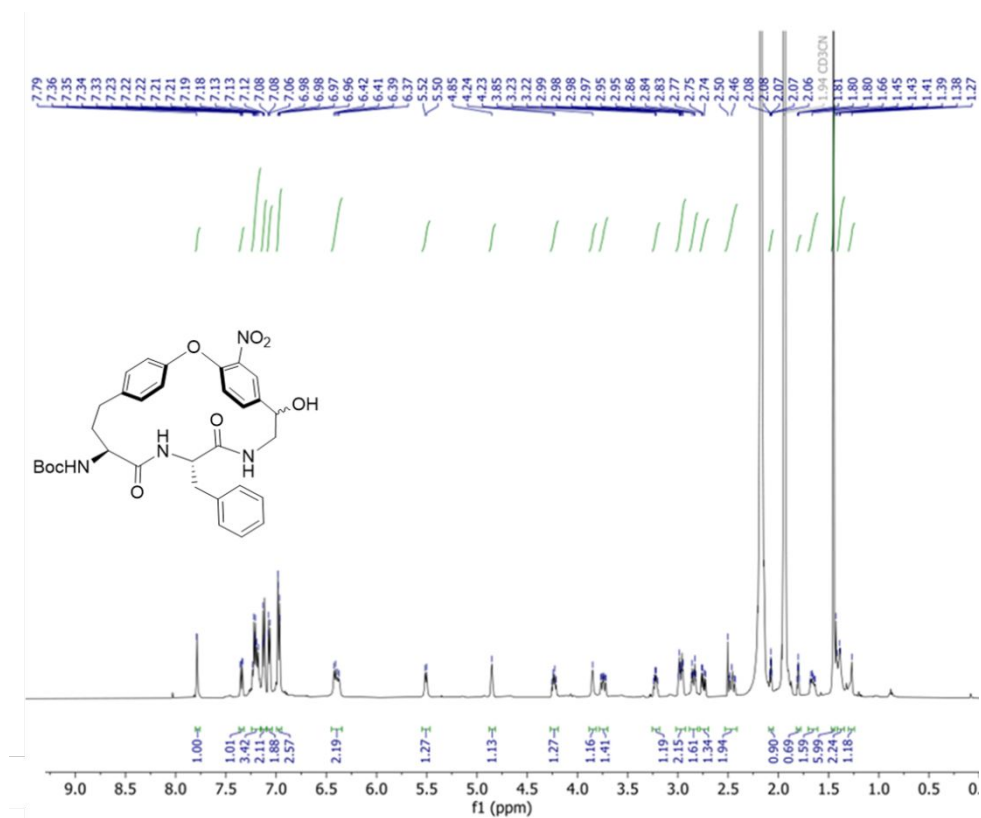
Compound 32: ^{13}C NMR (CD$_3$CN, 125 MHz)

Compound 34: ^{1}H NMR (DMSO-d$_6$, 500 MHz)

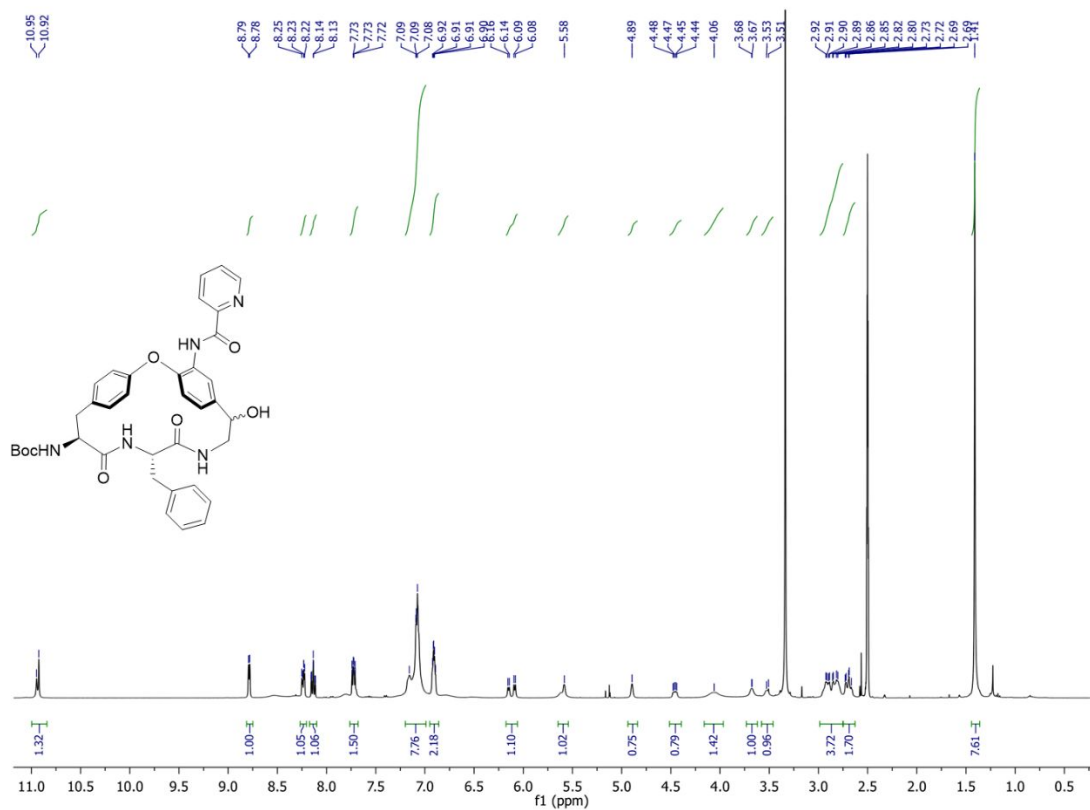**Compound 34: ^{13}C NMR (DMSO-d$_6$, 125 MHz)**

Compound 35: ^{1}H NMR (DMSO-d$_6$, 500 MHz)

Compound 35: ^{13}C NMR (DMSO-d$_6$, 500 MHz)

Compound 41: ^{1}H NMR (CDCl$_3$, 400 MHz)

Compound 41: ^{13}C NMR (CDCl$_3$, 100 MHz)

Compound 44: ^{1}H NMR (DMSO-d$_6$, 500 MHz)

