Supporting Information

A Process Intensified Flow Synthesis of 1*H*-4-Substituted Imidazoles – Towards the Continuous Production of Daclatasvir

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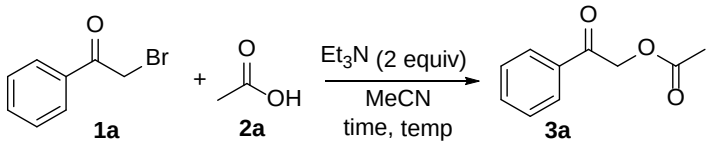
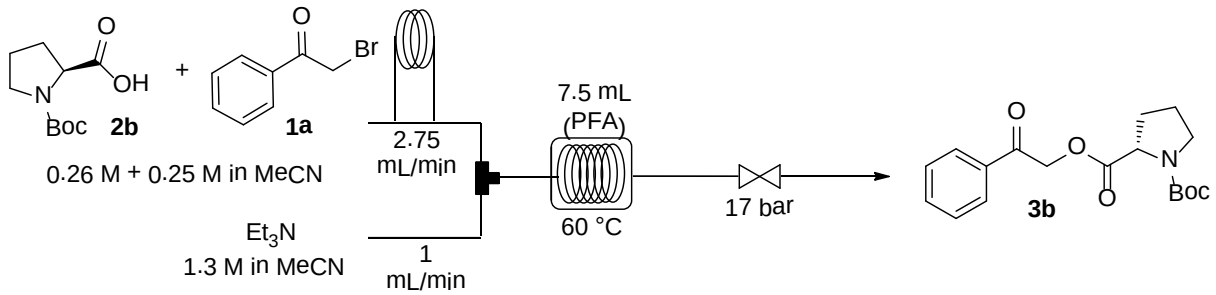
Table S1. Reaction of Bromoacetophenone 1a with Acetic Acid[a]



	reaction time (min)	Temp (°C)	AcOH (equiv)	**3a** (%)[b]
1	10	r.t.	1	72
2	20	r.t.	1	89
3	30	r.t.	1	95
4	40	r.t.	1	98
5	10	r.t.	1.2	77
6	20	r.t.	1.2	92
7	10	40	1.2	96
8	20	40	1.2	99
9	10	60	1.2	98
10[c]	20	60	1.2	100 (89.3% isolated)

[a]Conditions: 1 mmol of α-bromoacetophenone (199 mg), acetic acid and 2 mmol of the Et_3N in 6 mL of MeCN were stirred for the indicated time at the indicated temperature. [b]HPLC-UV/VIS peak area integration at 215 nm. [c]Reaction with 10 mmol α-bromoacetophenone.

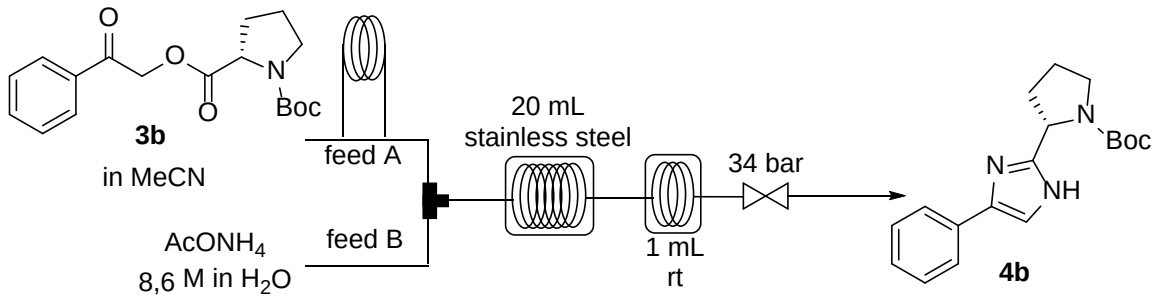
Table S2. Continuous Flow Formation of Acyloxy Ketone 3b[a]



	residence time (min)	flow rate feed A (mL/min)	flow rate feed B (mL/min)	Et_3N (equiv)	acyloxy ketone **3b** (%)[b]
1	5	0.4	1.1	1.9	>99
2	4	0.5	1.4	1.9	99
3	3	0.67	1.85	1.9	99
4	2	1.0	2.75	1.9	99
5	1	2.0	5.5	1.9	88

[a]Conditions: Feed A (0.25 M solution of **1a** and 0.26 M solution of **2b** in MeCN) and feed B (1.3 M solution of Et_3N in MeCN) were pumped through a 7.5 mL PFA reactor at 60 °C. [b]HPLC-UV/VIS peak area integration at 215 nm.

Table S3. Continuous Flow Formation of Imidazole 4b from Acyloxy Ketone 3b[a]



	Temp (°C)	residence time (min)	flow rate feed A (mL/min)	flow rate feed B (mL/min)	$AcONH_4$ (equiv)	acyloxy ketone **3b** (%)[b]	imidazole **4b** (%)[b]	oxazole **5b** (%)[b]	others (%)[b]
1	180	13	0.2	1.3	7.3	-	78	1	21
2	180	10	0.27	1.75	7.3	-	84	1	15
3	180	7	0.4	2.5	7.6	-	90	1	9
4	180	5	0.53	3.45	7.3	1	94	1	4
5	180	5	0.28	3.7	3.6	3	87	1	9
6	180	5	0.93	3.05	14.4	-	91	1	8
7	170	5	0.53	3.45	7.3	-	97	1	2
8	160	5	0.53	3.45	7.3	-	97	1	2
9	150	5	0.53	3.45	7.3	1	95	1	3
10	140	5	0.53	3.45	7.3	-	92	0	8
11	130	5	0.53	3.45	7.3	1	89	-	11
12	120	5	0.53	3.45	7.3	10	69	-	21
13[c]	160	5	0.2	1.5	7.3	-	98	0	1
14[c]	160	4	0.25	1.65	7.2	-	98	1	2
15[c]	160	3	0.33	2.15	7.2	2	96	1	1
16[c]	160	2	0.5	3.25	7.3	3	97	1	-
17[c]	160	1	1.0	6.5	7.3	11	79	1	0

[a]Conditions: Feed A (0.4 mmol solution of acyloxy ketone **3b** in MeCN; prepared in a sealed vessel batch microwave reactor) and feed B (8.6 M solution of $AcONH_4$ in H_2O) were pumped through a 20 mL stainless steel reactor (~7.3 equivalents of $AcONH_4$). [b]HPLC-UV/VIS peak area integration at 215 nm. rt = room temperature. [c]7.5 mL stainless steel reactor.

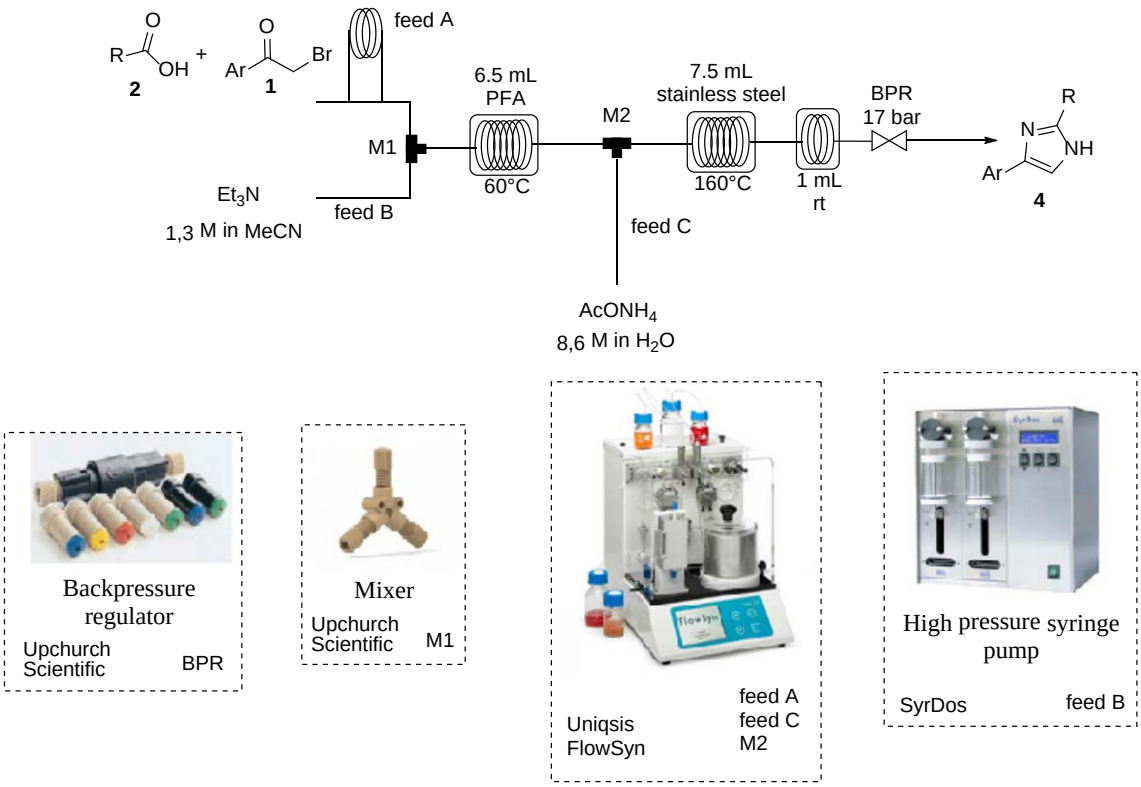


Figure S1. Continuous flow setup. Feed A and feed C were pumped into the flow reactor via two HPLC pumps (the HPLC pumps are part of the Uniqsis FlowSyn). Feed D was delivered by a high pressure syringe pump (SyrDos). Feed A and feed B were mixed in a Y-shaped mixer (M1; Upchurch Scientific), and the combined mixture went through a 6.5 mL PFA tubing in a water bath (perfluoroalkoxy alkane; 1.6 mm o.d.; 0.8 mm i.d.). The solution was combined with feed C in a second mixer (M2; mixer and pressure transducer of the Uniqsis FlowSyn), before the solution went through a 7.5 mL stainless steel reactor (1.6 mm o.d.; 1.0 mm i.d.). The stainless steel reactor was heated on the aluminum heating block of the Uniqsis FlowSyn. The processed mixture was cooled in a 1 mL stainless steel tubing in a water bath (1.6 mm o.d.; 1.0 mm i.d.) and left the system through a 17 bar back pressure regulator (BPR; Upchurch Scientific).

