

Synthesis, analytical characterization and human CB₁ receptor binding studies of the chloroindole analogues of the synthetic cannabinoid MDMB-CHMICA

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This supplementary information shows the recorded spectra of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7-Cl-MDMB-CHMICA via NMR, GC-MS, GC-sIR and UHPLC-UV/VIS and the corresponding graphs for competitive receptor binding studies. Additionally, all intermediates of the corresponding syntheses were characterized via NMR.

NMR Data

Figure S-1 to S-85 show the ^1H and ^{13}C NMR, COSY, HSQC and HMBC spectra of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7-Cl-MDMB-CHMICA and their corresponding intermediates while synthesis.

Methyl (*S*)-2-Amino-3,3-dimethylbutanoate-hydrochloride (22)

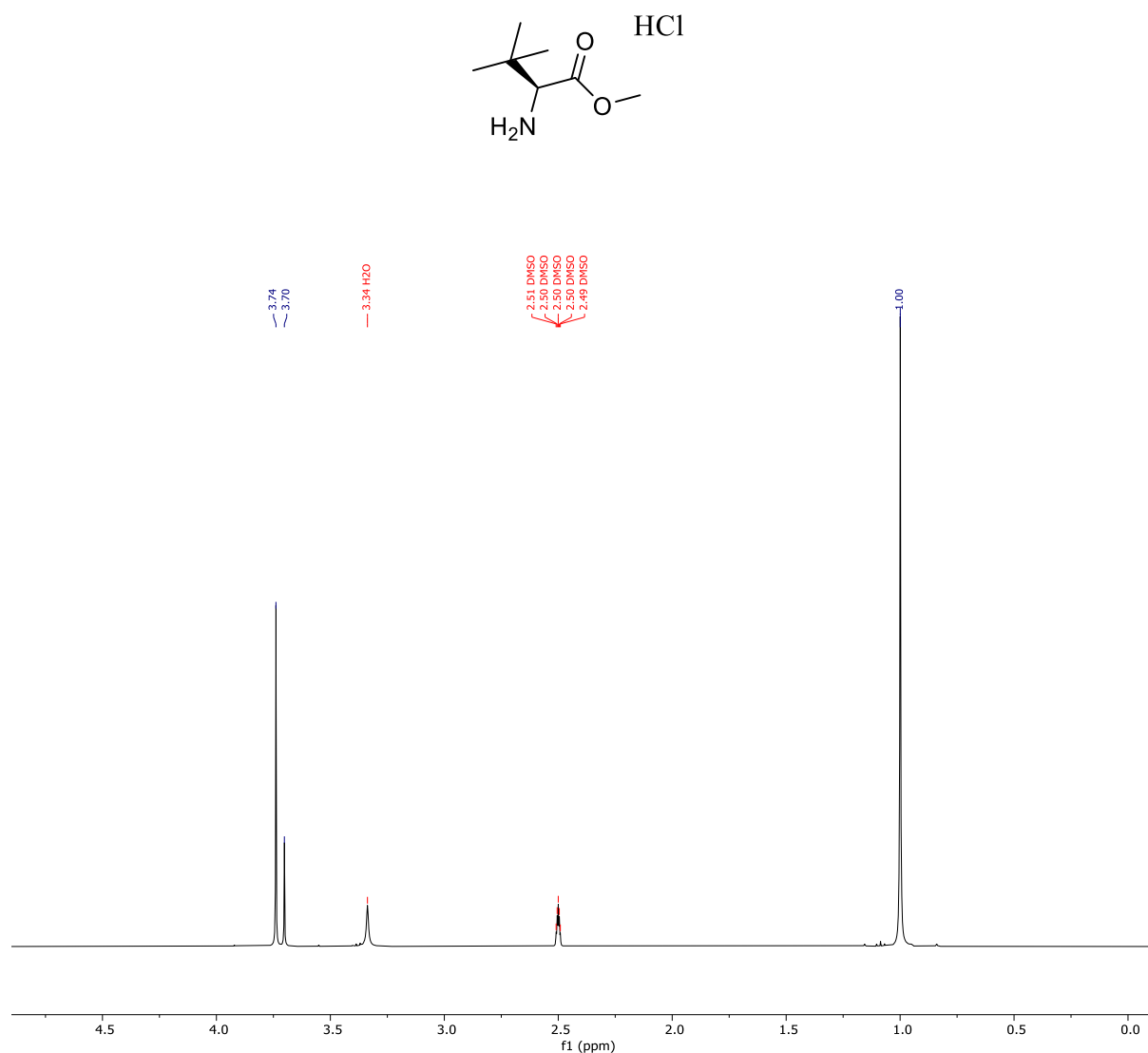


Figure S-1: ^1H -NMR of 22 (400 MHz, $\text{DMSO}-d_6$)

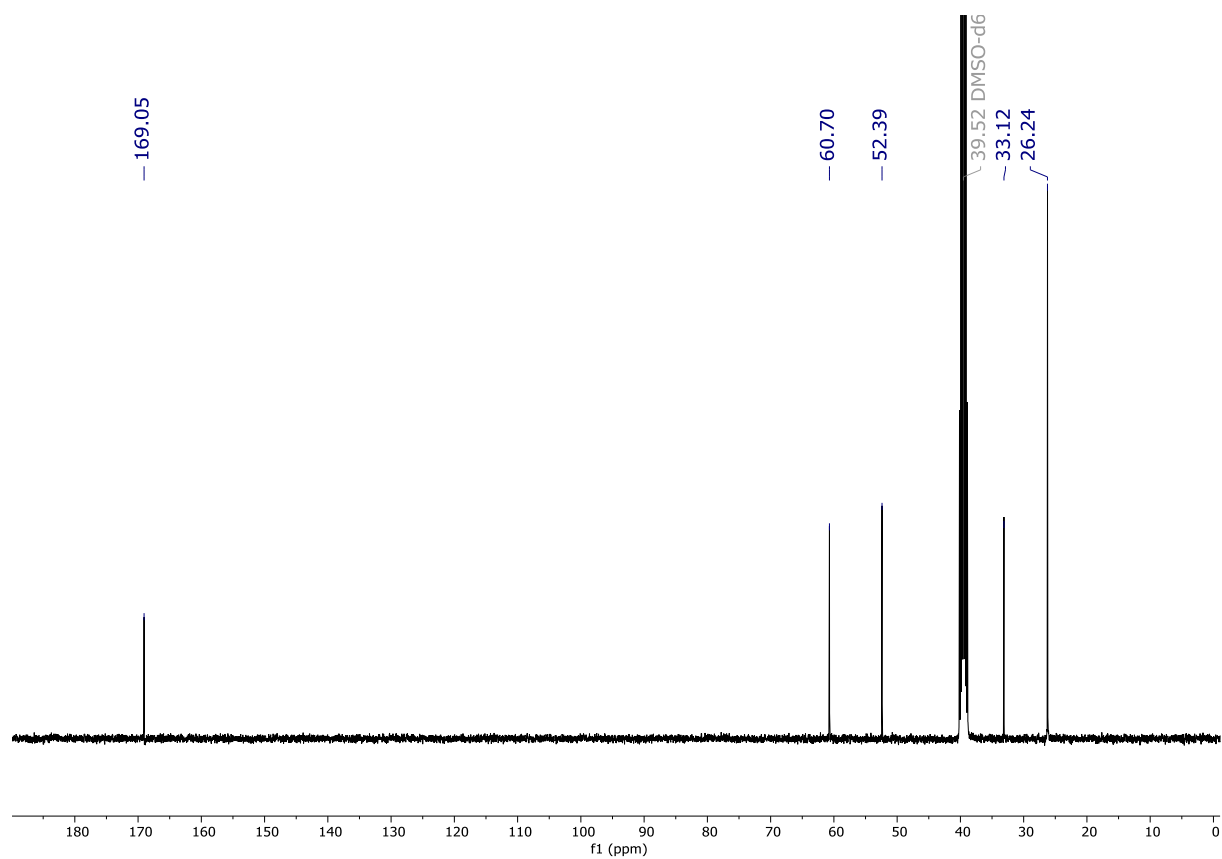


Figure S-2: ^{13}C -NMR of 22 (100.6 MHz, $\text{DMSO}-d_6$)

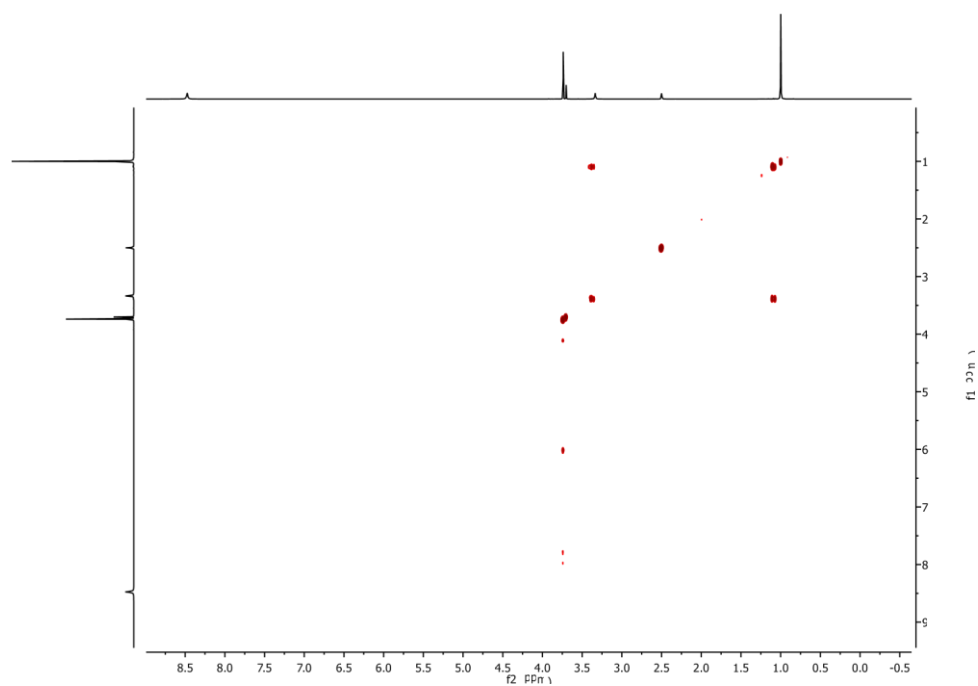


Figure S-3: COSY of 22 (400 MHz, $\text{DMSO}-d_6$):

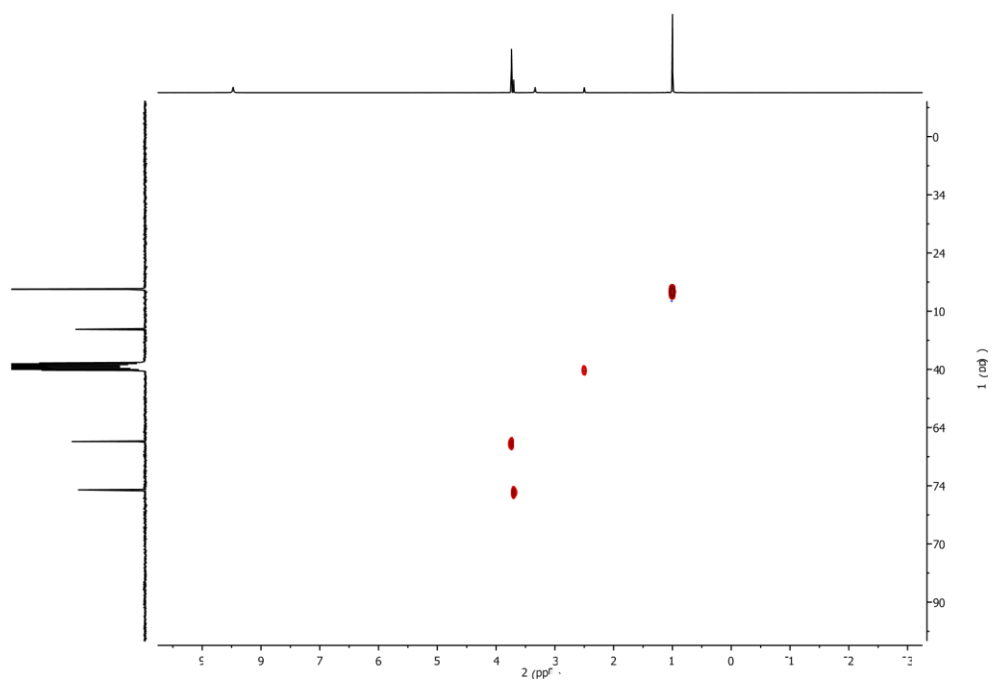


Figure S-4: HSQC of 22 (100.6 MHz, DMSO- d_6)

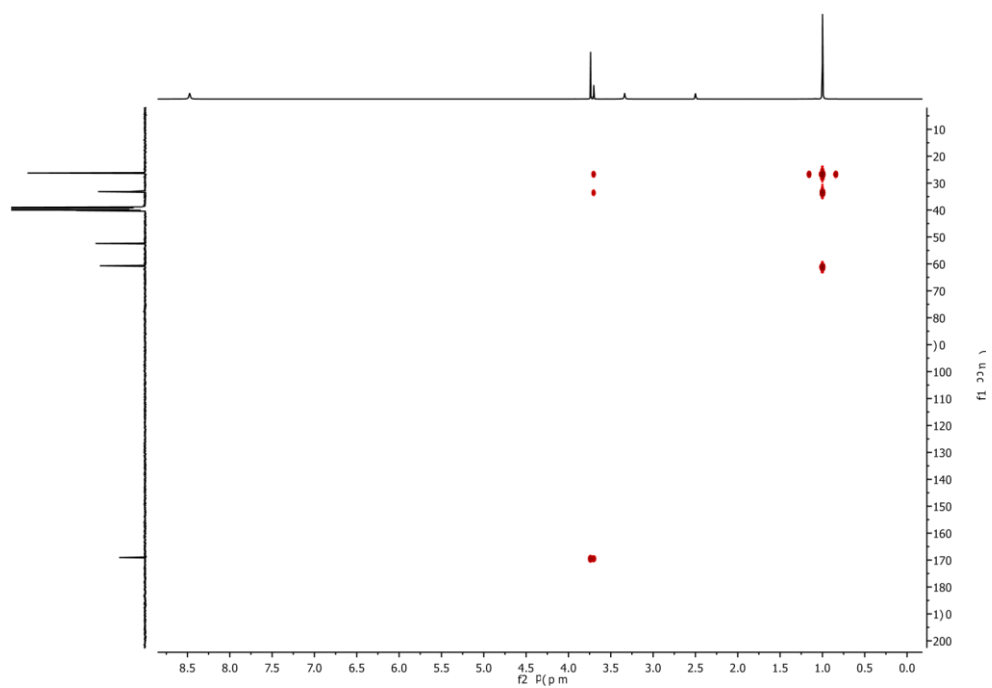


Figure S-5: HMBC of 22 (100.6 MHz, DMSO- d_6)

2-Chloro-1*H*-indole-3-carbaldehyde (7)

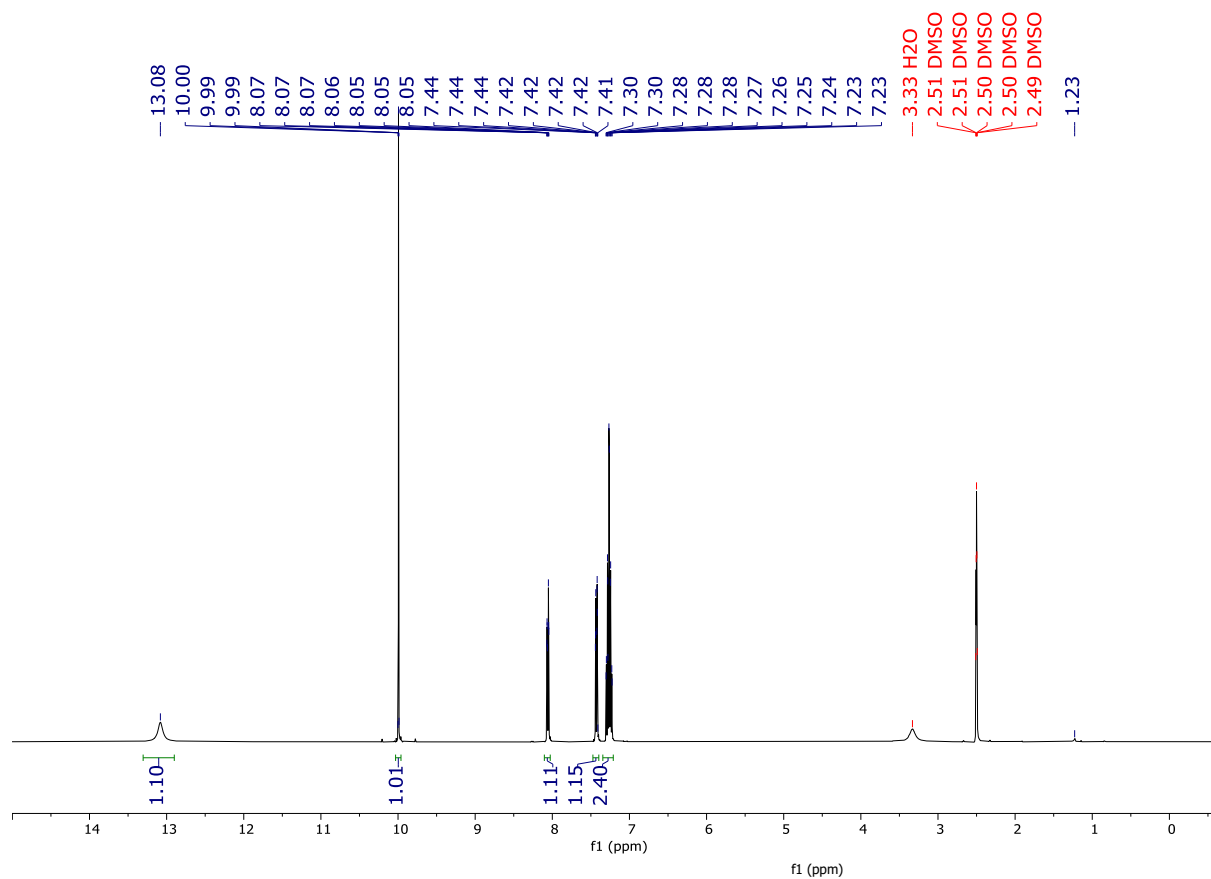
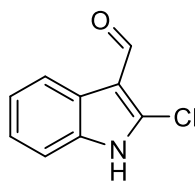


Figure S-6: ¹H-NMR of 7 (400 MHz, DMSO-*d*₆)

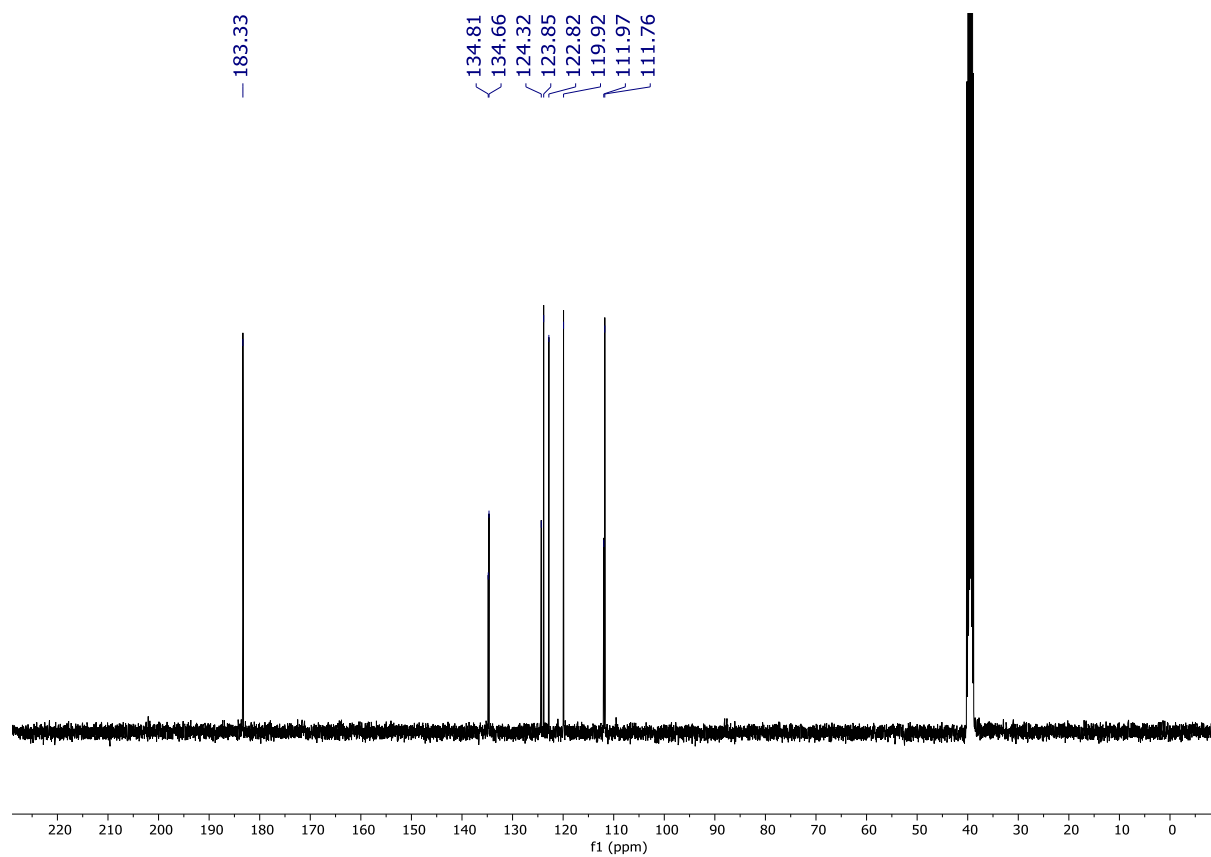


Figure S-7: ^{13}C -NMR of 7 (100.6 MHz, $\text{DMSO}-d_6$)

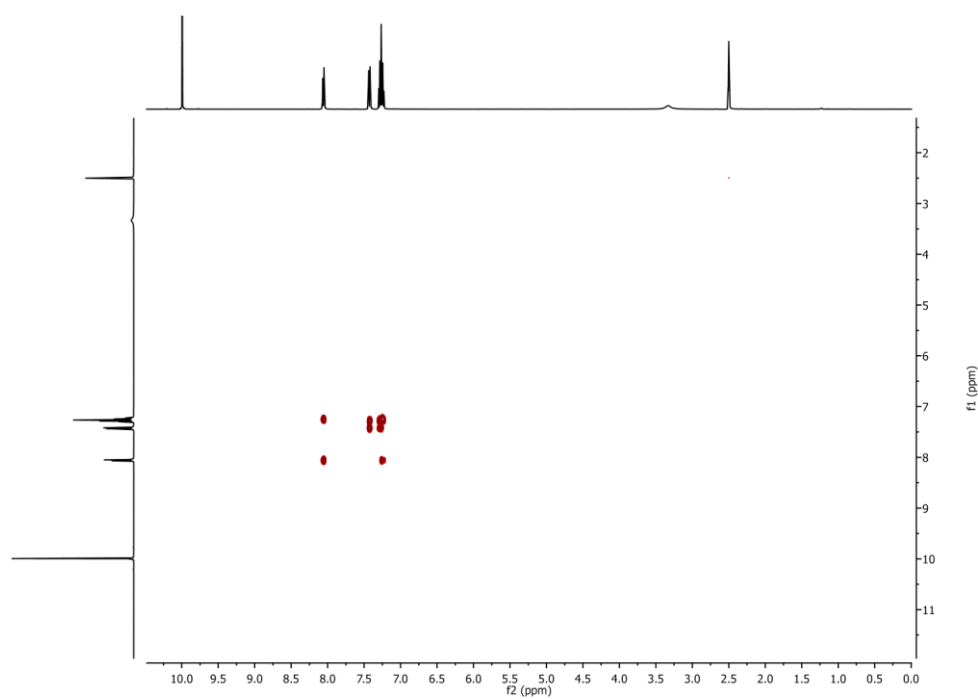


Figure S-8: COSY of 7 (400 MHz, $\text{DMSO}-d_6$)

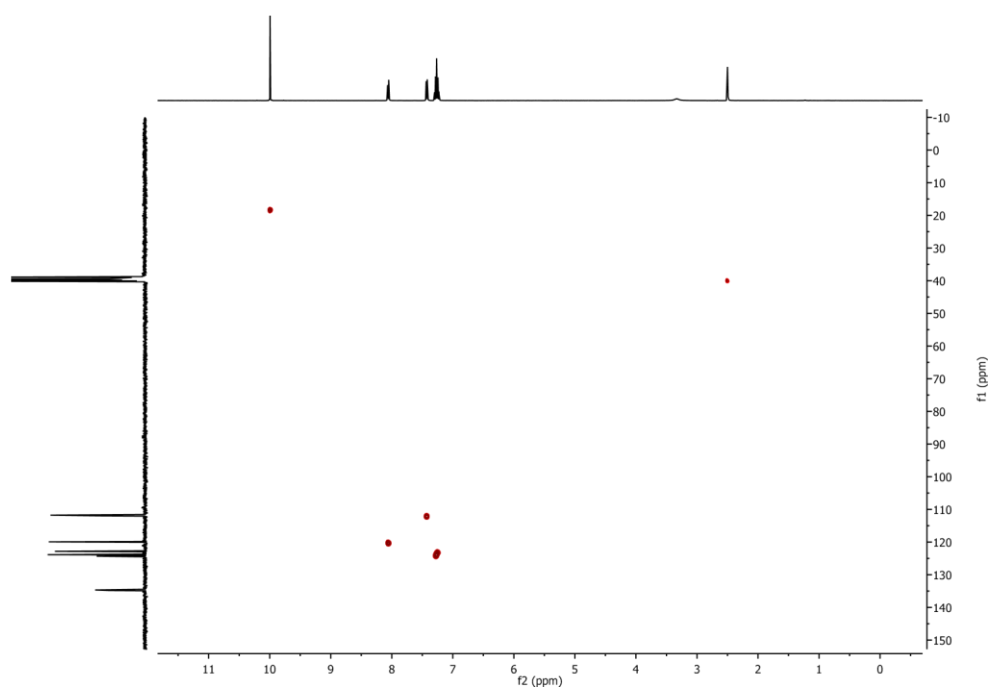


Figure S-9: HSQC of 7 (100.6 MHz, DMSO- d_6)

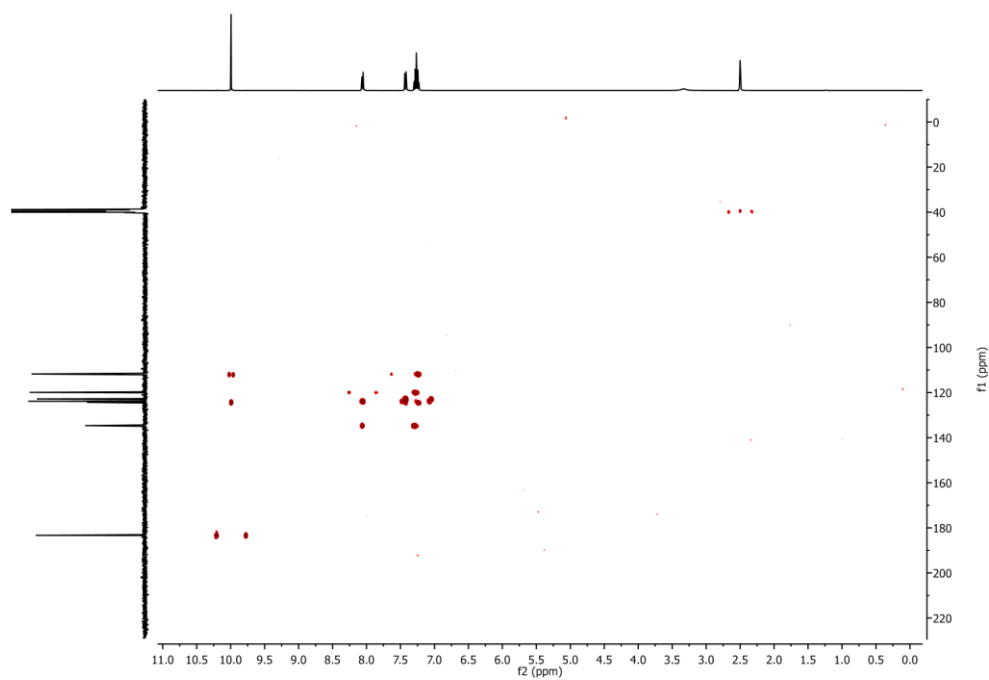


Figure S-10: HMBC of 7 (100.6 MHz, DMSO- d_6)

2-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carbaldehyde (9)

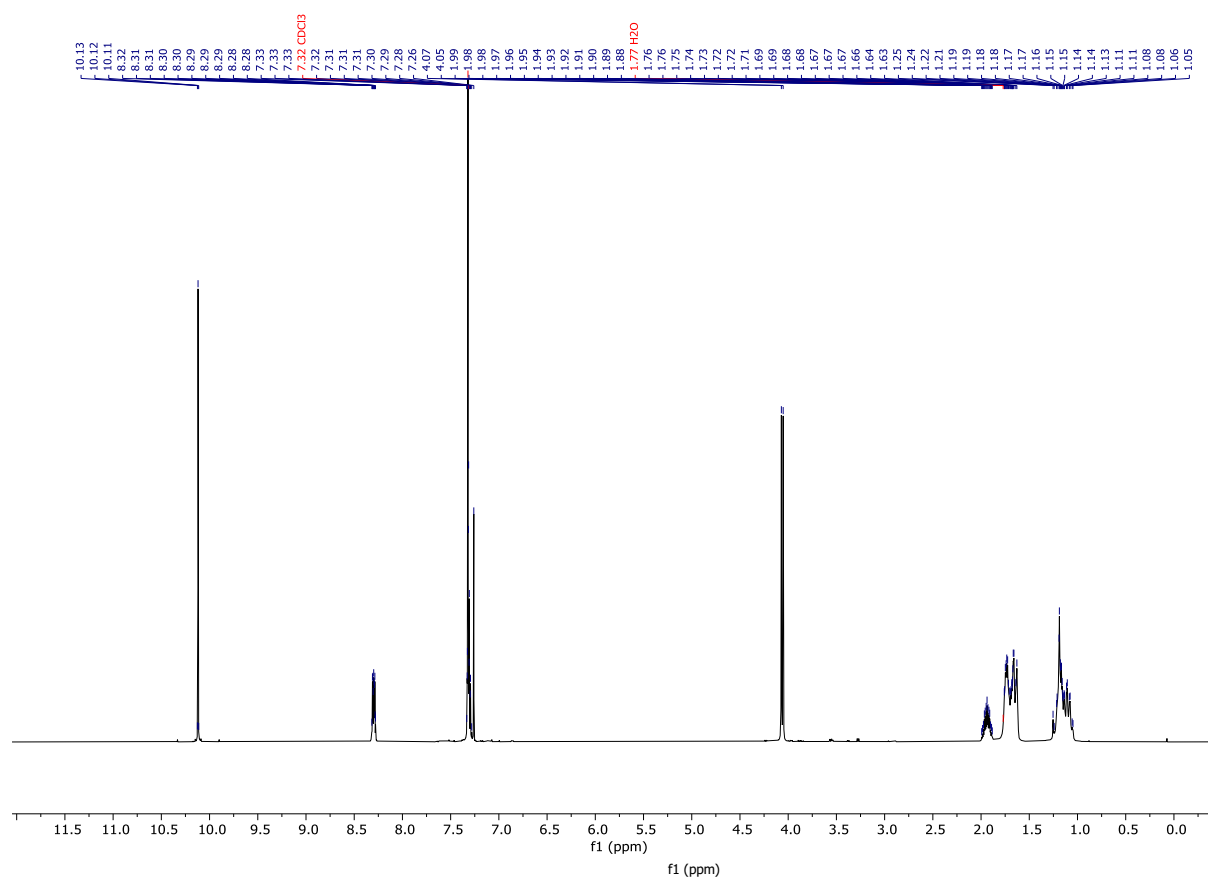
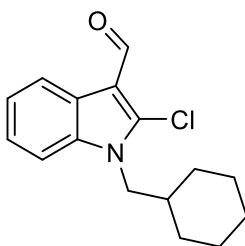


Figure S-11: ¹H-NMR of 9 (400 MHz, CDCl₃)

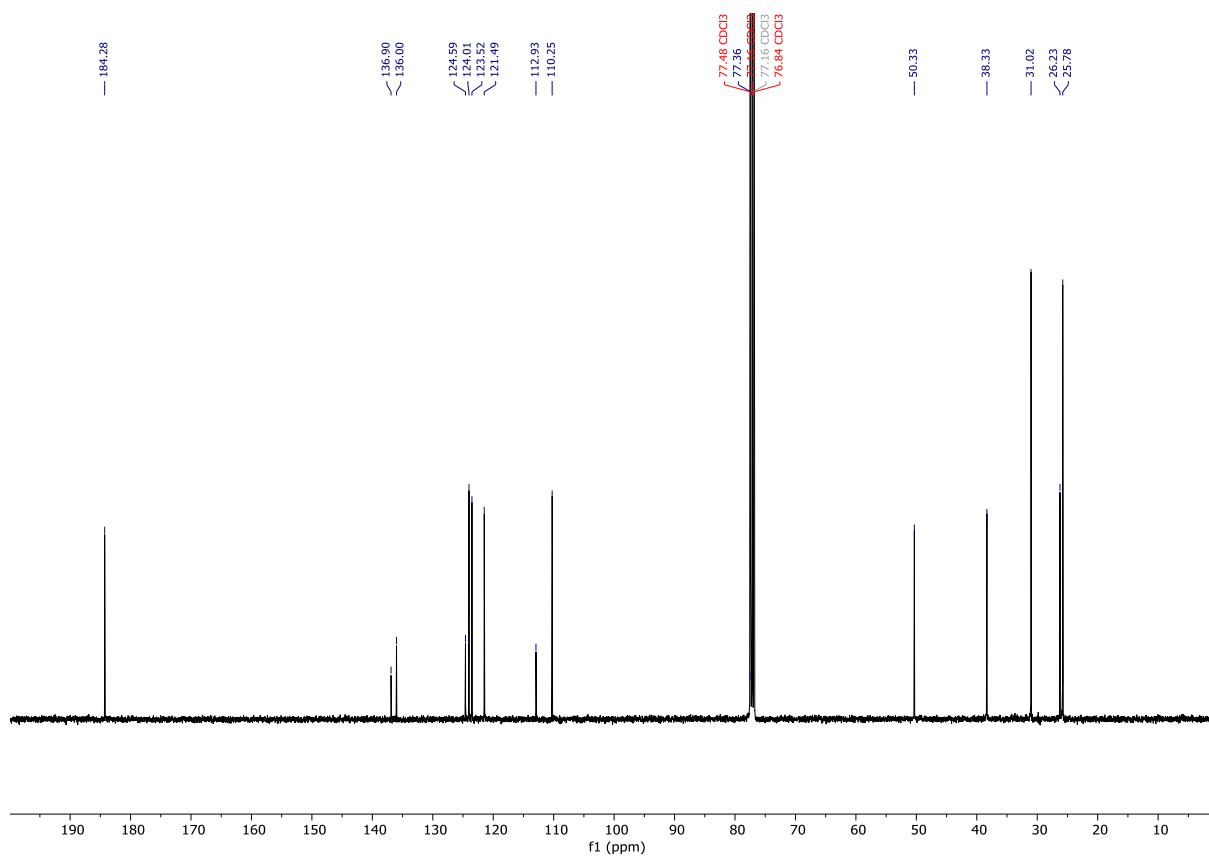


Figure S-12: ^{13}C -NMR of 9 (100.6 MHz, CDCl_3)