Compound 44: ^{13}C NMR (DMSO-d$_6$, 125 MHz)
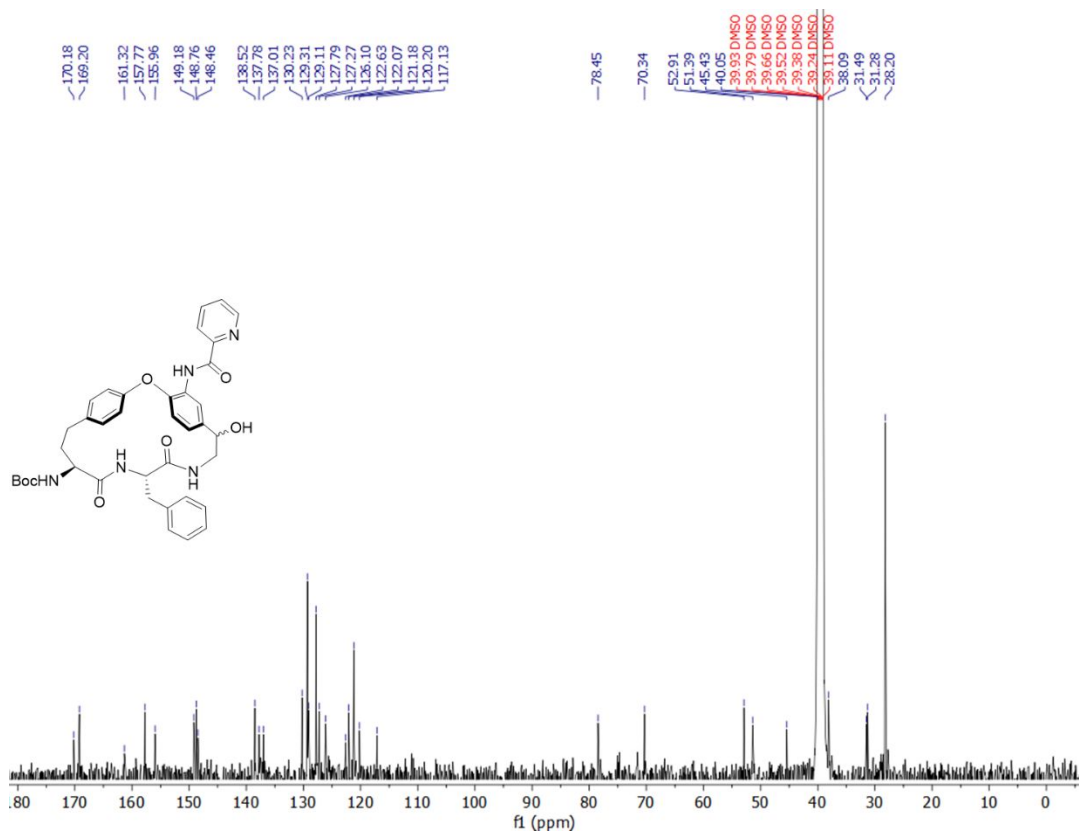
Compound 52: ^{1}H NMR (DMSO-d$_6$, 400 MHz)

Compound 52: ^{13}C NMR (DMSO-d$_6$, 100 MHz)

