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Supplementary information

Imitation of β-lactam binding enables broad-spectrum metallo-β-lactamase inhibitors

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Supplementary information for

Imitation of β-lactam binding enables broad spectrum metallo-β-lactamase inhibitors

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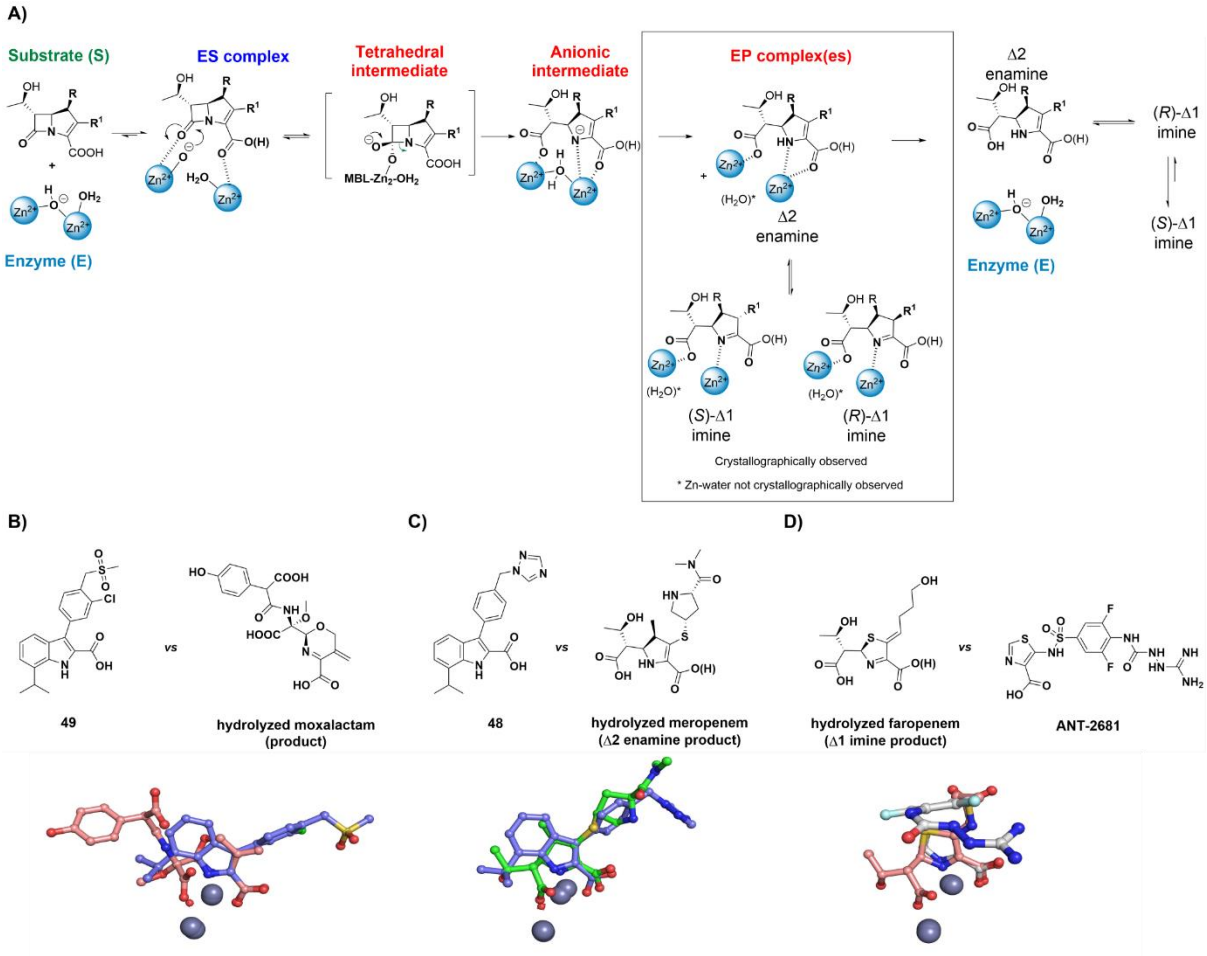
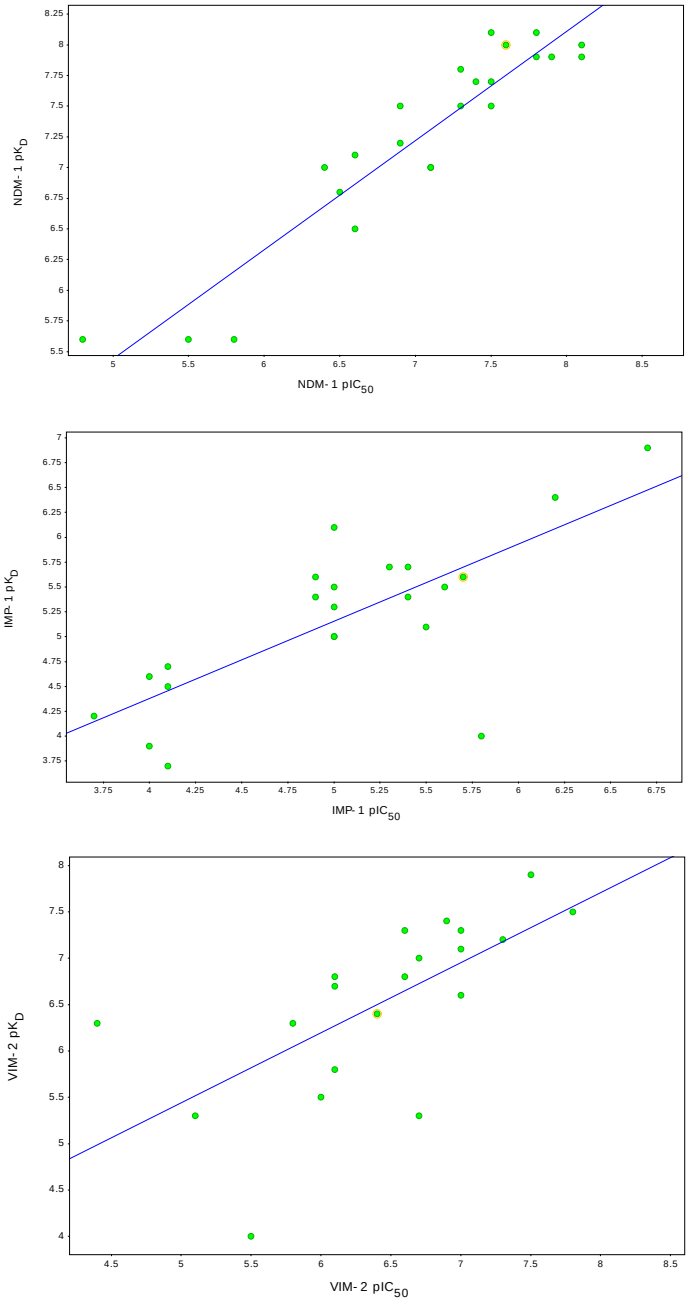
1 Supplementary Figures

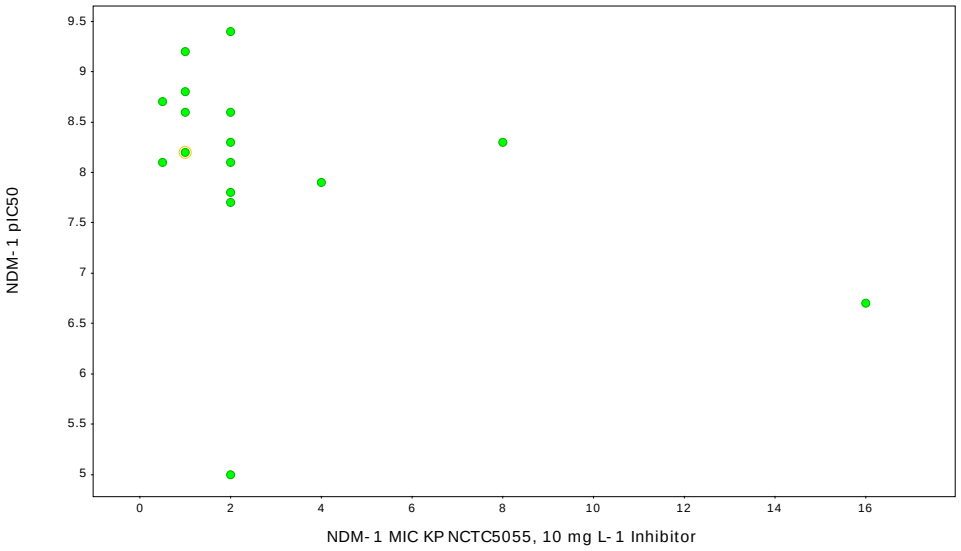
Supplementary Fig. 1. Indole carboxylate (InC) binding to MBLs mimics that of intact β-lactam substrates and/or products. A) Outline B1 MBL mechanism exemplified with a carbapenem. **B, C,** and **D)** Overlays comparing binding modes of InCs, hydrolyzed β-lactams, and a thiazole carboxylate, with four MBLs (**49** with L1, PDB ID: 7AFZ; hydrolyzed moxalactam with L1, PDB ID: 2AIO; **48** with NDM-7, PDB ID: 7AEZ; hydrolyzed meropenem with NDM1, PDB ID: 5YPM; hydrolyzed faropenem with VIM-2, PDB ID: 7A5Z and ANT-2681 with VIM-2, PDB ID: 6ZGM).

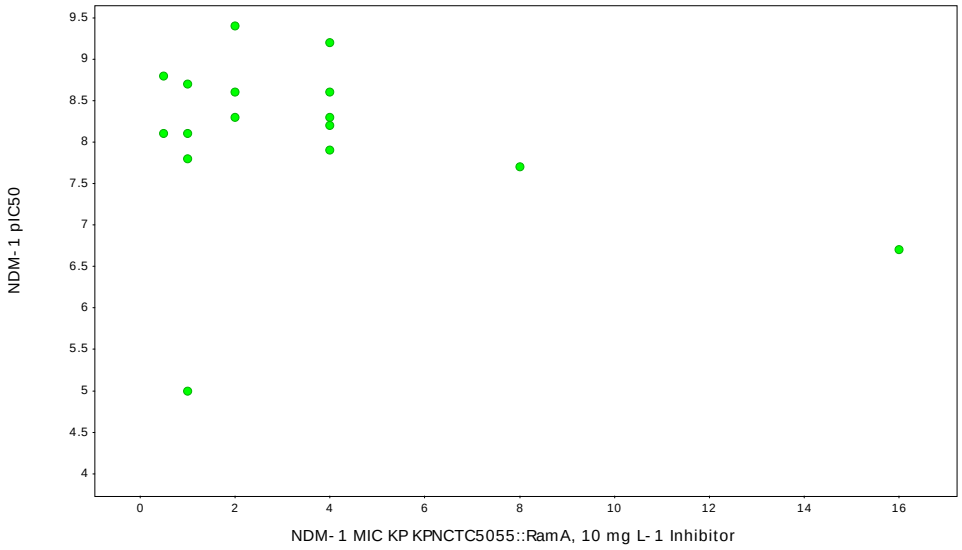


Supplementary Fig. 2. Exemplary plots showing the correlation between indole carboxylate inhibition potency (measured pIC_{50}s) and binding constants (K_Ds) for NDM-1, IMP-1 and VIM-2. For inhibition and binding data (based on surface plasmon resonance analyses) - see Supplementary Tables 1-6 and 8-10, respectively. See Experimental Section for assay details.

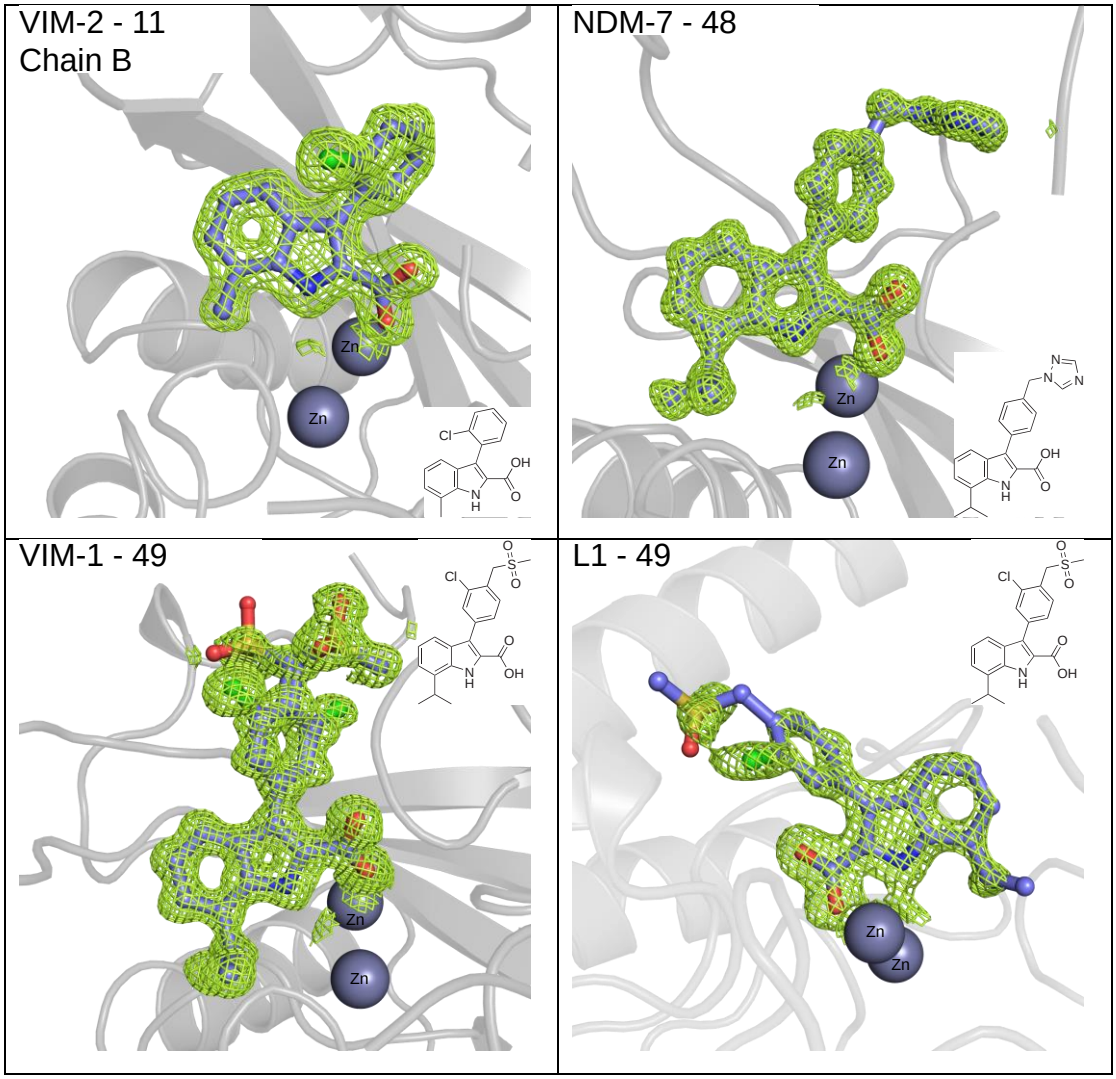


Supplementary Fig. 3. Exemplary plots showing the correlation between inhibition (measured pIC_{50}s) and cellular activity (MICs). These results were used to guide structure activity relationship (SAR) studies for optimisation of InC cell-penetration. For inhibition and microbiology data see Supplementary Tables 1-6 and 11-13, respectively. See Experimental Section for assay details.

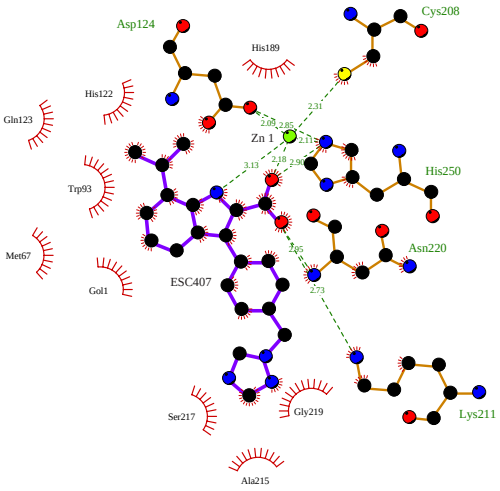




Supplementary Fig. 4. Electron density maps for the complexes derived from indole carboxylate-metallo-β-lactamase crystal structures. The electron density maps corresponding to the InCs at the active sites of VIM-2 (PDB ID: 7AFY), NDM-7(PDB ID: 7AEZ), VIM-1 (PDB ID: 7AEX) or L-1 (PDB ID: 7AFZ) are represented as Fo-Fc maps (green mesh) contoured at 3σ. Density was calculated from the final model, following the omission of the ligand, against experimental diffraction data. See Experimental Section for details. Note the highly conserved mode of binding for the indole carboxylate ring system.



Supplementary Fig. 5. Protein-ligand interactions between metallo-β-lactamases and indole carboxylates as described using LIGPLOT[1]. Hydrogen bonding interactions are shown as lines and ligand-protein hydrophobic contacts are as curved combs. PDB codes: VIM-2 (PDB ID: 7AFY), NDM-7(PDB ID: 7AEZ), VIM-1 (PDB ID: 7AEX) and L-1 (PDB ID: 7AFZ).



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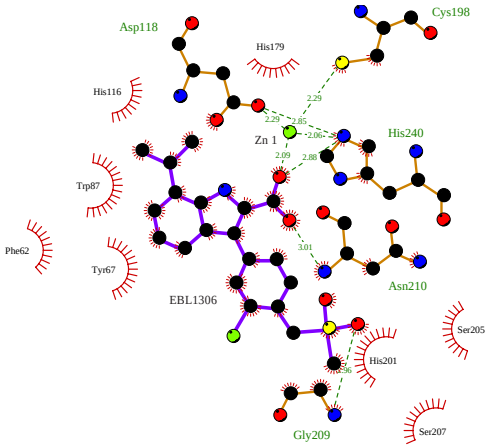
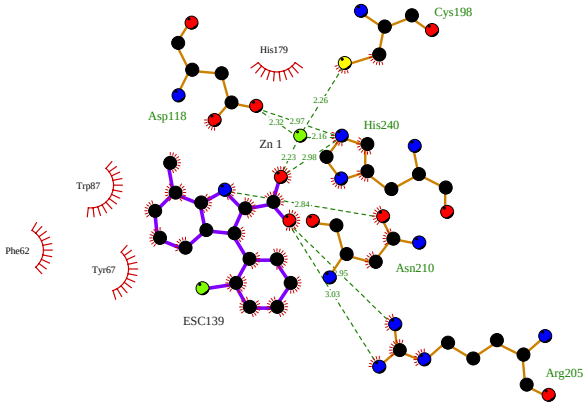
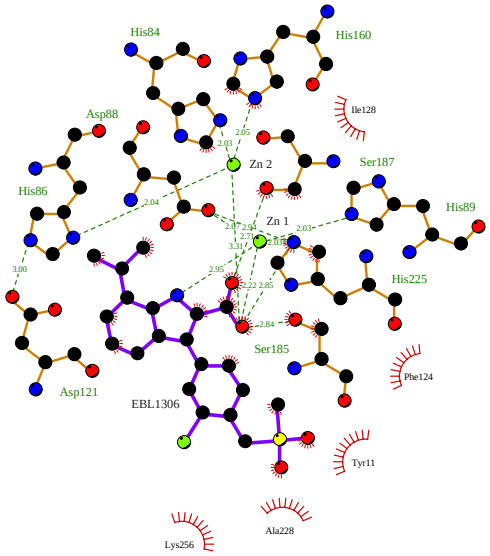


VIM-1 - 49



VIM-2 - 11



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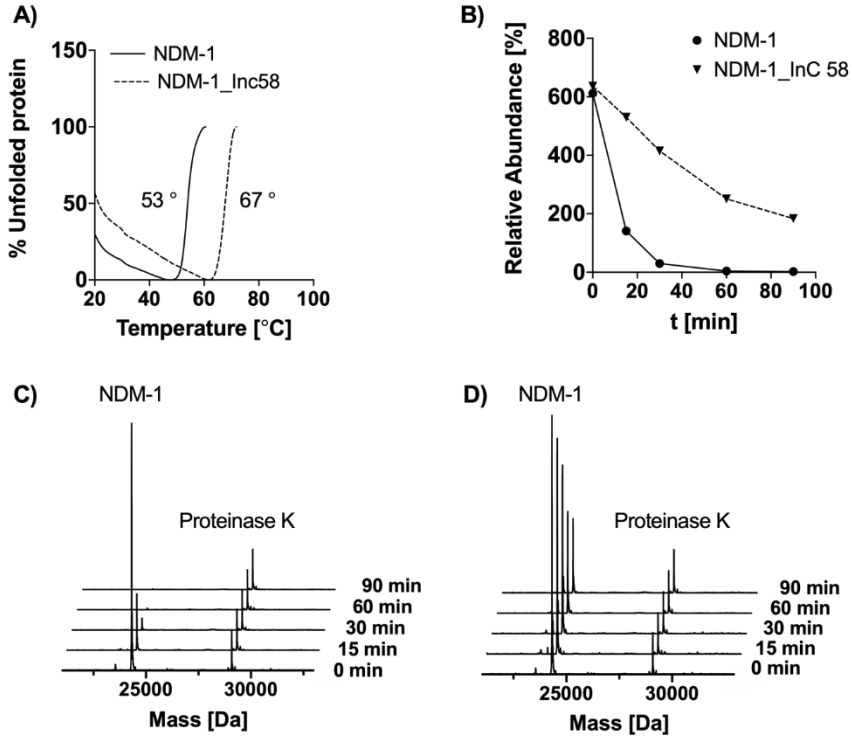
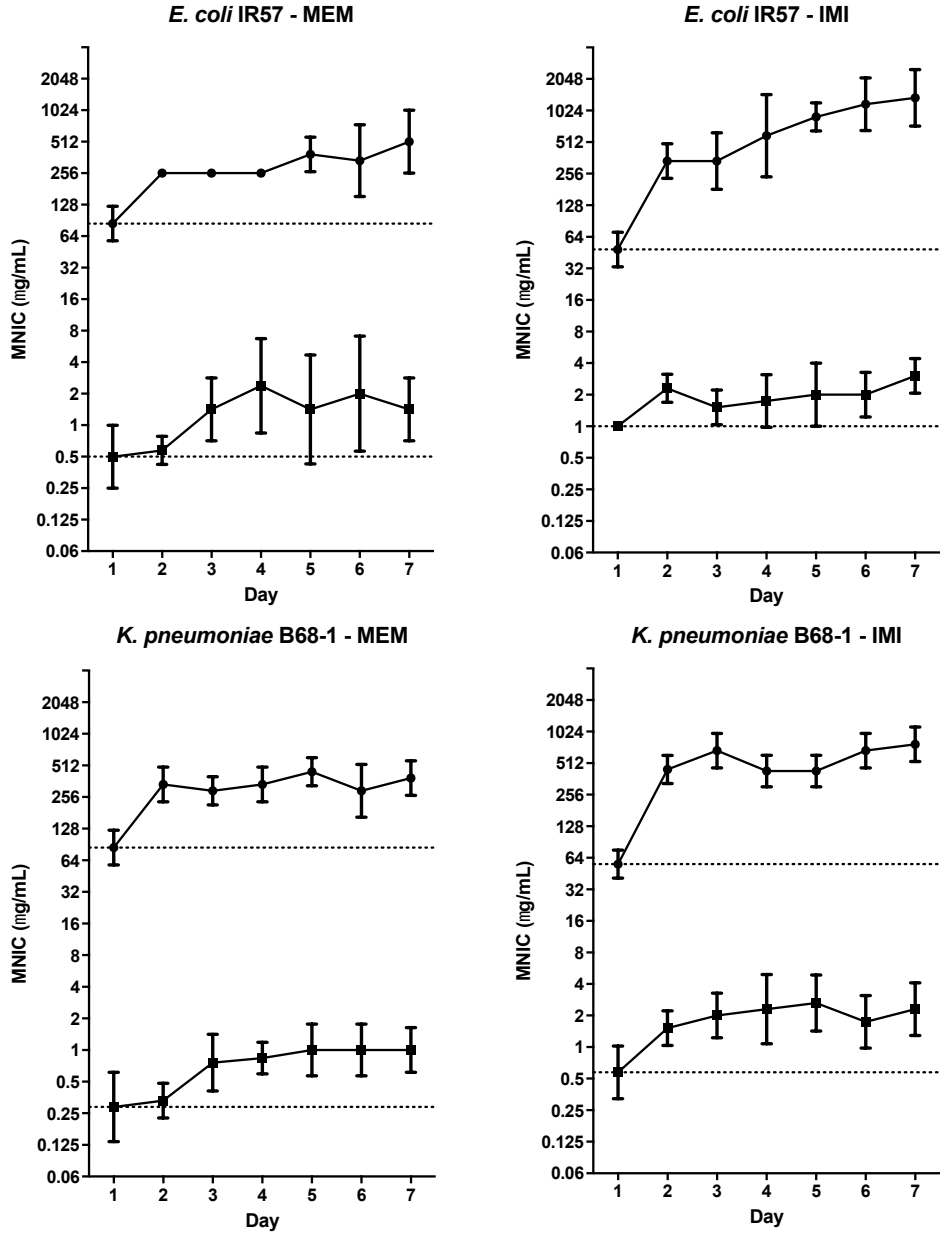
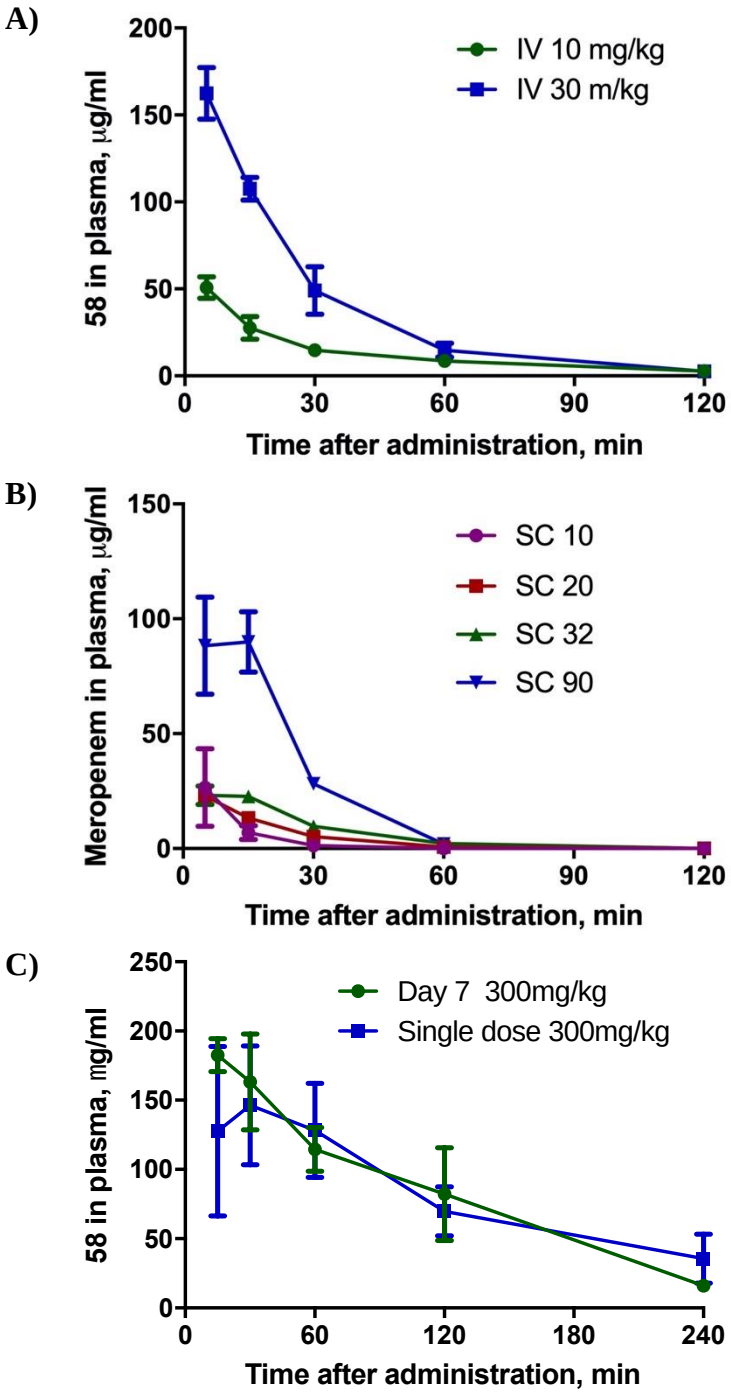
Supplementary Fig. 6. Stability studies on compound 58 and NDM-1. Thermal stability and Proteinase K stability assays show NDM-1 is more stable when complexed with **58**. **A)** Thermal stability of NDM-1 measured using differential scanning fluorimetry (DSF) without (Tm= 53 º) and with **58** (Tm= 67 º); **B)** Relative abundance of the NDM-1 peak relative to Proteinase K over time with or without **58**; **C)** and **D)** Time courses of deconvoluted LC-MS spectra monitoring NDM-1 proteolysis by Proteinase K in the absence (C) and (D) presence of **58**.



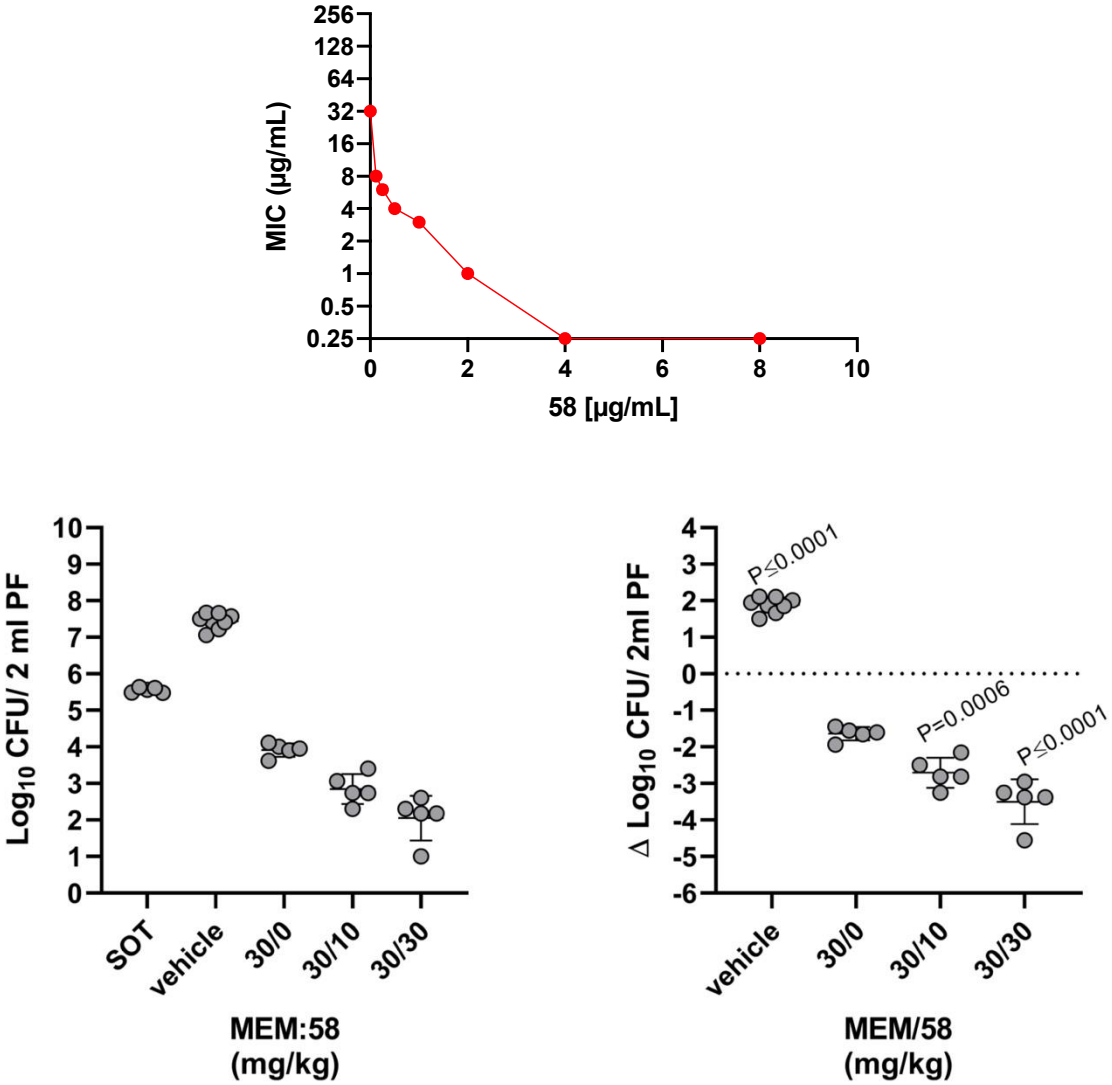
Supplementary Fig. 7. Seven day serial passage experiments. For strains (*E. coli* IR57 $bla_{\text{NDM-1}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{TEM-198}}$, bla_{AmpC}, $bla_{\text{OXA-1}}$ and bla_{FonA} and *K. pneumoniae* B68-1 $bla_{\text{NDM-1}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{TEM-168}}$, $bla_{\text{CMY-6}}$, $bla_{\text{SHV-33}}$, bla_{AmpC} and $bla_{\text{OXA-9}}$), the increase in the maximum non-inhibitory concentration (MNIC) after the serial passages was higher in the absence of **58** (top: MNIC values without and bottom: MNIC values with **58**), especially when using imipenem. These results complement the single-step FoR results (Supplementary Table 29) and suggest that, when performing serial passages with a high initial bacterial concentration, the presence of **58** hinders the development of resistance to meropenem or imipenem in both strains. The plots show the MNIC as the mean ± the standard deviation obtained from results of n= 4 biologically independent cultures for each condition and day. After 7 days of experiment, the increase in the MNIC was compared for each strain and antibiotic in the absence or presence of **58**. MNIC for meropenem (MEM) or imipenem (IMI) shown as solid black circles and MNIC for meropenem-**58** or imipenem-**58** combinations shown as solid black squares.



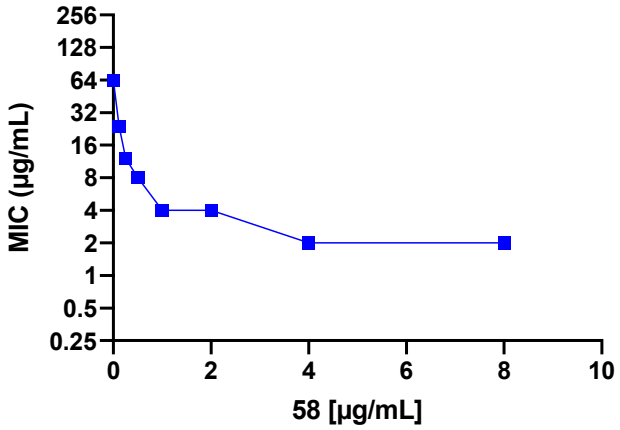
Supplementary Fig. 8. Exemplary PK profiles for meropenem and 58. A) 58 has a sufficient exposure level for efficacy at doses of 10 and 30 mg/kg; **B)** The $t_{1/2}$ of **58** exceeds that of meropenem. **58** is thus suitable for use in combination with meropenem. **C)** Exposure (AUC) of the dose of **58** at 300 mg/kg exceeds the exposure at effective doses 10 and 30 mg/kg 8-23 times. Each value represented as the average of measurements in 3 mice ±SD (standard deviation); n= 3 animals, each examined over one independent experiment.

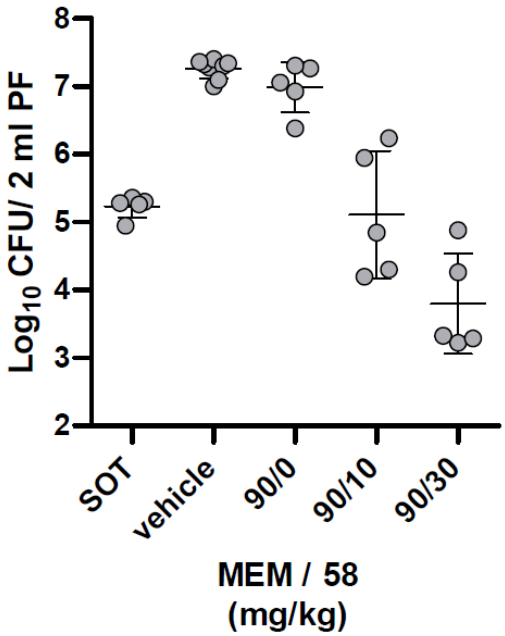


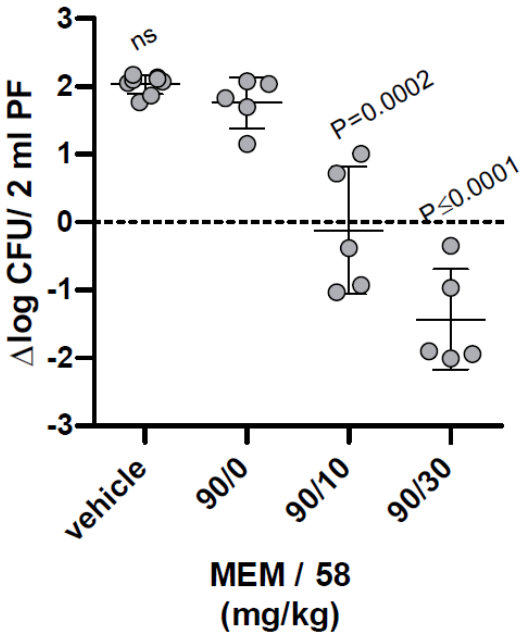
Supplementary Fig. 9. *In vivo* peritonitis model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* ATCC 25922 ISAb*a* 125 bla_{NDM-7}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *E. coli* ATCC 25922 ISAb*a* 125 bla_{NDM-7} strain, individual and mean ± SD CFU values. Statistical comparisons were performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test; vehicle n=8, other groups n = 5; n= 8 or 5 animals, each examined over one independent experiment. PF- peritoneal lavage fluid.



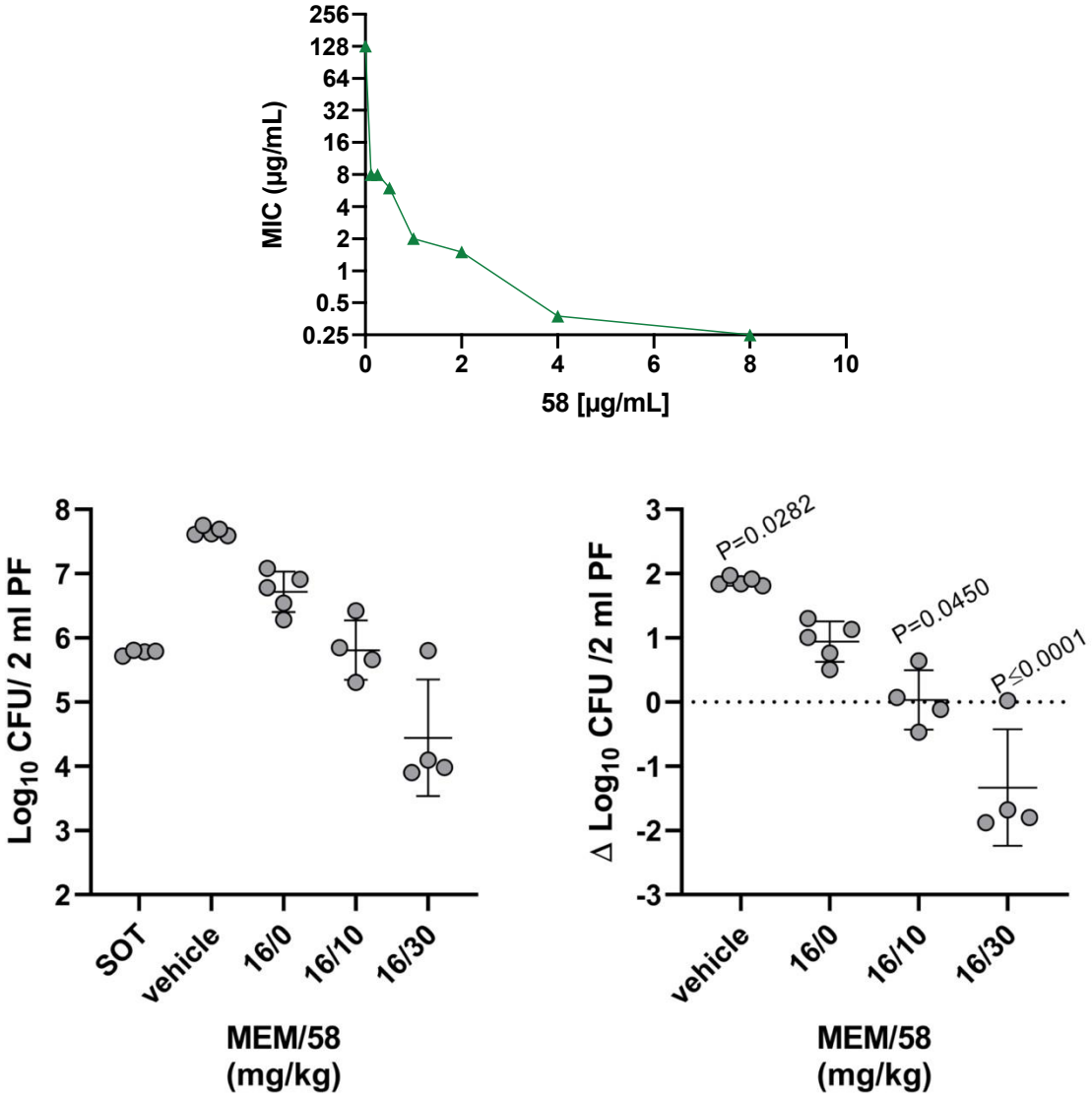
Supplementary Fig. 10. *In vivo* peritonitis model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* EC IR57 *bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{TEM-198}$, *bla*$_{AmpC}$, *bla*$_{OXA-1}$ and *bla*$_{FonA}$. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *E. coli* IR57 strain, individual and mean ± SD CFU values. Statistical comparisons were performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test; vehicle n= 8, other groups n= 5; n= 8 or 5 animals, each examined over four independent experiment; ns. – not significant.



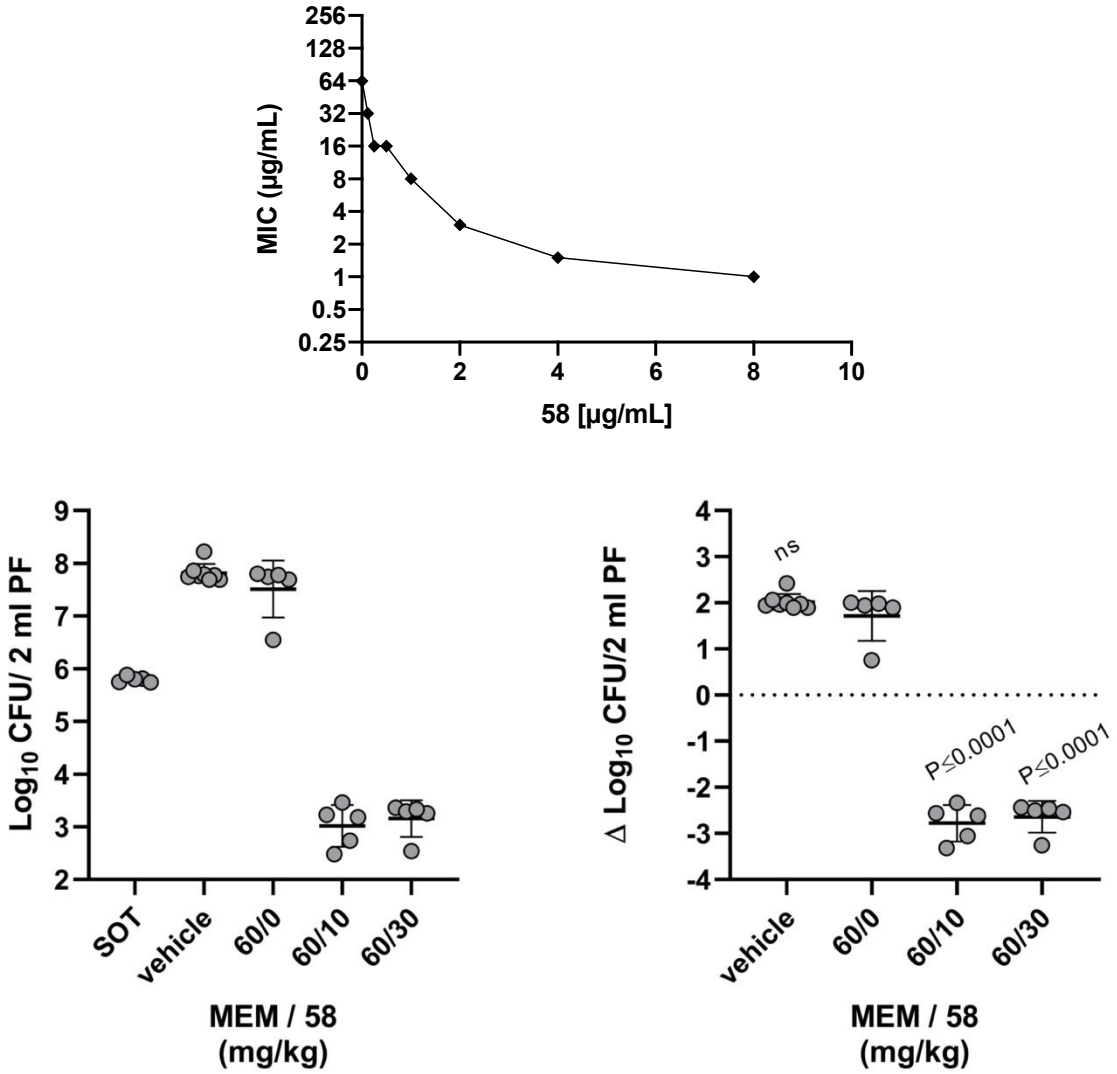




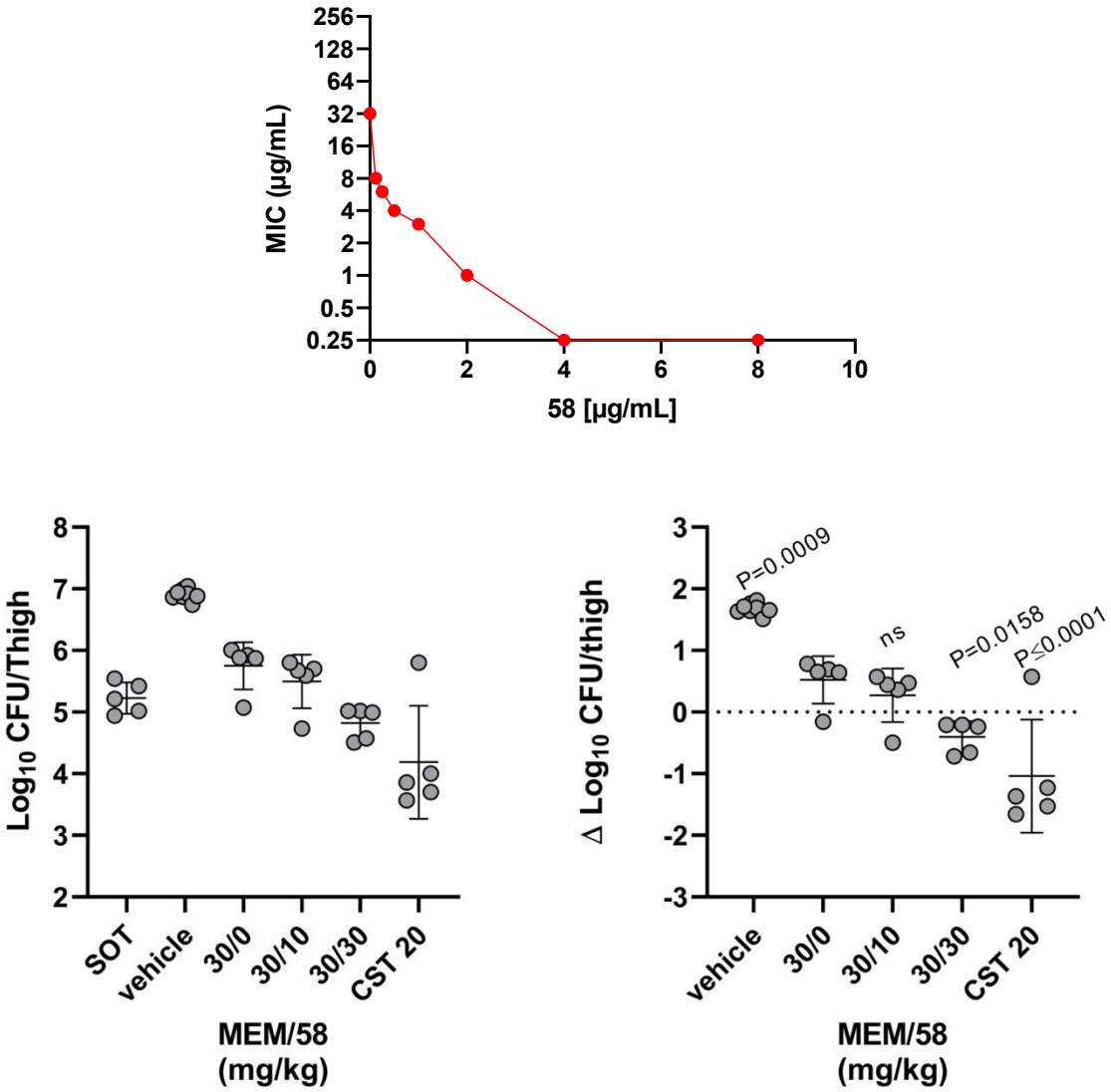
Supplementary Fig. 11. *In vivo* peritonitis model results for 58 and/or meropenem. Top - checkerboard analysis for *K. pneumoniae* B68-1 bla_{NDM-1}, $bla_{CTX-M-15}$, $bla_{TEM-168}$, bla_{CMY-6}, bla_{SHV-33}, bla_{AmpC} and bla_{OXA-9}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *K. pneumoniae* B68-1 strain, individual and mean ± SD CFU values. Statistical comparisons were performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, n = 5; n= 5 animals, each examined over one independent experiment.



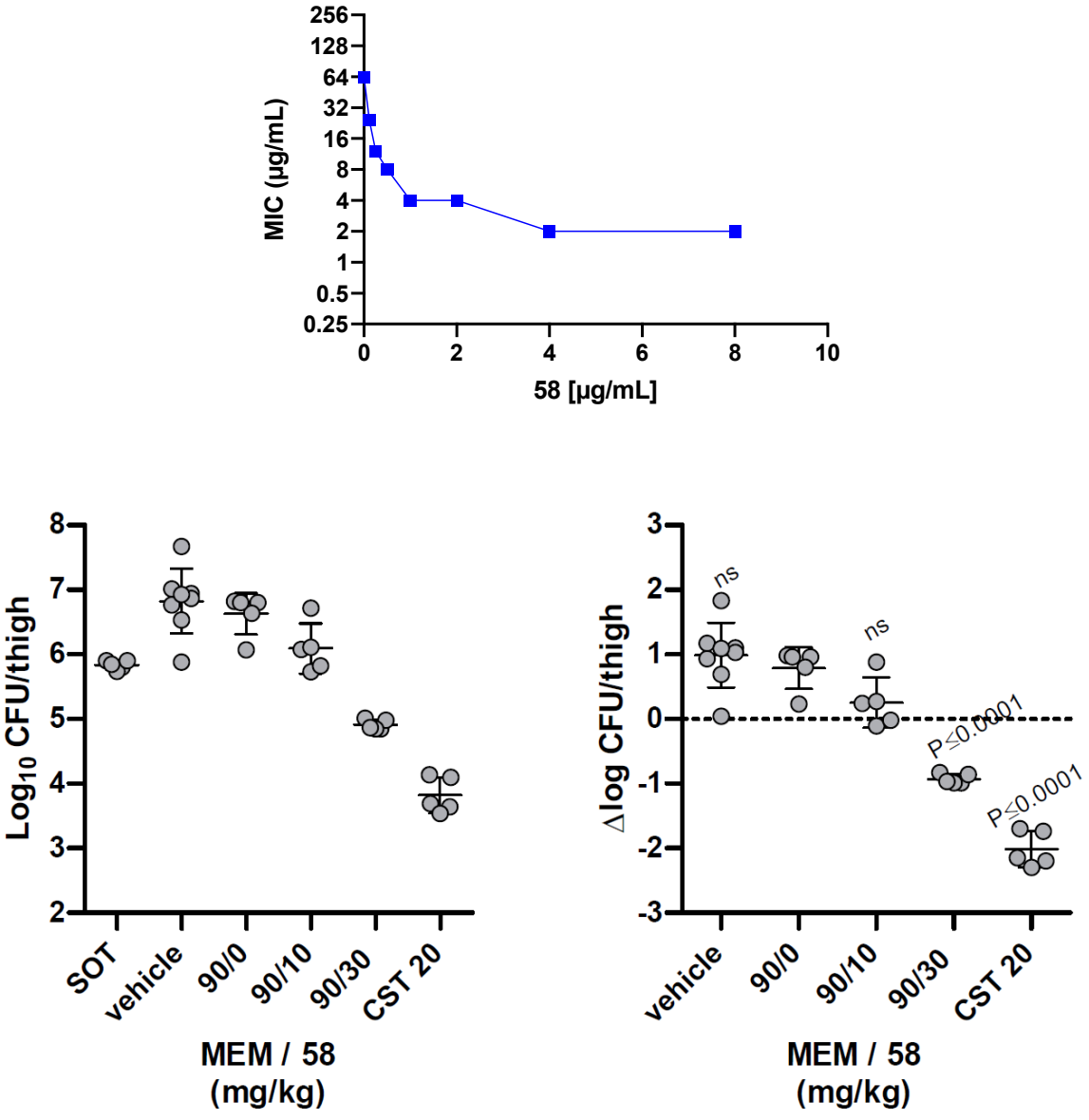
Supplementary Fig. 12. *In vivo* peritonitis model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* IHMA 997800 bla_{NDM-5}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{AmpC} and bla_{CMY-59}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of a carbapenem-resistant *E. coli* IHMA 997800 strain, individual and mean ± SD CFU values. Statistical comparisons were performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, vehicle n=8, other groups n = 5; n= 8 or 5 animals, each examined over one independent experiment; ns, not significant.



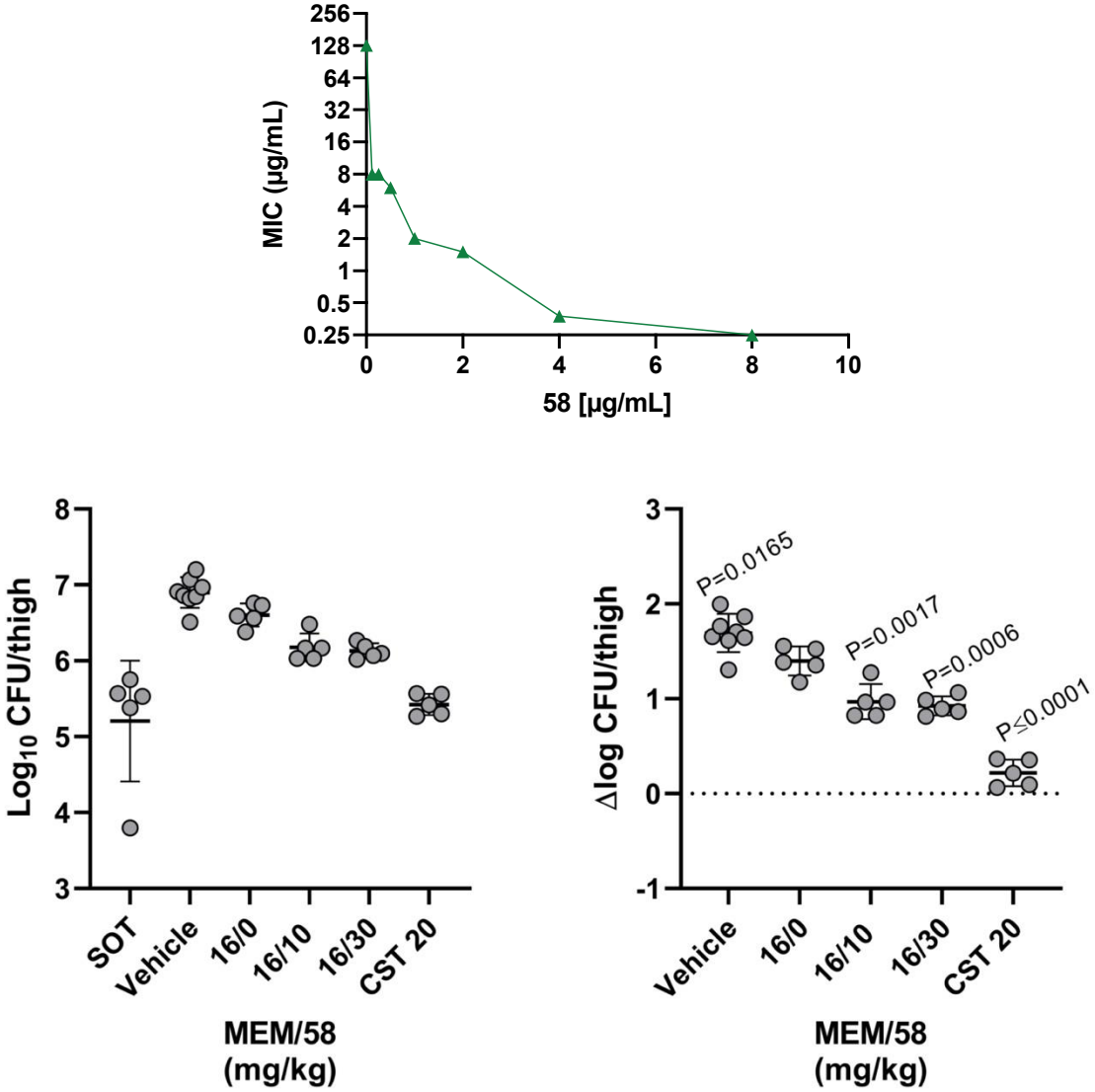
Supplementary Fig. 13. *In vivo* thigh model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* ATCC 25922 ISAb*a* 125 bla_{NDM-7}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *E. coli* ATCC 25922 bla_{NDM-7} strain, individual and mean ± SD CFU values. Statistical comparisons were performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, vehicle n=8, other groups n = 5; n= 8 or 5 animals, each examined over one independent experiment; ns.- not significant.



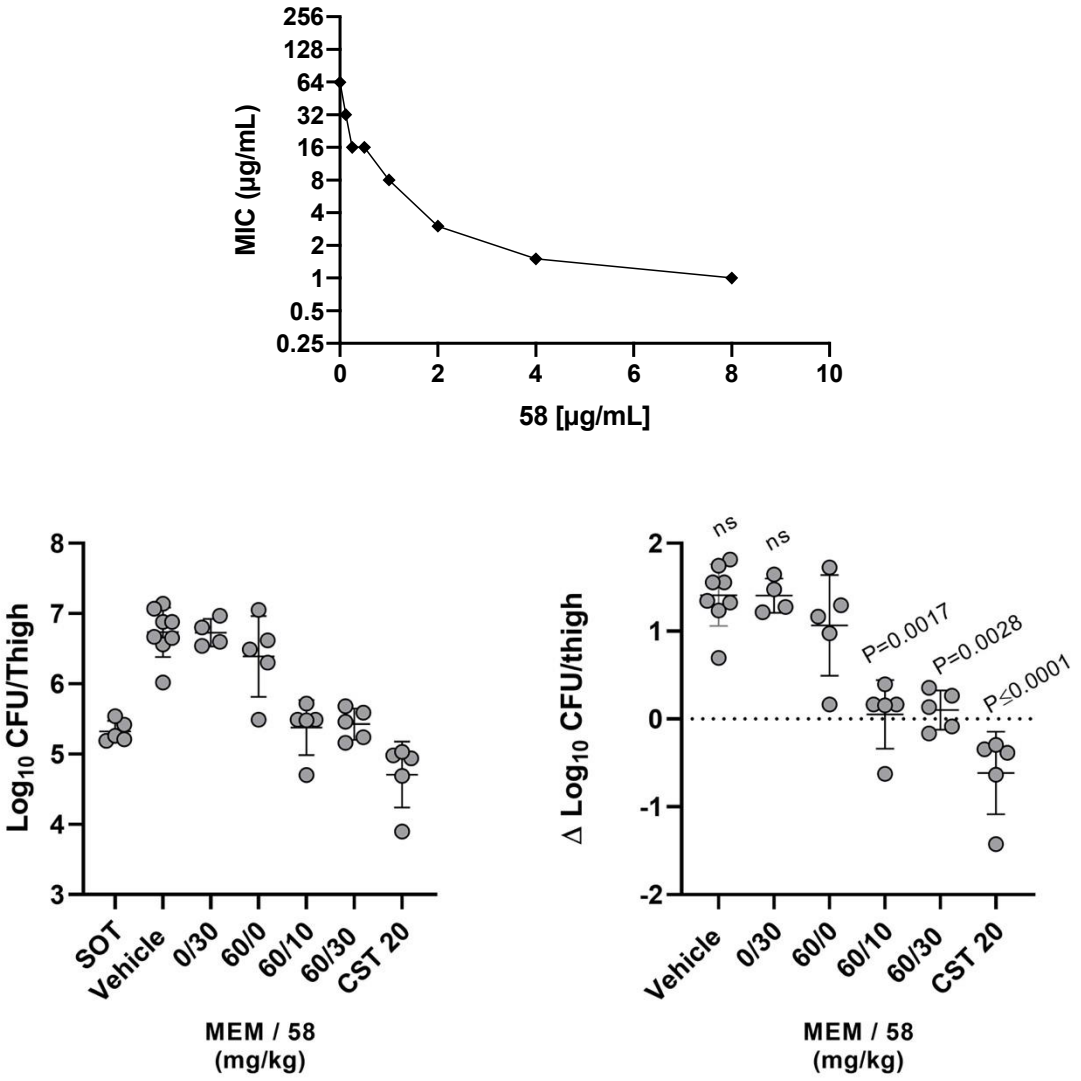
Supplementary Fig. 14. *In vivo* thigh model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* EC IR57 *bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{TEM-198}$, *bla*$_{AmpC}$, *bla*$_{OXA-1}$ and *bla*$_{FonA}$. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *E. coli* IR57 strain, individual and mean ± SD CFU values. Statistical comparison was performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, vehicle n=8, other groups n = 5; n= 8 or 5 animals, each examined over four independent experiment; ns. – not significant.



Supplementary Fig. 15. *In vivo* thigh model results for 58 and/or meropenem. Top - checkerboard analysis for *K. pneumoniae* B68-1 bla_{NDM-1}, $bla_{CTX-M-15}$, $bla_{TEM-168}$, bla_{CMY-6}, bla_{SHV-33}, bla_{AmpC} and bla_{OXA-9}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a single dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *K. pneumoniae* B68-1 strain, individual and mean ± SD CFU values. Statistical comparison was performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, vehicle n=8, other groups n = 5; n= 8 or 5 animals, each examined over one independent experiment.

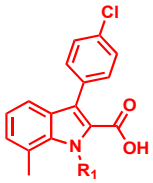


Supplementary Fig. 16. *In vivo* thigh model results for 58 and/or meropenem. Top - checkerboard analysis for *E. coli* IHMA 997800 bla_{NDM-5}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{AmpC} and bla_{CMY-59}. The plot show the MIC as the mean ± the standard deviation obtained from results of n= 3 biologically independent cultures. Bottom - the meropenem and **58** combination is efficacious with a sigle dose intravenous injection of meropenem and **58** (**58** dose 10 or 30 mg/kg). Treatment of the carbapenem-resistant *E. coli* IHMA 997800 strain, individual and mean ± SD CFU values. Statistical comparison was performed with Prism 8 using the one-way ANOVA, Dunnett's multiple comparisons test, vehicle n=8, 0/30 n=4, other groups n = 5; n= 8, 4 or 5 animals, each examined over three independent experiment.



2 Supplementary Tables

Supplementary Table 1. Studies on the importance of the indole NH group in indole carboxylate mediated MBL inhibition. Errors for pIC_{50} values are ±0.2 log fold. For assay details see Experimental Section.

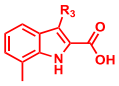


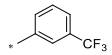
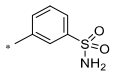
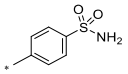
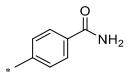
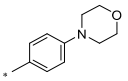
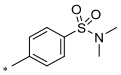
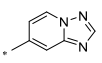
IC	R_1	pIC_{50}				
		NDM-1	VIM-2	IMP-1	VIM-1	Avg
3		6.3	4.7	4.7	-	5.2
4		7.8	6.6	5	5.5	6.2

Supplementary Table 2. Studies on the importance of the indole carboxylate C2 carboxylate. Errors for pIC_{50} values are ±0.2 log fold. Any values reported as <4 exhibited less than 50% inhibition at the maximum tested concentration. For assay details see Experimental Section.

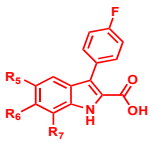
IC	R_2	pIC_{50}				
		NDM-1	VIM-2	IMP-1	VIM-1	Avg
5		9.4	7.5	6.3	-	7.7
6		4.7	4.7	4.7	-	4.7
7		<4.0	-	-	-	<4.0

Supplementary Table 3. Studies on the importance of the indole carboxylate C3 position to explore the effects of C3 substituent size, electronic properties and lipophilicity. Errors for pIC_{50} values are ±0.2 log fold. Any values reported as <3.7 exhibited less than 50% inhibition at the maximum tested concentration. For assay details see Experimental Section.



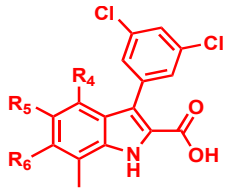
IC	R_3	pIC_{50}				
		NDM-1	VIM-2	IMP-1	VIM-1	Avg
1		7.4	6.1	5.5	5.3	6.1
8		7.5	6.4	5	5.4	6.1
9		6.9	6.7	4.1	5.5	5.8
10		7.2	6.5	4.6	-	6.1
11		6.9	6.9	-	-	6.9
12		6.5	6.6	5.8	-	6.3
13		7.5	6.7	5.4	-	6.5
14		7.6	7	5.7	6	6.6
15		7.3	6.1	4.9	5.5	6.0
16		7.8	7.3	5	-	6.7
17		6.6	4.9	4.3	5.3	5.3
18		8.1	7.8	5.4	6.2	6.9
19		7.9	5.8	5	-	6.2
20		8.3	6.6	6.1	4.9	6.5
21		5.9	6.7	4	5.5	5.5
22		7.2	7.4	4.2	6.1	6.2
23		7.6	7.1	4.9	5.9	6.4
24		6.4	4.4	4	-	4.9
25		4.8	-	4	<3.7	4.4
26		7.1	5.5	4.1	-	5.6

Supplementary Table 4. Summary of initial SAR studies for the indole carboxylate C6 and C5 positions to explore the effect of substituent size, electronic properties and lipophilicity. Errors for pIC_{50} values are ±0.2 log fold. For assay details see Experimental Section.



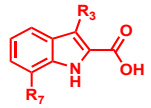
IC	R_7	R_6	R_5	pIC_{50}				
				NDM-1	VIM-2	IMP-1	VIM-1	Avg
1				7.4	6.1	5.5	5.3	6.1
27				5.7	4.8	4.1	3.3	4.5
28				5.2	4.4	4.7	-	4.8
29				7.5	6.1	4.8	-	6.1
30				6.9	6.2	4.0	-	5.7
31				6.9	6.3	4.6	5.1	5.7
32				7.5	6.4	5.1	5.4	6.1
33				7.8	6.3	5.8	5.6	6.4
34				7.6	6.4	5.7	5.4	6.3

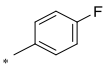
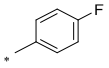
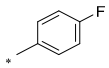
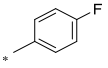
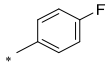
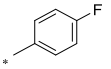
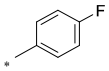
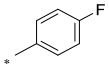
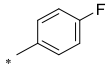
Supplementary Table 5. Summary of initial SAR studies for the indole carboxylate C4, C5 and C6 position to explore the effect of substituent size, electronic properties and lipophilicity. Errors for pIC_{50} values are ±0.2 log fold. For assay details see Experimental Section.



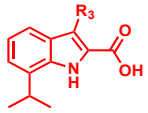
IC	R_4	R_5	R_6	pIC_{50}				
				NDM-1	VIM-2	IMP-1	VIM-1	Avg
35				7.5	7.7	5.8	6.2	6.8
36				7.6	7.2	5.8	6	6.9
37				7.2	7.8	5.8	6.4	6.8

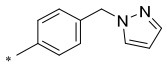
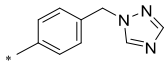
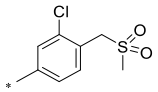
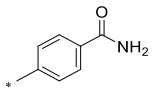
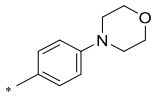
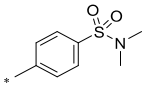
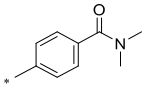
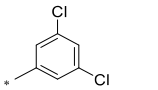
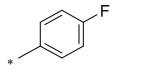
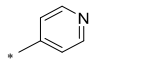
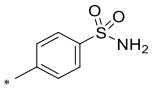
Supplementary Table 6. Summary of initial SAR studies for the indole carboxylate C7 position to explore the effect of substituent size, electronic properties and lipophilicity. Errors for pIC_{50} values are ±0.2 log fold. Any values reported as <3.7 exhibited less than 50% inhibition at the maximum tested concentration. For assay details see Experimental Section.



IC	R_7	R_3	pIC_{50}				
			NDM-1	VIM-2	IMP-1	VIM-1	Avg
38			5.5	-	<3.7	-	<5.5
39			6.6	6	5	4.6	5.6
40			5.8	5.1	4.1	4	4.8
1			7.4	6.1	5.5	5.3	6.1
41			6.6	6.1	-	4.5	5.7
42			7.9	7.3	-	6.3	7.2
43			6.6	-	5.6	5.7	6.0
44			8.1	7.5	6.7	7.2	7.4
45			7.7	6.5	5.4	6.5	6.5
46			7.1	7	6.2	7	6.8

Supplementary Table 7. Follow up SAR studies for the C3 indole carboxylate C3 position. Errors for pIC_{50} values are ±0.2 log fold. For assay details see Experimental Section.



IC	R_3	pIC_{50}				
		NDM-1	VIM-2	IMP-1	VIM-1	Avg
47		9.3	8.4	7.8	-	8.5
48		9.2	8	7.7	-	8.3
49		8.9	8.1	8.5	8	8.4
50		8.6	8.1	7.9	-	8.2
51		8.6	7.1	8	-	7.9
5		9.4	7.5	6.3	-	7.7
52		9.2	7.1	7.7	-	8.0
53		8.1	8.3	7.5	7.3	7.8
44		7.9	7.5	6.3	-	7.2
54		8.2	7.5	7.4	-	7.7
55		8.8	7.9	7.5	-	8.1

Supplementary Table 8. Fitted constants for the binding of selected indole carboxylates to NDM-1 as determined by SPR. For assay details see Experimental Section.

	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	Rmax	K_D (μM)	Res sd
1	8.04E+05	0.01709	7.834	0.0212	0.836
38	2.82E+05	0.75100	13.9	2.66	0.484
8	2.02E+06	0.03965	8.391	0.0196	0.408
11	7.51E+05	0.04321	10.17	0.0576	0.756
12	5.94E+05	0.09497	9.164	0.160	0.647
4	3.31E+06	0.03819	6.863	0.0115	0.489
40	1.74E+05	0.43270	13.64	2.49	0.804
39	3.27E+05	0.10330	13	0.316	0.778
43	1.88E+06	0.13570	11.49	0.0723	0.557
13	6.93E+05	0.02004	9.922	0.0289	0.471
16	4.96E+06	0.03647	8	0.00736	0.544
14	2.69E+06	0.03008	7.137	0.0112	0.558
44	8.45E+05	0.01157	5.518	0.0137	0.582
18	1.21E+06	0.01327	8.835	0.0110	0.472
19	9.49E+05	0.01334	8.292	0.0141	0.465
15	1.11E+06	0.03163	9.546	0.0286	0.503
9	1.37E+06	0.04107	7.431	0.0301	0.592
25	1.60E+05	0.39700	15.997	2.48	0.664
24	3.21E+05	0.03159	8.514	0.0984	0.564
26	4.89E+05	0.04578	9.979	0.0937	0.618
46	2.47E+05	0.02537	16.5	0.103	1.001

Supplementary Table 9. Fitted constants for the binding of selected indole carboxylates to IMP-1 as determined by SPR. For assay details see Experimental Section.

	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	Rmax	K_D (μM)	Res sd
1	2.59E+05	2.301	15.62	8.90	0.411
38	6.02E+04	3.500	22.27	58.1	0.353
8	4.52E+05	1.439	13.82	3.19	0.135
11	4.11E+04	2.731	29.80	66.4	0.26
12	6.94E+04	7.256	26.16	104.5	0.219
4	9.45E+04	0.896	24.71	9.48	0.242
40	1.58E+04	3.258	32.28	206.4	0.217
39	1.36E+05	1.299	20.76	9.54	0.229
43	1.58E+05	0.525	16.77	3.32	0.334
13	8.17E+04	0.364	20.43	4.45	0.567
16	1.66E+05	0.886	26.08	5.33	0.297
14	1.59E+05	0.378	22.07	2.38	0.371
44	3.42E+05	0.046	13.12	0.136	0.376
18	5.35E+05	1.138	14.76	2.13	0.114
19	5.20E+05	0.439	15.24	0.845	0.14
15	5.43E+05	1.436	11.90	2.65	0.116
9	1.16E+05	2.323	22.33	20.0	0.206
25	1.19E+04	1.677	11.72	140.4	0.202
24	2.98E+04	0.760	21.45	25.5	0.517
26	8.17E+04	2.477	14.15	30.3	0.144
46	1.92E+05	0.074	22.29	0.386	0.756

Supplementary Table 10. Fitted constants for the binding of selected indole carboxylates to VIM-2 as determined by SPR. For assay details see Experimental Section.

	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	Rmax	K_D (μM)	Res sd
1	1.59E+04	0.02715	2.529	1.71	0.46
38	2.87E+03	0.114	3.149	39.7	0.242
8	2.80E+05	0.1051	1.381	0.375	0.255
11	5.04E+05	0.02209	2.687	0.0438	0.366
12	6.40E+05	0.03365	2.263	0.0526	0.324
4	6.19E+05	0.09126	2.796	0.147	0.275
40				weak	0.617
39	5.38E+04	0.1896	3.46	3.52	0.327
43					
13				weak	0.65
16	5.96E+05	0.04124	4.038	0.0691	0.522
14	4.17E+05	0.03159	2.055	0.0758	0.24
44	2.13E+06	0.0255	2.3395	0.0120	0.306
18	1.11E+06	0.0361	1.5715	0.0326	0.149
19	2.12E+06	1.05	5.179	0.495	0.265
15	1.56E+06	0.3236	3.538	0.207	0.284
9	5.88E+05	0.0589	1.8762	0.100	0.269
25				weak	0.983
24	7.57E+04	0.0384	1.9276	0.507	0.179
26	1.22E+04	1.106	22.16	90.4	0.332
46	3.54E+05	0.0804	3.0127	0.227	0.229

Supplementary Table 11. Exemplary microbiology screening for selected indole carboxylates against a small panel of clinical isolates. The meropenem MIC (μg/mL) values in the presence of the stated inhibitor at the concentrations stated are given. MIC values for meropenem against two clinical *Escherichia coli* (EC) strains carrying IMP-1 (IMP), VIM-1 (VIM) or NDM-1 (NDM) transformants and *Klebsiella pneumoniae* (KP) and EC clinical isolates co-harboring different MBLs were determined.

10 μg/mL inhibitor

	EC S4			EC S10			KP S19	KP IR16	KP A34	EC EC10
	IMP-1	VIM-1	NDM-1	IMP-1	VIM-1	NDM-1	IMP-4	NDM-1	VIM-4	NDM-1
DMSO	>16	1	>16	16	0.5	>16	16	16	>16	>16
5	1	≤0.25	1	2	≤0.25	1	1	2	8	2
53	1	≤0.25	≤0.25	1	≤0.25	≤0.25	1	0.5	4	0.5
50	0.5	≤0.25	≤0.25	0.5	≤0.25	0.5	1	0.5	4	0.5
54	1	≤0.25	≤0.25	1	≤0.25	≤0.25	2	1	4	1
55	1	≤0.25	≤0.25	1	≤0.25	≤0.25	1	1	2	1
52	1	≤0.25	≤0.25	1	≤0.25	≤0.25	1	2	4	0.5
51	1	≤0.25	0.5	1	≤0.25	0.5	2	2	4	2

25 μg/mL inhibitor

	EC S4			EC S10			KP S19	KP IR16	KP A34	EC EC10
	IMP-1	VIM-1	NDM-1	IMP-1	VIM-1	NDM-1	IMP-4	NDM-1	VIM-4	NDM-1
DMSO	>16	1	>16	16	0.5	>16	16	16	>16	>16
5	1	≤0.25	≤0.25	1	≤0.25	≤0.25	1	2	4	2
53	≤0.25	≤0.25	≤0.25	0.5	≤0.25	≤0.25	0.5	≤0.25	2	0.5
50	0.5	≤0.25	≤0.25	≤0.25	≤0.25	0.5	1	0.5	2	0.25
54	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	1	1	2	0.5
55	0.5	≤0.25	≤0.25	1	≤0.25	≤0.25	1	1	1	0.5
52	1	≤0.25	≤0.25	1	0.5	0.5	0.5	1	4	0.5
51	0.5	≤0.25	0.5	1	≤0.25	0.5	1	2	4	2

Supplementary Table 12. Exemplary *in vitro* microbiological permeation and efflux studies. The meropenem MIC (μg/mL) values in the presence of an InC inhibitor at the concentrations stated are given. The meropenem MICs against NCTC 5055 or NCTC 5055:RamA carrying an empty pSU18 vector (no MBL control) were ≤ 0.0625 in all cases. DMSO was used in no inhibitor controls with the same final volume as used with inhibitor studies. LC-MS/MS proteomics and fluorescent dye accumulation assays reveal that RamA overproduction reduces permeability by causing overproduction of AcrABTolC, OqxABTolC and AcrEFTolC efflux pumps and reducing OmpK35 porin production[2]. RamA overproduction may also alter LPS structure[2]. The latter might explain the apparently paradoxical increases in inhibitor activity seen in some cases. All MBL genes were cloned alongside their natural promoters. Note that, the action of VIM-1 is enhanced by RamA overproduction, but the same effect is not apparent with NDM-1 or IMP-1. NDM-1 is likely produced at a higher level (as manifested by ~5-fold increased of total meropenem hydrolyzing specific activity) compared to IMP-1. KP – *Klebsiella pneumoniae;* IMP - IMP-1, VIM - VIM-1 and NDM – NDM-1 metallo-β-lactamases.

5 μg/mL inhibitor

KP NCTC 5055				KP NCTC 5055:RamA			
Inhibitor	IMP-1	VIM-1	NDM-1	Inhibitor	IMP-1	VIM-1	NDM-1
DMSO	16	4	64	DMSO	16	16	32
44	2	0.5	4	**44**	2	2	2
16	8	0.5	4	**16**	4	2	2
54	2	0.5	2	**54**	2	16	4
50	2	0.25	2	**50**	2	4	4
53	2	0.25	1	**53**	2	1	1
5	4	0.5	8	**5**	4	8	8
51	4	0.5	4	**51**	2	8	8
52	2	1	2	**52**	2	2	4
55	4	0.5	1	**55**	2	4	1

10 μg/mL inhibitor

KP NCTC 5055				KP NCTC 5055:RamA			
Inhibitor	IMP-1	VIM-1	NDM-1	Inhibitor	IMP-1	VIM-1	NDM-1
DMSO	16	4	64	DMSO	16	16	32
44	2	0.25	2	**44**	1	2	1
16	8	0.5	2	**16**	4	2	1
54	2	0.5	1	**54**	1	8	4
50	2	0.25	1	**50**	2	4	4
53	2	0.125	0.5	**53**	1	1	0.5
5	2	0.5	2	**5**	2	8	2
51	4	0.5	2	**51**	2	8	2
52	2	1	1	**52**	2	2	4
55	2	0.125	1	**55**	4	4	0.5

25 μg/mL inhibitor

KP NCTC 5055				KP NCTC 5055:RamA			
Inhibitor	IMP-1	VIM-1	NDM-1	Inhibitor	IMP-1	VIM-1	NDM-1
DMSO	16	4	64	DMSO	16	16	32
44	2	0.25	2	**44**	1	2	0.5
16	<=0.0625	<=0.0625	<=0.0625	**16**	<=0.0625	<=0.0625	<=0.0625
54	2	0.5	0.25	**54**	1	8	0.5
50	1	0.125	0.5	**50**	2	4	1
53	0.25	<=0.0625	0.125	**53**	0.25	<=0.0625	<=0.0625
5	2	0.5	0.5	**5**	4	8	1
51	2	0.125	1	**51**	2	8	1
52	2	0.25	0.25	**52**	2	2	0.5
55	1	<=0.0625	0.25	**55**	4	2	0.5

50 μg/mL inhibitor

KP NCTC 5055				KP NCTC 5055:RamA			
Inhibitor	IMP-1	VIM-1	NDM-1	Inhibitor	IMP-1	VIM-1	NDM-1
DMSO	16	2	64	DMSO	16	8	32
44	<=0.0625	<=0.0625	<=0.0625	**44**	<=0.0625	<=0.0625	<=0.0625
16	<=0.0625	<=0.0625	<=0.0625	**16**	<=0.0625	<=0.0625	<=0.0625
54	1	<=0.0625	0.125	**54**	1	8	0.5
50	1	<=0.0625	0.125	**50**	2	8	0.5
53	0.125	<=0.0625	<=0.0625	**53**	<=0.0625	<=0.0625	<=0.0625
5	2	0.25	0.25	**5**	2	8	0.25
51	2	0.25	0.5	**51**	2	8	2
52	1	0.25	<=0.0625	**52**	2	8	0.25
55	2	<=0.0625	0.125	**55**	1	1	0.5

Supplementary Table 13. *In vitro* cell-based screening results for selected indole carboxylates. Meropenem MIC (μg/mL) values in the presence of the stated inhibitor at the concentrations stated are given. Meropenem MIC values against three *Klebsiella pneumoniae* (KP) strains (including one MDR mutant - ECL8 delta ramR - with a RamA over-producing phenotype) and one laboratory generated strain of *Escherichia coli* (EC). In each case the strains produce IMP-1 (IMP), VIM-1 (VIM), or NDM-1 (NDM).

5 μg/mL inhibitor

	KP Strain SM			KP ECL8		KP ECL8 Δ*ramR*			EC TOP-10	
	IMP	VIM	NDM	IMP	NDM	IMP	VIM	NDM	IMP	NDM
DMSO	>16	2	>16	>16	>16	8	1	>16	>16	>16
44	8	≤0.25	4	8	4	8	≤0.25	8	1	2
16	8	≤0.25	4	8	2	8	0.5	8	16	4
5	2	0.5	2	16	4	4	0.5	8	2	4
53	4	0.5	2	8	2	4	≤0.25	2	1	2
50	2	≤0.25	1	4	2	4	0.5	8	4	0.5
54	2	≤0.25	2	4	4	4	≤0.25	8	1	1
55	4	≤0.25	1	8	2	4	≤0.25	4	1	2
52	2	≤0.25	1	8	2	4	0.5	4	1	1
51	4	≤0.25	2	8	2	4	0.5	8	1	4

10 μg/mL inhibitor

	KP Strain SM			KP ECL8		KP ECL8 Δ*ramR*			EC TOP-10	
	IMP	VIM	NDM	IMP	NDM	IMP	VIM	NDM	IMP	NDM
DMSO	>16	2	>16	>16	>16	8	1	>16	>16	>16
44	2	≤0.25	2	8	4	4	≤0.25	4	1	1
16	8	≤0.25	2	8	2	8	≤0.25	8	16	2
5	2	≤0.25	1	8	2	4	≤0.25	4	1	2
53	2	≤0.25	1	4	1	2	≤0.25	1	0.5	1
50	2	≤0.25	0.5	4	1	4	≤0.25	4	0.25	0.5
54	2	≤0.25	1	2	2	4	≤0.25	2	0.5	0.5
55	2	≤0.25	0.5	4	1	4	≤0.25	0.5	0.5	1
52	2	≤0.25	0.25	2	0.5	4	≤0.25	1	0.5	0.5
51	2	≤0.25	2	4	2	4	≤0.25	4	0.5	2

Supplementary Table 14 – Coverage of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* strains with 49 in combination with meropenem or imipenem. Results are shown for an agar dilution checkerboard analysis revealing the combined effect of **49** and meropenem or imipenem against 6 NDM producing *A. baumannii* strains and 7 VIM and 1 IMP producing *P. aeruginosa* strains. See Experimental Section for assay details.

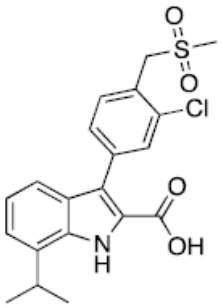
Meropenem	MIC (μg/ml)											
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
A. baumannii (n=6)												
Control					1							5
49 (4 μg/ml)					1				1	3		1
49 (8 μg/ml)					1			1	1	2		1
P. aeruginosa (n=8)												
Control							1		1		1	5
49 (4 μg/ml)			1					1	2		1	3
49 (8 μg/ml)		1						1	2		1	3

Imipenem	MIC (μg/ml)											
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
A. baumannii (n=6)												
Control					1						2	3
49 (4 μg/ml)					1			1		3	1	
49 (8 μg/ml)					1			1	1	1	2	
P. aeruginosa (n=8)												
Control								1		1	1	5
49 (4 μg/ml)						1		1	1	1		4
49 (8 μg/ml)						1		1		2		4

Supplementary Table 15. *In vitro* off target selectivity screening for InC 49 conducted at Cerep Panlabs (Eurofins). ham = hamster; hum = human.

Catalog Number	Assay name	Species	Repeats	Concentration	% Inhibition
200510	Adenosine A1	hum	2	100 µM	8
200610	Adenosine A2A	hum	2	100 µM	-17
203100	Adrenergic α1A	rat	2	100 µM	8
203200	Adrenergic α1B	rat	2	100 µM	3
203630	Adrenergic α2A	hum	2	100 µM	-1
204010	Adrenergic β1	hum	2	100 µM	-15
204110	Adrenergic β2	hum	2	100 µM	2
214600	Calcium Channel L-Type, Dihydropyridine	rat	2	100 µM	22
217030	Cannabinoid CB1	hum	2	100 µM	23
219500	Dopamine D1	hum	2	100 µM	7
219700	Dopamine D2S	hum	2	100 µM	17
226600	GABAA, Flunitrazepam, Central	rat	2	100 µM	10
226500	GABAA, Muscimol, Central	rat	2	100 µM	25
233000	Glutamate, NMDA, Phencyclidine	rat	2	100 µM	6
239610	Histamine H1	hum	2	100 µM	30
241000	Imidazoline I2, Central	rat	2	100 µM	21
252710	Muscarinic M2	hum	2	100 µM	9
252810	Muscarinic M3	hum	2	100 µM	-4
258590	Nicotinic Acetylcholine	hum	2	100 µM	-18
258700	Nicotinic Acetylcholine α1, Bungarotoxin	hum	2	100 µM	17
260410	Opiate µ (OP3, MOP)	hum	2	100 µM	8
264500	Phorbol Ester	mouse	2	100 µM	28
265600	Potassium Channel [KATP]	ham	2	100 µM	24
265900	Potassium Channel hERG	hum	2	100 µM	-19
268420	Prostanoid EP4 419648	hum	2	100 µM	59
270000	Rolipram	rat	2	100 µM	19
271700	Serotonin (5-Hydroxytryptamine) 5-HT2B	hum	2	100 µM	15
278110	Sigma σ1	hum	2	100 µM	16
279510	Sodium Channel, Site 2	rat	2	100 µM	-7
204410	Transporter, Norepinephrine (NET)	hum	2	100 µM	64

Supplementary Table 16. Exemplary physicochemical and ADME properties of InC **49** indicate two potential weaknesses of the initially developed inhibitors, i.e. relatively low metabolic stability and high plasma protein binding. Subsequent SAR was carried out to improve the series with respect to these two properties.



49

Physicochemical properties	
MW	405.89 g/mol
H-bond donors	2
H-bond acceptors	4
TPSA	87.23
cLogP	3.75
$cLogD_{7.4}$	0.4
exp LogD	0.5
calculated pKa	3.59
exp pKa	3.78
Solubility	2290 µM
Chemical stability at pH 7.4	>100 %

ADME	
Hep metabolism ($t_{1/2}$)	**human: 145 min, mouse: 23 min**
Plasma stability (min)	human: >100, mouse: >100, rat: >100; @ 3h
CYP3A4 inhibition	no inhibition at 30 µM
PPB (fu %)	**human: 0.072, mouse: 0.411**
hERG inhibition	> 30 µM
NaV1.5 inhibition	> 30 µM
Cytotoxicity (HepG2)	> 64 µM
Caco-2 permeability	Papp AB: 0.35x10E-6 cm/s Papp BA: 10.1x10E-6 cm/s Efflux ratio: 28.6

Supplementary Table 17. *In vitro* cell-based screening in the presence of serum. The meropenem MIC (μg/mL) values in the presence of InC **49** and serum at the concentrations stated are given.

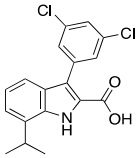
Strain: 91N (NDM-1 *E. coli*)	**MERO (μg/mL)**	**49**	
		4 μg/mL	**8 μg/mL**
NEAT BROTH	32	0.25	0.25
50% Pooled Human Serum	16	8	8
50% Heat Treated Human Serum	64	16	32
20% Human Serum Albumin	32	8	8
40% Human Serum Albumin	32	8	8

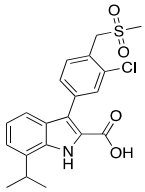
Strain: S117 (NDM-1 *E. coli*)	**MERO (μg/mL)**	**49**	
		4 μg/mL	**8 μg/mL**
NEAT BROTH	>64	2	2
50% Pooled Human Serum	32	16	16
50% Heat Treated Human Serum	16	16	16
20% Human Serum Albumin	>64	32	32
40% Human Serum Albumin	32	16	32

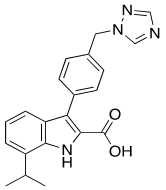
Supplementary Table 18. – Results of testing InC 49 for tolerability in mice at 10 and 100 mg/kg single doses. No adverse effects were observed. For assay details see Experimental Section.

Treatment	Mouse	Score							
		0-2 min	5 min	15 min	30 min	60 min	120 min	240 min	24 h
49 10 mg/kg	**1**	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
49 100 mg/kg	**4**	0	0	1*	0	0	0	0	0
	5	0	0	1*	0	0	0	0	0
	6	0	0	1*	0	0	0	0	0

Supplementary Table 19. Exemplary selected physicochemical and ADME properties of InCs **48**, **49** and **53**, highlighting two potential weakness of the initial inhibitors, i.e. relatively low metabolic stability and high plasma protein binding. Subsequent SAR was carried out to improve the series with respect to these two properties.







	53	**49**	**48**
Physicochemical properties			
MW	348.22 g/mol	405.89 g/mol	360.417 g/mol
H-bond donors	2	2	2
H-bond acceptors	2	4	4
TPSA	53.09	87.23	83.8
cLogP	5.75	3.75	3.87
$cLogD_{7.4}$	2.4	0.4	0.66
calculated pKa	3.58	3.59	3.60(Acidic), 1.99(Basic)
ADME			
Hep metabolism ($t_{1/2}$)	human: 29 min, mouse: 52 min	human: 145 min, mouse: 23 min	not tested
PPB (fu %)	human: 0.01, mouse: 0.02	human: 0.072, mouse: 0.411	human: 0.67, mouse: 0.26

Supplementary Table 20. Processing and refinement statistics for VIM-1 and VIM-2 inhibitor complex crystal structures.

Data Set	VIM-1:49 complex	VIM-2:11 complex
PDB	7AFY	7AFX
Resolution (outer shell) (Å)	40.18 - 1.105 (1.145 - 1.105)	29.14 - 1.636 (1.695 - 1.636)
Unit cell dimensions	39.64 68.01 40.23 90 92.94 90	103.25 79.06 67.95 90 130.366 90
Space group	P 1 21 1	C 1 2 1
Protein molecules per ASU†	1	2
Completeness (outer shell) (%)	98.41 (90.81)	96.82 (92.72)
Total reflection	165646 (15138)	95579 (9000)
No. of unique reflections (outer shell)	83803 (7727)	49675 (4690)
Multiplicity (outer shell)	2.0 (2.0)	1.9 (1.9)
CC-half	0.998 (0.842)	0.996 (0.721)
I/σ mean (outer shell)	13.28 (2.57)	9.37 (1.99)
R_{merge}	0.03448 (0.2674)	0.06129 (0.4198)
R_{meas}	0.04877 (0.3781)	0.08667 (0.5937)
R_{pim}	0.03448 (0.2674)	0.06129 (0.4198)
Wilson B	9.66	14.17
Refinement		
B factors:		
Overall	15.81	19.03
Protein	13.74	18.02
Ligand	12.88	18.00
Water	28.21	28.60
RMSD from ideal bond length (Å)‡	0.009	0.004
RMSD from ideal angles (degrees)	1.13	0.72
R_{work} **(%)**	0.1260	0.1605
R_{free} **(%)**	0.1453	0.1812

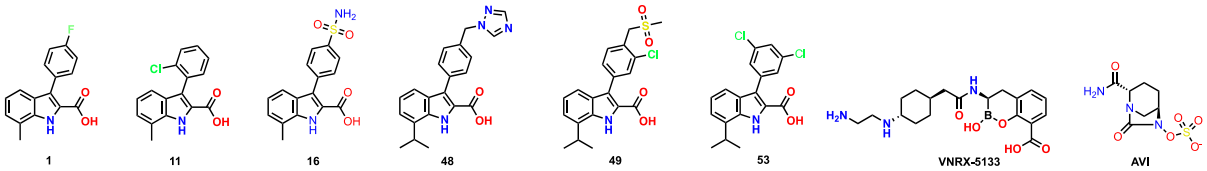
†ASU = asymmetric unit. ‡RMSD = root mean square deviation.

Supplementary Table 21. Processing and refinement statistics for the NDM-7 and L1 inhibitor complex crystal structures.

Data Set	NDM-7:48 complex	L1:49 complex
PDB	7AEZ	7AFZ
Resolution (outer shell) (Å)	27.72 - 1.018 (1.055 - 1.018)	66.62 – 1.50 (1.53 – 1.50)
Unit cell dimensions	41.74 58.73 83.89 90 90 90	104.78 104.78 98.11 90 90 120
Space group	P 21 21 21	P 6422
Protein molecules per ASU†	1	1
Completeness (outer shell) (%)	92.16 (49.48)	100.0 (100.0)
Total reflection	194733 (9970)	3531081 (142457)
No. of unique reflections (outer shell)	97736 (5179)	51300 (2506)
Multiplicity (outer shell)	2.0 (1.9)	68.8 (56.8)
CC-half	1 (0.865)	1 (0.564)
I/σ mean (outer shell)	25.51 (2.87)	23.4 (2.6)
R_{merge}	0.0205 (0.2615)	0.169 (3.312)
R_{meas}	0.02899 (0.3698)	0.170 (3.342)
R_{pim}	0.0205 (0.2615)	0.02 (0.440)
Wilson B	8.56	16.93
Refinement		
B factors:		
Overall	13.11	25.97
Protein	10.43	24.58
Ligand	18.83	47.5
Water	26.36	34.26
RMSD from ideal bond length (Å)‡	0.010	0.007
RMSD from ideal angles (degrees)	1.10	0.91
R_{work} (%)	0.1045	0.1523
R_{free} (%)	0.1133	0.1675

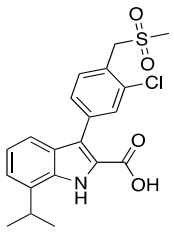
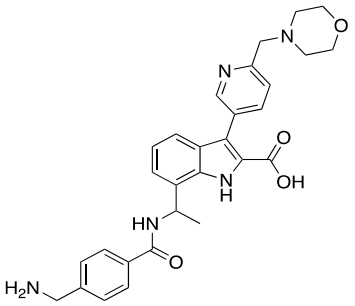
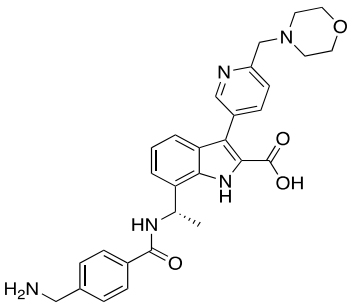
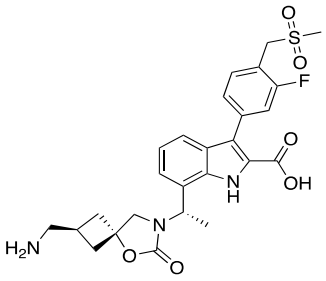
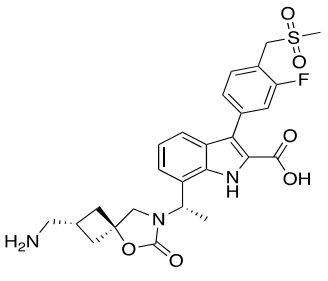
†ASU = asymmetric unit. ‡RMSD = root mean square deviation.

Supplementary Table 22. *In vitro* activity of selected indole carboxylates. pIC_{50} analysis reveals the ability of InCs as potent MBL inhibitors and less potent SBL inhibitors. VNRX - VNRX-5133/taniborbactam, AVI - avibactam and NI – no inhibition observed. SBLs and MBLs tested: TEM-1, a class A SBL; NDM-1, -7, VIM-1, -2, -4, -5, IMP-1 and SPM-1, class B1 MBLs; CphA and Sfh-1, class B2 MBLs; L1, a class B3 MBL; AmpC from *Pseudomonas aeruginosa*, a class C SBL; and the class D SBLs OXA-10 and -48. Errors for pIC_{50} values are ±0.2 log fold. Values reported as below a specified value than exhibited less than 50% inhibition at the maximum tested concentration.



	SBL	MBL											SBL		
	A	B1								B2		B3	C	D	
	TEM-116	NDM-1	NDM-7	VIM-1	VIM-2	VIM-4	VIM-5	IMP-1	SPM-1	CphA	Sfh-1	L1	AmpC	OXA-10	OXA-48
1	3.4	7.4	7.3	5.5	6.1	6.3	5.8	5.3	5	5.9	5.7	4.4	3.4	2.4	2.6
11	2.9	6.7	6.7	5.6	6.8	6.9	6.2	4.2	5.5	5.9	5	5.2	3.2	3.1	2.9
16	3.6	8.1	8.3	6.7	7.5	7.7	7.4	7.2	5.7	6.2	5	5.5	3.7	2.8	2.7
48	3.3	8.8	9	6.9	7.6	8	7.7	7.6	6.3	6.4	5.2	5.3	2.7	>2.4	2.6
53	5.1	8.1	8.3	7.3	8.3	8.3	8.9	7.5	7.3	6.2	5.7	6.3	4.7	3.7	3.1
49	3.4	8.9	9.1	8	8.1	8.5	8.4	8.1	7.6	5.9	5.8	7.3	2.7	2.7	2.7
VNRX	8.4	7.8	7.7	8.6	9.5	10.2	7.9	5.9	6.9	NI	NI	4.9	7.9	7.1	6.8
AVI	8.2	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	6.8	>4.4	5.2

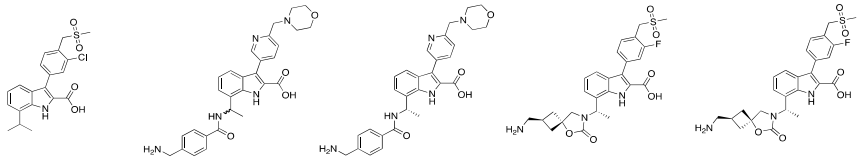
Supplementary Table 23. Optimization of the indole carboxylate C7 position, via imitation of the binding the β-lactam acetamido penicillin C6 or cephalosporin C7 side chain binding modes (See Main text Figure 3). Errors for pIC_{50} values are ±0.2 log fold. For assay details see Experimental Section.

IC	Structure	pIC_{50}				
		NDM-1	VIM-2	IMP-1	VIM-1	Avg
49		8.9	8.1	8.5	8	8.4
56		10.2	8.8	7.2	6.7	8.2
57		>10.2	>9.2	7.3	6.9	8.4
58		9.5	9.2	7.2	9.1	8.8
59		>10.2	9.8	8	9.4	9.35

Supplementary Table 24. Exemplary microbiology screening results for 58 and 59. Meropenem MIC (μg/mL) values in the presence of 8 μg/mL of **58** or **59** were determined. See Experimental Section for assay details.

STRAIN	SPECIES	GENOTYPE	MEM	MEM + 59	MEM + 58
76885-C	*A. baumannii*	**NDM**	>64	2	2
98077-B	*C. freundii*	**NDM**	64	0.25	0.25
S11-10	*E. cloacae*	**NDM**	64	32	64
55N	*E. coli*	**NDM**	16	0.25	0.25
B53	*E. coli*	**NDM**	64	0.5	0.25
S11-5	*E. kobei*	**NDM**	32	0.125	0.25
86259	*K. pneumoniae*	**NDM**	16	0.25	0.25
48F	*K. pneumoniae*	**NDM**	32	0.5	0.5
76664-G	*K. pneumoniae*	**NDM**	8	0.125	0.125
I39	*K. pneumoniae*	**NDM**	16	1	0.25
IR18	*K. pneumoniae*	**NDM**	32	0.5	0.5
76030-E-G	*A. baumannii*	**NDM-1**	>64	2	2
CH3504	*A. baumannii*	**NDM-1**	>64	8	8
S7-29	*A. baumannii*	**NDM-1**	>64	2	2
85511-E-Pi	*C. braakii*	**NDM-1**	32	0.5	0.5
84646-E-B	*C. freundii*	**NDM-1**	32	0.25	0.25
85524-E-Pi	*C. freundii*	**NDM-1**	18	0.25	0.25
85558-E-Pi	*C. freundii*	**NDM-1**	16	0.25	0.25
85569-E-Pi	*C. freundii*	**NDM-1**	32	0.125	0.125

Supplementary Table 25. Exemplary selected physicochemical and ADME properties of InC **56**, **57**, **58** and **59** highlighting the improved metabolic stability (> 450 min) and reduced plasma protein binding compared to **49**.



	49	**56**	**57**	**58**	**59**
Physicochemical properties					
MW	405.89 g/mol	513.598 g/mol	513.598 g/mol	529.580 g/mol	529.580 g/mol
H-bond donors	2	4	4	3	3
H-bond acceptors	4	7	7	6	6
TPSA	87.23	133.57	133.57	142.79	142.79
cLogP	3.75	-0.07	-0.07	-0.53	-0.53
$cLogD_{7.4}$	0.4	-0.08	-0.08	-0.53	-0.53
calculated pKa	3.59	3.53(Acidic); 9.16(Basic)	3.53(Acidic); 9.16(Basic)	3.57(Acidic); 10.10(Basic)	3.57(Acidic); 10.10(Basic)
ADME					
Hep metabolism ($t_{1/2}$)	human: 145 min, mouse: 23 min	human: >450 min, mouse: >450 min	not tested	human: >450 min, mouse: >450 min	human: >450 min, mouse: >450 min
PPB (fu %)	human: 0.072, mouse: 0.411	human: 43.87, mouse: 4.22	not tested	human: 35.27, mouse: 6.31	human: 23.68., mouse: 1.86

Supplementary Table 26. See 'raw_MICvalues.xlsx' for full data for Tables A, B, and C.
A) Composition of the MIC_{90} strain collections

Species	Number of strains	Proportion total (%)
E. coli	97	34.5
Klebsiella spp.	47	16.7
E. cloacae	51	18.1
Other *Enterobacter* spp.	20	7.1
Proteus mirabilis	6	2.1
Serratia marcescens	12	4.3
Citrobacter spp.	28	10.0
Providencia spp	20	7.1
Total	**281**	

Supplementary Table 26. B) Contingency table showing the composition of the strain panel used for this study.

Species group / Collection	*Escherichia coli*	*Enterobacter spp.*	*Klebsiella* spp.	*Citrobacter* spp.	*Providencia* spp.	*Serratia marcescens*	*Proteus mirabilis*	Total (for each collection)
Barnards[1]	3	10	42	1	1	9		66
India[2]	28	11			2			41
Karachi[3]		11		21				32
Pakistan[4]	17	8		3		3		31
Tanta[5]	10	6		1	8			25
Dhaka[6]	1	4			7		6	18
Bergamo[7]	18							18
Warsaw[8]	3	6	7	1				17
Peshawer[9]	2	3	1		1			7
Other[10]	13	12						25
Total (for each species group)	95	71	50	27	19	12	6	**Total 280**
Of which:								
NDM+	91	65	45	26	18	12	6	263
VIM+	4	5	5	1	1			16

[1]Barnards collection: property of Timothy Walsh (Oxford University). Funded by Gates Foundation. Isolates collected from 2015 to 2017 from Africa and South Asia.
[2]India collection: property of Timothy Walsh. Funded by Wellcome Trust. Isolates collected from 2010 to 2011. Isolates from Haryana and Chennai, India
[3]Karachi collection: property of Timothy Walsh. Funded by DOW Fellowship scheme (Ammara Mushtaq). Isolates collected from clinical and environmental sources in Karachi during the years 2013-2014.
[4]Pakistan collection: property of Timothy Walsh. Funded by Pakistan Fellowship scheme. Isolates collected from IPIMS, Islamabad, Pakistan during the year 2013.
[5]Tanta collection: property of Timothy Walsh. Funded by Egyptian-UK PhD initiative. Isolates collected from Tanta, Egypt during the years 2014-2015.
[6]Dhaka collection: property of Timothy Walsh. Funded by UK-Commonwealth Scholarship scheme. Isolates collected from DMCH, Dhaka and surroundings during the years 2017-2018.
[7]Bergamo collection: kindly provided by Dr. Eduardo Carretto. Isolates collected from Reggio Emilia, Bergamo during the year 2019.
[8]Warsaw collection: kindly provided by Dr. Marek Gniadkowsi. Isolates collected from 2018-2019 in Warsaw and surroundings.
[9]Peshawar collection: property of Timothy Walsh. Funded by GCRF. Isolates collected from Khyber Teaching Hospital, Peshawar during the year 2016.
[10]Other: isolates property of Timothy Walsh, collected from Islamabad, London and Spain during the years 2010-2015.

Supplementary Table 26. C) Exemplary sequencing data. Characterized β-lactamases present in the strain collection used for the clinical microbiology screening.

Strain	Species	Genotype
F019	*Enterobacter hormaechei*	NDM-7
F015	*Enterobacter hormaechei*	NDM-7
F579	*Enterobacter hormaechei*	VIM-4, CTX-M-3, OXA-10, ACT-15
F584	*Enterobacter hormaechei*	VIM-40, CTX-M-3, ACT-7
F586	*Enterobacter hormaechei*	VIM-20, CTX-M-3, ACT-7
F588	*Enterobacter hormaechei*	VIM-4, SHV-5, OXA-10, ACT-15
F587	*Enterobacter hormaechei*	VIM-2, CTX-M-3, SHV-5, ACT-7
F036	*Enterobacter cloacae* cplx	NDM-1
F040	*Enterobacter cloacae* cplx	NDM-1
F531	*Enterobacter cloacae* cplx	NDM-1, CTX-M-15, OXA-1, ACT-9
F543	*Enterobacter cloacae* cplx	NDM-5, CTX-M-15
F625	*Enterobacter cloacae* cplx	NDM-1, CTX-M-15, OXA-1
F011	*Escherichia coli*	NDM-5
F033	*Escherichia coli*	NDM-5
F174	*Escherichia coli*	NDM-5
F623	*Escherichia coli*	NDM-1, TEM-1, OXA-1
F583	*Escherichia coli*	NDM-5, CTX-M-15, OXA-1
F581	*Escherichia coli*	NDM-1, CTX-M-15, TEM-1, OXA-1
F007	*Klebsiella pneumoniae*	NDM-1
F021	*Klebsiella pneumoniae*	NDM-1
F022	*Klebsiella pneumoniae*	NDM-1
F061	*Klebsiella pneumoniae*	NDM-1
F639	*Klebsiella pneumoniae*	NDM-1
F003	*Klebsiella pneumoniae*	NDM-1
F012	*Klebsiella pneumoniae*	NDM-1
F057	*Klebsiella pneumoniae*	NDM-16
F626	*Klebsiella pneumoniae*	VIM-20, CTX-M-3, TEM-1, SHV-145
F619	*Klebsiella pneumoniae*	VIM-12, SHV-2, CMY-31
F585	*Klebsiella pneumoniae*	NDM-1, TEM-1, OXA-1, SHV-182
F628	*Klebsiella pneumoniae*	NDM-1, CTX-M-15, TEM-1, OXA-1, SHV-182
F580	*Citrobacter freundii* cplx	VIM-1, SHV-12, TEM-1, SCO-1, CMY-102
F600	*Escherichia coli*	VIM-1

Supplementary Table 26. D) Exemplary Resistomes of the bacterial isolates used in the study. Resistance genes were identified by search of genomic sequences using ResFinder 3.1[3].

Species	Oxford No.	NMI No.	Antimicrobial classes										
			β-lactams	aminoglycosides	fluoroquinolones	phenicols	sulphonamides	trimethoprim	tetracyclines	fosfomycin	rifampin	colistin	macrolides
E. horm.	F579	4969/09	*bla*$_{VIM-4}$, *bla*$_{CTX-M-3}$, *bla*$_{ACT-15}$, *bla*$_{OXA-10}$	*aadA2, ant(2'')-Ia, ant(3'')-Ia*	-	*catA2, catB3, cmlA1*	*sul1*	*dfrA19*	-	*fosA*	-	*mcr-9*	-
E. horm.	F584	8770/11	*bla*$_{VIM-40}$, *bla*$_{CTX-M-3}$, *bla*$_{ACT-7}$	*aph(3')-VI, aph(3'')-Ib, aph(6)-Id*	*oqxAB*	-	*sul1*	-	-	*fosA*	-	-	-
E. horm.	F586	195/11	*bla*$_{VIM-20}$, *bla*$_{CTX-M-3}$, *bla*$_{ACT-7}$	*aac(3)-IId, aadA2, aph(3')-Ia, armA*	*oqxAB*	-	*sul1*	*dfrA12*	-	*fosA*	-	-	*mph(A), mph(E), msr(E)*
E. horm.	F588	4083/09	*bla*$_{VIM-4}$, *bla*$_{SHV-5}$, *bla*$_{ACT-15}$, *bla*$_{OXA-10}$	*ant(2'')-Ia*	-	*catA2, catB3*	*sul2*	-	*tet(A)*	*fosA*	-	*mcr-9*	-
E. horm.	F587	4884/09	*bla*$_{VIM-2}$, *bla*$_{CTX-M-3}$, *bla*$_{SHV-5}$, *bla*$_{ACT-7}$	*aadA2, armA*	*oqxAB*	-	*sul1*	*dfrA12*	*tet(A)*	*fosA*	-	-	*mph(E), msr(E)*
E. cl. cplx	F531	4118/15	*bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{ACT-9}$, *bla*$_{OXA-1}$	*aac(6')-Ib3, aac(6')-IIc, aadA2, aph(3'')-Ib, aph(6)-Id, rmtC*	*qnrA1, qnrB19*	*catA2*	*sul1, sul2*	*dfrA12*	*tet(A)*	*fosA*	-	*mcr-9*	*mph(A)*
E. coli	F623	3640/16	*bla*$_{NDM-1}$, *bla*$_{TEM-1}$, *bla*$_{OXA-1}$	*aac(6')-Ib*	-	-	-	*dfrA14*	*tet(A)*	-	-	-	*mdf(A)*
E. coli	F583	4785/15	*bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{OXA-1}$	*aac(6')-Ib-cr, aac(3)-IIa, aadA5, rmtB*	*aac(6')-Ib-cr*	*catA1*	*sul1*	*dfrA1, dfrA17*	*tet(A)*	-	-	-	*mph(A), mdf(A)*
E. coli	F581	5428/11	*bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{TEM-1}$, *bla*$_{OXA-1}$	*aac(6')-Ib-cr, aac(3)-IIa, aadA2,* aph(3')-Ia, *aph(3'')-Ib, aph(6)-Id, rmtB*	*aac(6')-Ib-cr*	*catA1*	*sul1, sul2*	*dfrA12, dfrA14*	*tet(B)*	-	-	-	*mph(A), mdf(A)*
K. pneum.	F626	5466/12	*bla*$_{VIM-20}$, *bla*$_{CTX-M-3}$, *bla*$_{SHV-145}$, *bla*$_{TEM-1}$	*aac(3)-IId, armA*	*oqxAB*	-	*sul1*	-	-	*fosA5*	-	-	*mph(E), msr(E)*
K. pneum.	F619	6193/11	*bla*$_{VIM-12}$, *bla*$_{SHV-2}$, *bla*$_{CMY-31}$	*aac(6')-II, ant(3'')-Ia*	*qnrB1, oqxAB*		*sul1*	*dfrA1*	*tet(A)*	*fosA*	-	-	-
K. pneum.	F585	3243/13	*bla*$_{NDM-1}$, *bla*$_{SHV-182}$, *bla*$_{TEM-1}$, *bla*$_{OXA-1}$	*aac(6')-Ib-cr, aac(6')-Ib, aph(3'')-Ib, aph(6)-Id*	*aac(6')-Ib-cr, oqxAB*	-	*sul2*	*dfrA14*	*tet(A)*	*fosA*	-	-	*mph(A)*
K. pneum.	F628	6713/12	*bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *bla*$_{SHV-182}$, *bla*$_{TEM-1}$, *bla*$_{OXA-1}$	*aac(6')-Ib-cr, aac(6')-Ib, aph(3'')-Ib, aph(6)-Id*	*aac(6')-Ib-cr, oqxAB*	-	*sul2*	*dfrA14*	*tet(A)*	*fosA*	-	-	*mph(A)*
C. fr. cplx	F580	911/10	*bla*$_{VIM-1}$, *bla*$_{SHV-12}$, *bla*$_{CMY-102}$, *bla*$_{SCO-1}$, *bla*$_{TEM-1}$	*aac(3)-IIa, aph(3')-Ia, aph(3'')-Ib, aph(6)-Id*	*qnrB9*	*catA1, catB3*	*sul1, sul2*	*dfrA1, dfrA5*	*tet(A)*	-	*arr-3*	-	*ere(A)*

Supplementary Table 27. Coverage of clinically relevant bacterial strains for 58 in combination with meropenem, imipenem, or doripenem. Agar dilution checkerboard analysis showing the combined effects of **58** and meropenem, imipenem and doripenem against globally acquired representative MBL-producing Enterobacterales strain collection. EUCAST clinical breakpoints are the following, imipenem resistant > 4 μg/mL and meropenem > 8 μg/mL. CLSI clinical breakpoint for doripenem if > 2 μg/mL is resistant. MEM - meropenem, IMP – imipenem and DOR – doripenem. Values obtained from a single replicate performed throughout different days. See 'raw_MICvalues.xlsx' for full data.

		MEM	MEM+58	IMI	IMI+58	DOR	DOR+58
Escherichia coli **(n=95)**	MIC_{50}	64	1	32	0.5	32	0.25
	MIC_{90}	>64	2	64	1	64	0.5
Enterobacter spp. **(n=71)**	MIC_{50}	32	0.5	16	0.5	32	0.25
	MIC_{90}	>64	2	32	2	64	2
Klebsiella **spp. (n=50)**	MIC_{50}	16	0.25	8	0.25	8	0.25
	MIC_{90}	64	4	32	2	64	4
Citrobacter **spp. (n=27)**	MIC_{50}	16	0.25	8	0.5	16	0.125
	MIC_{90}	64	0.5	16	0.5	32	0.25
Providencia **spp. (n=19)**	MIC_{50}	4	0.25	8	4	4	0.25
	MIC_{90}	32	2	64	4	32	1
Serratia marcescens **(n=12)**	MIC_{50}	16	0.5	64	2	32	1
	MIC_{90}	16	0.5	64	2	32	1
Proteus mirabilis **(n=6)**	MIC_{50}	1	0.125	16	4	1	0.25
	MIC_{90}	4	0.125	32	4	4	0.5
Total (n=280)	MIC_{50}	32	0.5	16	0.5	16	0.25
	MIC_{90}	64	2	64	2	64	1

Supplementary Table 28 – Comparison of the effects of taniborbactam (VNRX-5133)[4] compared to 58 on Cefepime/meropenem MICs for selected NDM MBL-expressing *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KP) strains.

Strain	Species	Genotype	CEF/MEM MIC (μg/mL)	CEF/MEM +VNRX-5133 MIC (μg/mL)[5]	MEM+ 58 MIC (μg/mL)
S117	EC	NDM	>64	16/1	0.25
IR57	EC	NDM	>64	8/0.5	0.5
B64	KP	NDM	>64	0.25/0.25	0.25
B68-1	KP	NDM	>64	0.5/0.5	0.25
IR43	KP	NDM	>64	0.5/0.25	0.25
91N	EC	NDM	>64	4/0.125	0.125

Supplementary Table 29. Measured frequency of resistance. Three MDR/XDR strains were used to assess the frequency of resistance (FoR) for **58**. *E. coli* ATCC 25922 containing NDM-7 (*bla*$_{\text{NDM-7}}$), *E. coli* IR57 (*bla*$_{\text{NDM-1}}$, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{TEM-198}}$, *bla*$_{\text{AmpC}}$, *bla*$_{\text{OXA-1}}$, and *bla*$_{\text{FonA-2}}$) and *K. pneumoniae* B68-1 (*bla*$_{\text{NDM-1}}$, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{TEM-168}}$, *bla*$_{\text{CMY-6}}$, *bla*$_{\text{SHV-33}}$, *bla*$_{\text{AmpC}}$ and *bla*$_{\text{OXA-9}}$). The frequency of spontaneous mutational resistance to the combinations of meropenem or imipenem with **58** was low (< 10^{-7}, the limit of detection at 4x MIC) likely against the same three strains used for the *in vivo* studies. The limit of detection is due to a strong "inoculum effect" of MBL strains, which (at inocula equal or higher than 10^{-7}) release β-lactamases into the medium so decreasing the concentration of the carbapenem. To overcome this limitation we used a hypermutable (100x mutation rate) *E. coli GB20 (ΔampC mutS::Tn10)* strain[6], engineered by inserting the clinically derived IncX3 plasmid[7] which encodes for the NDM-5 gene; the subsequently observed frequency of carbapenems-inhibitor resistance (at 4x the MIC) was < 10^{-10}. Note that the aim was to detect mutations in MBL genes resulting in inhibitor resistance. Note that only in the GB20 strain were these mutants not detected (frequency of mutation < 10^{-10}) and the MBL sequence was intact in all strains that were recovered after exposure to high carbapenem concentrations in combination with **58.**

		EC ATCC NDM-7	EC IR57	KP B68-1	EC GB20 NDM-5
FoR	MEM	BLD*	~1.1×10^{-5}	BLD*	BLD*
	MEM+**58**	BLD*	~8.9×10^{-6}	BLD*	BLD*
	IMI	~5×10^{-5}	~1.1×10^{-6}	~1.2×10^{-5}	2×10^{-9}
	IMI+**58**	BLD*	4×10^{-7}	BLD*	BLD*

*BLD: below the level of detection. This level is 10^{-7} in the first three columns. For EC GB20, the BLD is 10^{-8} for the carbapenems only and ~10^{-10} for the carbapenem+**58** combinations. limit of detection. MEM-meropenem, IMI-imipenem.

Supplementary Table 30 *In vitro* off target selectivity screening for 58 conducted at Cerep Panlabs (Eurofins). ham= hamster; hum= human.

Cat #	Assay Name	Species	% Inhibition
200510	Adenosine A_1	hum	15
200610	Adenosine A_{2A}	hum	9
200720	Adenosine A_3	hum	14
203110	Adrenergic α_{1A}	hum	-14
203210	Adrenergic α_{1B}	hum	0
203400	Adrenergic α_{1D}	hum	8
203630	Adrenergic α_{2A}	hum	-3
204010	Adrenergic β_1	hum	5
204110	Adrenergic β_2	hum	2
206000	Androgen (Testosterone)	hum	2
212520	Bradykinin B_1	hum	13
212620	Bradykinin B_2	hum	2
214510	Calcium Channel L-Type, Benzothiazepine	rat	-2
214600	Calcium Channel L-Type, Dihydropyridine	rat	-2
216000	Calcium Channel N-Type	rat	5
217050	Cannabinoid CB_1	hum	3
219500	Dopamine D_1	hum	-2
219700	Dopamine D_{2S}	hum	6
219800	Dopamine D_3	hum	11
220000	Dopamine $D_{4.4}$	hum	0
224010	Endothelin ET_A	hum	-19
224110	Endothelin ET_B	hum	-2
225510	Epidermal Growth Factor (EGF)	hum	-16
226010	Estrogen ERα	hum	-4
226600	$GABA_A$, Flunitrazepam, Central	rat	15
226500	$GABA_A$, Muscimol, Central	rat	38
228610	$GABA_{B1A}$	hum	10
232030	Glucocorticoid	hum	28
232710	Glutamate, Kainate	rat	-1
232810	Glutamate, NMDA, Agonism	rat	-1
232910	Glutamate, NMDA, Glycine	rat	-6
233000	Glutamate, NMDA, Phencyclidine	rat	-4
239610	Histamine H_1	hum	3

239710	Histamine H_2	hum	2
239820	Histamine H_3	hum	-6
241000	Imidazoline I_2, Central	rat	11
243530	Interleukin IL-1 R1	hum	7
250460	Leukotriene, Cysteinyl $CysLT_1$	hum	10
251600	Melatonin MT1	hum	3
252610	Muscarinic M_1	hum	3
252710	Muscarinic M_2	hum	11
252810	Muscarinic M_3	hum	-5
257010	Neuropeptide Y Y_1	hum	7
257110	Neuropeptide Y Y_2	hum	4
258700	Nicotinic Acetylcholine α1, Bungarotoxin	hum	1
258730	Nicotinic Acetylcholine α3β4	hum	47
260130	Opiate δ_1 (OP1, DOP)	hum	17
260210	Opiate κ (OP2, KOP)	hum	0
260410	Opiate μ (OP3, MOP)	hum	-9
264500	Phorbol Ester	mouse	6
299037	Platelet Activating Factor (PAF)	hum	-22
265600	Potassium Channel [K_{ATP}]	ham	-11
265900	Potassium Channel hERG	hum	10
268420	Prostanoid EP_4	hum	76
299036	Purinergic P2X	rat	4
268820	Purinergic P2Y, Non-Selective	rat	18
270000	Rolipram	rat	5
271110	Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	hum	2
271700	Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	hum	0
271910	Serotonin (5-Hydroxytryptamine) 5-HT_3	hum	-2
299034	Sigma σ_1	hum	8
279510	Sodium Channel, Site 2	rat	11
255520	Tachykinin NK_1	hum	18
285900	Thyroid Hormone	rat	9
220320	Transporter, Dopamine (DAT)	hum	17
226400	Transporter, GABA	rat	-4
204410	Transporter, Norepinephrine (NET)	hum	19
274030	Transporter, Serotonin (5- Hydroxytryptamine) (SERT)	hum	20

n=2; **58** maximum concentration tested= 100 μM

Supplementary Table 31 – 58 tested for tolerability in mouse at multiple 7 day toxicology studies at 300 mg/kg SC dose. No major adverse effects were observed. For assay details see Experimental Section.

During the 7-day administration at 300 mg/kg daily dose a mild sedative effect (score 1) and slightly prolonged immobility periods (score 2) up to 2h were observed after administration. The body mass increase was similar for both the **58** treated and the vehicle-treated groups. After the sacrification of animals at day 7, no macroscopic changes in organs or at the site of administration were observed. To evaluate kidney and liver toxicity, concentrations of BUN, KIM-1, ALAT and ASAT were measured in plasma samples. Neither concentrations of BUN in plasma and KIM-1 in urine were increased in the treatment group suggesting that kidneys were not affected by **58**. Similarly, low levels of plasma ALAT and ASAT suggest that **58** does not induce liver damage.

Mouse	Score							
	0-2 min	5 min	15 min	30 min	60 min	120 min	240 min	24 h
1	0	0	1	2*	2	1	0	0
2	0	0	1	2*	1	1	0	0
3	0	0	1	2*	1	0	0	0

3 Supplementary Methods – Experimental Section

Materials and methods

General

Antibiotics (meropenem, imipenem, doripenem) were from Biosynth Carbosynth. Other materials were from commercial suppliers (Acros, Alfa Aesar, Glentham Life Sciences, Thermo Fisher Scientific and Sigma-Aldrich) or otherwise as stated.

Enzyme production and assays

Recombinant MBLs and SBLs were produced in *E. coli* and purified using reported procedures[8, 9, 10]; all purified enzymes were >95% pure (as judged by SDS-PAGE and MS analyses).

Inhibition activities of inhibitors were tested using a panel of recombinant enzymes covering all four Ambler classes of β-lactamase (A, B, C and D), including representatives from all three subclasses of MBL (i.e. enzymes from classes B1, B2 and B3). Activities were assayed by monitoring the release of a fluorophore following the enzymatic breakdown of the cephalosporin FC-5[8], with the exception of the class B2 MBLs, where the hydrolysis of meropenem was used as a readout. FC-5 assays were conducted in clear bottomed 384 black well microplates (Greiner) and the initial rate of reaction was assessed by monitoring the fluorescence intensity (λex = 380 nm and λem = 460 nm) using a Pherastar FS (BMG LabTech) plate reader. For the B2 MBLs, assays were carried out in 96 well UV star microplates (Greiner) and UV absorbance at λ = 600 nm monitored. Initial rates of reaction were determined and dose-response analyses conducted in GraphPad Prism.

Dose-response curves were fitted using the log(inhibitor) vs normalized response - variable slope model of GraphPad Prism 12. Each concentration point for routine screening was conducted with 4 intra-plate replicates. Reported errors for pIC_{50} values are ±0.2 log fold. Any values reported as below a specified value exhibited less than 50% inhibition at the maximum tested concentration.

SPR binding assays were carried out as reported[10].

X-ray Crystallography

VIM-2 and L1 were crystallized following reported procedures[11, 12]. NDM-7 and VIM-1 were crystallized using the sitting drop vapour diffusion method. A co-crystal structure of NDM-7:**48** (PDB 7AEZ) was solved using a crystal obtained from a well solution consisting of 0.1M Bis Tris pH = 5.5 and 25% PEG 3350. A co-crystal structure of VIM-1:**49** (PDB 7AEY) was obtained using a crystal from a well solution consisting of 2.2M ammonium phosphate and 0.1M TRIS-HCl, pH 8.5. L1 crystals were soaked for 2 hours in 5 mM **49** dissolved in the crystallisation buffer, then cryoprotected by the addition of 20%(v/v) glycerol. Data were collected at 100 K at the Diamond Light Source synchrotron IO3 (NDM-7:**48**, VIM-1:**49**), IO4 (VIM-2:**11**) and IO4-1 (L1:**49**) beamlines. Data were indexed and integrated with XDS (NDM-7, VIM-1 and VIM-2) or Mosflm(L1), and scaled using SHELX(NDM-7, VIM-1 and VIM-2) or Mosflm(L1) or Aimless (L1). Phaser was used to solve structures by molecular replacement, using the following PDB entries 5N5I for VIM1, 4TZF for NDM-7, 4BZ3 for VIM-2 and 5EVD for L-1, respectively as a search model. Fitting and refinement were carried out using COOT and PHENIX until R_{work} and R_{free} no longer converged. Inhibitor restraints were calculated using eLBOW in Phenix. The final statistics for data collection and refinement are given in Supplementary Tables 20-21.

Protein thermal shifts assays

Thermal shift measurements were performed as reported[13]. In brief, SYPRO orange dye (4x), NDM-1 (4 µM) were incubated with and without **58** (8 µM) in 10 mM Tris pH 8 buffer for 15 min at room temperature. All experiments were performed as a minimum in triplicate. Samples were heated from 4 to 99 °C in a Bio-Rad CFX96 real-time PCR machine with fluorescence measurements (Excitation 490 nm/Emission 580 nm) taken every 0.5 °C. Thermal denaturation raw data were extracted using CFX Manager software, normalized and fitted to a Boltzmann sigmoidal using CFXGraphPad Prism 9.0 software to obtain thermal shift values.

Proteolytic degradation assays

NDM-1 (3 µM) was incubated with and without **58** (10 µM) in 10 mM Tris pH 8, 5 mM $CaCl_2$ buffer, for 15 min at room temperature. Subsequently Proteinase K (1 µM) was added, and the reactions were incubated at 37 °C. After the indicated times aliquots of the reaction were quenched by addition of 10 mM phenylmethylsulfonyl fluoride (PMSF).

Mass spectra were acquired in positive mode using a 1290 Infinity II LC System (Agilent Technologies) equipped with a ProSwift RP-4H 1X50MM column (Thermo Fisher Scientific) and coupled to an Agilent 6550 accurate mass QTOF mass spectrometer. 2 µL of the samples were injected on the column and eluted in a gradient of 5-97% (v/v) acetonitrile : water, 0.1% formic acid, over 10 min. NDM-1 and Proteinase K co-eluted after approx. 5 min. Data was analysed using MassHunter Workstation Qualitative Analysis V.7 program (Agilent Technologies) and spectra were deconvoluted using the maximum entropy algorithm. NDM-1 signals were normalized to the Proteinase K signals.

Microbiology

All antibiotic susceptibility testing was performed using the agar or broth dilution method, in line with the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) requirements. The results were compared with the EUCAST Antibiotic Susceptibility breakpoints (www.eucast.org/clinical_breakpoints/). ATCC 25922 (*Escherichia coli*), ATCC 13883 (*Klebsiella pneumoniae*), ATCC 700603 (*Klebsiella pneumoniae*) were used for EUCAST-related and in-house quality control in all experiments. The minimum inhibitory concentration values obtained using the agar dilution method were analysed with Microsoft Excel 2016 and and further analysed and represented with R version 3.6.1 and Rstudio 1.2.1335 using the package ggplot2 version 3.3.2.

The frequency of resistance was tested by seeding 10^7 cells of MBL-containing strains on Müller-Hinton Agar Plates containing a carbapenems at a concentration 2-8 fold the original MIC. Note, that, at a higher inocula there is an inoculum effect (broken cells release MBLs reducing the amount of carbapenem on the plates). To overcome this problem, we used an engineered hypermutable strain (E. coli GB20), providing 100-1000x more mutants than the wild strain, so that 10^7 cells of this strain should correspond to 10^9-10^{10} cells of a wild strain. MICs of colonies growing on plates with carbapenems (with or without MBL inhibitors) were determined, and these colonies were re-isolated in drug-free medium and MICs was retested to assess the stability of the phenotypes. The MBL genes of these colonies were sequenced to investigate the presence of changes in the nucleotide sequence that might explain carbapenem or carbapenem plus inhibitor resistance.

Serial passages were performed for *K. pneumoniae* B68-1 and *E. coli* IR57, according to described methodology.[14] Briefly, cultures were prepared an initial concentration of $5 \cdot 10^5$ CFU/mL in 200 µL of cation-adjusted Müller Hinton broth containing different concentrations of meropenem (MEM) or imipenem (IMI) or meropenem+**58** or imipenem+**58** using a fixed **58** concentration of 8 µg/mL. On each following day and for each replicate, 1 µL of the culture showing growth at the maximum non-inhibitory concentration (MNIC) was inoculated into new broth preparations, yielding at initial bacterial concentration of $\approx 10^7$ CFU/mL.

ADME

pKa measurements were performed using a Sirius T3 automated instrument (Sirius Analytical Ltd.) equipped with a dip probe absorption spectroscopy (D-PAS) lamp for spectrophotometric titrations and pH-electrode for potentiometric titrations. The spectrophotometric titrations were normally performed using a 2–5 µL 10 mM DMSO stock solution of which is added to 25 µL of phosphate buffer. During titration, the instrument adds a predetermined volume of ionic-strength-adjusted (ISA) water, or a combination of ISA and ISA containing 80% methanol in the potentiometric titrations. Titrations from high to low or low to high were performed between pH 2-12. During the titration, the instrument collects a UV–vis spectrum by using the D-PAS technique to establish a titration curve. In the potentiometric method the instrument instead bases the titration on the amount of acid (HCl) and base (KOH) that is added. The electrode was calibrated using a blank titration from pH 1.8 to pH 12.0 before every individual determination. Measurements were performed under argon to minimize the effect of dissolved CO_2. Precipitation was continuously monitored at 500 nm. The temperature was controlled throughout the experiment at 25 ± 1°C.

To investigate chemical stability, the following buffers were used: 10 mM H_3PO_4/$KHPO_4$, pH 2, 10 mM KPO_4 buffer, pH 7.4 and 10 mM glycine/NaOH, pH 10. The test compound was pipetted into 6 HPLC vials and 1000 µl buffer - with or without isopropanol resulting in a final compound concentration of 2 µM. The stability samples were incubated at 37°C in a heater-shaker and at time-points 0h (i.e ~30sec), 0.5h, 1h, 2.5h, 4h and 24h. At the indicated time-points, a 100 µl sample was taken from each tube and transferred to a 96-well plate containing 100 µl MeCN. The plate was sealed and and the samples were analysed by LC-MS/MS (Waters Corp).

The investigate kinetic solubility a final compound concentration of 100 µM and 1% (v/v) DMSO were used. DMSO stocks of the compounds were added to 100 mM potassium phosphate buffer and incubated at 37°C for 24 hours in a heater-shaker. After incubation, the samples were centrifuged (3000 x g, 37°C, 30 min) to pellet insoluble material and an aliquot of the supernatant was taken for analysis. After dilution of the sample, the concentration of dissolved compound was quantified by liquid chromatography coupled to triple quadrupole mass spectrometry (LC-MS/MS, Waters Corp).

Metabolic stability assays were performed in cryopreserved human and mouse hepatocytes. The hepatocytes were thawed and added to "Thawing media", and centrifuged to pellet the hepatocytes. The cell pellet was taken up in Williams medium E (Invitrogen A1217601), the number of cells was calculated and adjusted to 1.0×10^6 cells/ml. The incubation was carried out on a heater-shaker at 37°C, in a 24-well Picoplate (round bottom, PerkinElmer), using an incubation volume of 770 µl. Thus, to obtain a final compound concentration of 1 µM, 0.7 µl of the 1 mM compound stock solution was pipetted to the wells of the plate. Reaction was initiated by adding 700 µl of cell suspension. Samples were incubated at 37°C for ~60 sec and a zero sample was taken, i.e. 100 µl sample was removed to a 96-well plate and the reaction

was quenched by adding 100 µl of 100% MeCN containing 50 nM Warfarin as an internal control. Consecutive samples were taken at time-points 5 min, 15 min, 30 min, 60 min, and 90 min. After finishing the experiment, samples were centrifuged at 3000 rpm for 15 min and before analysis by LC-MS/MS (Waters Corp, Milford, MA, USA).

The fraction of unbound drug (fu) in plasma from human or other animal species was determined by equilibrium dialysis at 37°C for 4 hours using the Rapid Equilibrium Dialysis (RED) device (ThermoFisher Scientific). The test compound (10 µM) was added to plasma and dialyzed against isotonic phosphate buffer (67mM, pH 7.4) over 4 hours at 37°C. After dialysis, compound concentrations in buffer and plasma were quantified by LC-MS/MS. In parallel the stability of the compound in plasma was determined by incubating drug-spiked plasma (10 µM) at 37°C for 4 hours, meanwhile the control plasma sample was kept in the freezer. The concentration of the compound in both samples was quantified by LC-MS/MS (Waters Corp, Milford, MA, USA).

Caco-2 cell monolayers (passage 94-105) were grown on a permeable filter support and used for transport study on day 21 after seeding. Prior to the experiment a solution of 10 µM compound was prepared and warmed to 37°C. The Caco-2 filters were washed with pre-warmed Hanks' Balanced Salt solution (HBSS) prior to the experiment; the experiment was started by applying the donor solution on the apical or basolateral side. Transport experiments were carried out at pH 7.4 in both the apical and basolateral chamber. The experiments were performed at 37°C with a stirring rate of 500 rpm. The receiver compartment was sampled at 15, 30 and 60 minutes. At 60 minutes a sample from the donor chamber was taken in order to calculate the mass balance of the compound. The samples (100 µl) were transferred to a 96-well plate containing 100 µl methanol and Warfarin as IS and was sealed until LC-MS/MS analysis (Waters Corp, Milford, MA, USA).

Cytochrome P450 3A4 (CYP3A4) inhibition assays were performed using pooled human liver microsomes (HLM) at a final concentration of 0.2 mg/ml in 100 mM phosphate buffer pH 7.4. The following marker substrates were used for CYP3A4 activity: midazolam at the final concentration of 5 µM and testosterone at 50 µM. The incubation time was 10 min for midazolam incubations and 30 min for testosterone. The compound was added to a 96-well plate (1 µl) from 100x stocks prepared in DMSO. Control wells contained only DMSO (1% (v/v) final concentration). The incubation concentration was 1, 10 and 100 µM. The final incubation volume was 100 µl. Reactions were started by addition of 25 µl 4 mM NADPH (in buffer) and stopped by addition of 100 µl ice-cold acetonitrile containing Warfarin as IS. After the assay the plate was sealed and centrifuged and analyzed by LC-MS/MS (Waters Corp, Milford, MA, USA).

The LC-MS/MS (Waters Corp, Milford, MA, USA) system consisted of a Waters Acquity UPLC coupled to a Waters XEVO TQ-S micro mass spectrometer (electrospray ionization, ESI). For chromatographic separation a general gradient of 5% to 100% of mobile phase B over a total running time of 2 min on a BEH RP C18 column. Mobile phases consisted of: A: 0.1% (v/v) formic acid in water, B: 0.1% (v/v) formic acid in 100% MeCN. The flow rate was set to 0.5 ml/min and 5 µL of the sample was injected.

***In vivo* efficacy studies**

Ethical considerations

Standards at the Statens Serum Institut for housing and care of animals comply with the latest and most comprehensive international guidelines, such as the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. All animal experiments were approved by the Danish National Committee of Animal Ethics, Ministry of Environment and Food, license 2019-15-0201-00019 (septicemia) or 2016-15-02-01-01049 (thigh infection), as well on-site veterinarians.

Temperature and humidity were recorded daily in the animal facilities. The temperature was 22^{o}C +/- 2 ^{o}C and was regulated by heating and cooling. The humidity was 55 +/- 10%. The air changes per hour were approximately 8-12 times (70-73 times per hours inside racks), and light/dark period was in 12-hours interval of 6 a.m.- 6 p.m./6 p.m. – 6 a.m. The mice had free access to domestic quality drinking water and food (Teklad Global diet 2916C-Envigo) and occasionally peanuts and sunflower seeds (Køge Korn A/S). The mice were housed in Type 3 macrolone cages with bedding from Tapvei. Further, the animals were offered Enviro-Dri nesting material and cardboard houses (Bio-serv).

Thigh model of infection.

Female NMRI mice (5-6 weeks old, 26-30 gram, n = 5) were rendered neutropenic via intraperitoneal injection of two doses of cyclophosphamide on day 4 and day 1 before infection. The animals were infected via intramuscular injection of an inoculum containing 10^6 CFU/mL of bacteria in the left thigh. The animals were treated with a single dose of meropenem subcutaneous +/- **58** (intravenous) 1h after inoculation, and animals were either euthanised at the start of treatment or at the study endpoint at 3 h after treatment initiation. Clinical scores were monitored at 1 and 4 hours post inoculation and were in all cases mild or moderate. Thighs were aseptically removed from the animals, homogenised, diluted, and plated for incubation. Bacterial counting was performed after 18-22h of incubation at 35°C in ambient air.

Septicaemia model of infection.

Immunocompetent female NMRI mice mice (5-6 weeks old, 26-30 gram, n = 5) were inoculated intraperitoneally with 0.5 ml inoculum containing 5 x 10^5 CFU suspended in 5% porcine mucin.

The animals were treated with a single dose of meropenem subcutaneous +/- **58** (intravenous) 1h after inoculation. Animals were either euthanised at the start of treatment or at the study endpoint at 3h after treatment initiation. Clinical scores were monitored at 1 and 4 hours post inoculation and were in all cases mild or moderate. Mice were anesthetized with a buprenorphine/tiletamine/zolazepam cocktail and bled, then euthanized and the peritoneum flushed with 2 ml sterile 0.9% NaCl and collected. The blood and/or peritoneal flush were serially diluted and plated for incubation. Bacterial counting was performed after 18-22h of incubation at 35°C in ambient air.

Safety evaluation of 49 and 58 in mice

Experimental procedures were carried out in accordance with the guidelines of the European Community and local laws and policies and were approved by the Latvian Animal Protection Ethical Committee, Food and Veterinary Service, Riga, Latvia. Animals (8-12 weeks old NMRI female mice from ENVIGO) were housed in the animal facilities at LIOS under standard conditions (21-23 °C, 12 h light-dark cycle) with unlimited access to food (R70 diet, Lantmännen Lantbruk, Sweden) and water. NMRI female mice were allowed an acclimatization period of 1 week before treatment. Animals were weighed on the day of treatment (before treatment) to calculate the required volume of working solution of compound

administered. To increase their solubility, **49** and **58** was formulated in a 20% β-cyclodextrin sulfobutyl ether sodium (CDS) water solution (15 mg/ml). In the vehicle group, a 20% CDS solution in water was administrated. **49** was tested after single intravenous administration at doses of 10 and 100 mg/kg. Manifestations of clinical signs post injection were compared to vehicle group. **58** applied at a dose of 300 mg/kg or the vehicle were administrated subcutaneously via a bolus injection (20 ml/kg) once a day for 7 days. Blood and urine samples for clinical chemistry measurements were collected 24 h after the last administration. Blood urea (BUN), kidney injury marker 1 (KIM-1), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) were measured using commercially available kits according to the manufacturer's instructions.

