

Supporting Information

Regioselective Incorporation of Backbone Constraints Compatible with Traditional Solid-Phase Peptide Synthesis

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Material and Methods

Solvents were used without further purification. The Rink amide resin (100-200 mesh, 1% DVB, 0.68 mmol/g) was used. Synthesis was carried out on Domino Blocks (www.torviq.com) in disposable polypropylene reaction vessels.

The volume of wash solvent was 10 mL per 1 g of resin (except Mitsunobu alkylation; the volume was 20 mL per 1 g of resin). For washing, resin slurry was shaken with the fresh solvent for at least 1 minute before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

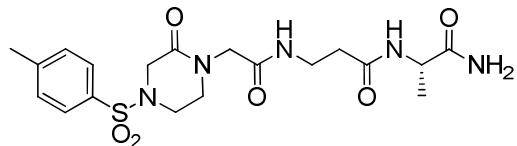
For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM, the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH. The LC/MS analyses were carried out using two instruments. The first one comprised a 3 x 50 mm C18 reverse phase column, 5 μ m particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 °C. The second instrument comprised a 2.1 x 50 mm C18 reverse phase column, 2.6 μ m particles, at 30°C and flow rate of 800 μ L/min. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 10% to 80% of B in 2.5 minutes; kept for 1.5 minute, flow rate of 0.8 mL/min. The column was re-equilibrated with 10% solution B for 1 minute. The APCI source operated at discharge current of 5 μ A, vaporizer temperature of 400 °C and capillary temperature of 200 °C.

Purification was carried out on C18 reverse phase column 19 x 100 mm, 5 μ m particles, gradient was formed from 10 mM aqueous ammonium acetate and acetonitrile, flow rate 15 mL/min.

NMR spectroscopy. All ^1H and ^{13}C NMR experiments were performed at magnetic field strengths of 14.09 T corresponding to ^1H resonance frequencies of 599.89 MHz, and at ambient temperature (~21 °C). ^1H spectra and ^{13}C spectra were referenced relative to the signal of DMSO (^1H δ = 2.49 ppm, ^{13}C δ = 39.50 ppm).

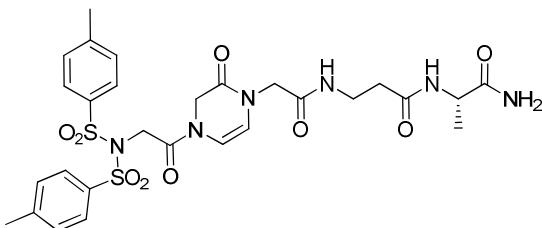
Analytical Data of Individual Compounds

(S)-N-(1-amino-1-oxopropan-2-yl)-3-(2-(2-oxo-4-tosylpiperazin-1-yl)acetamido)propanamide 7



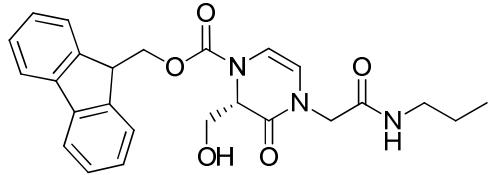
Yield 18.1 mg (53%) of amorphous solid. ^1H NMR (600 MHz, DMSO-d₆) δ = 7.97 (d, J = 7.6 Hz, 1 H), 7.93 (t, J = 5.7 Hz, 1 H), 7.73 - 7.68 (m, 2 H), 7.51 - 7.47 (m, 2 H), 7.28 (br. s., 1 H), 6.95 (br. s., 1 H), 4.22 - 4.12 (m, 1 H), 3.86 (d, J = 16.4 Hz, 1 H), 3.82 (d, J = 16.4 Hz, 1 H), 3.52 (s, 2 H), 3.37 - 3.33 (m, 2 H, overlapped with water), 3.27 - 3.17 (m, 4 H), 2.42 (s, 3 H), 2.33 - 2.18 (m, 2 H), 1.16 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (151 MHz, DMSO-d₆) δ 174.4, 170.0, 167.1, 163.5, 144.3, 131.4, 130.1, 127.8, 48.7, 48.6, 47.9, 46.9, 42.8, 35.3, 35.1, 21.1, 18.3. HRMS (ESI-TOF) m/z calcd for C₁₉H₂₈N₅O₆S [M + H]⁺ 454.1755, found 454.1732

(S)-N-(1-amino-1-oxopropan-2-yl)-3-(2-(4-(2-(4-methyl-N-tosylphenylsulfonamido)acetyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamido)propanamide 9



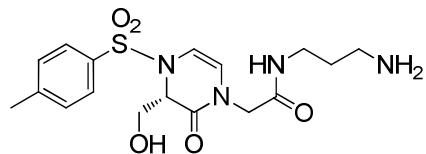
Yield 23.8 mg (48%) of amorphous solid, mixture of rotamers. ^1H NMR (600 MHz, DMSO-d₆) δ = 8.09 (t, J = 5.6 Hz, 1 H), 8.00 (d, J = 7.6 Hz, 1 H), 7.88 - 7.79 (m, 4 H), 7.48 - 7.38 (m, 4 H), 7.31 (br. s., 1 H), 6.96 (br. s., 1 H), 6.56 (d, J = 6.2 Hz, 1 H), 5.94 (d, J = 6.2 Hz, 1 H), 4.83 - 4.80 (m, 2 H), 4.24 - 4.16 (m, 1 H), 4.14 - 4.08 (m, 2 H), 3.41 - 3.34 (m, 2 H, overlapped with water), 3.32 - 3.22 (m, 2 H), 2.42 (s, 6 H), 2.36 - 2.21 (m, 2 H), 1.19 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (151 MHz, DMSO-d₆) δ 174.5, 170.0, 166.8, 163.9, 162.8, 145.1, 136.1, 129.5, 128.4, 115.8, 107.4, 48.8, 48.0, 47.7, 45.6, 35.3, 35.1, 21.2, 18.3. HRMS (ESI-TOF) m/z calcd for C₂₈H₃₅N₆O₉S₂ [M + H]⁺ 663.1901, found 663.1885

(S)-(9*H*-fluoren-9-yl)methyl 2-(hydroxymethyl)-3-oxo-4-(2-oxo-2-(propylamino)ethyl)-3,4-dihydropyrazine-1(2*H*)-carboxylate 11a



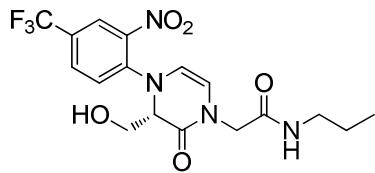
Yield 18.0 mg (80%) of amorphous solid, a mixture of rotamers. ^1H NMR (600 MHz, DMSO- d_6) δ 7.90 (t, 2 H), 7.83 (t, J = 5.3 Hz, 1 H), 7.67 (d, J = 7.0 Hz, 2 H), 7.47 - 7.39 (m, 2 H), 7.35 (t, J = 7.0 Hz, 2 H), 6.27 - 6.14 (m, 1 H), 5.78 - 5.72 (m, 1 H), 5.22 - 5.14 (m, 1 H), 4.61 - 4.52 (m, 2 H), 4.45 (d, J = 6.7 Hz, 1 H), 4.37 - 4.30 (m, 1 H), 4.15 - 3.95 (m, 2 H), 3.71 - 3.52 (m, 1 H), 3.07 - 2.93 (m, 2 H), 1.39 (dq, J = 7.3, 14.9 Hz, 3 H), 0.88 - 0.76 (m, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.7/166.6, 163.5/163.4, 152.4/152.2, 143.8/143.7, 143.5/143.5, 140.8/140.8, 140.7, 127.8/127.7, 127.2, 125.1, 124.9/124.8, 120.2, 120.1/120.1, 113.6/113.4, 108.1/107.4, 67.6/ 67.4, 61.6/ 60.8, 59.7/ 59.0, 48.4/ 48.3, 46.4, 40.3, 22.2/ 22.2, 11.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_5$ [M + H] $^+$ 450.2029, found 450.2021

(S)-N-(3-aminopropyl)-2-(3-(hydroxymethyl)-2-oxo-4-tosyl-3,4-dihydropyrazin-1(2H)-yl)acetamide 11b



Yield 7.9 mg (40%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.01 (t, J =5.7 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.66 (d, J =8.2 Hz, 2 H), 7.39 (d, J =7.9 Hz, 2 H), 6.05 - 6.08 (m, 1 H), 6.01 - 6.04 (m, 1 H), 4.28 - 4.34 (m, 1 H), 3.93 (d, J =16.1 Hz, 1 H), 3.77 (d, J =16.4 Hz, 1 H), 3.60 (dd, J =11.4, 6.7 Hz, 1 H), 3.47 - 3.51 (m, 1 H), 3.09 (q, J =6.6 Hz, 2 H), 2.69 - 2.79 (m, 2 H), 2.38 (s, 3 H), 1.59 - 1.68 (m, 2 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.0, 162.5, 144.1, 134.9, 129.9, 126.6, 119.6, 106.5, 61.0, 60.4, 47.8, 36.7, 35.7, 27.3, 21.1. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_5\text{S}$ [M + H] $^+$ 397.1546, found 397.1541

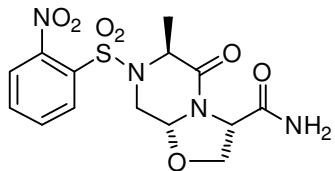
(S)-2-(3-(hydroxymethyl)-4-(2-nitro-4-(trifluoromethyl)phenyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)-N-propylacetamide 11c



Yield 9.2 mg (44%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.17 (d, J =1.5 Hz, 1 H), 7.89 - 7.94 (m, 1 H), 7.85 - 7.87 (m, 1 H), 7.83 (t, J =5.6 Hz, 1 H), 6.06 (d, J =5.3 Hz, 1 H), 5.49 (dd, J =5.3, 1.8 Hz, 1 H), 5.46 (m, 1 H), 4.67 (ddd, J =8.7, 3.6, 1.8 Hz, 1 H), 4.28 (d,

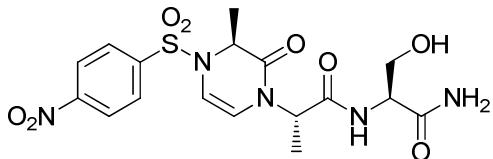
$J=16.1$ Hz, 1 H), 3.95 (d, $J=16.1$ Hz, 1 H), 3.84 (d, $J=8.2$ Hz, 1 H), 3.60 (d, $J=11.7$ Hz, 1 H), 2.97 - 3.10 (m, 2 H), 1.39 - 1.44 (m, 2 H), 0.84 (t, $J=7.5$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.6, 162.7, 141.1, 139.9, 129.54, 129.52, 123.5, 123.4 (q, $J=271$ Hz), 120.8 (q, $J=33$ Hz), 116.6, 110.6, 64.0, 58.8, 47.8, 40.5, 22.3, 11.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_4\text{O}_5$ [M + H]⁺ 417.1380, found 417.1367.

(3*S*,6*S*,8*aR*)-6-methyl-7-((2-nitrophenyl)sulfonyl)-5-oxohexahydro-2*H*-oxazolo[3,2-*a*]pyrazine-3-carboxamide 13



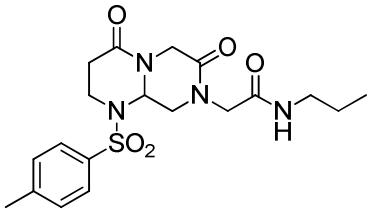
Yield 11.3 mg (27%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 8.22 (dd, $J=8.07$, 1.32 Hz, 1 H), 8.02 (dd, $J=8.07$, 1.32 Hz, 1 H), 7.93 (td, $J=7.70$, 1.32 Hz, 1 H), 7.87 (td, $J=7.78$, 1.47 Hz, 1 H), 7.59 (br. s., 1 H), 7.26 (br. s., 1 H), 4.76 (dd, $J=9.68$, 4.40 Hz, 1 H), 4.54 (q, $J=7.14$ Hz, 1 H), 4.48 (t, $J=7.78$ Hz, 1 H), 4.35 (t, $J=8.36$ Hz, 1 H), 4.21 (ddd, $J=13.79$, 4.40, 1.17 Hz, 1 H), 3.72 (dd, $J=8.66$, 7.19 Hz, 1 H), 3.25 (dd, $J=13.79$, 9.68 Hz, 1 H), 1.31 (d, $J=7.04$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 170.2, 165.6, 147.2, 135.2, 133.0, 131.9, 130.3, 124.6, 84.4, 68.8, 56.6, 53.3, 42.8, 16.6. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{NaO}_7\text{S}$ [M + Na]⁺ 407.0637, found 407.0642.

(*S*)-3-hydroxy-2-((*S*)-3-methyl-4-((*S*)-2-(4-nitrophenylsulfonamido)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2*H*)-yl)propanamide 15



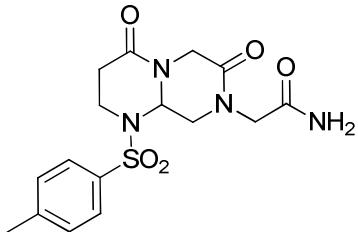
Yield 20.1 mg (52%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.36 (d, $J=7.0$ Hz, 2 H), 8.03 (d, $J=7.0$ Hz, 2 H), 7.78 (d, $J=7.6$ Hz, 1 H), 7.19 (br. s., 1 H), 7.10 (br. s., 1 H), 6.30 (d, $J=5.6$ Hz, 1 H), 6.13 (d, $J=5.3$ Hz, 1 H), 4.78 (t, $J=5.5$ Hz, 1 H), 4.71 (q, $J=7.0$ Hz, 1 H), 4.42 (q, $J=6.7$ Hz, 1 H), 4.06-4.00 (m, 1 H), 3.54 (dt, $J=10.7$, 5.4 Hz, 1 H), 3.42-3.38 (m, 1 H; overlapped with water), 1.22 (d, $J=6.7$ Hz, 3 H), 1.13 (d, $J=6.4$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 171.8, 169.1, 163.2, 150.2, 142.6, 128.2, 124.9, 118.2, 104.7, 61.5, 55.0, 53.9, 52.0, 16.4, 15.2. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{N}_5\text{O}_8\text{S}$ [M + H]⁺ 456.1189, found 456.1217.

2-[4-Oxo-1-(toluene-4-sulfonyl)-octahydro-pyrazino[1,2-a]pyrimidin-8-yl]-N-propyl-acetamide 17(1,1,1,1)



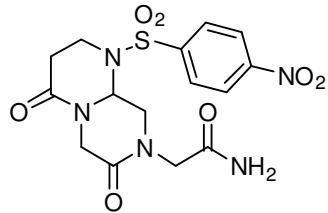
Yield 14.9 mg (49%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6) δ 7.98 (t, $J=5.7$ Hz, 1 H), 7.88 (d, $J=8.3$ Hz, 2 H), 7.43 (d, $J=8.3$ Hz, 2 H), 5.94 (dd, $J=10.4, 4.0$ Hz, 1 H), 4.63 (d, $J=17.7$ Hz, 1 H), 3.93 - 4.04 (m, 1 H), 3.74 - 3.91 (m, 4 H), 3.64 (br. s., 1 H), 3.26 - 3.34 (m, 1 H), 2.95 - 3.10 (m, 2 H), 2.40 (s, 3 H), 2.04 (dd, $J=17.7, 2.5$ Hz, 1 H), 1.69 (br. s., 1 H), 1.41 (q, $J=7.2$ Hz, 2 H), 0.83 (t, $J=7.5$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 167.1, 164.1, 164.0, 144.5, 136.5, 130.4, 127.1, 63.7, 51.0, 48.9, 44.9, 40.3, 38.3, 29.3, 22.5, 21.1, 11.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 423.1702, found 423.1697.

2-[4,7-Dioxo-1-(toluene-4-sulfonyl)-octahydro-pyrazino[1,2-a]pyrimidin-8-yl]-acetamide 17(2,1,1,1)



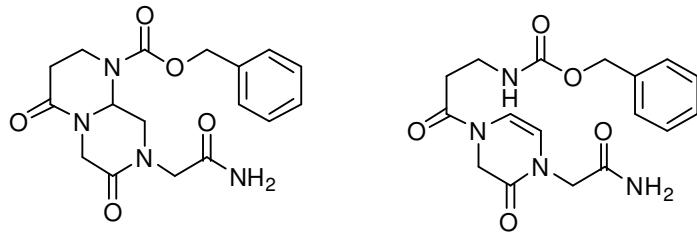
Yield 27.4 mg (76%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 7.88 (d, $J=8.5$ Hz, 2 H), 7.48 (s, 1 H), 7.44 (d, $J=8.5$ Hz, 2 H), 7.19 (s, 1 H), 5.98 (dd, $J=10.4, 4.3$ Hz, 1 H), 4.63 (d, $J=17.6$ Hz, 1 H), 3.95 (d, $J=16.7$ Hz, 1 H), 3.75 - 3.88 (m, 4 H), 3.61 - 3.71 (m, 1 H), 3.30 (dd, $J=11.2, 4.4$ Hz, 1 H), 2.40 (s, 3 H), 1.99 - 2.06 (m, 1 H), 1.66 - 1.75 (m, 1 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.4, 164.1, 163.9, 144.4, 136.5, 130.3, 127.0, 63.6, 50.9, 48.9, 44.8, 38.3, 29.3, 21.1. HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{21}\text{N}_4\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 381.1227, found 381.1198.

2-(1-((4-nitrophenyl)sulfonyl)-4,7-dioxohexahydro-1*H*-pyrazino[1,2-a]pyrimidin-8(*2H*)-yl)acetamide 17(2,1,1,2)



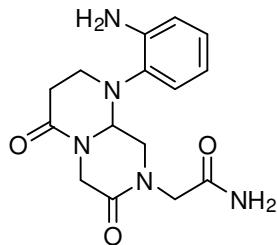
Yield 19.0 mg (65%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 8.41 (d, $J=9.1$ Hz, 2 H), 8.28 (d, $J=9.1$ Hz, 2 H), 7.49 (br. s., 1 H), 7.18 (br. s., 1 H), 6.03 (dd, $J=10.4, 4.3$ Hz, 1 H), 4.64 (d, $J=17.3$ Hz, 1 H), 3.92 - 3.98 (m, 2 H), 3.88 (t, $J=10.9$ Hz, 1 H), 3.77 - 3.84 (m, 2 H), 3.69 - 3.76 (m, 1 H), 3.31 (dd, $J=11.2, 4.1$ Hz, 1 H), 2.09 - 2.16 (m, 1 H), 1.82 - 1.90 (m, 1 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.4, 164.0, 163.9, 150.4, 144.6, 128.8, 125.1, 63.6, 50.8, 48.9, 44.9, 38.6, 29.8. HRMS (ESI-TOF) m/z calcd for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{NaO}_7\text{S} [\text{M} + \text{Na}]^+$ 434.0746, found 434.0756.

Mixture of isomers: Benzyl 8-(2-amino-2-oxoethyl)-4,7-dioxooctahydro-1*H*-pyrazino[1,2-*a*]pyrimidine-1-carboxylate 17(2,1,1,4) and Benzyl (3-(4-(2-amino-2-oxoethyl)-3,4-dihdropyrazin-1(2*H*)-yl)-3-oxopropyl) carbamate 18(2,1,1,4)



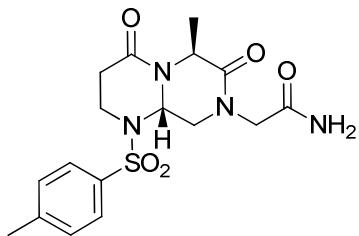
Total yield: 44% of amorphous solid. Yield bicyclic product: 3.1 mg (12%). Yield olefinic product: 8.4 mg (32%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 7.52 - 7.25 (m, 7 H + 7 H), 7.15 (br. s., 1 H), 6.41 (d, $J=6.2$ Hz, 1 H), 5.92 - 5.79 (m, 1 H + 1H), 5.17 (s, 2 H), 5.00 (s, 2 H), 4.67 (d, $J=17.6$ Hz, 1 H), 4.18 (s, 2 H), 4.04 (s, 2 H), 3.96 - 3.62 (m, 4 H), 3.29 - 3.20 (m, 2 H + 3 H), 2.61 (t, $J=6.7$ Hz, 2 H + 1 H), 2.35 - 2.22 (m, 1 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 169.4, 169.0, 168.6, 165.3, 164.2, 163.2, 162.7, 156.1, 137.2, 136.3, 128.6, 128.4, 128.1, 127.8, 127.7, 114.8, 108.5, 67.2, 65.3, 62.9, 48.9, 47.8, 47.7, 45.2, 45.0, 36.4, 36.2, 32.8, 32.7. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{21}\text{N}_4\text{O}_5 [\text{M} + \text{H}]^+$ 361.1506, found 361.1507.

2-(1-(2-aminophenyl)-4,7-dioxohexahydro-1*H*-pyrazino[1,2-*a*]pyrimidin-8(2*H*)-yl)acetamide 17(2,1,1,7)



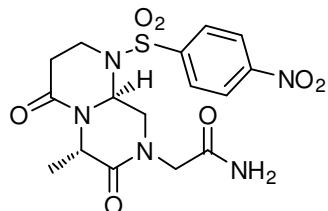
Yield 3.5 mg (50 %) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 7.43 (br. s., 1 H), 7.11 (br. s., 1 H), 6.93 (d, $J=7.9$ Hz, 1 H), 6.90 - 6.83 (m, 1 H), 6.68 (d, $J=7.9$ Hz, 1 H), 6.56 - 6.48 (m, 1 H), 5.11 (dd, $J=10.3, 3.5$ Hz, 1 H), 4.95 (s, 2 H), 4.74 (d, $J=17.9$ Hz, 1 H), 3.90 - 3.67 (m, 4 H), 3.29 - 3.01 (m, 3 H), 2.22 (br. s., 2 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 169.6, 165.8, 164.7, 143.4, 133.6, 125.7, 123.0, 116.4, 114.8, 69.5, 51.2, 48.8, 44.5, 42.5, 29.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{15}\text{H}_{20}\text{N}_5\text{O}_3$ [M + H] $^+$ 318.1566, found 318.1571.

2-[6-Methyl-4,7-dioxo-1-(toluene-4-sulfonyl)-octahydro-pyrazino[1,2-a]pyrimidin-8-yl]-acetamide 17(2,2,1,1)



Yield 29.1 mg (78%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 7.8 (d, $J=8.2$ Hz, 2 H) 7.5 (s, 1 H) 7.4 (d, $J=8.2$ Hz, 2 H) 7.2 (s, 1 H) 5.7 (dd, $J=10.6, 4.1$ Hz, 1 H) 4.9 - 4.8 (m, 1 H) 3.9 - 4.0 (m, 3 H) 3.8 - 3.9 (m, 1 H) 3.6 (ddd, $J=15.1, 12.8, 4.1$ Hz, 1 H) 3.3 (dd, $J=11.2, 4.1$ Hz, 1 H) 2.4 (s, 3 H) 2.1 (dd, $J=17.0, 3.8$ Hz, 1 H) 1.8 (ddd, $J=17.5, 12.8, 7.0$ Hz, 1 H) 1.3 (d, $J=7.3$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.4, 167.0, 163.7, 144.6, 136.2, 130.4, 127.0, 61.1, 51.5, 50.2, 49.4, 38.2, 29.4, 21.1, 16.1. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_5\text{S}$ [M + H] $^+$ 395.1384, found 395.1365.

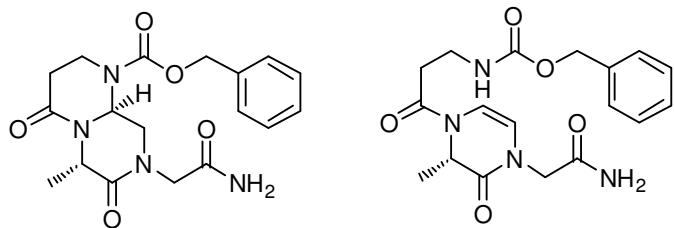
2-((6*S*,9*aS*)-6-methyl-1-((4-nitrophenyl)sulfonyl)-4,7-dioxohexahydro-1*H*-pyrazino[1,2-a]pyrimidin-8(2*H*)-yl)acetamide 17(2,2,1,2)**



Yield 19.0 mg (63%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 8.43 (d, $J=8.9$ Hz, 2 H), 8.26 (d, $J=8.9$ Hz, 2 H), 7.49 (br. s., 1 H), 7.16 (br. s., 1 H), 5.77 (dd, $J=10.6, 3.8$

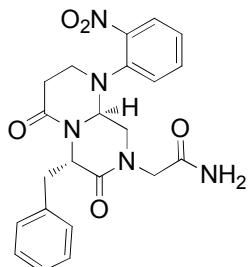
Hz, 1 H), 4.81 (q, $J=7.2$ Hz, 1 H), 3.98 - 4.07 (m, 1 H), 3.89 - 3.95 (m, 2 H), 3.81 (d, $J=16.4$ Hz, 1 H), 3.71 (ddd, $J=15.0, 12.8, 4.1$ Hz, 1 H), 3.28 (dd, $J=11.2, 3.8$ Hz, 1 H), 2.16 (dd, $J=17.8, 3.1$ Hz, 1 H), 1.99 (ddd, $J=17.6, 12.6, 7.0$ Hz, 1 H), 1.27 (d, $J=7.3$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.4, 167.0, 163.6, 150.5, 144.4, 128.7, 125.2, 61.1, 51.3, 50.4, 49.5, 38.5, 30.0, 16.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_5\text{NaO}_7\text{S} [\text{M} + \text{Na}]^+$ 448.0897, found 448.0910.

Mixture of isomers: (6*S*,9*aS*)-benzyl 8-(2-amino-2-oxoethyl)-6-methyl-4,7-dioxooctahydro-1*H*-pyrazino[1,2-*a*]pyrimidine-1-carboxylate 17(2,2,1,4) and (*S*)-benzyl (3-(4-(2-amino-2-oxoethyl)-2-methyl-3-oxo-3,4-dihydropyrazin-1(2*H*)-yl)-3-oxopropyl)carbamate 18(2,2,1,4)**



Total yield: 50% of amorphous solid. Yield bicyclic product: 4.7 mg (20%). Yield olefinic product: 7.2 mg (30%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 7.53 - 7.23 (m, 7 H + 6 H), 7.12 (d, $J=5.3$ Hz, 2 H), 6.31 (d, $J=5.6$ Hz, 1 H), 5.91 (d, $J=5.6$ Hz, 1 H), 5.79 (dd, J=10.4, 3.7 Hz, 1 H), 5.18 (s, 2 H), 5.00 (s, 2 H), 4.86 (q, J=6.8 Hz, 1 H + 1 H), 4.04 (s, 2 H), 3.96-3.74 (m, 3 H), 3.44 - 3.16 (m, 2 H + 4 H; overlapped with water), 2.69 - 2.56 (m, 2 H), 2.33 - 2.23 (m, 1 H), 1.33 (d, J=7.0 Hz, 3 H), 1.12 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 169.3, 168.9, 168.5, 167.2, 166.1, 164.9, 156.1, 137.2, 128.5, 128.4, 127.8, 115.4, 106.6, 67.3, 65.3, 60.1, 50.4, 50.2, 49.2, 47.6, 36.4, 32.9, 16.5, 15.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{N}_4\text{O}_5 [\text{M} + \text{H}]^+$ 375.1663, found 375.1689.

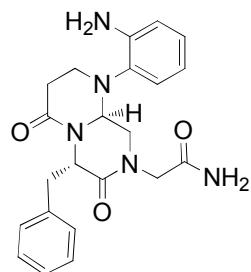
2-((6*S*,9*aR*)-6-benzyl-1-(2-nitrophenyl)-4,7-dioxohexahydro-1*H*-pyrazino[1,2-*a*]pyrimidin-8(2*H*)-yl)acetamide 17(2,3,1,6)**



Yield 9.2 mg (56%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 7.84 (dd, $J = 1.6, 8.1$ Hz, 1 H), 7.48 - 7.42 (m, 2 H), 7.36 - 7.29 (m, 3 H), 7.29 - 7.25 (m, 3 H), 6.73 (dd, $J = 1.0,$

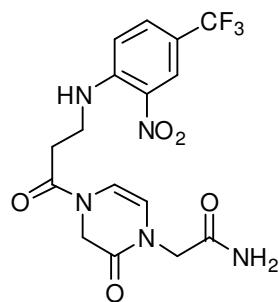
8.1 Hz, 1 H), 5.36 (dd, J = 5.6, 7.9 Hz, 1 H), 4.96 (dd, J = 3.8, 10.3 Hz, 1 H), 3.91 (d, J = 16.4 Hz, 1 H), 3.87 (d, J = 16.7 Hz, 1 H), 3.77 (dd, J = 10.7, 11.3 Hz, 1 H), 3.61 (dd, 1 H), 3.57 (ddd, J = 4.0, 10.9, 14.2 Hz, 1 H), 3.41 - 3.35 (m, 1 H), 3.20 (dd, J = 5.6, 14.4 Hz, 1 H), 3.16 (dd, J = 4.1, 11.4 Hz, 1 H), 3.05 (ddd, 1 H), 2.22 (ddd, J = 6.0, 11.2, 17.2 Hz, 1 H), 2.14 - 2.08 (m, 1 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.4, 166.6, 165.7, 146.0, 141.3, 137.1, 133.3, 129.5, 128.3, 126.7, 125.6, 125.6, 124.7, 67.5, 54.6, 51.3, 49.3, 44.5, 36.0, 29.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{N}_5\text{O}_5$ [M + H] $^+$ 438.1772, found 438.1783

2-((6*S*,9*aR*)-1-(2-aminophenyl)-6-benzyl-4,7-dioxohexahydro-1*H*-pyrazino[1,2-*a*]pyrimidin-8(2*H*)-yl)acetamide 17(2,3,1,7)



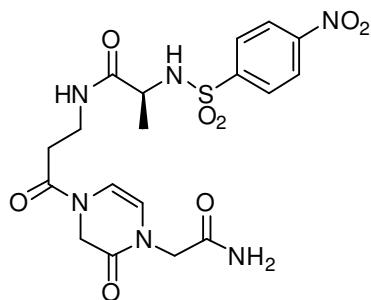
Yield 30 mg (66%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 7.44 (s, 1 H), 7.34 - 7.29 (m, 2 H), 7.29 - 7.26 (m, 2 H), 7.26 - 7.22 (m, 1 H), 7.14 (s, 1 H), 6.86 - 6.80 (m, 1 H), 6.64 (dd, J = 1.2, 7.9 Hz, 1 H), 6.37 - 6.34 (m, 1 H), 6.34 - 6.30 (m, 1 H), 5.38 (dd, J = 5.4, 7.8 Hz, 1 H), 4.89 (s, 2 H), 4.73 (dd, J = 3.8, 10.3 Hz, 1 H), 3.94 (d, J = 16.4 Hz, 1 H), 3.83 (d, J = 16.7 Hz, 1 H), 3.71 (dd, J = 10.6, 11.4 Hz, 1 H), 3.40 - 3.36 (m, 1 H), 3.29 (ddd, J = 4.0, 9.9, 13.4 Hz, 1 H), 3.21 (dd, J = 5.3, 14.4 Hz, 1 H), 3.14 (dd, J = 3.8, 11.7 Hz, 1 H), 2.88 (dt, J = 4.7, 13.3 Hz, 1 H), 2.22 - 2.16 (m, 1 H), 2.14 - 2.07 (m, 1 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.4, 166.8, 166.2, 143.5, 137.1, 133.5, 129.5, 128.2, 126.7, 125.7, 122.9, 116.1, 114.6, 67.5, 54.4, 51.9, 49.3, 42.2, 36.2, 29.5. HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_3$ [M + H] $^+$ 408.2030, found 408.2031

2-(4-((2-nitro-4-(trifluoromethyl)phenyl)amino)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2*H*)-yl)acetamide 18(2,1,1,5)



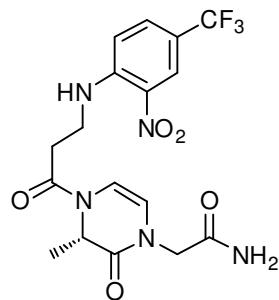
Yield 7.1 mg (46%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.62 (t, $J=5.6$ Hz, 1 H), 8.31 (s, 1 H), 7.79 (d, $J=9.1$ Hz, 1 H), 7.46 (s, 1 H), 7.37 - 7.25 (m, 1 H), 7.14 (br. s., 1 H), 6.45 (d, $J=5.9$ Hz, 1 H), 5.87 (d, $J=5.9$ Hz, 1 H), 4.21 (s, 2 H), 4.04 (s, 2 H), 3.81 - 3.61 (m, 2 H), 2.84 (t, $J=6.4$ Hz, 2 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 168.9, 168.7, 163.1, 146.6, 132.0, 130.2, 124.2, 123.9 (q, $J=270.0$ Hz), 115.9, 115.0, 114.9 (q, $J=33.5$ Hz), 108.3, 47.6, 45.2, 38.3, 31.7. HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_5\text{O}_5$ [M + H] $^+$ 416.1176, found 416.1184.

(S)-N-(3-(4-(2-amino-2-oxoethyl)-3-oxo-3,4-dihydropyrazin-1(2*H*)-yl)-3-oxopropyl)-2-(4-nitrophenylsulfonamido)propanamide 18(2,1,1,9)



Yield 44.8 mg (92%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.44 (d, $J=8.5$ Hz, 2 H), 8.06 (d, $J=8.5$ Hz, 3 H), 7.52 (br. s., 1 H), 7.20 (br. s., 1 H), 6.40 (d, $J=5.9$ Hz, 1 H), 5.91 (d, $J=5.9$ Hz, 1 H), 4.24 (s, 2 H), 4.10 (br. s., 2 H), 3.87 (q, $J=6.4$ Hz, 1 H), 3.17 (d, $J=5.3$ Hz, 2 H), 2.55 (br. s., 2 H; overlapped with DMSO- d_6), 1.94 (s, 1 H), 1.11 (d, $J=6.7$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 170.8, 169.0, 168.6, 163.1, 149.5, 146.7, 128.2, 124.3, 114.9, 108.4, 52.0, 47.6, 45.2, 34.5, 32.1, 19.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{N}_6\text{O}_8\text{S}$ [M + H] $^+$ 483.1293, found 483.1310.

