



Supporting Information

for

Exploring the scope of DBU-promoted amidations of 7-methoxycarbonylpterin

Anna R. Bockman and Jeffrey M. Praet

Beilstein J. Org. Chem. **2020**, *16*, 509–514. doi:10.3762/bjoc.16.46

General procedures, characterization data, and copies of NMR spectra

Table of contents

General information	S1
Synthesis	S1
Pseudo-first order kinetics	S5
Copies of ^1H and ^{13}C NMR spectra	S6
References	S21

General information:

All reagents used were of commercial quality and obtained from Aldrich Chemical Co. and used as received. ^1H and ^{13}C NMR spectra were recorded in $\text{DMSO}-d_6$ (or methanol- d_4 for NMR kinetics) with a Bruker spectrometer using the solvent as the reference. Chemical shifts are given in parts per million (ppm). IR data were collected with a NEXUS 670 FT-IR. Purity was assessed on a Waters UPLC with a QDa detector. High resolution mass spectrometry was performed with a Varian 9.4T QFT-ESI ICR system. Filtrations were performed by aid of reduced pressure. Amidation reactions were run using an Anton-Paar MonoWave50TM reactor, operated without microwave irradiation and simply worked as a controlled heating block.¹

Synthesis

7-Methoxycarbonylpterin (1): Compound **1** was prepared by our previously reported acyl-radical insertion reaction.²

General method for the DBU-assisted amidation:

Compound **1** (50 mg, 0.23 mmol) was suspended in 1.0 mL of anhydrous MeOH in an oven-dried borosilicate reaction vessel (Anton-Paar), and stirred to create a slurry. To this was added DBU (68 μL , 0.45 mmol, 2 equiv) which resulted in full dissolution of **1**. To this was added the amine (2 equiv). (**Note:** for amines containing an acidic functional group, e.g. Gly/Ser/Ala, 4 equiv DBU were used to ensure basic conditions). The reaction vessel was then fitted with a silicone cap containing a PTFE seal. The tube was placed in a MonoWave50TM reactor and irradiated for the time and temperature indicated. Once the reaction was complete, the mixture was diluted with 1 mL of DI water, and acidified by the dropwise addition of 3 M HCl, resulting in a yellow precipitate. The product was isolated by filtration, rinsed several times with water and MeOH, and dried over P_2O_5 in a vacuum oven.

(2-Amino-4-oxo-3,4-dihydropteridine-7-carbonyl)glycine (2): Compound **2** was synthesized by the general method above, using 34 mg glycine and 4 equiv DBU, resulting in 59 mg (99%) **2**. MP > 300°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm)= 12.72 (br, 1H),

11.61 (s, 1H), 9.04 (t, $J = 5.6$ Hz, 1H), 8.88 (s, 1H), 7.03 (br, 2H), 3.99 (d, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 171.2, 163.5, 160.8, 156.5, 154.9, 147.6, 136.9, 132.4, 41.5; HRMS-ESI (m/z) [M-H]⁻ calc. for (C₉H₇N₆O₄)⁻ 263.0534; found 263.0533. This is consistent with that reported in the literature.³

2-Amino-N-(4-nitrophenethyl)-4-oxo-3,4-dihydropteridine-7-carboxamide (3):

Compound **3** was synthesized by the general method, using 91 mg of 4-nitrophenethylamine hydrochloride and 4 equiv DBU, resulting in 77 mg (96%) of **3**. MP > 300°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm)= 11.58 (s, 1H), 8.98 (t, $J = 6$ Hz, 1H), 8.83 (s, 1H), 8.15 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 6.98 (br, 2H), 3.62 (q, $J = 6.8$ Hz, 2H), 3.04 (t, $J = 7$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 163.3, 160.8, 156.5, 154.8, 148.3, 148.1, 146.6, 137.0, 132.1, 130.5, 123.9, 40.8, 35.1; IR (cm⁻¹): 3414, 3216, 1722, 1637, 1514, 1342; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₅H₁₄N₇O₄)⁺ 356.1102; found 356.1101

2-Amino-N-benzyl-4-oxo-3,4-dihydropteridine-7-carboxamide (4): Compound **4** was synthesized by the general method, using 50 μL of benzylamine and 2 equiv DBU, resulting in 64 mg (91%) of **4**. MP > 300°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm)= 11.63 (s, 1H), 9.41 (t, $J = 6.3$ Hz, 1H), 8.88 (s, 1H), 7.35-7.2 (m, 5H), 7.01 (br, 2H), 4.57 (d, $J = 6$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 163.4, 160.8, 156.6, 154.8, 148.3, 139.6, 137.2, 132.1, 128.7 (2C), 127.8 (2C), 127.3, 42.9; IR (cm⁻¹): 3434, 3321, 3189, 1713, 1635, 1518, 1222, 772; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₄H₁₃N₆O₂)⁺ 297.1094; found 297.1095

(2-Amino-4-oxo-3,4-dihydropteridine-7-carbonyl)serine (5): Compound **5** was synthesized by the general method above, using 48 mg serine and 4 equiv DBU, resulting in 58 mg (88%) **5**. MP > 300°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm)= 13.02 (br, 1H), 11.65 (s, 1H), 8.89 (s, 1H), 8.68 (d, $J = 7.9$ Hz, 1H), 7.05 (br, 2H), 5.27 (br, s, 1H), 4.50 (dt, $J = 7.9, 3.6$ Hz, 1H), 3.93-3.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 171.9, 162.7, 160.8, 156.4, 155.0, 147.2, 136.7, 132.6, 61.5, 55.2; HRMS-ESI (m/z) [M-H]⁻ calc. for (C₁₀H₉N₆O₅)⁻ 293.0640; found 293.0638. This is consistent with that reported in the literature.³

2-Amino-4-oxo-N-propyl-3,4-dihydropteridine-7-carboxamide (6): Compound **6** was synthesized by the general method, using 37 μL of 1-propylamine and 2 equiv DBU, resulting in 49 mg (87%) of **6**. MP > 300°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm)= 11.68 (s, 1H), 8.86 (s, 1H), 8.82 (t, $J = 6$ Hz, 1H), 7.05 (br, 2H), 3.28 (q, $J = 7.2$ Hz, 2H), 1.57 (sext., $J = 7.2$ Hz, 2H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 163.2, 160.9, 156.3, 154.8, 148.4, 137.1, 132.0, 41.1, 22.8, 11.8; IR (cm⁻¹): 3260, 3130, 2964, 1705, 1644, 1518, 1397; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₀H₁₃N₆O₂)⁺ 249.1094; found 249.1095

2-Amino-N-(2-hydroxypropyl)-4-oxo-3,4-dihydropteridine-7-carboxamide (7):

Compound **7** was synthesized by the general method, using 35 μL of 1-amino-2-propanol and 2 equiv DBU, resulting in 51 mg (85%) of **7**. MP > 300°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm)= 11.59 (s, 1H), 8.87 (s, 1H), 8.61 (t, $J = 5.6$ Hz, 1H), 7.02 (br, 2H), 4.88 (d, $J = 4.8$ Hz, 1H), 3.82 (quint., $J = 6.4$ Hz, 1H), 3.36 (m, 1H), 3.21 (m, 1H), 1.08 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm)= 163.0, 160.9, 156.4, 154.9, 148.0, 136.9, 132.2, 65.3, 46.9, 21.6; IR (cm⁻¹): 3400-3100 (broad/overlapping), 2933, 1728, 1679, 1631, 1518, 1230; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₀H₁₃N₆O₃)⁺ 265.1044; found 265.1043

2-Amino-N-(4-aminophenethyl)-4-oxo-3,4-dihydropteridine-7-carboxamide (8):

Compound **8** was synthesized by the general method above, using 59 μ L 4-(2-aminoethyl)aniline and 2 equiv DBU, which provided 56 mg (76%) of **8**. mp > 300°C. 1 H NMR (400 MHz, DMSO-*d*₆) δ (ppm)= 11.59 (s, 1H), 8.85 (s, 1H), 8.74 (t, *J* = 5.6 Hz, 1H), 7.03 (br, 2H), 6.89 (d, *J* = 8 Hz, 2H), 6.51 (d, *J* = 8 Hz, 2H), 5.46 (br, 2H), 3.47 (q, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H); 13 C NMR (100 MHz, DMSO-*d*₆) δ (ppm)= 162.9, 160.8, 154.9, 148.2, 146.9, 137.0, 132.1, 129.4 (2C), 126.7, 121.2, 114.7 (2C), 41.3, 34.7; IR (cm⁻¹): 3413, 3340, 3195, 1731, 1655, 1530, 1426; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₅H₁₆N₇O₂)⁺ 326.1360; found 326.1358

2-Amino-N-(2-hydroxyethyl)-N-methyl-4-oxo-3,4-dihydropteridine-7-carboxamide

(9): Compound **9** was synthesized by the general method above, using 37 μ L *N*-methylaminoethanol and 2 equiv DBU. This resulted in 43 mg (71%) of **9** which exists as a 2:1 mixture of the *s-cis* and *s-trans* rotamers. MP > 300°C. 1 H NMR (400 MHz, DMSO-*d*₆) δ (ppm) = {two rotamers}⁴ 8.41 (s, 1H) {8.45 minor rotamer}, 7.07 (br, 2H) {overlapping minor rotamer}, 4.71 (t, *J* = 5.2 Hz, 1H) {4.84 minor rotamer}, 3.51 (q, *J* = 5.2 Hz, 2H) {3.65 minor rotamer}, 3.41 (t, *J* = 5.6 Hz, 2H) {3.55 minor rotamer}, 3.05 (s, 3H) {3.01 minor rotamer}; 13 C NMR (100 MHz, DMSO-*d*₆) δ (ppm)= {two rotamers} 167.0 {1.66.2 minor rotamer}, 161.2, 156.2, 155.1, 154.1 {153.9 minor rotamer}, 138.3 {137.6 minor rotamer}, 129.5 {129.8 minor rotamer}, 58.8 {58.7 minor rotamer}, 52.5 {50.2 minor rotamer}, 33.6 {37.9 minor rotamer}; IR (cm⁻¹): 3395, 3259, 3126, 2734, 1697, 1613, 1520, 1405, 1234; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₀H₁₃N₆O₃)⁺ 265.1044; found 265.1044

2-Amino-4-oxo-N-(2-(pyridin-2-yl)ethyl)-3,4-dihydropteridine-7-carboxamide (10):