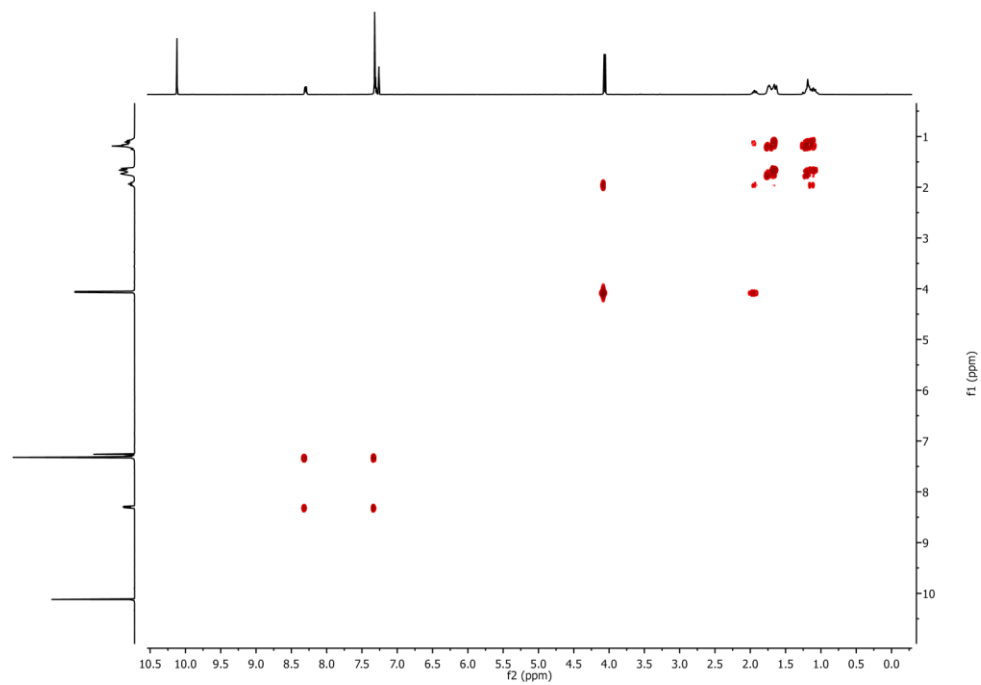


Figure S-13: COSY of 9 (400 MHz, CDCl_3)

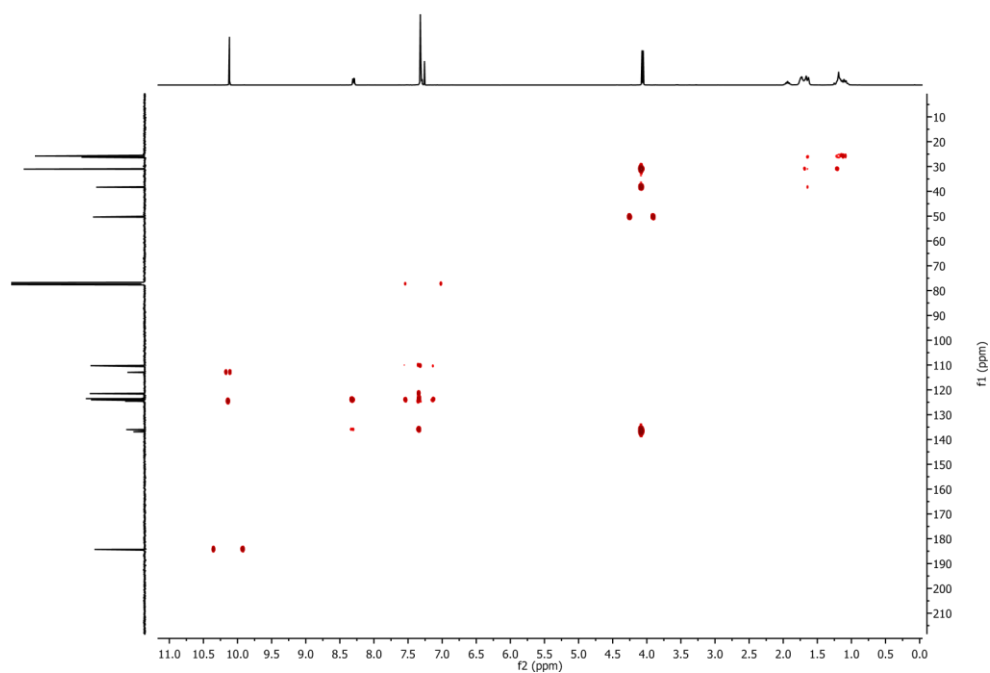


Figure S-14: HSQC of 9 (100.6 MHz, CDCl₃)

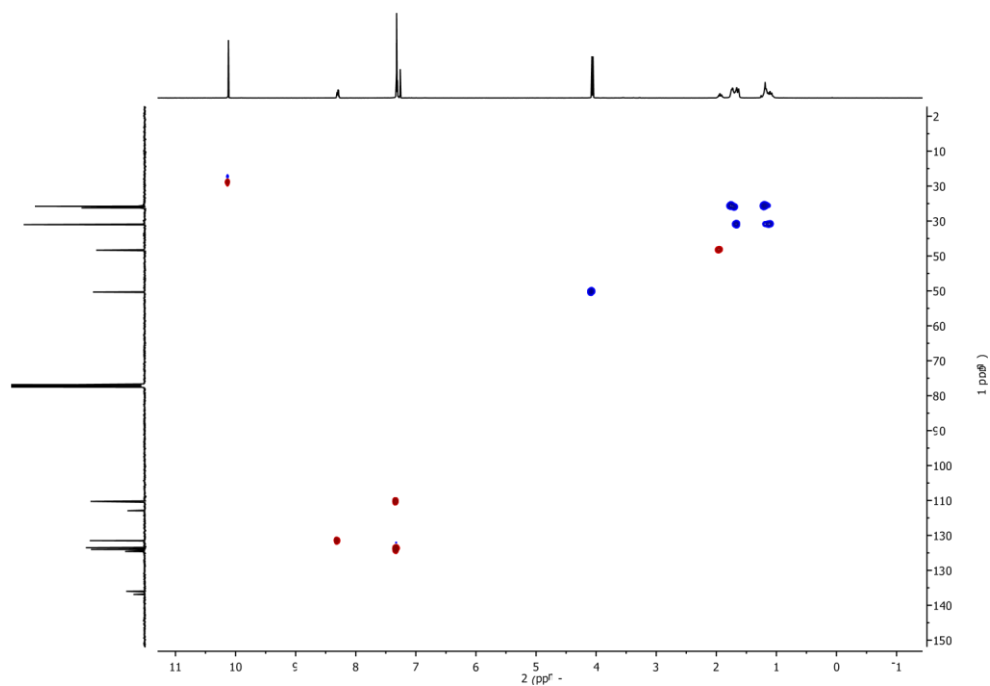


Figure S-15: HMBC of 9 (100.6 MHz, CDCl₃)

5-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carbaldehyde (10)

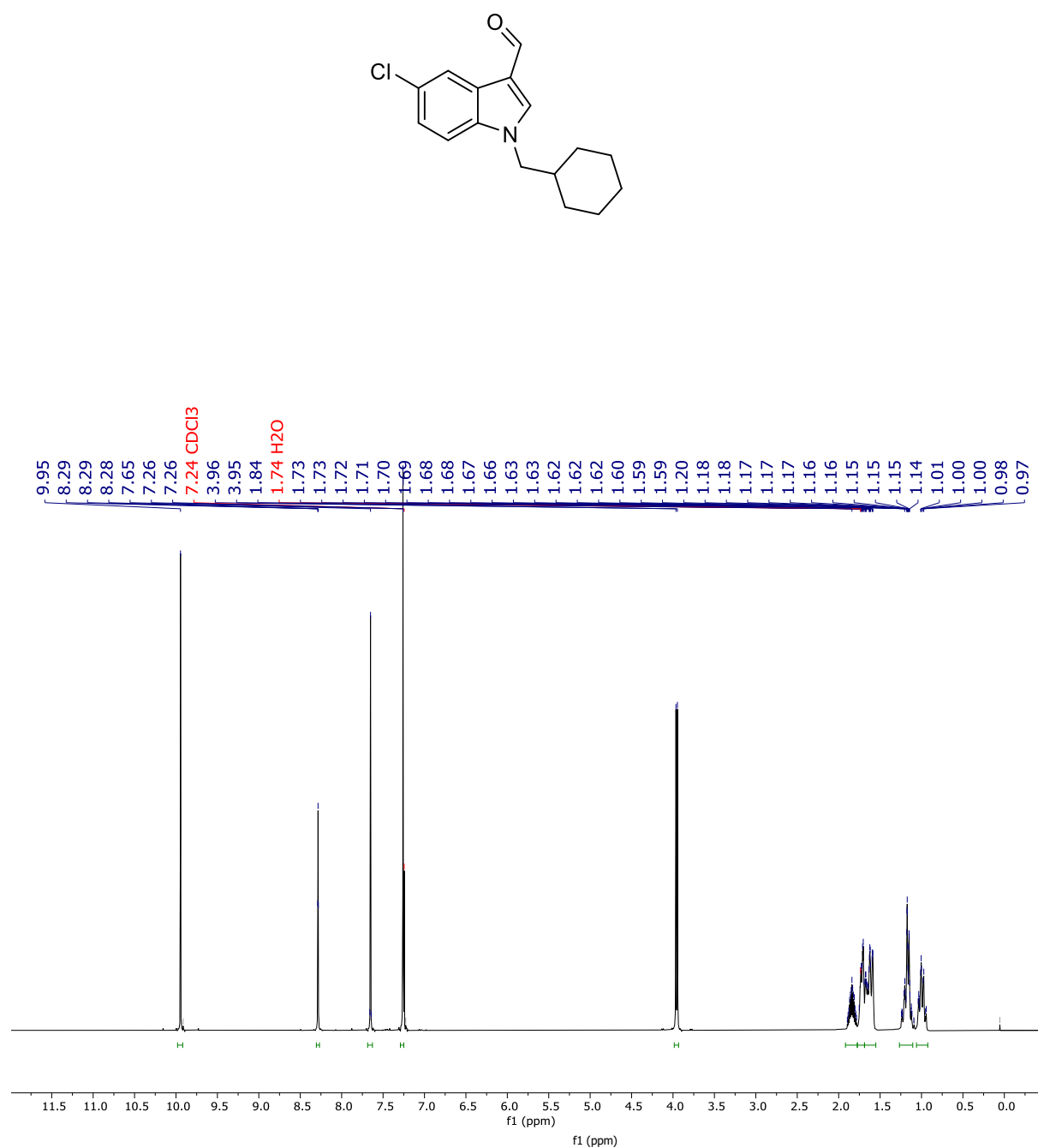


Figure S-16: ¹H-NMR of 10 (400 MHz, CDCl₃)

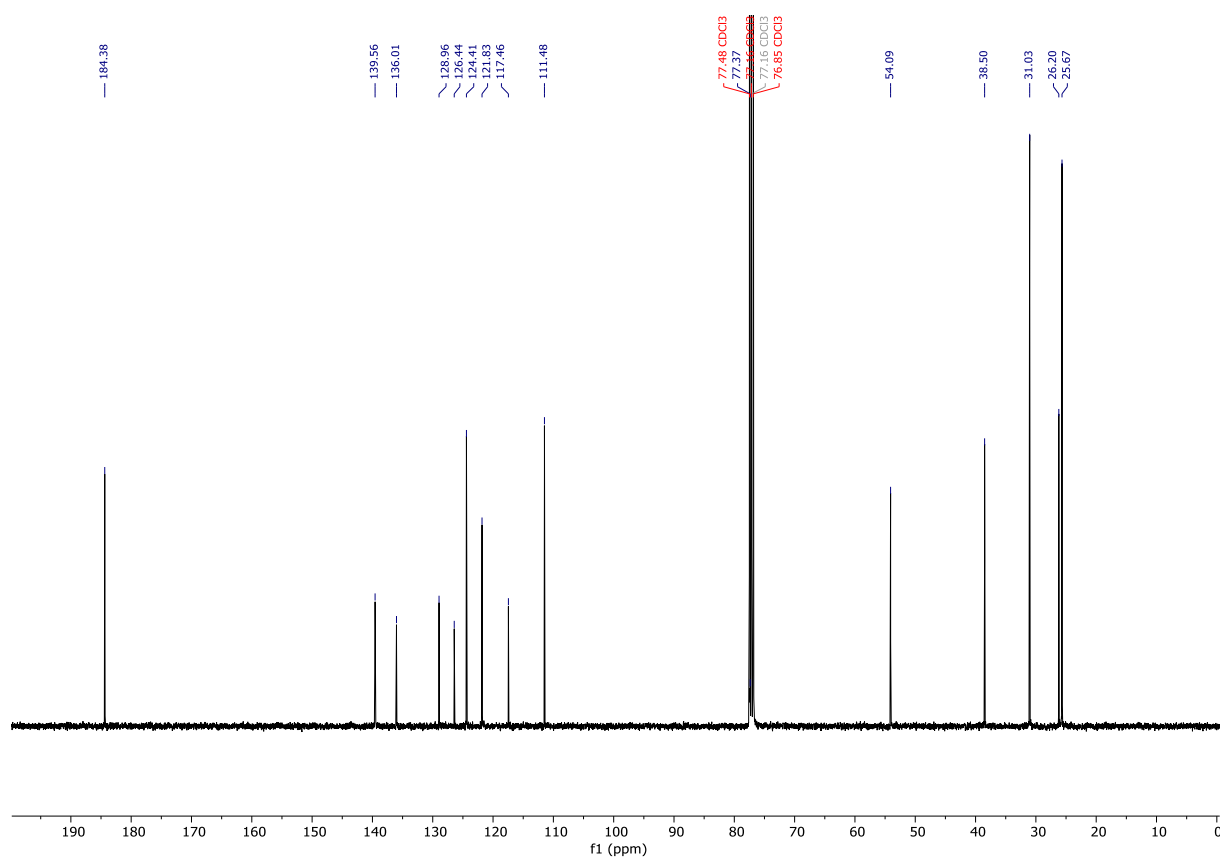


Figure S-17: ¹³C-NMR of 10 (100.6 MHz, CDCl₃)

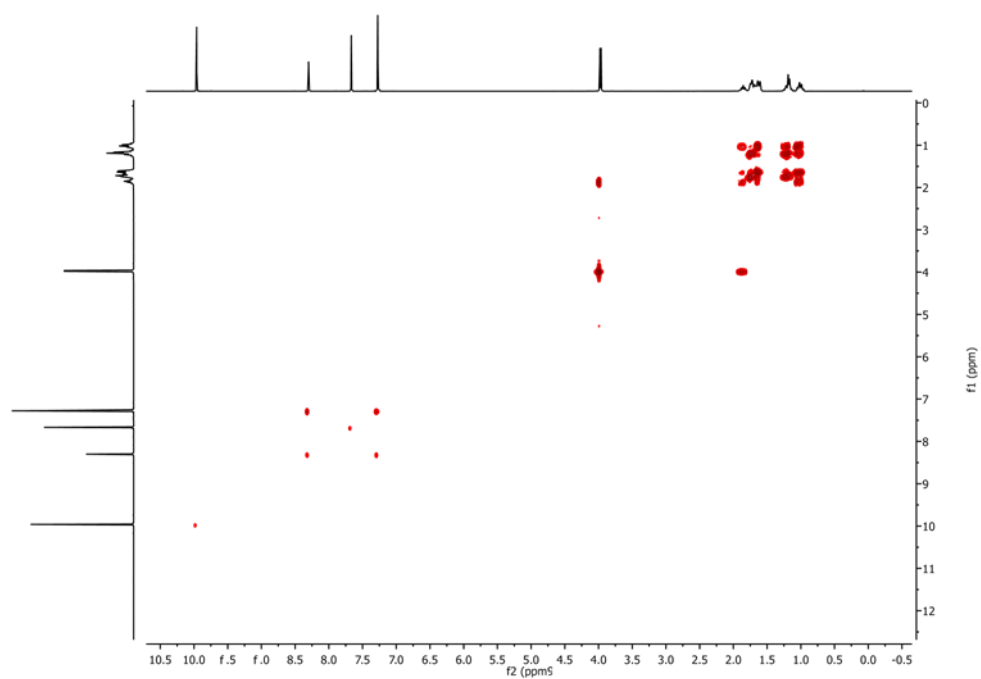


Figure S-18: COSY of 10 (400 MHz, CDCl₃)

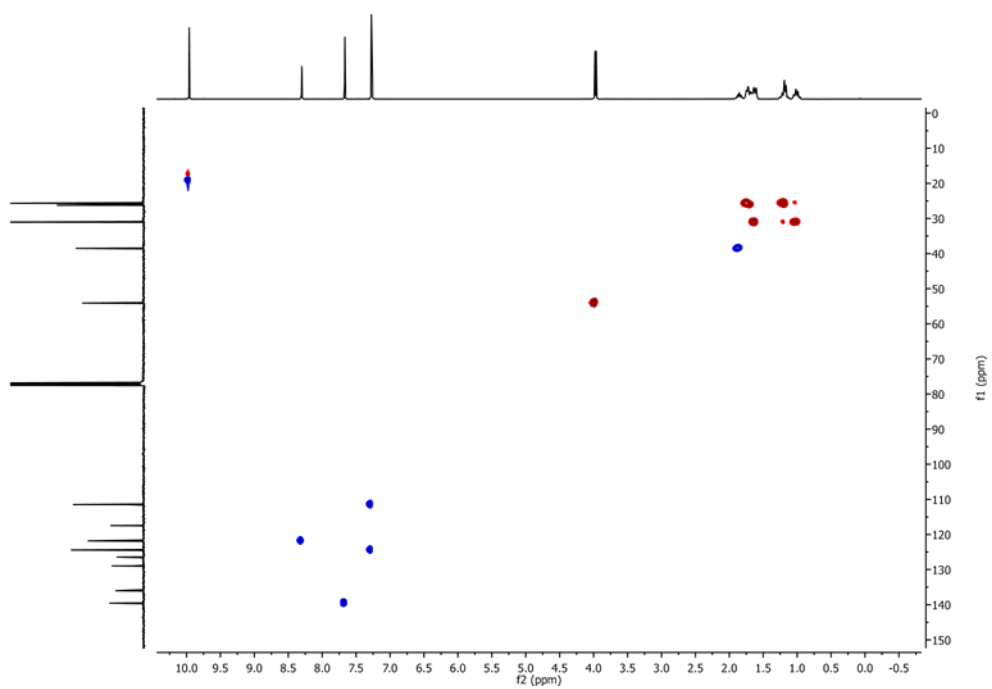


Figure S-19: HSQC of 10 (100.6 MHz, CDCl_3)

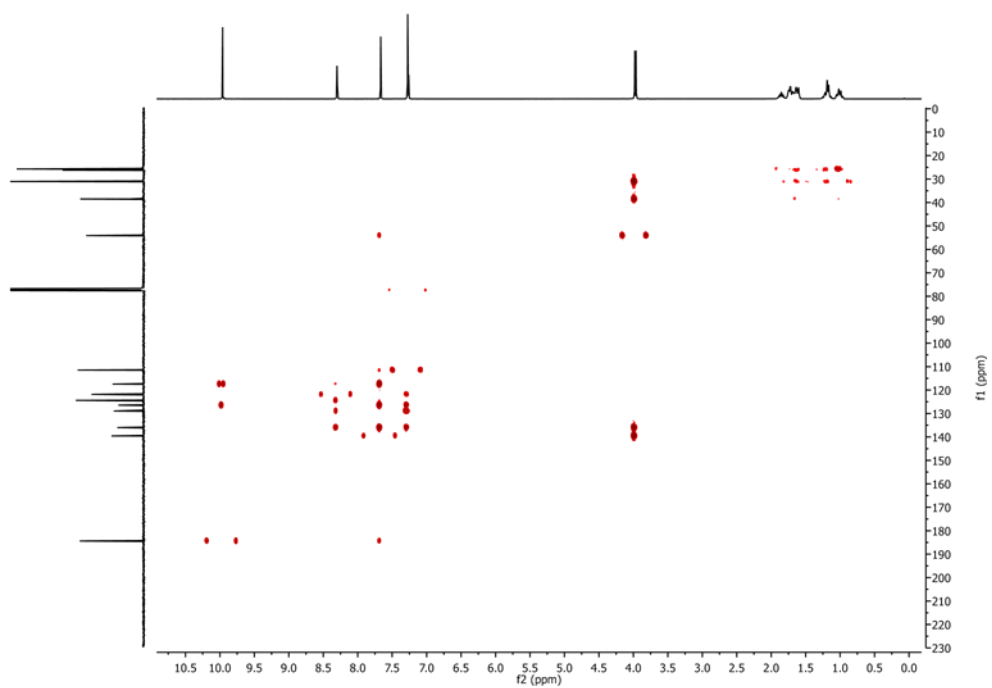


Figure S-20: HMBC of 10 (100.6 MHz, CDCl_3)

1-(4-Chloro-1(cyclohexylmethyl)-1H-indol-3-yl)-2,2,2-trifluorethan-1-one (16)

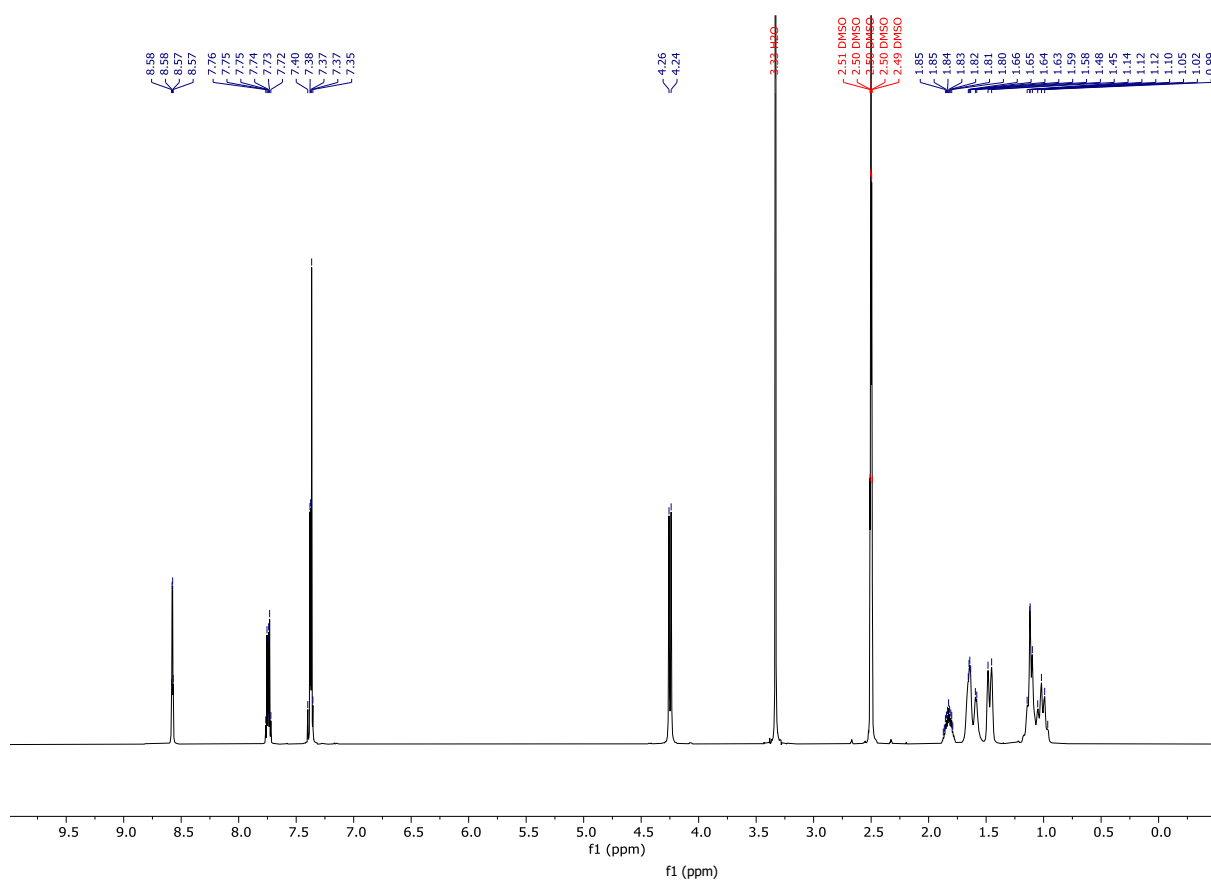
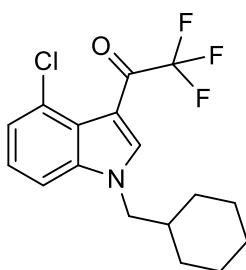


Figure S-21: ¹H-NMR of 16 (400 MHz, DMSO-*d*₆)

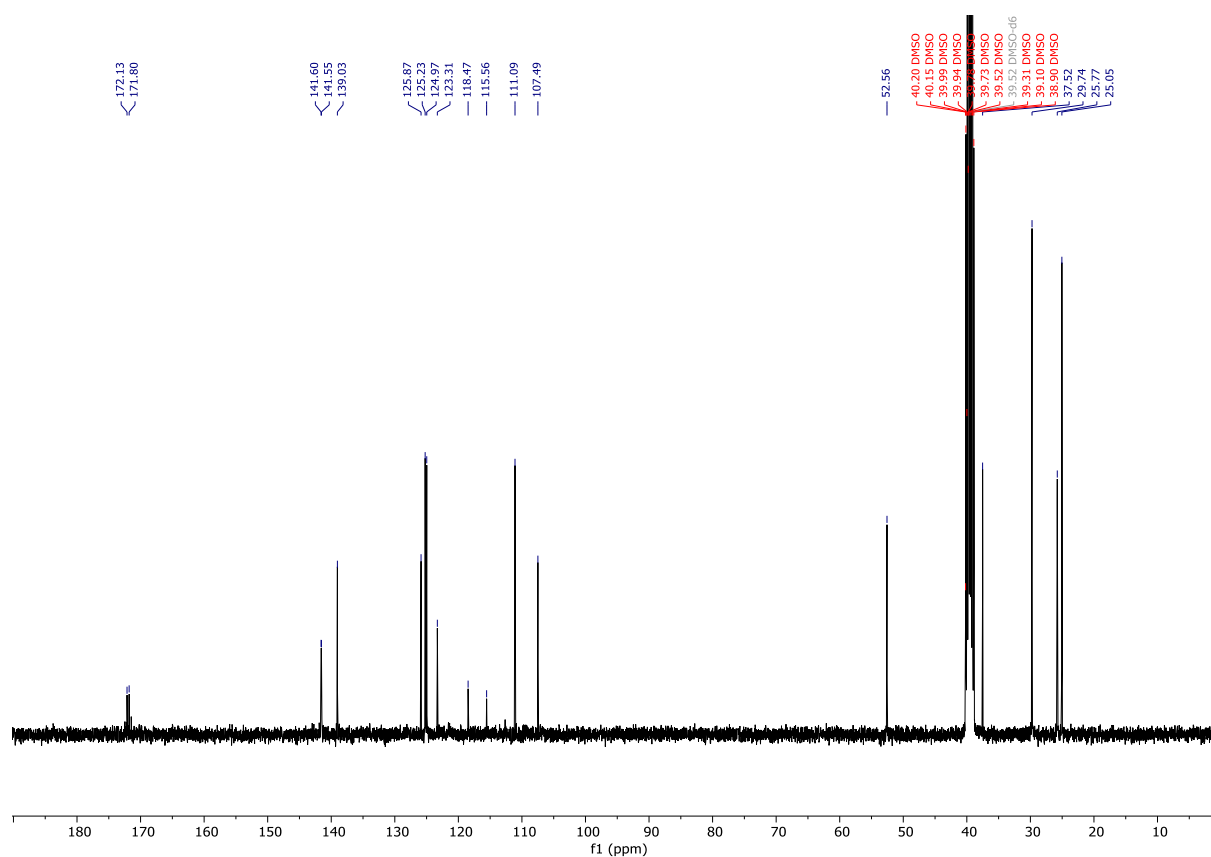


Figure S-22: ^{13}C -NMR of 16 (100.6 MHz, $\text{DMSO}-d_6$)

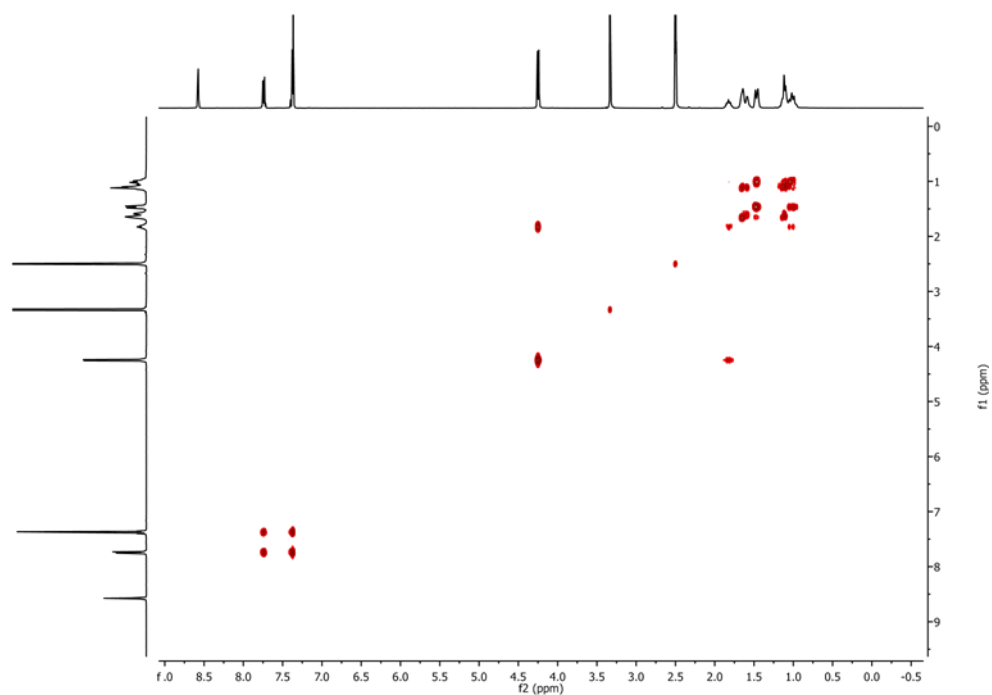


Figure S-23: COSY of 16 (400 MHz, $\text{DMSO}-d_6$)

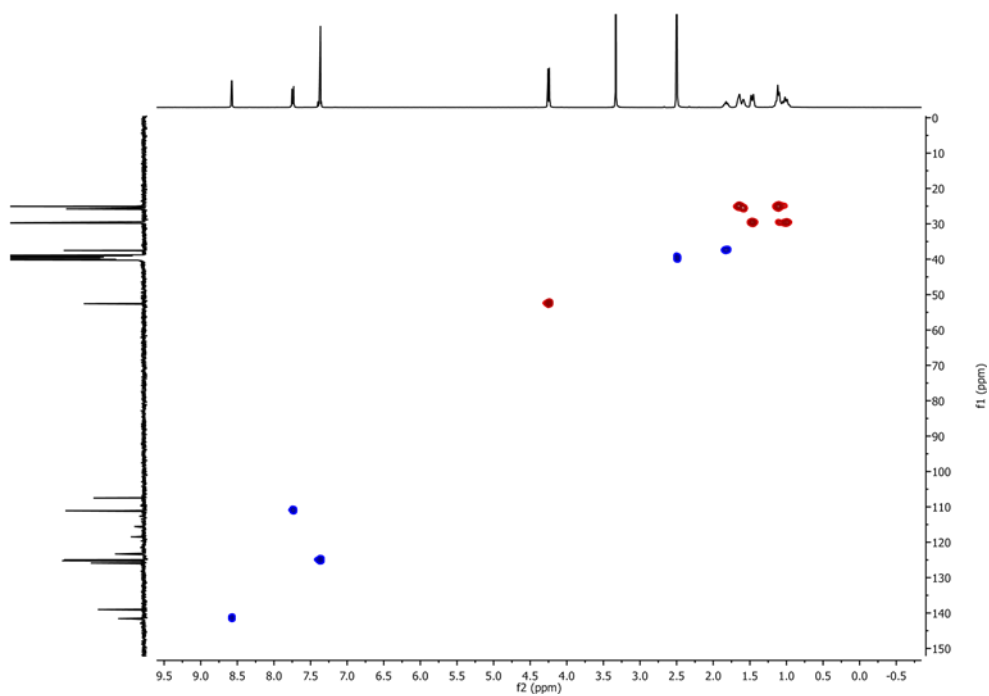


Figure S-24: HSQC of 16 (100.6 MHz, DMSO-*d*₆)

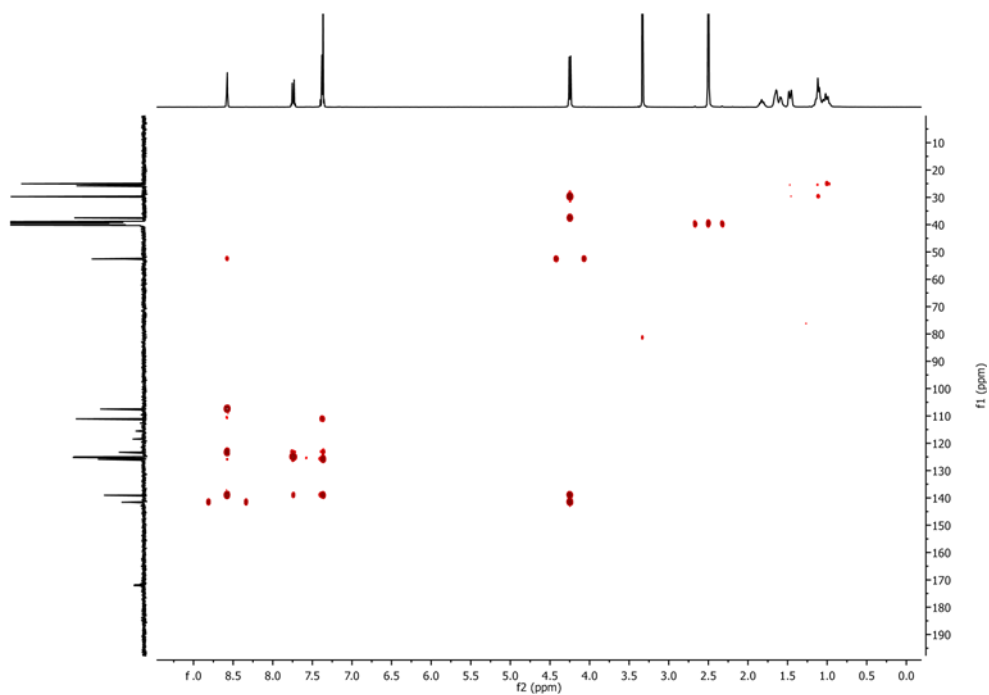


Figure S-25: HMBC of 16 (100.6 MHz, DMSO-*d*₆)

1-(6-Chloro-1(cyclohexylmethyl)-1*H*-indol-3-yl)-2,2,2-trifluoroethan-1-one (17)