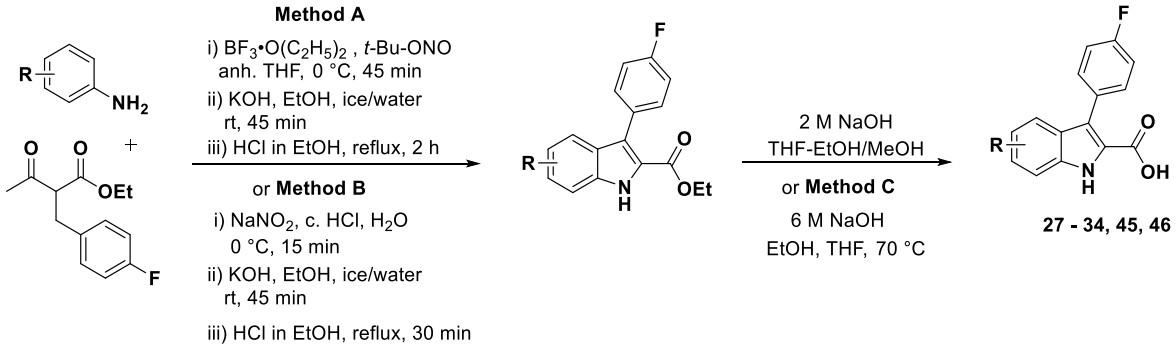
Clinical signs were scored 0-2, 5, 10, 15, 30, 60, 120, 240 min, and 24 h after the administration of the compound or vehicle solution. The following score system was used: Score: 0 – Healthy; 1 – mouse is affected a little (slightly slower/faster movements, little hedgehog fur, short itching (2-3 seconds)); 2 – mouse is affected (sitting still, but moves, when the cage is moved/rapid movements, small jumps, possibly hedgehog fur, hunched back, itching (4-6 seconds)); 3 – mouse is clearly affected (moving only when it is pushed to/very active movements, high jumps, half-closed eyes, hedgehog fur, hunch back, tucked up belly, goes on the toes, prolonged episodes of itching that repeat after short intervals), mouse is sacrificed if score 3 more than 30 min; 4 – mouse is very affected (moves very reluctantly although it is pushed, hedgehog fur, eyes closed, cool), sacrificed immediately to avoid suffering; 5 – mouse is motionless and cold (lying on the side), sacrificed immediately to avoid suffering; 6 – mouse is dead.

4 Supplementary Methods – Synthetic Chemistry

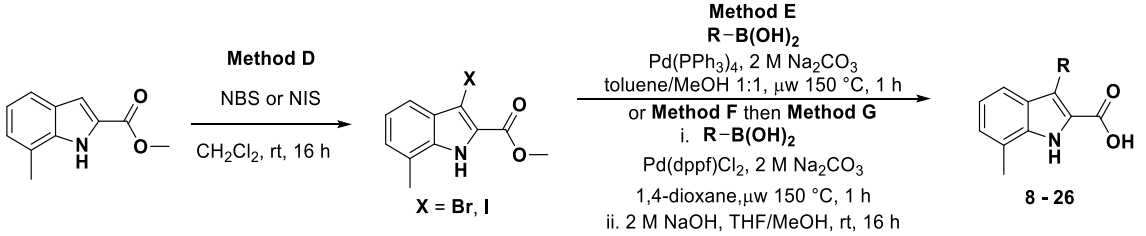
4.1 General Information

Reagents (including 3-phenyl-1*H*-indole-2-carboxylic acid, (**38**)) were from commercial suppliers and used as supplied. Solvents (including dried solvents) for chemical transformations, work-up and chromatography were from Sigma-Aldrich (HPLC grade) or Acros Organics, and were used without further purification. Silica gel 60 F254 analytical thin layer chromatography (TLC) plates were from Merck (Darmstadt, Germany) and visualized under UV light and/or with potassium permanganate stain. Chromatographic purifications were performed using prepacked SNAP columns and a Biotage Isolera Purification system. Deuterated solvents were from Sigma-Aldrich. All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVIII HD 400, AVII 500 or AVIII 600 spectrometers (400, 500 or 600 MHz for ^{1}H NMR and 101, 126 or 151 MHz for ^{13}C NMR). Chemical shifts (δ_H) are in parts per million (ppm) and are referenced to the residual solvent peak, and coupling constants (*J*) are reported in Hertz (Hz) and are reported to the nearest 0.5 Hz. Low resolution mass spectra (*m/z*) were recorded using a Waters LCT Premier spectrometer using electrospray ionisation (ESI). High resolution mass spectra were recorded using a Bruker µTOF (ESI) spectrometer by the internal service at the Department of Chemistry, University of Oxford. The *m/z* values are reported in Daltons. Compound names are as generated by MestReNova v14.1 software following IUPAC nomenclature.

4.2 Schemes for the preparation of indole carboxylic acids



Supplementary Scheme 1



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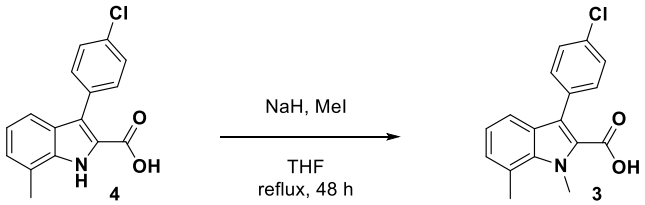

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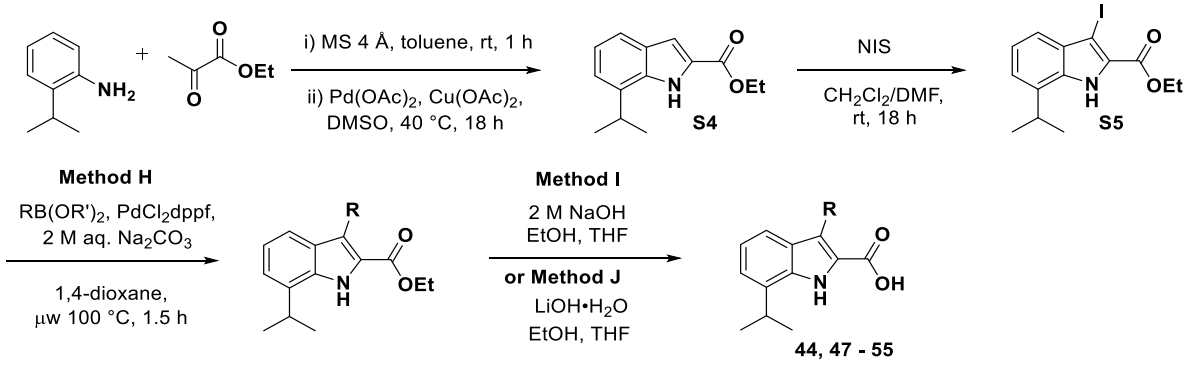

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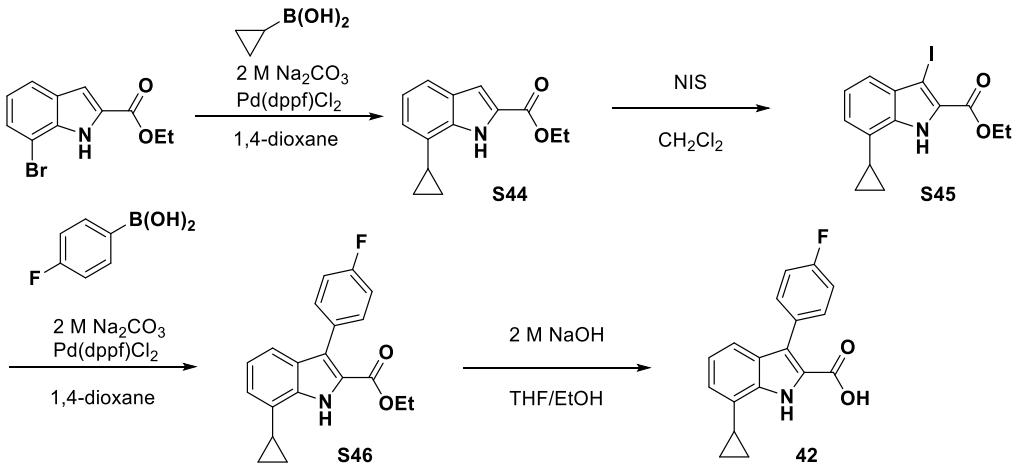

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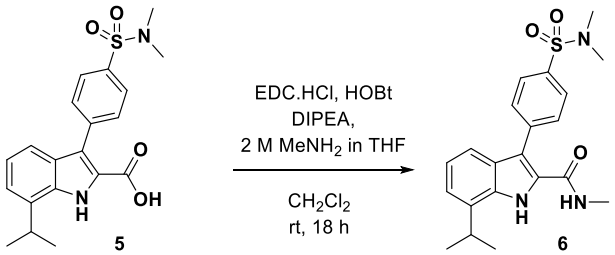
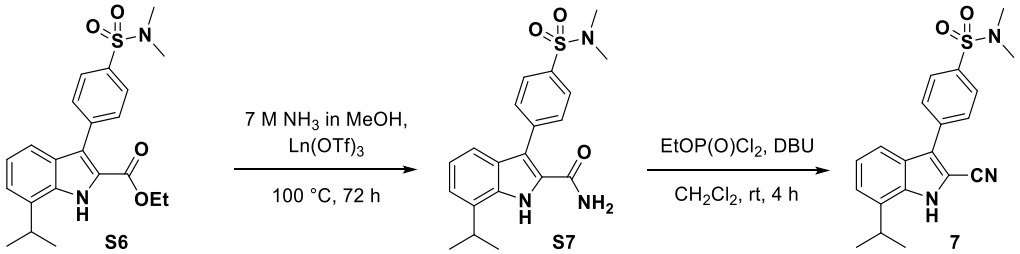
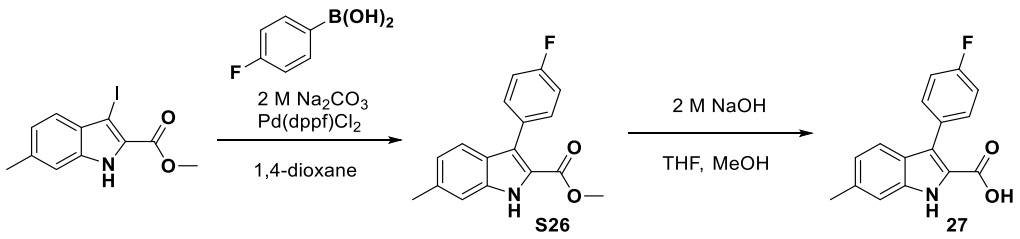


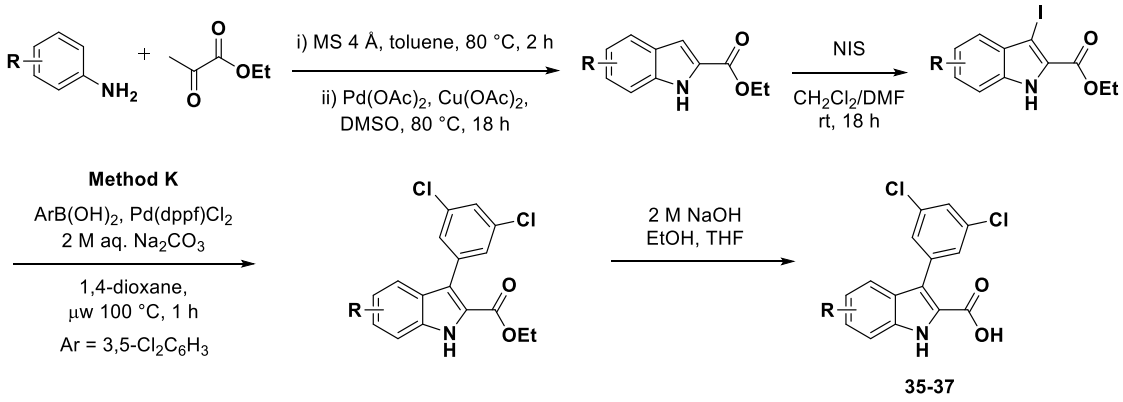
Supplementary Scheme 6



Supplementary Scheme 7



Supplementary Scheme 8



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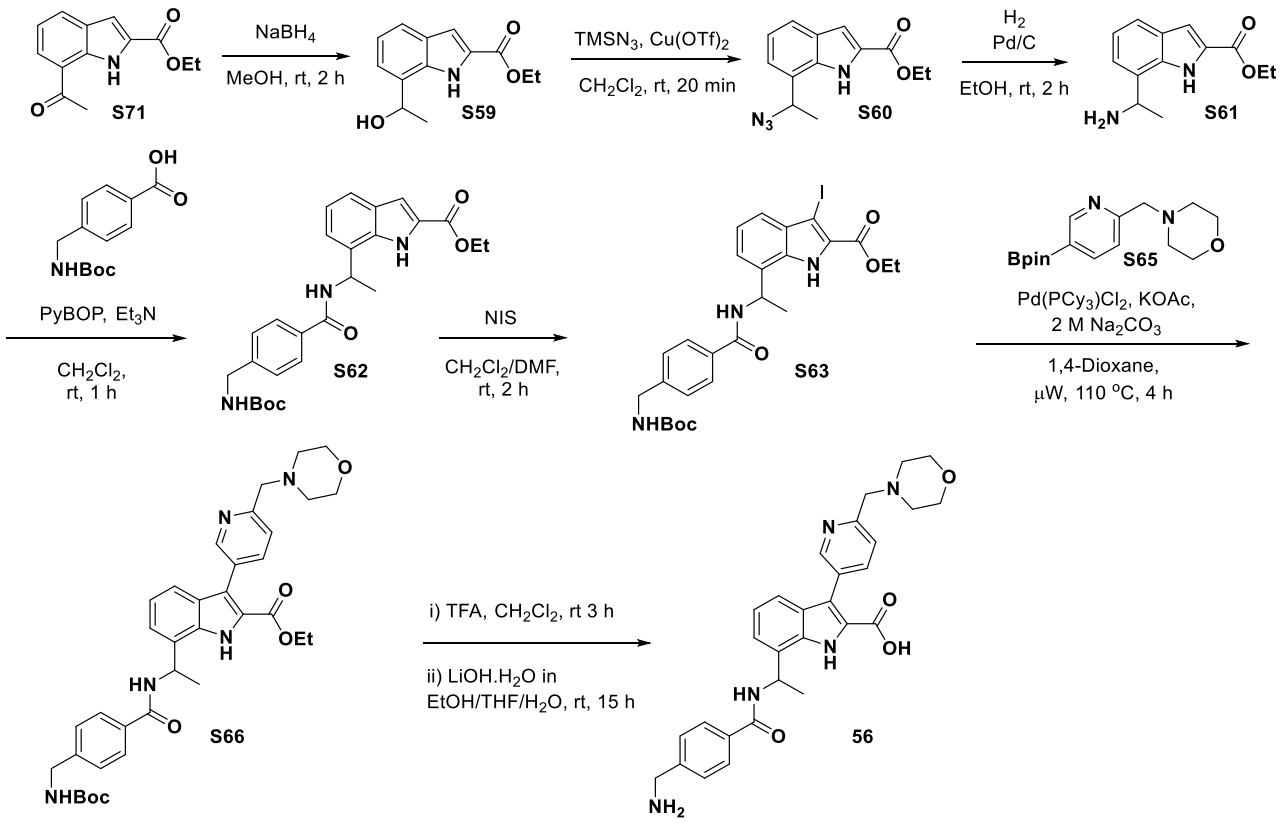
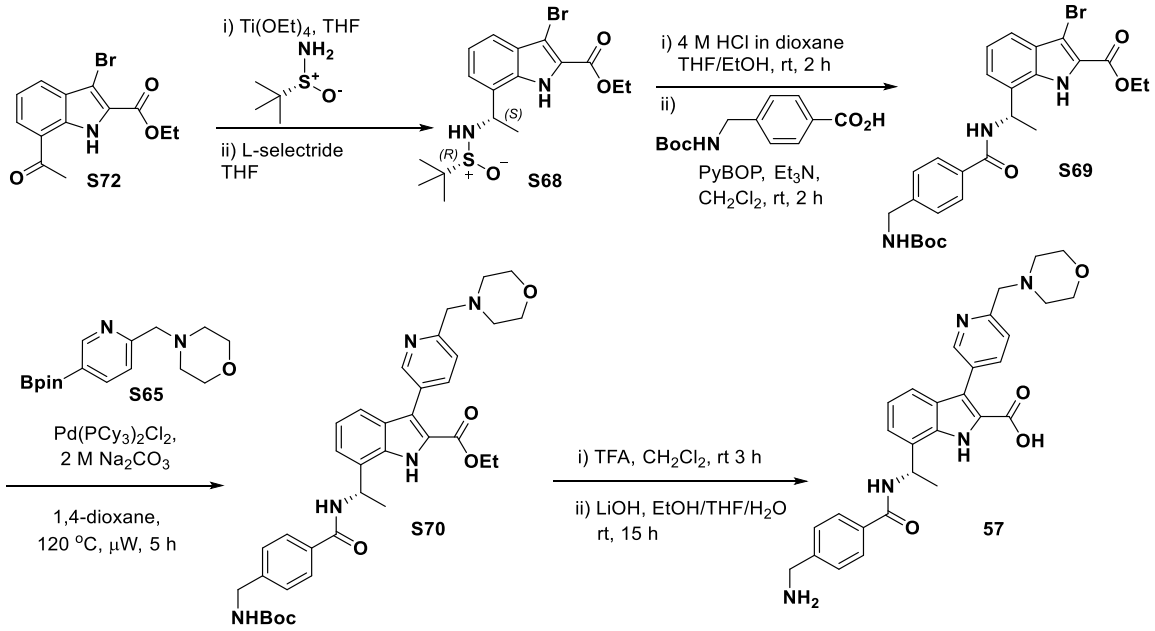
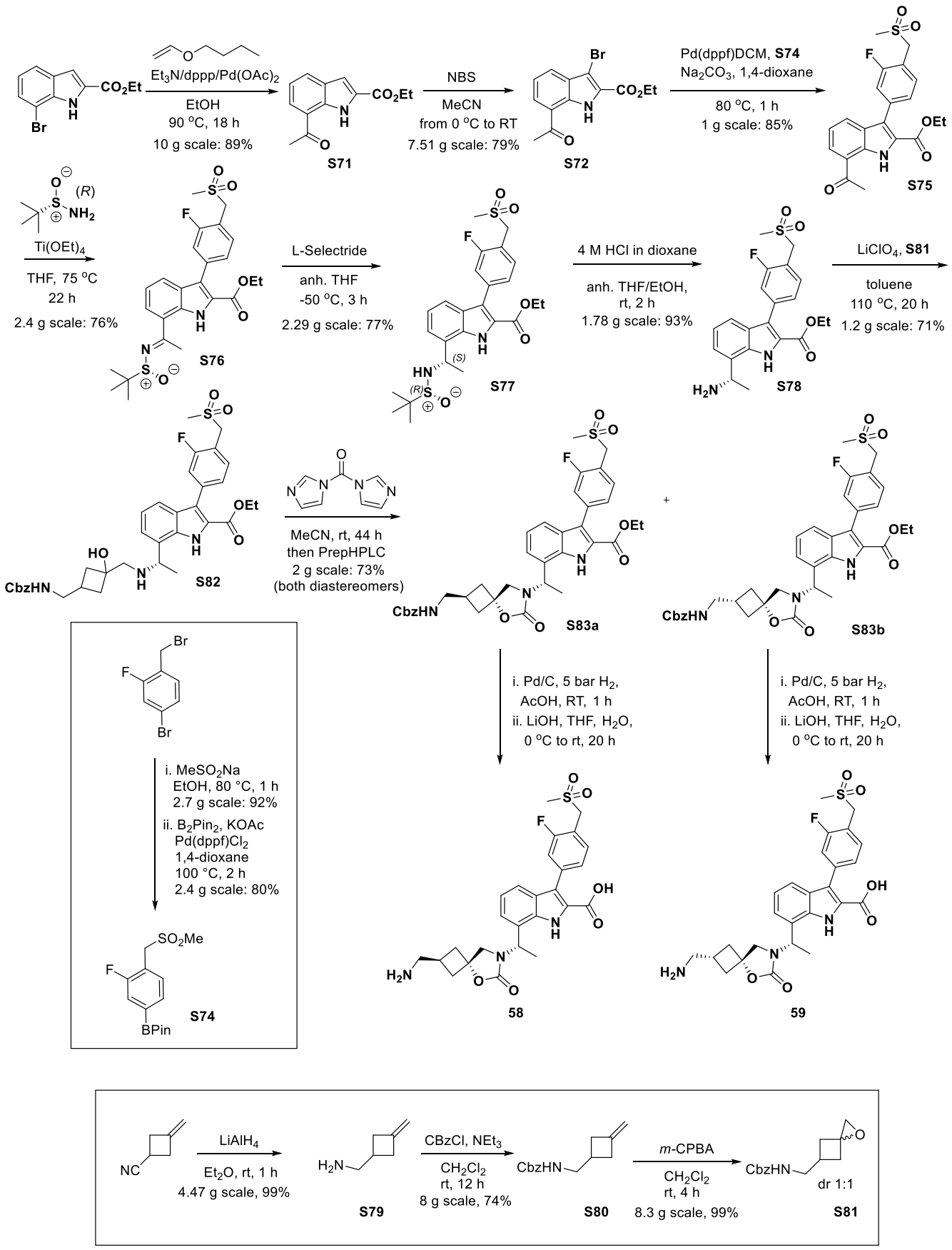


Supplementary Scheme 10



Supplementary Scheme 11



Supplementary Scheme 12

4.3 General Procedures for the preparation of indole carboxylic acids

Method A for indole synthesis using *tert*-butyl nitrite

Ethyl 2-[(4-fluorophenyl)methyl]-3-oxo-butanoate[15] (1.0 eq) was dissolved in EtOH (2.5 mL/mmol) and water (0.5 mL/mmol). Ice (~1g/mmol) and KOH (3.5 eq) were added; the resultant mixture (a yellow solution) was stirred at room temperature for 45 mins, then cooled to 0 °C. Simultaneously, in a separate flask the requisite aniline derivative (1.5 eq) was dissolved in THF anhydrous (1.5 mL/mmol). The solution was placed under argon and cooled to 0 °C, then $BF_3.O(C_2H_5)_2$ (2.2 eq) was added dropwise; stirring was continued at 0 °C for 5 mins. *tert*-Butyl nitrite (1.8 eq) was then added dropwise and the reaction stirred at 0 °C for 40 mins. The resultant thick suspension was slurried with the previously prepared enolate solution and the combined reaction mixture (a brown solution containing a white solid suspension) allowed to warm to room temperature, then stirred for 2 h. The reaction mixture was then concentrated under reduced pressure and partitioned between EtOAc (25 mL/mmol) and water (10 mL/mmol). The mixture was filtered to remove the insoluble white solid and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL/mmol), the organic extracts were then combined, washed with brine, dried over Na_2SO_4, filtered and solvent was evaporated under reduced pressure to afford crude intermediate. A solution of ethanolic HCl was prepared (2:1 EtOH / AcCl, 4 mL/mmol) and the intermediate dissolved in that and heated to reflux for 2 h. The reaction mixture was concentrated, then partitioned between EtOAc (12 mL/mmol) and water (7 mL/mmol). The organic layer was washed with sat. aq. $NaHCO_3$ solution (10 mL/mmol) and the aqueous washes combined and re-extracted with EtOAc (5 mL/mmol). The organic extracts were combined and washed with brine, dried over Na_2SO_4, filtered and solvent was evaporated under reduced pressure to give a crude residue which was purified by FCC to afford the corresponding product.

Method B for indole synthesis with sodium nitrite

To a cooled (0 °C) suspension of the appropriate aniline (1.0 eq) in 12 M aq HCl (0.5 mL/mmol) was added dropwise a solution of $NaNO_2$ (1.1 eq) in water (0.5 mL/mmol). The resultant orange solution was stirred at 0 °C for 15 mins, then added dropwise to a prepared mixture of ethyl 2-[(4-fluorophenyl)methyl]-3-oxo-butanoate[15] (1 mmol, 1.0 eq), KOH (3.5 eq) and ice (approx. 1 g/mmol) in water (0.5 mL/mmol) and ethanol (2.5 mL/mmol). The resultant mixture was stirred at room temperature for 4 h, then partitioned between EtOAc and water. The aqueous phase was further extracted with EtOAc; the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, then concentrated under reduced pressure and the crude material purified by FCC. The product was taken up in a solution of HCl in ethanol (0.87 mL/mmol, prepared by adding 0.23 mL/mmol of acetyl chloride to 1.5 mL/mmol ethanol), and heated to reflux for 30 min to 2 h. The mixture was cooled to room temperature, concentrated under reduced pressure, then partitioned between water and EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure and the crude material was purified by FCC to afford the substituted indole.

Method C for ester hydrolysis at 70 °C

A mixture of requisite 1*H*-indole-2-carboxylate ester (1 eq) and 6 M aq NaOH (0.32 mL/mmol) in 1:1 EtOH-THF was heated at 70 °C until complete consumption of starting material was apparent. The mixture was concentrated under reduced pressure; the resultant residue was partitioned between EtOAc and water. The aqueous phase was further washed with EtOAc then acidified using 1 M aq HCl. The acidic aqueous phase was extracted with EtOAc (x3) and the combined organic extracts washed with brine, dried over Na_2SO_4, filtered, then concentrated

under reduced pressure. The resultant material was taken up and subjected to FCC then dried under vacuum at 50 °C to give the desired compound.

Method D for C3 halogenation of the indole carboxylates

To a solution of the requisite 1*H*-indole-2-carboxylate ester (1 mmol, 1.0 eq) in CH_2Cl_2 (3 mL/mmol) was added *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) (1.05 mmol, 1.05 eq). The resultant mixture was stirred at room temperature overnight, then partitioned between CH_2Cl_2 and sat. aq. $NaHCO_3$ solution. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, then concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, adsorbed onto silica and purified by FCC to give the desired compound.

Method E for Suzuki-Miyaura Cross-Coupling at 150 °C

A suspension of methyl 3-bromo-7-methyl-1*H*-indole-2-carboxylate (**S2**) (1 mmol, 1.0 eq), the appropriate arylboronic acid (1.5 mmol, 1.5 eq), tetrakis(triphenylphosphine)palladium(0) (4.5 mol%) and 2 M aq Na_2CO_3 (2 mL/mmol) in methanol (4.5 mL/mmol) and toluene (4.5 mL/mmol) was subjected to microwave irradiation at 150 °C for 1 h. The mixture was filtered through Celite®, eluting with EtOAc and 1 M aq. HCl. The phases were separated and the aqueous phase further extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resultant material was subjected to FCC to give the desired compound.

Method F for Suzuki-Miyaura cross-coupling at 100 °C

A mixture of methyl 3-iodo-7-methyl-1*H*-indole-2-carboxylate (**S3**) (1 mmol, 1.0 eq), the requisite boronic acid (1.2 mmol, 1.2 eq), 2 M aq Na_2CO_3 (4 mmol, 4.0 eq) and $Pd(dppf)Cl_2$ (4 mol %) in 1,4-dioxane (9 mL/mmol) was purged with argon, then subjected to microwave irradiation at 100 °C for 1 h. The resultant mixture was filtered through Celite®, eluting with EtOAc and water. The filtrate was partitioned between EtOAc and 1 aq M HCl; the resultant aqueous phase was then further extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, then concentrated under reduced pressure. The residue was purified by FCC to give the desired compound.

Method G for ester hydrolysis at rt

To a solution of the requisite ester (1 mmol, 1.0 eq) in THF (6.4 mL/mmol) and methanol (3.2 mL/mmol) was added 2 M aq NaOH (5 mmol, 5.0 eq). The resultant mixture was stirred at room temperature for 16 h. The mixture was quenched with 5 M aq HCl and concentrated to remove organic solvent. The precipitate was collected by filtration, washed with water, then dried to give the desired compound.

Method H and Method I for Suzuki-Miyaura cross-coupling of iodo-indole S5

A mixture of iodo indole **S5** (1 mmol, 1.0 eq), the relevant boronic acid (1.2 mmol, 1.2 eq), 2 M aq Na_2CO_3 (4 mmol, 4.0 eq) and $Pd(dppf)Cl_2$ (4 mol %) in 1,4-dioxane (9 mL/mmol) was purged with argon, then subjected to microwave irradiation at 100 °C for 1.5 h (Method H) or heated under reflux for 4 h (Method I). The resultant mixture was filtered through Celite®, eluting with EtOAc and water. The filtrate was partitioned between EtOAc and 1 aq M HCl and the aqueous phase further extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, then concentrated under reduced pressure. The residue was purified by FCC to give the desired compound.

Method J for ester hydrolysis:
To a solution of the requisite ester (1 mmol, 1.0 eq) in THF (6.7 mL/mmol) and ethanol (3.3 mL/mmol) was added 2 M aq NaOH (8 mmol, 8.0 eq). The resultant mixture was stirred at the stated temperature and time duration. The mixture was quenched with 5 M aq HCl, then concentrated to remove organic solvent. The precipitate was collected by filtration, washed with water and dried under vacuum at 60 °C to give the desired compound.

Method K for transfer hydrogenation of cyclic alkene substituted indole carboxylates
A mixture of the unsaturated-1*H*-indole-2-carboxylate (1.0 eq) and ammonium formate (13 eq) in methanol (25 mL/mmol) was purged with argon then Pd/C (10%, 0.1 eq) was added and the mixture heated to reflux for 18 h. The resultant mixture was filtered through Celite® and eluted with further methanol. The filtrate was concentrated under reduced pressure and the residue partitioned between EtOAc and water. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Method L for *N*-Boc deprotection
To a solution of the *N*-Boc protected cyclic amine in CH_2Cl_2 (7.1 mL/mmol) was added trifluoroacetic acid (2.9 mL/mmol) and stirring was maintained at room temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in MeOH and loaded onto a SCX cartridge, then flushed with methanol and eluted with 2 M NH_3 in MeOH; and the volatiles removed *in vacuo* to afford the desired compound.

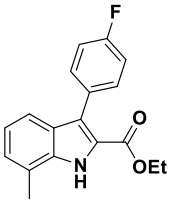
Method M for ester hydrolysis with lithium hydroxide
To a solution of the requisite ester (1 mmol, 1.0 eq) in THF (6.7 mL/mmol), ethanol (3.3 mL/mmol) and water (3.3 mL/mmol) was added $LiOH•H_2O$ (5 mmol, 5.0 eq). The resultant mixture was stirred at room temperature. The mixture was acidified to pH 2 with 2 M aq HCl and extracted with EtOAc (x2). The combined organic extracts were dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude residue was purified by FCC.

Method N for synthesis of pinacol esters via Miyaura borylation
A mixture of the requisite bromoaryl (1 mmol), bis(pinacolato)diboron (1.3 mmol), $Pd(dppf)Cl_2$ (0.05 mmol, 5 mol%) and potassium acetate (3.1 mmol) in 1,4-dioxane (3.8 mL/mmol) and DMSO (0.4 mL/mmol) was subjected to microwave irradiation at 150 °C. The resultant mixture was diluted with water and filtered through Celite®. The filtrate was extracted with EtOAc (x2) and the combined organic extracts were washed with brine (x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired compound. The crude material was used for subsequent Suzuki-Miyaura cross-coupling reaction.

4.4 Synthesis and Characterization of indole carboxylates and intermediates

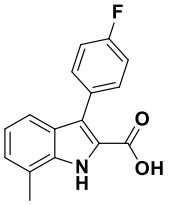
4.4.1 HTS

Ethyl 3-(4-fluorophenyl)-7-methyl-1*H*-indole-2-carboxylate (S1)



Method B using *o*-toluidine (0.23 mL, 2.1 mmol) followed by purification of part A by FCC (heptane: EtOAc 0-25%) and FCC of part B (heptane: CH_2Cl_2 0-50%) gave the desired compound **S1** in 21% isolated yield as a colorless oil (128 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.96 (1H, br. s, N*H*), 7.59 – 7.49 (2H, m, Ar-*H*), 7.45 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.22 – 7.04 (4H, m, Ar-*H*), 4.33 (2H, q, *J*= 7.0 Hz, O*CH*$_2$CH$_3$), 2.58 (3H, s, Ar-C*H*$_3$), 1.27 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

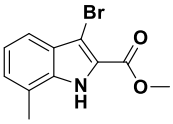
3-(4-Fluorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (1)



Method C using indole ester **S1** (128 mg, 0.43 mmol) followed by purification by FCC (CH_2Cl_2: EtOAc 0-50%) gave the desired compound **1** in 66% isolated yield as an off-white solid (76 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.85 (1H, br. s, COO*H*), 11.60 (1H, s, N*H*), 7.56 – 7.43 (2H, m, Ar-*H*), 7.33 – 7.19 (3H, m, Ar-*H*), 7.12 – 6.94 (2H, m, Ar-*H*), 2.55 (3H, s, Ar-C*H*$_3$); **LRMS** $[M-H]^-$ 268.00.

4.4.2 N1 modification

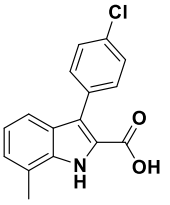
Methyl 3-bromo-7-methyl-1*H*-indole-2-carboxylate (S2)



Method D using methyl 7-methyl-1*H*-indole-2-carboxylate (500 mg, 2.64 mmol) afforded the desired compound **S2** in 91% isolated yield as a brown solid (647 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.98 (1H, br. s, N*H*), 7.58 – 7.50 (1H, m, Ar-*H*), 7.24 – 7.11 (2H, m, Ar-*H*), 4.03 (3H, s, OC*H*$_3$), 2.54 (3H, s, Ar-C*H*$_3$); **LC-MS** $[M+H]^+$ 268.00.

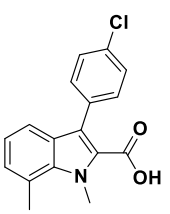
Methyl 3-iodo-7-methyl-1*H*-indole-2-carboxylate (**S3**) was synthesized according to a literature procedure and the data was in accordance with that previously reported.[16]

3-(4-Chlorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (4)



Method E using indole **S2** (60 mg, 0.22 mmol) followed by purification by preparative HPLC, gave the desired compound **4** in 27% isolated yield as an off-white solid (17 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.62 (1H, br. s, N*H*), 7.55 – 7.43 (4H, m, Ar-*H*), 7.26 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.08 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.04 – 6.94 (1H, m, Ar-*H*), 2.55 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.8 (*C*O$_2$H), 135.6, 133.1, 131.3, 126.8, 124.3, 122.3, 121.0 (Ar-*C*), 132.2, 127.7, 125.2, 120.7, 117.6 (Ar-*C*H), 17.1 (*C*H$_3$); **LRMS** $[M+H]^+$ 286.00; **HRMS** (TOF, ESI^+) m/z: $[M-H]^-$ Calcd for $C_{16}H_{11}O_2N^{35}Cl$ 284.04838; Found 284.04837.

3-(4-Chlorophenyl)-1,7-dimethyl-1*H*-indole-2-carboxylic acid (3)

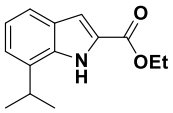


To a solution of 3-(4-chlorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (**4**) (31.4 mg, 0.11 mmol, 1.0 eq) in THF (1.5 mL) was added NaH (60%, 8.79 mg, 0.22 mmol, 2.0 eq). Effervescence occurred upon mixing and the mixture was stirred at room temperature for 5 mins, CH_3I (8.2 µL, 0.13 mmol, 1.2 eq) was then added as a solution in THF. The resulting mixture was heated to reflux for

24 h in a sealed tube. LCMS analysis suggested conversion of approximately 50% of the starting material. The mixture was cooled to room temperature and additional NaH (60%, 8.8 mg, 0.22 mmol) was added. After 5 mins, CH_3I (4.1 µL, 0.07 mmol, 0.6 eq) as a solution in THF. The mixture was heated for a further 23 h. The residue was partitioned between 1 M aq HCl and EtOAc, the organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was taken up in DMSO/MeOH (1:1, 1 mL) and purified by preparative HPLC. Fractions corresponding to the desired product were dried using the Genevac apparatus (to remove water) and the residues from each tube combined in methanol, concentrated under reduced pressure and dried under vacuum at 60 °C to afford the desired compound **3** in 41% yield as a colorless oil (13.4 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.02 (1H, br. s, CO_2H), 7.54 – 7.43 (2H, m, Ar-*H*), 7.38 (2H, d, *J*= 8.5 Hz, Ar-*H*), 7.22 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.06 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.01 – 6.93 (1H, m, Ar-*H*), 4.21 (3H, s, NCH_3), 2.80 (3H, s, Ar-CH_3); $[M+H]^+$ 300.20; **HRMS** (TOF, ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{13}O_2N^{35}Cl$ 298.06403; Found 298.06369.

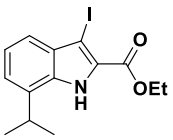
4.4.3 Modification of C2

Ethyl 7-(propan-2-yl)-1*H*-indole-2-carboxylate (S4)



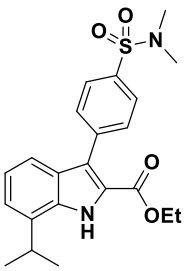
To a flask charged with anhydrous molecular sieves (4 Å, 18 g) under argon was added toluene (23 mL) followed by 2-isopropylaniline (5.24 mL, 36.9 mmol, 1.0 eq) and ethyl 2-oxopropanoate (8.2 mL, 73.8 mmol, 2.0 eq) and the resultant mixture was stirred at room temperature overnight. The mixture was filtered through cotton wool to remove sieves, rinsing with EtOAc; the filtrate was concentrated under reduced pressure. The residue was placed under argon, dissolved in DMSO (160 mL); copper (II) acetate (10.05 g, 55.4 mmol, 1.5 eq) and $Pd(OAc)_2$ (0.83 g, 3.7 mmol, 0.1 eq) were then added. The resultant mixture was heated to 40 °C for 18 h. The mixture was filtered through Celite®, eluting with EtOAc and 1 M HCl. The filtrate was separated and the aqueous phase further extracted with EtOAc; the combined organic extracts were washed with brine (x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The material was taken up in CH_2Cl_2, adsorbed onto silica and purified by FCC (EtOAc in cyclohexane, 0-10%) to give the desired product **S4** in 54% isolated yield as a yellow solid (4.6 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.00 (1H, br. s, N*H*), 7.59 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.30 (1H, d, *J* = 2.0 Hz, Ar- *H*), 7.27 – 7.23 (1H, m, Ar-*H*), 7.22 – 7.15 (1H, m, Ar-*H*), 4.48 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.34 (1H, hept, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.51 – 1.42 (9H, m, OCH_2CH_3 + $CH(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.4 (CO_2Et), 135.5, 132.2, 127.6, 127.2 (Ar-*C*), 121.3, 121.1, 120.2, 109.2 (Ar-*C*H), 61.1 (OCH_2CH_3), 29.2 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 14.5 (OCH_2CH_3).

Ethyl 3-iodo-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S5)



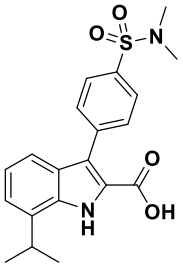
Method D using ethyl indole carboxylate **S4** (3.5 g, 15.2 mmol) in CH_2Cl_2:DMF (45 mL, 10:1), which afforded after purification by FCC (EtOAc in cyclohexane, 0-10%), the desired product **S5** in 92% isolated yield as a brown solid (4.98 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.22 (1H, br. s, N*H*), 7.43 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.28 – 7.20 (2H, m, Ar-*H*), 4.49 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.29 (1H, hept, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.50 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.39 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.3 (CO_2Et), 134.7, 132.4, 131.6, 127.0, 66.8 (Ar-*C*), 122.3, 122.1, 121.3 (Ar-*C*H), 61.7 (OCH_2CH_3), 28.9 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$), 14.5 (OCH_2CH_3).

Ethyl 3-(4-((dimethylamino)sulfonyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S6)



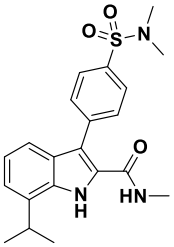
Method H using iodoindole **S5** (1.0 g, 2.8 mmol) followed by purification by FCC (EtOAc in cyclohexane, 0-20%), the desired product **S6** in 80% isolated yield as a yellow solid (1.6 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.04 (1H, br. s, N*H*), 7.91 – 7.83 (2H, m, Ar-*H*), 7.77 – 7.70 (2H, m, Ar-*H*), 7.42 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.27 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.21 – 7.14 (1H, m, Ar-*H*), 4.31 (2H, q, *J*= 7.0 Hz, OCH_2CH_3), 3.33 (1H, hept, *J*= 7.0 Hz, $CH(CH_3)_2$), 2.79 (6H, s, $N(CH_3)_2$), 1.44 (6H, d, *J*= 7.0 Hz, $CH(CH_3)_2$), 1.23 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.9, 139.0, 134.3, 134.1, 132.4, 131.4, 127.7, 127.3, 123.0, 122.5, 122.0, 122.0, 118.8, 61.3, 38.2, 29.2, 22.9, 14.2; **HRMS** (TOF, ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{27}O_4N_2S$ 415.16860; Found 415.16824.

3-(4-((Dimethylamino)sulfonyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (5)



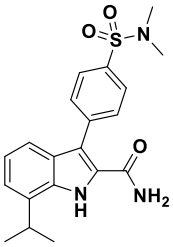
Method J using indole ester **S6** (90 mg, 0.22 mmol) at room temperature for 16 h followed by quenching of the reaction mixture with 1 M HCl and concentration *in vacuo* to remove organic solvent, partitioning between EtOAc and water, and then extraction followed by trituration with methanol gave the desired product **5** in 62% isolated yield as a white solid (52 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.03 (1H, br. s, CO_2H), 11.72 (1H, s, N*H*), 7.86 – 7.69 (4H, m, Ar-*H*), 7.31 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.21 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.14 – 7.00 (1H, m, Ar-*H*), 3.77 (1H, hept, *J*= 7.0 Hz, $CH(CH_3)_2$), 2.69 (6H, s, $N(CH_3)_2$), 1.29 (6H, d, *J*= 7.0 Hz, $CH(CH_3)_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (CO_2H), 139.2, 134.4, 133.5, 132.7, 126.8, 124.7 (Ar-*C*), 131.2, 127.0, 121.2, 120.5, 117.5 (Ar-*C*H), 37.7 ($N(CH_3)_2$), 26.9 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)_2$); **LRMS** $[M+H]^+$ 387.20; **HRMS** (TOF, ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{20}H_{21}O_4N_2S$ 385.12275; Found 385.12241.

3-(4-((Dimethylamino)sulfonyl)phenyl)-*N*-methyl-7-(propan-2-yl)-1*H*-indole-2-carboxamide (6)



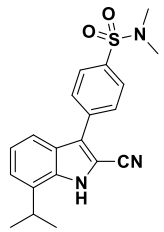
A mixture of carboxylic acid **5** (50 mg, 0.13 mmol, 1.0 eq), EDC•HCl (33.5 mg, 0.17 mmol, 1.3 eq) and HOBt (26.8 mg, 0.17 mmol, 1.3 eq) in CH_2Cl_2 (1.6 mL) was stirred at room temperature for 5 mins prior to addition of *N*,*N*-diisopropylethylamine (0.04 mL, 0.21 mmol, 1.6 eq) and 2 M methylamine in THF (0.065 mL, 0.13 mmol, 1.0 eq). The resulting mixture was stirred at room temperature for 18 h. The mixture was subjected directly to FCC (EtOAc-heptane, 0-50%) and the fractions corresponding to the desired product were combined and concentrated under reduced pressure to afford the desired compound **6** in >99% yield as a colorless oil (52.6 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.55 (1H, s, N*H*), 8.14 (1H, d, *J*= 4.5 Hz, CON*H*CH_3), 7.83 – 7.75 (2H, m, Ar-*H*), 7.75 – 7.67 (2H, m, Ar-*H*), 7.43 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.20 – 7.14 (1H, m, Ar-*H*), 7.14 – 7.05 (1H, m, Ar-*H*), 3.55 (1H, hept, *J*= 7.0 Hz, $CH(CH_3)_2$), 2.76 (3H, d, *J*= 4.5 Hz, $CONHCH_3$), 2.68 (6H, s, $N(CH_3)_2$), 1.33 (6H, d, *J*= 7.0 Hz, $CH(CH_3)_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.0 (*C*(O)NH-), 139.4, 133.7, 132.9, 132.1, 129.6, 126.0, 116.0 (Ar-*C*), 130.2, 127.4, 121.1, 119.4, 116.9 (Ar-*C*H), 37.7 ($NHCH_3$), 27.5 ($CH(CH_3)_2$), 26.0 ($N(CH_3)_2$), 23.0 ($CH(CH_3)_2$); **LRMS** $[M+H]^+$ 400.25; **HRMS** (TOF, ESI^+) m/z: $[M+H]^+$ Calcd for $C_{21}H_{26}O_3N_3S$ 400.16894; Found 400.16873.

3-(4-((Dimethylamino)sulfonyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxamide (S7)



Ethyl indole ester **S6** (400 mg, 0.97 mmol, 1.0 eq) with $Ln(OTf)_3$ (0.283 mg, 0.48 mmol, 0.5 eq) in 7 M NH_3 in methanol (1.46 mL) was sealed in a microwave vial under nitrogen and heated at 100 °C in a sand-bath for 72 h. When the reaction was finished, the mixture was concentrated under reduced pressure and purified by FCC (cyclohexane/EtOAc, 1:1) to give the desired compound **S7** in 70% isolated yield as an amorphous white solid (260 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.46 (1H, s, N*H*), 7.83 – 7.69 (4H, m, Ar-*H*), 7.55 (2H, s, CONH_2), 7.37 (1H, d, *J*= 9.0 Hz, Ar-*H*), 7.17 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.13 – 7.05 (1H, m, Ar-*H*), 3.57 (1H, hept, *J*= 7.0 Hz, C*H*$(CH_3)_2$), 2.68 (6H, s, N$(CH_3)_2$), 1.32 (6H, d, *J*= 7.0 Hz, CH$(CH_3)_2$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 163.0, 139.4, 133.6, 132.9, 132.3, 130.6, 127.3, 126.3, 121.1, 119.5, 117.0, 116.9, 37.7, 27.5, 23.0; **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{20}H_{24}O_3N_3S$ 386.15329; Found 386.15323.

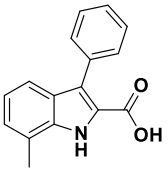
4-(2-Cyano-7-(propan-2-yl)-1*H*-indol-3-yl)-*N*,*N*-dimethylbenzenesulfonamide (7)



To a suspension of 7-isopropyl-1H-indole-2-carboxamide **S7** (200 mg, 0.52 mmol, 1.0 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.47 mL, 3.12 mmol, 6.0 eq) in dry CH_2Cl_2 (2.6 mL) was stirred at room temperature for 30 mins. Then, ethyl dichlorophosphate was added dropwise (0.34 g, 2.08 mmol, 4.0 eq) and the reaction mixture was stirred at room temperature for 4 h. The mixture was partitioned between CH_2Cl_2 and sat. aqueous NH_4Cl. The aqueous phase was further extracted with CH_2Cl_2 and the combined organic extracts washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, adsorbed onto silica and purified by FCC (cyclohexane/EtOAc, 2:1) to give the desired compound **7** in 75% isolated yield as an amorphous white solid (143 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.32 (1H, s, N*H*), 7.99 – 7.86 (4H, m, Ar-*H*), 7.66 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.33 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.30 – 7.24 (1H, m, Ar-*H*), 3.30 (1H, hept, *J*= 7.0 Hz, C*H*$(CH_3)_2$), 2.82 (6H, s, 2xNCH_3), 1.42 (6H, d, *J*= 7.0 Hz, CH$(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 136.9, 135.9, 135.1, 132.9, 129.4, 128.6, 127.5, 124.7, 123.2, 122.8, 118.4, 114.6, 104.0, 38.1, 29.3, 22.7; **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}O_2N_3S$ 368.14272; Found 368.14261.

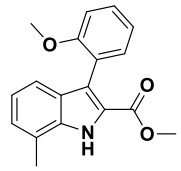
4.4.4 Initial Screen of C3 substituted indole carboxylates

7-Methyl-3-phenyl-1*H*-indole-2-carboxylic acid (8)



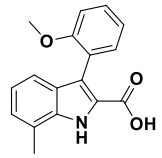
Method E using indole **S2** (60 mg, 0.22 mmol) followed by purification by FCC (CH_2Cl_2:MeOH 1-10%), then by preparative HPLC gave the desired compound **8** in 57% isolated yield as a pale pink solid (32 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.81 (1H, br. s, CO_2H/N*H*), 11.55 (1H, s, CO_2H/N*H*), 7.51 – 7.39 (4H, m, Ar-*H*), 7.26 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.07 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.08 – 6.92 (2H, m, Ar-*H*), 2.55 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.0 (*C*O_2H), 135.6, 134.1, 130.4, 127.7, 127.0, 126.6, 125.1, 123.9, 122.5, 122.2, 120.5, 117.9, 17.1 (*C*H_3); **LC-MS** $[M+H]^+$ 252.15; **HRMS** (TOF, ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}O_2NNa$ 274.08385; Found 274.08378.

Methyl 3-(2-methoxyphenyl)-7-methyl-1*H*-indole-2-carboxylate (S8)



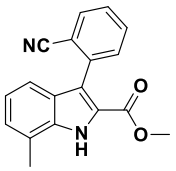
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane : EtOAc 0-25%) and then FCC using heptane : CH_2Cl_2 0-50% gave the desired compound **S8** in 88% isolated yield as an off-white solid (66 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.87 (1H, br. s, N*H*), 7.45 – 7.32 (3H, m, Ar-*H*), 7.16 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.14 – 6.98 (3H, m, Ar-*H*), 3.80 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 2.57 (3H, s, C*H*$_3$).

3-(2-Methoxyphenyl)-7-methyl-1*H*-indole-2-carboxylic acid (9)



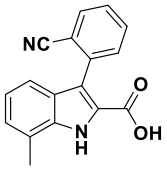
Method G using indole **S8** (64 mg, 0.22 mmol) followed by precipitation gave the desired compound **9** in 85% isolated yield as a white solid (52 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.55 (1H, br. s, CO_2H), 11.49 (1H, br. s, N*H*), 7.38 - 7.28 (1H, m, Ar-*H*), 7.24 (1H, dd, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.13 - 6.96 (4H, m, Ar-*H*), 6.95 - 6.87 (1H, m, Ar-*H*), 3.65 (3H, s, C*H*$_3$), 2.54 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.1 (*C*O_2H), 157.1, 135.6, 127.3, 125.1, 123.4, 122.0, 118.5 (Ar-*C*), 131.7, 128.3, 124.6, 120.1, 119.8, 118.2, 111.1 (Ar-*C*H), 55.1 (O*C*H$_3$), 17.1 (*C*H$_3$); **LRMS** $[M+H]^+$ 282.20; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{15}O_3NNa$ 304.09441; Found 304.09445.

Methyl 3-(2-cyanophenyl)-7-methyl-1*H*-indole-2-carboxylate (S9)



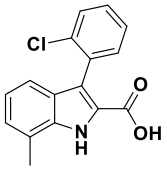
Method F using iodo indole **S3** (100 mg, 0.32 mmol) followed by purification by FCC (heptane : CH_2Cl_2 0-100%) gave the desired compound **S9** in 22% isolated yield as an off-white solid (20 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.07 (1H, br. s, N*H*), 7.99 – 7.90 (1H, m, Ar-*H*), 7.80 (1H, td, *J* = 7.7, 1.3 Hz, Ar-*H*), 7.65 – 7.55 (2H, m, Ar-*H*), 7.15 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.09 – 6.99 (1H, m, Ar-*H*), 3.75 (3H, s, OC*H*$_3$), 2.59 (3H, s, C*H*$_3$); **LRMS** $[M-H]^-$ 289.20.

3-(2-Cyanophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (10)



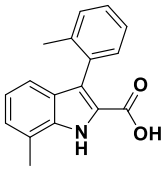
Method G using indole **S9** (33 mg, 0.11 mmol) followed by acid-base extraction, then drying *in vacuo* gave the desired compound **10** in 93% isolated yield as a colorless solid (29 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.03 (1H, br. s, CO_2H), 11.91 (1H, s, N*H*), 7.91 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.82 – 7.72 (1H, m, Ar-*H*), 7.62 – 7.52 (2H, m, Ar-*H*), 7.17 – 7.07 (2H, m, Ar-*H*), 7.07 – 6.96 (1H, m, Ar-*H*), 2.58 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.5 (*C*O_2H), 138.3, 135.5, 132.7, 132.6, 131.3, 127.7, 126.9, 125.6, 125.3, 122.5, 121.0, 118.7, 118.2, 117.3, 113.5 (Ar-C + *C*N), 17.1 (*C*H$_3$); **LRMS** $[M+H]^+$ 277.05; **HRMS** (TOF, ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{12}O_2N_2Na$ 299.07910; Found 299.07904.

3-(2-Chlorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (11)



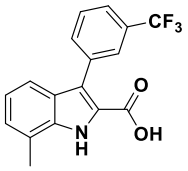
Method E using indole **S2** (60 mg, 0.22 mmol) afforded the desired compound **11** after purification by preparative HPLC in 26% isolated yield as an off-white solid (17 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.87 (1H, br. s, N*H*), 7.49 – 7.42 (1H, m, Ar-*H*), 7.38 – 7.23 (3H, m, Ar-*H*), 7.21 – 7.15 (1H, m, obscured by res. sol., Ar-*H*), 7.12 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.05 - 6.96 (1H, m, Ar-*H*), 2.48 (3H, s, C*H*$_3$); **LC-MS** $[M-H]^-$ 284.00.

7-Methyl-3-(2-methylphenyl)-1*H*-indole-2-carboxylic acid (12)



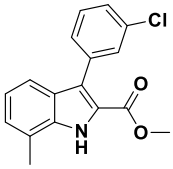
Method E using indole **S2** (95 mg, 0.90 mmol) followed by purification by FCC (CH_2Cl_2:MeOH 1-10%), then by preparative HPLC, gave the desired compound **12** in 45% isolated yield as an off-white solid (27 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 8.84 (1H, br. s, N*H*), 7.29 – 7.17 (4H, m, obscured by res. sol., Ar-*H*), 7.13 – 7.07 (2H, m, Ar-*H*), 7.01 – 6.94 (1H, m, Ar-*H*), 2.48 (3H, s, CH_3), 2.08 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.0 (*C*O_2H), 136.7, 135.6, 134.3, 127.3, 124.7, 122.2, 121.8 (Ar-*C*), 130.6, 129.4, 126.9, 125.1, 125.0, 120.3, 118.0 (Ar-*C*H), 19.8, 17.1 (*C*H_3); **LC-MS** $[M+H]^+$ 266.10; HRMS (TOF, ESI^-) m/z: $[M-H]^-$ Calcd for $C_{17}H_{14}O_2N$ 264.10300; Found 264.10263.

7-Methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-indole-2-carboxylic acid (13)



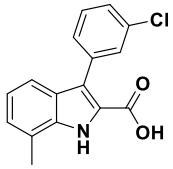
Method E using indole **S2** (60 mg, 0.22 mmol) followed by purification by FCC (CH_2Cl_2:MeOH 1-5%), then preparative HPLC, gave the desired compound **13** in 27% isolated yield as an off-white solid (19 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.70 (1H, br. s, N*H*), 7.84 – 7.75 (2H, m, Ar-*H*), 7.74 – 7.63 (2H, m, Ar-*H*), 7.26 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.10 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.07 – 6.96 (1H, m, Ar-*H*), 2.57 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (*C*O_2H), 135.6, 135.3, 134.4, 128.8, 128.7, 128.4, 126.9, 126.7, 125.5, 125.2, 123.2, 122.4, 120.9, 117.3, 39.5, 17.1 (*C*H_3); **LRMS** $[M+H]^+$ 320.15; **HRMS** (TOF, ESI^-) m/z: $[M-H]^-$ Calcd for $C_{17}H_{11}O_2NF_3$ 318.07474; Found 318.07474.

Methyl 3-(3-chlorophenyl)-7-methyl-1*H*-indole-2-carboxylate (S10)



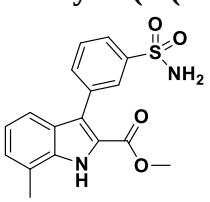
Method F using iodo indole **S3** (90 mg, 0.30 mmol) followed by purification by FCC (heptane : EtOAc 0-20%), then by FCC (heptane : CH_2Cl_2 0-50%) gave the desired compound **S10** in 47% isolated yield as an off-white solid (42 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.84 (1H, br. s, N*H*), 7.50 – 7.44 (1H, m, Ar-*H*), 7.41 – 7.24 (4H, m, Ar-*H*), 7.13 – 7.07 (1H, m, Ar-*H*), 7.06 – 6.98 (1H, m, Ar-*H*), 3.77 (3H, s, OCH_3), 2.48 (3H, s, CH_3).

3-(3-Chlorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (14)



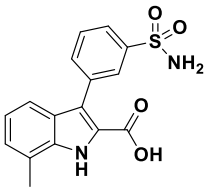
Method G using indole **S10** (42 mg, 0.14 mmol) followed by acidification, precipitation and then filtration gave the desired compound **14** in 97% isolated yield as a colorless solid (39 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.66 (1H, br. s, N*H*), 7.52 – 7.38 (4H, m, Ar-*H*), 7.26 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.09 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.04 – 6.96 (1H, m, Ar-*H*), 2.56 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.8 (*C*O_2H), 136.4, 135.5, 132.3, 129.5, 126.7, 124.6, 120.6 (Ar-*C*), 130.1, 129.1, 126.5, 125.2, 122.3, 120.8, 117.5 (Ar-*C*H), 17.1 (CH_3); **LRMS** $[M+H]^+$ 286.00; **HRMS** (TOF, ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{11}O_2N^{35}Cl$ 284.04838; Found 284.04819.

Methyl 3-(3-(aminosulfonyl)phenyl)-7-methyl-1*H*-indole-2-carboxylate (S11)



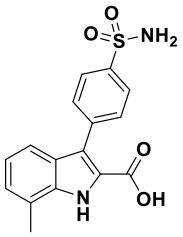
Method F using iodo indole **S3** (89 mg, 0.28 mmol) followed by purification by FCC (CH_2Cl_2 : EtOAc 0-75%) gave the desired compound **S11** in 75% isolated yield as an off-white solid (73 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.88 (1H, br. s, N*H*), 8.01 – 7.89 (1H, m, Ar-*H*), 7.82 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.74 – 7.68 (1H, m, Ar-*H*), 7.67 – 7.59 (1H, m, Ar-*H*), 7.42 (2H, s, SO_2NH_2), 7.33 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.14 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.09 – 7.00 (1H, m, Ar-*H*), 3.76 (3H, s, OCH_3), 2.58 (3H, s, CH_3).

3-(3-(Aminosulfonyl)phenyl)-7-methyl-1*H*-indole-2-carboxylic acid (15)



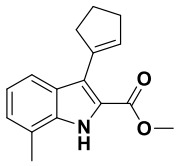
Method G using indole **S11** (73 mg, 0.21 mmol) followed by acidification, precipitation and then filtration gave the desired compound **15** in 88% isolated yield as a colorless solid (61 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.98 (1H, br. s, CO_2H/N*H*), 11.73 (1H, br. s, CO_2H/N*H*), 7.93 (1H, app s, Ar-*H*), 7.80 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.73 – 7.66 (1H, m, Ar-*H*), 7.66 – 7.57 (1H, m, Ar-*H*), 7.39 (2H, s, SO_2NH_2), 7.29 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.11 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.06 – 6.97 (1H, m, Ar-*H*), 2.57 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (*C*O_2H), 143.7, 135.6, 134.9, 126.7, 124.4, 122.4, 120.9 (Ar-*C*), 134.0, 128.4, 127.2, 125.3, 123.8, 120.9, 117.5 (Ar-*C*H), 17.1 (*C*H_3); **LRMS** $[M+H]^+$ 331.10; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{14}O_4N_2NaS$ 353.05775; Found 353.05667.

3-(4-(Aminosulfonyl)phenyl)-7-methyl-1*H*-indole-2-carboxylic acid (16)



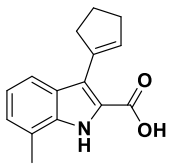
Method E using indole **S2** (60 mg, 0.22 mmol, 1.0 eq) and (4-sulfamoylphenyl)boronic acid (67.5 mg, 0.34 mmol, 1.5 eq) followed by purification by FCC (MeOH in CH_2Cl_2, 1-10%) gave the desired compound **16** in 23% isolated yield as a brown solid (17 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.74 (1H, br. s, N*H*), 7.88 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.66 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.40 (2H, br. s, SO_2NH_2), 7.28 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.10 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.05 – 6.96 (1H, m, Ar-*H*), 2.56 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.8 (*C*O_2H), 142.1, 137.9, 135.6, 126.7, 122.4 (Ar-*C*), 130.8, 125.3, 125.1, 120.9, 117.5 (Ar-*C*H), 17.1 (*C*H_3); **LRMS** $[M+H]^+$ 331.05; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{13}O_4N_2S$ 329.06015; Found 329.06008.

Methyl 3-(cyclopent-1-en-1-yl)-7-methyl-1*H*-indole-2-carboxylate (S12)



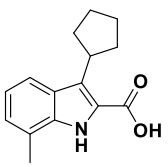
Method F using iodo indole **S3** (160 mg, 0.51 mmol) followed by purification by FCC (heptane: EtOAc 0-20%) gave the desired compound **S12** in 70% isolated yield (90 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.70 (1H, br. s, N*H*), 7.63 – 7.55 (1H, m, Ar-*H*), 7.20 – 7.04 (2H, m, Ar-*H*), 6.05 – 5.98 (1H, m, =C*H*), 3.96 (3H, s, OCH_3), 2.83 (2H, app td, *J* = 7.5, 2.0 Hz, CH_2), 2.68 – 2.58 (2H, m, CH_2), 2.53 (3H, s, CH_3), 2.09 (2H, app q, *J* = 7.5 Hz, CH_2).

3-(Cyclopent-1-en-1-yl)-7-methyl-1*H*-indole-2-carboxylic acid (S13)



Method G using indole **S12** (88 mg, 0.35 mmol) followed by acidification, precipitation, filtration and then purification by FCC (CH_2Cl_2 : MeOH 0-35%) gave the desired compound **S13** in 44% isolated yield as an off-white solid (37 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.91 (1H, br. s, CO_2H/N*H*), 11.32 (1H, br. s, CO_2H/N*H*), 7.41 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.10 – 6.90 (2H, m, Ar-*H*), 5.90 – 5.78 (1H, m, =C*H*), 2.81 –2.69 (2H, m, CH_2), 1.97 (2H, app q, *J* = 7.5 Hz, CH_2); *Note*: 3H of methyl and 2H of cyclopentenyl obscured by DMSO; **LRMS** $[M+H]^+$ 242.20.

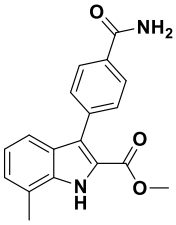
3-Cyclopentyl-7-methyl-1*H*-indole-2-carboxylic acid (17)



Method K using indole **S13** (35 mg, 0.15 mmol) followed by purification by preparative HPLC gave the desired compound **17** in 71% isolated yield (25 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.93 (1H, br. s, CO_2H/N*H*), 11.00 (1H, br. s, CO_2H/N*H*), 7.56 – 7.45 (1H, m, Ar-*H*), 7.03 (1H, d, *J*= 7.0 Hz, Ar-*H*), 6.95 (1H, dd, *J*= 8.1, 6.9 Hz, Ar-*H*), 4.22 – 4.06 (1H, m, C*H*), 2.48 (3H, s, CH_3), 2.00 – 1.80 (6H, m, CH_2), 1.75 – 1.60 (2H, m, CH_2); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm

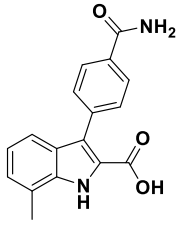
163.7 (*C*O_2H), 136.2, 126.4, 125.4, 123.8, 122.3 (Ar-*C*), 124.5, 119.2, 118.8 (Ar-*C*H), 35.8 (cyclopentyl-*C*H), 32.8, 26.3 (cyclopentyl-*C*H_2), 17.1 (*C*H_3); **LRMS** $[M+H]^+$ 244.10; **HRMS** (TOF, ESI^-) m/z: $[M-H]^-$ Calcd for $C_{15}H_{16}O_2N$ 242.11865; Found 242.11846.

Methyl 3-(4-carbamoylphenyl)-7-methyl-1*H*-indole-2-carboxylate (S14)



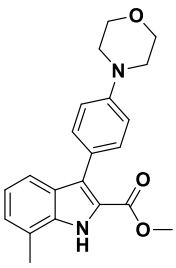
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by trituration of the crude material with MeOH gave the desired compound **S14** in 96% isolated yield as an off-white solid (78 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.79 (1H, br. s, N*H*), 8.03 (1H, br. s, CONH_2), 7.95 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.54 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.38 (1H, br. s, CONH_2), 7.31 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.12 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.06 – 6.98 (1H, m, Ar-*H*), 3.76 (3H, s, OCH_3), 2.57 (3H, s, CH_3); **LRMS** $[M+H]^+$ 309.15.

3-(4-Carbamoylphenyl)-7-methyl-1*H*-indole-2-carboxylic acid (18)



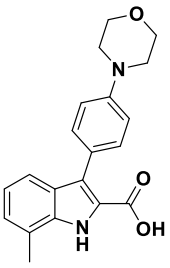
Method G using indole **S14** (73 mg, 0.24 mmol) followed by acidification, precipitation and then filtration gave the desired compound **18** in 84% isolated yield as a colorless solid (58 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.92 (1H, br. s, CO_2H), 11.66 (1H, br. s, N*H*), 8.01 (1H, br. s, CONH_2), 7.93 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.54 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.36 (1H, br. s, CONH_2), 7.28 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.09 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.05 – 6.95 (1H, m, Ar-*H*), 2.56 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 167.9 (*C*(O)NH), 162.9 (*C*O_2H), 137.3, 135.6, 132.4, 126.8, 124.3, 122.3, 121.6 (Ar-*C*), 130.2, 127.0, 125.2, 120.8, 117.8 (Ar-*C*H), 17.2 (*C*H_3); **LRMS** $[M+H]^+$ 295.15; **HRMS** (TOF, ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}O_3N_2$ 295.10772; Found 295.10791.

Methyl 7-methyl-3-(4-(morpholin-4-yl)phenyl)-1*H*-indole-2-carboxylate(S15)



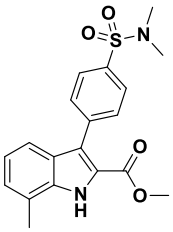
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane: CH_2Cl_2 0-100% then CH_2Cl_2: EtOAc 0-25%) gave the desired compound **S15** in 41% isolated yield as a pale brown solid (37 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.73 (1H, br. s, N*H*), 7.47 – 7.38 (3H, m, Ar-*H*), 7.08 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.02 – 6.96 (1H, m, Ar-*H*), 6.96 – 6.89 (2H, m, Ar-*H*), 3.87 – 3.80 (4H, m, morpholine CH_2), 3.77 (3H, s, OCH_3), 3.23 – 3.13 (4H, m, morpholine CH_2), 2.48 (3H, s, CH_3); **LRMS** $[M-H]^-$ 351.15.

7-Methyl-3-(4-(morpholin-4-yl)phenyl)-1*H*-indole-2-carboxylic acid (19)



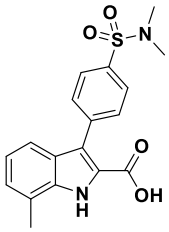
Method G using indole **S15** (37 mg, 0.10 mmol) followed by purification by ion exchange chromatography (SCX-2 MeOH then 2 M NH_3 in MeOH solution) and then by FCC (Hypersep-Si CH_2Cl_2: MeOH 0-6%) gave the desired compound **19** in 80% isolated yield as a colorless solid (28 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.38 (1H, br. s, N*H*), 7.35 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.29 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.08 – 6.90 (4H, m, Ar-*H*), 3.82 – 3.72 (4H, m, morpholine C*H*$_2$), 3.17 (4H, m, morpholine C*H*$_2$), 2.54 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.2 (*C*O_2H), 149.6, 135.5, 133.2, 127.1, 122.0 (Ar-*C*), 131.1, 124.8, 120.2, 118.1, 114.3 (Ar-*C*H), 66.2, 48.4 (*C*H_2), 17.1 (*C*H_3); **LRMS** $[M+H]^+$ 337.20; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}O_3N_2$ 337.15467; Found 337.15433.

Methyl 3-(4-((dimethylamino)sulfonyl)phenyl)-7-methyl-1*H*-indole-2-carboxylate (S16)



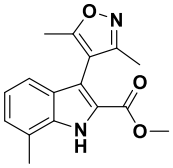
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane: EtOAc 0-50%) gave the desired compound **S16** in 72% isolated yield as an off-white solid (68 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.97 (1H, br. s, N*H*), 7.89 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.76 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.47 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.23 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.18 – 7.10 (1H, m, Ar-*H*), 3.87 (3H, s, OC*H*$_3$) , 2.82 (6H, s, N(C*H*$_3$)$_2$), 2.60 (3H, s, C*H*$_3$); **LRMS** $[M+H]^+$ 373.00.

3-(4-((Dimethylamino)sulfonyl)phenyl)-7-methyl-1*H*-indole-2-carboxylic acid (20)



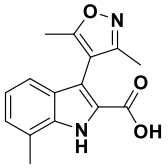
Method G using indole **S16** (66 mg, 0.18 mmol) followed by acidification, precipitation and then filtration gave the desired compound **20** in 87% isolated yield as a brown solid (55 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.04 (1H, br. s, CO_2*H*), 11.78 (1H, br. s, N*H*), 7.84 – 7.78 (2H, m, Ar-*H*), 7.78 – 7.72 (2H, m, Ar-*H*), 7.32 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.11 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.07 – 6.99 (1H, m, Ar-*H*), 2.68 (6H, s, N(C*H*$_3$)$_2$), 2.57 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.6 (*C*O_2H), 139.1, 135.6, 132.7, 126.6, 124.5, 122.5, 120.6 (Ar-*C*), 131.2, 127.0, 125.4, 121.0, 117.6 (Ar-*C*H), 37.7 (N(C*H*$_3$)$_2$), 17.1 (C*H*$_3$); **LRMS** $[M+H]^+$ 359.20; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{18}H_{17}O_4N_2S$ 357.09145; Found 357.09117.

Methyl 3-(3,5-dimethyl-1,2-oxazol-4-yl)-7-methyl-1*H*-indole-2-carboxylate (S17)



Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane: EtOAc 0-25%) and by FCC (heptane: CH_2Cl_2 0-50%) gave the desired compound **S17** in 63% isolated yield as an off-white solid (45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.00 (1H, br. s, N*H*), 7.35 – 7.15 (2H, m, Ar-*H*), 7.16 – 7.09 (1H, m, Ar-*H*), 3.89 (3H, s, OC*H*$_3$), 2.59 (3H, s, C*H*$_3$), 2.29 (3H, s, C*H*$_3$), 2.15 (3H, s, C*H*$_3$); **LRMS** $[M+H]^+$ 285.15.

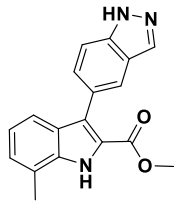
3-(3,5-Dimethyl-1,2-oxazol-4-yl)-7-methyl-1*H*-indole-2-carboxylic acid (21)



Method G using indole **S17** (43 mg, 0.15 mmol) followed by acidification, precipitation and then filtration gave the desired compound **21** in 84% isolated yield as a colorless solid (34 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.81 (1H, br. s, N*H*), 7.17 – 7.06 (2H, m, Ar-*H*), 7.05 – 6.94 (1H, m, Ar-*H*), 2.56 (3H, s, C*H*$_3$), 2.20 (3H, s, C*H*$_3$), 2.02 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 165.6 (*C*O_2H), 162.5, 159.6, 135.7, 127.0, 126.1, 122.6, 109.4, 109.2 (Ar-

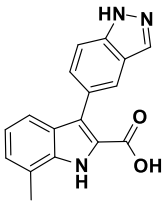
C), 125.3, 120.7, 117.8 (Ar-*C*H), 17.1, 11.5, 10.3 (*C*H$_3$); **LRMS** [M+H]$^+$ 271.15; **HRMS** (TOF, ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{15}H_{15}O_3N_2$ 271.10772; Found 271.10773.

Methyl 3-(1*H*-indazol-5-yl)-7-methyl-1*H*-indole-2-carboxylate (S18)



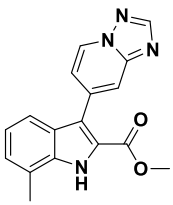
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane: EtOAc 0-50%) gave the desired compound **S18** in 66% isolated yield as a pale yellow solid (51 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.12 (1H, br. s, N*H*), 11.64 (1H, br. s, N*H*), 8.15 – 8.07 (1H, m, Ar-*H*), 7.87 – 7.77 (1H, m, Ar-*H*), 7.59 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.44 (1H, dd, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.31 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.11 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.05 – 6.95 (1H, m, Ar-*H*), 3.73 (3H, s, OC*H*$_3$), 2.57 (3H, s, C*H*$_3$); **LRMS** [M+H]$^+$ 306.15.

3-(1*H*-Indazol-5-yl)-7-methyl-1*H*-indole-2-carboxylic acid (22)



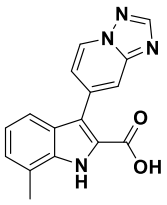
Method G using indole **S18** (49 mg, 0.16 mmol) followed by acidification, precipitation and then filtration gave the desired compound **22** in 98% isolated yield as a pale brown solid (46 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.51 (1H, br. s, N*H*), 8.17 – 8.04 (1H, m, Ar-*H*), 7.87 – 7.75 (1H, m, Ar-*H*), 7.57 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.34 – 7.22 (1H, m, Ar-*H*), 7.13 – 7.04 (1H, m, Ar-*H*), 7.02 – 6.91 (1H, m, Ar-*H*), 2.56 (3 H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (*C*O$_2$H), 139.9, 135.7, 127.3, 127.2, 124.8, 123.1, 122.3, 120.0 (Ar-*C*), 133.4, 125.7, 125.1, 121.9, 120.4, 118.1, 108.2 (Ar-*C*H), 17.1 (*C*H$_3$); **LRMS** [M+H]$^+$ 292.15; **HRMS** (TOF, ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{14}O_2N_3$ 292.10805; Found 292.10809.

Methyl 7-methyl-3-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-1*H*-indole-2-carboxylate (S19)



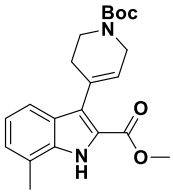
Method F using iodo indole **S3** (80 mg, 0.25 mmol) followed by purification by FCC (heptane: EtOAc 0-100%) gave the desired compound **S19** in 50% isolated yield (39 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.96 (1H, br. s, N*H*), 9.06 (1H, s, Ar-*H*), 8.55 (1H, s, Ar-*H*), 7.91 (1H, d, *J* = 9.0 Hz, Ar-*H*), 7.78 (1H, d, *J* = 9.0 Hz, Ar-*H*), 7.38 (1H, dd, *J* = 8.0 Hz, Ar-*H*), 7.15 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.10 – 7.00 (1H, m, Ar-*H*), 3.78 (3H, s, OC*H*$_3$), 2.59 (3H, s, C*H*$_3$); **LRMS** [M+H]$^+$ 307.05.

7-Methyl-3-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-1*H*-indole-2-carboxylic acid (23)



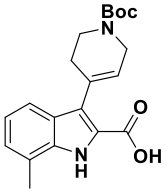
Method G using indole **S19** (37 mg, 0.12 mmol) followed by acidification, precipitation and then filtration gave the desired compound **23** in 89% isolated yield as a pale brown solid (31 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.84 (1H, br. s, N*H*), 9.03 (1H, s, Ar-*H*), 8.55 (1H, s, Ar-*H*), 7.95 – 7.83 (1H, m, Ar-*H*), 7.82 – 7.71 (1H, m, Ar-*H*), 7.35 (1H, dd, *J* = 8.0 Hz, Ar-*H*), 7.12 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.09 – 6.97 (1H, m, Ar-*H*), 2.58 (3H, s, C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.6 (*C*O$_2$H), 154.0, 149.0, 135.6, 133.9, 128.9, 127.0, 125.5, 125.0, 122.5, 121.2, 121.0, 117.5, 117.1, 114.8 (Ar-C), 17.1 (*C*H$_3$); **LRMS** [M+H]$^+$ 293.10; **HRMS** (TOF, ESI-) m/z: [M-H]- Calcd for $C_{16}H_{11}O_2N_4$ 291.08875; Found 291.08865.

Methyl 3-(1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7-methyl-1*H*-indole-2-carboxylate (S20)



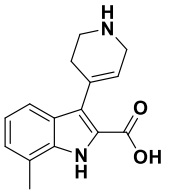
Method F using iodo indole **S3** (160 mg, 0.51 mmol) followed by purification by FCC (heptane: EtOAc 0-100%) gave the desired compound **S20** in 83% isolated yield (157 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.78 (1H, br. s, N*H*), 7.59 – 7.45 (1H, m, Ar-*H*), 7.20 – 7.05 (2H, m, Ar-*H*), 5.85 – 5.75 (1H, m, =C*H*), 4.24 – 4.08 (2H, m, CH_2), 3.95 (3H, s, OCH_3), 3.78 – 3.66 (2H, m, CH_2), 2.61 – 2.47 (5H, m, CH_2+CH_3), 1.55 (9H, s, C(CH_3)$_3$); **LRMS** $[M+H]^+$ 306.15.

3-(1-(*tert*-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7-methyl-1*H*-indole-2-carboxylic acid (S21)



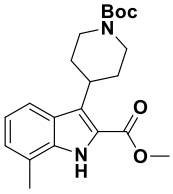
Method G using indole **S20** (160 mg, 0.43 mmol) followed by acidification, precipitation and then filtration gave the desired compound **S21** in 86% isolated yield as a pale brown solid (133 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.93 (1H, br. s, CO_2H/N*H*), 11.38 (1H, s, CO_2H/N*H*), 7.38 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.08 – 6.90 (2H, m, Ar-*H*), 5.74 – 5.60 (1H, m, =C*H*), 4.10 – 3.95 (2H, m, CH_2), 3.55 (2H, app t, *J* = 5.0 Hz, CH_2), 2.50 (3H, s, CH_3 obscured by residual DMSO peak), 2.43 (2H, br. s, CH_2), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (*C*O_2H), 154.1 (-N*C*(O)O^{t}Bu), 135.5, 130.1, 126.5, 125.1, 123.8, 123.7, 122.0, 120.1, 118.1, 78.7 (-NC(O)O*C*CH$_3$), 43.5 (*C*H$_2$), 39.5 (*C*H$_2$), 29.4 (*C*H$_2$), 28.2 (-NC(O)OC*C*H$_3$), 17.0 (*C*H$_3$); **LRMS** $[M-H]^-$ 355.20; **HRMS** (TOF, ESI^+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}O_4N_2Na$ 379.16283; Found 379.16312.

7-Methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-2-carboxylic acid (24)



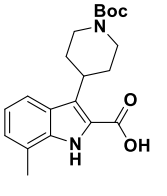
Method L using indole **S21** (50 mg, 0.14 mmol) gave the desired compound **24** in 66% isolated yield as a pale yellow amorphous solid (24 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 10.66 (1H, br. s, CO_2H/N*H*), 7.46 – 7.25 (1H, m, Ar-*H*), 6.97 – 6.78 (2H, m, Ar-*H*), 5.70 – 5.52 (1H, m, =C*H*), 3.84 – 3.66 (2H, m, CH_2), 3.30 – 3.20 (2H, m, CH_2 obscured by water peak), 2.97 – 2.77 (2H, m, CH_2), 2.60 – 2.35 (3H, m, CH_3, obscured by DMSO); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 165.0 (*C*O_2H), 133.9, 132.4, 127.0, 121.2 (Ar-*C*/CH=*C*), 122.9, 119.0, 117.3 (Ar-*C*H), 118.1 (*C*H=C), 41.6, 40.7, 26.4 (*C*H$_2$), 17.0 (*C*H$_3$); **LRMS** $[M+H]^+$ 257.15; **HRMS** (TOF, ESI^-) m/z: $[M-H]^-$ Calcd for $C_{15}H_{15}O_2N_2$ 255.11390; Found 255.11394.

Methyl 3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-7-methyl-1*H*-indole-2-carboxylate (S22)



Method K using indole **S20** (150 mg, 0.41 mmol) gave the desired compound **S22** in >99% isolated yield (150 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.55 (1H, br. s, N*H*), 7.61 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.07 – 6.99 (1H, m, Ar-*H*), 6.98 – 6.89 (1H, m, Ar-*H*), 4.27 – 4.13 (2H, m, CH_2), 3.88 (3H, s, OCH_3), 3.87 – 3.75 (1H, m, C*H*), 2.85 – 2.73 (2H, m, CH_2), 2.41 (3H, s, CH_3), 2.19 – 2.03 (2H, m, CH_2), 1.75 – 1.65 (2H, m, CH_2), 1.44 (9H, s, C(CH_3)$_3$).

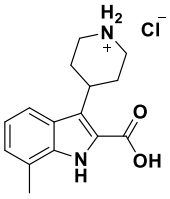
3-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-7-methyl-1*H*-indole-2-carboxylic acid (S23)



Method G using indole **S22** (151 mg, 0.41 mmol) followed by acidification, precipitation and then filtration gave the desired compound **S23** in 89% isolated yield as an off-white solid (129 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.09 (1H, br. s, N*H*), 7.53 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.05 – 6.87 (2H, m, Ar-*H*), 4.20 – 3.97 (2H, m, CH_2), 3.88 (1H, app t, *J* = 12.0 Hz, C*H*), 2.90 – 2.69 (2H, m, CH_2),

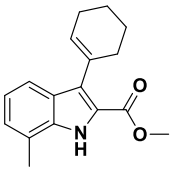
2.48 (3H, s, CH_3), 2.17 – 1.95 (2H, m, CH_2), 1.73 – 1.55 (2H, m, CH_2), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.5 (*C*O_2H), 154.0 (N*C*(O)O^{t}Bu), 135.9, 126.1, 125.7, 124.6, 123.5, 122.3 (Ar-*C*), 119.4, 119.0 (Ar-*C*H), 78.5 (N*C*(O)O*C*CH$_3$), 33.5 (*C*H), 31.1 (*C*H$_2$), 28.2 (N*C*(O)OC*C*H$_3$), 17.1 (*C*H$_3$); **LRMS** [M-H]$^-$ 357.20; **HRMS** (TOF, ESI$^+$) m/z: [M+Na]$^+$ Calcd for $C_{20}H_{26}O_4N_2Na$ 381.17848; Found 381.17850.

4-(2-Carboxy-7-methyl-1*H*-indol-3-yl)piperidin-1-ium chloride (25)



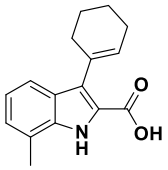
Method L using indole **S23** (50 mg, 0.14 mmol) followed by purification and acidification with 1 M aq HCl in Et$_2$O gave the desired compound **25** in 70% isolated yield as a pale yellow amorphous solid (29 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.12 (1H, br. s, CO_2H/N*H*), 11.18 (1H, br. s, CO_2H/N*H*), 8.86 (2H, br. s, NH_2), 7.78 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.07 – 6.89 (2H, m, Ar-*H*), 4.03 (1H, t, *J* = 12.5 Hz, C*H*), 3.50 – 3.25 (2H, m, CH_2, obscured by water peak), 3.00 (2H, t, *J* = 12.0 Hz, CH_2), 2.61 – 2.38 (5H, m, CH_2 + CH_3, obscured by DMSO), 1.86 – 1.72 (2H, m, CH_2); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 163.5 (*C*O_2H), 136.0, 125.4, 124.9, 123.6, 122.4 (Ar-*C*), 124.6, 119.4, 119.2 (Ar-*C*H), 44.0 (*C*H$_2$), 31.2 (*C*H), 27.7 (*C*H$_2$), 17.2 (*C*H$_3$); **LRMS** [M+H]$^+$ 259.15; **HRMS** (TOF, ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{15}H_{19}O_2N_2$ 259.14520; Found 259.14413.

Methyl 3-(cyclohex-1-en-1-yl)-7-methyl-1*H*-indole-2-carboxylate (S24)



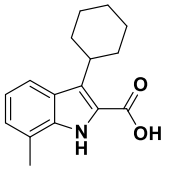
Method F using iodo indole **S3** (160 mg, 0.51 mmol) followed by purification by FCC (heptane: EtOAc 0-15%) gave the desired compound **S24** in 37% isolated yield (51 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.52 (1H, br. s, N*H*), 7.45 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.09 – 6.94 (2H, m, Ar-*H*), 5.73 (1H, dt, *J* = 3.5, 2.0 Hz, =C*H*), 3.86 (3H, s, OCH_3), 2.43 (3H, s, CH_3), 2.33 – 2.24 (2H, m, CH_2), 2.23 – 2.15 (2H, m, CH_2), 1.80 – 1.63 (4H, m, CH_2).

3-(Cyclohex-1-en-1-yl)-7-methyl-1*H*-indole-2-carboxylic acid (S25)



Method G using indole **S24** (49 mg, 0.18 mmol) followed by acidification, precipitation and filtration gave the desired compound **S25** in 70% isolated yield as a yellow solid (32 mg) which was taken through to the hydrogenation step.

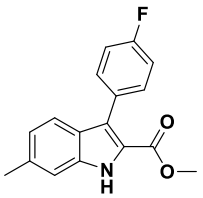
3-Cyclohexyl-7-methyl-1*H*-indole-2-carboxylic acid (26)



Method K using indole **S25** (33 mg, 0.13 mmol) followed by purification by preparative HPLC gave the desired compound **26** in 38% isolated yield (13 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 8.58 (1H, br. s, N*H*), 7.74 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.10 – 7.01 (1H, m, Ar-*H*), 7.00 – 6.93 (1H, m, Ar-*H*), 3.80 – 3.62 (1H, m, C*H*), 2.43 (3H, s, CH_3), 2.05 – 1.70 (7H, m, CH_2), 1.52 – 1.24 (3H, m, CH_2); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.7 (*C*O_2H), 136.0, 128.2, 125.8, 123.1, 122.1 (Ar-*C*), 124.4, 119.7, 119.1 (Ar-*C*H), 35.3 (cyclohexyl-*C*H), 32.3, 26.8, 25.7 (cyclohexyl-*C*H$_2$), 17.1 (*C*H$_3$); **LRMS** [M+H]$^+$ 258.15; **HRMS** (TOF, ESI$^-$) m/z: [M-H]$^-$ Calcd for $C_{16}H_{18}O_2N$ 256.13430; Found 256.13434.

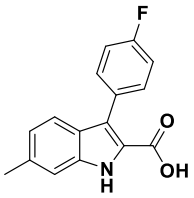
4.4.5 Modifications to positions C4-6 of indole carboxylates

Methyl 3-(4-fluorophenyl)-6-methyl-1*H*-indole-2-carboxylate (S26)



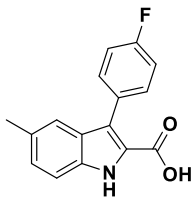
A mixture of methyl 3-iodo-6-methyl-1*H*-indole-2-carboxylate[17] (80 mg, 0.25 mmol, 1.0 eq), 4-fluorophenylboronic acid (43 mg, 0.3 mmol, 1.2 eq), 2 M aq Na_2CO_3 (0.51 mL, 1.02 mmol, 4.0 eq), and $Pd(dppf)Cl_2$ (9.3 g, 0.01 mmol, 4 mol%) in 1,4-dioxane (2.2 mL) was purged with argon, then subjected to microwave irradiation at 100 °C for 1 h. The resultant mixture was filtered through Celite®, eluting with EtOAc and water. The filtrate was partitioned between EtOAc and 1 M aq HCl. The organics were extracted, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FCC (EtOAc-heptane, 0-25%) to afford the desired product **S26** in 87% isolated yield (63 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.84 (1H, br. s, N*H*), 7.60 – 7.45 (3H, m, Ar-*H*), 7.25 (1H, s, Ar-*H*), 7.22 – 7.12 (2H, m, Ar-*H*), 7.02 (1H, d, *J*= 8.5 Hz, Ar-*H*), 3.84 (3H, s, OC*H*$_3$), 2.51 (3H, m, Ar-C*H*$_3$); **LRMS** $[M+H]^+$ 284.20.

3-(4-Fluorophenyl)-6-methyl-1*H*-indole-2-carboxylic acid (27)



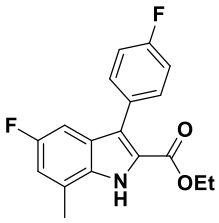
To a solution of the indole ester **S26** (60 mg, 0.21 mmol, 1.0 eq) in THF (1.4 mL) and MeOH (0.7 mL) was added 2 M NaOH (0.53 mL, 1.06 mmol, 5 eq). The resultant mixture was stirred at room temperature for 24 h, then treated with 1 M aq HCl and concentrated to remove organic solvents. The resultant solid was collected by filtration, washed with water, then air dried for 20 min prior to further drying under vacuum at 60 °C overnight. The desired product **27** was obtained in 80% isolated yield as a white solid (45 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm12.81 (1H, br. s, COO*H*), 11.68 (1H, s, N*H*), 7.51 (2H, dd, *J*= 8.5, 6.0 Hz, Ar-*H*), 7.34 (1H, d, *J*= 8.5 Hz, Ar-*H*), 7.30 – 7.18 (3H, m, Ar-*H*), 6.92 (1H, d, *J*= 8.5 Hz, Ar-*H*), 2.41 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.8 (*C*O_2H), 160.7 (d, J_{FC}= 243.0 Hz), 136.3, 134.3, 130.2 (d, J_{FC}= 3.0 Hz), 123.1, 120.8, 132.3 (d, J_{FC}= 8.0 Hz), 125.0, 122.4, 120.0, 114.6 (d, J_{FC}= 21.0 Hz, Ar-*C*H), 112.0 (Ar-*C*), 21.5 (*C*H_3); **LRMS** $[M+H]^+$ 270.15; **HRMS** (TOF, ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}O_2NF$ 270.09248; Found 270.09262.

3-(4-Fluorophenyl)-5-methyl-1*H*-indole-2-carboxylic acid (28)



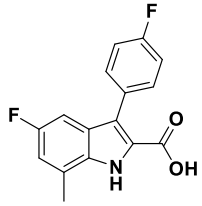
Method J using the corresponding ethyl ester (27 mg, 0.09 mmol) for 2 h at 50 °C and after acidification and purification by preparative HPLC afforded the desired compound **28** in 49% yield as an off-white solid (12 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.63 (1H, br. s, N*H*), 7.59 - 7.47 (2H, m, Ar-*H*), 7.37 (1H, d, *J*= 8.5 Hz, Ar-*H*), 7.31 - 7.18 (3H, m, Ar-*H*), 7.15 - 7.05 (1H, m, Ar-*H*), 2.34 (3H, s, Ar-C*H*$_3$); **LCMS** $[M+H]^+$ 270.20.

Ethyl 5-fluoro-3-(4-fluorophenyl)-7-methyl-1*H*-indole-2-carboxylate (S27)



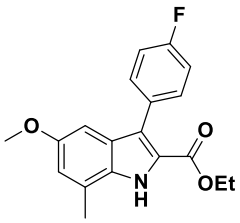
Method A using 4-fluoro-2-methylaniline (0.35 mL, 3.15 mmol) followed by purification by FCC (CH_2Cl_2 in heptane, 15-75%) gave the desired compound **S27** in 46% isolated yield as a pale brown solid (304 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.86 (1H, br. s, N*H*), 7.55 – 7.45 (2H, m, Ar-*H*), 7.21 – 7.12 (2H, m, Ar-*H*), 7.07 (1H, dd, *J*= 9.5, 2.0 Hz, Ar-*H*), 6.98 (1H, dd, *J*= 9.5, 1.5 Hz, Ar-*H*), 4.32 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 2.57 (3H, s, Ar-C*H*$_3$), 1.26 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$); **LRMS** $[M+H]^+$ 316.30.

5-Fluoro-3-(4-fluorophenyl)-7-methyl-1*H*-indole-2-carboxylic acid (29)



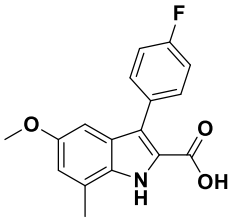
To a solution of indole ester **S27** (304 mg, 0.96 mmol, 1.0 eq) in THF (4.0 mL) and MeOH (4.0 mL) was added 2 M NaOH (4.0 mL, 8.0 mmol, 8 eq); the solution was then stirred at 50 °C for 2 h. The mixture was cooled to room temperature, then quenched with 5 aq M HCl (2.0 mL) and treated with water until a small quantity of orange solid precipitated, which was removed by filtration. The filtrate was concentrated under reduced pressure until a large quantity of pale yellow solid precipitated out of solution. This was filtered and the precipitate washed with water and a small volume of 3:1 water/MeOH. The solid obtained was dried under reduced pressure to afford the desired product **29** in 70% isolated yield as a pale brown solid (220 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 11.75 (1H, s, N*H*), 7.48 (2H, ddd, *J*= 8.5, 5.5, 2.5 Hz, Ar-*H*), 7.28 – 7.22 (2H, m, Ar-*H*), 7.01 – 6.96 (1H, m, Ar-*H*), 6.91 (1H, dd, *J*= 9.5, 2.5 Hz, Ar-*H*), 2.56 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.6, 162.0, 160.4, 158.3, 156.7, 132.2, 132.2, 132.1, 130.0, 126.8, 126.7, 125.6, 124.7, 124.7, 121.3, 121.3, 114.7, 114.6, 114.0, 113.8, 101.5, 101.4, 16.9; **LRMS** $[M-H]^-$ 286.20; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_{10}O_2NF_2$ 286.06851; Found 286.06833.

Ethyl 3-(4-fluorophenyl)-5-methoxy-7-methyl-1*H*-indole-2-carboxylate (S28)



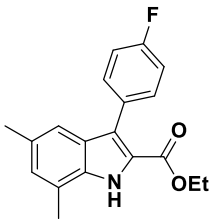
Method A using 4-methoxy-2-methylaniline (0.41 mL, 3.15 mmol) followed by purification by FCC (EtOAc in heptane, 15-75%) gave the desired compound **S28** in 42% isolated yield as a pale brown solid (289 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.71 (1H, br. s, N*H*), 7.48 – 7.36 (2H, m, Ar-*H*), 7.14 – 7.02 (2H, m, Ar-*H*), 6.78 (1H, d, *J*= 1.0 Hz, Ar-*H*), 6.70 (1H, d, *J*= 2.0 Hz, Ar-*H*), 4.21 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 3.70 (3H, s, Ar-OC*H*$_3$), 2.44 (3H, s, Ar-C*H*$_3$), 1.16 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$); **LRMS** $[M+H]^+$ 328.20.

3-(4-Fluorophenyl)-5-methoxy-7-methyl-1*H*-indole-2-carboxylic acid (30)



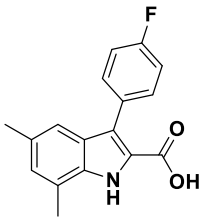
To a solution of indole ester **S28** (287 mg, 0.88 mmol, 1.0 eq) in THF (4.0 mL) and MeOH (4.0 mL) was added 2 M NaOH (4.0 mL, 8.0 mmol, 9 eq); the solution was then stirred at 50 °C for 2 h. The mixture was cooled to room temperature, then quenched with 5 M aq HCl and concentrated to remove organic solvent. The resultant aqueous suspension was filtered and washed with a small volume of 1:1 MeOH/water to afford a mixture of brown solids. The solids were dissolved in a minimum amount of hot EtOH and water was added until a pale brown solid precipitated from solution. The solid was collected by filtration and washed with 3:1 water/EtOH, then dried under vacuum to afford the product, which indicated 90% purity by LCMS. This material was re-purified by preparative HPLC to afford the desired product **30** in 29% isolated yield as a pale yellow solid (75 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 11.48 (1H, s, N*H*), 7.49 (2H, ddd, *J*= 8.5, 5.5, 2.5 Hz, Ar-*H*), 7.27 – 7.21 (2H, m, Ar-*H*), 6.76 (1H, dd, *J*= 2.5, 1.0 Hz, Ar-*H*), 6.63 (1H, d, *J*= 2.5 Hz, Ar-*H*), 3.67 (3H, s, Ar-OC*H*$_3$), 2.51 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.8, 161.9, 160.3, 154.3, 132.2, 132.2, 131.0, 130.6, 130.6, 127.0, 124.3, 123.6, 121.0, 116.5, 114.6, 114.5, 97.5, 55.1, 17.0; **LRMS** $[M+H]^+$ 300.15; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{13}O_3NF$ 298.08849; Found 298.08823.

Ethyl 3-(4-fluorophenyl)-5,7-dimethyl-1*H*-indole-2-carboxylate (S29)



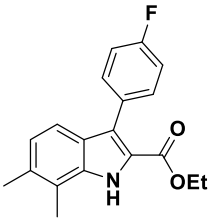
Method A using 2,4-dimethylaniline (0.39 mL, 3.15 mmol) followed by purification by FCC (CH_2Cl_2 in heptane, 10-75%) gave the desired compound **S29** in 34% isolated yield as a yellow solid (220 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.79 (1H, br. s, N*H*), 7.59 – 7.44 (2H, m, Ar-*H*), 7.24 – 7.10 (3H, m, Ar-*H*), 7.03 (1H, s, Ar-*H*), 4.31 (2H, q, *J*= 7.5 Hz, OC*H*$_2$CH$_3$), 2.54 (3H, s, Ar-C*H*$_3$), 2.41 (3H, s, Ar-C*H*$_3$), 1.26 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$); **LRMS** $[M+H]^+$ 312.20.

3-(4-Fluorophenyl)-5,7-dimethyl-1*H*-indole-2-carboxylic acid (31)



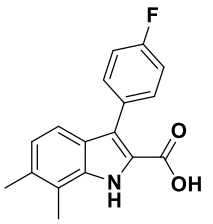
To a solution of indole ester **S29** (220 mg, 0.71 mmol, 1.0 eq) in THF (4.0 mL) and MeOH (4.0 mL) was added 2 M NaOH (4.0 mL, 8.0 mmol, 11 eq); the solution was then stirred at 50 °C for 2 h. The mixture was cooled to room temperature, then quenched with 5 M HCl (2 mL) and concentrated to remove organic solvents. The suspension was filtered and the solids were dissolved in a minimum volume of MeOH. Water was then added to the solution to precipitate a pale yellow solid, which was filtered. The solids obtained were washed with water, then dried under vacuum to afford the desired product **31** in 62% isolated yield as a pale yellow solid (125 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 11.46 (1H, s, N*H*), 7.47 (2H, ddd, *J*= 8.5, 5.5, 2.5 Hz, Ar-*H*), 7.25 (2H, tt, *J*= 9.5, 3.0 Hz, Ar-*H*), 7.01 (1H, s, Ar-*H*), 6.91 (1H, s, Ar-*H*), 2.51 (3H, s, Ar-C*H*$_3$), 2.30 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.8, 161.9, 160.3, 134.0, 132.3, 132.2, 130.6, 130.6, 129.3, 127.2, 127.2, 123.9, 121.9, 120.9, 116.8, 114.6, 114.4, 21.1, 17.0; **LRMS** $[M-H]^-$ 282.20; **HRMS** (TOF,ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{13}O_2NF$ 282.09358; Found 282.09332.

Ethyl 3-(4-fluorophenyl)-6,7-dimethyl-1*H*-indole-2-carboxylate (S30)



Method A using 2,3-dimethylaniline (0.14 mL, 1.15 mmol) followed by purification by FCC (CH_2Cl_2 in heptane, 0-100%) gave the desired compound **S30** in 21% isolated yield as an off-white solid (69.7 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.77 (1H, br. s, N*H*), 7.58 – 7.47 (2H, m, Ar-*H*), 7.34 (1H, d, *J*= 8.5 Hz, Ar-*H*), 7.15 (2H, t, *J*= 8.5 Hz, Ar-*H*), 7.02 (1H, t, *J*= 8.5 Hz, Ar-*H*), 4.32 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 2.46 (6H, d, *J*= 9.5 Hz, 2xAr-C*H*$_3$), 1.27 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

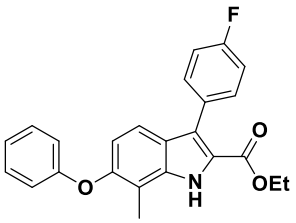
3-(4-Fluorophenyl)-6,7-dimethyl-1*H*-indole-2-carboxylic acid (32)



To a solution of indole ester **S30** (66.7 mg, 0.21 mmol, 1.0 eq) in THF (1.4 mL) and EtOH (0.7 mL) was added 2 M aq NaOH (0.54 mL, 1.08 mmol, 5.0 eq), then stirred at room temperature for 20 h, after which LCMS indicated some starting material remaining. Additional 2 M aq NaOH (0.54 mL, 1.08 mmol, 5.0 eq) was added and stirred for 3 days. The mixture was quenched with 1 M aq HCl (4 mL), then concentrated to remove the organic solvent. The resultant precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired compound **32** was obtained in 86% isolated yield as a yellow solid (52 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.76 (1H, br. s, COO*H*), 11.33 (1H, s, N*H*), 7.48 (2H, dd, *J*= 8.5, 6.0 Hz, Ar-*H*), 7.25 (2H, t, *J*= 9.0 Hz, Ar-*H*), 7.15 (1H, d, *J*= 8.5 Hz, Ar-*H*), 6.92 (1H, d, *J*= 8.5 Hz, Ar-*H*), 2.47 (3H, s, Ar-C*H*$_3$), 2.33 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (*C*O$_2$H), 160.7 (d, J_{FC}= 243.0 Hz, Ar-*C*F), 136.3, 132.0, 130.5 (d, J_{FC}= 3.0 Hz), 125.5, 123.5, 121.5, 119.7 (Ar-*C*), 132.3 (d, J_{FC}= 8.0 Hz), 123.6, 117.1, 114.5 (d, J_{FC}= 21.0 Hz, Ar-*C*H), 19.3 (*C*H$_3$), 13.2 (*C*H$_3$);

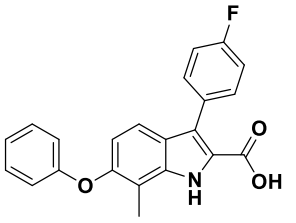
[M+H]$^+$ 284.15; **HRMS** (TOF, ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{15}O_2NF$ 284.10813; Found 284.10831.

Ethyl 3-(4-fluorophenyl)-7-methyl-6-phenoxy-1*H*-indole-2-carboxylate (S31)



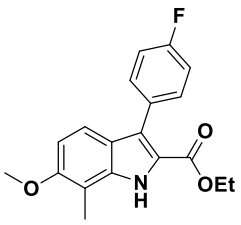
Method A using 2-methyl-3-phenoxyaniline (230 mg, 1.15 mmol) followed by purification by FCC (EtOAc in heptane, 0-15%) gave the desired compound **S31** in 38% isolated yield as an off-white solid (154 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.88 (1H, br. s, N*H*), 7.58 – 7.49 (2H, m, Ar-*H*), 7.41 (1H, d, *J*= 9.0 Hz, Ar-*H*), 7.35 – 7.25 (2H, m, Ar-*H*), 7.16 (2H, t, *J*= 9.0 Hz, Ar-*H*), 7.08 – 7.01 (1H, m, Ar-*H*), 6.98 (1H, t, *J*= 9.0 Hz, Ar-*H*), 6.93 (1H, d, *J*= 8.0 Hz, Ar-*H*), 6.87 (1H, d, *J*= 9.0 Hz, Ar-*H*), 4.33 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 2.44 (3H, s, Ar-C*H*$_3$), 1.27 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

3-(4-Fluorophenyl)-7-methyl-6-phenoxy-1*H*-indole-2-carboxylic acid (33)



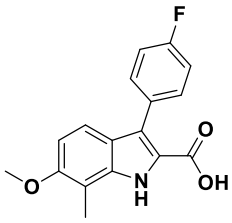
To a solution of indole ester **S31** (150 mg, 0.39 mmol, 1.0 eq) in THF (2.6 mL) and EtOH (1.3 mL) was added 2 M aq NaOH (0.96 mL, 1.95 mmol, 5.0 eq), then stirred at room temperature for 42 h. The mixture was quenched with 5 M HCl (2 mL), then concentrated to remove the organic solvent. The resultant precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired compound **33** was obtained in 98% isolated yield as a yellow solid (137 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.87 (1H, br. s, COO*H*), 11.70 (1H, s, N*H*), 7.52 (2H, dd, *J*= 8.5, 5.5 Hz, Ar-*H*), 7.36 – 7.20 (5H, m, Ar-*H*), 7.06 – 6.99 (1H, m, Ar-*H*), 6.85 (2H, d, *J*= 8.0 Hz, Ar-*H*), 6.76 (1H, d, *J*= 8.5 Hz, Ar-*H*), 2.40 (3H, s, Ar-C*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (*C*O$_2$H), 161.3 (d, *J* = 243.0 Hz, Ar-*C*F), 158.4, 150.3, 136.5, 124.6, 124.2, 121.8, 113.7 (Ar-*C*), 132.3 (d, *J* = 8.0 Hz, Ar-*C*H), 130.1 (d, *J* = 3.0 Hz, Ar-*C*), 129.8, 122.0, 118.9, 116.2, 115.2 (Ar-*C*H), 114.6 (d, *J* = 21.5 Hz, Ar-*C*H), 10.4 (*C*H$_3$); **LRMS** [M+H]$^+$ 362.25; **HRMS** (TOF, ESI$^+$) *m/z*: [M+Na]$^+$ Calcd for $C_{22}H_{16}O_3NFNa$ 384.10064; Found 384.10080.

Ethyl 3-(4-fluorophenyl)-6-methoxy-7-methyl-1*H*-indole-2-carboxylate (S32)



Method A using 3-methoxy-2-methylaniline (432 mg, 3.15 mmol) followed by purification by FCC (CH_2Cl_2 in heptane, 0-75%) gave the desired compound **S32** in 27% isolated yield as an off-white solid (186 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.68 (1H, br. s, N*H*), 7.58 – 7.48 (2H, m, Ar-*H*), 7.39 (1H, d, *J*= 9.0 Hz, Ar-*H*), 7.21 – 7.10 (2H, m, Ar-*H*), 6.91 (1H, d, *J*= 9.0 Hz, Ar-*H*), 4.31 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 3.93 (3H, s, Ar-OC*H*$_3$), 2.42 (3H, s, Ar-C*H*$_3$), 1.27 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

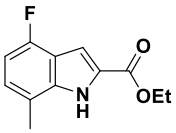
3-(4-Fluorophenyl)-6-methoxy-7-methyl-1*H*-indole-2-carboxylic acid (34)



To a solution of indole ester **S32** (180 mg, 0.55 mmol, 1.0 eq) in THF (3.7 mL) and EtOH (1.8 mL) was added 2 M NaOH (2.75 mL, 5.55 mmol, 10.0 eq), then stirred at room temperature for 4 days. The mixture was quenched with 5 M HCl (2 mL), then concentrated to remove the organic solvent. The resultant precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired compound **34** was obtained in 98% isolated yield as a white solid (161 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.71 (1H, br. s, COO*H*), 11.28 (1H, s, N*H*), 7.55 – 7.43 (2H, m, Ar-*H*), 7.33 – 7.15 (3H, m, Ar-*H*), 6.91 (1H, d, *J*= 9.0 Hz, Ar-*H*), 3.82 (3H, s, Ar-OC*H*$_3$), 2.38

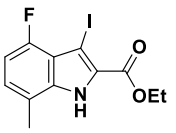
(3H, s, Ar-CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.8 (CO_2H), 161.2 (d, J_{FC}= 243.0 Hz), 154.8, 136.8, 132.3 (d, J_{FC}= 8.0 Hz), 130.4 (d, J_{FC}= 3.0 Hz), 123.6, 122.2, 121.7, 118.1, 114.6 (d, J_{FC}= 21.0 Hz), 108.0, 107.7 (Ar-C), 56.4 (OCH_3), 9.9 (CH_3); **LRMS** $[M+H]^+$ 300.15; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{14}O_3NFNa$ 322.08499; Found 322.08497.

Ethyl 4-fluoro-7-methyl-1*H*-indole-2-carboxylate (S33)



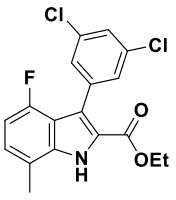
To a solution of 4-fluoro-2-methylaniline (2.0 g, 16.0 mmol) in anhydrous DMSO (5 mL) with 4 Å molecular sieves (5 g) was added ethyl pyruvate (3.07 ml, 32.0 mmol, 2.0 eq.) under argon and the reaction mixture heated at 80 °C for 2 h 15 mins and then cooled and filtered to another flask charged with palladium acetate (732 mg, 3.2 mmol, 0.20 eq) and copper diacetate (3.55 g, 19.2 mmol, 1.2 eq.) and then rinsed with anhydrous DMSO (10 mL); 4 Å molecular sieves (1.0 g) was then added. The reaction mixture was stirred at 80 °C for 15 h to afford a dark brown solution which was filtered through a pad of Celite®, washed with EtOAc (100 ml) and the organics were washed sequentially with 1 aq M HCl (40 ml), water (2 x 50 ml) and brine (2x 50 ml), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting brown oil was purified by automated FCC (heptane/EtOAc gradient: 5→20%) to afford the desired product **S33** in 14% yield as a yellow oil (492 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (1H, br s), 7.30 (1H, d, J = 2.2 Hz), 7.03 – 6.98 (1H, m), 6.72 (1H, dd, J = 10.1, 7.9 Hz), 4.43 (2H, q, J = 7.1 Hz), 2.50 – 2.46 (3H, m), 1.43 (3H, t, J = 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.0, 155.9 (d, J_{CF}= 248.0 Hz), 138.4 (d, J_{CF}= 9.8 Hz), 127.5, 125.8 (d, J_{CF}= 7.4 Hz), 117.1 (d, J_{CF}= 4.3 Hz), 116.9 (d, J_{CF}= 23.0 Hz), 105.3 (d, J_{CF}= 4.2 Hz), 105.1, 61.4, 16.3, 14.5; **LRMS** $[M+H]^+$ 221.1.

Ethyl 4-fluoro-3-iodo-7-methyl-1*H*-indole-2-carboxylate (S34)



To a solution of indole **S33** (482 mg, 2.2 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon was added *N*-iodosuccinimide (490 mg, 2.2 mmol, 1.0 eq.) at room temperature and the reaction was stirred for 19 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with sat aq $NaHCO_3$ (15 ml), water, then brine and dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the desired compound **S34** in 93% isolated yield as a brown solid (700 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.09 (1H, s), 7.05 – 6.95 (1H, m), 6.75 (1H, dd, J = 7.9, 11.2 Hz), 4.47 (2H, q, J= 7.1 Hz), 2.46 – 2.43 (3H, m), 1.48 (3H, t, J= 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.0, 156.0 (d, J_{CF}= 251.6 Hz), 137.8 (d, J_{CF}= 8.0 Hz), 127.6, 126.4 (d, J_{CF}= 7.7 Hz), 119.8 (d, $J_{C,F}$ = 16.7 Hz), 117.3 (d, J_{CF}= 4.6 Hz), 106.5 (d, J_{CF}= 19.1 Hz), 61.9, 57.4 (d, J_{CF}= 4.0 Hz), 16.2, 14.5; **LRMS** $[M+H]^+$ 348.0.

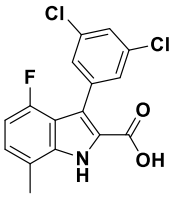
Ethyl 3-(3,5-dichlorophenyl)-4-fluoro-7-methyl-1*H*-indole-2-carboxylate (S35)



Iodoindole **S34** (400 mg, 1.15 mmol), 3,5-dichlorophenylboronic acid (220 mg, 1.15 mmol, 1.0 eq) and Pd(dppf)Cl_2 (42 mg, 0.058 mmol, 0.05 eq.) were weighed into a microwave tube and 1,4-dioxane (3 ml) and 2 M aq Na_2CO_3 (1.65 ml) were added. The reaction mixture was heated under microwave irradiation for 1 h at 100 °C, cooled, filtered through a pad of Celite® eluting with EtOAc; the organic layer was then washed with 1 M aq HCl (20 ml), brine (2 x 20 ml), dried (Na_2SO_4), filtered and concentrated. The resulting brown oil was purified by FCC (heptane/EtOAc 10 to 20%) to afford the desired compound **S35** in 55% yield as an orange solid (231 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.01 (1H, br s), 7.41 – 7.39 (2H, m), 7.38 – 7.36 (1H, m), 7.08 – 7.02 (1H, m), 6.72 (1H, dd, J = 11.1, 7.9 Hz), 4.28 (2H, q, J = 7.1 Hz), 2.52 – 2.49 (3H,

m), 1.23 (3H, t, J = 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.6, 156.1 (d, J_{CF}= 250.0 Hz), 137.0 (d, J_{CF}= 9.0 Hz), 136.8 (d, J_{CF}= 1.8 Hz), 133.6, 129.6 (d, J_{CF}= 1.9 Hz), 127.4, 126.4 (d, J_{CF}= 7.7 Hz), 123.8, 119.6 (d, J_{CF}= 3.1 Hz), 117.2 (d, J_{CF}= 4.4 Hz), 116.1 (d, J_{CF}= 18.3 Hz), 106.3 (d, J_{CF}= 19.2 Hz), 61.5, 16.2, 14.0; **LRMS** $[M+H]^+$ 365.9.

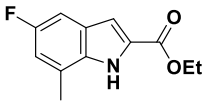
3-(3,5-Dichlorophenyl)-4-fluoro-7-methyl-1*H*-indole-2-carboxylic acid (35)



To a solution of indole carboxylate ester **S35** (216 mg, 0.59 mmol) in THF (5 ml) and EtOH (2 mL) was added 2 M aq NaOH (3 ml) and the reaction was stirred at room temperature for 24 h and then poured into 1 M aq HCl (20 mL); the resultant precipitate was filtered and washed with water. The crude precipitate was purified by recrystallization (heptane/acetone 5:1) to afford the desired compound **35** in 64% isolated yield as colorless crystals (127 mg).

^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.40 – 7.37 (3H, m), 7.05 – 6.99 (1H, m), 6.66 (1H, dd, J = 11.4, 7.9 Hz), 2.54 – 2.51 (3H, m); **^{13}C NMR** (101 MHz, CD_3OD) δ ppm 164.1, 157.1 (d, J_{CF}= 247.1 Hz), 139.5 (d, $J_{C,F}$ = 1.4 Hz), 139.0 (d, J_{CF}= 9.1 Hz), 134.6, 130.7 (d, J_{CF}= 1.8 Hz), 127.7, 126.6 (d, J_{CF}= 7.8 Hz), 126.2, 120.1 (d, J_{CF}= 3.1 Hz), 119.6 (d, J_{CF}= 4.4 Hz), 117.1 (d, J_{CF}= 17.9 Hz), 106.4 (d, J_{CF}= 19.2 Hz), 16.7; **HRMS** (TOF-ESI$^-$): calcd for $C_{16}H_9NO_2FCl_2$ [*M*-H]$^-$: 335.9994, found: 335.9989.

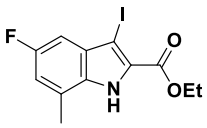
Ethyl 5-fluoro-7-methyl-1*H*-indole-2-carboxylate (S36)



To a solution of 5-fluoro-2-methylaniline (2.0 g, 16.0 mmol) in anhydrous DMSO (7.5 mL) with 4 Å molecular sieves (5 g) was added ethyl pyruvate (3.77 ml, 32.0 mmol, 2.0 eq.) under argon and the reaction mixture heated at 80 °C for 2 h and then cooled and filtered to another flask charged with palladium acetate (732 mg, 3.2 mmol, 0.20 eq) and copper diacetate (4.44 g, 24.0 mmol, 1.2 eq.) and rinsed with anhydrous DMSO (7.5 mL); 4 Å molecular sieves (1 g) were then added. The reaction mixture was stirred at 80 °C for 15 h to afford a dark brown solution which was filtered through a pad of Celite®, washed with EtOAc (100 ml) and the organics were washed sequentially with 1 M aq HCl (40 ml), water (2 x 50 ml) and brine (2x 50 ml), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting brown oil was purified by FCC (heptane/EtOAc gradient: 5→20%) to afford the desired product **S36** in 39% yield as a yellow oil (1.39 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (1H, br s), 7.19-7.13 (2H, m), 6.90 (1H, ddd, J = 1.0, 2.4, 9.8 Hz), 4.42 (2H, q, J = 7.1 Hz), 2.56 – 2.50 (3H, m), 1.42 (3H, t, J = 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.1, 158.3 (d, J_{CF}= 236.5 Hz), 133.4, 128.7, 127.2 (d, J_{CF}= 10.9 Hz), 123.0 (d, J_{CF}= 9.5 Hz), 114.8 (d, J_{CF}= 26.7 Hz), 109.1 (d, J_{CF}= 5.5 Hz), 104.3 (d, J_{CF}= 23.3 Hz), 61.3, 16.9 (d, J_{CF}= 1.5 Hz), 14.5; **LRMS** $[M+H]^+$ 347.9.

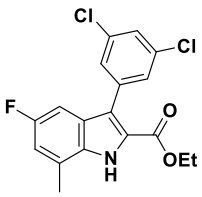
Ethyl 5-fluoro-3-iodo-7-methyl-1*H*-indole-2-carboxylate (S37)



To a solution of indole **S36** (1.0 g, 4.5 mmol) in anhydrous CH_2Cl_2 (20 mL) under argon was added *N*-iodosuccinimide (1.0 mg, 4.5 mmol, 1.0 eq.) at room temperature and the reaction was stirred for 19 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with sat aq $NaHCO_3$ (15 ml), and brine and dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the desired compound **S37** in 93% yield as a red solid (1.46 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.09 (1H, br s), 7.09 – 7.04 (1H, m), 6.97 – 6.93 (1H, m), 4.47 (2H, q, J = 7.1 Hz), 2.53 – 2.49 (3H, m), 1.48 (3H, t, J = 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 160.9, 158.9 (d, J_{CF}= 238.6 Hz), 132.5, 131.7 (d, J_{CF}= 11.0 Hz), 128.5, 123.4 (d, J_{CF}= 9.3 Hz), 116.1 (d, J_{CF}= 26.8 Hz), 105.7 (d, J_{CF}= 24.4 Hz), 65.8 (d, J_{CF}= 5.6 Hz), 61.8, 16.5 (d, J_{CF}= 1.4 Hz), 14.5; **LRMS** $[M+H]^+$ 221.1.

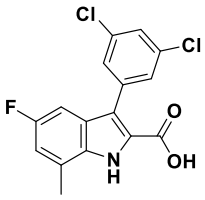
Ethyl 3-(3,5-dichlorophenyl)-5-fluoro-7-methyl-1*H*-indole-2-carboxylate (S38)



Iodoindole **S37** (650 mg, 1.87 mmol), 3,5-dichlorophenylboronic acid (357 mg, 1.87 mmol, 1.0 eq) and Pd(dppf)Cl_2 (69 mg, 0.094 mmol, 0.05 eq.) were weighed into a microwave tube and 1,4-dioxane (3 ml) and 2 M aq Na_2CO_3 (1.65 ml) were added. The reaction mixture was heated under microwave irradiation for 1 h at 100 °C, cooled, filtered through a pad of Celite® eluting with EtOAc; the organic layer was then washed with 1 M HCl (30 ml), brine (2 x 30 ml), dried (Na_2SO_4), filtered and concentrated. The resulting brown oil was purified by FCC (heptane/EtOAc 10 to 20%) to afford the desired compound **S38** in 64% isolated yield as an off-white solid (437 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.99 (1H, br s), 7.44 – 7.36 (3H, m), 7.09 – 7.05 (1H, m), 6.99 – 6.94 (1H, m), 4.32 (2H, q, J= 7.1 Hz), 2.56 – 2.54 (3H, m), 1.27 (3H, t, J = 7.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.7, 158.9 (d, J_{CF}= 238.3 Hz), 136.5, 134.4, 132.1, 129.1, 127.4, 127.2 (d, J_{CF}= 10.3 Hz), 124.5, 123.3 (d, J_{CF}= 9.3 Hz), 121.3 (d, J_{CF}= 5.8 Hz), 115.7 (d, $J_{C,F}$ = 26.8 Hz), 103.0 (d, $J_{C,F}$ = 24.0 Hz), 61.6, 16.8 (d, $J_{C,F}$ = 1.4 Hz), 14.1; **LRMS** $[M+H]^+$ 366.0.

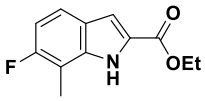
3-(3,5-Dichlorophenyl)-5-fluoro-7-methyl-1*H*-indole-2-carboxylic acid (36)



To a solution of indole carboxylate ester **S38** (398 mg, 1.09 mmol) in THF (7 ml) and EtOH (3 mL) was added 2 M aq NaOH (5 ml) and the reaction was stirred at rt for 18 h and then poured into 1 M aq HCl (20 mL); the resultant precipitate was filtered and washed with water. The crude precipitate was purified by recrystallization (heptane/acetone 5:1, 6 mL) to afford the desired compound **36** in 42% yield as colorless crystals (156 mg).

^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.48 – 7.40 (3H, m), 6.97 – 6.89 (2H, m), 2.54 – 2.50 (3H, m); **^{13}C NMR** (101 MHz, CD_3OD) δ ppm 164.2, 160.1 (d, J_{CF}= 236.0 Hz), 139.1, 135.5, 134.0, 130.2, 128.2 (d, J_{CF}= 10.3 Hz), 127.8, 127.0, 125.9 (d, J_{CF}= 9.3 Hz), 121.9 (d, J_{CF}= 5.6 Hz), 115.8 (d, J_{CF}= 26.8 Hz), 102.6 (d, J_{CF}= 23.9 Hz), 17.2 (d, J_{CF}= 1.4 Hz); **HRMS** (TOF-ESI$^+$): calcd for $C_{16}H_{11}NO_2FCl_2$ $[M+H]^+$: 338.0151, found: 338.0149.

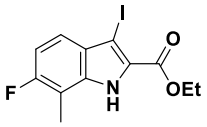
Ethyl 6-fluoro-7-methyl-1*H*-indole-2-carboxylate (S39)



To a solution of 3-fluoro-2-methylaniline (2.0 g, 16.0 mmol) in anhydrous DMSO (5 mL) with 4 Å molecular sieves (5 g) was added ethyl pyruvate (3.07 ml, 32.0 mmol, 2.0 eq.) under argon and the reaction mixture heated at 80 °C for 2 h 15 min and then cooled and filtered to another flask charged with palladium acetate (732 mg, 3.2 mmol, 0.20 eq) and copper diacetate (3.55 g, 19.2 mmol, 1.2 eq.) and rinsed with anhydrous DMSO (10 mL); 4 Å molecular sieves (1 g) were then added. The reaction mixture was stirred at 80 °C for 15 h to afford a dark brown solution which was filtered through a pad of Celite®, washed with EtOAc (100 ml) and the organics were washed sequentially with 1 M aq HCl (40 ml), water (2 x 50 ml) and brine (2x 50 ml), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting brown oil was purified by automated FCC (heptane/EtOAc gradient: 2→20%) to afford the desired product **S39** in 9.4% yield as a yellow solid (333 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.95 (1H, br s), 7.52 – 7.38 (1H, m), 7.20 (1H, d, J= 2.2 Hz), 6.91 (1H, dd, J = 10.1, 8.7 Hz), 4.42 (2H, q, J= 7.1 Hz), 2.42 (3H, d, J= 1.7 Hz), 1.42 (3H, t, J= 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1, 159.3 (d, J_{CF}= 240.2 Hz), 137.5 (d, J_{CF}= 9.6 Hz), 128.0 (d, J_{CF}= 3.6 Hz), 123.7, 120.9 (d, J_{CF}= 10.4 Hz), 110.7 (d, J_{CF}= 26.6 Hz), 109.5, 107.0 (d, J_{CF}= 22.0 Hz), 61.2, 14.6, 9.1 (d, J_{CF}= 4.3 Hz); **LRMS** $[M+H]^+$ 221.1.

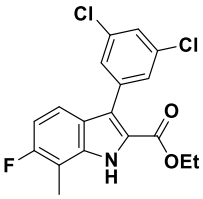
Ethyl 6-fluoro-3-iodo-7-methyl-1*H*-indole-2-carboxylate (S40)



To a solution of indole **S39** (312 mg, 1.4 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon was added *N*-iodosuccinimide (318 mg, 1.4 mmol, 1.0 eq.) at room temperature and the reaction was stirred for 3 days at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with sat. $NaHCO_3$ (15 ml), water, then brine and dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude red solid by recrystallization (heptane EtOAc mixtures) afforded the desired compound **S40** in 59% isolated yield as an off-white solid (287 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (1H, br s), 7.38 – 7.31 (1H, m), 7.02 – 6.95 (1H, m), 4.47 (2H, q, J = 7.1 Hz), 2.41 (3H, d, J= 1.7 Hz), 1.48 (3H, t, J= 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9, 160.0 (d, J_{CF}= 242.0 Hz), 136.4 (d, J_{CF}= 9.7 Hz), 127.9 (d, J_{CF}= 3.7 Hz), 127.8, 122.2 (d, J_{CF}= 10.5 Hz), 111.5 (d, J_{CF}= 26.6 Hz), 107.0 (d, J_{CF}= 22.2 Hz), 66.8, 61.7, 14.5, 8.9 (d, $J_{C,F}$ = 4.1 Hz); **LRMS** $[M+H]^+$ 348.0.

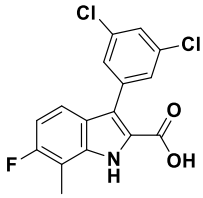
Ethyl 3-(3,5-dichlorophenyl)-6-fluoro-7-methyl-1*H*-indole-2-carboxylate (S41)



Iodoindole **S40** (287.2 mg, 0.83 mmol), 3,5-dichlorophenylboronic acid (157.9 mg, 0.83 mmol, 1.0 eq) and Pd(dppf)Cl_2 (30.3 mg, 0.041 mmol, 0.05 eq.) were weighed into a microwave tube and 1,4-dioxane (3 ml) and 2 M aq Na_2CO_3 (1.65 ml) were added. The reaction mixture was heated under microwave irradiation for 1 h at 100 °C, cooled, filtered through a pad of Celite® eluting with EtOAc; the organic layer was then washed with 1 M aq HCl (20 ml), brine (2 x 20 ml), dried (Na_2SO_4), filtered and concentrated to afford the desired compound **S41** as an off-white solid in quantitative yield (341 mg) which was used with further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 (1H, br s), 7.43 – 7.40 (2H, m), 7.40 – 7.37 (1H, m), 7.37 – 7.33 (1H, m), 6.95 (1H, t, J = 9.4 Hz), 4.32 (2H, d, J= 7.1 Hz), 2.45 (3H, d, J=1.7 Hz), 1.27 (3H, t, J =7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.8, 159.7 (d, J_{CF}= 242 Hz), 136.5, 136.2 (d, J_{CF}= 9.8 Hz), 134.3, 129.2, 127.4, 123.7 (d, J_{CF}= 3.0 Hz), 123.6, 121.6 (d, J_{CF}= 1.3 Hz), 119.7 (d, J_{CF}= 10.6 Hz), 111.4 (d, J_{CF}= 27.2 Hz), 107.1 (d, J_{CF}= 22.4 Hz), 61.5, 14.1, 9.1 (d, J_{CF}= 4.1 Hz); **LRMS** $[M+H]^+$ 366.0.

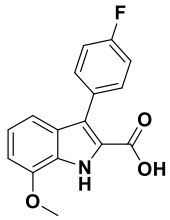
3-(3,5-Dichlorophenyl)-6-fluoro-7-methyl-1*H*-indole-2-carboxylic acid (37)



To a solution of indole carboxylate ester **S41** (283 mg, 0.77 mmol) in THF (3 ml) and EtOH (1 mL) was added 2 M aq NaOH (1.5 ml) and the reaction was stirred at room temperature for 23 h and then poured into 1 M aq HCl (20 mL); the resultant precipitate was filtered and washed with water. The crude precipitate was further purified by FCC (CH_2Cl_2/ MeOH, 0 to 10%) and then recrystallized (heptane/acetone mixture) to afford the desired compound **37** in 50% isolated yield as colorless crystals (130 mg).

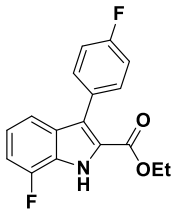
^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.44 – 7.43 (2H, m), 7.42 – 7.41 (1H, m), 7.30 – 7.24 (1H, m), 6.94 – 6.88 (1H, m), 2.47 (3H, d, J = 1.8 Hz); **^{13}C NMR** (101 MHz, CD_3OD) δ ppm 164.3, 160.8 (d, J_{CF}= 238.4 Hz), 139.0, 137.9 (d, J_{CF}= 9.6 Hz), 135.5, 130.3, 127.8, 126.2, 125.0, 122.3, 119.9 (d, J_{CF}= 10.6 Hz), 111.6 (d, J_{CF}= 27.1 Hz), 109.0 (d, J_{CF}= 21.9 Hz), 9.1 (d, J_{CF}= 4.6 Hz); **HRMS** (TOF-ESI$^-$): calcd for $C_{16}H_9NO_2FCl_2$ $[M-H]^-$: 335.9994, found: 335.9991.

3-(4-Fluorophenyl)-7-methoxy-1*H*-indole-2-carboxylic acid (39)



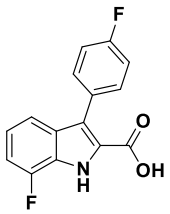
The indole ester was prepared according to **Method B** using 2-methoxyaniline (0.24 mL, 2.1 mmol); purification by FCC (CH_2Cl_2 in heptane, 20-80%) gave the ethyl ester in 17% isolated yield as a yellow solid (108 mg). To a suspension of this indole ester (108 mg, 0.34 mg, 1.0 eq) in EtOH (10 mL) and water (10 mL) was added NaOH (138 mg, 3.45 mmol, 10.0 eq) and the resultant solution stirred at room temperature for 30 min. The reaction mixture was then heated to 50 °C and stirred for 2 h. The reaction mixture was cooled, acidified with 2 M aq HCl, then extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Following purification by FCC (EtOAc in heptane, 0-80%), the desired compound **39** was obtained in 63% isolated yield as a white solid (62 mg).
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.59 (1H, s, N*H*), 7.49 (2H, ddt, *J*= 8.5, 5.0, 3.0 Hz, Ar-*H*), 7.28 – 7.22 (2H, m, Ar-*H*), 7.03 – 6.98 (2H, m, Ar-*H*), 6.85 – 6.80 (1H, m, Ar-*H*), 3.93 (3H, s, OC*H*$_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.5, 162.1, 160.2, 146.7, 132.3, 132.2, 130.3, 130.3, 128.5, 126.7, 124.1, 121.3, 121.1, 114.6, 114.5, 112.4, 104.5, 55.5; **LRMS** $[M-H]^-$ 284.00; **HRMS** (TOF, ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}O_3NF$ 286.08849; Found 286.08749.

Ethyl 7-fluoro-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (S42)



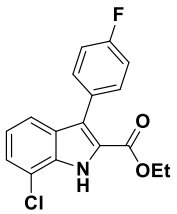
Method B using *o*-fluoroaniline (0.20 mL, 2.1 mmol) followed by purification of part B by FCC (heptane: CH_2Cl_2 10-50%) gave the desired compound **S42** in 13% isolated yield as a yellow solid (84 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.36 – 8.91 (1H, m, N*H*), 7.58 – 7.48 (2H, m, Ar-*H*), 7.41 – 7.33 (1H, m, Ar-*H*), 7.17 (2H, t, *J*= 9.0 Hz, Ar-*H*), 7.12 – 7.05 (2H, m, Ar-*H*) , 4.34 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 1.28 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

7-Fluoro-3-(4-fluorophenyl)-1*H*-indole-2-carboxylic acid (40)



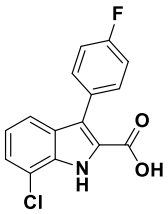
Method C using indole ester **S42** (84 mg, 0.28 mmol) followed by purification by FCC (CH_2Cl_2: EtOAc 0-100%) gave the desired compound **40** in 46% isolated yield as a yellow solid (35 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 12.27 (1H, s, N*H*), 7.56 – 7.46 (2H, m, 1H, Ar-*H*), 7.31 – 7.20 (3H, m, Ar-*H*), 7.11 (1H, dd, *J*= 11.3, 7.7 Hz, Ar-*H*), 7.04 (1H, td, *J*= 7.9, 4.6 Hz, Ar-*H*); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.4, 161.4 (d, J_{CF}= 244 Hz), 149.3 (d, J_{CF}= 247 Hz), 132.4 (d, J_{CF}= 8.0 Hz), 130.8 (d, J_{CF}= 5.4 Hz), 129.8 (d, J_{CF}= 3.2 Hz), 125.7, 124.3 (d, J_{CF}= 13.2 Hz), 121.3, 120.6 (d, J_{CF}= 5.6 Hz), 116.4 (d, J_{CF}= 3.3 Hz), 114.7 (d, J_{CF}= 22.8 Hz), 109.2 (d, J_{CF}= 17.0 Hz); **LRMS** $[M-H]^-$ 272.00; **HRMS** (TOF, ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{15}H_8O_2NF_2$ 272.05286; Found 272.05270.

Ethyl 7-chloro-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (S43)



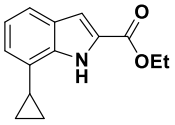
Method B using 2-chloroaniline (0.22 mL, 2.1 mmol) followed by purification of part B by FCC (heptane: CH_2Cl_2 0-50%) gave the desired compound **S43** in 28% isolated yield as a colorless oil (186 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.15 (1H, m, N*H*), 7.58 – 7.48 (3H, m, Ar-*H*), 7.39 (1H, t, *J*= 7.5 Hz, Ar-*H*), 7.23 - 7.05 (3H, m, Ar-*H*) , 4.34 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 1.29 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$).

7-Chloro-3-(4-fluorophenyl)-1*H*-indole-2-carboxylic acid (41)



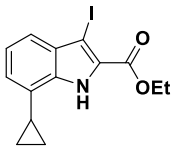
Method C using indole ester **S43** (186 mg, 0.59 mmol) followed by purification by FCC (CH_2Cl_2: MeOH 0-5%) gave the desired compound **41** in 61% isolated yield as a pale yellow solid (103 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.01 (1H, br. s, COO*H*), 11.92 (1H, s, N*H*), 7.57 – 7.47 (2H, m, Ar-*H*), 7.40 (2H, dd, *J*= 8.0, 3.0 Hz, Ar-*H*), 7.28 (2H, t, *J*= 9.0 Hz, Ar-*H*), 7.15 – 7.03 (1H, m, Ar-*H*); **LRMS** $[M-H]^-$ 288.00.

Ethyl 7-cyclopropyl-1*H*-indole-2-carboxylate (S44)



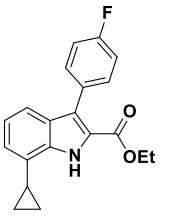
A mixture of 7-bromo-1*H*-indole-2-carboxylate (300 mg, 1.12 mmol. 1.0 eq) cyclopropylboronic acid (102 mg, 2.24 mmol, 2.0 eq), 2 M aq Na_2CO_3 (2.8 mL,5.6 mmol, 5.0 eq) and Pd(dppf)Cl_2 (41 mg, 0.06 mmol, 5 mol%) in 1,4-dioxane (9.7 mL) was purged with argon, then subjected to microwave irradiation at 100 °C for 2 h. The resultant mixture was filtered through Celite, eluting with EtOAc and water. The filtrate was partitioned between EtOAc and 1 M aq HCl. The organics were extracted, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FCC (EtOAc in heptane, 0-15%) to afford the desired product **S44** which coeluted with an impurity, and the mixture was used in the next step without further purification.

Ethyl 7-cyclopropyl-3-iodo-1*H*-indole-2-carboxylate (S45)



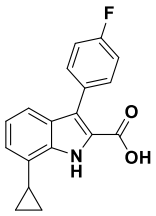
To the crude cyclopropyl indole **S44** (130 mg, 0.57 mmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) was added *N*-iodosuccinimide (134 mg, 0.6 mmol, 1.05 eq). The resultant mixture was stirred at room temperature for 16 h. The mixture was partitioned between EtOAc and sat. aq $NaHCO_3$. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FCC (EtOAc in heptane, 0-10%) to afford the desired product **S45** in 75% isolated yield as a yellow solid (152 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.30 (1H, br. s, N*H*), 7.43 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.23 – 7.14 (1H, m, Ar-*H*), 7.13 – 7.08 (1H, m, Ar-*H*), 4.51 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 2.15 – 2.01 (1H, m, cyclopropyl-C*H*), 1.52 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$), 1.13 – 1.01 (2H, m, cyclopropyl-C*H*$_2$), 0.84 – 0.75 (2H, m, cyclopropyl-C*H*$_2$); **LRMS** $[M+H]^+$ 356.15.

Ethyl 7-cyclopropyl-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (S46)



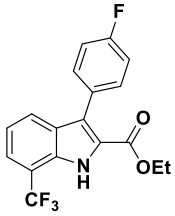
A solution of iodo indole **S45** (90 mg, 0.25 mmol. 1.0 eq), obtained as described above, 4-fluorophenylboronic acid (35 mg, 0.25 mmol, 1.0 eq), 2 M aq Na_2CO_3 (0.5 mL, 1.0 mmol, 4.0 eq) and Pd(dppf)Cl_2 (9.2 mg, 0.01 mmol, 4 mol%) in 1,4-dioxane (2.2 mL) was purged with argon, then subjected to microwave irradiation at 100 °C for 1 h. The resultant mixture was filtered through Celite®, eluting with EtOAc and water. The filtrate was partitioned between EtOAc and 1 M aq HCl. The combined organics were extracted, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FCC (EtOAc in heptane, 0-10%) to afford the desired product **S46** in 71% isolated yield as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.10 (1H, br. s, N*H*), 7.58 – 7.47 (2H, m, Ar-*H*), 7.47 – 7.39 (1H, m, Ar-*H*), 7.18 – 7.05 (4H, m, Ar-*H*), 4.32 (2H, q, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 2.18 – 2.07 (1H, m, cyclopropyl-C*H*), 1.26 (3H, t, *J*= 7.0 Hz, OCH$_2$C*H*$_3$), 1.12 – 0.99 (2H, m, cyclopropyl-C*H*$_2$), 0.88 – 0.76 (2H, m, cyclopropyl-C*H*$_2$).

7-Cyclopropyl-3-(4-fluorophenyl)-1*H*-indole-2-carboxylic acid (42)



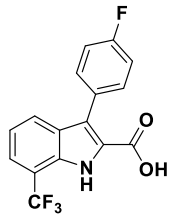
To a solution of the indole ester **S46** (47.5 mg, 0.15 mmol, 1.0 eq) in THF (1.0 mL) and EtOH (0.5 mL) was added 2 M aq NaOH (0.59 mL, 1.18 mmol, 8 eq). The resultant mixture was heated 50 °C for 3 h, then treated with 1 M aq HCl (2 mL) and concentrated to remove organic solvents. The resultant solid was collected by filtration, washed with water, then air dried for 30 min prior to further drying under vacuum at 50 °C. The desired product **42** was obtained in >99% isolated yield as a white solid (45 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.88 (1H, br. s, COO*H*), 11.65 (1H, s, N*H*), 7.56 – 7.44 (2H, m, Ar-*H*), 7.31 – 7.16 (3H, m, Ar-*H*), 6.98 (1H, t, *J*= 7.5 Hz, Ar-*H*), 6.81 (1H, d, *J*= 7.5 Hz, Ar-*H*), 2.70 – 2.57 (1H, m, CH_2CHCH_2), 1.05 – 0.94 (2H, m, CH_2CHCH_2), 0.78 – 0.67 (2H, m, CH_2CHCH_2); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (CO_2H), 161.2 (d, *J* = 243.0 Hz, Ar-*C*F), 136.0, 130.4 (d, *J* = 3.0 Hz), 128.3, 126.8, 124.2, 121.4 (Ar-*C*), 132.3 (d, *J* = 8.0 Hz), 120.8, 118.7, 117.3, 114.6 (d, *J* = 21.0 Hz) (Ar-*C*H), 10.2 (*C*H), 8.2 (CH_2); **LRMS** $[M+H]^+$ 296.15; **HRMS** (TOF, ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{14}O_2NFNa$ 318.09008; Found 318.09012.

Ethyl 3-(4-fluorophenyl)-7-(trifluoromethyl)-1*H*-indole-2-carboxylate (S47)



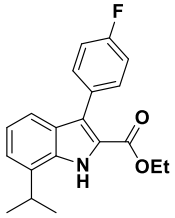
Method B using 2-(trifluoromethyl)aniline (0.26 mL, 2.1 mmol) followed by purification of part B by FCC (heptane: CH_2Cl_2 0-50%) gave the desired compound **S47** in 34% isolated yield as a yellow solid (255 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.22 (1H, br. s, N*H*), 7.78 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.66 (1H, d, *J*= 7.5 Hz, Ar-*H*), 7.57 – 7.43 (2H, m, Ar-*H*), 7.35 – 7.10 (3H, m, Ar-*H*), 4.35 (2H, q, *J*= 7.0 Hz, OCH_2CH_3), 1.28 (3H, t, *J*= 7.0 Hz, OCH_2CH_3); **LRMS** $[M-H]^-$ 350.20.

3-(4-Fluorophenyl)-7-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (43)



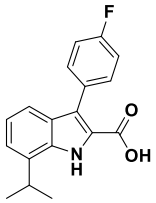
Method C using indole ester **S47** (225 mg, 0.64 mmol) followed by acidification, precipitation and filtration gave the desired compound **43** in 72% isolated yield as an off-white solid (149 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 11.67 (1H, s, N*H*), 7.72 (1H, d, *J*= 8.1 Hz, Ar-*H*), 7.69 (1H, d, *J*= 7.4 Hz, Ar-*H*), 7.52 (2H, ddd, *J*= 8.6, 5.4, 2.6 Hz, Ar-*H*), 7.32 – 7.24 (3H, m, Ar-*H*); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.2 (CO_2H), 161.5 (d, J_{FC}= 235 Hz), 132.3 (d, J_{FC}= 8.2 Hz), 130.5 (q, J_{FC}= 1.8 Hz), 129.2 (d, J_{FC}= 3.2 Hz), 129.0, 126.4, 125.3, 124.1 (q, J_{FC}= 272 Hz), 122.5 (q, J_{FC}= 5.0 Hz), 121.4, 119.9, 114.8 (d, J_{FC}= 21.2 Hz), 113.4 (q, *J*= 32.6 Hz, CF_3); **LRMS** $[M-H]^-$ 322.20; **HRMS** (TOF, ESI^-) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_8O_2NF_4$ 322.04966; Found 322.04941.