Compound **10** was synthesized by the general method, using 54 μ L 2-(2-aminoethyl)pyridine and 2 equiv DBU, which provided 46 mg (66%) of **10**. mp > 300°C. 1 H NMR (400 MHz, DMSO- *d*₆) δ (ppm)= 11.63 (s, 1H), 8.95 (t, *J* = 6 Hz, 1H), 8.85 (s, 1H), 8.54 (d, *J* = 4 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 6 Hz, 1H), 7.02 (br, 2H), 3.71 (q, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.8 Hz, 2H); 13 C NMR (100 MHz, DMSO-*d*₆) δ (ppm)= 165.5, 163.2, 160.9, 159.1, 154.8, 148.8, 148.1, 137.9, 137.0, 132.1, 124.0, 122.3, 39.1, 37.0; IR (cm⁻¹): 3126, 2973, 1672, 1609, 1436, 1134, 767; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₄H₁₄N₇O₂)⁺ 312.1203; found 312.1203

2-Amino-N-isopropyl-4-oxo-3,4-dihydropteridine-7-carboxamide (11): Compound **11** was synthesized by the general method, using 40 μ L of 2-propylamine and 2 equiv DBU, resulting in 37 mg (66%) of **11**. MP > 300°C. 1 H NMR (400 MHz, DMSO-*d*₆) δ (ppm)= 11.59 (s, 1H), 8.85 (s, 1H), 8.48 (d, *J* = 8 Hz, 1H), 6.98 (br, 2H), 4.14 (oct, *J* = 6.8 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 6H); 13 C NMR (100 MHz, DMSO-*d*₆) δ (ppm)= 165.5, 162.3, 160.9, 154.8, 148.5, 137.1, 131.9, 41.4, 22.5 (2C); IR (cm⁻¹): 3141, 2974, 1695, 1633, 1515, 1386; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₀H₁₃N₆O₂)⁺ 249.1094; found 249.1093

2-Amino-4-oxo-N-(1-phenylethyl)-3,4-dihydropteridine-7-carboxamide (12):

Compound **12** was synthesized by the general method, using 59 μ L of α -methylbenzylamine and 2 equiv DBU, resulting in 42 mg (60%) of **12**. MP > 300°C. 1 H NMR (400 MHz, DMSO-*d*₆) δ (ppm)= 11.65 (s, 1H), 9.07 (d, *J* = 8.4 Hz, 1H), 8.83 (s, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.03 (br, 2H), 5.19 (quint, *J* = 7.6 Hz, 1H), 1.54 (d, *J* = 7.2 Hz, 3H); 13 C NMR (100 MHz, DMSO-*d*₆) δ (ppm)= 162.6, 161.0, 156.5, 154.9, 148.4, 144.5, 137.2, 132.1, 128.8 (2C), 127.3, 126.7 (2C), 48.9,

22.3; IR (cm⁻¹): 3405, 3141, 1643, 1515, 1397, 773, 693; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₅H₁₅N₆O₂)⁺ 311.1251; found 311.1252

(2-Amino-4-oxo-3,4-dihydropteridine-7-carbonyl)alanine (13): Compound **13** was synthesized by the general method above, using 41 mg alanine and 4 equiv DBU, resulting in 31 mg (49%) **13**. MP > 300°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ(ppm)= 12.90 (br, 1H), 11.67 (s, 1H), 8.86 (s, 1H), 8.83 (d, *J* = 8 Hz, 1H), 7.04 (br, 2H), 4.48 (quint, *J* = 7.2 Hz, 1H), 1.45 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ(ppm)= 173.9, 165.6, 162.8, 160.8, 154.9, 147.6, 136.9, 132.4, 48.3, 17.7; HRMS-ESI (m/z) [M-H]⁻ calc. for (C₁₀H₉N₆O₄)⁻ 277.0691; found 277.0689. This is consistent with that reported in the literature.³

Methyl 5-((2-amino-4-oxo-3,4-dihydropteridine-7-carboxamido)methyl)furan-2-carboxylate (14): Compound **14** was synthesized by the general method above, using 69 mg methyl 5-(aminomethyl)-furan-2-carboxylate⁵ and 2 equiv DBU. This resulted in a mixture of the product and 7-carboxy-pterin, which was sonicated in a dilute aqueous solution of NaHCO₃ to dissolve the acid and the product was isolated by filtration, resulting in 37 mg (47%) **14** after drying. MP > 300°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ(ppm)= 11.62 (s, 1H), 9.45 (t, *J* = 6 Hz, 1H), 8.88 (s, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.02 (br, 2H), 6.5 (d, *J* = 3.2 Hz, 1H), 4.56 (d, *J* = 6 Hz, 2H), 3.79 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ(ppm)= 163.5, 160.8, 158.7, 157.4, 156.2, 154.8, 147.9, 143.2, 137.2, 132.3, 119.8, 110.0, 52.1, 36.7; IR (cm⁻¹): 3126, 1681, 1518, 1338, 1204, 1016, 761 HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₄H₁₃N₆O₅)⁺ 345.0942; found 345.0942

2-Amino-7-(morpholine-4-carbonyl)pteridin-4(3*H*)-one (15): Compound **15** was synthesized by the general method above, using 40 μL morpholine and 2 equiv DBU. Initially this resulted in a 1:1 mixture of the product and 7-carboxy-pterin, which was sonicated in a dilute aqueous solution of NaHCO₃ to dissolve the carboxylate, and the product was collected by filtration, resulting in 28 mg (44%) **15** after drying. MP > 300°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ(ppm)= 11.64 (s, 1H), 8.49 (s, 1H), 7.07 (br, 2H), 3.68 (m, 4H), 3.58 (m, 2H), 3.49 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ(ppm)= 164.9, 161.2, 156.3, 155.2, 152.8, 137.9, 130.1, 66.7, 66.4, 47.4, 42.5; IR (cm⁻¹): 3438, 3336, 3084, 2986, 2934, 1720, 1632, 1595, 1204; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₁H₁₃N₆O₃)⁺ 277.1044; found 277.1043

2-Amino-*N*-benzyl-*N*-methyl-4-oxo-3,4-dihydropteridine-7-carboxamide (16): Synthesis of **16** required a modified method, where 0.3 mL (10 equiv) of *N*-methyl-benzylamine was added to the solution of 50 mg 7CMP (**1**) in 1 mL MeOH and 2 equiv of DBU. The reaction vessel was sealed and heated to 130 °C for 3 h. Work-up proceeded as described in the general method, providing 44 mg (63%) of **16**, existing as an equal mixture of the *s-cis* and *s-trans* rotamers. MP > 300°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ(ppm)= {two rotamers}⁴ 11.57 {overlapping rotamer} (s, 1H), 8.53 {8.49} (s, 1H), 7.42-7.27 {overlapping rotamer} (m, 5H), 7.03 {overlapping rotamer} (br, 2H), 4.72 {4.58} (s, 2H), 2.91 {2.90} (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ(ppm)= {two rotamers} 166.7 {166.5}, 161.1 {overlapping}, 155.2 {overlapping}, 153.6 {153.5}, 137.7 {137.6}, 137.2 {137.1}, 130.1 {130.0}, 129.1(2C) {129.0}, 128.9 {128.8}, 128.1(2C) {127.9}, 127.8 {overlapping}, 53.7 {50.4}, 36.6 {32.9}; IR (cm⁻¹): 3150, 2744, 1696, 1658, 1512, 1407, 1334, 777, 637; HRMS-ESI (m/z) [M+H]⁺ calc. for (C₁₅H₁₅N₆O₂)⁺ 311.1251; found 311.1251

Pseudo-first order kinetics NMR data collection:

Kinetics for the DBU-amidation was followed by ^1H NMR for a representative set of amines. Pseudo-first order conditions were used, whereby the amine was in large excess and its change in concentration was negligible.⁵ Therefore, the rate could be viewed as:

Rate = $k_{\text{obs}}[7\text{-CMP}]$, where $k_{\text{obs}} = k[\text{Amine}]_0$

Therefore the integrated rate law becomes $\ln[7\text{-CMP}]_t = \ln[7\text{-CMP}]_0 + k_{\text{obs}}t$, and plotting $\ln[7\text{-CMP}]$ vs t gives a slope of k_{obs} . The k value for the 2nd order rate is thus determined by dividing k_{obs} by the initial amine concentration.⁵

A typical ^1H NMR experiment begins by suspending 7-CMP in anhydrous methanol- d_4 , followed by the addition of DBU and a large excess of the amine to provide a homogeneous solution. This solution is then transferred to an NMR tube, and a spectrum is collected every 60 min for 4–8 h. For faster reactions, data was collected every 20 min for the first hour. As glycine gave a particularly rapid reaction, data was collected every 10 min for the first 2 h. The disappearance of the aromatic C₆-H proton of 7-CMP (appears at 8.8 ppm in methanol- d_4) was coupled with the growth of the aromatic C₆-H proton for the amide product (typically appears between 8.91–8.95 ppm in methanol- d_4). Ratios of integrals were converted to % (7-CMP) and % (product), which was in turn converted to $[7\text{-CMP}]_t$.