Compound 53: ^{1}H NMR (CD$_3$CN, 400 MHz)
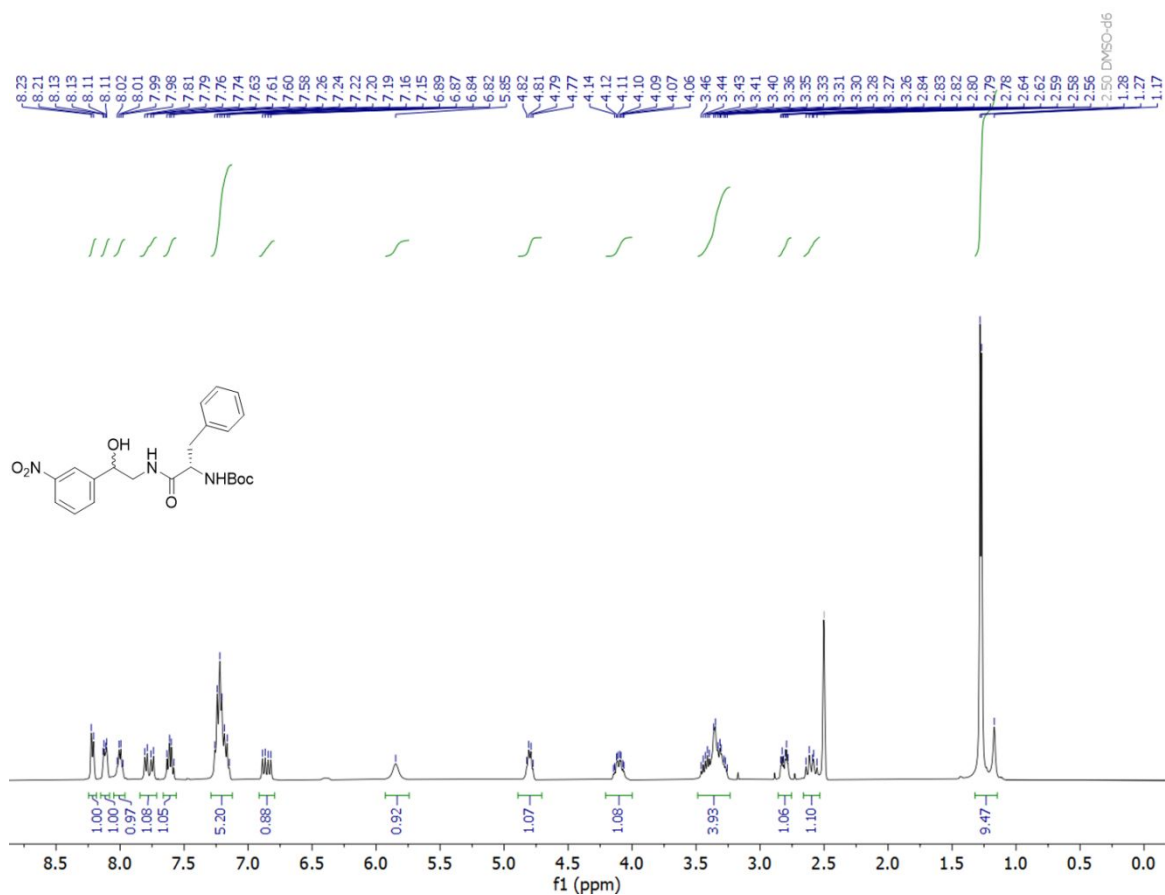
Compound 53: ^{13}C NMR (CD$_3$CN, 100 MHz)
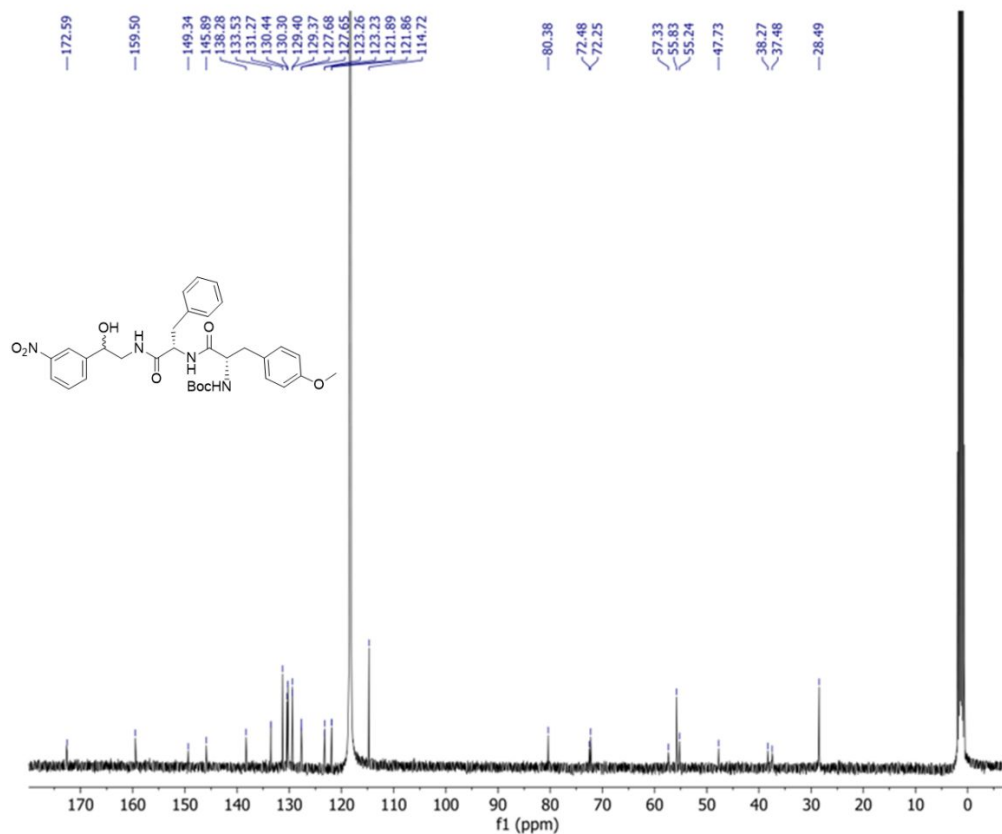
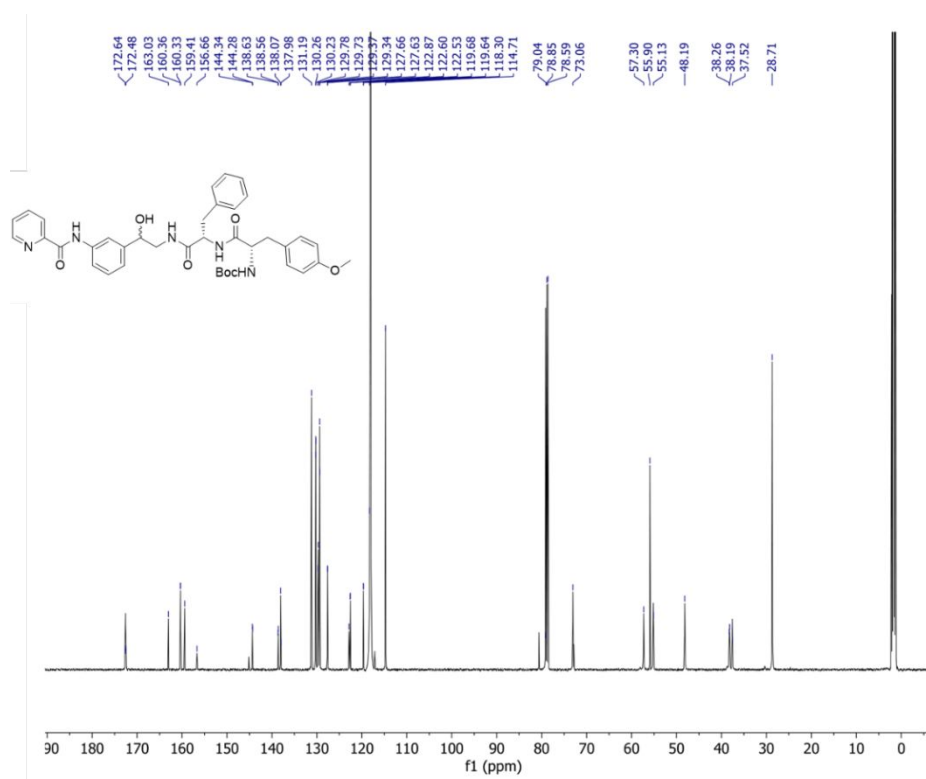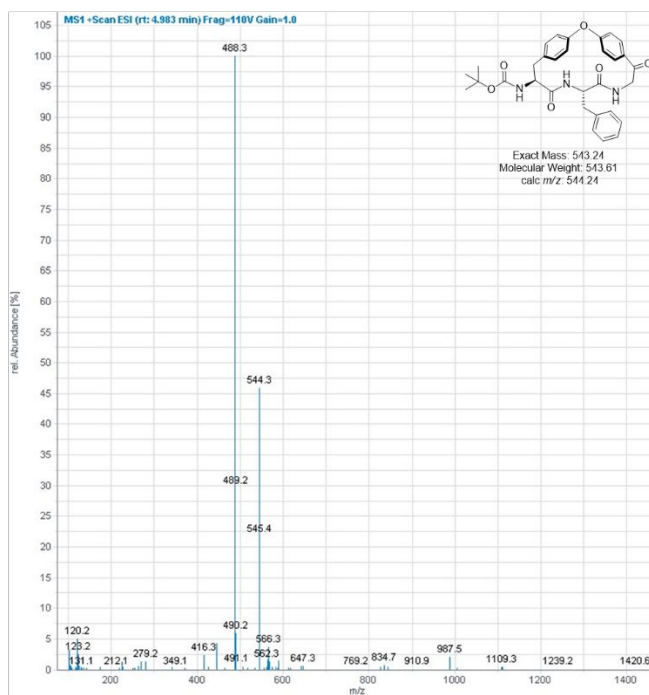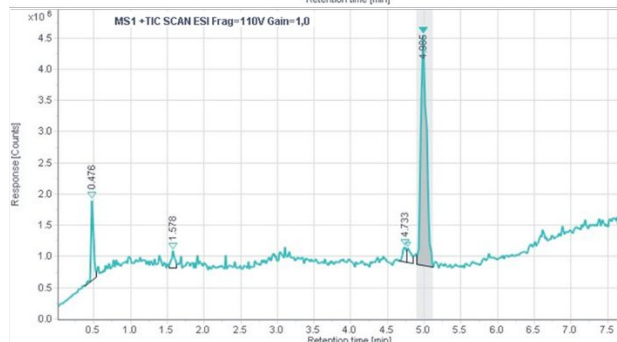**Compound 54: ^{1}H NMR (CD$_3$CN, 500 MHz)**
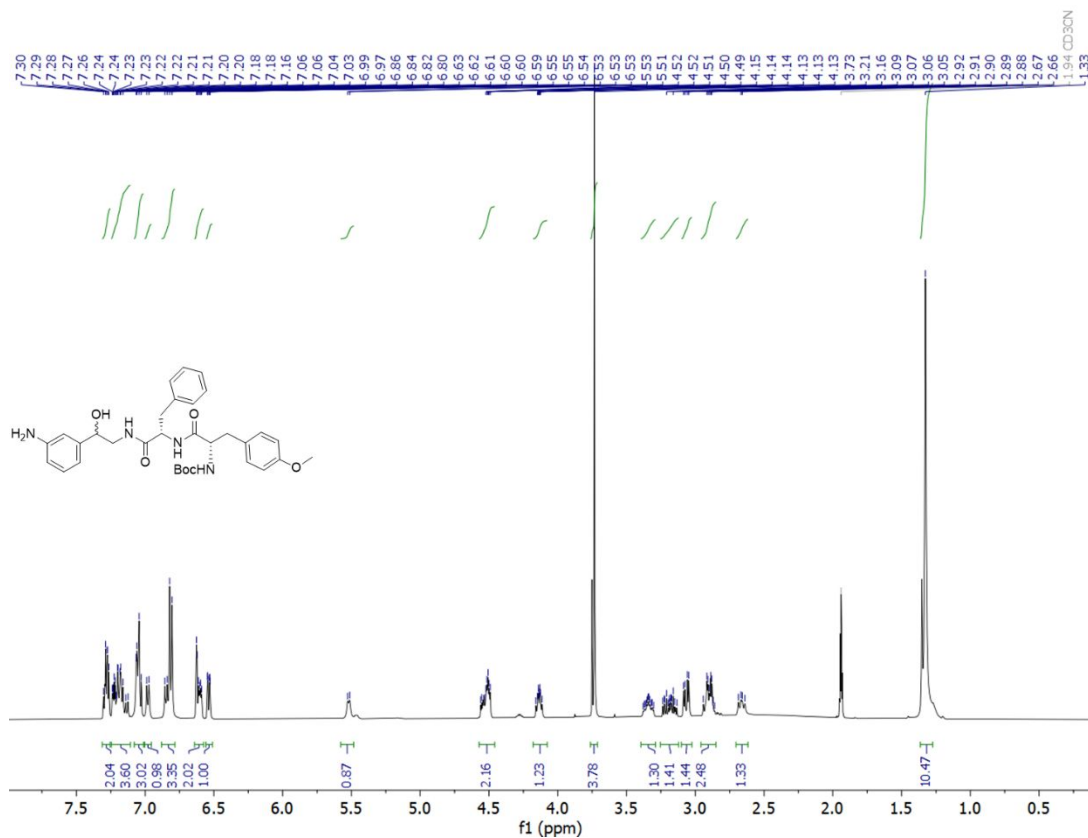
Compound 54: ^{13}C NMR (CD$_3$CN, 125 MHz)
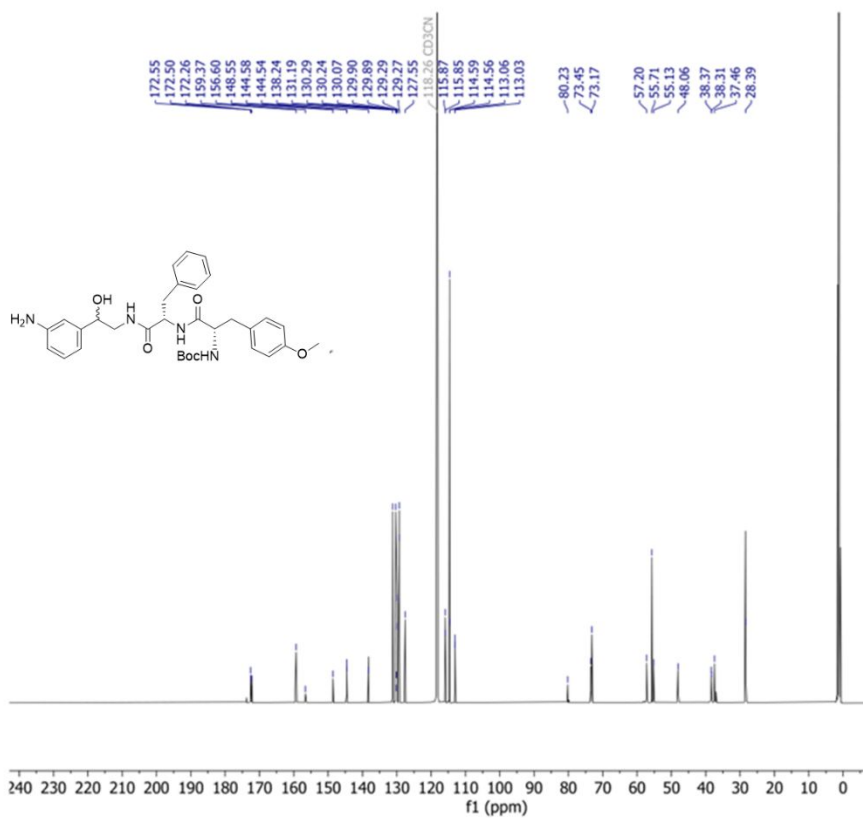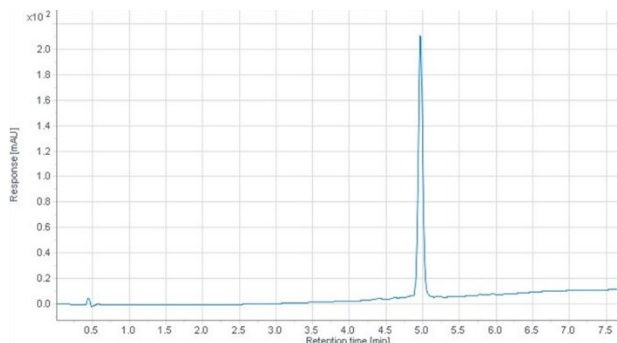

