

Supplementary Material

Synthesis of medium-sized rings via Conjugate Addition/Ring Expansion (CARE) cascade reactions of diketopiperazines and related bislactams

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Christopher D. Spicer,^a and William P. Unsworth^{a*}

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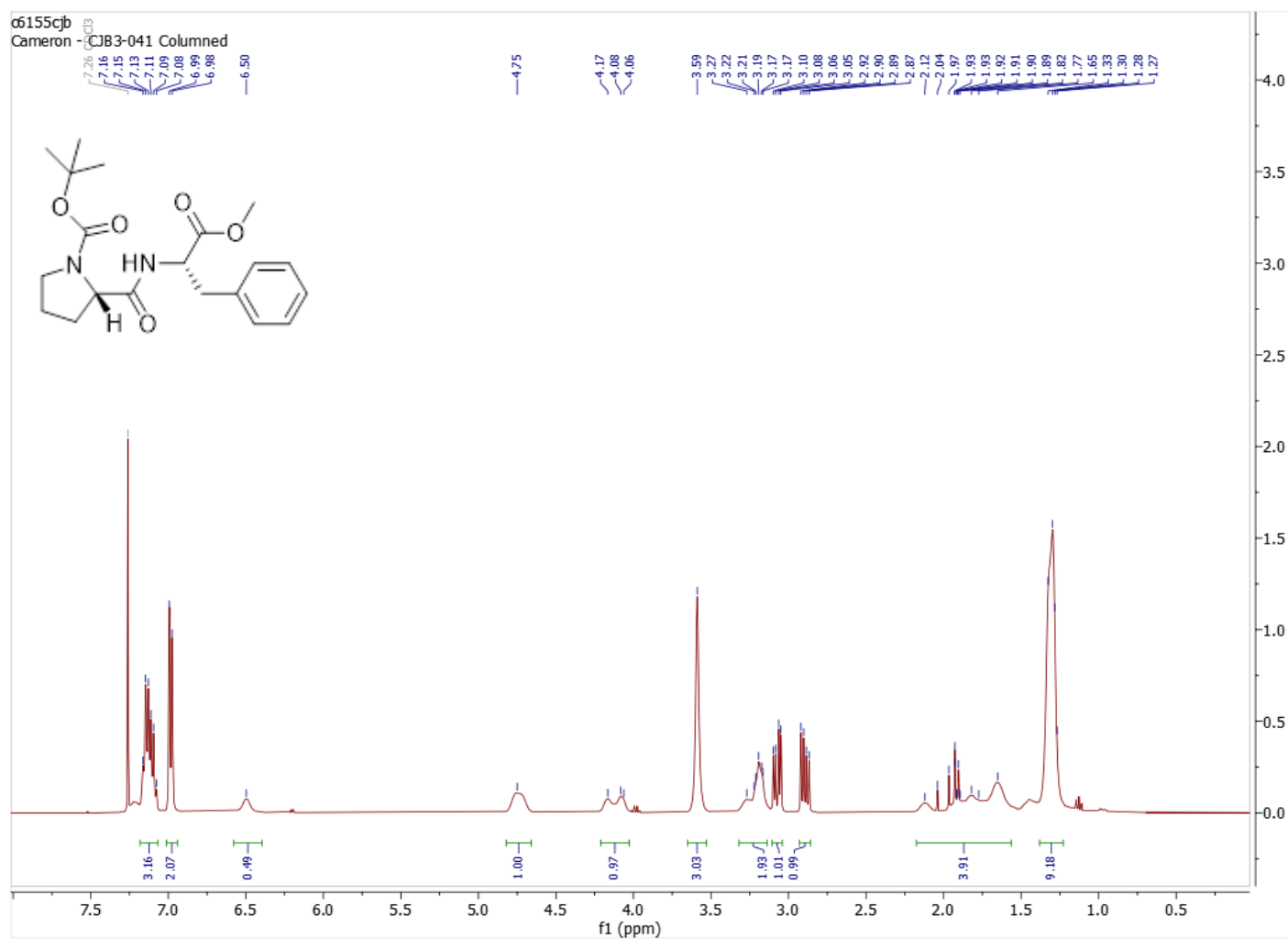
^b Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street,
London WC1H 0AJ (UK)

Email: william.unsworth@york.ac.uk

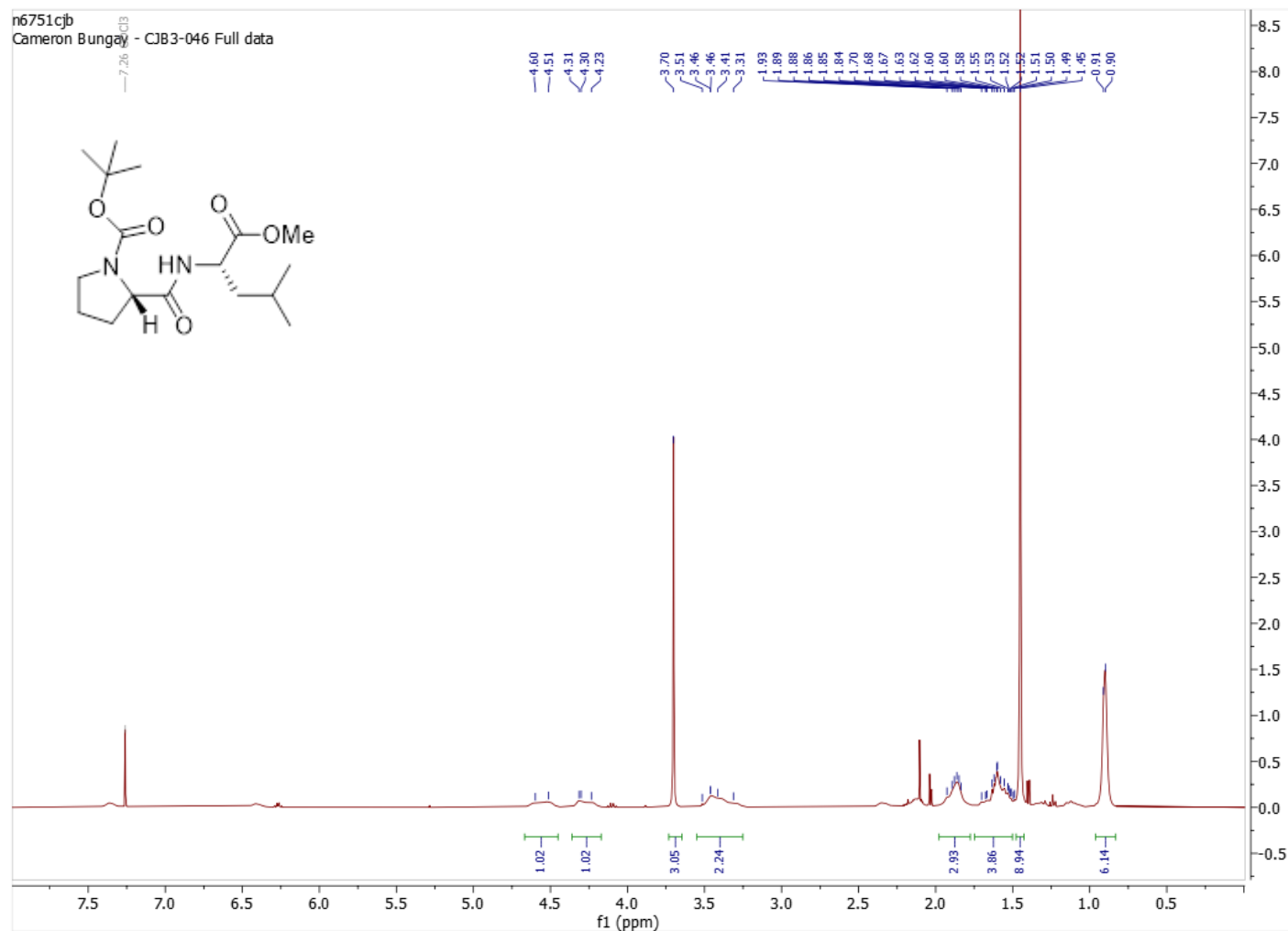
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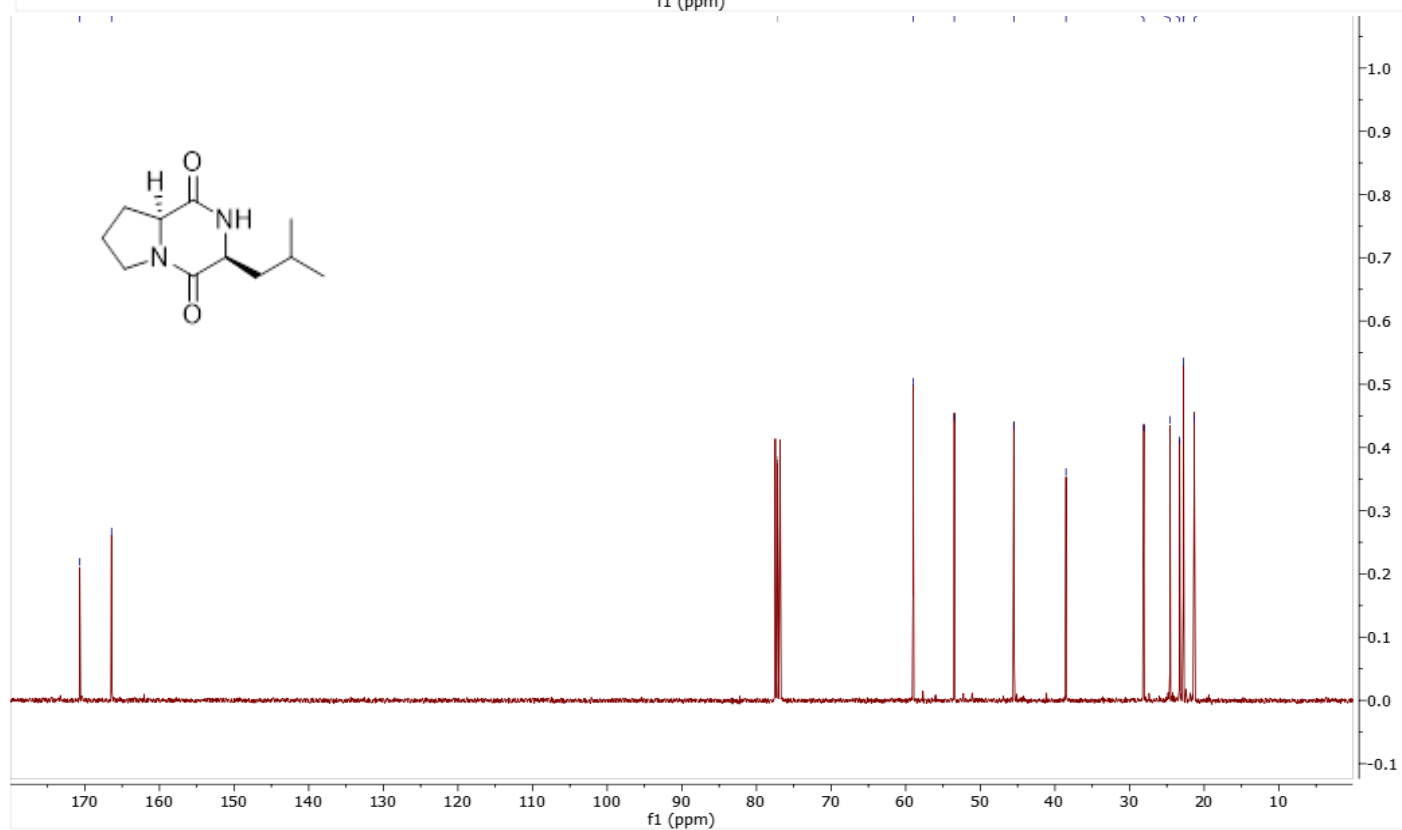
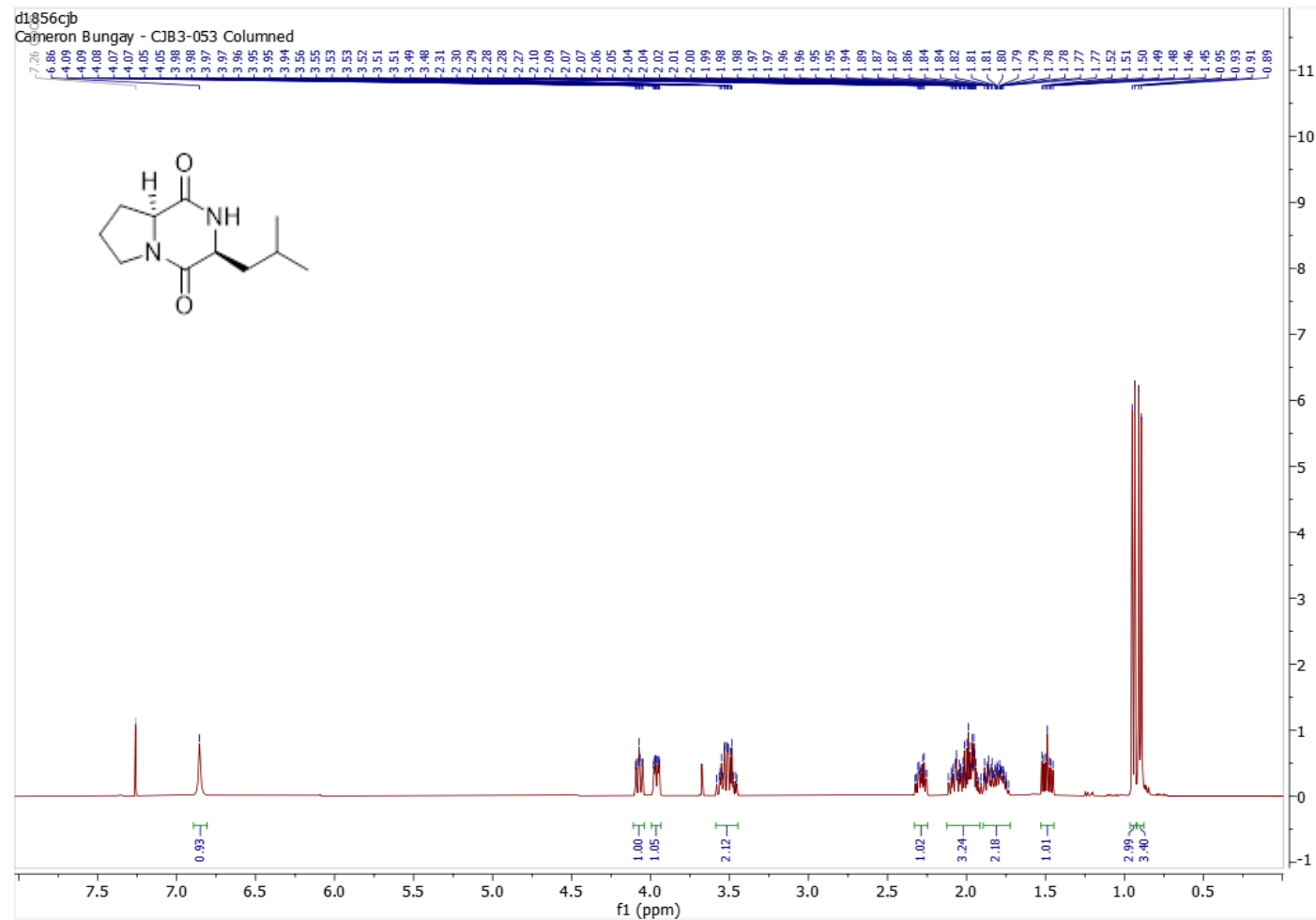
Copies of ¹ H and ¹³ C-NMR spectra of the synthesized compounds	S2
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***tert*-Butyl (S)-2-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate** – in CDCl₃; 400 MHz for ¹H

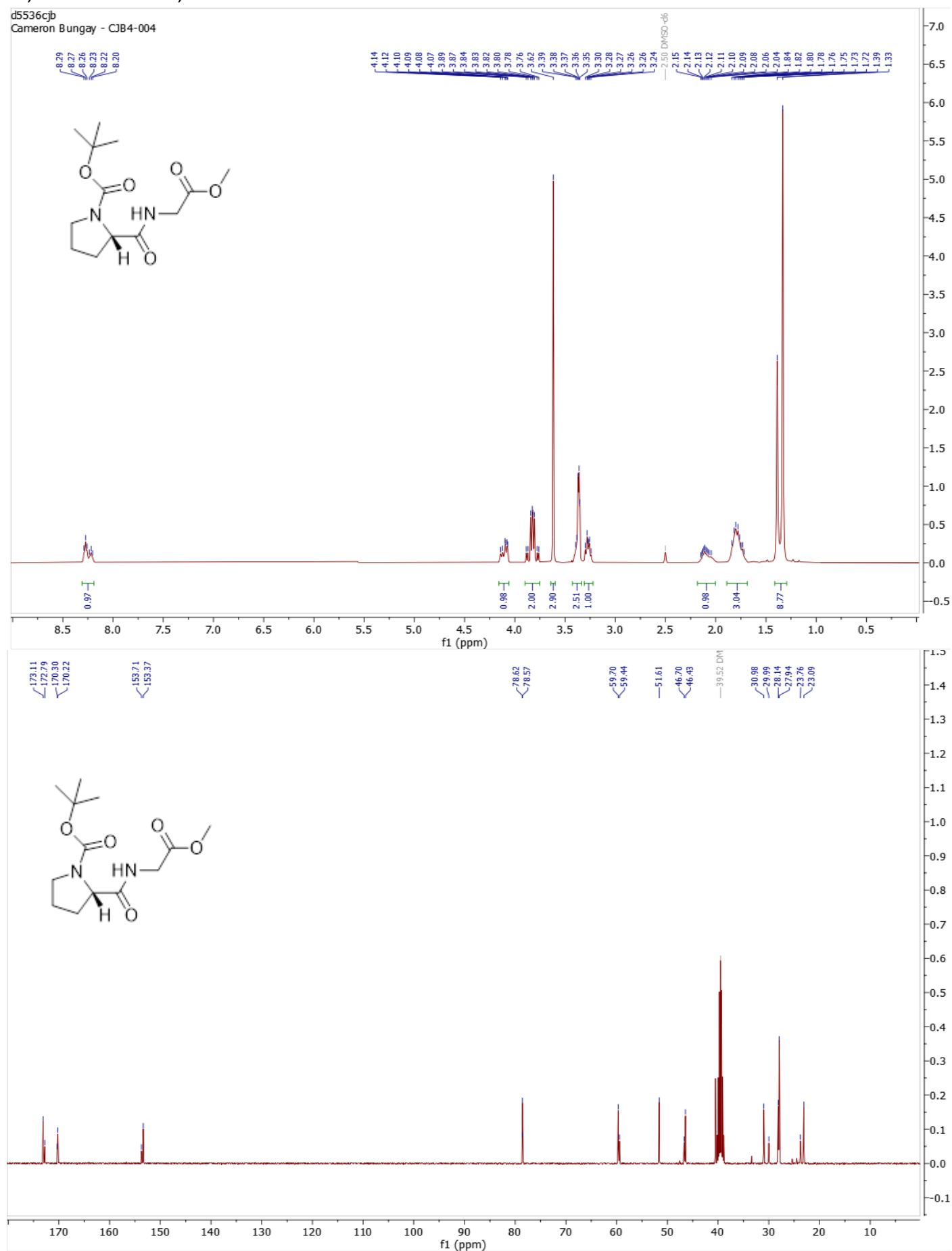


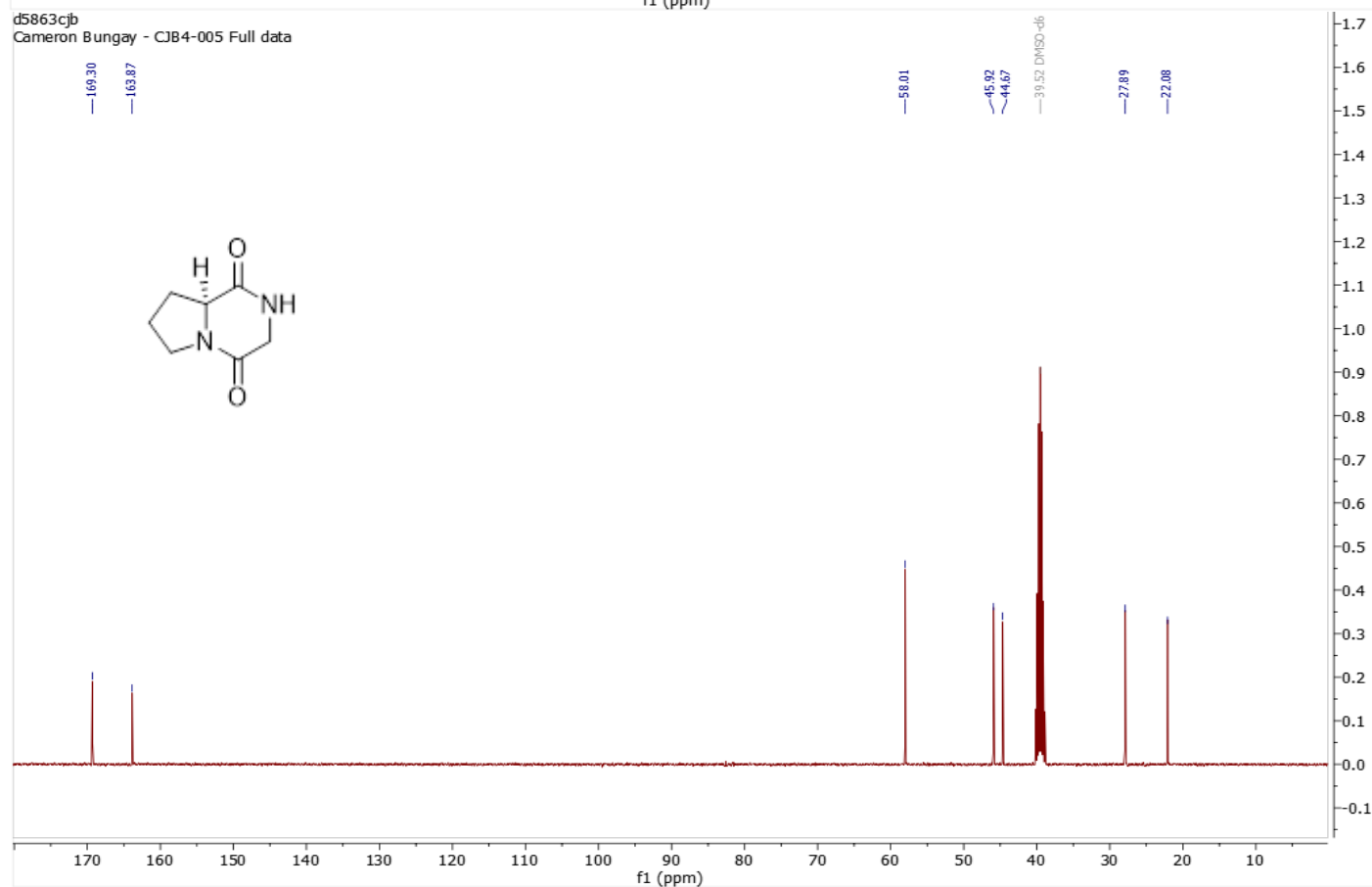
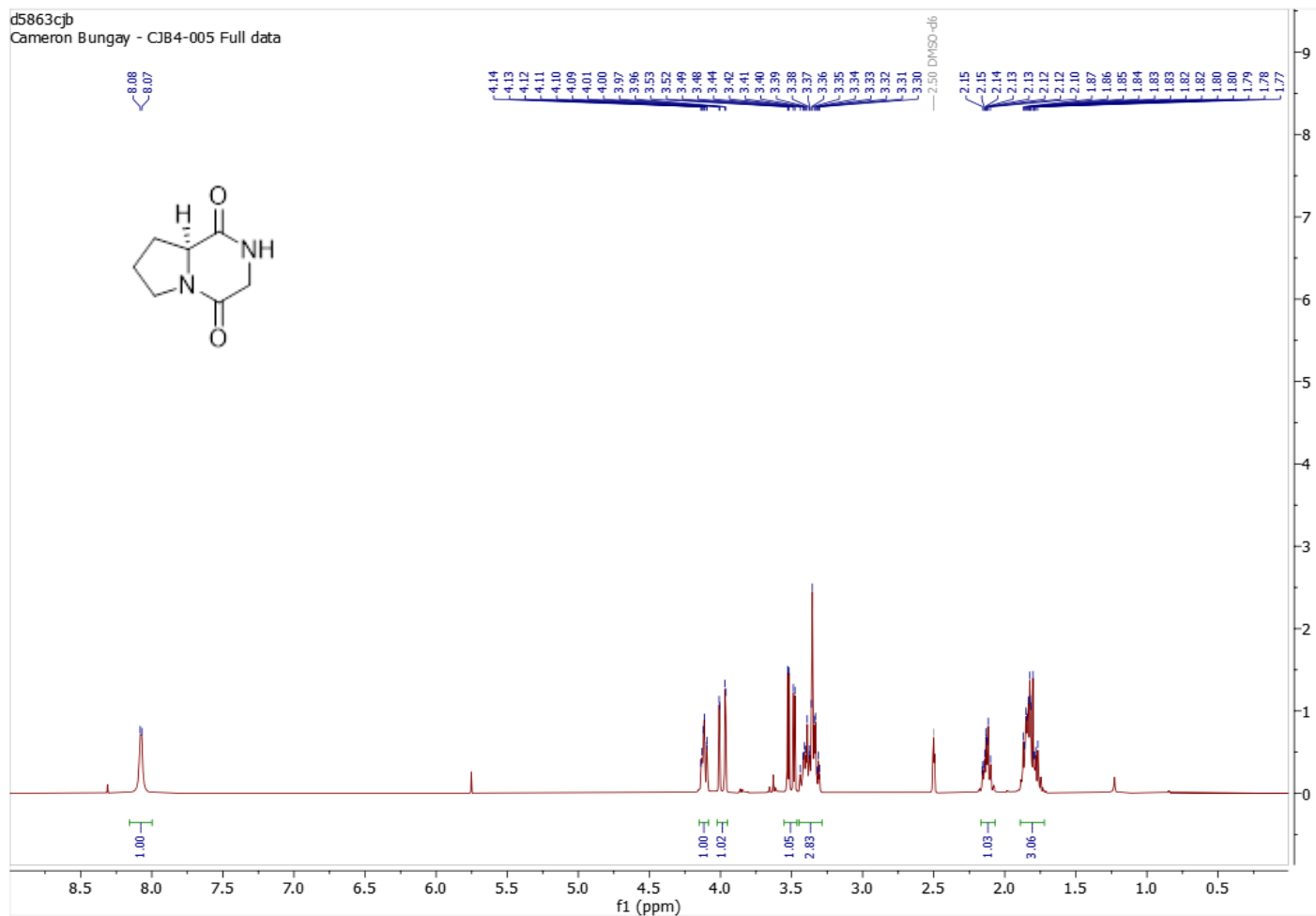
***tert*-Butyl (S)-2-(((S)-1-methoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate** – in CDCl₃; 400 MHz for ¹H



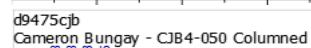
(3*S*,8*aS*)-3-Isobutylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (11b) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

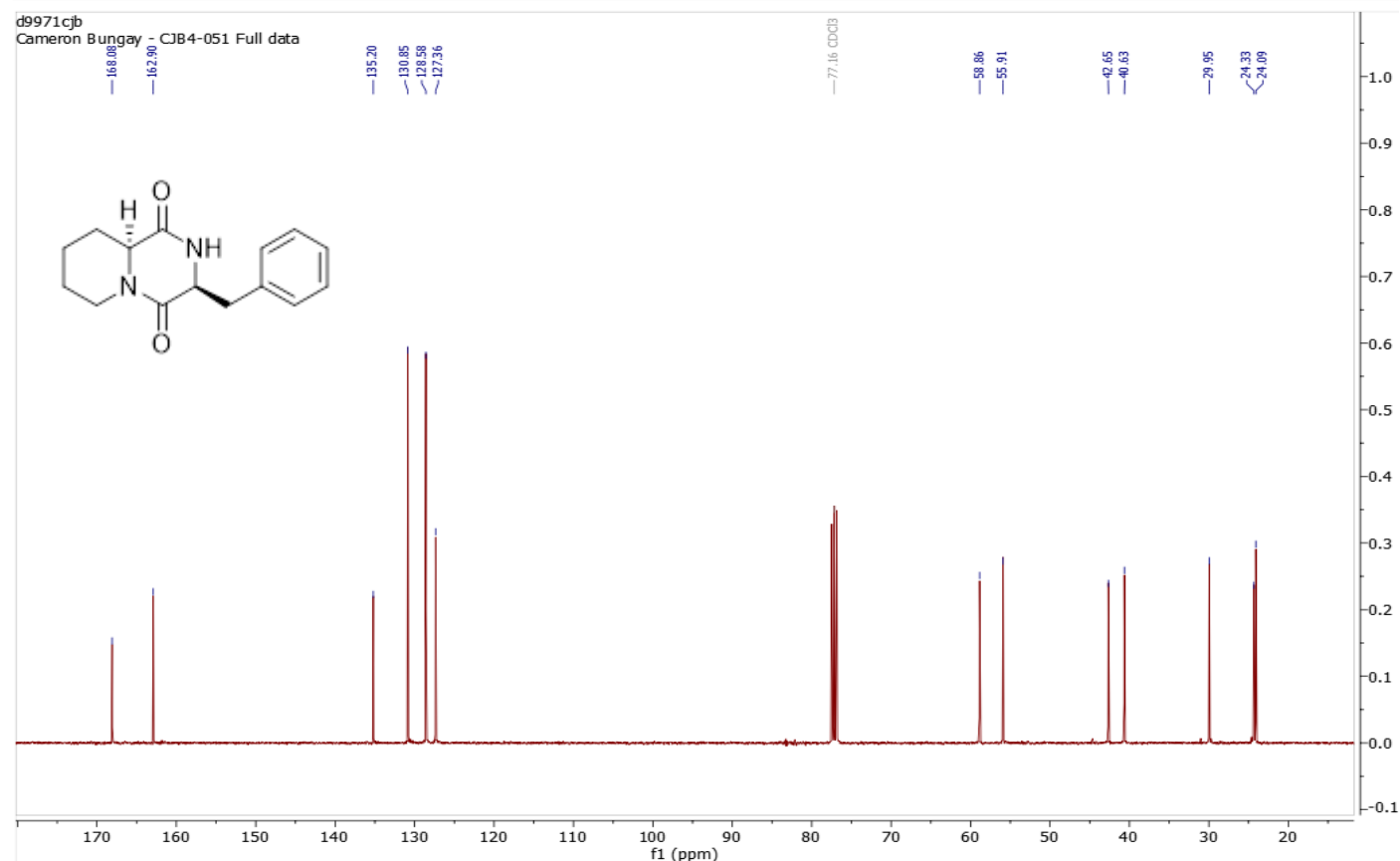
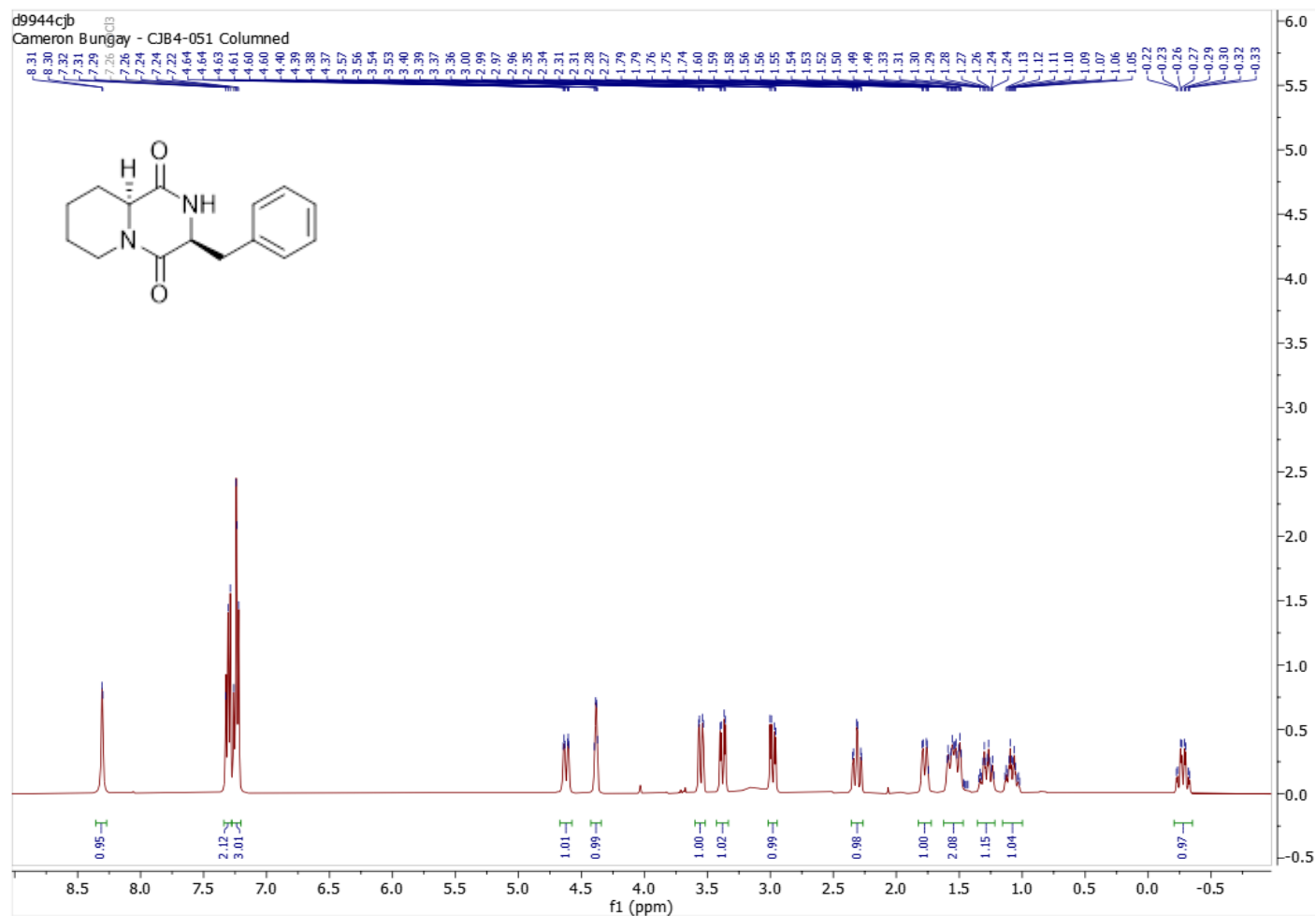
***tert*-Butyl (S)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate** – in d₆-DMSO; 400 MHz for ¹H, 100 MHz for ¹³C, as a 2:1 mixture of rotamers