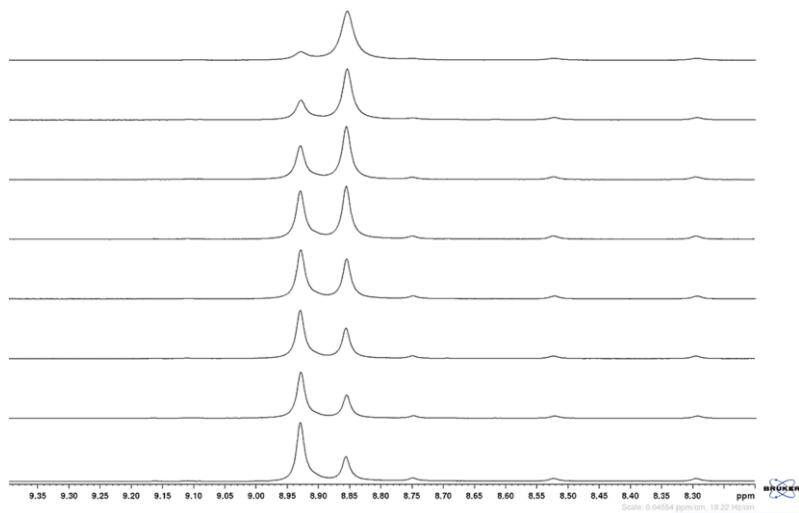
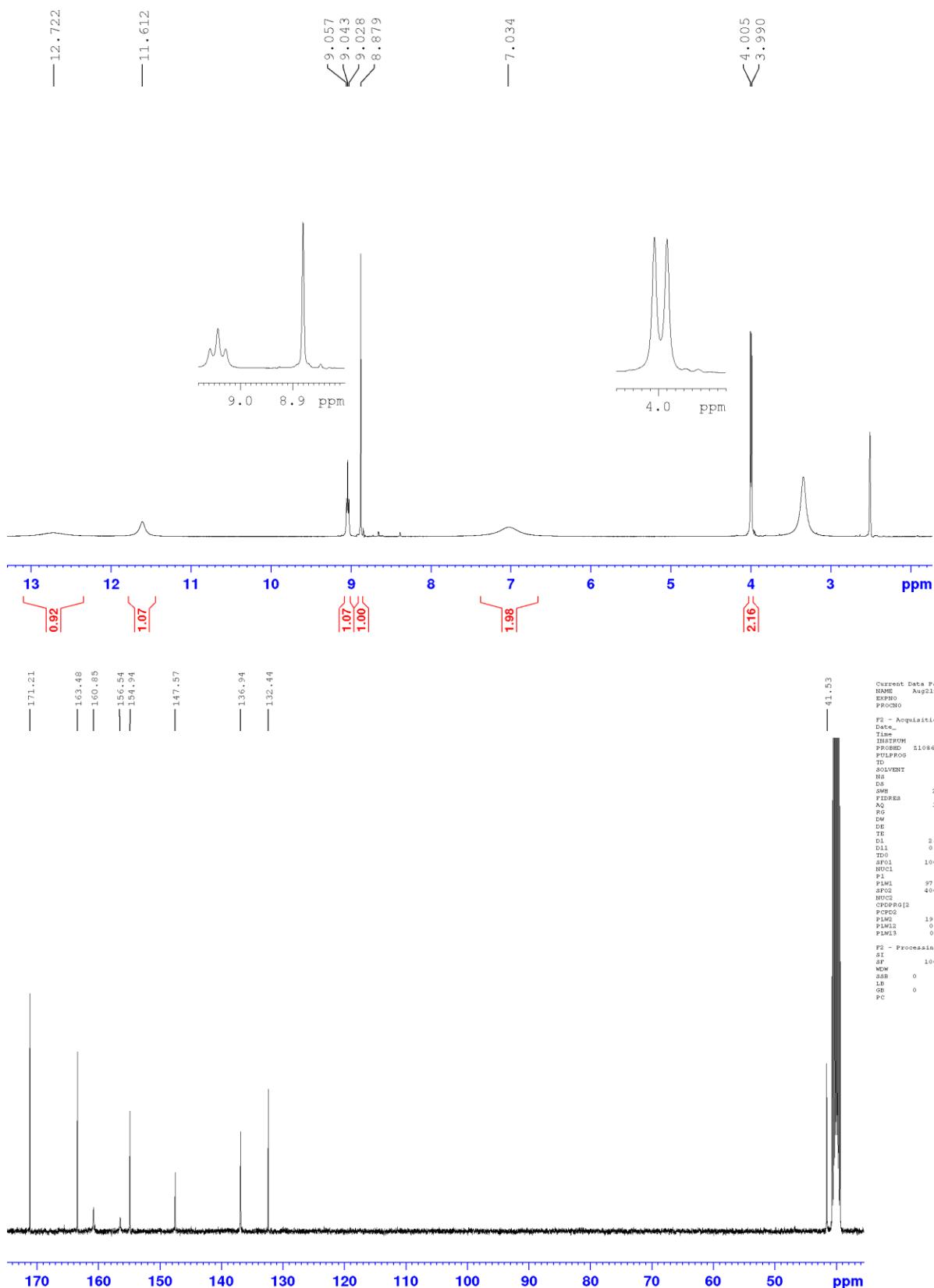
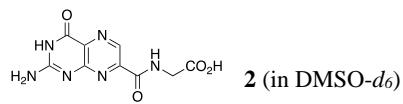
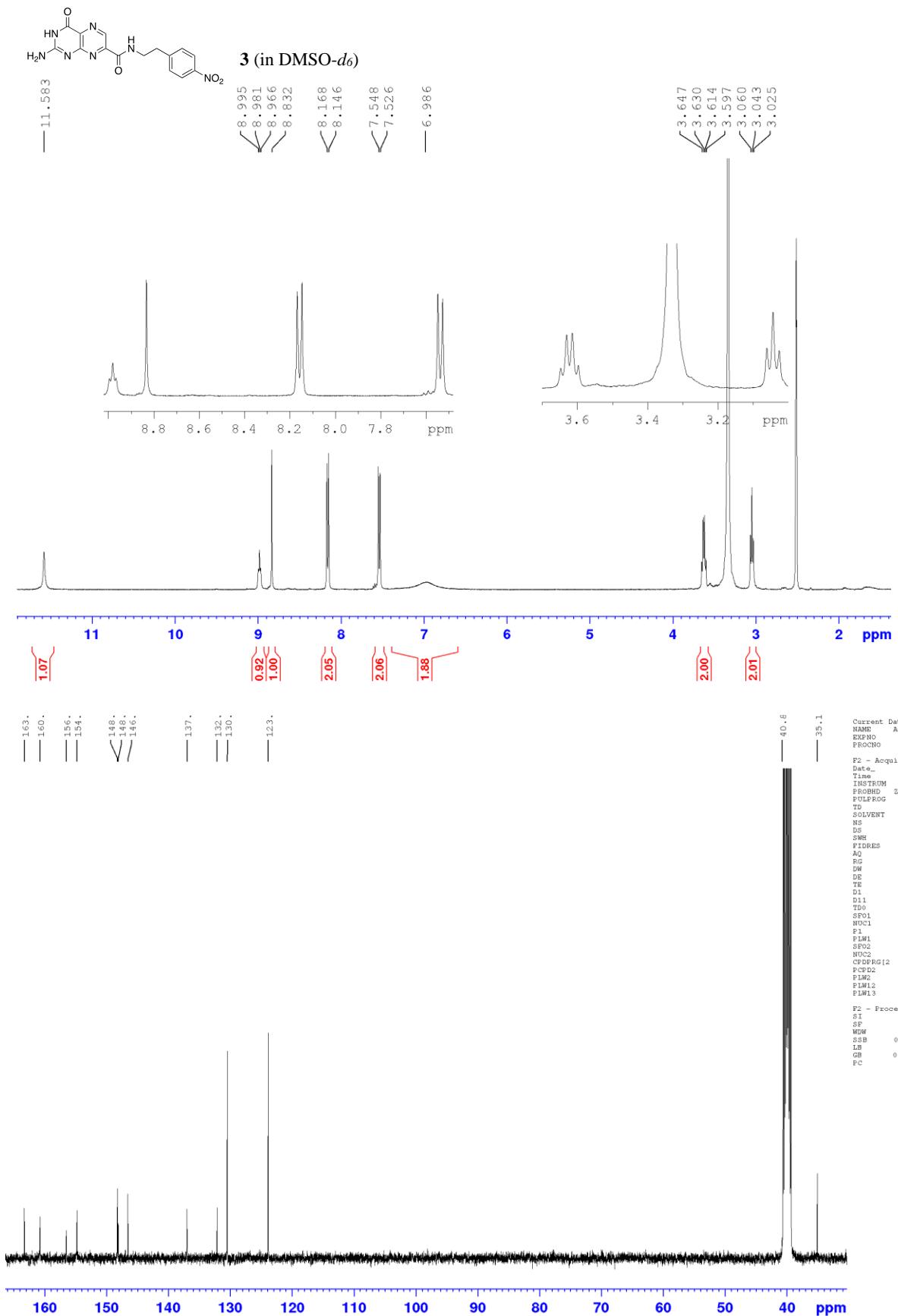
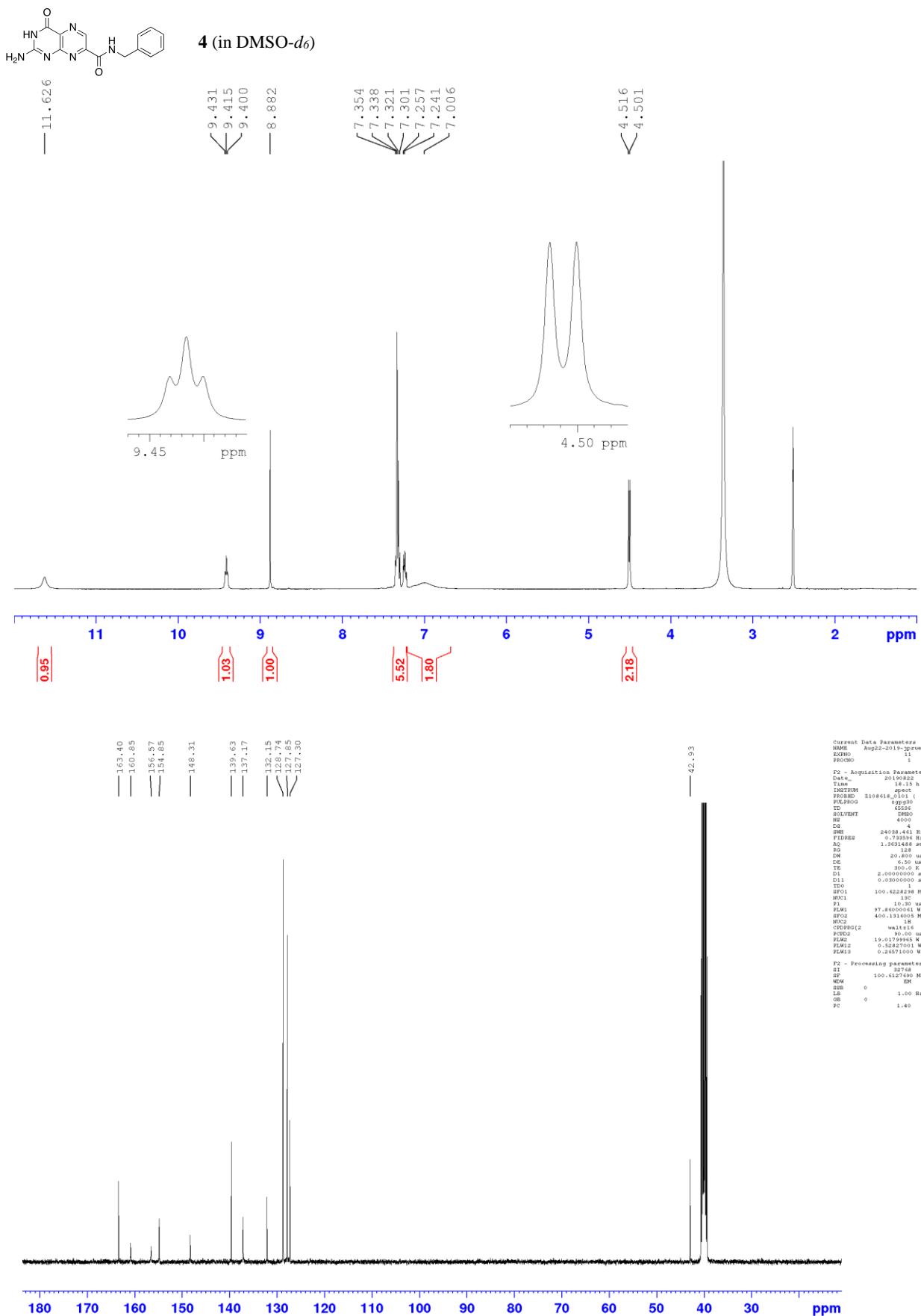