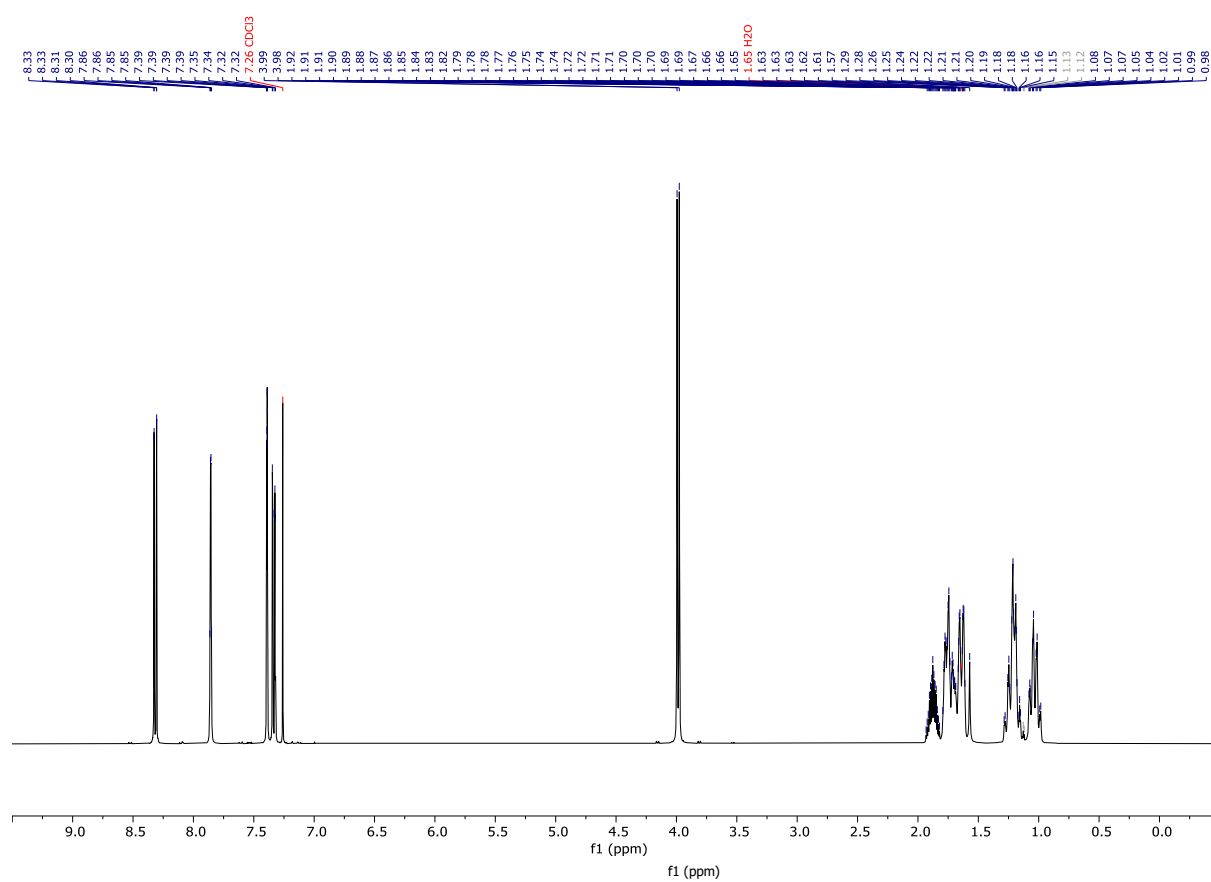
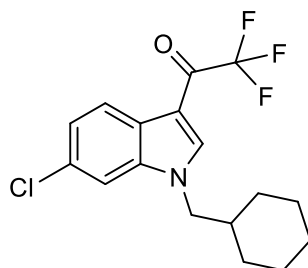


Figure S-26: ^1H -NMR of 17 (400 MHz, CDCl_3)

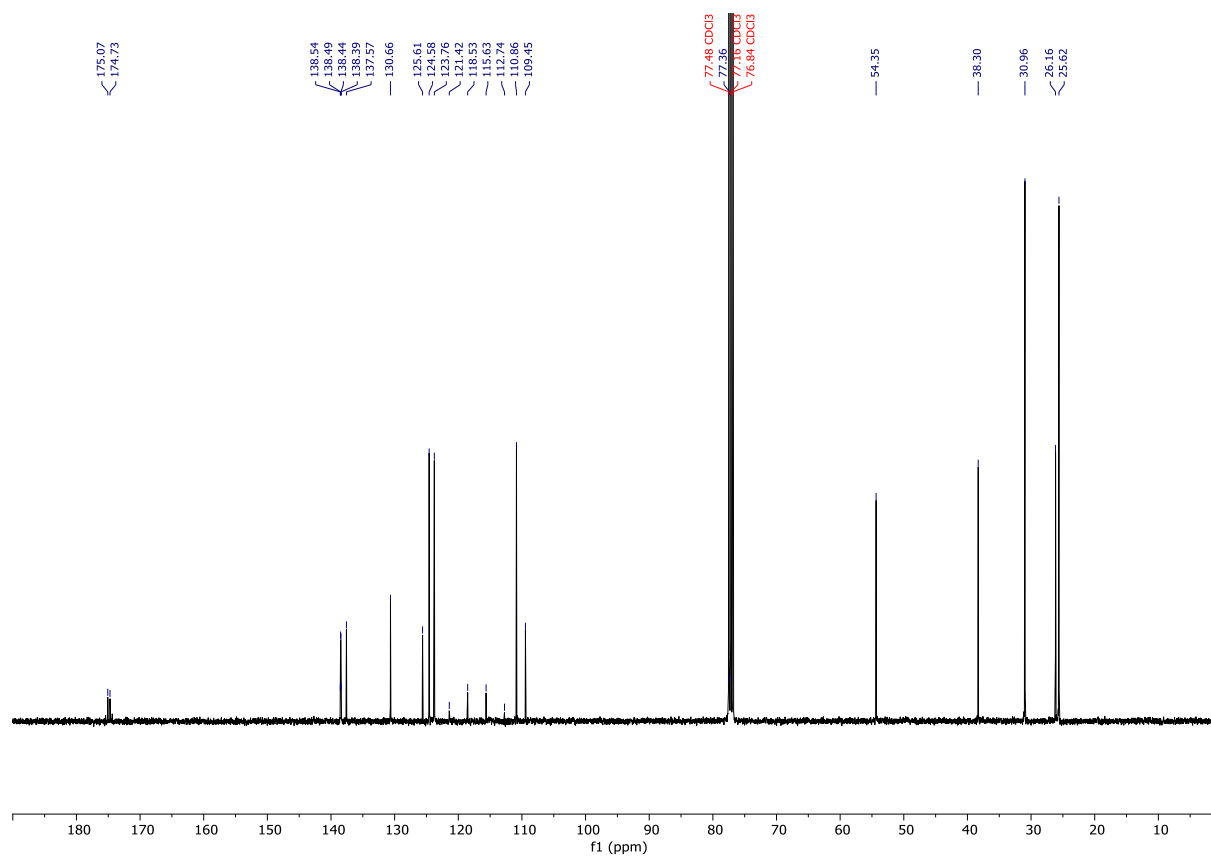


Figure S-27: ^{13}C -NMR of 17 (100.6 MHz, CDCl_3)

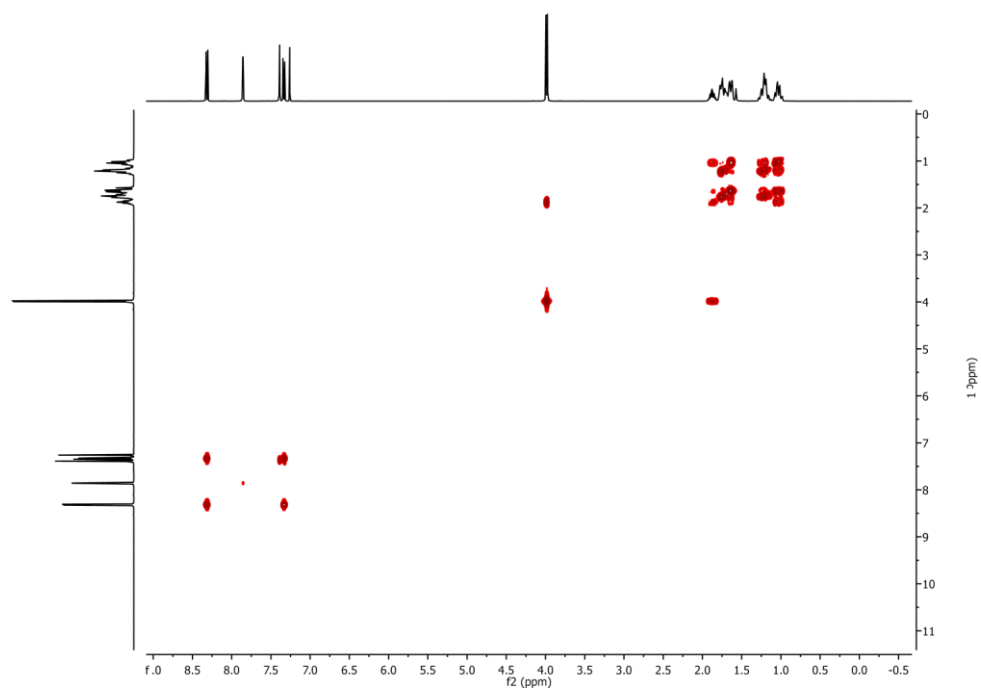


Figure S-28: COSY of 17 (400 MHz, CDCl_3)

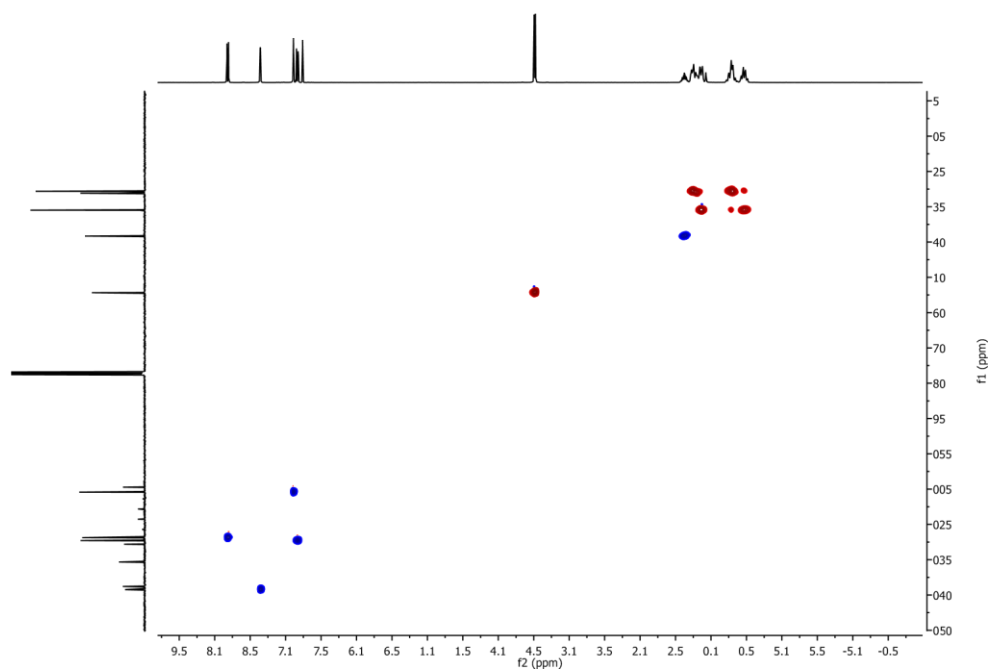


Figure S-29: HSQC of 17 (100.6 MHz, CDCl₃)

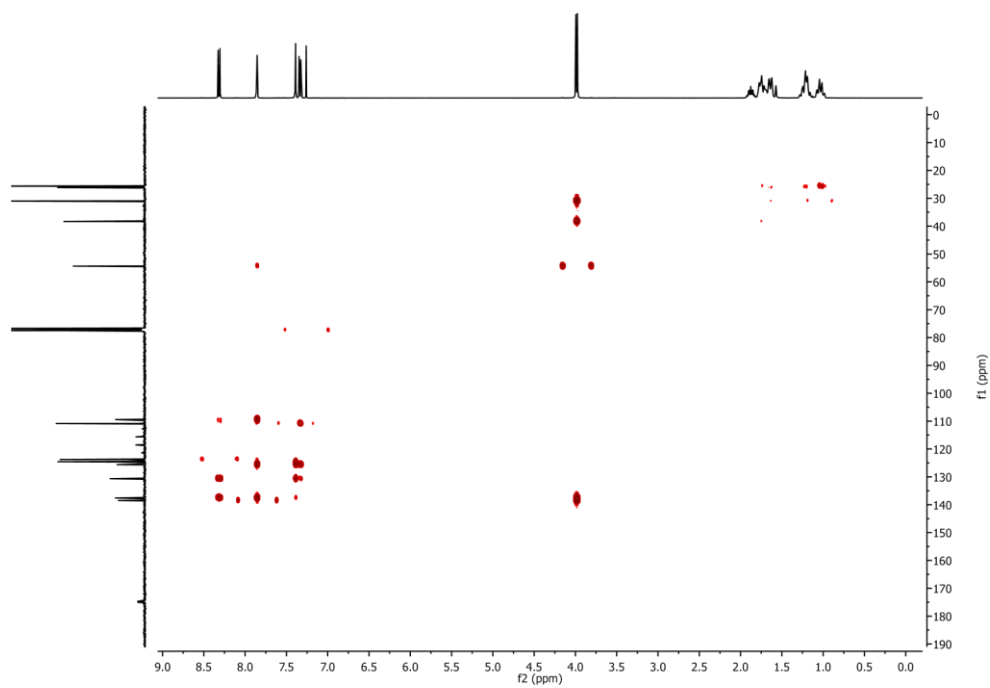


Figure S-30: HMBC of 17 (100.6 MHz, CDCl₃)

1-(7-Chloro-1(cyclohexylmethyl)-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (18)

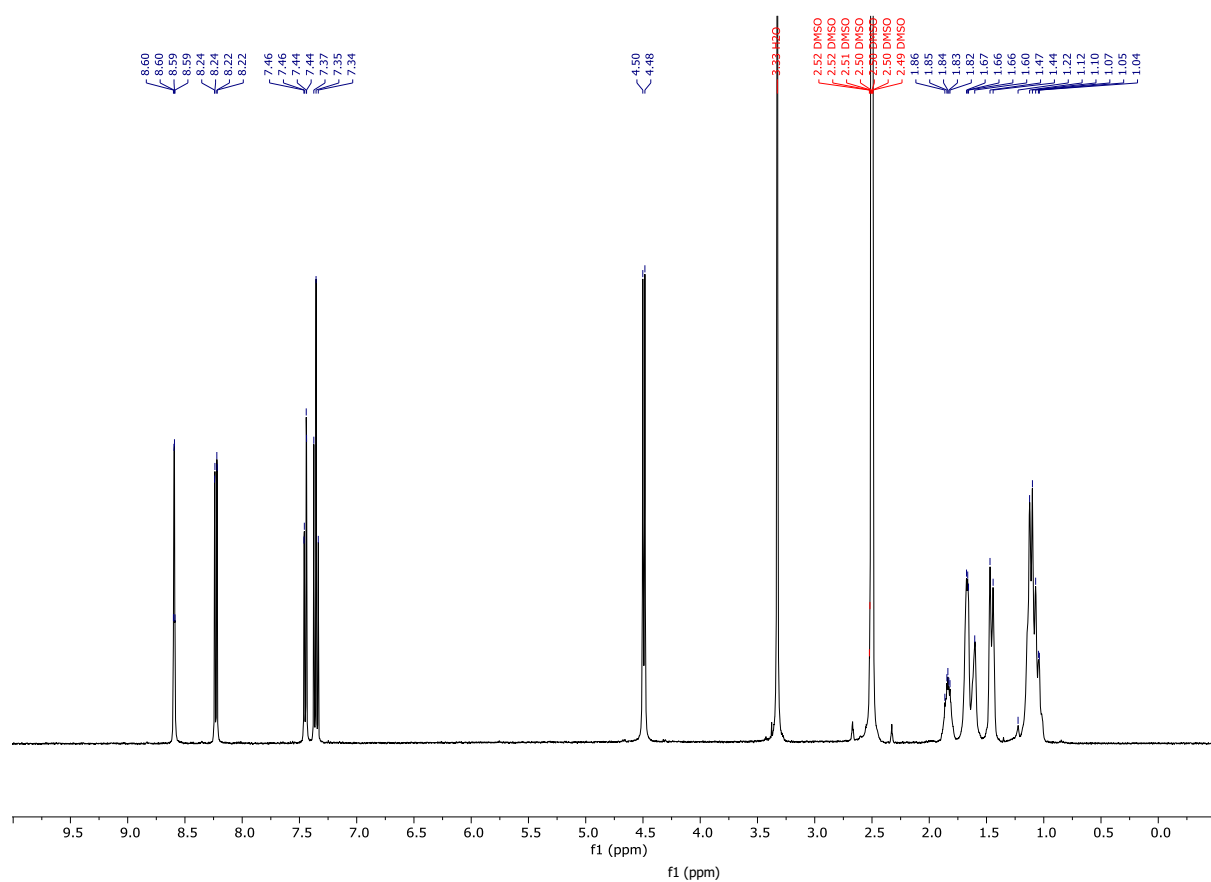
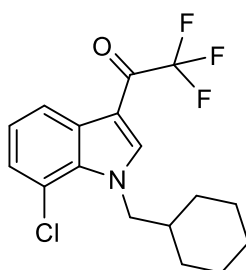


Figure S-31: $^1\text{H-NMR}$ of 18 (400 MHz, $\text{DMSO-}d_6$)

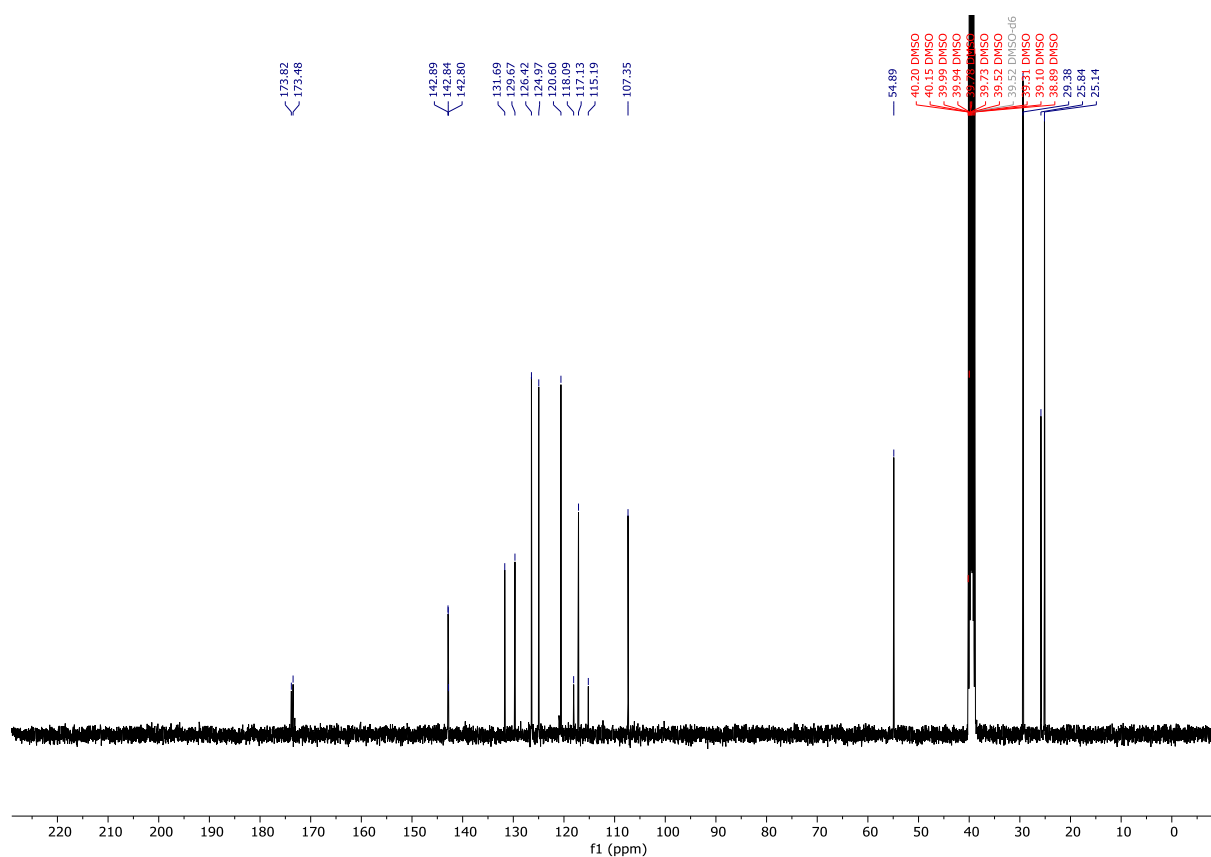


Figure S-32: ^{13}C -NMR of 18 (100.6 MHz, $\text{DMSO}-d_6$)

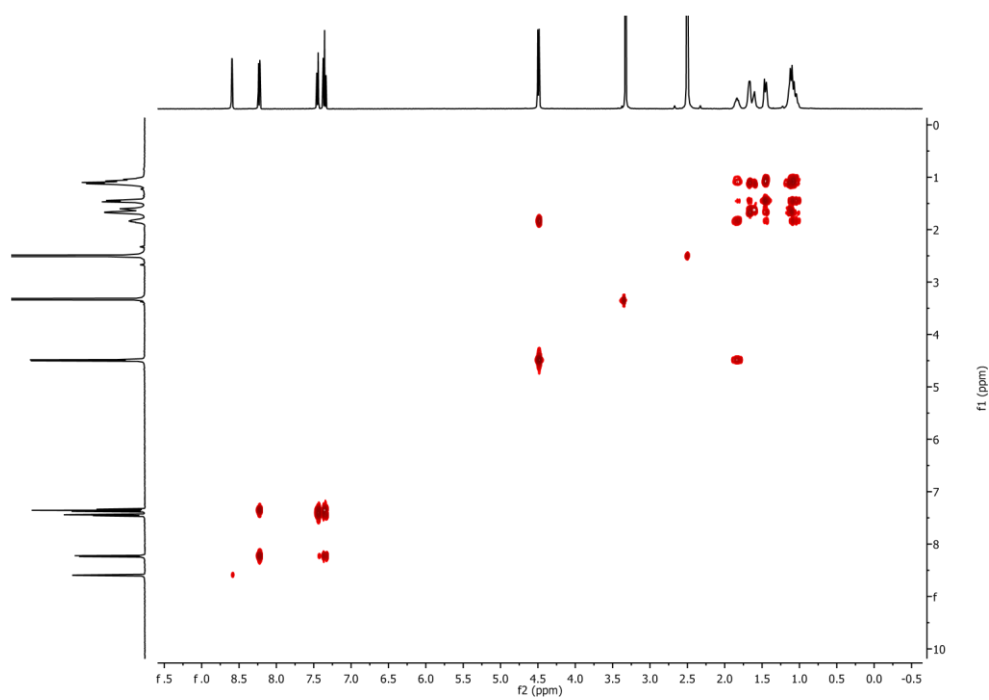


Figure S-33: COSY of 18 (400 MHz, $\text{DMSO}-d_6$)

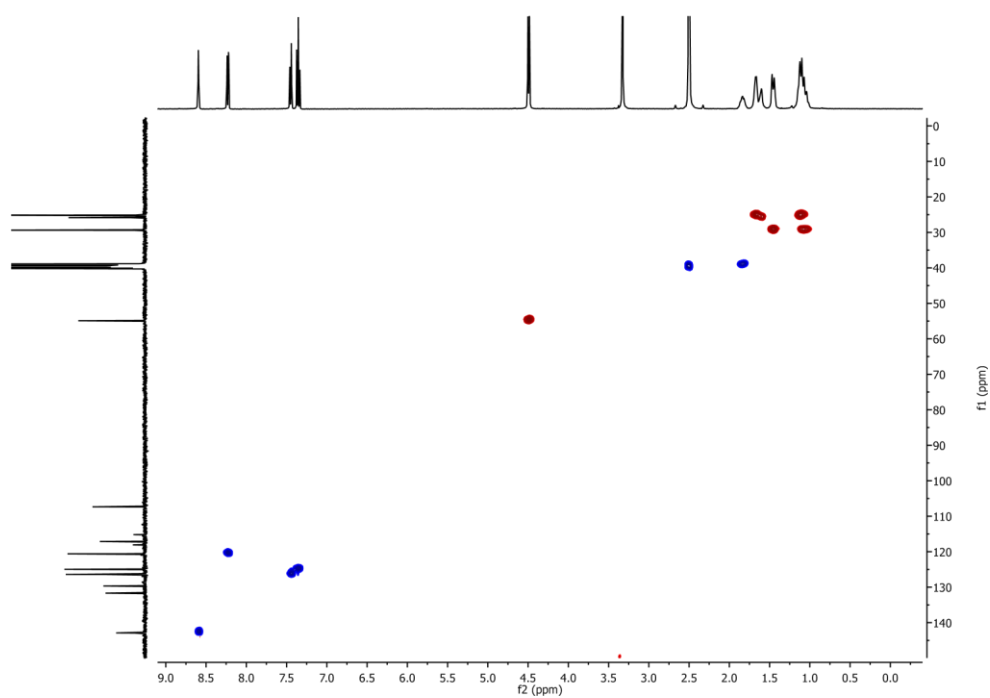


Figure S-34: HSQC of 18 (100.6 MHz, DMSO-*d*₆)

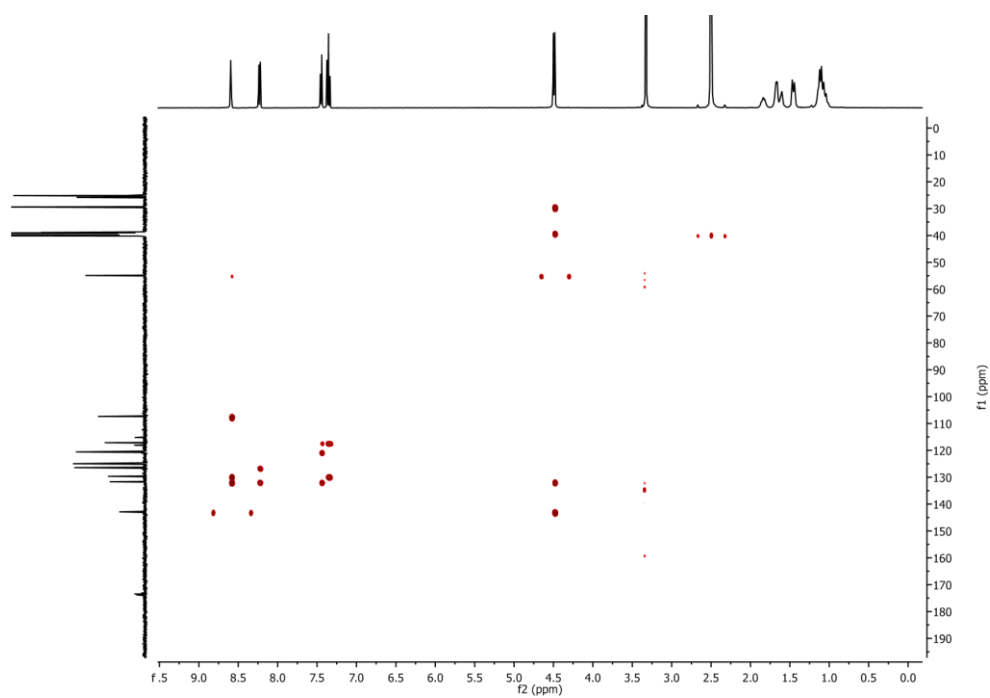


Figure S-35: HMBC of 18 (100.6 MHz, DMSO-*d*₆)

2-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid (11)

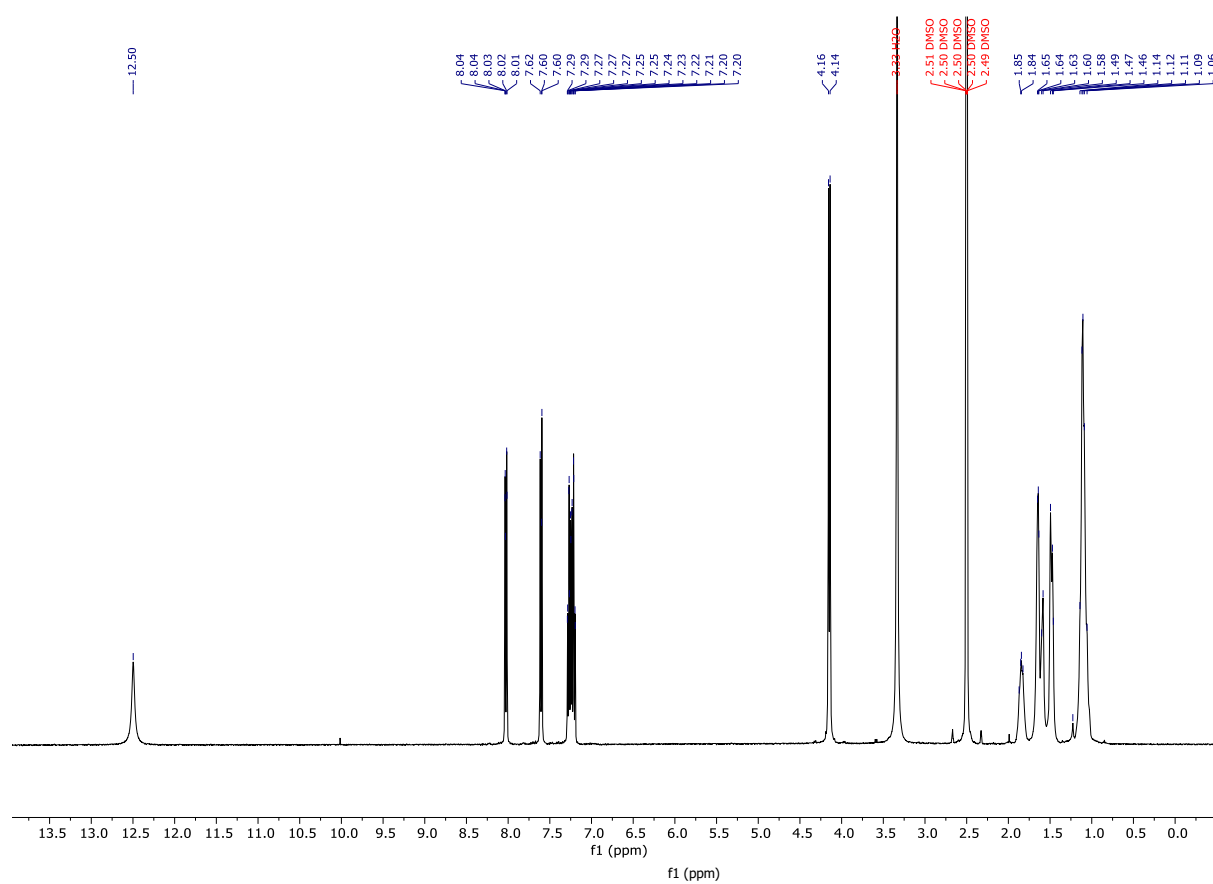
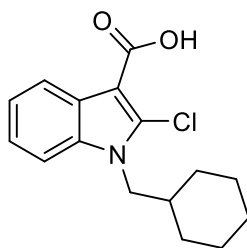


Figure S-36: ¹H-NMR of 11 (400 MHz, DMSO-*d*₆)

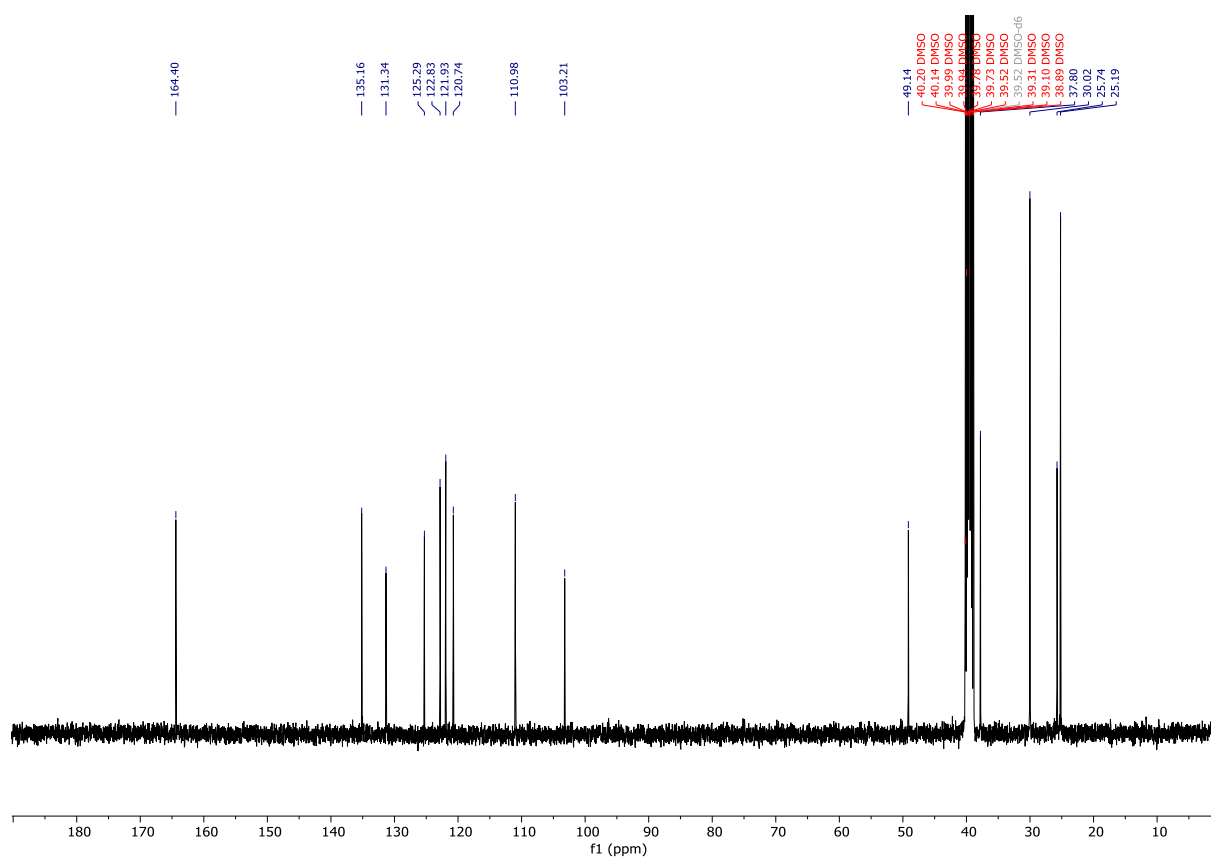


Figure S-37: ^{13}C -NMR of 11 (100.6 MHz, $\text{DMSO}-d_6$)

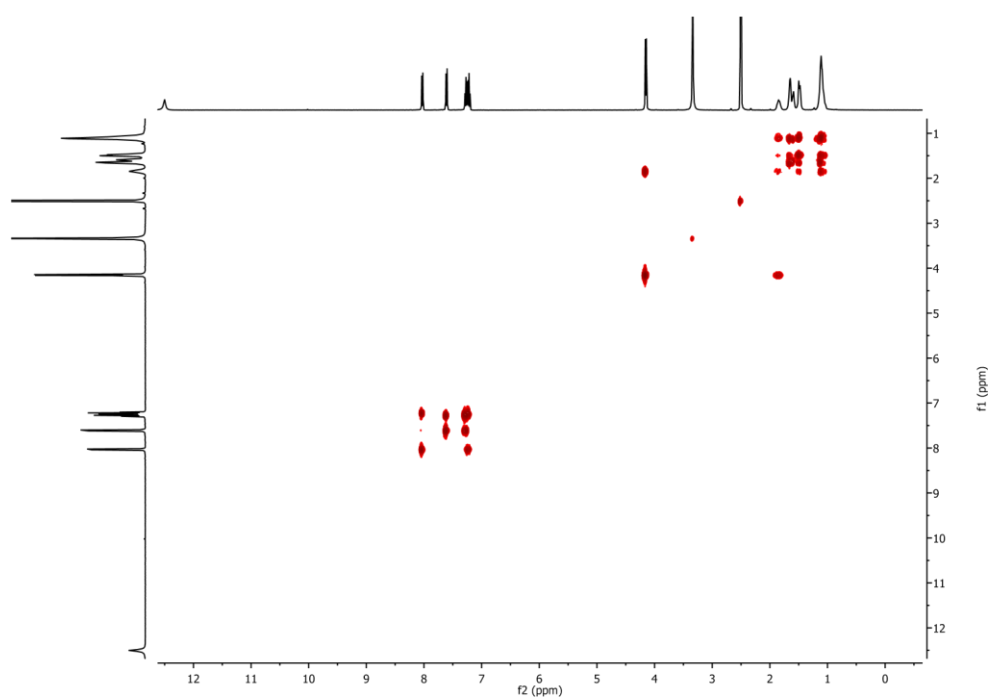


Figure S-38: COSY of 11 (400 MHz, $\text{DMSO}-d_6$)

