

Supplementary material for

Synthesis of carfentanil amide opioids using the Ugi multicomponent reaction

András Váradi^a, Travis C. Palmer^a, Nathan Haselton^a, Daniel Afonin^a, Joan J. Subrath^a, Valerie Le Rouzic^a, Amanda Hunkele^a, Gavril W. Pasternak^a, Gina F. Marrone^a, Attila Borics^b and Susruta Majumdar^{a,*}

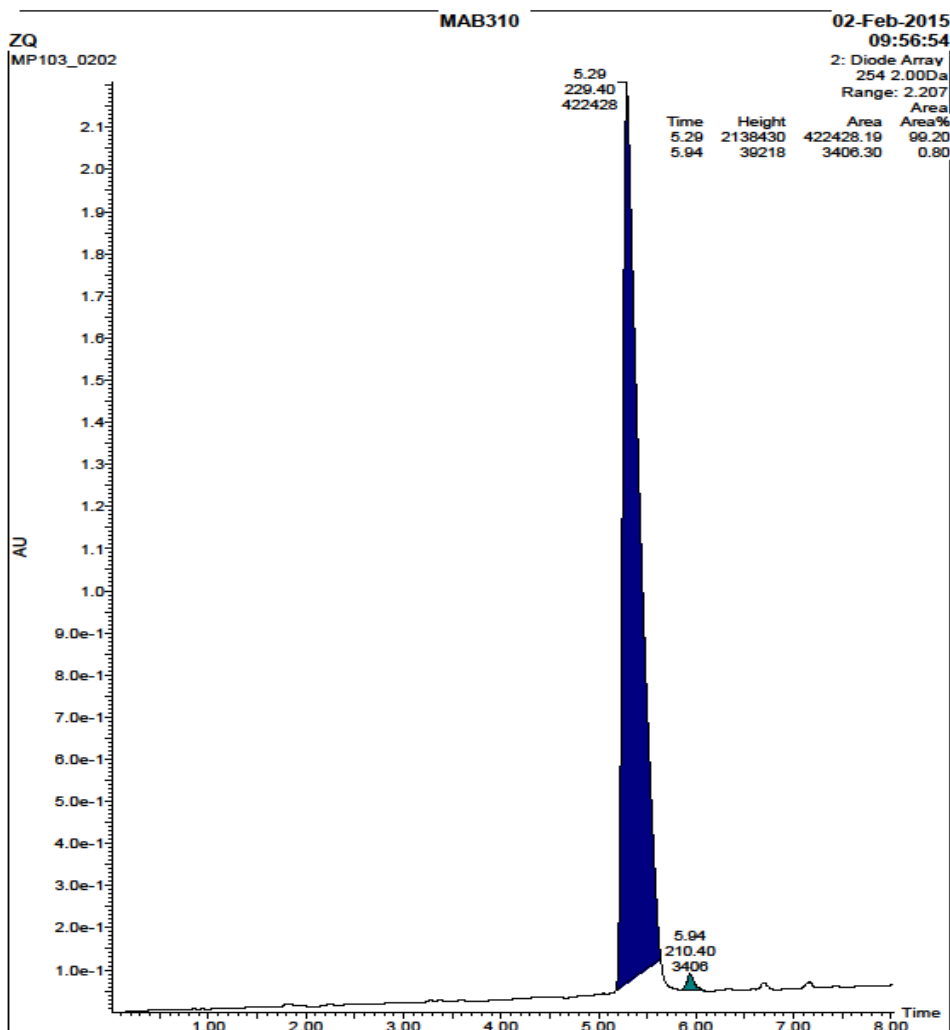
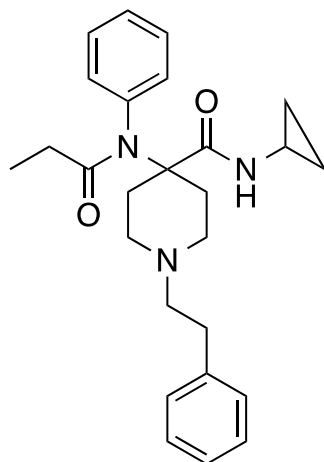
^aDepartment of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 (USA)

^bInstitute of Biochemistry, Biological Research Centre, Hungarian Academy of Sciences, Temesvári krt. 62, Szeged, Hungary H-6726