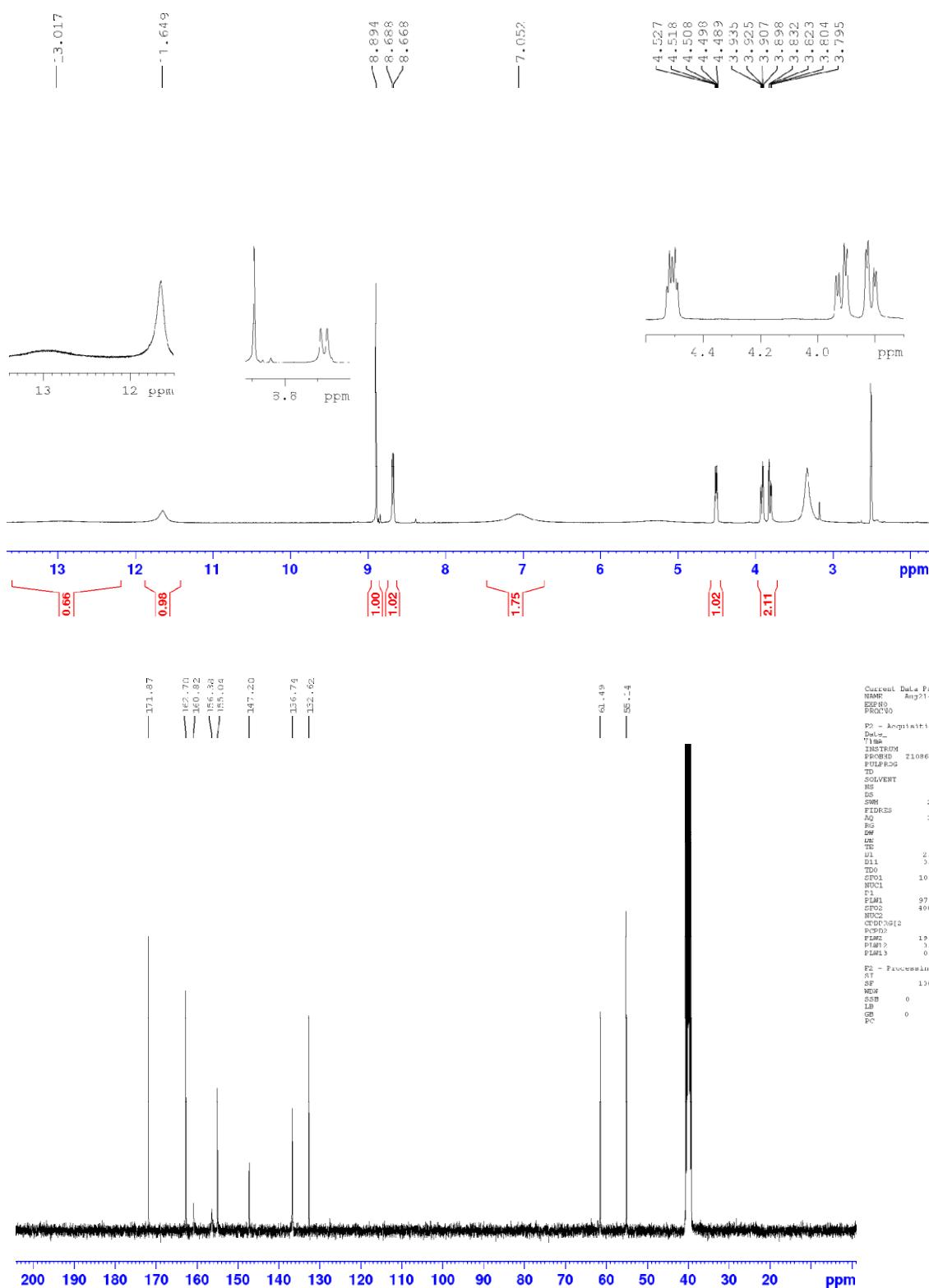
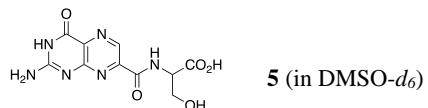
Figure S1: Representative NMR data, showing the shift in the pterin C₆-H signal as 7-CMP reacts with glycine from $t = 5$ min (top) to $t = 75$ min (bottom) in methanol- d_4 .

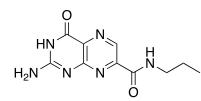
Copies of ^1H and ^{13}C spectra:



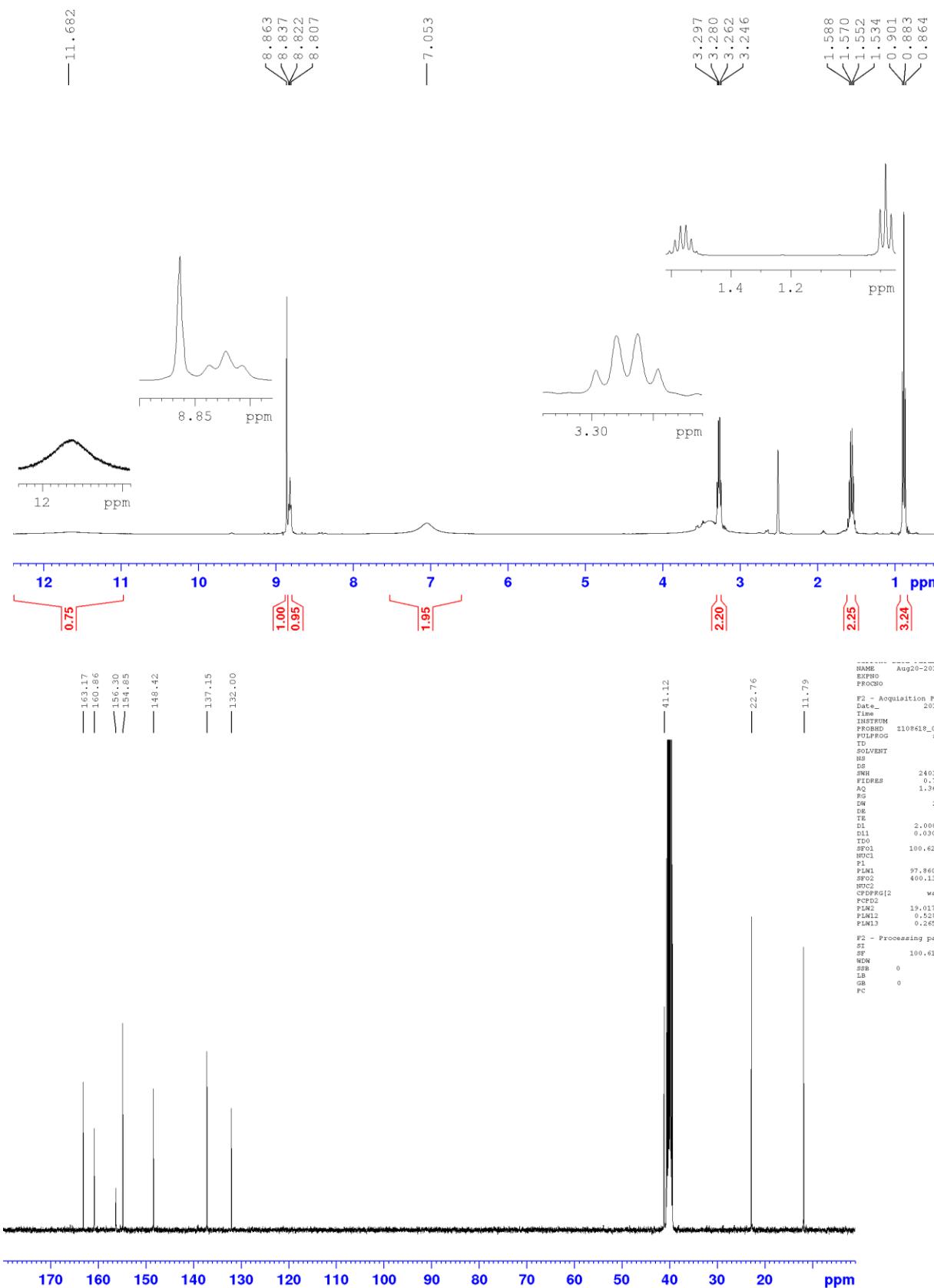


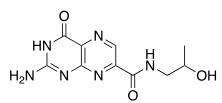




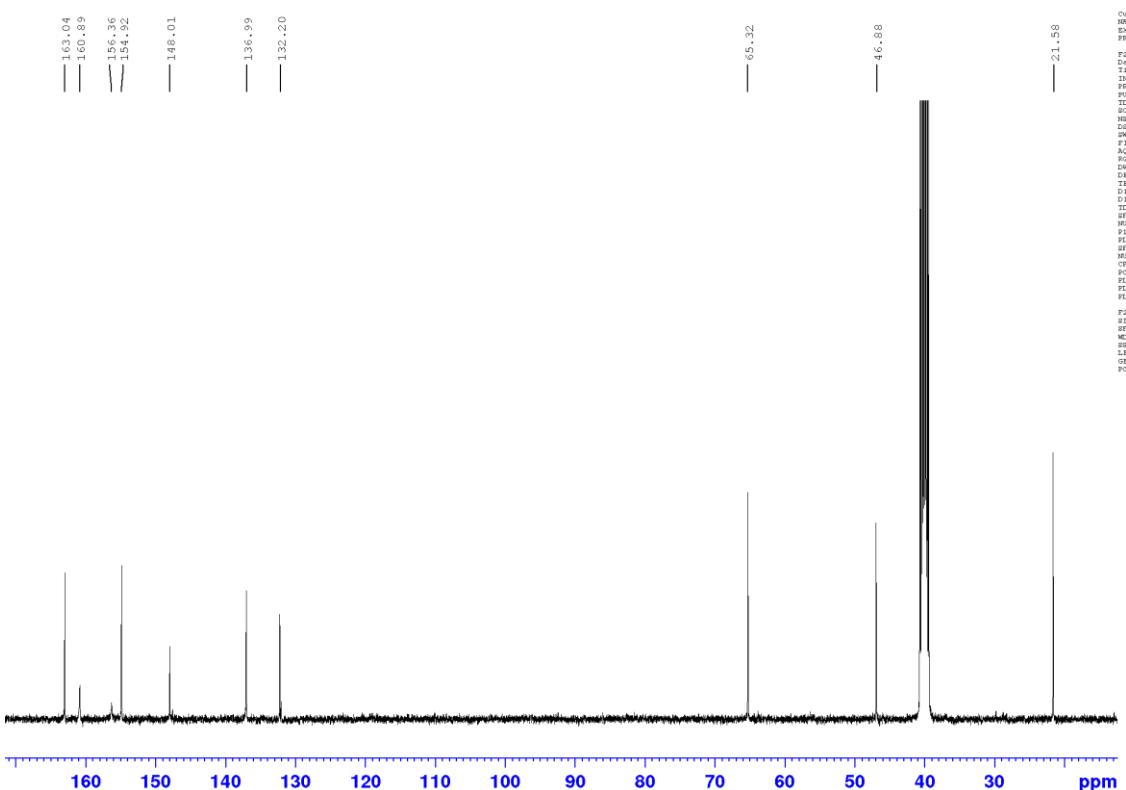
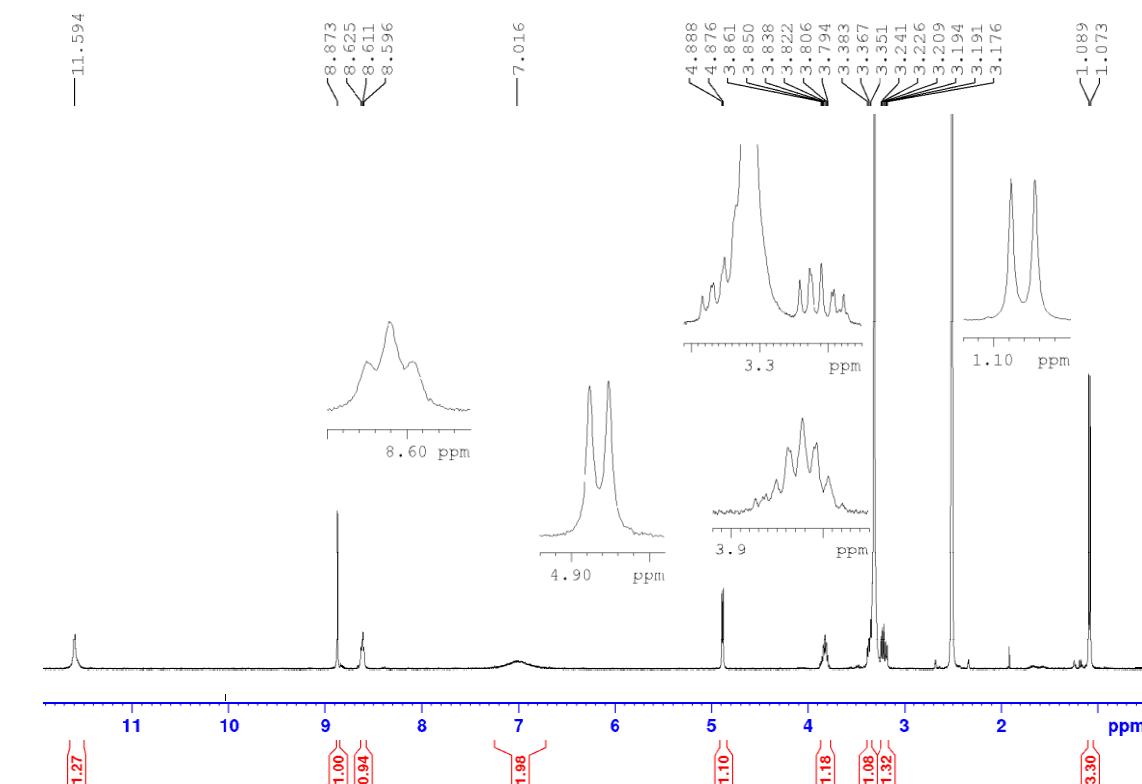


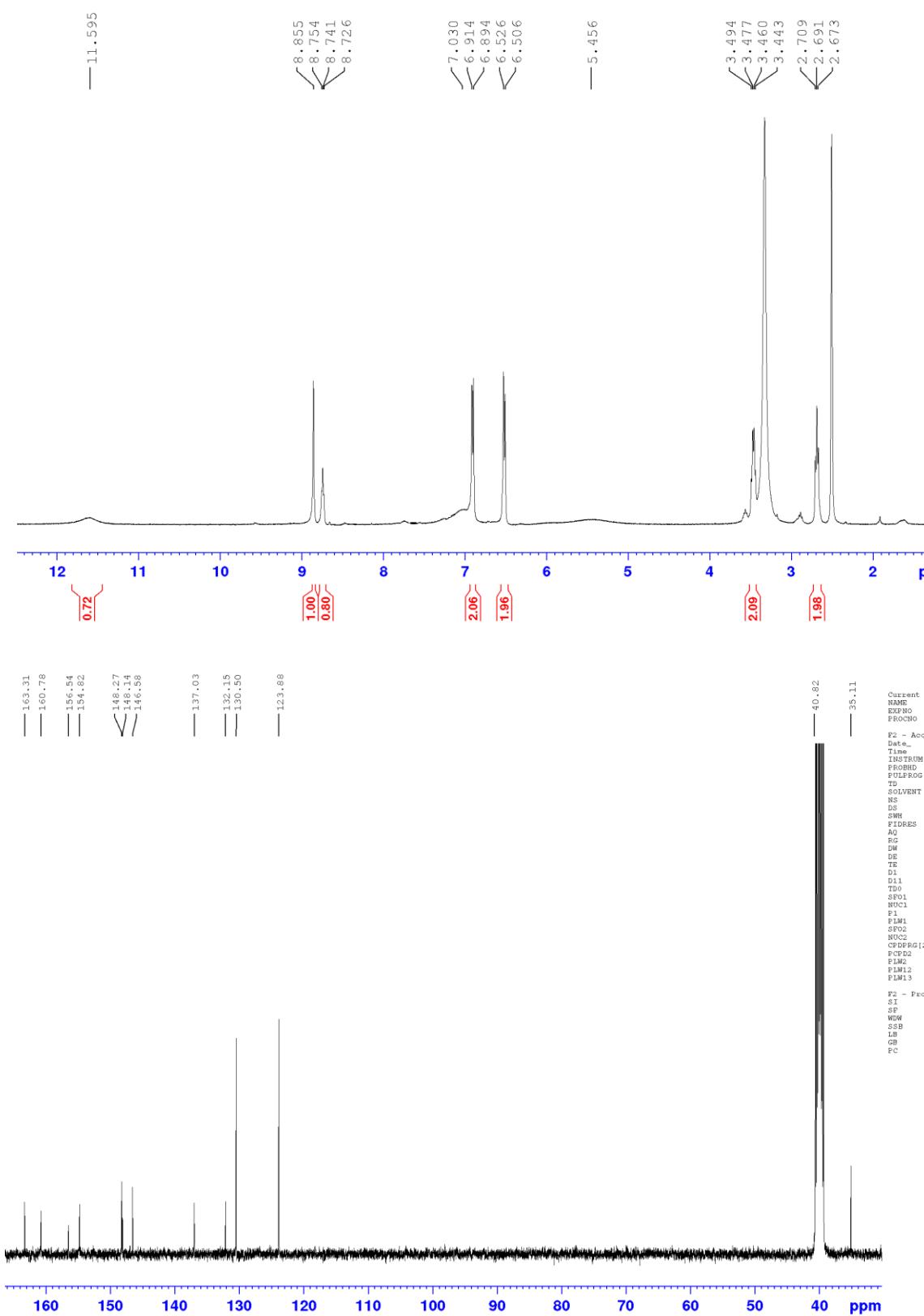
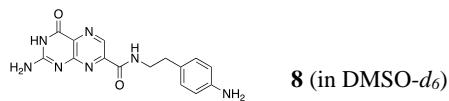
6 (in $\text{DMSO}-d_6$)