Ethyl 3-(4-fluorophenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S48)



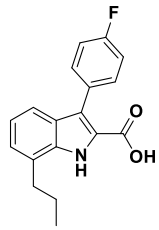
Method H using iodoindole **S5** (100 mg, 0.28 mmol) followed by purification by FCC (CH_2Cl_2 in cyclohexane, 0-100%) gave the desired product **S48** in 85% isolated yield as a brown solid (76 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.00 (1H, s, NH), 7.52 (2H, dd, *J* = 9.0, 6.0 Hz, Ar-C*H*), 7.44 (1H, dt, *J* = 8.0, 1.0 Hz, Ar- C*H*), 7.28 – 7.24 (1H, m, Ar-C*H*), 7.19 – 7.12 (3H, m, Ar-C*H*), 4.32 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.33 (1H, h, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.44 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.3 (CO_2Et), 162.3 (d, *J* = 246.0 Hz), 134.3, 132.2, 129.8 (d, *J* = 3.5 Hz), 128.1, 123.6, 122.7 (Ar-*C*), 132.4 (d, *J* = 8.0 Hz), 121.7, 121.6, 119.2, 114.8 (d, *J* = 21.5 Hz) (Ar-*C*H), 61.1 (OCH_2CH_3), 29.2 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 14.2 (OCH_2CH_3); **LRMS** $[M+H]^+$ 326.25; **HRMS** (TOF, ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{20}O_2NFNa$ 348.13703; Found 348.13708.

3-(4-Fluorophenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (44)



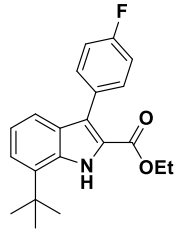
A solution of indole ester **S48** (190 mg, 0.58 mmol, 1.0 eq) in ethanol (4 mL) and water (1 mL) was treated with NaOH (46.7 mg, 1.17 mmol, 2.0 eq), then heated at 70 °C for 2.5 h. The mixture was quenched with 1 M HCl, then twice extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude product was purified by FCC (MeOH in CH_2Cl_2, 0-5%) to afford the desired product **44** in 49% isolated yield as a pale yellow solid (85 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.00 (1H, s, N*H*), 7.60 – 7.52 (2H, m, Ar-*H*), 7.46 (1H, d, *J*= 8.0 Hz,, Ar-*H*), 7.33 – 7.26 (1H, m, Ar-*H*), 7.23 – 7.13 (3H, m, Ar-*H*), 3.33 (1H, hept, *J*= 7.0 Hz, C*H*$(CH_3)_2$), 1.45 (6H, d, *J*= 7.0 Hz, CH(C*H*$_3)_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (*C*O_2H), 161.2 (d, *J* = 243.0 Hz), 134.3, 133.3, 130.4 (d, *J* = 3.0 Hz), 127.2, 124.1, 121.4 (Ar-*C*), 132.3 (d, *J* = 8.0 Hz), 120.8, 120.3, 117.7, 114.6 (d, *J* = 21.0 Hz) (Ar-*C*H), 26.9 (*C*H$(CH_3)_2$), 23.1 (CH(*C*H$_3)_2$); **LC-MS** $[M+H]^+$ 298.15; **HRMS** (TOF, ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{16}O_2NFNa$ 320.10573; Found 320.10583.

3-(4-Fluorophenyl)-7-propyl-1*H*-indole-2-carboxylic acid (45)



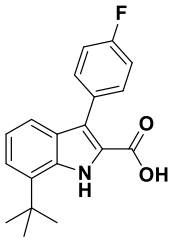
The corresponding indole ester was prepared according to **Method B** using 2-propylaniline (0.15 mL, 1.05 mmol); purification by FCC (CH_2Cl_2 in heptane, 0-50%) gave the indole ethyl ester in 26% isolated yield (90 mg). To a suspension of this indole ester (90 mg, 0.28 mg, 1.0 eq) in EtOH (10 mL) and water (2 mL) was added NaOH (75 mg, 1.88 mmol, 6.7 eq) and the resultant solution heated to 55 °C and stirred for 1.5 h. The reaction mixture was cooled, acidified with 1 M aq HCl, then extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Following purification by FCC (EtOAc in CH_2Cl_2, 0-100%), the desired compound **45** was obtained in 73% isolated yield as an off-white solid (60 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 11.61 (1H, s, N*H*), 7.49 (2H, ddd, *J*= 8.5, 5.5, 2.5 Hz, Ar-*H*), 7.25 (3H, ddd, *J*= 9.0, 7.0, 2.0 Hz, Ar-*H*), 7.08 (1H, d, *J*= 7.0 Hz, Ar-*H*), 7.03 – 6.98 (1H, m, Ar-*H*), 2.99 – 2.90 (2H, m, C*H*$_2$-CH_2-CH_3), 1.65 (2H, sxt, *J*= 7.5 Hz, CH_2-C*H*$_2$-CH_3), 0.97 (3H, t, *J*= 7.5 Hz, CH_2-CH_2-C*H*$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.9, 161.8 (d, J_{CF}= 243 Hz), 135.0, 132.3 (d, J_{CF}= 8.1 Hz), 132.4 (d, J_{CF}= 3.2 Hz), 130.5, 130.4, (d, J_{CF}= 3.2 Hz), 127.2, 127.0, 124.4, 124.0, 121.3, 120.6, 117.8, 114.5 (d, J_{CF}= 21.3 Hz), 114.5, 32.3, 23.3, 13.9; **LRMS** $[M-H]^-$ 296.20; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{18}H_{15}O_2NF$ 296.10923; Found 296.10895.

Ethyl 7-(*tert*-butyl)-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (S49)



Method A using 2-(*tert*-butyl)aniline (0.33 mL, 2.1 mmol) followed by purification by FCC (CH_2Cl_2 in heptane, 25-50%) gave the desired compound **S49** in 25% isolated yield as a brown solid (181 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.00 (1H, br. s, N*H*), 7.55 – 7.49 (2H, m, Ar-*H*), 7.46 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.31 (1H, d, *J*= 6.5 Hz, Ar-*H*), 7.22 – 7.09 (3H, m, Ar-*H*), 4.32 (2H, q, *J*= 7.0 Hz, OC*H*$_2$$CH_3$), 1.65 – 1.53 (9H, m, CH(C*H*$_3)_3$), 1.26 (3H, t, *J*= 7.0 Hz, OCH_2C*H*$_3$); **LRMS** $[M+H]^+$ 340.20.

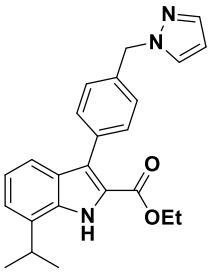
7-*tert*-Butyl-3-(4-fluorophenyl)-1*H*-indole-2-carboxylic acid (46)



To a solution of indole ester **S49** (181 mg, 0.53 mmol, 1.0 eq) in THF (2.0 mL) and MeOH (2.0 mL) was added 2 M aq NaOH (2.0 mL, 4.0 mmol, 7.5 eq); the solution was then stirred at 50 °C for 2 h. The mixture was cooled to room temperature, then quenched with 5 M aq HCl (1.5 mL). The resultant precipitant was collected by filtration to afford a pale brown solid which was washed with MeOH to afford the desired compound **46** in 65% isolated yield as a white solid (108 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 10.29 (1H, s, N*H*), 7.52 – 7.47 (2H, m, Ar-*H*), 7.31 – 7.24 (3H, m, Ar-*H*), 7.22 (1H, dd, *J*= 7.5, 1.0 Hz, Ar-*H*), 7.05 (1H, t, *J*= 7.5 Hz, Ar-*H*), 1.50 (9H, s, CH(C*H*$_3$)$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.7, 161.3 (d, J_{CF}= 243 Hz), 160.5, 134.7, 133.0, 132.3 (d, J_{CF}= 8.1 Hz), 130.1, 128.4, 124.0, 121.4, 121.1, 120.7, 118.6, 114.6 (d, J_{CF}= 21.2 Hz), 34.3, 30.0; **LRMS** $[M+H]^+$ 312.20; **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{19}H_{17}O_2NF$ 310.12488; Found 310.12485.

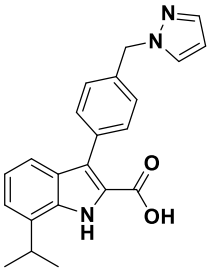
4.4.6 Second generation C3

Ethyl 7-(propan-2-yl)-3-(4-(1*H*-pyrazol-1-ylmethyl)phenyl)-1*H*-indole-2-carboxylate (S50)



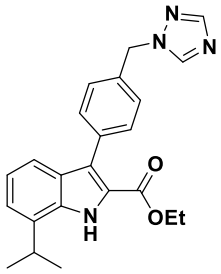
Method H using using iodoindole **S5** (630 mg, 1.76 mmol) followed by purification by FCC (EtOAc in cyclohexane, 0-50%) gave the desired product **S50** in 66% isolated yield as a pale yellow solid (447 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.00 (1H, br. s, N*H*), 7.60 (1H, dd, *J* = 2.0, 1.0 Hz, Ar-*H*), 7.56 – 7.52 (2H, m, Ar-*H*), 7.47 – 7.43 (2H, m, Ar-*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.26 – 7.23 (1H, m, Ar-*H*), 7.16 – 7.11 (1H, m, Ar-*H*), 6.32 (1H, t, *J* = 2.0 Hz, Ar-*H*), 5.42 (2H, s, C*H*$_2$), 4.30 (2H, q, *J* = 7.0 Hz, C*H*$_2$CH$_3$), 3.33 (1H, hept, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$), 1.43 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$), 1.22 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.2 (*C*O$_2$Et), 139.6, 131.2, 127.1, 121.6, 121.5, 119.3, 106.1 (Ar-*C*H), 135.6, 134.3, 133.7, 132.1, 129.4, 128.0, 124.1, 122.7 (Ar-*C*), 61.0 (O*C*H$_2$CH$_3$), 55.9 (*C*H$_2$), 29.1 (*C*H(CH$_3$)$_2$), 22.8 (CH(*C*H$_3$)$_2$), 14.2 (OCH$_2$*C*H$_3$); **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{25}O_2N_3Na$ 410.18390; Found 410.18349.

7-(Propan-2-yl)-3-(4-(1*H*-pyrazol-1-ylmethyl)phenyl)-1*H*-indole-2-carboxylic acid (47)



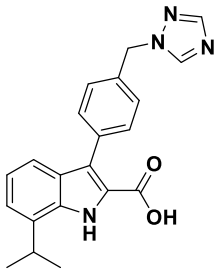
Method M using indole ester **S50** (250 mg, 0.65 mmol) followed by purification by FCC (MeOH in CH_2Cl_2, 0-10%) gave the desired compound **47** in 65% isolated yield as a white solid (152 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.51 (1H, br. s, N*H*), 7.91 – 7.89 (1H, m, Ar-*H*), 7.49 (1H, dd, *J* = 2.0, 0.5 Hz, Ar-*H*), 7.43 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.28 – 7.14 (4H, m, Ar-*H*), 7.06 – 6.99 (1H, m, Ar-*H*), 6.30 (1H, t, *J* = 2.0 Hz, Ar-*H*), 5.40 (2H, s, C*H*$_2$), 3.74 (1H, hept, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$), 1.27 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (*C*O$_2$H), 139.0, 130.5, 130.3, 126.8, 120.8, 120.2, 117.8, 105.5 (Ar-*C*H), 136.1, 134.4, 133.4, 133.2, 127.2, 124.1, 122.0 (Ar-*C*), 54.5 (*C*H$_2$), 26.9 (*C*H(CH$_3$)$_2$), 23.1 (CH(*C*H$_3$)$_2$); **LRMS** $[M+H]^+$ 360.20.

Ethyl 7-(propan-2-yl)-3-(4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl)-1*H*-indole-2-carboxylate (S51)



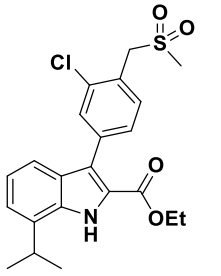
Method H using iodoindole **S5** (261 mg, 0.73 mmol) followed by purification by FCC (EtOAc in CH_2Cl_2, 0-50%) gave the desired product **S51** in 49% isolated yield as a yellow solid (139 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.91 (1H, br. s, N*H*), 8.12 (1H, s, Ar-*H*), 8.01 (1H, s, Ar-*H*), 7.59 – 7.54 (2H, m, Ar-*H*), 7.43 (1H, dt, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.37 – 7.33 (2H, m, Ar-*H*), 7.26 – 7.20 (1H, m, Ar-*H*), 7.13 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 5.43 (2H, s, CH_2), 4.29 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 3.31 (1H, hept, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$), 1.43 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.22 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 162.1 (*C*O$_2$Et), 152.3, 143.2, 131.5, 127.6, 121.8, 121.7, 119.2 (Ar-*C*H), 134.5, 134.3, 133.4, 132.2, 127.9, 123.8, 122.7 (Ar-*C*), 61.1 (O*C*H$_2$CH$_3$), 53.7 (*C*H$_2$), 29.3 (*C*H(CH$_3$)$_2$), 22.9 (CH(*C*H$_3$)$_2$), 14.3 (OCH$_2$*C*H$_3$); **LRMS** $[M+H]^+$ 389.20.

7-(Propan-2-yl)-3-(4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl)-1*H*-indole-2-carboxylic acid (48)



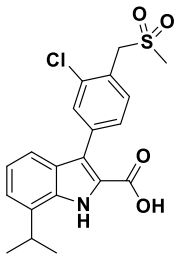
Method M using indole ester **S51** (139 mg, 0.36 mmol) followed by purification by FCC (MeOH in CH_2Cl_2, 0-10%) gave the desired compound **48** in >99% isolated yield as a white solid (129 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.87 (1H, br. s, CO$_2$*H*/N*H*), 11.58 (1H, br. s, CO$_2$*H*/N*H*), 8.77 (1H, s, Ar-*H*), 8.06 (1H, s, Ar-*H*), 7.50 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.36 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.28 (1H, dd, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.23 – 7.18 (1H, m, Ar-*H*), 7.07 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 5.52 (2H, s, CH_2), 3.78 (1H, hept, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$), 1.31 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.9 (*C*O$_2$H), 151.8, 144.3, 130.7, 127.1, 120.8, 120.3, 117.8 (Ar-*C*H), 134.6, 134.4, 133.8, 133.3, 124.1, 121.9 (Ar-*C*), 52.0 (*C*H$_2$), 26.9 (*C*H(CH$_3$)$_2$), 23.1 (CH(*C*H$_3$)$_2$); **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}O_2N_4$ 361.16590; Found 361.16574.

Ethyl 3-(3-chloro-4-((methylsulfonyl)methyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S52)



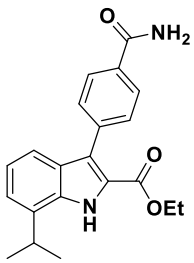
Method H using iodoindole **S5** (1.19 g, 3.33 mmol) followed by purification by FCC (EtOAc in CH_2Cl_2, 0-2%) gave the desired product **S52** in 89% isolated yield as a white solid (1.17 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.12 (1H, s, N*H*), 7.71 – 7.65 (2H, m, Ar-*H*), 7.54 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.47 – 7.44 (1H, m, Ar-*H*), 7.29 – 7.25 (1H, m, Ar-*H*), 7.20 – 7.15 (1H, m, Ar-*H*), 4.57 (2H, s, CH_2), 4.32 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 3.34 (1H, hept, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$), 2.90 (3H, s, CH_3), 1.43 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.26 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.9 (*C*O$_2$Et), 136.9, 134.3, 133.7, 127.5, 125.2, 123.0, 121.8 (Ar-*C*), 132.4, 132.2, 130.1, 122.0 122.0, 118.9 (Ar-*C*H), 61.4 (O*C*H$_2$CH$_3$), 58.0 (*C*H$_2$), 39.9 (*C*H$_3$), 29.2 (*C*H(CH$_3$)$_2$), 22.9 (CH(*C*H$_3$)$_2$), 14.2 (OCH$_2$*C*H$_3$); **HRMS** (TOF, ESI$^-$) *m/z*: $[M-H]^-$ Calcd for $C_{22}H_{23}O_4NClS$ 432.10418; Found 432.10430.

3-(3-Chloro-4-((methylsulfonyl)methyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (49)



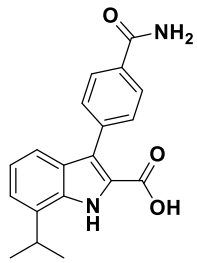
Method M using indole ester **S52** (0.94 g, 2.17 mmol) followed by purification of the crude product by FCC (MeOH in CH_2Cl_2, 0-10%), then trituration (10% CH_2Cl_2 in cyclohexane) and then filtration gave the desired product **49** in 77% isolated yield as a white solid (0.677 g). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 12.99 (1H, br. s, N*H*/CO_2*H*), 11.66 (1H, s, N*H*/CO_2*H*), 7.65 – 7.58 (2H, m, Ar-C*H*), 7.51 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-C*H*), 7.30 (1H, d, *J* = 8.0 Hz, Ar-C*H*), 7.20 (1H, d, *J* = 7.0 Hz, Ar-C*H*), 7.11 – 7.06 (1H, m, Ar-C*H*), 4.71 (2H, s, CH_2), 3.76 (1H, hept, *J* = 7.0 Hz, C*H*(CH_3)$_2$), 3.07 (3H, s, CH_3), 1.28 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 162.6 (*C*O_2H), 136.5, 134.3, 133.6, 133.4, 132.5, 131.2, 129.3, 126.8, 125.0, 124.4 121.1, 120.4, 120.1, 117.5 (Ar-*C*), 56.5 (*C*H_2), 40.5 (*C*H_3), 26.9 (*C*H(CH_3)$_2$), 23.1 (CH(*C*H_3)$_2$); **HRMS** (TOF, ESI$^-$) *m/z*: [M-H]$^-$ Calcd for $C_{20}H_{19}O_4NClS$ 404.07288; Found 404.07285.

Ethyl 3-(4-carbamoylphenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S53)



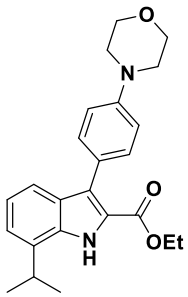
Method H using iodoindole **S5** (60 mg, 0.17 mmol) followed by purification by FCC (EtOAc in heptane, 0-100%) gave the desired product **S53** in 53% isolated yield (31.2 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.69 (1H, br. s, N*H*), 8.08 – 7.89 (3H, m, Ar-*H* & N*H*), 7.54 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.37 (1H, br. s, N*H*), 7.29 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.22 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.12 – 7.04 (1H, m, Ar-*H*), 4.22 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 3.76 (1H, hept, *J* = 7.0 Hz, C*H*(CH_3)$_2$), 1.30 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.16 (3H, t, *J* = 7.0 Hz, OCH_2CH_3).

3-(4-Carbamoylphenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (50)



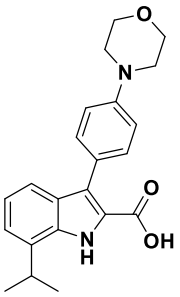
Method J using indole ester **S53** (31 mg, 0.09 mmol) at room temperature for 20 h gave the desired product **50** in 93% isolated yield as a pale yellow solid (27 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.89 (1H, br. s, CO_2*H*), 11.61 (1H, br. s, N*H*), 8.07 – 7.87 (3H, m, Ar-*H* & N*H*), 7.54 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.35 (1H, br. s, N*H*), 7.27 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.19 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.11 – 7.01 (1H, m, Ar-*H*), 3.76 (1H, hept, *J* = 7.0 Hz, C*H*(CH_3)$_2$), 1.29 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 167.9 (*C*ONH_2), 162.9 (*C*O_2H), 137.3, 134.4, 133.3, 132.4, 127.0, 124.3, 121.6 (Ar-*C*), 130.2, 126.9, 120.9, 120.3, 117.7 (Ar-*C*H), 26.9 (*C*H(CH_3)$_2$), 23.1 (CH(*C*H_3)$_2$); **LRMS** [M+H]$^+$ 323.15; **HRMS** (TOF, ESI$^+$) *m/z*: [M+H]$^+$ Calcd for $C_{19}H_{19}O_3N_2$ 323.13902; Found 323.13913.

Ethyl 3-(4-(morpholin-4-yl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S54)



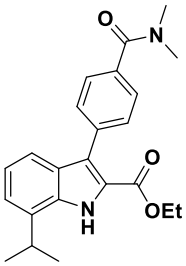
Method H using iodoindole **S5** (60 mg, 0.17 mmol) followed by purification by FCC (EtOAc in heptane, 0-25%) gave the desired product **S54** in 44% isolated yield (29.2 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.42 (1H, br. s, N*H*), 7.39 – 7.26 (3H, m, Ar-*H*), 7.18 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.10 – 6.97 (3H, m, Ar-*H*), 4.22 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 3.82 – 3.68 (5H, m, C*H*(CH_3)$_2$ + morpholine-CH_2), 3.22 – 3.12 (4H, m, morpholine-CH_2), 1.29 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.20 (3H, t, *J* = 7.0 Hz, OCH_2CH_3).

3-(4-(Morpholin-4-yl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (51)



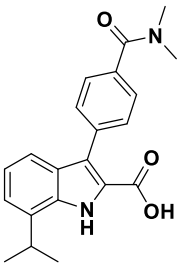
Method J using indole ester **S54** (31 mg, 0.09 mmol) at room temperature for 4 days, then 70 °C for 2 h with additional 2 M aq NaOH (0.18 mL, 0.36 mmol, 4.0 eq) followed by purification by ion exchange chromatography using a 2 g SCX-2 cartridge, eluting with methanol then with 2 M NH_3 in methanol; combining and concentrating basic fractions *in vacuo* gave the desired product **51** in 77% isolated yield (20 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.69 (1H, br. s, CO_2H/N*H*), 11.35 (1H, s, CO_2H/N*H*), 7.35 (2H, d, *J* = 9.0 Hz, Ar-*H*), 7.28 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.16 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.06 – 6.97 (3H, m, Ar-*H*), 3.84 – 3.65 (5H, m, C*H*$(CH_3)_2$ & morpholine-CH_2), 3.17 (4H, t, *J* = 4.5 Hz, morpholine-CH_2), 1.28 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 163.1 (*C*O_2H), 149.6, 134.4, 133.1, 127.4, 124.7, 123.7, 122.6 (Ar-*C*), 131.0, 120.4, 120.1, 118.0, 114.3 (Ar-*C*H), 66.2, 48.3 (*C*H_2), 26.9 (*C*H$(CH_3)_2$), 23.1 (CH(*C*H_3)$_2$); **LRMS** $[M+H]^+$ 365.20; **HRMS** (TOF, ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{25}O_3N_2$ 365.18597; Found 365.18521.

Ethyl 3-(4-(dimethylcarbamoyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S55)



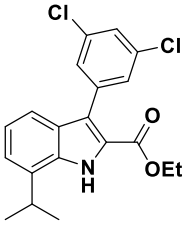
Method H using iodoindole **S5** (90 mg, 0.25 mmol) followed by purification by FCC (EtOAc in heptane, 0-100%) gave the desired product **S55** in 78% isolated yield (74.6 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.95 (1H, br. s, N*H*), 7.64 – 7.58 (2H, m, Ar-*H*), 7.56 – 7.50 (2H, m, Ar-*H*), 7.47 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.31 – 7.24 (1H, m, Ar-*H*), 7.20 – 7.13 (1H, m, Ar-*H*), 4.32 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 3.35 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 3.25 – 3.04 (6H, m, N(CH_3)$_2$), 1.46 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.25 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3).

3-(4-(dimethylcarbamoyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (52)



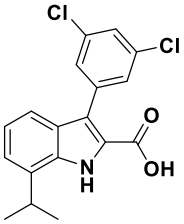
Method J using indole ester **S55** (72.5 mg, 0.19 mmol) at room temperature for 24 h gave the desired product **52** in 92% isolated yield (62 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.89 (1H, br. s, CO_2H), 11.59 (1H, br. s, N*H*), 7.56 – 7.50 (2H, m, Ar-*H*), 7.50 – 7.42 (2H, m, Ar-*H*), 7.30 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.19 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.12 – 7.02 (1H, m, Ar-*H*), 3.76 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 3.02 (6H, s, N(CH_3)$_2$), 1.29 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 170.2 (*C*(O)N(Me)$_2$), 162.9 (*C*O_2H), 135.3, 134.5, 134.4, 133.3, 127.1, 124.2, 121.7 (Ar-*C*), 130.2, 126.5, 120.9, 120.4, 117.7 (Ar-*C*H), 34.8 (*C*H_3), 26.9 (*C*H$(CH_3)_2$), 23.1 (CH(*C*H_3)$_2$); **LRMS** $[M+H]^+$ 351.20; **HRMS** (TOF, ESI^+) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_3N_2$ 351.17032; Found 351.17004.

Ethyl 3-(3,5-dichlorophenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S56)



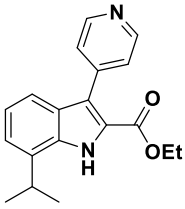
Method I using iodoindole **S5** (5 g, 14.0 mmol) followed by purification by FCC (EtOAc in cyclohexane, 0-10%) gave the desired product **S56** in 88% isolated yield as a yellow solid (4.6 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.23 (1H, s, N*H*), 7.49 – 7.44 (3H, m, Ar-*H*), 7.41 (1H, t, *J* = 2.0 Hz, Ar-*H*), 7.28 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.22 – 7.17 (1H, m, Ar-*H*), 4.35 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 3.36 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.44 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.30 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.1, 137.0, 134.3, 134.2, 132.4, 129.3, 127.5, 127.1, 123.2, 122.0, 121.9, 121.3, 118.7, 61.4, 22.8, 14.1; **LRMS** $[M+H]^+$ 376.0.

3-(3,5-Dichlorophenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (53)



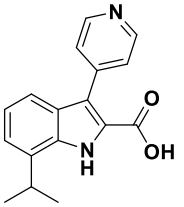
Method J using indole ester **S56** (69 mg, 0.18 mmol) with heating at 50 °C for 2.5 h gave the desired product **53** in 83% isolated yield as an off-white solid (53 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.04 (1H, br. s, CO_2H), 11.74 (1H, s, N*H*), 7.59 (1H, t, *J* = 2.0 Hz, Ar-*H*), 7.50 (2H, d, *J* = 2.0 Hz, Ar-*H*), 7.30 – 7.16 (2H, m, Ar-*H*), 7.14 – 7.03 (1H, m, Ar-*H*), 3.76 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.28 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$);**^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 166.6 (*C*O_2H), 136.4, 134.7, 132.5, 129.1, 127.7, 123.8, 122.8, 122.4, 119.1 (Ar-*C*), 29.3 (*C*H$(CH_3)_2$), 22.8 (CH(*C*H$_3)_2$); **LRMS** $[M+H]^+$ 348.05; **HRMS** (TOF, ESI$^-$) m/z: $[M-H]^-$ Calcd for $C_{18}H_{14}O_2N^{35}Cl_2$ 346.03961; Found 346.04068.

Ethyl 7-(propan-2-yl)-3-(pyridin-4-yl)-1*H*-indole-2-carboxylate (S57)



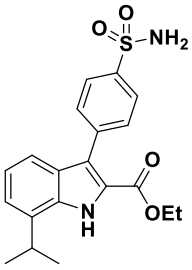
Method H using iodoindole **S5** (60 mg, 0.17 mmol) followed by purification by FCC (EtOAc in heptane, 0-50%) gave the desired product **S57** in 80% isolated yield (41.2 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.04 (1H, s, N*H*), 8.76 – 8.66 (2H, m, Ar-*H*), 7.54 – 7.42 (3H, m, Ar-*H*), 7.31 – 7.27 (1H, m, Ar-*H*), 7.23 – 7.14 (1H, m, Ar-*H*), 4.34 (2H, q, *J* = 7.5 Hz, OC*H*$_2$CH$_3$), 3.35 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.46 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$), 1.27 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$); **LRMS** $[M+H]^+$ 309.20.

7-(Propan-2-yl)-3-(pyridin-4-yl)-1*H*-indole-2-carboxylic acid (54)



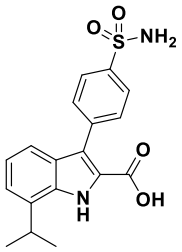
Method J using indole ester **S57** (39 mg, 0.13 mmol) at room temperature for 20 h followed by acidification (1 M aq HCl), removal of organics *in vacuo* and purification by ion exchange chromatography (5 g SCX-2 cartridge, eluting with methanol, then with 2 M NH_3 in methanol); basic fractions were combined and concentrated *in vacuo* and then drying under high vacuum gave the desired product **54** in 91% isolated yield (62 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 13.06 (1H, s, CO_2H), 11.78 (1H, s, N*H*), 8.61 (2H, d, *J* = 6.0 Hz, Ar-*H*), 7.54 – 7.45 (2H, m, Ar-*H*), 7.31 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.21 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.15 – 7.03 (1H, m, Ar-*H*), 3.77 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.28 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.6 (*C*O_2H), 149.0 (Ar-*C*H), 142.3 (Ar-*C*), 134.4 (Ar-*C*), 133.6 (Ar-*C*), 126.5 (Ar-*C*), 125.5 (Ar-*C*H), 124.6 (Ar-*C*), 121.3 (Ar-*C*H), 120.5 (Ar-*C*H), 119.5 (Ar-*C*), 117.4 (Ar-*C*H), 26.9 (*C*H$(CH_3)_2$), 23.1 (CH(*C*H$_3)_2$); **LRMS** $[M+H]^+$ 281.15; **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}O_2N_2$ 281.12845; Found 281.12842.

Ethyl 3-(4-(aminosulfonyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylate (S58)



Method H using iodoindole **S5** (70 mg, 0.2 mmol) followed by purification by FCC (EtOAc in heptane, 0-50%) gave the desired product **S58** in 41% isolated yield (30.9 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 11.76 (1H, br. s, N*H*), 7.89 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.66 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.30 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.23 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.14 – 7.05 (1H, m, Ar-*H*), 4.24 (2H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 3.77 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.30 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$), 1.18 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); **LRMS** $[M+H]^+$ 387.15.

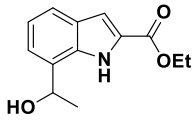
3-(4-(Aminosulfonyl)phenyl)-7-(propan-2-yl)-1*H*-indole-2-carboxylic acid (55)



Method J using indole ester **S58** (45 mg, 0.12 mmol) at room temperature for 28 h followed by removal of organic solvents, then partitioning between EtOAc and water and washing the organic phase with 2 M NaOH, and combining and acidifying the aqueous phases to pH 1; reextraction (EtOAc), drying (brine, Na_2SO_4) then concentration *in vacuo* gave the desired product **55** in 97% isolated yield (26 mg). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 12.94 (1H, br. s, CO_2H), 11.69 (1H, br. s, N*H*), 7.88 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.66 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.39 (2H, s, NH_2), 7.31 – 7.15 (2H, m, Ar-*H*), 7.13 – 7.02 (1H, m, Ar-*H*), 3.77 (1H, hept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.27 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 162.7 (*C*O_2H), 142.1, 137.9, 134.4, 133.5, 126.9, 124.4, 121.0 (Ar-*C*), 130.8, 125.1, 121.1, 120.5, 117.5 (Ar-*C*H), 26.9 (*C*H$(CH_3)_2$), 23.1 (CH(*C*H_3)$_2$); **LRMS** $[M-H]^-$ 357.00; **HRMS** (TOF, ESI$^-$) m/z: $[M-H]^-$ Calcd for $C_{18}H_{17}O_4N_2S$ 357.09145; Found 357.09116.

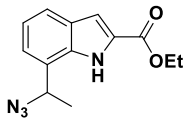
4.4.7 Lead optimization

Ethyl 7-(1-hydroxyethyl)-1*H*-indole-2-carboxylate (S59)



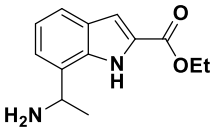
To ethyl 7-acetyl-1*H*-indole-2-carboxylate (**S71**) (500 mg, 2.16 mmol, 1.0 eq) in EtOH (44 mL), cooled in an ice bath to 0 °C was added $NaBH_4$ (164 mg, 4.32 mmol, 2.0 eq); the mixture was stirred at room temperature for 2 h. Upon completion, the solvents were removed *in vacuo* and the crude residue was treated with sat. aq $NaHCO_3$ (10 mL), then extracted with EtOAc (2 x10 mL). The combined EtOAc extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain the desired compound **S59** in 90% isolated yield as a white solid (506 mg, 99%).
^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 9.64 (1H, br. s, N*H*), 7.60 (1H, dt, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.23 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.13 – 7.01 (2H, m, Ar-*H*), 5.26 (1H, qd, *J* = 6.5, 3.5 Hz, CH_3C*H*OH), 4.40 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 2.28 (1H, d, *J* = 3.5 Hz, O*H*), 1.66 (3H, d, *J* = 6.5 Hz, CH_3CHOH), 1.41 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 162.1 (*C*O_2Et), 134.6, 128. 9, 128.5, 127.8 (Ar-*C*), 121.9, 121.6, 120.5, 108.7 (Ar-*C*H), 70.5 (CH_3*C*HOH), 61.1 (O*C*$H_2$$CH_3$), 24.1 (*C*$H_3$CHOH), 14.6 ($OCH_2$*C*$H_3$); **LRMS** $[M-H]^-$ 232.1; **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}O_3N$ 234.11247; Found 234.11275.

3-(1-(2-(Ethoxycarbonyl)-1*H*-indol-7-yl)ethyl)triaza-1,2-dien-2-ium-1-ide (S60)



To ethyl 7-(1-hydroxyethyl)-1*H*-indole-2-carboxylate (**S59**) (94 mg, 0.403 mmol, 1.0 eq) in CH_2Cl_2 (0.8 mL) was added $TMSN_3$ (0.08 mL, 0.604 mmol, 1.5 eq) and $Cu(OTf)_2$ (7.3 mg, 0.02 mmol, 0.05 eq) and the reaction mixture stirred for 20 min. Upon completion, the reaction mixture was diluted with water (5 mL), then extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain the desired compound **S60** as a white solid which was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.24 (1H, s, N*H*), 7.65 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.25 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.19 (1H, ddd, *J* = 7.0, 1.0, 0.5 Hz, Ar-*H*), 7.12 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 4.94 (1H, q, *J* = 7.0 Hz, CH_3C*H*N_3), 4.43 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 1.70 (3H, d, *J* = 7.0 Hz, C$H_3$$CHN_3$), 1.43 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 162.0 (*C*O_2Et), 134.2, 128.7, 128.1, 124.5 (Ar-*C*), 122.9, 122.8, 120.7, 109.0 (Ar-*C*H), 61.3 (O*C*$H_2$$CH_3$), 60.0 ($CH_3$*C*$HN_3$), 20.5 (*C*$H_3$$CHN_3$), 14.6 ($OCH_2$*C*$H_3$); **LRMS** $[M+H]^+$ 259.0; **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}O_2N_4$ 257.10440; Found 257.10443.

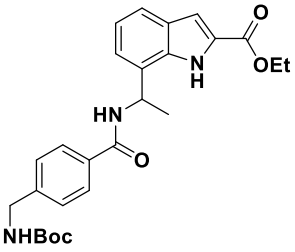
Ethyl 7-(1-aminoethyl)-1*H*-indole-2-carboxylate (S61)



To azide **S60** (138 mg, 0.534 mmol, 1.0 eq) in EtOH (2.7 mL) was added 10% Pd/C (56.9 mg, 0.0534 mmol, 0.1 eq); and the resultant mixture sparged with H_2. The reaction mixture was then left to stir for 2 h with a H_2 balloon attachment (with the needle reaching the solvent) until completion. The reaction mixture was filtered through a plug of Decalite®, rinsing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to obtain the crude product **S61**, which was used in the next step without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 10.52 (1H, s, N*H*), 7.57 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.21 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.10 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.06 (1H, t, *J* = 7.5 Hz, Ar-*H*), 4.54 (1H, q, *J* = 6.5 Hz, CH_3CHNH_2), 4.41 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 1.51 (3H, d, *J* = 6.5 Hz, CH_3CHNH_2), 1.42 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 162.4 (CO_2Et), 135.8, 130.0, 128.4, 127.5 (Ar-*C*), 122.2, 121.3, 120.7, 108.5 (Ar-*C*H), 61.1 (OCH_2CH_3), 51.5 (CH_3CHNH_2), 25.3 (CH_3CHNH_2), 14.7 (OCH_2CH_3); **LRMS** $[M\text{-}NH_2]^+$ 216.0; **HRMS** (TOF, ESI$^+$) m/z: $[M\text{-}NH_2]^+$ Calcd for $C_{13}H_{14}O_2N$ 216.10191; Found 216.10210.

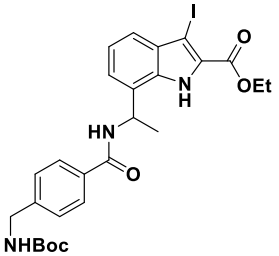
Ethyl 7-(1-((4-(((*tert*-butoxycarbonyl)amino)methyl)benzoyl)amino)ethyl)-1*H*-indole-2-carboxylate (S62)



To a solution of 4-[(*tert*-butoxycarbonylamino)methyl]benzoic acid (143 mg, 0.568 mmol, 1.2 eq) in CH_2Cl_2 (1.4 mL) was added amine **S61** (110 mg, 0.474 mmol, 1.0 eq), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluoro-phosphate (296 mg, 0.568 mmol, 1.2 eq) and Et_3N (0.198 mL, 1.42 mmol, 3.0 eq). The resultant mixture was stirred for 1 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 1 M HCl (2 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using a Biotage KP-Sil column, with gradient elution from 100% CH_2Cl_2 to 20% EtOAc in CH_2Cl_2. The desired product **S62** was obtained in 99% isolated yield over three steps as a white solid (220 mg).

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 10.63 (1H, s, N*H*), 7.72 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.63 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.30 (3H, dd, *J* = 13.0, 7.5 Hz, Ar-*H*), 7.22 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.11 (1H, t, *J* = 7.5 Hz, Ar-*H*), 6.34 (1H, d, *J* = 9.5 Hz, N*H*), 5.99 – 5.85 (1H, m, CH_3CH), 4.88 (1H, s, N*H*), 4.53 – 4.34 (2H, m, OCH_2CH_3), 4.31 (2H, d, *J* = 6.0 Hz, CH_2), 1.83 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.52 – 1.33 (12H, m, OCH_2CH_3+$C(CH_3)_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 167.5, 161.8, 156.0 (*C*=O), 143.3, 136.0, 132.9, 128.3, 126.5 (Ar-*C*), 127.9, 127.6, 122.4, 120.6, 120.3, 108.6 (Ar-*C*H), 79.9 ($C(CH_3)_3$), 61.0 (OCH_2CH_3), 44.4 (CH_2), 44.0 (CH_3CH), 28.5 ($C(CH_3)_3$), 19.0 (CH_3CH), 14.6 (OCH_2CH_3); **HRMS** (TOF, ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{31}O_5N_3Na$ 488.21564; Found 488.21559.

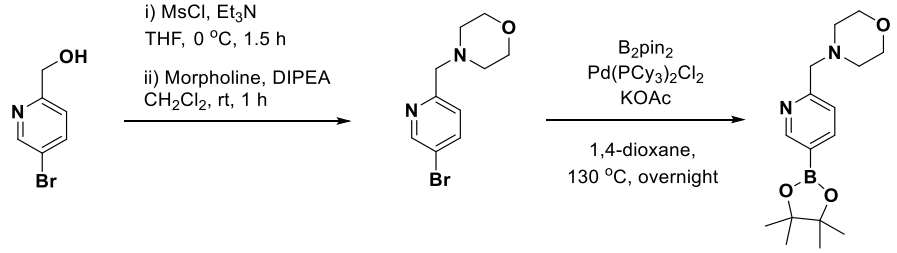
Ethyl 7-(1-((4-(((*tert*-butoxycarbonyl)amino)methyl)benzoyl)amino)ethyl)-3-iodo-1*H*-indole-2-carboxylate (S63)



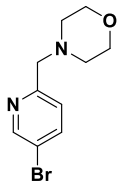
To a solution of ethyl indole **S62** (220 mg, 0.473 mmol, 1.0 eq) in CH_2Cl_2/DMF (4.4 mL, 10:1) was added *N*-iodosuccinimide (117 mg, 0.52 mmol, 1.1 eq) and the reaction mixture stirred for 2 h. Upon completion, the reaction mixture was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL); the organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* and purification by FCC (BIOTAGE KP-Sil 25 g column, with gradient

elution from 100% CH_2Cl_2 to 20% EtOAc in CH_2Cl_2) gave the desired product **S63** in 87% yield as a pale yellow solid (243 mg).
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ ppm 11.97 (1H, s, N*H*), 9.00 (1H, d, *J* = 8.0 Hz, N*H*), 7.84 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.44 (1H, t, *J* = 6.0 Hz, N*H*), 7.39 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.32 (3H, dd, *J* = 11.5, 8.0 Hz, Ar-*H*), 7.17 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 5.97 – 5.51 (1H, m, CH_3CH), 4.49 – 4.30 (2H, m, OCH_2CH_3), 4.16 (2H, d, *J* = 6.0 Hz, CH_2), 1.59 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.41 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.39 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) δ ppm 165.9, 160.3, 155.8 (*C*=O), 143.7, 134.5, 132.6, 131.0, 130.0, 127.2 (Ar-*C*), 127.4, 126.6, 122.3, 121.3, 121.2 (Ar-*C*H), 77.9 ($C(CH_3)_3$), 66.8 (*C*I), 60.8 (OCH_2CH_3), 44.4 (CH_3CH), 43.1 (CH_2), 28.2 ($C(CH_3)_3$), 20.6 (CH_3CH), 14.2 (OCH_2CH_3); **HRMS** (TOF, ESI$^-$) m/z: $[M-H]^-$ Calcd for $C_{26}H_{29}O_5N_3I$ 590.11574; Found 590.11667.

Synthesis of the C-3 side chain:

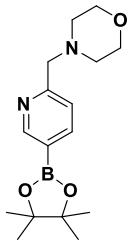


4-((5-Bromopyridin-2-yl)methyl)morpholine (S64)



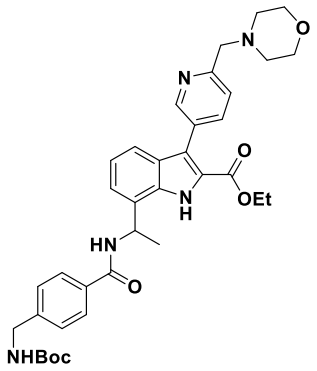
To a solution of (5-bromopyridin-2-yl)methanol (2 g, 10.6 mmol, 1.0 eq) in THF (32 mL) at 0 °C were added Et_3N (4.43 mL, 31.9 mmol, 1.2 eq) and methanesulfonyl chloride (1.65 mL, 21.3 mmol, 2.0 eq); the resultant mixture was stirred at 0 °C for 1.5 h. The reaction mixture was partitioned between EtOAc (30 mL) and water (10 mL); the organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue obtained was then dissolved in CH_2Cl_2 (32 mL) and this solution morpholine (1.02 mL, 11.7 mmol, 2.0 eq) and *N*,*N*-diisopropylethylamine (2.22 mL, 12.8 mmol, 1.2 eq) were added and the reaction mixture stirred at room temperature for 1 h by which point no limiting reagent was observed. The organic solution was washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using a BIOTAGE KP-Sil 25 g column, with gradient elution from 100% cyclohexane to 100% EtOAc. The desired product **S64** was obtained in 93% isolated yield as a yellow oil which solidified upon standing (2.55 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H, dd, *J* = 2.5, 0.5 Hz, Ar-*H*), 7.77 (1H, dd, *J* = 8.5, 2.5 Hz, Ar-*H*), 7.33 (1H, d, *J* = 8.5 Hz, Ar-*H*), 3.76 – 3.68 (4H, m, morpholino-CH_2), 3.60 (2H, s, CH_2), 2.52 – 2.46 (4H, m, morpholino-CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 156.9, 119.2 (Ar-*C*), 150.5, 139.1, 124.7 (Ar-*C*H), 67.0 (morpholino-CH_2), 64.3 (CH_2), 53.8 (morpholino-CH_2); **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{10}H_{14}O_1N_2{}^{79}Br$ 257.02840; Found 257.02840.

4-((5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)morpholine (S65)



To pyridyl bromide **S64** (490 mg, 1.91 mmol, 1 eq), bis(pinacolato)diboron (581 mg, 2.29 mmol, 1.2 eq), potassium acetate (281 mg, 2.86 mmol, 1.5 eq) in 1,4-dioxane (7.8 mL) in a microwave vial was added $Pd(PCy_3)_2Cl_2$ (70 mg, 0.095 mmol, 0.05 eq). The reaction vial was sealed and the resultant mixture was degassed with argon, then heated at 130 °C for 15 h. Upon completion, the resultant mixture was cooled, then filtered through Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* to obtain the desired compound **S65**, which was used for the subsequent Suzuki-Miyaura cross-coupling reaction without further purification. $[M+H]^+$ 305.2.

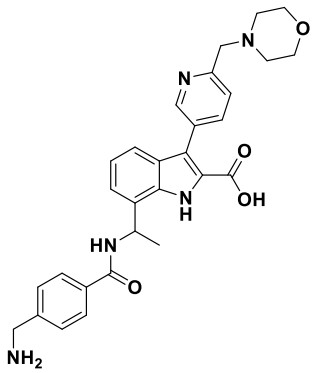
Ethyl 7-(1-((4-(((*tert*-butoxycarbonyl)amino)methyl)benzoyl)amino)ethyl)-3-(6-(morpholin-4-ylmethyl)pyridin-3-yl)-1*H*-indole-2-carboxylate (S66)



To the crude pinacol ester **S65** (148 mg, 0.487 mmol, 1.2 eq) in 1,4-dioxane (10 mL) in a microwave vial, was added iodo indole **S63** (240 mg, 0.406 mmol, 1.0 eq), $Pd(PCy_3)_2Cl_2$ (15 mg, 0.02 mmol, 0.05 eq), 2 M Na_2CO_3 (0.81 mL, 1.62 mmol, 4 eq). The reaction mixture was purged with argon and subjected to microwave irradiation at 110 °C for 5 h. The reaction mixture was filtered through Celite, eluting with EtOAc (20 mL) and water (10 mL). The organics were separated from the filtrate and the aqueous layer further extracted with EtOAc (2x10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude material was purified using a BIOTAGE KP-Sil 25 g column [100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2] to afford the desired product **S66** in 73% yield as a yellow solid (191 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.99 (1H, s, N*H*), 8.80 – 8.65 (1H, m, Ar-*H*), 7.86 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.78 – 7.69 (2H, m, Ar-*H*), 7.54 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.47 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.36 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.28 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.12 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 6.54 (1H, d, *J* = 9.5 Hz, N*H*), 5.94 (1H, dt, *J* = 9.0, 7.0 Hz, CH_3CH), 4.96 (1H, s, N*H*), 4.47 – 4.19 (4H, m, OCH_2CH_3+CH_2), 3.75 (4H, t, *J* = 4.5 Hz, morpholino-CH_2), 3.71 (2H, s, CH_2), 2.56 (4H, t, *J* = 4.5 Hz, morpholino-CH_2), 1.85 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.44 (9H, s, $C(CH_3)_3$), 1.33 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 167.6, 161.5, 156.5 (*C*=O), 150.6, 138.6, 135.0, 132.7, 128.4, 127.9, 127.6, 127.5, 126.7, 124.0, 122.5, 121.4, 120.9, 120.9, 120.1 (Ar-*C*+Ar-*C*H), 75.1 ($C(CH_3)_3$), 67.1 (morpholino-CH_2), 65.0 (CH_2), 61.0 (OCH_2CH_3), 54.0 (morpholino-CH_2), 44.3 (CH_2), 43.8 (CH_3CH), 28.5 ($C(CH_3)_3$), 18.9 (CH_3CH), 14.3 (OCH_2CH_3); **HRMS** (TOF, ESI^-) m/z: $[M-H]^-$ Calcd for $C_{36}H_{44}O_6N_5$ 642.32861; Found 642.32885.

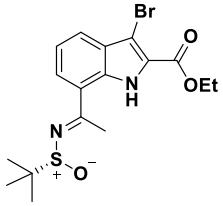
7-(1-((4-(Aminomethyl)benzoyl)amino)ethyl)-3-(6-(morpholin-4-ylmethyl)pyridin-3-yl)-1*H*-indole-2-carboxylic acid (56)



To a solution of *N*-Boc protected amine **S66** (191 mg, 0.297 mmol, 1.0 eq) dissolved in CH_2Cl_2 (3.7 mL), cooled to 0 °C, was added trifluoroacetic acid (TFA, 0.23 mL, 2.97 mmol, 10.0 eq) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resultant mixture was concentrated *in vacuo* co-evaporating with toluene. The crude residue was dissolved in THF/EtOH/H_2O (4 mL, 2:1:1) and treated with LiOH•H_2O (63 mg, 1.49 mmol, 5.0 eq). The resultant solution was stirred at room temperature overnight. Upon completion, the resultant mixture was acidified to pH 1 with 2 M HCl, then concentrated *in vacuo*. The crude residue was purified using a BIOTAGE C18 SNAP-ultra column, with gradient elution using MeOH-H_2O. The solvents used for column purification were prepared by adding 1 mL of 2 M HCl to 1 L each of MeCN and of H_2O. The fractions containing the product were concentrated *in vacuo* and the resultant residue was re-suspended in 1:1 MeCN:H_2O, then lyophilized to obtain the desired product **56** in >99% yield as a HCl salt as a yellow powder (199 mg).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.80 (1H, s, CO_2H), 9.16 (1H, d, *J* = 8.0 Hz, N*H*), 8.77 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.47 (2H, br. s, NH_2), 8.05 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.94 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.71 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.59 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.37 (2H, t, *J* = 7.0 Hz, Ar-*H*), 7.12 (1H, t, *J* = 7.5 Hz, Ar-*H*), 5.80 (1H, app p, *J* = 7.0 Hz, CH_3CH), 4.57 (2H, s, CH_2), 4.08 (2H, app q, *J* = 6.0 Hz, CH_2), 3.90 (4H, t, *J* = 4.5 Hz, morpholino-CH_2), 3.36 – 3.29 (4H, m, morpholino-CH_2, obscured by water), 1.63 (3H, d, *J* = 7.0 Hz, CH_3CH); **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 165.5, 162.5 (*C*=O), 150.5, 138.9, 128.7, 127.6, 124.4, 121.8, 121.0, 118.6 (Ar-*C*H), 148.0, 137.2, 134.2, 133.5, 130.3, 129.9, 127.4, 124.8, 117.9 (Ar-*C*), 63.1 (morpholino-CH_2), 59.6 (CH_2), 51.5 (morpholino-CH_2), 45.1 (CH_3CH), 41.8 (CH_2), 20.8 (CH_3CH); **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{29}H_{32}O_4N_5$ 514.24488; Found 514.24474.

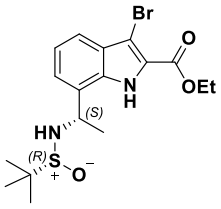
(((1*E*)-1-(3-bromo-2-(ethoxycarbonyl)-1*H*-indol-7-yl)ethylidene)amino)((*R*)-*tert*-butyl)sulfaniumolate (S67)



To a solution of ketone **S72** (4.00 g, 12.9 mmol, 1.00 eq) in anhydrous THF (32 mL) under Ar atmosphere was added (*R*)-*t*-Bu sulfinimide (1.76 g, 14.2 mmol, 1.10 eq) and titanium ethoxide (4.92 mL, 23.2 mmol, 1.80 eq) at room temperature and the resulting yellow solution was heated at 75 °C for 24 h in a sealed tube. The resulting brown solution was cooled to rt, diluted with EtOAc, poured into a beaker with brine with stirring for 15 min; the resulting greenish yellow slurry was filtrated through a pad of Celite®, the filter cake washed with EtOAc, filtrate washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by FCC [100% CH_2Cl_2 to 2% MeOH in CH_2Cl_2] to afford the desired product **S67** in 82% yield as a yellow solid (4.39 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.16 (1H, br. s, N*H*), 7.87 (1H, dd, *J*= 5.3, 0.9 Hz, Ar-*H*), 7.85 (1H, dd, *J*= 4.9, 0.9 Hz, Ar-*H*), 7.29 (1H, t, *J*= 7.8 Hz, Ar-*H*), 4.45 (2H, qd, *J*= 7.1, 2.0 Hz, OCH_2CH_3), 2.91 (3H, s, CH_3), 1.43 (3H, t, *J*= 7.1 Hz, OCH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 178.6, 160.3, 133.6, 129.2, 128.1, 126.7, 125.2, 121.5, 120.9, 98.9, 61.5, 56.8, 22.7, 19.9, 14.6; **LRMS** $[M+H]^+$ 413.1; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}BrN_2O_3S$ 413.0535; Found 413.0545.

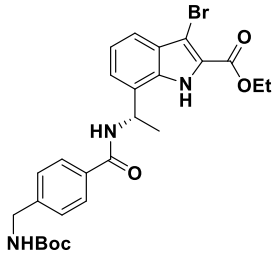
(((1*S*)-1-(3-Bromo-2-(ethoxycarbonyl)-1*H*-indol-7-yl)ethyl)amino)((*R*)-*tert*-butyl)sulfaniumolate (S68)



To a solution of the imine **S67** (4.38 g, 10.6 mmol) in anhydrous THF (44 mL) at -76 °C was added 1 M L-Selectride in THF (11.7 mL, 11.7 mmol, 1.10 eq) dropwise and the resulting yellow suspension was stirred for 1 h between -76 and -70 °C before warming to rt. The reaction mixture was quenched by the addition of sat. NH_4Cl; the aqueous layer was extracted with EtOAc (x2), the organic layers were combined, washed with water (x2), then brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude material by FCC [CH_2Cl_2 to CH_2Cl_2:MeOH 50:1] and then repurification (x2) of mixed fractions by FCC [petroleum ether: EtOAc 2:1 to EtOAc] afforded the desired compound **S68** as a yellow foam in 69% yield (3.02 g).

[α]$_D^{20}$ = -76.0 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.97 (1H, br. s, N*H*), 7.62 (1H, dt, *J*= 8.1, 1.0 Hz, Ar-*H*), 7.27 (1H, ddd, *J*= 7.2, 1.2, 0.6 Hz, Ar-*H*), 7.17 (1H, dd, *J*= 8.1, 7.2 Hz, Ar-*H*), 4.91 (1H, qd, *J*= 6.7, 2.7 Hz, C*H*CH_3), 4.51 – 4.34 (2H, m, OC*H*$_2$$CH_3$), 3.74 (1H, d, *J*= 2.8 Hz, N*H*CH), 1.68 (3H, d, *J*= 6.8 Hz, CHC*H*$_3$), 1.42 (3H, t, *J*= 7.1 Hz, OCH_2C*H*$_3$), 1.24 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 160.9, 133.1, 128.9, 126.3, 125.0, 124.3, 121.5, 121.2, 98.6, 61.5, 55.8, 52.7, 22.9, 22.8, 14.4; **LRMS** $[M+H]^+$ 415.1; **HRMS** (TOF, ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{24}N_2O_3SBr$ 415.0691; Found 415.0687.

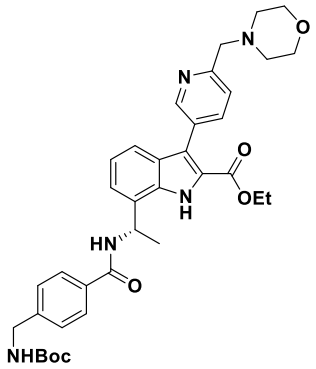
Ethyl 3-bromo-7-((1*S*)-1-((4-(((*tert*-butoxycarbonyl)amino)methyl)benzoyl)amino)ethyl)-1*H*-indole-2-carboxylate (S69)



To a solution of *N*-protected amine **S68** (500 mg, 1.2 mmol, 1.0 eq) in anhydrous THF (4.3 mL) in EtOH (1.8 mL) was added 4 M aq HCl in dioxane (0.96 mL, 3.85 mmol, 3.2 eq) at room temperature. The reaction mixture was stirred for 1 h by which point complete conversion of starting material was observed. The resultant mixture was concentrated *in vacuo* and the solid obtained was suspended in Et_2O then filtered. The precipitate obtained was washed with Et_2O and air-dried to obtain the desired product as an off-white solid (380 mg, >99%). In a separate flask, to a solution of 4-[(*tert*-butoxycarbonylamino)methyl]benzoic acid (289 mg, 1.15 mmol, 1.2 eq) in CH_2Cl_2 (12 mL) was added the indole amine (299 mg, 0.96 mmol, 1.0 eq), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (599 mg, 1.15 mmol, 1.2 eq) and Et_3N (0.4 mL, 2.88 mmol, 3.0 eq). The resultant mixture was stirred at rt for 1 h. Upon completion of the reaction, the solvents were concentrated *in vacuo* and the crude product was purified using a Biotage SNAP-ultra column, with gradient elution from 100% CH_2Cl_2 to 20% EtOAc in CH_2Cl_2 to afford the desired product **S69** in >99% yield as a white solid (555 mg).

^{1}H NMR (500 MHz, DMSO) δ ppm 11.88 (1H, s, N*H*), 9.04 (1H, d, *J* = 8.0 Hz, N*H*), 7.81 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.44 (1H, d, *J* = 8.0 Hz, N*H*), 7.38 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.19 (1H, t, *J* = 7.5 Hz, Ar-*H*), 5.72 (1H, app p, *J* = 7.0 Hz, CH_3C*H*), 4.58 – 4.31 (2H, m, OC*H*$_2$$CH_3$), 4.14 (2H, d, *J* = 6.0 Hz, C*H*$_2$), 1.57 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.40 – 1.32 (12H, m, OCH_2C*H*$_3$ & C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, DMSO) δ ppm 166.6, 160.5, 156.3 (*C*=O), 144.1, 133.8, 132.8, 130.3, 127.7, 127.6, 127.1, 124.5, 122.8, 121.8, 119.3, 97.2 (Ar-*C*H+Ar-*C*), 78.5 (*C*(CH$_3$)$_3$), 61.4 (O*C*H$_2$CH$_3$), 44.8 (CH$_3$*C*H), 43.4 (*C*H$_2$), 28.5 (C(*C*H$_3$)$_3$), 20.7 (*C*H$_3$CH), 14.6 (OCH_2*C*H$_3$); **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{26}H_{30}O_5N_3{}^{79}BrNa$ 566.12610; Found 566.12605.

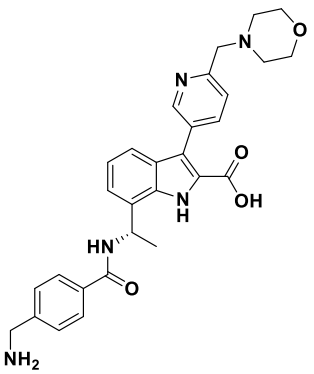
Ethyl 7-((1*S*)-1-((4-(((*tert*-butoxycarbonyl)amino)methyl)benzoyl)amino)ethyl)-3-(6-(morpholin-4-ylmethyl)pyridin-3-yl)-1*H*-indole-2-carboxylate (S70)



To the boronate **S65** (369 mg, 1.21 mmol, 1.2 eq) in 1,4-dioxane (9 mL) in a microwave vial, were added bromo indole **S69** (550 mg, 1.01 mmol, 1.0 eq), $Pd(PCy_3)_2Cl_2$ (37.3 mg, 0.051 mmol, 0.05 eq), 2 M aq Na_2CO_3 (2.02 mL, 4.04 mmol, 4.0 eq). The reaction mixture was purged with argon, then subjected to microwave irradiation at 120 °C for 6 h. The reaction mixture was filtered through Celite®, eluting with EtOAc (40 mL) and water (20 mL). The organics were separated from the filtrate and the aqueous layer further extracted with EtOAc (2x20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using a BIOTAGE SNAP-Ultra 10 g column, with gradient elution from 100% EtOAc to 2% MeOH in EtOAc to give the desired product **S70** in >99% yield as a yellow solid (655 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.73 (1H, s, N*H*), 9.01 (1H, d, *J* = 8.0 Hz, N*H*), 8.57 (1H, dd, *J* = 2.5, 1.0 Hz, Ar-*H*), 7.89 – 7.83 (3H, m, Ar-*H*), 7.52 (1H, dd, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.45 – 7.28 (5H, m, Ar-*H*+N*H*), 7.11 (1H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 5.80 (1H, app t, *J* = 7.0 Hz, CH_3CH), 4.24 (2H, app qd, *J* = 7.0, 2.0 Hz, OCH_2CH_3), 4.16 (2H, d, *J* = 6.0 Hz, CH_2), 3.66 (2H, s, CH_2), 3.65 – 3.60 (4H, m, morpholino-CH_2), 2.49 – 2.44 (4H, m, morpholino-CH_2), 1.64 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.39 (9H, s, $C(CH_3)_3$), 1.17 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 165.9, 161.1, 156.3 (*C*=O), 149.7, 143.7, 138.0, 133.8, 132.6, 129.7, 127.9, 127.4, 127.2, 126.6, 123.6, 122.8, 122.2, 121.8, 121.0, 119.2, 118.9 (Ar-*C*+Ar-*C*H), 77.9 ($C(CH_3)_3$), 66.2 (morpholino-CH_2), 64.0 (CH_2), 60.5 (OCH_2CH_3), 53.3.3, 53.3 (morpholino-CH_2), 44.7 (CH_3CH), 43.1 (CH_2), 28.2 ($C(CH_3)_3$), 20.5 (CH_3CH), 13.8 (OCH_2CH_3); **HRMS** (TOF, ESI$^-$) m/z: $[M+H]^+$ Calcd for $C_{36}H_{44}O_6N_5$ 642.32861; Found 642.32813.

7-((1*S*)-1-((4-(aminomethyl)benzoyl)amino)ethyl)-3-(6-(morpholin-4-ylmethyl)pyridin-3-yl)-1*H*-indole-2-carboxylic acid (57)

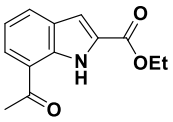


To a solution of *N*-Boc amine **S70** (303 mg, 0.47 mmol, 1.0 eq) in CH_2Cl_2 (2.8 mL), cooled to 0 °C, was added TFA (0.36 mL, 4.7 mmol, 10.0 eq) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resultant mixture was concentrated *in vacuo* co-evaporating with toluene. The crude residue was dissolved in THF/EtOH/H_2O (12 mL, 2:1:1) and treated with LiOH•H_2O (198 mg, 4.7 mmol, 10.0 eq). The resultant solution was stirred at room temperature overnight. Upon completion, the resultant mixture was acidified to pH 2 with 2 M aq HCl, then concentrated *in vacuo*. The product was purified by prep HPLC, with gradient elution from 2% MeCN in water to 40% MeCN in water over 17 min, then up to 98% MeCN in water over 3 min. Both solvents were acidified to a final concentration of 0.01% (v/v) formic acid. The fractions containing product were concentrated *in vacuo*, then re-suspended in 18 mL of water-MeCN. The solution was treated with 2 mL of 100 mM HCl, so the final HCl concentration was 10 mM. The sample was then lyophilized to obtain the desired product **57** in >99% yield as its HCl salt as a yellow powder (298 mg, >99%, yellow powder).

^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.84 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.08 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.95 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.62 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.56 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.48 – 7.42 (2H, m, Ar-*H*), 7.17 (1H, t, *J* = 7.5 Hz, Ar-*H*), 5.87 (1H, q, *J* =

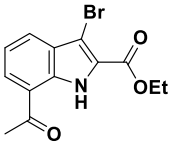
7.0 Hz, CH_3CH), 4.58 (2H, s, CH_2), 4.18 (2H, s, CH_2), 4.09 – 3.84 (4H, m, morpholino-CH_2), 3.46 (4H, t, *J* = 5.0 Hz, morpholino-CH_2), 1.79 (3H, d, *J* = 7.0 Hz, CH_3CH); **^{13}C NMR** (126 MHz, CD_3OD) δ ppm 167.2, 162.0, (*C*=O), 150.2, 138.6, 127.9, 127.2, 122.8, 120.9, 120.3, 118.3 (Ar-*C*H), 146.6, 135.9, 134.1, 133.6, 130.4, 126.8, 123.5, 117.8 (Ar-*C*), 62.8 (morpholino-CH_2), 59. 5 (CH_2), 51.5 (morpholino-CH_2), 43.9 (CH_3CH), 41.7 (CH_2), 17.6 (CH_3CH); **HRMS** (TOF, ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{29}H_{32}O_4N_5$ 514.24488; Found 514.24467.

Ethyl 7-acetyl-1*H*-indole-2-carboxylate (S71)



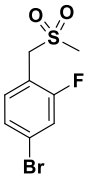
To ethyl 7-bromo-1*H*-indole-2-carboxylate (10.0 g, 37.3 mmol, 1 eq), $Pd(OAc)_2$ (251 mg, 1.12 mmol, 0.03 eq) and 1,3-bis(diphenylphosphino)propane (DPPP, 923 mg, 2.24 mmol, 0.06 eq) was added degassed EtOH (75 ml) at room temperature under Ar atmosphere, followed by triethylamine (15.6 mL, 112 mmol, 3.0 eq) and butyl vinyl ether (15.1 mL, 112 mmol, 3.0 eq). The reaction mixture was then heated to 80 °C for 18 h and then the volatiles removed *in vacuo* and the residue was redissolved in 2:1 THF: CH_2Cl_2 (110 mL) and treated with 4 M HCl (40 mL) and stirred for 1 h. The yellow reaction mixture was then diluted with EtOAc (500 mL) and the organic layer washed with H_2O (200 mL), sat. $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4, filtered and evaporated to dryness. The yellow oil was washed with hexane (100 mL) and the yellow precipitate was filtered off and dried *in vacuo* to afford the desired compound **S71** in 89% yield as an off-white solid (7.70 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.80 (1H, br. s, N*H*), 7.93 (1H, dt, *J*= 8.0, 0.9 Hz, Ar-*H*), 7.89 (1H, dd, *J*= 7.5, 1.0 Hz, Ar-*H*), 7.26 (1H, d, *J*= 2.4 Hz, Ar-*H*), 7.21 (1H, t, *J*= 7.7 Hz, Ar-*H*), 4.43 (2H, q, J = 7.1 Hz, OCH_2CH_3), 2.71 (3H, s, CH_3), 1.43 (3H, t, *J*= 7.1 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 199.8, 161.4, 135.3, 129.4, 129.1, 128.9, 128.2, 121.1, 120.0, 108.4, 61.2, 26.6, 14.5; **LRMS** $[M+H]^+$ 232.1; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{13}NO_3$ 232.0978; Found 232.0974.

Ethyl 7-acetyl-3-bromo-1*H*-indole-2-carboxylate (S72)



To a solution of indole **S71** (7.51 g, 32.5 mmol) in MeCN (105 mL) at 0 °C was added *N*-bromosuccinimide (6.07 g, 34.1 mmol, 1.05 eq) and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then diluted with EtOAc (300 mL) and the organic layer was washed sequentially with 10% $Na_2S_2O_3$ (2 x 100 mL), H_2O (4 x 100 mL) and brine (200 mL), dried over Na_2SO_4 and filtered through a pad of silica gel and concentrated *in vacuo* to give the product as a yellow solid which was purified by recrystallization (from hot 50 mL heptane and 7 mL EtOAc) to afford the desired compound **S72** in 79% yield as yellow plates (7.99 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 10.87 (1H, s, N-*H*), 7.98 – 7.91 (2H, m, Ar-*H*), 7.30 (1H, dd, *J* = 8.1, 7.4 Hz, Ar-*H*), 4.47 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.72 (3H, s, CH_3), 1.46 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 199.7, 160.2, 133.9, 129.3, 129.2, 127.7, 125.7, 121.1, 120.6, 98.5, 61.6, 26.6, 14.45; LRMS $[M+H]^+$ 310.0; **HRMS** (TOF, ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{12}BrNO_3$ 310.0078; Found 310.0079.

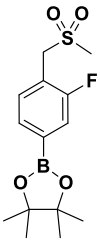
4-Bromo-2-fluoro-1-((methylsulfonyl)methyl)benzene (S73)



Degassed EtOH (22 mL) was added to a mixture of 4-bromo-1-(bromomethyl)-2-fluorobenzene (2.95 g, 11.0 mmol) and sodium methanesulfinate (1.46 g, 14.3 mmol, 1.3 eq) at rt. The resultant reaction mixture stirred at 80 °C for 1 h before being concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O and the organic layer was washed additionally with H_2O (× 3), brine, dried over $MgSO_4$ and

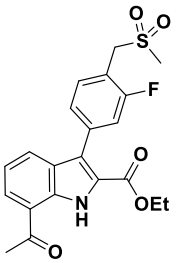
concentrated *in vacuo*. The crude mixture was washed on a P3 frit (eluent hexane/ Et_2O, 1:1) and concentrated *in vacuo* to give the desired product **S73** in 92% yield as a colorless solid (2.71 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42 – 7.33 (3H, m, Ar-*H*), 4.27 (2H, s, C*H*$_2$SO$_2$CH$_3$), 2.83 (3H, br q, *J* = 0.9 Hz, C*H*$_3$); **LRMS** [M-SO_2Me]$^+$ 186.9.

2-(3-Fluoro-4-((methylsulfonyl)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S74)



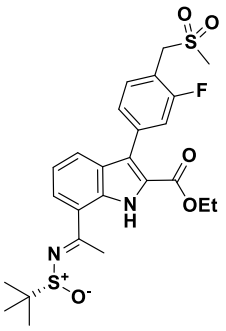
Argon was bubbled through a mixture of arylbromide **S73** (2.55 g, 9.55 mmol), bis(pinacolato)diboron (2.67 g, 10.5 mmol, 1.1 eq), potassium acetate (2.81 g, 28.6 mmol) and Pd(dppf)Cl_2•DCM (234 mg, 0.286 mmol, 0.03 eq) in 1,4-dioxane (38 mL) at rt for 10 min. The resultant reaction mixture was left to stir at 100 °C for 2 h then cooled to rt, poured into Et_2O (100 mL) and stirred at rt for 30 min. The solution was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent hexane/EtOAc, 2:1 to 1:1) followed by recrystallization from a minimum amount of toluene. The crystals were filtered off, washed with cold toluene (× 2) and hexane. The desired product **S74** was obtained in 88% yield as large beige prisms (2.40 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.63 (1H, dd, *J* = 7.4, 1.1 Hz, Ar-*H*), 7.55 (1H, dd, *J* = 10.1, 1.1 Hz, Ar-*H*), 7.49 (1H, t, *J* = 7.4 Hz, Ar-*H*), 4.33 (2H, s, C*H*$_2$SO$_2$CH$_3$), 2.79 (3H, br q, *J* = 0.9 Hz, C*H*$_3$), 1.34 (12H, s, 4 x C*H*$_3$); **LCMS** [M+H]$^+$ 315.0.

Ethyl 7-acetyl-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S75)



A suspension of bromoindole **S72** (1.00 g, 3.22 mmol, 1.0 eq), the pinacol ester S74 (1.11 g, 3.55 mmol, 1.1 eq) and Pd(dppf)Cl_2•DCM (132 mg, 0.16 mmol, 0.05 eq) in dioxane (26 mL) was degassed by bubbling Ar for 10 min at RT and then a solution of 2 M aq Na_2CO_3 (7 mL) was added. The reaction mixture was stirred for 1 h at 80 °C and then cooled to RT and was quenched by the addition of ammonium pyrrolidinedithiocarbamate (80 mg, 0.48 mmol, 0.15 eq) in H_2O (1 mL) and stirred for 30 min; then partitioned between CH_2Cl_2 and H_2O, filtered through Celite®, and the organic layer was washed with H_2O, brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by FCC (CH_2Cl_2: EtOAc 20:1) followed by washing of the product with cold EtOAc (–78 °C) afforded the desired compound **S75** in 85% yield as a colorless solid (1.14 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 10.98 (1H, s, N-*H*), 7.97 (1H, dd, *J* = 7.5, 1.0 Hz, Ar-*H*), 7.88 (1H, d, *J* = 8.1, 0.9 Hz, Ar-*H*), 7.59 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.46 – 7.34 (2H, m, Ar-*H*), 7.27 (1H, t, *J* = 7.3 Hz, Ar-*H*), 4.40 (2H, s, C*H*$_2$SO$_2$CH$_3$), 4.35 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 2.90 (3H, d, *J* = 7.3 Hz, C*H*$_3$), 2.75 (3H, s, CH$_2$SO$_2$C*H*$_3$), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$);
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 199.9 (*C*=O), 160.9 (*C*OOEt), 160.5 (d, J_{FC} = 247.8 Hz, Ar*C*F), 136.9 (d, J_{FC} = 9.0 Hz), 134.2, 132.3 (d, J_{FC} = 3.4 Hz), 128.9, 128.9, 127.8, 127.5 (d, J_{FC} = 3.3 Hz), 124.8, 121.7 (d, J_{FC} = 2.1 Hz), 121.1, 120.7, 118.2 (d, J_{FC} = 22.4Hz) 114.8 (d, J_{FC} = 14.8 Hz), 61.4 (O*C*H$_2$CH$_3$), 54.3 (d, J_{FC} = 2.8 Hz S(=O)$_2$*C*H$_2$), 39.6 (d, J_{FC} = 2.4 Hz, S(=O)$_2$*C*H$_3$), 26.7 (C(=O)*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$); **LCMS** [M+H]$^+$ 418.03; **HRMS** (TOF, ESI$^+$) m/z: [M+Na]$^+$ Calcd for $C_{21}H_{20}FNO_5SNa$ 440.0938; Found 440.0951.

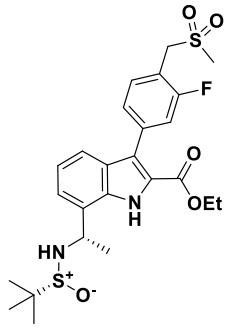
(*R*)-*tert*-Butyl(((1*E*)-1-(2-(ethoxycarbonyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indol-7-yl)ethylidene)amino)sulfaniumolate (S76)



To a suspension of ketone **S75** (2.40 g, 5.75 mmol, 1.0 eq) in anhydrous THF (7.2 mL) under an Ar atmosphere, was added $Ti(OEt)_4$ (2.41 mL, 11.5 mmol, 2.0 eq) followed by addition of (*R*)-*t*Bu-sulfinimide (1.05 g, 8.60 mmol, 1.50 eq) at room temp and the resulting yellow suspension was refluxed at 80 °C for 26 h. The reaction mixure was cooled to RT, diluted with CH_2Cl_2 and poured into brine (30 mL) and the resulting slurry was stirred vigorously for 15 min then filtered through a pad of Celite® eluting with EtOAc. The organics were combined, washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (hexane:EtOAc 1:1 to EtOAc) afforded the desired compound **S76** in 76% yield as a green solid (2.30 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 11.29 (1H, s, N-*H*), 7.88 (1H, d, *J*= 7.7 Hz, Ar-*H*), 7.83 (1H, d, *J*= 8.0 Hz, Ar-*H*), 7.59 (1H, t, *J* = 7.9 Hz, Ar-*H*), 7.47 – 7.34 (2H, m, Ar-*H*), 7.33 – 7.13 (1H, m, Ar-*H*), 4.40 (2H, s, CH_2SO$_2$CH$_3$), 4.34 (2H, qd, *J* = 7.2, 1.2 Hz, OCH_2CH$_3$), 2.95 (3H, s, CH_3), 2.90 (3H, s, CH_3), 1.45 (9H, s, (CH_3)$_3$), 1.31 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 178.7, 160.9, 160.5 (d, J_{FC}= 247.6 Hz), 136.9 (d, J_{FC}= 8.9 Hz), 133.8, 132.3 (d, J_{FC}= 3.3 Hz), 128.8, 127.7, 127.5 (d, J_{FC}= 3.2 Hz), 126.7, 124.2, 122.0 (d, J_{FC}= 2.0 Hz), 121.5, 121.0, 118.3 (d, J_{FC}= 22.5 Hz), 114.9 (d, J_{FC}= 14.6 Hz), 61.3, 56.8, 54.3 (d, J_{FC}= 2.9 Hz), 39.6 (d, J_{FC}= 2.5 Hz), 22.7, 20.0, 14.4; **LCMS** $[M+H]^+$ 521.46.

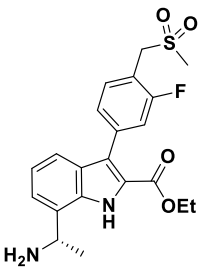
***tert*-Butyl(((1*S*)-1-(2-(ethoxycarbonyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indol-7-yl)ethyl)amino)-(*R*)-sulfaniumolate (S77)**



To the imine **S76** (2.29 g, 4.35 mmol, 1.0 eq) in anhydrous THF (22 mL) cooled to -76 °C was added L-Selectride® (1 M in THF, 8.7 mL, 8.7 mmol, 2.0 eq) dropwise and the resulting brownish green suspension was stirred at this temperature for 5 h and then the reaction mixture was allowed to slowly warm to 0 °C and the reaction was quenched with the addition of 30 mL sat. aq. NH_4Cl. The mixture was extracted with EtOAc (250 mL x 2); the organic layers were combined, washed with water (100 mL x 2), brine, dried over Na_2SO_4 and filtered through a plug of silica, washed with EtOAc and concentrated *in vacuo*. Purification by FCC (hexane: EtOAc 1:1, then EtOAc) afforded the desired compound **S77** in 77% yield (1.79 g).

[α]$_D^{20}$ = -32.3 (*c* 0.96, MeOH); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 9.87 (1H, s, N-*H*), 7.57 (2H, dt, *J* = 7.9, 3.8 Hz, Ar-*H*), 7.47 – 7.35 (2H, m, Ar-*H*), 7.32 (1H, d, *J* = 7.1, Ar-*H*), 7.15 (1H, dd, *J* = 8.1, 7.2 Hz, Ar-*H*), 4.93 (1H, qd, *J* = 6.7, 2.8 Hz, C*H*CH$_3$), 4.40 (2H, s, CH_2SO$_2$CH$_3$), 4.40 – 4.19 (2H, m, OCH_2CH$_3$), 3.60 (1H, d, *J* = 2.8 Hz, N-H), 2.89 (3H, d, *J* = 0.9 Hz, CH$_2$SO$_2$CH_3), 1.75 (3H, d, *J* = 6.8 Hz, CH_3), 1.27 (12H, m, (CH_3)$_3$, OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.5, 160.5 (d, J_{FC}= 247.3 Hz), 137.5 (d, J_{FC}= 9.0 Hz), 133.4, 132.2 (d, J_{FC}= 3.2 Hz), 128.5, 127.5 (d, J_{FC}= 3.3 Hz), 126.1, 124.7, 123.3, 121.9 (d, J_{FC}= 2.0 Hz), 121.5, 121.2, 118.2 (d, J_{FC}= 22.5 Hz), 114.6 (d, J_{FC}= 14.7 Hz), 61.3, 55.9, 54.4 (d, J_{FC}= 2.9 Hz), 52.9, 39.6 (d, J_{FC}= 2.6 Hz), 22.9, 22.8, 14.2; **LCMS** $[M+H]^+$ 523.51; **HRMS** (TOF, ESI^+) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{31}FN_2O_5S_2Na$ 545.1551; Found 545.1555.

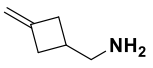
Ethyl 7-((1*S*)-1-aminoethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S78)



To a solution of **S77** (1.77 g, 3.33 mmol, 1.0 eq) in THF (24 mL) was added EtOH (10 mL) followed by 4 M HCl in dioxane (3.33 mL, 13.3 mmol, 4.0 eq) at room temperature and the reaction was stirred for 2 h. The resulting suspension was concentrated *in vacuo*, and the crude product triturated with Et_2O and the resulting solid was dissolved in CH_2Cl_2 (250 mL) and carefully extracted with sat. aq. $NaHCO_3$ (2 x 75 mL), brine (100 mL), dried (Na_2SO_4), filtered and the volatiles removed *in vacuo*. The resulting solid was washed with heptane to afford the desired product **S78** in 93% yield as a beige solid (1.32 g).

[α]$_D^{20}$ = +17.3 (*c* 1.0, DMSO); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 10.80 (1H, s, N-*H*), 7.61 – 7.33 (4H, m, Ar-*H*), 7.19 – 7.04 (2H, m, Ar-*H*), 4.59 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 4.39 (2H, s, C$H_2SO_2CH_3$), 4.32 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.88 (3H, d, *J* = 0.9 Hz, $CH_2SO_2CH_3$), 1.55 (3H, d, *J* = 6.6 Hz, CH_3), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ ppm 161.1, 160.4 (d, J_{FC}= 247.1 Hz), 136.2 (d, J_{FC}= 8.8 Hz), 133.6, 132.5 (d, J_{FC}= 3.6 Hz), 127.3, 126.6 (d, J_{FC}= 2.6 Hz), 124.4, 124.2, 122.3, 121.2, 121.1 (d, J_{FC}= 2.0 Hz), 120.7, 117.6 (d, J_{FC}= 22.2 Hz), 114.8 (d, J_{FC}= 15.4 Hz), 67.0, 60.7, 53.1, 44.9, 20.3, 13.8; **LCMS** $[M+H]^+$ 419.30; **HRMS** (TOF, ESI^+) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{23}FN_2O_4Na$ 441.1255; Found 441.1252.

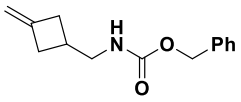
(3-Methylidenecyclobutyl)methanamine (S79)



To a stirred solution of 3-methylene-1-cyano-cyclobutane (5.00 mL, 46.0 mmol) in Et_2O (70 ml) at 0 °C was slowly added 2.4 M $LiAlH_4$ solution in THF (32.6 mL, 78.2 mmol, 1.70 eq) and the reaction was allowed to warm to room temperature over one hour. The reaction flask was then placed in a cool water bath (10 °C) and the reaction mixture was then quenched by the addition of H_2O (3 mL, with stirring for 5 min), 15% aq. NaOH (3 mL, with stirring for 5 min) then H_2O (9 mL, with stirring for 15 min); and then the reaction was warmed to RT and stirred for 15 min and filtered and washed with Et_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated (note: product is low boiling: 132 °C, 744 torr) to afford the desired compound **S79** as a pale yellow oil in 99% yield (4.47 g) which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.75 (2H, p, *J* = 2.5 Hz, CH_2), 2.82 – 2.68 (4H, m, NH_2CH_2, $(CH_ACH_B)_2$), 2.39 – 2.24 (3H, m, C*H*, $(CH_ACH_B)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 146.9, 106.3, 47.7, 35.3, 33.1.

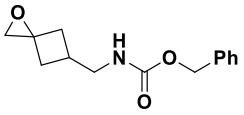
Benzyl ((3-methylidenecyclobutyl)methyl)carbamate (S80)



To a stirred solution of amine **S79** (4.47 g, 45.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C was slowly added Et_3N (7.62 mL, 54.7 mmol, 1.2 eq) and benzyl chloroformate (8.55 g, 50.1 mmol, 1.1 eq). The resultant reaction mixture was allowed to warm to rt and left to stir overnight. H_2O was then added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (eluent MTBE/hexane, 20:80 to 50:50) and the desired product **S80** was obtained in 74% yield as a colorless oil (8.0 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.41 – 7.27 (5H, m, Ar-*H*), 5.10 (2H, s, CH_2Ph), 4.77 (2H, p, *J* = 2.3 Hz, CH_2), 3.29 (2H, t, *J*= 6.5 Hz, NH_2CH_2), 2.85 – 2.69 (2H, m, $(CH_ACH_B)_2$), 2.47 (1H, h, *J*= 6.7, C*H*), 2.41 – 2.26 (2H, m, $(CH_ACH_B)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 156.6, 145.9, 136.6, 128.6, 128.6, 128.2, 106.9, 66.8, 46.0, 35.3, 30.0; **LRMS** 232.1.

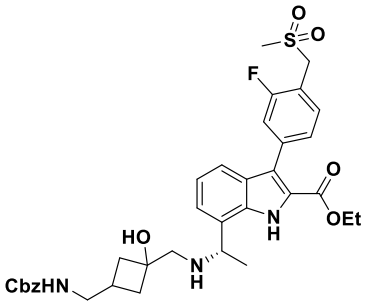
Benzyl (1-oxaspiro[2.3]hex-5-ylmethyl)carbamate (S81)



To a solution of alkene **S80** (8.00 g, 33.6 mmol) in CH_2Cl_2 (70 mL) was added *m*-CPBA (9.93 g, 40.3 mmol, 1.2 eq) at 0 °C. The mixture was allowed to warm to 22 °C and stirred for 4 h. An aqueous solution of Na_2SO_3 was then added and the reaction mixture was stirred for 20 min. The organic and aqueous layers were separated, and the latter was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the epoxide **S81** as a 1:1 mixture of diasteromers in 99% yield (8.49 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.40 – 7.30 (5H, m, Ar-*H*), 5.10 (2H, s, C*H*$_2$Ph), 4.83 (1H, s, N-*H*), 3.42 – 3.24 (2H, m, NH_2CH_2), 2.75 – 2.03 (7H, m, (C*H*$_2$)$_2$, OC*H*$_2$, C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 156.7, 156.6, 136.6, 128.7, 128.3, 128.3, 66.9, 58.6, 56.9, 52.6, 52.5, 46.3, 45.8, 34.7, 33.9, 27.0, 26.4; **LRMS** $[M+H]^+$ 248.0.

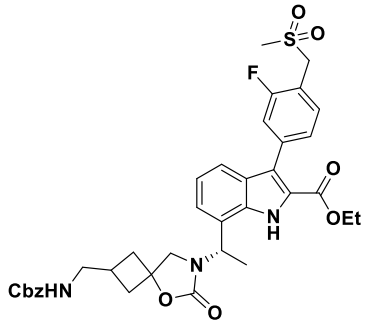
Ethyl 7-((1*S*)-1-(((3-((((benzyloxy)carbonyl)amino)methyl)-1-hydroxycyclobutyl)methyl)amino)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S82)



A suspension of amine **S78** (1.20 g, 2.87 mmol, 1.08 eq), the epoxide **S81** (655 mg, 2.65 mmol, 1.0 eq) and $LiClO_4$ (284 mg, 2.52 mmol, 0.95 eq) in anhydrous toluene (12 mL) was heated at 110 °C for 20 h. The resulting yellow solution was cooled to rt and diluted with EtOAc and water; the layers were separated and the aqueous layer extracted with EtOAc (2 x) and the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (CH_2Cl_2 : MeOH 50:1 to 20:1) afforded the desired compound **S82** as a mixture of diastereomers in 71% yield (1.38 g) *(which due to apparent partial instability was quickly taken through to the oxazolidone ring forming reaction).*

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.75 (1H, s, N-*H*), 7.59 – 7.47 (2H, m, Ar-*H*), 7.46 – 7.36 (2H, m, Ar-*H*), 7.36 – 7.26 (5H, m, Ar-*H*), 7.17 (1H, ddd, *J* = 7.4, 2.4, 1.1 Hz, Ar-*H*), 7.10 (1H, dd, *J* = 8.1, 7.1 Hz, Ar-*H*), 5.05 (2H, d, *J* = 12.5 Hz, C*H*$_2$Ph), 4.93 – 4.82 (1H, m, C*H*CH$_3$), 4.39 (2H, s, C*H*$_2$SO$_2$CH$_3$), 4.34 – 4.13 (3H, m, OC*H*$_2$CH$_3$, N-*H*), 3.29 – 2.99 (2H, m), 2.88 (3H, dd, *J* = 2.5, 0.8 Hz, CH$_2$SO$_2$C*H*$_3$), 2.78 (1H, t, *J* = 12.8 Hz), 2.63 – 2.36 (2H, m), 2.25 – 2.07 (2H, m), 1.93 (1H, q, *J* = 9.0 Hz), 1.76 (2H, td, *J*= 12.8, 7.6 Hz), 1.54 (3H, dd, *J*= 6.6, 2.7 Hz, CHC*H*$_3$), 1.20 (3H, t, *J* = 7.1 Hz); **LCMS** $[M+H]^+$ 666.62.

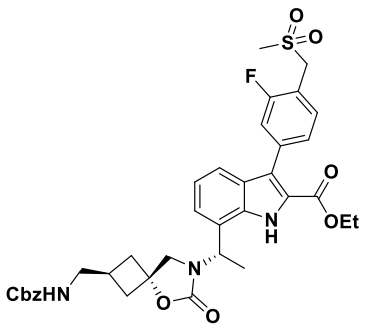
Ethyl 7-((1*S*)-1-(2-((((benzyloxy)carbonyl)amino)methyl)-6-oxo-5-oxa-7-azaspiro[3.4]oct-7-yl)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S83)



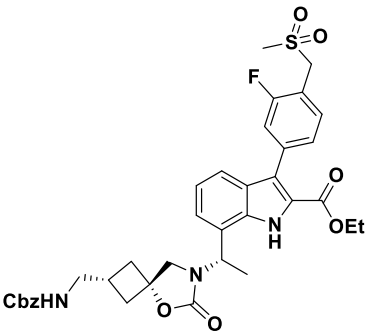
To a solution of the aminoalcohol **S82** (2.00 g, 2.73 mmol, 1.0 eq) in MeCN (30 mL) was added 1,1'-carbonyldiimidazole (CDI, 887 mg, 5.47 mmol, 2.00 eq) and the reaction mixture was stirred at RT for 21 h. UPLC analysis of the reaction mixture showed a conversion of 65% and a further portion of CDI was added (443 mg, 1.0) and stirring was continued for a further 23 h; UPLC analysis at this stage showed 95% conversion. The reaction mixture was concentrated *in vacuo*, suspended in EtOAc and the precipitate was filtered off; the filtrate was washed with aq 1 M HCl (150 mL), the aqueous layer was extracted with EtOAc (x2) and the combined organics were washed with water (100 mL), sat.

$NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by FCC (CH_2Cl_2: MeOH 20:1) afforded the desired compound **S83** as a mixture of diastereomers in 73% yield (1.38 g).

Further purification by preparative HPLC (Daicel Chiralpak ID, 250 × 30 mm, 5 μm particle size, 0-20 min heptane: CH_2Cl_2: *i*PrOH 55:20:25, then 20-40 min heptane: CH_2Cl_2: *i*PrOH 25:50:25, 30 mL/min) gave first **S83a** (679 mg, t_r = 15.0 min), then **S83b** (595 mg, t_r = 35.0 min).

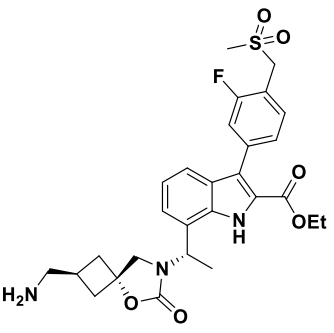


Data **S83a:** $[\alpha]_D^{20}$ = +107.3 (*c* 0.5, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 10.60 (1H, s), 7.63 – 7.51 (2H, m), 7.46 – 7.37 (2H, m), 7.37 – 7.26 (6 H, m), 7.15 (1H, dd, *J* = 8.1, 7.2 Hz), 5.61 (1H, q, *J* = 7.0 Hz), 5.06 (2H, s), 4.86 (1H, s), 4.42 – 4.25 (4H, m), 3.59 (1H, d, *J* = 8.9 Hz), 3.23 (2H, t, *J* = 5.8 Hz), 3.07 (1H, d, *J* = 8.8 Hz), 2.88 (3H, d, *J* = 0.9 Hz), 2.32 (1H, dd, *J* = 11.4 Hz, 7.1), 2.25 – 1.94 (4H, m), 1.74 (3H, d, *J* = 7.1 Hz), 1.35 (3H, t, *J* = 7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.7, 161.0, 159.2, 158.0, 156.8, 137.4, 137.3, 136.4, 134.5, 132.2, 132.2, 128.7, 128.4, 128.2, 127.9, 127.3, 124.0, 123.2, 122.4, 121.9, 121.4, 120.8, 118.2, 118.0, 114.6, 114.4, 79.0, 67.0, 61.2, 54.4, 53.6, 51.6, 47.1, 45.4, 39.5, 39.0, 37.5, 27.4, 15.9, 14.2; **LRMS** $[M+H]^+$ 692.6.



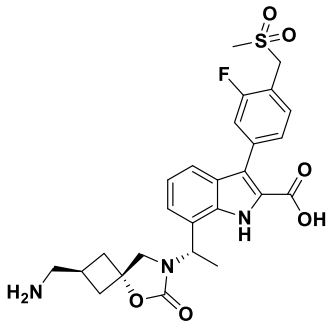
Data **S83b:** $[\alpha]_D^{20}$ = +62.0 (*c* 0.5, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 10.62 (1H, s), 7.64 – 7.52 (2H, m), 7.48 – 7.37 (2H, m), 7.29 (1H, d, *J* = 7.2 Hz), 7.19 – 7.11 (1H, m), 5.62 (1H, q, *J* = 7.0 Hz), 4.34 (4H, dd, *J* = 15.5, 8.4 Hz), 3.61 (1H, d, *J* = 8.8 Hz), 3.10 (1H, d, *J* = 8.8 Hz), 2.89 (3H, s), 2.37 (1H, d, *J* = 5.8 Hz), 2.24 – 2.08 (3H, m), 2.01 (2H, s), 1.75 (3H, d, *J* = 7.1 Hz), 1.35 (3H, t, *J* =7.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 161.7, 161.0, 159.3, 158.0, 156.6, 137.4, 137.3, 136.4, 134.5, 132.2, 128.7, 128.3, 128.3, 127.9, 127.4, 127.3, 124.0, 123.2, 122.3, 121.9, 121.4, 120.8, 118.2, 118.0, 114.6, 114.4, 76.2, 67.0, 61.2, 54.4, 53.6, 51.3, 47.1, 45.7, 39.5, 39.4, 38.2, 25.6, 15.9, 14.2; **LRMS** $[M+H]^+$ 692.6.

Ethyl 7-((1*S*)-1-((*2S,4r*)-(2-(aminomethyl)-6-oxo-5-oxa-7-azaspiro[3.4]oct-7-yl)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S84)



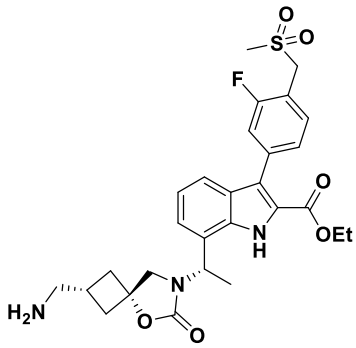
N-CBz protected amine **S83a** (679 mg, 0.982 mmol) was dissolved in CH_2Cl_2 (45 mL) and was stirred with activated charcoal (300 mg) for 10 min, then filtered through a pad of silica gel and then Celite, the filter cake washed with CH_2Cl_2 then EtOAc; then the volatiles were concentrated *in vacuo*. The starting material was then dissolved in AcOH (45 mL) and 10% Pd/C (313 mg, 0.294 mmol, 0.30 eq) was added. The reaction mixture was then placed under 5 bar hydrogen pressure for 1 h; UPLC analysis showed full conversion so the reaction mixture was filtrated through Celite, the filter cake washed with CH_2Cl_2, EtOAc, then EtOH, and the filtrate was concentrated *in vacuo* (with addition of toluene then $CHCl_3$ to remove residual AcOH) to afford the crude compound **S84** in >99% yield as a yellow foam (660 mg) which was used directly in the subsequent ester hydrolysis step.

7-((1*S*)-1-(*2S,4r*)-(2-(aminomethyl)-6-oxo-5-oxa-7-azaspiro[3.4]oct-7-yl)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylic acid (58)



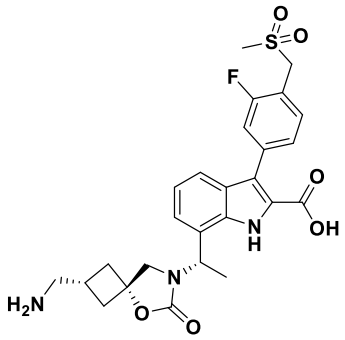
The ethyl ester **S84** (606 mg, 0.961 mmol) was dissolved in THF (18 mL) and a solution of LiOH•H_2O (242 mg, 5.78 mmol, 6.0 eq) in H_2O (18 mL) was added at 0 °C and the reaction was slowly warmed to RT and stirred overnight. UPLC analysis after 14 h showed 90% conversion and after 20 h 98% conversion was reached, whereupon the reaction mixture was quenched by the addition of AcOH (0.39 mL, 6.73 mmol, 7 eq) and concentrated *in vacuo*. Purification by RP chromatography (Biotage KP-C18 HS 30 g column, MeCN: 0.1% AcOH in H_2O gradient 5:95% to 95:5%) and then by preparative RP-HPLC afforded the desired compound **58** in 57% yield as a white solid (292 mg, > 98% purity by HPLC at 210 nm).
[α]$_D^{20}$ = +63.0 (*c* 1.0, DMSO); **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 10.30 (s, 1H), 8.88 – 7.70 (br s, 2H), 7.55 – 7.36 (m, 4H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 5.43 (q, *J* = 7.0 Hz, 1H), 4.55 (s, 2H), 3.66 (d, *J* = 9.6 Hz, 1H), 3.04 (s, 3H), 2.88 – 2.74 (m, 2H), 2.61 – 2.54 (m, 1H,overlapped with DMSO signal), 2.47 – 2.42 (m, 1H, overlapped with DMSO signal), 2.38 – 2.29 (m, 1H), 2.22 – 2.12 (m, 1H), 2.00 – 1.91 (m, 1H), 1.60 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 164.5, 161.4, 159.0, 156.4, 138.5, 138.4, 133.3, 132.0, 131.8, 127.8, 126.3, 123.7, 119.7, 119.6, 119.3, 117.7, 117.5, 114.5, 112.8, 112.7, 78.2, 53.1, 51.5, 47.1, 43.0, 37.7, 37.2, 25.1, 16.5; **LCMS** $[M+H]^+$ 530.44.

Ethyl 7-((1*S*)-1-((*2R,4s*)-(2-(aminomethyl)-6-oxo-5-oxa-7-azaspiro[3.4]oct-7-yl)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylate (S85)



N-CBz protected amine **S83b** (595 mg, 0.860 mmol) was dissolved in CH_2Cl_2 (40 mL) and was stirred with activated charcoal (300 mg) for 10 min, then filtered through a pad of silica gel and Celite®, the filter cake washed with CH_2Cl_2 then EtOAc; then the volatiles were concentrated *in vacuo*. The starting material was then dissolved in AcOH (40 mL) and 10% Pd/C (275 mg, 0.258 mmol, 0.30 eq) was added. The reaction mixture was then placed under 5 bar hydrogen pressure for 1 h; UPLC analysis showed full conversion so the reaction mixture was filtrated through a pad of Celite, the filter cake washed with CH_2Cl_2, EtOAc, then EtOH, and the filtrate was concentrated *in vacuo* (with addition of toluene then $CHCl_3$ to remove residual AcOH) to afford the crude compound **S85** in 94% yield as an off-white foam (453 mg) which was used directly in the subsequent ester hydrolysis step.

7-((1*S*)-1-(*2R,4s*)-(2-(aminomethyl)-6-oxo-5-oxa-7-azaspiro[3.4]oct-7-yl)ethyl)-3-(3-fluoro-4-((methylsulfonyl)methyl)phenyl)-1*H*-indole-2-carboxylic acid (59)



The ethyl ester **S85** (453 mg, 0.812 mmol) was dissolved in THF (2.5 mL) and a solution of LiOH•H_2O (136 mg, 0.325 mmol, 4.0 eq) in H_2O (2.5 mL) was added at 0 °C and the reaction was slowly warmed to RT and stirred for 22 h. UPLC analysis after 22 h showed full conversion, the reaction mixture was quenched by the addition of a solution of $KHSO_4$ (342 mg, 2.44 mmol, 3 eq) in H_2O (0.8 mL) and THF was partly concentrated and the resultant slurry was stirred overnight. The resultant suspension was filtrated, washed wth H_2O (x3) and dried under reduced pressure over P_2O_5. The crude reaction mixture was dissolved in

DMSO and TFA (1 eq) was added. Purification by RP chromatography afforded the desired compound **59** in 50% yield as a yellow solid (215 mg, >98% purity by HPLC).
[α]$_D^{23}$ = +47.1 (*c* 0.92, DMSO); **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 10.39 (1H, s), 8.28 (3H, s), 7.51 – 7.37 (4H, m), 7.20 (1H, d, *J* = 7.3 Hz), 7.04 (1H, t, *J* = 7.7 Hz), 5.48 (1H, q, *J* = 7.0 Hz), 4.55 (2H, s), 3.71 (1H, d, *J* = 9.4 Hz), 3.09 (1H, d, *J* = 9.4 Hz), 3.04 (3H, s), 2.89 (2H, d, *J* = 5.1 Hz), 2.39 (1H, dd, *J* = 11.5, 6.6 Hz), 2.20 – 2.05 (4H, m), 1.63 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, DMSO-d_6) δ ppm 164.3, 161.4, 159.0, 156.4, 138.5, 138.4, 133.2, 132.0, 131.7, 127.9, 126.3, 123.4, 119.8, 119.6, 119.4, 117.7, 117.5, 114.6, 112.8, 112.7, 75.5, 53.1, 51.0, 47.0, 43.4, 38.6, 38.1, 23.4, 16.3; **LRMS** $[M+H]^+$ 530.346.

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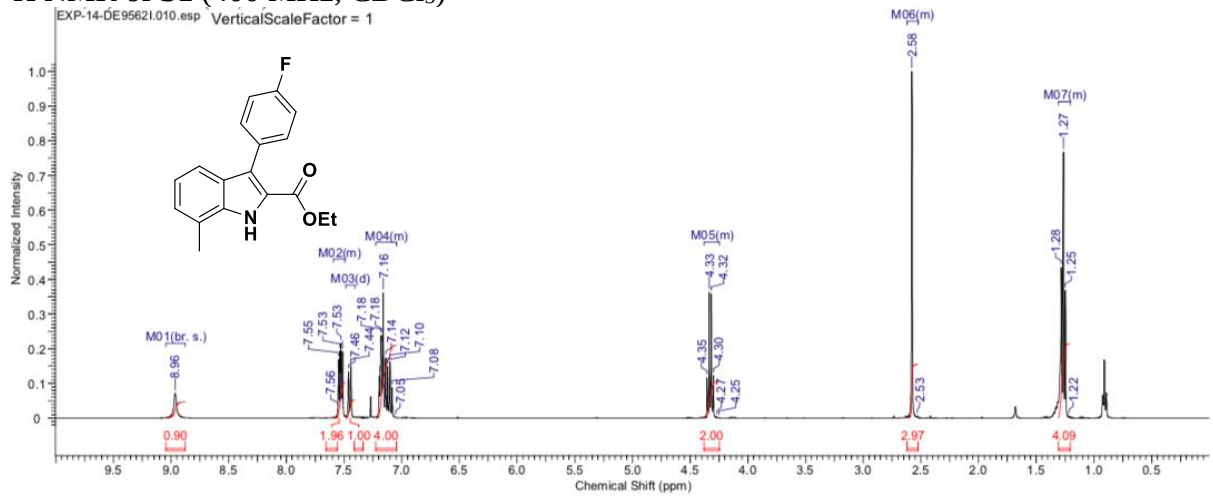
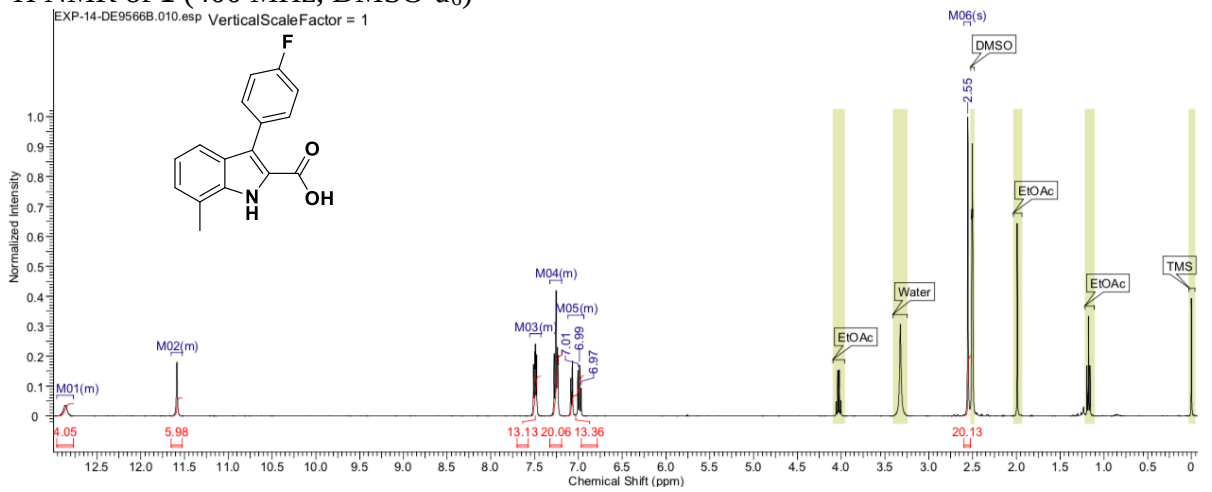
6 NMR Spectra

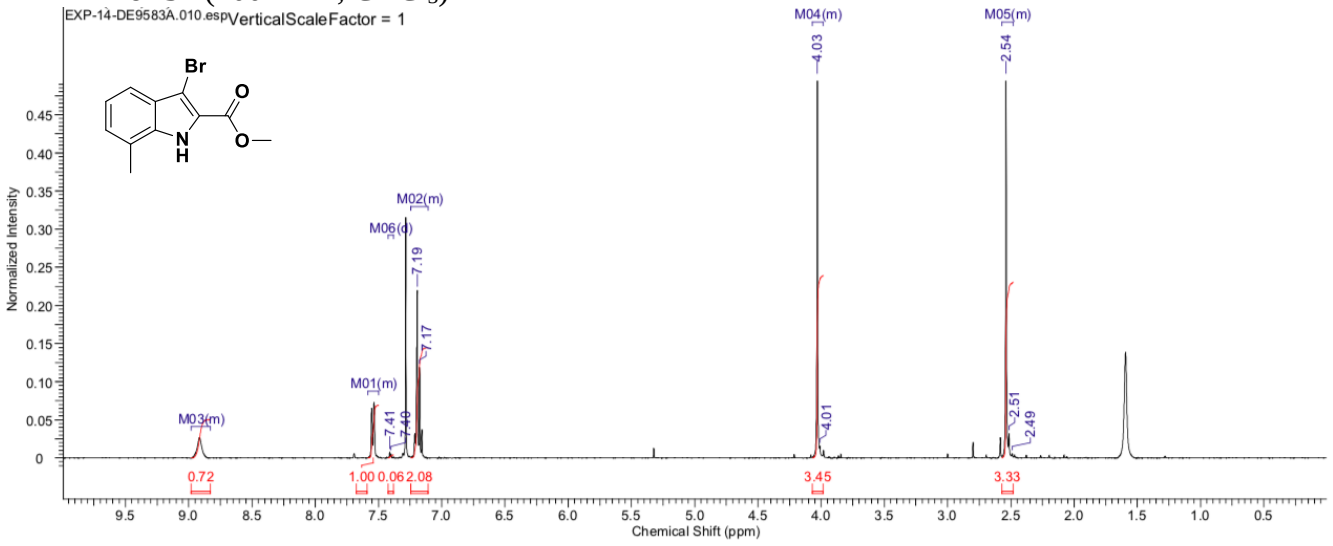
^{1}H NMR of **S1** (400 MHz, $CDCl_3$)



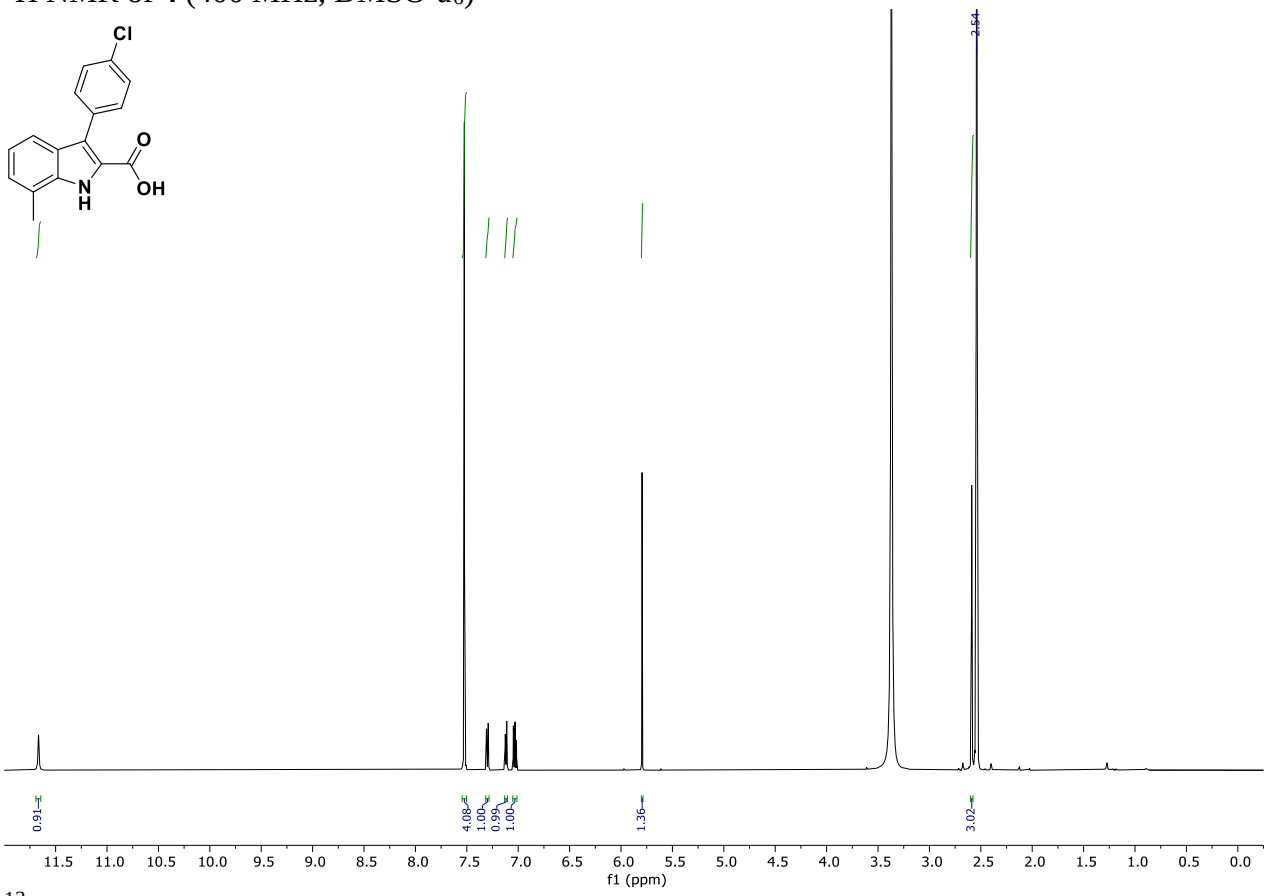
^{1}H NMR of **1** (400 MHz, DMSO-d_6)



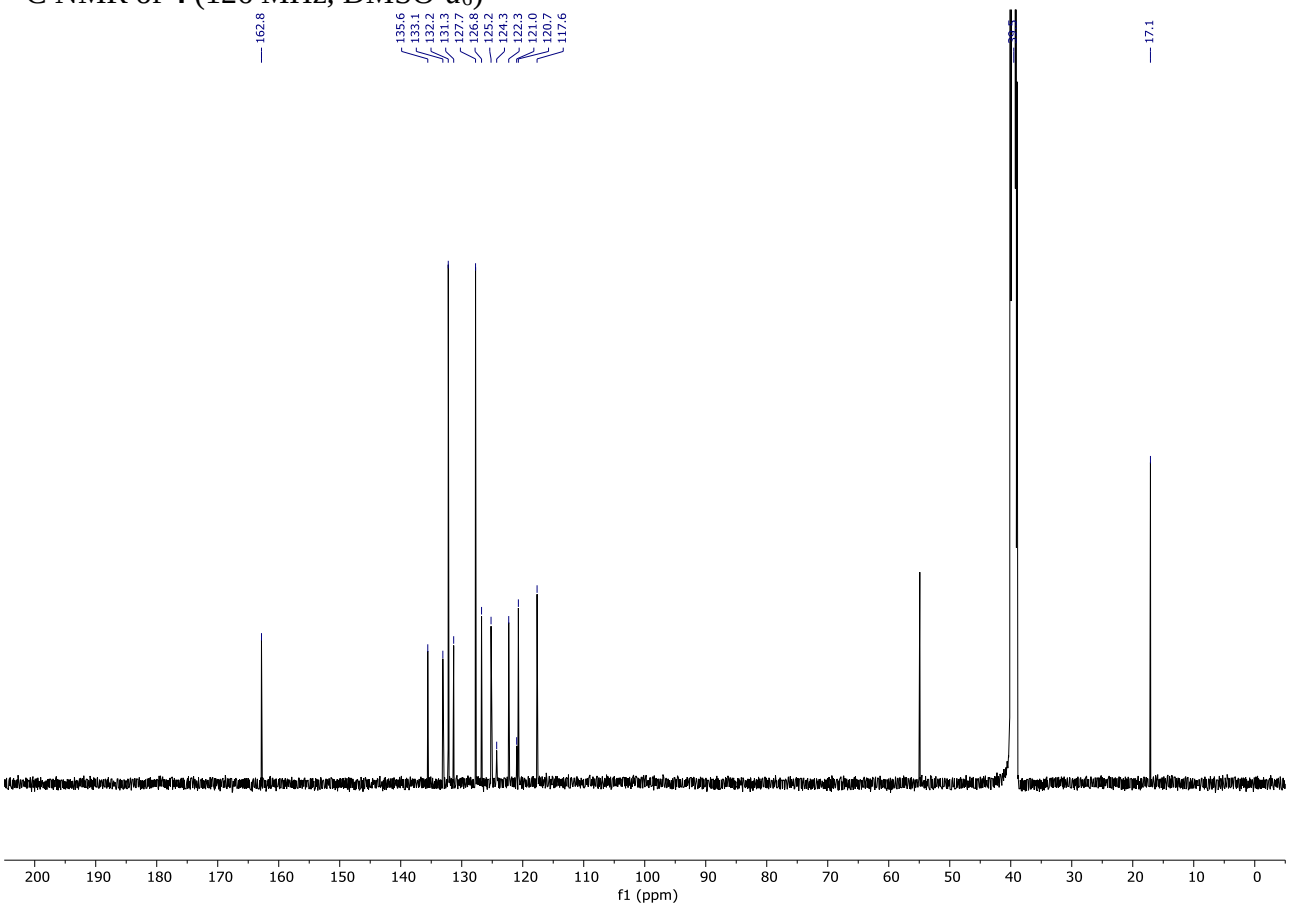
^{1}H NMR of **S2** (400 MHz, $CDCl_3$)



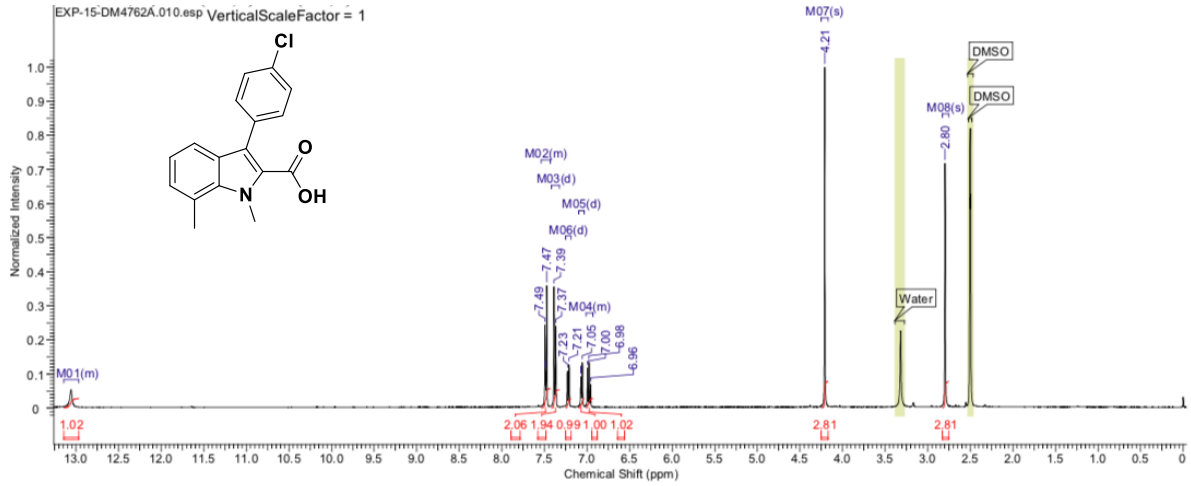
^{1}H NMR of **4** (400 MHz, DMSO-d_6)



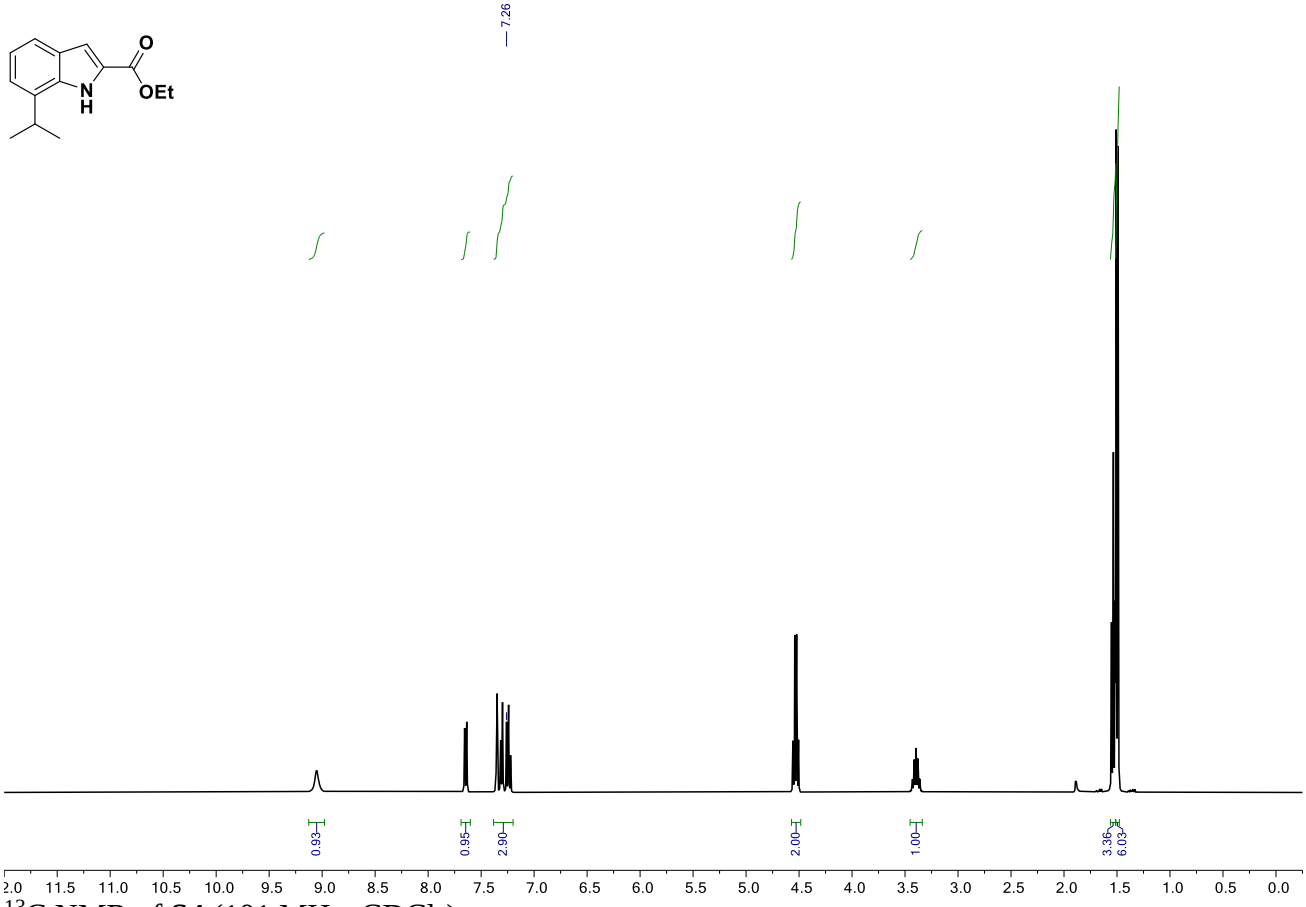
^{13}C NMR of **4** (126 MHz, DMSO-d_6)



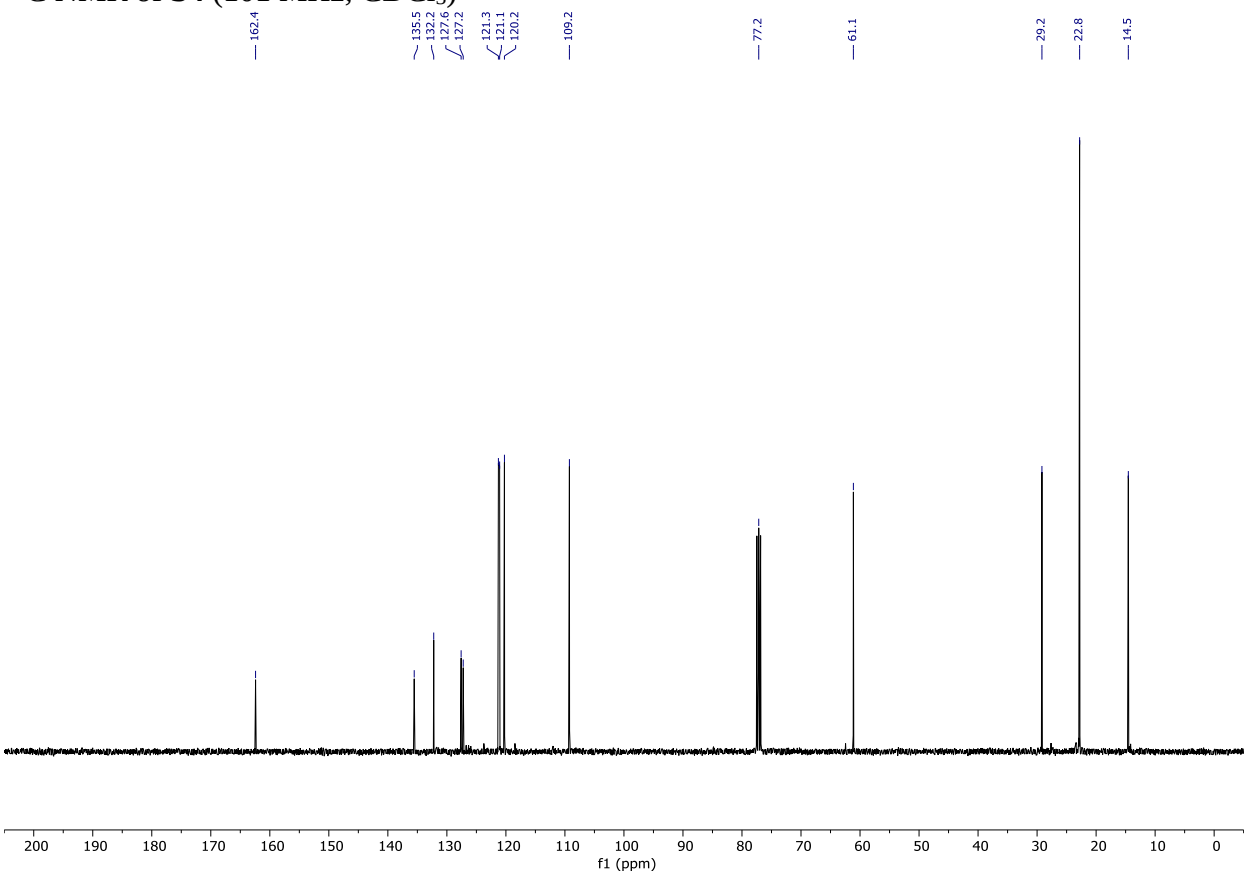
^{1}H NMR of **3** (400 MHz, DMSO-d_6)



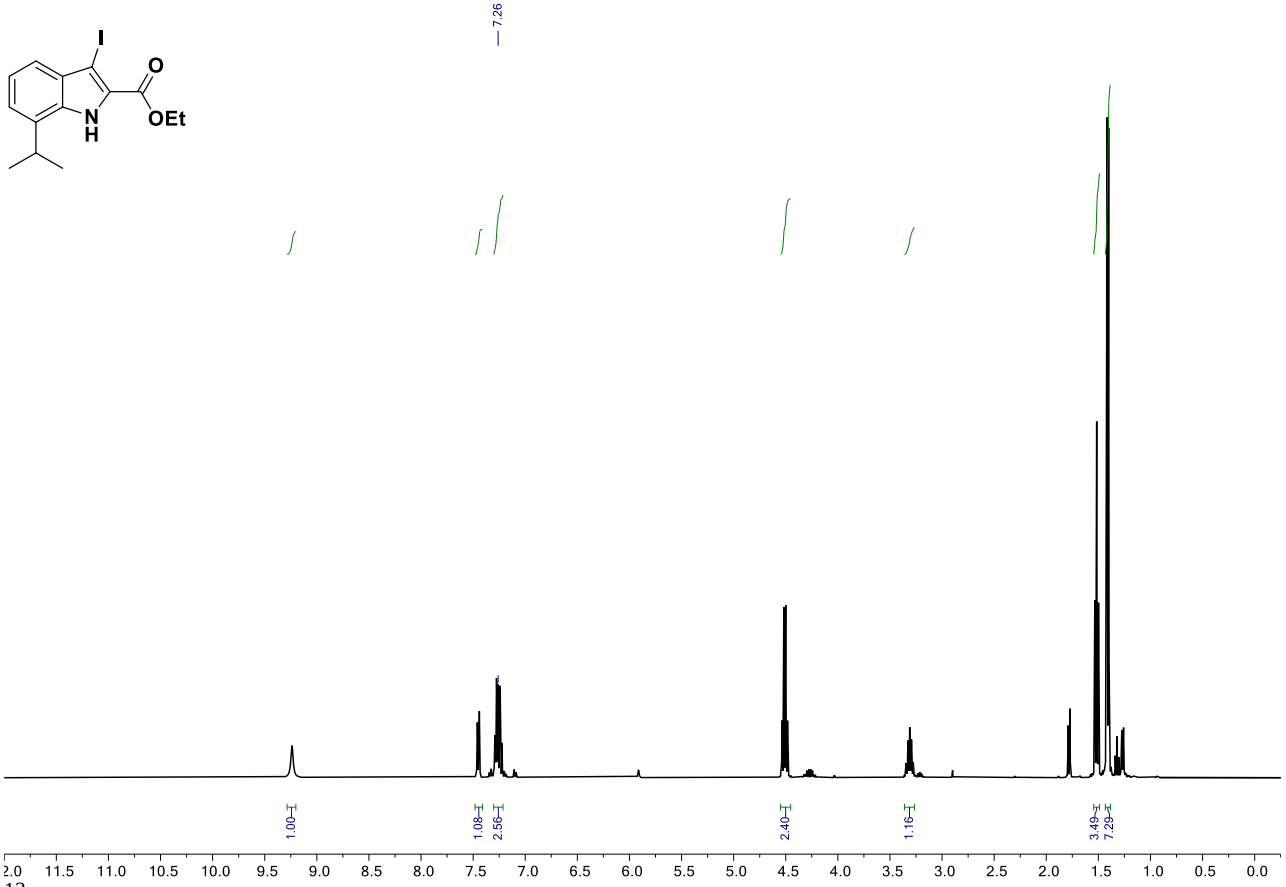
^{1}H NMR of **S4** (400 MHz, $CDCl_3$)



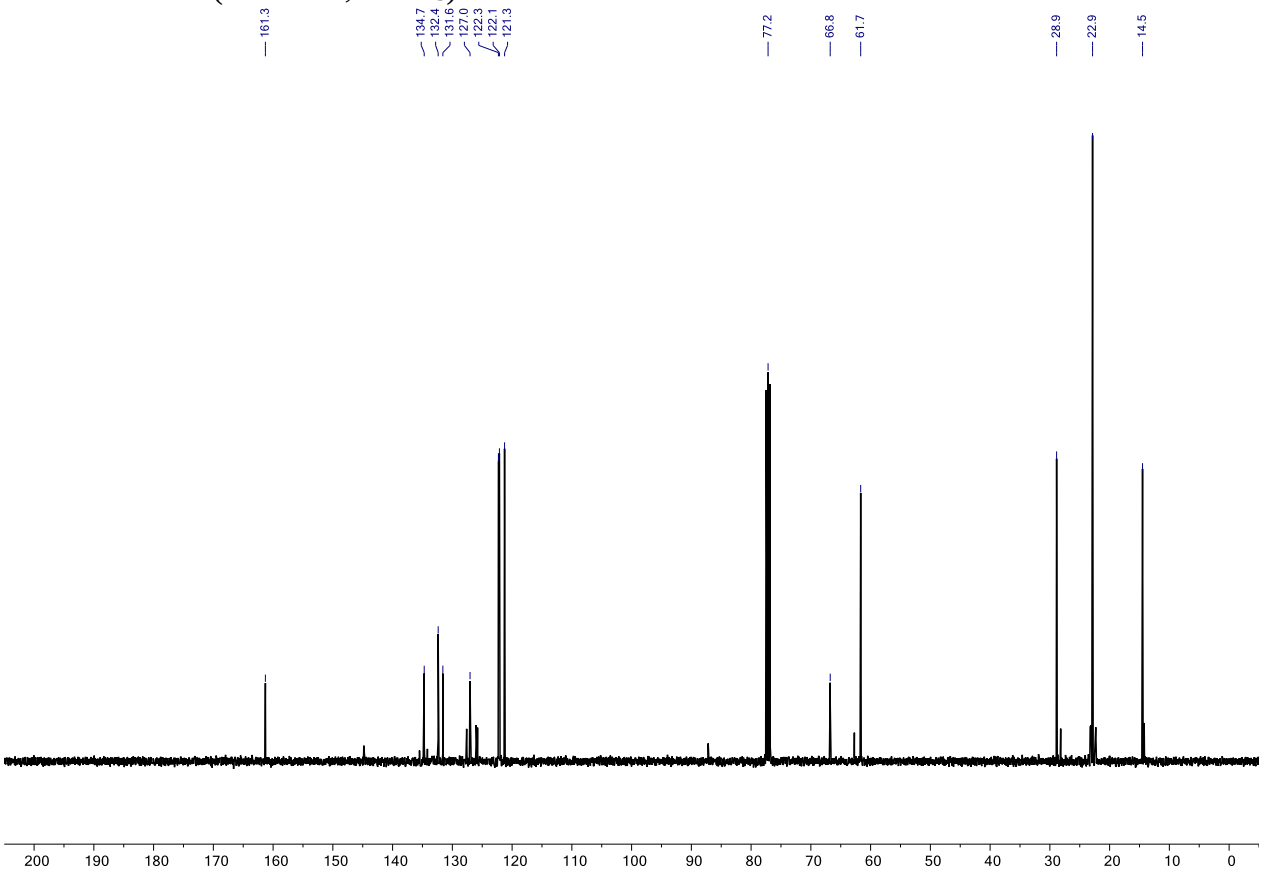
^{13}C NMR of **S4** (101 MHz, $CDCl_3$)



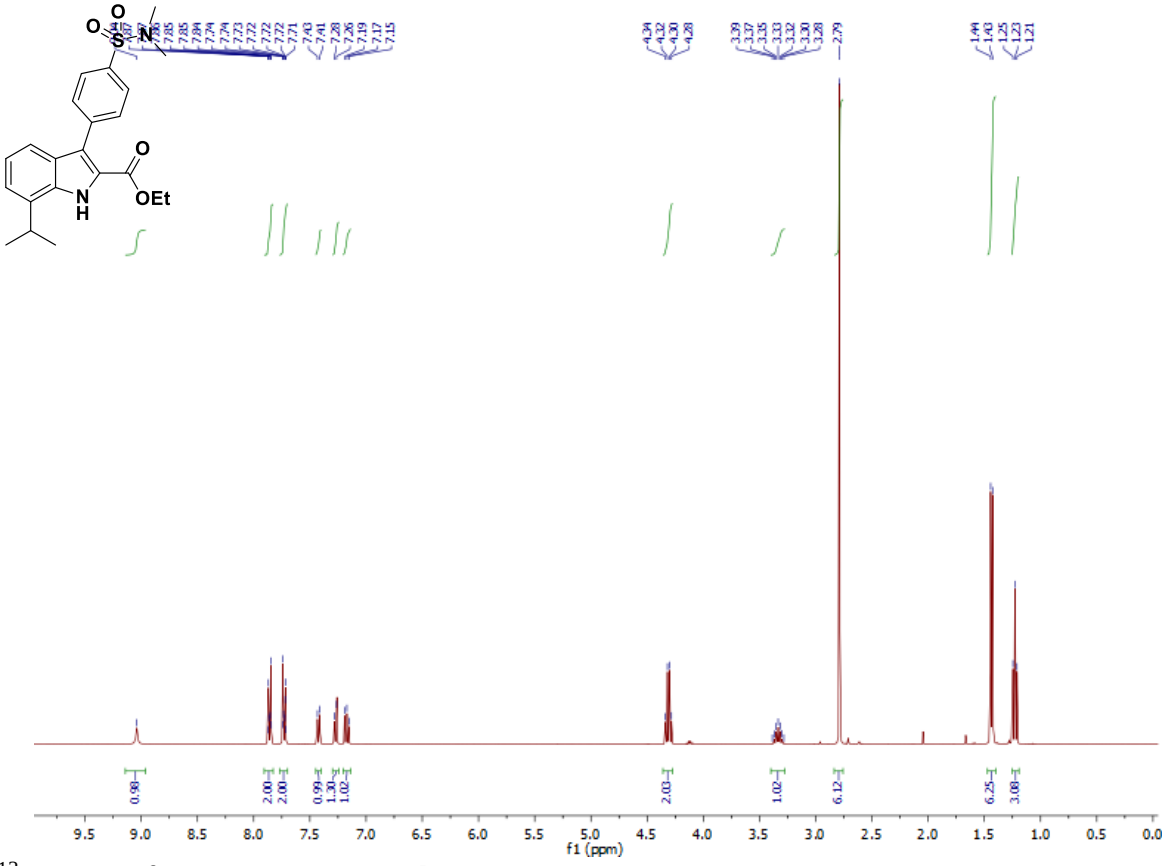
^{1}H NMR of **S5** (400 MHz, $CDCl_3$)



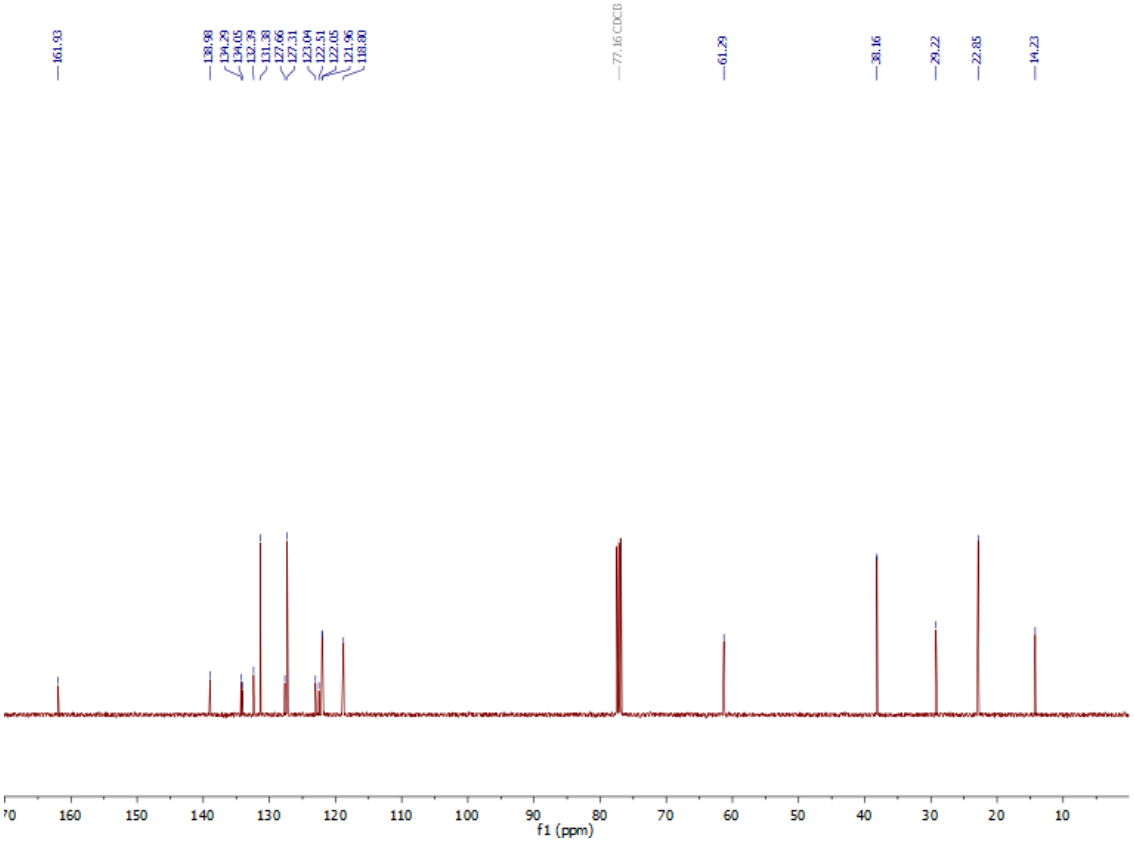
^{13}C NMR of **S5** (101 MHz, $CDCl_3$)



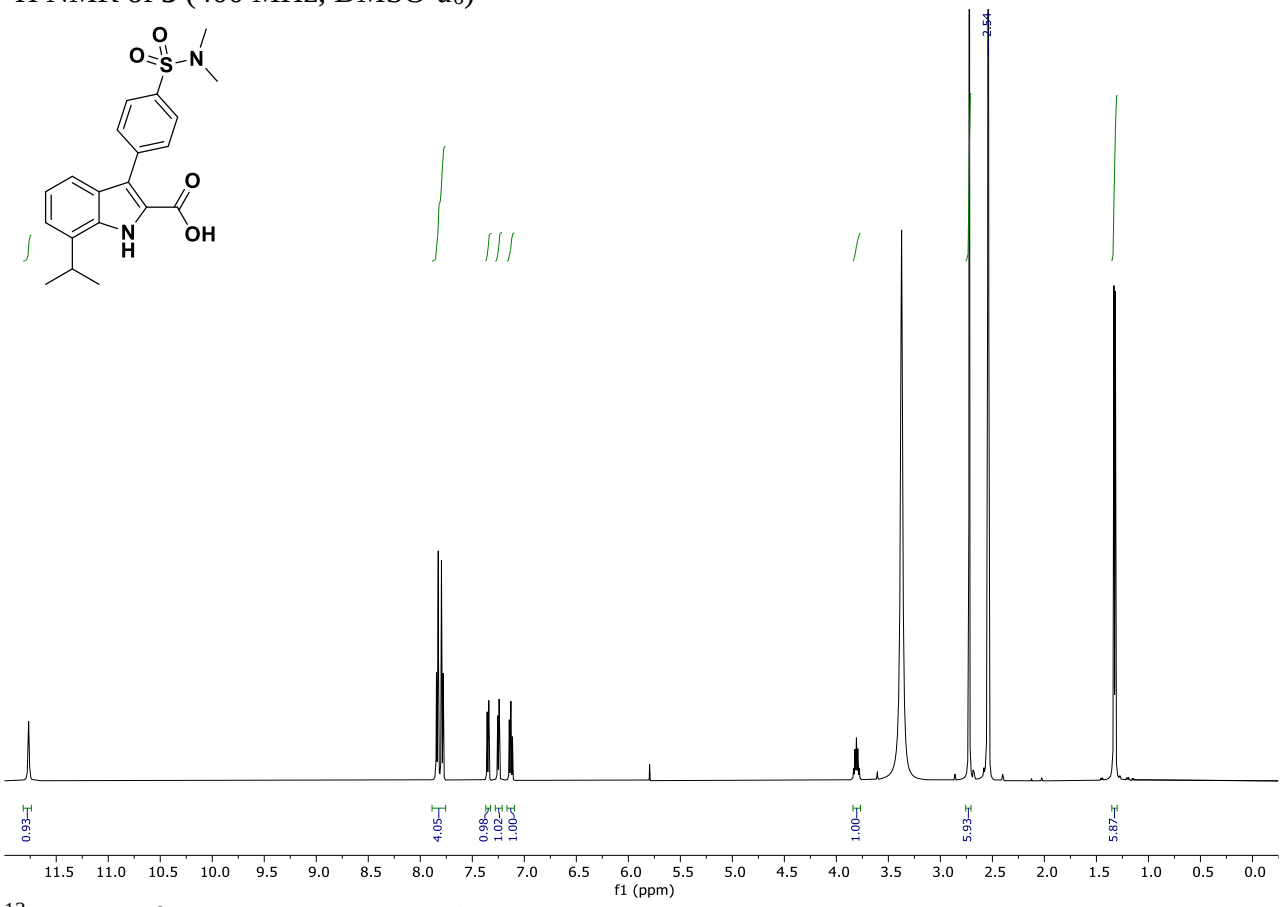
^{1}H NMR of **S6** (400 MHz, $CDCl_3$)