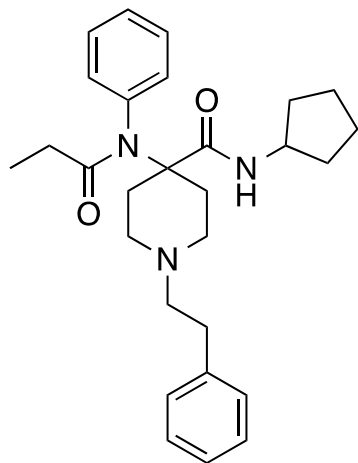
1. Compound analysis

***N*-cyclopropyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (4):**

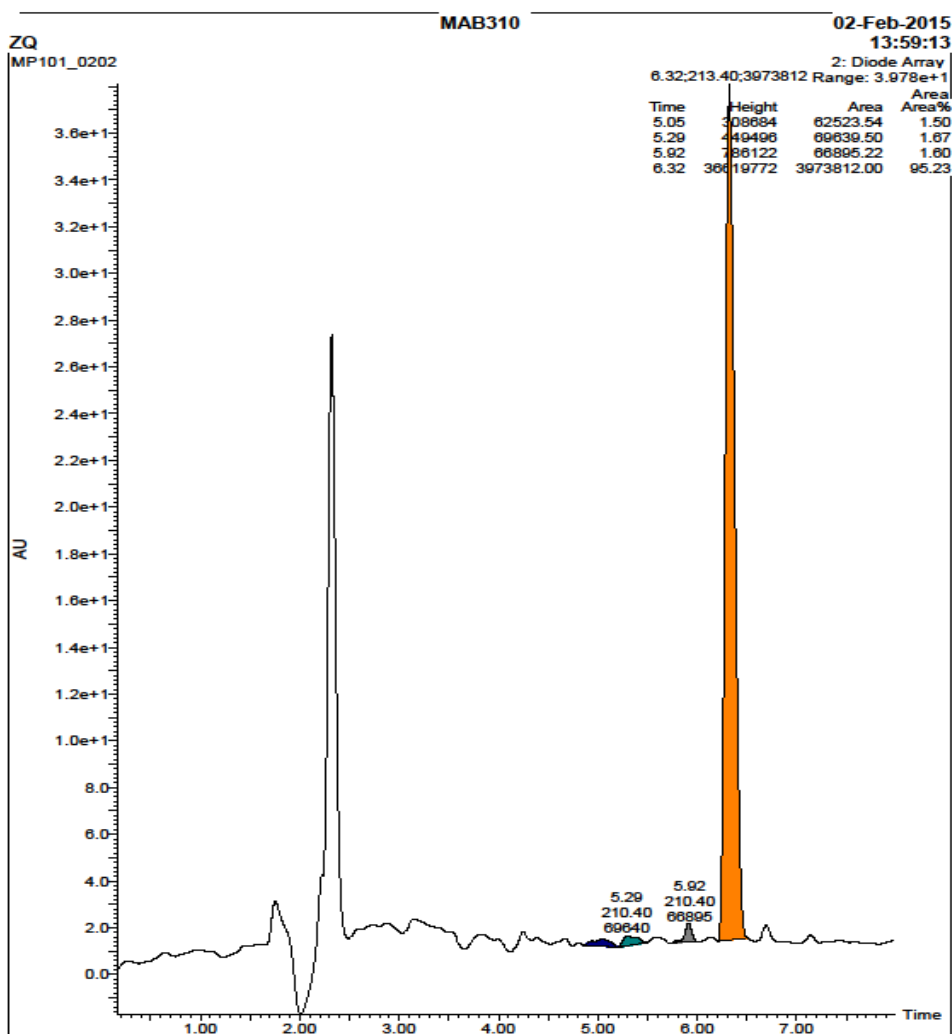
Prepared by the general procedure, using cyclopropyl isocyanide (29.5 mg, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 42%. IR (NaCl): 3347, 2937, 2382, 1662, 1593, 1491, 1453, 1347, 1248, 1120, 748, 701, 610. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.21 (m, 3H), 7.18 – 7.08 (m, 4H), 7.04 (d, *J* = 7.4 Hz, 1H), 7.03 – 6.98 (m, 2H), 6.80 (s, 1H), 2.66 (dq, *J* = 7.0, 3.4 Hz, 1H), 2.62 – 2.50 (m, 4H), 2.37 (dd, *J* = 10.5, 6.0 Hz, 2H), 2.28 (d, *J* = 13.6 Hz, 2H), 2.12 (t, *J* = 11.4 Hz, 2H), 1.74 (q, *J* = 7.4 Hz, 2H), 1.67 (d, *J* = 12.1 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.71 – 0.61 (m, 2H), 0.40 (td, *J* = 2.9, 1.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 175.7, 174.6, 140.1, 130.9, 129.3, 128.8, 128.7, 128.6, 126.2, 64.3, 60.5, 50.6, 34.2, 33.9, 30.2, 9.5, 9.4, 6.8. HRMS calcd for C₂₆H₃₄N₃O₂ (MH⁺), 420.2651; found, 420.2656. HPLC 5.29 min; purity: 99.20%.