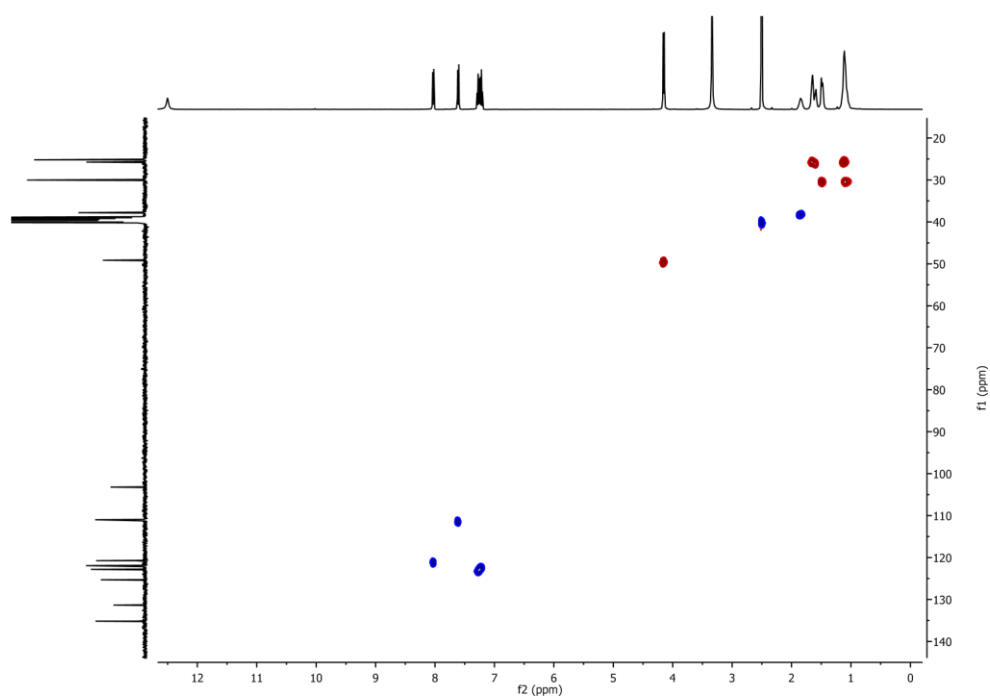


Figure S-39: HSQC of 11 (100.6 MHz, DMSO- d_6)

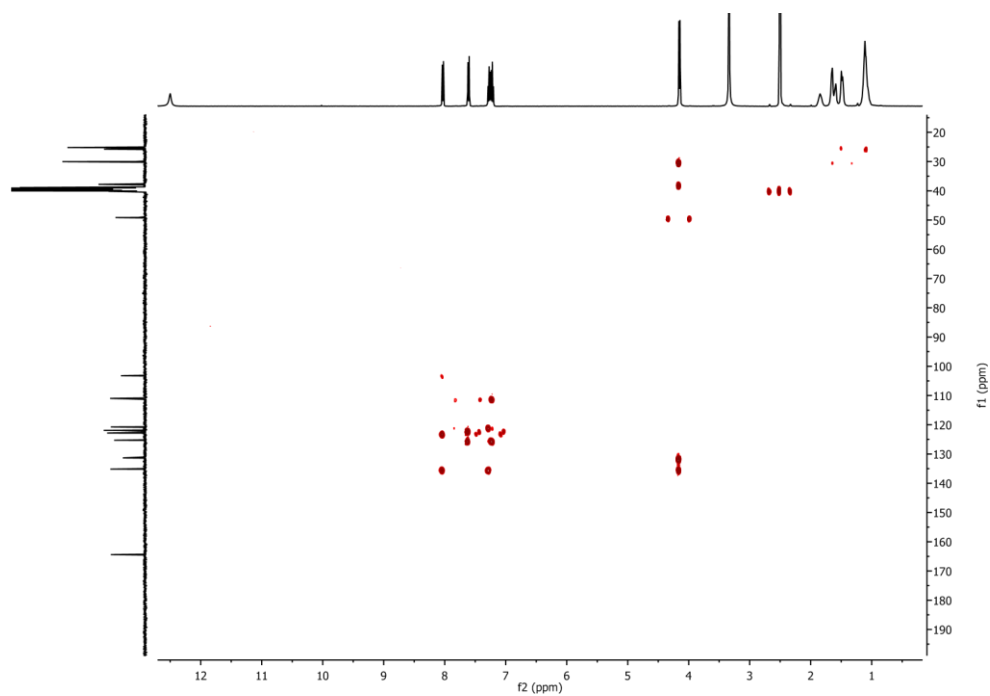


Figure S-40: HMBC of 11 (100.6 MHz, DMSO- d_6)

5-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid (12)

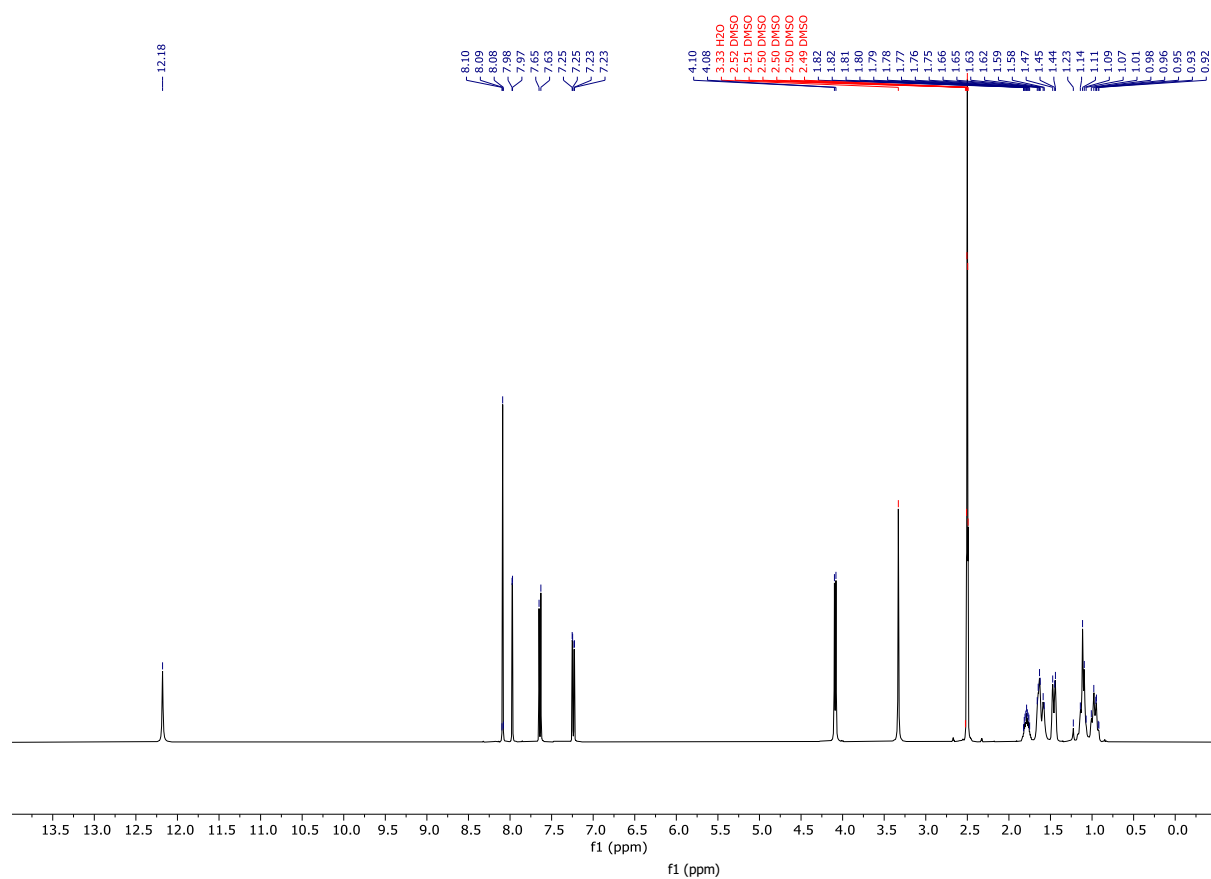
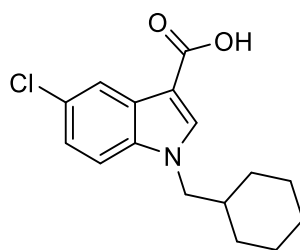


Figure S-41: ¹H-NMR of 12 (400 MHz, DMSO-*d*₆)

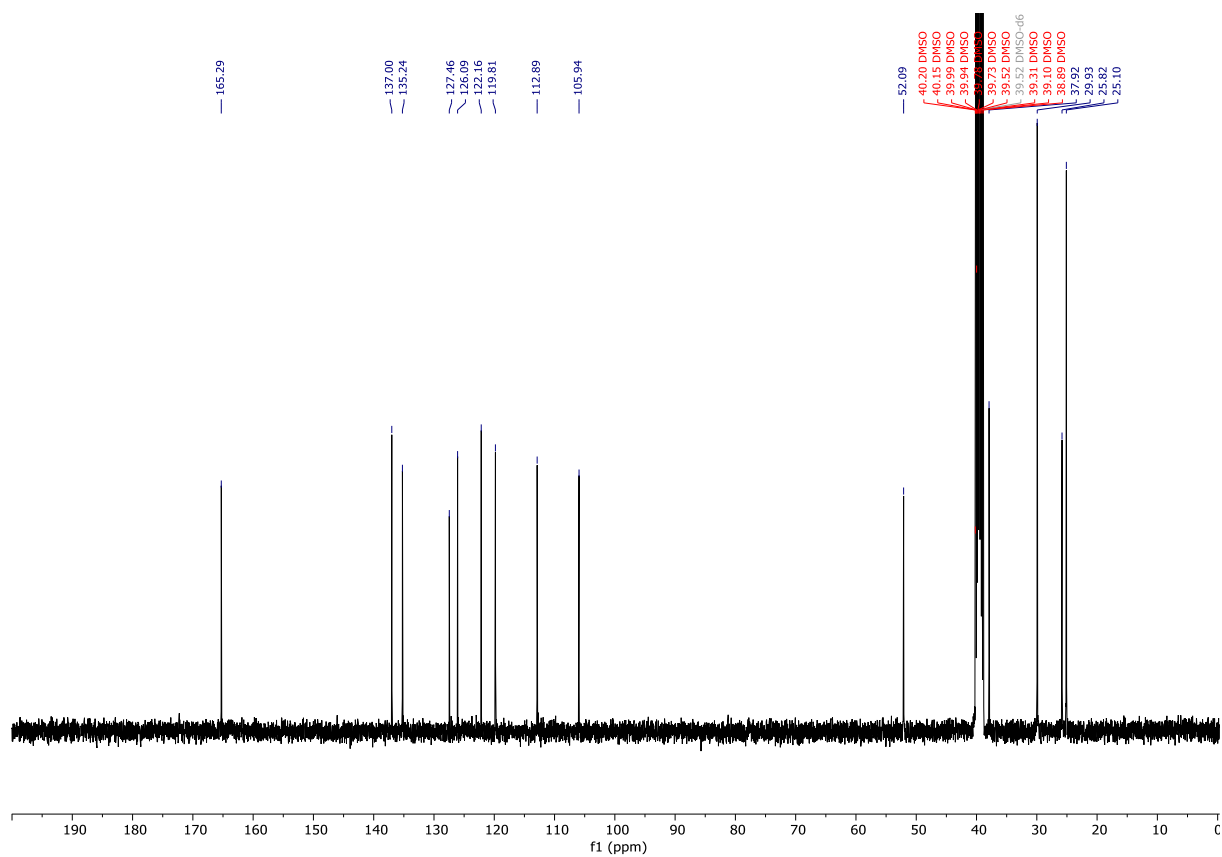


Figure S-42: ^{13}C -NMR of 12 (100.6 MHz, $\text{DMSO}-d_6$)

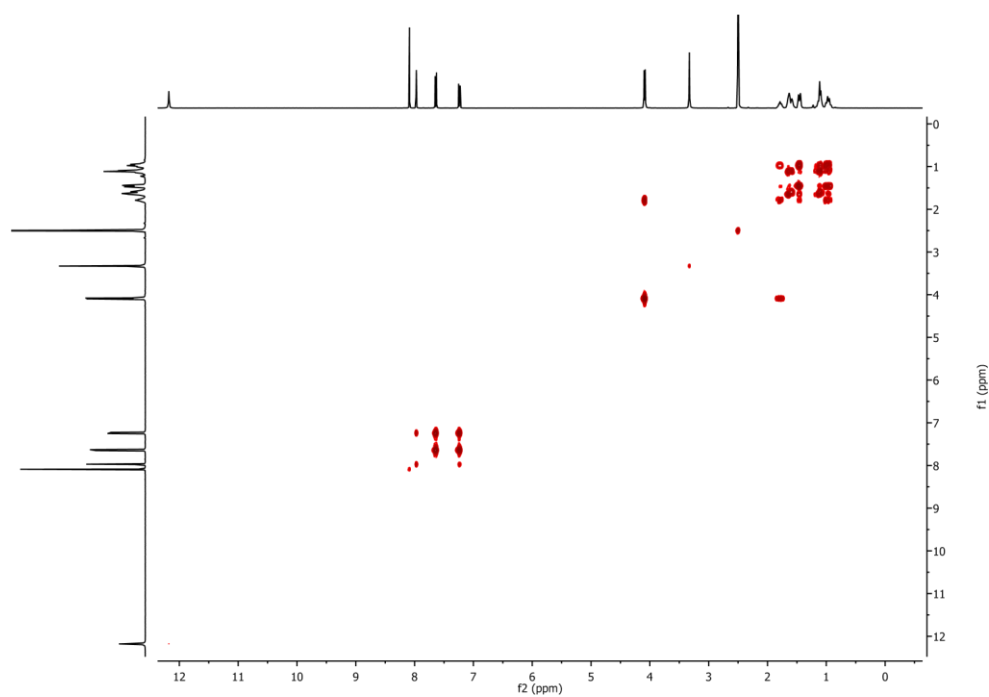


Figure S-43: COSY of 12 (400 MHz, $\text{DMSO}-d_6$)

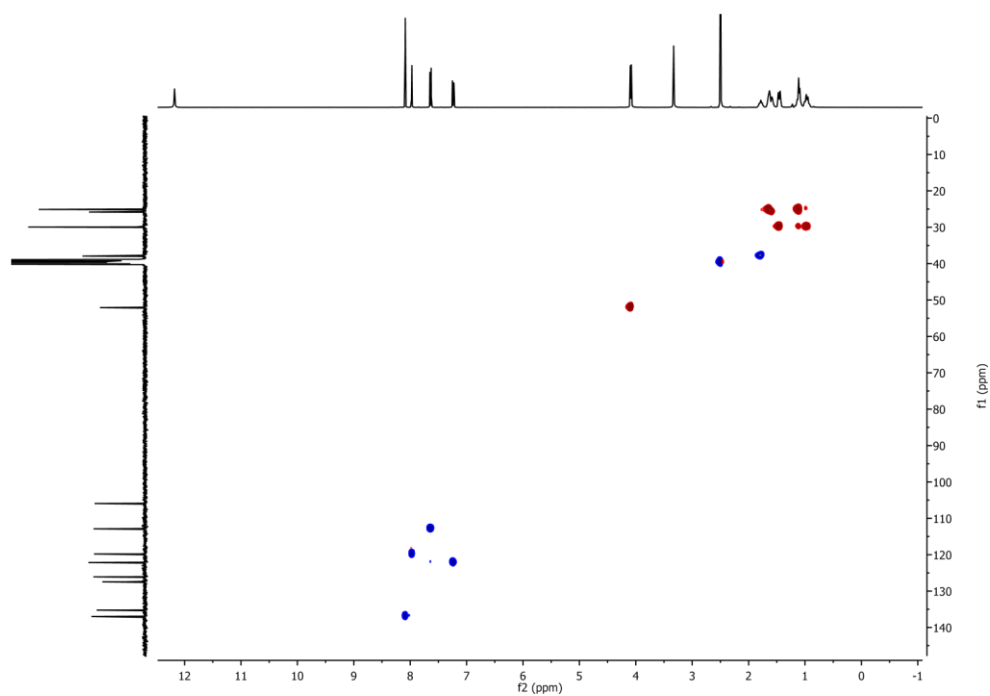


Figure S-44: HSQC of 12 (100.6 MHz, DMSO- d_6)

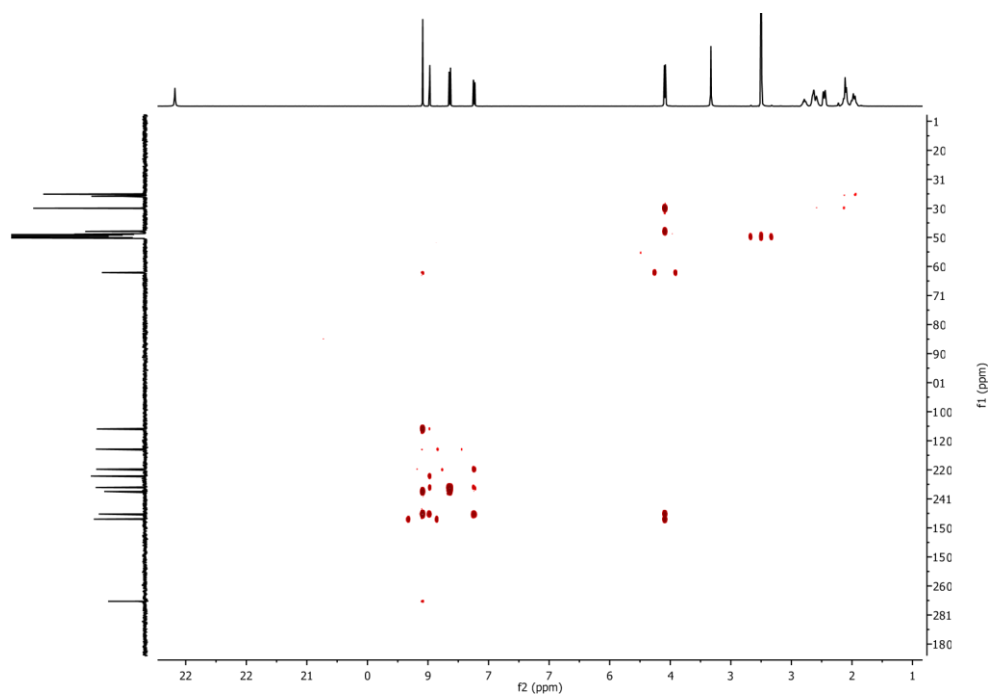


Figure S-45: HMBC of 12 (100.6 MHz, DMSO- d_6)

4-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid (19)

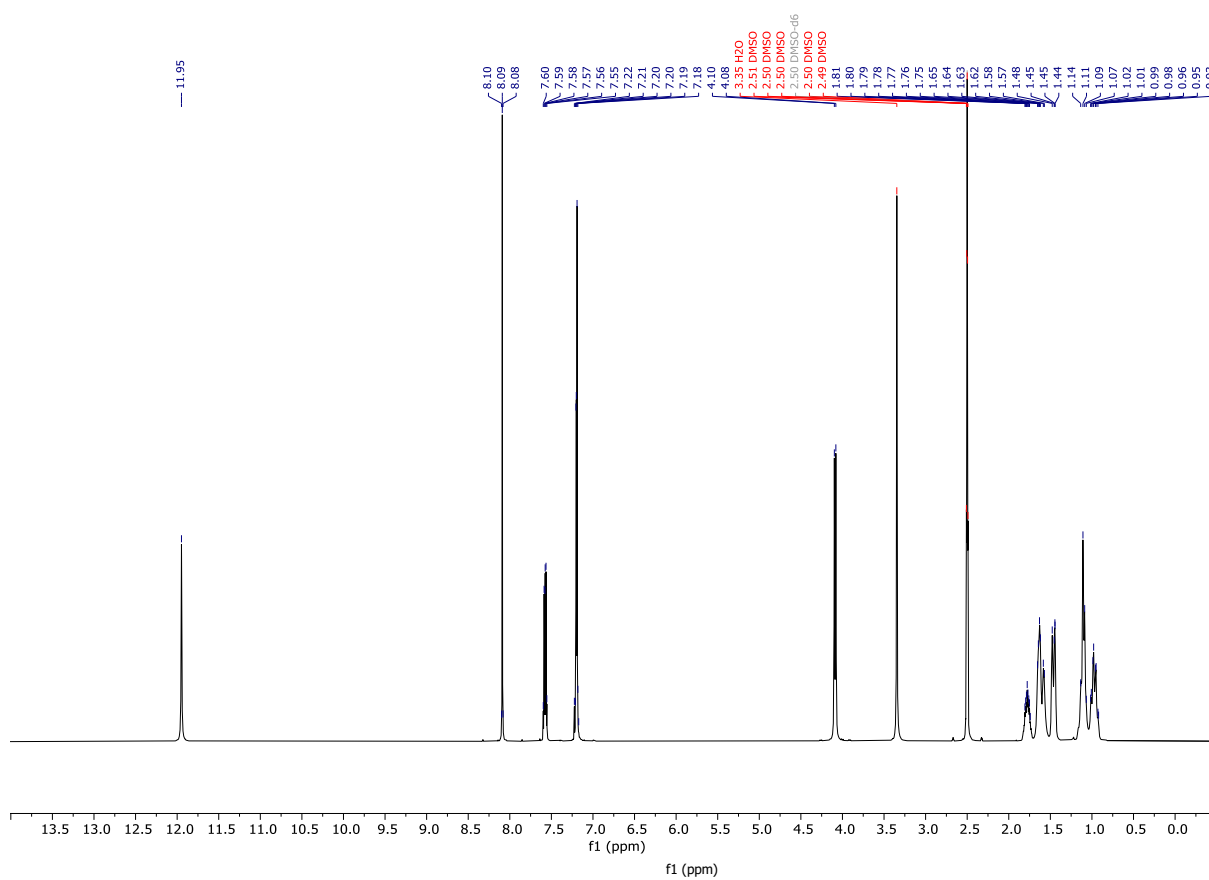
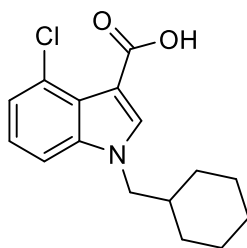


Figure S-46: ¹H-NMR of 19 (400 MHz, DMSO-*d*₆)

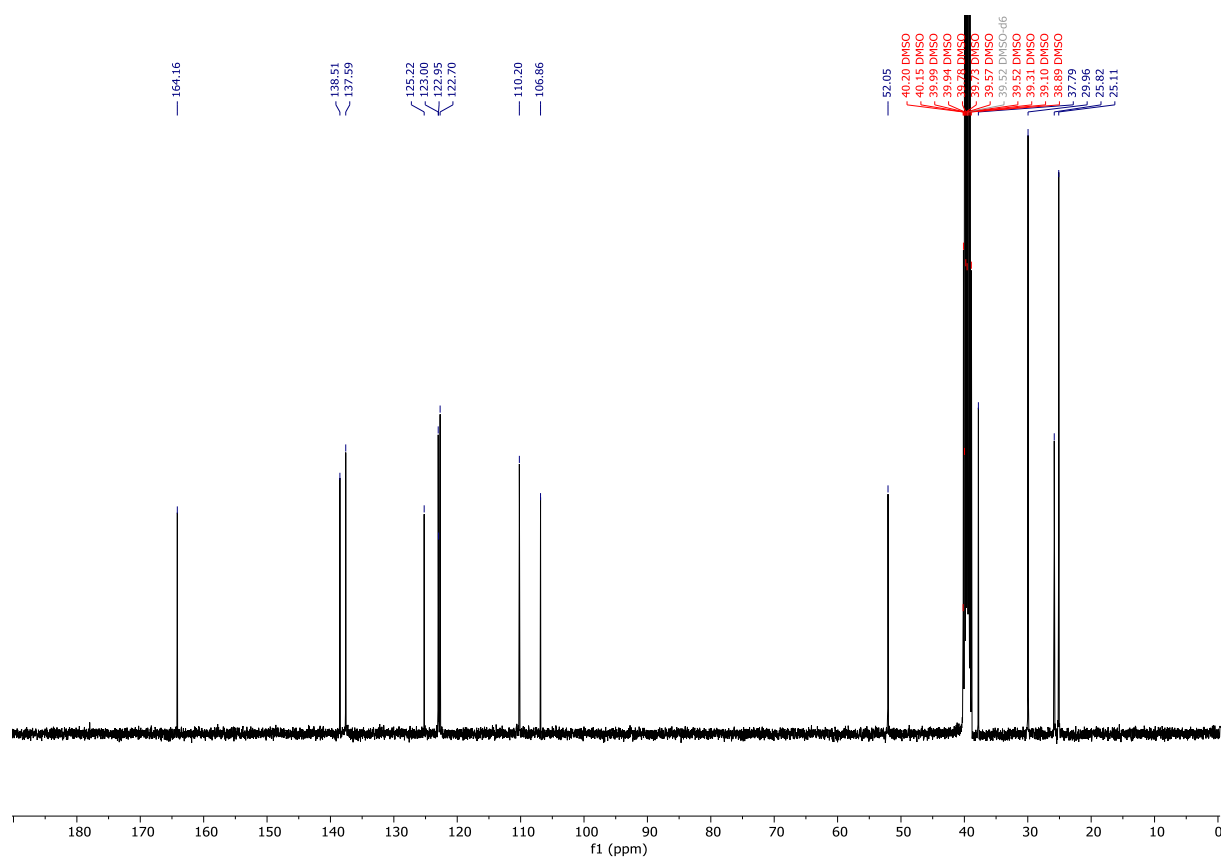


Figure S-47: ^{13}C -NMR of 19 (100.6 MHz, $\text{DMSO}-d_6$)

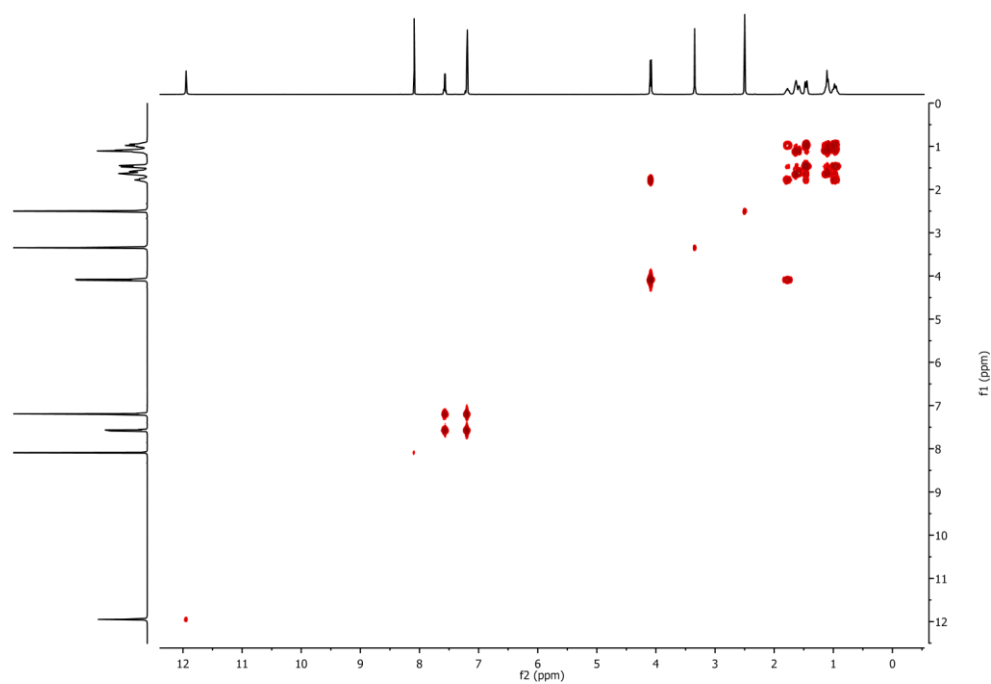


Figure S-48: COSY of 19 (400 MHz, $\text{DMSO}-d_6$)

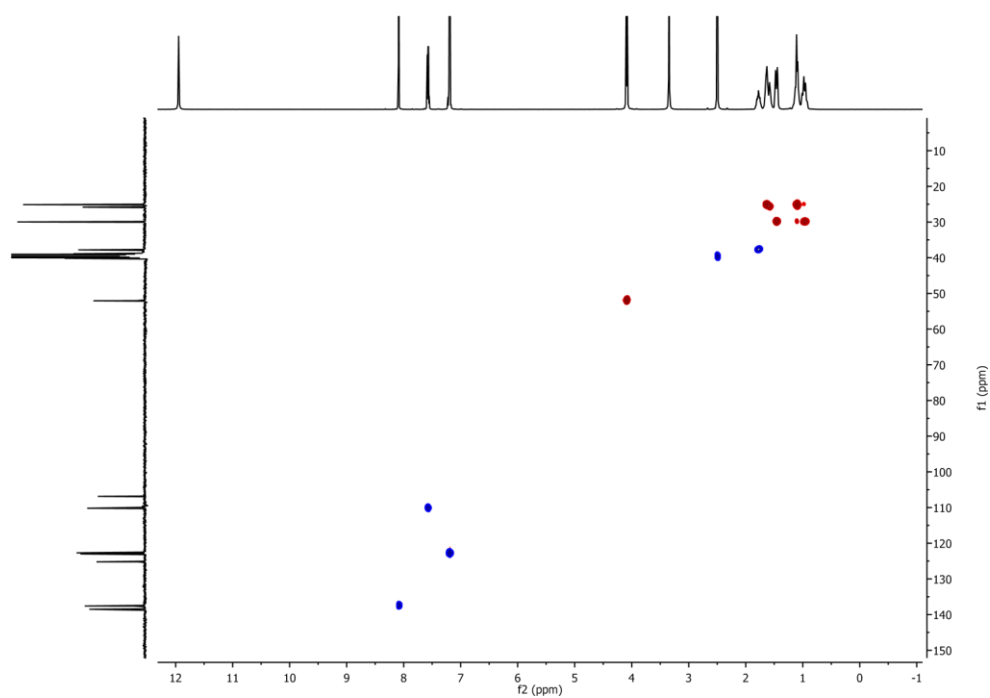


Figure S-49: HSQC of 19 (100.6 MHz, DMSO- d_6)

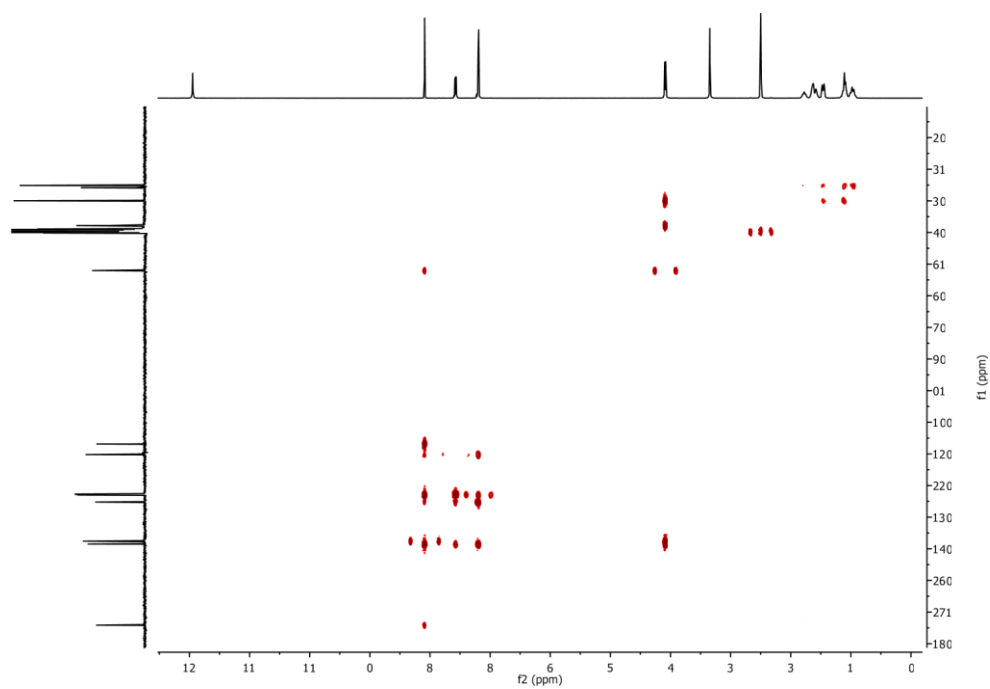


Figure S-50: HMBC of 19 (100.6 MHz, DMSO- d_6)

6-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid (20)

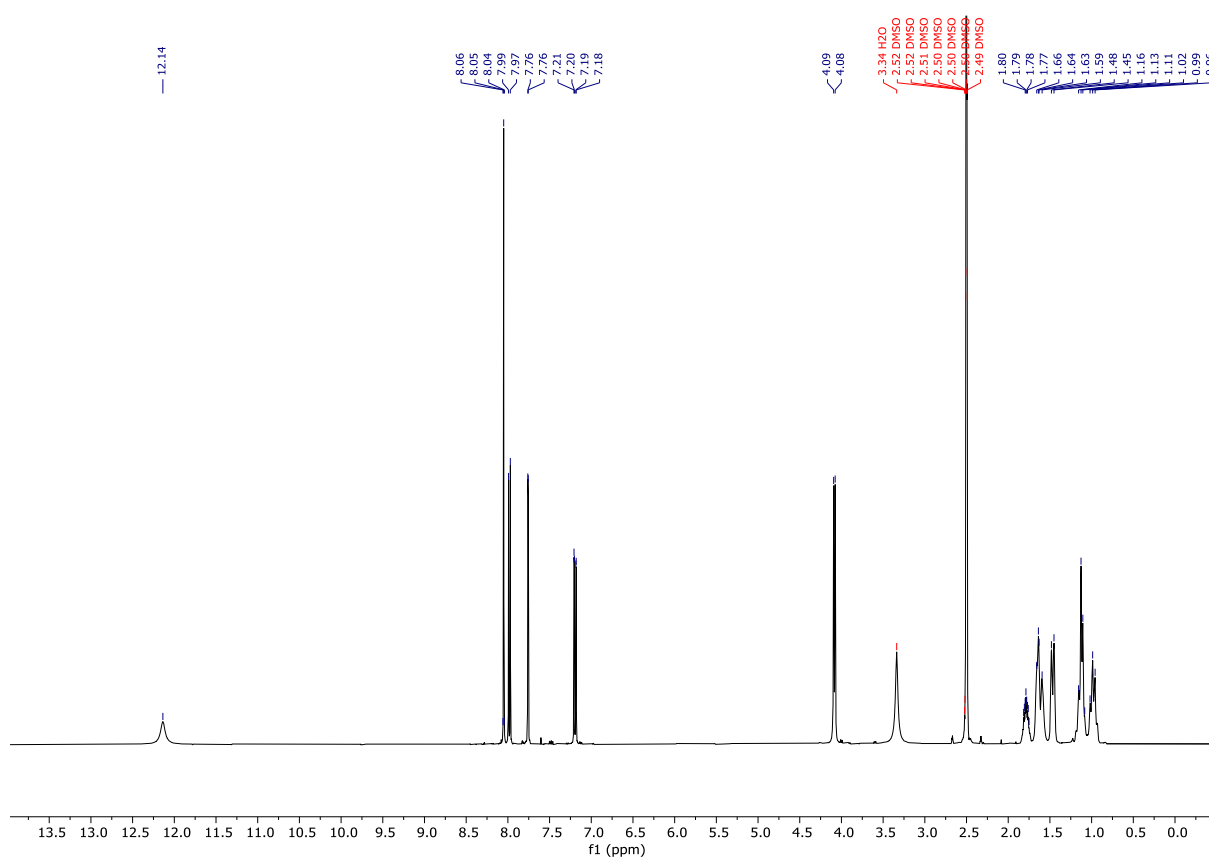
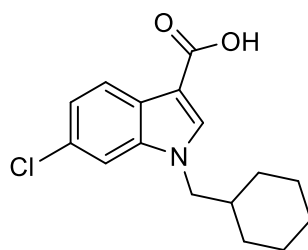


