Iridium-Catalyzed C–H Borylation of 2-Pyridones; Bisfunctionalisation of CC4

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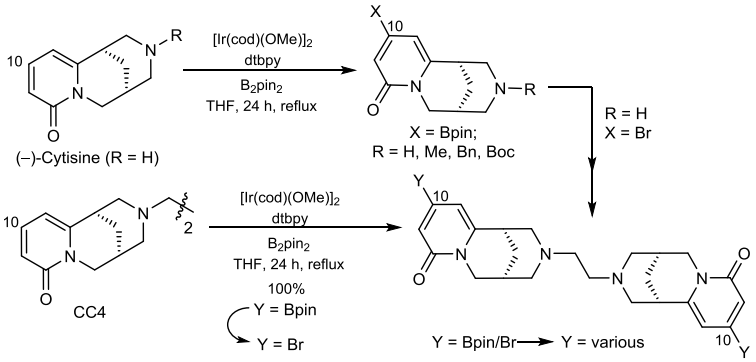

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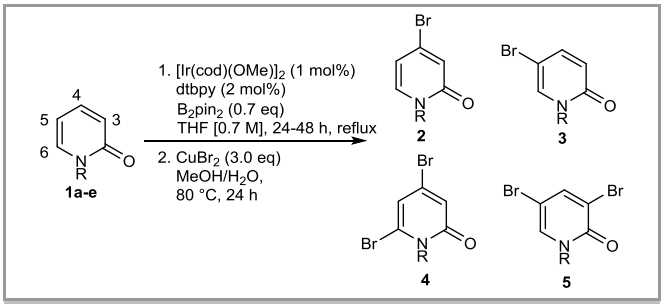
Abstract The high regioselectivity associated with the Ir-catalyzed borylation of pyridones has been exploited to provide a very direct and efficient entry to C(10) doubly substituted CC4 variants of cytisine. Two approaches have been evaluated based on (i) C–H activation of cytisine (or an N-substituted derivative) followed by N-alkylation (to enable dimer formation) and (ii) direct C-H activation and borylation of CC4 itself. Both approaches provide access to C(10)-functionalized CC4 derivatives, but direct borylation of CC4 allows for a wider range of functional group interconversions to be tolerated.

Key words 2-Pyridone, iridium-catalyzed borylation, C–H functionalization, CC4, cytisine.

The Ir-catalyzed borylation of arenes and heteroarenes offers a very direct entry to boronic esters that underpins a wide range of effective synthetic transformations.[1] With arenes, C–H activation process is generally sterically controlled, but within heteroarenes electronic effects (e.g. relative acidity) of competing C–H sites influences the regiochemical outcome.[2] Pyridines and related heterocycles have received attention,[3] and the recent publication of Hirano and Miura[4] describing Ir-catalyzed borylation of 2-pyridones prompts us to report our related results in this area.

Pyridones, which offer a predictable but constrained selectivity for electrophilic substitution at C(3) and C(5), have added complexity: two potential metal binding sites associated with the substrate. In earlier work, Hirano and Miura[5] exploited an N-pyridyl moiety as a directing function (to functionalize at C(6)) but otherwise access to pyridone-based boronic esters relies on electrophilic halogenation as a key step.[6] As a consequence, direct C–H functionalization offers an opportunity to extend significantly the range of pyridone substitution patterns available.

We had carried out broadly the same study of both simple and more complex 2-pyridones to determine basic reactivity patterns as described by Hirano and Miura.[4] Our results paralleled those reported earlier although we assessed product distribution (and reaction efficiency) following in situ bromination[7] of the initial Bpin ester to give bromopyridones **2**-**5** (**Scheme 1**, **Table 1**). There were, however, differences in terms of the approach we have used which we note here. In our hands, for example, the parent 2-pyridone **1a** was unreactive[8] towards C–H activation; we observed no conversion under our standard conditions where we used dtbpy as the bipyridyl ligand. More generally, and based on our experience with related substrates, the presence of an acidic NH (as in **1a**) inhibits Ir-catalyzed borylation.



Scheme 1 Ir-Catalyzed borylation/*in situ* bromination[7] of simple 2-pyridones.

Table 1 Regiochemistry of C–H activation in simple 2-pyridones.

Substrate	Conversion	**2**:**3**:**4**:**5**[a]	Isolated yields[b]
1a R = H	0%[c]	-	No conversion observed
1b R = Me	100%	5:35:39:21	**2b**+**3b** (38%); **4b** (22%); **5b** (11%)
1c R = Bu	≥90%	26:53:6:15	**2c** + **3c** (69%); **5c** (10%)
1d R = Bn	≥90%	35:65:0:0	**2d** + **3d** (83%)
1e R = Boc	0%[c]	-	No conversion observed

[a]Product ratios, following in situ bromination[7] were based on ^{1}H NMR; see text and Supporting Information. [b]Monobromo isomers **2** and **3** were inseparable by chromatography and the combined yield is shown. [c]see text.[8,9]

Within the simple pyridone series shown in Scheme 1, some level of double C–H activation was also observed (via dibrominated products **4** and **5**) but consistently C(5) substitution (**3** + **5**) was preferred over C(4) (**2** + **4**). Double insertion observed was a result of C–H activation/borylation rather than an additional bromination occurring in step 2 (Scheme 1) [9] and the proportion of dibrominated adducts observed appears to link to the size of the N-substituent (compare products from **1b** vs. **1c** vs. **1d**). Interestingly, the N-benzyl variant **1d** gave only pyridone substitution with no indication that borylation of the N-benzyl residue was competitive; however, see below. The N-Boc variant **1e** failed to react but the issue here was that rapid N-Boc cleavage occurred under the reaction conditions (based on ^{1}H NMR analysis) releasing the unreactive parent 2-pyridone **1a**.

Our primary interest in this area has, however, been on the application of this C-H activation process to the development of novel heterocyclic ligands that are specific for the α4β2 nicotinic acetylcholine receptor (nAChR).[10] This subtype is the high affinity nicotine receptor and, with smoking responsible for some 7 million deaths annually (with an associated huge social burden in terms of healthcare expenditure and lost productivity[11]), is a target of interest for treating tobacco addiction. The pyridone-based cytisine (Tabex®) **6a**[12], as well as the structurally related varenicline (Chantix®)[13], target the α4β2 nAChR providing the basis of a smoking cessation therapy.

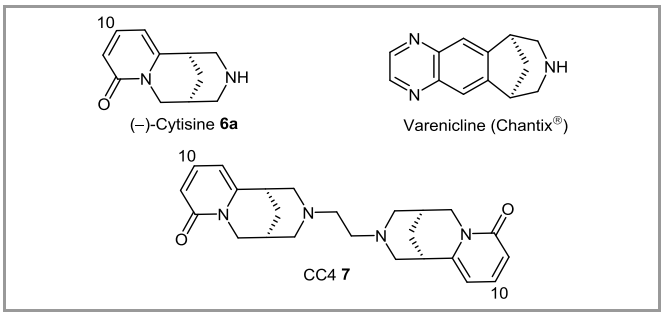


Figure 1 (-)-Cytisine **6a**, varenicline, and CC4 **7**. C(10) within the pyridone moiety is indicated.

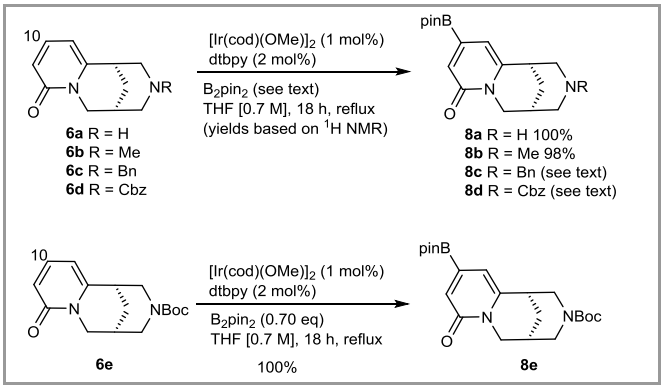
In their 2017 paper,[4] Hirano and Miura described the borylation of N-Boc cytisine **6e** (see below), and here we wish to report our independent work in this area and an extension to more complex cytisine-based ligands.

We have evaluated (–)-cytisine **6a** as well as a series of derivatives, including N-Boc cytisine **6e** and CC4 **7**, as substrates for Ir-catalyzed borylation with the objective of gaining access to C(10). CC4 **7** is a cytisine-based dimer ligand where the ability to access C(10) was of particular interest given this ligand's nicotinic profile. In 2013 Gotti and Sparatore reported CC4 **7** as a partial agonist for both the α4β2 and α6β2 nAChR subtypes and suggested an improved profile for smoking cessation due to the great selectivity displayed by CC4 for β2-containing nAChR subtypes.[14]

Our hypothesis, based on crystallographic data based on cytisine and varenicline bound to acetylcholine binding protein (AChBP)[15], was that substitution at C(10) provides an opportunity to interact with the variable (complementary) region of the nAChR, which is associated with subtype differentiation.[16] Previous work by Kozikowski and Kellar, as well ourselves, had generated C(10)-substituted variants of cytisine.[17] However, these involved lengthy synthetic sequences that limited the range of variation that was accessible. Further, this earlier work gave racemic products, which is problematic especially when contemplating construction of dimeric ligands based on CC4.

In this paper, we have evaluated two approaches to the synthesis of C(10) modified variants of CC4 **7**: (i) C–H activation of cytisine to enable access to a C(10)-modified "monomer" unit (e.g. bromide **9**), dimer formation (*via* N-alkylation)) followed by further elaboration; and (ii) direct and double C–H activation at C(10) of CC4 **7**, followed by further functional group manipulation.

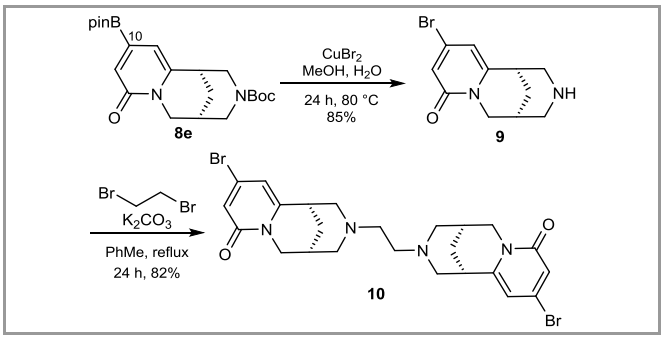
The first approach required C–H activation of (–)-cytisine **6a**, itself an effective substrate for Ir-catalyzed borylation (**Scheme 2**). Complete conversion (as judged by ^{1}H NMR) did require an excess (1.5 equivalents) of B_2pin_2, however, isolation and purification of the product C(10) boronate ester **8a** proved problematic. N-Methyl cytisine **6b** is also an efficient substrate, however, N-benzyl cytisine **6c** and N-Cbz cytisine **6d** showed competing borylation within the aryl moiety of the N-protecting group; it is interesting to compare this to the reactivity of pyridone **1d**. Further details of this study, including optimization of key reaction parameters, are available in the Supporting Information.



Scheme 2 Site selective Ir-catalyzed borylation of (–)-cytisine **6a**, N-substituted cytisine derivatives **6b-d**, and N-Boc cytisine **6e**.

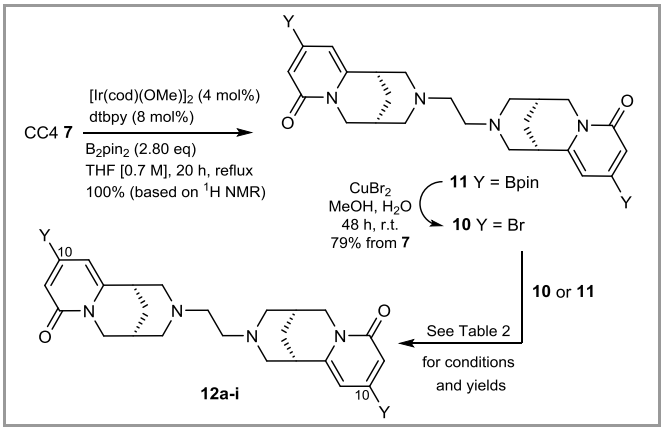
In common with Hirano and Miura, we observed very efficient Ir-catalyzed borylation of N-Boc cytisine **6e** (**Scheme 2**). In our hands, and using dtbpy as the preferred ligand in combination with 0.7 equivalents of B_2pin_2, we achieved essentially quantitative borylation of **6e** to give **8e**. This was completely selective for C(10) and was readily scaled (to 5 grams, 17 mmol of **6e**). This result compares to 77% yield (on a 0.2 mmol scale, but using a different pyridyl ligand) reported earlier.[4] Isolation of (crude) **8e** was straightforward with no requirement for any further purification in terms of the use of this Bpin intermediate in subsequent manipulations.

Boronate **8e** was converted efficiently to 10-bromocytisine **9** (with concomitant N-Boc cleavage occurring under the Cu-mediated conditions used) and dimer formation using 1,2-dibromoethane provided the CC4-based bisbromide **10** in good (70%) overall yield (**Scheme 3**). Bisbromide **10** was a key intermediate for accessing a range of C(10)-substituted CC4 variants (see below).



Scheme 3 Synthesis of 10-bromo CC4 **10** *via* C(10) functionalization of N-Boc cytisine **8e** followed by dimer formation based on 10-bromocytisine **9**.

Ir-catalyzed borylation of CC4 **7**, so double C-H activation at C(10), offers the advantage of more direct access to bisbromide **10** and this proceeds smoothly (**Scheme 4**).



Scheme 4 Double C-H activation of CC4 **7**; use of bisbromide **10** and bisboronate **11** to generate a series of C(10) substituted CC4 ligands **12a-i**.

Table 2 CC4 derivatives **12a-i** via modification of **10** or **11**.

10-substituent (Y)	Reaction conditions (% yield)
12a[a] Y = CN	$Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 80 °C (88%)
12b[a] Y = Me	$PdCl_2(PPh_3)_2$, Me_4Sn, PhMe, 100 °C (83%)
12c[a] Y = 4-MeC_6H_5	$PdCl_2(PPh_3)_3$, 4-TolB$(OH)_2$, K_2CO_3, THF/H_2O, 80 °C (91%)
12d[a] Y = $NHAc$[c]	$Pd(OAc)_2$, Xantphos, $MeCONH_2$, Cs_2CO_3, dioxane (71%)
12e[a] Y = NMe_2[c]	$Pd(OAc)_2$, BINAP, $HNMe_2$, NaO*t*Bu, PhMe, 65 °C (71%)
12f[a] Y = 	$Pd(OAc)_2$, BINAP, morpholine, NaO*t*Bu, PhMe, 100 °C (82%)
12g[a] Y = CO_2Me[c]	$Pd(OAc)_2$ (40 mol%), dppp, Et_3N, CO, DMF/MeOH (0.1 M in **10**), 80 °C (85%)
12h[a] Y= $CH{=}CHCO_2Et$[c]	$Pd_2(dba)_3$, P(*t*Bu)$_3$, Cy_2NMe, ethyl acrylate, dioxane (72%)
12i[b] Y= OH[c]	NaOH, 30% H_2O_2 (54%)

[a]Prepared from bisbromide **10**. [b]Prepared from bisboronate **11**. [c]Products were isolated as the HCl salts.

The transformation of CC4 **7** (likely due to the presence of two basic amine centers) required an excess of B_2pin_2 (2.80 equivalents) to achieve full conversion. However, workup was particularly straightforward and simply involved washing the crude (solid) product with diethyl ether. This served to remove the excess of B_2pin_2 as well as other byproducts, providing **11** with a high level of purify and in essentially quantitative yield. Bisboronate **11** was then readily and efficiently converted to the key bisbromide **10**. Both bisbromide **10** and bisboronate ester **11** are of value and have been applied to generate a representative series of CC4 derivatives **12a-i** (**Scheme 4, Table 2**). Pd(0) catalyzed C-C bond formation provides the bis(cyano), bis(methyl)[18] and the Suzuki cross coupled products **12a-c**. respectively. Transformations of bromide **10** also encompassed amidation (to give **12d**) and amination (to give **12e** and **12f**), as well as carbonylation (to give **12g**) and Heck coupling (to give **12h**) reactions. We have evaluated use of Cu(I)-based amidation (to prepare **12d**) but reaction of bisbromide **10** with acetamide and CuI (with TMEDA) led to the formation of an insoluble solid suggestive of a complex being formed between **10** and Cu(I).

The use of bisboronate **11** to access C(10)-functionalised CC4 derivatives was exemplified by direct oxidation of **11**, leading to the bishydroxy ligand **12i** in 54% yield. Further studies in this area are underway but bisboroate ester **11** has been successfully used in Suzuki cross couplings reactions involving aryl halides.

In summary, and with full acknowledgement to the recent work of Hirano and Miura,[4] we have also successfully applied iridium-catalyzed borylation to 2-pyridones, with our focus around biologically important substrates exemplified by cytisine **6a** and CC4 **7**. Pyridones are generally excellent substrates for this mode of C-H activation although our experience is that NH pyridones (as in **1a**) are less effective. In addition, the presence of a basic (amine) center (as in **6a** and **7**) does tend to require an excess of B_2pin_2 for complete conversion. Nevertheless, and given exceptionally clean conversions, product isolation is straightforward and the crude boronate esters (e.g. **11**) are very effective as substrates for downstream functionalisation. Details of receptor binding studies (including nicotinic subtype selectivities) and full agonist functional characteristics of the novel CC4 ligands described here will be reported in due course.

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All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were obtained by distillation using standard procedures or by using the Anhydrous Engineering Ltd. double alumina and alumina-copper catalyzed drying columns. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen; glassware and needles were flamed-dried prior to use or placed in the oven (150 °C) for at least 2 h and allowed to cool either in a desiccator, under vacuum, or an atmosphere of nitrogen. Thin layer chromatography was performed using aluminium backed 60 F254 silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ or ninhydrin solution and heat. Flash column chromatography was performed on silica gel (Aldrich 40-63 μm, 230-400 mesh) and reverse phase chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elution on pre-packed Biotage® C18 columns. Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or neat films in the range of 600-4000 cm^{-1}. NMR spectra were recorded using either a Varian 400 MHz or 500 MHz, or JEOL ECP 400 MHz spectrometer. Chemical shifts are quoted in parts per million, coupling constants are given in Hz to the nearest 0.5 Hz. ^1H and ^{13}C NMR spectra are referenced to the appropriate residual peak. DEPT 135, COSY, HSQC and HMBC were used where necessary in assigning NMR spectra. Melting points were determined using Reichert melting point apparatus. Mass spectra were determined by the University of Bristol mass spectroscopy service by either chemical ionisation (CI^+), electrospray ionization (ESI^+) or electron impact (EI^+) using a Bruker Daltonics Apex IV spectrometer.

