Electronic Supplementary Material (ESI) for RSC Advances.

Data-Driven Development of a Selective and Scalable *N*1-Indazole Alkylation

Supporting Information

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Contents

General Considerations

Reagents and solvents were purchased from commercial suppliers or external vendors and used without further purification.

Reactions were conducted on Mettler Toledo EasyMax 102 reactors. Hydrogenation reactions were conducted in Type 3 Buchiglasuster reactors.

Melting points were measured with a Stuart SMP50 Automatic Digital Melting Point Apparatus.

Infrared spectra were recorded on a Thermo Scientific Nicolet iS50 FTIR Spectrometer equipped with a diamond ATR module.

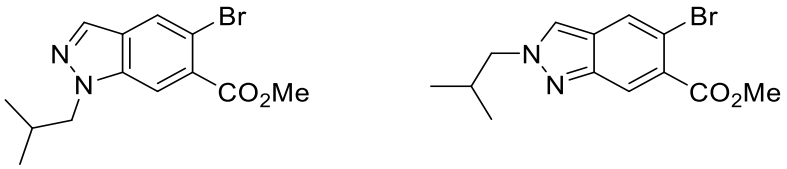
NMR spectra for characterisation were obtained on a Bruker AVANCE Neo 400 MHz spectrometer. Chemical shifts are reported in ppm and coupling constants are reported in Hz and rounded to the nearest 0.5 Hz. ^{1}H and ^{13}C chemical shifts are referenced to the appropriate residual solvent signal.[1]

High resolution mass spectra were recorded on an Agilent 6550 iFunnel Q-TOF LC/MS or ThermoFisher Orbitrap Exploris 120 Mass Spectrometers. High resolution values are calculated to four decimal places from the molecular formula and within a tolerance of ±5 ppm.

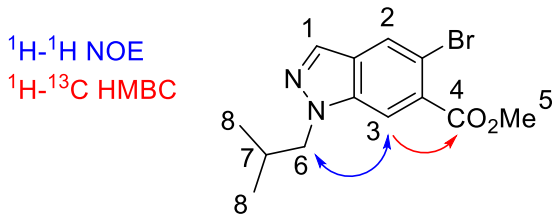
Initial Synthesis and NMR Assignment (unoptimized)

Synthesis and Characterisation

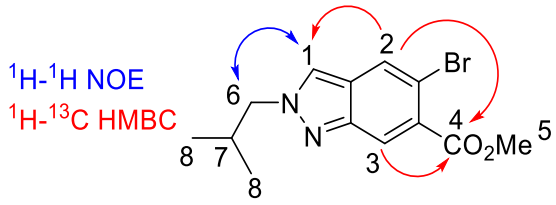
Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate and methyl 5-bromo-2-isobutyl-2*H*-indazole-6-carboxylate (2a and 3a)



1-Bromo-2-methylpropane (0.85 mL, 7.84 mmol, 1.0 equiv) was added to potassium carbonate (1.20 g, 8.63 mmol, 1.1 equiv) and methyl 5-bromo-1*H*-indazole-6-carboxylate (2.00 g, 7.84 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (20 mL). The reaction mixture was heated to 120 °C for 1 hour, then cooled to 20 °C. The reaction mixture was diluted with MTBE (100 mL), then washed with H_2O (100 mL), sat. brine (100 mL) and 5% $LiCl_{(aq)}$ (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 40% EtOAc in heptane) to afford methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (1.15 g, 3.70 mmol, 47%) as an orange oil, followed by methyl 5-bromo-2-isobutyl-2*H*-indazole-6-carboxylate (0.62 g, 1.98 mmol, 25%) as a yellow oil.



ν_{max} (neat) /cm^{-1} 2957, 1729, 1470, 1244; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, **H2**), 7.97 (s, 1H, **H1**), 7.85 (s, 1H, **H3**), 4.19 (d, *J* = 7.5 Hz, 2H, **H6**), 3.99 (s, 3H, **H5**), 2.42 – 2.25 (m, 1H, **H7**), 0.93 (d, *J* = 6.5 Hz, 6H, **H8**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3 (**C4**), 138.1, 131.6, 129.9, 126.5, 126.4, 112.6, 111.5, 56.8, 52.4, 30.2, 20.8; **HRMS** (ESI$^+$) calc. for $C_{13}H_{16}{}^{79}BrN_2O_2$ ([M+H]$^+$) 311.0390; found 311.0392.



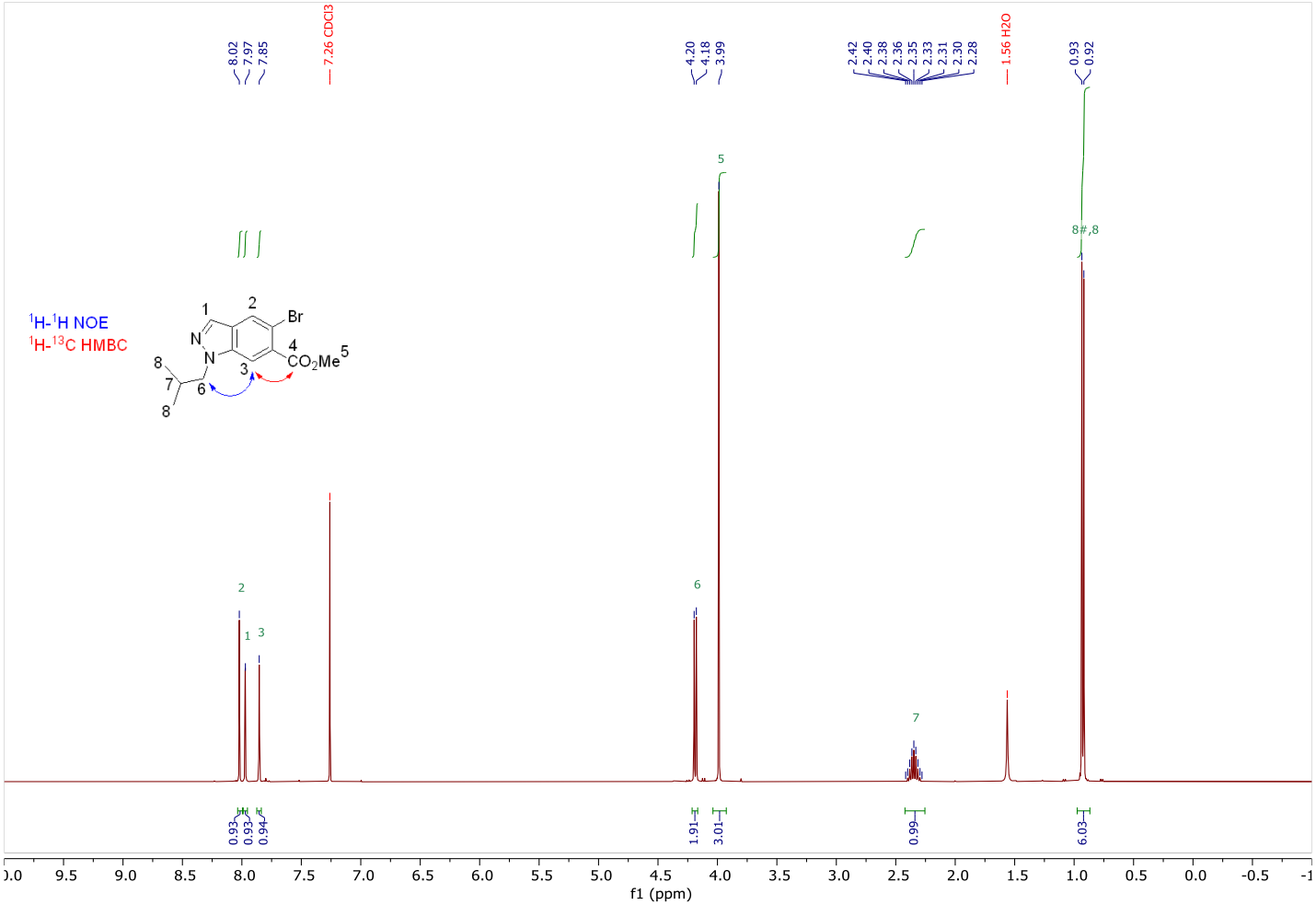
ν_{max} (neat) /cm^{-1} 2958, 1726, 1256, 1215, 1093, 1012, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, **H3**), 7.92 (s, 1H, **H2**), 7.84 (s, 1H, **H1**), 4.18 (d, *J* = 5.5 Hz, 2H, **H6**), 3.93 (s, 3H, **H5**), 2.47 – 2.24 (m, 1H, **H7**), 0.91 (d, *J* = 6.5 Hz, 6H, **H8**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 146.6, 129.8, 125.3, 123.8, 123.6, 122.9, 121.9, 112.0, 61.7, 52.6, 30.0, 20.0; **HRMS** (ESI$^+$) calc. for $C_{13}H_{16}{}^{79}BrN_2O_2$ ([M+H]$^+$) 311.0390; found 311.0385.

NB: Crude *N*1:*N*2 ratio was 58:42 by LCMS (225 nm)

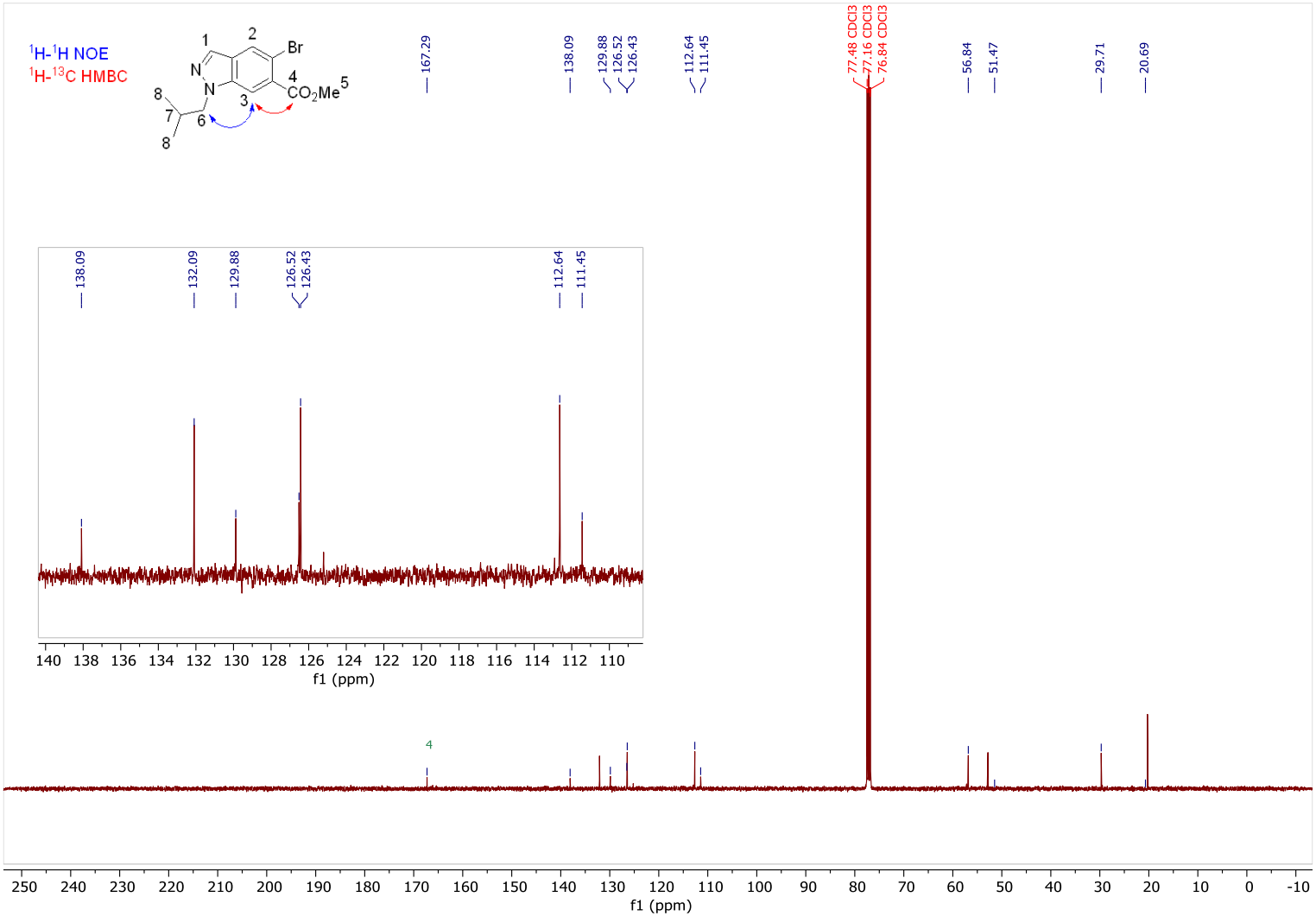
NMR Spectra for Assignment

Methyl 5-bromo-2-isobutyl-1*H*-indazole-6-carboxylate

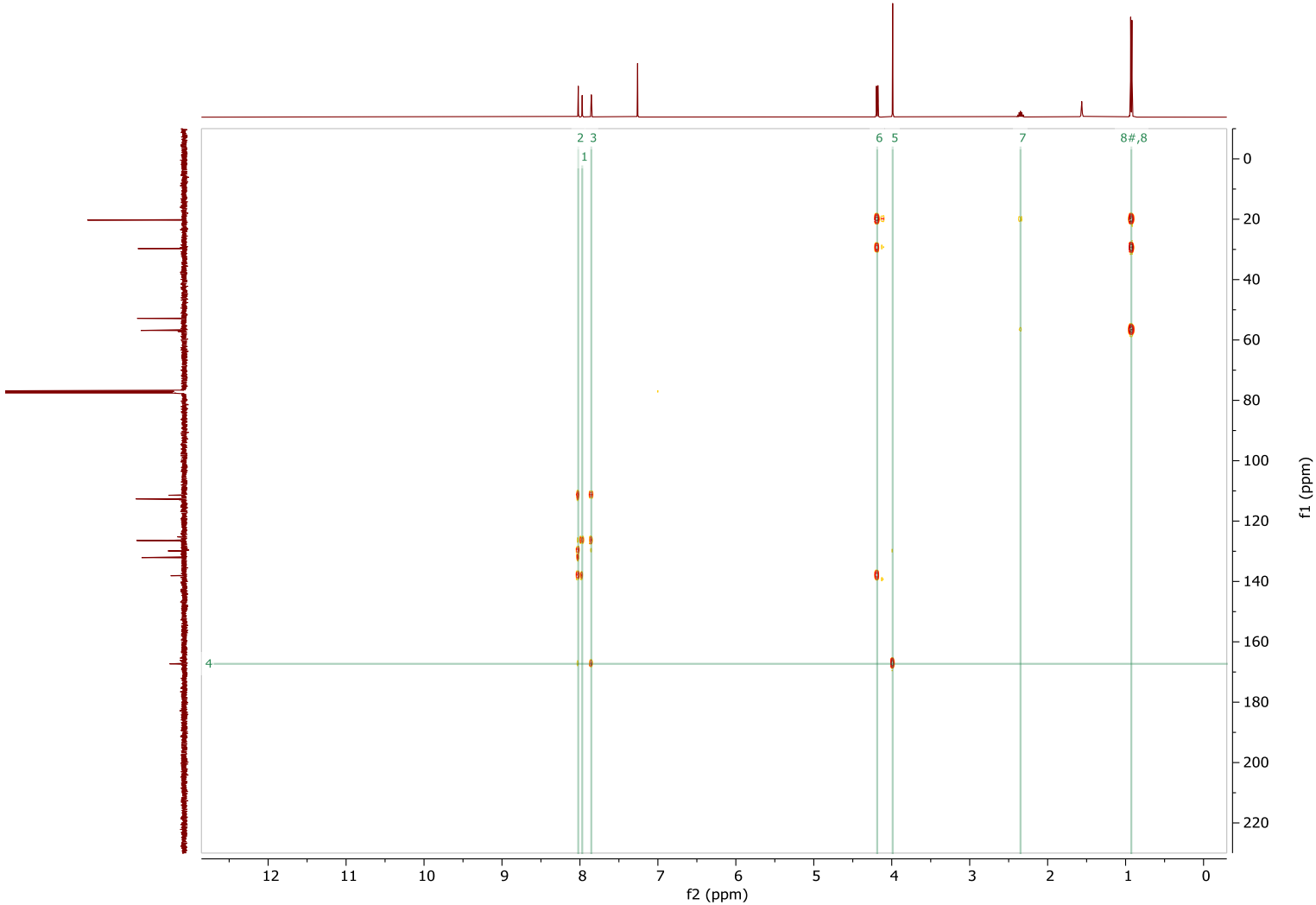
^{1}H NMR (400 MHz, $CDCl_3$)



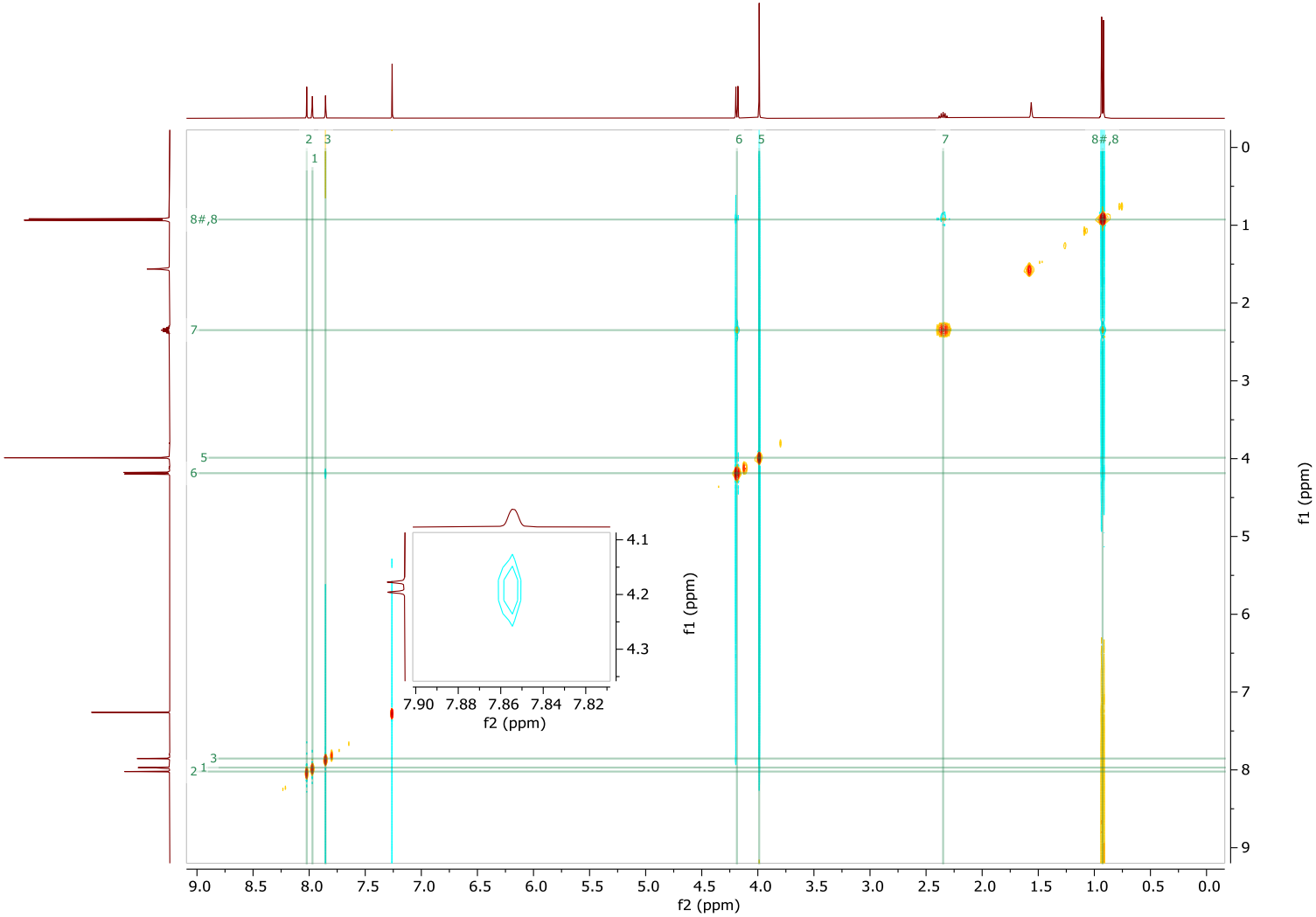
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

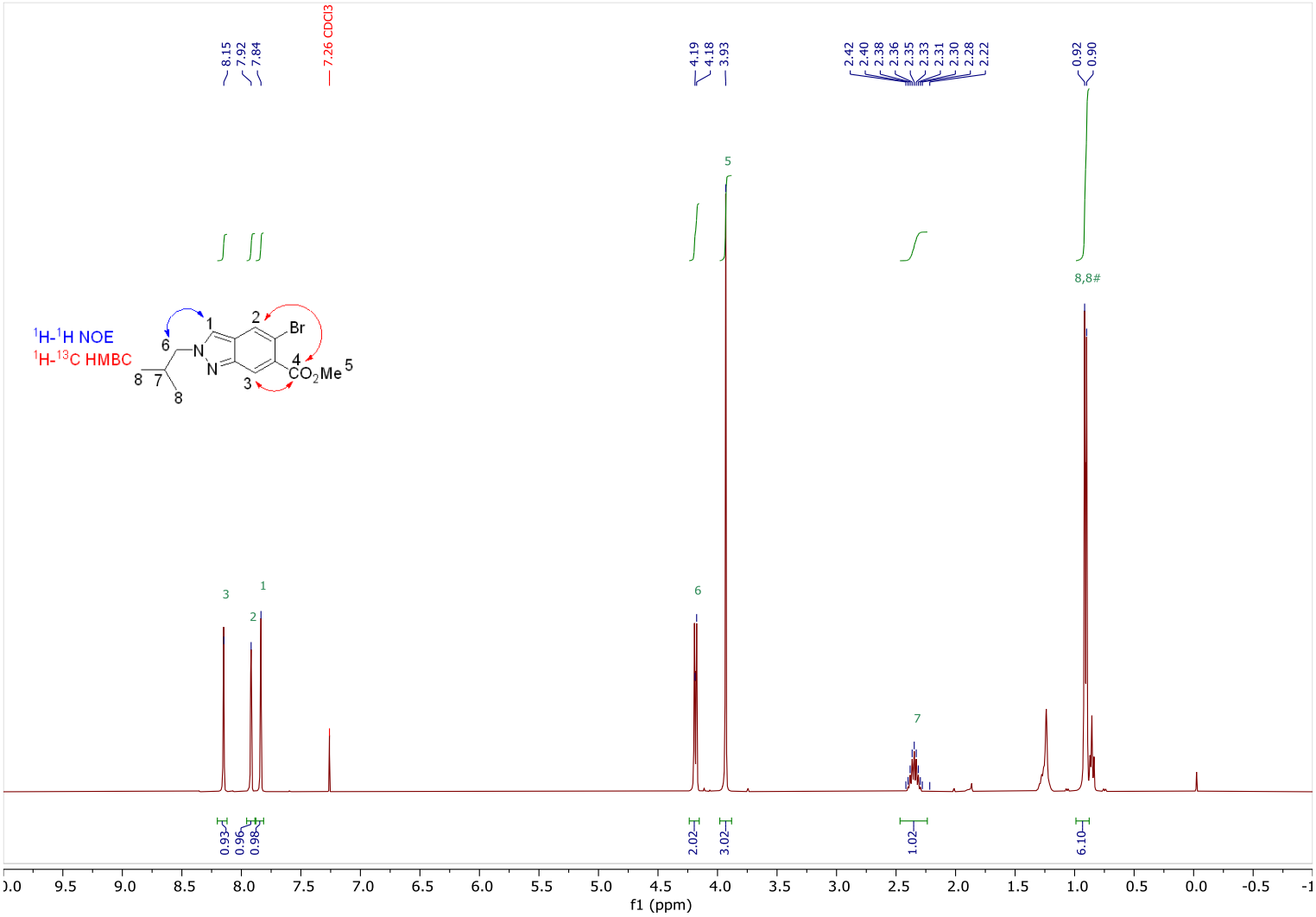


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

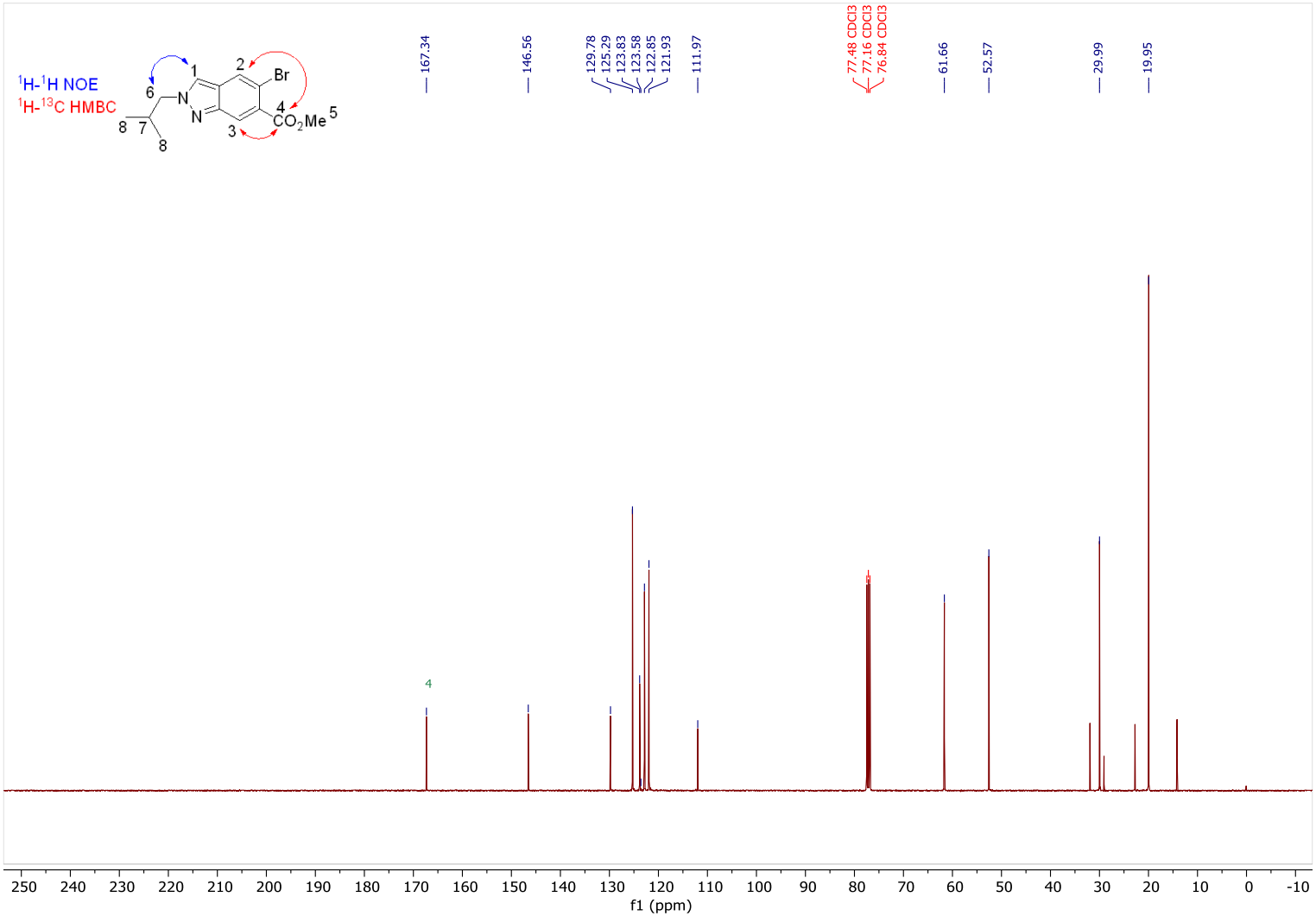


Methyl 5-bromo-1-isobutyl-2*H*-indazole-6-carboxylate

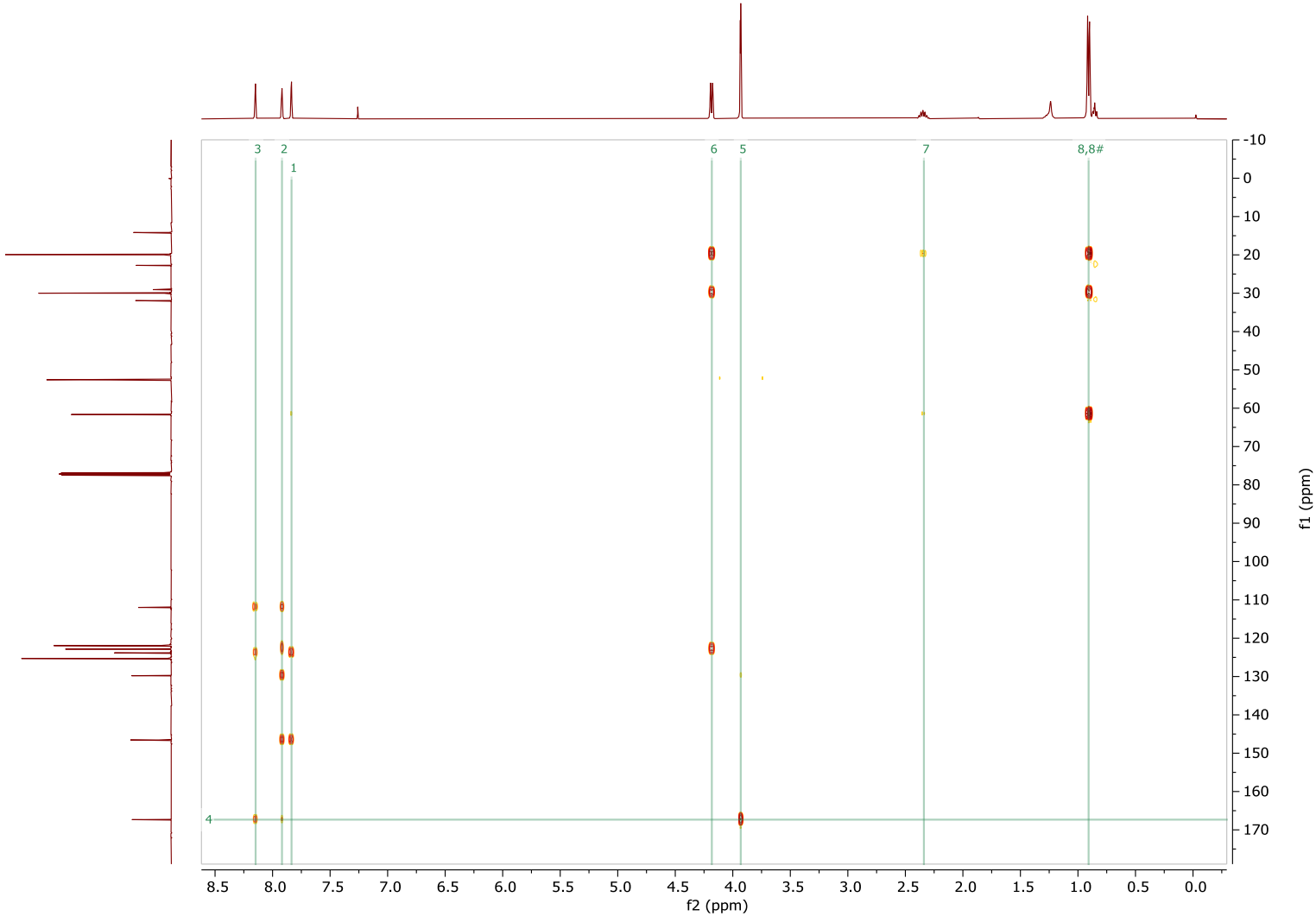
^{1}H NMR (400 MHz, $CDCl_3$)



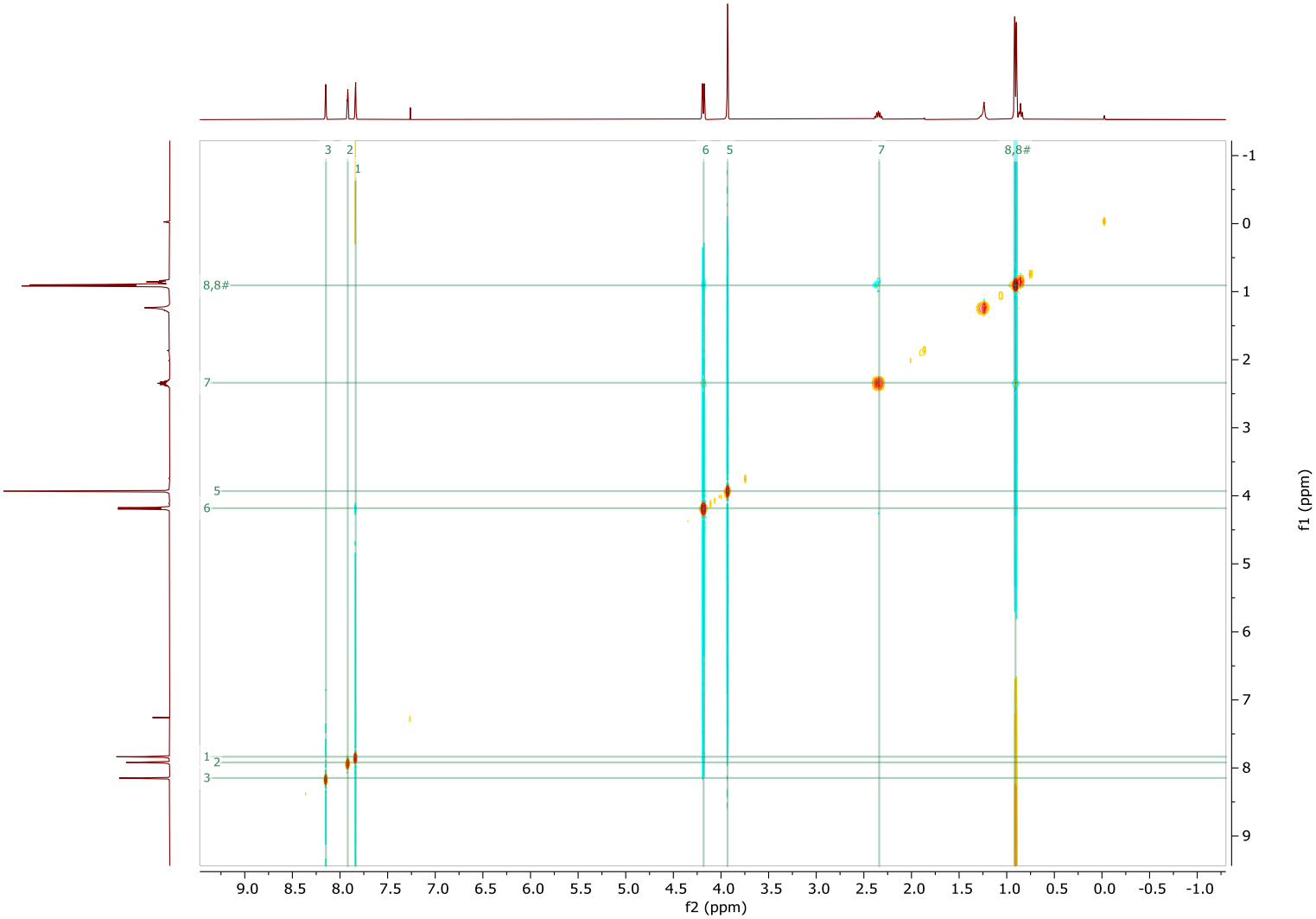
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

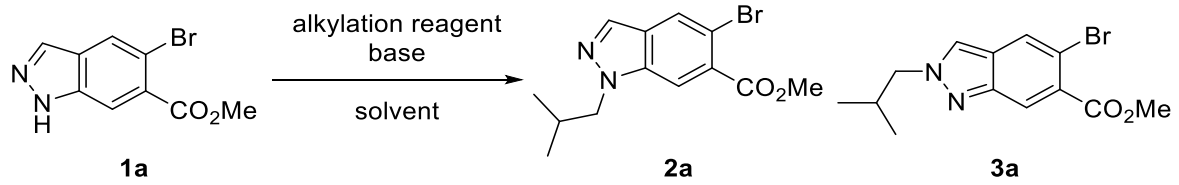


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)



Lab Chemist Investigation

Alkylation reagent was added to base, methyl 5-bromo-1*H*-indazole-6-carboxylate **1a**, and solvent in a sealed vial. The vial was stirred at the indicated temperature and time. A sample for LCMS analysis was prepared from 20 µL of reaction mixture in MeCN:H_2O (4:1, 1 mL). Conversion and *N*1:*N*2 ratio determined by LCMS at 225 nm.



1a **2a** **3a**

entry	alkylation reagent	base	solvent	temp	time	conversion (ratio **2a**:**3a**)
1	^{i}BuBr (1.0 equiv)	K_2CO_3 (1.1 equiv)	DMF	120 °C	1 h	90% (58:42)
2	^{i}BuBr (1.1 equiv)	K_2CO_3 (1.1 equiv)	DMF	120 °C	1 h	>99% (58:42)
3	^{i}BuBr (1.2 equiv)	NaH (60%) (1.2 equiv)	DMF	0 °C	2 h	31% (53:47)
4	^{i}BuBr (1.5 equiv)	K_2CO_3 (1.5 equiv)	THF	70 °C	21 h	15% (41:59)
5	^{i}BuBr (1.2 equiv)	NaH (60%) (1.2 equiv)	THF	0 °C	21 h	2% (56:44)
6	^{i}BuBr (1.1 equiv)	Et_3N (1.4 equiv)	CH_2Cl_2	40 °C	3 h	1% (69:31)
7	^{i}BuI (1.1 equiv)	Et_3N (1.4 equiv)	CH_2Cl_2	40 °C	3 h	7% (4:96)
8	^{i}BuOH (5.0 equiv)	PPh_3 (2.0 equiv) DIAD (2.0 equiv)	THF	60 °C 2 h	2 h	>99% (53:47)

High-Throughput Experimentation Investigation

Screen Design

Base selection

entry	base	selected descriptors		
		p*K*a of conjugate acid	form (rt)	type
1	Na_2CO_3	20.8±0.1 (DMSO)[2]	Solid	Carbonate
2	K_2CO_3	20.8±0.1 (DMSO)[2]	Solid	Carbonate
3	Cs_2CO_3	20.8±0.1 (DMSO)[2]	Solid	Carbonate
4	K_3PO_4	12.35 (H_2O)[3]	Solid	Phosphate
5	KO^{t}Bu	16.54 (H_2O)[4]	Solid	Alkoxide
6	$KOSiMe_3$	11[5]	Solid	Alkoxide
7	DMAP	11.2 (THF)[6]	Solid	Amine
8	TBD	21.0 (THF)[6]	Solid	Amine
9	pyridine	5.5 (THF)[6]	Liquid	Amine
10	2,6-di-^{t}butylpyridine	3.58 (EtOH/H_2O 1:1)[7]	Liquid	Amine
11	Et_3N	12.5 (THF)[6]	Liquid	Amine
12	NaH (60%)	35.3±0.3 (THF/18-crown-6)[8]	Solid	Hydride

Reagent selection

entry	reagent	selected descriptors	
		leaving group	b.p. (°C)
1	isobutyl bromide	bromide	90-92[a]
2	isobutyl iodide	iodide	120-121[a]
3	isobutyl mesylate	mesylate	82 (6.0 mmHg)[b]
4	isobutyl tosylate	tosylate	163-165 (6.0 mmHg)[c]

[a]Sigma-Aldrich. [b]Fisher Scientific. [c]ref 9.

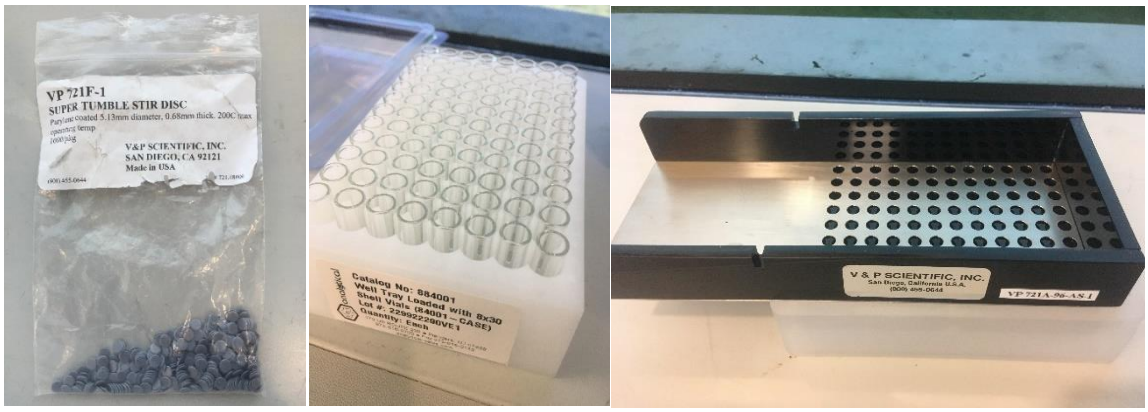
Solvent selection

entry	reagent	class	selected descriptors				
			Hansen solubility parameter[a]			Polarity *P'*[b]	b.p. (°C)[c]
			δ_d	δ_p	δ_h		
1	MeCN	nitrile	15.3	18.0	16.1	5.8	82
2	THF	ether	16.8	5.7	8.0	4.0	66
3	NMP	amide	18.0	12.3	7.2	6.7	202
4	PhMe	aromatic	18.0	1.4	2.0	2.4	110

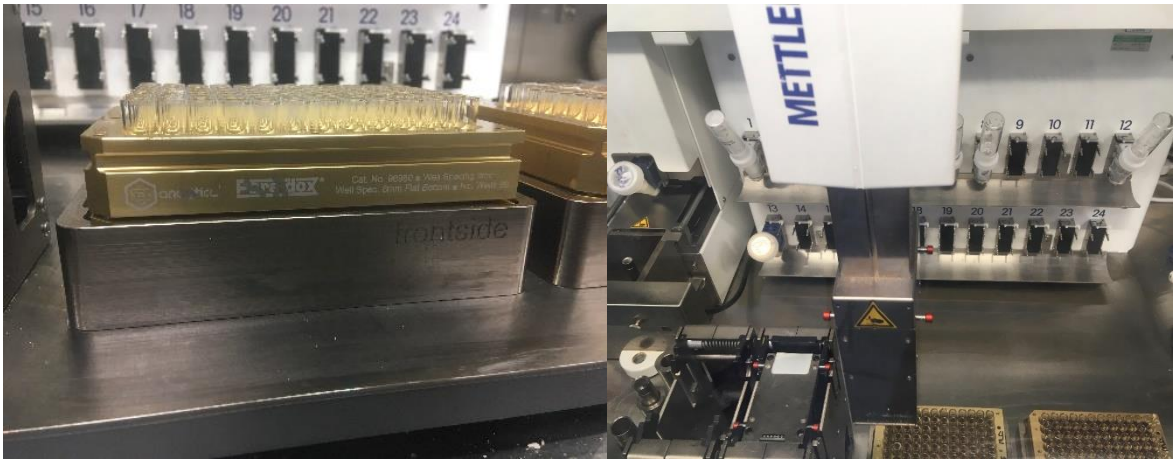
[a]ref 10. [b]ref 11. [c]Sigma-Aldrich.

Procedure

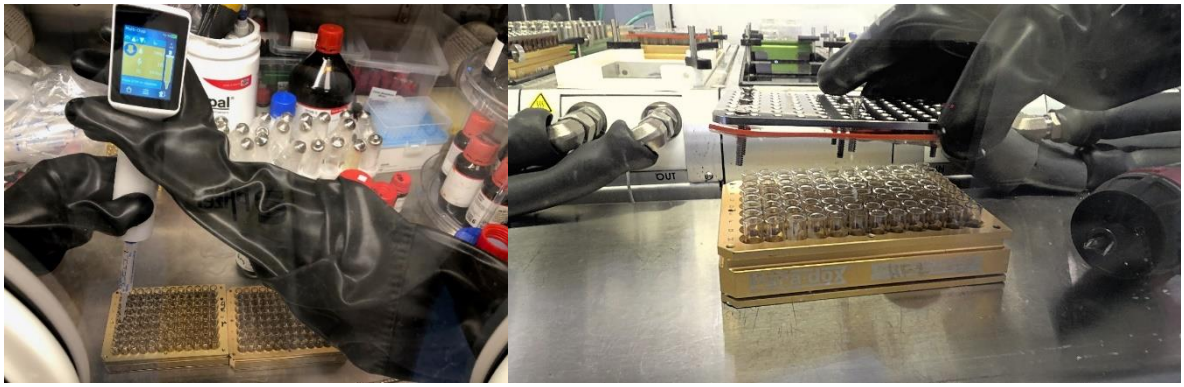
Within a nitrogen glovebox (<100ppm O2), 2×96-well Paradox plates were prepared with 0.8 mL glass shell vials equipped with a tumble stir disc using a stir disc plate dispenser. Methyl 5-bromo-1*H*-indazole-6-carboxylate (15 mg, 58.8 µmol, 1.0 equiv) and solid bases (64.7 µmol, 1.1 equiv) were dispensed using the Mettler Toledo QX96. Solvents (300 µL) were dispensed using an autorepeat pipette follow by alkylation reagent (58.8 µmol, 1.0 equiv), and liquid bases (64.7 µmol, 1.1 equiv). Plates were sealed, and reaction mixtures stirred at Tj 50 °C for 16 h at 500 rpm. Reaction plates were sampled using the 6-tip syringe arm on the Unchained Labs CM3 robot, set to dilute 15 µL of reaction mixture with MeCN:Water (1:1, 700 µL) into a 96 well sample plate. An image of the plate contents was taken at the end of the reaction to illustrate physical form of each reaction vial and its contents.



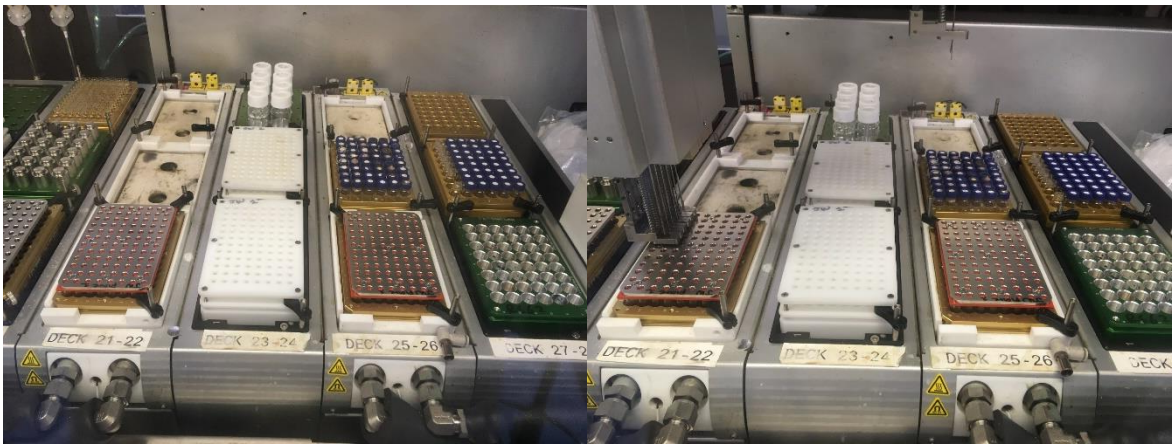
Left: Super tumble stir discs. **Middle**: 0.8 mL glass shell vials. **Right**: Stir disc plate dispenser.



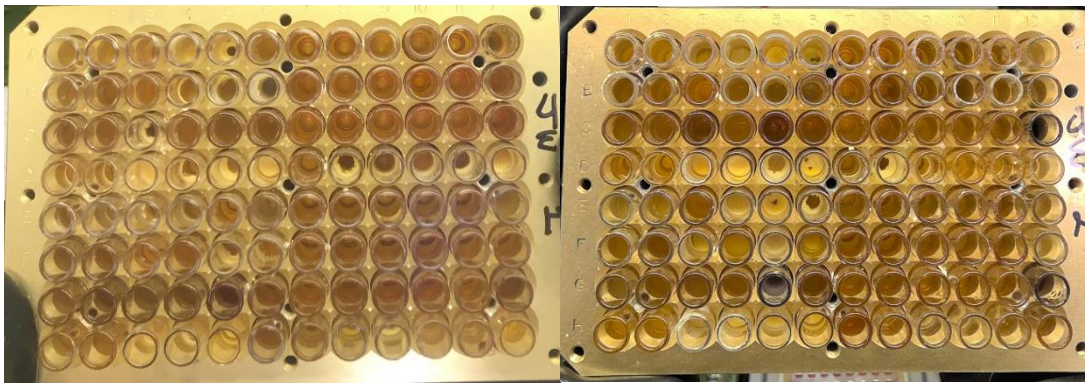
Left: Glass vials in 96-well Paradox plates. **Right**: Mettler Toledo QX96 powder dispensing robot.



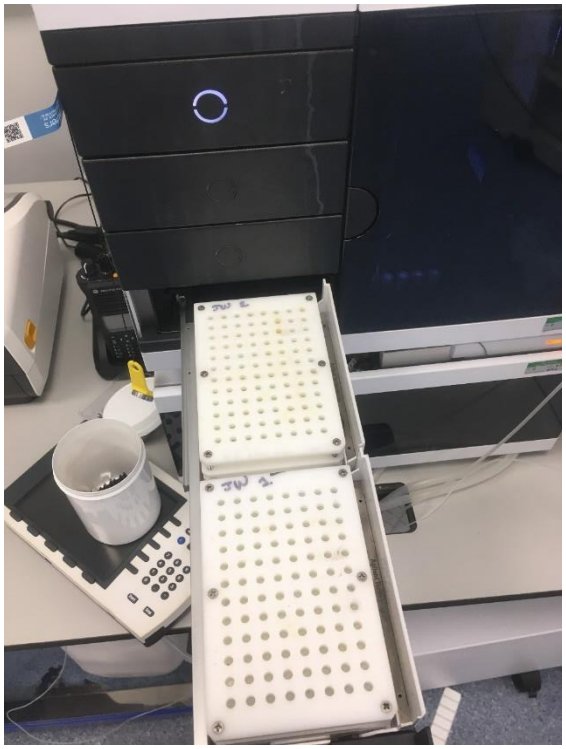
Left: Liquid reagents and solvents dispensed with autopiptte and Eppendorf Combitips. **Right**: Plates sealed with PFA sheet, red rubber mat and metal gasket.



Left: Plates (Deck 21-22 and 25-26) stirring on the Unchained Labs CM3 deck. **Right**: 6-tip syringe arm sampling reactions.



Reaction sample visuals.



Samples prepared for analysis.

HTE Analysis

LCMS instrument parameters

entry	parameter	details
1	system	Agilent 1290
2	column	CORTECS C18 Column 90 Å, 1.6 µm, 2.1 × 50 mm, Waters
3	mobile phase A	0.1% wt. HCOOH in H_2O
4	mobile phase B	MeCN
5	flow rate	1.0 mL/min
6	column temp.	65 °C
7	max pressure limit	1300 bar
8	injection volume	1 µL
9	detection	190-400 nm, 2 nm step 40 Hz data collection rate

LCMS method gradient

time (min)	mobile phase A%	mobile phase B%
0.00	95	5
1.00	0	100
1.30	0	100
1.31	95	5

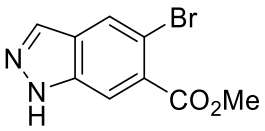
Key retention times

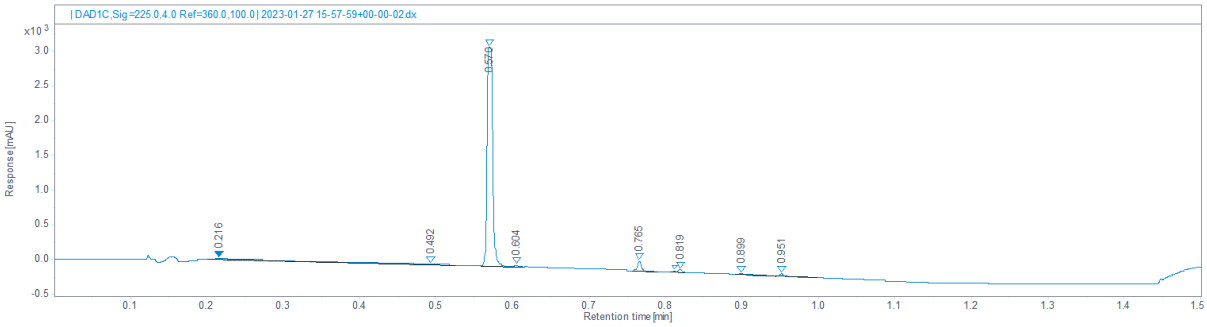
1a: rt = 0.57 min

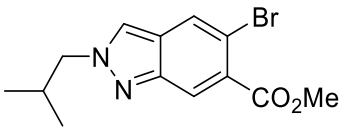
2a: rt = 0.82 min

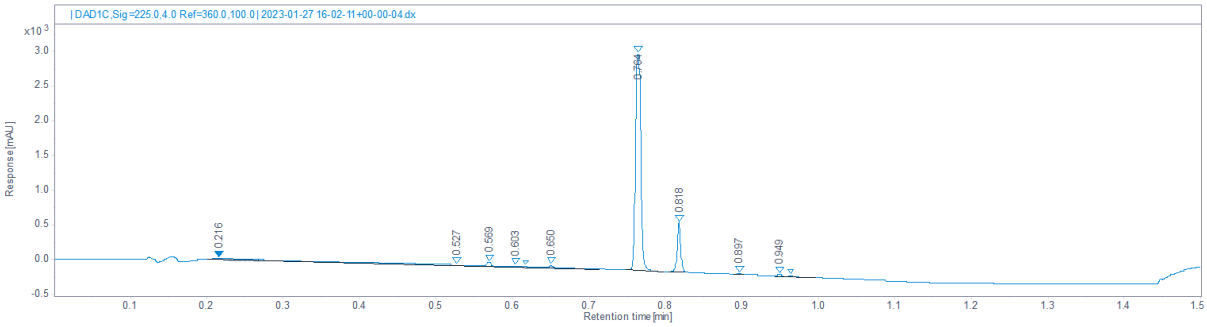
2b: rt = 0.76 min

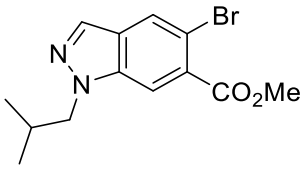
Reference LC traces

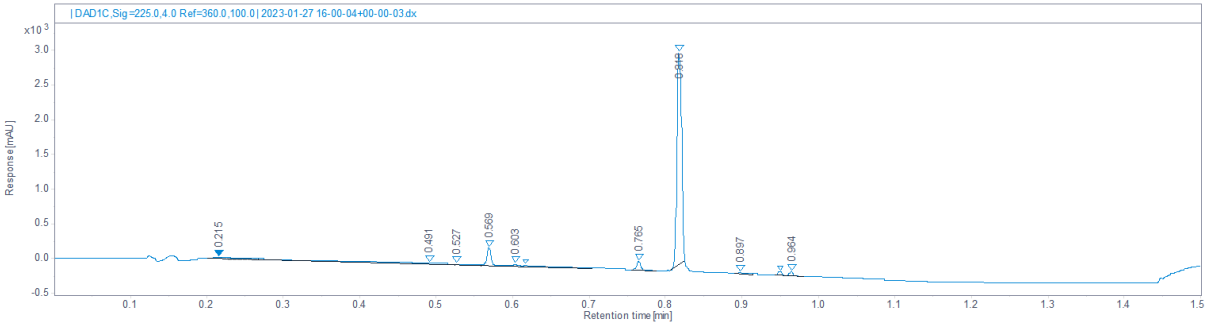






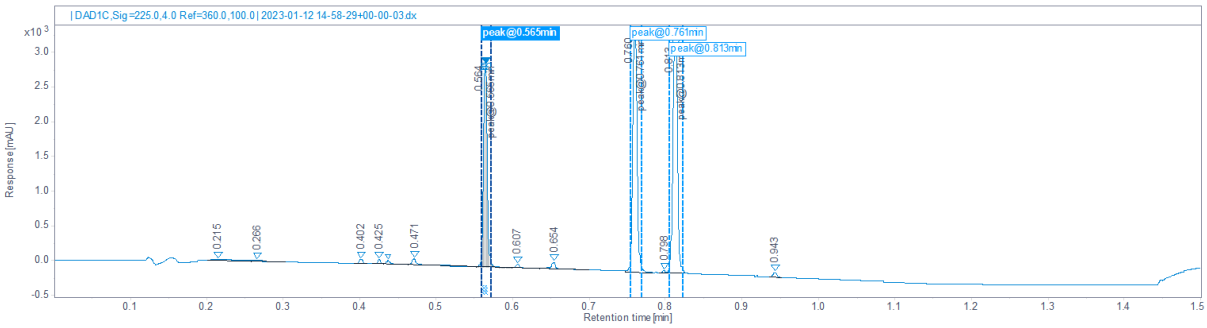






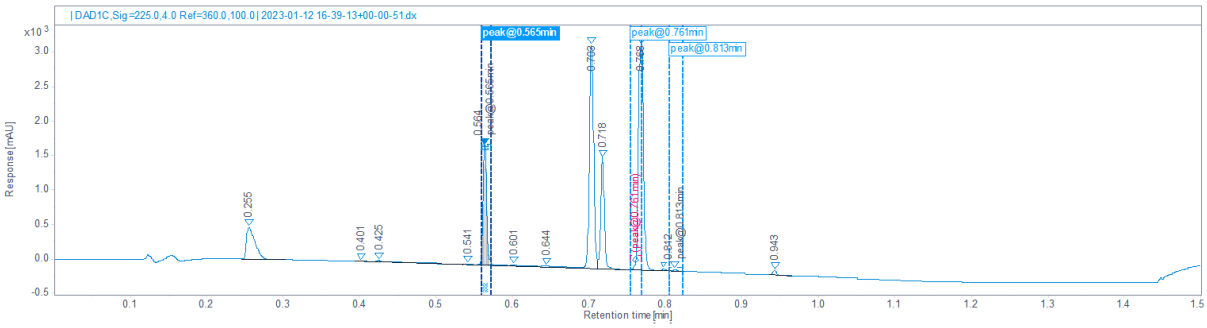
Selected LC traces

Representative example



Hydrolysis example

Peaks at 0.703 min and 0.768 min had mass ion corresponding to hydrolysed product.



HTE Results

Visualisation Analysis

Heat map of results.

n1/n2 per solvent, SM 2 and Base

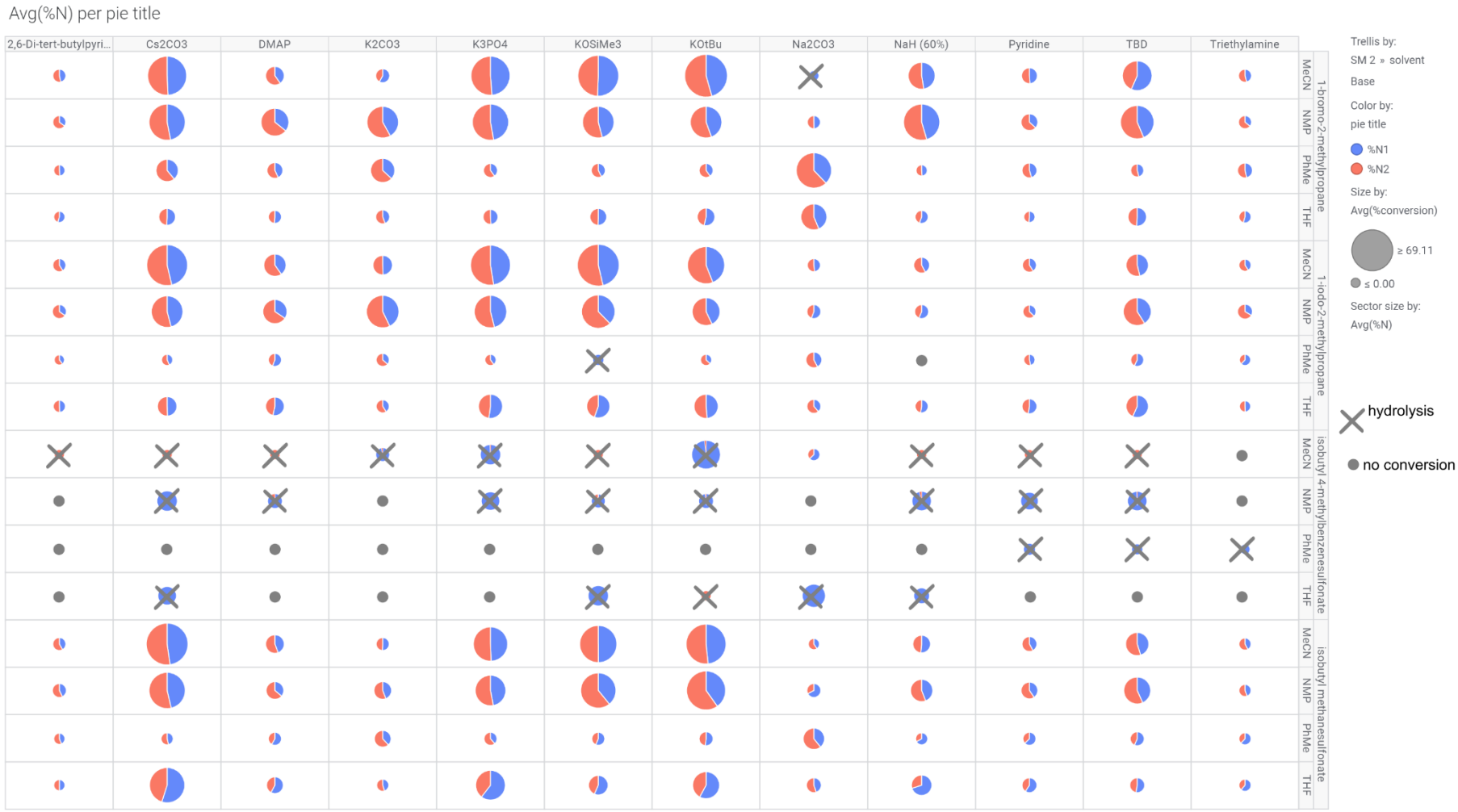
Base

solvent	SM 2	2,6-Di-tert-butylpyridine	Cs2CO3	DMAP	K2CO3	K3PO4	KOSiMe3	KOtBu	Na2CO3	NaH (60%)	Pyridine	TBD	Triethylamine
MeCN	1-bromo-2-methylpropane	0.86	0.97	0.67	1.38	0.95	1.02	0.84		0.91	0.96	1.30	0.85
	1-iodo-2-methylpropane	0.69	0.87	0.67	0.98	0.90	0.86	0.79	0.92	0.73	0.70	0.86	0.69
	isobutyl 4-methylbenzenesulfonate								1.69				
	isobutyl methanesulfonate	0.71	0.92	0.80	1.03	0.98	1.00	0.94	0.69	1.07	0.73	0.82	0.73
NMP	1-bromo-2-methylpropane	0.55	0.89	0.56	0.72	0.90	0.85	0.80	0.98	0.83	0.58	0.78	0.56
	1-iodo-2-methylpropane	0.53	0.85	0.52	0.75	0.86	0.60	0.75	1.27	1.30	0.59	0.70	0.50
	isobutyl 4-methylbenzenesulfonate												
	isobutyl methanesulfonate	0.75	0.87	0.57	0.79	0.89	0.64	0.67	2.06	0.79	0.68	0.77	0.79
PhMe	1-bromo-2-methylpropane	0.95	0.64	0.76	0.58	0.67	0.74	0.67	0.61	0.96	0.84	0.85	0.87
	1-iodo-2-methylpropane	0.65	0.77	1.28	0.58	0.67		0.59	0.74		0.88	1.34	1.65
	isobutyl 4-methylbenzenesulfonate												
	isobutyl methanesulfonate	0.78	0.86	1.41	0.62	0.63	1.29	1.08	0.65	2.04	1.69	1.31	1.64
THF	1-bromo-2-methylpropane	1.20	1.04	1.07	0.80	0.97	1.02	1.16	0.78	1.25	1.08	1.05	1.21
	1-iodo-2-methylpropane	0.97	0.98	1.15	0.70	1.10	1.25	0.95	0.64	1.11	1.12	1.31	0.98
	isobutyl 4-methylbenzenesulfonate												
	isobutyl methanesulfonate	1.01	1.22	1.38	0.83	1.53	1.31	1.38	0.81	2.34	1.46	1.13	1.58

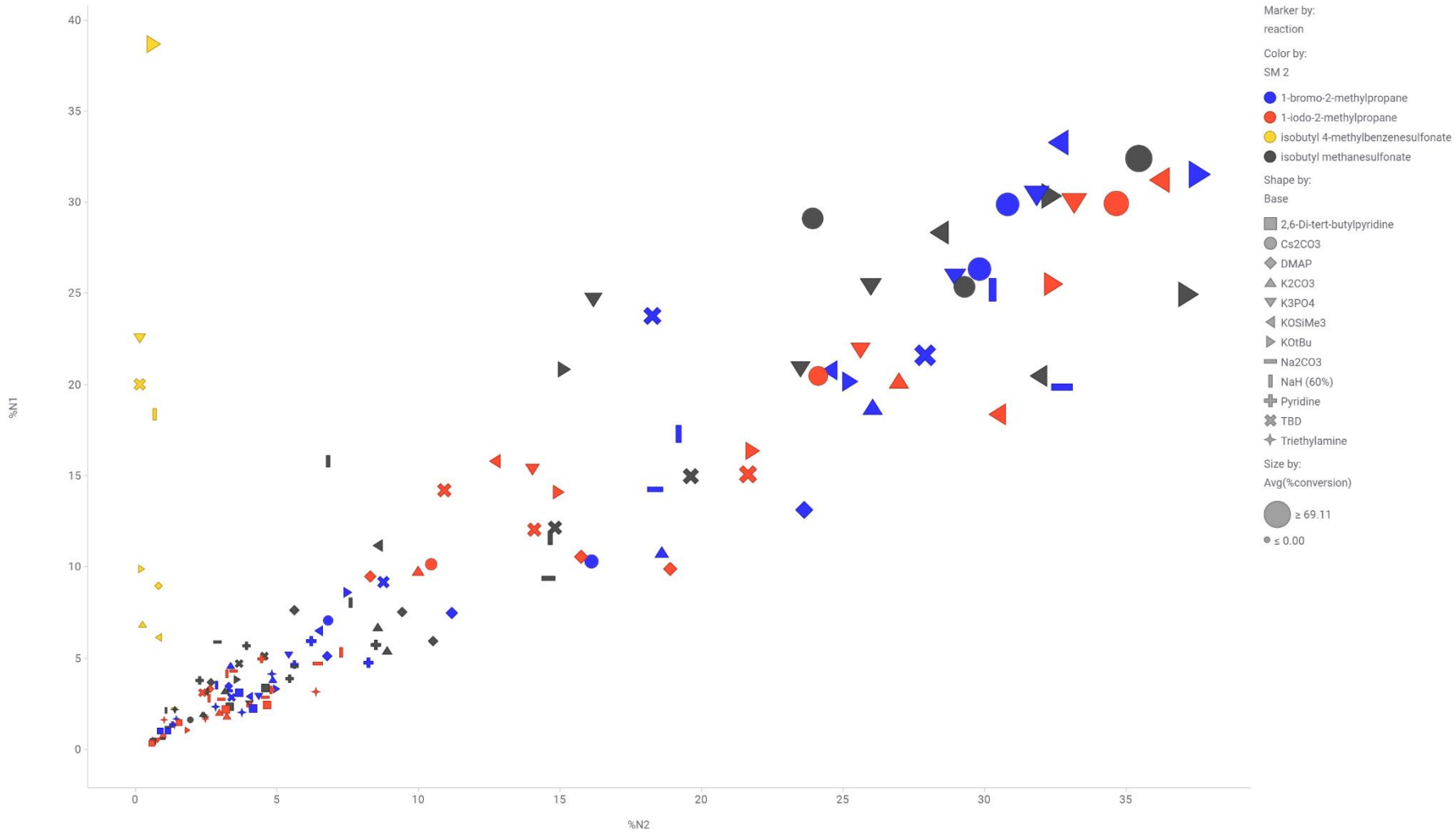
solvent » SM 2

Sum(n1/n2)

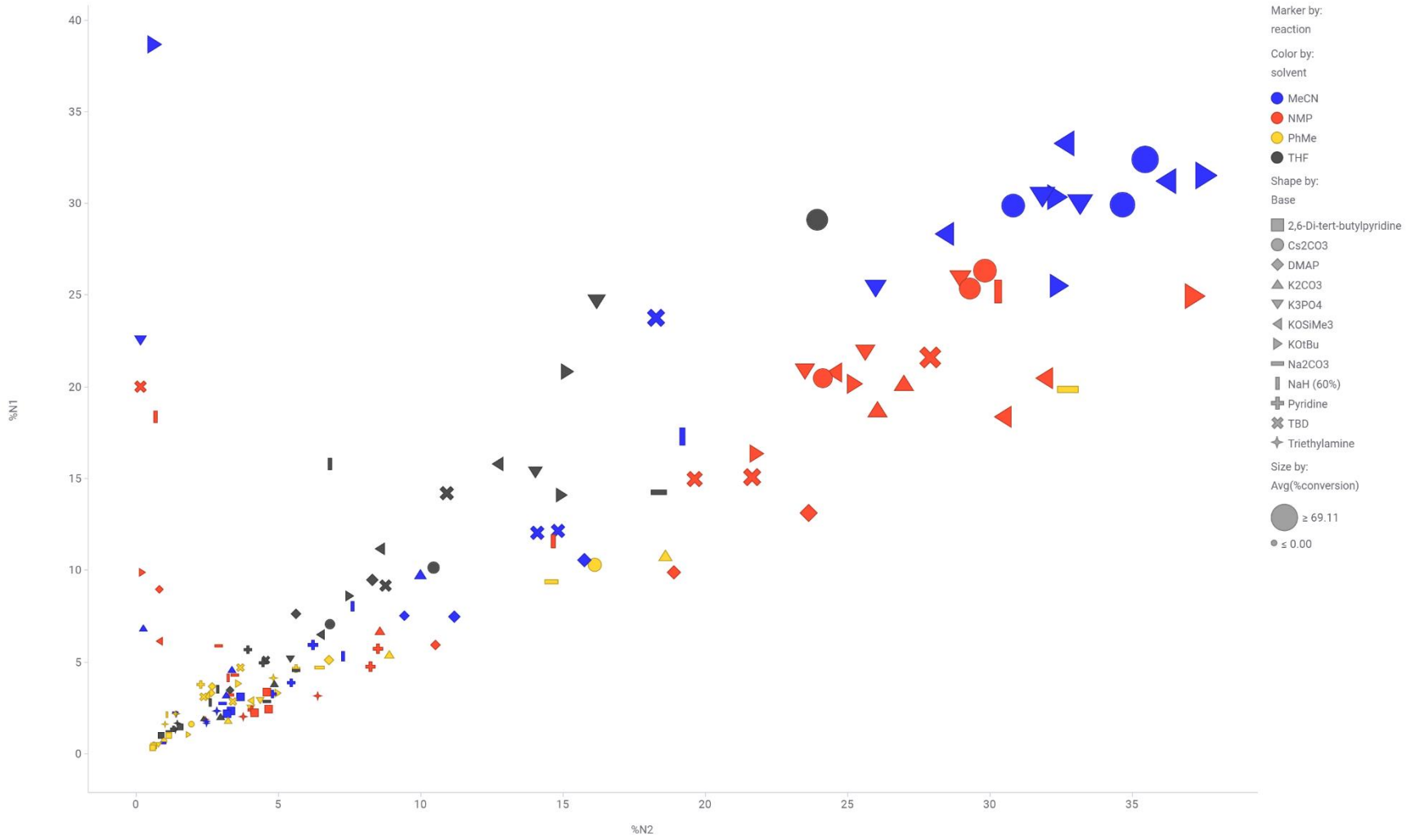
Colors:
Max
Min



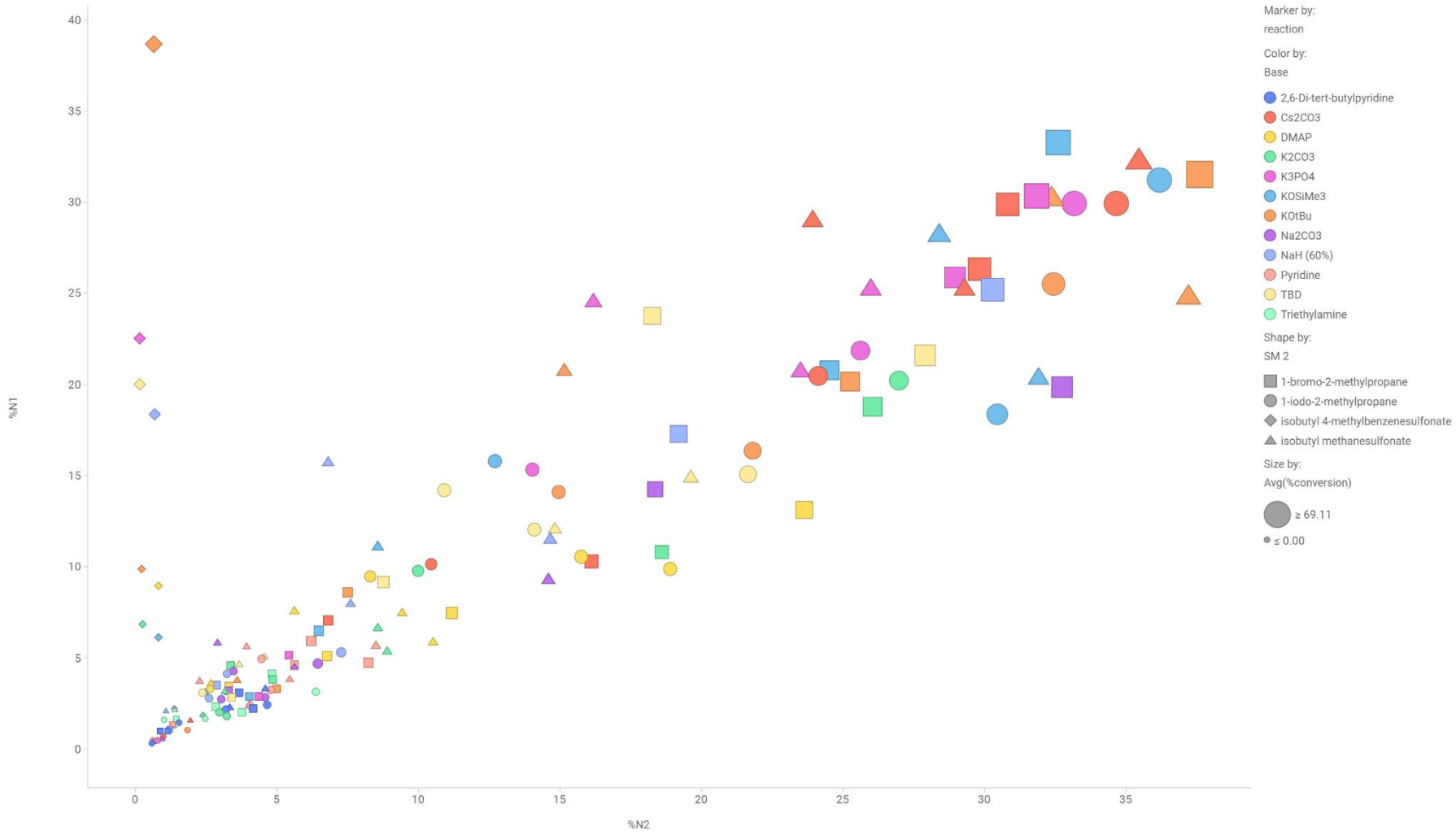
Pie chart array visualization of results. Pies sized by conversion.



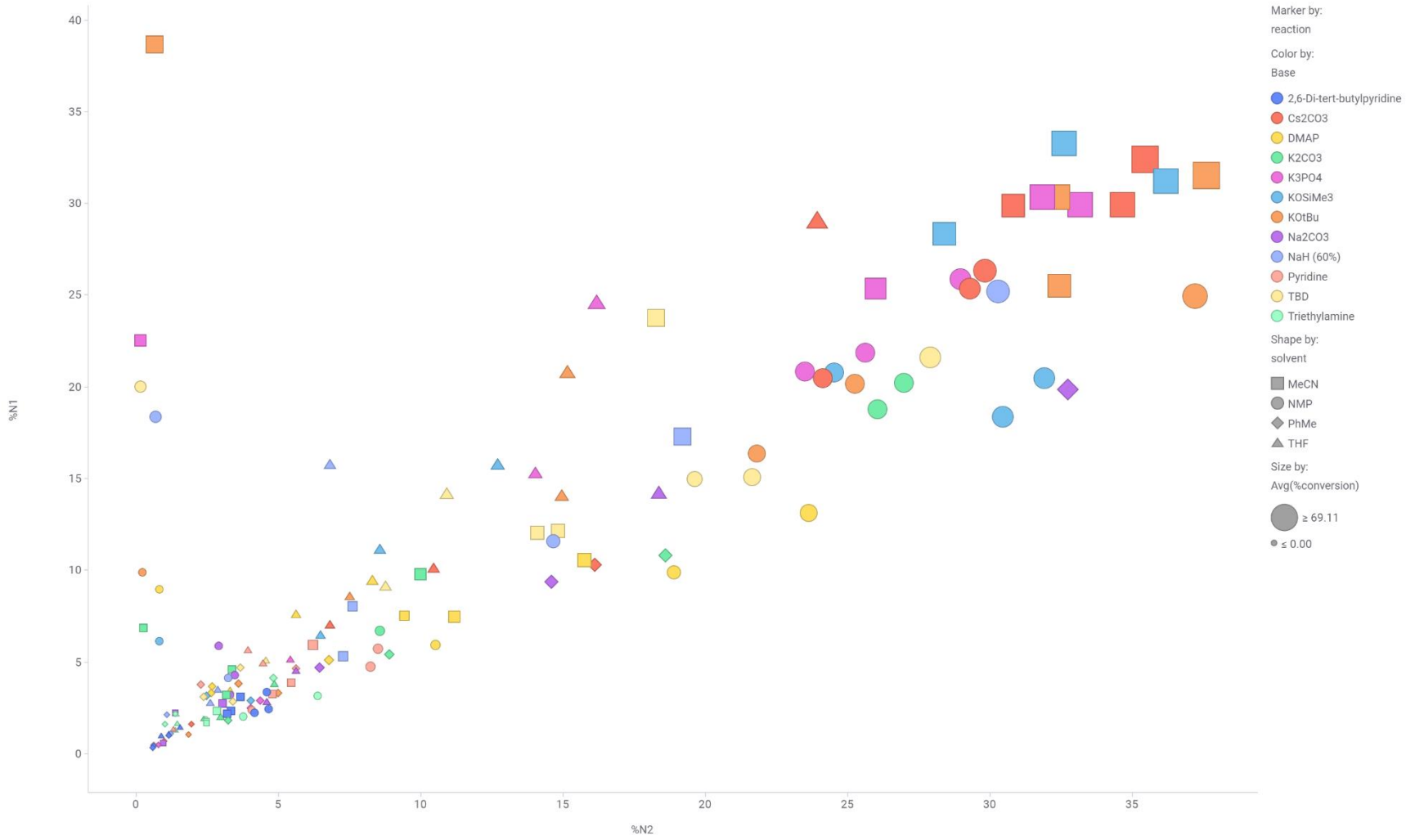
%*N*1 vs. %*N*2 scatter. Colours correspond to reagent. Shapes correspond to bases. Sized by conversion. Outliers due to hydrolysis side products.



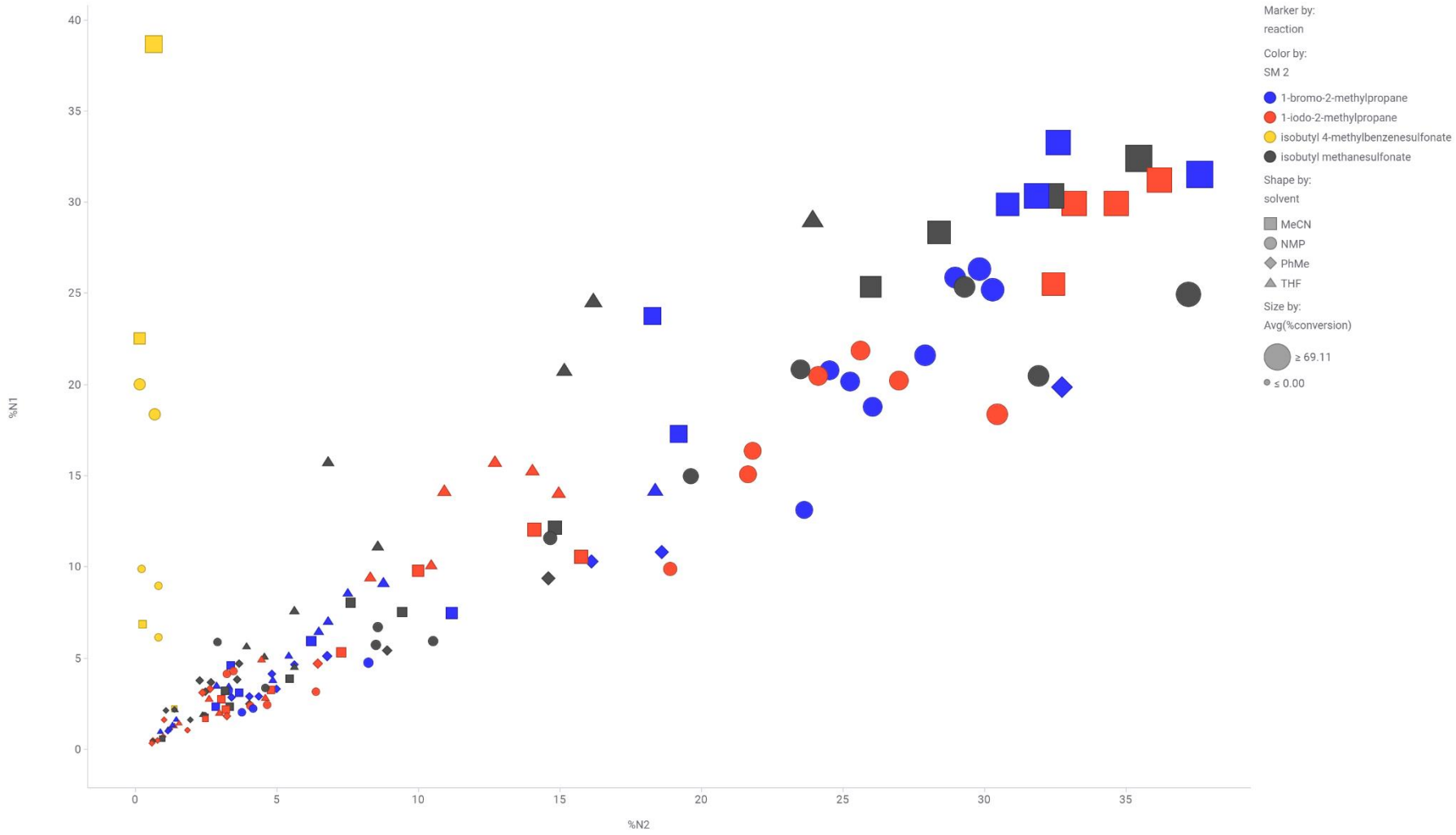
%*N*1 vs. %*N*2 scatter. Colours correspond to solvent. Shapes correspond to bases. Sized by conversion. Outliers due to hydrolysis side products.



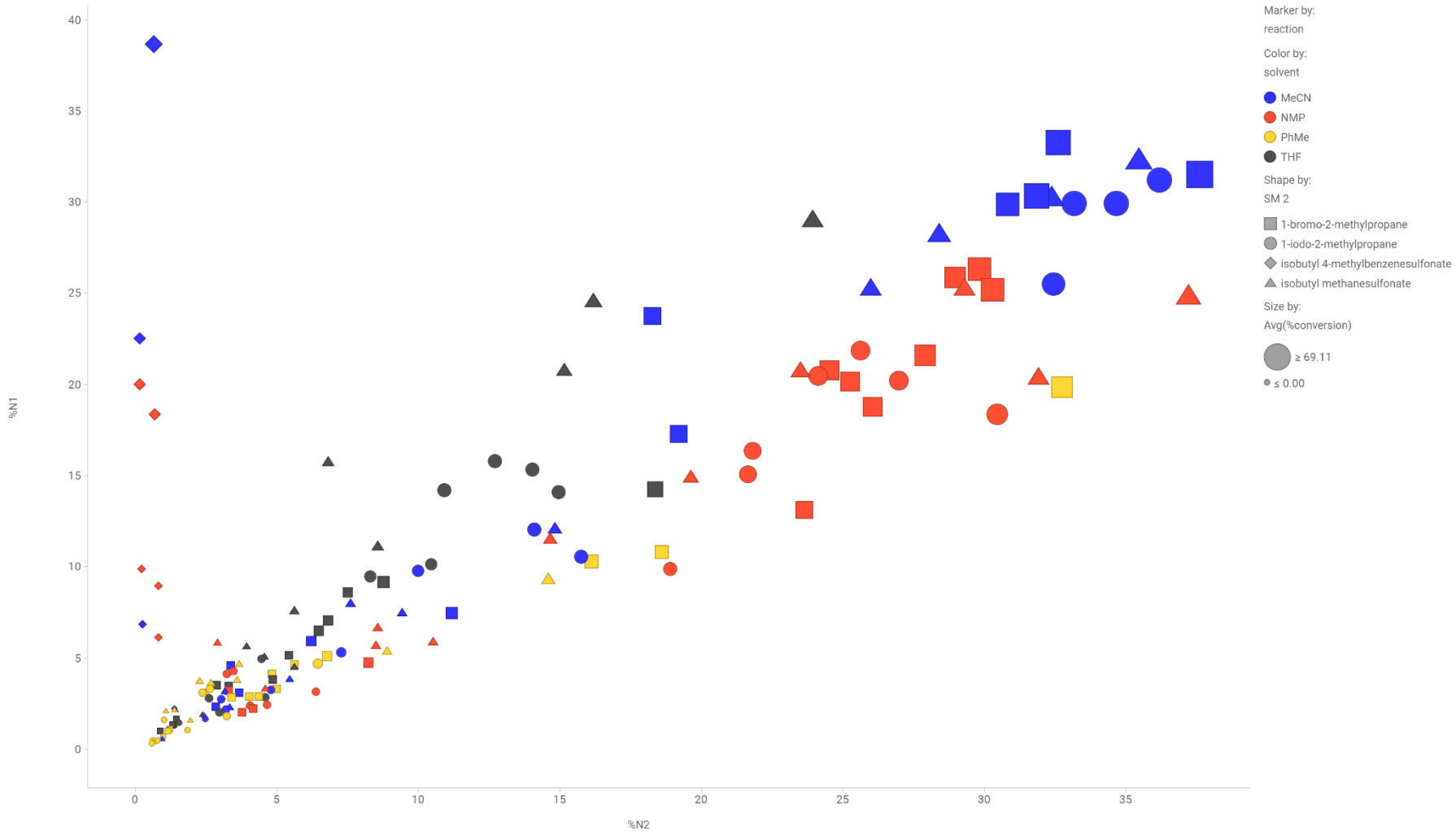
%*N*1 vs. %*N*2 scatter. Colours correspond to bases. Shapes correspond to reagents. Sized by conversion. Outliers due to hydrolysis side products.



%*N*1 vs. %*N*2 scatter. Colours correspond to bases. Shapes correspond to solvent. Sized by conversion. Outliers due to hydrolysis side products.



%*N*1 vs. %*N*2 scatter. Colours correspond to reagent. Shapes correspond to solvents. Sized by conversion. Outliers due to hydrolysis side products.



%*N*1 vs. %*N*2 scatter. Colours correspond to solvent. Shapes correspond to reagent. Sized by conversion. Outliers due to hydrolysis side products.

Raw data

reaction	location	SM 1	mg	SM 2	eq	Base	wt%	MW	D	eq	solvent	%*N*1	%*N*2	%SM	n1/n2
1	A1	1a	15	1-bromo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	MeCN	0.44			Hydrolysis
2	A2	1a	15	1-bromo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	MeCN	4.61	3.33	79.13	1.384384384
3	A3	1a	15	1-bromo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	MeCN	29.92	30.78	32.83	0.972059779
4	A4	1a	15	1-bromo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	MeCN	30.35	31.82	28.55	0.95380264
5	A5	1a	15	1-bromo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	MeCN	31.53	37.58	12.68	0.839010112
6	A6	1a	15	1-bromo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	MeCN	33.29	32.59	22.88	1.021478981
7	A7	1a	15	1-bromo-2-methylpropane	1	DMAP	1	122.17	1	1.100	MeCN	7.51	11.14	67.9	0.674147217
8	A8	1a	15	1-bromo-2-methylpropane	1	TBD	1	139.2	1	1.100	MeCN	23.78	18.23	35.3	1.304443225
9	A9	1a	15	1-bromo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	MeCN	5.95	6.17	80.64	0.964343598
10	A10	1a	15	1-bromo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	MeCN	3.12	3.62	83.85	0.861878453
11	A11	1a	15	1-bromo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	MeCN	2.38	2.81	84.4	0.846975089
12	A12	1a	15	1-bromo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	MeCN	17.34	19.16	33.01	0.905010438
13	B1	1a	15	1-bromo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	THF	14.27	18.33	42.03	0.778505183
14	B2	1a	15	1-bromo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	THF	3.85	4.81	70.48	0.8004158
15	B3	1a	15	1-bromo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	THF	7.07	6.79	59.39	1.041237113
16	B4	1a	15	1-bromo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	THF	5.21	5.38	60.45	0.968401487
17	B5	1a	15	1-bromo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	THF	8.65	7.46	58.48	1.159517426
18	B6	1a	15	1-bromo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	THF	6.53	6.43	22.82	1.0155521
19	B7	1a	15	1-bromo-2-methylpropane	1	DMAP	1	122.17	1	1.100	THF	3.51	3.28	30.41	1.070121951
20	B8	1a	15	1-bromo-2-methylpropane	1	TBD	1	139.2	1	1.100	THF	9.2	8.74	63.84	1.052631579
21	B9	1a	15	1-bromo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	THF	1.39	1.29	85.05	1.07751938
22	B10	1a	15	1-bromo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	THF	1.01	0.84	86.47	1.202380952
23	B11	1a	15	1-bromo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	THF	1.72	1.42	53.56	1.211267606
24	B12	1a	15	1-bromo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	THF	3.54	2.83	47.2	1.250883392
25	C1	1a	15	1-bromo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	NMP	3.23	3.28	43.13	0.984756098
26	C2	1a	15	1-bromo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	NMP	18.83	26.03	14.61	0.723396081
27	C3	1a	15	1-bromo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	NMP	26.38	29.79	1.59	0.885532058

28	C4	1a	15	1-bromo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	NMP	25.92	28.94	5.3	0.895646164
29	C5	1a	15	1-bromo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	NMP	20.19	25.22	11.35	0.800555115
30	C6	1a	15	1-bromo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	NMP	20.82	24.49	17.41	0.850142915
31	C7	1a	15	1-bromo-2-methylpropane	1	DMAP	1	122.17	1	1.100	NMP	13.16	23.6	33.14	0.557627119
32	C8	1a	15	1-bromo-2-methylpropane	1	TBD	1	139.2	1	1.100	NMP	21.65	27.89	14.78	0.776263894
33	C9	1a	15	1-bromo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	NMP	4.79	8.2	48.09	0.584146341
34	C10	1a	15	1-bromo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	NMP	2.26	4.13	46.33	0.547215496
35	C11	1a	15	1-bromo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	NMP	2.08	3.73	55.96	0.557640751
36	C12	1a	15	1-bromo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	NMP	25.23	30.26	6.53	0.833773959
37	D1	1a	15	1-bromo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	PhMe	19.91	32.7	24.12	0.608868502
38	D2	1a	15	1-bromo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	PhMe	10.85	18.57	42.35	0.584275714
39	D3	1a	15	1-bromo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	PhMe	10.32	16.09	43.84	0.641392169
40	D4	1a	15	1-bromo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	PhMe	2.91	4.34	21.93	0.670506912
41	D5	1a	15	1-bromo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	PhMe	3.32	4.95	59.44	0.670707071
42	D6	1a	15	1-bromo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	PhMe	2.95	4	45.4	0.7375
43	D7	1a	15	1-bromo-2-methylpropane	1	DMAP	1	122.17	1	1.100	PhMe	5.13	6.74	39.12	0.761127596
44	D8	1a	15	1-bromo-2-methylpropane	1	TBD	1	139.2	1	1.100	PhMe	2.86	3.38	34.99	0.846153846
45	D9	1a	15	1-bromo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	PhMe	4.67	5.59	44.25	0.835420394
46	D10	1a	15	1-bromo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	PhMe	1.04	1.1	77.4	0.945454545
47	D11	1a	15	1-bromo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	PhMe	4.14	4.78	47.09	0.866108787
48	D12	1a	15	1-bromo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	PhMe	1.14	1.19	68.67	0.957983193
49	E1	1a	15	1-iodo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	MeCN	2.76	3	66.64	0.92
50	E2	1a	15	1-iodo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	MeCN	9.79	9.96	69.65	0.982931727
51	E3	1a	15	1-iodo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	MeCN	29.95	34.62	25.64	0.865106875
52	E4	1a	15	1-iodo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	MeCN	29.96	33.14	30.96	0.904043452
53	E5	1a	15	1-iodo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	MeCN	25.54	32.4	30.93	0.788271605
54	E6	1a	15	1-iodo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	MeCN	31.24	36.16	16.58	0.863938053
55	E7	1a	15	1-iodo-2-methylpropane	1	DMAP	1	122.17	1	1.100	MeCN	10.6	15.71	55.1	0.674729472
56	E8	1a	15	1-iodo-2-methylpropane	1	TBD	1	139.2	1	1.100	MeCN	12.05	14.05	59.99	0.857651246
57	E9	1a	15	1-iodo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	MeCN	3.31	4.76	85.22	0.695378151

58	E10	1a	15	1-iodo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	MeCN	2.21	3.18	86.27	0.694968553
59	E11	1a	15	1-iodo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	MeCN	1.69	2.44	86.68	0.692622951
60	E12	1a	15	1-iodo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	MeCN	5.32	7.25	36.95	0.733793103
61	F1	1a	15	1-iodo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	THF	2.9	4.56	35.19	0.635964912
62	F2	1a	15	1-iodo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	THF	2.04	2.93	54.99	0.696245734
63	F3	1a	15	1-iodo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	THF	10.16	10.41	38.97	0.97598463
64	F4	1a	15	1-iodo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	THF	15.38	14	47.89	1.098571429
65	F5	1a	15	1-iodo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	THF	14.14	14.91	48.83	0.948356808
66	F6	1a	15	1-iodo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	THF	15.84	12.68	47.49	1.249211356
67	F7	1a	15	1-iodo-2-methylpropane	1	DMAP	1	122.17	1	1.100	THF	9.52	8.26	28.4	1.152542373
68	F8	1a	15	1-iodo-2-methylpropane	1	TBD	1	139.2	1	1.100	THF	14.21	10.87	63.26	1.307267709
69	F9	1a	15	1-iodo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	THF	4.98	4.43	42.27	1.124153499
70	F10	1a	15	1-iodo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	THF	1.47	1.52	88.23	0.967105263
71	F11	1a	15	1-iodo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	THF	1.33	1.36	69.58	0.977941176
72	F12	1a	15	1-iodo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	THF	2.85	2.56	29.5	1.11328125
73	G1	1a	15	1-iodo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	NMP	4.34	3.43	28.33	1.265306122
74	G2	1a	15	1-iodo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	NMP	20.22	26.96	18.98	0.75
75	G3	1a	15	1-iodo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	NMP	20.51	24.11	18.25	0.850684363
76	G4	1a	15	1-iodo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	NMP	21.89	25.59	17.86	0.85541227
77	G5	1a	15	1-iodo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	NMP	16.4	21.79	18.33	0.752638825
78	G6	1a	15	1-iodo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	NMP	18.4	30.43	18.75	0.604666448
79	G7	1a	15	1-iodo-2-methylpropane	1	DMAP	1	122.17	1	1.100	NMP	9.9	18.86	23.66	0.524920467
80	G8	1a	15	1-iodo-2-methylpropane	1	TBD	1	139.2	1	1.100	NMP	15.13	21.63	26.99	0.699491447
81	G9	1a	15	1-iodo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	NMP	2.4	4.04	44.79	0.594059406
82	G10	1a	15	1-iodo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	NMP	2.47	4.63	56.69	0.533477322
83	G11	1a	15	1-iodo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	NMP	3.2	6.34	52.08	0.504731861
84	G12	1a	15	1-iodo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	NMP	4.16	3.2	26.28	1.3
85	H1	1a	15	1-iodo-2-methylpropane	1	Na2CO3	1	105.99	1.000	1.100	PhMe	4.71	6.4	28.39	0.7359375
86	H2	1a	15	1-iodo-2-methylpropane	1	K2CO3	1	138.21	1.000	1.100	PhMe	1.85	3.19	55.88	0.579937304

87	H3	1a	15	1-iodo-2-methylpropane	1	Cs2CO3	1	325.82	1	1.100	PhMe	0.73	0.95	69.11	0.768421053
88	H4	1a	15	1-iodo-2-methylpropane	1	K3PO4	1	212.27	1	1.100	PhMe	0.5	0.75	59.54	0.666666667
89	H5	1a	15	1-iodo-2-methylpropane	1	KOtBu	1	112.22	1.000	1.100	PhMe	1.06	1.81	51.42	0.585635359
90	H6	1a	15	1-iodo-2-methylpropane	1	KOSiMe3	1	128.29	1	1.100	PhMe	2.4			Hydrolysis
91	H7	1a	15	1-iodo-2-methylpropane	1	DMAP	1	122.17	1	1.100	PhMe	3.33	2.61	26.15	1.275862069
92	H8	1a	15	1-iodo-2-methylpropane	1	TBD	1	139.2	1	1.100	PhMe	3.14	2.34	21.28	1.341880342
93	H9	1a	15	1-iodo-2-methylpropane	1	Pyridine	1	79.1	0.973	1.100	PhMe	0.52	0.59	62.81	0.881355932
94	H10	1a	15	1-iodo-2-methylpropane	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	PhMe	0.36	0.55	77.68	0.654545455
95	H11	1a	15	1-iodo-2-methylpropane	1	Triethylamine	1	101.19	0.726	1.100	PhMe	1.62	0.98	51.16	1.653061224
96	H12	1a	15	1-iodo-2-methylpropane	1	NaH (60%)	0.6	24	1	1.100	PhMe	0		31.52	no reaction
97	A1	1a	15	isobutyl methanesulfonate	1	Na2CO3	1	105.99	1.000	1.100	MeCN	0.64	0.93	83.46	0.688172043
98	A2	1a	15	isobutyl methanesulfonate	1	K2CO3	1	138.21	1.000	1.100	MeCN	3.25	3.15	76.15	1.031746032
99	A3	1a	15	isobutyl methanesulfonate	1	Cs2CO3	1	325.82	1	1.100	MeCN	32.41	35.42	24.87	0.915019763
100	A4	1a	15	isobutyl methanesulfonate	1	K3PO4	1	212.27	1	1.100	MeCN	25.38	25.94	32.39	0.978411719
101	A5	1a	15	isobutyl methanesulfonate	1	KOtBu	1	112.22	1.000	1.100	MeCN	30.37	32.35	18.51	0.938794436
102	A6	1a	15	isobutyl methanesulfonate	1	KOSiMe3	1	128.29	1	1.100	MeCN	28.35	28.38	28.71	0.998942918
103	A7	1a	15	isobutyl methanesulfonate	1	DMAP	1	122.17	1	1.100	MeCN	7.53	9.41	76.09	0.80021254
104	A8	1a	15	isobutyl methanesulfonate	1	TBD	1	139.2	1	1.100	MeCN	12.19	14.79	43.35	0.824205544
105	A9	1a	15	isobutyl methanesulfonate	1	Pyridine	1	79.1	0.973	1.100	MeCN	3.93	5.42	81.19	0.725092251
106	A10	1a	15	isobutyl methanesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	MeCN	2.35	3.3	85.49	0.712121212
107	A11	1a	15	isobutyl methanesulfonate	1	Triethylamine	1	101.19	0.726	1.100	MeCN	1.79	2.45	85.43	0.730612245
108	A12	1a	15	isobutyl methanesulfonate	1	NaH (60%)	0.6	24	1	1.100	MeCN	8.07	7.57	41.74	1.066050198
109	B1	1a	15	isobutyl methanesulfonate	1	Na2CO3	1	105.99	1.000	1.100	THF	4.55	5.59	42.73	0.813953488
110	B2	1a	15	isobutyl methanesulfonate	1	K2CO3	1	138.21	1.000	1.100	THF	1.93	2.33	60.23	0.82832618
111	B3	1a	15	isobutyl methanesulfonate	1	Cs2CO3	1	325.82	1	1.100	THF	29.13	23.91	39.94	1.218318695
112	B4	1a	15	isobutyl methanesulfonate	1	K3PO4	1	212.27	1	1.100	THF	24.67	16.14	38.02	1.52850062
113	B5	1a	15	isobutyl methanesulfonate	1	KOtBu	1	112.22	1.000	1.100	THF	20.86	15.14	22.75	1.377807133
114	B6	1a	15	isobutyl methanesulfonate	1	KOSiMe3	1	128.29	1	1.100	THF	11.18	8.53	14.51	1.31066823
115	B7	1a	15	isobutyl methanesulfonate	1	DMAP	1	122.17	1	1.100	THF	7.68	5.57	23.3	1.378815081

116	B8	1a	15	isobutyl methanesulfonate	1	TBD	1	139.2	1	1.100	THF	5.14	4.54	72.45	1.13215859
117	B9	1a	15	isobutyl methanesulfonate	1	Pyridine	1	79.1	0.973	1.100	THF	5.69	3.91	26.86	1.455242967
118	B10	1a	15	isobutyl methanesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	THF	1.11	1.1	92.71	1.009090909
119	B11	1a	15	isobutyl methanesulfonate	1	Triethylamine	1	101.19	0.726	1.100	THF	2.2	1.39	57.93	1.582733813
120	B12	1a	15	isobutyl methanesulfonate	1	NaH (60%)	0.6	24	1	1.100	THF	15.85	6.78	41.53	2.337758112
121	C1	1a	15	isobutyl methanesulfonate	1	Na2CO3	1	105.99	1.000	1.100	NMP	5.9	2.86	30.28	2.062937063
122	C2	1a	15	isobutyl methanesulfonate	1	K2CO3	1	138.21	1.000	1.100	NMP	6.75	8.53	39.4	0.791324736
123	C3	1a	15	isobutyl methanesulfonate	1	Cs2CO3	1	325.82	1	1.100	NMP	25.37	29.28	3.52	0.866461749
124	C4	1a	15	isobutyl methanesulfonate	1	K3PO4	1	212.27	1	1.100	NMP	20.84	23.47	14.63	0.887942054
125	C5	1a	15	isobutyl methanesulfonate	1	KOtBu	1	112.22	1.000	1.100	NMP	24.97	37.18	6.12	0.671597633
126	C6	1a	15	isobutyl methanesulfonate	1	KOSiMe3	1	128.29	1	1.100	NMP	20.49	31.88	7.79	0.64272271
127	C7	1a	15	isobutyl methanesulfonate	1	DMAP	1	122.17	1	1.100	NMP	5.96	10.5	31.71	0.567619048
128	C8	1a	15	isobutyl methanesulfonate	1	TBD	1	139.2	1	1.100	NMP	15	19.6	25.11	0.765306122
129	C9	1a	15	isobutyl methanesulfonate	1	Pyridine	1	79.1	0.973	1.100	NMP	5.75	8.45	41.83	0.680473373
130	C10	1a	15	isobutyl methanesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	NMP	3.39	4.55	44.93	0.745054945
131	C11	1a	15	isobutyl methanesulfonate	1	Triethylamine	1	101.19	0.726	1.100	NMP	1.9	2.39	50.34	0.794979079
132	C12	1a	15	isobutyl methanesulfonate	1	NaH (60%)	0.6	24	1	1.100	NMP	11.59	14.64	12.86	0.791666667
133	D1	1a	15	isobutyl methanesulfonate	1	Na2CO3	1	105.99	1.000	1.100	PhMe	9.4	14.57	31.86	0.64516129
134	D2	1a	15	isobutyl methanesulfonate	1	K2CO3	1	138.21	1.000	1.100	PhMe	5.47	8.85	25.76	0.618079096
135	D3	1a	15	isobutyl methanesulfonate	1	Cs2CO3	1	325.82	1	1.100	PhMe	1.64	1.9	61.95	0.863157895
136	D4	1a	15	isobutyl methanesulfonate	1	K3PO4	1	212.27	1	1.100	PhMe	2.51	3.99	43.5	0.629072682
137	D5	1a	15	isobutyl methanesulfonate	1	KOtBu	1	112.22	1.000	1.100	PhMe	3.87	3.57	41.51	1.084033613
138	D6	1a	15	isobutyl methanesulfonate	1	KOSiMe3	1	128.29	1	1.100	PhMe	3.17	2.45	24.47	1.293877551
139	D7	1a	15	isobutyl methanesulfonate	1	DMAP	1	122.17	1	1.100	PhMe	3.7	2.63	18.72	1.406844106
140	D8	1a	15	isobutyl methanesulfonate	1	TBD	1	139.2	1	1.100	PhMe	4.73	3.62	23.09	1.306629834
141	D9	1a	15	isobutyl methanesulfonate	1	Pyridine	1	79.1	0.973	1.100	PhMe	3.8	2.25	19.39	1.688888889
142	D10	1a	15	isobutyl methanesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	PhMe	0.45	0.58	84.44	0.775862069
143	D11	1a	15	isobutyl methanesulfonate	1	Triethylamine	1	101.19	0.726	1.100	PhMe	2.23	1.36	41.83	1.639705882
144	D12	1a	15	isobutyl methanesulfonate	1	NaH (60%)	0.6	24	1	1.100	PhMe	2.16	1.06	44.37	2.037735849

145	E1	1a	15	isobutyl 4-methylbenzenesulfonate	1	Na2CO3	1	105.99	1.000	1.100	MeCN	2.26	1.34	51.07	1.686567164
146	E2	1a	15	isobutyl 4-methylbenzenesulfonate	1	K2CO3	1	138.21	1.000	1.100	MeCN				Hydrolysis
147	E3	1a	15	isobutyl 4-methylbenzenesulfonate	1	Cs2CO3	1	325.82	1	1.100	MeCN				Hydrolysis
148	E4	1a	15	isobutyl 4-methylbenzenesulfonate	1	K3PO4	1	212.27	1	1.100	MeCN				Hydrolysis
149	E5	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOtBu	1	112.22	1.000	1.100	MeCN				Hydrolysis
150	E6	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOSiMe3	1	128.29	1	1.100	MeCN				Hydrolysis
151	E7	1a	15	isobutyl 4-methylbenzenesulfonate	1	DMAP	1	122.17	1	1.100	MeCN				Hydrolysis
152	E8	1a	15	isobutyl 4-methylbenzenesulfonate	1	TBD	1	139.2	1	1.100	MeCN				Hydrolysis
153	E9	1a	15	isobutyl 4-methylbenzenesulfonate	1	Pyridine	1	79.1	0.973	1.100	MeCN				Hydrolysis
154	E10	1a	15	isobutyl 4-methylbenzenesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	MeCN				Hydrolysis
155	E11	1a	15	isobutyl 4-methylbenzenesulfonate	1	Triethylamine	1	101.19	0.726	1.100	MeCN				no reaction
156	E12	1a	15	isobutyl 4-methylbenzenesulfonate	1	NaH (60%)	0.6	24	1	1.100	MeCN				Hydrolysis
157	F1	1a	15	isobutyl 4-methylbenzenesulfonate	1	Na2CO3	1	105.99	1.000	1.100	THF				Hydrolysis
158	F2	1a	15	isobutyl 4-methylbenzenesulfonate	1	K2CO3	1	138.21	1.000	1.100	THF				no reaction
159	F3	1a	15	isobutyl 4-methylbenzenesulfonate	1	Cs2CO3	1	325.82	1	1.100	THF				Hydrolysis
160	F4	1a	15	isobutyl 4-methylbenzenesulfonate	1	K3PO4	1	212.27	1	1.100	THF				no reaction
161	F5	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOtBu	1	112.22	1.000	1.100	THF				Hydrolysis
162	F6	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOSiMe3	1	128.29	1	1.100	THF				Hydrolysis
163	F7	1a	15	isobutyl 4-methylbenzenesulfonate	1	DMAP	1	122.17	1	1.100	THF				no reaction
164	F8	1a	15	isobutyl 4-methylbenzenesulfonate	1	TBD	1	139.2	1	1.100	THF				no reaction
165	F9	1a	15	isobutyl 4-methylbenzenesulfonate	1	Pyridine	1	79.1	0.973	1.100	THF				no reaction
166	F10	1a	15	isobutyl 4-methylbenzenesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	THF				no reaction
167	F11	1a	15	isobutyl 4-methylbenzenesulfonate	1	Triethylamine	1	101.19	0.726	1.100	THF				no reaction
168	F12	1a	15	isobutyl 4-methylbenzenesulfonate	1	NaH (60%)	0.6	24	1	1.100	THF				Hydrolysis
169	G1	1a	15	isobutyl 4-methylbenzenesulfonate	1	Na2CO3	1	105.99	1.000	1.100	NMP				no reaction
170	G2	1a	15	isobutyl 4-methylbenzenesulfonate	1	K2CO3	1	138.21	1.000	1.100	NMP				no reaction
171	G3	1a	15	isobutyl 4-methylbenzenesulfonate	1	Cs2CO3	1	325.82	1	1.100	NMP				Hydrolysis
172	G4	1a	15	isobutyl 4-methylbenzenesulfonate	1	K3PO4	1	212.27	1	1.100	NMP				Hydrolysis
173	G5	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOtBu	1	112.22	1.000	1.100	NMP				Hydrolysis

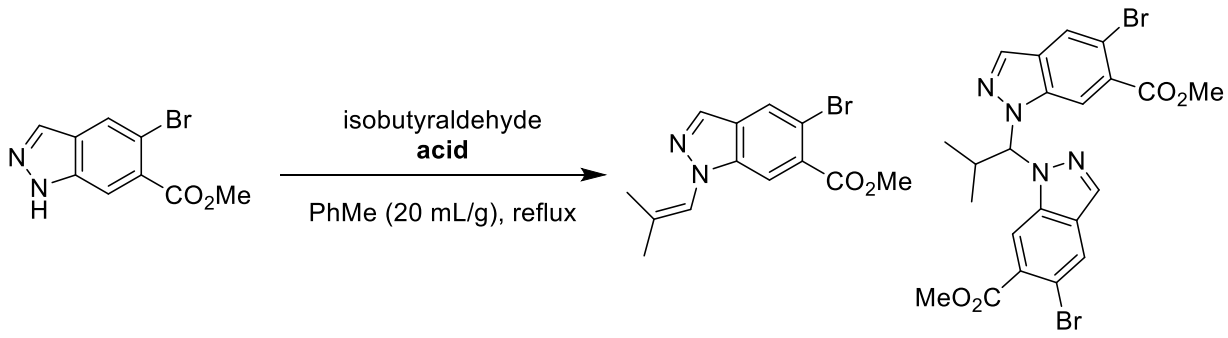
174	G6	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOSiMe3	1	128.29	1	1.100	NMP	Hydrolysis
175	G7	1a	15	isobutyl 4-methylbenzenesulfonate	1	DMAP	1	122.17	1	1.100	NMP	Hydrolysis
176	G8	1a	15	isobutyl 4-methylbenzenesulfonate	1	TBD	1	139.2	1	1.100	NMP	Hydrolysis
177	G9	1a	15	isobutyl 4-methylbenzenesulfonate	1	Pyridine	1	79.1	0.973	1.100	NMP	Hydrolysis
178	G10	1a	15	isobutyl 4-methylbenzenesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	NMP	no reaction
179	G11	1a	15	isobutyl 4-methylbenzenesulfonate	1	Triethylamine	1	101.19	0.726	1.100	NMP	no reaction
180	G12	1a	15	isobutyl 4-methylbenzenesulfonate	1	NaH (60%)	0.6	24	1	1.100	NMP	Hydrolysis
181	H1	1a	15	isobutyl 4-methylbenzenesulfonate	1	Na2CO3	1	105.99	1.000	1.100	PhMe	no reaction
182	H2	1a	15	isobutyl 4-methylbenzenesulfonate	1	K2CO3	1	138.21	1.000	1.100	PhMe	no reaction
183	H3	1a	15	isobutyl 4-methylbenzenesulfonate	1	Cs2CO3	1	325.82	1	1.100	PhMe	no reaction
184	H4	1a	15	isobutyl 4-methylbenzenesulfonate	1	K3PO4	1	212.27	1	1.100	PhMe	no reaction
185	H5	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOtBu	1	112.22	1.000	1.100	PhMe	no reaction
186	H6	1a	15	isobutyl 4-methylbenzenesulfonate	1	KOSiMe3	1	128.29	1	1.100	PhMe	no reaction
187	H7	1a	15	isobutyl 4-methylbenzenesulfonate	1	DMAP	1	122.17	1	1.100	PhMe	no reaction
188	H8	1a	15	isobutyl 4-methylbenzenesulfonate	1	TBD	1	139.2	1	1.100	PhMe	Hydrolysis
189	H9	1a	15	isobutyl 4-methylbenzenesulfonate	1	Pyridine	1	79.1	0.973	1.100	PhMe	Hydrolysis
190	H10	1a	15	isobutyl 4-methylbenzenesulfonate	1	2,6-Di-tert-butylpyridine	1	191.31	0.852	1.100	PhMe	no reaction
191	H11	1a	15	isobutyl 4-methylbenzenesulfonate	1	Triethylamine	1	101.19	0.726	1.100	PhMe	Hydrolysis
192	H12	1a	15	isobutyl 4-methylbenzenesulfonate	1	NaH (60%)	0.6	24	1	1.100	PhMe	no reaction

Reaction Optimization

Enamine Formation

Isobutyraldehyde was added to methyl 5-bromo-1*H*-indazole-6-carboxylate **1a** (1.0 equiv), acid, and solvent in a reactor vessel equipped with a Dean-Stark condenser. The reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 3 hours. A sample for LCMS analysis was prepared at the indicated time. Conversion and **4a**:**5a** ratio determined by LCMS at 225 nm.