Synthesis of 4,4'-Bis(2-bromoacetyl)biphenyl (1m). 0.2 mmol (48 mg) of 4,4’diacetylbiphenyl, 0.4 mmol (71 mg) of NBS and 0.04 mmol (7.6 mg) of *p*-toluenesulfonic acid were weighted into a 10 mL microwave vessel equipped with a magnetic stir bar. 2 mL of dichloromethane were added; the vessel was closed and heated in a microwave reactor for 30 min at 80°C. The solvent was evaporated and the solid was recrystallized from acetonitrile to provide 62 mg (78%) of 4,4'-bis(2-bromoacetyl)biphenyl **1m** as a white solid.

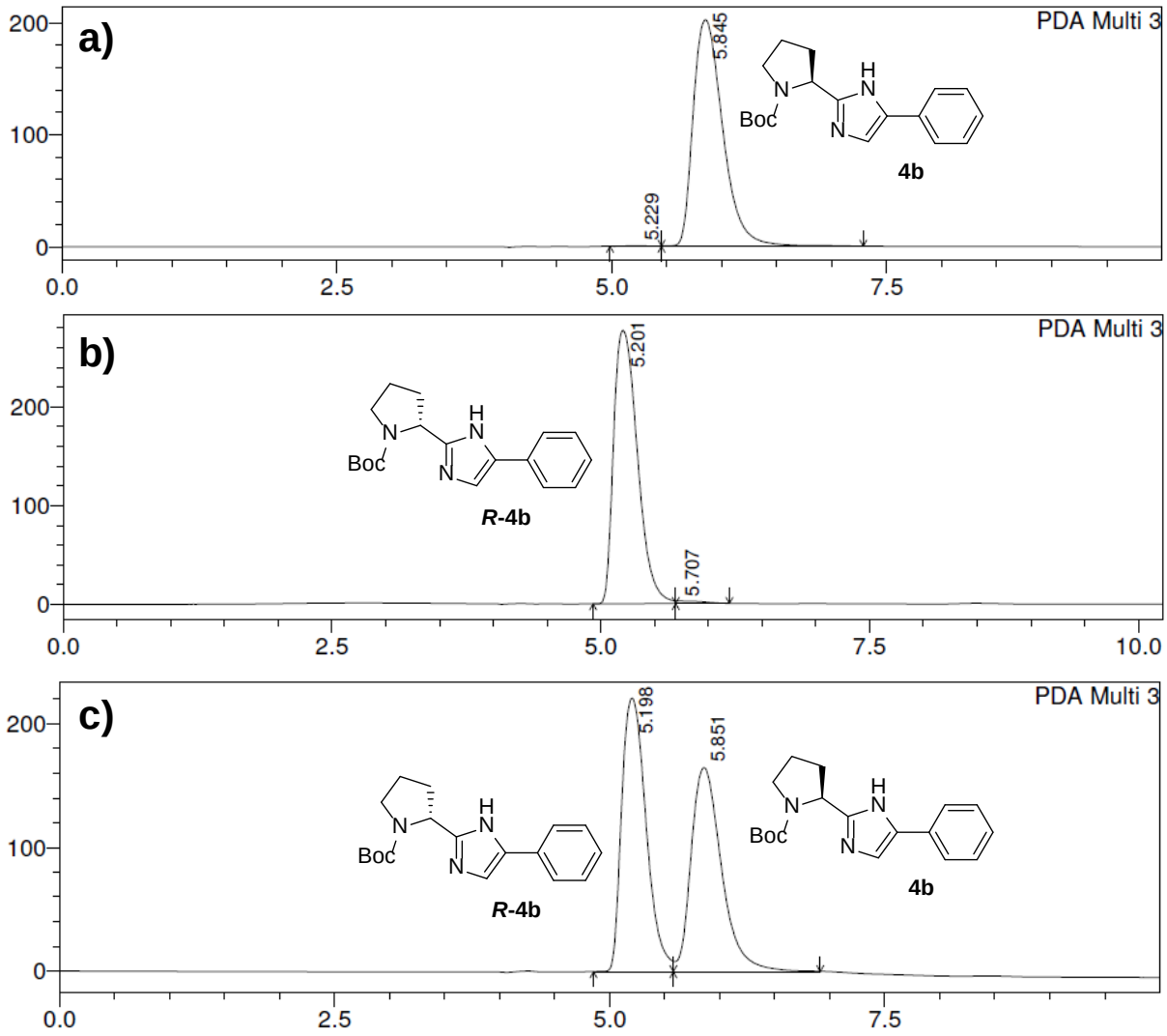
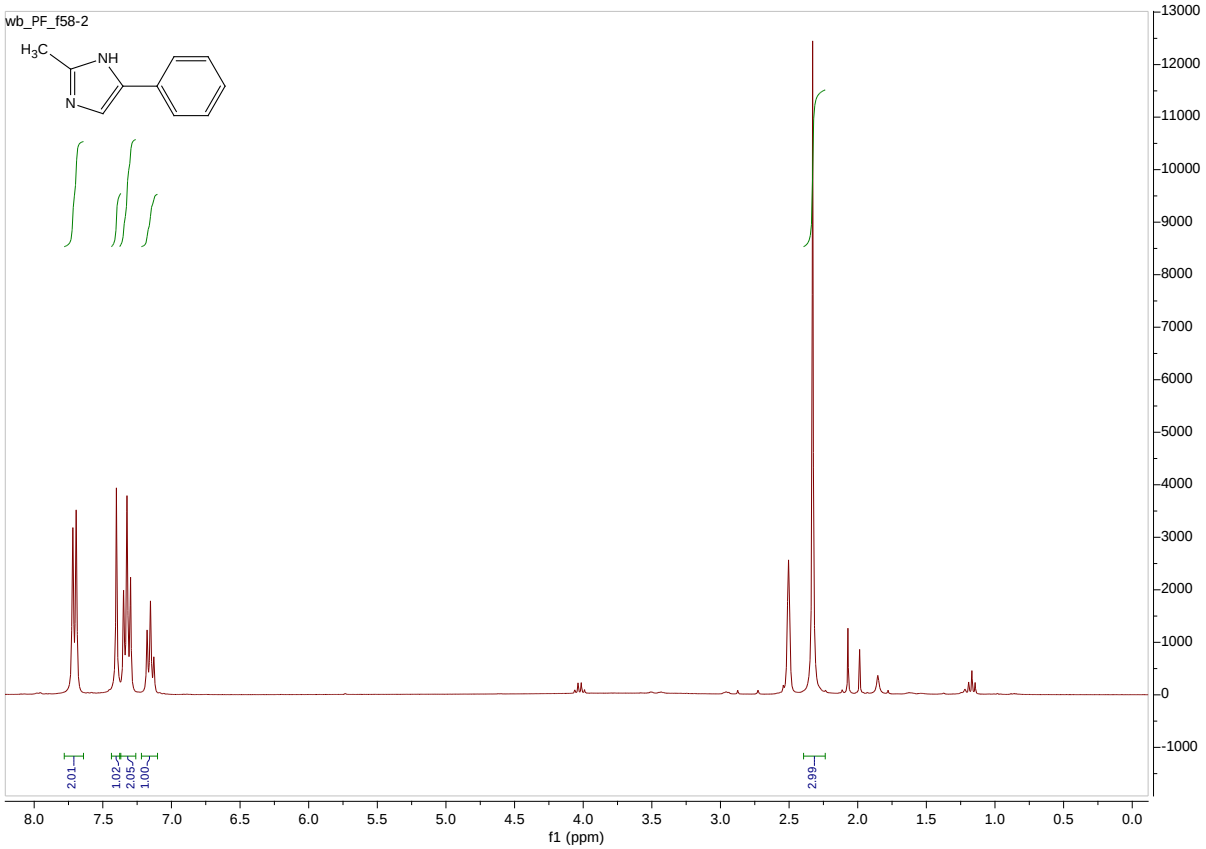


Figure S2. Chiral HPLC chromatograms of imidazole **4b** (a), ***R*-4b** (b) and a mixture of **4b** and **R-4b** (c). Column: Daicel Chiralcel OD-H; eluent: n-heptane/2-propanol 70/30; oven temp: 25°C; isocratic flow 0.7 mL/min.