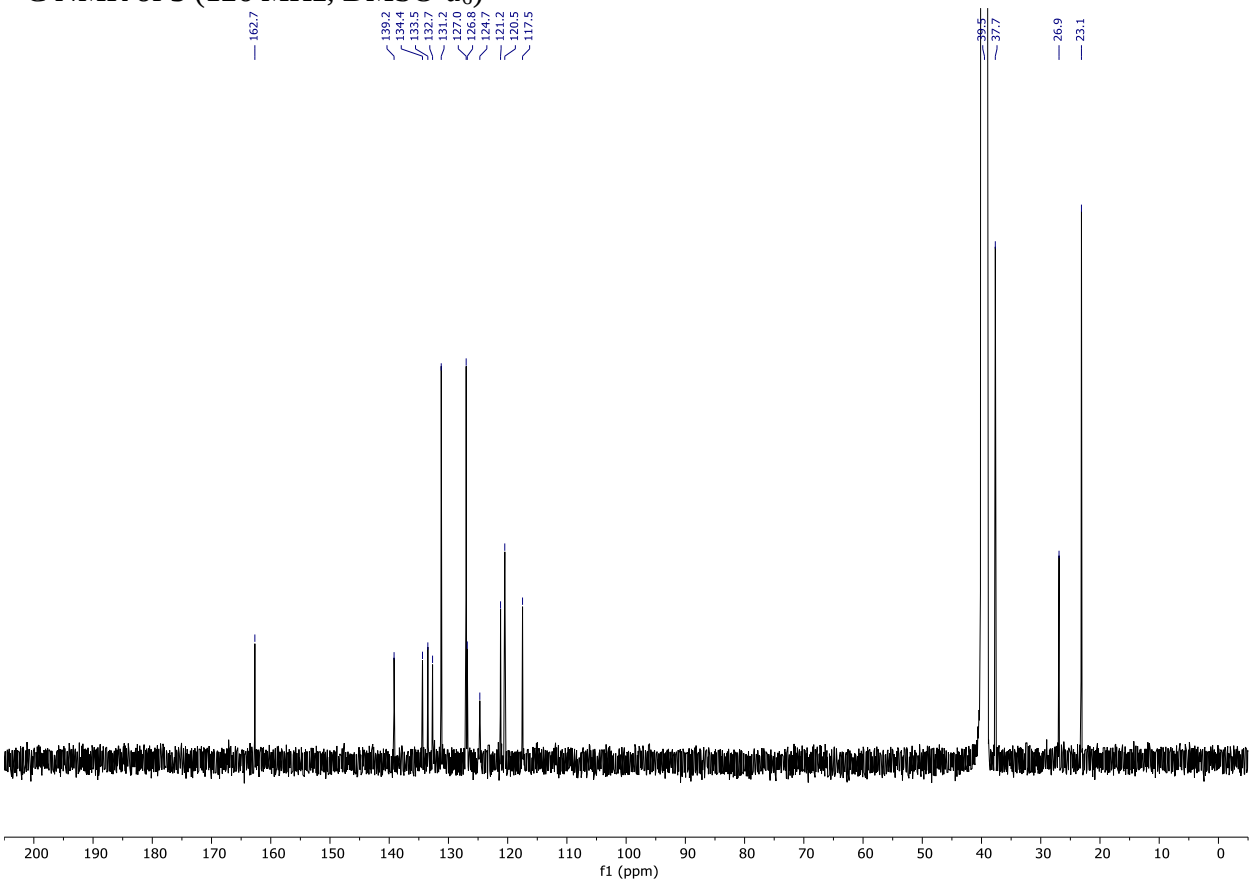
^{13}C NMR of **S6** (101 MHz, $CDCl_3$)



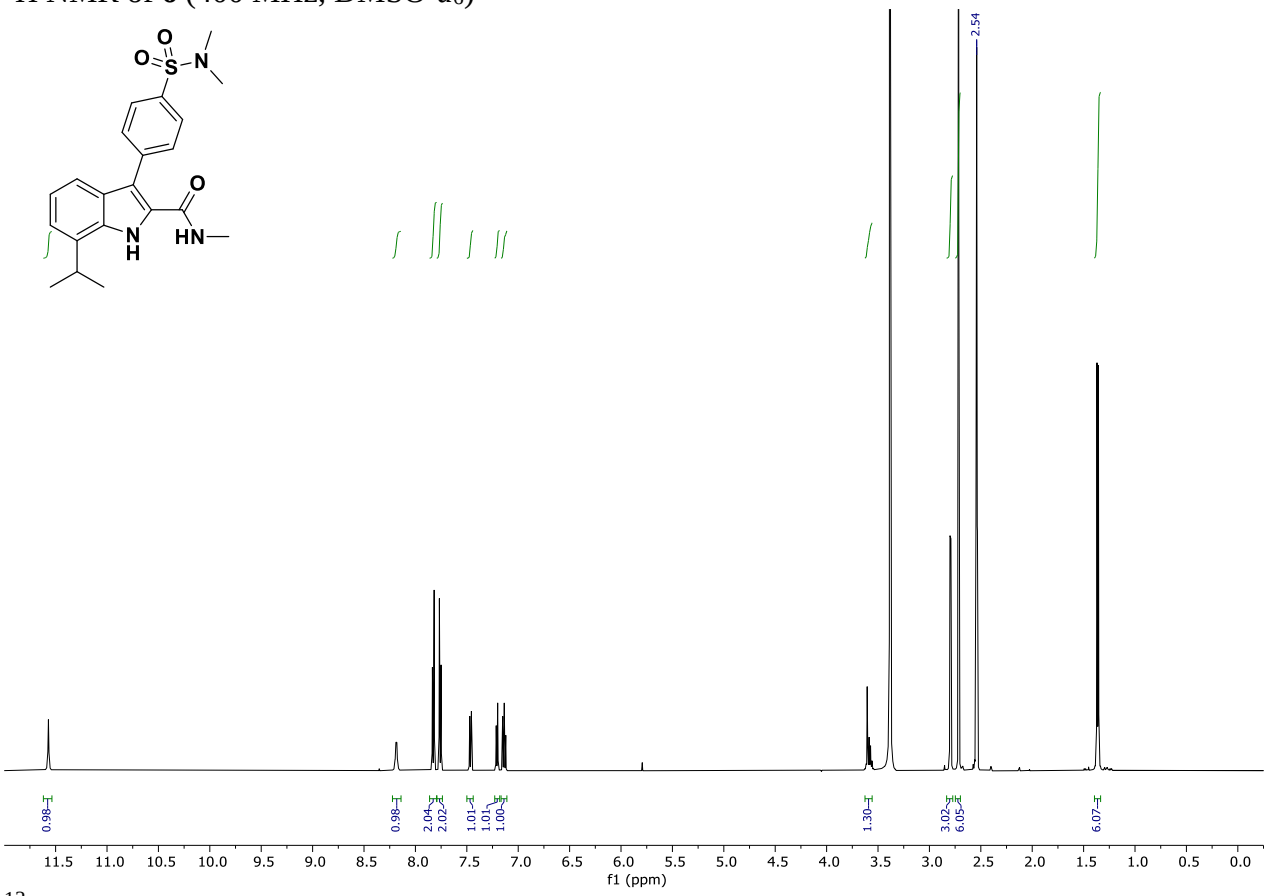
^{1}H NMR of **5** (400 MHz, DMSO-d_6)



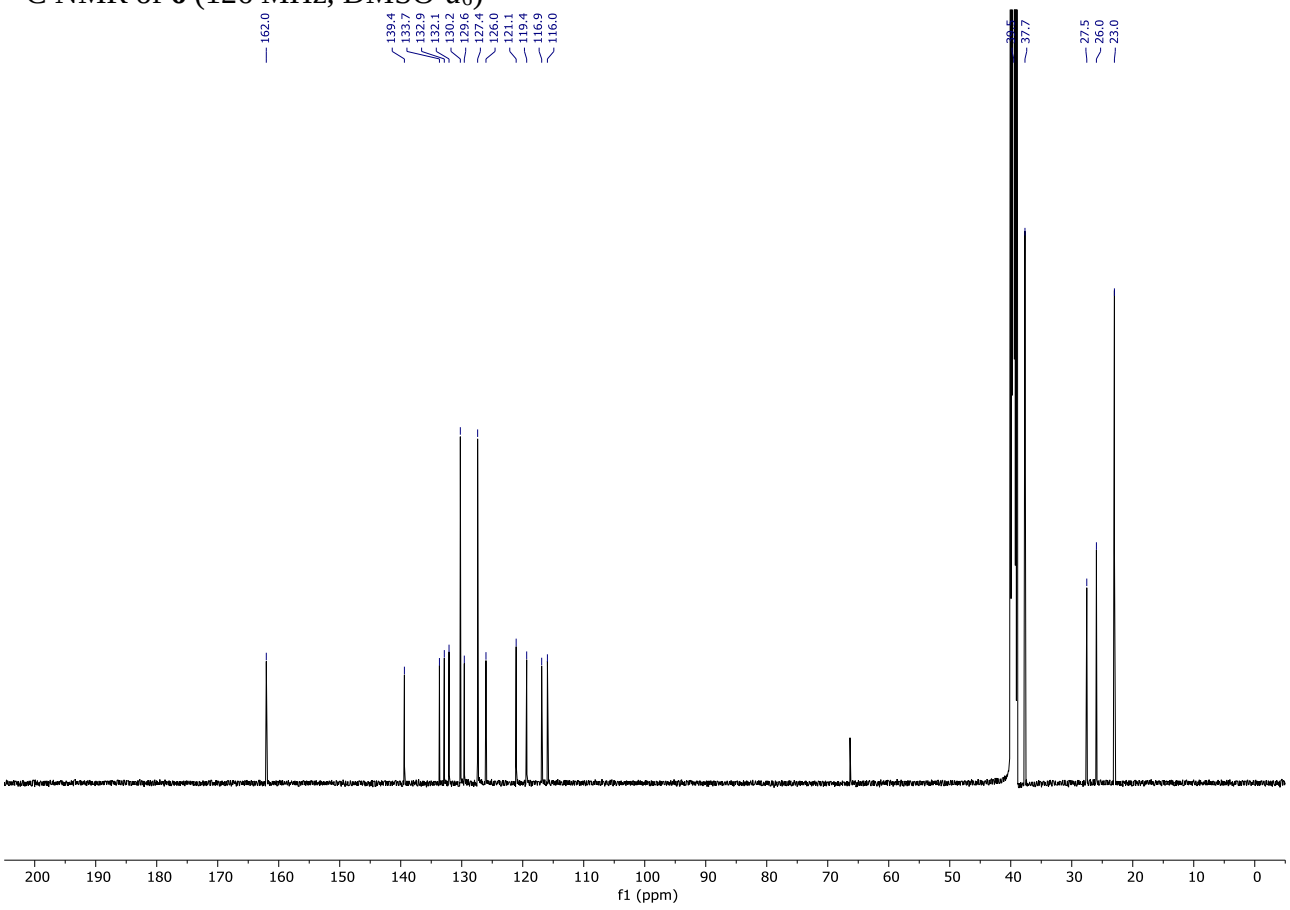
^{13}C NMR of **5** (126 MHz, DMSO-d_6)



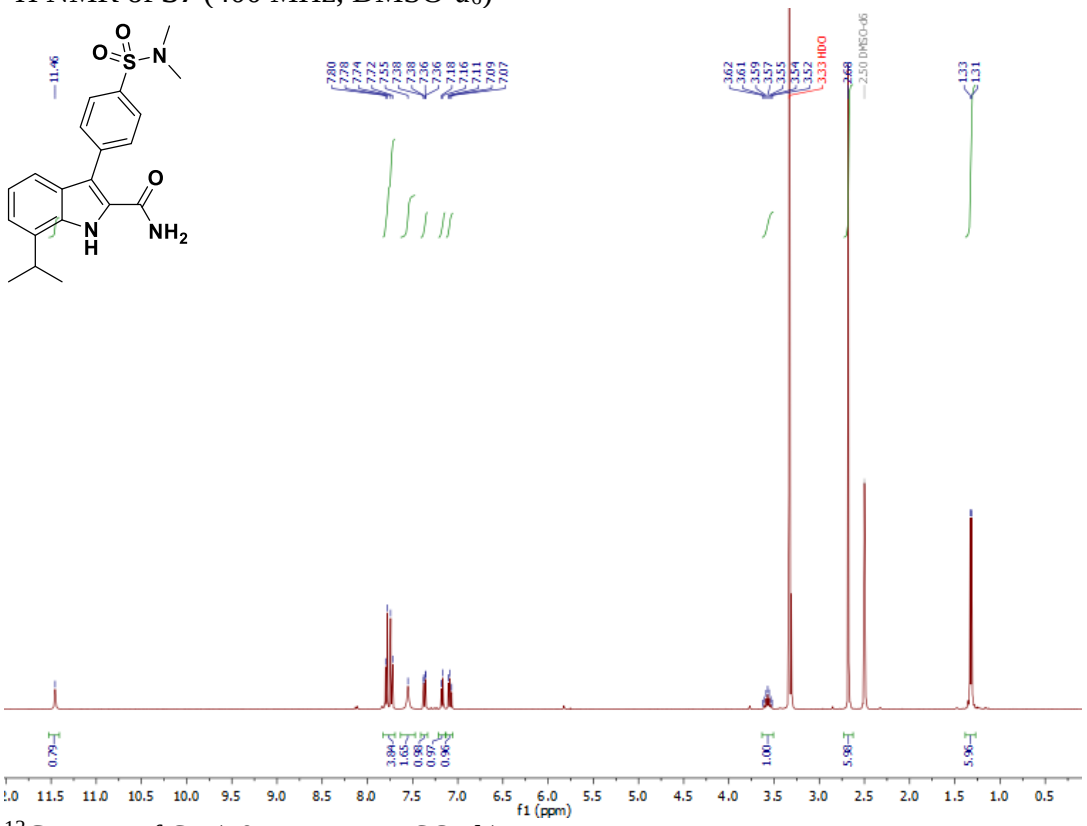
^{1}H NMR of **6** (400 MHz, DMSO-d_6)



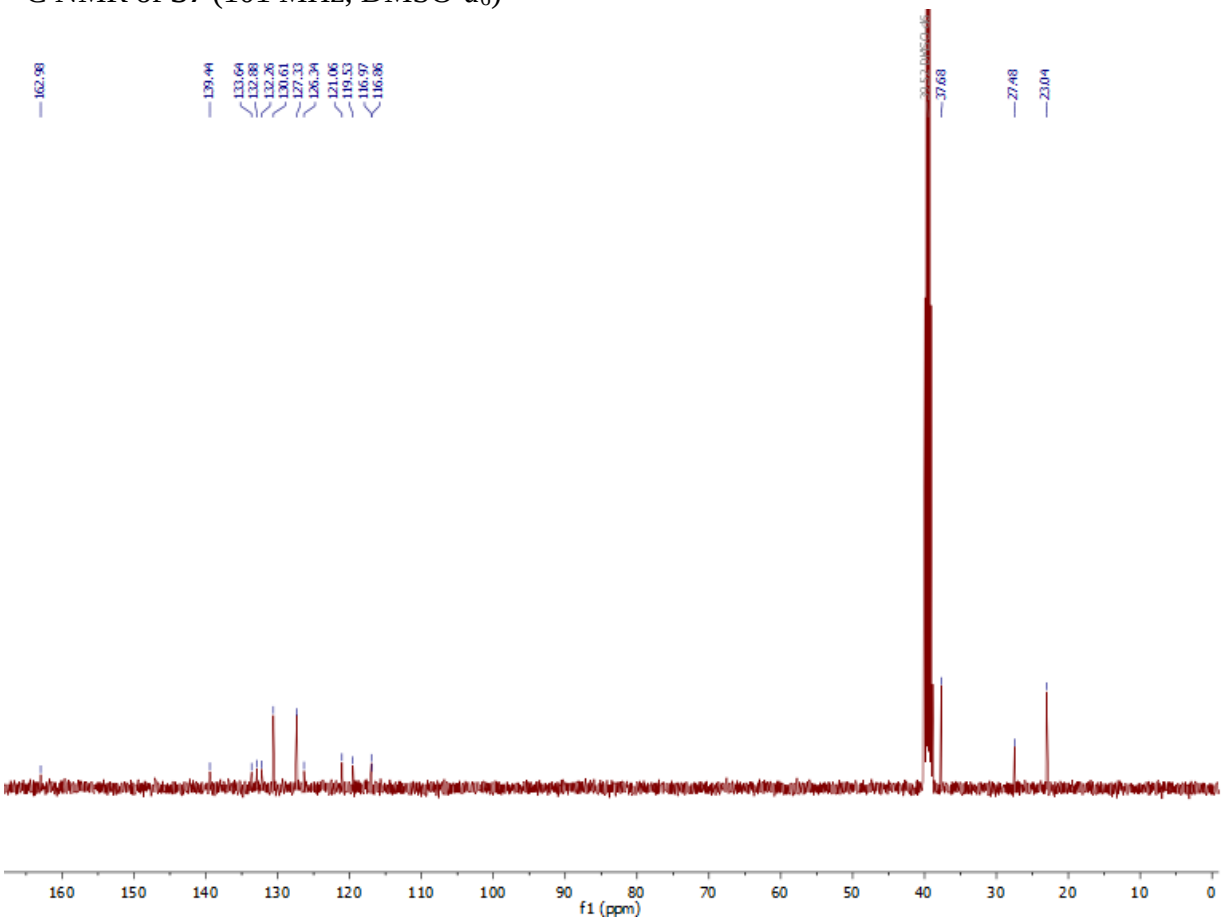
^{13}C NMR of **6** (126 MHz, DMSO-d_6)



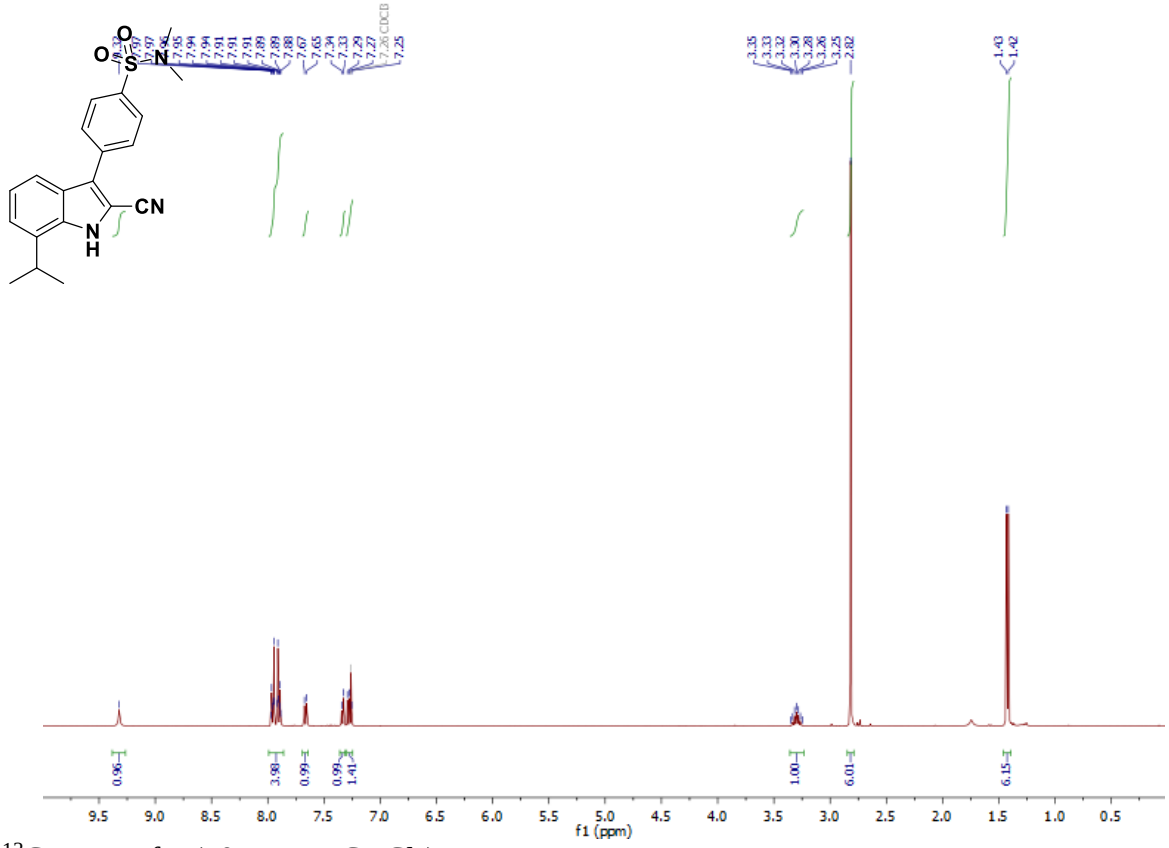
^{1}H NMR of **S7** (400 MHz, DMSO-d_6)



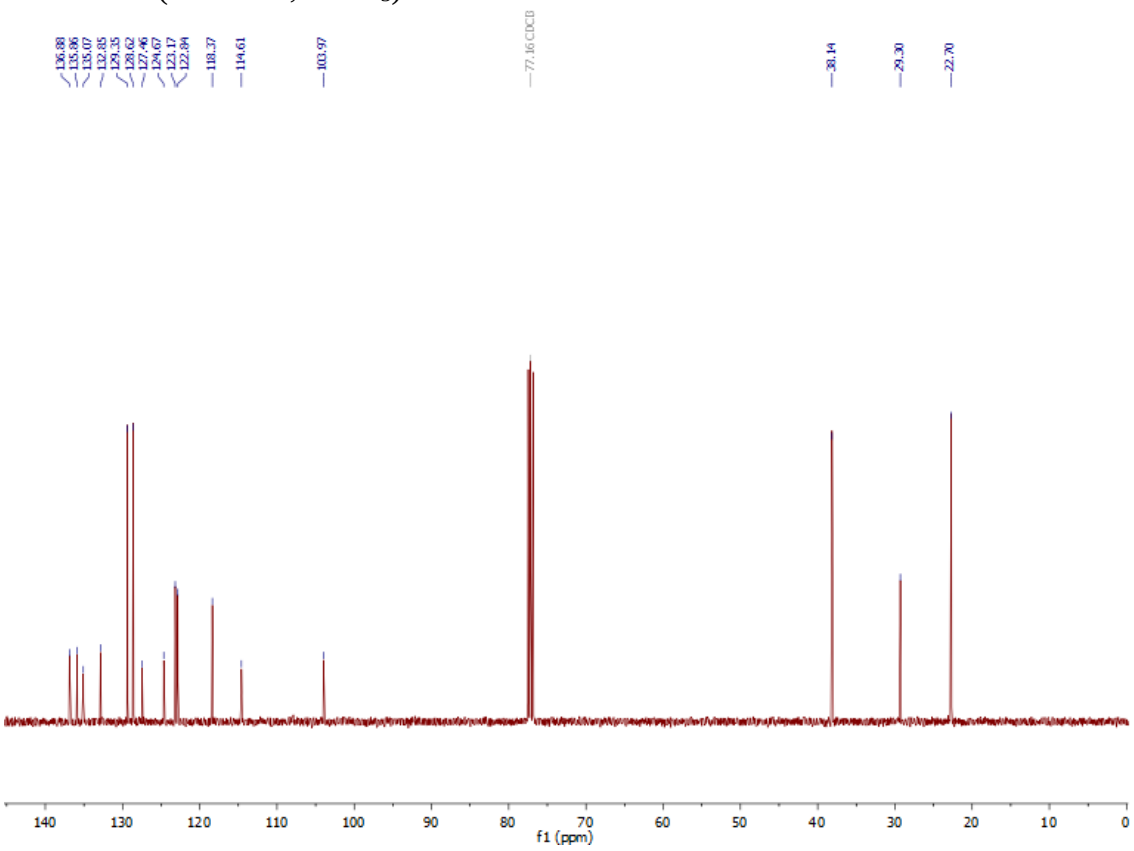
^{13}C NMR of **S7** (101 MHz, DMSO-d_6)



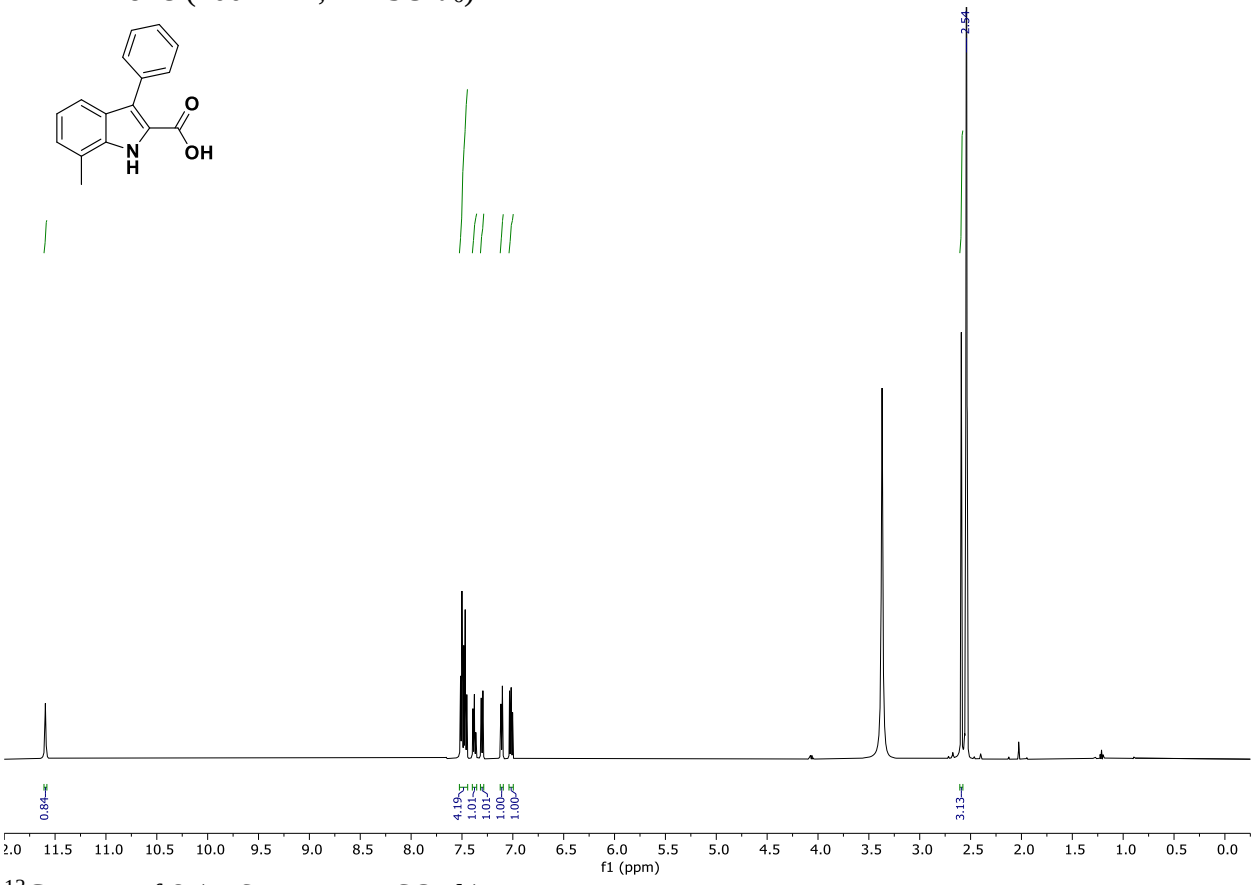
^{1}H NMR of **7** (400 MHz, $CDCl_3$)



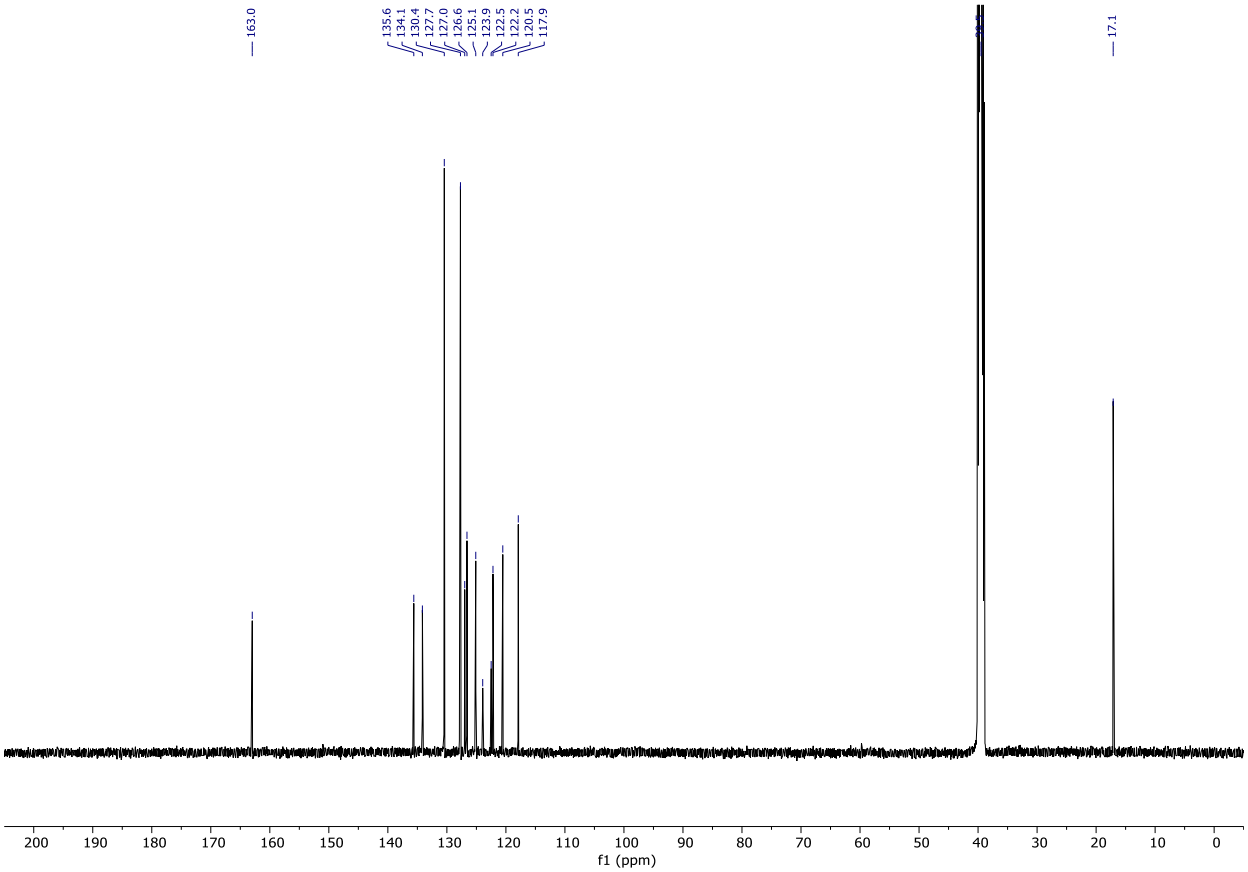
^{13}C NMR of **7** (101 MHz, $CDCl_3$)



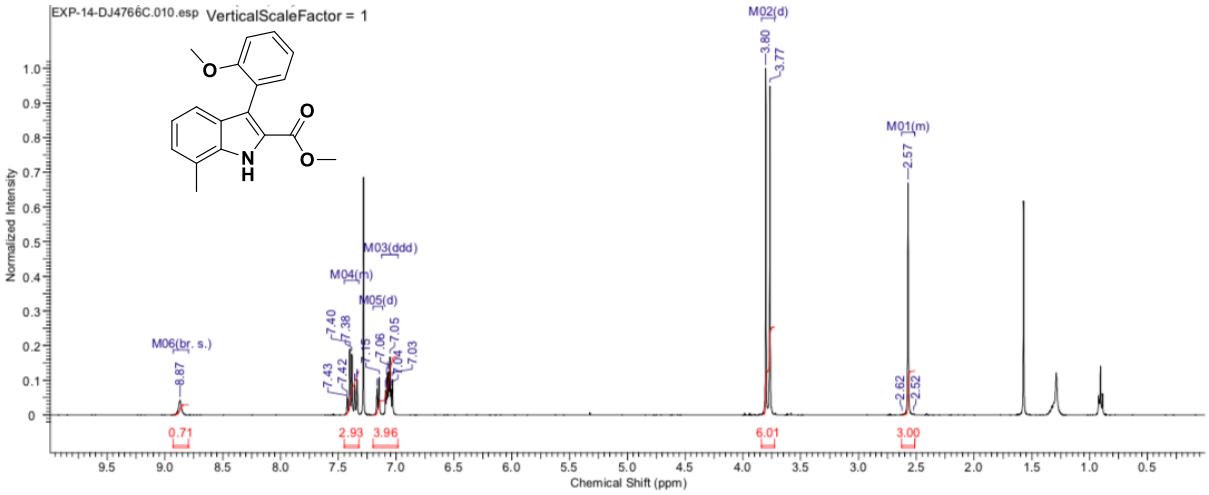
^{1}H NMR of **8** (400 MHz, DMSO-d_6)



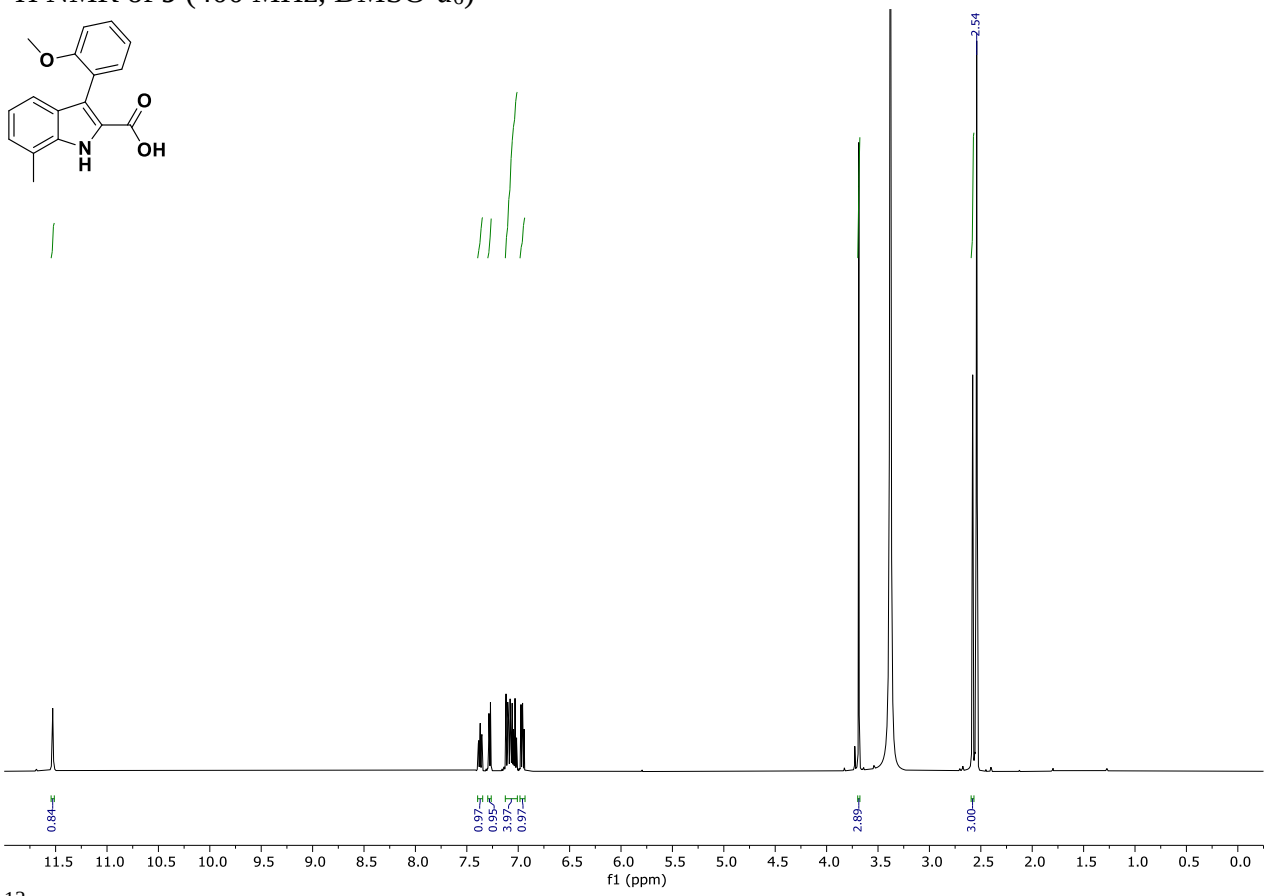
^{13}C NMR of **8** (126 MHz, DMSO-d_6)



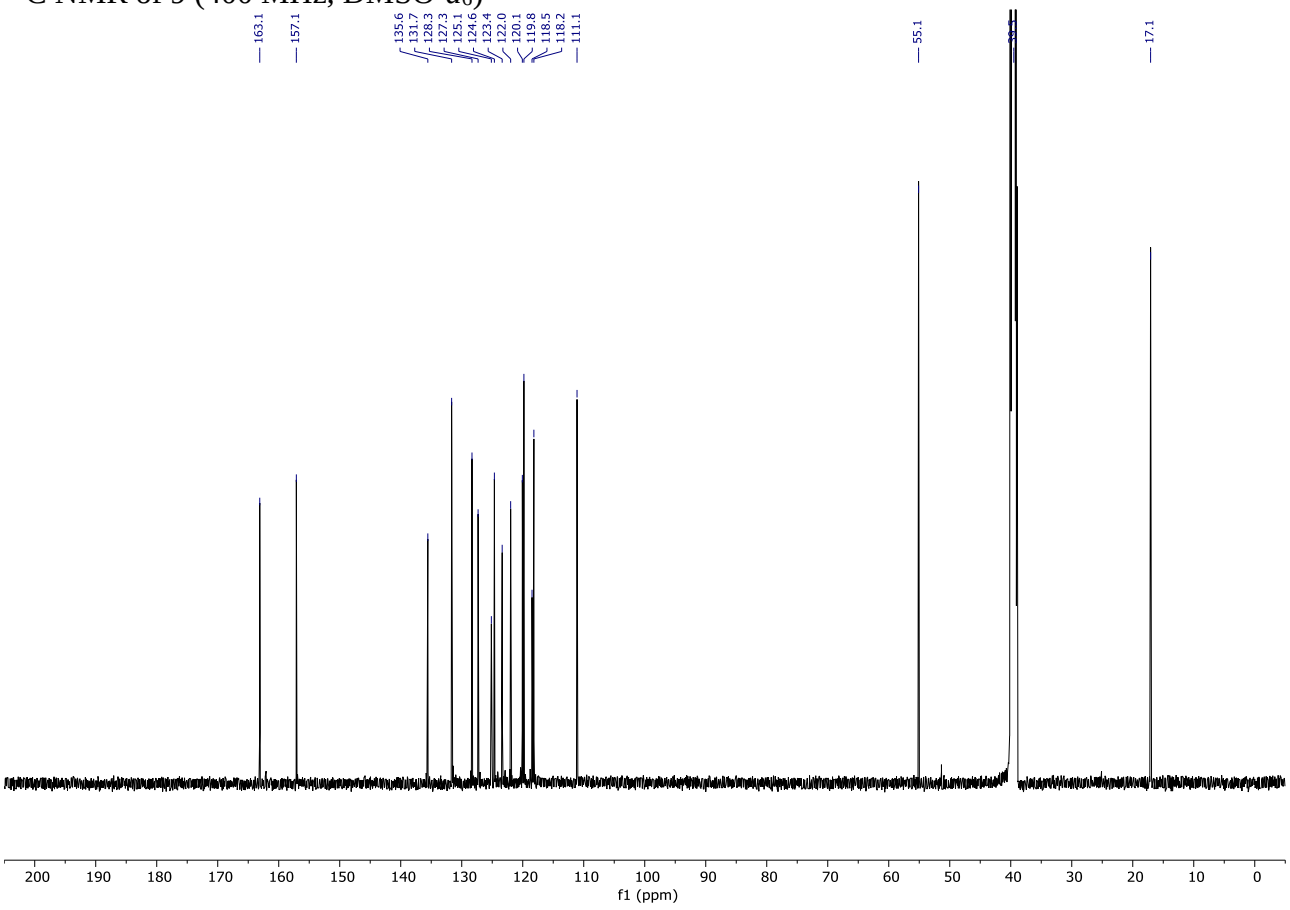
^{1}H NMR of **S8** (400 MHz, $CDCl_3$)



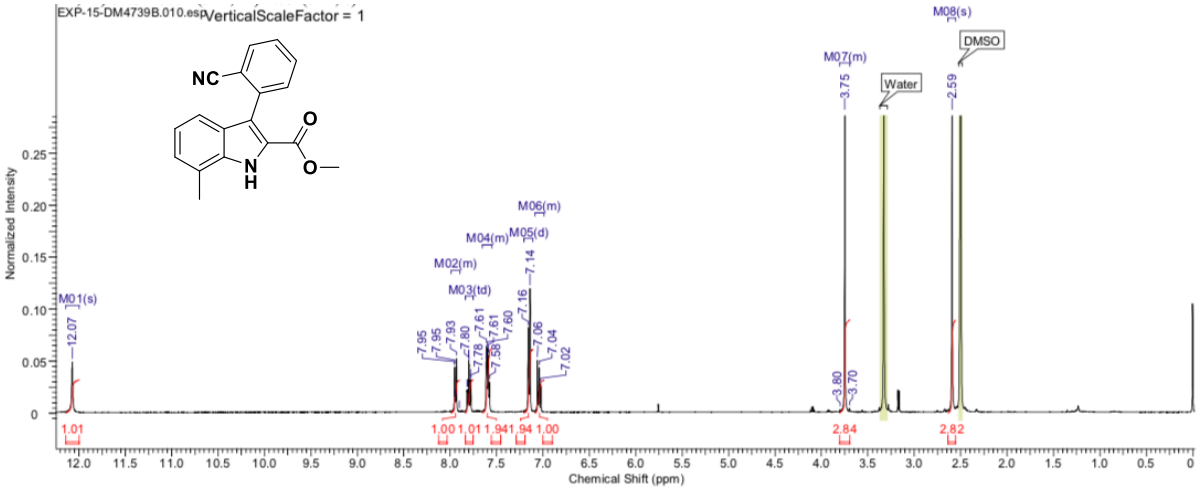
^{1}H NMR of **9** (400 MHz, DMSO-d_6)



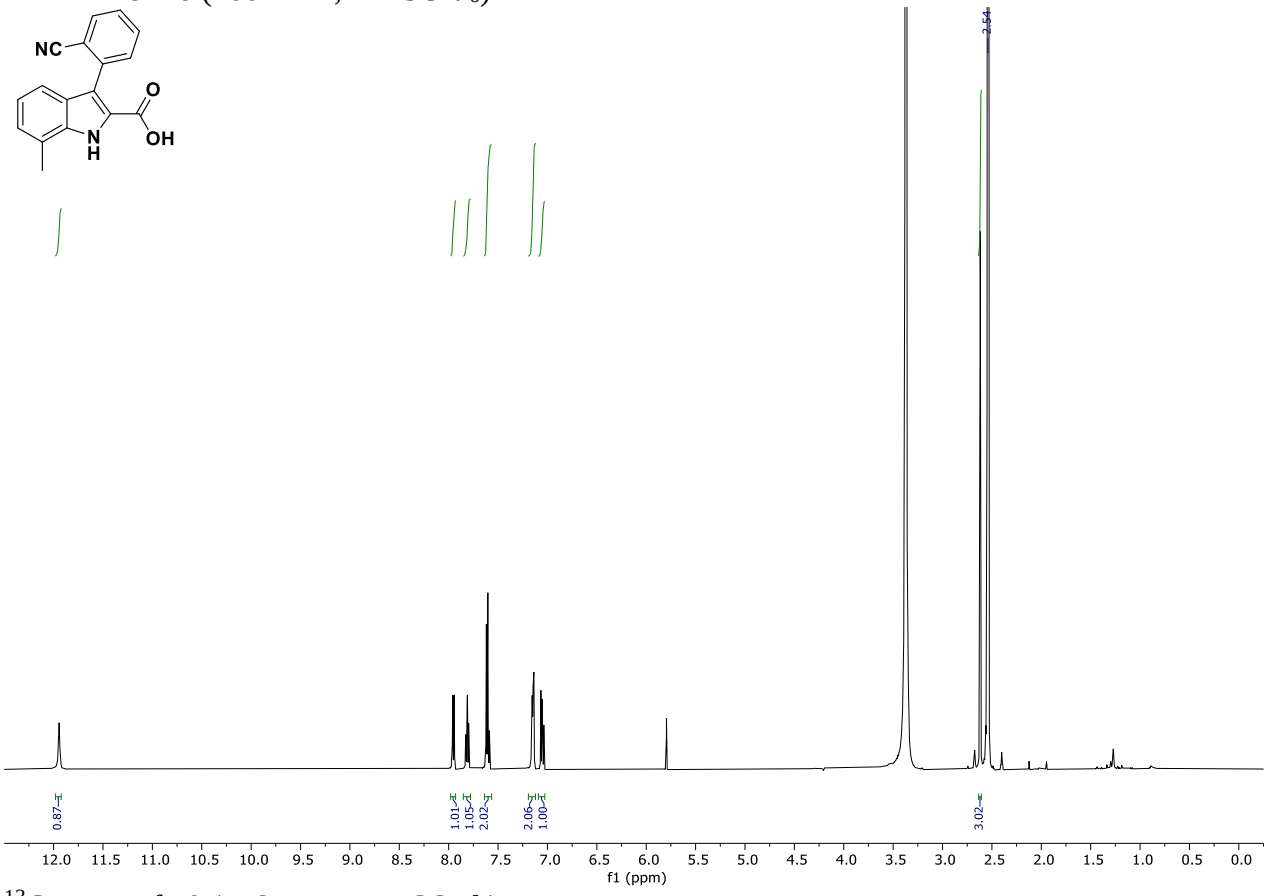
^{13}C NMR of 9 (400 MHz, DMSO-d_6)



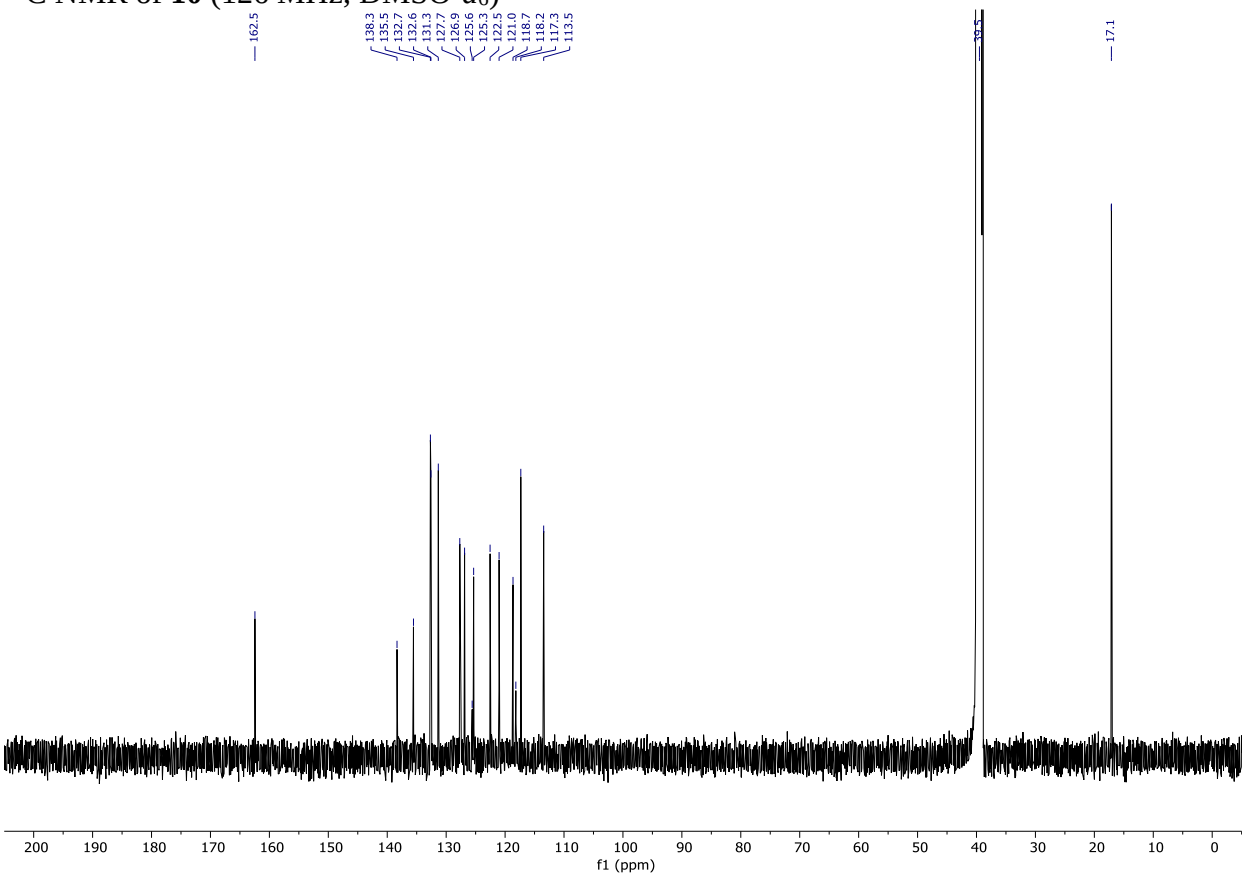
^{1}H NMR of **S9** (400 MHz, DMSO-d_6)



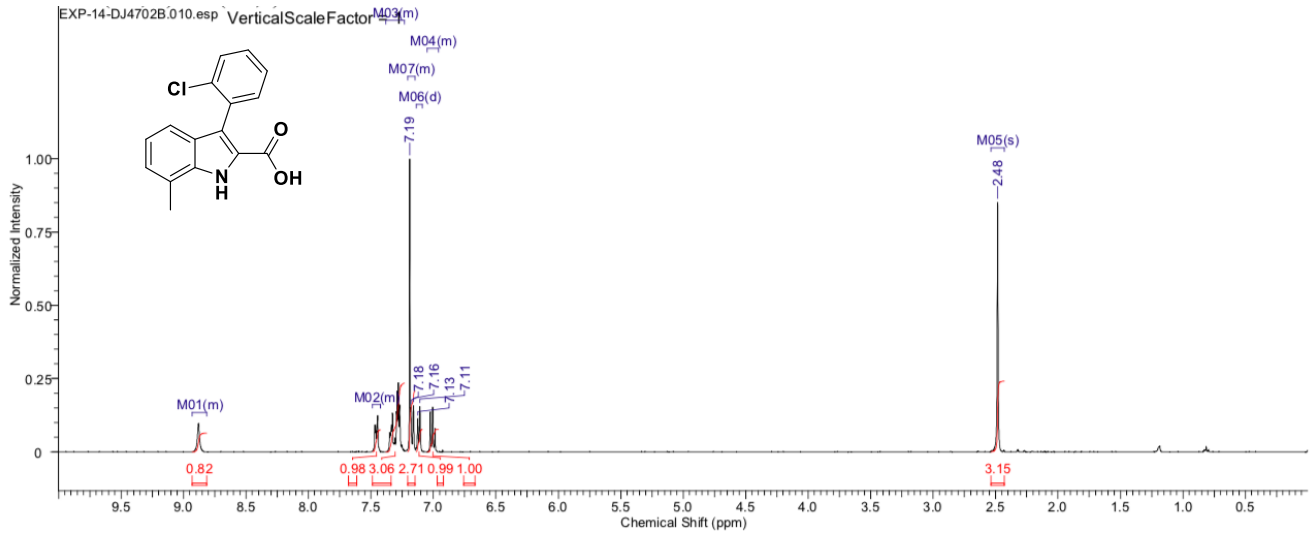
^{1}H NMR of **10** (400 MHz, DMSO-d_6)



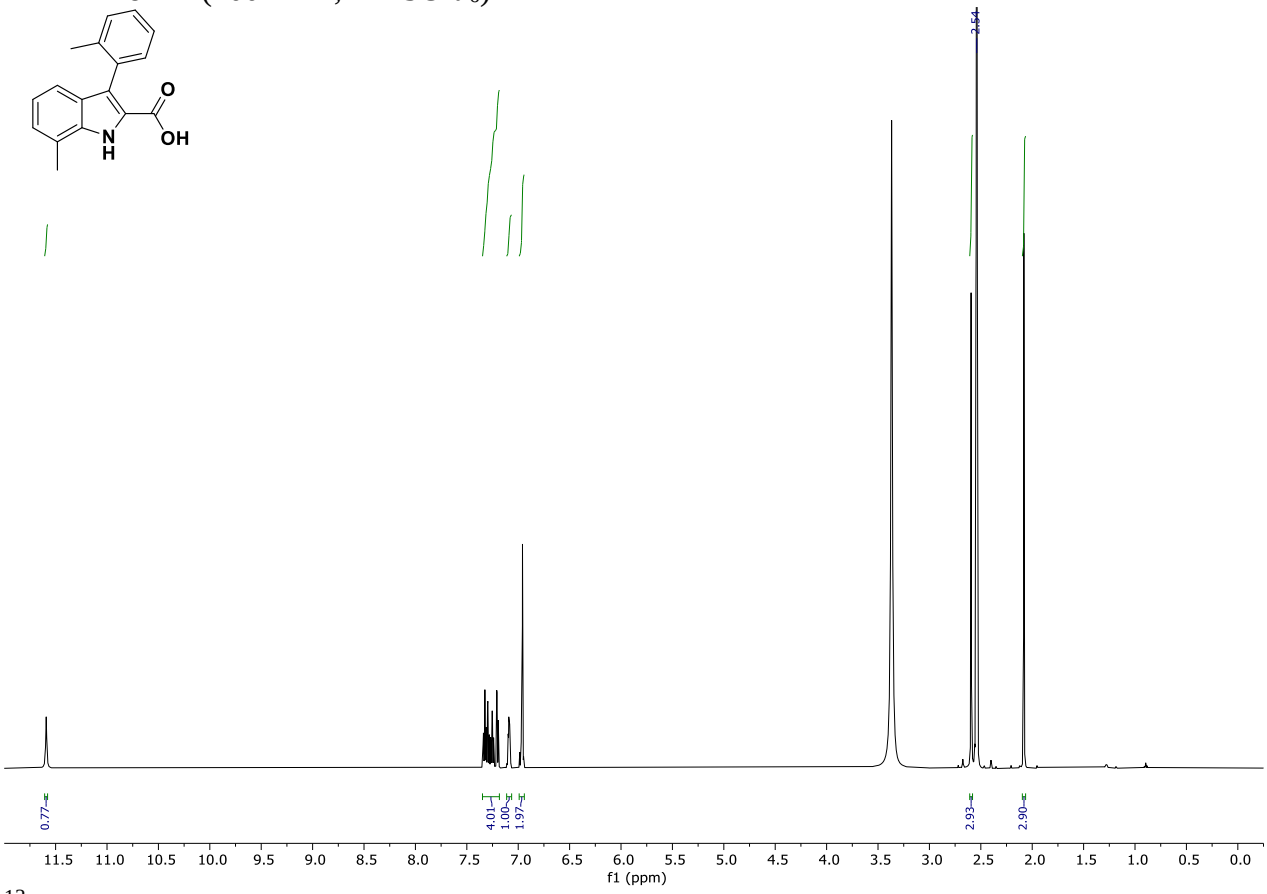
^{13}C NMR of **10** (126 MHz, DMSO-d_6)



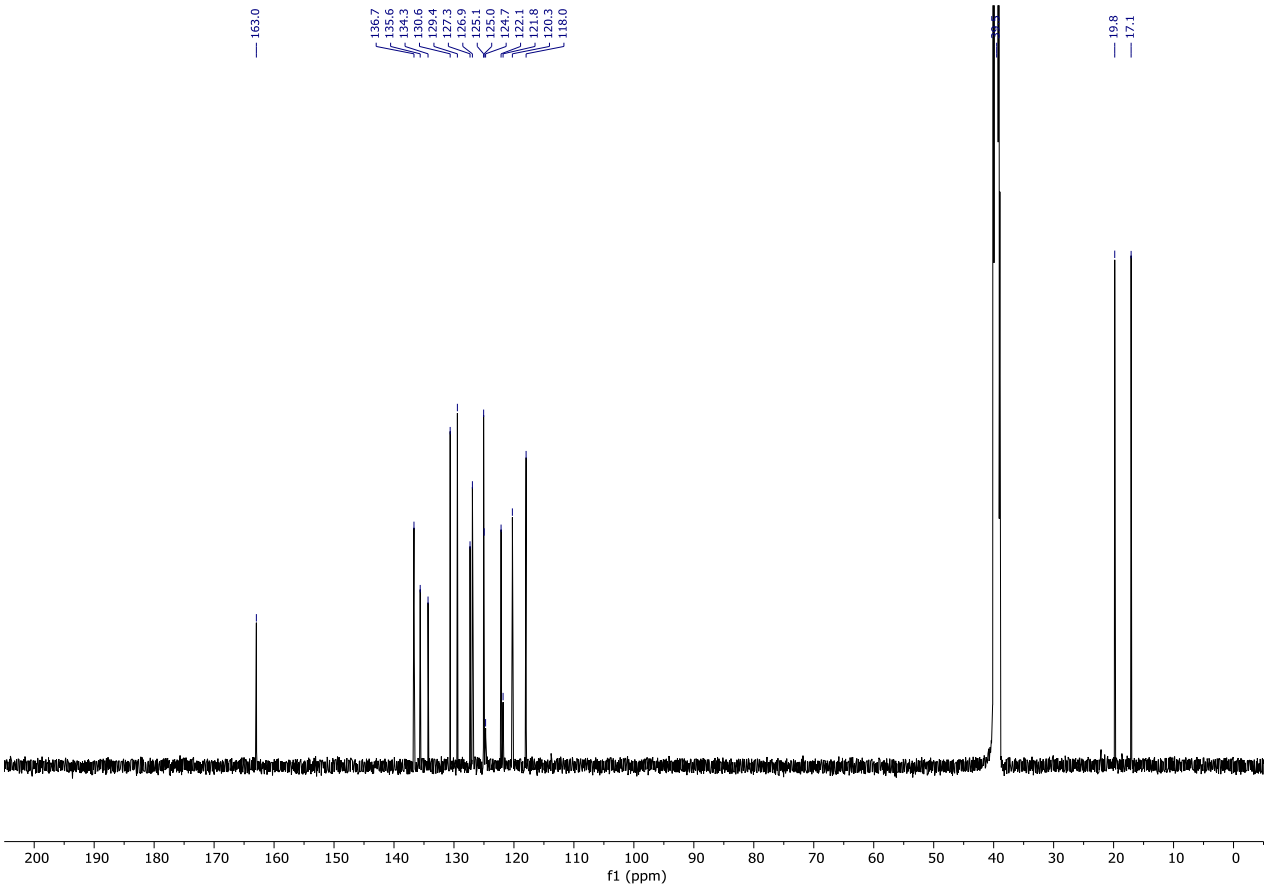
^{1}H NMR of **11** (400 MHz, $CDCl_3$)



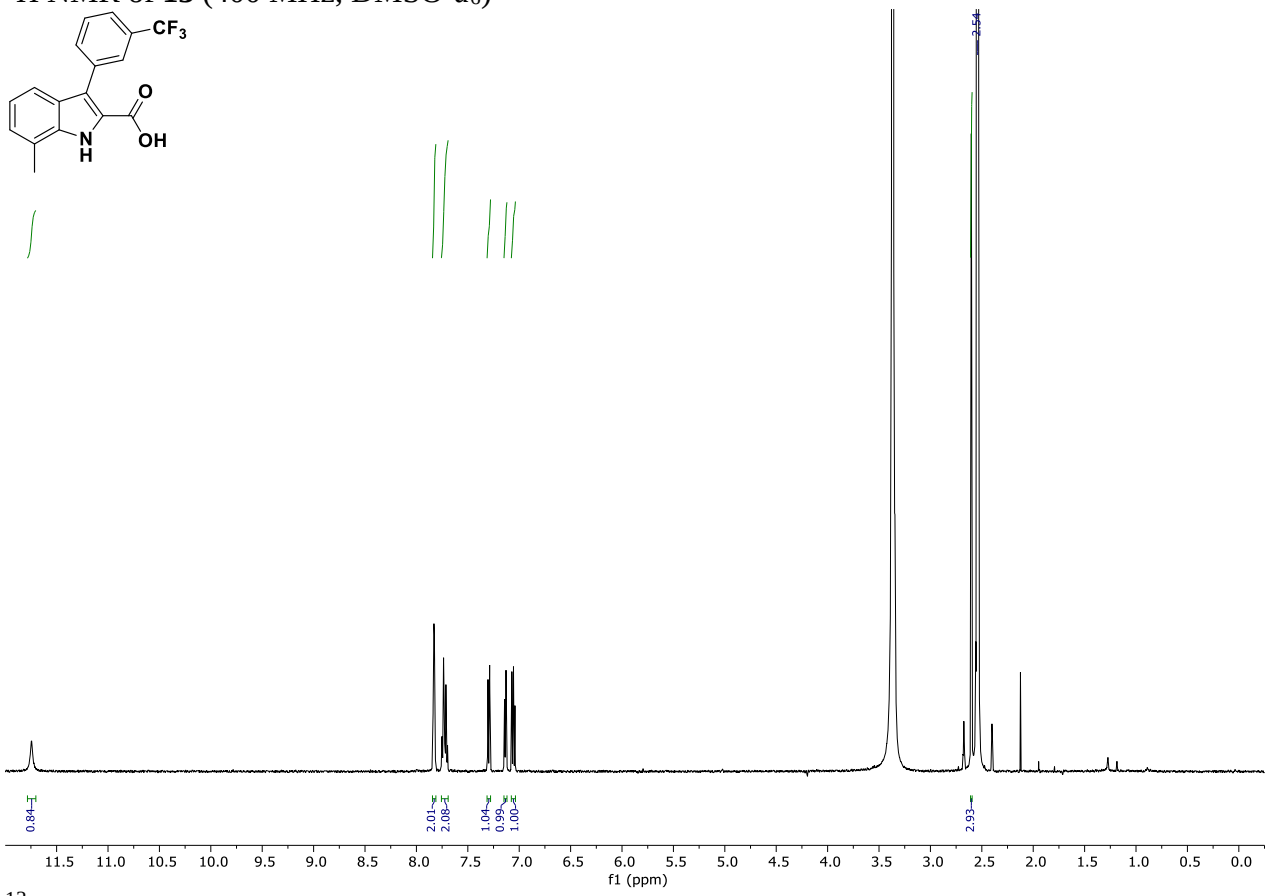
^{1}H NMR of **12** (400 MHz, DMSO-d_6)



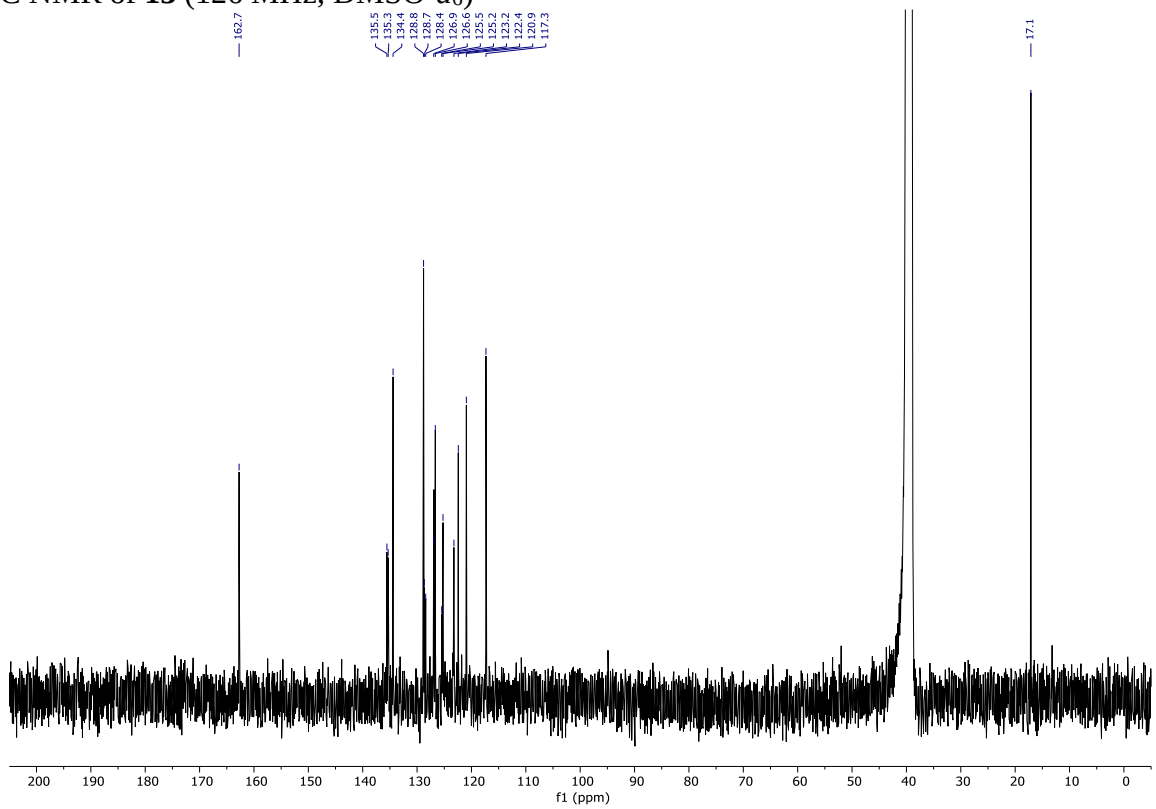
^{13}C NMR of **12** (126 MHz, DMSO-d_6)



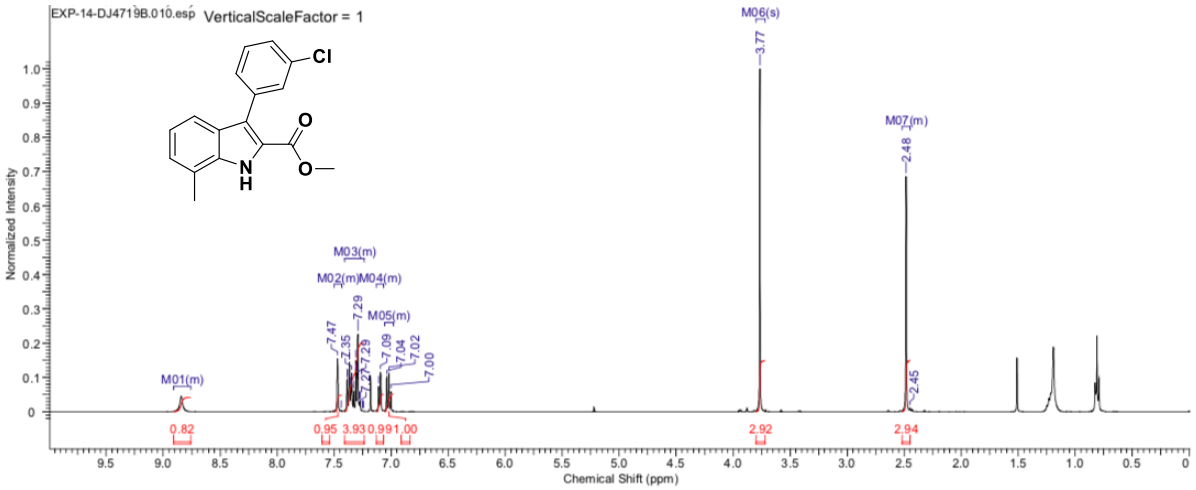
^{1}H NMR of **13** (400 MHz, DMSO-d_6)



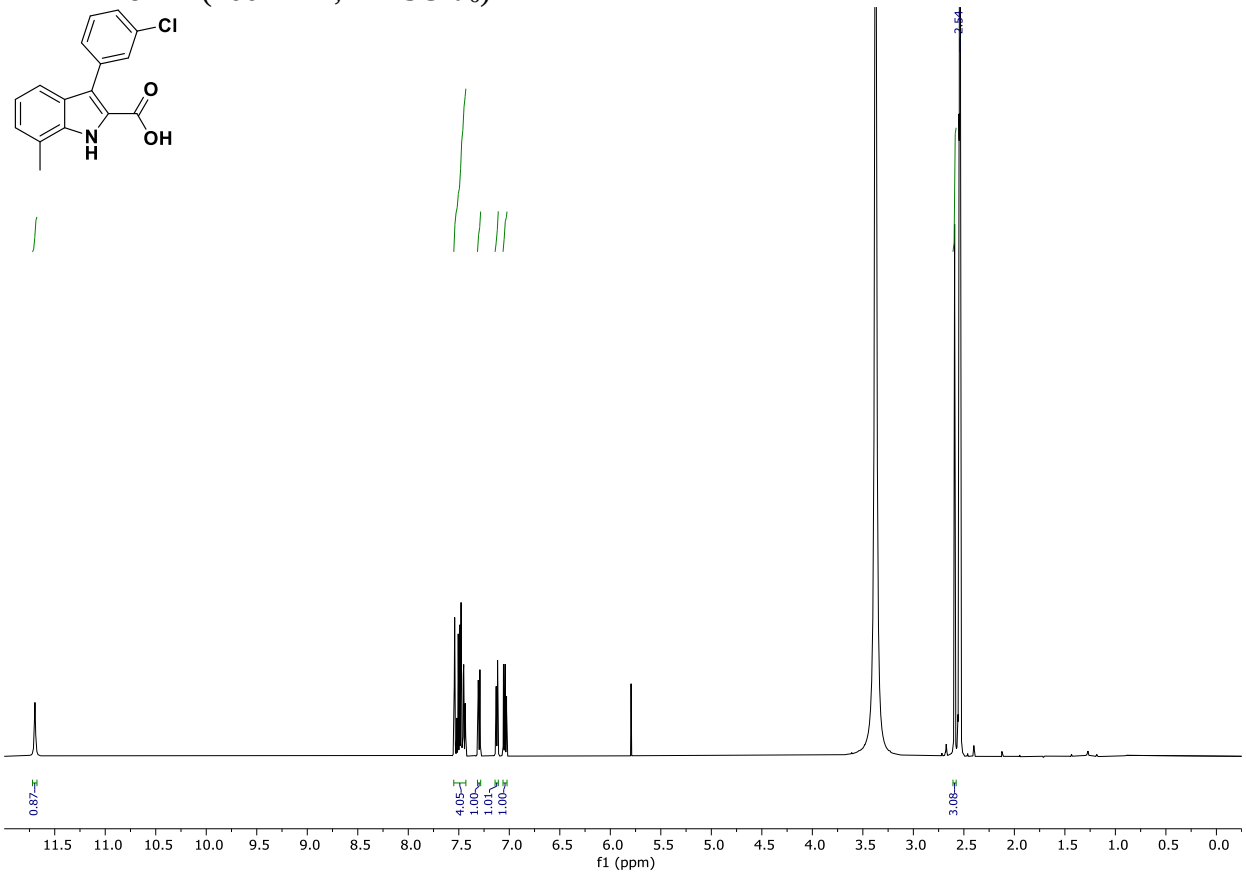
^{13}C NMR of **13** (126 MHz, DMSO-d_6)



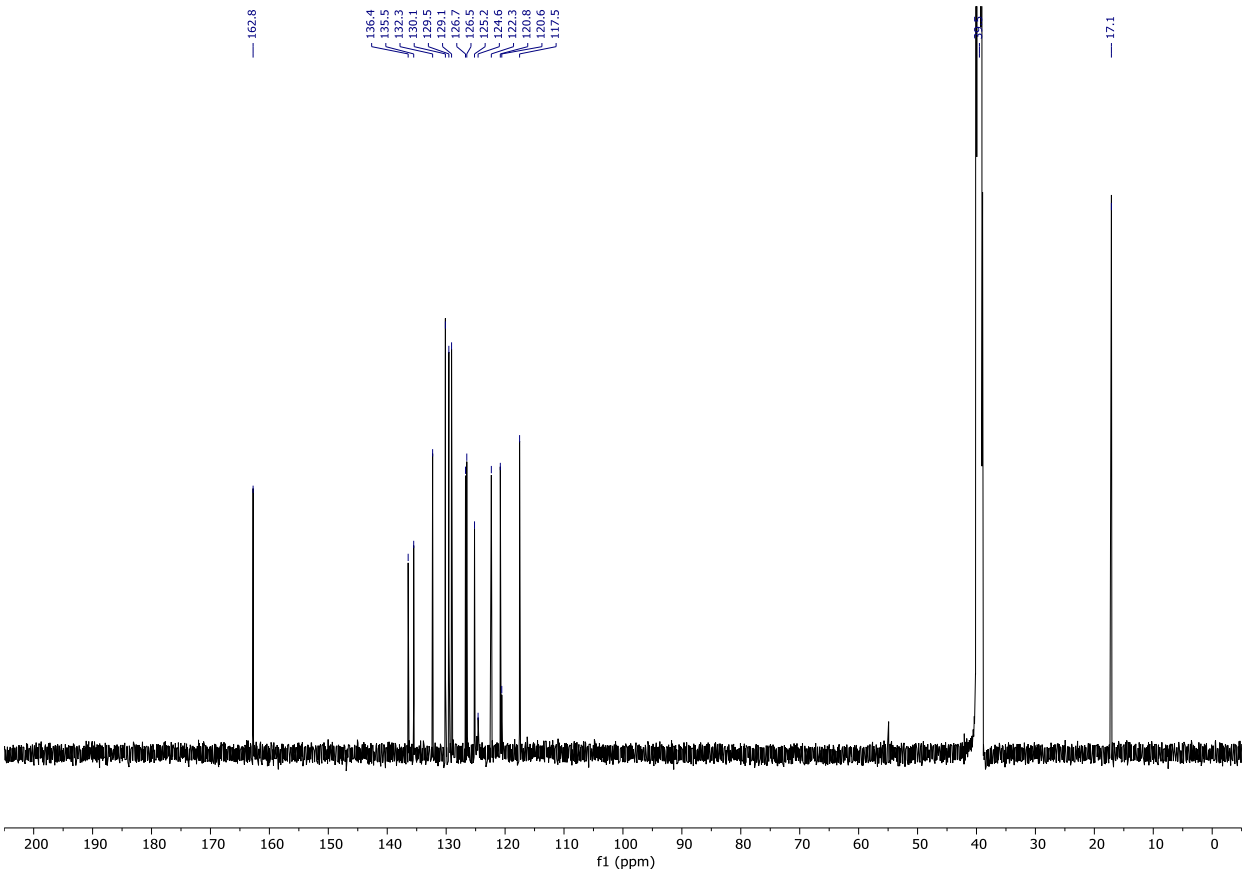
^{1}H NMR of **S10** (400 MHz, $CDCl_3$)



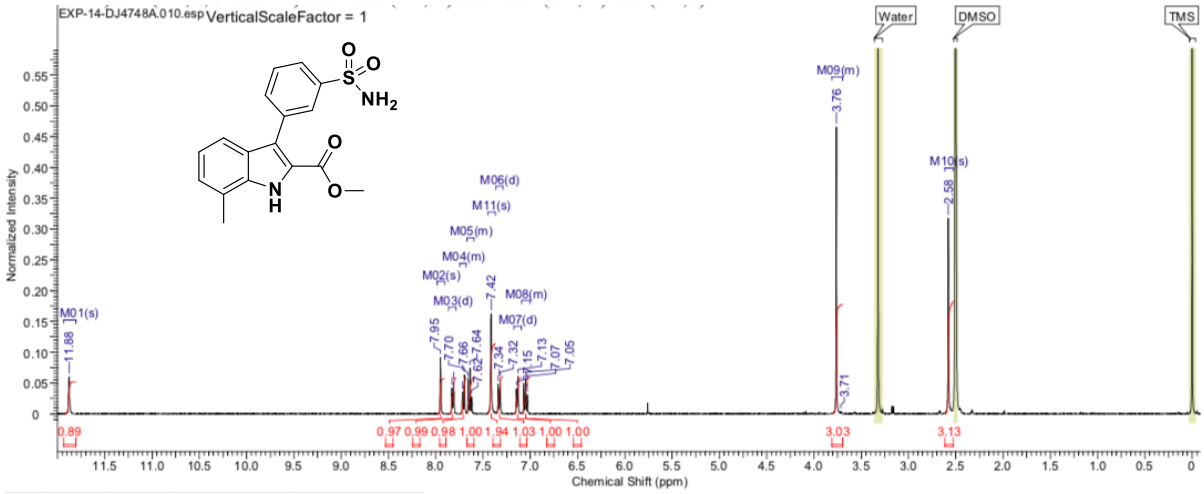
^{1}H NMR of **14** (400 MHz, DMSO-d_6)



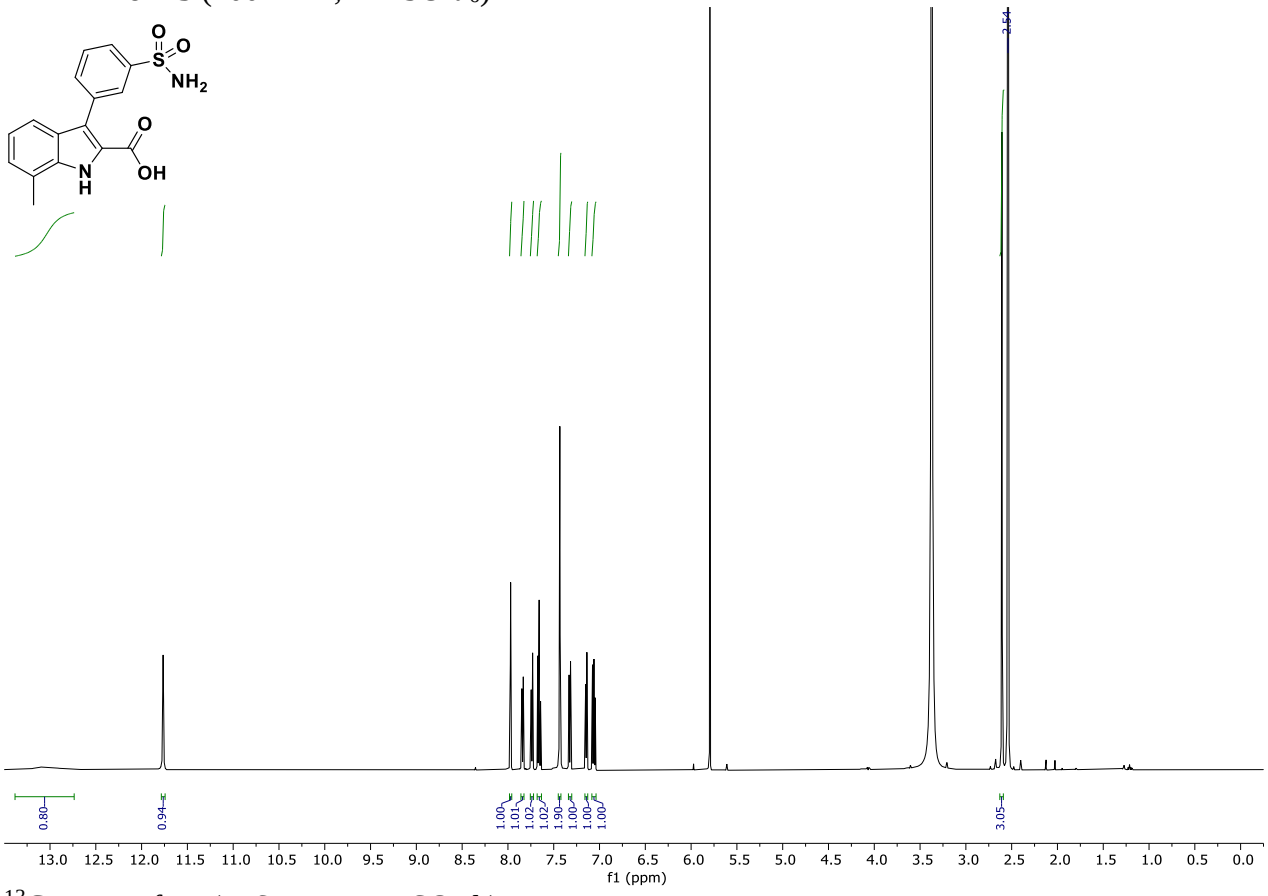
^{13}C NMR of **14** (126 MHz, DMSO-d_6)



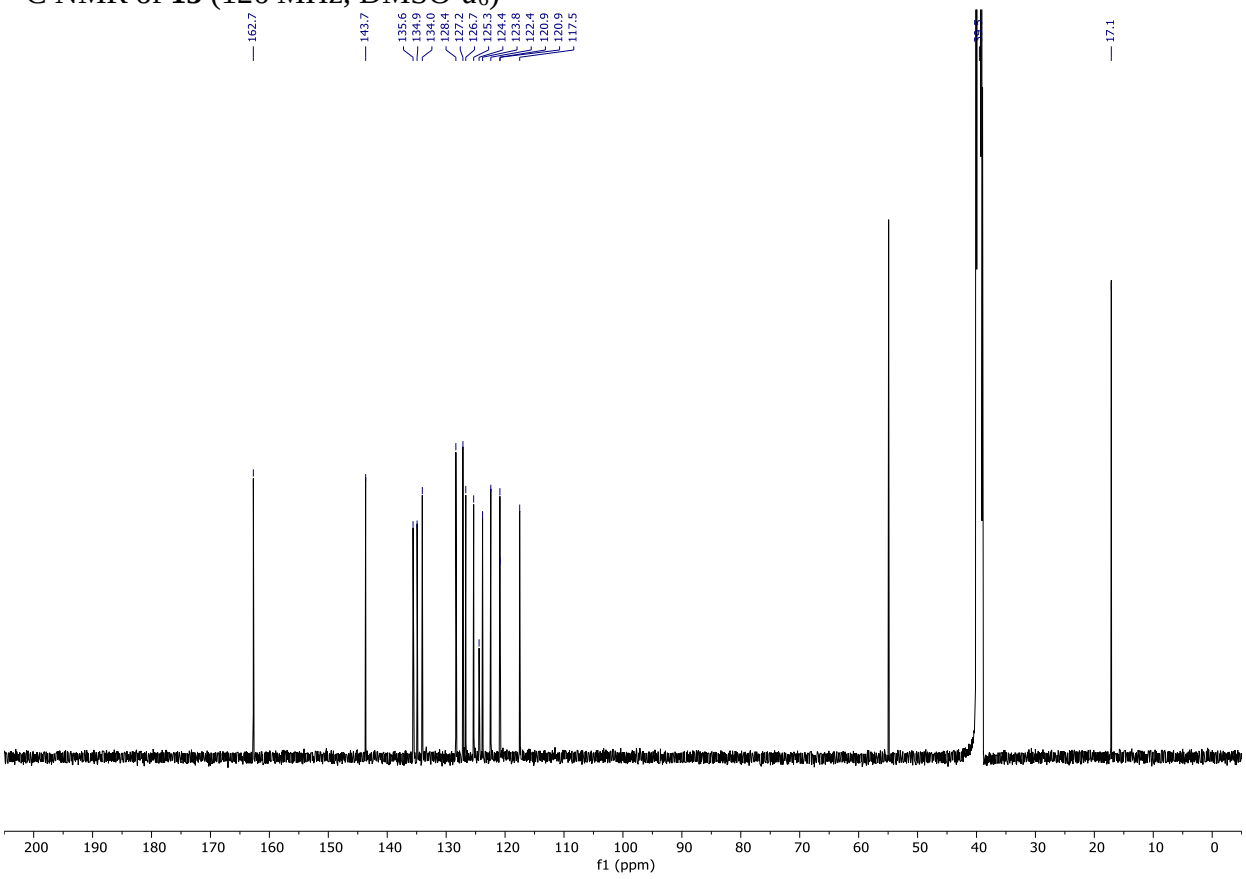
^{1}H NMR of **S11** (400 MHz, DMSO-d_6)



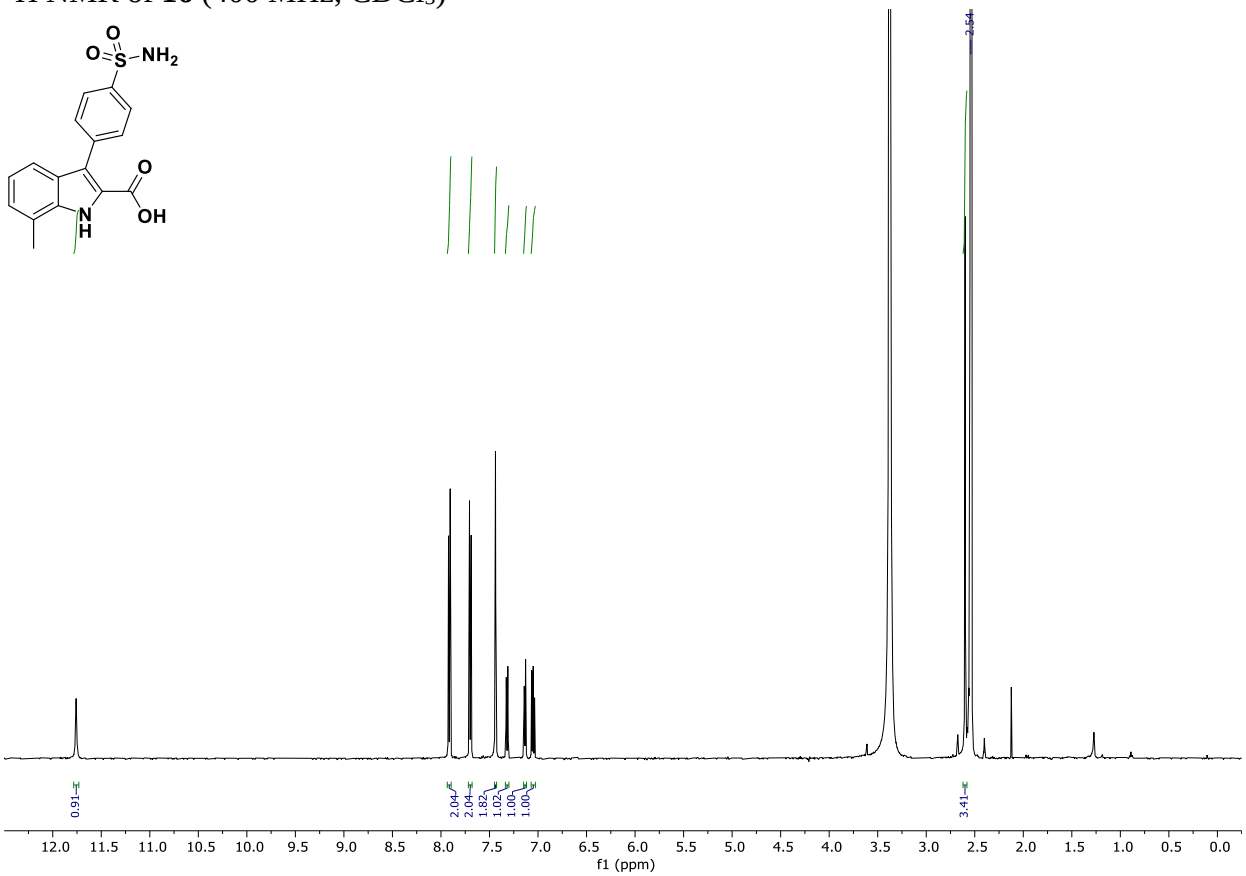
^{1}H NMR of **15** (400 MHz, DMSO-d_6)



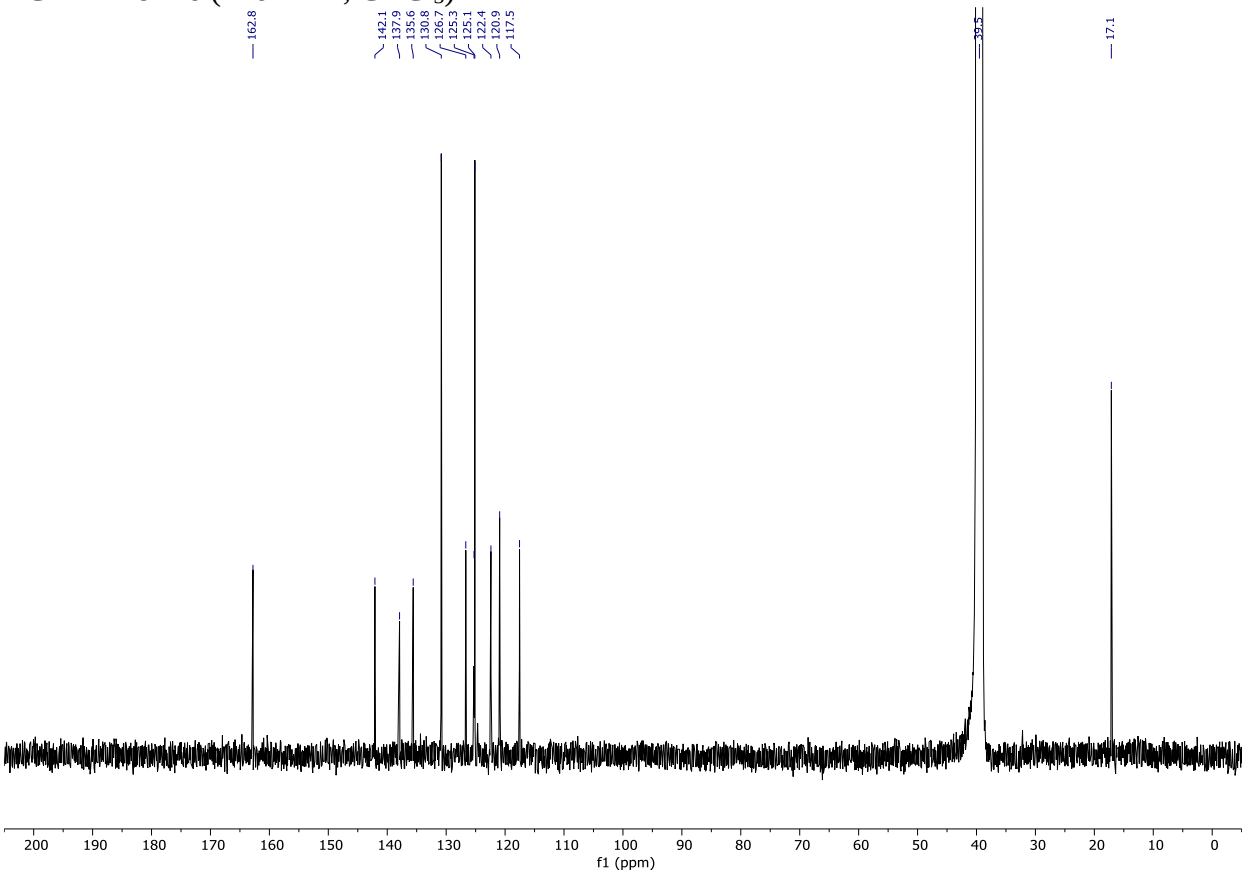
^{13}C NMR of **15** (126 MHz, DMSO-d_6)



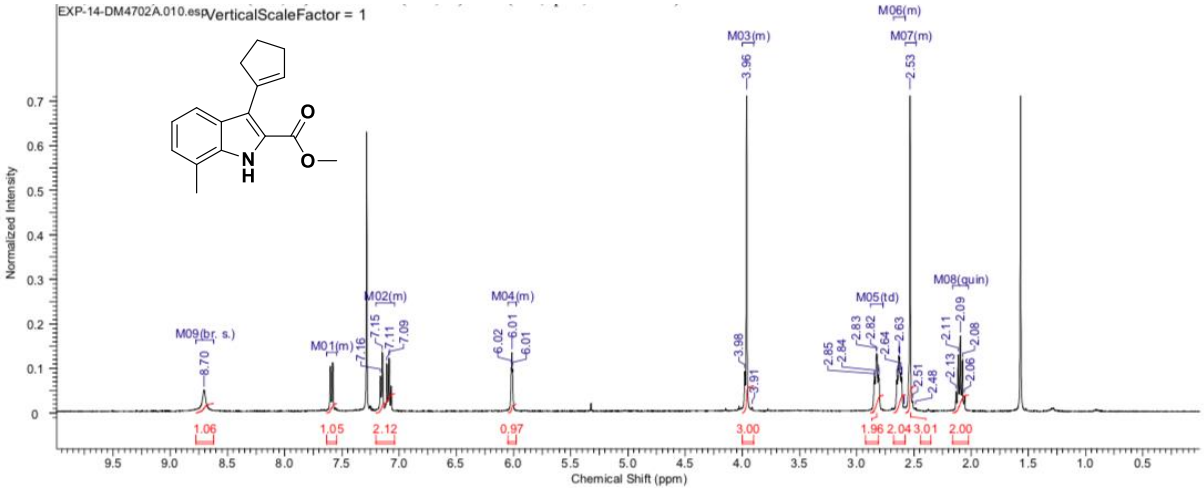
^{1}H NMR of **16** (400 MHz, $CDCl_3$)



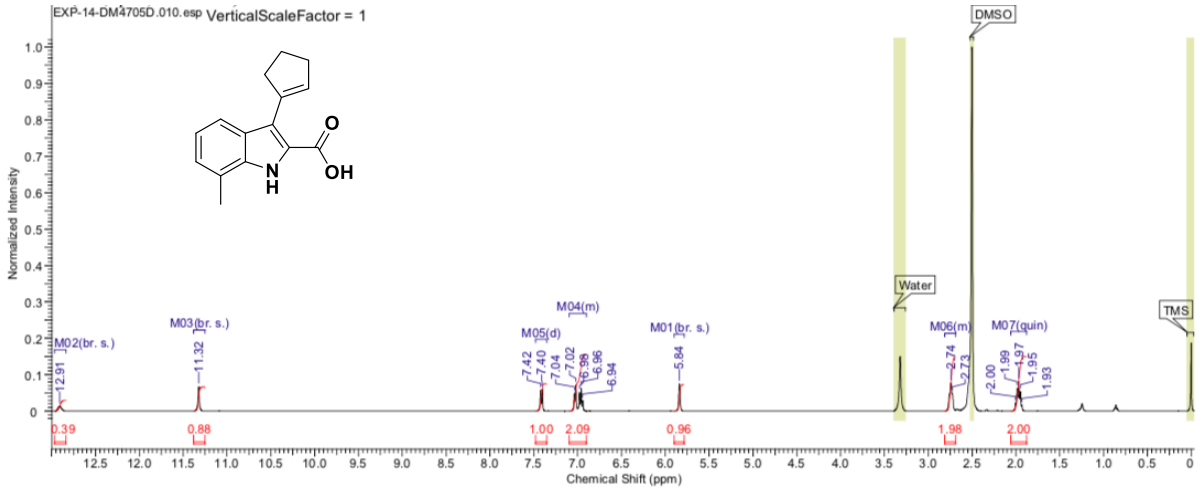
^{13}C NMR of **16** (126 MHz, $CDCl_3$)



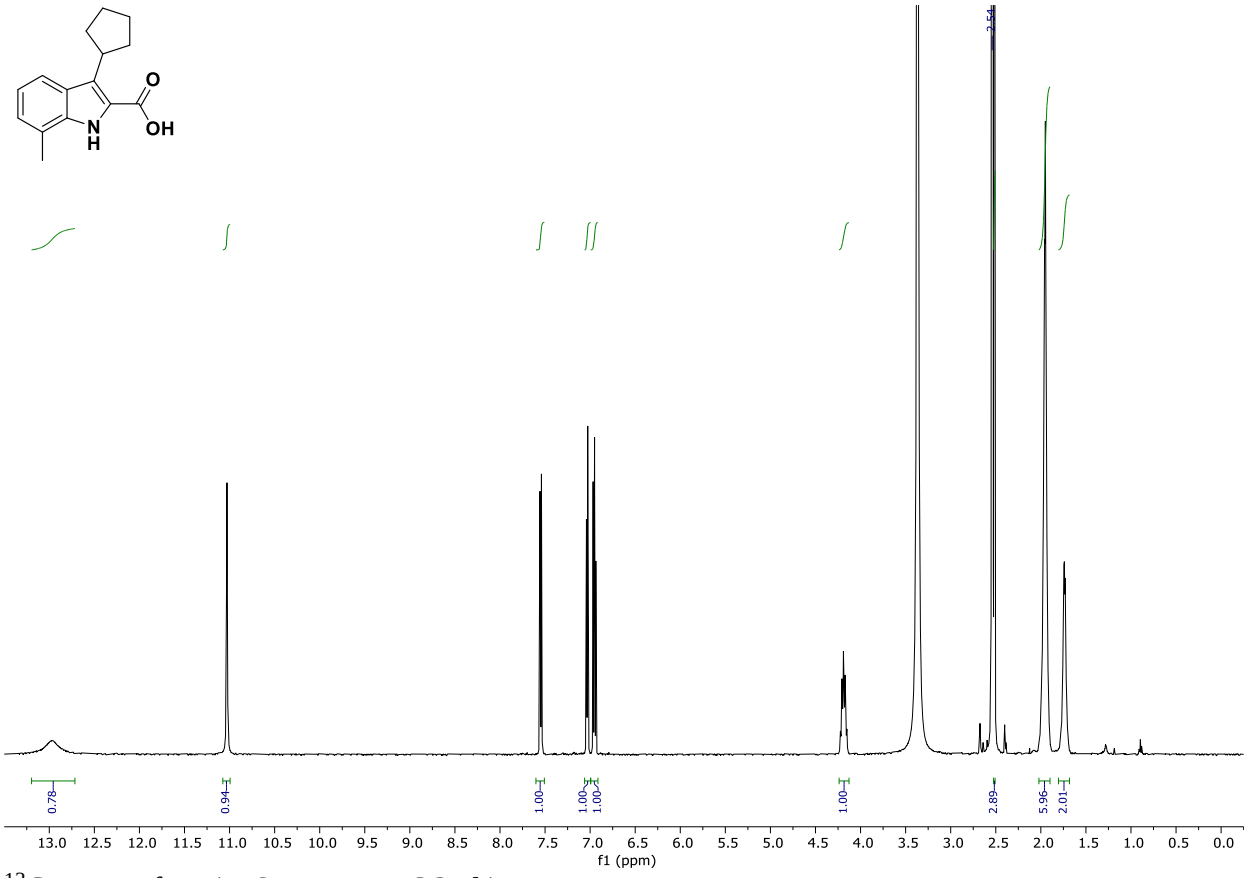
^{1}H NMR of **S12** (400 MHz, $CDCl_3$)



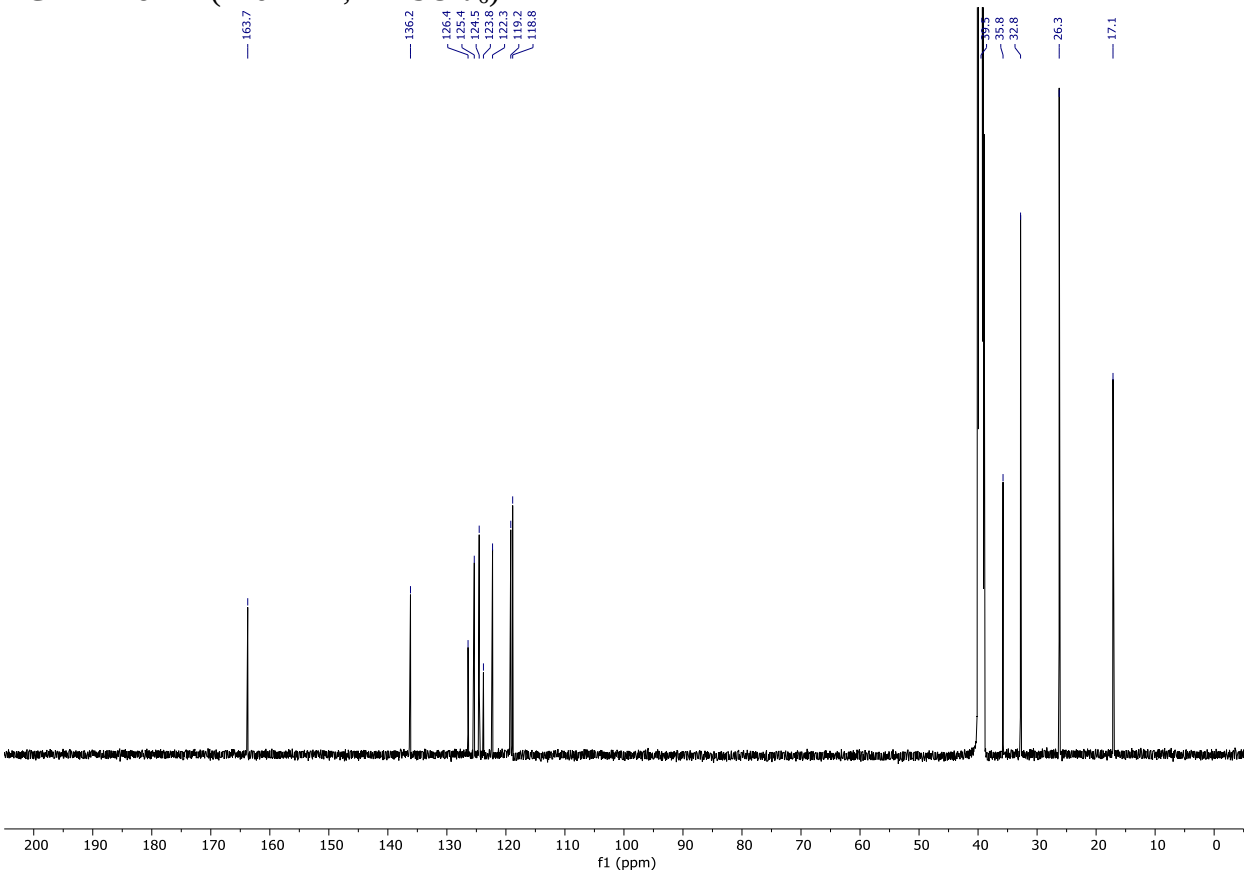
^{1}H NMR of **S13** (400 MHz, DMSO-d_6)



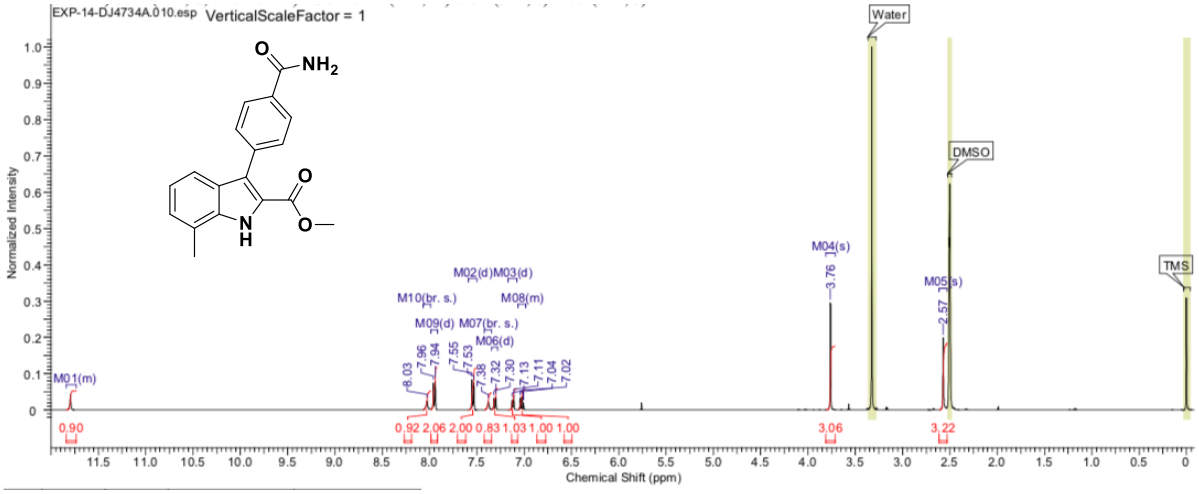
^{1}H NMR of **17** (400 MHz, DMSO-d_6)



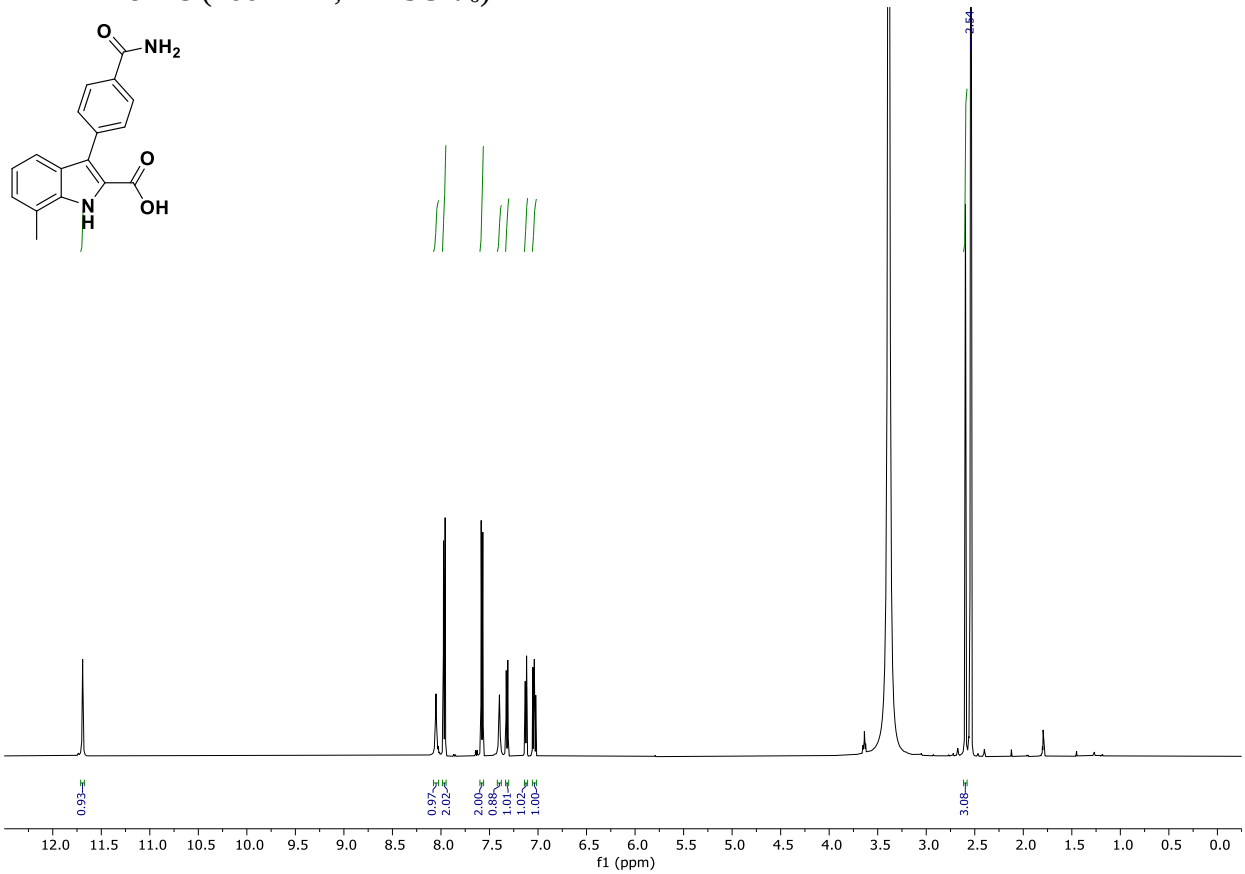
^{13}C NMR of 17 (126 MHz, DMSO-d_6)



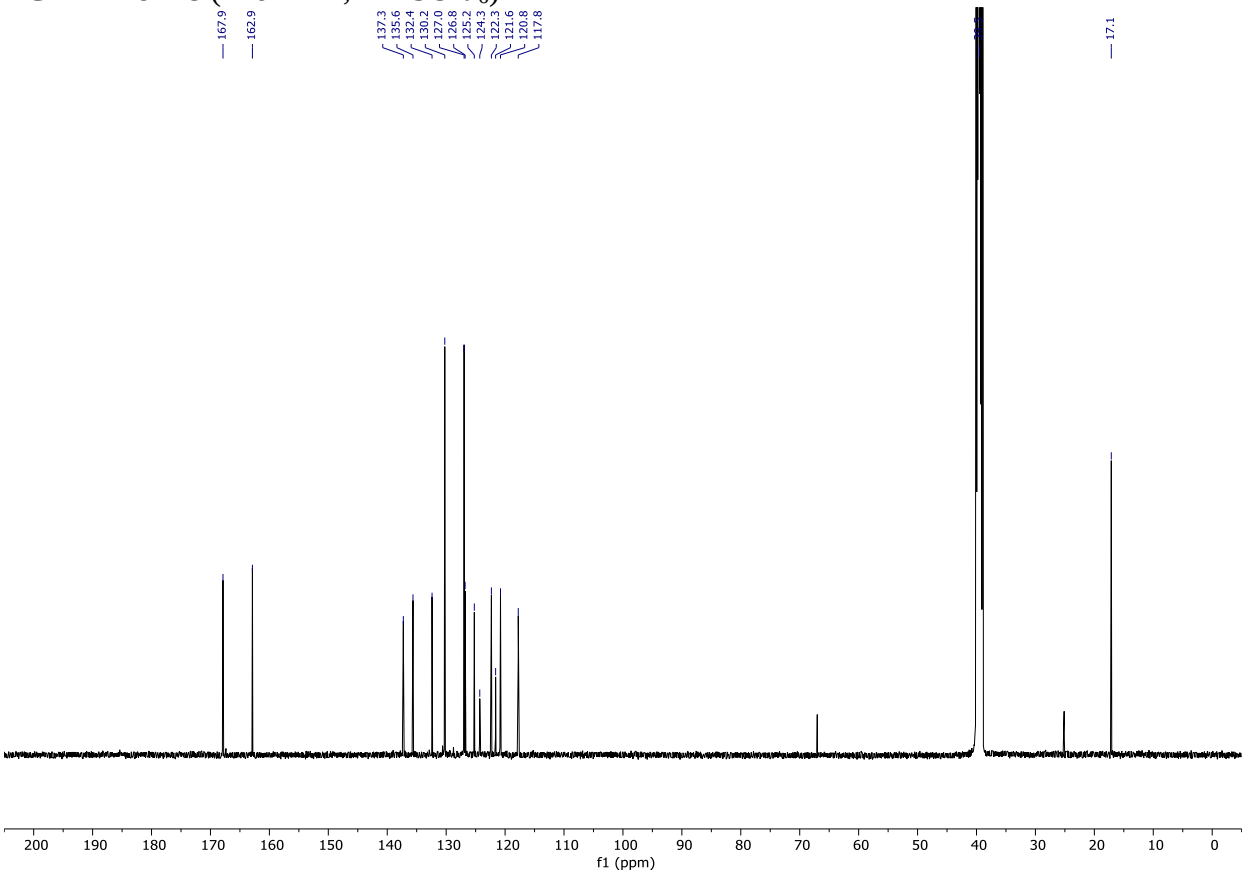
^{1}H NMR of **S14** (400 MHz, DMSO-d_6)



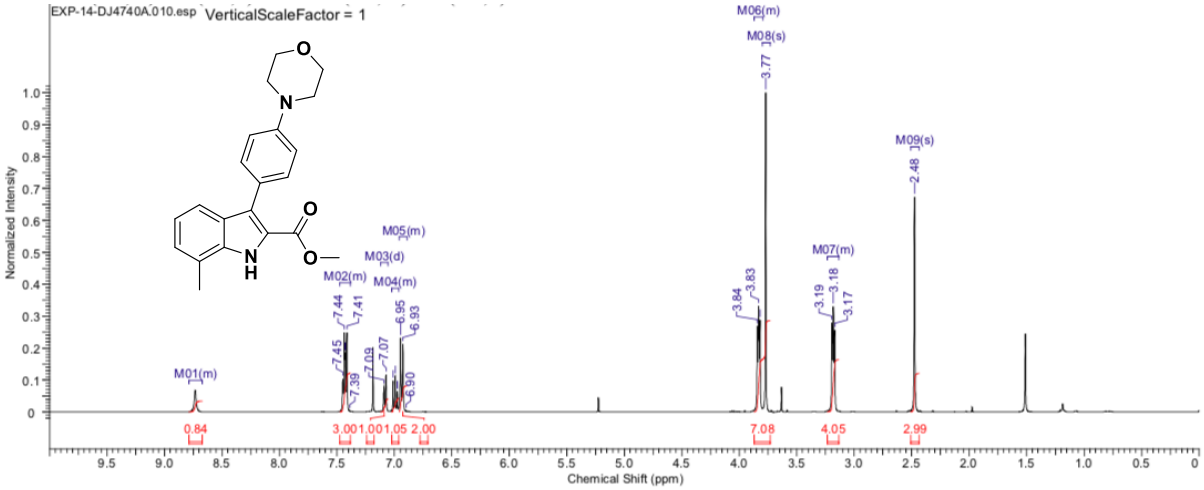
^{1}H NMR of **18** (400 MHz, DMSO-d_6)



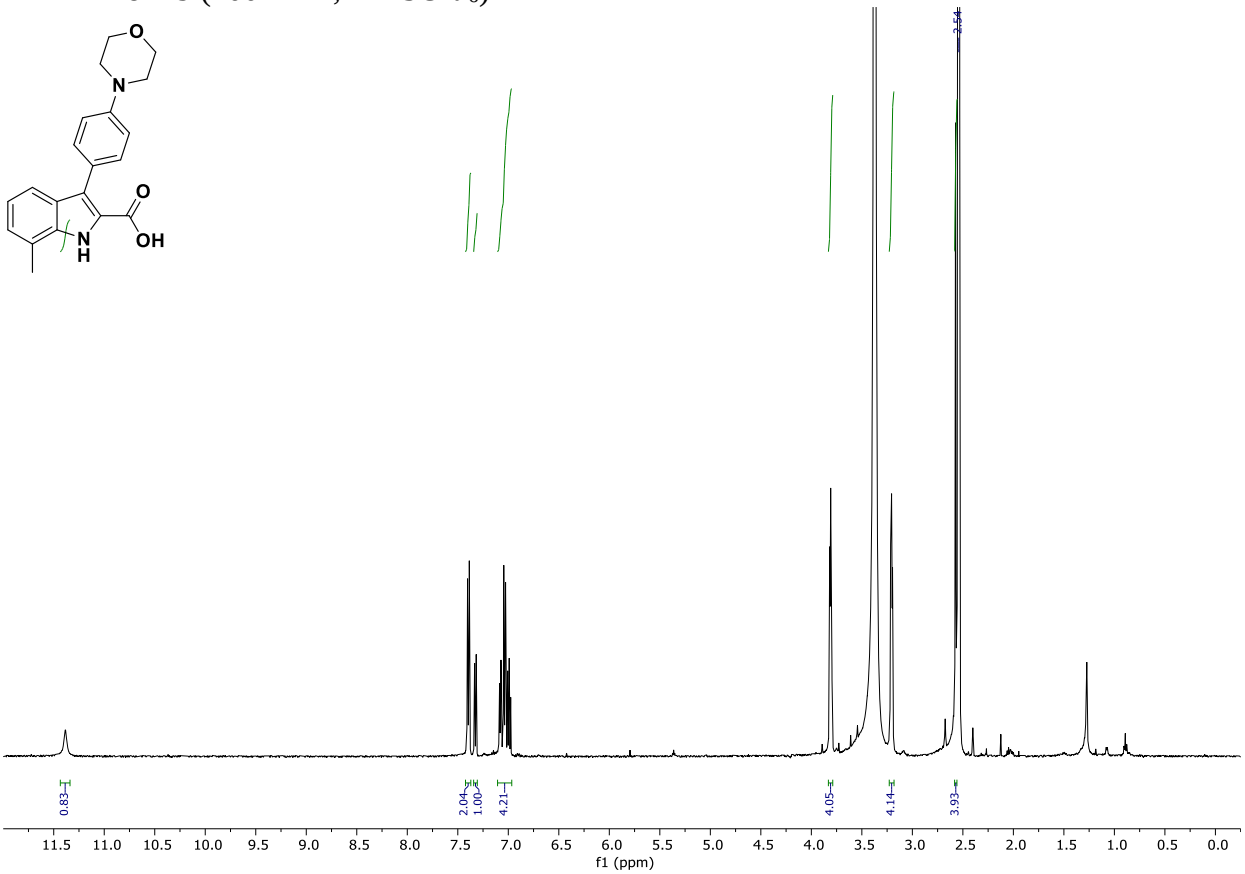
^{13}C NMR of **18** (126 MHz, DMSO-d_6)



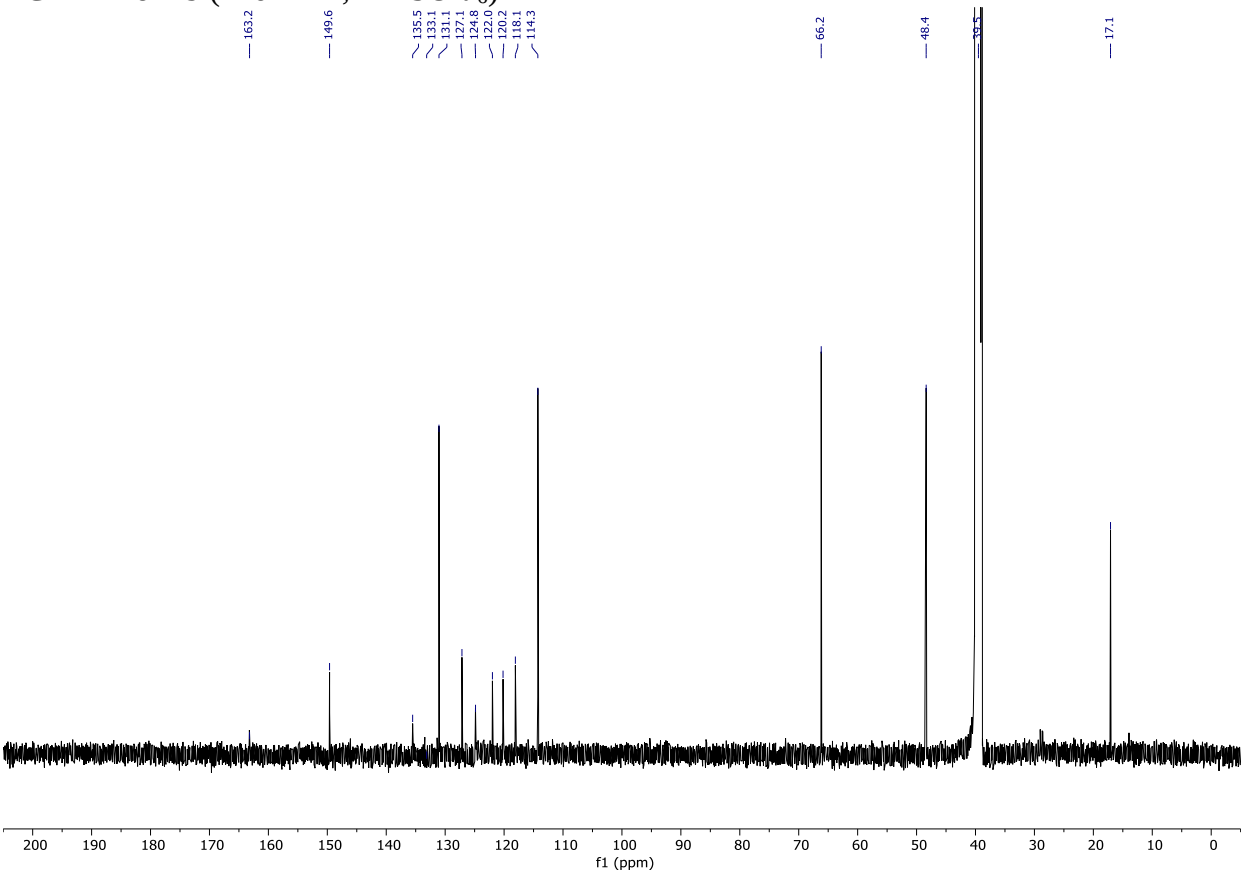
^{1}H NMR **S15** (400 MHz, $CDCl_3$)



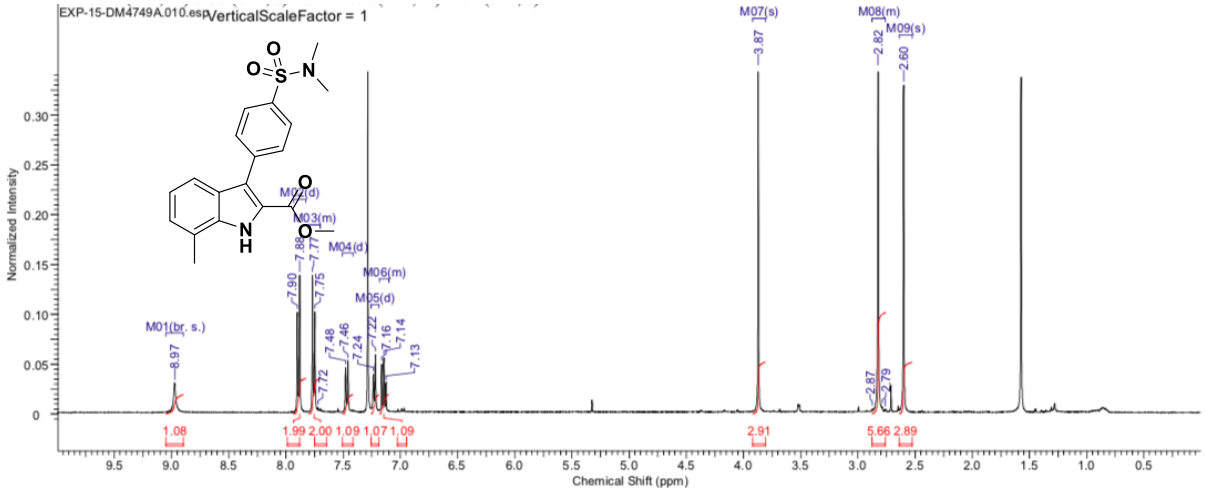
^{1}H NMR of **19** (400 MHz, DMSO-d_6)



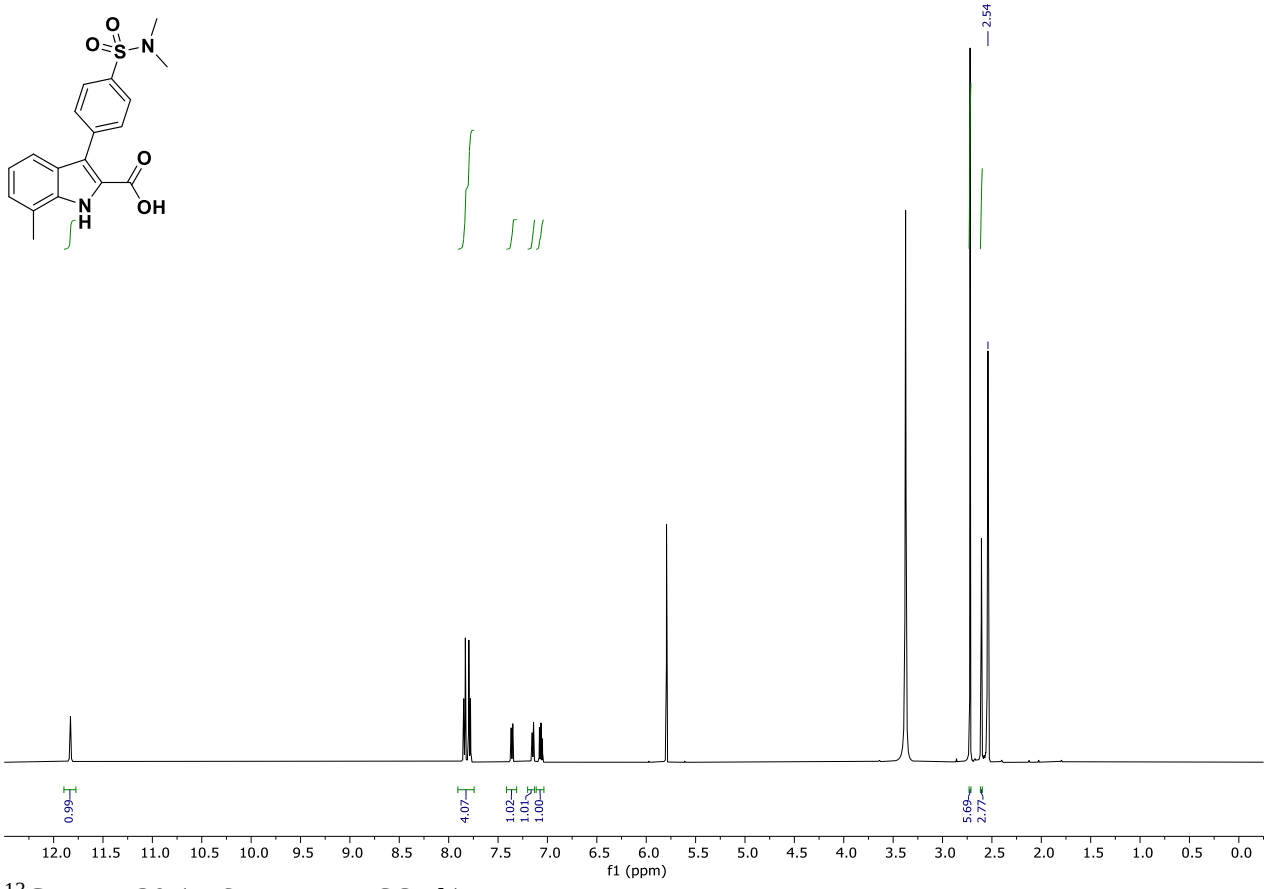
^{13}C NMR of **19** (126 MHz, DMSO-d_6)



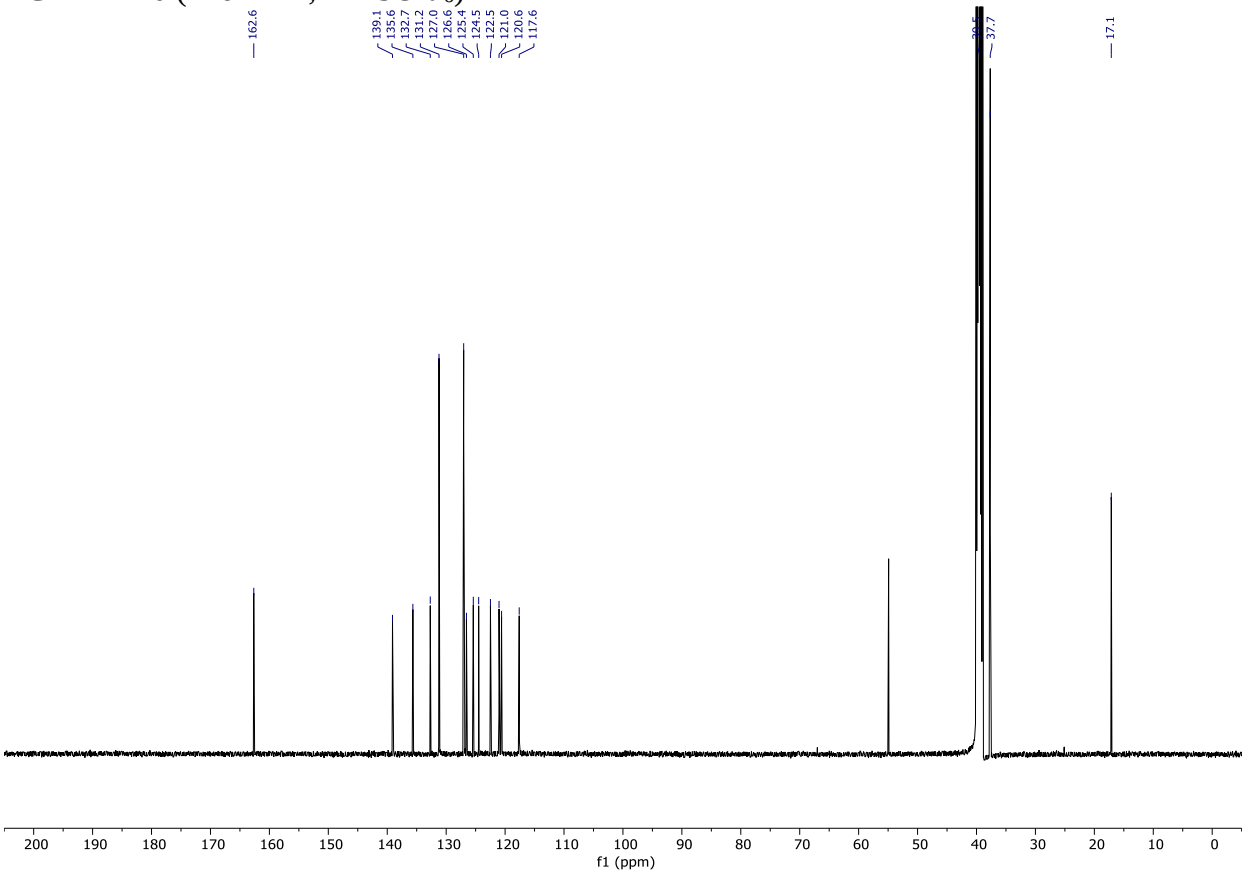
^{1}H NMR of **S16** (400 MHz, $CDCl_3$)



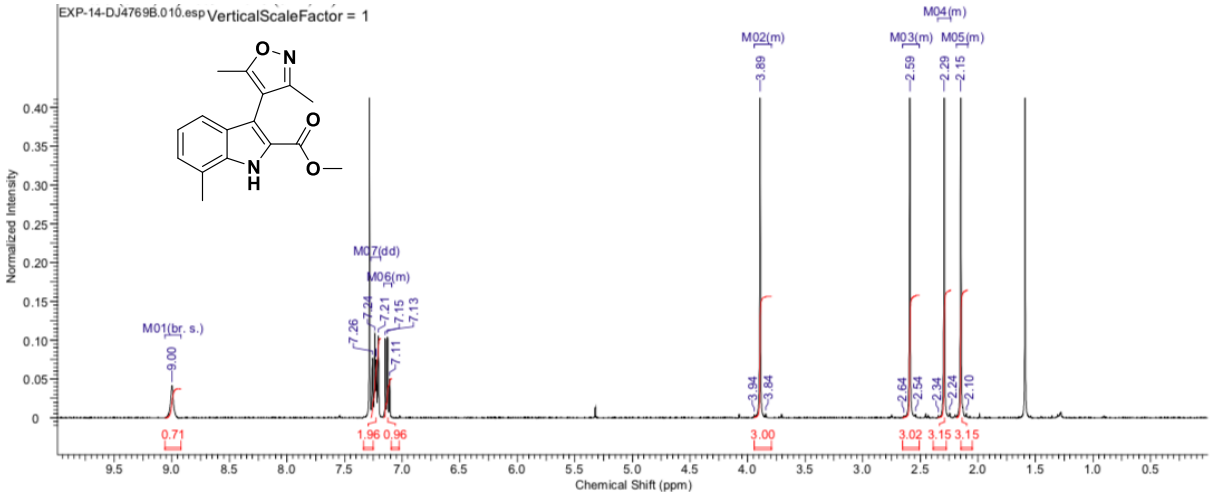
^{1}H NMR of **20** (400 MHz, DMSO-d_6)



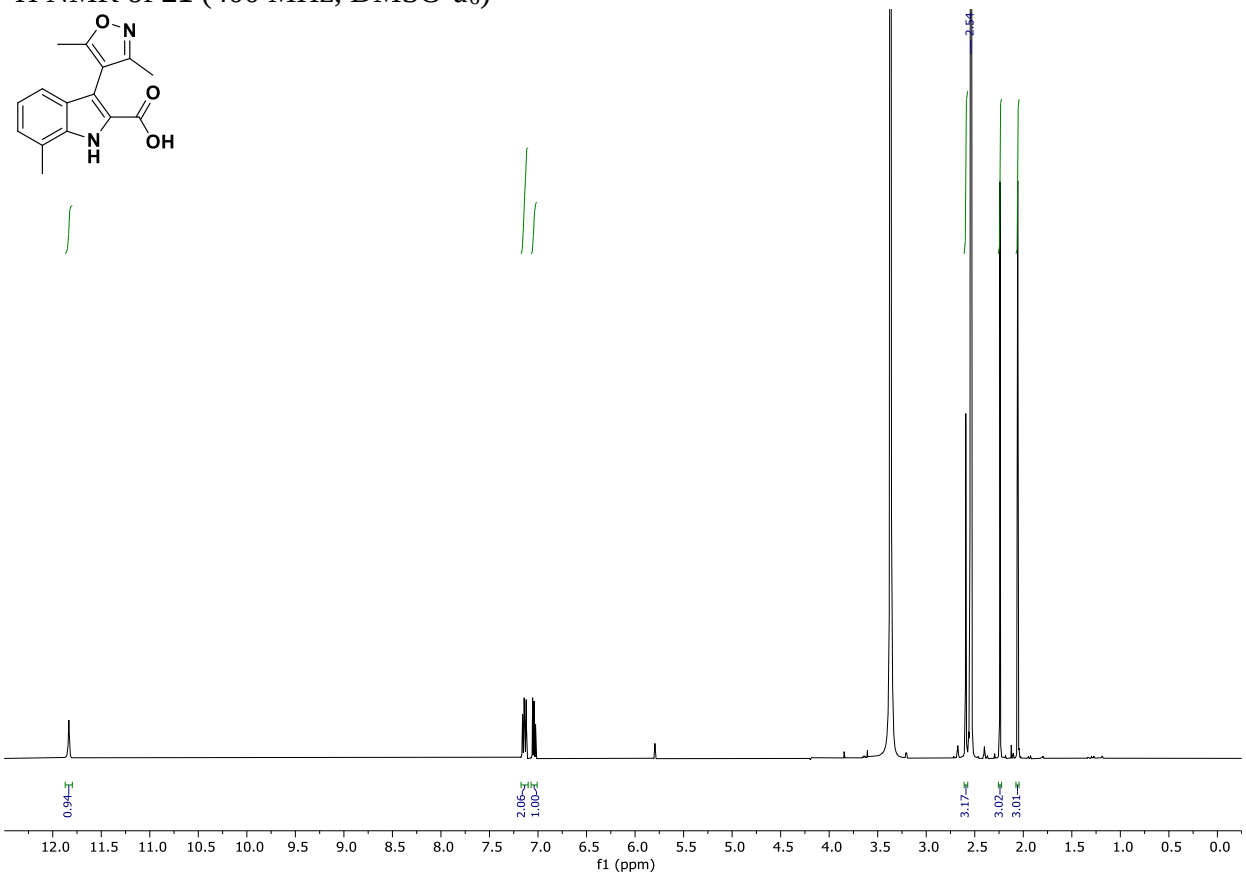
^{13}C NMR **20** (126 MHz, DMSO-d_6)



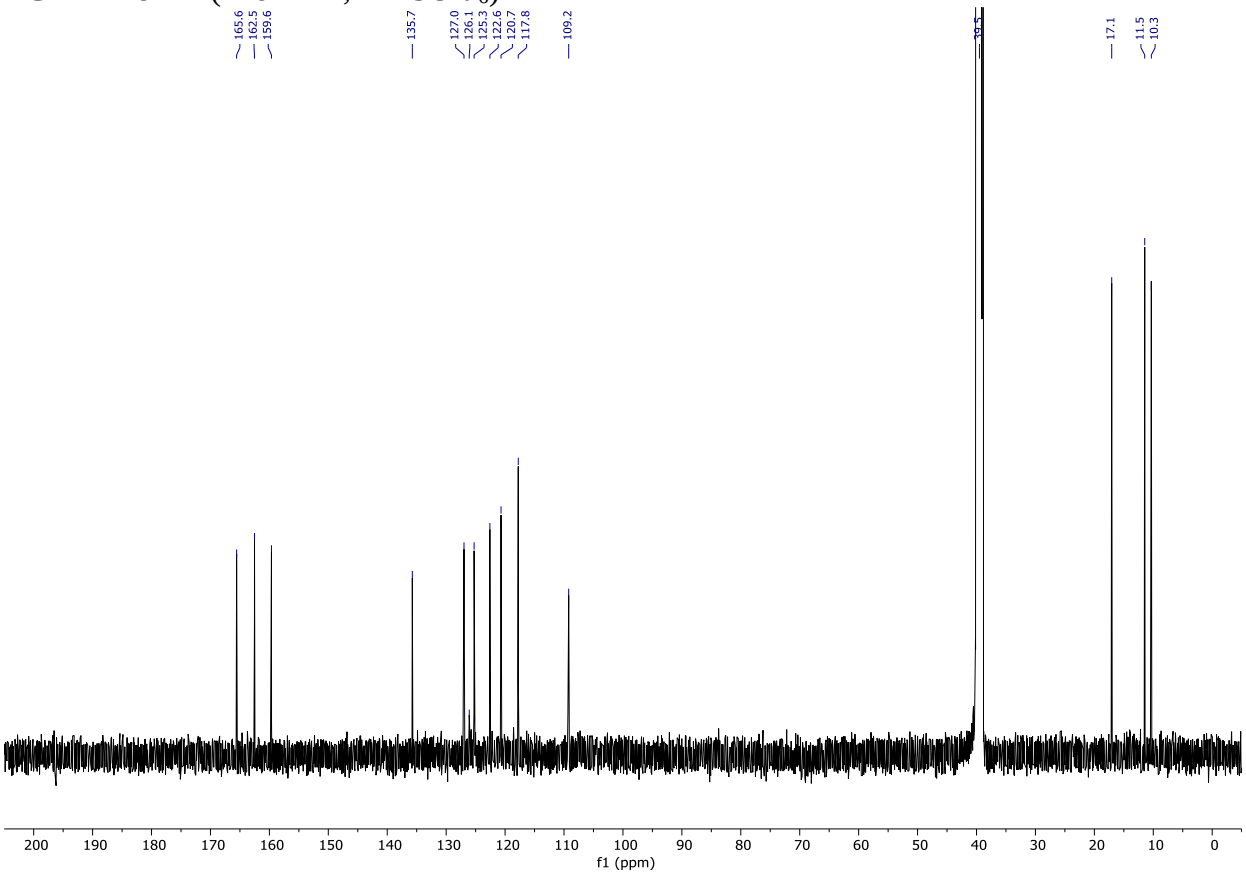
^{1}H NMR of **S17** (400 MHz, $CDCl_3$)



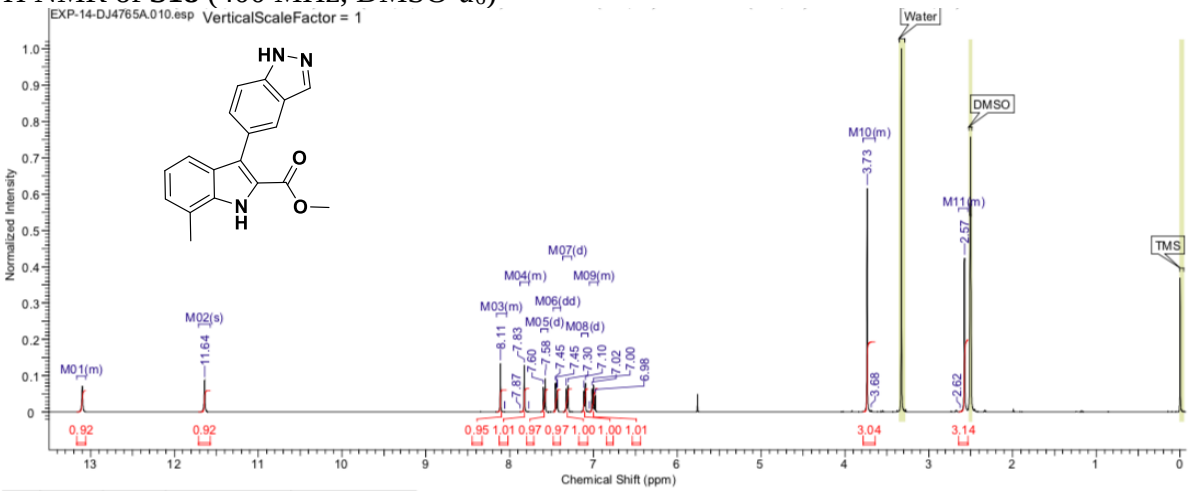
^{1}H NMR of **21** (400 MHz, DMSO-d_6)



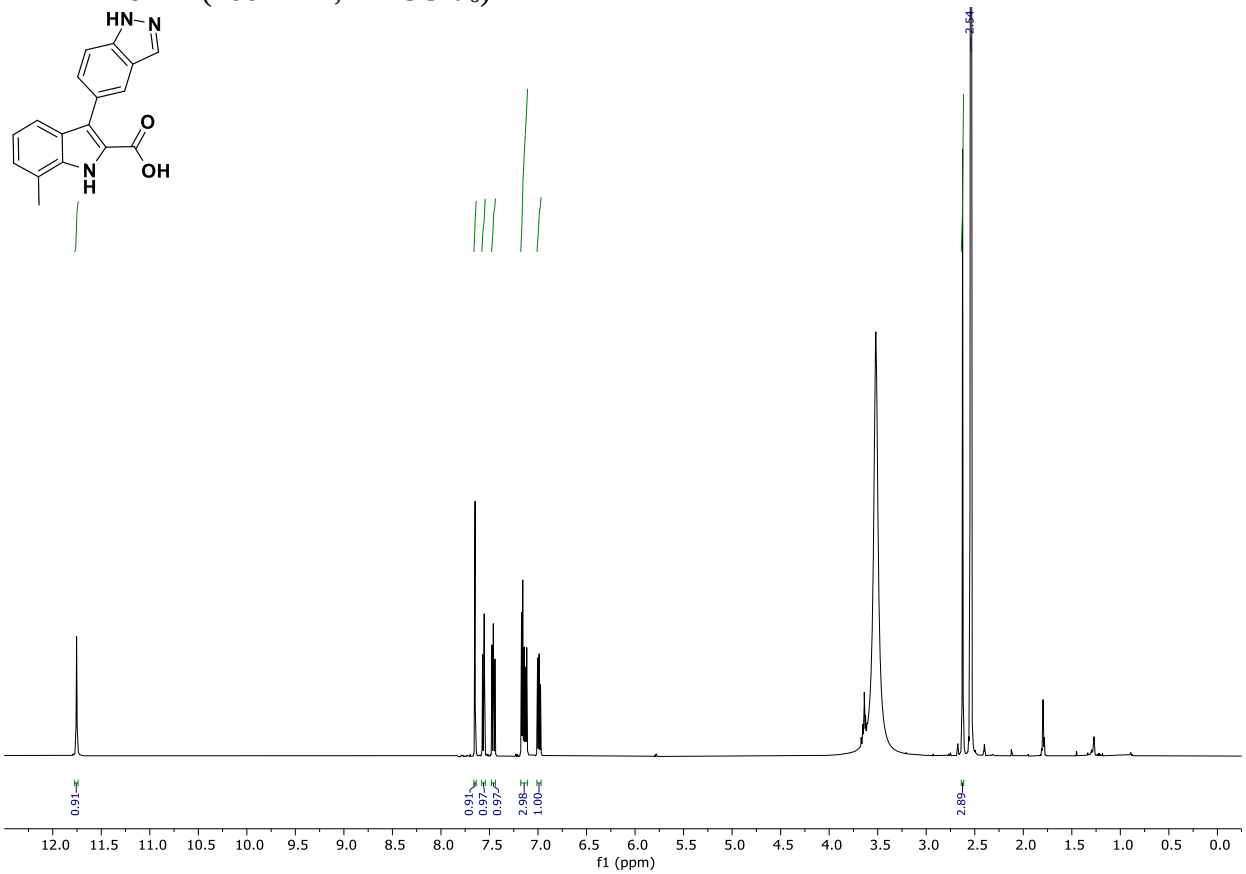
^{13}C NMR of **21** (126 MHz, DMSO-d_6)