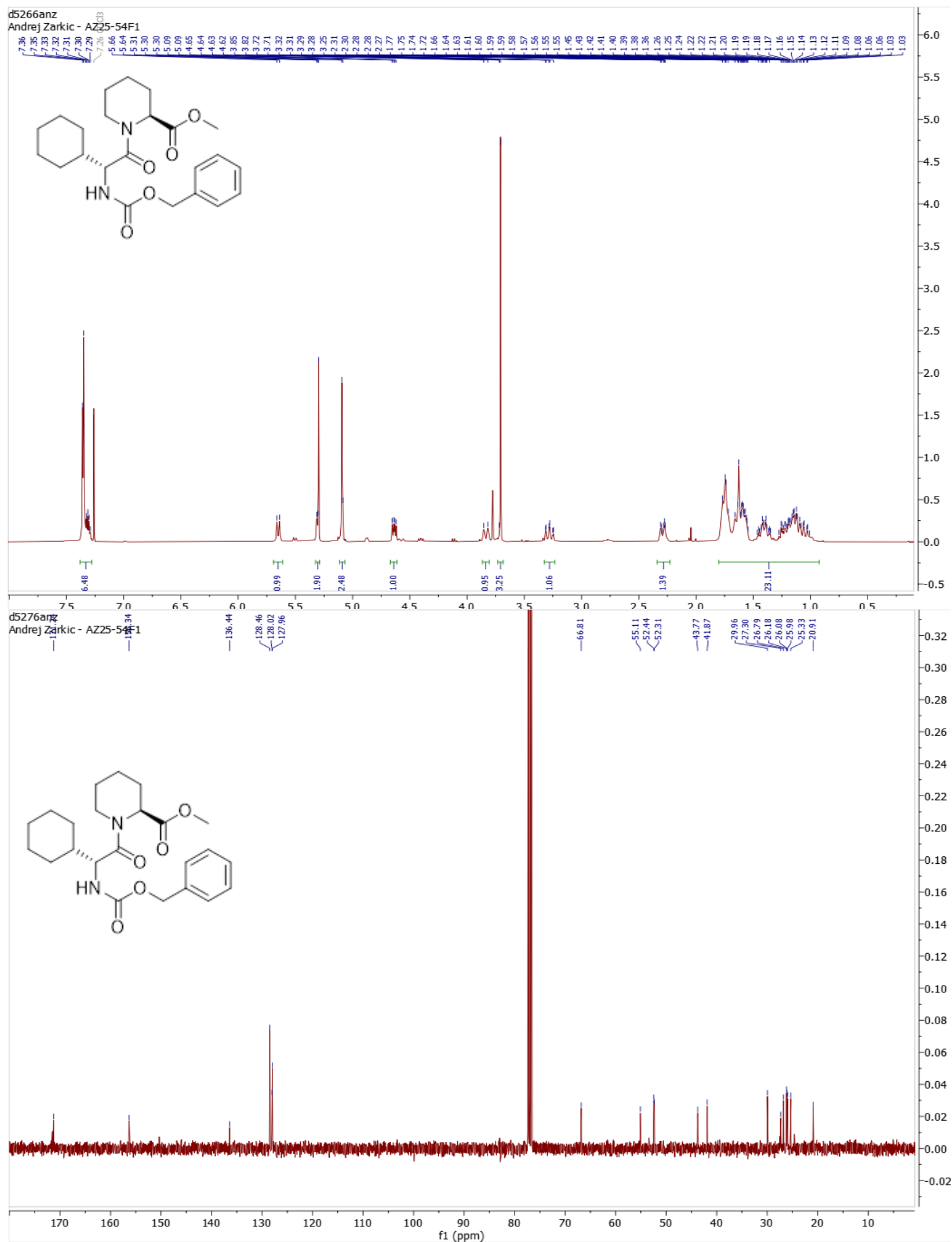


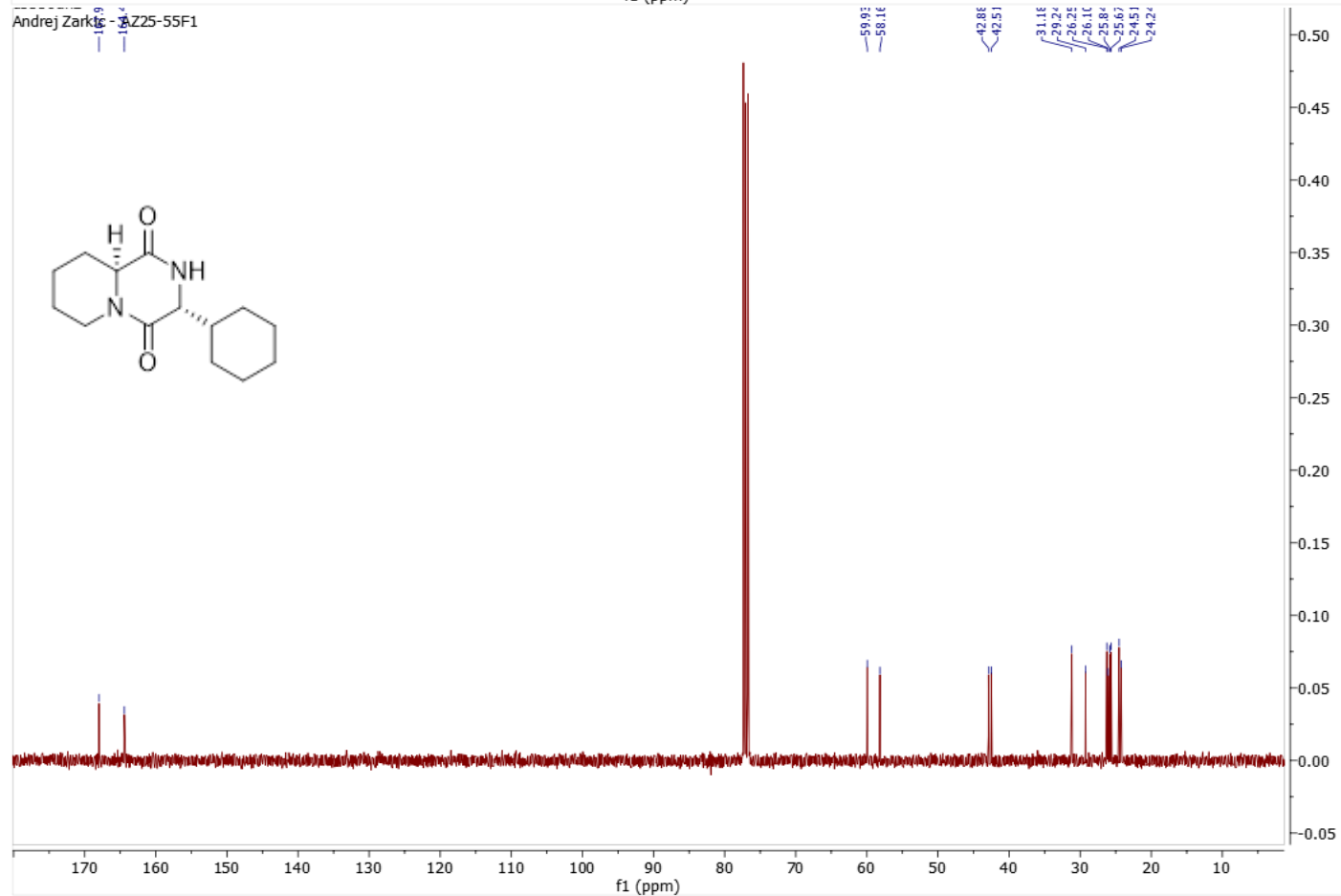
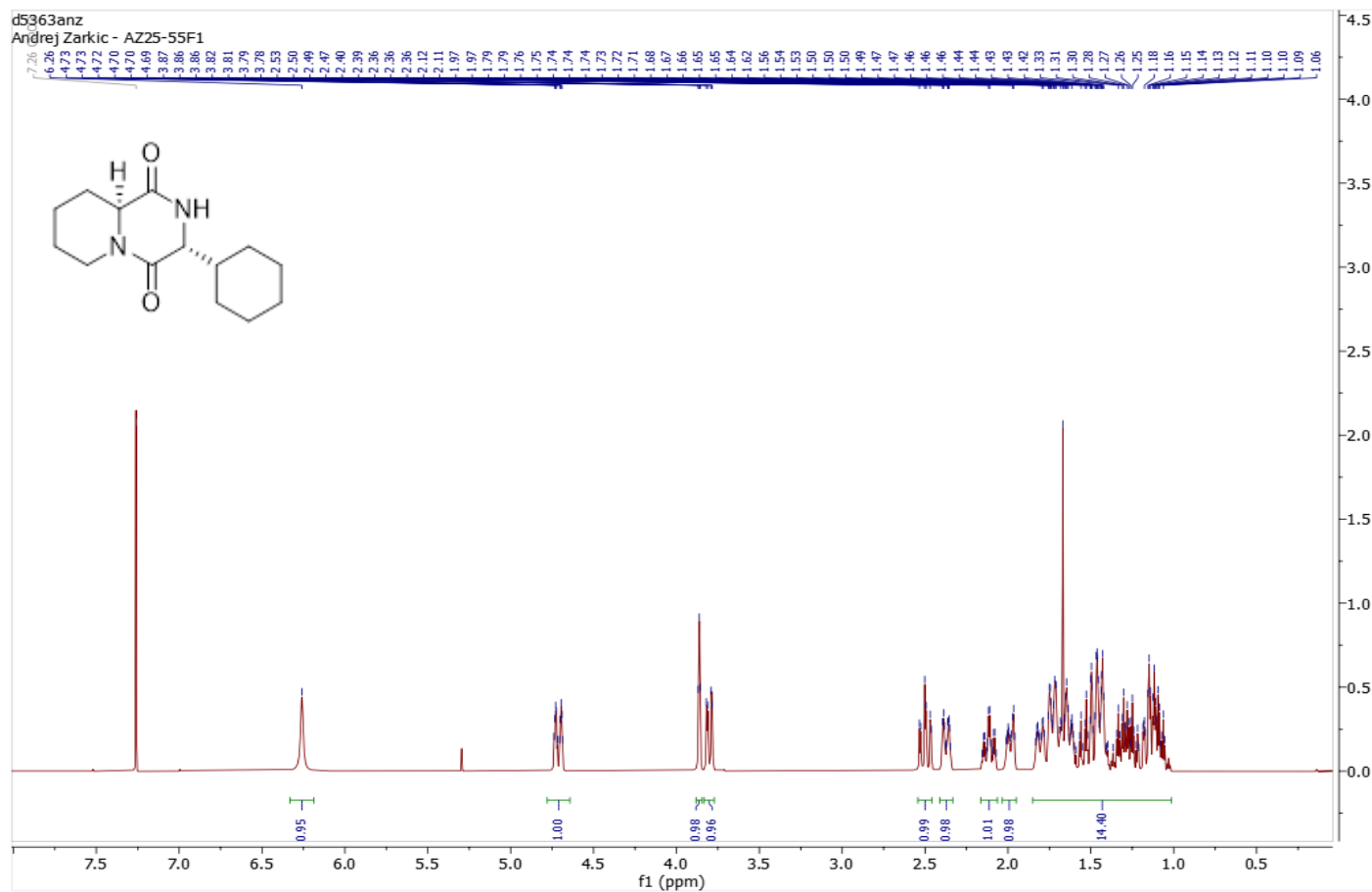
(S)-Hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (11c) – in d₆-DMSO CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

d9475cjb
Cameron Bungay - CJB4-050 Columned

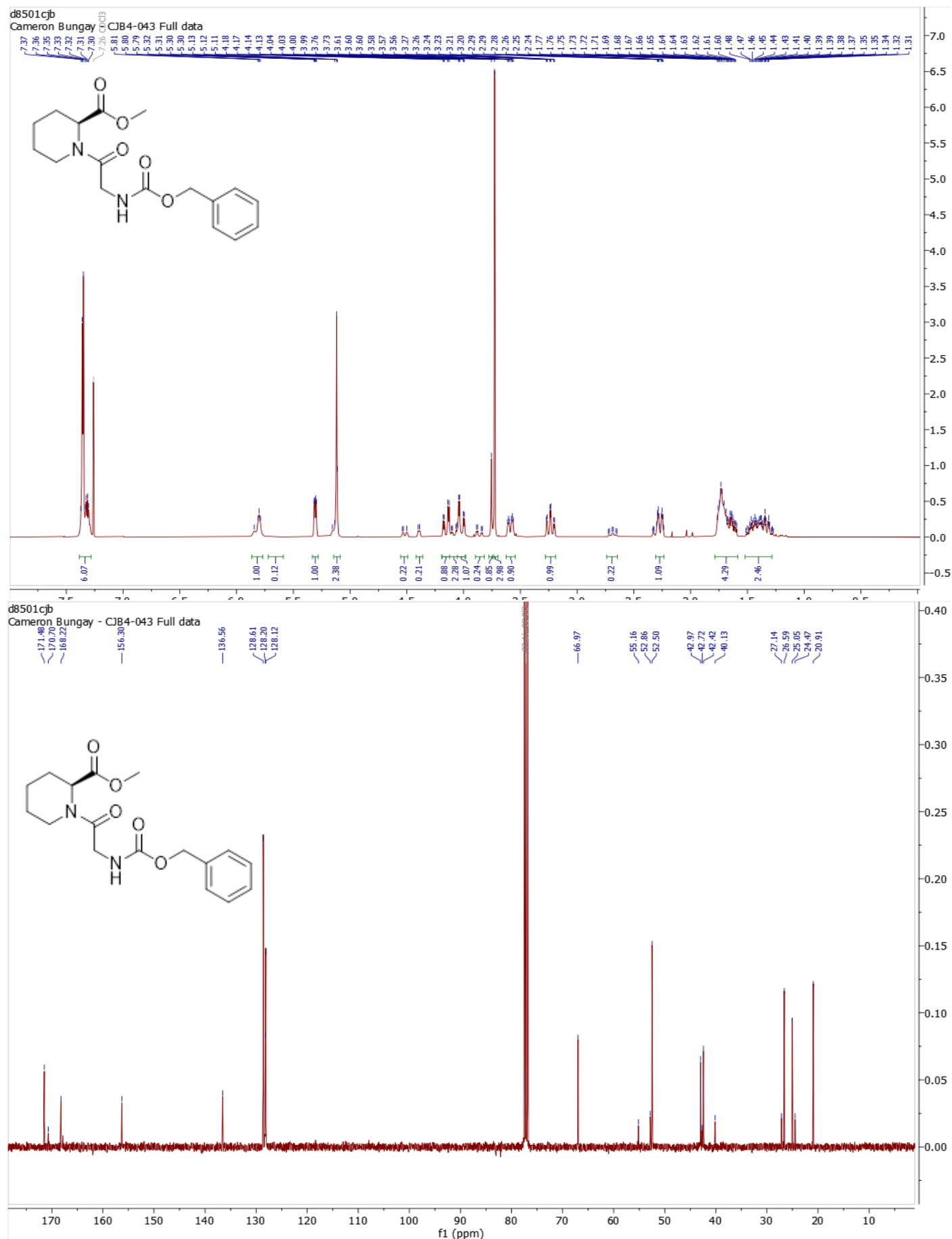


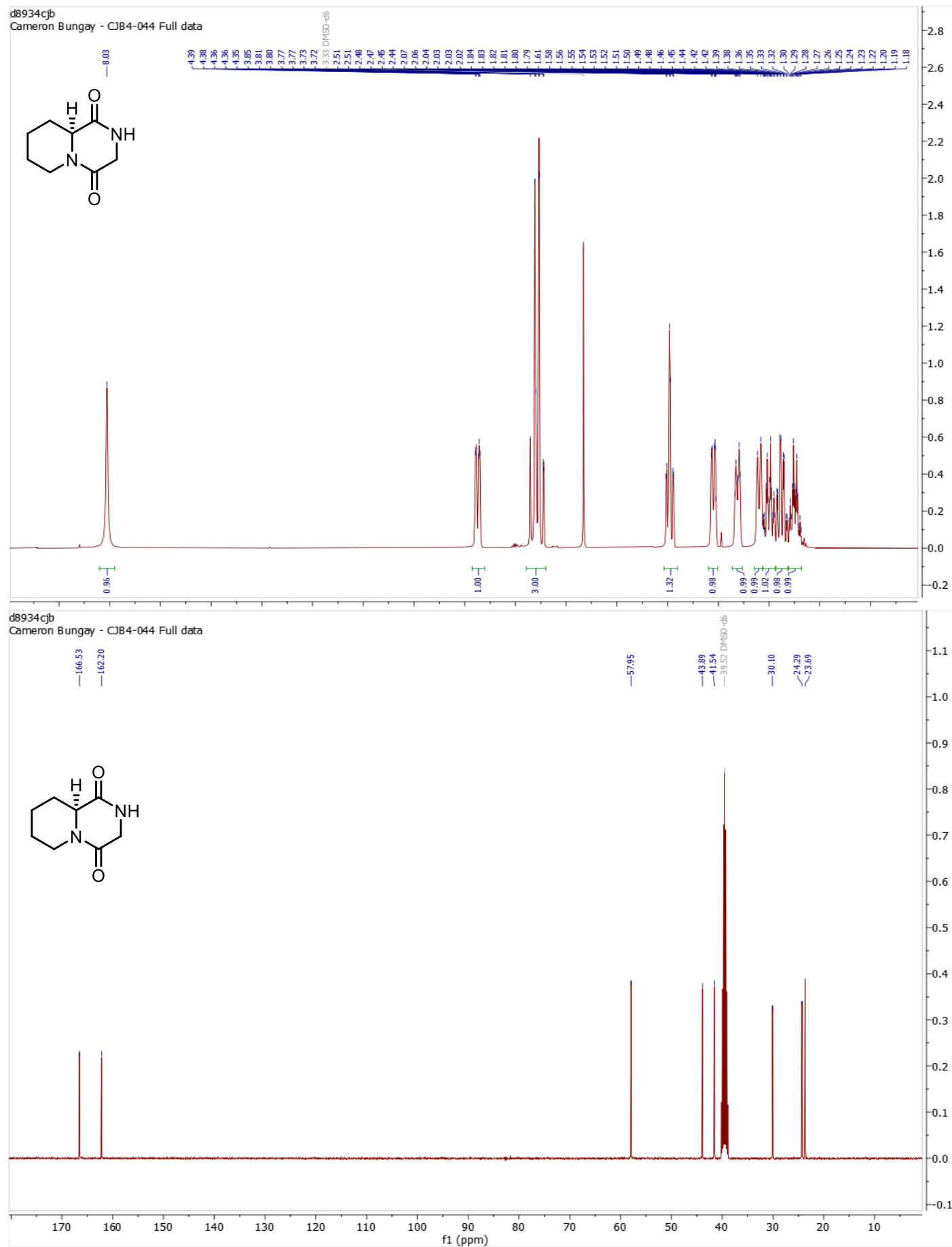
(3*S*,9*aS*)-3-Benzylhexahydro-4*H*-pyrido[1,2-*a*]pyrazine-1,4(6*H*)-dione (11d) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

Methyl (2S)-1-[(2R)-2-(benzyloxycarbonylamino)-2-cyclohexyl-acetyl]piperidine-2-carboxylate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

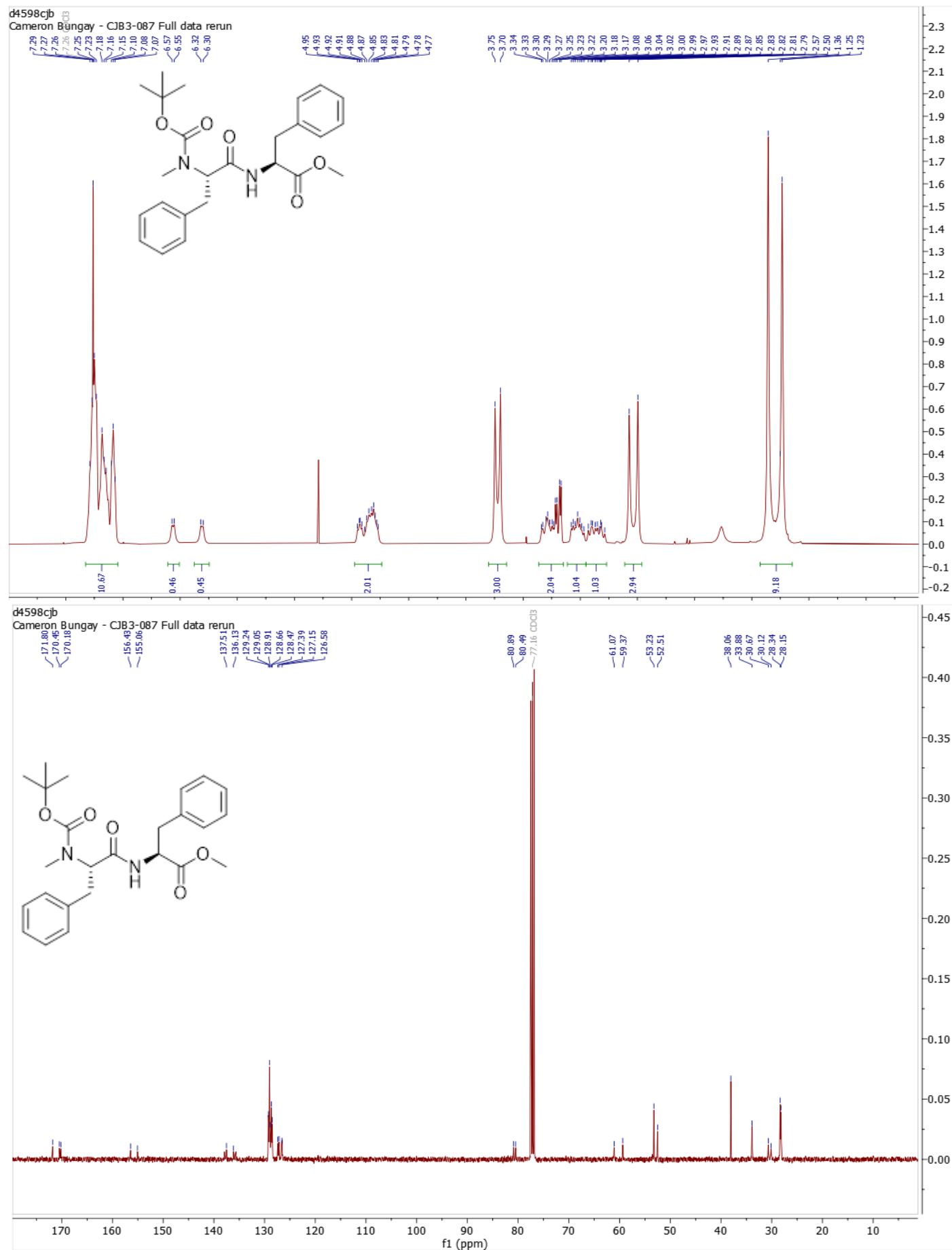
(3*R*,9*aS*)-3-cyclohexyl-3,6,7,8,9,9*a*-hexahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-dione (11e) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

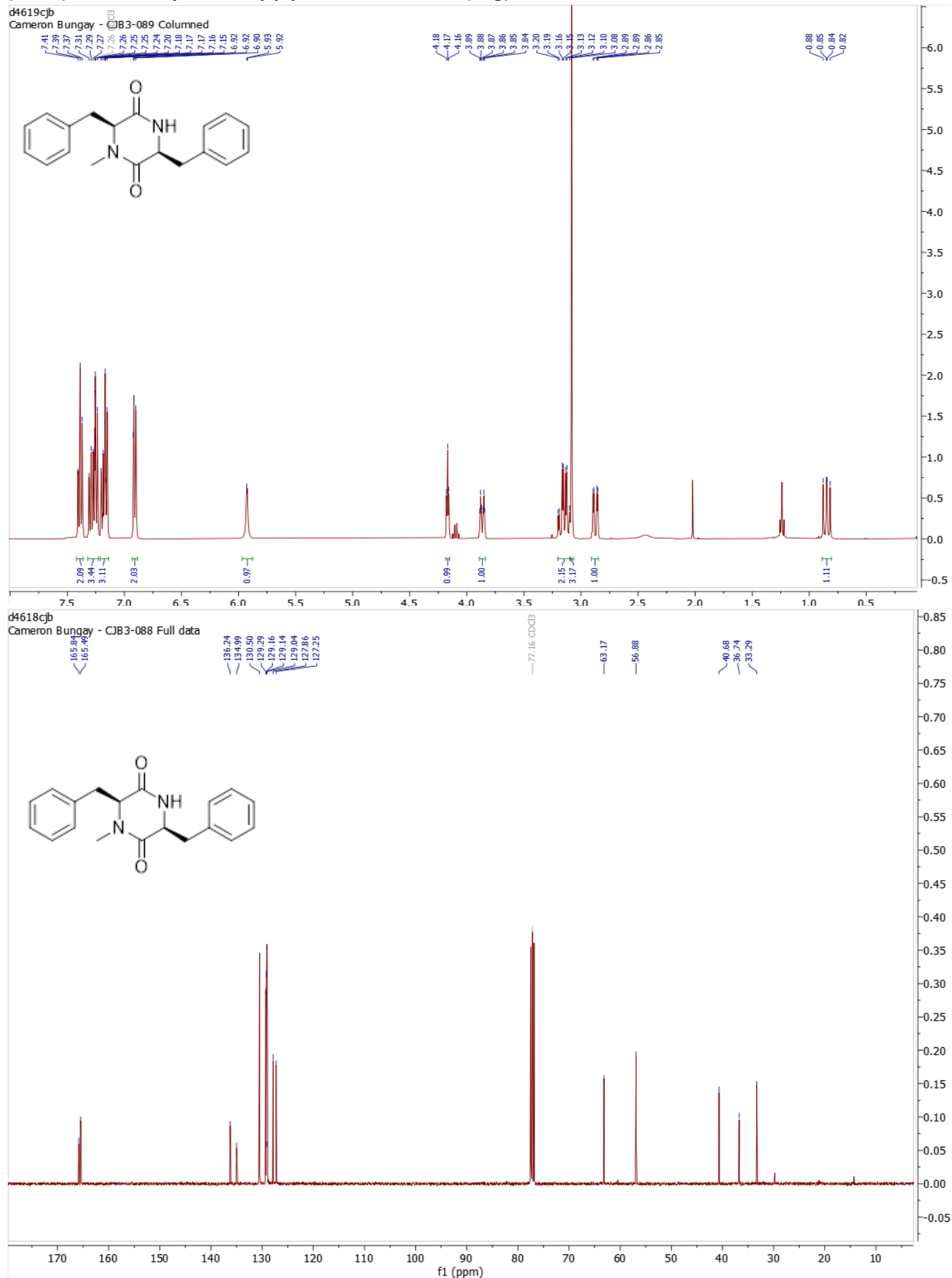
Methyl (S)-1-(((benzyloxy)carbonyl)glycyl)piperidine-2-carboxylate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 4:1 mixture of rotamers

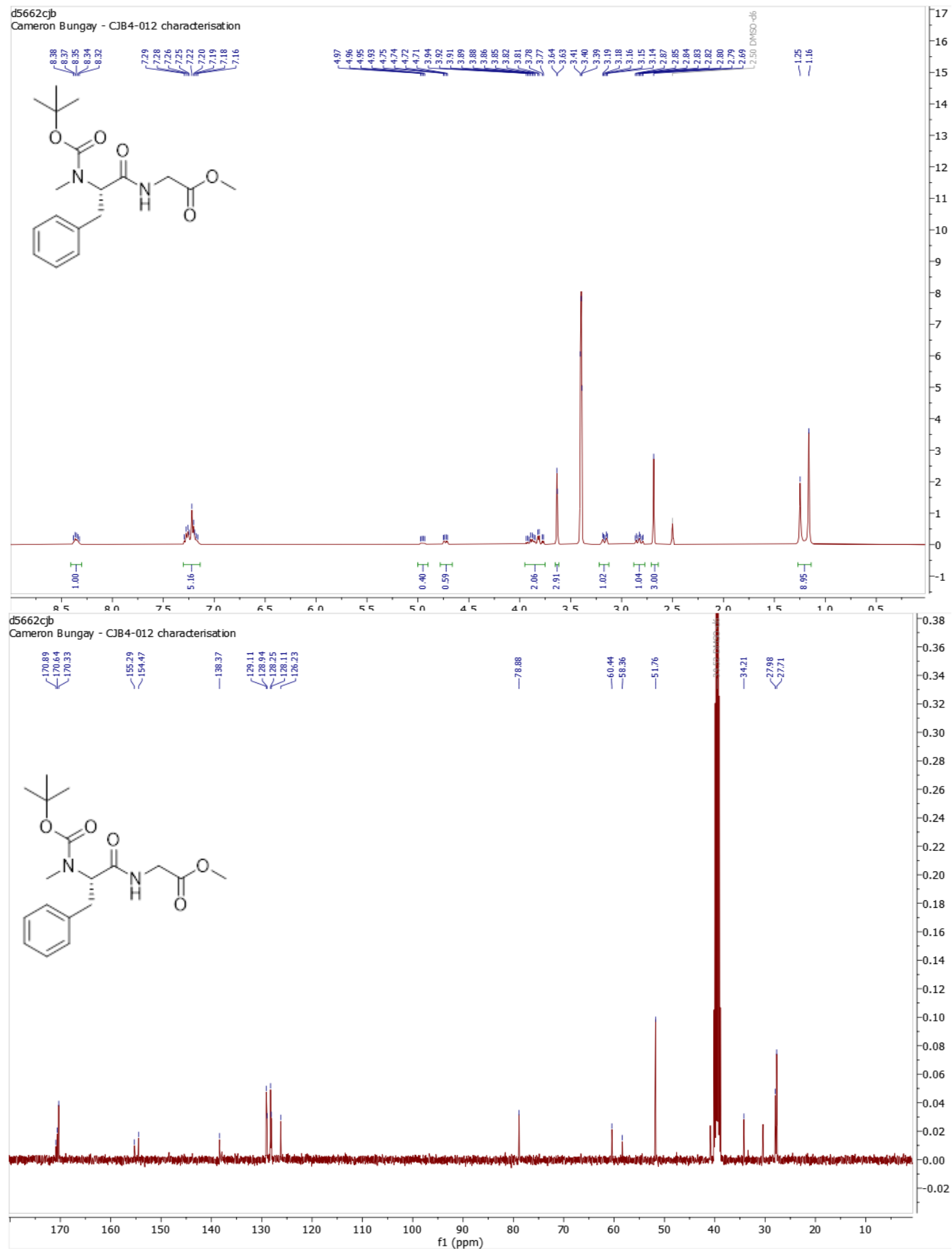


(S)-Hexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (11f) – in d₆-DMSO ; 400 MHz for ¹H, 100 MHz for ¹³C

Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanyl-*L*-phenylalaninate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 1:1 mixture of rotamers



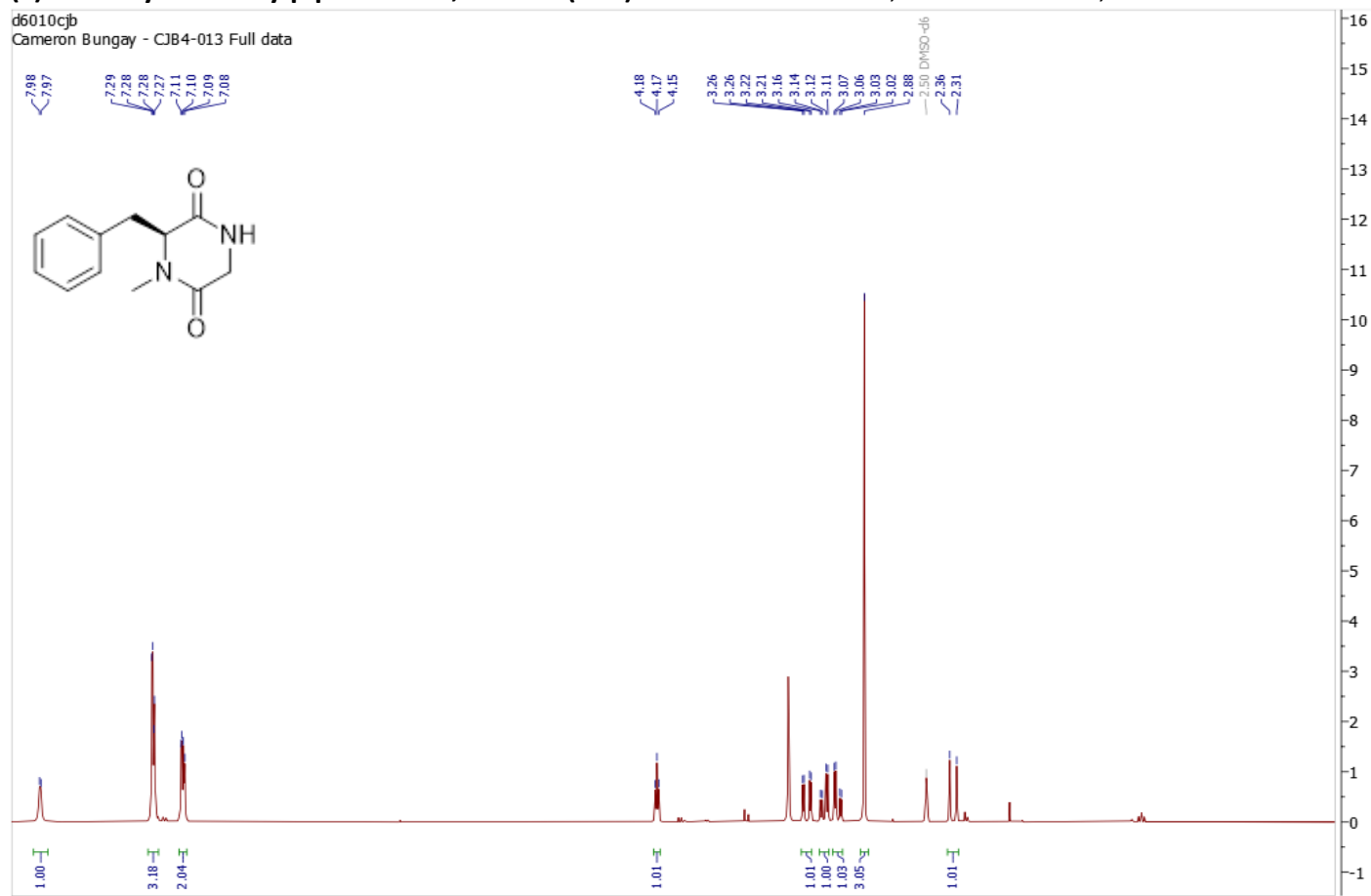
(3S,6S)-3,6-Dibenzyl-1-methylpiperazine-2,5-dione (11g) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanylglycinate – in d_6 -DMSO; 400 MHz for ^1H , 100 MHz for ^{13}C , as a 1:1 mixture of rotamers

(S)-6-Benzyl-1-methylpiperazine-2,5-dione (11h) – in d₆-DMSO CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

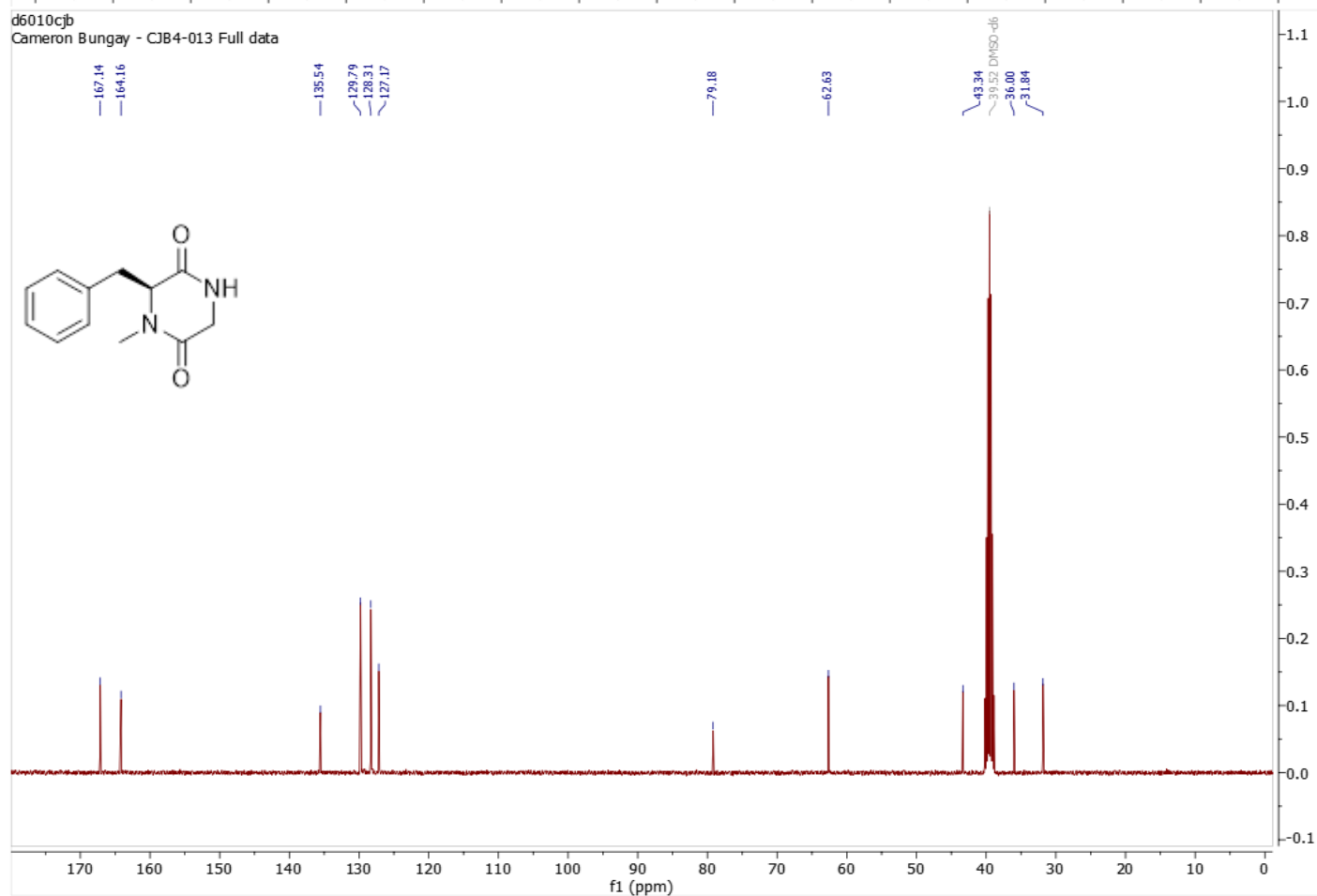
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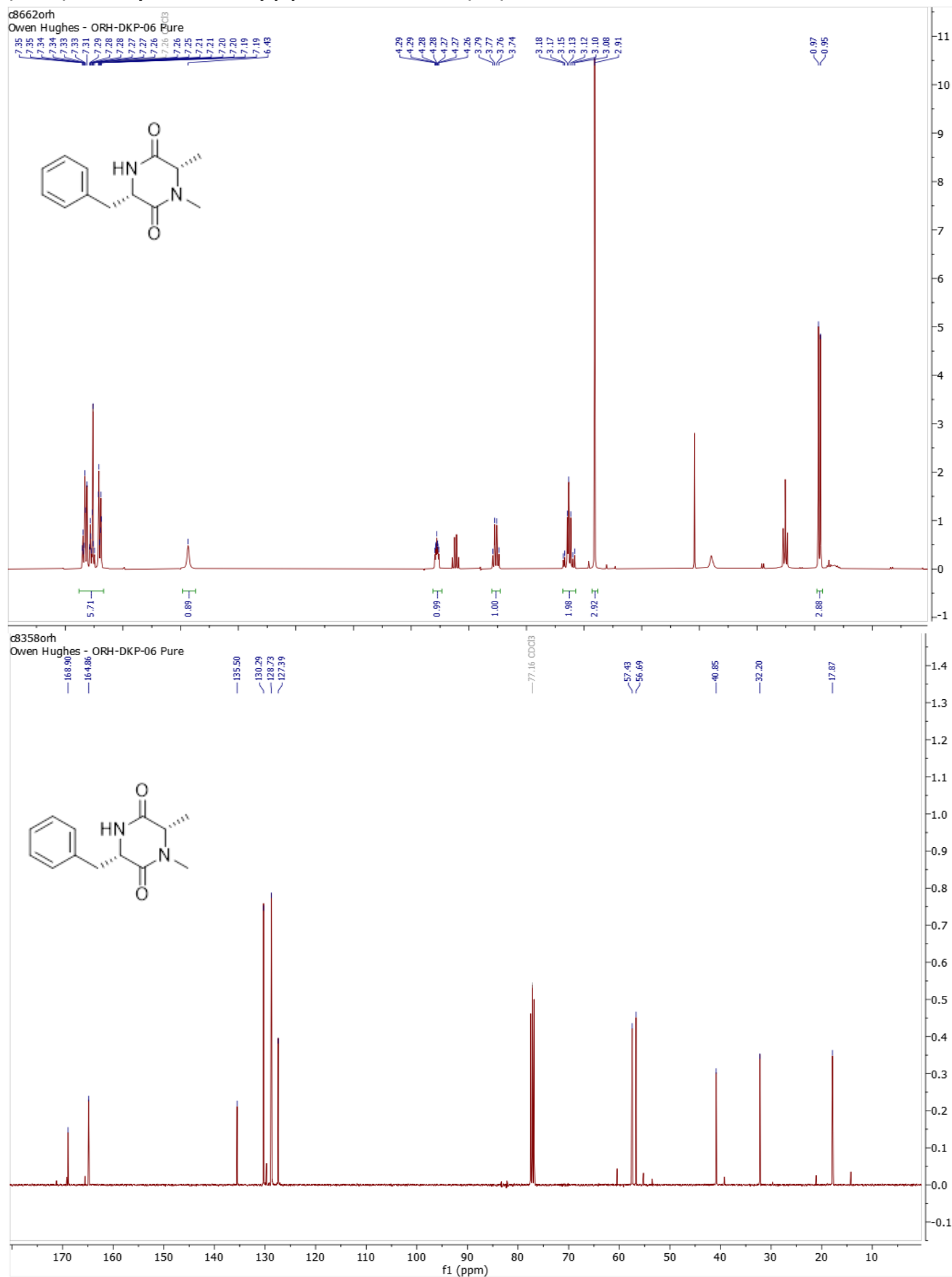
Cameron Bungay - CJB4-013 Full data

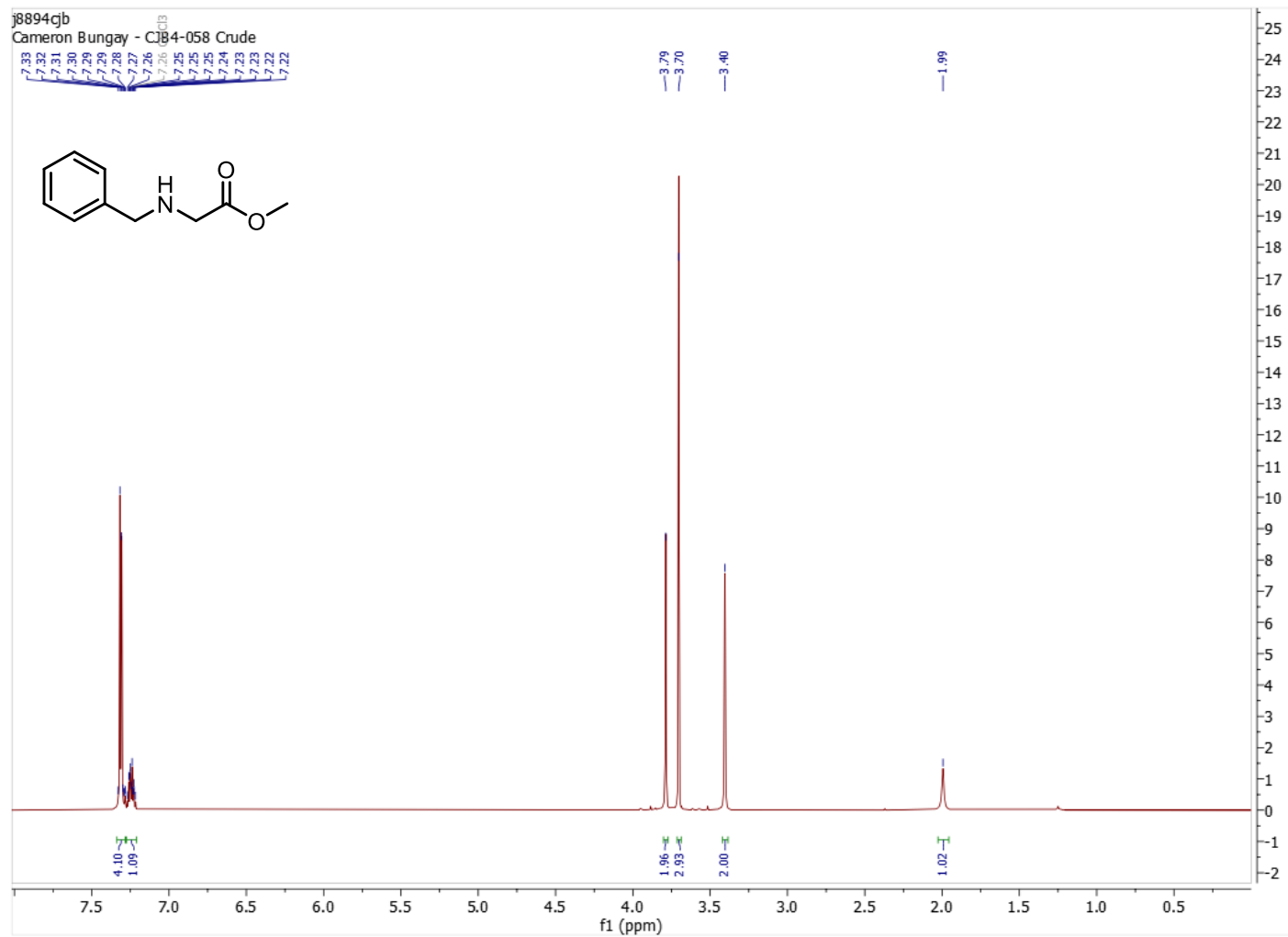


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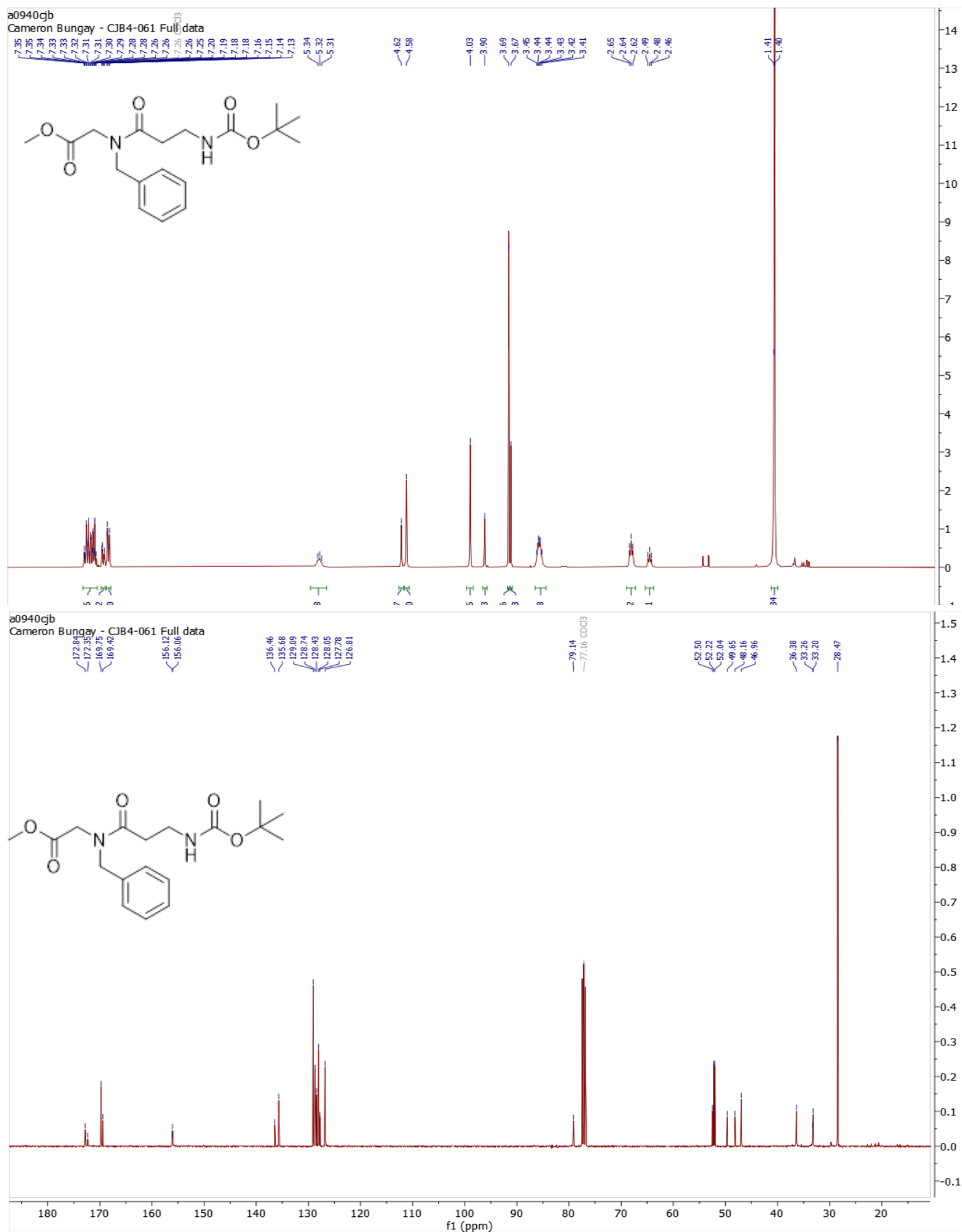
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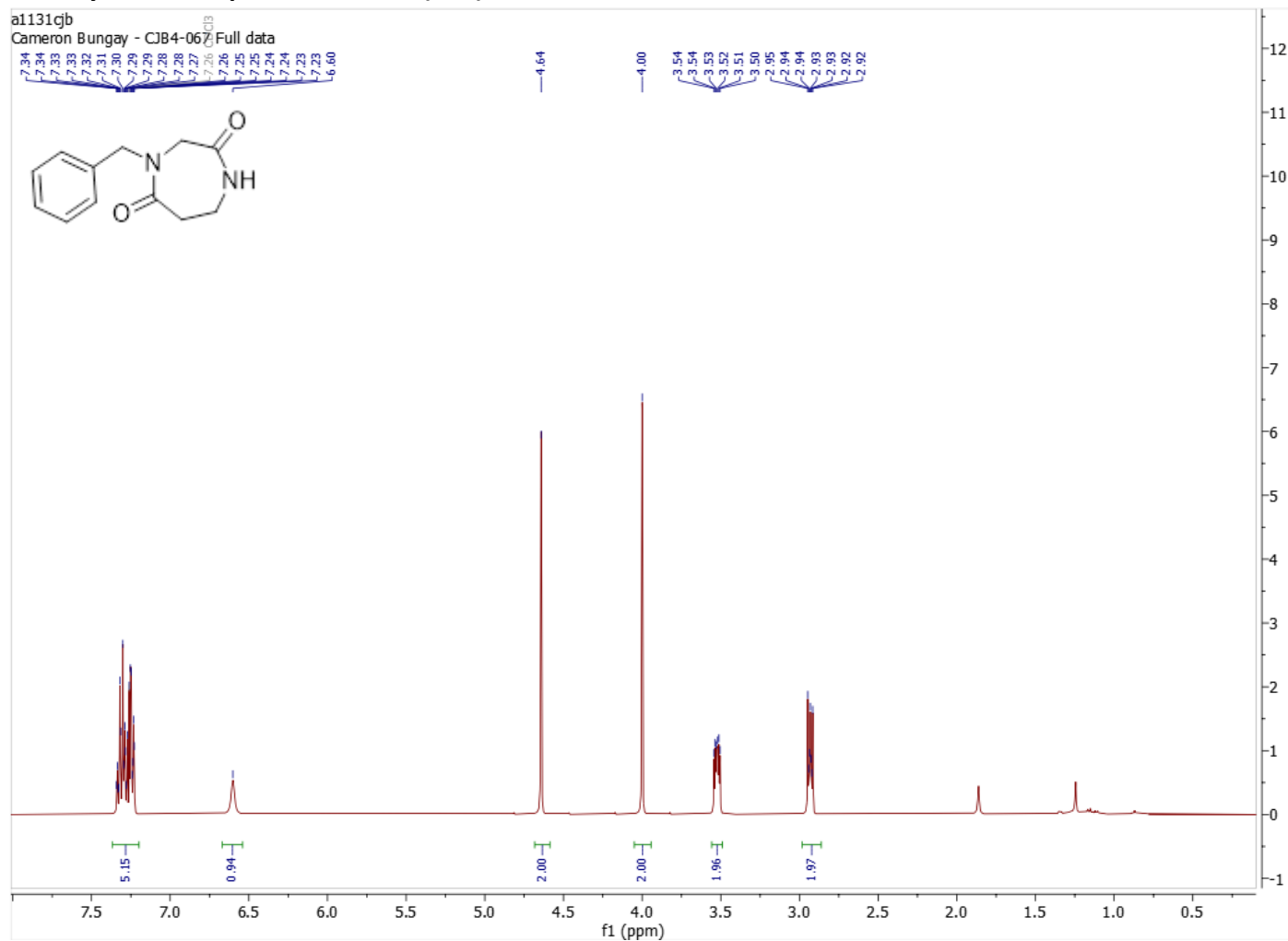


(3S,6S)-3-Benzyl-1,6-dimethylpiperazine-2,5-dione (11i) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

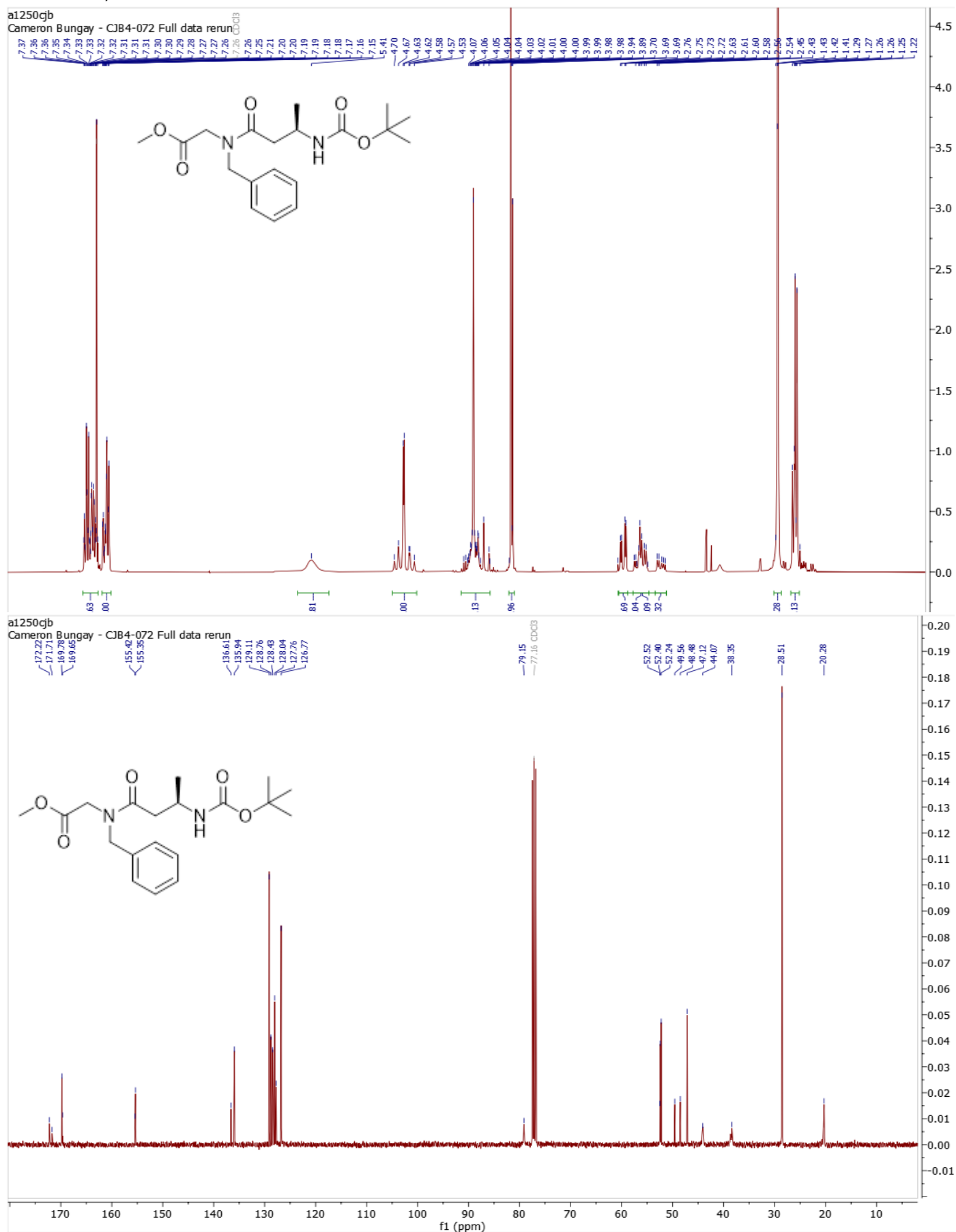
Methyl benzylglycinate – in CDCl₃; 400 MHz for ¹H

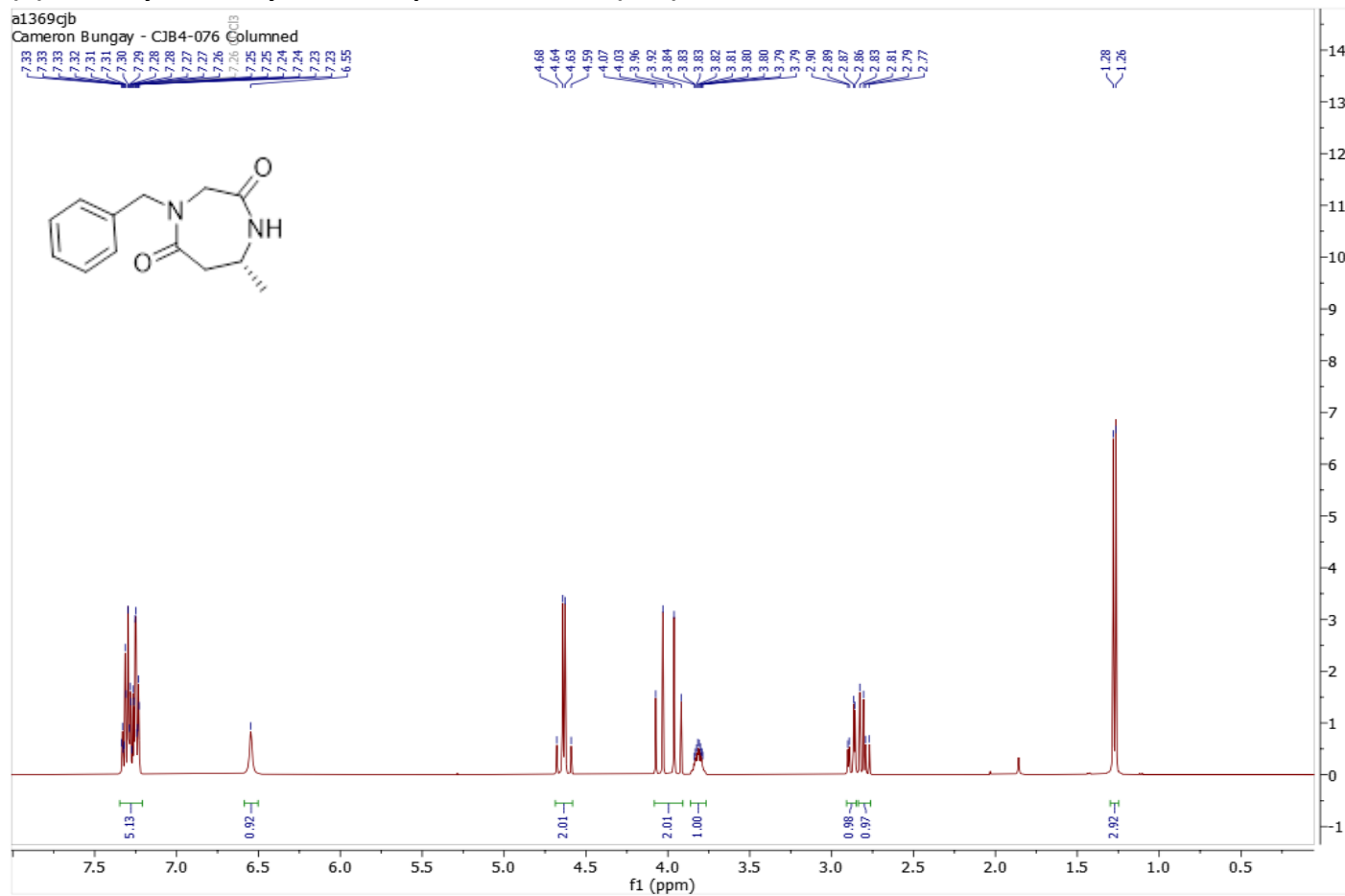
Methyl *N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)propanoyl)glycinate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 5:2 mixture of rotamers