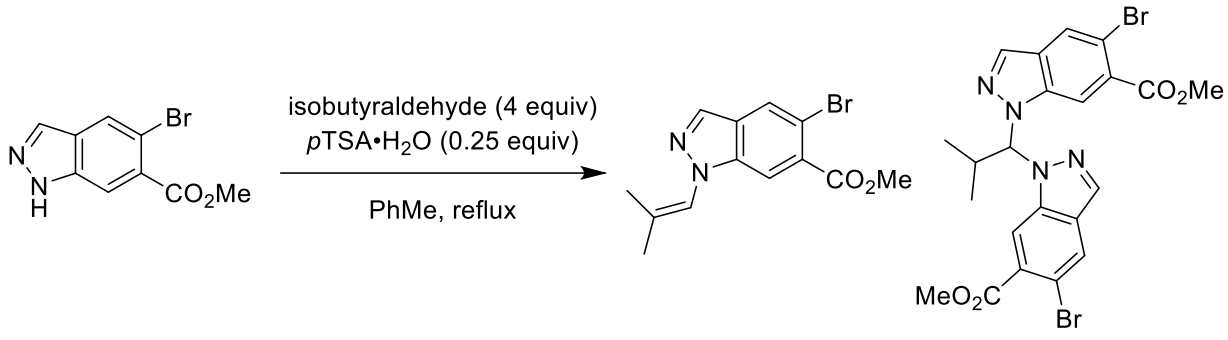
Acid and acid equiv



1a **4a** **5a**

entry	acid	isobutyraldehyde (equiv)	conversion (ratio **4a**:**5a**)
1	none	2.0	0%
2	MsOH (0.25 equiv)	2.0	99% (98:2)
3	*p*TSA·H_2O (0.25 equiv)	2.0	96% (95:5)
4	***p*TSA·H_2O (0.25 equiv)**	**3.0**	**99% (98:2)**
5	*p*TSA·H_2O (1.0 equiv)	2.0	70% (90:10)
6	*p*TSA·H_2O (0.085 equiv)	3.0	>99% (97:3)

Dehydration method

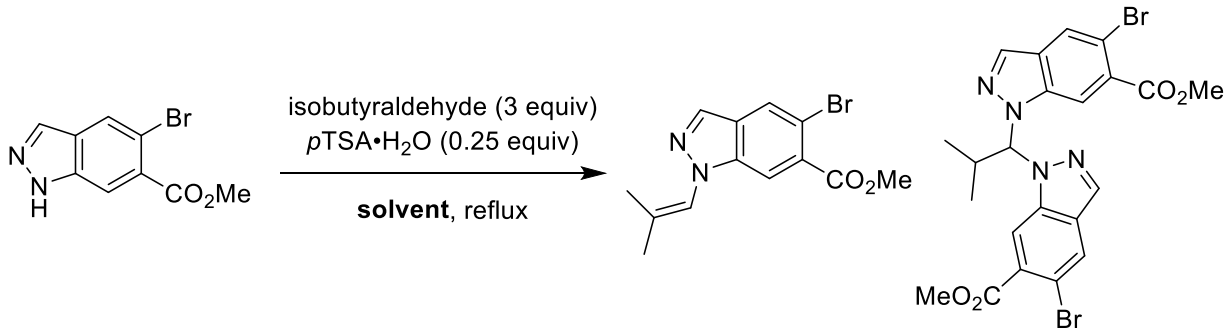


1a **4a** **5a**

entry	apparatus	conversion (ratio **4a**:**5a**)
1	**Dean-Stark condenser**	**>99% (99:1)**
2	reflux condenser	95% (82:18)
3	4 Å MS (24 h)	97% (52:48)

Reaction mixtures sampled at reflux.

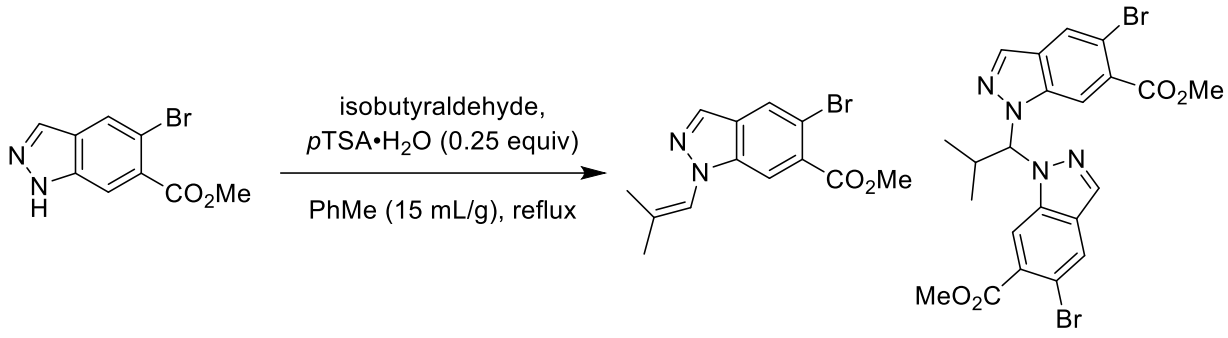
Solvent and concentration



1a **4a** **5a**

entry	solvent	isobutyraldehyde (equiv)	time	conversion (ratio **4a**:**5a**)
1	PhMe (10 mL/g)	3.0	5 h 30 min	93% (83:17)
2	**PhMe (15 mL/g)**	**3.0**	**3 h**	**>99% (99:1)**
3	PhMe (20 mL/g)	3.0	4 h	95% (89:11)
4	PhMe (15 mL/g)	2.0	4 h	98% (82:8)
5	CyH (15 mL/g)	2.0	4 h	86% (8:92)

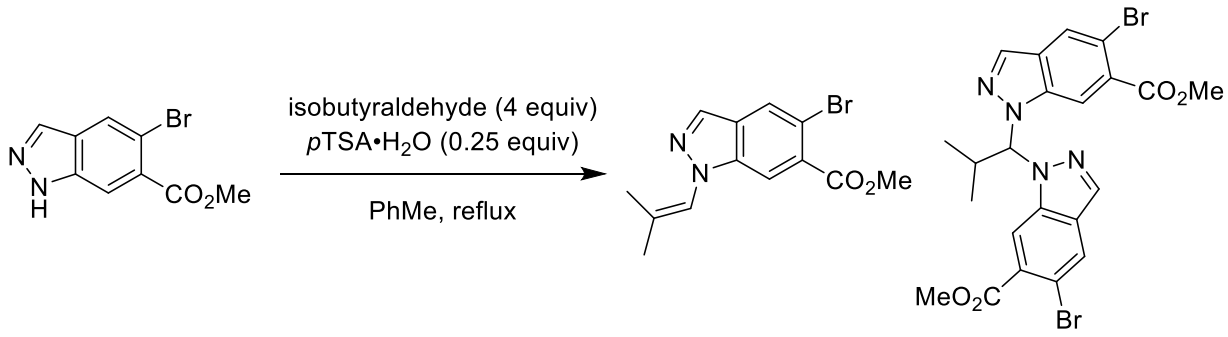
Aldehyde equiv



1a **4a** **5a**

entry	isobutyraldehyde (equiv)	conversion (ratio **4a**:**5a**)
1	2	95% (90:10)
2	**3**	**>99% (98:2)**
3	4	>99% (99:1)

Quench



1a **4a** **5a**

entry	quench	sampling temperature (°C)	conversion (ratio **4a**:**5a**)
1	pre-quench	110	>99% (100:0)
2	Et_3N (0.25 equiv) at reflux	20	>99% (100:0)
3	none	20	97% (96:4)

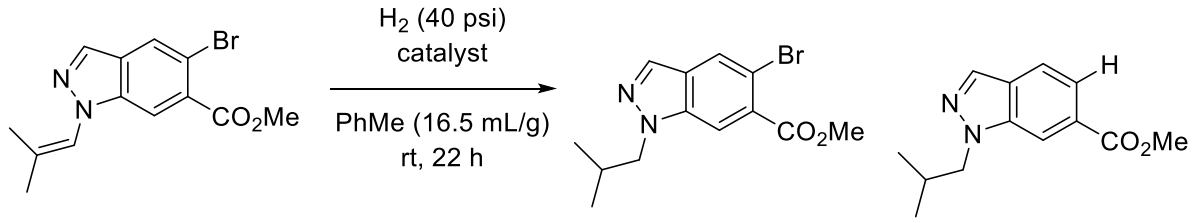
Enamine Hydrogenation

Isobutyraldehyde (3.0 equiv) was added to methyl 5-bromo-1*H*-indazole-6-carboxylate **1a** (1.0 equiv), *p*TSA·H_2O (0.25 equiv), and PhMe (15 mL/g) in a reactor vessel equipped with a Dean-Stark condenser. The reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 3 h. Et_3N (0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O, 1 M HCl, sat. brine, dried over $MgSO_4$, filtered, and concentrated to afford crude enamine product. The crude enamine product was dissolved in PhMe.

Hydrogenation catalysts were screened in Argonaut Endeavor catalyst screening systems. The catalyst was added to crude enamine solution (3 mL), and the reaction mixture was stirred under an atmosphere of H_2 at 40 psi for 22 h.

Hydrogenation temperature optimisation reactions were conducted in Type 3 Buchiglasuster reactors. 5% Pt/C (0.013 equiv) was added to crude enamine solution, and the reaction mixture was stirred under an atmosphere of H_2 at 40 psi until completion.

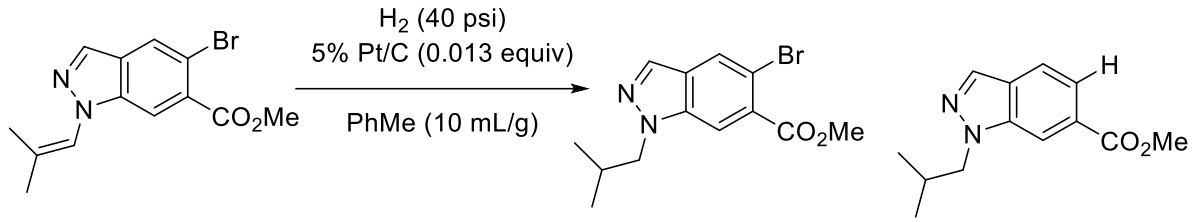
Catalyst



4a **2a** **8a**

entry	catalyst	conversion (ratio **2a**:**8a**)
1	**Pt/C (JM B103032-5, 5%) (0.013 equiv)**	**100 (97:3)**
2	Pt/C (JM B103032-5, 5%) (0.009 equiv)	89 (100:0)
3	Pd/C (JM 5R39, 5%) (0.013 equiv)	100 (69:31)
4	Rh/C (JM 5R594, 5%) (0.013 equiv)	100 (99:1)

Temperature and time



4a **2a** **8a**

entry	temp (°C)	time (h)	conversion (ratio **2a**:**8a**)
1	rt	14	99 (99:1)
2	**30**	**10**	**100 (99:1)**
3	40	10	100 (99:1)

Reaction Scope

General Procedure

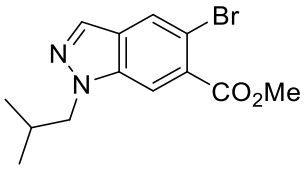
Aldehyde/ketone (3.0 equiv) was added to substrate (2.0 g, 1.0 equiv), *p*TSA·H_2O (0.25 equiv), and PhMe (30 mL) in a 50 mL EasyMax reactor vessel. A Dean-Stark condenser was equipped and the reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 3 h. Et_3N (0.27 mL, 1.96 mmol, 0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O (8 mL), 1 M HCl (8 mL), sat. brine (8 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude enamine product.

The crude enamine product was dissolved in toluene (20 mL). 5% Pt/C was added, and the reaction mixture was stirred under an atmosphere of H_2 at 40 psi and 30 °C for 24 hours (or until completion). The resulting reaction mixture was filtered through arbocel, washed with PhMe, and concentrated to afford crude hydrogenated product. The crude hydrogenated product was purified by flash silica chromatography to afford the title compound.

NB: Reaction selectivity determined by ^1H NMR and LCMS of crude enamine product. *N*2 isomer not detected unless otherwise stated.

Product Characterisation

Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (2a)

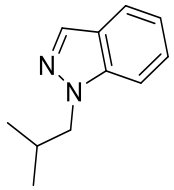


Prepared according to the general procedure from methyl 5-bromo-1*H*-indazole-6-carboxylate (2.00 g, 7.84 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow solid (1.85 g, 5.94 mmol, 76% yield (over 2 steps)).

mp 56-58 °C; **ν_{max}** (neat) /cm^{-1} 2957, 1729, 1470, 1244; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 4.19 (d, *J* = 7.5 Hz, 2H), 3.99 (s, 3H), 2.42 – 2.25 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 138.1, 131.6, 129.9, 126.5, 126.4, 112.6, 111.5, 56.8, 52.4, 30.2, 20.8; **HRMS** (ESI$^+$) calc. for $C_{13}H_{16}{}^{79}BrN_2O_2$ ([M+H]$^+$) 311.0390; found 311.0392.

NB: Spectra consistent with previous route above.

1-isobutyl-1*H*-indazole (2b)

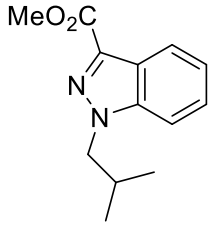


Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (2.26 g, 12.97 mmol, 77% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2959, 1616, 1465, 1294; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 1.0 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.21 (d, *J* = 7.0 Hz, 2H), 2.21 (nonet, *J* = 7.0 Hz, 1H), 0.85 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 139.6, 132.3, 125.8, 123.2, 120.7,

120.1, 109.7, 55.1, 29.1, 19.8; **HRMS** (ESI$^+$) calc. for $C_{11}H_{15}N_2$ ([M+H]$^+$) 175.1230; found 175.1233.

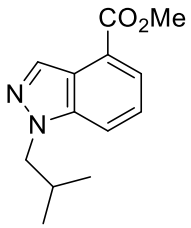
Methyl 1-isobutyl-1*H*-indazole-3-carboxylate (2c)



Prepared according to the general procedure from methyl 1*H*-indazole-3-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (1.70 g, 7.32 mmol, 64% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2959, 1709, 1478, 1270, 1236; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.08 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.85 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.34 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.34 (d, *J* = 7.5 Hz, 2H), 3.92 (s, 3H), 2.34 – 2.19 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 7H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 162.4, 140.8, 133.6, 126.6, 123.1, 122.7, 121.1, 110.9, 55.9, 51.6, 29.1, 19.7; **HRMS** (ESI$^+$) calc. for $C_{13}H_{17}N_2O_2$ [M+H]$^+$ 233.1285, found 233.1277.

Methyl 1-isobutyl-1*H*-indazole-4-carboxylate (2d)

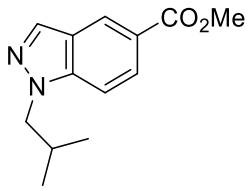


Prepared according to the general procedure from methyl 1*H*-indazole-4-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (1.91 g, 8.22 mmol, 72% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2958, 1713, 1449, 1271, 1229; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 4.29 (d, *J* = 7.0 Hz, 2H),

3.94 (s, 3H), 2.28 – 2.18 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.0, 140.1, 132.7, 125.4, 123.6, 121.9, 121.3, 115.3, 55.3, 52.1, 29.2, 19.7; **HRMS** (ESI$^+$) calc. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1286.

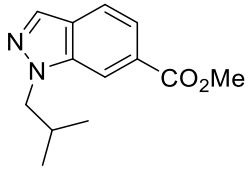
Methyl 1-isobutyl-1*H*-indazole-5-carboxylate (2e)



Prepared according to the general procedure from methyl 1*H*-indazole-5-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (2.26 g, 9.73 mmol, 86% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2959, 1712, 1434, 1247; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.25 (s, 1H), 7.94 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 4.25 (d, *J* = 7.5 Hz, 2H), 3.87 (s, 3H), 2.28 – 2.17 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.0, 141.8, 135.1, 126.6, 124.6, 123.5, 122.4, 110.4, 55.8, 52.5, 29.6, 20.2; **HRMS** (ESI$^+$) calc. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1286.

Methyl 1-isobutyl-1*H*-indazole-6-carboxylate (2f)

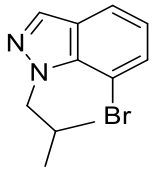


Prepared according to the general procedure from methyl 1*H*-indazole-6-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow solid (1.84 g, 7.92 mmol, 70% yield (over 2 steps)).

mp 54-56 °C; **ν_{max}** (neat) /cm^{-1} 2954, 1714, 1432, 1275, 1234; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.33 – 8.32 (m, 1H), 8.19 (d, *J* = 1.0 Hz, 1H), 7.88 (dd, *J* = 8.5 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.32 (d, *J* = 7.5, 2H), 3.91 (s, 3H), 2.30 – 2.17 (m, 1H), 0.85 (d, *J* = 6.5, 6H);); **^{13}C NMR** (101

MHz, DMSO-d_6) δ 166.6, 139.0, 132.7, 127.2, 125.8, 121.1, 120.2, 111.8, 55.3, 52.2, 29.2, 19.7; **HRMS** (ESI$^+$) calc. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1286.

7-bromo-1-isobutyl-1*H*-indazole (2h)

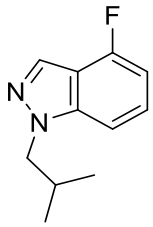


Isobutyraldehyde (2.78 mL, 30.45 mmol, 3.0 equiv) was added to 7-bromo-1*H*-indazole (2.0 g, 10.15 mmol, 1.0 equiv), *p*TSA·H_2O (0.48 g, 2.54 mmol, 0.25 equiv), and PhMe (30 mL) in a 50 mL EasyMax reactor vessel. A Dean-Stark condenser was equipped and the reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 6 h. Et_3N (0.35 mL, 2.54 mmol, 0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O (8 mL), 1 M HCl (8 mL), sat. brine (8 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford 7-bromo-1-(2-methylprop-1-en-1-yl)-1H-indazole (1.00 g, 3.96 mmol, 39% yield) and 7-bromo-1*H*-indazole starting material (0.8 g, 4.1 mmol, 40% yield (or 65% yield brsm)).

7-bromo-1-(2-methylprop-1-en-1-yl)-1H-indazole was dissolved in toluene (20 mL). 5% Pt/C (0.013 equiv) was added, and the reaction mixture was stirred under an atmosphere of H_2 at 40 psi and 30 °C for 24 hours. The resulting reaction mixture was filtered through arbocel, washed with PhMe, and concentrated to afford crude hydrogenated product. The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (0.70 g, 2.77 mmol, 27% yield (over 2 steps) (or 45% yield brsm (over 2 steps))).

ν_{max} (neat) /cm^{-1} 2957, 1607, 1447, 1291; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 4.53 (d, *J* = 7.5 Hz, 2H), 2.25-2.15 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 136.1, 133.0, 131.0, 126.5, 121.7, 120.9, 102.0, 56.7, 30.5, 19.4; **HRMS** (ESI$^+$) calc. for $C_{11}H_{14}{}^{79}BrN_2$ [M+H]+ 253.0335, found 253.0334

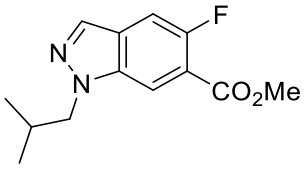
4-fluoro-1-isobutyl-1*H*-indazole (2i)



Prepared according to the general procedure from 4-fluoro-1*H*-indazole (2.00 g, 14.69 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) to afford the title compound as a pale-yellow oil (2.23 g, 11.58 mmol, 79% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2962, 1633, 1458, 1284; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (d, *J* = 1.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.5, 5.0 Hz, 1H), 6.89 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.24 (d, *J* = 7.0 Hz, 2H), 2.27-2.17 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 6H);**^{19}F NMR** (376 MHz, DMSO) δ -118.97 (dd, *J* = 10.5, 5.0); **^{13}C NMR** (100 MHz, DMSO) δ 155.3 (d, *J* = 247 Hz), 142.9 (d, *J* = 10 Hz), 129.1 (d, *J* = 2 Hz), 127.5 (d, *J* = 8 Hz), 113.7 (d, *J* = 23 Hz), 107.0 (d, *J* = 4 Hz), 105.0 (d, *J* = 18 Hz), 56.0, 29.6, 20.2. 13C NMR (101 MHz, DMSO) δ 155.3 (d, J = 249.0 Hz), 142.9 (d, *J* = 9.5 Hz), 129.1 (d, *J* = 2.0 Hz), 127.5 (d, *J* = 7.5 Hz), 113.7 (d, *J* = 23.5 Hz), 107.0 (d, J = 4.0 Hz), 104.9 (d, *J* = 18.0 Hz), 56.0, 29.6, 20.2; **HRMS** (ESI^+) calc. for $C_{11}H_{14}FN_2$ $[M+H]^+$ 193.1136, found 193.1143.

Methyl 5-fluoro-1-isobutyl-1*H*-indazole-6-carboxylate (2j)

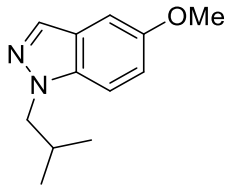


Prepared according to the general procedure from methyl 5-fluoro-1*H*-indazole-6-carboxylate (2.00 g, 10.30 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as an off-white solid (2.12 g, 8.47 mmol, 82% yield (over 2 steps)).

mp 66-68 °C; **ν_{max}** (neat) /cm^{-1} 2956, 1726, 1466, 1254, 1074, 844, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (ddd, *J* = 5.5, 1.0, 0.5 Hz, 1H), 8.15 (d, *J* = 1.0 Hz, 1H), 7.68 (dd, *J* = 11.0, 0.5 Hz, 1H), 4.31 (d, *J* = 7.5 Hz, 2H), 3.90 (s, 3H), 2.29 – 2.14 (m, *J* = 7.0 Hz, 1H), 0.84 (d, *J* = 6.5 Hz,

6H);**^{19}F NMR** (376 MHz, DMSO) δ -123.44 (dd, *J* = 11.0, 5.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5 (d, *J* = 4.0 Hz), 154.8 (d, *J* = 246.5 Hz), 135.6, 132.5 (d, *J* = 5.5 Hz), 125.1 (d, *J* = 10.5 Hz), 117.8 (d, *J* = 16.2 Hz), 113.6 (d, *J* = 2.5 Hz), 106.6 (t, *J* = 24.5 Hz), 55.5, 52.5, 29.2, 19.7; **HRMS** (ESI^+) calc. $C_{13}H_{16}FN_2O_2$ ($[M+H]^+$) 251.1190; found 251.1205.

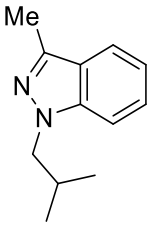
1-isobutyl-5-methoxy-1*H*-indazole (2k)



Prepared according to the general procedure from 5-methoxy-1*H*-indazole (2.00 g, 13.50 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) to afford the title compound as an off-white solid (1.45 g, 7.09 mmol, 53% yield (over 2 steps)).

mp 46-49 °C; **ν_{max}** (neat) /cm^{-1} 2968, 1626, 1468, 1288; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.0 Hz, 1H), 7.57 (dt, *J* = 9.0, 1.0 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.02 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.16 (d, *J* = 7.0 Hz, 2H), 3.78 (s, 3H), 2.24-2.14 (m, 1H), 0.83 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 153.9, 135.6, 131.5, 123.5, 117.8, 110.7, 100.0, 55.3×2, 29.2, 19.8; **HRMS** (ESI^+) calc. for $C_{12}H_{17}N_2O$ $[M+H]^+$ 205.1335, found 205.1346.

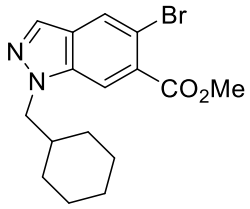
1-isobutyl-3-methyl-1H-indazole (2l)



Prepared according to the general procedure from 3-methyl-1*H*-indazole (2.00 g, 15.31 mmol, 1.0 equiv) and isobutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (2.01 g, 10.68 mmol, 71% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2959, 1615, 1507, 1453, 1350, 1198, 1074, 1009, 761, 738, 634, 430; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.68 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.55 (dt, *J* = 8.5, 1.0 Hz, 1H, 7.34 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.08 (ddd, *J* = 7.5, 7.0, 1.0 Hz, 1H), 4.11 (d, *J* = 7.0 Hz, 2H), 2.48 (s, 3H), 2.29 – 2.11 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 120.6, 119.8, 109.9, 55.4, 29.6, 20.4, 12.1; **HRMS** (ESI$^+$) calc. for $C_{12}H_{17}N_2$ $[M+H]^+$ 189.1386, found 189.1395.

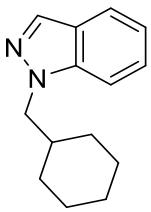
Methyl 5-bromo-1(cyclohexylmethyl)-1*H*-indazole-6-carboxylate (2m)



Prepared according to the general procedure from methyl 5-bromo-1*H*-indazole-6-carboxylate (2.00 g, 7.84 mmol, 1.0 equiv) and cyclohexanecarboxaldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-yellow oil (1.77 g, 5.04 mmol, 64% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2924, 1731, 1468, 1284, 1253; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.01 (d, *J* = 1.0 Hz, 2H), 7.96 (d, *J* = 1.0 Hz, 1H), 7.84 (t, *J* = 1.0 Hz, 1H), 4.20 (d, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 2.06-1.94 (m, 1H), 1.73-1.65 (m, 3H), 1.58-1.54 (m, 2H), 1.27-1.13 (m, 3H), 1.07-0.97 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 138.2, 132.1, 129.8, 126.5, 126.4, 112.7, 115.4, 55.7, 52.8, 38.9, 31.0, 26.4, 25.8; **HRMS** (ESI$^+$) calc. for $C_{16}H_{20}{}^{79}BrN_2O_2$ $[M+H]^+$ 351.0703, found 351.0706.

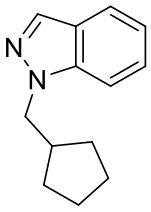
1-(cyclohexylmethyl)-1*H*-indazole (2n)



Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and cyclohexanecarboxaldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 5% EtOAc in heptane) to afford the title compound as a clear oil (2.35 g, 11.00 mmol, 65% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2921, 2850, 1464, 1448, 750, 737; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.64 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.23 (d, *J* = 7.0 Hz, 2H), 1.95-1.84 (m, 1H), 1.67 – 1.59 (m, 2H), 1.59 – 1.54 (m, 1H), 1.51 – 1.41 (m, 2H), 1.17 – 1.06 (m, 3H), 1.00 (qd, *J* = 12.0, 3.0 Hz, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 132.3, 125.7, 120.7, 120.1, 109.7, 53.9, 38.3, 30.1, 25.8, 25.1; **HRMS** (ESI$^+$) calc. for $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1543, found 215.1557.

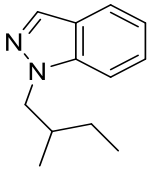
1-(cyclopentylmethyl)-1*H*-indazole (2o)



Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and cyclopentanecarboxaldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.013 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 4% EtOAc in heptane) to afford the title compound as an orange oil (1.79 g, 8.97 mmol, 53% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2950, 1616, 1464, 1296; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.31 (d, *J* = 7.5 Hz, 2H), 2.49 – 2.40 (m, 1H), 1.65 – 1.42 (m, 6H), 1.33 – 1.21 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 139.3, 132.2, 125.7, 123.3, 120.7, 120.1, 109.6, 52.4, 40.2, 29.7, 24.4; **HRMS** (ESI$^+$) calc. for $C_{13}H_{17}N_2$ $[M+H]^+$ 201.1386, found 201.1397.

1-(2-methylbutyl)-1*H*-indazole (2p)

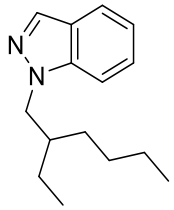


Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and 2-methylbutyraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica

chromatography (elution gradient 0 to 10% EtOAc in heptane) to afford the title compound as a clear oil (2.33 g, 12.36 mmol, 73% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2950, 1616, 1464, 1296; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 1.0 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.64 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.29 (dd, *J* = 14.0, 6.5 Hz, 1H), 4.19 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.09 – 1.91 (m, 1H), 1.42 – 1.24 (m, 1H), 1.21 – 1.05 (m, 1H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 139.6, 132.3, 125.8, 123.3, 120.7, 120.1, 109.6, 53.6, 35.4, 26.2, 16.7, 10.9; **HRMS** (ESI$^+$) calc. for $C_{12}H_{17}N_2$ [M+H]$^+$ 189.1386, found 189.1392.

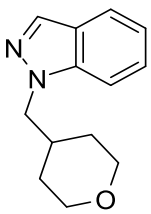
1-(2-ethylhexyl)-1*H*-indazole (2q)



Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and 2-ethylhexanal. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 5% EtOAc in heptane) to afford the title compound as a pale-yellow oil (3.33 g, 14.43 mmol, 85% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2958, 1616, 1465, 1241; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.74 (dt, *J* =8.0, 1.0 Hz, 1H), 7.61 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.28 (d, *J* = 7.0 Hz, 2H), 1.95 (m, 1H), 1.21 (m, 8H), 0.84 (t, *J* =7.5 Hz, 3H), 0.79 (t, *J* =7.0 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 139.6, 132.2, 125.8, 123.3, 120.7, 120.1, 109.5, 51.5, 39.5, 29.9, 27.9, 23.4, 22.3, 13.7, 10.4; **HRMS** (ESI$^+$) calc. for $C_{15}H_{23}N_2$ [M+H]$^+$ 231.1855, found 231.1865.

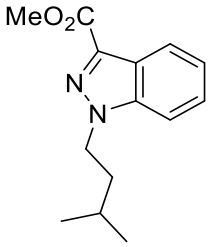
1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-indazole (2r)



Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and tetrahydropyran-4-carbaldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 30% EtOAc in heptane) to afford the title compound as a white solid (2.19 g, 10.12 mmol, 60% yield (over 2 steps)).

mp 71-73 °C; **ν_{max}** (neat) /cm^{-1} 2937, 1436, 1093, 743, 444; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 1.0 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.69 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.30 (d, *J* = 7.0 Hz, 2H), 3.80 (ddd, *J* = 11.5, 4.0, 2.0 Hz, 2H), 3.21 (td, *J* = 11.5, 3.0 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.40 – 1.22 (m, 4H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 140.2, 133.0, 126.4, 123.8, 121.2, 120.7, 110.2, 67.0, 53.8, 36.3, 30.6; **HRMS** (ESI^+) calc. for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1335, found 217.1350.

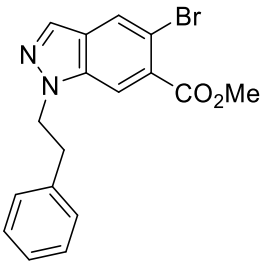
Methyl 1-isopentyl-1*H*-indazole-3-carboxylate (2s)



Prepared according to the general procedure from methyl 1*H*-indazole-3-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and isovaleraldehyde. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) to afford the title compound as a yellow oil (1.25 g, 5.12 mmol, 45% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2955, 1710, 1478, 1226, 1158, 1117, 745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.31 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H), 4.53 – 4.44 (m, 2H), 4.03 (s, 3H), 1.91 – 1.79 (m, 2H), 1.69 – 1.56 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9, 132.1, 125.6, 123.6, 120.7, 120.2, 109.6, 58.3, 31.9, 24.2; **HRMS** (ESI^+) calc. $C_{14}H_{19}N_2O_2$ ($[M+H]^+$) 247.1441; found 247.1453.

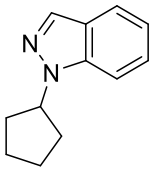
Methyl 5-bromo-1-(2-phenylethyl)-1*H*-indazole-6-carboxylate (2t)



Prepared according to the general procedure from methyl 5-bromo-1*H*-indazole-6-carboxylate (2.00 g, 7.84 mmol, 1.0 equiv) and phenylacetaldehyde. The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a dark-yellow oil (1.04 g, 2.90 mmol, 38% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2949, 1730, 1467, 1254, 1238; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.13 (d, *J* = 1.0 Hz, 1H), 8.12 (d, *J* = 1.0 Hz, 1H), 7.94 (t, *J* = 1.0 Hz, 1H), 7.20-7.13 (m, 5H), 4.70 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.14 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7, 138.2, 137.4, 132.3, 129.7, 128.7, 128.2, 126.3, 125.5×2, 112.5, 109.6, 52.5, 49.8, 35.5; **HRMS** (ESI$^+$) calc. for [M+H]$^+$ 359.0389, found 359.0379.

1-cyclopentyl-1*H*-indazole (2u)

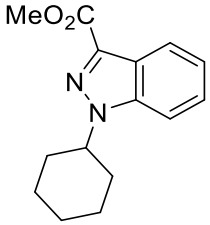


Prepared according to the general procedure from 1*H*-indazole (2.00 g, 16.93 mmol, 1.0 equiv) and cyclopentanone. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a clear oil (0.97 g, 5.27 mmol, 31% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2955, 1614, 1206, 911, 751, 737, 429; **^{1}H NMR** (400 MHz, DMSO) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 0.8 Hz, 1H), 5.21 – 5.07 (m, 1H), 2.18 – 2.06 (m, 2H), 2.06 – 1.95 (m, 2H), 1.92 – 1.81 (m, 2H), 1.73 – 1.62 (m, 2H); **^{13}C NMR** (101 MHz, DMSO) δ

138.9, 132.1, 125.6, 123.6, 120.7, 120.2, 109.6, 58.3, 31.9, 24.2; **HRMS** (ESI^+) calc. $C_{12}H_{15}N_2$ ($[M+H]^+$) 187.1230; found 187.1242.

Methyl 1-cyclohexyl-1*H*-indazole-3-carboxylate (2v)



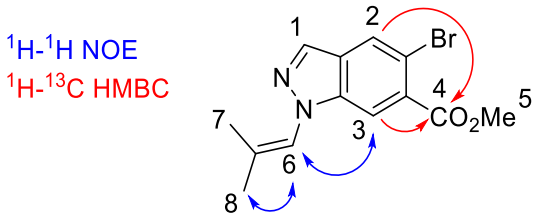
Prepared according to the general procedure from methyl 1*H*-indazole-3-carboxylate (2.00 g, 11.35 mmol, 1.0 equiv) and cyclohexanone. Hydrogenation followed the general procedure, with 5% Pt/C (0.039 equiv). The crude hydrogenated product was purified by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) to afford the title compound as a pale-yellow oil (1.56 g, 6.04 mmol, 53% yield (over 2 steps)).

ν_{max} (neat) /cm^{-1} 2930, 1710, 1475, 1166, 1121, 750; **^{1}H NMR** (400 MHz, DMSO) δ 8.24 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.53 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.41 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.30 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.52 (tt, *J* = 11.5, 4.5 Hz, 1H), 4.03 (s, 3H), 2.23 – 2.04 (m, 4H), 1.98 (dt, *J* = 13.5, 3.0 Hz, 2H), 1.83 – 1.72 (m, 1H), 1.57 – 1.41 (m, 2H), 1.37 (tt, *J* = 13.0, 3.0 Hz, 1H); **^{13}C NMR** (101 MHz, DMSO) δ 163.4, 139.9, 134.4, 126.5, 124.1, 123.1, 122.4, 110.0, 59.6, 52.1, 32.4, 25.8, 25.3; **HRMS** (ESI^+) calc. $C_{15}H_{19}N_2O_2$ ($[M+H]^+$) 259.1441; found 259.1453.

Mechanistic Investigations

Synthesis and Characterisation of Intermediates

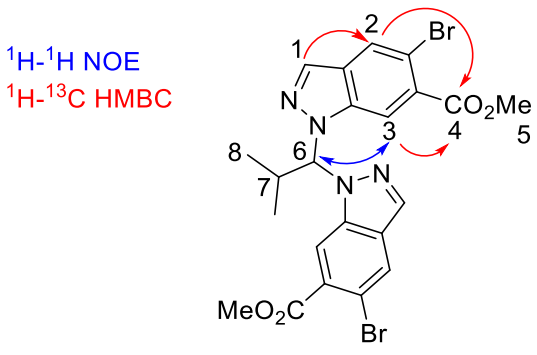
Methyl 5-bromo-1-(2-methylprop-1-en-1-yl)-1*H*-indazole-6-carboxylate (4a)



Isobutyraldehyde (2.1 mL, 23.53 mmol, 3.0 equiv) was added to methyl 5-bromo-1*H*-indazole-6-carboxylate (2.0 g, 7.84 mmol, 1.0 equiv) and *p*TSA·H_2O (0.38 g, 1.96 mmol, 0.25 equiv) in PhMe (30 mL) in a 50 mL EasyMax reactor vessel. A Dean-Stark condenser was equipped and the reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 5 h. Et_3N (0.27 mL, 1.96 mmol, 0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O (8 mL), sat. brine (8 mL), and concentrated to afford crude product. The crude product was purified by flash silica chromatograph (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a pale-orange solid (1.56 g, 5.05 mmol, 64%).

mp 87-89 °C; **ν_{max}** (neat) /cm^{-1} 2967, 1723, 1448, 1409, 1240, 771; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 1.0 Hz, 1H, **H1**), 8.21 (d, *J* = 0.5 Hz, 1H, **H2**), 7.97 (dd, *J* = 1.0, 0.5 Hz, 1H, **H3**), 7.02 (hept, *J* = 1.5 Hz, 1H, **H6**), 3.90 (s, 3H, **H5**), 1.93 (d, *J* = 1.5 Hz, 3H, **H8**), 1.78 (d, *J* = 1.5 Hz, 3H, **H7**); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.5 (**C4**), 137.2, 133.5, 131.8, 130.4, 125.8, 125.3, 119.0, 112.6, 110.5, 52.7, 22.5, 18.3; **HRMS** (ESI$^+$) calc. for $C_{13}H_{14}{}^{79}BrN_2O_2$ ([M+H]$^+$) 309.0233; found 309.0232.

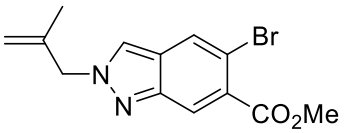
Dimethyl 1,1'-(2-methylpropane-1,1-diyl)bis(5-bromo-1*H*-indazole-6-carboxylate) (5a)



Isobutyraldehyde (0.39 mL, 4.30 mmol, 2.2 equiv) was added to methyl 5-bromo-1*H*-indazole-6-carboxylate (1.0 g, 3.92 mmol, 1.0 equiv), *p*TSA·H_2O (75.7 mg, 0.39 mmol, 0.20 equiv), and molecular sieves (4 Å, 3.0 g) in PhMe (15 mL). The reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled to rt, filtered through arbocel, and washed with EtOAc (40 mL). The filtrate was washed with sat. $NaHCO_3$ (15 mL), sat. brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatograph (elution gradient 0 to 30% EtOAc in heptane) to afford the title compound as an off-white solid (0.51 g, 0.91 mmol, 47%).

mp 77-79 °C; $\boldsymbol{\nu_{max}}$ (neat) /cm^{-1} 2952, 1728, 1464, 1254, 1099, 803; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (s, 2H, **H3**), 8.23 (s, 2H, **H1**), 8.15 (s, 2H, **H2**), 7.41 (d, *J* = 10.5 Hz, 1H, **H6**), 3.94 (s, 6H, **H5**), 3.69 – 3.60 (m, 1H, **H7**), 0.87 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5 (**C4**), 137.5, 134.2 (**C1**), 130.5, 126.2 (**C2**), 126.1, 112.7 (**C3**), 110.8, 75.4, 52.8, 30.5, 18.1; **HRMS** (ESI^+) calc. for $C_{13}H_{14}{}^{79}BrN_2O_2$ ($[M\text{-}C_9H_6BrN_2O_2]^+$) 309.0233; found 309.0240.

Methyl 5-bromo-2-(2-methylallyl)-2*H*-indazole-6-carboxylate



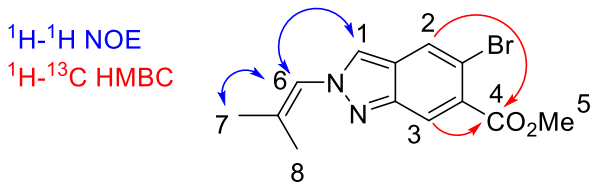
Prepared according to a modified literature procedure.[12]

1,8-Diazabicyclo[5.4.0]undec-7-ene (45 µL, 0.30 mmol, 0.3 equiv) was added to a solution of 2-methyl-2-propen-1-ol (0.25 mL, 3.00 mmol, 3.0 equiv) and trichloroacetonitrile (0.45 mL, 4.50 mmol, 4.5 equiv) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at rt for 5 h. Methyl 5-bromo-1H-indazole-6-carboxylate (0.26 g, 1.00 mmol, 1.0 equiv) was added and allowed to dissolve. Triflic acid (0.12 mL, 1.33 mmol, 1.3 equiv) was added. The reaction mixture was stirred at rt for 18 h. The reaction mixture was washed with 1 M NaOH (2 mL×2) and H_2O (2 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 mL×2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a brown oil (0.18 g, 0.59 mmol, 59% yield).

$\boldsymbol{\nu_{max}}$ (neat) /cm^{-1} 2947, 1716, 1475, 1256; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 1.0, 1H), 7.97 (d, *J* = 1.0, 1H), 7.92 (d, *J* = 1.0, 1H), 5.08 – 5.05 (m, 1H), 4.98 (br s, 2H), 4.93 – 4.91 (m, 1H),

3.96 (s, 3H), 1.70 – 1.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 146.6, 139.7, 130.0, 125.3, 124.1, 122.5, 122.0, 115.5, 112.2, 60.3, 52.5, 19.7; **HRMS** (ESI^+) calc. for $C_{13}H_{14}{}^{79}BrN_2O_2$ ($[M+H]^+$) 309.0233; found 309.0232.

Methyl 5-bromo-2-(2-methylprop-1-en-1-yl)-2*H*-indazole-6-carboxylate (6a)

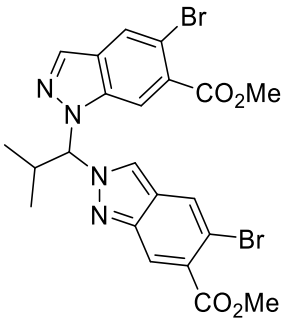


methyl 5-bromo-2-(2-methylallyl)-2*H*-indazole-6-carboxylate (50 mg, 0.16 mmol, 1.0 equiv) was added to a solution of KO^tBu (18 mg, 0.16 mmol, 1.0 equiv) in DMSO (0.5 mL). The reaction mixture was stirred at rt until full conversion to the enamine. MeI (20 µL, 0.32 mmol, 2.0 equiv) was added, and the reaction stirred until full conversion. The reaction mixture was diluted with EtOAc (10 mL), then washed with H_2O (10 mL), sat. brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane) to afford the title compound as a clear oil (18 mg, 0.06 mmol, 10% yield).

ν_{max} (neat) /cm^{-1} 2916, 1714, 1452, 1255; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 1.0 Hz, 1H, **H3**), 7.97 (d, *J* = 1.0 Hz, 1H, **H2**), 7.91 (d, *J* = 1.0 Hz, 1H, **H1**), 6.97 – 6.90 (m, 1H, **H6**), 3.96 (s, 3H, **H5**), 1.96 (d, *J* = 1.5 Hz, 3H, **H7**), 1.91 (d, *J* = 1.5 Hz, 3H, **H8**); **^{13}C NMR** (101 MHz, $CDCl_3$) 167.3 (**C4**), 146.6, 135.0, 130.3, 125.4, 123.7, 123.3, 123.0, 122.2, 112.4, 52.7, 23.4, 18.7; **HRMS** (ESI^+) calc. for $C_{13}H_{14}{}^{79}BrN_2O_2$ ($[M+H]^+$) 309.0233; found 309.0201.

NB: Initial isomerisation causes significant levels of ester hydrolysis. Addition of MeI required to reform the methyl ester *in situ*.

Methyl 5-bromo-2-(1-(5-bromo-6-(methoxycarbonyl)-1*H*-indazol-1-yl)-2-methylpropyl)-2*H*-indazole-6-carboxylate (7a)



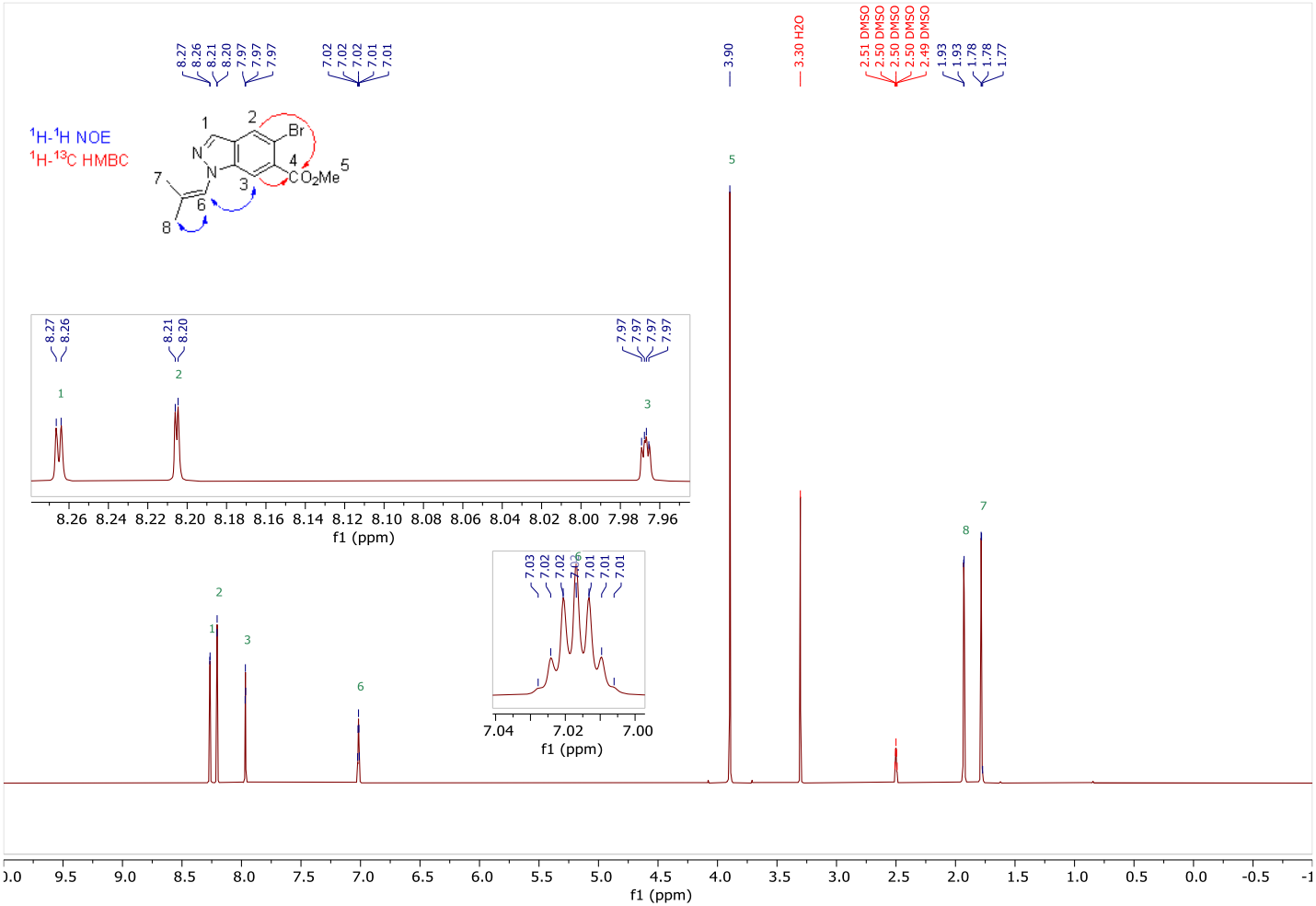
methyl 5-bromo-1*H*-indazole-6-carboxylate (2.0 g, 7.84 mmol, 1.0 equiv) and *p*TSA·H_2O (0.37 g, 1.96 mmol, 0.25equiv) in PhMe (30 mL) were heated to a vigorous reflux (jacket temperature = 140 °C) in a 50 mL EasyMax reactor vessel. Isobutyraldehyde (2.1 mL, 23.53 mmol, 3.0 equiv) was added, and the reaction mixture was stirred for 1 min. Et_3N (0.27 mL, 1.96 mmol, 0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O (8 mL), 1 M HCl (8 mL), sat. brine (8 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude product. The crude product was purified by flash silica chromatograph (elution gradient 0 to 50% EtOAc in heptane) to afford the title compound as an off-white solid (0.15 g, 0.27 mmol, 7% yield).

mp 180-182 °C; **ν_{max}** (neat) /cm^{-1} 2952, 1712, 1697, 1465, 1256; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.59 (s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 8.05 (s, 1H), 7.32 (d, *J* = 10.5 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.54 – 3.44 (m, 1H), 0.88 – 0.83 (m, 6H); **^{13}C NMR** (DMSO, 101 MHz) δ 166.6×2, 145.2, 138.1, 135.0, 131.0, 130.9, 126.1×2, 126.0, 123.7, 123.0, 120.8, 112.4, 111.0, 110.7, 78.4, 52.8, 52.3, 31.6, 18.0×2; **HRMS** (ESI^+) calc. for $C_{13}H_{14}{}^{79}BrN_2O_2$ ([M-$C_9H_6BrN_2O_2$]$^+$) 309.0233; found 309.0219.

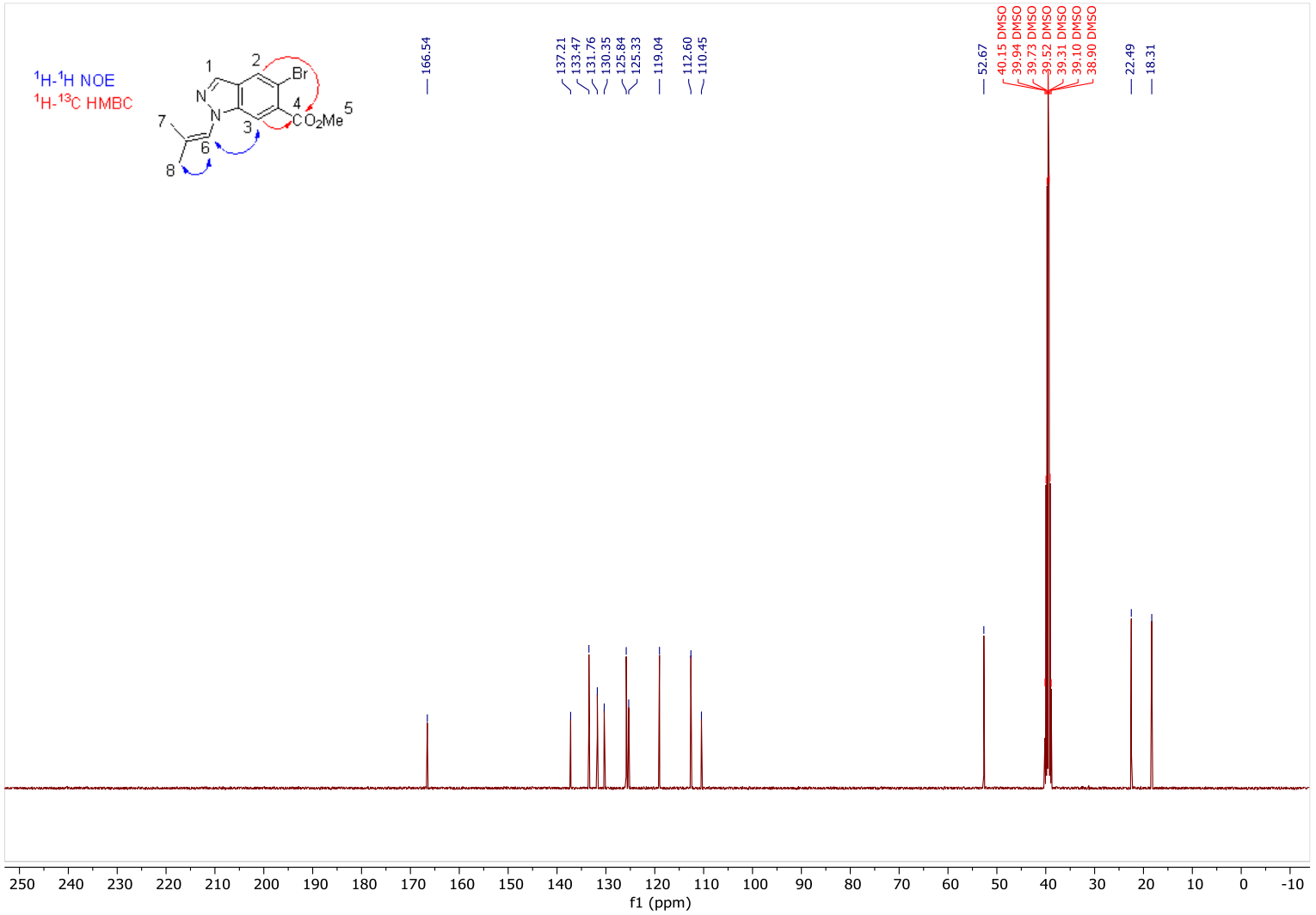
NMR Spectra for Assignment

Methyl 5-bromo-1-(2-methylprop-1-en-1-yl)-1H-indazole-6-carboxylate (4a)

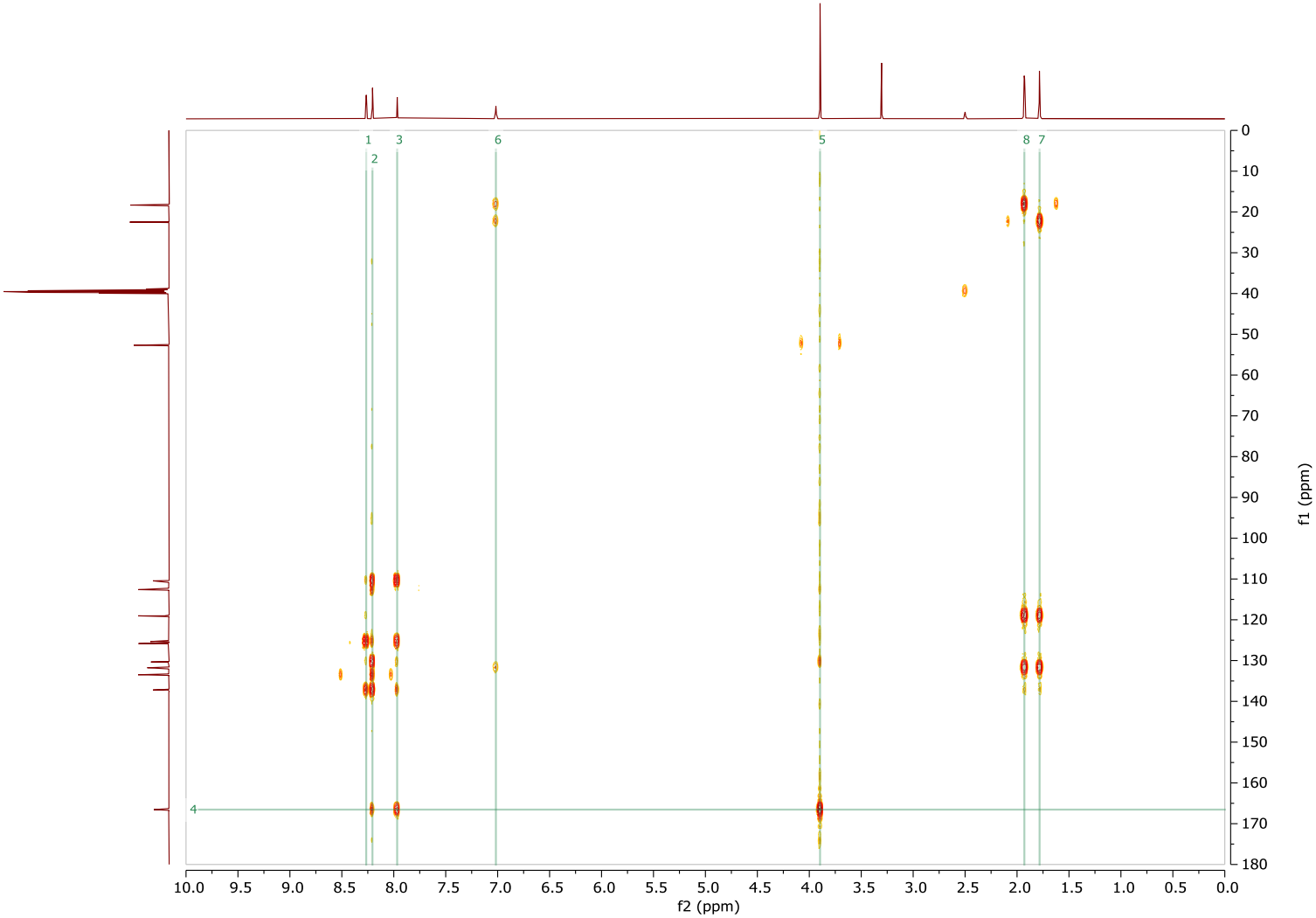
^{1}H NMR (400 MHz, $CDCl_3$)



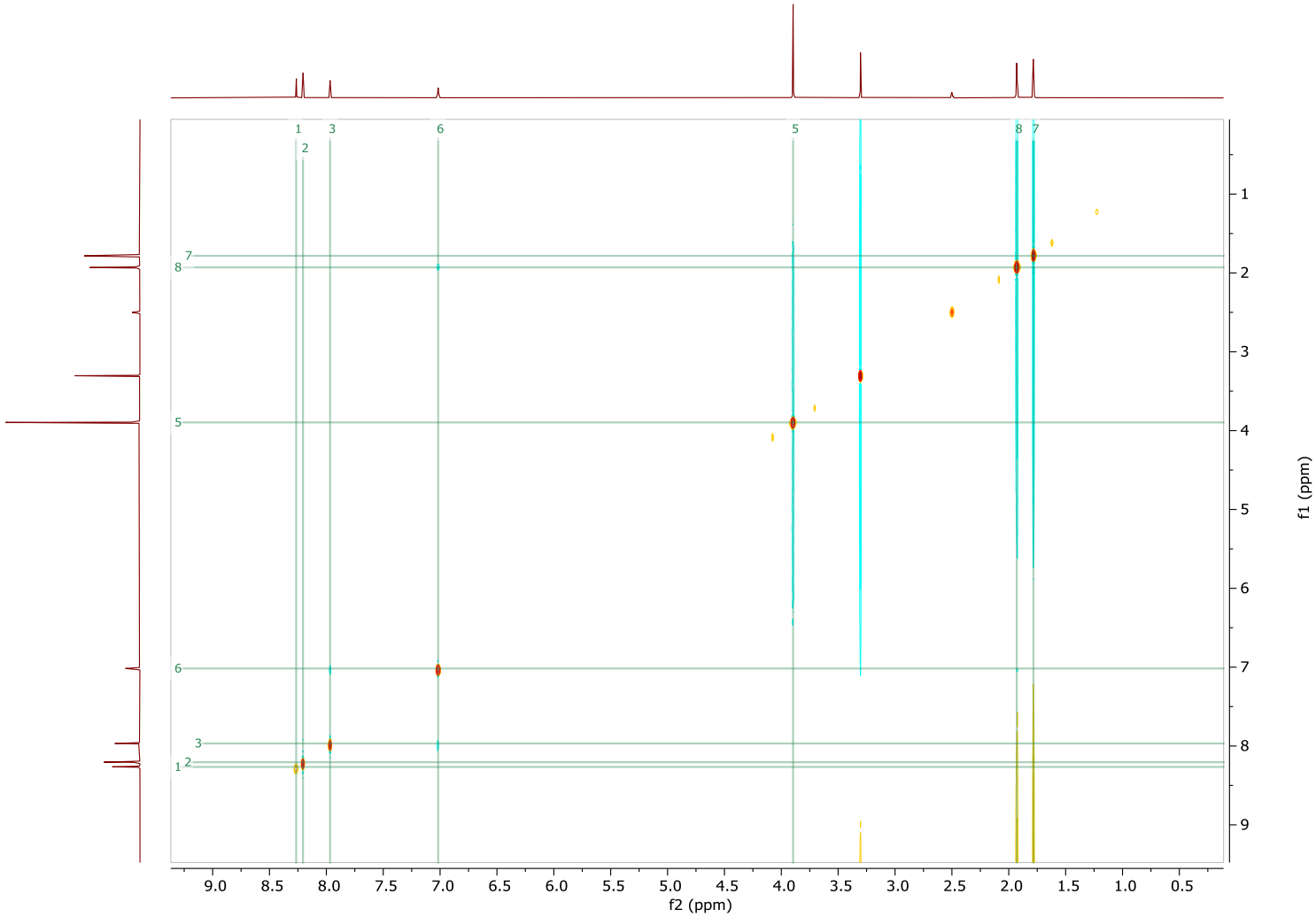
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

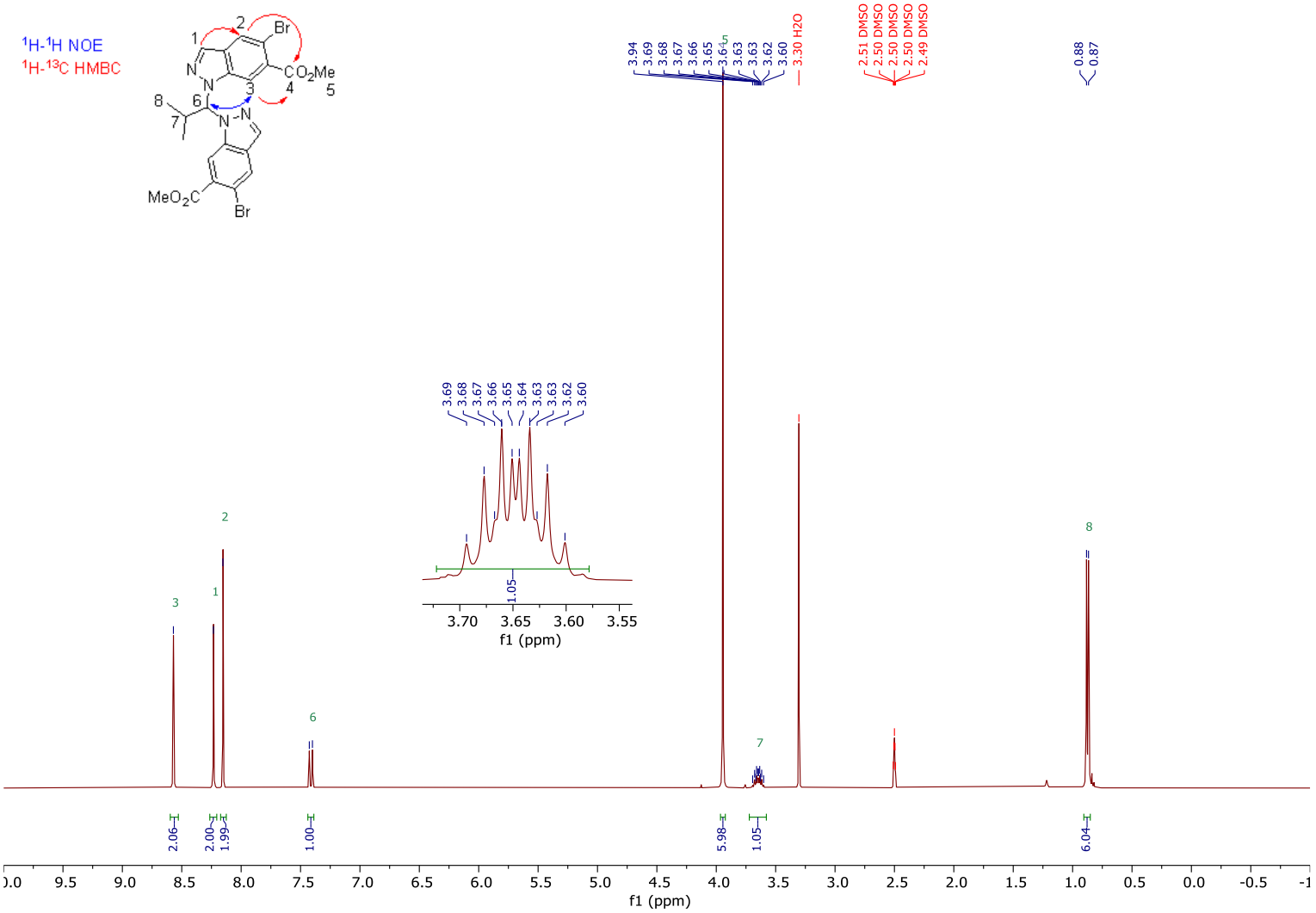


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

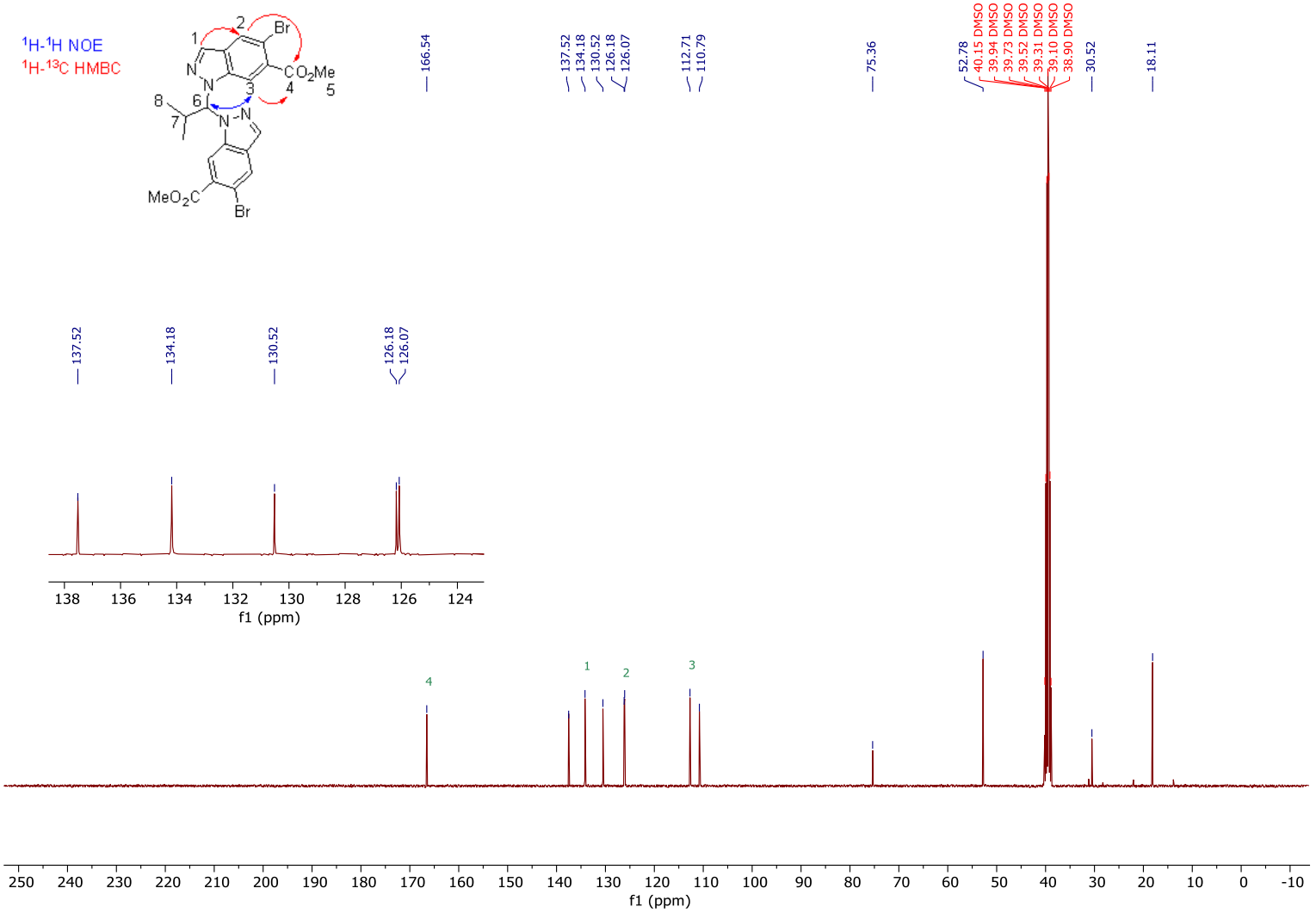


Dimethyl 1,1'-(2-methylpropane-1,1-diyl)bis(5-bromo-1*H*-indazole-6-carboxylate) (5a)

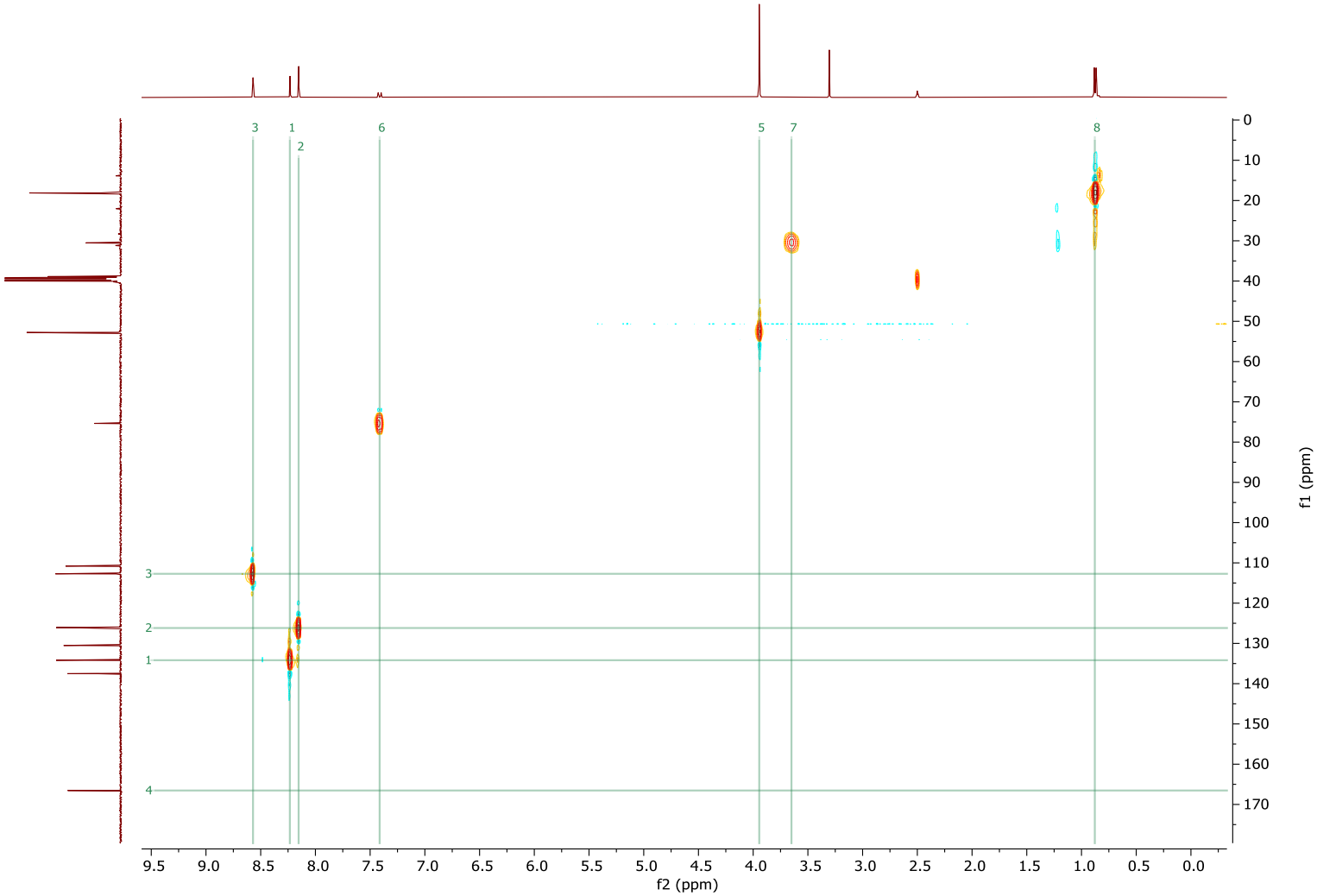
^{1}H NMR (400 MHz, $CDCl_3$)



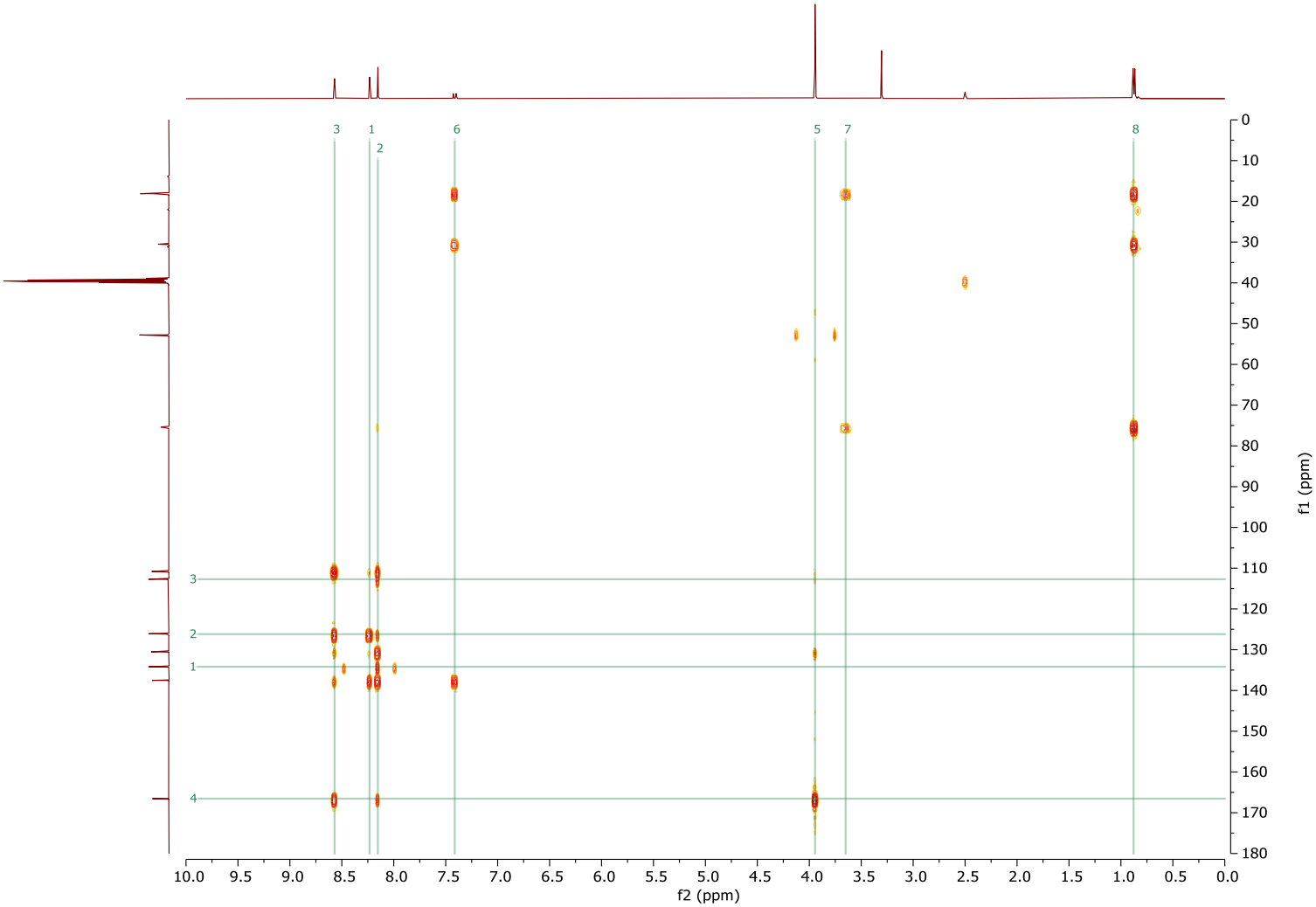
^{13}C NMR (101 MHz, $CDCl_3$)



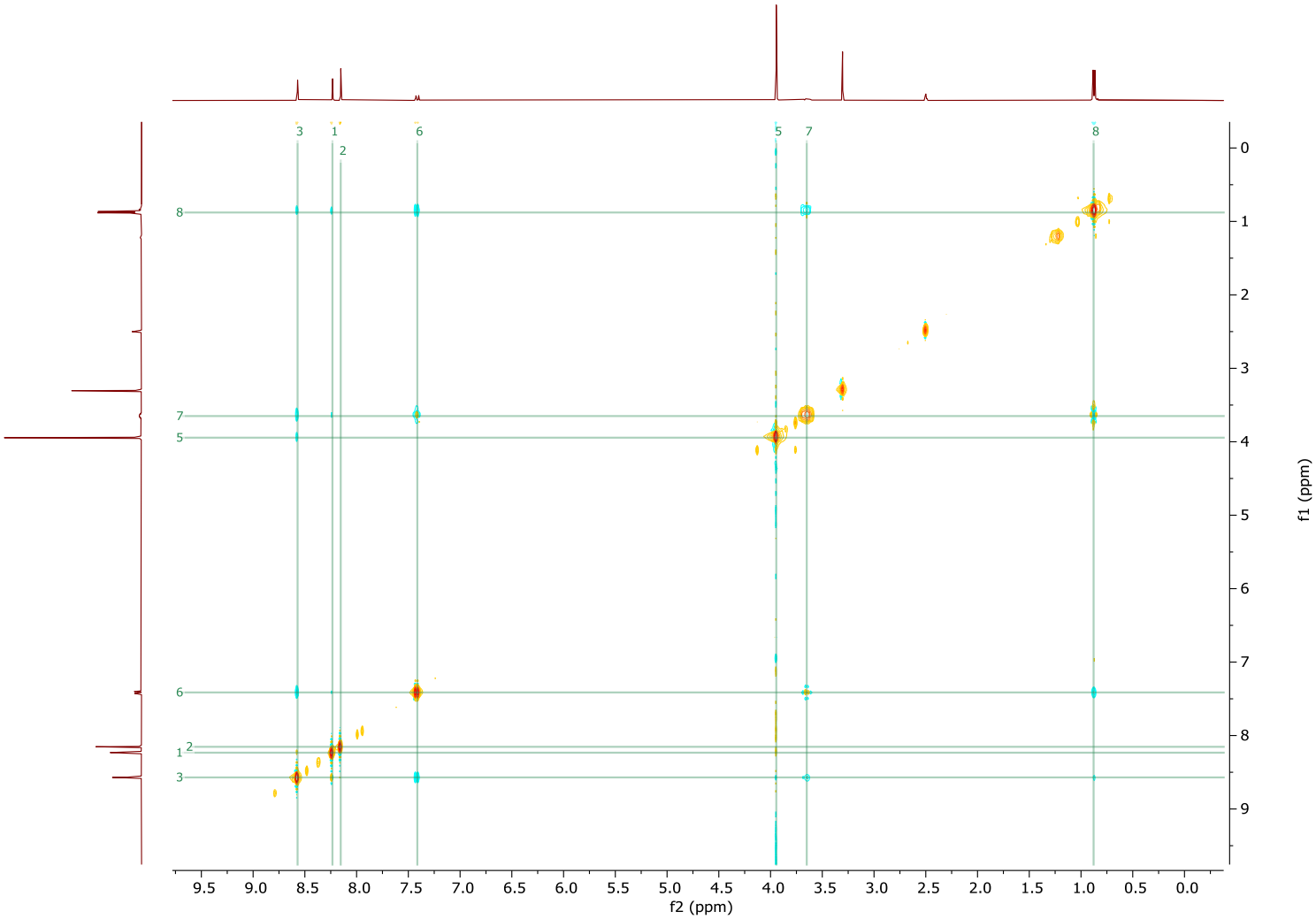
^{1}H-^{13}C HSQC ($CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

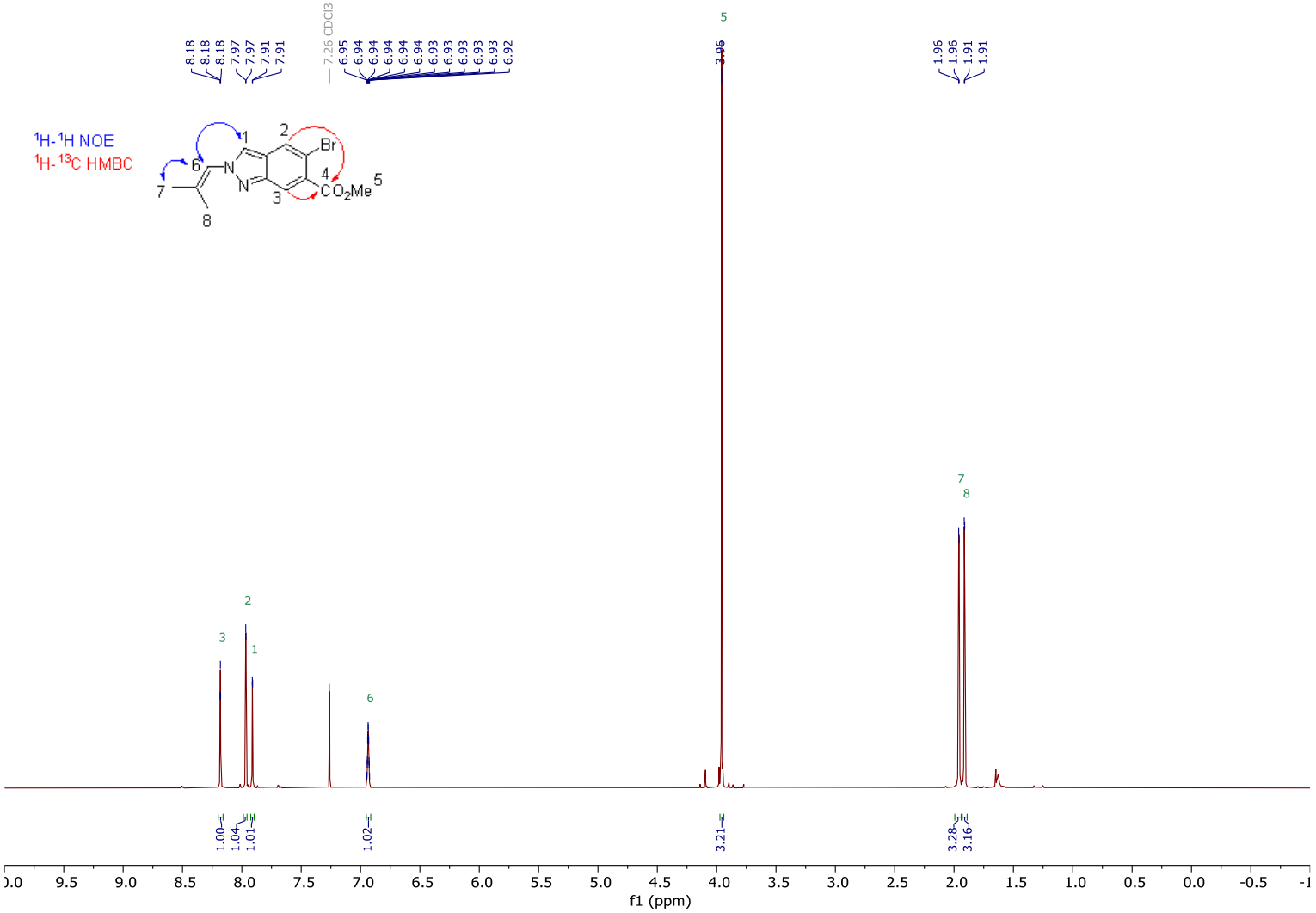


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

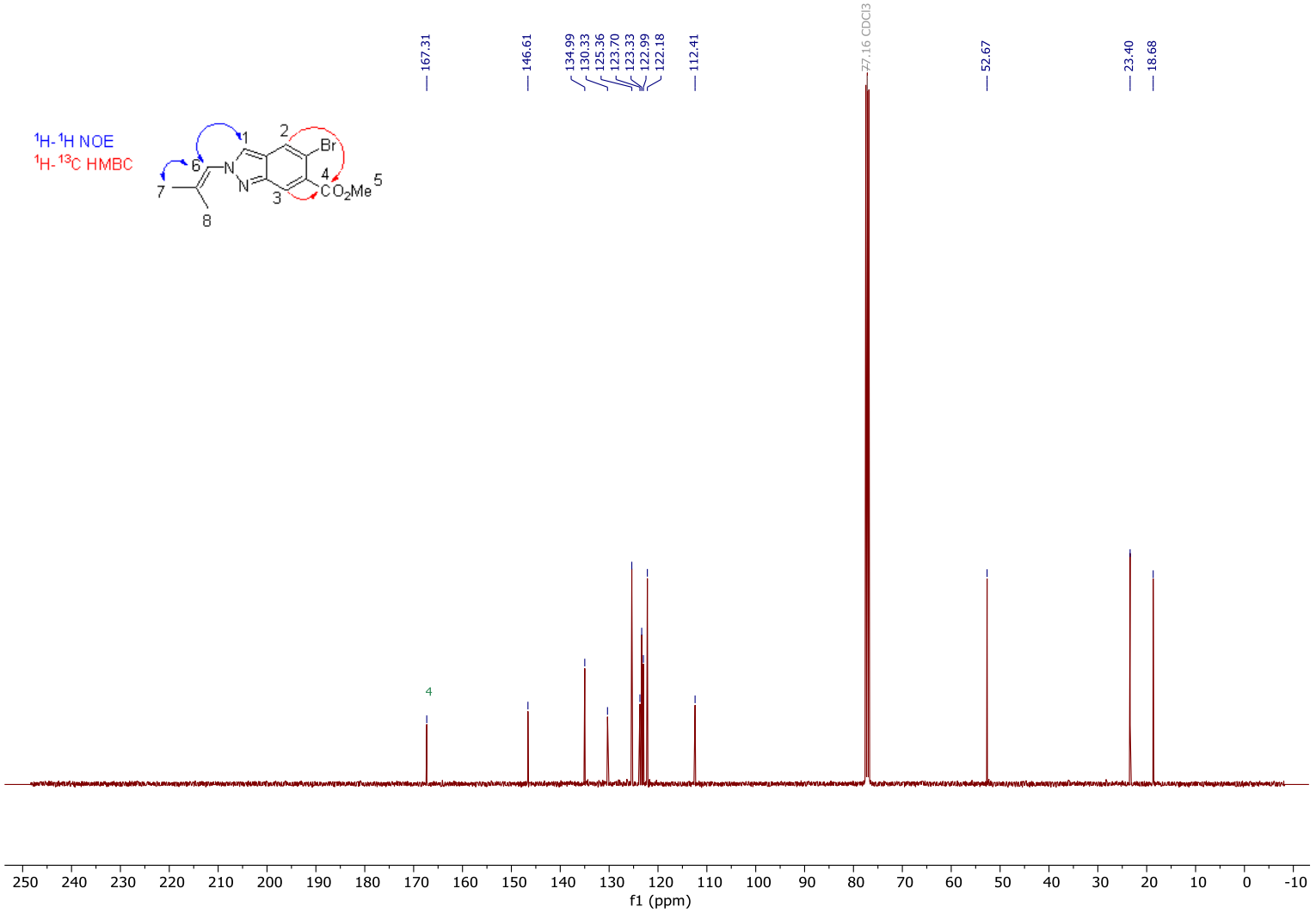


Methyl 5-bromo-2-(2-methylprop-1-en-1-yl)-2*H*-indazole-6-carboxylate (6a)

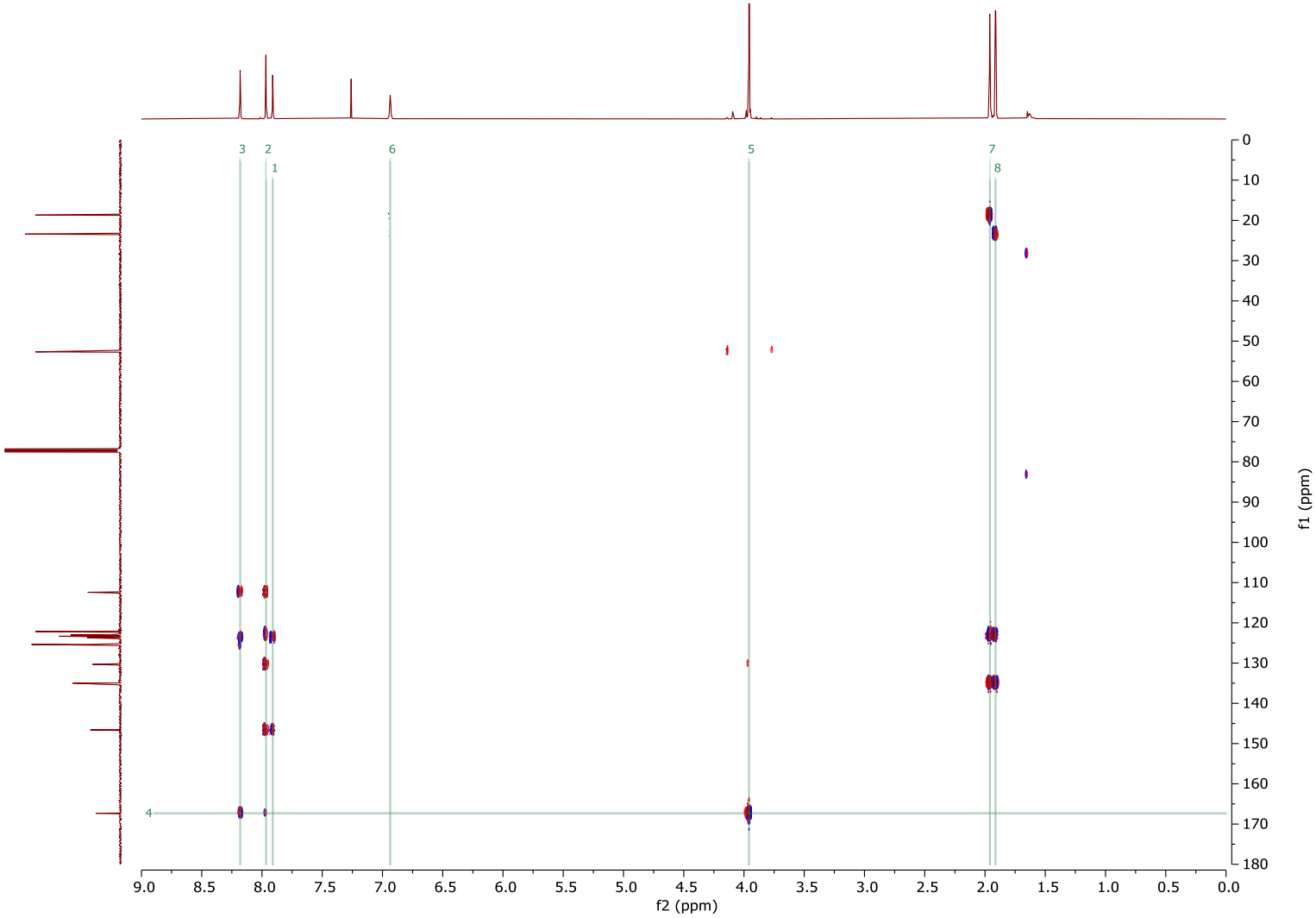
^{1}H NMR (400 MHz, $CDCl_3$)



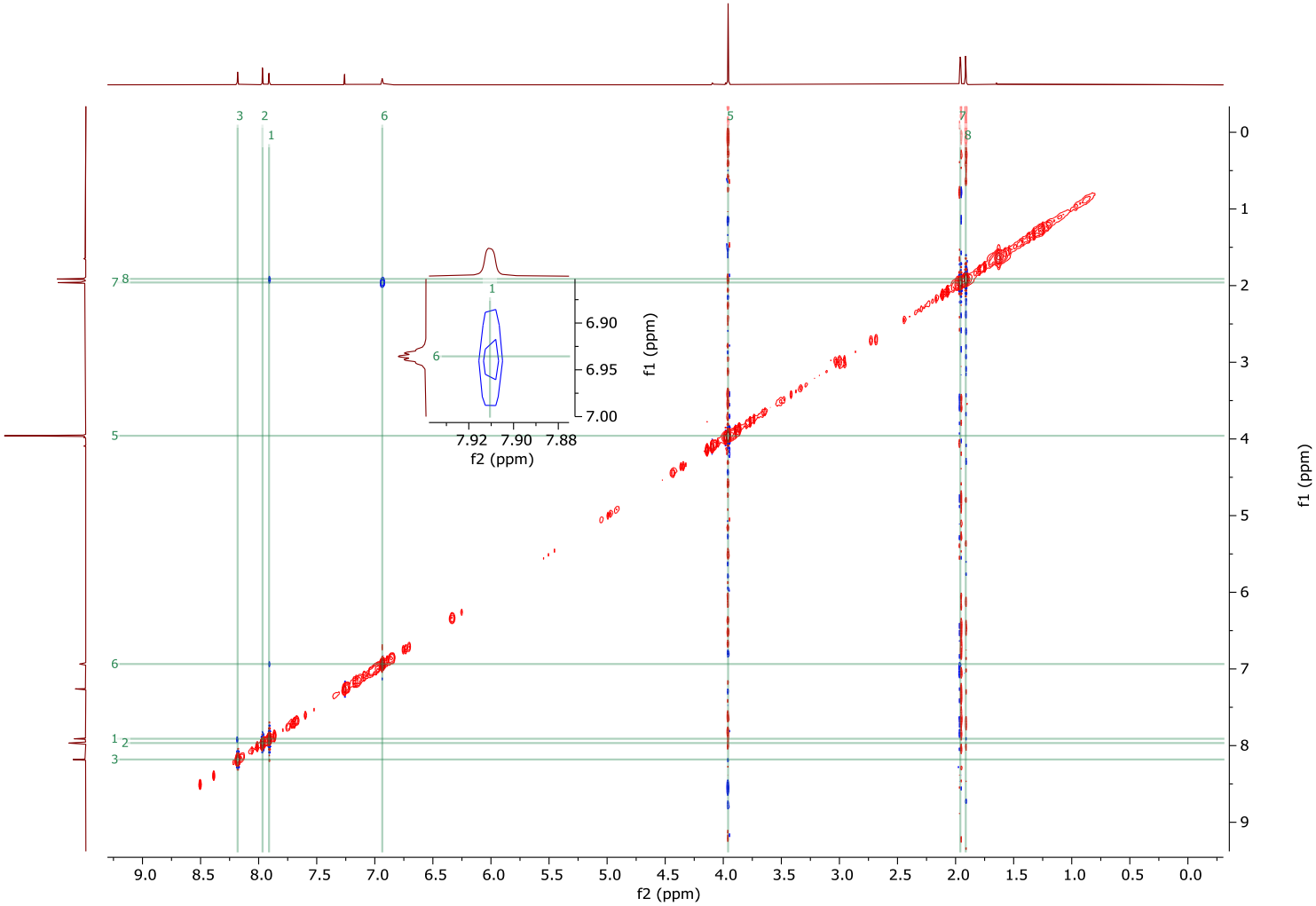
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

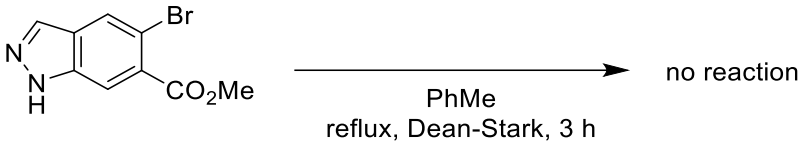


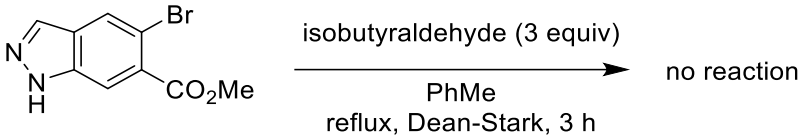
^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)



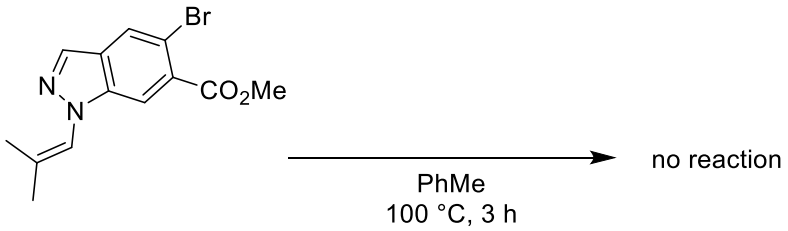
Control reactions

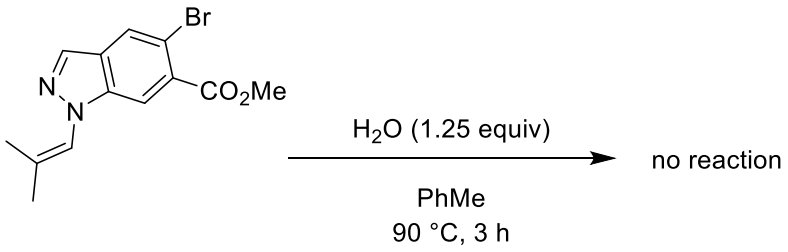
Methyl 5-bromo-1*H*-indazole-6-carboxylate





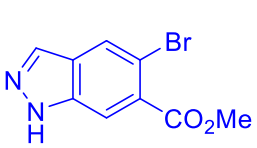
Methyl 5-bromo-1-(2-methylprop-1-en-1-yl)-1*H*-indazole-6-carboxylate



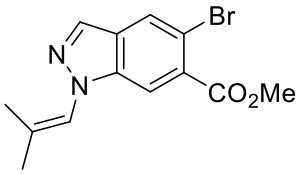


Time course data

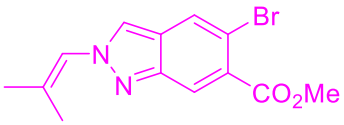
Compound structure and numbering



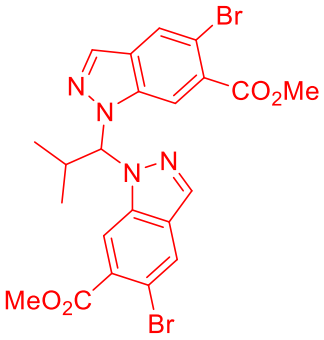
1a



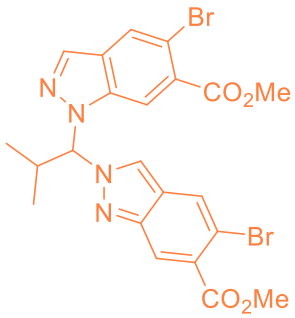
4a



6a

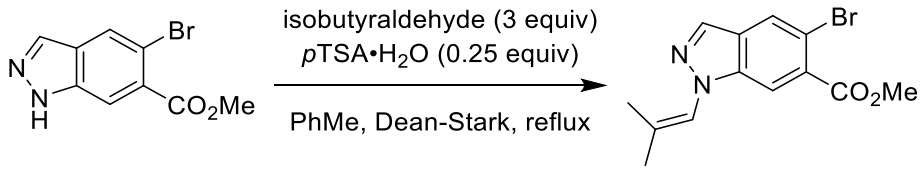


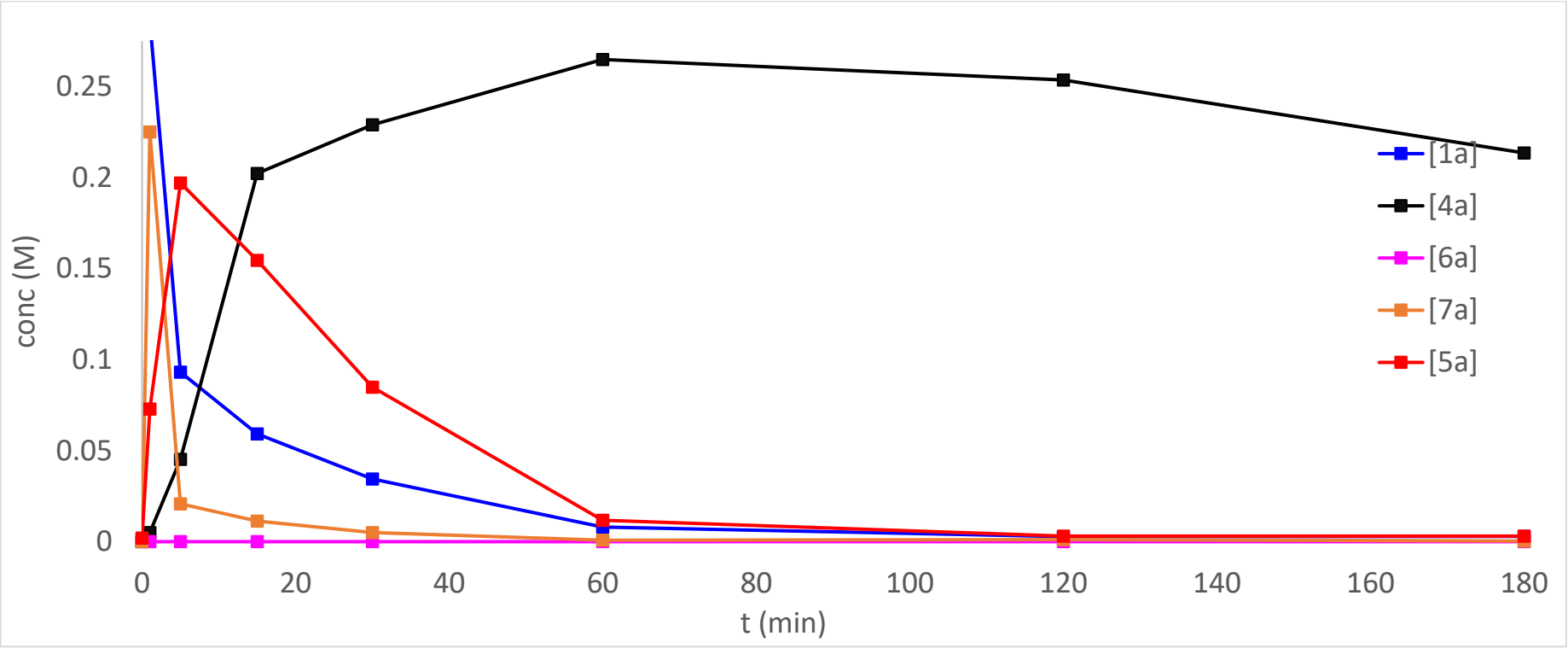
5a



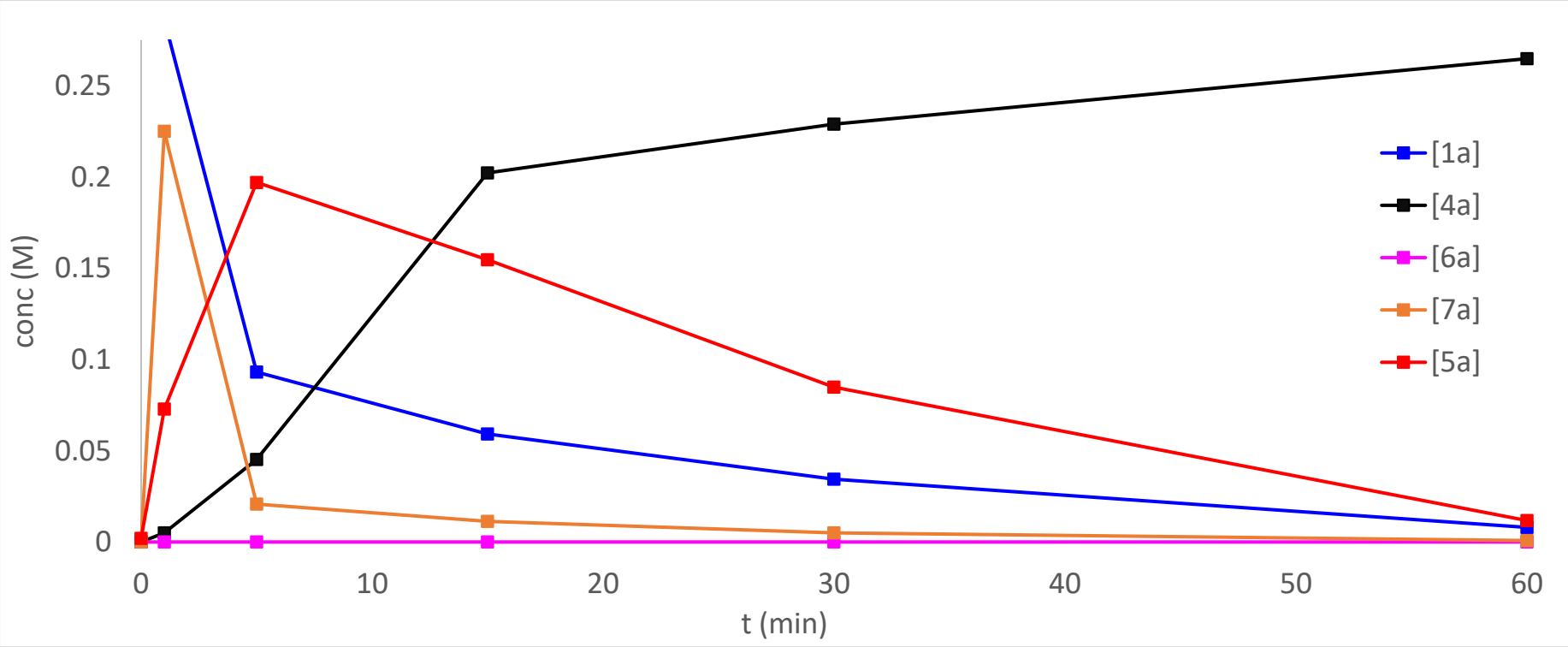
7a

'Standard conditions'



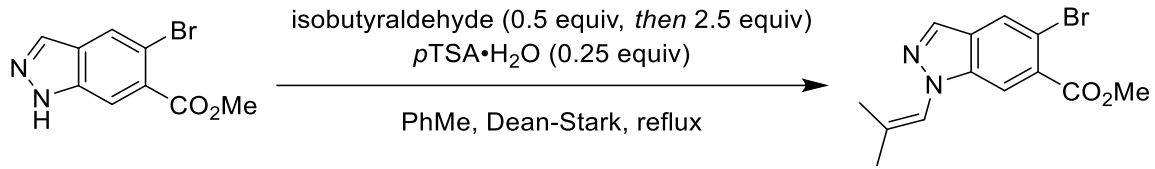


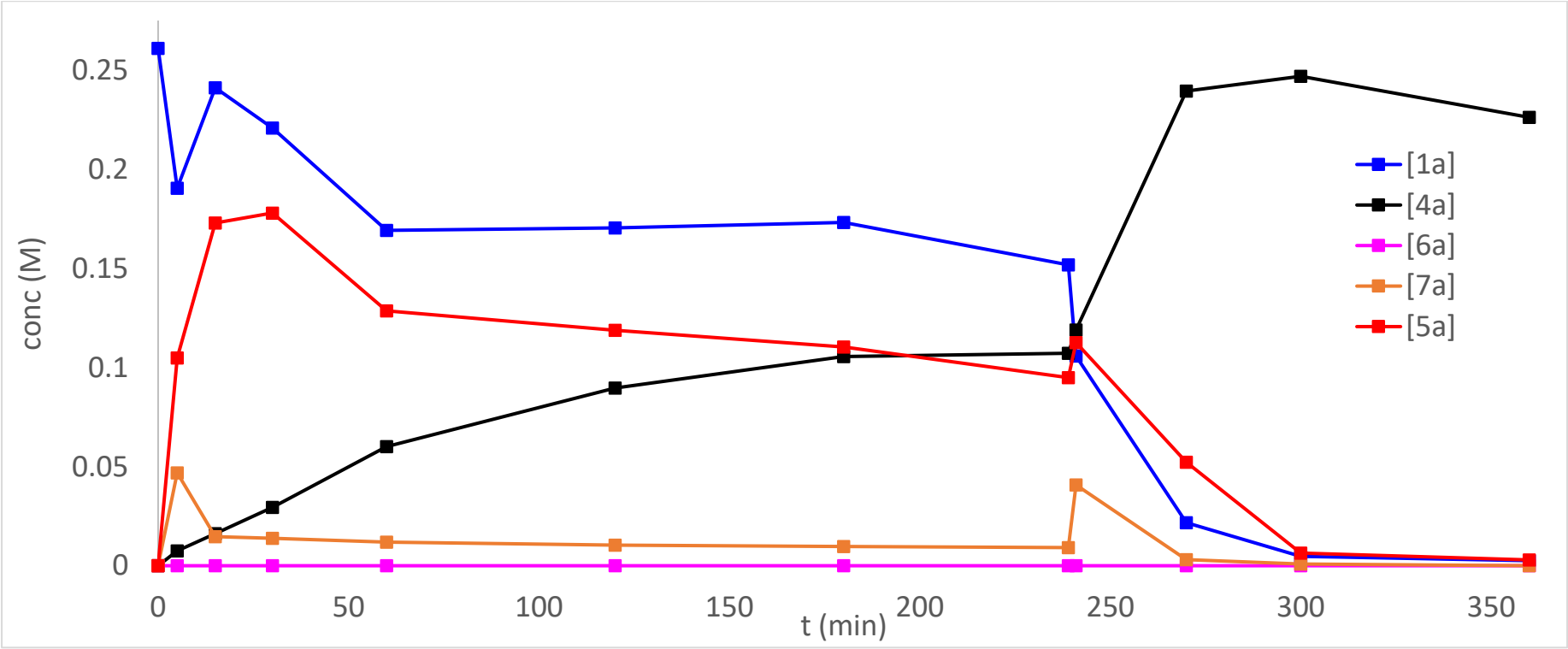
Concentration of **1a**, **4a**, **5a**, **6a**, and **7a** over time of standard reaction conditions up to 3 h.