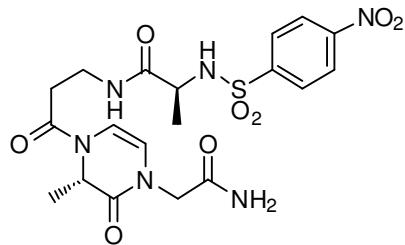
(S)-2-(3-methyl-4-(3-((2-nitro-4-(trifluoromethyl)phenyl)amino)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2*H*)-yl)acetamide 18(2,2,1,5)



Yield 35.2 mg (85%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.62 (t, $J=5.4$ Hz, 1 H), 8.29 (s, 1 H), 7.77 (d, $J=9.1$ Hz, 1 H), 7.46 (br. s., 1 H), 7.29 (d, $J=9.1$ Hz, 1 H), 7.12 (br. s., 1 H), 6.35 (d, $J=5.9$ Hz, 1 H), 5.93 (d, $J=5.9$ Hz, 1 H), 4.88 (q, $J=6.9$ Hz, 1 H), 4.05 (s,

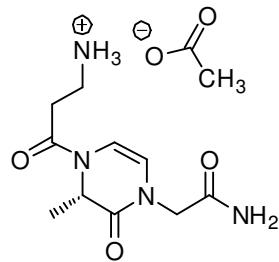
2 H), 3.70 (br. s., 2 H), 2.97 - 2.84 (m, 1 H), 2.82 - 2.68 (m, 1 H), 1.14 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 168.9, 165.9, 146.6, 132.0, 130.2, 124.1, 123.9 (q, $J=270.1$ Hz), 115.9, 115.6, 115.0 (q, $J=33.9$ Hz), 106.4, 50.3, 47.5, 38.3, 31.9, 15.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_5\text{O}_5$ [M + H] $^+$ 430.1333, found 430.1342.

(S)-*N*-(3-((S)-4-(2-amino-2-oxoethyl)-2-methyl-3-oxo-3,4-dihydropyrazin-1(2*H*)-yl)-3-oxopropyl)-2-(4-nitrophenylsulfonamido)propanamide 18(2,2,1,9)



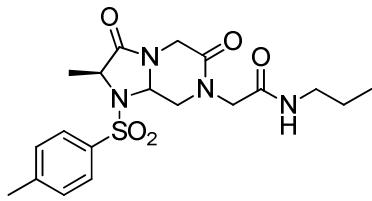
Yield 12.7 mg (45%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.39 (d, $J=8.8$ Hz, 2 H), 8.01 (d, $J=8.8$ Hz, 3 H), 7.47 (br. s., 1 H), 7.13 (br. s, 1 H), 6.25 (d, $J=5.9$ Hz, 1 H), 5.92 (d, $J=5.9$ Hz, 1 H), 4.86 (q, $J=6.6$ Hz, 1 H), 4.06 (s, 2 H), 3.82 (q, $J=6.6$ Hz, 1 H), 3.19 - 3.04 (m, 2 H), 2.57 - 2.38 (m, 1 H; overlapped with DMSO- d_6), 2.39-2.24 (m, 1 H), 1.12 (d, $J=7.0$ Hz, 3 H), 1.06 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 170.8, 168.9, 168.5, 166.0, 149.5, 146.7, 128.2, 124.4, 115.5, 106.4, 51.9, 50.3, 47.6, 34.4, 32.3, 19.0, 15.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_6\text{O}_8\text{S}$ [M + H] $^+$ 497.1449, found 497.1468.

(S)-3-(4-(2-amino-2-oxoethyl)-2-methyl-3-oxo-3,4-dihydropyrazin-1(2*H*)-yl)-3-oxopropan-1-aminium acetate 18(2,2,1,12)



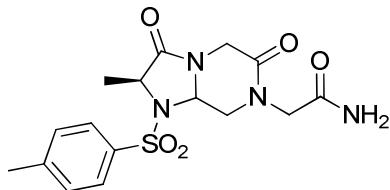
Yield 7.6 mg (46%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 7.47 (br. s., 1 H), 7.10 (br. s., 1 H), 6.30 (dd, $J=6.0$, 1.6 Hz, 1 H), 5.97 (d, $J=5.9$ Hz, 1 H), 4.89 (qd, $J=6.9$, 1.5 Hz, 1 H), 4.13 - 3.99 (m, 2 H), 2.98 (td, $J=6.4$, 3.1 Hz, 2 H), 2.78 (dt, $J=17.1$, 6.4 Hz, 1 H), 2.61 (dt, $J=17.0$, 6.6 Hz, 1 H), 1.87 (s, 3 H), 1.16 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 168.8, 168.7, 168.2, 165.9, 115.9, 106.2, 50.3, 47.5, 35.3, 31.8, 21.5, 15.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{10}\text{H}_{17}\text{N}_4\text{O}_3$ [M + H] $^+$ 241.1301, found 241.1303.

2-[2-Methyl-3,6-dioxo-1-(toluene-4-sulfonyl)-hexahydro-imidazo[1,2-*a*]pyrazin-7-yl]-*N*-propyl-acetamide 20(1,1,2,1)



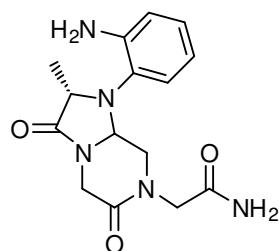
Yield 5.2 mg (15%) of amorphous solid of a mixture of two diastereoisomers (72:28). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.93 - 8.02 (m, 1 H) 7.81 - 7.88 (m, 2 H) 7.41 - 7.52 (m, 2 H) 5.48 - 5.57 (m, 1 H) 5.37 (dd, *J*=9.3, 4.0 Hz, 1 H) 3.61 - 4.32 (m, 5 H) 3.46 - 3.59 (m, 1 H) 3.03 (q, *J*=6.6 Hz, 2 H) 2.38 - 2.45 (m, 3 H) 1.35 - 1.48 (m, 3 H) 1.28 (d, *J*=6.6 Hz, 2 H) 0.79 - 0.90 (m, 3 H) ¹³C NMR (75 MHz, DMSO-*d*₆) δ 167.5, 167.1, 163.3, 163.2, 144.9, 144.1, 137.2, 130.4, 130.1, 128.1, 127.1, 66.6, 55.9, 52.6, 49.9, 42.8, 40.3, 22.4, 21.1, 19.9, 16.9, 11.4. HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₆N₄O₅S [M + H]⁺ 423.1702, found 423.1680.

2-[2-Methyl-3,6-dioxo-1-(toluene-4-sulfonyl)-hexahydro-imidazo[1,2-a]pyrazin-7-yl]-acetamide 20(2,1,2,1)



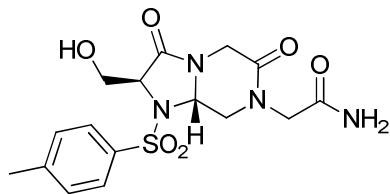
Yield 24.3 mg (67%) of amorphous solid, mixture of two diastereoisomers (63:37). ¹H NMR (600 MHz, DMSO-*d*₆) of major diastereoisomer δ 7.86 - 7.82 (m, 2 H), 7.48 (br. s., 1 H), 7.46 - 7.42 (m, 2 H), 7.18 (br. s., 1 H), 5.58 - 5.51 (m, 1 H), 4.25 (d, *J* = 17.9 Hz, 1 H), 4.19 - 4.13 (m, 1 H), 4.00 (d, *J* = 16.4 Hz, 1 H), 3.90 (d, *J* = 16.4 Hz, 1 H), 3.84 (dd, *J* = 3.8, 11.2 Hz, 1 H), 3.79 (d, *J* = 17.9 Hz, 1 H), 3.55 (dd, *J* = 9.5, 11.2 Hz, 1 H), 2.41 (s, 3 H), 1.28 (d, *J* = 6.7 Hz, 3 H) ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.5/169.5, 167.5/167.2, 163.3/163.2, 144.9/144.1, 137.2/132.0, 130.3/130.1, 128.0/127.0, 66.6/66.3, 56.1/55.8, 54.4/52.6, 50.0/49.9, 43.2/42.8, 21.1/21.0, 19.8/16.8. HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₁N₄O₅S [M + H]⁺ 381.1227, found 381.1193.

2-((2*S*)-1-(2-aminophenyl)-2-methyl-3,6-dioxohexahydroimidazo[1,2-a]pyrazin-7(1*H*)-yl)acetamide 20(2,1,2,7)



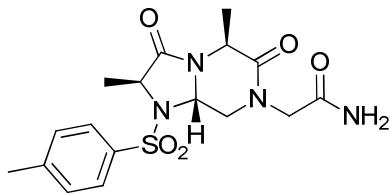
Yield 4.6 mg (16%) of amorphous solid, mixture of two diastereoisomers (64:36). ^1H NMR (600 MHz, DMSO- d_6): δ 7.40 (br. s., 1 H), 7.32 (d, $J=6.7$ Hz, 1 H), 7.06 (br. s., 1 H), 6.97 - 6.93 (m, 1 H), 6.70 (dd, $J=7.9$, 1.2 Hz, 1 H), 6.60 - 6.55 (m, 1 H), 5.07 (s, 2 H), 4.82 (dd, $J=8.7$, 2.2 Hz, 1 H), 4.22 (d, $J=17.9$ Hz, 1 H), 3.97 (d, $J=16.7$ Hz, 1 H), 3.86 - 3.78 (m, 3 H), 3.50 (dd, $J=11.6$, 9.0 Hz, 1 H), 3.28 (dd, $J=11.6$, 3.7 Hz, 1 H), 1.11 (d, $J=6.5$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 170.3, 169.6, 164.3, 147.8, 130.3, 127.5, 126.7, 116.6, 114.7, 72.0, 62.4, 53.5, 49.6, 43.2, 16.8. HRMS (ESI-TOF) m/z calcd for $\text{C}_{15}\text{H}_{20}\text{N}_5\text{O}_3$ [M + H] $^+$ 318.1561, found 318.1575.

2-((2*S*,8*aS*)-2-(hydroxymethyl)-3,6-dioxo-1-tosylhexahydroimidazo[1,2-*a*]pyrazin-7(1*H*)-yl)acetamide 20(2,1,6,1)



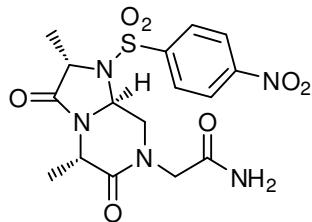
Yield 15.8 mg (44%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 7.83 (d, $J=8.0$ Hz, 2 H), 7.48 (s, 1 H), 7.40 (d, $J=8.0$ Hz, 2 H), 7.16 - 7.19 (m, 1 H), 5.34 (dt, $J=9.0$, 3.0 Hz, 1 H), 4.85 (br. s., 1 H), 4.26 (d, $J=17.9$ Hz, 1 H), 4.15 (d, $J=1.5$ Hz, 1 H), 3.95 - 4.01 (m, 2 H), 3.88 - 3.94 (m, 2 H), 3.73 (d, $J=17.9$ Hz, 1 H), 3.69 (d, $J=11.4$ Hz, 1 H), 3.48 (dd, $J=11.3$, 9.5 Hz, 1 H), 2.40 (s, 3 H).. ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.6, 165.7, 163.3, 143.8, 136.5, 129.8, 127.2, 67.1, 63.0, 59.1, 52.8, 49.9, 42.7, 21.1. HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_6\text{S}$ [M + H] $^+$ 397.1182, found 397.1170.

2-((2*S*,5*S*,8*aS*)-2,5-dimethyl-3,6-dioxo-1-tosylhexahydroimidazo[1,2-*a*]pyrazin-7(1*H*)-yl)acetamide 20(2,2,2,1)



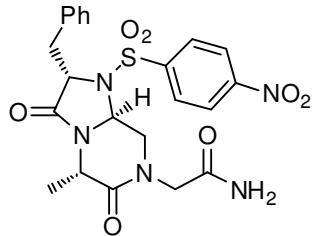
Yield 19.7 mg (53%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6): δ 7.9 (d, $J=8.2$ Hz, 2 H), 7.4 - 7.5 (m, 3 H), 7.2 (s, 1 H), 5.6 (ddd, $J=9.4$, 3.5, 2.3 Hz, 1 H), 4.4 (q, $J=7.2$ Hz, 1 H), 4.1 (qd, $J=6.7$, 2.3 Hz, 1 H), 4.1 (d, $J=16.4$ Hz, 1 H), 3.8 - 3.9 (m, 2 H), 3.6 (dd, $J=11.2$, 9.4 Hz, 1 H), 2.4 (s, 3 H), 1.3 (d, $J=7.3$ Hz, 3 H), 1.3 (d, $J=6.7$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.5, 167.5, 166.5, 144.1, 137.2, 130.1, 127.0, 65.0, 55.6, 53.2, 50.4, 49.0, 21.0, 17.4, 17.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_5\text{S}$ [M + H] $^+$ 395.1384, found 395.1364.

2-((2S,5S,8aS)-2,5-dimethyl-1-((4-nitrophenyl)sulfonyl)-3,6-dioxohexahydroimidazo[1,2-a]pyrazin-7(1H)-yl)acetamide 20(2,2,2,2)



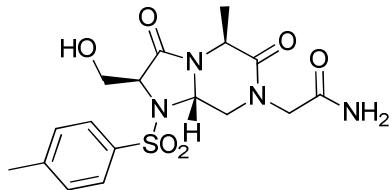
Yield 16.9 mg (55%) of amorphous solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.41 (d, *J*=8.9 Hz, 2 H), 8.27 (d, *J*=8.9 Hz, 2 H), 7.47 (br. s., 1 H), 7.18 (br. s., 1 H), 5.77 - 5.69 (m, 1 H), 4.40 (q, *J*=7.0 Hz, 1 H), 4.27 (q, *J*=6.5 Hz, 1 H), 4.08 (d, *J*=16.7 Hz, 1 H), 3.90 - 3.78 (m, 2 H), 3.61 (t, *J*=10.3 Hz, 1 H), 1.34 (d, *J*=7.0 Hz, 3 H), 1.31 (d, *J*=6.7 Hz, 2 H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 169.5, 167.2, 166.5, 150.2, 145.4, 128.8, 124.9, 65.2, 56.0, 53.2, 50.4, 49.1, 17.4, 17.0. HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₀N₅O₇S [M + H]⁺ 426.1078, found 426.1088.

2-((2S,5S,8aS)-2-benzyl-5-methyl-1-((4-nitrophenyl)sulfonyl)-3,6-dioxohexahydroimidazo[1,2-a]pyrazin-7(1H)-yl)acetamide 20(2,2,5,2)



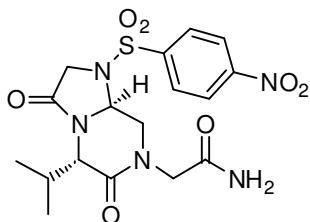
Yield 9.0 mg (45%) of amorphous solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.42 - 8.29 (m, 4 H), 7.36 - 7.19 (m, 6 H), 7.07 (br. s., 1 H), 4.89 (d, *J*=9.1 Hz, 1 H), 4.62 (br. s., 1 H), 4.18 (q, *J*=6.7 Hz, 1 H), 3.87 - 3.71 (m, 3 H), 3.47 (dd, *J*=14.1, 4.7 Hz, 1 H), 3.25 - 3.19 (m, 1 H), 3.18 - 3.07 (m, 1 H), 0.82 (d, *J*=7.3 Hz, 3 H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 169.4, 166.2, 165.0, 150.2, 144.8, 134.8, 130.1, 128.9, 128.4, 127.0, 124.9, 65.9, 61.3, 52.1, 50.3, 48.4, 36.8, 16.5. HRMS (ESI-TOF) *m/z* calcd for C₂₂H₂₄N₅O₇S [M + H]⁺ 502.1391, found 502.1429.

2-((2S,5S,8aS)-2-(hydroxymethyl)-5-methyl-3,6-dioxo-1-tosylhexahydroimidazo[1,2-a]pyrazin-7(1H)-yl)acetamide 20(2,2,6,1)



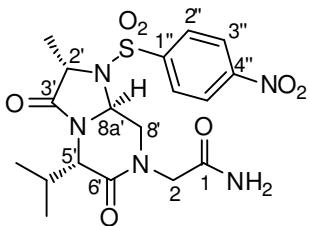
Yield 19.7 mg (53%). ^1H NMR (600 MHz, DMSO- d_6) δ 7.73 (d, $J=8.0$ Hz, 2 H), 7.42 (br. s., 1 H), 7.37 (d, $J=8.0$ Hz, 2 H), 7.10 (br. s., 1 H), 5.31 (dd, $J=7.9, 3.5$ Hz, 1 H), 4.57 (q, $J=7.2$ Hz, 1 H), 4.04 (d, $J=16.4$ Hz, 1 H), 3.89 - 3.94 (m, 2 H), 3.78 (d, $J=16.4$ Hz, 1 H), 3.67 (dd, $J=12.5, 5.1$ Hz, 1 H), 3.62 (dd, $J=11.7, 7.9$ Hz, 1 H), 3.49 (dd, $J=11.9, 3.7$ Hz, 2 H), 2.38 (s, 3 H), 1.27 (d, $J=7.3$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.3, 167.4, 162.6, 142.6, 138.8, 129.5, 126.6, 78.2, 66.7, 51.8, 50.8, 49.6, 49.0, 21.0, 17.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_6\text{S} [\text{M} + \text{H}]^+$ 411.1320, found 411.1320.

2-((5*S*,8*aS*)-5-isopropyl-1-((4-nitrophenyl)sulfonyl)-3,6-dioxohexahydroimidazo[1,2-*a*]pyrazin-7(1*H*)-yl)acetamide 20(2,4,1,2)**



Yield 22.5 mg (58%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.54 - 8.44 (m, 2 H), 8.35 (d, $J=8.8$ Hz, 2 H), 7.46 (br. s., 1 H), 7.12 (br. s., 1 H), 5.31 (dd, $J=9.2, 3.8$ Hz, 1 H), 4.37 (d, $J=16.6$ Hz, 1 H), 4.14 (d, $J=16.5$ Hz, 1 H), 4.06 (d, $J=4.0$ Hz, 1 H), 4.02 - 3.79 (m, 2 H), 3.78 - 3.68 (m, 1 H), 3.55 (dd, $J=11.4, 4.1$ Hz, 1 H), 2.23 (dd, $J=11.2, 6.8$ Hz, 1 H), 0.51 (d, $J=6.8$ Hz, 3 H), 0.41 (d, $J=6.8$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.3, 167.1, 165.3, 150.7, 140.9, 129.6, 125.0, 67.4, 58.7, 52.5, 50.2, 48.3, 31.2, 19.1, 17.8. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{21}\text{N}_5\text{NaO}_7\text{S} [\text{M} + \text{Na}]^+$ 462.1054, found 462.1088.

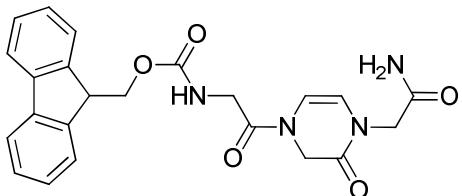
2-((2*S*,5*S*,8*aS*)-5-isopropyl-2-methyl-1-((4-nitrophenyl)sulfonyl)-3,6-dioxohexahydro-imidazo[1,2-*a*]pyrazin-7(1*H*)-yl)acetamide 20(2,4,2,2)**



This compound has been fully characterized by 2D NMR experiments to determine the stereochemistry of the new chiral carbon (C_{8a}), and it was used as a model compound. Yield 14.6 mg (58%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.42 (d, $J=8.8$ Hz, 2 H, $\text{H}_{3''}$), 8.27 (d, $J=8.8$ Hz, 2 H, $\text{H}_{2''}$), 7.44 (s, 1 H, $-\text{CONH}_2$), 7.12 (s, 1 H, $-\text{CONH}_2$), 5.59 - 5.56 (m, 1 H, H_{8a}), 4.26 (d, $J=4.1$ Hz, 1 H, H_5), 4.25 - 4.21 (m, 1 H, H_2), 4.00 - 3.96 (m, 1 H, H_2), 3.91 - 3.86 (m, 1 H, H_2), 3.81 (dd, $J=11.2, 3.8$ Hz, 1 H, $\text{H}_{8'}$), 3.62 - 3.57 (m, 1 H,

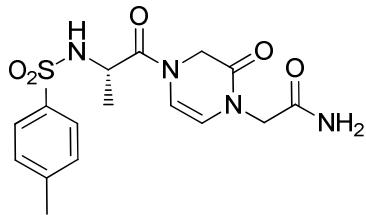
H_8), 2.41 (dq, $J=11.2, 6.8$ Hz, 1 H, -C₅H-CH(CH₃)₂), 1.37 (d, $J=6.7$ Hz, 3 H, -C₂H-CH₃), 0.87 (d, $J=6.7$ Hz, 3 H, -C₅H-CH(CH₃)₂), 0.81 (d, $J=6.7$ Hz, 3 H, -C₅H-CH(CH₃)₂). ¹³C NMR (151 MHz, DMSO-d₆): δ ppm 169.4 (C₁), 169.0 (C₃), 165.3 (C₆), 150.2 (C_{4'}), 145.2 (C_{1''}), 128.7 (C_{2''}), 124.9 (C_{3''}), 67.2 (C_{8a'}), 58.4 (C₅), 55.4 (C₂), 53.1 (C₈), 50.3 (C₂), 31.9 (-C₅H-CH(CH₃)₂), 19.7 (-C₅H-CH(CH₃)₂), 18.2 (-C₅H-CH(CH₃)₂), 17.6 (-C₂H-CH₃). HRMS (ESI-TOF) m/z calcd for C₁₈H₂₄N₅O₇S [M + H]⁺ 454.1391, found 454.1413.

[2-(4-Carbamoylmethyl-3-oxo-3,4-dihydro-2H-pyrazin-1-yl)-2-oxo-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester 21(2,1,1,3)



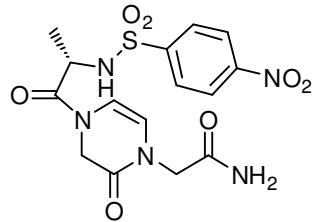
Yield 3.7 mg (14%) of amorphous solid. ¹H NMR (600 MHz, DMSO-d₆) δ 7.90 (d, $J=7.6$ Hz, 2 H), 7.73 (d, $J=7.3$ Hz, 2 H), 7.58 (t, $J=6.2$ Hz, 1 H), 7.47 (s, 1 H), 7.42 (t, $J=7.5$ Hz, 2 H), 7.31 - 7.36 (m, 2 H), 7.14 (s, 1 H), 6.46 - 6.50 (m, 1 H), 5.86 - 5.91 (m, 1 H), 4.28 - 4.32 (m, 3 H), 4.20 (s, 2 H), 4.05 (s, 2 H), 3.96 (d, $J=6.16$ Hz, 2 H). ¹³C NMR (75 MHz, DMSO-d₆) δ 168.9, 165.0, 163.0, 156.6, 143.8, 140.7, 127.6, 125.2, 120.1, 115.2, 107.5, 65.7, 47.6, 46.6, 45.4, 42.0. HRMS (ESI-TOF) m/z calcd for C₂₃H₂₃N₄O₅ [M + H]⁺ 435.1654, found 435.1663.

2-{2-Oxo-4-[2-(toluene-4-sulfonylamino)-propionyl]-3,4-dihydro-2H-pyrazin-1-yl}-acetamide 21(2,1,2,1)



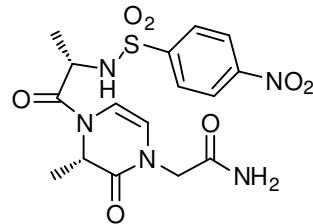
Yield 5.3 mg (15%) of amorphous solid. ¹H NMR (600 MHz, DMSO-d₆): δ 7.61 (d, $J=8.2$ Hz, 2 H), 7.48 (s, 1 H), 7.31 (d, $J=7.9$ Hz, 2 H), 7.16 (s, 1 H), 6.52 (d, $J=6.2$ Hz, 1 H), 5.90 (d, $J=5.9$ Hz, 1 H), 4.37 (q, $J=6.9$ Hz, 1 H), 4.10 (d, $J=16.7$ Hz, 1 H), 4.06 (d, $J=16.4$ Hz, 1 H), 3.94 (d, $J=17.3$ Hz, 1 H), 3.79 (d, $J=17.3$ Hz, 1 H), 2.33 (s, 3 H), 1.07 (d, $J=6.7$ Hz, 3 H). ¹³C NMR (151 MHz, DMSO-d₆): δ 168.9, 168.8, 162.8, 142.7, 137.9, 129.3, 126.5, 115.8, 107.4, 48.0, 47.4, 45.2, 21.0, 18.1. HRMS (ESI-TOF) m/z calcd for C₁₆H₂₁N₄O₅S [M + H]⁺ 381.1227, found 381.1193.

(S)-2-(4-(2-(4-nitrophenylsulfonamido)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,1,2,2)



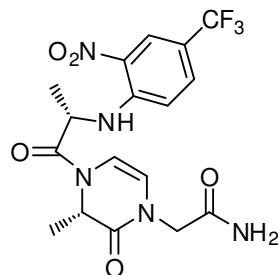
Yield 17.8 mg (65%) of amorphous solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.33 (d, *J*=8.8 Hz, 2 H), 7.97 (d, *J*=8.8 Hz, 2 H), 7.53 (br. s., 1 H), 7.19 (br. s., 1 H), 6.54 (d, *J*=5.9 Hz, 1 H), 5.94 (d, *J*=5.9 Hz, 1 H), 4.54 - 4.41 (m, 1 H), 4.16 - 4.02 (m, 2 H), 3.94 - 3.77 (m, 2 H), 1.15 (d, *J*=6.7 Hz, 3 H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 169.0, 168.6, 162.7, 149.4, 146.3, 128.2, 124.3, 116.4, 107.4, 48.3, 47.4, 45.1, 18.2. HRMS (ESI-TOF) *m/z* calcd for C₁₅H₁₈N₅O₇S [M + H]⁺ 412.0921, found 412.0948.

2-((S)-3-methyl-4-((S)-2-(4-nitrophenylsulfonamido)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,2,2,2)



Yield 9.1 mg (30%) of amorphous solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.39 (d, *J*=8.7 Hz, 2 H), 8.05 (d, *J*=8.7 Hz, 2 H), 7.45 (br. s., 1 H), 7.09 (br. s., 1 H), 6.50 (d, *J*=5.3 Hz, 1 H), 5.96 (d, *J*=5.9 Hz, 1 H), 4.64 (q, *J*=7.0 Hz, 1 H), 4.51 (q, *J*=7.0 Hz, 1 H), 4.13 - 3.94 (m, 2 H), 1.10 (d, *J*=6.7 Hz, 3 H), 0.92 (d, *J*=6.7 Hz, 3 H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 168.8, 168.7, 165.9, 149.5, 146.9, 128.2, 124.5, 116.4, 105.6, 50.7, 49.1, 47.5, 18.2, 14.9. HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₀N₅O₇S [M + H]⁺ 426.1078, found 426.1098.

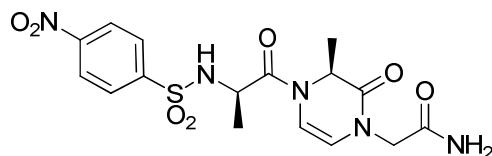
2-((S)-3-methyl-4-((S)-2-((2-nitro-4-(trifluoromethyl)phenyl)amino)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,2,2,5)



Yield 4 mg (15%) of amorphous solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.09 (d, *J*=6.4 Hz, 1 H), 8.36 (s, 1 H), 7.88 (d, *J*=9.1 Hz, 1 H), 7.50 (br. s., 1 H), 7.37 (d, *J*=9.1 Hz, 1 H), 7.12 (br.

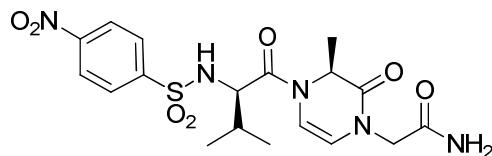
s., 1 H), 6.71 (d, $J=5.9$ Hz, 1 H), 6.11 (d, $J=5.9$ Hz, 1 H), 5.19 (quin, $J=6.4$ Hz, 1 H), 4.90 (q, $J=6.6$ Hz, 1 H), 4.09 (s, 2 H), 1.36 (d, $J=6.7$ Hz, 3 H), 1.21 (d, $J=6.7$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 169.4, 168.8, 166.1, 144.9, 132.2, 130.5, 124.3, 123.8 (q, $J=270.5$ Hz), 116.8, 116.6, 115.5 (q, $J=34.0$ Hz), 105.8, 51.3, 48.9, 47.6, 17.6, 15.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_5\text{O}_5$ [M + H] $^+$ 430.1333, found 430.1353.

2-((S)-3-methyl-4-((R)-2-(4-nitrophenylsulfonamido)propanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,2,3,2)



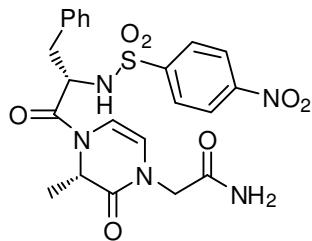
Yield 32.0 mg (87%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.64 (br. s., 1 H), 8.27 (d, $J=9.1$ Hz, 2 H), 7.92 (d, $J=9.1$ Hz, 2 H), 7.57 (s, 1 H), 7.19 (s, 1 H), 6.38 (dd, $J=6.0$, 1.6 Hz, 1 H), 5.98 (d, $J=5.9$ Hz, 1 H), 4.42 (q, $J=6.8$ Hz, 1 H), 4.17 (d, $J=16.4$ Hz, 1 H), 4.12 (qd, $J=7.0$, 1.3 Hz, 1 H), 4.07 (d, $J=16.4$ Hz, 1 H), 1.19 (d, $J=7.0$ Hz, 3 H), 0.97 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 169.0, 168.4, 165.3, 149.3, 145.9, 128.2, 124.1, 117.1, 105.1, 49.9, 48.0, 47.2, 18.2, 14.9. HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_5\text{NaO}_7\text{S}$ [M + Na] $^+$ 448.0897, found 448.0922.

2-((S)-3-methyl-4-((R)-3-methyl-2-(4-nitrophenylsulfonamido)butanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,2,4,2)



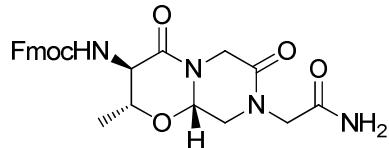
Yield 23.7 mg (75%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.56 (br. s., 1 H), 8.24 (d, $J=9.0$ Hz, 2 H), 7.90 (d, $J=9.0$ Hz, 2 H), 7.59 (s, 1 H), 7.18 (s, 1 H), 6.50 (dd, $J=6.2$, 1.5 Hz, 1 H), 5.93 (d, $J=6.2$ Hz, 1 H), 4.08 - 4.15 (m, 2 H), 4.04 (d, $J=8.8$ Hz, 1 H), 3.99 - 4.02 (m, 1 H), 1.86 (dq, $J=15.5$, 6.7 Hz, 1 H), 1.01 (d, $J=6.7$ Hz, 3 H), 0.95 (d, $J=6.7$ Hz, 3 H), 0.83 (d, $J=6.7$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ 168.9, 167.7, 165.1, 149.1, 145.8, 128.1, 123.9, 116.8, 104.9, 56.9, 49.8, 46.9, 31.0, 18.4, 17.9, 15.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{N}_5\text{NaO}_7\text{S}$ [M + Na] $^+$ 476.1210, found 476.1223.

2-((S)-3-methyl-4-((S)-2-(4-nitrophenylsulfonamido)-3-phenylpropanoyl)-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamide 21(2,2,5,2)



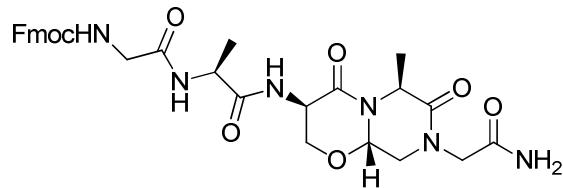
Yield 3.0 mg (15%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.22 (d, $J=8.7$ Hz, 2 H), 7.83 (d, $J=8.7$ Hz, 2 H), 7.41 (br. s., 1 H), 7.10 (s, 7 H), 6.48 (d, $J=5.6$ Hz, 1 H), 5.94 (d, $J=5.9$ Hz, 1 H), 4.60 - 4.50 (m, 2 H), 4.07 - 3.85 (m, 2 H), 2.89 - 2.79 (m, 1 H), 2.66 (dd, $J=13.6$, 9.8 Hz, 1 H), 0.89 (d, $J=7.0$ Hz, 3 H). HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{N}_5\text{O}_7\text{S}$ [M + H] $^+$ 502.1391, found 502.1389.

(9*H*-fluoren-9-yl)methyl ((2*R*,3*R*,9*aS*)-8-(2-amino-2-oxoethyl)-2-methyl-4,7-dioxooctahydro pyrazino[2,1-*b*][1,3]oxazin-3-yl)carbamate 22(2,1,7,3)**



Yield 23.3 mg (54%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6) δ 7.86 - 7.94 (m, 2 H), 7.73 (d, $J=7.2$ Hz, 2 H), 7.48 (br. s., 1 H), 7.38 - 7.45 (m, 2 H), 7.29 - 7.37 (m, 2 H), 7.13 - 7.19 (m, 1 H), 5.22 (dd, $J=8.6$, 3.0 Hz, 1 H), 3.99 - 4.47 (m, 8 H), 3.80 - 3.91 (m, 1 H), 3.59 - 3.74 (m, 2 H), 3.47 (d, $J=3.0$ Hz, 1 H), 1.03 (d, $J=6.1$ Hz, 3 H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.5, 164.4, 164.2, 156.8, 144.0, 143.8, 140.8, 127.7, 127.1, 125.4, 125.3, 120.20, 120.16, 80.4, 72.1, 65.8, 53.6, 50.8, 48.8, 46.8, 43.8, 15.7. HRMS (ESI-TOF) m/z calcd for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_6$ [M + H] $^+$ 479.1931, found 479.1934.

