Supplementary Information

Development of CYP8B1-specific inhibitors for metabolic diseases

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Table of Contents

1. **General Information**……3

i) Solvents and reagents…….……..…3

ii) Reaction setup, progress monitoring, and product purification.....3

iii) Analytical instrumentation……...…..…3

2. **Chemical Syntheses and Product Characterizations**…….4

i) General procedure for the synthesis of pyrazolopyrimidinone intermediates.....4

ii) Synthesis and characterization of pyrazolopyrimidinone intermediates.....5

iii) General procedure for the synthesis of benzamide (benzylic chloride) intermediates.....7

iv) Synthesis and characterization of benzamide (benzylic chloride) intermediates.....8

v) General procedure for the synthesis of CYP8B1 inhibitors (8B1i-1 – 8B1i-7).....13

vi) Synthesis and characterization of CYP8B1 inhibitors (8B1i-1 – 8B1i-7).....13

3. **References**…….....24

4. **NMR Spectra**…….....25

1. General Information

i) Solvents and reagents

Commercial reagents and solvents were purchased from Sigma Aldrich, MilliporeSigma, Fisher Scientific, Enamine, Aaron Chemicals, Ambeed, and TCI, and used without additional purification. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF), diisopropylethylamine (DIPEA), and pyridine were purchased in Sure/Seal or AcroSeal bottling and dispensed under N_2. Deuterated chloroform ($CDCl_3$) (containing 0.03 vol.% of tetramethylsilane in the $CDCl_3$ bottle) was obtained from MilliporeSigma.

ii) Reaction setup, progress monitoring, and product purification

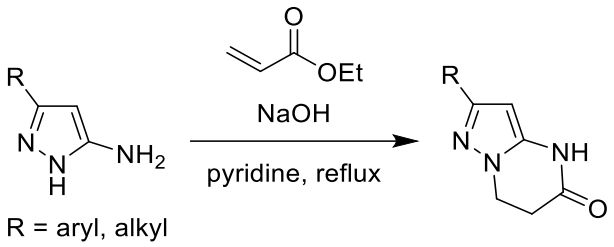
Chemical reactions were performed under ambient atmosphere unless otherwise specified. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using Merck 60 F254 aluminum-backed plates and visualized using UV light (254 nm) (and *para*-anisaldehyde stain). Purification and isolation of products were performed via silica gel column chromatography and/or recrystallization. Flash column chromatography was performed using Supelco silica gel (230–400 mesh). Organic solutions were concentrated under reduced pressure using a Buchi® rotatory evaporator equipped with a temperature-controlled water bath.

iii) Analytical instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were obtained on a Bruker Ascend (700 MHz) spectrometer. NMR spectra were obtained with a spectrometer temperature of 25 °C unless otherwise specified. Chemical shifts (δ) are referenced to the residual solvent signals ($CDCl_3$: δ_H 7.26, δ_C 77.16). Coupling constants are reported in Hz, and multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, qt = quartet of triplets, ddd = doublet of doublets of doublets, and br = broad. High-resolution mass spectrometry (HRMS) was performed using an Agilent 6545 LC/SFC Hybrid Q-TOF spectrometer. ^{1}H and ^{13}C peak assignments were verified by heteronuclear single quantum coherence (HSQC) and homonuclear correlation spectroscopy (COSY).

2. Chemical Syntheses and Product Characterizations

i) General procedure for the synthesis of pyrazolopyrimidinone intermediates



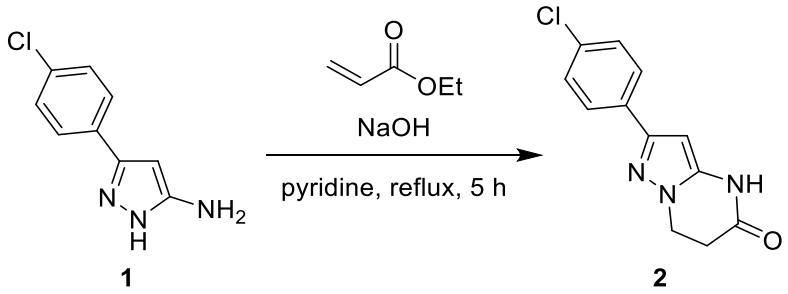
Using a modified procedure of Brenneman,[1] a stirred mixture of pyrazolylamine (1 equiv) and NaOH (3 equiv or greater) in pyridine was slowly added ethyl acrylate (1.2 equiv) at rt. The reaction mixture was then stirred under reflux for 2 h or longer. The remaining NaOH was removed by gravity filtration, and the reaction mixture was concentrated under reduced pressure. Workup and purification were performed by either *method A* or *method B*.

Method A: The crude material was acidified with 2% and/or 10% HCl (aq) to pH 4 and placed in an ice bath. The resulting solid precipitate was collected by vacuum filtration and purified by recrystallization and/or flash column chromatography to afford the desired product.

Method B: The crude material was acidified with 2% and/or 10% HCl (aq) to pH 4, and the aqueous solution was extracted with ethyl acetate (EtOAc, 4 x 3 mL). The organic layer was washed sequentially with water (3 mL) and brine (3 mL). The organic solution was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography (and recrystallization) to afford the desired product.

ii) Synthesis and characterization of pyrazolopyrimidinone intermediates

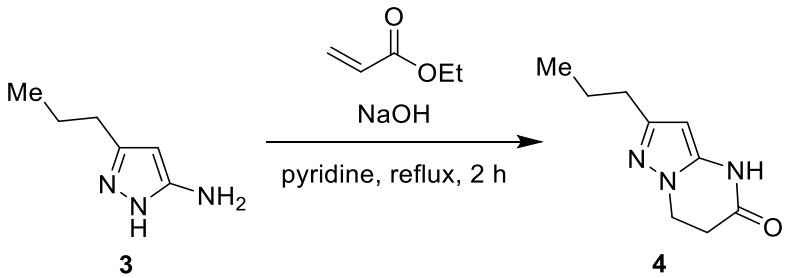
2-(*para*-Chlorophenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (*para*-chlorophenyl pyrazolopyrimidinone intermediate) (2)



1 **2**

To a stirred mixture of pyrazolylamine **1** (1.94 g, 10.0 mmol, 1 equiv) and NaOH (1.20 g, 30.0 mmol, 3 equiv) in pyridine (50 mL) was slowly added ethyl acrylate (1.3 mL, 12 mmol, 1.2 equiv) at rt. The reaction mixture was then stirred under reflux for 5 h. The remaining NaOH was removed by gravity filtration, and the reaction mixture was concentrated under reduced pressure. Using workup and purification method A, the crude material was acidified with 2% HCl (aq) (15 mL) followed by 10% HCl (aq) (2 mL) to pH 4 and placed in an ice bath. The resulting solid precipitate was collected by vacuum filtration and purified by recrystallization [ethanol (EtOH)] to afford a white solid **2** (1.48 g, 59%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.94 (br. s, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 5.97 (s, 1H), 4.40 (t, J = 7.1 Hz, 2H), 2.97 (t, J = 7.1 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 166.3, 150.8, 139.3, 134.1, 131.6, 129.0, 126.9, 87.3, 43.4, 31.3. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{12}H_{11}ClN_3O$: 248.0585. Found: 248.0588.

2-Propyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (propyl pyrazolopyrimidinone intermediate) (4)

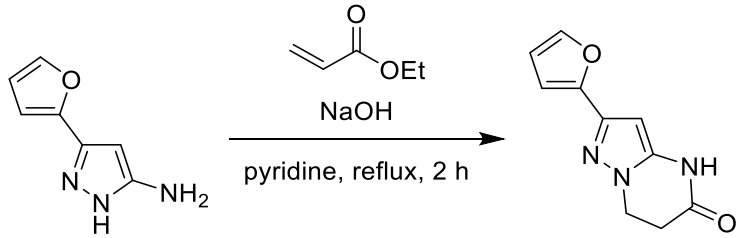


3 **4**

To a stirred mixture of pyrazolylamine **3** (125.2 mg, 1.000 mmol, 1 equiv) and NaOH (0.24 g, 6.0 mmol, 6 equiv) in pyridine (5 mL) was slowly added ethyl acrylate (0.13 mL, 1.2 mmol, 1.2 equiv) at rt. The reaction mixture was then stirred under reflux for 2 h. The

remaining NaOH was removed by gravity filtration, and the reaction mixture was concentrated under reduced pressure. Using workup and purification method B, the crude material was acidified with 2% HCl (aq) (2 mL) to pH 4, and the aqueous solution was extracted with EtOAc (4 x 3 mL). The organic layer was washed sequentially with water (3 mL) and brine (3 mL). The organic solution was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography [2% methanol (MeOH) in CH_2Cl_2] to afford a tan solid **4** (10.9 mg, 6%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.20 (br. s, 1H), 5.53 (s, 1H), 4.27 (t, J = 7.1 Hz, 2H), 2.90 (t, J = 7.1 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.63 (sext, J = 7.5 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.9, 154.2, 138.6, 89.1, 42.9, 31.3, 30.7, 22.8, 14.0. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_9H_{14}N_3O$: 180.1131. Found: 180.1143.

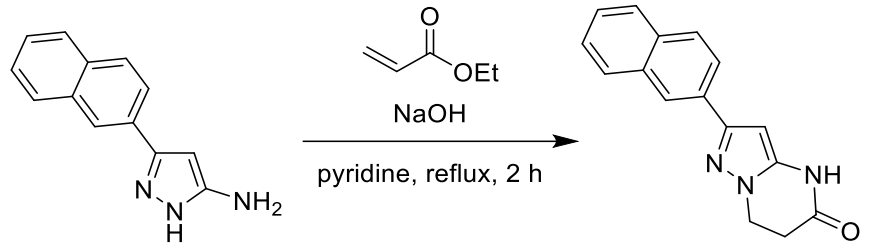
2-(Furan-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (furanyl pyrazolopyrimidinone intermediate) (6)



5 **6**

To a stirred mixture of pyrazolylamine **5** (149.2 mg, 1.000 mmol, 1 equiv) and NaOH (0.24 g, 6.0 mmol, 6 equiv) in pyridine (5 mL) was slowly added ethyl acrylate (0.13 mL, 1.2 mmol, 1.2 equiv) at rt. The reaction mixture was then stirred under reflux for 2 h. The remaining NaOH was removed by gravity filtration, and the reaction mixture was concentrated under reduced pressure. Using workup and purification method A, the crude material was acidified with 10% HCl (aq) (3 mL) to pH 4 and placed in an ice bath. The resulting solid precipitate was collected by vacuum filtration and purified by recrystallization (EtOH) to afford tan crystals **6** (112.6 mg, 55%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.03 (br. s, 1H), 7.44 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 3.4 Hz, 1H), 6.46 (dd, J = 3.3, 1.8 Hz, 1H), 5.93 (s, 1H), 4.39 (t, J = 7.1 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 166.8, 148.4, 144.4, 142.2, 139.0, 111.5, 106.3, 87.3, 43.4, 31.2. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{10}H_{10}N_3O_2$: 204.0768. Found: 204.0775.

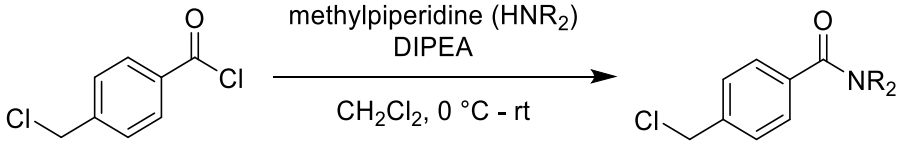
2-(Naphthalen-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (naphthyl pyrazolopyrimidinone intermediate) (8)



7 **8**

To a stirred mixture of pyrazolylamine **7** (209.3 mg, 1.000 mmol, 1 equiv) and NaOH (0.24 g, 6.0 mmol, 6 equiv) in pyridine (5 mL) was slowly added ethyl acrylate (0.13 mL, 1.2 mmol, 1.2 equiv) at rt. The reaction mixture was then stirred under reflux for 2 h. The remaining NaOH was removed by gravity filtration, and the reaction mixture was concentrated under reduced pressure. Using workup and purification method A, the crude material was acidified with 2% HCl (aq) (2 mL) followed by 10% HCl (aq) (0.5 mL) to pH 4 and placed in an ice bath. The resulting solid vacuum precipitate was collected by filtration and purified by recrystallization (EtOH) followed by gradient flash column chromatography (30 – 80% EtOAc in hexanes) to afford a white solid **8** (8.6 mg, 3%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.09 (br. s, 1H), 7.90 (dd, J = 8.6, 1.7 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.51 – 7.44 (m, 2H), 6.13 (s, 1H), 4.45 (t, J = 7.1 Hz, 2H), 3.00 (t, J = 7.1 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 166.7, 152.0, 139.3, 133.7, 133.5, 130.5, 128.5, 128.4, 127.9, 126.5, 126.2, 124.4, 123.8, 87.6, 43.5, 31.3. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{16}H_{14}N_3O$: 264.1131. Found: 264.1130.

iii) General procedure for the synthesis of benzamide (benzylic chloride) intermediates

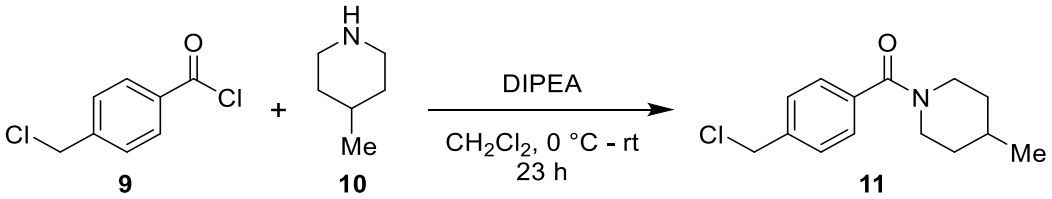


Using a modified procedure of Csakai,[2] an ice bath-cooled solution of *para*-(chloromethyl)benzoyl chloride (189.0 mg, 1.000 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.35 mL, 2.0 mmol, 2 equiv) followed by methylpiperidine (0.13 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred in the ice bath for 30 min and then at rt for 17 h or longer. The reaction mixture was washed sequentially with water (5 mL)

and brine (5 mL), and the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to afford the desired product.

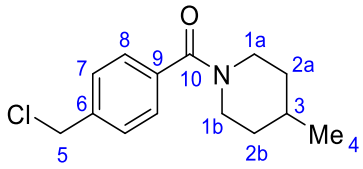
iv) Synthesis and characterization of benzamide (benzylic chloride) intermediates

(*para*-(Chloromethyl)phenyl)(4-methylpiperidin-1-yl)methanone [4-methylpiperidinyl benzamide (benzylic chloride)] (11)



9 **10** **11**

To an ice bath-cooled solution of *para*-(chloromethyl)benzoyl chloride **9** (189.0 mg, 1.000 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.35 mL, 2.0 mmol, 2 equiv) followed by 4-methylpiperidine **10** (0.13 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred in the ice bath for 30 min and then stirred at rt for 23 h. The reaction was sequentially washed with water (5 mL) and brine (5 mL), and the organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to afford a white solid **11** (184.9 mg, 73%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.66 (br. s, 1H), 4.59 (s, 2H), 3.68 (br. s, 1H), 2.97 (br. s, 1H), 2.76 (br. s, 1H), 1.75 (br. s, 1H), 1.68 – 1.62 (m, 1H), 1.59 (br. s, 1H), 1.22 (br. s, 1H), 1.09 (br. s, 1H), 0.97 (d, J = 6.5 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.8, 138.8, 136.7, 128.7, 127.4, 48.2, 45.8, 42.7, 34.9, 33.9, 31.3, 21.8. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}ClNO$: 252.1150. Found: 252.1162.

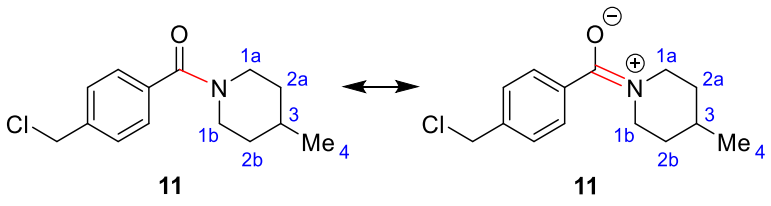


11

Experimental ^{1}H and ^{13}C NMR Data* at 25 °C for benzamide 11

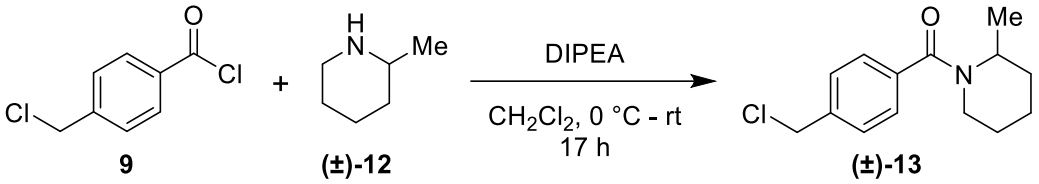
Assignment	^{13}C (δ)	^{1}H (δ)
1	48.2, 42.7	4.66 (br. s, 1H), 3.68 (br. s, 1H), 2.97 (br. s, 1H), 2.76 (br. s, 1H)
2	34.9, 33.9	1.75 (br. s, 1H), 1.59 (br. s, 1H), 1.22 (br. s, 1H), 1.09 (br. s, 1H)
3	31.3	1.68 – 1.62 (m, 1H)
4	21.8	0.97 (d, *J* = 6.5 Hz, 3H)
5	45.8	4.59 (s, 2H)
6	136.7	--
7	127.4	7.38 (d, *J* = 8.2 Hz, 2H)
8	128.7	7.41 (d, *J* = 8.1 Hz, 2H)
9	138.8	--
10	169.8	--

* Assignments here are based on HSQC. Due to hindered rotation along the amide C-N/=N bond, carbon 1a (C1a) and carbon 1b (C1b) are distinct from each other on the NMR timescale (**Scheme 1**). Similarly, C2a and C2b are also distinct from each other. As a result, C1 and C2 each appear as distinct signals in the ^{13}C NMR spectrum. On the other hand, H1 and H2 each appear as four broad singlets by ^{1}H NMR spectroscopy arising from their axial and equatorial positioning, as well as the rotational constraint by the amide CN double bond.



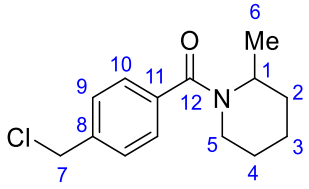
Scheme 1. Resonance structures of 4-methylpiperidinyl benzamide **11**.

(±)-(*para*-(Chloromethyl)phenyl)(2-methylpiperidin-1-yl)methanone [(±)-(2-methylpiperidinyl benzamide (benzylic chloride)] [(±)-13]



9 **(±)-12** **(±)-13**

To an ice bath-cooled solution of *para*-(chloromethyl)benzoyl chloride **9** (189.0 mg, 1.000 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.35 mL, 2.0 mmol, 2 equiv) followed by (±)-2-methylpiperidine **(±)-12** (0.13 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred in the ice bath for 30 min and then at rt for 17 h. The reaction mixture was sequentially washed with water (5 mL) and brine (5 mL), and the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to afford a white solid **(±)-13** (230.4 mg, 92%). ^{1}H NMR (700 MHz, $CDCl_3$, 40 °C): δ 7.41 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.59 (s, 2H), 4.28 (br. s, 2H), 2.99 (br. s, 1H), 1.74 – 1.62 (m, 4H), 1.53 (br. s, 1H), 1.47 (br. s, 1H), 1.24 (d, J = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$, 40 °C): δ 170.0, 138.6, 137.4, 128.8, 127.0, 45.8, 30.5, 26.2, 19.0, 16.3. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}ClNO$: 252.1150. Found: 252.1163.



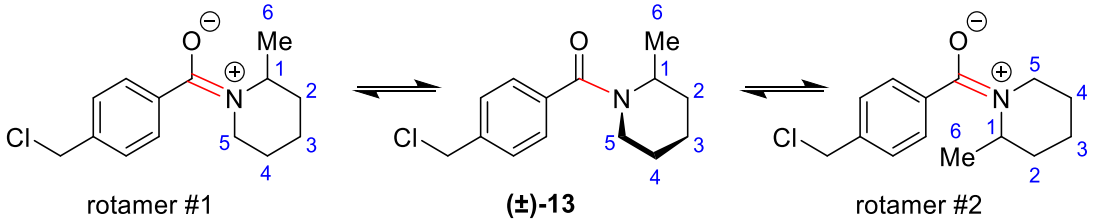
(±)-13

Experimental ^{1}H and ^{13}C NMR Data* at 40 °C for benzamide (±)-13

Assignment	^{13}C (δ)	^{1}H (δ)
1	†	4.28 (br. s, 1H)
2	30.5 or 26.2	1.74 – 1.62 (m, 1H), [1.53 (br. s, 1H) or 1.47 (br. s, 1H)]
3	19.0	1.74 – 1.62 (m, 2H)
4	30.5 or 26.2	1.74 – 1.62 (m, 1H), [1.53 (br. s, 1H) or 1.47 (br. s, 1H)]
5	†	4.28 (br. s, 1H), 2.99 (br. s, 1H)

6	16.3	1.24 (d, *J* = 6.9 Hz, 3H)
7	45.8	4.59 (s, 2H)
8	137.4	--
9	127.0	7.35 (d, *J* = 8.1 Hz, 2H)
10	128.8	7.41 (d, *J* = 8.2 Hz, 2H)
11	138.6	--
12	170.0	--

* Assignments here are based on HSQC and COSY. Correlations between hydrogens and carbons for assignments 1 and 5 are not detected by HSQC at 40 °C, but they are observed at 10 °C. Peaks appear as broad singlets by ^{1}H NMR due to unresolved rotameric mixtures on the NMR timescale (**Scheme 2**). The ^{1}H and ^{13}C NMR spectra at 10 °C are also included underneath the spectra recorded at 40 °C (see page S39-41).
† Signal is not observed in ^{13}C NMR spectrum at 40 °C due to severe broadening by quadrupolar coupling.



Scheme 2. Rotameric equilibrium of 2-methylpiperidinyl benzamide **(±)-13**.

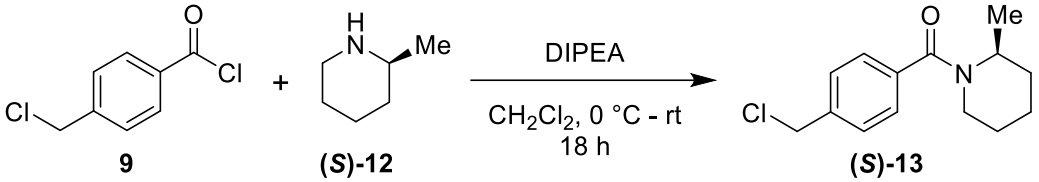
Experimental ^{1}H and ^{13}C NMR Data* at 10 °C for benzamide (±)-13

Assignment	**^{13}C (δ)**	**^{1}H (δ)**
1	50.5, 44.3	5.01 (br. s, 0.5H), 3.96 (br. s, 0.5H)
2	(30.8, 30.0) or (26.4, 25.8)	1.77 – 1.10 (br. m, 2H)
3	19.0	1.77 – 1.10 (br. m, 2H)
4	(30.8, 30.0) or (26.4, 25.8)	1.77 – 1.10 (br. m, 2H)
5	43.1, 36.9	4.56 (br. s, 0.5H), 3.49 (br. s, 0.5H), 3.08 (br. s, 0.5H), 2.89 (br. s, 0.5H)
6	16.8, 15.8	1.23 (br. s, 3H)
7	45.8	4.59 (s, 2H)
8	137.2	--

9	127.1, 126.8	7.35 (d, *J* = 7.8 Hz, 2H)
10	128.8	7.41 (d, *J* = 7.8 Hz, 2H)
11	138.5	--
12	170.0	--

* Assignments here are based on HSQC and COSY. C1, C2, C4, C5, C6, and C9 each appear as two peaks in the ^{13}C NMR due to unresolved rotameric mixtures. There is a 1:1.1 rotameric mixture based on ^{1}H NMR.

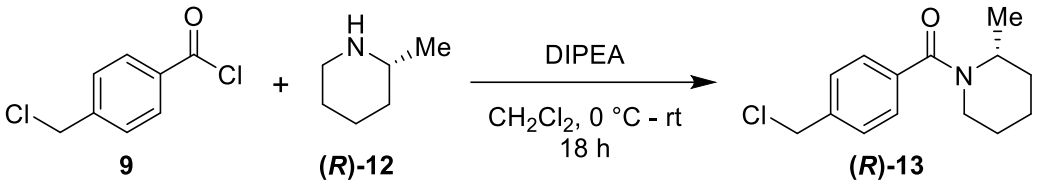
(*S*)-(*para*-(Chloromethyl)phenyl)(2-methylpiperidin-1-yl)methanone [(*S*)-(2-methylpiperidinyl benzamide (benzylic chloride)] [(*S*)-13]



9 **(*S*)-12** **(*S*)-13**

To an ice bath-cooled solution of *para*-(chloromethyl)benzoyl chloride (189.0 mg, 1.000 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.35 mL, 2.0 mmol, 2 equiv) followed by (*S*)-2-methylpiperidine **(*S*)-12** (0.13 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred in the ice bath for 30 min and then at rt for 18 h. The reaction mixture was sequentially washed with water (5 mL) and brine (5 mL), and the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to afford a white solid **(*S*)-13** (219.6 mg, 87%). The spectroscopic data for this enantiomer were consistent with the racemic mixture.