Compound 55: ^{1}H NMR (CD$_3$CN, 400 MHz)
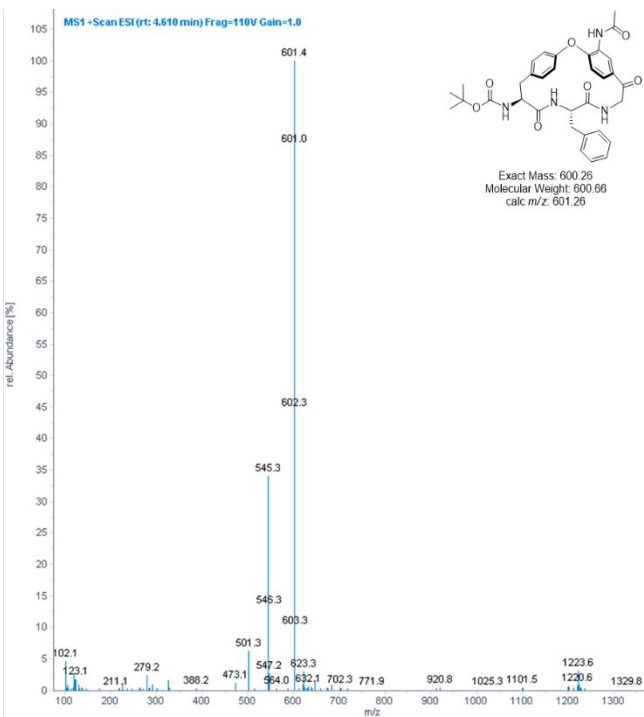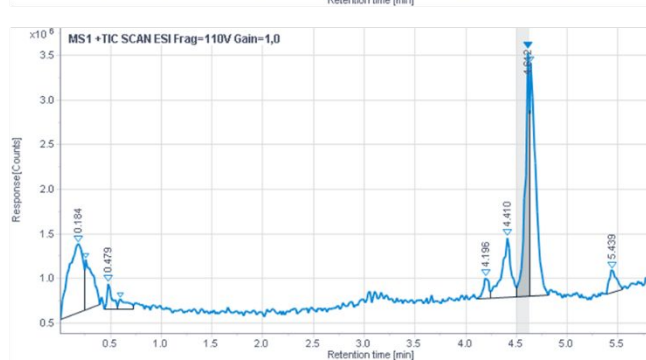

S50
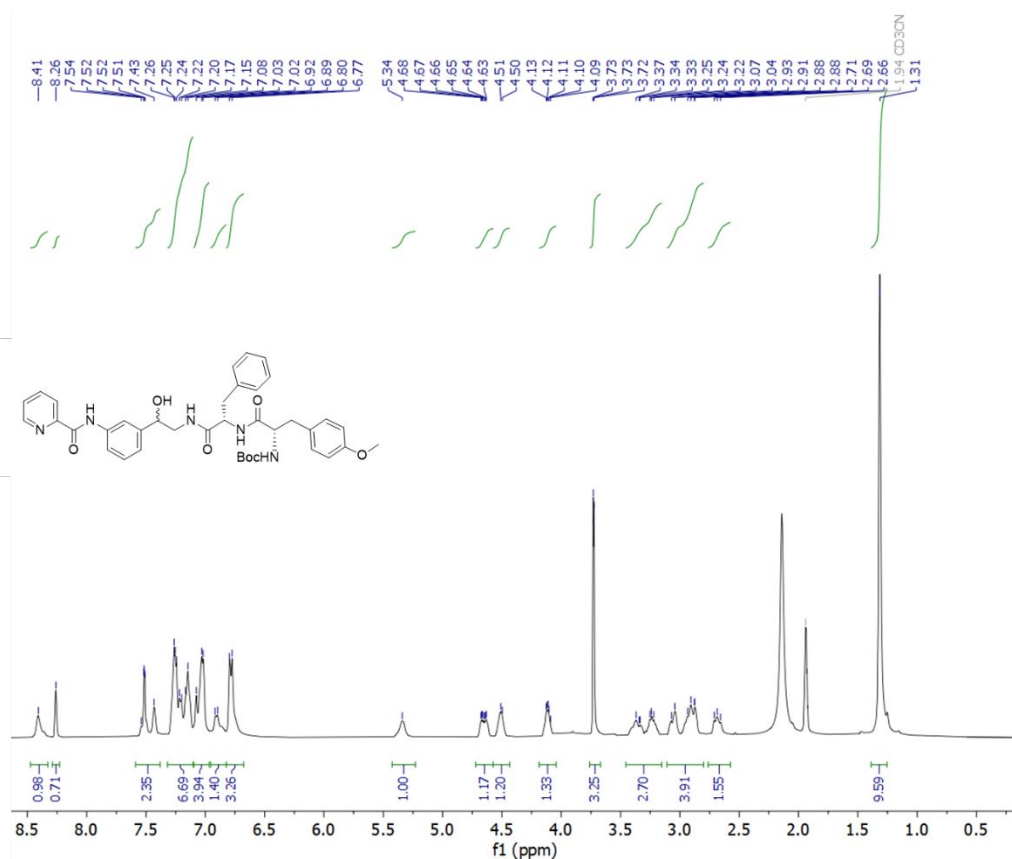
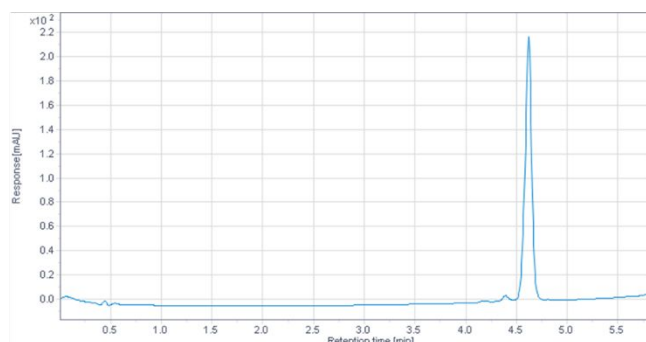**Compound 55: ¹³C NMR (CD₃CN, 100 MHz)**