***N*-cyclopentyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (5):**

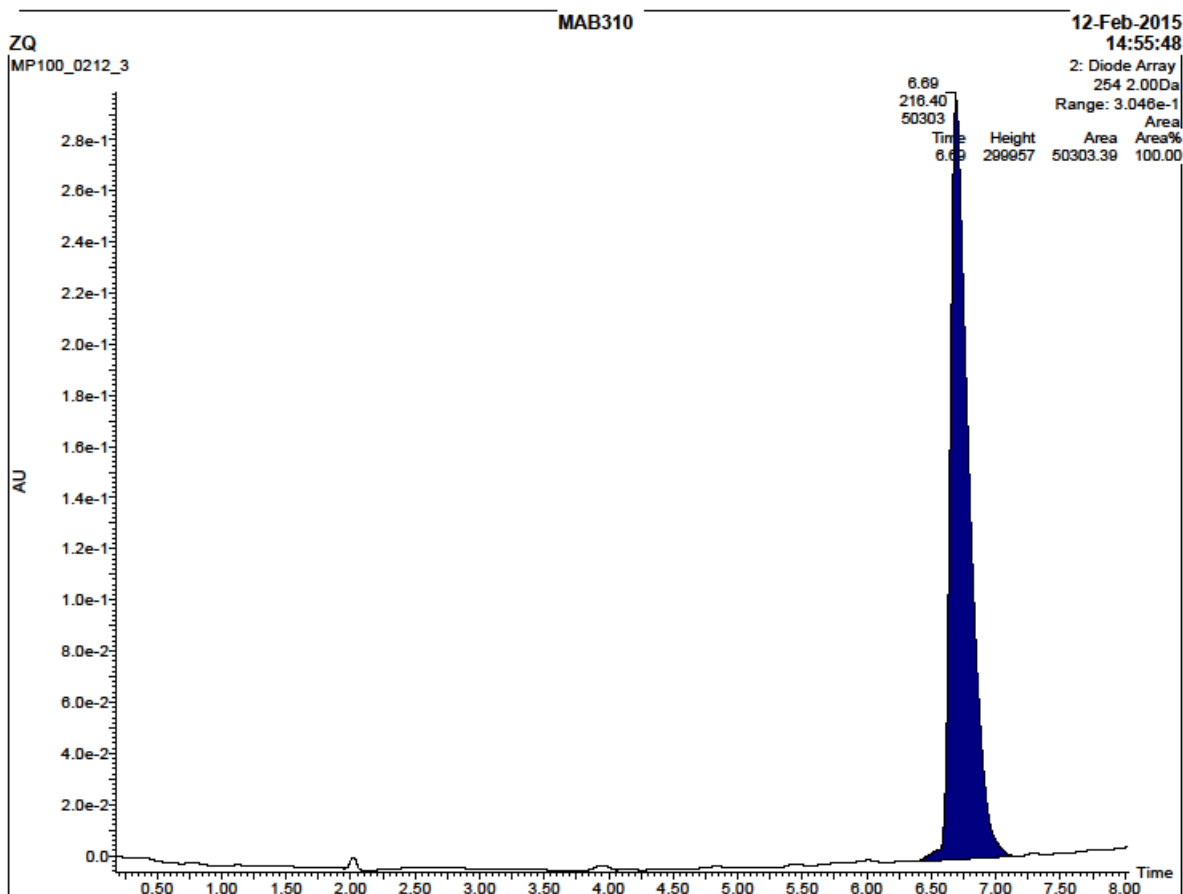
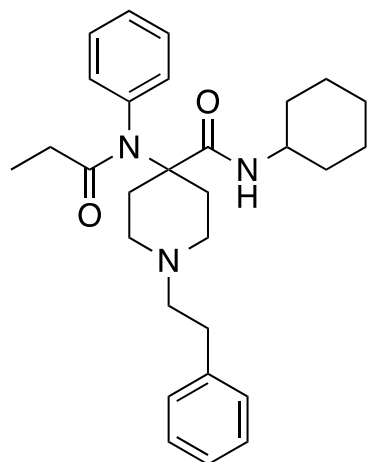