(*R*)-(*para*-(Chloromethyl)phenyl)(2-methylpiperidin-1-yl)methanone (2-methylpiperidinyl benzamide (benzylic chloride)] [(*R*)-13]

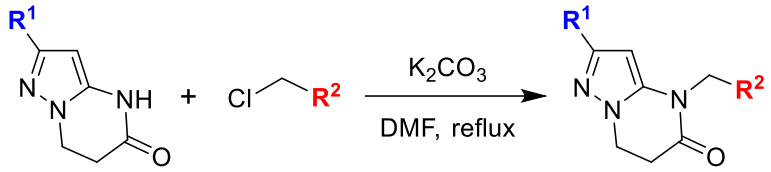


9 **(*R*)-12** **(*R*)-13**

To an ice bath-cooled solution of *para*-(chloromethyl)benzoyl chloride (189.0 mg, 1.000 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.35 mL, 2.0 mmol, 2 equiv) followed by (*R*)-2-methylpiperidine **(*R*)-12** (0.13 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred in the ice bath for 30 min and then at rt for 18 h. The reaction mixture

was sequentially washed with water (5 mL) and brine (5 mL), and the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to afford a white solid **(*R*)-13** (185.3 mg, 73%). The spectroscopic data for this enantiomer were consistent with the racemic mixture.

v) General procedure for the synthesis of CYP8B1 inhibitors (8B1i-1 – 8B1i-7)

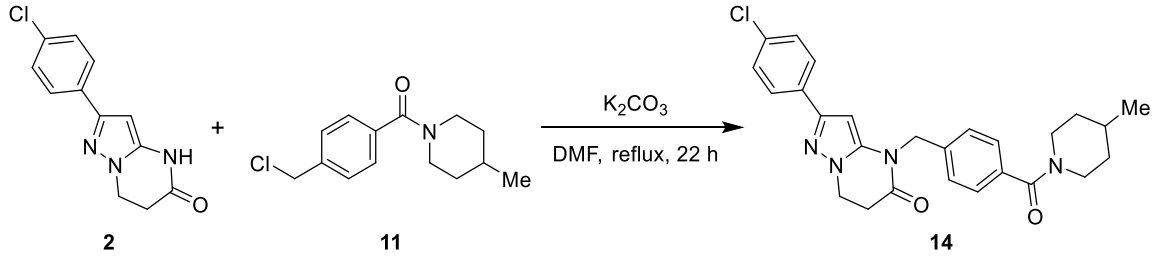


R^1 = aryl, alkyl
R^2 = aryl

Using a modified procedure of Brenneman[1] and Guerrini[3], a mixture of pyrazolopyrimidinone (1 equiv), benzylic chloride (1 equiv or excess), and potassium carbonate (excess) in DMF was stirred under reflux for 15 h or longer. Upon cooling to rt, the reaction mixture was added water and cooled in an ice bath to induce precipitation. The crude solid was collected by vacuum filtration and purified by recrystallization and/or column chromatography to afford the desired product.

vi) Synthesis and characterization of CYP8B1 inhibitors (8B1i-1 – 8B1i-7)

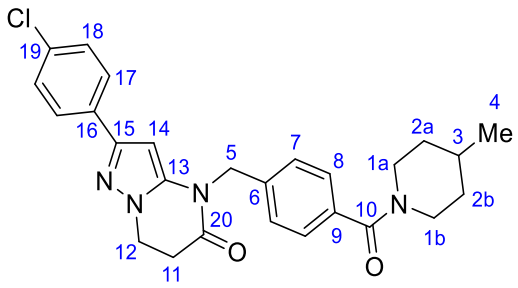
2-(*para*-Chlorophenyl)-4-(4-(4-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-1) (14)



2 **11** **14**

A mixture of pyrazolopyrimidinone **2** (297 mg, 1.20 mmol, 1 equiv), benzylic chloride **11** (317 mg, 1.26 mmol, 1.05 equiv), and potassium carbonate (232 mg, 1.68 mmol, 1.4 equiv) in DMF (10 mL) was stirred under reflux for 22 h. Upon cooling to rt, the reaction mixture was added water (20 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by recrystallization

(EtOH/water) to afford a white solid **14** (533 mg, 96%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.28 (m, 4H), 5.91 (s, 1H), 4.99 (s, 2H), 4.63 (br. s, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.67 (br. s, 1H), 3.06 (t, *J* = 7.1 Hz, 2H), 2.95 (br. s, 1H), 2.74 (br. s, 1H), 1.74 (br. s, 1H), 1.66 – 1.59 (br. m, 1H), 1.56 (br. s, 1H), 1.21 (br. s, 1H), 1.07 (br. s, 1H), 0.95 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.8, 165.3, 150.5, 142.2, 137.2, 136.3, 134.0, 131.4, 128.9, 127.6, 127.3, 126.8, 88.4, 48.2, 47.4, 43.4, 42.6, 34.9, 33.9, 31.7, 31.2, 21.8. HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{26}H_{28}ClN_4O_2$: 463.1895. Found: 463.1901.



14

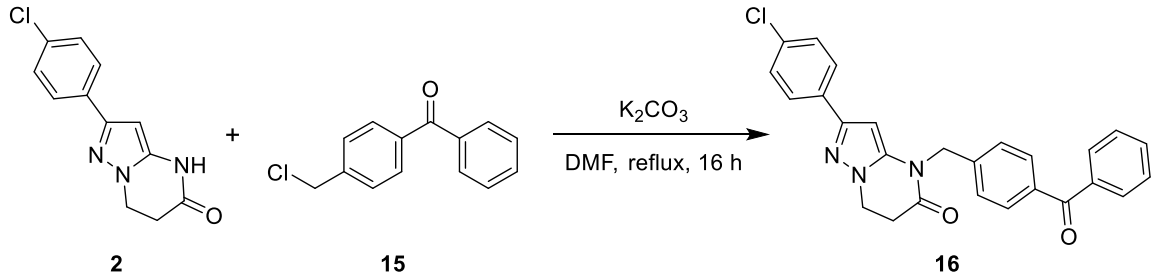
Experimental ^{1}H and ^{13}C NMR Data* at 25 °C for 8B1i-1 (14)

Assignment	^{13}C (δ)	^{1}H (δ)
1	48.2, 42.6	4.63 (br. s, 1H), 3.67 (br. s, 1H), 2.95 (br. s, 1H), 2.74 (br. s, 1H)
2	34.9, 33.9	1.74 (br. s, 1H), 1.56 (br. s, 1H), 1.21 (br. s, 1H), 1.07 (br. s, 1H)
3	31.7	1.66 – 1.59 (br. m, 1H)
4	21.8	0.95 (d, *J* = 6.5 Hz, 3H)
5	43.4	4.99 (s, 2H)
6	136.3	--
7	128.9, 127.6, 127.4, or 126.8	7.34 – 7.28 (m, 2H)
8	128.9, 127.6, 127.4, or 126.8	7.36 (d, *J* = 8.1 Hz, 2H)
9	137.2	--
10	169.8	--
11	31.2	3.06 (t, *J* = 7.1 Hz, 2H)

12	47.4	4.39 (t, *J* = 7.1 Hz, 2H)
13	150.5	--
14	88.4	5.91 (s, 1H)
15	142.2	--
16	131.4	--
17	128.9, 127.6, 127.4, or 126.8	7.62 (d, *J* = 8.5 Hz, 2H)
18	128.9, 127.6, 127.4, or 126.8	7.34 – 7.28 (m, 2H)
19	134.0	--
20	165.3	--

* Assignments are based on the 1D and 2D NMR data of the starting materials.

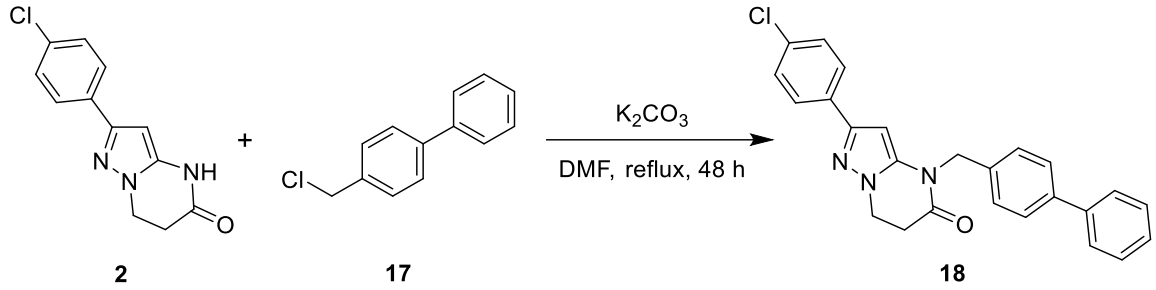
4-(4-Benzoylbenzyl)-2-(*para*-chlorophenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-2) (16)



2 **15** **16**

A mixture of pyrazolopyrimidinone **2** (12.4 mg, 0.0500 mmol, 1 equiv), benzylic chloride **15** (12.7 mg, 0.0550 mmol, 1.1 equiv), and potassium carbonate (10.0 mg, 0.0723 mmol, 1.4 equiv) in DMF (1 mL) was stirred under reflux for 16 h. Upon cooling to rt, the reaction mixture was added water (2 mL) and cooled in an ice bath to induce precipitation. The crude solid was collected by vacuum filtration and purified by recrystallization (EtOH) to afford a white solid **16** (15.3 mg, 69%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.82 – 7.75 (m, 4H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.92 (s, 1H), 5.08 (s, 2H), 4.43 (t, *J* = 7.1 Hz, 2H), 3.10 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 196.2, 165.4, 150.7, 142.3, 140.4, 137.5, 137.4, 134.1, 132.7, 131.4, 130.8, 130.2, 129.0, 128.5, 127.2, 126.8, 88.4, 47.5, 43.5, 31.8. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{26}H_{21}ClN_3O_2$: 442.1317. Found: 442.1312.

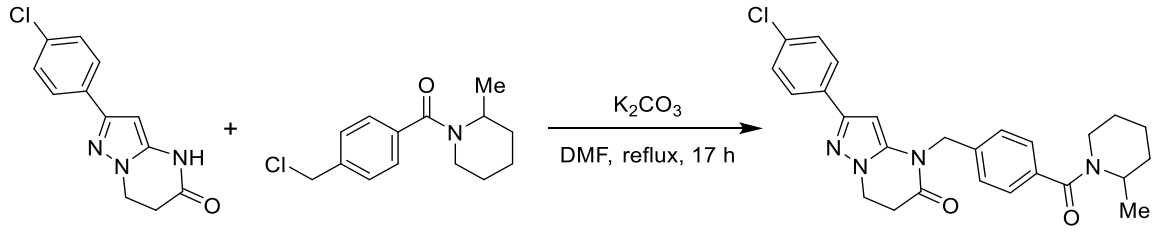
4-([1,1'-Biphenyl]-4-ylmethyl)-2-(*para*-chlorophenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-3) (18)



2 **17** **18**

A mixture of pyrazolopyrimidinone **2** (12.4 mg, 0.0500 mmol, 1 equiv), benzylic chloride **17** (16.2 mg, 0.0800 mmol, 1.6 equiv), and potassium carbonate (14.8 mg, 0.107 mmol, 2.1 equiv) in DMF (1 mL) was stirred under reflux for 48 h. Upon cooling to rt the reaction mixture was added water (2 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by recrystallization (EtOH) to afford a white solid **18** (20.3 mg, 98%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.64 (d, J = 8.6 Hz, 2H), 7.58 – 7.54 (m, 4H), 7.43 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.36 – 7.32 (m, 3H), 5.98 (s, 1H), 5.04 (s, 2H), 4.42 (t, J = 7.1 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 165.3, 150.6, 142.5, 141.1, 140.7, 134.9, 134.0, 131.5, 129.0*, 127.9, 127.7, 127.6, 127.2, 126.8, 88.5, 47.5, 43.5, 31.8. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{25}H_{21}ClN_3O$: 414.1368. Found: 414.1370.

(±)-2-(*para*-Chlorophenyl)-4-(4-(2-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-4] [(±)-19]

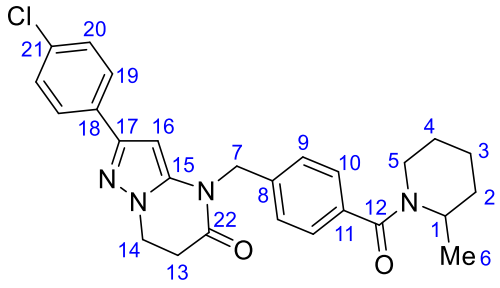


2 **(±)-13** **(±)-19**

A mixture of pyrazolopyrimidinone **2** (1.06 g, 4.27 mmol, 1 equiv), benzylic chloride **(±)-13** (1.13 g, 4.49 mmol, 1.05 equiv), and potassium carbonate (0.83 g, 6.0 mmol, 1.4 equiv) in DMF (30 mL) was stirred under reflux for 17 h. Upon cooling to rt, the reaction

* ^{13}C NMR spectrum shows one less expected aromatic carbon peak. HSQC shows two overlapping carbon peaks at 129.0 ppm correlating to two nonequivalent sets of hydrogens.

mixture was added water (60 mL) and cooled in an ice bath to induce precipitation. The crude solid was collected by vacuum filtration and purified by recrystallization (EtOH) to afford a white solid **(±)-19** (1.62 g, 86%). ^{1}H NMR (700 MHz, $CDCl_3$, 40 °C): δ 7.62 (d, J = 8.4 Hz, 2H), 7.36 – 7.29 (m, 6H), 5.91 (s, 1H), 4.99 (s, 2H), 4.39 (t, J = 7.1 Hz, 2H), 4.12 (br. s, 2H), 3.05 (t, J = 7.1 Hz, 2H), 2.97 (br. s, 1H), 1.72 – 1.60 (br. m, 4H), 1.55 (br. s, 1H), 1.44 (br. s, 1H), 1.21 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$, 40 °C): δ 170.0, 165.3, 150.6, 142.3, 137.0, 136.9, 134.0, 131.5, 128.9, 127.4, 127.2, 126.8, 88.4, 47.4, 43.5, 31.7, 30.5, 26.2, 19.0, 16.3. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{26}H_{28}ClN_4O_2$: 463.1895. Found: 463.1907.



(±)-19

Experimental ^{1}H and ^{13}C NMR Data* at 40 °C for (±)-8B1i-4 [(±)-19]

Assignment	^{13}C (δ)	^{1}H (δ)
1	†	4.12 (br. s, 1H)
2	30.5 or 26.2	1.72 – 1.62 (m, 1H), [1.55 (br. s, 1H) or 1.44 (br. s, 1H)]
3	19.0	1.72 – 1.62 (m, 2H)
4	30.5 or 26.2	1.72 – 1.62 (m, 1H), [1.55 (br. s, 1H) or 1.44 (br. s, 1H)]
5	†	4.12 (br. s, 1H), 2.97 (br. s, 1H)
6	16.3	1.21 (d, J = 7.0 Hz, 3H)
7	47.4	4.99 (s, 2H)
8	137.0, 136.9, 134.0, or 131.5	--
9	128.9, 127.4, or 127.2	7.36 – 7.29 (m, 2H)

10	128.9, 127.4, or 127.2	7.36 – 7.29 (m, 2H)
11	137.0, 136.9, 134.0, or 131.5	--
12	170.0	--
13	31.7	3.05 (t, *J* = 7.1 Hz, 2H)
14	43.5	4.39 (t, *J* = 7.1 Hz, 2H)
15	150.6	--
16	88.4	5.91 (s, 1H)
17	142.3	--
18	137.0, 136.9, 134.0, or 131.5	--
19	126.8	7.62 (d, *J* = 8.4 Hz, 2H)
20	128.9, 127.4, or 127.2	7.36 – 7.29 (m, 2H)
21	137.0, 136.9, 134.0, or 131.5	--
22	165.3	--

* Assignments are supported by HSQC and COSY. Correlations between hydrogens and carbons for assignments 1 and 5 are not detected by HSQC at 40 °C, but they are observed at 10 °C. Signals appear as broad singlets in the ^{1}H NMR spectrum due to unresolved rotameric mixtures on the NMR timescale. The ^{1}H and ^{13}C NMR spectra at 10 °C are also included underneath the spectra recorded at 40 °C (see page S55-56).
† Signal is not observed by ^{13}C NMR spectroscopy at 40 °C due to severe broadening by quadrupolar coupling.

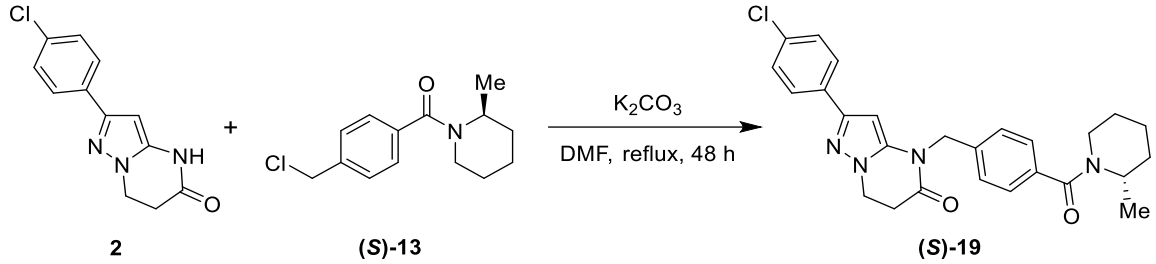
Experimental ^{1}H and ^{13}C NMR Data* at 10 °C for (±)-8B1i-4 [(±)-19]

Assignment	^{13}C (δ)	^{1}H (δ)
1	50.3, 44.3	4.98 (br. s, 0.5H), 3.94 (br. s, 0.5H)
2	(30.7, 29.9) or (26.4, 25.7)	1.76 – 1.33 (br. m, 2H)
3	18.9	1.76 – 1.33 (br. m, 2H)
4	(30.7, 29.9) or (26.4, 25.7)	1.76 – 1.33 (br. m, 2H)

5	43.1, 36.8	4.52 (br. s, 0.5H), 3.46 (br. s, 0.5H), 3.06 (br. s, 0.5H), 2.86 (br. s, 0.5H)
6	16.8, 15.7	1.20 (br. s, 3H)
7	47.3	4.98 (s, 2H)
8	136.8, 136.6, 133.9, or 131.2	--
9	127.2, 126.8	7.37 – 7.27 (m, 2H)
10	128.9	7.37 – 7.27 (m, 2H)
11	136.8, 136.6, 133.9, or 131.2	--
12	169.9	--
13	31.6	3.06 (t, J = 7.0 Hz, 2H)
14	43.3	4.39 (t, J = 7.0 Hz, 2H)
15	150.4	--
16	88.4	5.91 (s, 1H)
17	142.1	--
18	136.8, 136.6, 133.9, or 131.2	--
19	126.7	7.61 (d, J = 8.3 Hz, 2H)
20	127.3	7.37 – 7.27 (m, 2H)
21	136.8, 136.6, 133.9, or 131.2	--
22	165.3	--

* Assignments are supported by HSQC and COSY. C1, C2, C4, C5, C6, and C9 each appear as two signals in the ^{13}C NMR spectrum due to unresolved signals arising from the rotameric species.

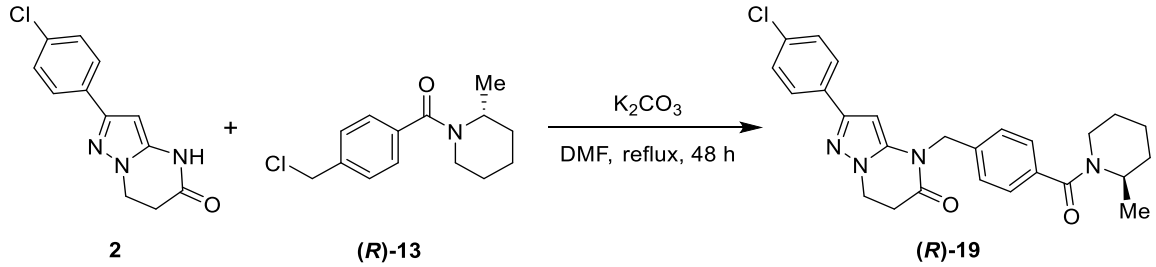
(*S*)-2-(*para*-Chlorophenyl)-4-(4-(2-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(*S*)-8B1i-4] [(*S*)-19]



2 **(*S*)-13** **(*S*)-19**

A mixture of pyrazolopyrimidinone **2** (24.8 mg, 0.100 mmol, 1 equiv), benzylic chloride **(*S*)-13** (35.3 mg, 0.140 mmol, 1.4 equiv), and potassium carbonate (24.8 mg, 0.180 mmol, 1.8 equiv) in DMF (2 mL) was stirred under reflux for 48 h. Upon cooling to rt, the reaction mixture was added water (4 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by flash column chromatography (40 – 80% EtOAc in hexanes) to afford a white solid **(*S*)-19** (38.3 mg, 83%). The spectroscopic data for this enantiomer were consistent with the racemic mixture.

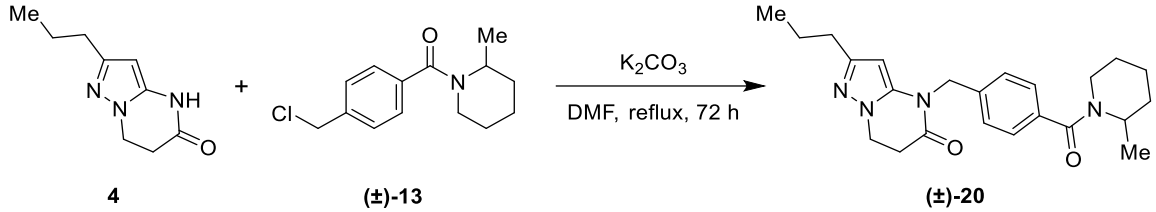
(*R*)-2-(*para*-Chlorophenyl)-4-(4-(2-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(*R*)-8B1i-4] [(*R*)-19]



2 **(*R*)-13** **(*R*)-19**

A mixture of pyrazolopyrimidinone **2** (24.8 mg, 0.100 mmol, 1 equiv), benzylic chloride **(*R*)-13** (35.3 mg, 0.140 mmol, 1.4 equiv), and potassium carbonate (24.8 mg, 0.180 mmol, 1.8 equiv) in DMF (2 mL) was stirred under reflux for 48 h. Upon cooling to rt, the reaction mixture was added water (4 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by flash column chromatography (40 – 80% EtOAc in hexanes) to afford a white solid **(*R*)-19** (46.0 mg, 99%). The spectroscopic data for this enantiomer were consistent with the racemic mixture.

(±)-4-(4-(2-Methylpiperidine-1-carbonyl)benzyl)-2-propyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-5] [(±)-20]

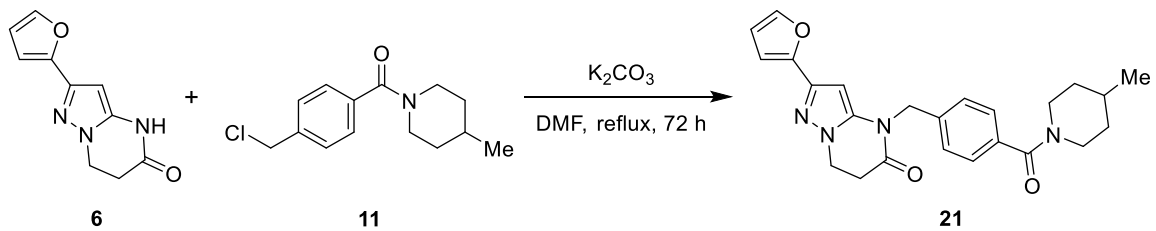


4 **(±)-13** **(±)-20**

A mixture of pyrazolopyrimidinone **4** (10.2 mg, 0.0569 mmol, 1 equiv), benzylic chloride **(±)-13** (37.2 mg, 0.148 mmol, 2.6 equiv), and potassium carbonate (27.5 mg, 0.200 mmol, 3.5 equiv) in DMF (1 mL) was stirred under reflux for 72 h. Upon cooling to rt, the reaction mixture was added water (2 mL) and then let to evaporate to dryness. The resulting crude solid was purified by gradient flash column chromatography (1 – 2% MeOH in CH_2Cl_2) to afford a white solid **(±)-20** (21.7 mg, 97%). ^{1}H NMR (700 MHz, $CDCl_3$, 40 °C): δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.45 (s, 1H), 4.93 (s, 2H), 4.28 (t, *J* = 7.1 Hz, 2H), 4.20 (br. s, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.97 (br. s, 1H), 2.48 (t, *J* = 7.6 Hz, 2H), 1.72 – 1.63 (m, 4H), 1.61 (sext, *J* = 7.4 Hz, 2H), 1.52 (br. s, 1H), 1.45 (br. s, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$, 40 °C): δ 170.2, 165.6, 154.0, 141.5, 137.3, 136.8, 127.5, 127.1, 90.2, 47.4, 43.1, 31.9, 30.8, 30.5, 26.2, 22.8, 19.1, 16.3, 14.0.* HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{23}H_{31}N_4O_2$: 395.2442. Found: 395.2458.

* There are 21 signals expected in the ^{13}C NMR spectrum; however, only 19 signals are present. The missing two signals correspond to the CH_2 and CH adjacent to the amide nitrogen of the piperidinyl ring. These two carbons are also not observed in the ^{13}C NMR spectrum at 40 °C for the 2-methylpiperidinyl benzamide (benzylic chloride) **(±)-13** and (±)-8B1i-4 [**(±)-19**].