Expanded view of the concentration of **1a**, **4a**, **5a**, **6a**, and **7a** over time of standard reaction conditions up to 1 h.

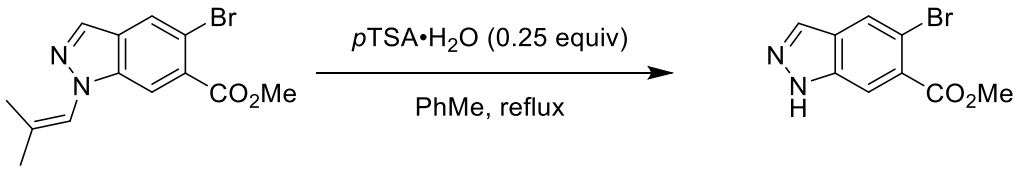
0.5 equiv isobutyraldehyde, then 2.5 equiv isobutyraldehyde

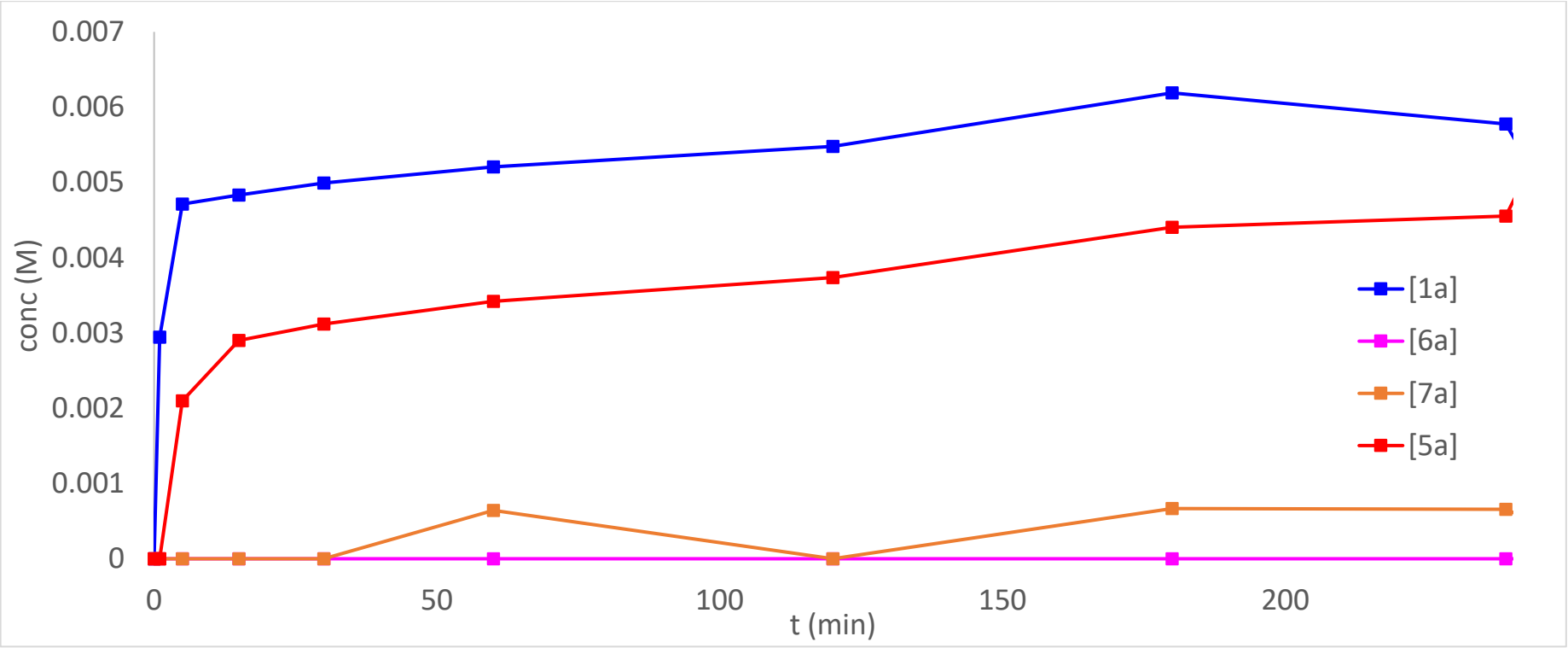




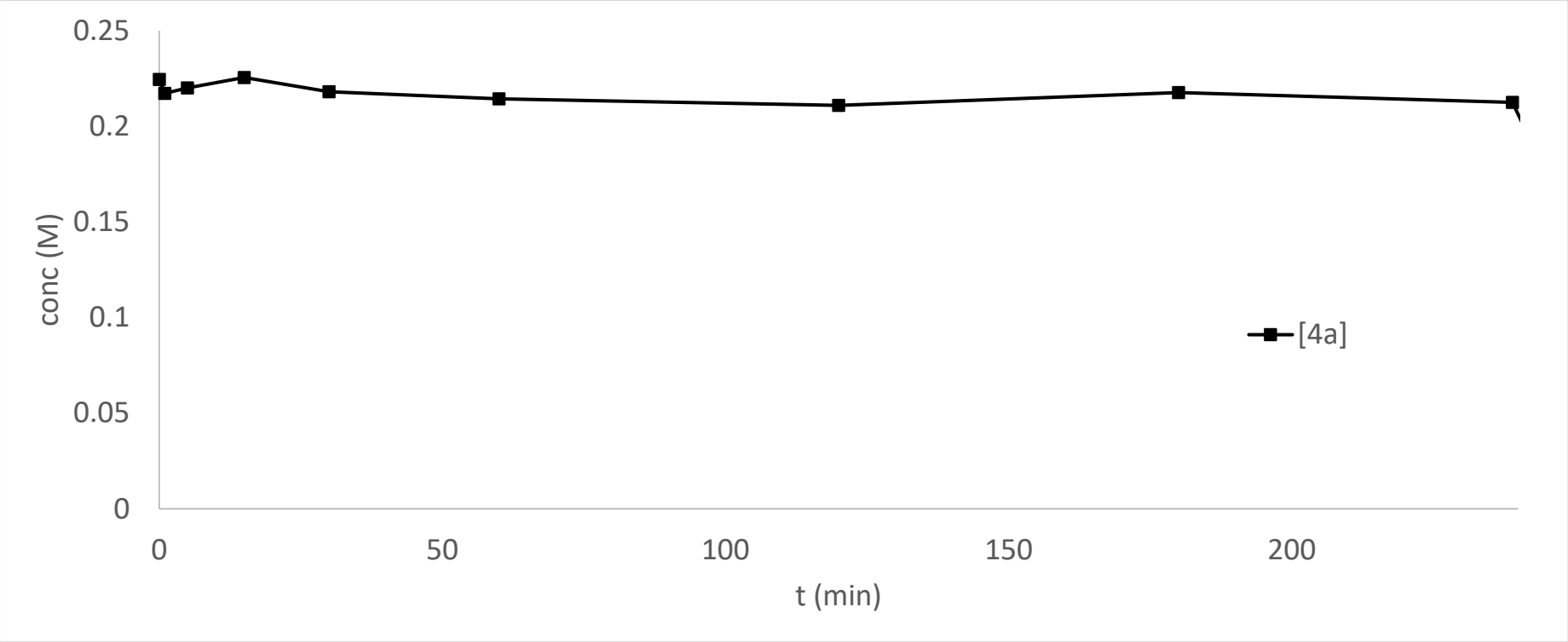
Concentration of **1a**, **4a**, **5a**, **6a**, and **7a** over time of reaction with 0.5 equiv isobutyraldehyde, then additional 2.5 equiv isobutyraldehyde at 4 h.

Reversion of 4a





Concentration of **1a**, **5a**, **6a**, and **7a** over time from heating **4a** with *p*TSA·H2O at reflux over 4 h.

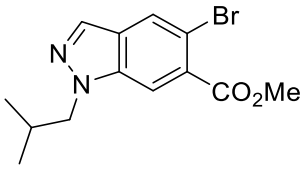


Concentration of course of **1a** from heating **4a** with *p*TSA·H_2O at reflux over 4 h.

Process Optimization and Scale-Up

Crystallisation Discovery and Development

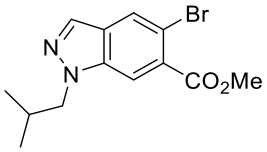
Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (2a) solubility



methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (40 mg, 0.13 mmol, 1.0 equiv) was dispensed into 2 mL HPLC vial vials equipped with a stirrer bar. Solvent (400 µL) was added, and the vials were stirred at 25 °C overnight.

entry	solvent	visual	solubility (mg/mL)
1	MeOH	solution	>90
2	IPA	solution	>90
3	^{t}AmylOH	solution	>90
4	Acetone	solution	>90
5	MIBK	solution	>90
6	EtOAc	solution	>90
7	^{i}BuOAc	solution	>90
8	MTBE	solution	>90
9	^{t}AmylOMe	solution	>90
10	1,2-dimethoxyethane	solution	>90
11	THF	solution	>90
12	2-MeTHF	solution	>90
13	Anisole	solution	>90
14	MeCN	solution	>90
15	Butyronitrile	solution	>90
16	PhMe	solution	>90
17	PhMe and MeOH (70:30)	solution	>90
18	MeCN and H_2O (80:20)	solution	>90
19	THF and H_2O (80:20)	solution	>90
20	Acetone and H_2O (80:20)	solution	>90
21	IPA and H_2O (80:20)	solution	>90
22	2-MeTHF and H_2O (80:20)	biphasic	n/a

Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate HTE salt screen



A 96-well Paradox plate was prepared with 0.8 mL glass shell vials equipped with a super tumble stir disc using a stir disc plate dispenser. Solid acids (0.032 mmol, 1.0 equiv) were dispensed. Solutions of 50 mg mL^{-1} methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate in MeCN, IPA, EtOAc, and PhMe (200 µL, 0.032 mmol, 1.0 equiv) were dispensed. Liquid acids (0.032 mmol, 1.0 equiv) were dispensed. The vials were stirred at 25 °C and 500 rpm overnight.

Solvent Selection

entry	reagent	class	selected descriptors				
			Hansen solubility parameter[a]			Polarity *P'*[b]	b.p. (°C)[c]
			δ_d	δ_p	δ_h		
1	MeCN	nitrile	15.3	18.0	16.1	5.8	82
2	IPA	alcohol	15.8	6.1	16.4	3.9	82
3	EtOAc	ester	15.8	5.3	7.2	4.4	77
4	PhMe	aromatic	18.0	1.4	2.0	2.4	110

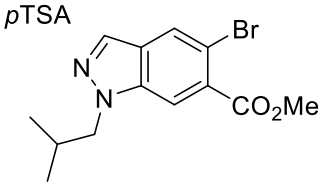
[a]ref [10]. [b]ref [11]. [c]Sigma-Aldrich.

Acid selection

entry	acid	selected descriptors	
		form (rt)	type
1	(-)-Camphorsulfonic acid	Solid	sulfonic acid
2	Citric acid	Solid	tris-carboxylic acid
3	Fumaric acid	Solid	bis-carboxylic acid
4	Maleic acid	Solid	bis-carboxylic acid
5	Malonic acid	Solid	bis-carboxylic acid
6	Methanesulfonic acid (5 M in IPA)	Solution	sulfonic acid
7	1,5-Napthalenedisulfonic acid	Solid	bis-sulfonic acid
8	D-(-)-Tartaric acid	Solid	bis-carboxylic acid
9	HCl (5 M in IPA)	Solution	mineral acid
10	N-Acetyl-L-leucine	Solid	carboxylic acid
11	*p*TSA·H_2O	Solid	sulfonic acid
12	Phosphoric acid (5 M in IPA)	Solution	mineral acid
13	Acetic acid (5 M in IPA)	Solution	carboxylic acid
14	(-)-*O*,*O*'-Di-p-toluoyl-L-tartaric acid	Solid	bis-carboxylic acid
15	L-(-)-Malic acid	Solid	bis-carboxylic acid
16	none	n/a	n/a
17	Salicylic acid	Solid	carboxylic acid
18	Sulfuric acid (5 M in IPA)	Solution	mineral acid
19	Benzoic acid	Solid	carboxylic acid
20	Formic acid (5 M in IPA)	Solution	carboxylic acid
21	L-(+)-Mandelic acid	Solid	carboxylic acid
22	Oxalic acid	Solid	bis-carboxylic acid
23	Succinic acid	Solid	bis-carboxylic acid
24	Trifluoroacetic acid (5 M in IPA)	Solution	carboxylic acid

Salt screen results

Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA initial synthesis (unoptimized)



Isobutyraldehyde (5.37 mL, 58.81 mmol, 3.0 equiv) was added to methyl 5-bromo-1*H*-indazole-6-carboxylate (5.0 g, 19.60 mmol, 1.0 equiv), *p*TSA·H_2O (0.93 g, 4.90 mmol, 0.25 equiv), and PhMe (75 mL) in a 100 mL EasyMax reactor vessel. A Dean-Stark condenser was equipped and the reaction mixture was heated to a vigorous reflux (jacket temperature = 140 °C) for 3 h. Et_3N (0.68 mL, 4.90 mmol, 0.25 equiv) was added, then the reaction mixture was cooled to rt. The reaction mixture was washed with H_2O (20 mL), 1 M HCl (20 mL) and sat. brine (20 mL). The organic layer was concentrated to *ca*. 50 mL by distillation at atmospheric pressure to afford a solution of crude enamine in PhMe.

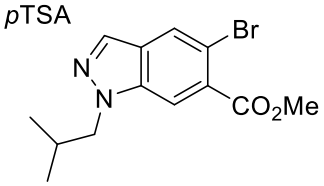
5% Pt/C (0.99 g, 0.25 mmol, 0.013 equiv) was added to the crude enamine solution, and the reaction mixture was stirred under an atmosphere of H_2 at 40 psi and 30 °C for 24 hours. The resulting reaction mixture was filtered through arbocel, washed with PhMe, and concentrated to afford crude product.

Crude product was dissolved in PhMe (40 mL) and heated to 50 °C. A solution of *p*TSA·H_2O (3.13 g, 16.46 mmol, 0.84 equiv) in IPA (3.1 mL) was added slowly. The reaction mixture was cooled to 40 °C, then cooled to 5 °C over 5 h, then held at 5 °C overnight. A slurry was observed. The product was collected by filtration, washed with PhMe (25 mL×2), and dried to afford methyl 5-bromo-1-isobutyl-1H-indazole-6-carboxylate·*p*TSA (2.33 g, 4.82 mmol, 25% yield (over 2 steps)) as an off-white solid.

mp 137-138 °C; **ν_{max}** (neat) /cm^{-1} 2955, 1742, 1460, 1242; **^{1}H NMR** (400 MHz, MeOD) δ 8.08 (d, *J* = 0.5 Hz, 1H), 8.05 (d, *J* = 1.0 Hz, 1H), 8.00 (dd, *J* = 1.0, 0.5 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.28 – 7.20 (m, 2H), 4.24 (d, *J* = 7.5 Hz, 2H), 3.95 (s, 3H), 2.37 (s, 3H), 2.36 – 2.22 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, MeOD) δ 168.8, 143.0, 142.0, 139.3, 133.3, 132.0, 129.9, 127.4, 127.2, 127.0, 113.5, 111.8, 57.2, 53.2, 30.8, 21.3, 20.3; **HRMS** (ESI^+) calc. for $C_{13}H_{16}{}^{79}BrN_2O_2$ ([M-$C_7H_7O_3S$]$^+$) 311.0390; found 311.0382.

NB: Repeats achieved up to 53% yield.

Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA solubility



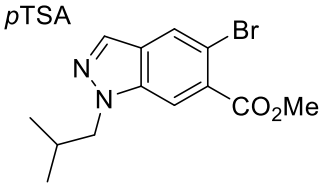
methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (50 mg, 0.10 mmol, 1.0 equiv) was dispensed into 2 mL HPLC vial vials equipped with a stirrer bar. Solvent (500 µL) was added, and the vials were stirred at 25 °C overnight sampled, then 50 °C overnight and sampled again.

When sampled, the vials were centrifuged rpm for 30 min. Supernatant (30 µL) was removed and dissolved in MeCN (1 mL) for LCMS. Solubility was determined by LCMS with methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA external standard. External standard prepared by diluting methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (100 mg, 0.20 mmol) in MeOH (1 mL), then diluting 30 µL of this solution in MeCN (1 mL).

entry	solvent	visual at 25 °C	solubility at 25 °C (g /L)	visual at 50 °C	solubility at 50 °C (g /L)	difference in solubility (g /L)
1	MeCN	slurry	31.6	solution, crust on vial	68.0	36.4
2	PhMe	slurry	0.0	slurry	19.4	19.4
3	PhMe and MeCN (50:50)	slurry	50.6	solution, crust on vial	86.4	35.8
4	PhMe and MeCN (25:75)	slurry	45.3	solution, crust on vial	86.4	41.1
5	PhMe and MeCN (75:25)	slurry	38.4	solution, crust on vial	83.9	45.5
6	Heptane and MeCN (25:75)	slurry	30.6	solution, crust on vial	89.6	59
7	MeTHF	hazy solution	>101.3	solution	>81.1	n/a
8	Acetone	solution	>87.4	dark brown solution	>98.7	n/a
9	MEK	slurry	76.5	light brown solution	>90.7	n/a
10	MTBE	slurry	20.1	hazy solution, crust on vial	58.5	38.4
11	EtOAc	slurry	37.9	solution, crust on vial	68.4	30.5
12	MIBK	slurry	38.5	thin slurry	75.7	37.2
13	THF	solution	>77.2	solution	>82.7	n/a
14	Anisole	slurry	19.2	thin slurry	48.8	29.6
15	Butryonitrile	slurry	37.6	solution, crust on vial	89.3	51.7
16	^{t}AmylOMe	solution	>97.5	solution	>90.0	n/a
17	EtOH	solution	>96.1	solution	>98.0	n/a
18	MeOH	solution	>92.6	solution	>98.4	n/a
19	Ethyl lactate	slurry	43.4	solution	>75.9	n/a
20	IPA	solution	>94.5	solution	>99.6	n/a
21	^{i}BuOAc	slurry	21.4	slurry	41.4	20
22	1,2-dimethoxyethane	hazy solution	>95	solution	>101.6	n/a
23	MeCN and H_2O (50:50)	hazy solution	>42.6	hazy solution	56.1	n/a
24	PhMe and MeOH (70:30)	solution	>91.5	solution	>92.1	n/a
25	MeCN and H_2O (80:20)	solution	>98.3	solution	>102.8	n/a
26	Cyclohexanone	light yellow solution	>106.1	brown solution	>108.5	n/a
27	Heptane	slurry	0.0	slurry	0.0	0
28	Cyclohexane	slurry	0.0	slurry	0.0	0

29	H_2O	solids	0.0	solution, crust on vial	0.0	0
30	CH_2Cl_2	solution	>83.0	solution	>106.3	n/a
31	HFIP	solution	>82.2	solution	>93.0	n/a
32	Dioxane	hazy solution	>88.9	solution, crust on vial	93.9	n/a
33	CPME	slurry	23.5	thin slurry	57.8	34.3
34	dibutyl ether	slurry	0.0	slurry	0.0	0
35	^{t}AmylOMe	slurry	0.0	thin slurry	30.6	30.6

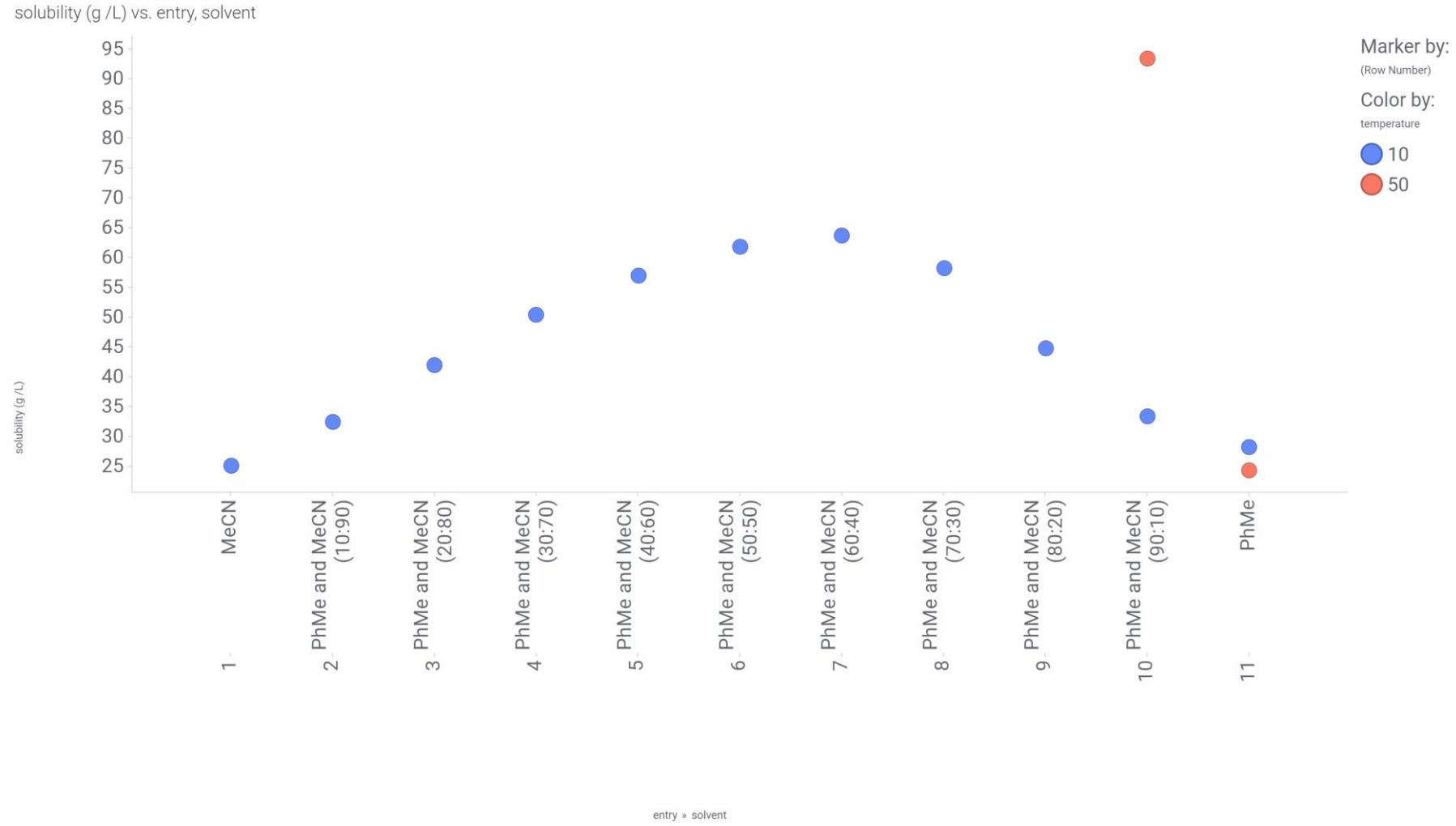
Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA solubility in MeCN and PhMe mixtures



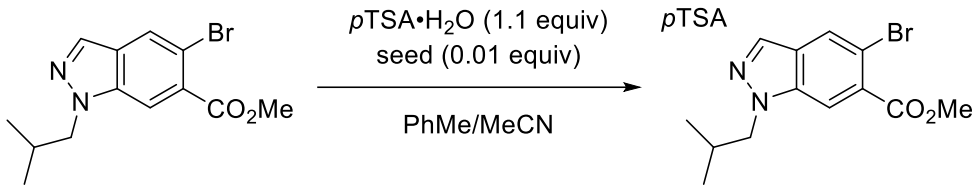
methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (102 mg, 0.21 mmol, 1.0 equiv) was dispensed into 2 mL HPLC vial vials equipped with a stirrer bar. Solvent (750 µL) was added, and the vials were stirred at 10 °C overnight, then 50 °C overnight.

When sampled, the vials were centrifuged for 30 min. Supernatant (30 µL) was removed and dissolved in MeOH (1 mL) for LCMS. Solubility was determined by LCMS with methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA external standard. External standard prepared by diluting methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (136 mg, 0.28 mmol) in MeOH (1 mL), then diluting 30 µL of this solution in MeOH (1 mL).

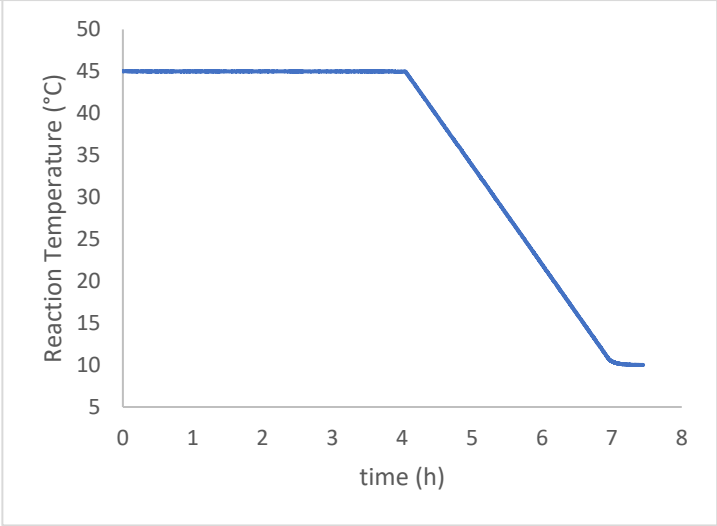
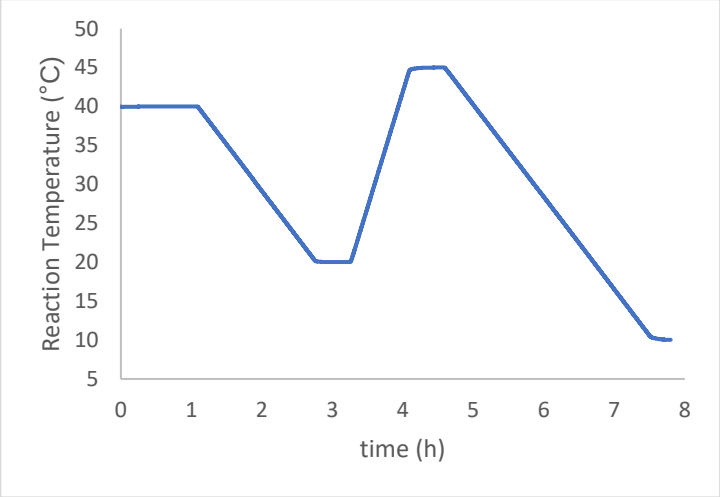
entry	solvent	visual at 10 °C	solubility at 10 °C (g /L)	visual at 50 °C	solubility at 50 °C (g /L)
1	MeCN	slurry	25.1	solution	>136
2	PhMe and MeCN (10:90)	slurry	32.5	solution	>136
3	PhMe and MeCN (20:80)	slurry	42.0	solution	>136
4	PhMe and MeCN (30:70)	slurry	50.5	solution	>136
5	PhMe and MeCN (40:60)	slurry	57.1	solution	>136
6	PhMe and MeCN (50:50)	slurry	61.8	solution	>136
7	PhMe and MeCN (60:40)	slurry	63.7	solution	>136
8	PhMe and MeCN (70:30)	slurry	58.2	solution	>136
9	PhMe and MeCN (80:20)	slurry	44.8	solution	>136
10	PhMe and MeCN (90:10)	slurry	33.5	slurry	93.4
11	PhMe	slurry	28.3	slurry	24.4


solubility (g /L) vs. entry, solvent
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
solubility (g /L)
MeCN
PhMe and MeCN (10:90)
PhMe and MeCN (20:80)
PhMe and MeCN (30:70)
PhMe and MeCN (40:60)
PhMe and MeCN (50:50)
PhMe and MeCN (60:40)
PhMe and MeCN (70:30)
PhMe and MeCN (80:20)
PhMe and MeCN (90:10)
PhMe
1
2
3
4
5
6
7
8
9
10
11
entry » solvent
Marker by:
(Row Number)
Color by:
temperature
10
50

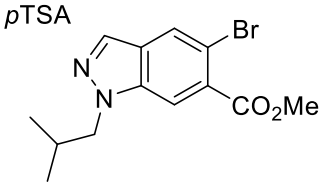
Heat/cool cycle



*p*TSA·H_2O (6.25 g, 32.3 mmol, 1.1 equiv) was added to a solution of methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (7.50 g, 29.4 mmol, 1.0 equiv) in PhMe (50.25 mL) and MeCN (16.5 mL) at 50 °C. The solution was adjusted to the indicated temperature, seeded with methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (0.16 g, 0.294 mmol, 0.01 equiv) (t = 0) and the temperature was controlled as indicated. The slurry was left to stir at 10 °C overnight. Solids were collected by filtration (4.2 cm diameter filter, 50 kPa vacuum), washed with PhMe, and dried to afford methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA.

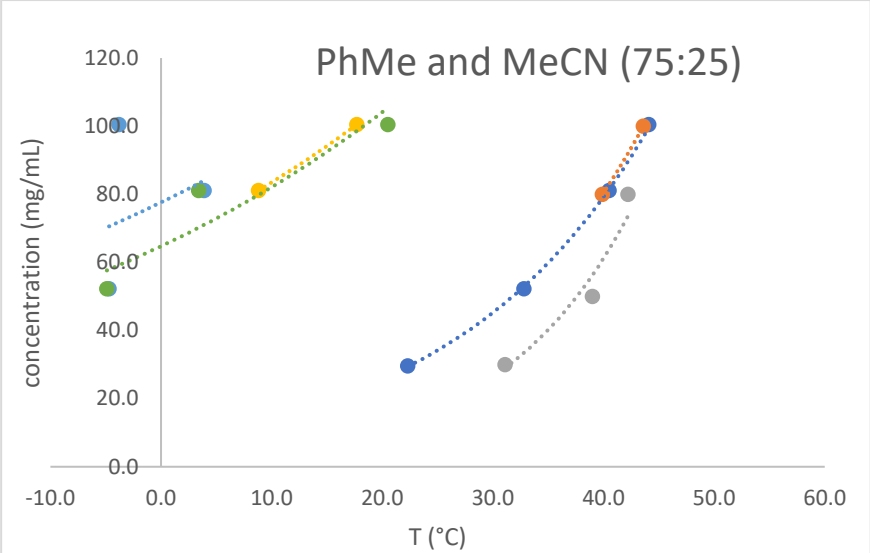
entry	temperature/time control	yield	filtration time	microscope visual (same scale)
1		73%	29 s	
2		76%	16 s	

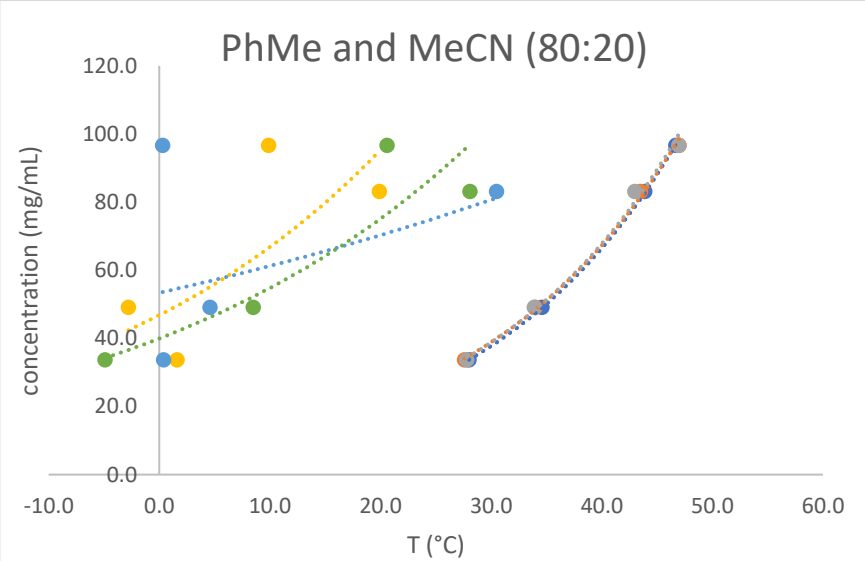
Temperature dependent solubility

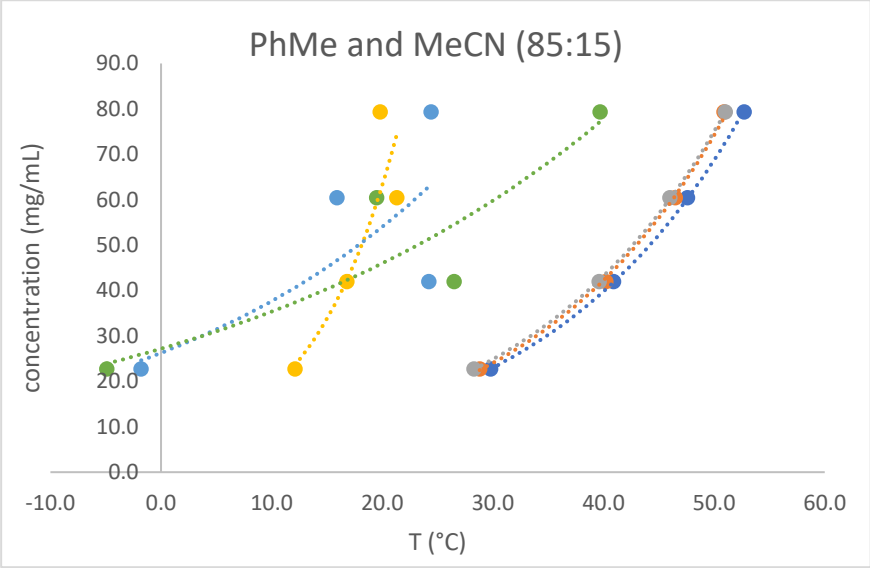


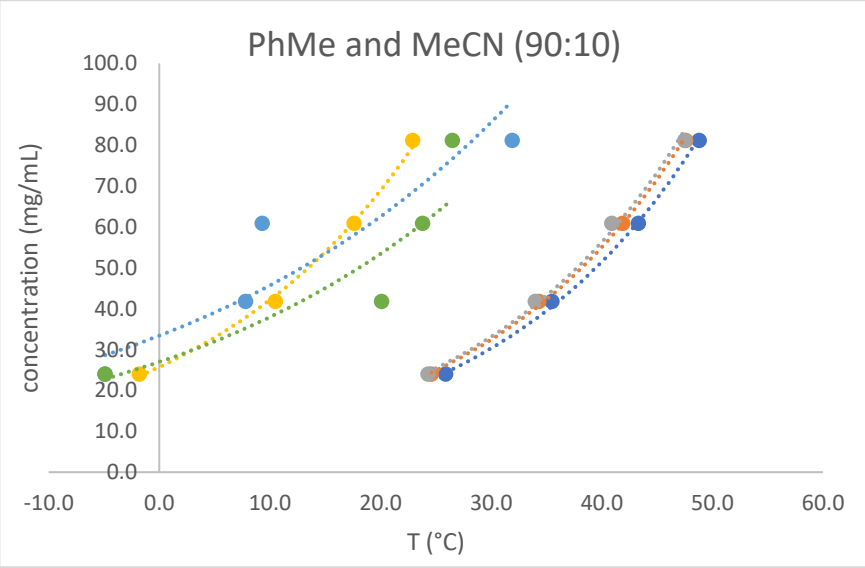
Temperature dependent solubility data was collected on a Technobis Crystal16. Vials were charged with methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA and dissolved in solvents as indicated. Samples were placed in a Crystal16, held at 20 °C for 30 min, heated to 75 °C at 0.2 °C/min then cooled to -5 °C at 0.1 °C/min. The cycle was repeated three times.

entry	mass (mg)	solvents	dissolution temperature (°C)			crystallization temperature (°C)		
			cycle 1	cycle 2	cycle 3	cycle 1	cycle 2	cycle 3
1	29.6	PhMe and MeCN (1 mL, 75:25)	22.3					
	52.3		32.8		31.1		-4.7	-4.9
	81.1		40.5	39.9	39.0	8.8	3.9	3.4
	100.5		44.1	43.6	42.2	17.7	-3.8	20.5
2	33.7	PhMe and MeCN (1 mL, 80:20)	28.0	27.6	27.8	1.6	0.4	-4.9
	49.1		34.6	34.0	33.9	-2.8	4.6	8.5
	83.1		43.9	43.5	43.0	19.9	30.5	28.1
	96.7		46.7	47.0	47.0	9.9	0.3	20.6
3	24.0	PhMe and MeCN (1 mL, 85:15)	25.9	24.6	24.3	-1.8	-4.9	-4.9
	41.8		35.5	34.3	34.0	10.5	7.8	20.1
	60.9		43.3	41.9	40.9	17.6	9.3	23.8
	81.2		48.8	47.6	47.5	22.9	31.9	26.5
4	22.7	PhMe and MeCN (1 mL, 90:10)	29.8	28.8	28.3	12.1	-1.8	-4.9
	42.0		40.9	40.2	39.6	16.8	24.2	26.5
	60.4		47.6	46.5	46.0	21.3	15.9	19.5
	79.3		52.7	50.9	51.0	19.8	24.4	39.7

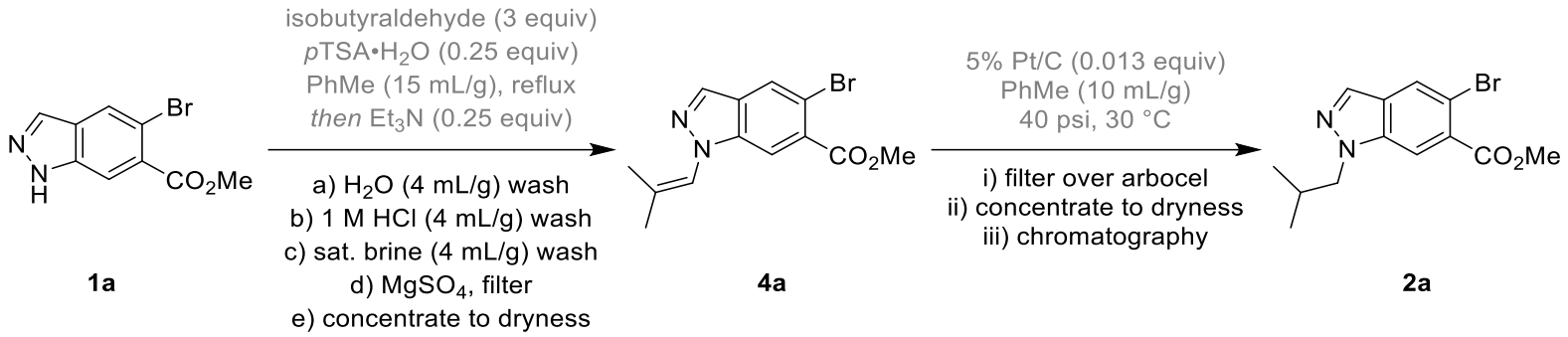

PhMe and MeCN (75:25)
concentration (mg/mL)
T (°C)


PhMe and MeCN (80:20)
concentration (mg/mL)
T (°C)


PhMe and MeCN (85:15)
concentration (mg/mL)
T (°C)


PhMe and MeCN (90:10)
concentration (mg/mL)
T (°C)

Workup Improvements



entry	modifications (step 1)	modifications (step 2)	conversion (ratio **4a**:**5a**)	conversion (ratio **2a**:**8a**)	yield (over two steps)
1	none	none	97% (99:1)	>99% (100:0)	76%
2	PhMe (20 mL/g); no Et_3N a) no H_2O wash b) no HCl wash c) 23% brine wash (10 mL/g) d) $NaHCO_3$ wash (2 × 8 mL/g) e) no concentration		96% (91:9)	99% (100:0)	55%
3	isobutyraldehyde (2 equiv); no Et_3N used directly for hydrogenation	none (sludge formed during hydrogenation)	97% (92:8)	51% (100:0)	42% (as *p*TSA salt)
4	**b) no HCl wash** **c) 23% brine wash** **d) no $MgSO_4$ filtration** **e) concentration to 10 mL/g**	**ii) concentrate to 10 mL/g** **iii) crystallisation (*p*TSA salt)**	**99% (97:3)**	**>99% (98:2)**	**67% (as *p*TSA salt)**

Process Safety Analysis

General Procedure for Differential Scanning Calorimetry (DSC)

All DSC measurements were performed on a Mettler-Toledo differential scanning calorimeter. Approximately 3 to 5 mg of solid or 5 to 10 mg of liquid was weighed into a 40 µL gold-plated high pressure DSC test cell system consisting of a crucible, rupture disk, and lid. The test cell was then sealed using a Jossi press. The test was as follows: ramp from 25 to 400 °C at 5 °C min^{-1}. Sample cells were reweighed after analysis to ensure no samples leaked during the test.

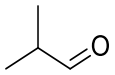
General Procedure for Thermal Screening Unit (TSU)

All TSU measurements were performed on a HEL Thermal Screening Unit. A Hastelloy TSU cell incorporating a side insert thermocouple well, ¼ in. stem and a ¼ in. Swagelok nut and ferrule swaged onto the stem was weighed and the mass recorded. The material under study was charged to the test cell. The cell was reweighed and the mass recorded. Samples were tested by heating at 2 K min^{-1} from rt to 250 °C or a maximum pressure of 50 bara. Once the test cell cooled, the final pressure was noted and residual pressure calculated. The cell was reweighed and the mass recorded.

General Procedure for Accelerating Rate Calorimetry (ARC)

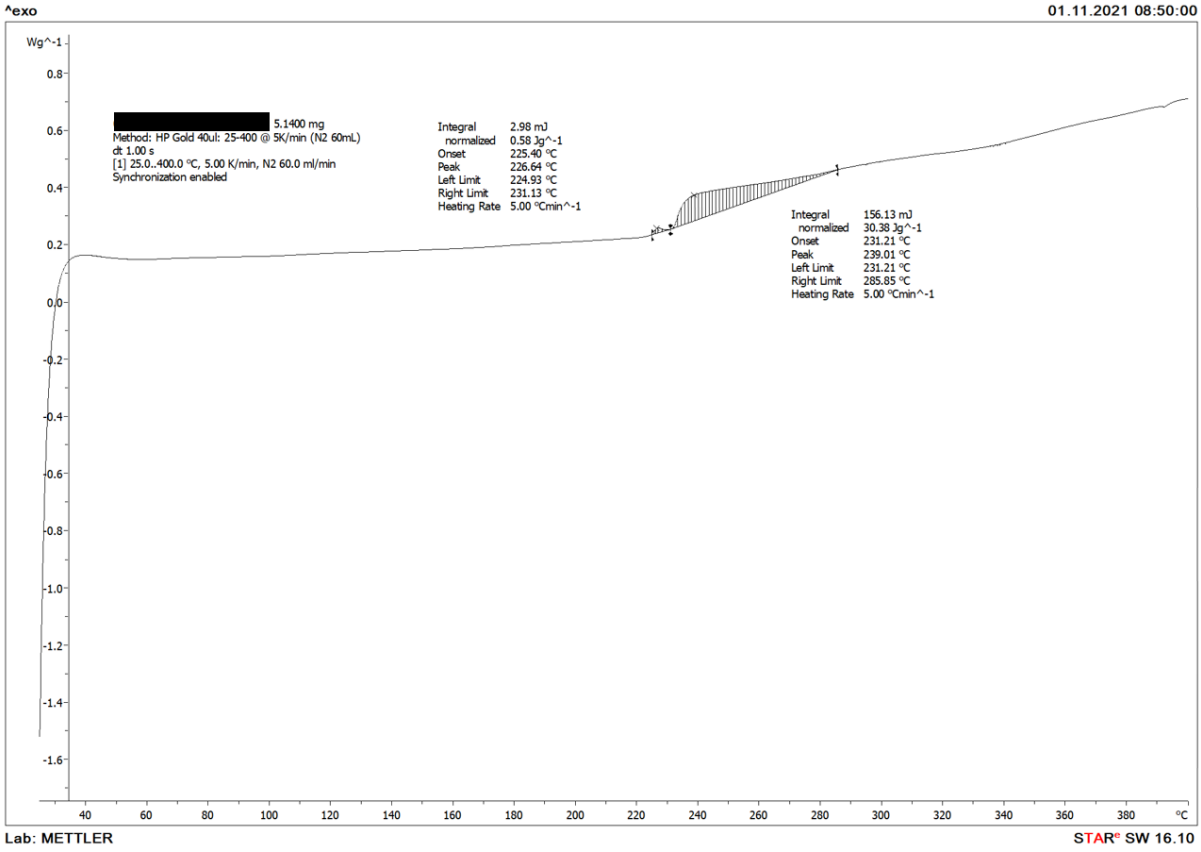
All ARC measurements were performed on a Thermal Hazard Technology Accelerating Rate Calorimeter. A Hastelloy ARC test cell incorporating a bottom thermocouple clip and ¼ in stem and the mass recorded. A ¼ in Swagelok nut and ferrule were swaged onto the stem and the mass recorded. The material under study was charged to the test cell the mass recorded to allow the sample mass to be calculated. Samples were tested using a heat−wait−search procedure starting at 40 °C and heating in 5 K increments to a maximum temperature of 350 °C or a maximum pressure of 100 bara. Once the test cell had cooled the final pressure was noted and residual pressure calculated. The cell was reweighed and the mass recorded.

Isobutyraldehyde



DSC

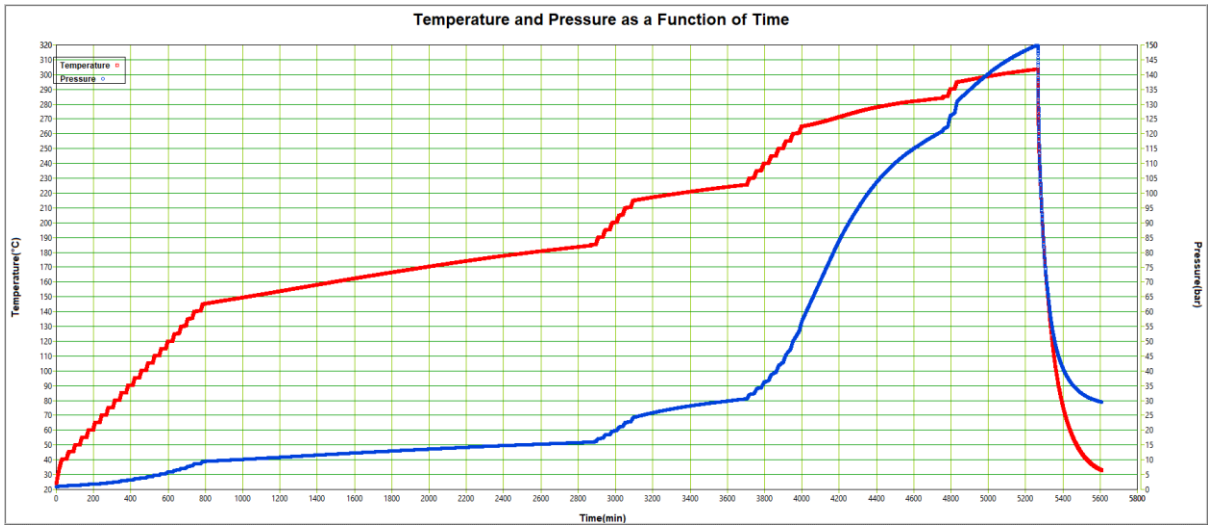
left limit (°C)	energy (J g^{-1})	peak comments
225	-1	Exotherm
231	-30	Exotherm



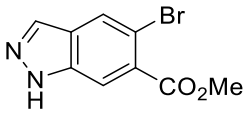
ARC

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 32 °C (bar)	Max sample temp (°C)
145	0.022	70					
215	0.021	18	Unable to determine[a]	Unable to determine[a]	185	+28.5	303
265	0.038	35					
295	0.025	>15					

[a]TMR and TD24 were not determined due to there being an insufficient number of data points.
Phi Factor = 1.79

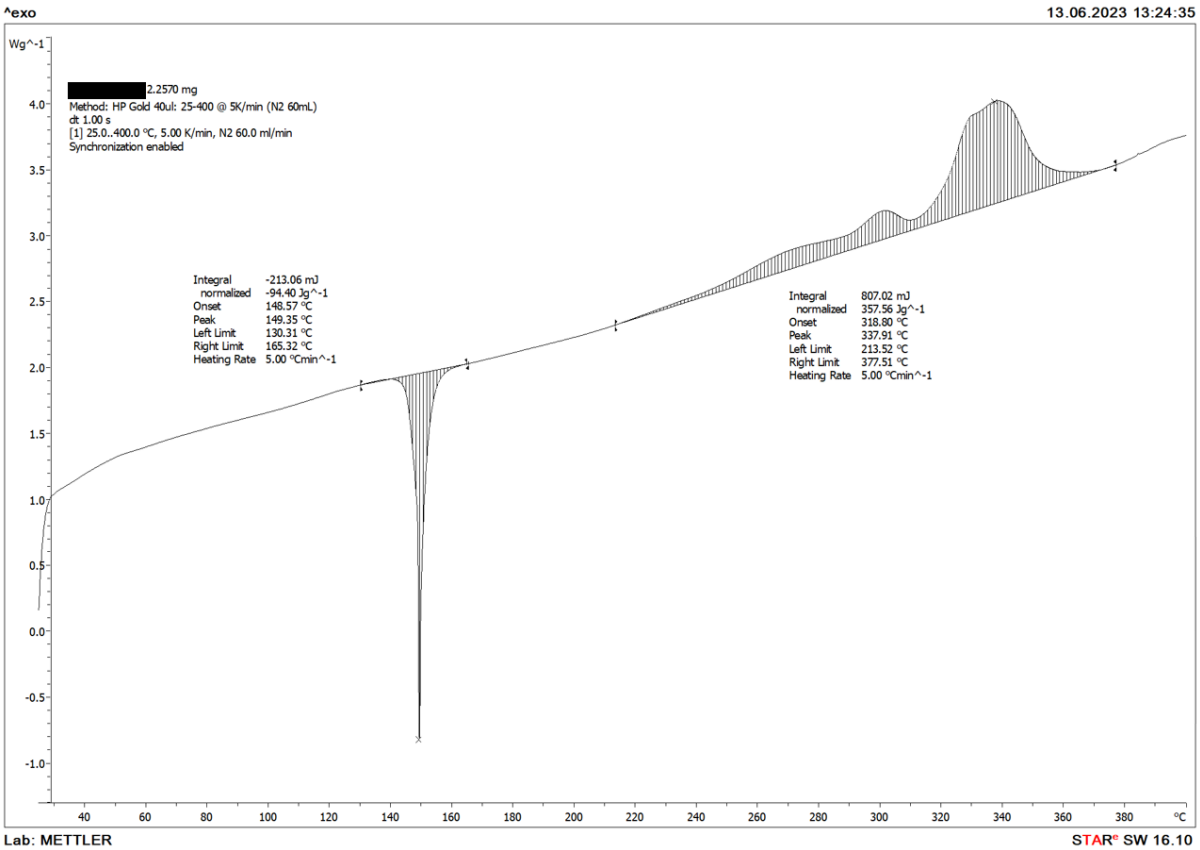


Methyl 5-bromo-1H-indazole-6-carboxylate (1a)



DSC

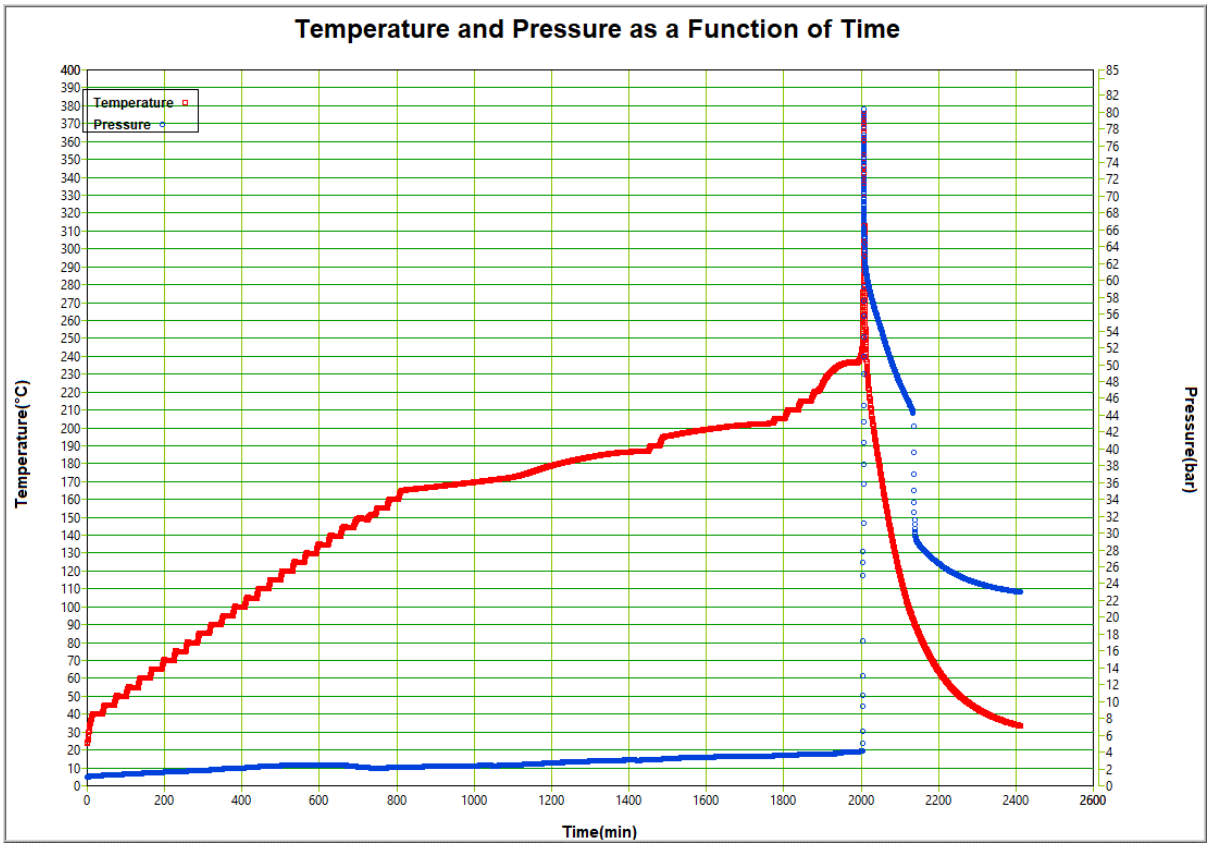
left limit (°C)	energy (J g^{-1})	peak comments
130	95	Endotherm
213	-358	Exotherm



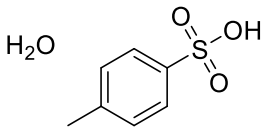
ARC

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 34 °C (bar)	Max sample temp (°C)
165 195 222	0.072 0.051 >137	46 17 >317	2.58 days @150 °C	154	259	+21.7	375

Phi Factor = 2.07

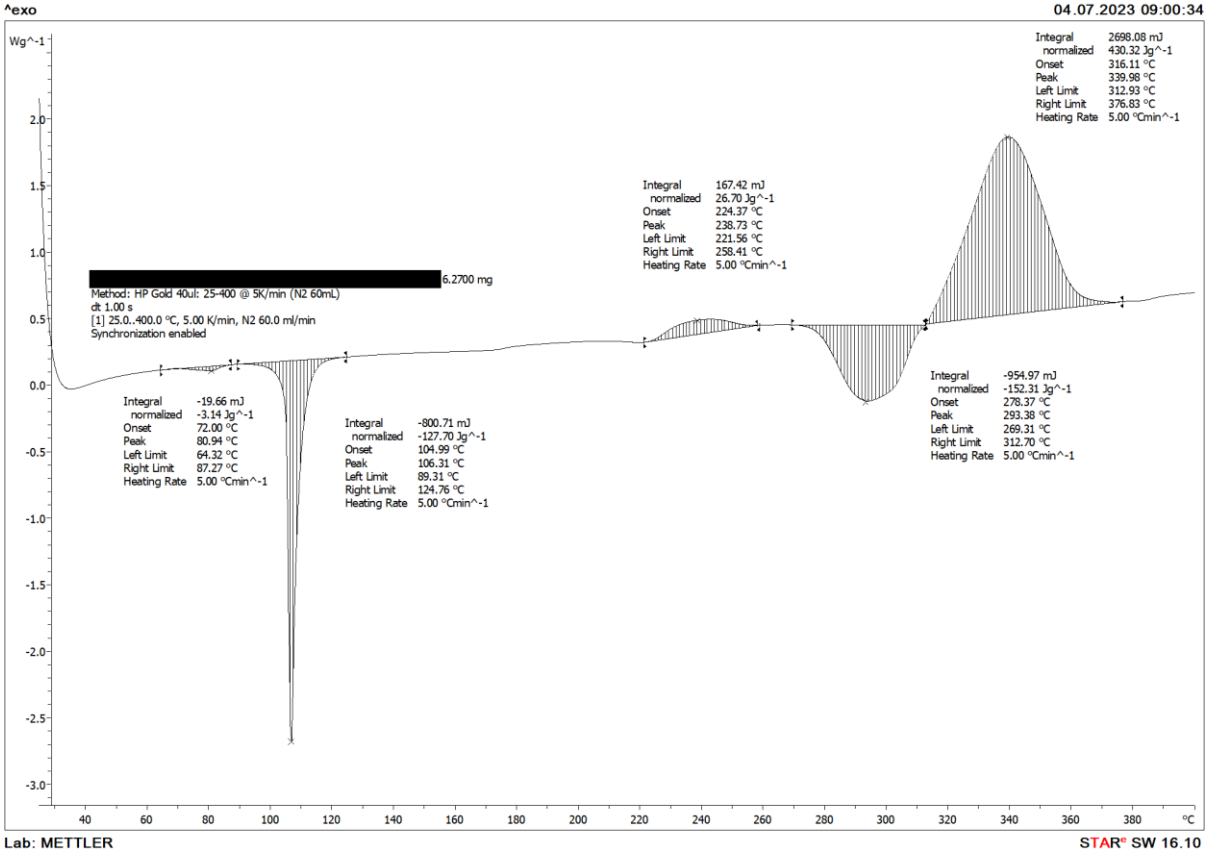


_p_TSA·H_2O



DSC

left limit (°C)	energy (J g^{-1})	peak comments
64	4	Endotherm
89	128	Endotherm
221	-27	Exotherm
269	153	Endotherm
312	-431	Exotherm

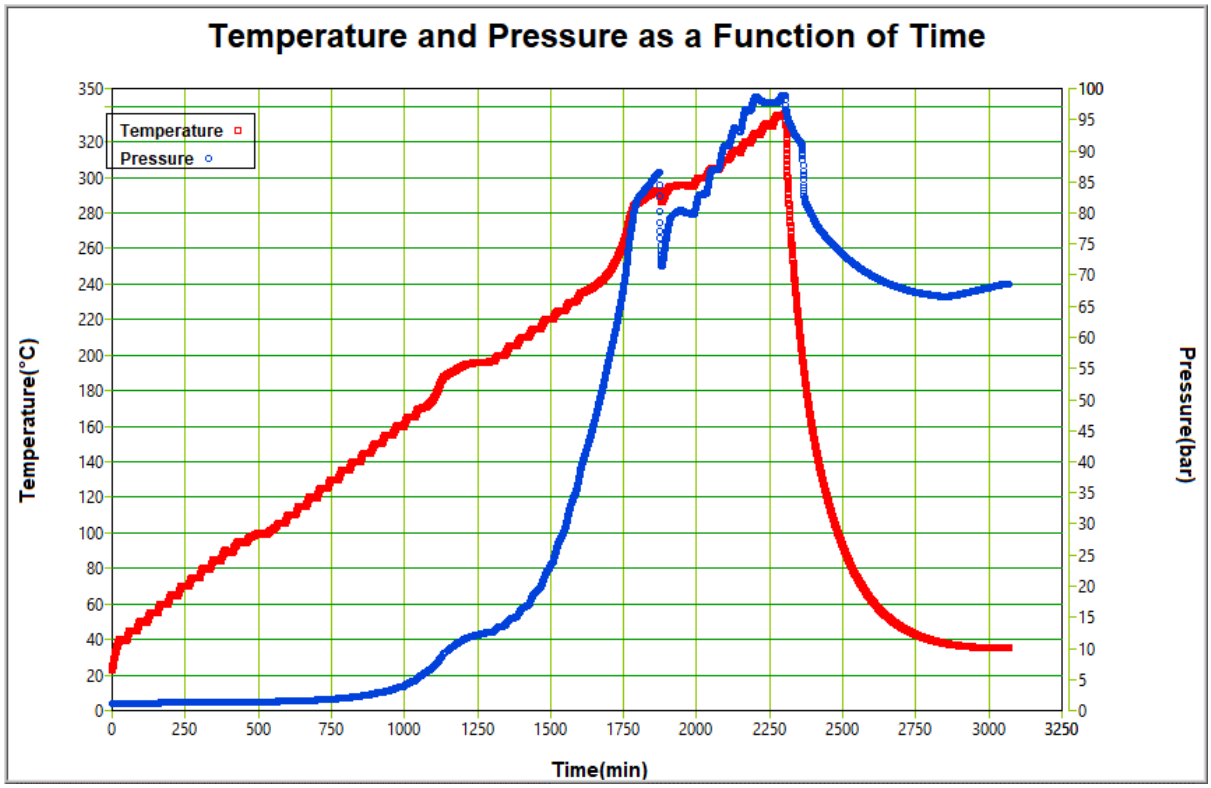


ARC

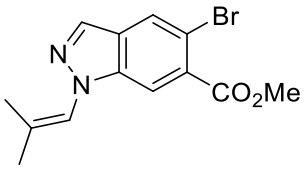
Thermal inertia = 1.76.

Thermal Onset (°C)	Phi-corrected Adiabatic temp rise (°C)	TMR @temp (Phi corr)	Gas onset from T&P trace (°C)	ΔP at 25°C (bar)	Max sample temp (°C)
170 235	46 >97[a]	Not Calculated[b] TMR @ 180 °C = 5.27 days TD24 = 201 °C	135	not calculated[c]	293[d]

[a]The test cell appears to of leaked from 293 °C, due to this the phi corrected adiabatic temperature rise and TMR/TD24 has been calculated up to 290 °C. This is considered conservative as a max rate may not have been reached.
[b]The TMR/TD24 for the first exotherm was not calculated because the exotherm follows non standard kinetics.
[c]Residual pressure was not calculated due to the test cell leaking from 293 °C.
[d]test cell leaked from 293 °C.

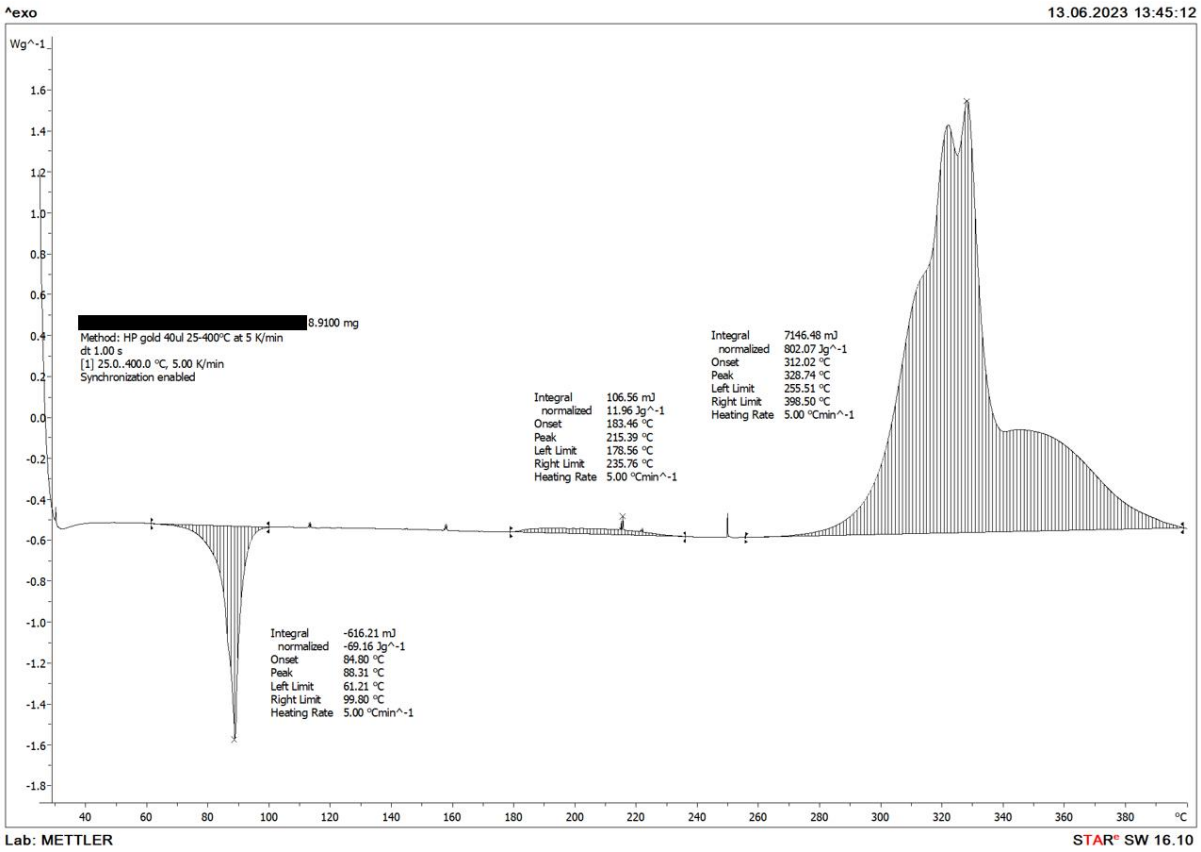


Methyl 5-bromo-1-(2-methylprop-1-en-1-yl)-1*H*-indazole-6-carboxylate (4a)



DSC

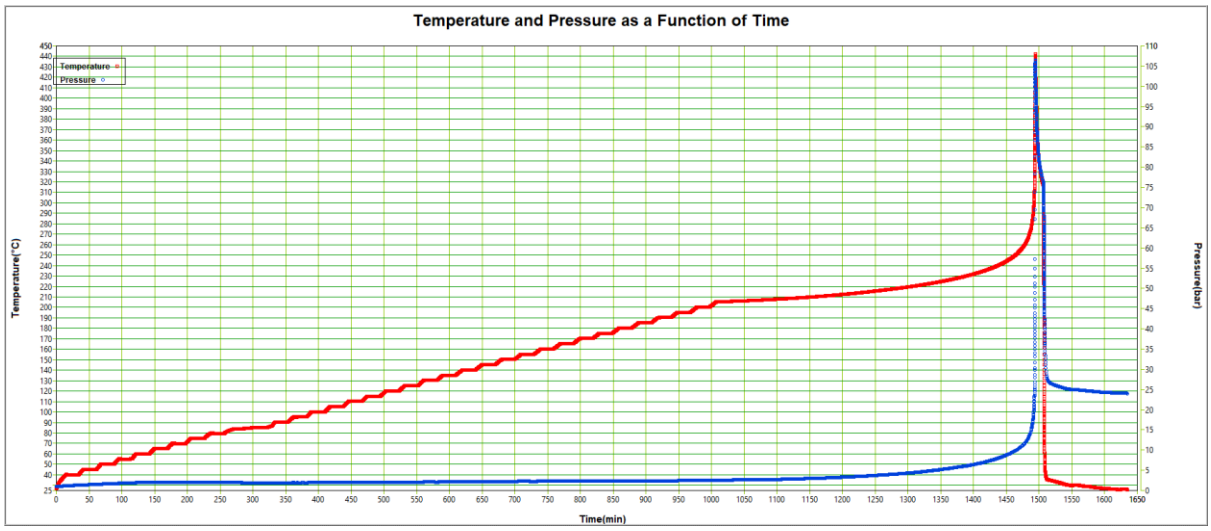
left limit (°C)	energy (J g^{-1})	peak comments
61	69	Endotherm
178	-12	Exotherm
255	-803	Exotherm



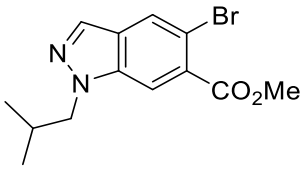
ARC

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 26 °C (bar)	Max sample temp (°C)
205	>147	>503	Not Calculated[a]	Not Calculated[a]	120	+23.03	442

[a]TMR and TD24 were not calculated due to the heating rate of the exotherm exceeding the rate of the heaters.
Phi Factor = 2.12

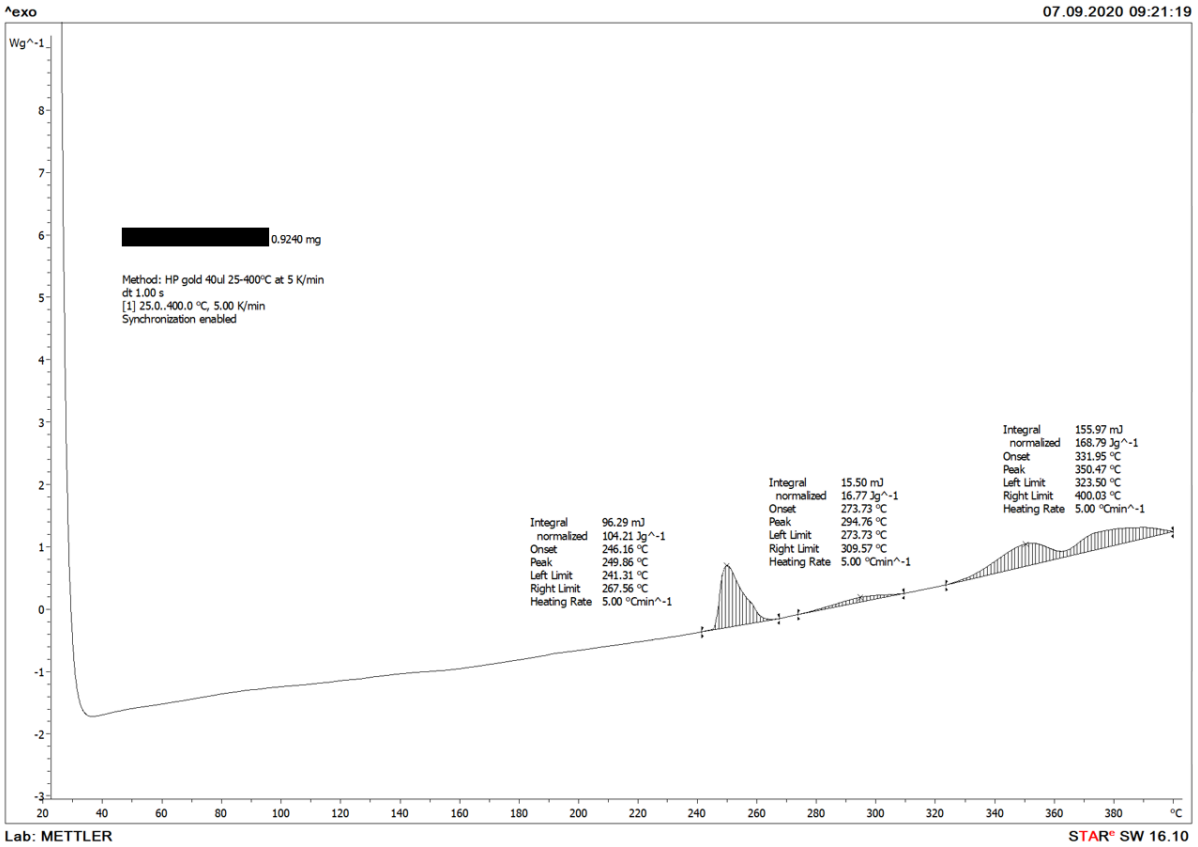


Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate (2a)



DSC

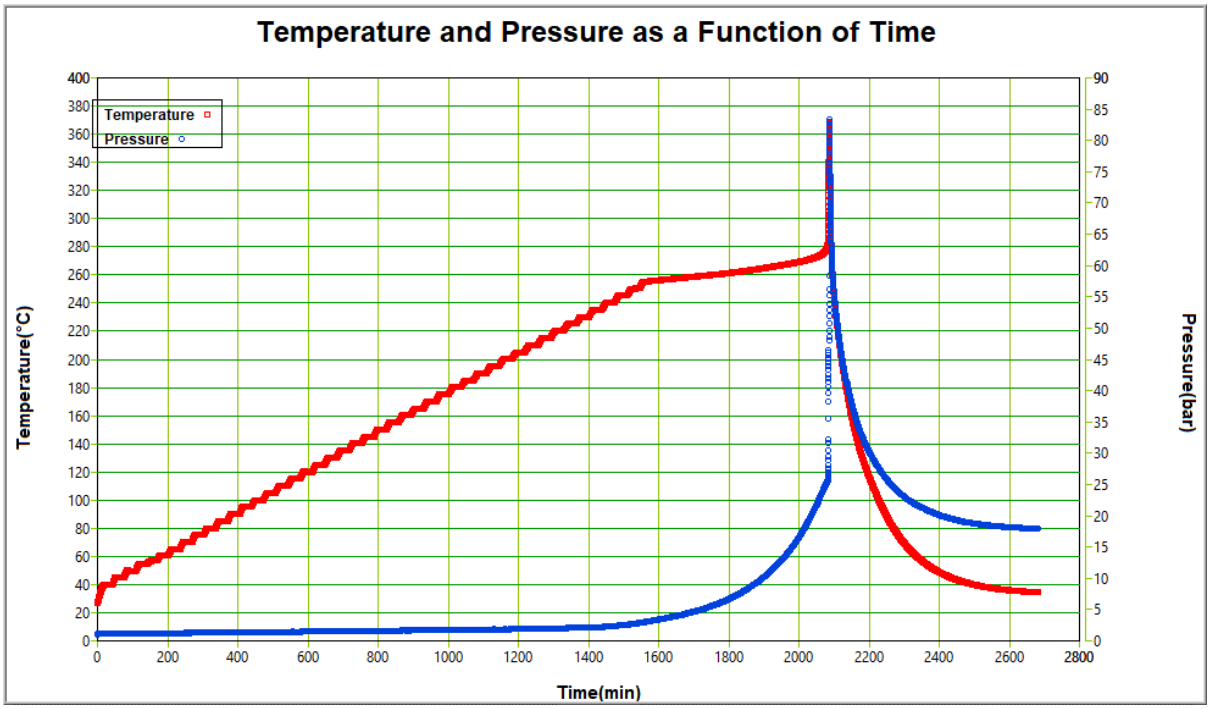
left limit (°C)	energy (J g^{-1})	peak comments
241	-105	Exotherm
273	-17	Exotherm
323	-169	Exotherm



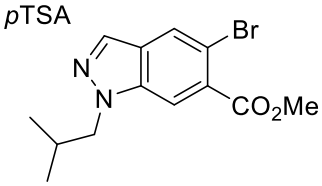
ARC

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 34 °C (bar)	Max sample temp (°C)
255	>600	>228	Not Calculated[a]	Not Calculated[a]	223	+16.83	367

[a]TMR and TD24 were not calculated due to the exotherm heating rate exceeded the sample heaters.
Phi Factor = 2.03

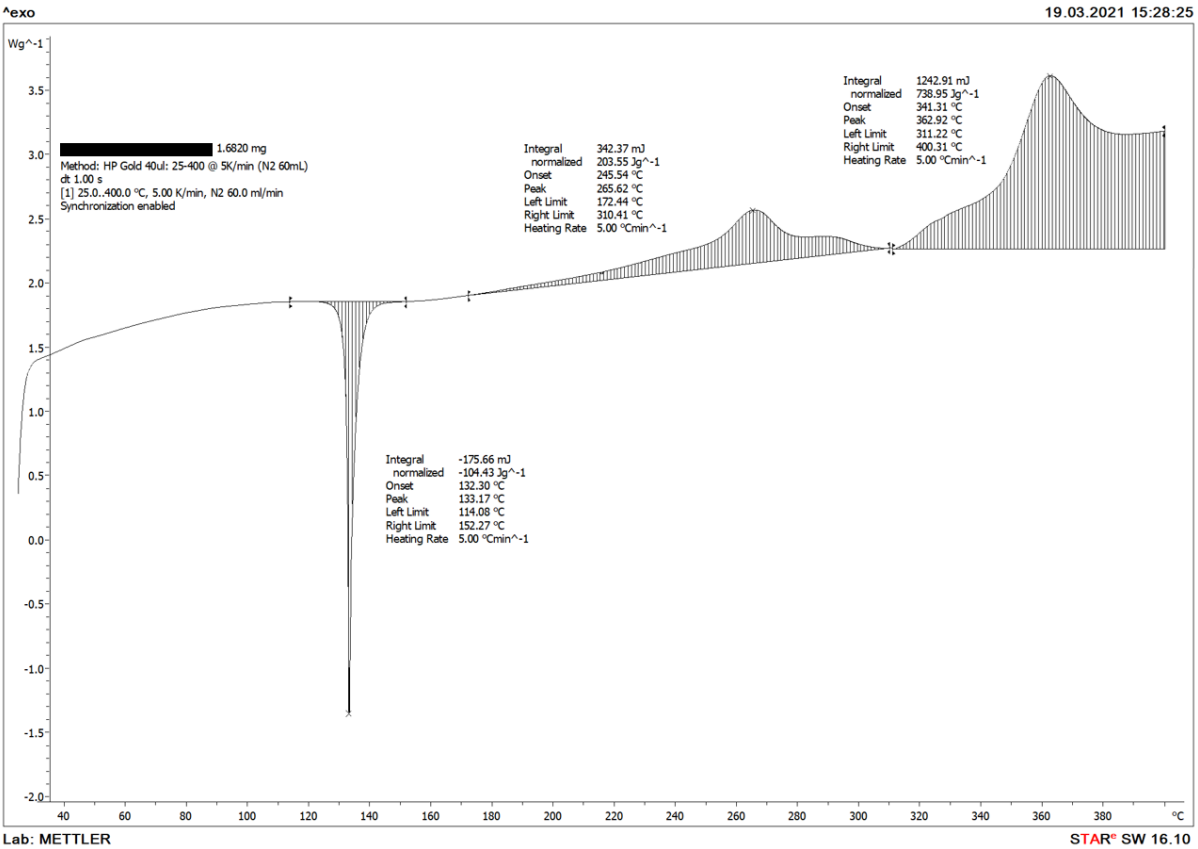


Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA (2a·*p*TSA)



DSC

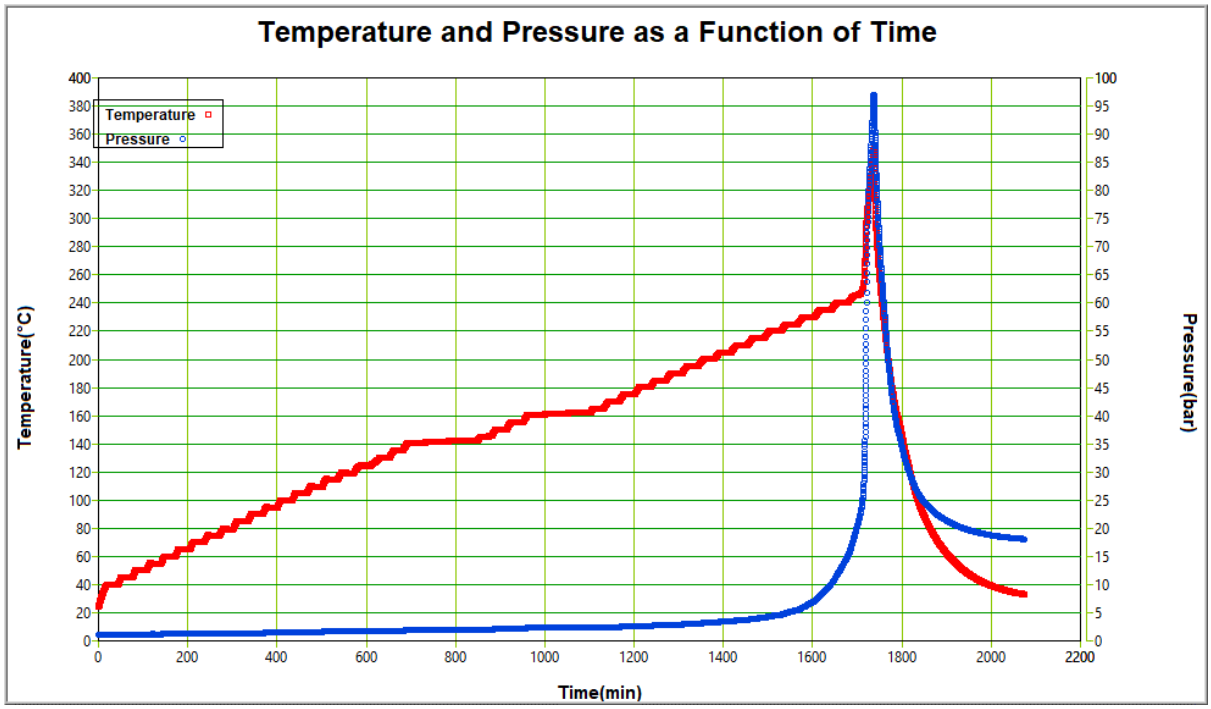
left limit (°C)	energy (J g^{-1})	peak comments
114	105	Endotherm
172	-204	Exotherm
311	>-739	Exotherm



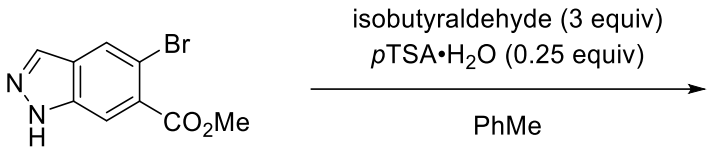
ARC

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 33 °C (bar)	Max sample temp (°C)
140	0.023	5					
160	0.021	5					
245	12.203	>210	Not Calculated[a]	Not Calculated[a]	196	+16.96	350

[a]TMR and TD24 were not calculated due to an insufficient number of data points for the first and second exotherm. For the third exotherm TMR and TD24 were not calculated due to the exotherm showing non-standard kinetics.
Phi Factor = 2.03



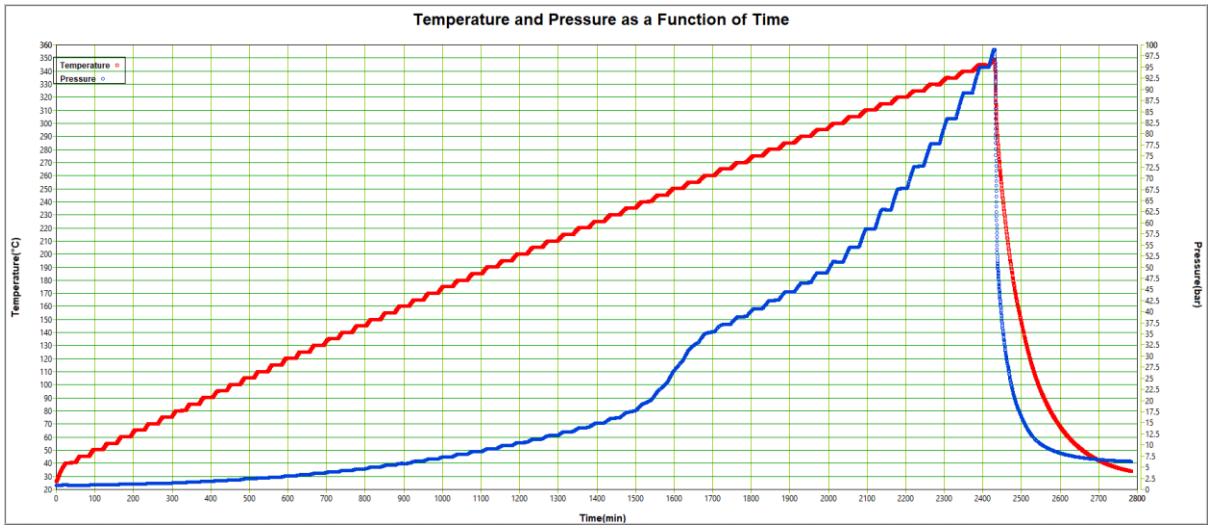
Synthesis of 4a from 1a: reaction mixture at start, ARC



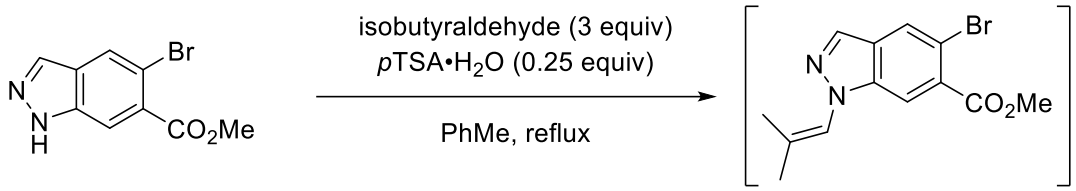
Representative sample with methyl 5-bromo-1*H*-indazole-6-carboxylate (1.0 equiv), *p*TSA·H_2O (0.25 equiv), and isobutyraldehyde (3.0 equiv) in PhMe (15 mL/g).

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 33 °C (bar)	Max sample temp (°C)
None Detected	N/A	N/A	N/A	N/A	235	+5.32	349

Phi Factor = 1.73

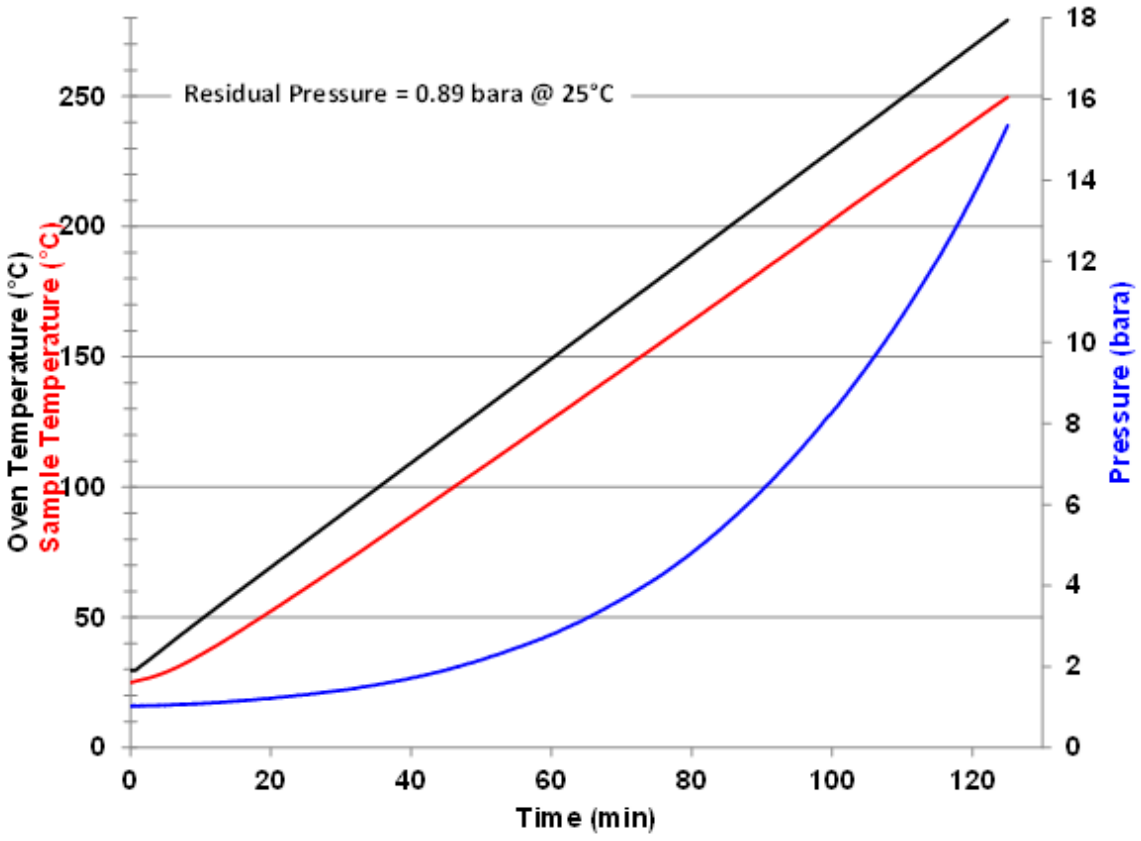


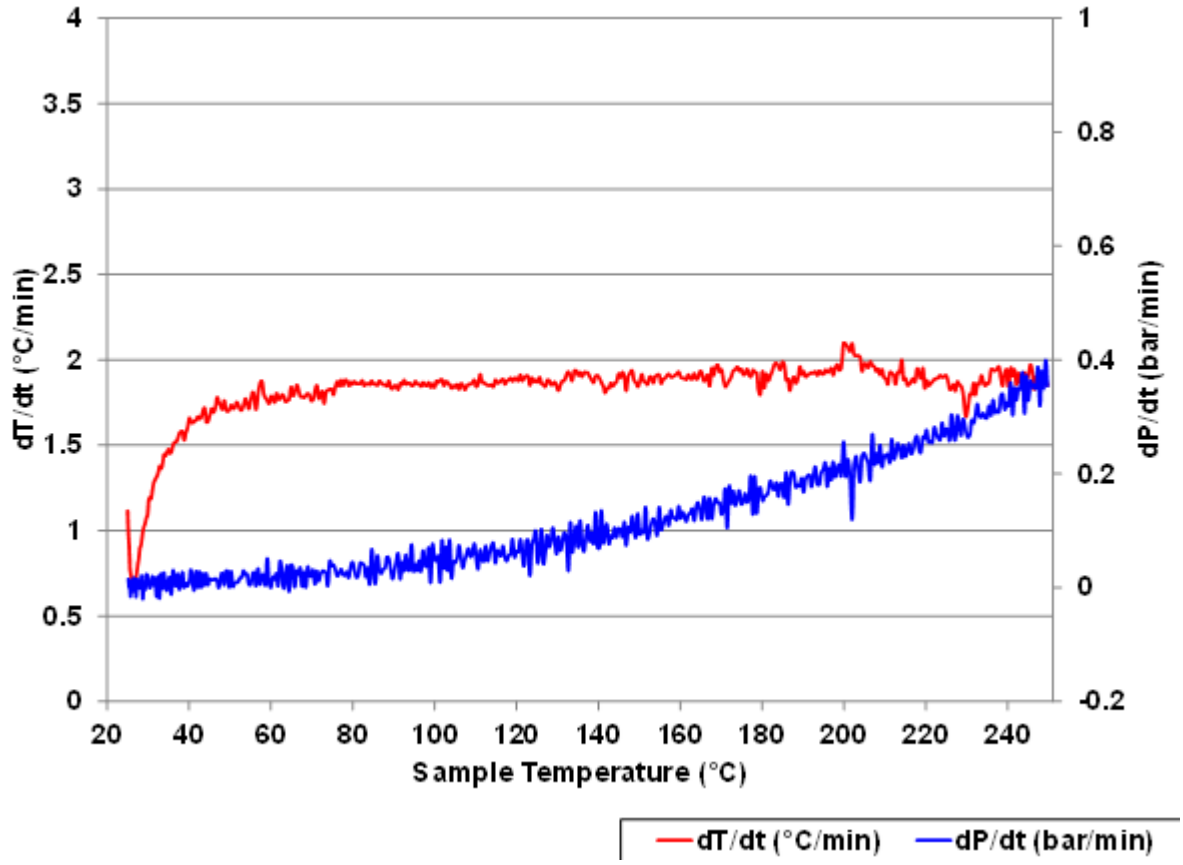
Synthesis of 4a from 1a: reaction mixture at completion, Ramp TSU



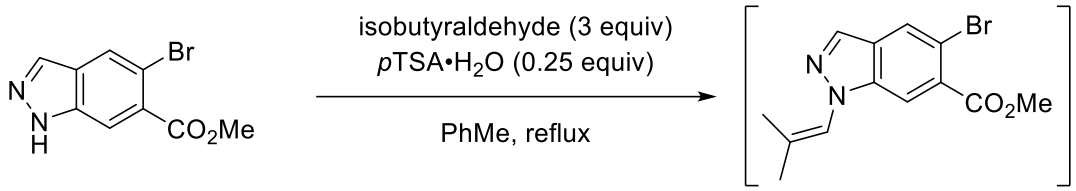
Representative sample taken after reaction completion and workup, then over concentration to *ca*. 5 mL /g.

Thermal onset (°C)	Max ΔdT/dt from exotherm (K/min)	Gas onset from Antoine Plot (°C)	ΔP at 25 °C (bar)	Max sample temp of test (°C)
198	0.15	None detected	-0.14	249




4
3.5
3
2.5
2
1.5
1
0.5
0
dT/dt (°C/min)
1
0.8
0.6
0.4
0.2
0
-0.2
dP/dt (bar/min)
20
40
60
80
100
120
140
160
180
200
220
240
Sample Temperature (°C)
dT/dt (°C/min)
dP/dt (bar/min)

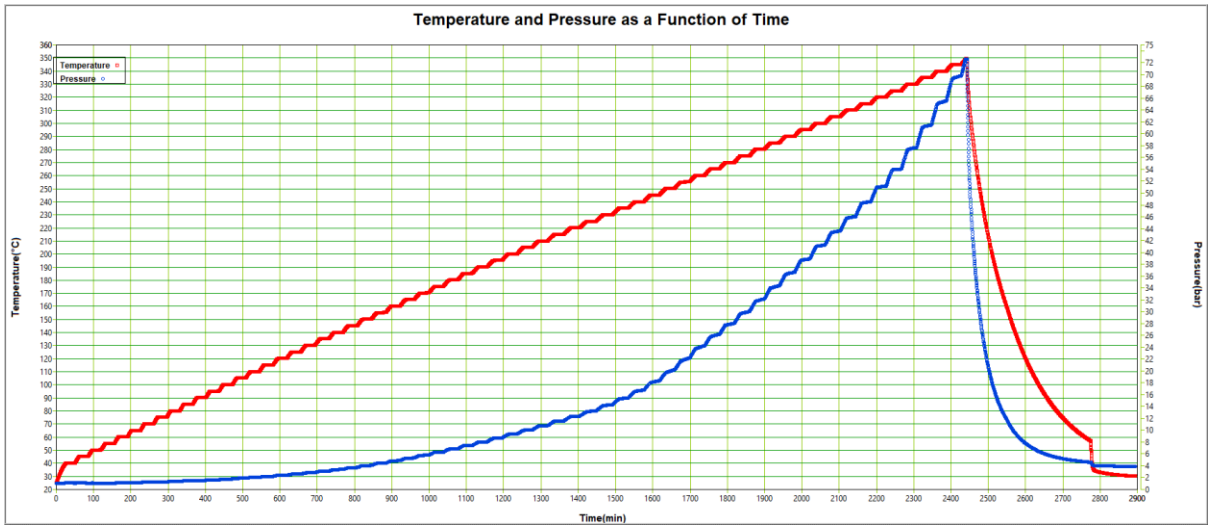
Synthesis of 4a from 1a: reaction mixture at completion, ARC



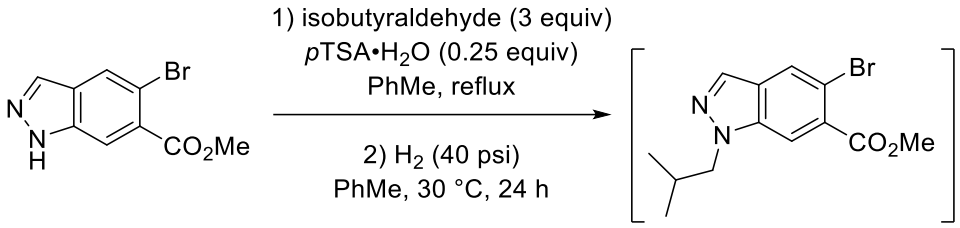
Representative sample taken after reaction completion and held at reflux for additional 1.5 h.