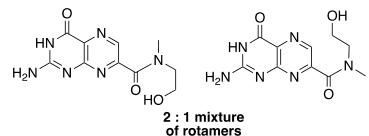




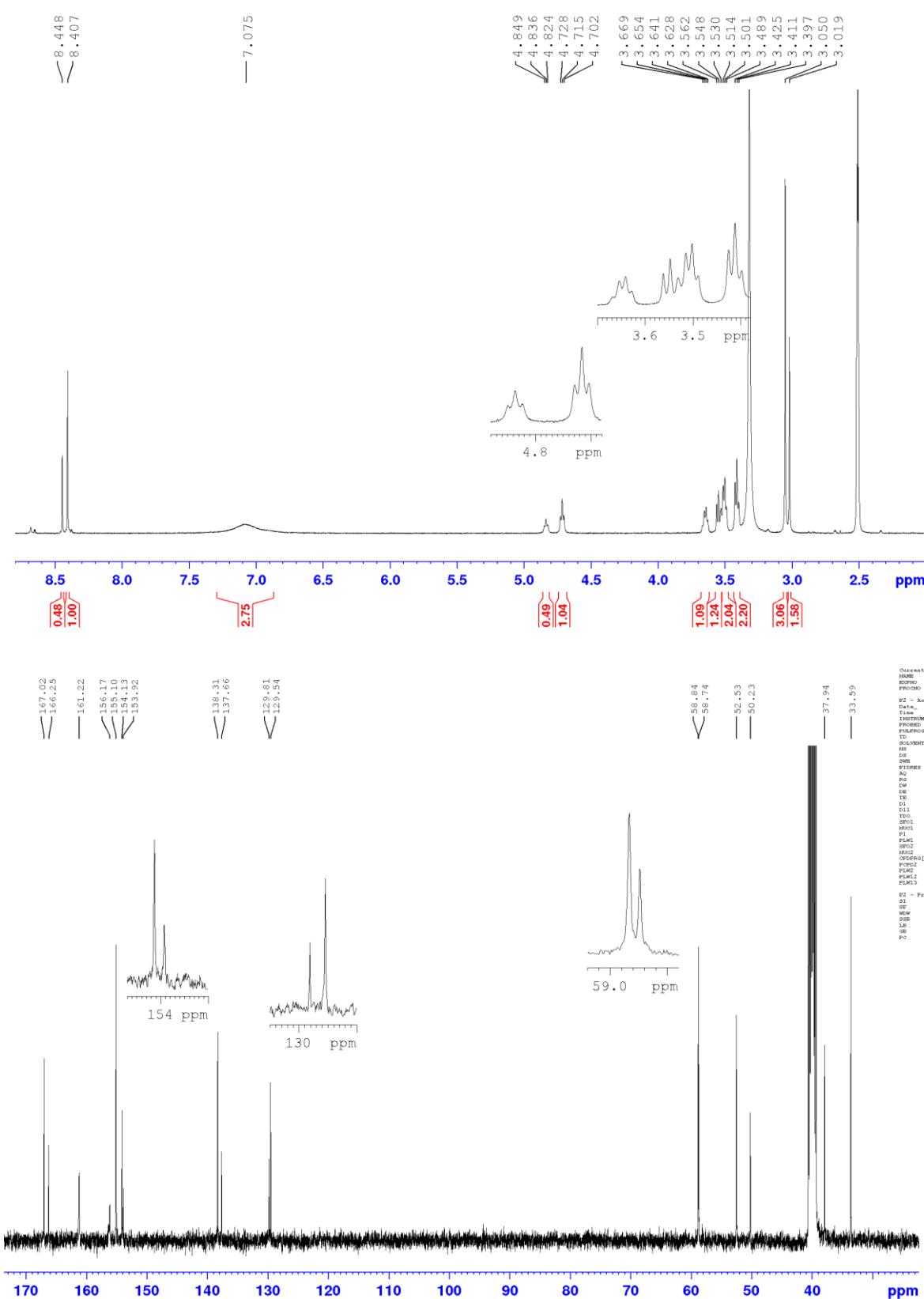
7 (in DMSO-*d*₆)