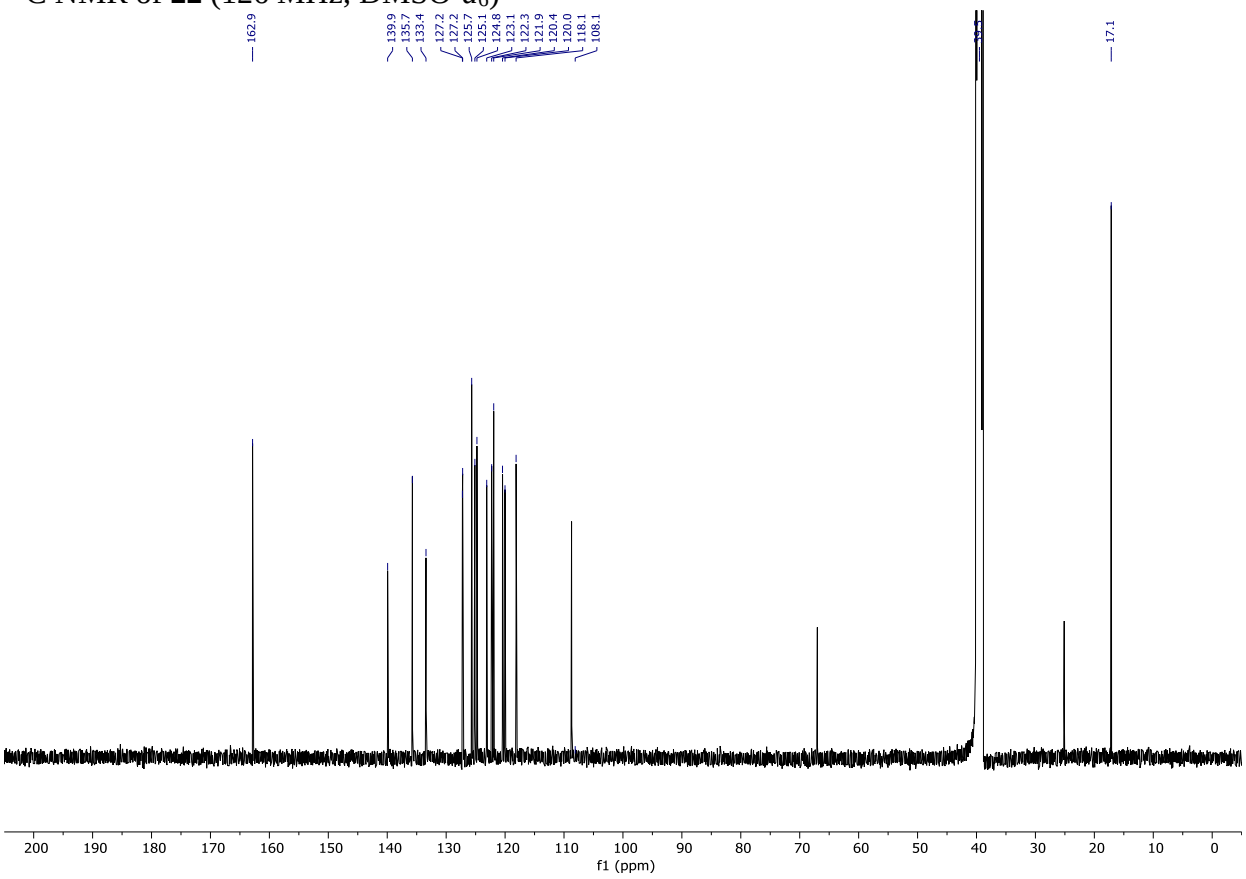
^{1}H NMR of **S18** (400 MHz, DMSO-d_6)



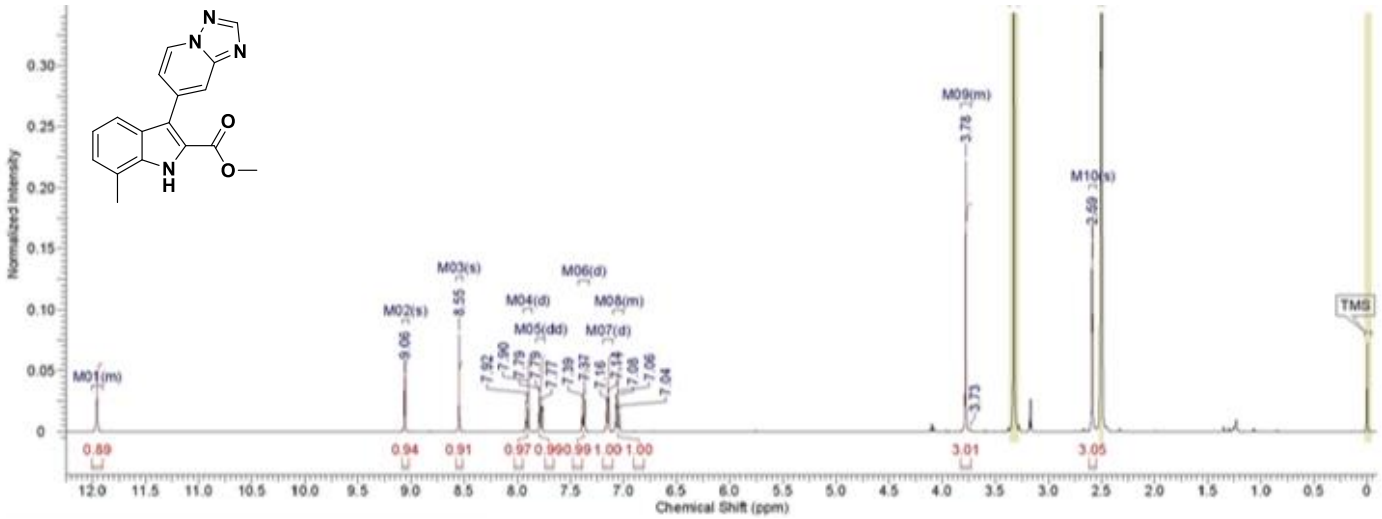
^{1}H NMR of **22** (400 MHz, DMSO-d_6)



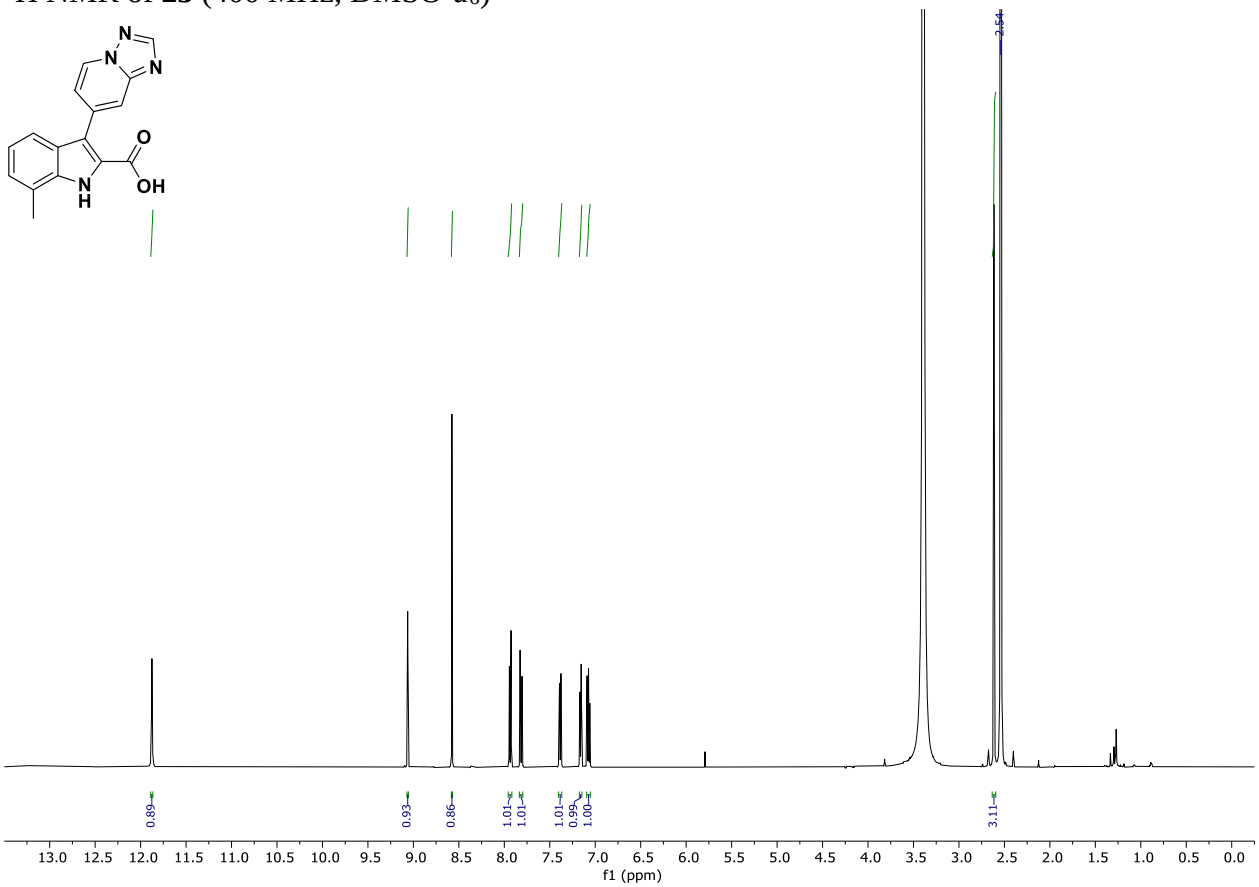
^{13}C NMR of **22** (126 MHz, DMSO-d_6)



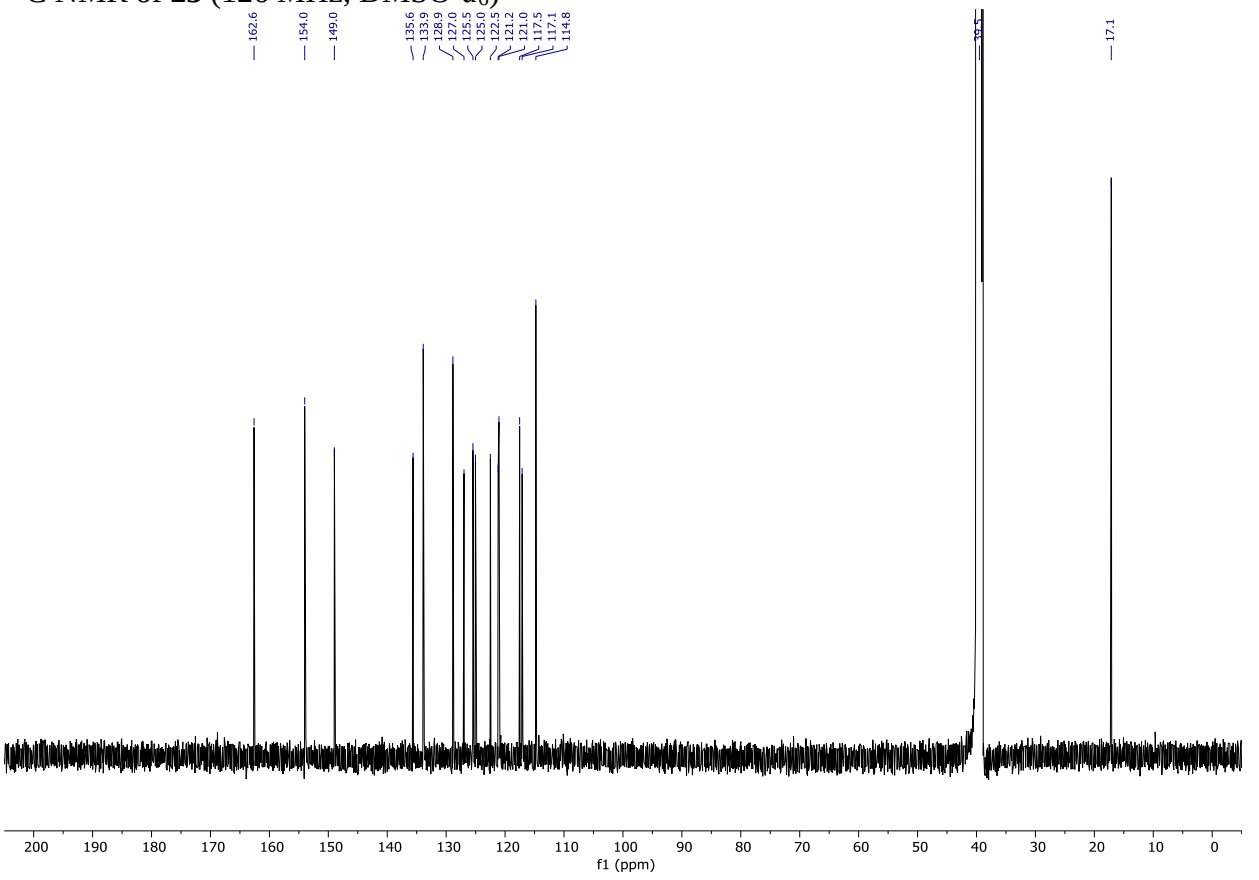
^{1}H NMR of **S19** (400 MHz, DMSO-d_6)



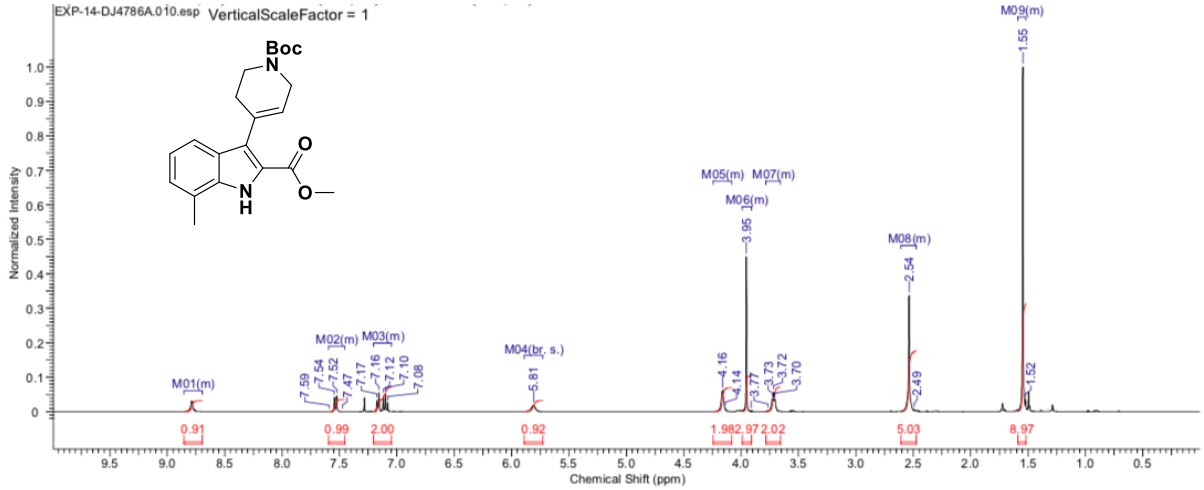
^{1}H NMR of **23** (400 MHz, DMSO-d_6)



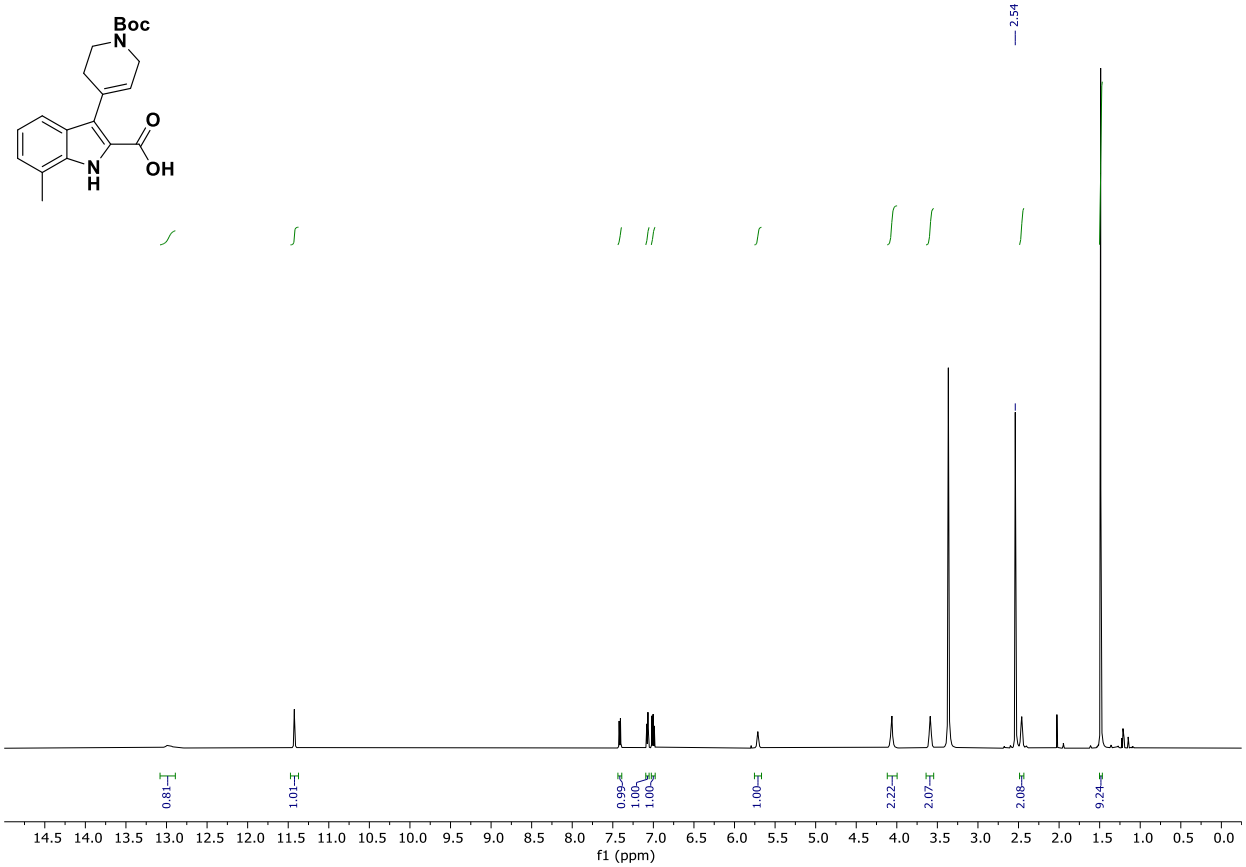
^{13}C NMR of **23** (126 MHz, DMSO-d_6)



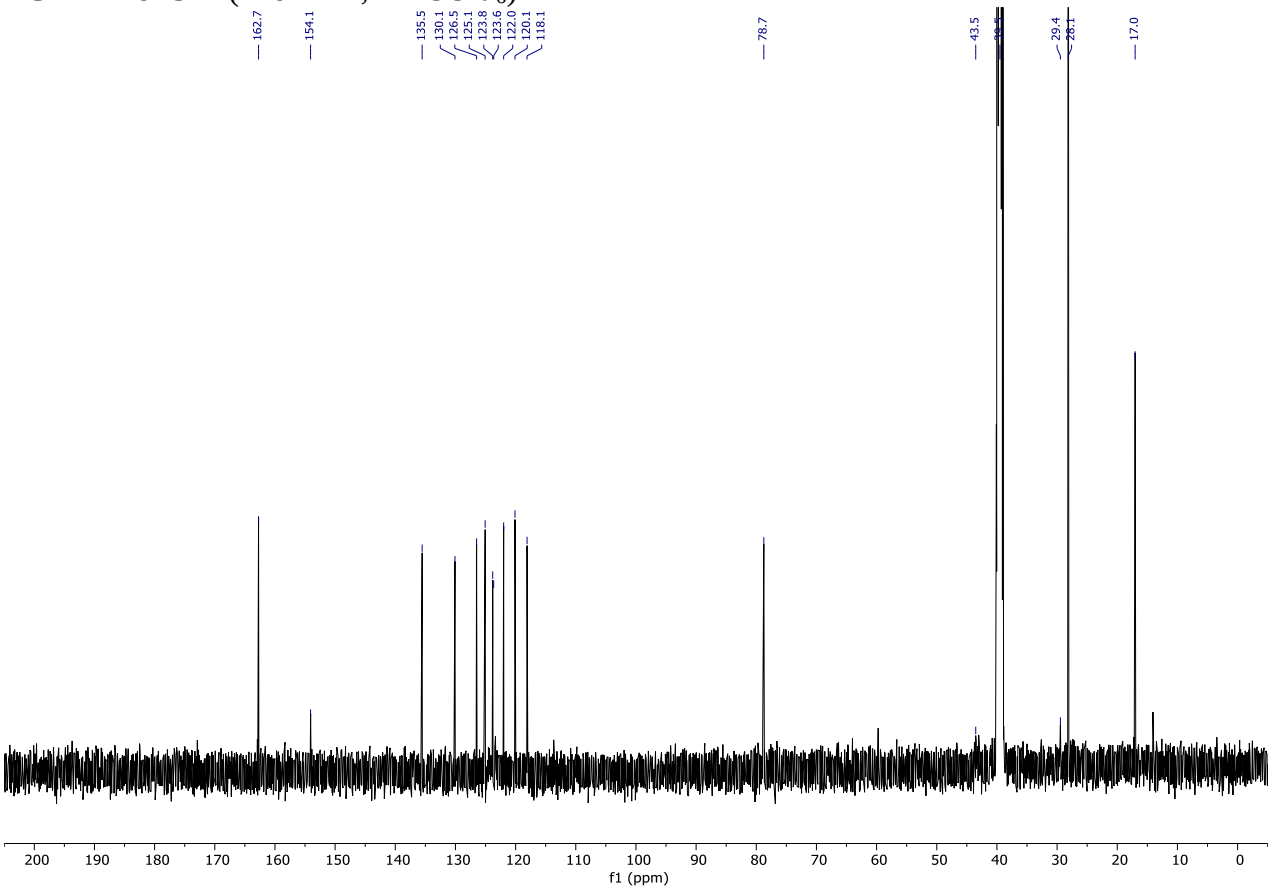
^{1}H NMR of **S20** (400 MHz, $CDCl_3$)



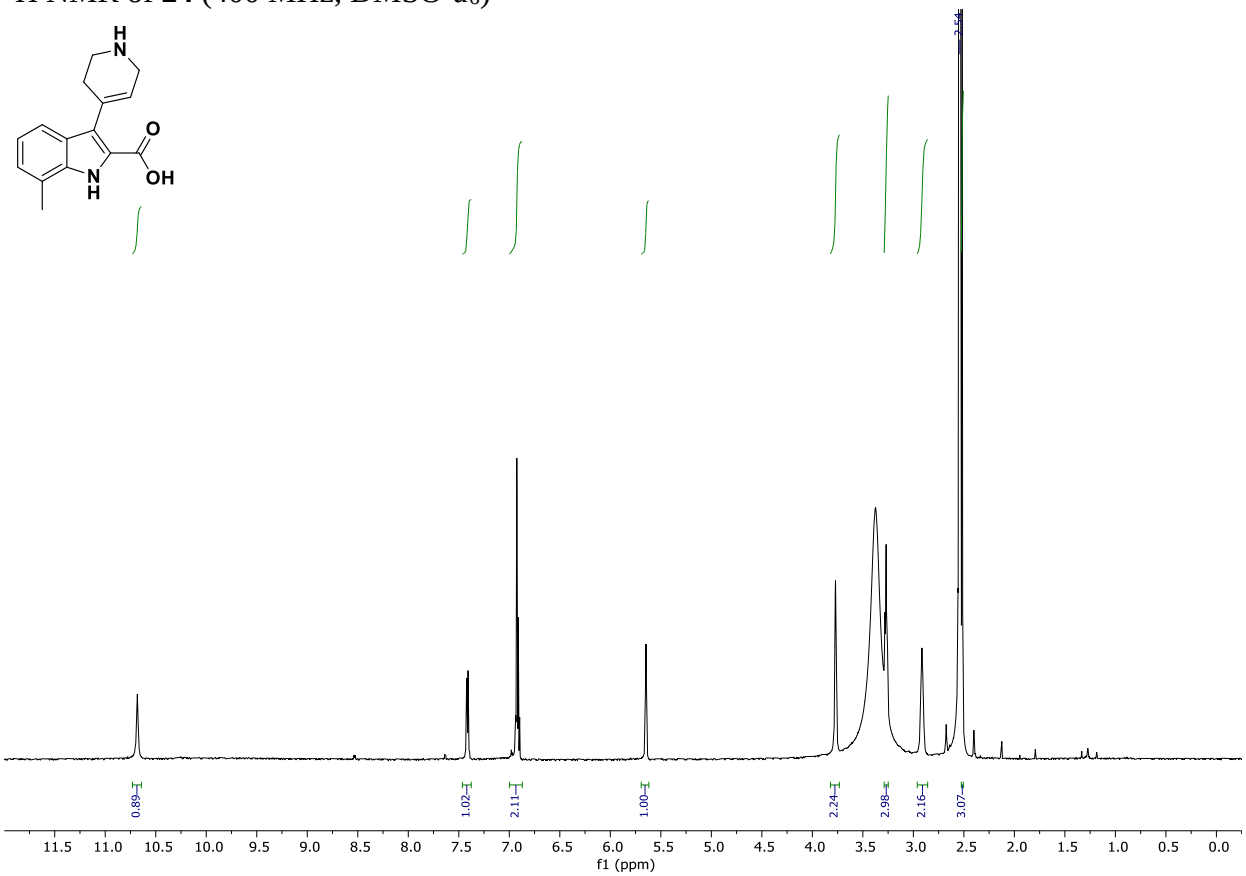
^{1}H NMR of **S21** (400 MHz, DMSO-d_6)



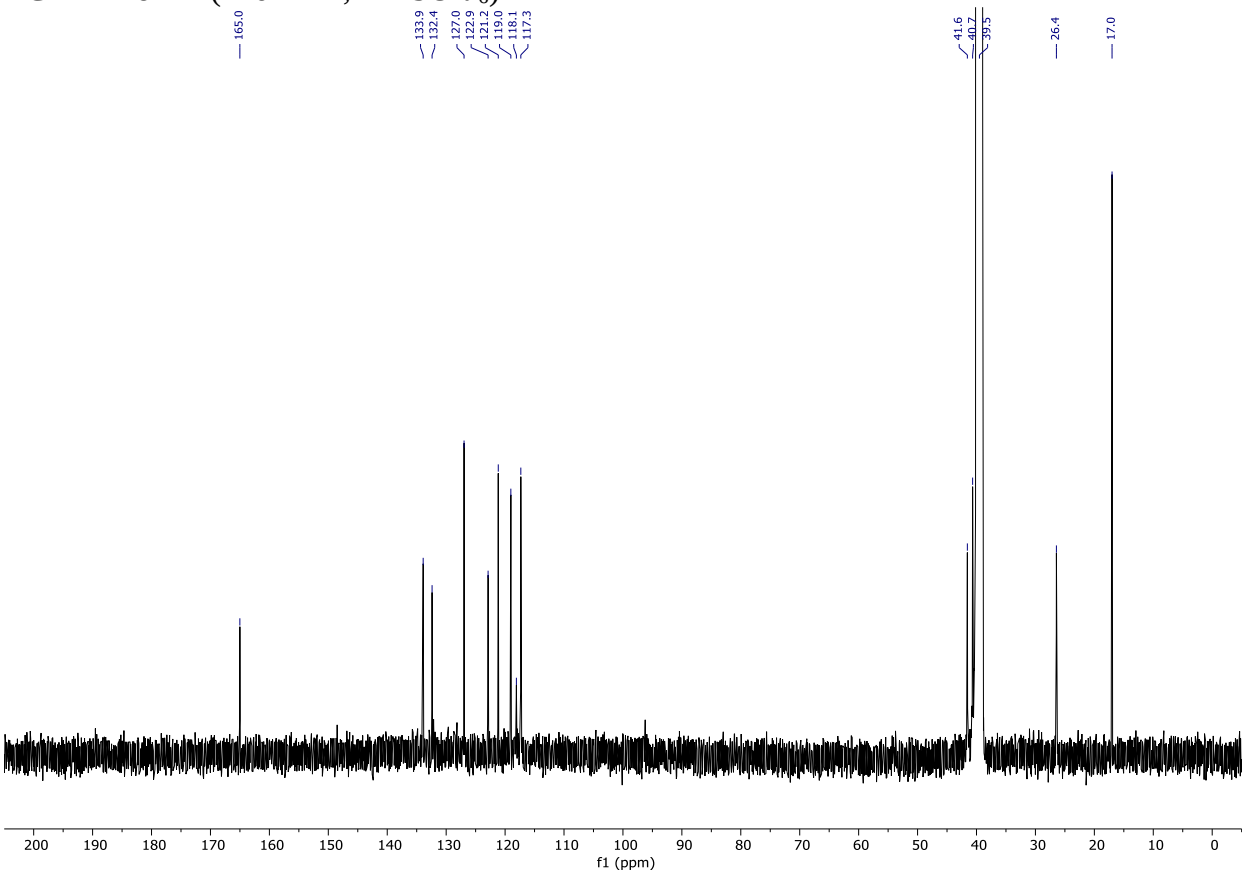
^{13}C NMR of **S21** (126 MHz, DMSO-d_6)



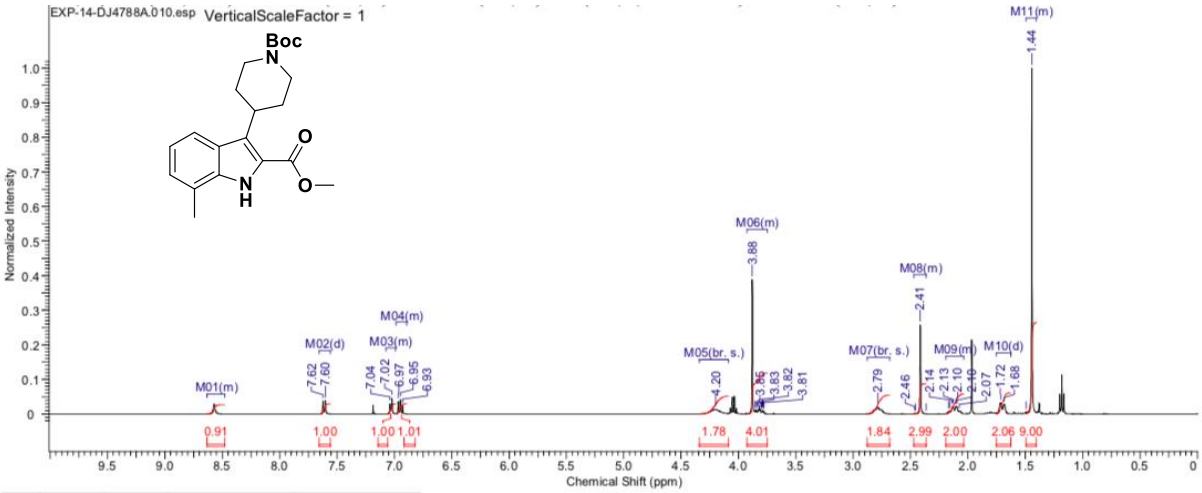
^{1}H NMR of **24** (400 MHz, DMSO-d_6)



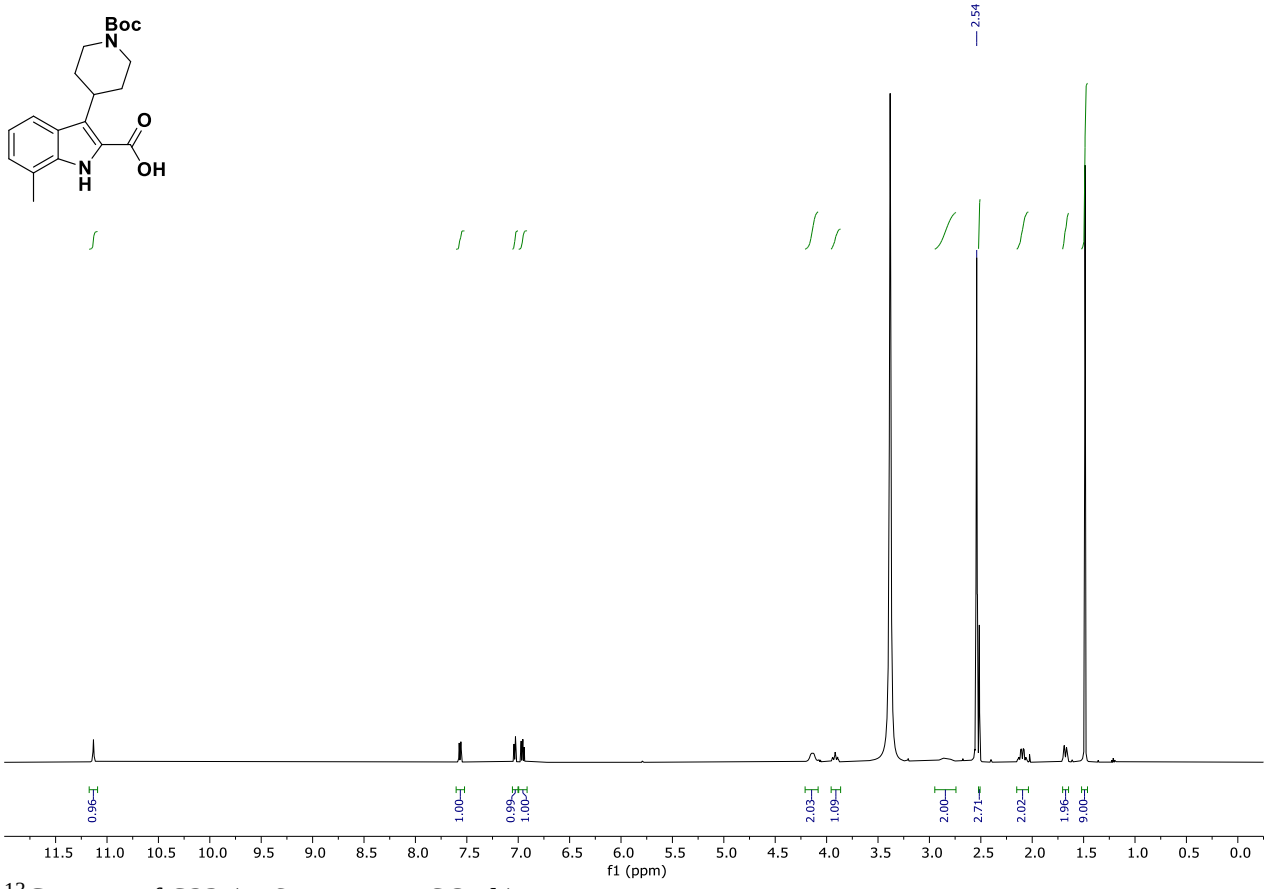
^{13}C NMR of **24** (126 MHz, DMSO-d_6)



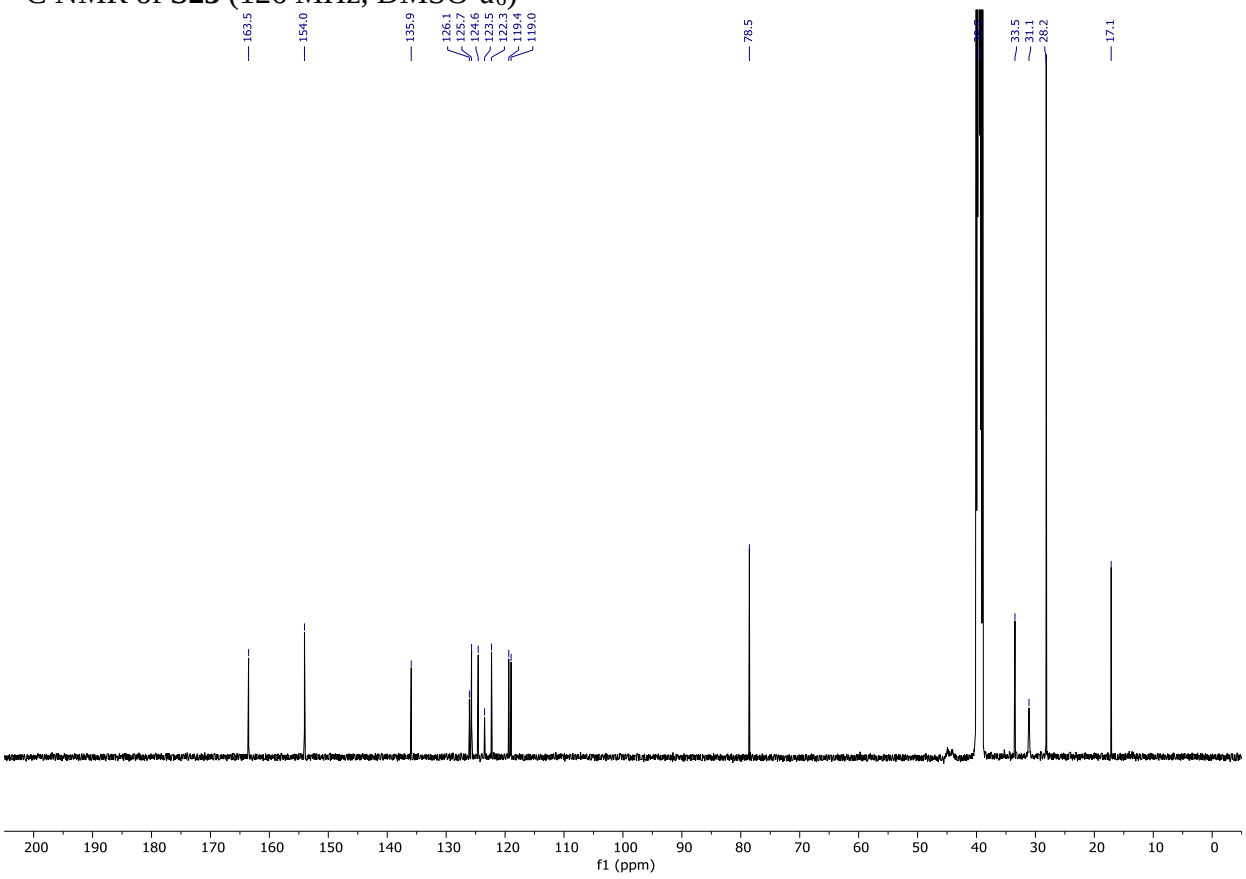
^{1}H NMR of **S22** (400 MHz, $CDCl_3$)



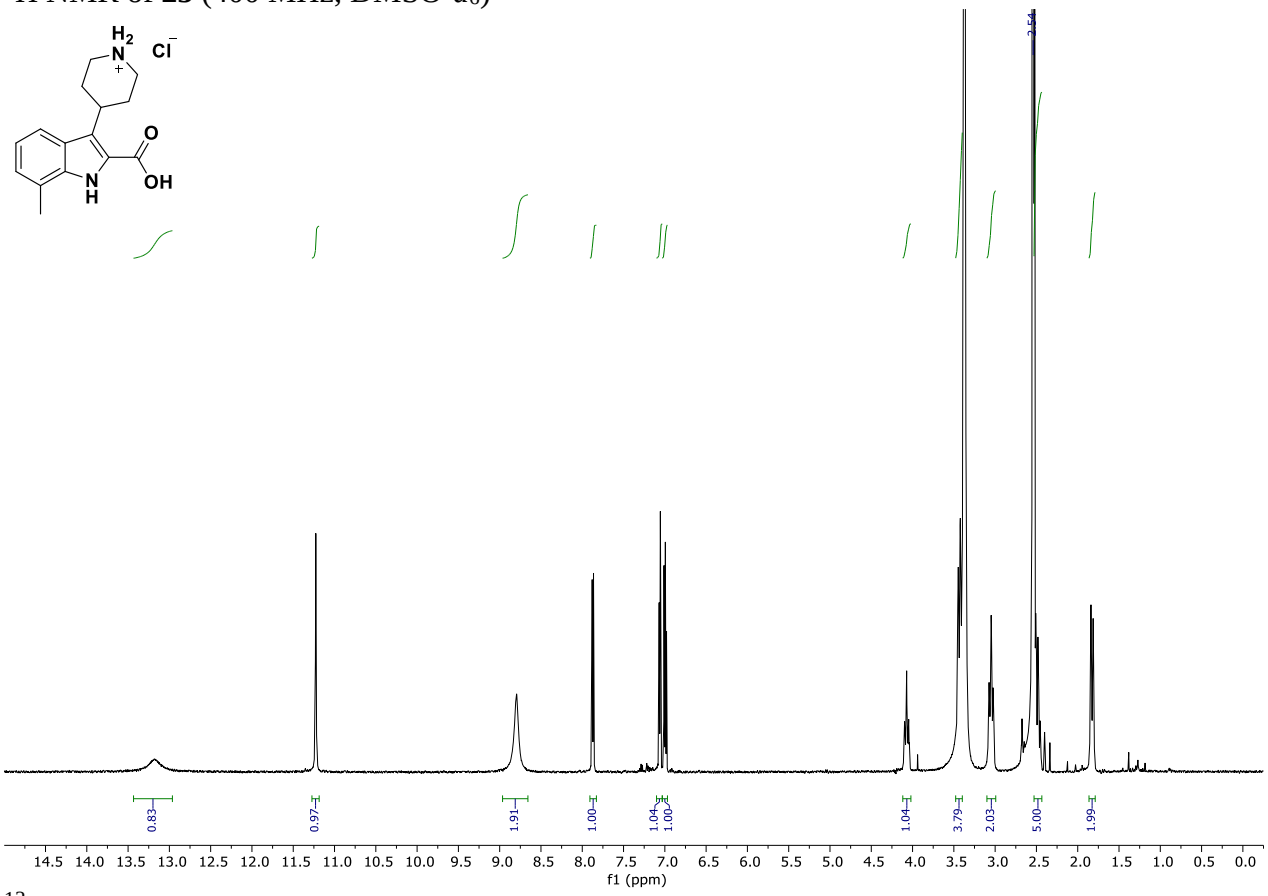
^{1}H NMR of **S23** (400 MHz, DMSO-d_6)



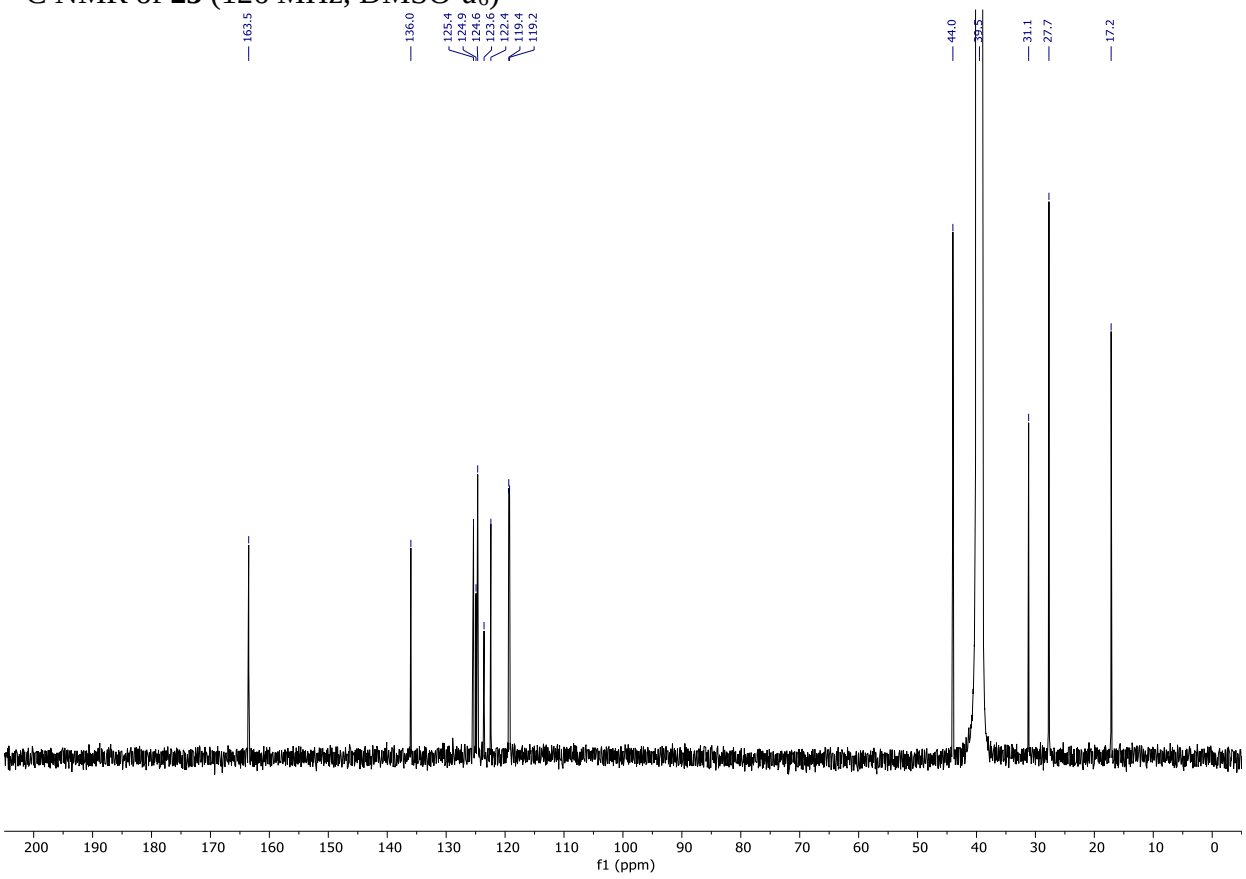
^{13}C NMR of **S23** (126 MHz, DMSO-d_6)



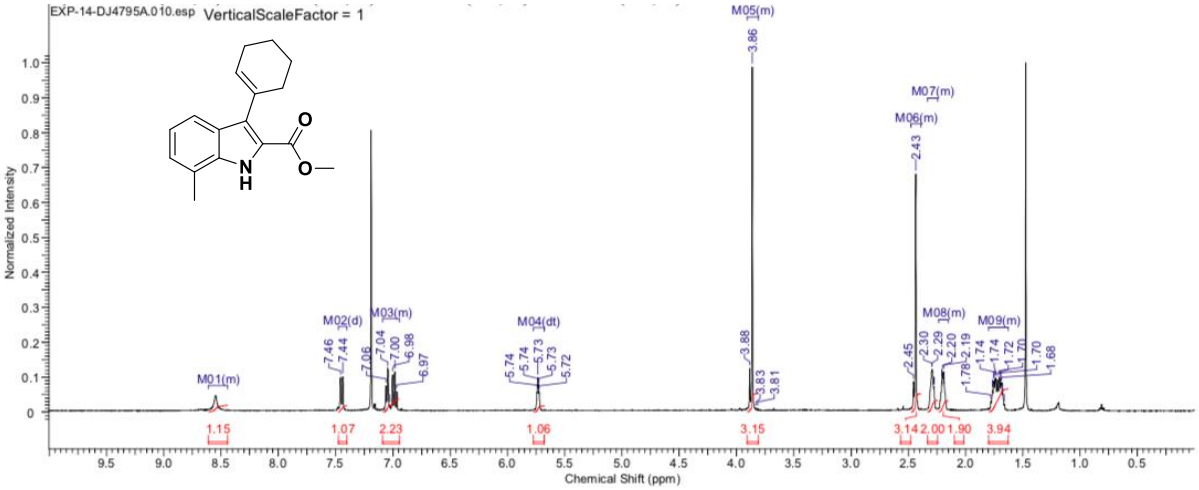
^{1}H NMR of **25** (400 MHz, DMSO-d_6)



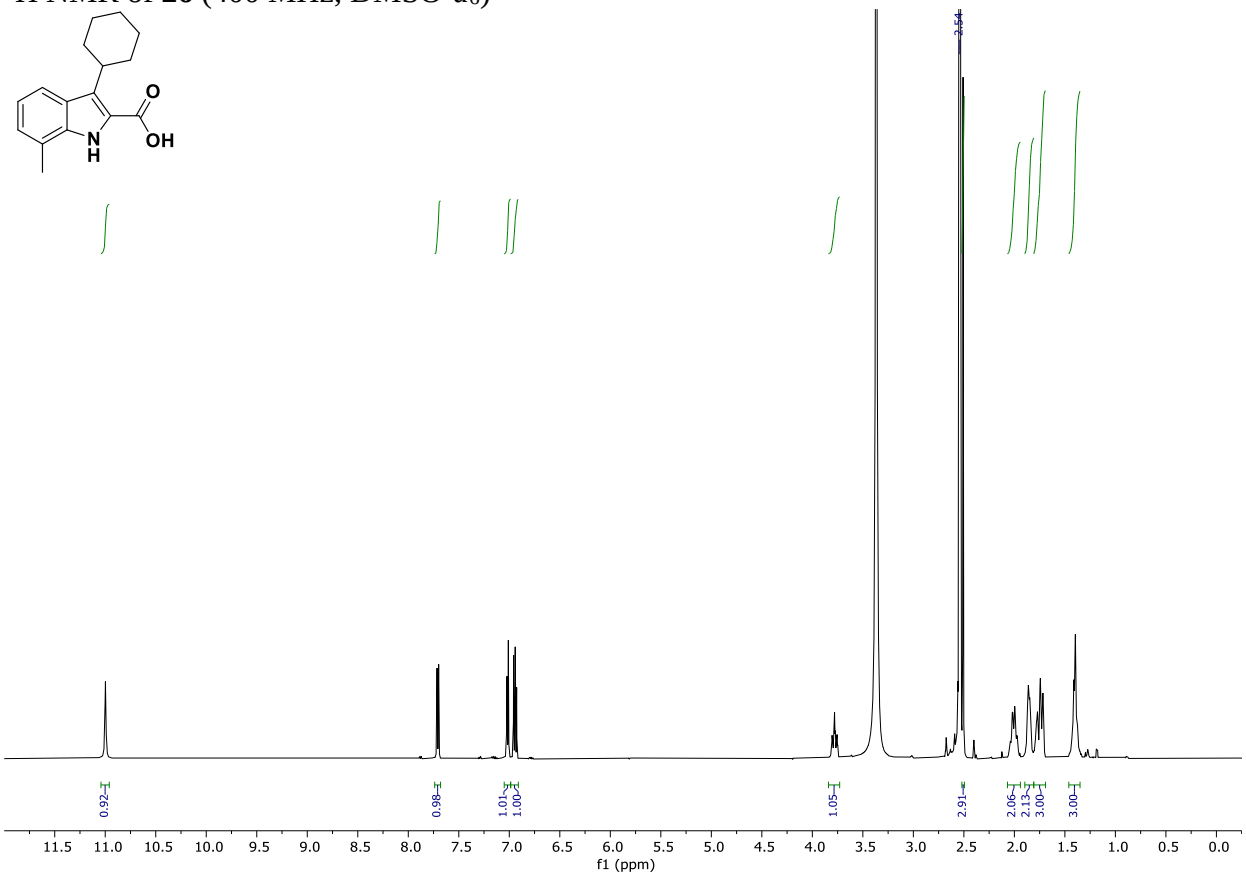
^{13}C NMR of **25** (126 MHz, DMSO-d_6)



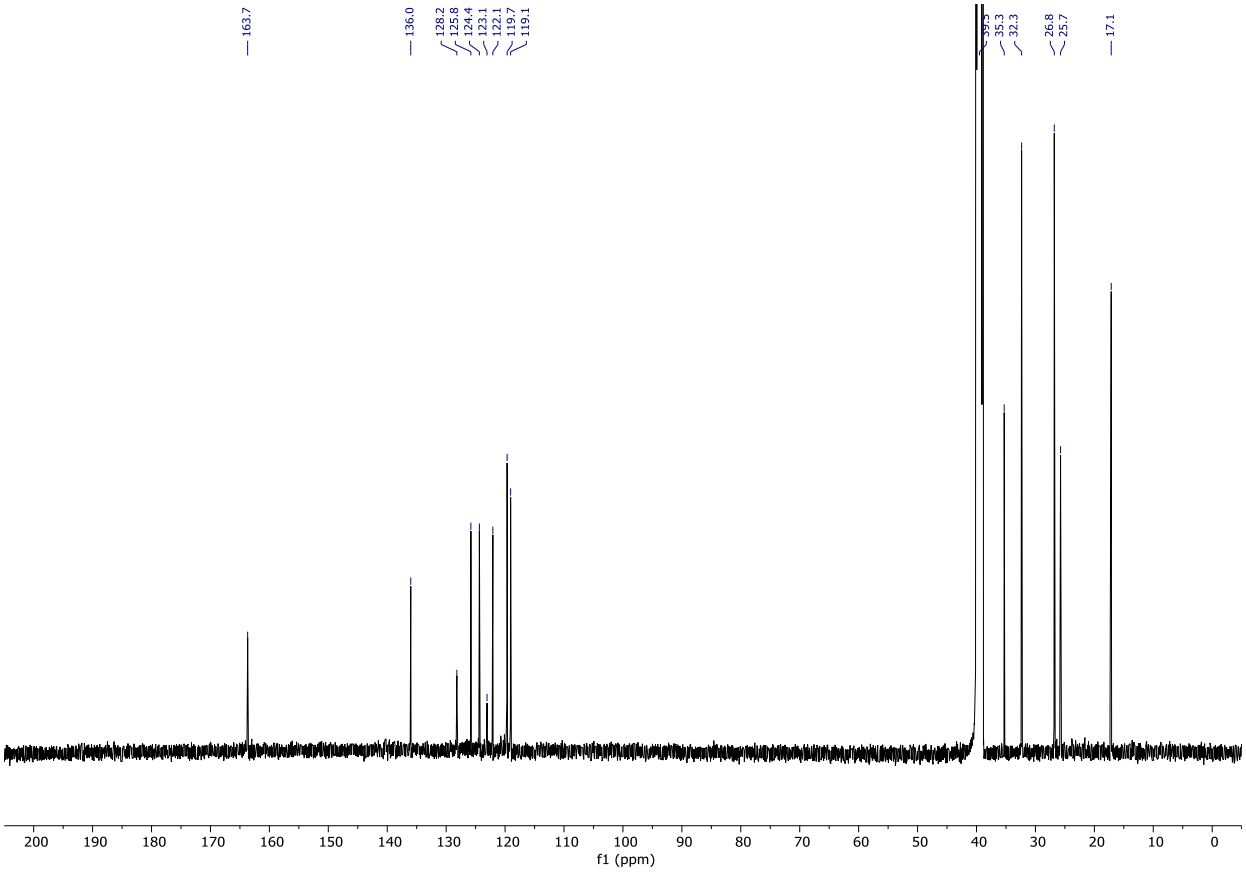
^{1}H NMR of **S24** (400 MHz, $CDCl_3$)



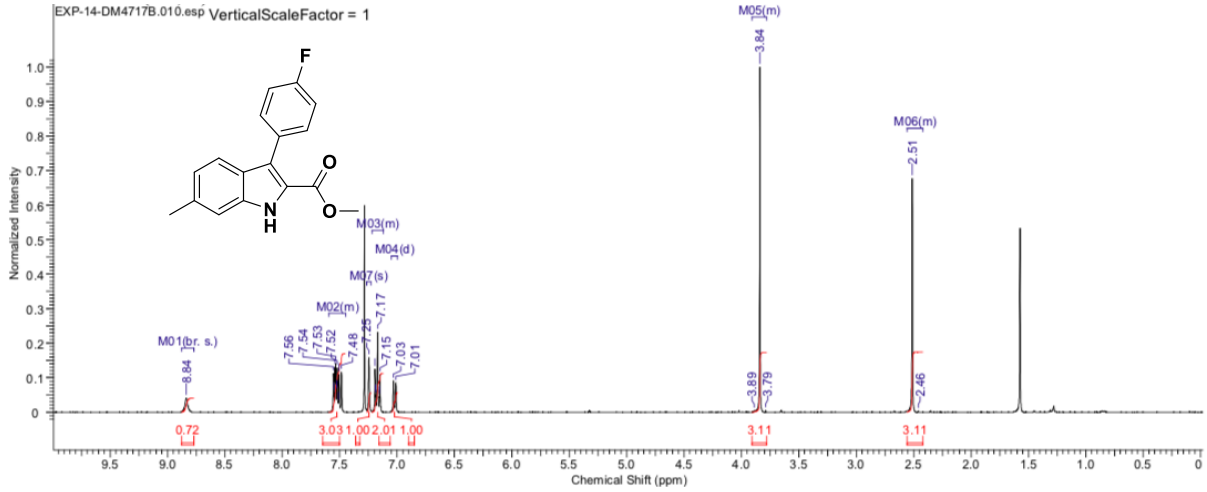
^{1}H NMR of **26** (400 MHz, DMSO-d_6)



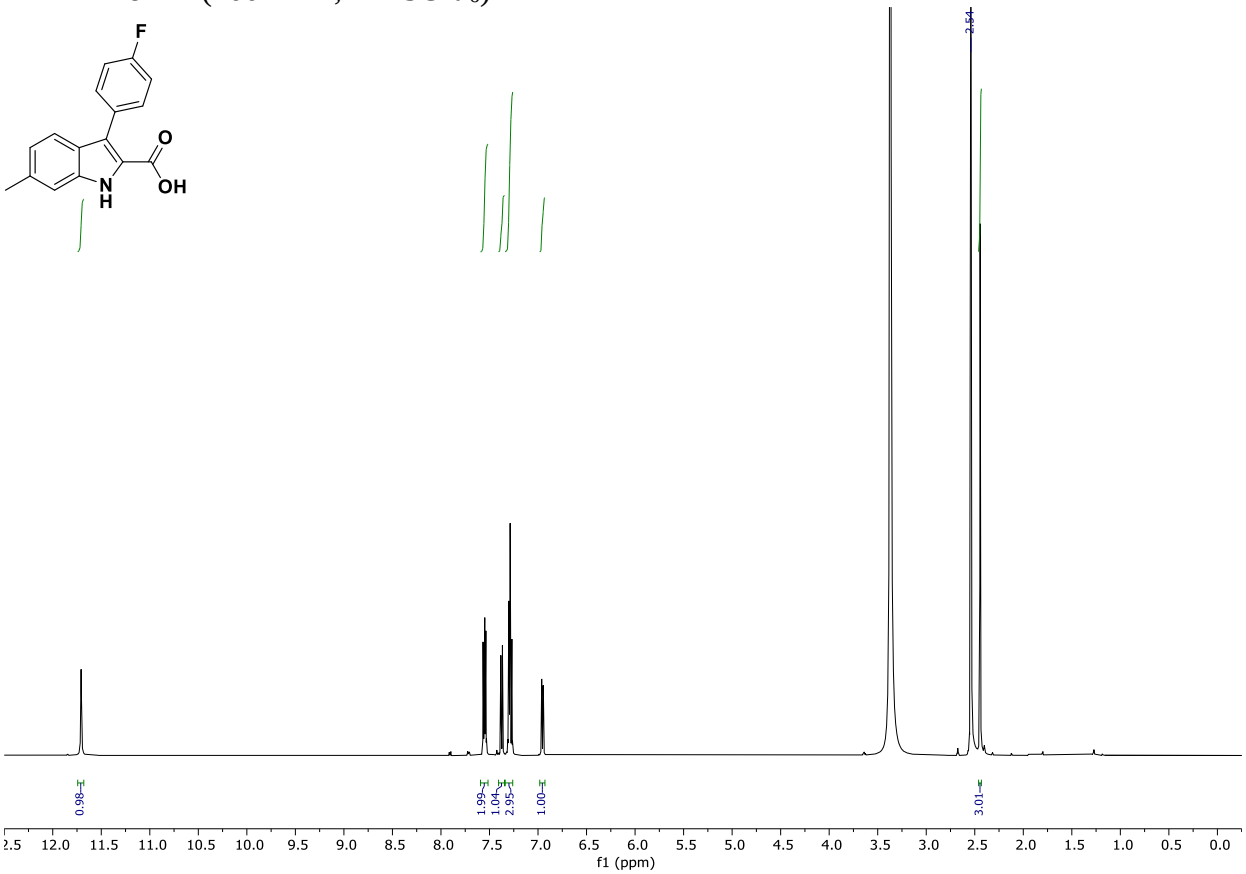
^{13}C NMR of **26** (126 MHz, DMSO-d_6)



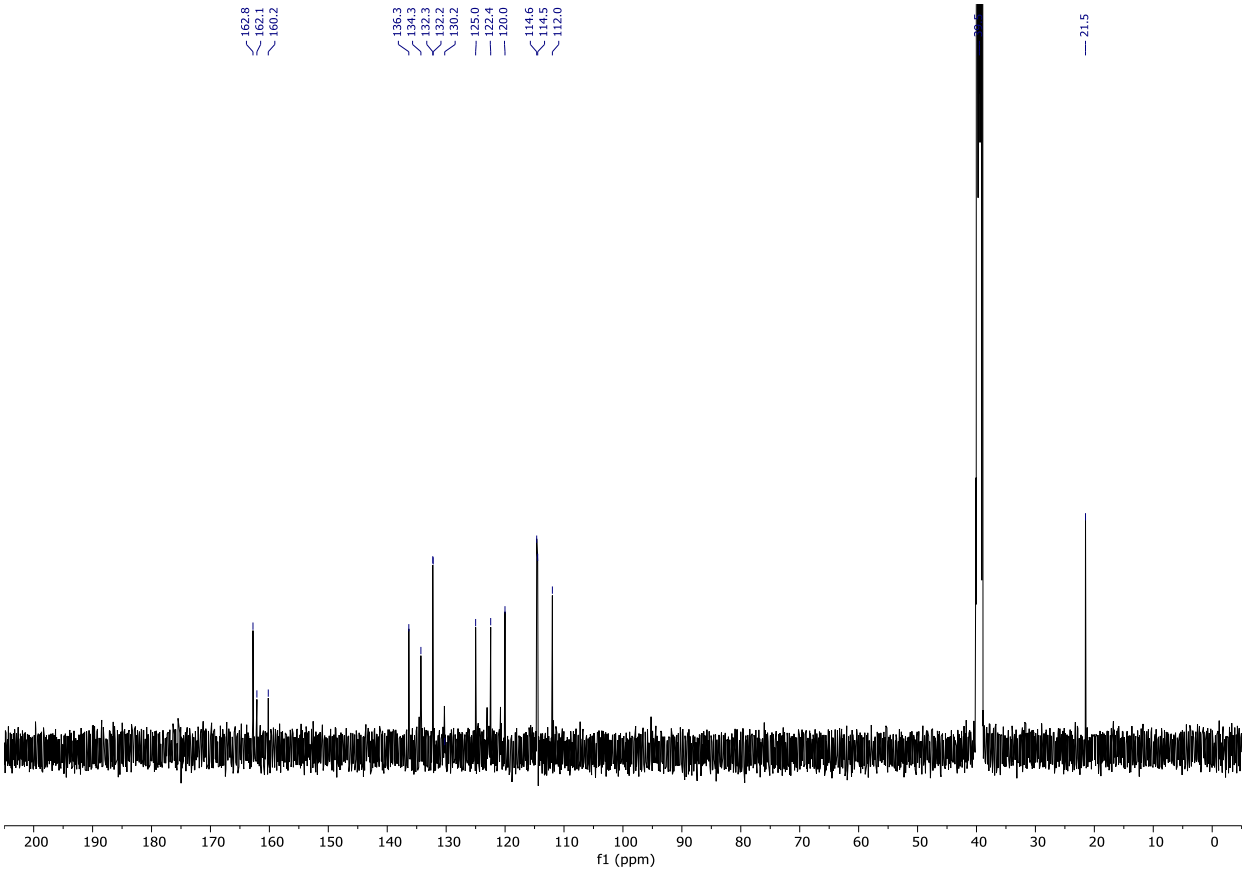
^{1}H NMR of **S26** (400 MHz, $CDCl_3$)



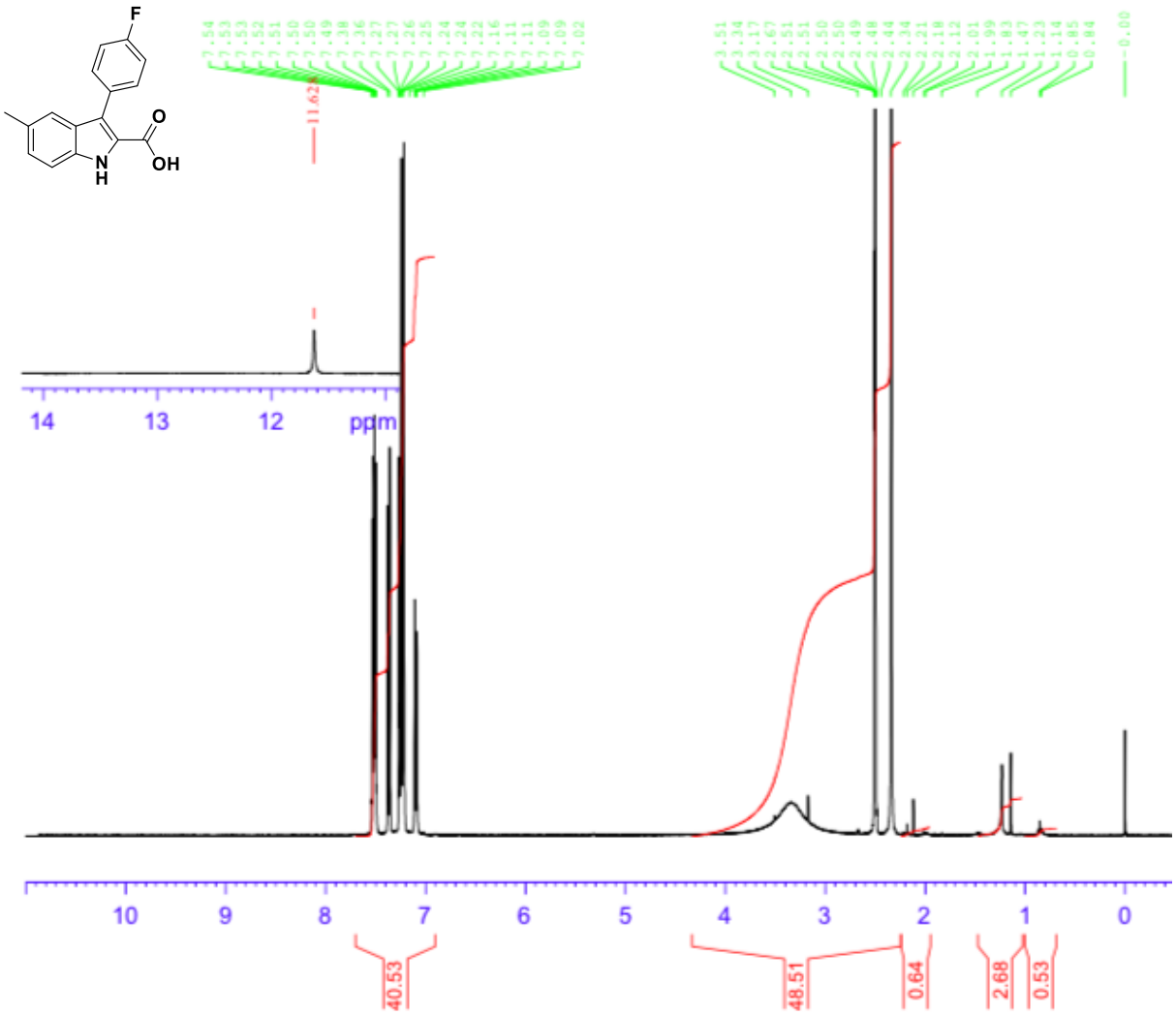
^{1}H NMR of **27** (400 MHz, DMSO-d_6)



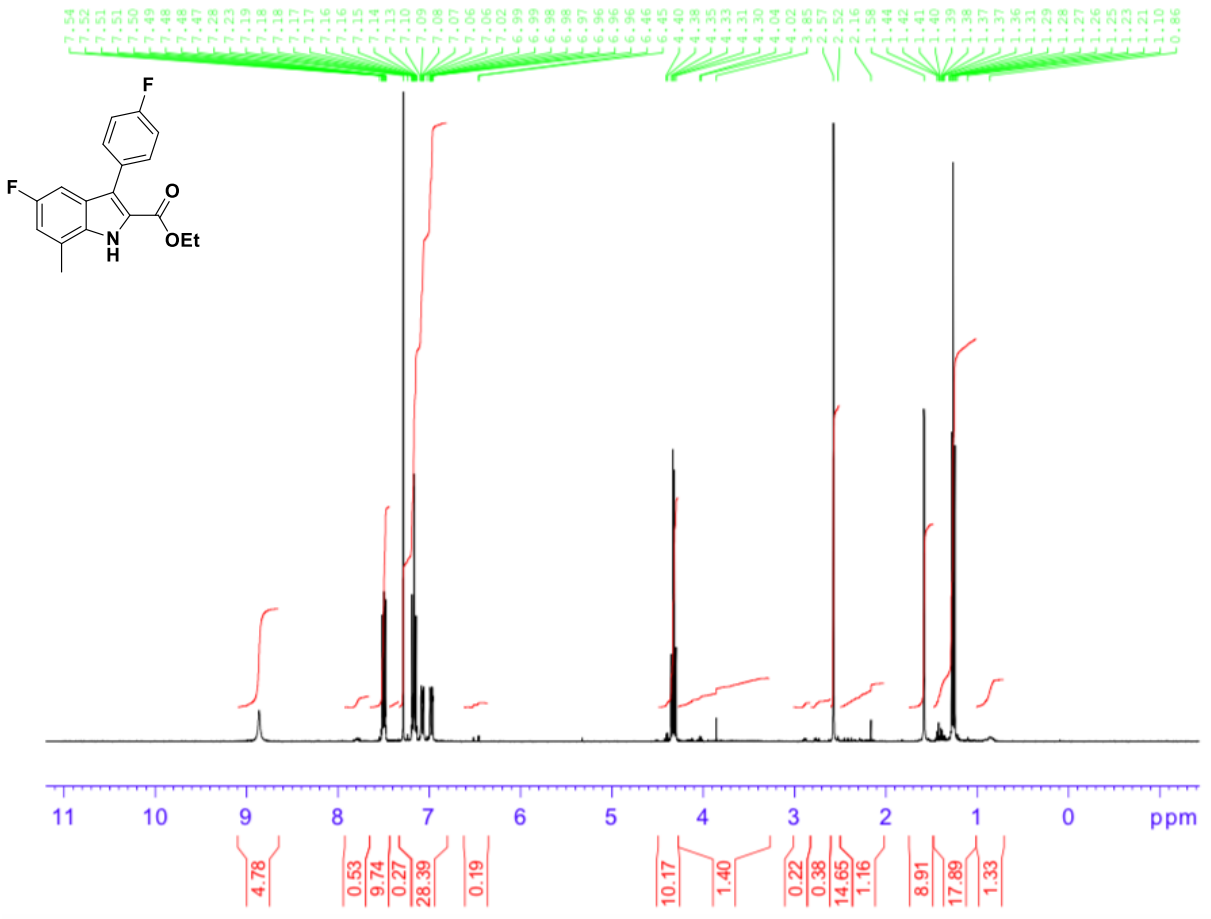
^{13}C NMR of **27** (126 MHz, DMSO-d_6)



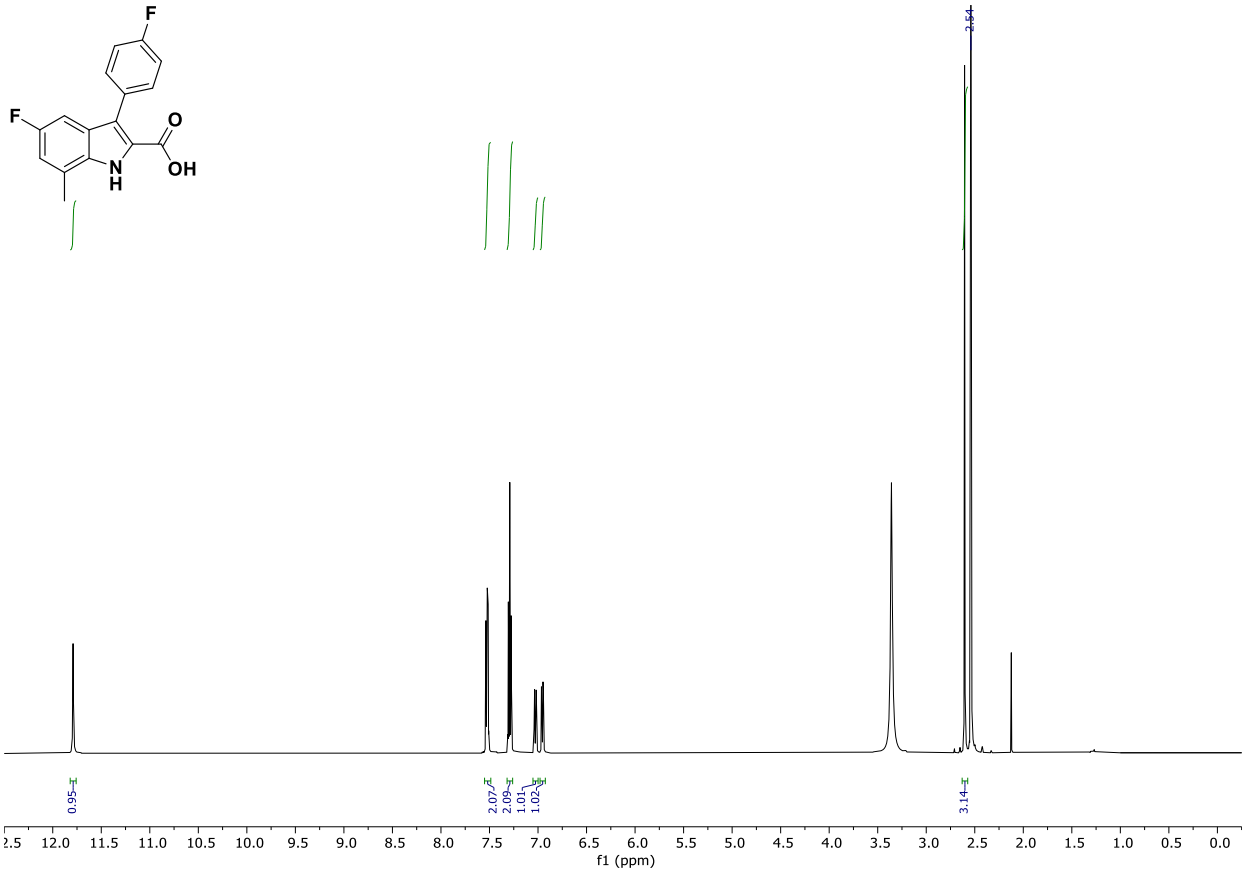
^{1}H NMR of **28** (400 MHz, DMSO-d_6)



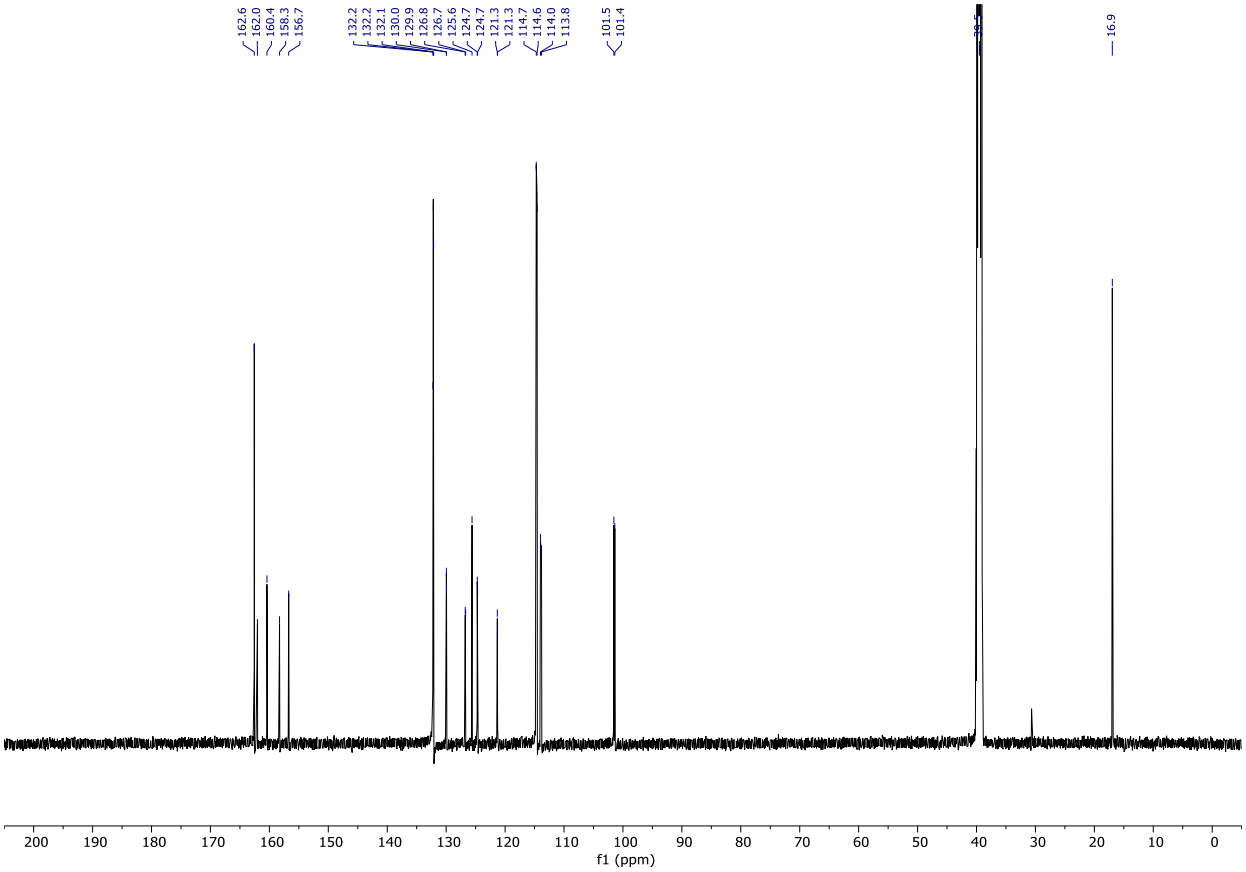
^{1}H NMR of **S27** (400 MHz, $CDCl_3$)



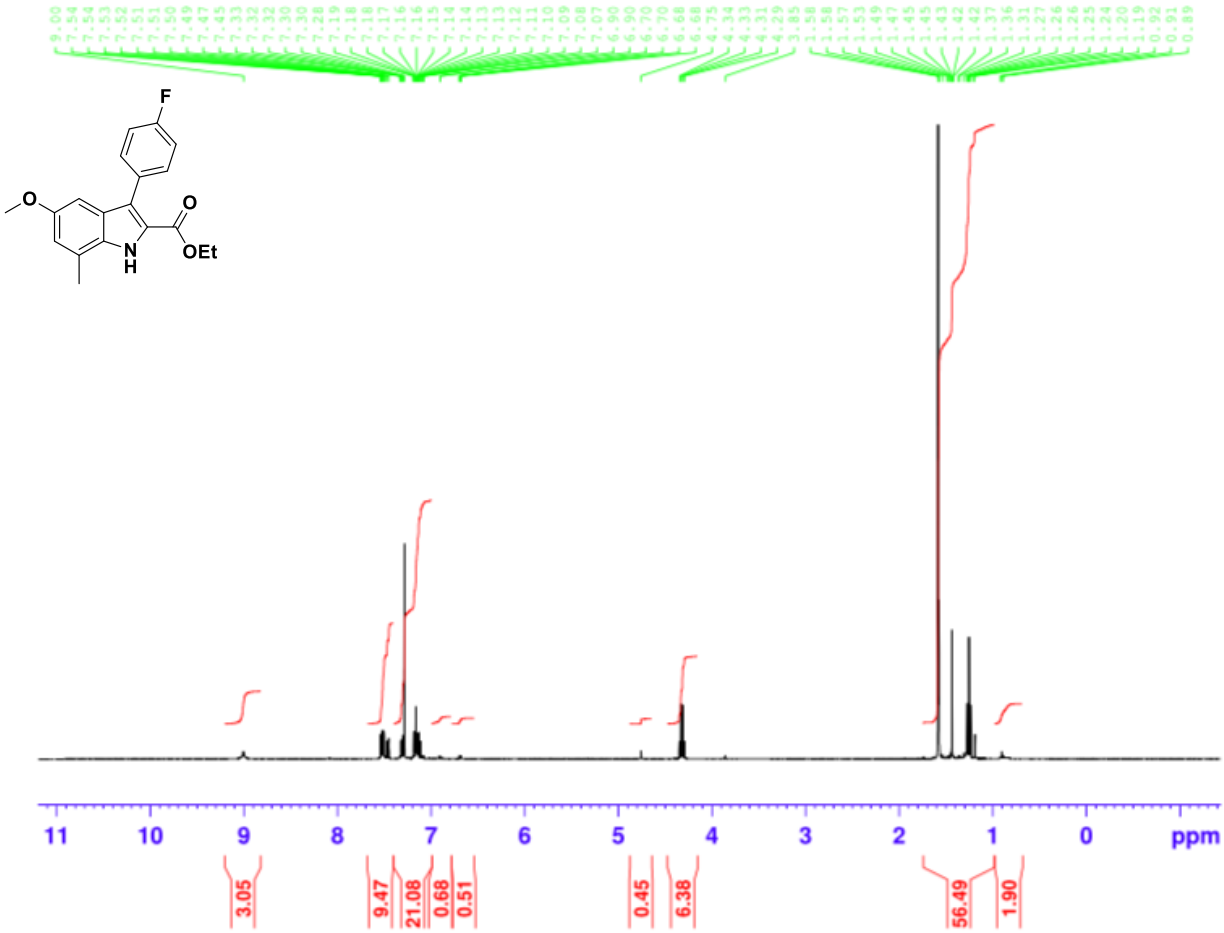
^{1}H NMR of **29** (600 MHz, DMSO-d_6)



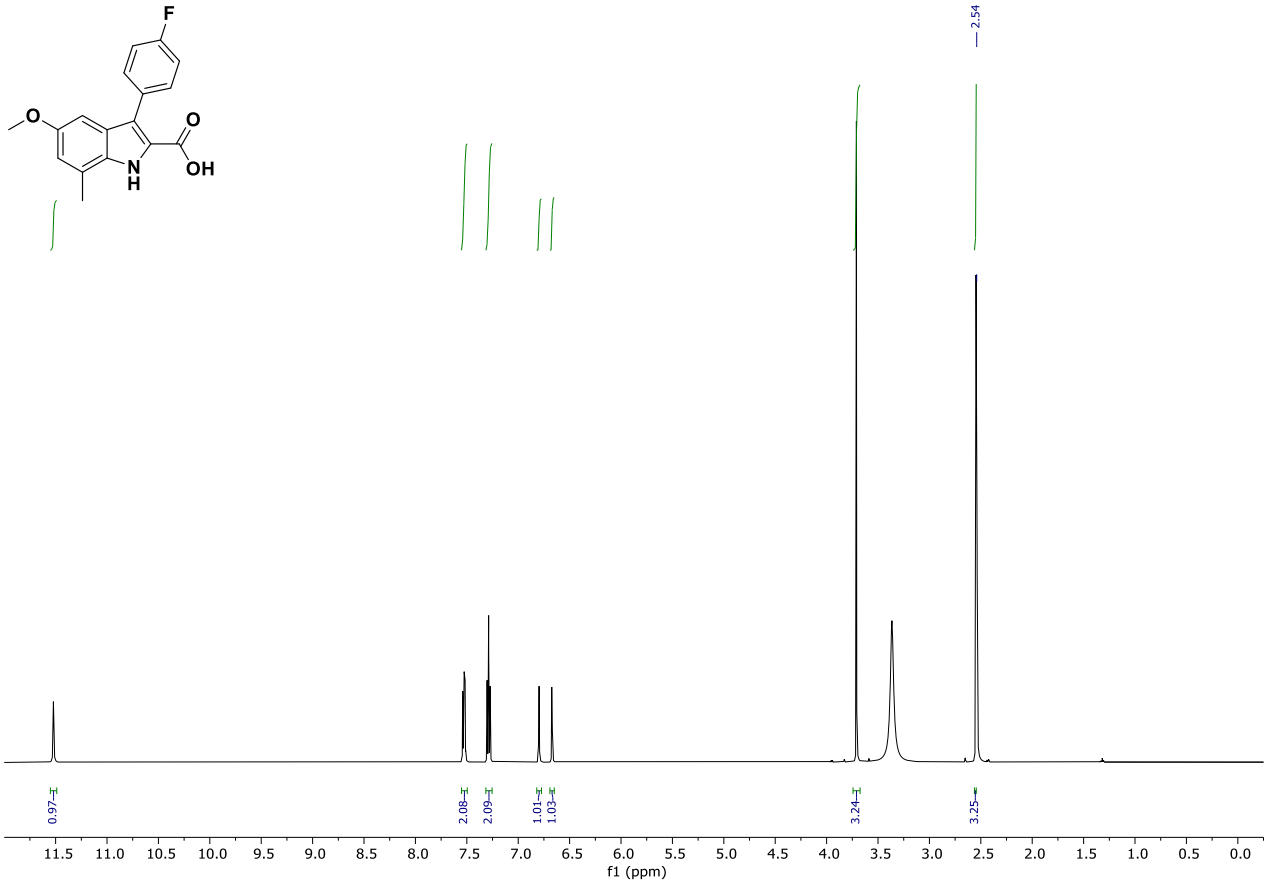
^{13}C NMR of **29** (151 MHz, DMSO-d_6)



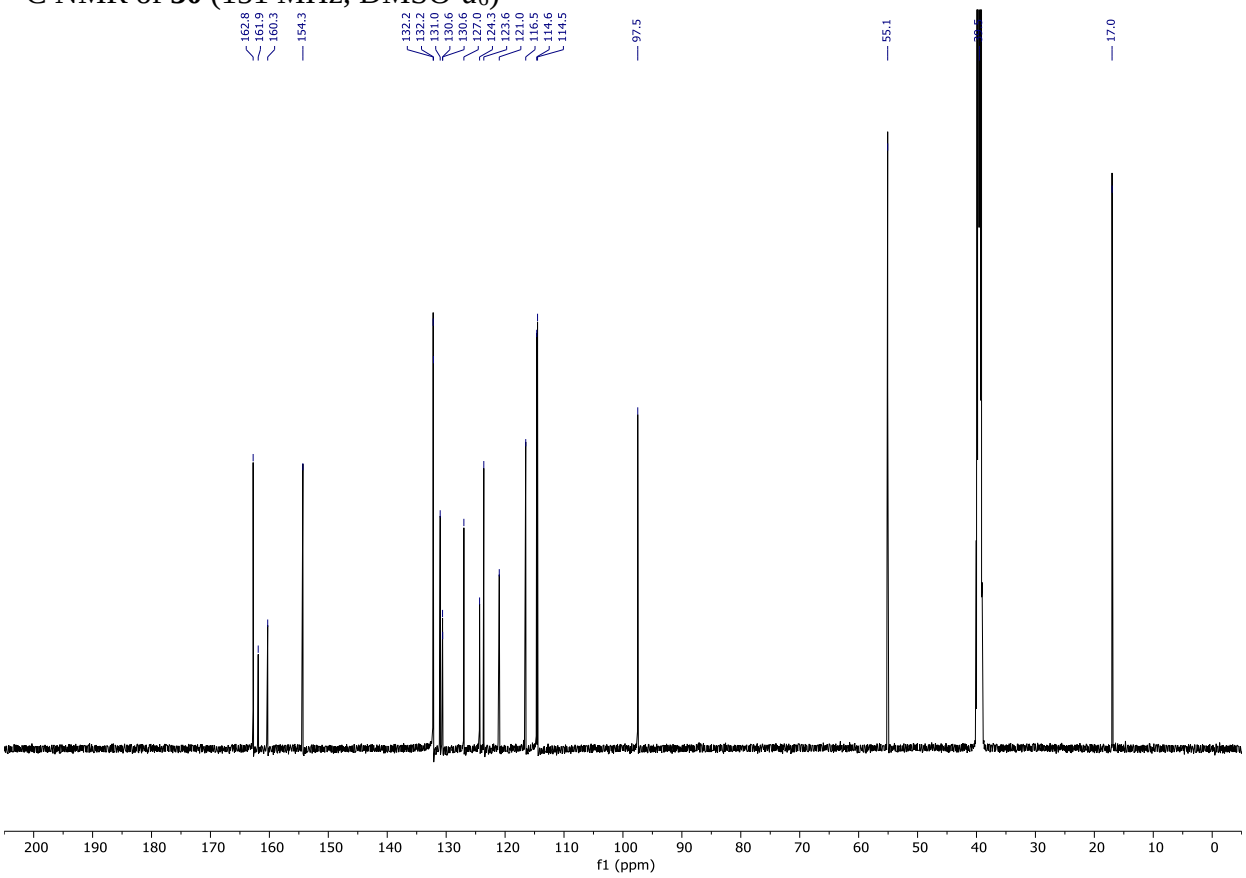
^{1}H NMR of **S28** (400 MHz, $CDCl_3$)



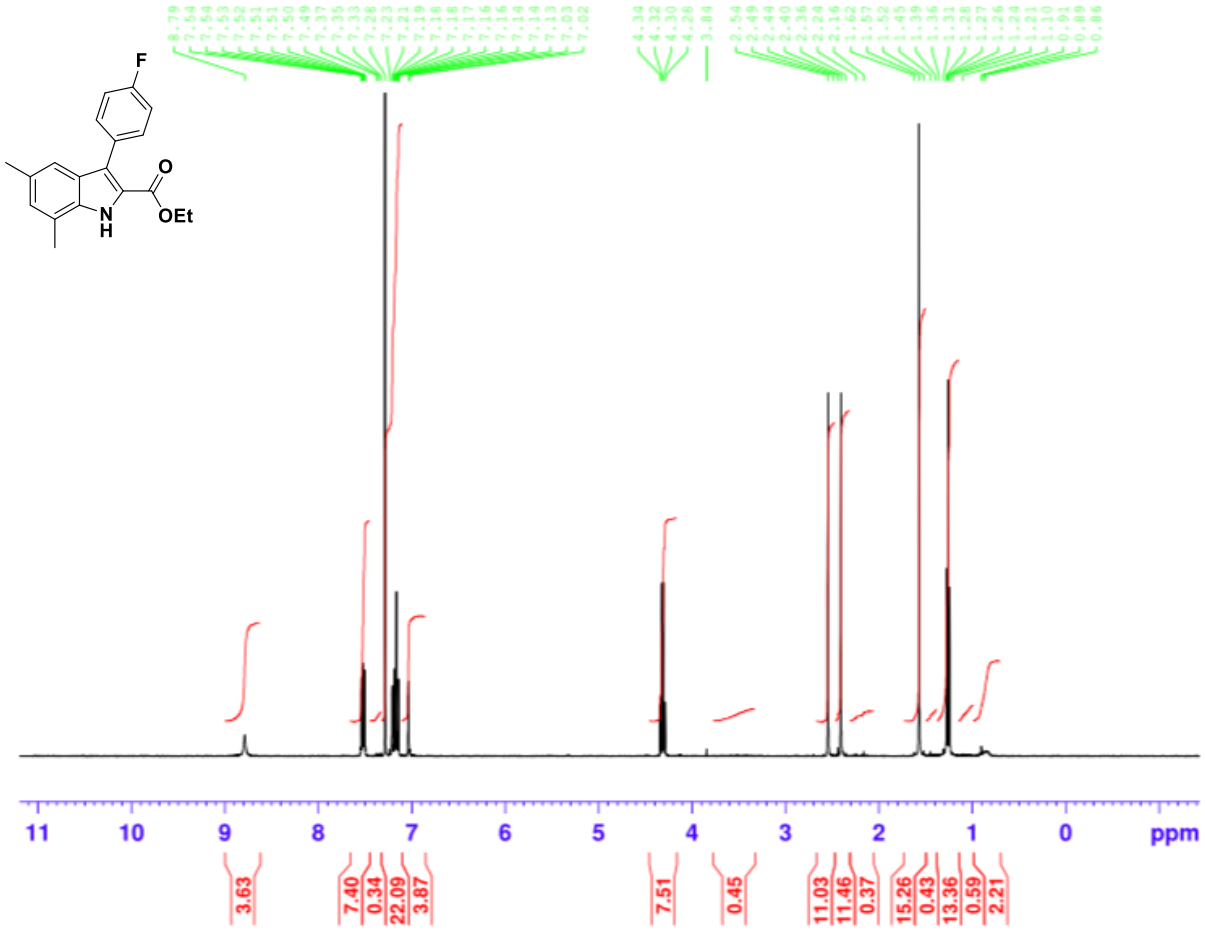
^{1}H NMR of **30** (600 MHz, DMSO-d_6)



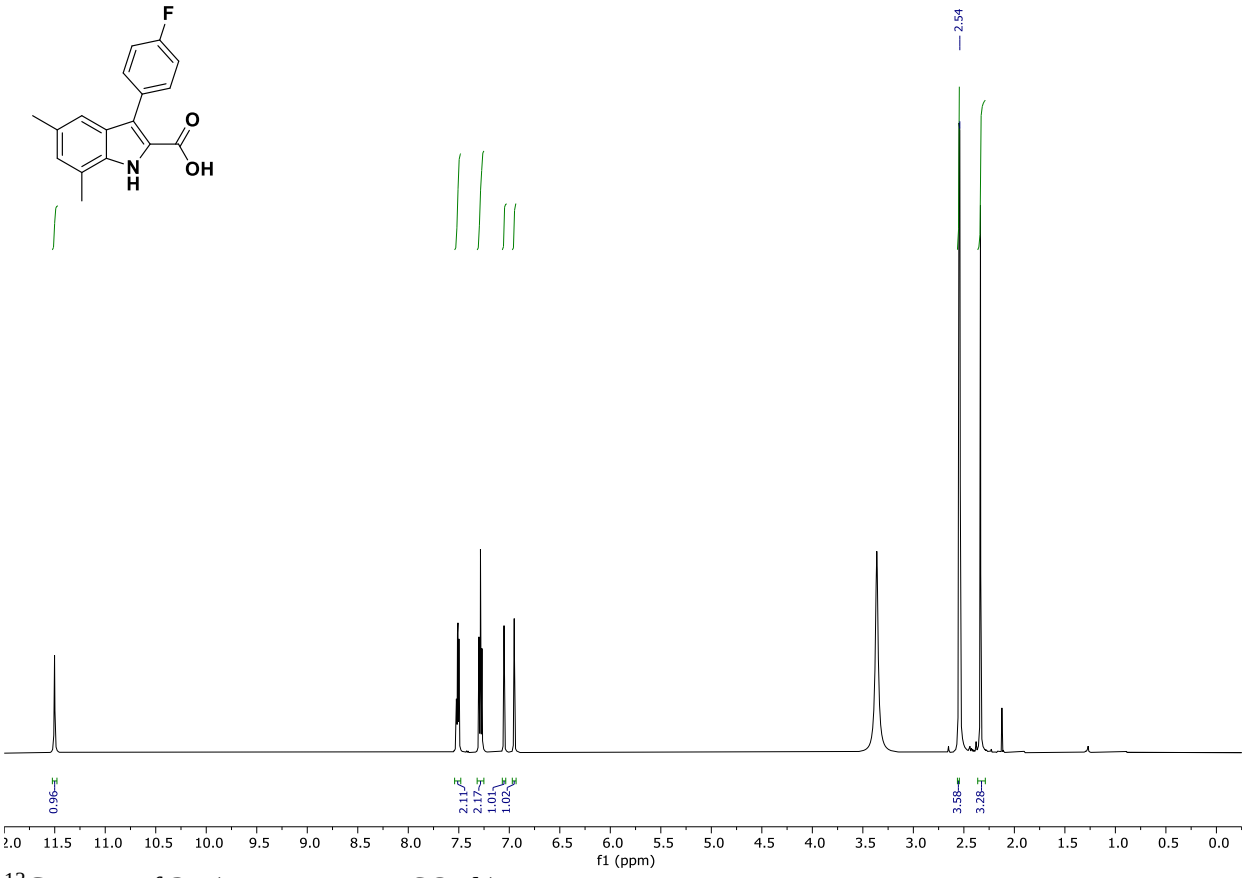
^{13}C NMR of **30** (151 MHz, DMSO-d_6)



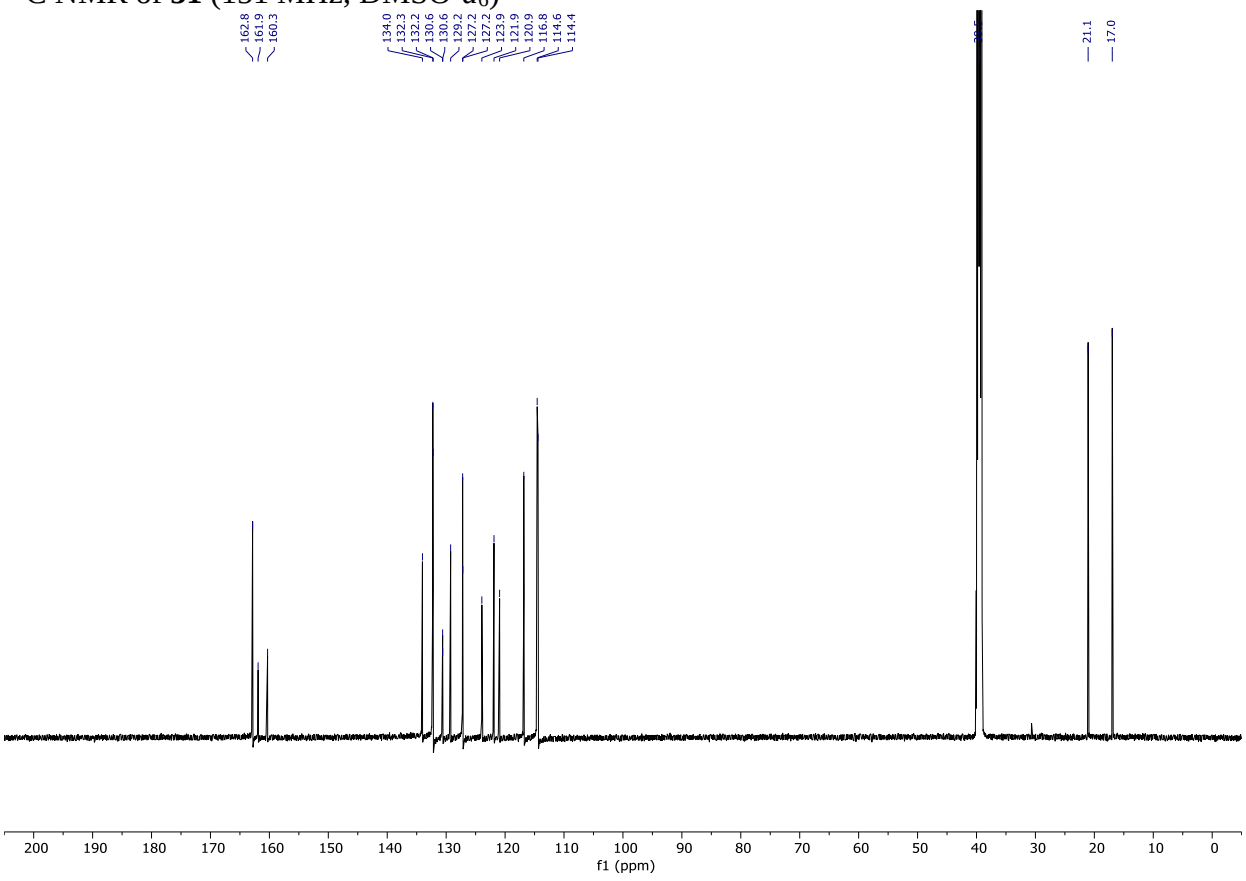
^{1}H NMR of **S29** (400 MHz, $CDCl_3$)



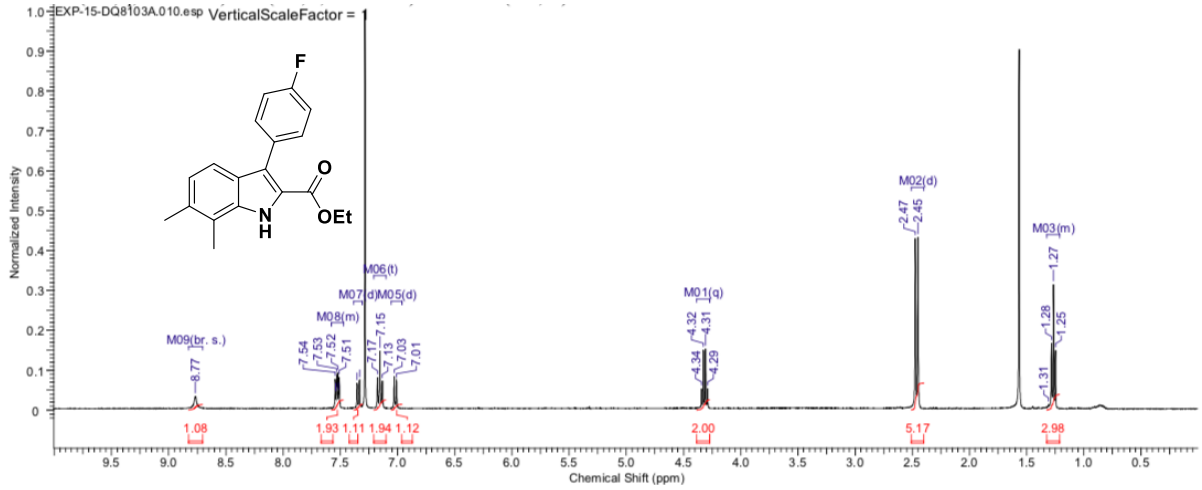
^{1}H NMR of **31** (600 MHz, DMSO-d_6)



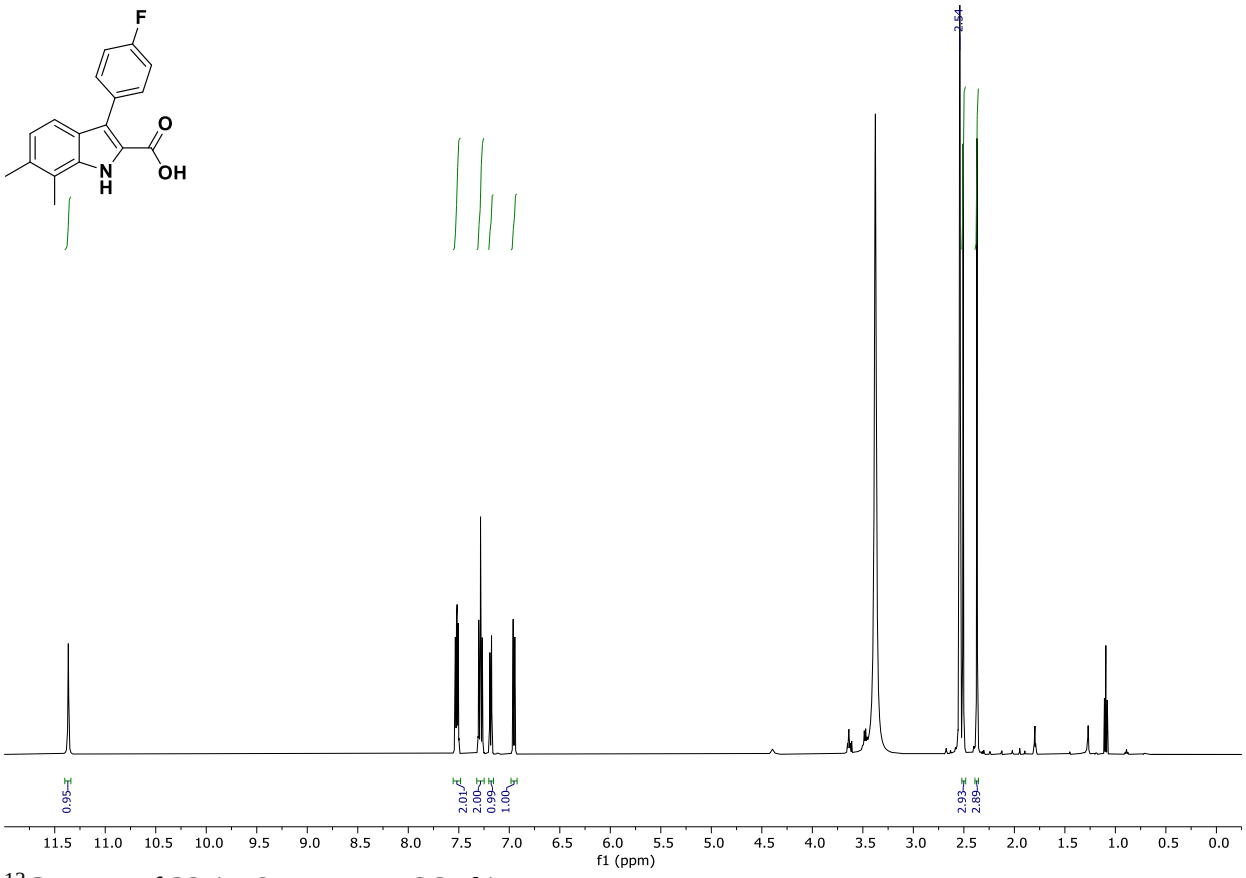
^{13}C NMR of **31** (151 MHz, DMSO-d_6)



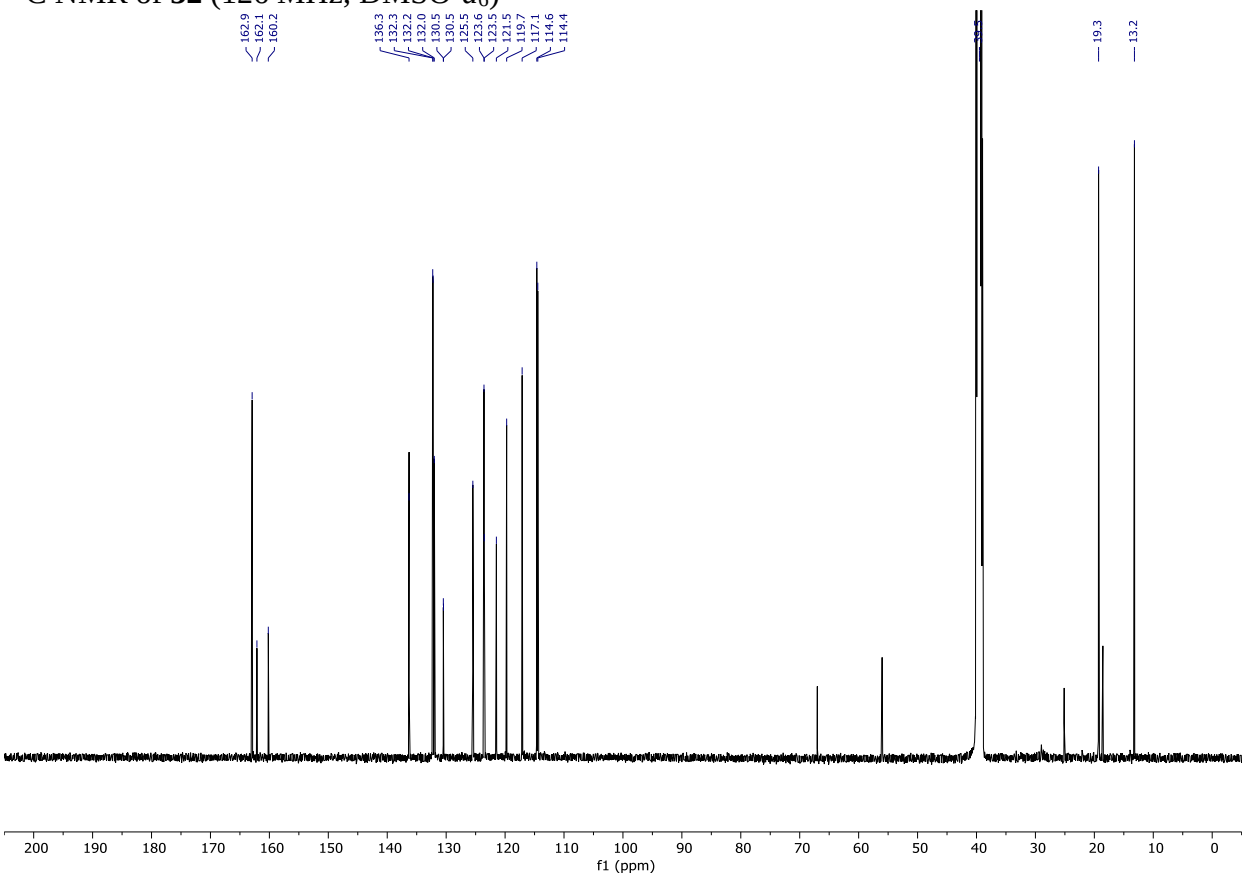
^{1}H NMR of **S30** (400 MHz, $CDCl_3$)



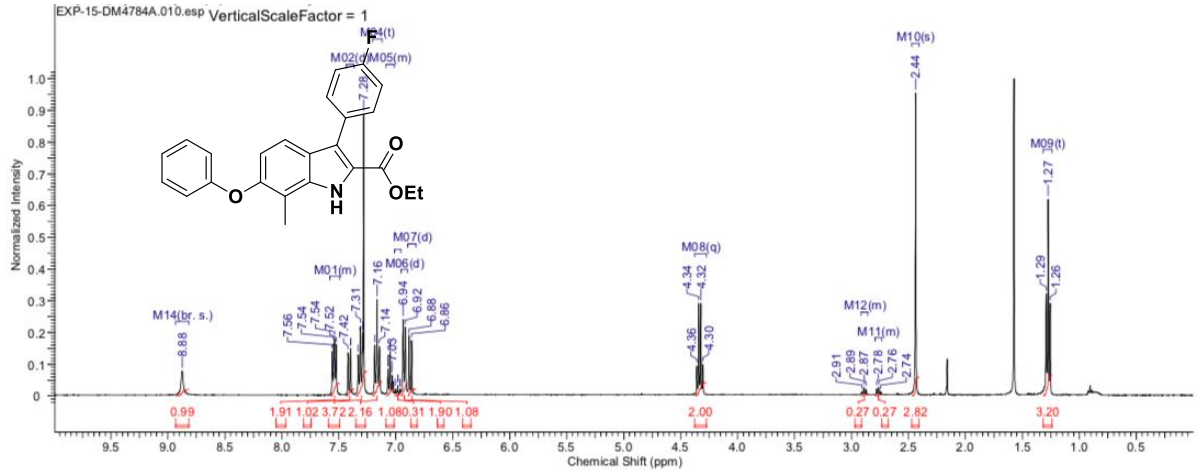
^{1}H NMR of **32** (400 MHz, DMSO-d_6)



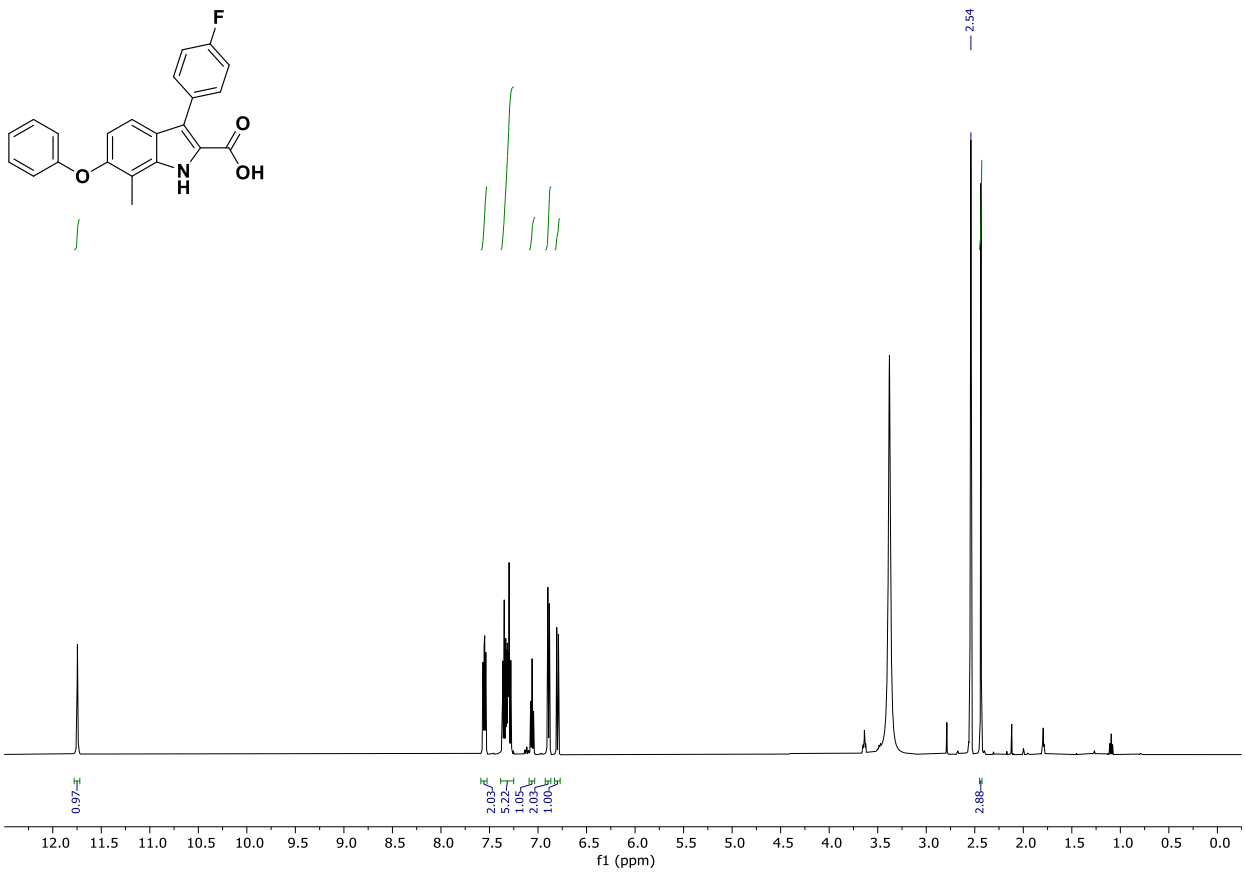
^{13}C NMR of **32** (126 MHz, DMSO-d_6)



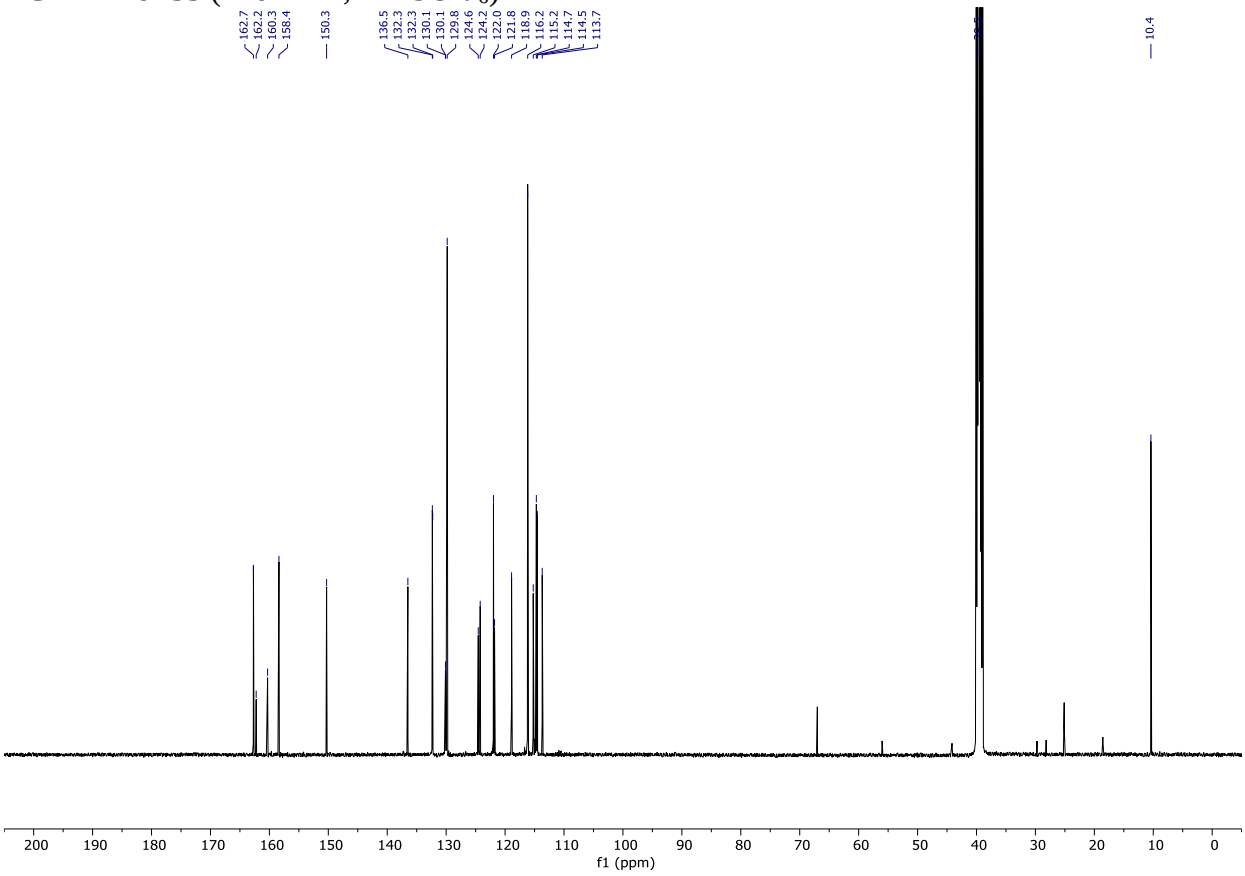
^{1}H NMR of **S31** (400 MHz, $CDCl_3$)



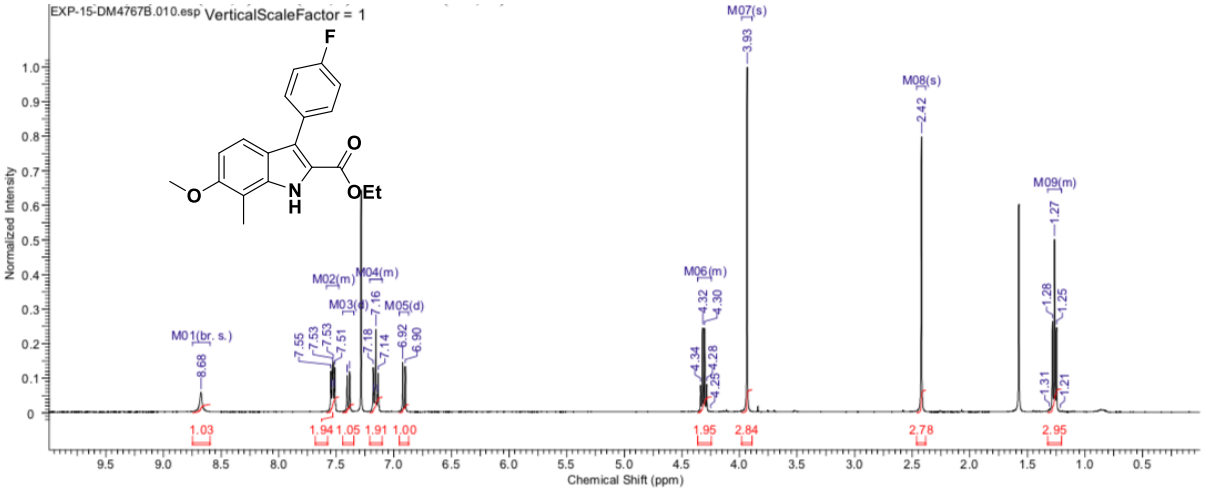
^{1}H NMR of **33** (400 MHz, DMSO-d_6)



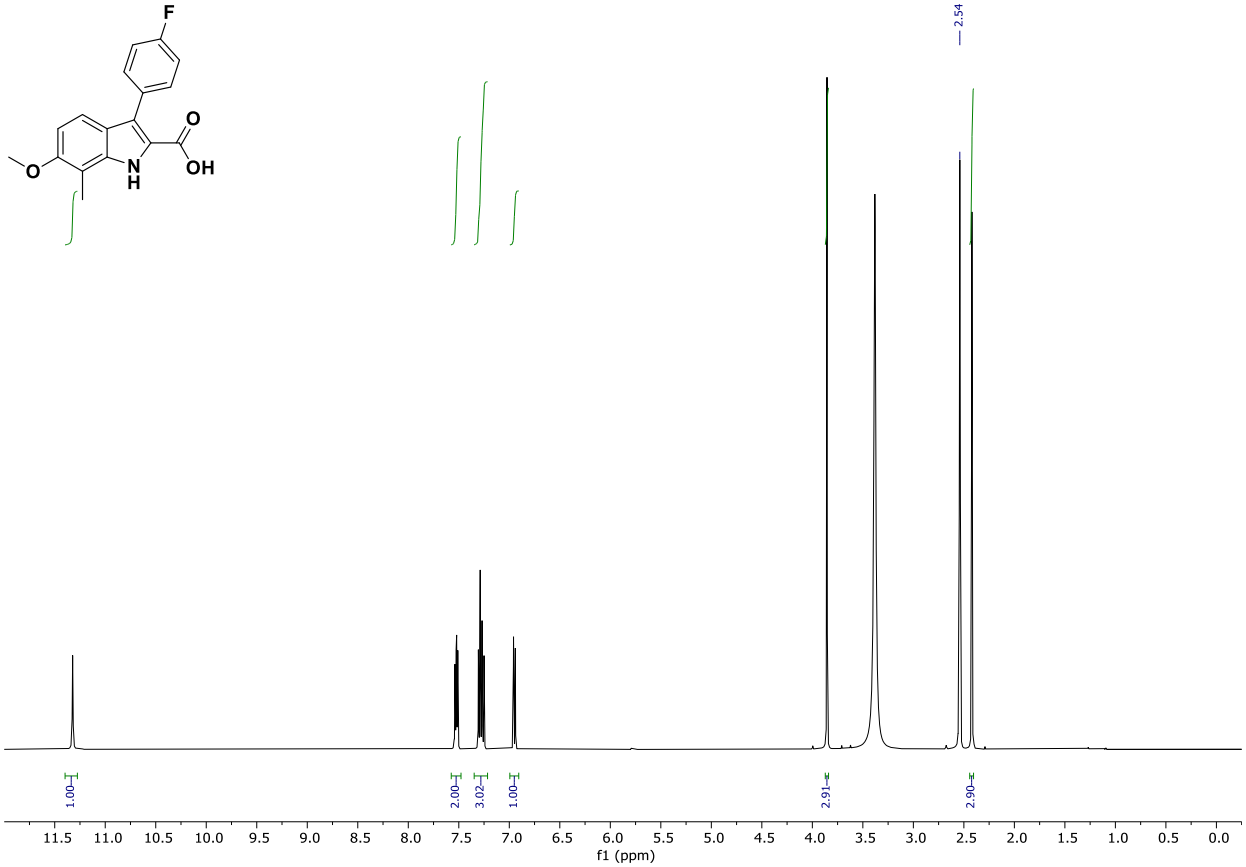
^{13}C NMR of **33** (126 MHz, DMSO-d_6)



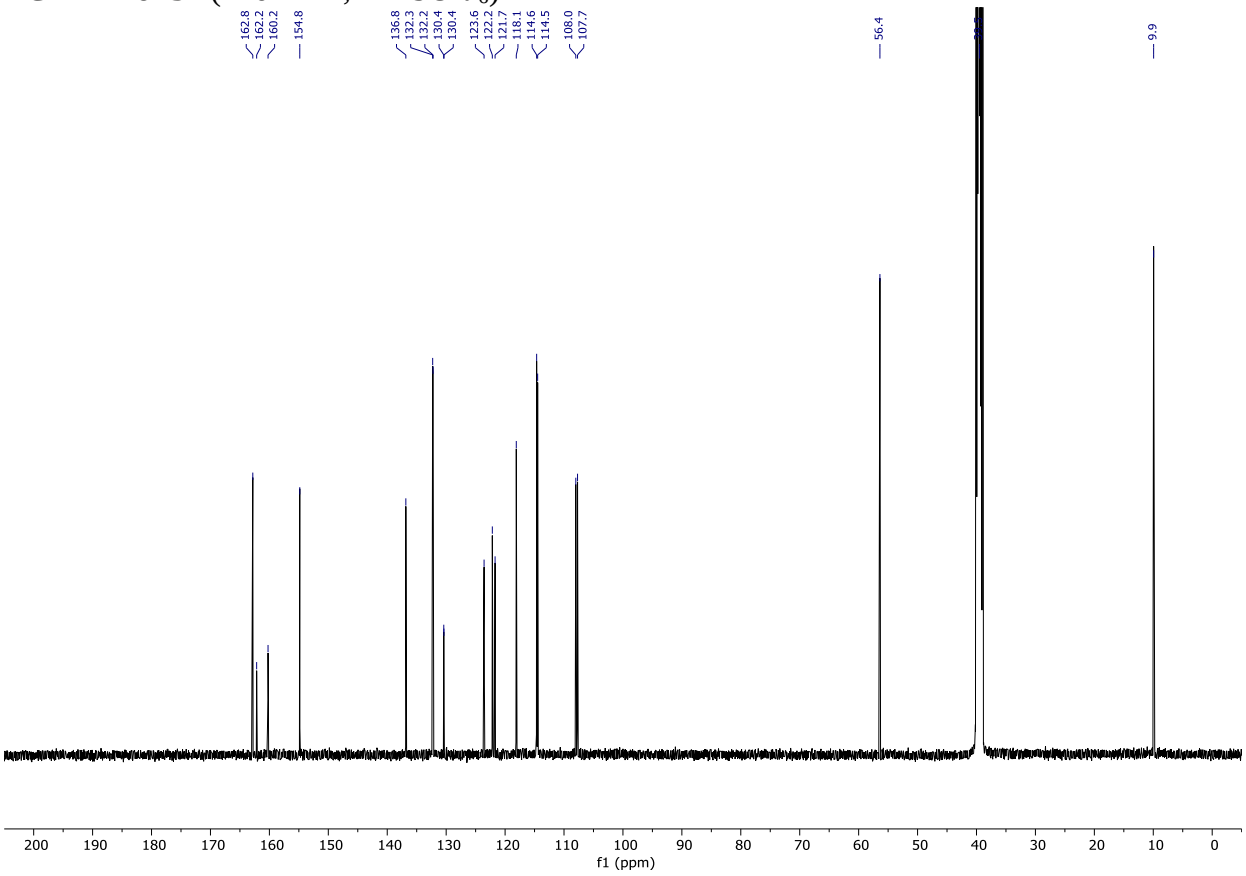
^{1}H NMR of **S32** (400 MHz, $CDCl_3$)



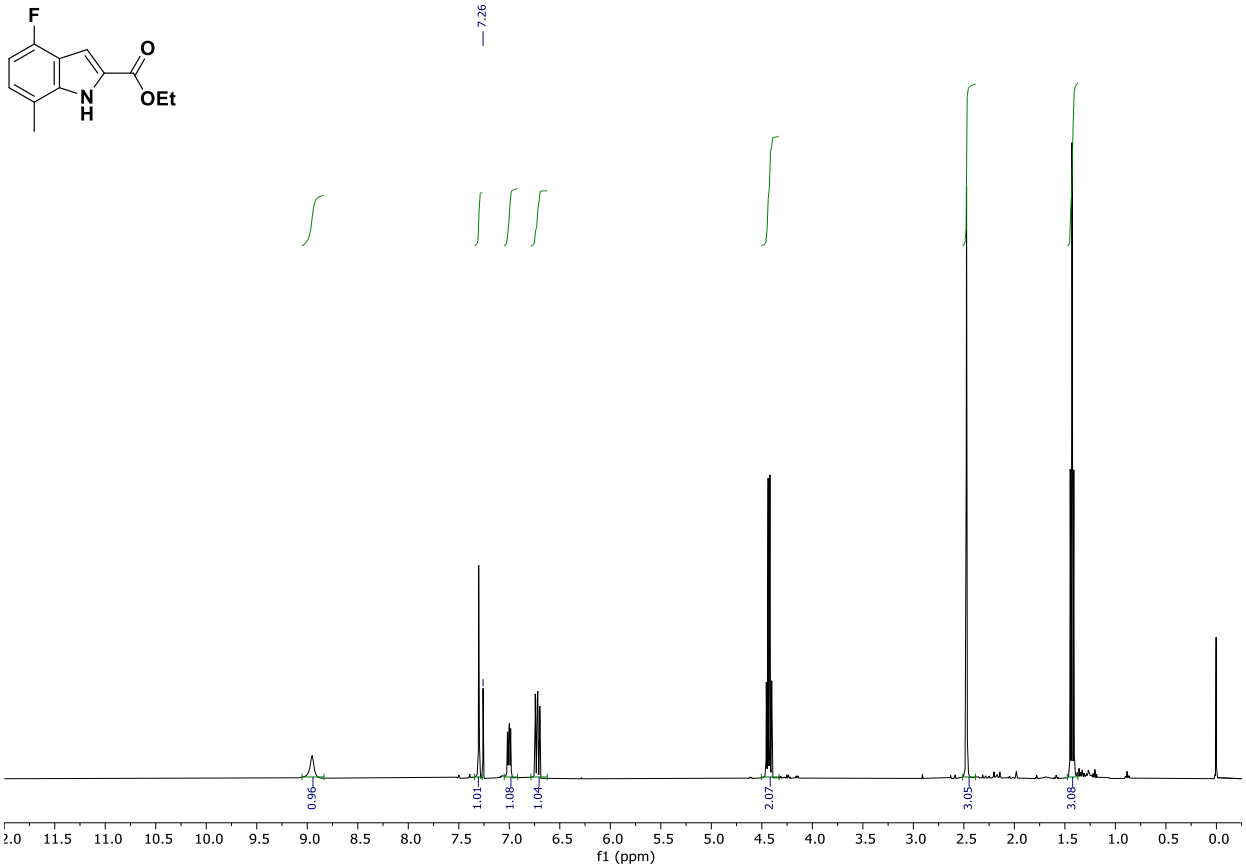
^{1}H NMR of **34** (400 MHz, DMSO-d_6)



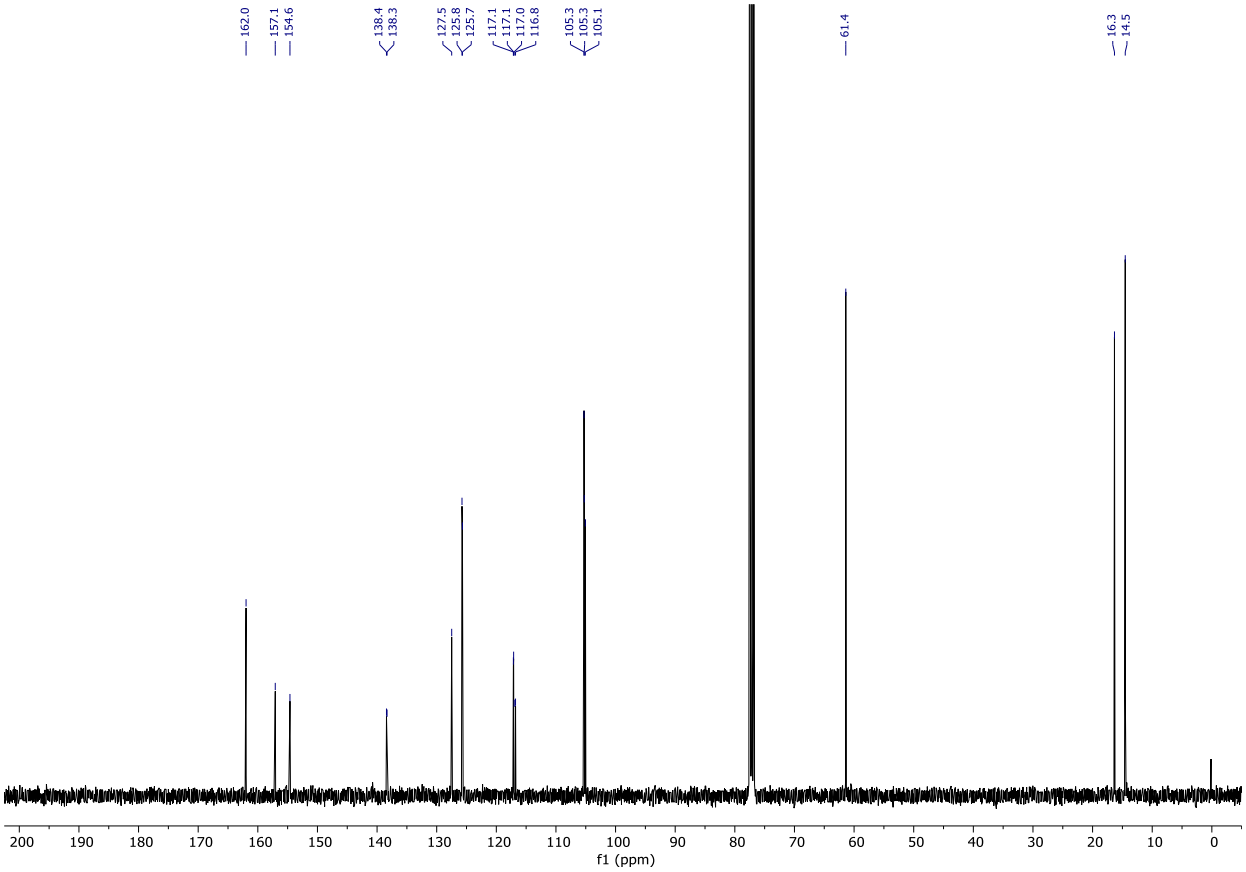
^{13}C NMR of **34** (126 MHz, DMSO-d_6)



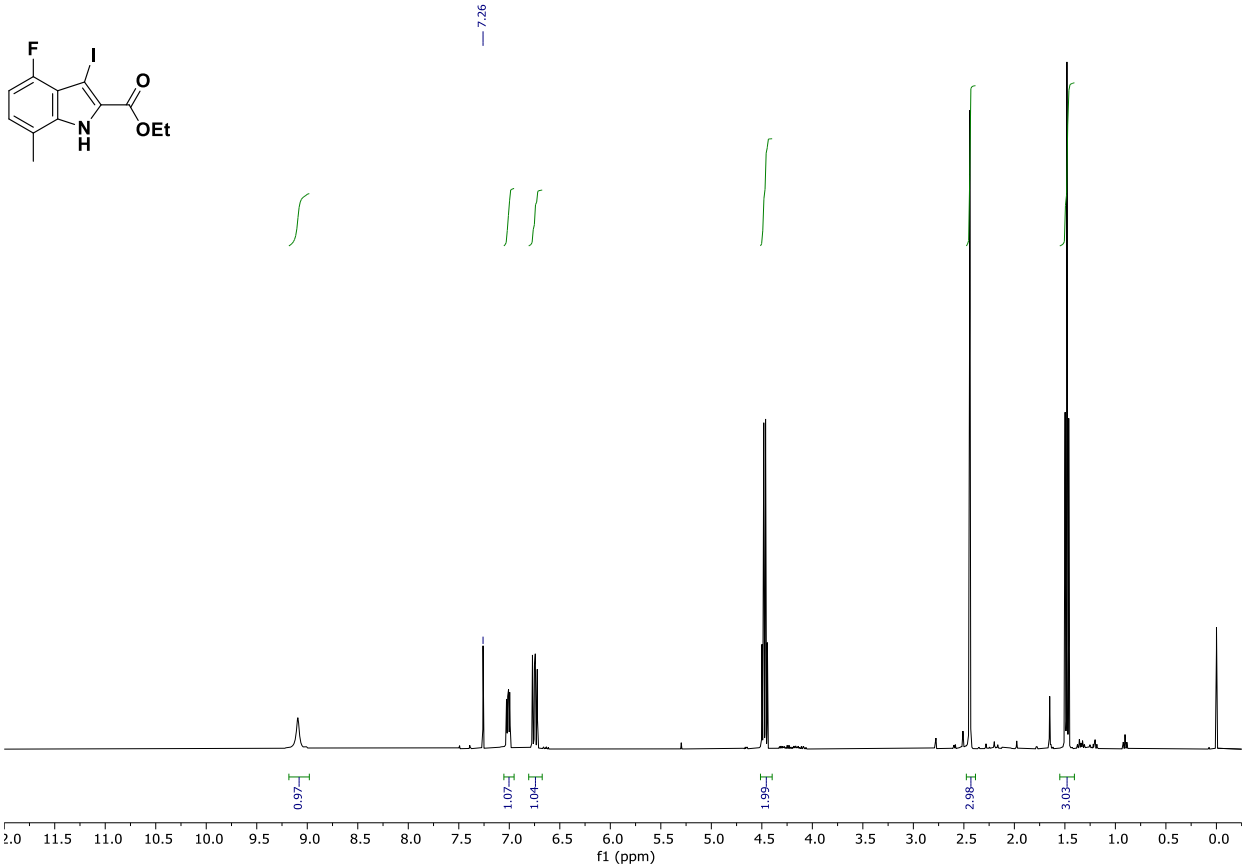
^{1}H NMR of **S33** (400 MHz, $CDCl_3$)



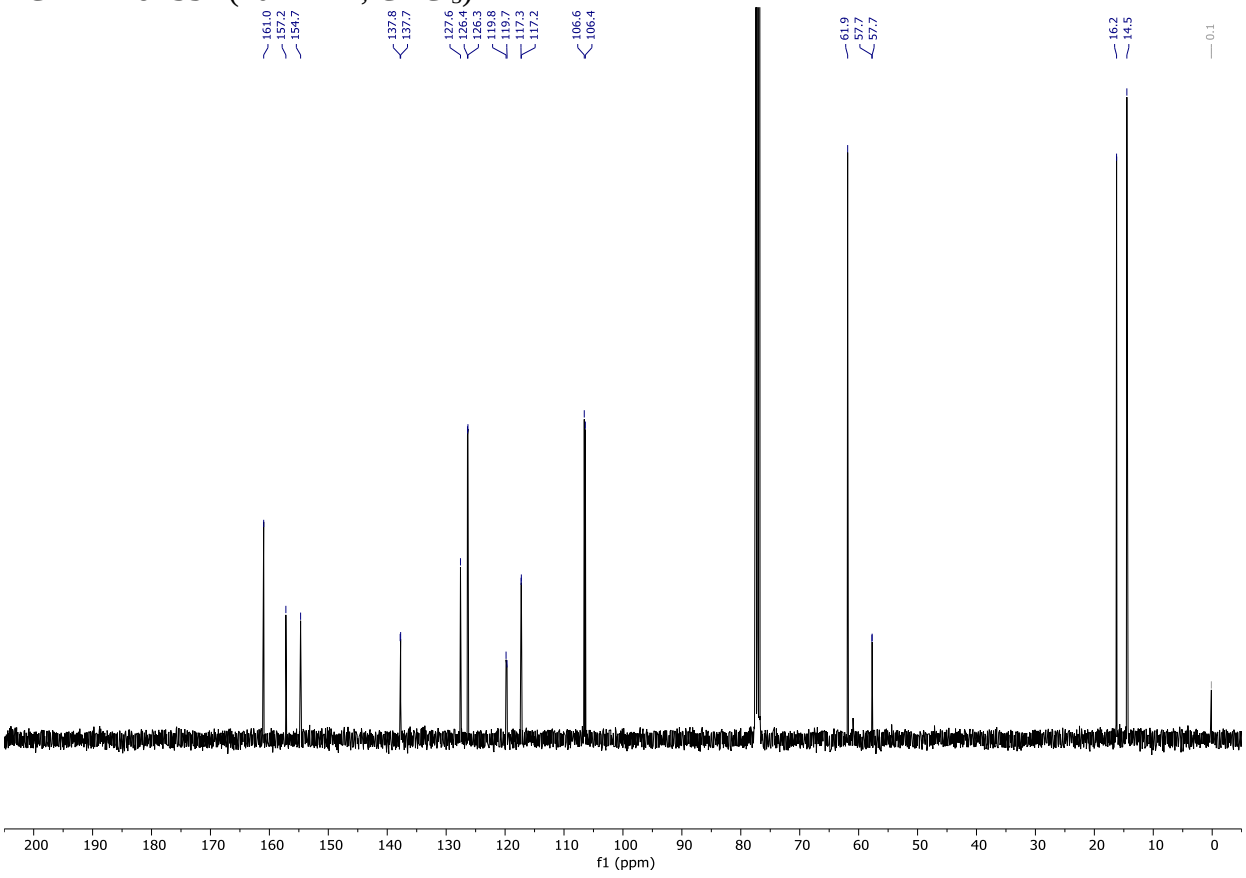
^{13}C NMR of **S33** (101 MHz, $CDCl_3$)



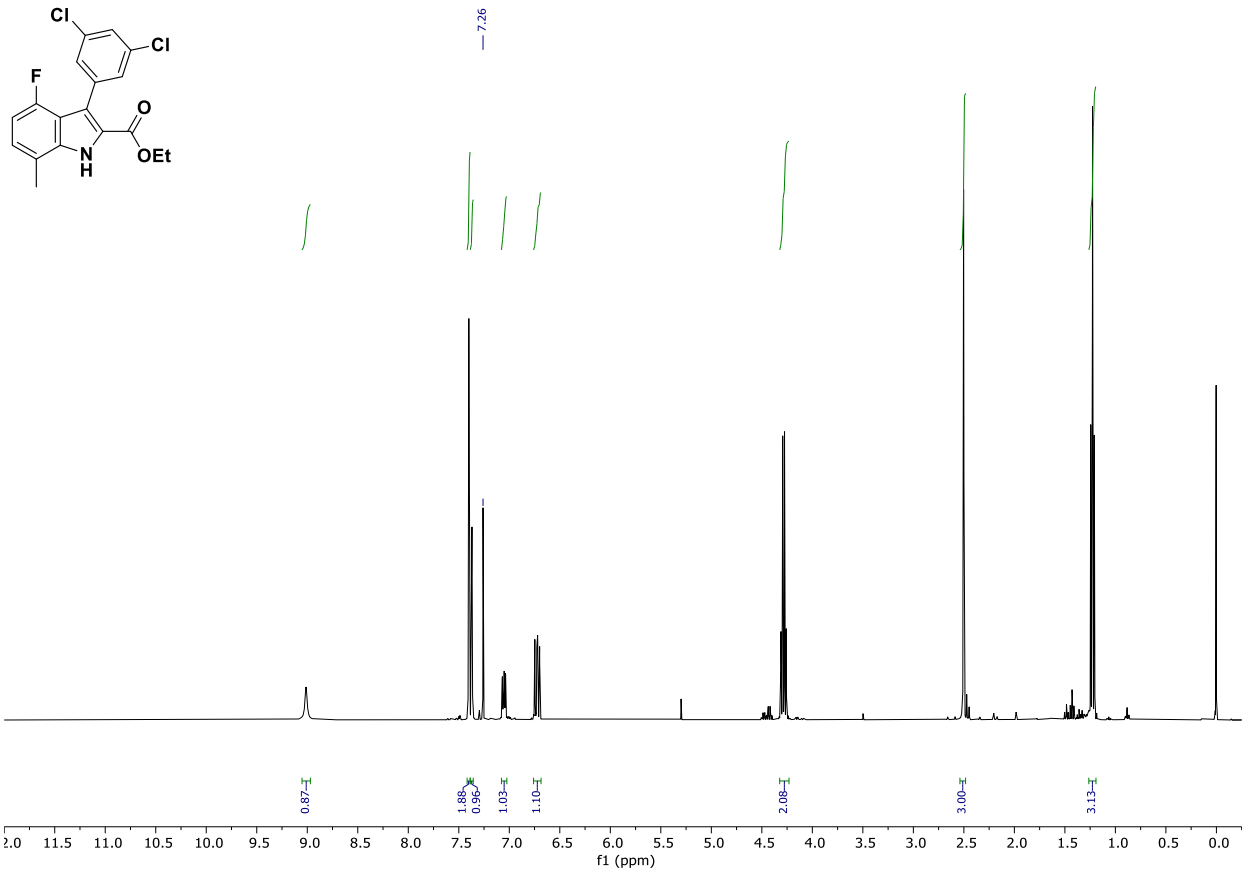
^{1}H NMR of **S34** (400 MHz, $CDCl_3$)