2-(Furan-2-yl)-4-(4-(4-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-6) (21)

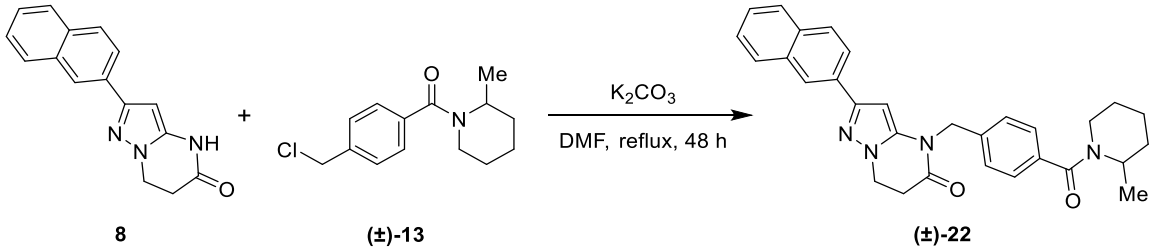


6 **11** **21**

A mixture of pyrazolopyrimidinone **6** (10.2 mg, 0.0500 mmol, 1 equiv), benzylic chloride **11** (17.6 mg, 0.0700 mmol, 1.4 equiv), and potassium carbonate (14.1 mg, 0.102 mmol, 2

equiv) in DMF (1 mL) was stirred under reflux for 72 h. Upon cooling to rt, the reaction mixture was added water (1 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford a pale-yellow solid **21** (18.7 mg, 89%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.44 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.89 (s, 1H), 4.98 (s, 2H), 4.64 (br. s, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.67 (br. s, 1H), 3.05 (t, *J* = 7.1 Hz, 2H), 2.95 (br. s, 1H), 2.74 (br. s, 1H), 1.74 (br. s, 1H), 1.65 – 1.60 (br. m, 1H), 1.57 (br. s., 1H), 1.21 (br. s., 1H), 1.08 (s, 1H), 0.96 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.9, 165.3, 148.2, 144.1, 142.2, 141.9, 137.1, 136.3, 127.6, 127.5, 111.5, 106.2, 88.4, 48.2, 47.4, 43.4, 42.7, 34.9, 33.9, 31.7, 31.3, 21.8. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{24}H_{27}N_4O_3$: 419.2078. Found: 419.2097.

(±)-4-(4-(2-Methylpiperidine-1-carbonyl)benzyl)-2-(naphthalen-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-7] [(±)-22]



8 **(±)-13** **(±)-22**

A mixture of pyrazolopyrimidinone **8** (8.6 mg, 0.033 mmol, 1 equiv), benzylic chloride **(±)-13** (10.2 mg, 0.0405 mmol, 1.2 equiv), and potassium carbonate (7.7 mg, 0.056 mmol, 1.7 equiv) in DMF (0.8 mL) was stirred under reflux for 48 h. Upon cooling to rt, the reaction mixture was added water (2 mL) and cooled in an ice bath to induce formation of a solid. The crude solid was collected by vacuum filtration and purified by gradient flash column chromatography (40 – 80% EtOAc in hexanes) to afford a white solid **(±)-22** (4.7 mg, 30%). ^{1}H NMR (700 MHz, $CDCl_3$, 40 °C): δ 8.14 (s, 1H), 7.90 – 7.84 (m, 3H), 7.82 (d, *J* = 6.9 Hz, 1H), 6.10 (s, 1H), 5.05 (s, 2H), 4.46 (t, *J* = 7.1 Hz, 2H), 4.29 (br. s, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.24 (br. s, 1H), 1.71 – 1.62 (m, 4H), 1.52 (br. s, assumed 1H*), 1.45 (br. s), 1.22 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$, 40 °C): δ 170.1, 165.4, 151.8, 142.4, 137.1, 136.9, 133.7, 133.5, 130.4, 128.5, 128.4, 127.9,

127.5, 127.3, 126.5, 126.2, 124.4, 123.8, 88.8, 47.6, 43.6, 31.9, 30.5, 26.2, 19.1, 16.4.[†]

HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{30}H_{31}N_4O_2$: 479.2442. Found: 479.2450.

[*] This data is supported by HSQC analysis.
[†] There are 28 signals expected in the ^{13}C NMR spectrum; however, only 26 signals are present. The missing two signals correspond to the CH_2 and CH adjacent to the amide nitrogen of the piperidinyl ring. These two carbons are also not observed in the ^{13}C NMR spectrum at 40 °C for the 2-methylpiperidinyl benzamide (benzylic chloride) **(±)-13** and (±)-8B1i-4 [**(±)-19**].

3. References

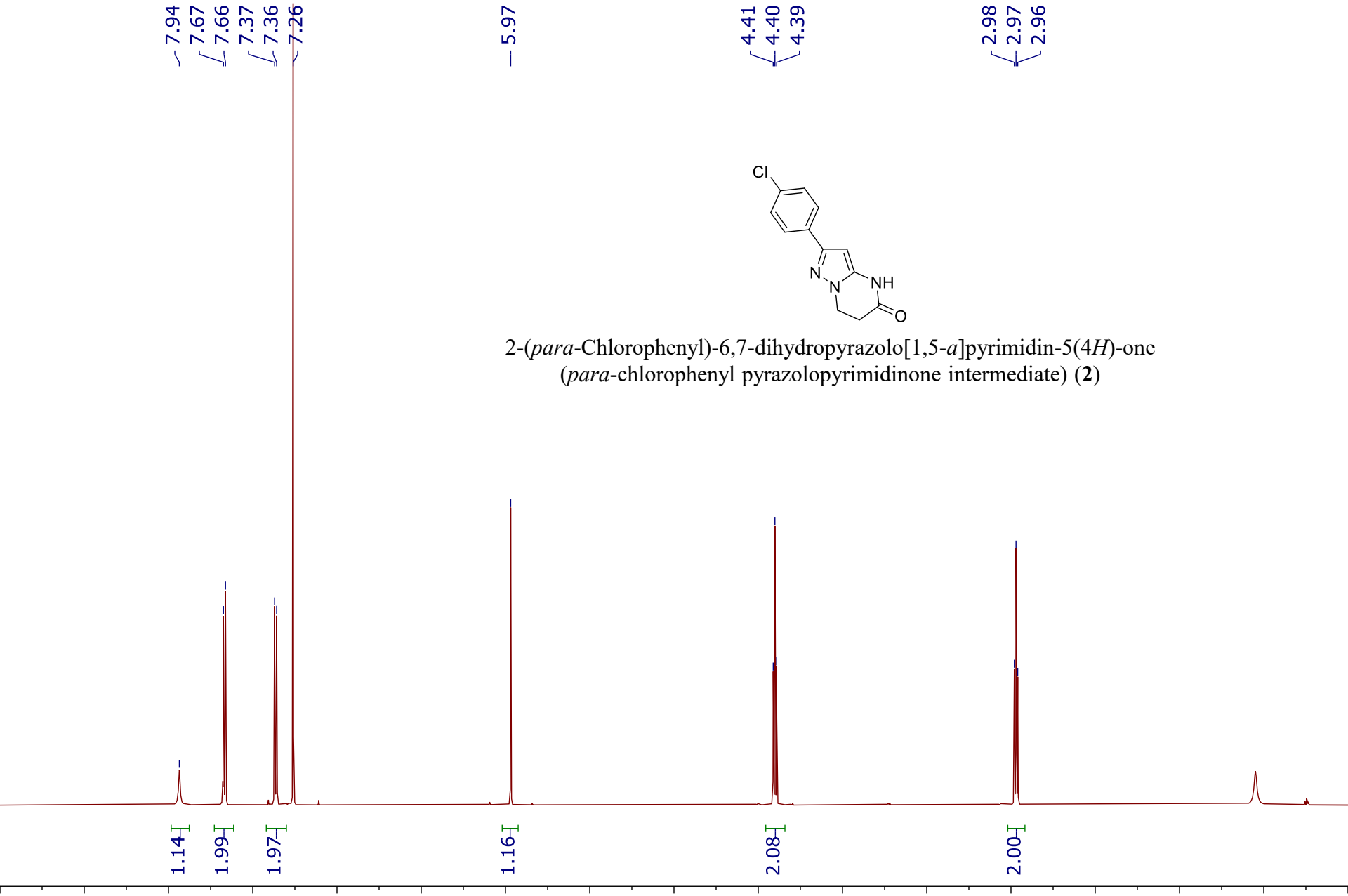
1) Brenneman, J. B., Bonafoux, D., and Feutrill, J. Nitrogen-containing fused bicyclic compounds and their use as ubiquitin-specific-processing protease 1 (USP1) inhibitors. Patent WO 2021247606, December 9, 2021.

2) Csakai, A., Smith, C., Davis, E., Martinko, A., Coulup, S., and Yin, H. Saccharin derivatives as inhibitors of interferon-mediated inflammation. *J. Med. Chem.* **57**, 5348–5355 (2014).

3) Guerrini, G., Ciciani, G., Ciattini, S., Crocetti, L., Daniele, S., Martini, C., Melani, F., Vergelli, C., and Giovannoni, M. P. Pyrazolo[1,5-a]quinazoline scaffold as 5-deaza analogue of pyrazolo[5,1-c][1,2,4]benzotriazine system: Synthesis of new derivatives, biological activity on $GABA_A$ receptor subtype and molecular dynamic study. *J. Enzyme Inhib. Med. Chem.* **31**, 195–204 (2016).

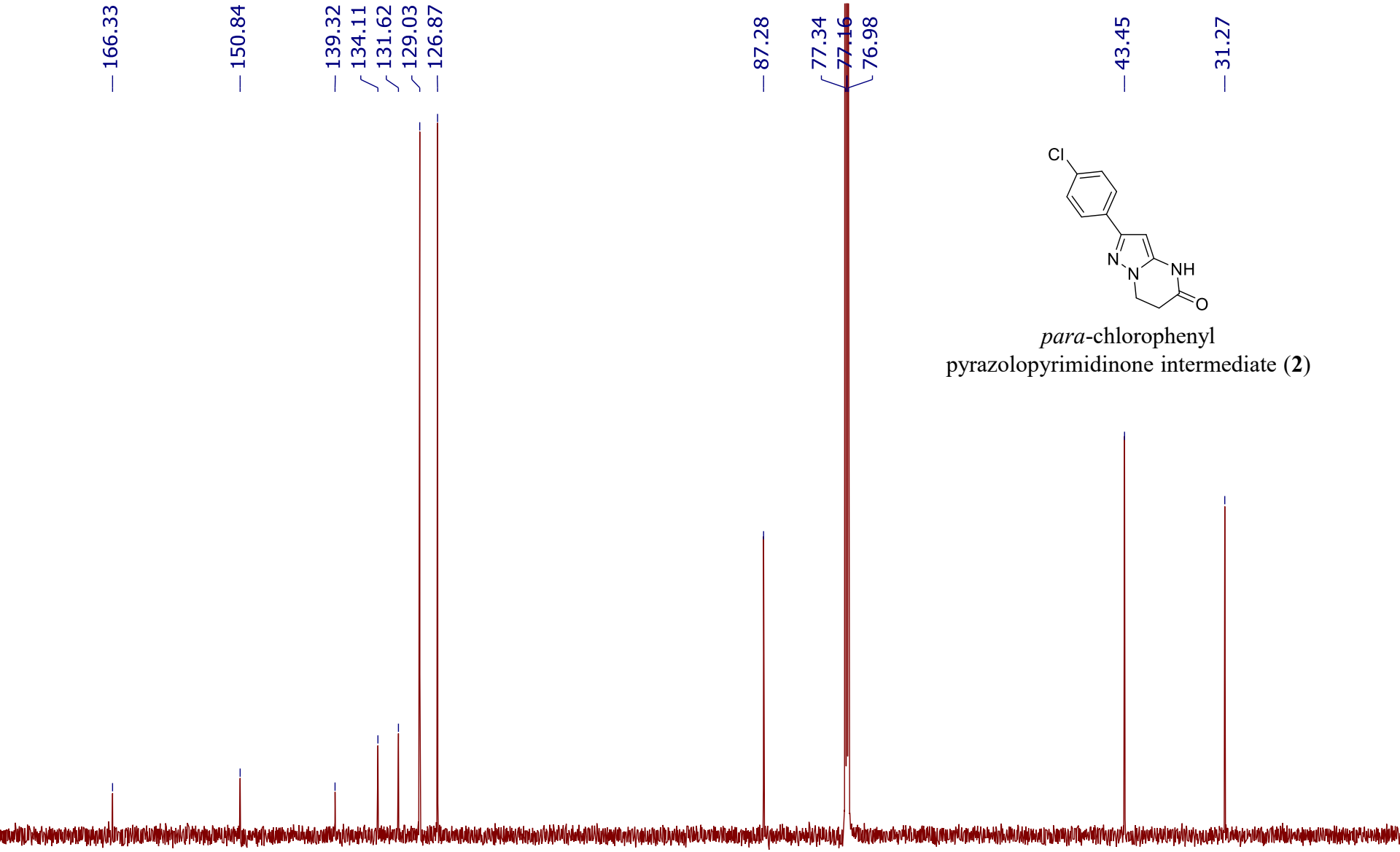
4. NMR Spectra

^{1}H, 700 MHz, $CDCl_3$



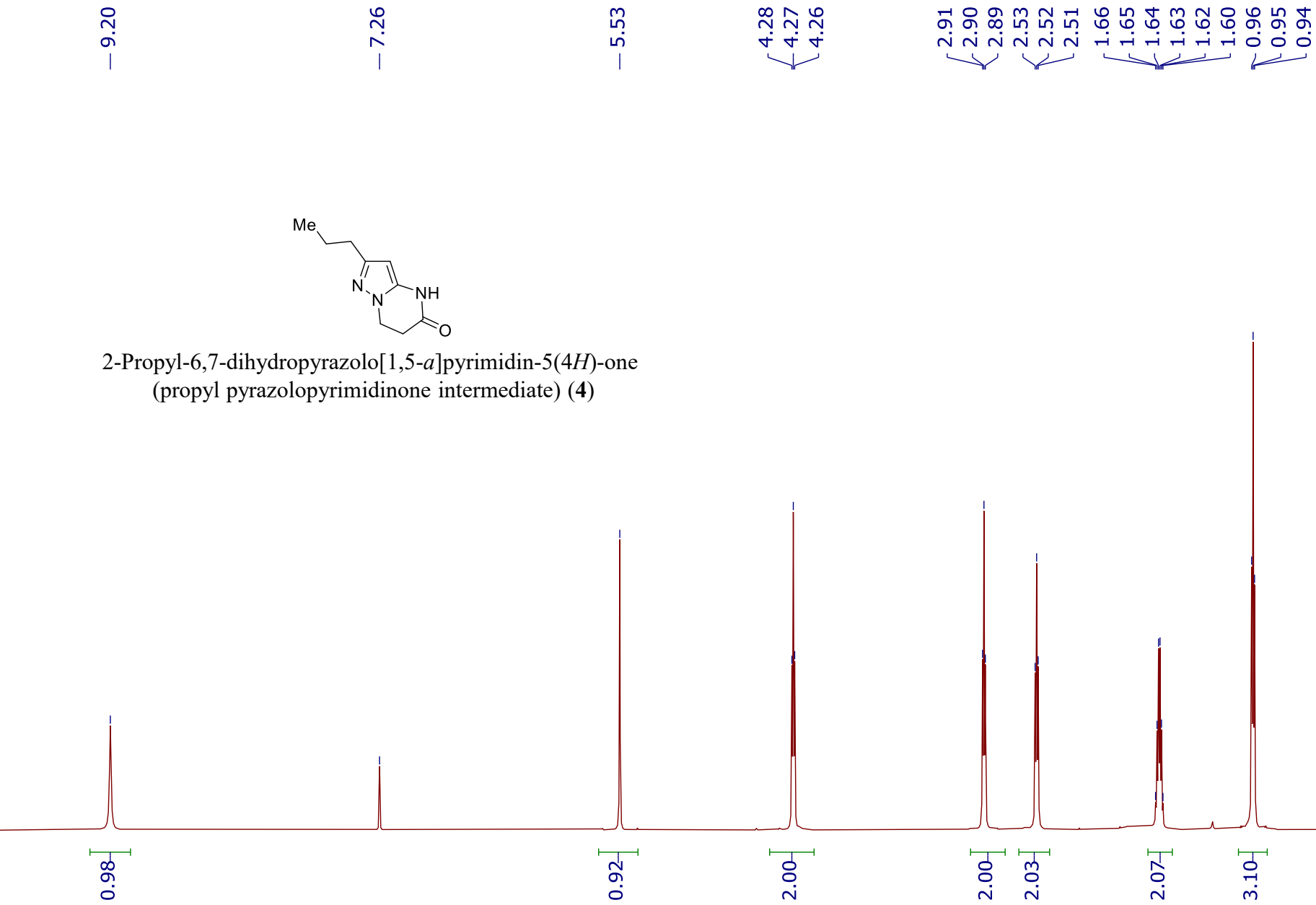
2-(*para*-Chlorophenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one
(*para*-chlorophenyl pyrazolopyrimidinone intermediate) (**2**)

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$



para-chlorophenyl pyrazolopyrimidinone intermediate (**2**)

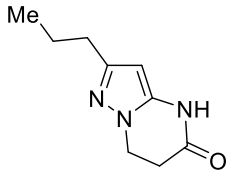
^{1}H, 700 MHz, $CDCl_3$



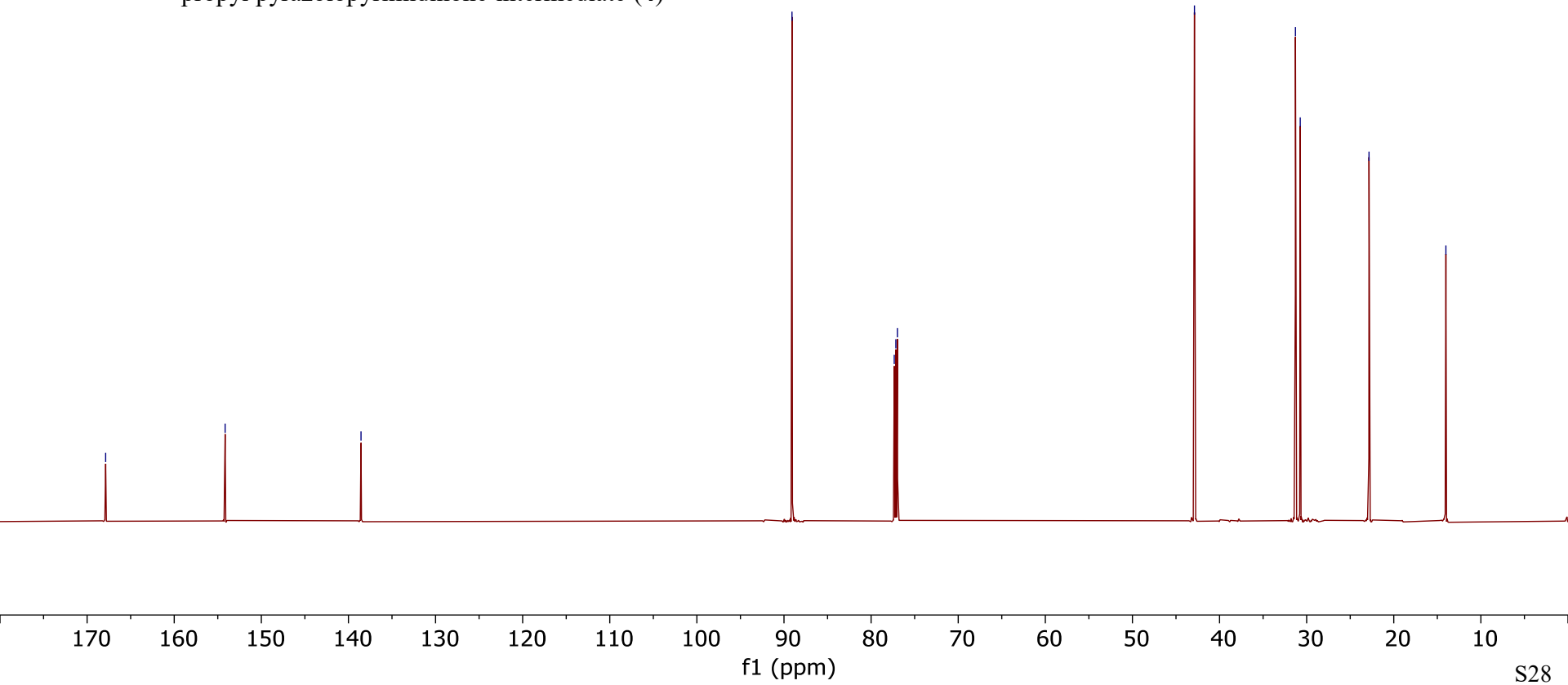
2-Propyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one
(propyl pyrazolopyrimidinone intermediate) (**4**)

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$

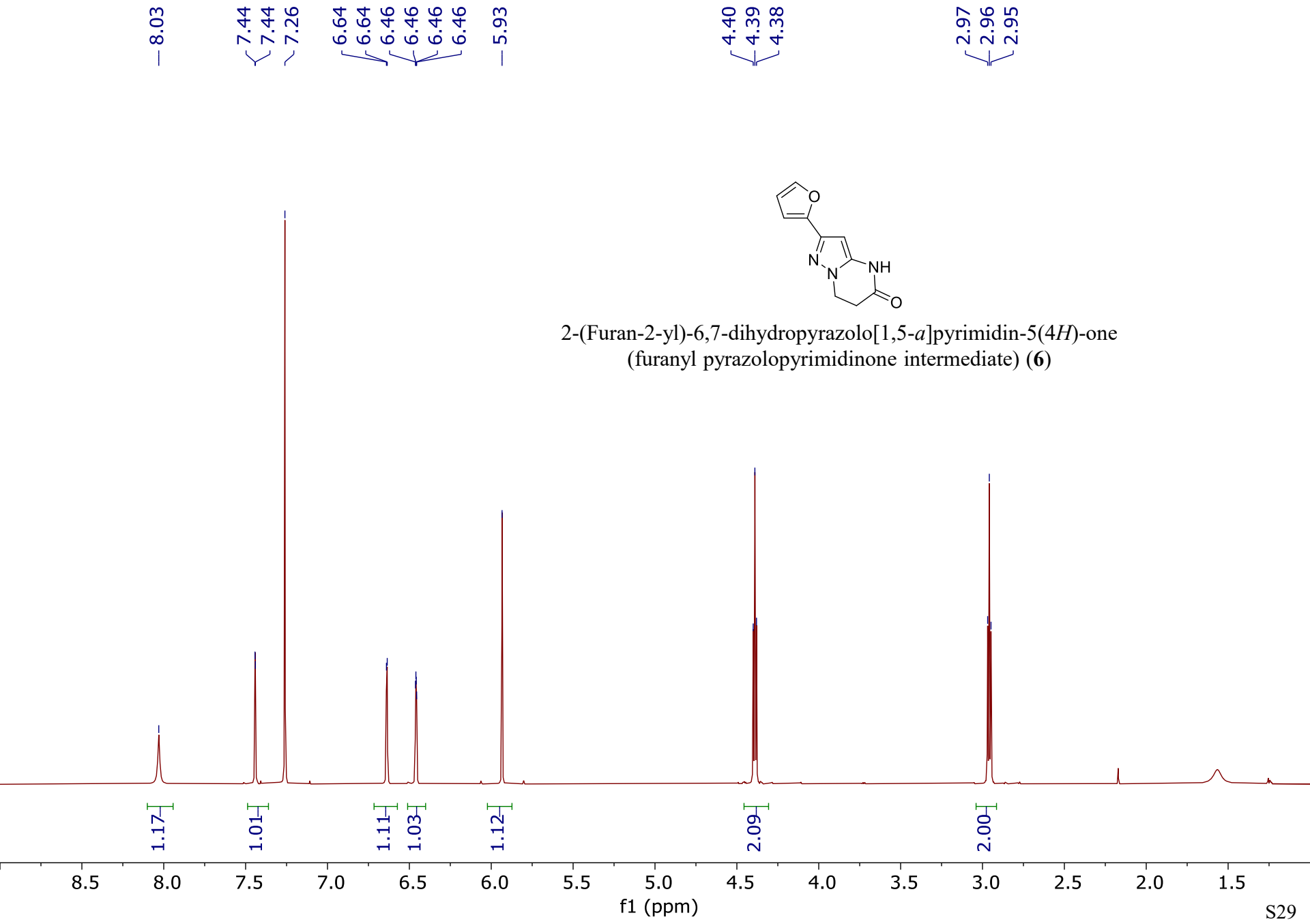
167.87
154.16
138.56
89.08
77.34
77.16
76.98
42.88
31.29
30.74
22.84
14.02



propyl pyrazolopyrimidinone intermediate (**4**)