Figure S-51: ¹H-NMR of 20 (400 MHz, DMSO-*d*₆)

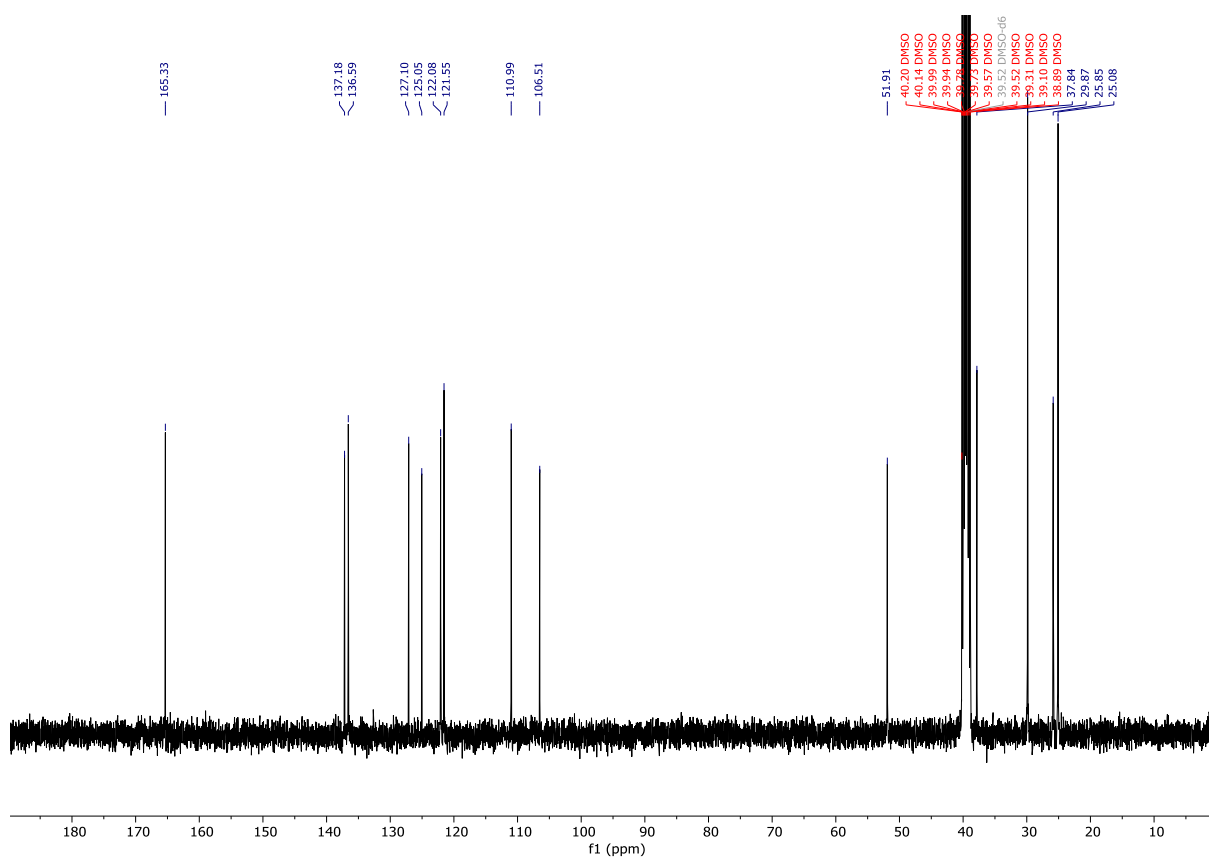


Figure S-52: ^{13}C -NMR of 20 (100.6 MHz, $\text{DMSO}-d_6$)

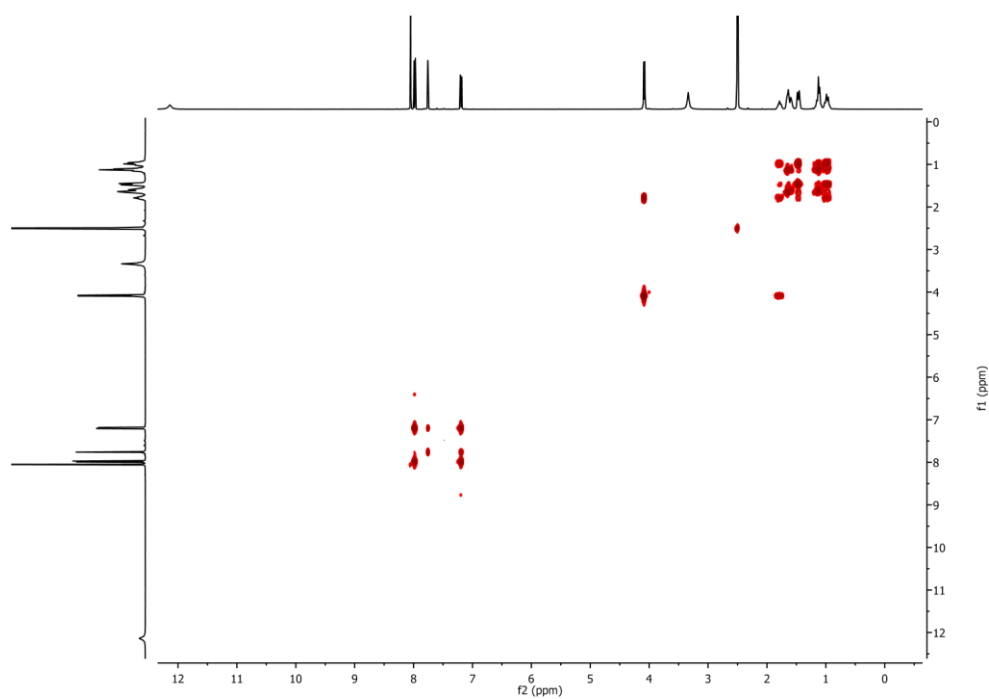


Figure S-53: COSY of 20 (400 MHz, $\text{DMSO}-d_6$)

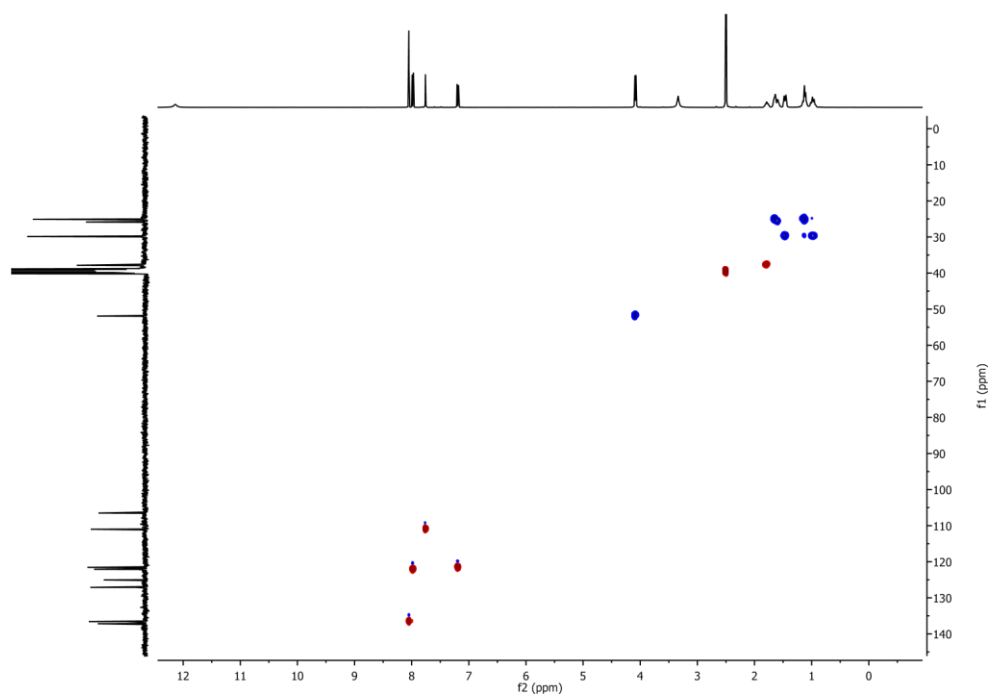


Figure S-54: HSQC of 20 (100.6 MHz, DMSO-*d*₆)

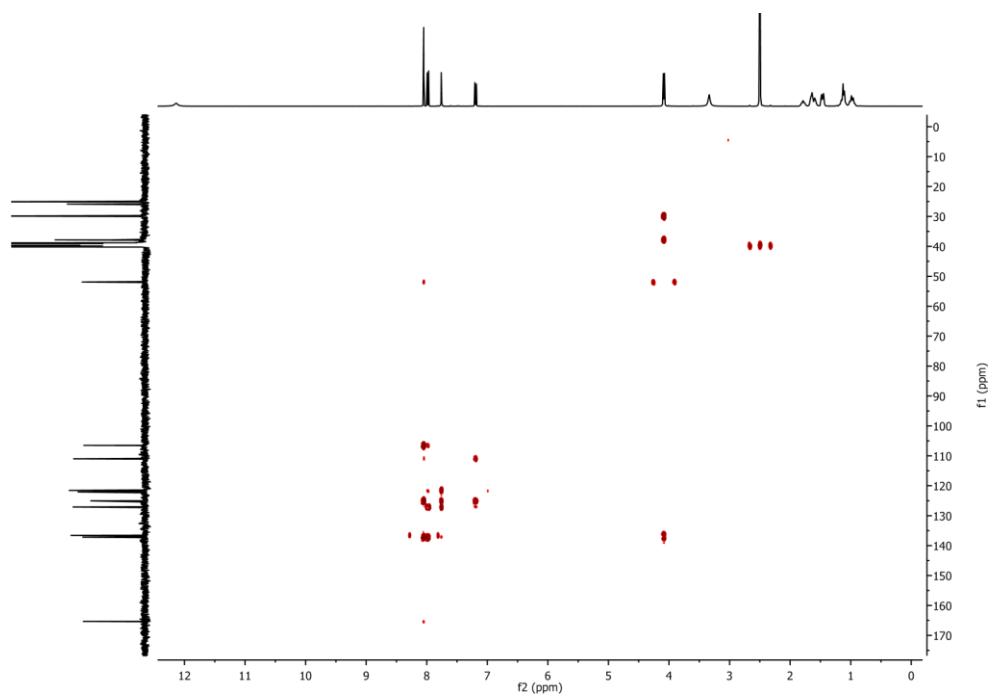


Figure S-55: HMBC of 20 (100.6 MHz, DMSO-*d*₆)

7-Chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid (21)

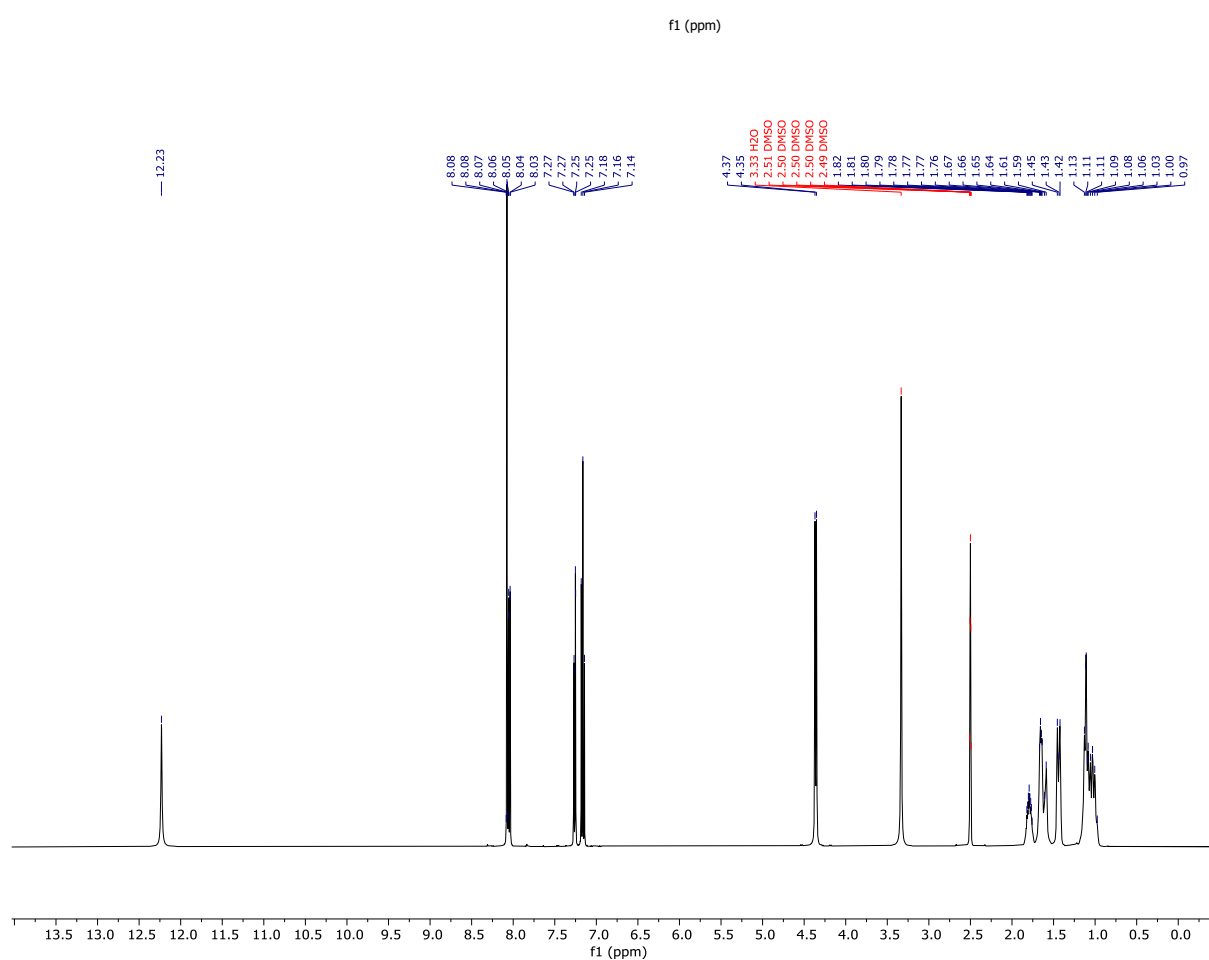
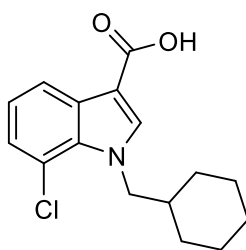


Figure S-56: ¹H-NMR of 21 (400 MHz, DMSO-d₆)

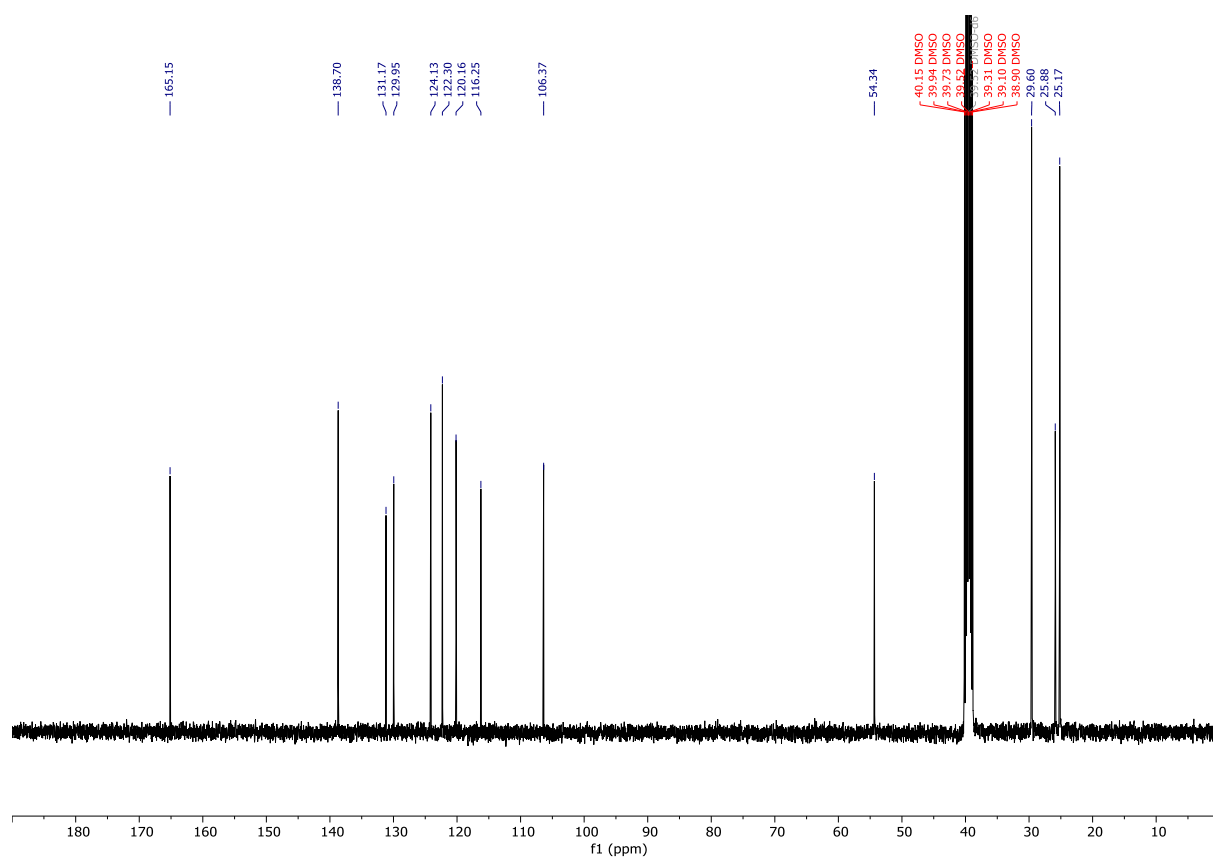


Figure S-57: ^{13}C -NMR of 21 (100.6 MHz, $\text{DMSO}-d_6$)

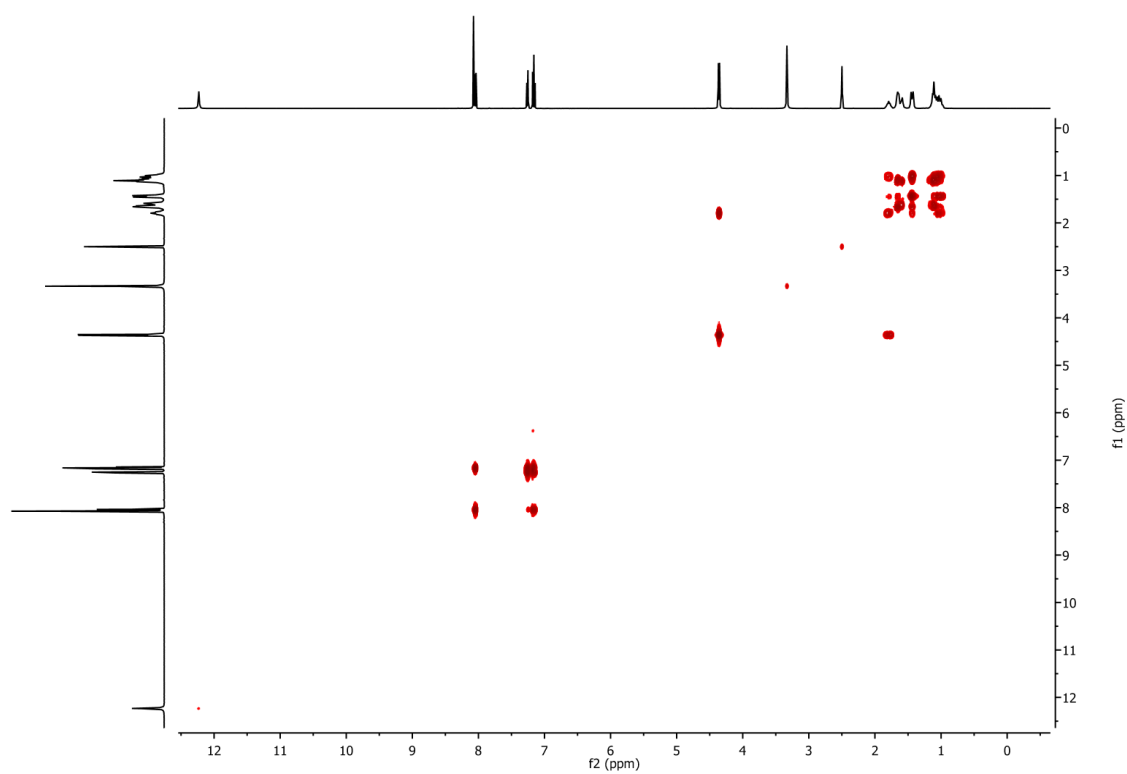


Figure S-58: COSY of 21 (400 MHz, $\text{DMSO}-d_6$)

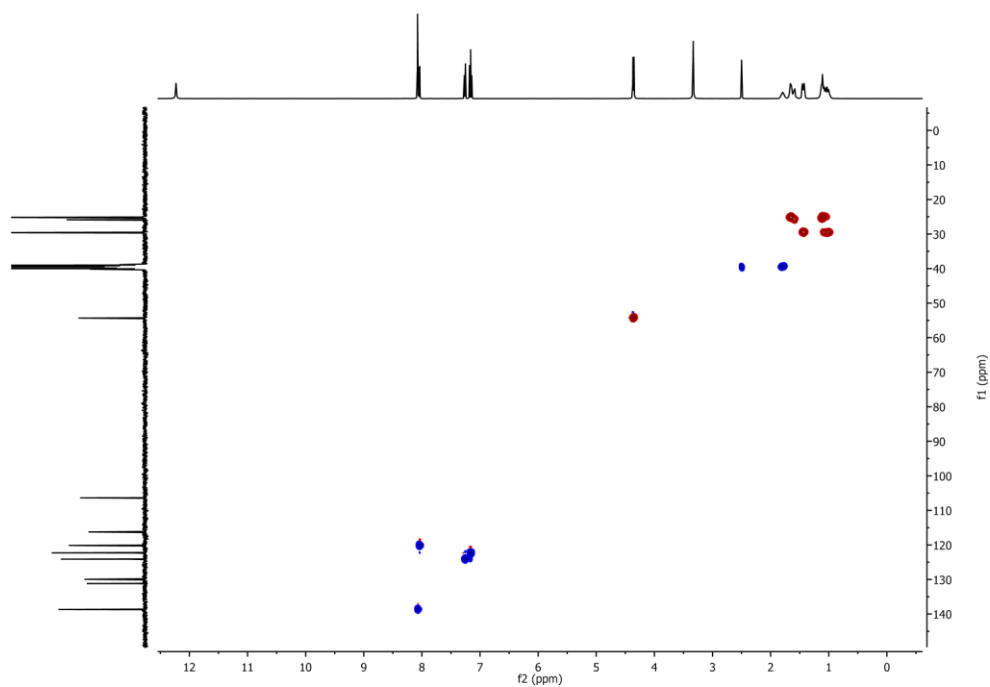


Figure S-59: HSQC of 21 (100.6 MHz, $\text{DMSO}-d_6$)

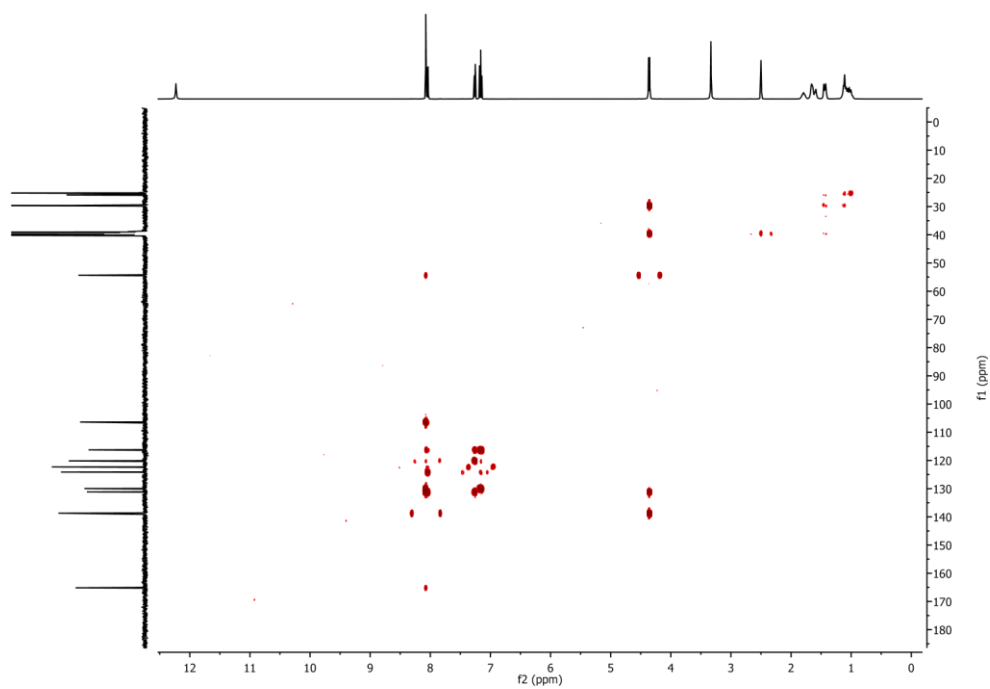


Figure S-60: HMBC of 21 (100.6 MHz, $\text{DMSO}-d_6$)

Methyl (S)-2-(2-chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate (2-Chloro-MDMB-CHMICA) (2)

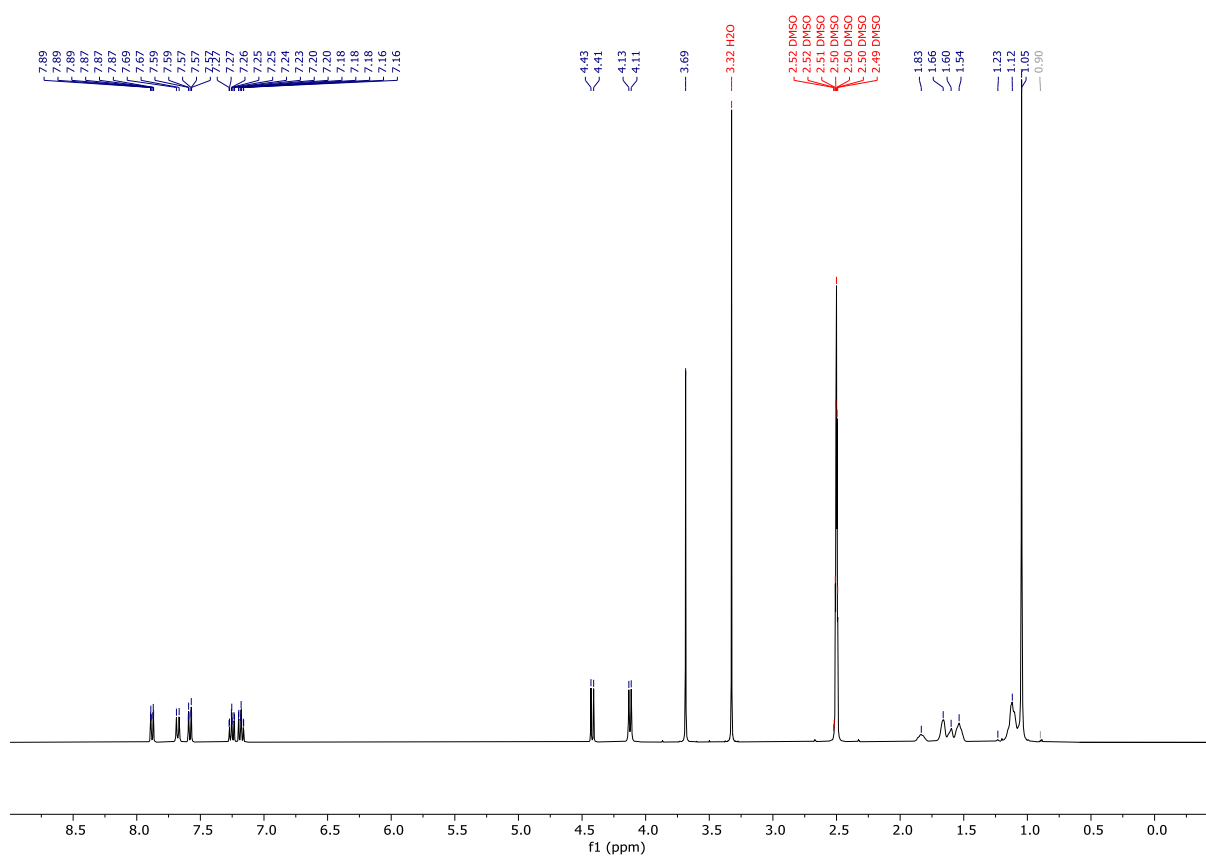
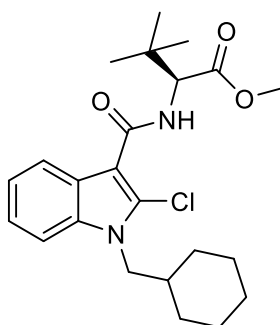


Figure S-61: ¹H-NMR of 2 (400 MHz, DMSO-*d*₆)

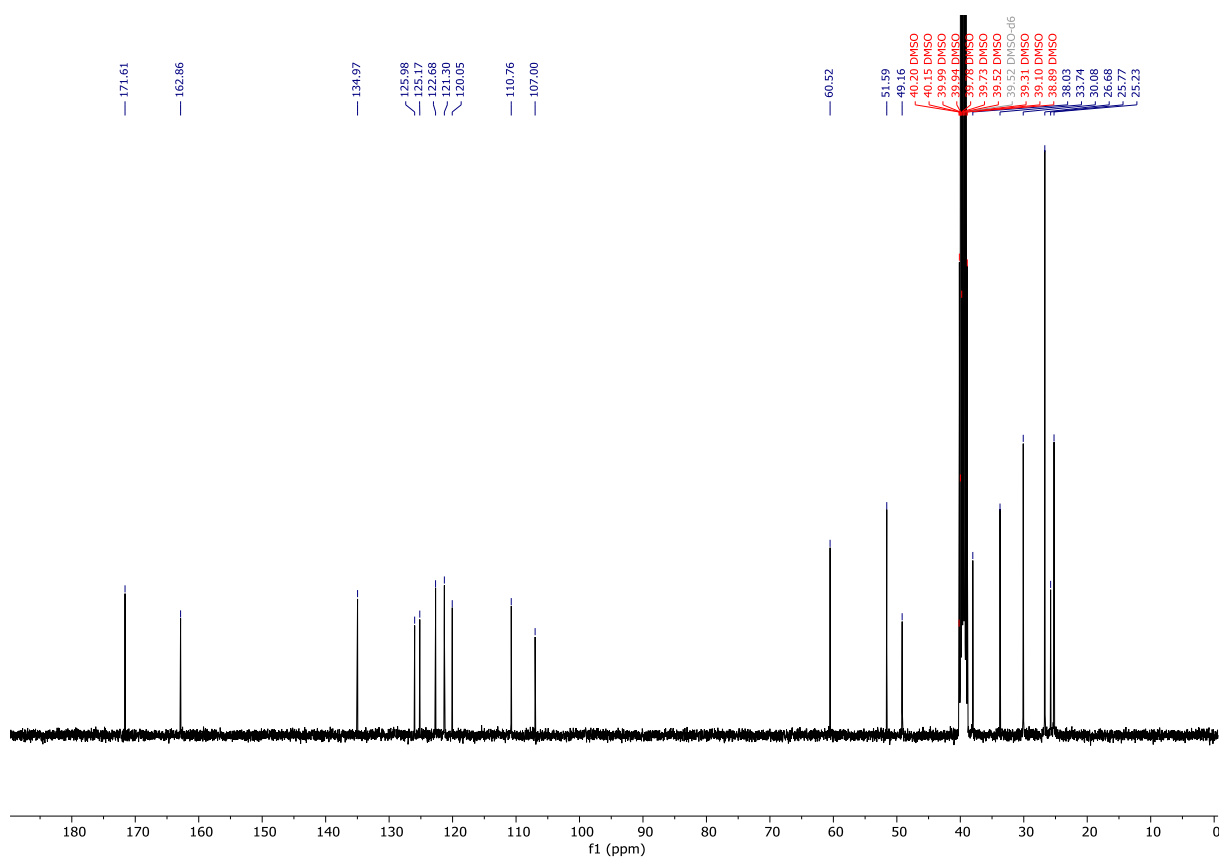


Figure S-62: ^{13}C -NMR of **2** (100.6 MHz, $\text{DMSO}-d_6$)

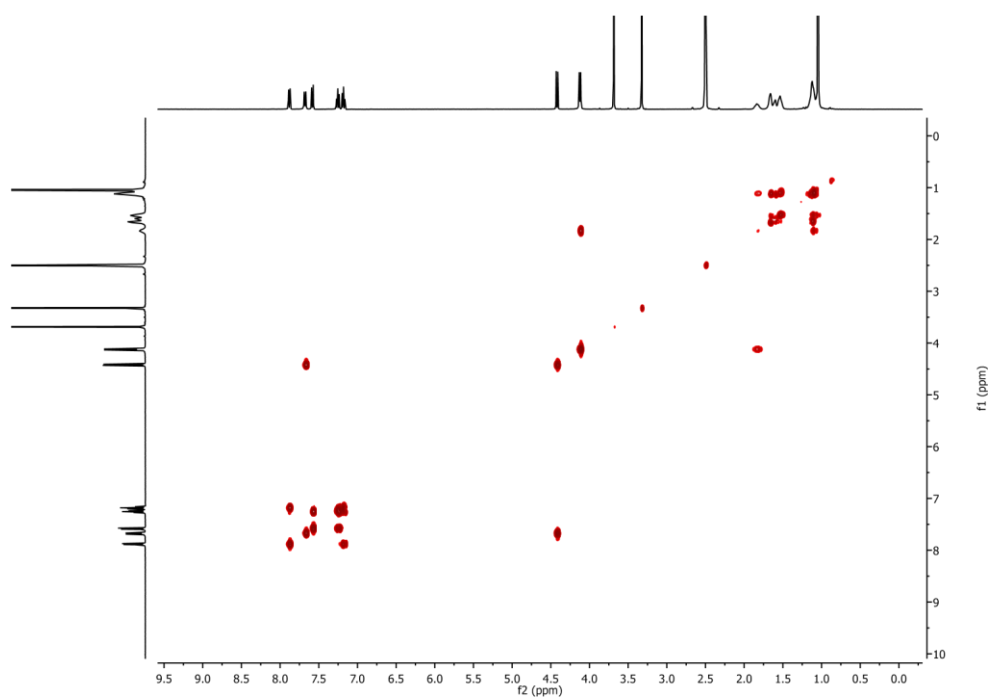


Figure S-63: COSY of **2** (400 MHz, $\text{DMSO}-d_6$)

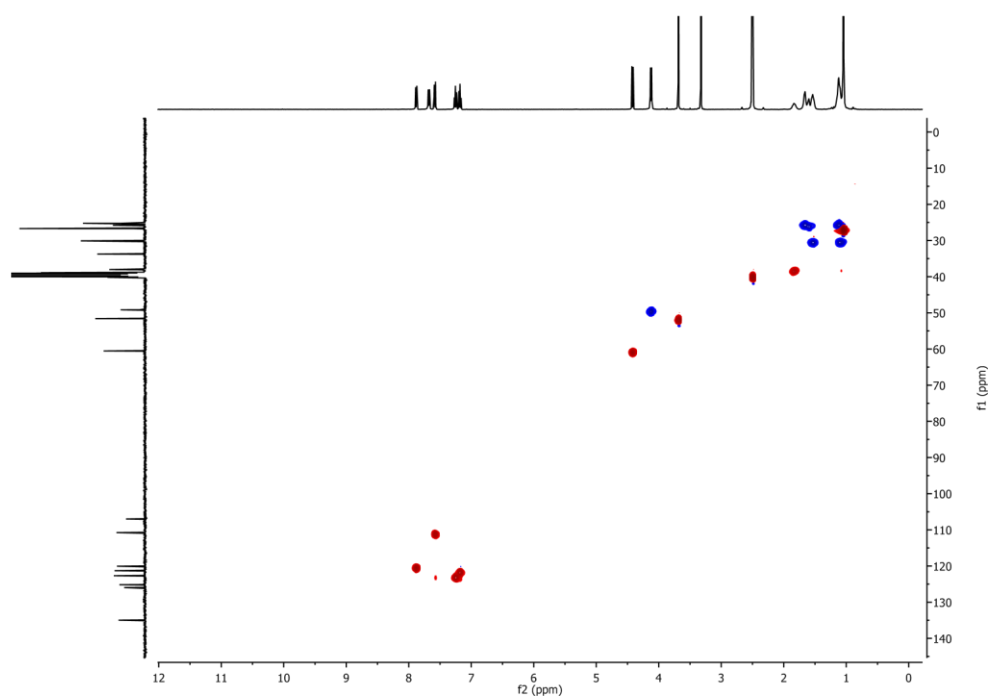


Figure S-64: HSQC of **2** (100.6 MHz, DMSO- d_6)