One-pot iridium-catalyzed borylation of 2-pyridones and subsequent bromination; General Procedure 1.

A Schlenk tube was charged with the 2-pyridone substrate (1.0 mmol) [in the case of a liquid substrate, this was added neat after the solvent], $[Ir(cod)(OMe)]_2$ (6.6 mg, 0.01 eq), 4,4'-di-tert-butyl-2,2'-dipyridyl (5.4 mg, 0.02 eq) and bis(pinacolato)diboron (178 mg, 0.70 eq). After purging with nitrogen, deoxygenated and dry THF (1.4 mL) was added and the reaction mixture was heated at reflux for 48 h (in cases where full conversion occurred after 24 h, the reaction was halted at that time). The volatile materials were then removed under reduced pressure and the crude product was dissolved in MeOH (2.5 mL) and a solution of $CuBr_2$ (670 mg, 3.0 mmol) in H_2O (2.5 mL) was added. The reaction mixture was heated at 80 °C for 18 h under air, cooled to r.t., diluted with NH_4OH (5 mL, 15% aq.) and extracted with DCM (5 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude reaction mixture by flash column chromatography on silica gel afforded the desired product.

Table 1 shows the product distributions of **2-5** but no attempt was made to optimize monosubstitution (vs disubstitution) in the case of **1b** or **1c**.

Tandem borylation/bromination of 1-methylpyridin-2(1*H*)-one (1b).

According to General Procedure 1, analysis of the ^{1}H NMR of the crude reaction mixture showed a conversion of 100%. Products 5-bromo-1-methylpyridin-2(1*H*)-one (**3b**), 4-bromo-1-methylpyridin-2(1*H*)-one (**2b**), 4,6-dibromo-1- methylpyridin-2(1*H*)-one (**4b**) and 3,5-dibromo-1-methylpyridin-2(1*H*)-one (**5b**) were generated in a 35:5:39:21 ratio.

Purification by flash column chromatography on silica gel (*n*-Hexane-EtOAc, 70:30 to EtOAc, 100%) gave:

An inseparable 95:5 mixture of **5-bromo-1-methylpyridin-2(1H)-one** (**3b**) and **4-bromo-1-methylpyridin-2(1*H*)-one** (**2b**) (71 mg, 38%) as an orange oil.

Data for **2b** (minor component):

R_f = 0.24 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 6.28 (dd, *J* = 2.0, 7.5 Hz, 1 H), 3.50 (s, 3 H). The spectroscopic properties of this compound were consistent with data available in literature.[19a]

Data for **3b** (major component):

R*f* = 0.24 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.5 Hz, 1 H), 7.33 (dd, *J* = 2.5, 9.5 Hz, 1 H), 6.46 (d, *J* = 9.5 Hz, 1 H), 3.50 (s, 3 H). The spectroscopic properties of this compound were consistent with data available in literature.[19a]

4,6-Dibromo-1-methylpyridin-2(1*H*)-one (**4b**) (58 mg, 22%) as an off-white solid; R_f = 0.59 (EtOAc).

IR (neat): 3111, 2922, 2851, 1650, 1566, 1495 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 6.66 (s, 1 H), 3.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 134.8, 128.3, 120.7, 114.4, 36.4.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_6H_6{}^{79}Br_2NO$: 265.8811; found: 265.8799.

3,5-Dibromo-1-methylpyridin-2(1*H*)-one (**5b**) (28 mg, 11%) as an -whitewhite solid solid; R_f = 0.51 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 2.0 Hz, 1 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 3.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 143.8, 137.5, 117.4, 96.5, 39.0. The spectroscopic properties of this compound were consistent with the data available in literature.[19b]

Tandem borylation/bromination reaction of 1-butylpyridin-2(1*H*)-one (**1c**).

According to General Procedure 1, analysis of the ^{1}H NMR of the crude reaction mixture showed a conversion of ≥90%. Products 5-bromo-1-butylpyridin-2(1*H*)-one (**3c**), 4-bromo-1-butylpyridin-2(1*H*)-one (**2c**), 4,6-dibromo-1-butylpyridin-2(1*H*)-one (**4c**) and 3,5-dibromo-1-butylpyridin-2(1*H*)-one (**5c**) were generated in a 53:26:6:15 ratio.

Purification by flash chromatography on silica gel (*n*-Hexane-EtOAc, 75:25) gave:

3,5-Dibromo-1-butylpyridin-2(1*H*)-one (**5c**) (31 mg, 10%) as a yellow oil; R*f* = 0.38 (*n*-Hexane-EtOAc, 70:30).

IR (neat): 2957, 2929, 1646, 1587, 1514, 1436, 1373, 1215, 1124, 847, 756, 711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 2.5 Hz, 1 H), 7.37 (d, *J* = 2.5 Hz, 1 H), 3.93 (t, *J* = 7.5 Hz, 2 H), 1.75-1.67 (m, 2 H), 1.39-1.30 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 143.5, 136.8, 117.8, 96.4, 51.4, 31.1, 19.8, 13.6.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_9H_{12}{}^{79}Br_2NO$: 307.9280; found: 307.9279.

An inseparable mixture 68:32 of **5-bromo-1-butylpyridin-2(1*H*)-one** (**3c**) and **4-bromo-1-butylpyridin-2(1*H*)-one** (**2c**) (158 mg, 69%) as a yellow oil.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_9H_{13}{}^{79}BrNO$: 230.0175; found: 230.0175.

Data for **2c** (minor component):

R_f = 0.22 (*n*-Hexane-EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 7.5 Hz, 1 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 6.28 (dd, *J* = 2.0, 7.5 Hz, 1 H), 3.93 (t, *J* = 7.5 Hz, 2 H), 1.75-1.67 (m, 2 H), 1.39-1.30 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 137.3, 135.0, 123.0, 110.0, 49.4, 31.1, 19.8, 13.6.

Data for **3c** (major component):

R_f = 0.17 (*n*-Hexane-EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 2.5 Hz, 1 H), 7.28 (dd, *J* = 2.5, 9.5 Hz, 1 H), 6.43 (d, *J* = 9.5 Hz, 1 H), 3.87 (m, 2 H), 1.71-1.62 (m, 2 H), 1.38-1.27 (m, 2 H), 0.93-0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 142.1, 137.3, 122.2, 97.6, 49.8, 31.3, 19.8, 13.6.

5-Bromo-1-benzylpyridin-2(1*H*)-one (3d) and **4-bromo-1-benzylpyridin-2(1*H*)-one** (**2d**).

Prepared from 1-benzylpyridin-2(1*H*)-one (**1d**) using General Procedure 1. Analysis of the ^{1}H NMR of the crude product showed a conversion of ≥90% and a 65:35 ratio of 5-bromo-1-benzylpyridin-2(1*H*)-one (**3d**) and 4-bromo-1-benzylpyridin-2(1*H*)-one (**2d**) respectively. Purification by flash column chromatography on silica gel (*n*-Hexane-EtOAc, 75:25) gave:

An inseparable mixture 65:35 of **5-bromo-1-benzyylpyridin-2(1*H*)-one** (**3d**) and **4-bromo-1-benzyylpyridin-2(1*H*)-one** (**2d**) (219 mg, 83%) as a pale yellow oil**.**

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{12}H_{11}{}^{79}BrNO$: 264.0019; found: 264.0014.

Data for **2d** (minor component):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.21 (m, 5 H), 7.10 (d, *J* = 7.0 Hz, 1 H), 6.83 (s, 1 H), 6.50 (d, *J* = 10.0 Hz, 1 H), 5.06-4.98 (m, 2 H).

Data for **3d** (major component):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.21 (m, 7 H), 6.51 (d, *J* = 10.0 Hz, 1 H), 5.07 (s, 2 H). The spectroscopic properties of this compound were consistent with the data available in literature.[19c]

Iridium-catalyzed C–H borylation of (–)-cytisine (**6a**).

Synthesis of **10-(Bpin)cytisine** (**8a**).

A Schlenk tube was charged with (–)-cytisine (**6a**) (190 mg, 1.0 mmol), $[Ir(cod)(OMe)]_2$ (6.6 mg, 0.01 eq), 4,4'-2,2'-di-tert-butylbispyridyl

(5.4 mg, 0.02 eq) and bis(pinacolato)diboron (380 mg, 1.50 eq) and was placed under vacuum and backfilled with nitrogen for three times. THF (1.4 mL) was added and the reaction mixture was heated at reflux for 24 h. After this time, the volatile materials were removed under reduced pressure and **8a**, which was unstable to silica chromatography, was partially characterized without further purification and obtained as a brown foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 1.0 Hz, 1 H), 6.27 (s, 1 H), 4.11 (d, *J* = 15.5 Hz, 1 H), 3.86 (dd, *J* = 6.5, 15.5 Hz, 1 H), 3.15-2.78 (m, 5 H), 3.21 (s, 1 H), 1.94-1.91 (m, 2 H), 1.23 (s, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 149.2, 124.1, 108.8, 84.4, 82.7, 53.3, 52.3, 49.6, 35.1, 27.5, 25.5, 14.5.

Iridium-catalyzed C–H borylation of N-Boc cytisine (6e).

Synthesis of **N-Boc 10-(Bpin)cytisine (8e).**

A Schlenk tube was charged with N-Boc cytisine (**6e**) (290 mg, 1.0 mmol), $[Ir(cod)(OMe)]_2$ (6.6 mg, 0.01 eq), 4,4'-di-tert-butyl-2,2'-dipyridyl (5.4 mg, 0.02 eq) and bis(pinacolato)diboron (178 mg, 0.70 eq) and was placed under vacuum and backfilled with nitrogen for three times. THF (1.4 mL) was added and the reaction mixture was heated at reflux for 18 h. After this time, ^{1}H NMR showed essentially 100% conversion, the volatile materials were removed under reduced pressure without external heating. The crude product **8e** was shown to be essentially pure by ^{1}H NMR. Simple trituration of crude **8e** in Et_2O removed the excess of B_2pin_2 as well as other related byproducts, providing **8e** in quantitative yield in a high level of purity as a pale yellow foam; R_f = 0.23 (DCM-MeOH, 95:5).

IR (neat): 3433, 2977, 1688, 1657, 1563, 1423 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1 H), 6.31 (s, 1 H), 4.34-4.10 (m, 3 H), 3.80 (dd, *J* = 6.5, 15.5 Hz, 1 H), 3.07-2.91 (m, 3 H), 2.41 (s, 1 H), 1.95-1.88 (m, 2 H), 1.41-1.09 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 154.6/154.3 (rotamers), 147.9/147.5 (rotamers), 124.4, 109.3/108.8 (rotamers), 84.4, 82.6/80.3, 79.7/75.0 (2 C, rotamers), 51.7/50.6/50.3/49.2 (2 C, rotamers), 48.9, 34.7, 28.0 (4 C), 27.5, 26.1, 24.8/24.6 (3 C, rotamers); C-Bpin was not observed.

^{11}B NMR (96.4 MHz, $CDCl_3$): δ = 28.94 (br s).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{22}H_{33}BN_2NaO_5$: 439.2379; found: 439.2373.

The spectroscopic properties of this compound were consistent with the data reported by Hirano and Miura.[4]

10-Bromocytisine 9

A Schlenk tube was charged with *N*-Boc cytisine **6e** (2.90 g, 10 mmol), $[Ir(cod)(OMe)]_2$ (66 mg, 1 mol%), 4,4'-di-*tert*-butyl-2,2'-bispyridine (54 mg, 2 mol%), and bis(pinacolato)diboron (1.78 g, 7.0 mmol). After purging with N_2, THF (14 mL) was added and the reaction mixture was heated at reflux for 24 h. The solution was cooled to r.t. and concentrated *in vacuo* without external heating to give crude **8e**, which was used directly in the next step without further purification.

To a solution of crude **8e** in MeOH (25 mL), was added a solution of copper(II)bromide (6.70 g, 30 mmol) in water (25 mL). The reaction mixture was stirred at 80 °C for 24 h under air. NH_4OH (50 mL, 15% aq. sol.) was added, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic phases were concentrated *in vacuo* andthe residue was distributed between HCl (50 mL, 3 M aq. sol.) and DCM (50 mL). The aqueous phase was washed with DCM (2 × 50 mL), basified with NH_4OH (conc.) until pH = 10 and extracted with DCM (5 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **9** (2.28 g, 85%) as a colourless solid, mp 153 °C (DCM-MeOH); R_f = 0.20 (DCM-MeOH, 90:10).

IR (neat): 3335, 3061, 2934, 2791, 2741, 1622, 1531 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 1 H), 1.94 (s, 2 H), 2.33 (m, 1 H), 2.87 (m, 1 H), 2.97 – 3.10 (m, 4 H), 3.83 (dd, *J* = 15.5, 6.5 Hz, 1 H), 4.04 (d, *J* = 15.5 Hz, 1 H), 6.17 (d, *J* = 2.0 Hz, 1 H), 6.67 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 27.6, 35.5, 49.8, 52.9, 53.7, 108.8, 118.7, 135.0, 151.6, 162.5.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{11}H_{14}{}^{79}BrN_2O$: 269.0284, found: 269.0289.

Bromide **9** was previously reported by Durkin using a very different approach and only as the racemate.[17c]

1,2-Bis(10-bromo-*N*-cytisinyl)ethane 10

(a) via dimer formation using bromide 9

A solution of bromide **9** (2.28 g, 8.40 mmol) and K_2CO_3 (934 mg, 6.72 mmol) in toluene (4.2 mL) containing 1,2-dibromoethane (0.40 mL, 4.20 mmol) was heated in a re-sealable tube at 110 °C for 24 h. After cooling, the solution was filtered through Celite® and washed with MeOH. Purification of the residue by flash column chromatography [DCM-MeOH-NH_4OH, 95:5:0.5] gave bisbromide **10** (1.95 g, 82%) as a pale yellow solid.

(b) via double C–H activation of CC4 7

A Schlenk tube was charged with CC4 **7** (168 mg, 0.41 mmol), $[Ir(cod)(OMe)]_2$ (11 mg, 0.04 eq), 4,4'-di-tert-butyl-2,2'-dipyridyl (8.8 mg, 0.08 eq) and bis(pinacolato)diboron (293 mg, 2.8 eq) and was placed under vacuum and backfilled with nitrogen for three times. THF (2.0 mL, 0.7 M) was added and the reaction mixture was heated at reflux for 20 h. After this time ^{1}H NMR showed essentially 100% conversion. The volatile materials were removed under reduced pressure without external heating and simple trituration (washing) of crude product using Et_2O provided **11** (270 mg, 100%) as a pale yellow solid; m.p. = 159-162 °C.

IR (neat): 2936, 1652, 1562, 1333, 1142, 847, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (s, 2 H), 6.23 (s, 2 H), 3.98 (d, *J* = 15.5 Hz, 2 H), 3.84 (dd, *J* = 7.0 15.5 Hz, 2 H), 2.82 (s, 4 H), 2.73 (m, 2 H), 2.35 (s, 2 H), 2.27-2.11 (m, 8 H), 1.80 (d, *J* = 12.5 Hz, 2 H), 1.69 (m, 2 H), 1.35 (s, 24 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0, 150.5, 123.7, 107.9, 84.3, 60.4, 60.1, 55.2, 50.1, 35.5, 28.0, 25.4, 24.8, 24.6.

The bisboronate **11** (prepared above) was dissolved in MeOH (2.5 mL) and the solution was cooled to 0 °C. A solution of $CuBr_2$ (550 mg, 2.47 mmol) in water (2.5 mL) was added and the reaction mixture was stirred for 48 h under air before being quenched by the addition of NH_4OH (15 mL, 15% aq. sol). The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude product by flash column chromatography afforded bisbromide **10** (185 mg, 79%) as a pale yellow solid; mp 173 °C (DCM-*n*-Hexane), R_f = 0.31 (DCM-MeOH, 95:5).

$[\alpha]_D{}^{24}$ = –108 (c 1.0, MeOH).

IR (neat): 2935, 2785, 1634, 1534, 811 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 13.0 Hz, 2 H), 1.80 (d, *J* = 13.0 Hz, 2 H), 2.09 – 2.26 (m, 6 H), 2.26 – 2.38 (s, 4 H), 2.67 (d, *J* = 11.5 Hz, 2 H), 2.76 (s, 2 H), 2.83 (d, *J* = 11.5 Hz, 2 H), 3.75 (dd, *J* = 15.0, 6.5 Hz, 2 H), 3.92 (d, *J* = 15.0, 2 H), 6.12 (d, *J* = 2.0, 2 H), 6.65 (d, *J* = 2.0, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.8, 27.9, 35.7, 50.2, 55.2, 60.2, 60.6, 108.5, 118.6, 134.7, 152.3, 162.5.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{24}H_{29}{}^{79}Br_2N_4O_2$: 563.0652, found: 563.0647.

1,2-Bis(10-cyano-*N*-(–)-cytisinyl)ethane 12a

A Schlenk tube was charged with bromide **10** (169 mg, 0.30 mmol), $Pd(PPh_3)_4$ (27 mg, 0.08 eq) and zinc cyanide (42 mg, 1.2 eq), placed under vacuum and backfilled with nitrogen for three times. DMF (1 mL, 0.8 M) was added, and the reaction mixture was stirred at 80 °C for 24 h. The solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography [DCM-MeOH, 2% MeOH] afforded **12a** (119 mg,

88%) as a pale-yellow solid, m.p. = 168-171 °C, R_f = 0.11 [DCM-MeOH, 2% MeOH].

IR (neat): 3350, 1647, 1562, 1534, 1473, 2236 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 2.0 Hz, 2 H), 6.02 (d, *J* = 2.0 Hz, 2 H), 3.92 (d, *J* = 15.0 Hz, 2 H), 2.09 (dd, *J* = 6.5, 15.0 Hz, 2 H), 2.88 (s, 2 H), 2.81 (d, *J* = 11.5 Hz, 2 H), 2.69 (d, *J* = 11.5, 2 H), 2.36 (s, 2 H), 2.20 (m, 8 H), 1.83 (d, *J* = 15.0 Hz, 2 H), 1.72 (d, *J* = 15.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 154.4, 122.6, 121.1, 116.3, 103.6, 60.3, 60.0, 55.1, 50.6, 35.6, 27.6, 25.3.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{26}H_{28}N_6NaO_2$: 479.2166, found: 479.2164.