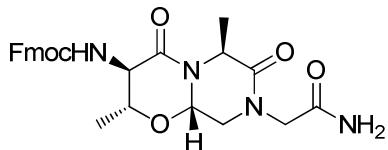
(9*H*-fluoren-9-yl)methyl (2-(((*S*)-1-(((3*R*,6*S*,9*aS*)-8-(2-amino-2-oxoethyl)-6-methyl-4,7-dioxooctahdropyrazino[2,1-*b*][1,3]oxazin-3-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl carbamate 22(2,2,6,14)**



Yield 42.0 mg (77%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.48 (d, $J=8.5$ Hz, 1 H), 8.05 (d, $J=7.3$ Hz, 1 H), 7.88 (d, $J=7.3$ Hz, 2 H), 7.70 (d, $J=7.3$ Hz, 2 H), 7.51 (t, $J=6.2$ Hz, 1 H), 7.46 (br. s., 1 H), 7.41 (t, $J=7.3$ Hz, 2 H), 7.33 (t, $J=7.3$ Hz, 2 H), 7.12 (br. s., 1 H), 5.40 (dd, $J=7.5$, 3.7 Hz, 1 H), 4.71 (q, $J=7.3$ Hz, 1 H), 4.48 (dt, $J=8.2$, 5.3 Hz, 1 H), 4.33 (t,

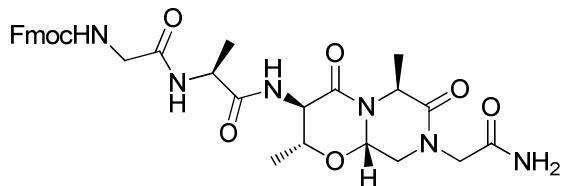
$J=7.3$ Hz, 1 H), 4.28 (d, $J=7.0$ Hz, 2 H), 4.22 (t, $J=6.9$ Hz, 1 H), 4.00 - 4.04 (m, 2 H), 3.86 (d, $J=16.7$ Hz, 1 H), 3.75 (dd, $J=11.2$, 5.3 Hz, 1 H), 3.63 - 3.69 (m, 3 H), 3.54 - 3.58 (m, 1 H), 1.33 (d, $J=7.0$ Hz, 3 H), 1.22 (d, $J=7.0$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 172.6, 169.6, 168.8, 167.9, 164.2, 156.7, 143.9, 140.8, 127.8, 127.3, 125.4, 120.3, 78.2, 65.9, 65.6, 50.7, 49.8, 49.2, 48.1, 48.0, 46.7, 43.4, 18.7, 17.2. HRMS (ESI-TOF) m/z calcd for $\text{C}_{30}\text{H}_{34}\text{N}_6\text{NaO}_8$ [M + Na] $^+$ 629.2330, found 629.2364.

(9*H*-fluoren-9-yl)methyl ((2*R*,3*R*,6*S*,9*aS*)-8-(2-amino-2-oxoethyl)-2,6-dimethyl-4,7-dioxoocta hydropyrazino[2,1-*b*][1,3]oxazin-3-yl)carbamate 22(2,2,7,3)**



Yield 65.0 mg (90%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 7.93 (d, $J=9.4$ Hz, 1 H), 7.89 (d, $J=7.6$ Hz, 2 H), 7.74 (dd, $J=7.6$, 2.3 Hz, 2 H), 7.44 (s, 1 H), 7.41 (t, $J=7.5$ Hz, 2 H), 7.33 (m, $J=7.4$, 7.4, 2.9, 1.0 Hz, 2 H), 7.13 (s, 1 H), 5.31 (dd, $J=8.5$, 3.5 Hz, 1 H), 4.64 (q, $J=7.2$ Hz, 1 H), 4.39 (dd, $J=10.4$, 7.2 Hz, 1 H), 4.31 (dd, $J=10.6$, 7.0 Hz, 1 H), 4.23 (t, $J=6.9$ Hz, 1 H), 4.09 - 4.16 (m, 3 H), 3.77 (d, $J=16.4$ Hz, 1 H), 3.68 (dd, $J=11.6$, 8.7 Hz, 1 H), 3.44 (dd, $J=11.4$, 3.5 Hz, 1 H), 1.34 (d, $J=7.3$ Hz, 3 H), 1.03 (d, $J=6.2$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.4, 167.4, 163.6, 156.9, 143.9, 140.8, 127.7, 127.1, 125.3, 120.1, 78.2, 71.6, 65.8, 53.9, 51.4, 49.4, 49.1, 46.8, 17.2, 15.6. HRMS (ESI-TOF) m/z calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_6$ [M + Na] $^+$ 515.1901, found 515.1908.

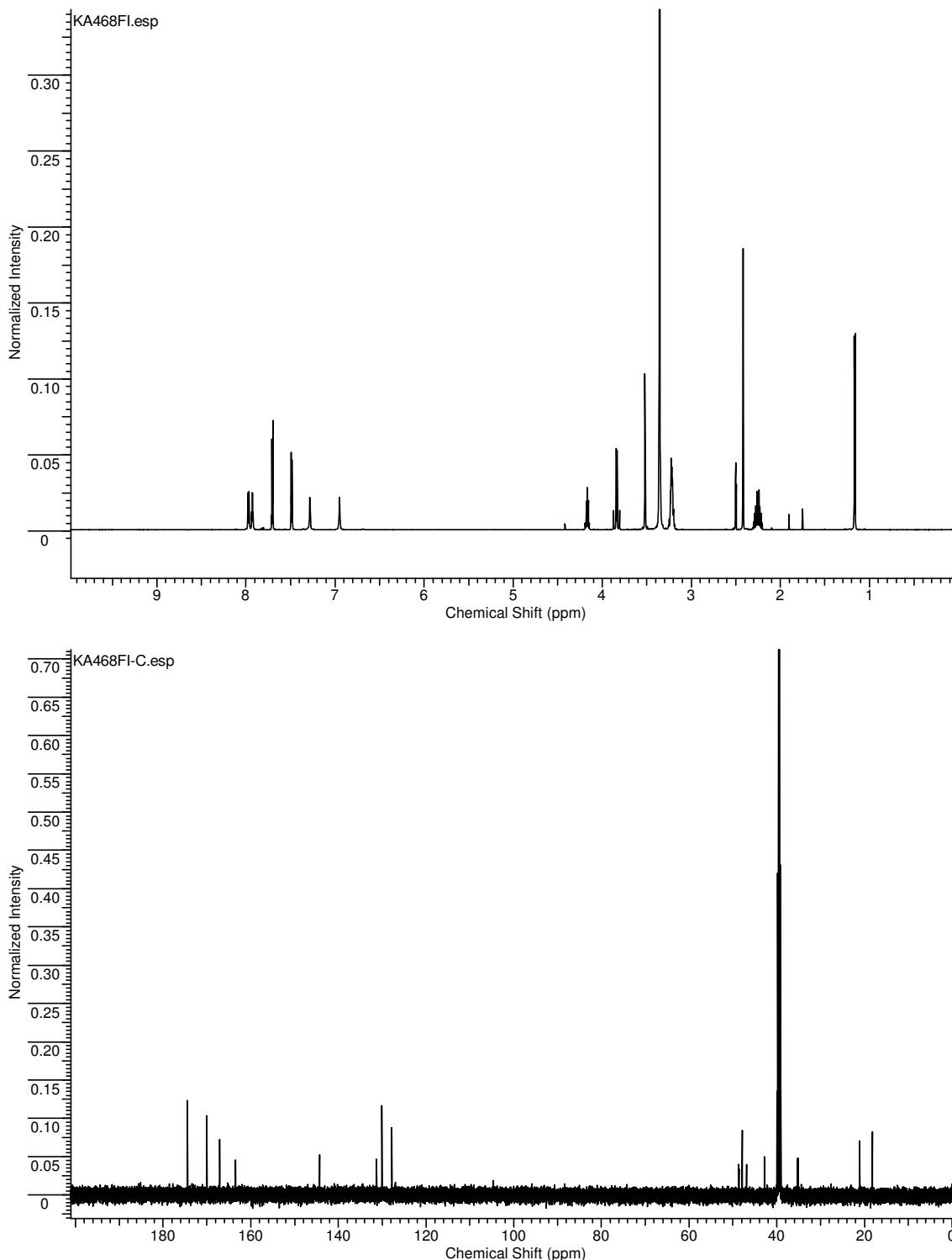
(9*H*-fluoren-9-yl)methyl (2-(((*S*)-1-(((2*R*,3*R*,6*S*,9*aS*)-8-(2-amino-2-oxoethyl)-2,6-dimethyl-4,7-dioxoocta hydropyrazino[2,1-*b*][1,3]oxazin-3-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamate 22(2,2,7,14)**



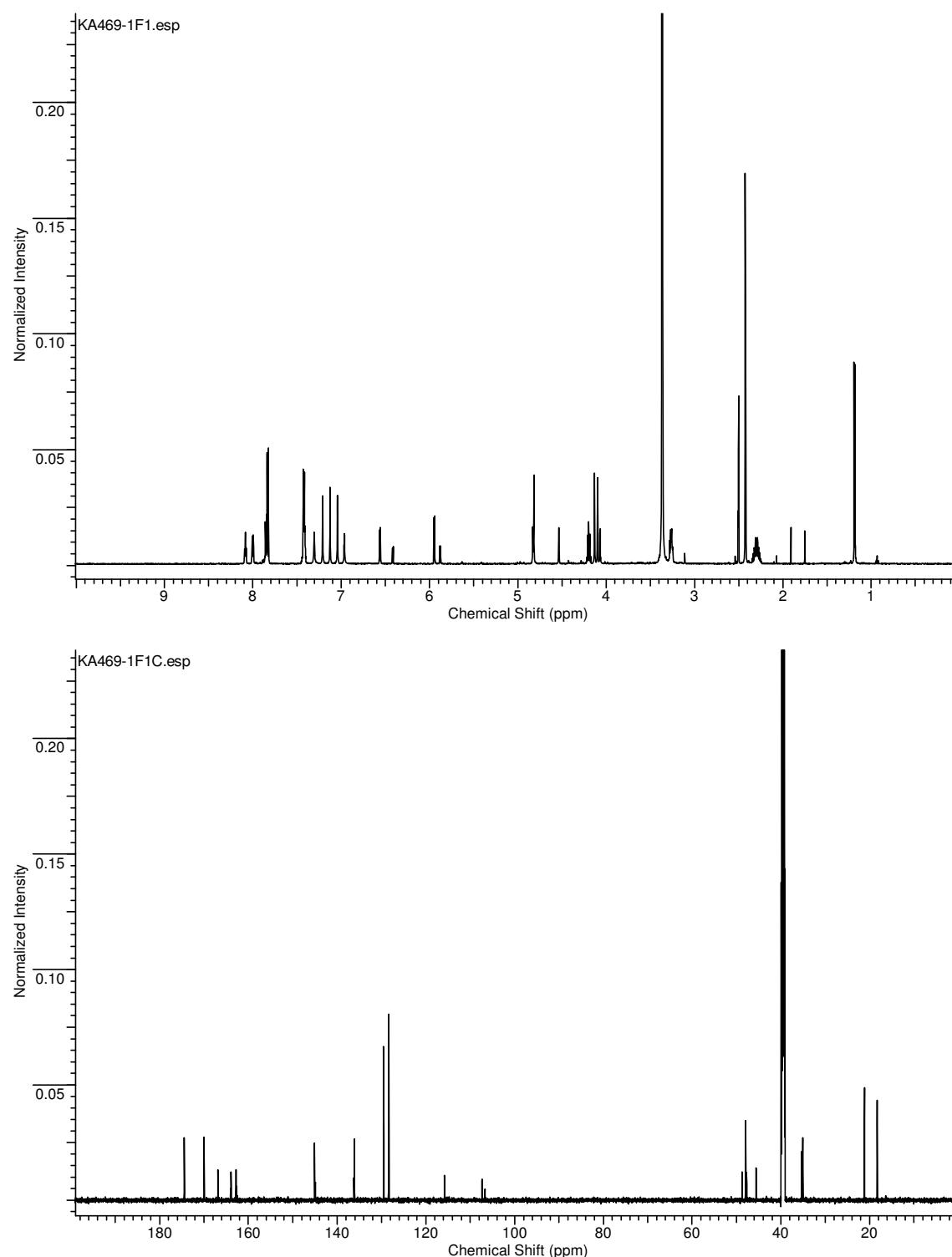
Yield 86.0 mg (92%) of amorphous solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.35 (d, $J=9.1$ Hz, 1 H), 8.07 (d, $J=7.3$ Hz, 1 H), 7.88 (d, $J=7.6$ Hz, 2 H), 7.71 (d, $J=7.3$ Hz, 2 H), 7.54 (t, $J=6.2$ Hz, 1 H), 7.47 (s, 1 H), 7.41 (t, $J=7.3$ Hz, 2 H), 7.33 (t, $J=7.5$ Hz, 2 H), 7.14 (s, 1 H), 5.33 (dd, $J=8.5$, 3.5 Hz, 1 H), 4.65 (q, $J=6.9$ Hz, 1 H), 4.41 (dd, $J=9.1$, 2.9 Hz, 1 H), 4.35 - 4.40 (m, 1 H), 4.24 - 4.32 (m, 2 H), 4.22 (t, $J=7.0$ Hz, 1 H), 4.11 - 4.17 (m, 2 H), 3.78 (d, $J=16.4$ Hz, 1 H), 3.65 - 3.70 (m, 1 H), 3.60 - 3.65 (m, 2 H), 3.51 (dd, $J=11.6$, 3.4 Hz, 1 H), 1.33 (d, $J=7.0$ Hz, 3 H), 1.22 (d, $J=7.0$ Hz, 3 H), 1.01 (d, $J=6.2$ Hz, 3 H). ^{13}C NMR (151 MHz, DMSO- d_6): δ

172.9, 169.4, 168.7, 167.5, 163.7, 156.5, 143.9, 140.8, 127.7, 127.1, 125.3, 120.2, 78.2, 71.6, 65.8, 51.8, 51.5, 49.5, 49.1, 48.1, 46.7, 43.3, 18.5, 17.2, 15.7. HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{37}N_6O_8$ [M + H]⁺ 621.2667, found 621.2675.

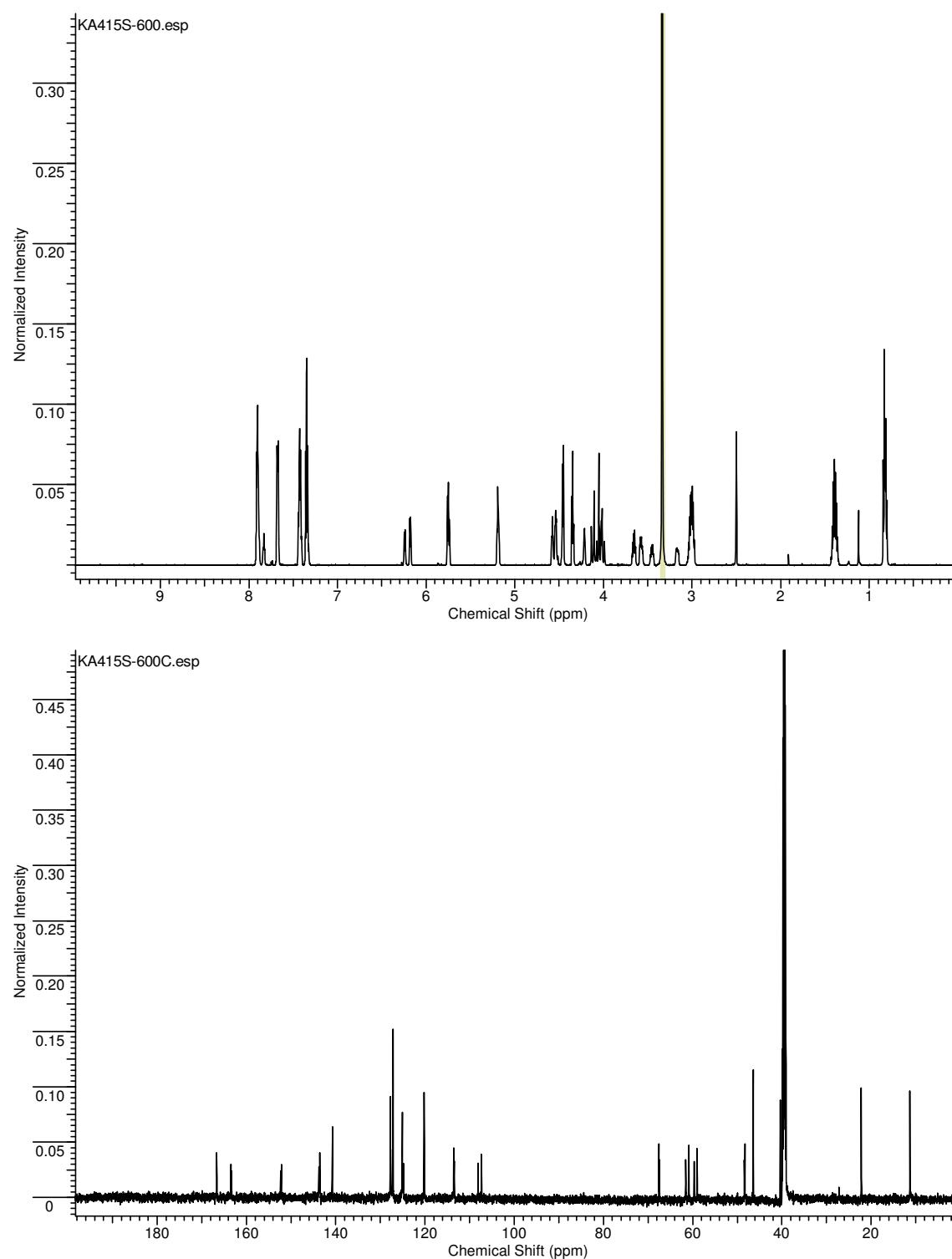
¹H and ¹³C NMR spectra (*d*₆-DMSO) for compound 7



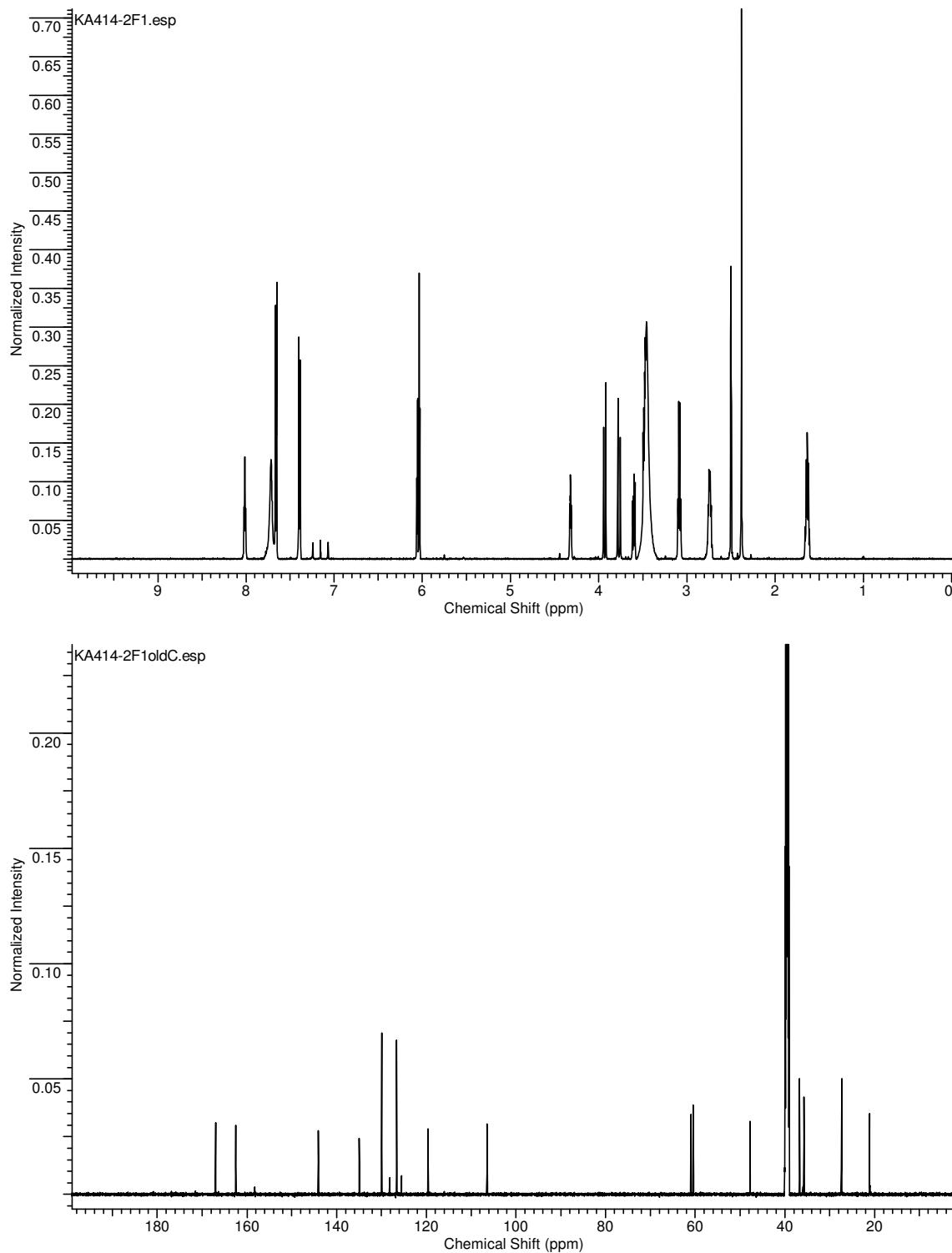
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 9



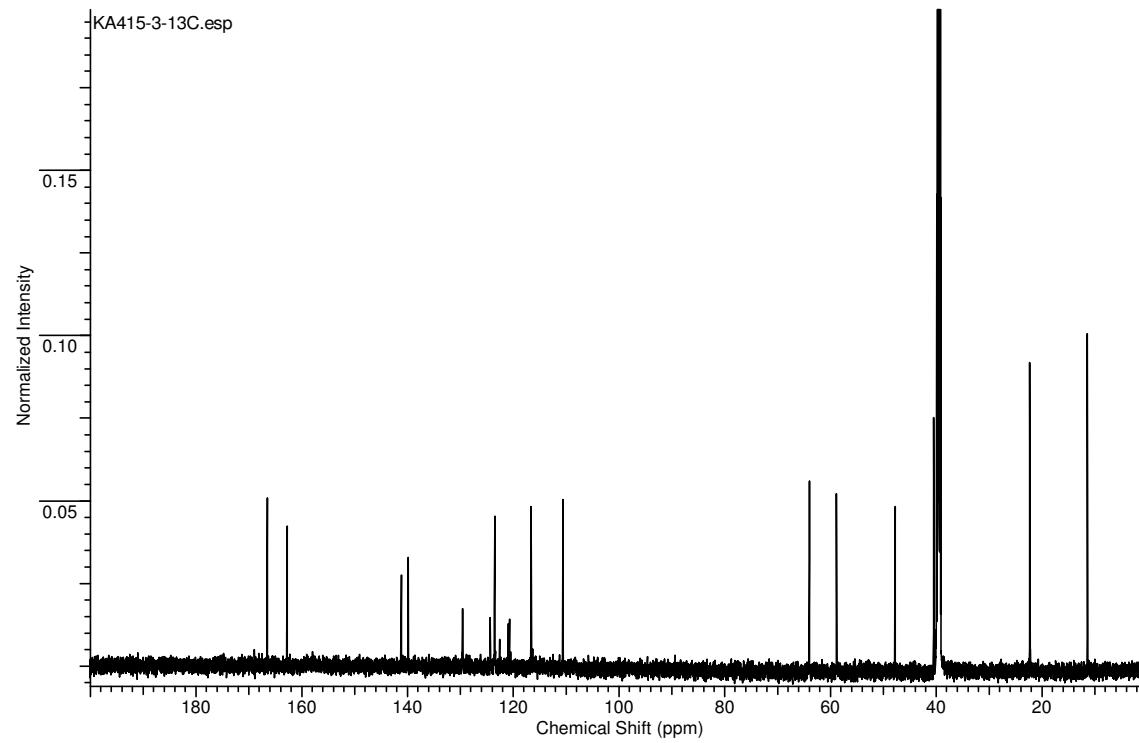
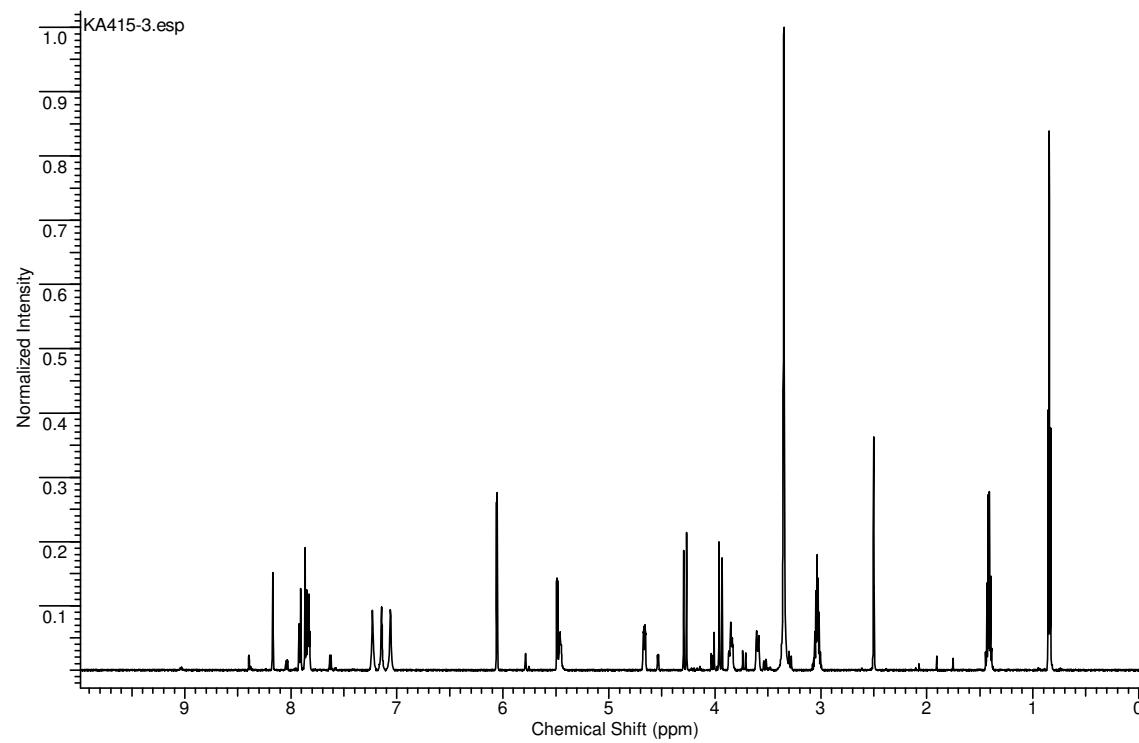
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 11a



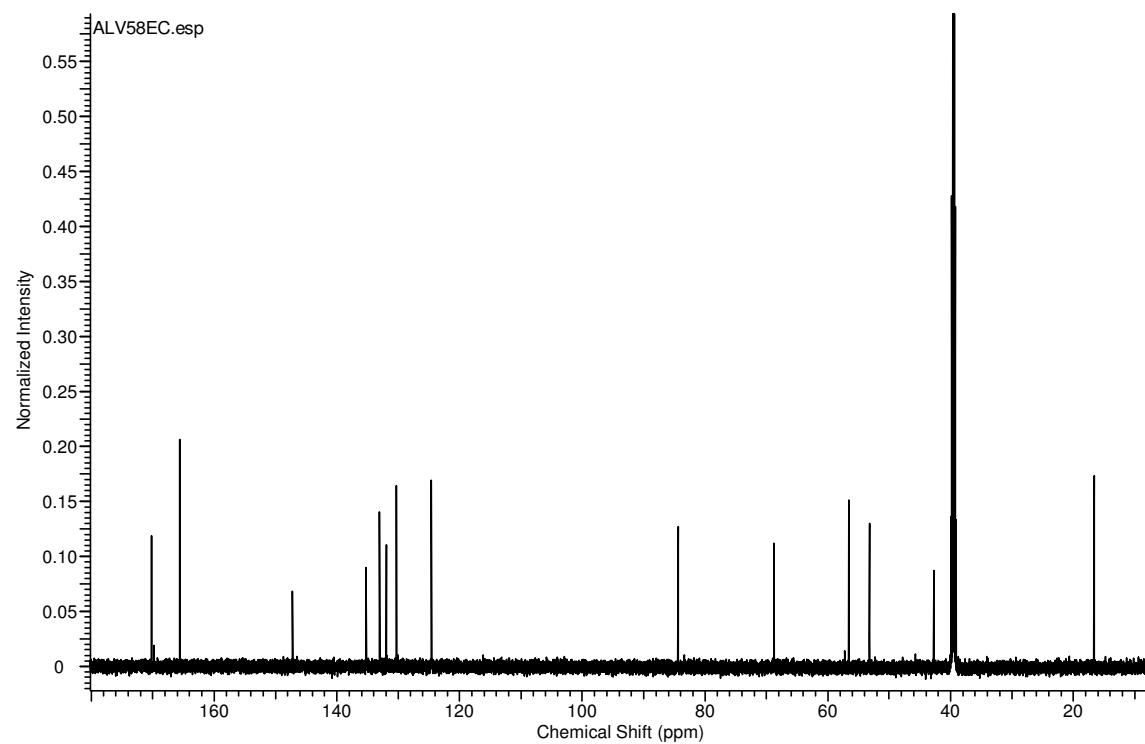
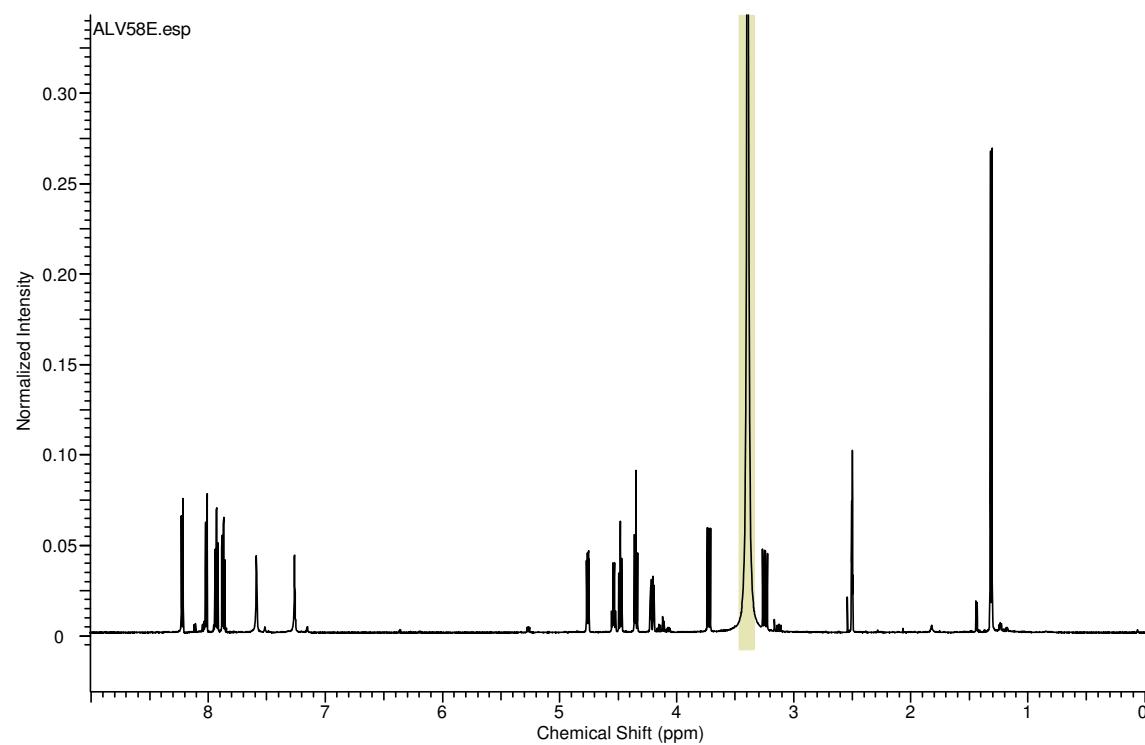
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 11b



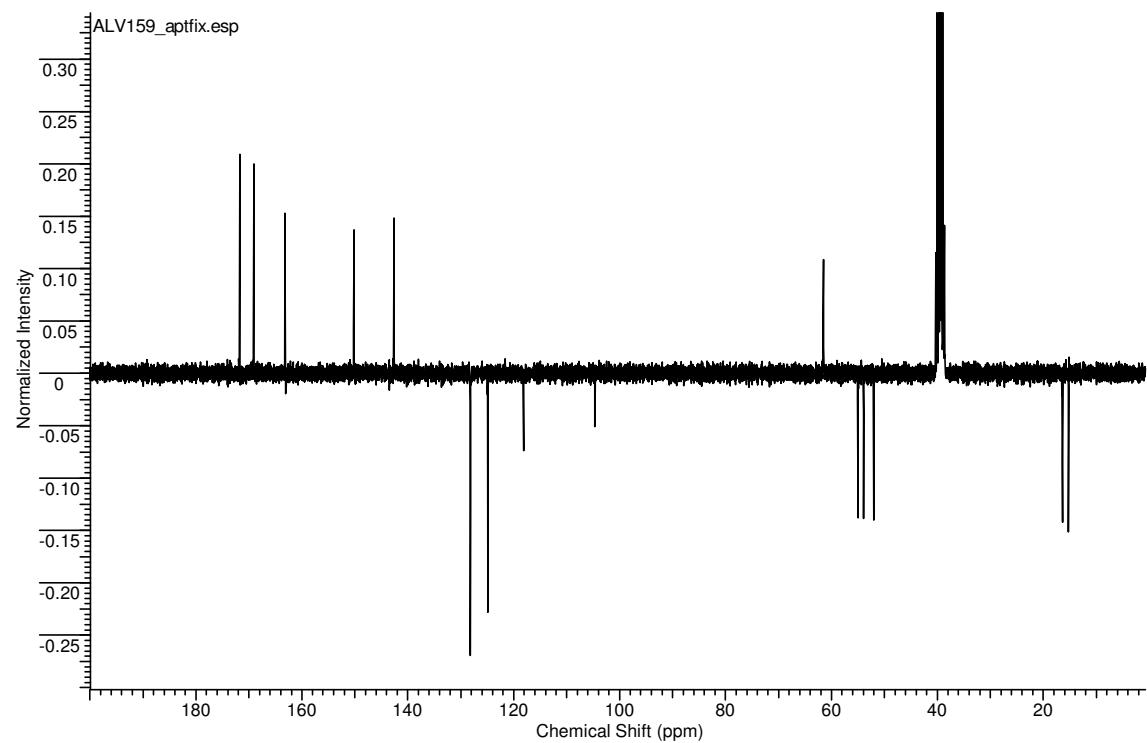
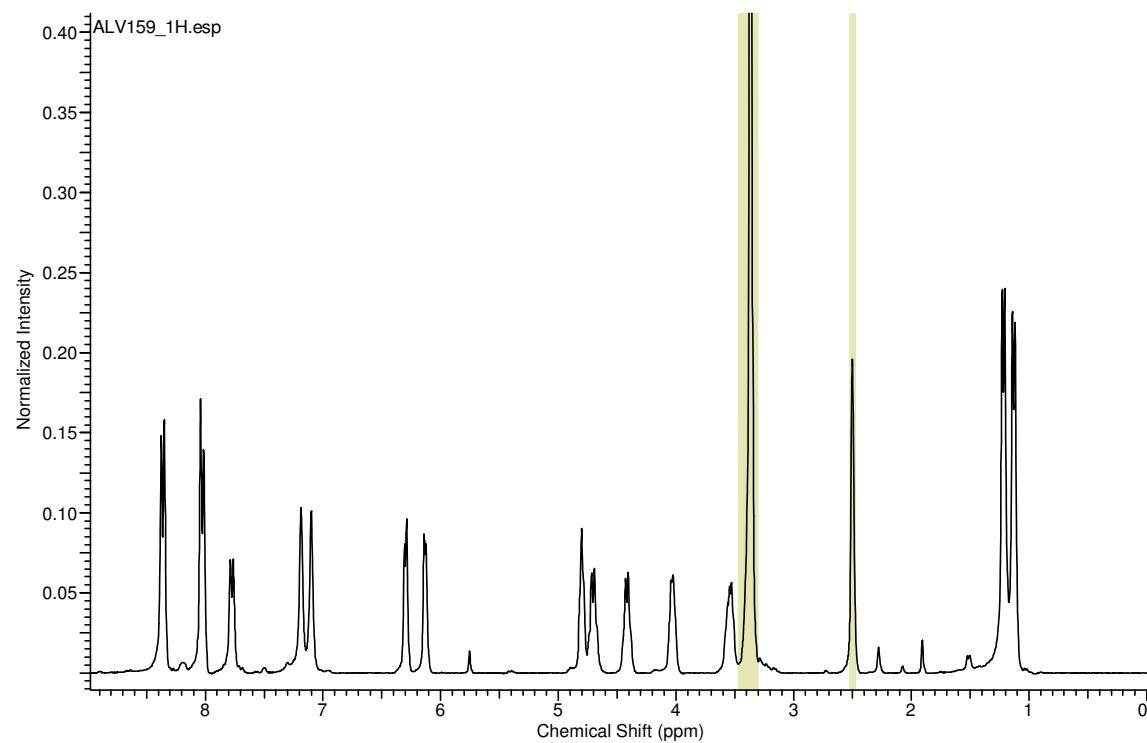
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 11c