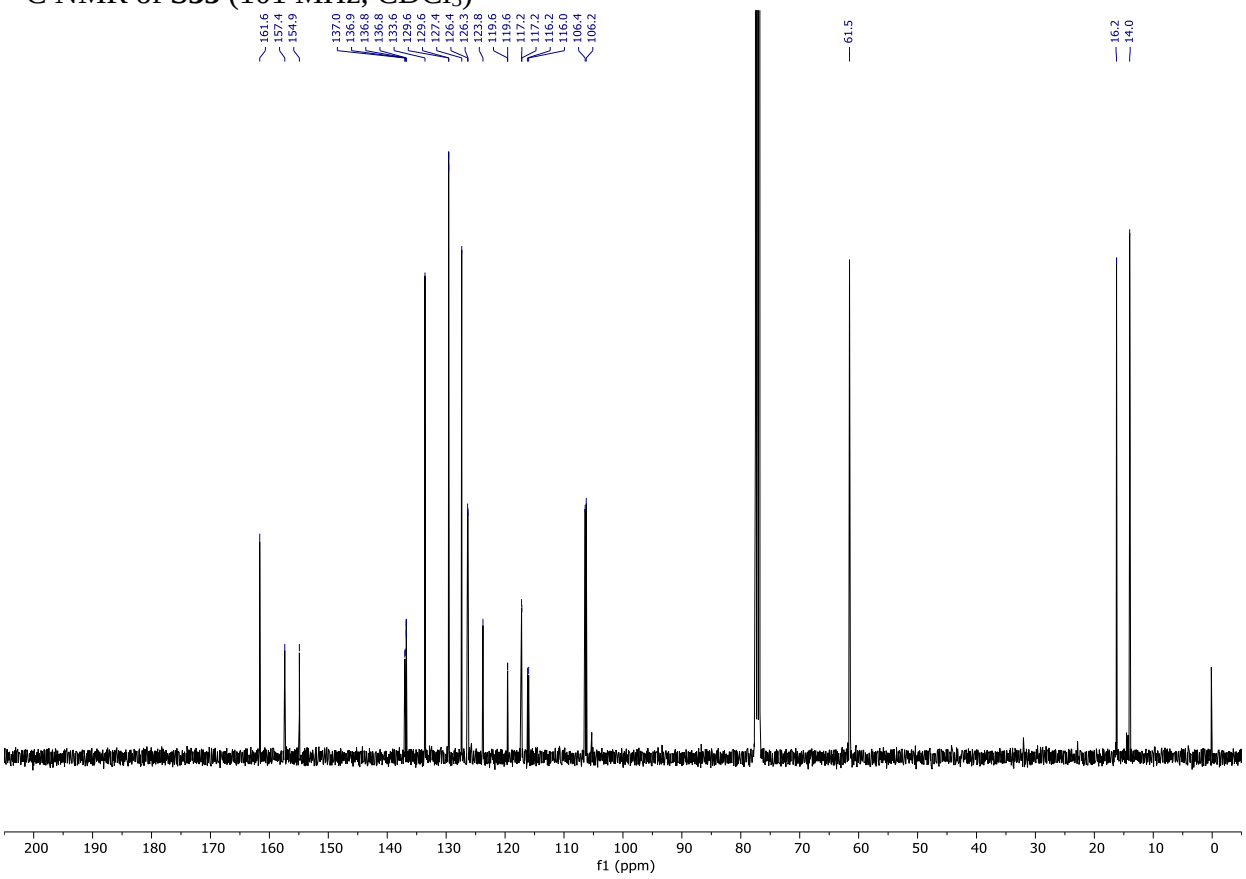
^{13}C NMR of **S34** (101 MHz, $CDCl_3$)



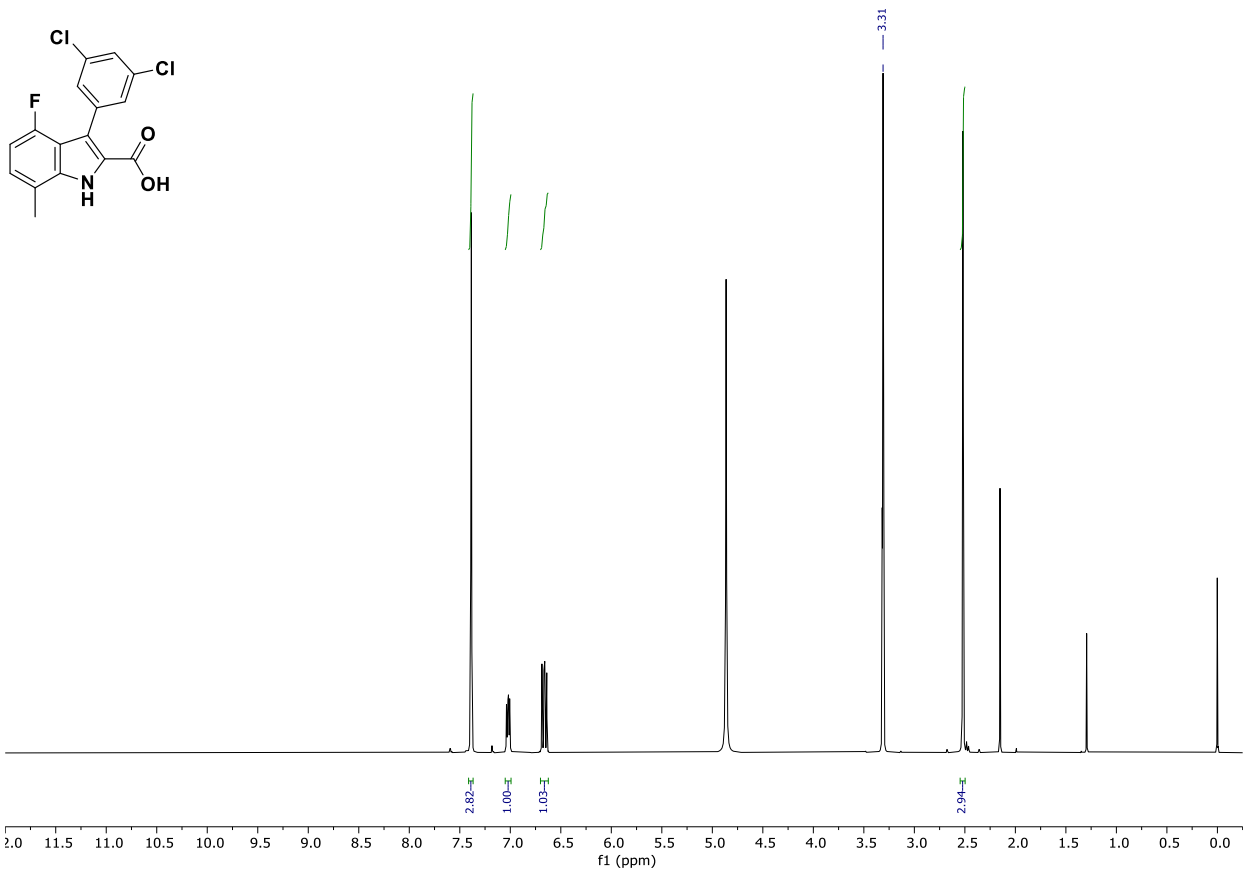
^{1}H NMR of **S35** (400 MHz, $CDCl_3$)



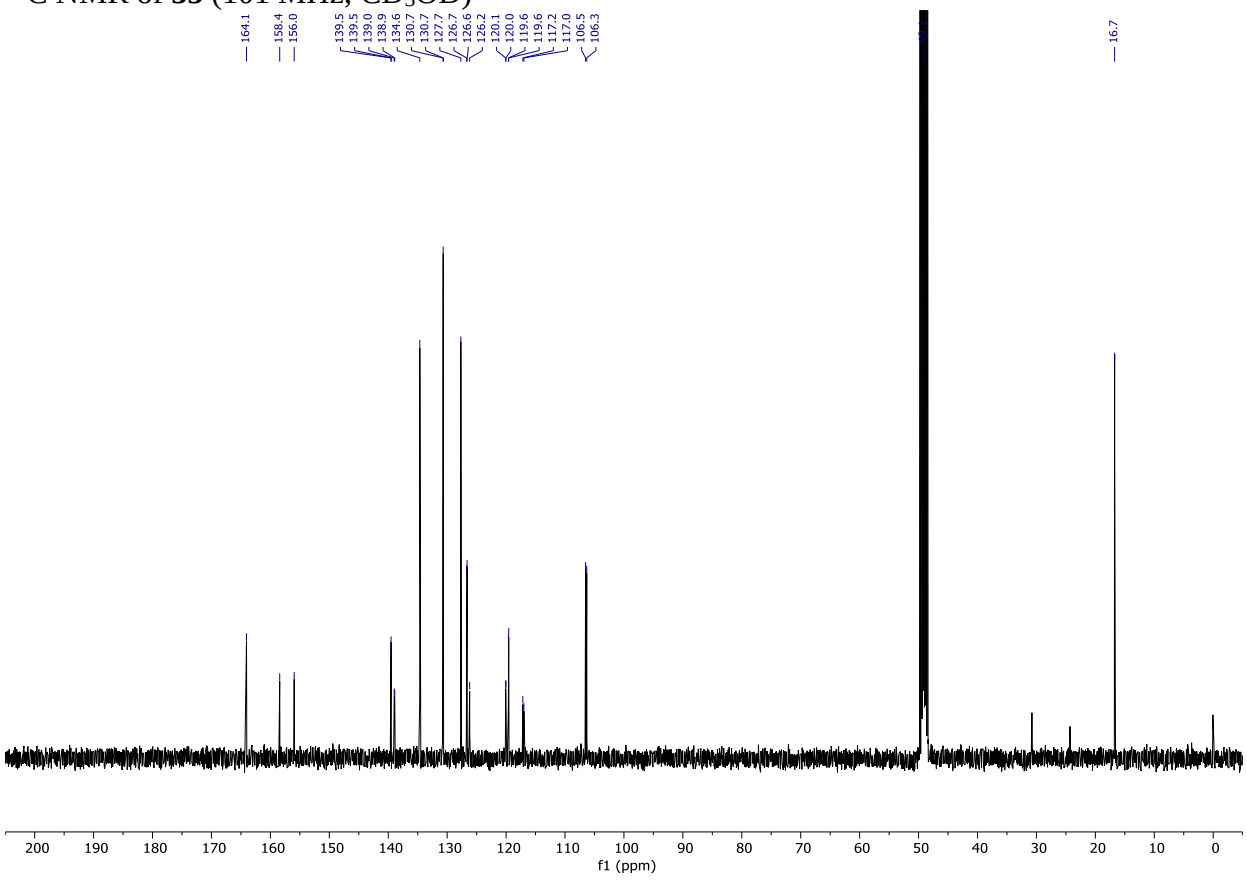
^{13}C NMR of **S35** (101 MHz, $CDCl_3$)



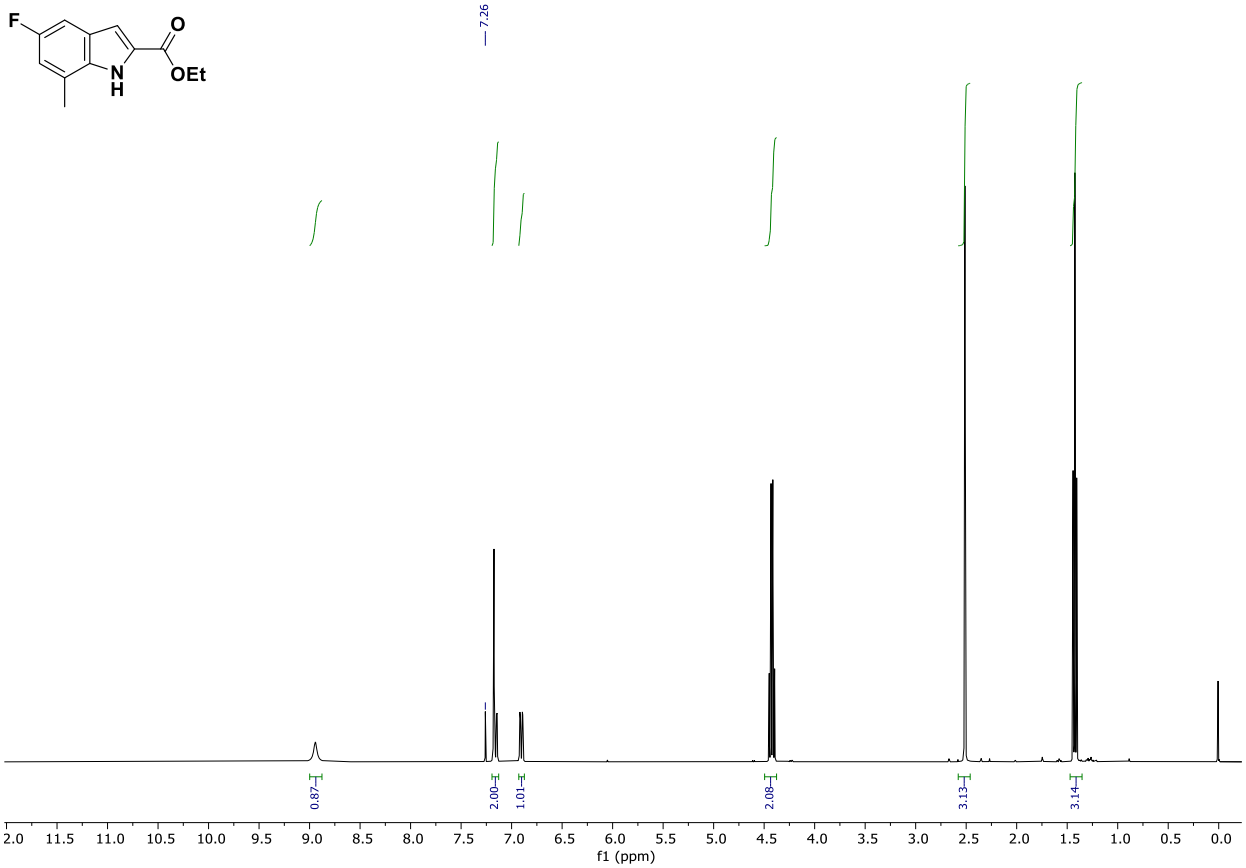
^{1}H NMR of **35** (400 MHz, CD_3OD)



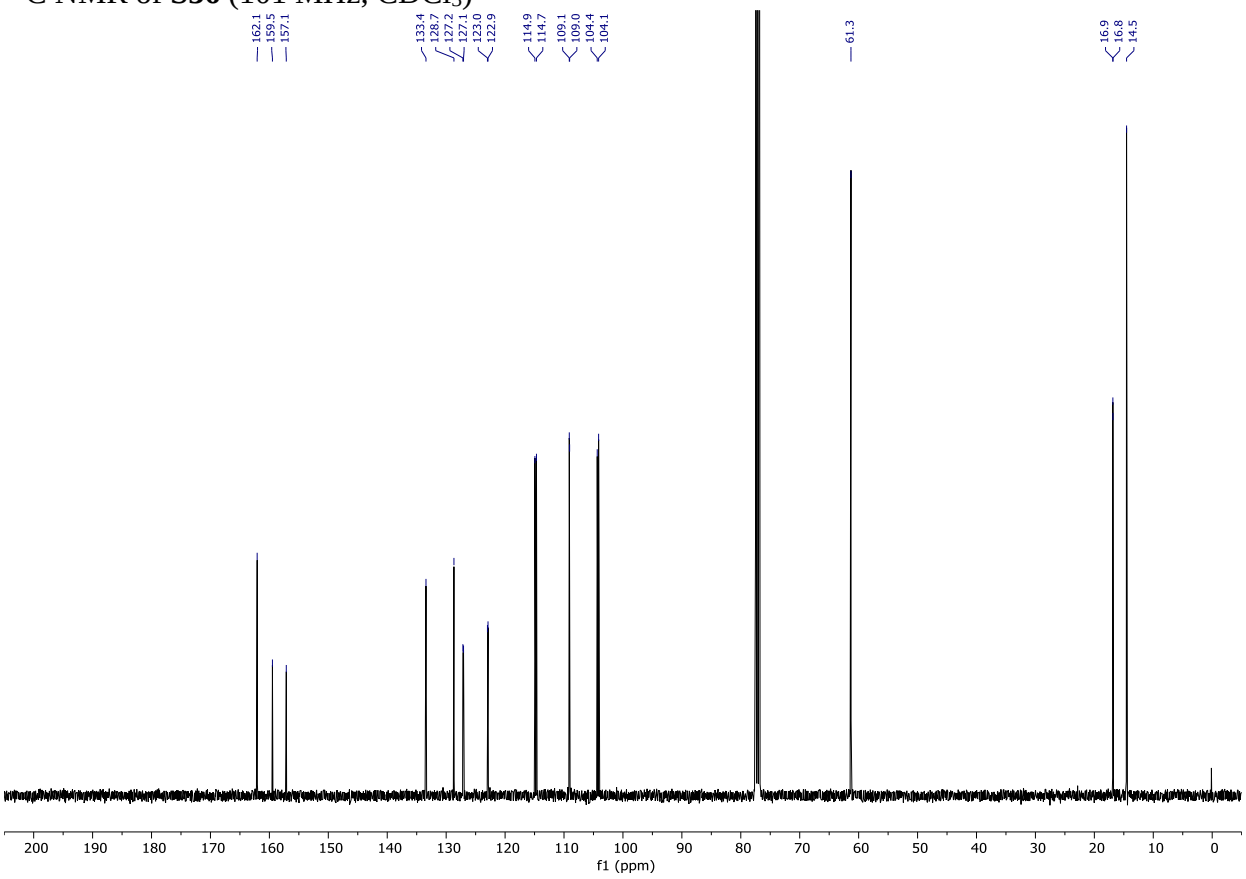
^{13}C NMR of **35** (101 MHz, CD_3OD)



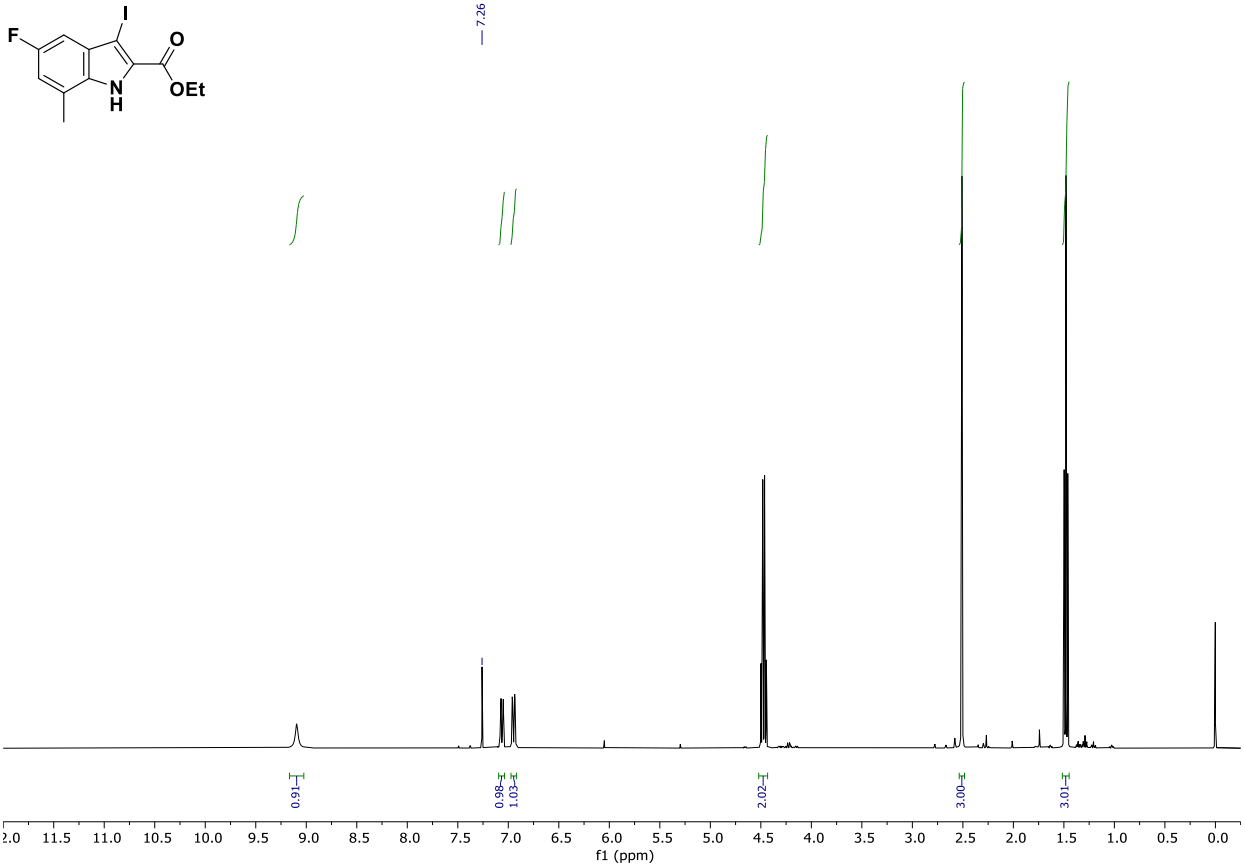
^{1}H NMR of **S36** (400 MHz, $CDCl_3$)



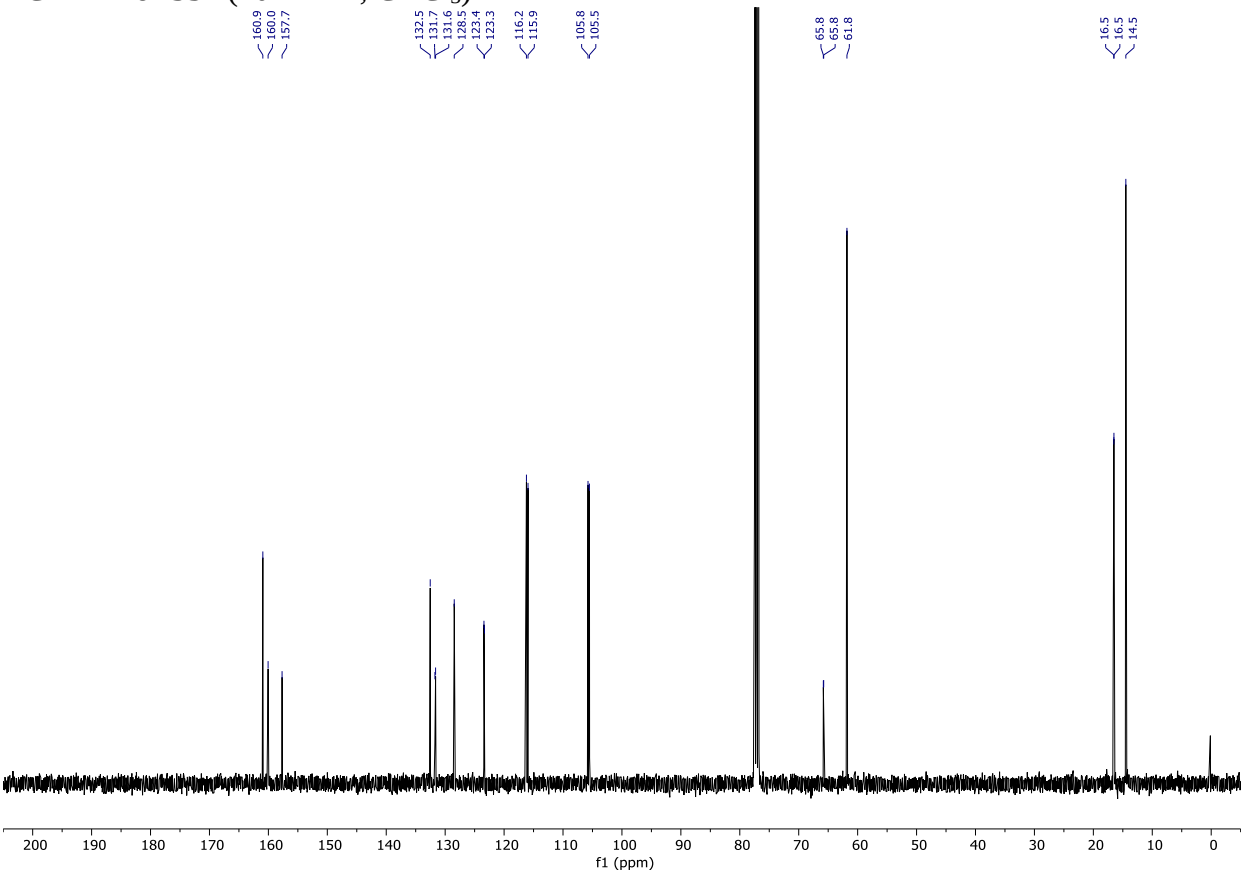
^{13}C NMR of **S36** (101 MHz, $CDCl_3$)



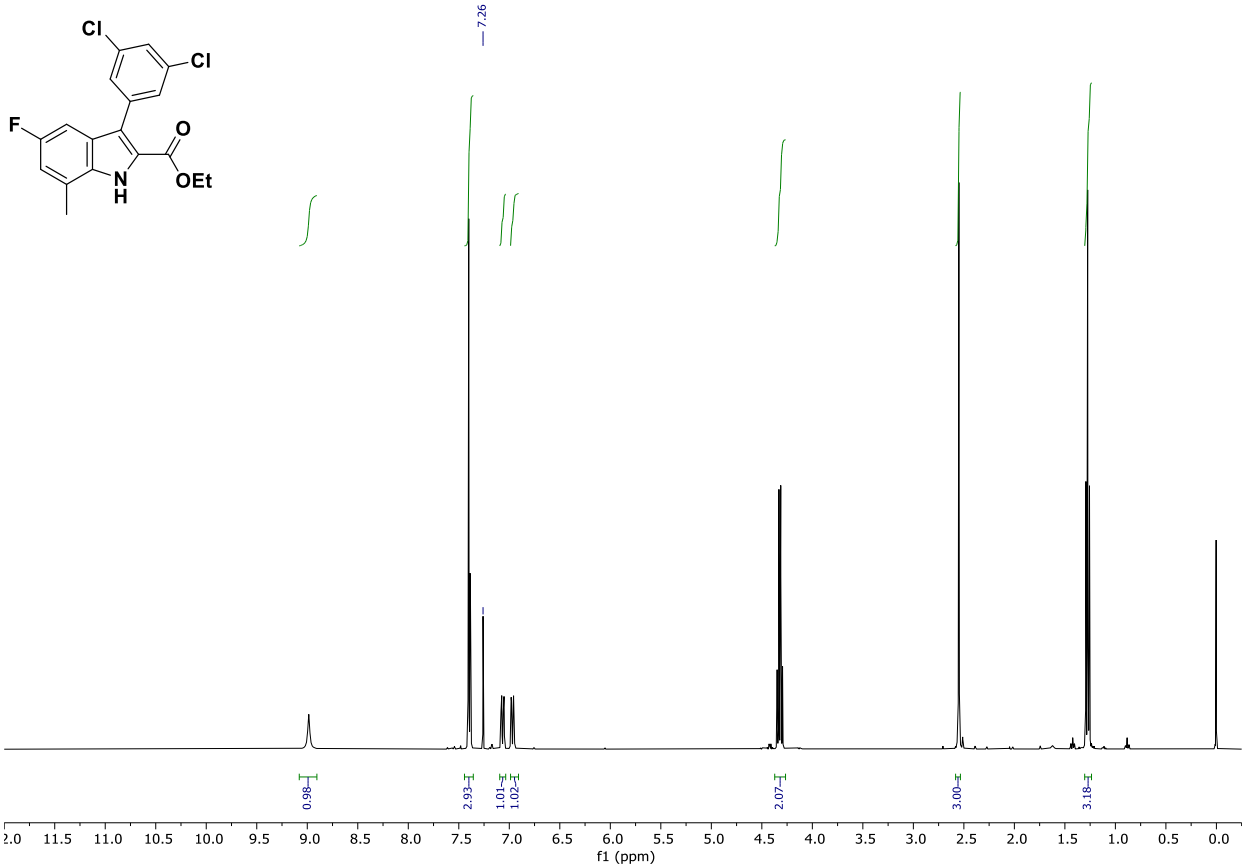
^{1}H NMR of S37 (400 MHz, $CDCl_3$)



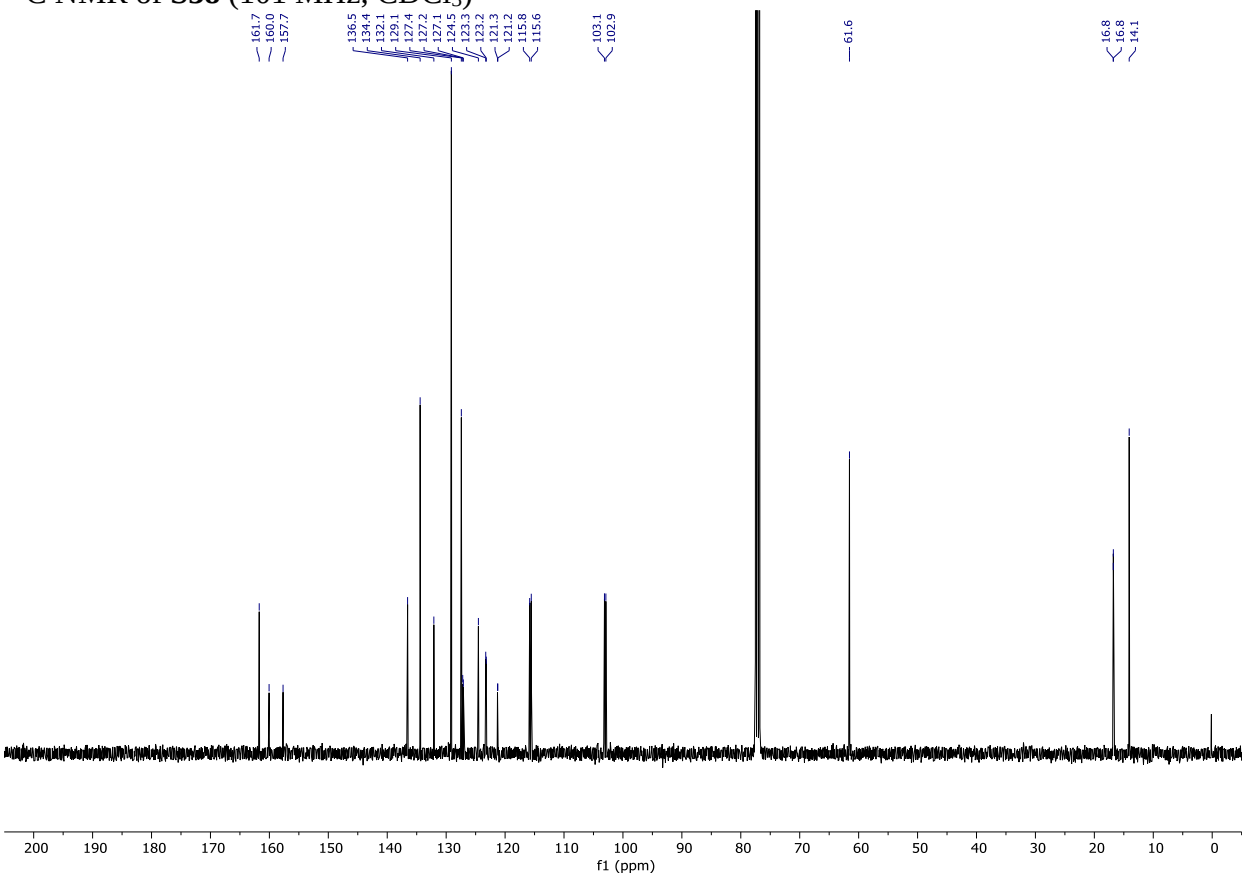
^{13}C NMR of **S37** (101 MHz, $CDCl_3$)



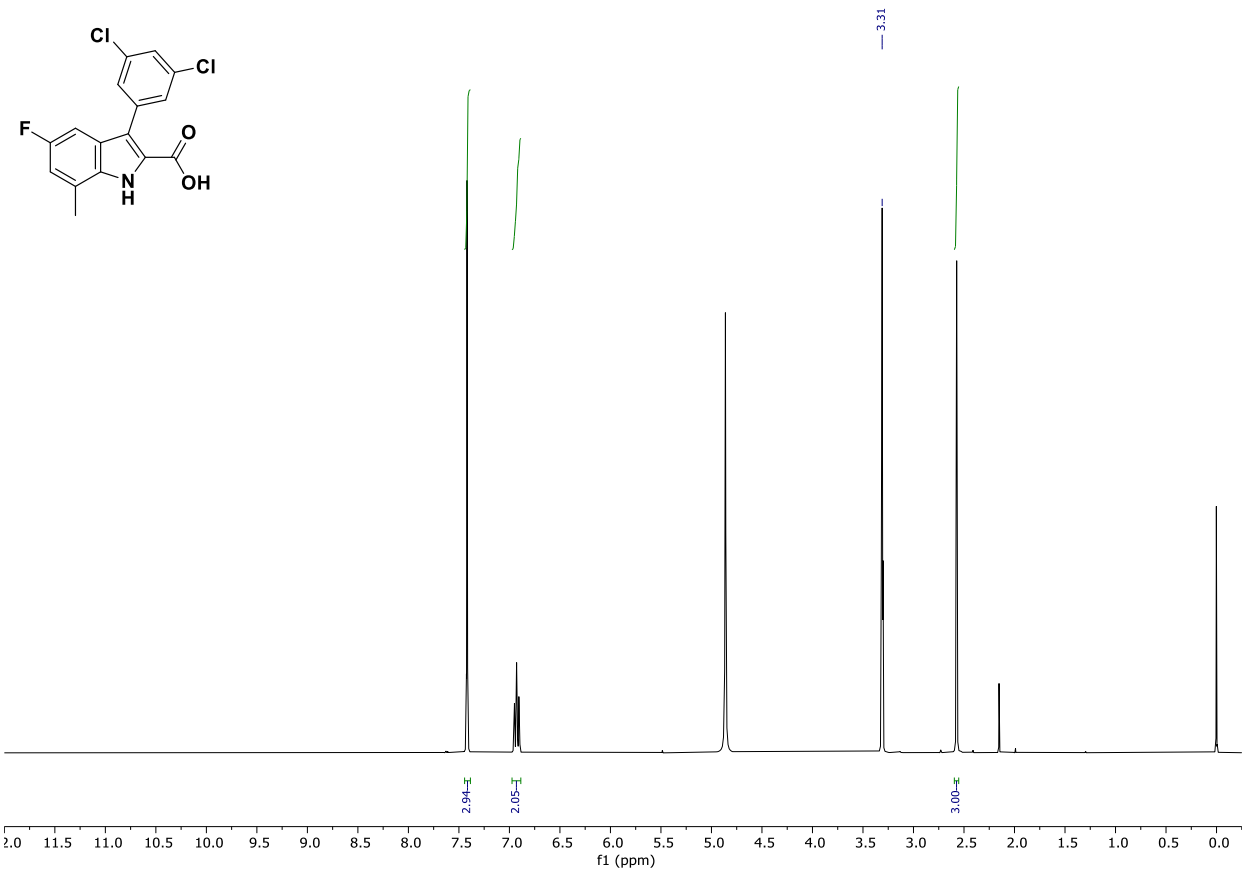
^{1}H NMR of **S38** (400 MHz, $CDCl_3$)



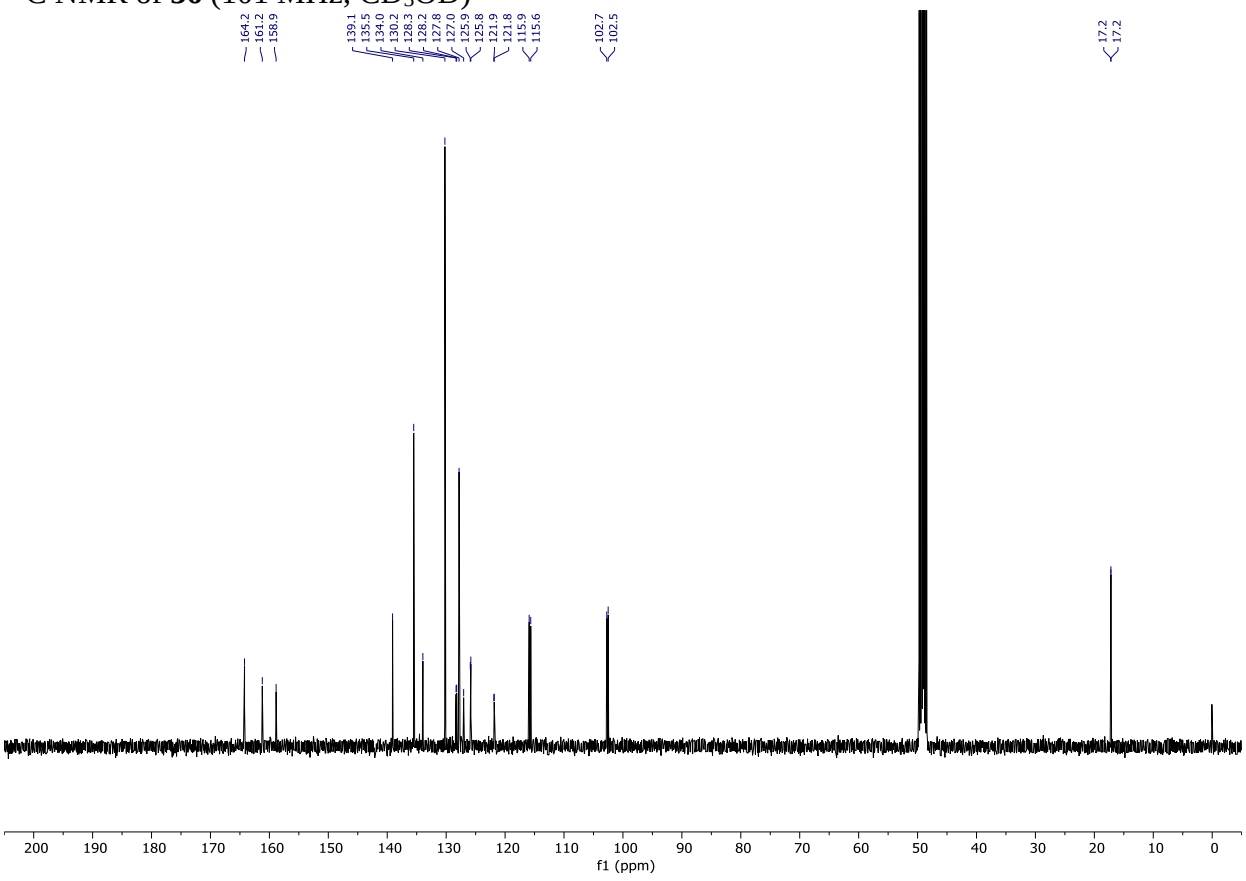
^{13}C NMR of **S38** (101 MHz, $CDCl_3$)



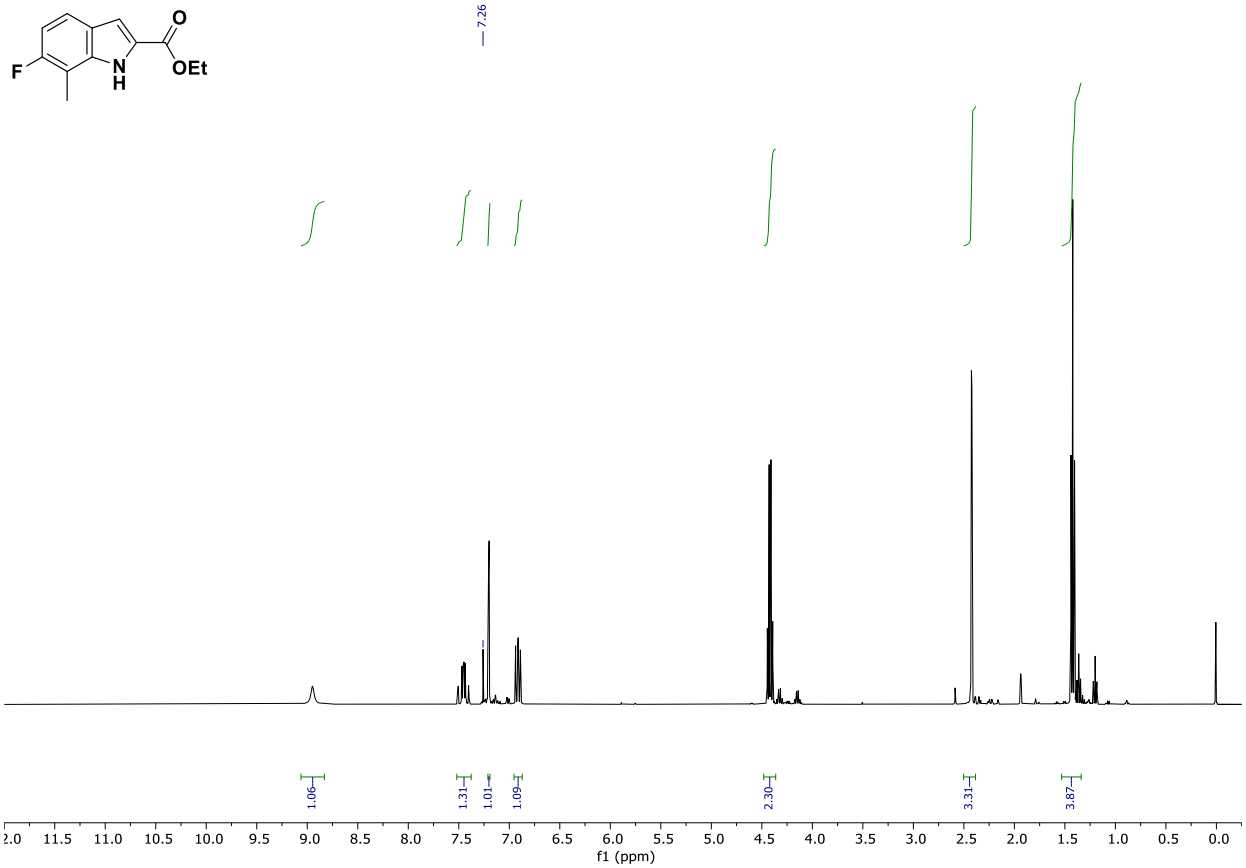
^{1}H NMR of **36** (400 MHz, CD_3OD)



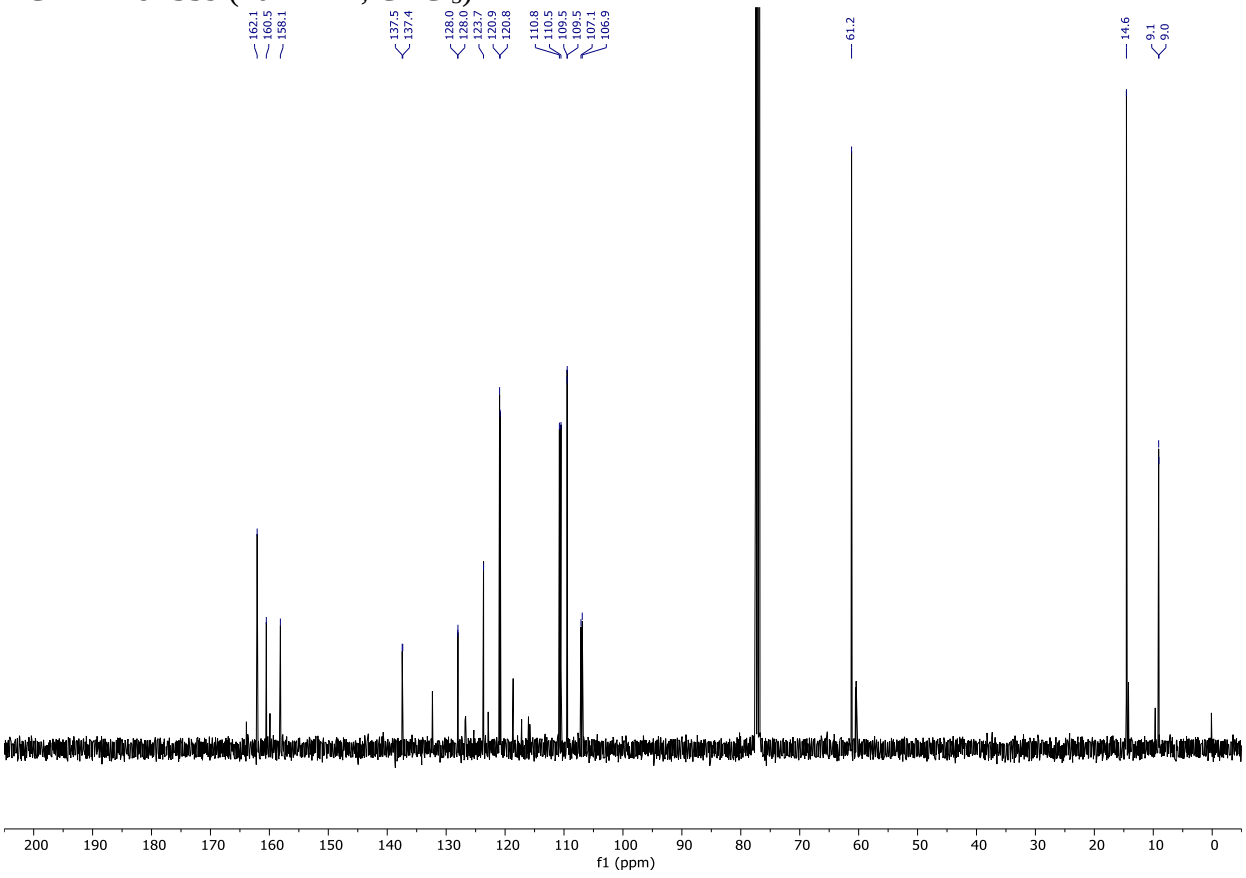
^{13}C NMR of **36** (101 MHz, CD_3OD)



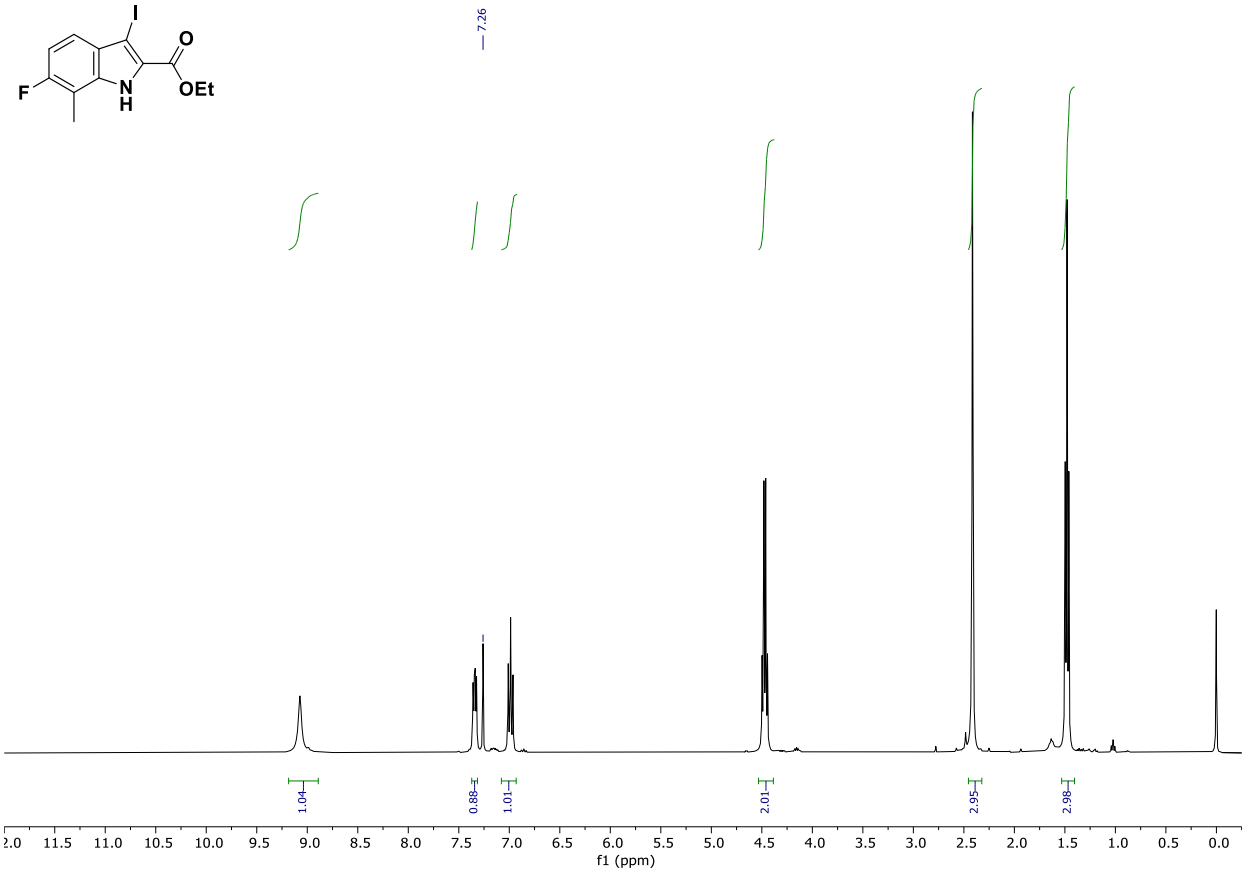
^{1}H NMR of **S39** (400 MHz, $CDCl_3$)



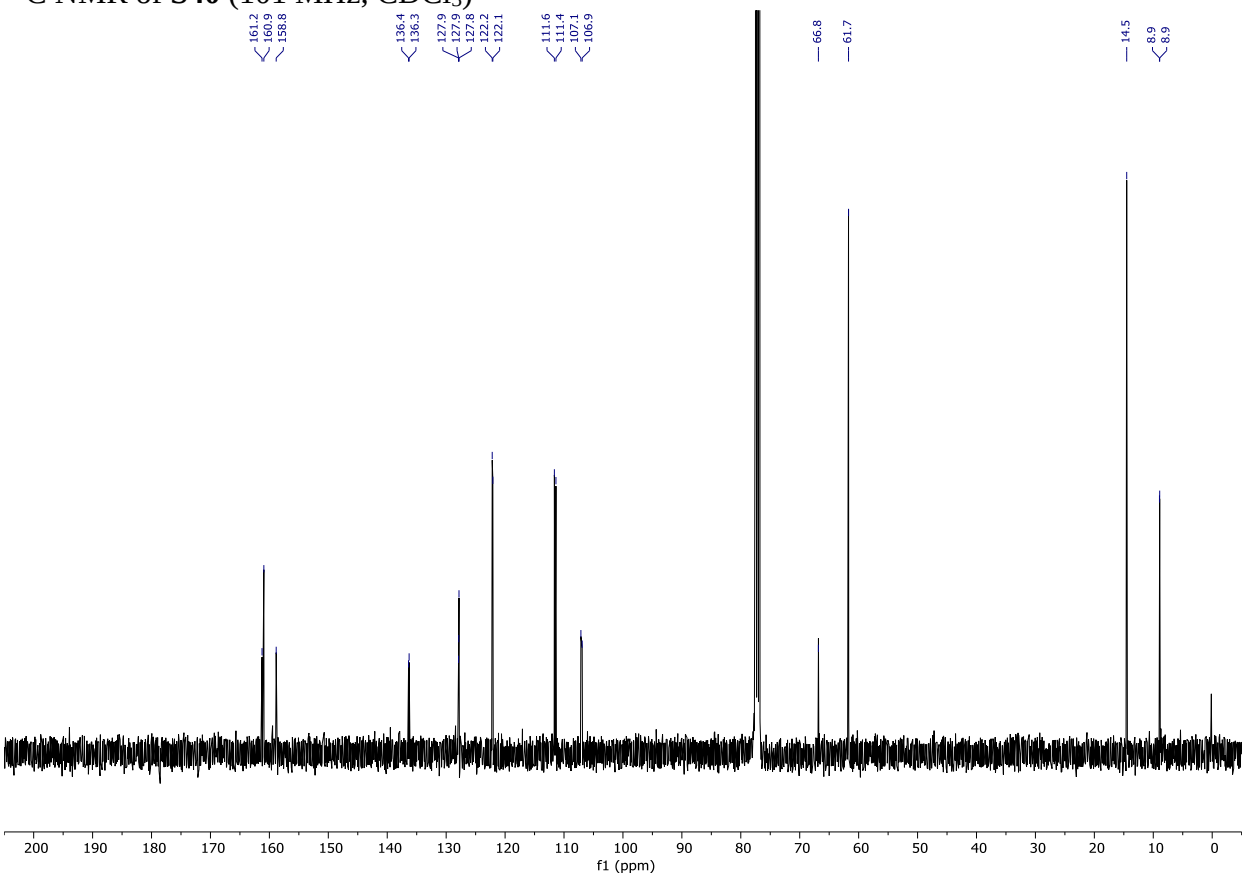
^{13}C NMR of **S39** (101 MHz, $CDCl_3$)



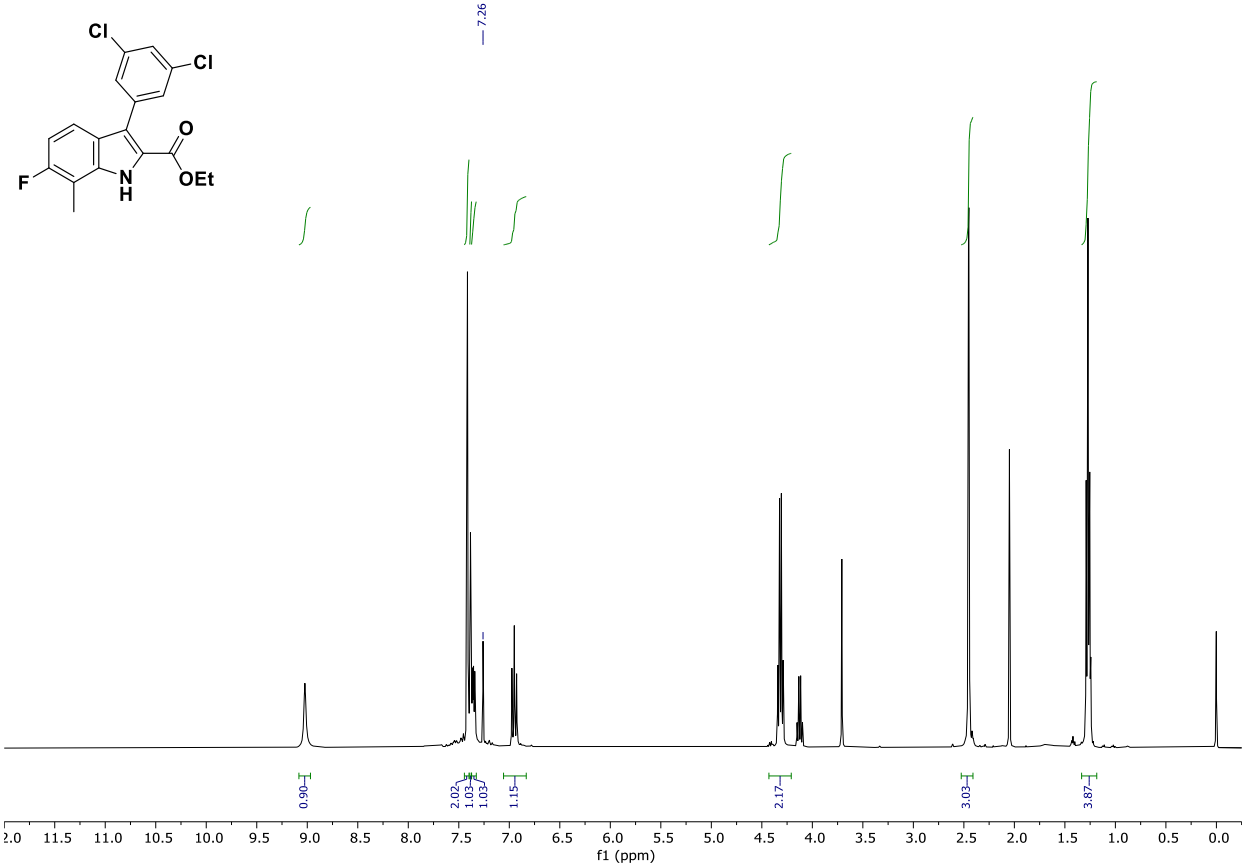
^{1}H NMR of **S40** (400 MHz, $CDCl_3$)



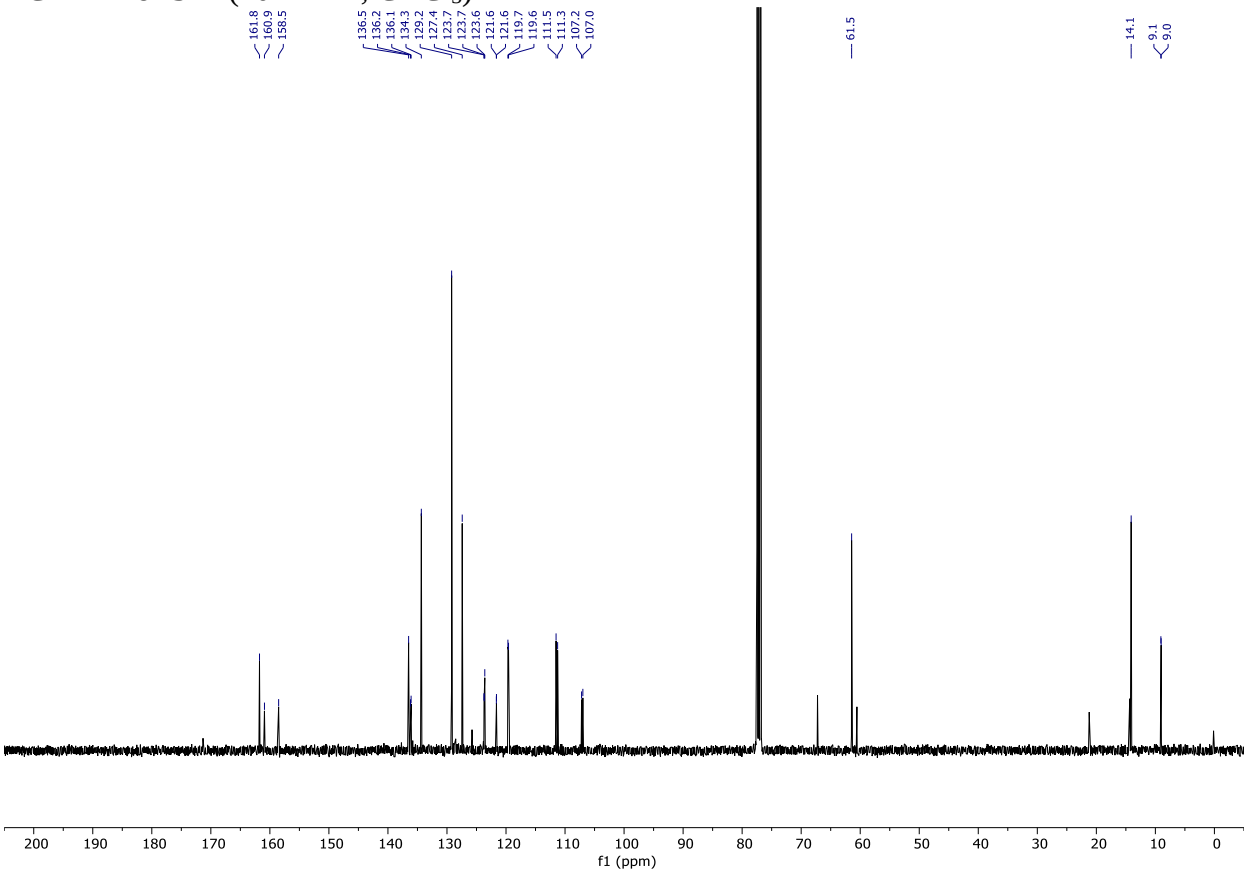
^{13}C NMR of **S40** (101 MHz, $CDCl_3$)



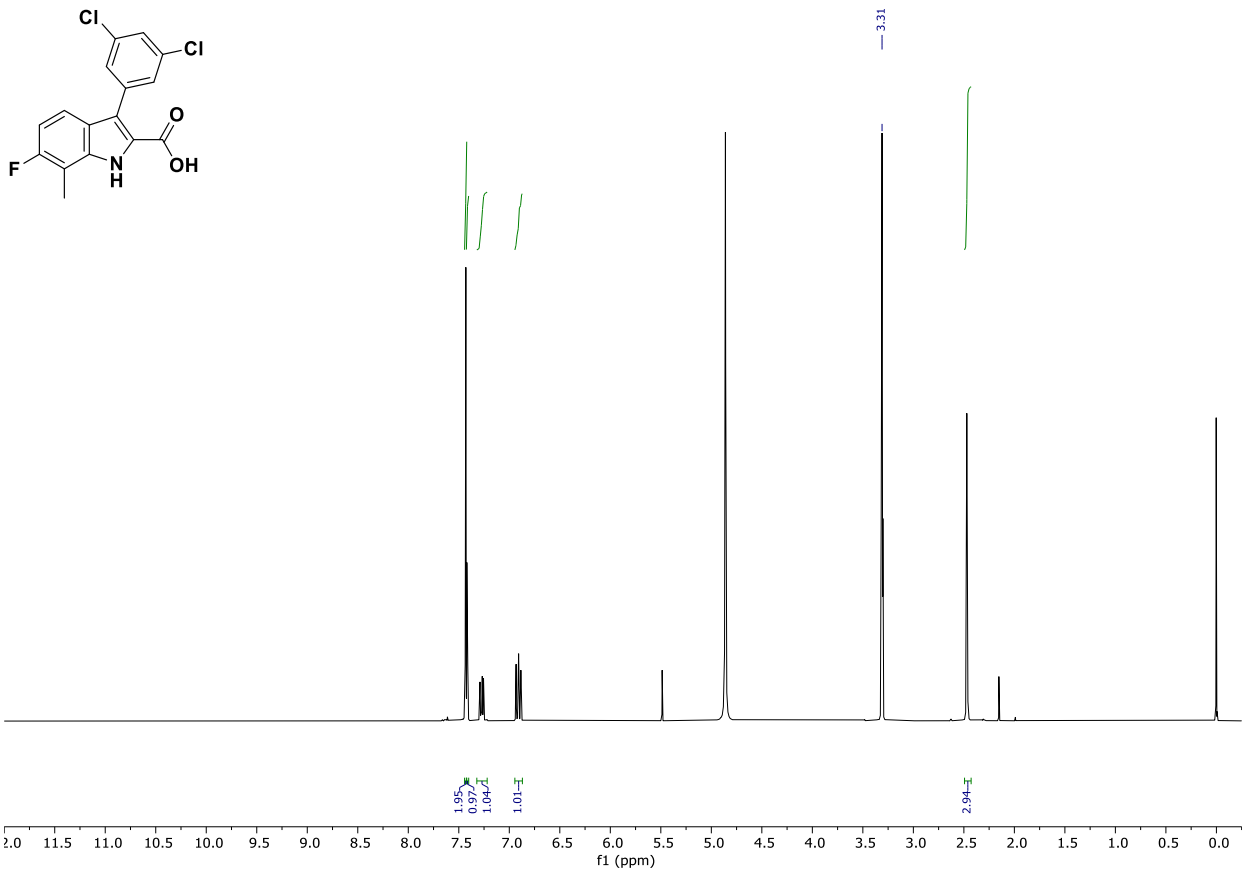
^{1}H NMR of **S41** (400 MHz, $CDCl_3$)



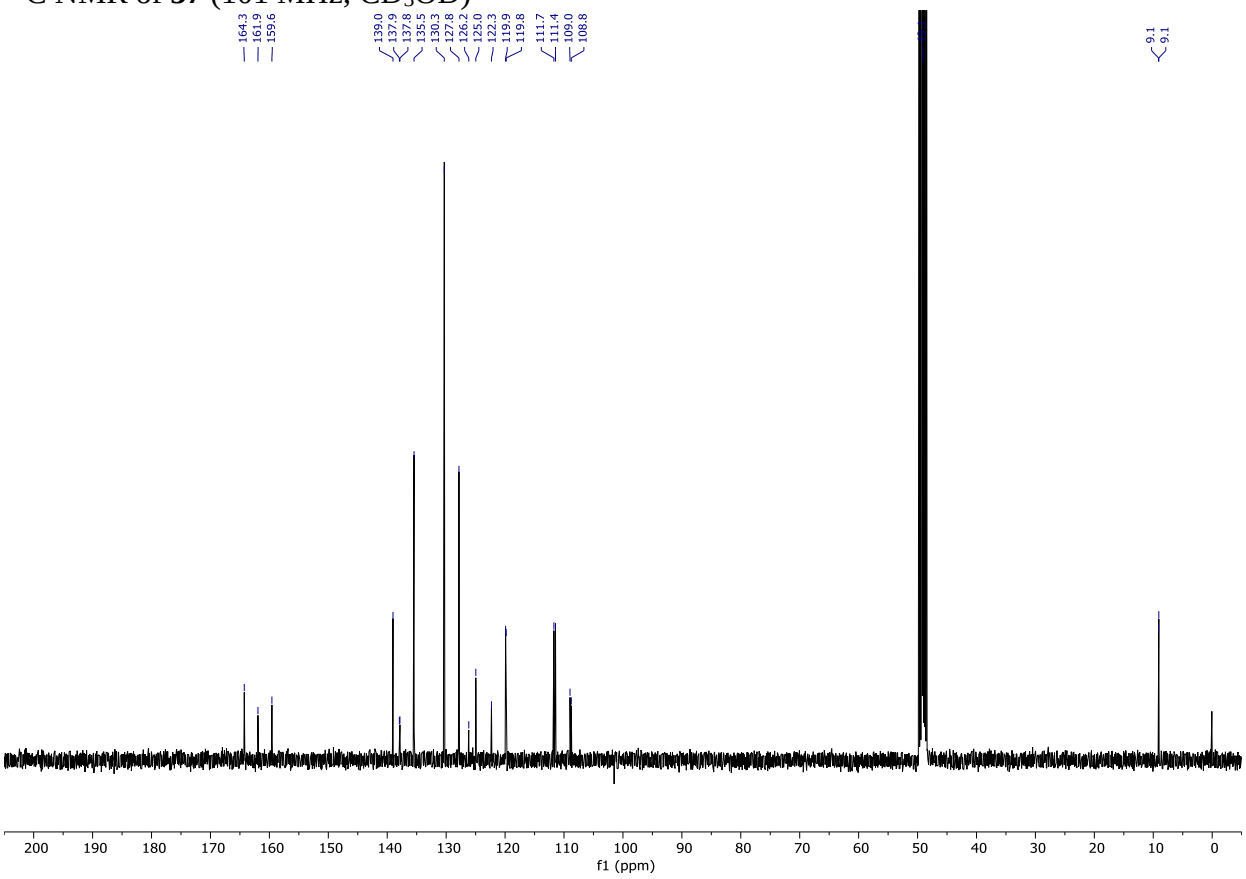
^{13}C NMR of **S41** (101 MHz, $CDCl_3$)



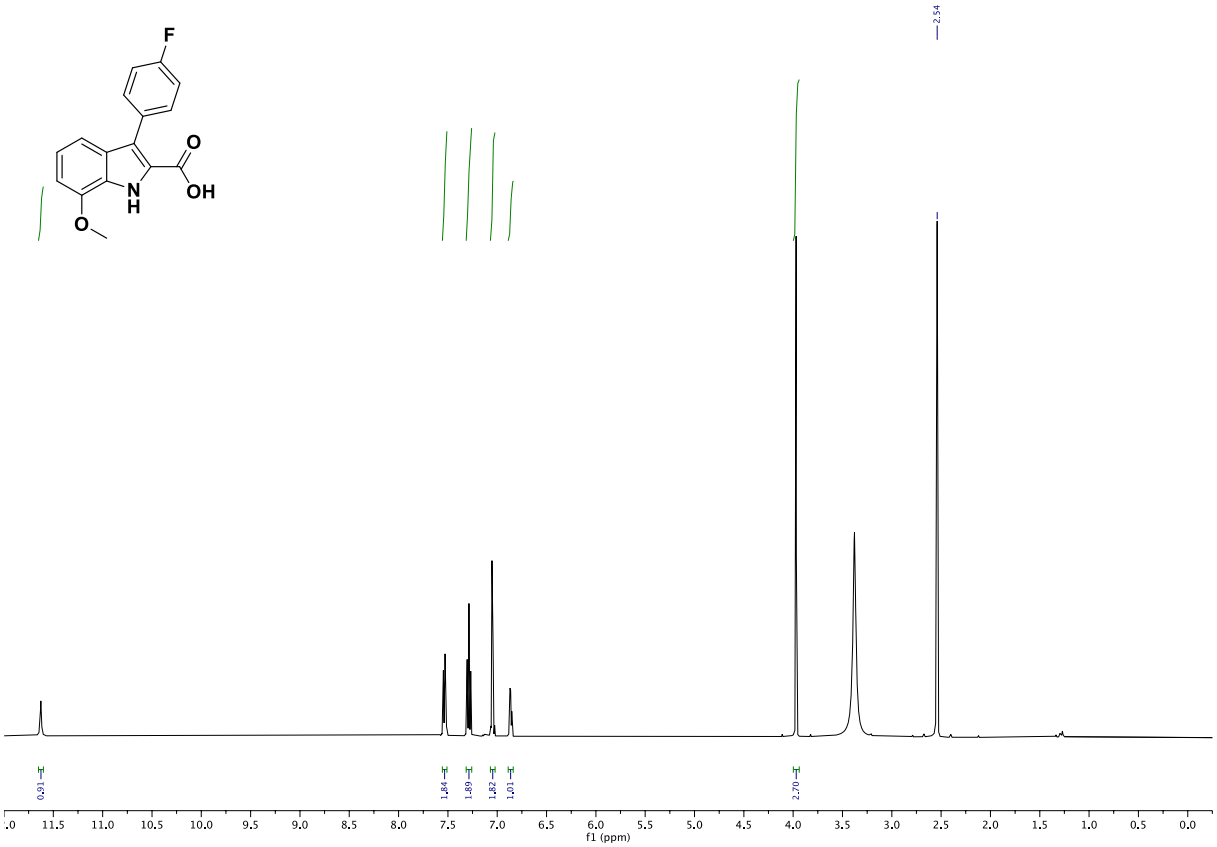
^{1}H NMR of **37** (400 MHz, CD_3OD)



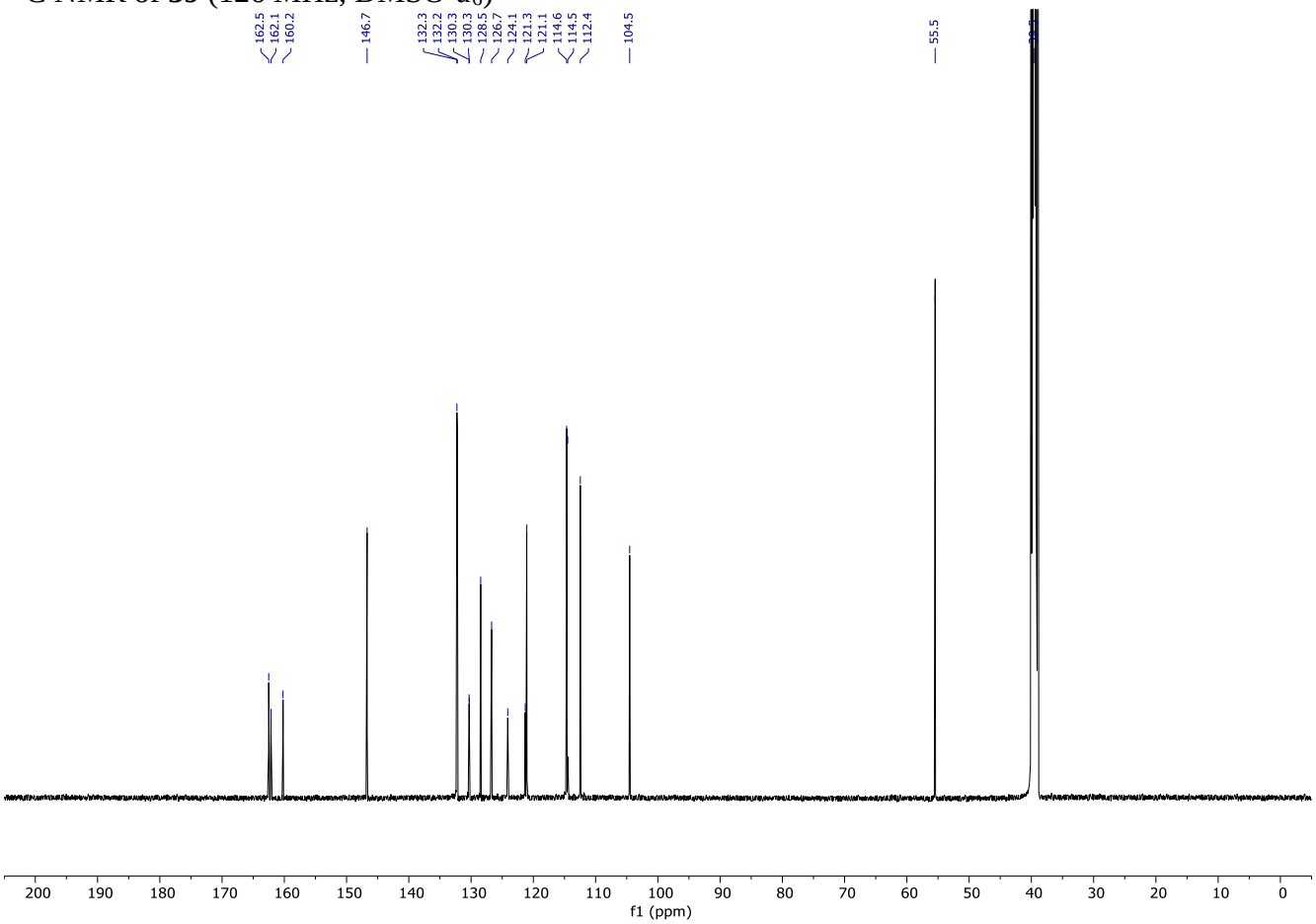
^{13}C NMR of **37** (101 MHz, CD_3OD)



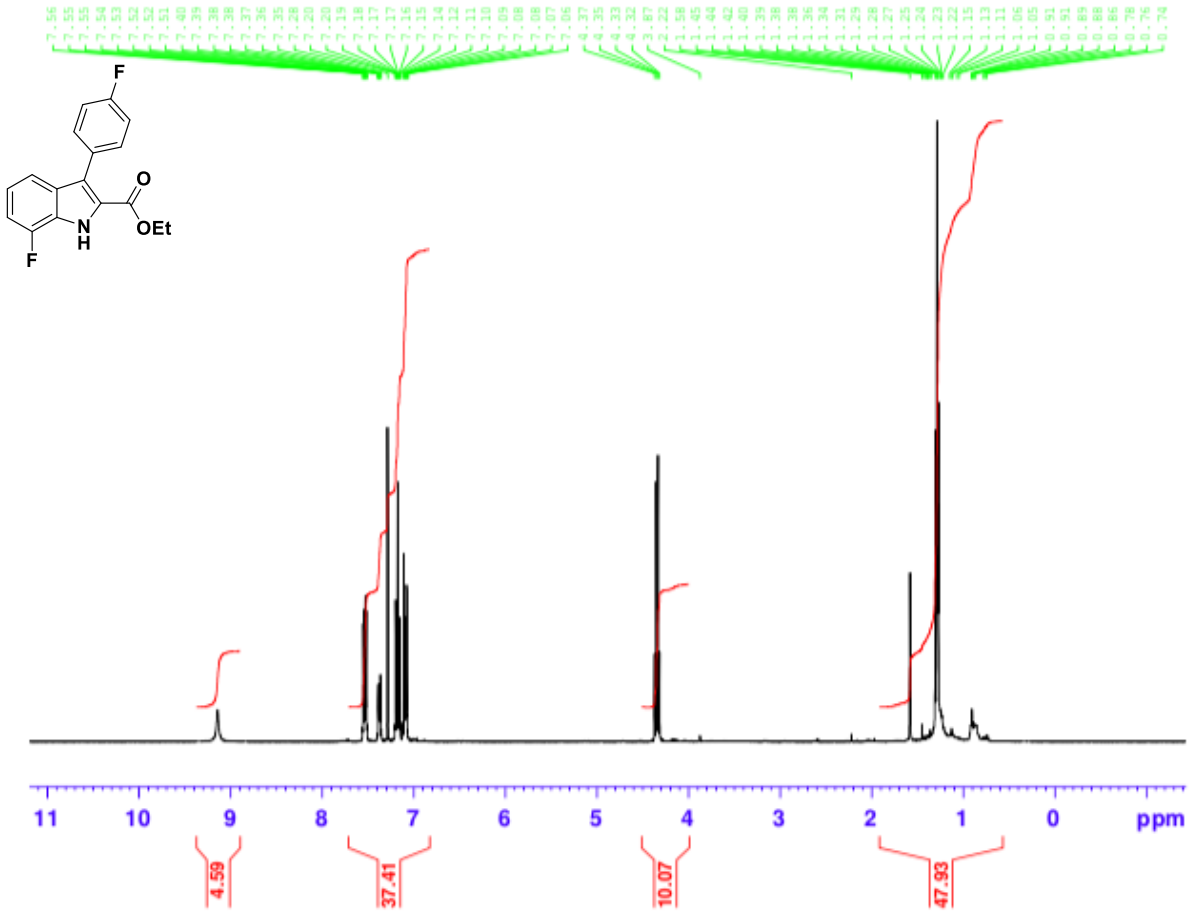
^{1}H NMR of **39** (500 MHz, DMSO-d_6)



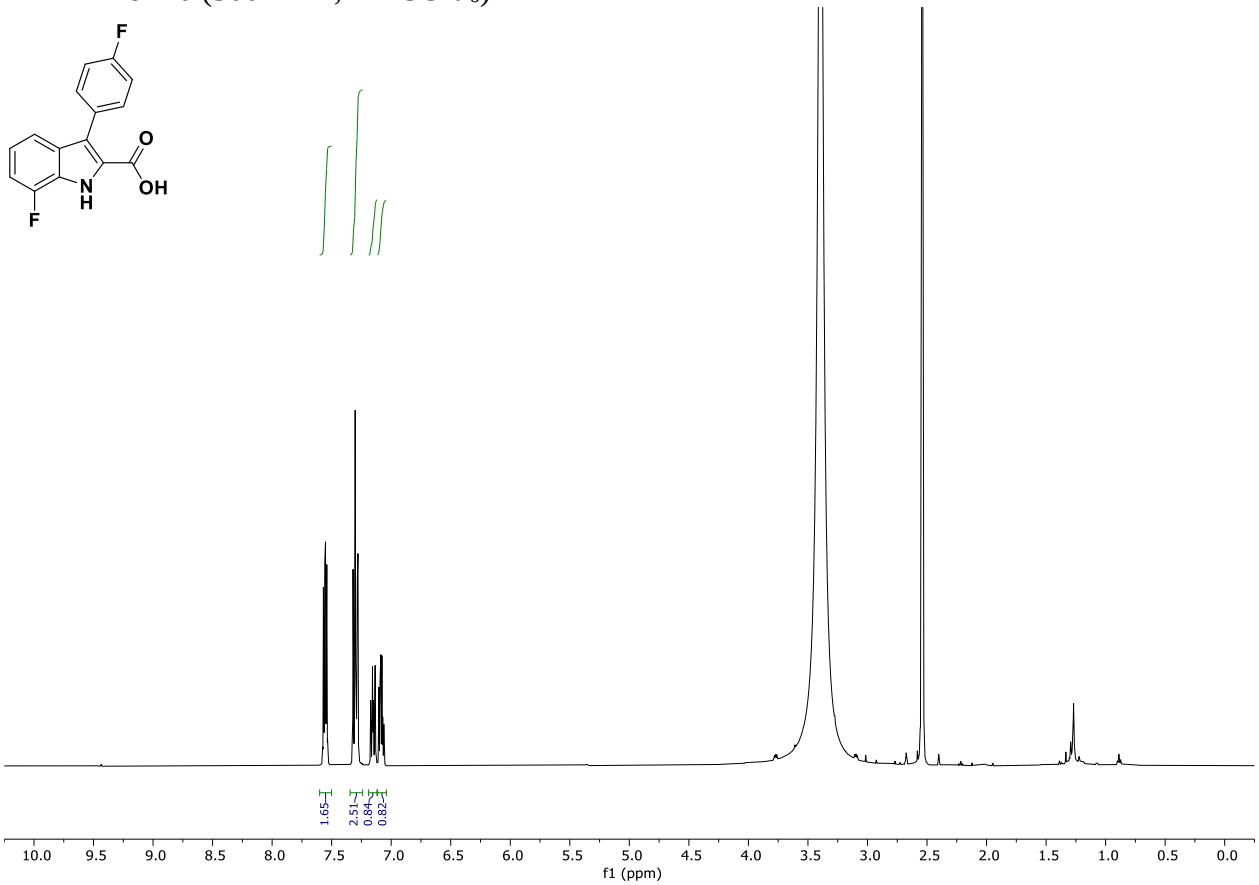
^{13}C NMR of **39** (126 MHz, DMSO-d_6)



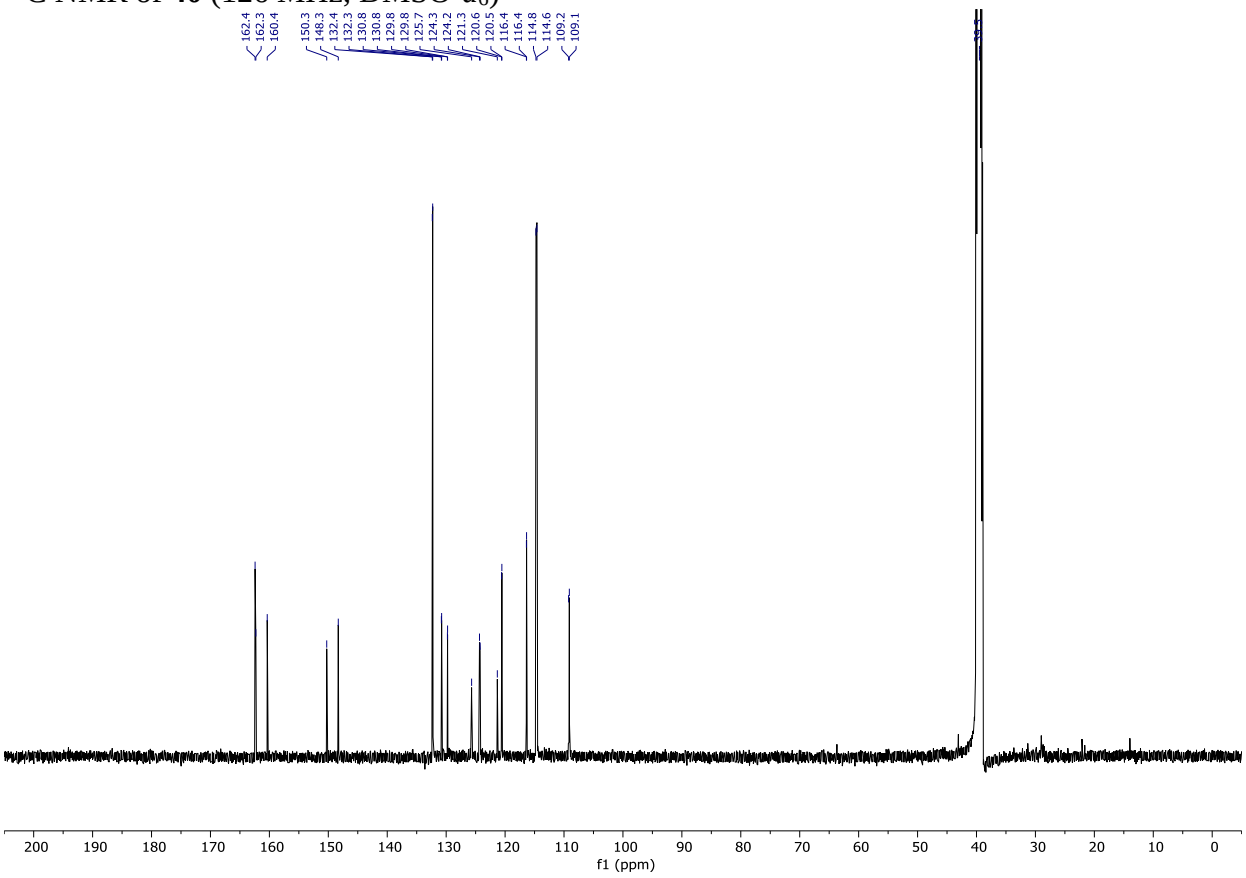
^{1}H NMR of **S42** (400 MHz, $CDCl_3$)



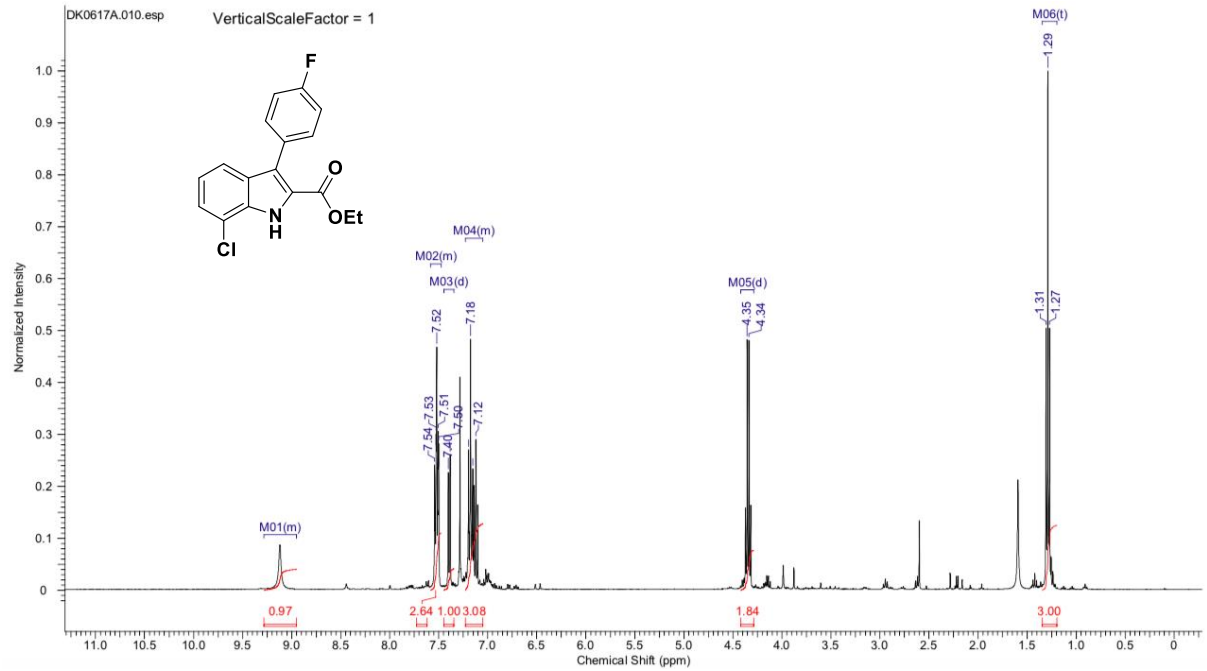
^{1}H NMR of **40** (500 MHz, DMSO-d_6)



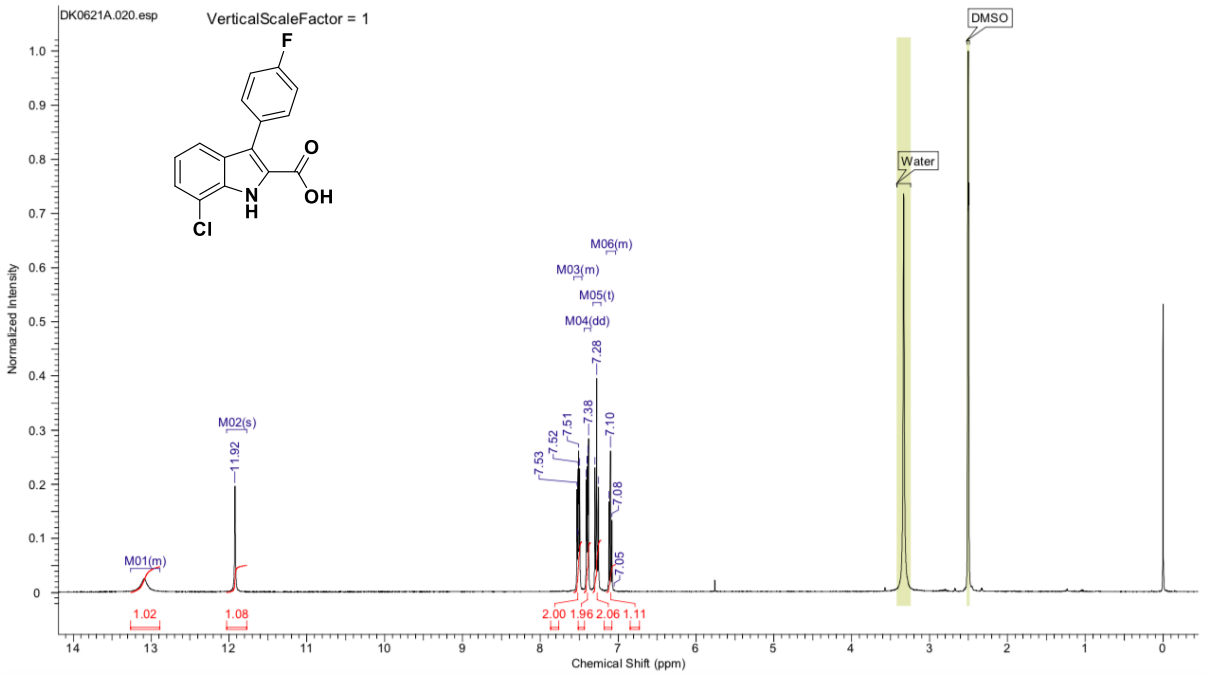
^{13}C NMR of **40** (126 MHz, DMSO-d_6)



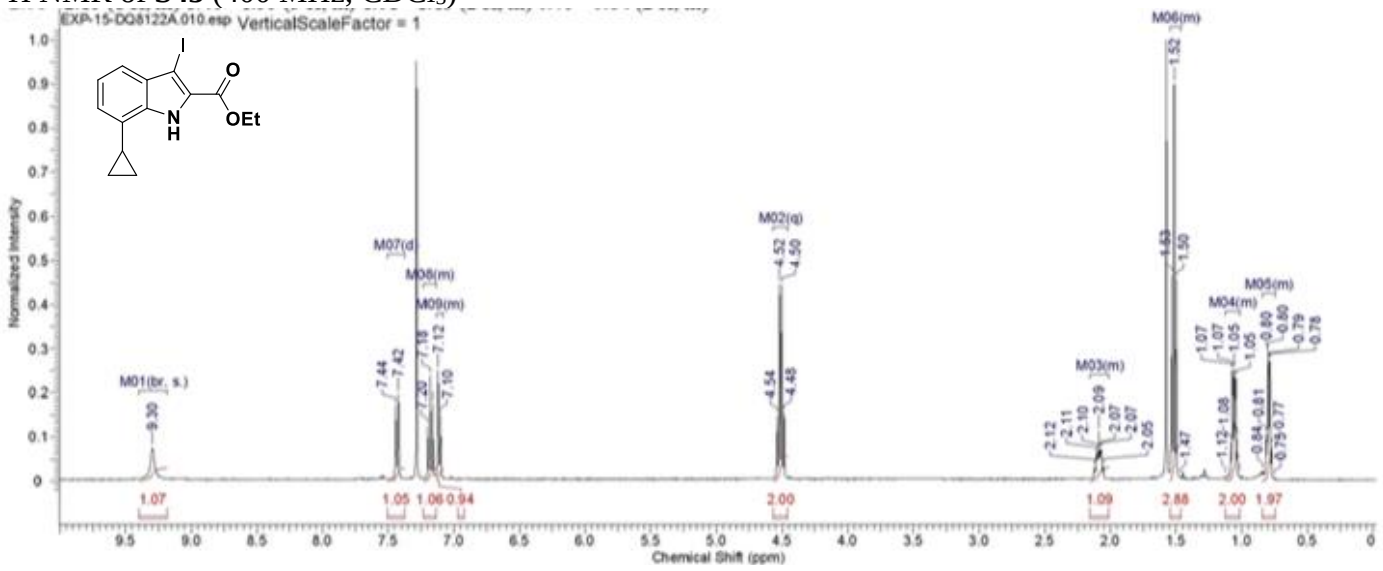
^{1}H NMR of **S43** (400 MHz, $CDCl_3$)



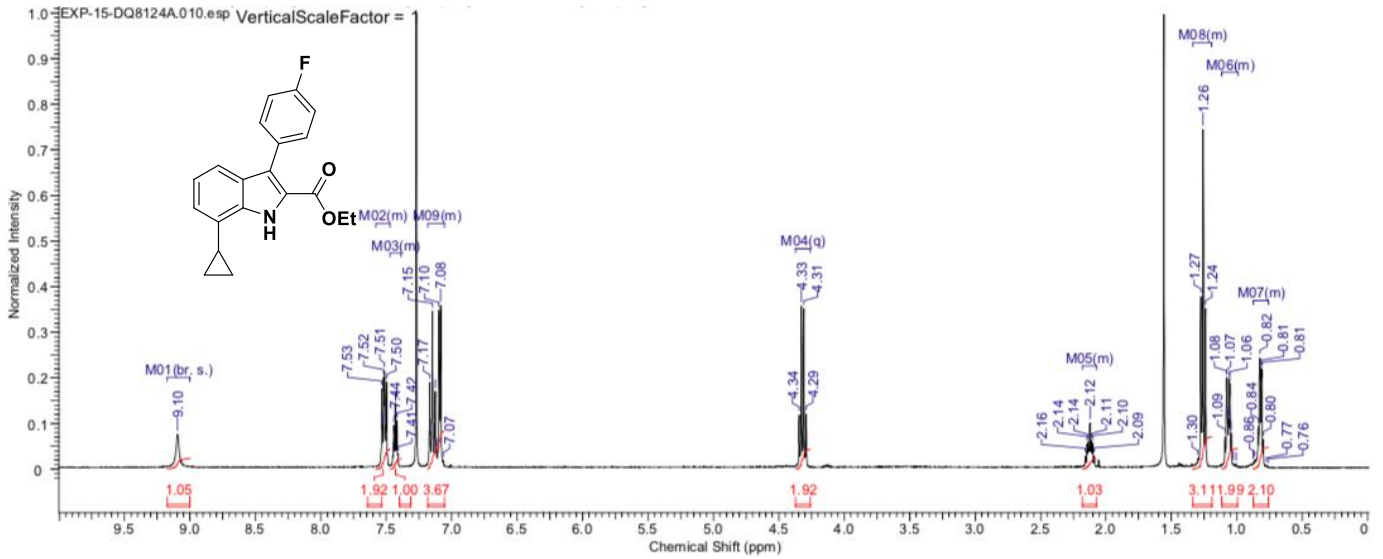
^{1}H NMR of **41** (400 MHz, DMSO-d_6)



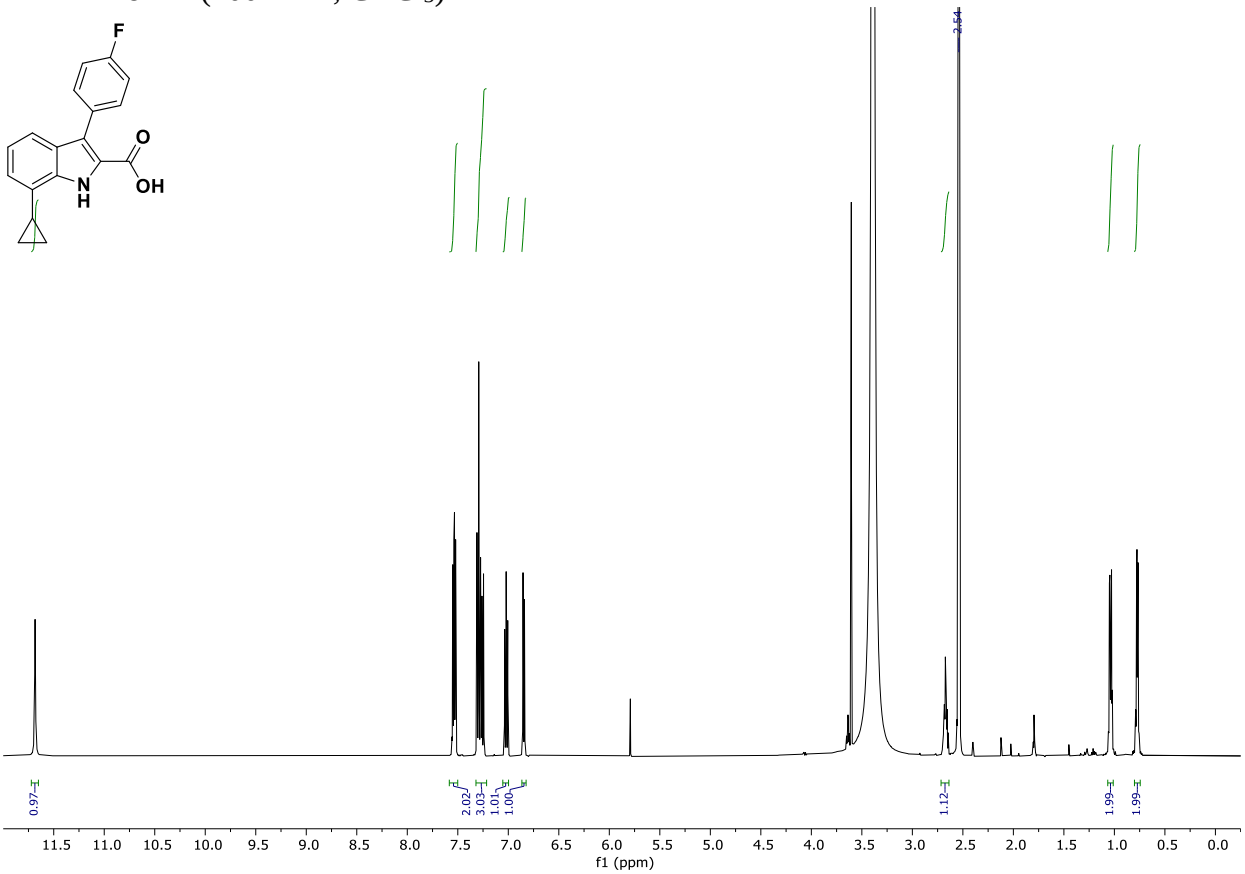
^{1}H NMR of **S45** (400 MHz, $CDCl_3$)



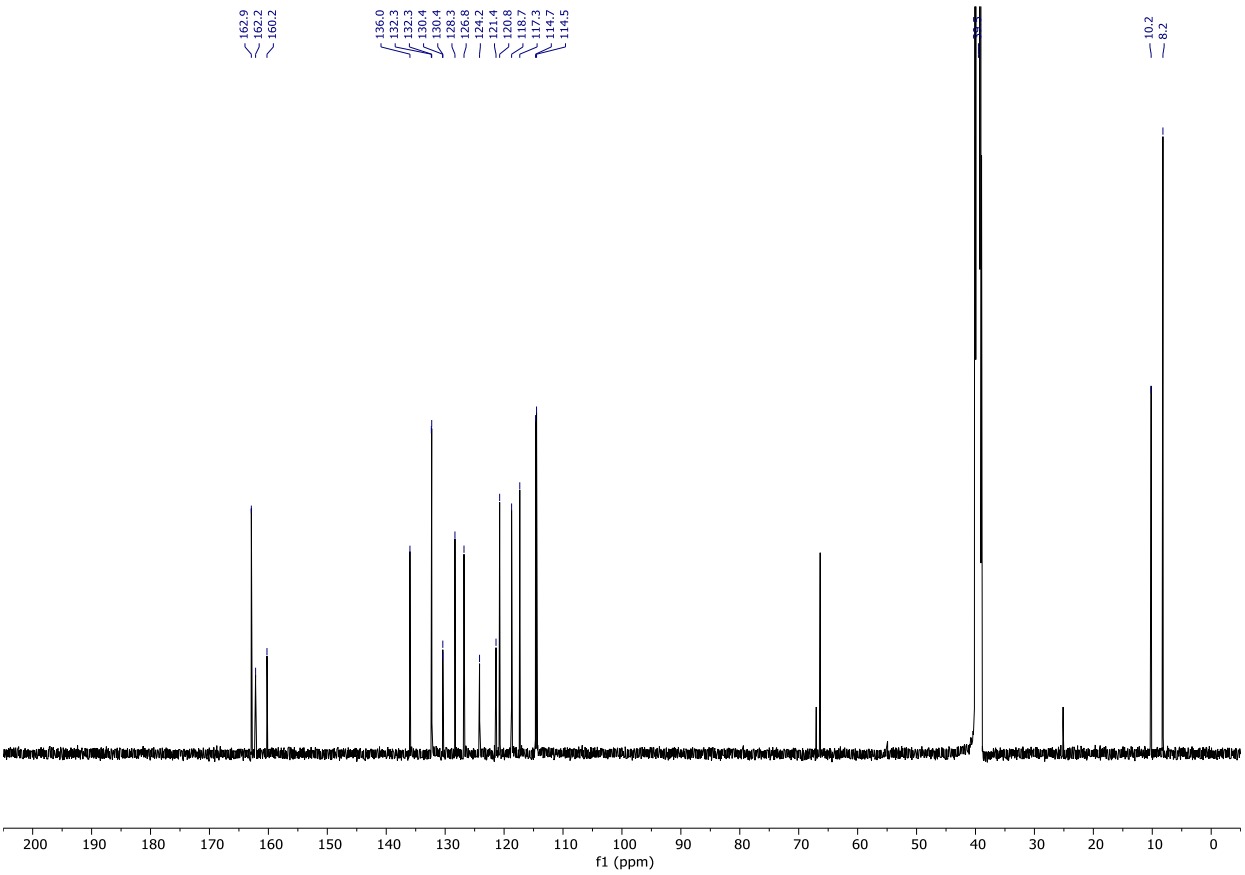
^{1}H NMR of **S46** (400 MHz, $CDCl_3$)



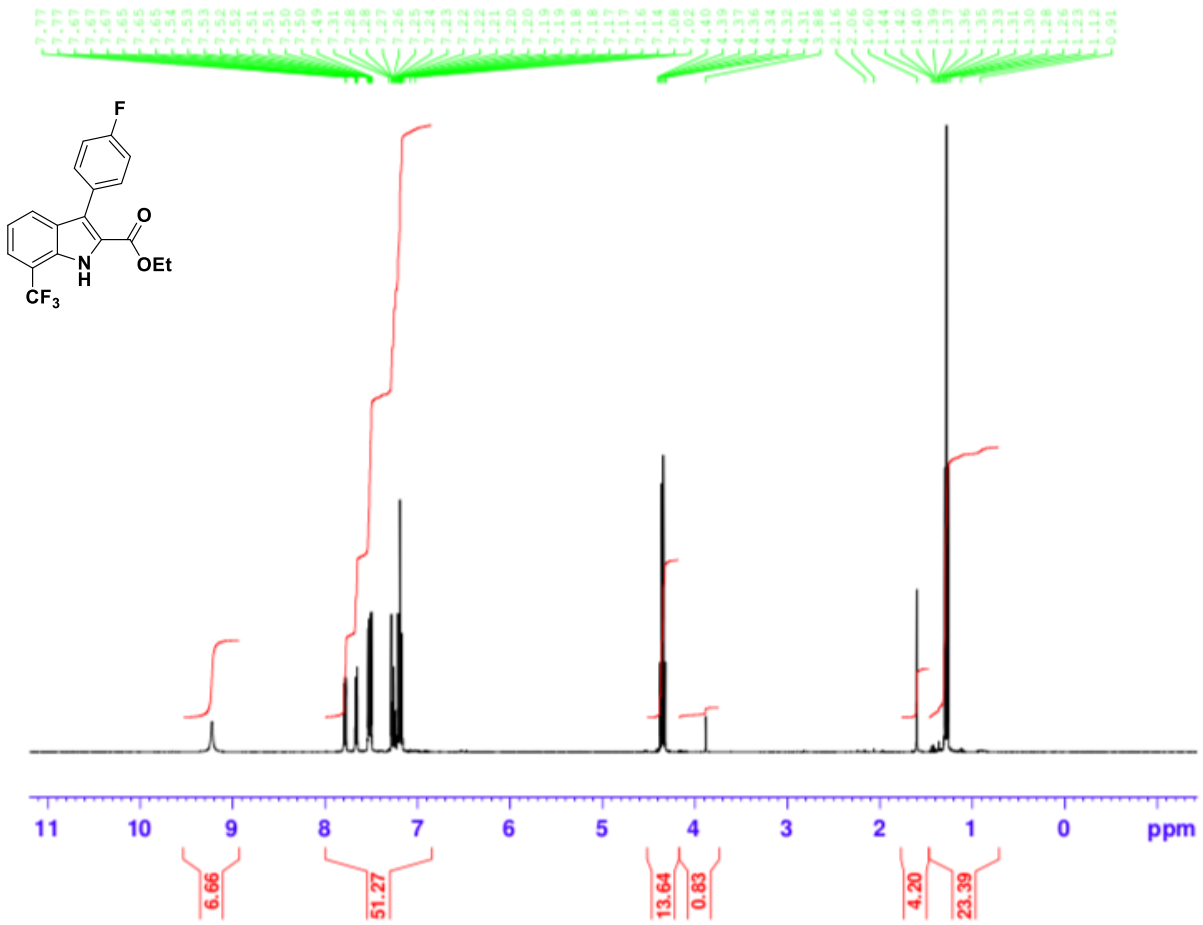
^{1}H NMR of **42** (400 MHz, $CDCl_3$)



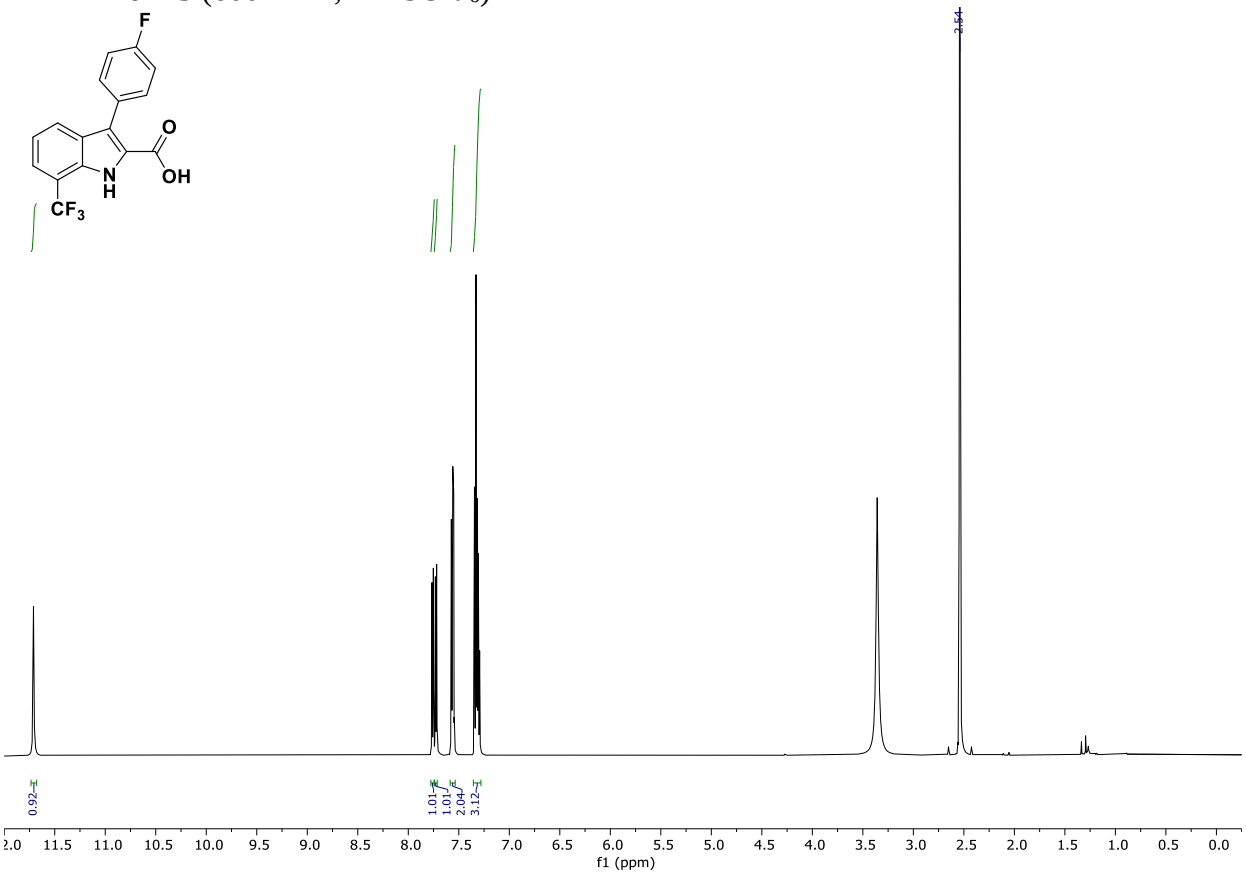
^{13}C NMR of **42** (126 MHz, $CDCl_3$)



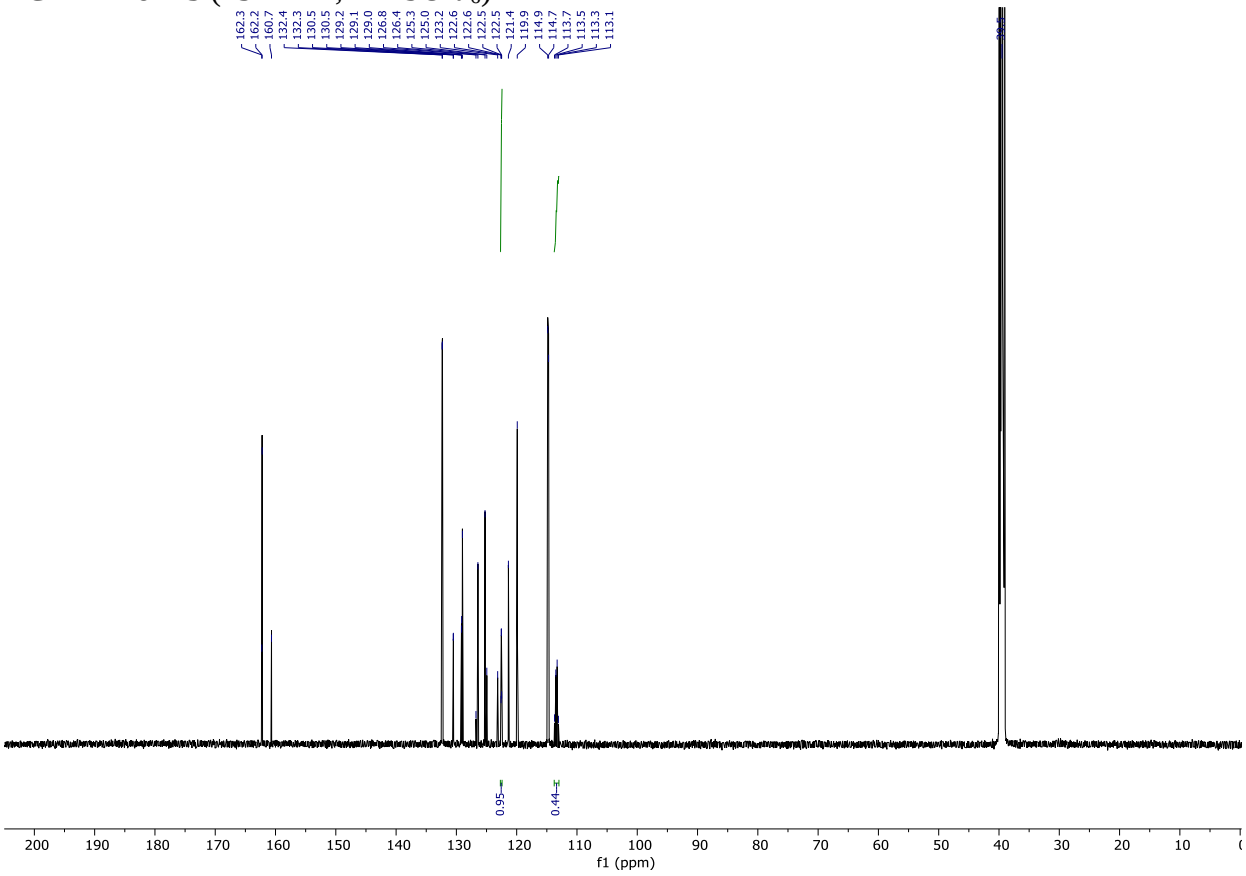
^{1}H NMR of **S47** (400 MHz, $CDCl_3$)



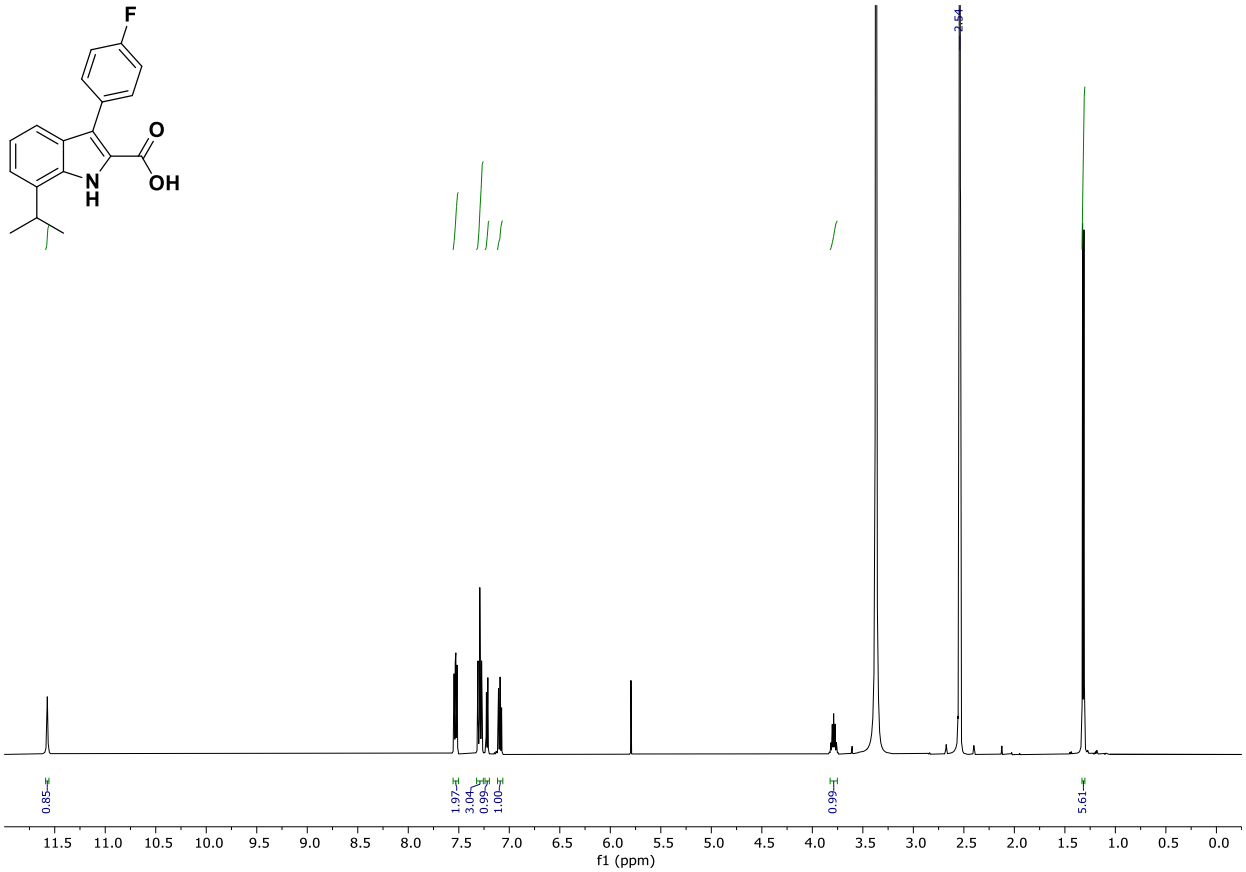
^{1}H NMR of **43** (600 MHz, DMSO-d_6)



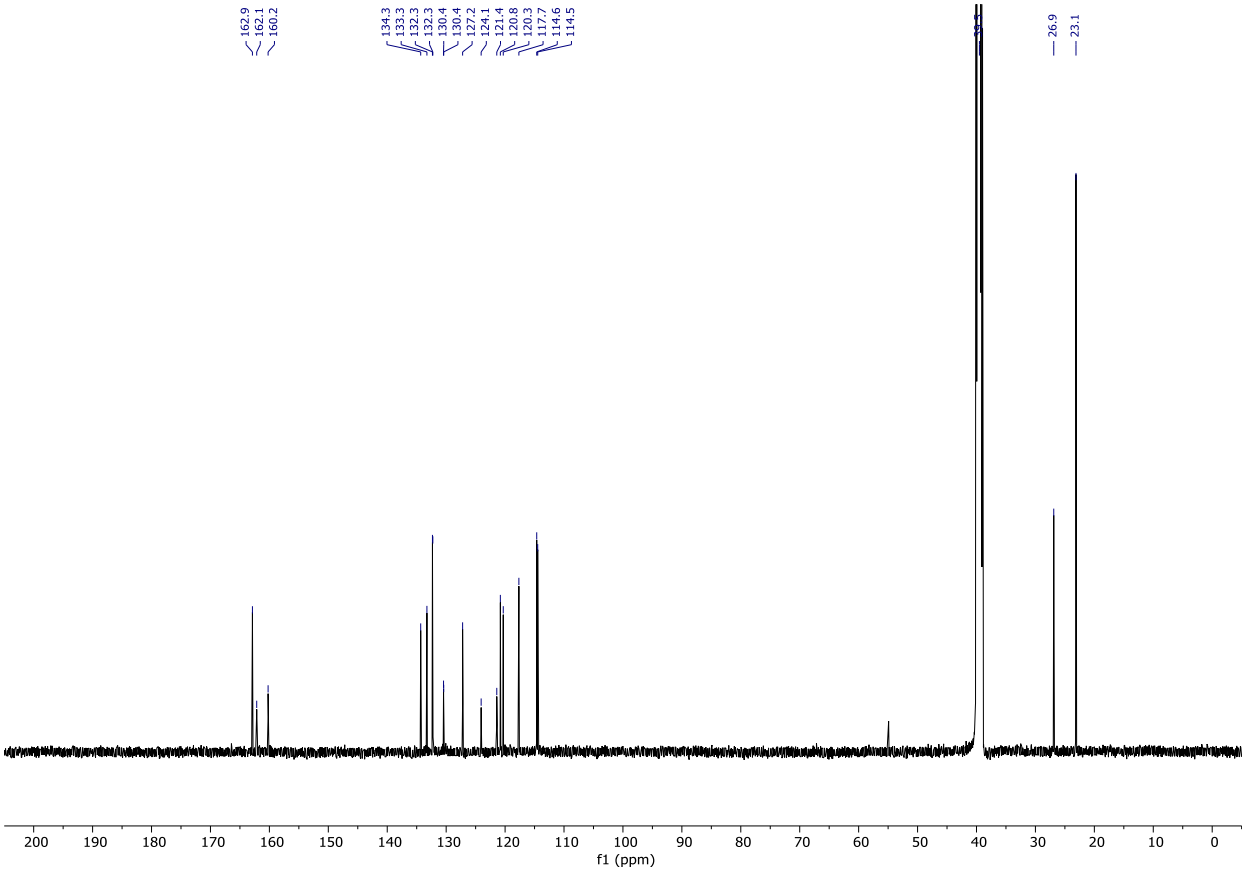
^{13}C NMR of **43** (151MHz, DMSO-d_6)



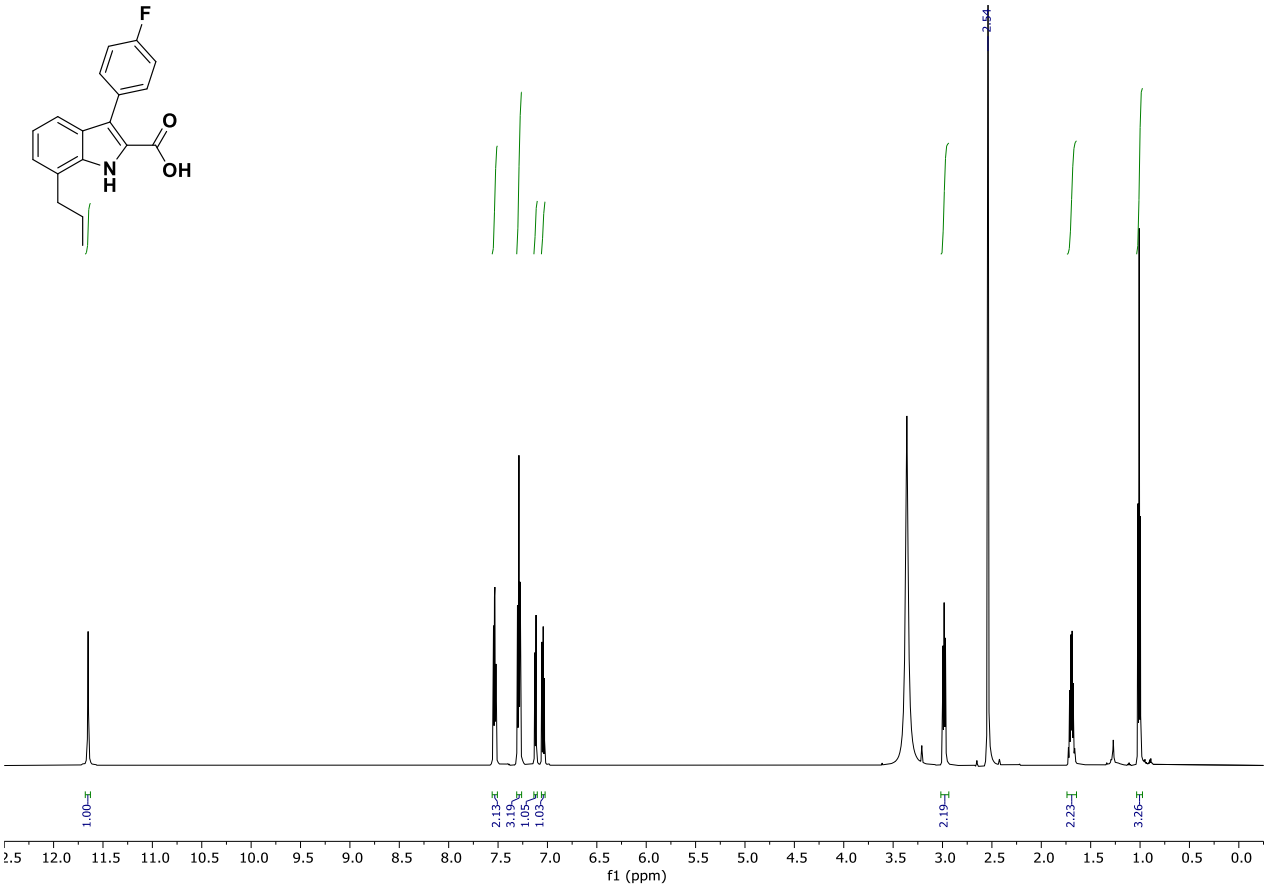
^{1}H NMR of **44** (400 MHz, DMSO-d_6)



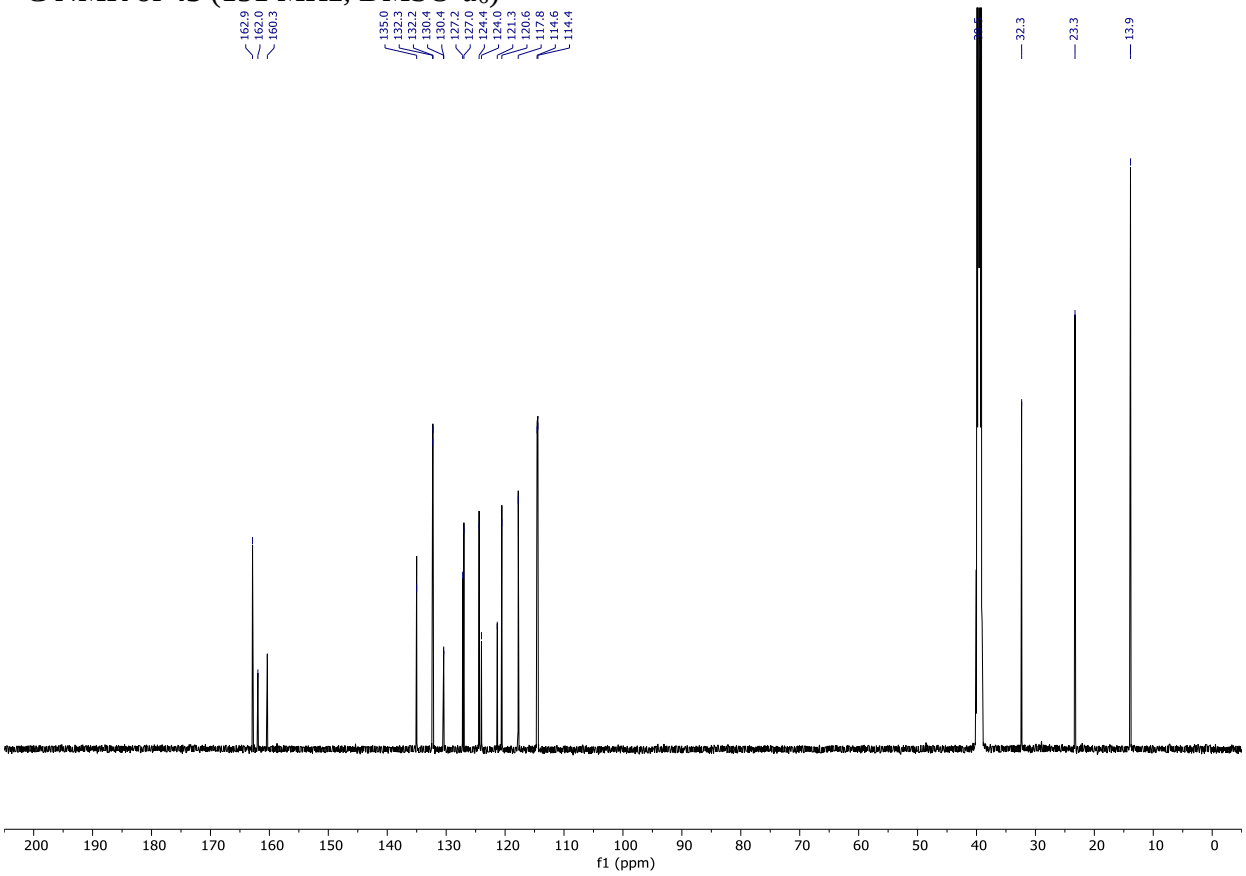
^{13}C NMR of **44** (126 MHz, DMSO-d_6)



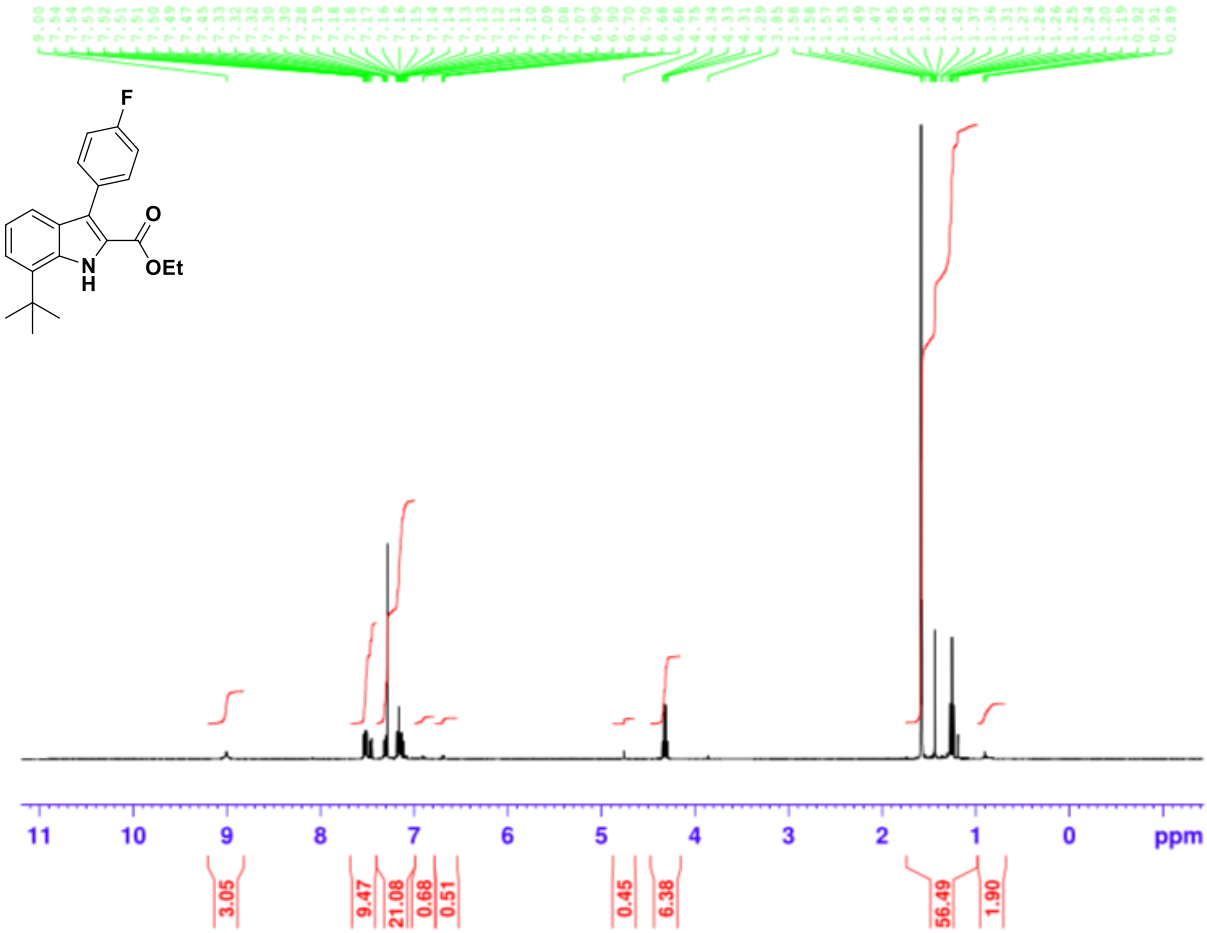
^{1}H NMR of **45** (600 MHz, DMSO-d_6)



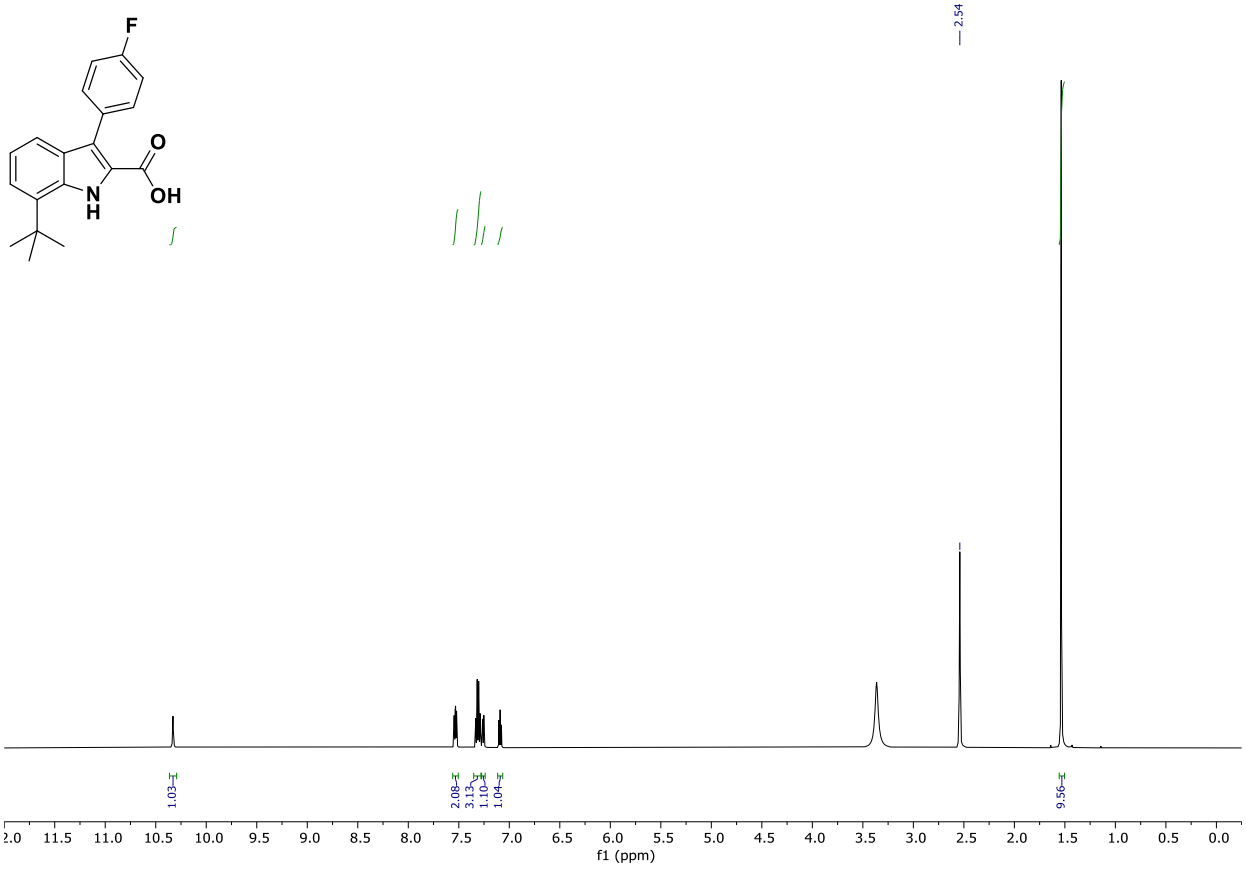
^{13}C NMR of **45** (151 MHz, DMSO-d_6)



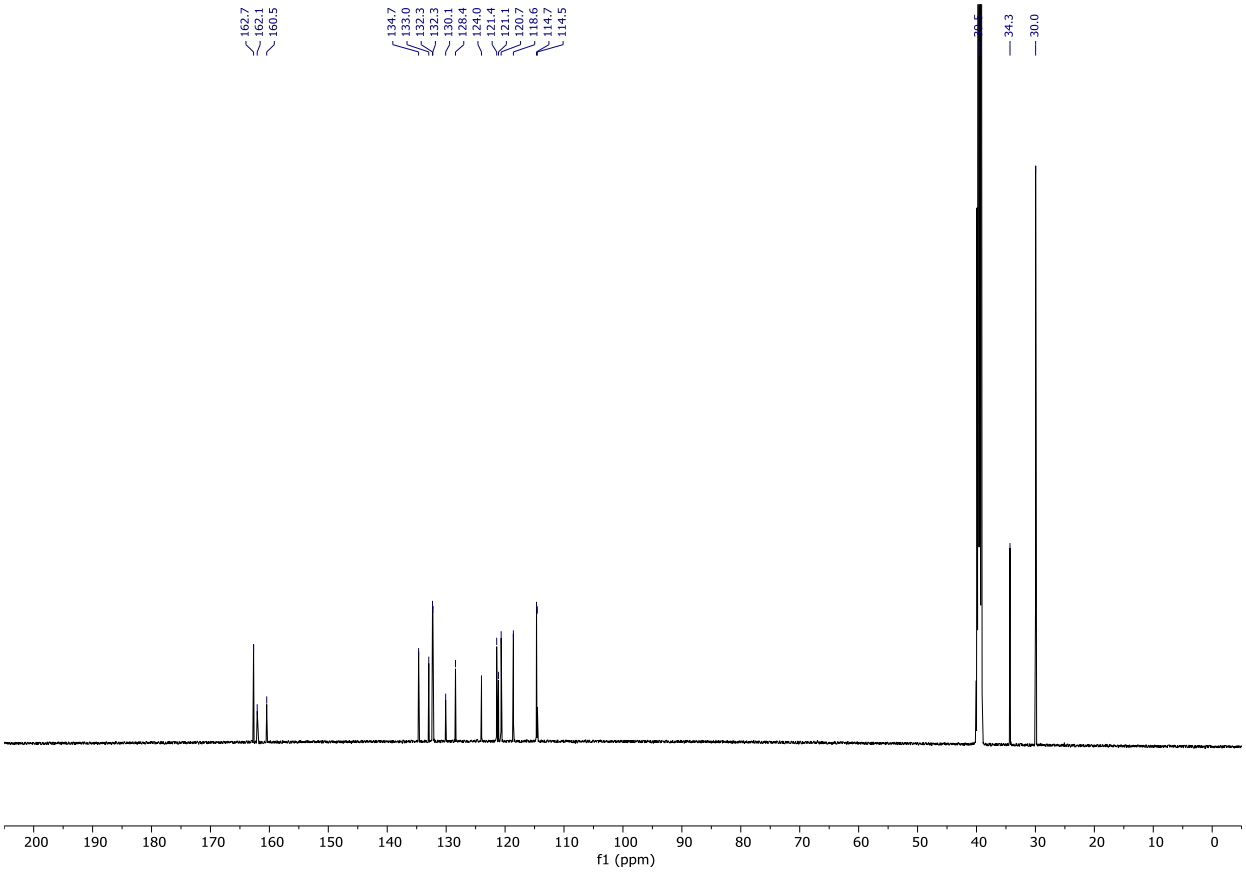
^{1}H NMR of **S49** (400 MHz, $CDCl_3$)



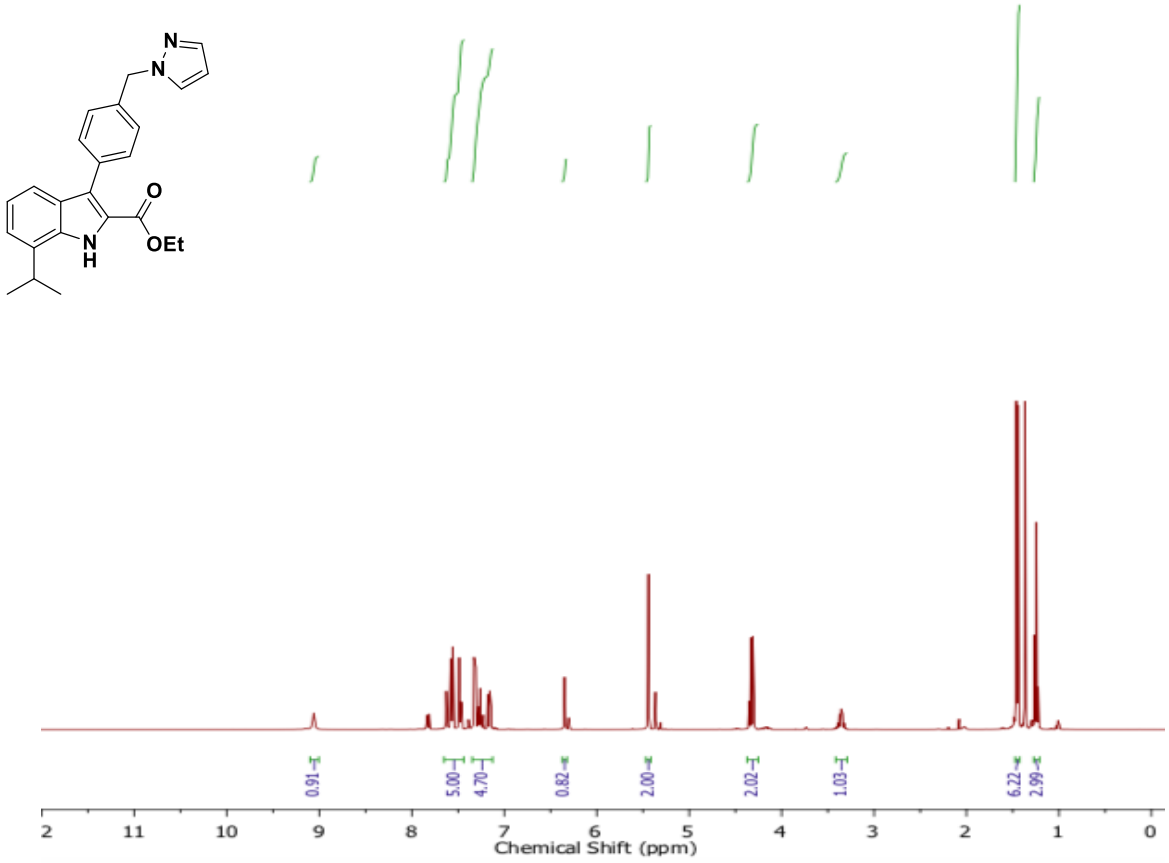
^{1}H NMR of **46** (600 MHz, DMSO-d_6)