1,2-Bis(10-Methyl-N-cytisinyl)ethane 12b

A Schlenk tube was charged with bromide **10** (175 mg, 0.31 mmol), $PdCl_2(PPh_3)_2$ (22 mg, 0.10 eq) and it was placed under vacuum and backfilled with nitrogen for three times. The solids were dissolved in toluene (2 mL), tetrametyltin (0.22 mL, 5.0 eq) was added and the solution was heated at 100 °C for 24 h. The mixture was cooled, EtOAc (15 mL) was added and the solution was filtered through celite® and concentrated. Purification of the crude product by flash column chromatography [DCMMeOH, 5% MeOH] afforded 12b (111 mg, 83%) as a colourless foam, R_f = 0.47 [DCM-MeOH, 5% MeOH].

IR (neat): 3406, 2931, 1645, 1539, 1471, 1367, 1136, 617 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.23 (s, 2 H), 5.74 (s, 2 H), 3.95 (dd, *J* = 15.0 Hz, 2 H), 3.78 (dd, *J* = 7.0, 17.0 Hz, 2 H), 2.83 (d, *J* = 10.0 Hz, 2 H), 2.74 (s, 2 H), 2.66 (d, *J* = 10.0 Hz, 2 H), 2.34 (s, 2 H), 2.25 (m, 2 H), 2.21-2.11 (m, 12 H), 1.78 (d, *J* = 12.0 Hz, 2 H), 1.67 (d, *J* = 12.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 150.6, 149.7, 115.2, 106.8, 60.6, 60.1, 55.0, 49.7, 35.5, 28.0, 25.6, 21.2.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{26}H_{34}N_4NaO_2$: 457.2574, found: 457.2574.

1,2-Bis(10-*p*-tolyl-*N*-cytisinyl)ethane 12c

A Schlenk tube was charged with **10** (282 mg, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 50 µmol, 10 mol%), *p*-tolyl boronic acid (163 mg, 1.20 mmol) and K_2CO_3 (347 mg, 2.50 mmol). After purging with nitrogen, THF (5.0 mL) and water (1.2 mL) were added and the reaction mixture was heated at reflux for 23 h. The solution was cooled to r.t. and distributed between DCM(5 mL) and water (5.0 mL), and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography [DCM-MeOH-NH_4OH, 95:5:0.5] gave **12c** (266 mg, 91%) as a yellow solid, m.p. > 200 °C (DCM-*n*-Hexane), R_f = 0.20 [DCM-MeOH, 95:5].

$[\alpha]_D^{24}$ = –120 (c 1.0, MeOH).

IR (neat): 2933, 2768, 1648, 1564, 809 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (d, *J* = 13.0 Hz, 2 H), 1.83 (d, *J* = 13.0 Hz, 2 H), 2.13 (s, 2 H), 2.24 (m, 4 H), 2.37 (m, 10 H), 2.67 (m, 2 H), 2.83 (m, 4 H), 3.83 (dd, *J* = 6.5, 15.0 Hz, 2 H), 4.00 (d, *J* = 15.0 Hz, 2 H), 6.02 (d, *J* = 2.0 Hz, 2 H), 6.60 (d, *J* = 2.0 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 4 H), 7.34 (d, *J* = 8.0 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.3, 26.0, 28.1, 36.0, 50.0, 55.0, 60.2, 60.5, 103.7, 112.6, 126.6, 129.7, 135.1, 139.2, 150.4, 151.6, 163.8.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{38}H_{44}N_4O_2$: 587.3381, found: 587.3366.

1,2-Bis(10-(*N*-acetylamino)-*N*-cytisinyl)ethane hydrochloride salt 12d

A Schlenk tube was charged with dibromide **10** (141 mg, 0.25 mmol), acetamide (35 mg, 0.60 mmol), $Pd(OAc)_2$ (1 mg, 5 µmol, 2 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (6 mg, 10 µmol, 4 mol%), and Cs_2CO_3 (244 mg, 0.75 mmol). After purging with nitrogen, 1,4-dioxane (0.50 mL) was added and the reaction mixture was stirred at 100 °C for 20 h. The solution was cooled to r.t. and diluted with DCM (10 mL), filtered through Celite®, and concentrated *in vacuo*. Purification of the residue by flash column chromatography [DCM:MeOH:NH_4OH, 95:5:0.5 to 92:8:0.8] gave **12d** (110 mg, 84%) as a colourless solid. The resulting solid was dissolved in a solution of HCl in MeOH (0.37 mL, 0.5 M), acetone was added (40 mL), and the solution was stirred for 3 h. The precipitate was filtered off and dried *in vacuo* to give the HCl salt of **12d** (105 mg, 71%) as pale yellow solid, m.p. > 200 °C (MeOH-acetone), R_f = 0.12 [DCM-MeOH, 90:10].

$[\alpha]_D^{24}$ = –122 (c 1.0, MeOH).

IR (neat): 2933, 2793, 1699, 1640, 1548, 1257, 845, 728 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 1.66 (s, 4 H), 2.00 – 2.20 (m, 12 H), 2.25 – 2.35 (m, 4 H), 2.60 (d, *J* = 11.0 Hz, 2 H), 2.75 – 2.89 (m, 4 H), 3.75 (m, 4 H), 6.46 (m, 2 H), 6.50 (m, 2 H), 7.17 (m, 2 H).

^{13}C NMR (101 MHz, D_2O): δ = 23.6, 24.5, 27.3, 35.3, 50.3, 54.2, 59.1, 59.7, 100.0, 101.8, 148.6, 153.4, 165.3, 173.6.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{28}H_{37}N_6O_4$: 521.2871, found: 521.2859.

1,2-Bis(10-(*N*,*N'*-dimethylamino)-*N*-cytisinyl)ethane hydrochloride salt 12e

A sealed tube with screwed cap was charged with dibromide **10** (141 mg, 0.25 mmol), $Pd(OAc)_2$ (6 mg, 25 µmol, 10 mol%), BINAP (21 mg, 35 µmol, 14 mol%) and NaO*t*Bu (120 mg, 1.25 mmol). After purged with N_2, toluene (1.7 mL) and dimethylamine (0.50 mL, 1 M in THF, 0.50 mmol) were added. The tube was sealed and the reaction mixture was stirred at 65 °C for 20 h. The solution was cooled to r.t. and distributed between water (10 mL) and DCM (10 mL), and the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography [DCM-MeOH-NH_4OH, 95:5:0.5 to 92:8:0.8] gave **12e** (96 mg, 78%) as a pale yellow solid. The resulting solid was dissolved in a solution of HCl in MeOH (0.37 mL, 0.5 M), acetone was added (40 mL) and the mixture was stirred for 3 h. The precipitate was filtered off and dried *in vacuo* to give the HCl salt of **12e** (100 mg, 71%) as pale yellow solid, m.p. > 200 °C (MeOH-acetone), Rf = 0.18 [DCM-MeOH, 90:10].

$[\alpha]_D^{25}$ = +5 (c 1.0, water).

IR (neat): 2926, 2800, 1635, 1531, 1331, 1138, 801 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 1.95 (s, 4 H), 2.71 (s, 2 H), 2.95 (s, 12 H), 3.17 (dd, *J* = 1.5, 12.5 Hz, 2 H), 3.24 (dd, *J* = 1.5, 12.1 Hz, 2 H), 3.37 (m, 6 H), 3.49 (d, *J* = 12.5 Hz, 2 H), 3.57 (d, *J* = 12.5 Hz, 2 H), 3.92 (dd, *J* = 15.0, 6.0 Hz, 2 H), 4.00 (d, *J* = 15.0 Hz, 2 H), 6.31 (s, 2 H), *H5 and H5' were not detected*.

^{13}C NMR (101 MHz, D_2O): δ = 22.6, 26.2, 33.0, 39.1, 48.3, 51.7, 57.7, 58.4, 101.5, 146.7, 157.6, 161.4.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{28}H_{41}N_6O_2$: 493.3286, found: 493.3279.

1,2-Bis(10-morpholino-*N*-cytisinyl)ethane 12f

A Schlenk tube was charged with dibromide **10** (141 mg, 0.25 mmol), morpholine (87 µL, 1.00 mmol), $Pd(OAc)_2$ (6 mg, 25 µmol, 10 mol%), BINAP (21 mg, 35 µmol, 14 mol%) and NaO*t*Bu (120 mg, 1.25 mmol). After purged with N_2, toluene (1.7 mL) was added and the reaction mixture was stirred at 100 °C for 21 h. The solution was distributed between water (10 mL) and DCM (10 mL), and the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography [DCM-MeOH-NH_4OH, 95:5:0.5 to 92:8:0.8] gave **12f** (119 mg, 82%) as a pale yellow solid, m.p. > 200 °C (DCM-*n*-Hexane), R_f = 0.18 (DCM-MeOH, 90:10).

$[\alpha]_D^{24}$ = –38 (c 1.0, MeOH).

IR (neat): 2926, 2851, 1636, 1530, 1236, 1119, 803 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 13.0 Hz, 2 H), 1.77 (d, *J* = 13.0 Hz, 2 H), 2.16 – 2.26 (m, 8 H), 2.30 (s, 2 H), 2.70 (m, 4 H), 2.82 (m, 2 H), 3.19 (m, 8 H), 3.67 (dd, *J* = 7.0, 14.5 Hz, 2 H), 3.77 (t, *J* = 5.0 Hz, 8 H), 3.88 (d, *J* = 14.5 Hz, 2 H), 5.63 (d, *J* = 2.5 Hz, 2 H), 5.66 (d, *J* = 2.5 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 26.2, 28.0, 36.2, 46.7, 49.2, 55.2, 60.1, 61.0, 66.5, 94.7, 95.3, 100.0, 151.1, 157.2, 164.5.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{32}H_{45}N_6O_4$: 577.34297, found: 577.3509.

Methyl 1,2-bis(*N*-(-)-cytisinyl)ethane-10-carboxylate hydrochloride salt 12g

A Schlenk flask was charged with dibromide **10** (141 mg, 0.25 mmol), trimethylamine (87 μL, 0.62 mmol), 1,3-bis(diphenylphosphino)propane (20 mg, 20 mol%) and $Pd(OAc)_2$ (22 mg, 40 mol%). After purging with nitrogen, DMF (0.6 mL) and MeOH (0.6 mL) were added, and the flask was placed under a CO atmosphere (approx. 1 atm, balloon) and the reaction mixture was heated at 80 °C for 20 h. The solution was cooled to r.t., filtered through Celite®, and concentrated *in vacuo*. Purification of the residue by flash column chromatography [DCM-MeOH-NH_4OH, 95:5:0.5] gave **12g** (111 mg, 85%) as a dark yellow solid. The resulting solid was dissolved in a solution of HCl in MeOH (0.37 mL, 0.5 M in MeOH), acetone was added (40 mL) and the mixture was stirred for 3 h. The precipitate was filtered off and dried *in vacuo* to give **12g,** (111 mg, 85%) as yellow solid, m.p. > 200 °C, (MeOH-acetone), R_f = 0.28 [DCM-MeOH, 95:5).

$[\alpha]_D^{25}$ = –180 (c 1.0, water).

IR (neat): 2953, 1720, 1658, 1576, 1545, 1442, 1251, 775 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 1.98 (s, 4 H), 2.79 (s, 2 H), 3.17 (d, *J* = 12.5 Hz, 2 H), 3.25 (d, *J* = 10.5 Hz, 2 H), 3.33 (s, 4 H), 3.45 (m, 4 H), 3.55 (d, *J* = 12.5 Hz, 2 H), 3.83 (s, 6 H), 3.91 (dd, *J* = 16.0, 6.5 Hz, 2 H), 4.00 (d, *J* = 16.0 Hz, 2 H), 6.80 (s, 2 H), 6.97 (s, 2 H).

^{13}C NMR (101 MHz, D_2O): δ = 22.4, 26.3, 33.1, 49.0, 51.5, 53.4, 57.6, 58.4, 107.5, 118.4, 141.32, 148.1, 164.8, 166.5.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{28}H_{35}N_4O_6$: 523.2551, found 523.2550.

Diethyl 1,2-bis(*N*-(–)-cytisinyl)ethane-10-ethyl acrylate hydrochloride salt 12h

A Schlenk tube was charged with dibromide **10** (141 mg, 0.25 mmol) and $Pd_2(dba)_3$ (11 mg, 5 mol%), placed under vacuum and backfilled with nitrogen for three times. 1,4-dioxane (2.2 mL) was added, followed by tri--butylphosphine (0.25 mL, 0.1 M in 1,4-dioxane, 10 mol%), dicyclohexylmethylamine (0.12 mL, 0.55 mmol), and ethyl acrylate (0.11 mL, 1.00 mmol) respectively. The reaction mixture was stirred at room temperature for 24 h. $Pd_2(dba)_3$ (11 mg, 5 mol%), tri-*tert*-butylphosphine (0.25 mL, 0.1 M in 1,4-dioxane, 10 mol%) and ethyl acrylate (0.11 mL, 1.00 mmol) were added butylphosphine (0.25 mL, 0.1 M in 1,4-dioxane, 10 mol%) and ethyl acrylate (0.11 mL, 1.00 mmol) were added and the reaction mixture was stirred further for 24 h. The mixture was filtered through Celite® and washed with EtOAc (20 mL), and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography [CH_2Cl_2-MeOH-NH_4OH, 95:5:0.5] gave a brown solid (111 mg, 85%). The resulting solid was dissolved in HCl (0.37 mL, 0.5 M in MeOH). Acetone was added (40 mL) and the mixture was stirred for 3 h. The precipitate was filtered off and dried *in vacuo* to give **12h** (121 mg, 72%) as a yellow solid; m.p. > 200 °C, R_f = 0.22 [CH_2Cl_2-MeOH, 95:5].

$[\alpha]_D^{25}$ = –75 (c 1.0, water).

IR (neat): 2945, 1720, 1656, 1574, 1544, 1443, 1253, 1178, 1092 cm-^{1}.

^{1}H NMR (400 MHz, D_2O): δ = 1.22 (t, *J* = 7.0 Hz, 6 H), 1.91 (s, 4 H), 2.66 (s, 2 H), 2.95 (m, 4 H), 3.07 (s, 4 H), 3.18 (d, *J* = 12.0 Hz, 2 H), 3.26 (s, 2 H), 3.37 (d, *J* = 12.0 Hz, 2 H), 3.84 (dd, *J* = 6.5, 16.0 Hz, 2 H), 3.98 (d, *J* = 16.0 Hz, 2 H), 4.18 (q, *J* = 7.0 Hz, 4 H), 6.51 (s, 2 H), 6.52 (d, *J* = 16.0 Hz, 2 H), 6.54 (s, 2 H), 7.39 (d, *J* = 16.0 Hz,2 H).

^{13}C NMR (101 MHz, D_2O): δ = 13.4, 23.0, 26.5, 33.6, 49.2, 52.4, 57.8, 58.9, 62.3, 106.5, 116.5, 124.3, 141.3, 146.3, 148.6, 164.8, 168.0.

HRMS-ESI: m/z [M+H]$^+$ calcd for $C_{34}H_{43}N_4O_6$: 603.3177, found: 603.3169.

1,2-Bis(10-hydroxy-N-cytisinyl)ethane hydrochloride salt 12i

A Schlenk tube was charged with CC4 **7** (203 mg, 0.50 mmol), $[Ir(cod)(OMe)]_2$ (6.6 mg, 0.02 eq), 4,4'-di-tert-butyl-2,2'-dipyridyl (5.4 mg, 0.04 eq) and bis(pinacolato)diboron (177 mg, 1.4 eq) and was placed under vacuum and backfilled with nitrogen for three times. THF (1.0 mL, 0.5 M) was added and the reaction mixture was heated at reflux for 20 h. After this time ^{1}H NMR showed essentially 100% conversion. The solution was allowed to reach r.t. and then cooled to 0 °C. A solution 2M NaOH (1.5 mL, 6 eq.) was added followed by the addition of H_2O_2 (1.0 mL, 30% w/w in water), the Schlenk tube was removed from the ice bath and the reaction mixture was stirred for 24 h. The solvent was removed *in vacuo*. The crude was dissolved in a solution of HCl in MeOH (1 mL, 0.5 M) and Et_2O (15 mL) was added. The precipitate was filtered off and dried under vacuum. Purification by reverse phase chromatography using a Biotage SNAP Ultra C18 12g column and gradient elution (water to MeCN) afforded **12i** (118 mg, 54%) as a colorless solid; mp > 200 °C.

$[\alpha]_D^{20}$ = –115 (c 6.5, MeOH).

IR (neat): 2974, 1638, 1543, 1085, 1044, 878, 624.

^{1}H NMR (500 MHz, MeOD): δ = 5.85 (d, *J* = 2.5 Hz, 2 H), 5.71 (d, *J* = 2.5 Hz, 2 H), 3.88 (d, *J* = 15.5 Hz, 2 H), 3.73 (dd, *J* = 15.5, 7.5 Hz, 2 H), 2.89 (d, *J* = 11.0 Hz, 2 H), 2.82 (s, 2 H), 2.72 (d, *J* = 11.0 Hz, 2 H), 2.38-2.28 (m, 4 H), 2.26-2.16 (m, 6 H), 1.82 (d, *J* = 13.5 Hz, 2 H), 1.69 (d, *J* = 13.5 Hz, 2 H).

^{13}C NMR (125 MHz, D_2O): δ = 167.3, 165.7, 152.9, 99.7, 95.9, 60.2, 59.8, 54.8, 49.6, 35.6, 28.0, 25.2.

HRMS-ESI m/z [M+H]$^+$ calcd for $C_{24}H_{30}N_4NaO_4$:461.2159, found 461.2137.

Funding Information

We thank Achieve Life Sciences and Allychem Co. Ltd. for generous gifts of (–)-cytisine and bis(pinacolato)diboron respectively, and financial support from the Royal Thai Government, University of Bristol and EPSRC (EP/N024117/1) is acknowledged.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

YES (this text will be updated with links prior to publication)

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(8) Catalyst inhibition by coordination of **1a** would explain the issues we have observed for unsubstituted (i.e. NH) pyridones. No C–H activation of substrate **1b** (which is otherwise a viable substrate) was observed when a mixture of **1a** and **1b** was used, suggesting that **1a** deactivates the Ir catalyst. Catalyst inhibition via coordination of an azinyl N to a vacant coordination site on Ir also retards reactions involving pyridines, see refs. (2g) and (2j).