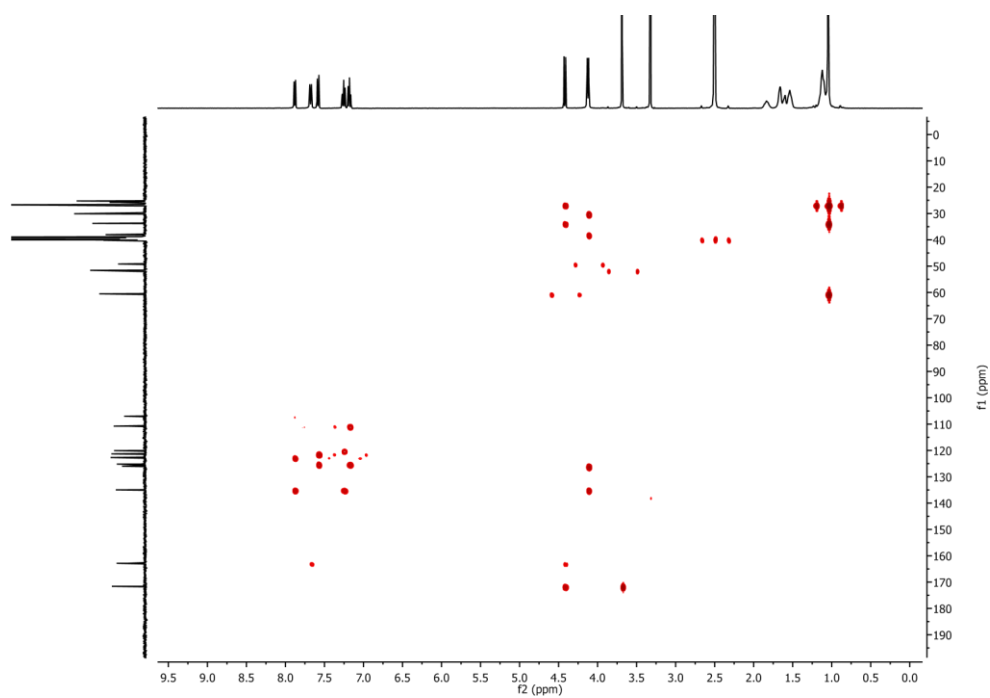


Figure S-65: HMBC of **2** (100.6 MHz, DMSO- d_6)

Methyl (S)-2-(4-chloro-1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate (4-Chloro-MDMB-CHMICA) (3)

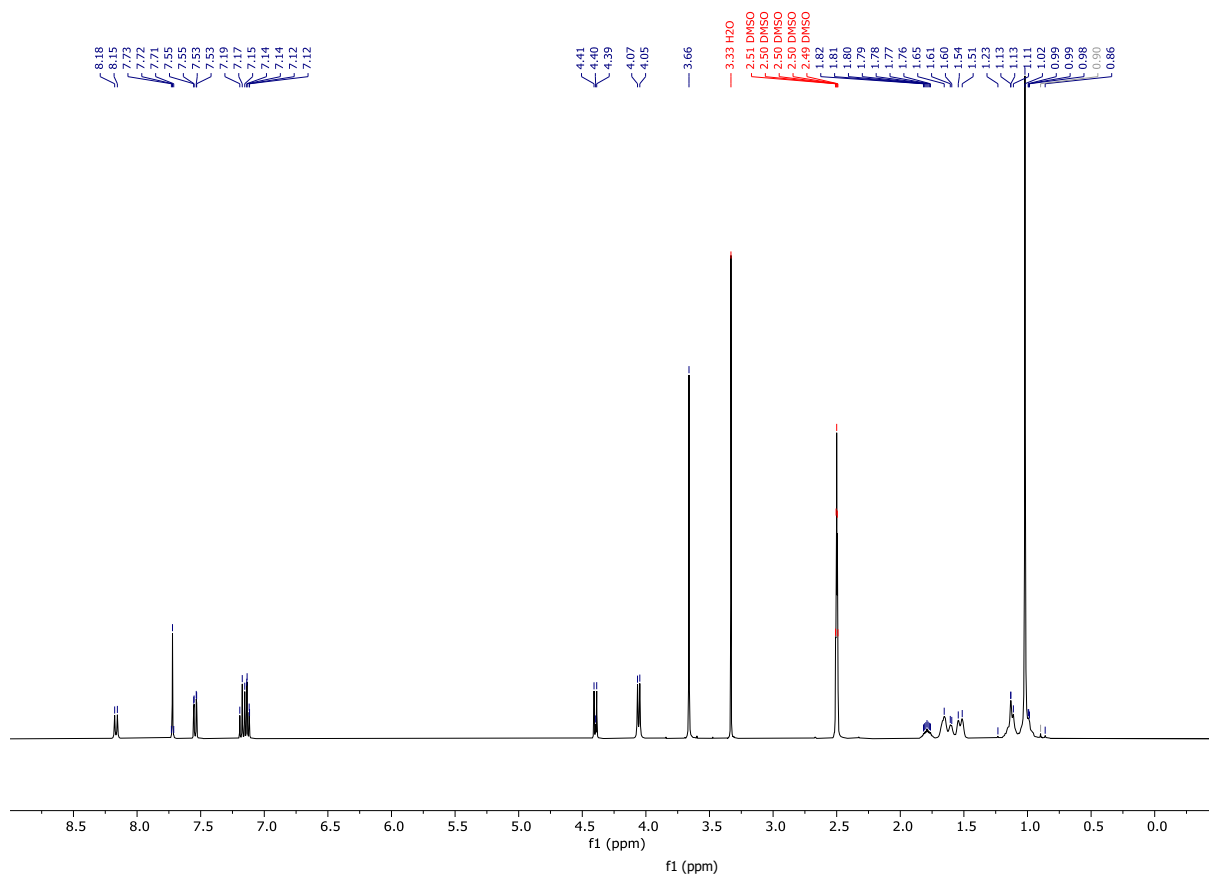
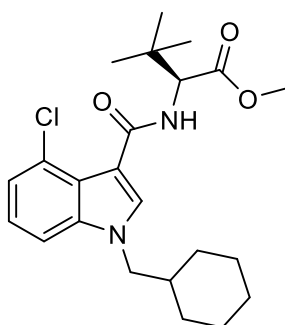


Figure S-66: ¹H-NMR of 3 (400 MHz, DMSO-*d*₆)

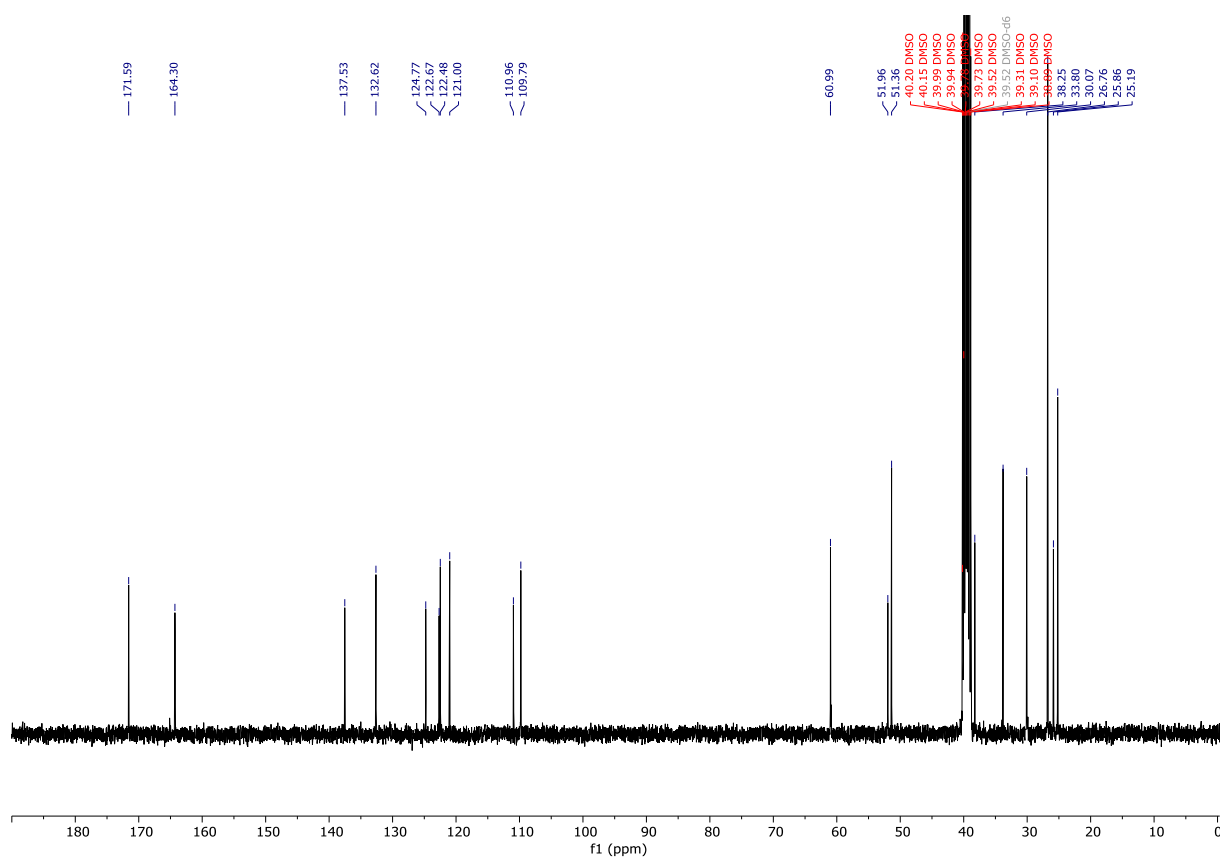


Figure S-67: ^{13}C -NMR of **3** (100.6 MHz, $\text{DMSO}-d_6$)

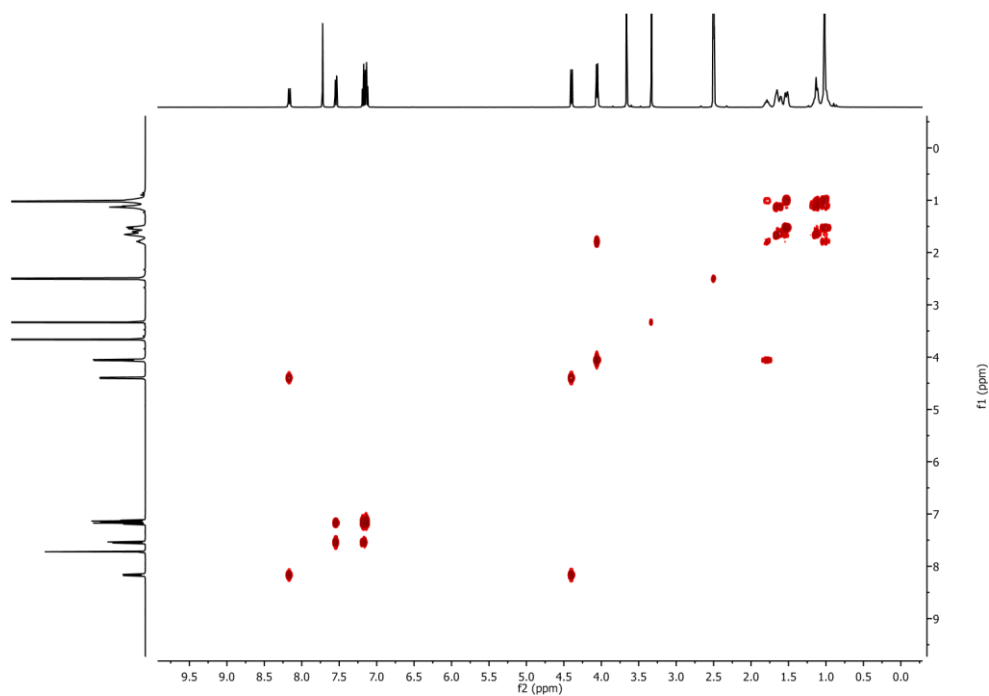


Figure S-68: COSY of **3** (400 MHz, $\text{DMSO}-d_6$)

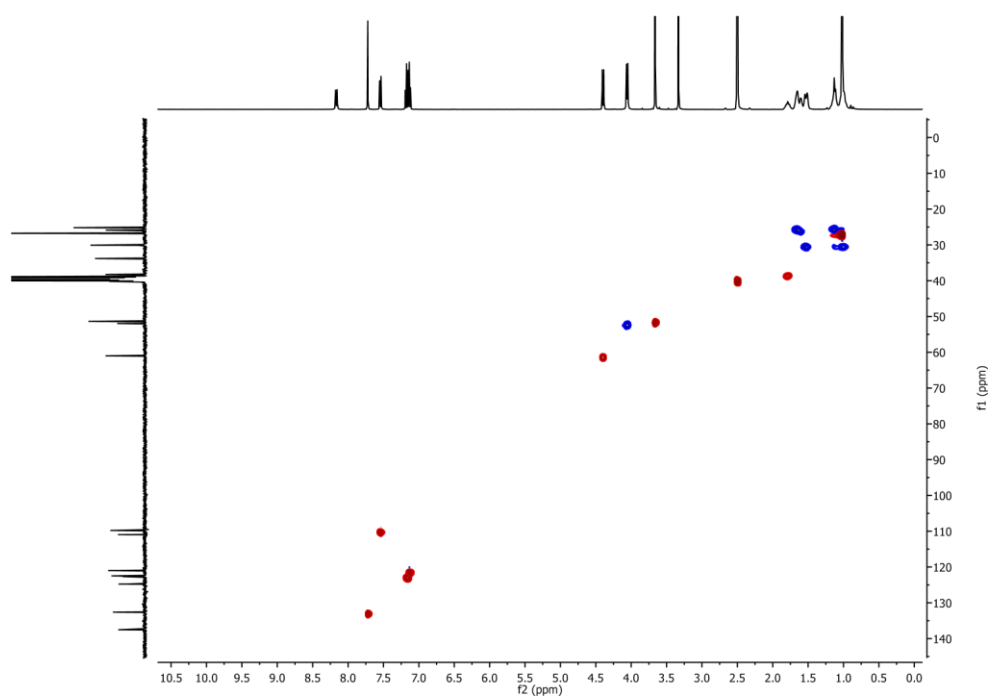


Figure S-69: HSQC of **3** (100.6 MHz, DMSO-*d*₆)

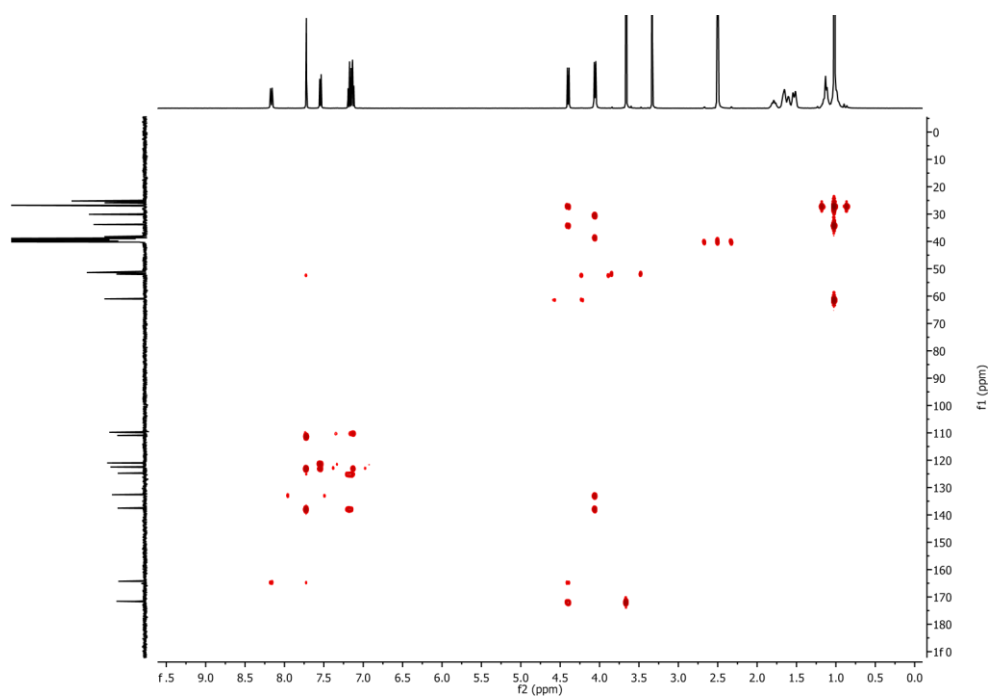


Figure S-70: HMBC of **3** (100.6 MHz, DMSO-*d*₆)

Methyl (*S*)-2-(5-chloro-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate (5-Chloro-MDMB-CHMICA) (4)

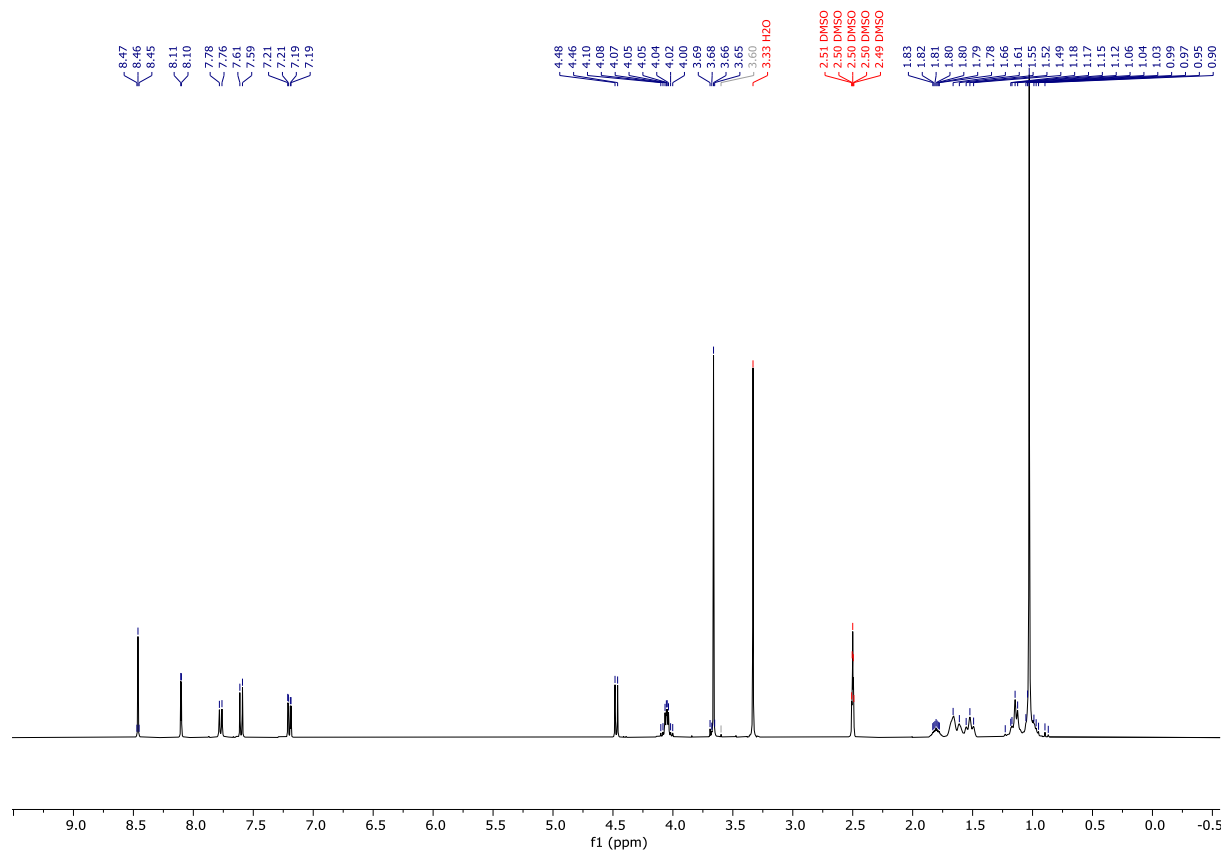
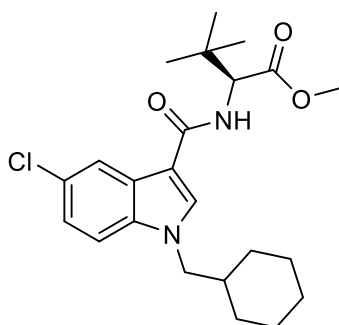


Figure S-71: ¹H-NMR of 4 (400 MHz, DMSO-*d*₆)

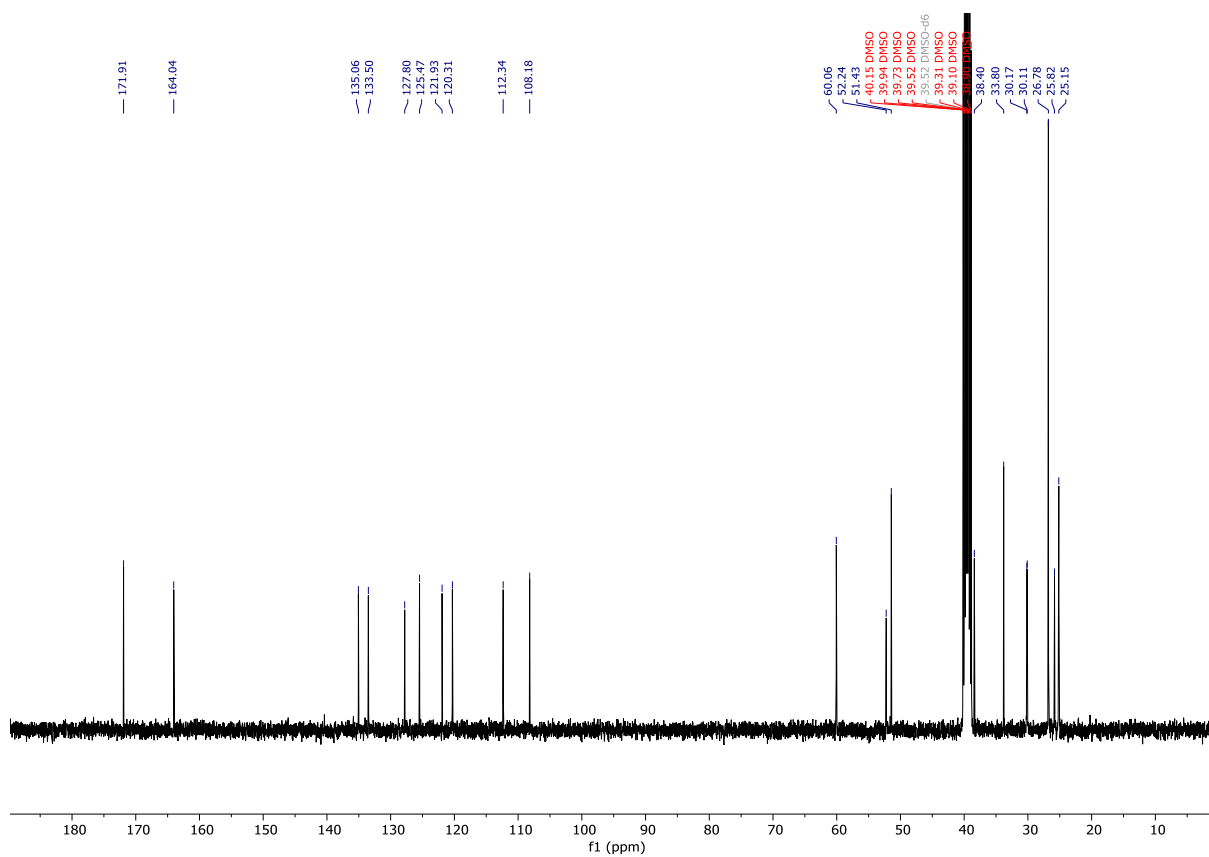


Figure S-72: ^{13}C -NMR of **4** (100.6 MHz, $\text{DMSO}-d_6$)

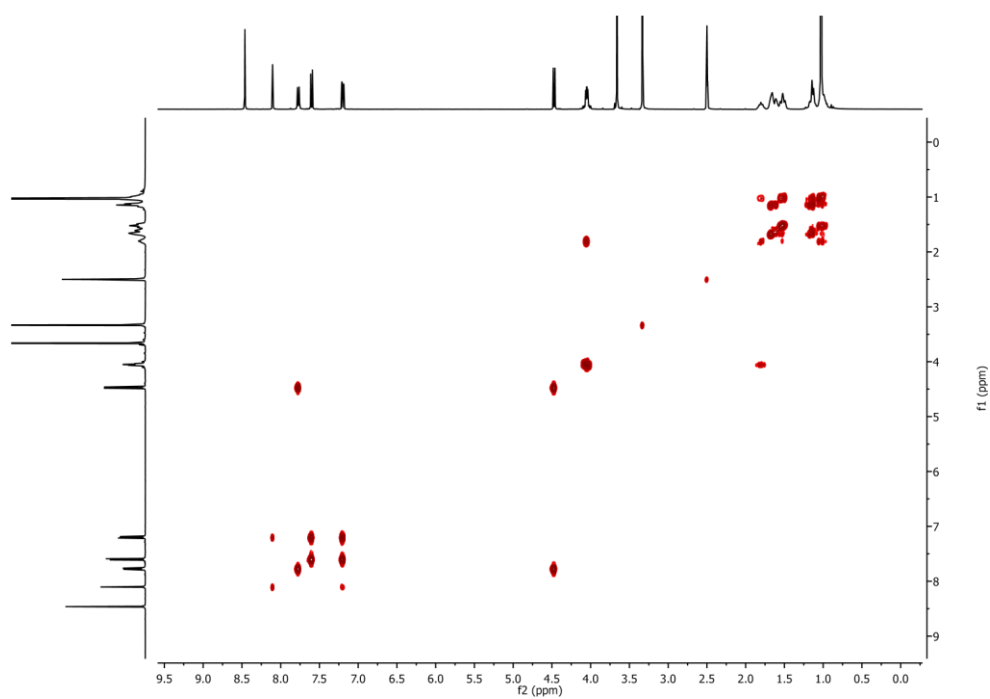


Figure S-73: COSY of **4** (400 MHz, $\text{DMSO}-d_6$)

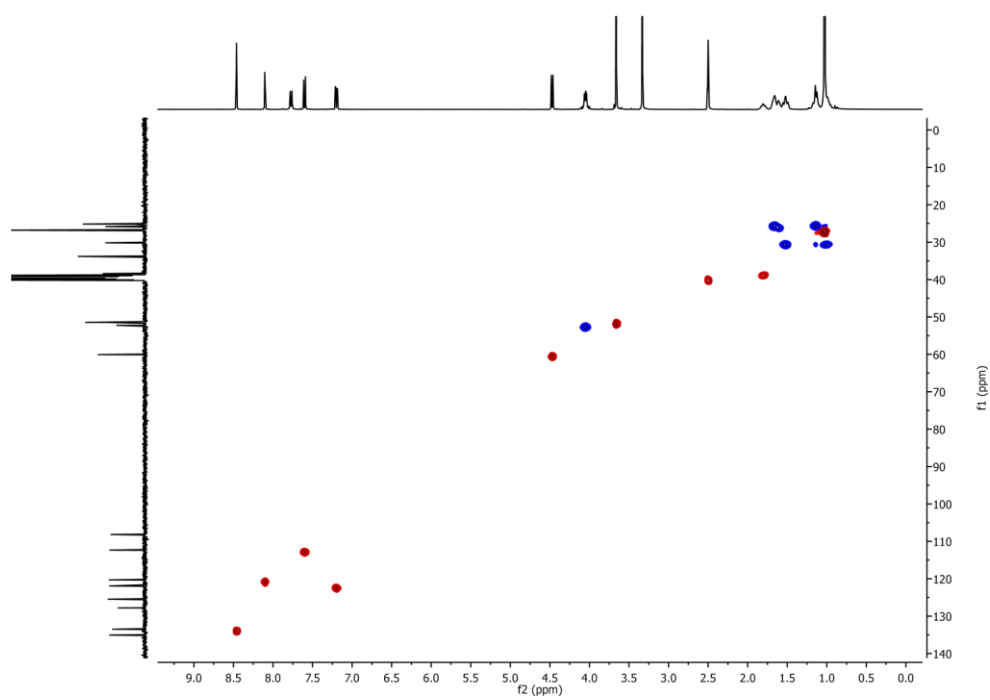


Figure S-74: HSQC of 4 (100.6 MHz, DMSO- d_6)

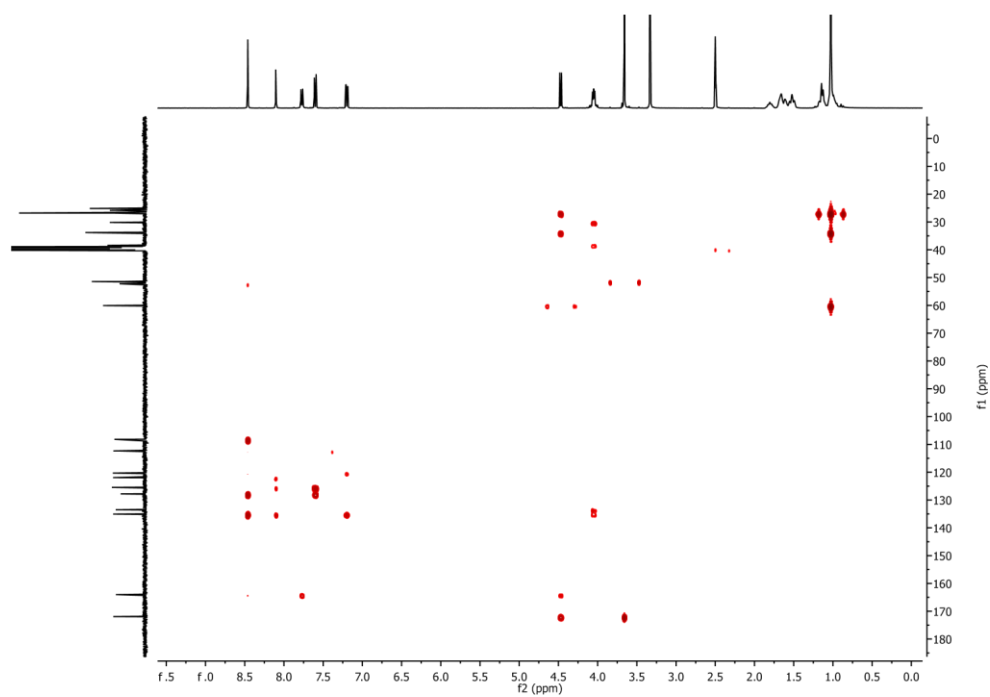


Figure S-75: HMBC of 4 (100.6 MHz, DMSO- d_6)

Methyl (S)-2-(6-chloro-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate (6-Chloro-MDMB-CHMICA) (5)

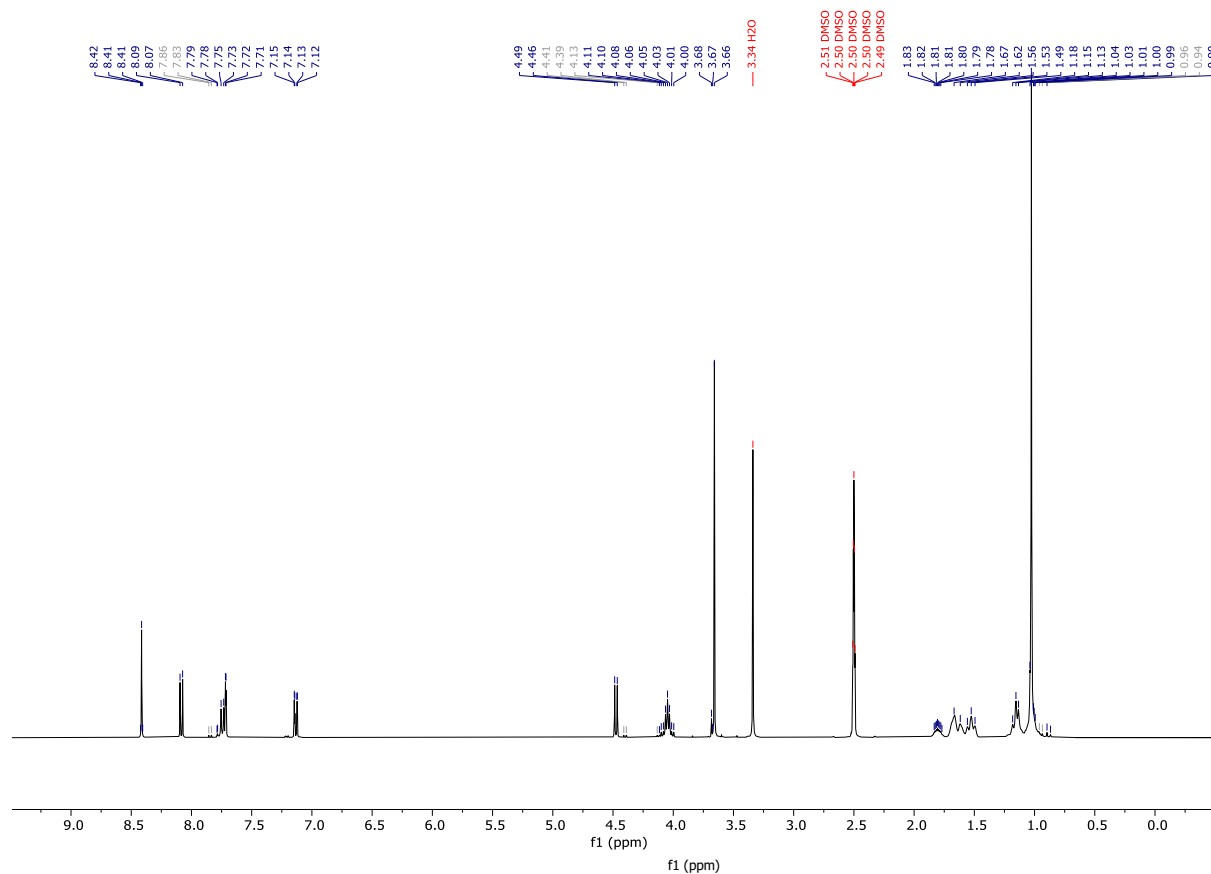
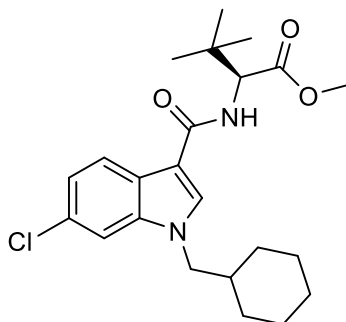


Figure S-76: ^1H -NMR of 5 (400 MHz, $\text{DMSO}-d_6$)