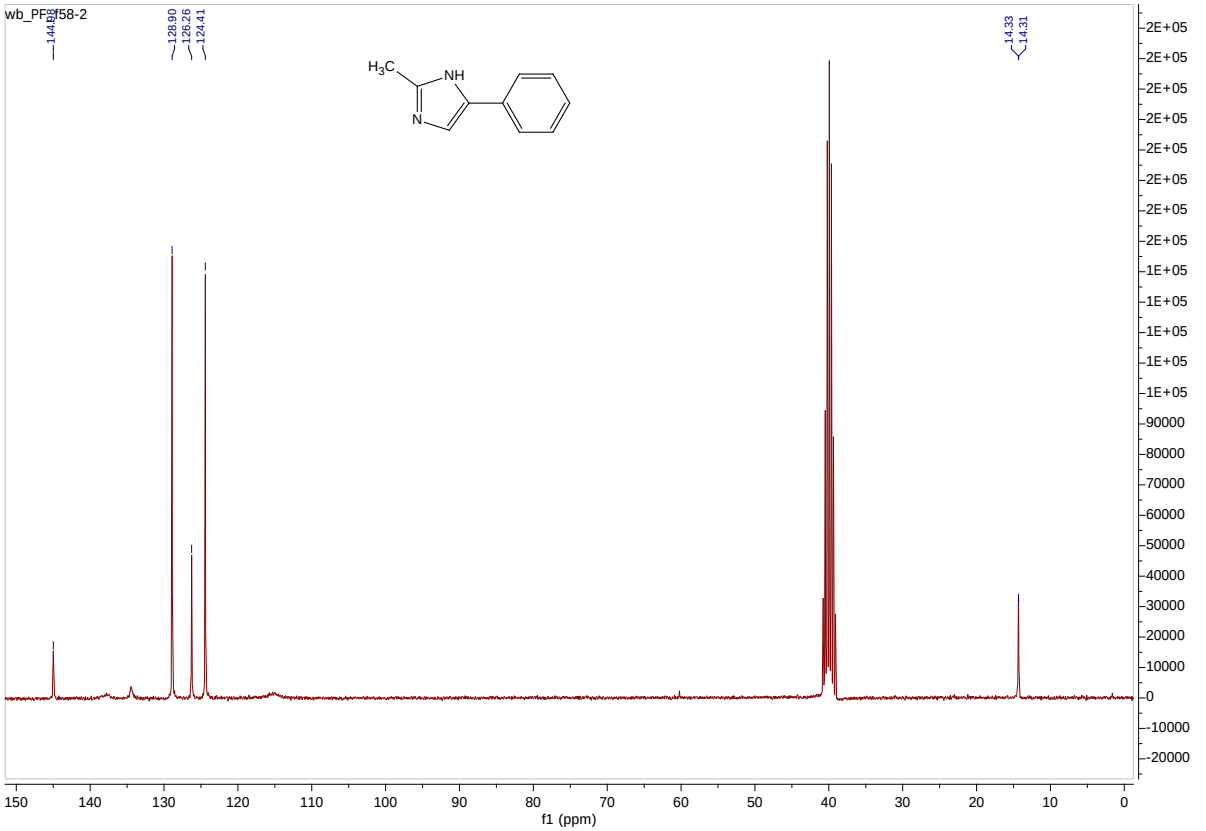


Figure S3. ^{1}H-NMR and ^{13}C-NMR of 2-methyl-5-phenyl-1*H*-imidazole (**4a**).

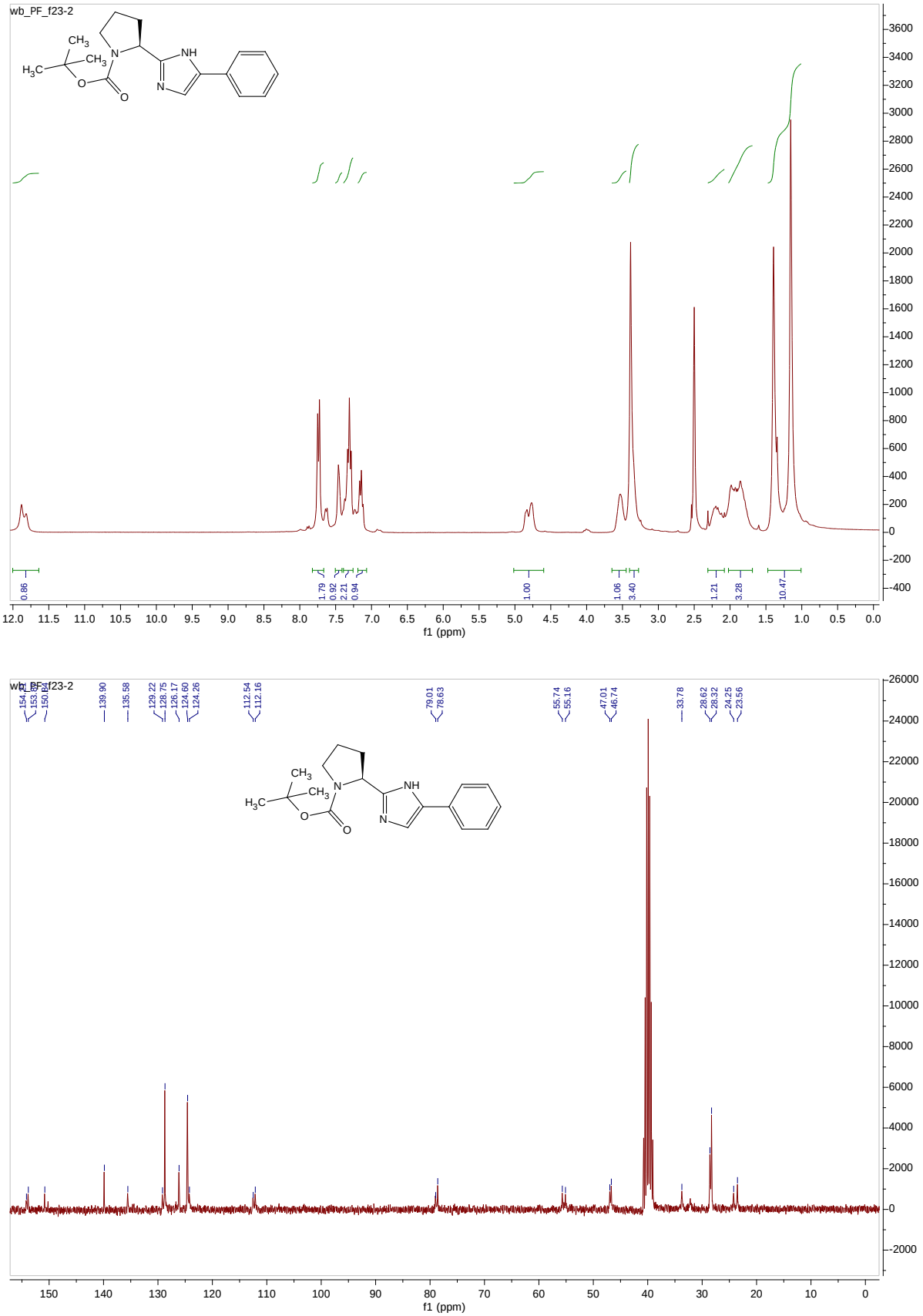


Figure S4. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-phenyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4b**).

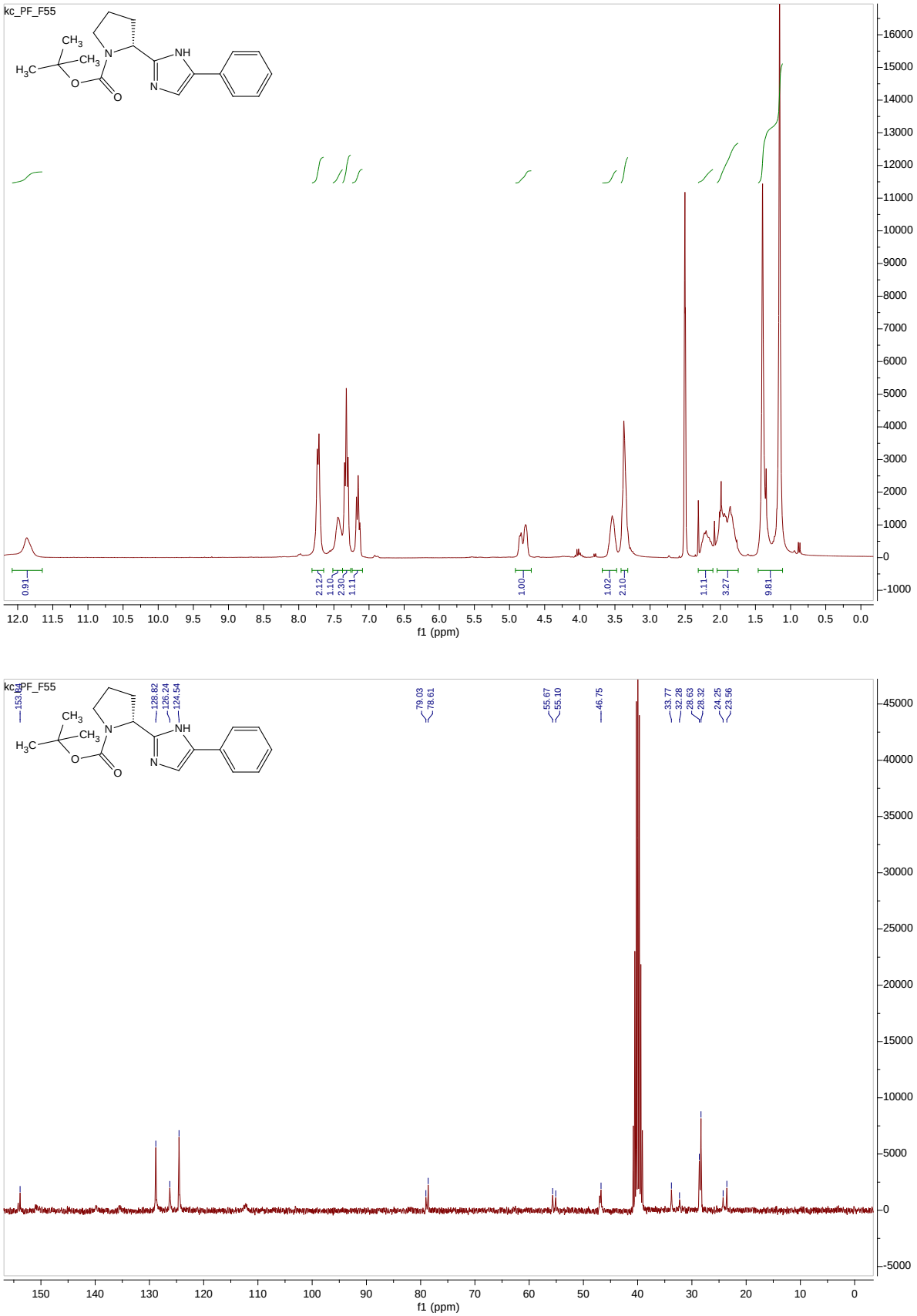


Figure S5. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*R*)-2-(5-phenyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**R-4b**).