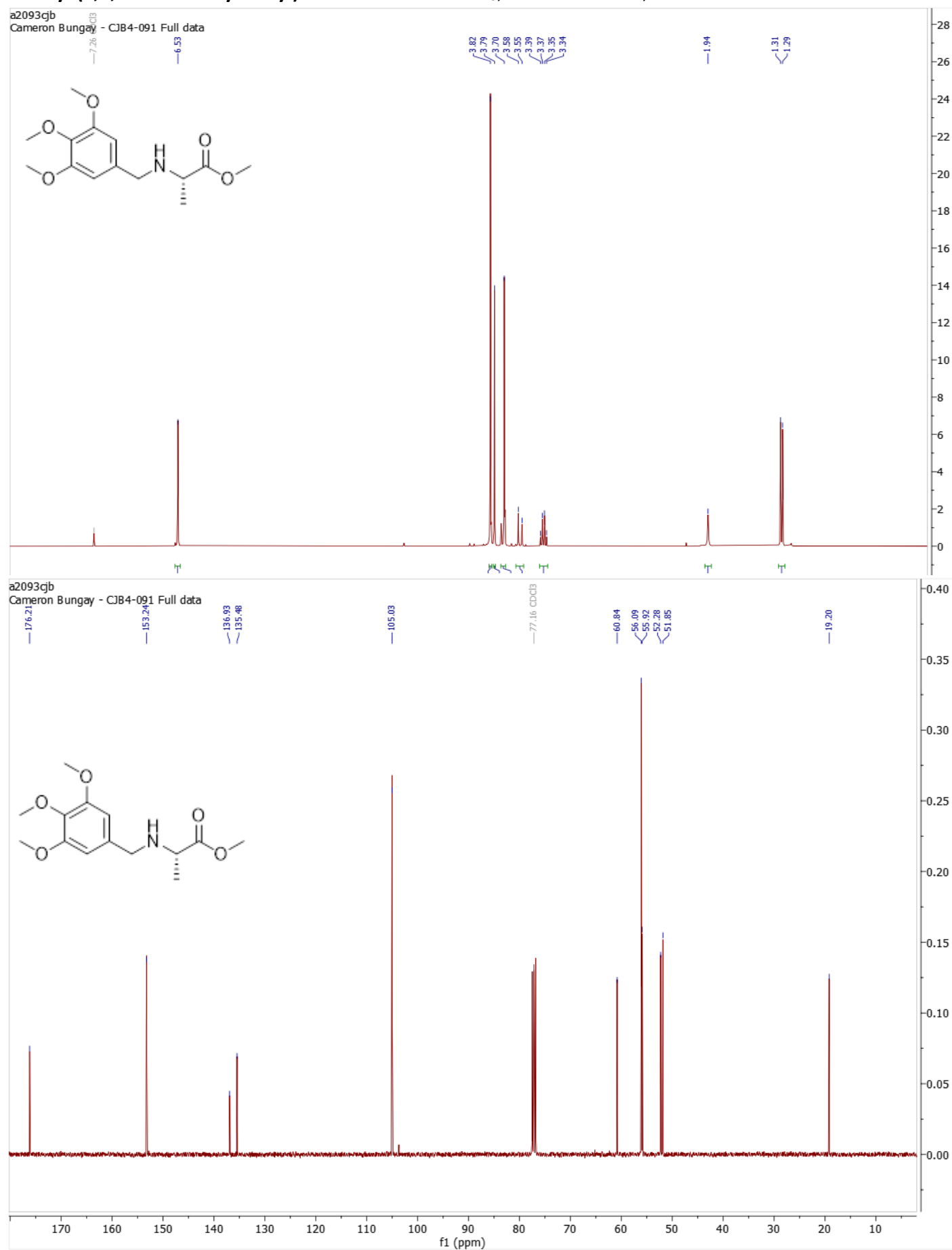


4-Benzyl-1,4-diazepane-2,5-dione (12a) – in CDCl₃; 400 MHz for ¹H

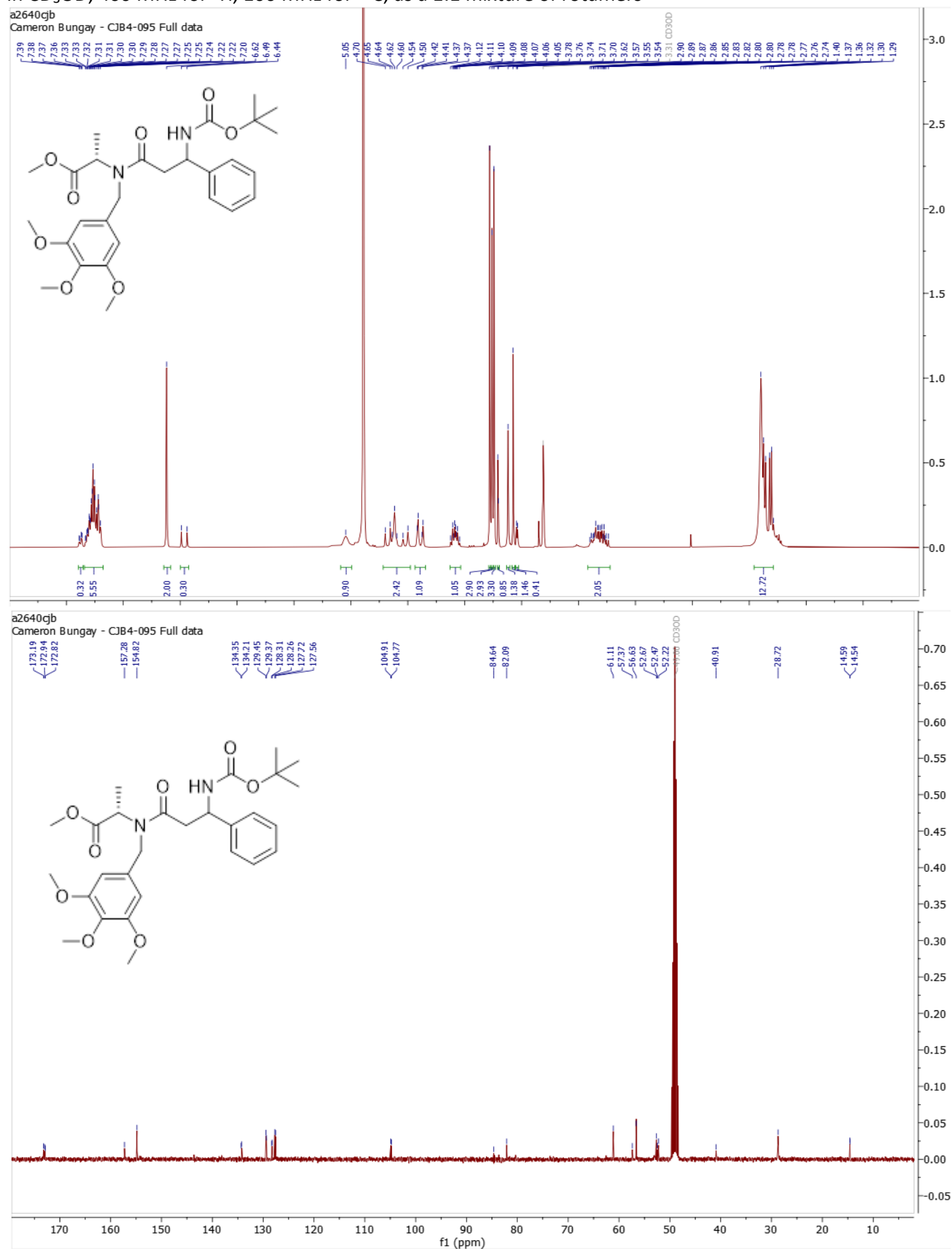
Methyl (*R*)-*N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)butanoyl)glycinate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 2:1 mixture of rotamers



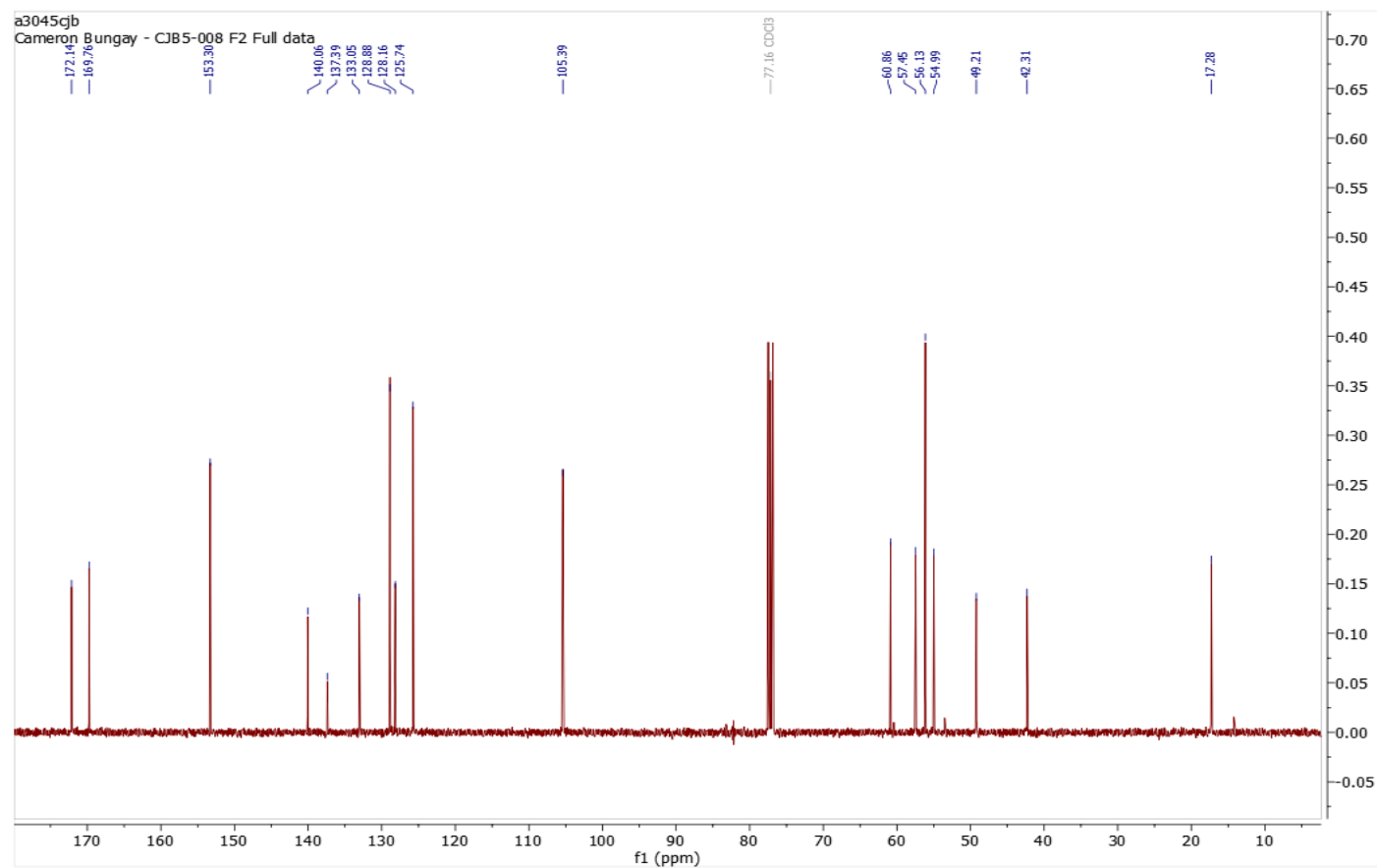
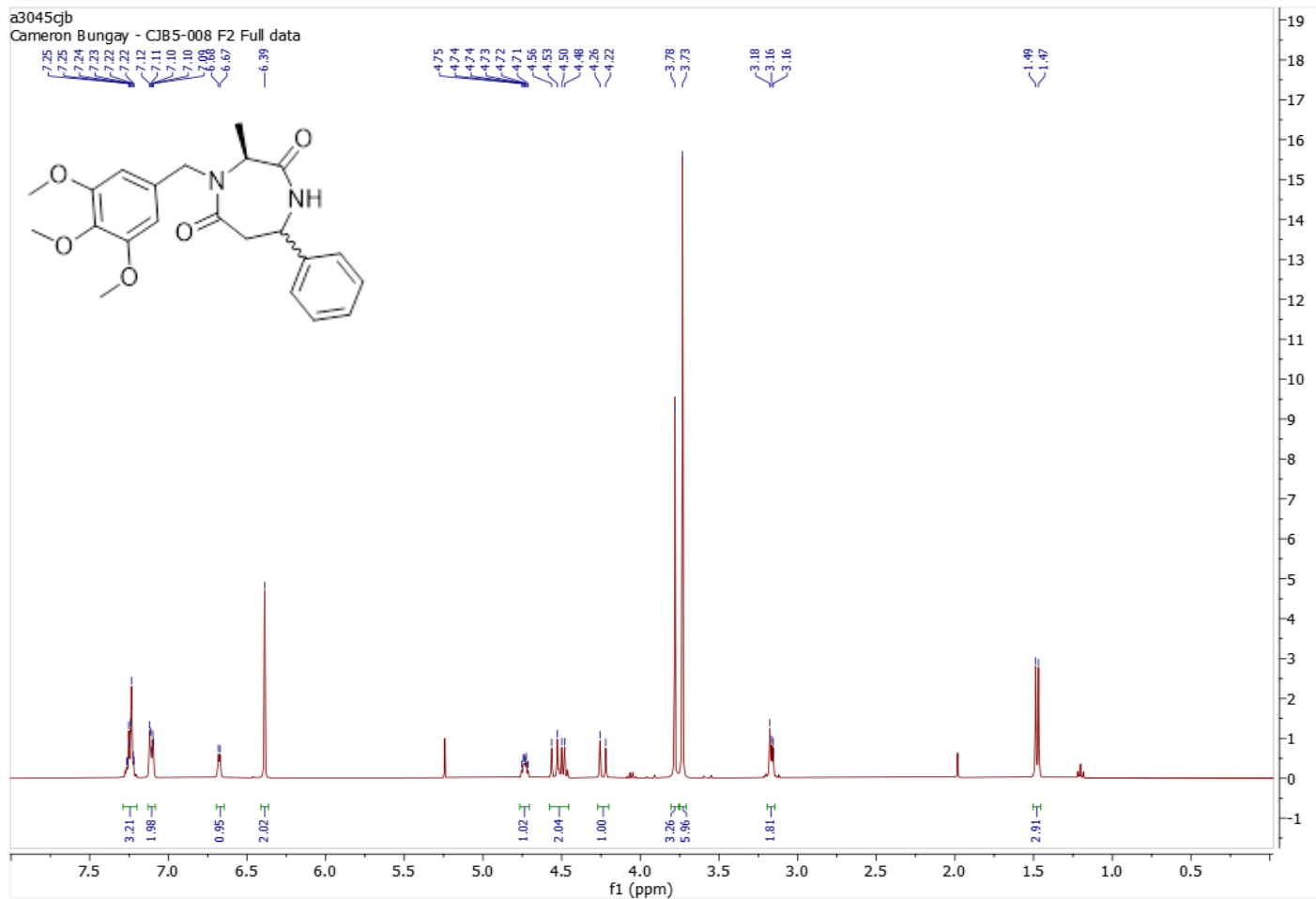
(R)-4-Benzyl-7-methyl-1,4-diazepane-2,5-dione (12b) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

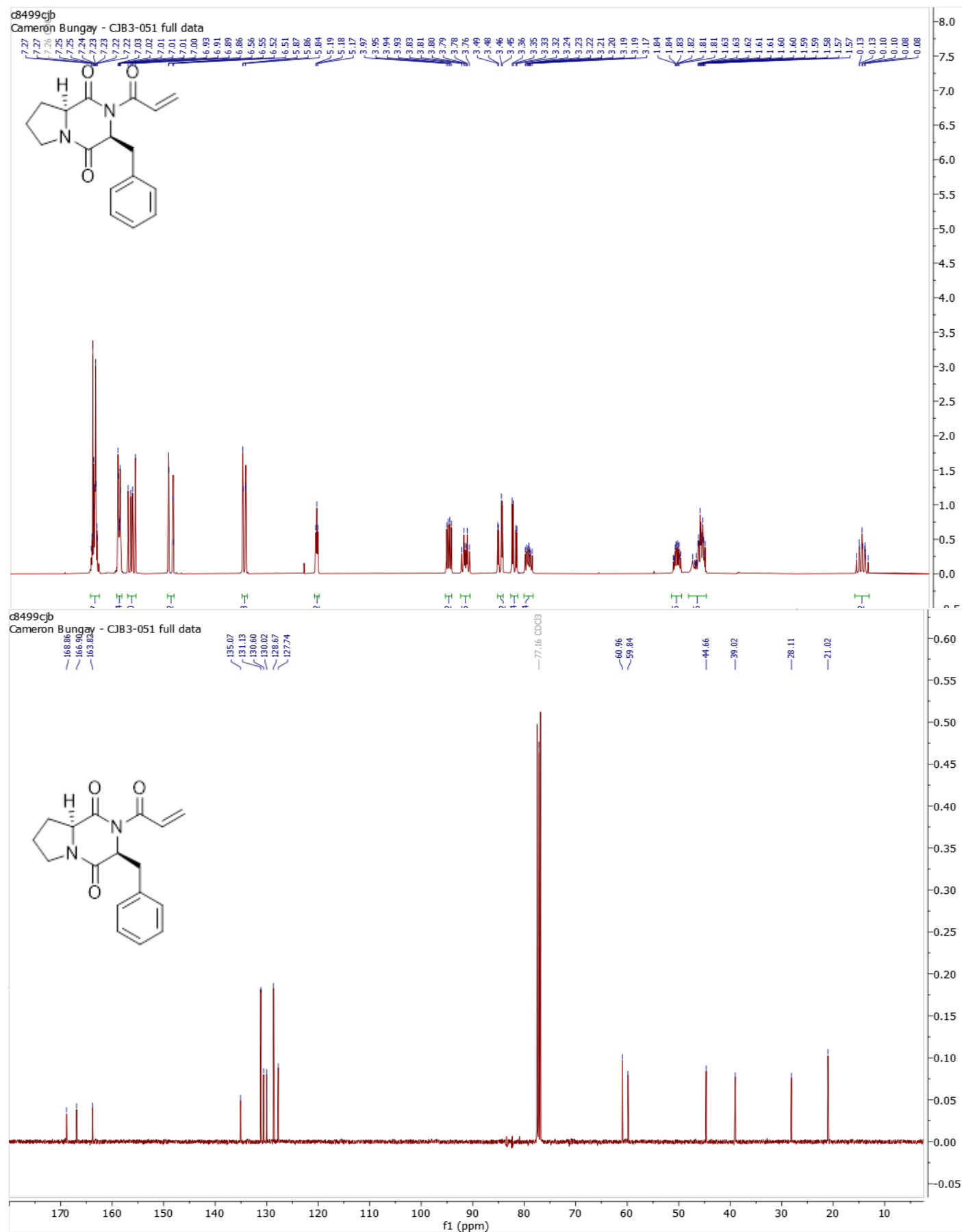
Methyl (3,4,5-trimethoxybenzyl)-L-alaninate – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

Methyl *N*-(3-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoyl)-*N*-(3,4,5-trimethoxybenzyl)-*L*-alaninate –
in CD₃OD; 400 MHz for ¹H, 100 MHz for ¹³C, as a 1:1 mixture of rotamers

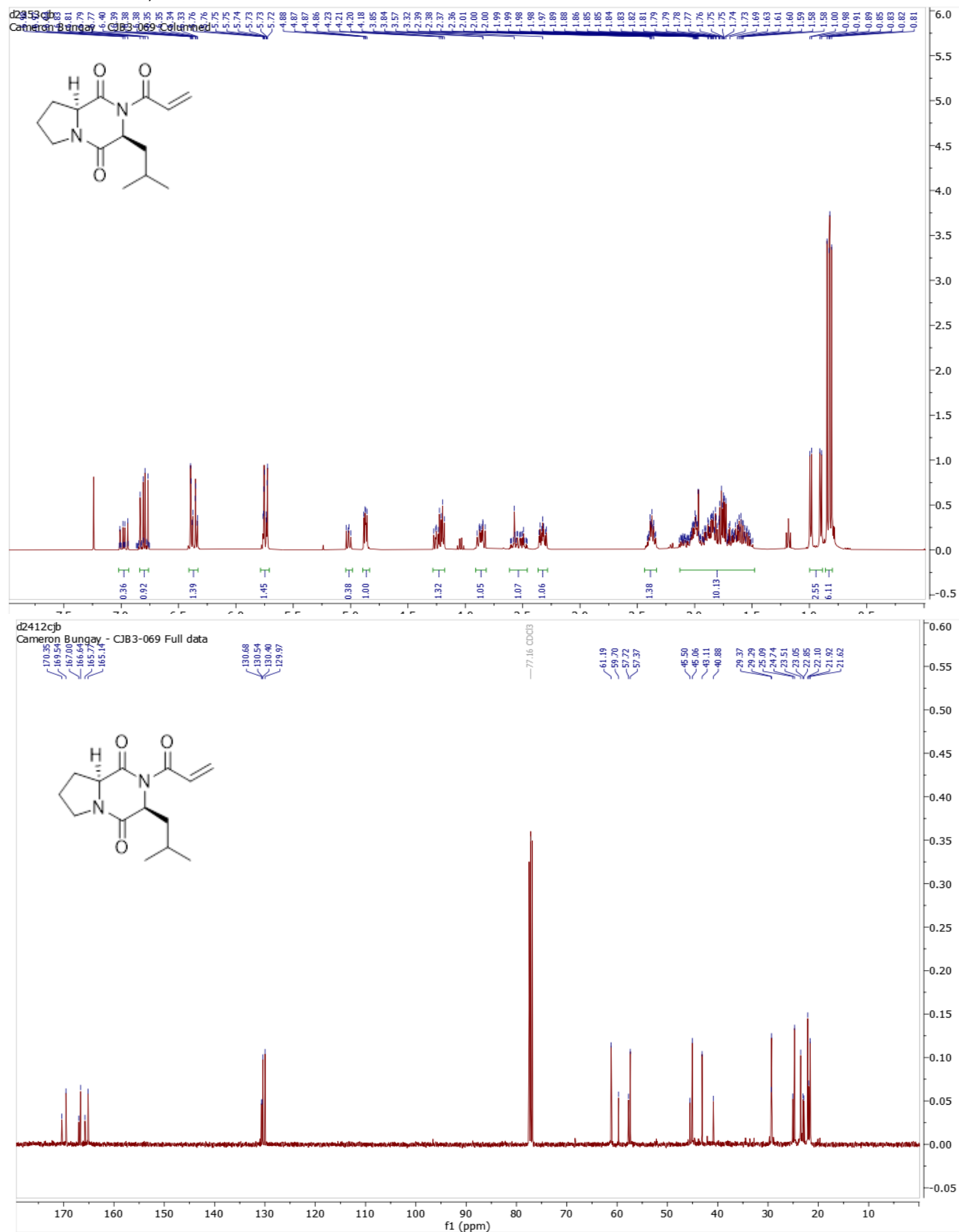


Diastereomer A – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

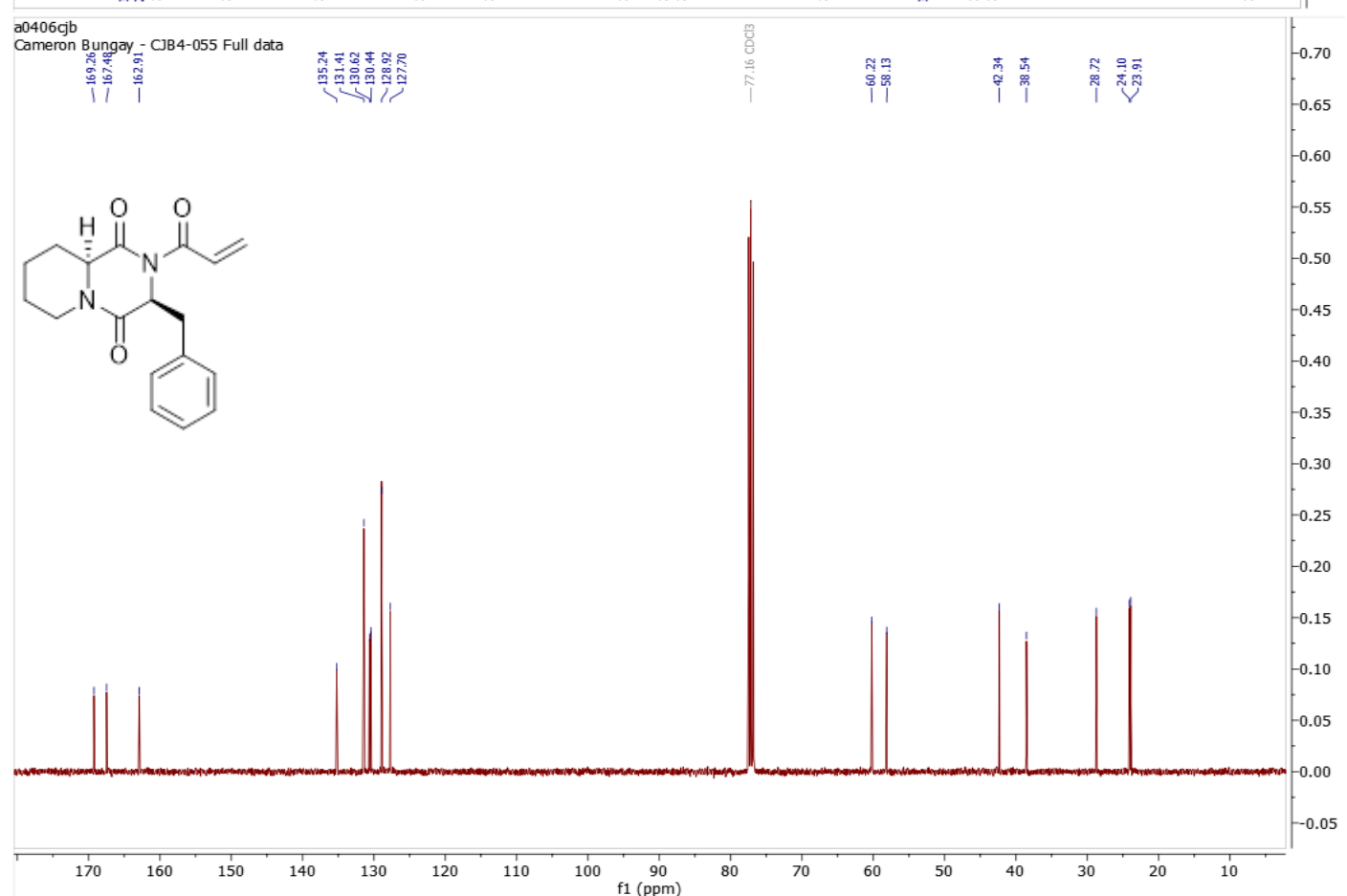
Diastereomer B – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

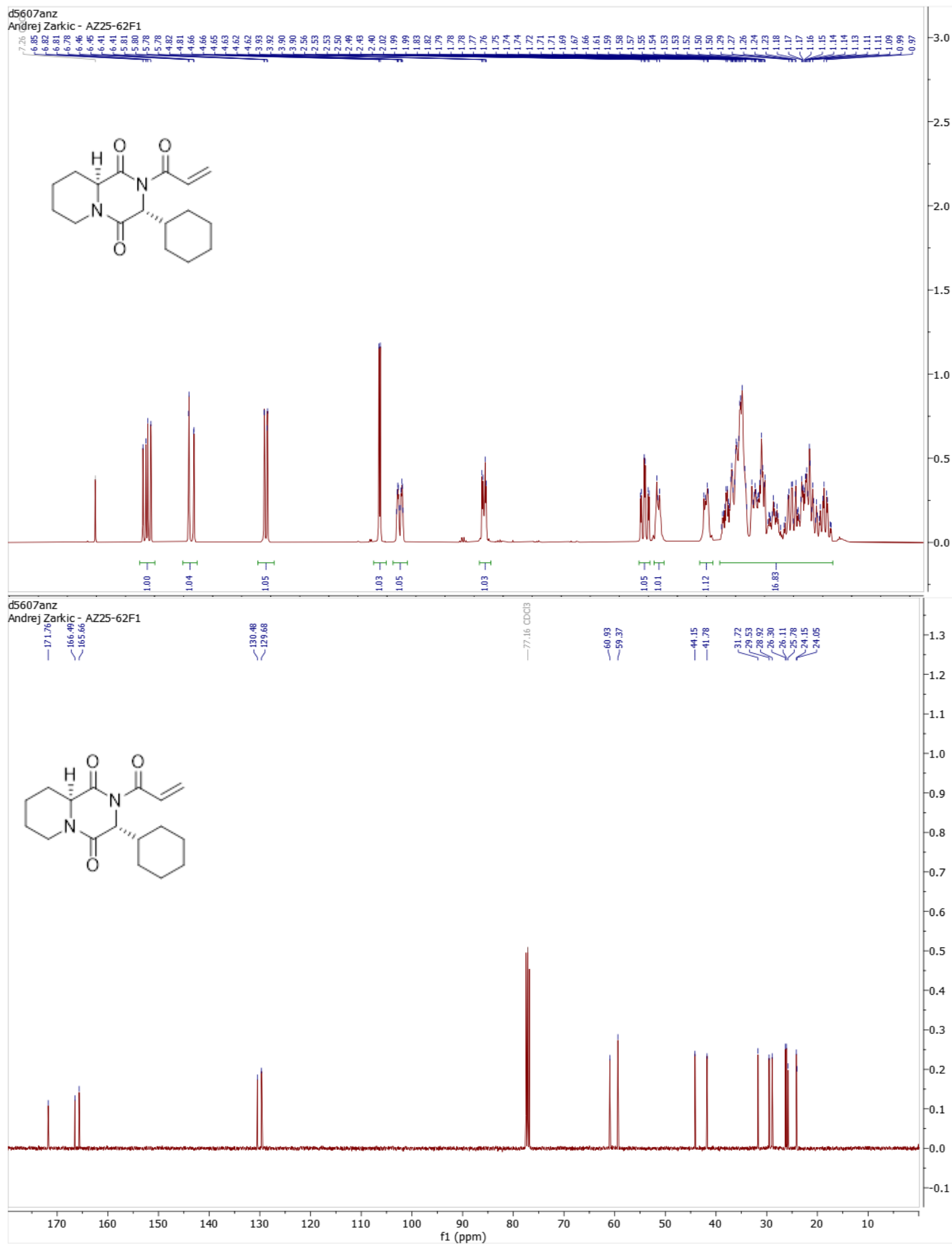
(3*S*,8*aS*)-2-acryloyl-3-benzylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (13a) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

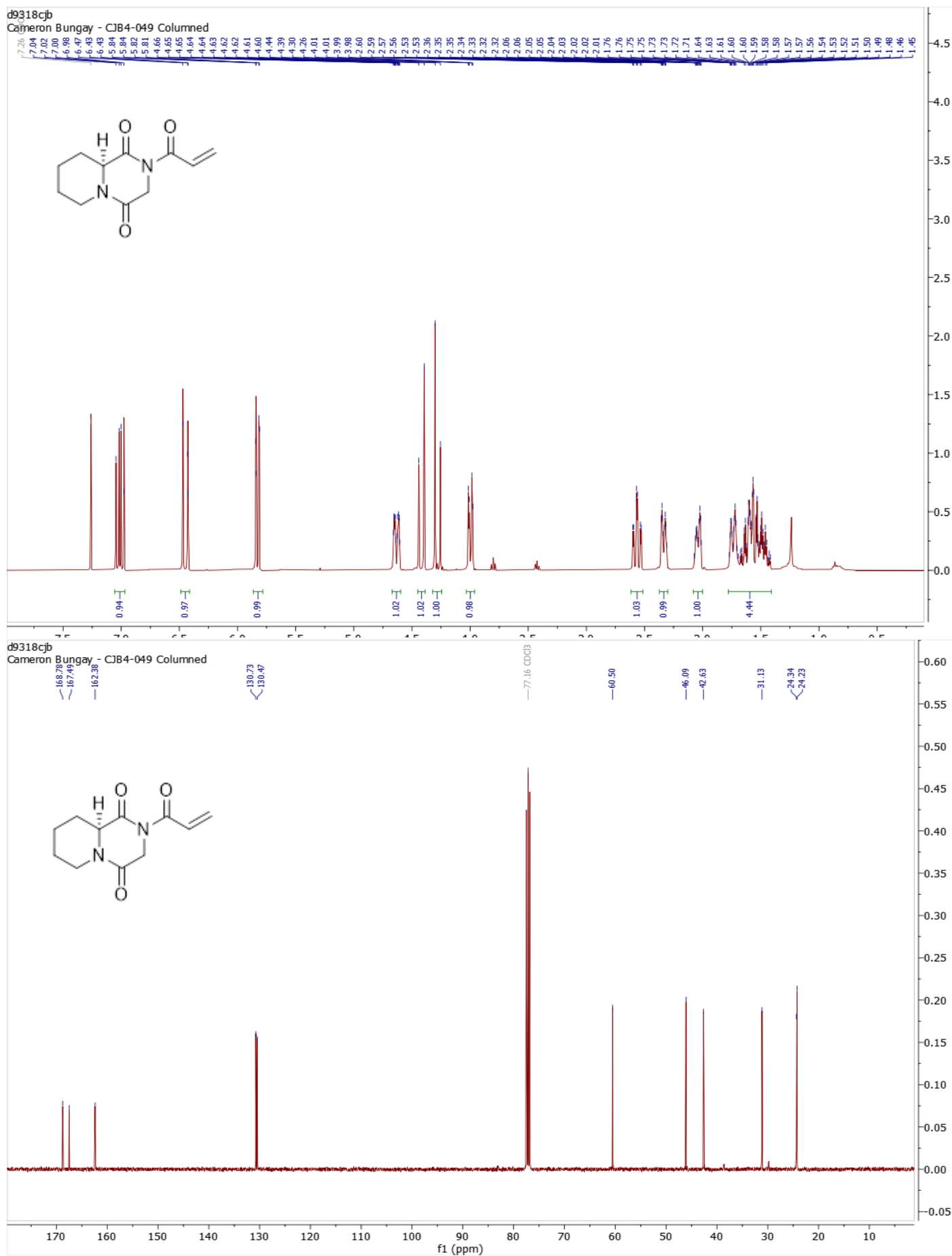
(3*S*,8*aS*)-2-Acryloyl-3-isobutylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (13b) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 3:1 mixture of rotamers