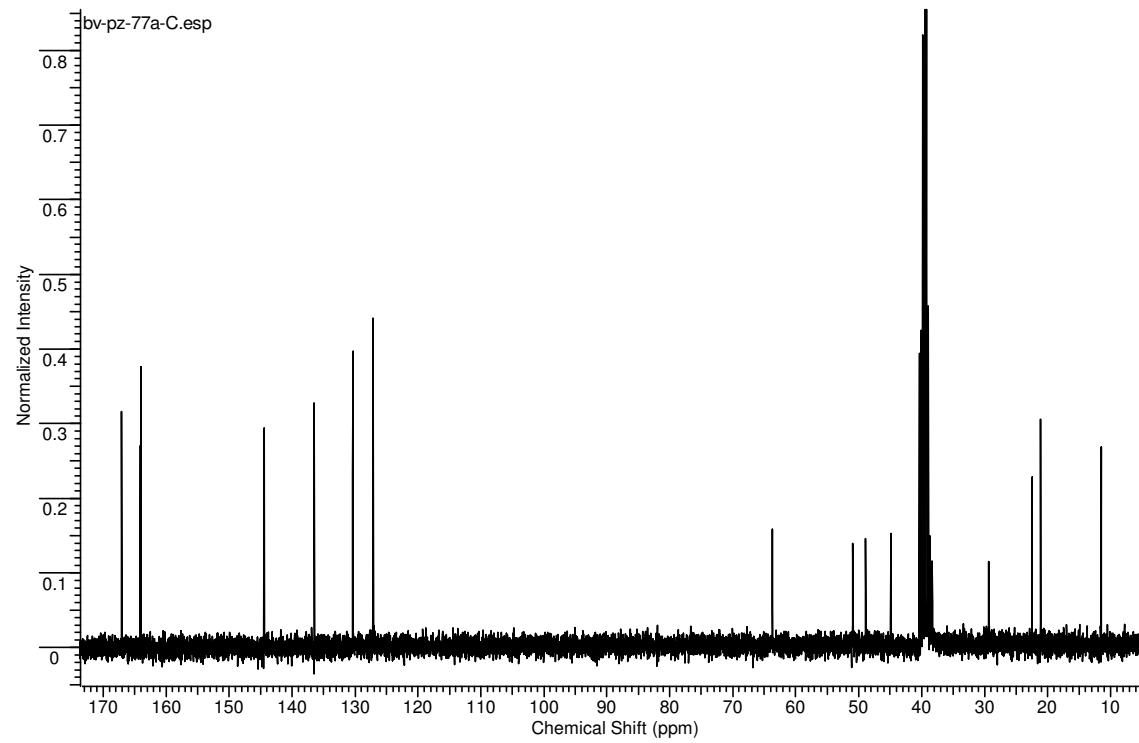
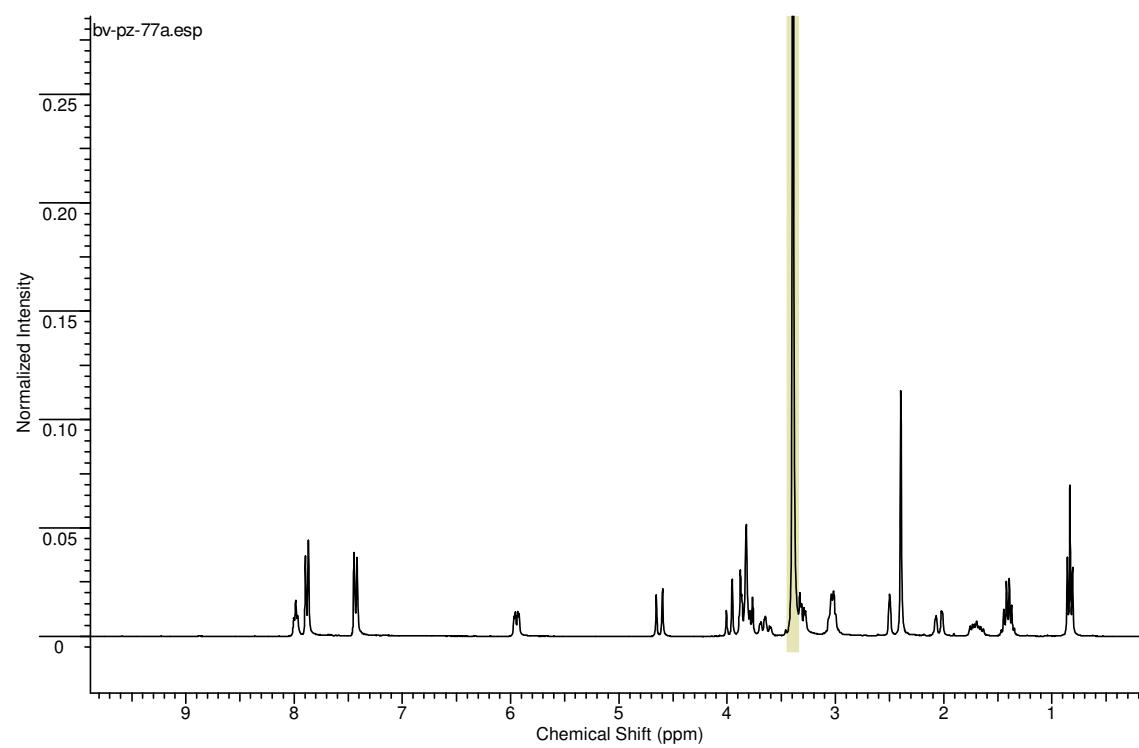
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 13



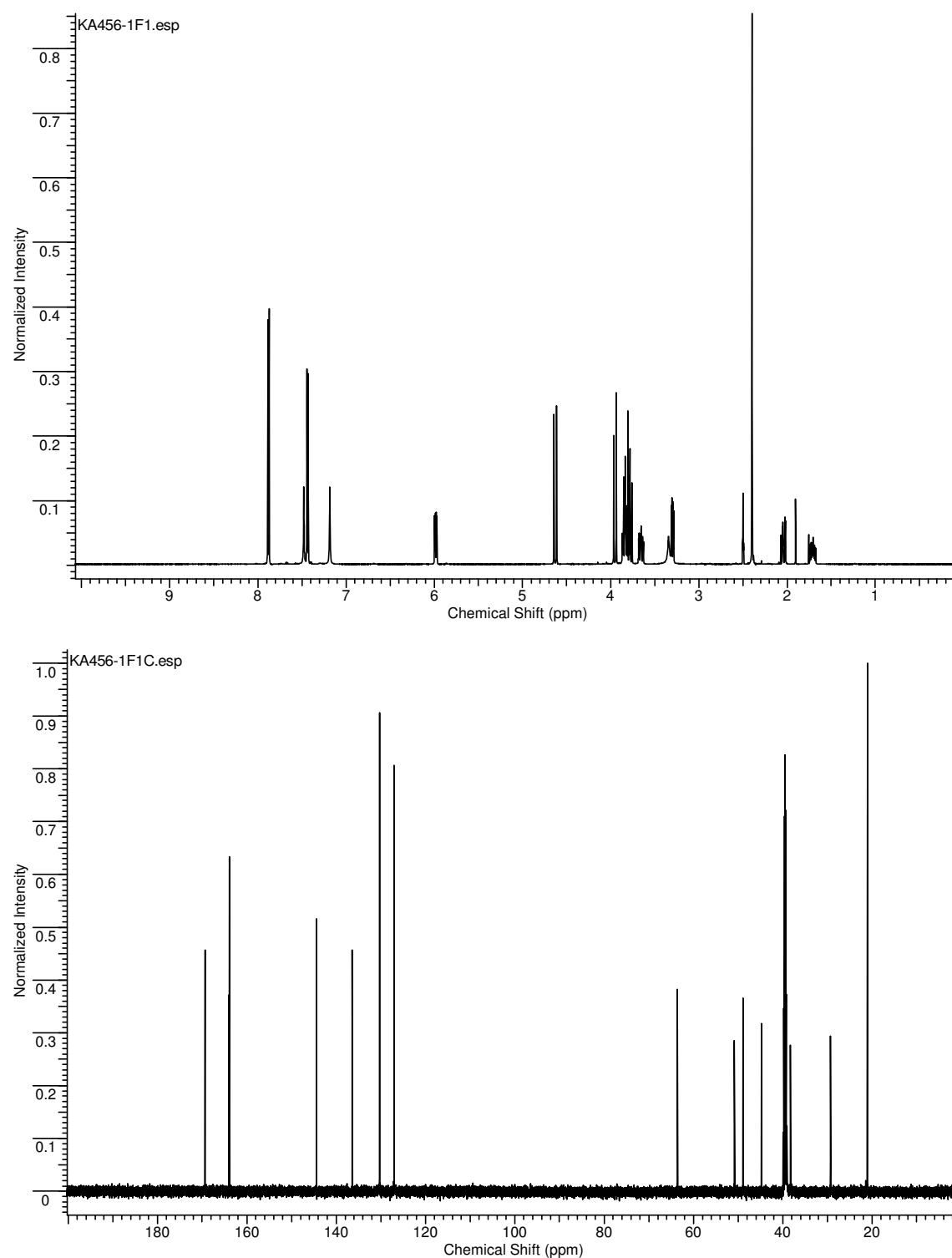
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 15



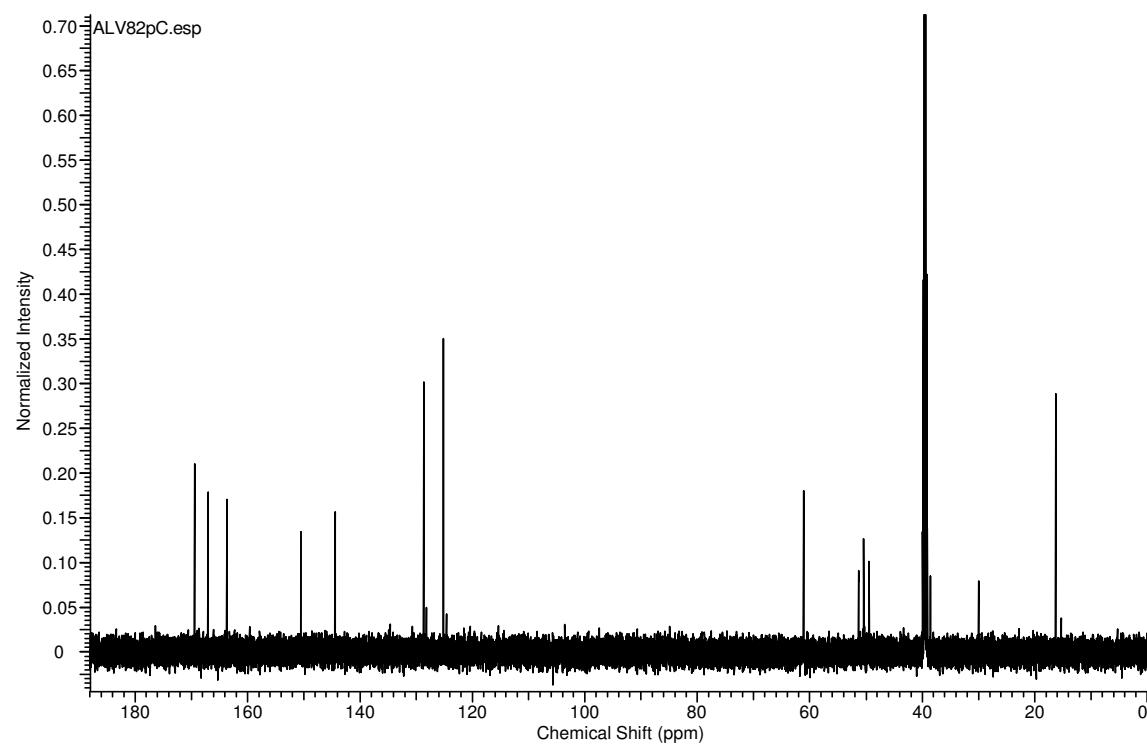
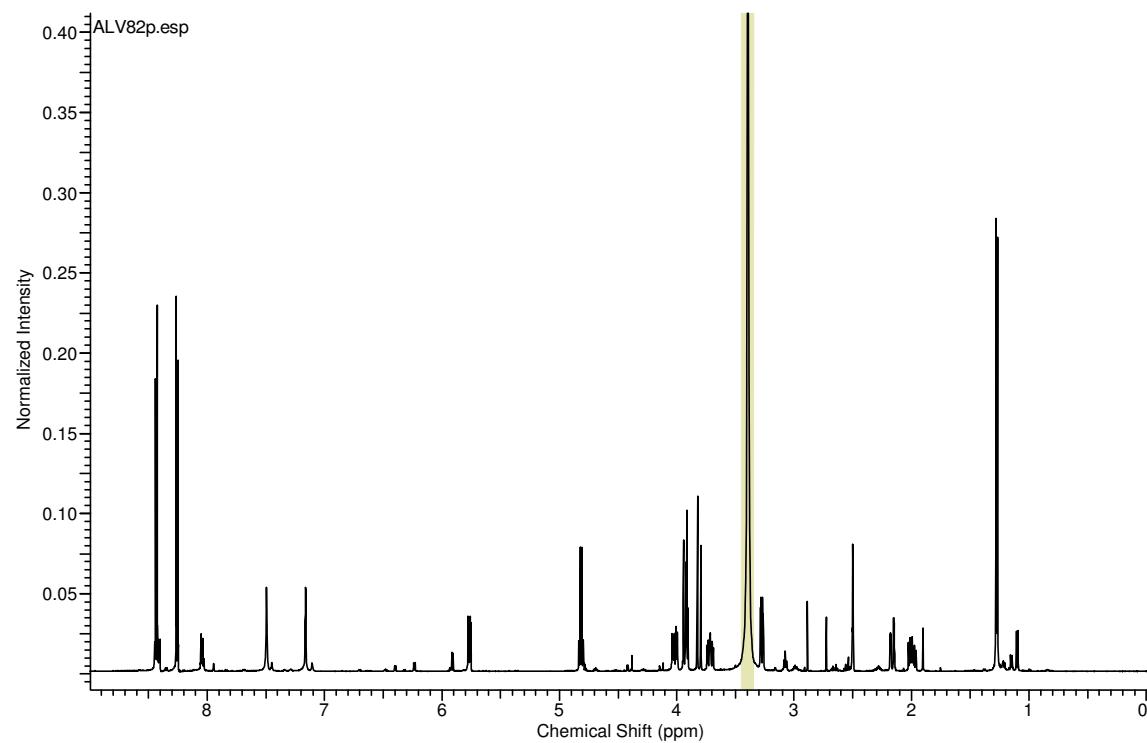
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(1,1,1,1)



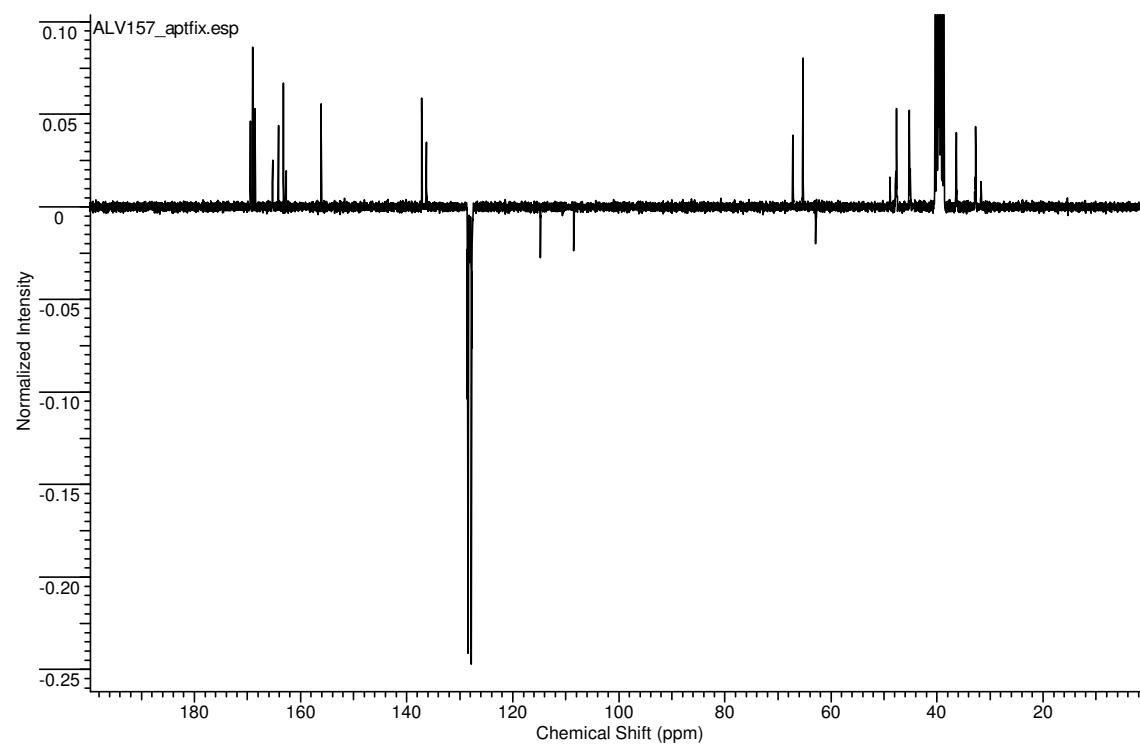
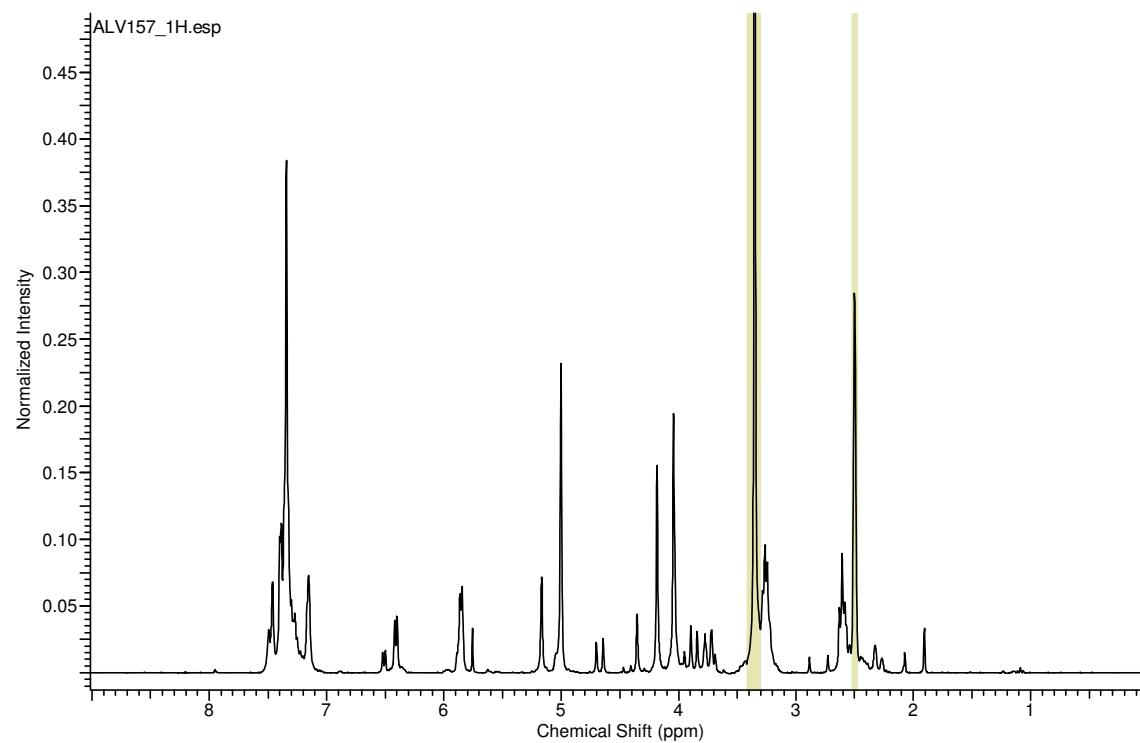
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,1,1,1)



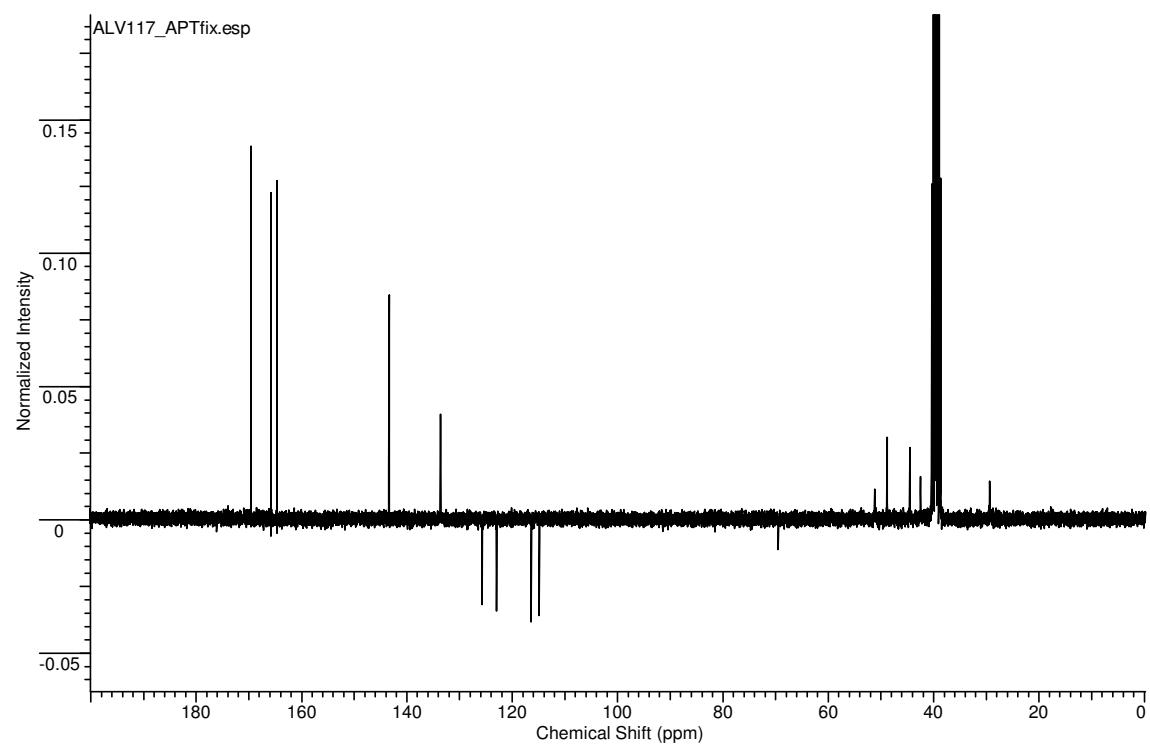
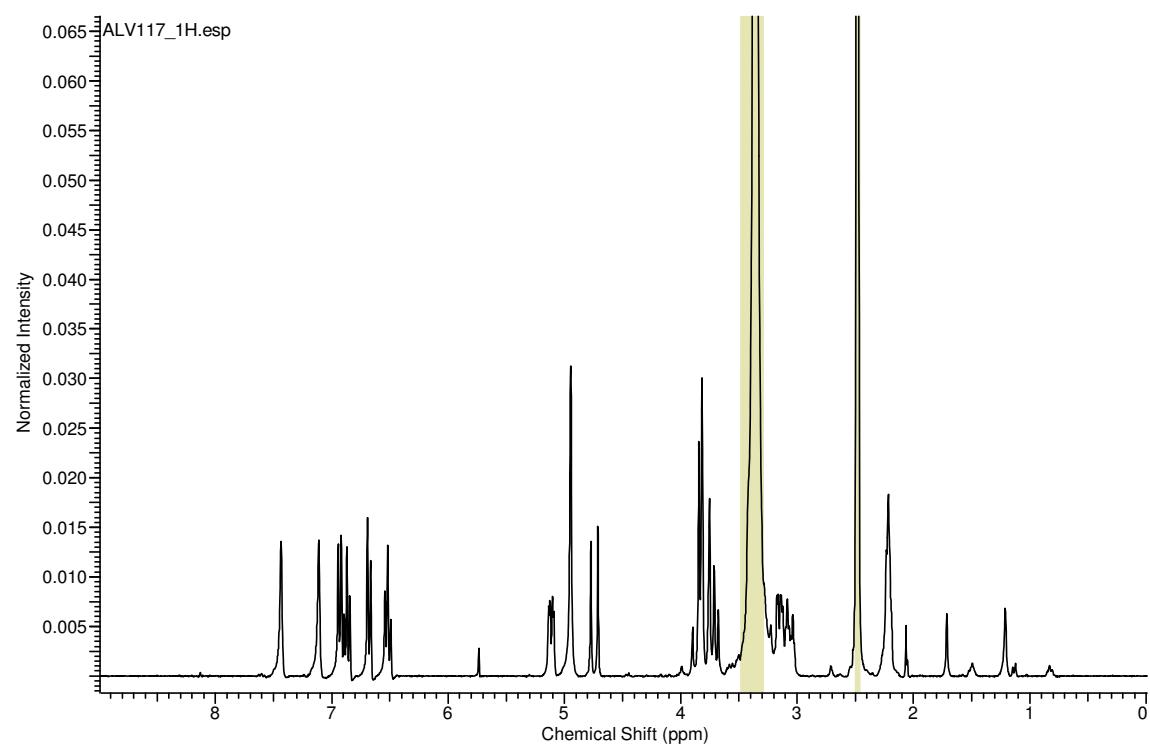
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,1,1,2)



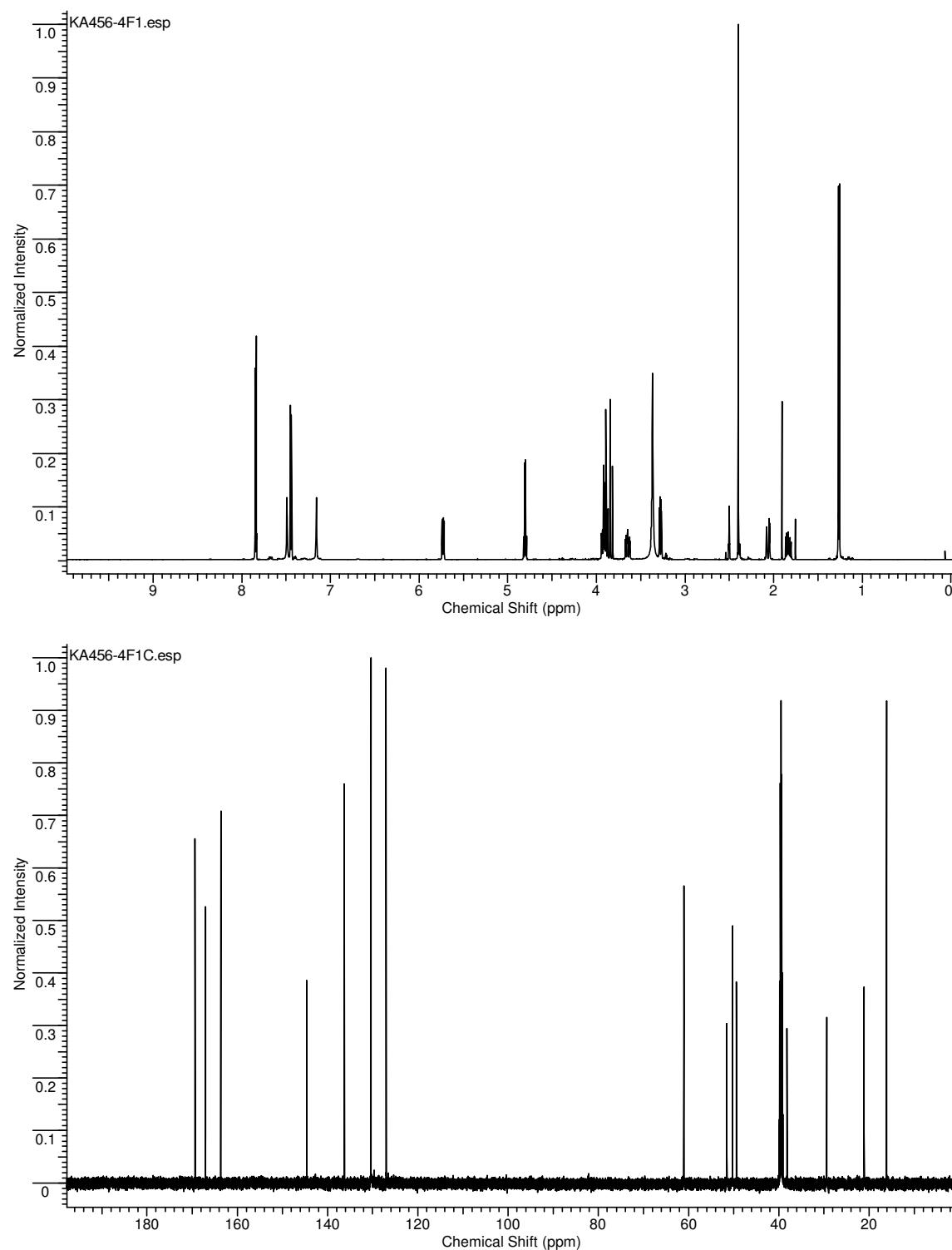
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,1,1,4) + 18(2,1,1,4)



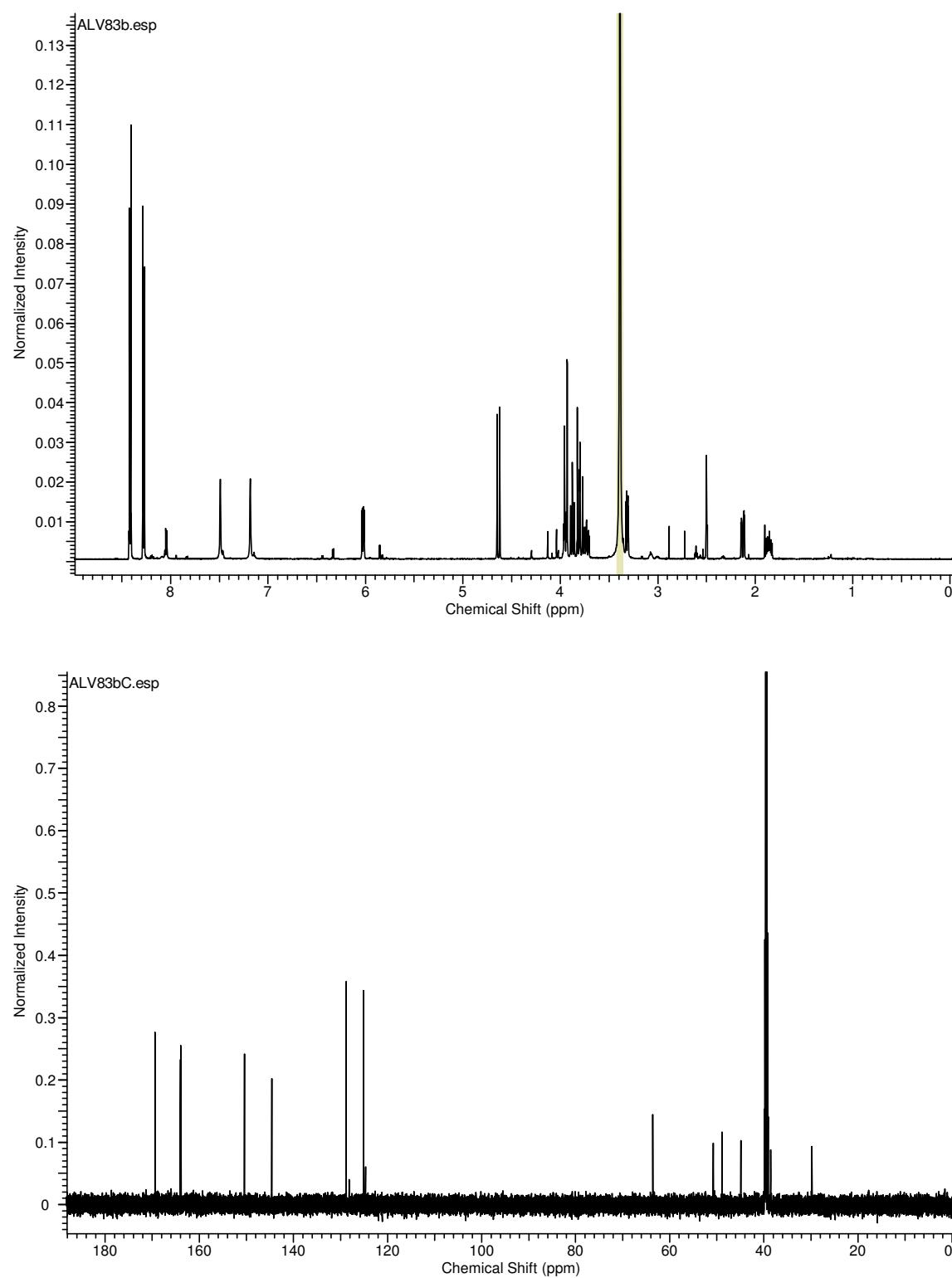
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,1,1,7)