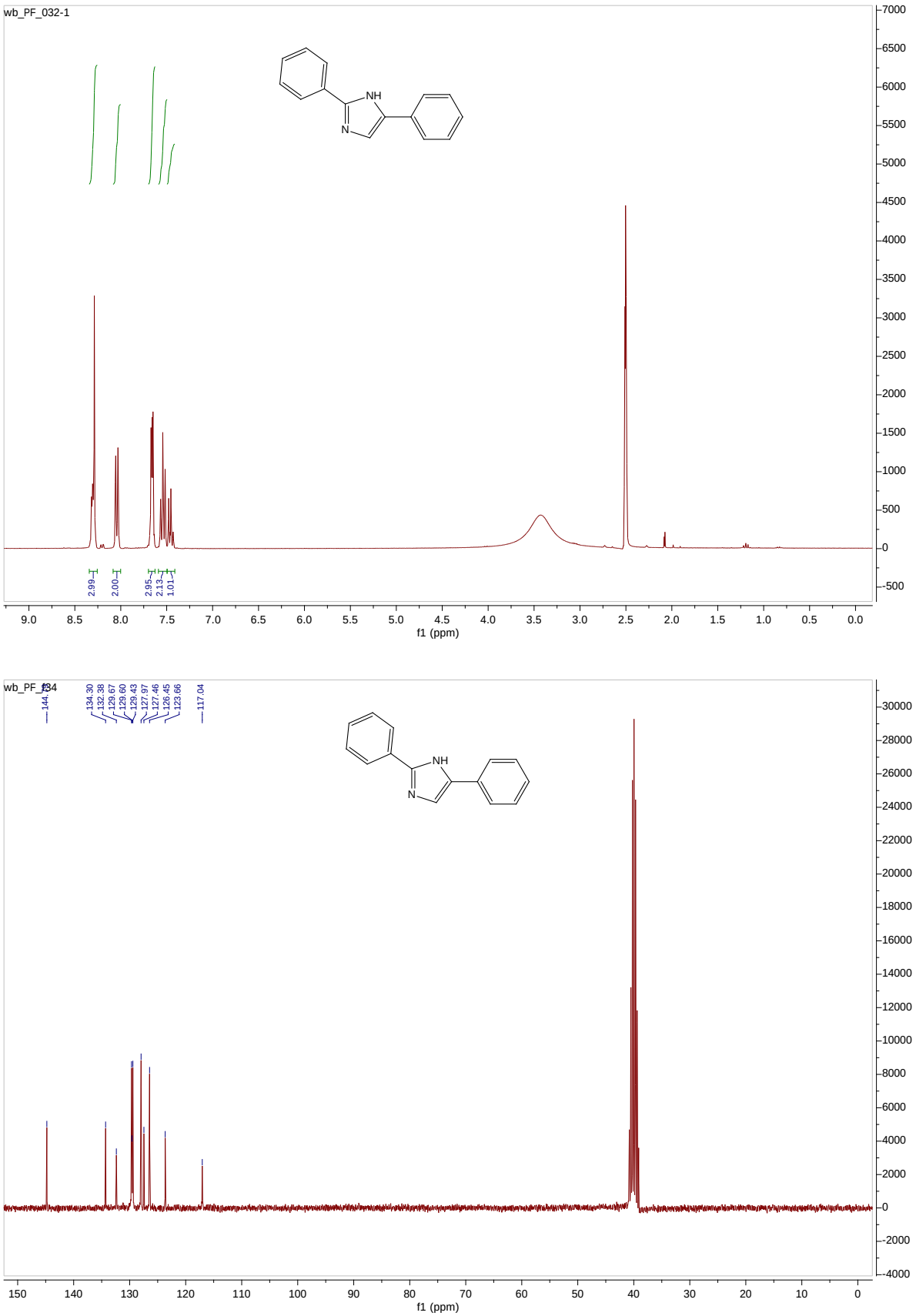
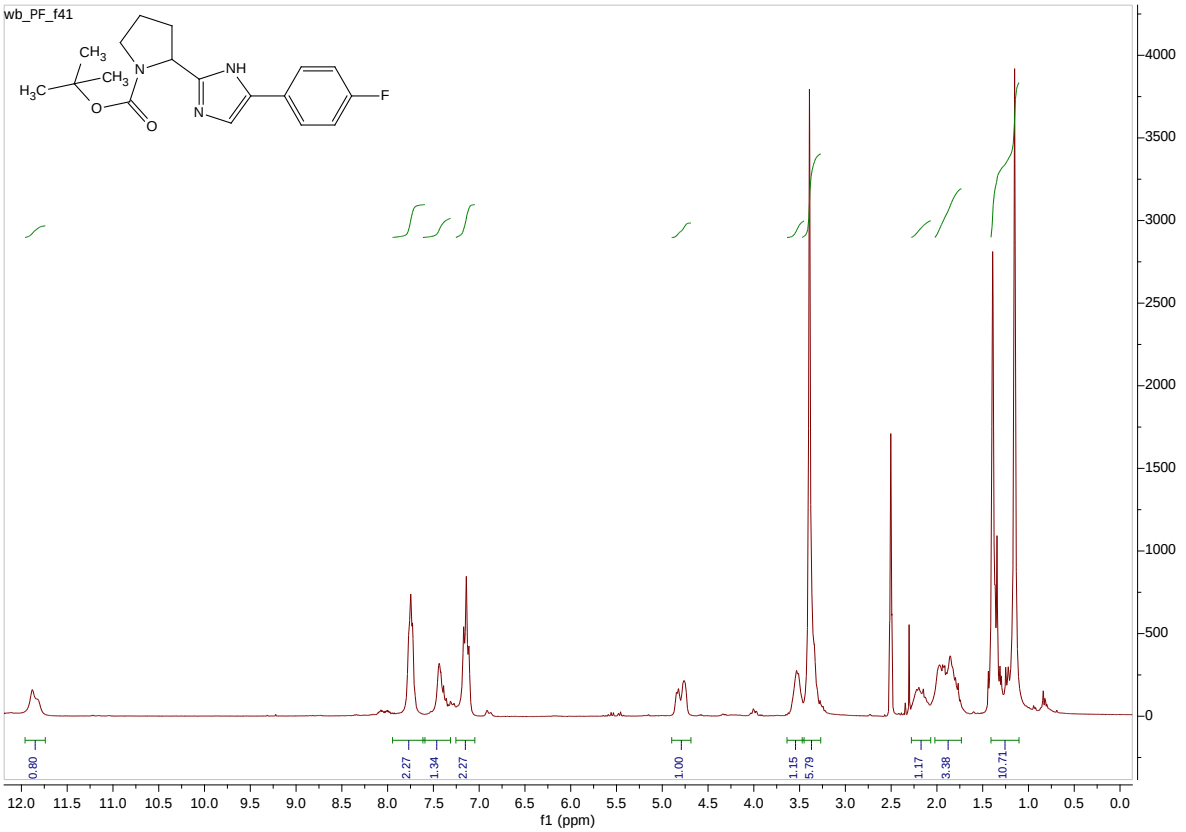


Figure S6. ^{1}H-NMR and ^{13}C-NMR of 2,5-diphenyl-1*H*-imidazole (**4c**).



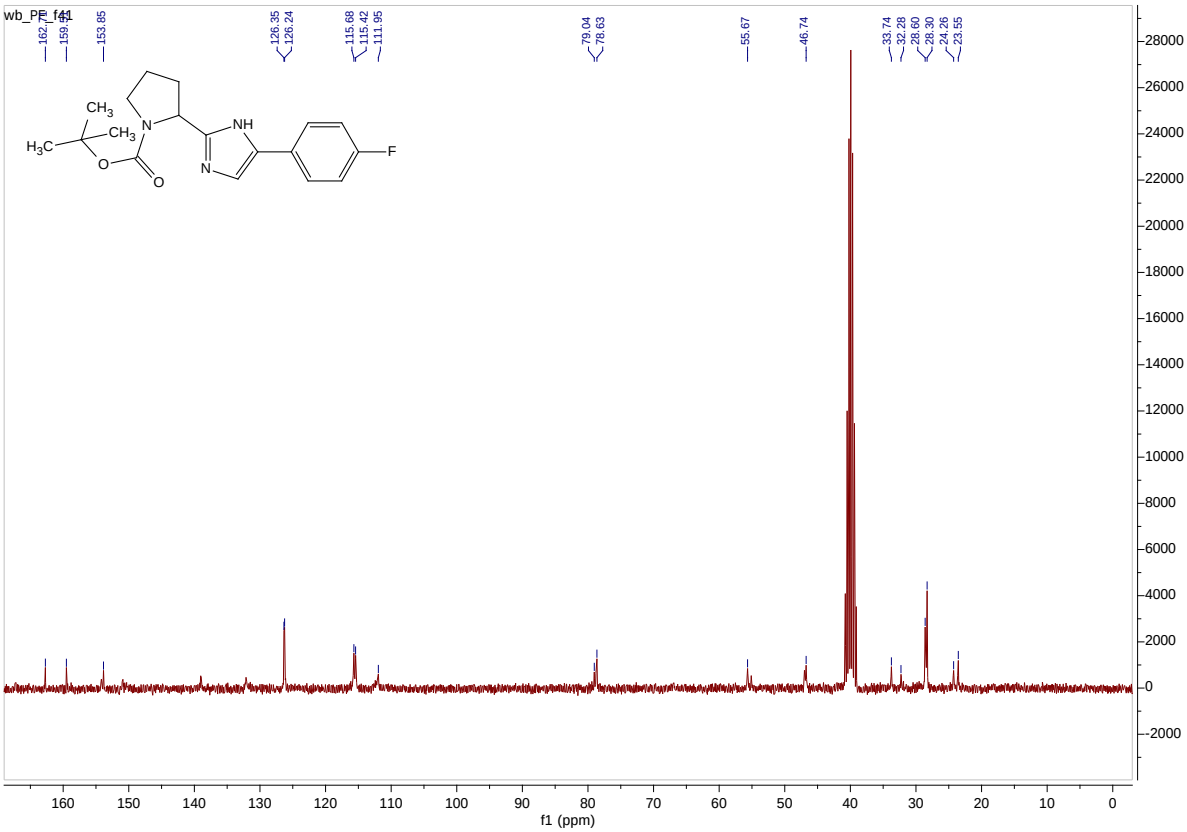
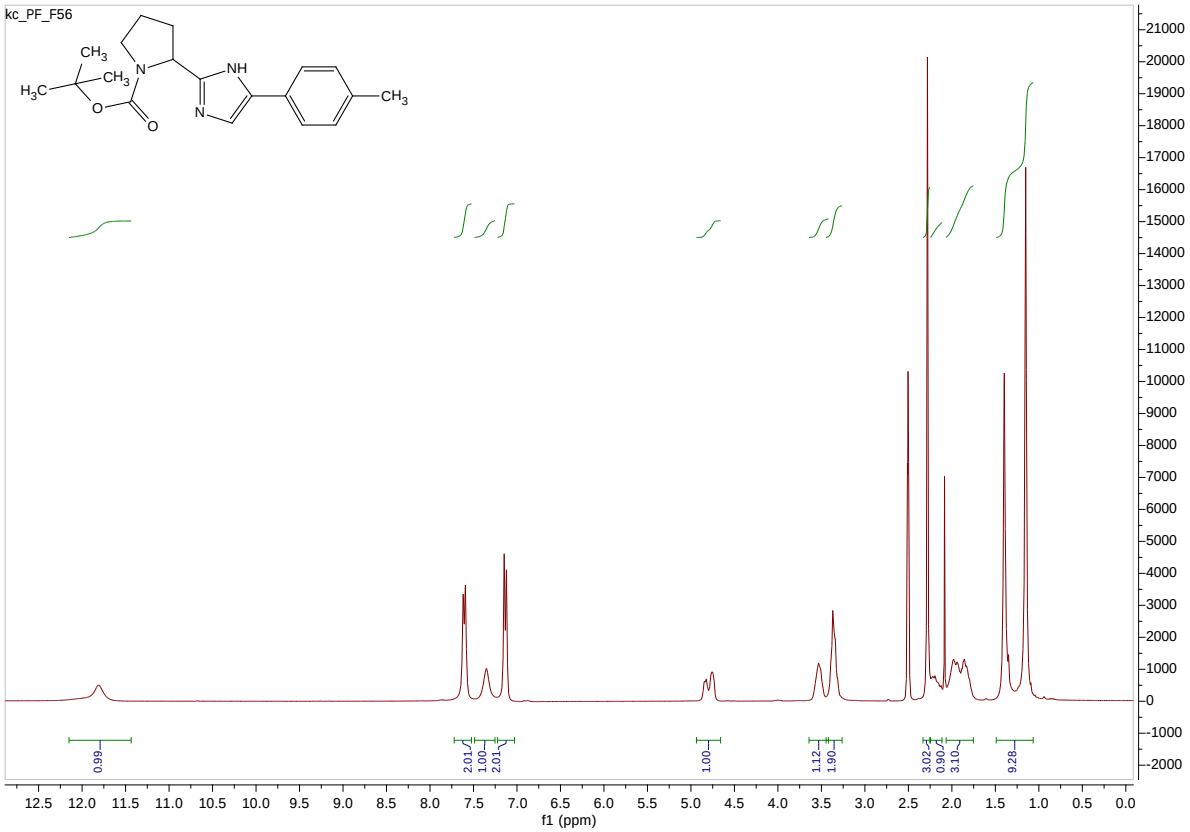