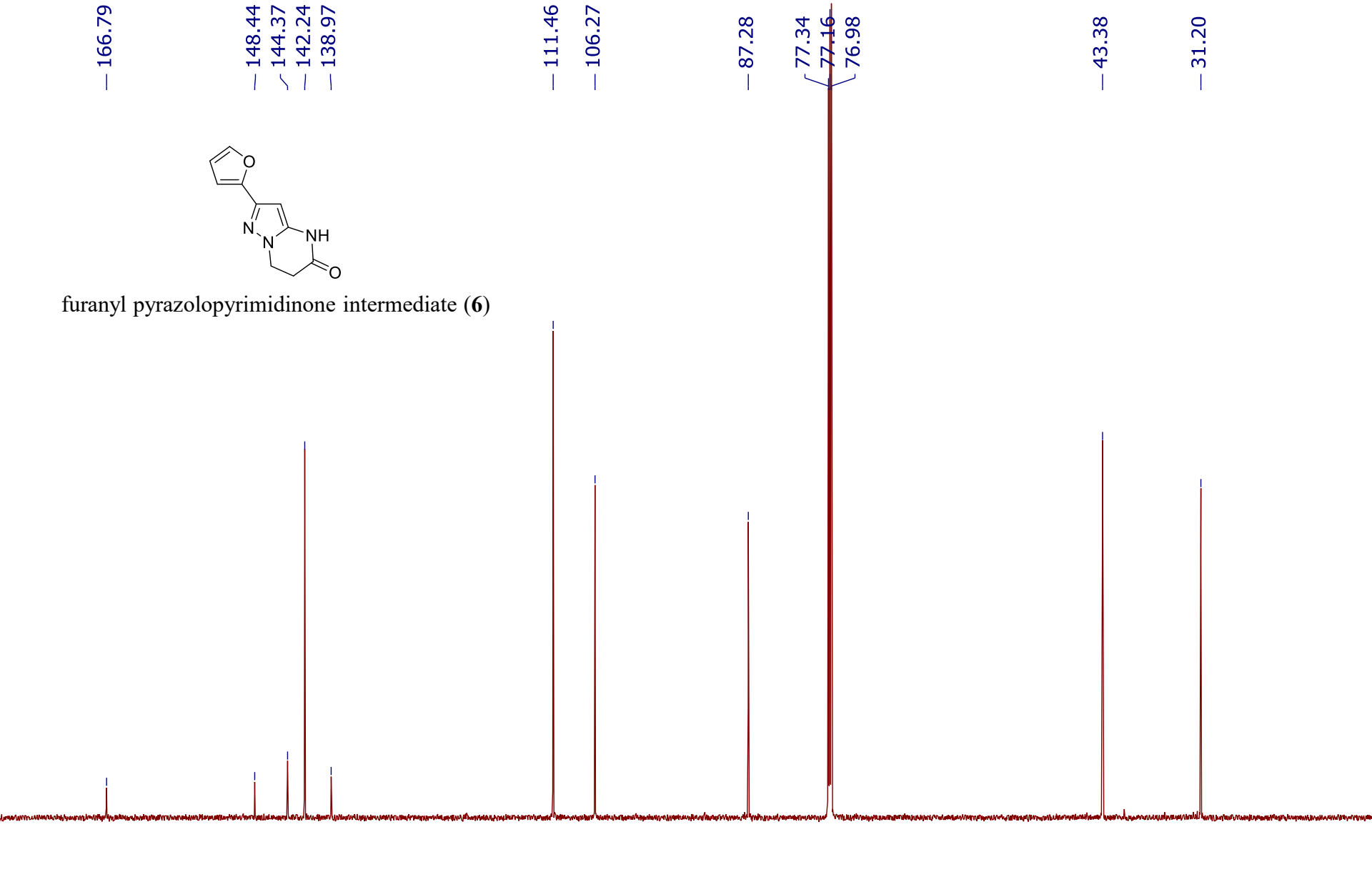


^{1}H, 700 MHz, $CDCl_3$



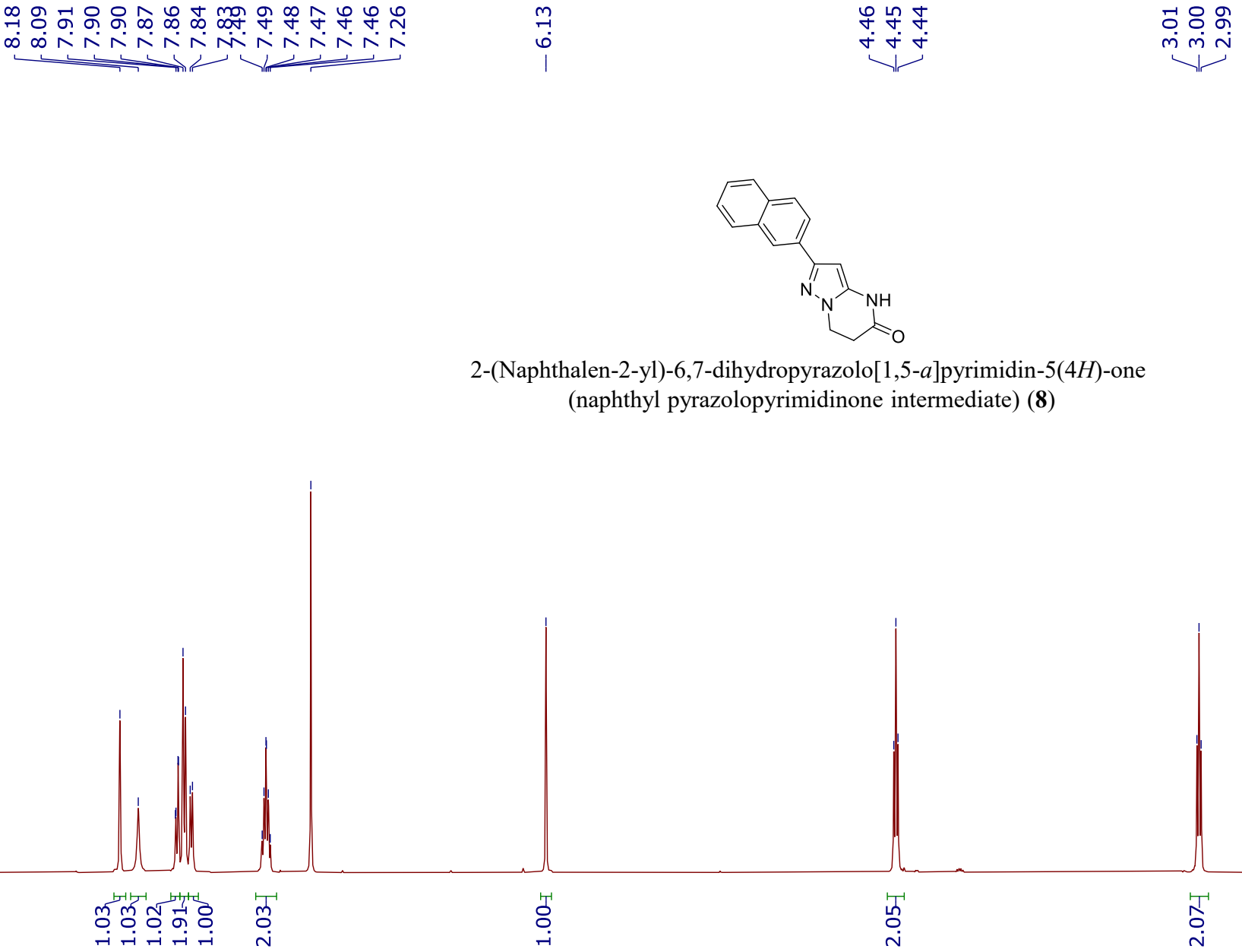
2-(Furan-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one
(furanyl pyrazolopyrimidinone intermediate) (**6**)

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$



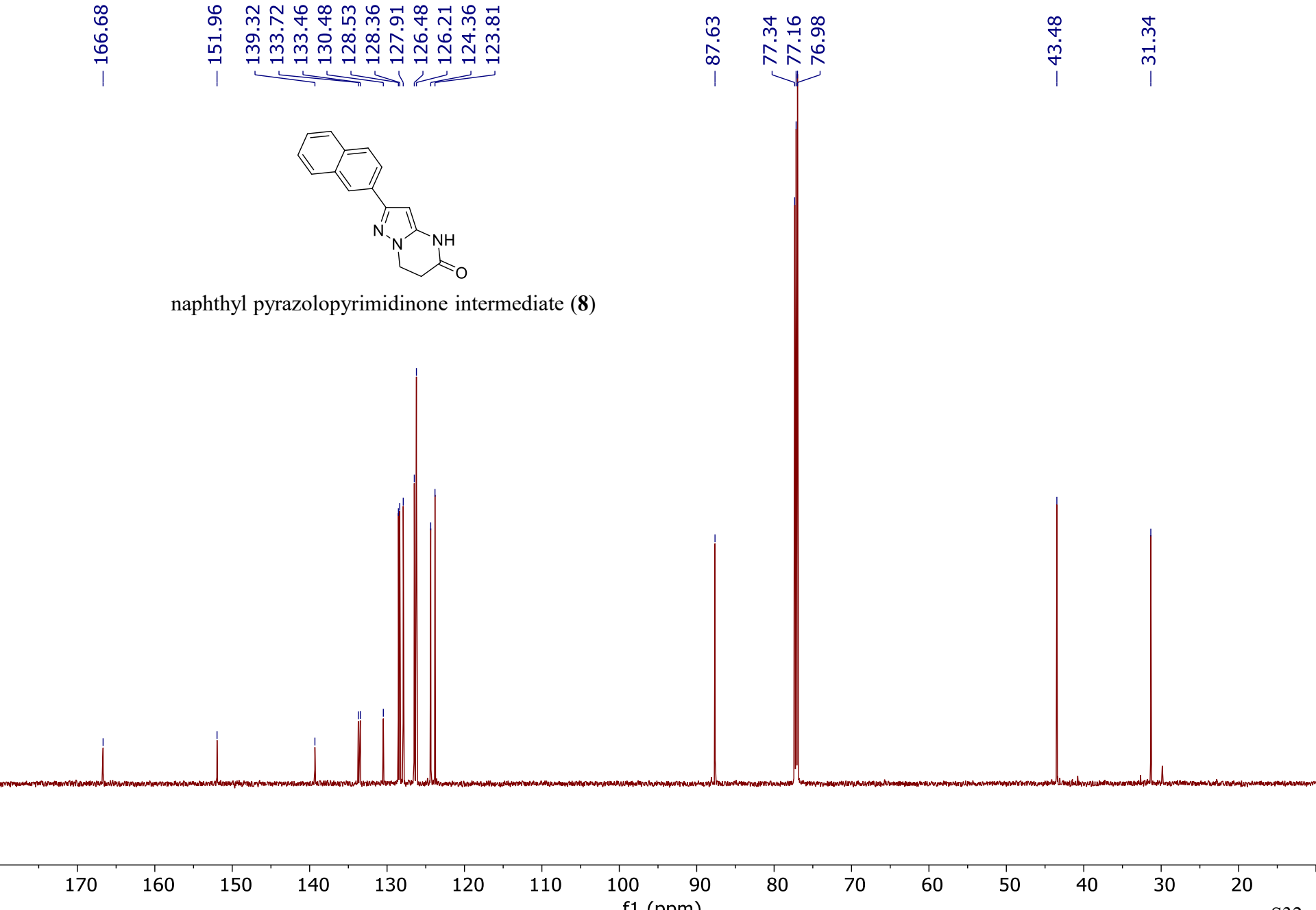
furanyl pyrazolopyrimidinone intermediate (**6**)

^{1}H, 700 MHz, $CDCl_3$



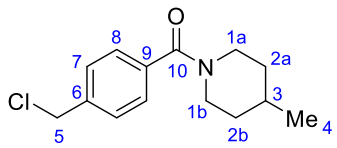
2-(Naphthalen-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one
(naphthyl pyrazolopyrimidinone intermediate) (**8**)

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$



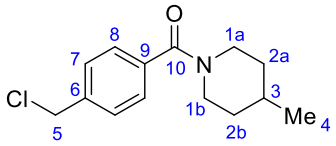
naphthyl pyrazolopyrimidinone intermediate (**8**)

^{1}H, 700 MHz, $CDCl_3$



(*para*-(Chloromethyl)phenyl)(4-methylpiperidin-1-yl)methanone
[4-methylpiperidinyl benzamide (benzylic chloride)] (**11**)

169.80
138.76
136.74
128.73
127.41
77.34
77.16
76.98
48.20
45.78
42.66
34.87
33.93
31.28
21.85

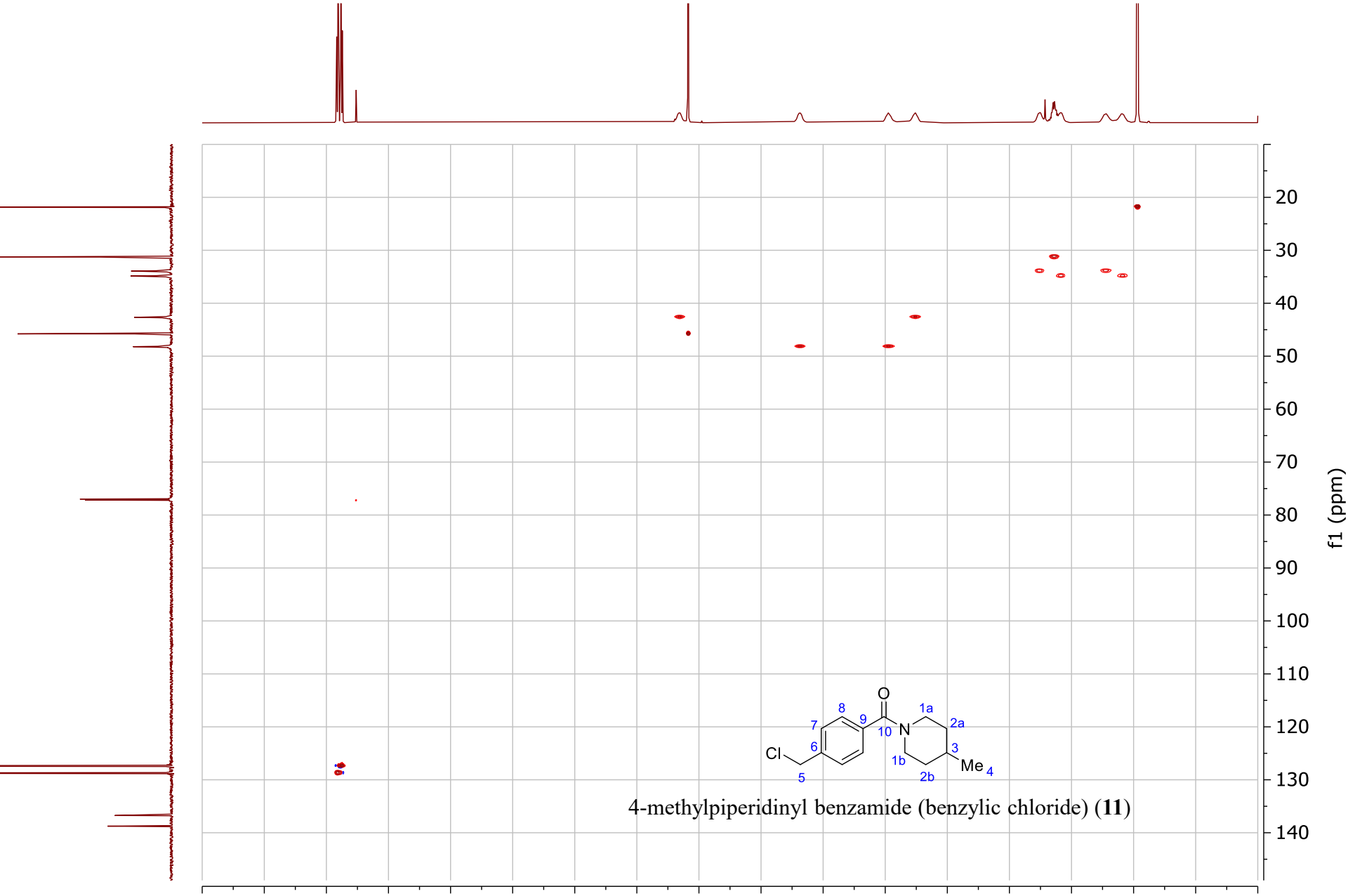


4-methylpiperidinyl benzamide (benzylic chloride) (**11**)

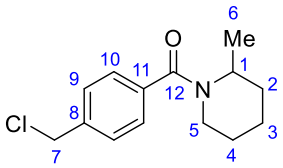
8 7 9 6 10 1 5 1 2 3 4

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

f1 (ppm)

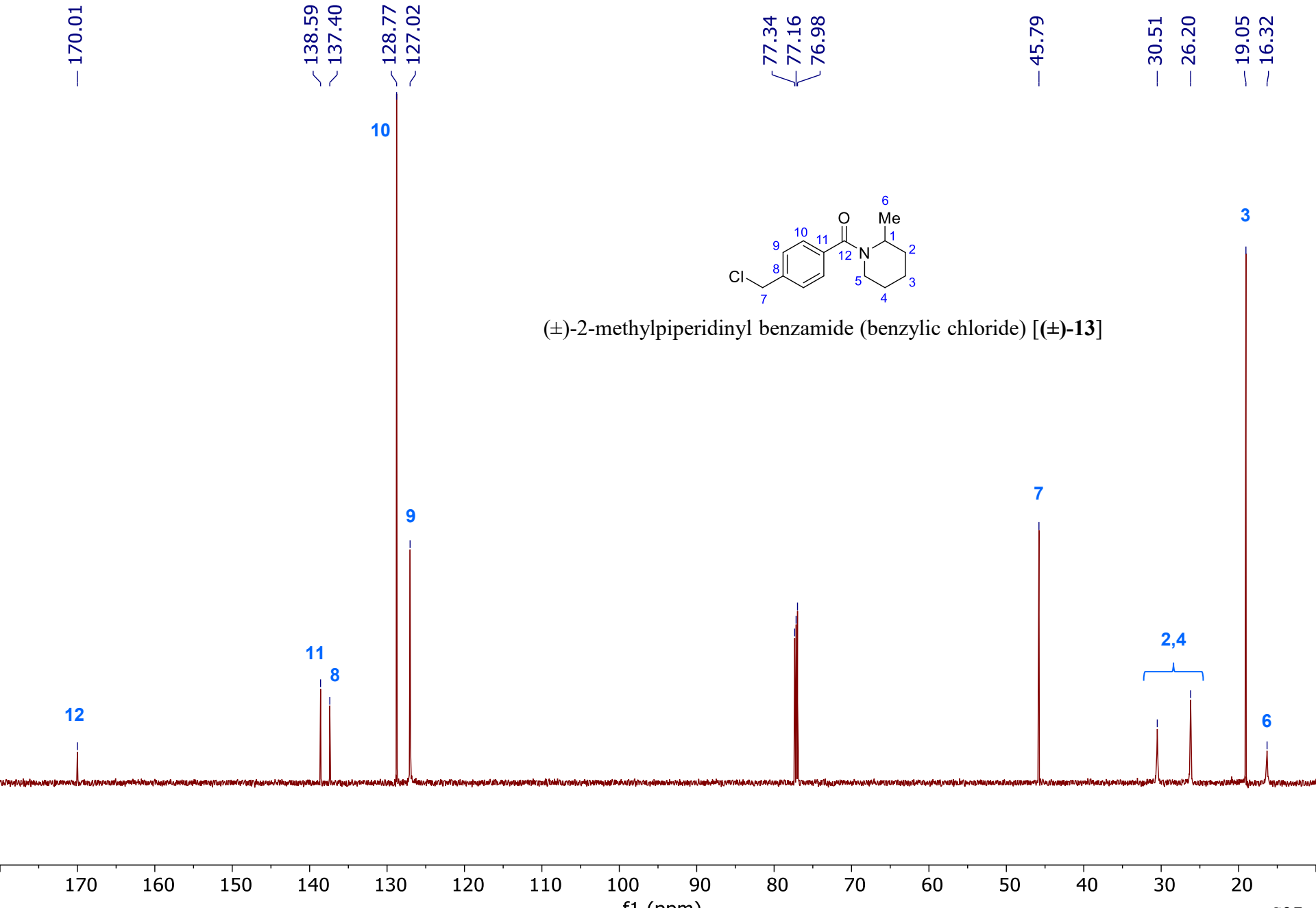


4-methylpiperidinyl benzamide (benzylic chloride) (**11**)



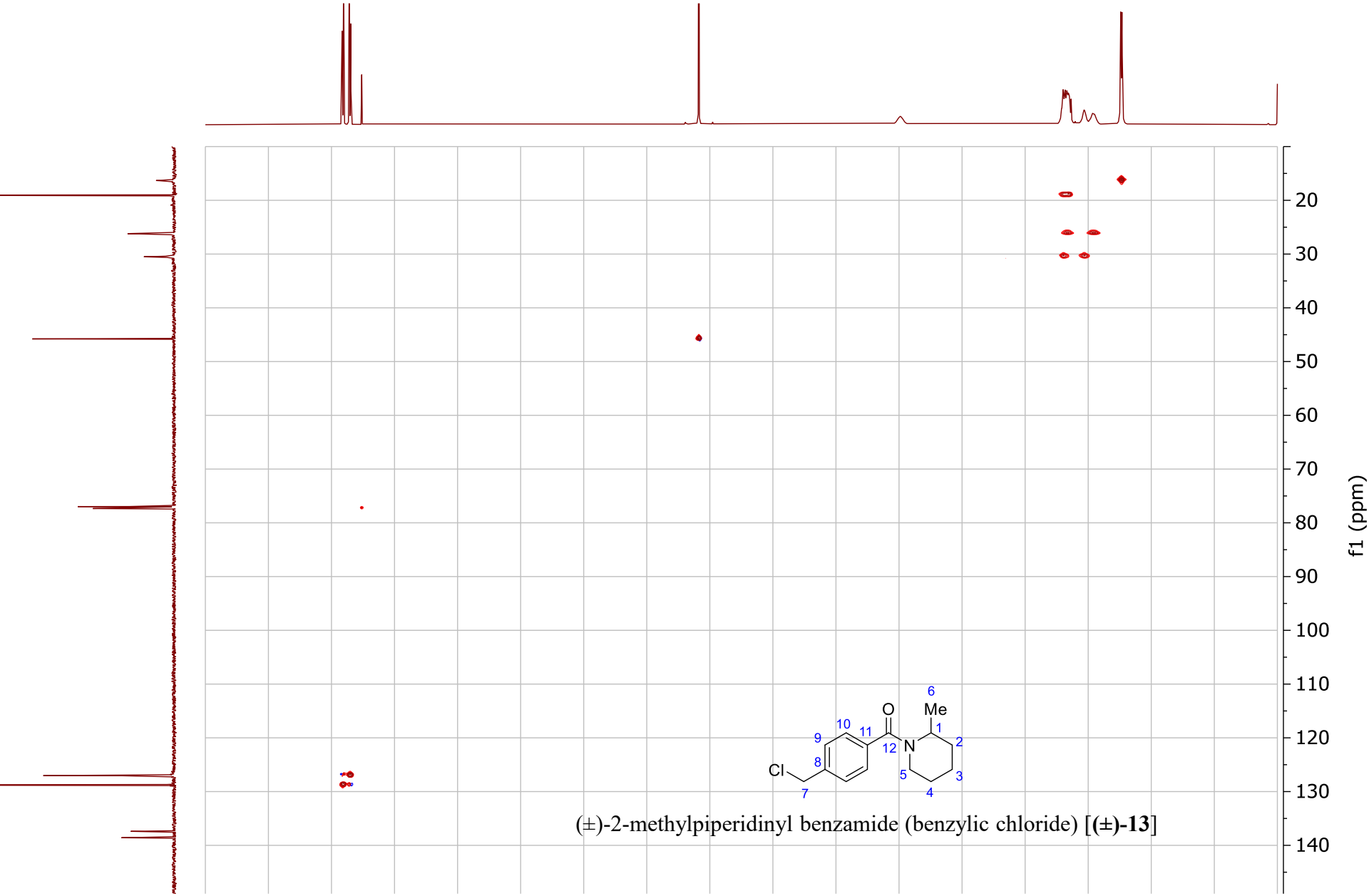
(±)-(*para*-(Chloromethyl)phenyl)(2-methylpiperidin-1-yl)methanone
[(±)-2-methylpiperidinyl benzamide (benzylic chloride)] [**(±)-13**]