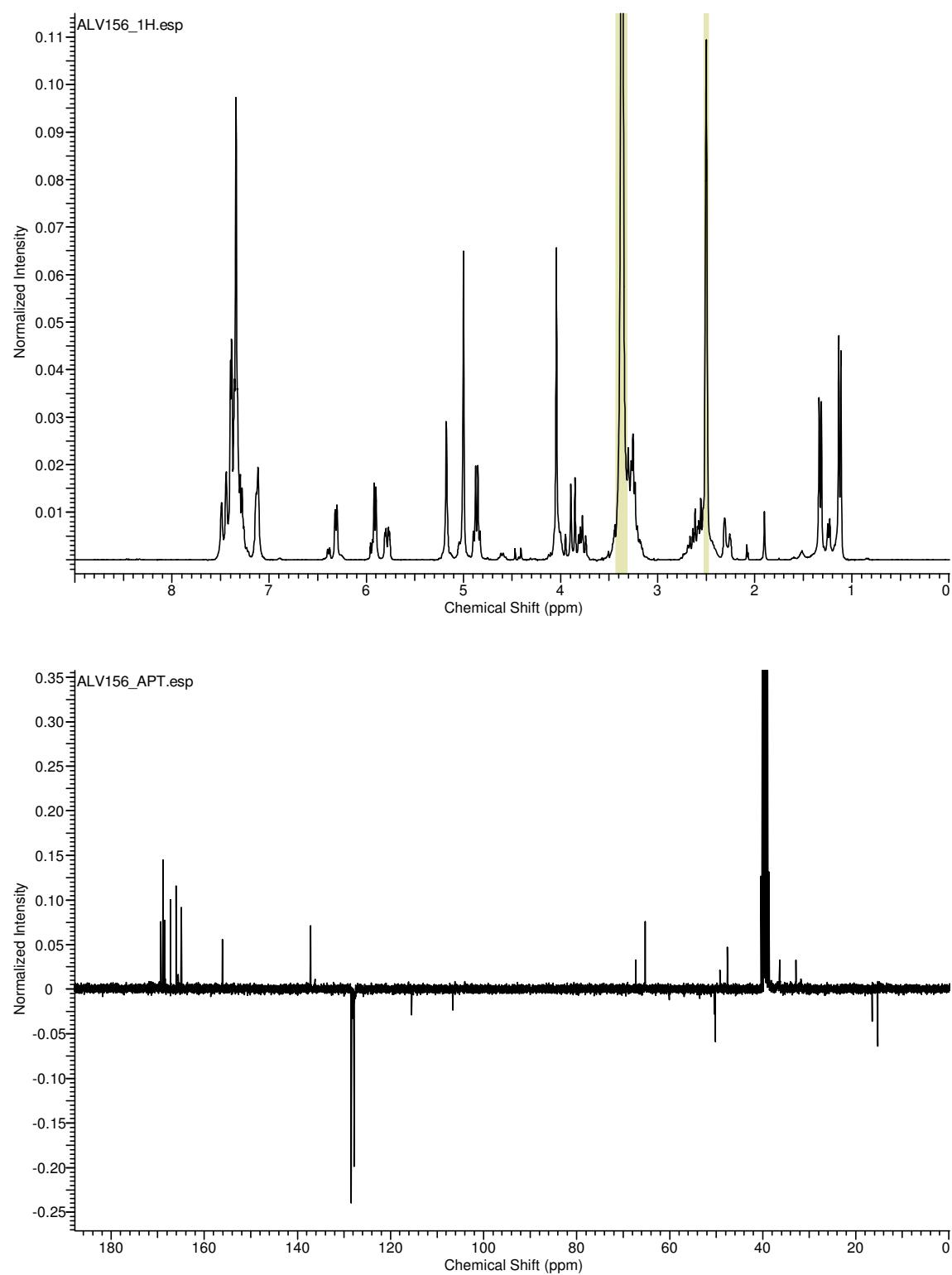
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,2,1,1)



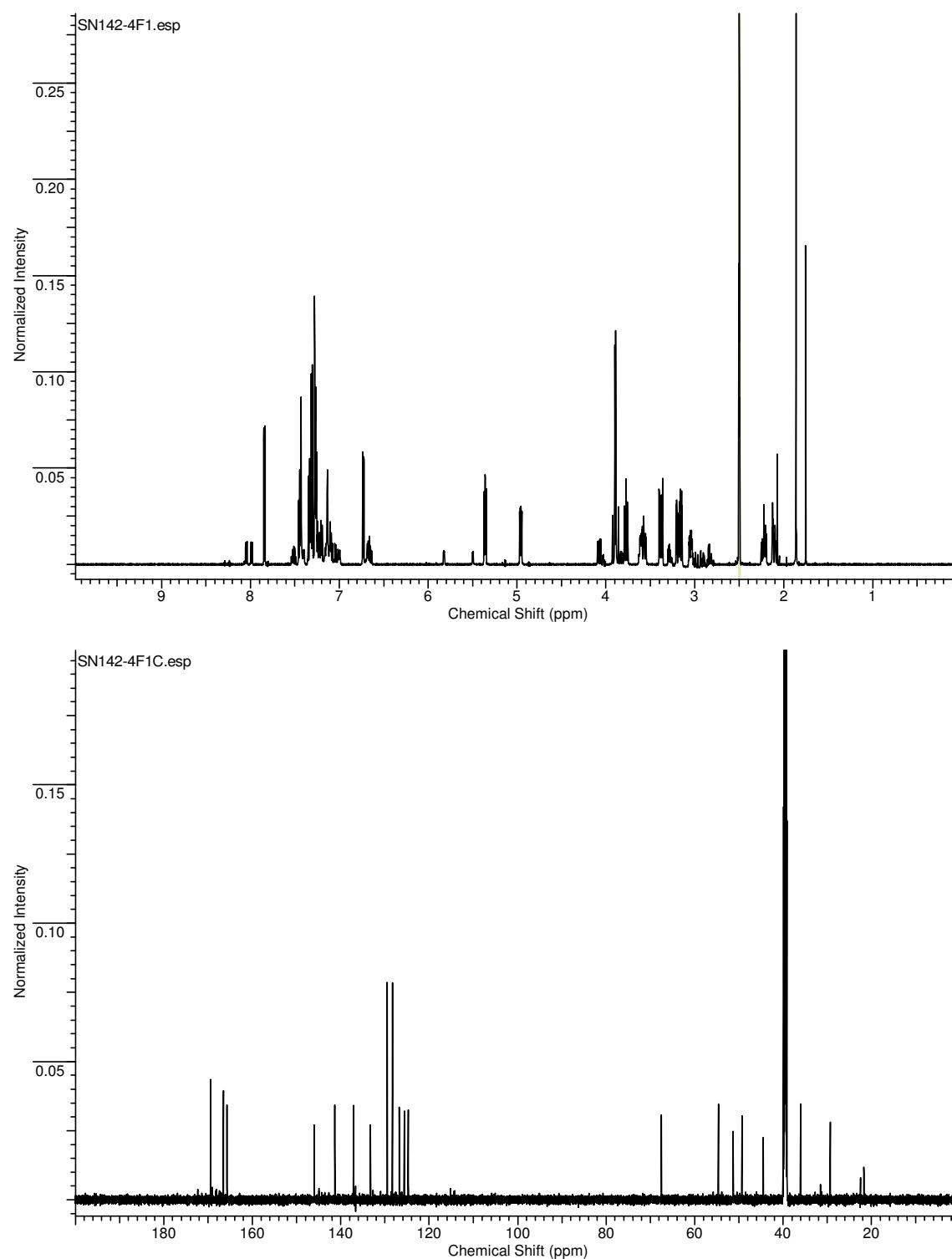
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,2,1,2)



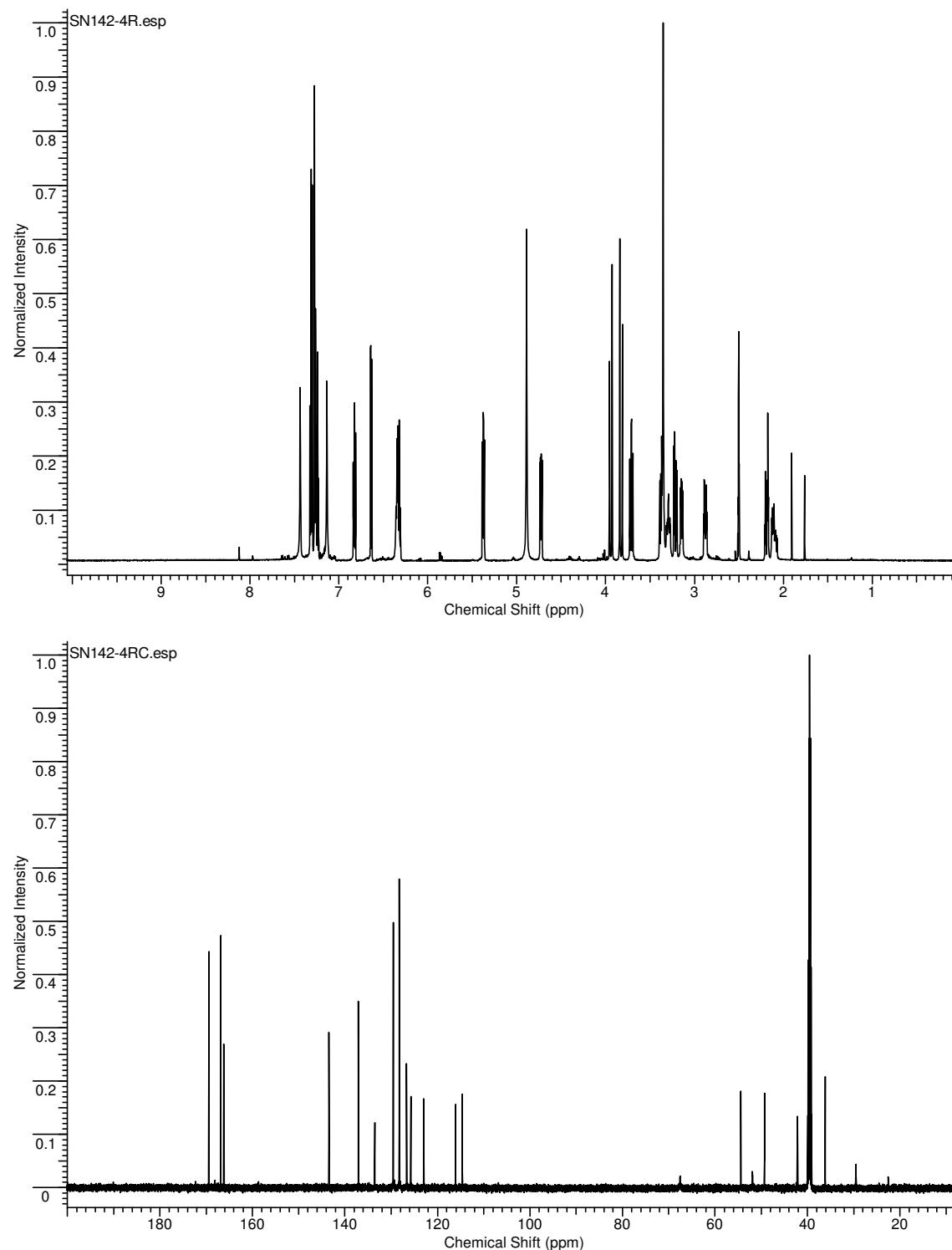
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,2,1,4) + 18(2,2,1,4)



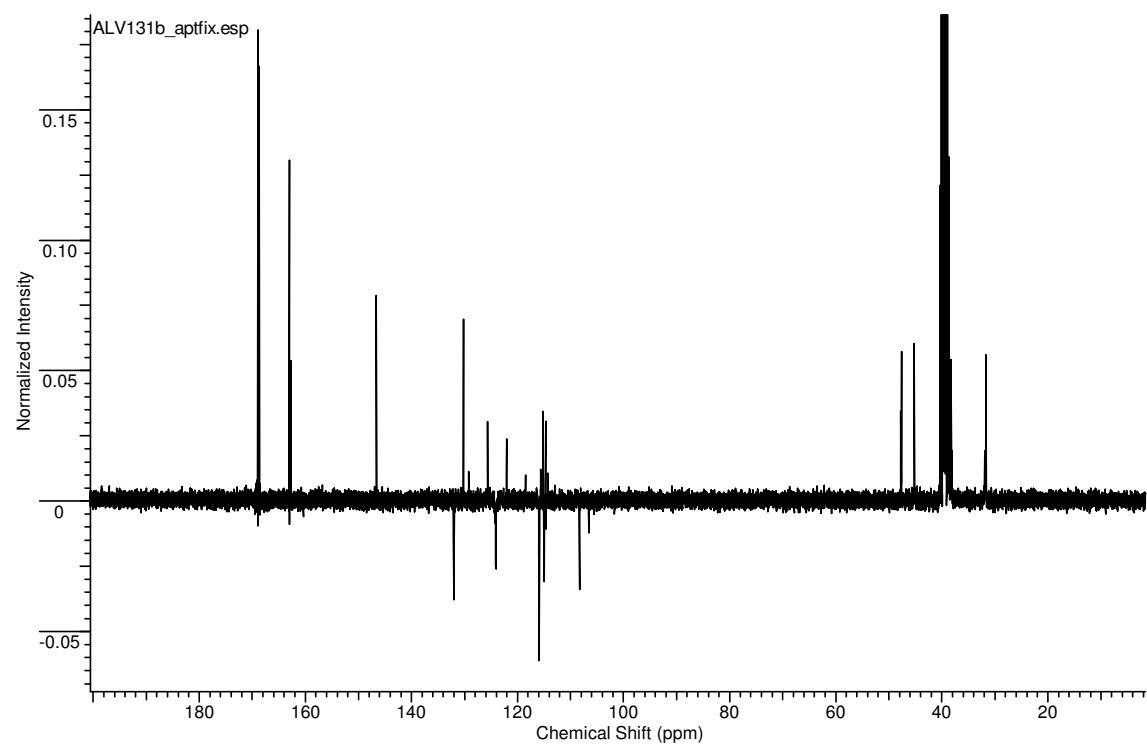
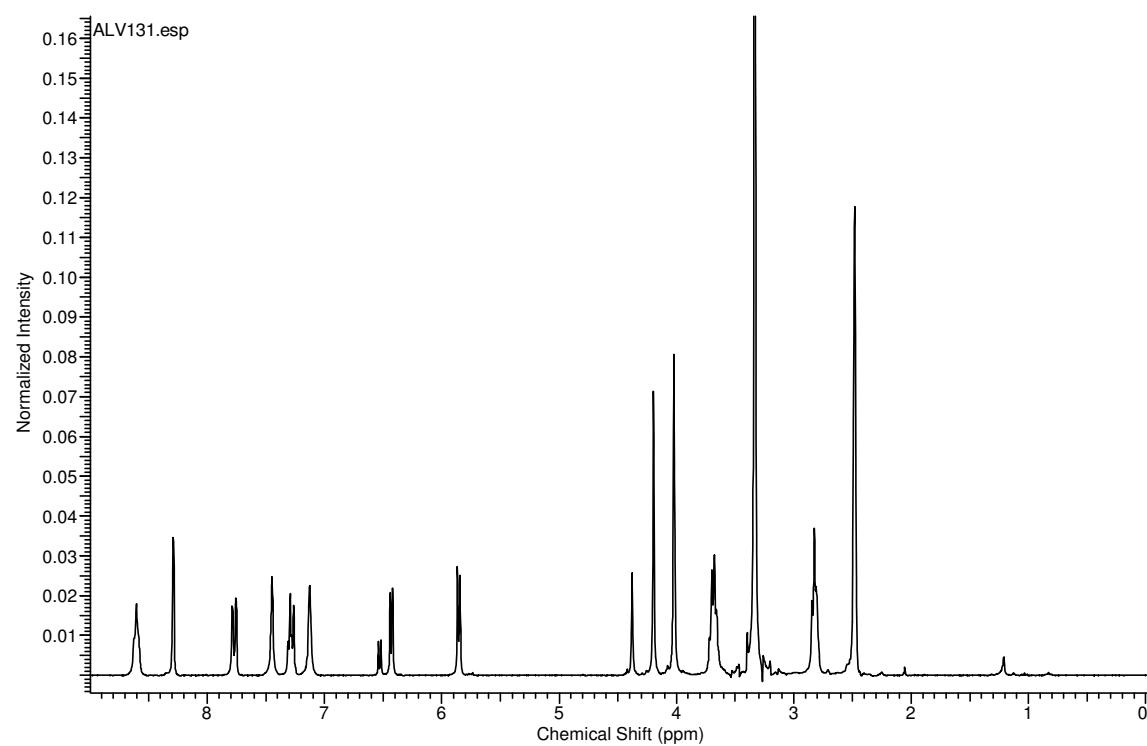
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,3,1,6)



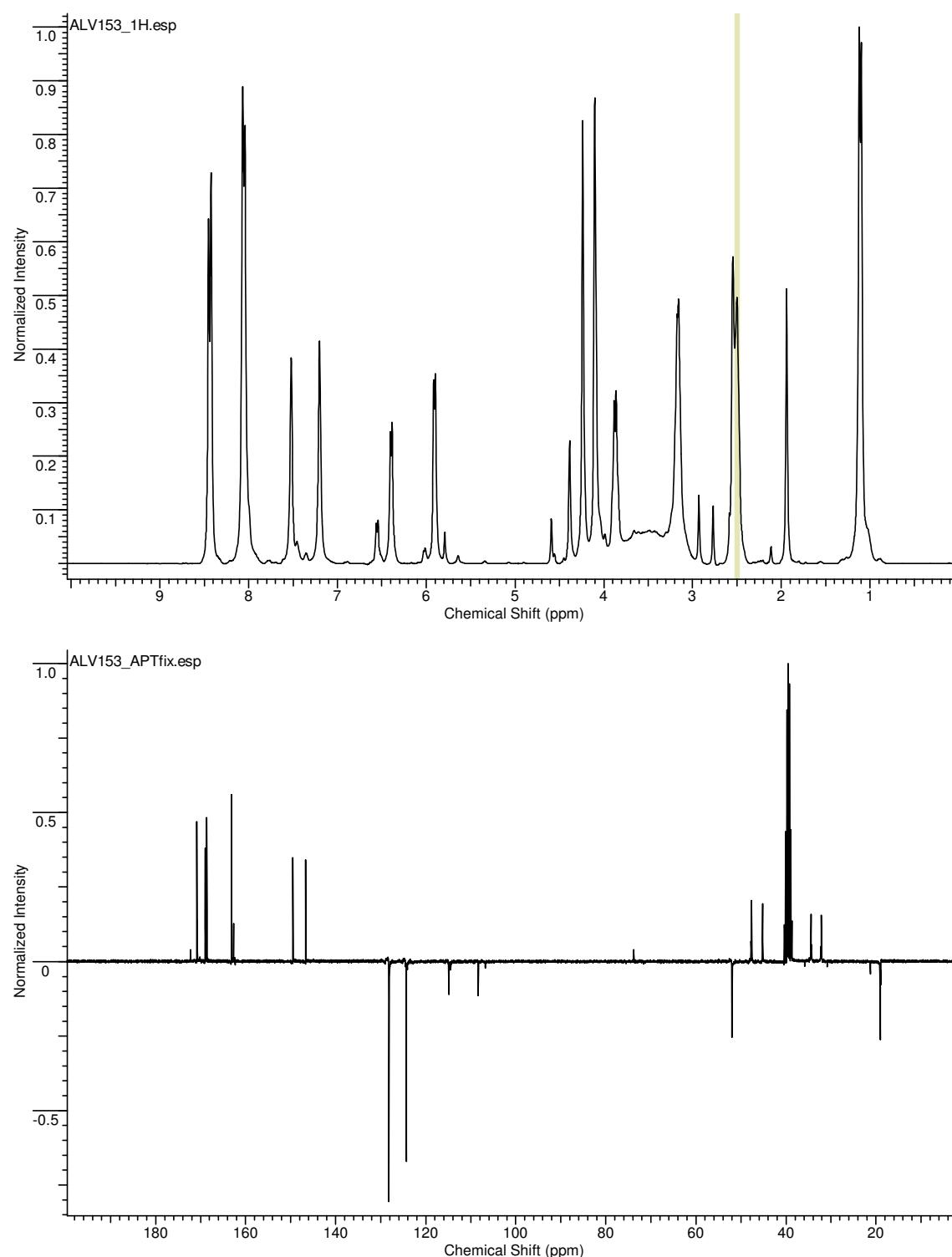
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 17(2,3,1,7)



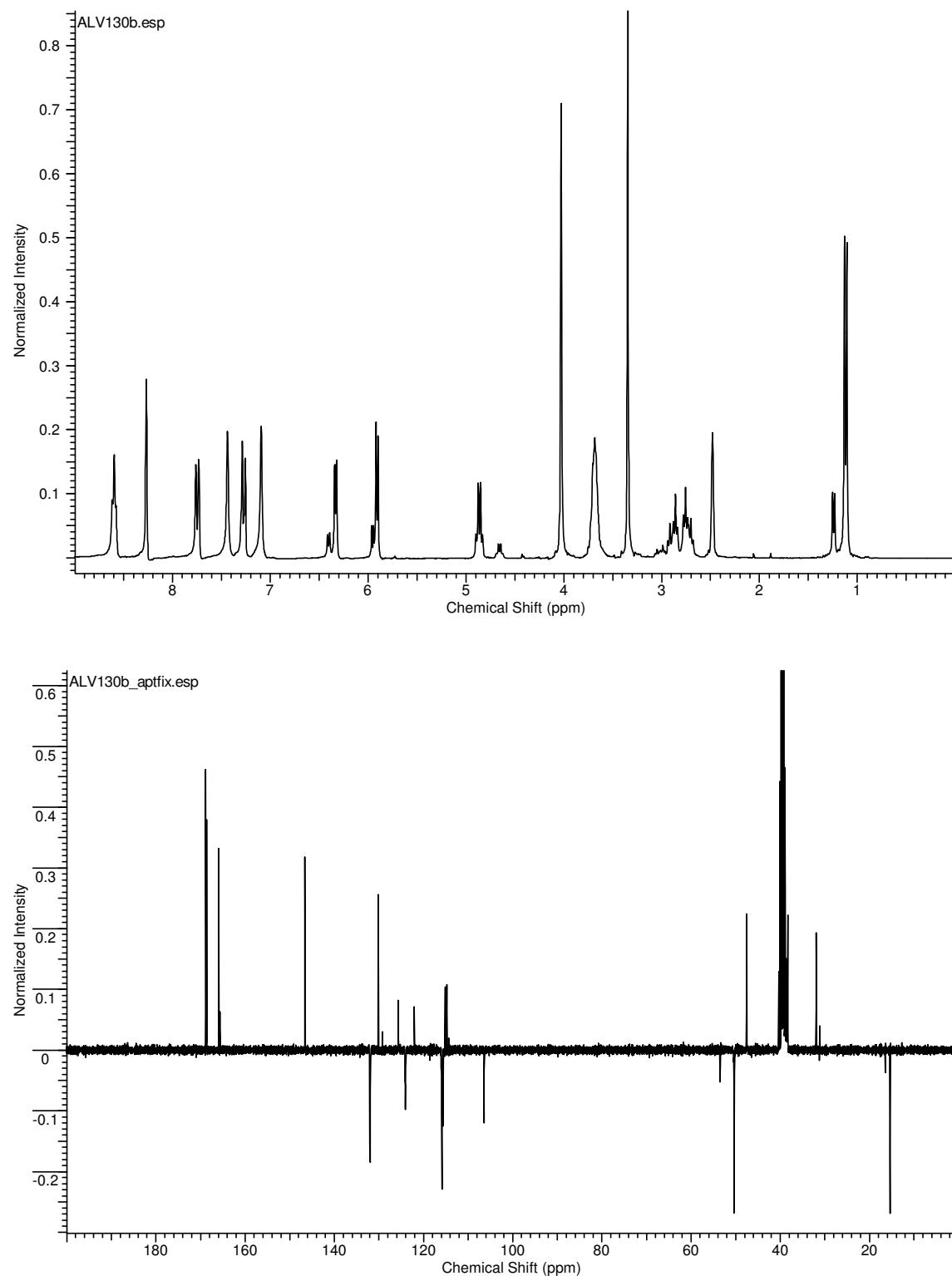
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 18(2,1,1,5)



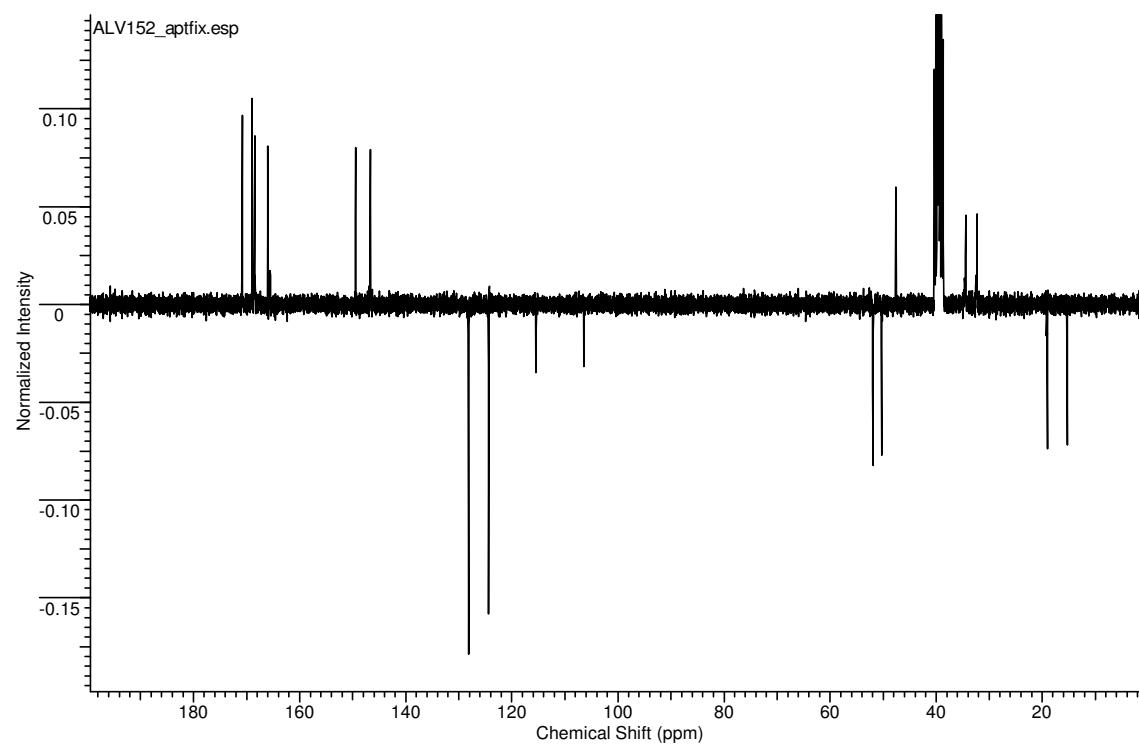
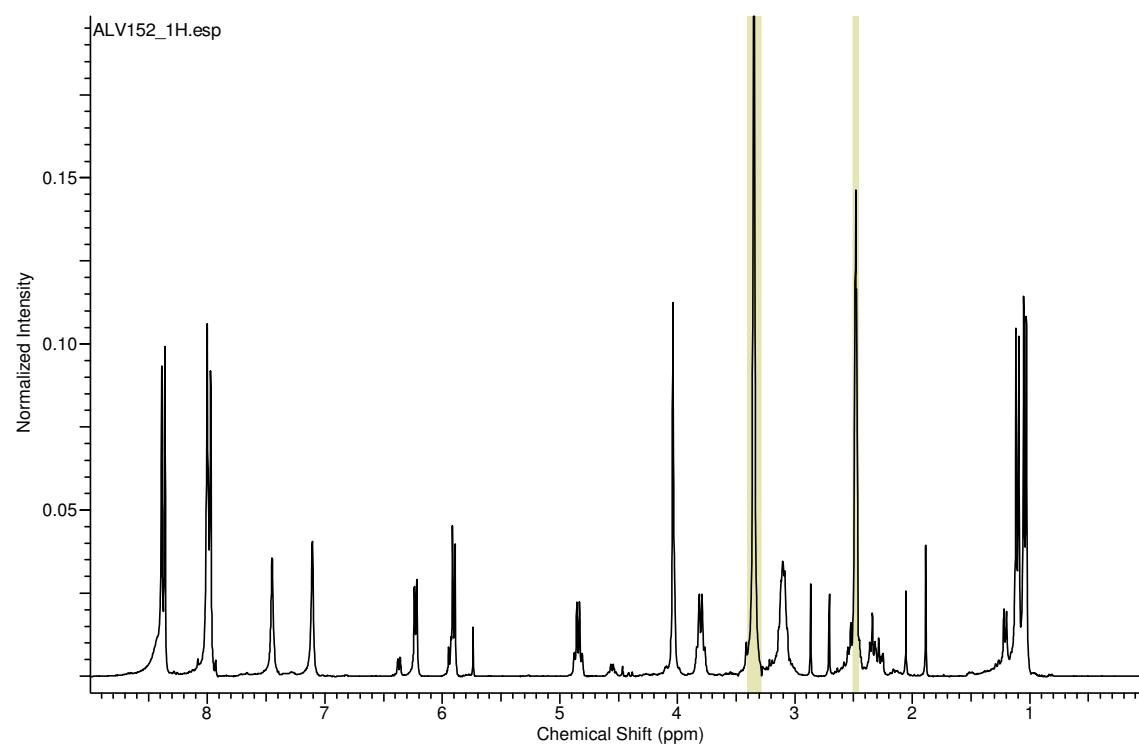
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 18(2,1,1,9)



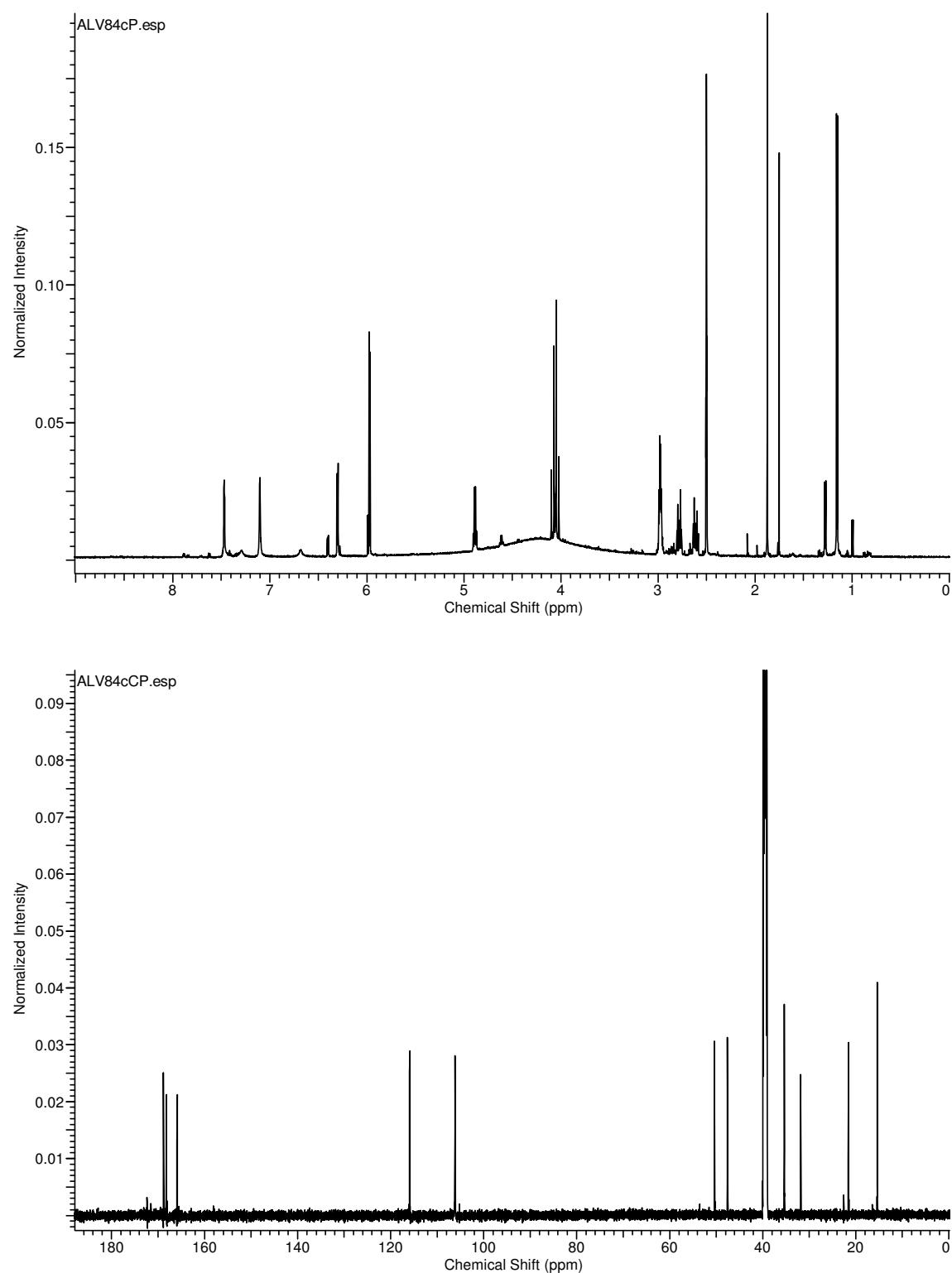
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 18(2,2,1,5)