Figure S7. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(4-fluorophenyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4d**).



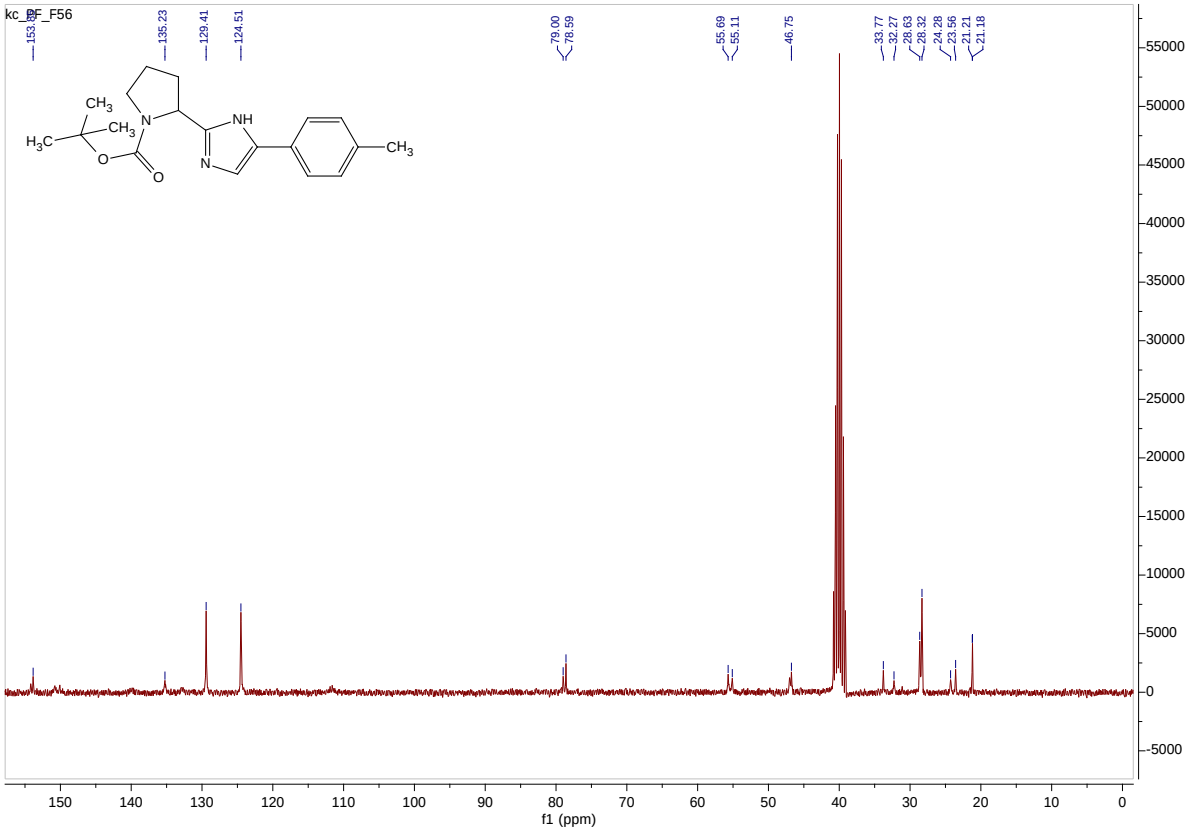
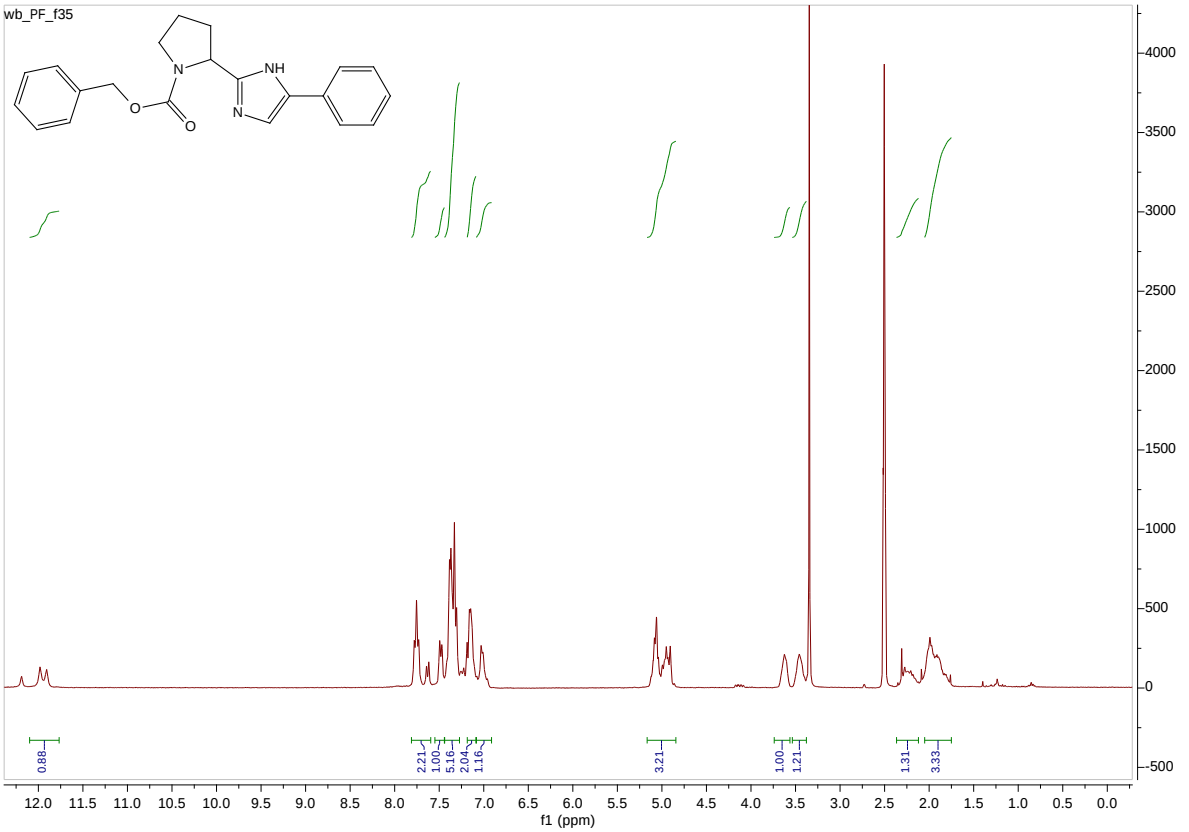


Figure S8. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4e**).