Thermal Onset (°C)	Max Rate (K/min)	Phi-corrected Adiabatic temp rise (K)	TMR@ temp (Phi corr)	TD24 (°C)	Gas onset from Antoine Plot (°C)	ΔP at 30 °C (bar)	Max sample temp (°C)
None Detected	N/A	N/A	N/A	N/A	232	+2.87	349

Phi Factor = 1.85

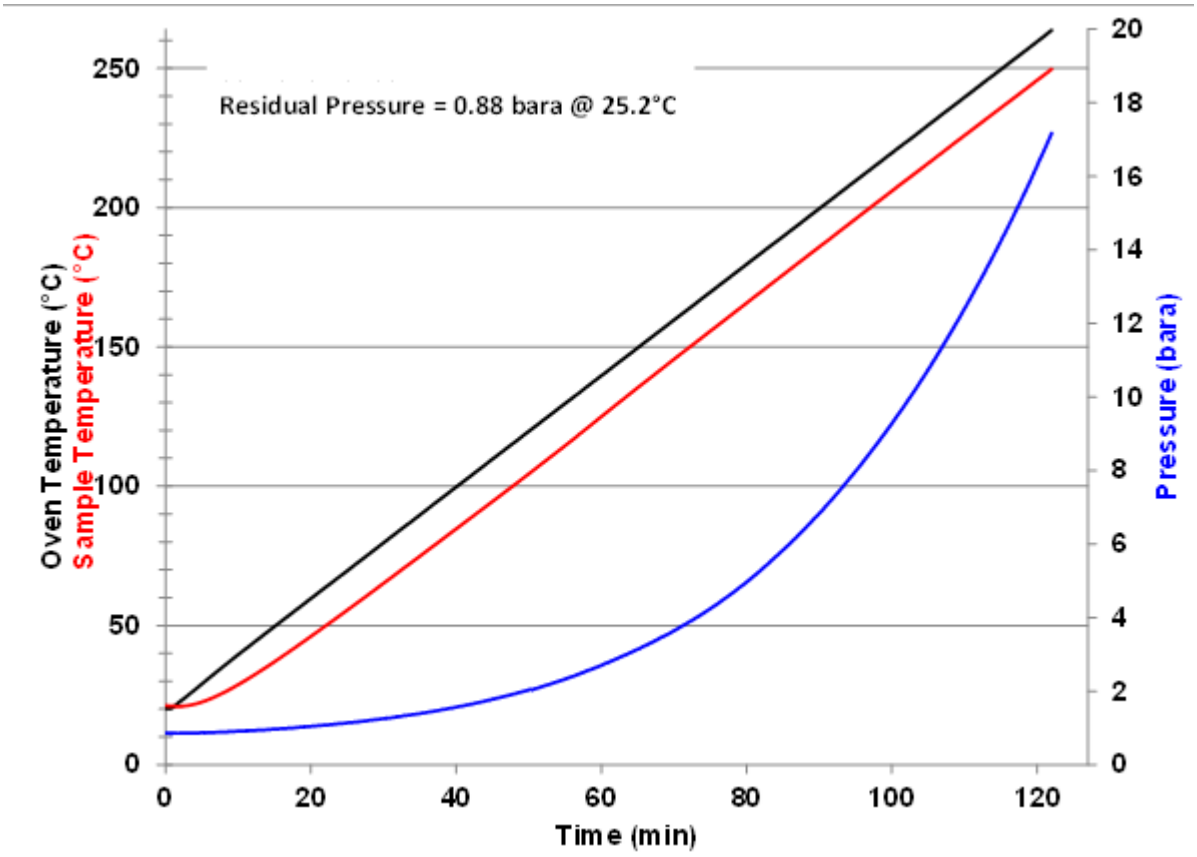


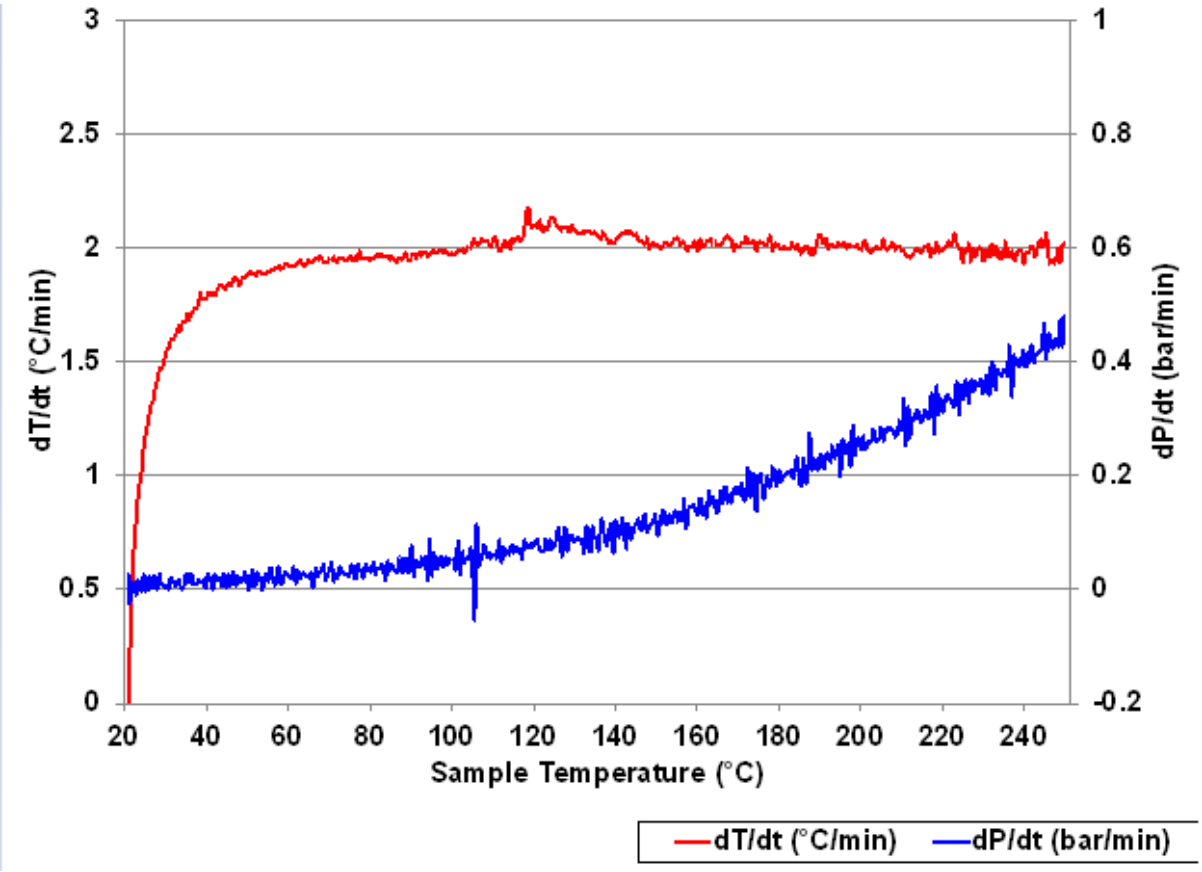
Synthesis of 2a from 4a: reaction mixture at completion, Ramp TSU



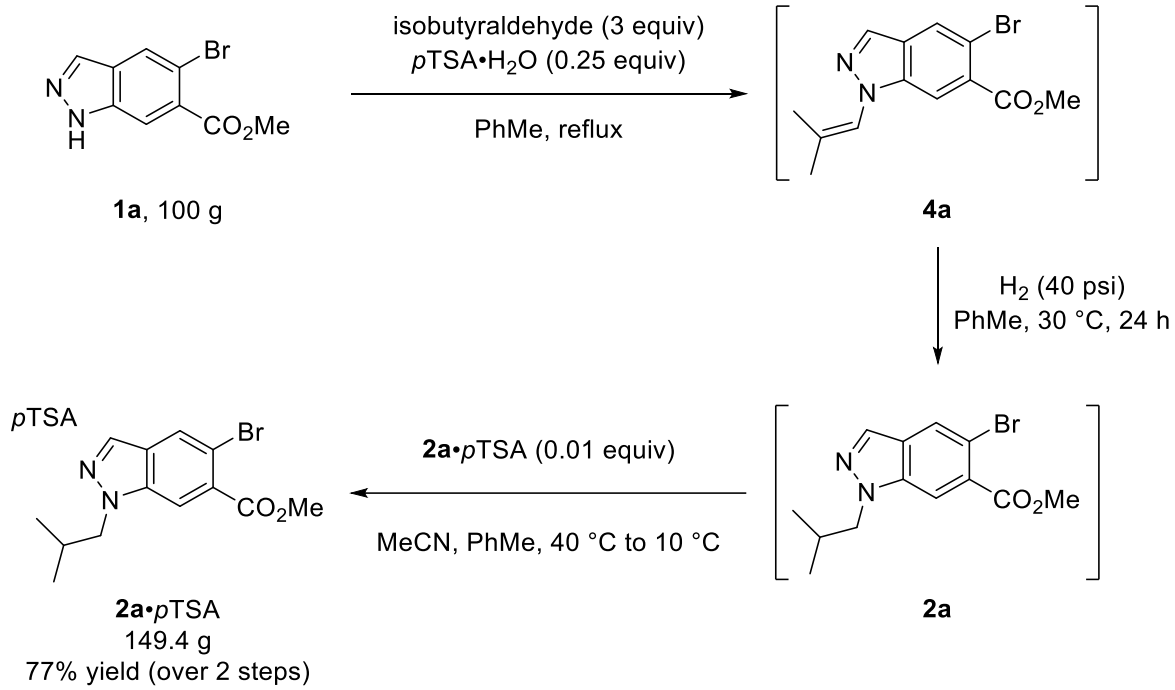
Representative sample taken after reaction completion and held at reflux for additional 1.5 h.

Thermal onset (°C)	Max ΔdT/dt from exotherm (K/min)	Gas onset from Antoine Plot (°C)	ΔP at 25 °C (bar)	Max sample temp of test (°C)
110	0.19	None detected	0	249




3
2.5
2
1.5
1
0.5
0
1
0.8
0.6
0.4
0.2
0
-0.2
dT/dt (°C/min)
dP/dt (bar/min)
20
40
60
80
100
120
140
160
180
200
220
240
Sample Temperature (°C)
dT/dt (°C/min)
dP/dt (bar/min)

100 g Scale Procedure (1a·*p*TSA)



A 2 L Reactor Ready Vessel equipped with a Dean-Stark condenser was charged with methyl 5-bromo-1*H*-indazole-6-carboxylate (100.0 g, 0.392 mol, 1.0 equiv) and *p*TSA·H_2O (18.6 g, 0.098 mol, 0.25 equiv). PhMe (1.5 L) was added, followed by isobutyraldehyde (107 mL, 1.18 mol, 3.0 equiv). The jacket temperature was increased to 140 °C over 2 h, then the reaction mixture was stirred at a vigorous reflux for 3 h. Triethylamine (13.7 mL, 0.098 mol, 0.25 equiv) was added dropwise subsurface. The jacket temperature was cooled to 20 °C over 2 h, then left standing overnight. The reaction mixture was transferred to a 5 L Reactor Ready. The reaction mixture was washed with H_2O (400 mL) and 23% brine (400 mL). The organic layer was concentrated to *ca*. 1 L by distillation at atmospheric pressure to afford a solution of crude **4a** in PhMe.

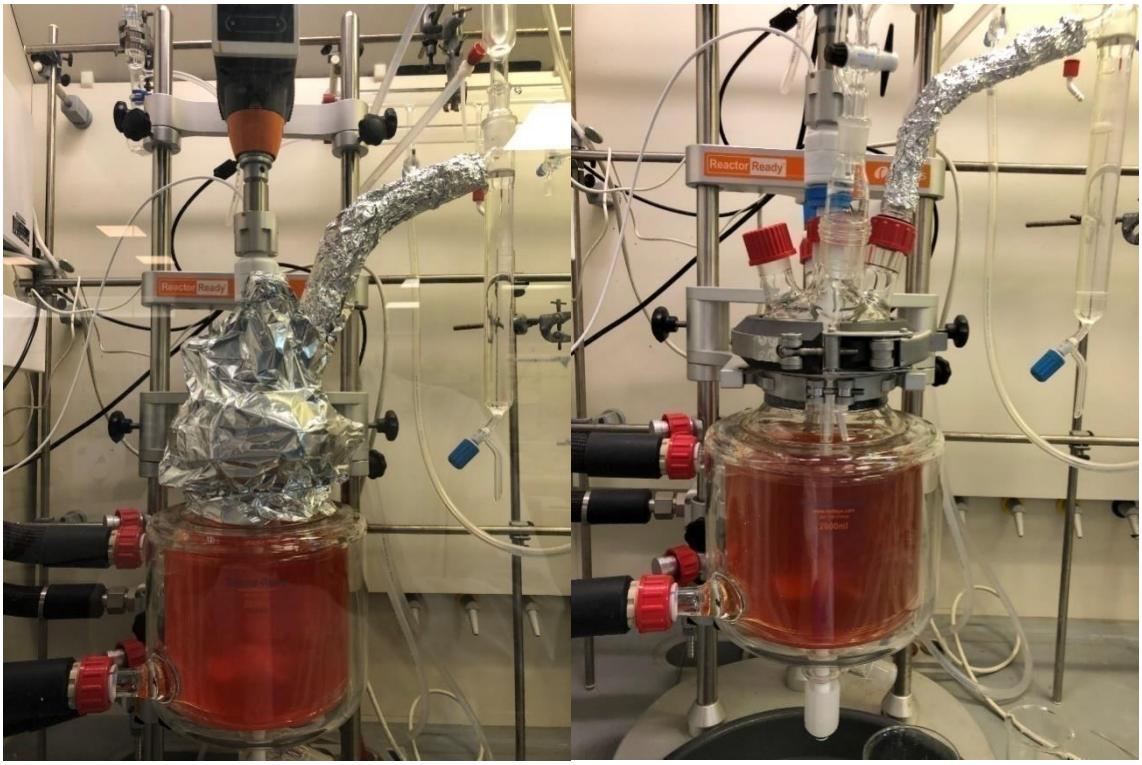
A 5 L Type 3 Buchiglasuster reactor was charged with 5% Pt/C (19.9 g, 0.005 mol, 0.013 equiv) and crude enamine solution. The reaction mixture was stirred under an atmosphere of H_2 at 40 psi and 30 °C for 24 hours. The resulting reaction mixture was filtered through arbocel and washed with PhMe (300 mL) to afford a solution of crude **1a** in PhMe.

The solution of **1a** in PhMe was concentrated to *ca*. 670 mL by distillation at atmospheric pressure. MeCN (220 mL) was charged, and the reaction mixture heated to 50 °C (internal temperature) and held for 5 min. The mixture was charged with *p*TSA (83.3 g, 0.43 mol, 1.1

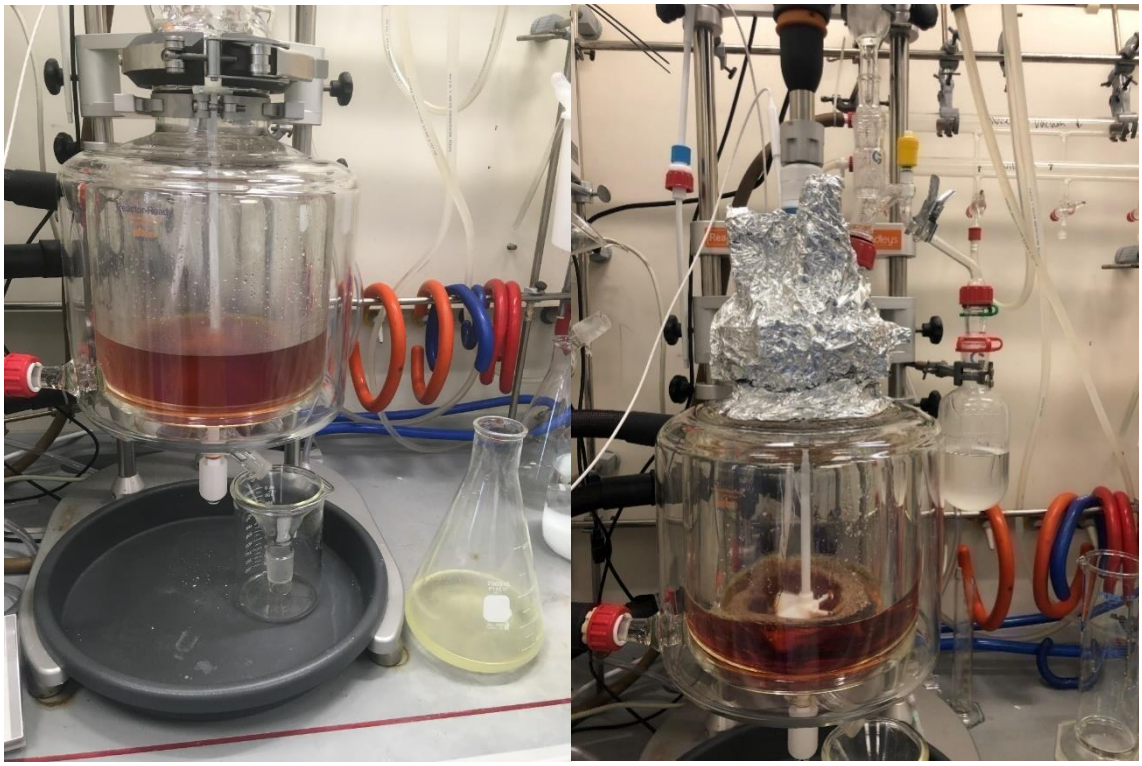
equiv) in a single portion. The mixture was cooled to 40 °C and held for 5 min. The mixture was seeded with **1a**·*p*TSA (2.1 g, 0.04 mol, 0.01 equiv). The slurry was held at 40 °C for 1 h, cooled to 30 °C at 0.2 °C/min, held for 30 min, heated to 40 °C at 1 °C/min, held for 1 h, cooled to 10 °C at 0.2 °C/min, then held at 10 °C overnight. The resulting solids were collected by vacuum filtration and dried on a tray in an oven **to** afford **1a**·(*p*TSA)$_{1.25}$ as an off-white solid (149.4 g, 0.284 mol, 72% yield (over 2 steps)).

NB: Final product contained 1.25 equiv *p*TSA by ^{1}H NMR. Characterisation otherwise consistent with **1a**·*p*TSA as reported above.

Left: Starting solids and solvent: *p*TSA·H_2O, **1a**, and PhMe. **Right**: Solids charged into 2 L reactor ready vessel.

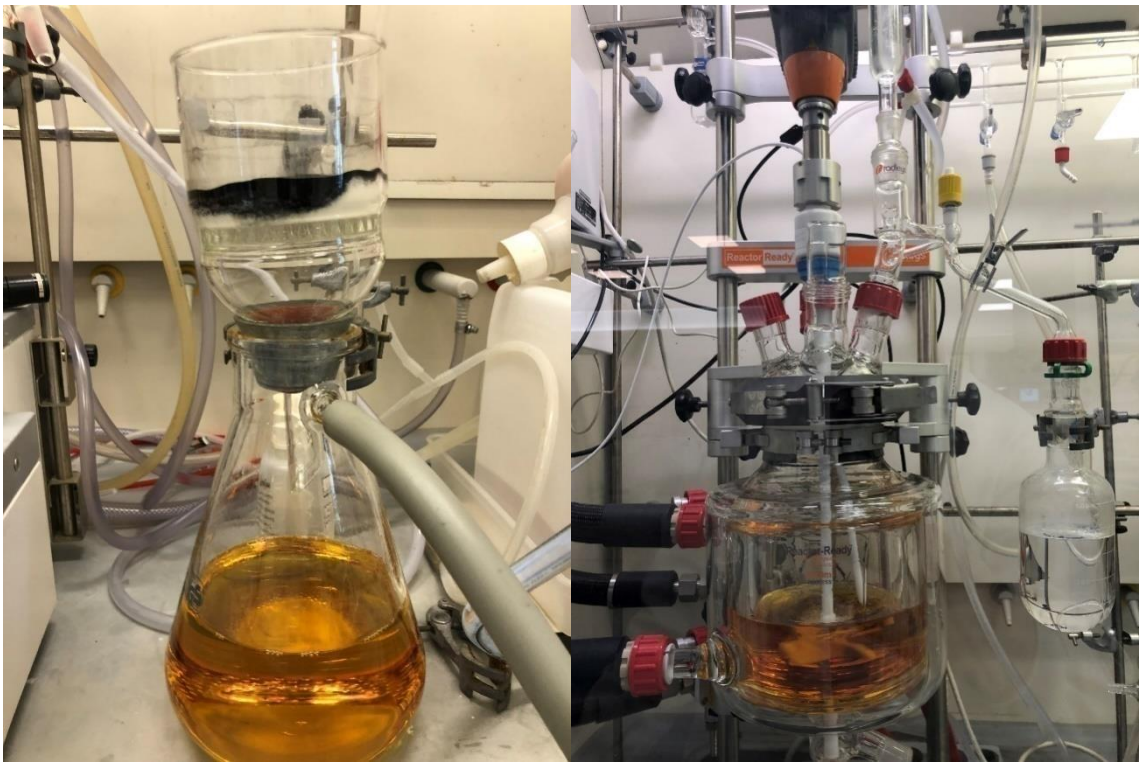


Left: Reaction mixture equipped with Dean-Stark condenser. **Right**: Subsurface Et_3N addition with dropping funnel and feed tube.

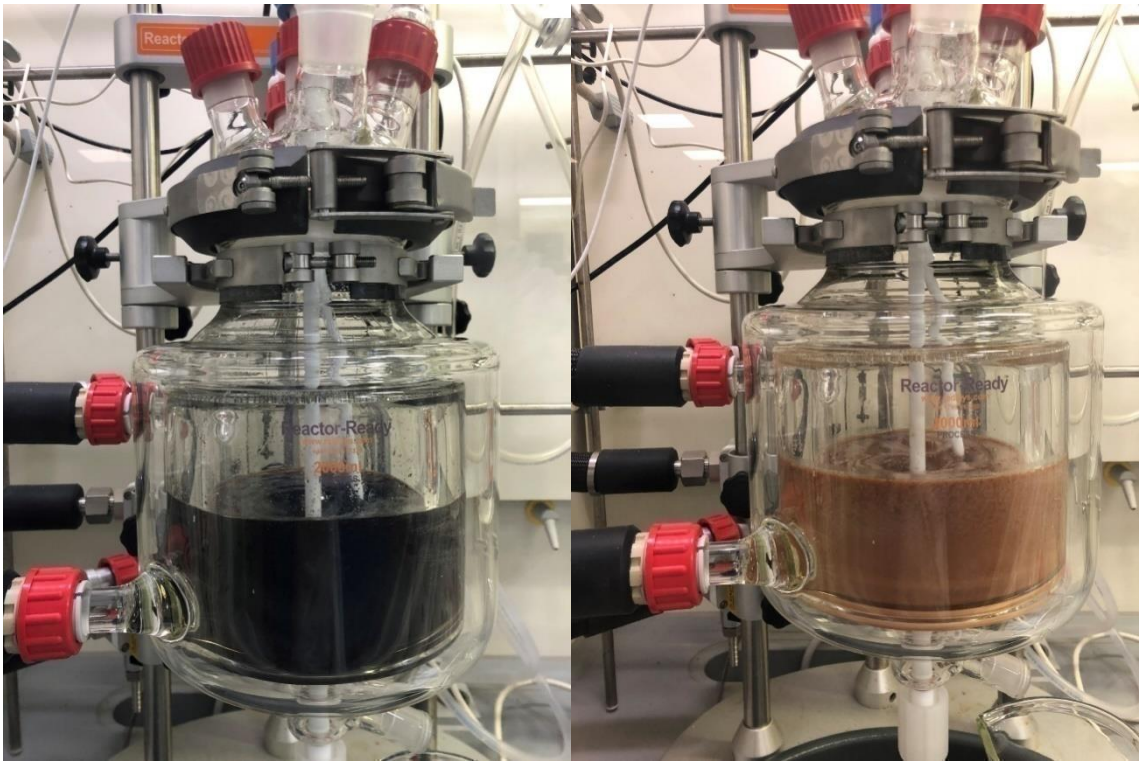


Left: Reaction mixture in 5 L Reactor Ready, after H_2O wash. Right: Reaction mixture atmospheric distillation down to *ca*. 1 L.

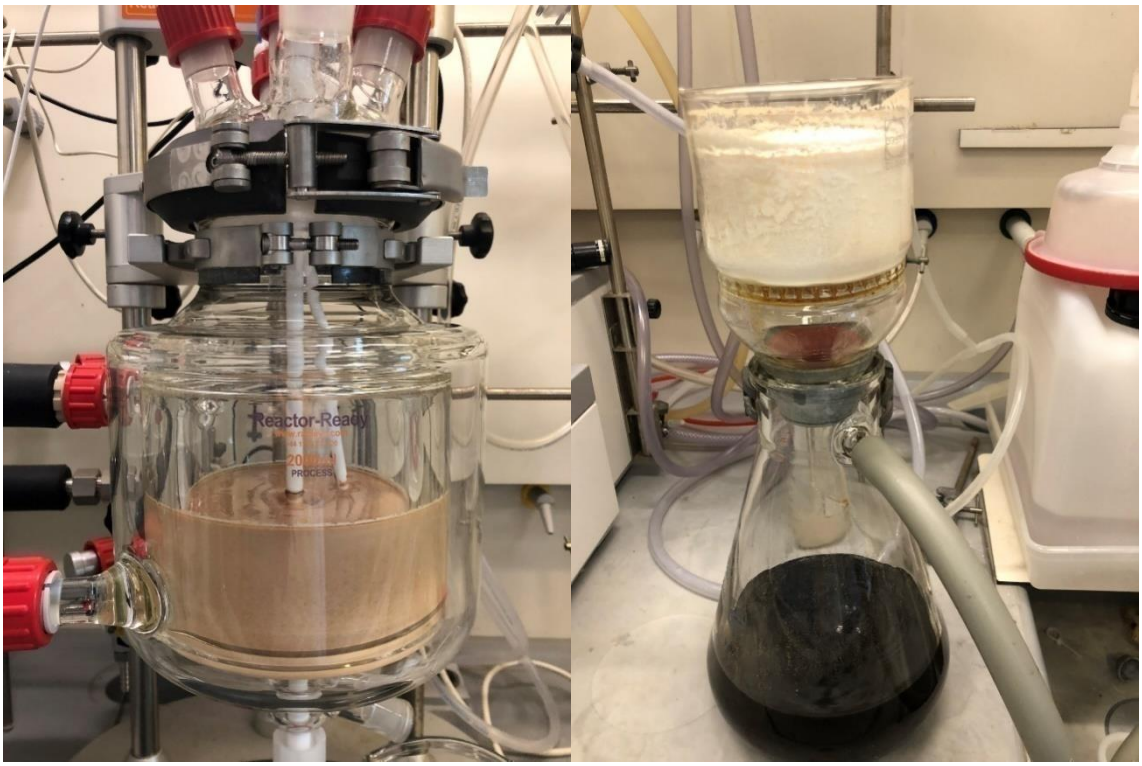
Left: Hydrogenation reactor charged with reaction mixture. **Right**: Hydrogenation reactor closure during set-up.



Left: Catalyst removal by filtration over arbocel under N_2. **Right**: Distillation of liquors down to *ca*. 670 mL.



Left: Mixture upon addition of MeCN. **Right**: Mixture once seeded.



Left: Mixture at 10 °C after crystallization. **Right**: Collection of product by vacuum filtration.

Top: Product tray drying. **Bottom**: Final product in 500 mL beaker.

PMI estimations

PMI estimations used an adapted PMI calculation tool from the ACS Green Chemistry Institute.

General Procedure (1a)

	Value	Units
Assay Batch Size (input pure)	2.0	g
Assay Kg product (output pure)	1.9	g
Reagents		
pTSA·H2O	0.38	g
isobutryaldehyde	1.70	g
Et3N	0.20	
Pt/C (5%)	0.40	g
Solvents		
Toluene (reaction)	26.1	g
Toluene (wash)	17.2	g
Toluene (reaction)	17.4	g
Toluene (1st wash)	5.3	g
Toluene (2nd wash)	17.4	g
Ethyl acetate (column)	500.0	g
Heptane (column)	500.0	g
Aqueous		
H2O	8.0	g
1M HCl	8.0	g
NaCl(aq)	8.0	g
MgSO4	5.0	g
Metrics		
Mass Substrate (g)		2
Mass Reagents (g)		3
Mass Solvents (g)		1083
Mass Aqueous (g)		29
PMI		**588.0**
PMI Substrate, Reagents, Solvents		572.7
PMI Substrates and Reagents		2.5
PMI Solvents		570.3
PMI Water		15.3

100 g Scale Procedure (1a·*p*TSA)

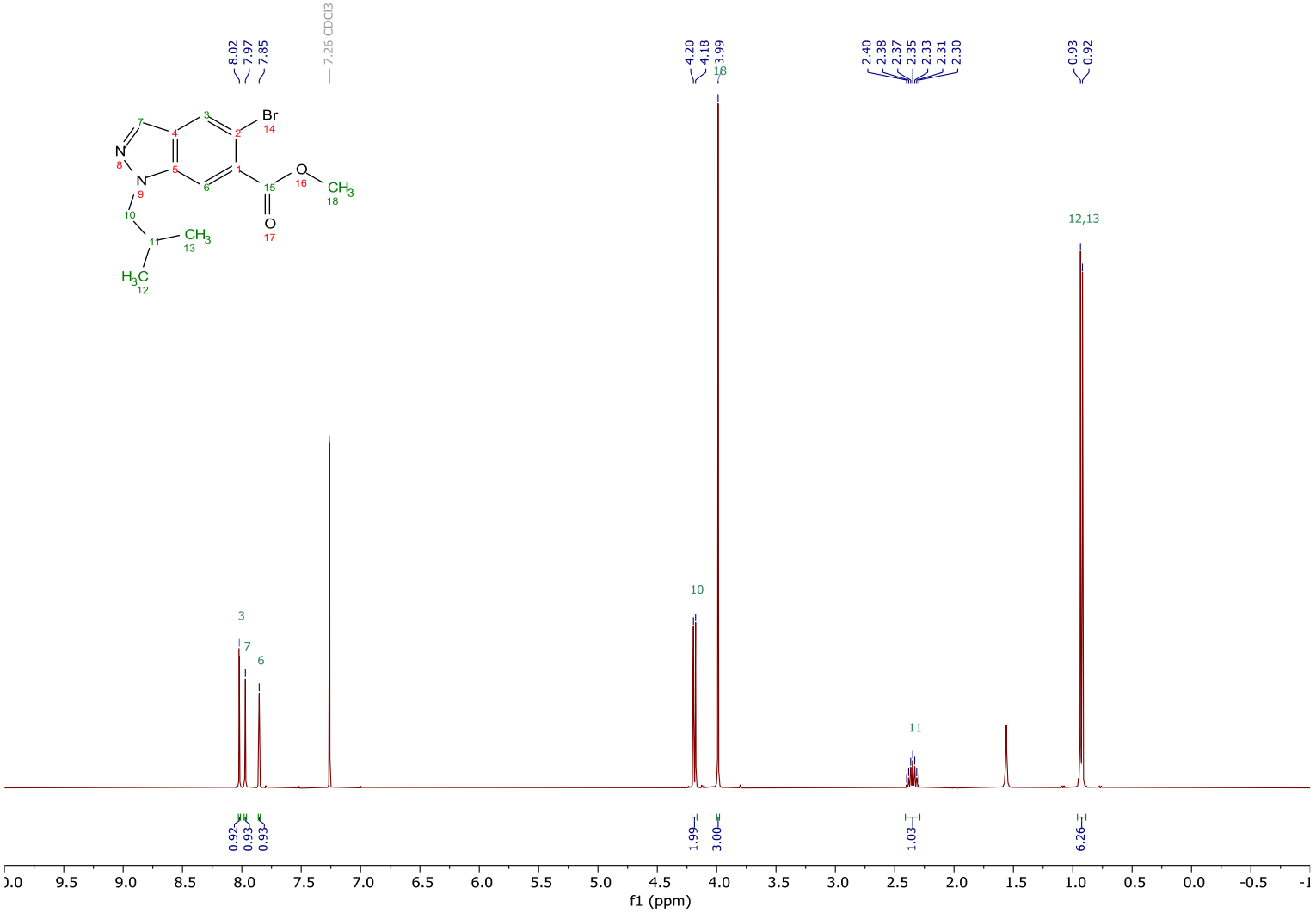
	Value	Units
Assay Batch Size (input pure)	100.0	g
Assay Kg product (output pure)	136.4	g
Reagents		
pTSA·H2O	18.60	g
isobutryaldehyde	84.81	g
Et3N	8.83	
Pt/C (5%)	19.89	
pTSA·H2O	83.3	
seed	2.1	g
Solvents		
Toluene (reaction)	1306.5	g
Toluene (reactor wash)	261.3	g
MeCN (cryst)	172.3	g
Toluene (cake wash)	174.2	g
Aqueous		
H2O	400.0	g
NaCl(aq)	475.6	g

Metrics	
Mass Substrate (g)	100
Mass Reagents (g)	218
Mass Solvents (g)	1914
Mass Aqueous (g)	876
PMI	**22.8**
PMI Substrate, Reagents, Solvents	16.4
PMI Substrates and Reagents	2.3
PMI Solvents	14.0
PMI Water	6.4

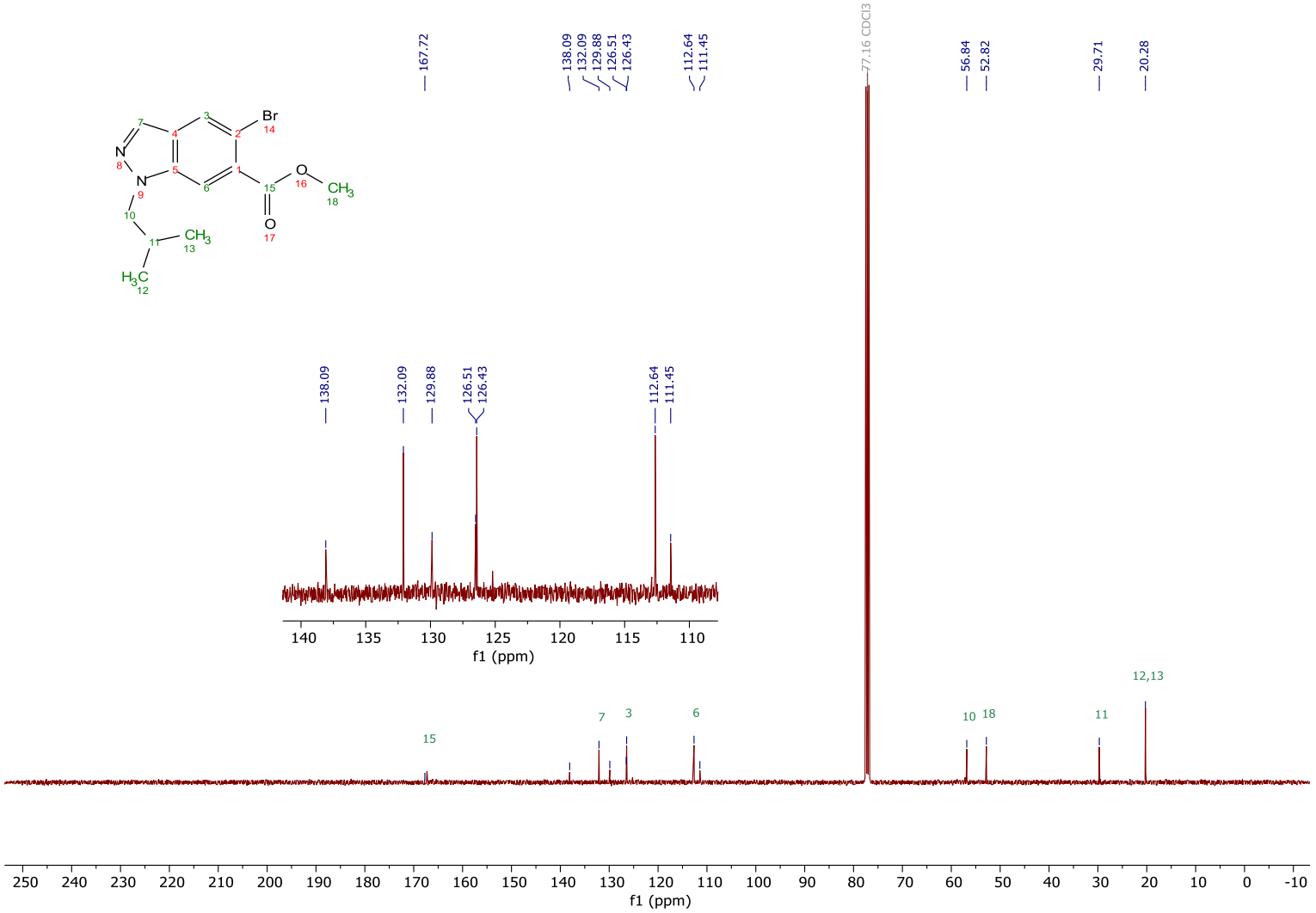
NMR Spectra of Products

Methyl 5-bromo-2-isobutyl-1*H*-indazole-6-carboxylate (2a)

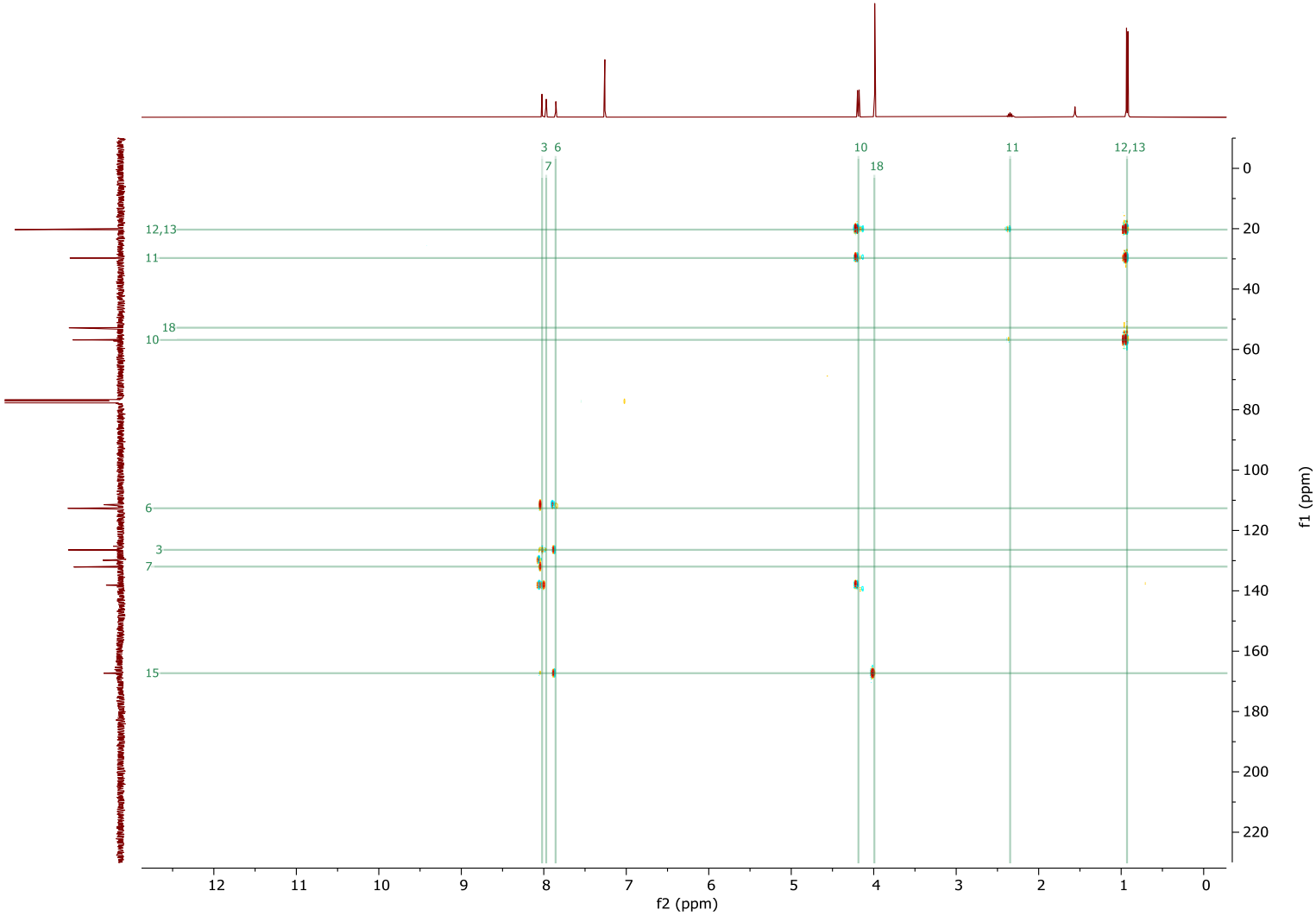
^{1}H NMR (400 MHz, $CDCl_3$)



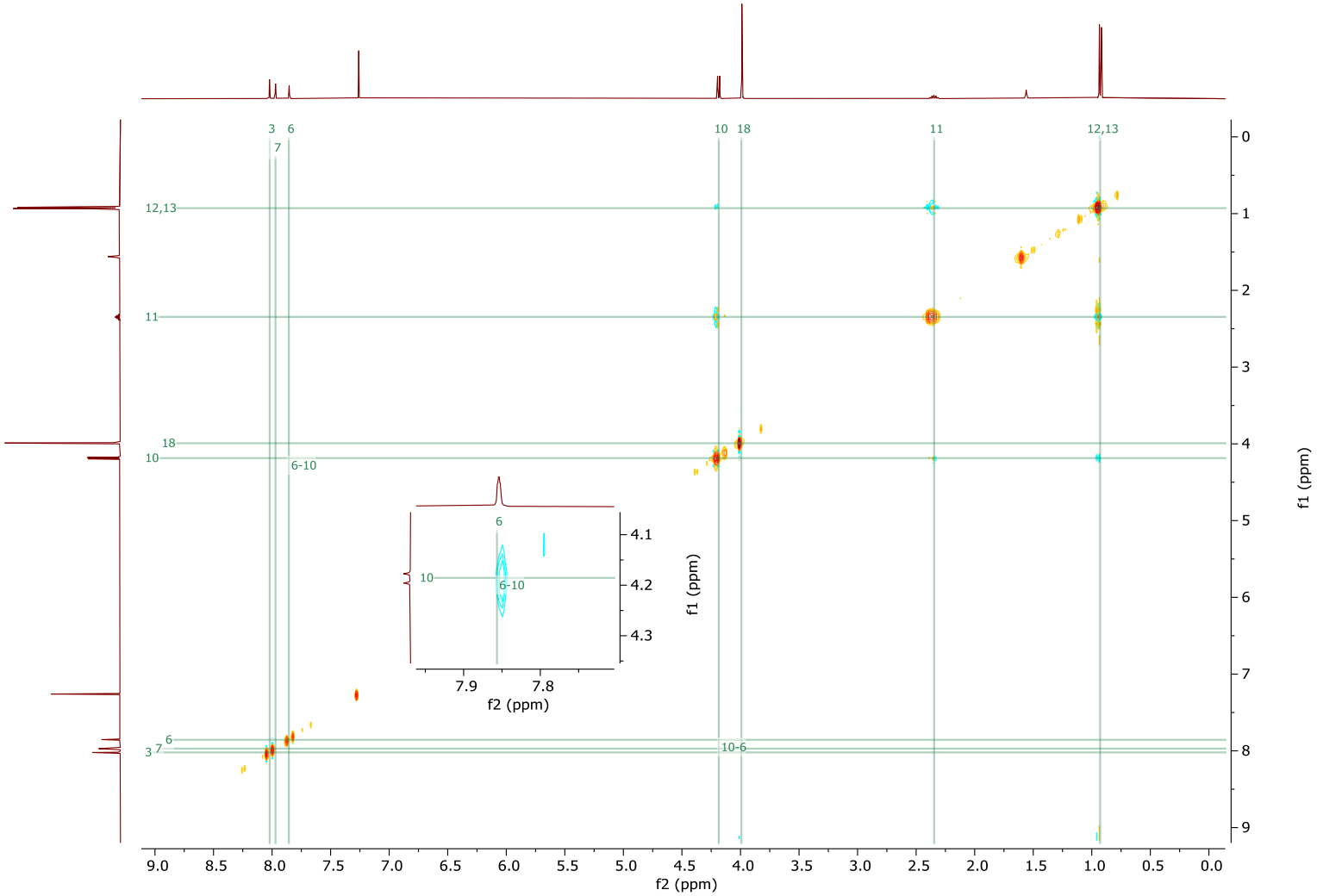
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

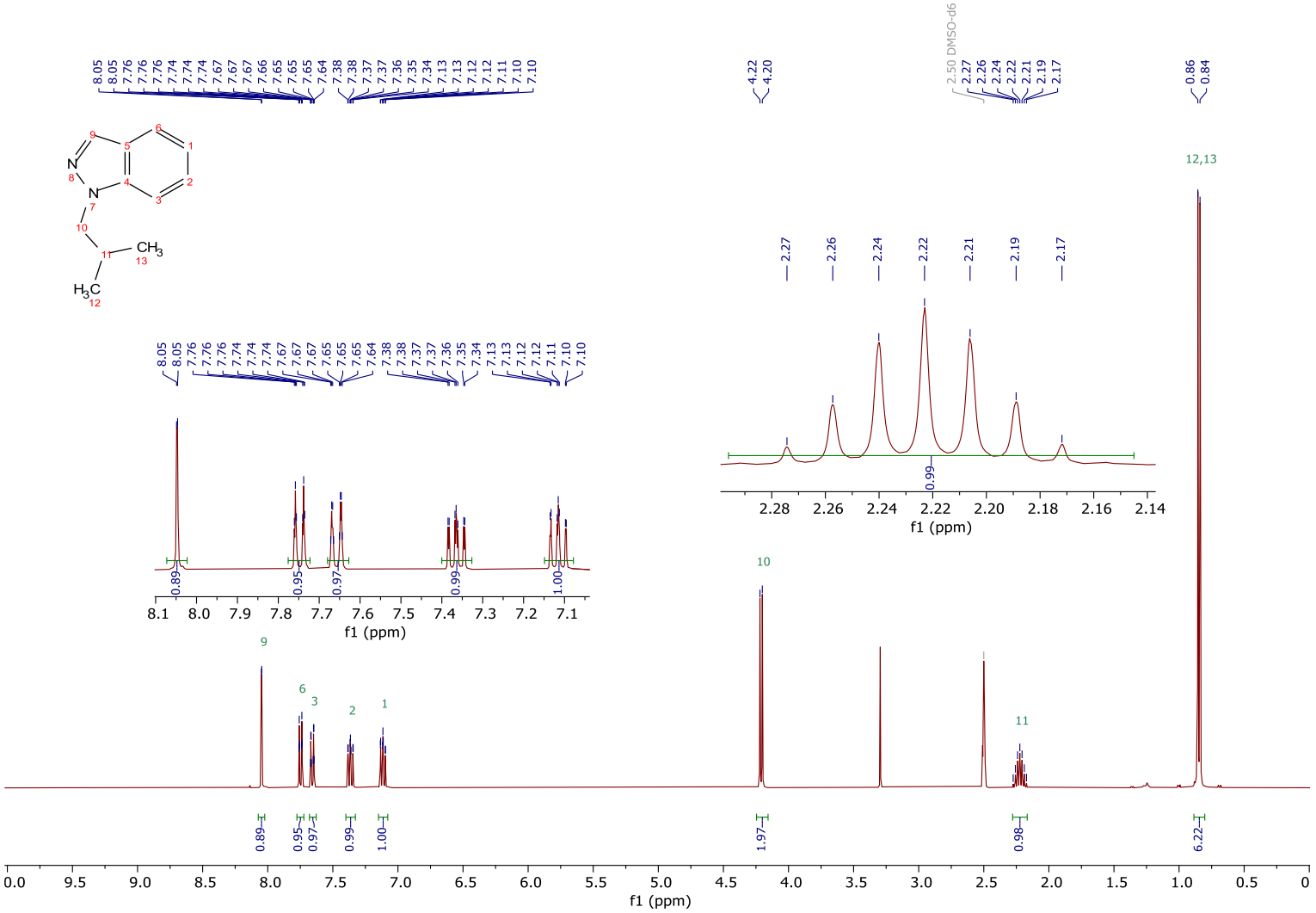


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

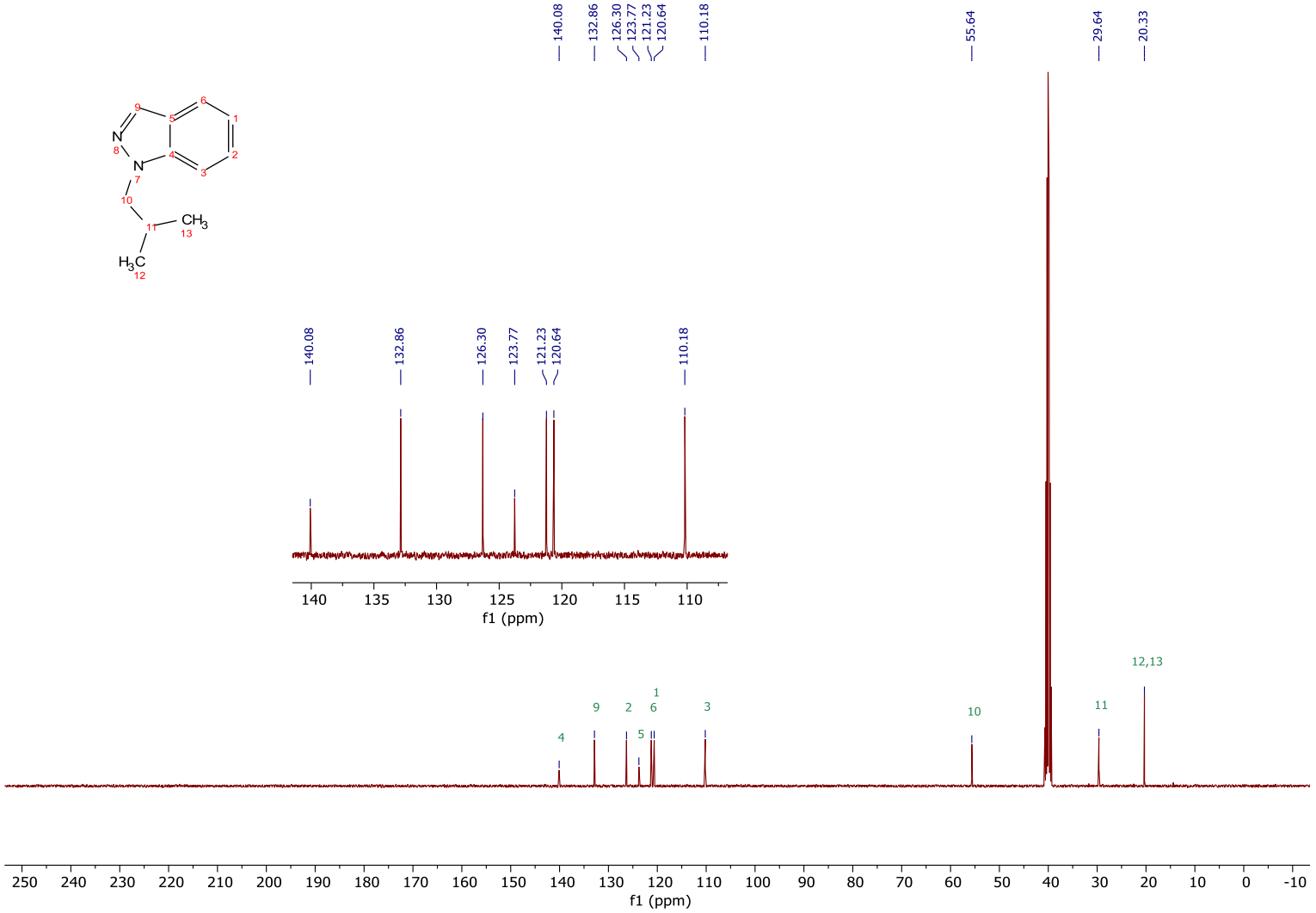


1-isobutyl-1*H*-indazole (2b)

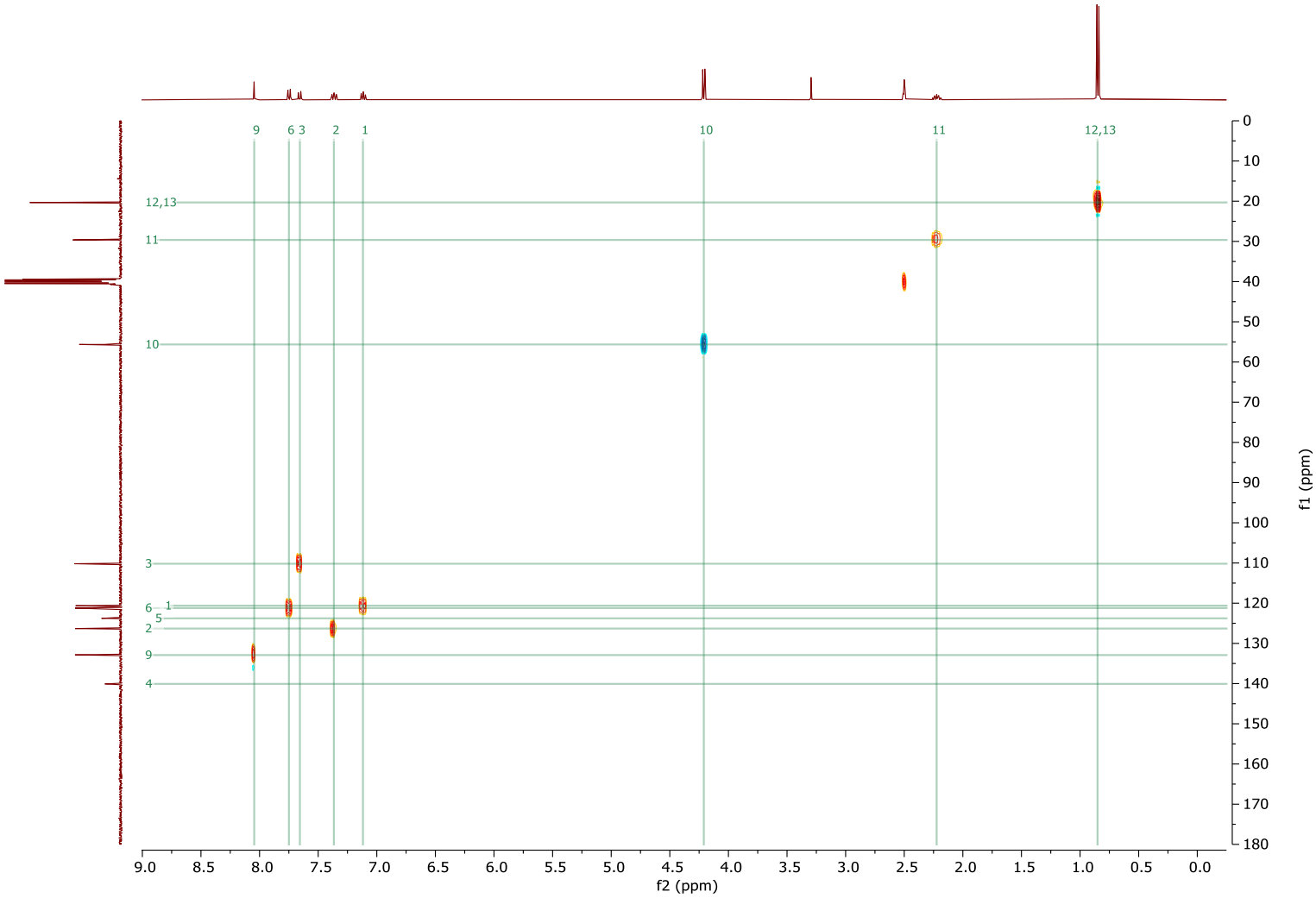
^{1}H NMR (400 MHz, DMSO-d_6)



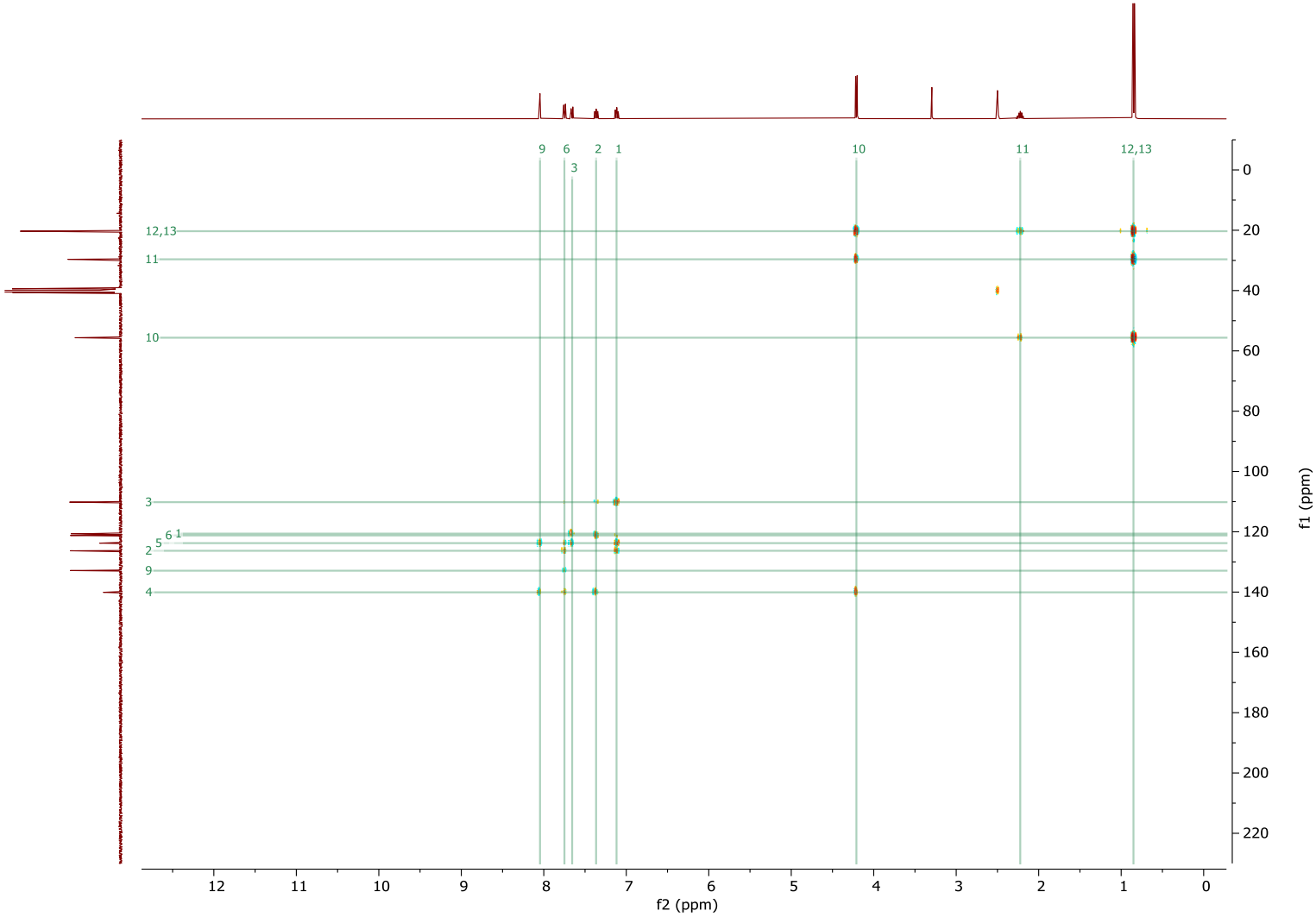
^{13}C NMR (101 MHz, DMSO-d_6)



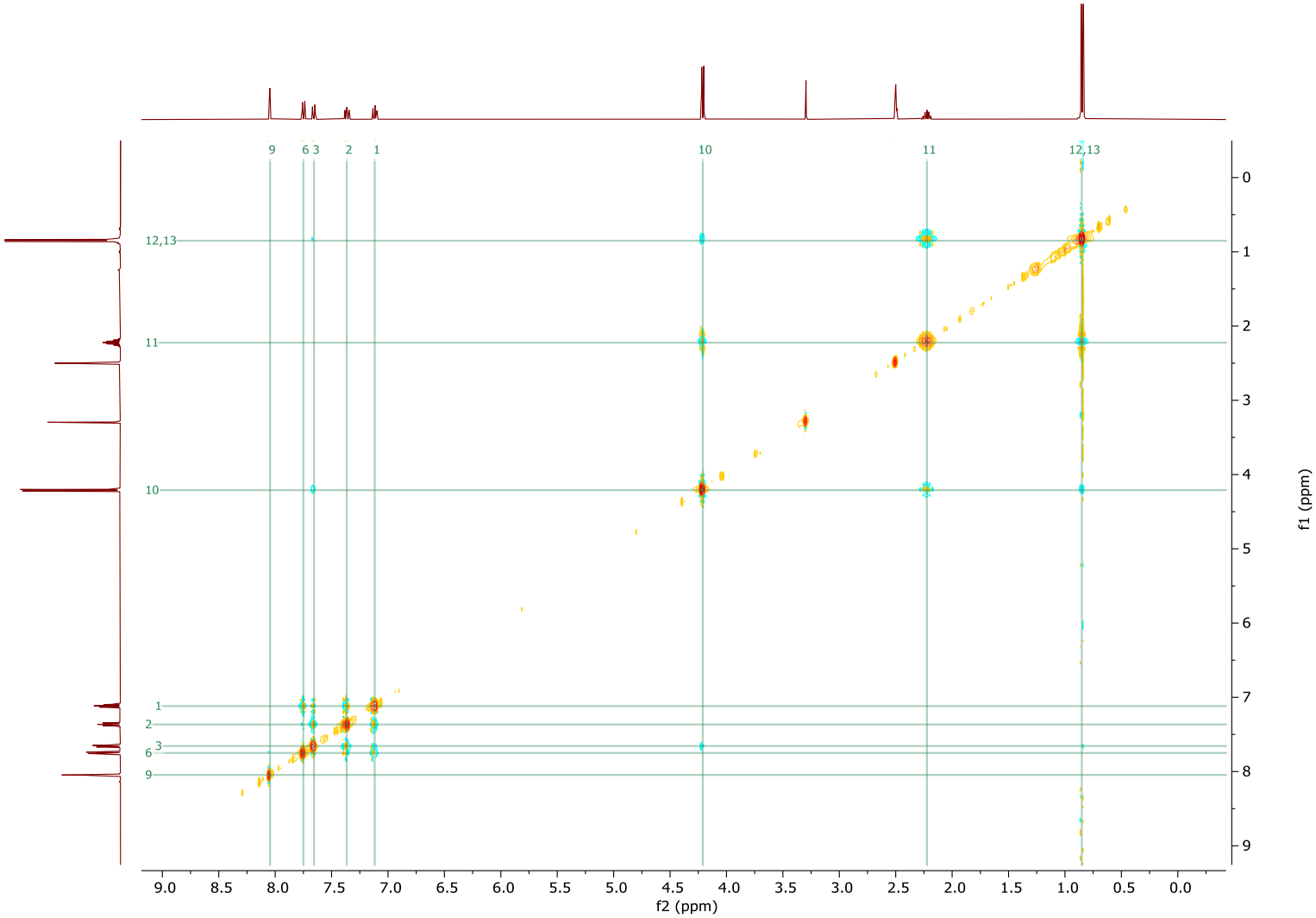
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

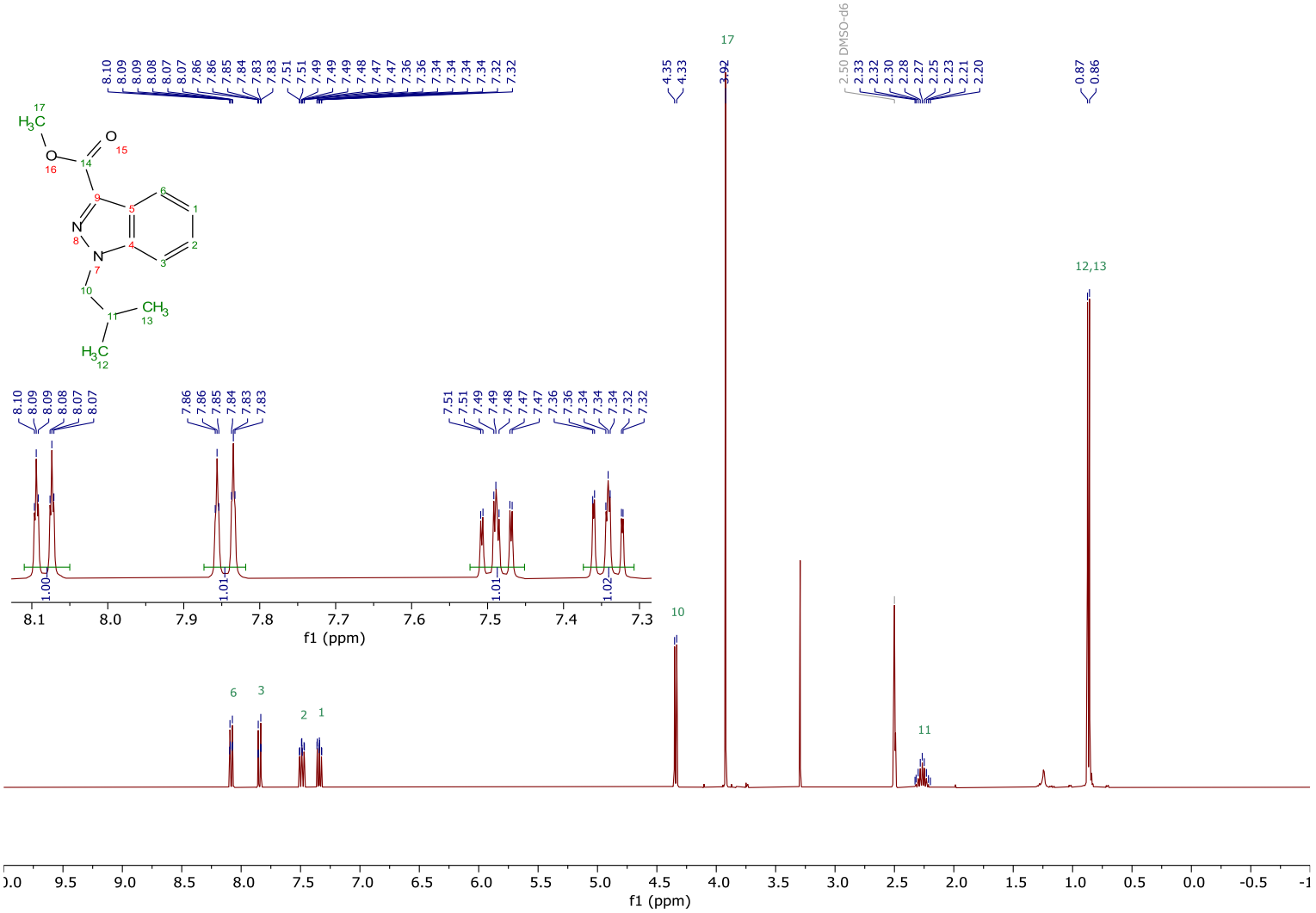


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

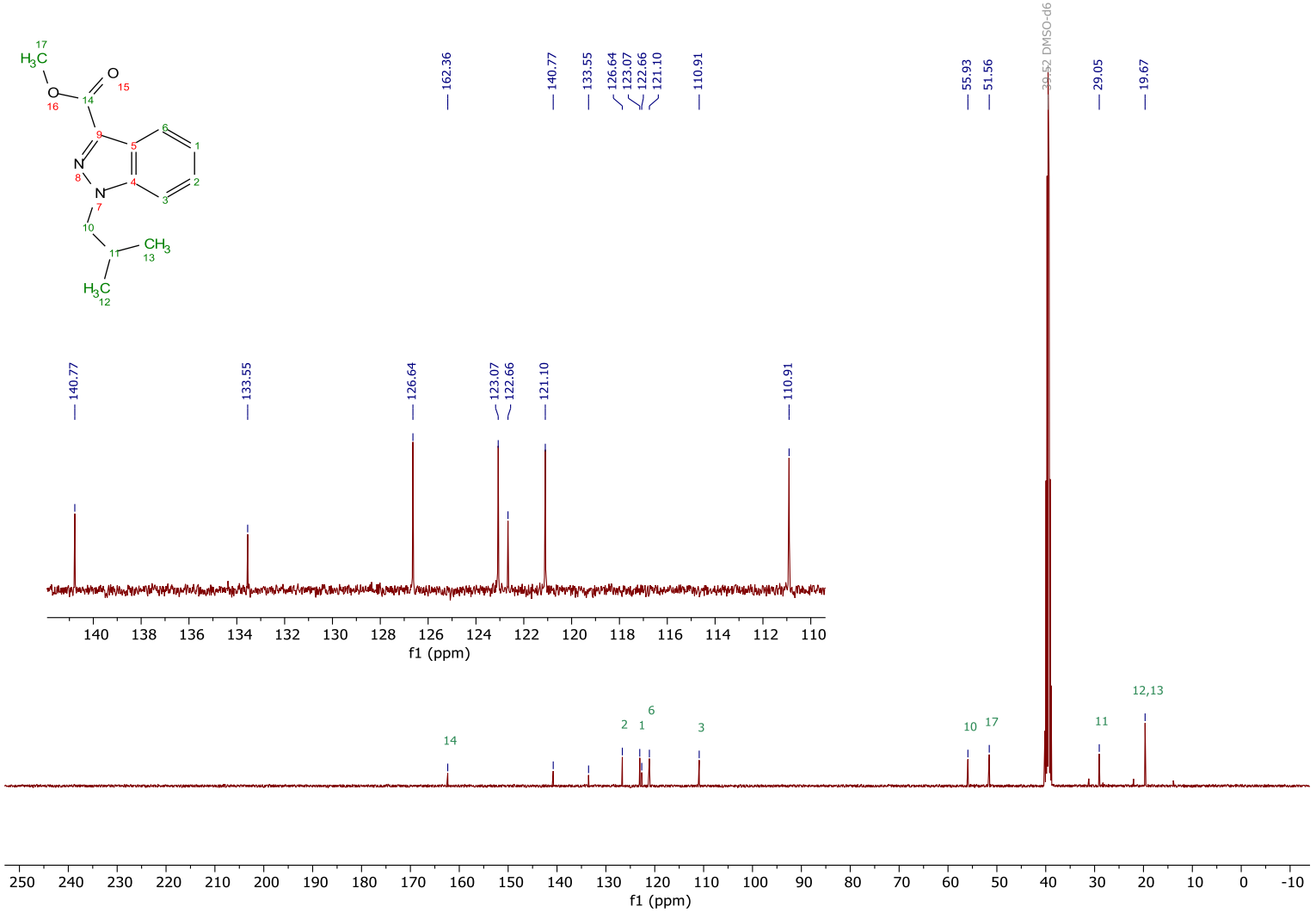


Methyl 1-isobutyl-1*H*-indazole-3-carboxylate (2c)

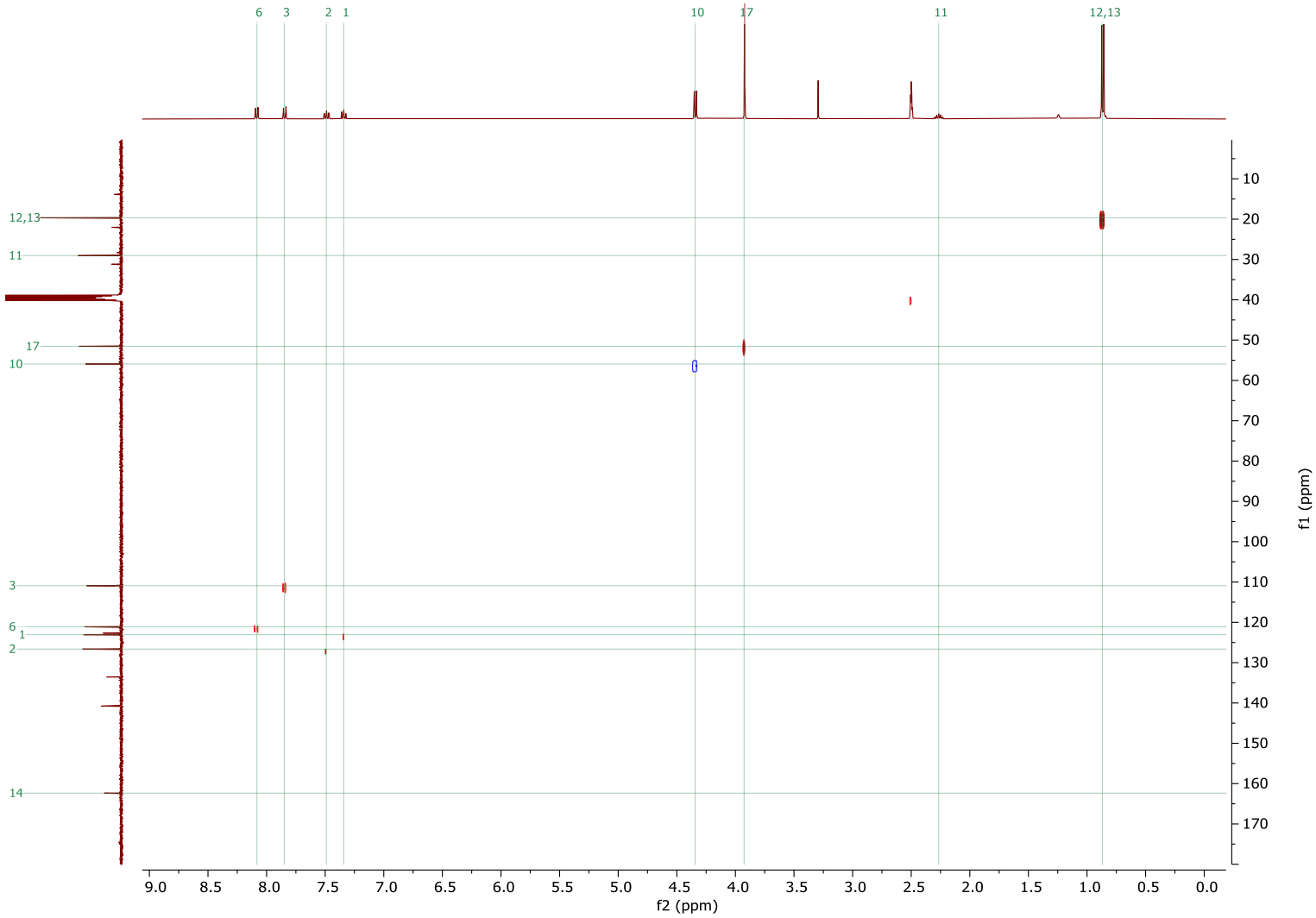
^{1}H NMR (400 MHz, DMSO-d_6)



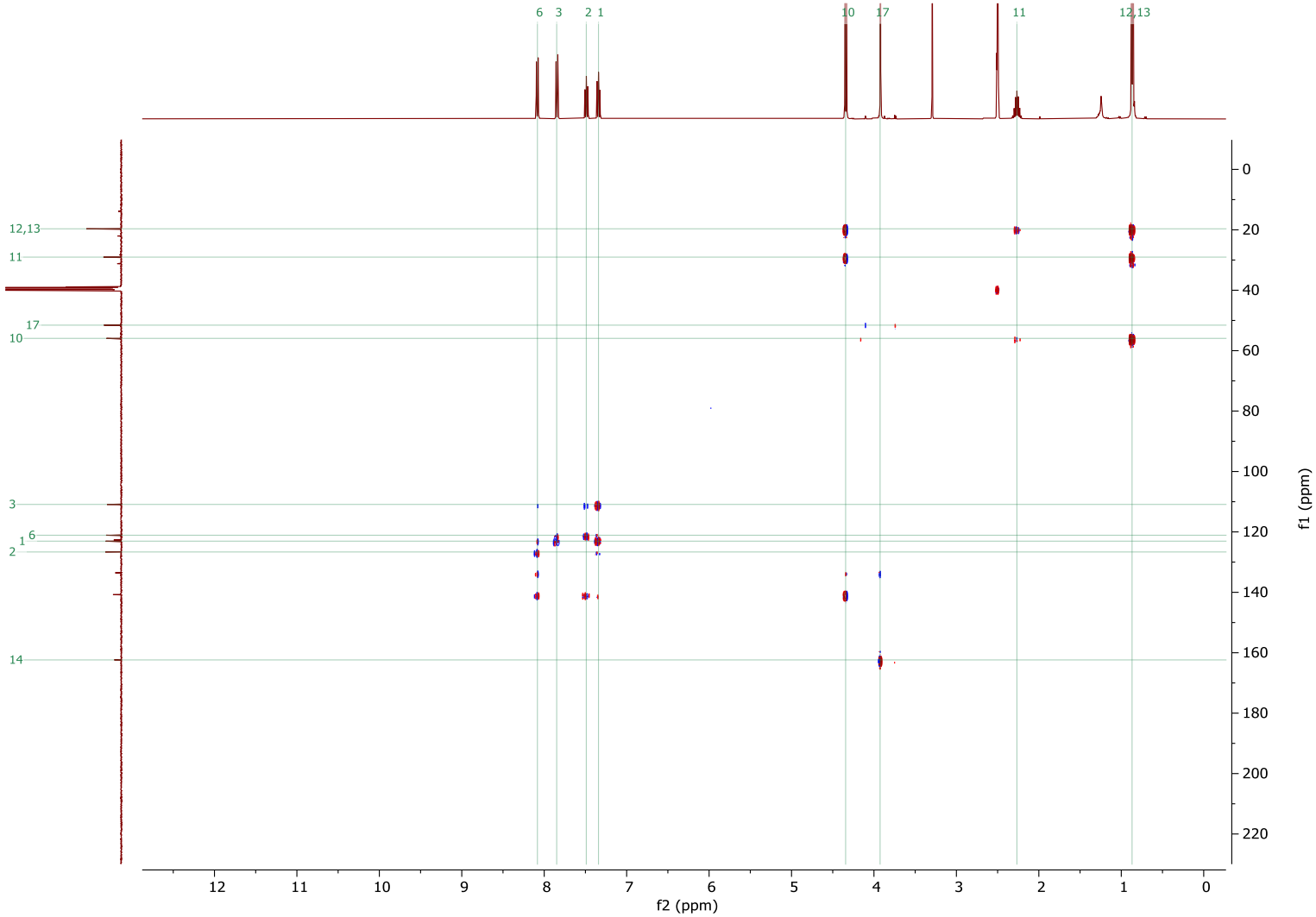
^{13}C NMR (101 MHz, DMSO-d_6)



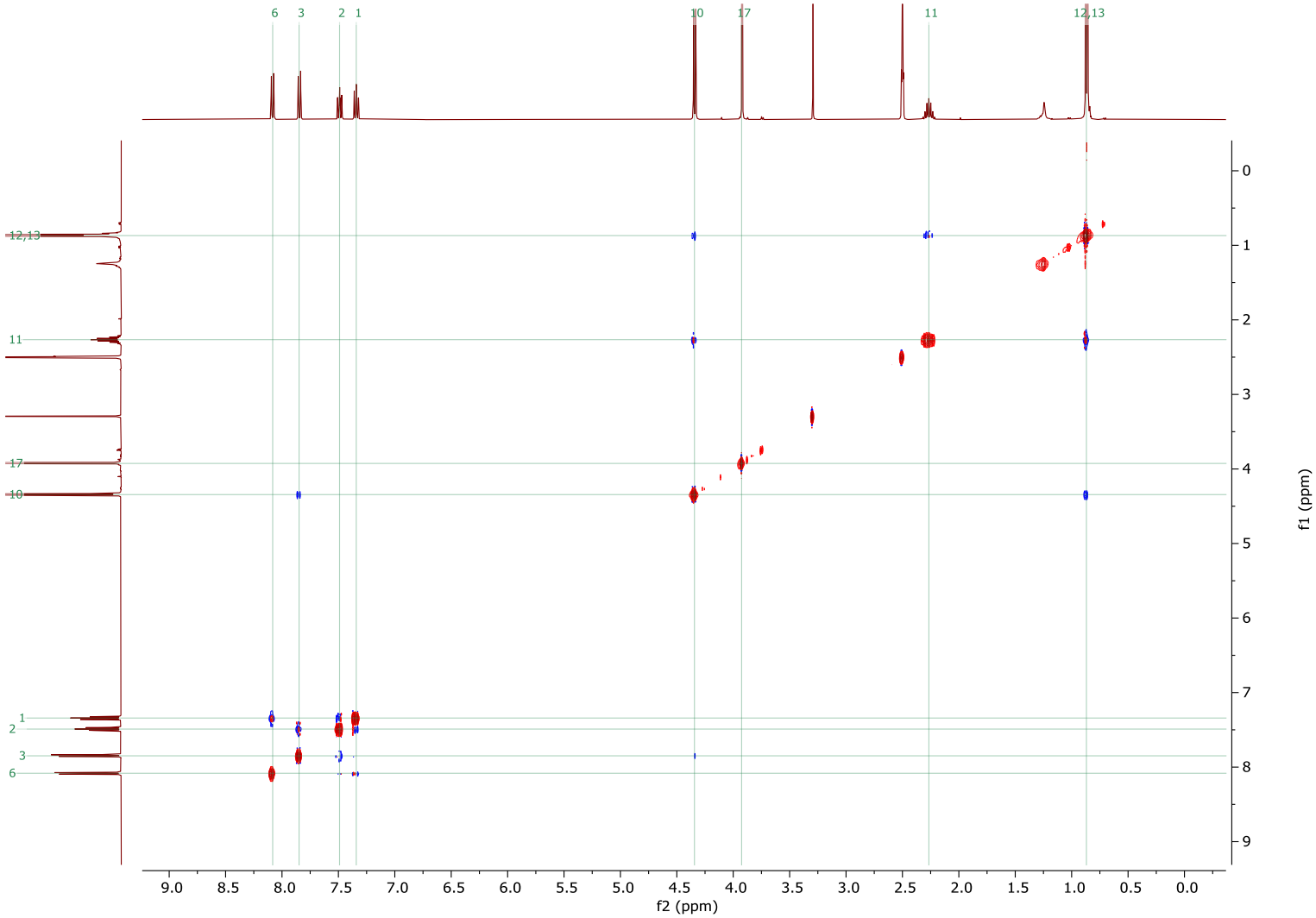
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

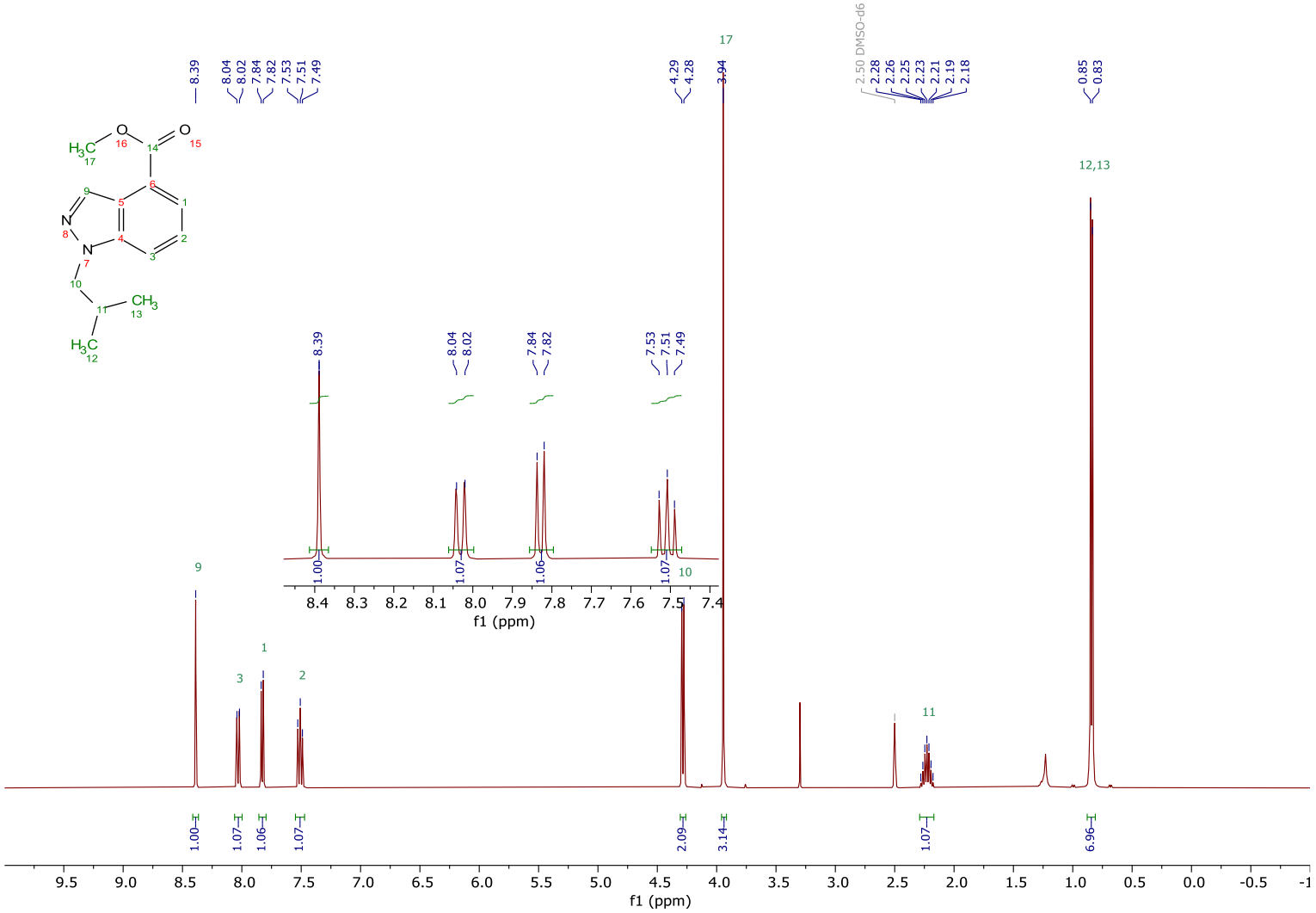


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

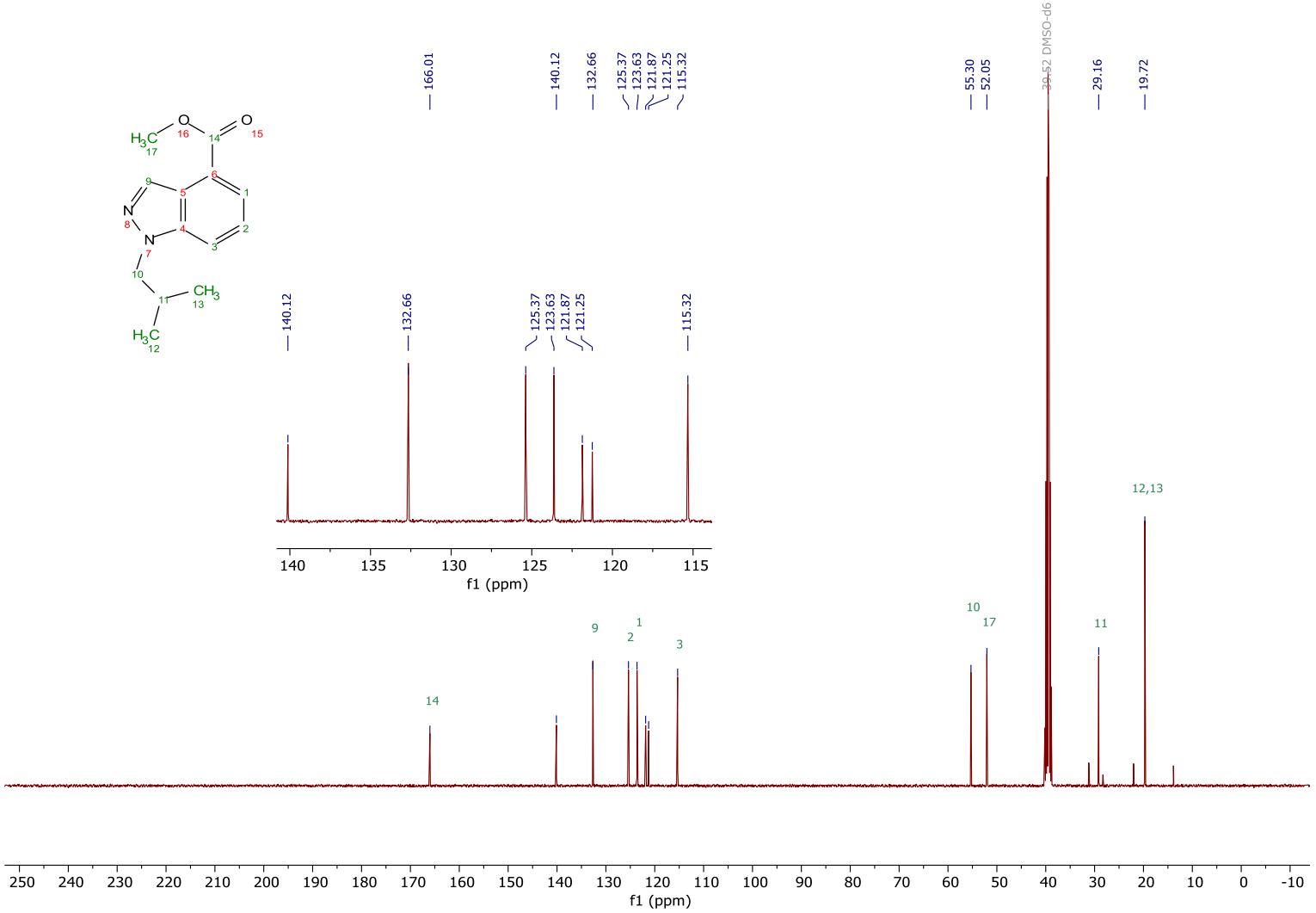


Methyl 1-isobutyl-1*H*-indazole-4-carboxylate (2d)

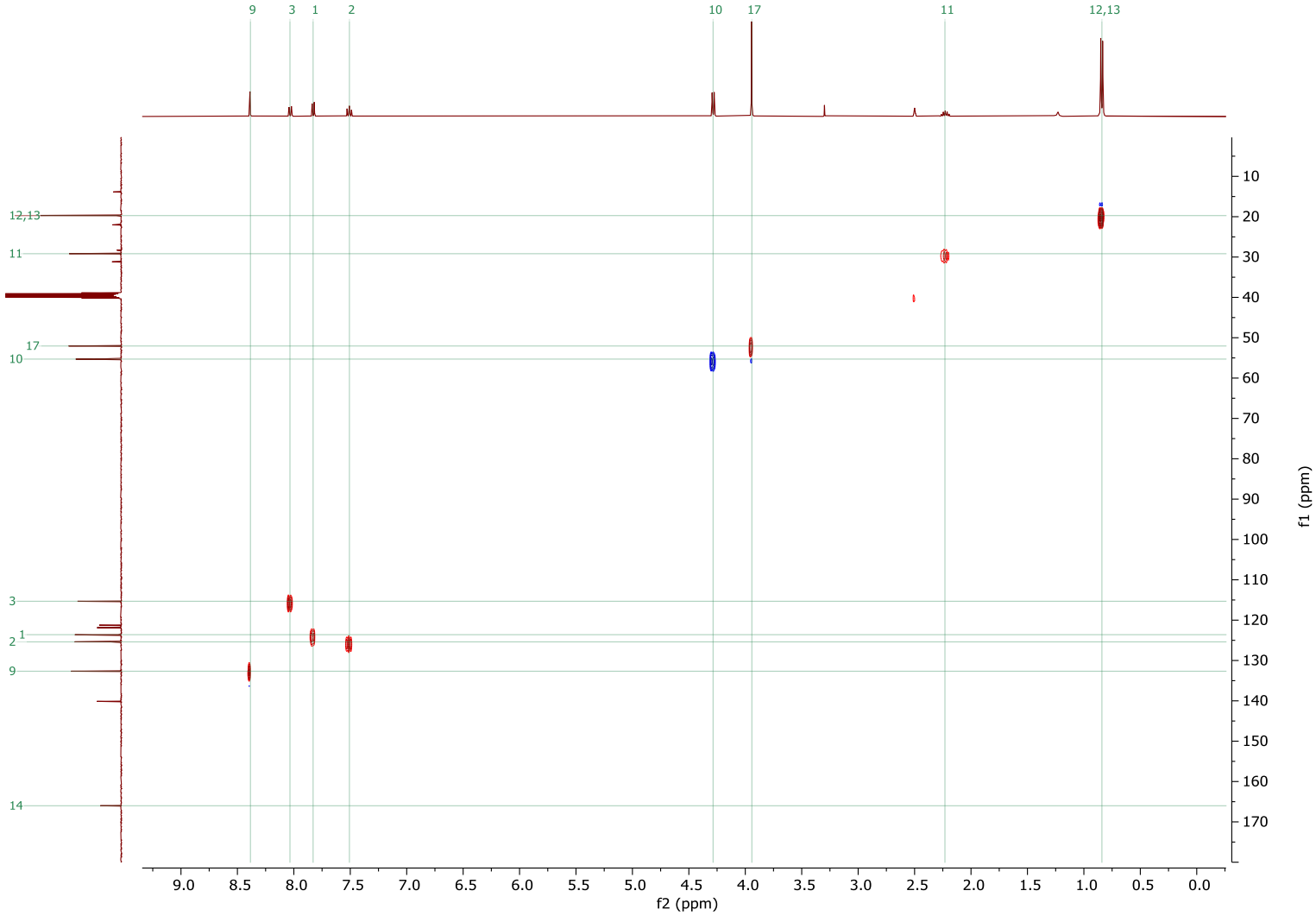
^{1}H NMR (400 MHz, DMSO-d_6)



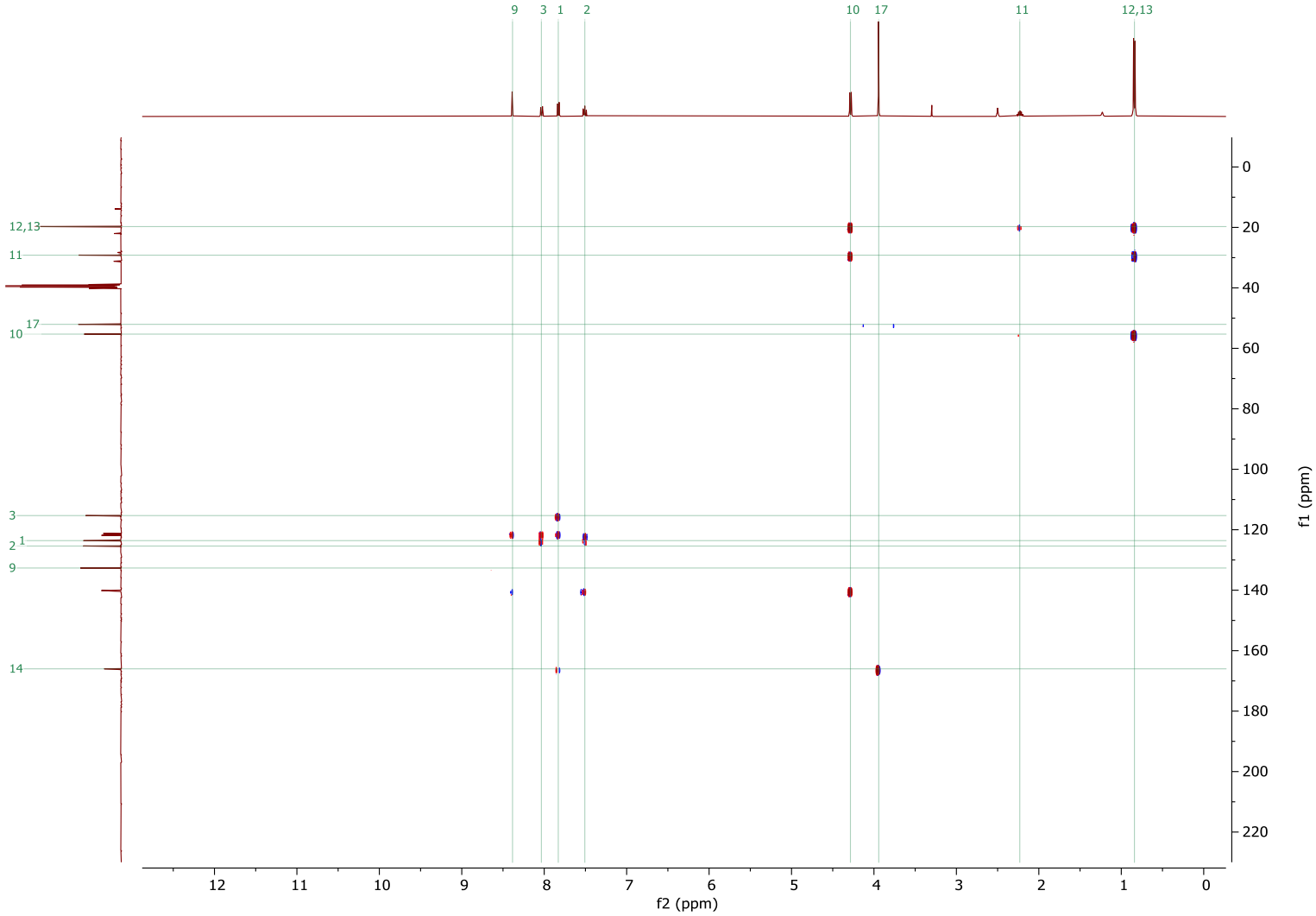
^{13}C NMR (101 MHz, DMSO-d_6)



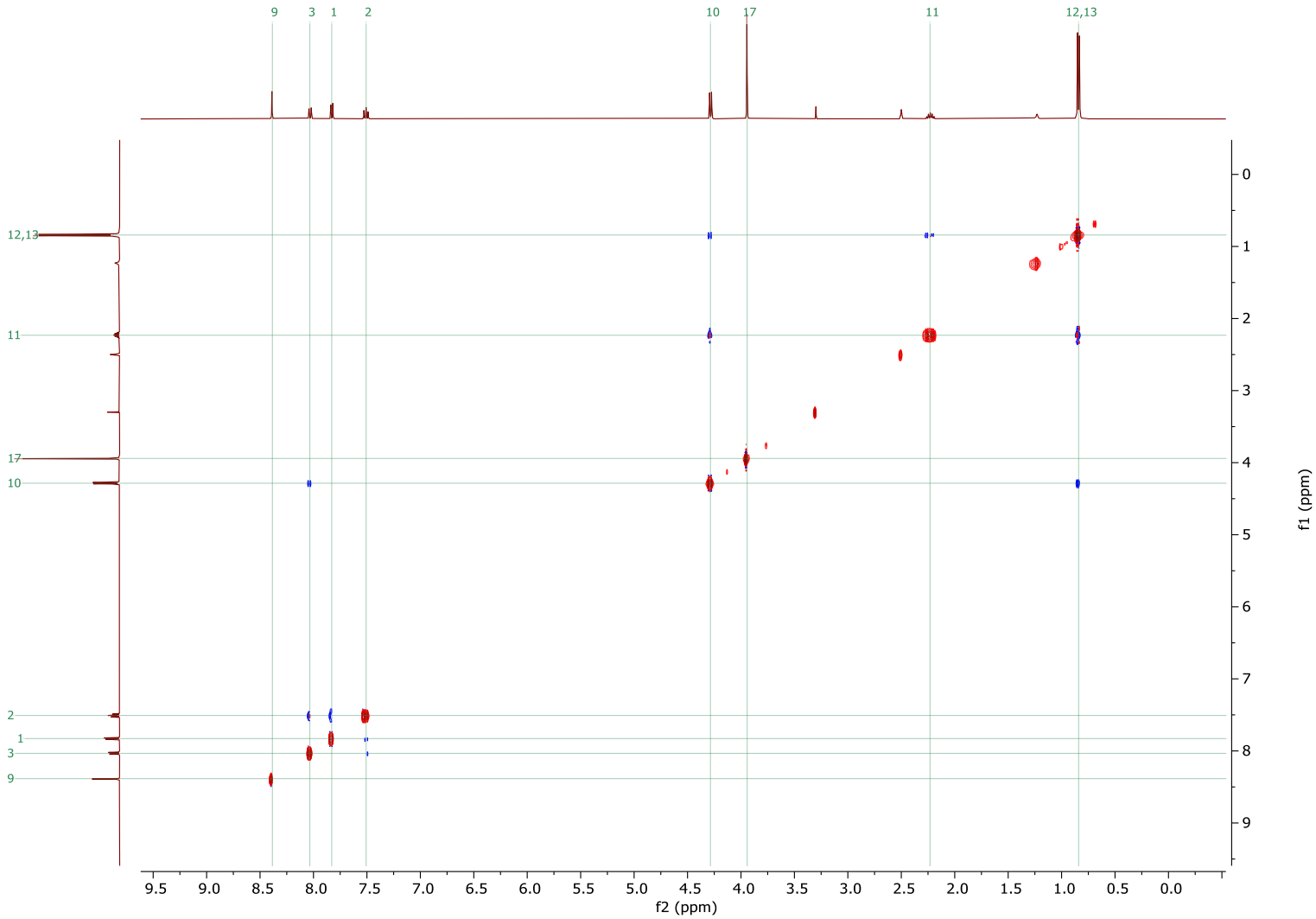
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

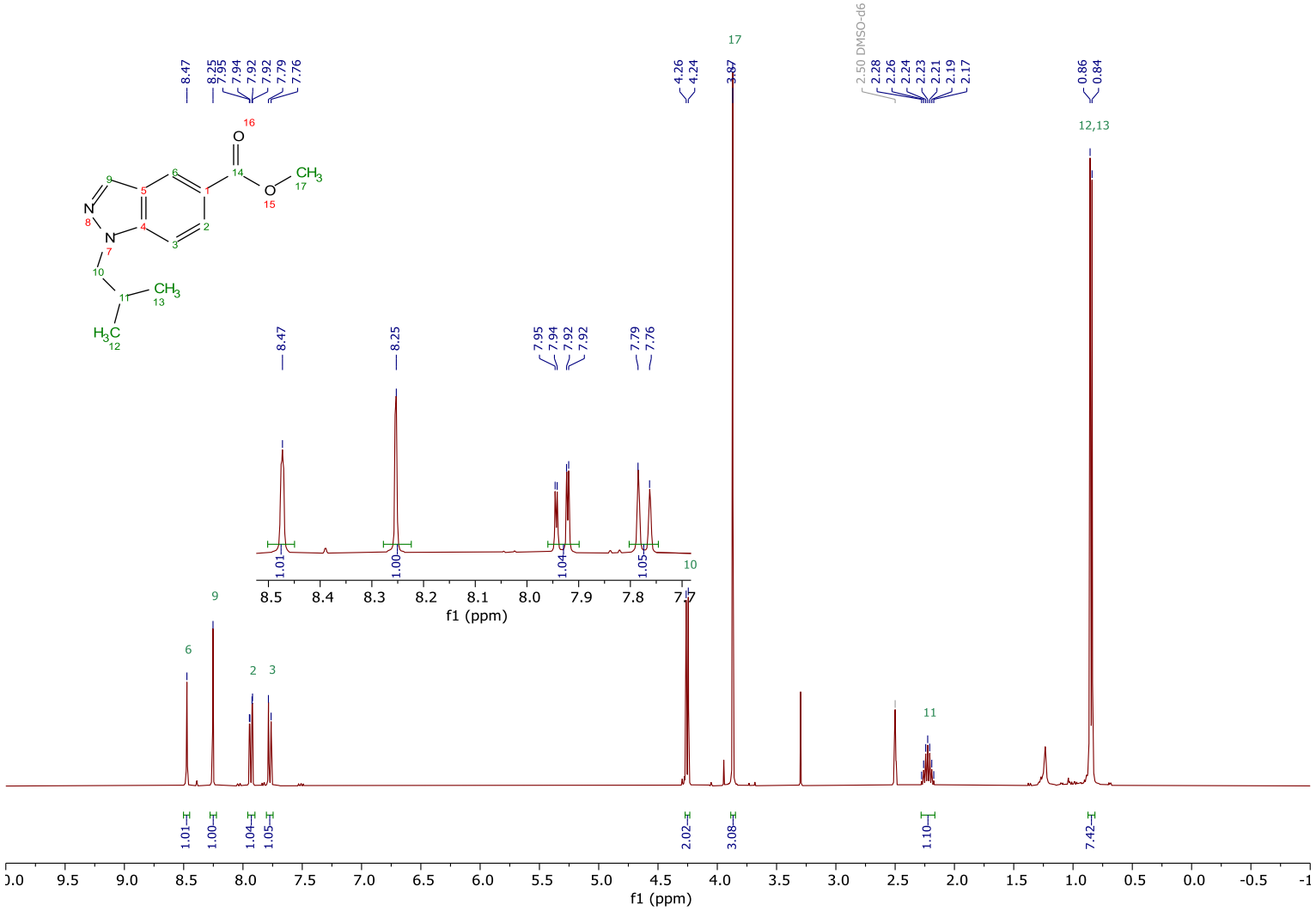


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

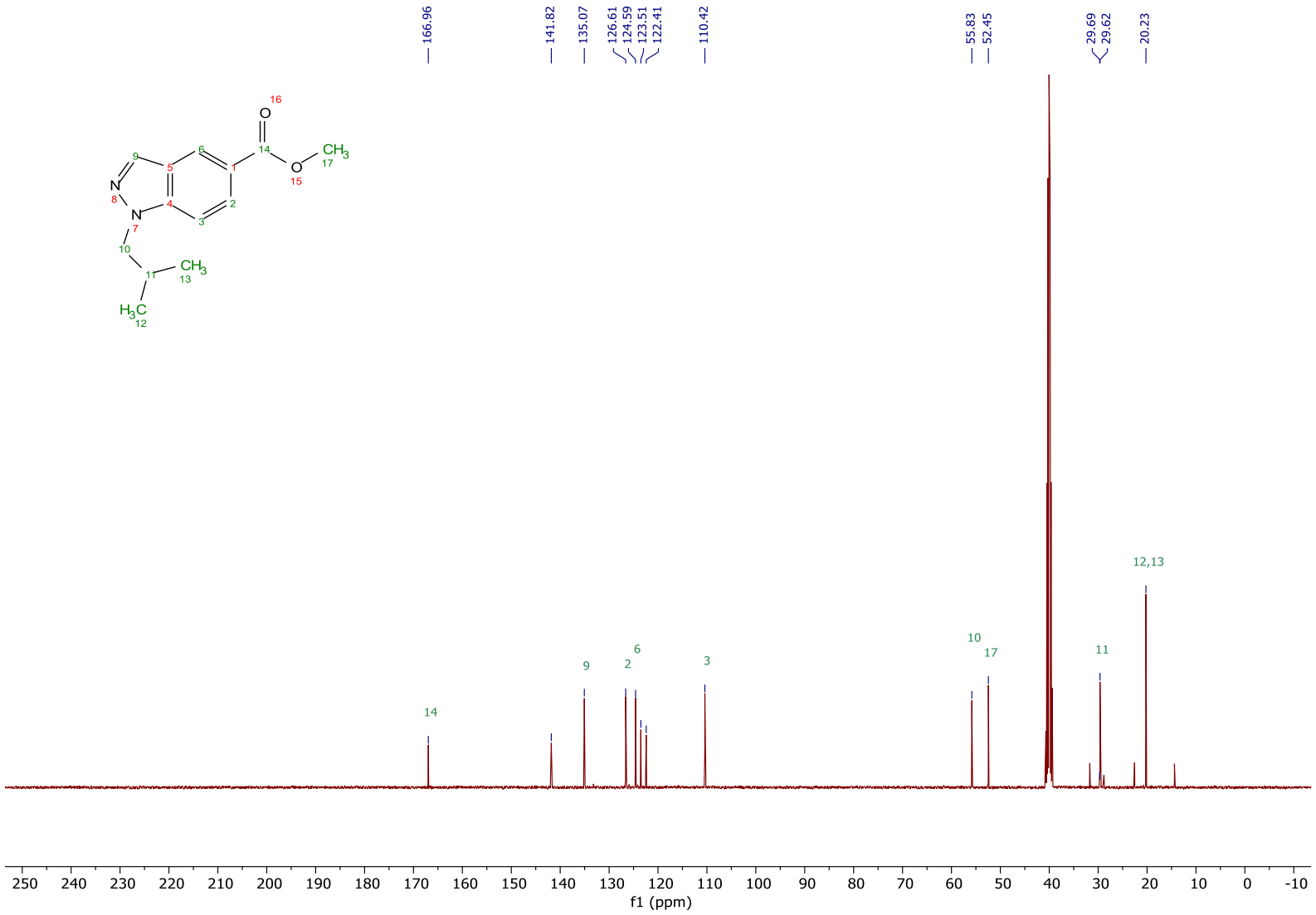


Methyl 1-isobutyl-1*H*-indazole-5-carboxylate (2e)