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$, 40 °C

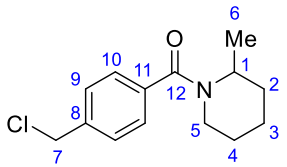


(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

HSQC, 700, 176 MHz, $CDCl_3$, 40 °C

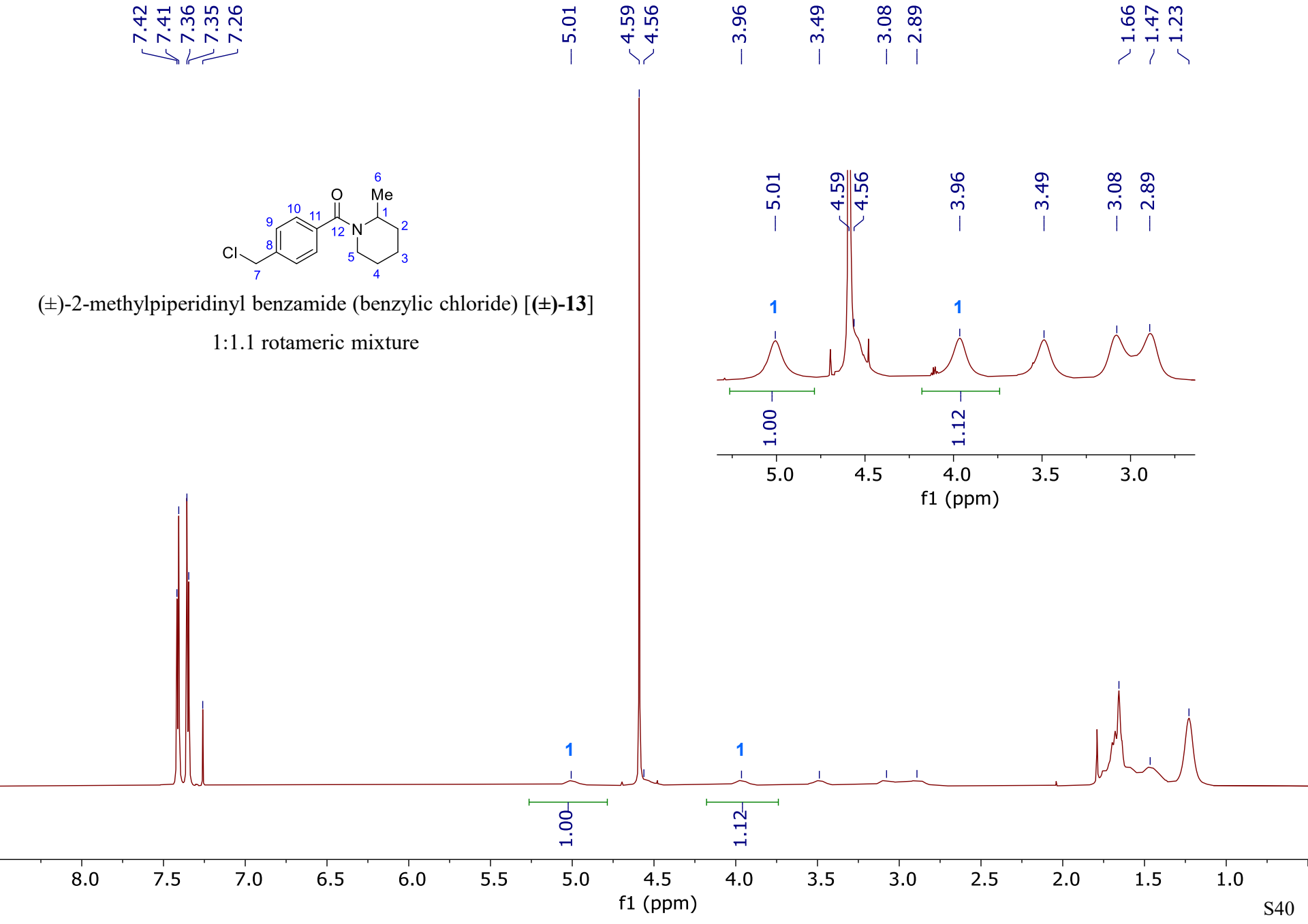


(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]



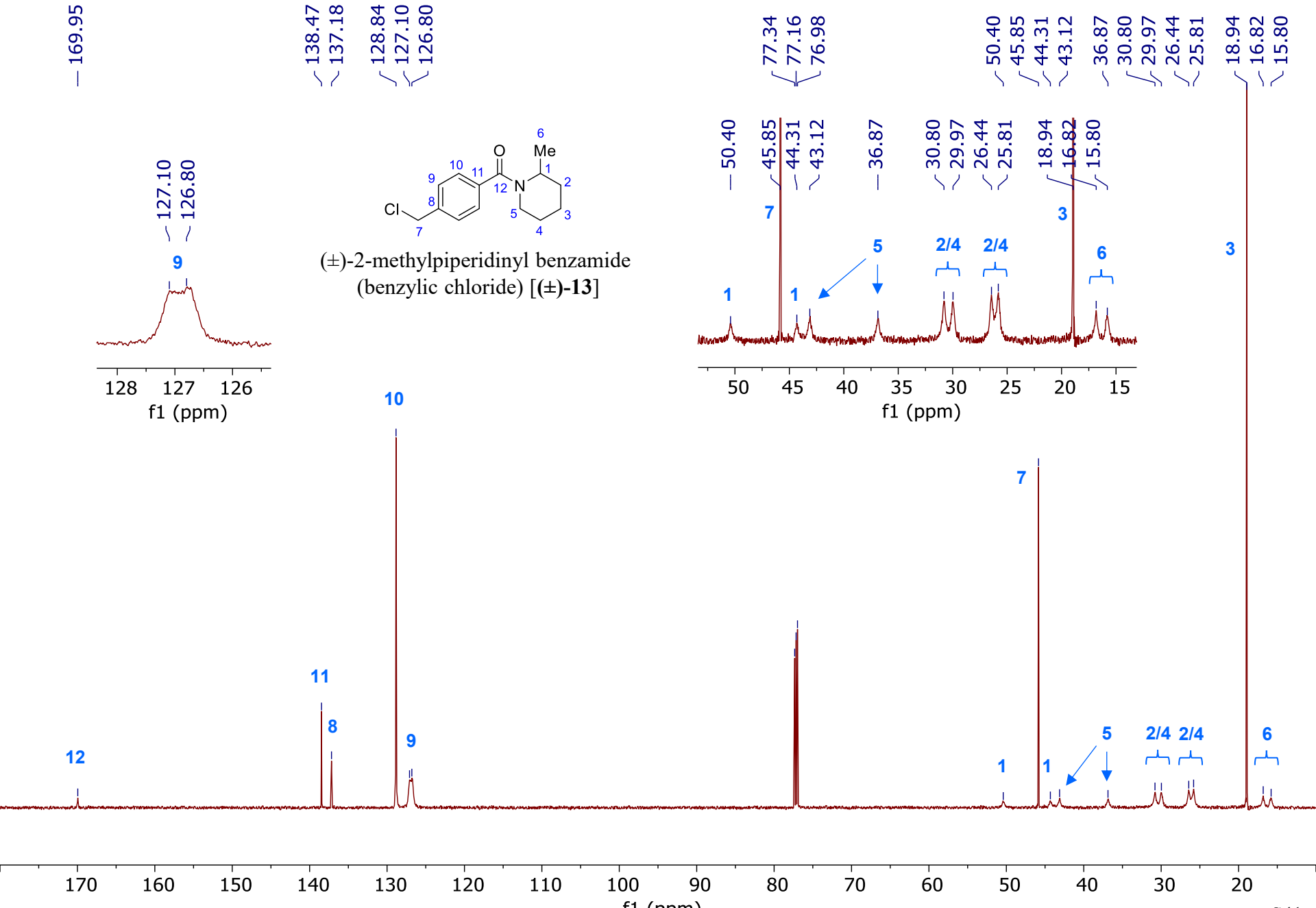
(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

^{1}H, 700 MHz, $CDCl_3$, 10 °C



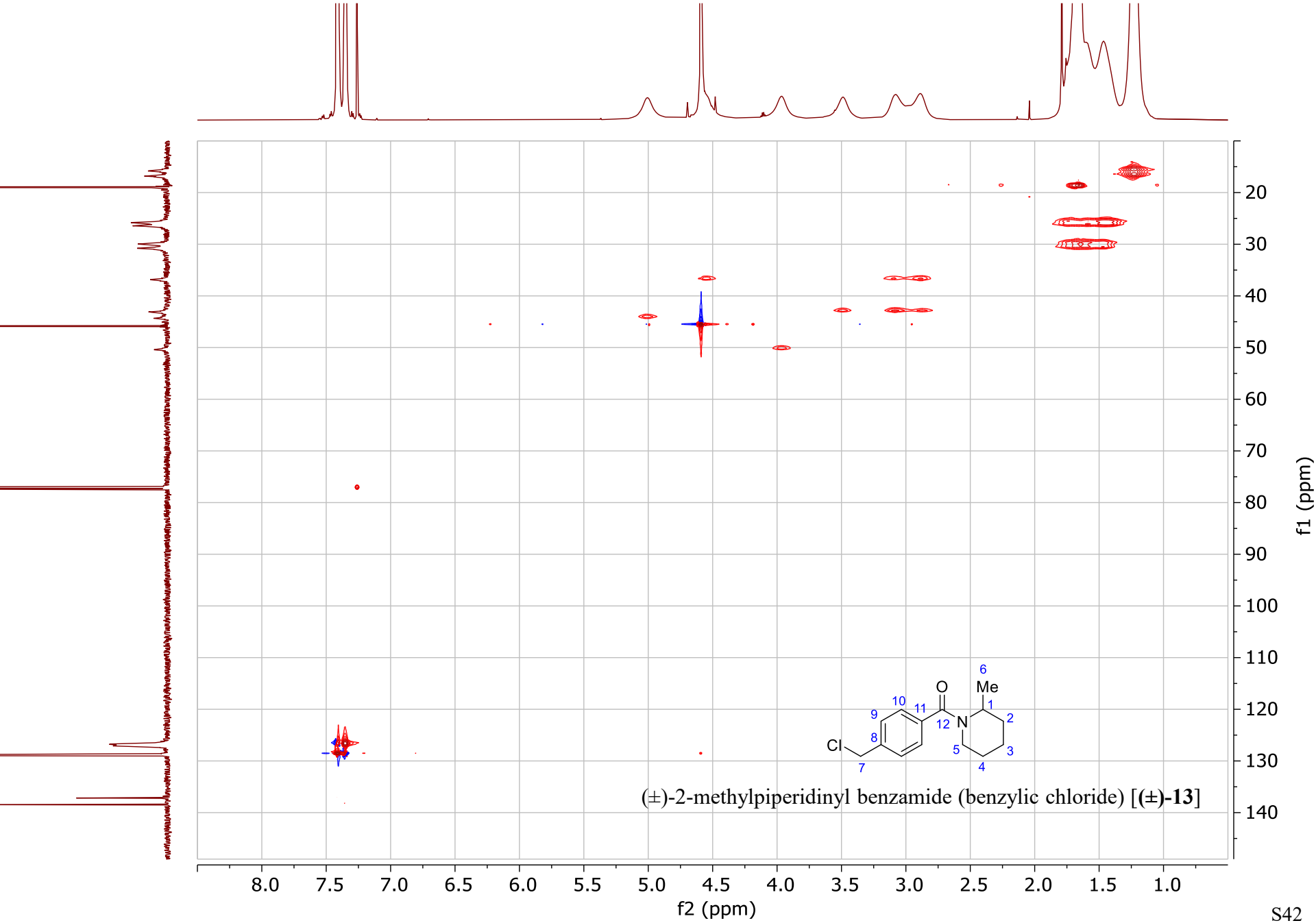
(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

1:1.1 rotameric mixture



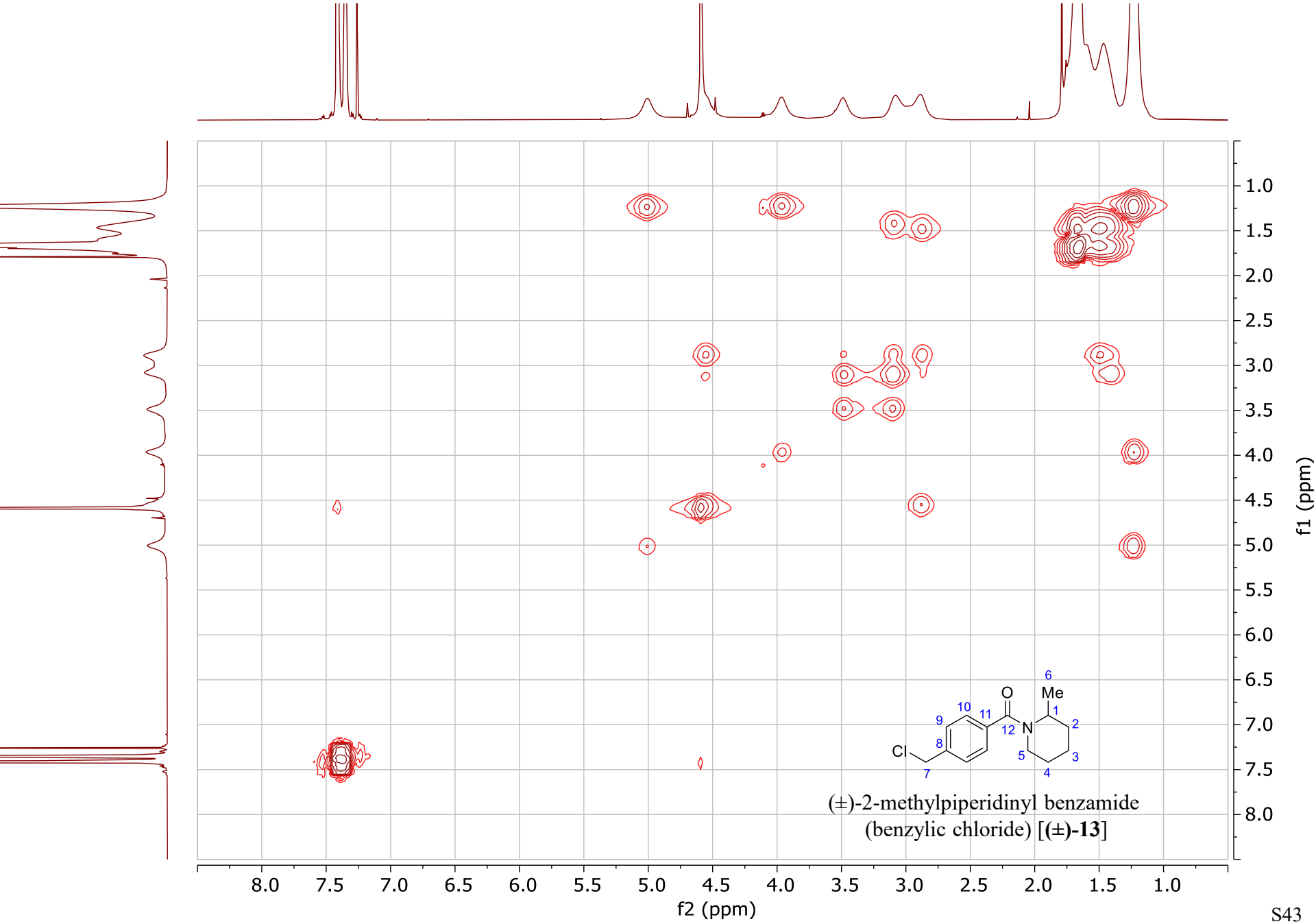
(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

HSQC, 700, 176 MHz, $CDCl_3$, 10 °C

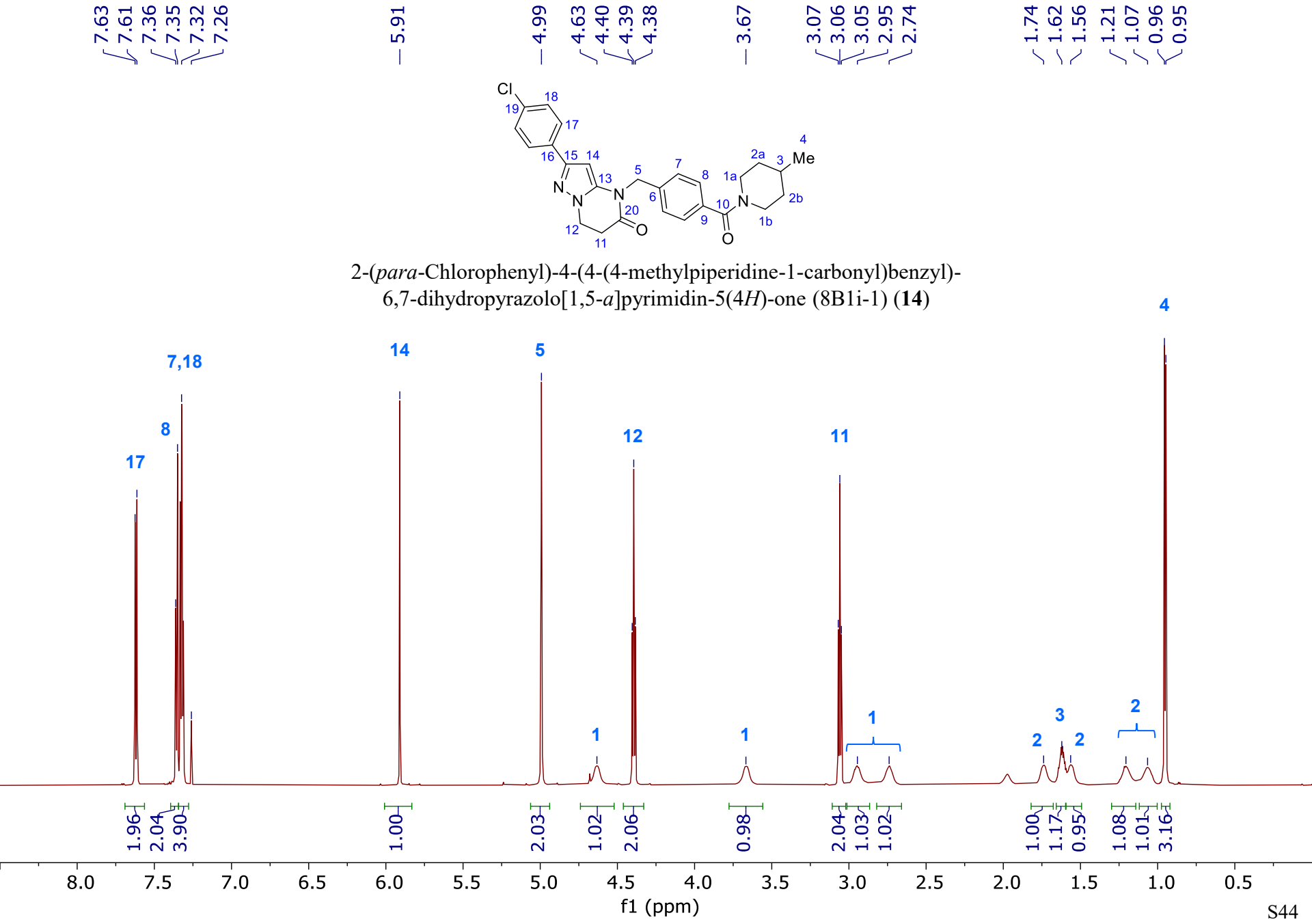


(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

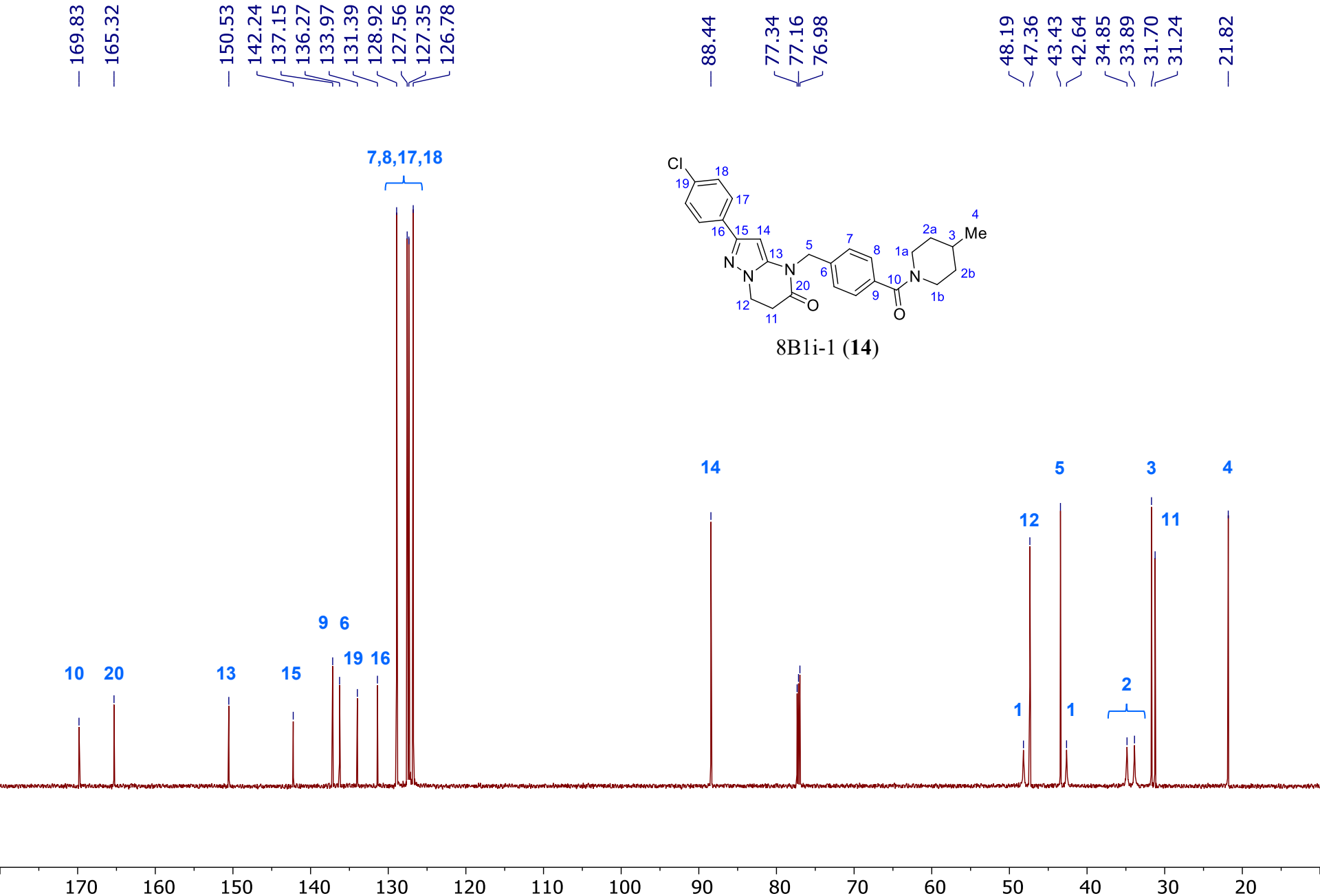
COSY, 700 MHz, $CDCl_3$, 10 °C



(±)-2-methylpiperidinyl benzamide (benzylic chloride) [**(±)-13**]

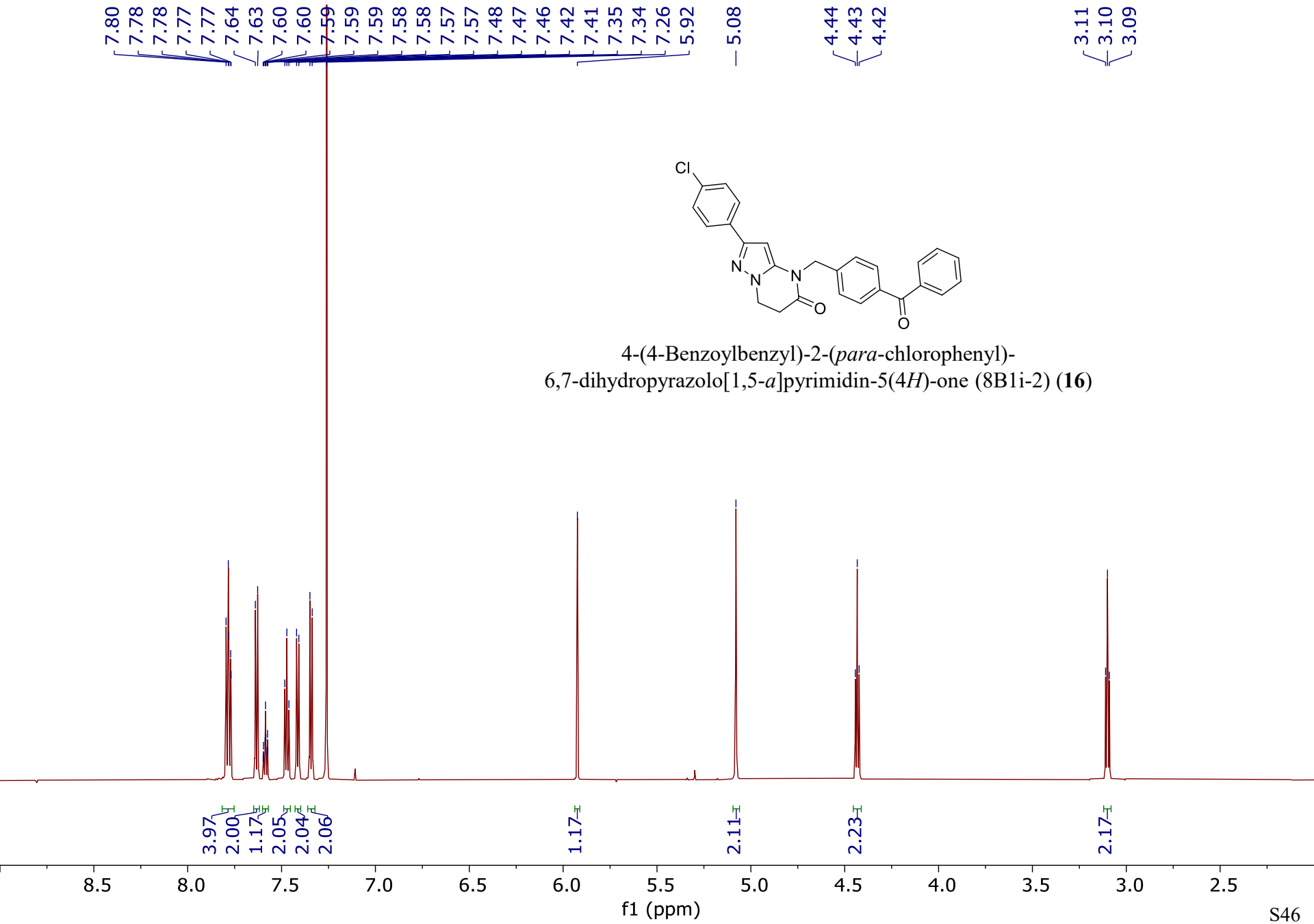


2-(*para*-Chlorophenyl)-4-(4-(4-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-1) (**14**)