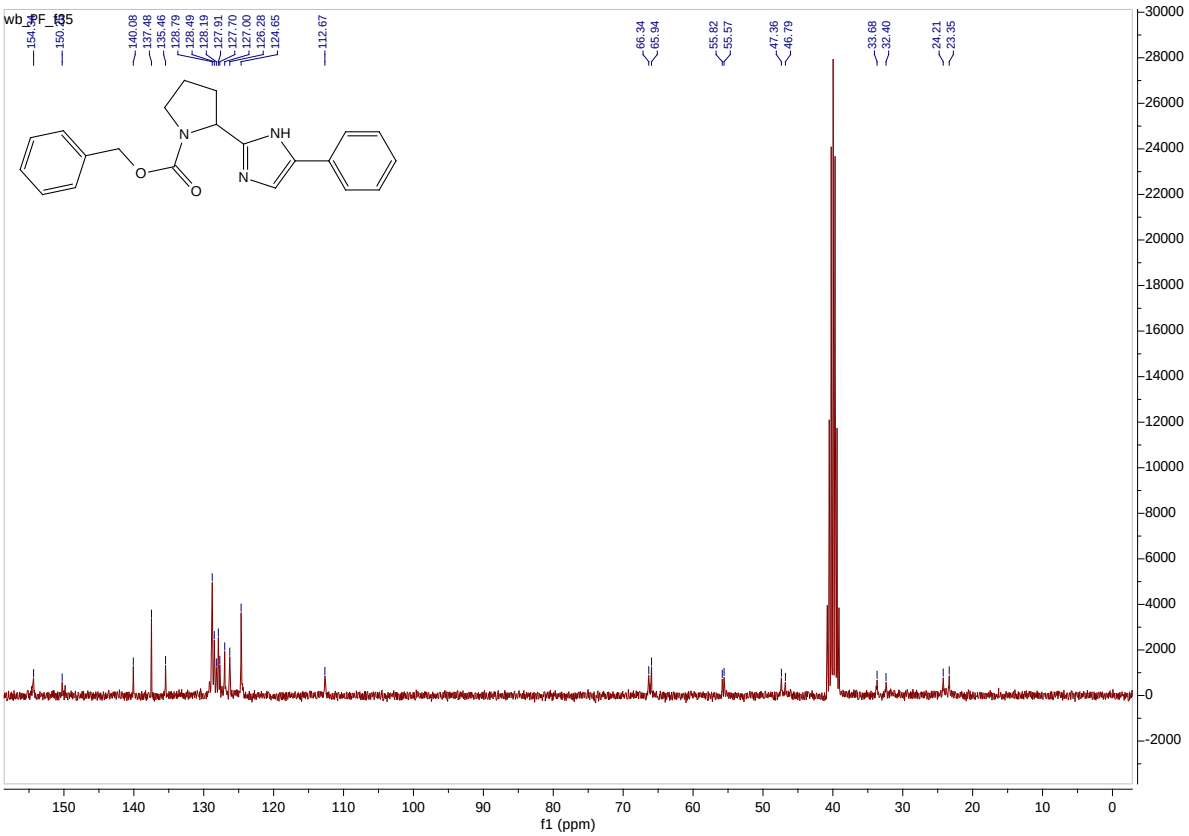


Figure S9. ^{1}H-NMR and ^{13}C-NMR of benzyl (*S*)-2-(5-phenyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylat (**4f**).

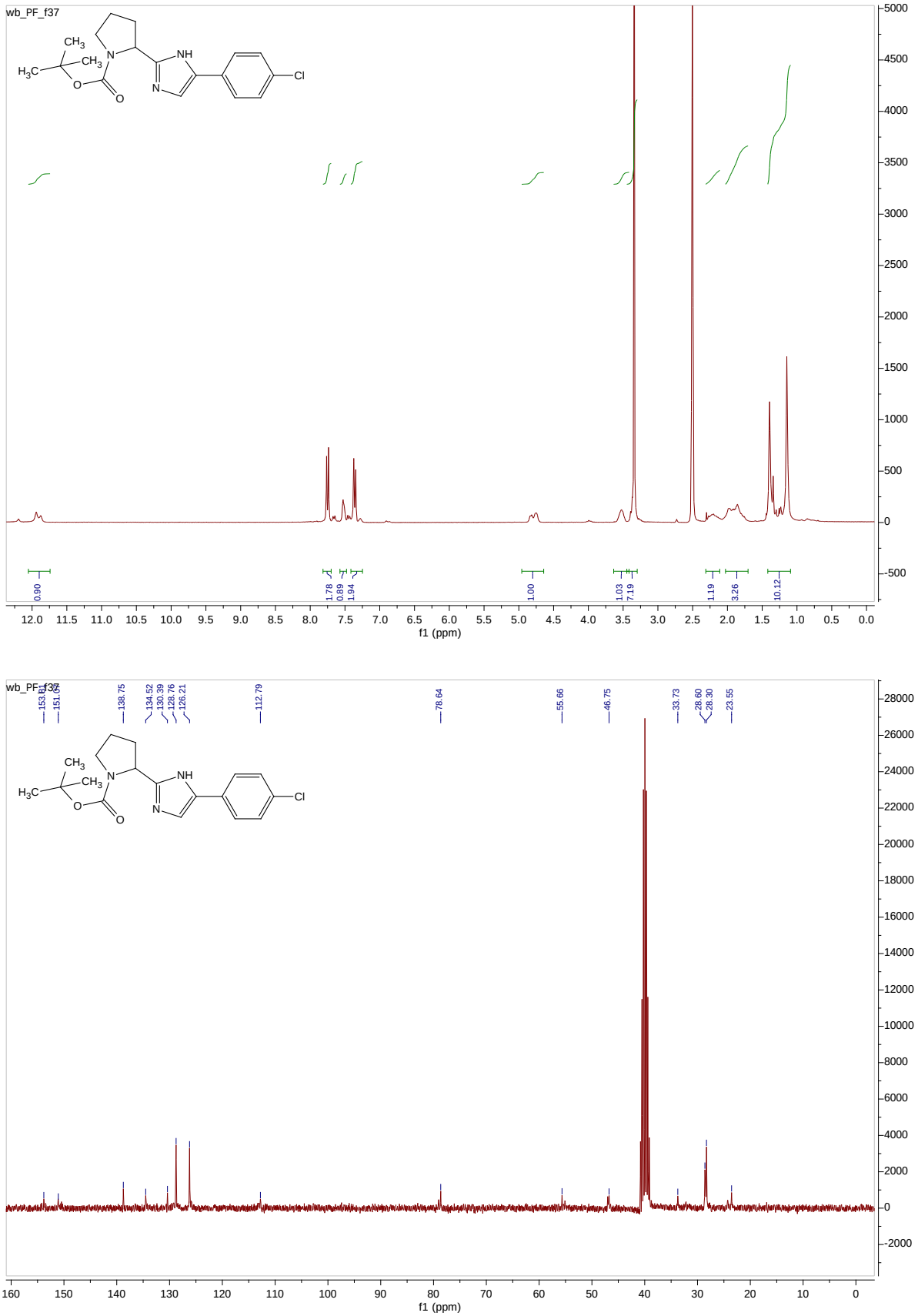


Figure S10. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(4-chlorophenyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4g**).

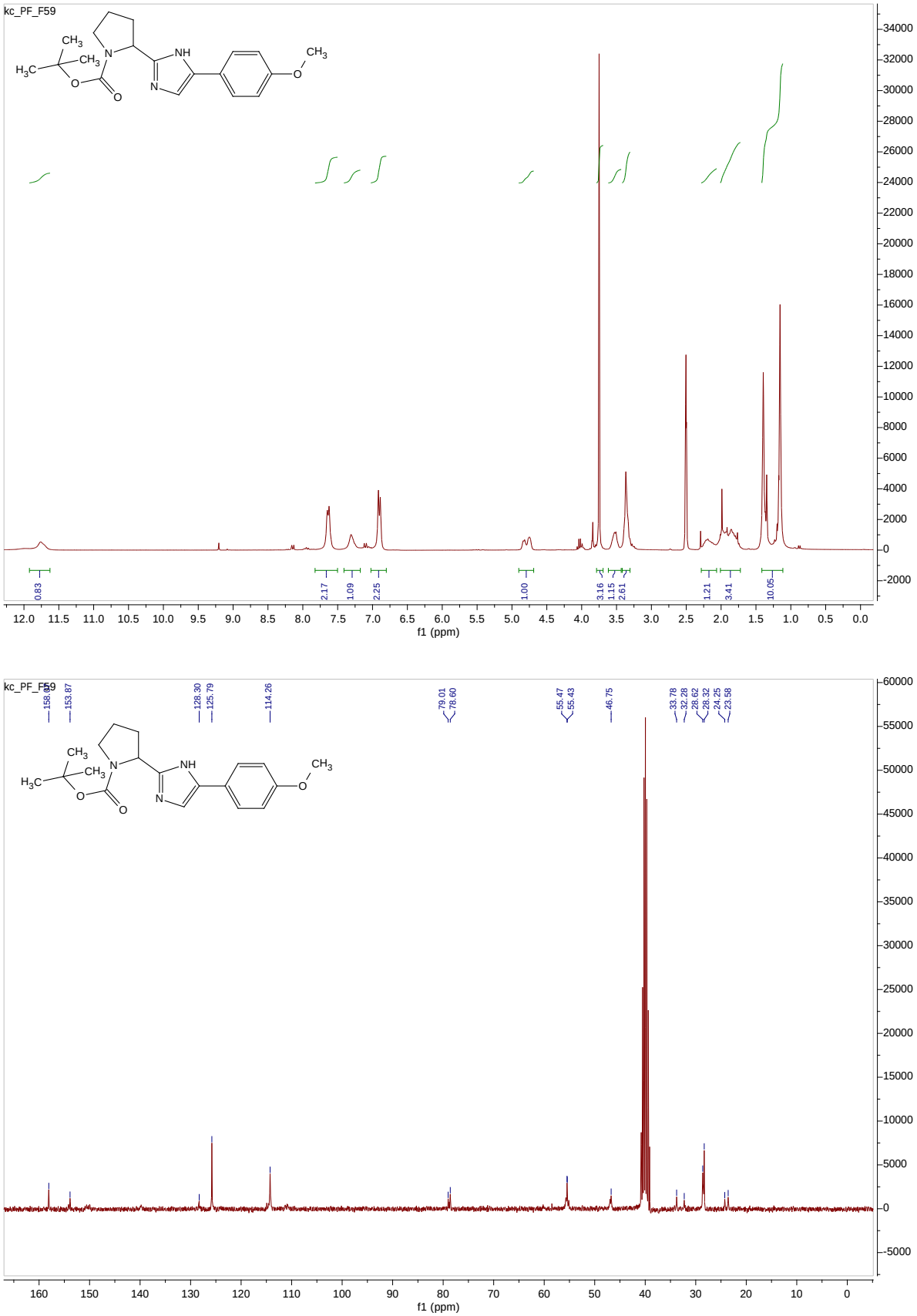


Figure S11. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(4-methoxyphenyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4h**).