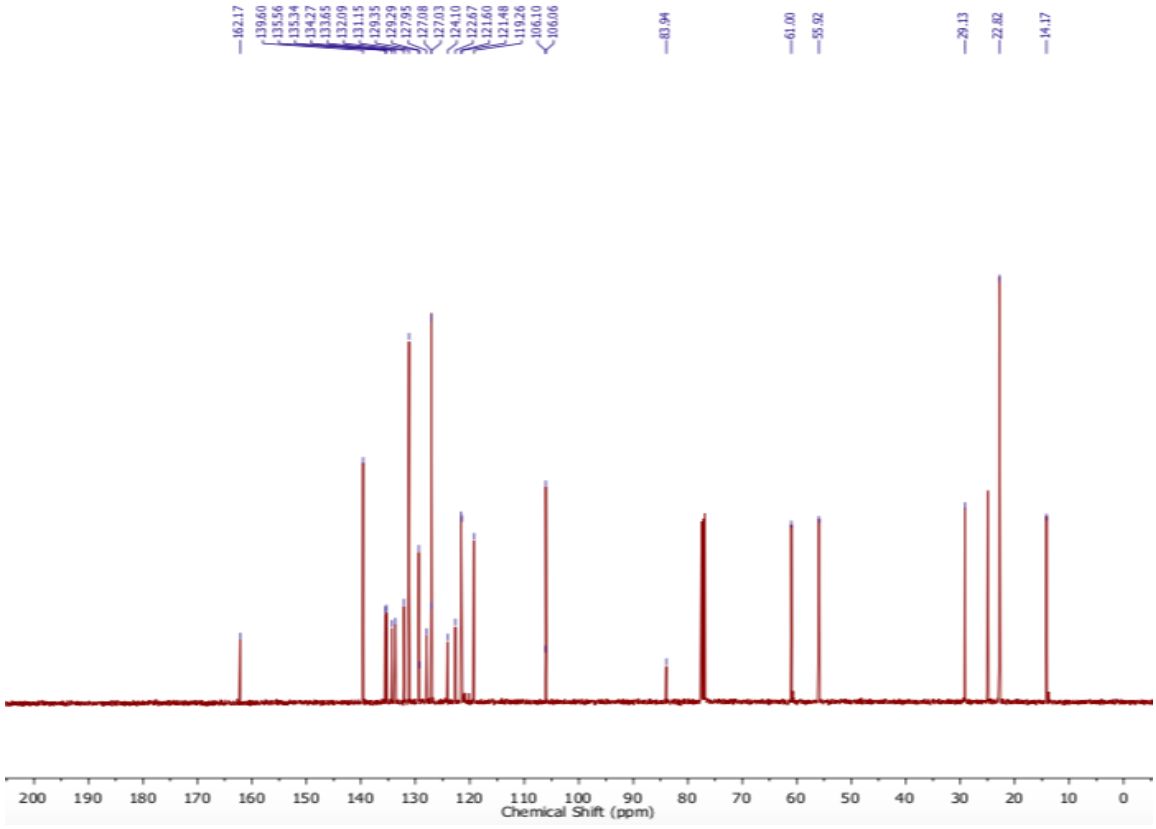
^{13}C NMR of **46** (151 MHz, DMSO-d_6)



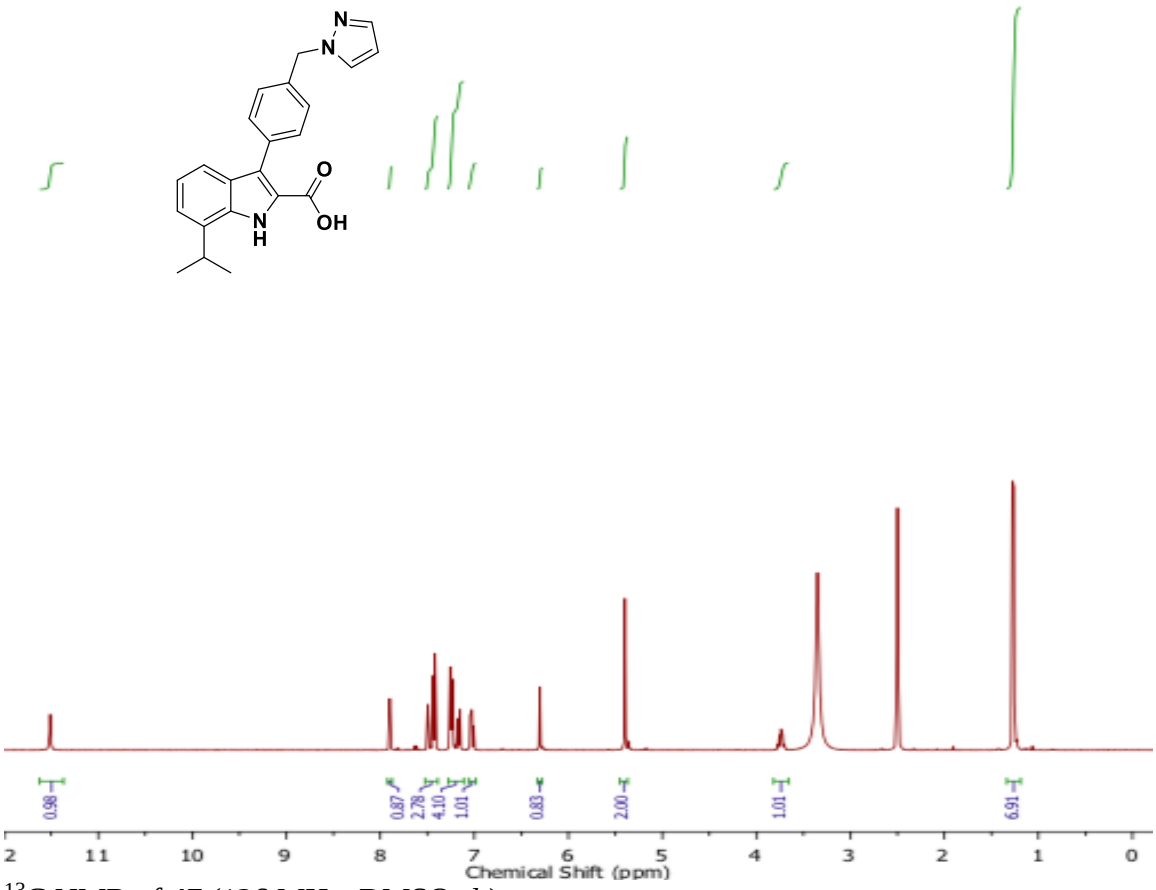
^{1}H NMR of **S50** (400 MHz, $CDCl_3$)



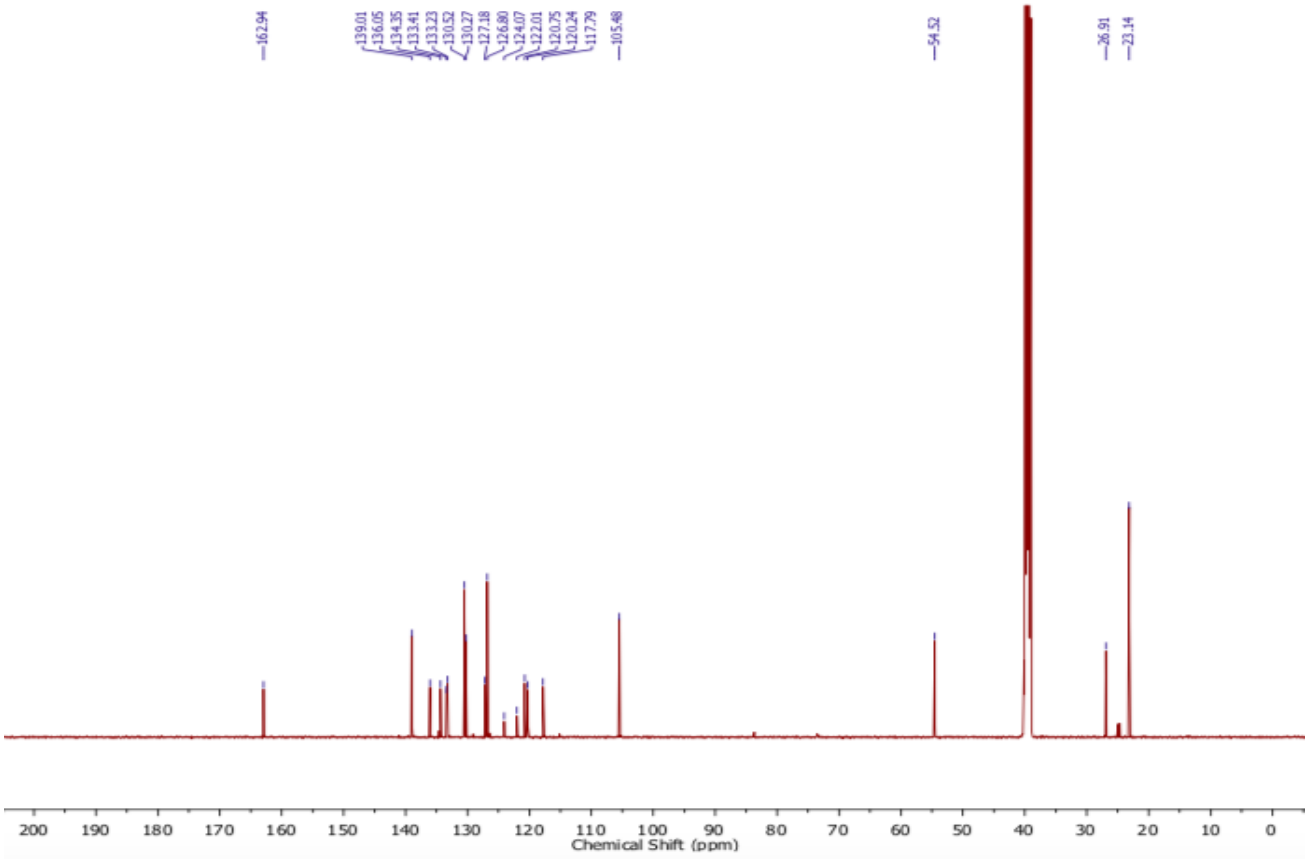
^{13}C NMR of **S50** (101 MHz, $CDCl_3$)



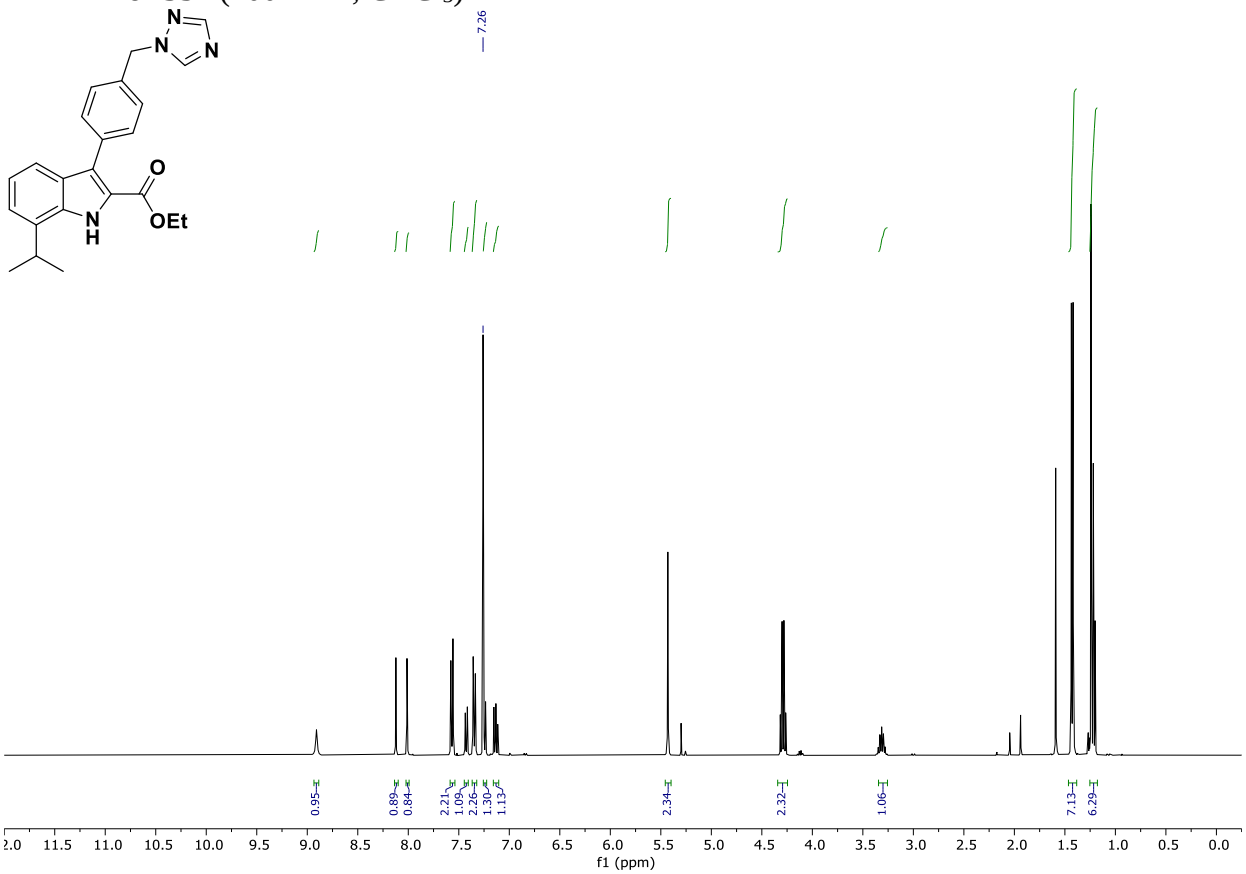
^{1}H NMR of **47** (400 MHz, DMSO-d_6)



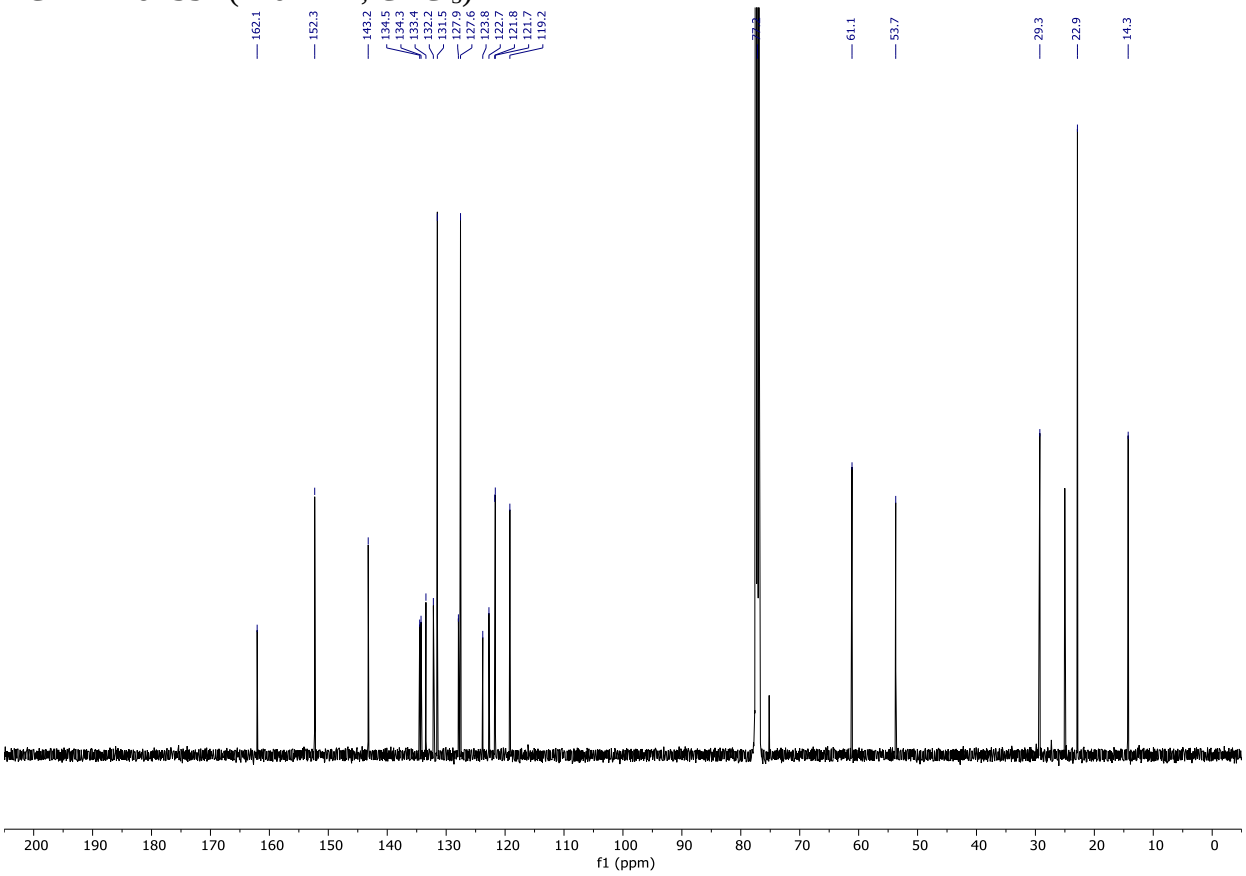
^{13}C NMR of **47** (126 MHz, DMSO-d_6)



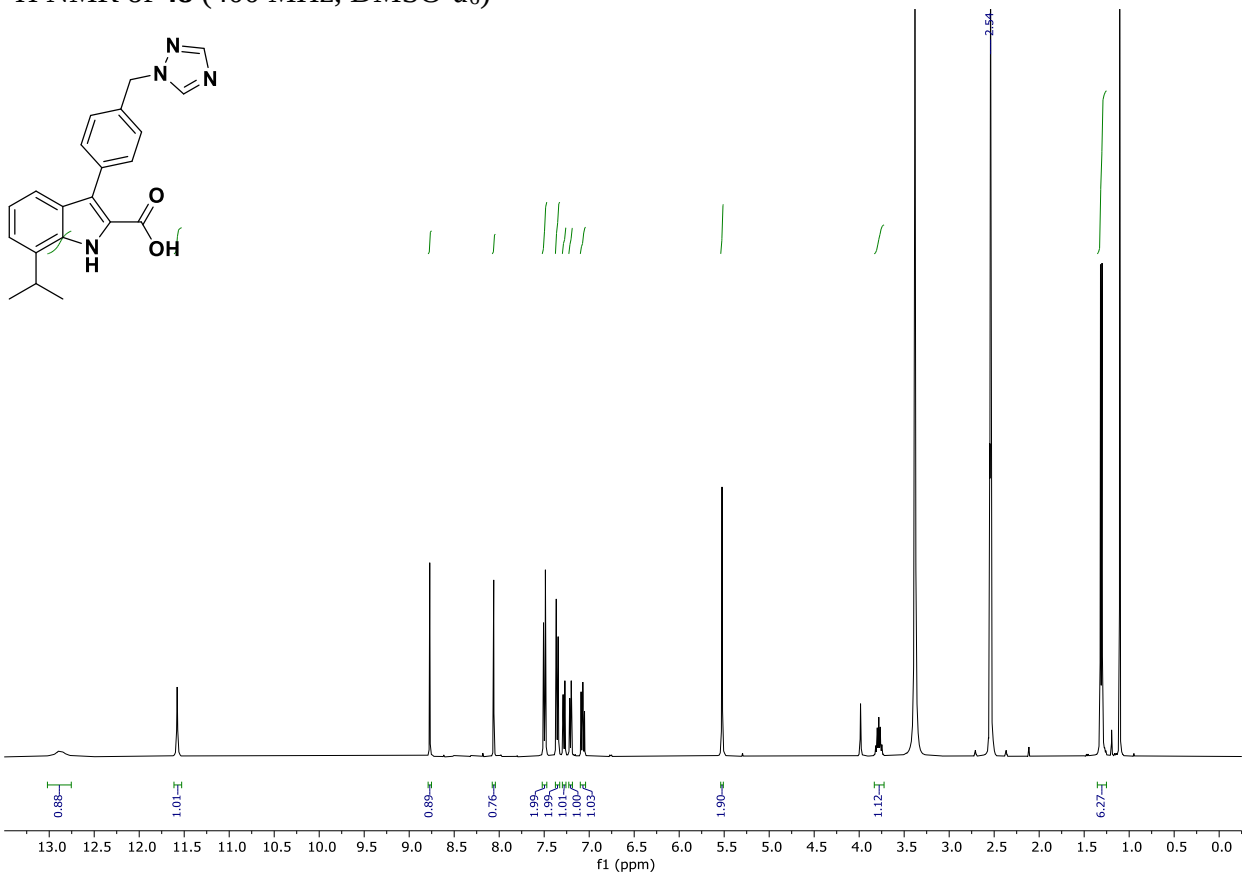
^{1}H NMR of **S51** (400 MHz, $CDCl_3$)



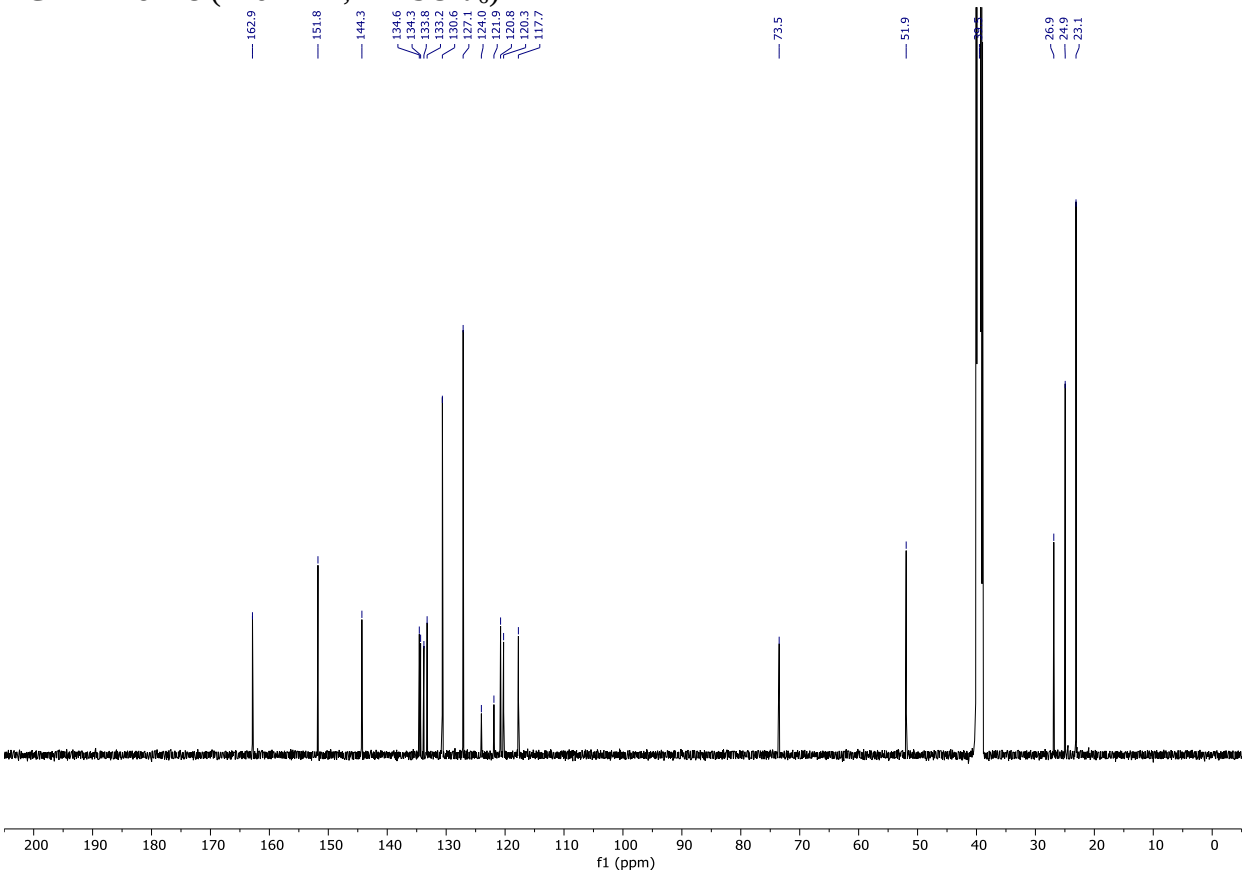
^{13}C NMR of **S51** (126 MHz, $CDCl_3$)



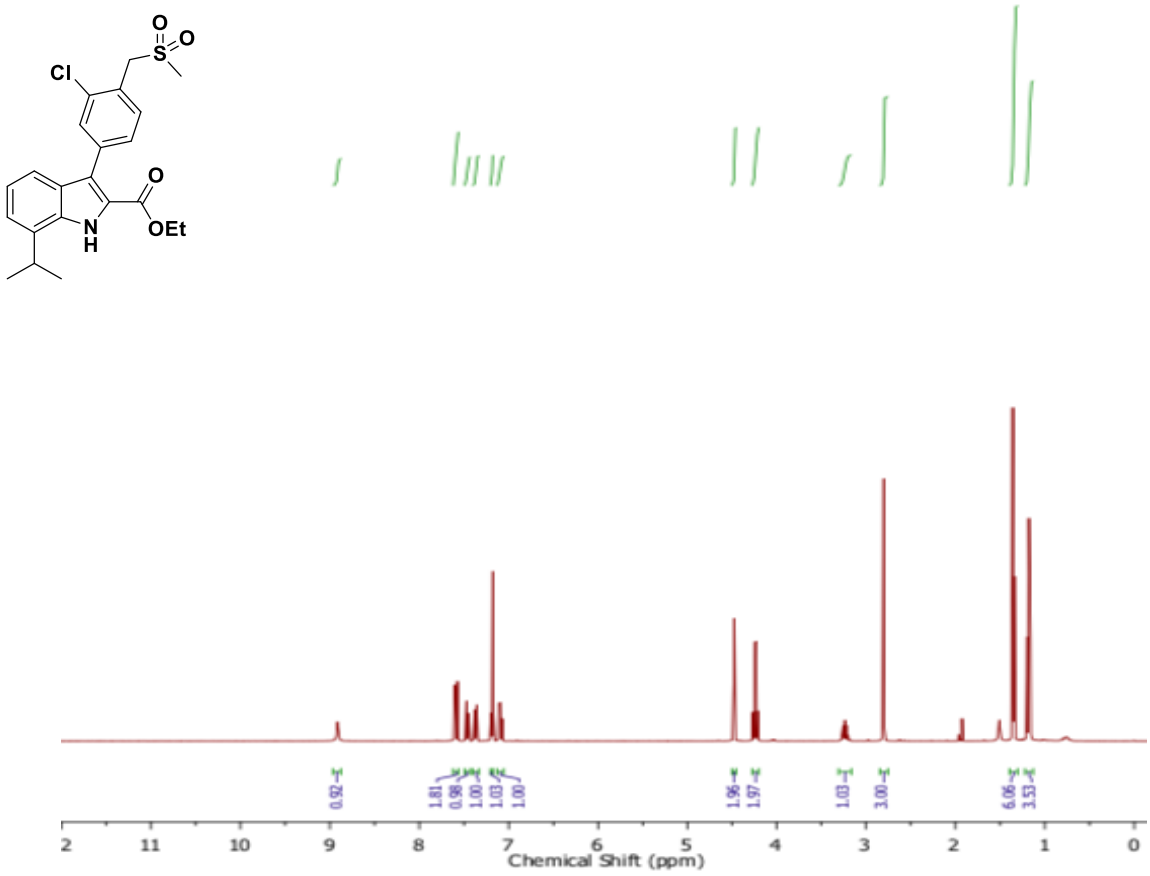
^{1}H NMR of **48** (400 MHz, DMSO-d_6)



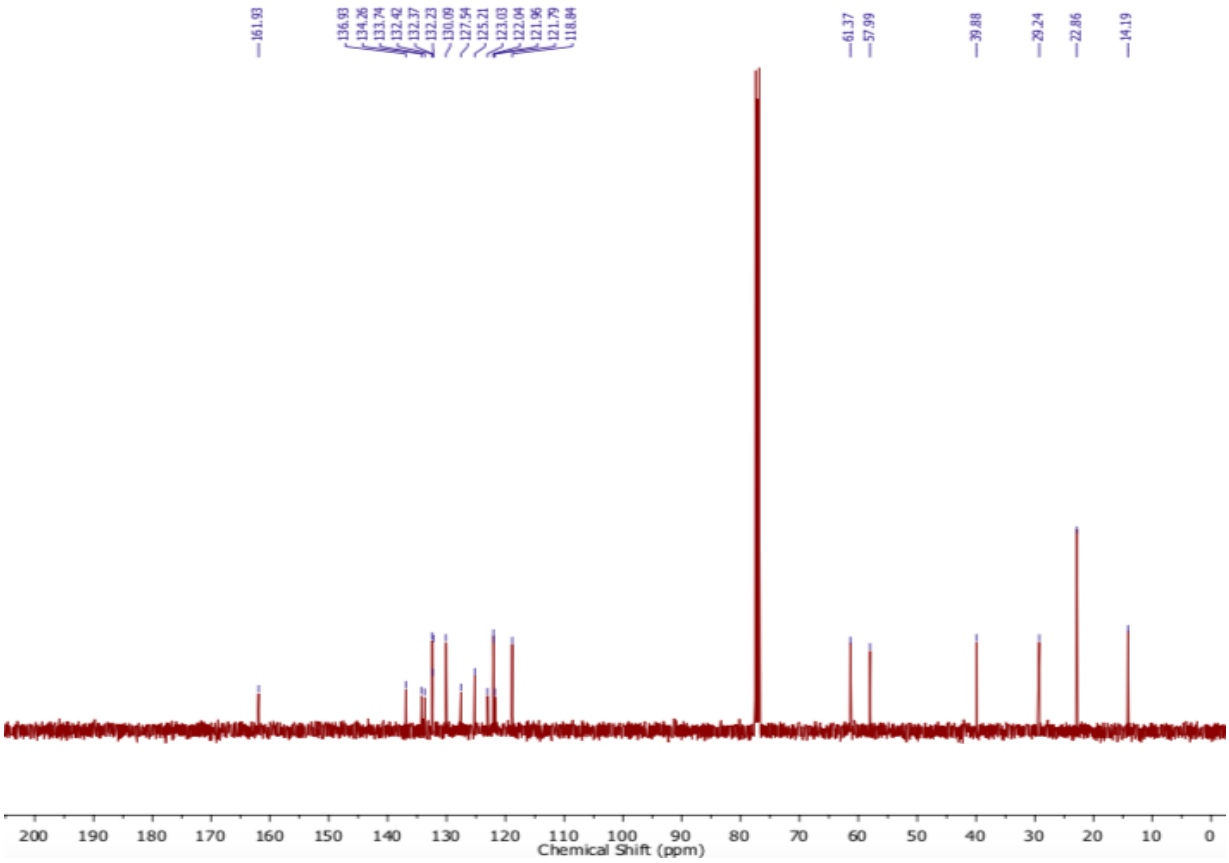
^{13}C NMR of **48** (126 MHz, DMSO-d_6)



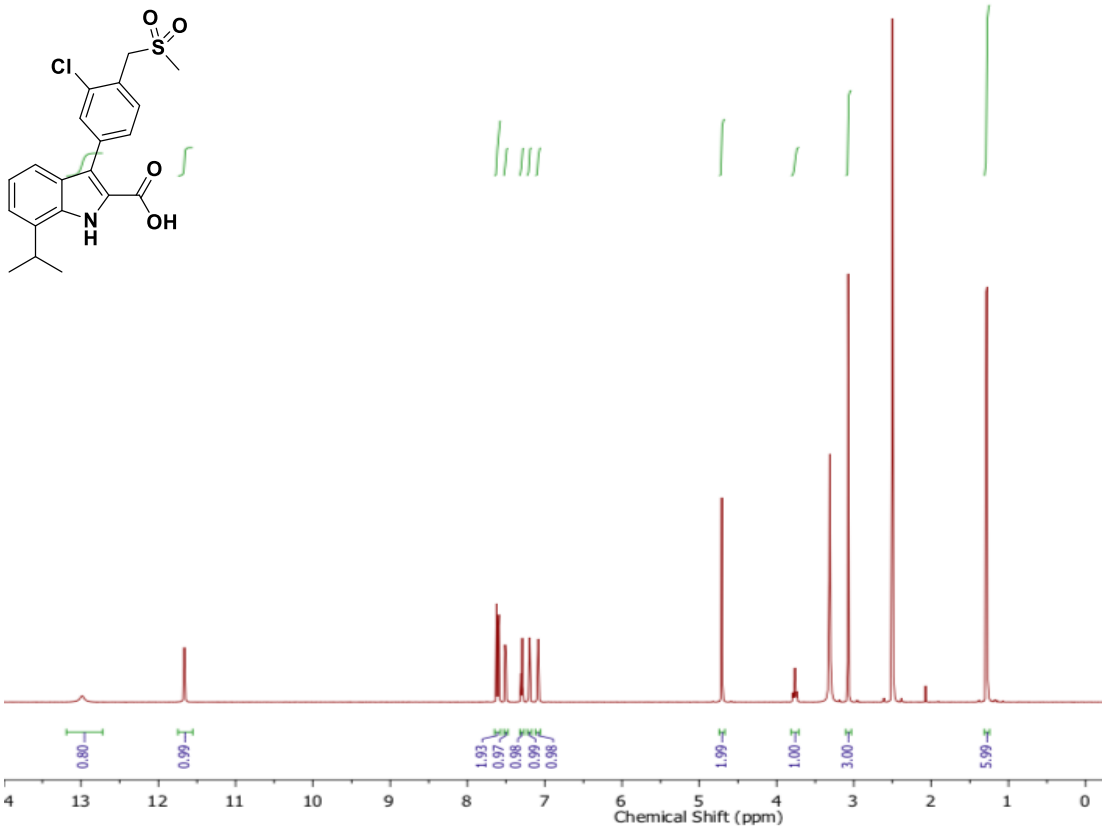
^{1}H NMR of **S52** (400 MHz, $CDCl_3$)



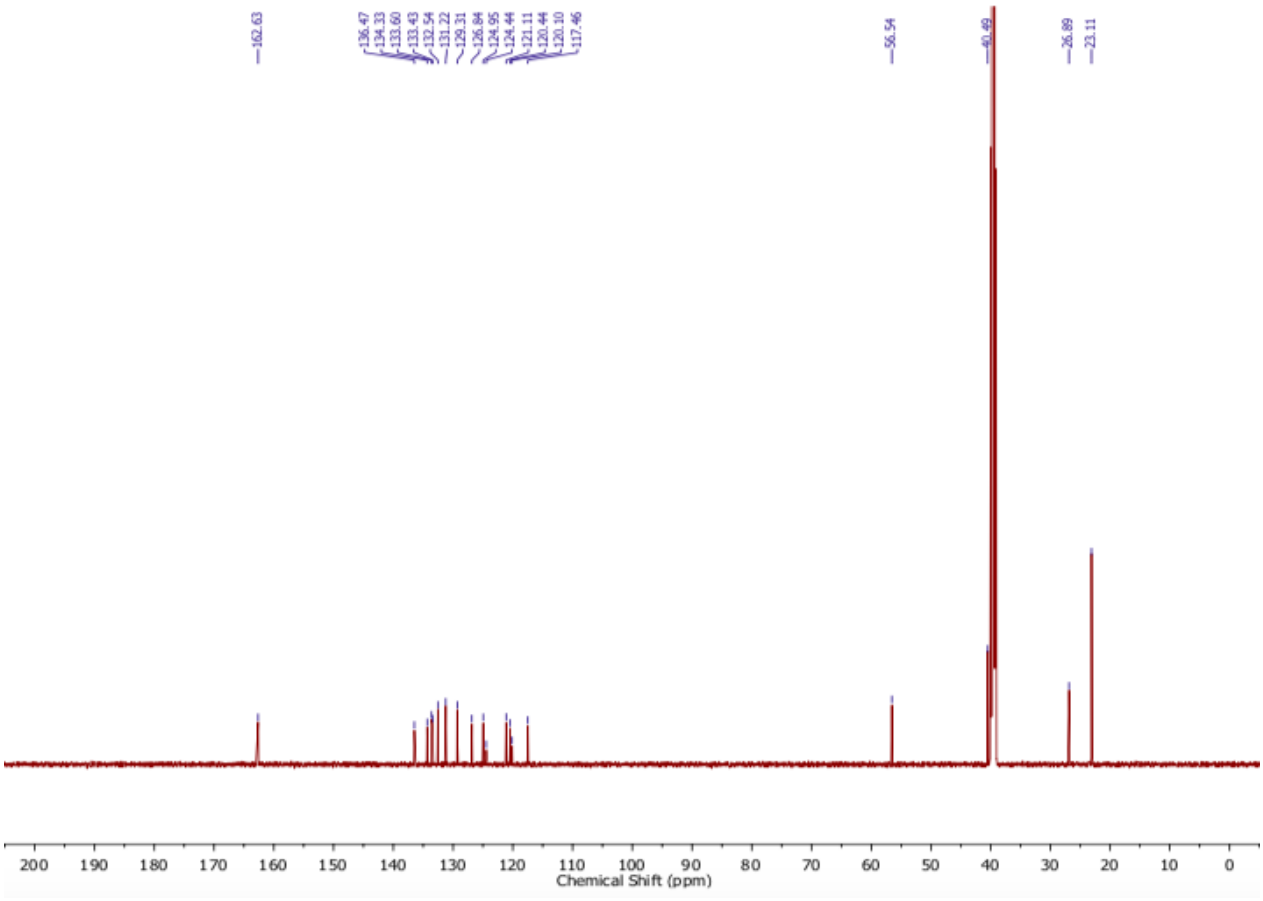
^{13}C NMR of **S52** (101 MHz, $CDCl_3$)



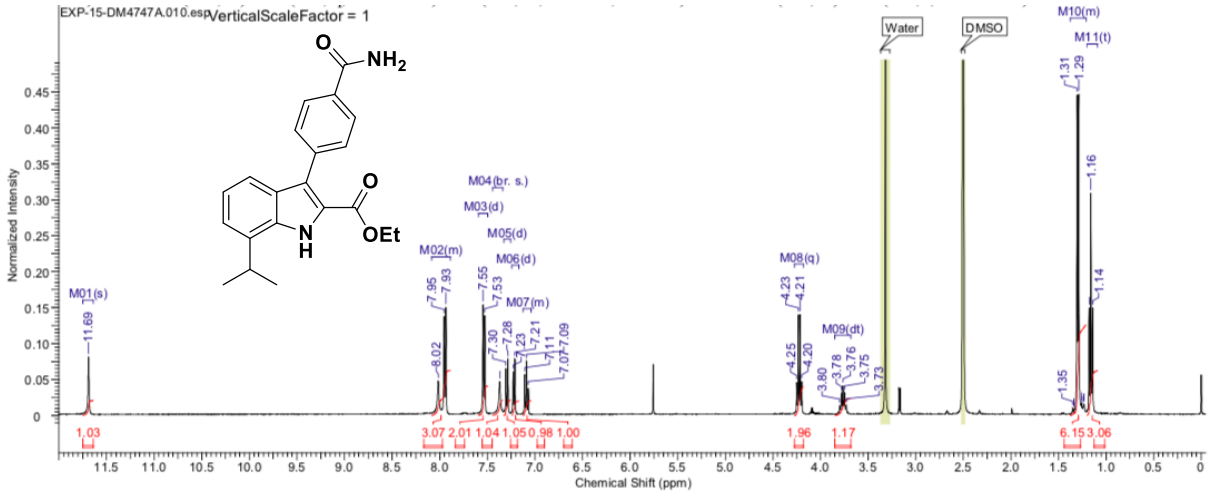
^{1}H NMR of **49** (600 MHz, DMSO-d_6)



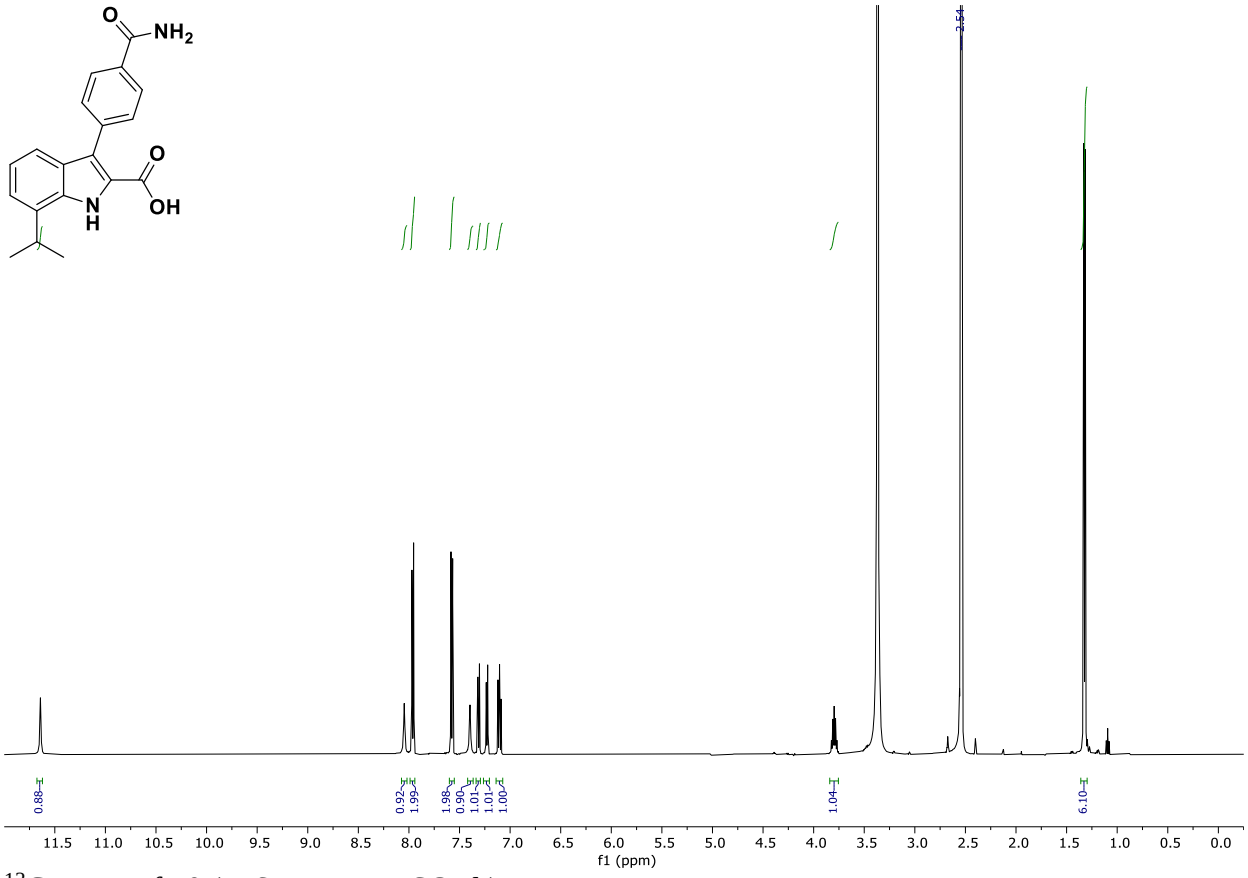
^{13}C NMR of **49** (151 MHz, DMSO-d_6)



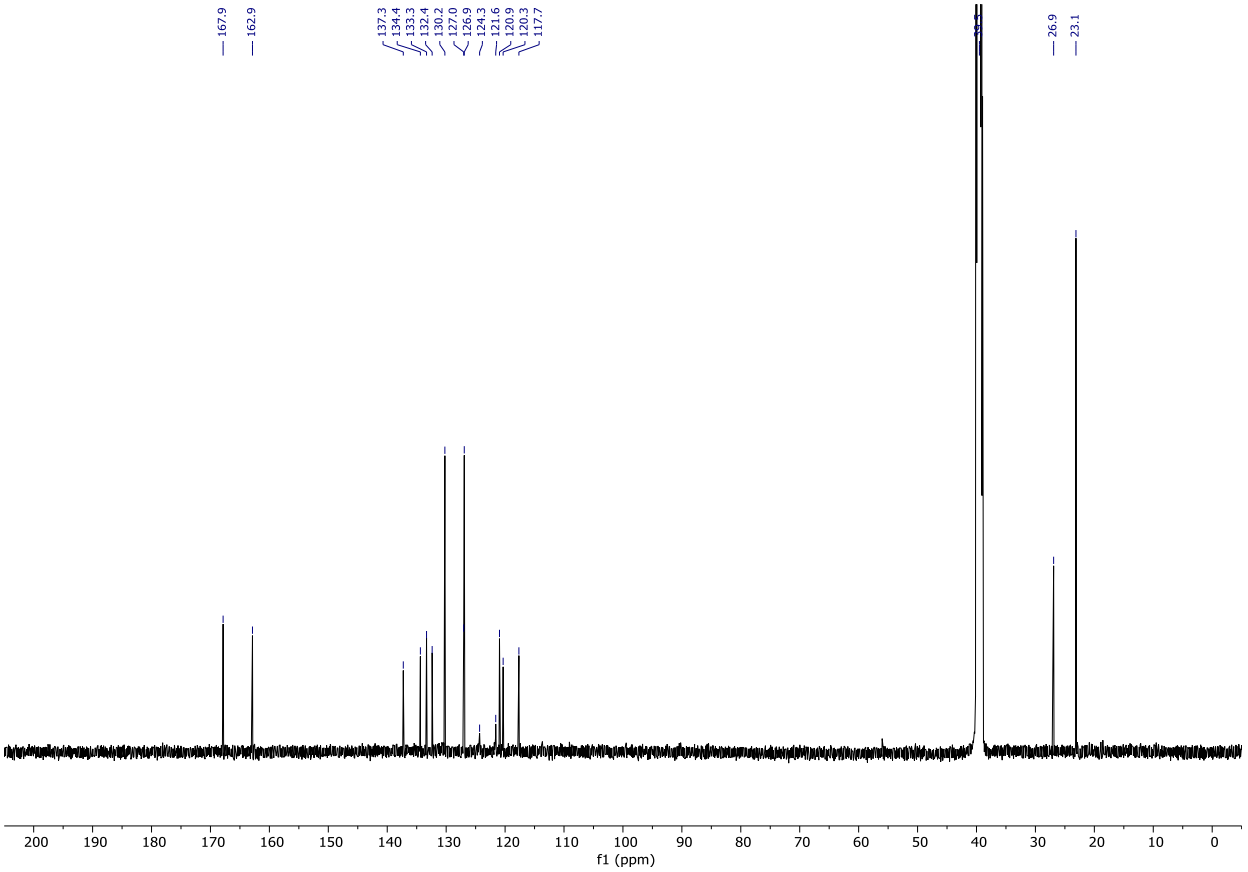
^{1}H NMR of **S53** (400 MHz, DMSO-d_6)



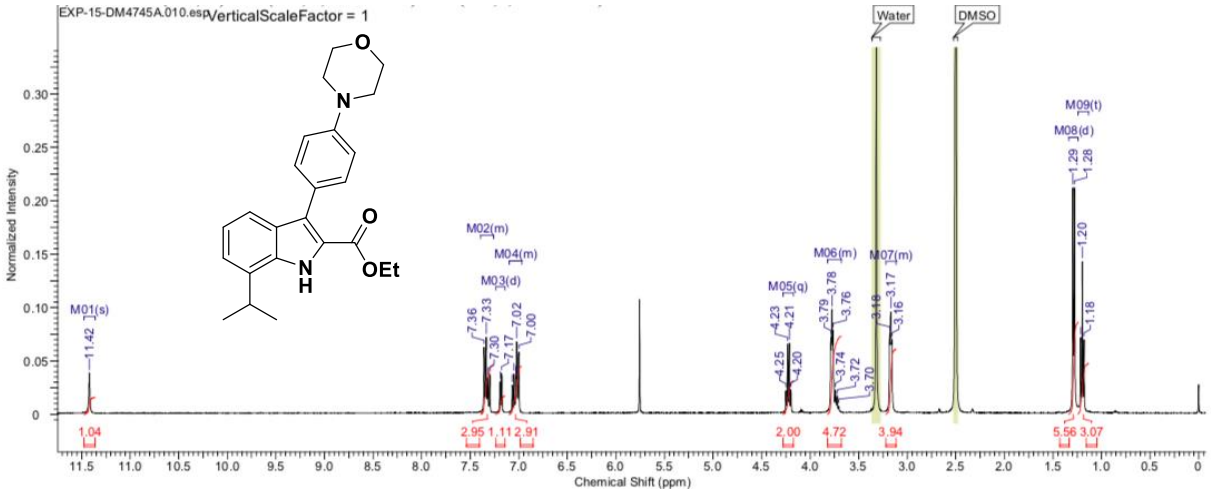
^{1}H NMR of **50** (400 MHz, DMSO-d_6)



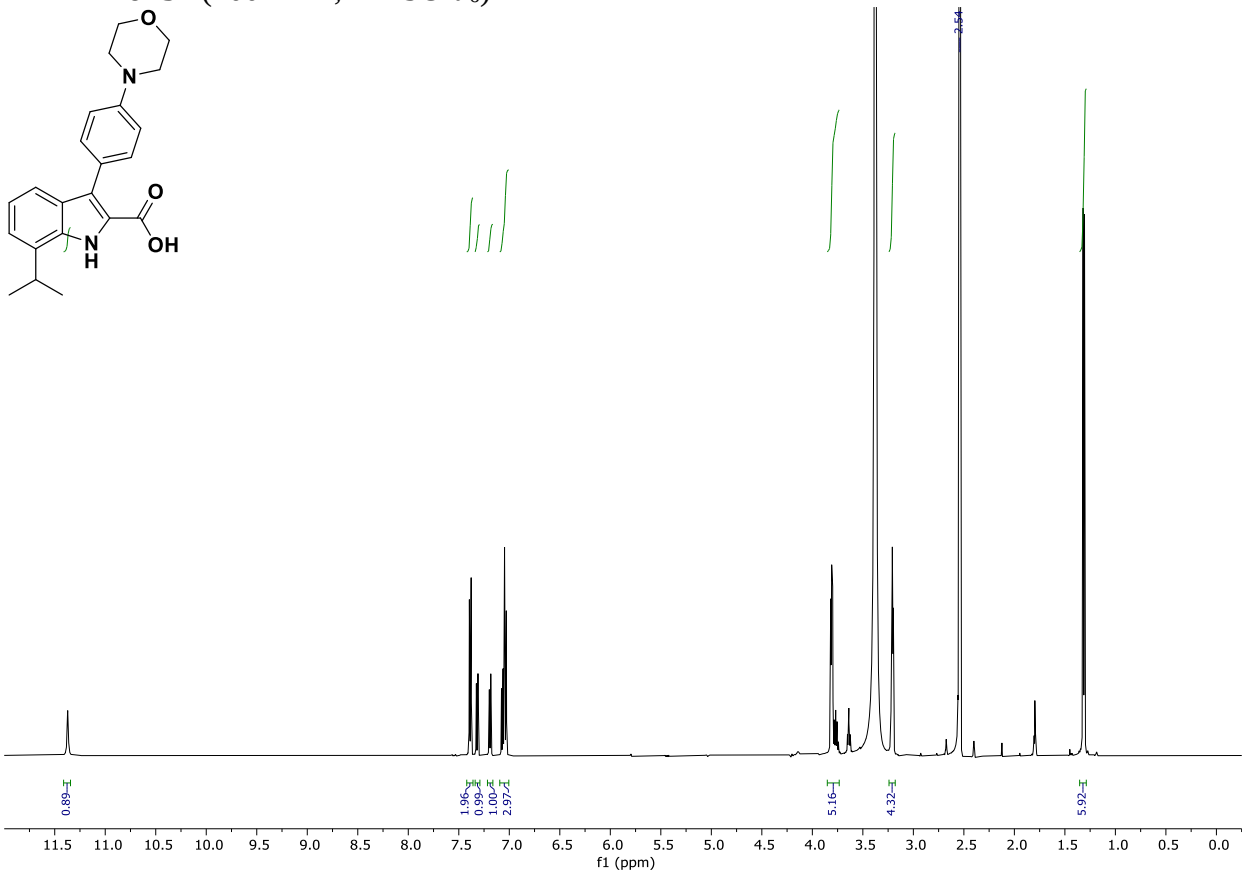
^{13}C NMR of **50** (126 MHz, DMSO-d_6)



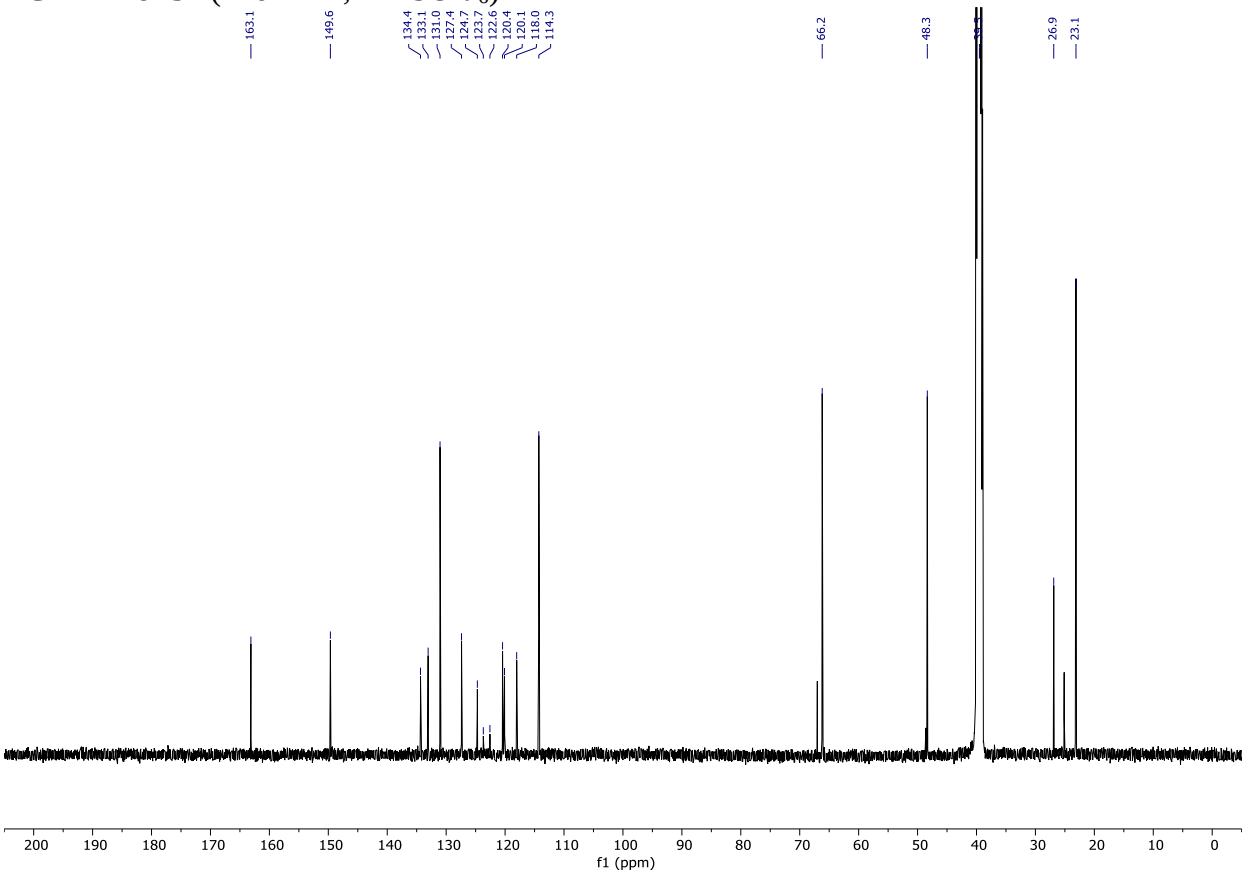
^{1}H NMR of **S54** (400 MHz, DMSO-d_6)



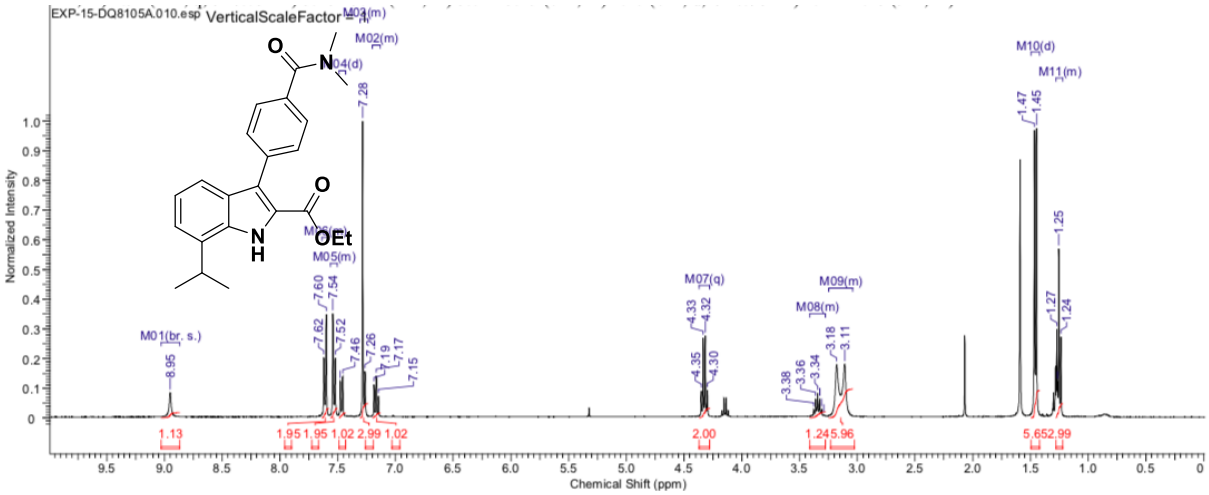
^{1}H NMR of **51** (400 MHz, DMSO-d_6)



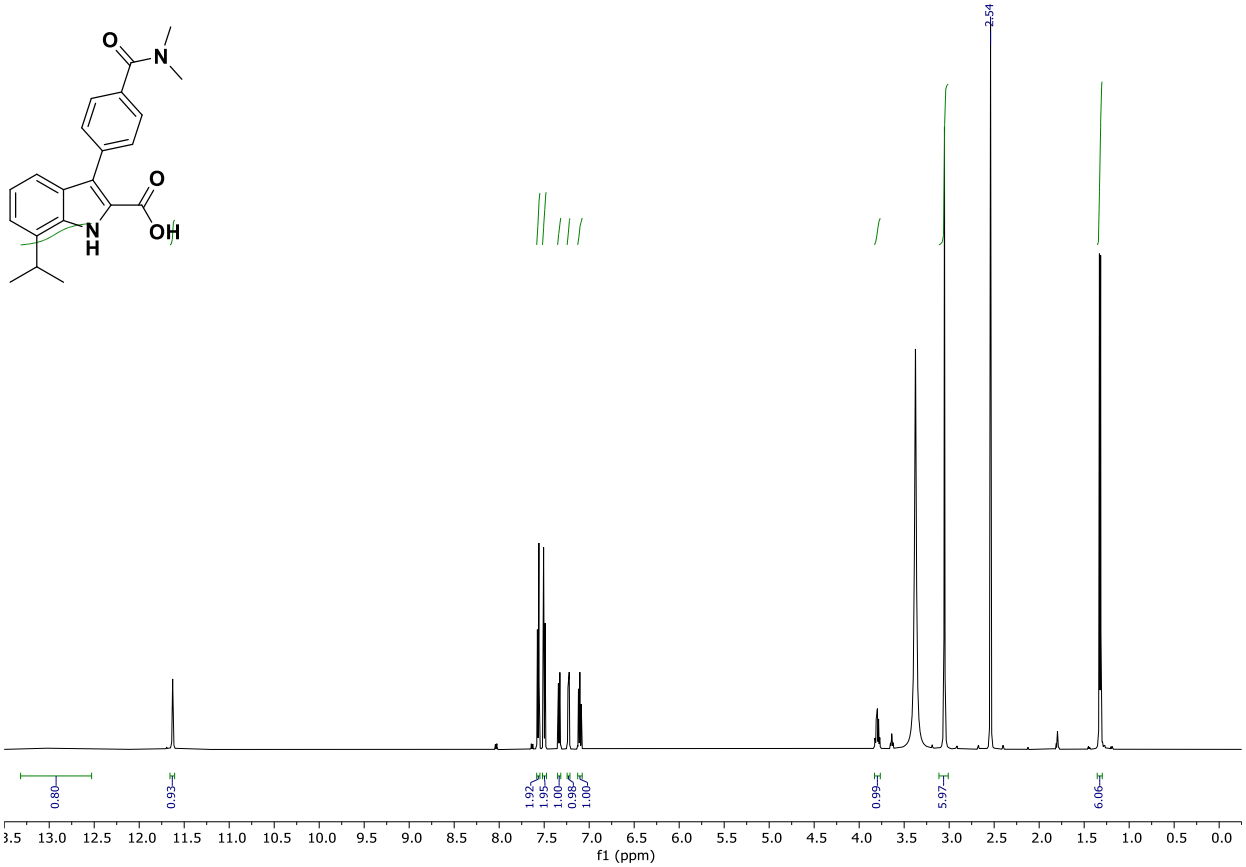
^{13}C NMR of **51** (126 MHz, DMSO-d_6)



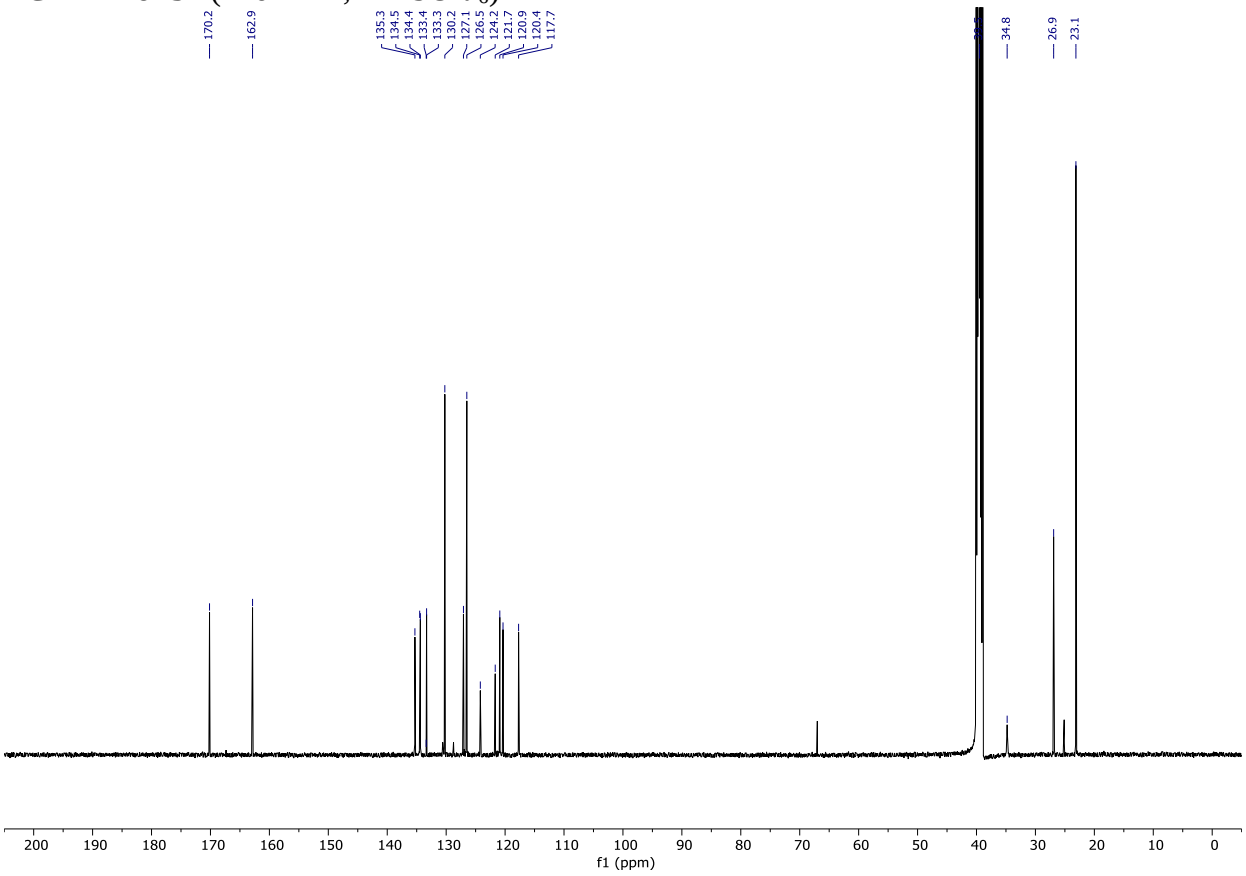
^{1}H NMR of **S55** (400 MHz, $CDCl_3$)



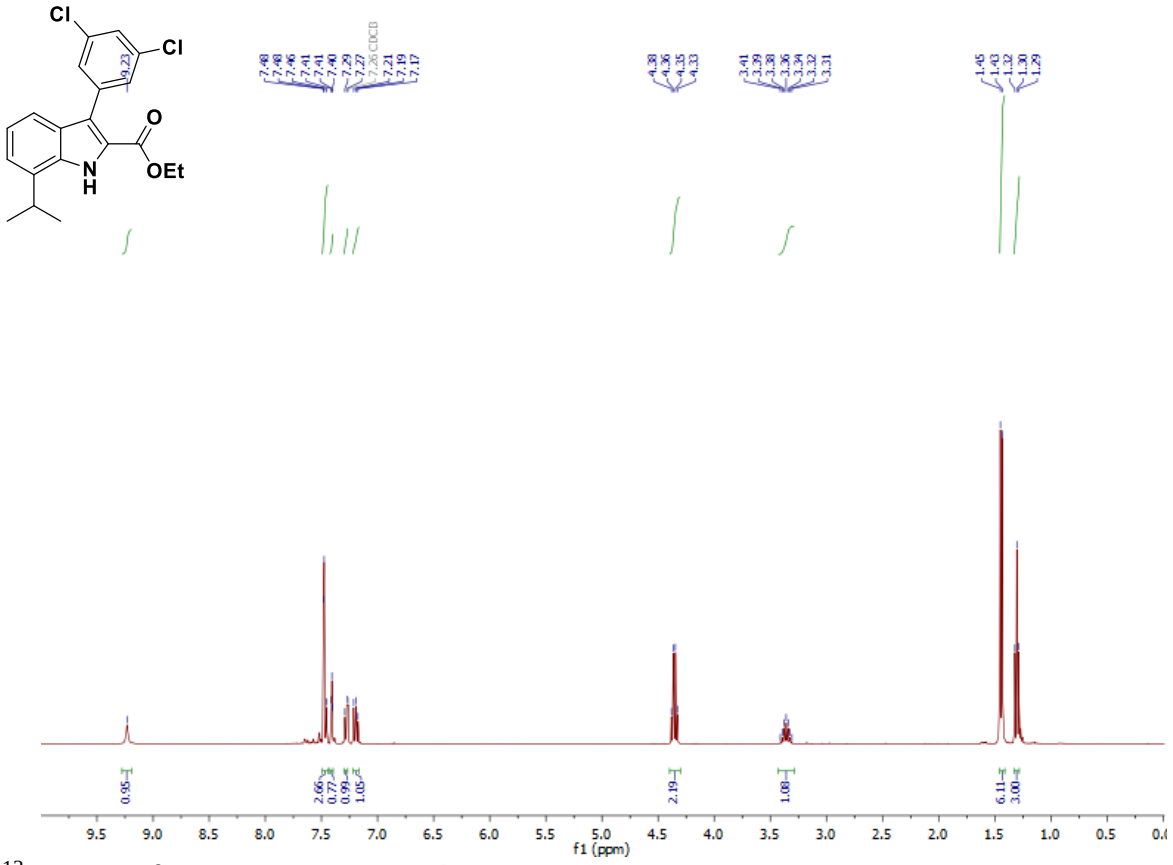
^{1}H NMR of **52** (400 MHz, DMSO-d_6)



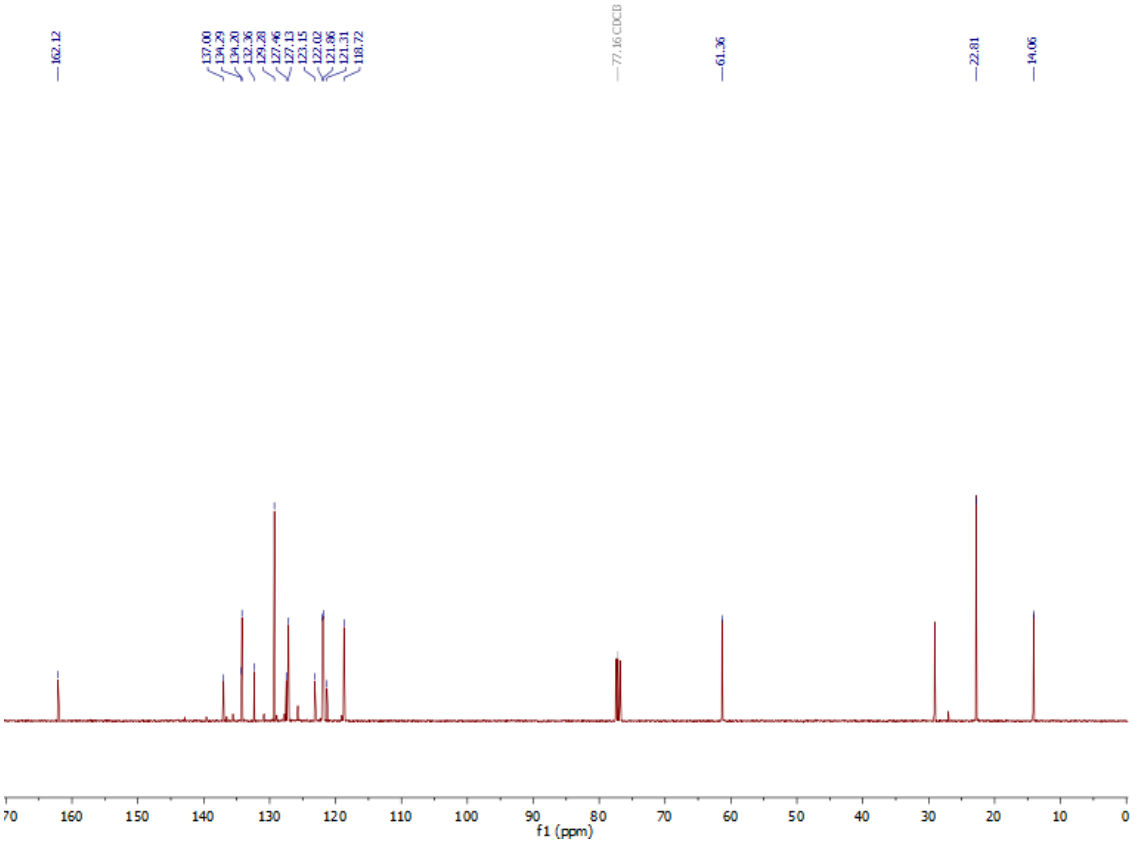
^{13}C NMR of **52** (126 MHz, DMSO-d_6)



^{1}H NMR of **S56** (400 MHz, $CDCl_3$)

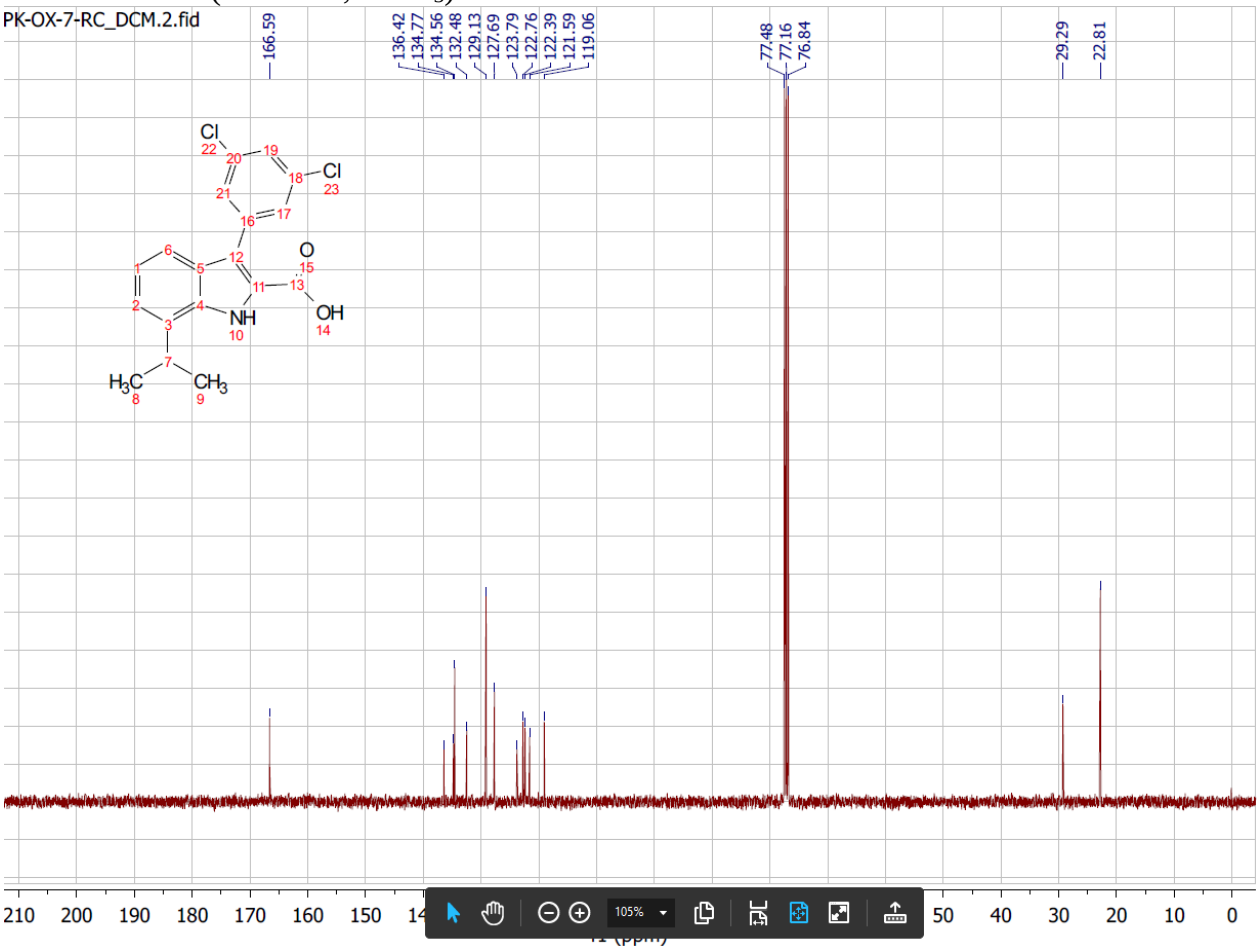


^{13}C NMR of **S56** (101 MHz, $CDCl_3$)

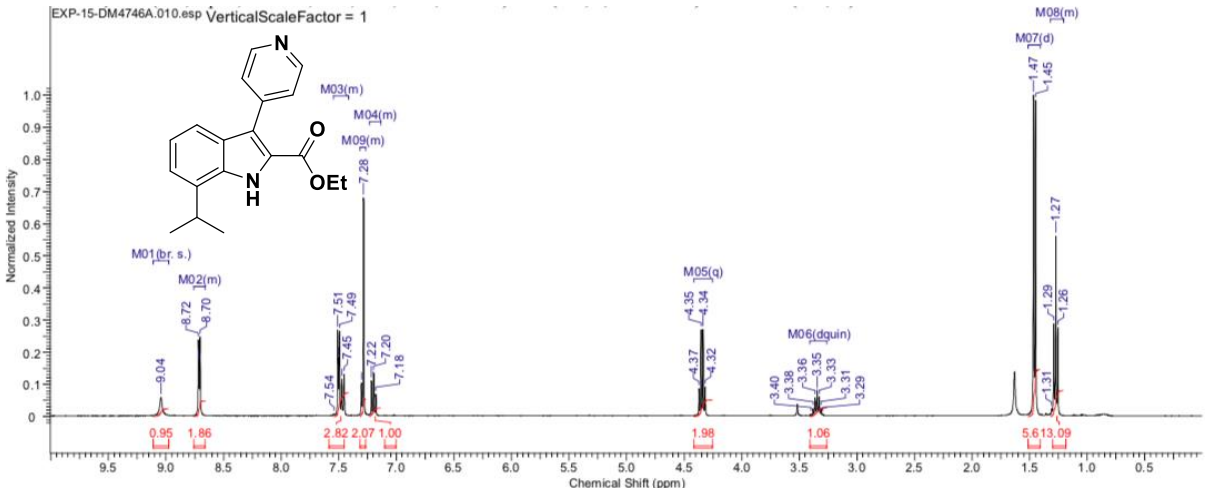


^{1}H NMR of **53** (400 MHz, $CDCl_3$)

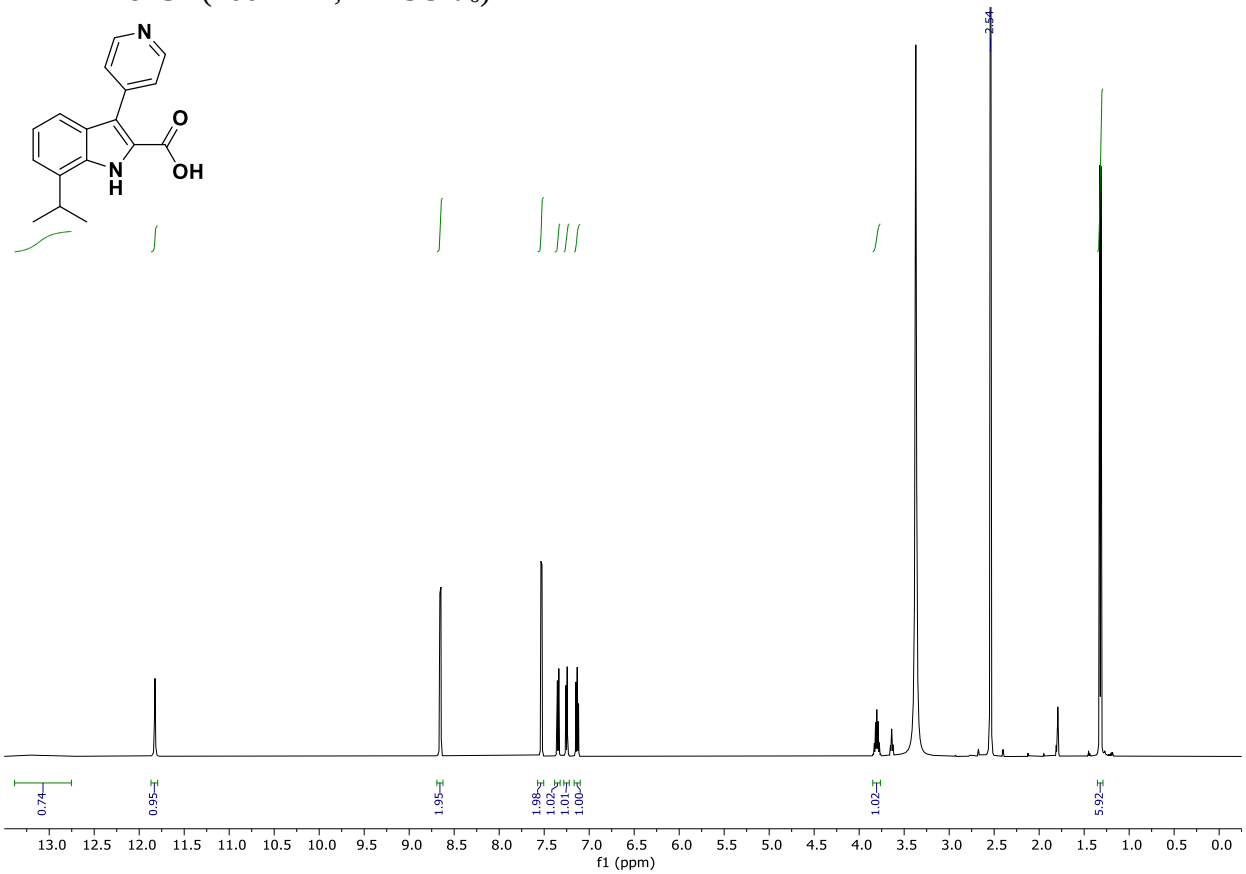
^{13}C NMR of **53** (126 MHz, $CDCl_3$)



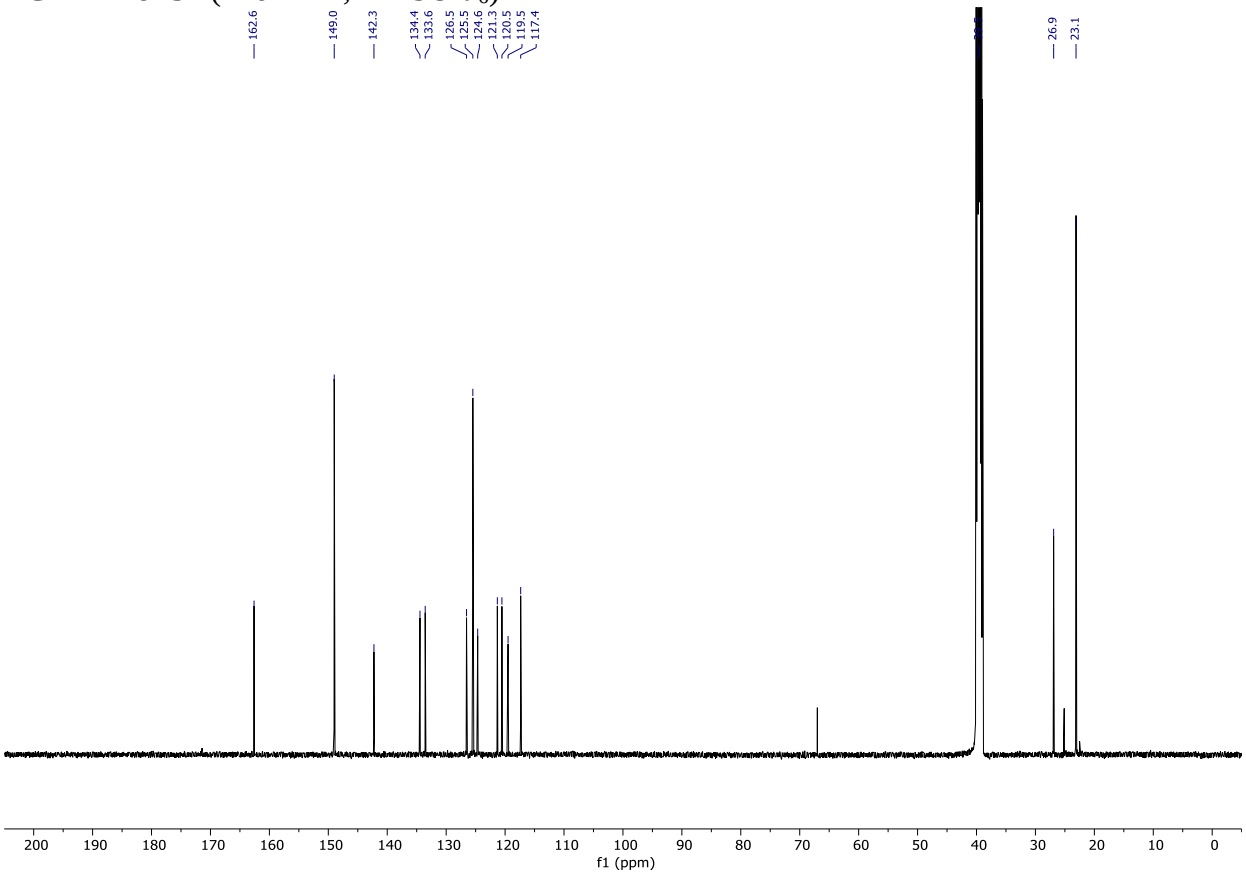
^{1}H NMR of **S57** (400 MHz, $CDCl_3$)



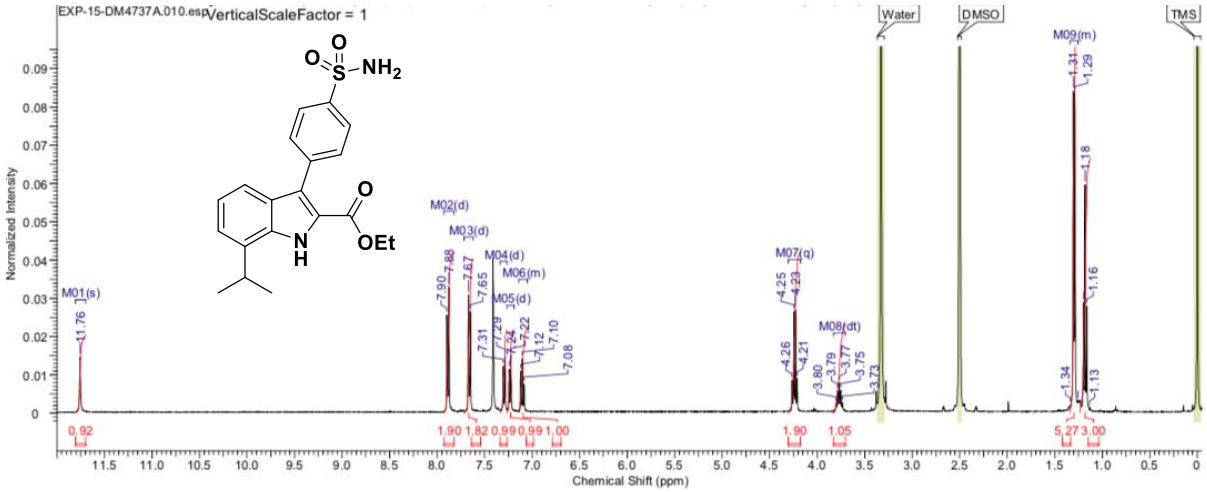
^{1}H NMR of **54** (400 MHz, DMSO-d_6)



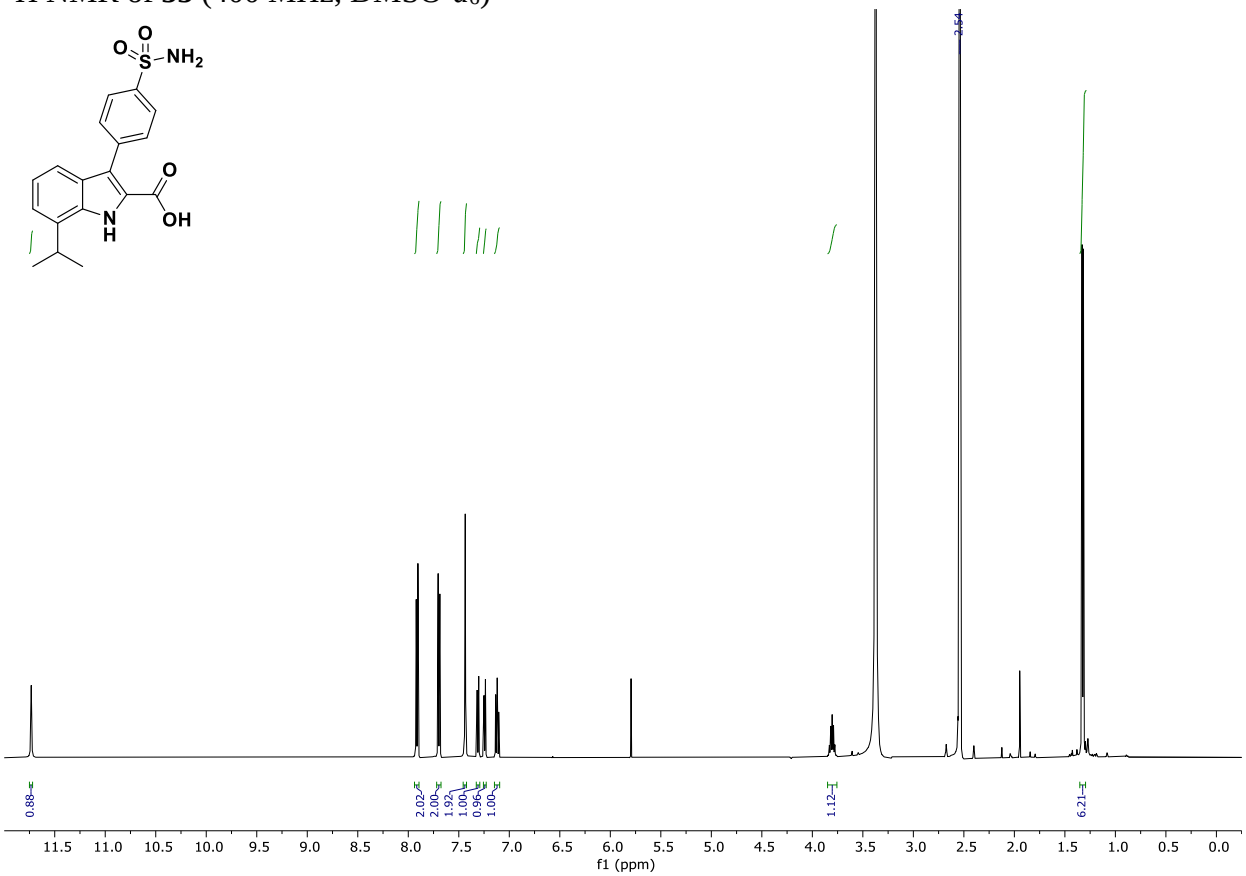
^{13}C NMR of **54** (126 MHz, DMSO-d_6)



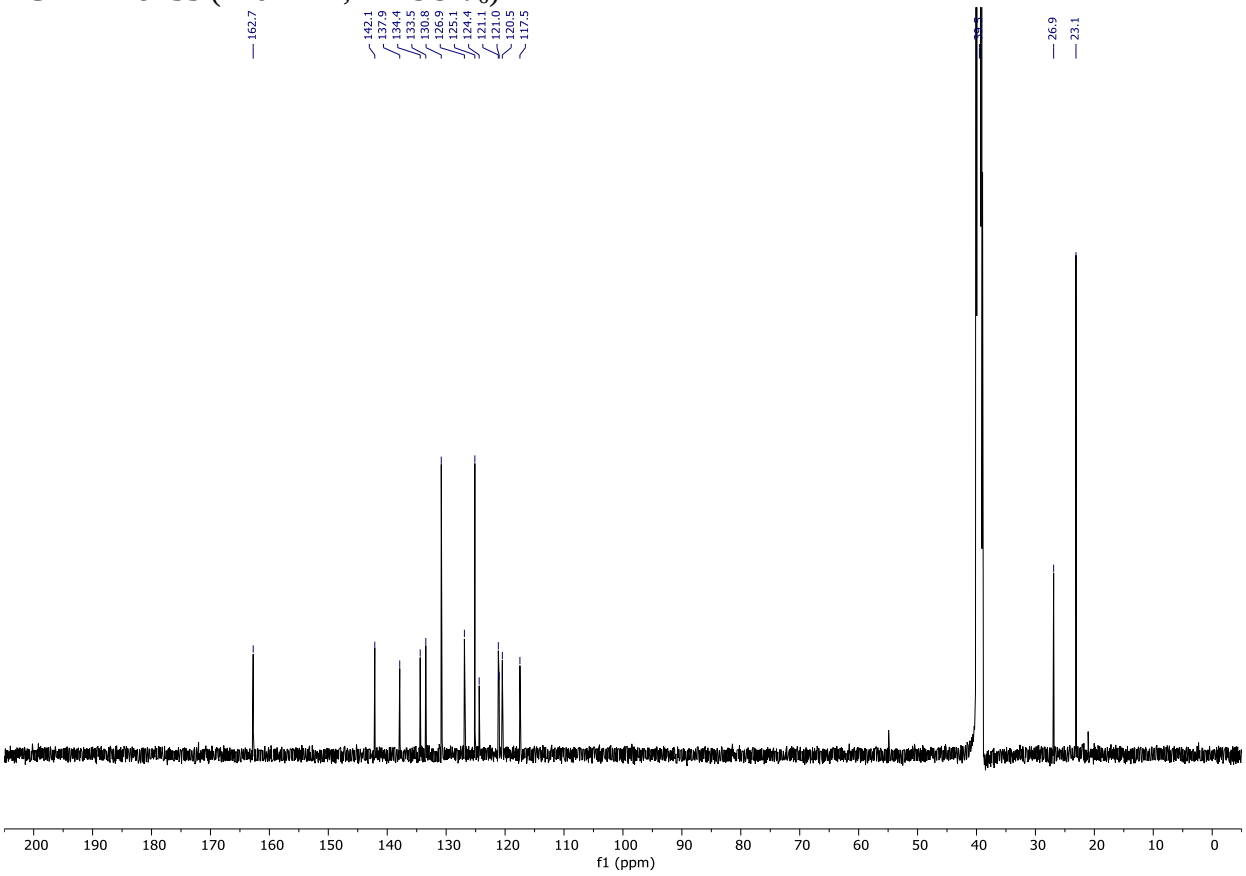
^{1}H NMR of **S58** (400 MHz, DMSO-d_6)



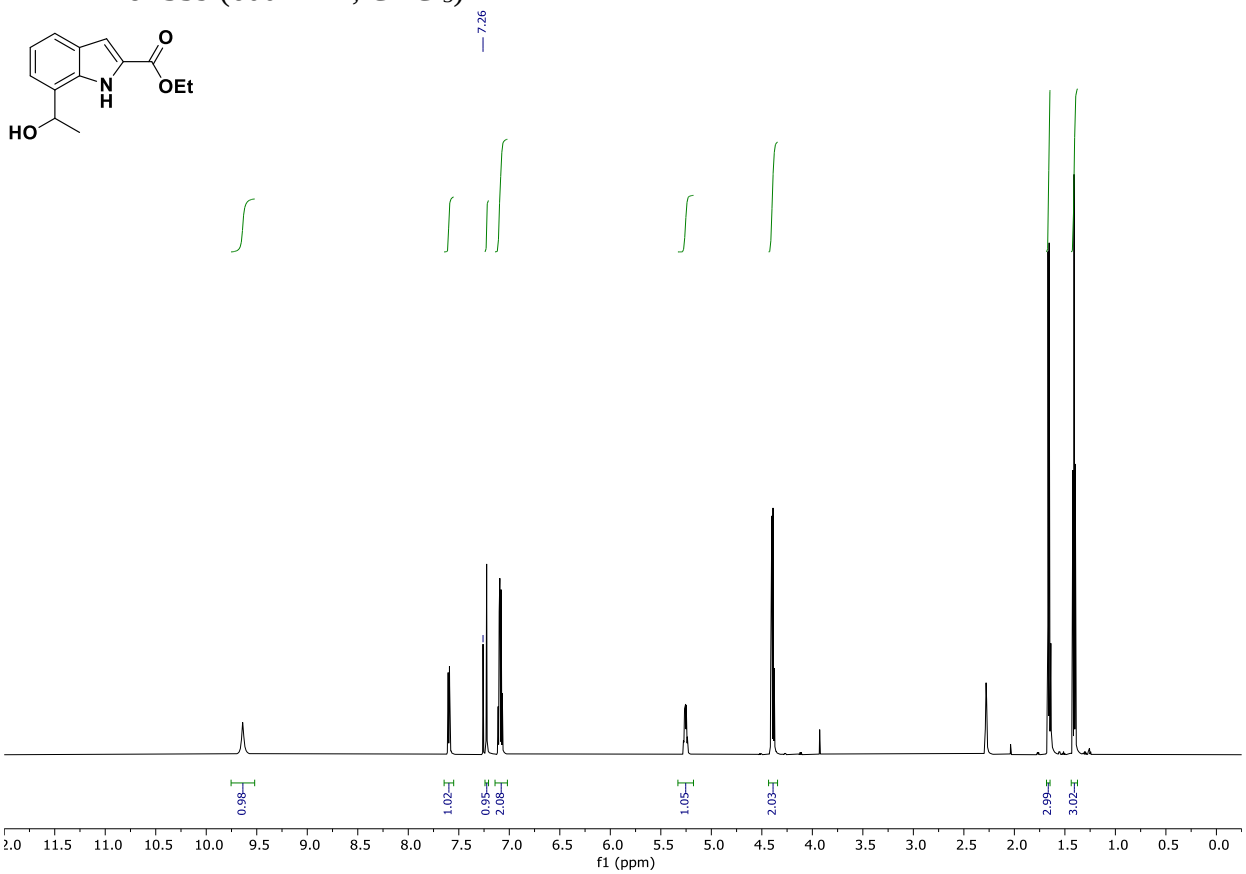
^{1}H NMR of **55** (400 MHz, DMSO-d_6)



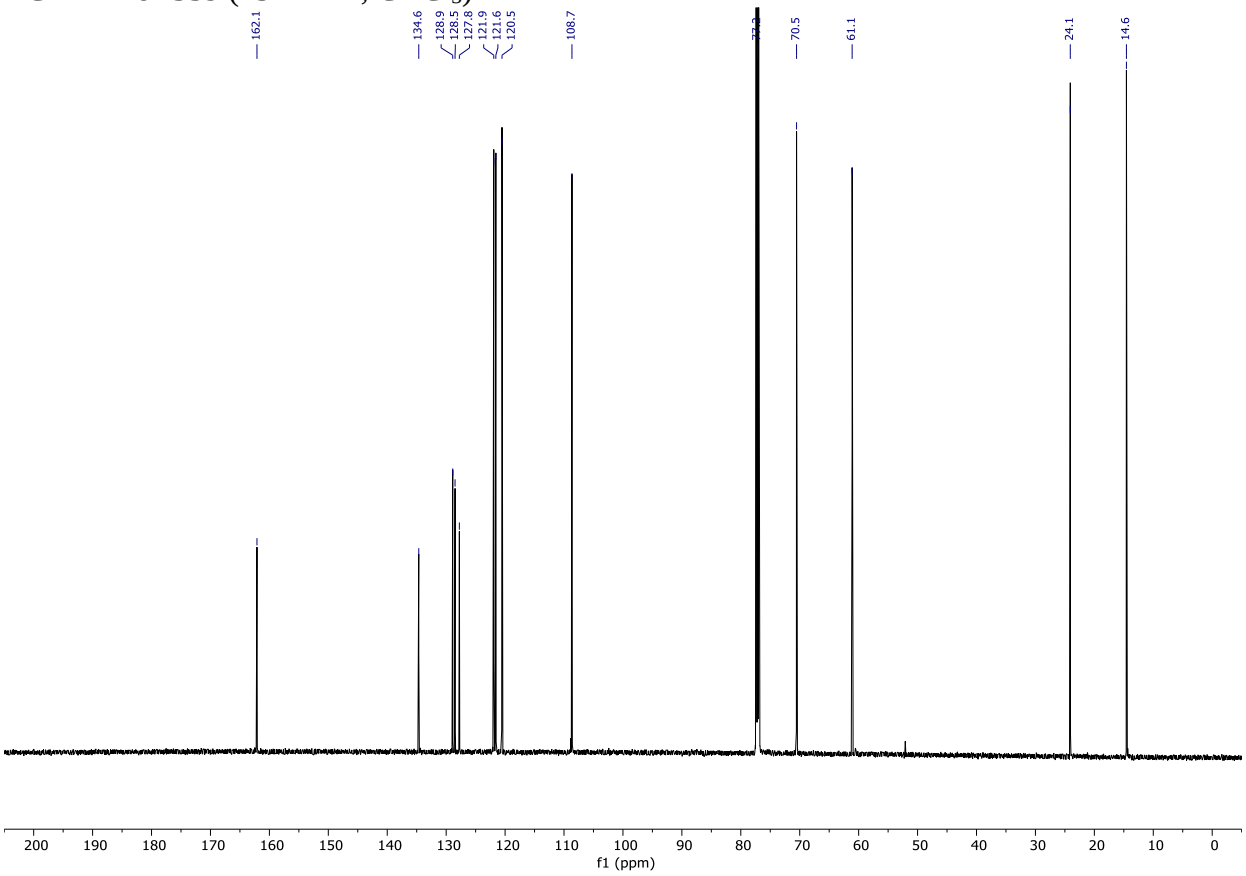
^{13}C NMR of **55** (126 MHz, DMSO-d_6)



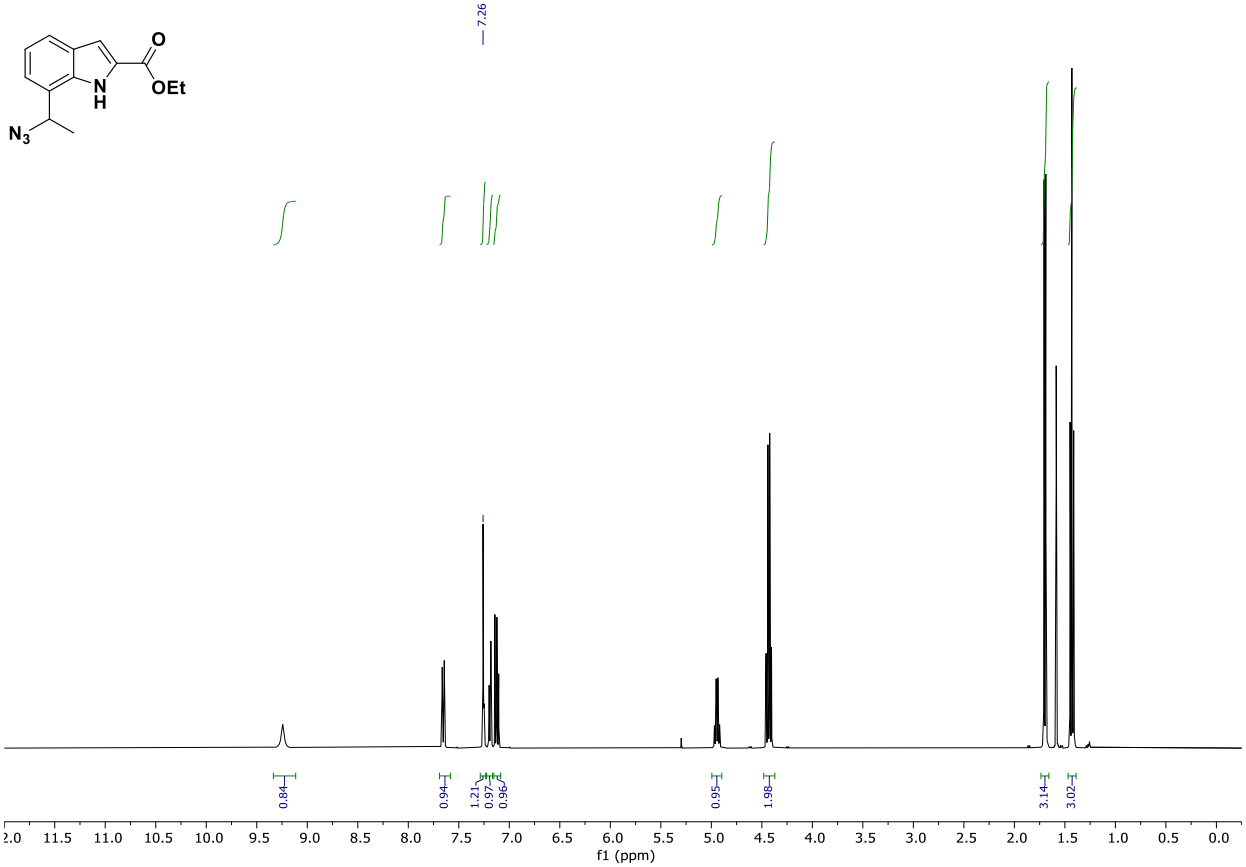
^{1}H NMR of **S59** (600 MHz, $CDCl_3$)



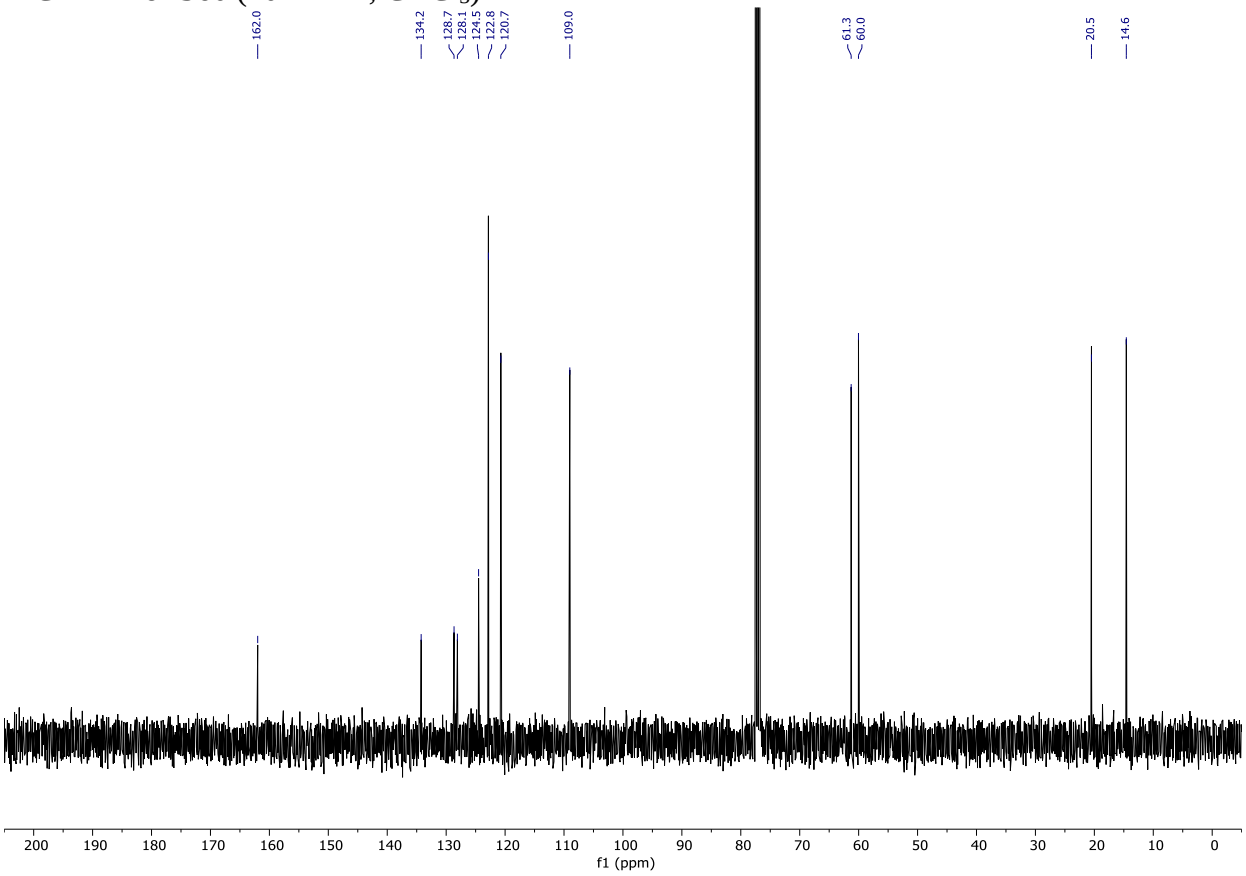
^{13}C NMR of **S59** (151 MHz, $CDCl_3$)



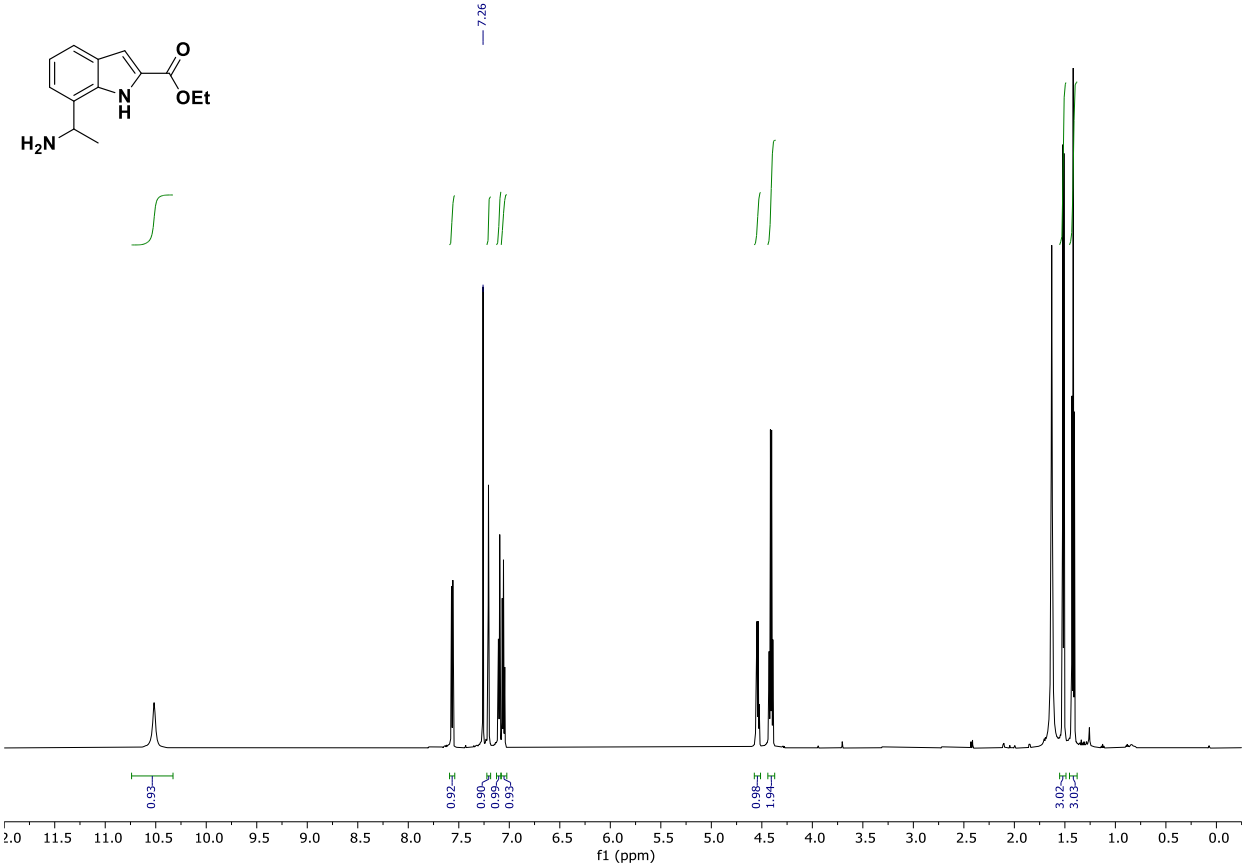
^{1}H NMR of **S60** (400 MHz, $CDCl_3$)



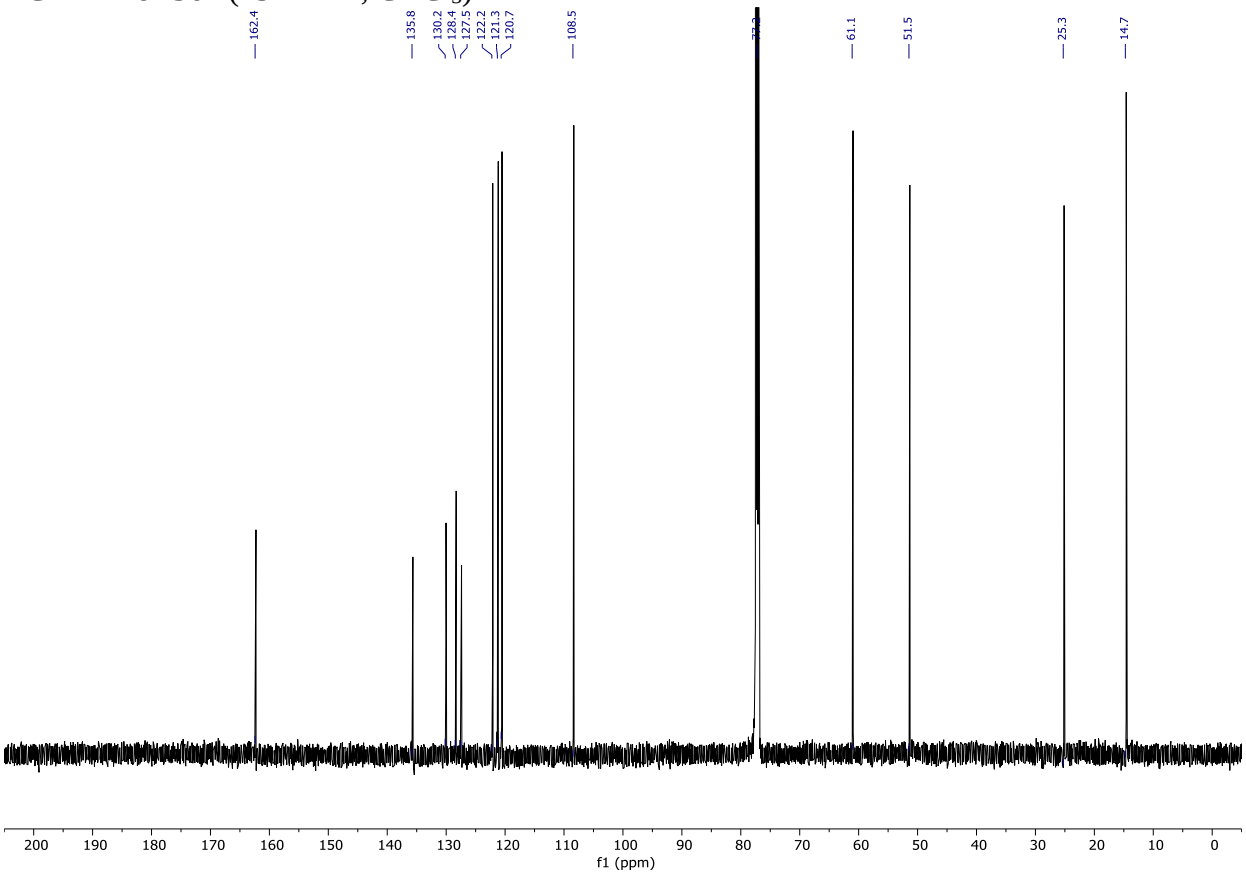
^{13}C NMR of **S60** (101 MHz, $CDCl_3$)



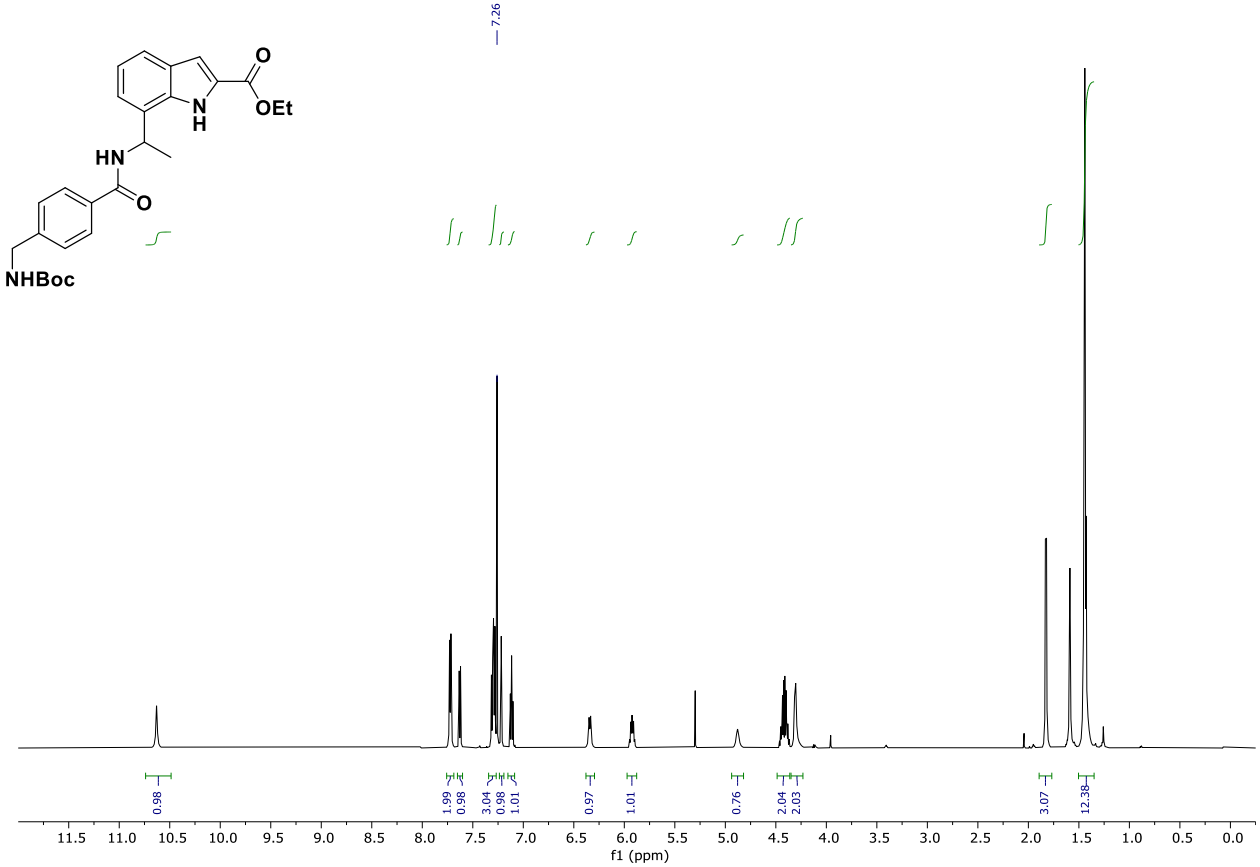
^{1}H NMR of **S61** (600 MHz, $CDCl_3$)



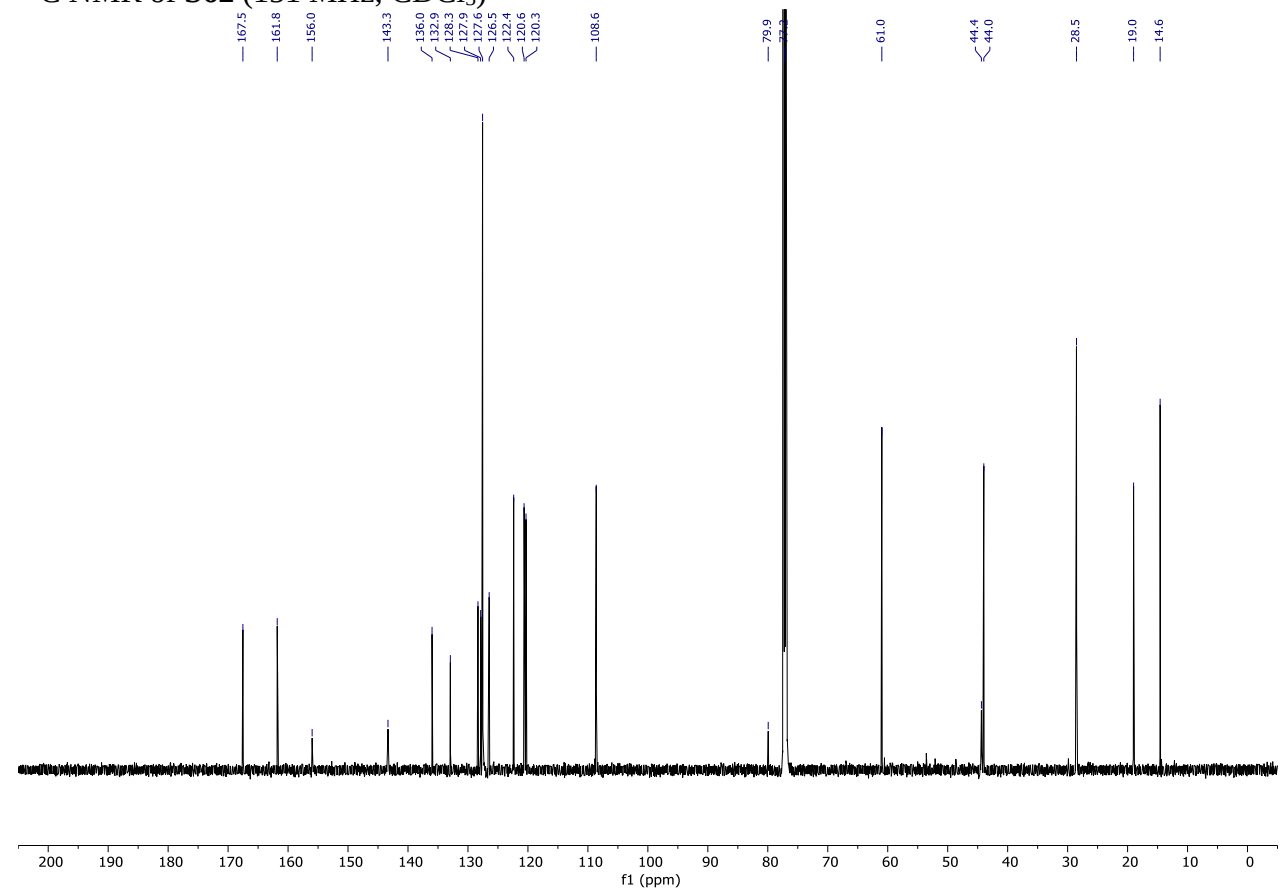
^{13}C NMR of **S61** (151 MHz, $CDCl_3$)



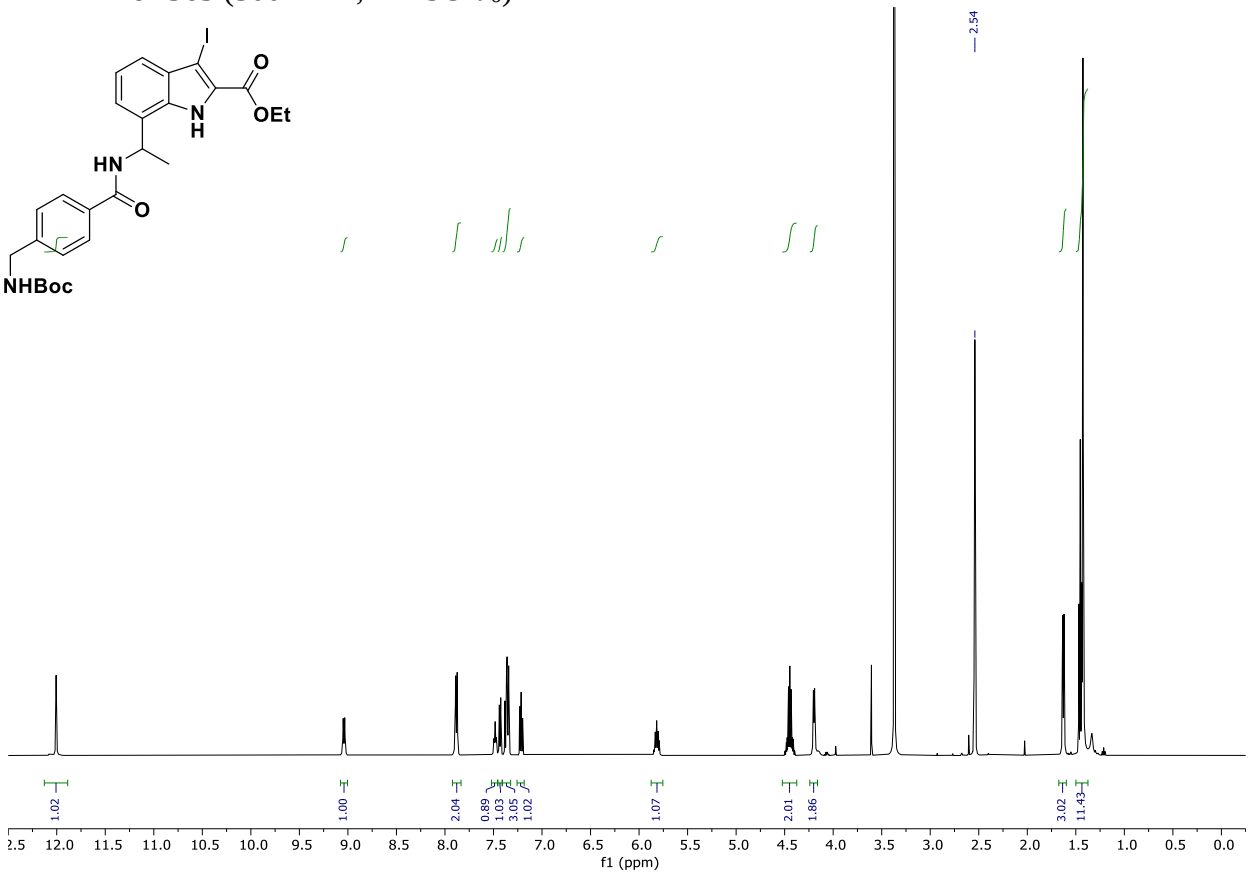
^{1}H NMR of **S62** (600 MHz, $CDCl_3$)



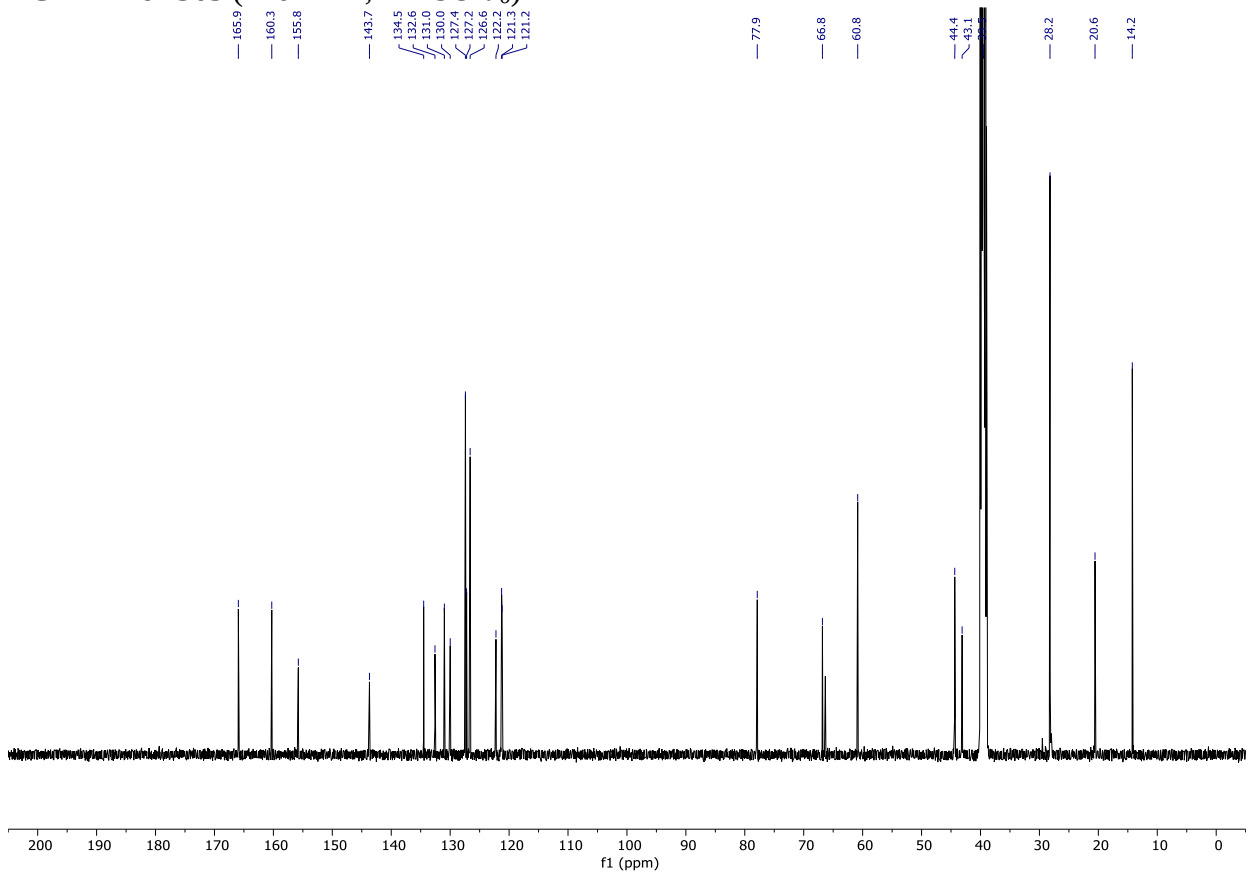
^{13}C NMR of **S62** (151 MHz, $CDCl_3$)



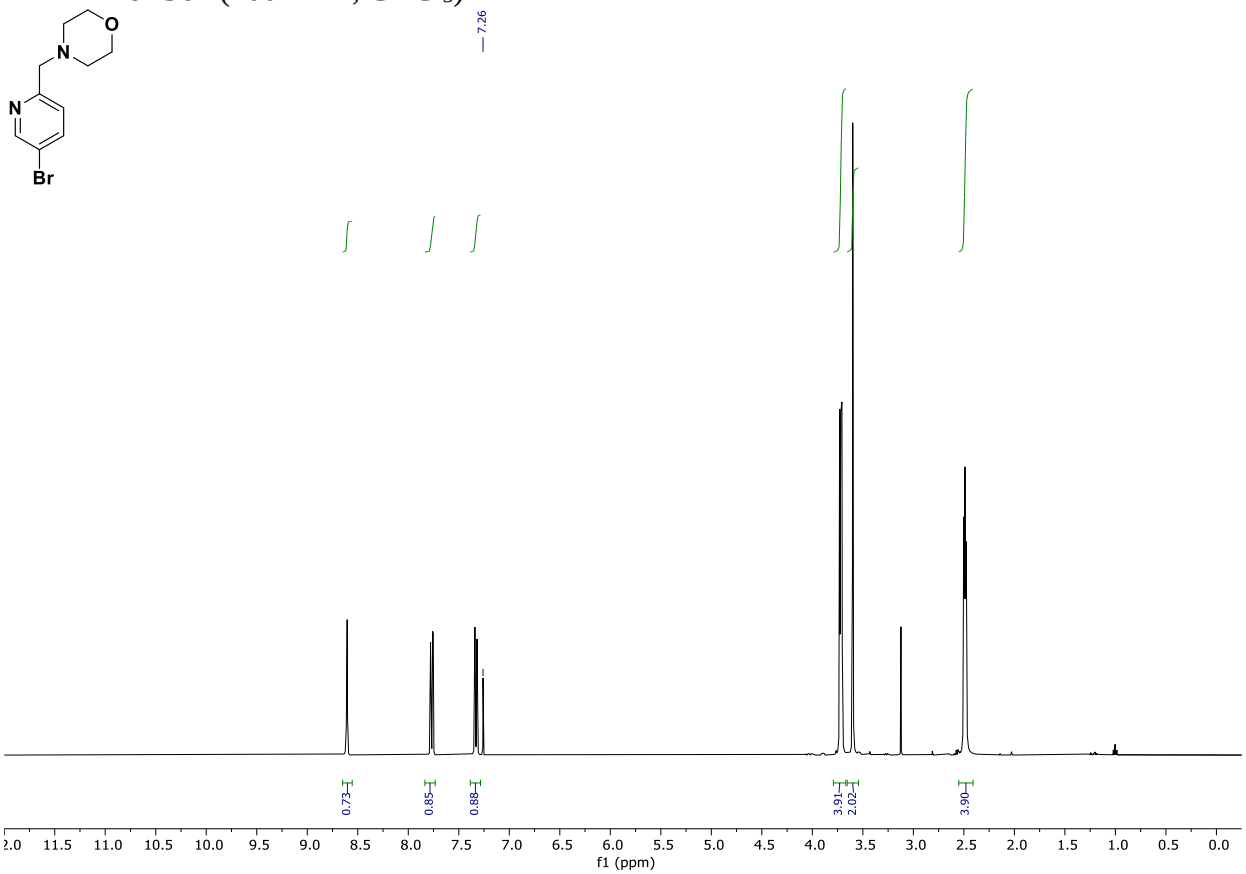
^{1}H NMR of **S63** (500 MHz, DMSO-d_6)



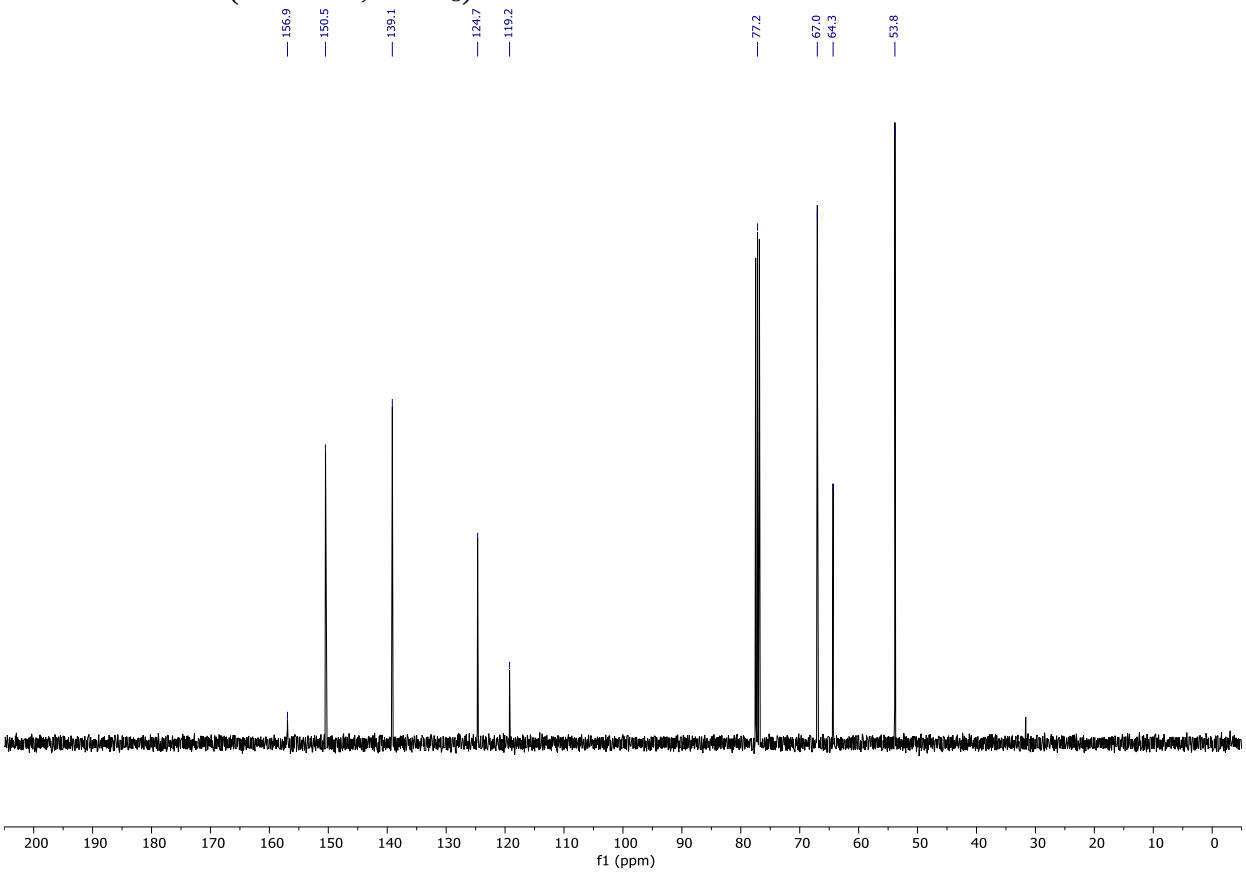
^{13}C NMR of **S63** (126 MHz, DMSO-d_6)



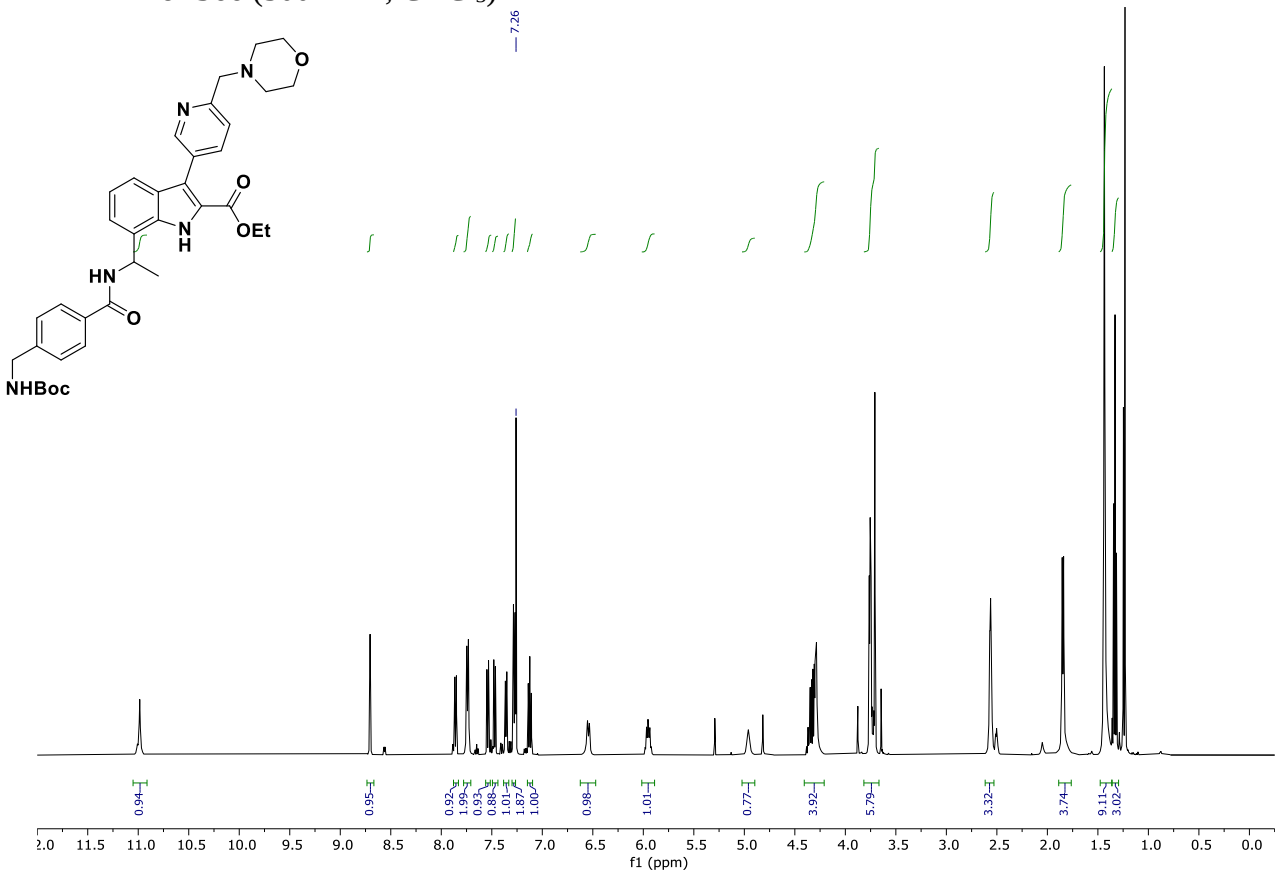
^{1}H NMR of **S64** (400 MHz, $CDCl_3$)



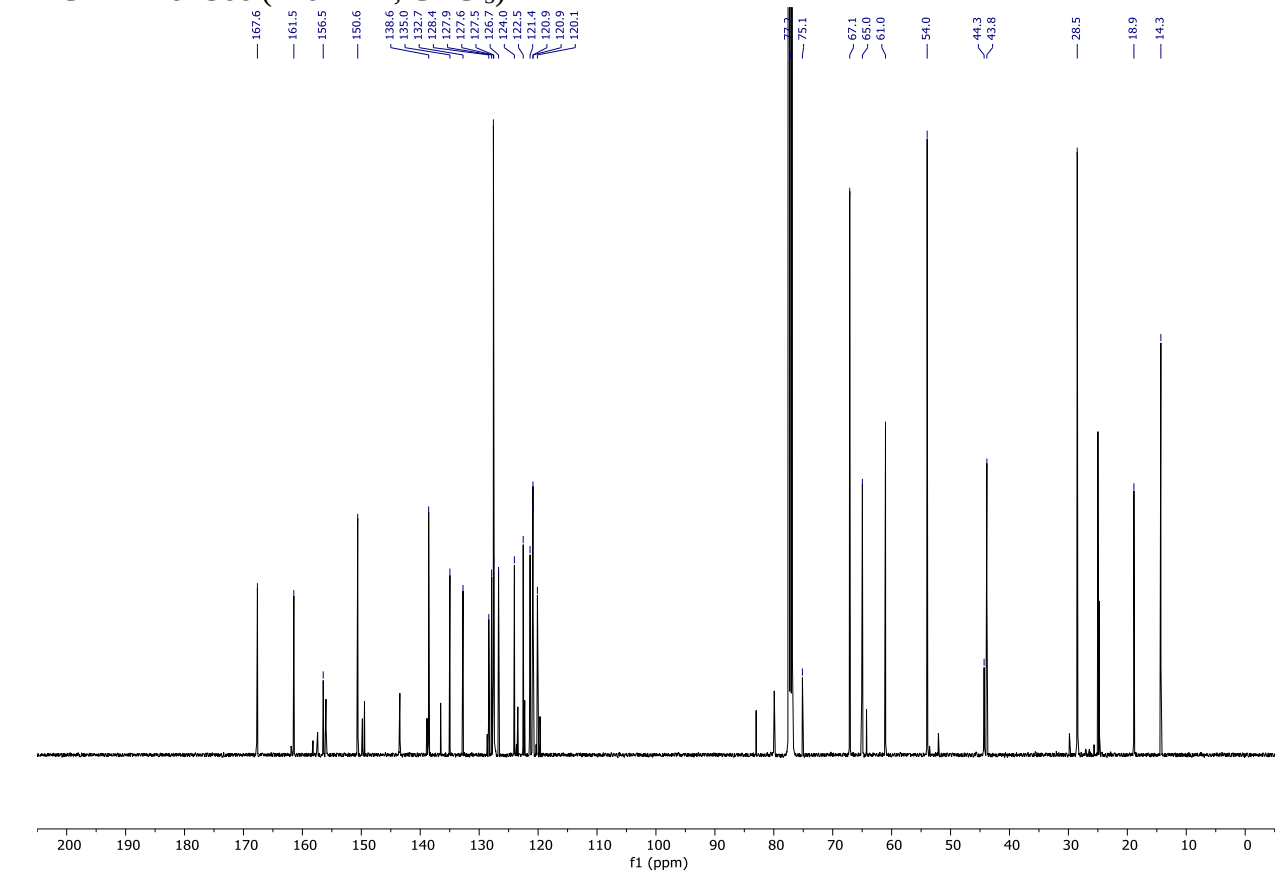
^{13}C NMR of **S64** (101 MHz, $CDCl_3$)