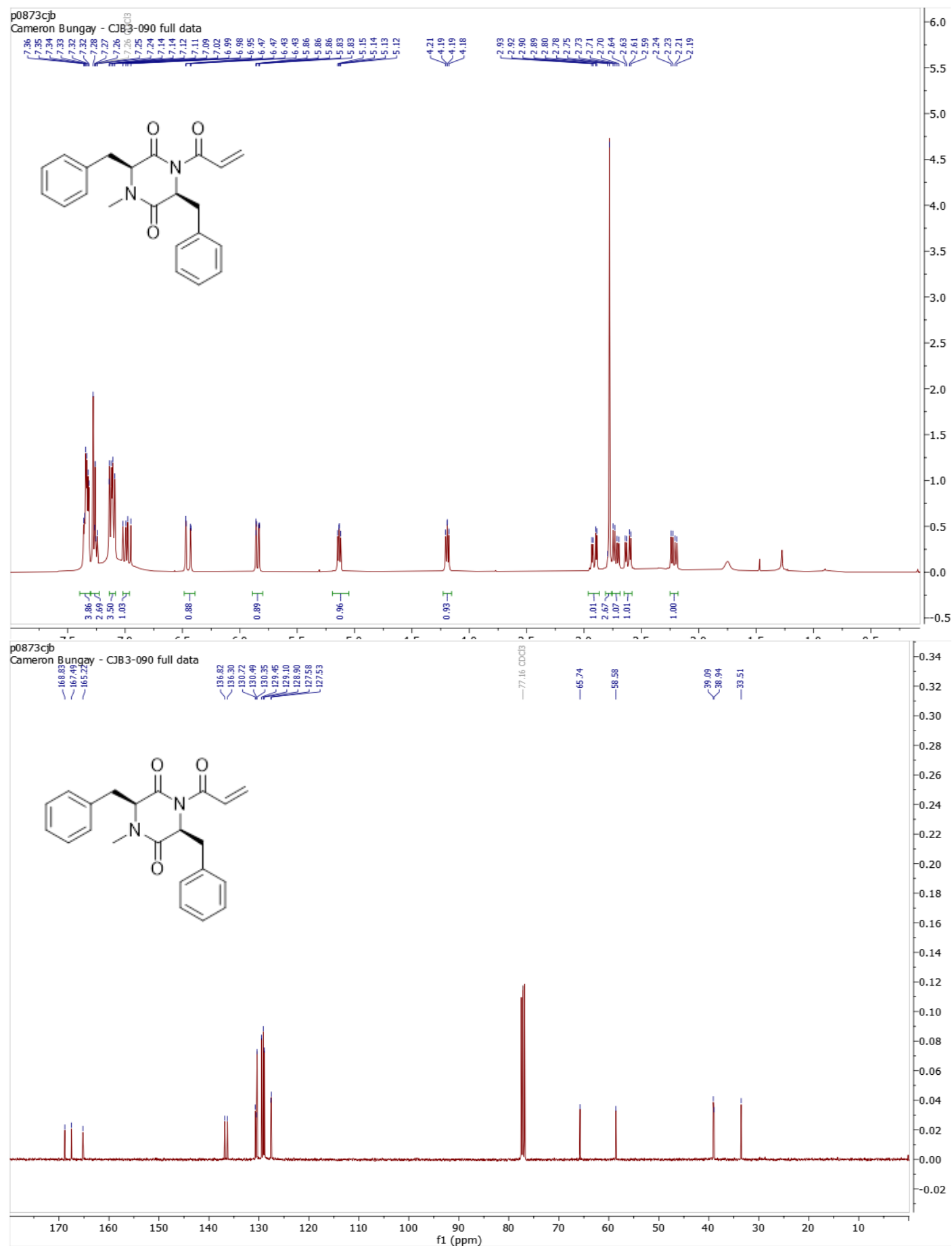


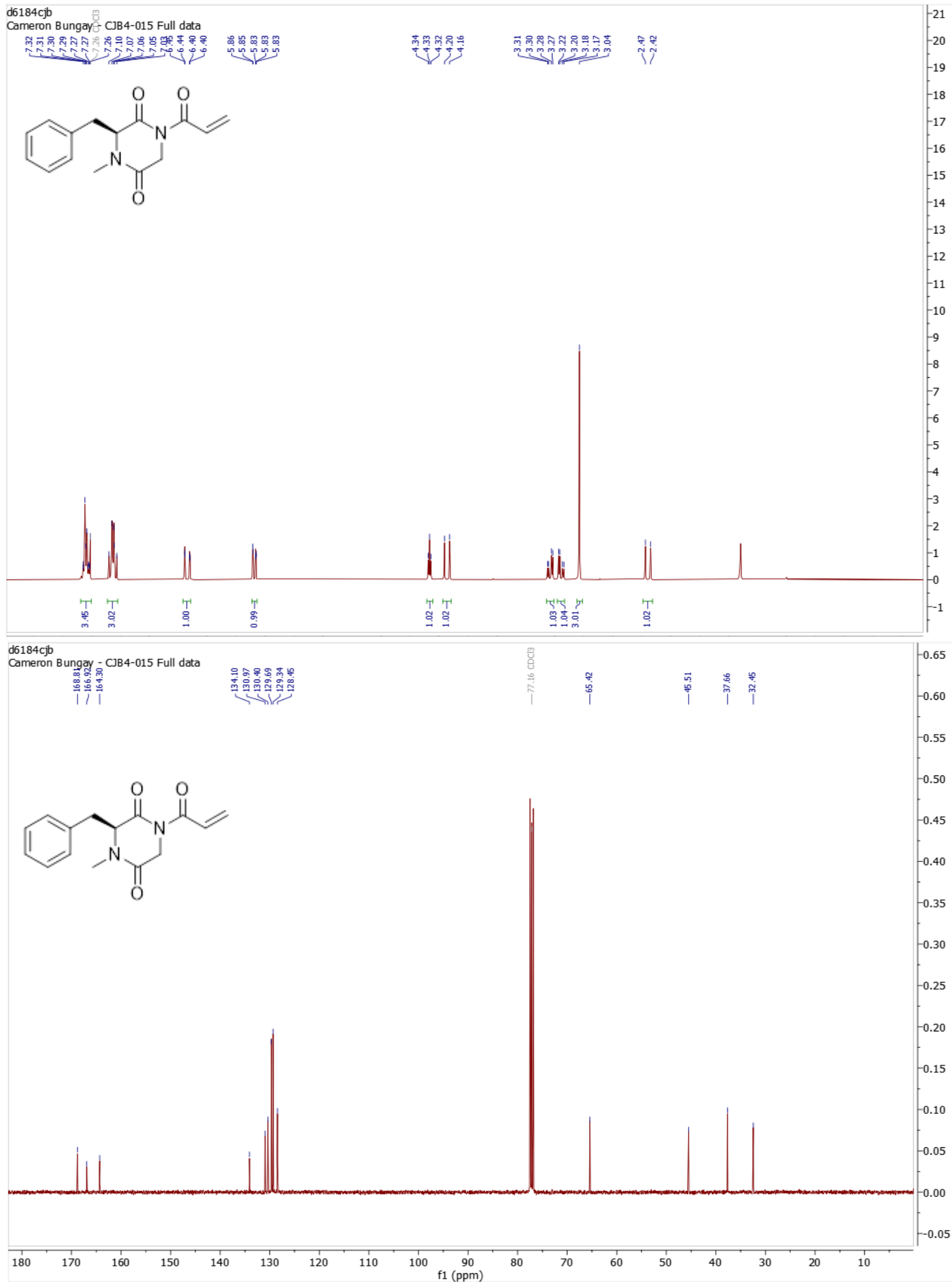
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Cameron Bungay - CJB4-055 Full data	

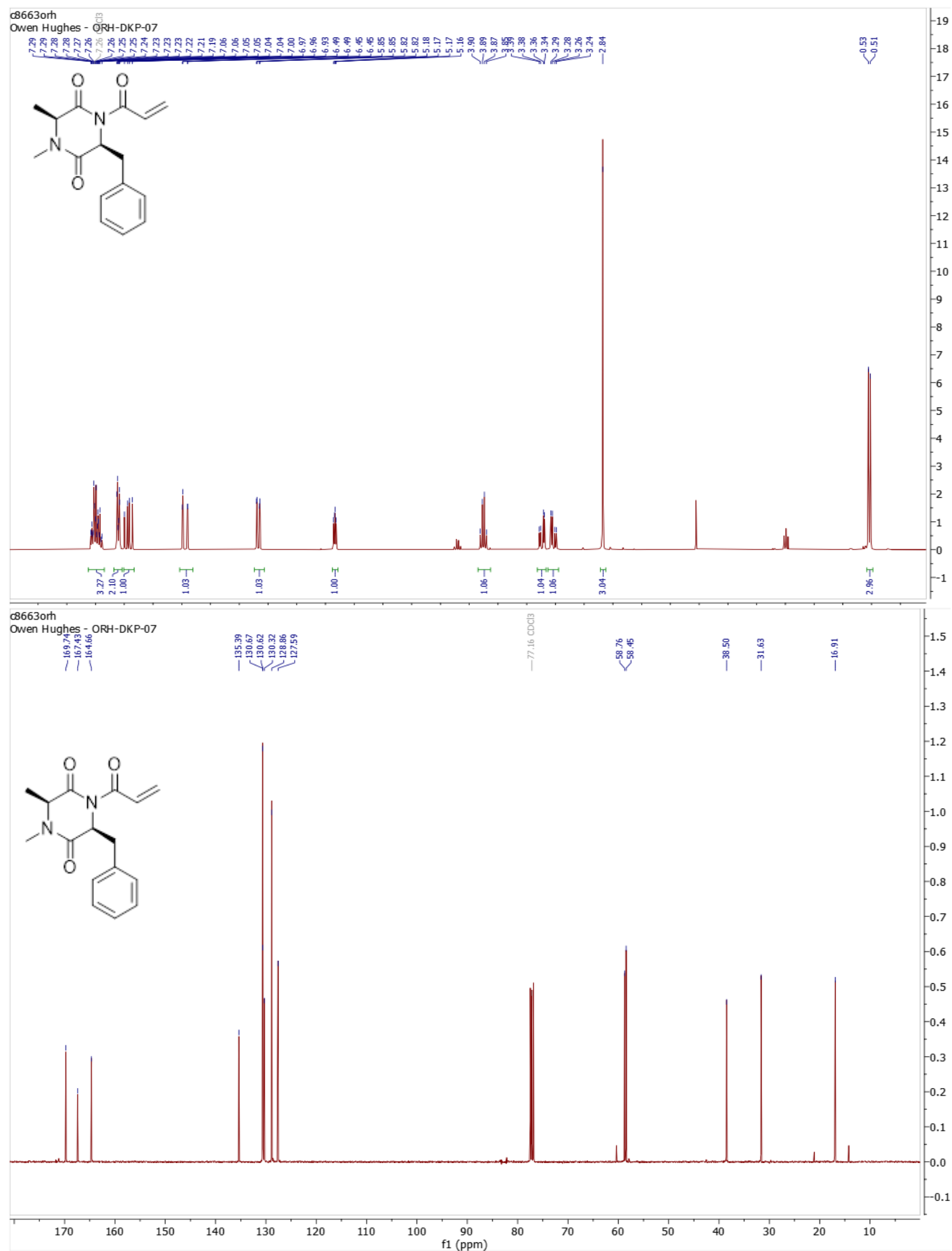


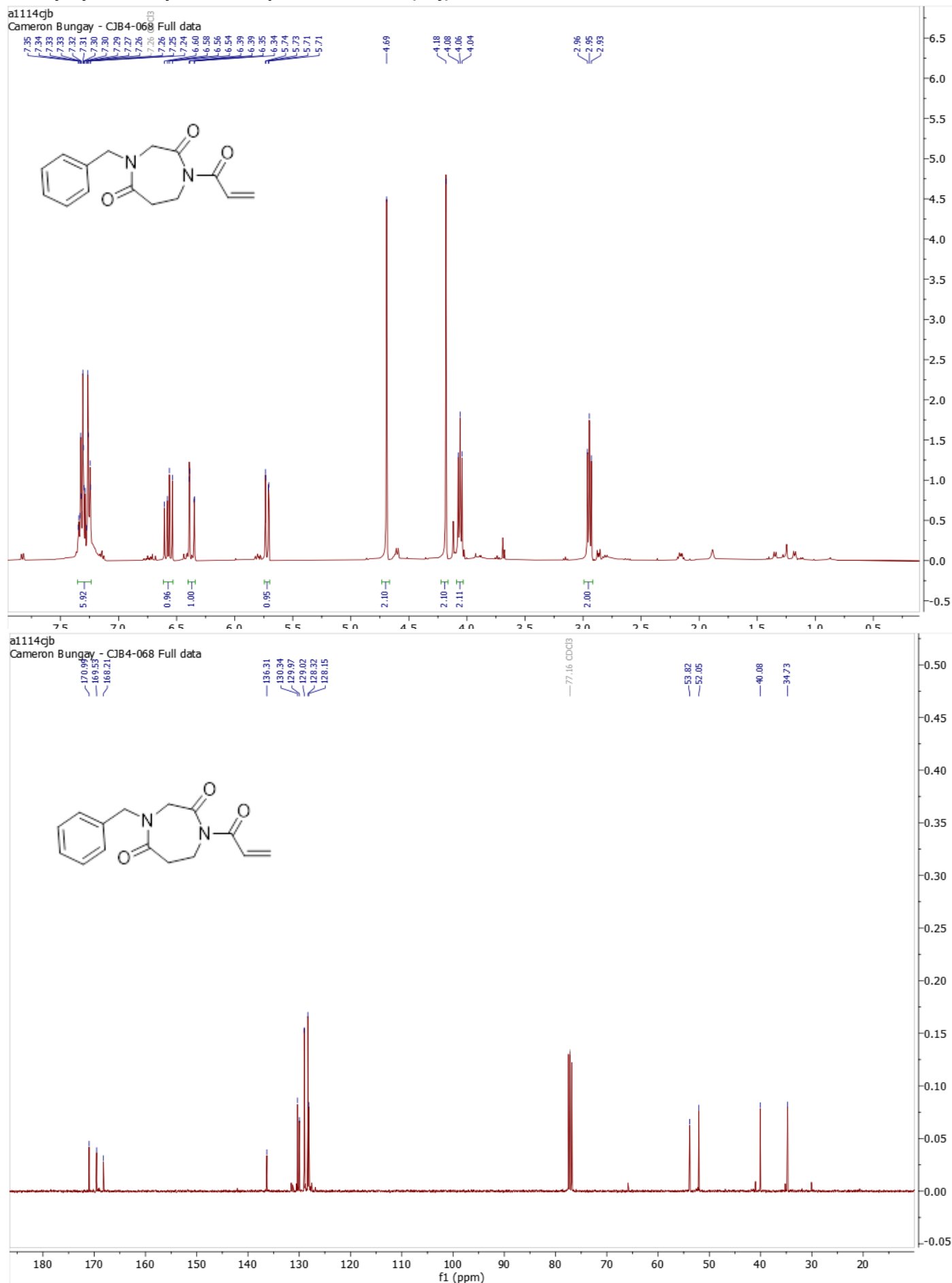
(3*R*,9*aS*)-3-cyclohexyl-2-prop-2-enoyl-3,6,7,8,9*a*-hexahydropyrido[1,2-*a*]pyrazine-1,4-dione (13e) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

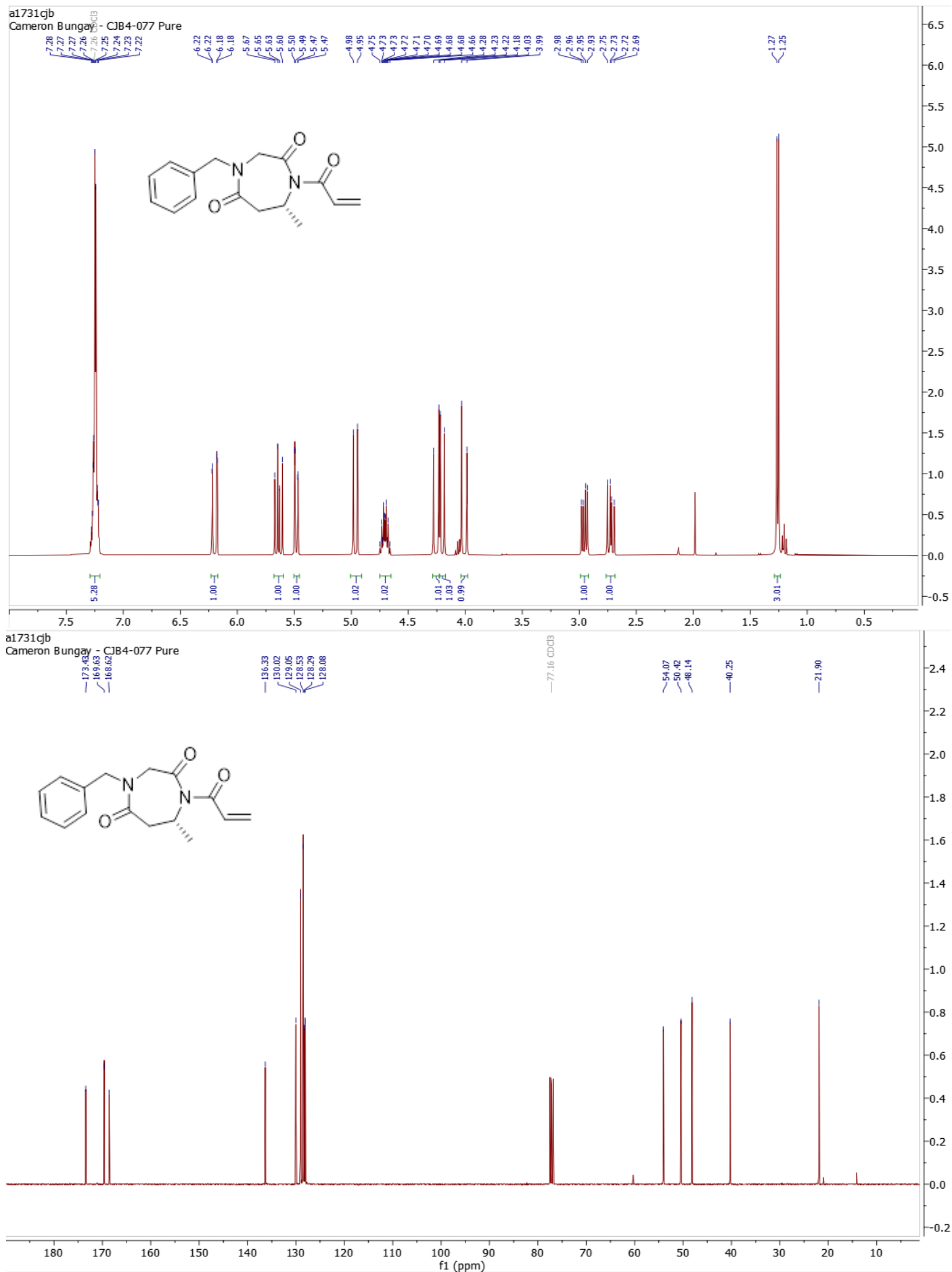
(S)-2-Acryloylhexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (13f) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

(3*S*,6*S*)-1-Acryloyl-3,6-dibenzyl-4-methylpiperazine-2,5-dione (13g) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

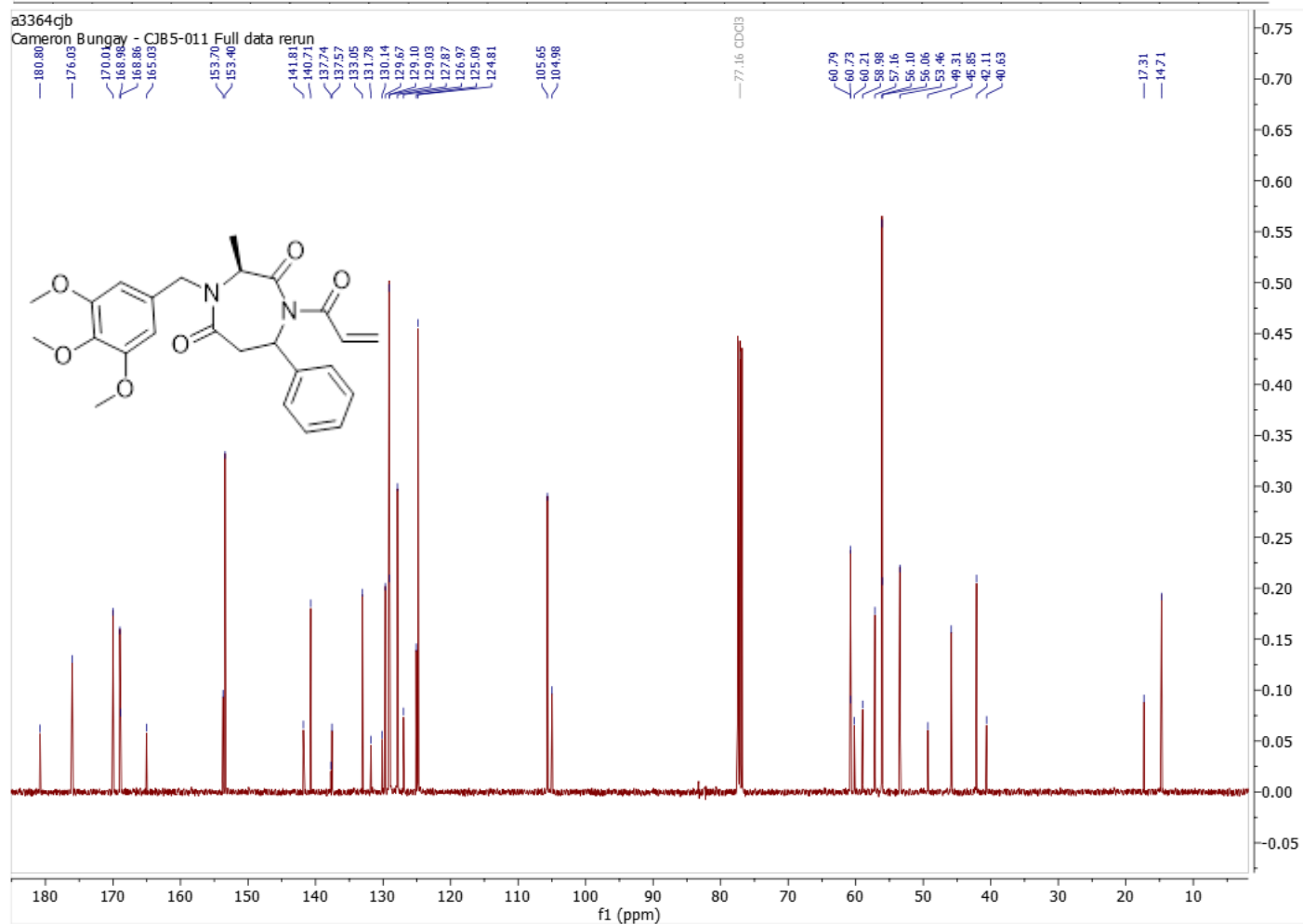
(S)-1-Acryloyl-3-benzyl-4-methylpiperazine-2,5-dione (13h) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

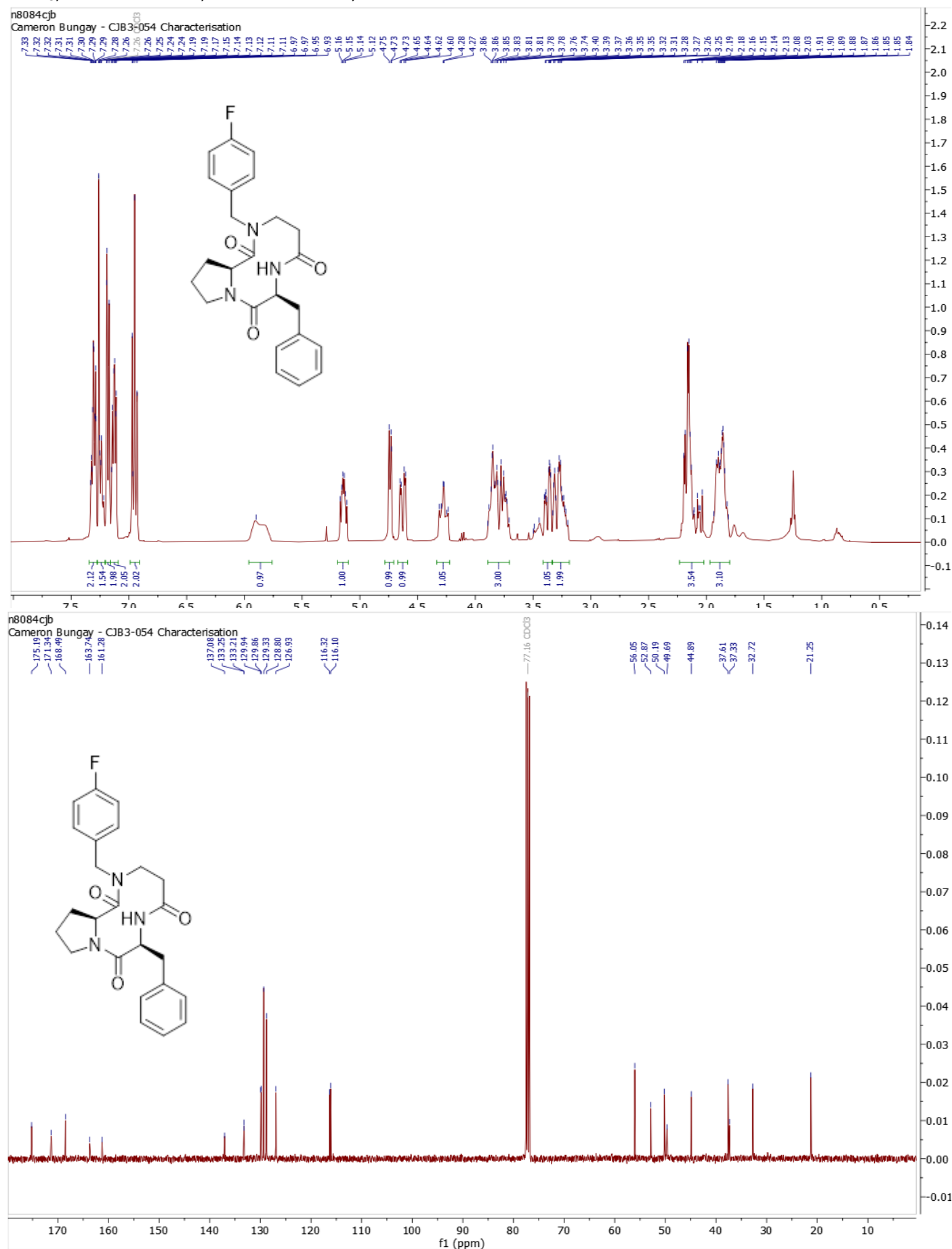
(3S,6S)-1-acryloyl-6-benzyl-3,4-dimethylpiperazine-2,5-dione (13i) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

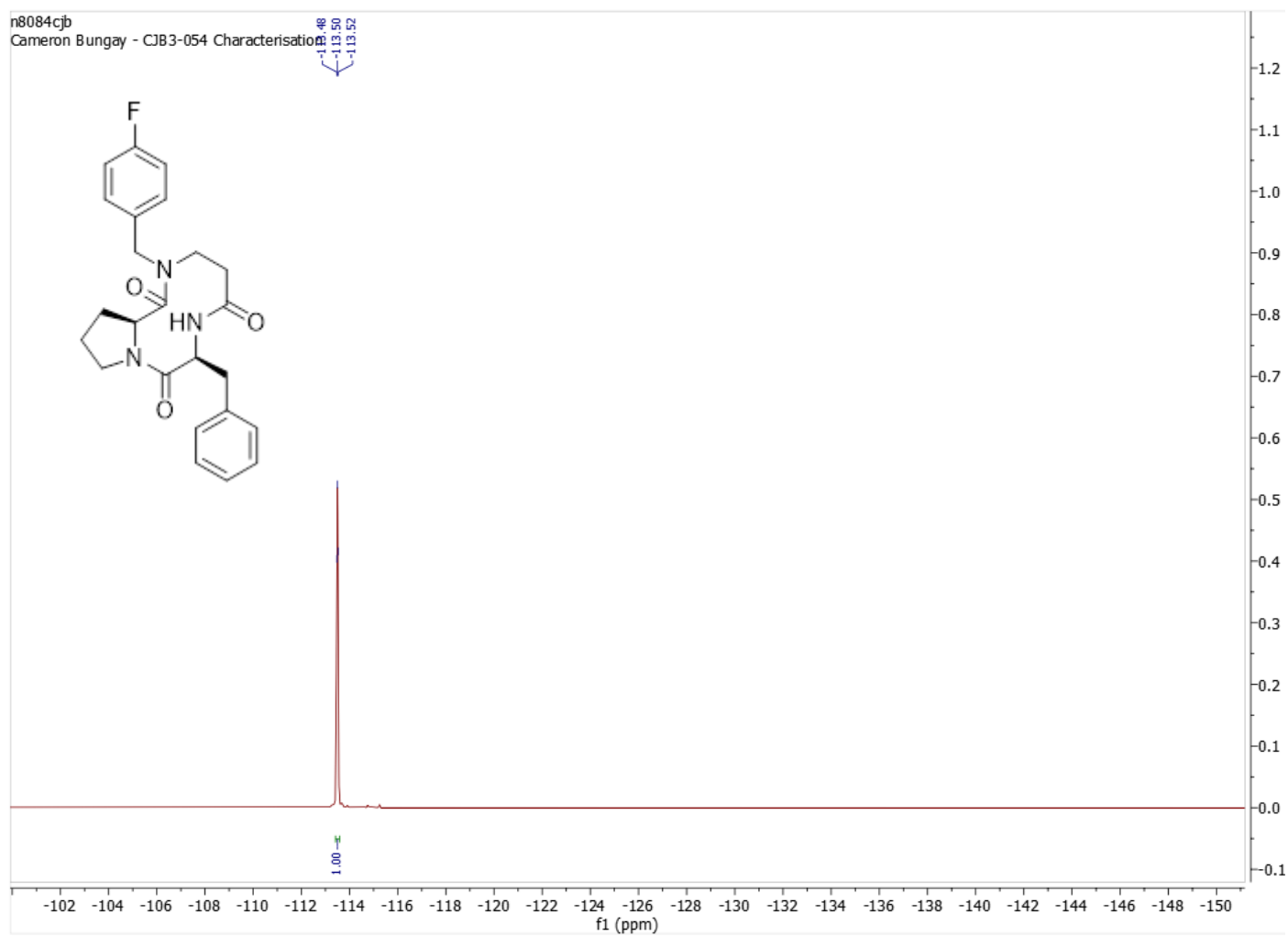
1-Acryloyl-4-benzyl-1,4-diazepane-2,5-dione (13j) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

(R)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione (13k) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