Prepared by the general procedure, using cyclopentyl isocyanide (48.6 μ l, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 75%. IR (NaCl): 2943, 1664, 1593, 1492, 1452, 1373, 1247, 701. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, J = 7.4 Hz, 3H), 7.27 – 7.20 (m, 3H), 7.19 – 7.14 (m, 1H), 7.16 – 7.10 (m, 2H), 6.91 (d, J = 7.1 Hz, 1H), 4.24 (h, J = 6.6 Hz, 1H), 2.72 (t, J = 8.2 Hz, 4H), 2.51 (t, J = 8.2 Hz, 2H), 2.45 (d, J = 13.7 Hz, 2H), 2.31 – 2.23 (m, 2H), 2.03 – 1.93 (m, 2H), 1.86 (q, J = 7.4 Hz, 2H), 1.79 (s, 2H), 1.72 – 1.66 (m, 2H), 1.61 (td, J = 6.9, 3.6 Hz, 3H), 1.53 – 1.44 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 172.2, 130.8, 129.3, 128.9, 128.8, 128.6, 128.6, 126.2, 64.6, 60.5, 51.7, 50.7, 34.4, 33.1, 30.3, 24.0, 9.6. HRMS calcd for $\text{C}_{28}\text{H}_{38}\text{N}_3\text{O}_2$ (MH $^+$), 448.2964; found, 448.2959. HPLC 6.32 min; purity: 95.23%.