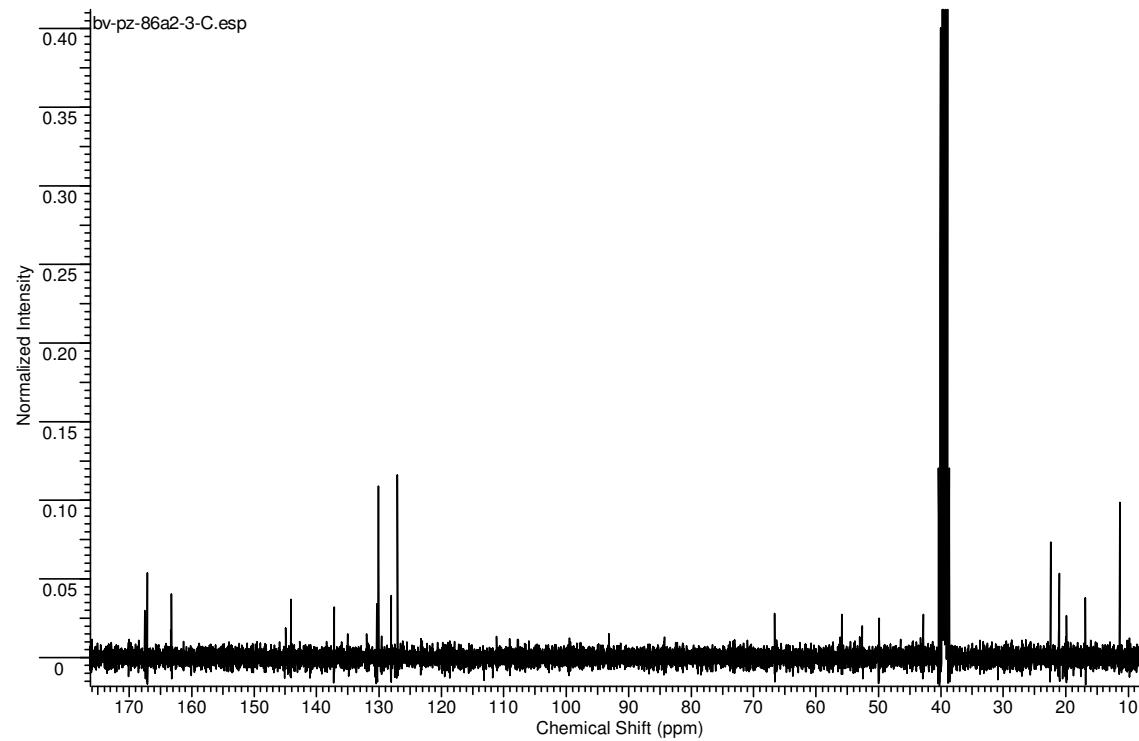
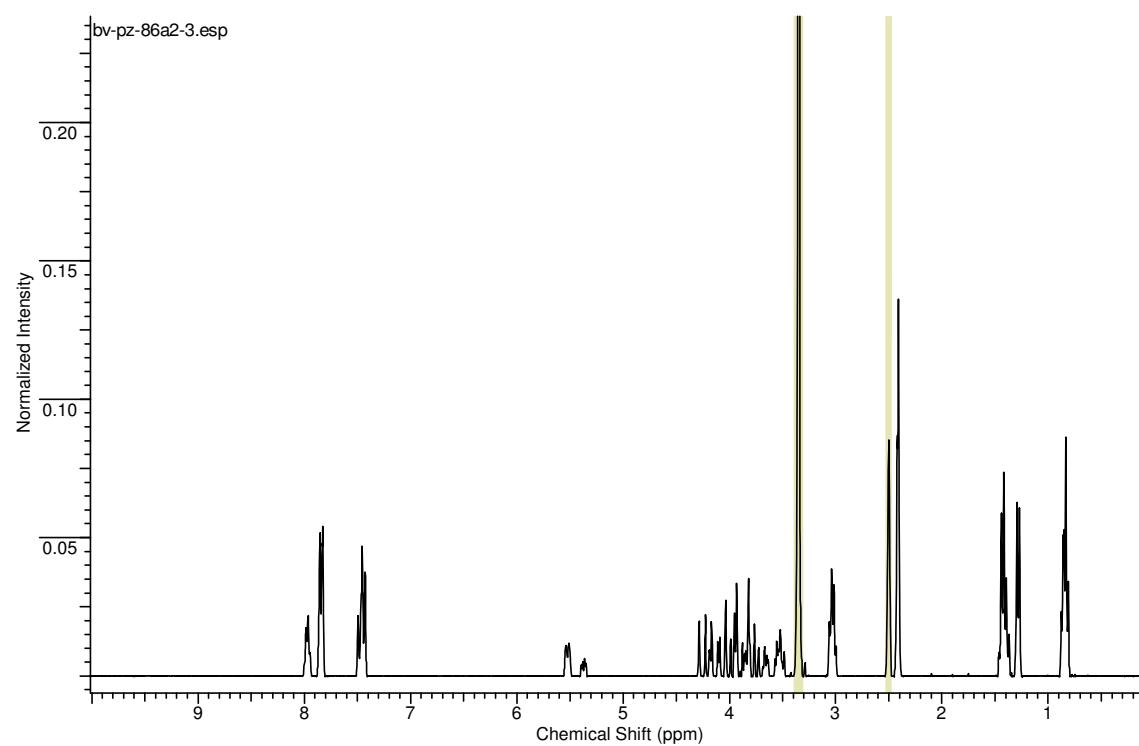
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 18(2,2,1,9)



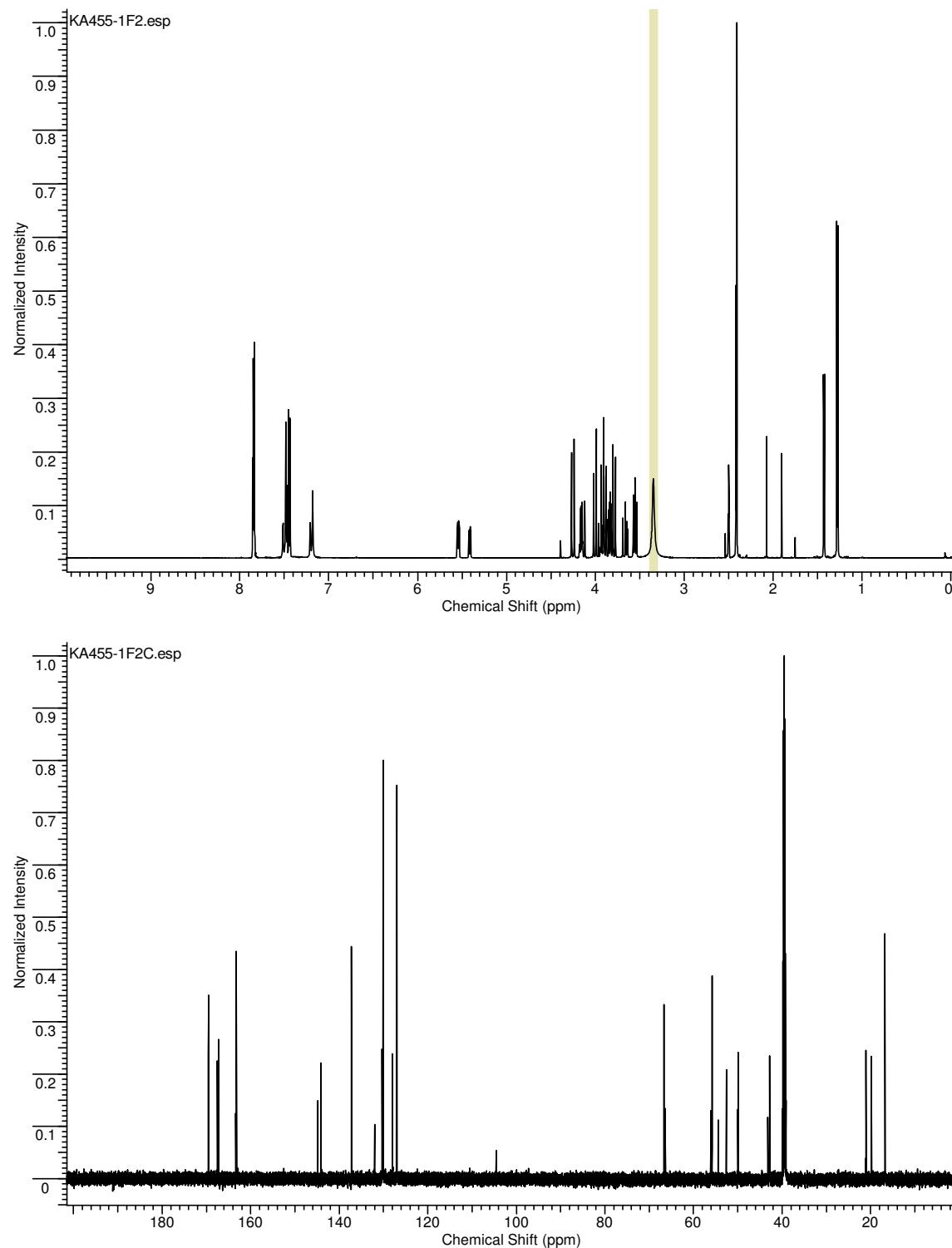
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 18(2,2,1,12)



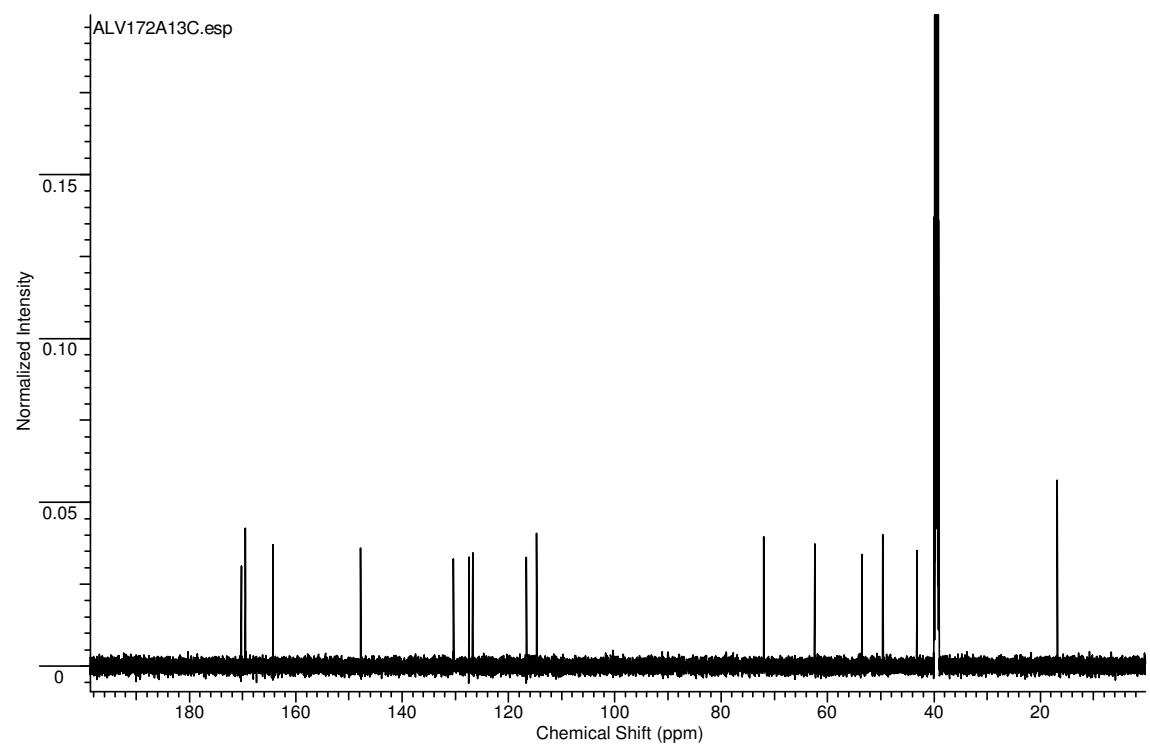
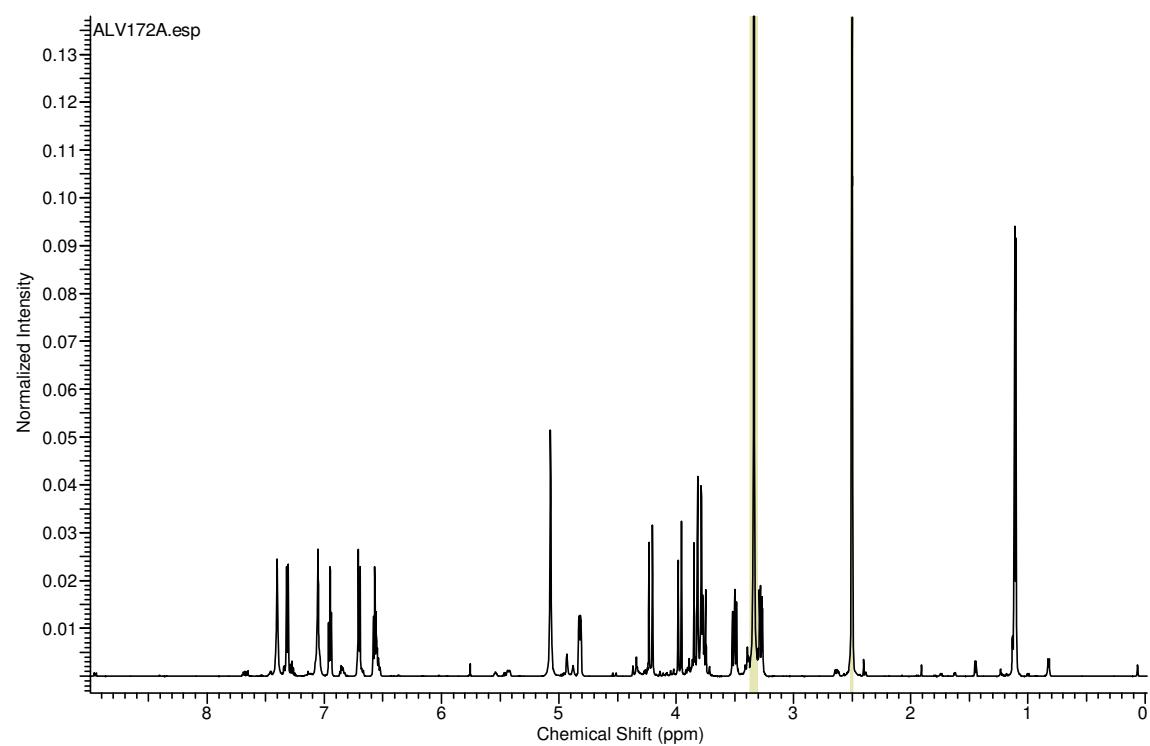
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(1,1,2,1)



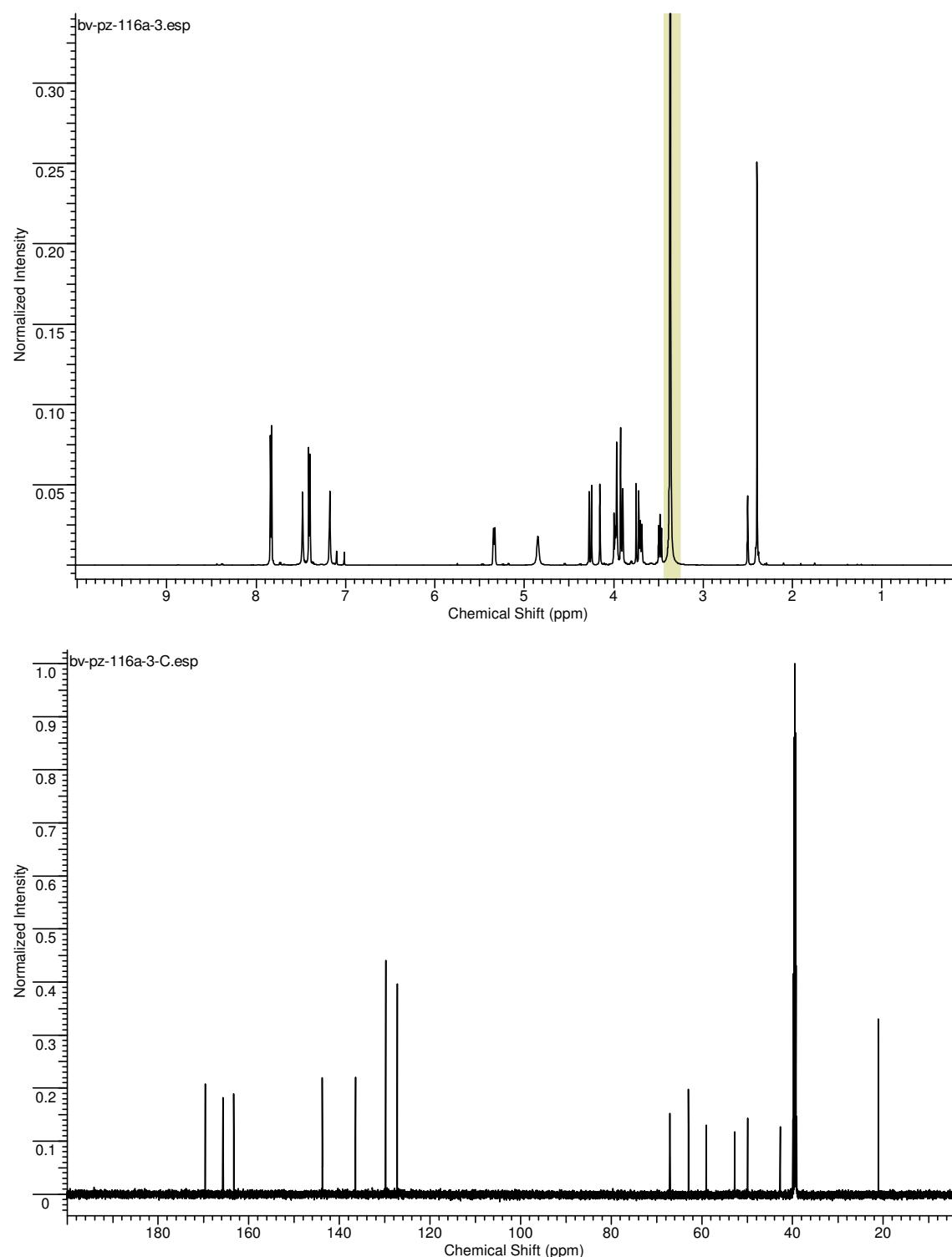
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,1,2,1)



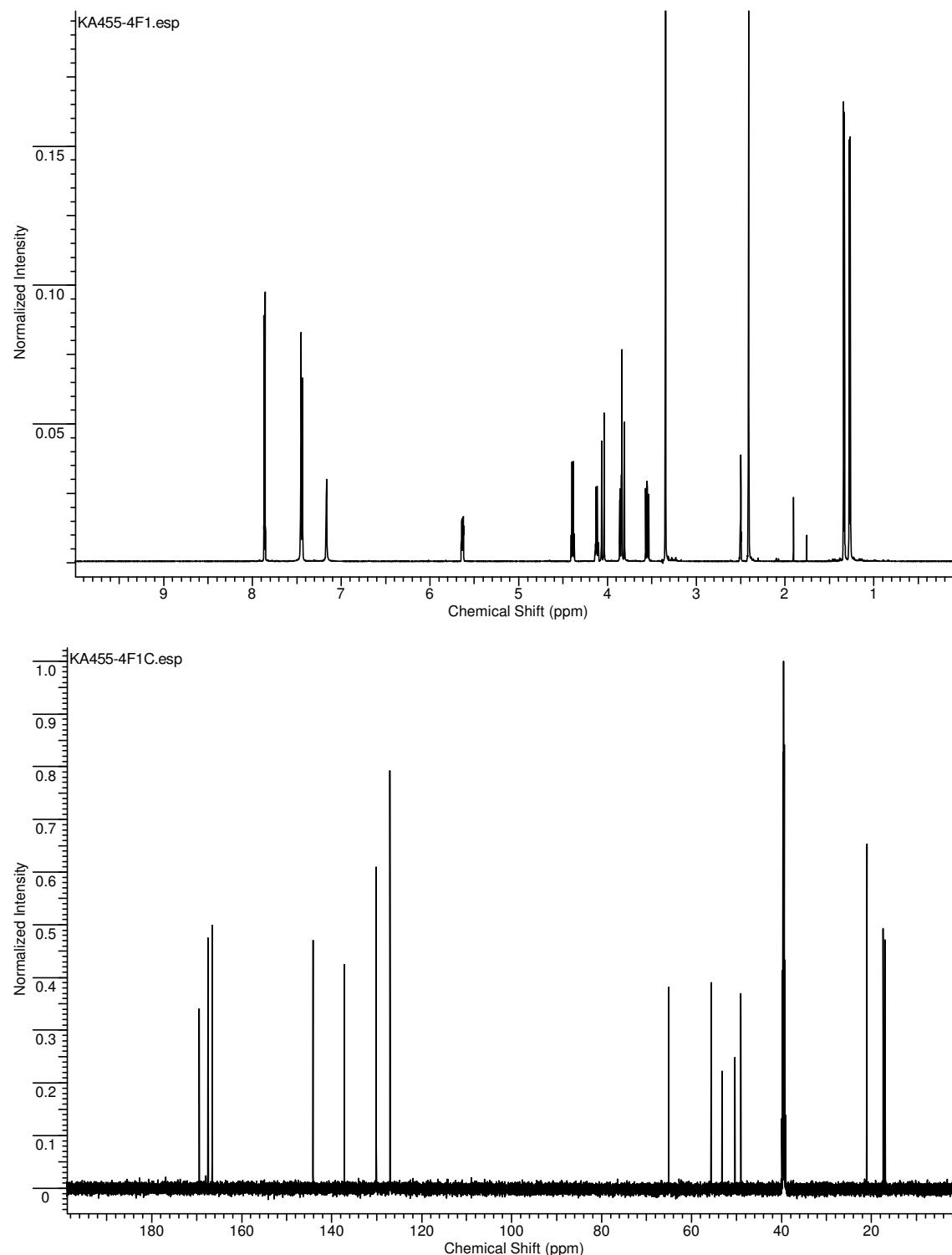
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,1,2,7)



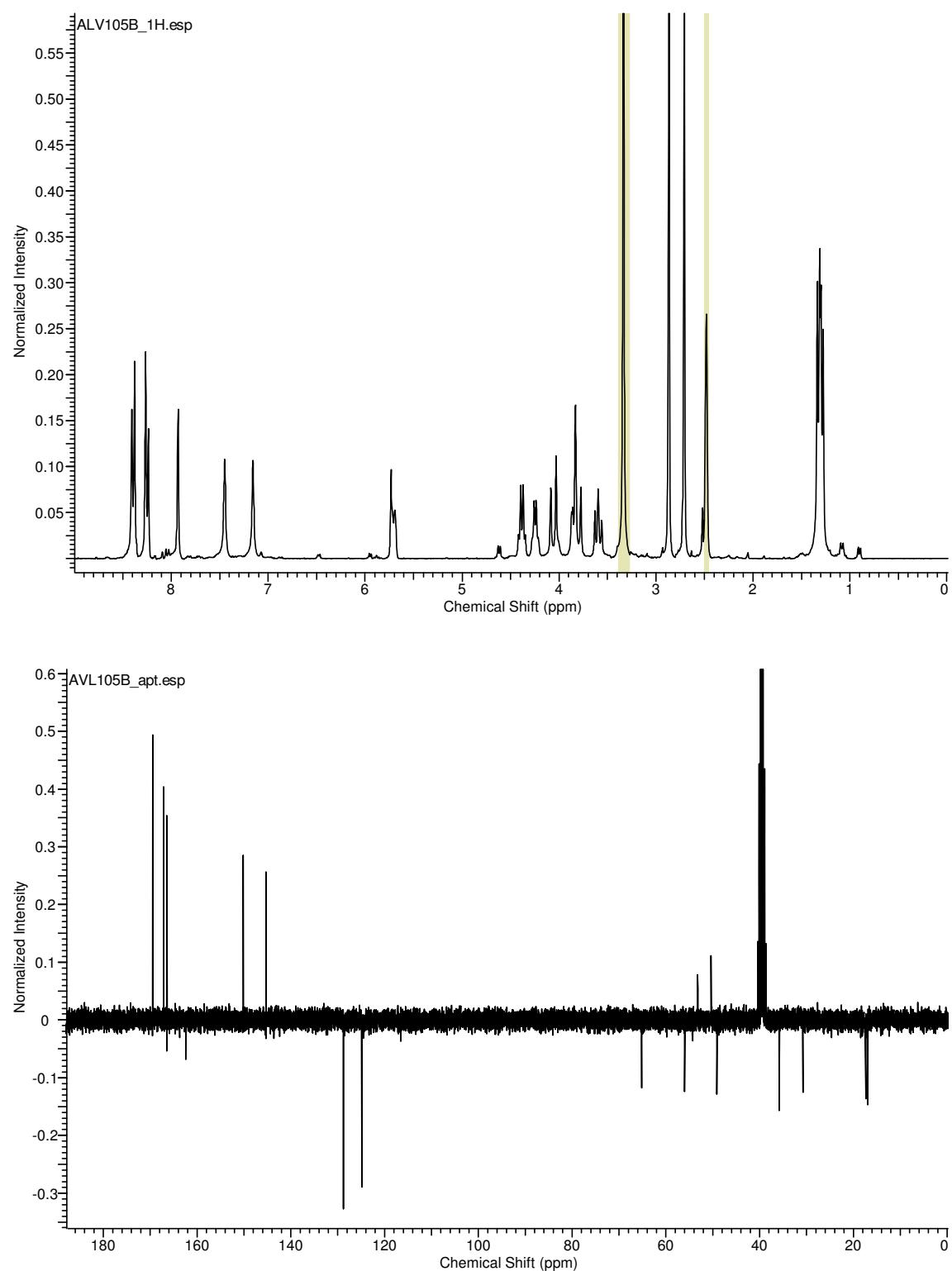
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,1,6,1)



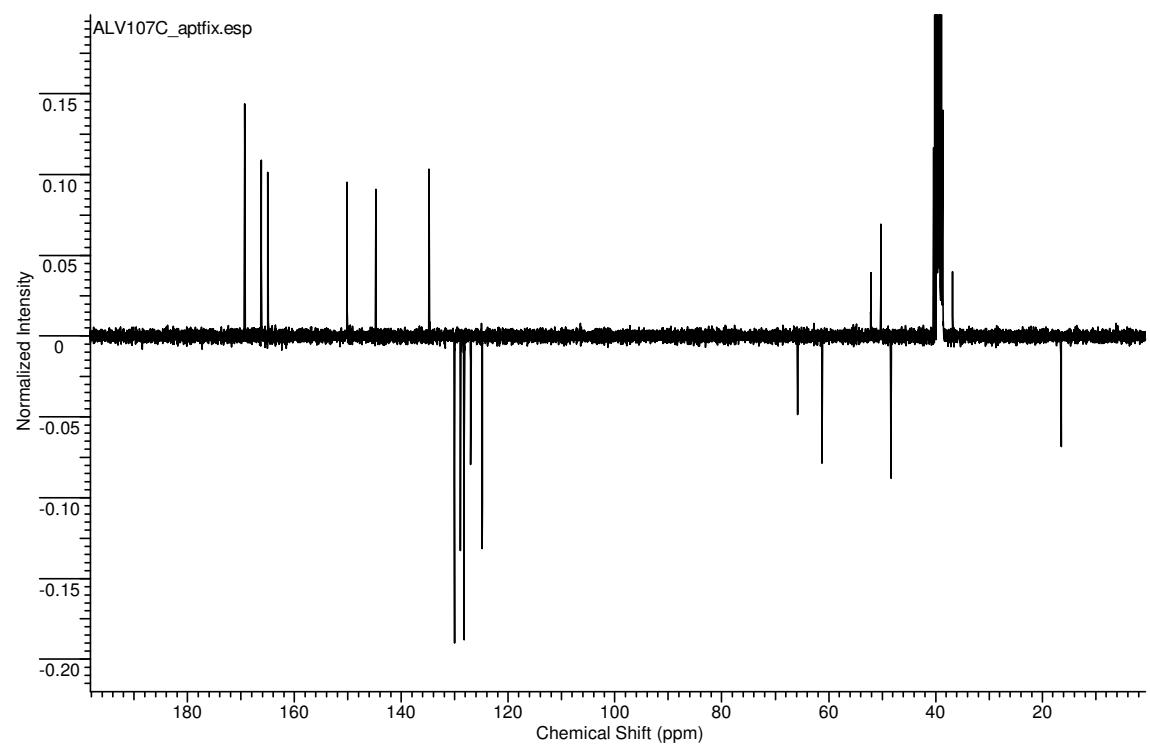
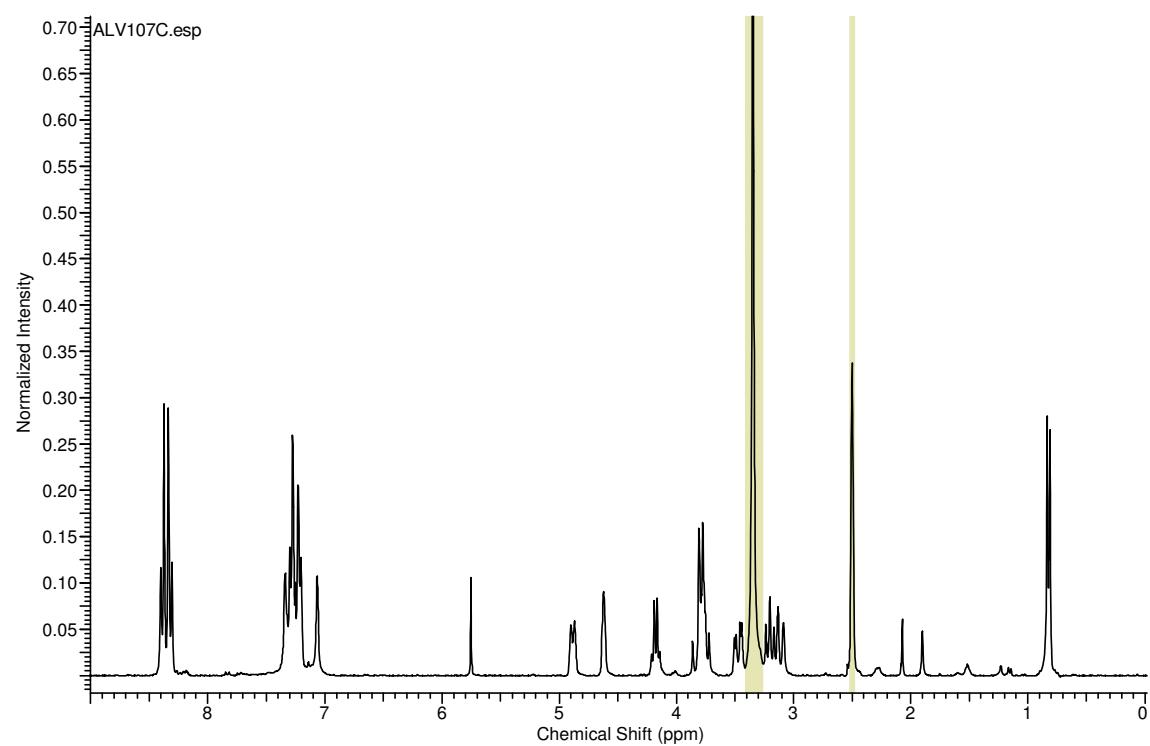
¹H and ¹³C NMR spectra (*d*₆-DMSO) for compound 20(2,2,2,1)



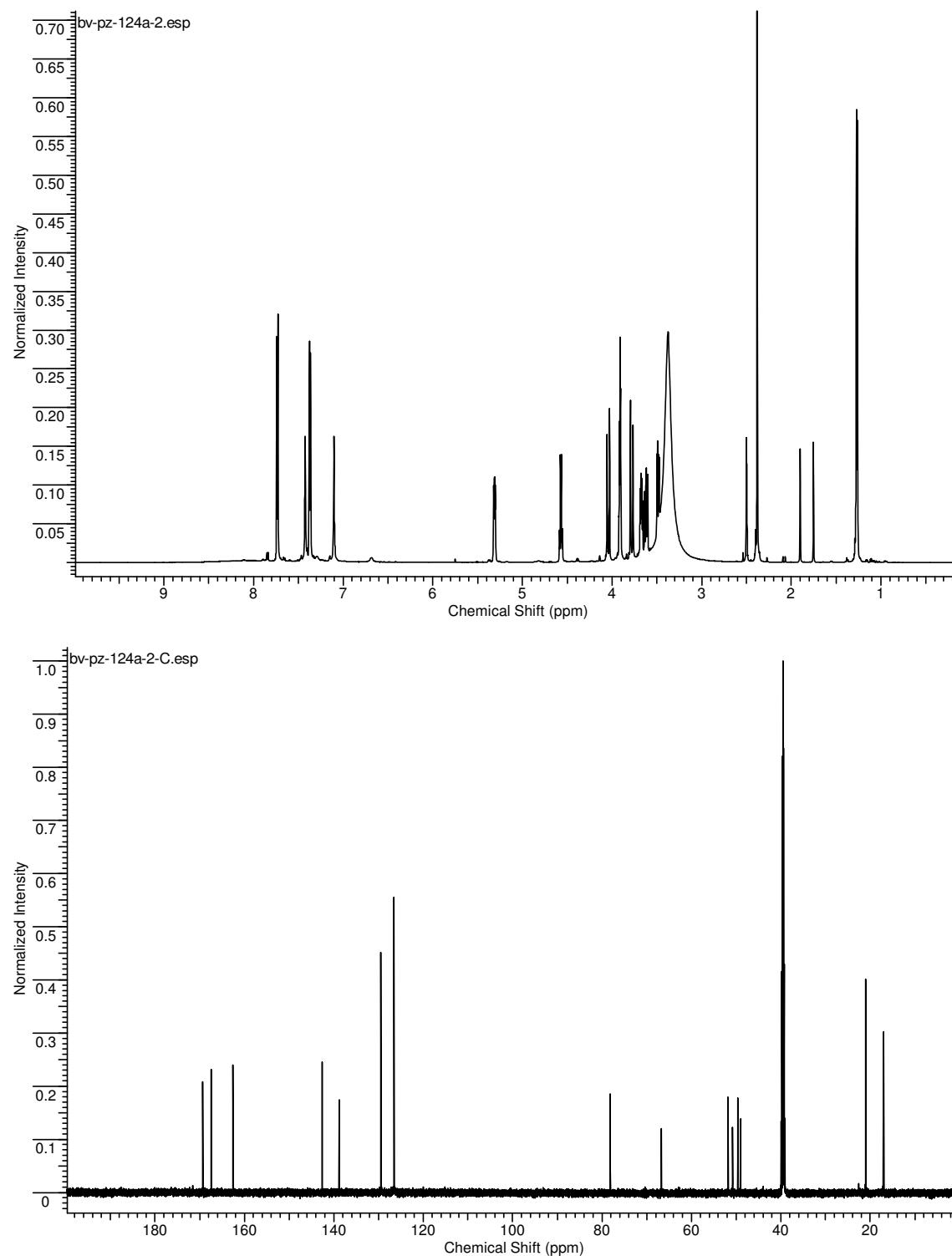
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,2,2,2)