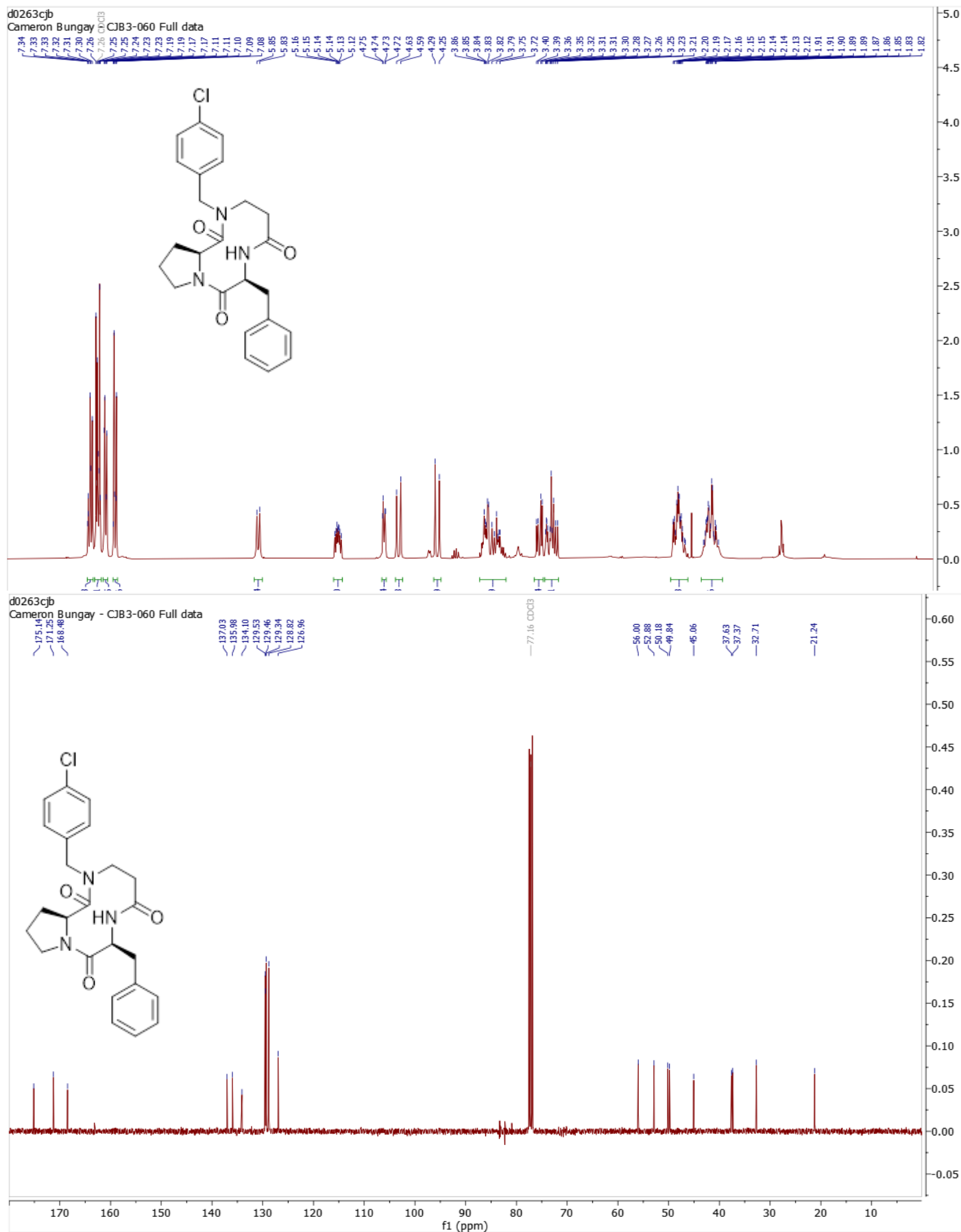
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Cameron Bungay - CJB5-011 Full data rerun



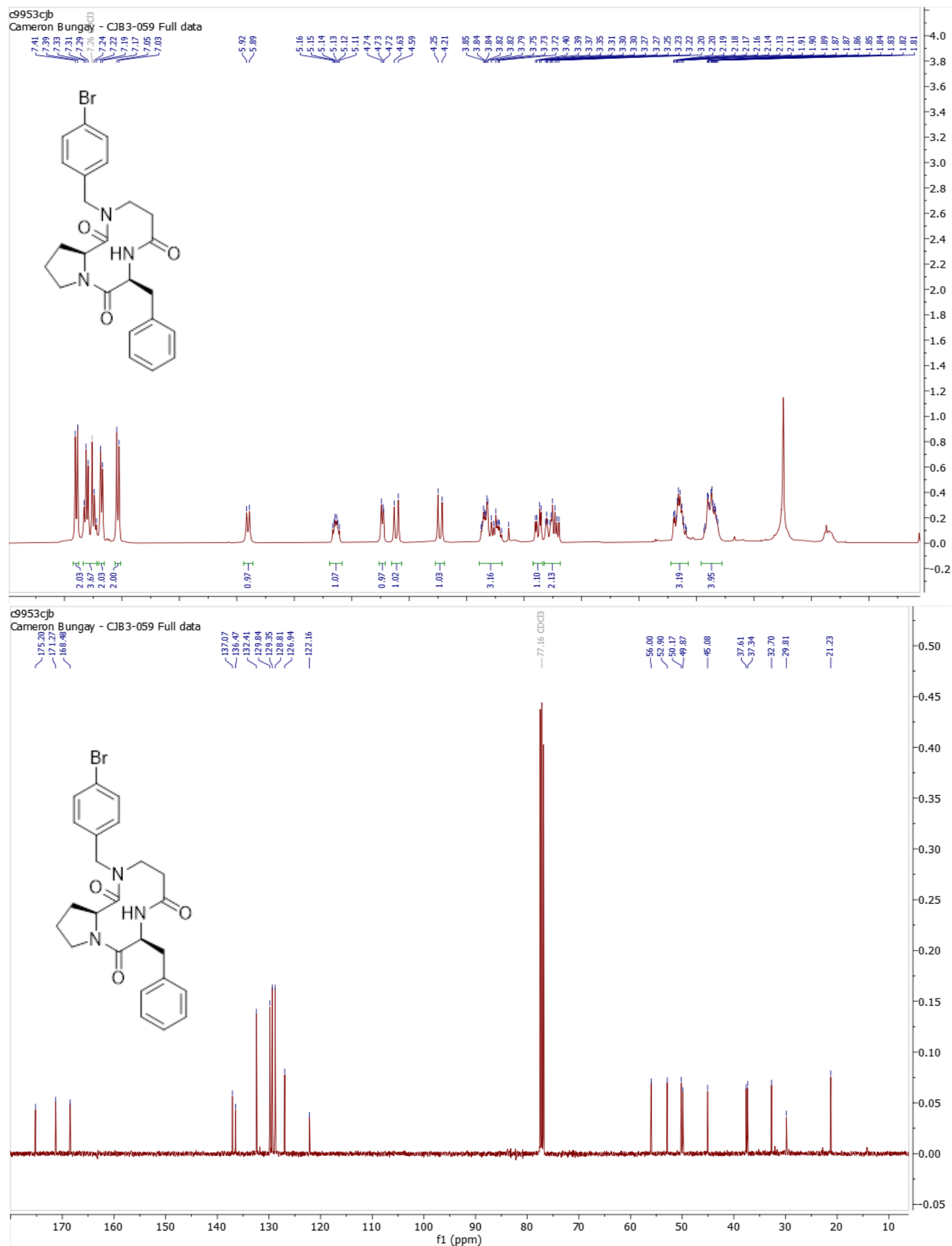
(7*S*,12*aS*)-7-Benzyl-2-(4-fluorobenzyl)octahydropyrrolo[2,1-*c*][1,4,7]triazecine-1,5,8(2*H*)-trione (14a) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F

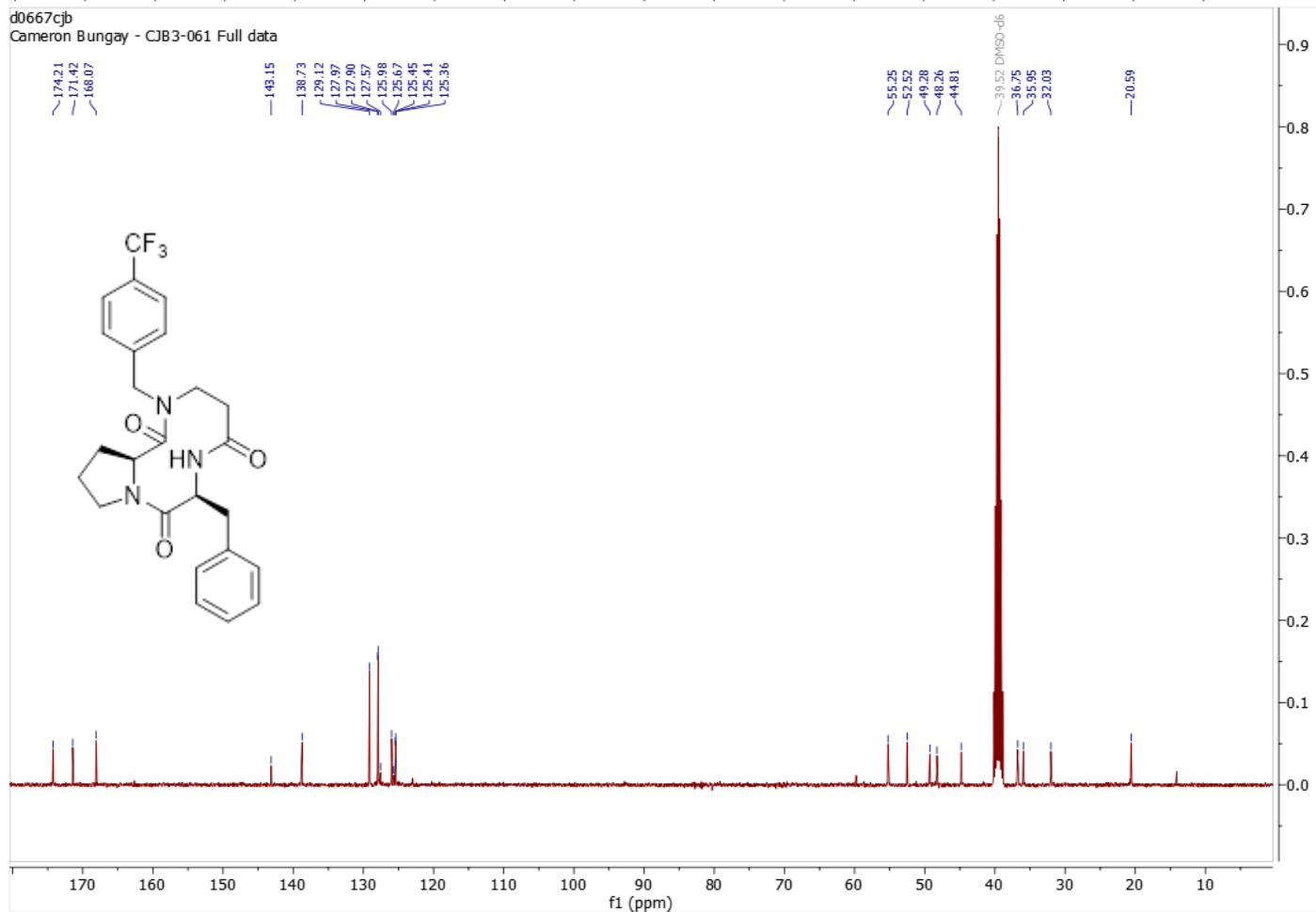
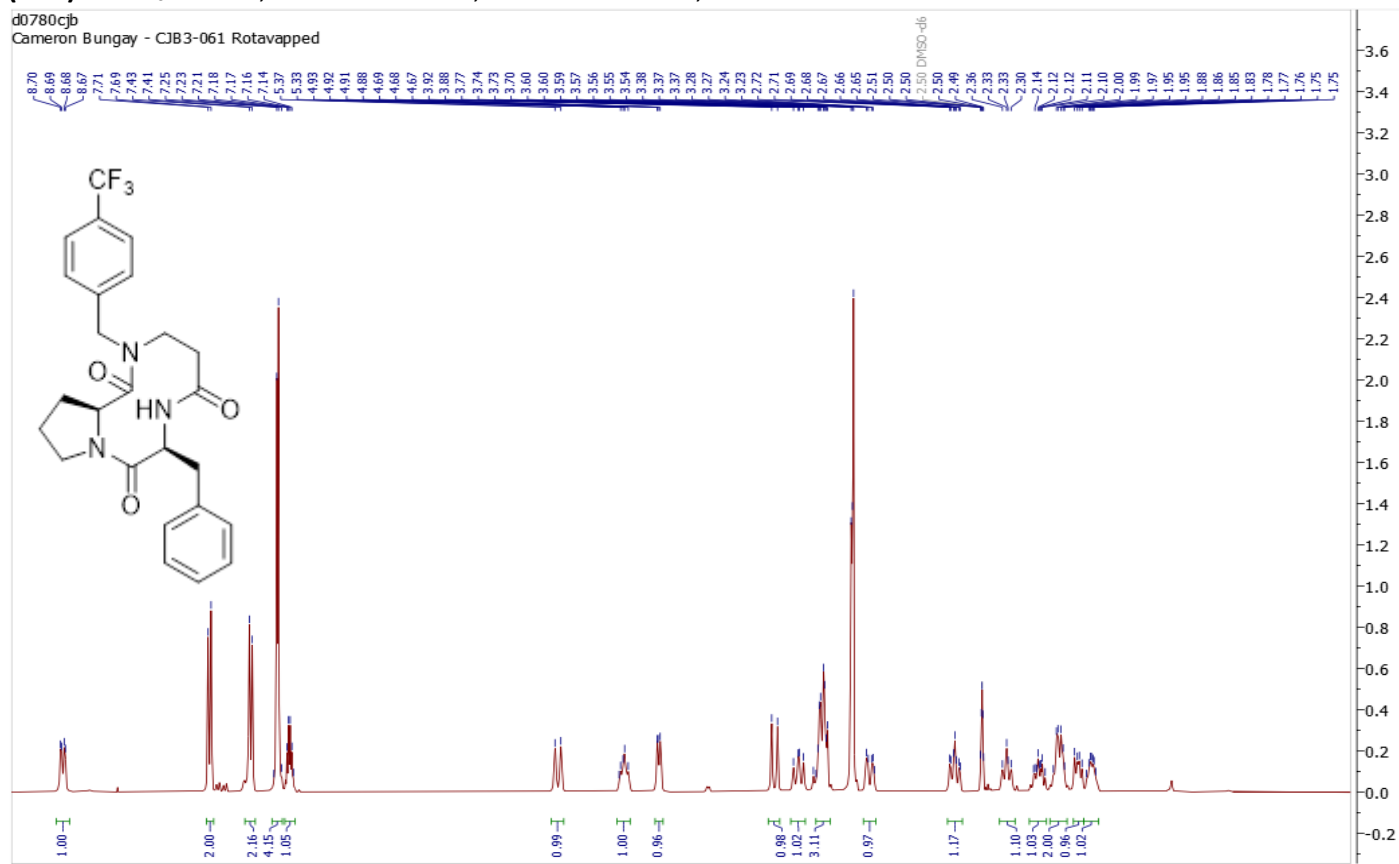


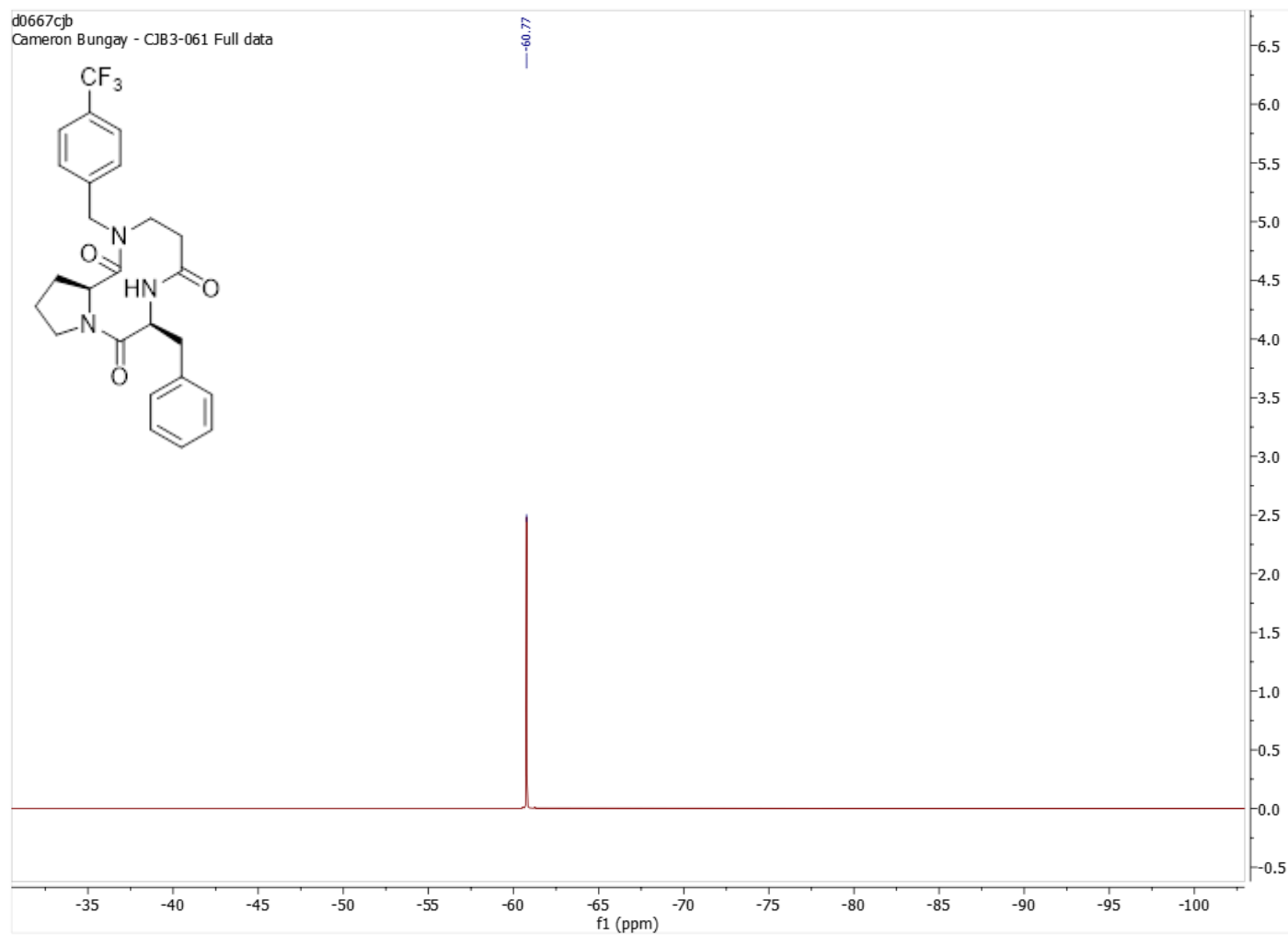
(7*S*,12*aS*)-7-Benzyl-2-(4-chlorobenzyl)octahydropyrrolo[2,1-*c*][1,4,7]triazecine-1,5,8(2*H*)-trione (**14b**) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C



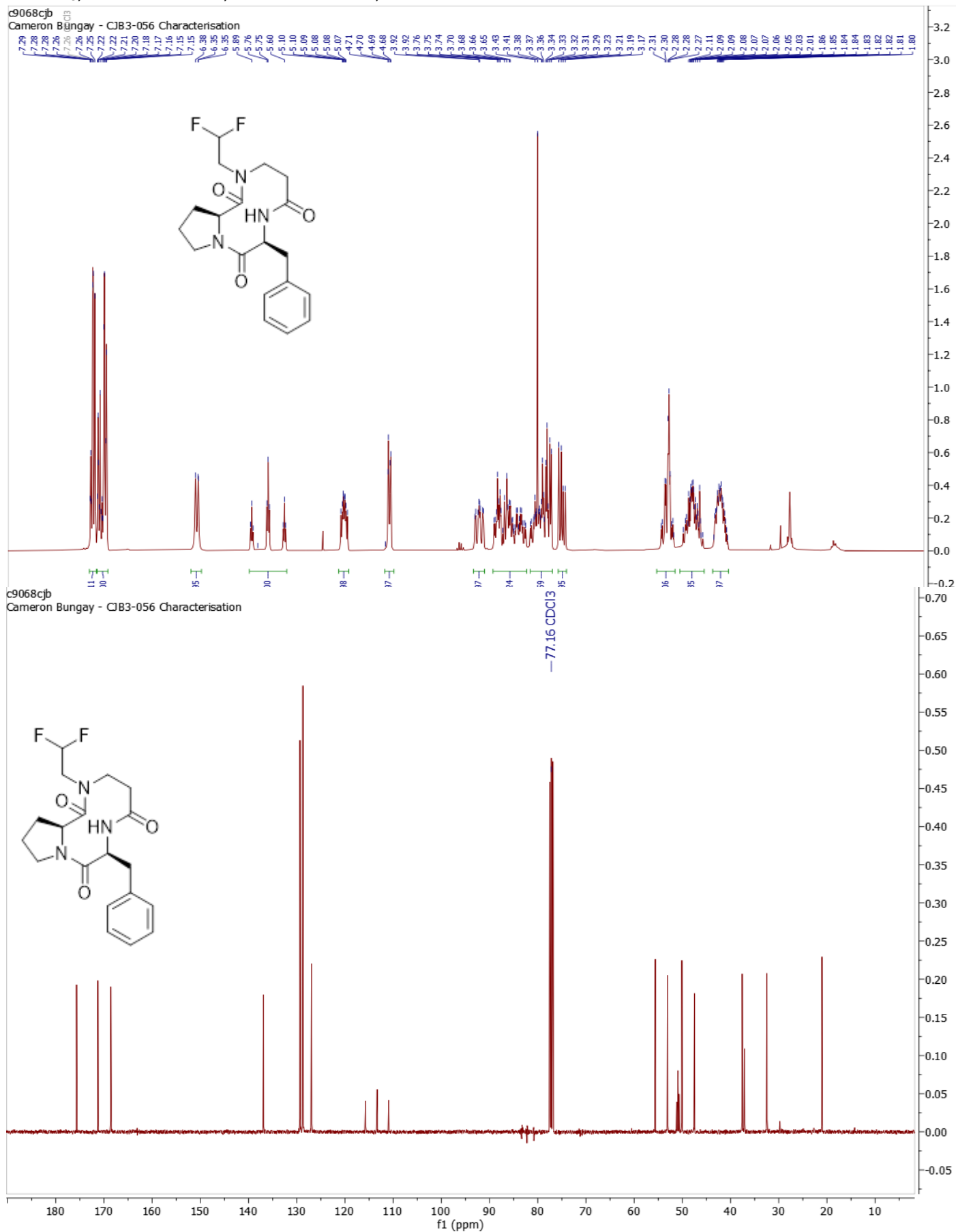
(7S,12aS)-7-Benzyl-2-(4-bromobenzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14c) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

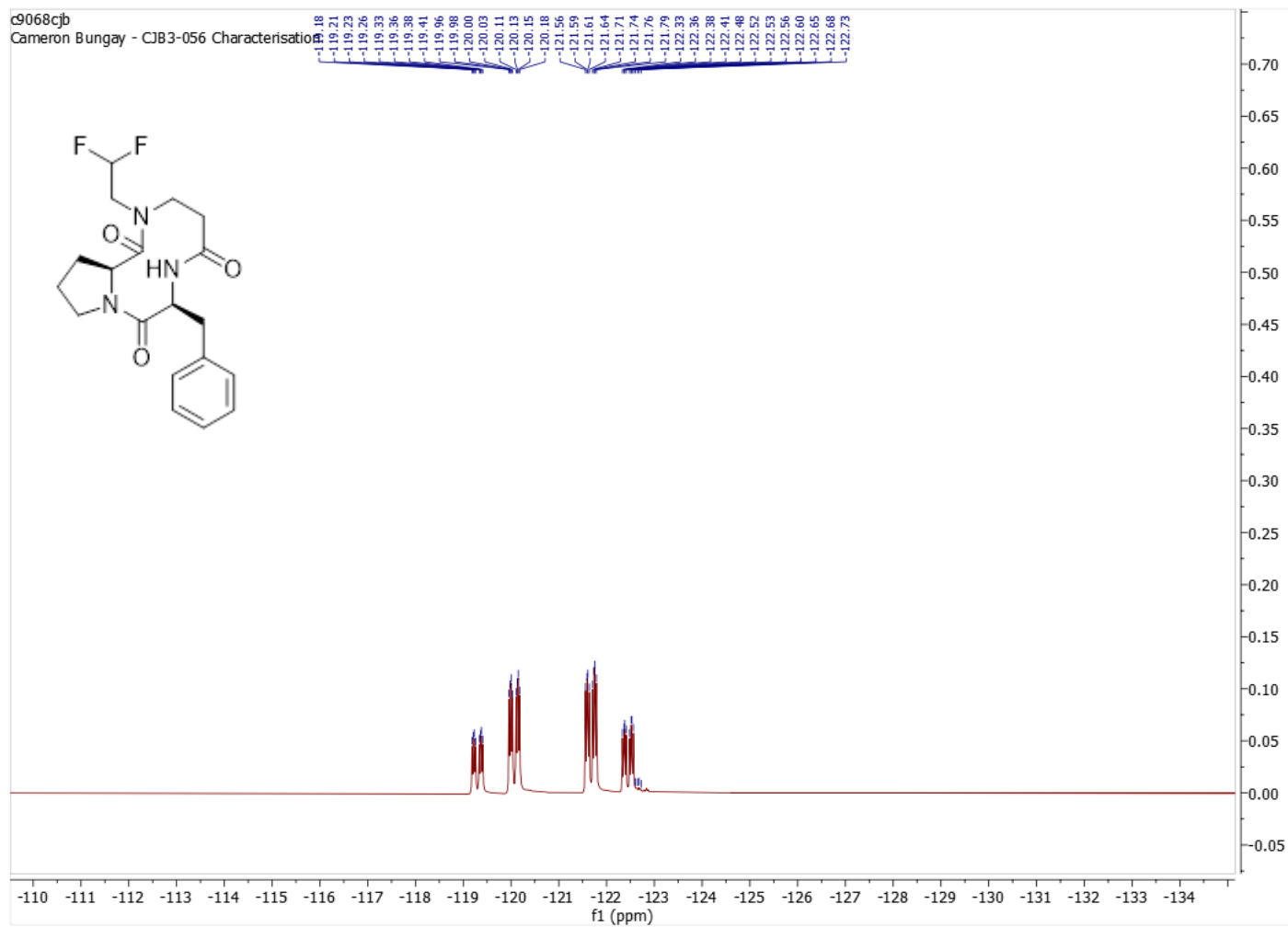


(7*S*,12*aS*)-7-Benzyl-2-(4-(trifluoromethyl)benzyl)octahydropyrrolo[2,1-*c*][1,4,7]triazecine-1,5,8(2*H*)-trione (14*d*) – in *d*₆-DMSO; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F

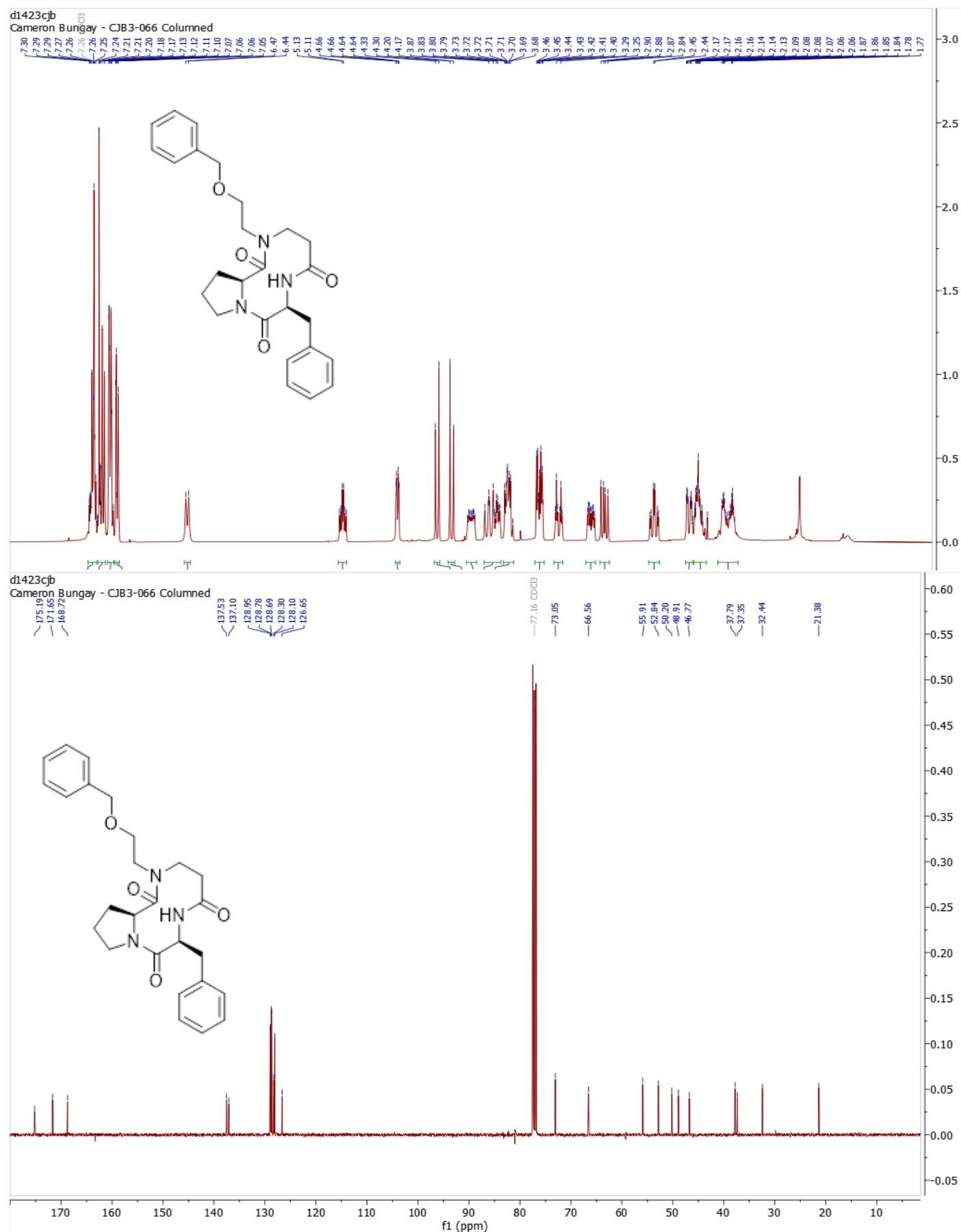


(7*S*,12*aS*)-7-benzyl-2-(2,2-difluoroethyl)octahydropyrrolo[2,1-*c*][1,4,7]triazecine-1,5,8(2*H*)-trione (14e) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F





(7S,12aS)-7-Benzyl-2-(2-(benzyloxy)ethyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14f) –
in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