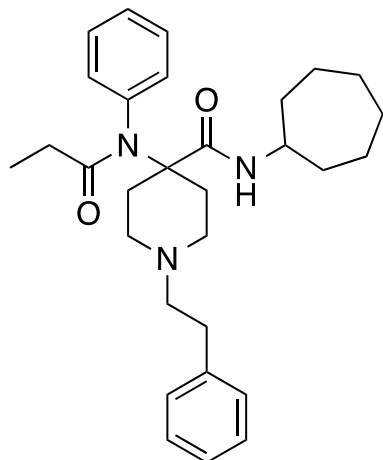


***N*-cyclohexyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (6):**

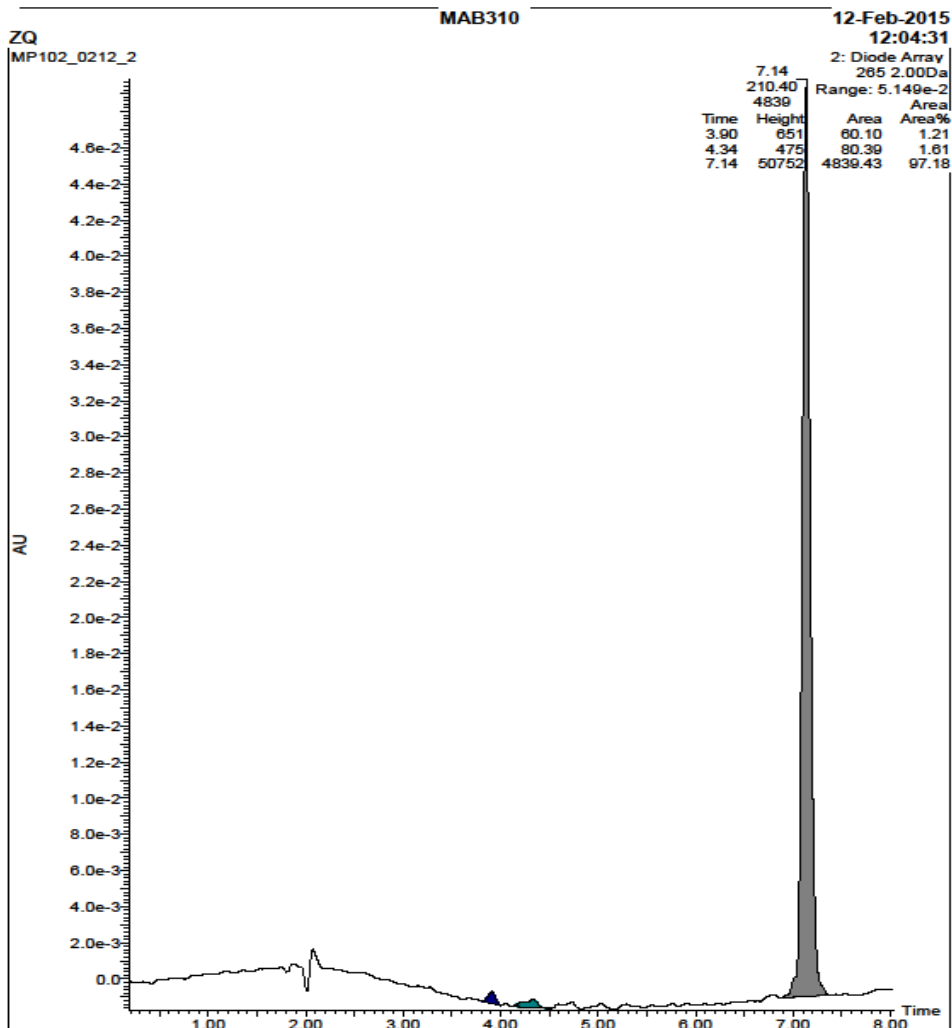
Prepared by the general procedure, using cyclohexyl isocyanide (54.7 μ l, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 99%. IR (NaCl): 3360, 3026, 2932, 2853, 1741, 1665, 1594, 1528, 1493, 1451, 1374, 1250, 1150, 1120, 1087, 1029, 891, 771, 735, 701. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 3H), 7.30 – 7.15 (m, 5H), 7.15 – 7.11 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 3.88 – 3.77 (m, 1H), 2.85 – 2.78 (m, 2H), 2.75 – 2.68 (m, 4H), 2.55 – 2.48 (m, 2H), 2.48 – 2.42 (m, 3H), 2.33 – 2.24 (m, 2H), 1.97 – 1.90 (m, 2H), 1.86 (q, J = 7.4 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.71 (dt, J = 13.4, 4.1 Hz, 2H), 1.63 – 1.54 (m, 1H), 1.44 – 1.31 (m, 2H), 1.22 (td, J = 11.8, 4.0 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 171.6, 140.3, 130.9, 129.3, 128.9, 128.8, 128.6, 128.6, 128.6, 126.2, 64.6, 60.5, 59.5, 53.3, 50.7, 48.6, 41.4, 34.4, 34.4, 33.9, 33.1, 30.4, 25.9, 25.0, 9.7. HRMS calcd for $\text{C}_{29}\text{H}_{40}\text{N}_3\text{O}_2$ (MH^+), 462.3121; found, 462.3103. HPLC 6.69 min; purity: 100%.



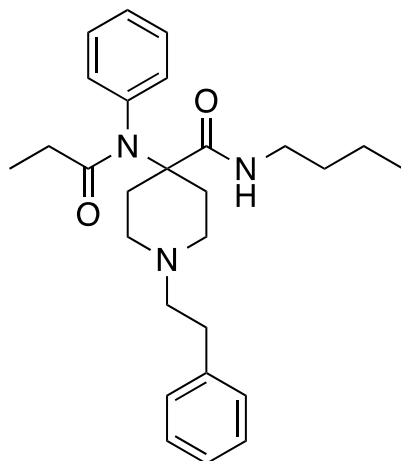
***N*-cycloheptyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (7):**