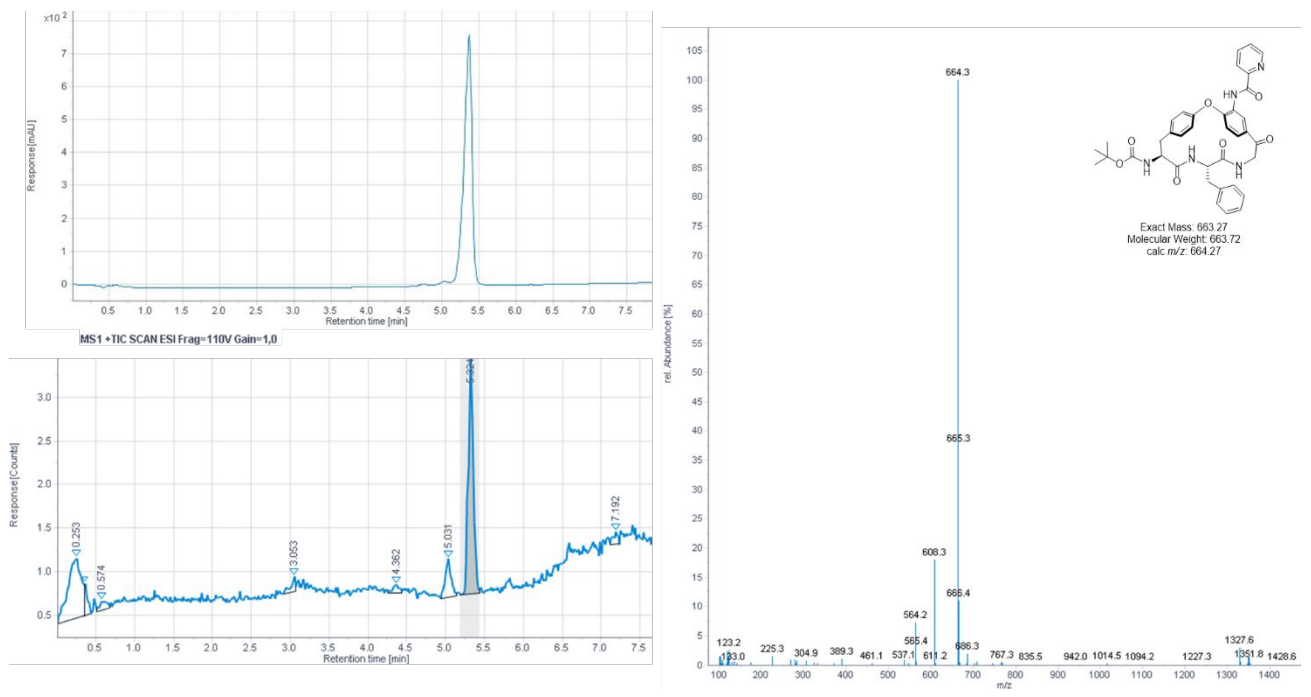# HPLC CHROMATOGRAMS AND MASS SPECTRA

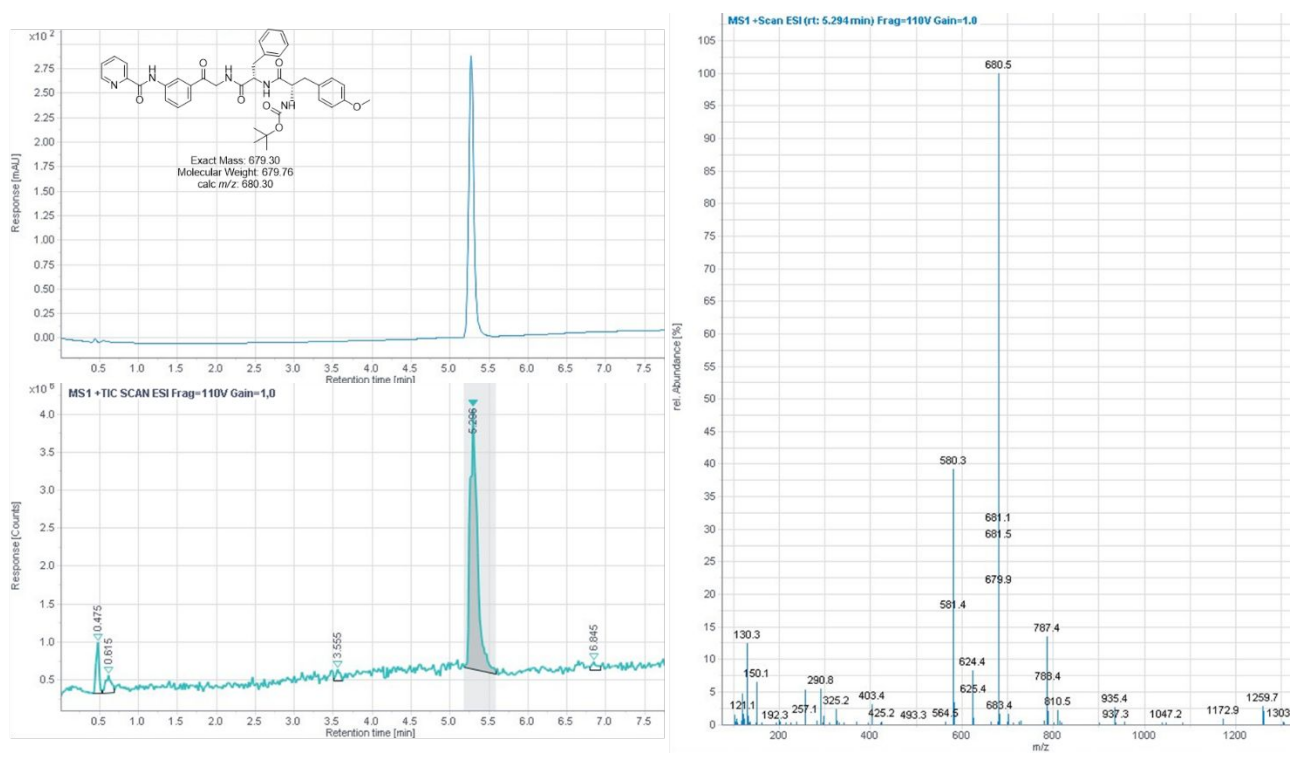## LC-MS after purification by HPLC: Compound 1