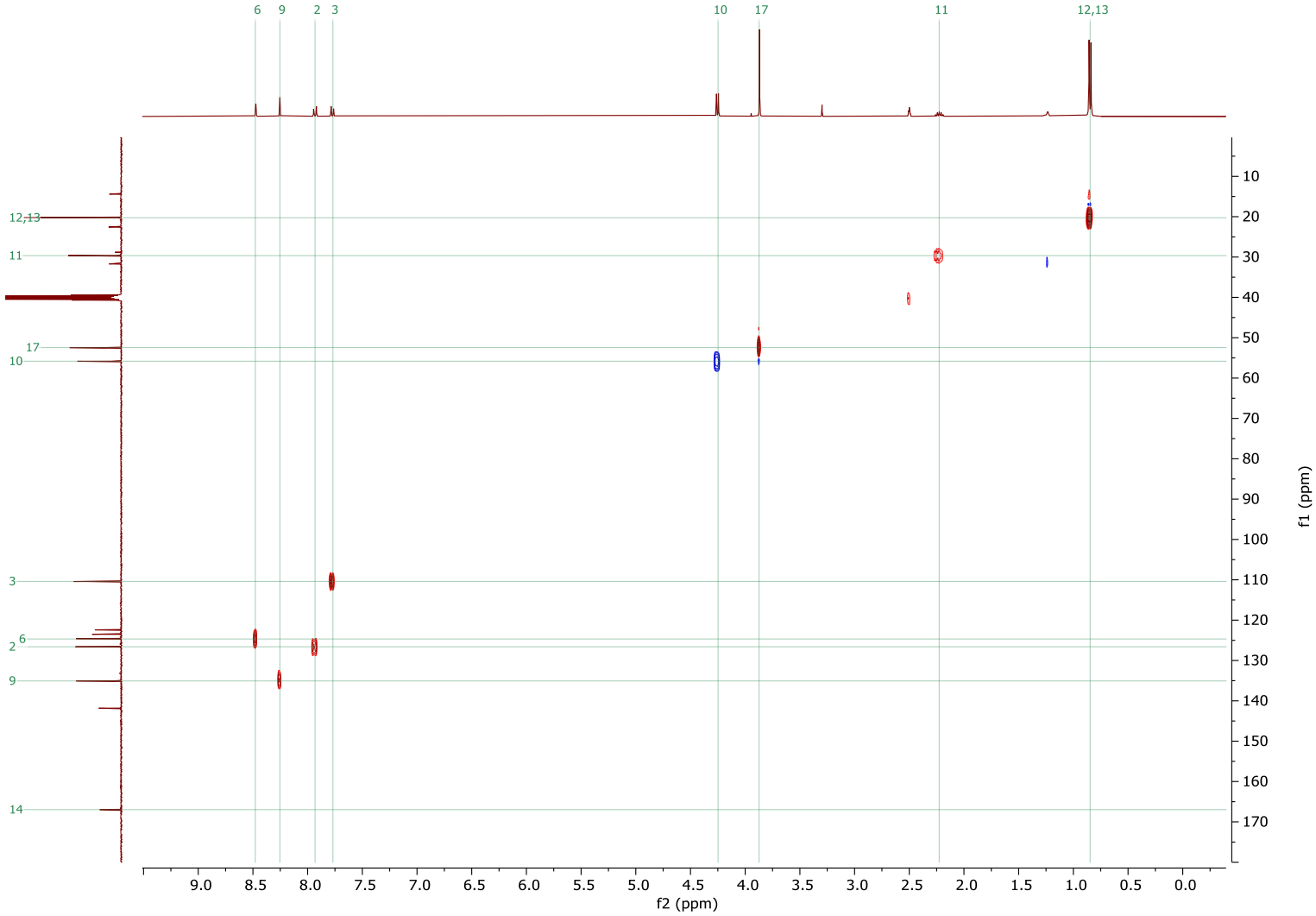
^{1}H NMR (400 MHz, DMSO-d_6)



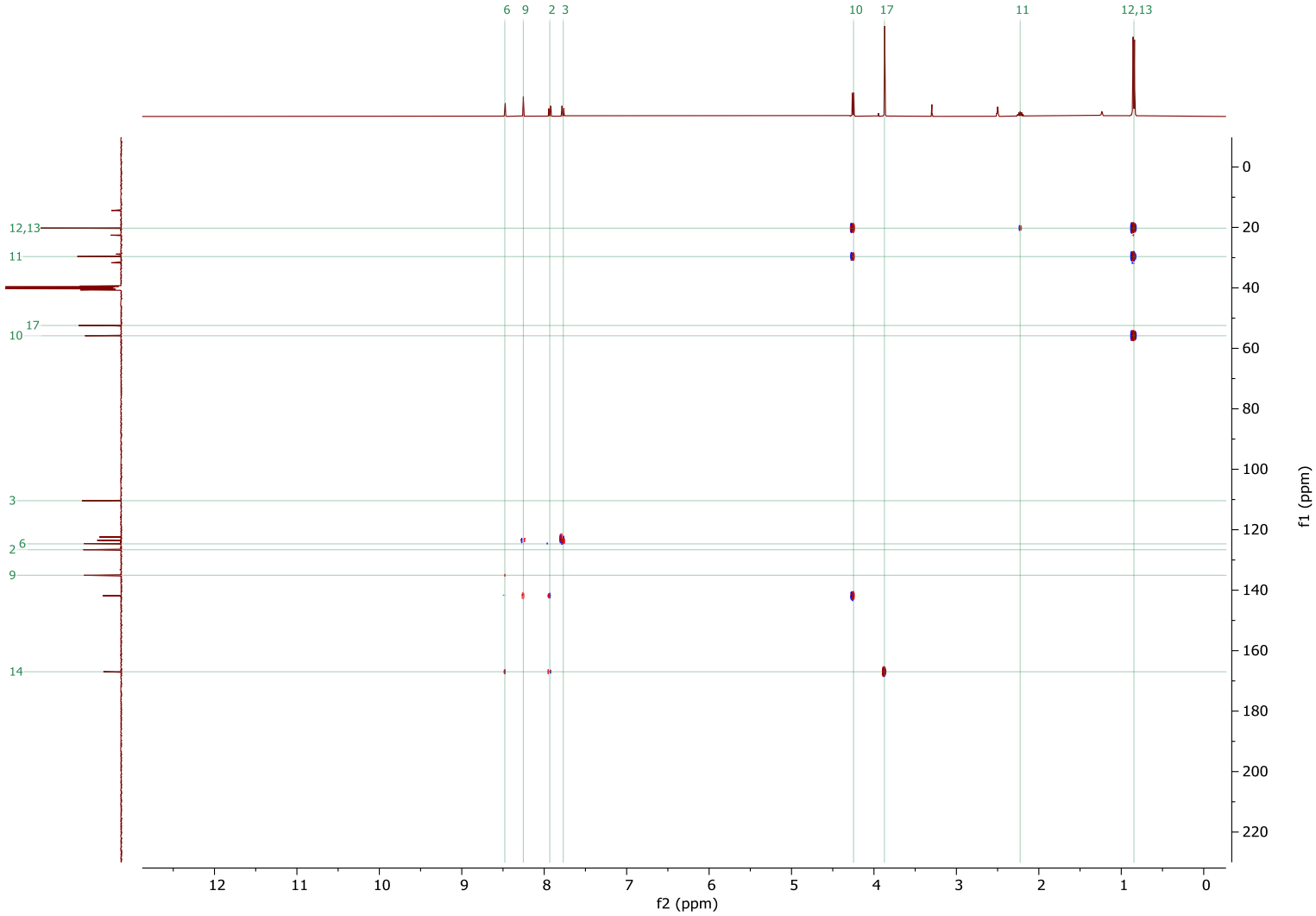
^{13}C NMR (101 MHz, DMSO-d_6)



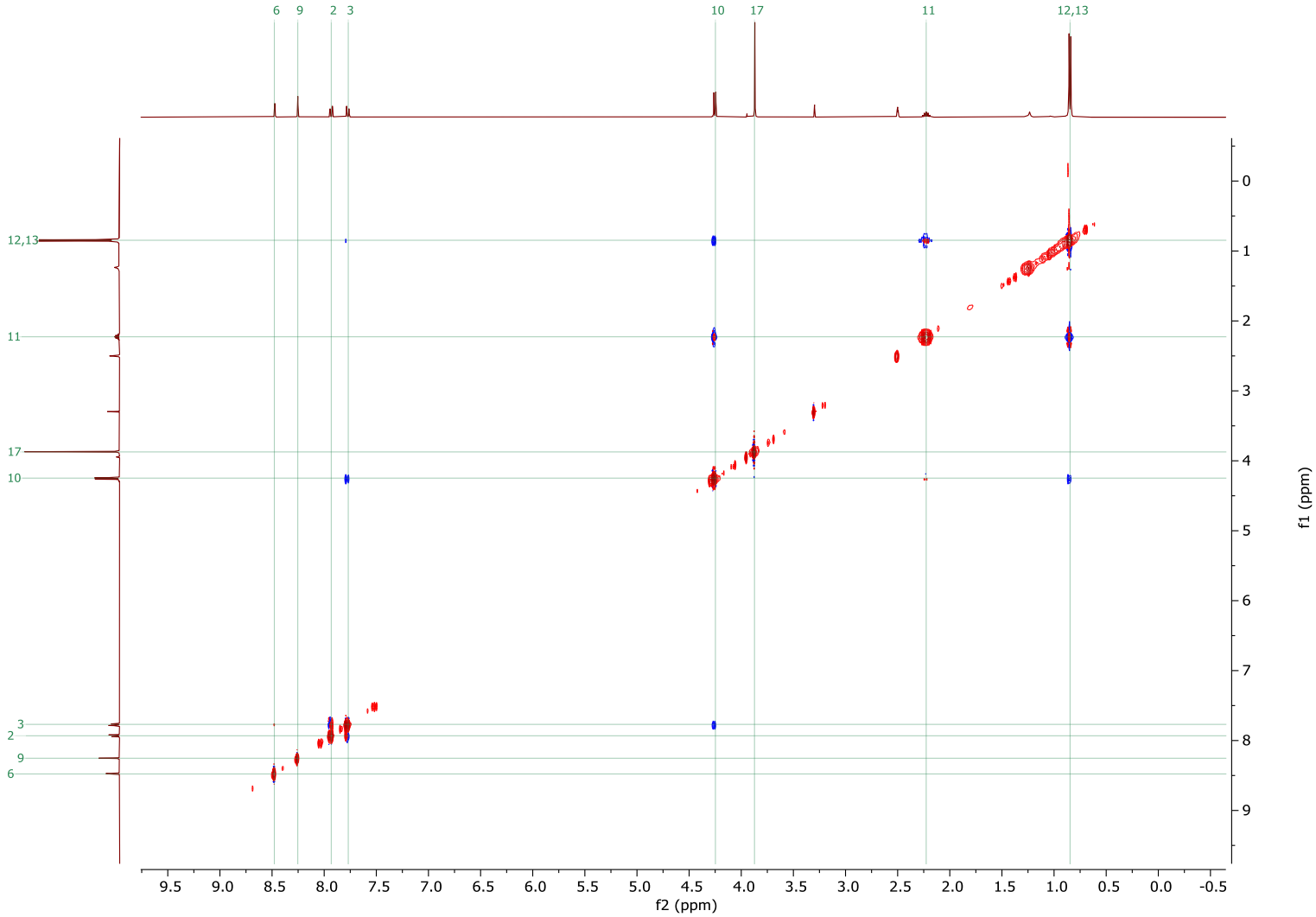
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

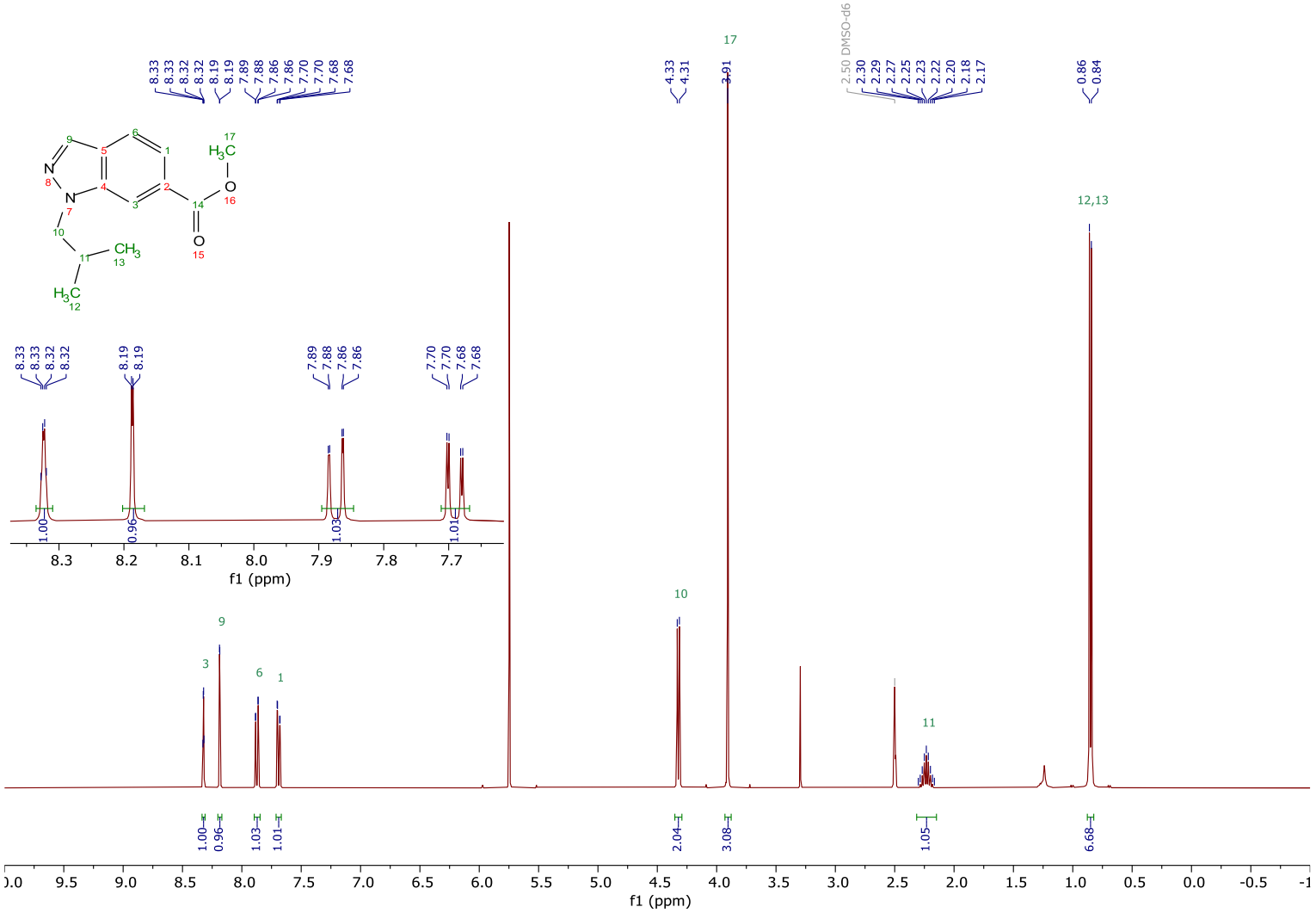


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

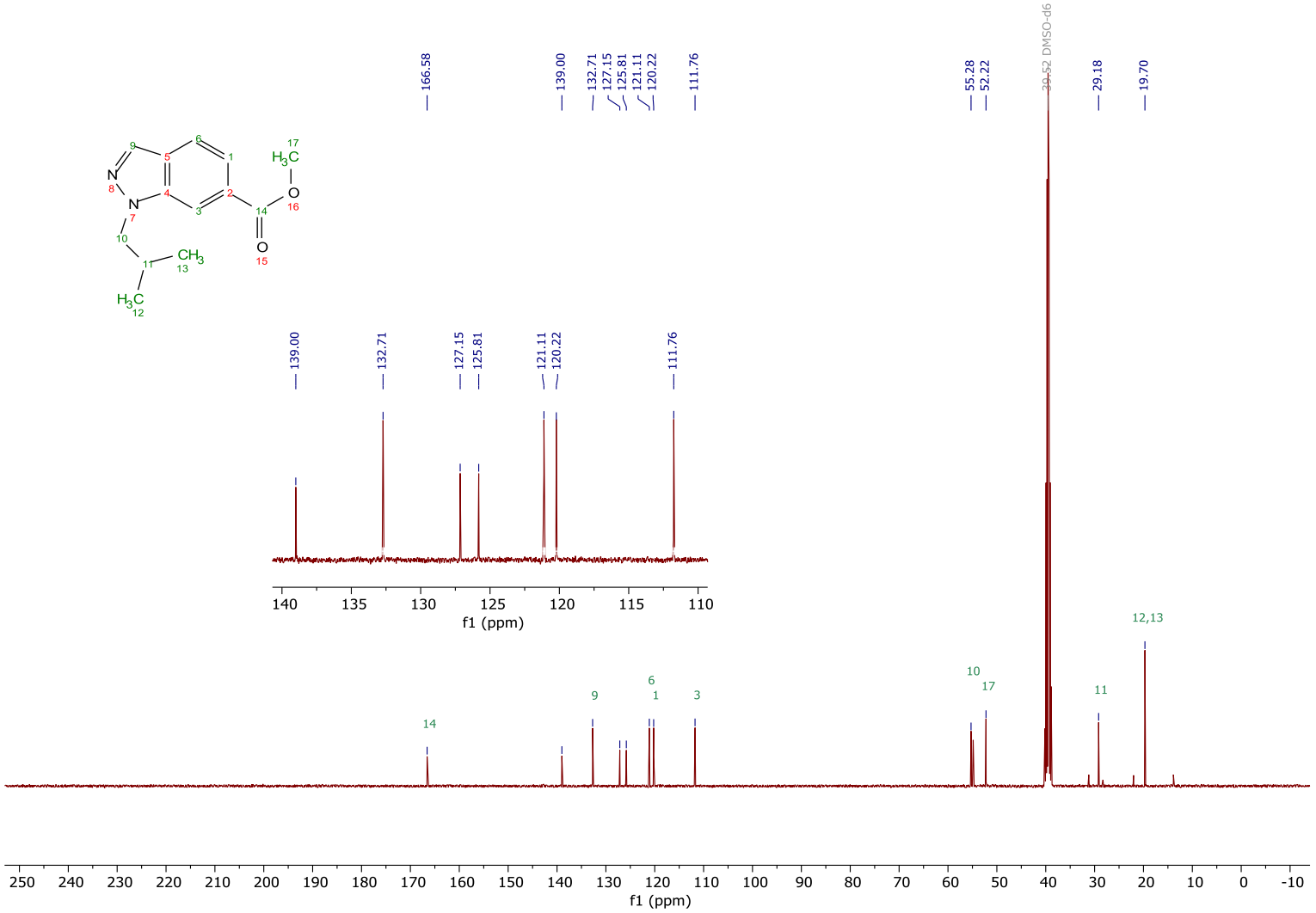


Methyl 1-isobutyl-1*H*-indazole-6-carboxylate (2f)

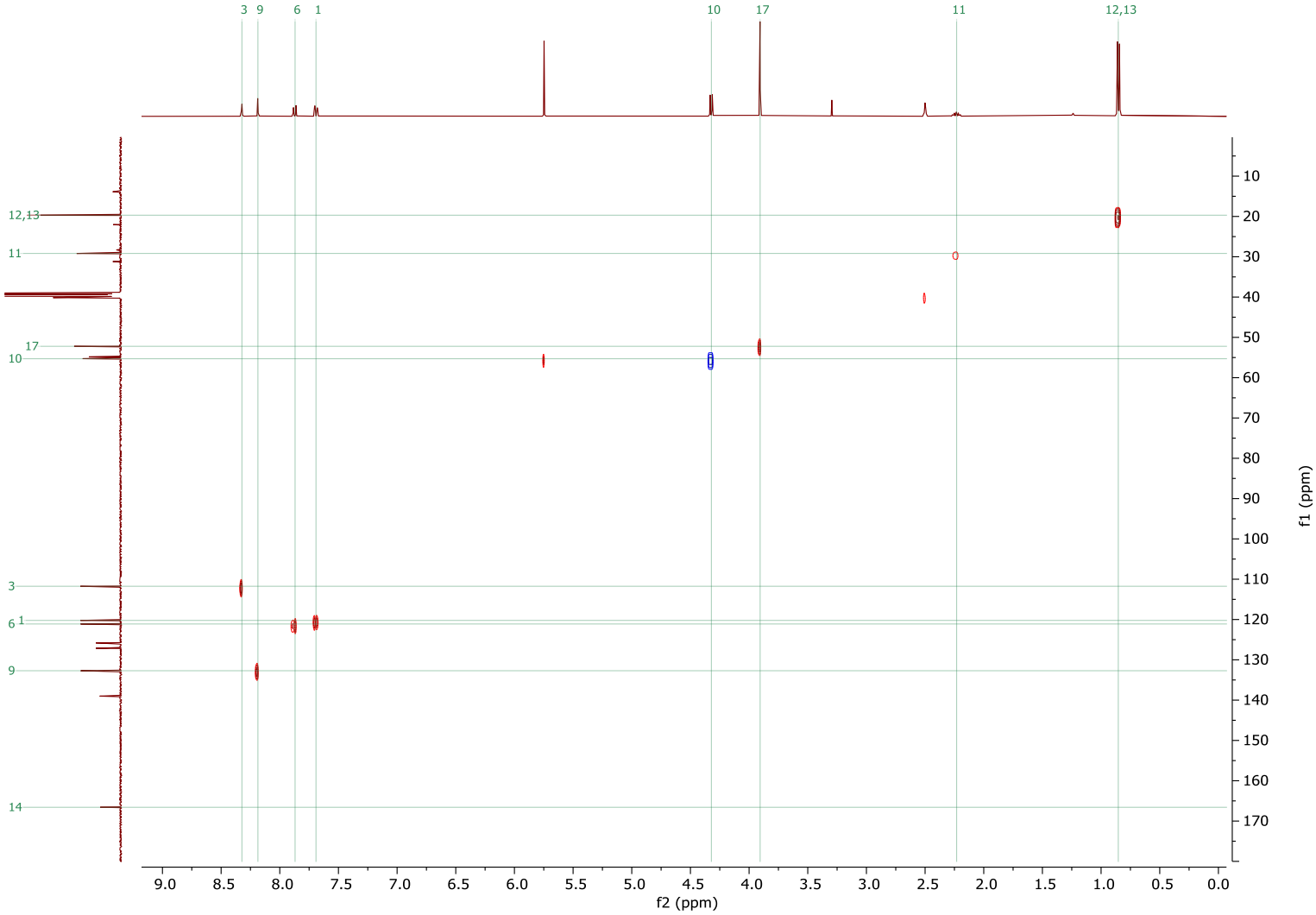
^{1}H NMR (400 MHz, DMSO-d_6)



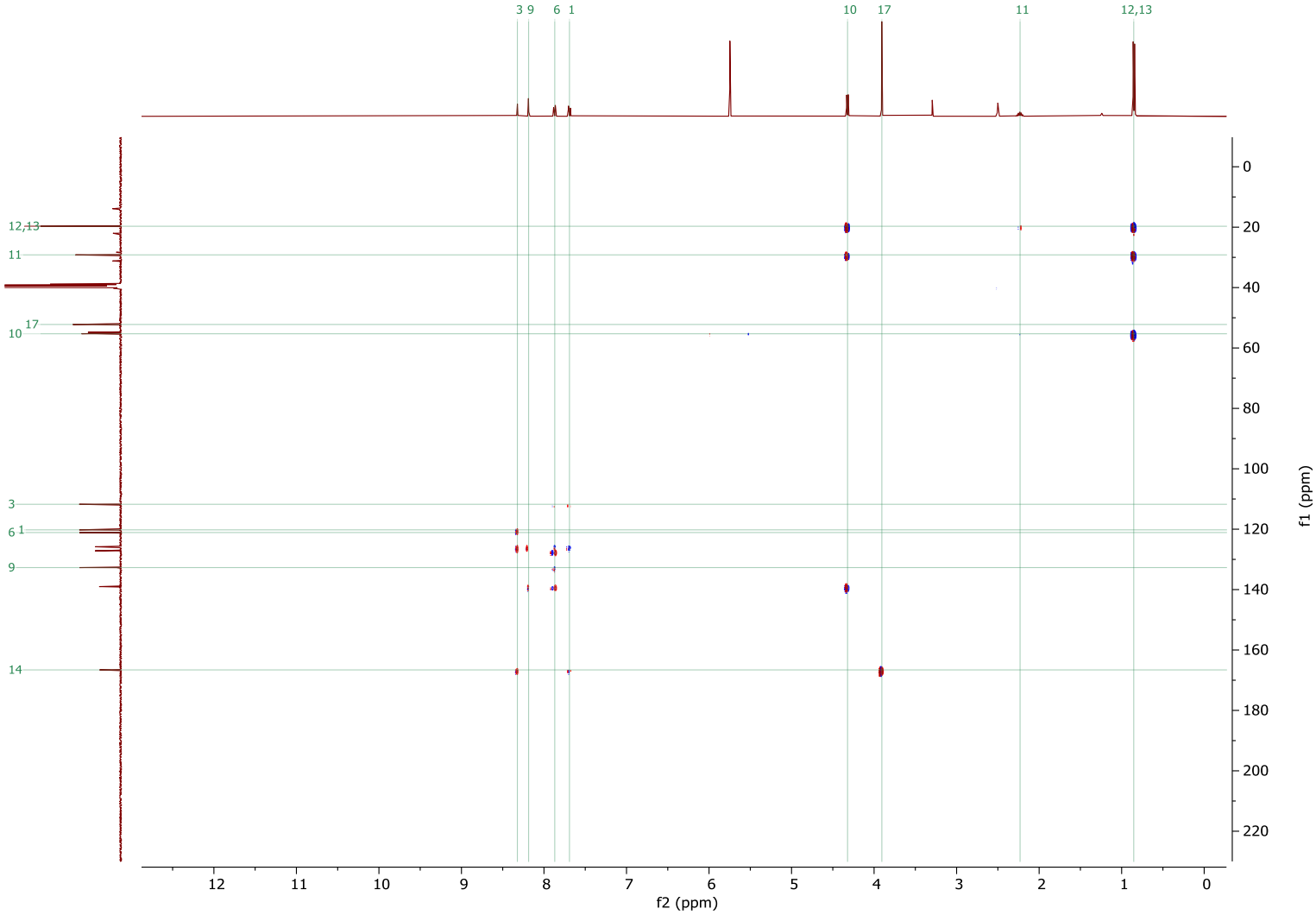
^{13}C NMR (101 MHz, DMSO-d_6)



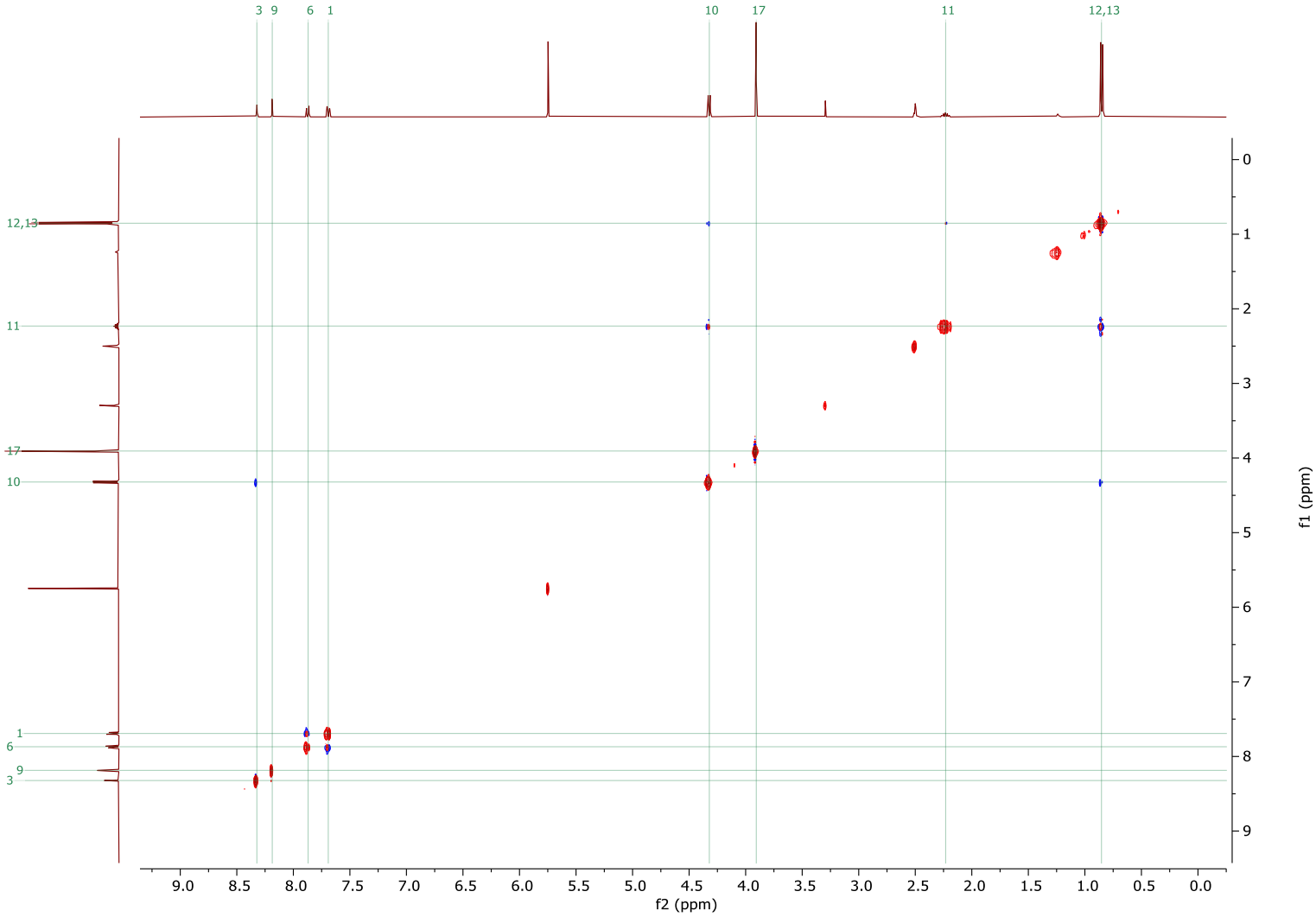
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

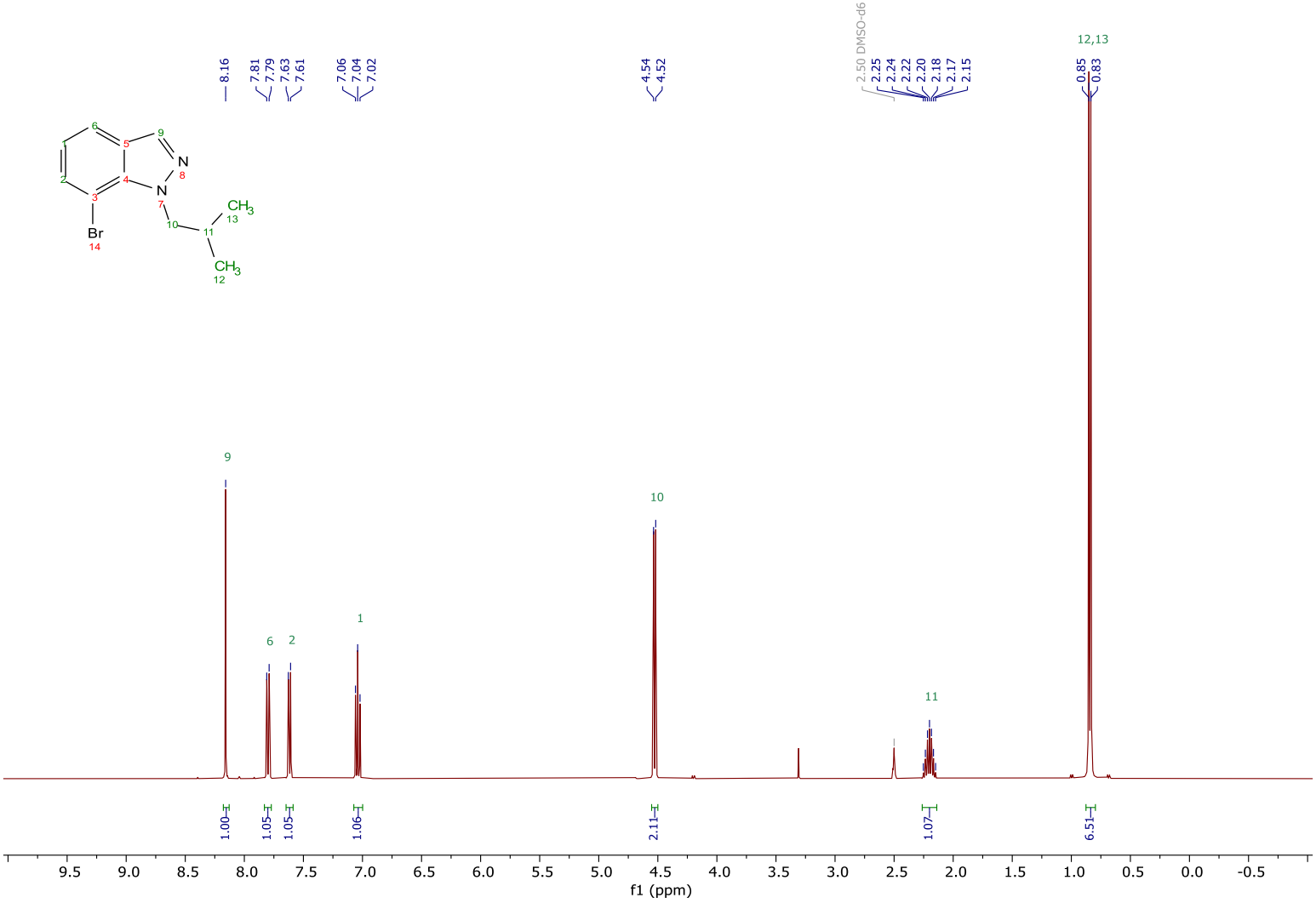


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

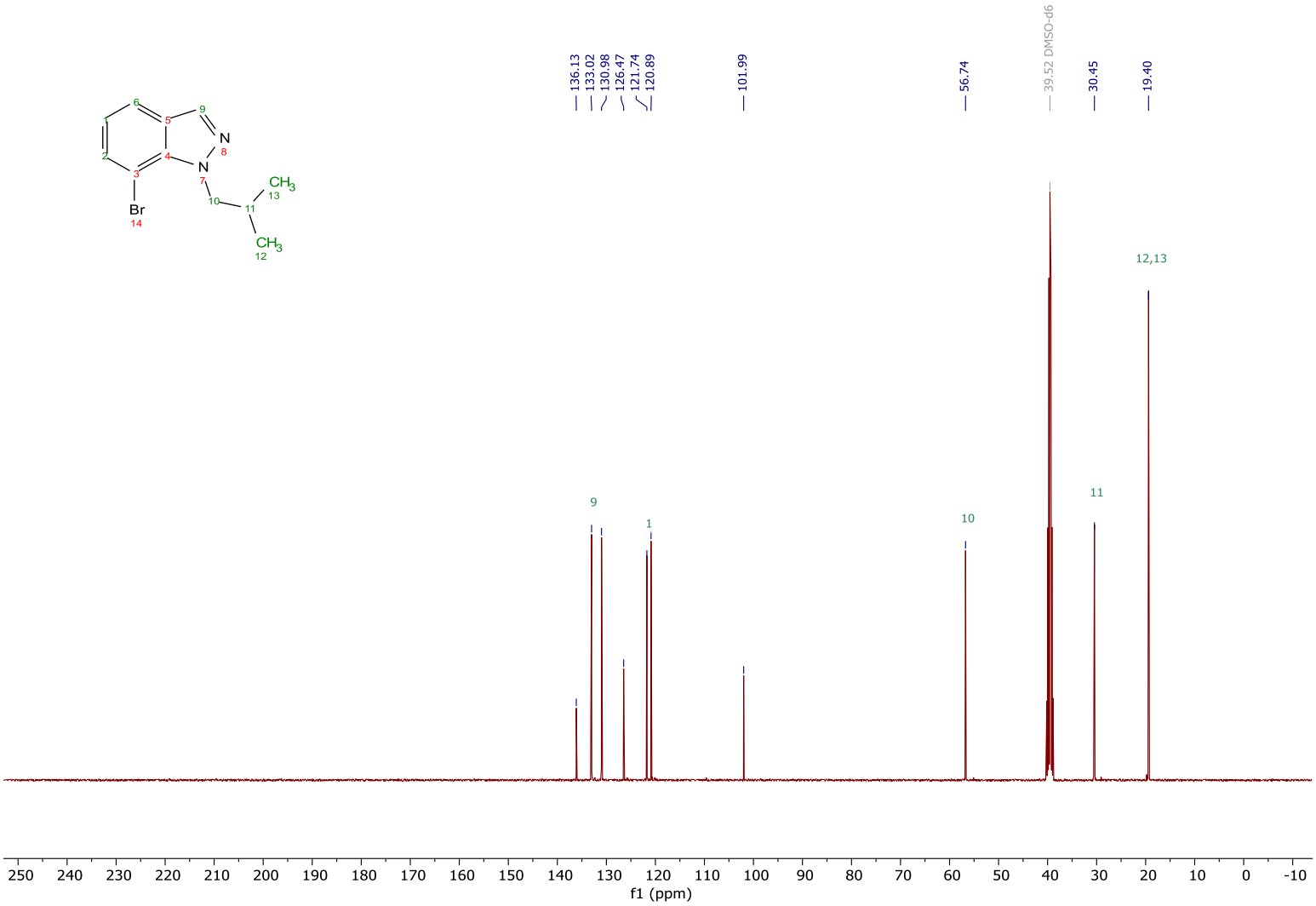


7-bromo-1-isobutyl-1*H*-indazole (2h)

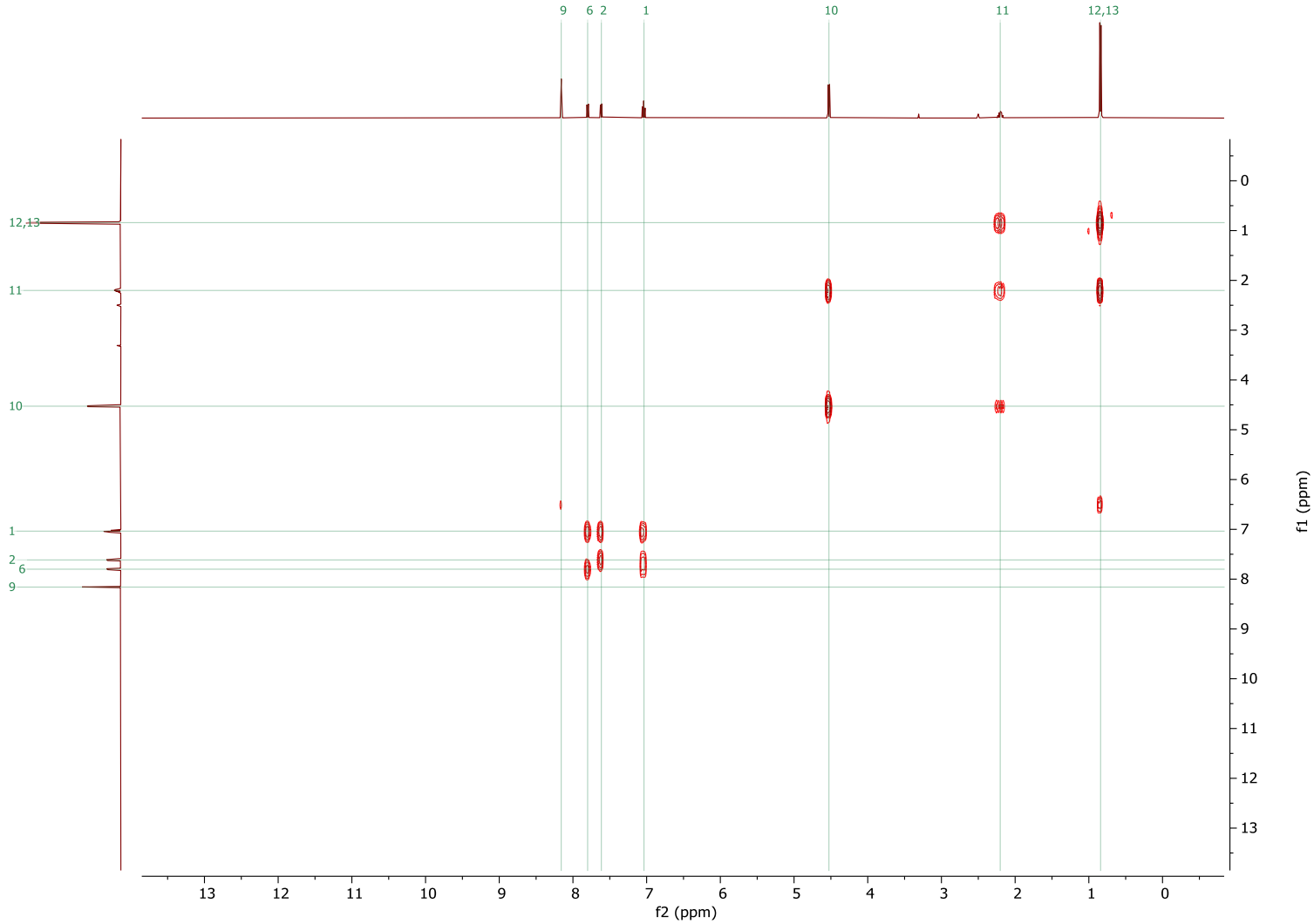
^{1}H NMR (400 MHz, DMSO-d_6)



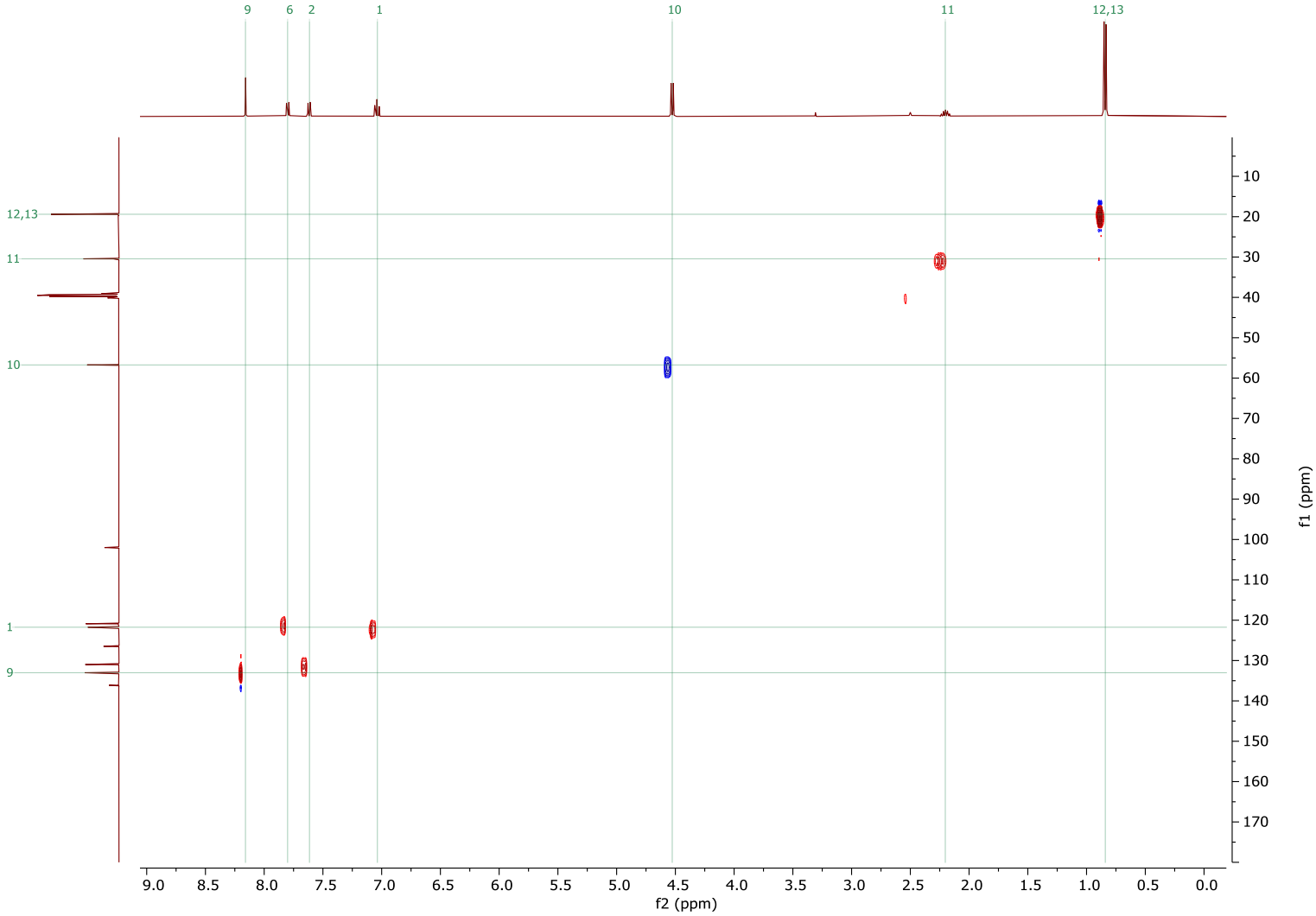
^{13}C NMR (101 MHz, DMSO-d_6)



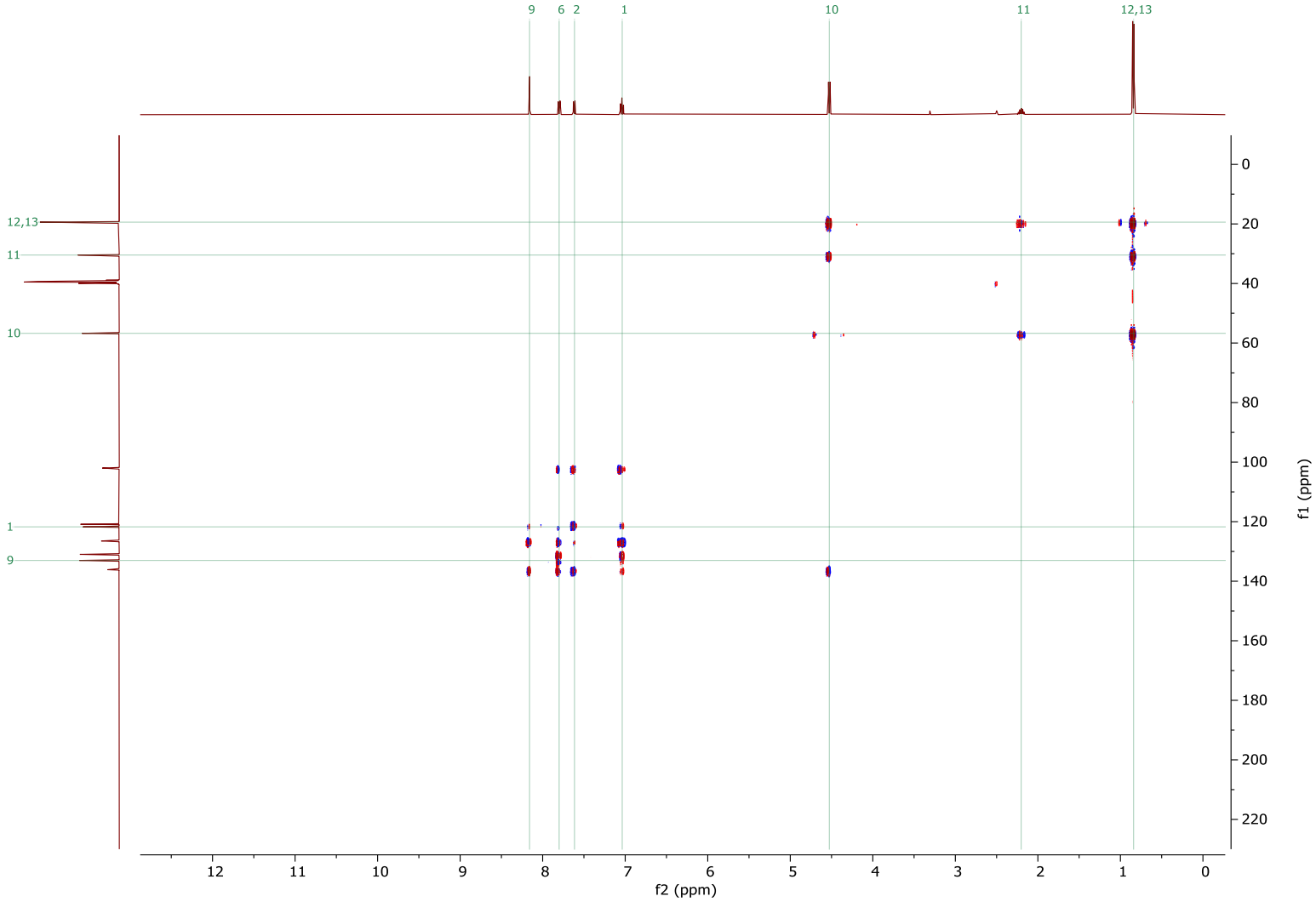
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



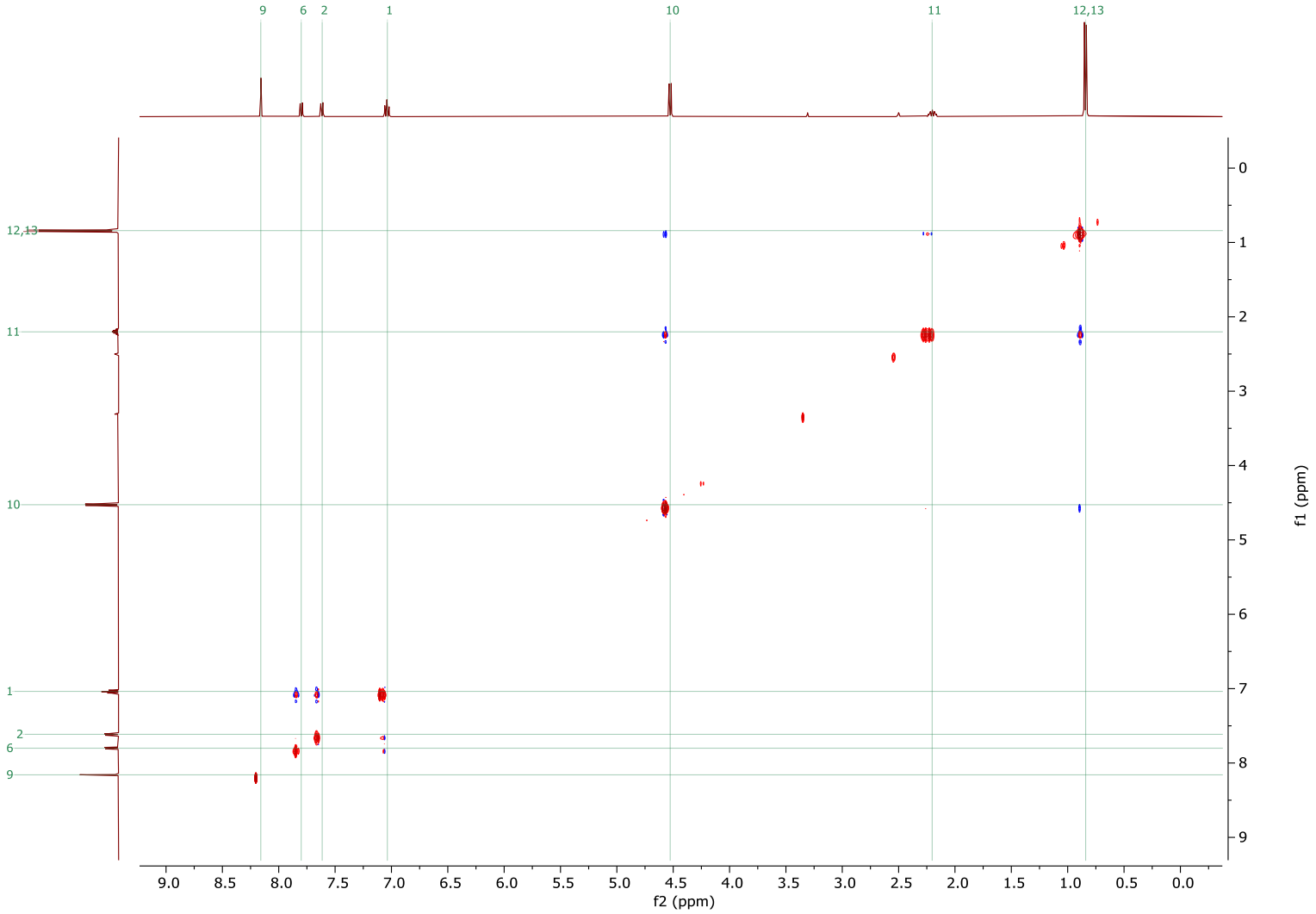
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

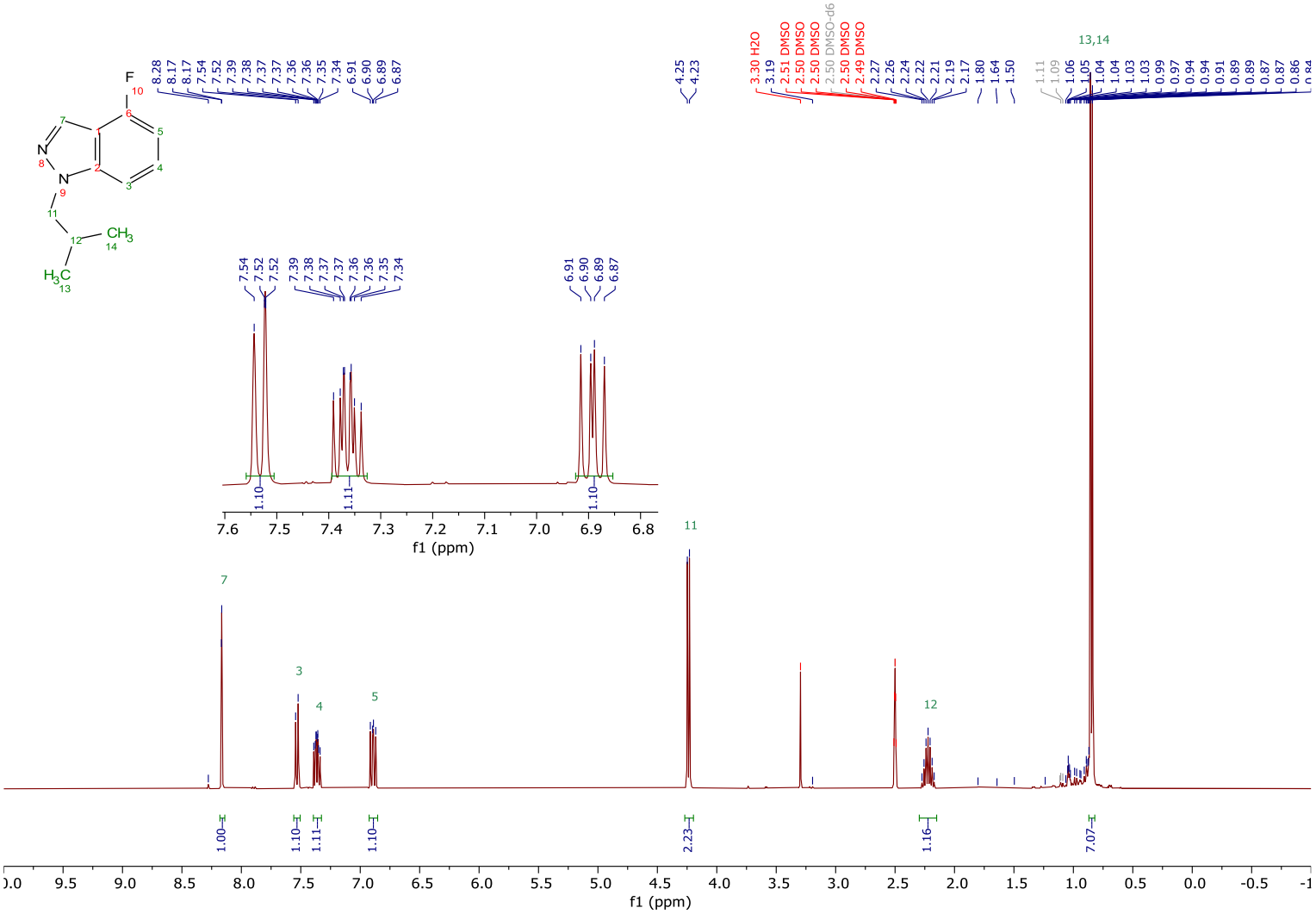


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

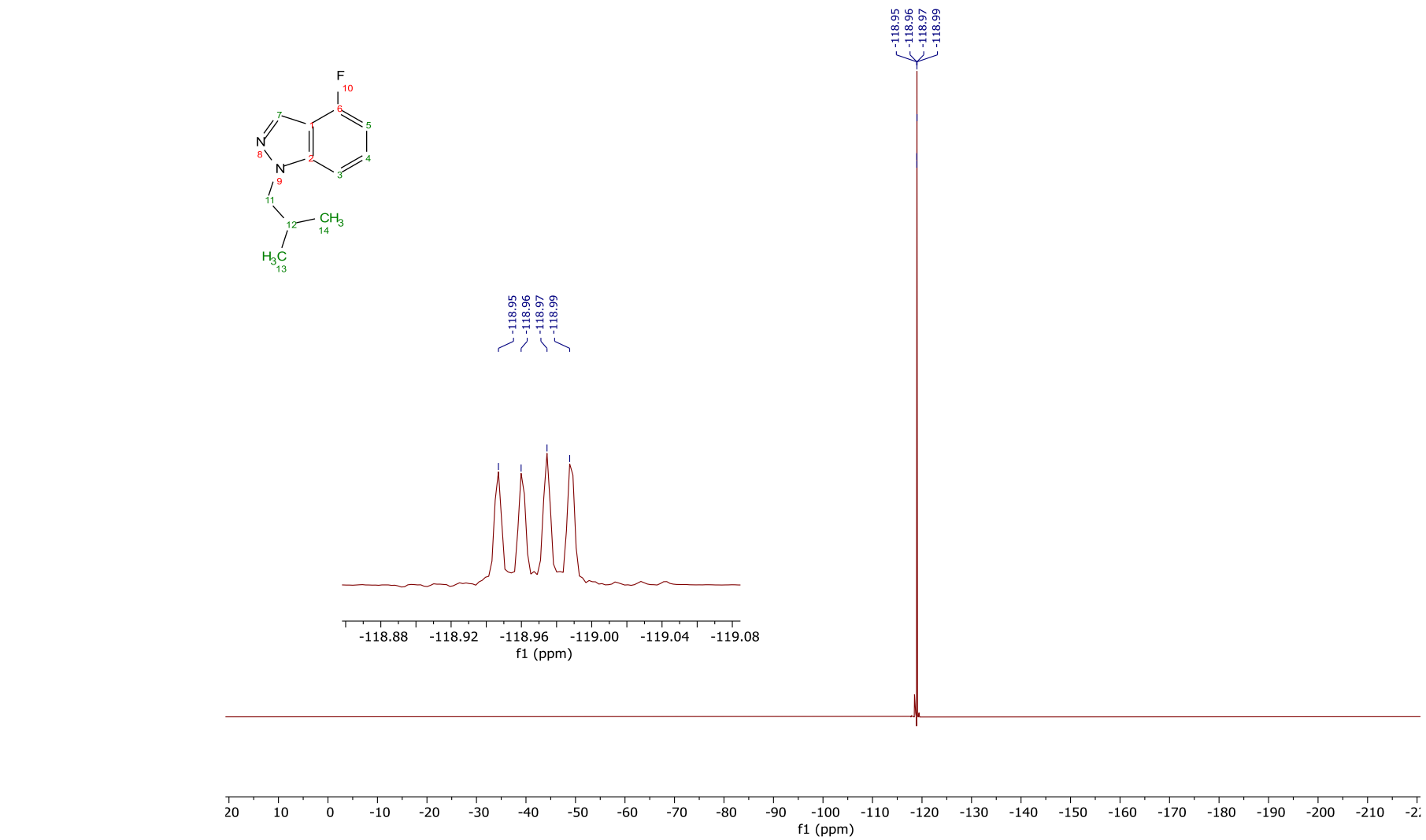


4-fluoro-1-isobutyl-1*H*-indazole (2i)

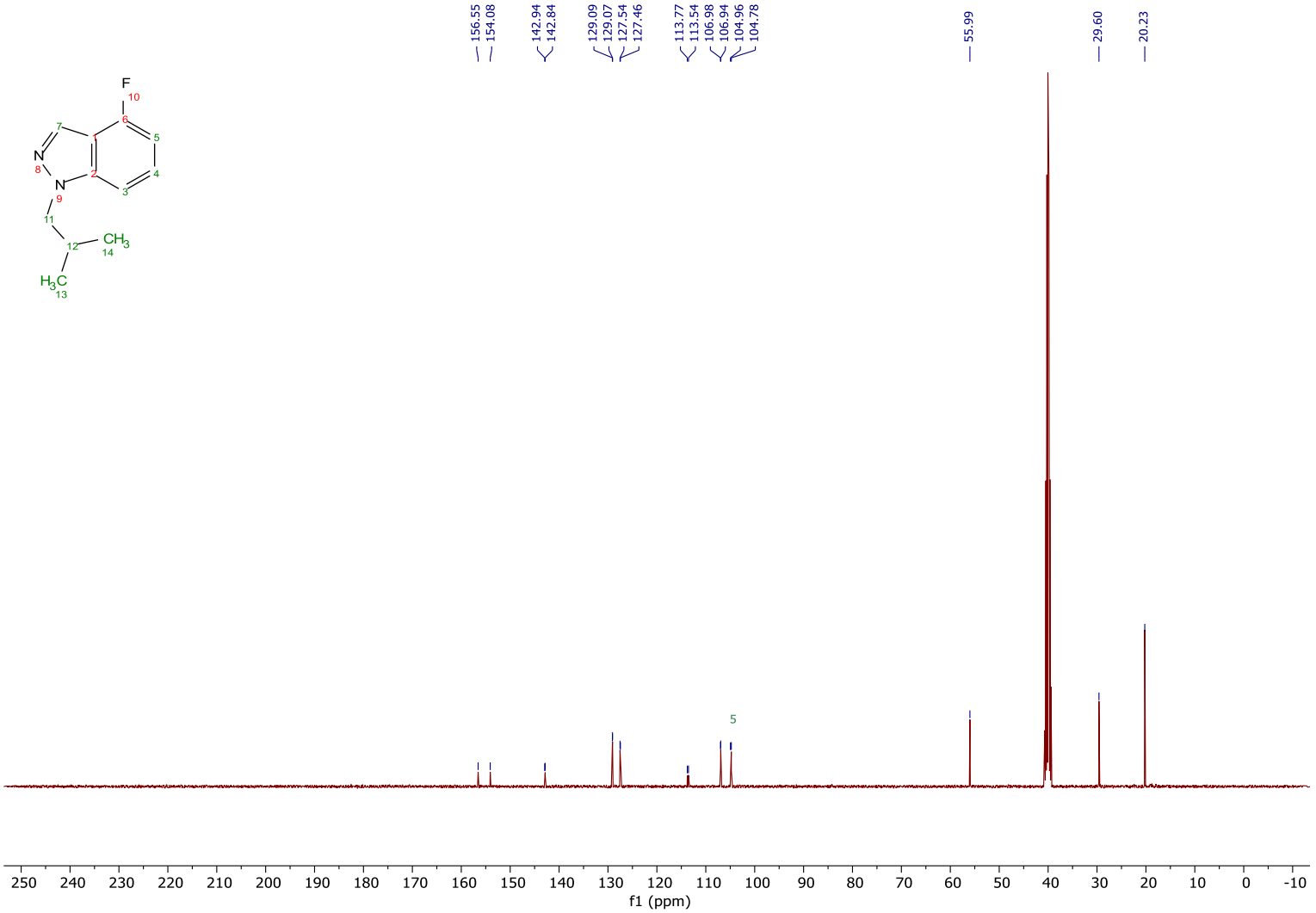
^{1}H NMR (400 MHz, DMSO-d_6)



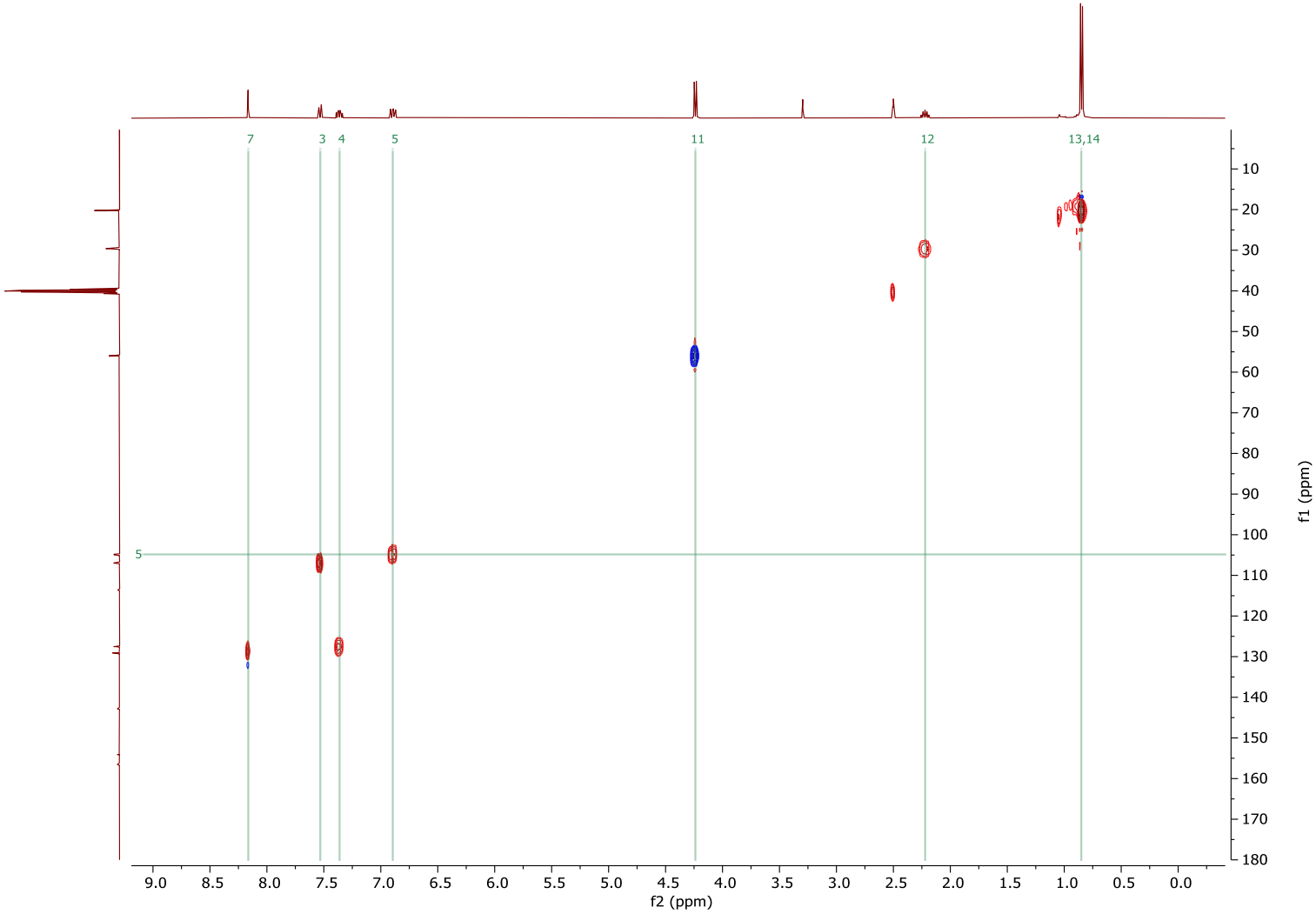
^{19}F NMR (376 MHz, DMSO-d_6)



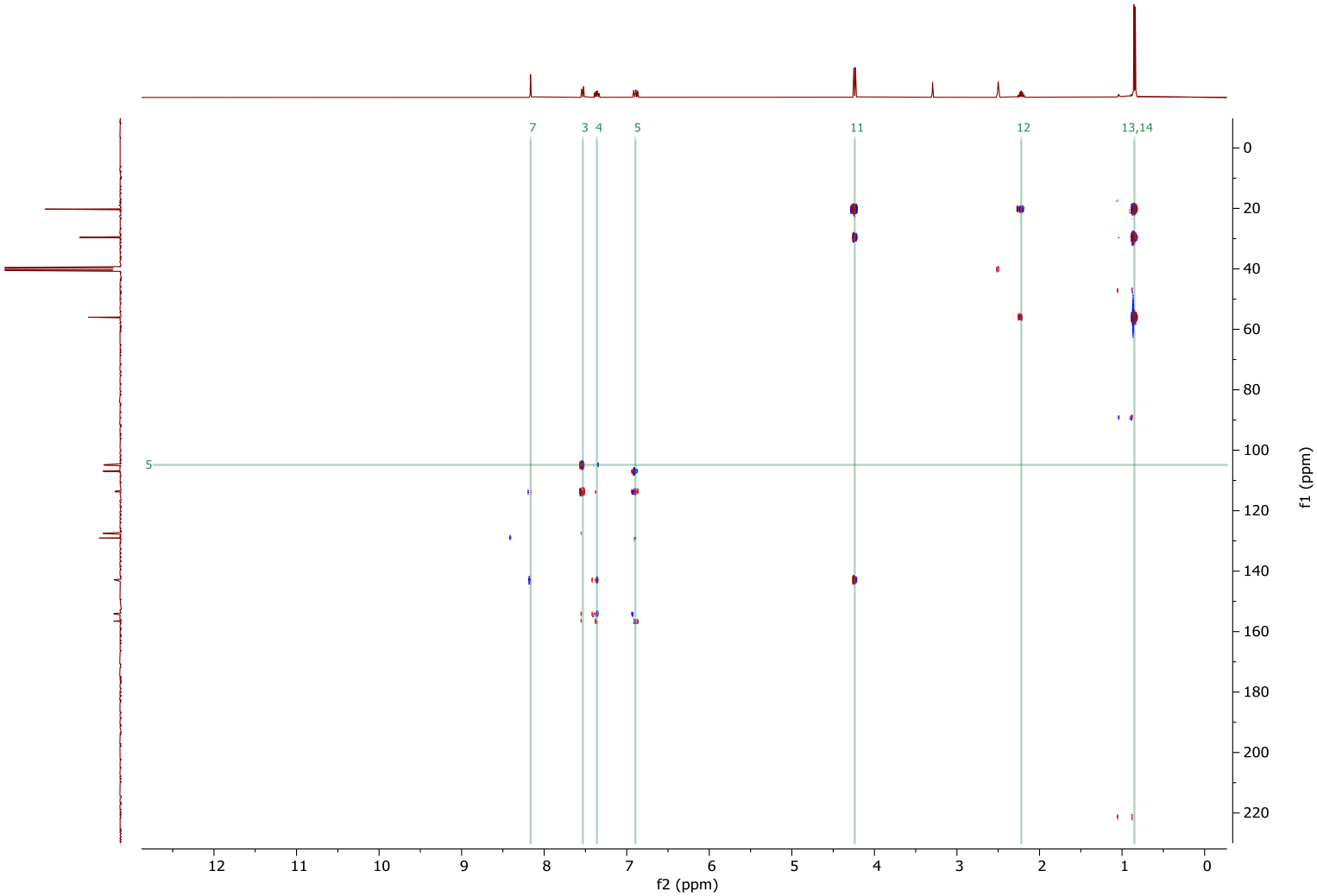
^{13}C NMR (101 MHz, DMSO-d_6)



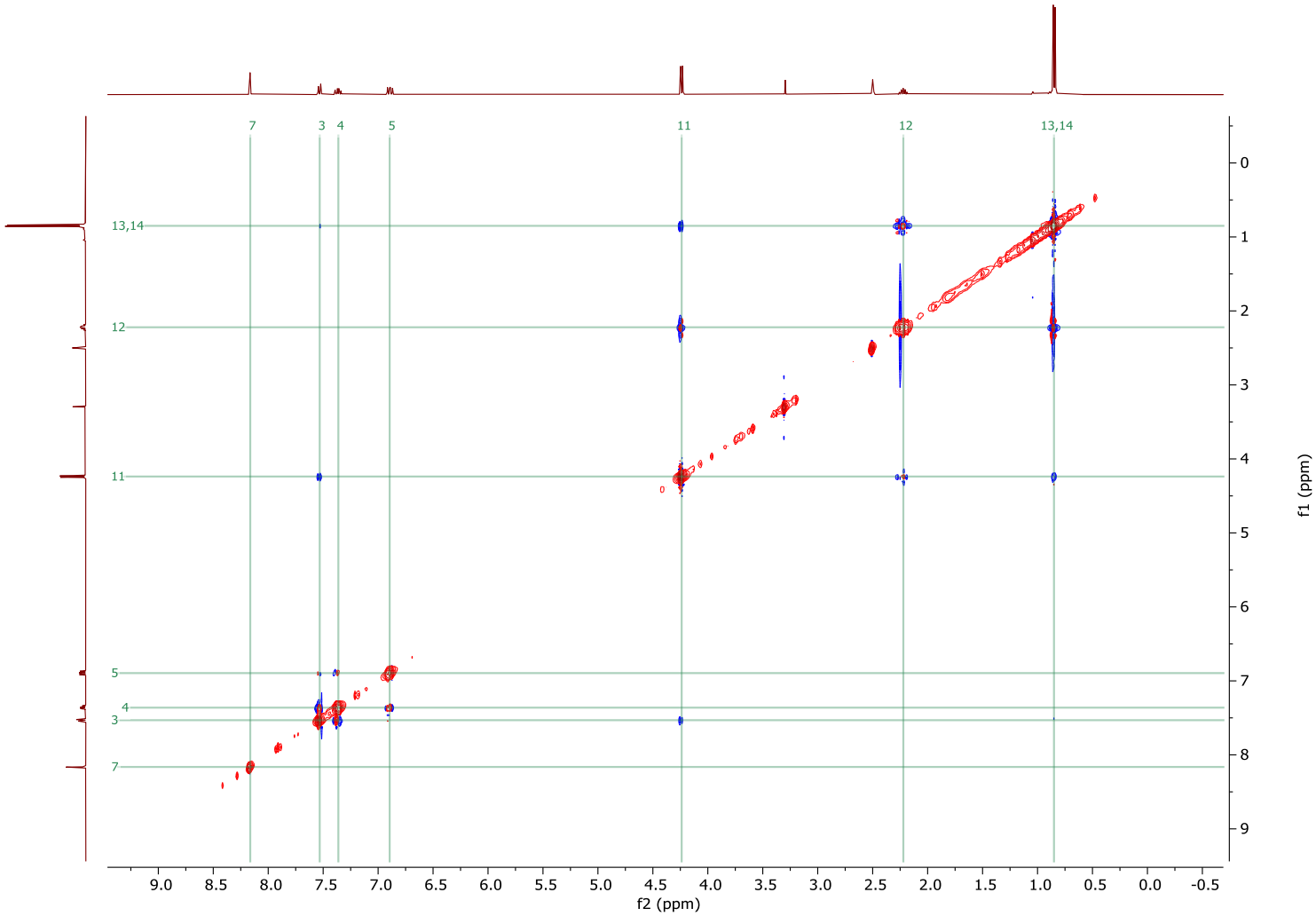
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

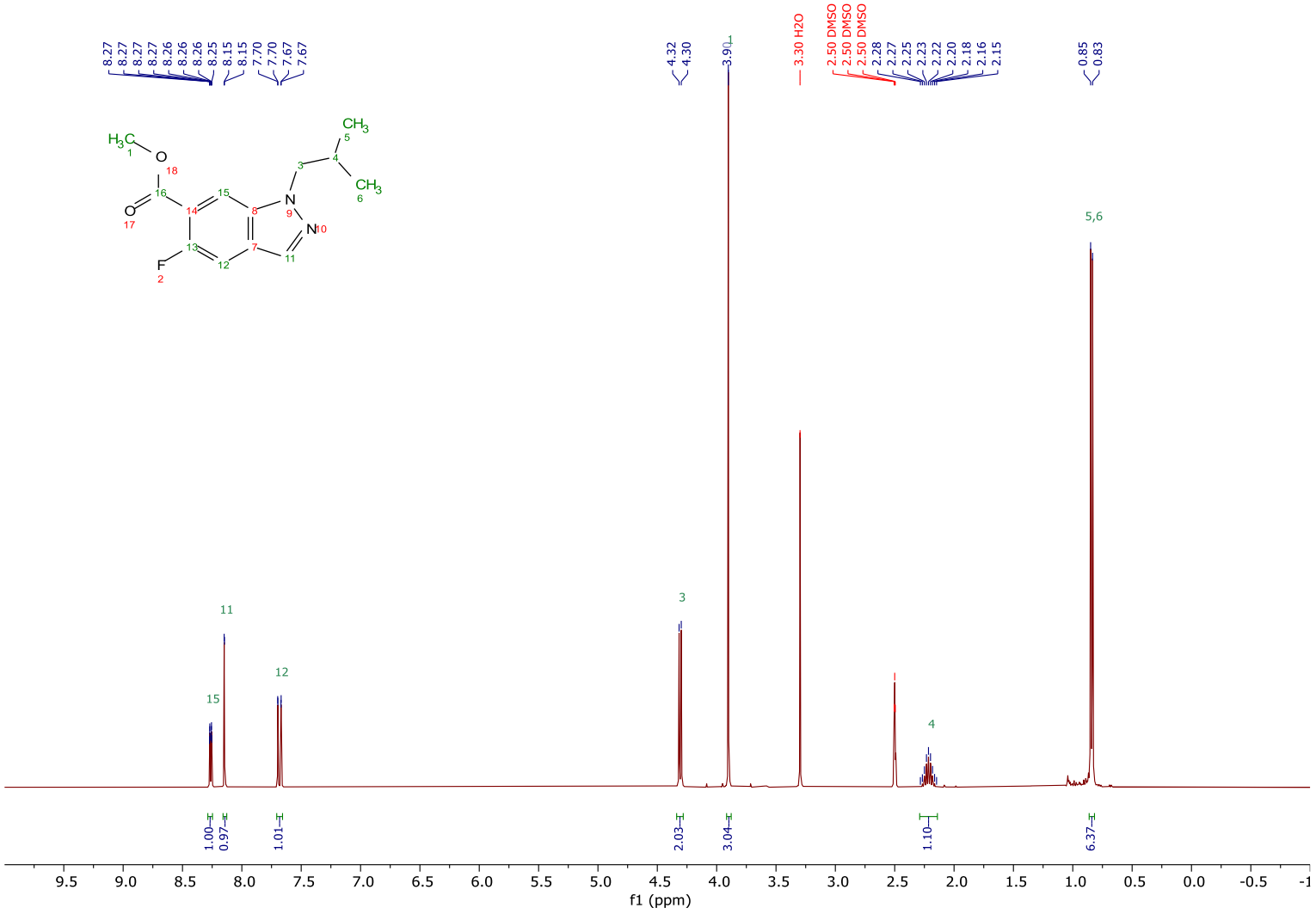


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

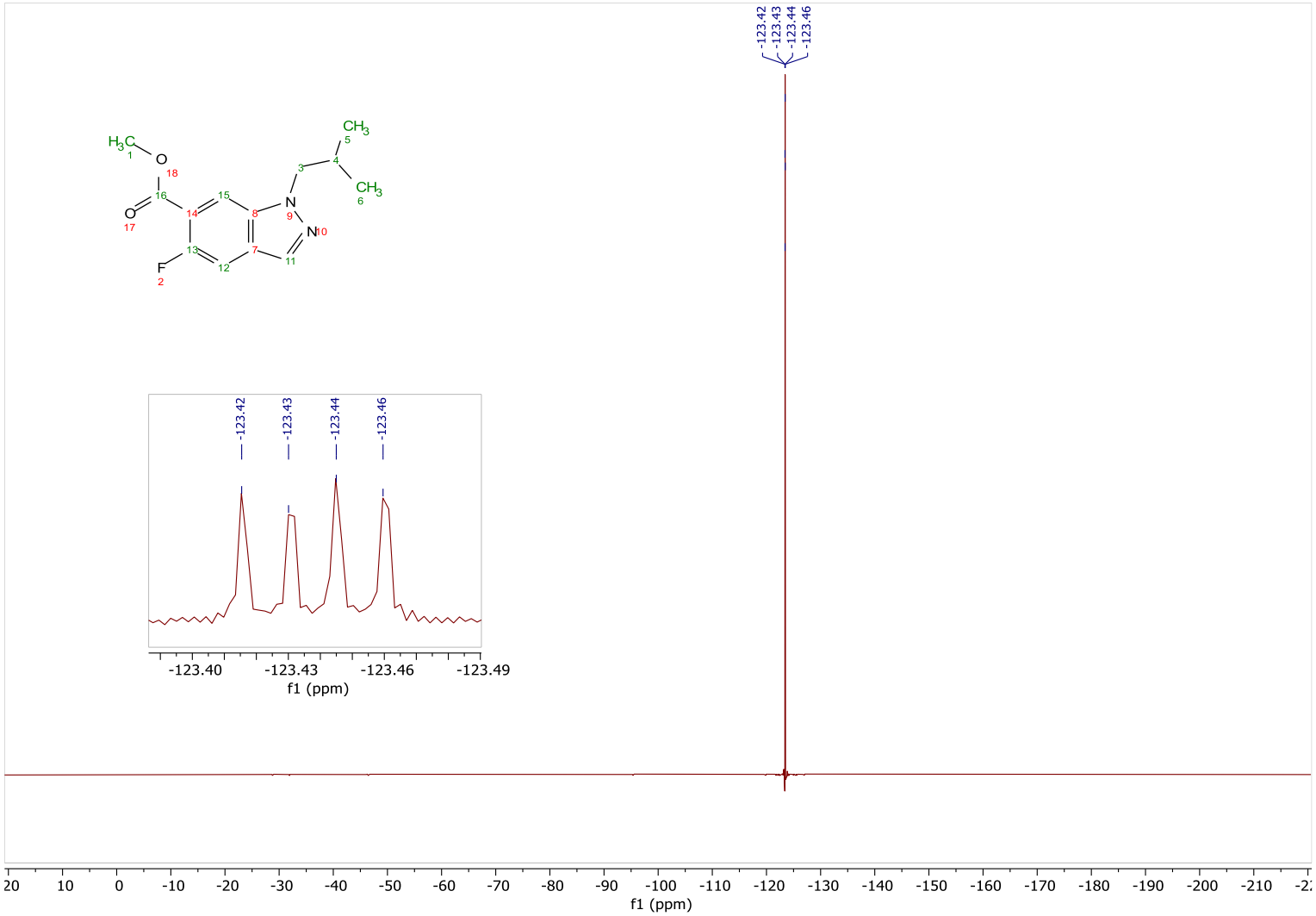


Methyl 5-fluoro-1-isobutyl-1H-indazole-6-carboxylate (2j)

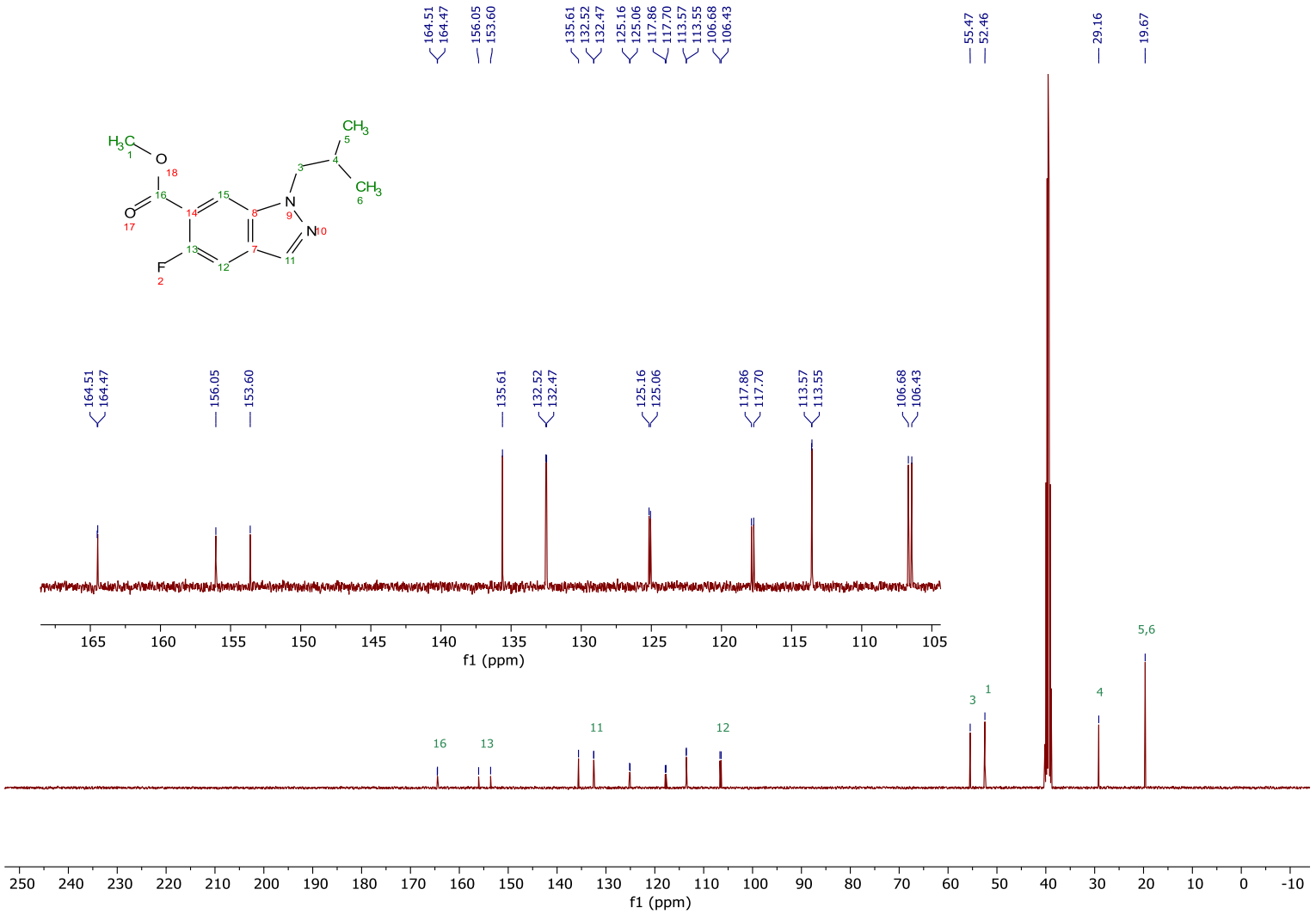
^{1}H NMR (400 MHz, DMSO-d_6)



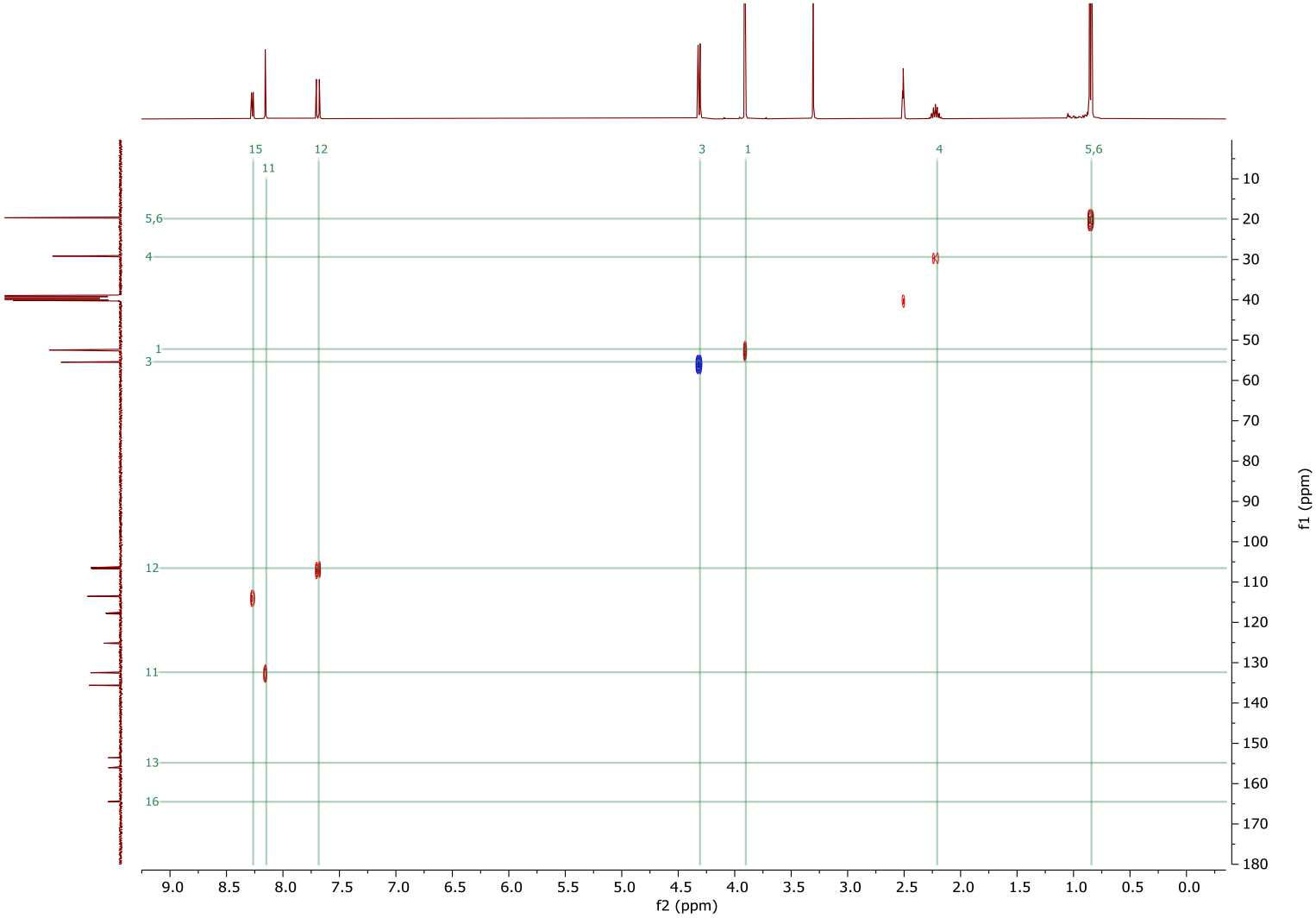
^{19}F NMR (376 MHz, DMSO-d_6)



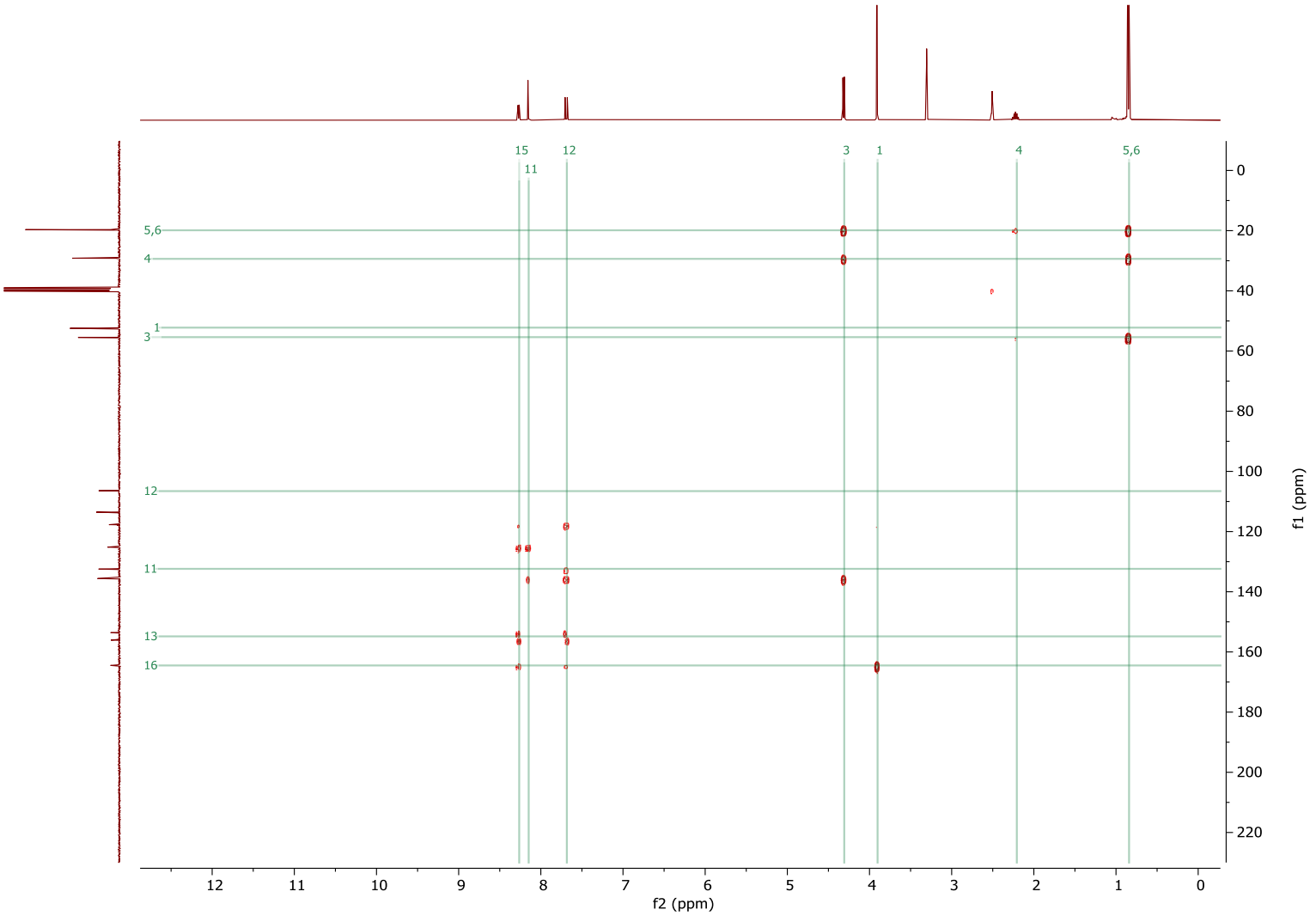
^{13}C NMR (101 MHz, DMSO-d_6)



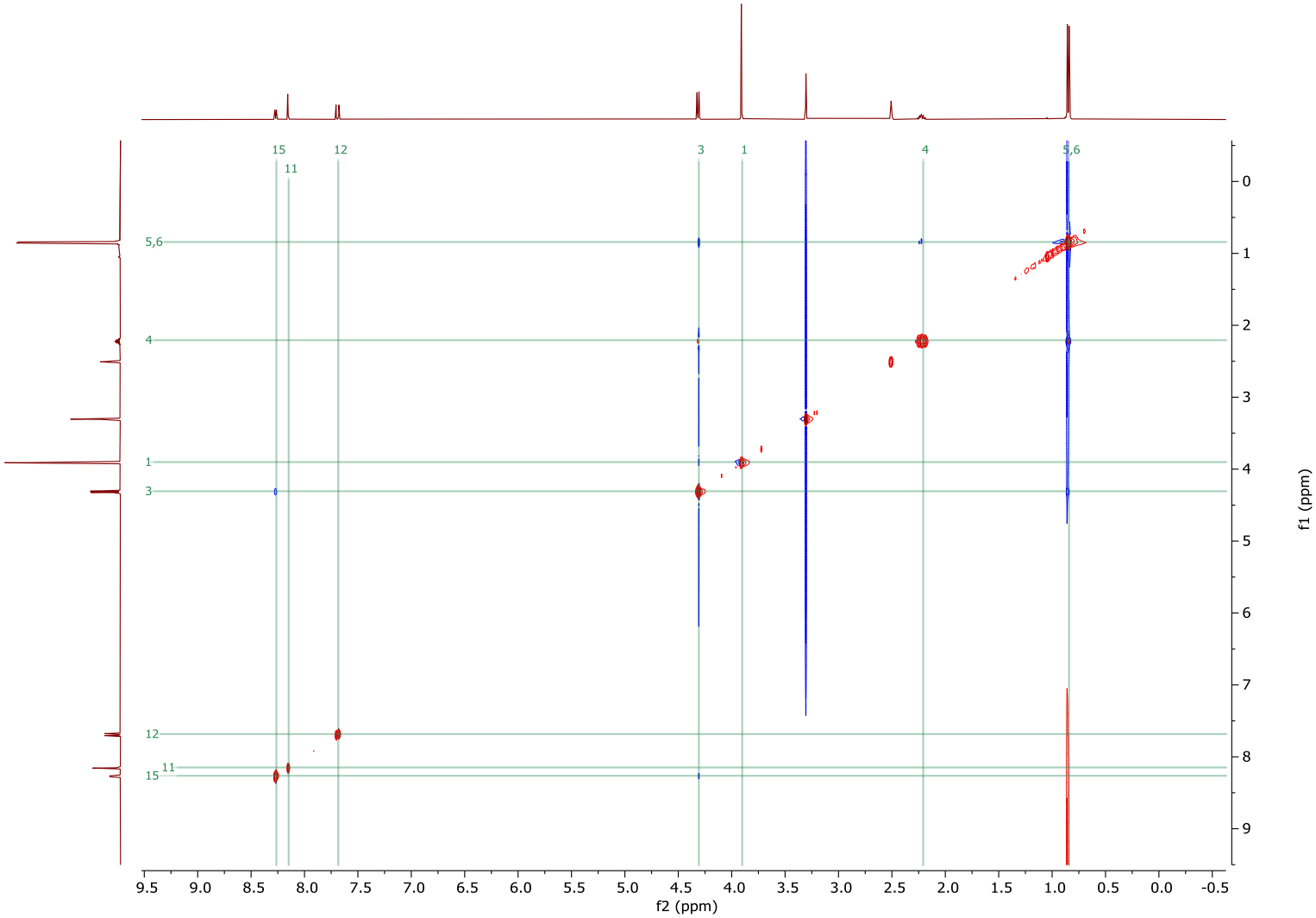
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

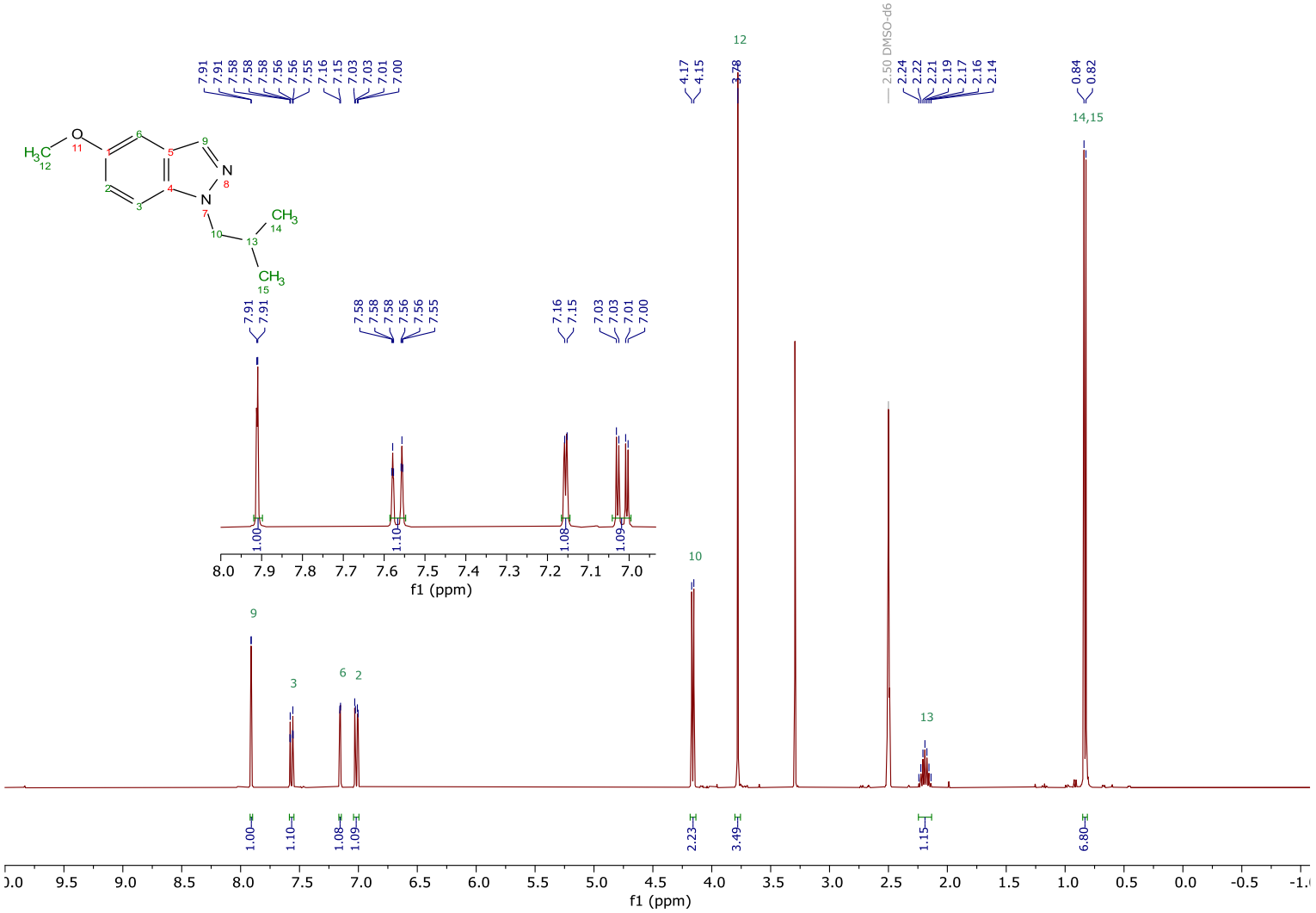


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

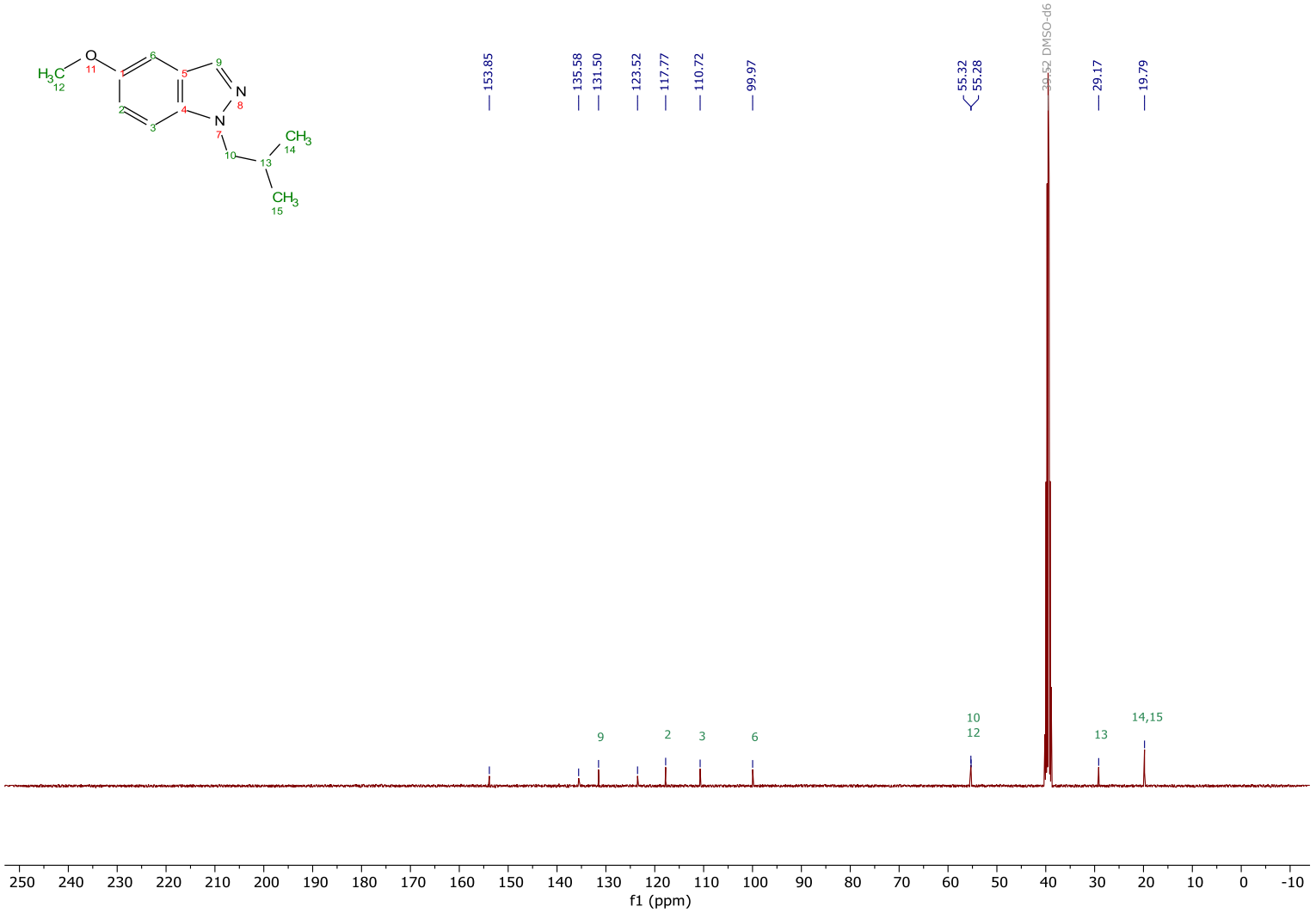


1-isobutyl-5-methoxy-1*H*-indazole (2k)