(9) In the case of simple pyridone substrates (Table 1), no mono C–H insertion at C(3) and/or C(6) was detected, demonstrating that initial reaction occurs at C(4) and/or C(5) (to give **2** and **3**). This then leads to subsequent activation of (and reaction at) C(6) or C(3) respectively leading to the double C–H insertion products **4** and **5**. Reaction of **1b** with 0.5 eq. of B_2pin_2 led to a lower conversion and reaction of **1b** with 1.0 eq. of B_2pin_2 led to faster conversion (24 h instead of 48 h). In both cases, the same proportions of products **2**-**5** were observed. Monobromides **2** and **3** did not undergo further (i.e. additional) substitution when exposed to the bromination conditions shown in Scheme 1.

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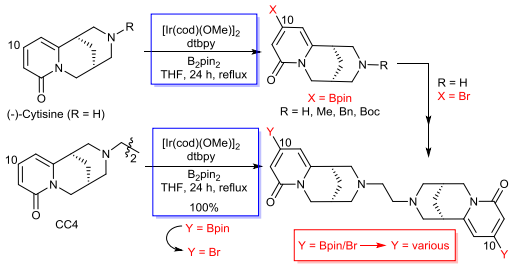
(20) We have carried out preliminary pharmacological evaluation (using binding methods obtained as described earlier[14]) of two ligands **12d** and **12g** shown in this paper. Ligand **12d** had Ki values of 4142 nM at human α4β2; 45610 nM at human α7. Ligand **12g** had Ki values of 7360 nM at human α4β2; 45890 nM at human α7. This indicates that these two substitution changes (NHAc and CO_2Me respectively) lead to both a significant reduction of binding affinity at each of α4β2 and α7, as well as a loss of subtype selectivity by one to two orders of magnitude across these two nicotinic receptors, as compared to CC4. Details of a more extensive study to understand the structure-activity relationships involved here will be published in due course.

Graphical Abstract



Supporting Information

Iridium-catalyzed C–H Borylation of 2-Pyridones; Bisfunctionalisation of CC4

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Table of Contents

1. General Experimental Details.

All reagents were purchase from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were obtained by distillation using standard procedures or by using the Anhydrous Engineering Ltd. double alumina and alumina-copper catalyzed drying columns.

Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen; glassware and needles were flamed-dried prior to use or placed in the oven (150 °C) for at least 2 h and allowed to cool either in a desiccator, under vacuum, or an atmosphere of nitrogen. Thin layer chromatography was performed using aluminium backed 60 F254 silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat.

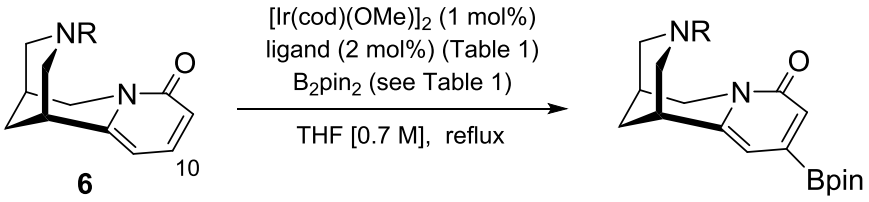
Flash column chromatography was performed on silica gel (Aldrich 40-63 µm, 230-400 mesh). Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or neat films in the range of 600-4000 cm^{-1}.

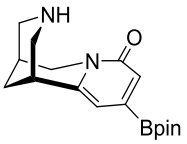
NMR spectra were recorded using either a Varian 400 MHz or 500 MHz, or JEOL ECP 400 MHz spectrometer. Chemical shifts are quoted in parts per million, coupling constants are given in Hz to the nearest 0.5 Hz. ^{1}H and ^{13}C NMR spectra are referenced to the appropriate residual peak. DEPT 135, COSY, HSQC and HMBC were used where necessary in assigning NMR spectra.

Mass spectra were determined by the University of Bristol mass spectroscopy service by either chemical ionisation (CI^+), electrospray ionization (ESI^+) or electron impact (EI^+) using a Bruker Daltonics Apex IV spectrometer.

2. Optimization studies for the Ir-catalyzed borylation of cytisine derivatives.

Table 1. Ligand and substrate optimization studies.



Entry	Substrate	Conditions[a]	Product %[b]
1	(–)-Cytisine **6a**	dtbpy; 1.50 eq. B_2pin_2; 24 h	 100%
2	(–)-Cytisine **6a**	Me4phen; 3.00 eq. B_2pin_2; 24 h	100%
3	(–)-Cytisine **6a**	neocuproine; 1.50 eq. B_2pin_2; 24 h	100%
4	N-Boc cytisine **6e**	dtbpy; 0.70 eq. B_2pin_2; 18 h	**8e** (R = Boc) 100%
5	N-Methyl cytisine **6b**	as entry 4	(R = Me) 98%
6	N-Bn-cytisine **6c**	as entry 4	Over-borylation[c]
7	N-Cbz cytisine **6d**	as entry 4	Over-borylation[c] 88%

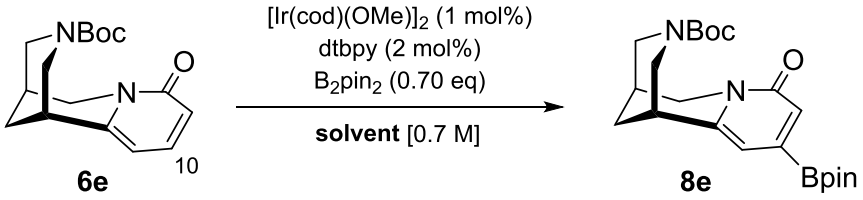
dtbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl; Me4phen = 3,4,7,8-tetramethyl-1,10-phenanthroline; neocuproine = 2,9-dimethyl-1,10-phenanthroline.

[a] Standard conditions are as shown above.

[b] Yields shown represent conversion as judged by ^{1}H NMR; purification of the initially-formed boronate esters was avoided (and was unnecessary) with full characterization carried out on the corresponding 10-bromo derivative.

[c] ^{1}H NMR indicated competing and unselective borylation in the Bn and Cbz aryl moiety. The borylation site within the N-arylated substituent was not determined and an overall solution yield (to assess conversion) was only obtained for entry 7. Similar competing C–H insertion reactions were also observed with N-Fmoc cytisine (not shown here).

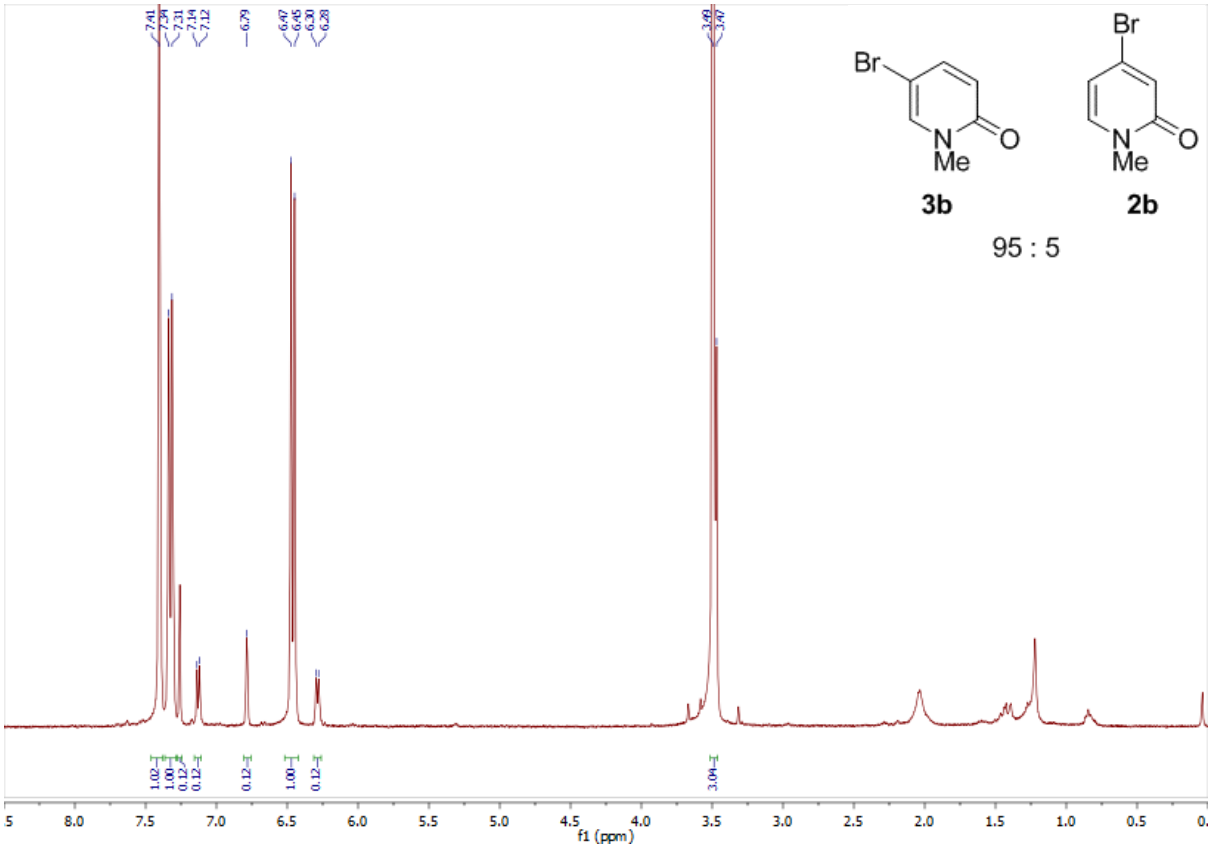
Table 2. Solvent screening for the borylation of N-Boc cytisine 6e.



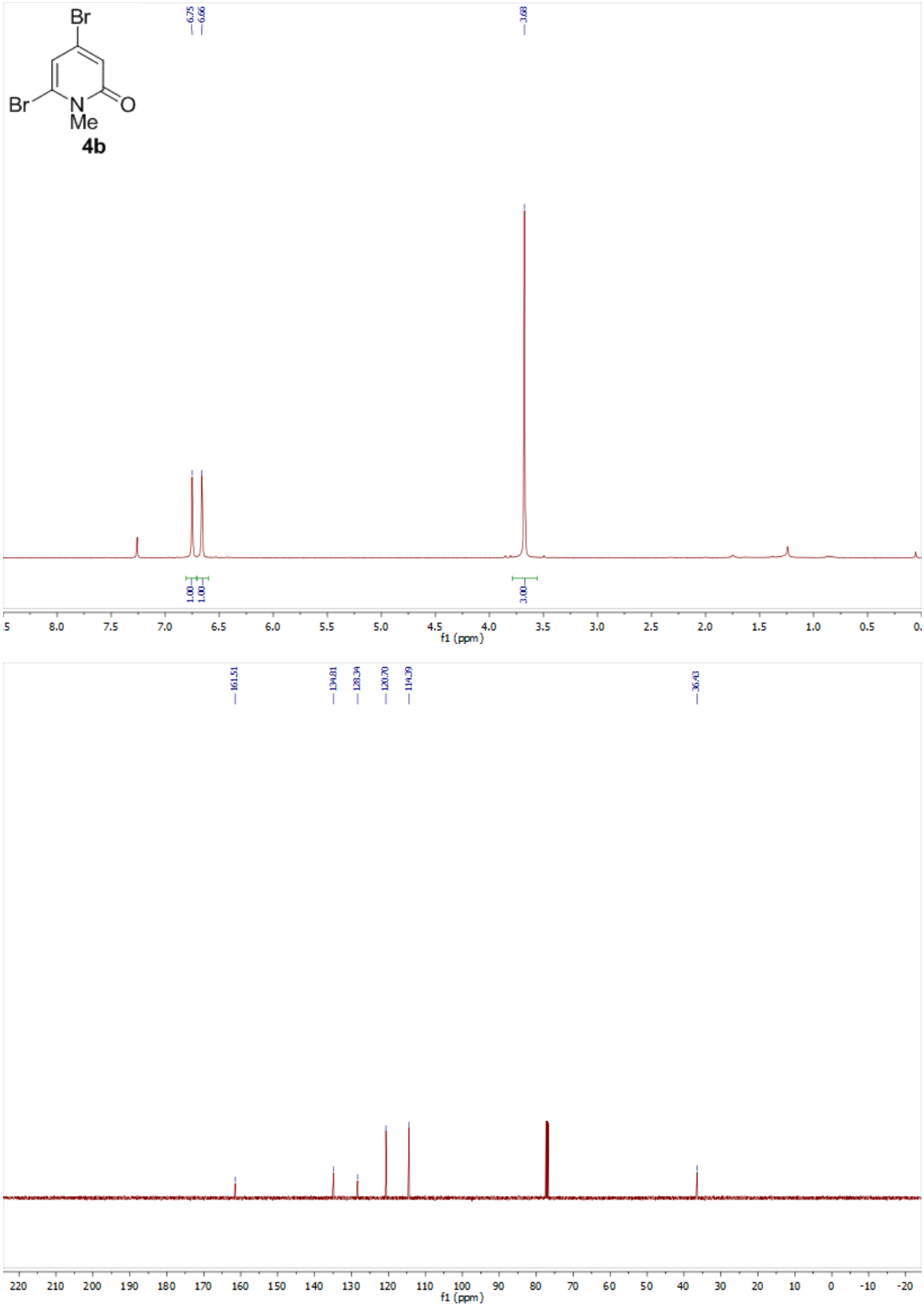
Entry	Solvent	Temp, Time (h)	^{1}H NMR Conversion (%)
1	Ethyl acetate	70 °C, 24 h	6
2	Dioxane	70 °C, 24 h	60
3	Chloroform	60 °C, 24 h	-
4	Butanone	70 °C, 24 h	16
5	$F_3CC_6H_5$	70 °C, 24 h	9
6	**Cyclohexane**	**70 °C, 24 h**	**86**
7	**THF**	**70 °C, 18 h**	**100**

3. Copies of $^{1}H/^{13}C$ NMR Spectra.

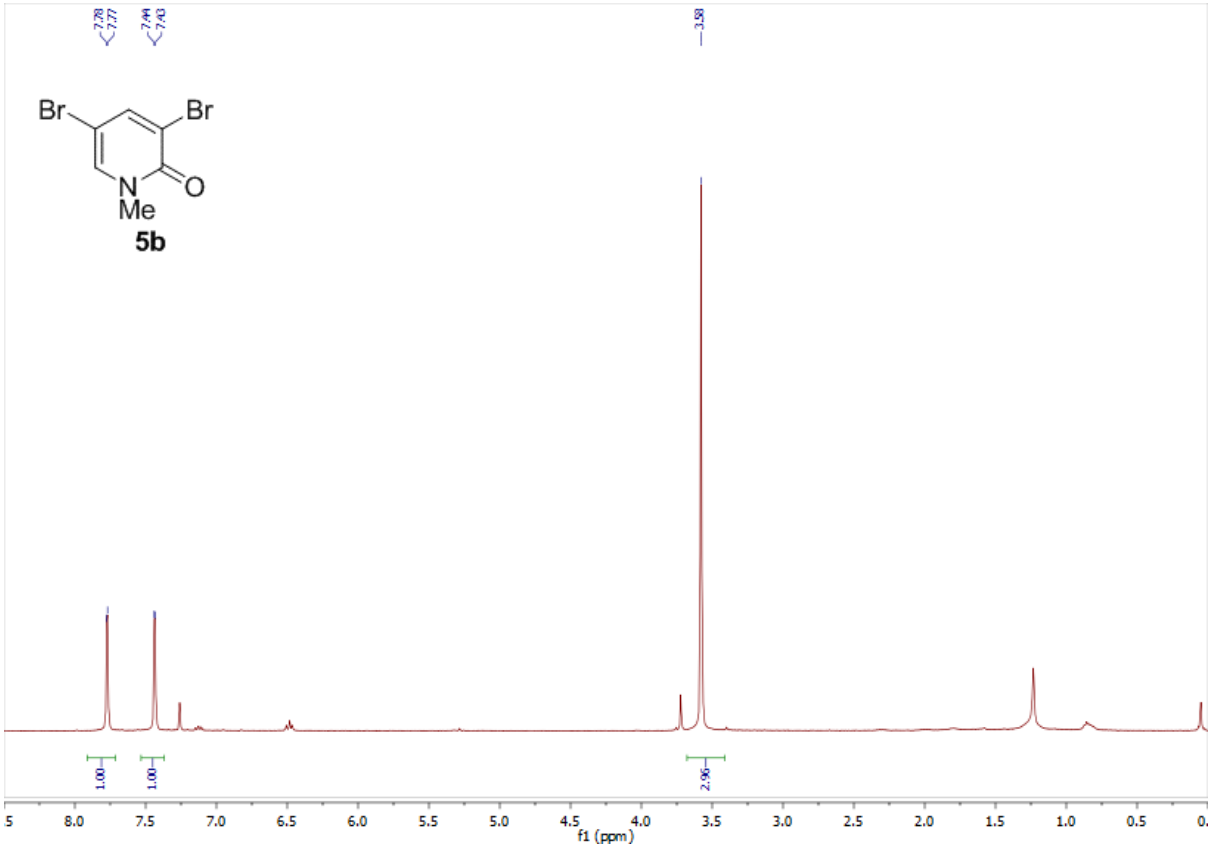
^{1}H of a 95:5 mixture of **3b** + **2b**