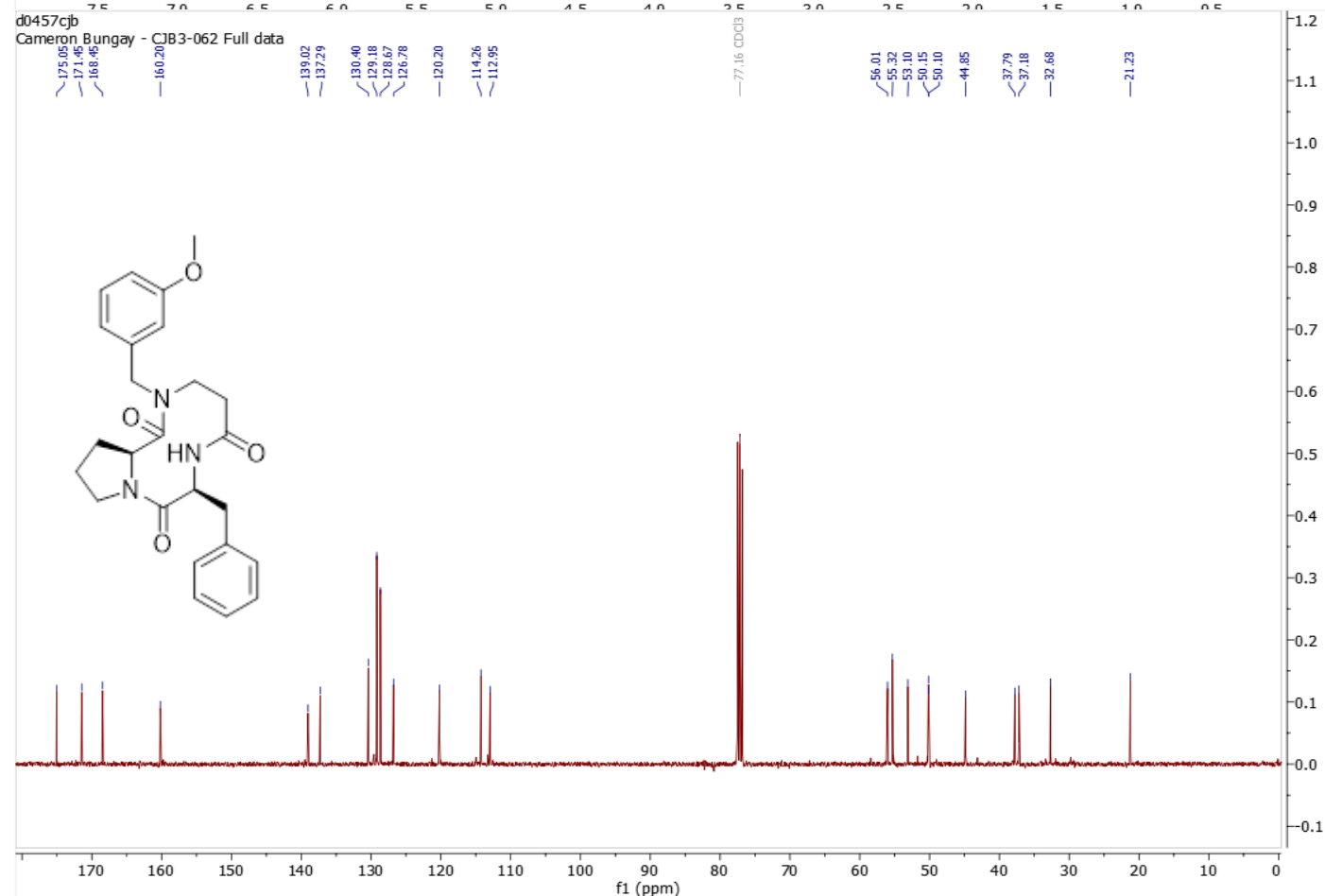


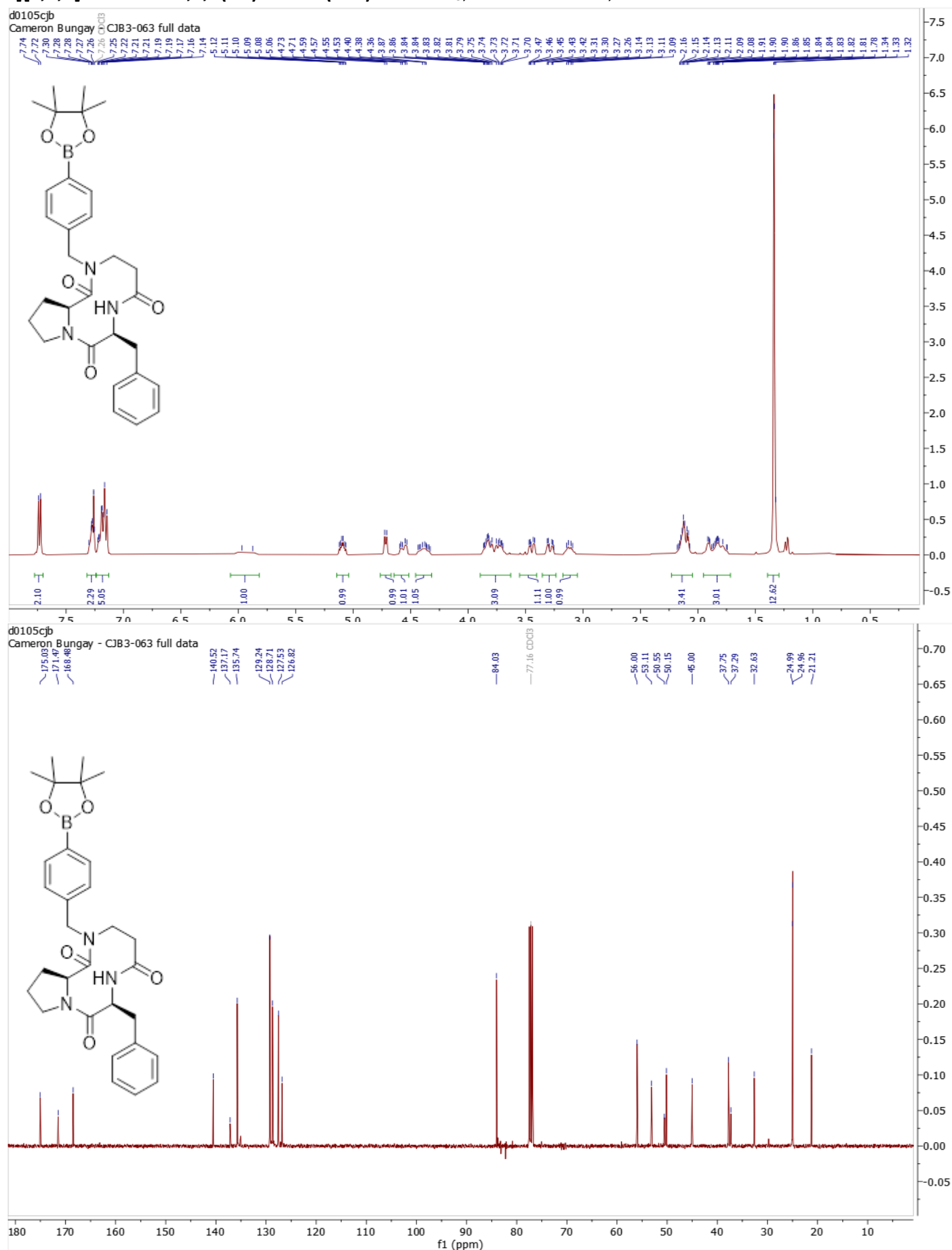
00457cjb
Cameron Bungay - CJB3-062 Full data

Chemical structure of 3jbm: COc1ccc(cc1)CN(C(=O)N[C@@H](Cc2ccccc2)C(=O)N3CCCC3)C(=O)N3CCCC3

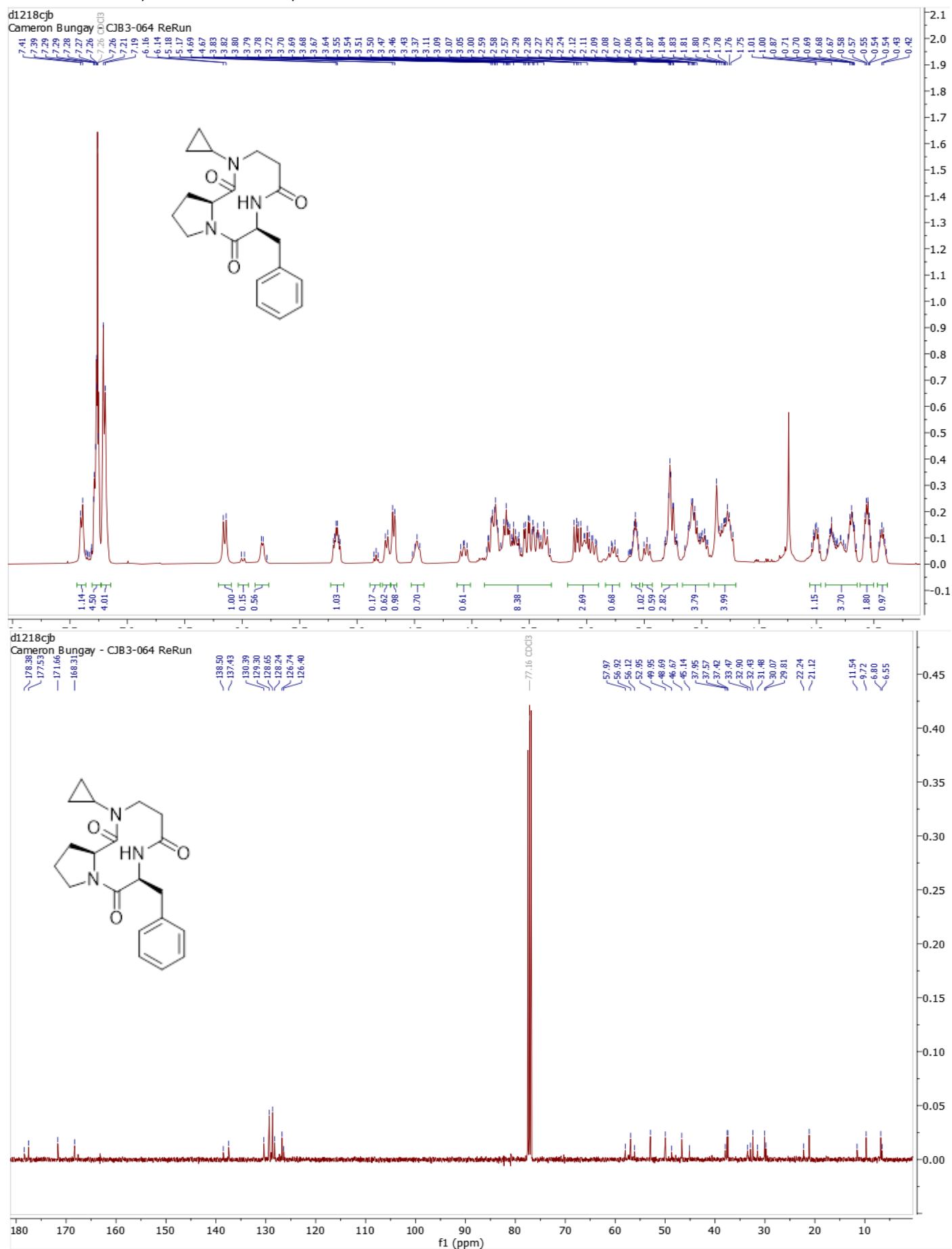
¹H NMR spectrum (400 MHz, CDCl₃) showing peaks from 0 to 8.5 ppm. Integration values are provided below the baseline for each major peak group.

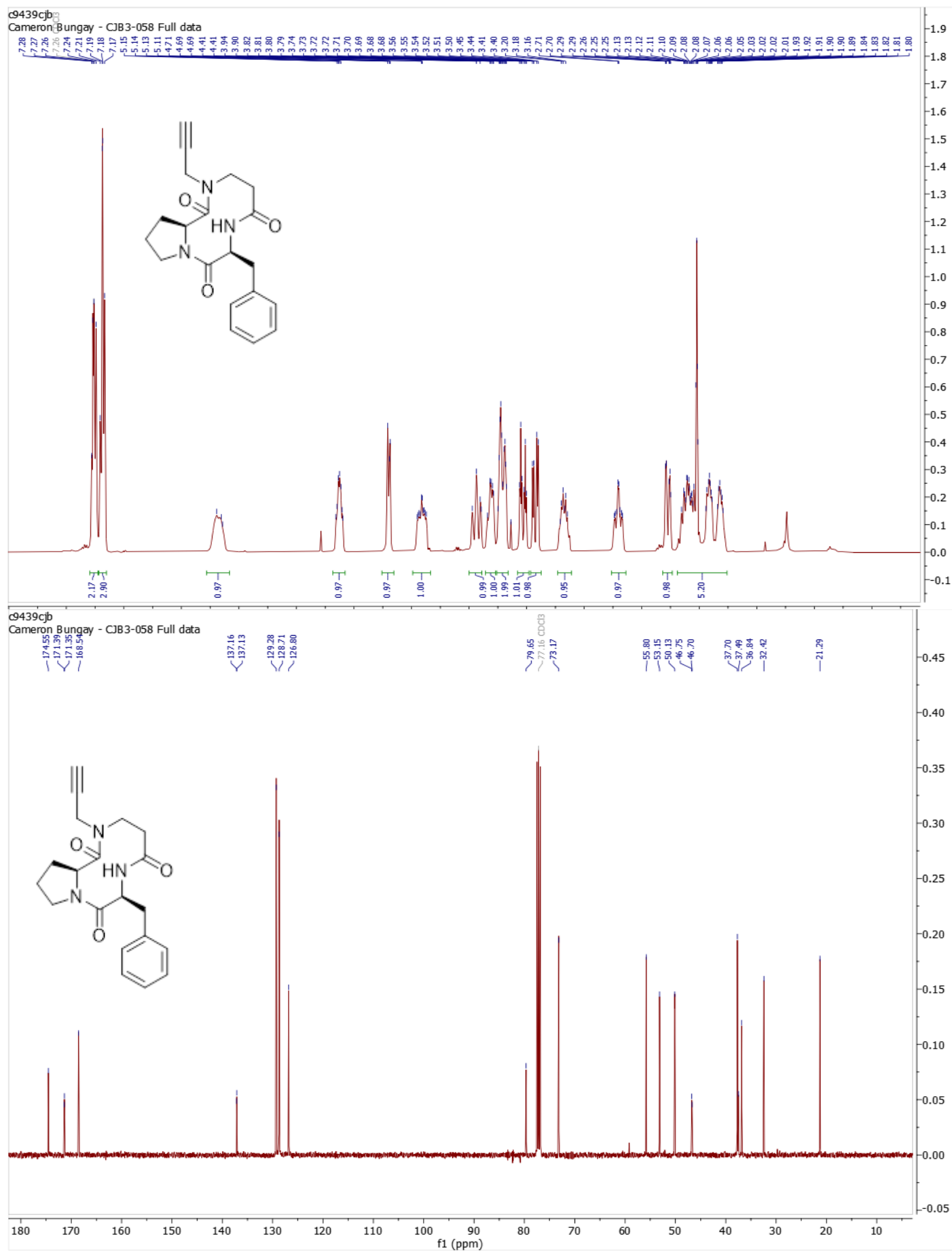
Chemical Shift (ppm)	Integration
7.29, 7.28, 7.27, 7.26, 7.25, 7.22, 7.21, 7.18, 7.17, 7.16, 7.15, 7.15, 6.83, 6.82, 6.81, 6.80, 6.77, 6.76, 6.74, 6.74, 6.72, 6.72, 6.72, 5.99, 5.96, 5.92, 5.91, 4.75, 4.75, 4.73, 4.73, 4.66, 4.63, 4.26, 4.23, 3.83, 3.79, 3.77, 3.76, 3.75, 3.74, 3.71, 3.52, 3.51, 3.48, 3.47, 3.33, 3.11, 3.09, 3.08, 3.05, 2.17, 2.16, 2.16, 2.15, 2.15, 2.14, 2.14, 2.13, 1.94, 1.93, 1.93, 1.92, 1.90, 1.89, 1.87, 1.86, 1.85	2.38, 4.34, 1.27, 2.21, 0.95, 1.02, 1.02, 1.00, 1.00, 6.70, 1.12, 0.98, 1.01, 3.02, 3.41



(7*S*,12*aS*)-7-Benzyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)octahydropyrrolo[2,1-*c*][1,4,7]triazecine-1,5,8(2*H*)-trione (14h) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

(7S,12aS)-7-Benzyl-2-cyclopropyloctahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14i) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 5:3 mixture of diastereomers



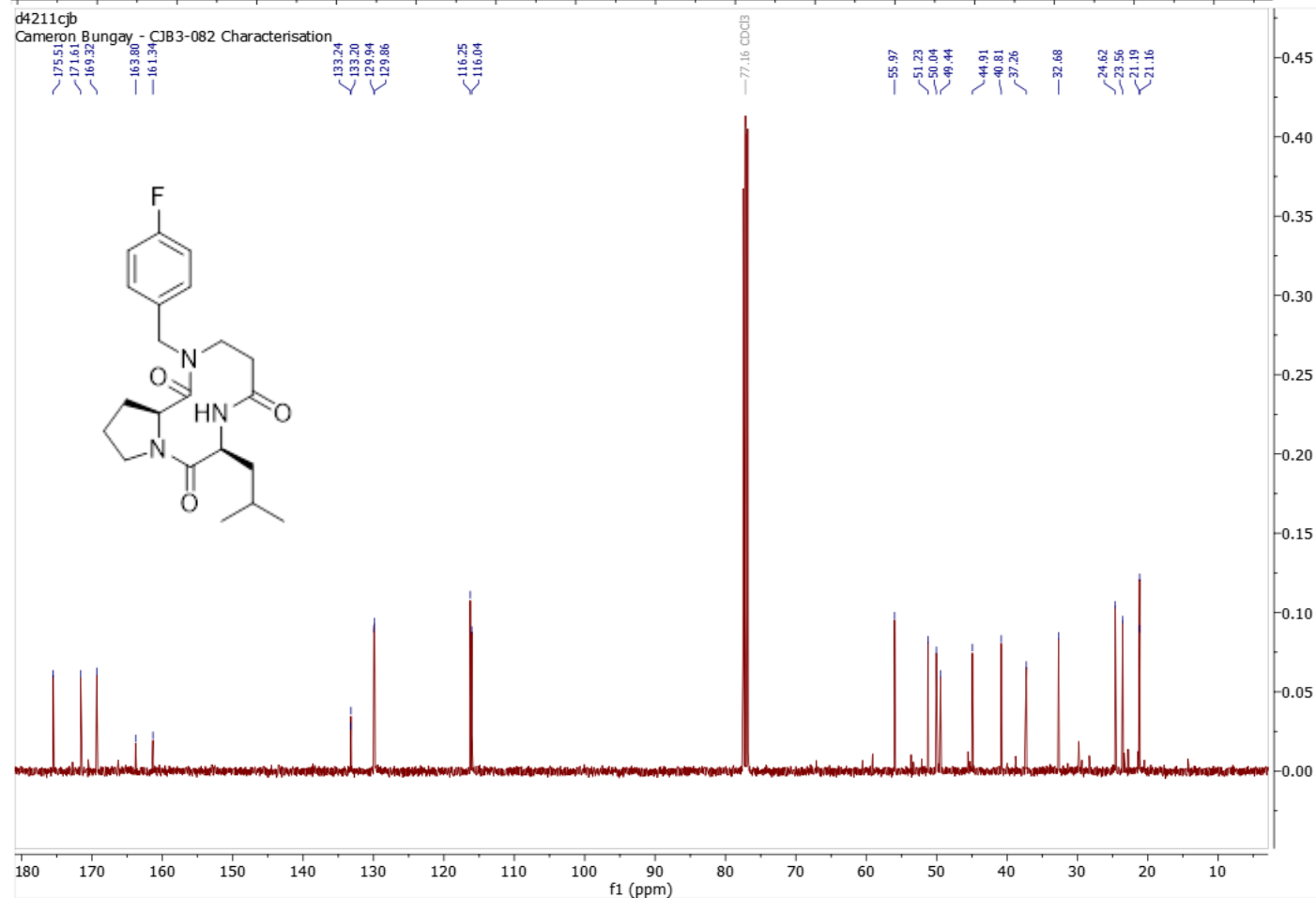
(7S,12aS)-7-Benzyl-2-(prop-2-yn-1-yl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14j) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C

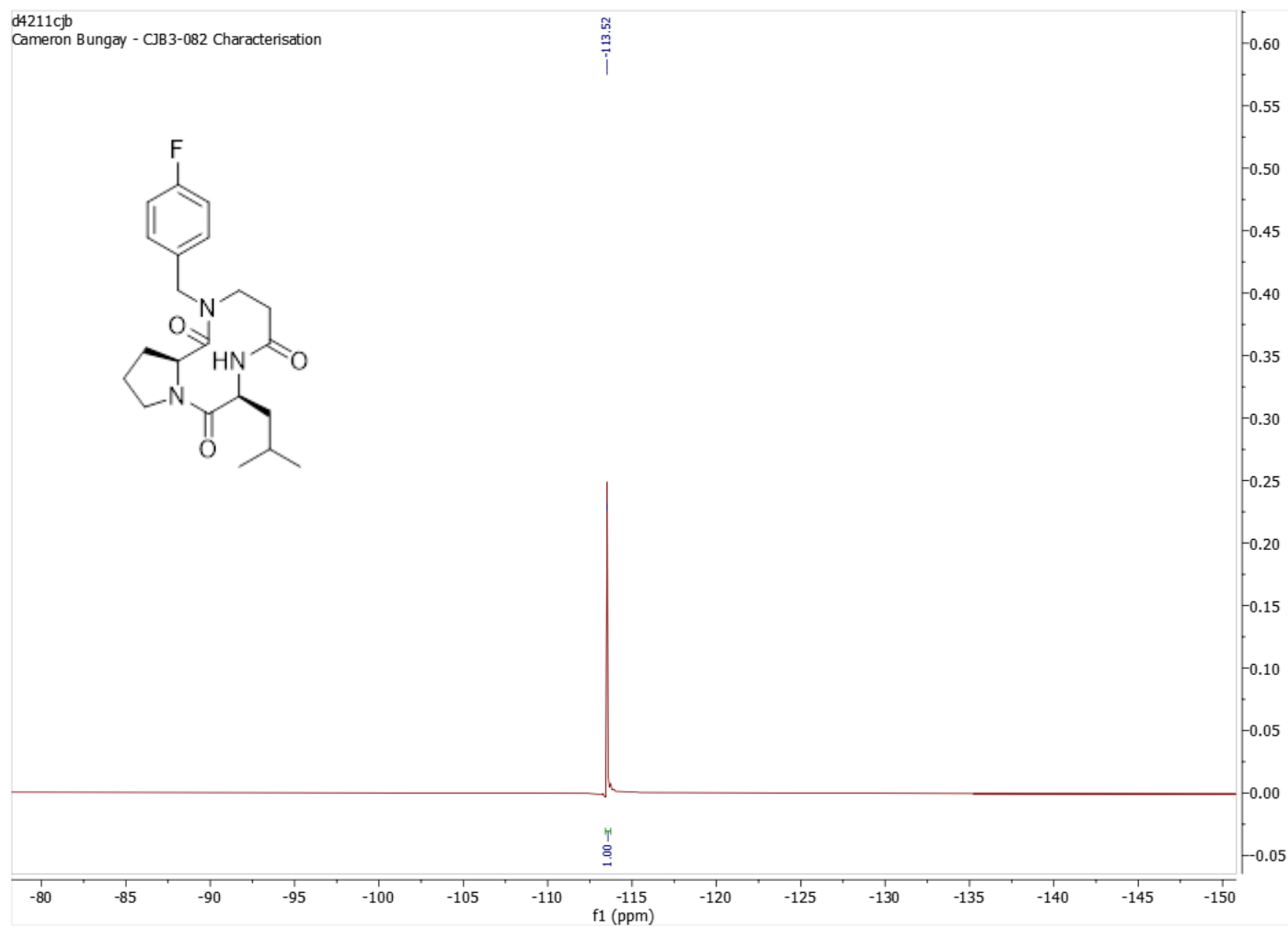
04211cjb
Cameron Bungay - CJ83-082 Characterisation

Chemical structure of compound 8j: CC(C)C(=O)N1CCC(=O)N1Cc2ccc(F)cc2

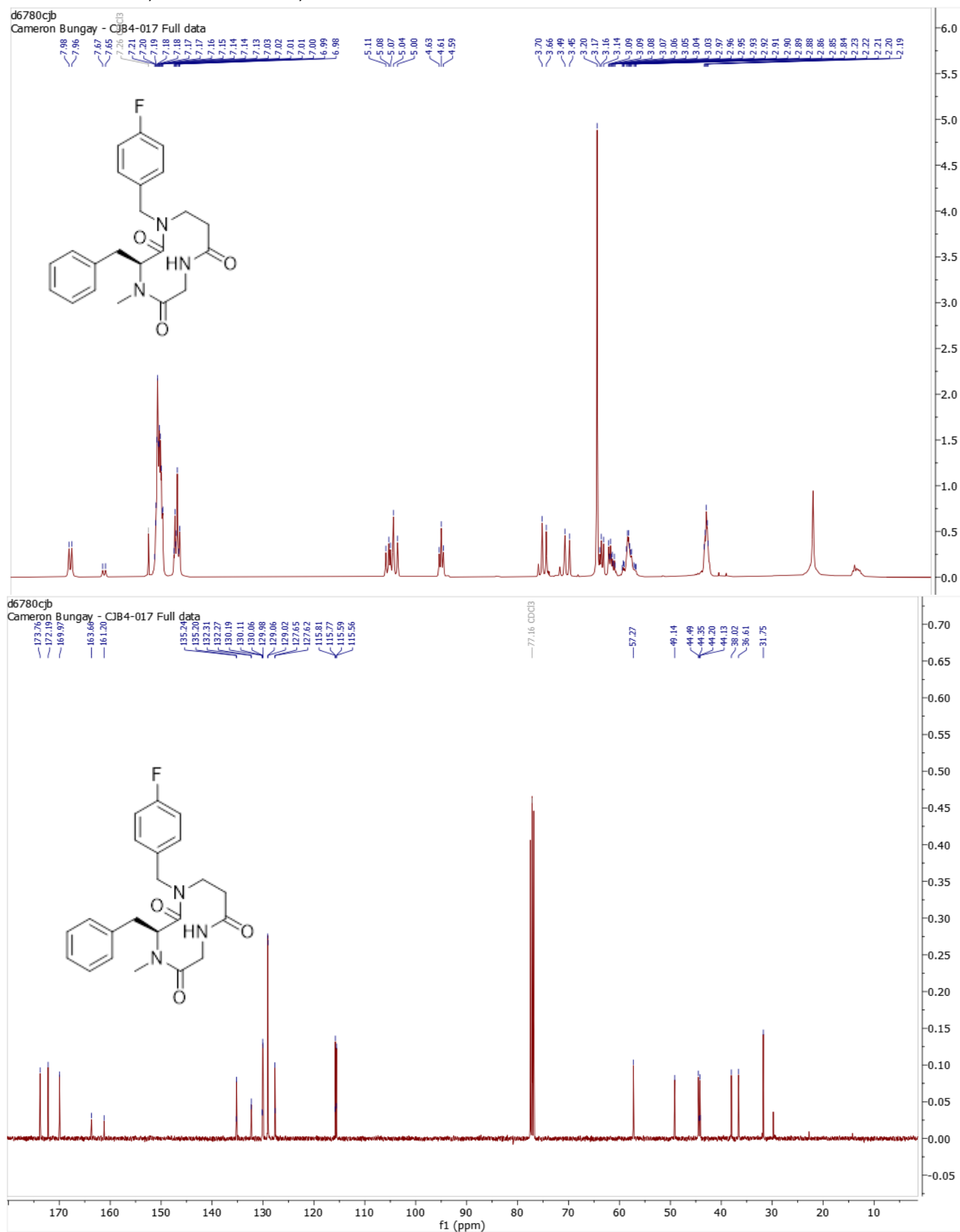
¹H NMR spectrum (CDCl₃) showing peaks and integration values:

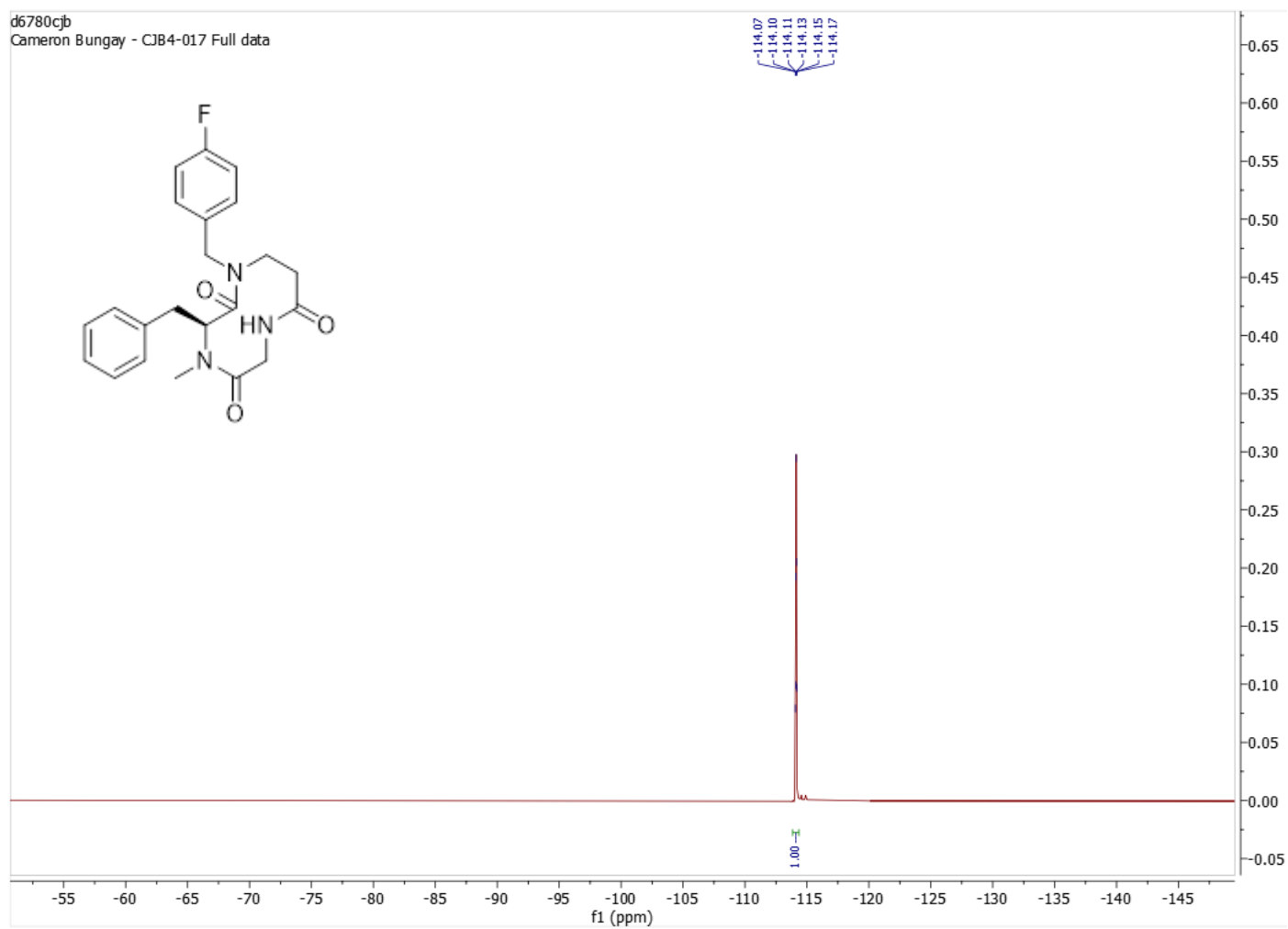
Chemical Shift (ppm)	Integration
7.26, 7.25, 7.24, 7.23, 7.05, 7.04, 7.03, 7.02, 7.01, 6.19, 4.96, 4.92, 4.81, 4.81, 4.79, 4.76, 4.75, 4.74, 4.15, 4.11, 3.89, 3.85, 3.85, 3.82, 3.76, 3.75, 3.74, 3.71, 3.70, 3.63, 3.38, 3.37, 3.34, 3.34, 2.36, 2.35, 2.35, 2.33, 2.32, 2.23, 2.23, 2.20, 2.20, 2.17, 2.16, 2.15, 2.14, 2.13, 2.12, 2.12, 2.11, 2.10, 2.08, 2.08, 2.07, 2.03, 2.01, 1.91, 1.91, 1.90, 1.89, 1.85, 1.84, 1.83, 1.51, 1.50, 1.49, 1.49, 1.47, 1.46, 1.43, 0.92, 0.91, 0.90, 0.89, 0.88	2.68, 2.05, 0.99, 1.00, 1.07, 0.99, 1.15, 1.06, 2.37, 1.03, 1.08, 8.76, 2.41, 3.07, 3.19