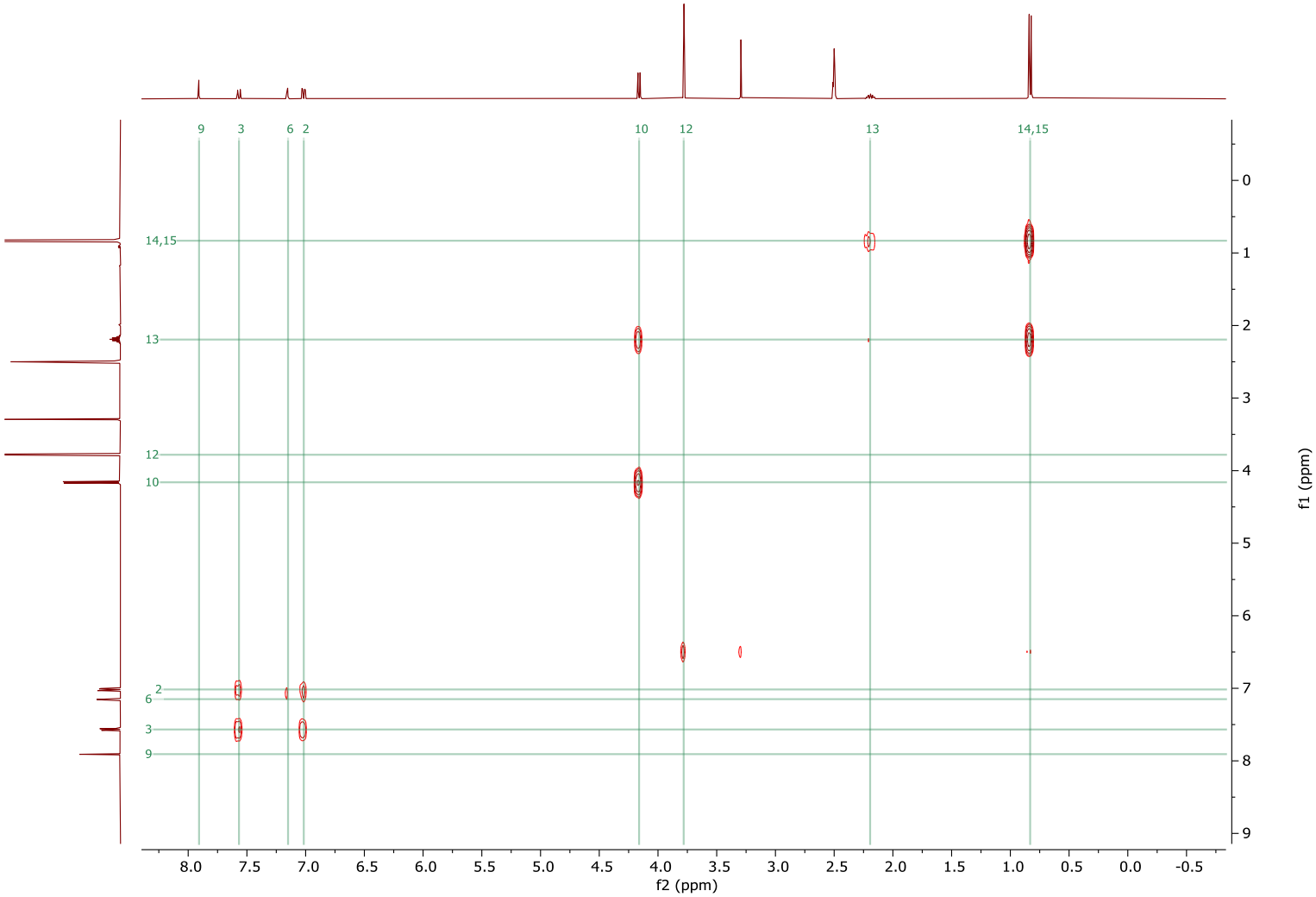
^{1}H NMR (400 MHz, DMSO-d_6)



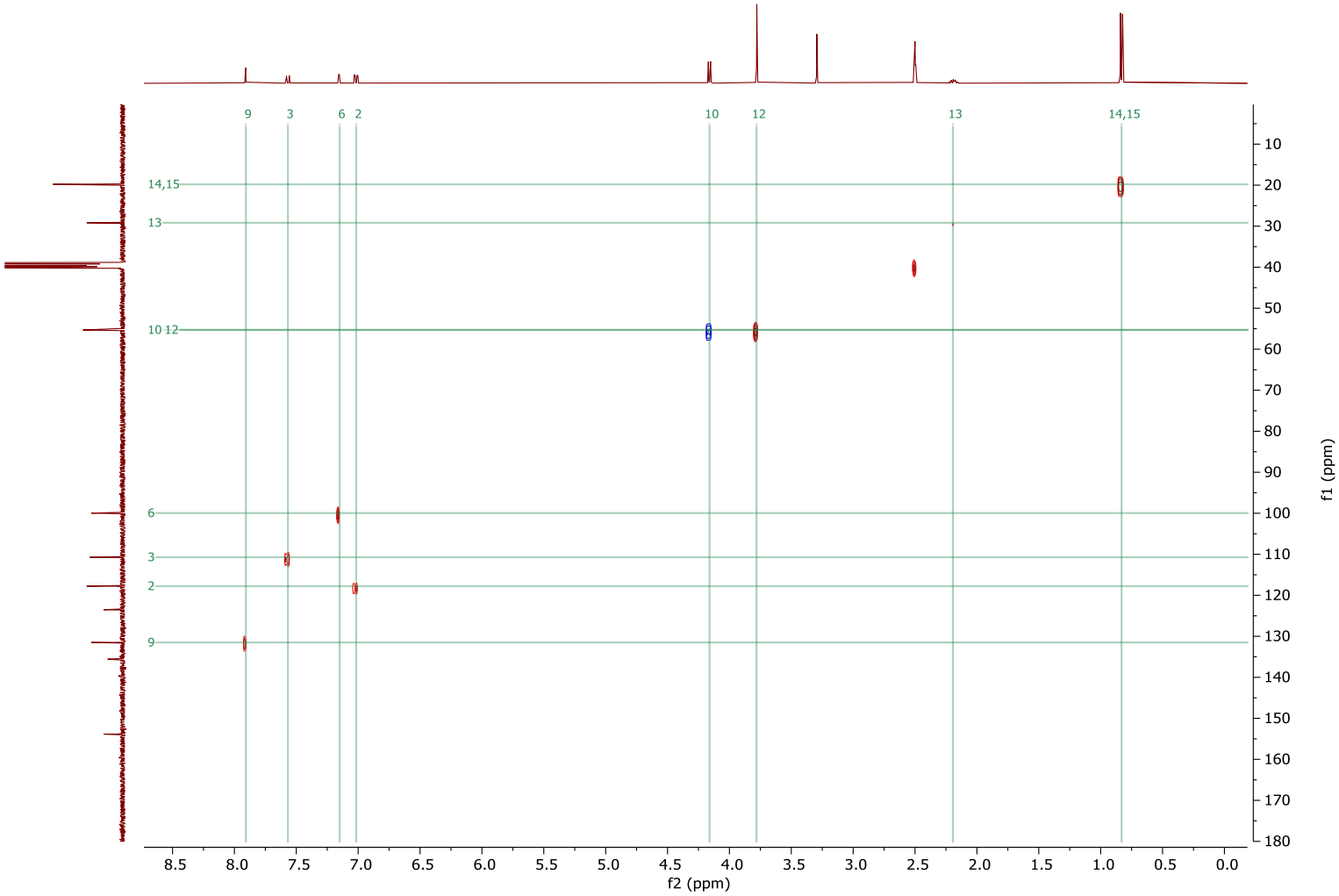
^{13}C NMR (101 MHz, DMSO-d_6)



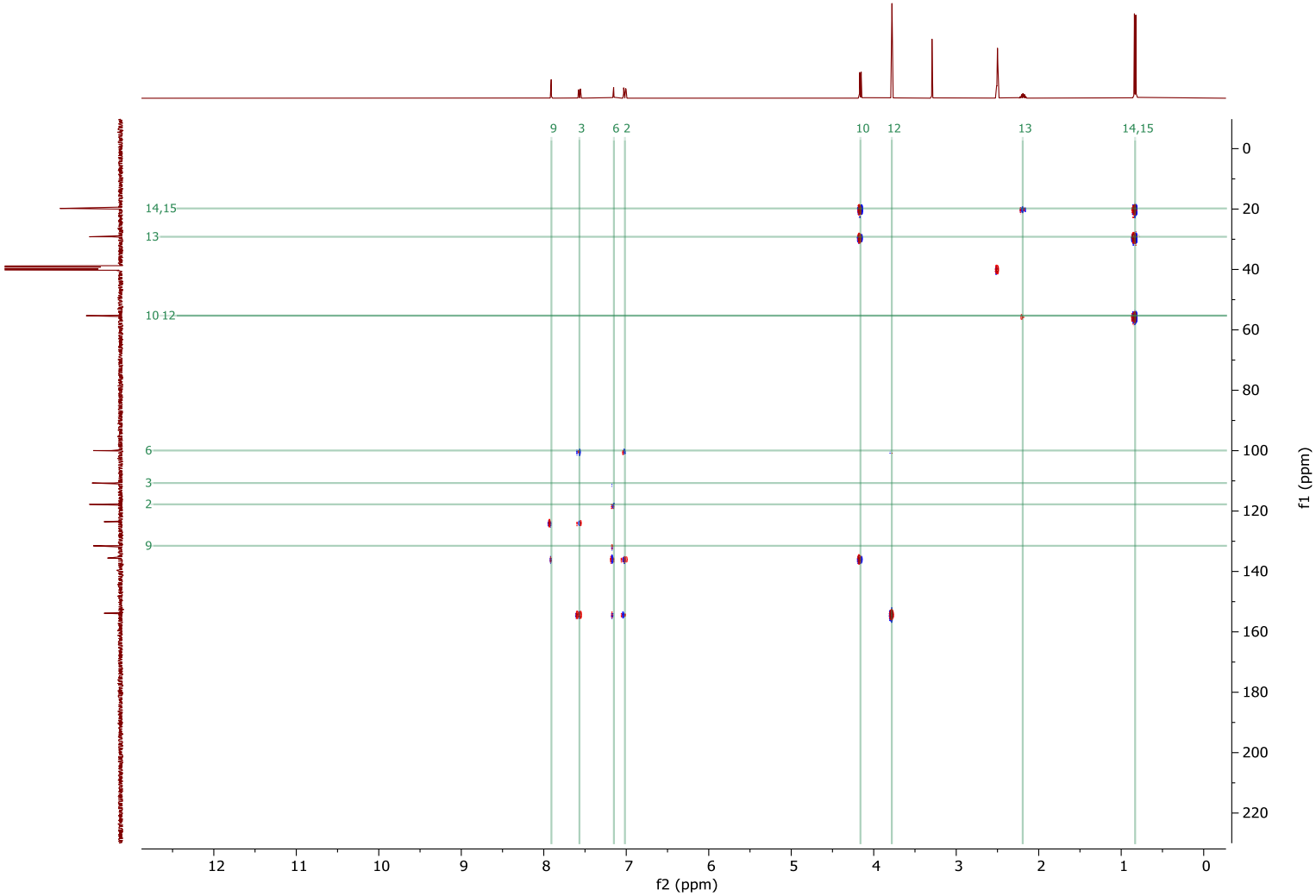
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



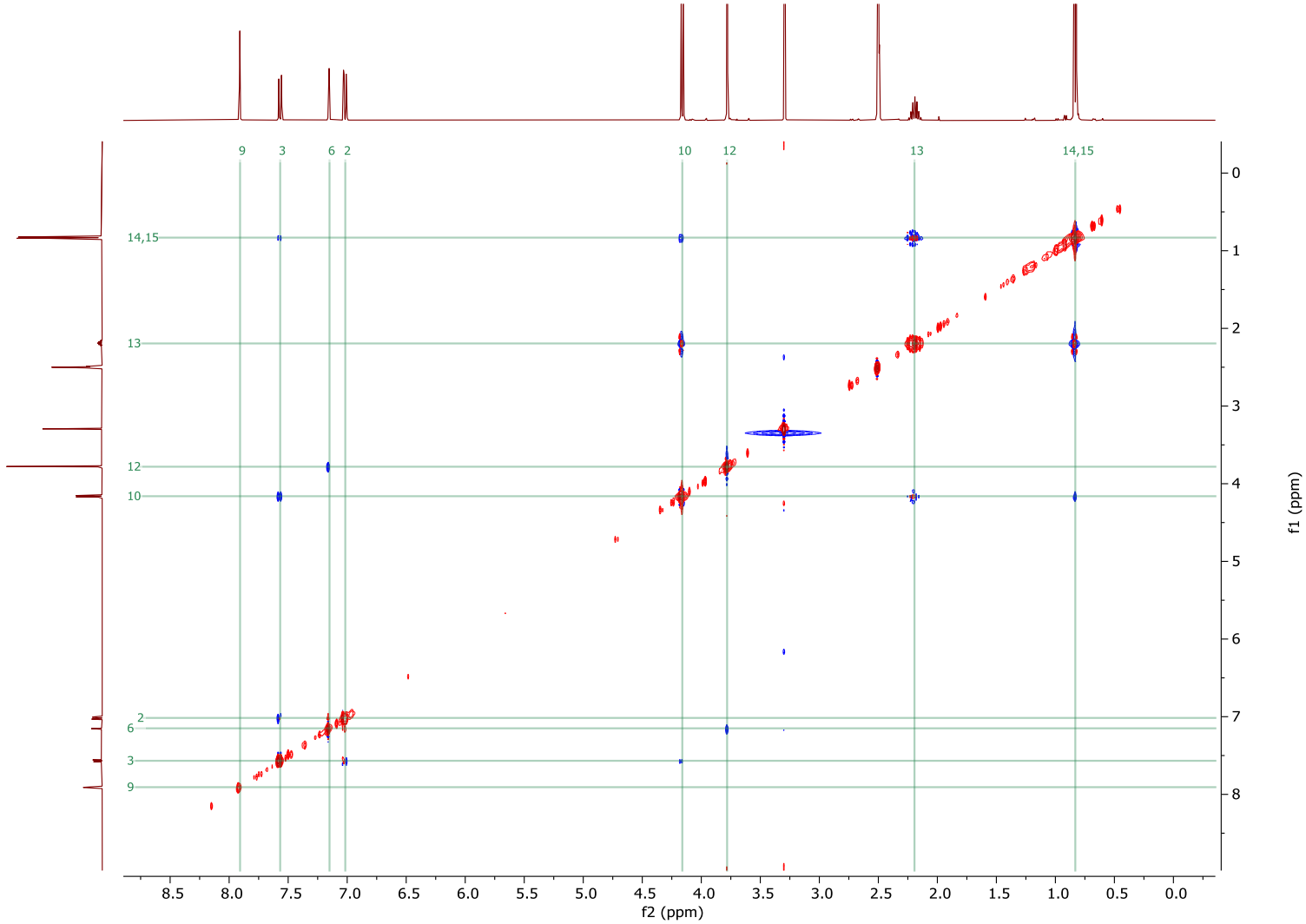
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

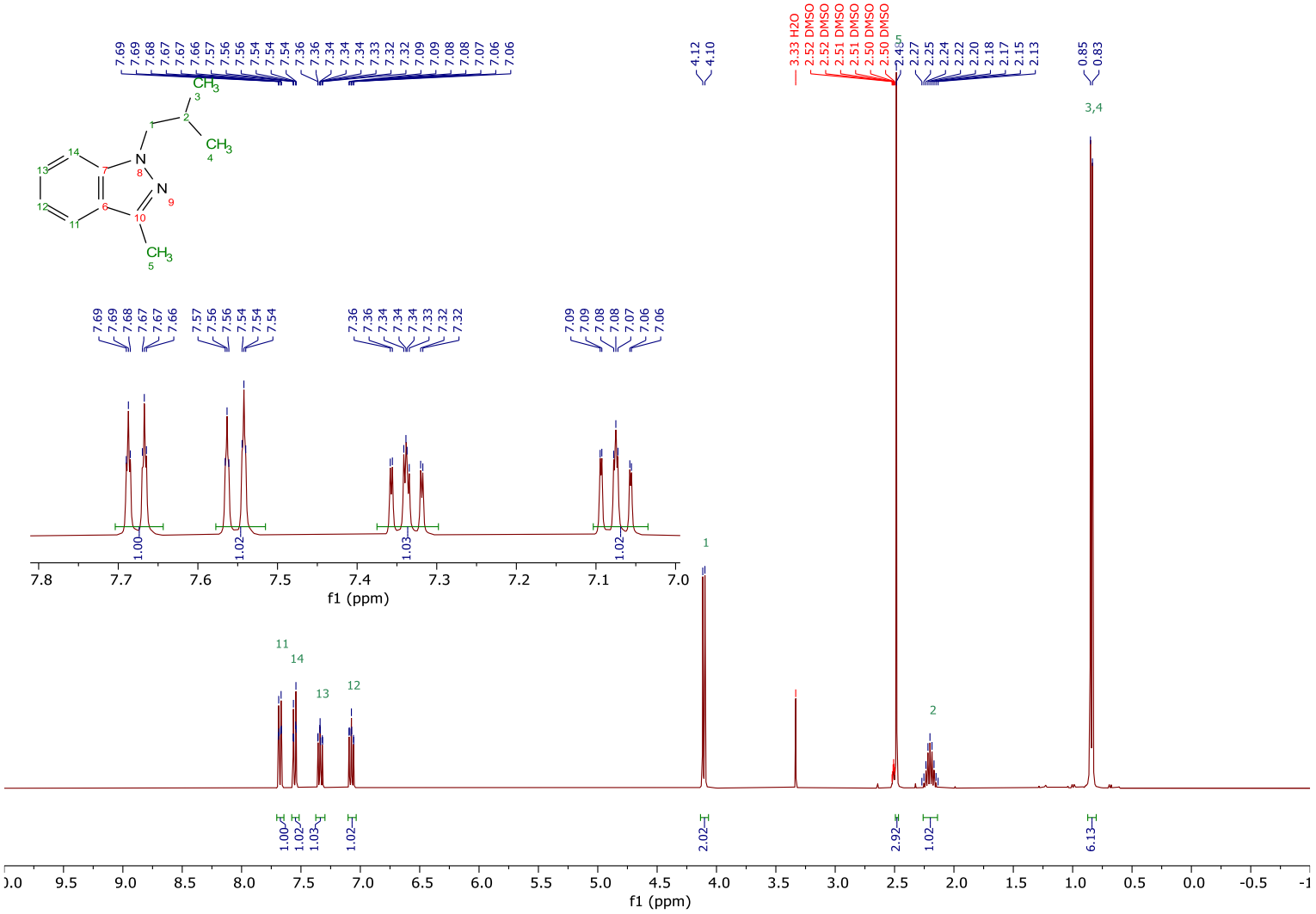


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

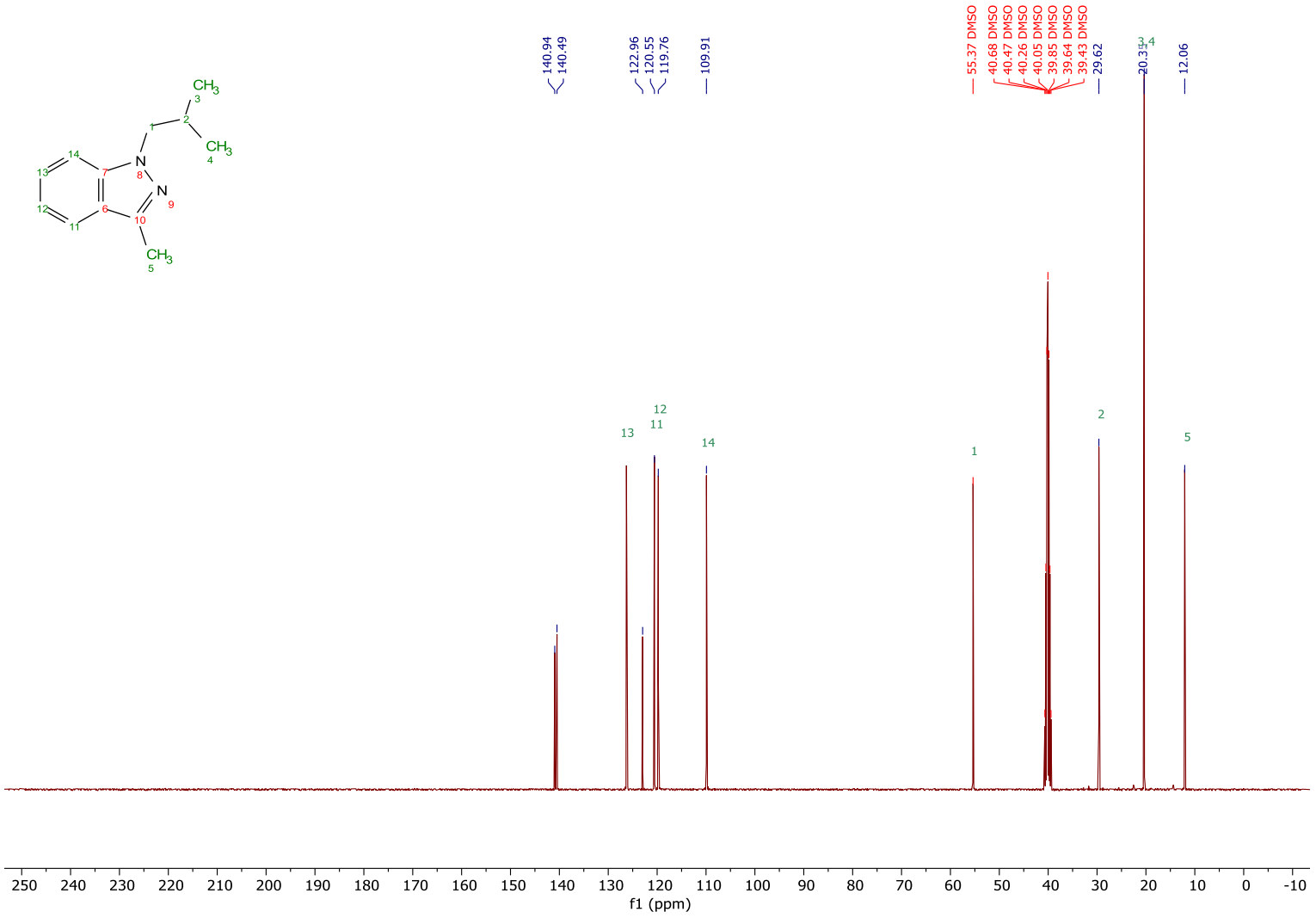


1-isobutyl-3-methyl-1*H*-indazole (2l)

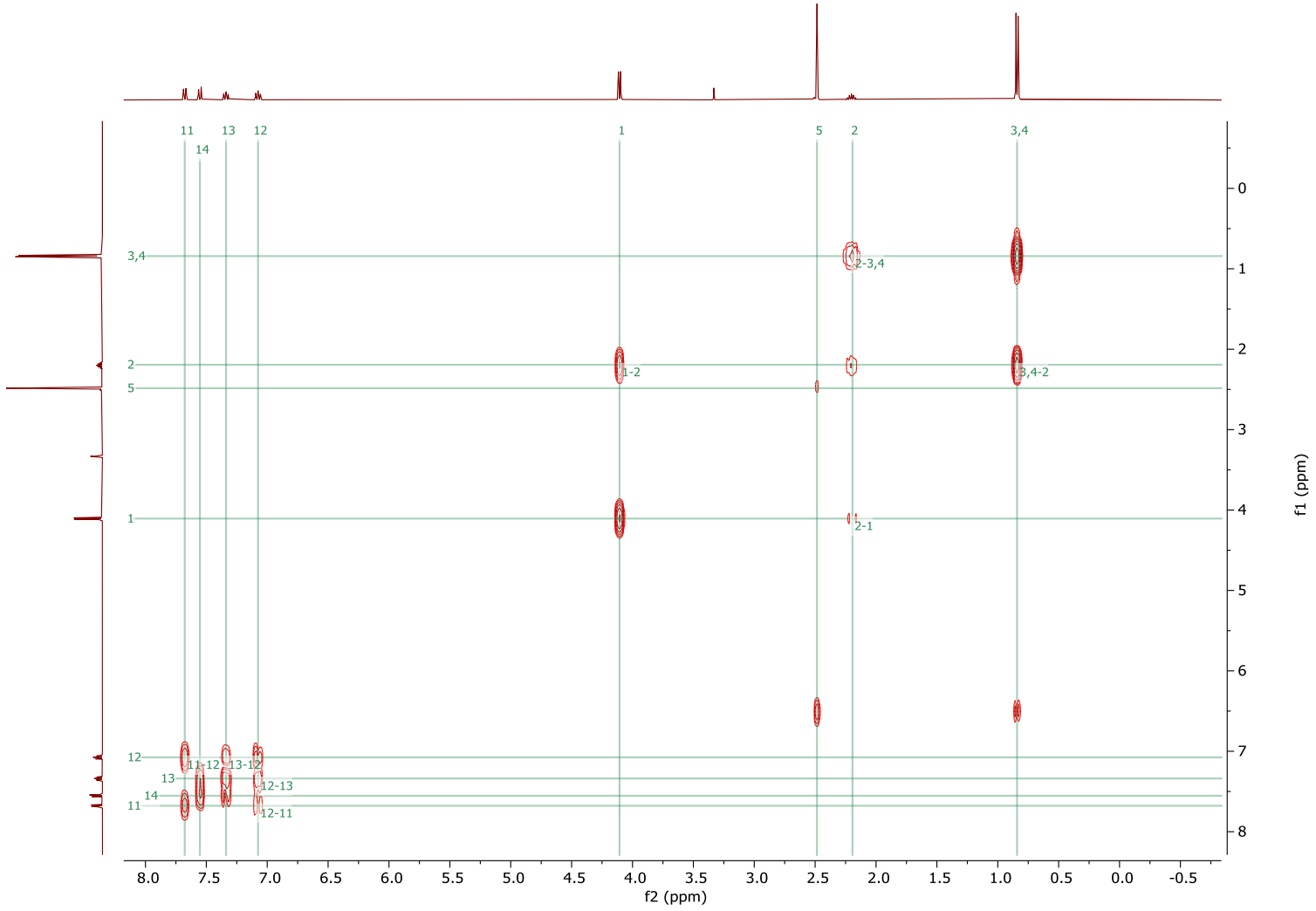
^{1}H NMR (400 MHz, DMSO-d_6)



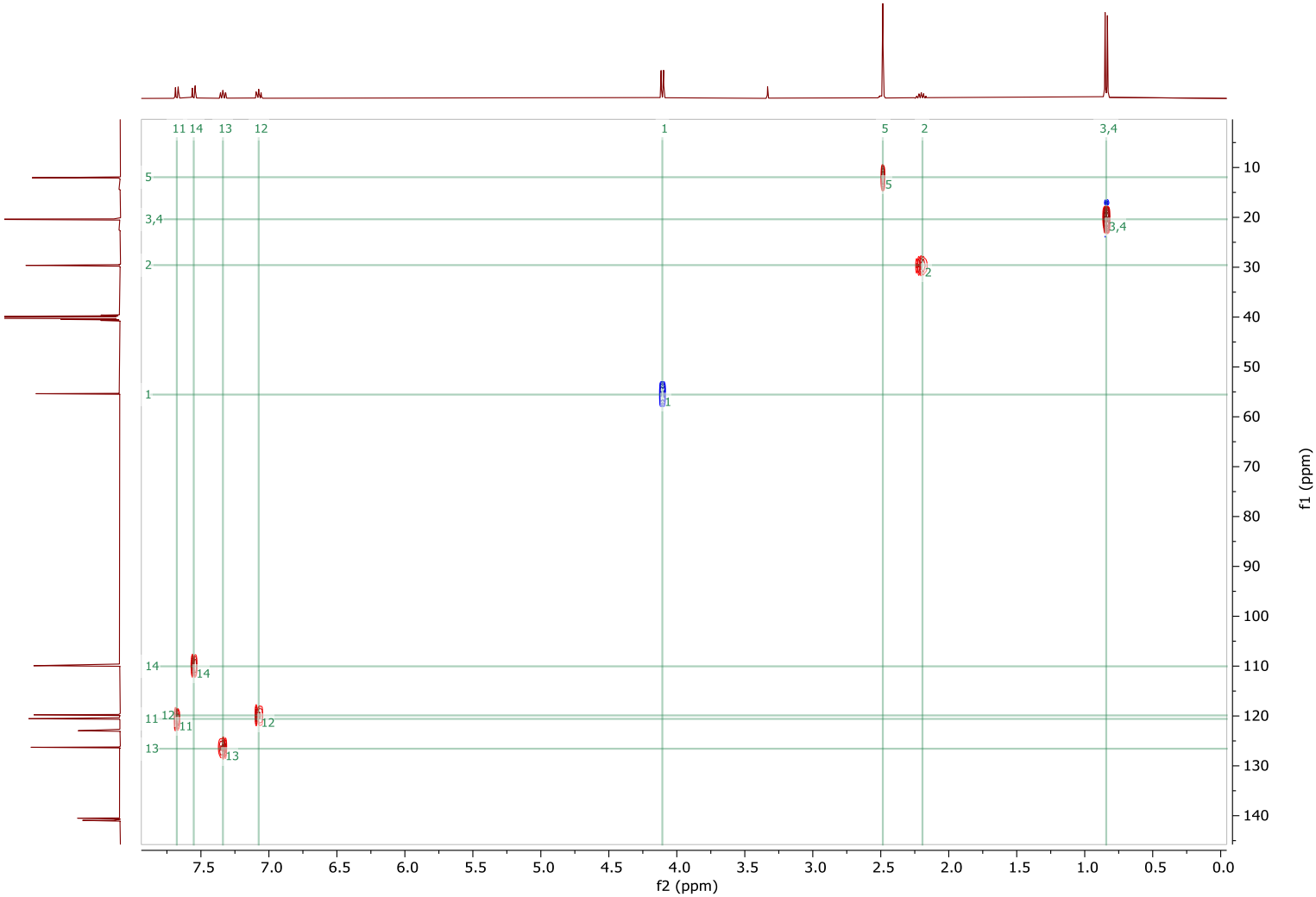
^{13}C NMR (101 MHz, DMSO-d_6)



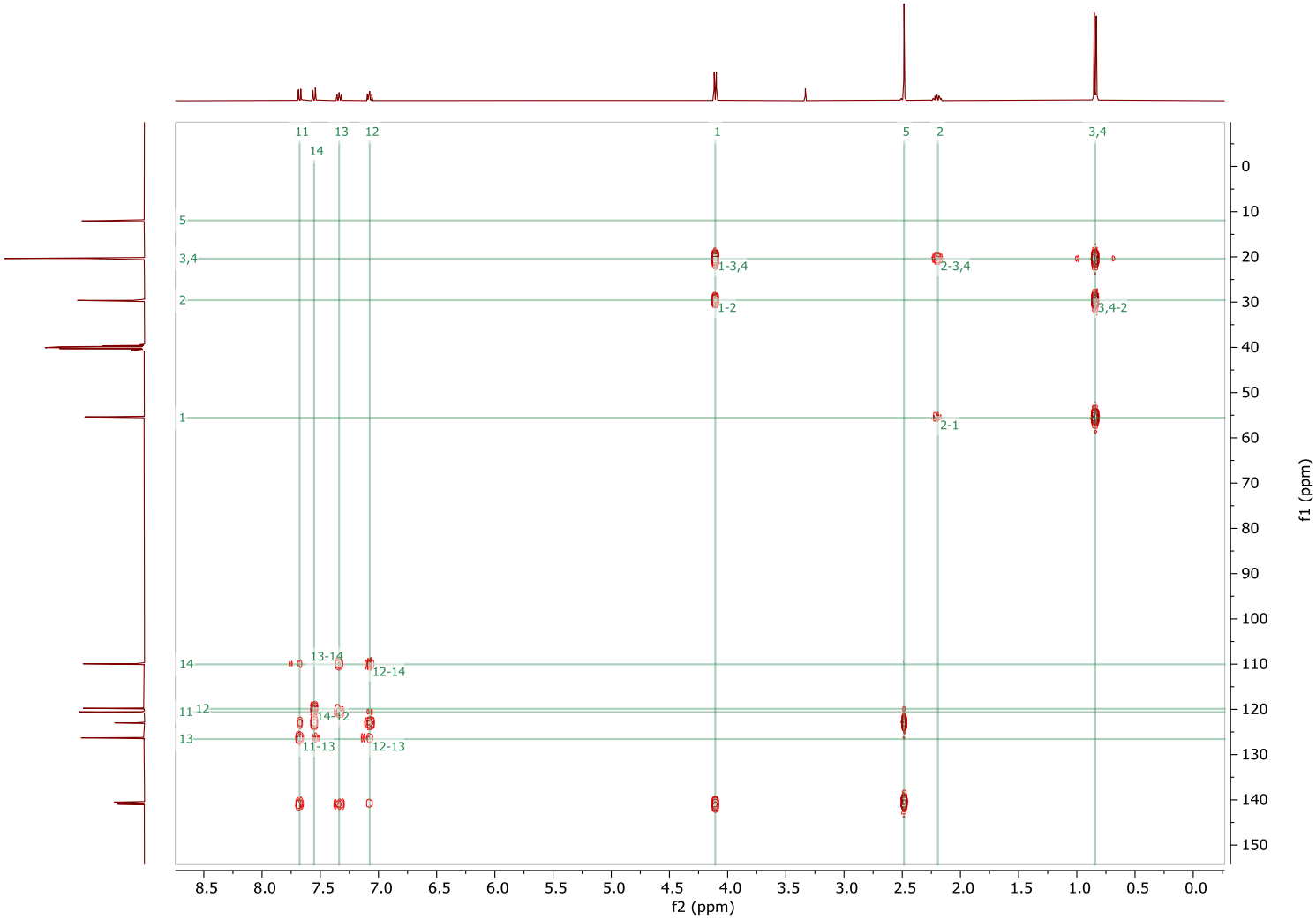
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



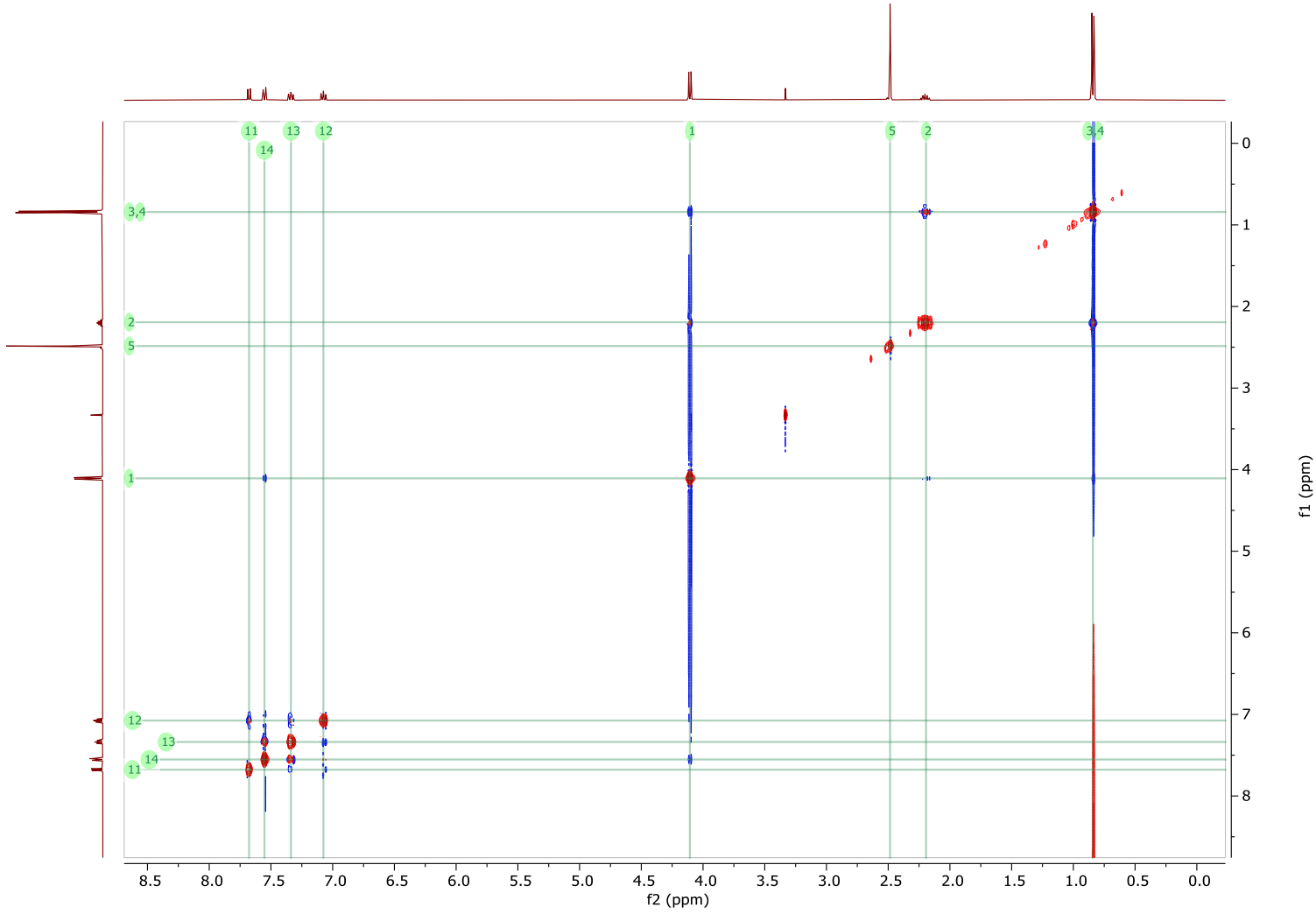
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

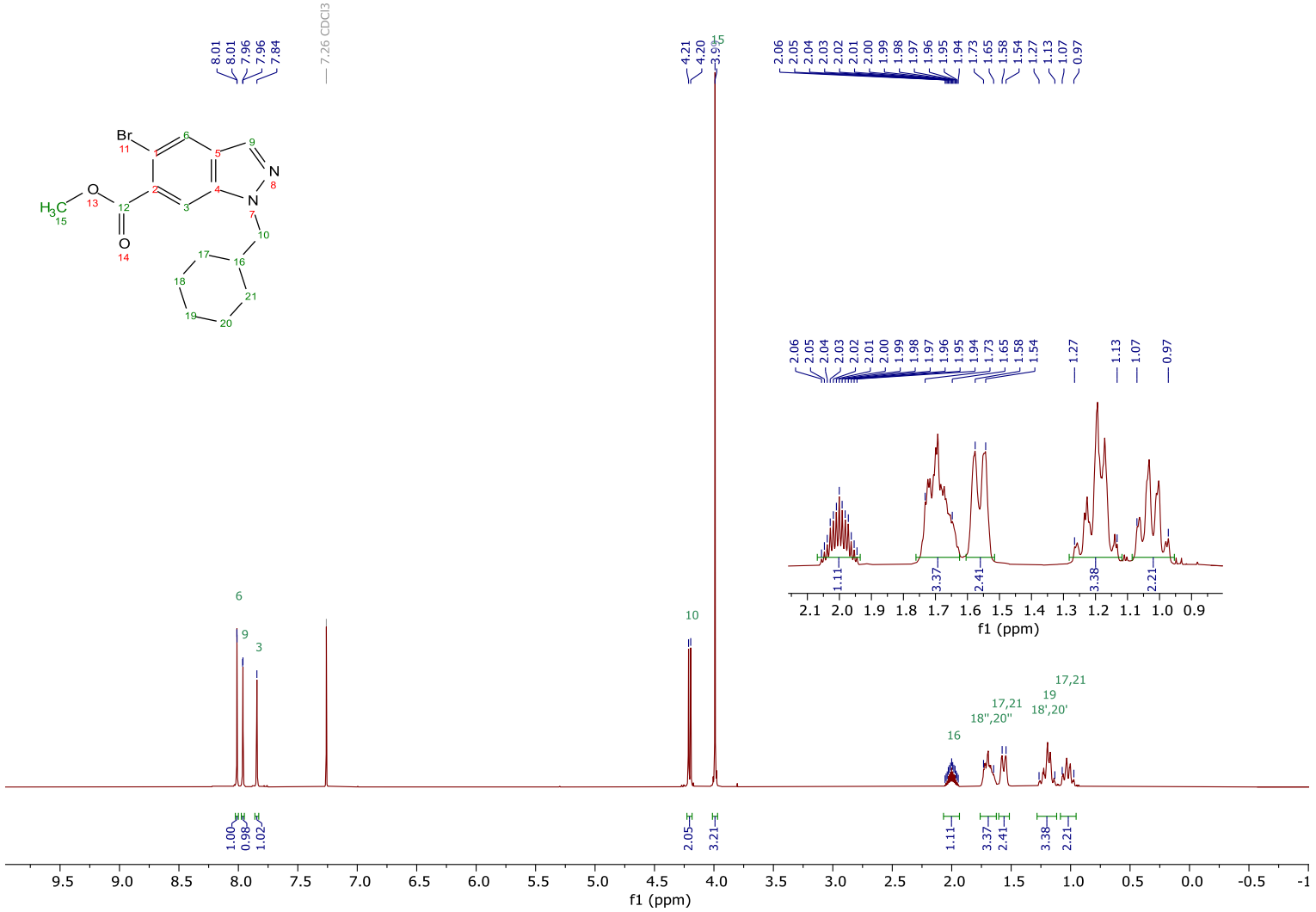


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

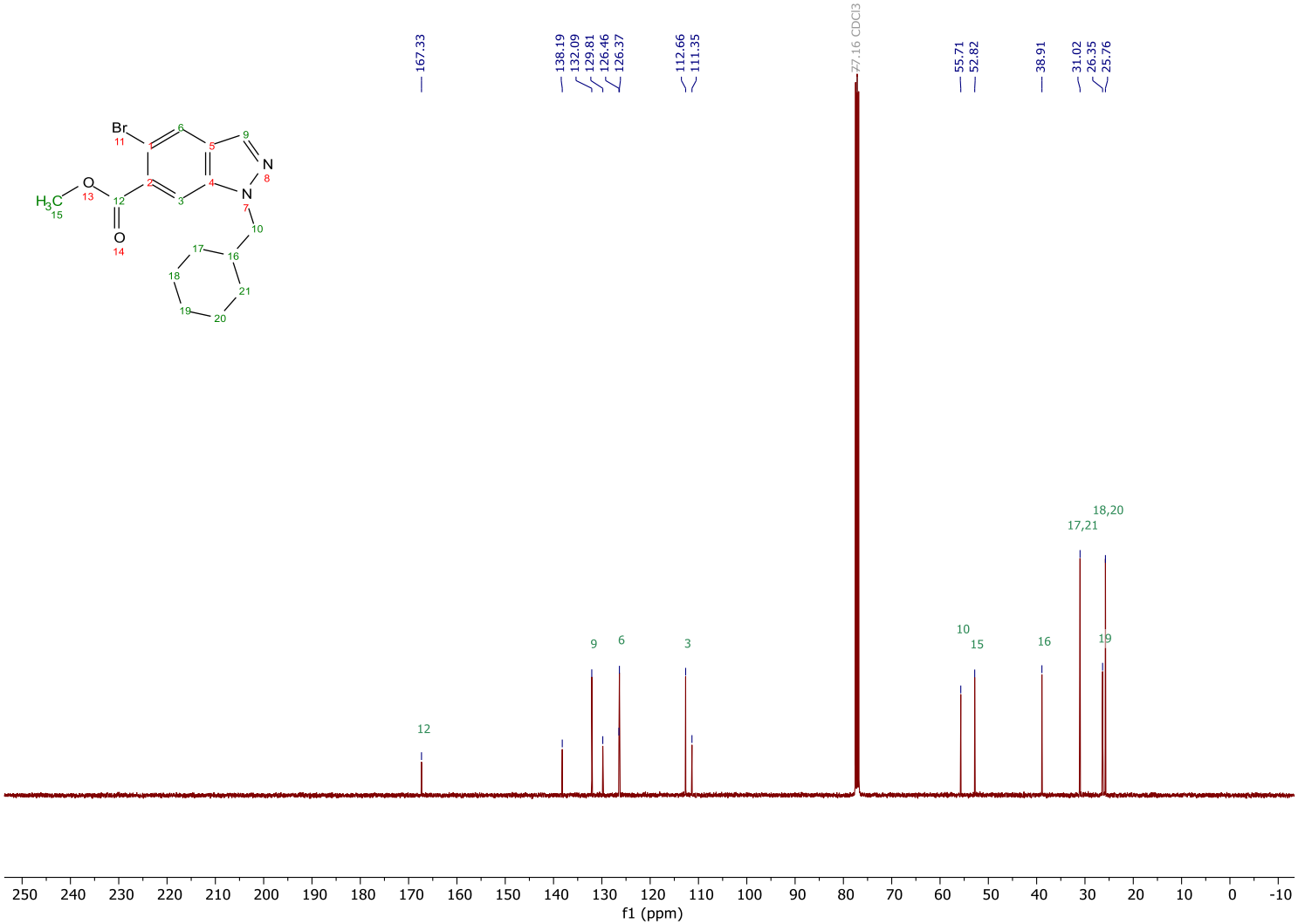


Methyl 5-bromo-1(cyclohexylmethyl)-1*H*-indazole-6-carboxylate (2m)

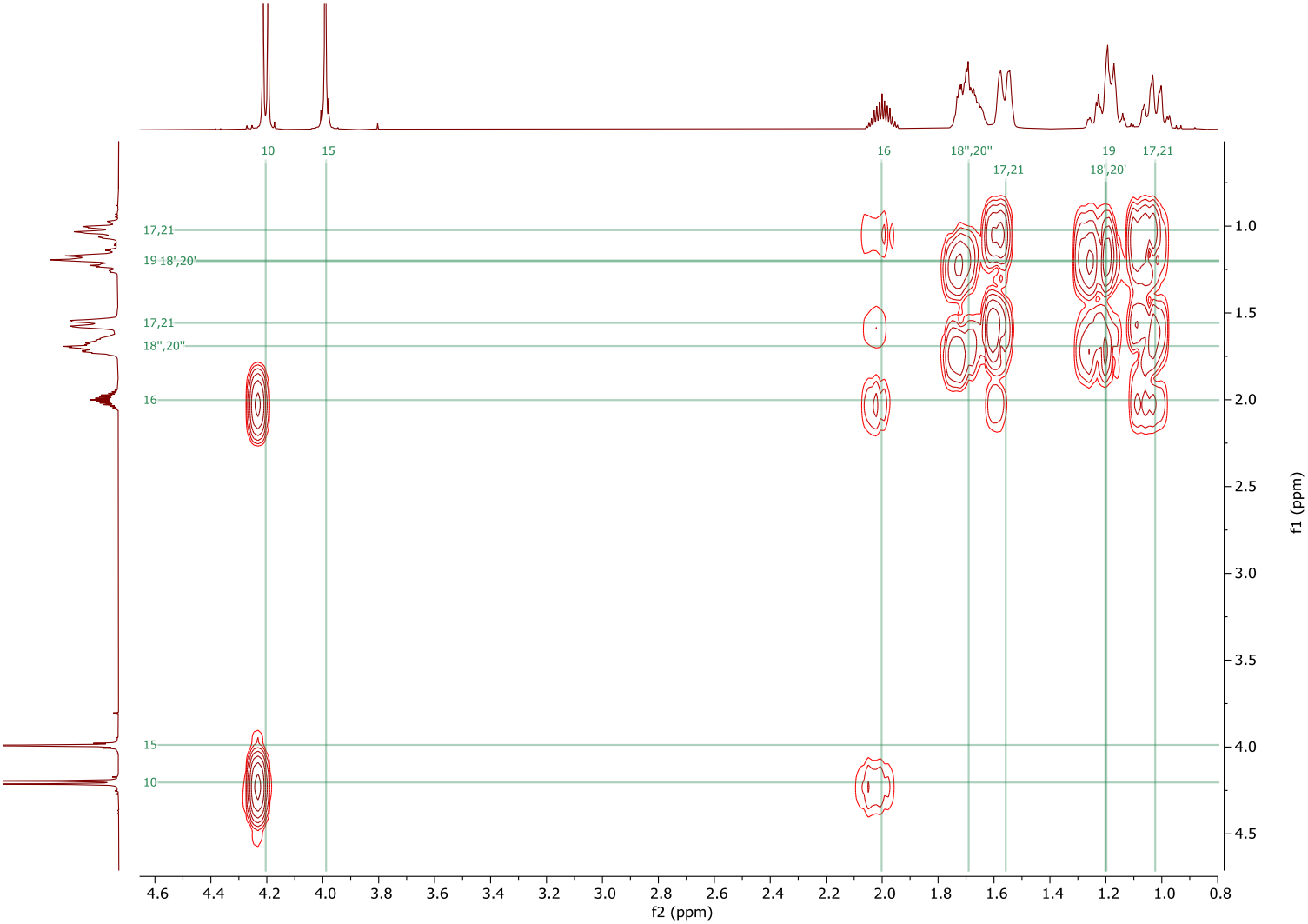
^{1}H NMR (400 MHz, $CDCl_3$)



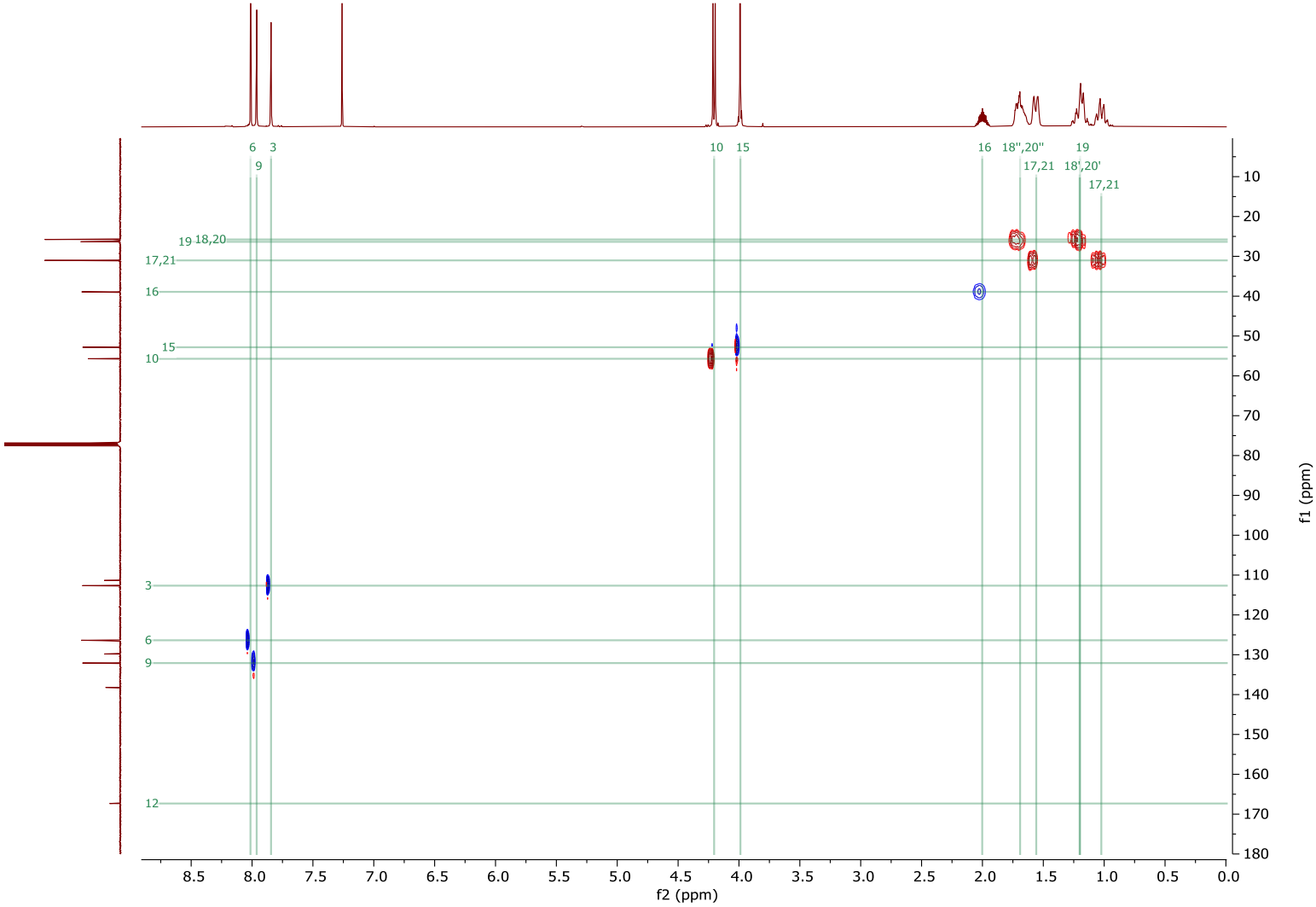
^{13}C NMR (101 MHz, $CDCl_3$)



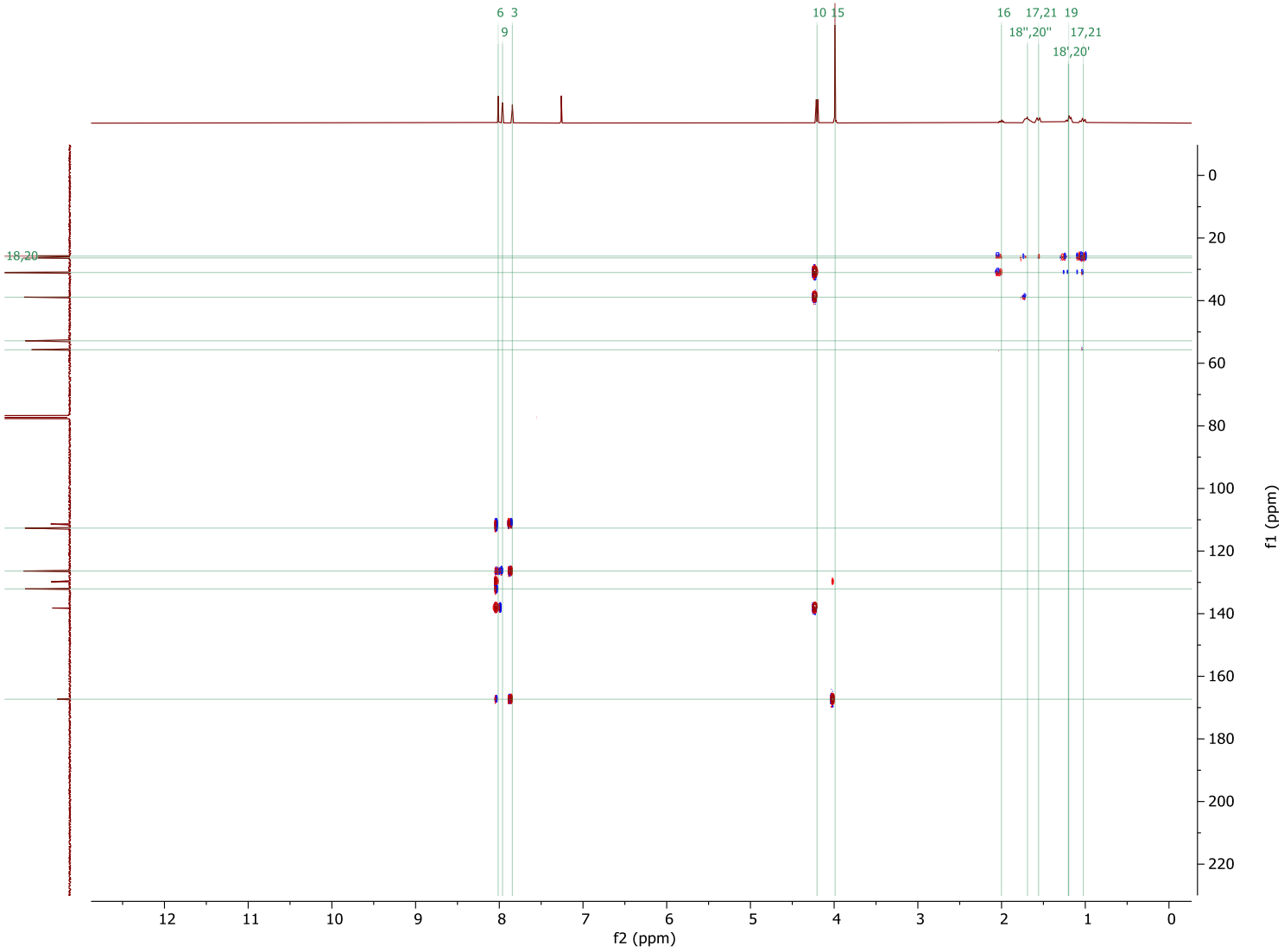
^{1}H-^{1}H COSY (400 MHz, $CDCl_3$)



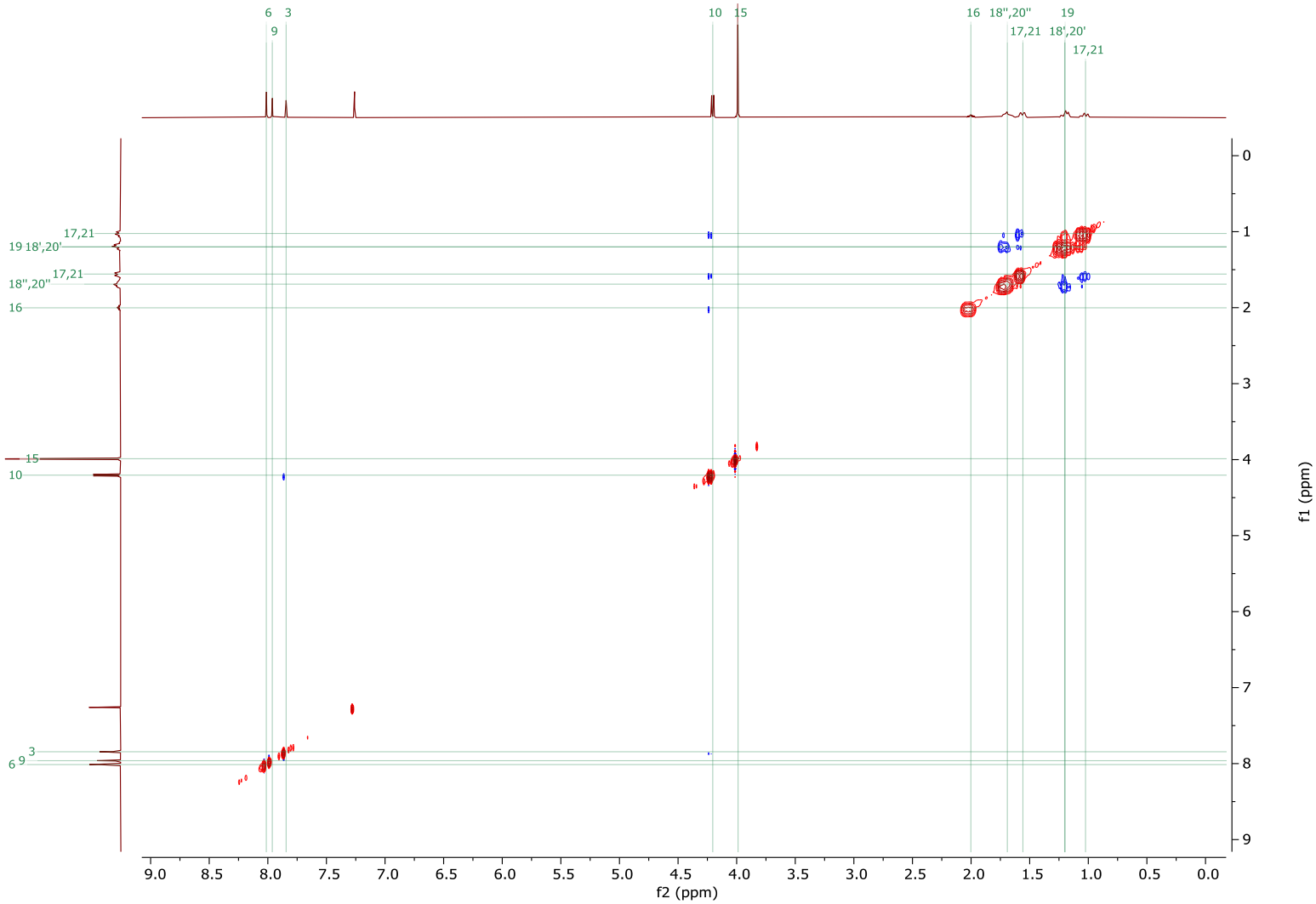
^{1}H-^{13}C HSQC ($CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

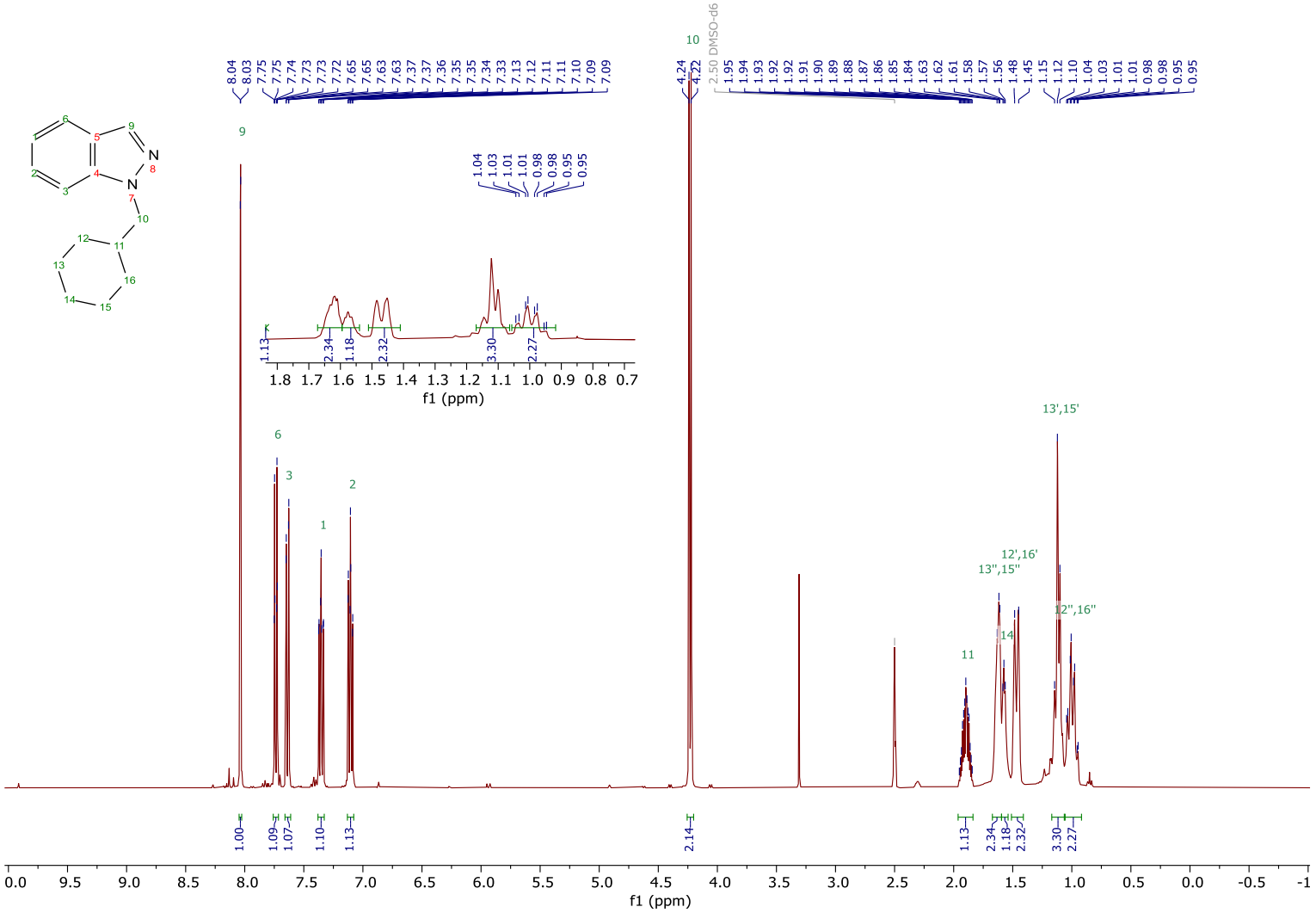


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

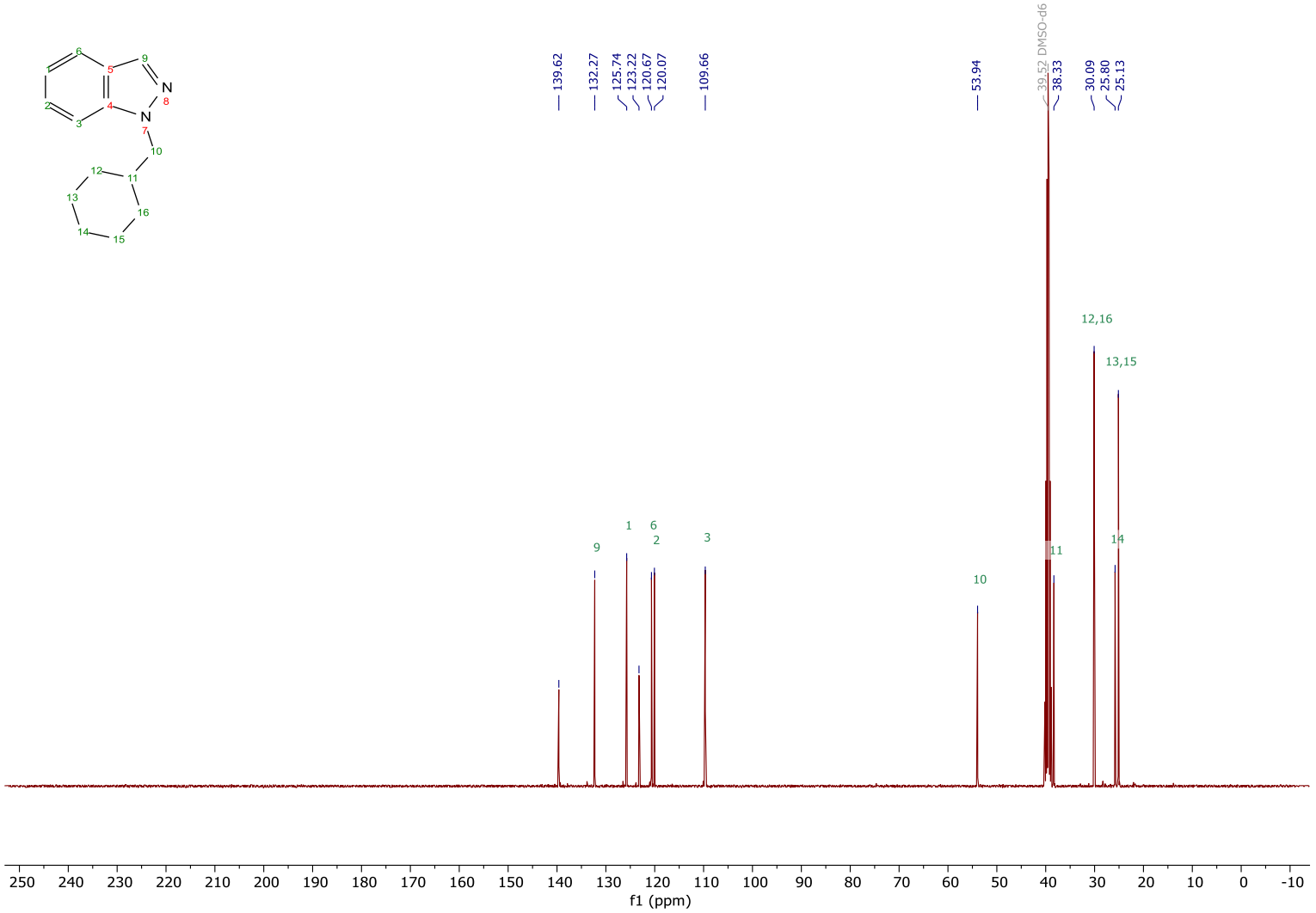


1-(cyclohexylmethyl)-1*H*-indazole (2n)

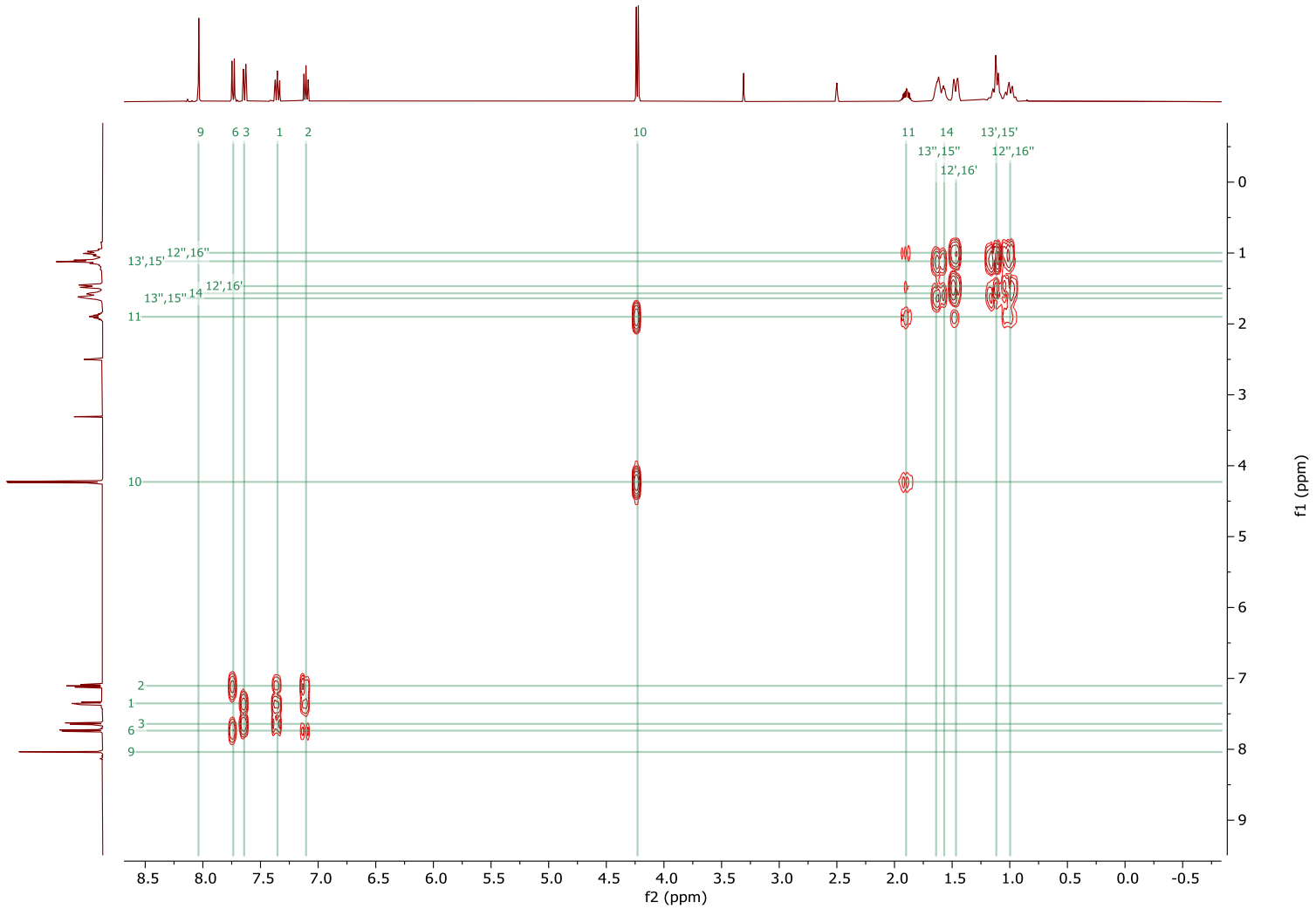
^{1}H NMR (400 MHz, DMSO-d_6)



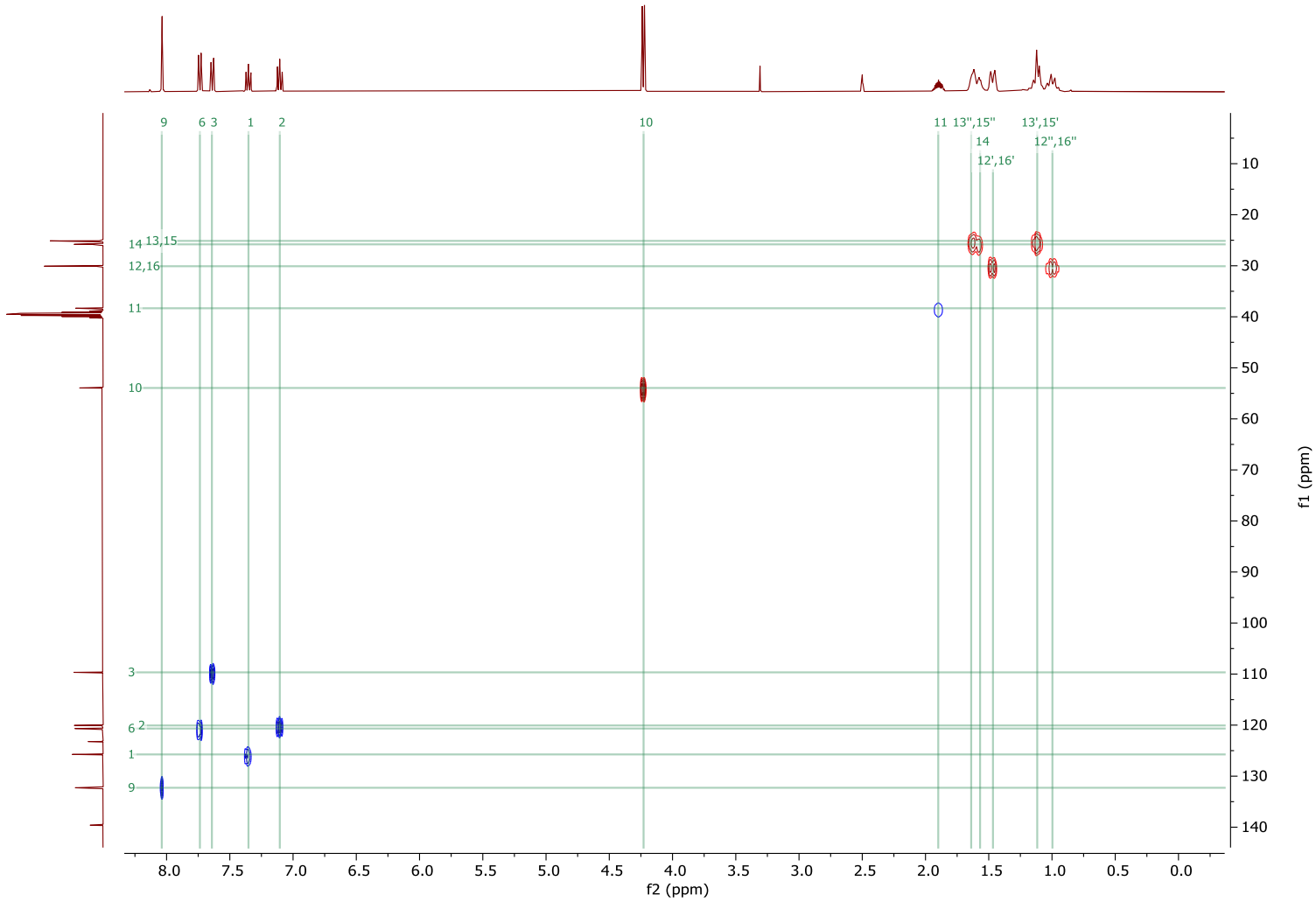
^{13}C NMR (101 MHz, DMSO-d_6)



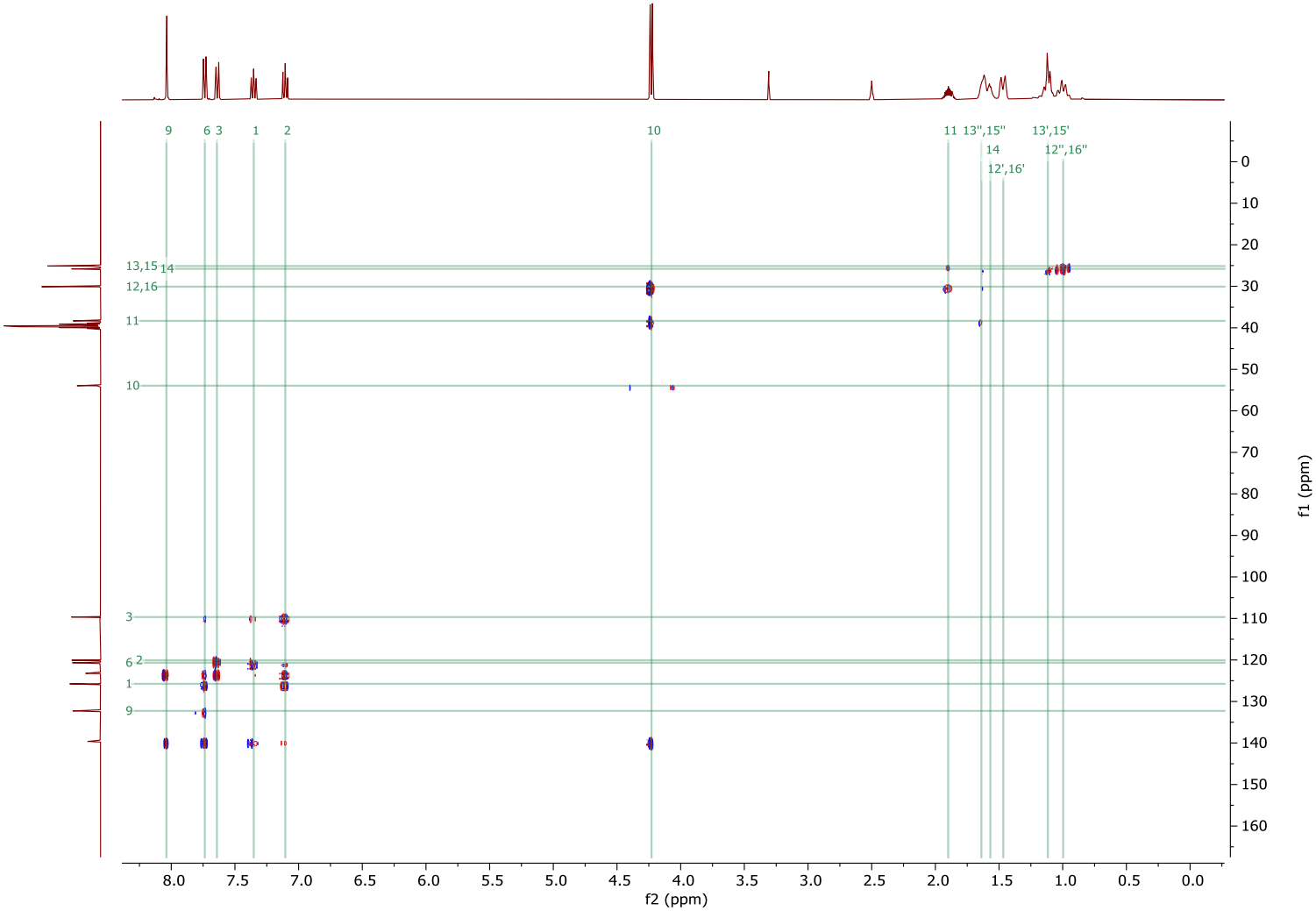
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



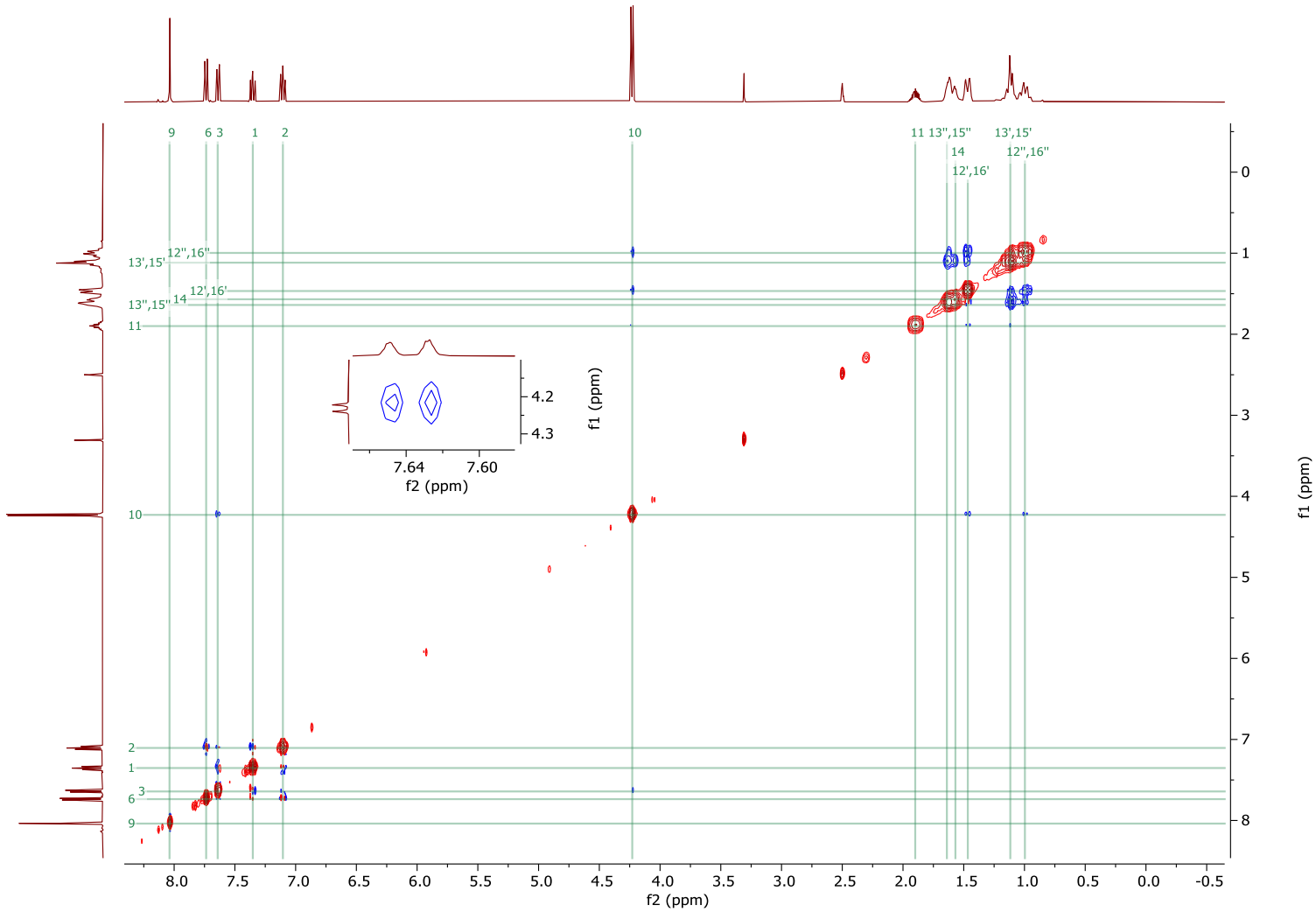
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

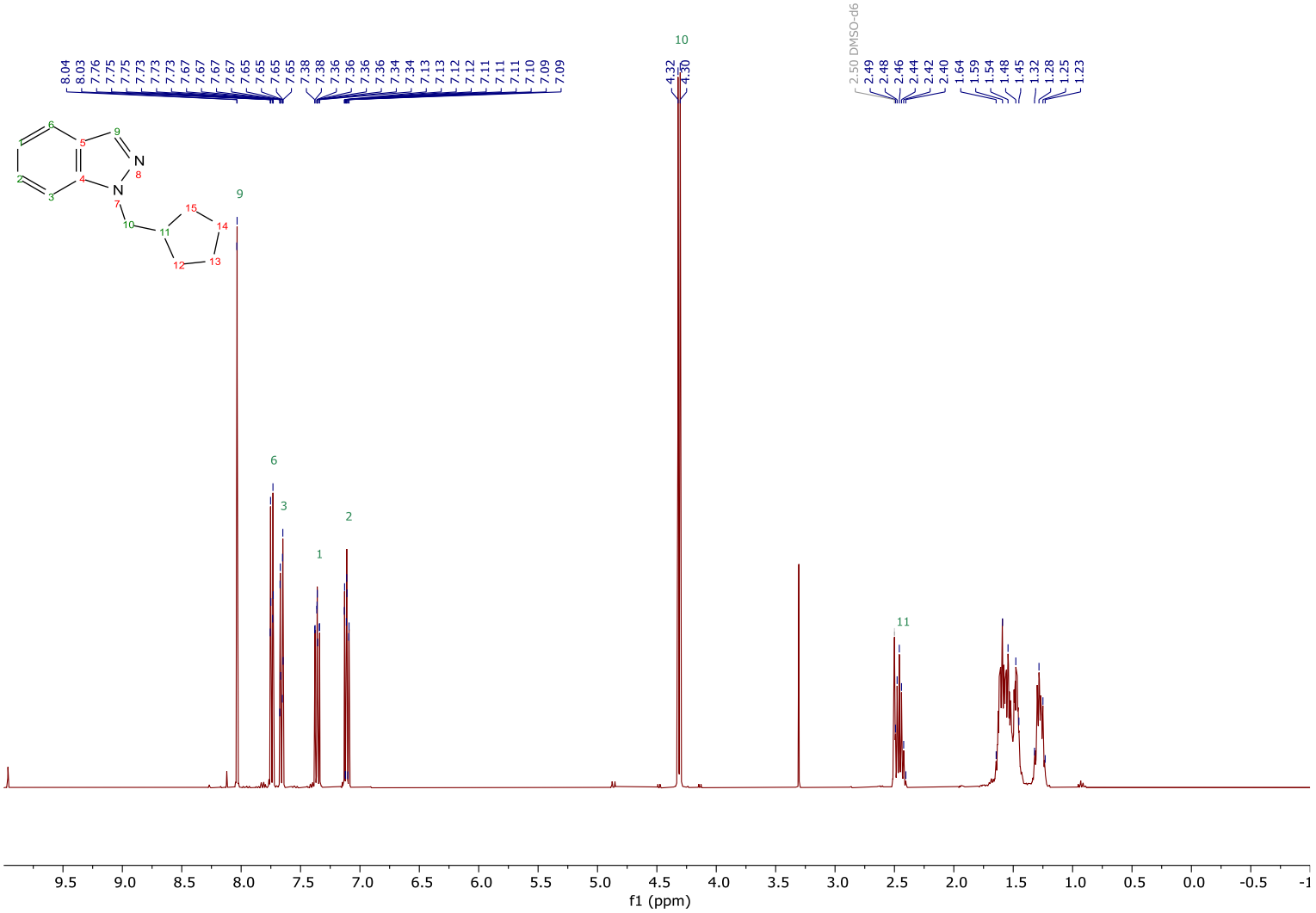


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

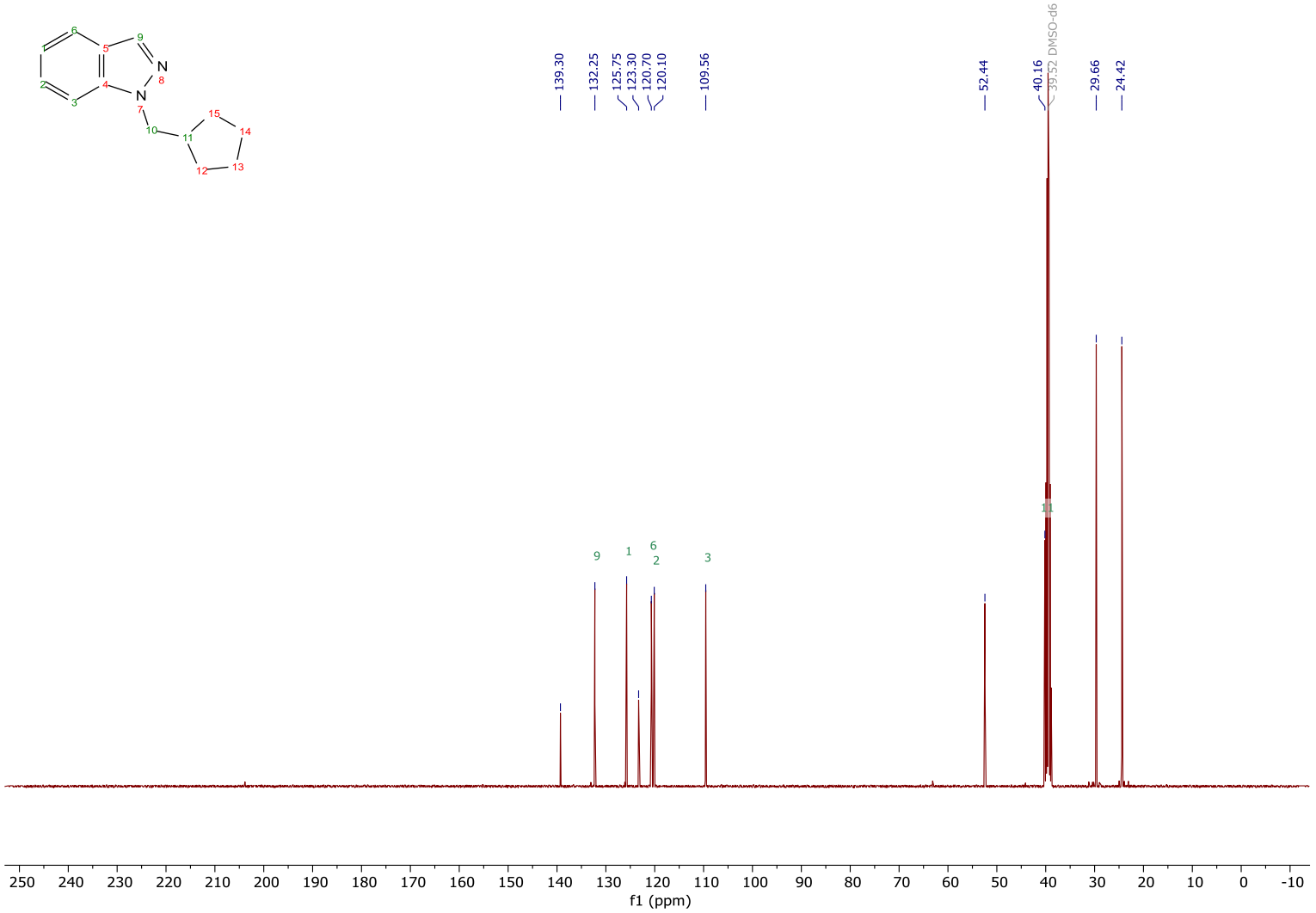


1-(cyclopentylmethyl)-1*H*-indazole (2o)

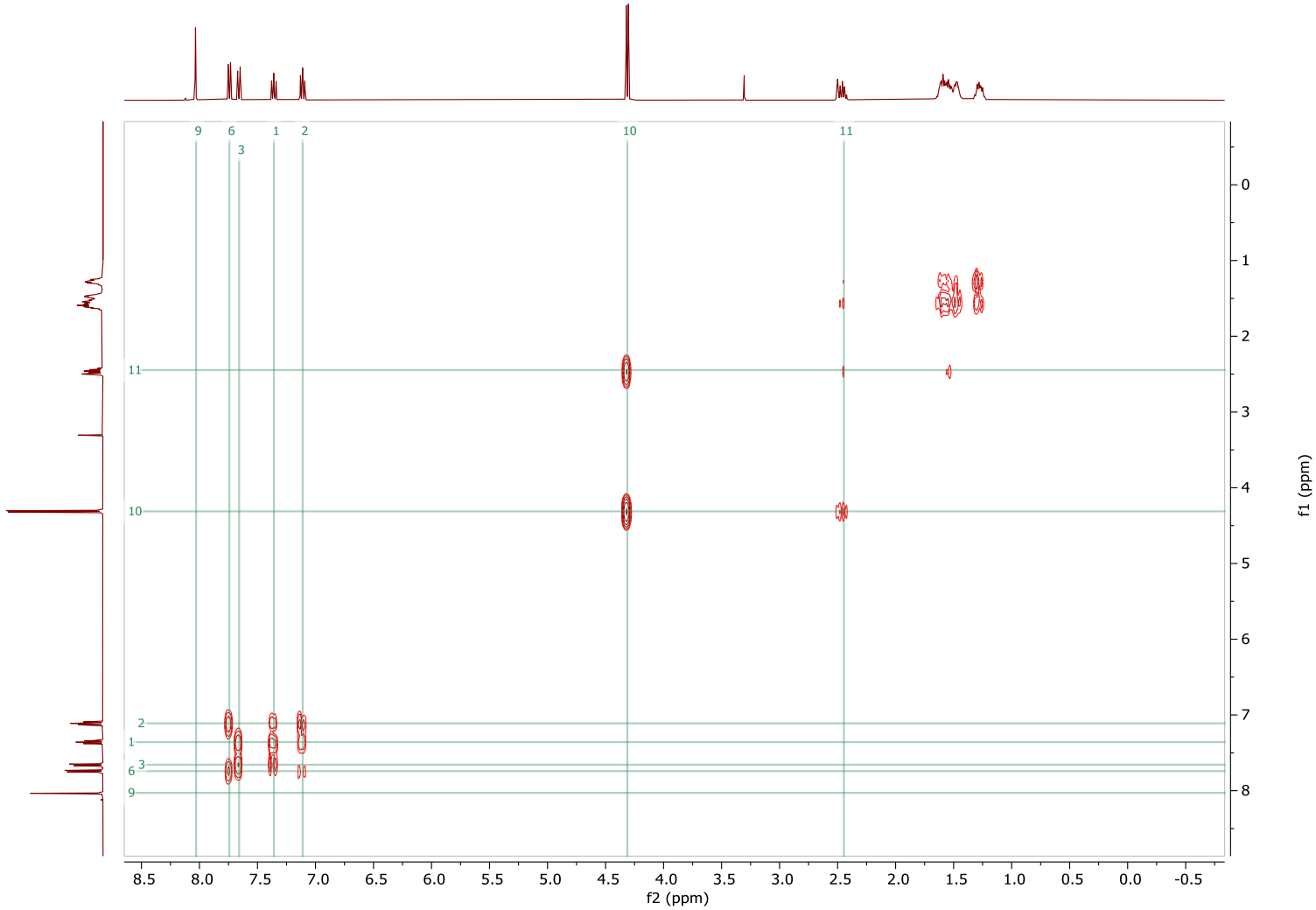
^{1}H NMR (400 MHz, DMSO-d_6)



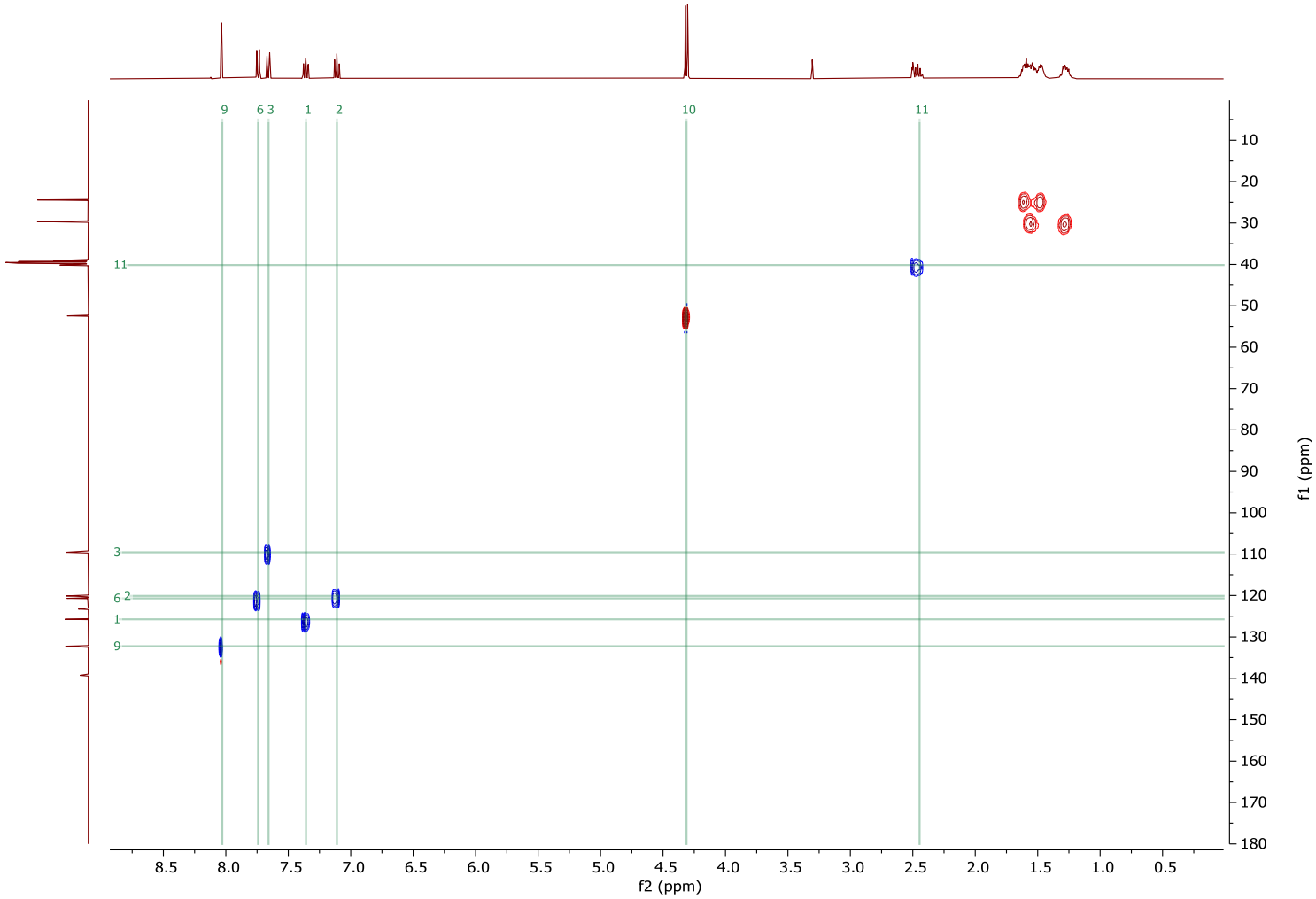
^{13}C NMR (101 MHz, DMSO-d_6)



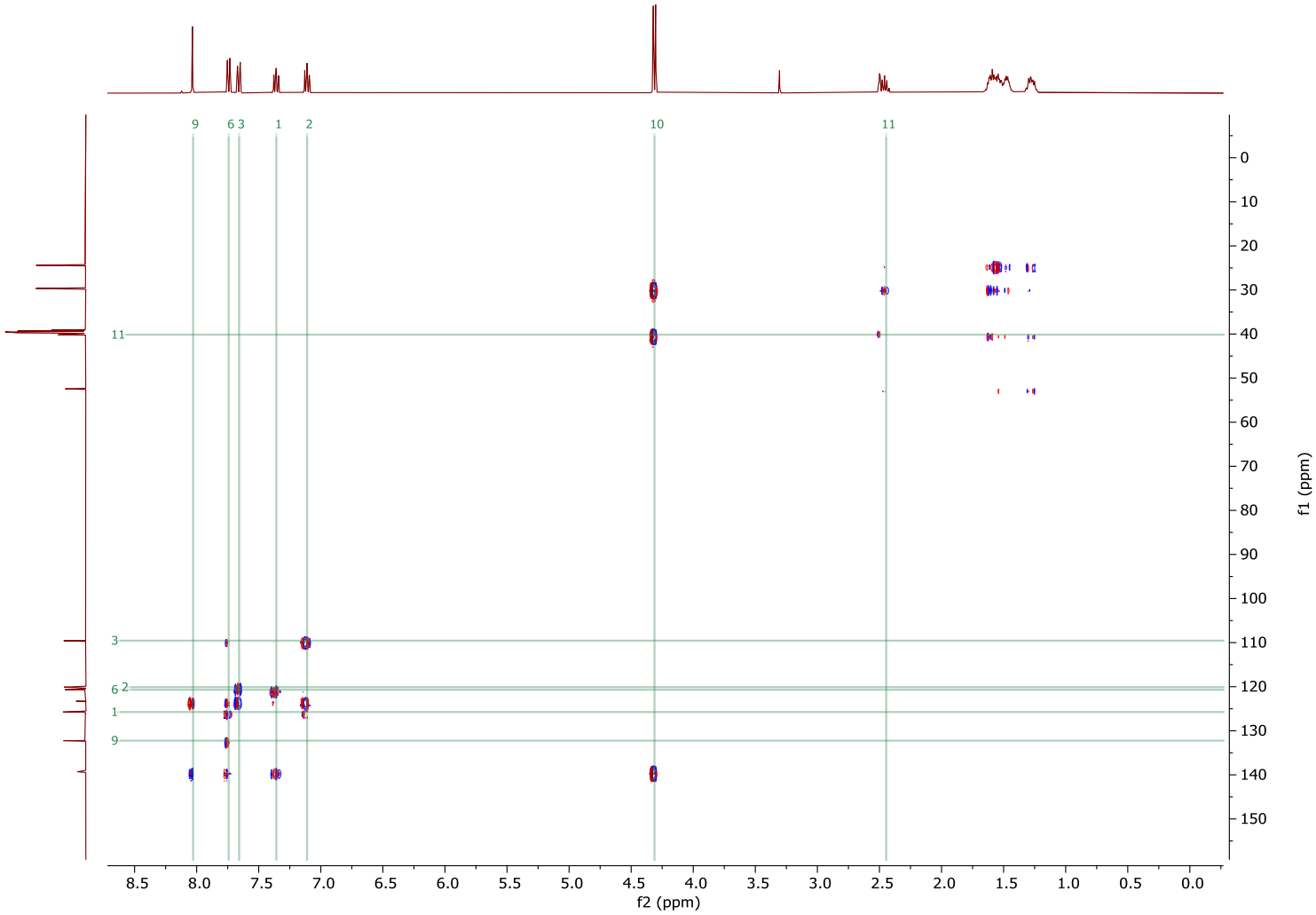
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



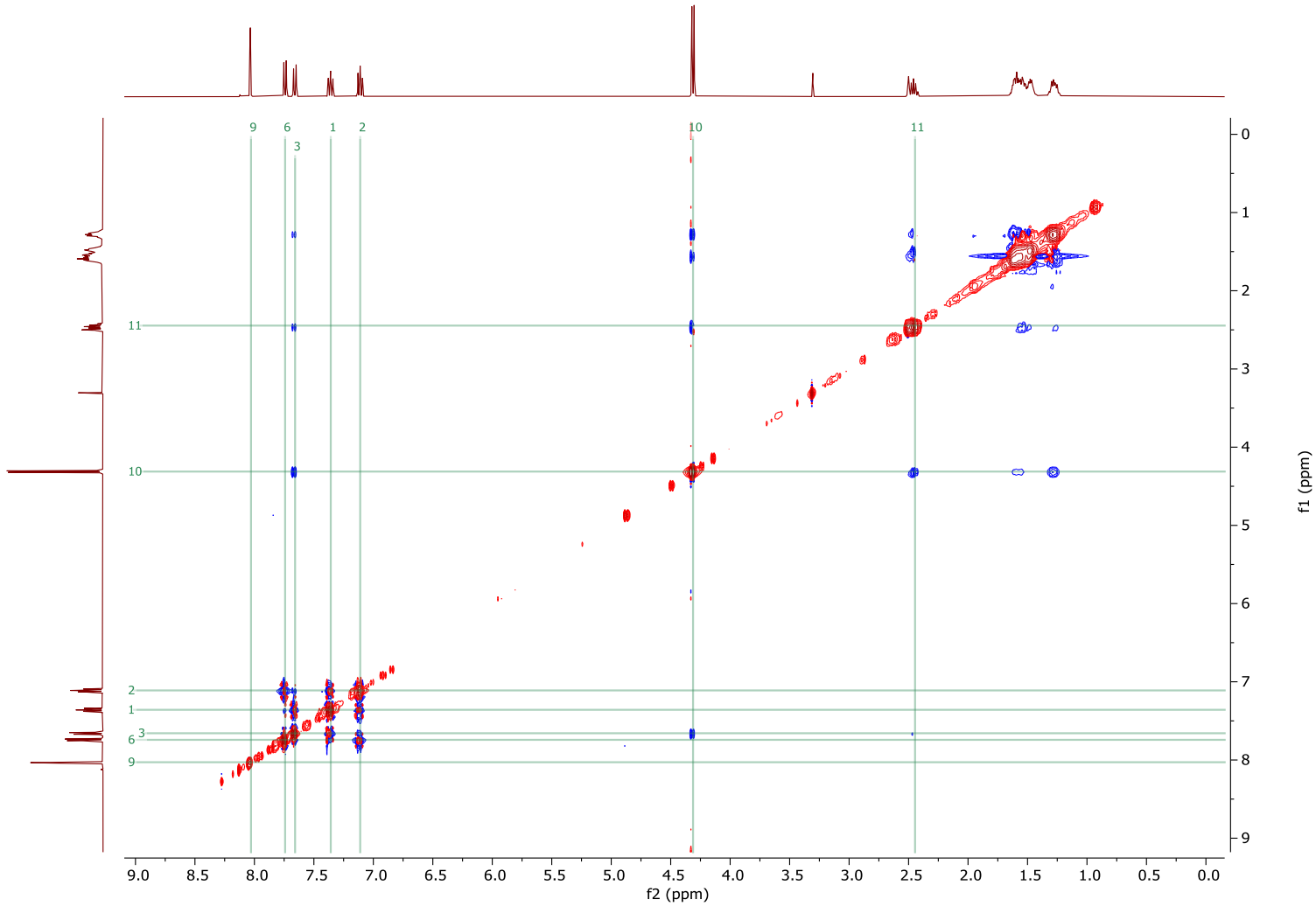
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