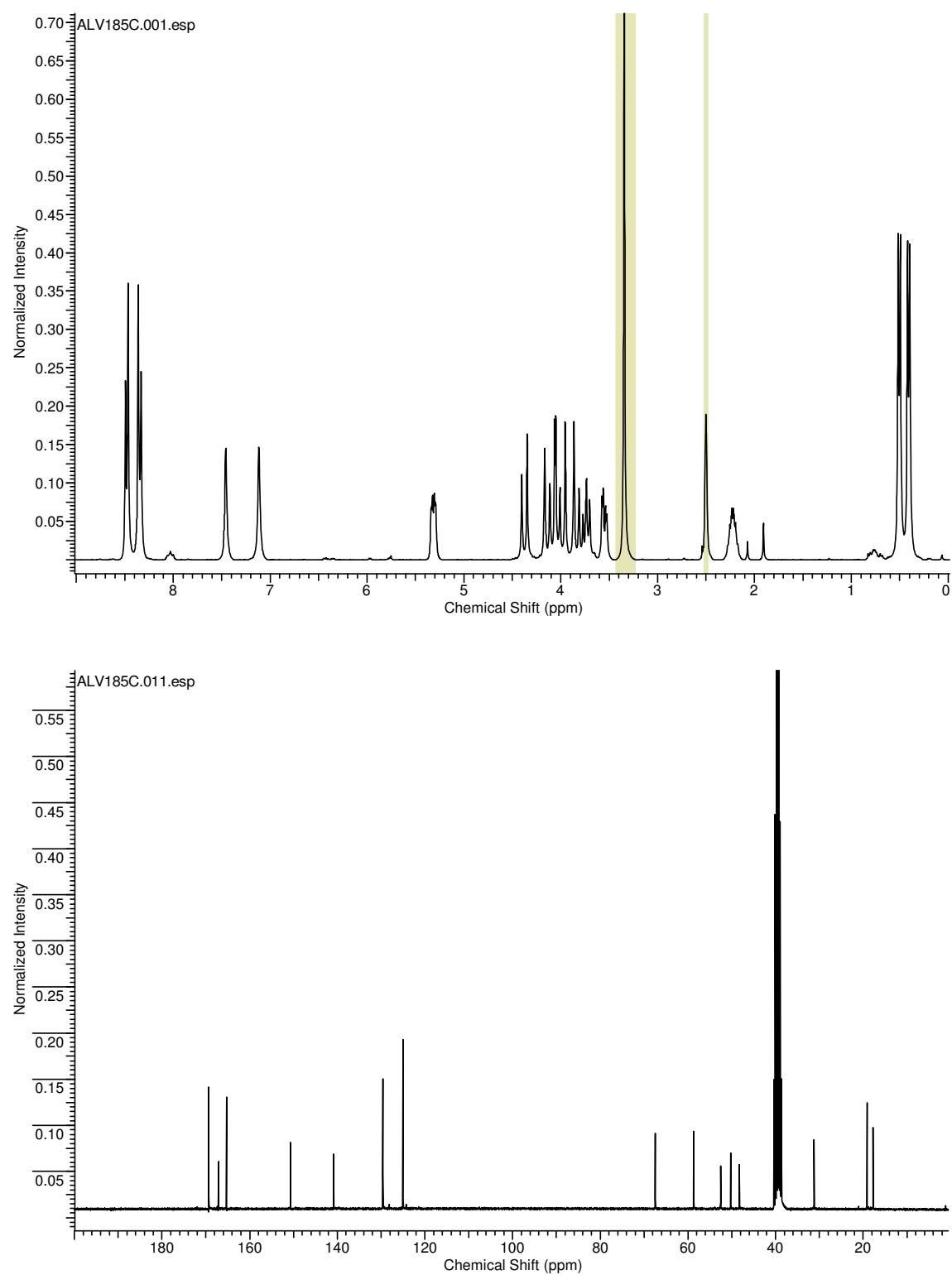
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,2,5,2)



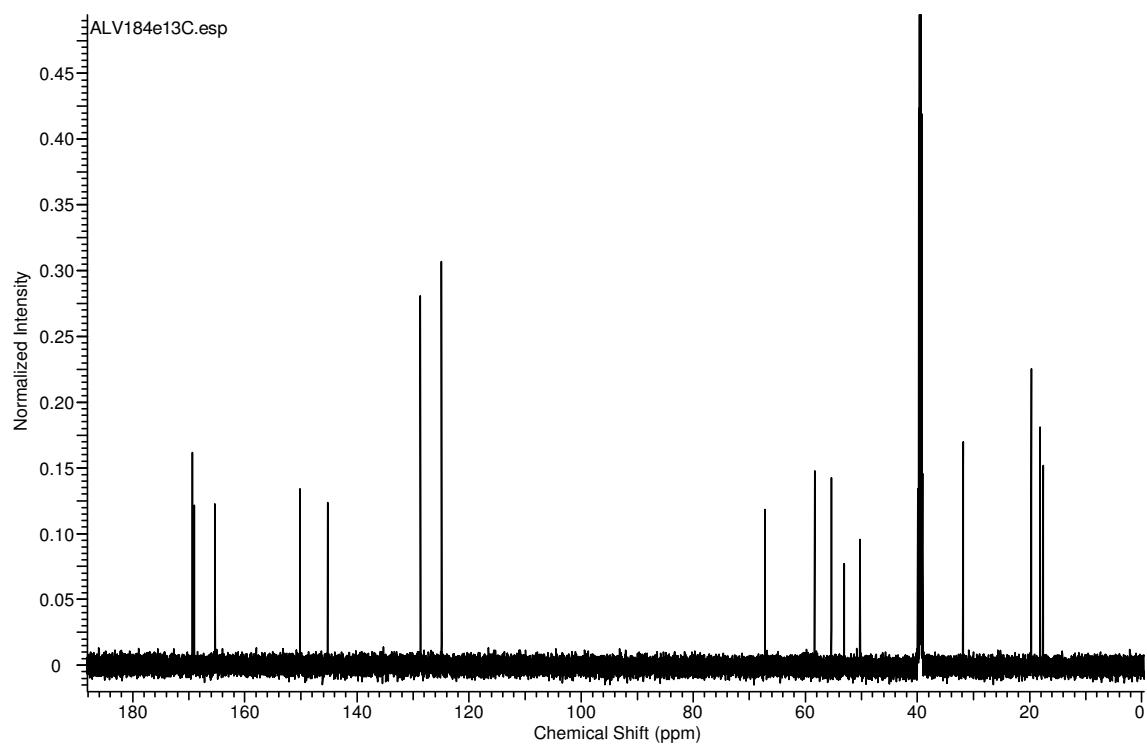
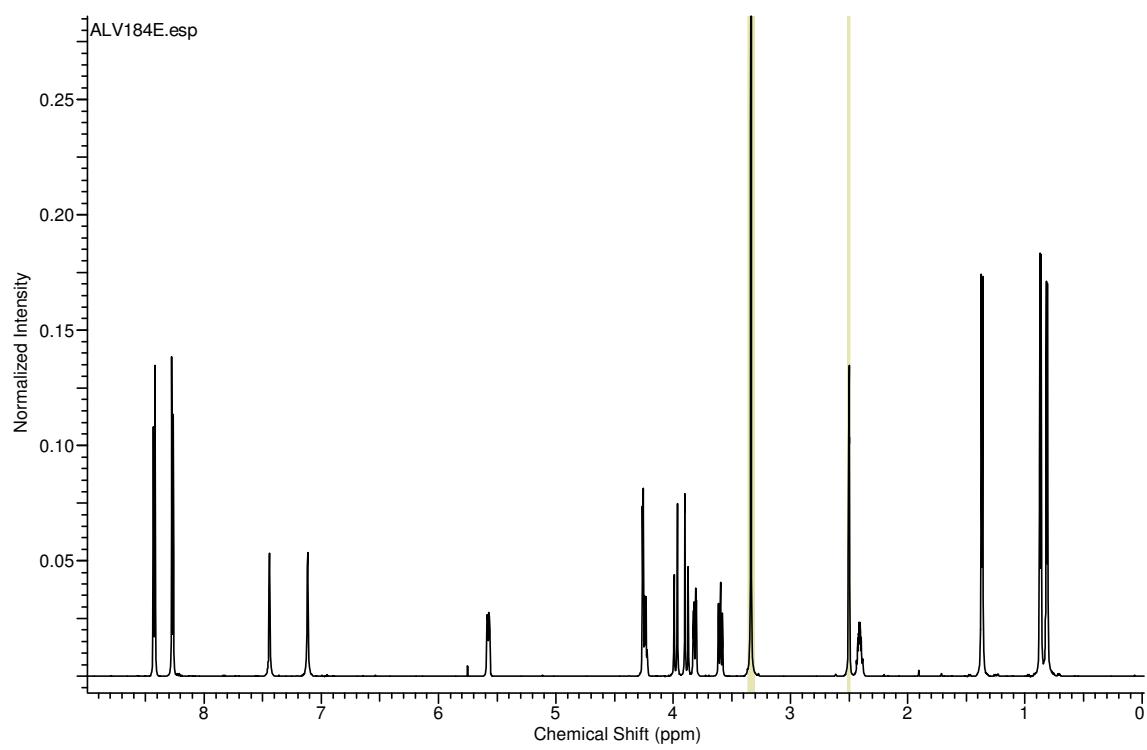
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,2,6,1)

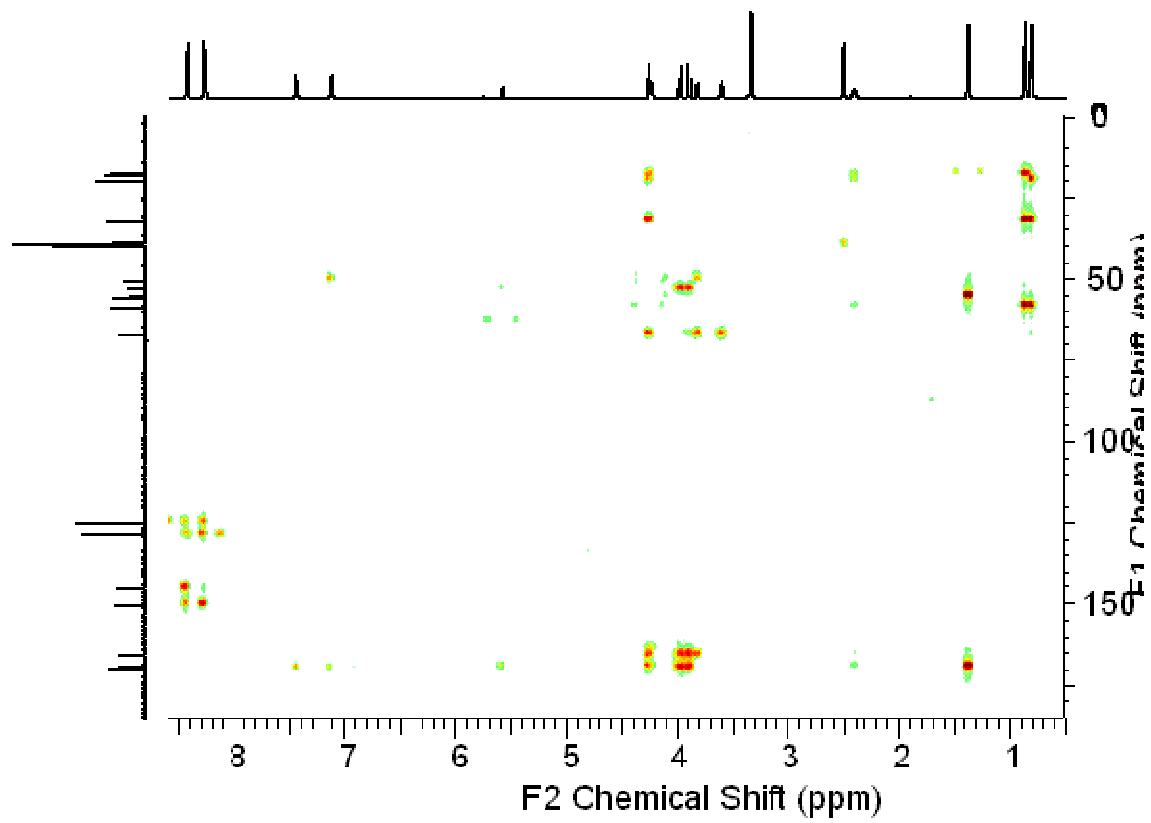
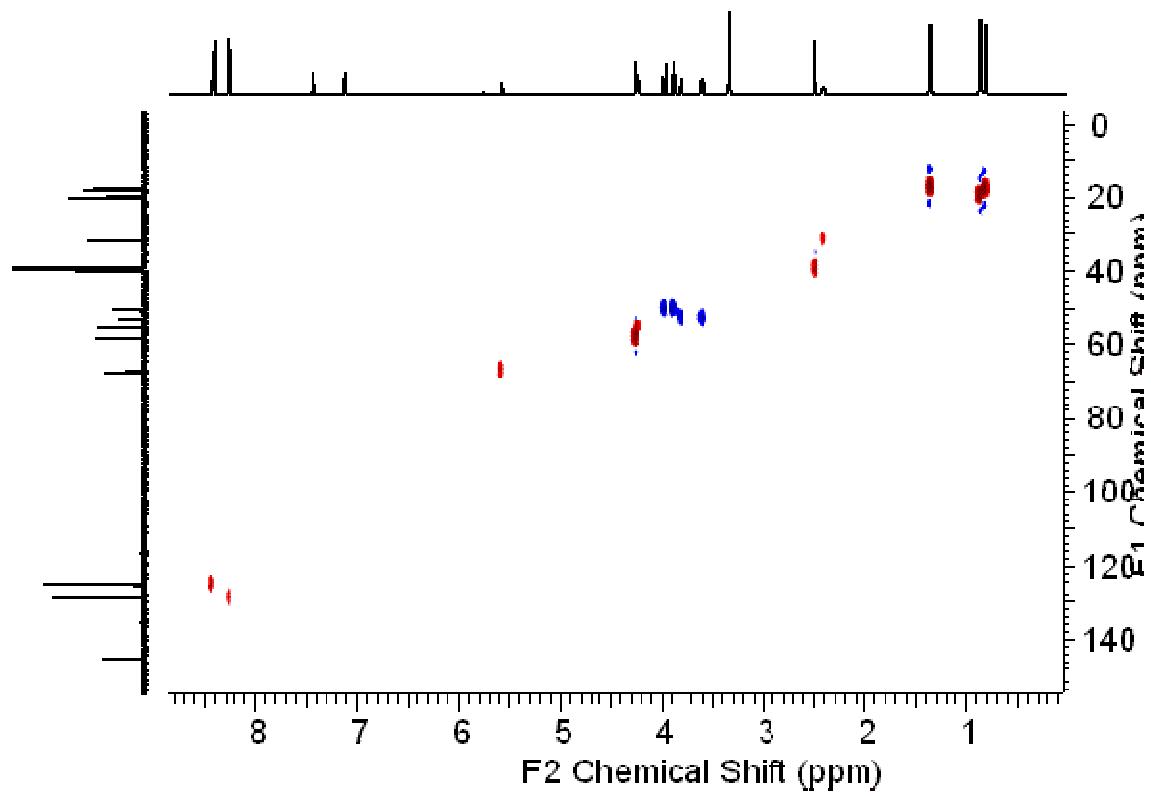


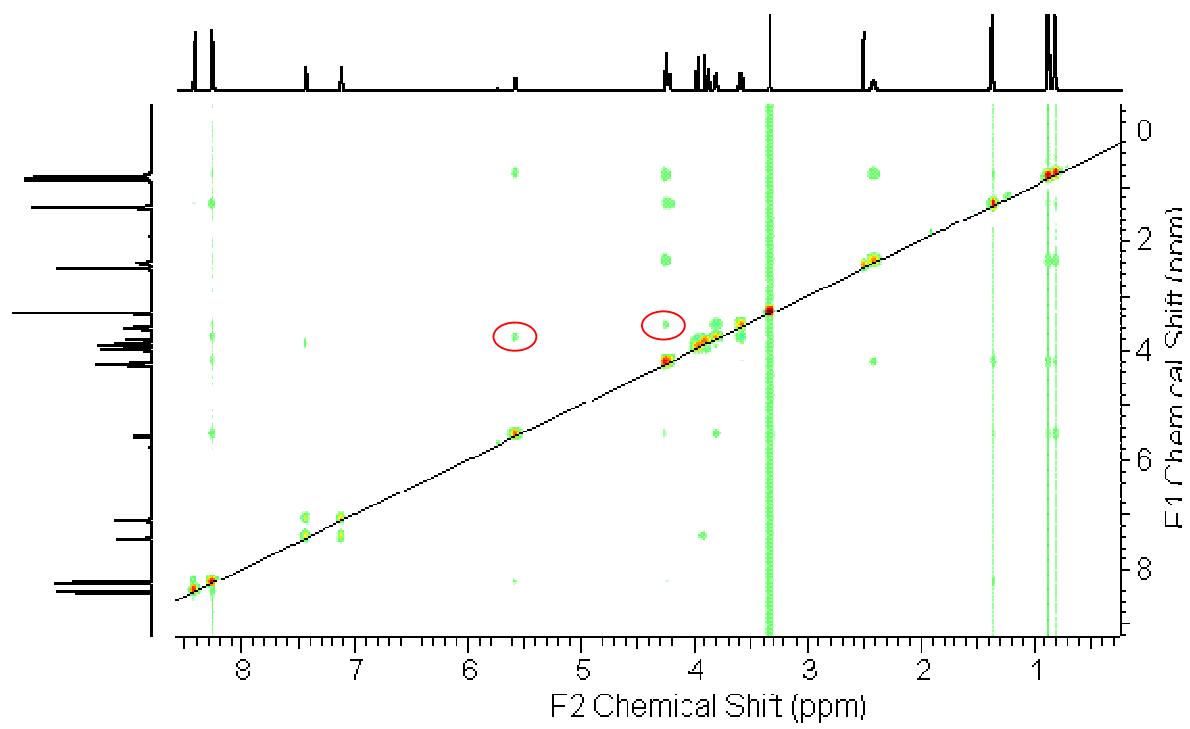
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 20(2,4,1,2)



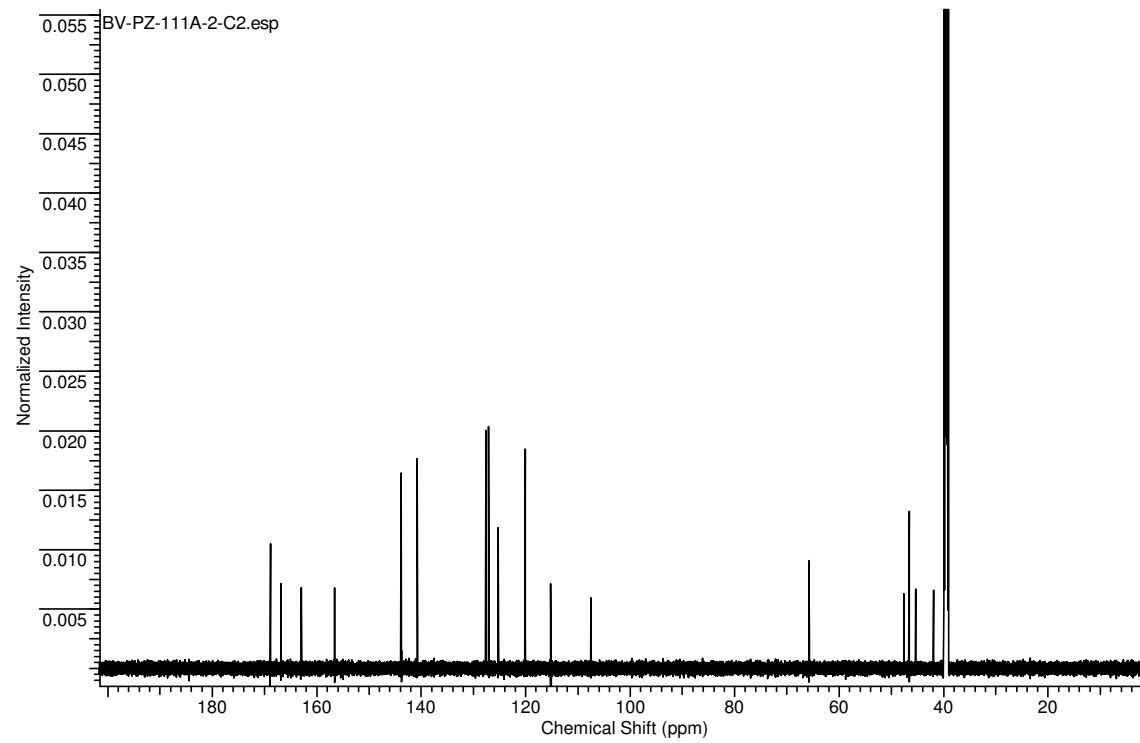
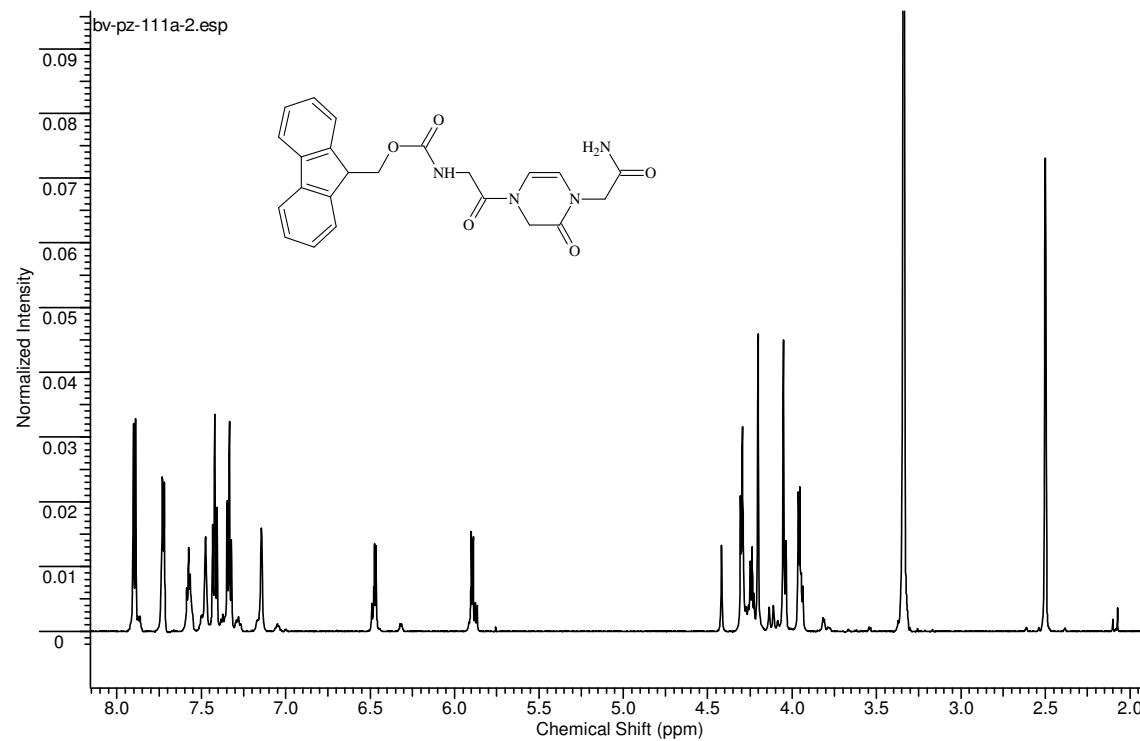
¹H, ¹³C, Hsqc, Hmhc and Roesy NMR spectra (*d*₆-DMSO) for compound 20(2,4,2,2)



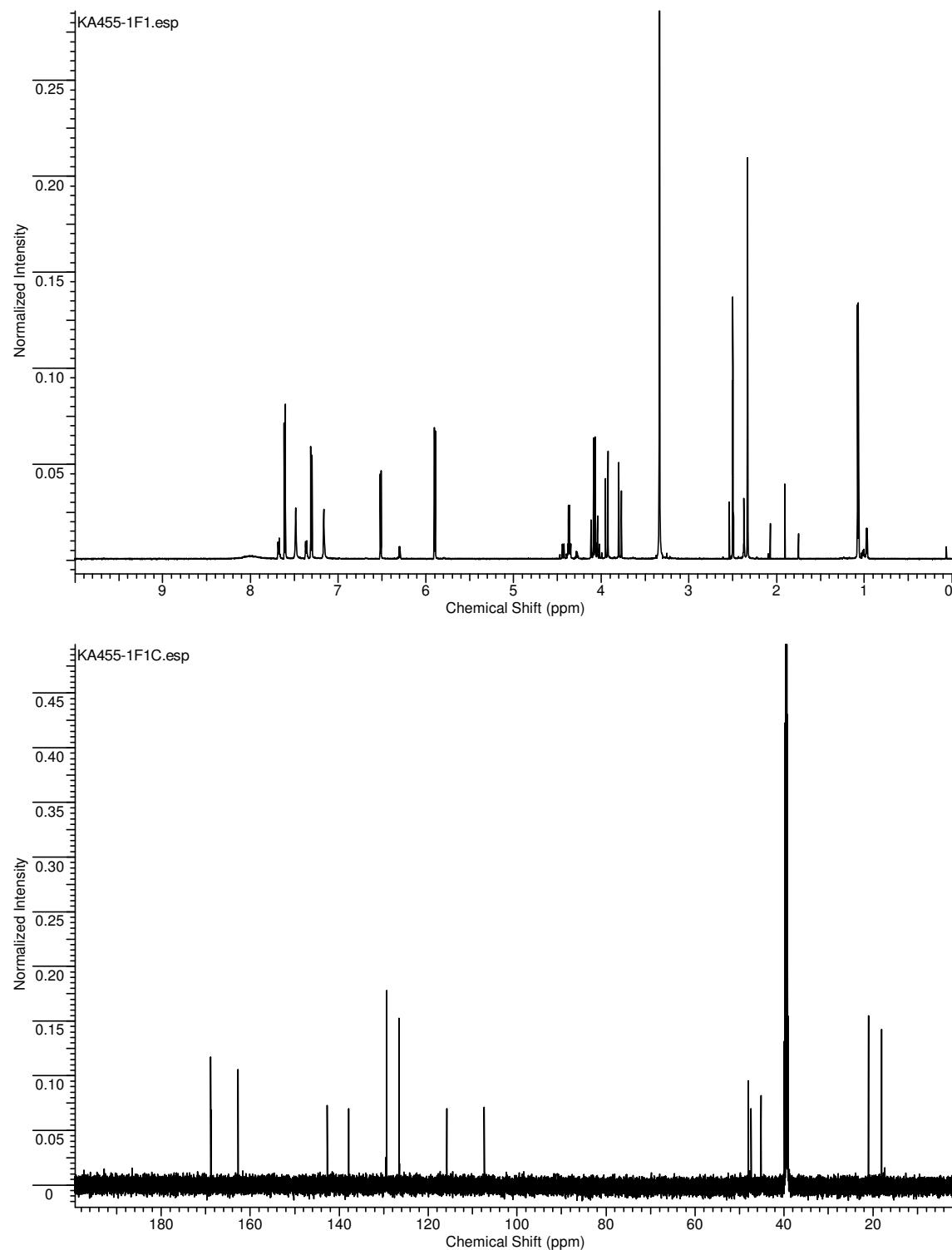




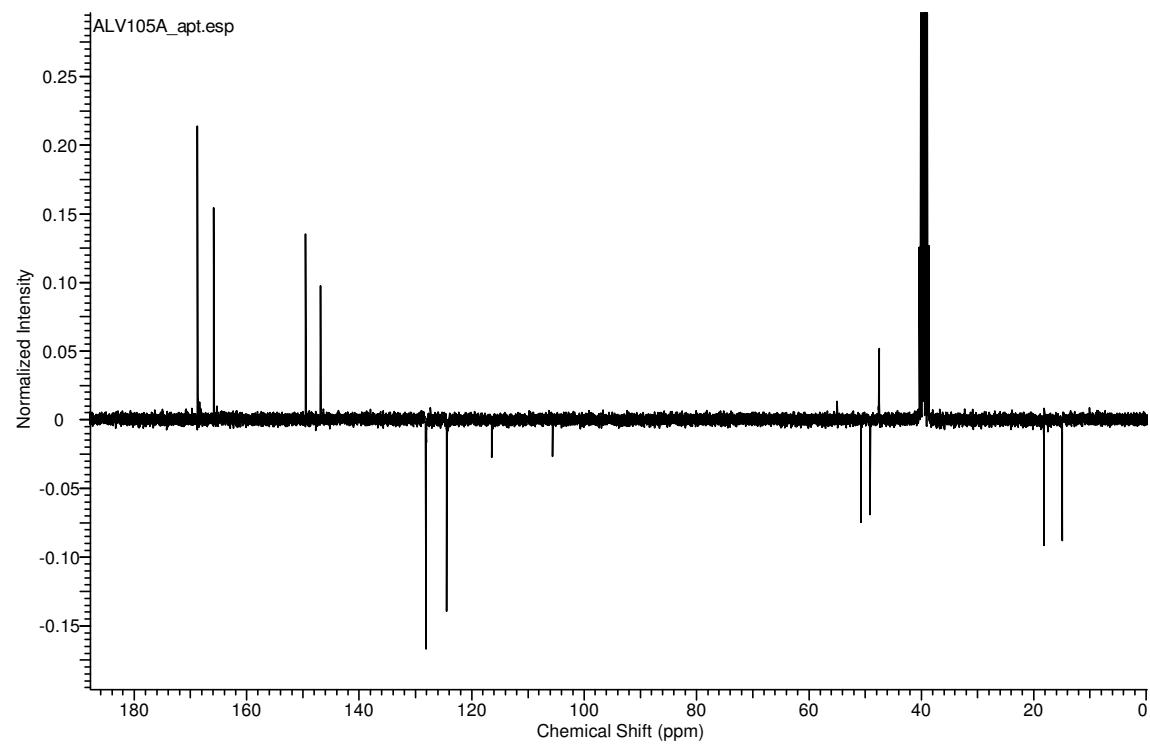
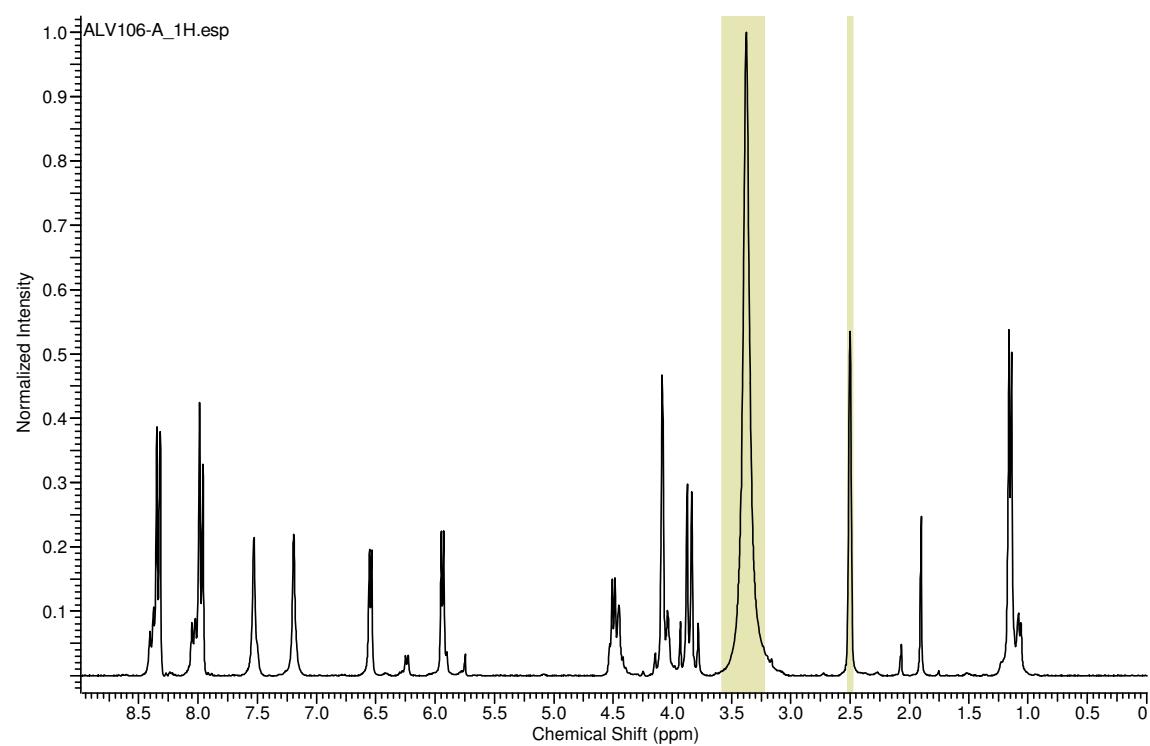
¹H and ¹³C NMR spectra (*d*₆-DMSO) for compound 21(2,1,1,3)