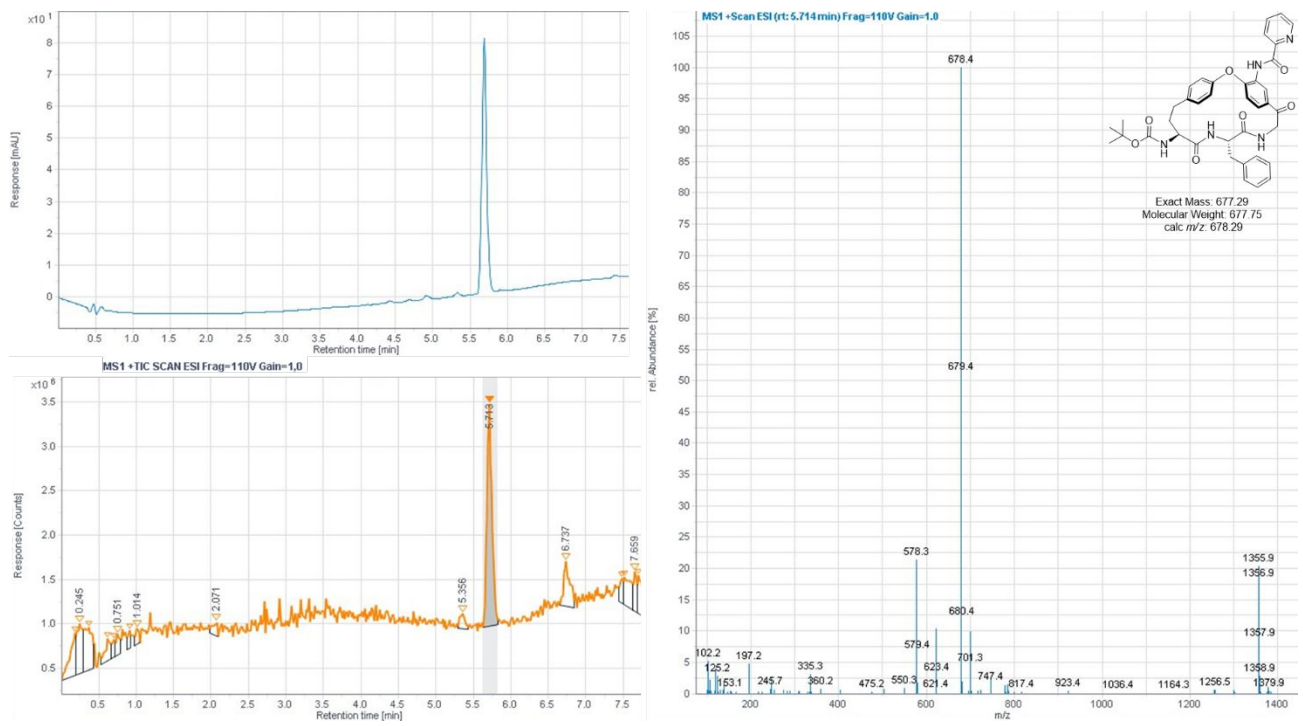## LC-MS after purification by HPLC: Compound 2

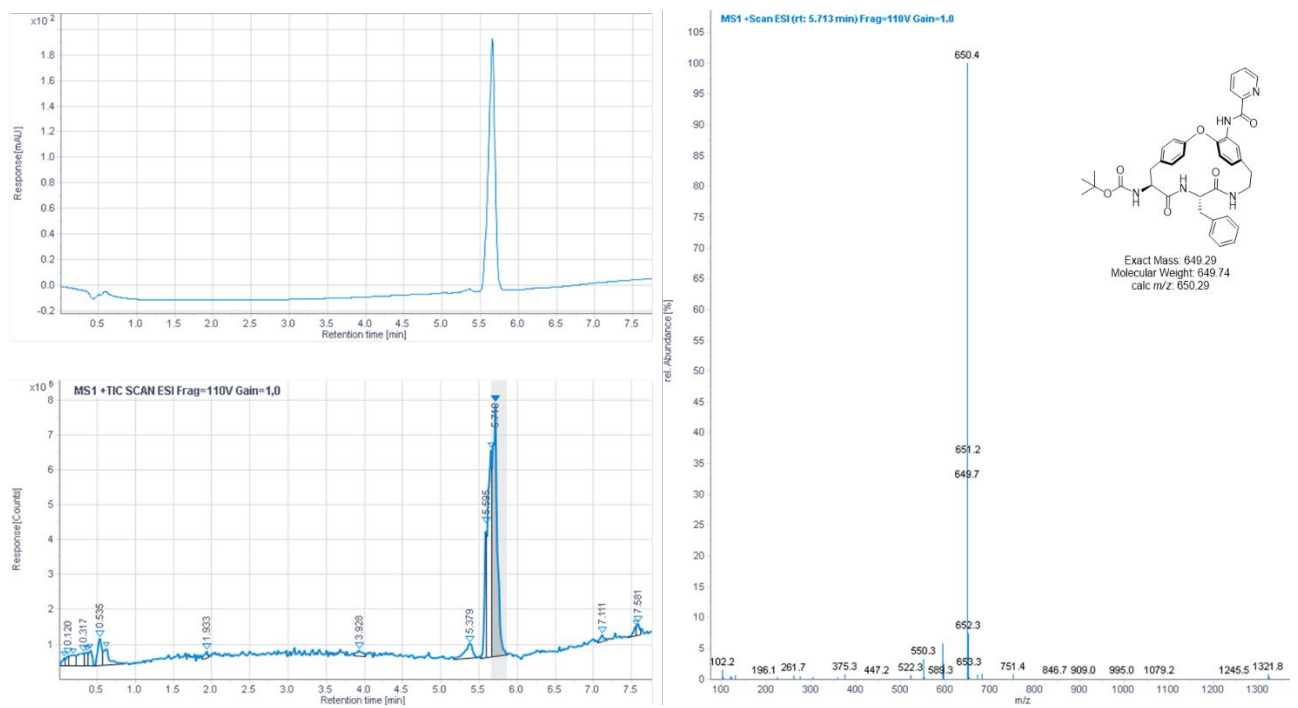**LC-MS after purification by HPLC purification: Compound 3**