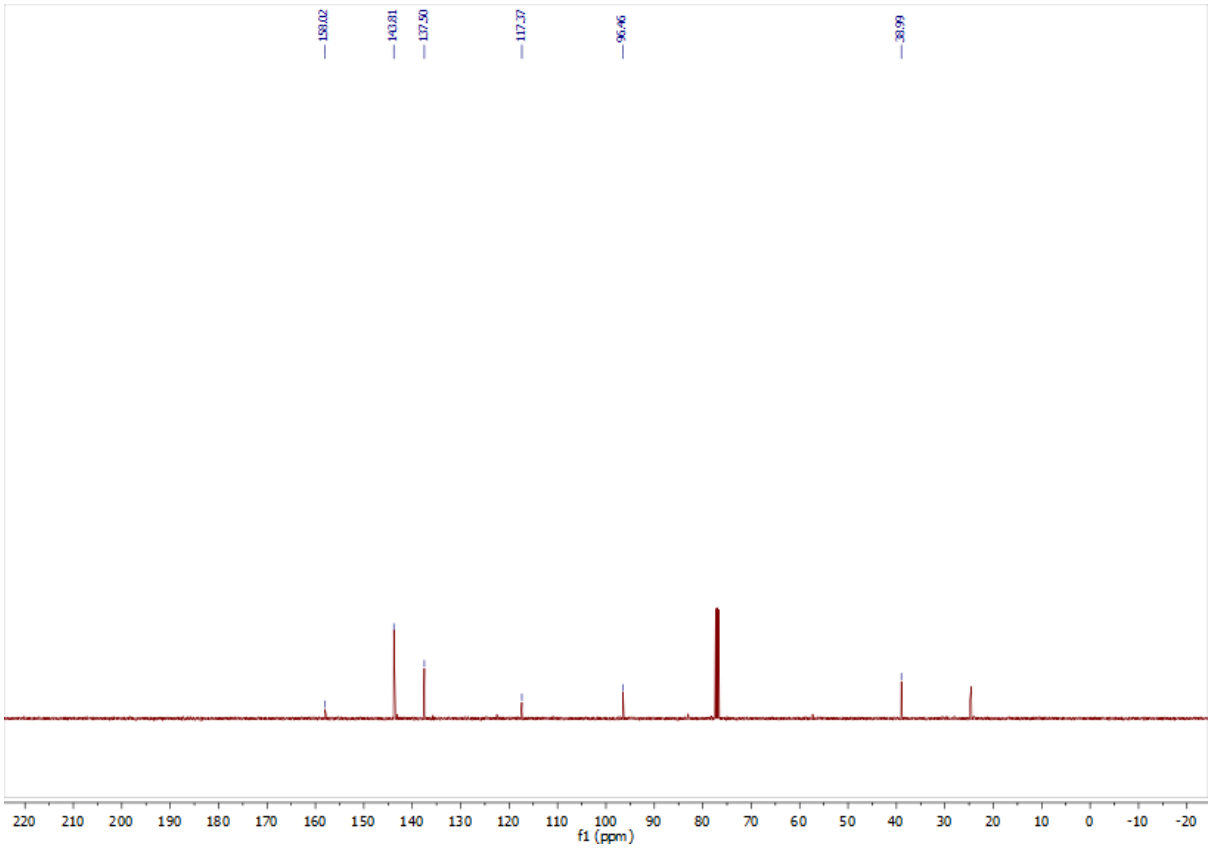


^{1}H and ^{13}C of **4b**

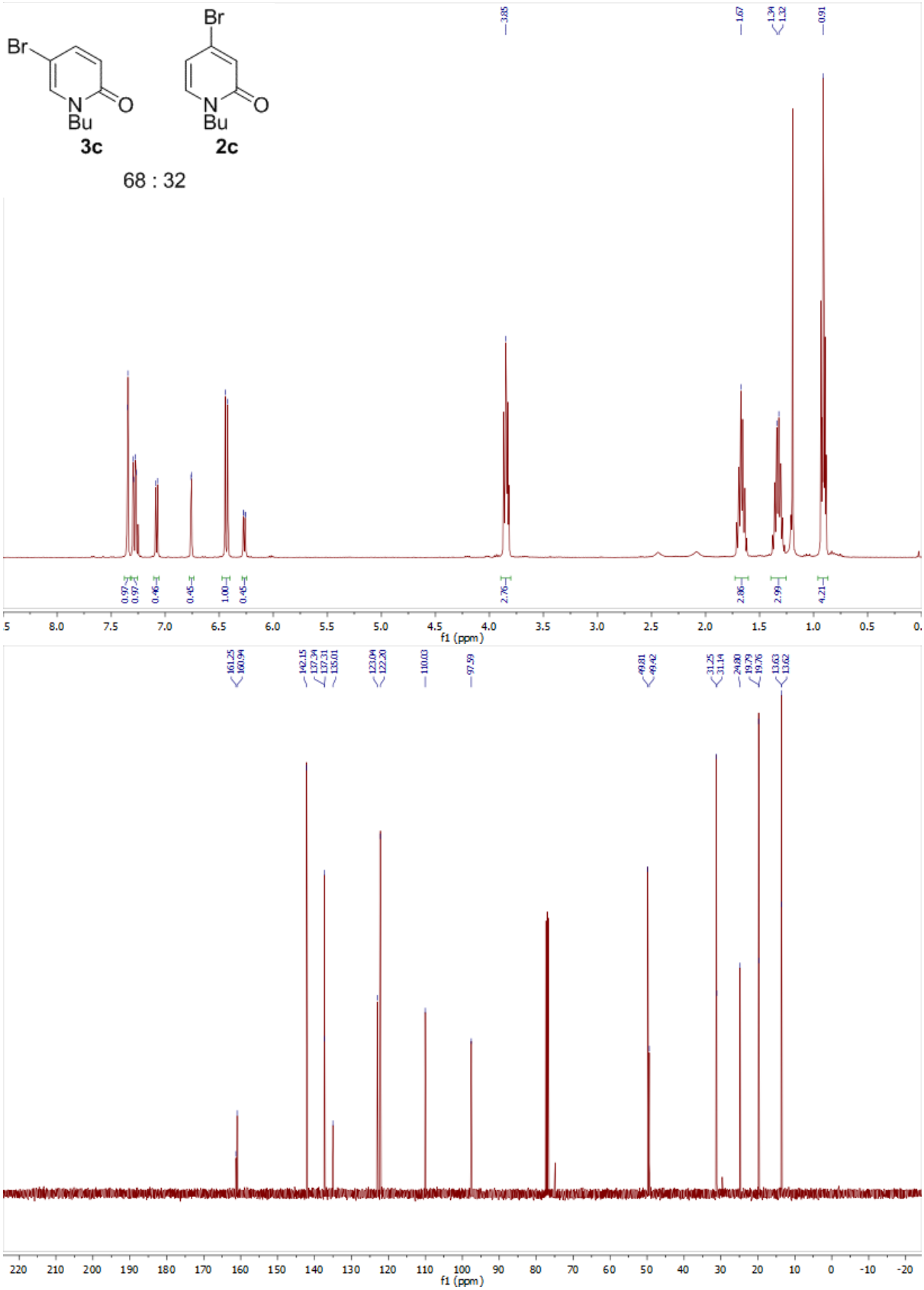


^{1}H and ^{13}C of **5b**

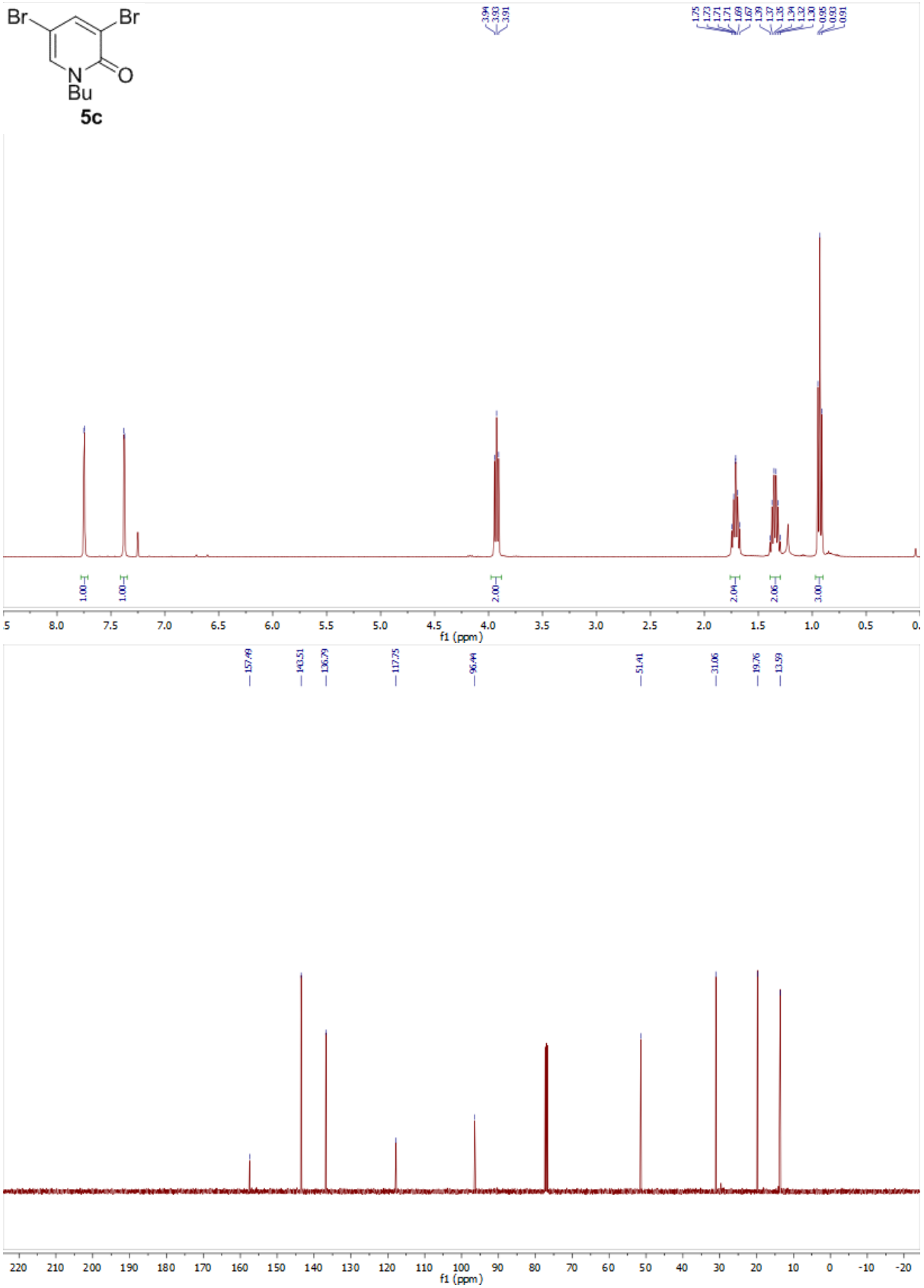




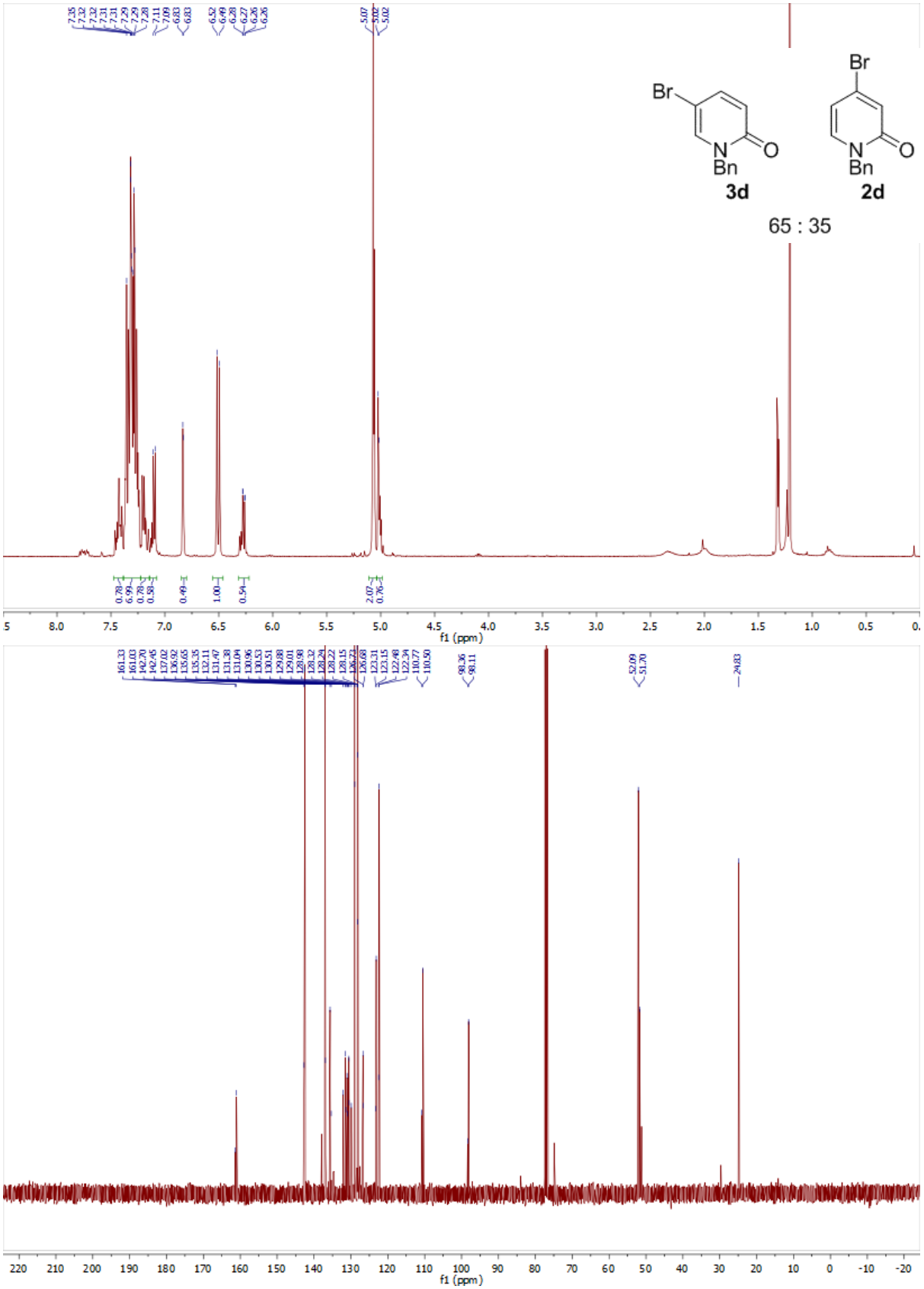
^{1}H and ^{13}C of a 68:32 mixture of **3c** + **2c**