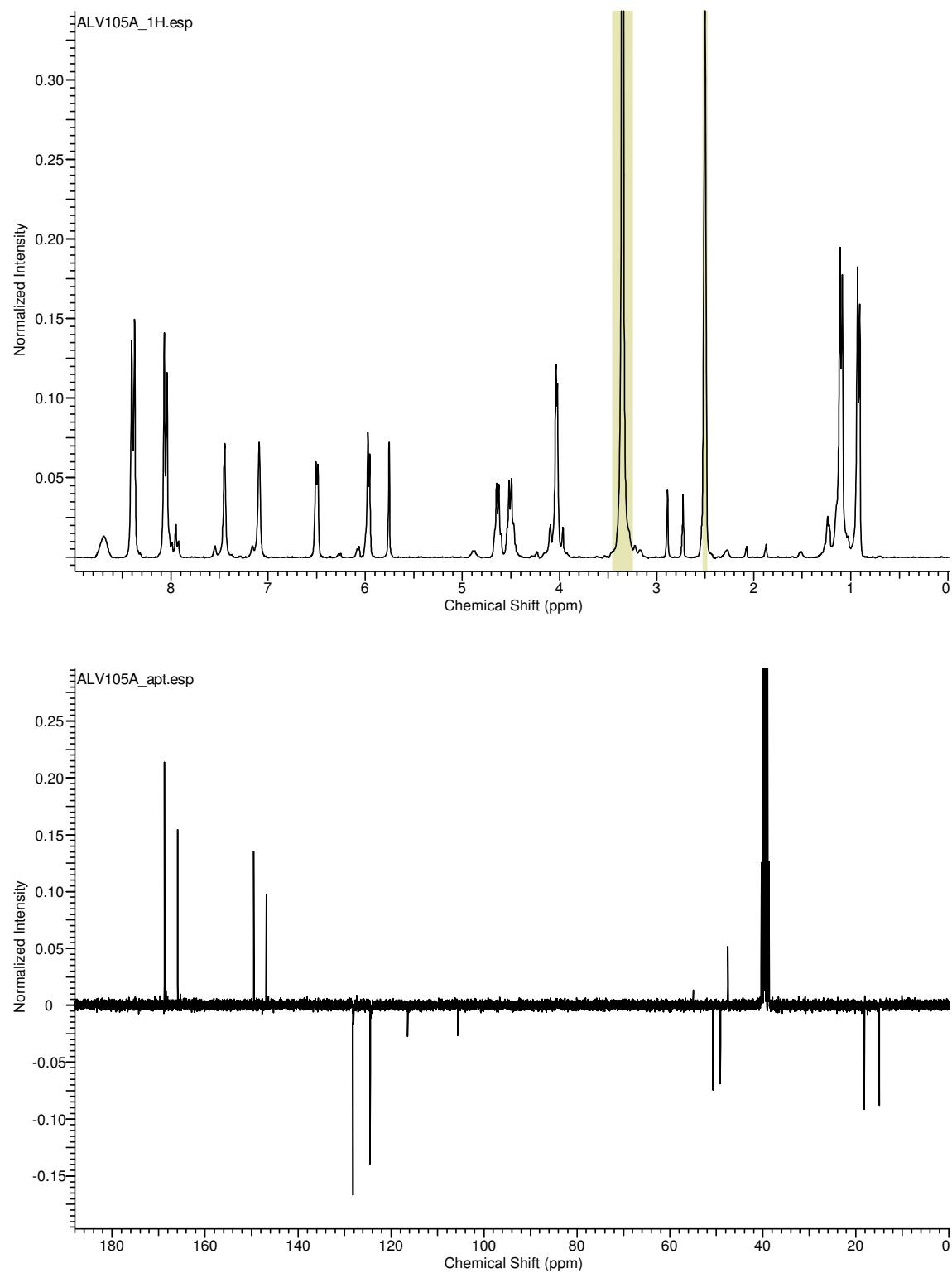
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,1,2,1)



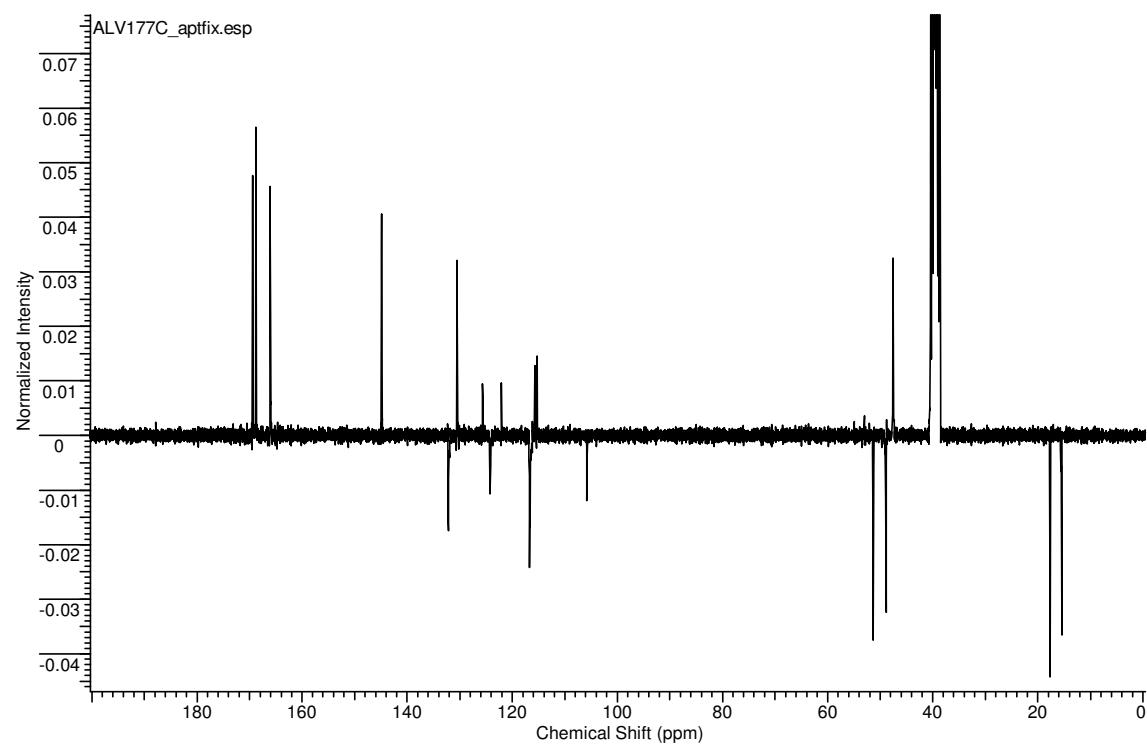
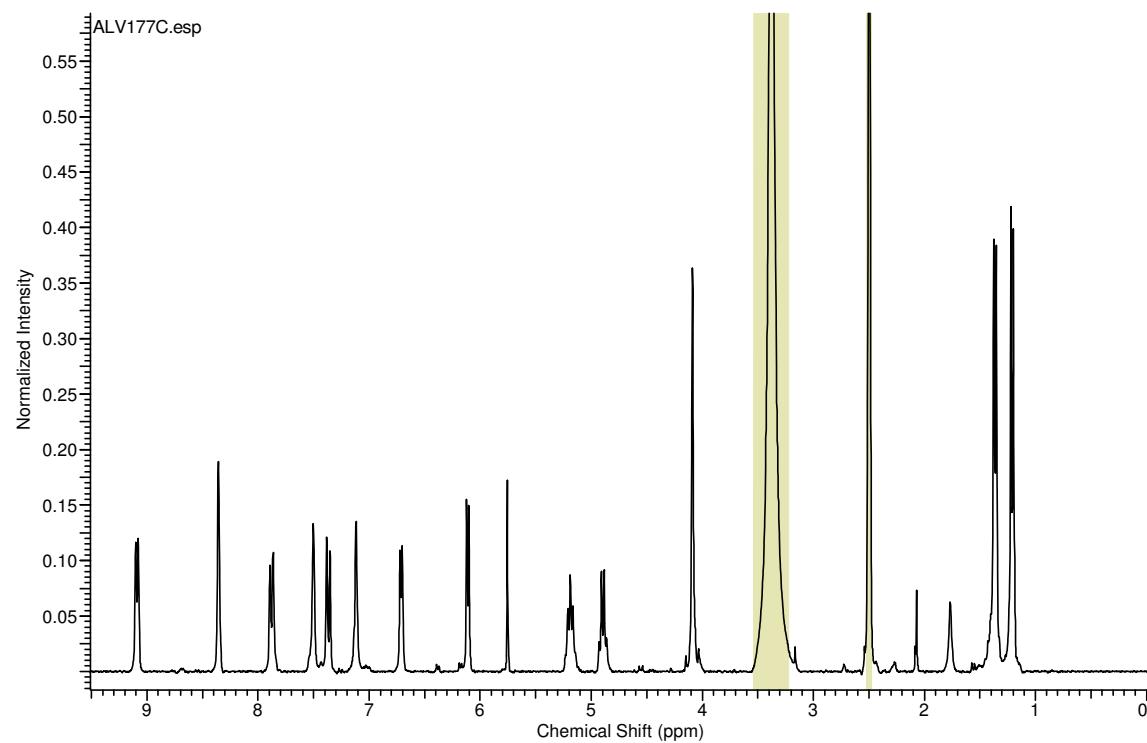
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,1,2,2)



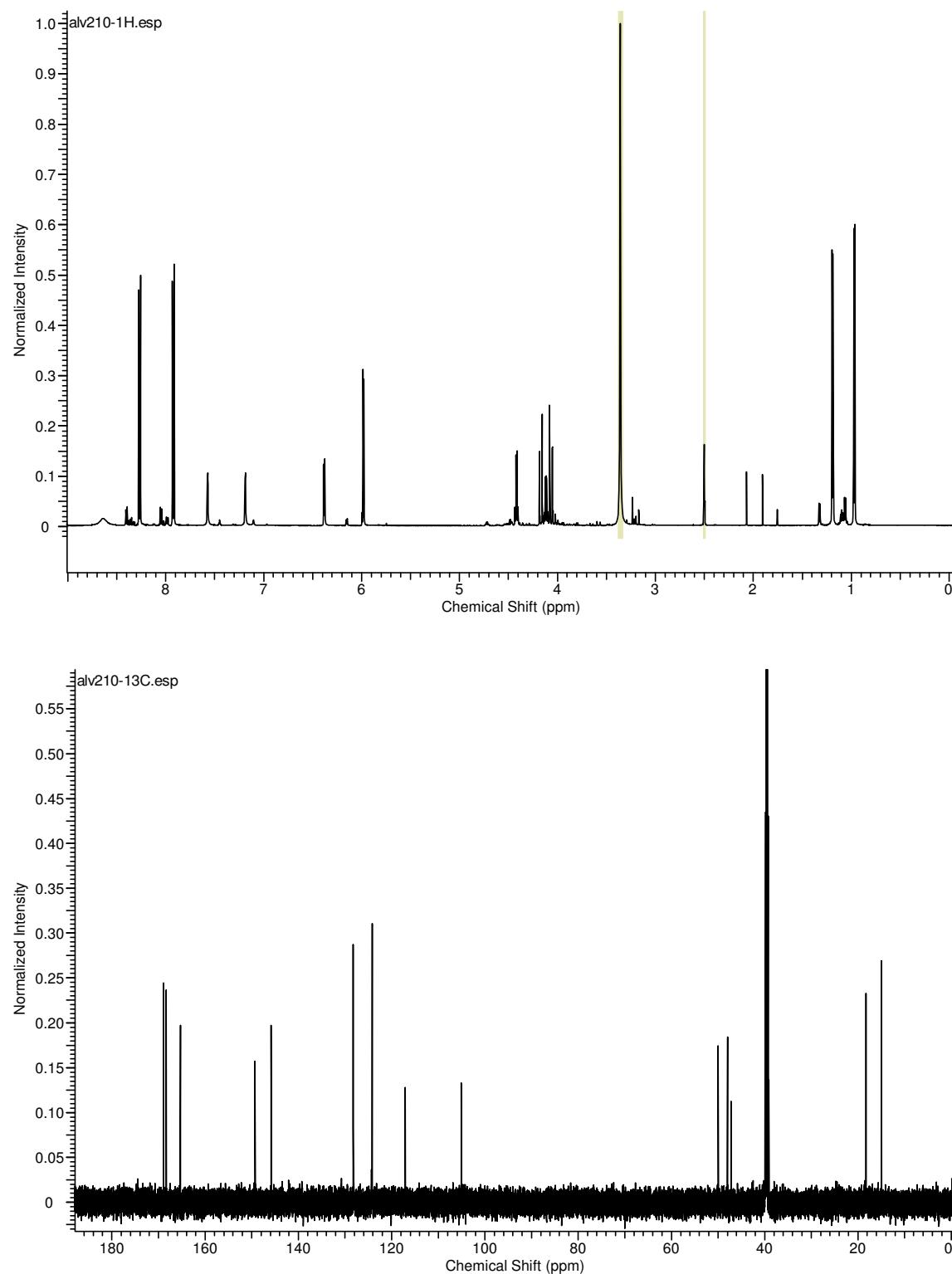
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,2,2,2)



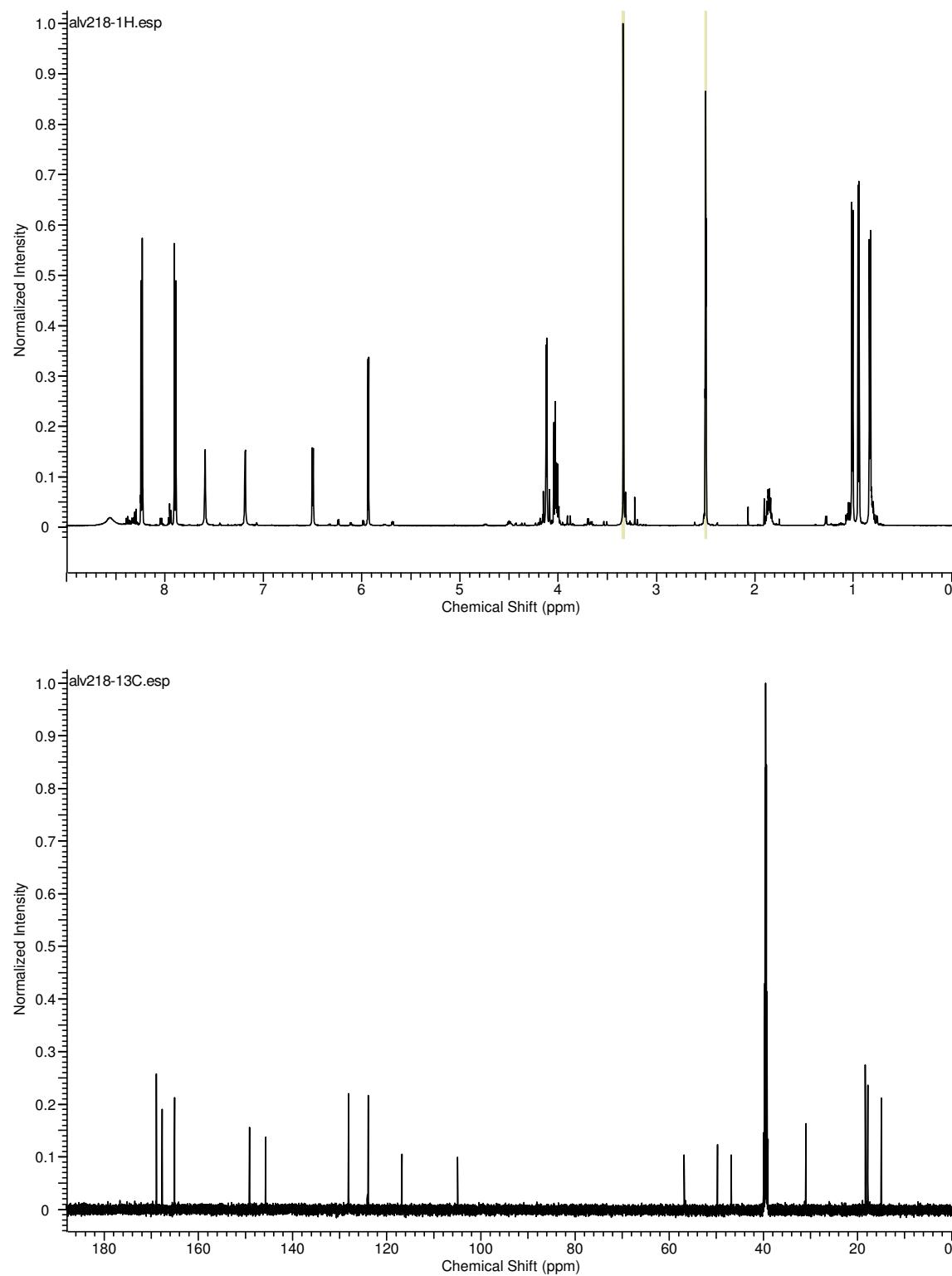
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,2,2,5)



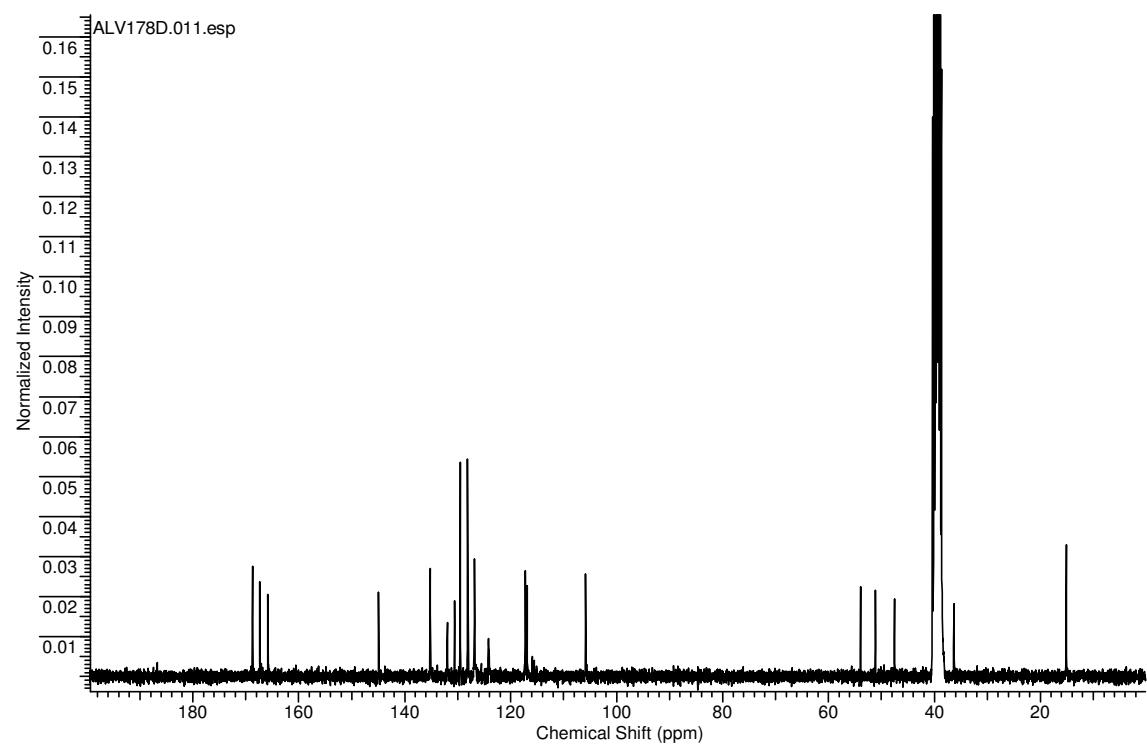
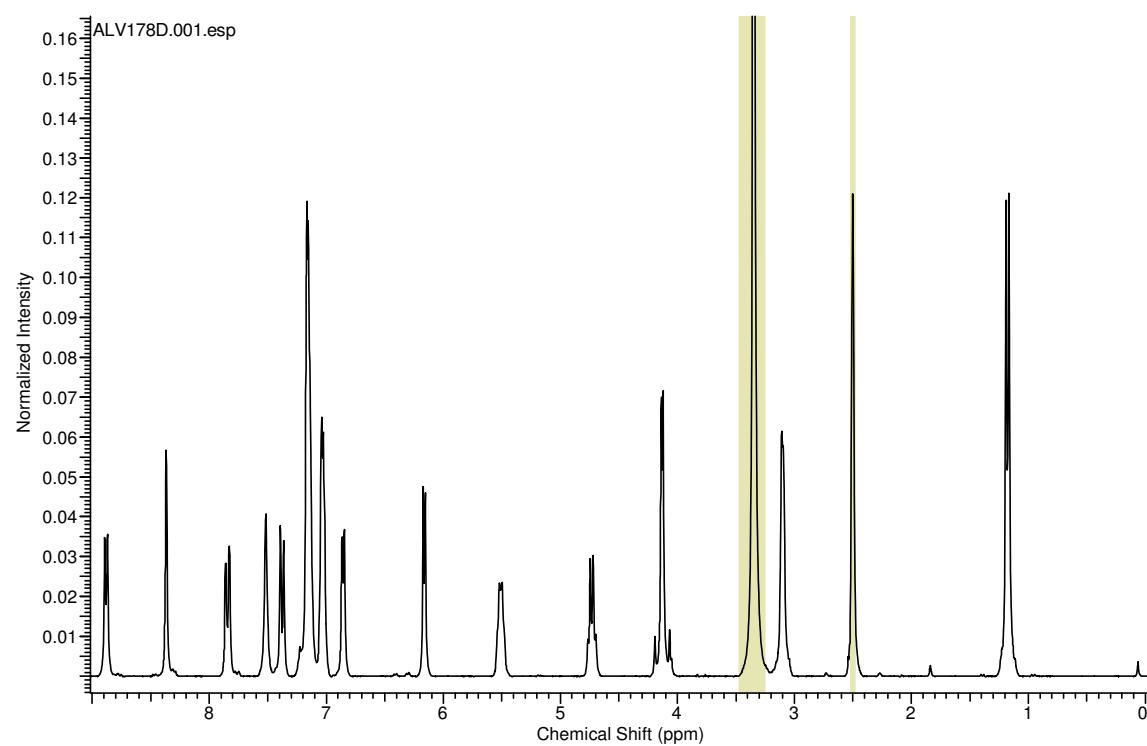
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,2,3,2)



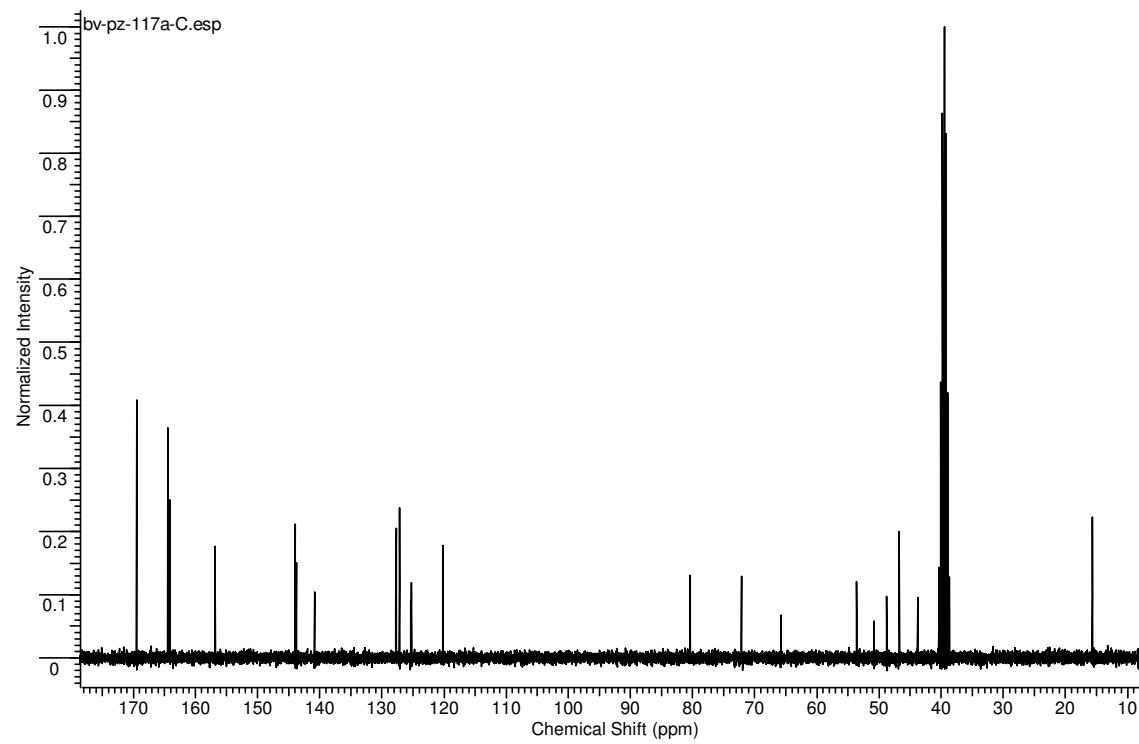
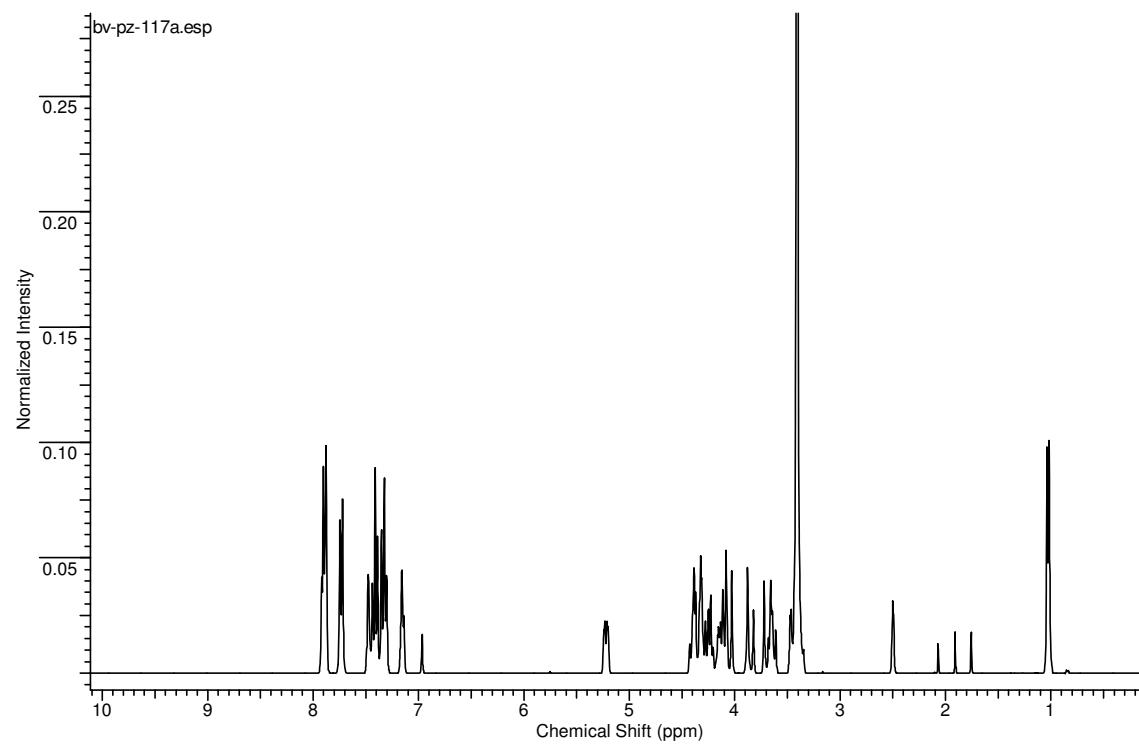
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,2,4,2)



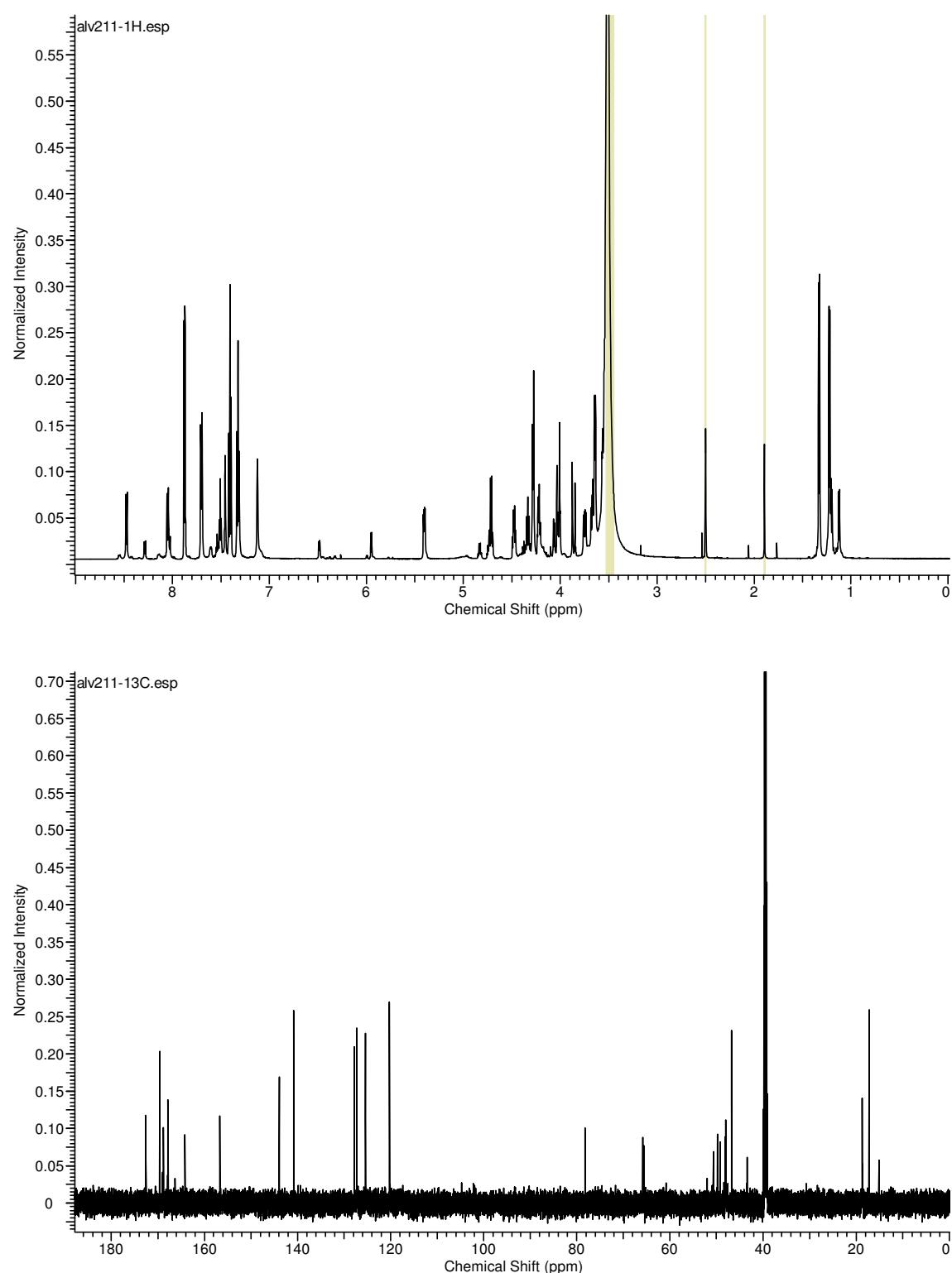
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 21(2,2,5,5)



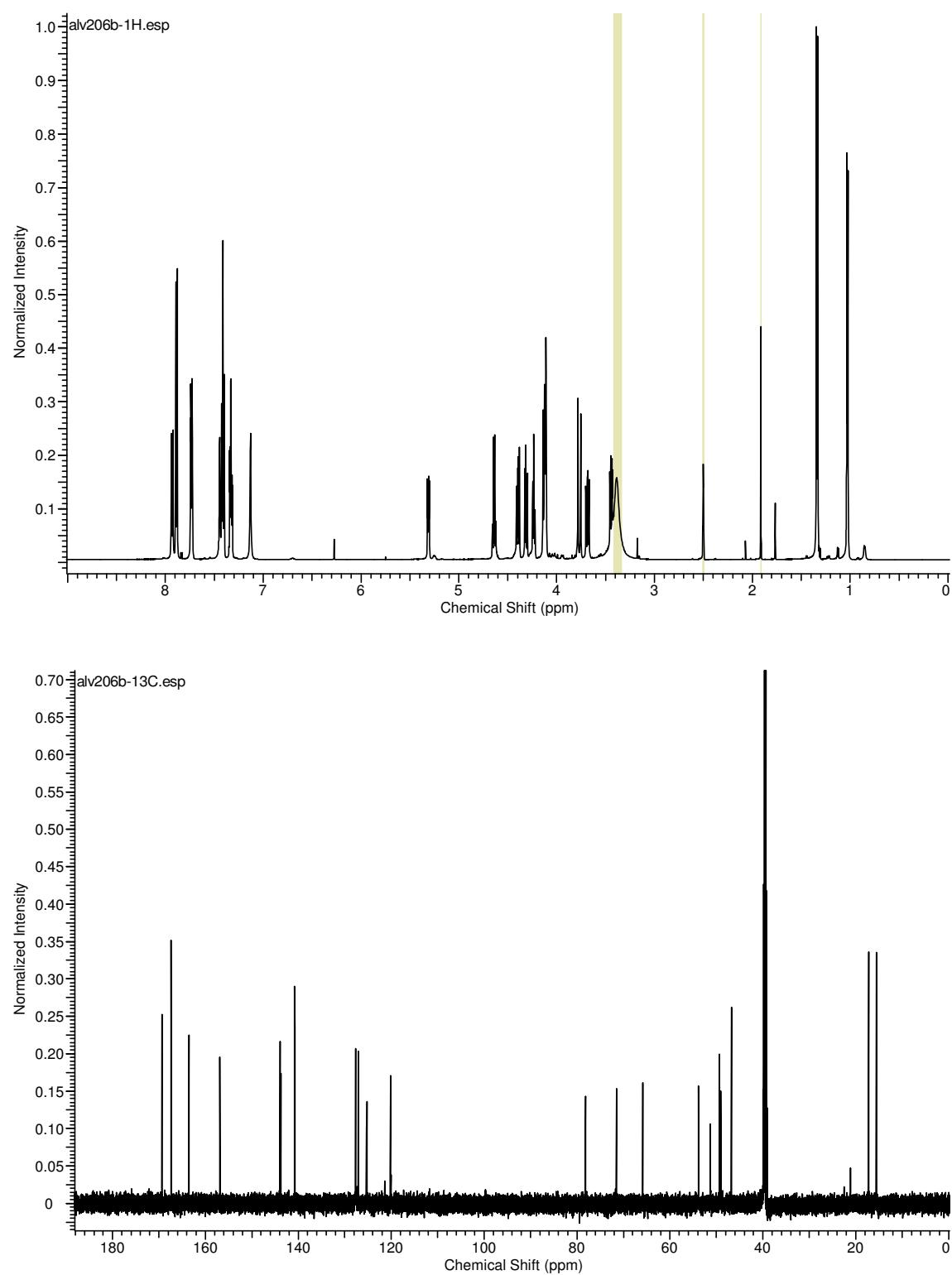
^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 22(2,1,7,3)



^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 22(2,2,6,14)



^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 22(2,2,7,3)



^1H and ^{13}C NMR spectra (d_6 -DMSO) for compound 22(2,2,7,14)