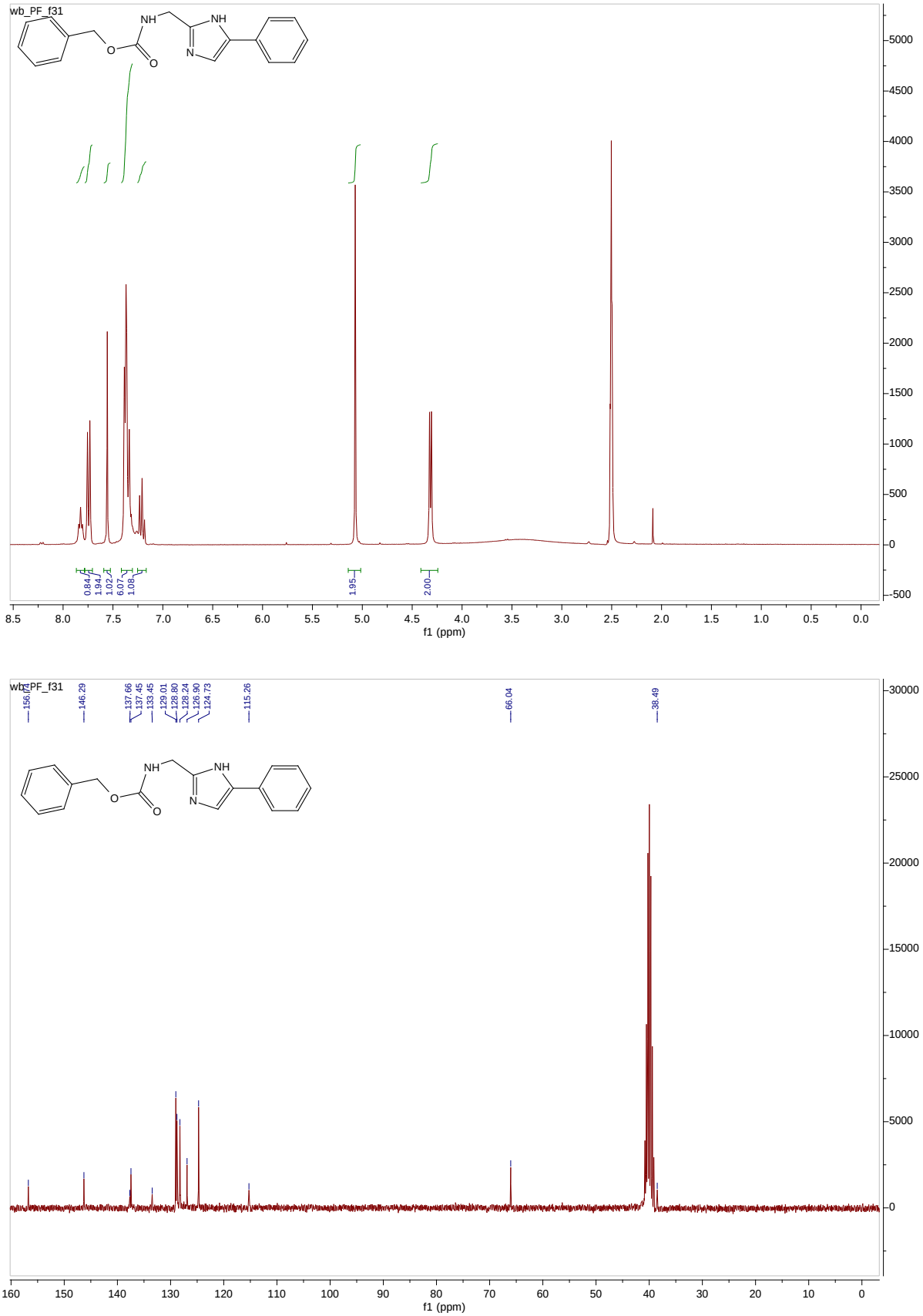


Figure S12. ^{1}H-NMR and ^{13}C-NMR of benzyl ((5-phenyl-1*H*-imidazol-2-yl)methyl)carbamate (**4i**).

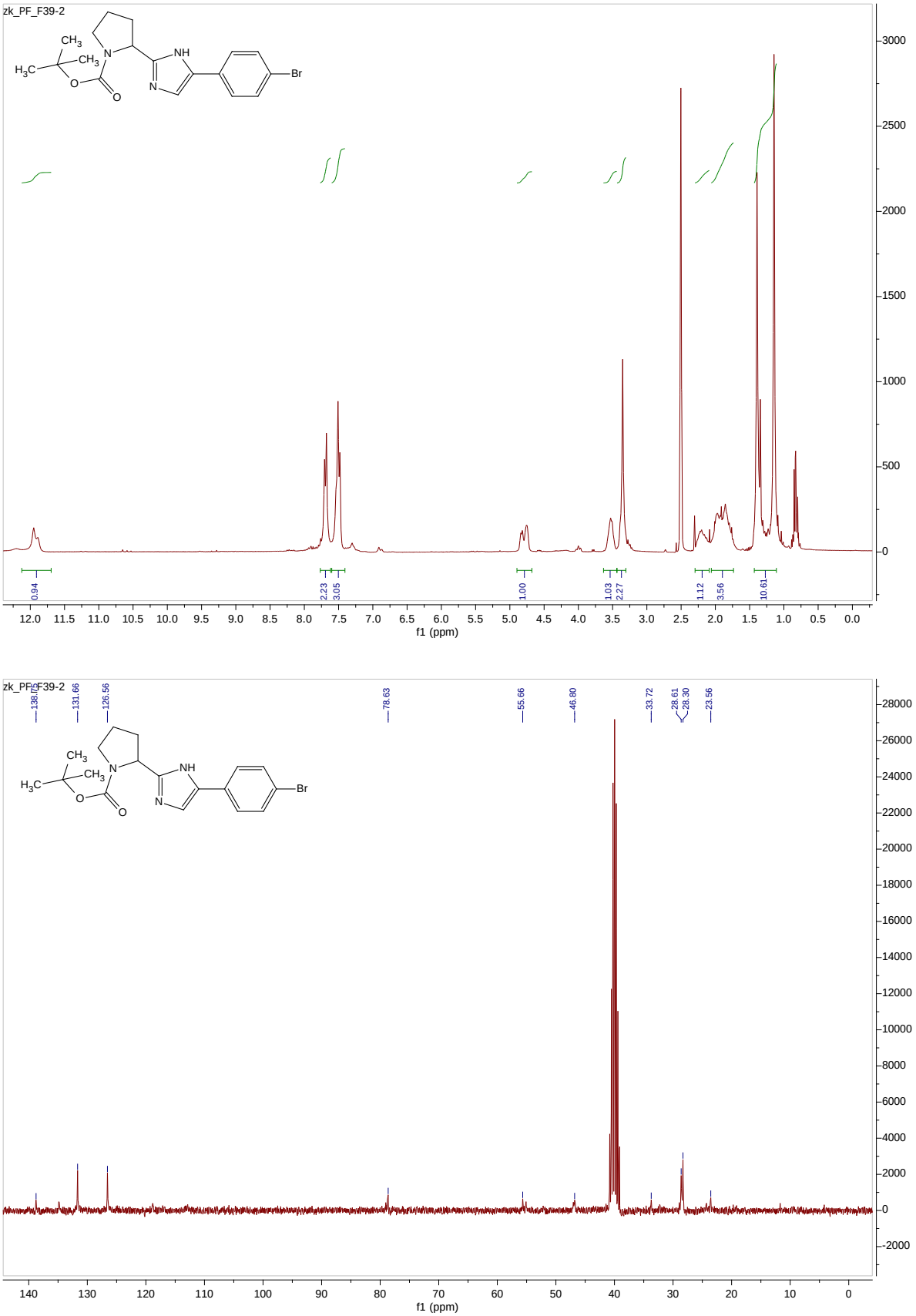


Figure S13. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(4-bromophenyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4j**).