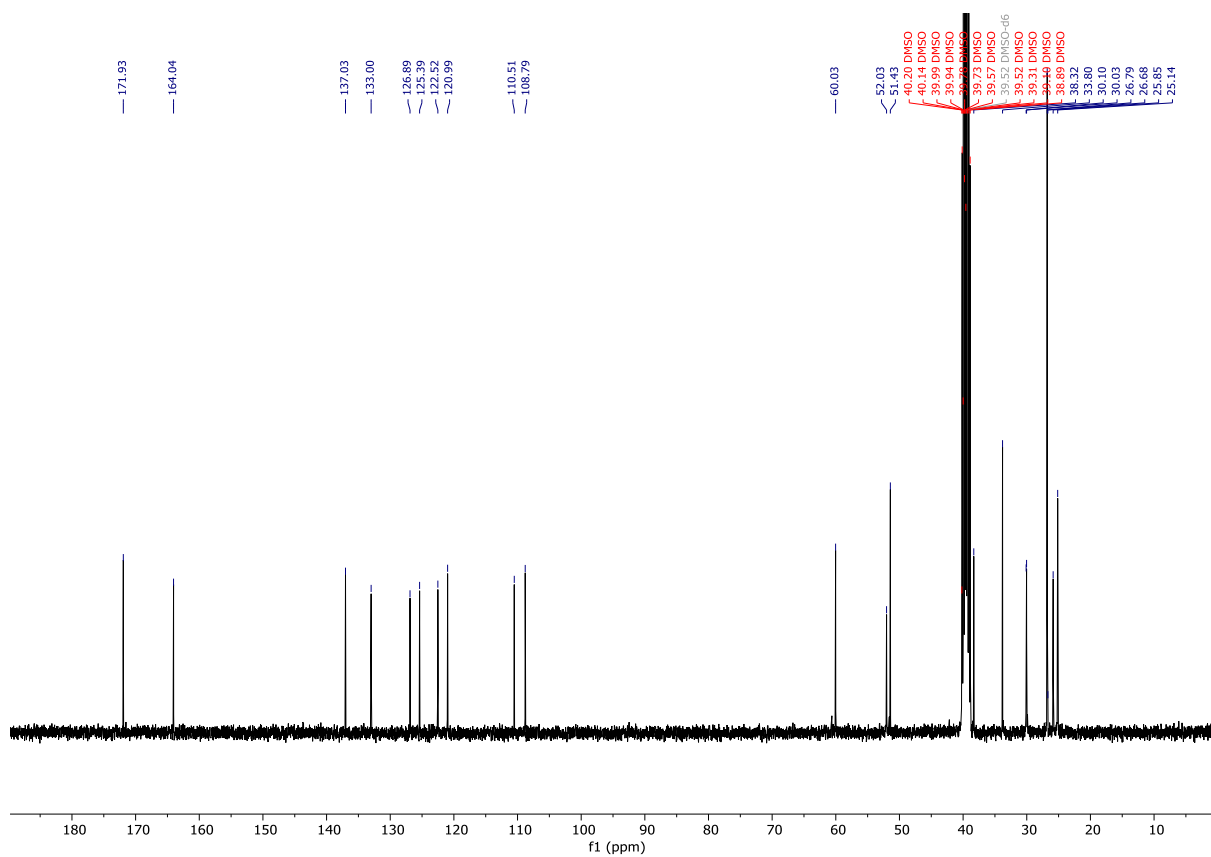


Figure S-77: ^{13}C -NMR of **5** (100.6 MHz, $\text{DMSO}-d_6$)

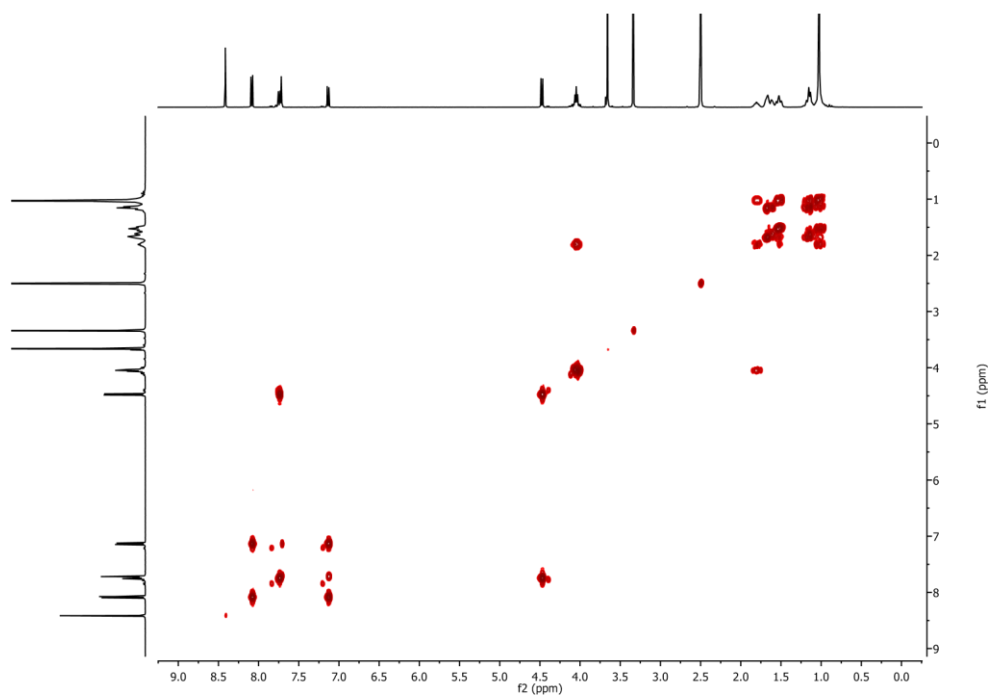


Figure S-78: COSY of **5** (400 MHz, $\text{DMSO}-d_6$)

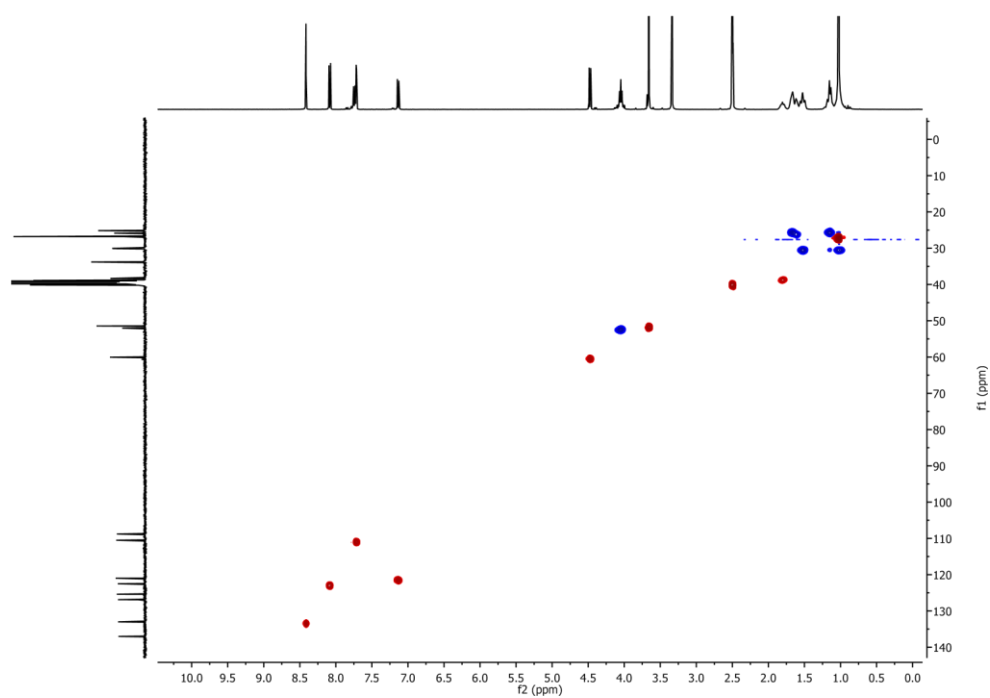


Figure S-79: HSQC of **5** (100.6 MHz, DMSO- d_6)

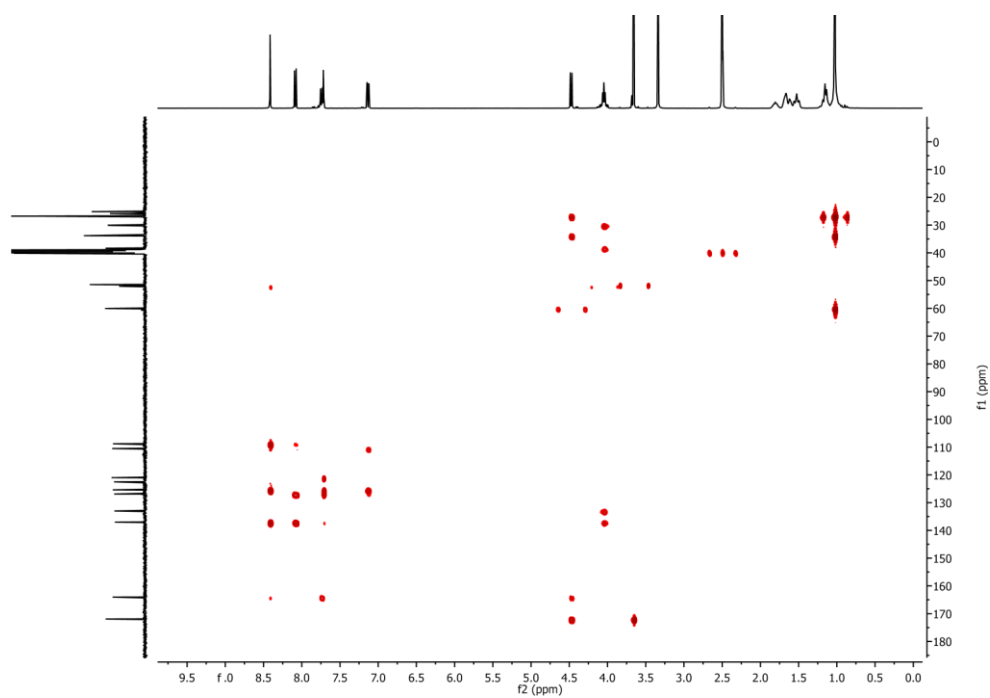


Figure S-80: HMBC of **5** (100.6 MHz, DMSO- d_6)

Methyl (S)-2-(7-chloro-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate (7-Chloro-MDMB-CHMICA) (6)

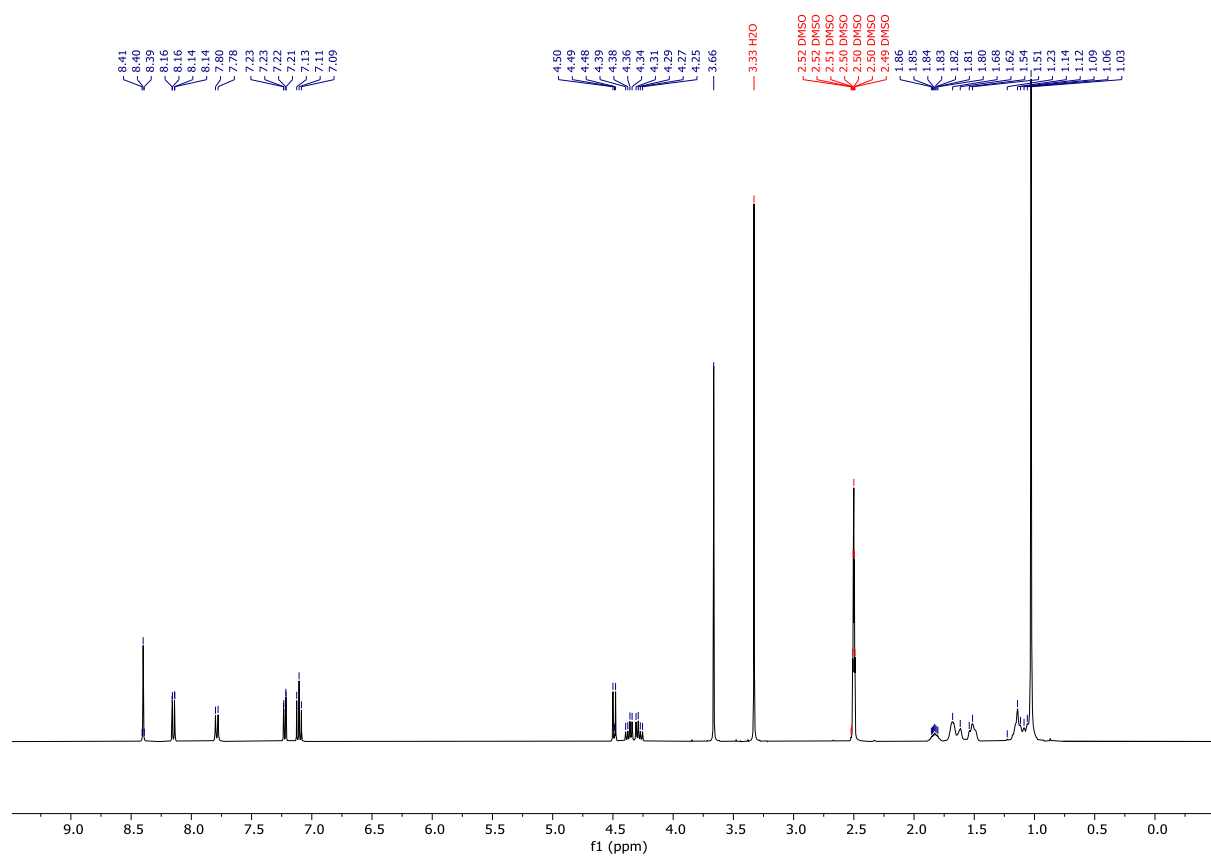
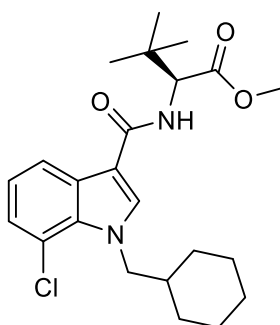


Figure S-81: ^1H -NMR of 6 (400 MHz, $\text{DMSO-}d_6$)

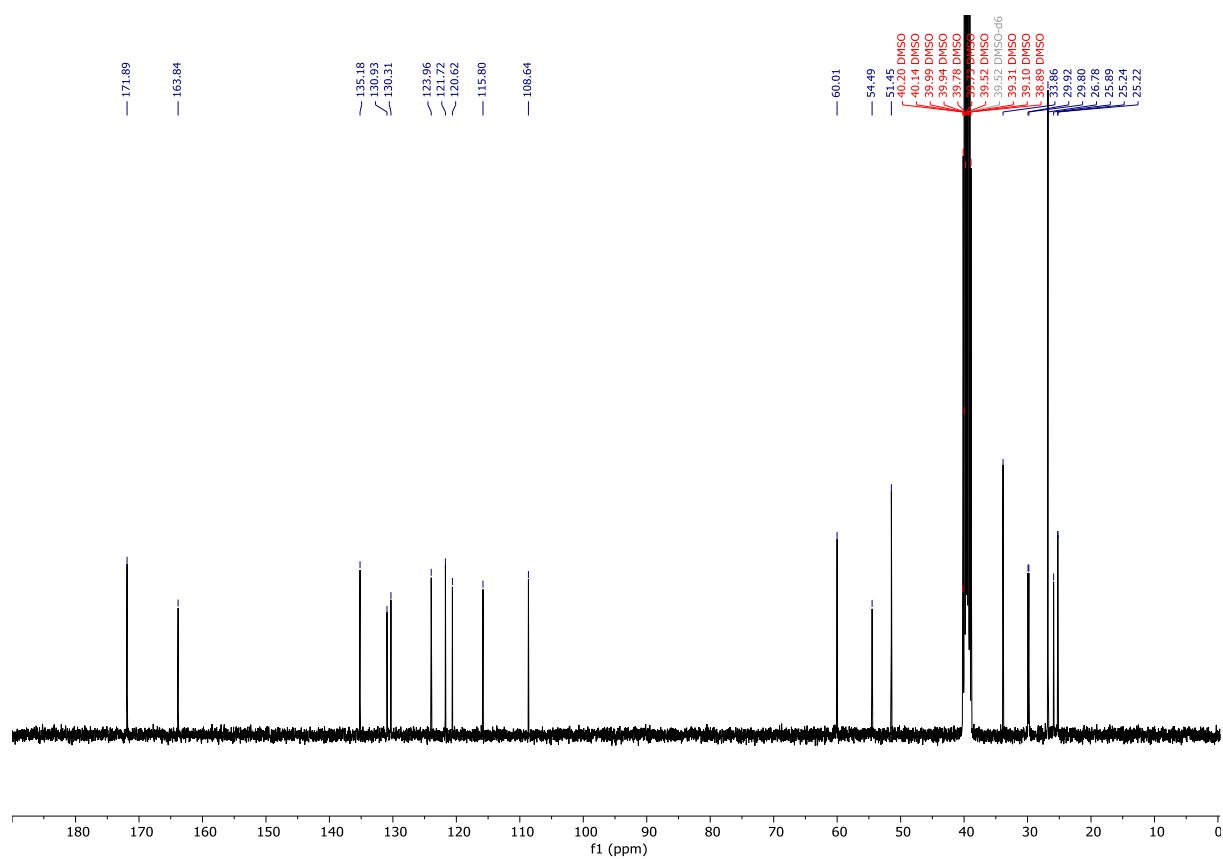


Figure S-82: ^{13}C -NMR of **6** (100.6 MHz, $\text{DMSO}-d_6$)

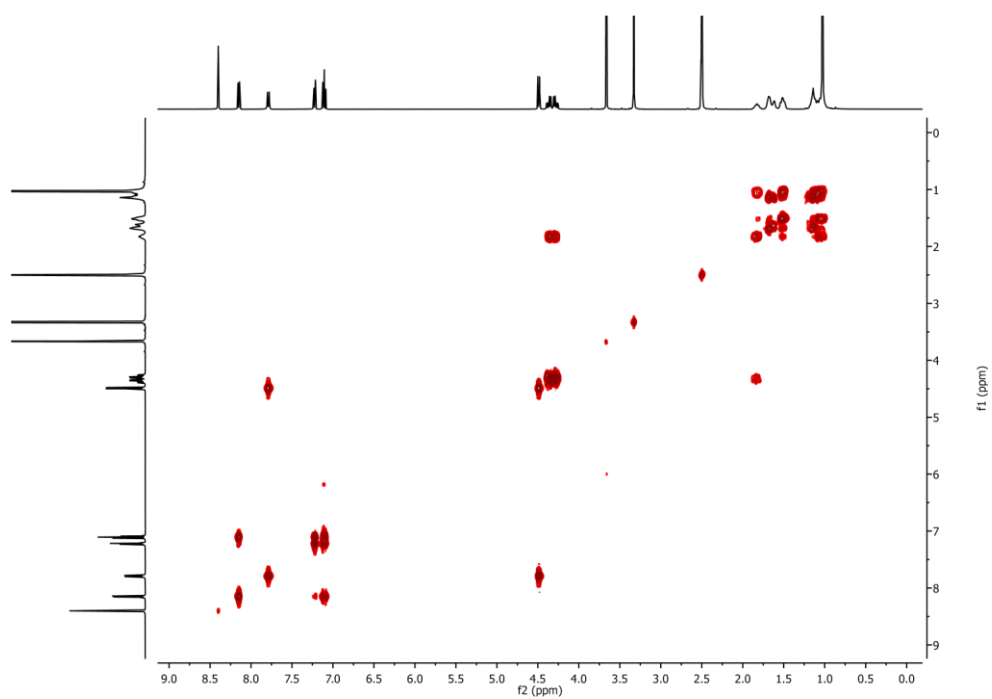


Figure S-83: COSY of **6** (400 MHz, $\text{DMSO}-d_6$)

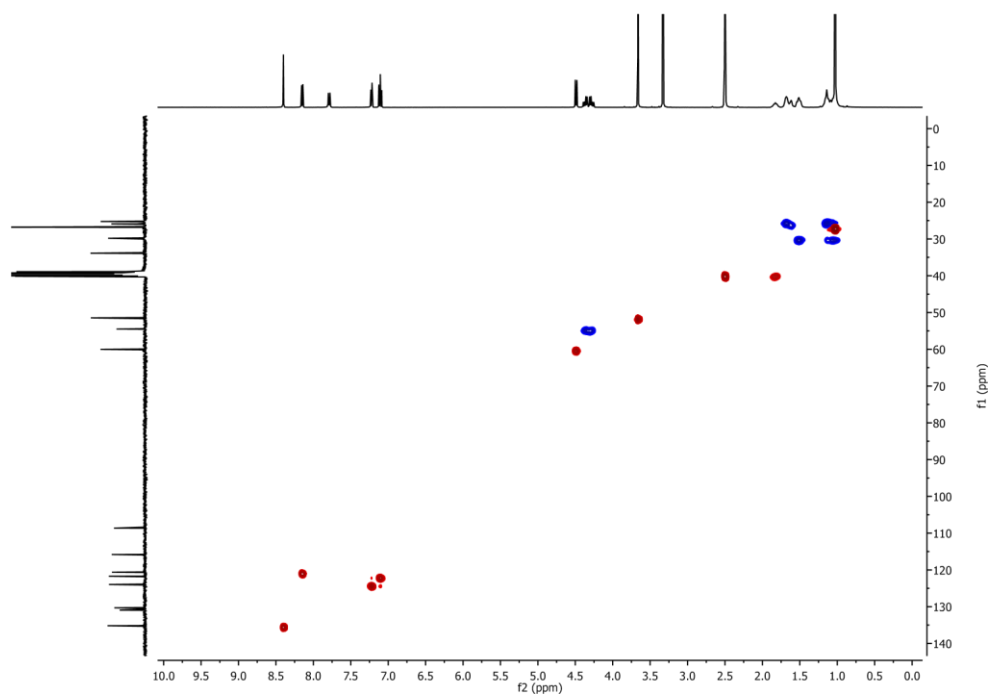


Figure S-84: HSQC of 6 (100.6 MHz, DMSO- d_6)

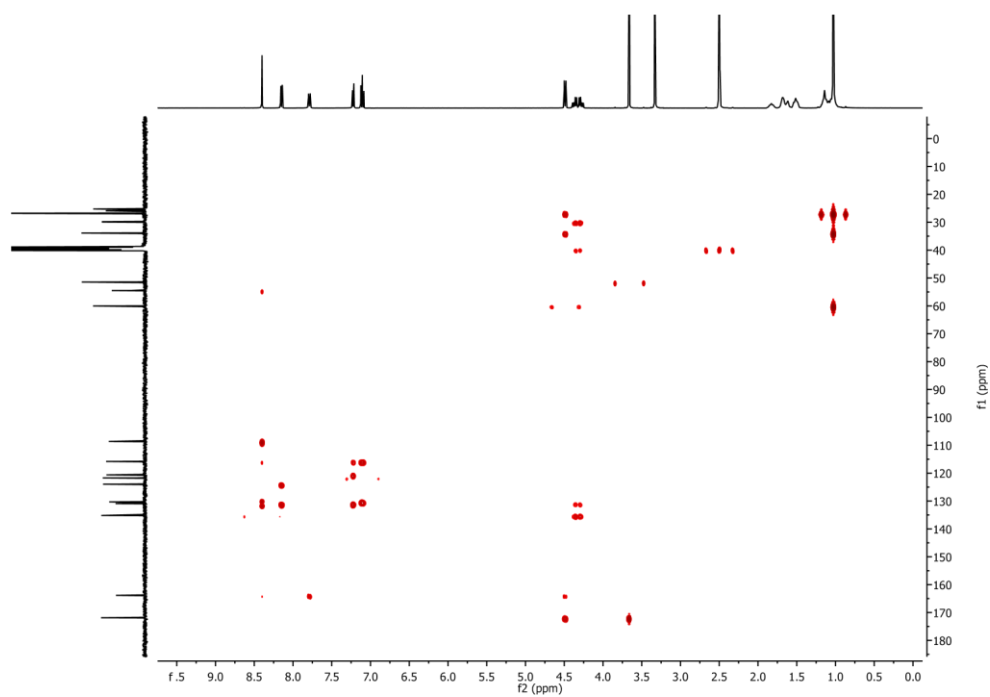


Figure S-85: HMBC of 6 (100.6 MHz, DMSO- d_6)

GC-MS spectra

Figure S-86 to S-90 show the EI-GC-MS spectra of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7-Cl-MDMB-CHMICA.

2Cl-MDMB-CHMICA

+ EI Full ms [40.00-600.00] RI: 3232

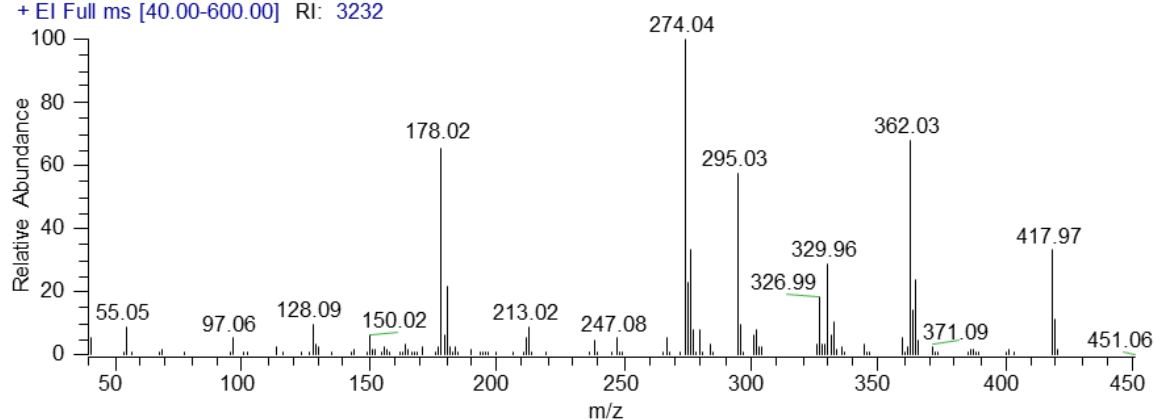


Figure S-86: EI-GC-MS spectrum of 2-Cl-MDMB-CHMICA

4Cl-MDMB-CHMICA

+ EI Full ms [40.00-600.00] RI: 3238

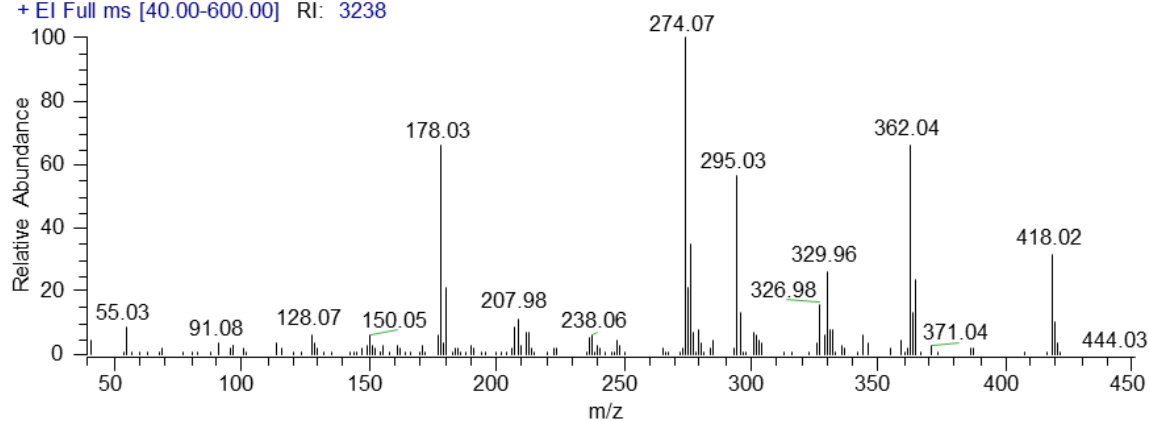


Figure S-87: EI-GC-MS spectrum of 4-Cl-MDMB-CHMICA

5Cl-MDMB-CHMICA

+ EI Full ms [40.00-600.00] RI: 3238

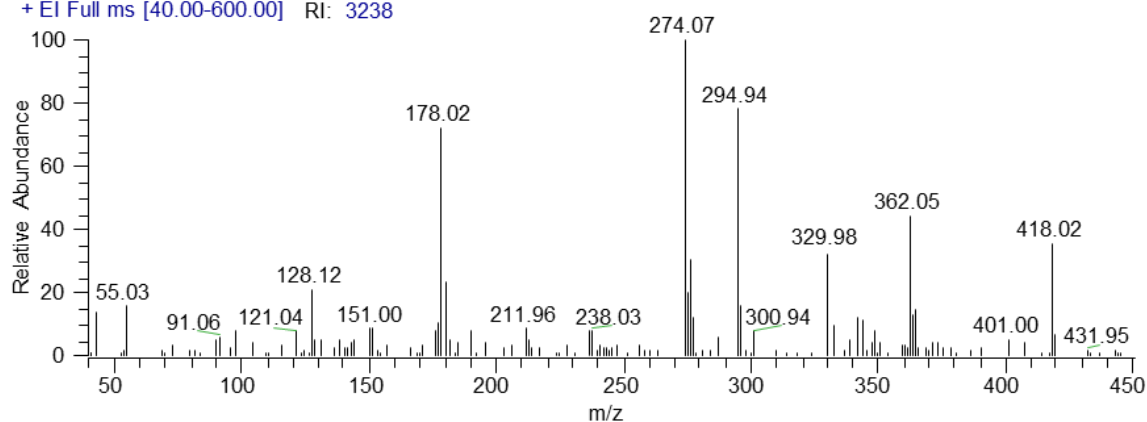


Figure S-88: EI-GC-MS spectrum of 5-Cl-MDMB-CHMICA

6Cl-MDMB-CHMICA

+ EI Full ms [40.00-600.00] RI: 3315

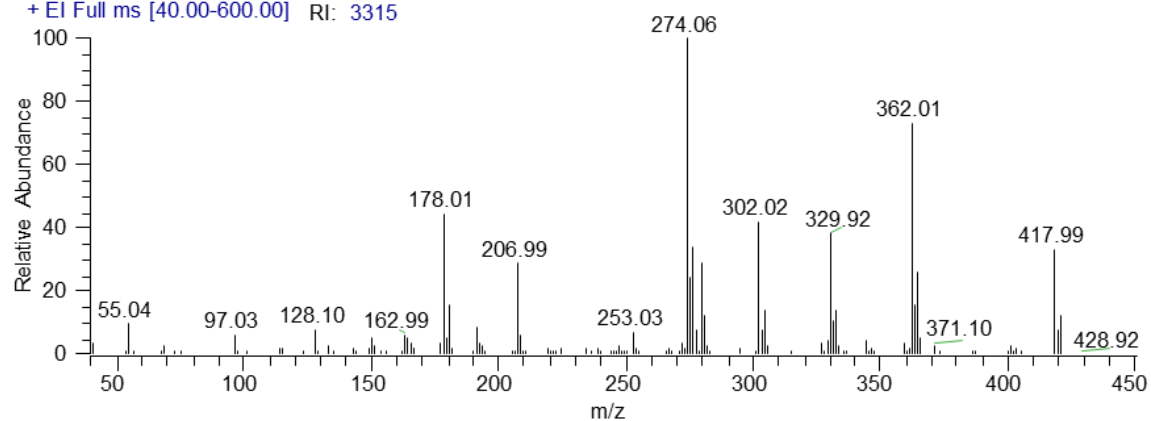


Figure S-89: EI-GC-MS spectrum of 6-Cl-MDMB-CHMICA

7Cl-MDMB-CHMICA

+ EI Full ms [40.00-600.00] RI: 3222

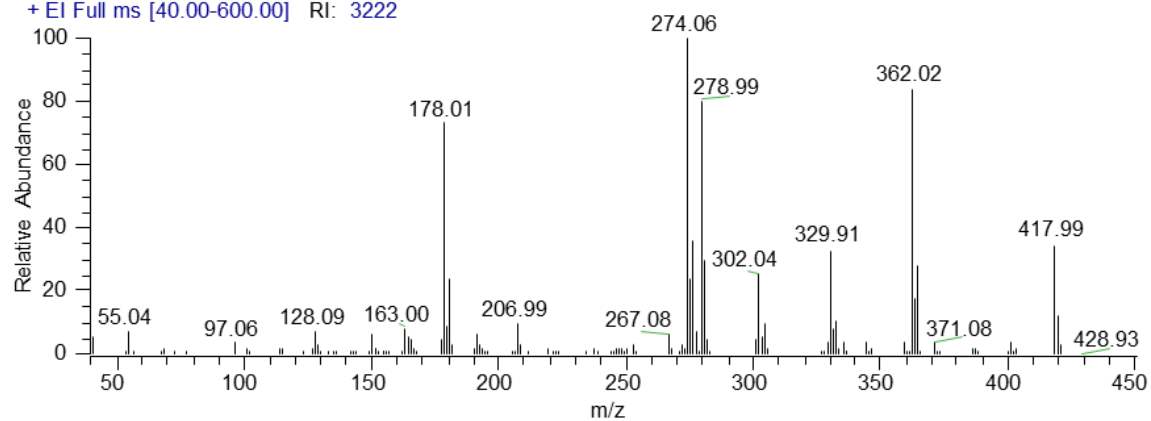


Figure S-90: EI-GC-MS spectrum of 7-Cl-MDMB-CHMICA

IR Spectra

Figure S-91 to S-97 show the GC-sIR spectra (overview and fingerprint area) of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7Cl-MDMB-CHMICA.