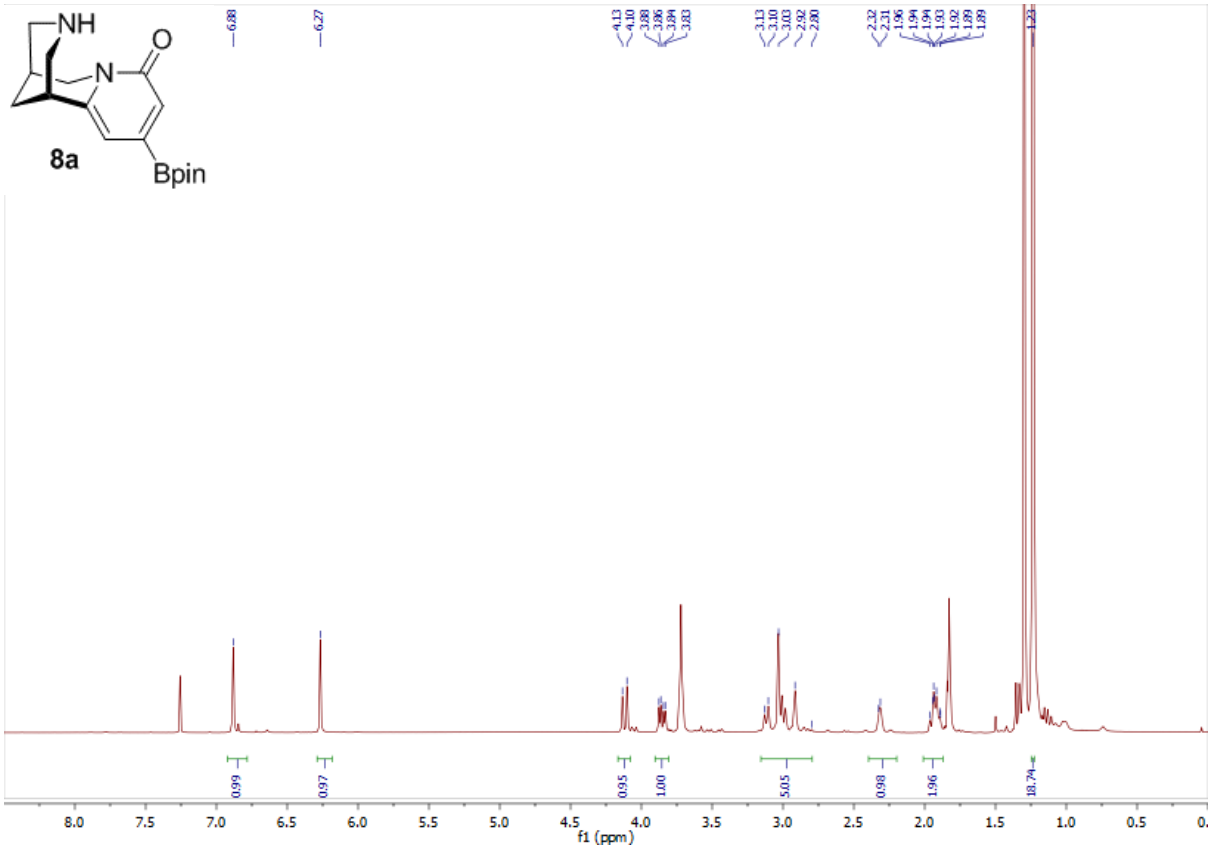
^{1}H and ^{13}C of **5c**

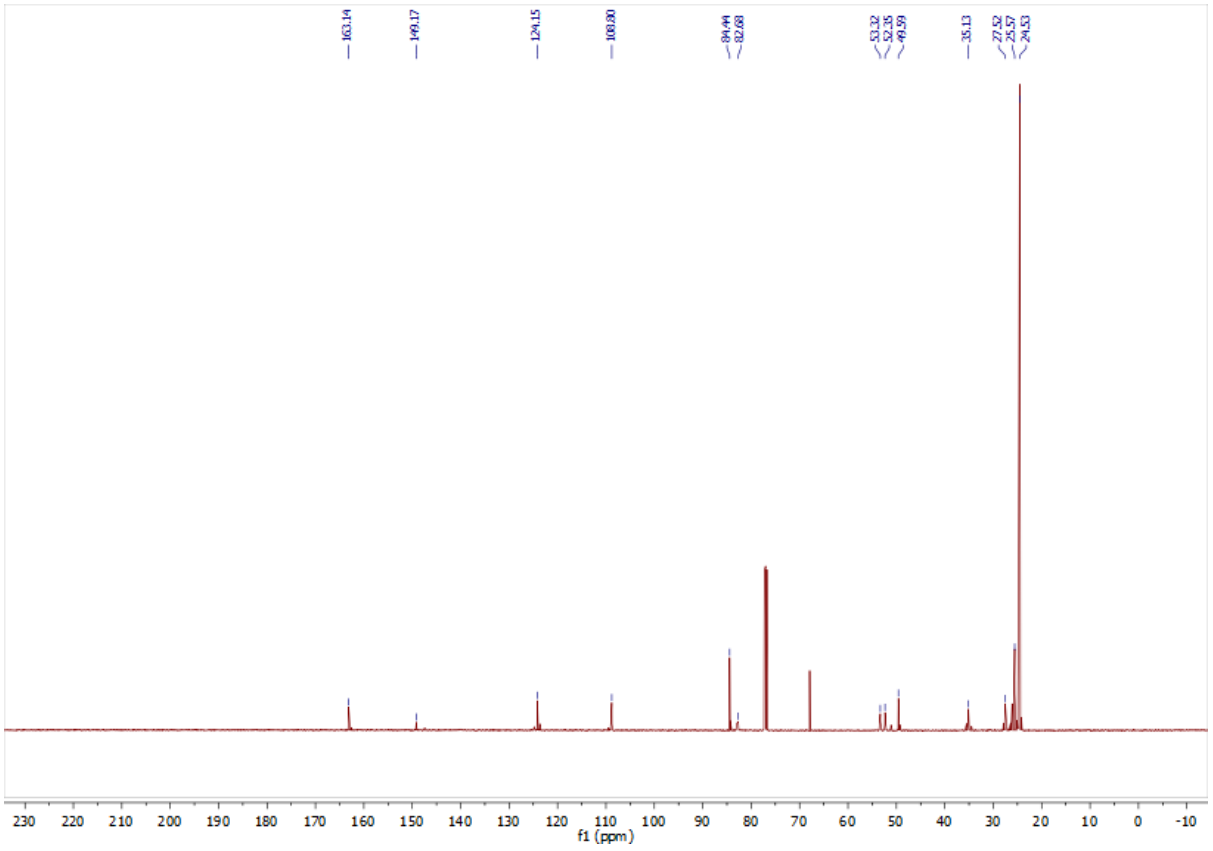


^{1}H and ^{13}C of a 65:35 mixture of **3d** + **2d**

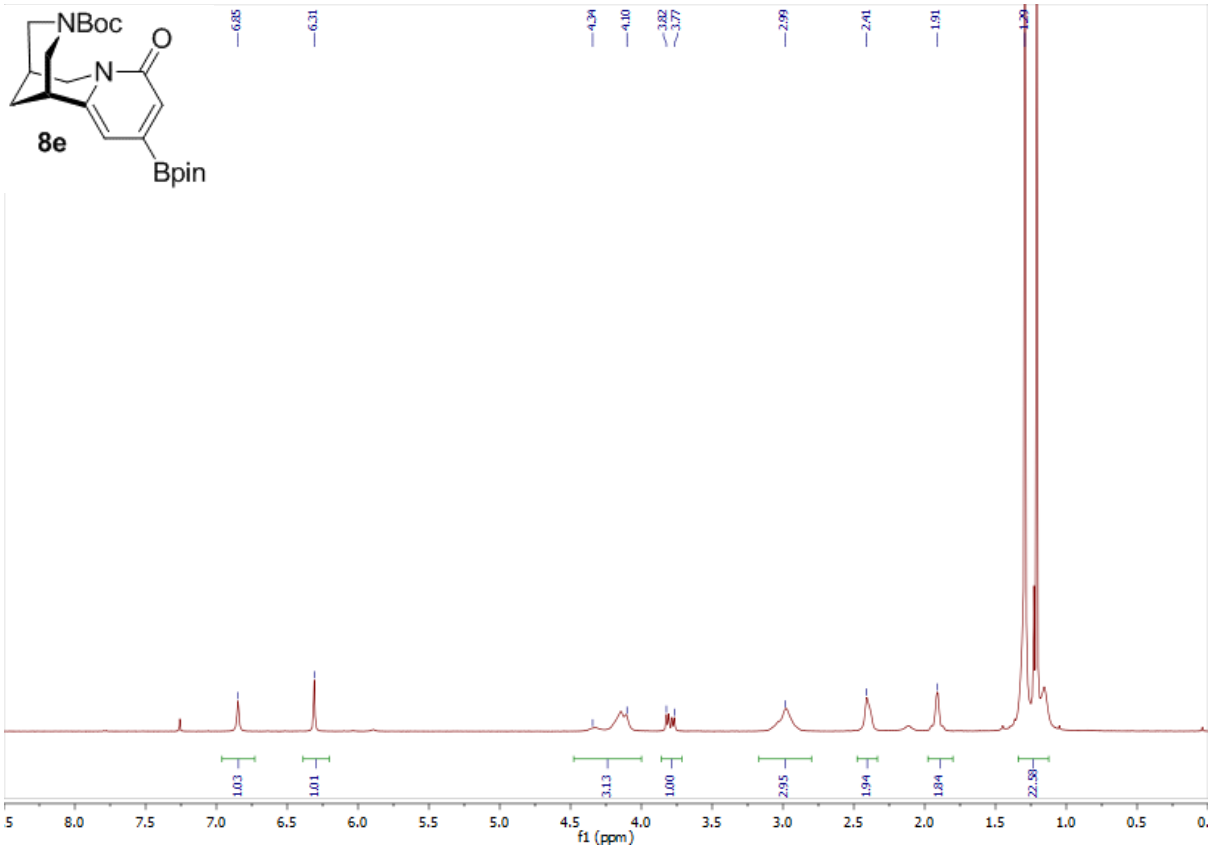


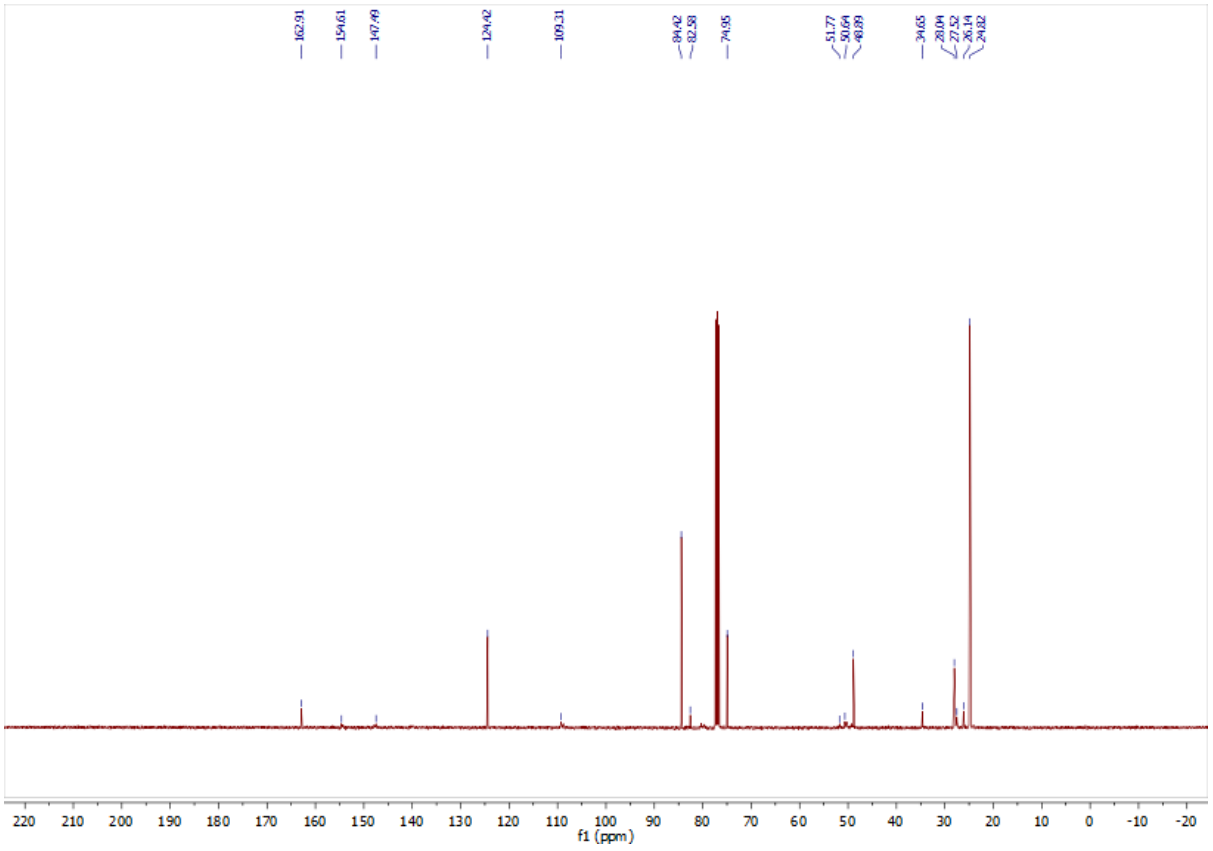
^{1}H and ^{13}C of 10-Bpin-cytisine **8a**