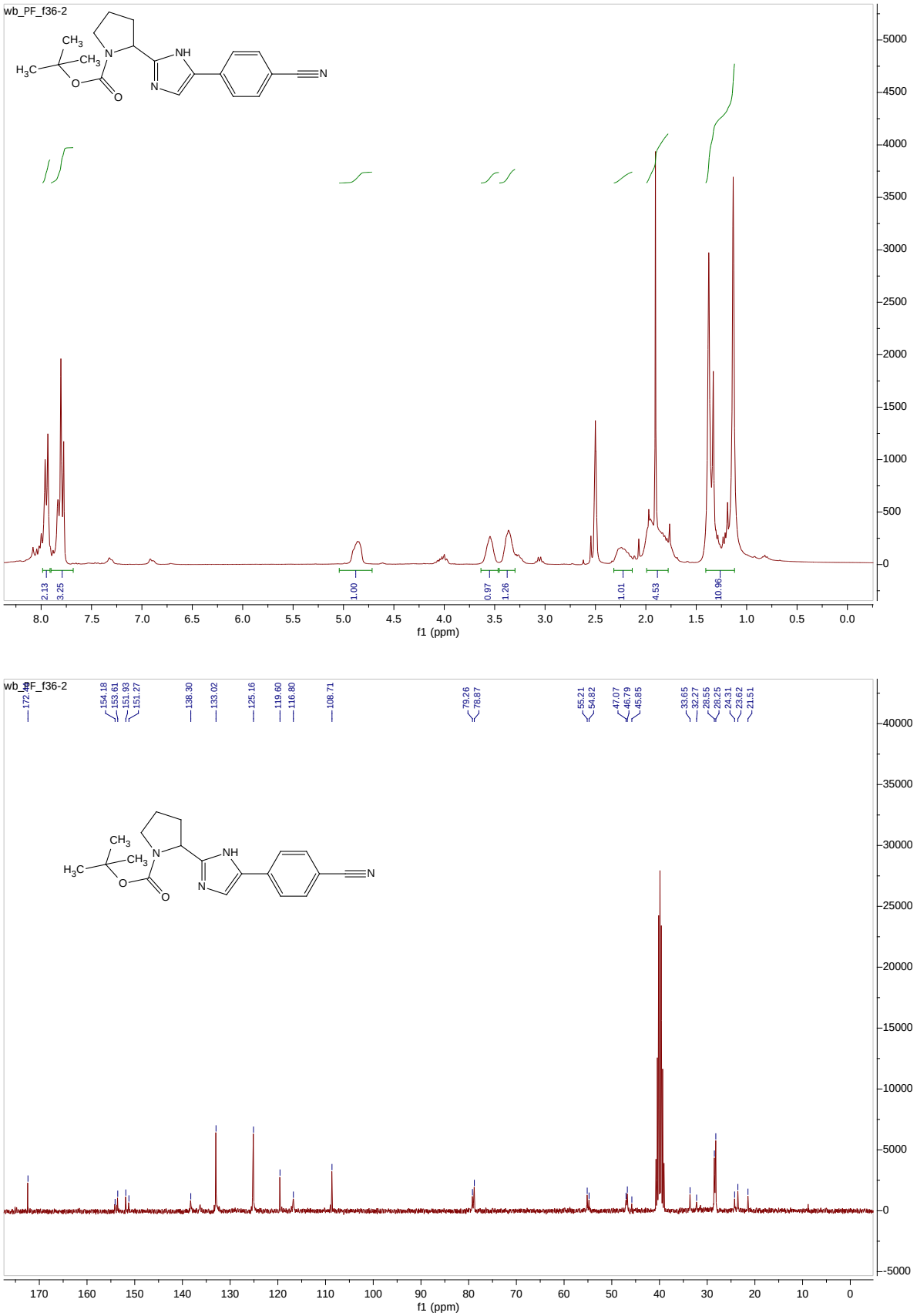


Figure S14. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-2-(5-(4-cyanophenyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**4k**).

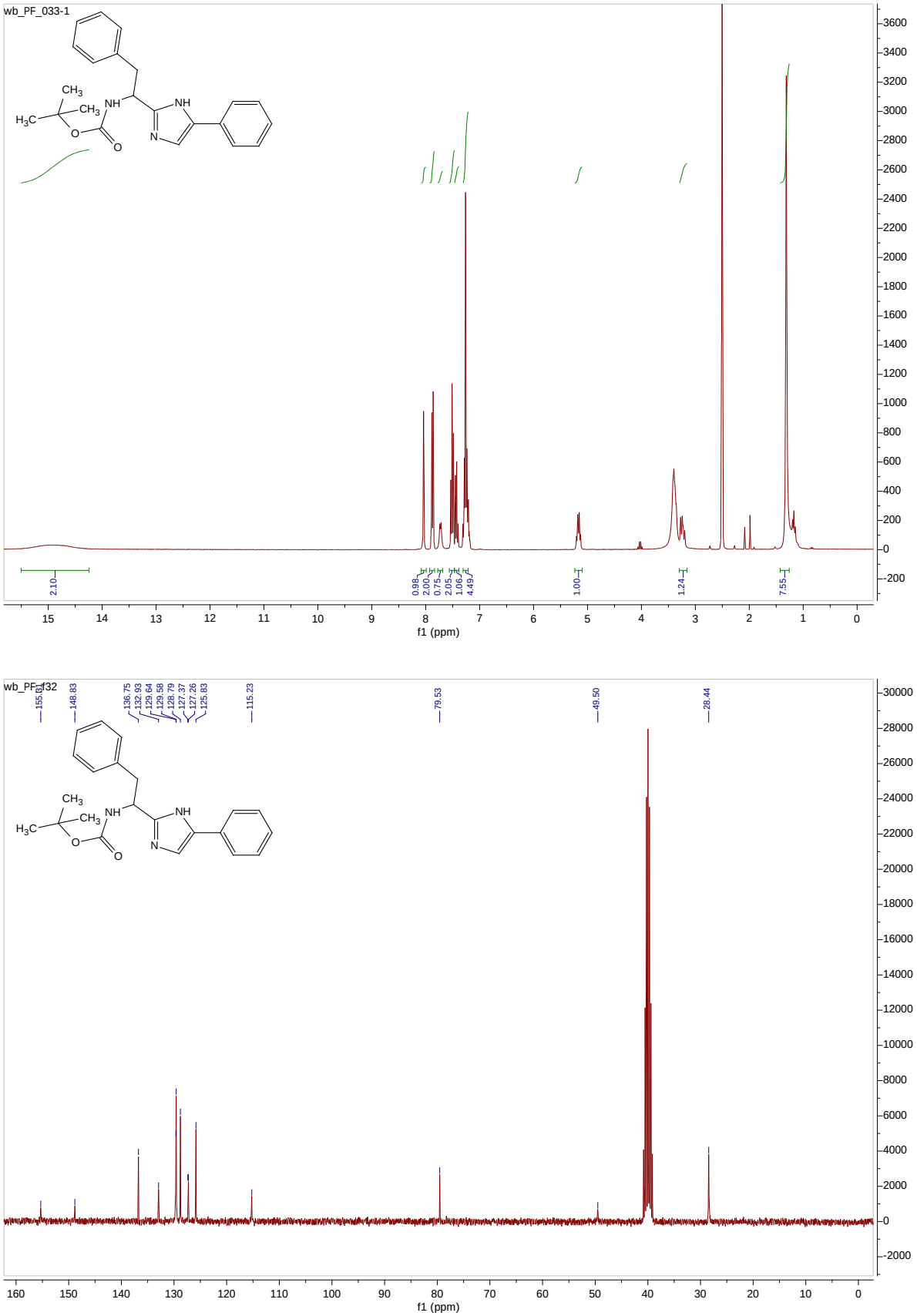


Figure S15. ^{1}H-NMR and ^{13}C-NMR of *tert*-butyl (*S*)-(2-phenyl-1-(5-phenyl-1*H*-imidazol-2-yl)ethyl)carbamate (**4l**).

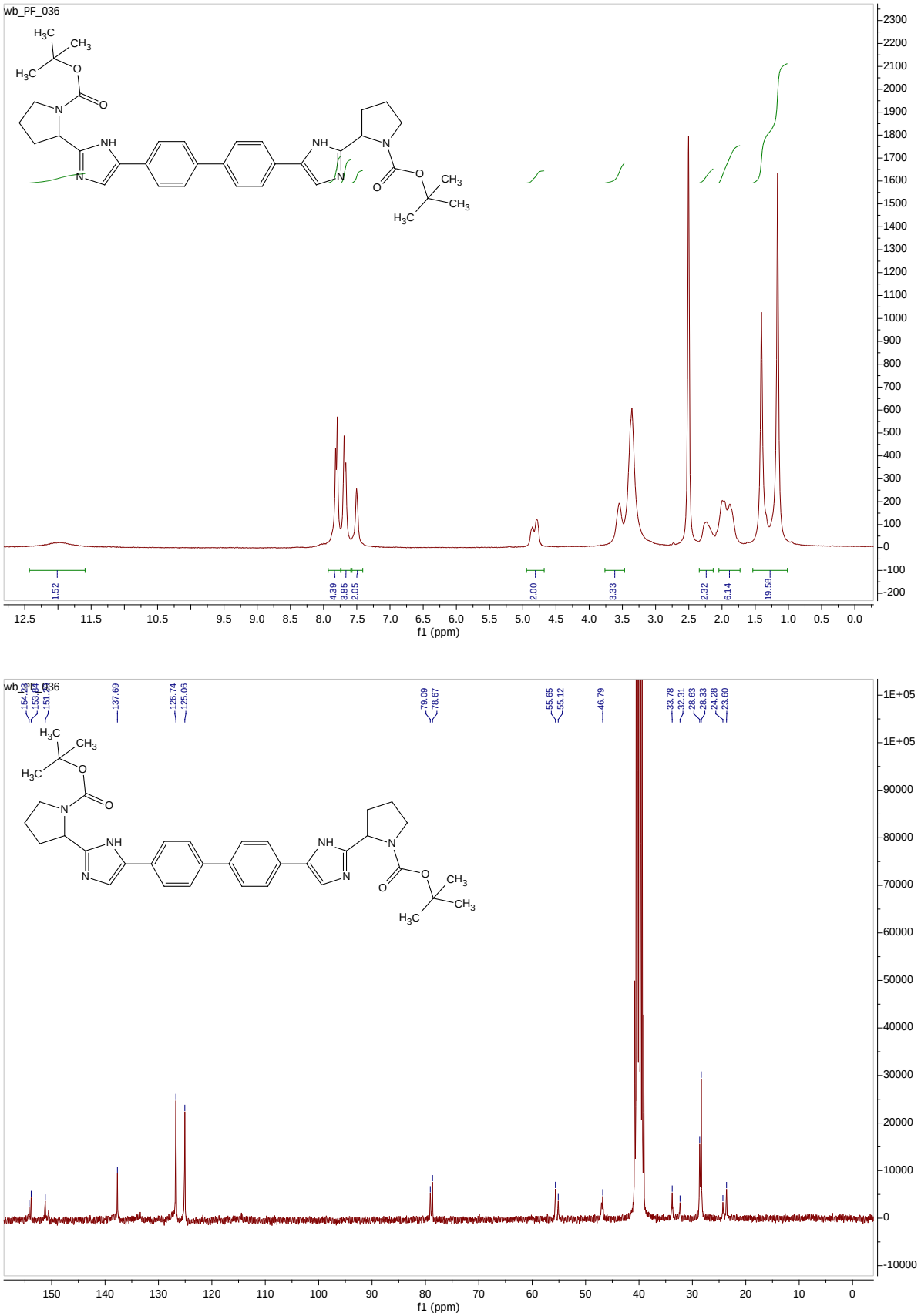


Figure S16. ^{1}H-NMR and ^{13}C-NMR of di-*tert*-Butyl 2,2'-([1,1'-biphenyl]-4,4'-diylbis(1*H*-imidazole-5,2-diyl))(2*S*,2'*S*)-bis(pyrrolidine-1-carboxylate) (**4m**).