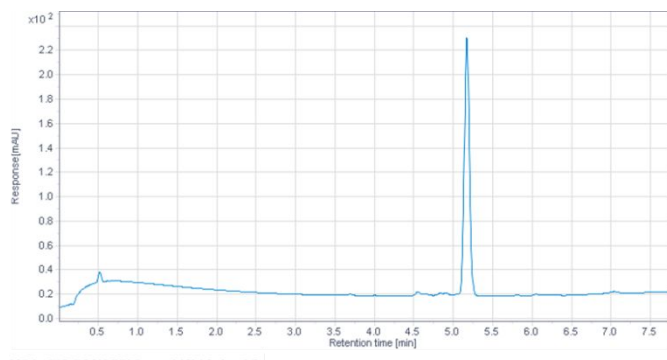**LC-MS after purification by HPLC: Compound 4**
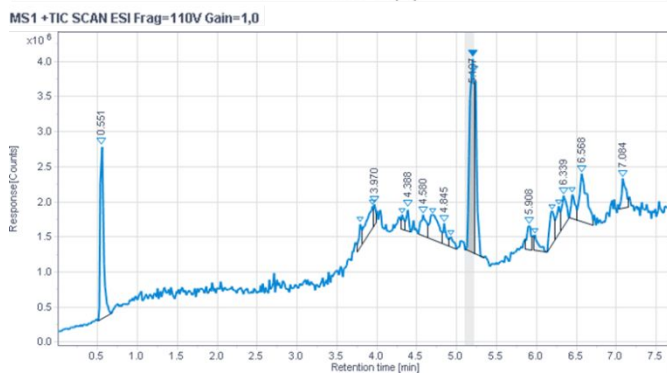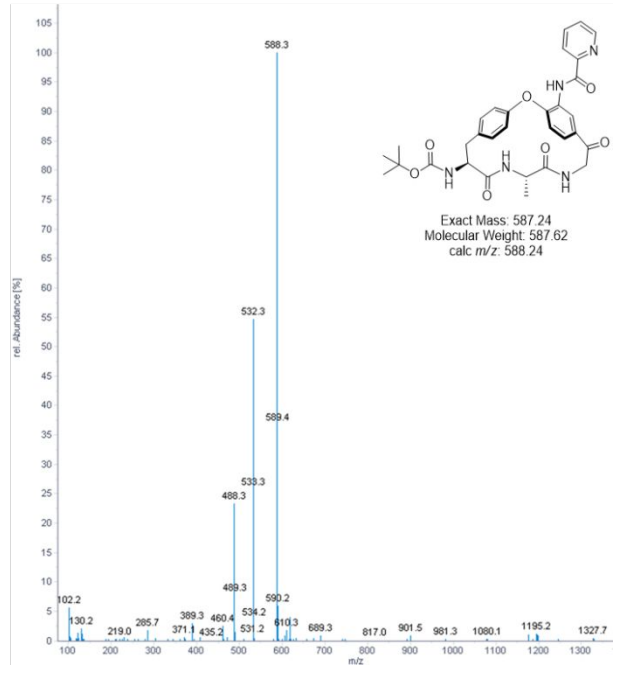
LC-MS after purification by HPLC: Compound 5
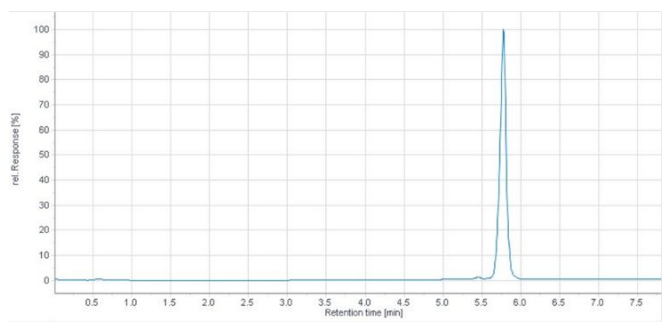