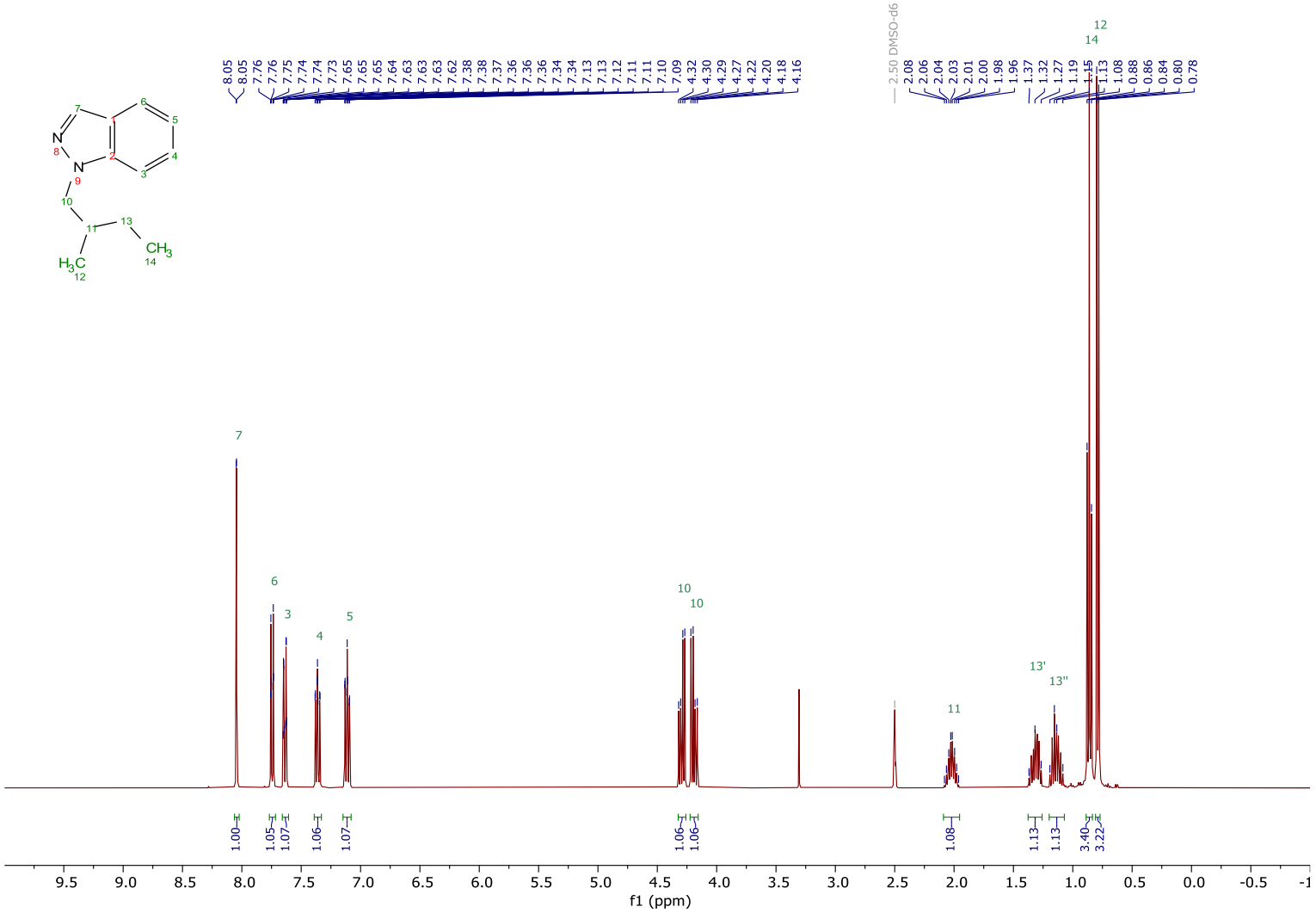


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

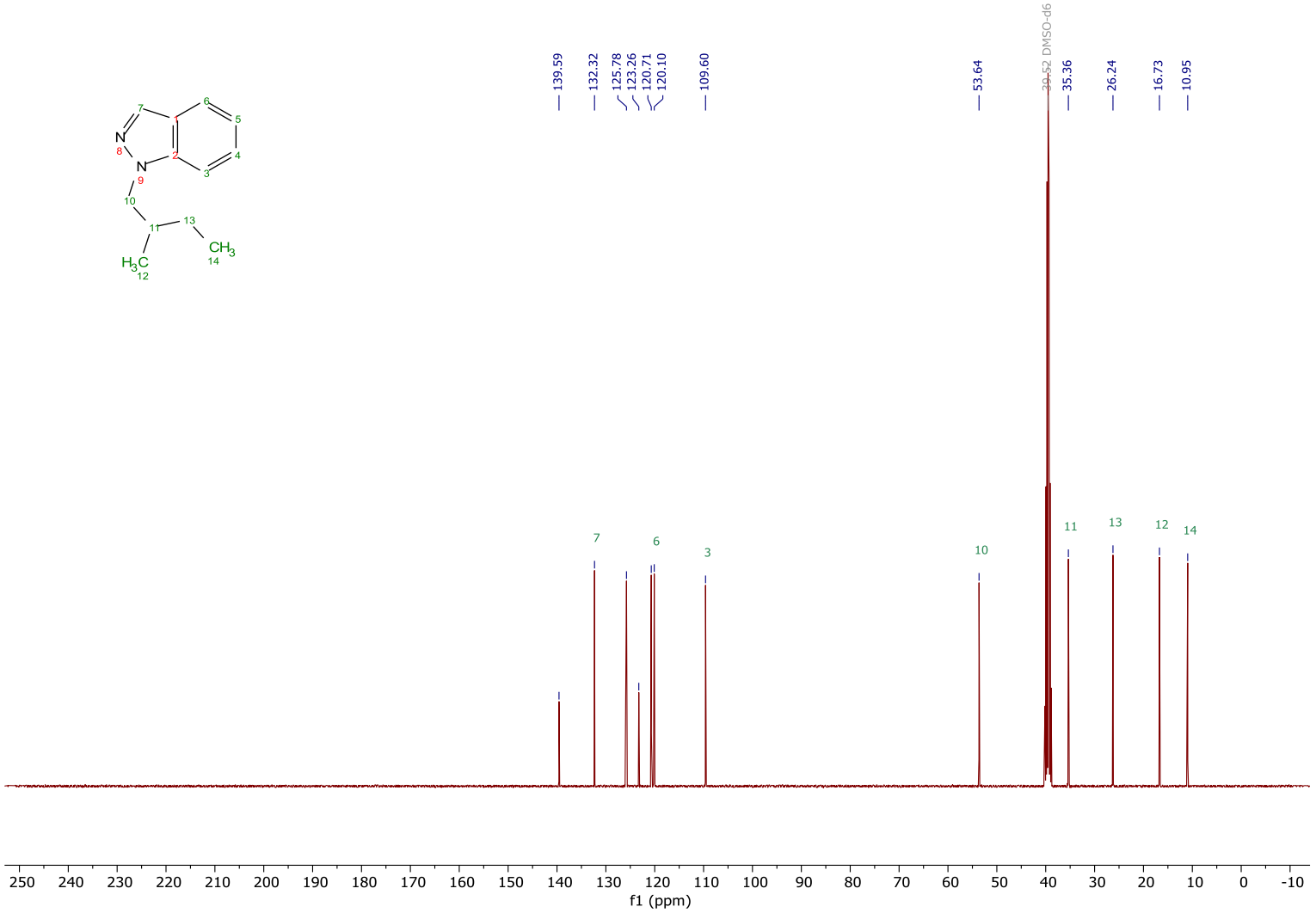


1-(2-methylbutyl)-1*H*-indazole (2p)

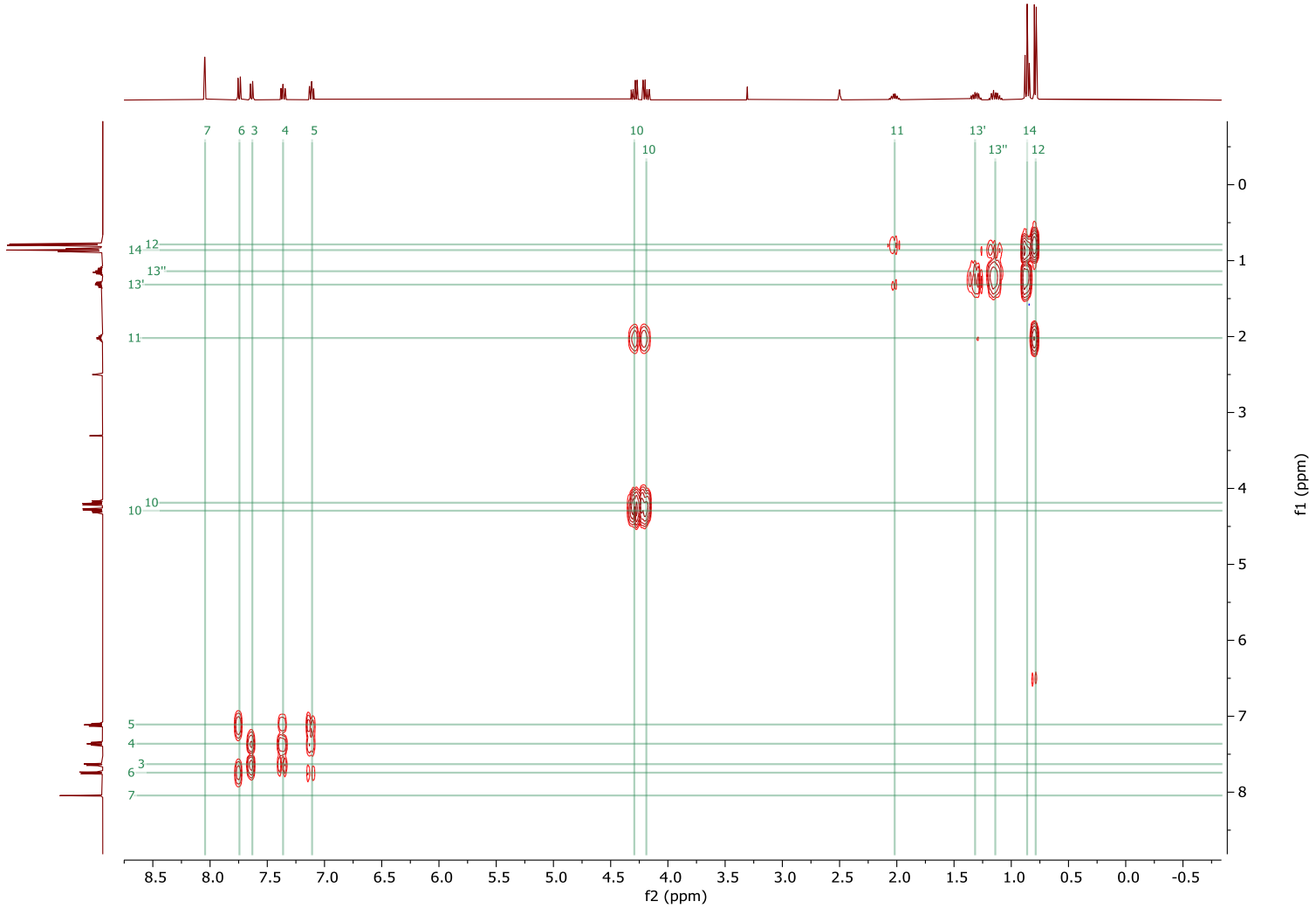
^{1}H NMR (400 MHz, DMSO-d_6)



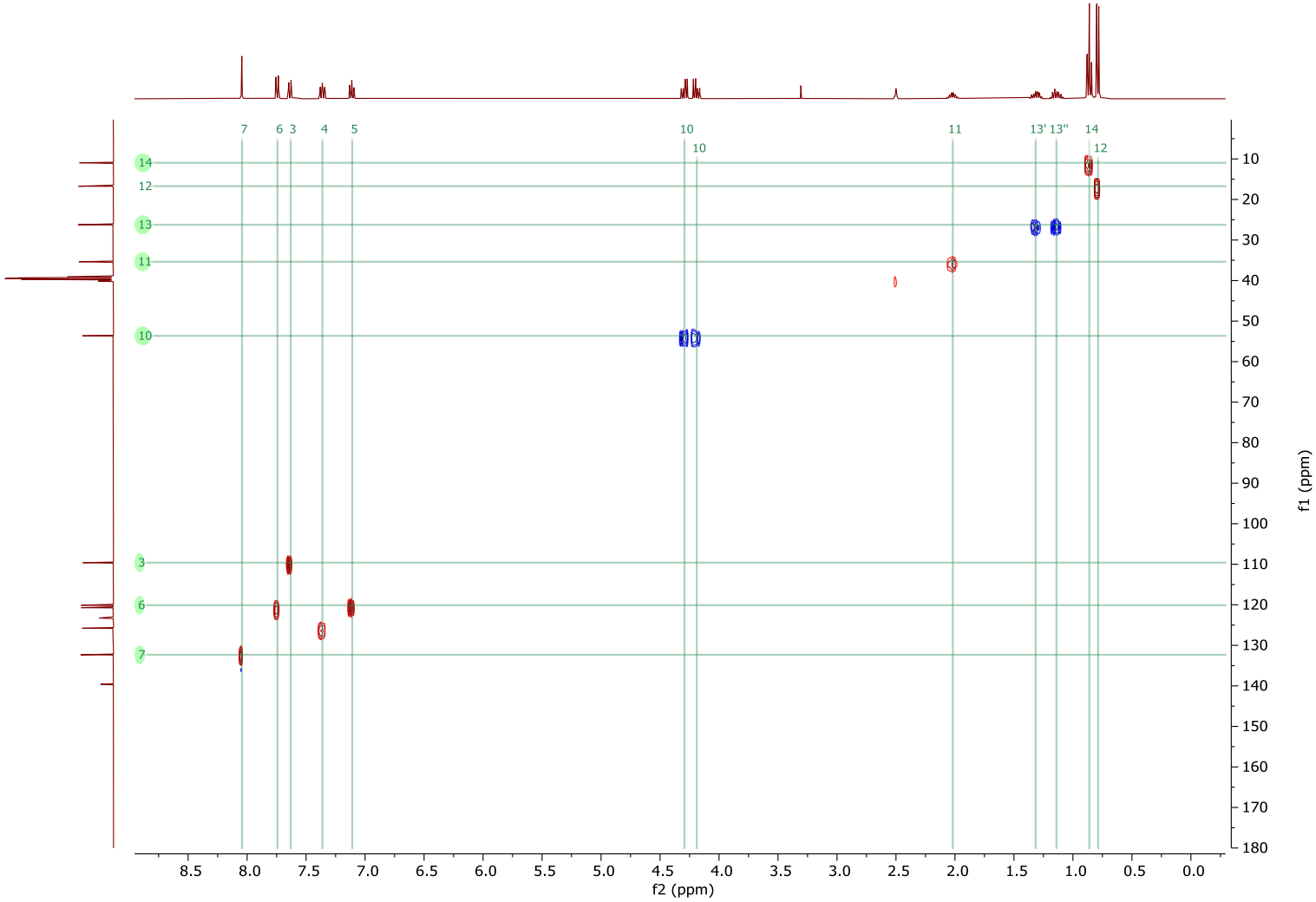
^{13}C NMR (101 MHz, DMSO-d_6)



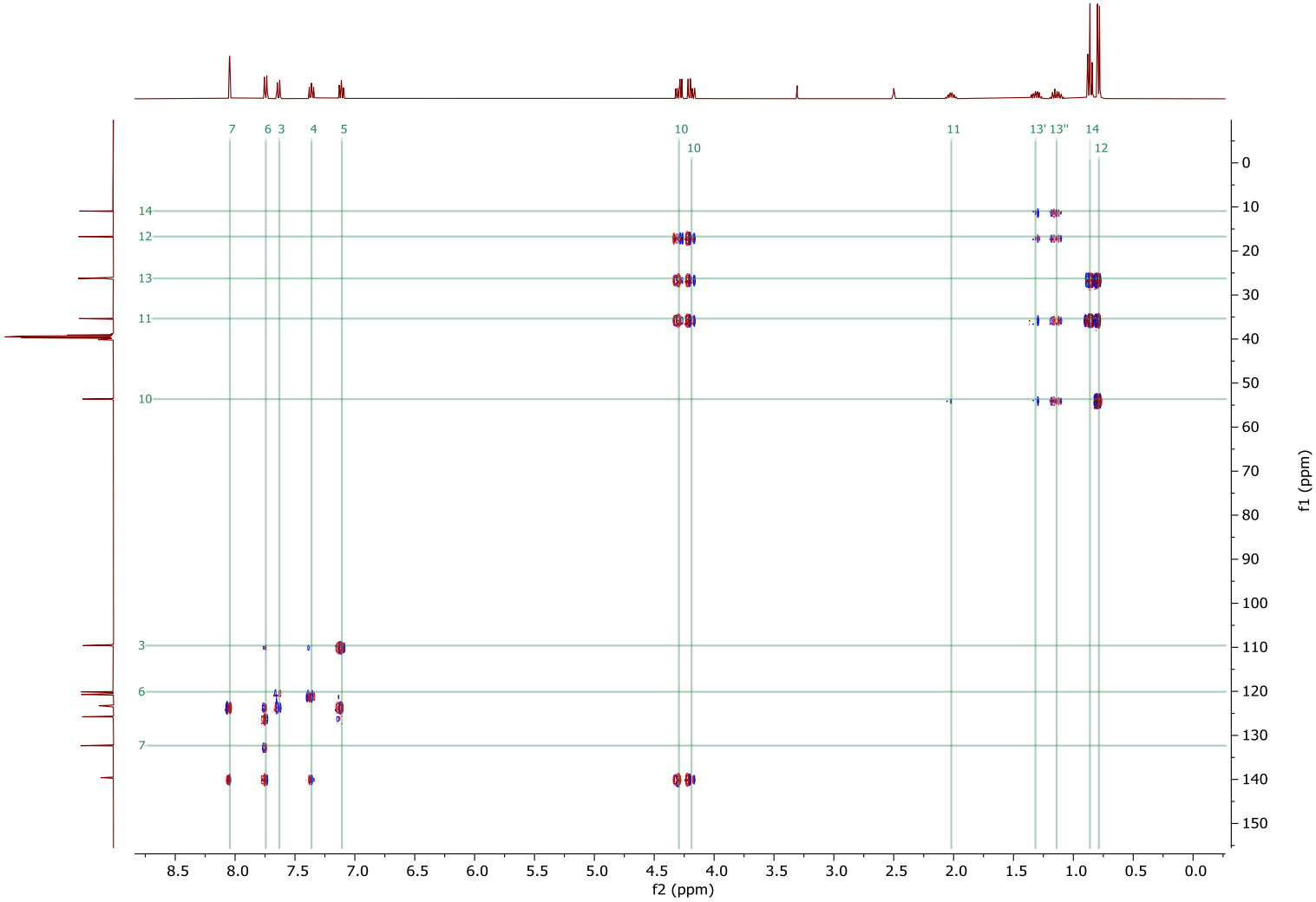
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



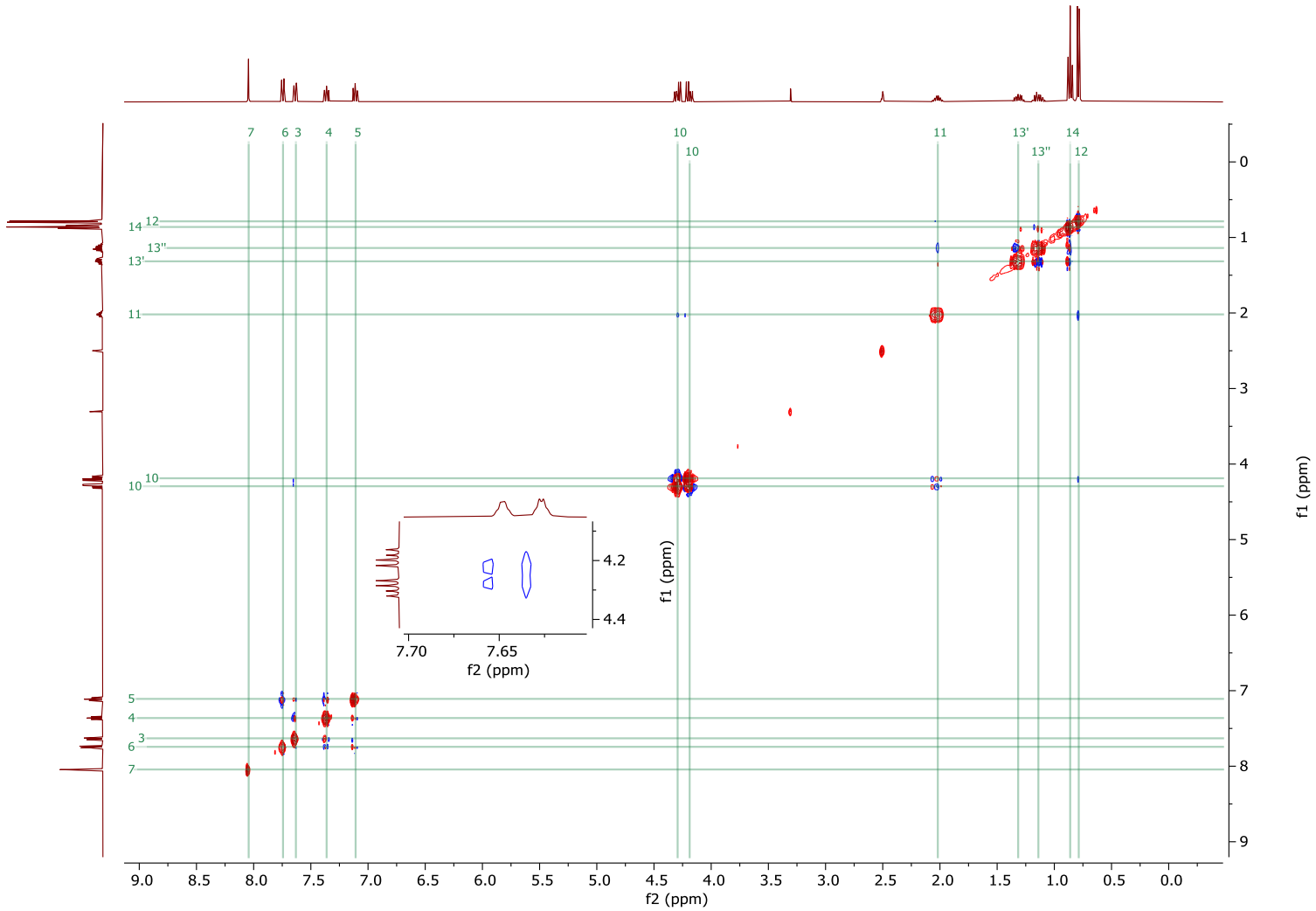
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

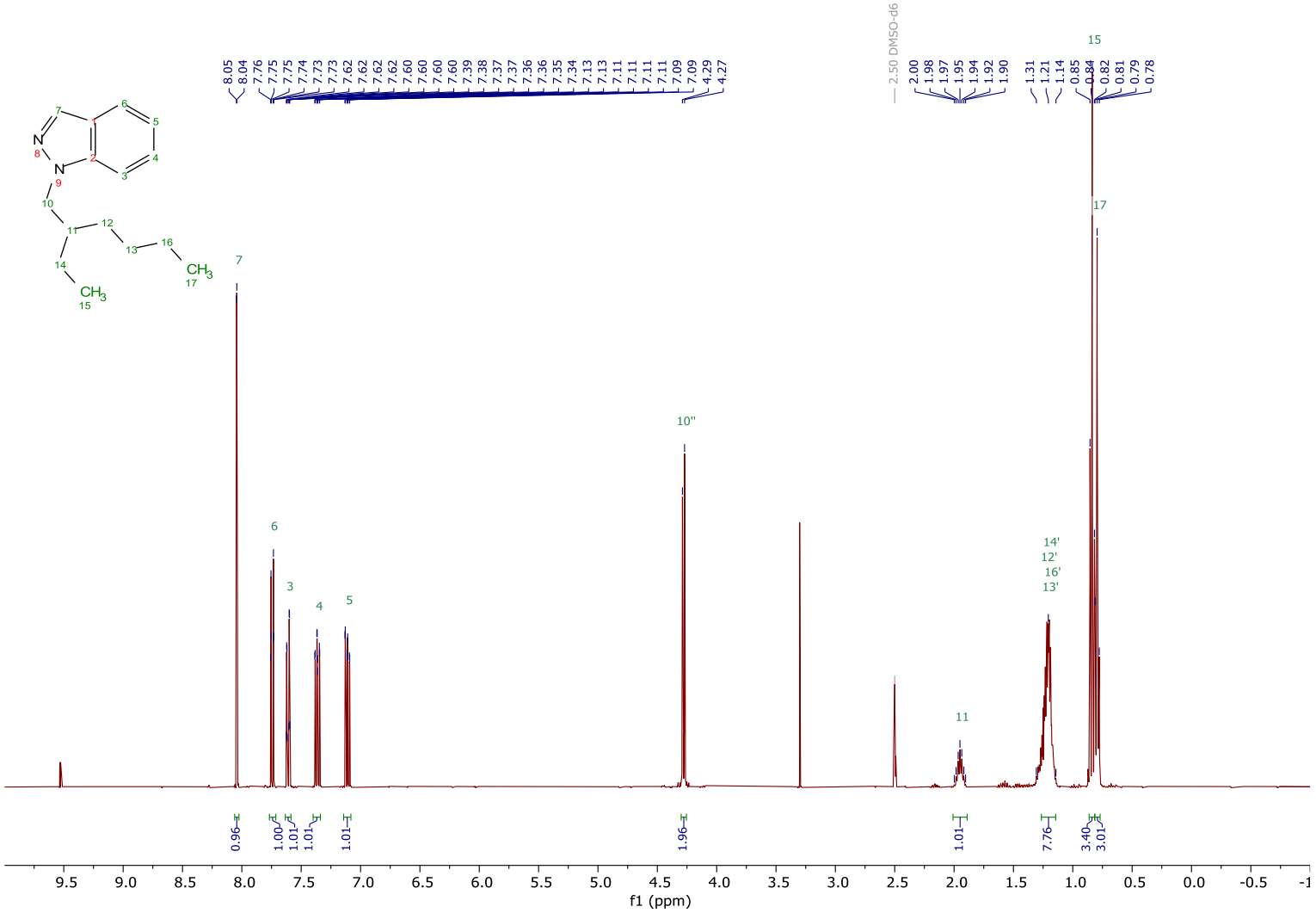


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

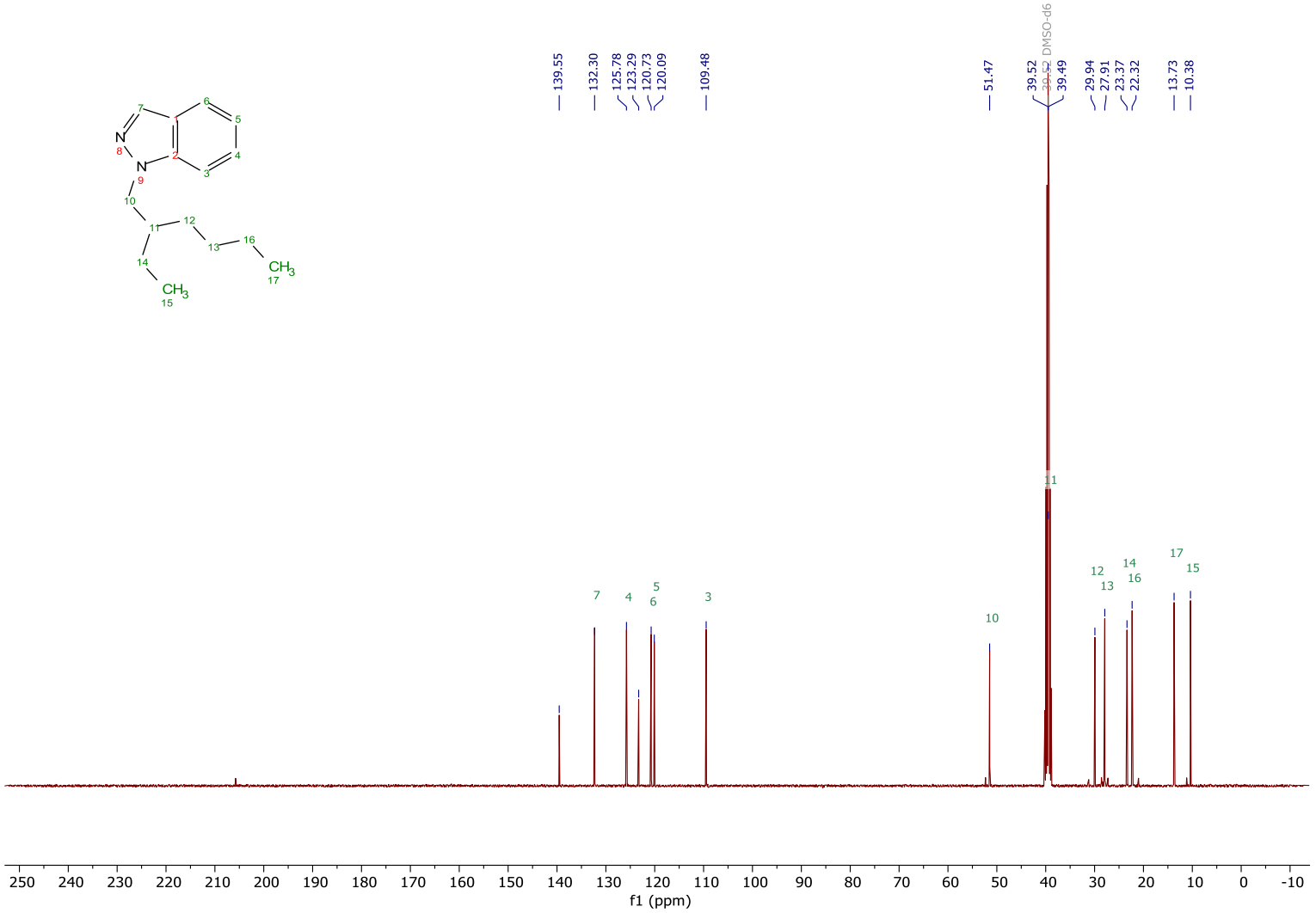


1-(2-ethylhexyl)-1*H*-indazole (2q)

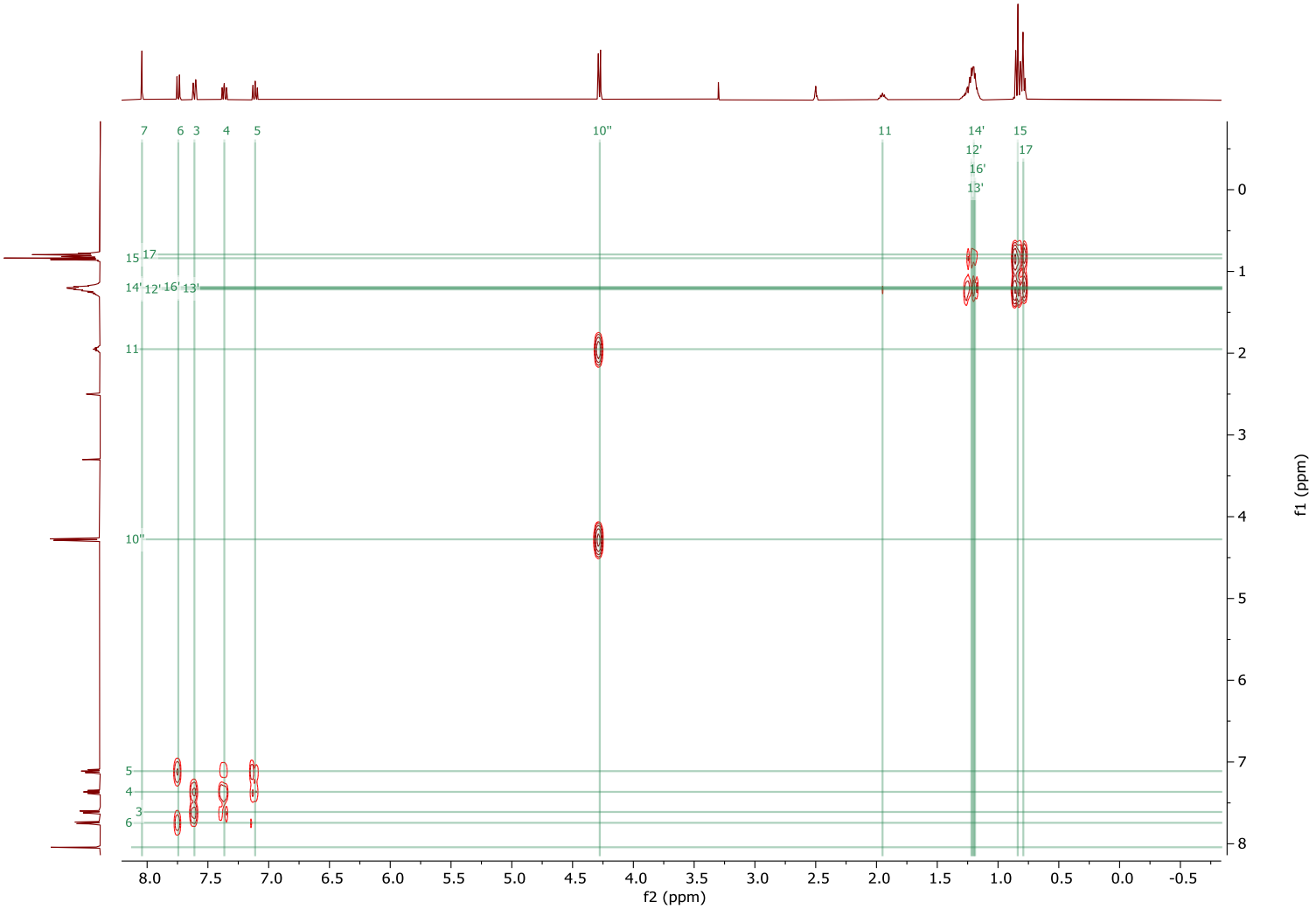
^{1}H NMR (400 MHz, DMSO-d_6)



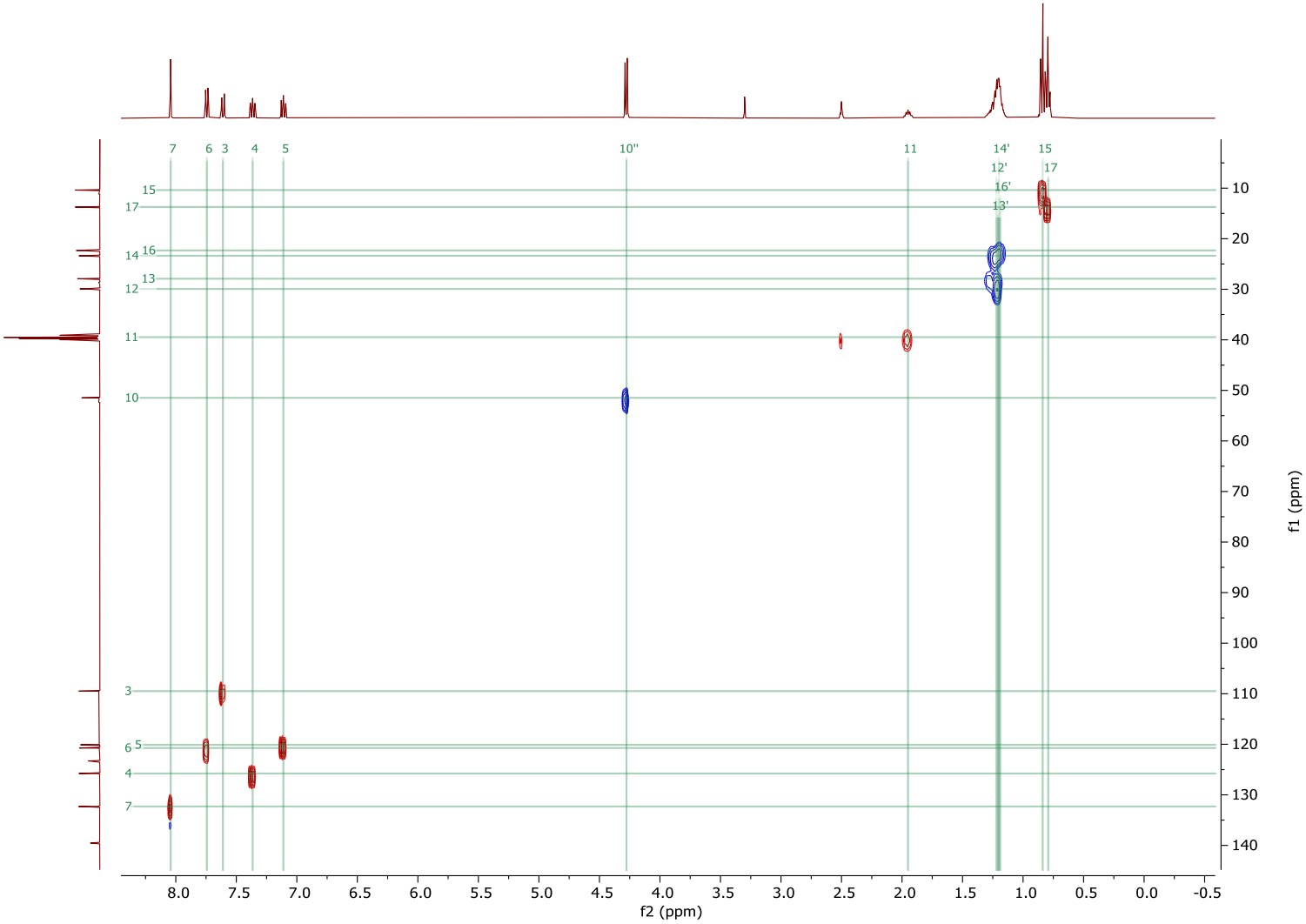
^{13}C NMR (101 MHz, DMSO-d_6)



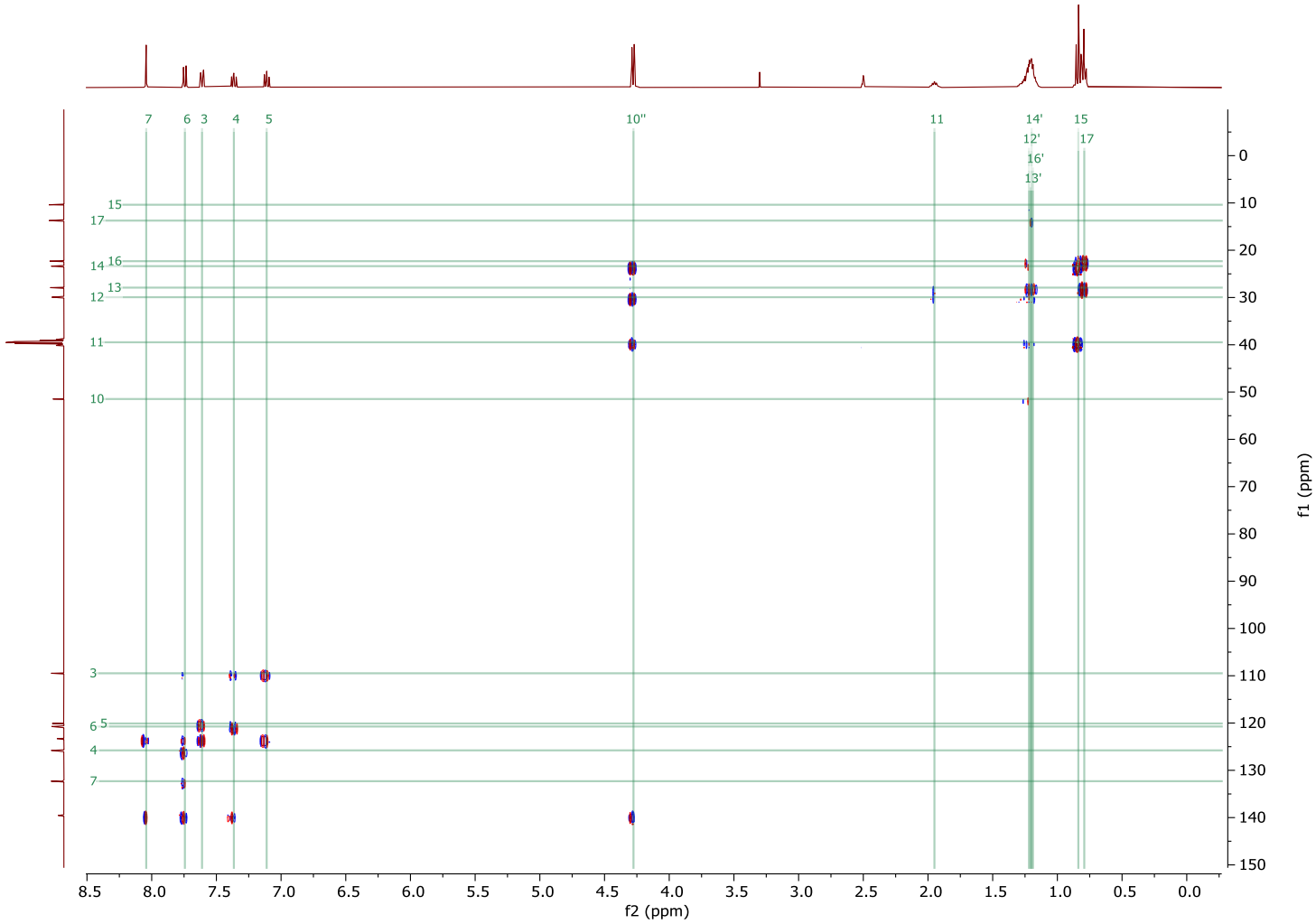
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



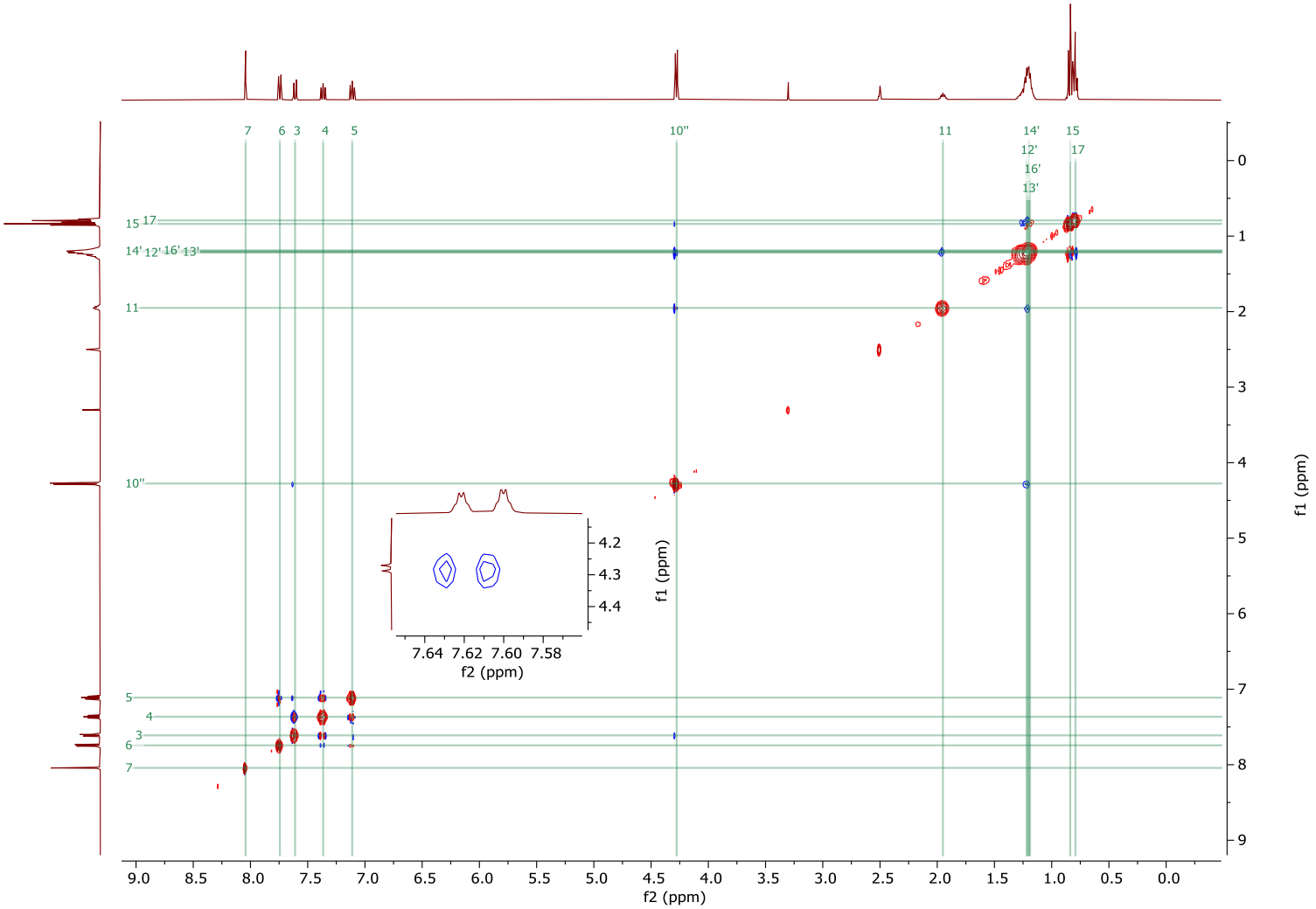
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

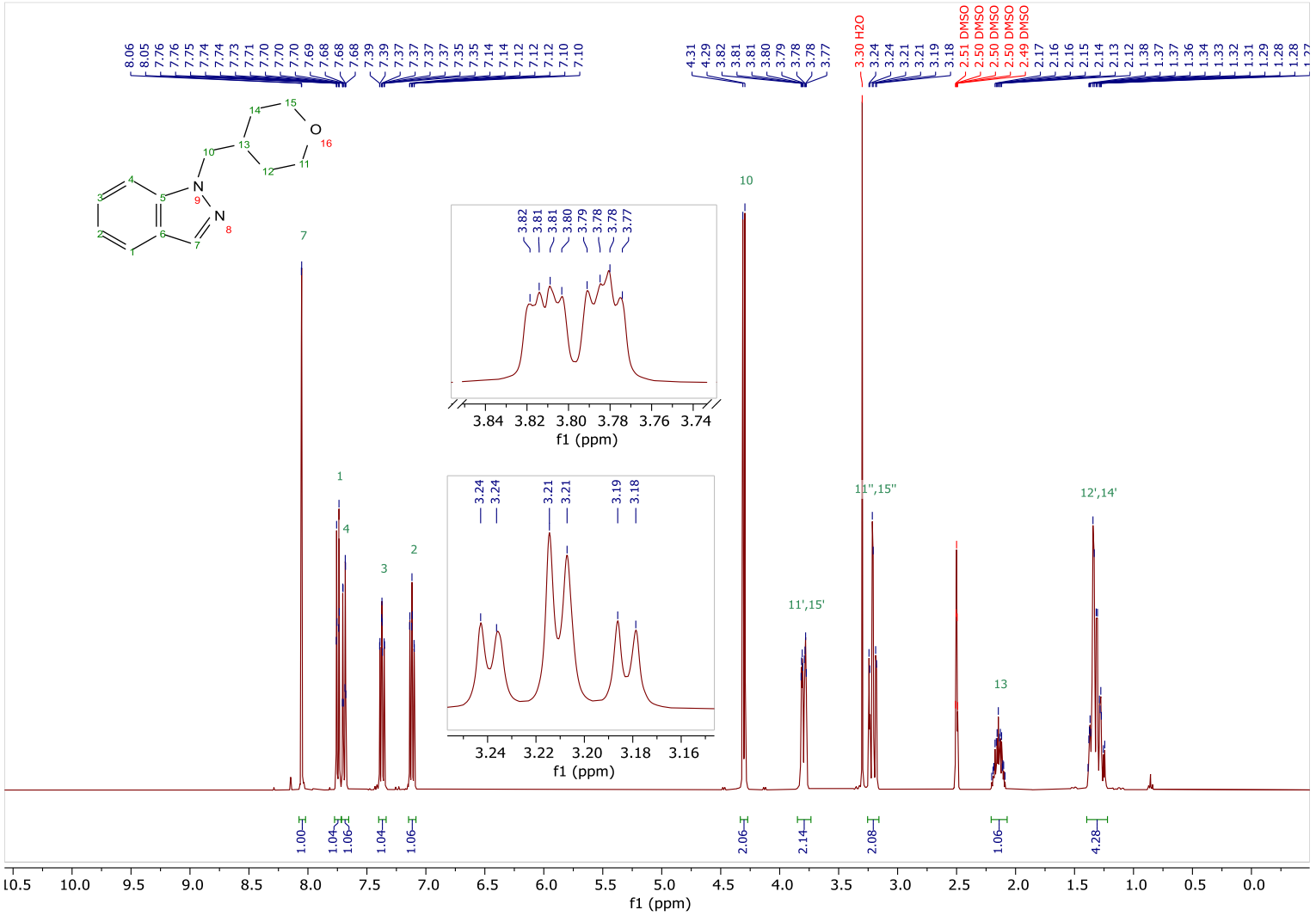


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

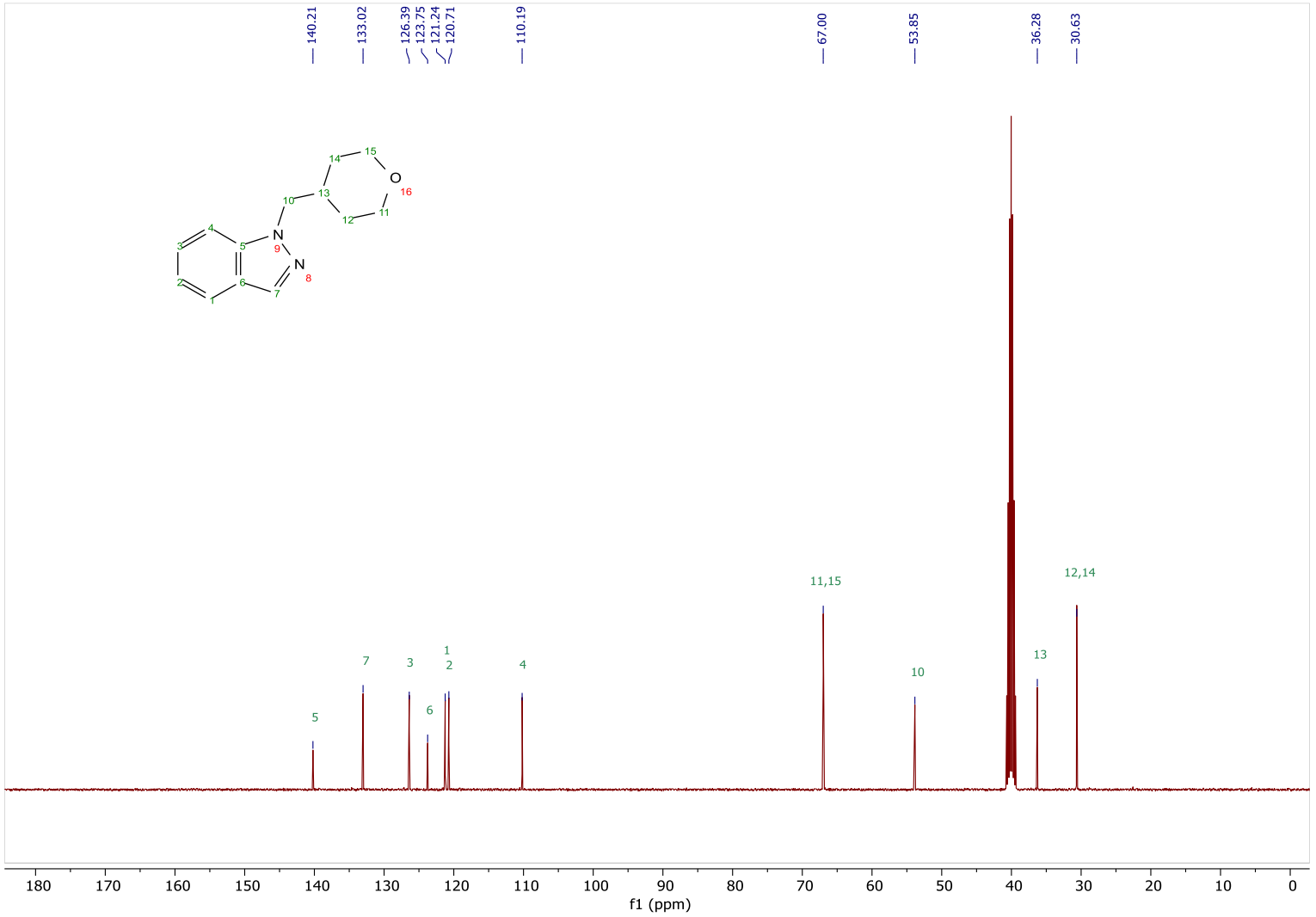


1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-indazole (2r)

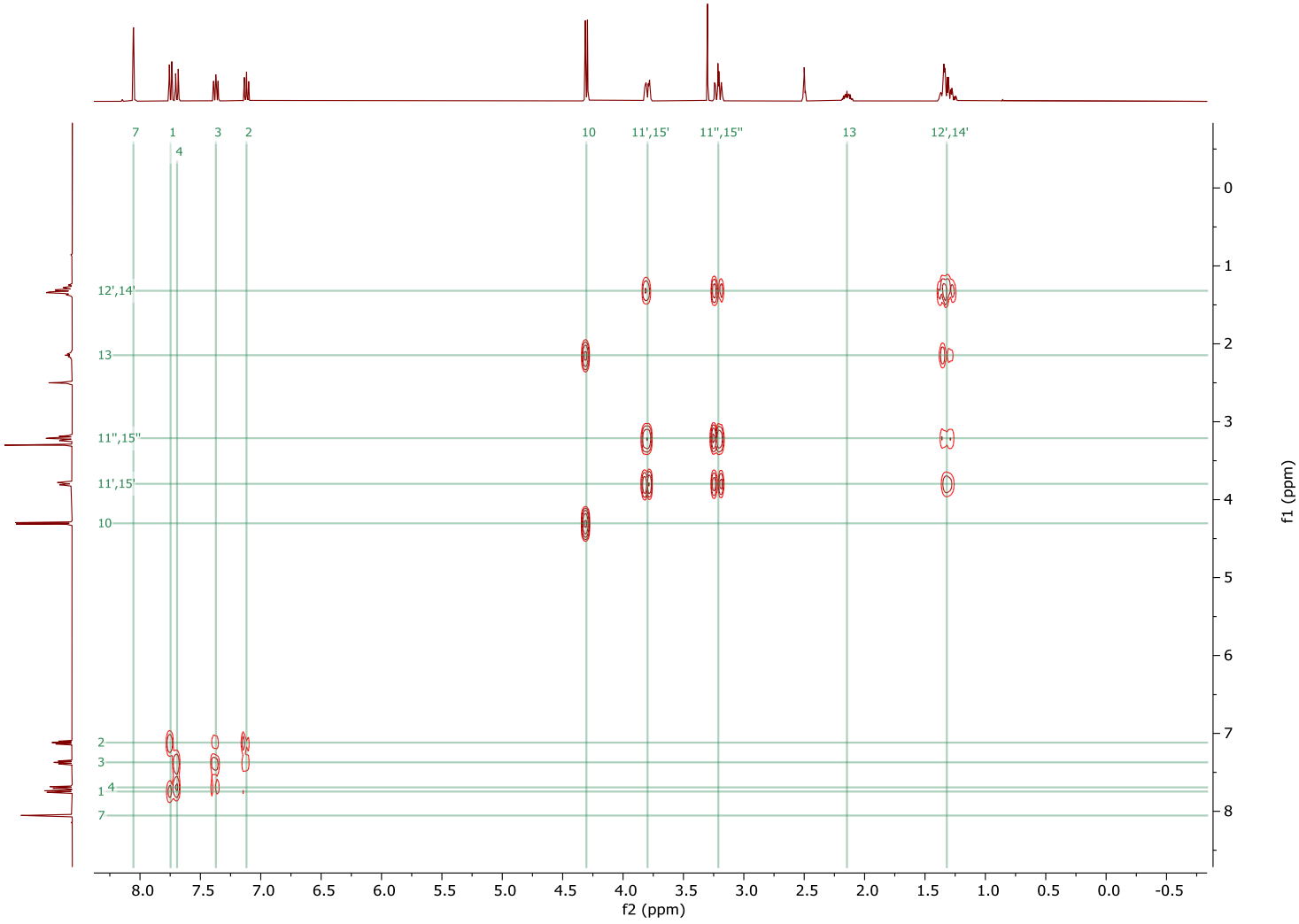
^{1}H NMR (400 MHz, DMSO-d_6)



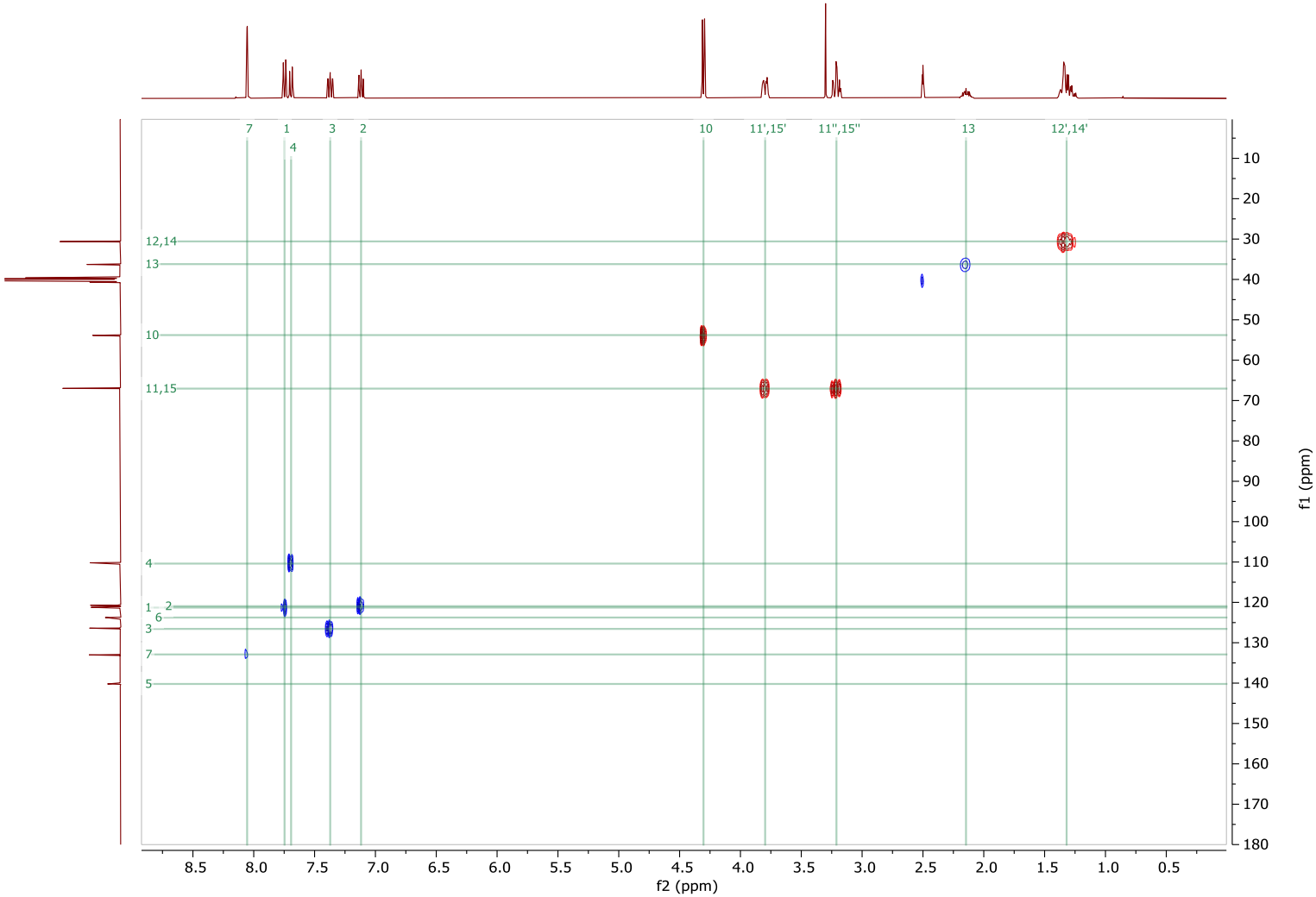
^{13}C NMR (101 MHz, DMSO-d_6)



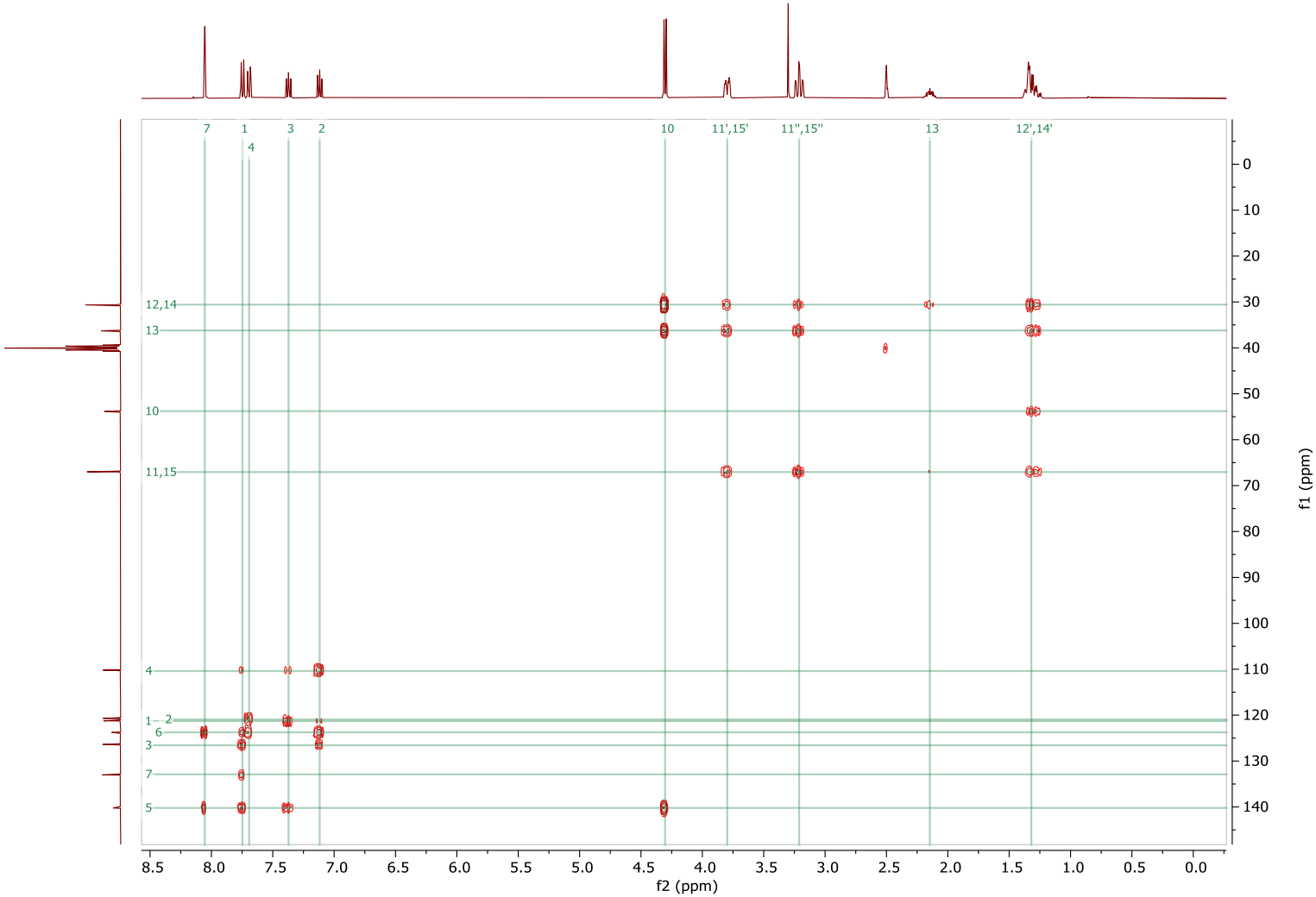
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



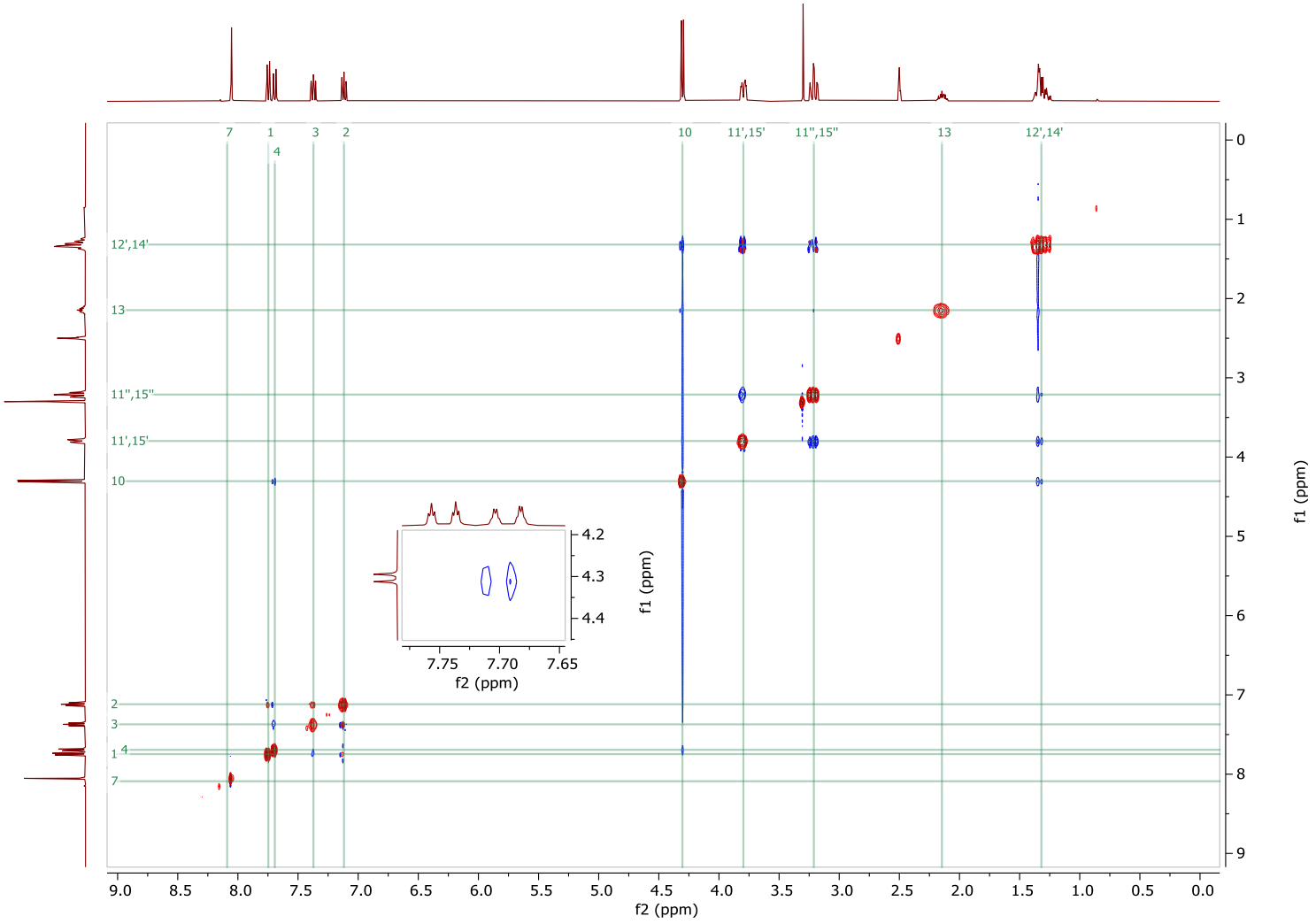
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

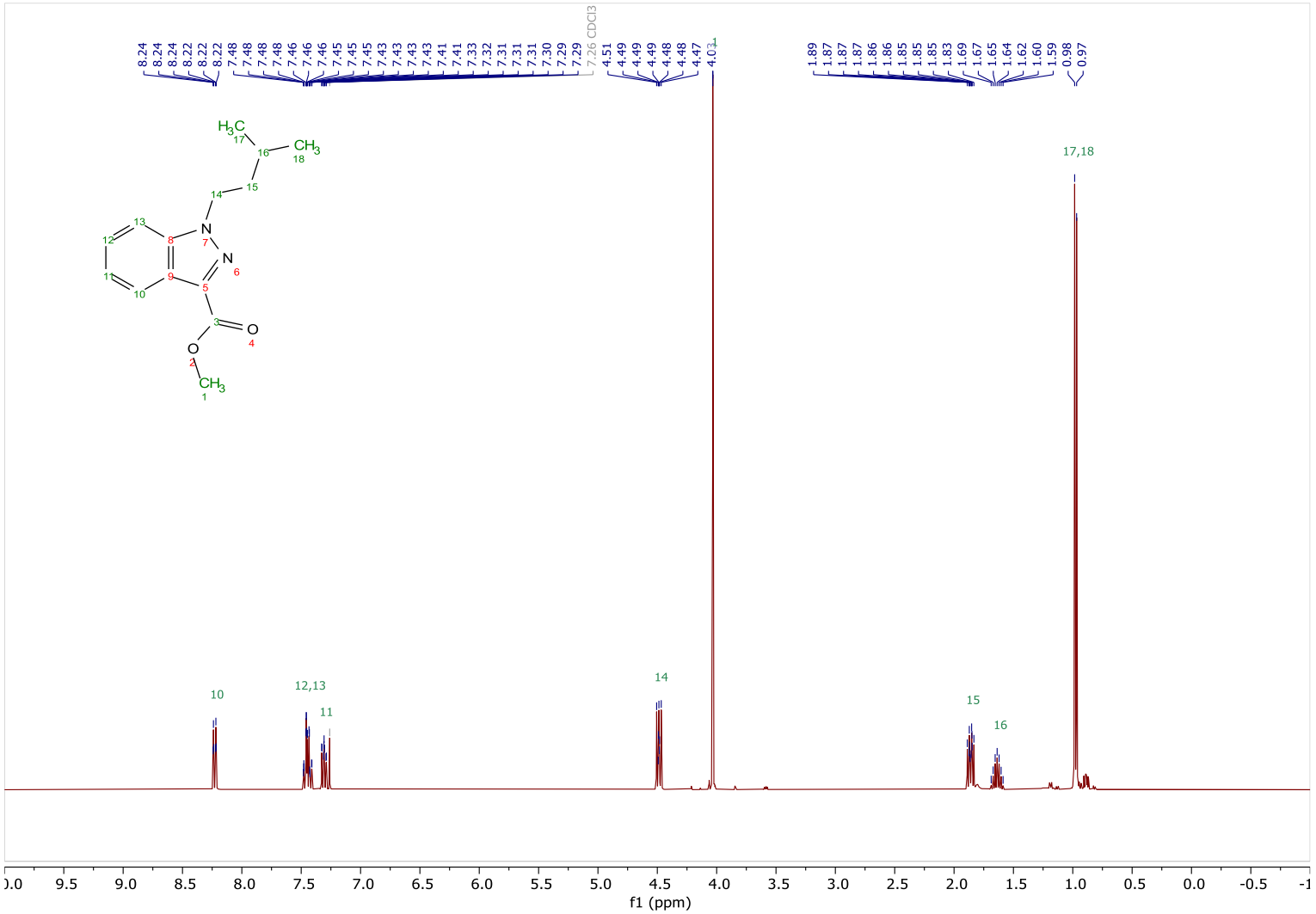


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

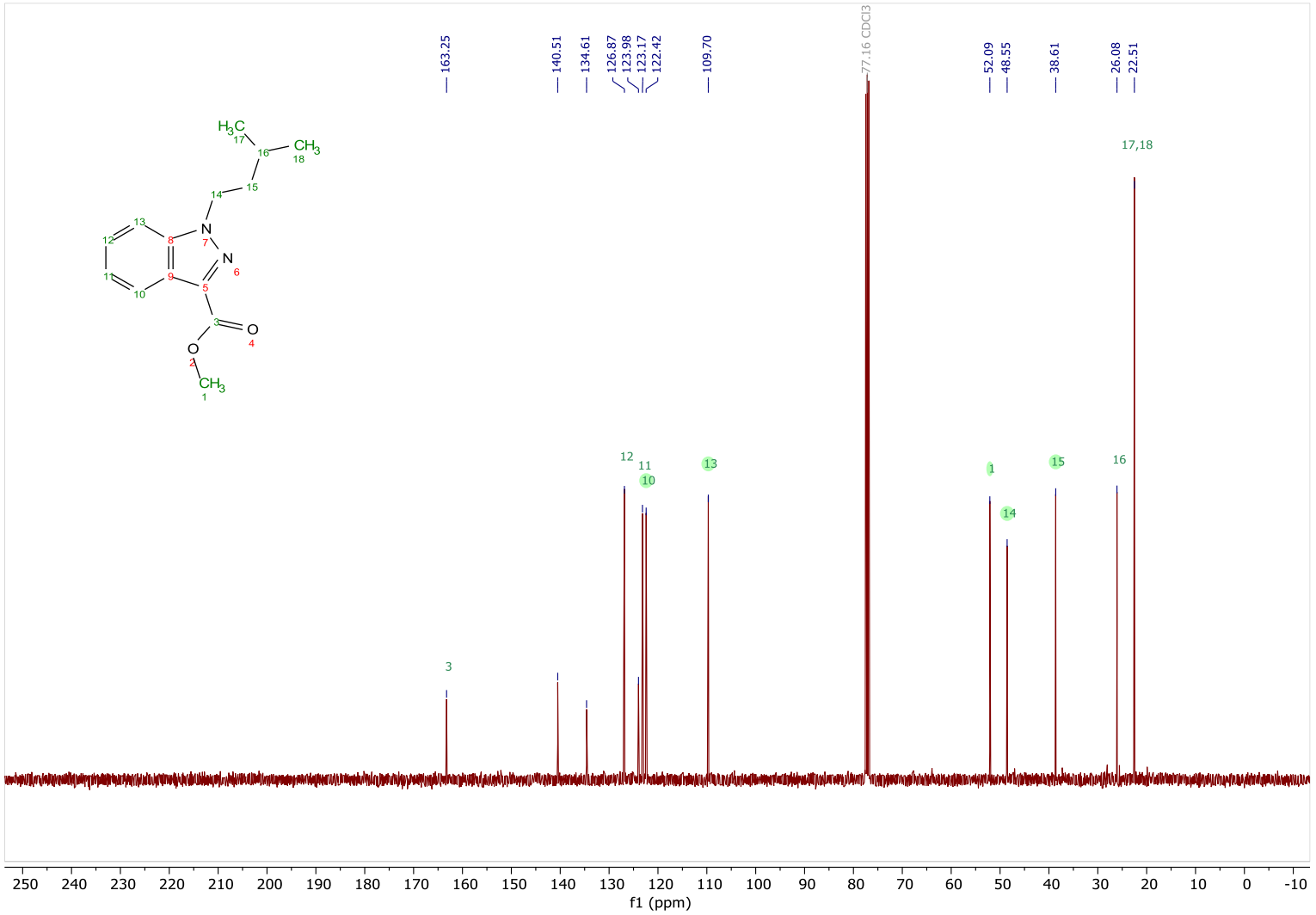


Methyl 1-isopentyl-1*H*-indazole-3-carboxylate (2s)

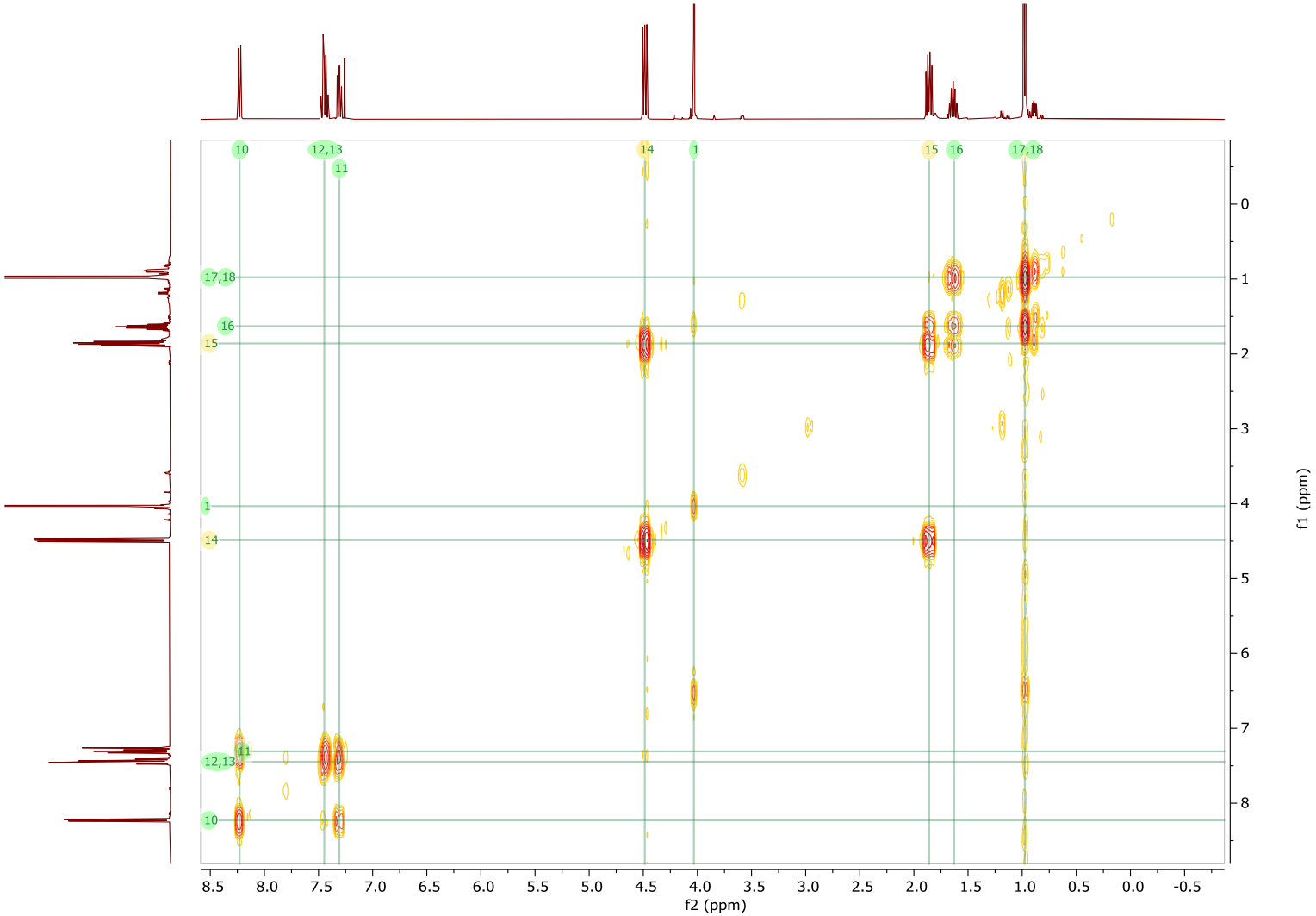
^{1}H NMR (400 MHz, $CDCl_3$)



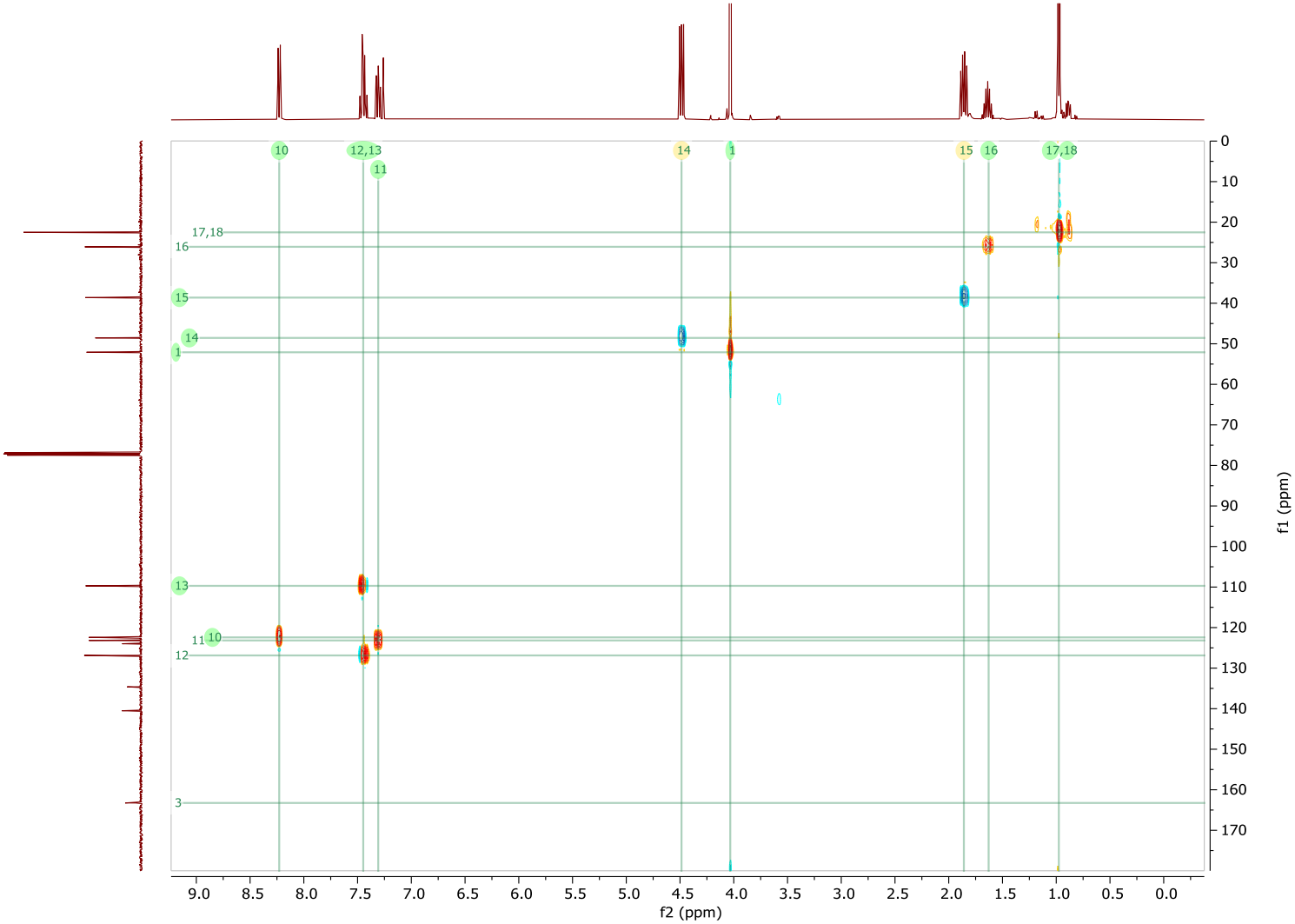
^{13}C NMR (101 MHz, $CDCl_3$)



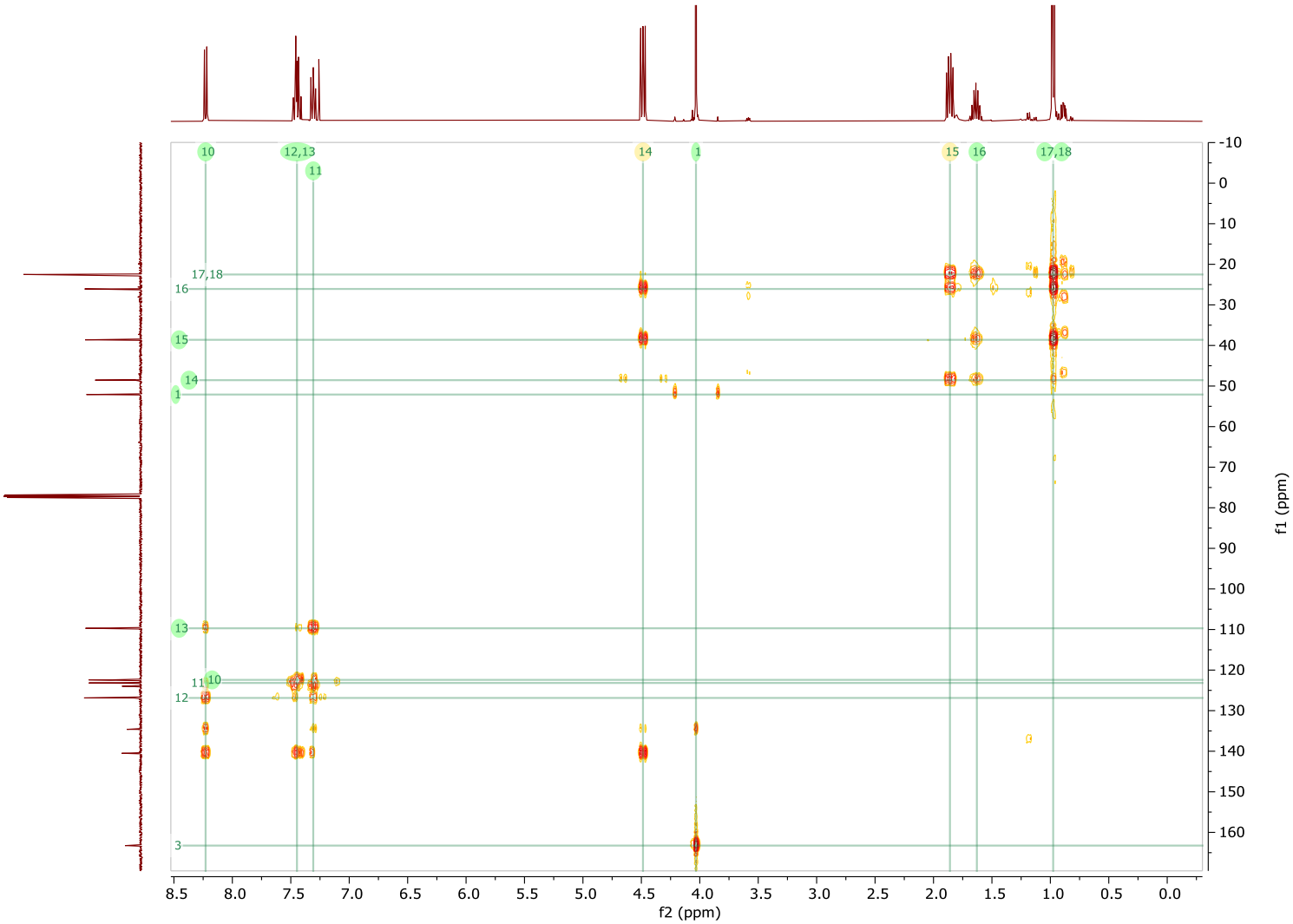
^{1}H-^{1}H COSY (400 MHz, $CDCl_3$)



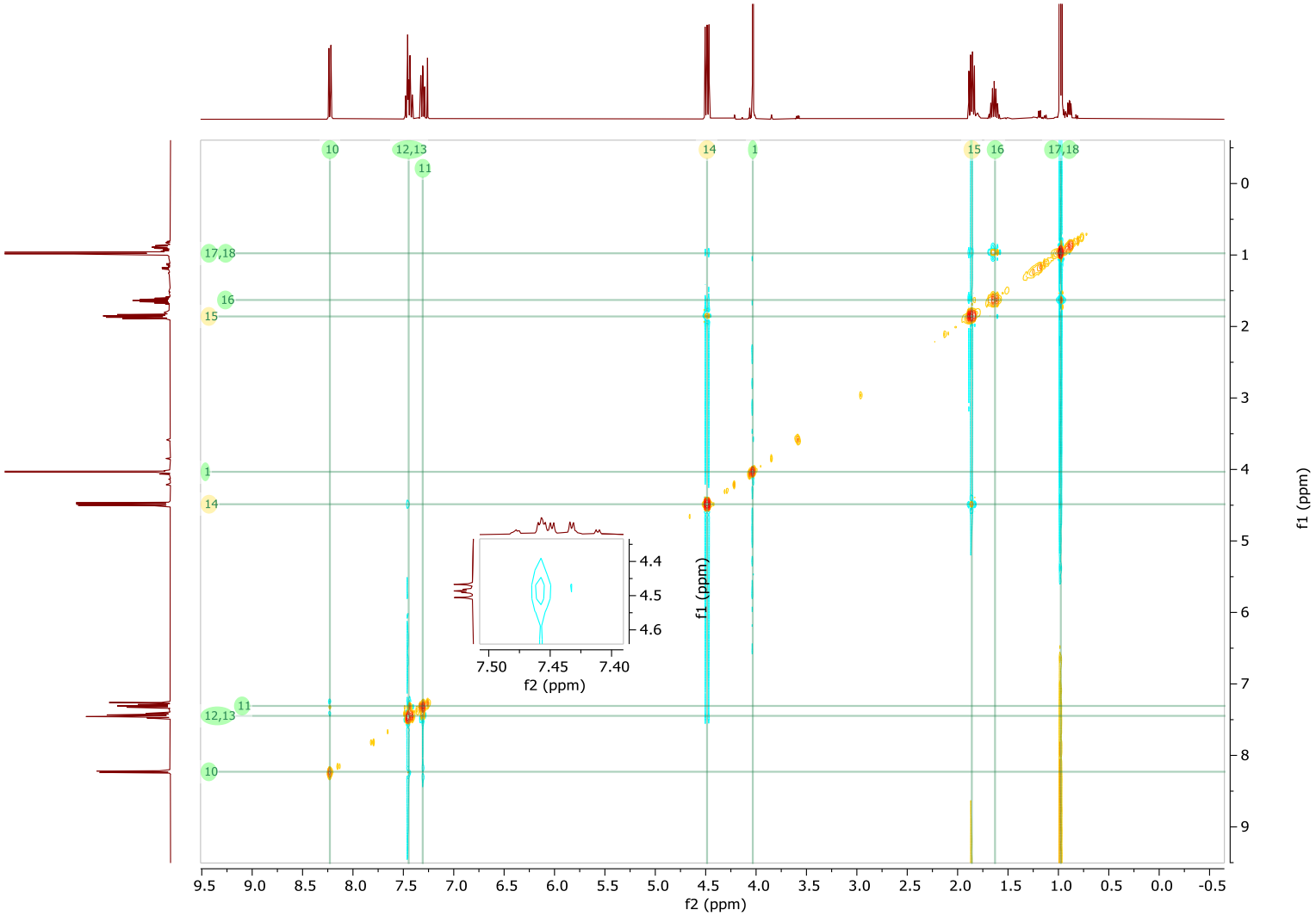
^{1}H-^{13}C HSQC ($CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

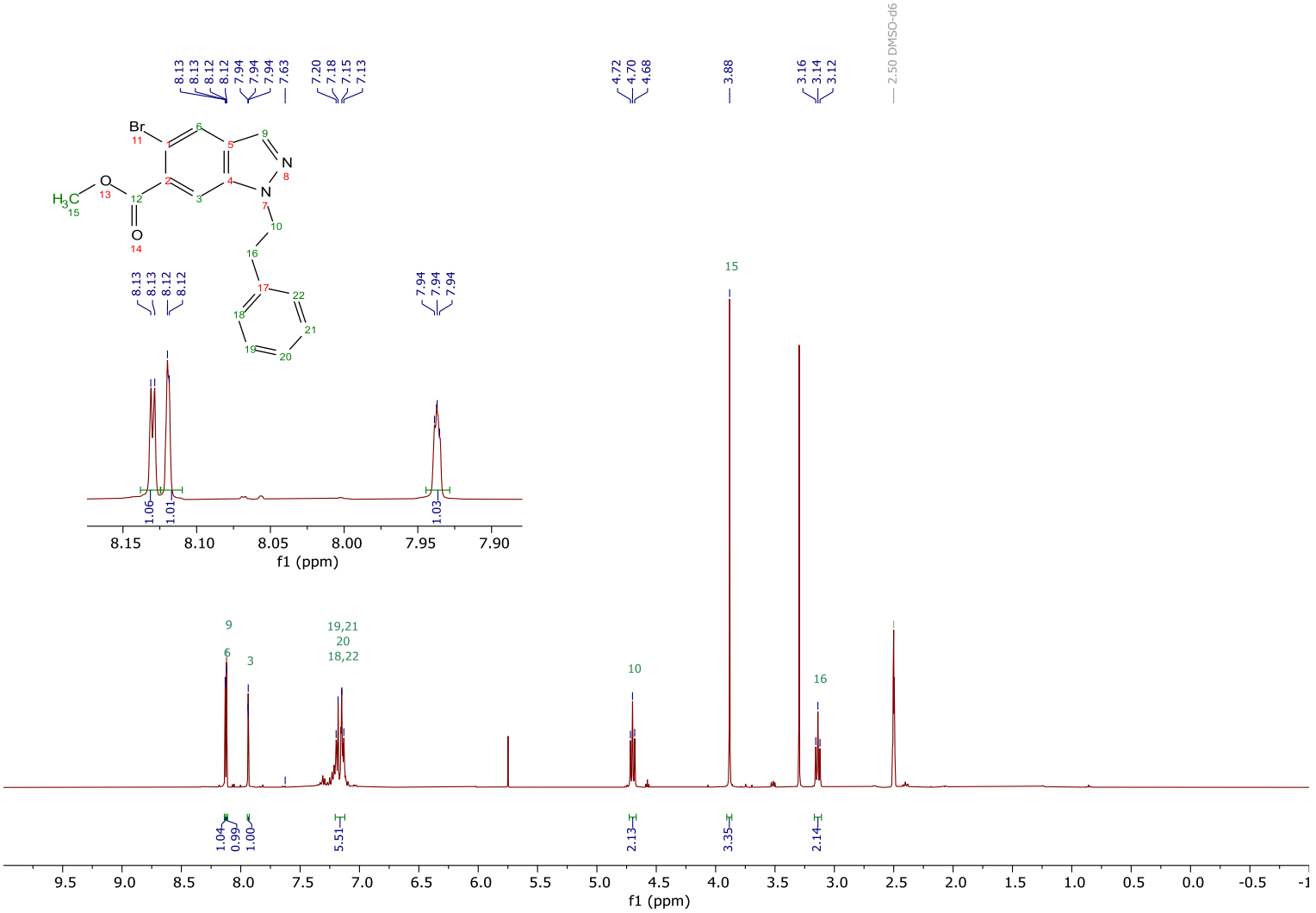


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

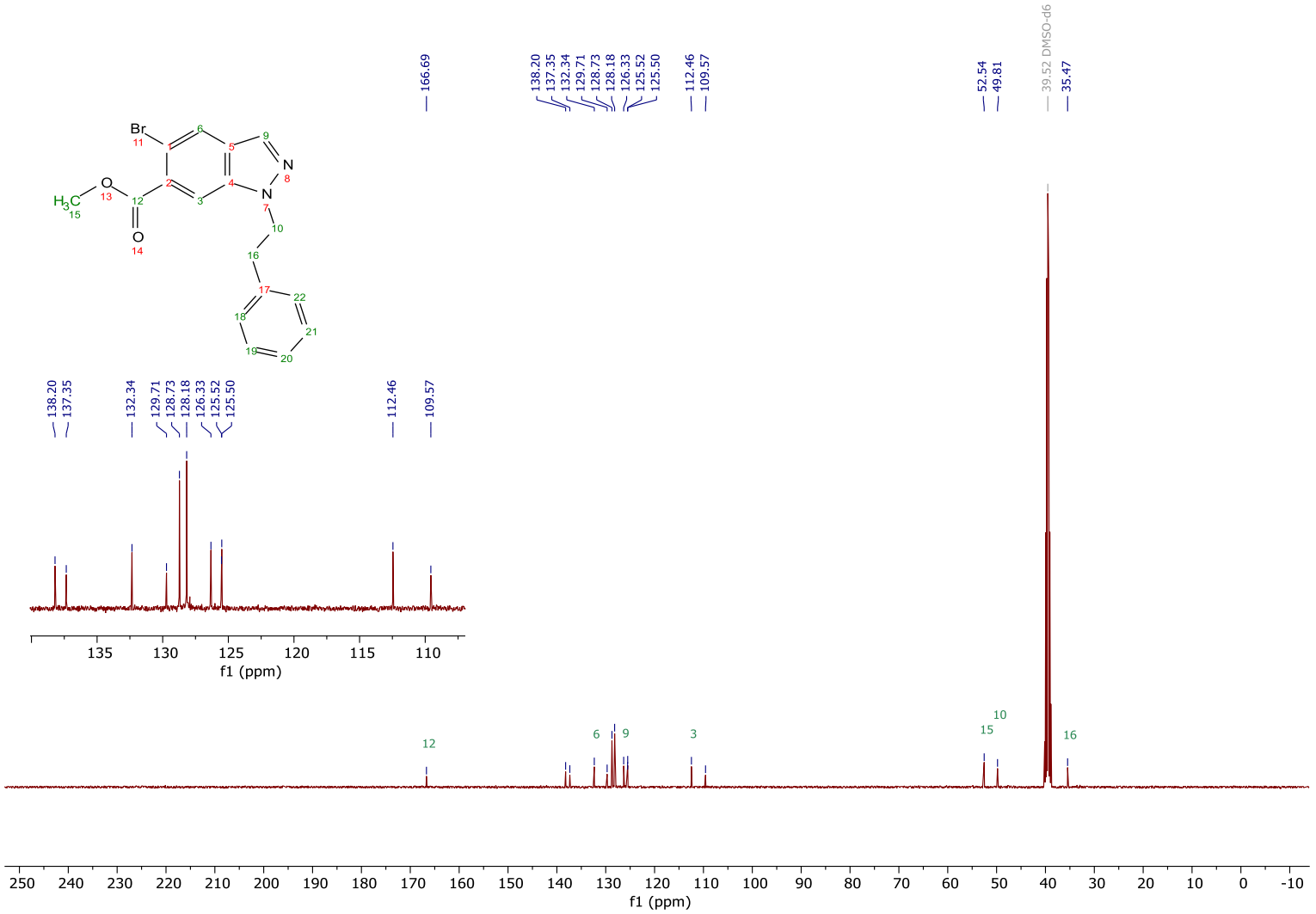


Methyl 5-bromo-1-(2-phenylethyl)-1*H*-indazole-6-carboxylate (2t)

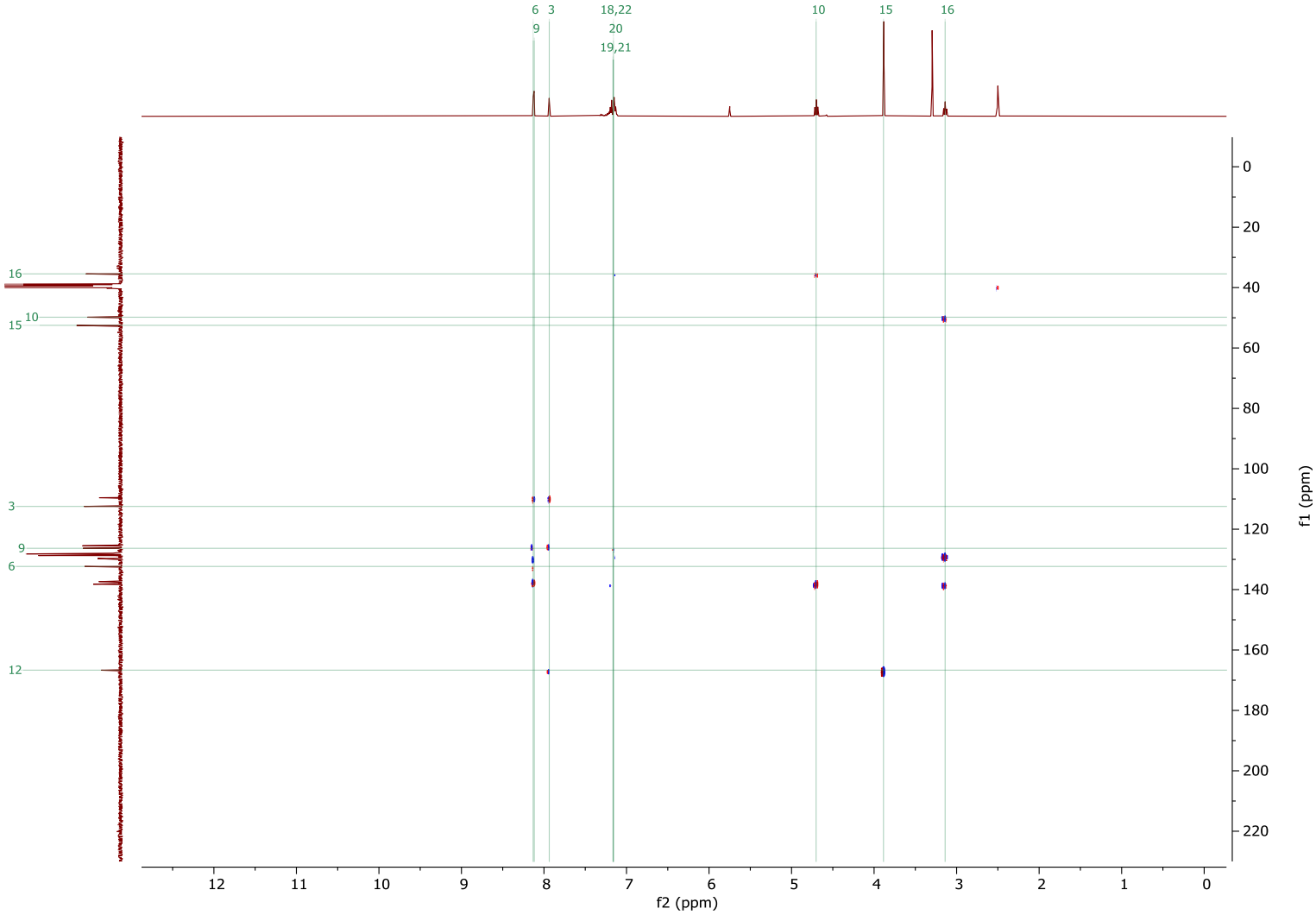
^{1}H NMR (400 MHz, DMSO-d_6)



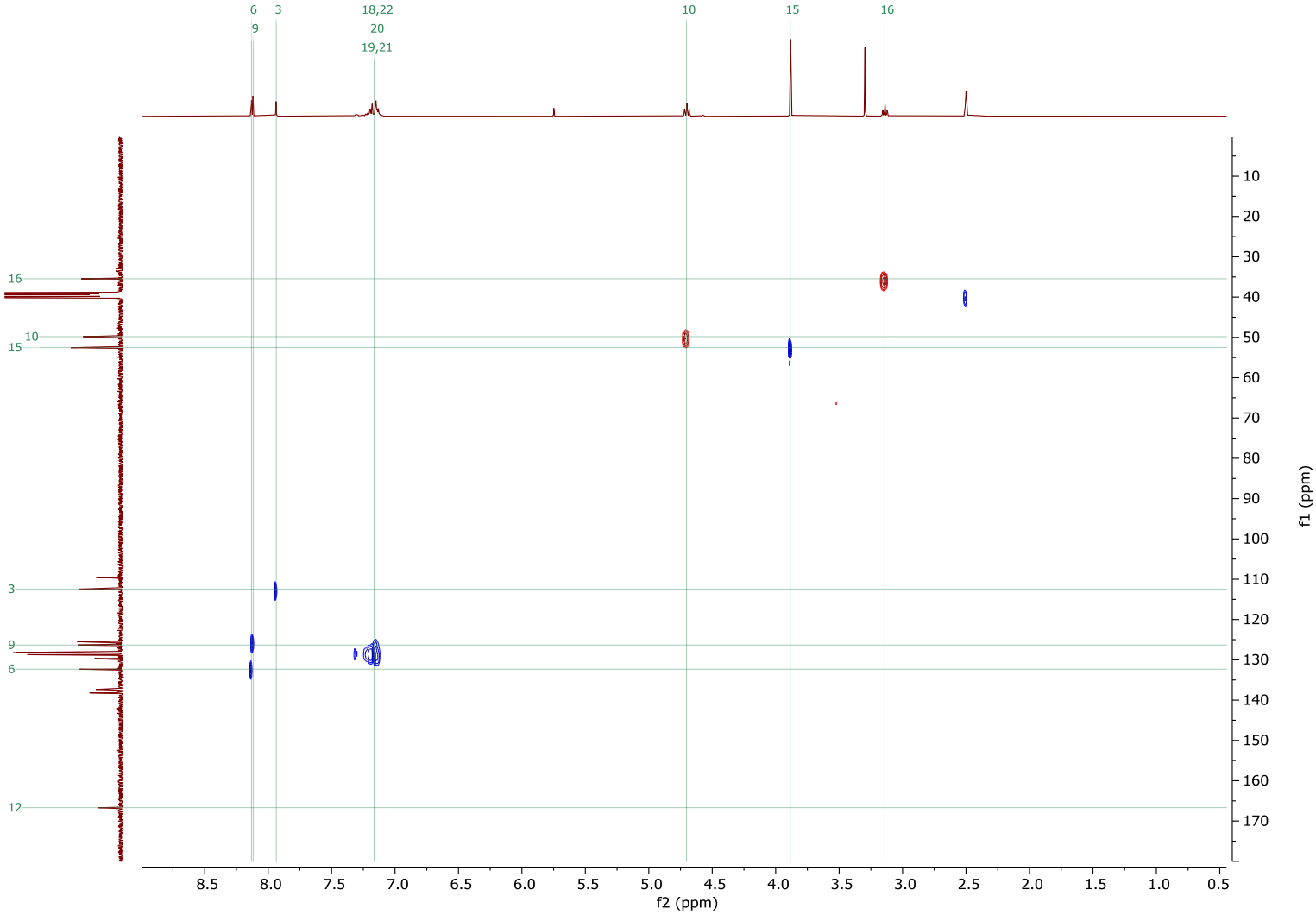
^{13}C NMR (101 MHz, DMSO-d_6)