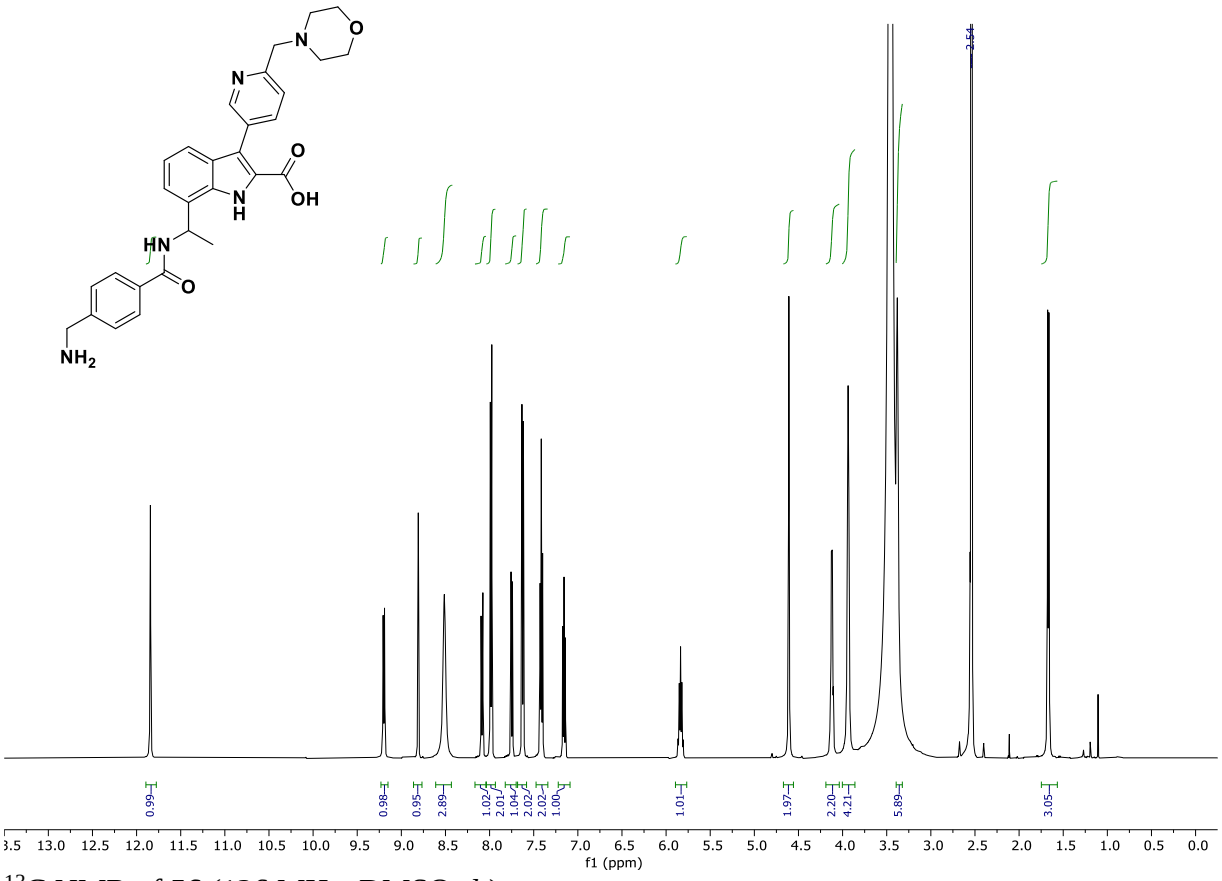
^{1}H NMR of **S66** (500 MHz, $CDCl_3$)



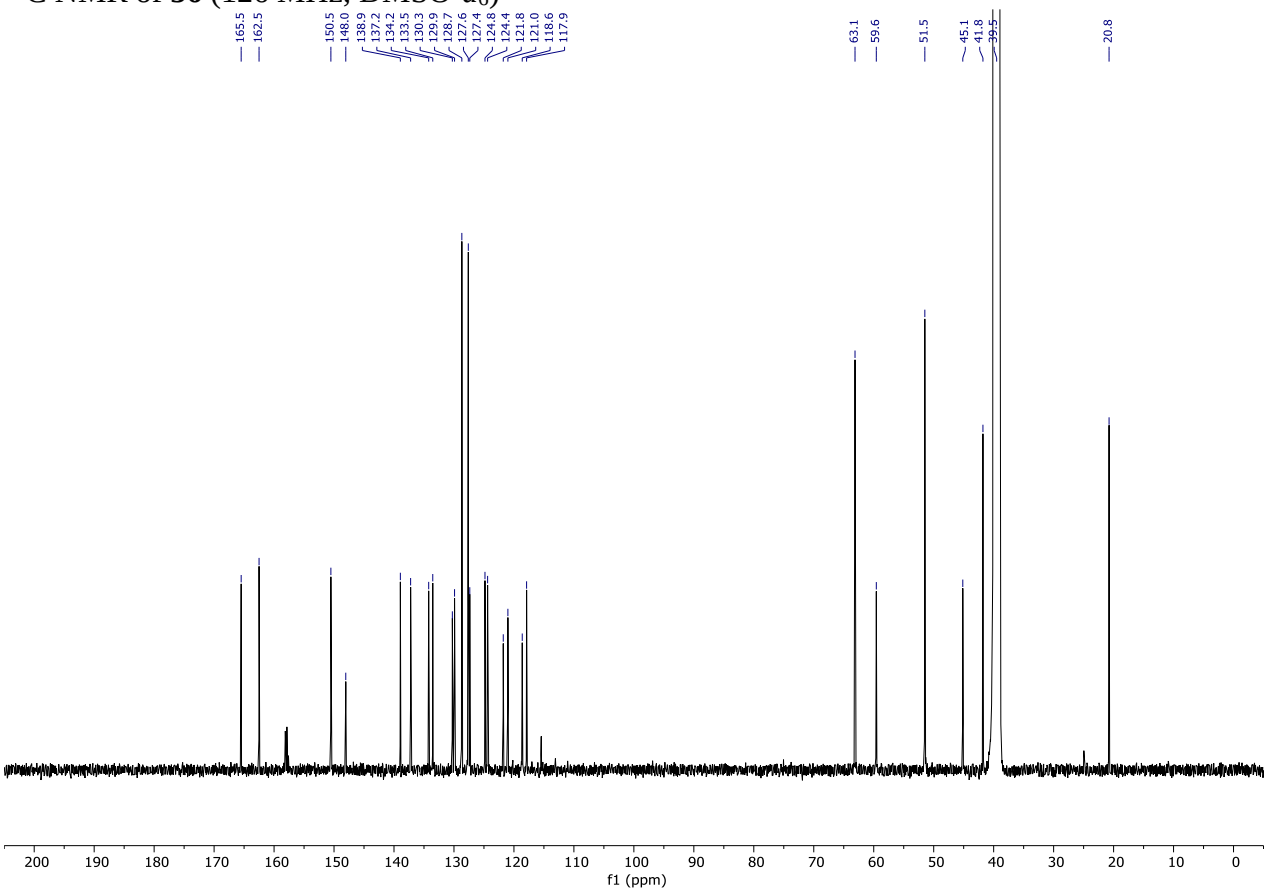
^{13}C NMR of **S66** (126 MHz, $CDCl_3$)



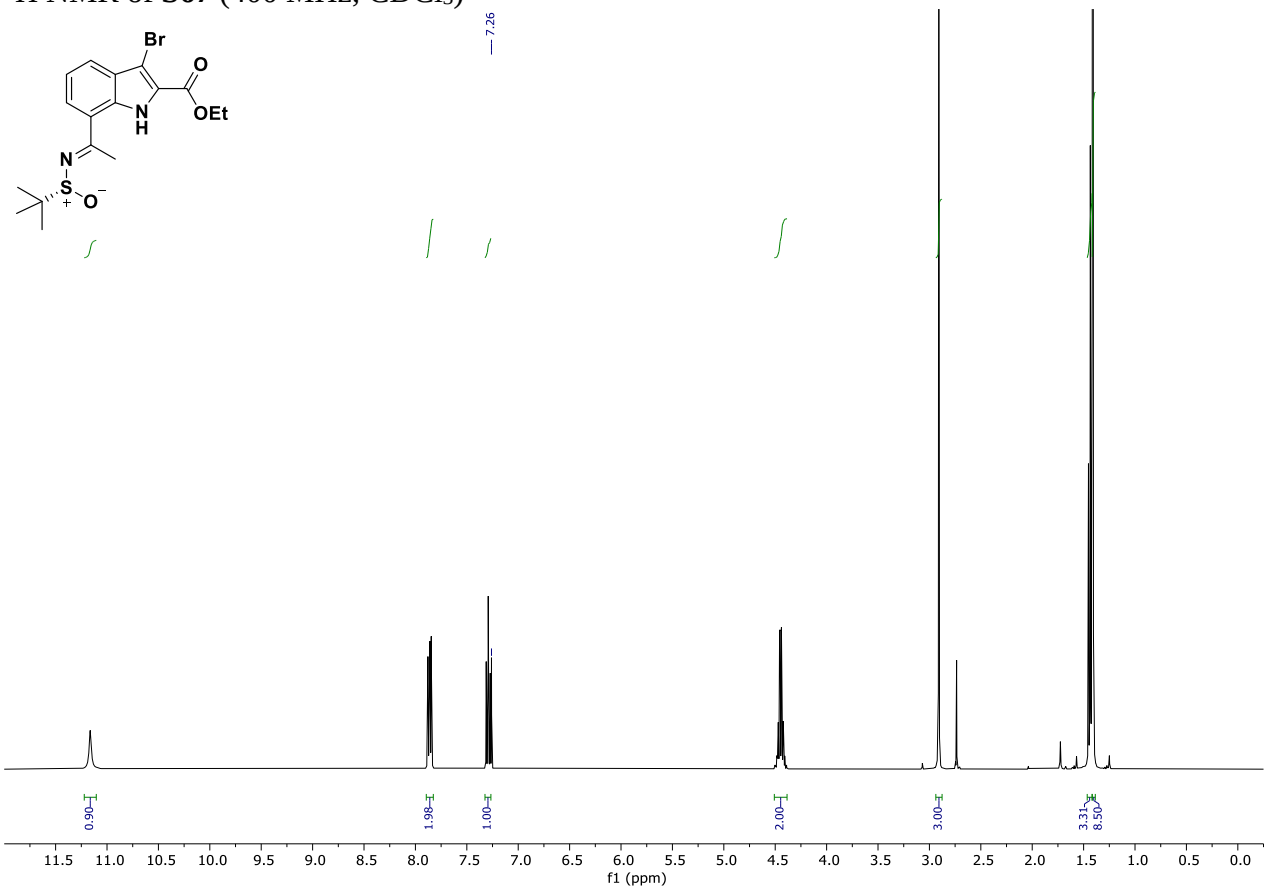
^{1}H NMR of **56** (500 MHz, DMSO-d_6)



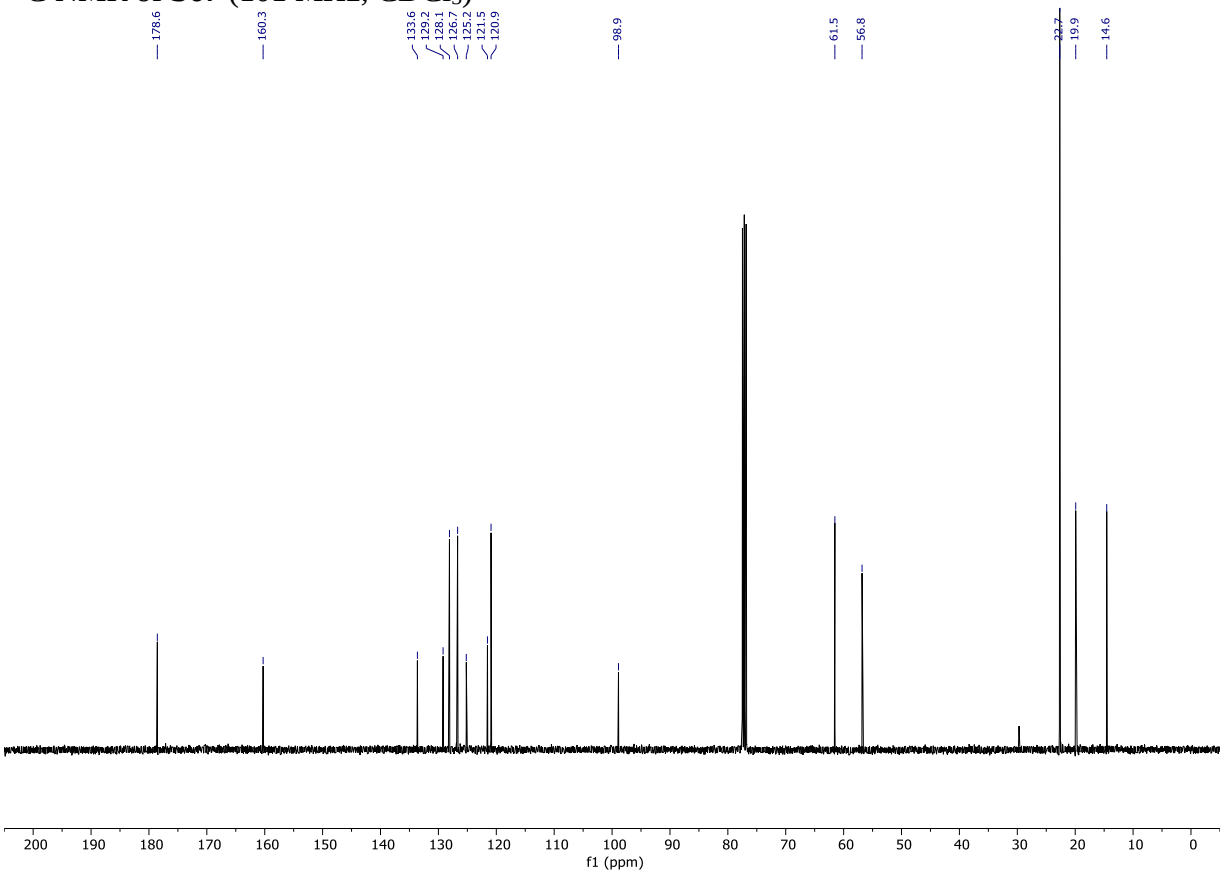
^{13}C NMR of **56** (126 MHz, DMSO-d_6)



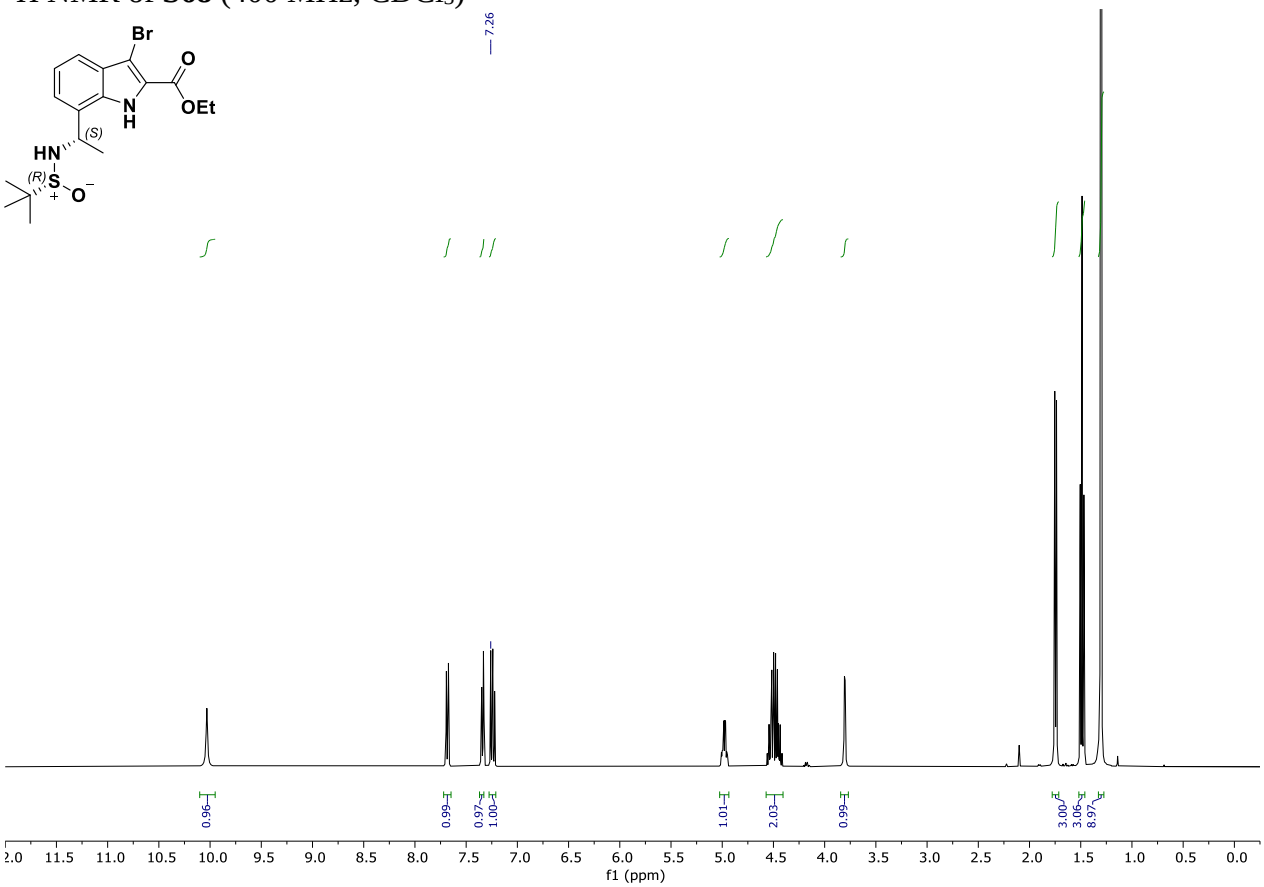
^{1}H NMR of **S67** (400 MHz, $CDCl_3$)



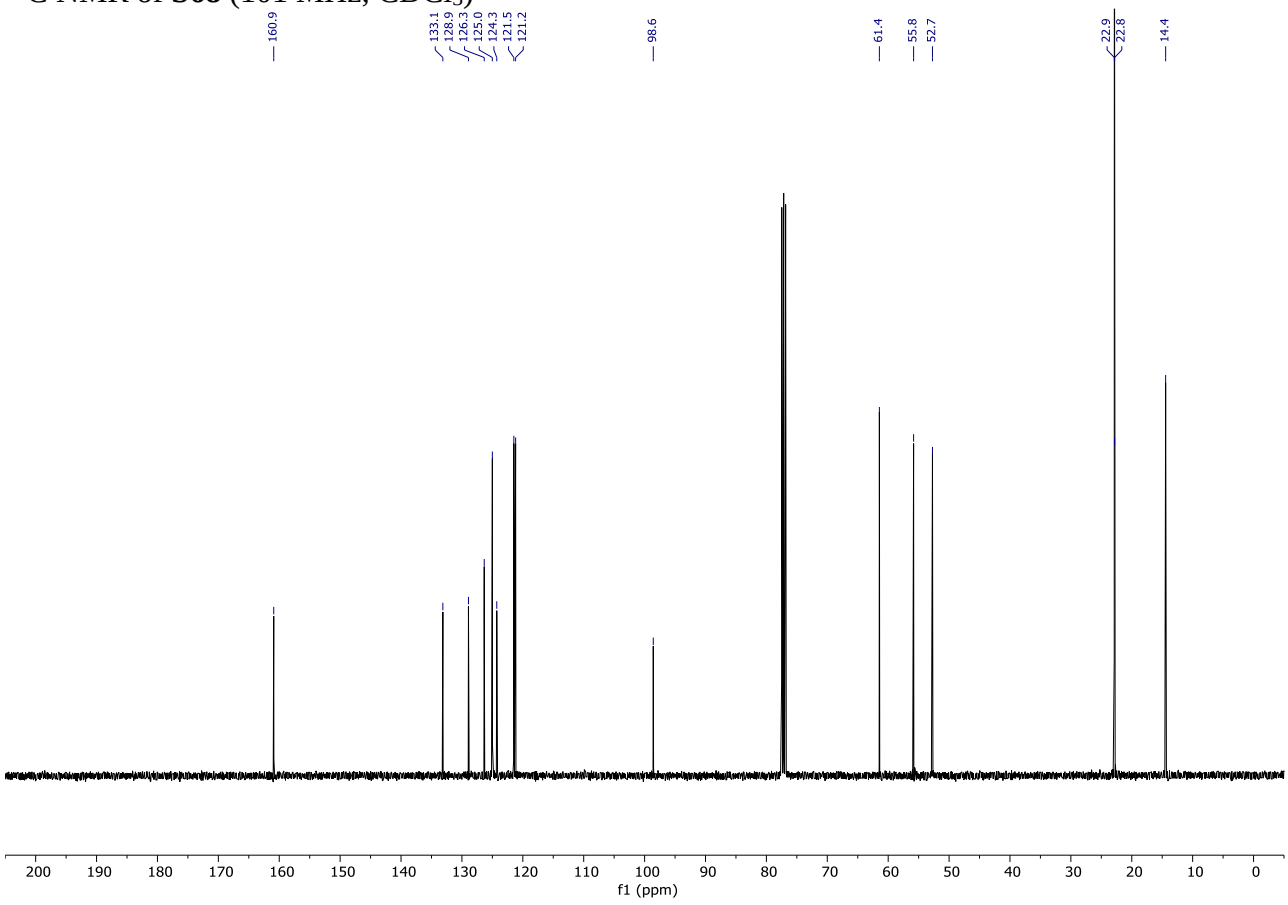
^{13}C NMR of **S67** (101 MHz, $CDCl_3$)



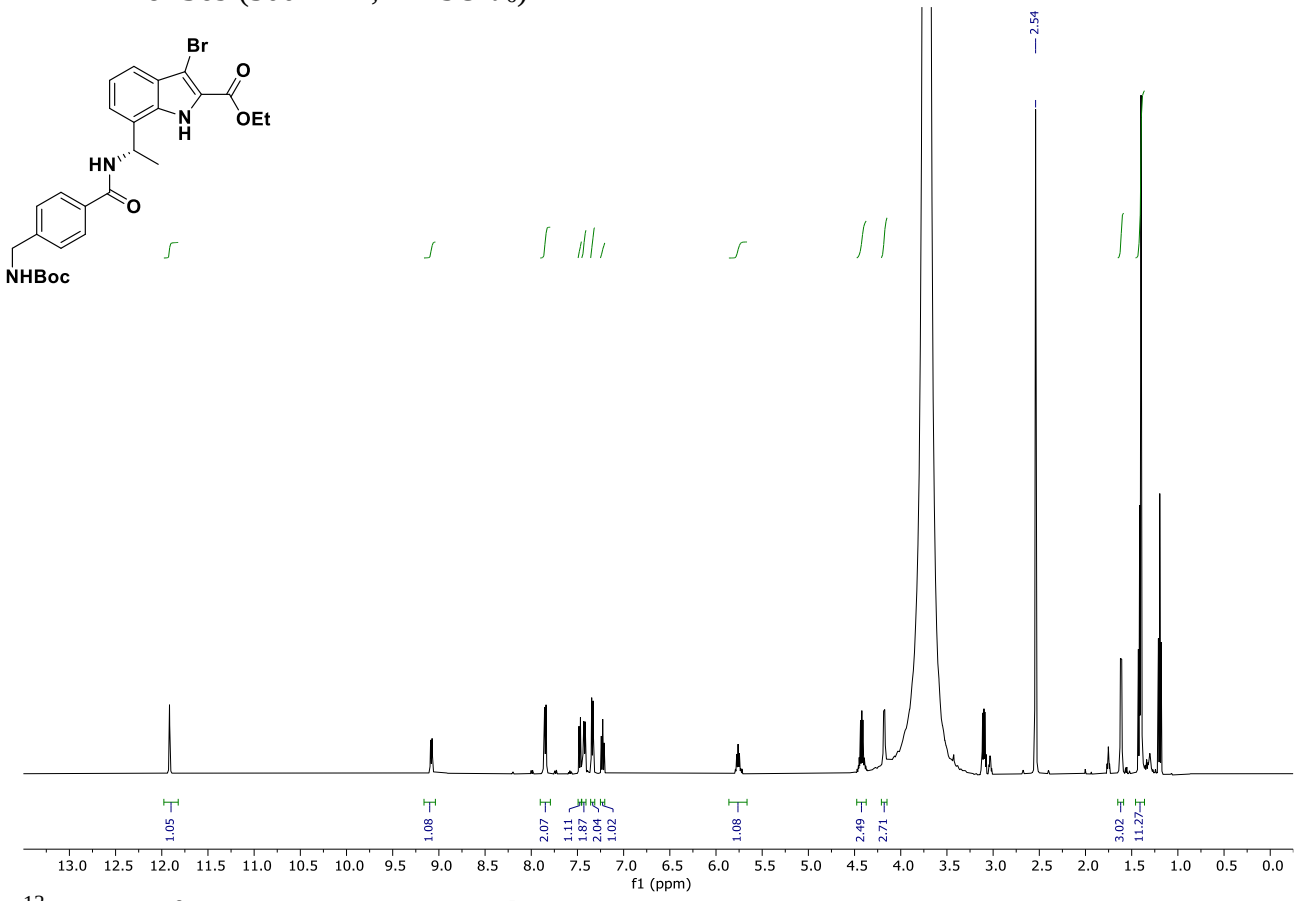
^{1}H NMR of **S68** (400 MHz, $CDCl_3$)



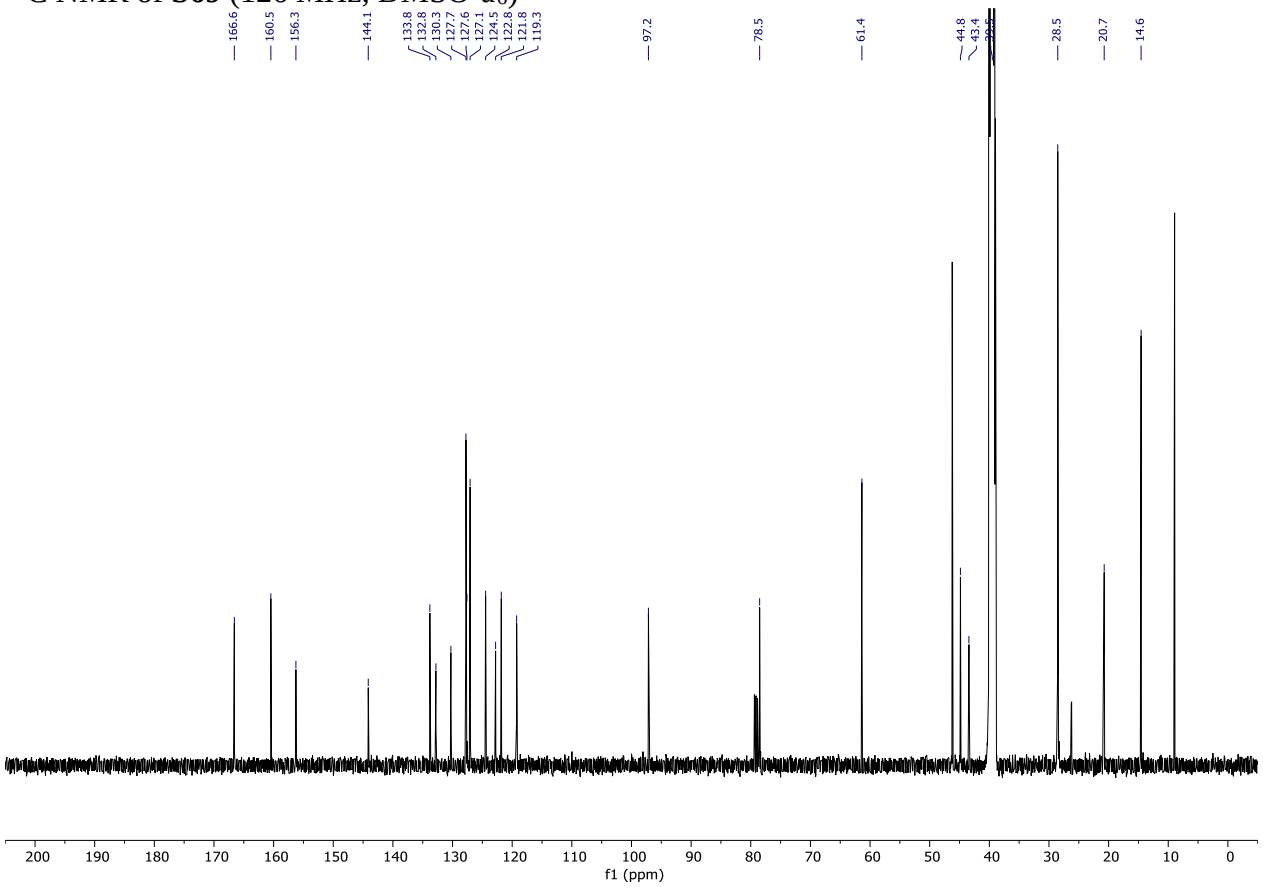
^{13}C NMR of **S68** (101 MHz, $CDCl_3$)



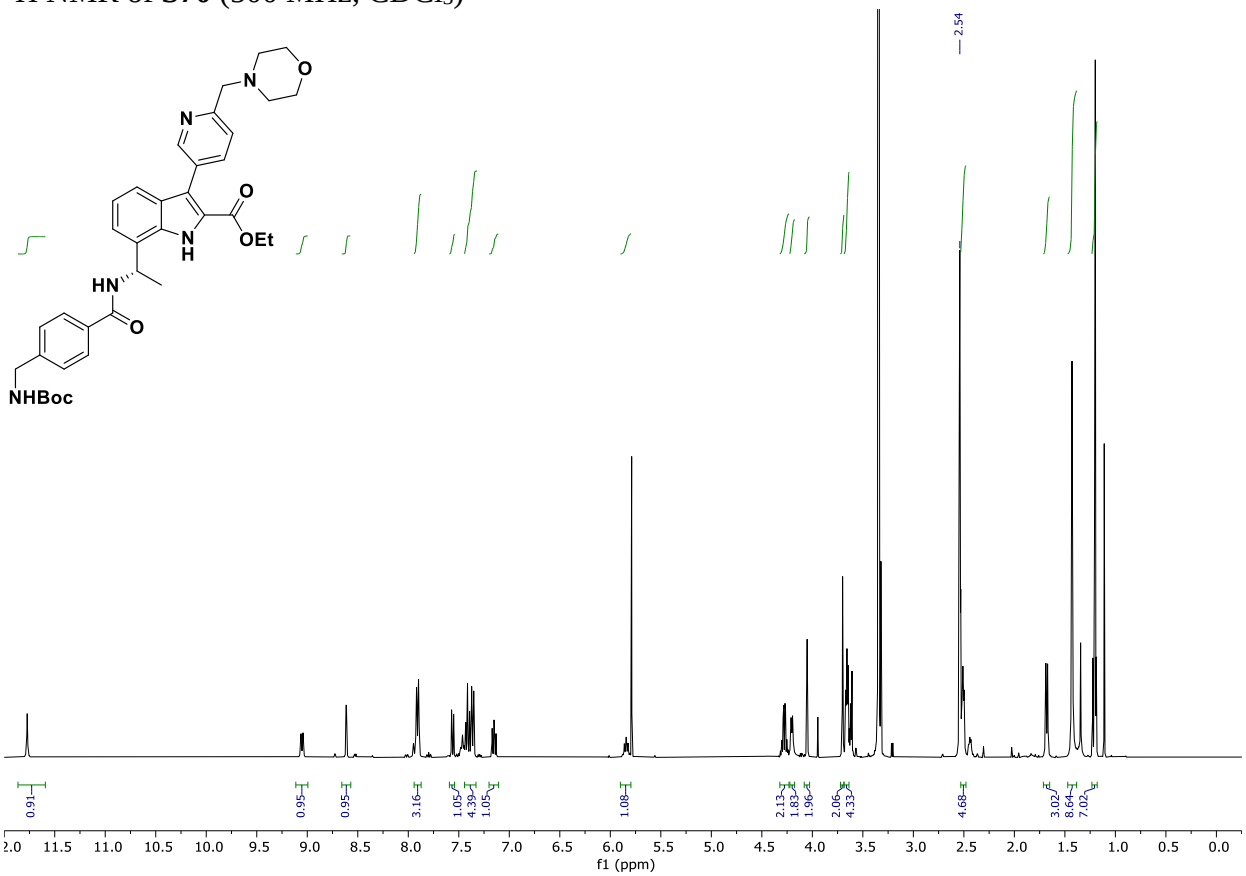
^{1}H NMR of **S69** (500 MHz, DMSO-d_6)



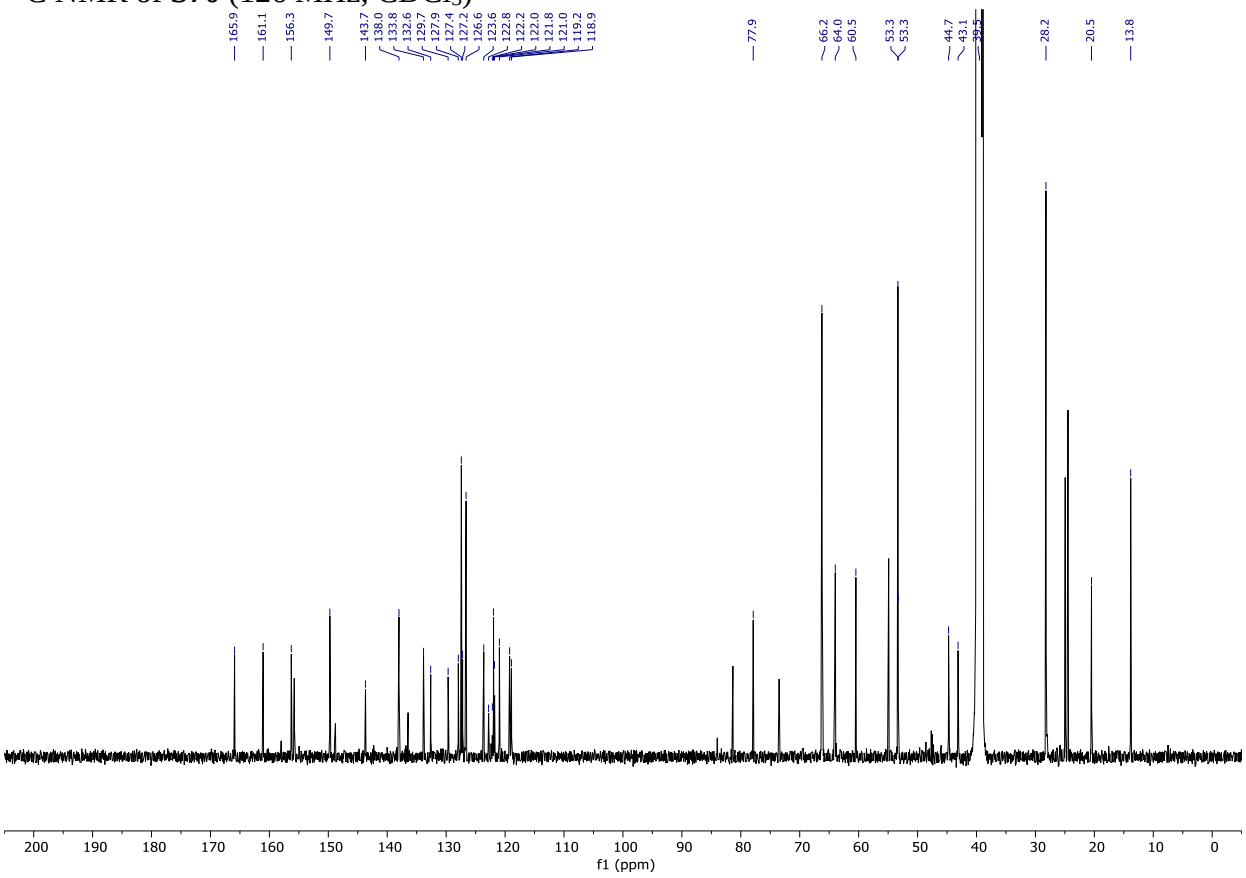
^{13}C NMR of **S69** (126 MHz, DMSO-d_6)



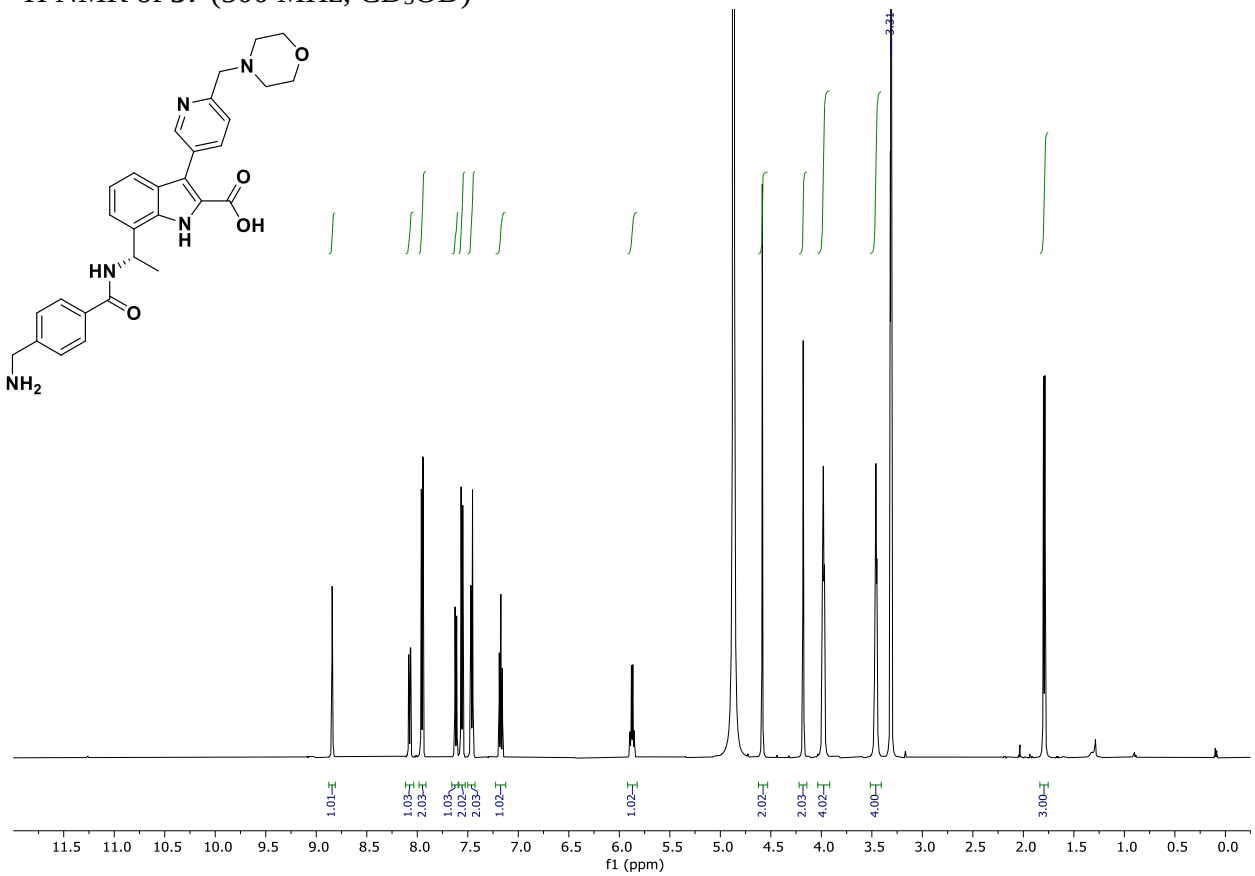
^{1}H NMR of **S70** (500 MHz, $CDCl_3$)



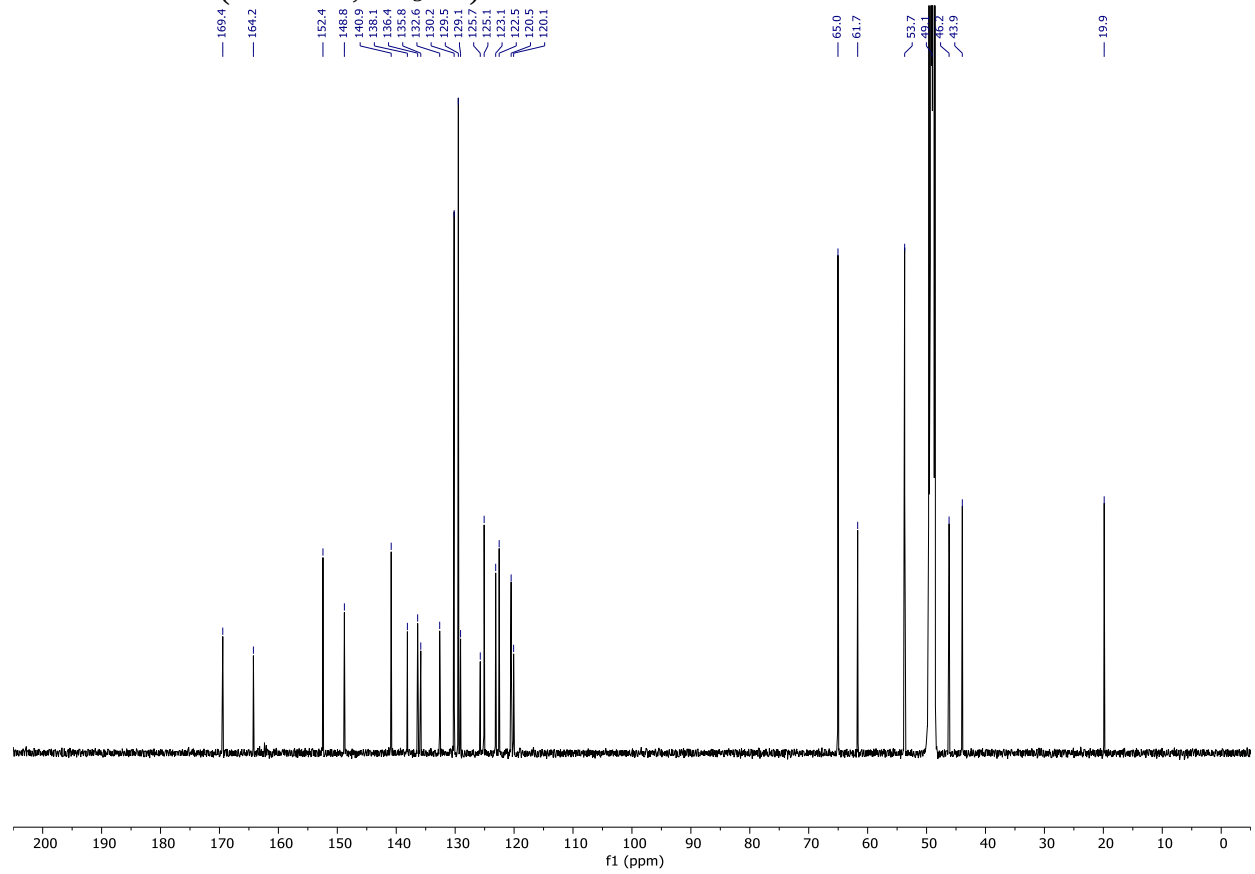
^{13}C NMR of **S70** (126 MHz, $CDCl_3$)



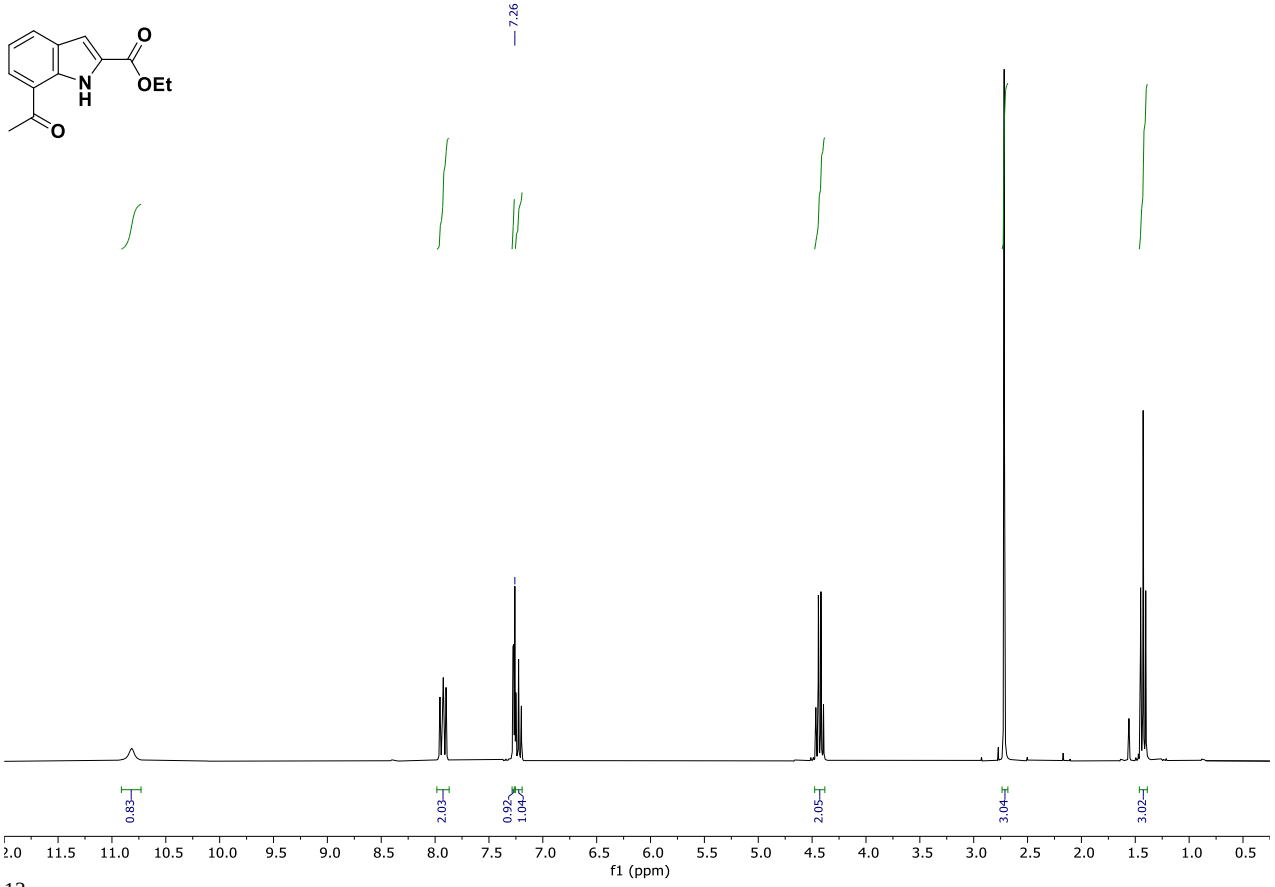
^{1}H NMR of **57** (500 MHz, CD_3OD)



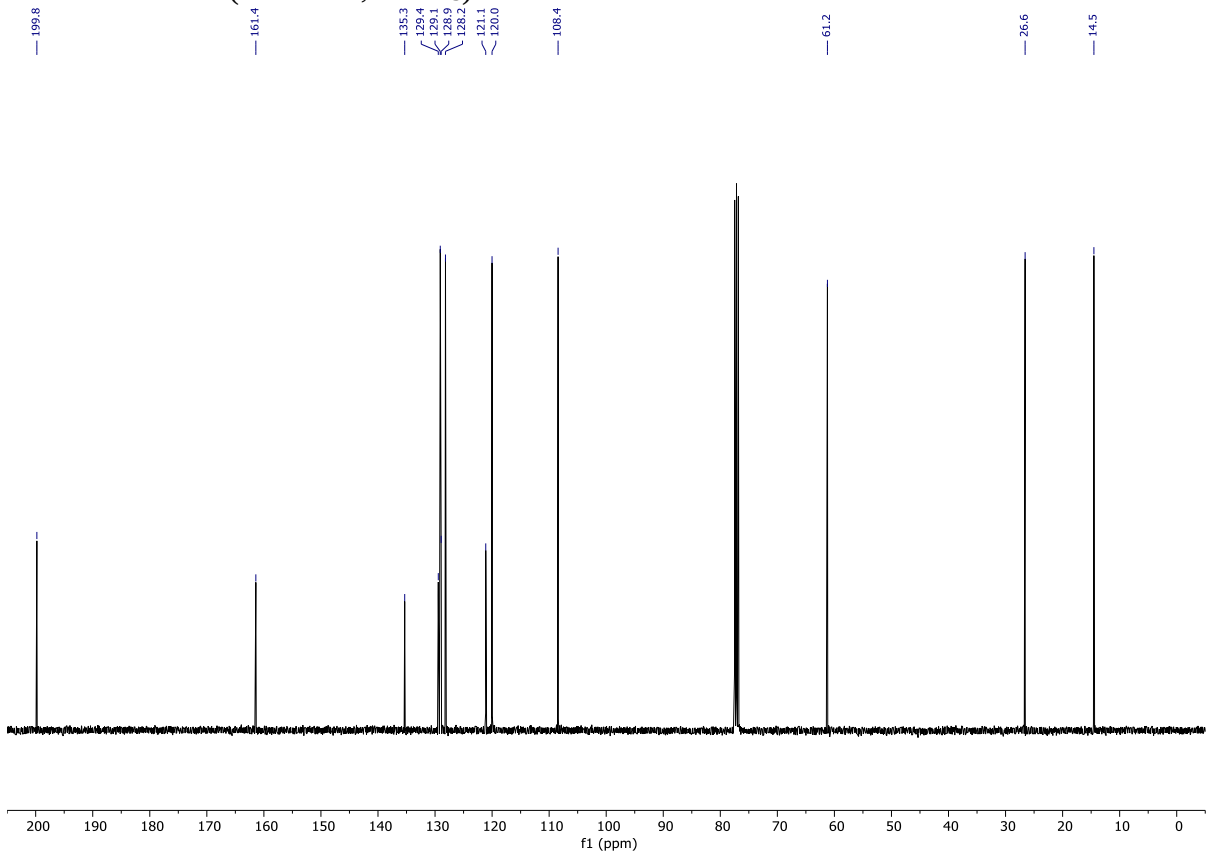
^{13}C NMR of **57** (126 MHz, CD_3OD)



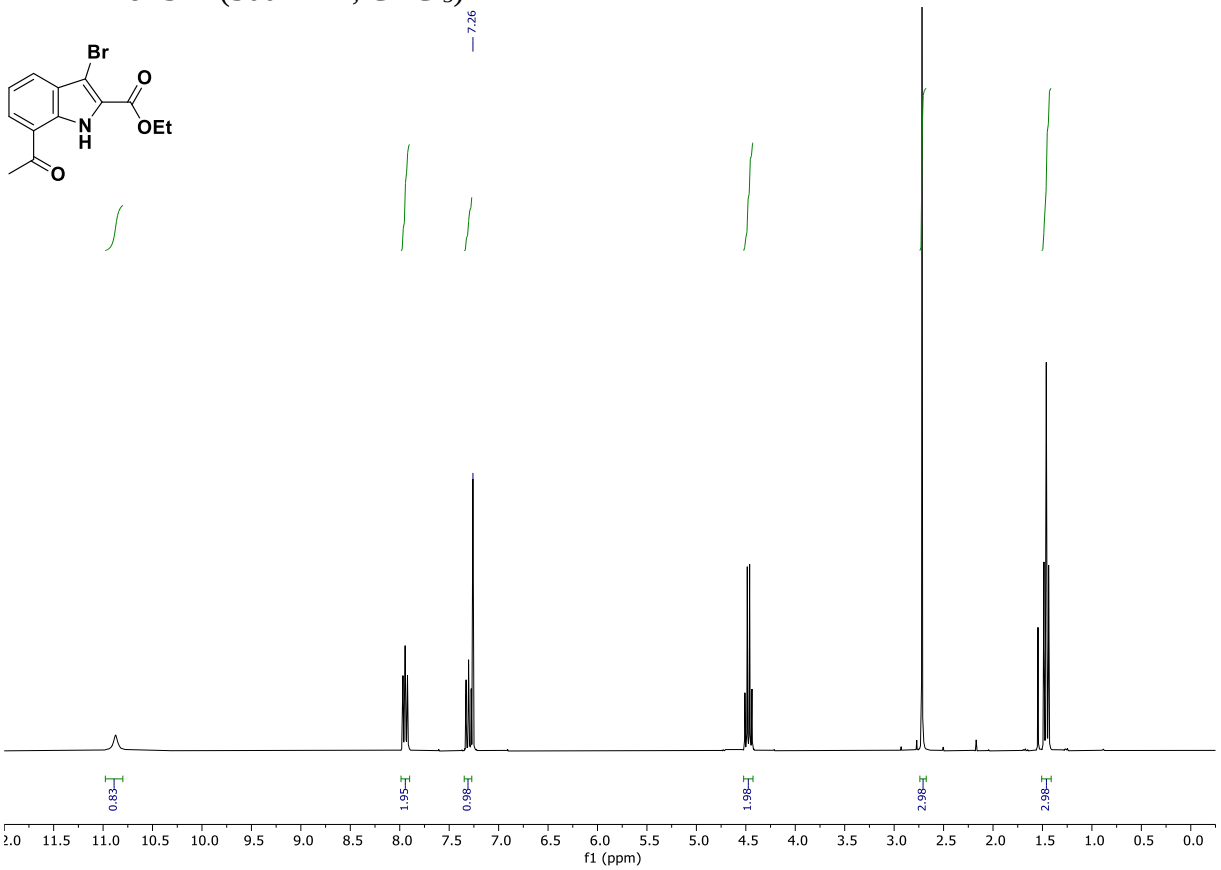
^{1}H NMR of **S71** (300 MHz, $CDCl_3$)



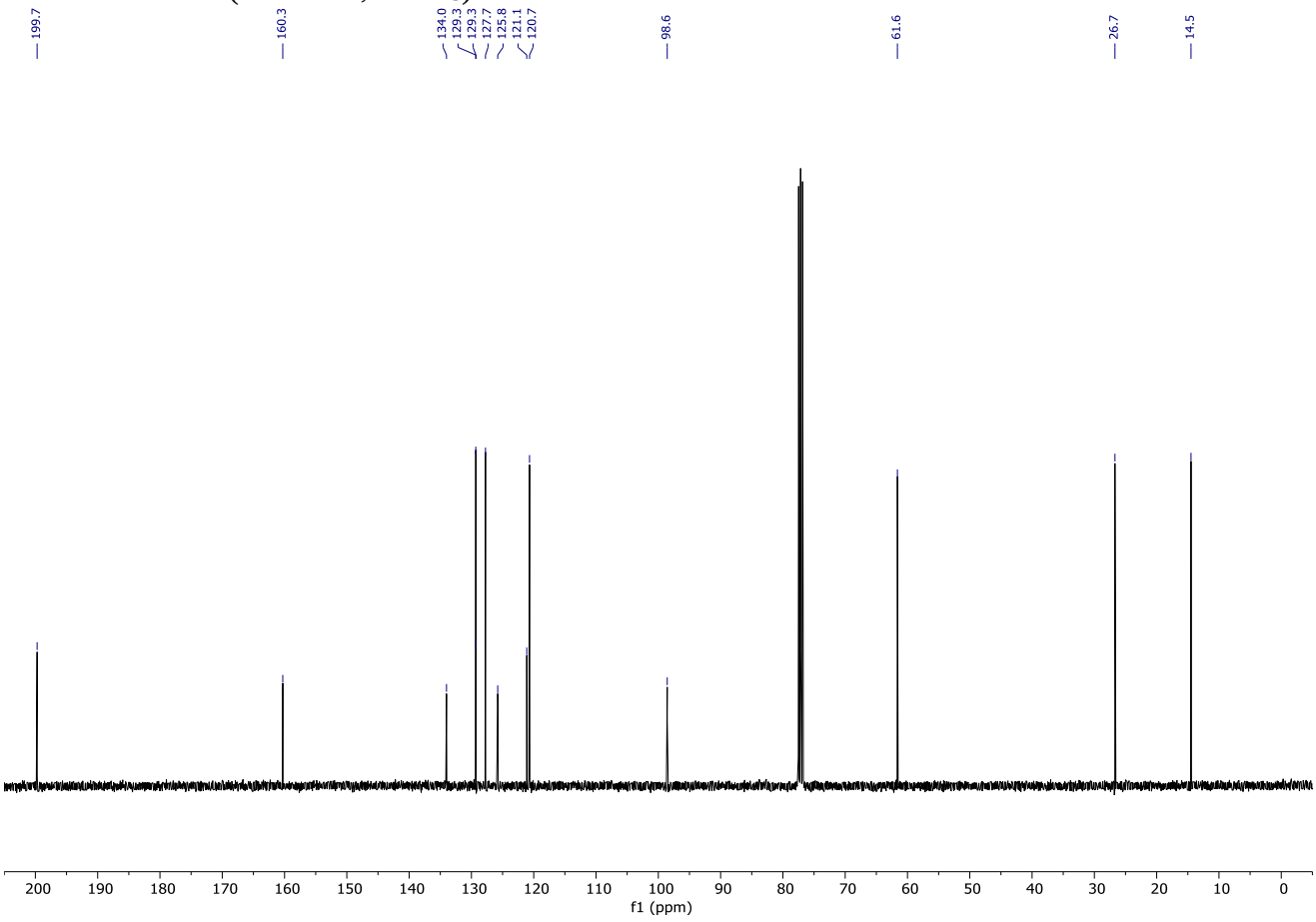
^{13}C NMR of **S71** (101 MHz, $CDCl_3$)



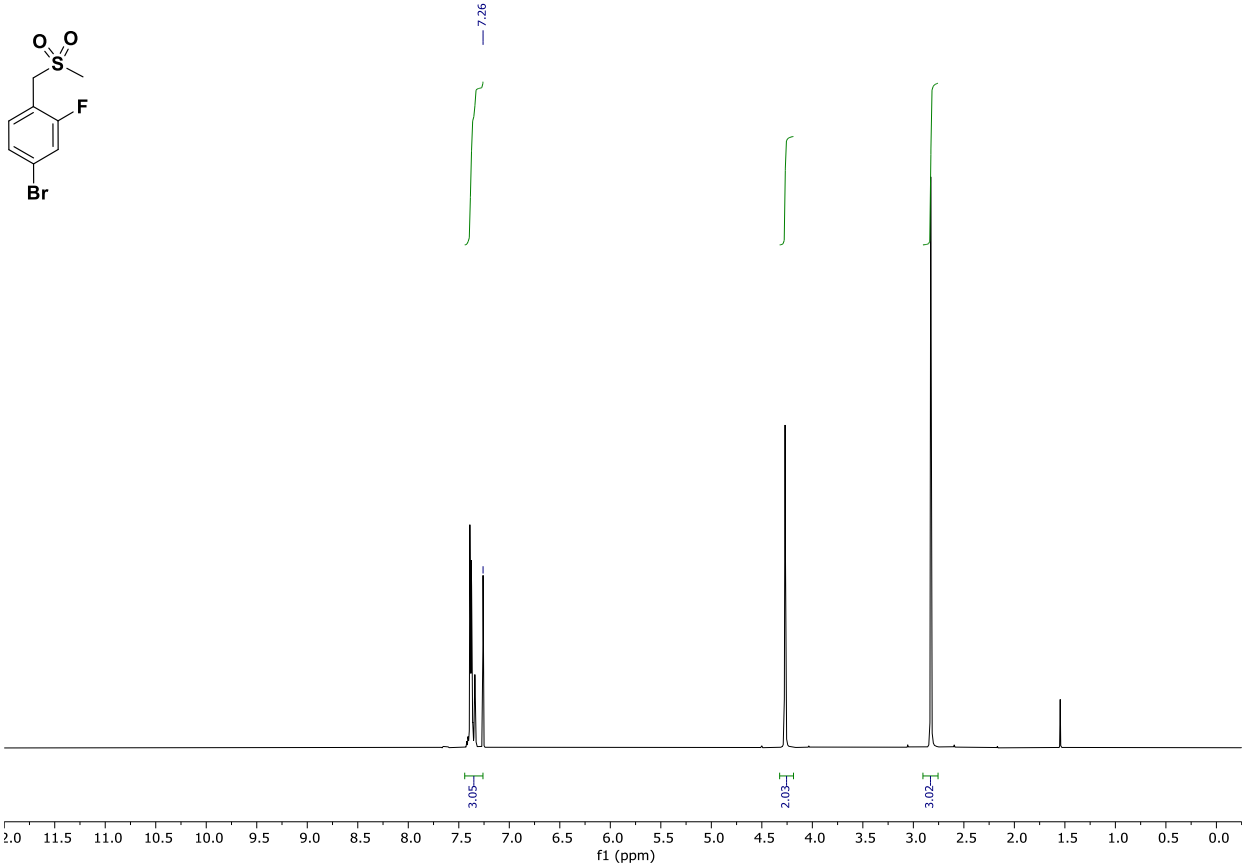
^{1}H NMR of **S72** (300 MHz, $CDCl_3$)



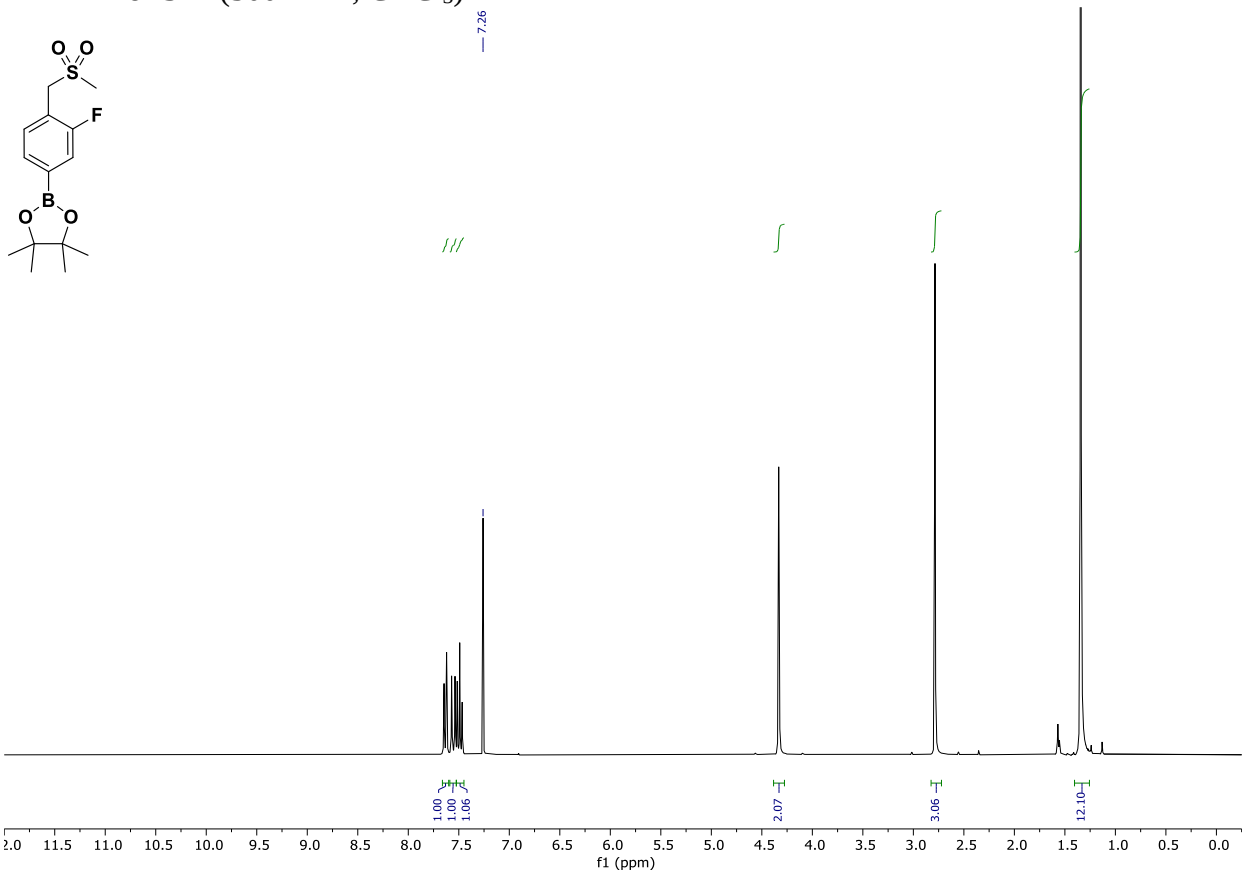
^{13}C NMR of **S72** (101 MHz, $CDCl_3$)



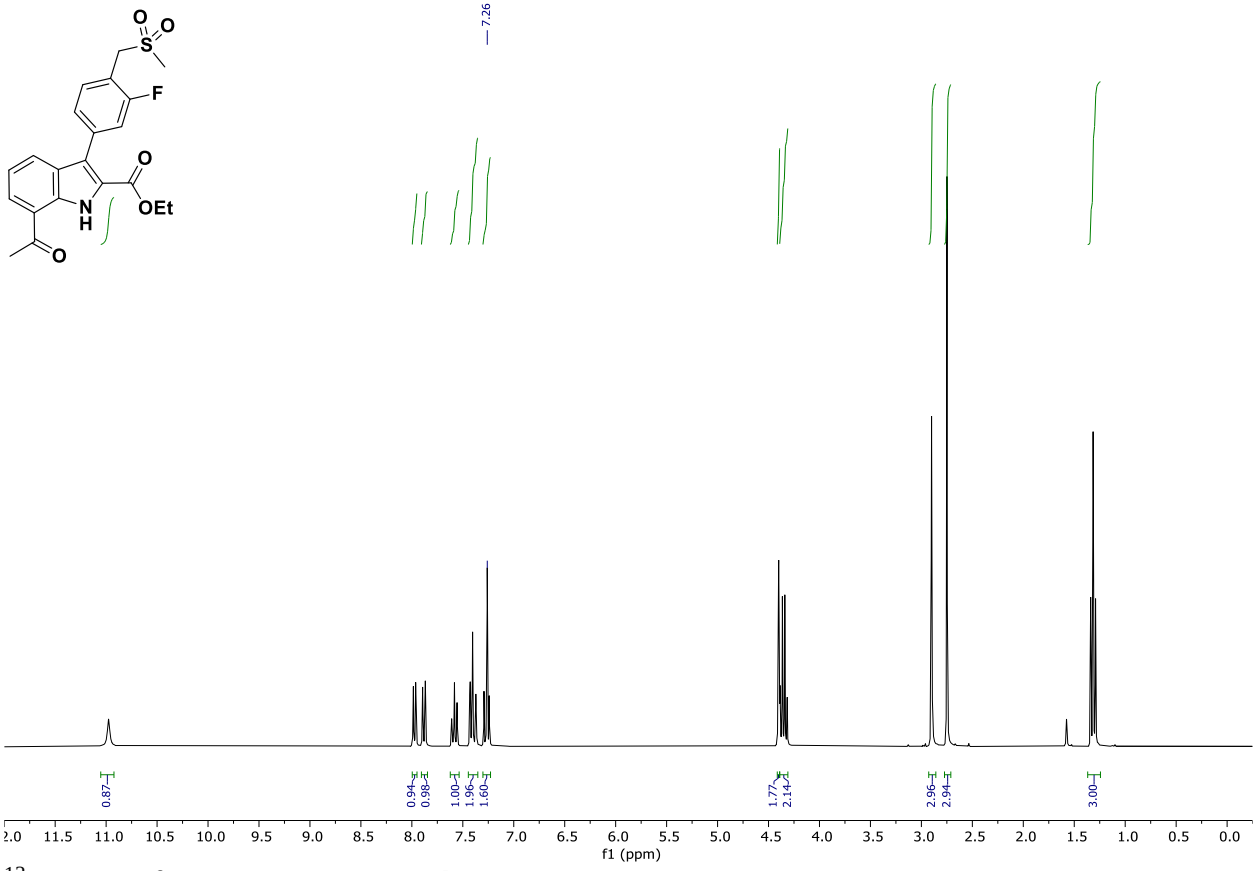
^{1}H NMR of S73 (300 MHz, $CDCl_3$)



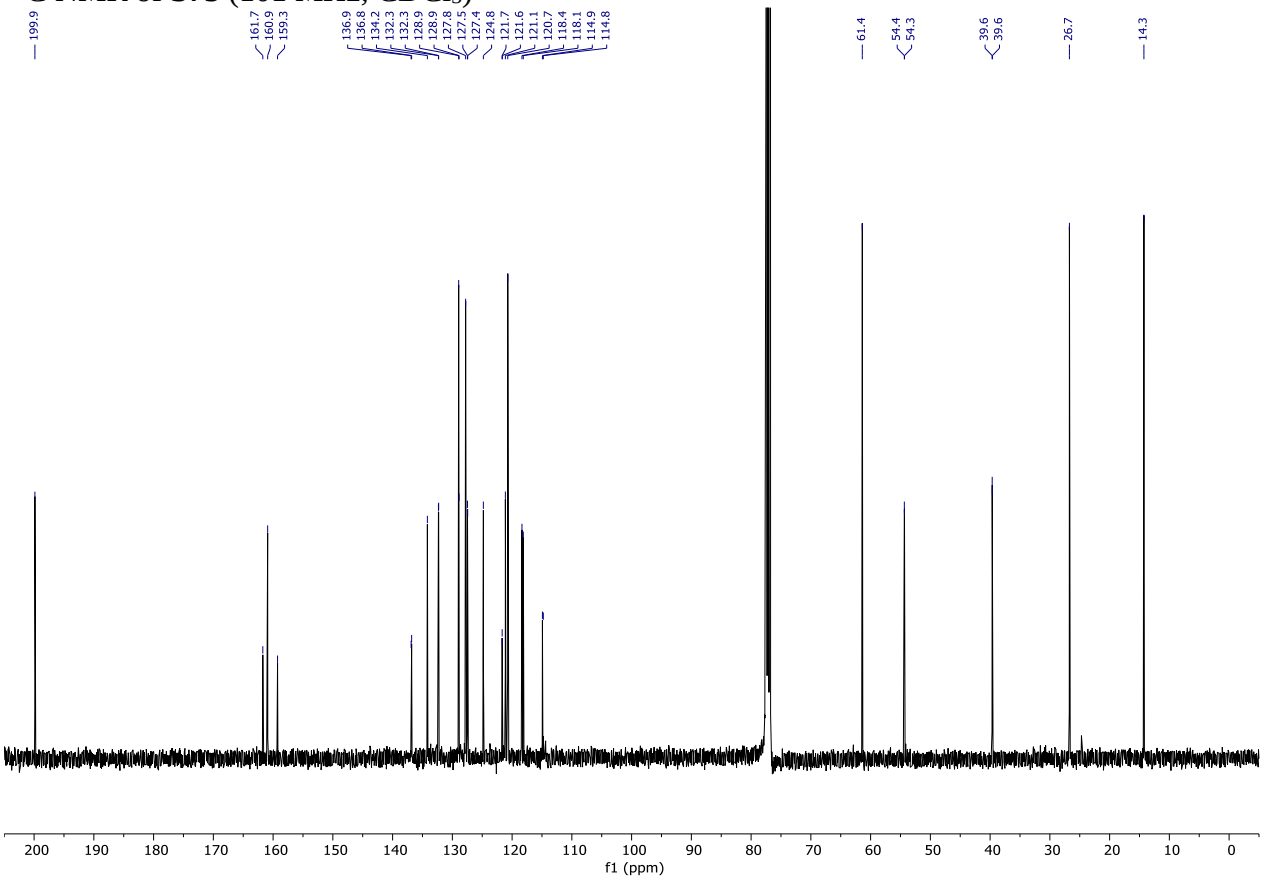
^{1}H NMR of **S74** (300 MHz, $CDCl_3$)



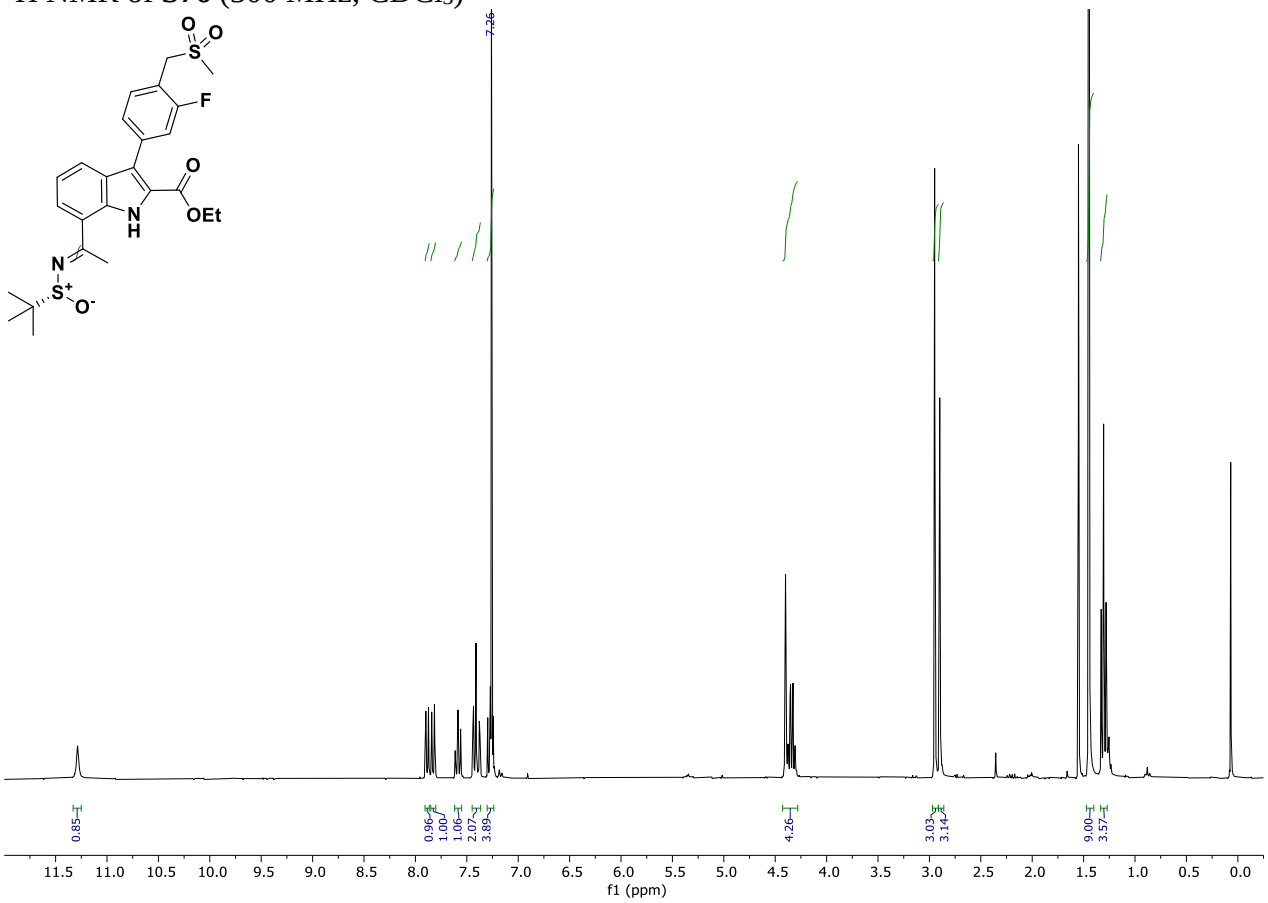
^{1}H NMR of **S75** (300 MHz, $CDCl_3$)



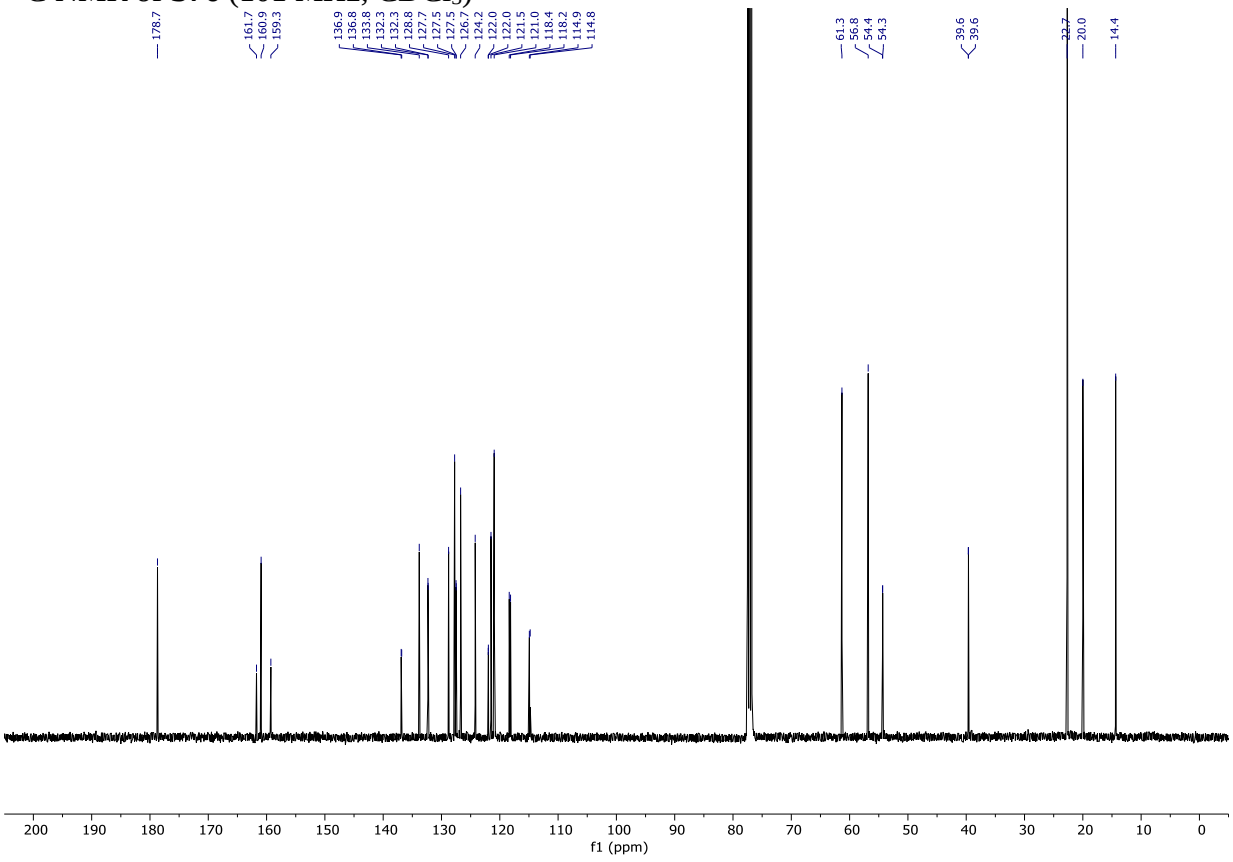
^{13}C NMR of **S75** (101 MHz, $CDCl_3$)



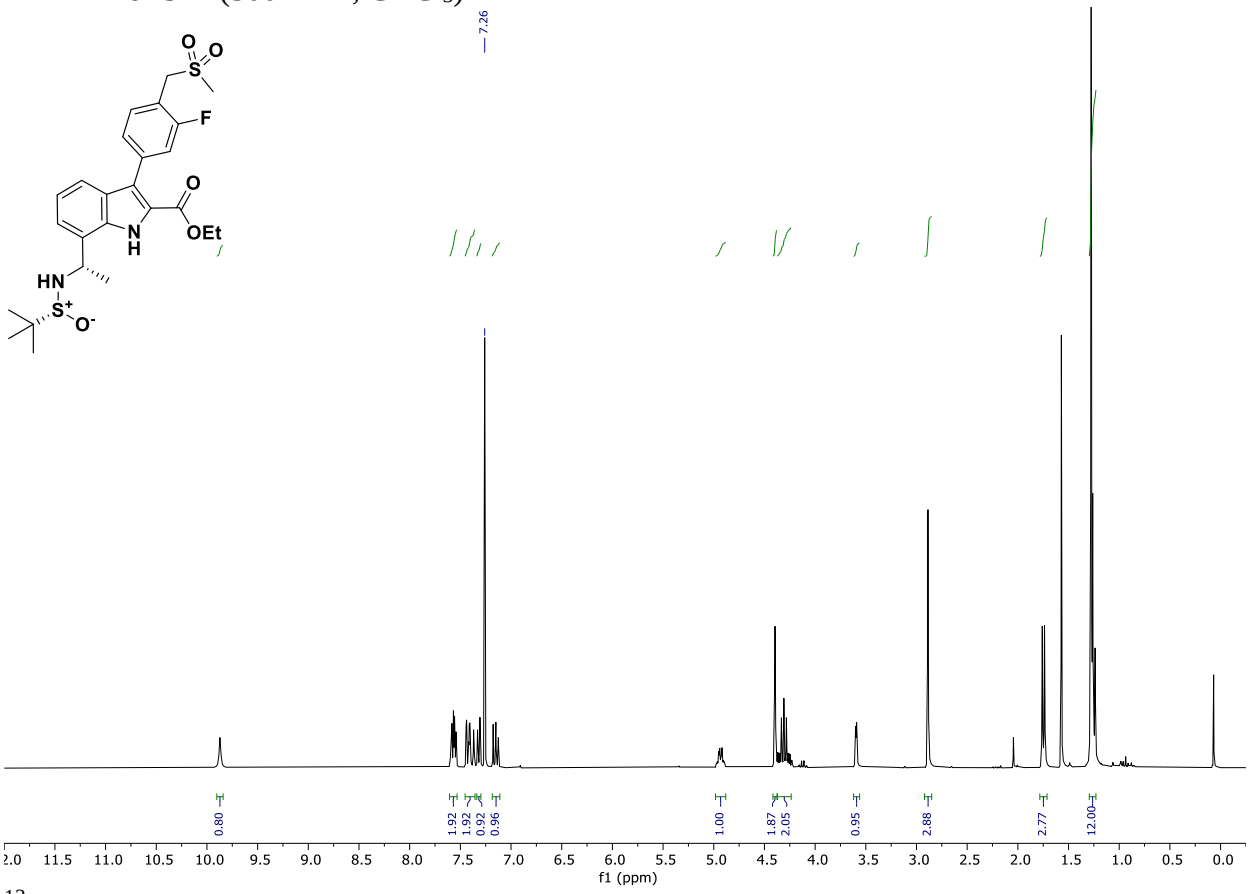
^{1}H NMR of **S76** (300 MHz, $CDCl_3$)



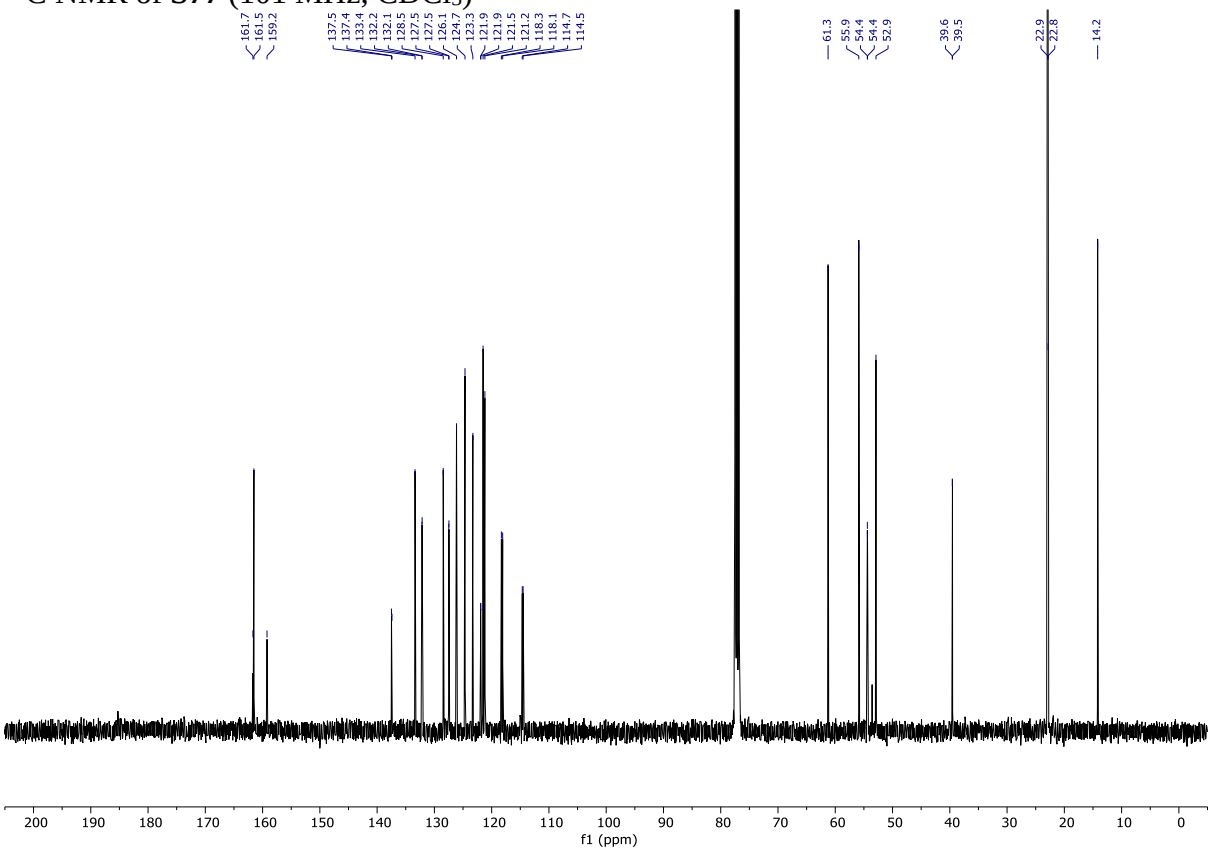
^{13}C NMR of **S76** (101 MHz, $CDCl_3$)



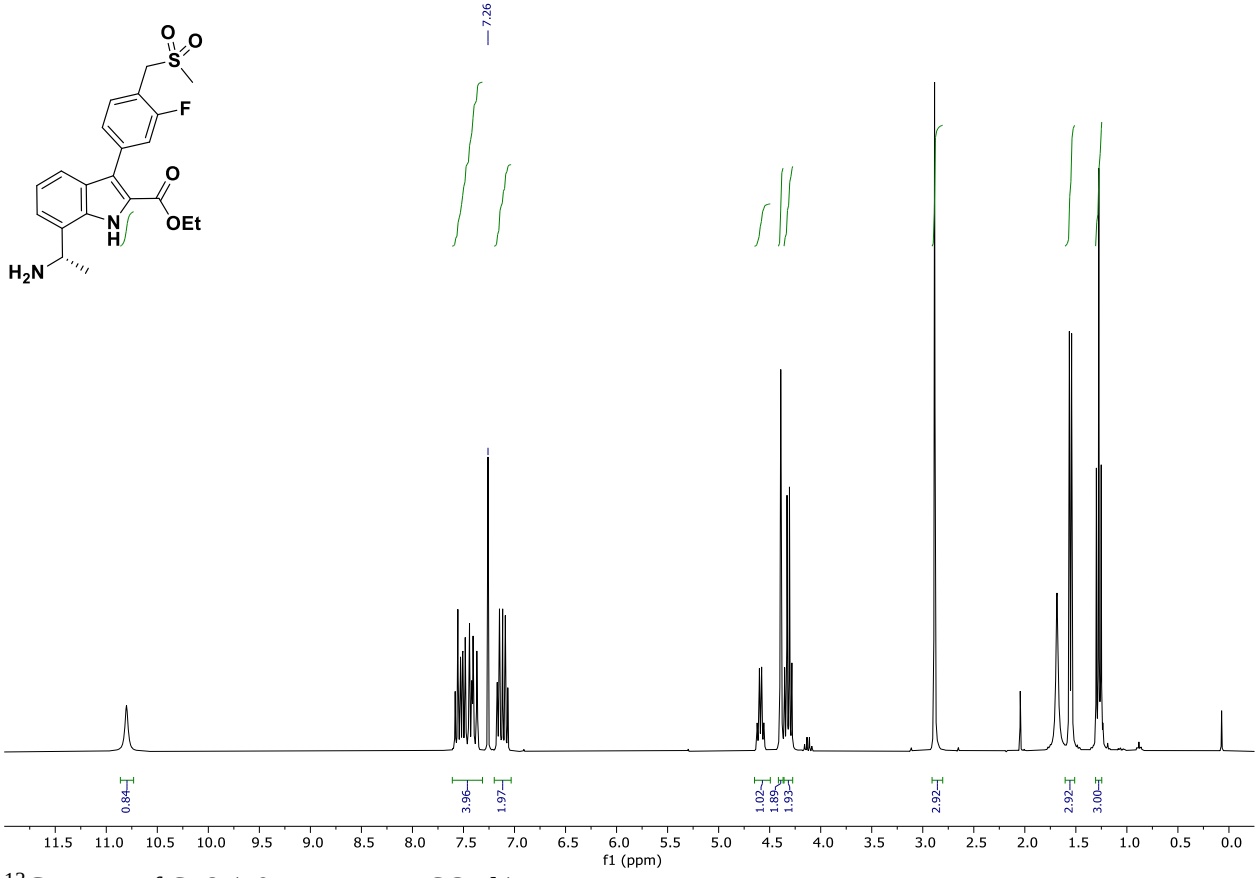
^{1}H NMR of **S77** (300 MHz, $CDCl_3$)



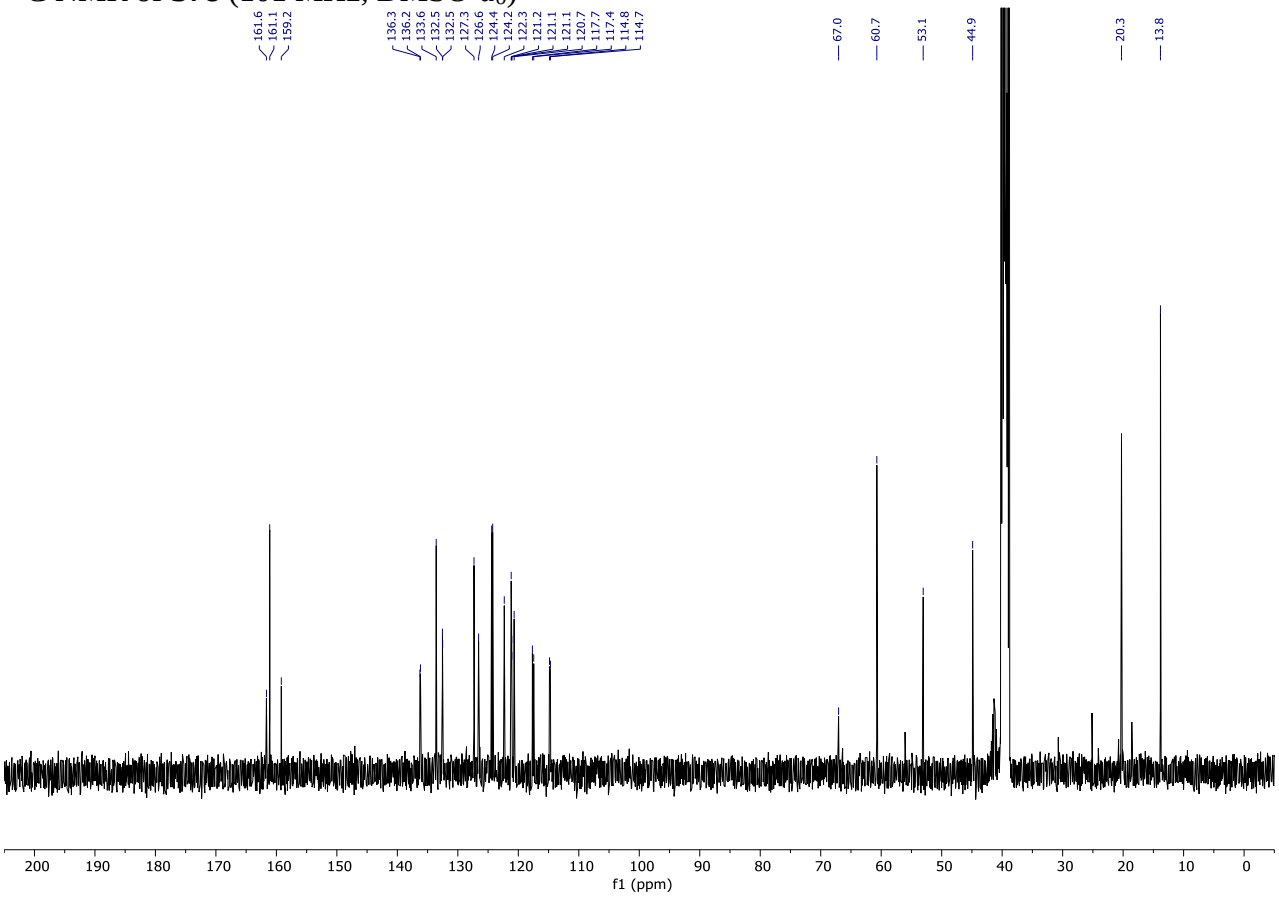
^{13}C NMR of **S77** (101 MHz, $CDCl_3$)



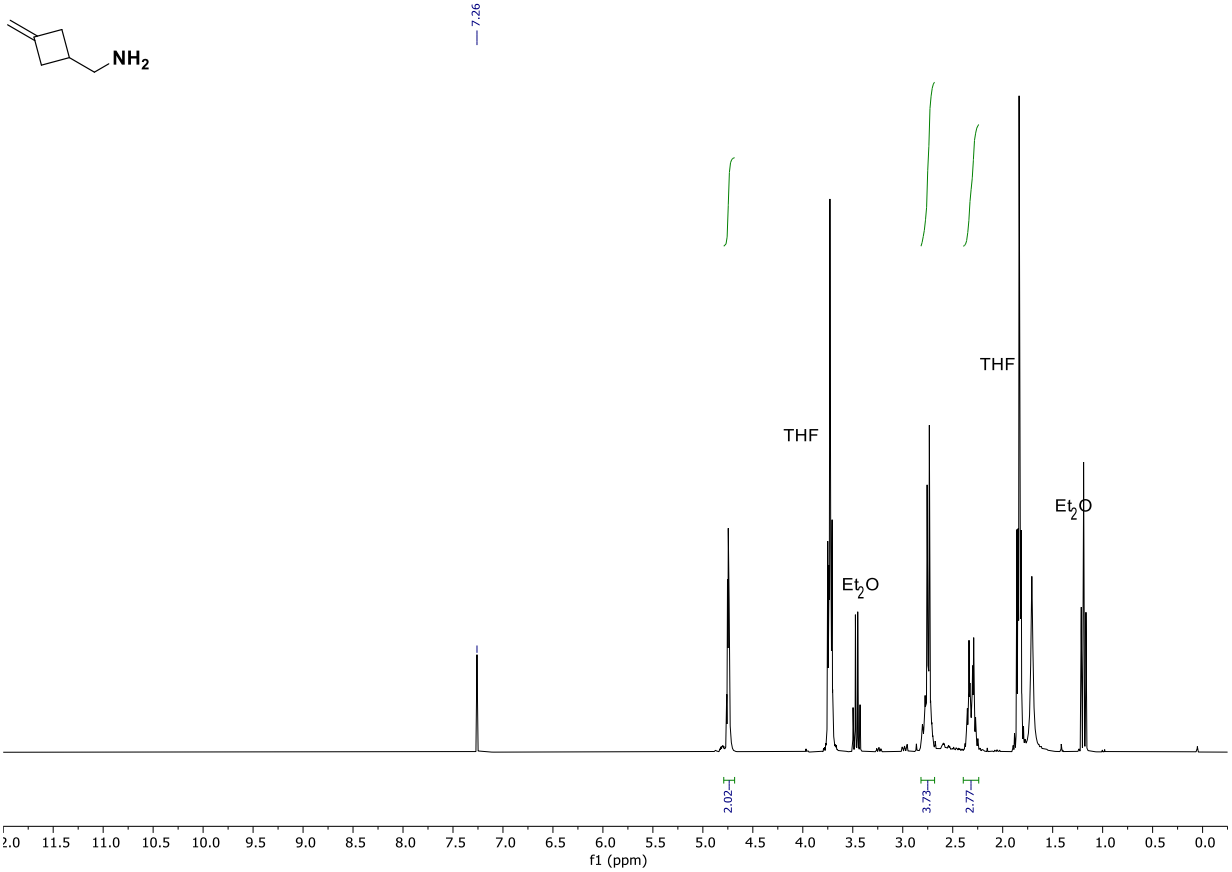
^{1}H NMR of **S78** (300 MHz, $CDCl_3$)



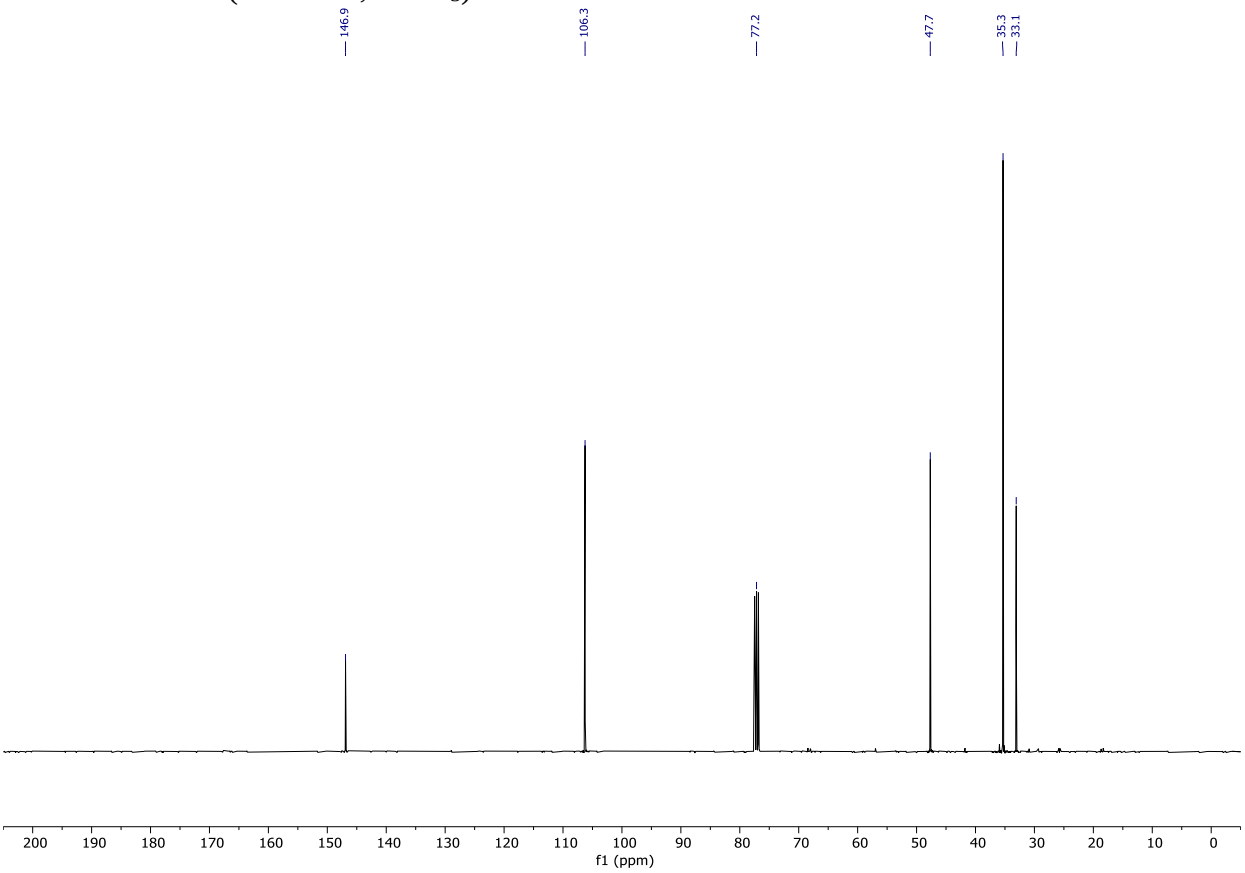
^{13}C NMR of **S78** (101 MHz, DMSO-d_6)



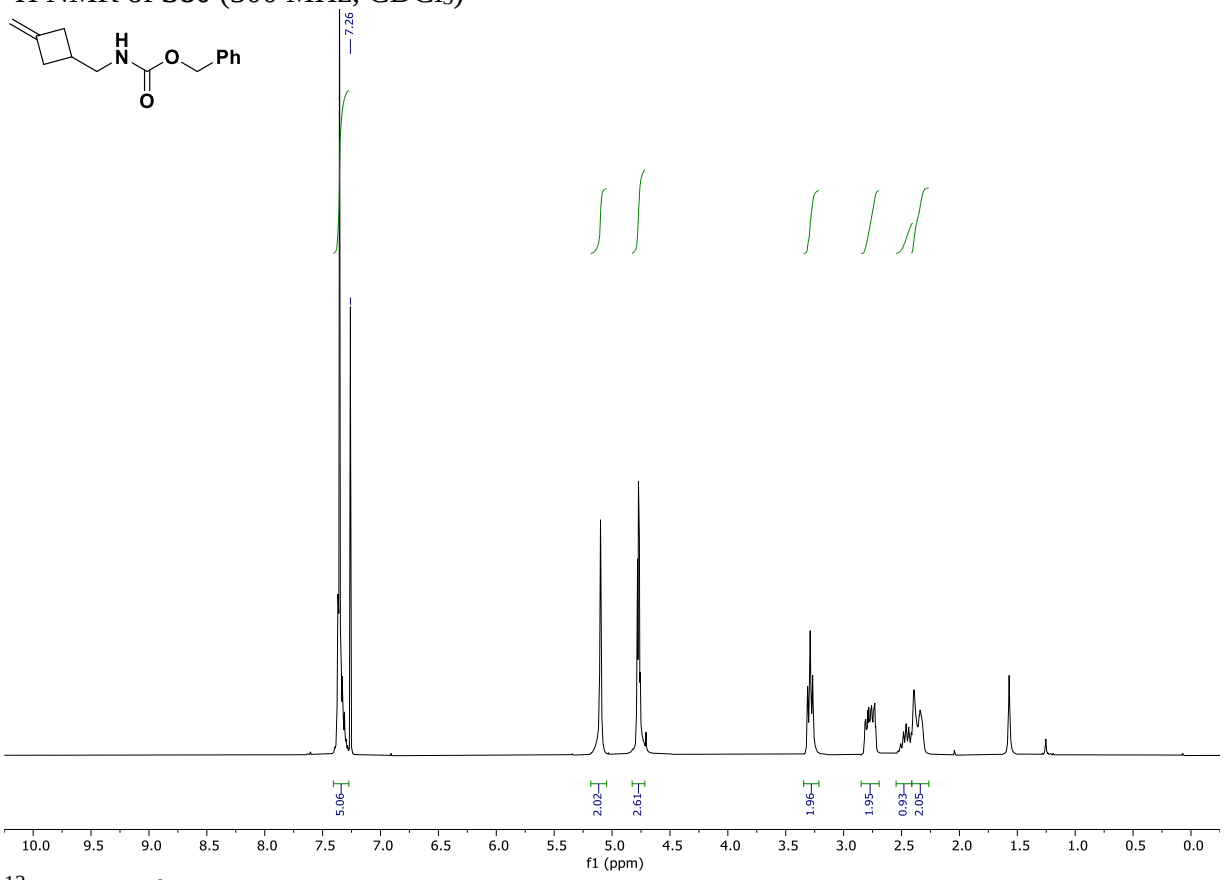
^{1}H NMR of S79 (300 MHz, $CDCl_3$)



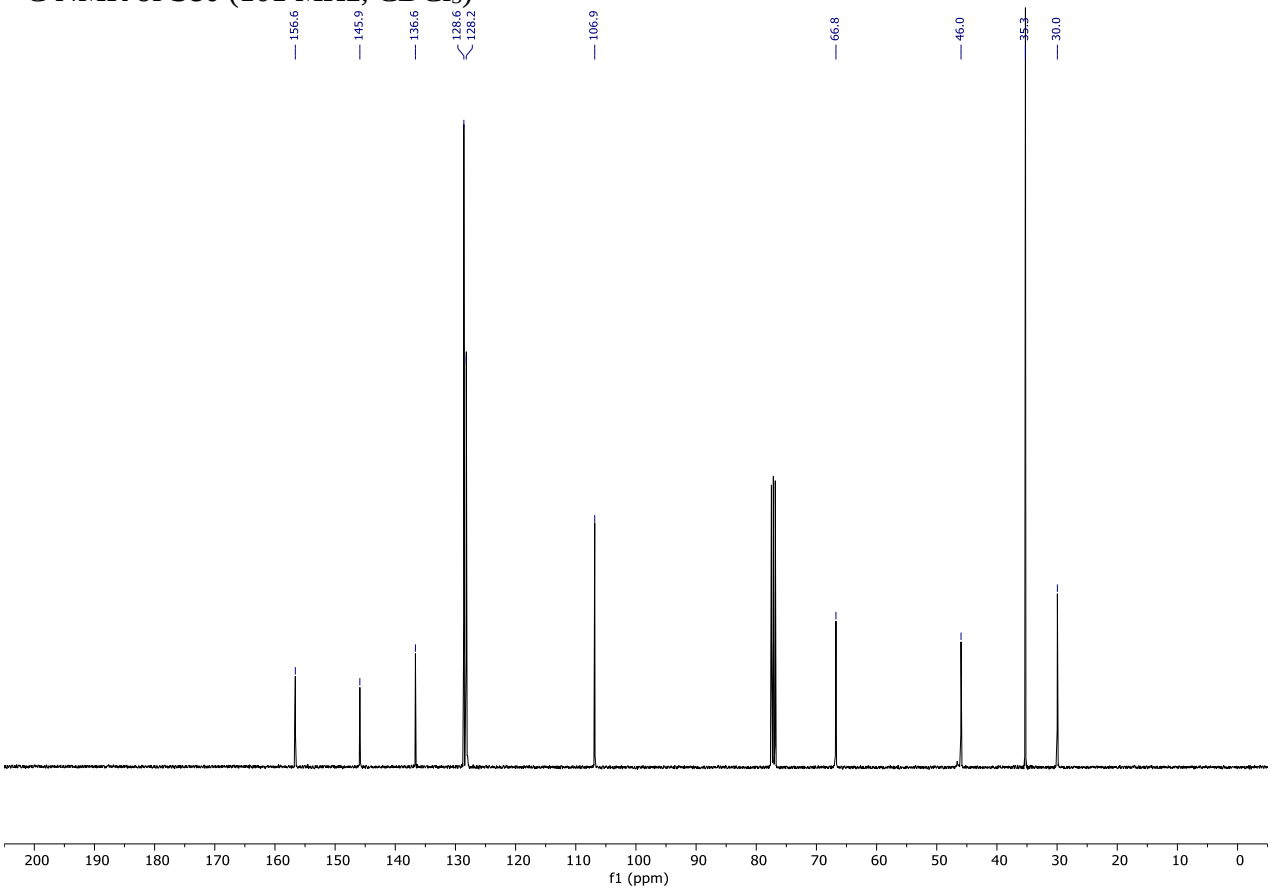
^{13}C NMR of **S79** (101 MHz, $CDCl_3$)



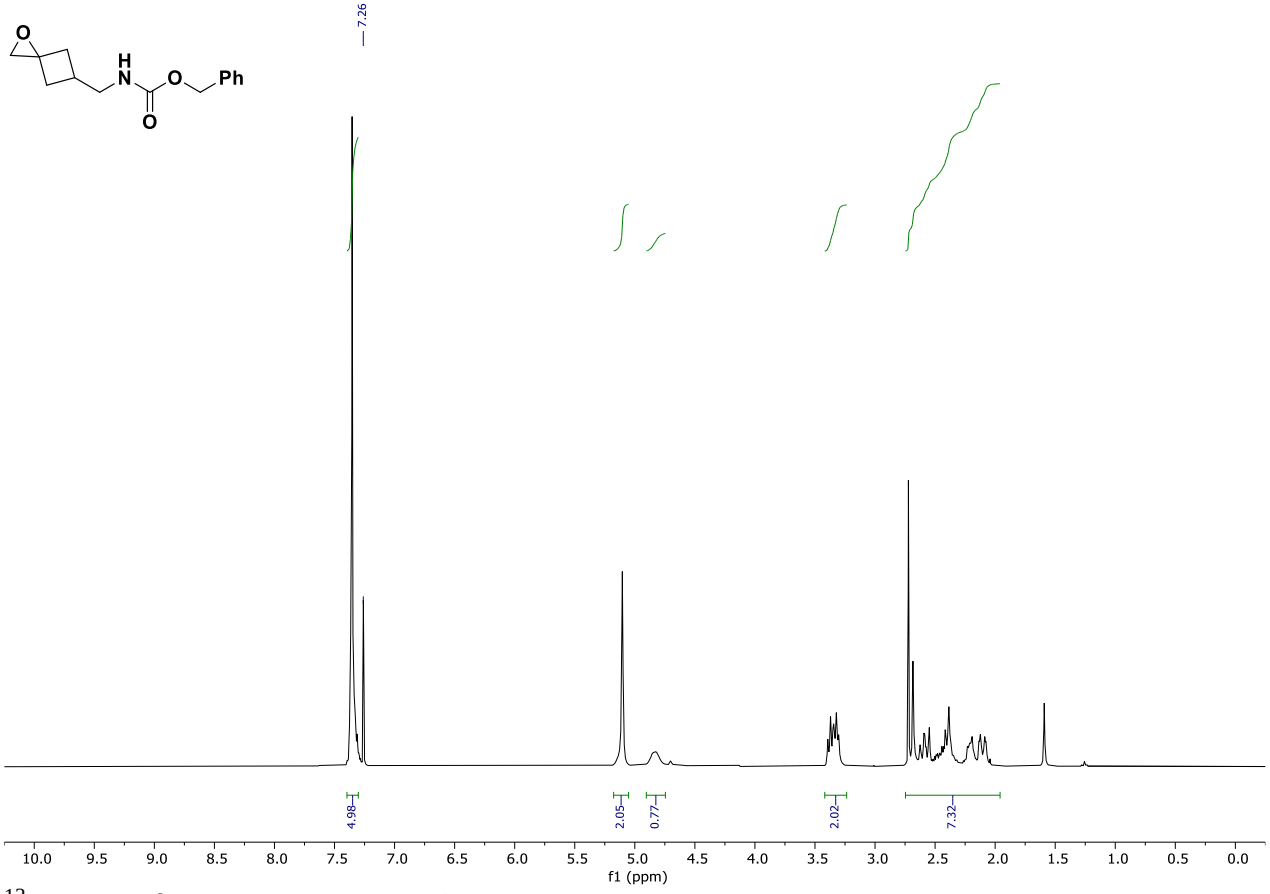
^{1}H NMR of **S80** (300 MHz, $CDCl_3$)



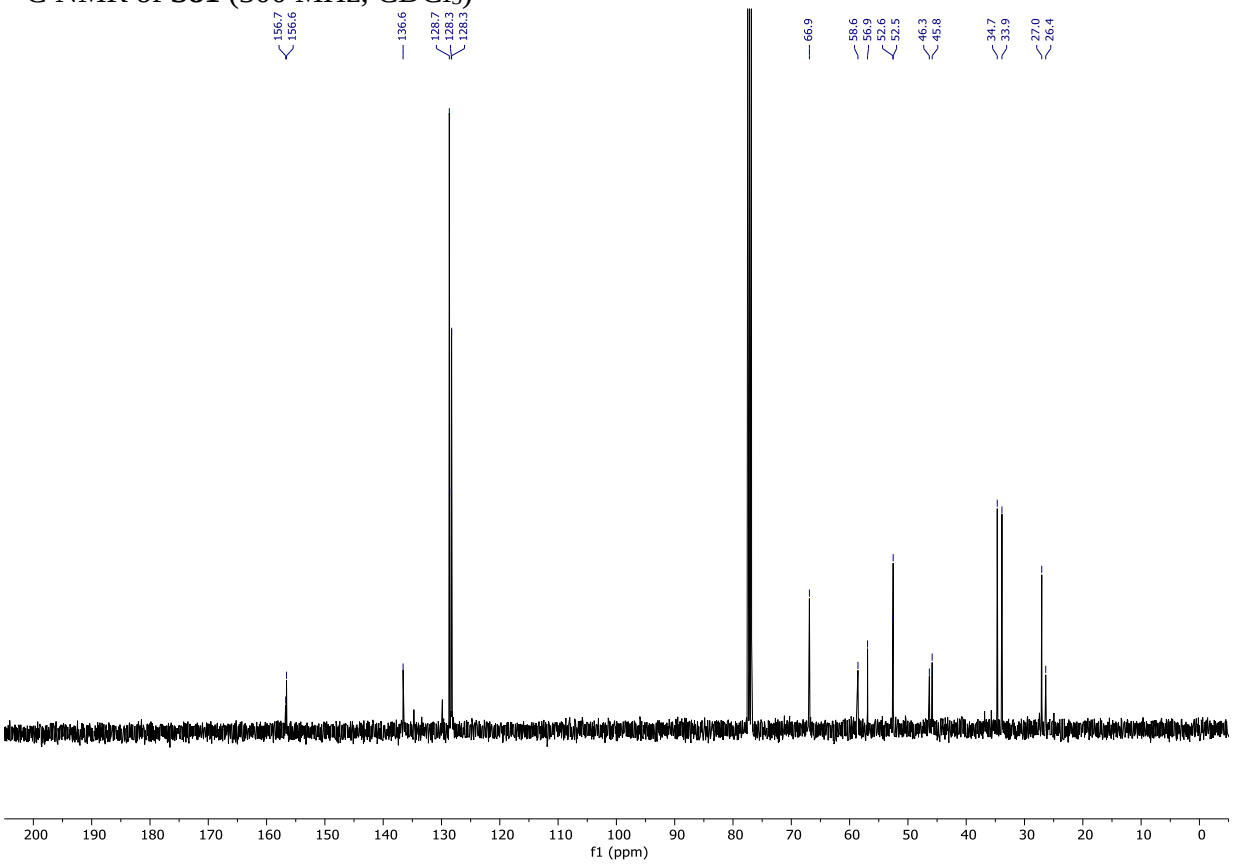
^{13}C NMR of **S80** (101 MHz, $CDCl_3$)



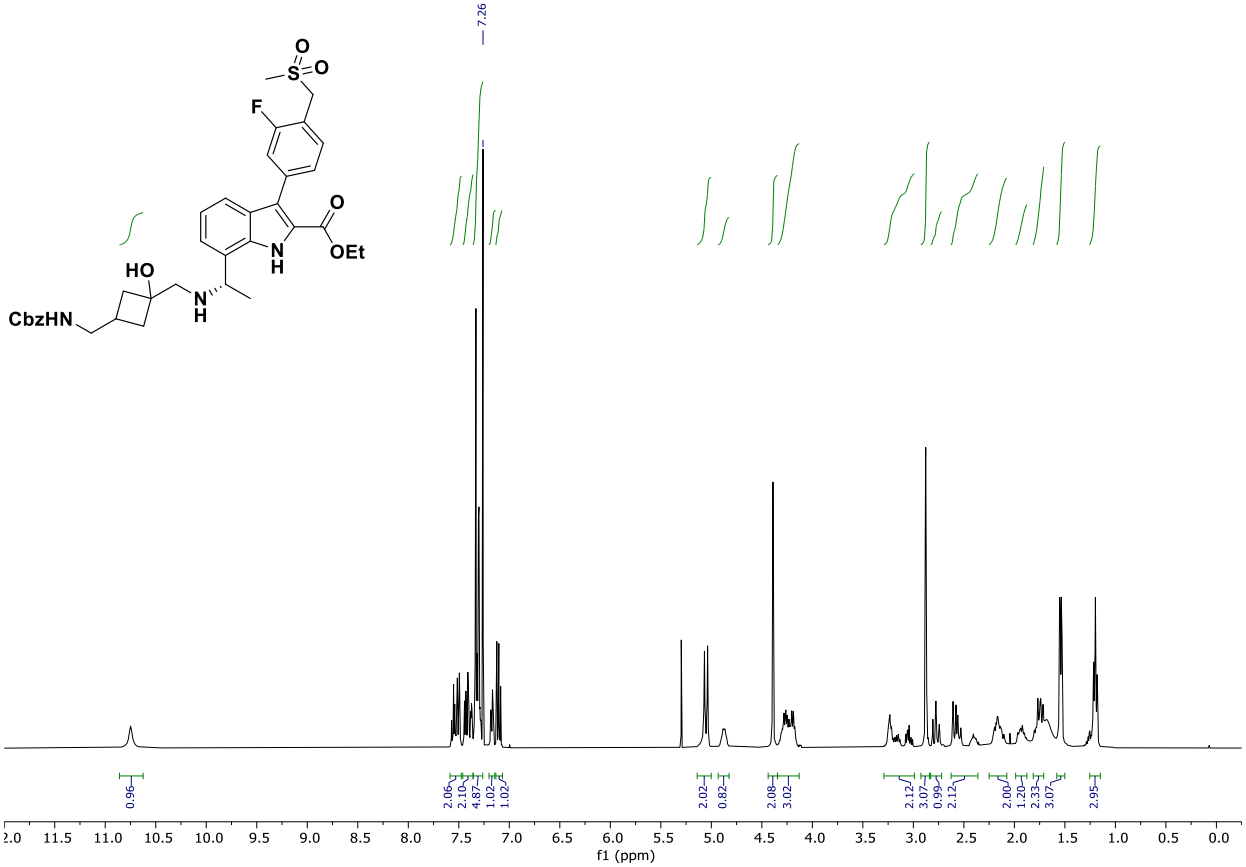
^{1}H NMR of **S81** (300 MHz, $CDCl_3$)



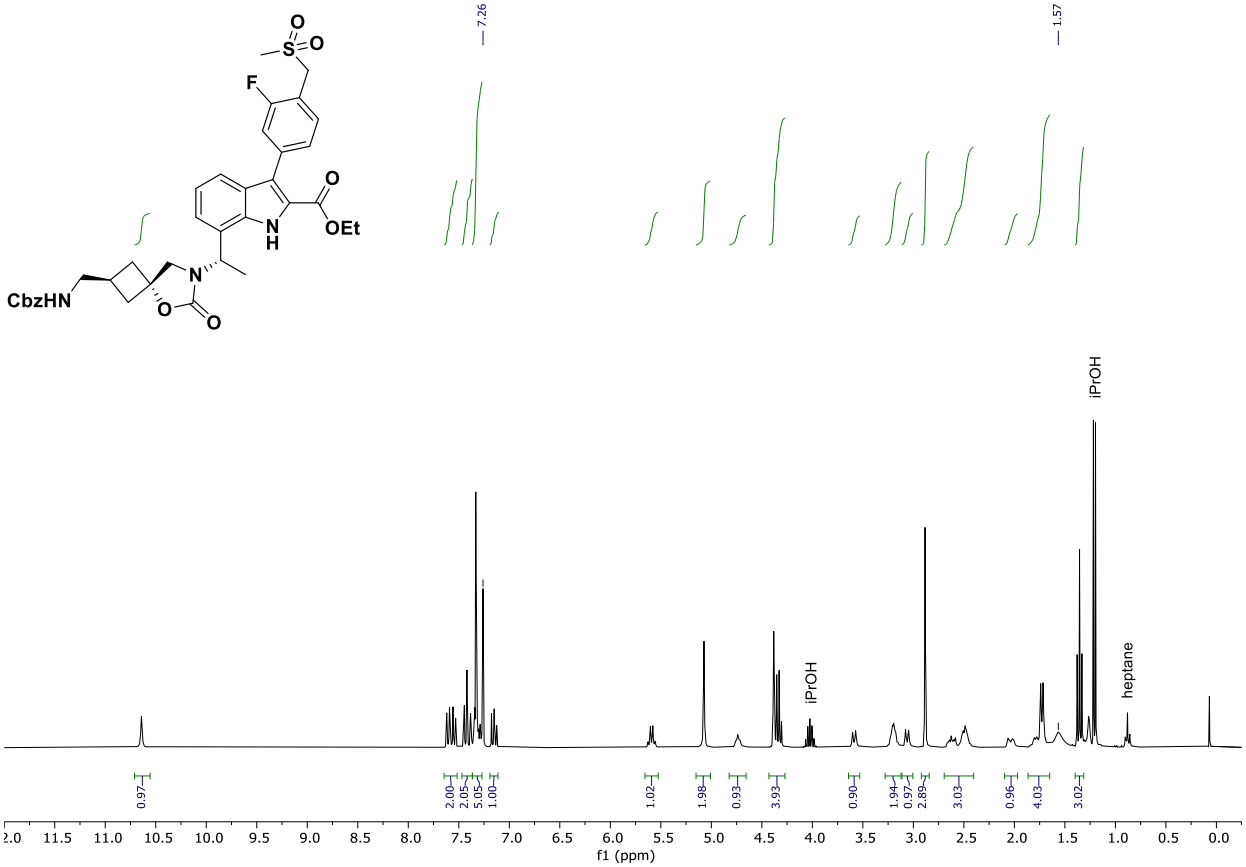
^{13}C NMR of **S81** (300 MHz, $CDCl_3$)



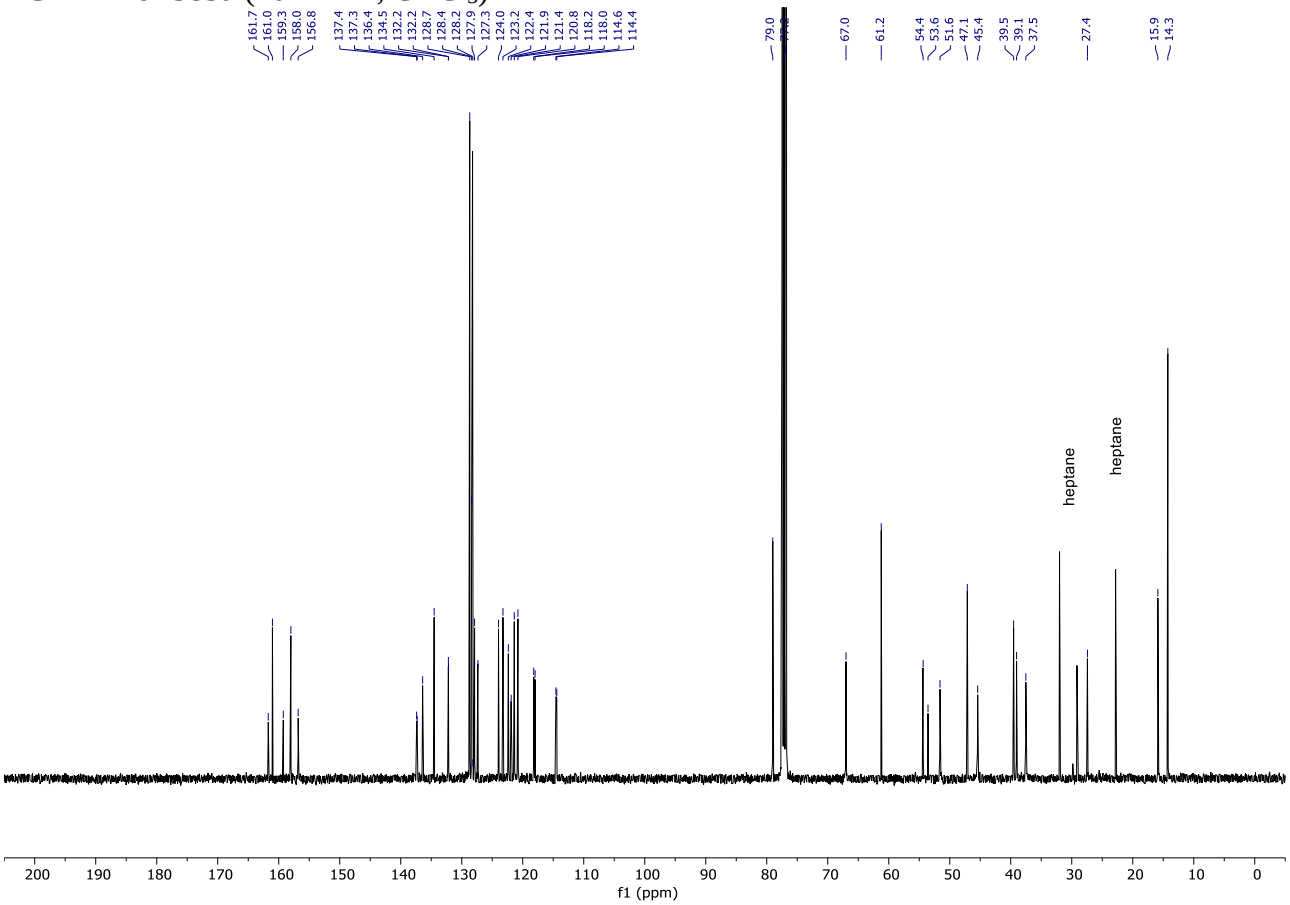
^{1}H NMR of **S82** (400 MHz, $CDCl_3$)



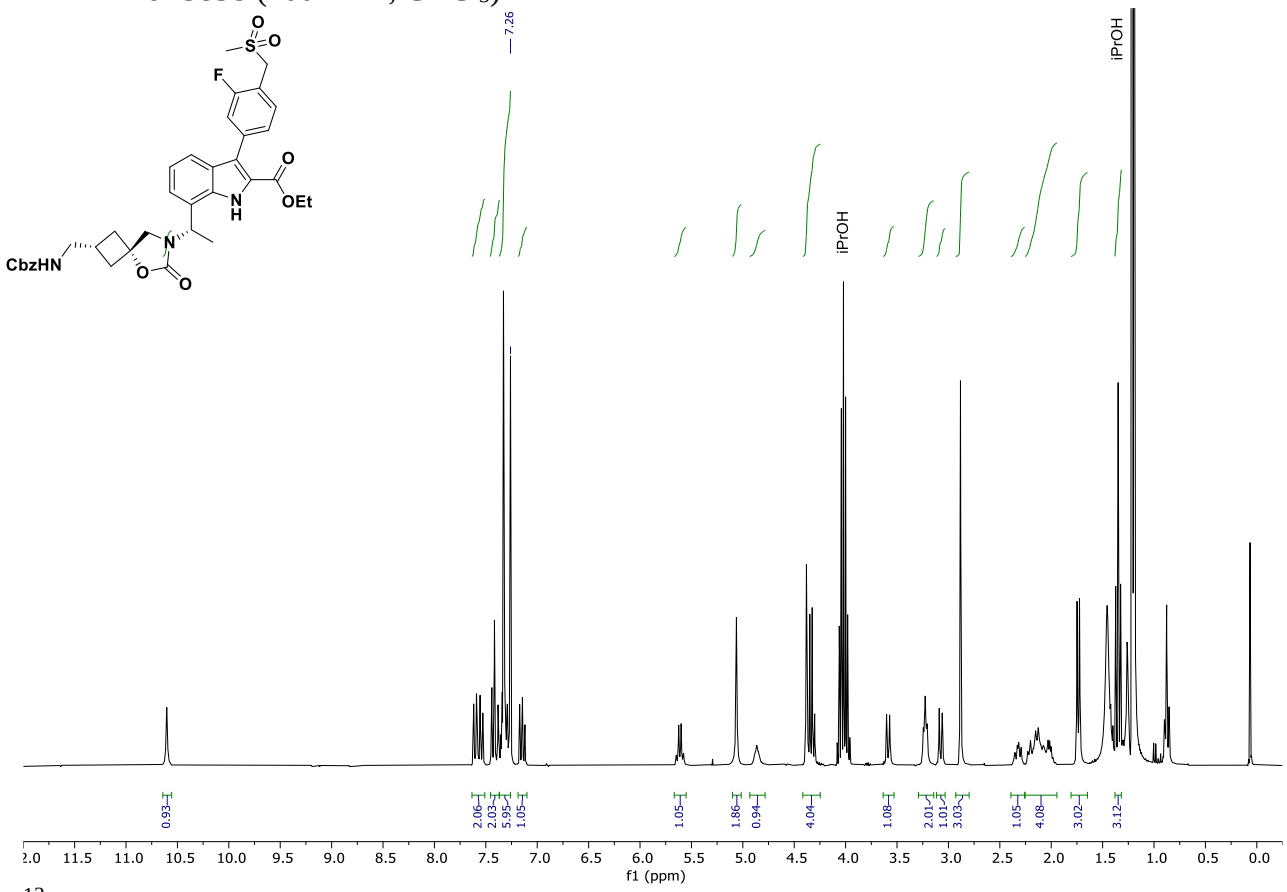
^{1}H NMR of **S83a** (400 MHz, $CDCl_3$)



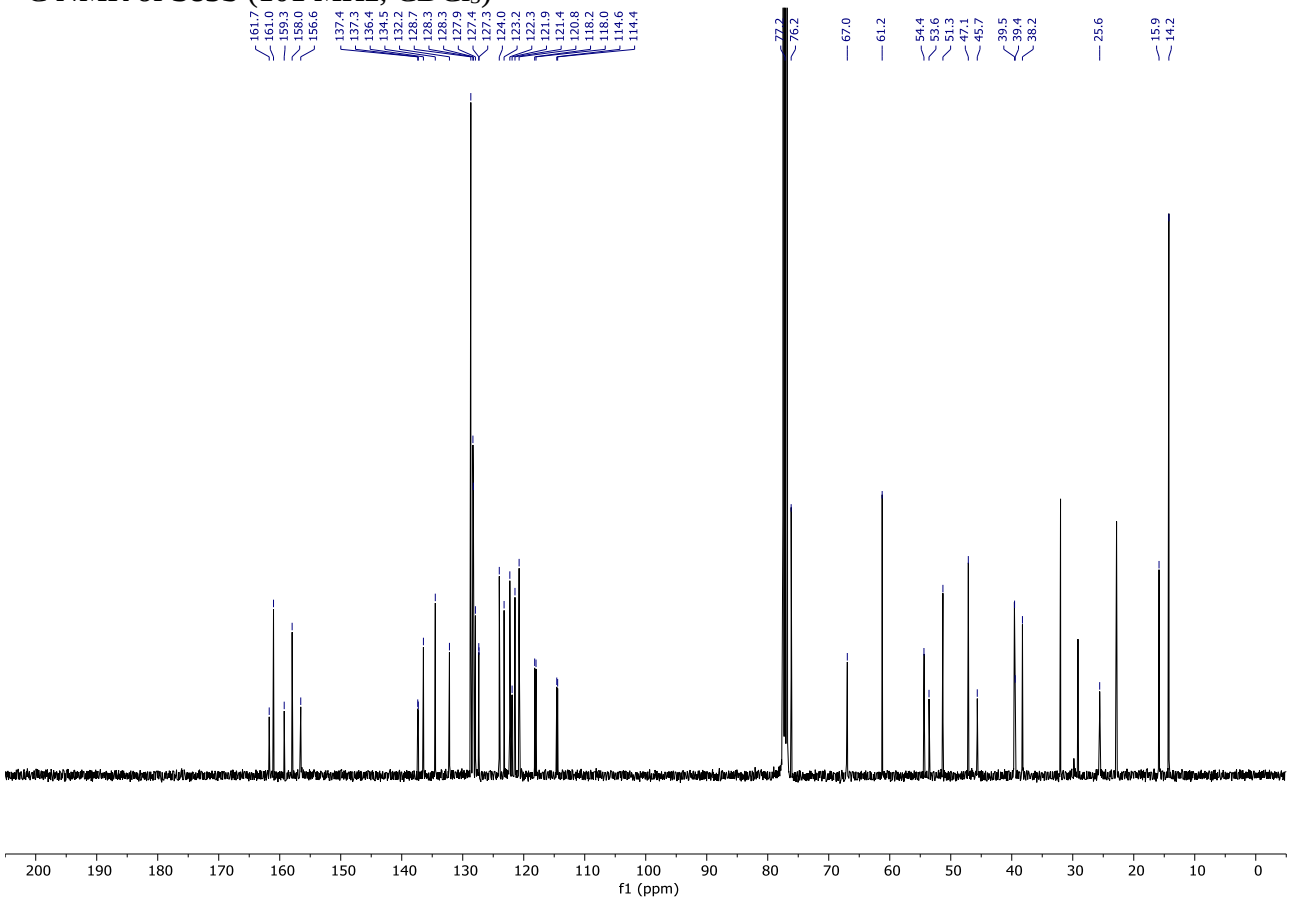
^{13}C NMR of **S83a** (101 MHz, $CDCl_3$)



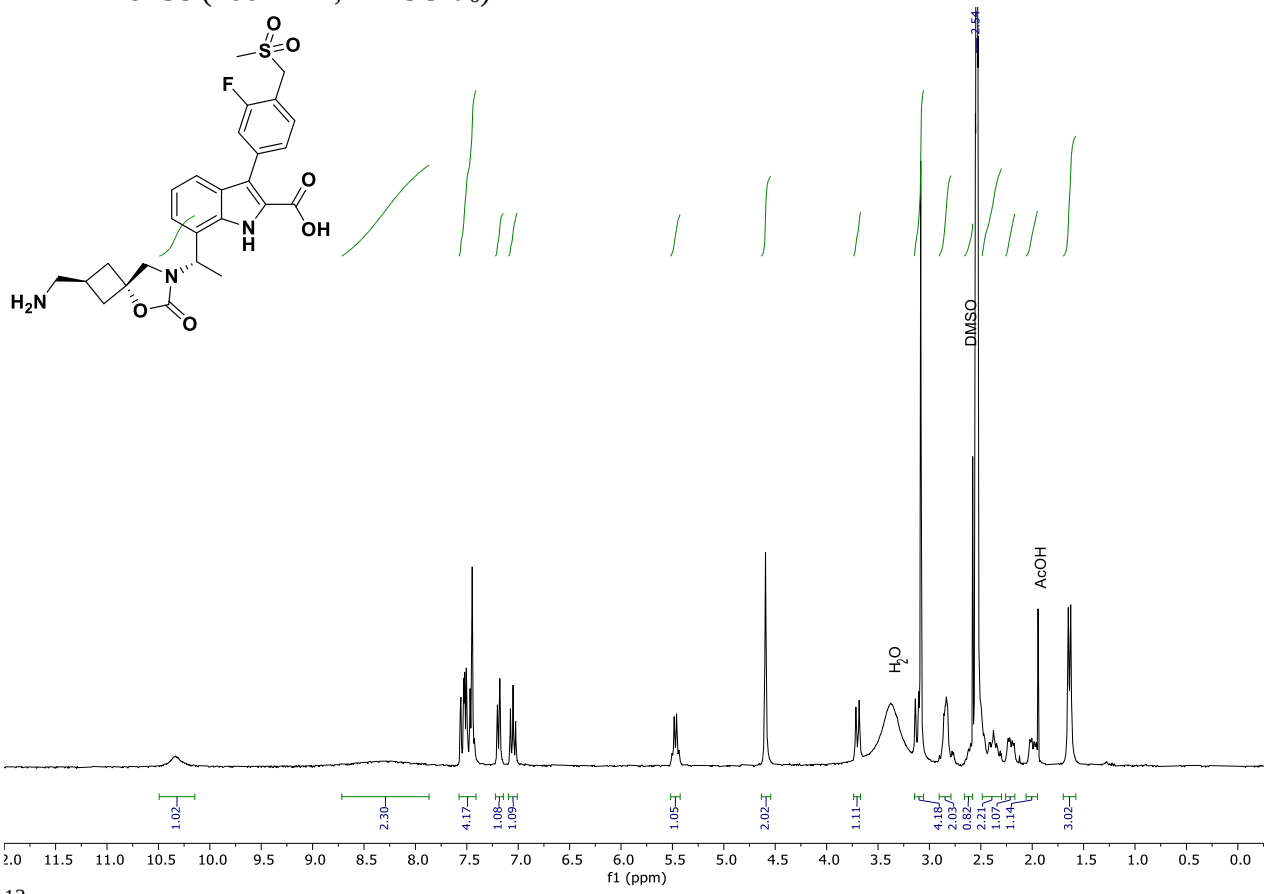
^{1}H NMR of **S83b** (400 MHz, $CDCl_3$)



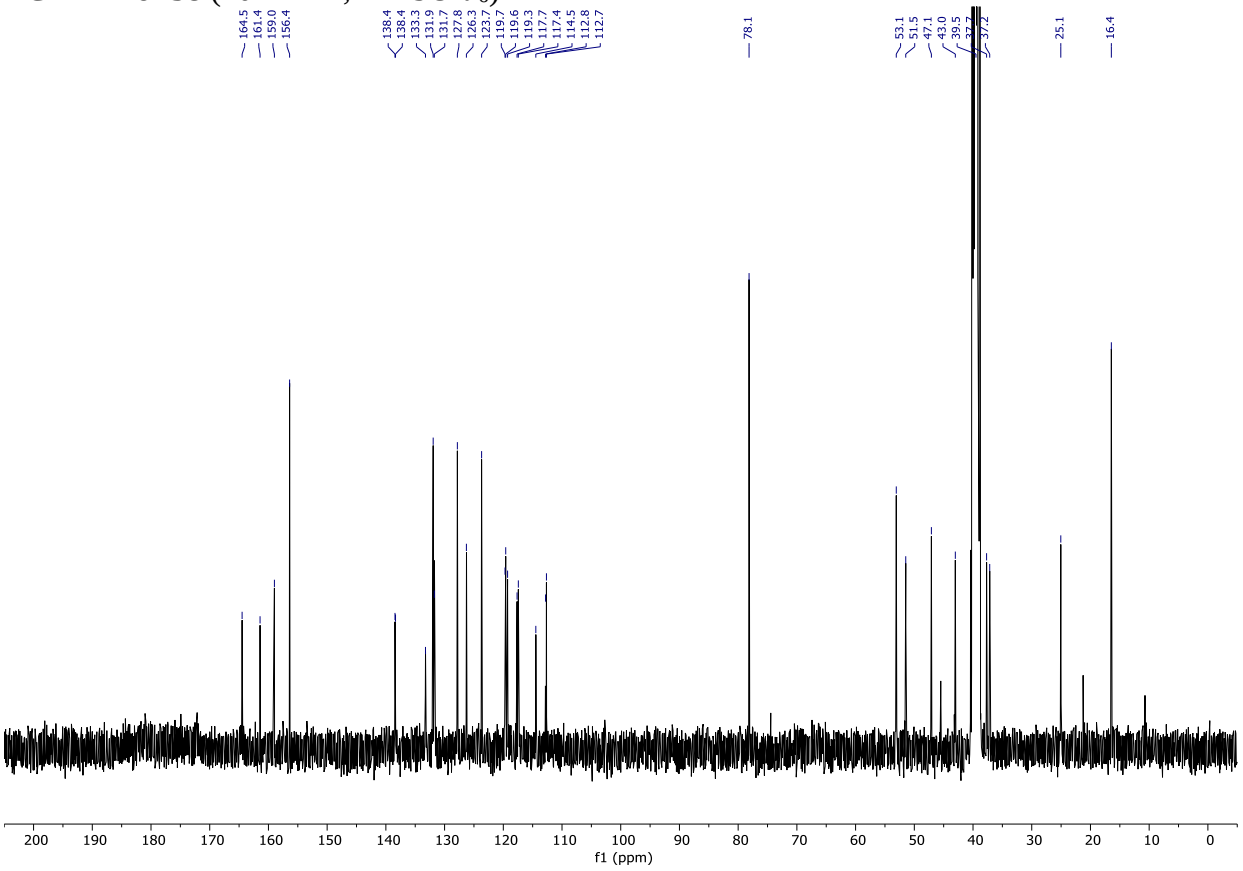
^{13}C NMR of **S83b** (101 MHz, $CDCl_3$)



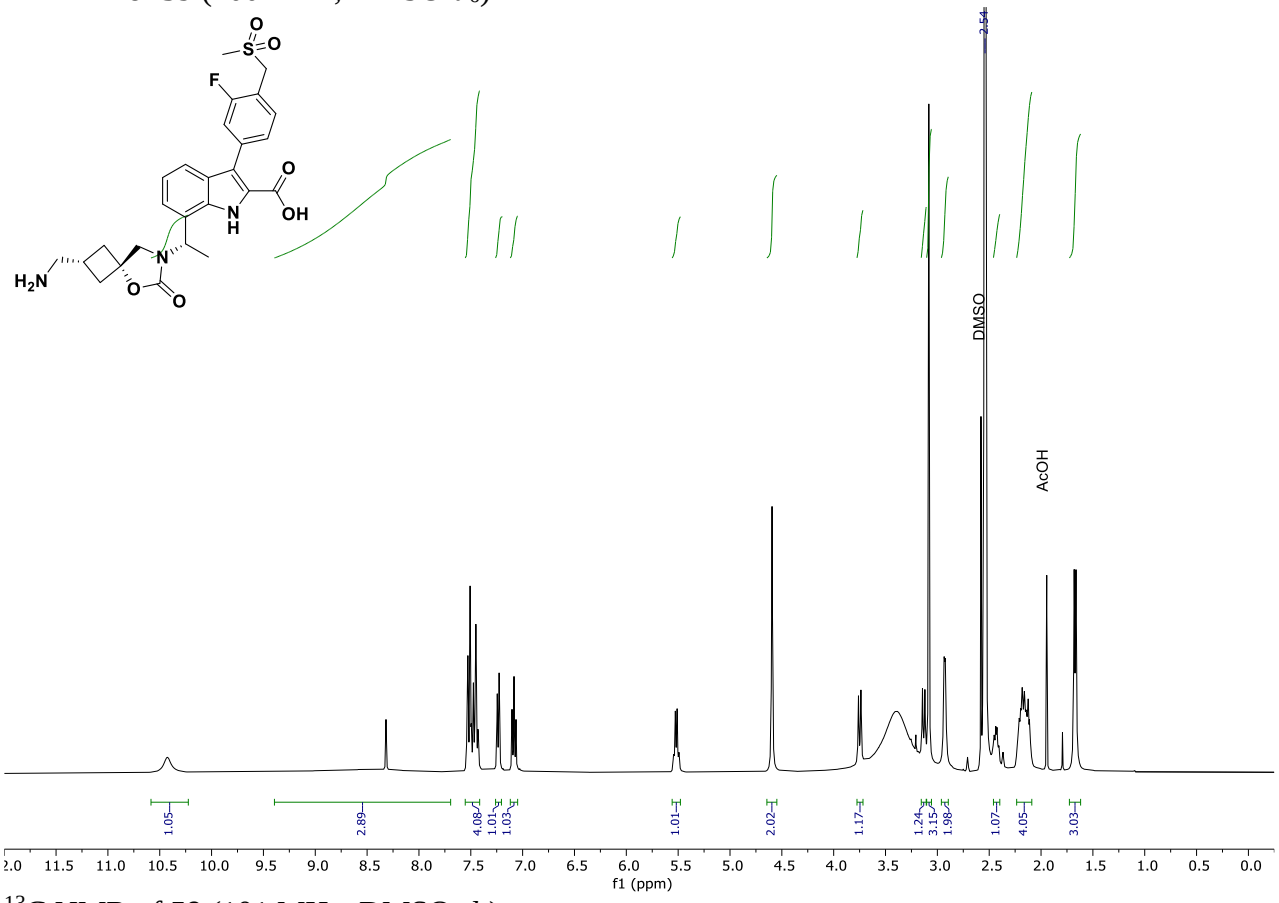
^{1}H NMR of **58** (400 MHz, DMSO-d_6)



^{13}C NMR of **58** (101 MHz, DMSO-d_6)



^{1}H NMR of **59** (400 MHz, DMSO-d_6)



^{13}C NMR of **59** (101 MHz, DMSO-d_6)