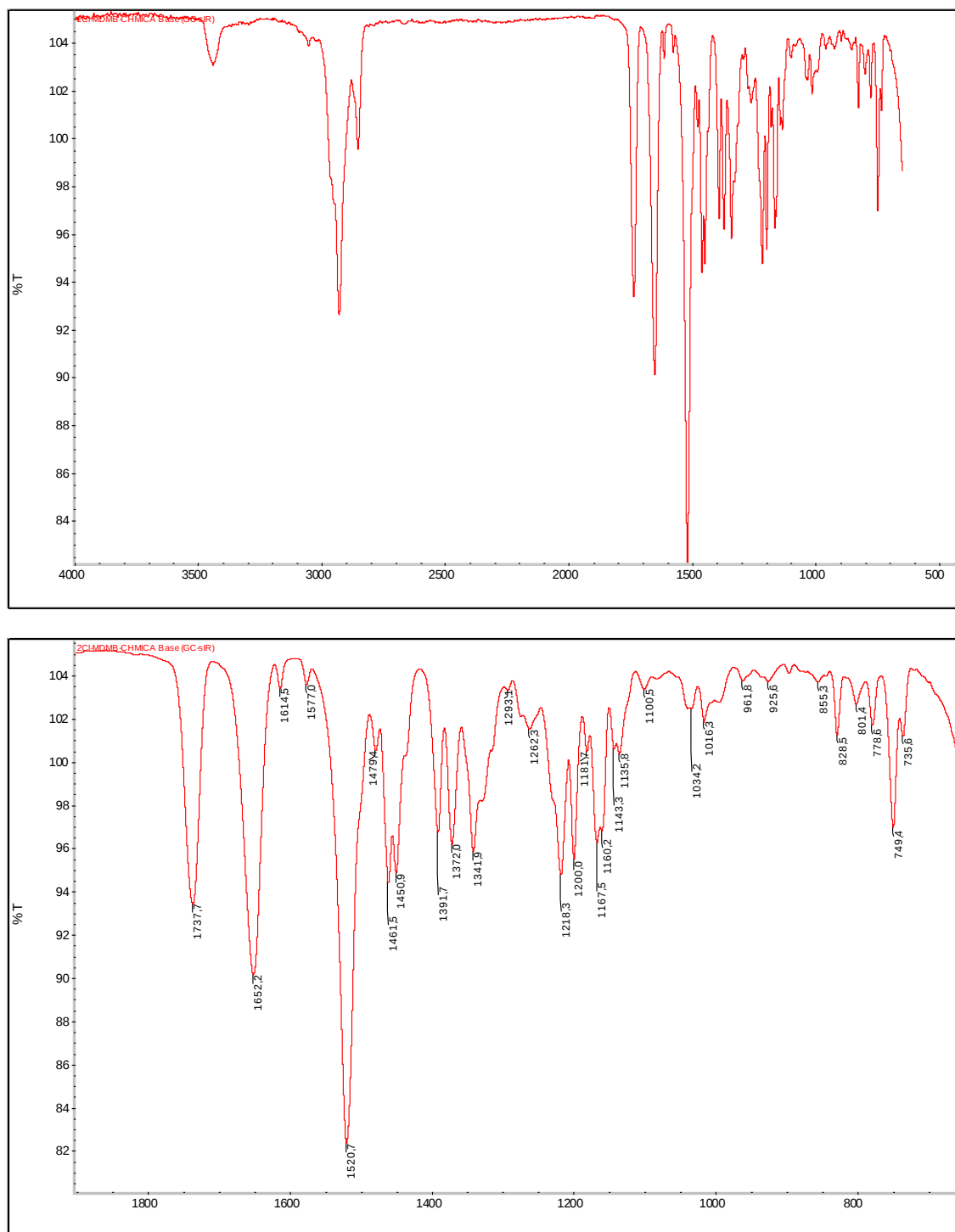


Figure S-91: (Top) GC-sIR spectrum of 2-Cl-MDMB-CHMICA. (Bottom) Zoom into the corresponding fingerprint area

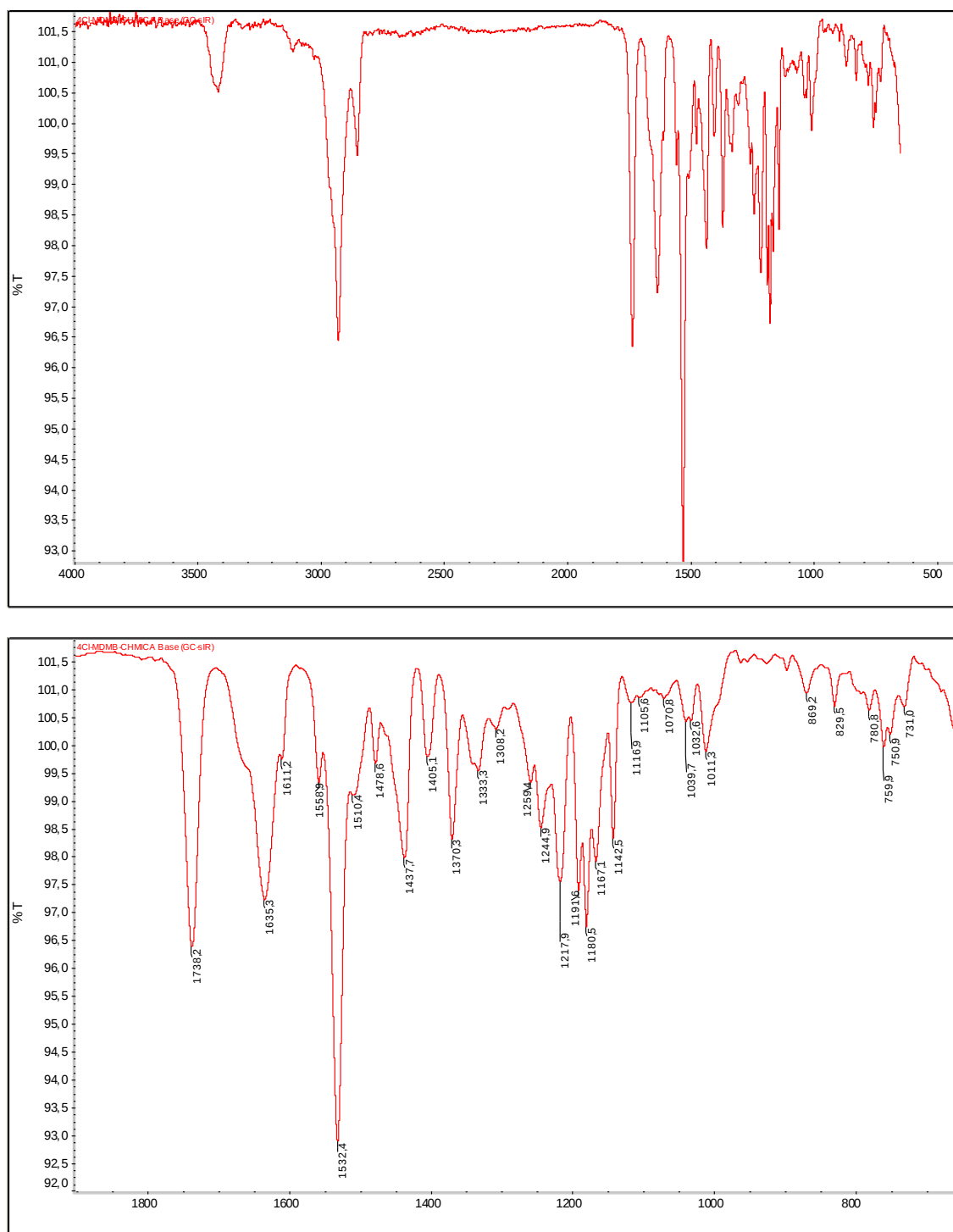


Figure S-92: (Top) GC-sIR spectrum of 4-Cl-MDMB-CHMICA. (Bottom) Zoom into the corresponding fingerprint area

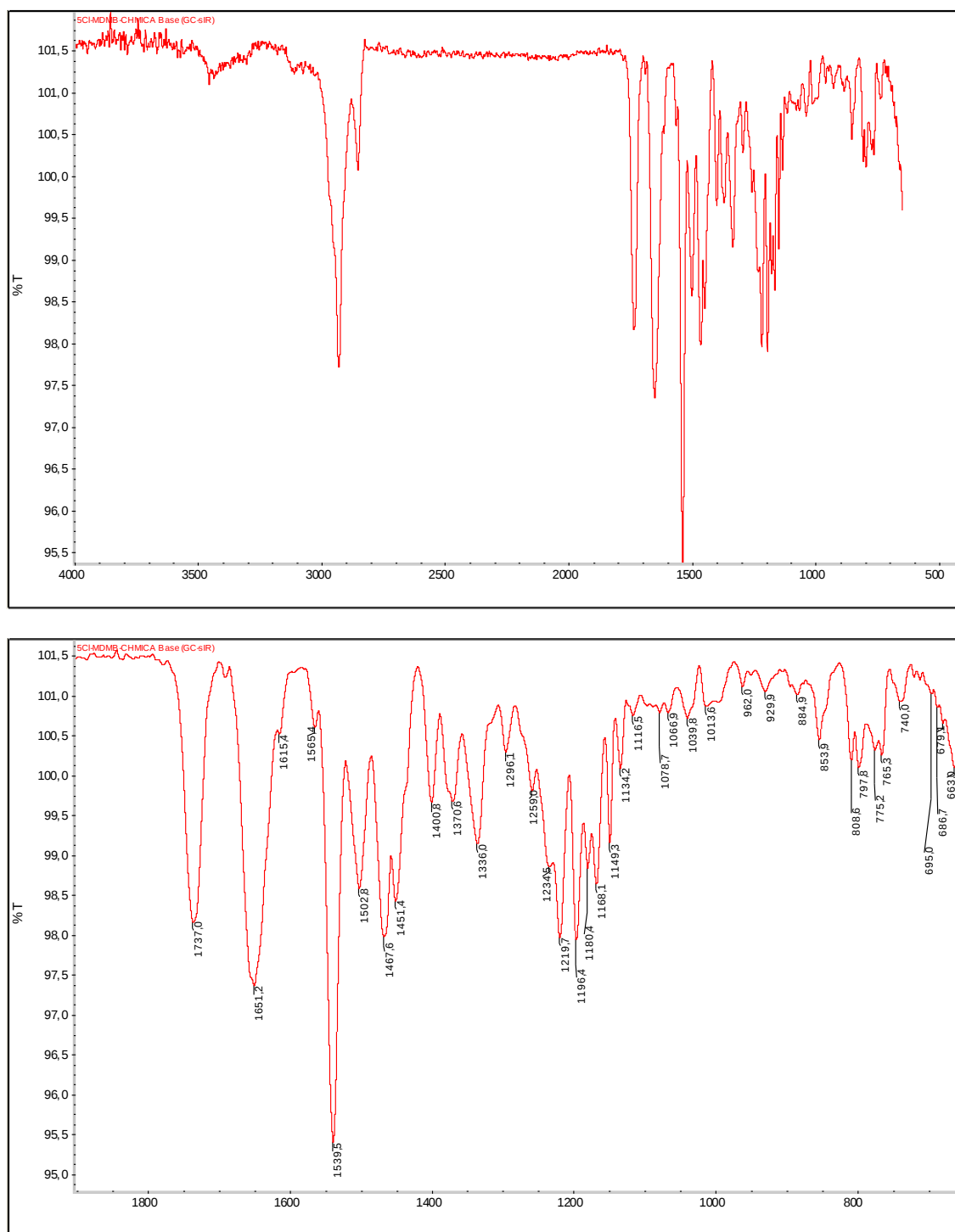


Figure S-93: (Top) GC-sIR spectrum of 5-Cl-MDMB-CHMICA. (Bottom) Zoom into the corresponding fingerprint area

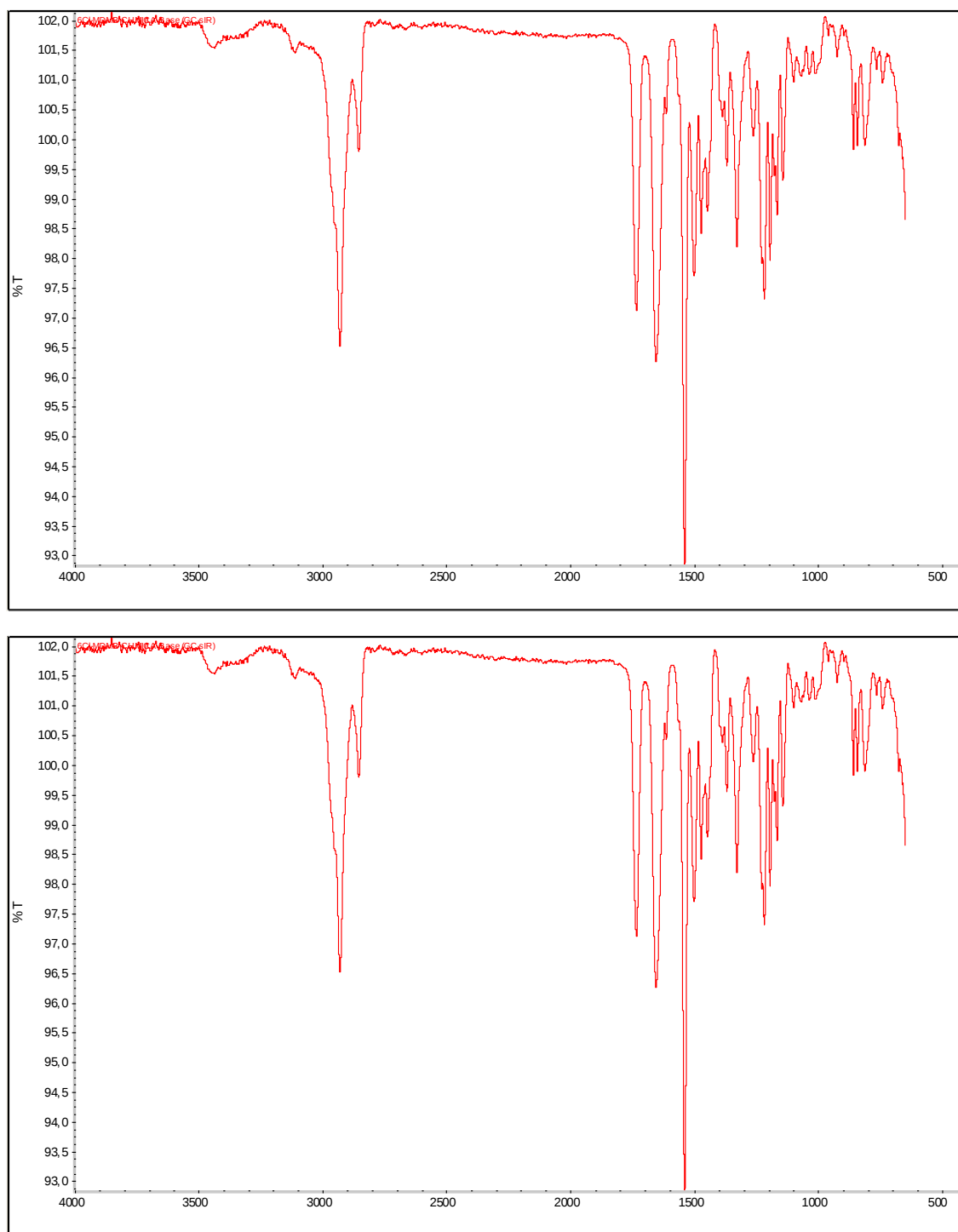


Figure S-94: (Top) GC-sIR spectrum of 6-Cl-MDMB-CHMICA. (Bottom) Zoom into the corresponding fingerprint area

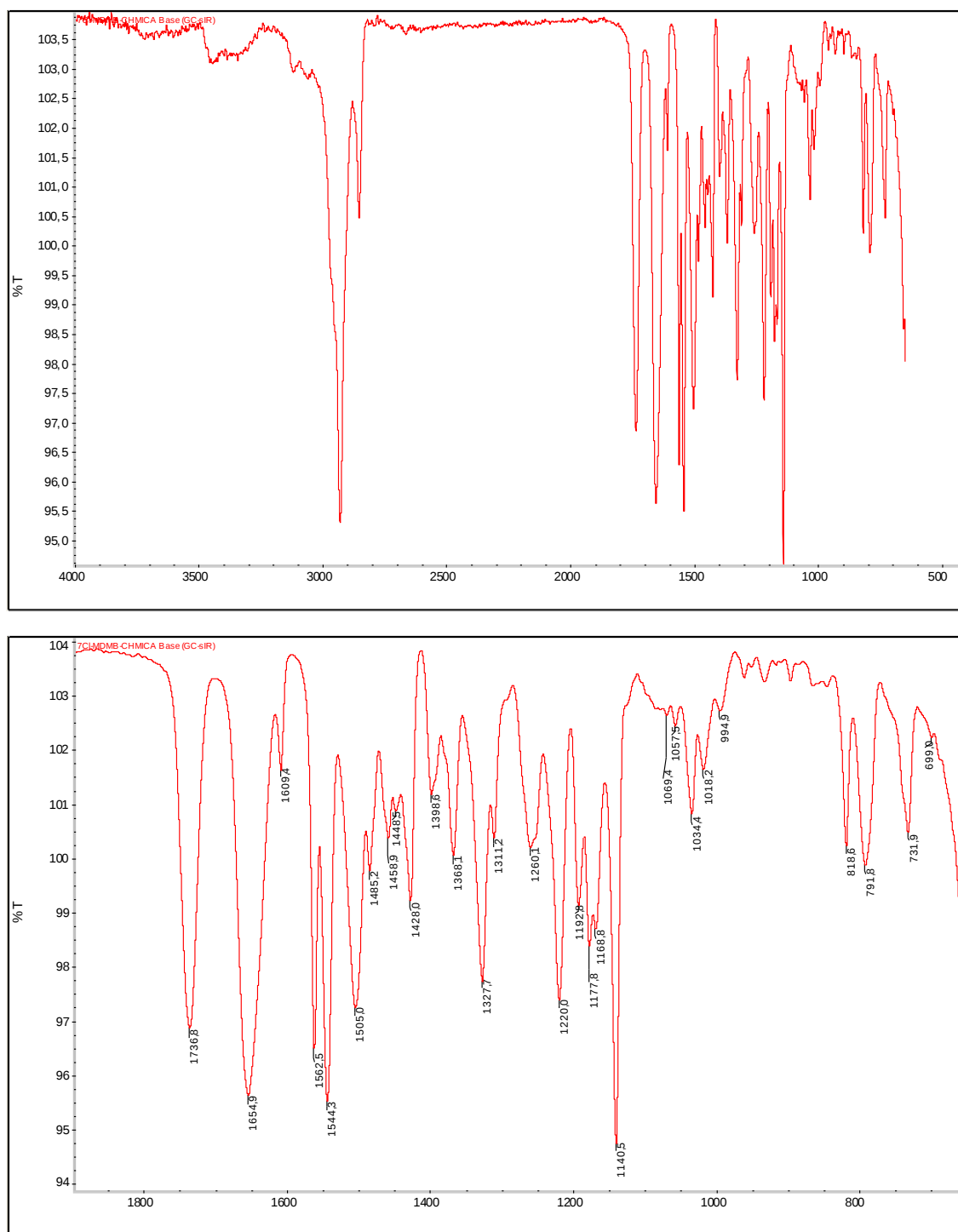


Figure S-95: (Top) GC-sIR spectrum of 7-Cl-MDMB-CHMICA. (Bottom) Zoom into the corresponding fingerprint area

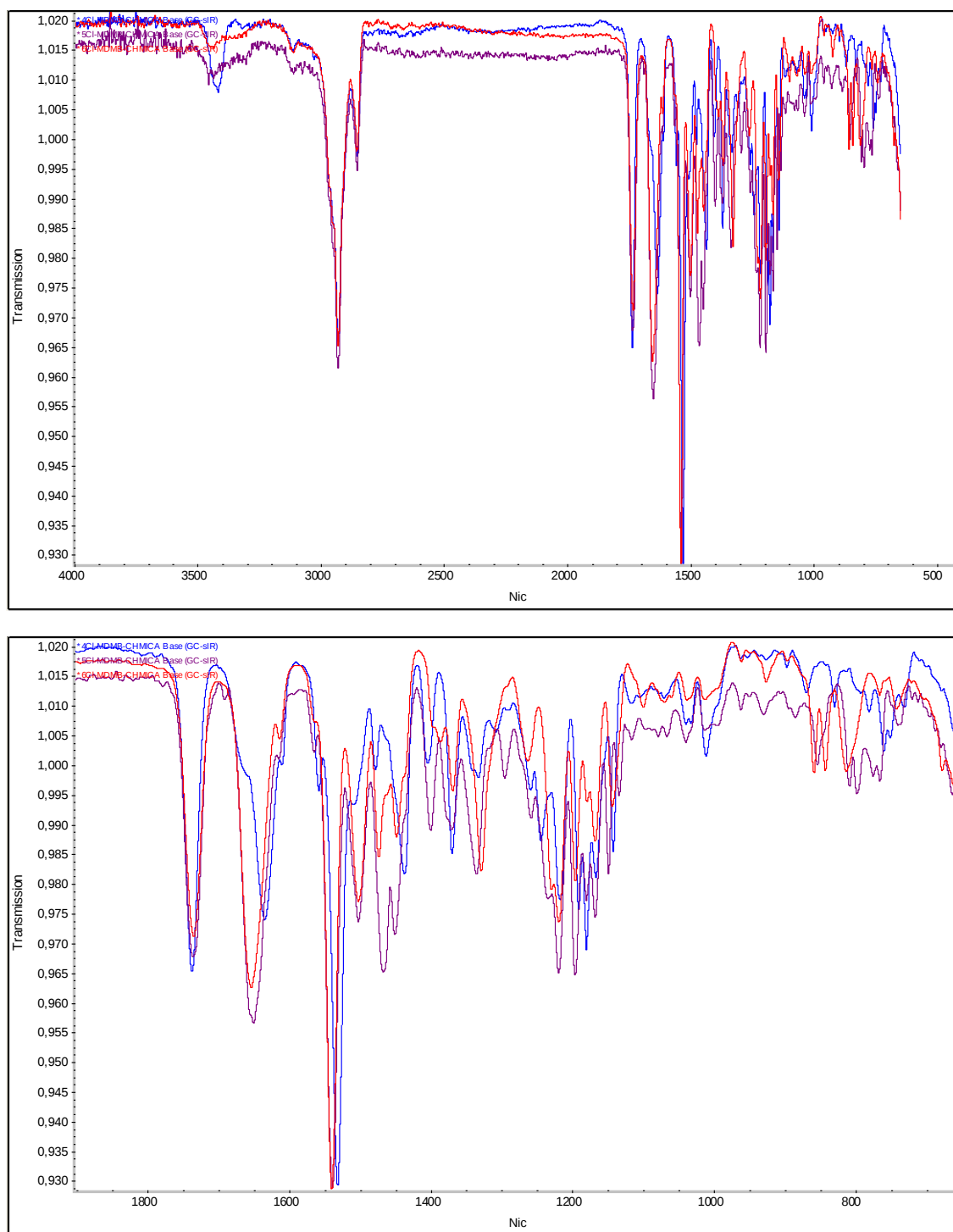


Figure S-96: (Top) stacked GC-sIR spectrum of 4-Cl- (blue), 5-Cl (purple) and 6-Cl-MDMB-CHMICA (red). (Bottom) Zoom into the corresponding fingerprint area

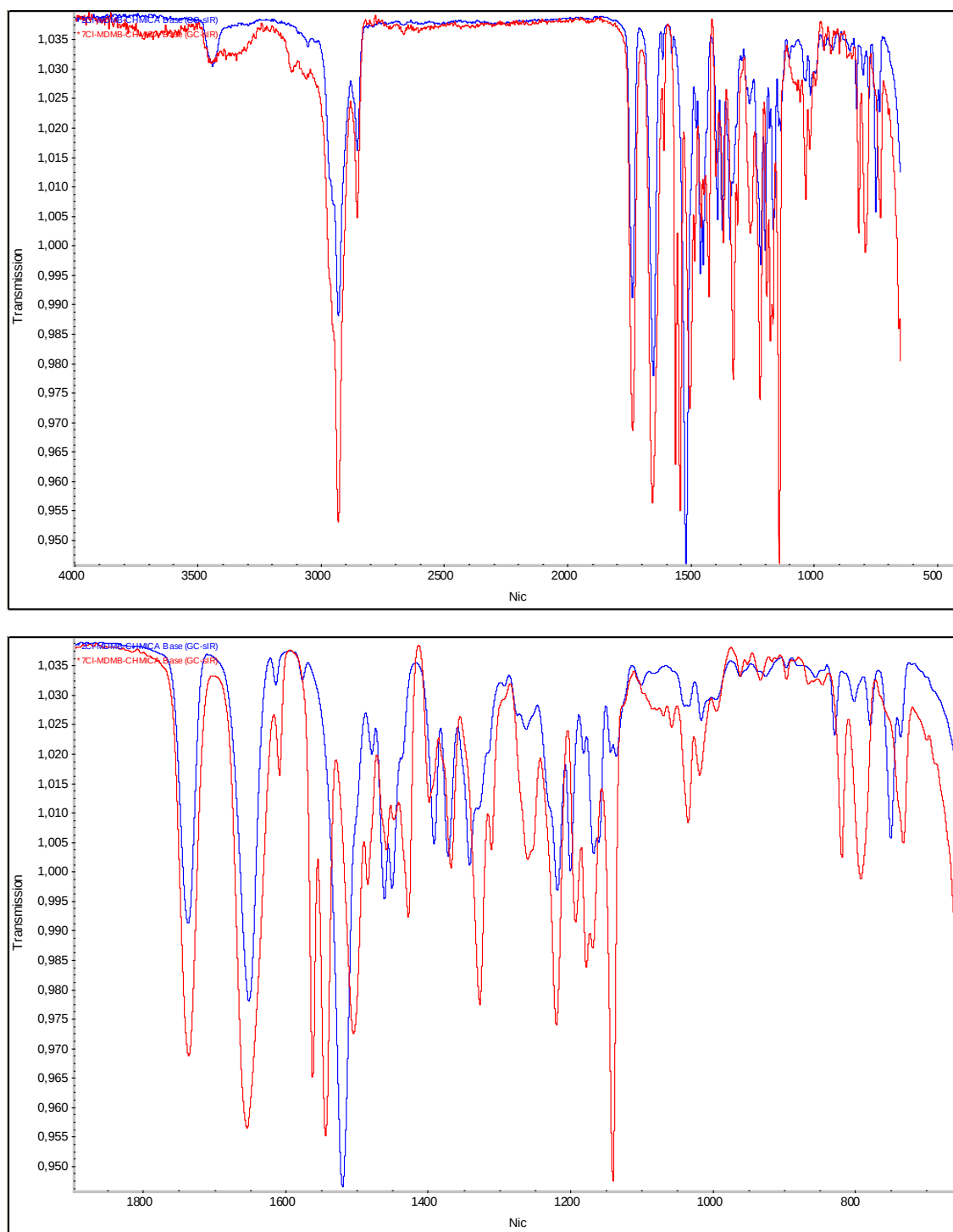


Figure S-97: (Top) stacked GC-sIR spectrum of 2-Cl (blue) and 7-Cl-MDMB-CHMICA (red). (Bottom) Zoom into the corresponding fingerprint area

UV Spectra

Figure S-98 to S-102 show the UV/VIS spectra of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7-Cl-MDMB-CHMICA.

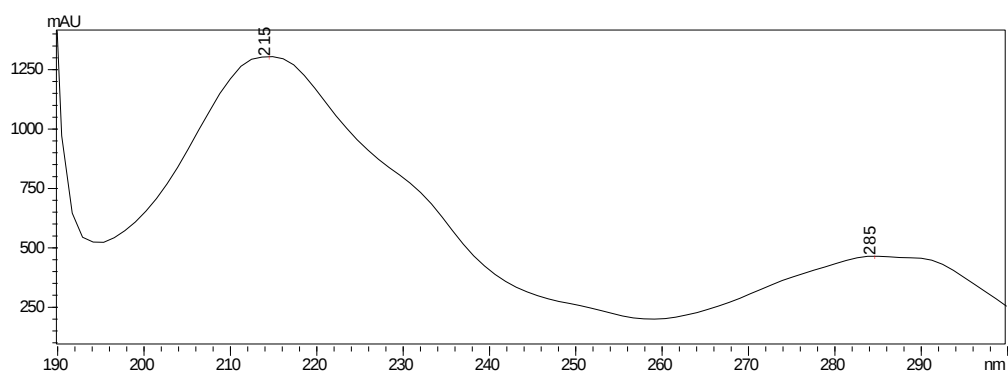


Figure S-98: UV/VIS spectrum of 2-Cl-MDMB-CHMICA

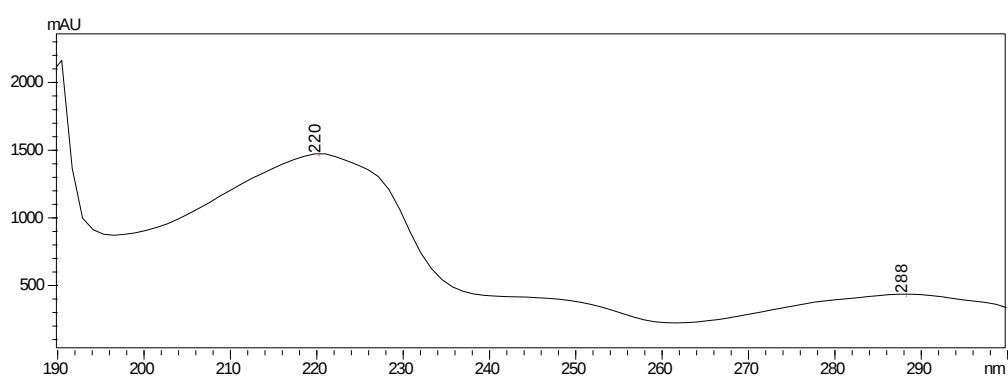


Figure S-99: UV/VIS spectrum of 4-Cl-MDMB-CHMICA

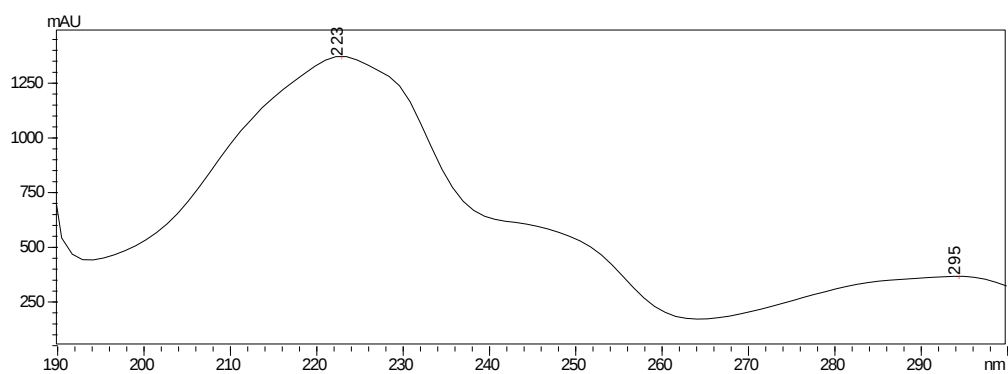


Figure S-100: UV/VIS spectrum of 5-Cl-MDMB-CHMICA

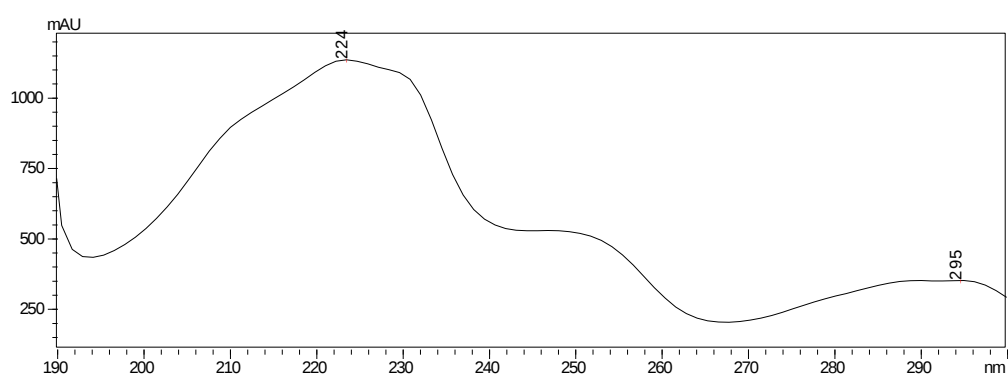


Figure S-101: UV/VIS spectrum of 6-Cl-MDMB-CHMICA

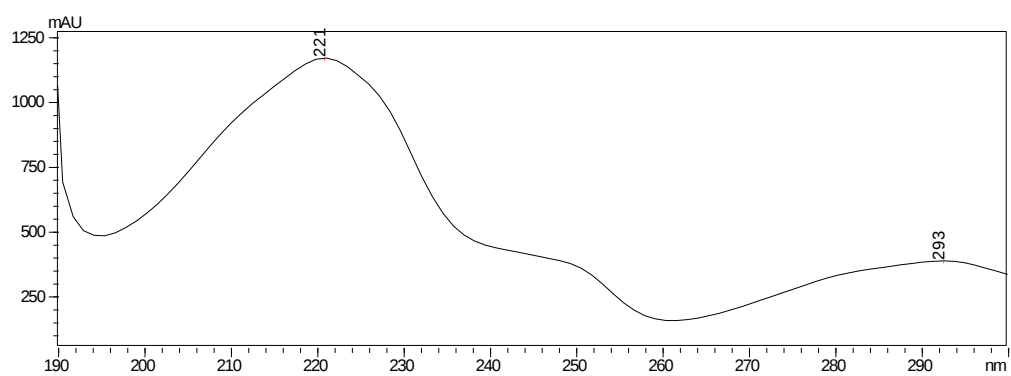


Figure S-102: UV/VIS spectrum of 7-Cl-MDMB-CHMICA

CB₁ receptor binding assay

Figure S-103 to S-107 show CB₁ receptor binding assay of 2-Cl-, 4-Cl-, 5-Cl-, 6-Cl- and 7-Cl-MDMB-CHMICA.

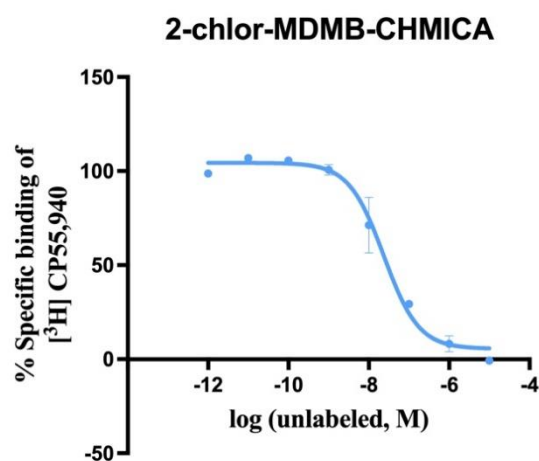


Figure S-103: CB₁ receptor binding assay of 2-Cl-MDMB-CHMICA: calculated K_i (nM) 0.58, Fit K_i (R₂) 0.973

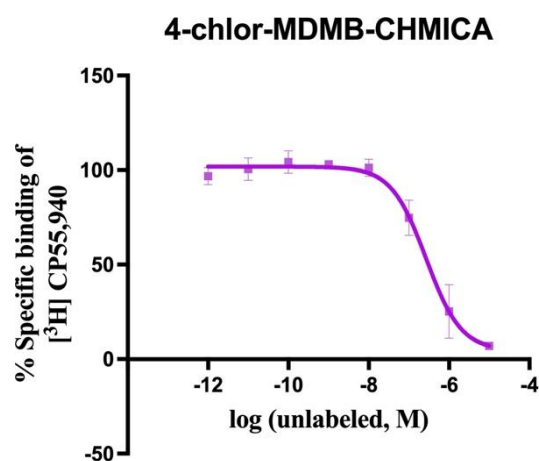


Figure S-104: CB₁ receptor binding assay of 4-Cl-MDMB-CHMICA: calculated K_i (nM) 6.55, Fit K_i (R₂) 0.970

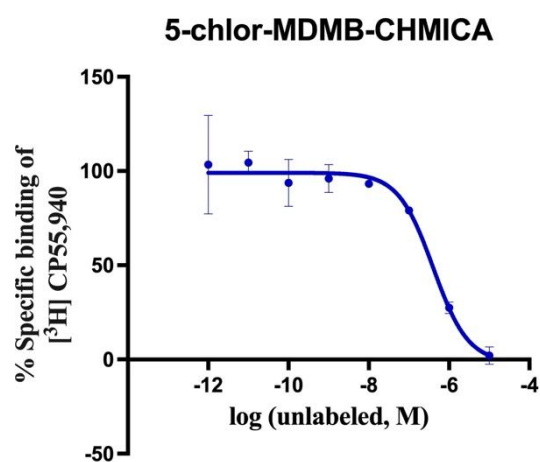


Figure S-105: CB₁ receptor binding assay of 5-Cl-MDMB-CHMICA: calculated K_i (nM) 9.81, Fit K_i (R_2) 0.947

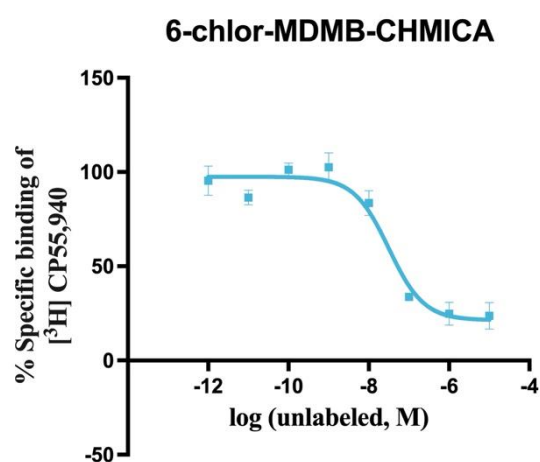


Figure S-106: CB₁ receptor binding assay of 6-Cl-MDMB-CHMICA: calculated K_i (nM) 0.77, Fit K_i (R_2) 0.955

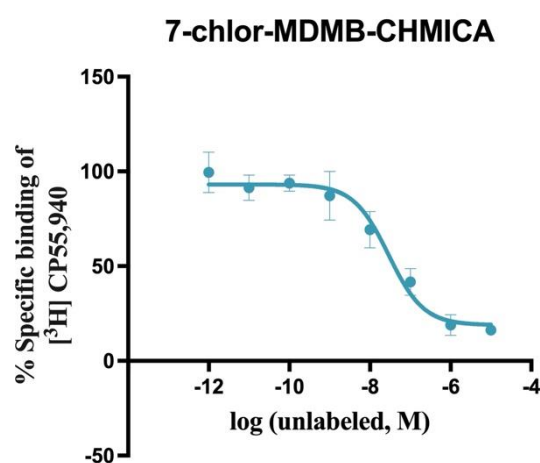


Figure S-107: CB₁ receptor binding assay of 7-Cl-MDMB-CHMICA: calculated K_i (nM) 0.70, Fit K_i (R_2) 0.947