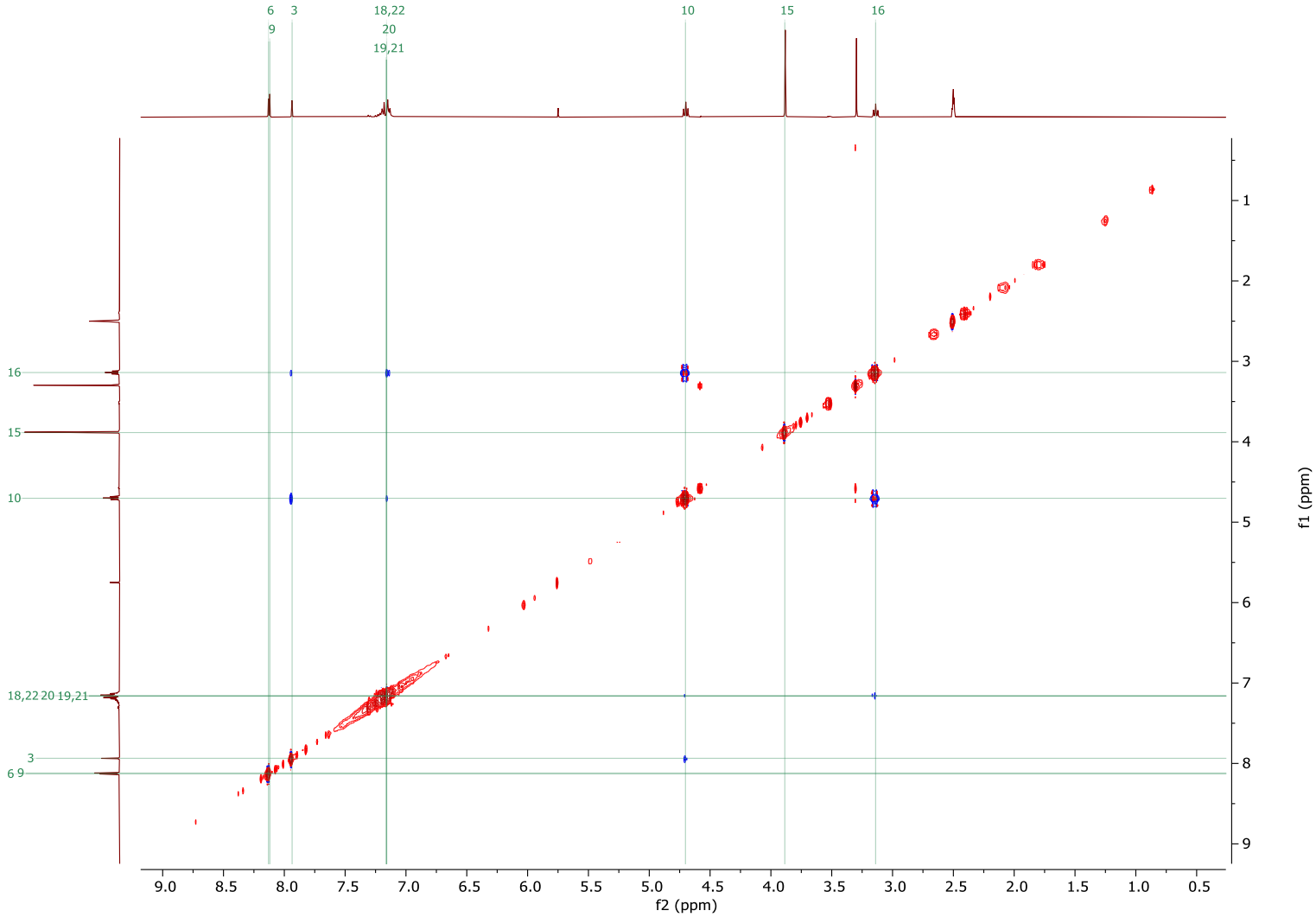
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

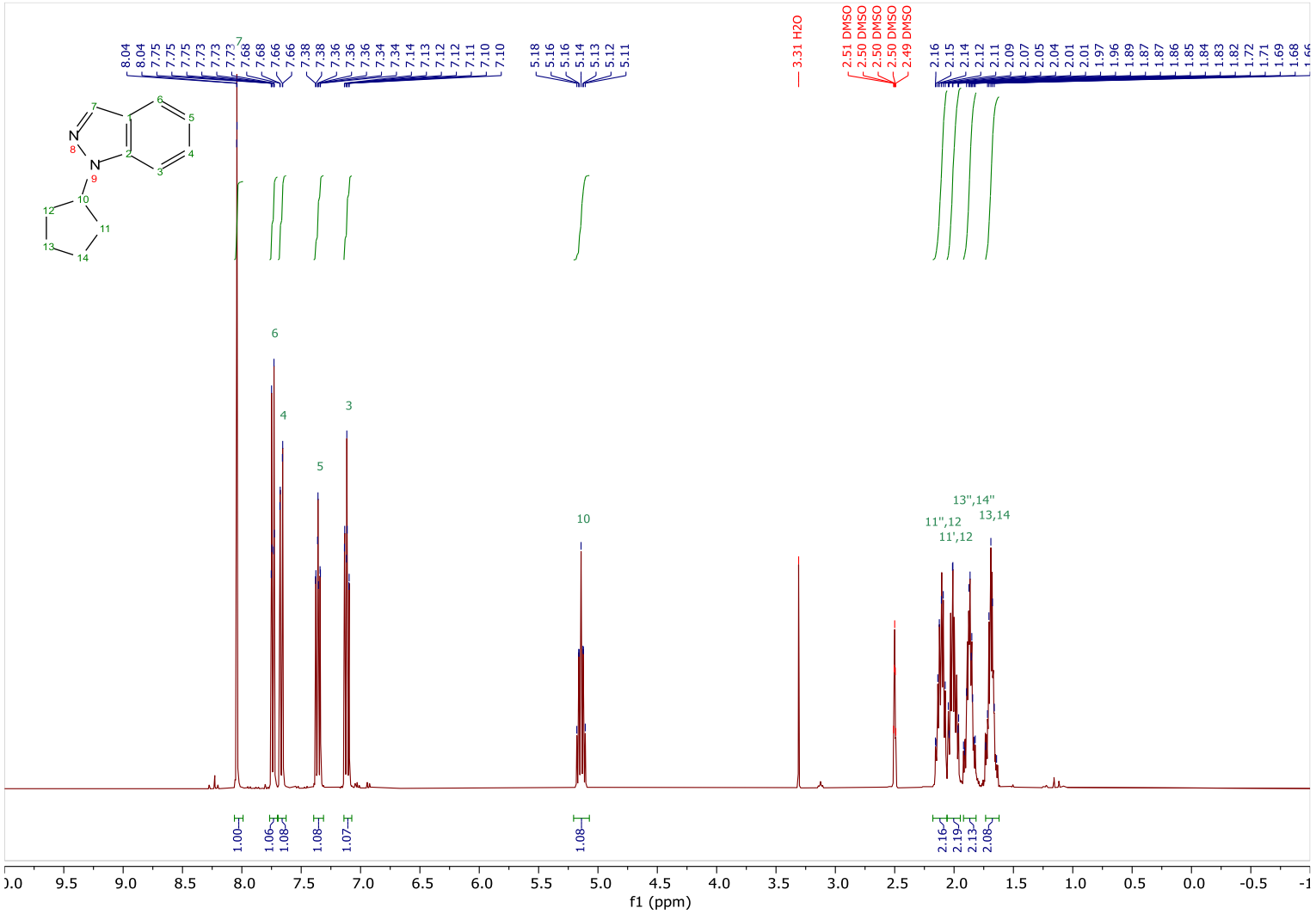


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

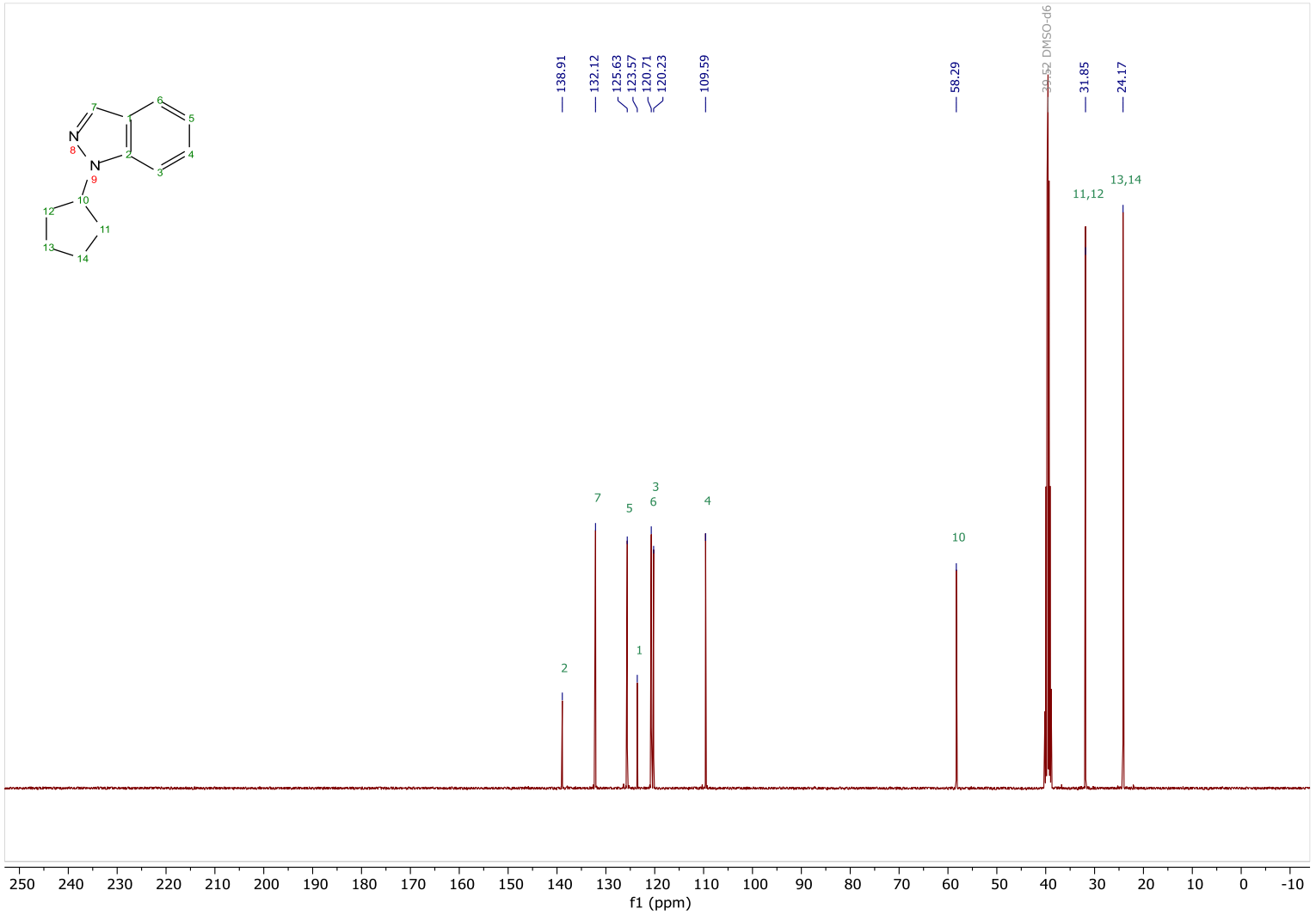


1-cyclopentyl-1*H*-indazole (2u)

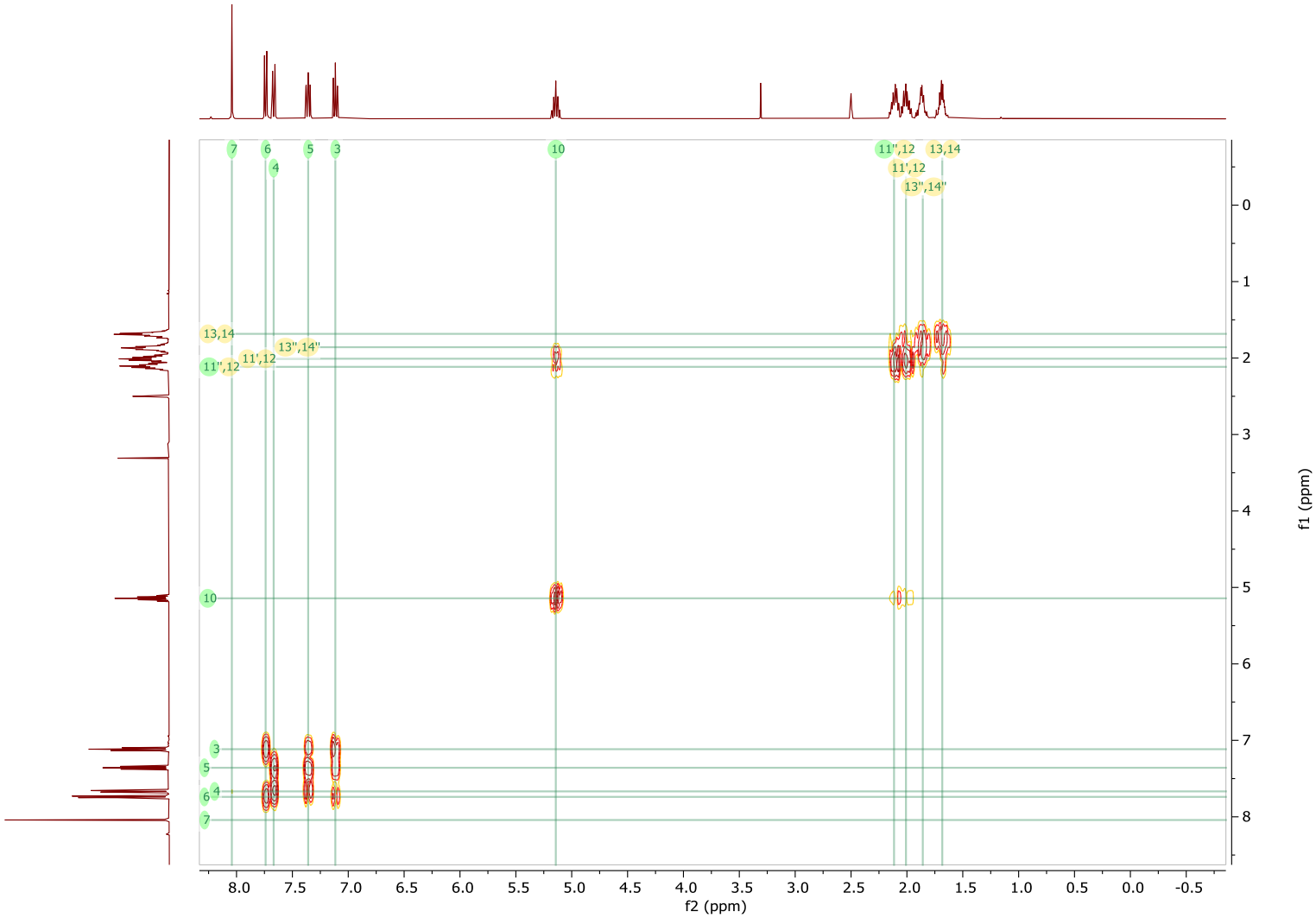
^{1}H NMR (400 MHz, DMSO-d_6)



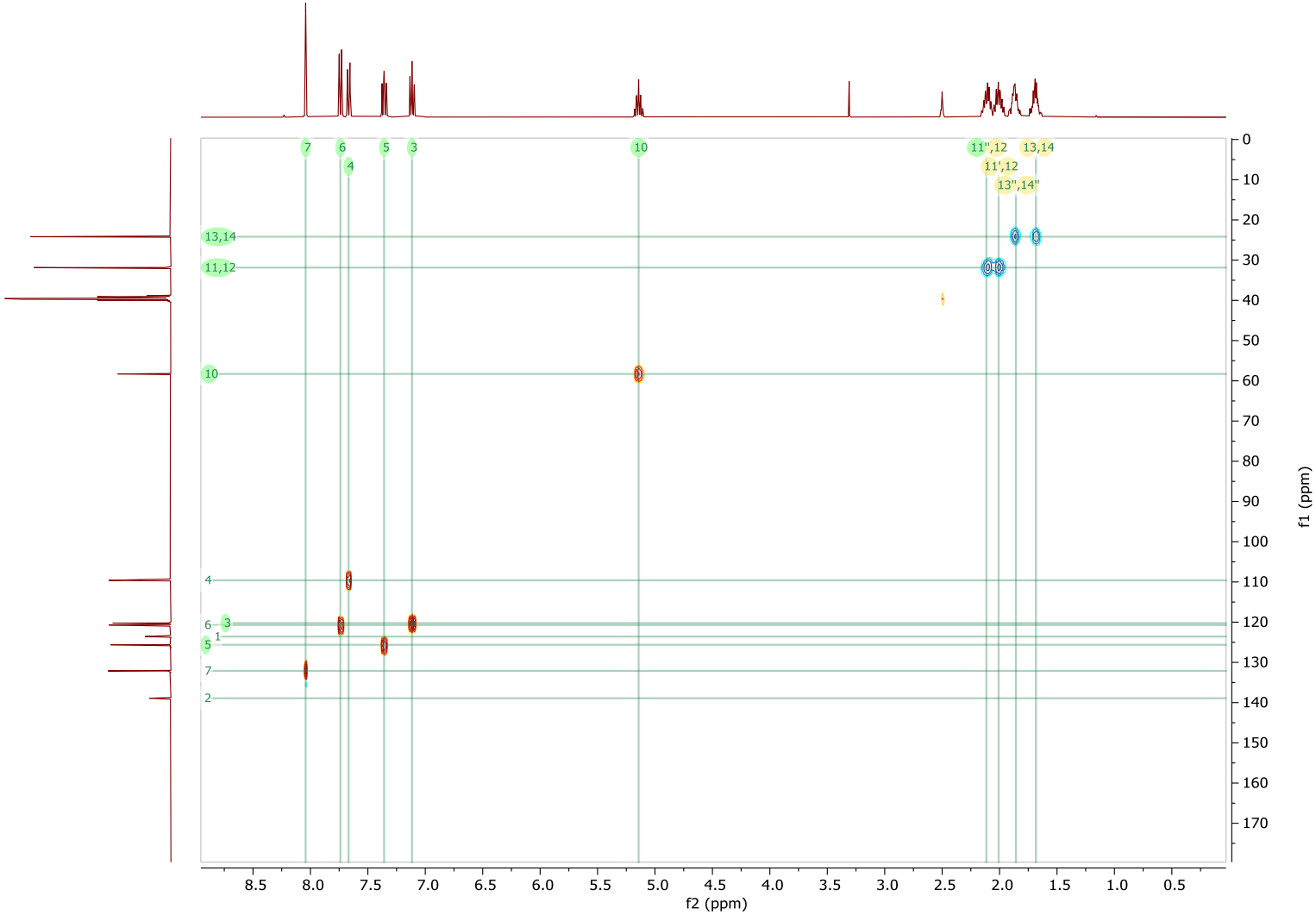
^{13}C NMR (101 MHz, DMSO-d_6)



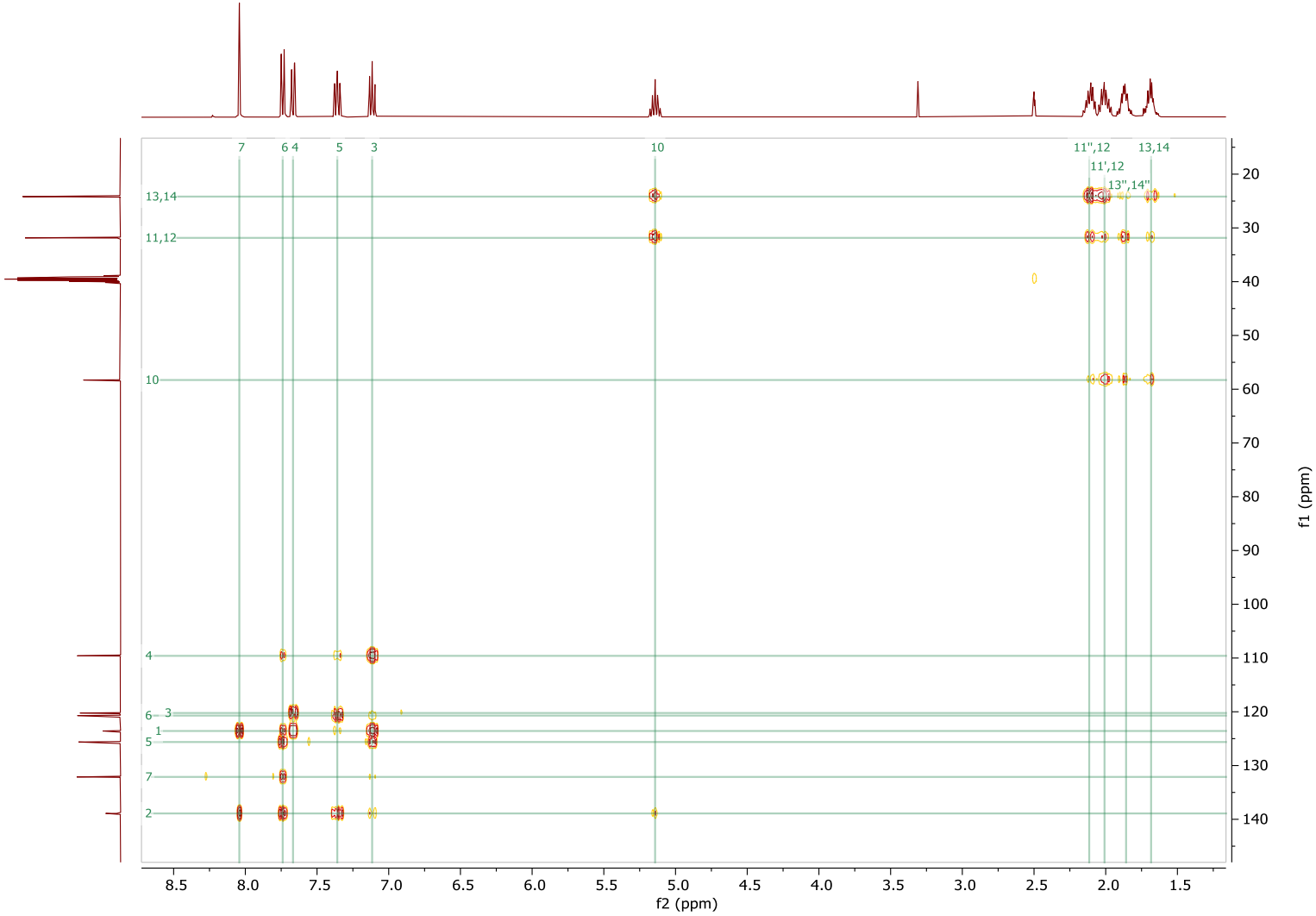
^{1}H-^{1}H COSY (400 MHz, DMSO-d_6)



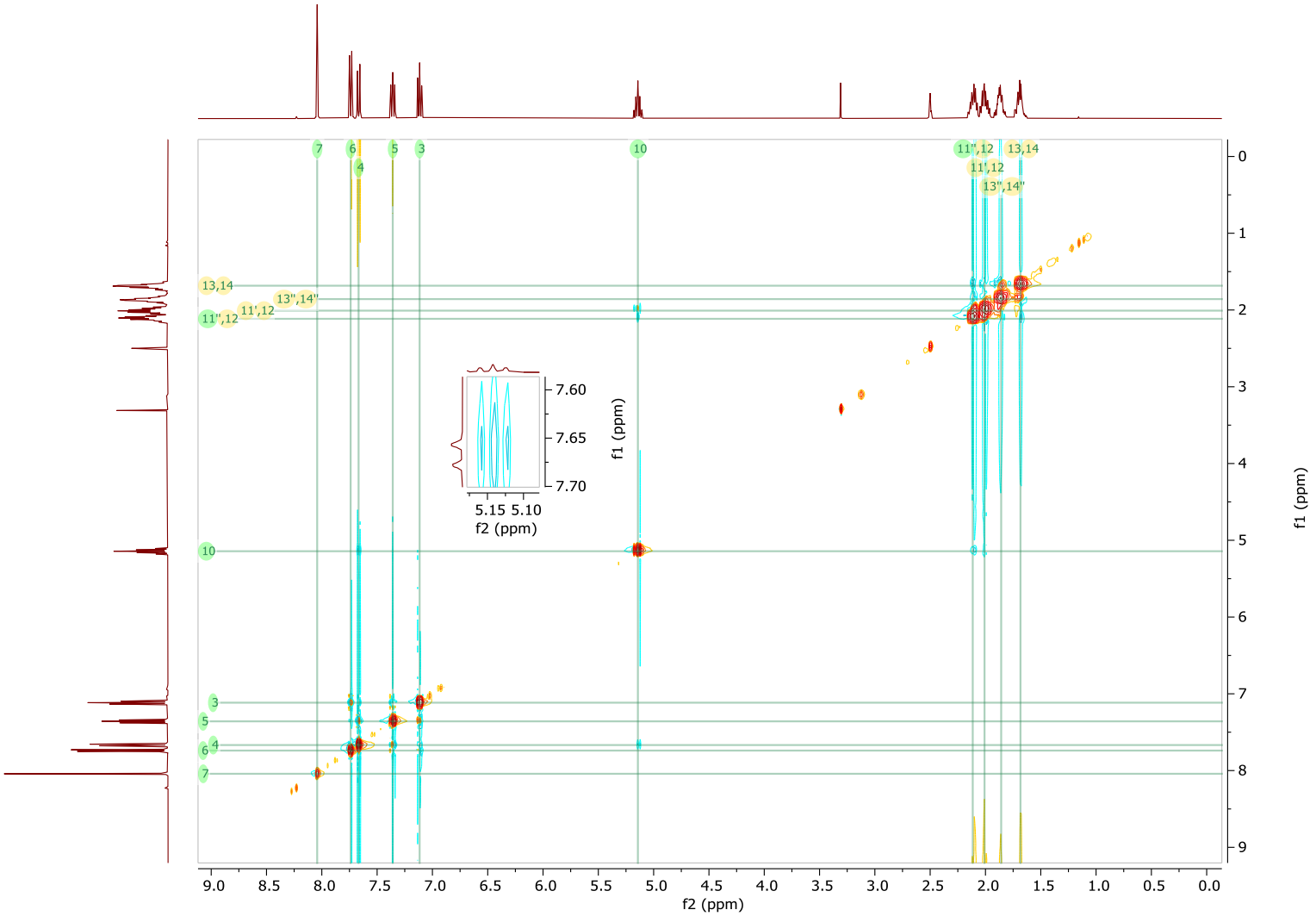
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

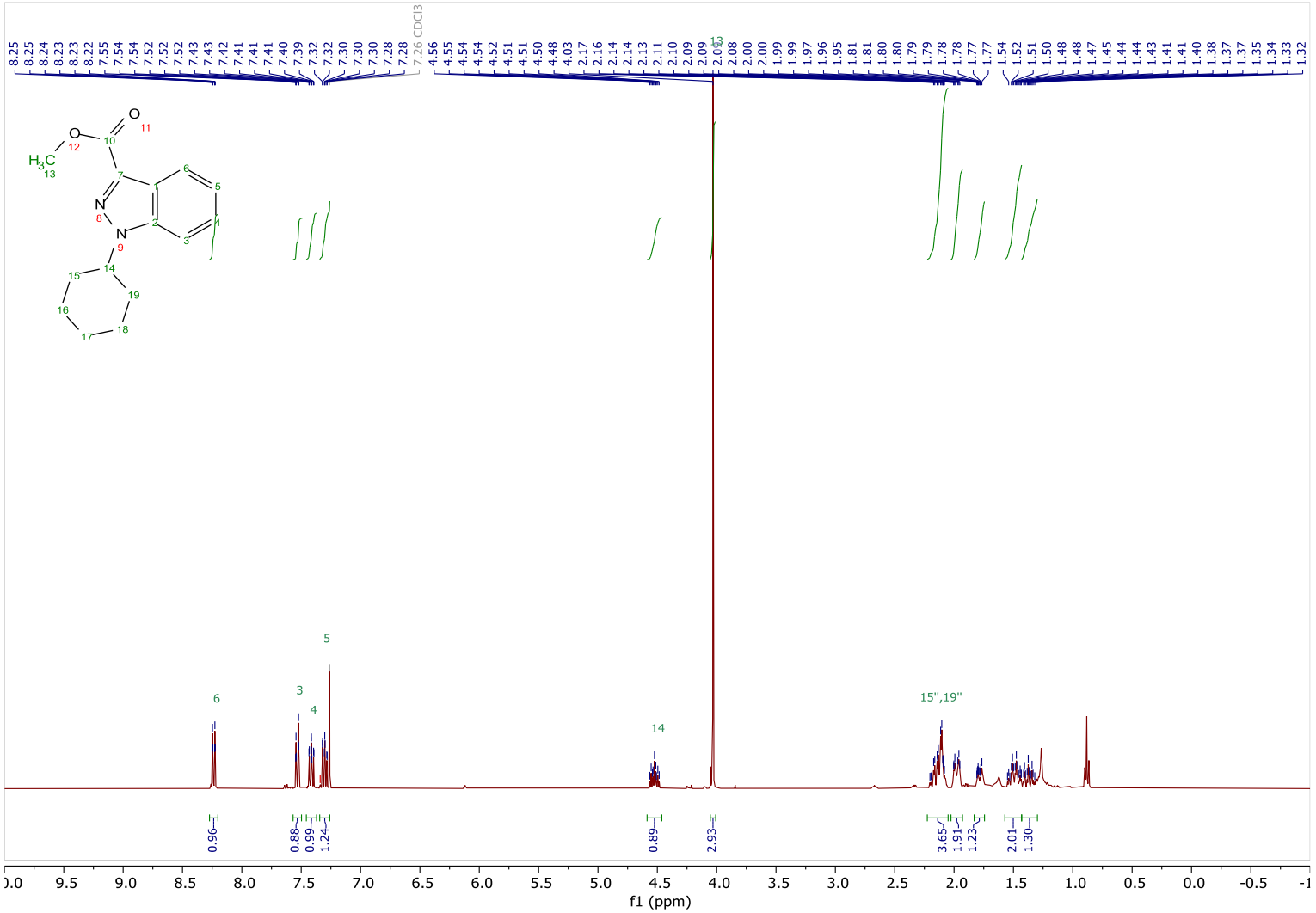


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

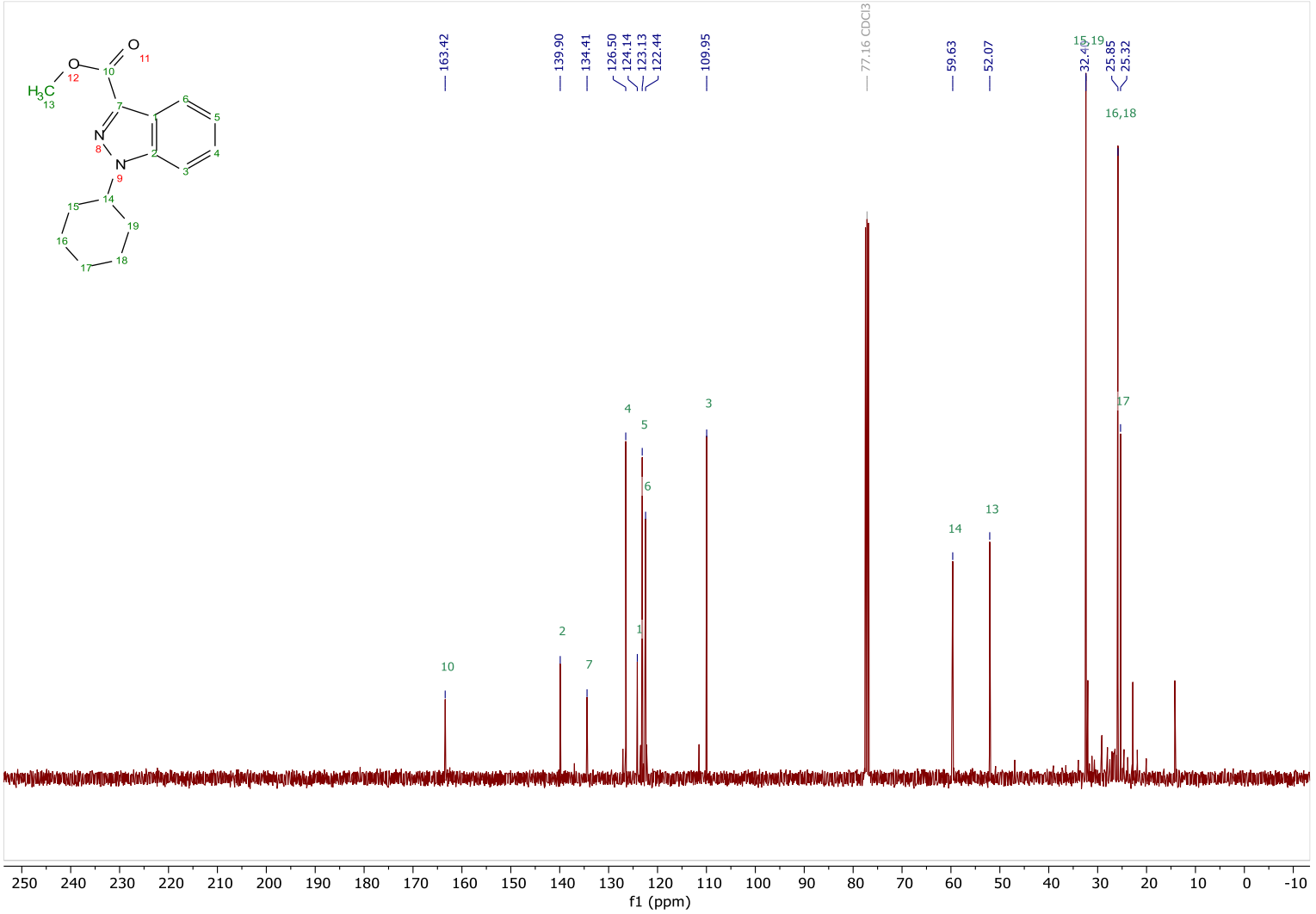


Methyl 1-cyclohexyl-1*H*-indazole-3-carboxylate (2v)

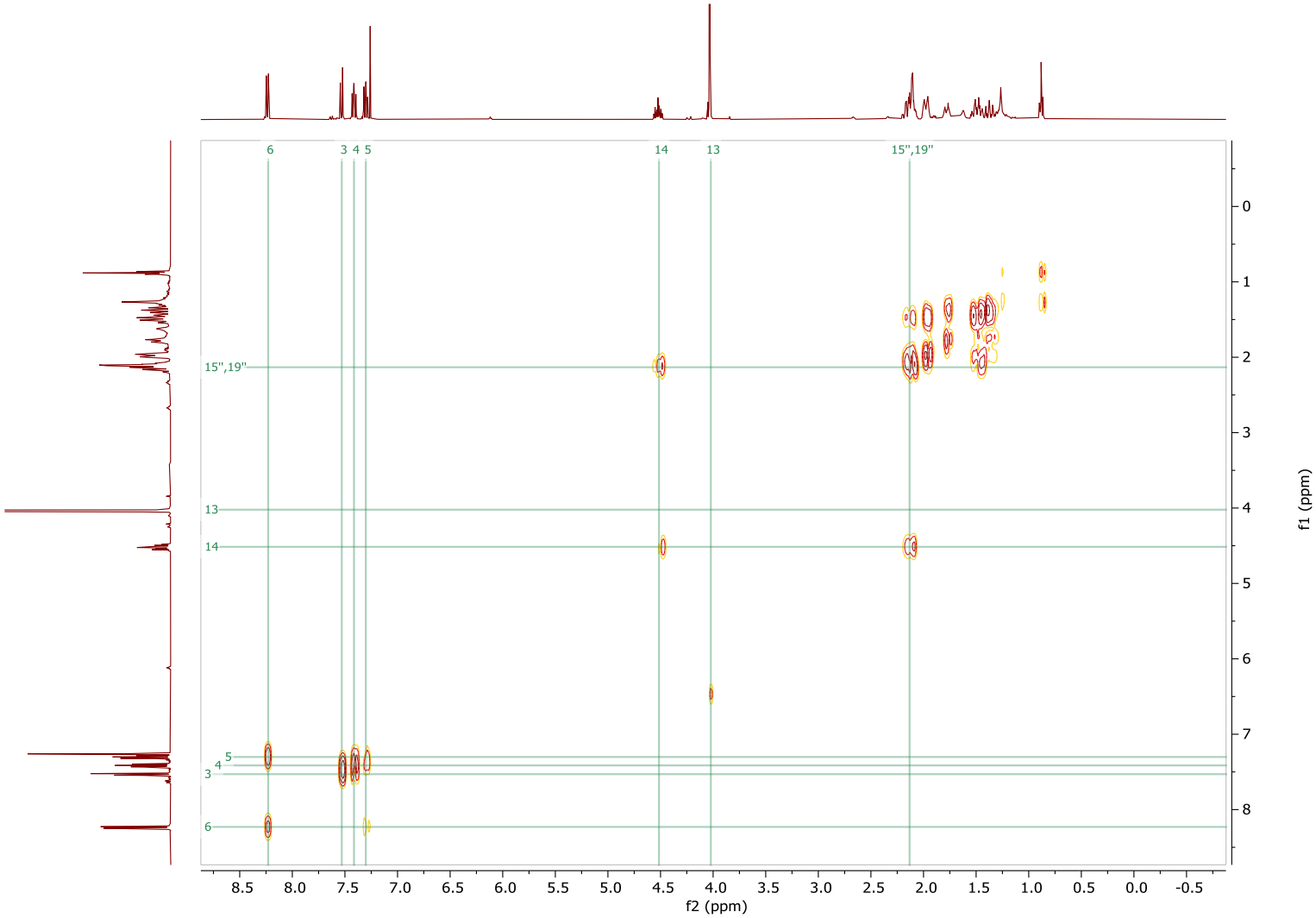
^{1}H NMR (400 MHz, $CDCl_3$)



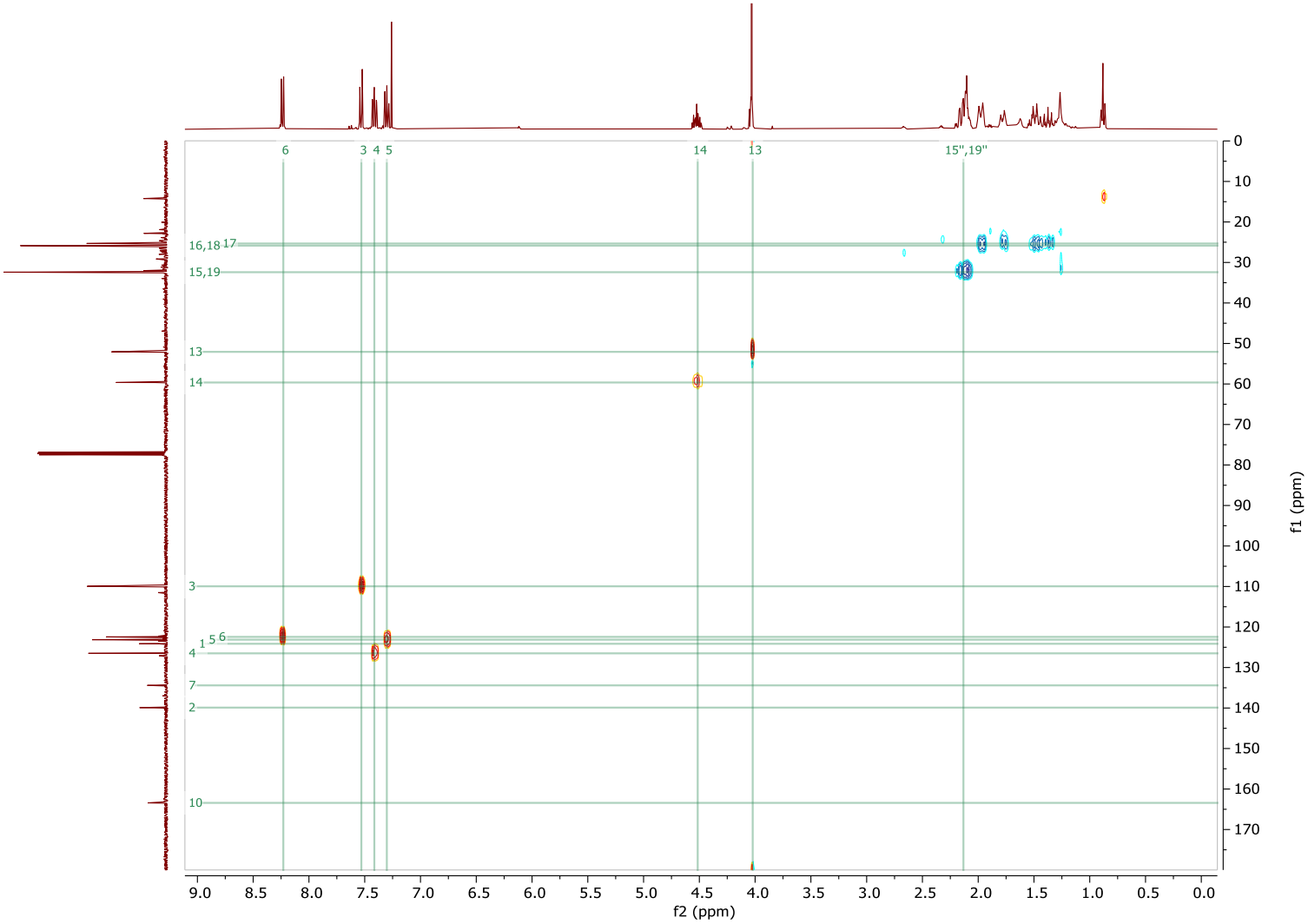
^{13}C NMR (101 MHz, $CDCl_3$)



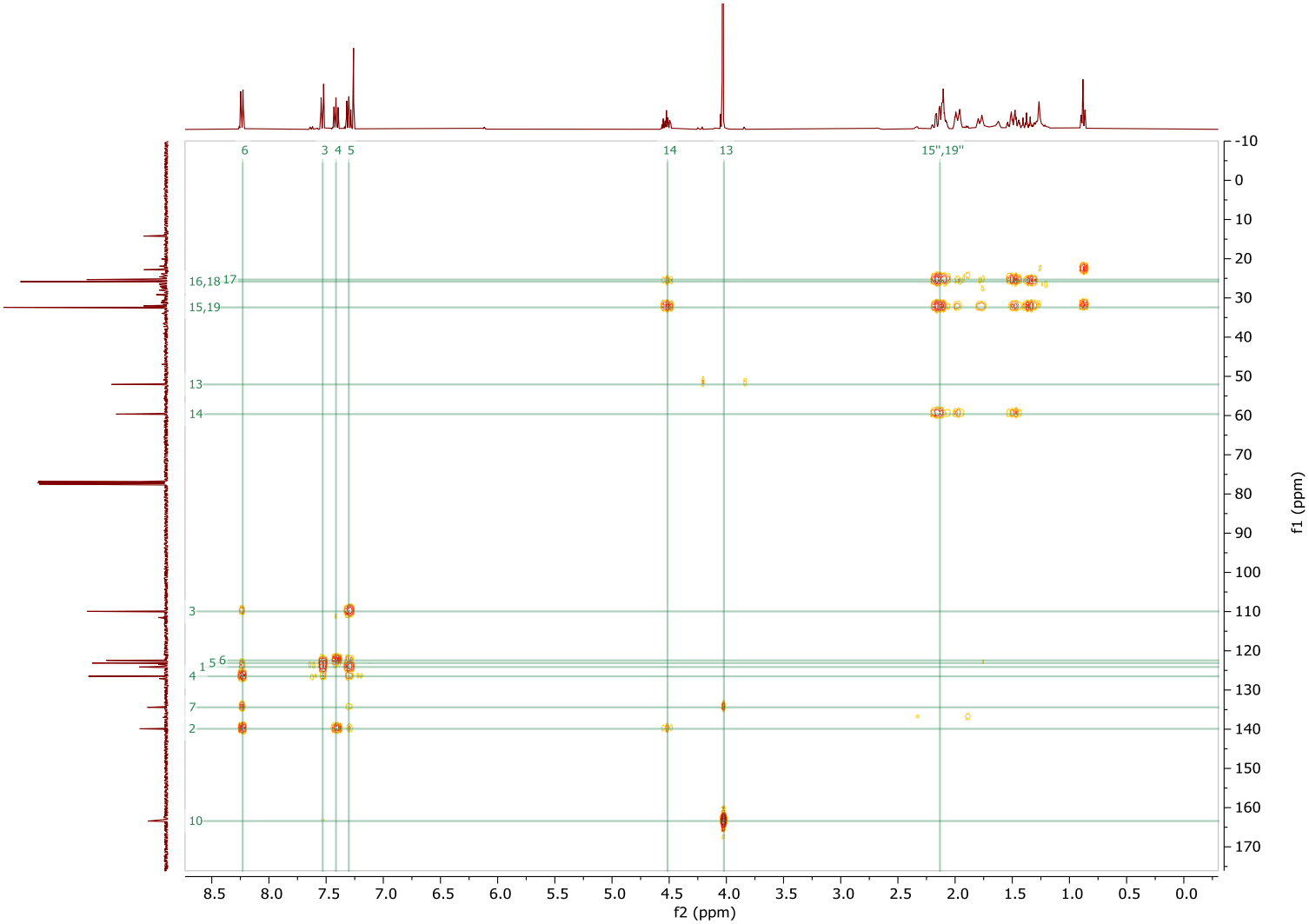
^{1}H-^{1}H COSY (400 MHz, $CDCl_3$)



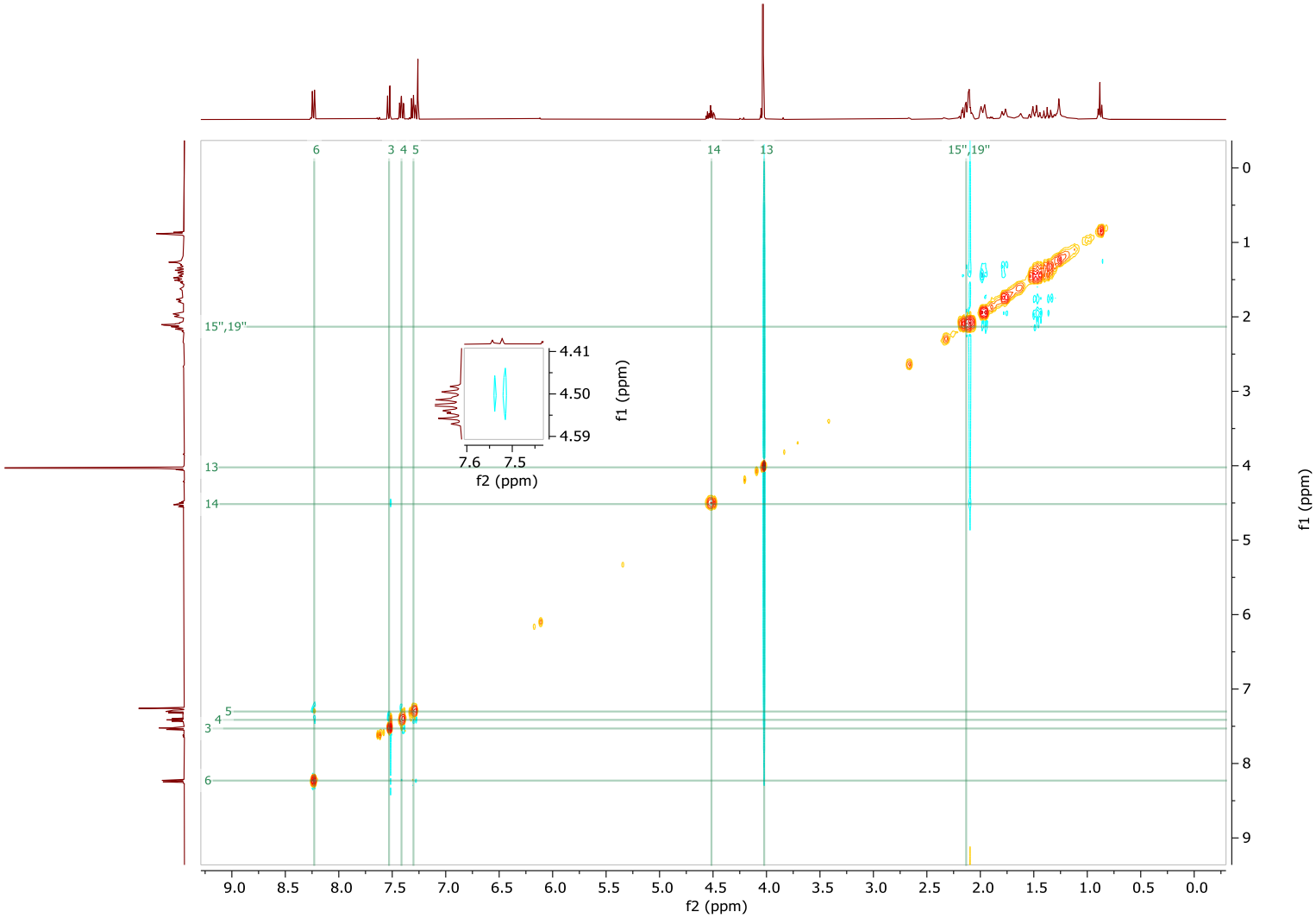
^{1}H-^{13}C HSQC ($CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

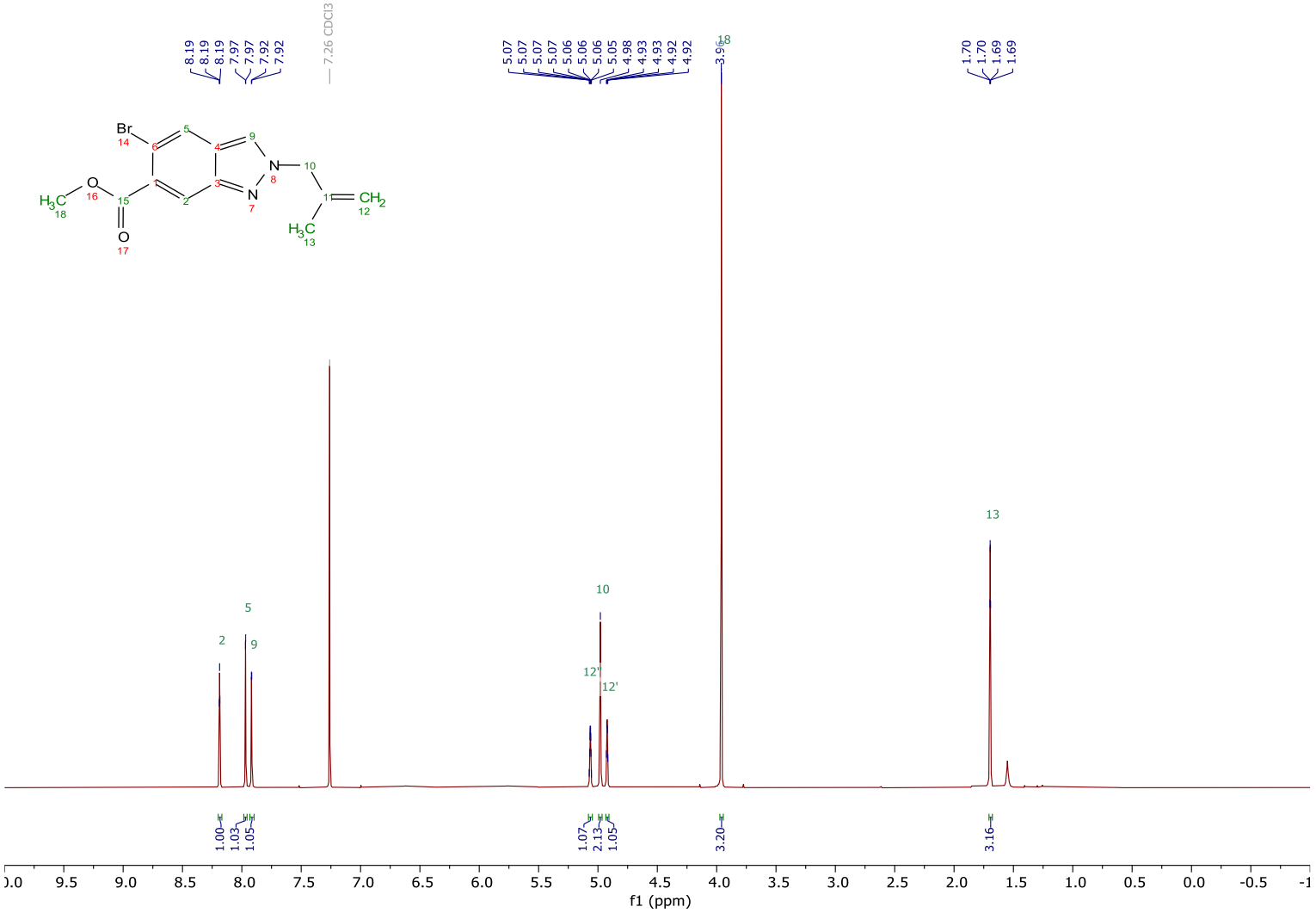


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

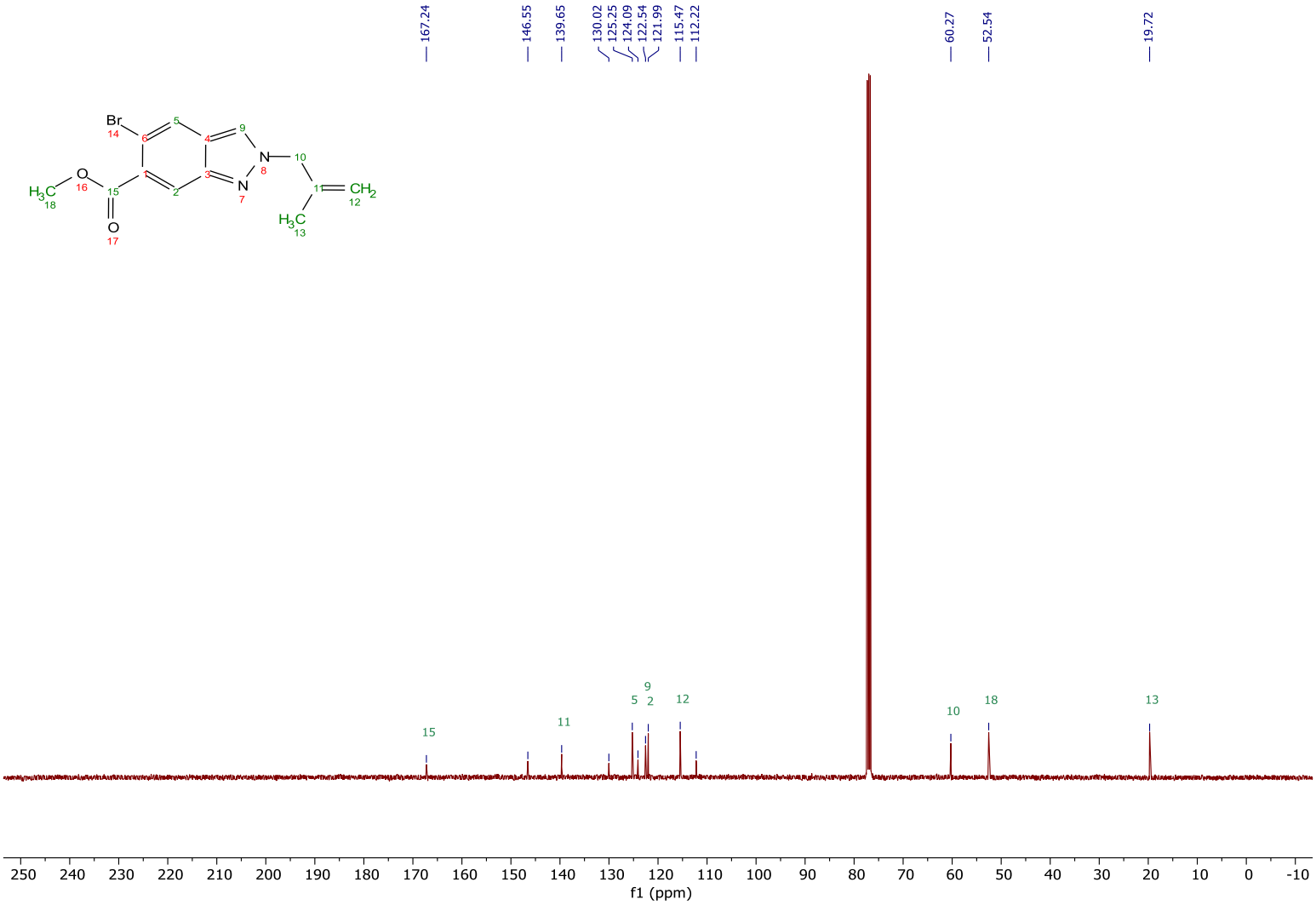


Methyl 5-bromo-2-(2-methylallyl)-2*H*-indazole-6-carboxylate

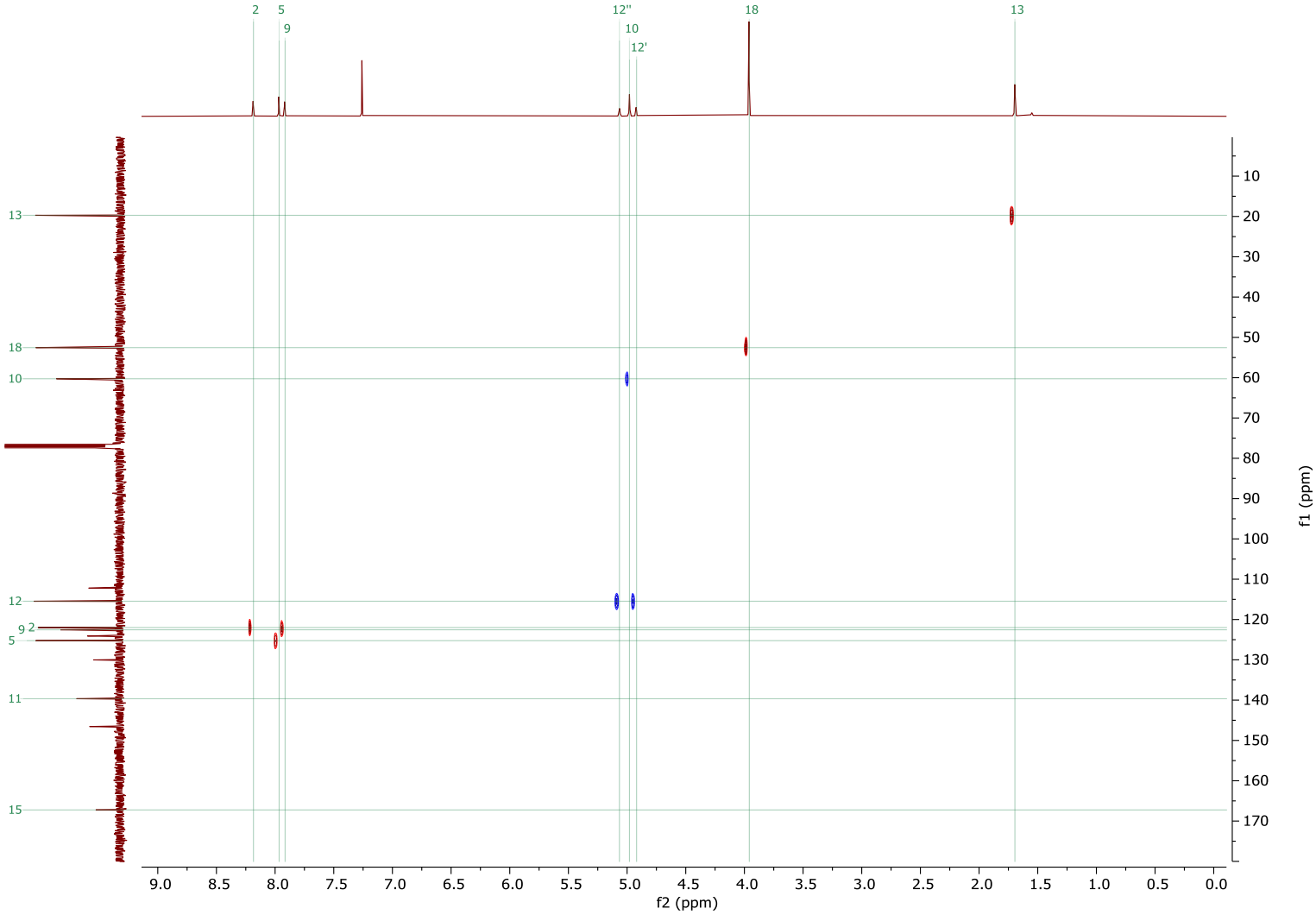
^{1}H NMR (400 MHz, $CDCl_3$)



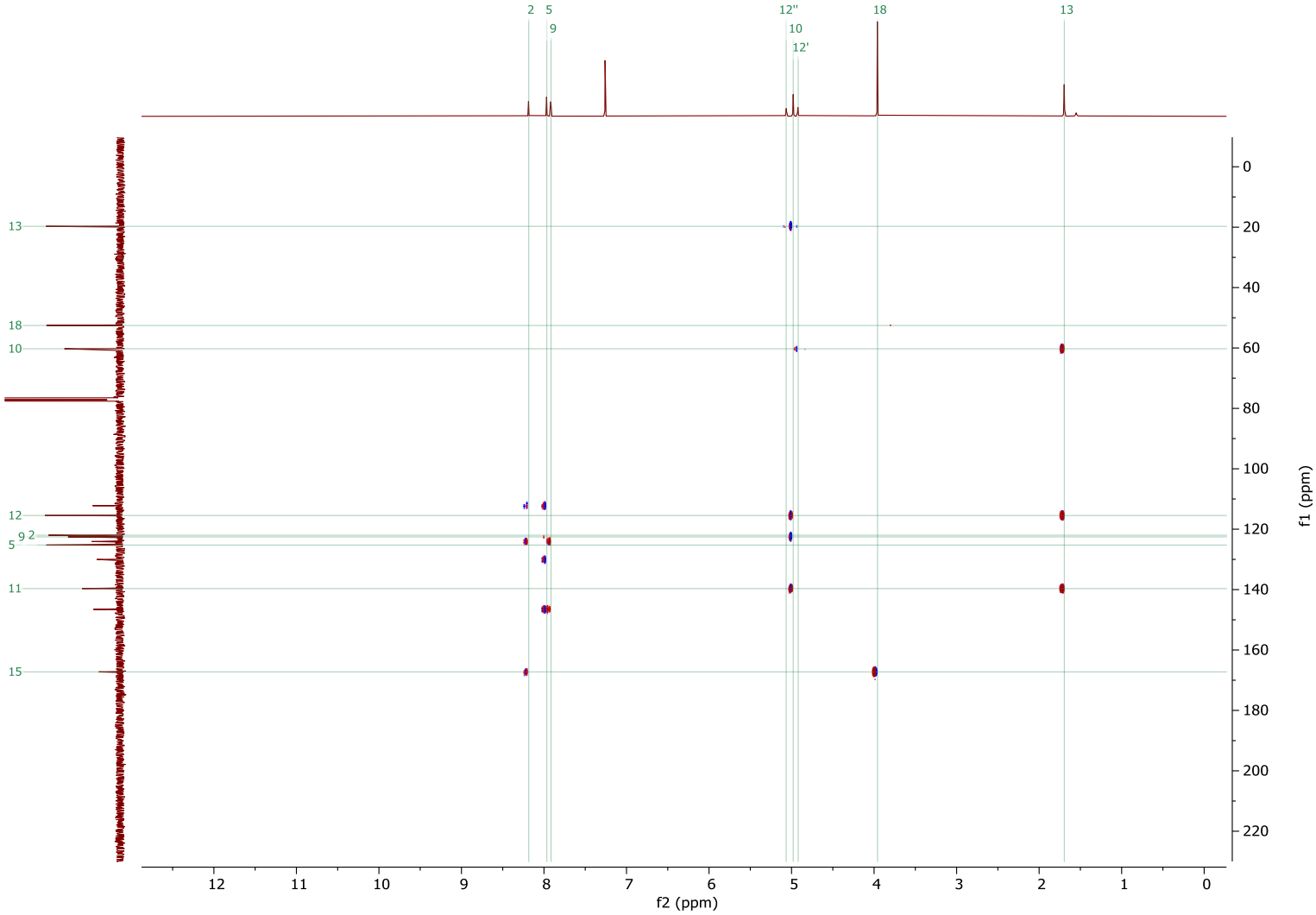
^{13}C NMR (101 MHz, $CDCl_3$)



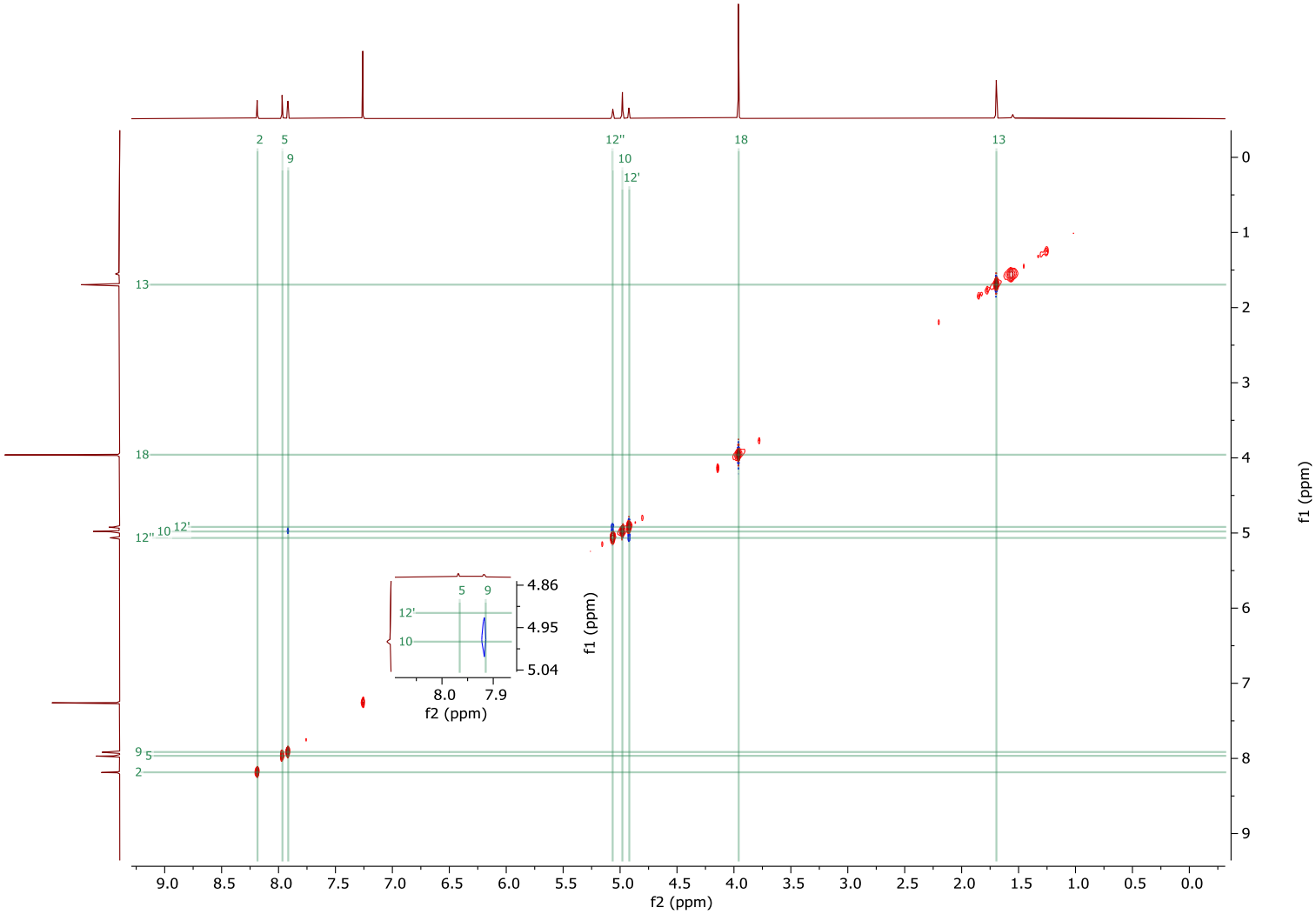
^{1}H-^{13}C HSQC ($CDCl_3$)



^{1}H-^{13}C HMBC ($CDCl_3$)

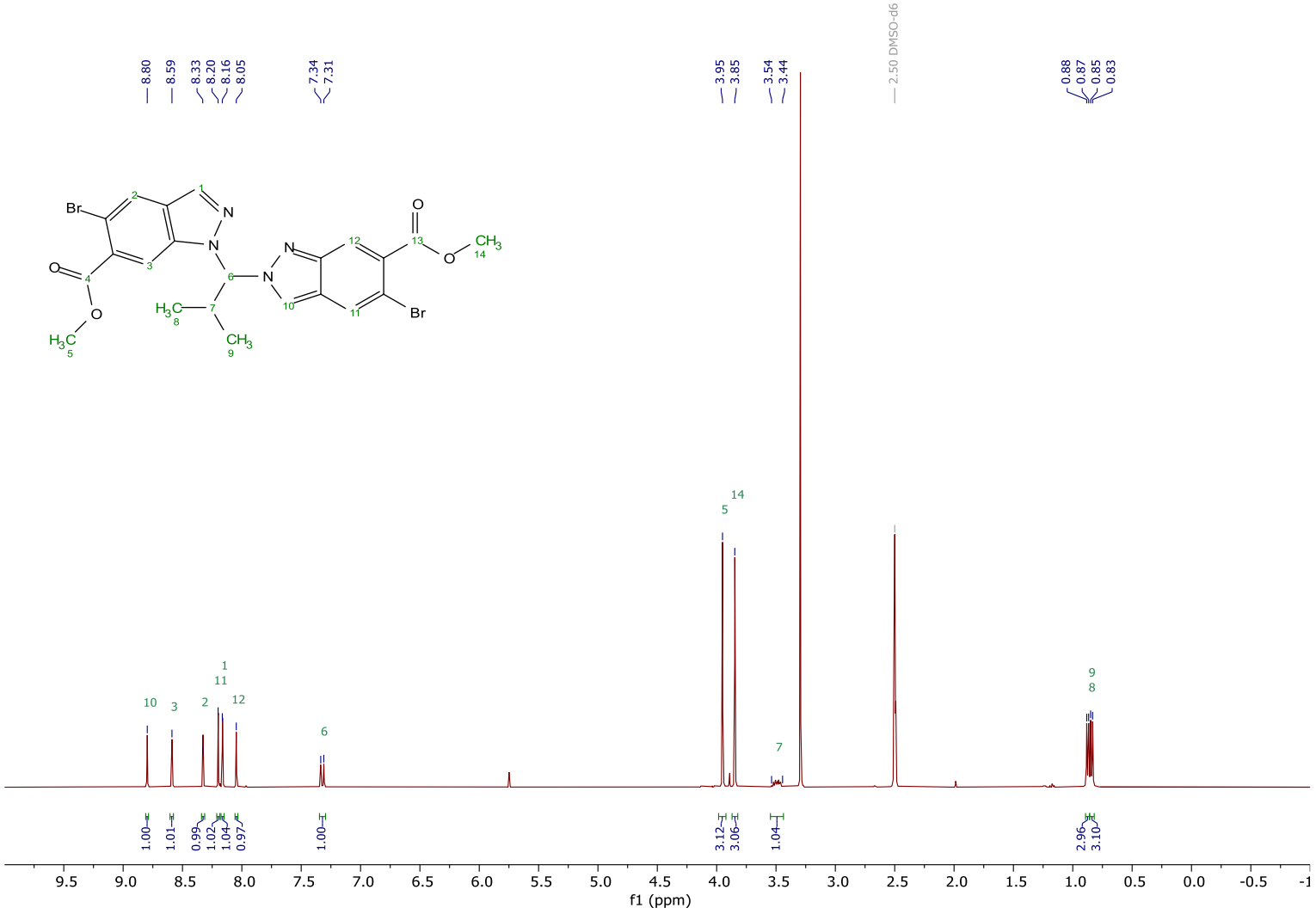


^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)

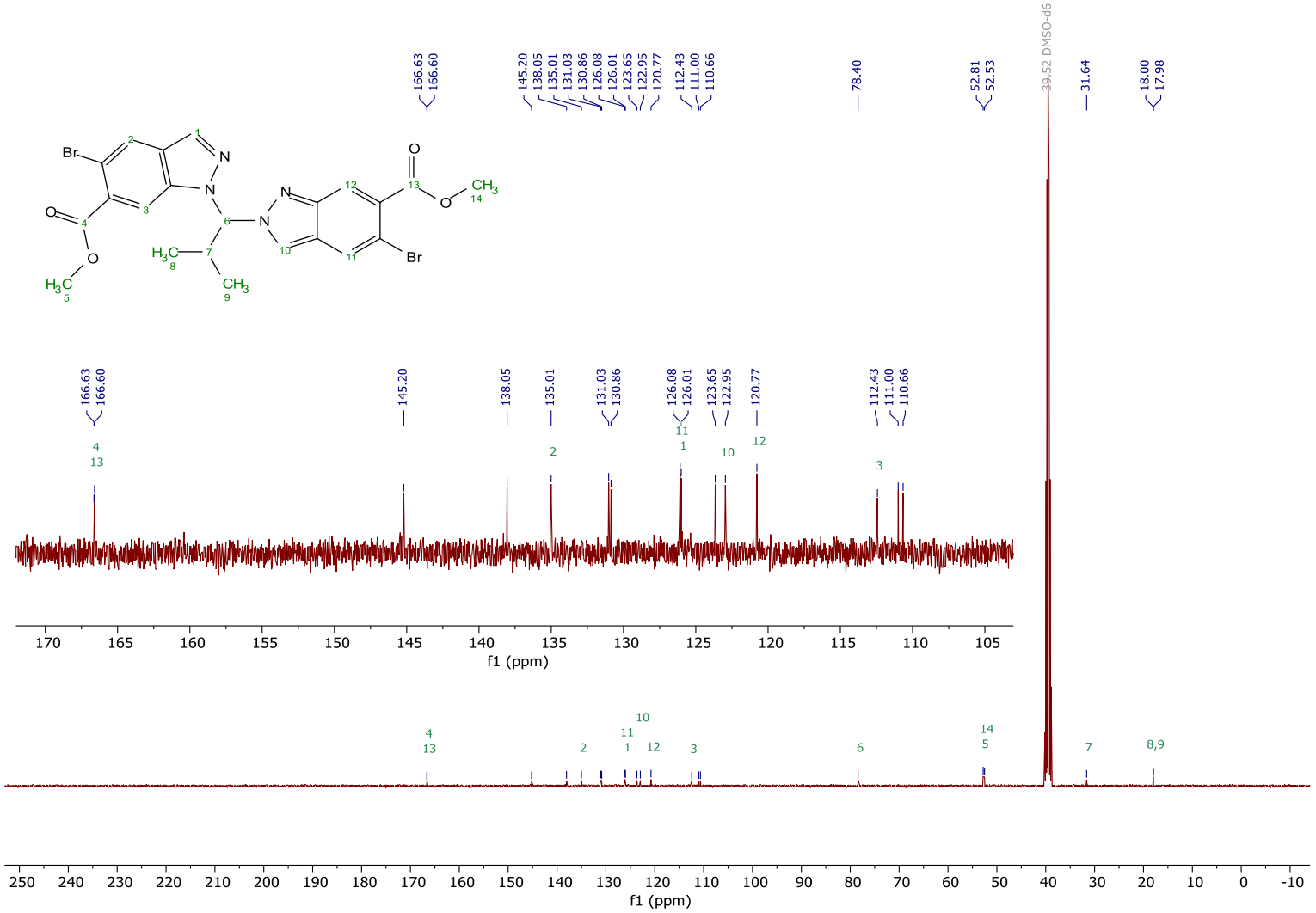


Methyl 5-bromo-2-(1-(5-bromo-6-(methoxycarbonyl)-1*H*-indazol-1-yl)-2-methylpropyl)-2*H*-indazole-6-carboxylate

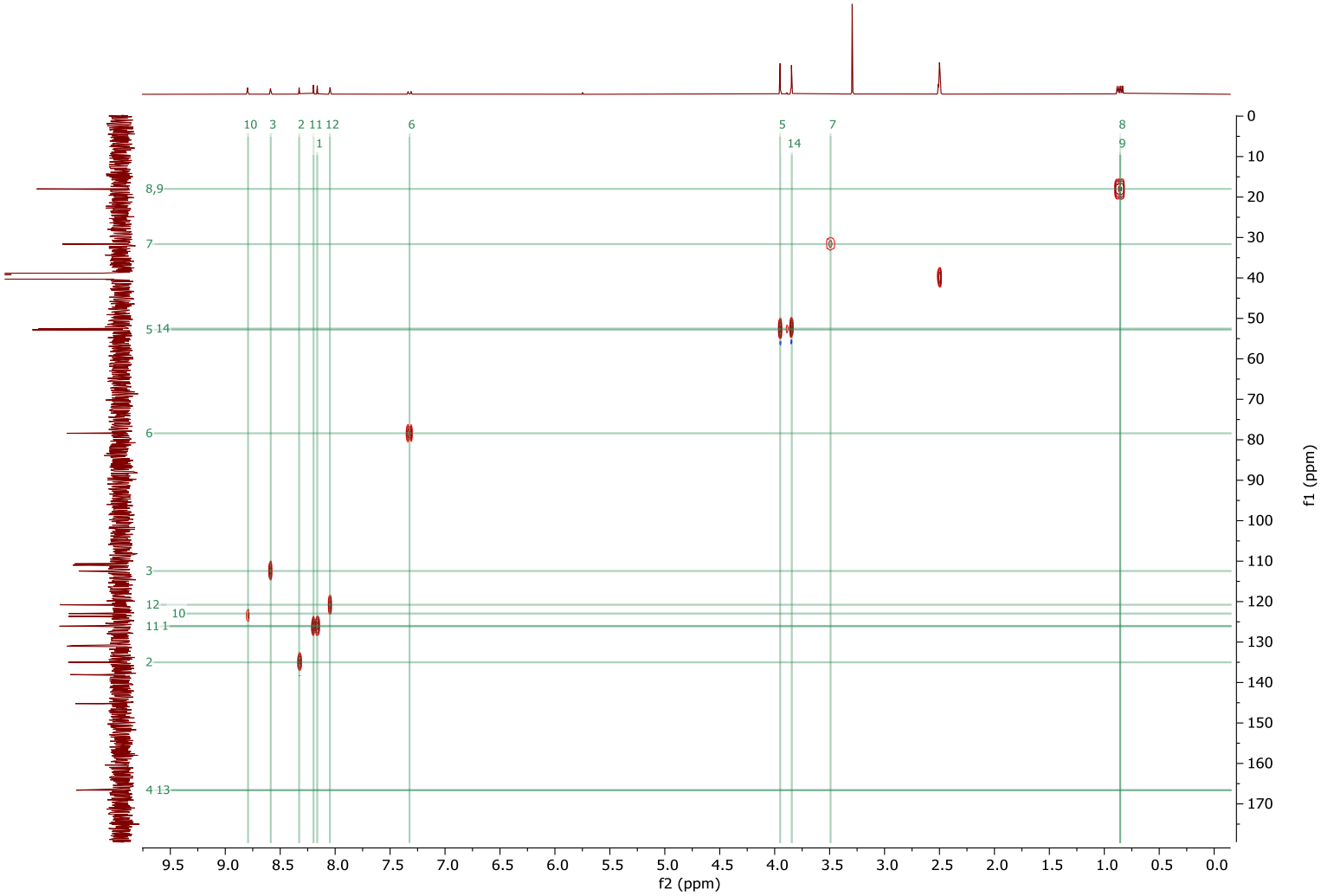
^{1}H NMR (400 MHz, DMSO-d_6)



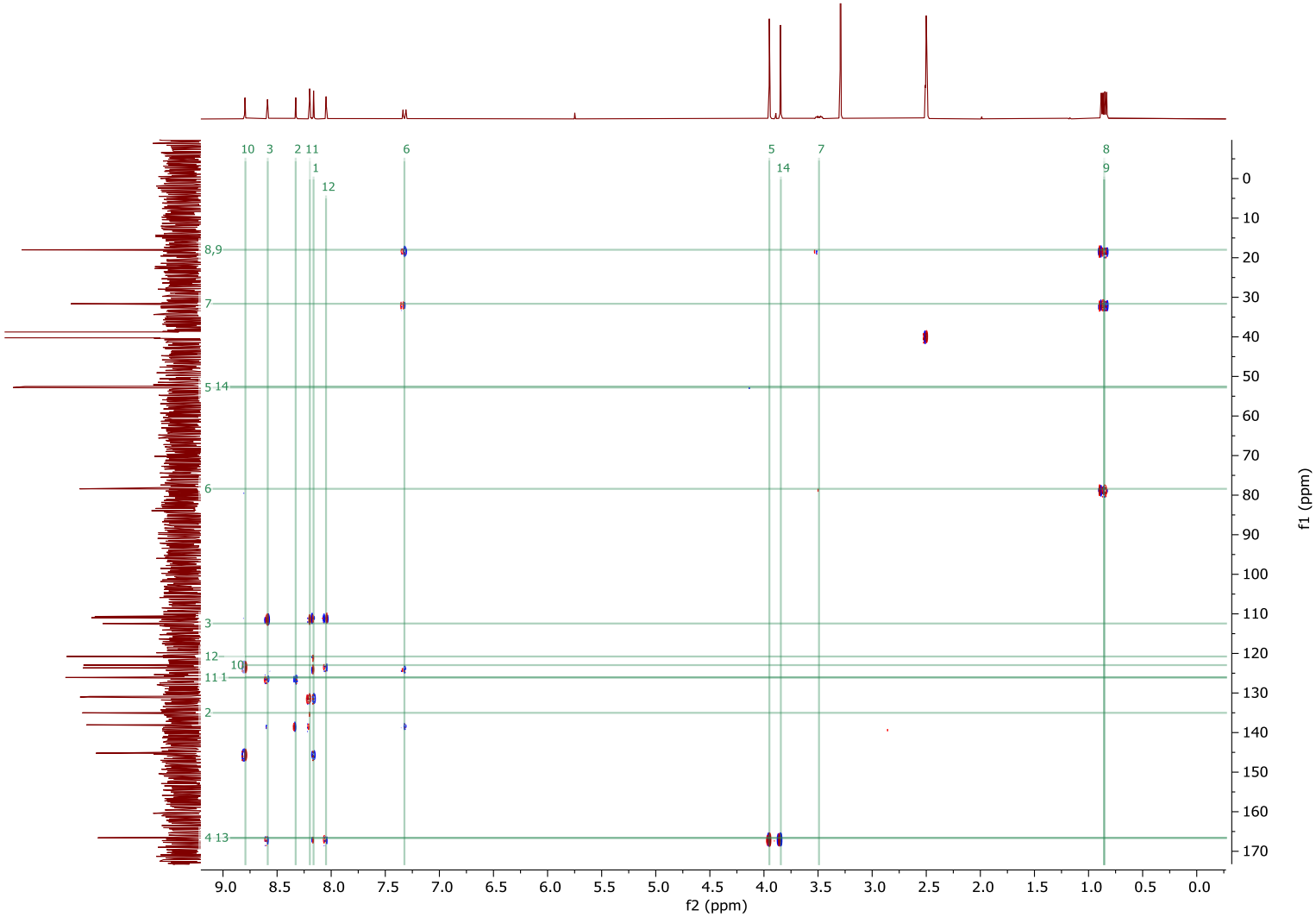
^{13}C NMR (101 MHz, DMSO-d_6)



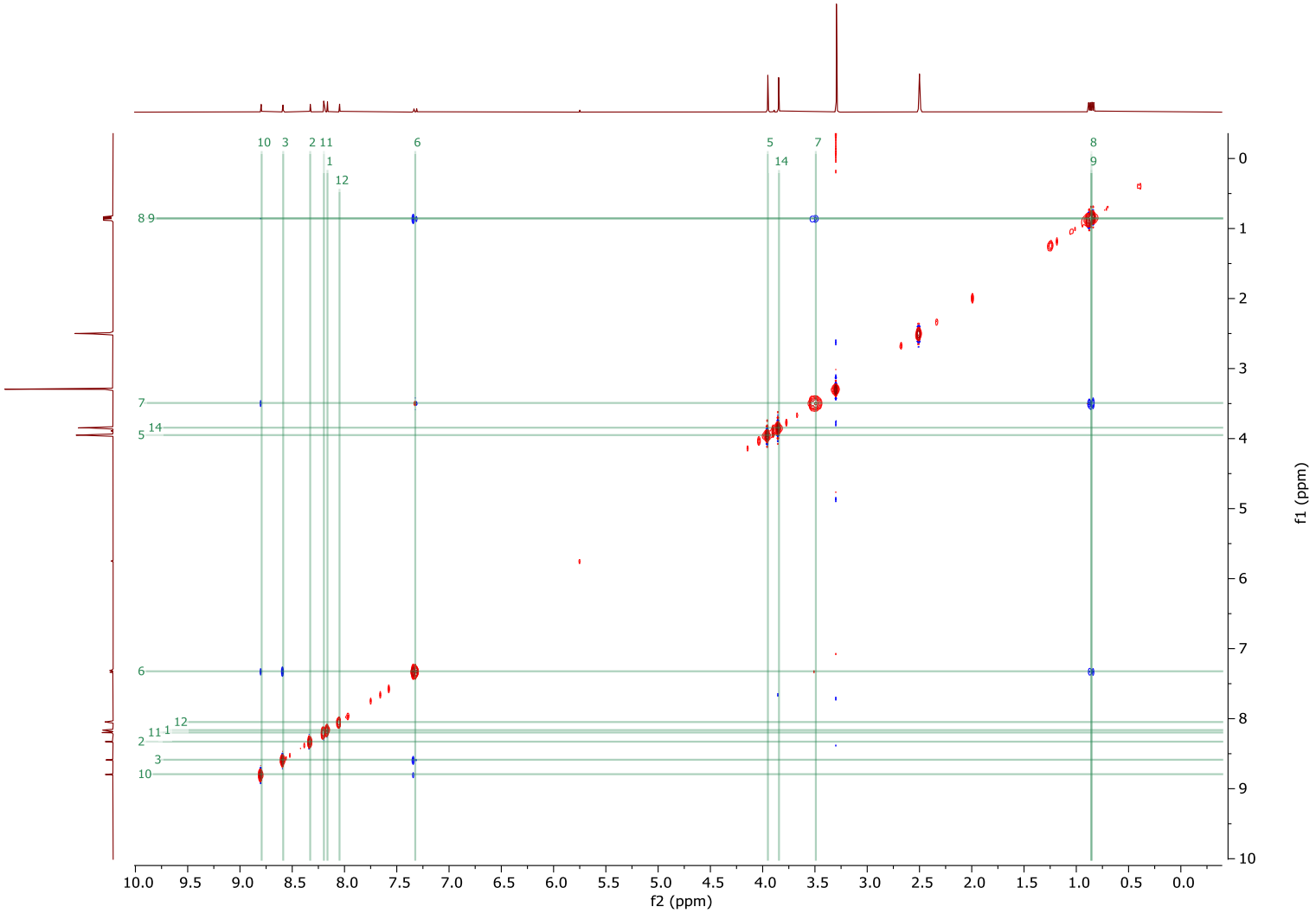
^{1}H-^{13}C HSQC (DMSO-d_6)



^{1}H-^{13}C HMBC (DMSO-d_6)

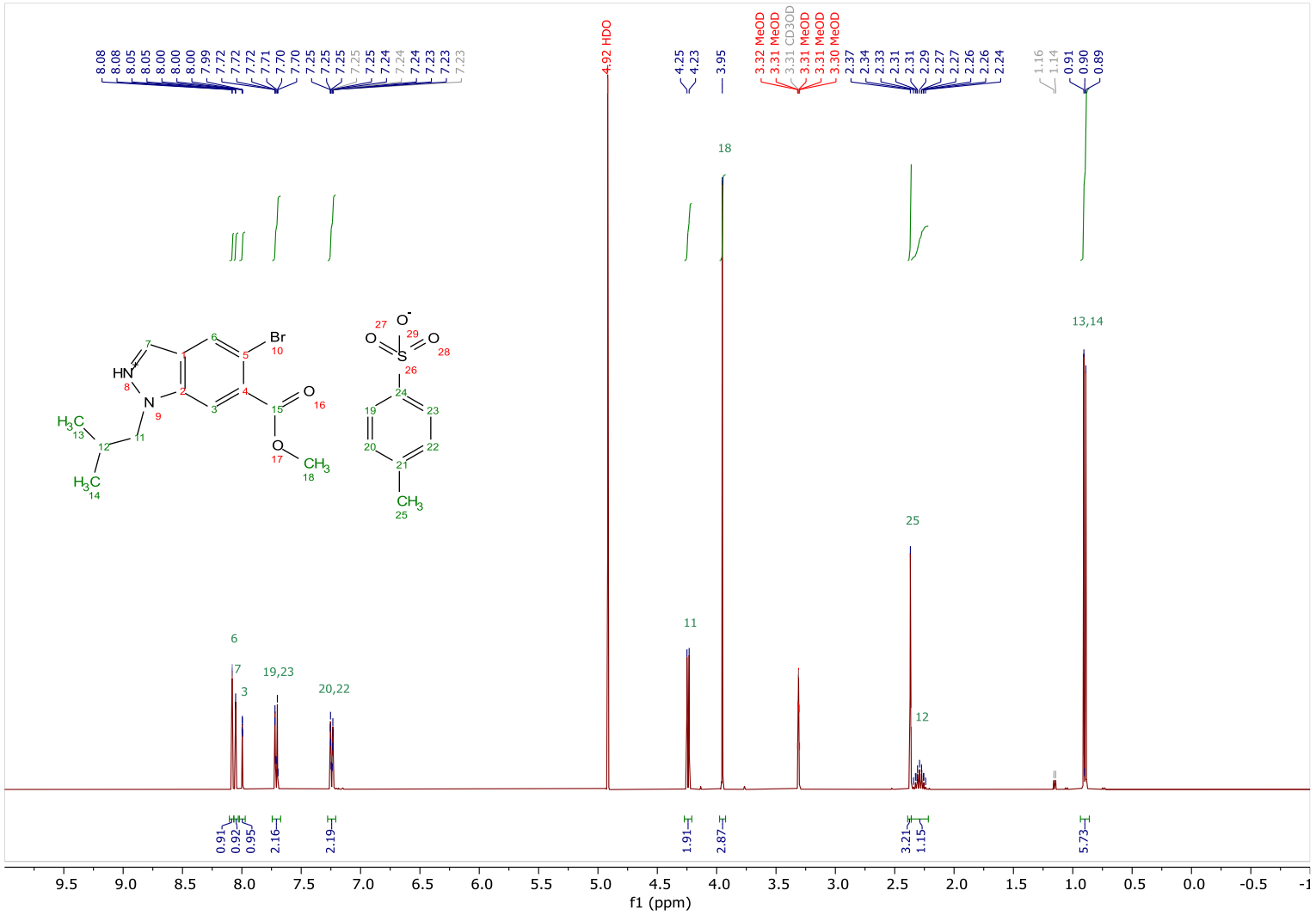


^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6)

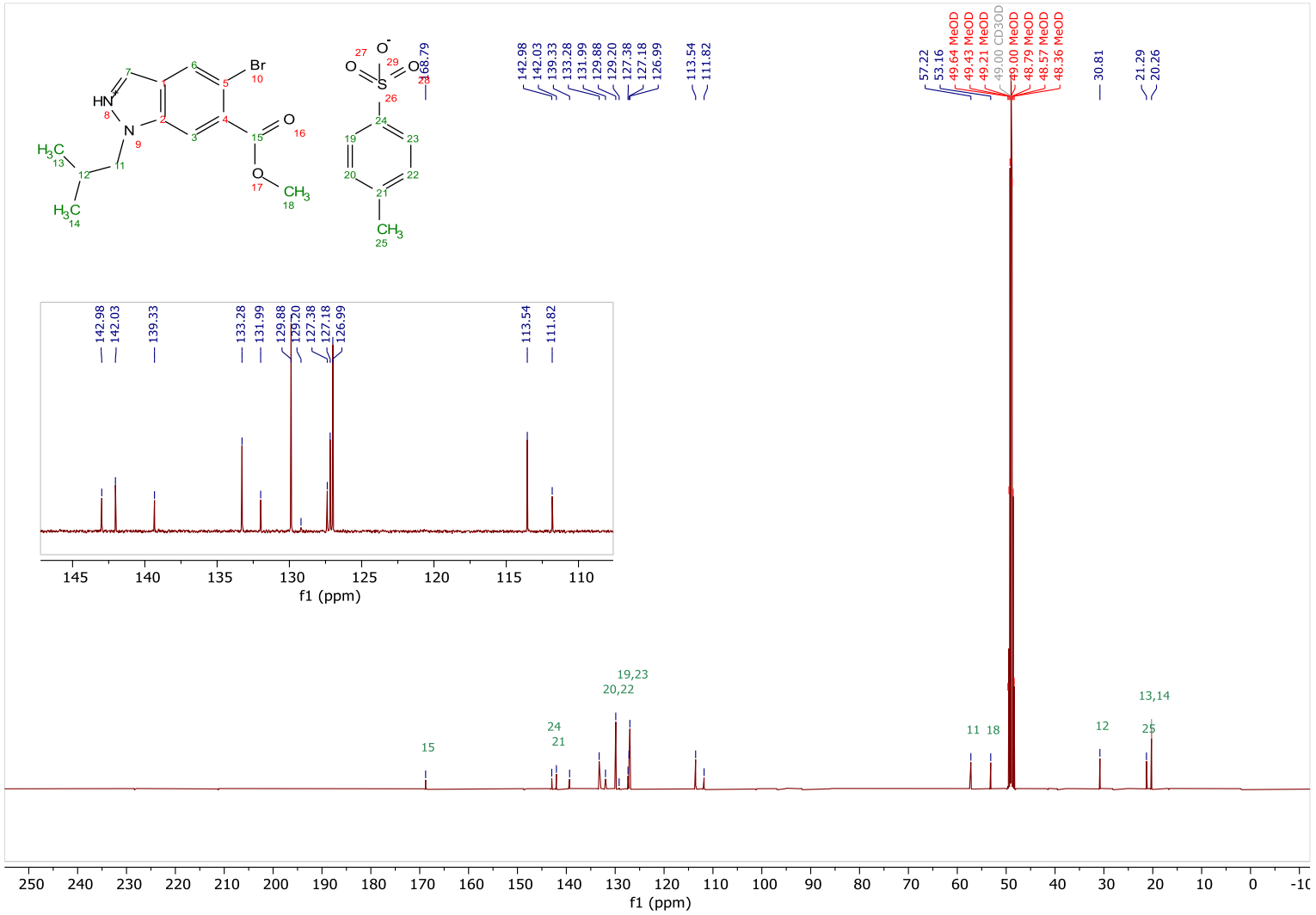


Methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate·*p*TSA

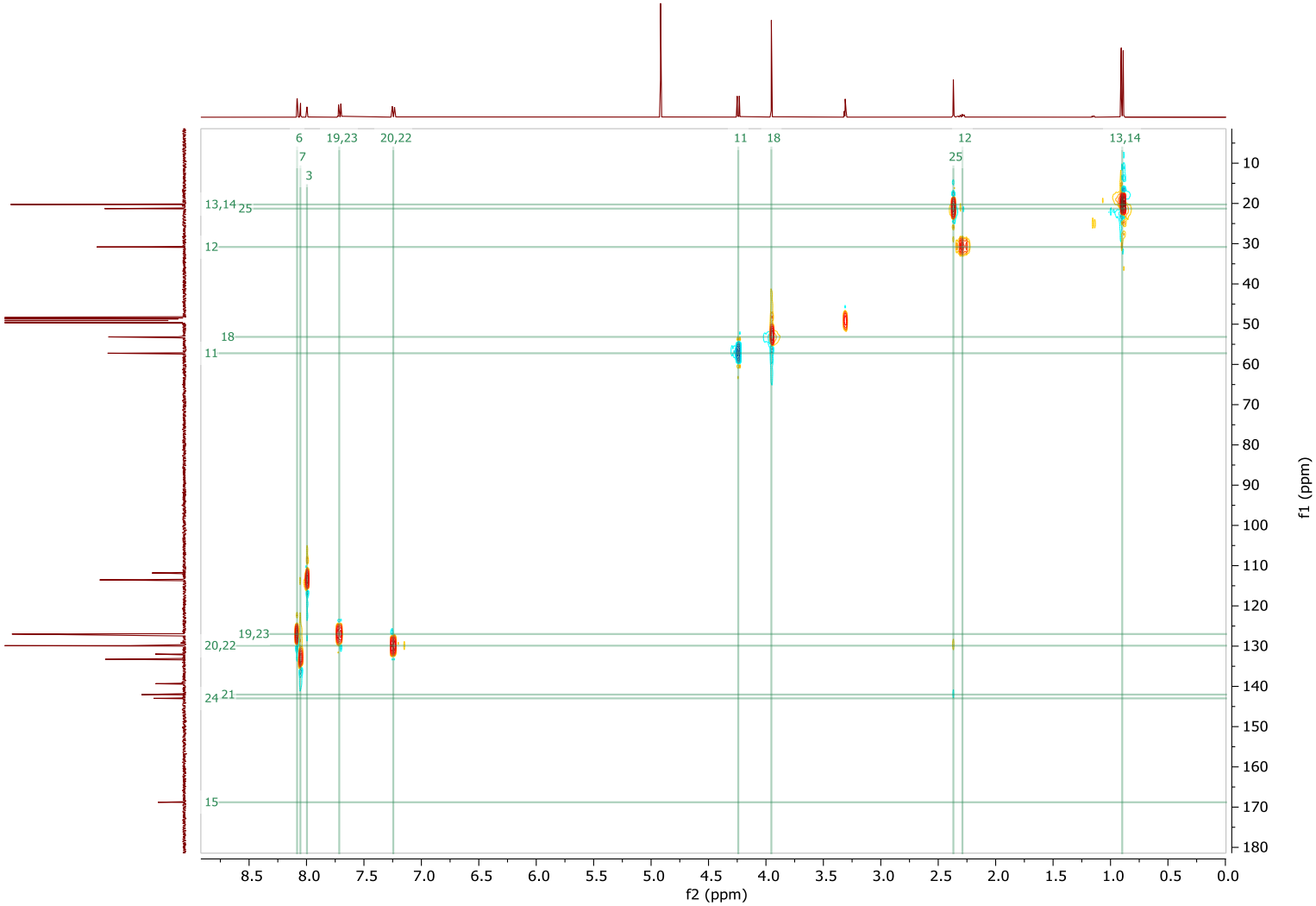
^{1}H NMR (400 MHz, MeOD)



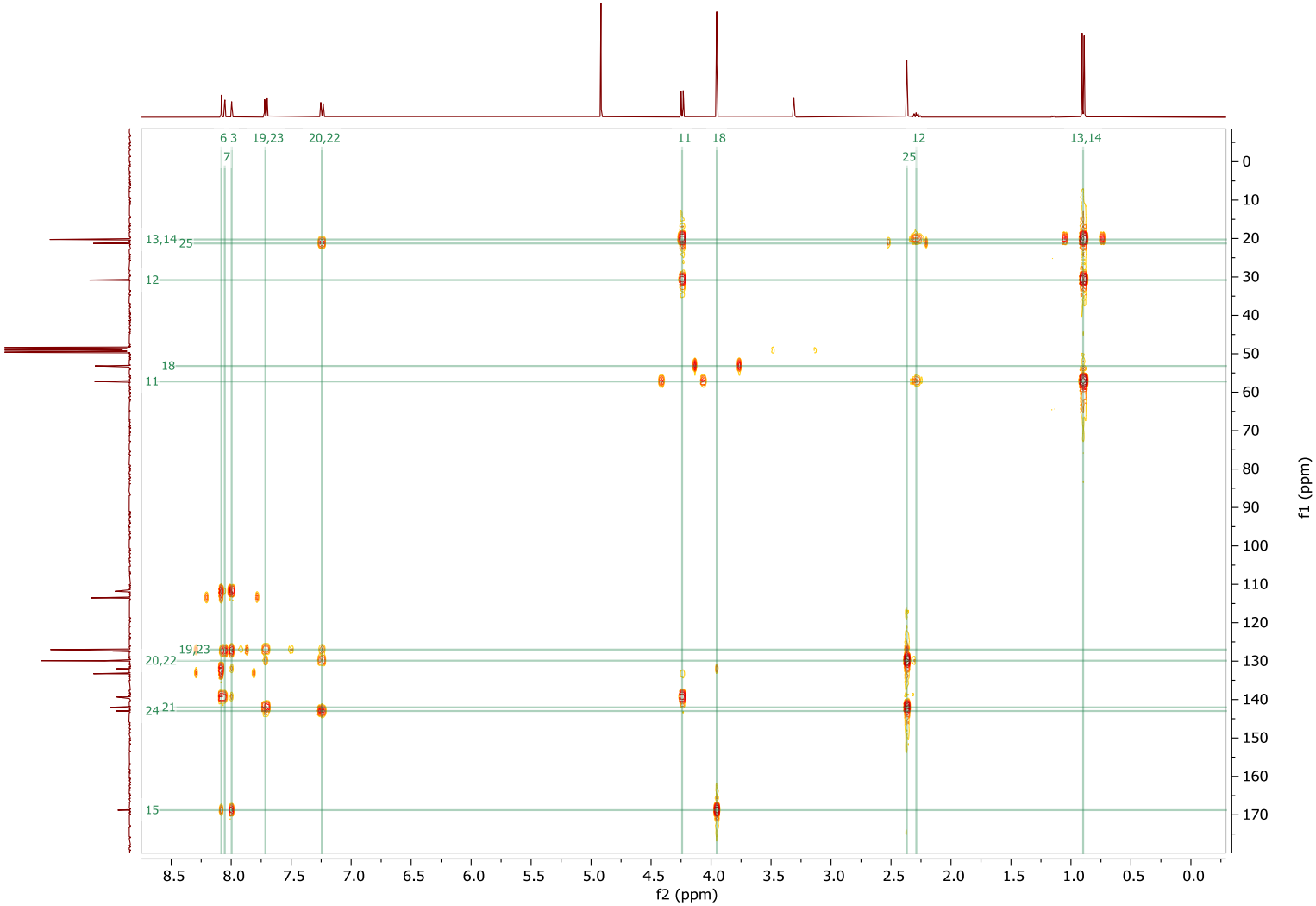
^{13}C NMR (101 MHz, MeOD)



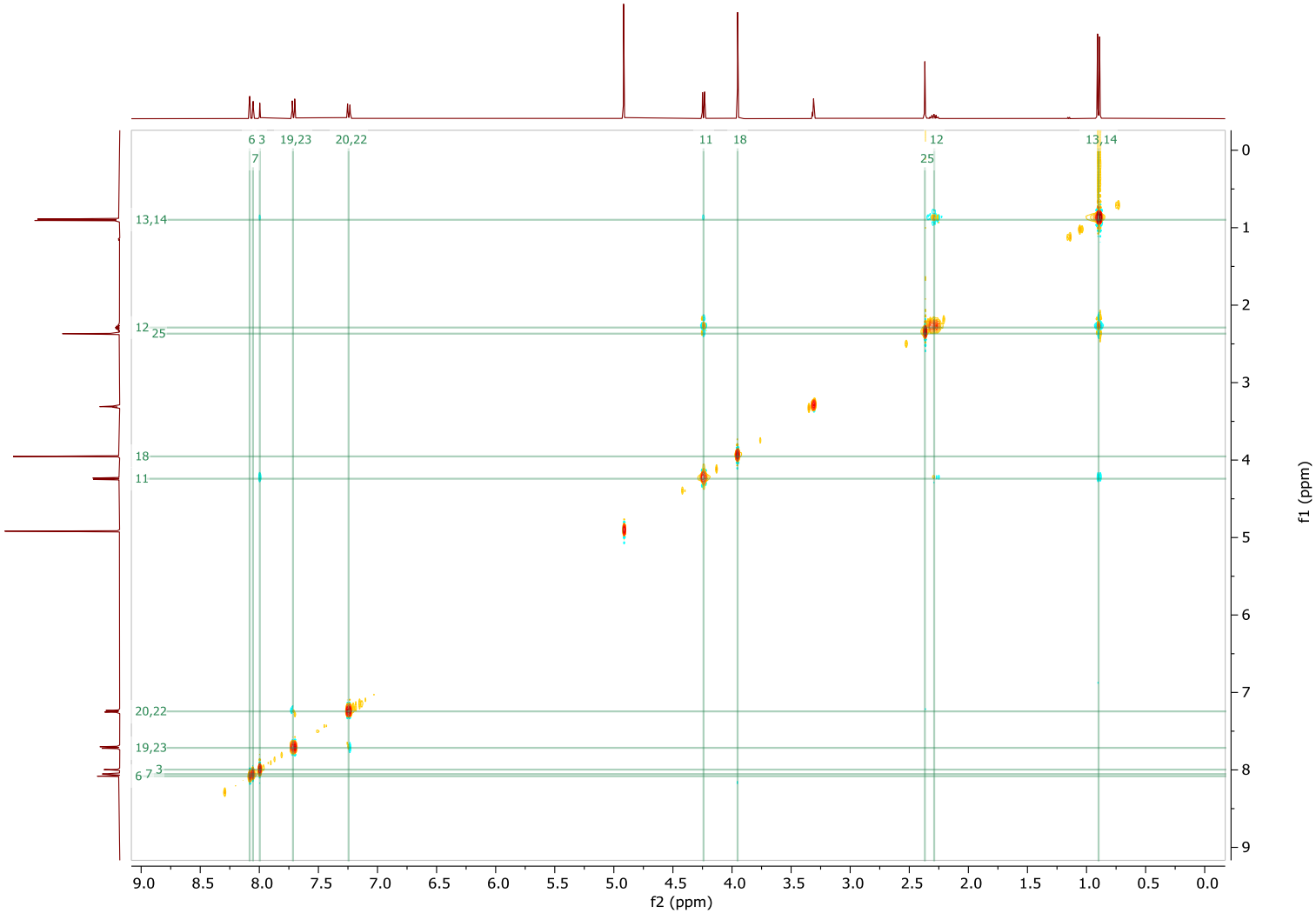
^{1}H-^{13}C HSQC (MeOD)



^{1}H-^{13}C HMBC (MeOD)



^{1}H-^{1}H NOESY (400 MHz, MeOD)



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