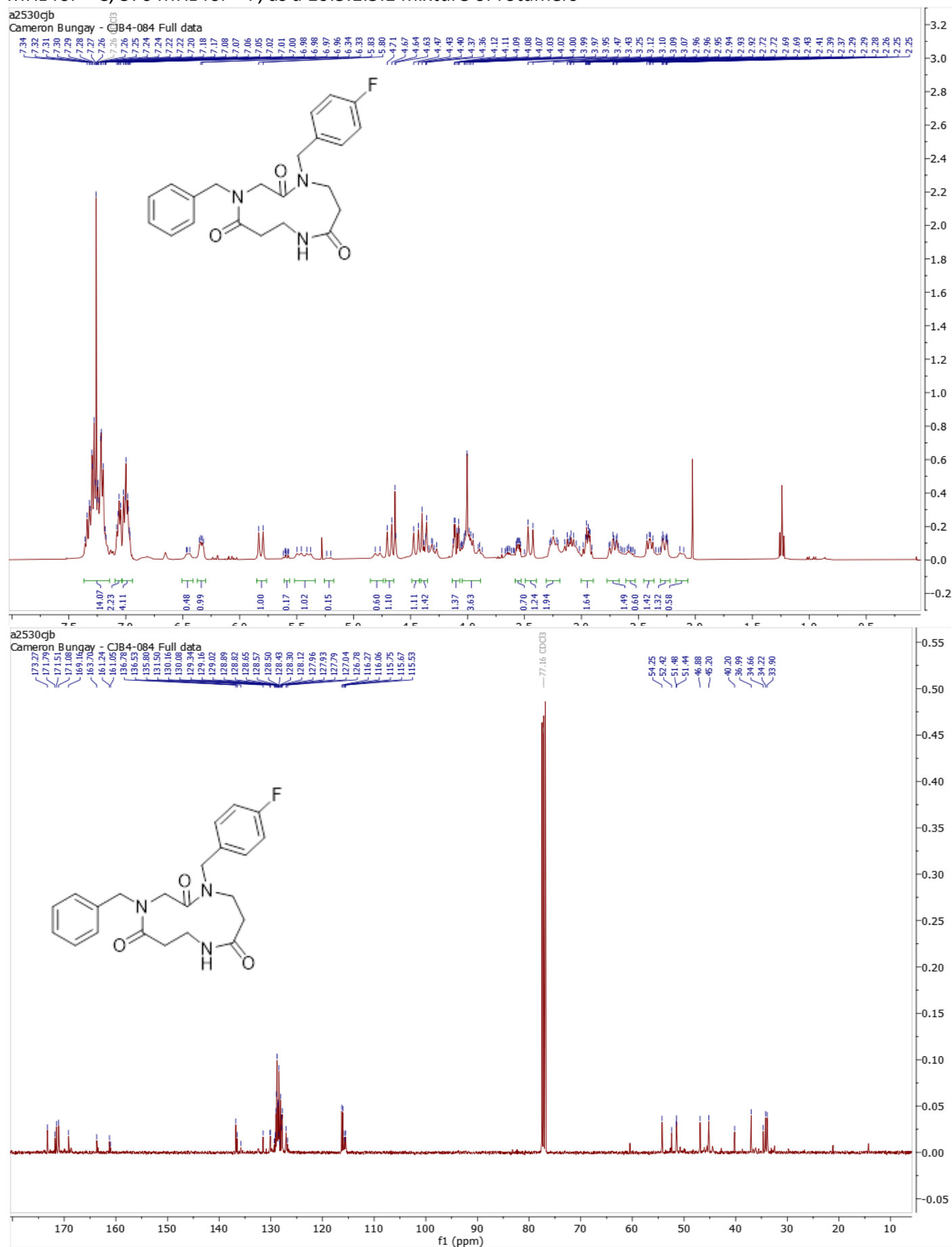


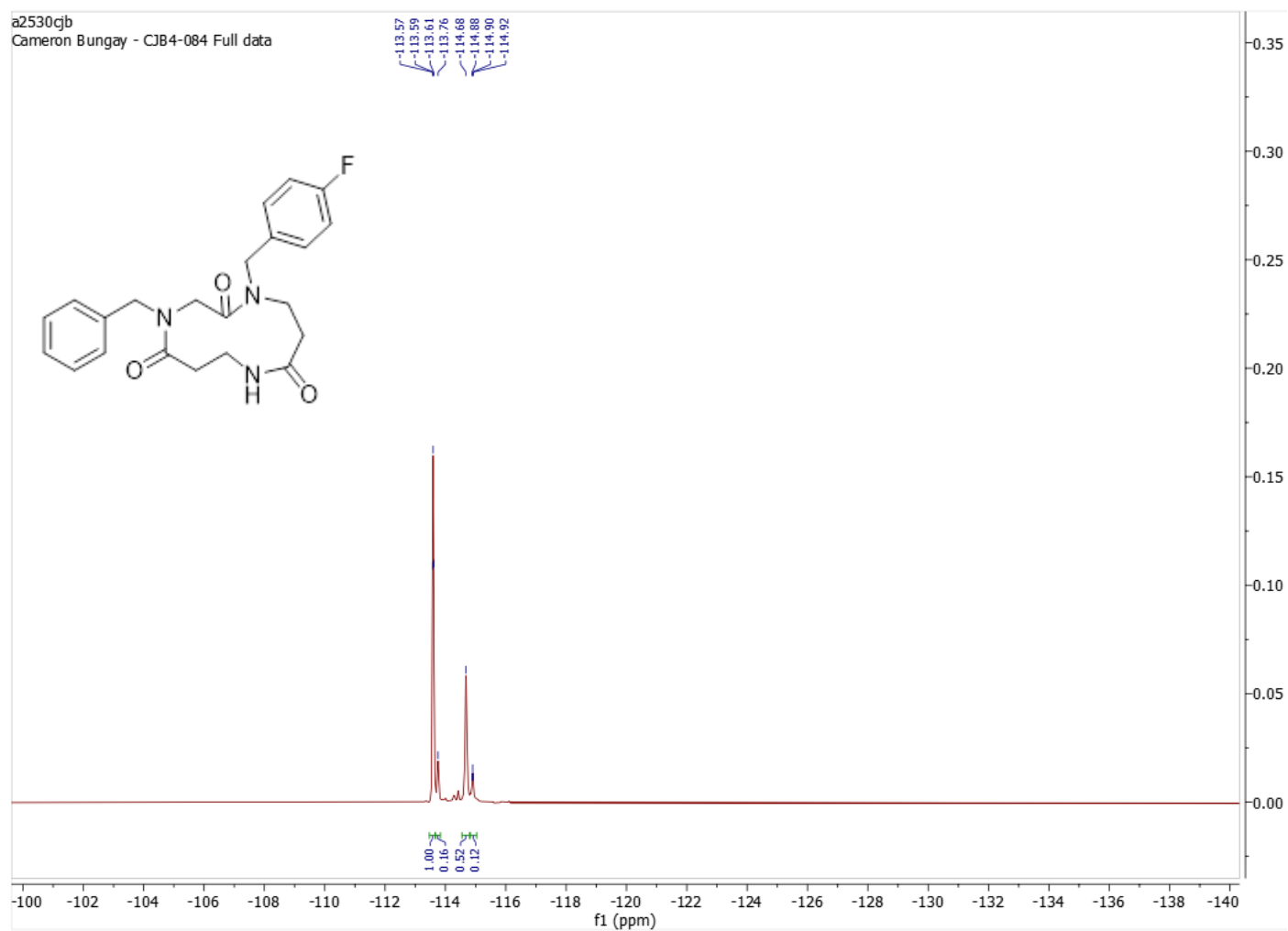


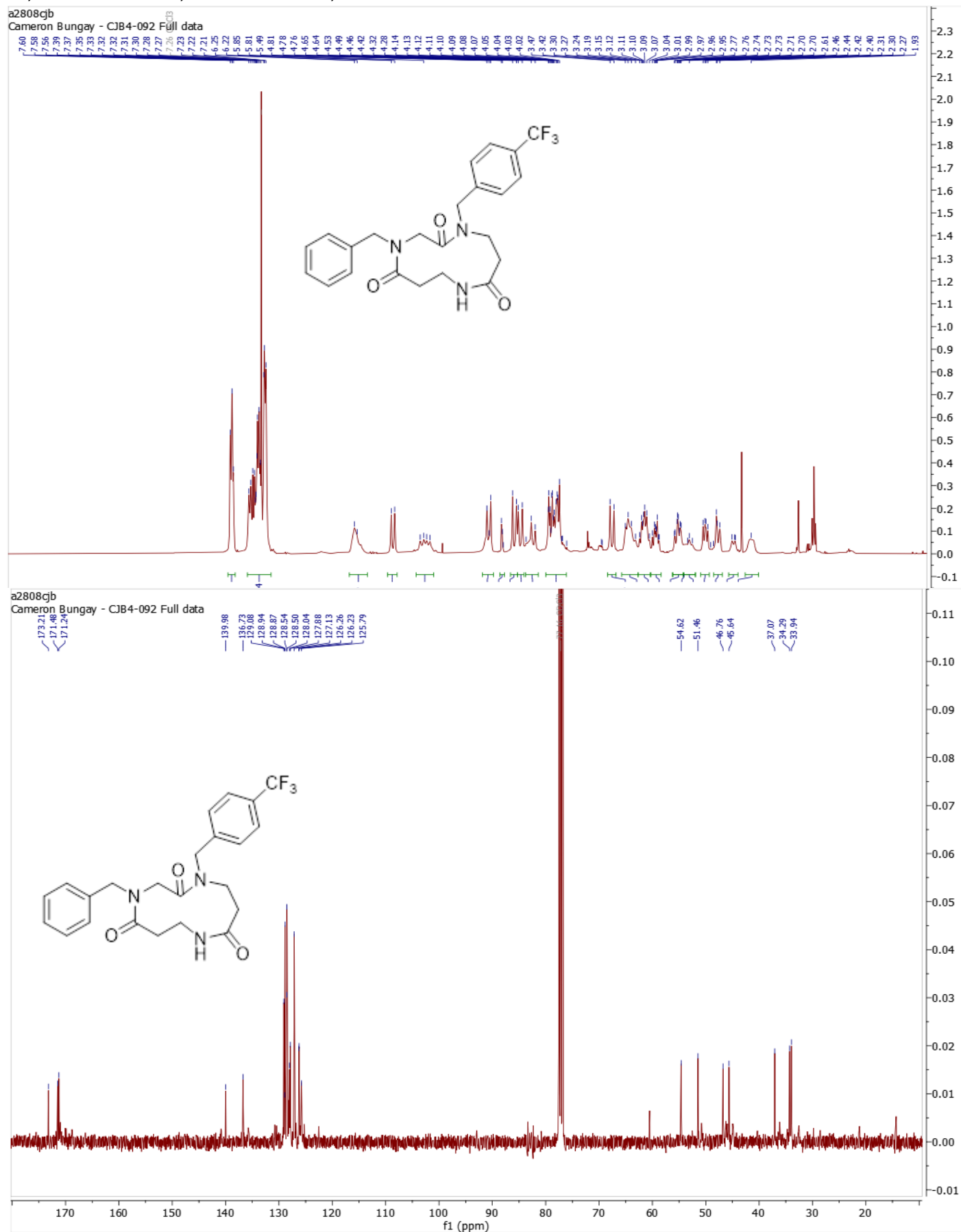
(S)-3-benzyl-1-(4-fluorobenzyl)-4-methyl-1,4,7-triazecane-2,5,8-trione (15b) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F, as a 14:1 mixture of rotamers

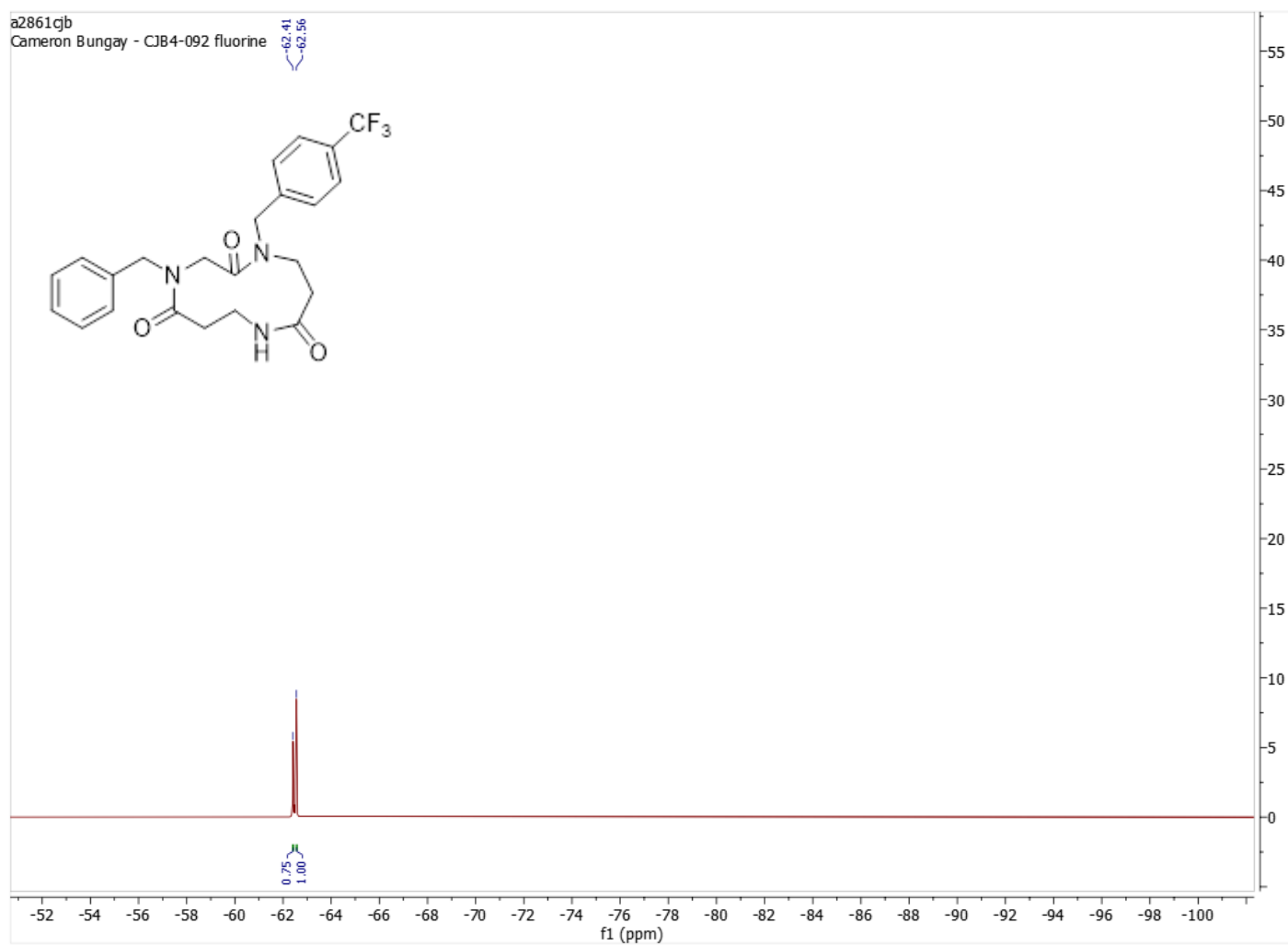




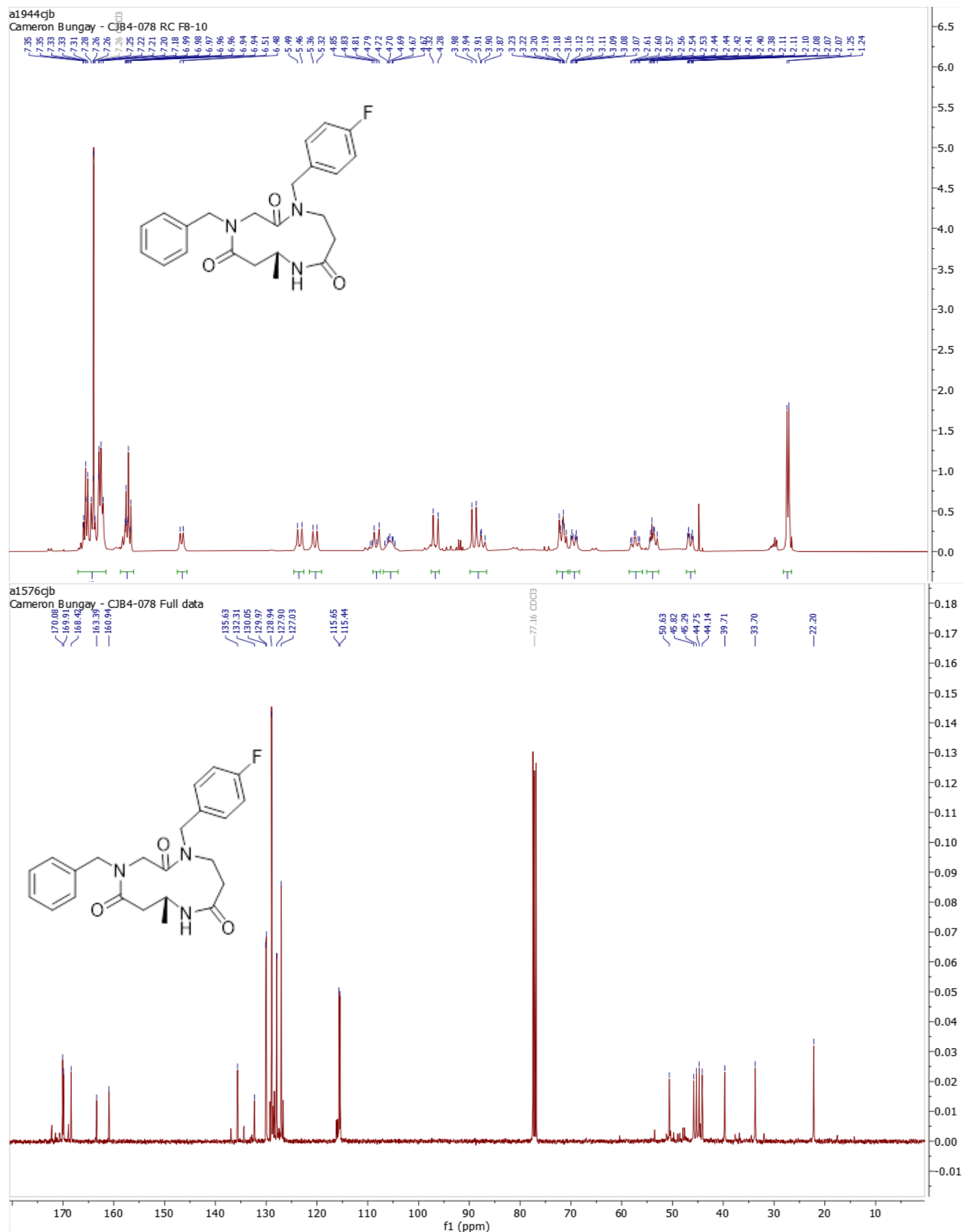
4-Benzyl-1-(4-fluorobenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15c) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F, as a 10:5:1.5:1 mixture of rotamers

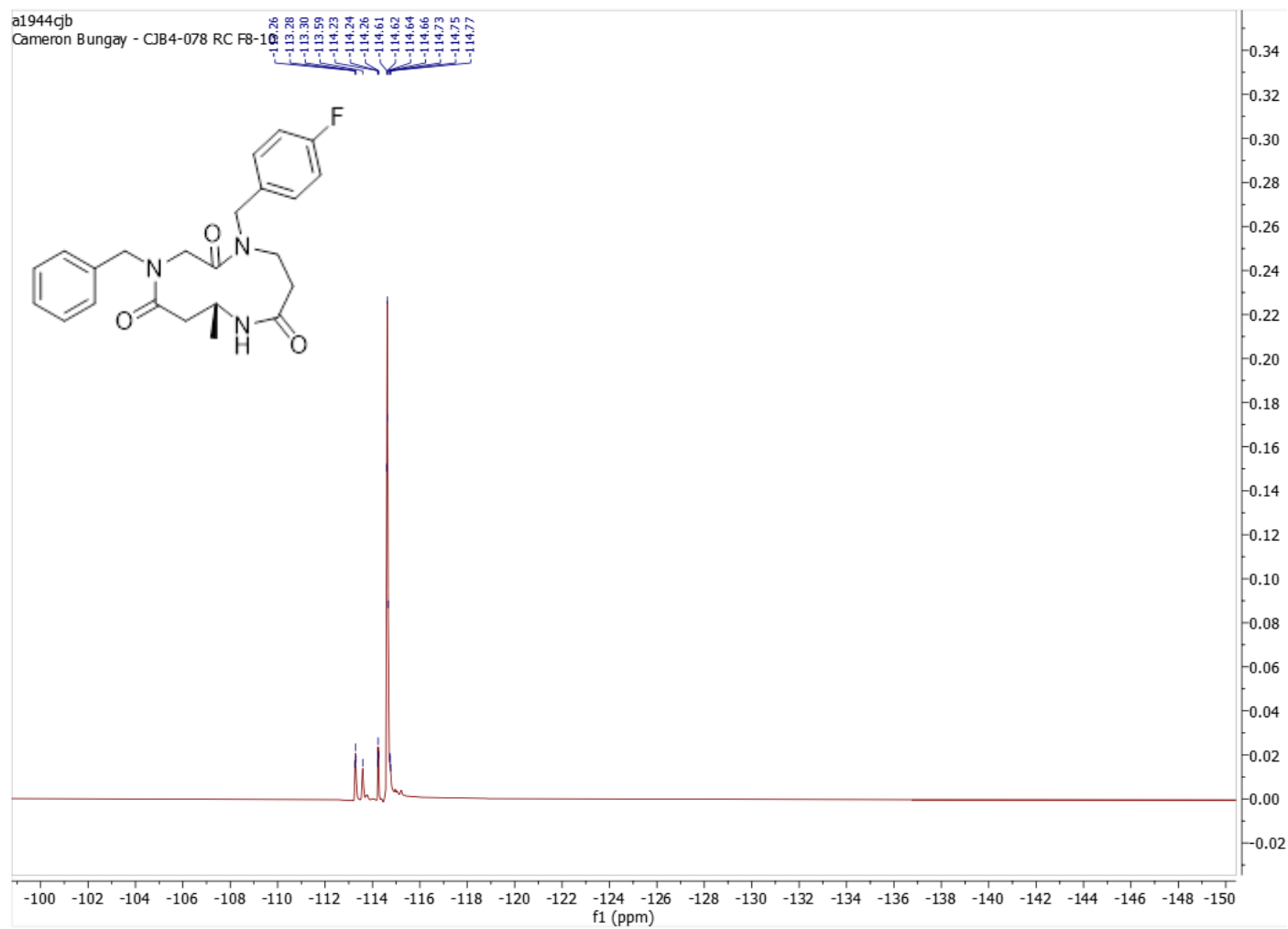


4-Benzyl-1-(4-trifluoromethylbenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15d) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F, as a 4:3 mixture of rotamers

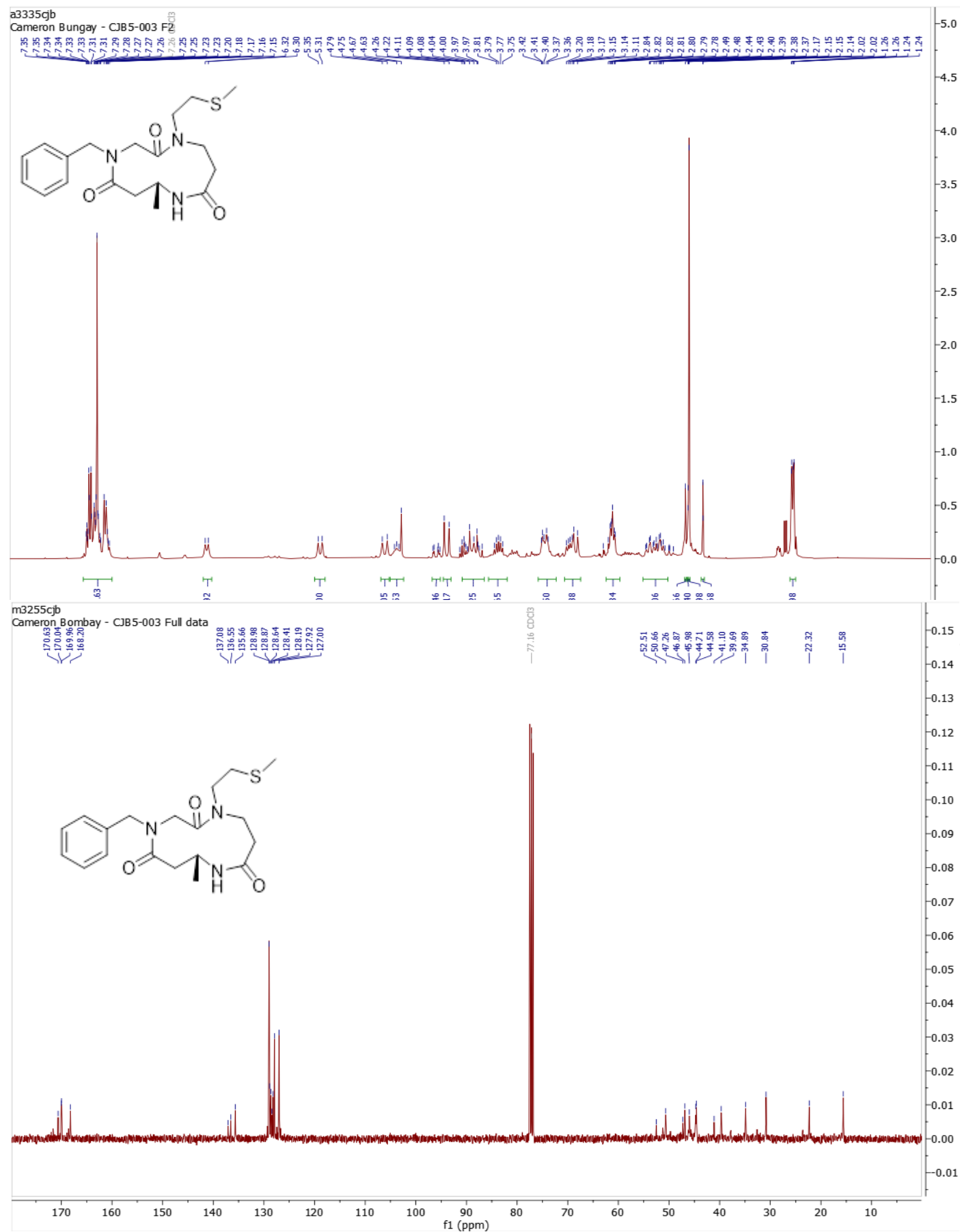


(R)-4-Benzyl-1-(4-fluorobenzyl)-7-methyl-1,4,8-triazacycloundecane-2,5,9-trione (15e) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F, as a 13:1:1:1 mixture of rotamers

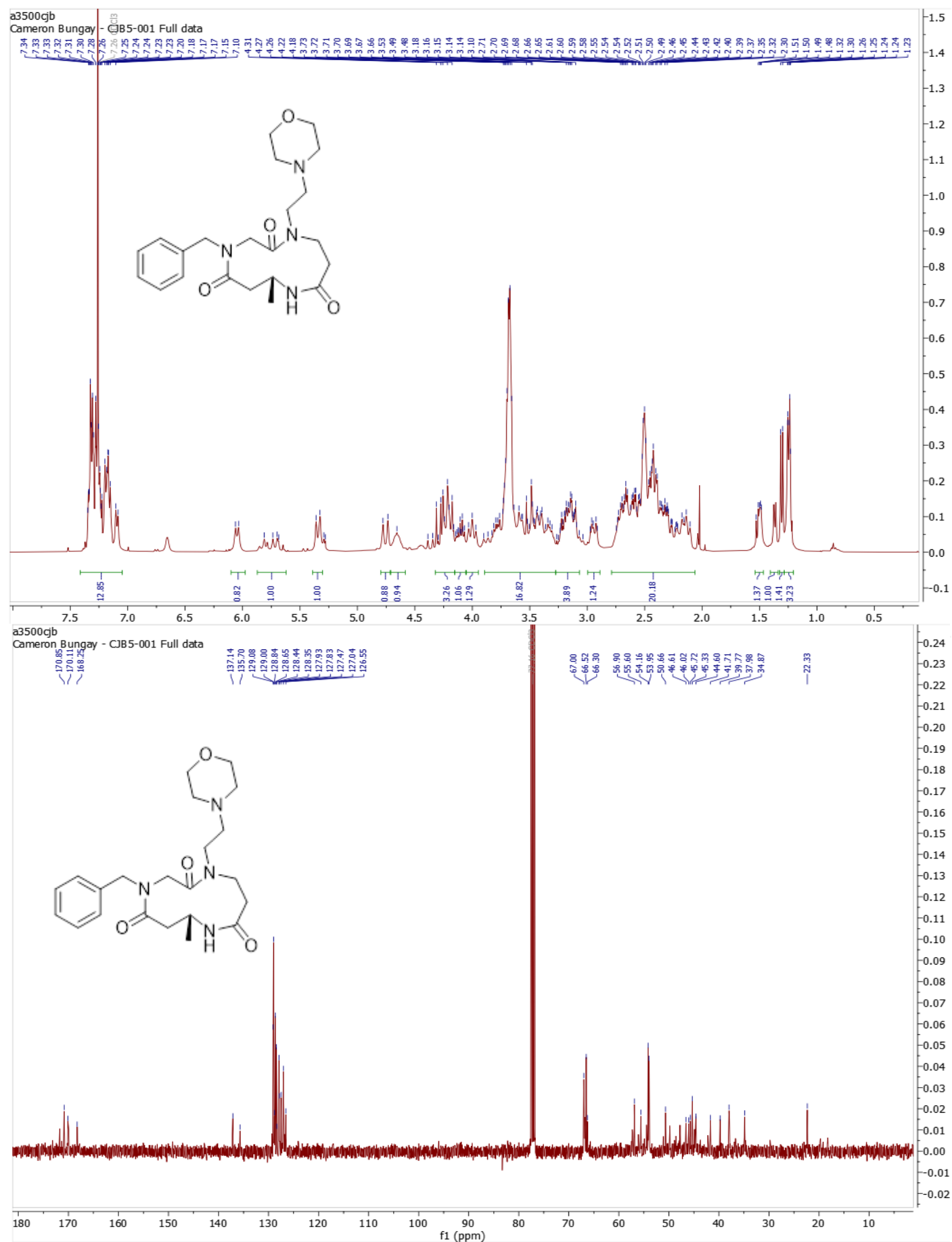




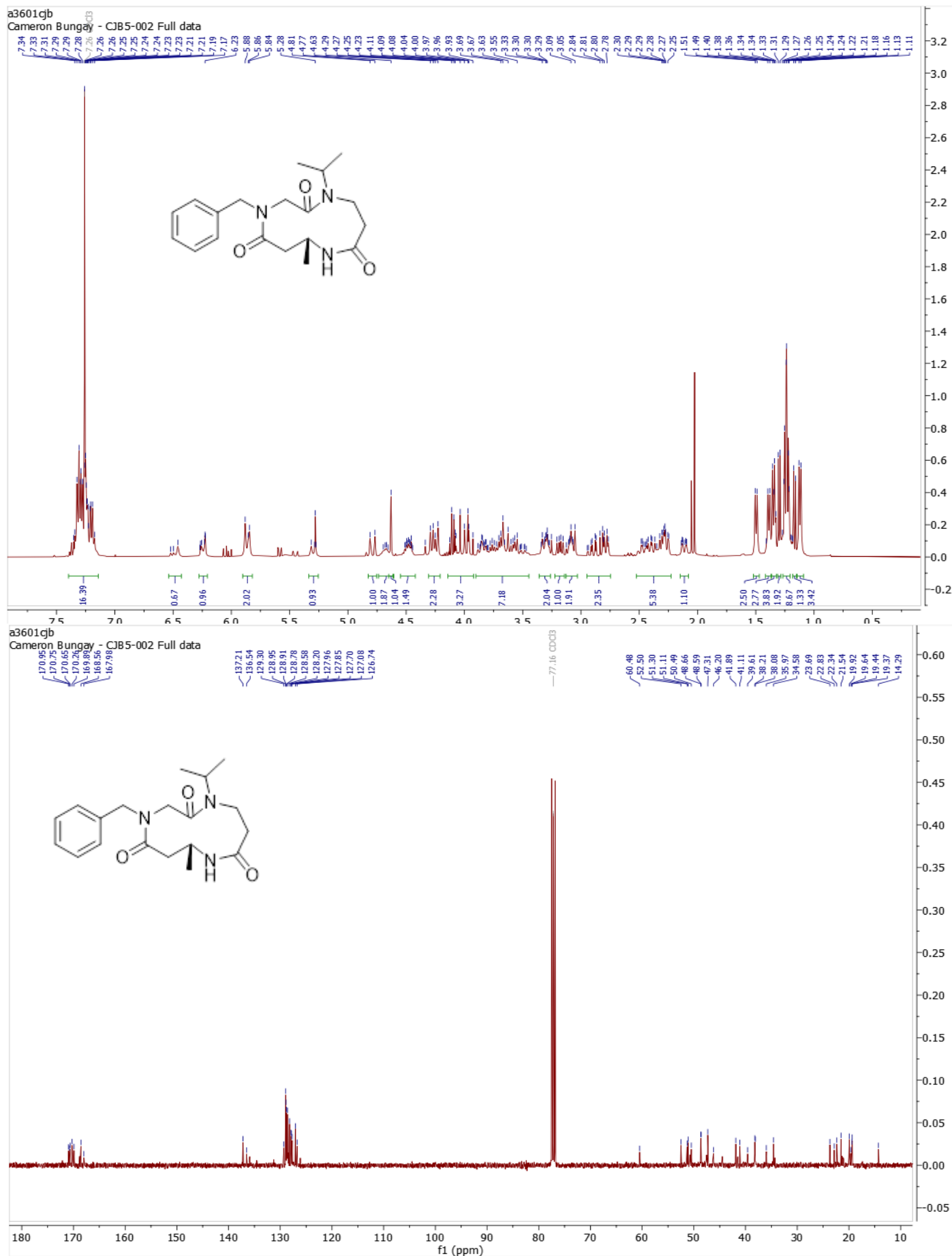
(R)-4-Benzyl-7-methyl-1-(2-(methylthio)ethyl)-1,4,8-triazacycloundecane-2,5,9-trione (15f) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 4:1:1:1 mixture of rotamers



(R)-4-Benzyl-7-methyl-1-(2-morpholinoethyl)-1,4,8-triazacycloundecane-2,5,9-trione (15g) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, as a 6:3:3:2 mixture of rotamers



(R)-4-Benzyl-1-isopropyl-7-methyl-1,4,8-triazacycloundecane-2,5,9-trione (15h) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C. In solution in CDCl₃, the title compound exists as a ~4:2:1:1 mixture of rotamers



(3S)-1-(4-Fluorobenzyl)-3-methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15i) – in CDCl₃; 400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F, as a 5:3:3 mixture of rotamers/diastereomers