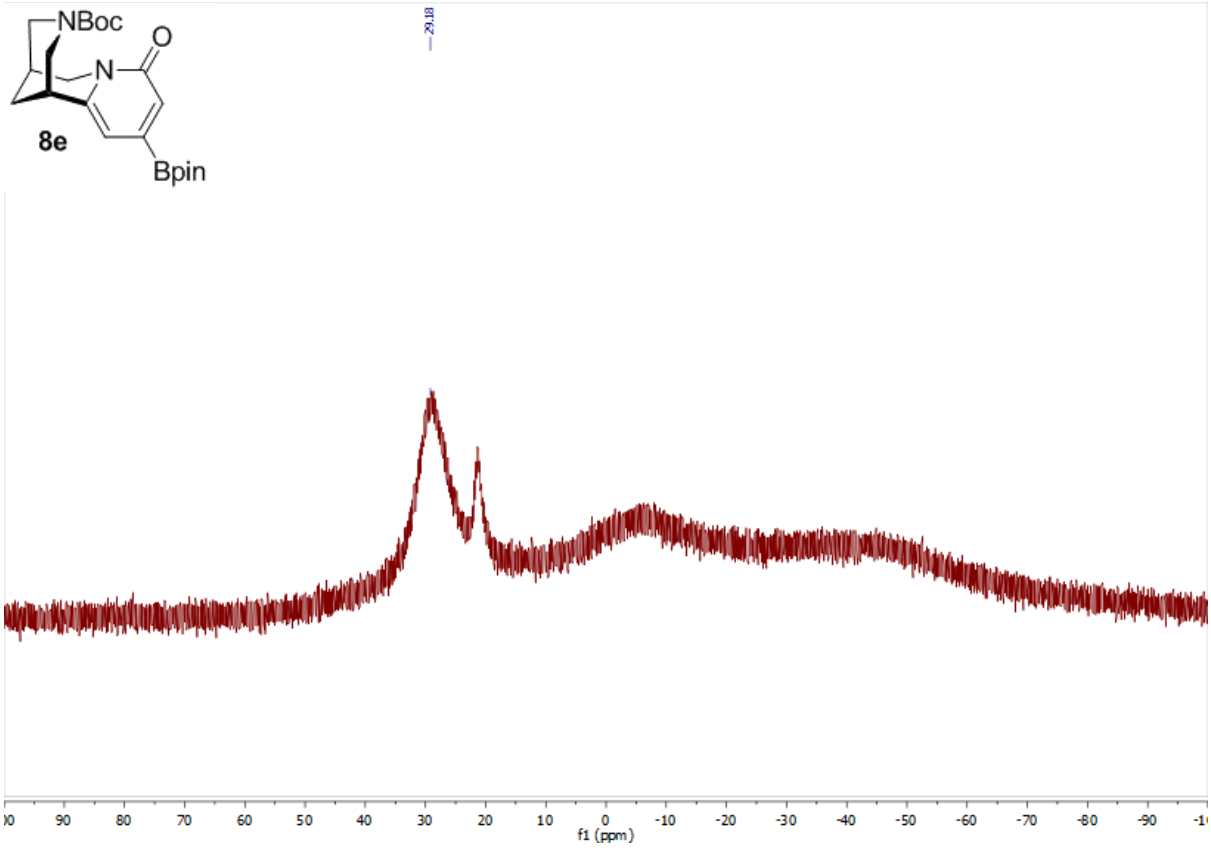


^{1}H and ^{13}C of N-Boc cytisine **8e**

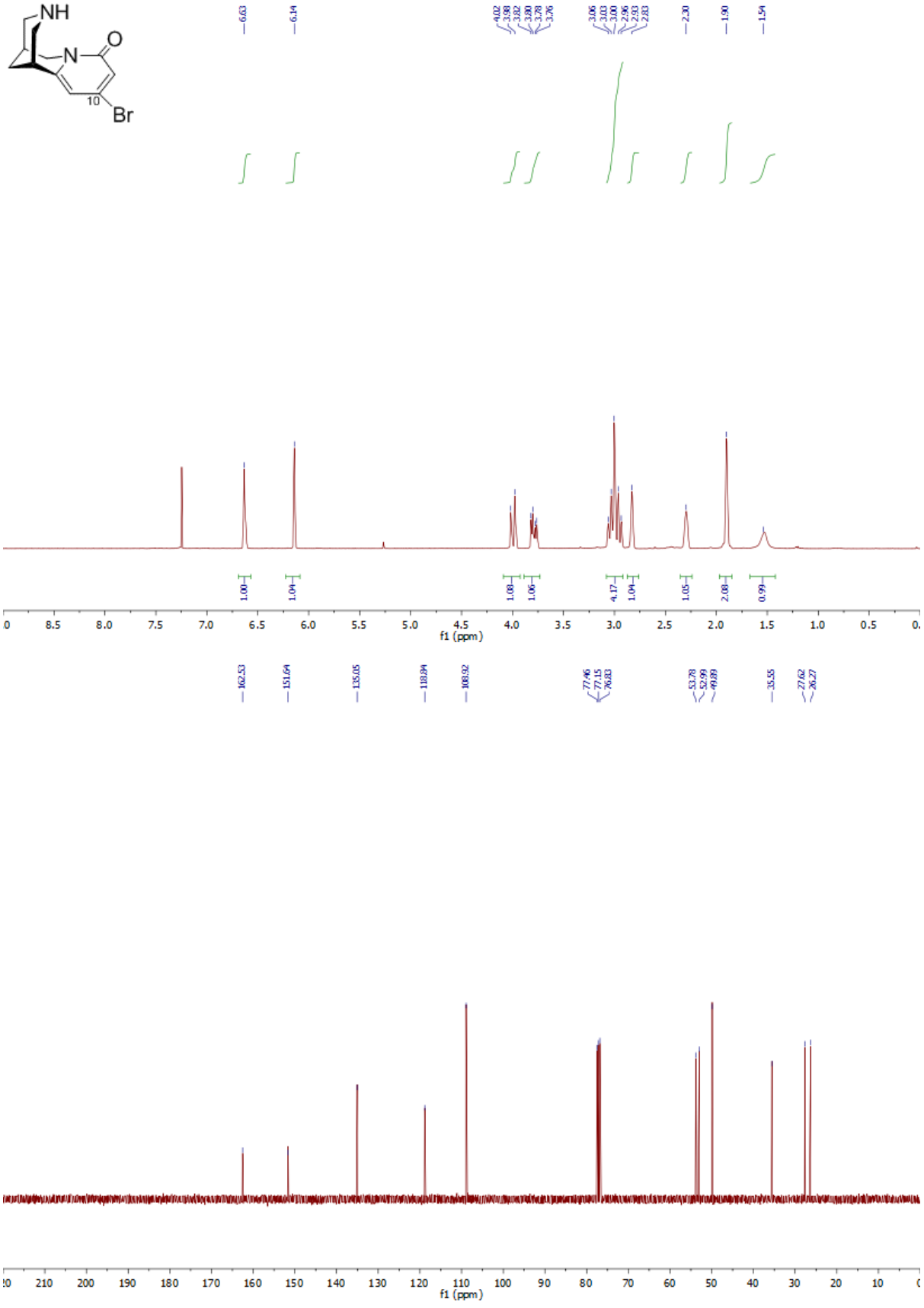




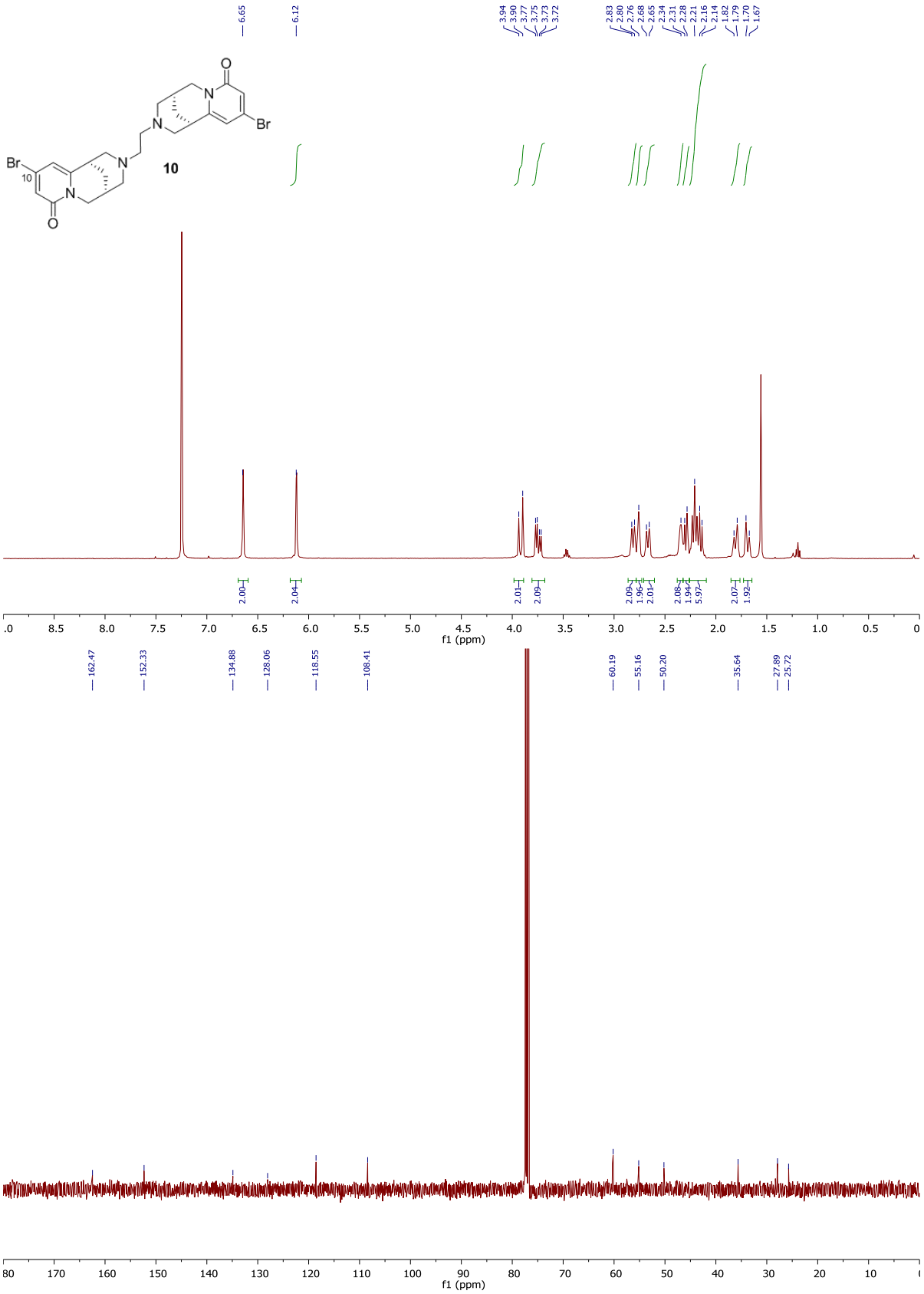
^{11}B NMR of N-Boc cytisine **8e**



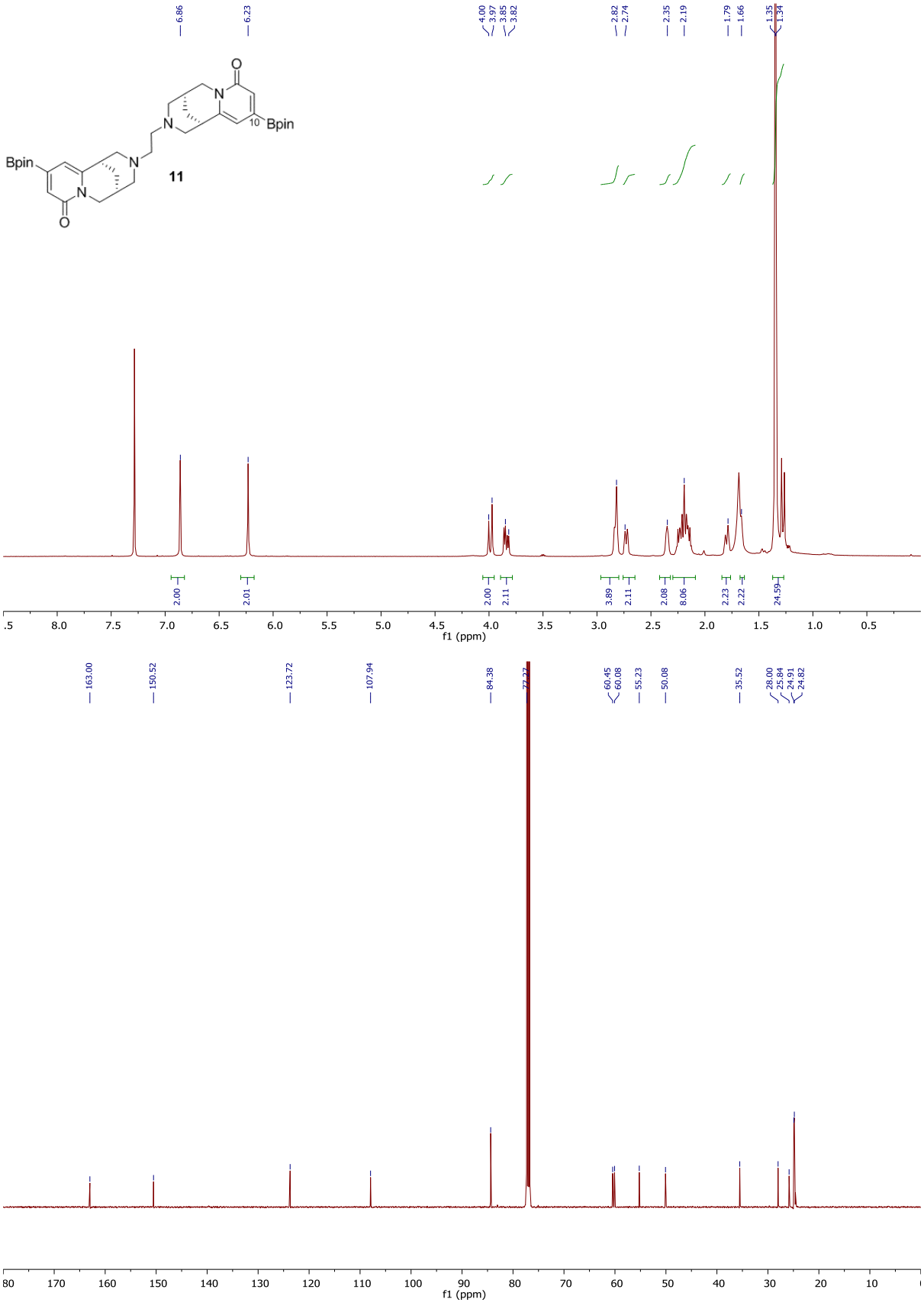
^{1}H and ^{13}C of 10-bromocytisine **9**