LC-MS after purification by HPLC: Compound 6

LC-MS after purification by HPLC: Compound 7

MS1 +Scan ESI (rt: 5.201 min) Frag=110V Gain=1.0

Exact Mass: 587.24
Molecular Weight: 587.62
calc *m/z*: 588.24

MS1 +TIC SCAN ESI Frag=110V Gain=1,0

LC-MS after purification by HPLC: Compound 8

MS1 +Scan ESI (rt: 5.838 min) Frag=110V Gain=1.0

Exact Mass: 663.27
Molecular Weight: 663.72
calc *m/z*: 664.27

MS1 +TIC SCAN ESI Frag=110V Gain=1,0

LC-MS after purification by HPLC: Compound 9

LC-MS after purification by HPLC: Compound 10
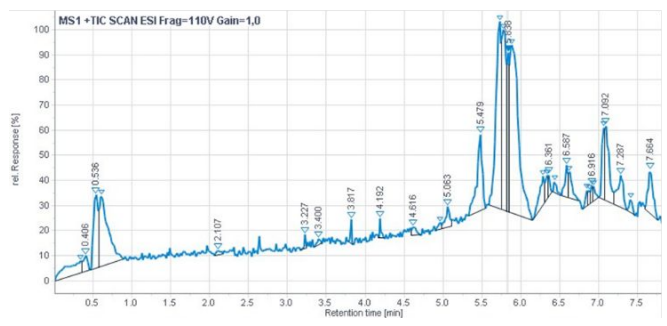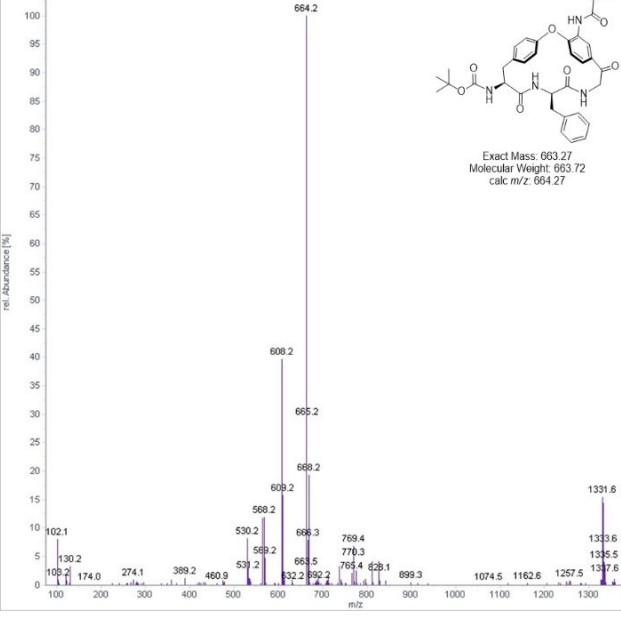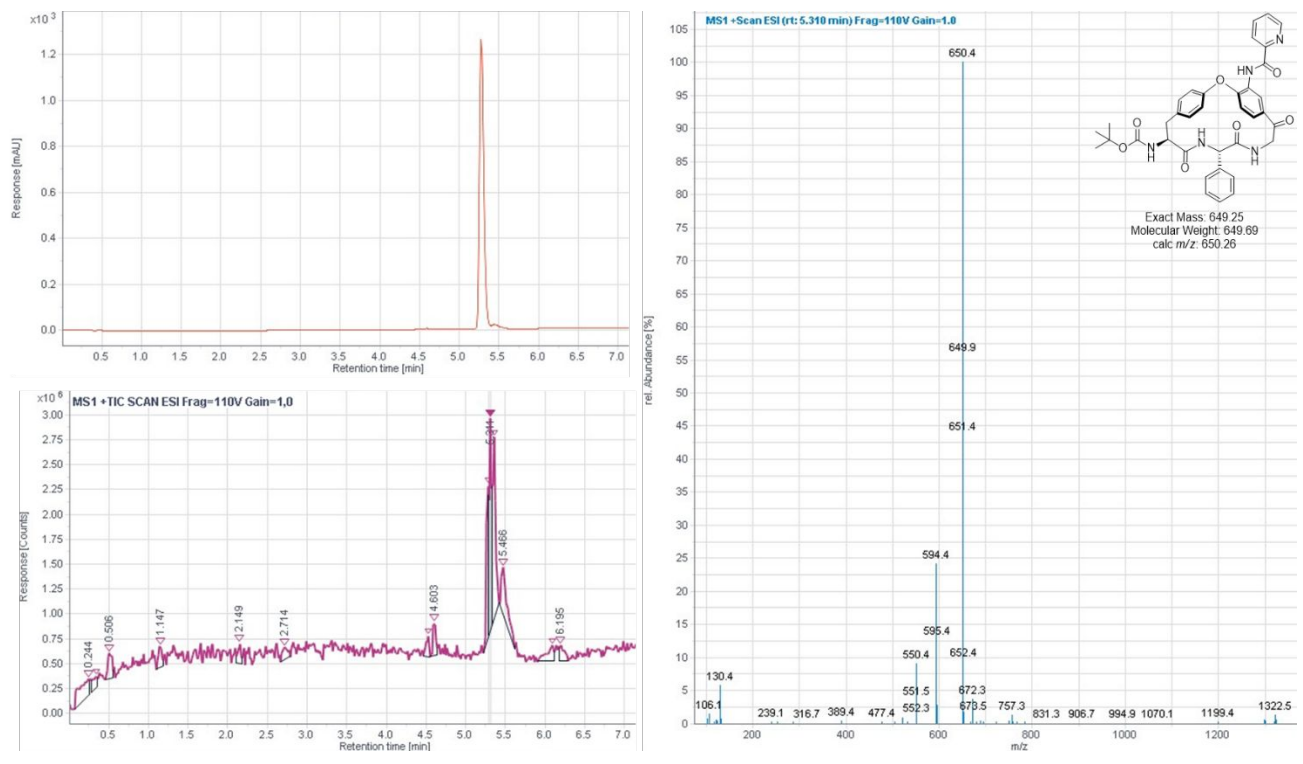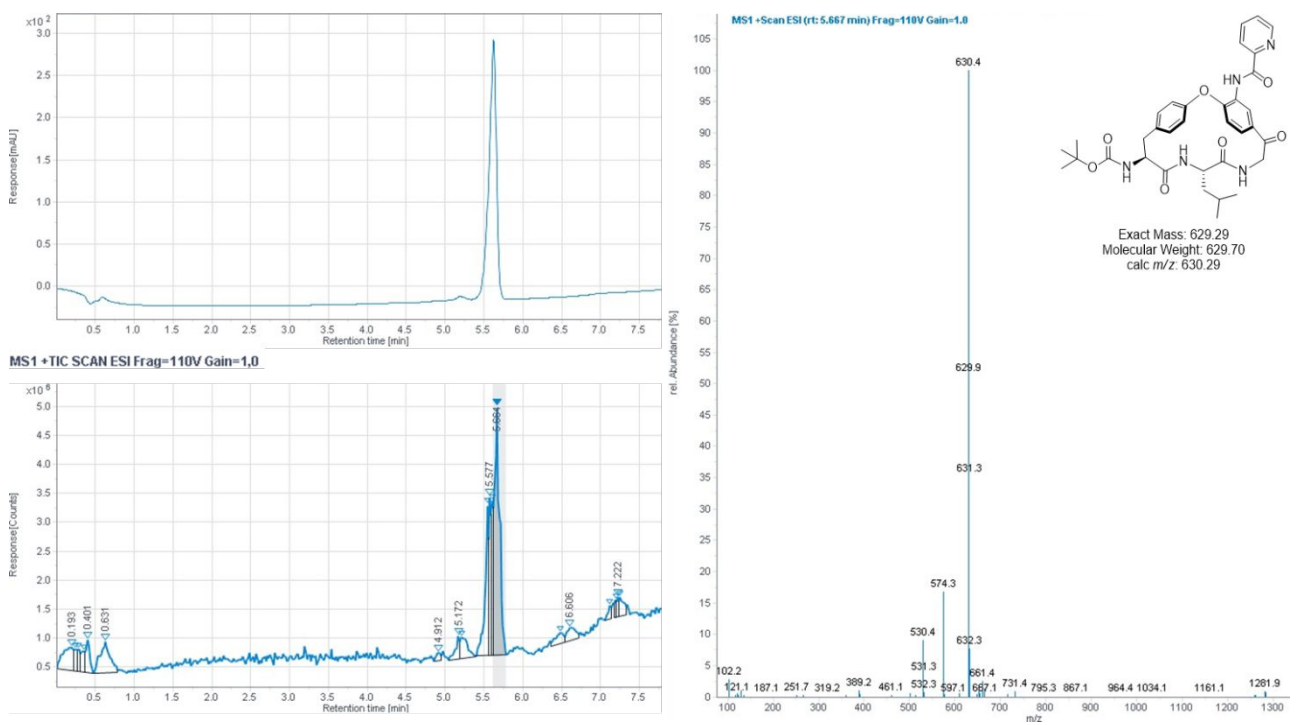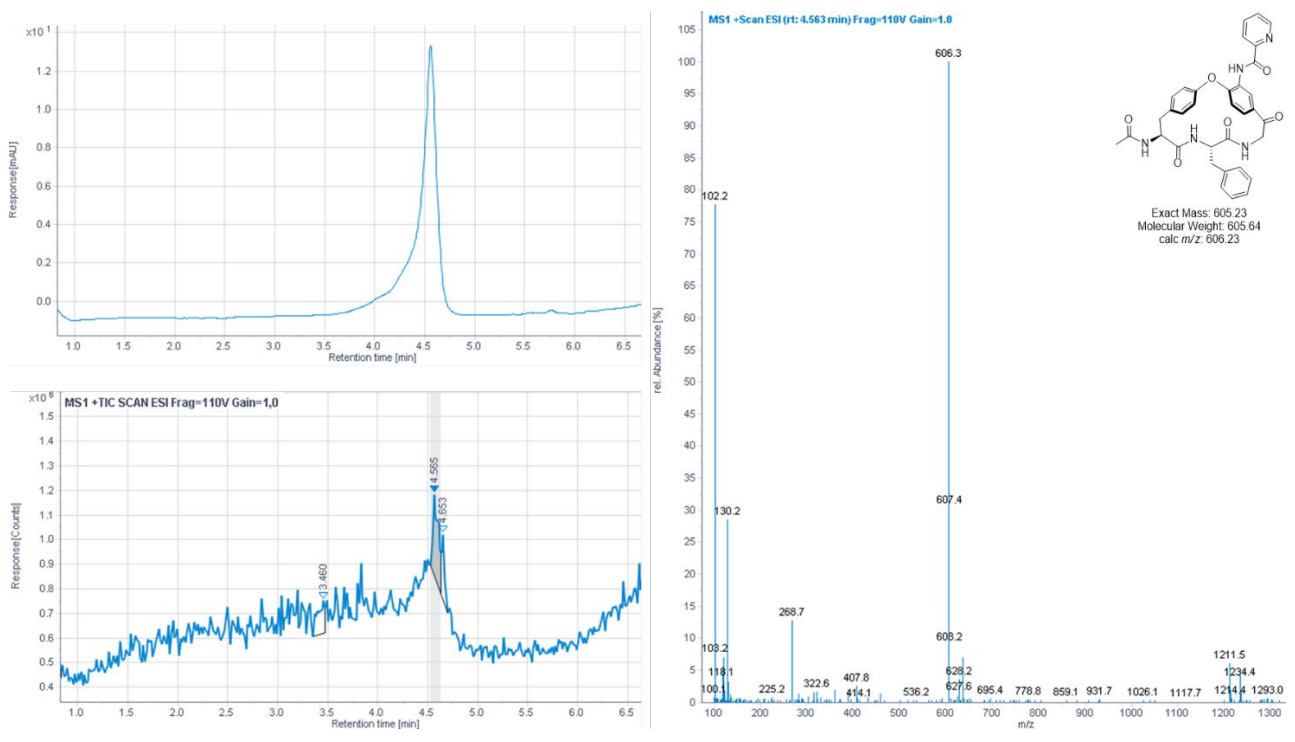
LC-MS after purification by HPLC: Compound 11

LC-MS after purification by HPLC: Compound 12