169.83
165.32
150.53
142.24
137.15
136.27
133.97
131.39
128.92
127.56
127.35
126.78
88.44
77.34
77.16
76.98
48.19
47.36
43.43
42.64
34.85
33.89
31.70
31.24
21.82
7,8,17,18
14
5
3
4
12
11
9
6
19
16
10
20
13
15
1
1
2
Cl
Me
N
O
f1 (ppm)

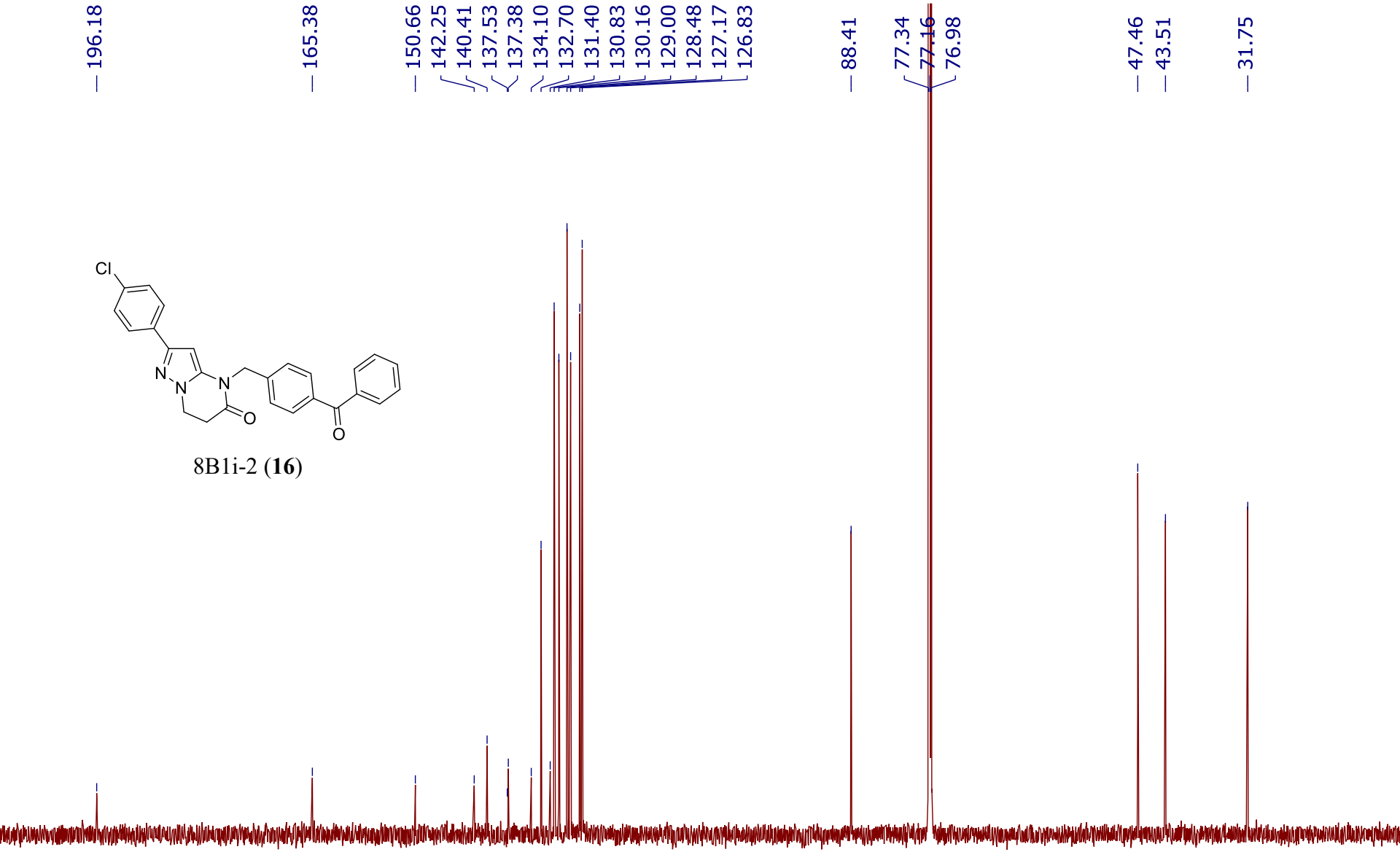
8B1i-1 (**14**)

^{1}H, 700 MHz, $CDCl_3$



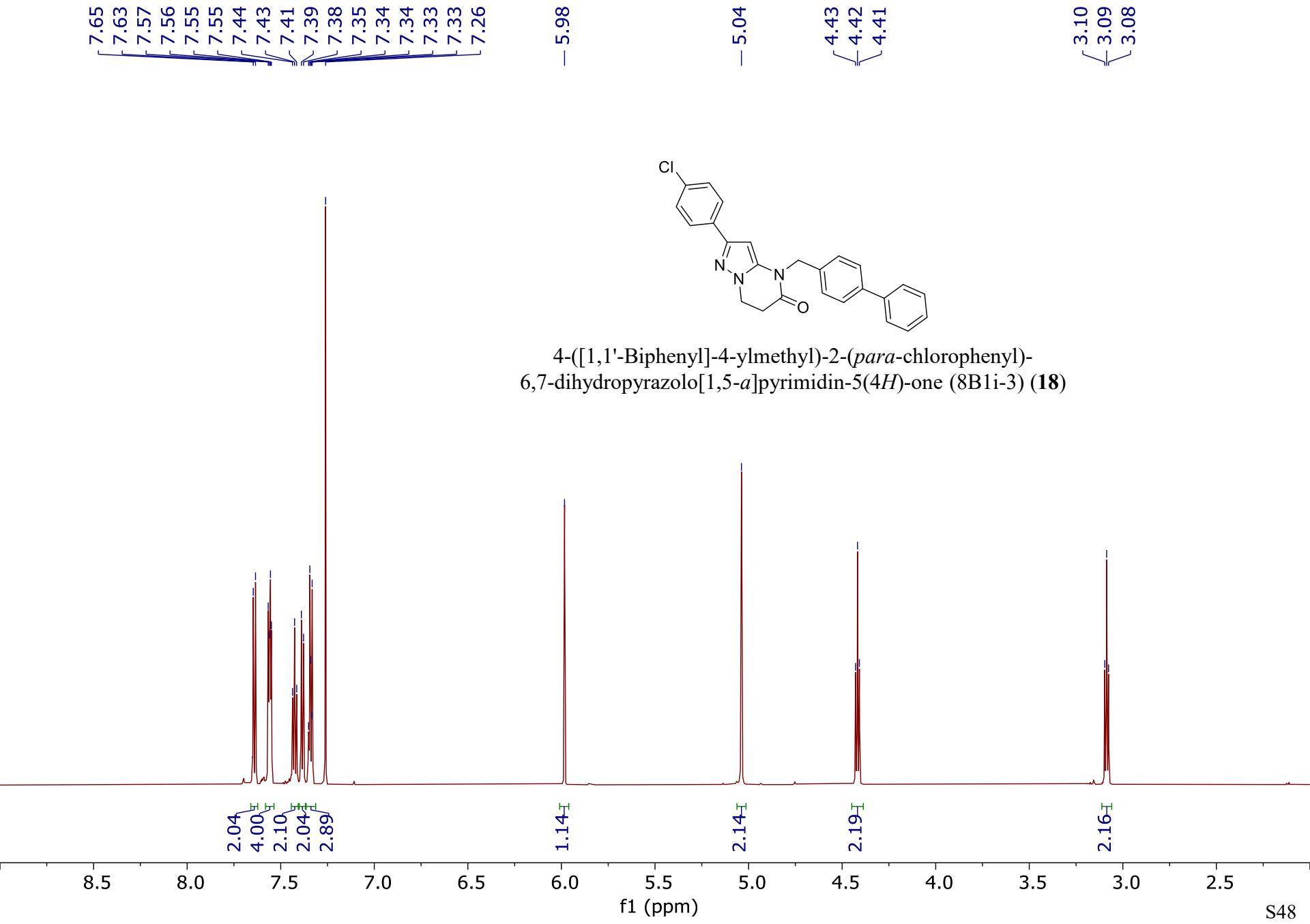
4-(4-Benzoylbenzyl)-2-(*para*-chlorophenyl)-
6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-2) (**16**)

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$



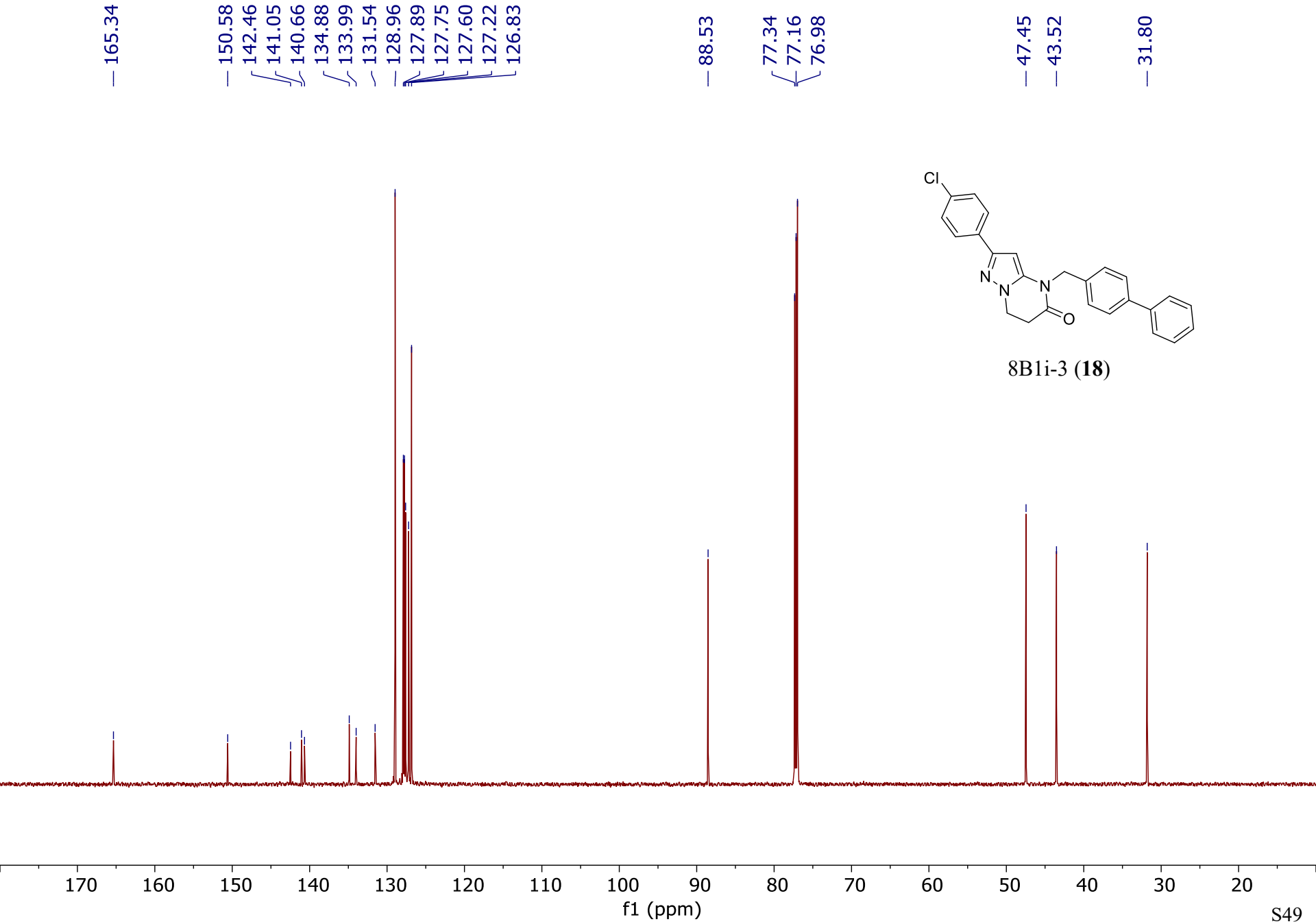
8B1i-2 (**16**)

^{1}H, 700 MHz, $CDCl_3$



4-([1,1'-Biphenyl]-4-ylmethyl)-2-(*para*-chlorophenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-3) (**18**)

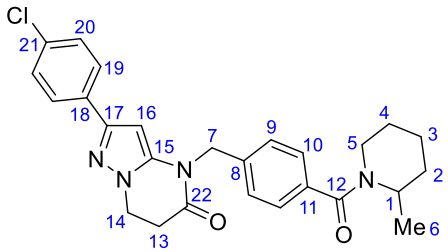
$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$



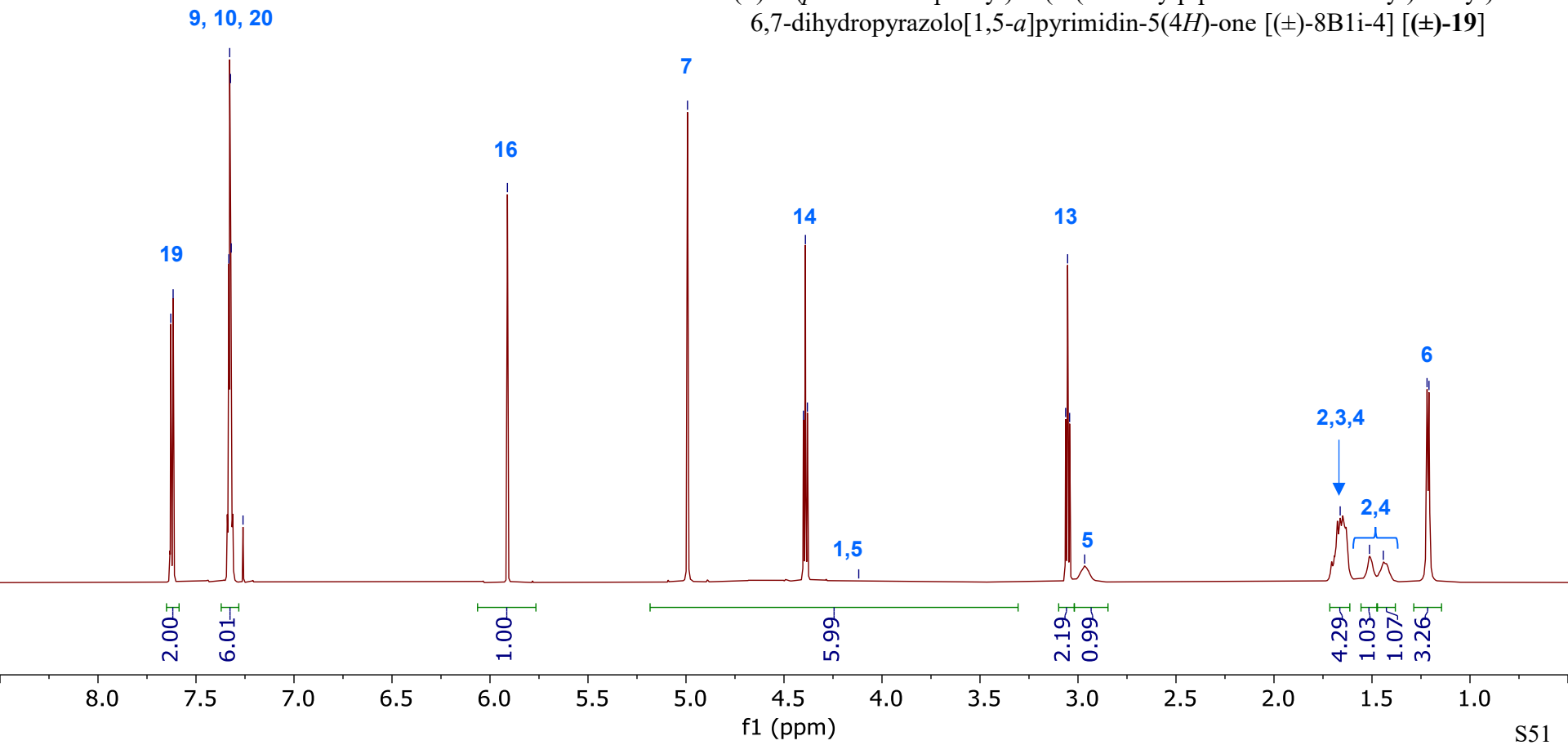
8B1i-3 (**18**)

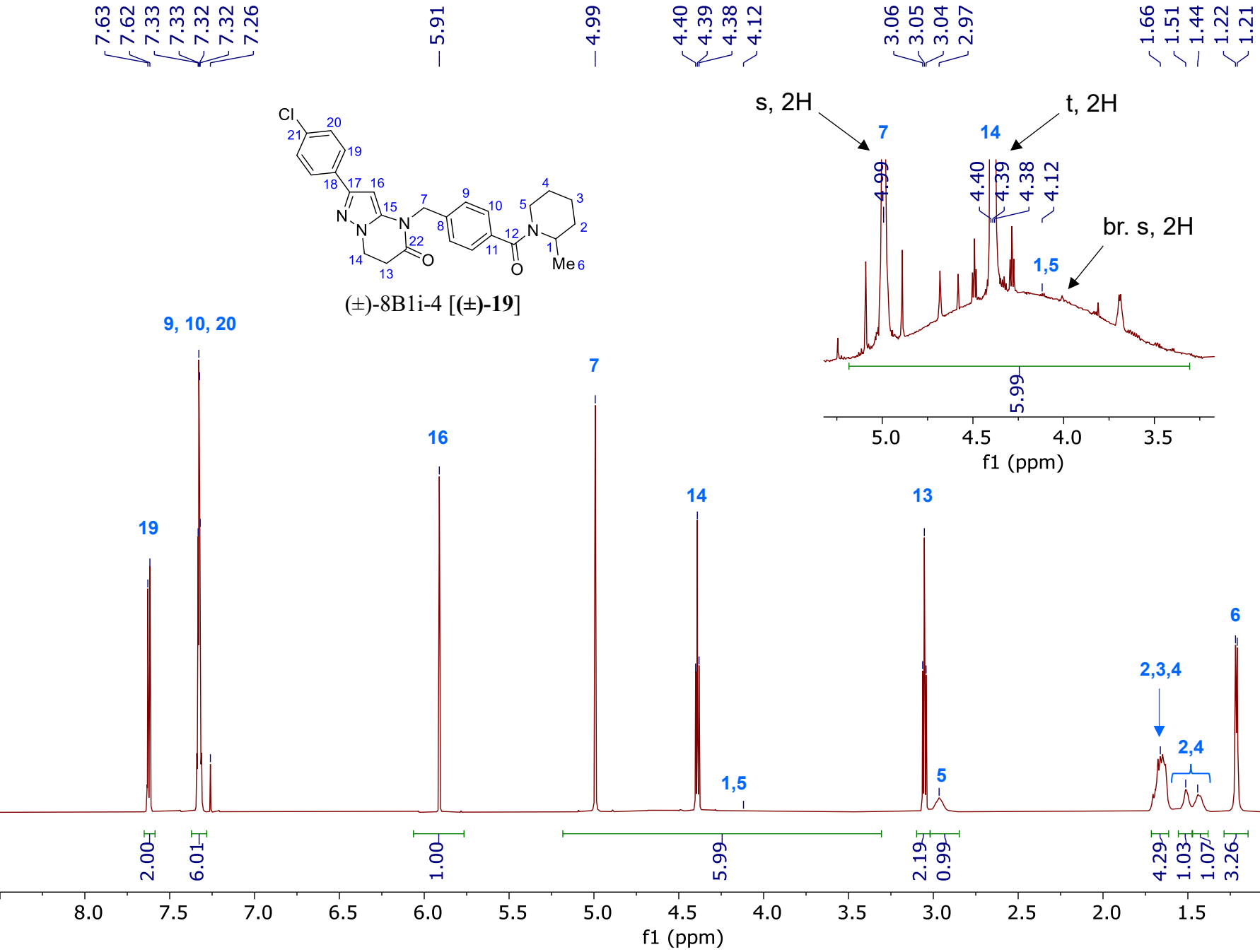

Cl
N
N
N
O
8B1i-3 (18)
121
122
123
124
125
126
127
128
129
130
131
132
133
134
f1 (ppm)
7.95 7.90 7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95
f2 (ppm)

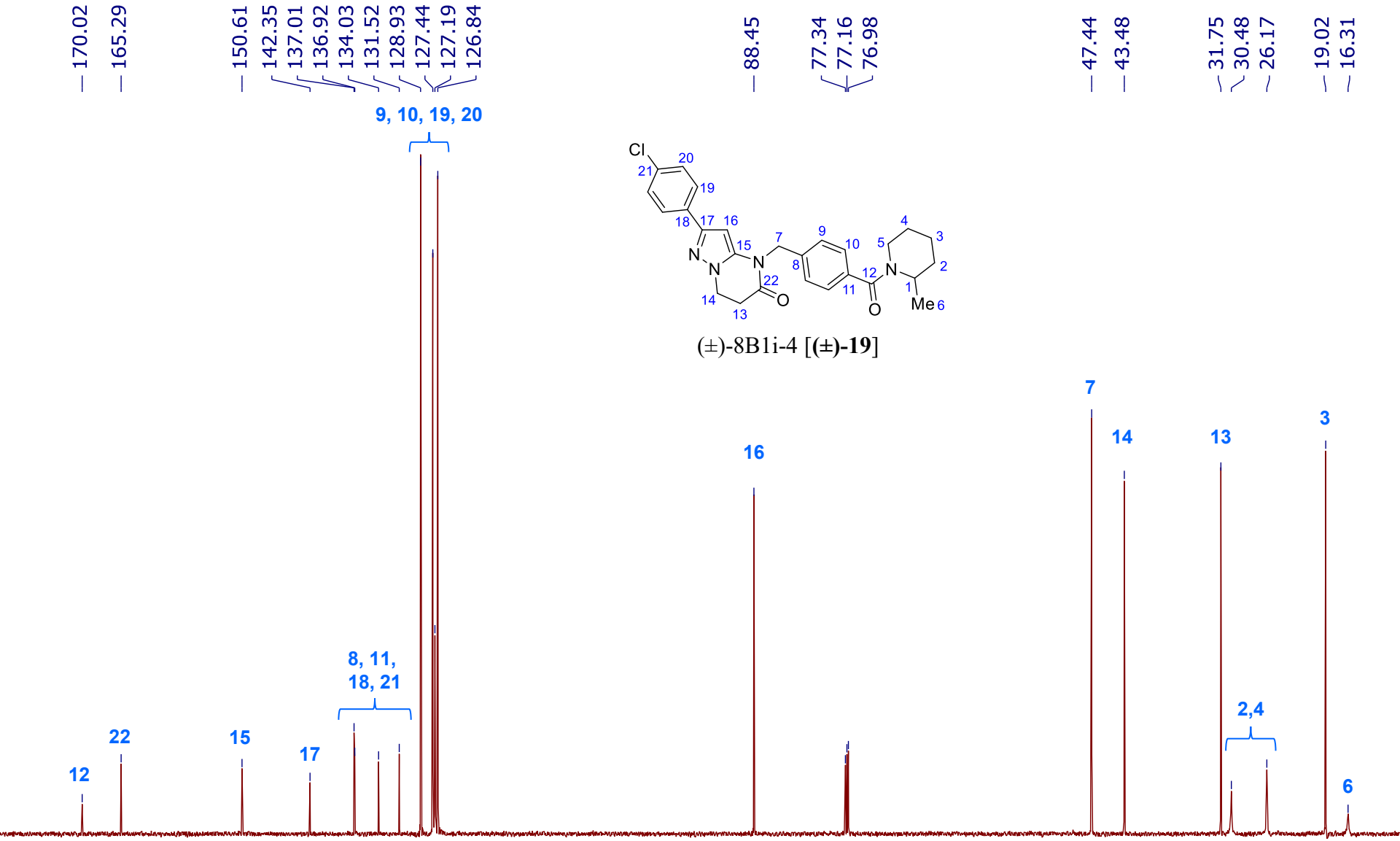
7.63 7.62 7.33 7.33 7.32 7.32 7.26 — 5.91 — 4.99 4.40 4.39 4.38 4.12 3.06 3.05 3.04 2.97 1.66 1.51 1.44 1.22 1.21



(±)-2-(*para*-Chlorophenyl)-4-(4-(2-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-4] [**(±)-19**]