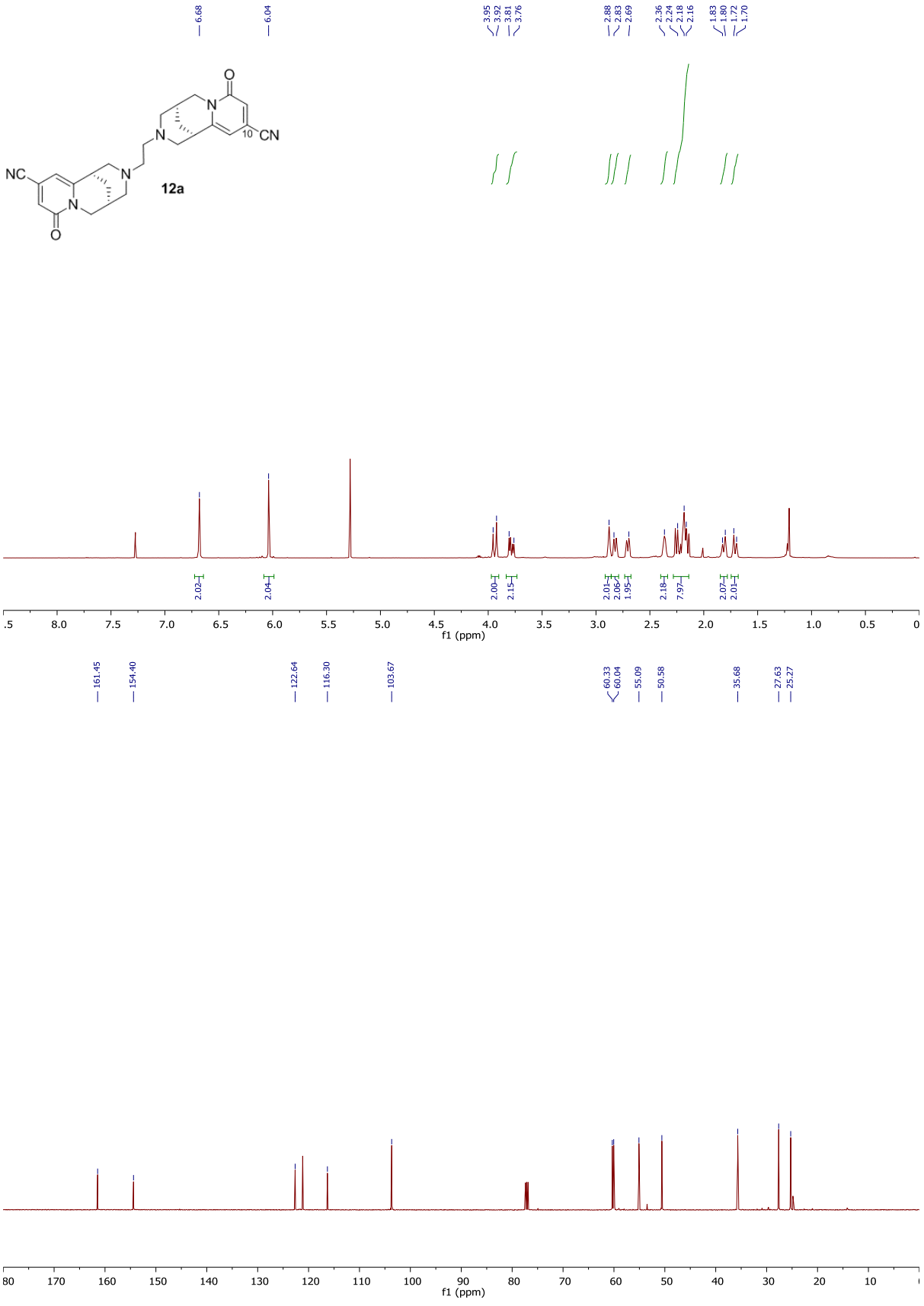
^{1}H and ^{13}C of bisbromide **10**



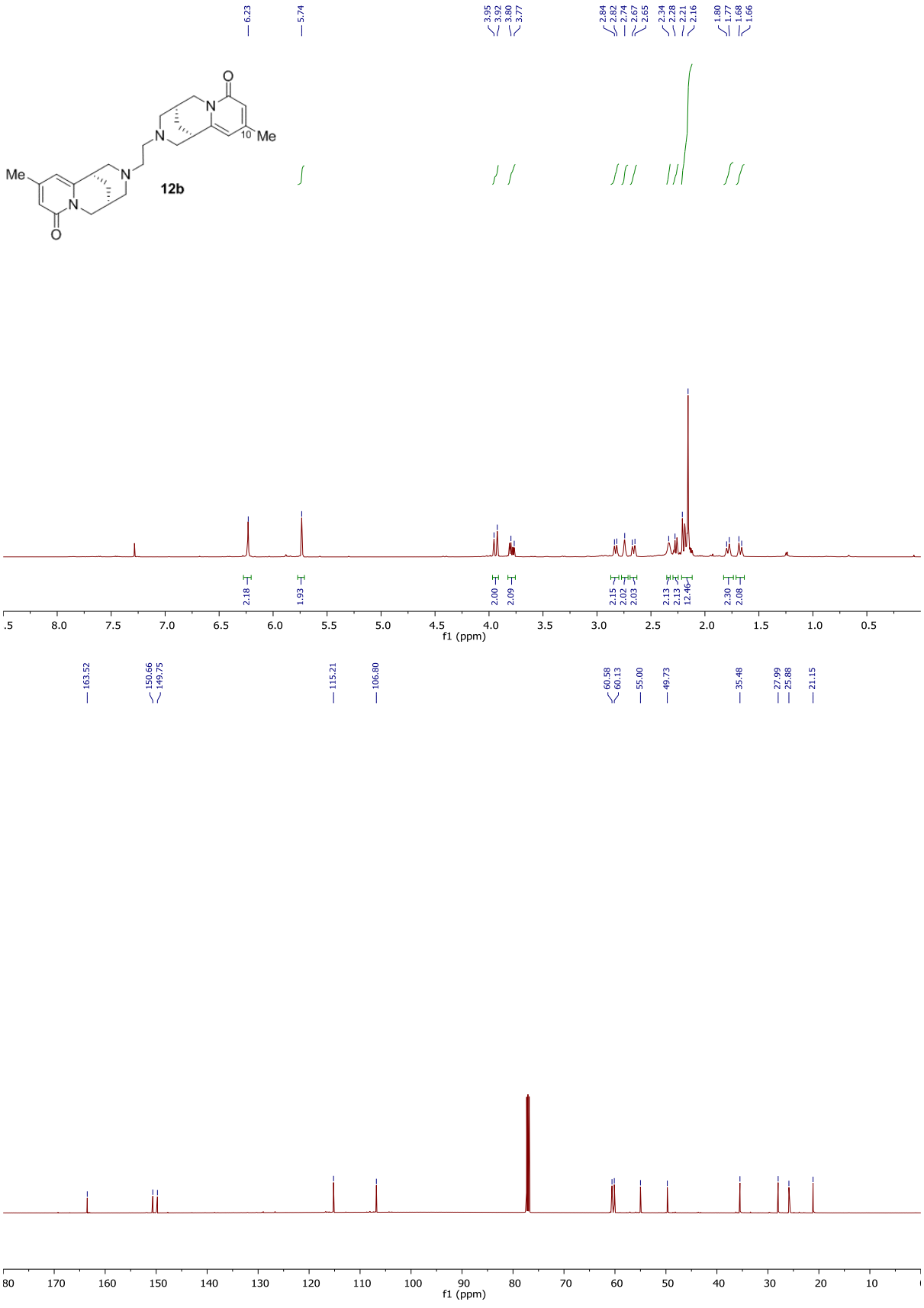
^{1}H and ^{13}C of bisboronate **11**



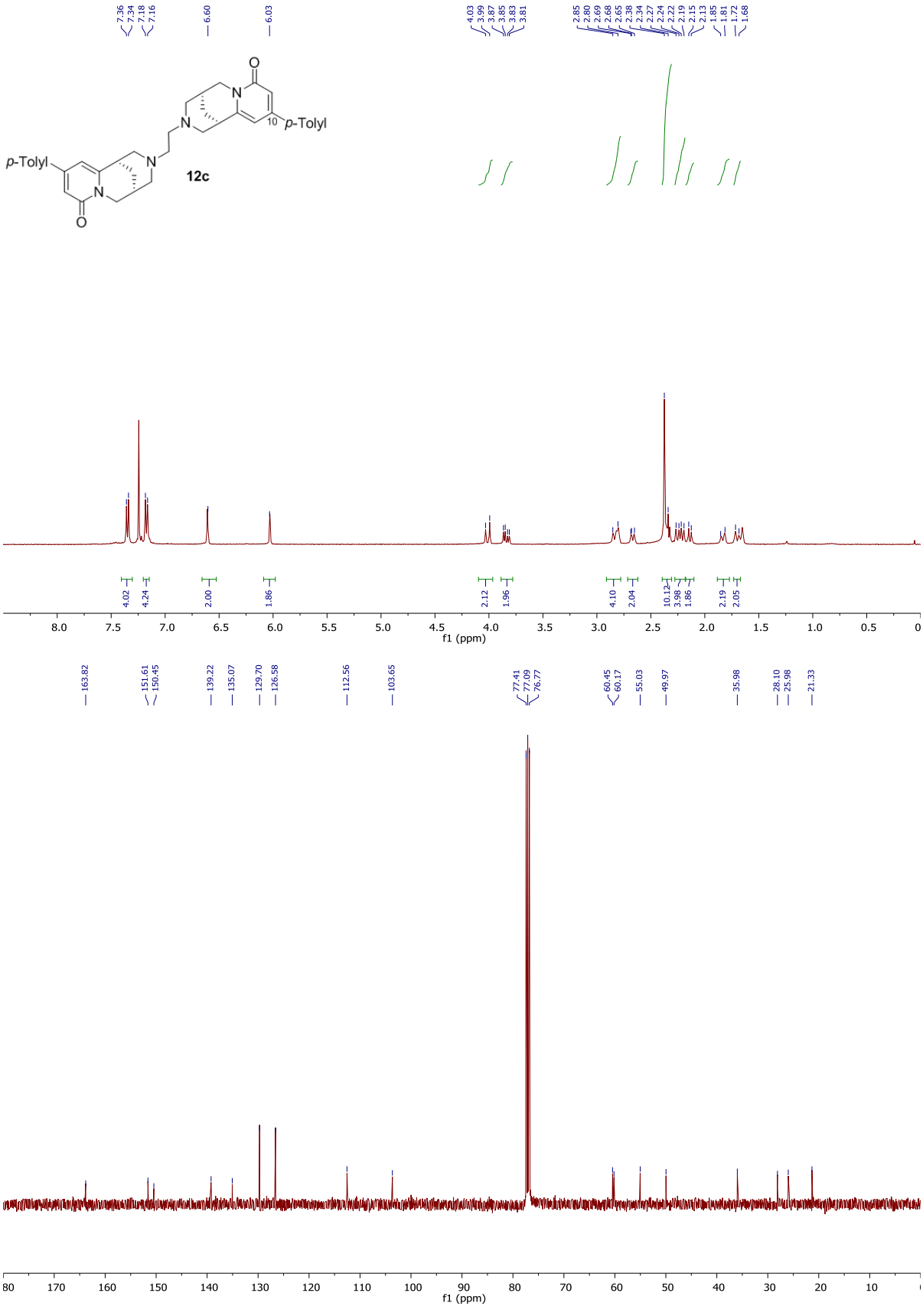
^{1}H and ^{13}C of derivative **12a**



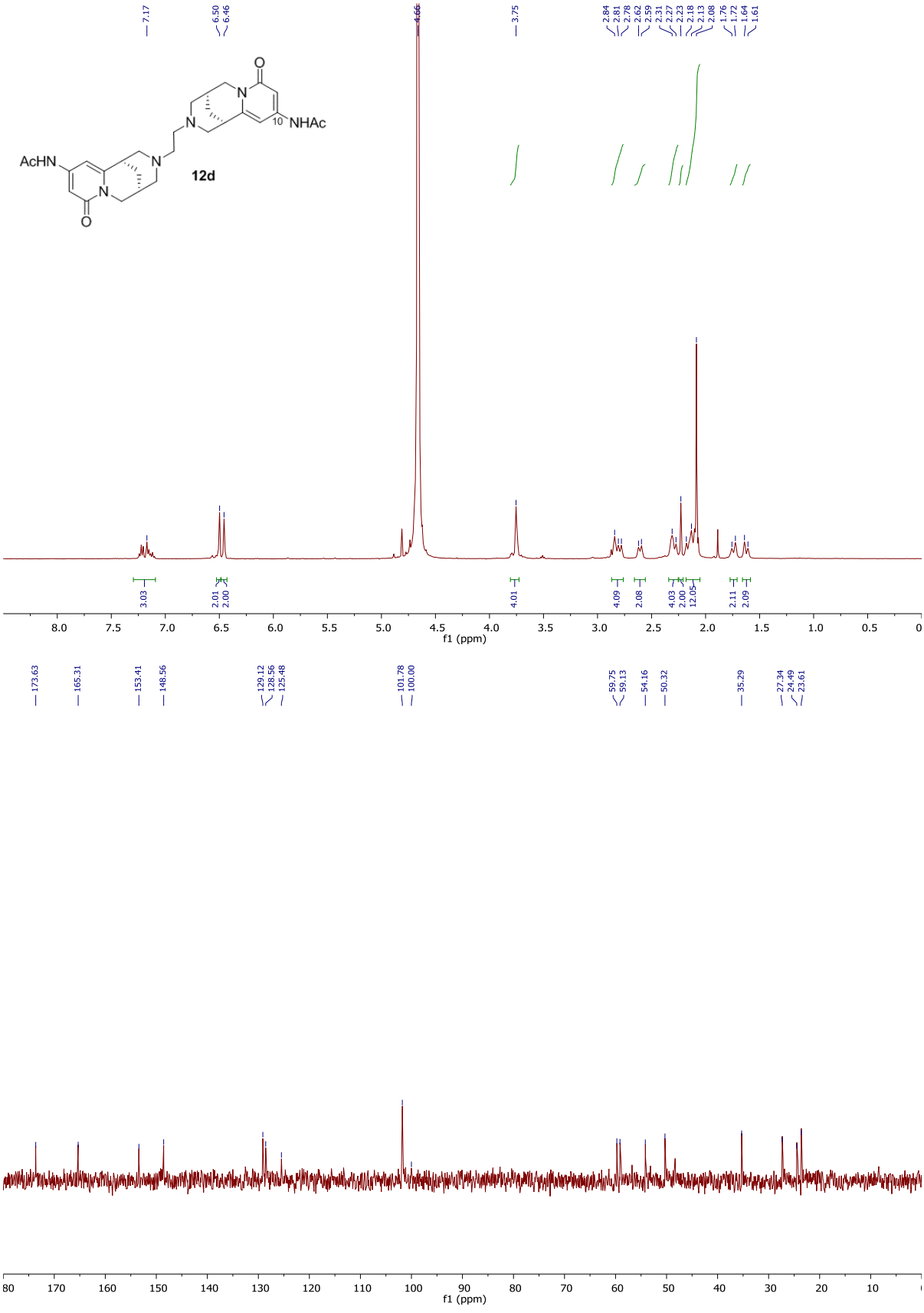
^{1}H and ^{13}C of derivative **12b**



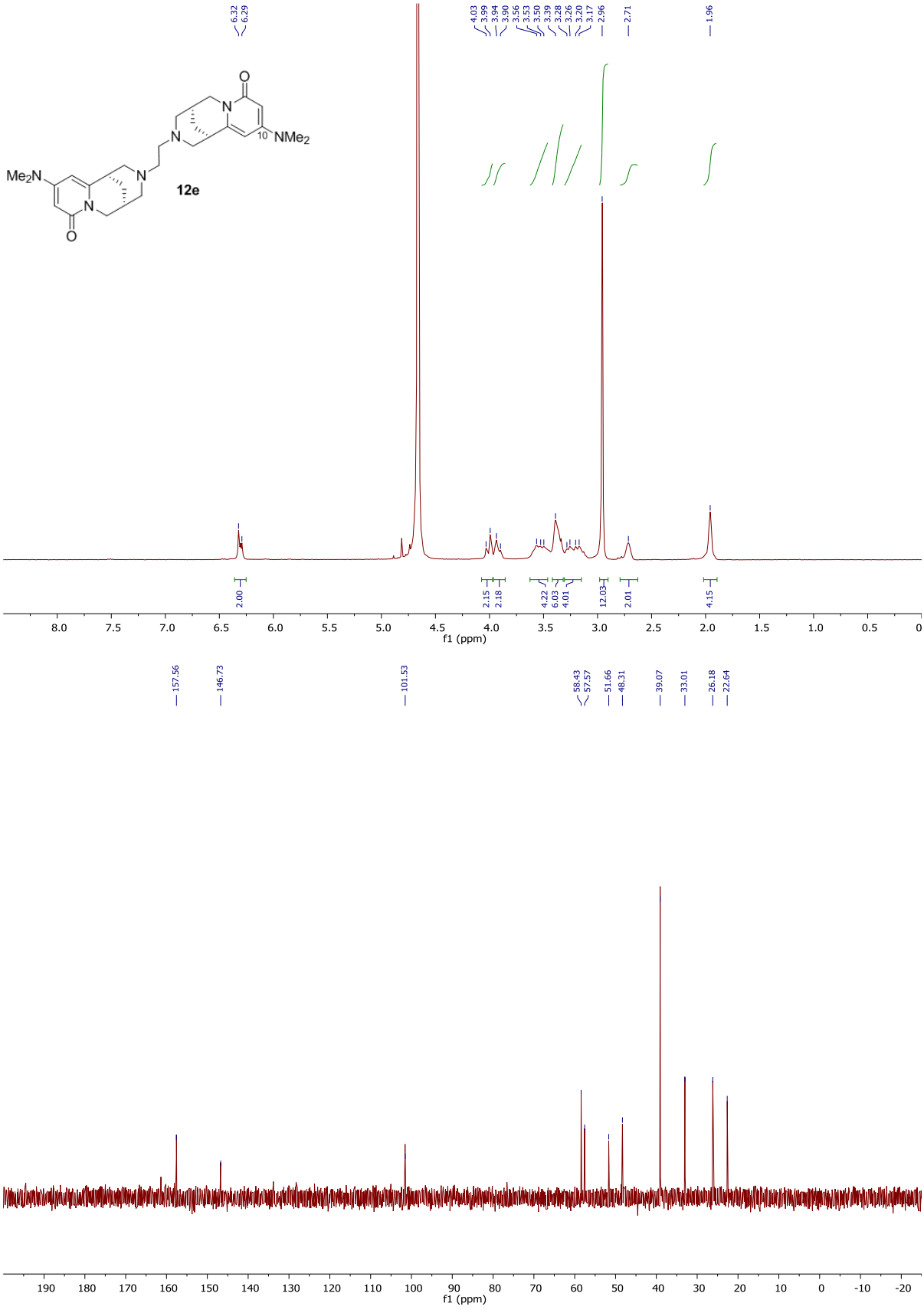
^{1}H and ^{13}C of derivative **12c**



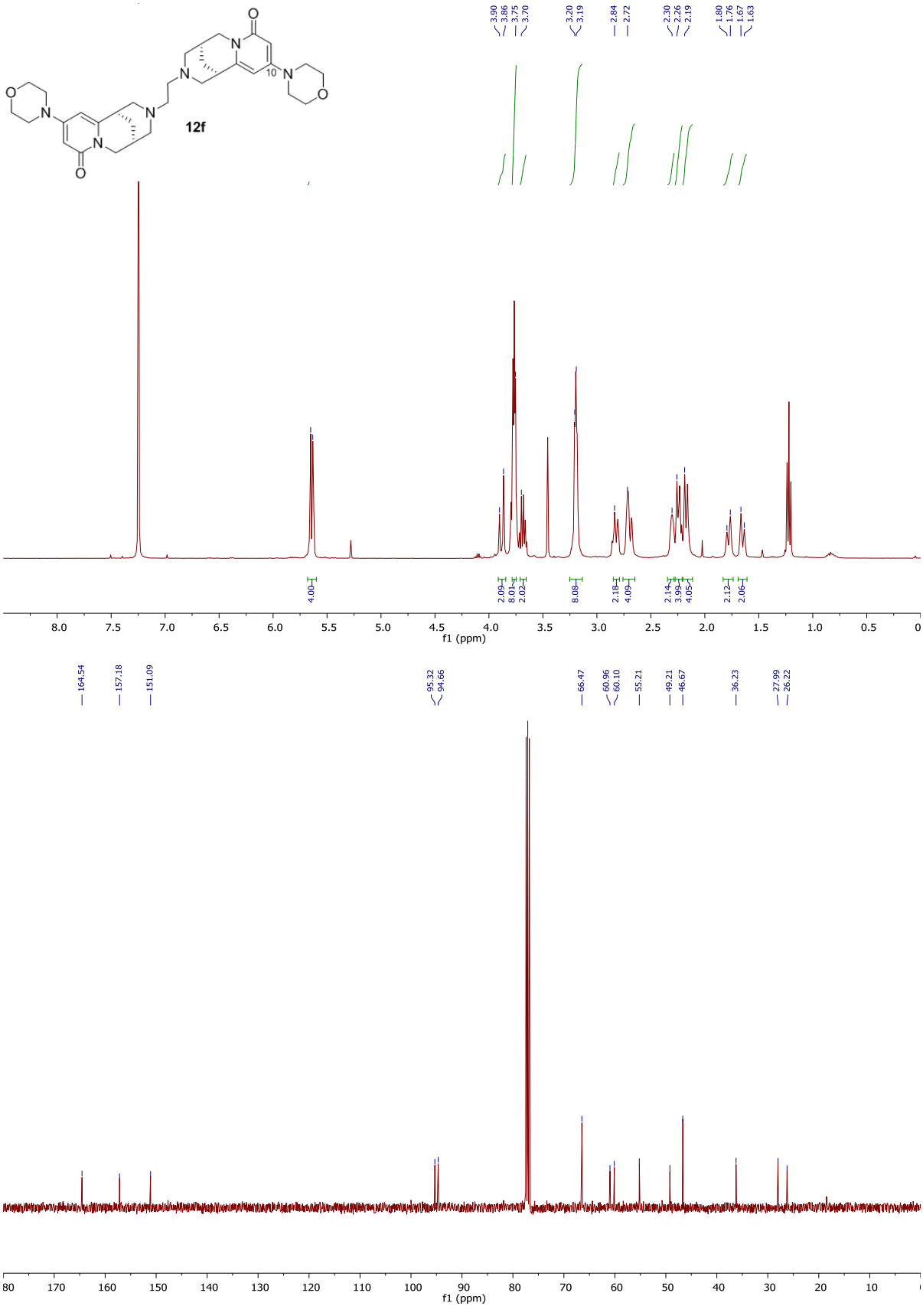
^{1}H and ^{13}C of derivative **12d** (hydrochloride salt)



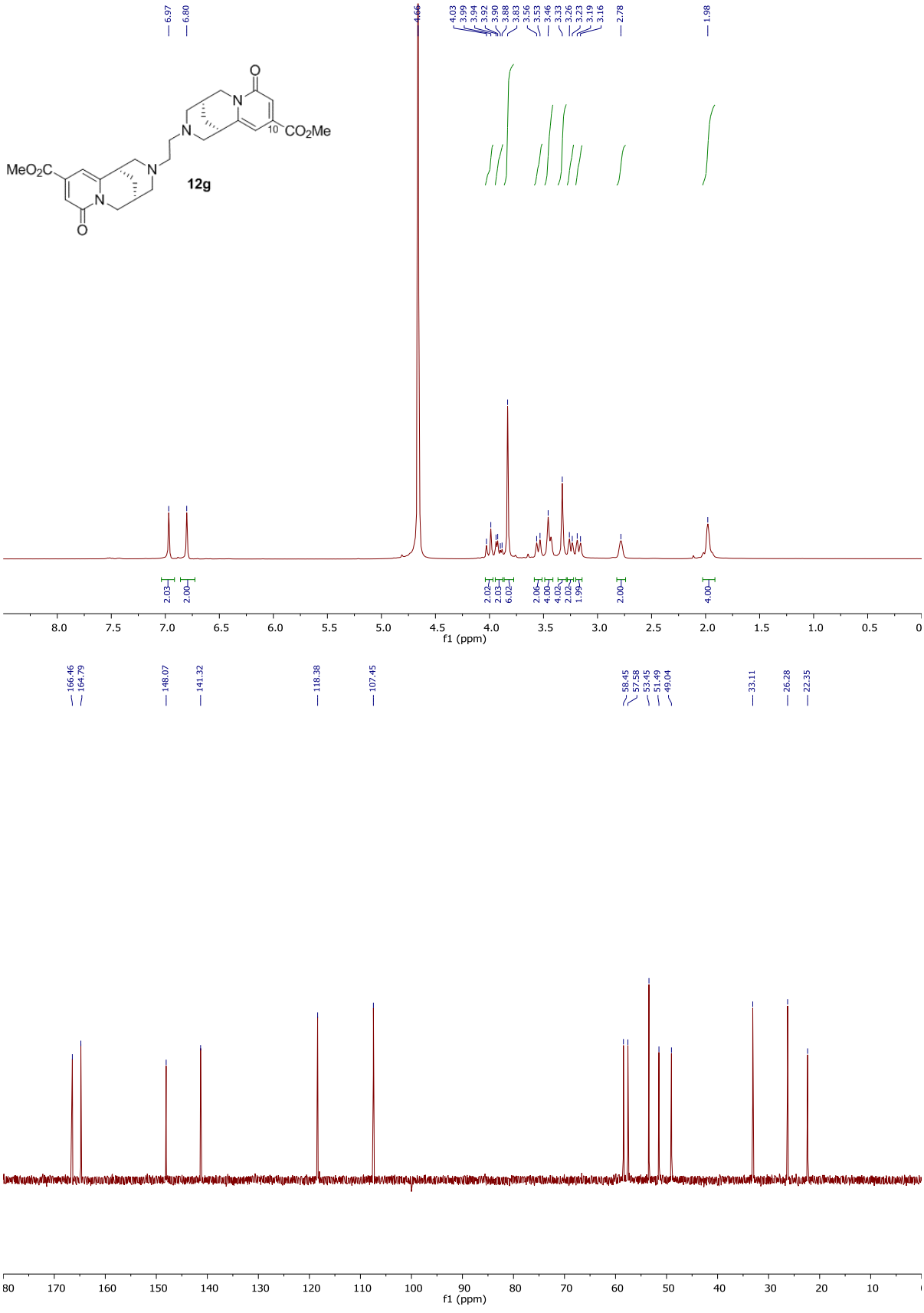
^{1}H and ^{13}C of derivative **12e** (hydrochloride salt)



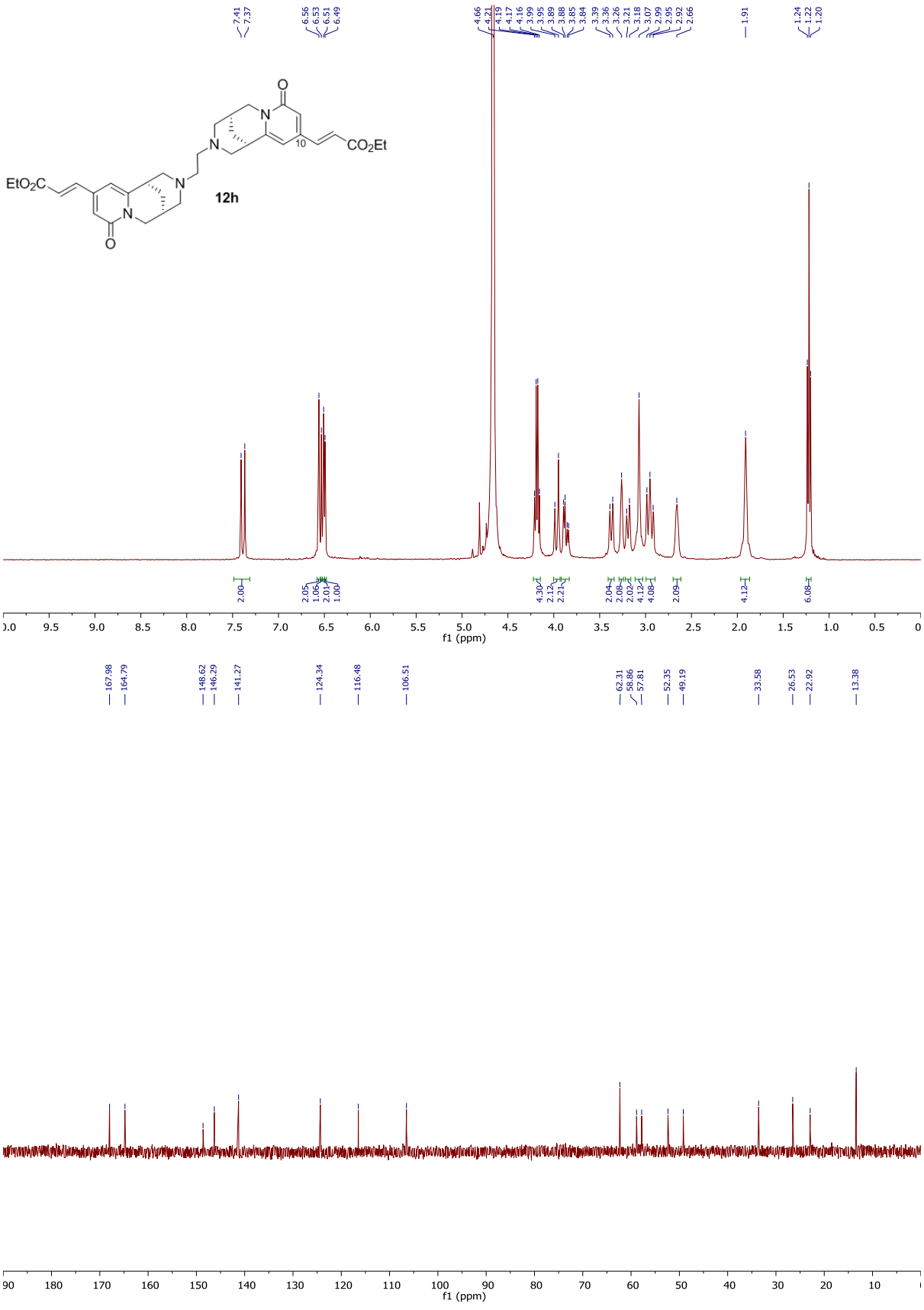
^{1}H and ^{13}C of derivative **12f**



^{1}H and ^{13}C of derivative **12g** (hydrochloride salt)



^{1}H and ^{13}C of derivative **12h** (hydrochloride salt)



^{1}H and ^{13}C of derivative **12i**