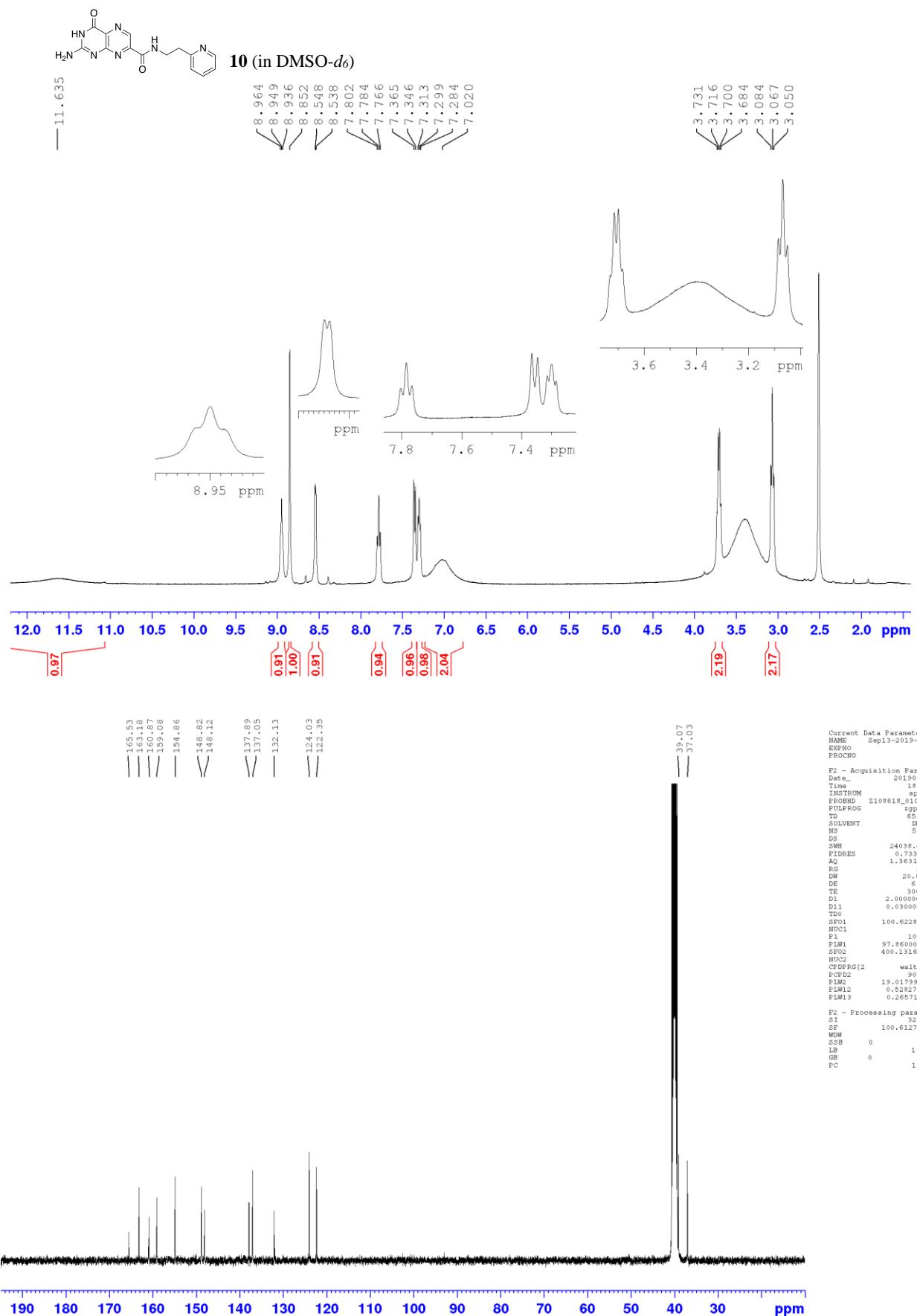


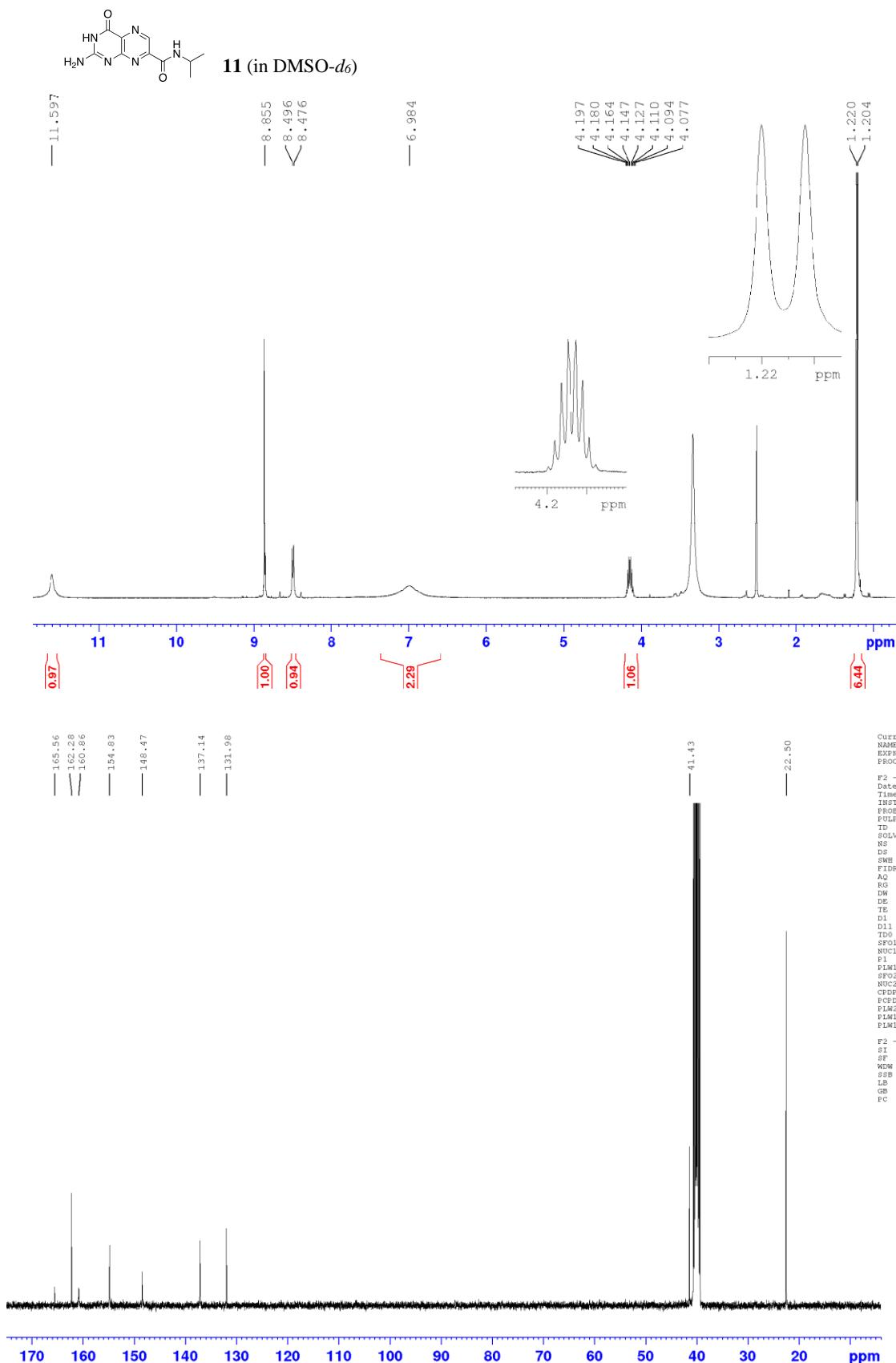


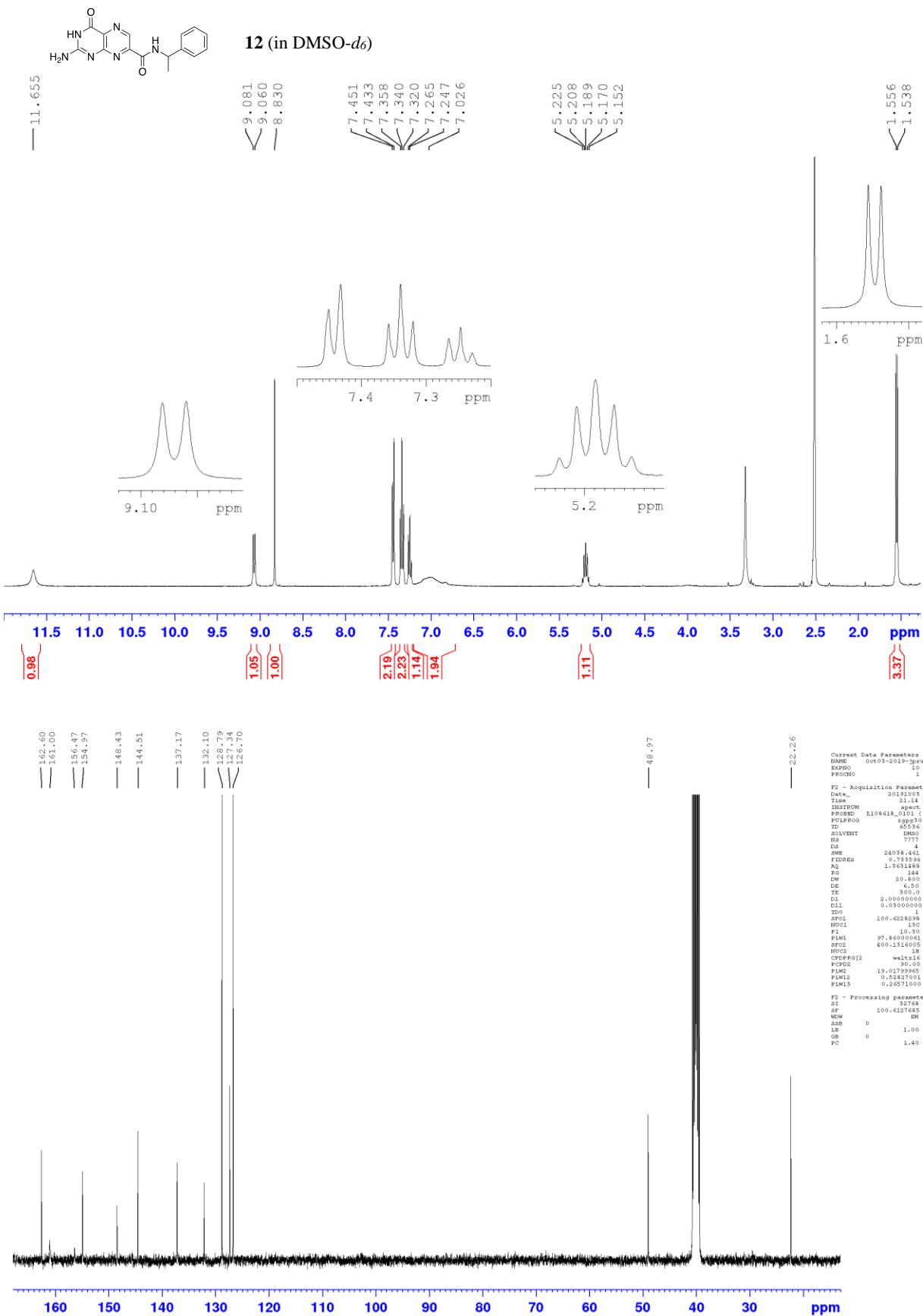


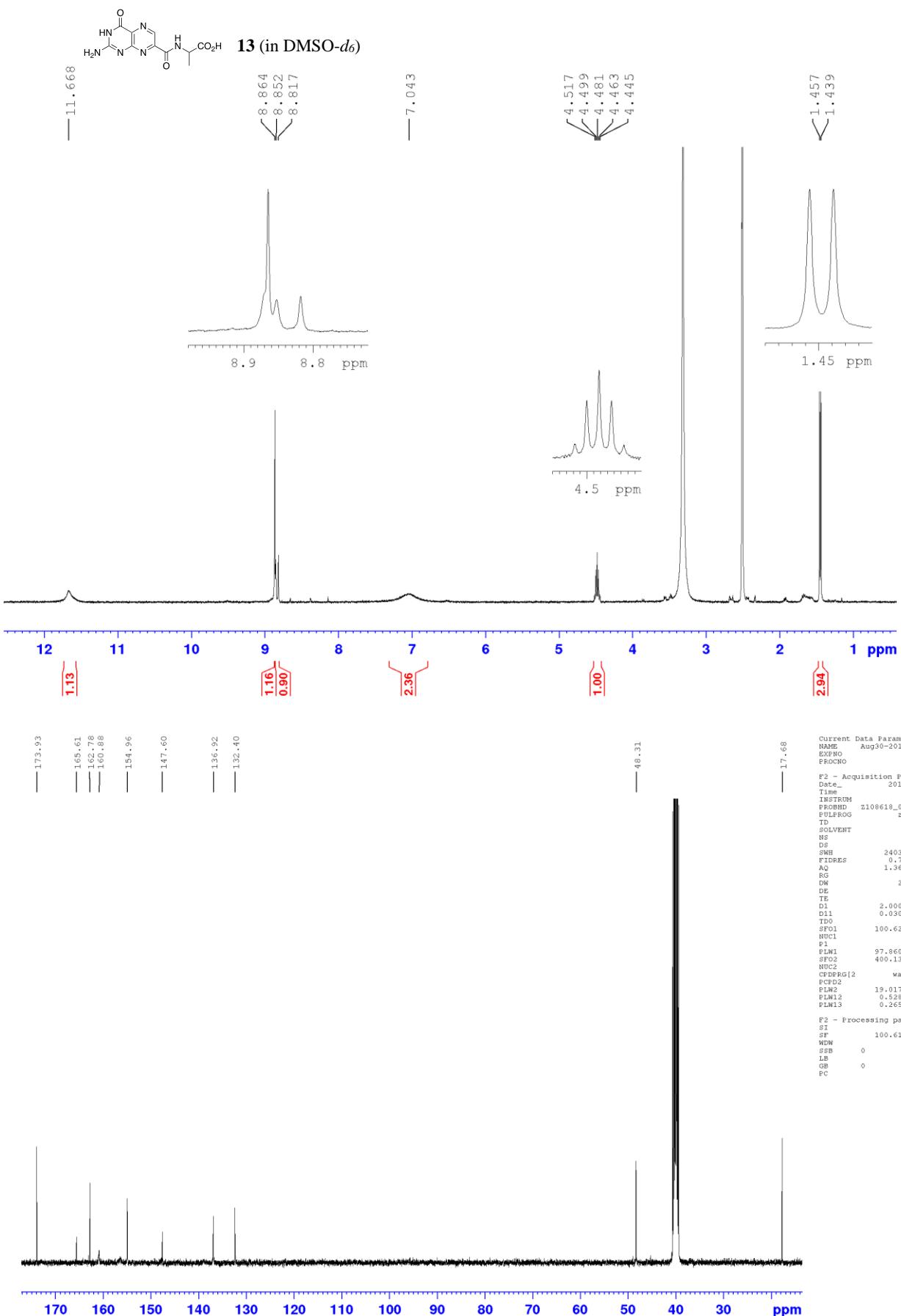
9 (in DMSO-*d*₆)