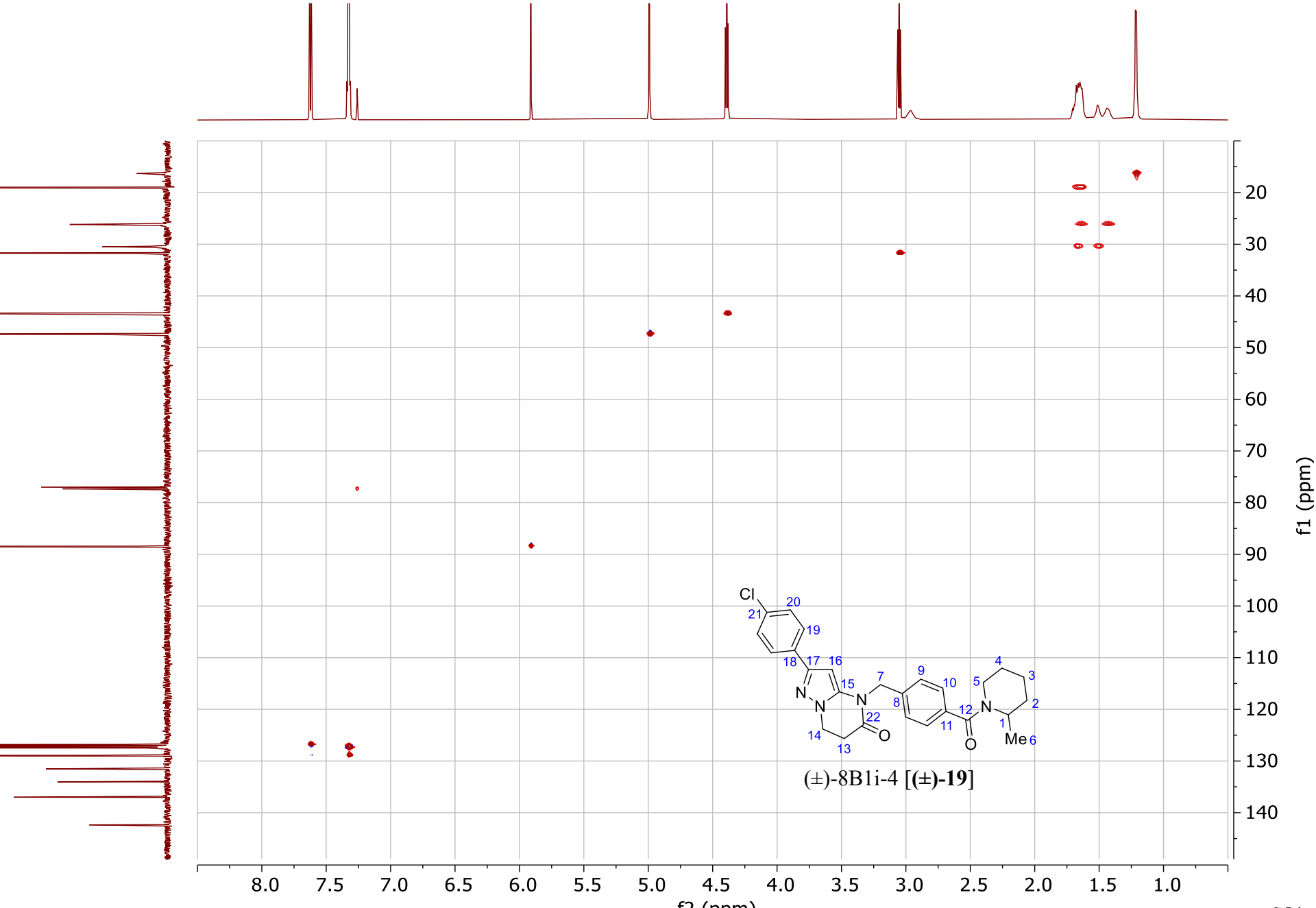



7.63
7.62
7.33
7.33
7.32
7.32
7.26
5.91
4.99
4.40
4.39
4.38
4.12
3.06
3.05
3.04
2.97
1.66
1.51
1.44
1.22
1.21
Cl
20
21
19
18
17
16
15
N
N
7
9
10
8
22
O
14
13
4
5
3
2
12
N
1
11
O
Me 6
(±)-8B1i-4 [(±)-19]
s, 2H
t, 2H
br. s, 2H
7
14
1,5
4.99
4.40
4.39
4.38
4.12
5.99
5.0
4.5
4.0
3.5
f1 (ppm)
9, 10, 20
19
16
7
14
13
1,5
5
2,3,4
2,4
6
2.00
6.01
1.00
5.99
2.19
0.99
4.29
1.03
1.07
3.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

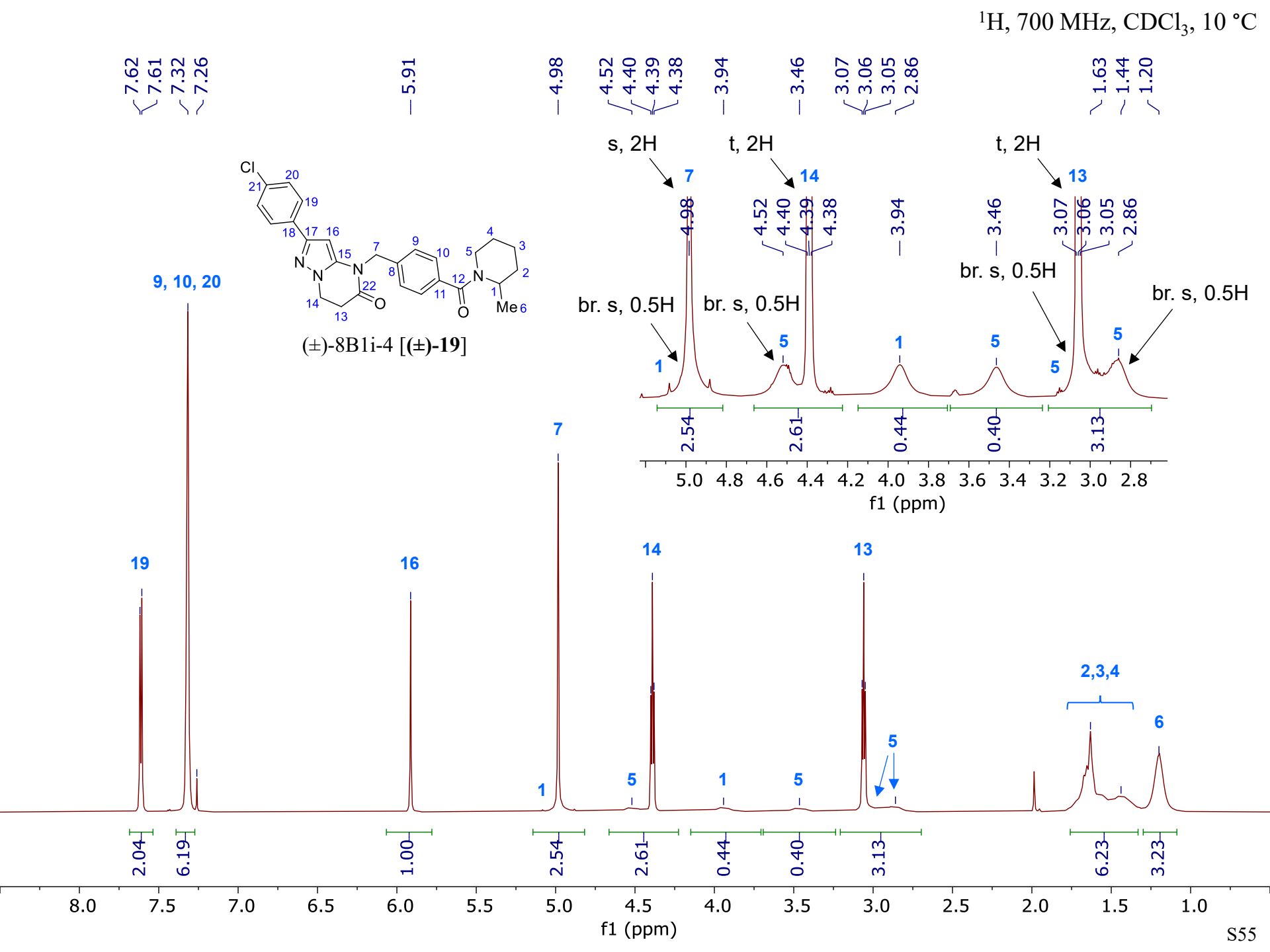

170.02
165.29
150.61
142.35
137.01
136.92
134.03
131.52
128.93
127.44
127.19
126.84
88.45
77.34
77.16
76.98
47.44
43.48
31.75
30.48
26.17
19.02
16.31
9, 10, 19, 20
16
7
14
13
3
8, 11,
18, 21
2,4
22
15
17
12
6
Cl
N
O
Me
f1 (ppm)

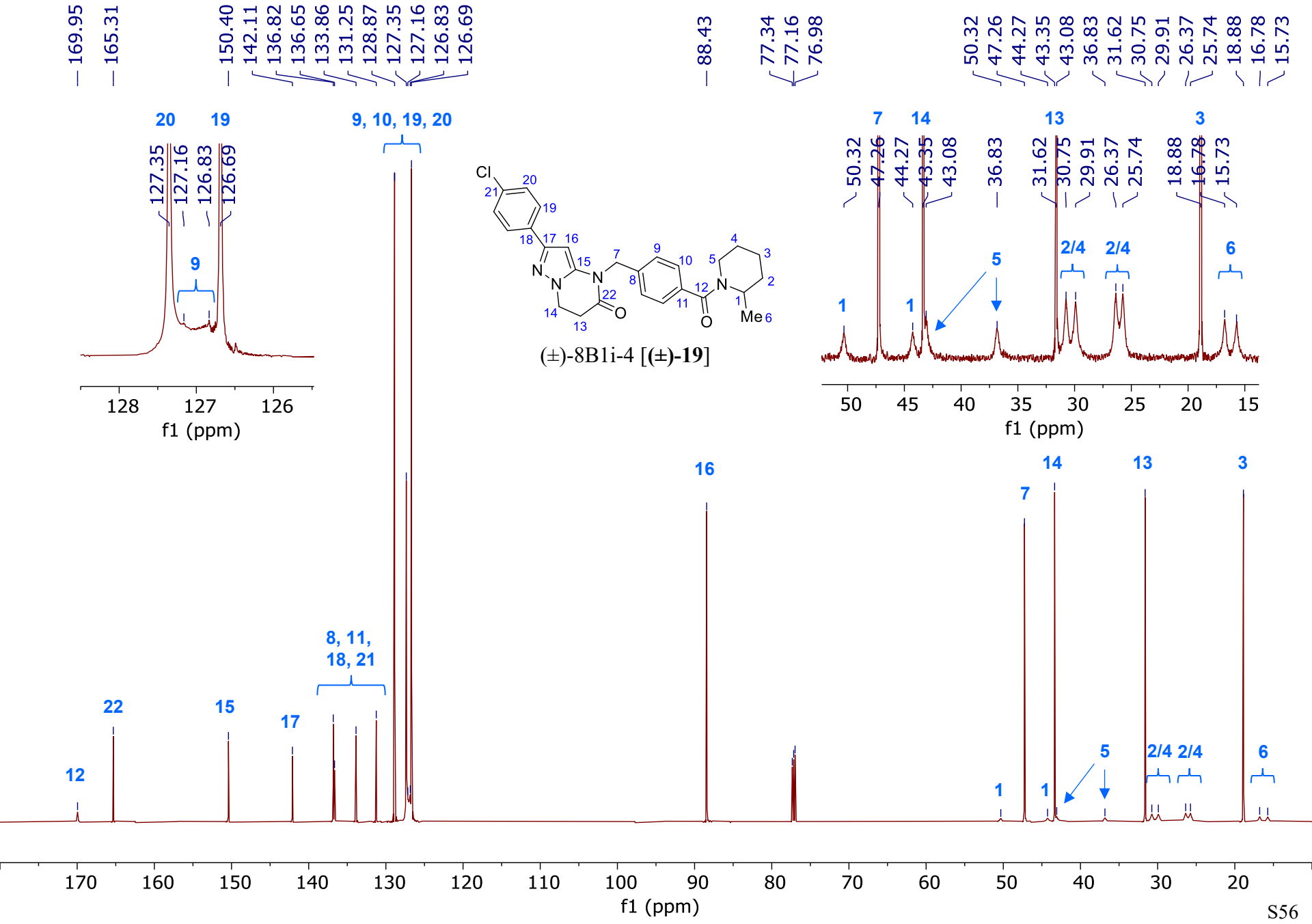
(±)-8B1i-4 [(±)-**19**]

HSQC, 700, 176 MHz, $CDCl_3$, 40 °C

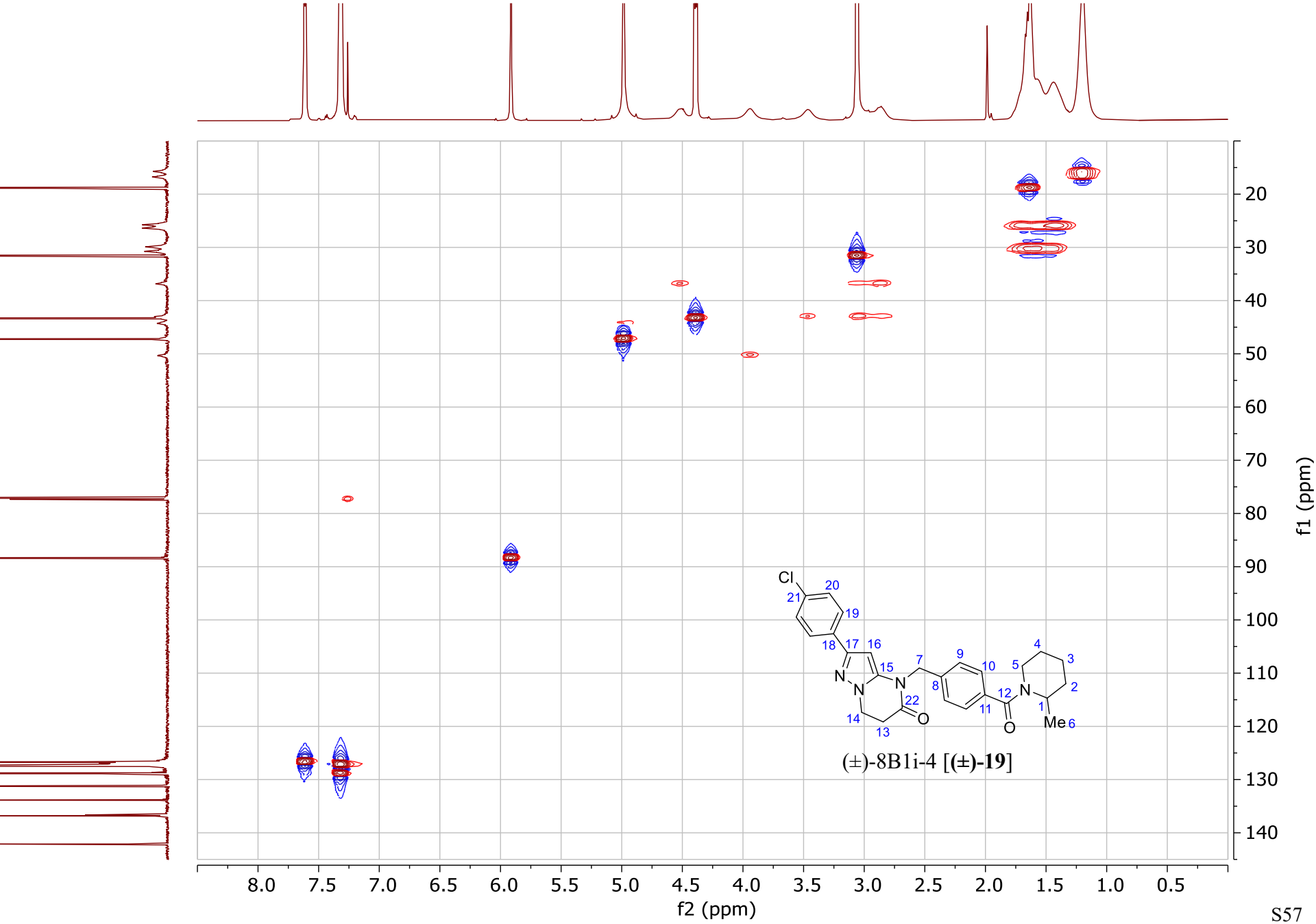


(±)-8B1i-4 [**(±)-19**]


7.62
7.61
7.32
7.26
5.91
4.98
4.52
4.40
4.39
4.38
3.94
3.46
3.07
3.06
3.05
2.86
1.63
1.44
1.20
Cl
20
21
19
18
17
16
15
N
N
7
8
9
10
11
12
N
O
O
22
14
13
5
4
3
2
1
Me
6
(±)-8B1i-4 [(±)-19]
s, 2H
t, 2H
t, 2H
7
14
13
br. s, 0.5H
br. s, 0.5H
br. s, 0.5H
br. s, 0.5H
1
5
1
5
5
5
2.54
2.61
0.44
0.40
3.13
5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
f1 (ppm)
9, 10, 20
19
16
7
14
13
2,3,4
6
5
1
5
1
5
2.04
6.19
1.00
2.54
2.61
0.44
0.40
3.13
6.23
3.23
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

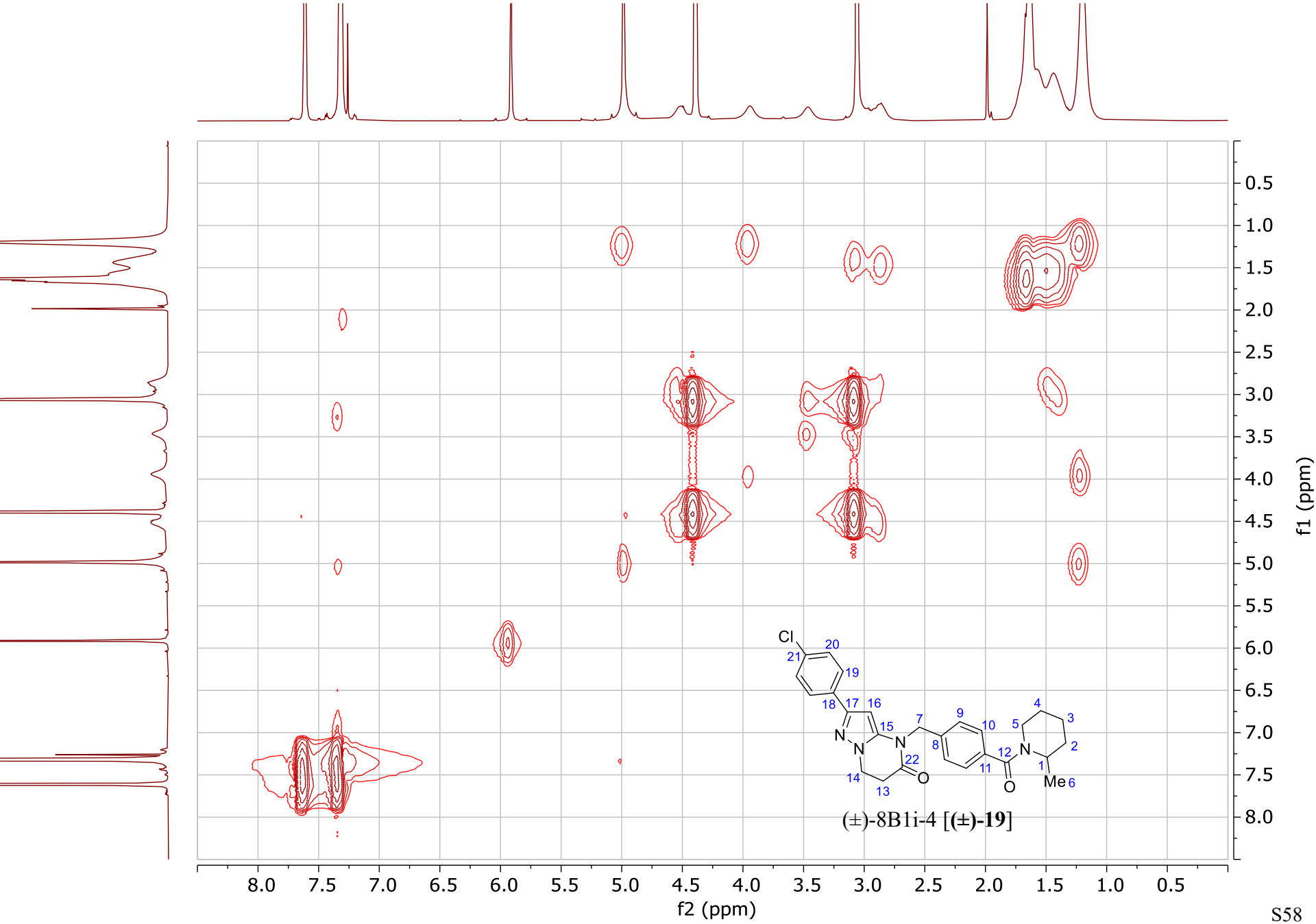

169.95
165.31
150.40
142.11
136.82
136.65
133.86
131.25
128.87
127.35
127.16
126.83
126.69
88.43
77.34
77.16
76.98
50.32
47.26
44.27
43.35
43.08
36.83
31.62
30.75
29.91
26.37
25.74
18.88
16.78
15.73
20
19
9, 10, 19, 20
9
7
14
13
3
2/4
2/4
6
5
1
1
16
8, 11,
18, 21
22
15
17
12
f1 (ppm)

(±)-8B1i-4 [**(±)-19**]


f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
20
30
40
50
60
70
80
90
100
110
120
130
140
Cl
N
O
Me

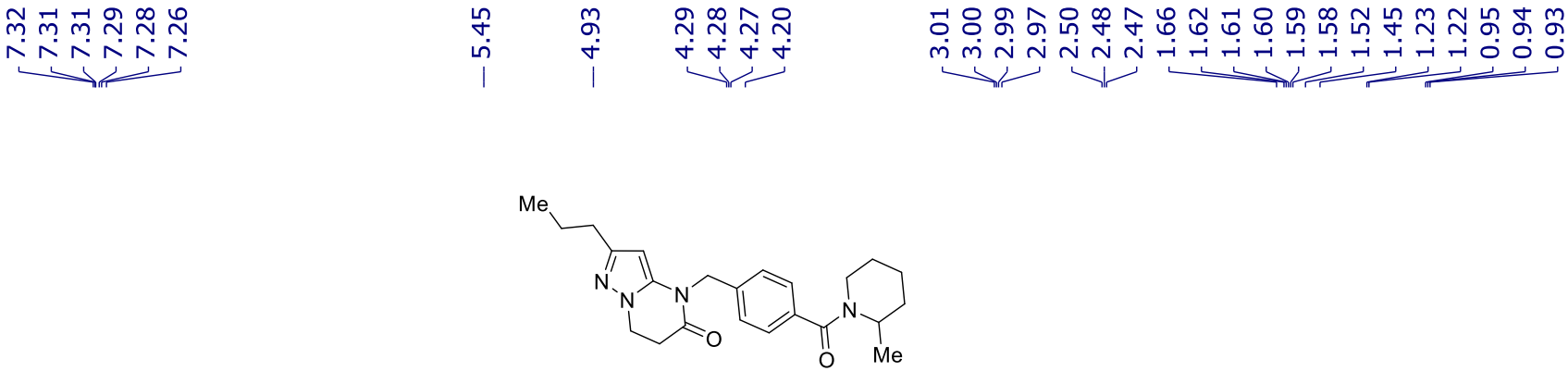
(±)-8B1i-4 [**(±)-19**]

COSY, 700 MHz, $CDCl_3$, 10 °C

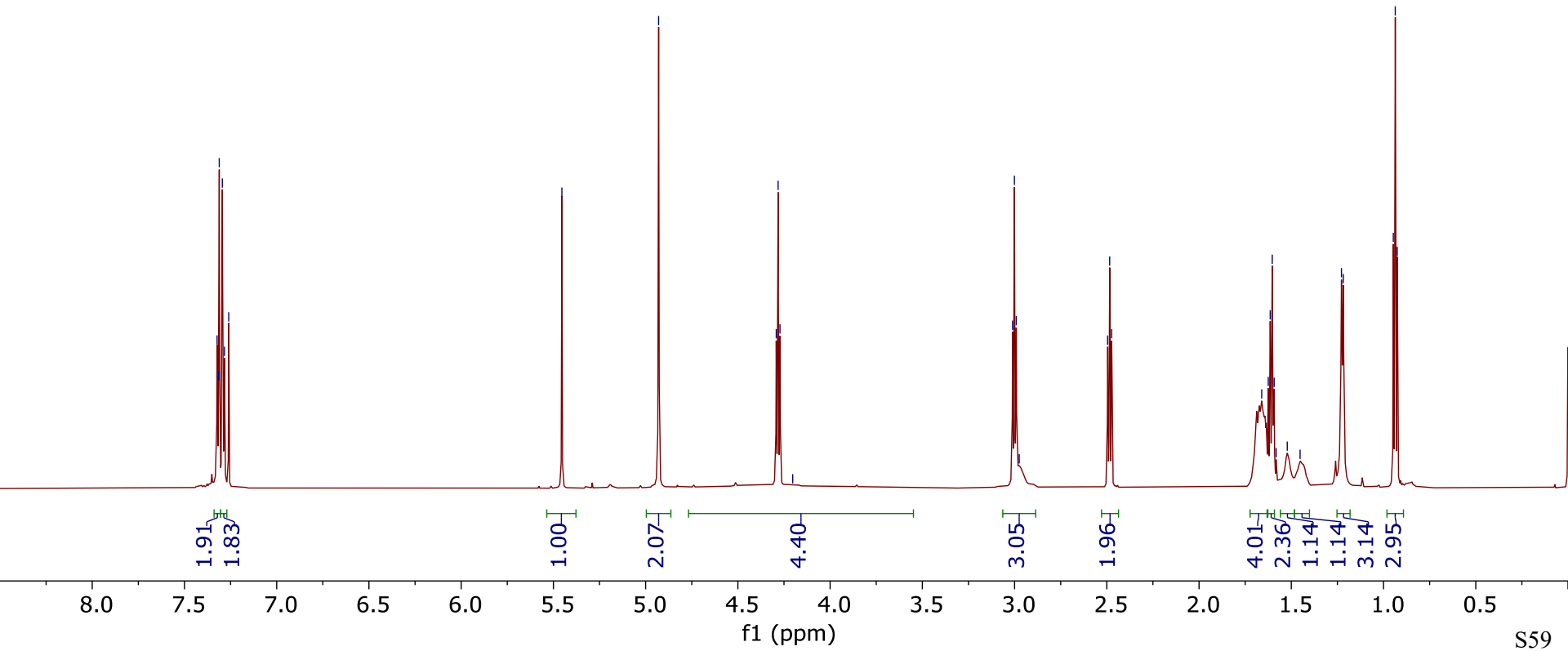


(±)-8B1i-4 [**(±)-19**]

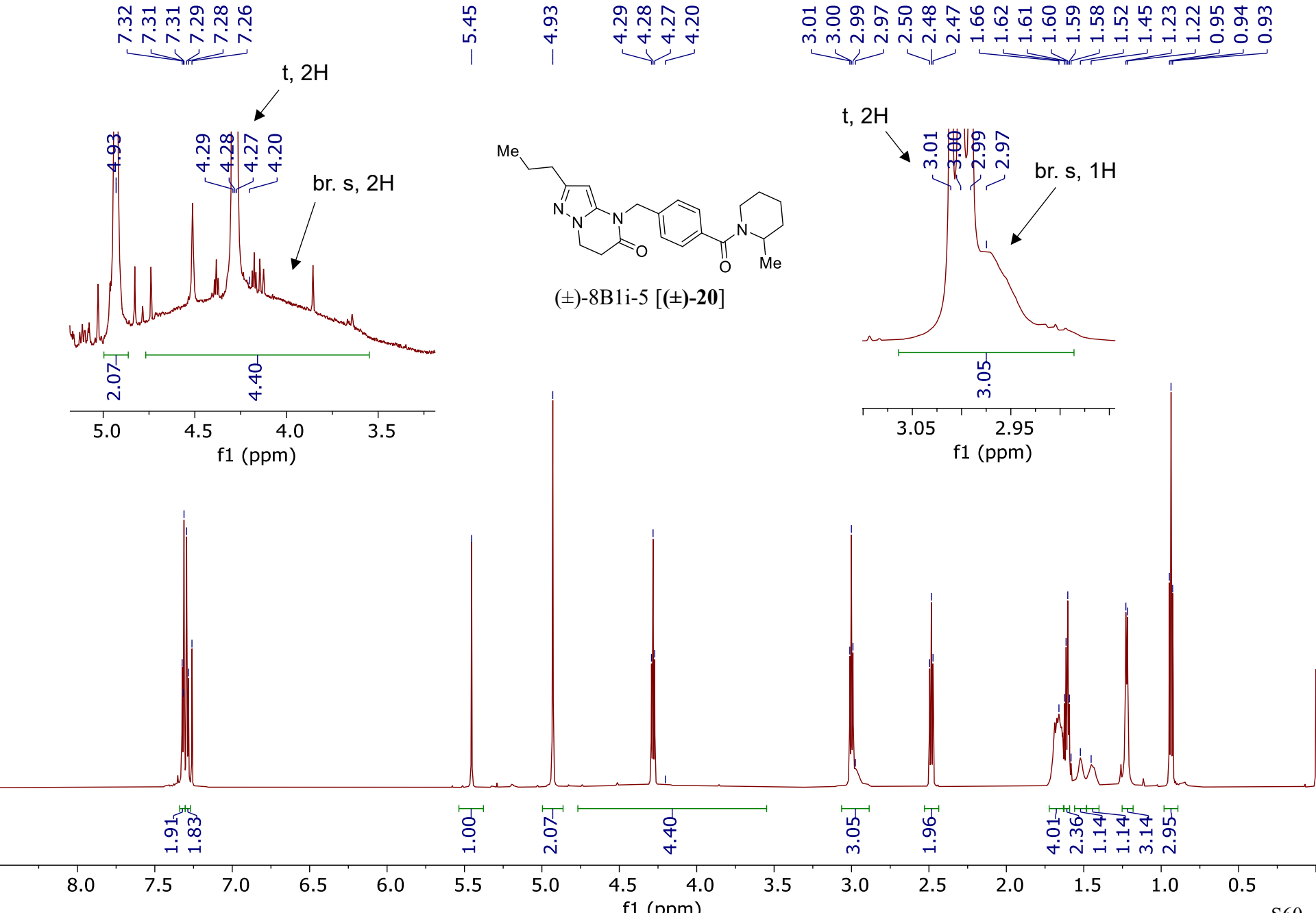
^{1}H, 700 MHz, $CDCl_3$, 40 °C



(±)-4-(4-(2-Methylpiperidine-1-carbonyl)benzyl)-2-propyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-5] [**(±)-20**]



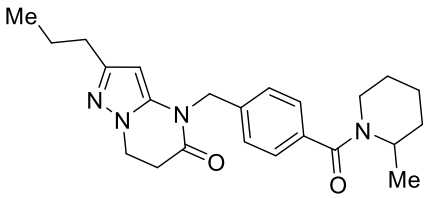
^{1}H, 700 MHz, $CDCl_3$, 40 °C



(±)-8B1i-5 [**(±)-20**]

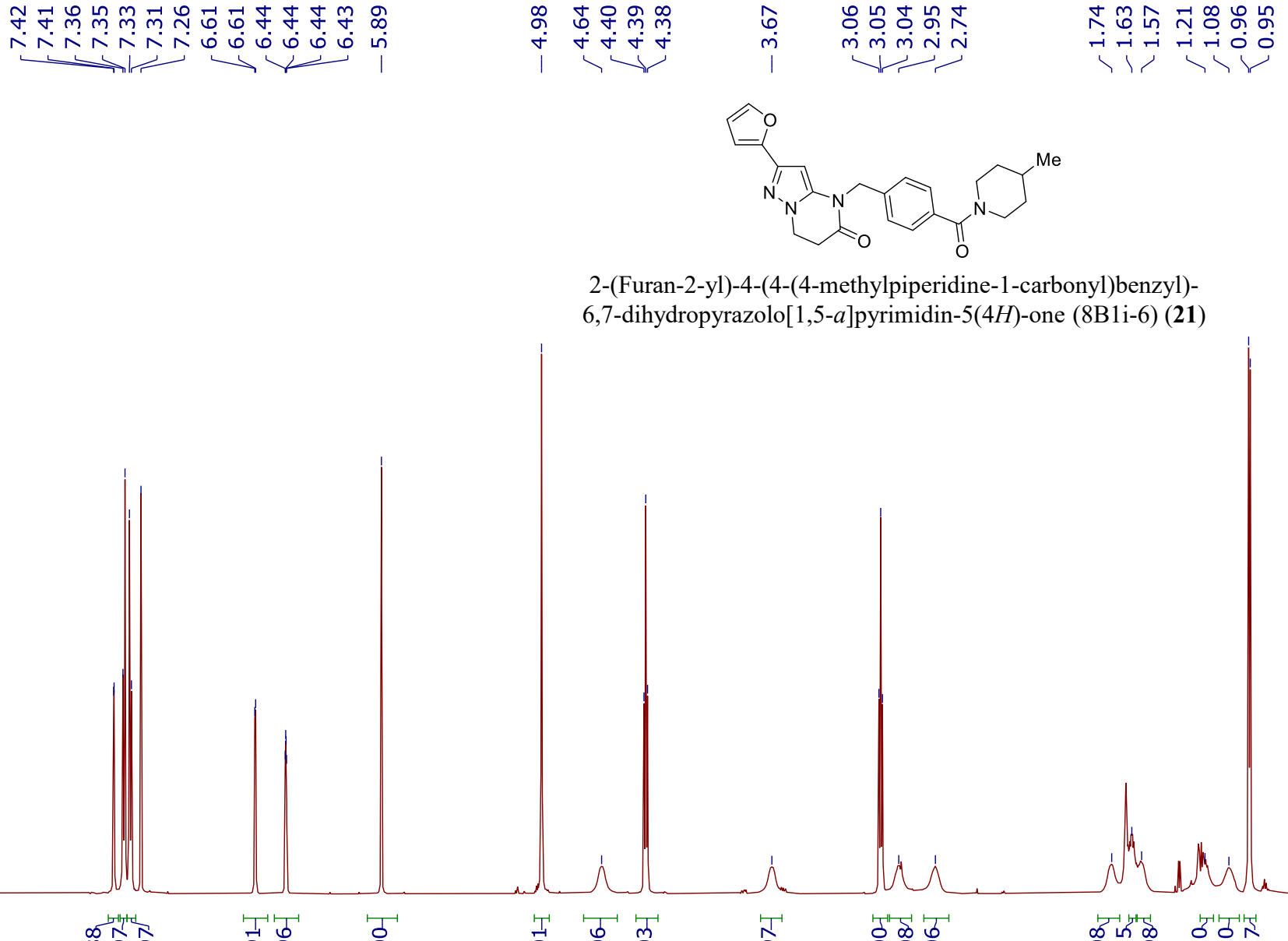
$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$, 40 °C

170.16
165.56
153.95
141.53
137.32
136.80
127.54
127.09
90.18
77.34
77.16
76.98
47.36
43.09
31.90
30.79
30.52
26.21
22.81
19.06
16.33
14.00



(±)-8B1i-5 [**(±)-20**]

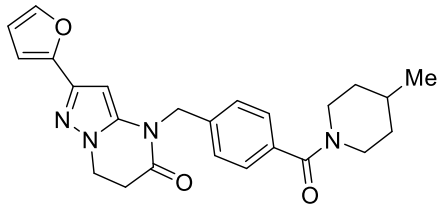
^{1}H, 700 MHz, $CDCl_3$



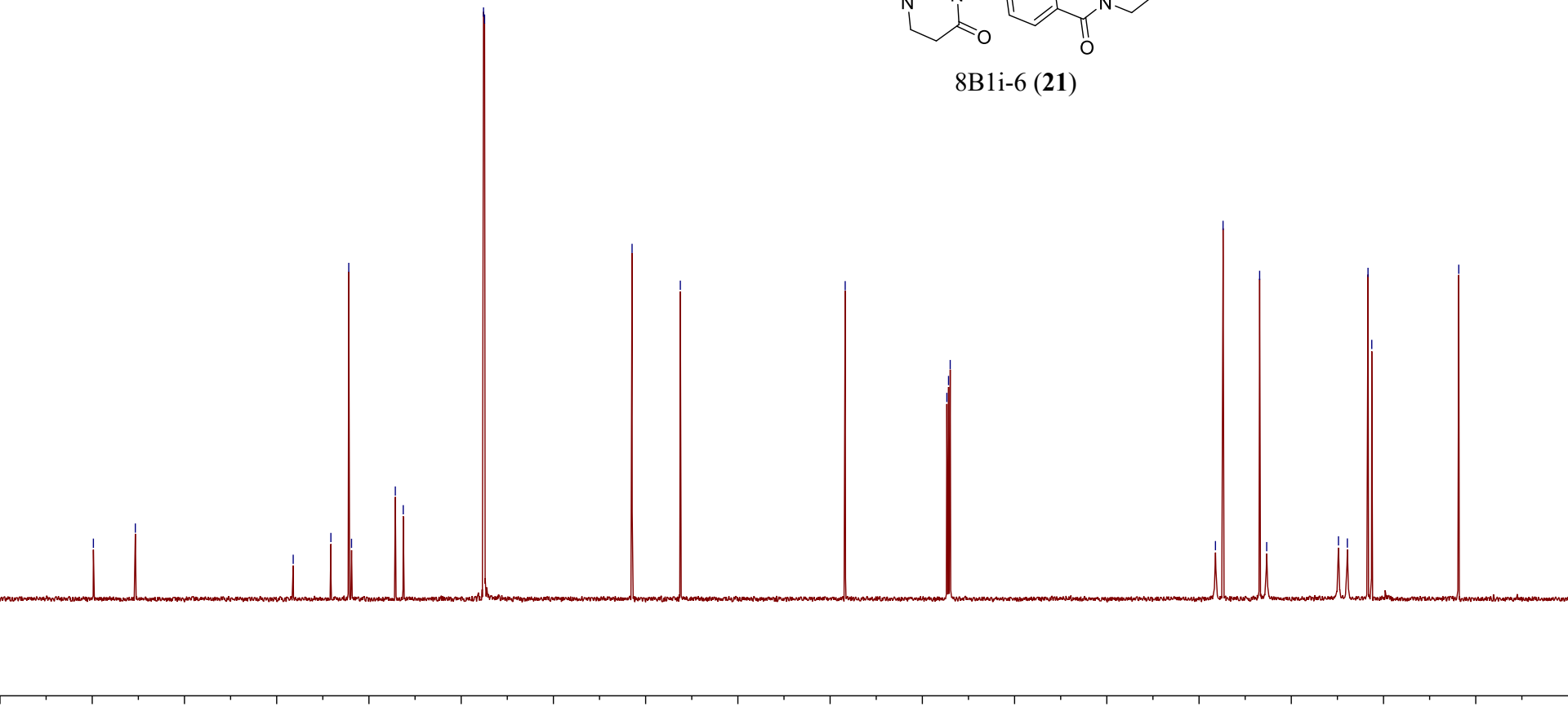
2-(Furan-2-yl)-4-(4-(4-methylpiperidine-1-carbonyl)benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (8B1i-6) (**21**)

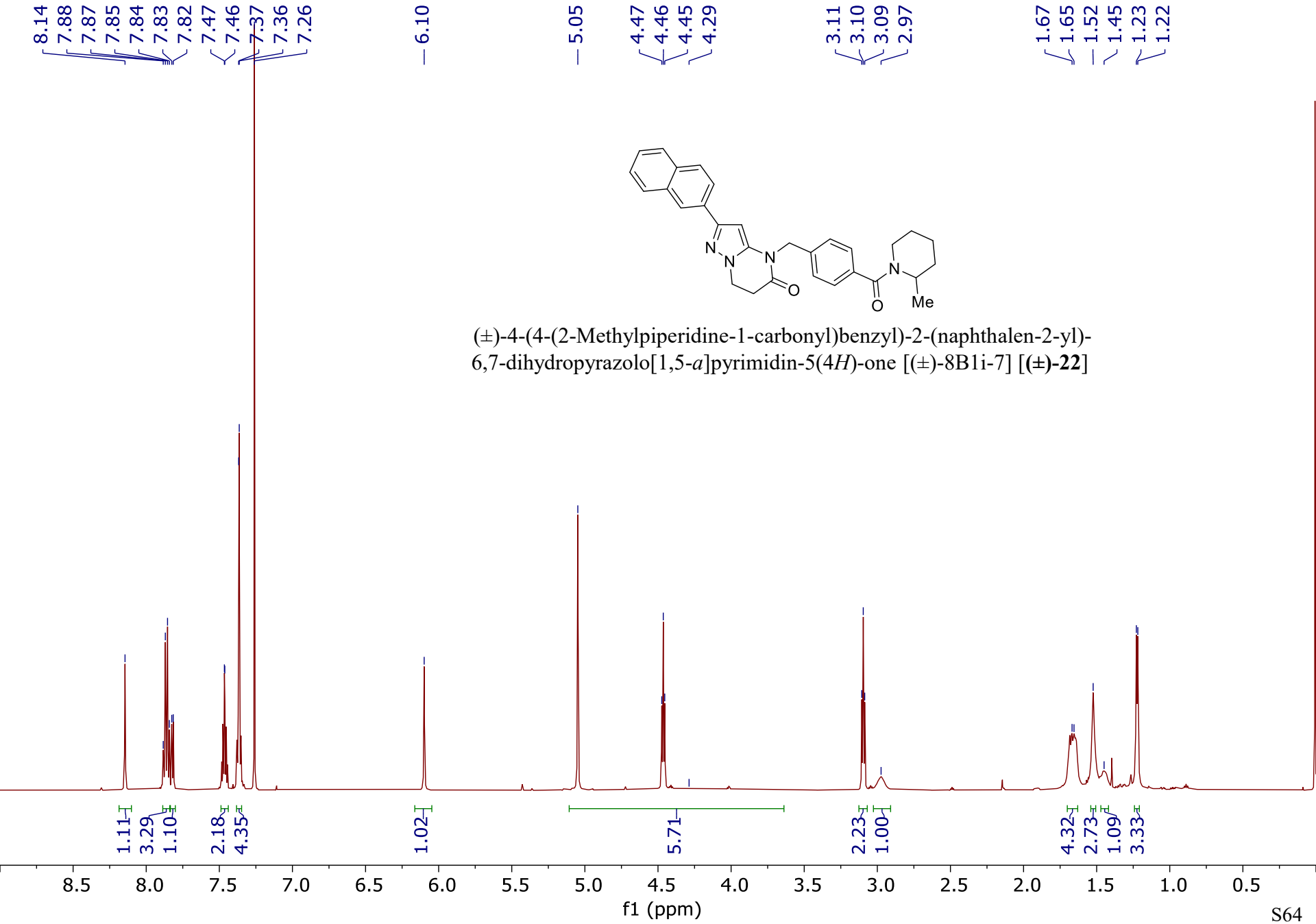
$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$

169.87
165.33
148.21
144.12
142.19
141.89
137.14
136.28
127.58
127.46
111.47
106.24
88.37
77.34
77.16
76.98
48.22
47.40
43.43
42.67
34.88
33.92
31.68
31.27
21.84



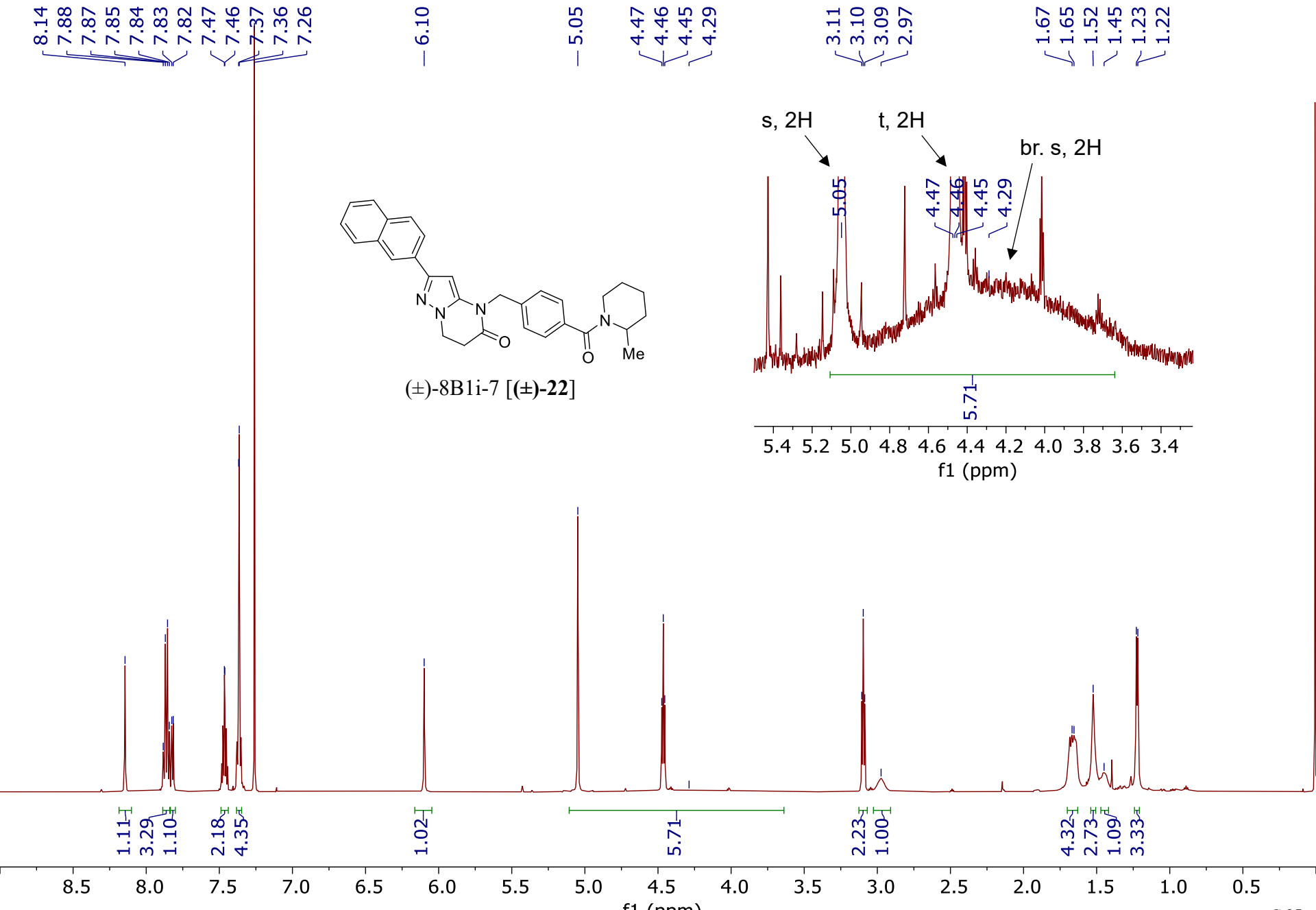
8B1i-6 (**21**)





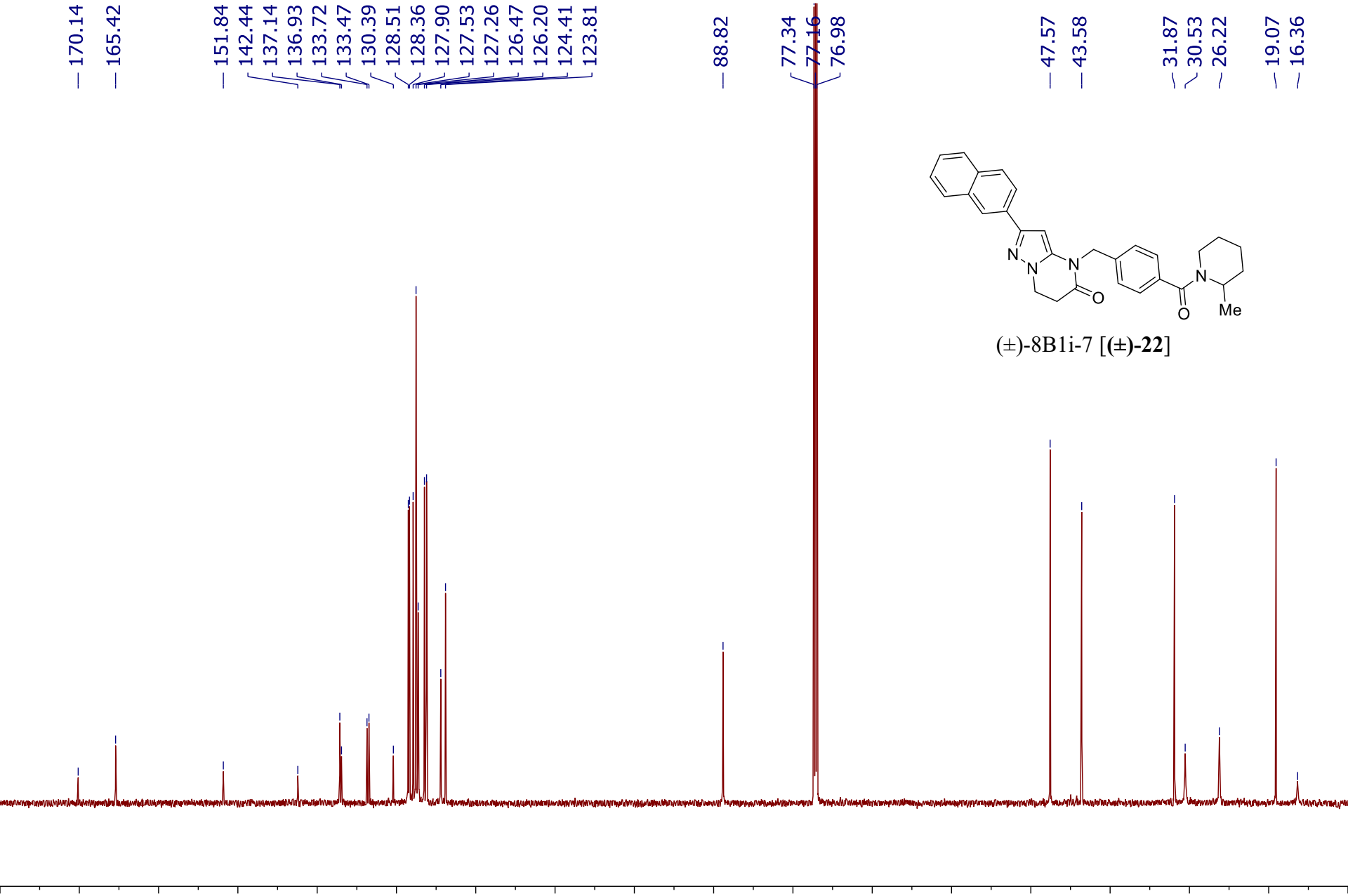
(±)-4-(4-(2-Methylpiperidine-1-carbonyl)benzyl)-2-(naphthalen-2-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one [(±)-8B1i-7] [**(±)-22**]

^{1}H, 700 MHz, $CDCl_3$, 40 °C



(±)-8B1i-7 [**(±)-22**]

$^{13}C\{^{1}H\}$, 176 MHz, $CDCl_3$, 40 °C



(±)-8B1i-7 [**(±)-22**]

HSQC, 700, 176 MHz, $CDCl_3$, 40 °C