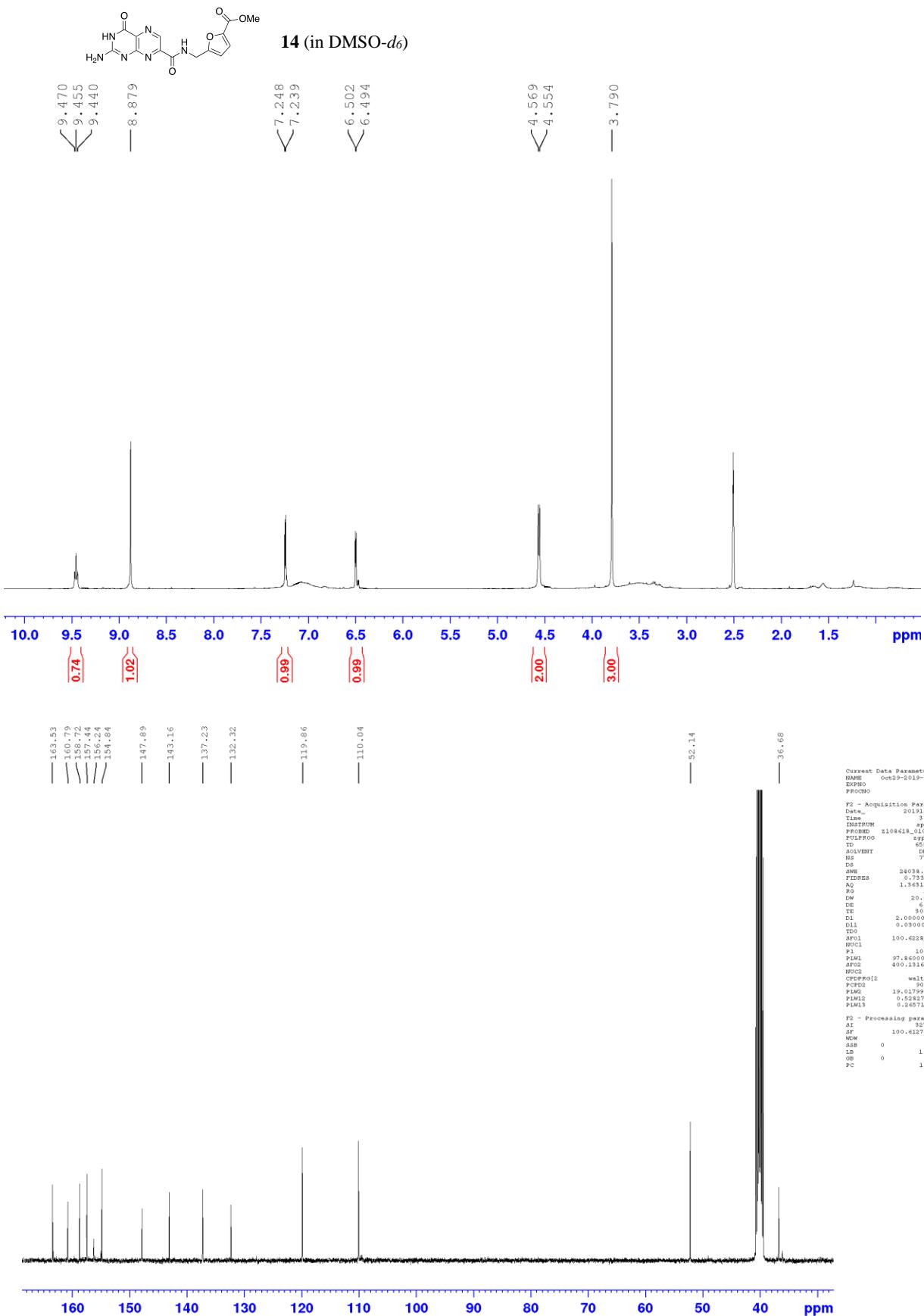


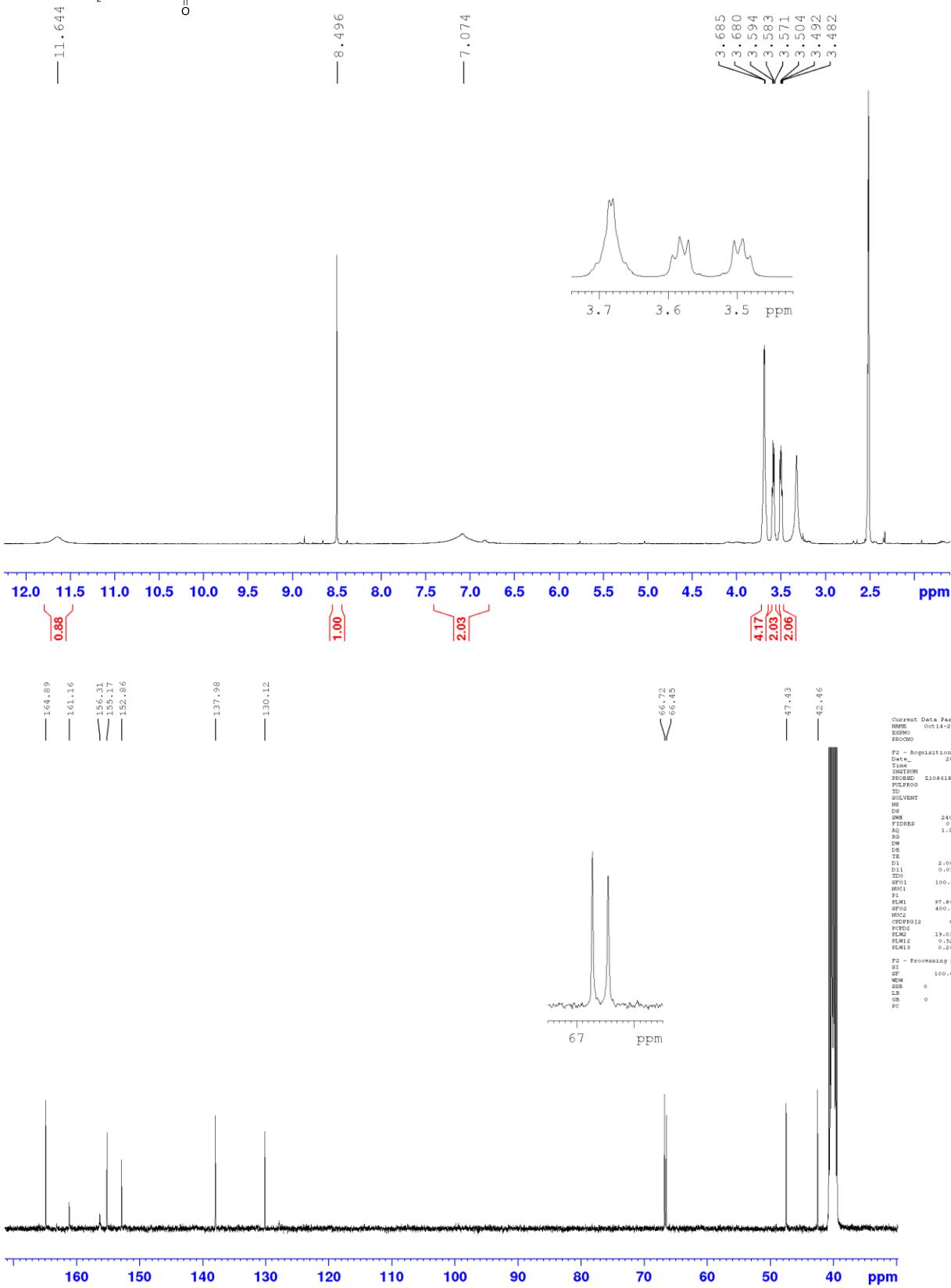
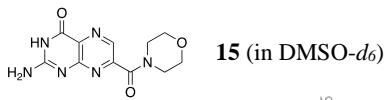


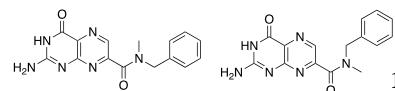






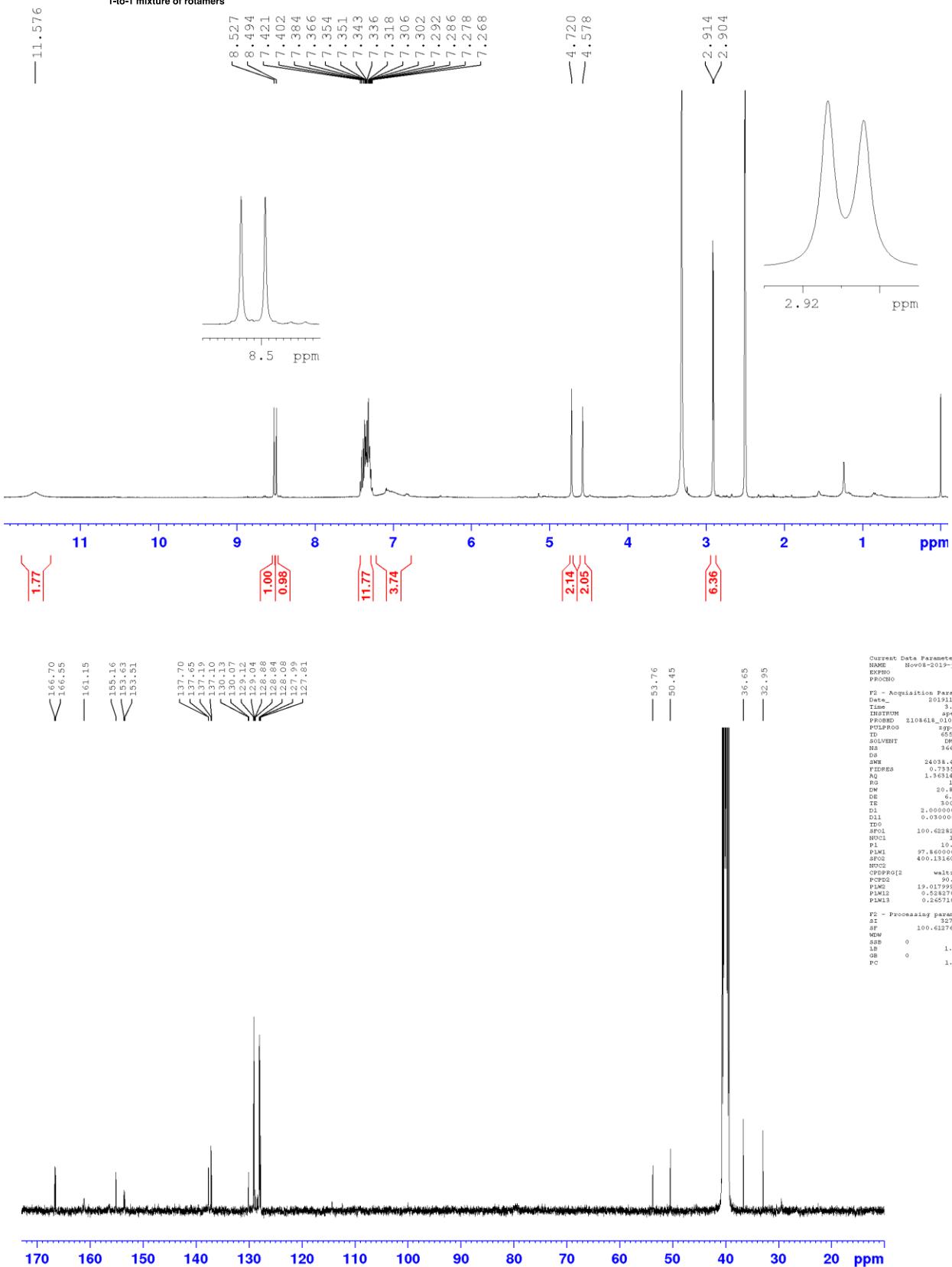






16 (in DMSO-*d*₆)

1-to-1 mixture of rotamers



References:

- 1) Obermayer, D.; Znidar, D.; Glotz, G.; Stadler, A.; Dallinger, D.; Kappe, C. *J. Org. Chem.* 81 **2016** 11788-11801
- 2) J.M. Pruet, J.D. Robertus, E.V. Anslyn, *Tetrahedron Lett.* 51 **2010** 2539
- 3) Saito R.; Suzuki S.; Sasaki K. *Bioorg Med Chem Lett* **2016**, 26: 4870.
- 4) This way of indicating amide rotamers in NMR was used in the following report: X. Li; S. Danishefsky, *J. Am. Chem. Soc.* 130 **2008**, 5446
- 5) T.K. Chakraborty, S. Tapadar, S.K. Kumar, *Tetrahedron Lett.* 43 **2002**, 1317
- 6) E.V. Anslyn, D. Dougherty, *Modern Physical Organic Chemistry*; University Science Books, **2006**, p 387