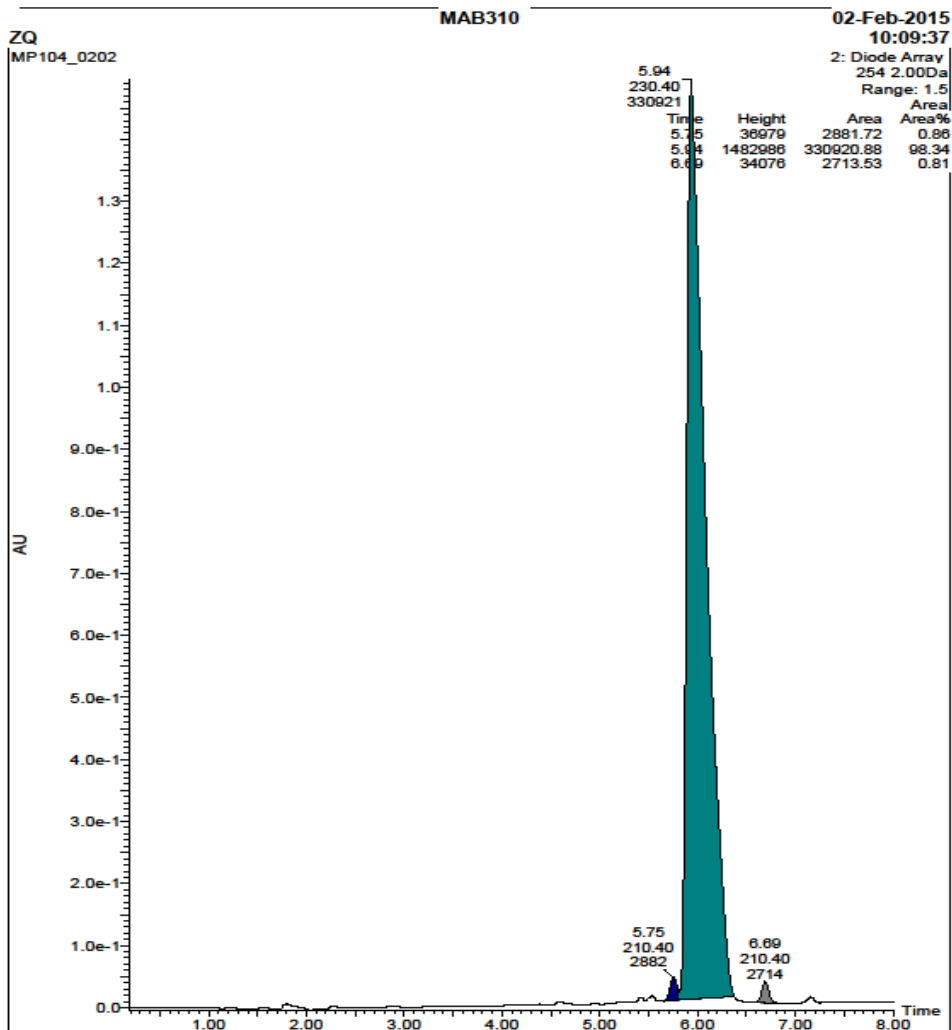
Prepared by the general procedure, using cycloheptyl isocyanide (54.2 mg, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 47%. IR (NaCl): 2928, 1664, 1492, 1373, 1247, 701. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 3H), 7.23 (d, *J* = 7.4 Hz, 4H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.90 (s, 1H), 4.02 – 3.93 (m, 1H), 2.82 (dd, *J* = 7.8, 4.3 Hz, 2H), 2.74 (d, *J* = 8.1 Hz, 2H), 2.58 (s, 2H), 2.46 (d, *J* = 13.5 Hz, 3H), 2.29 (q, *J* = 7.6 Hz, 1H), 1.94 (dt, *J* = 12.6, 4.1 Hz, 2H), 1.87 (q, *J* = 7.4 Hz, 3H), 1.68 – 1.56 (m, 4H), 1.52 (dd, *J* = 7.1, 4.6 Hz, 5H), 1.12 (t, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl₃) δ 175.8, 171.3, 140.0, 130.7, 129.5, 128.8, 128.7, 126.5, 64.0, 59.7, 50.9, 50.2, 35.1, 33.4, 30.3, 28.1, 24.4, 9.9, 9.6. HRMS calcd for C₃₀H₄₂N₃O₂ (MH⁺), 476.3277; found, 476.3264. HPLC 7.14 min; purity: 97.18 %.



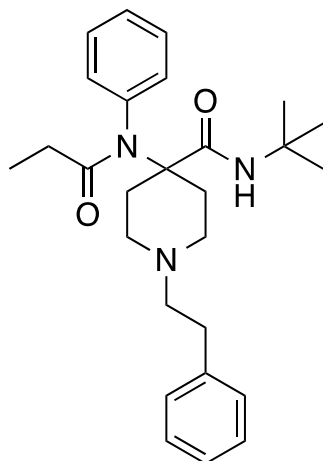
N-butyl-1-phenethyl-4-(N-phenylpropionamido)piperidine-4-carboxamide (8): Prepared by the general procedure, using butyl isocyanide (46.0 μ l, 0.44 mmol, 1 eq.) and N-phenethyl-4-



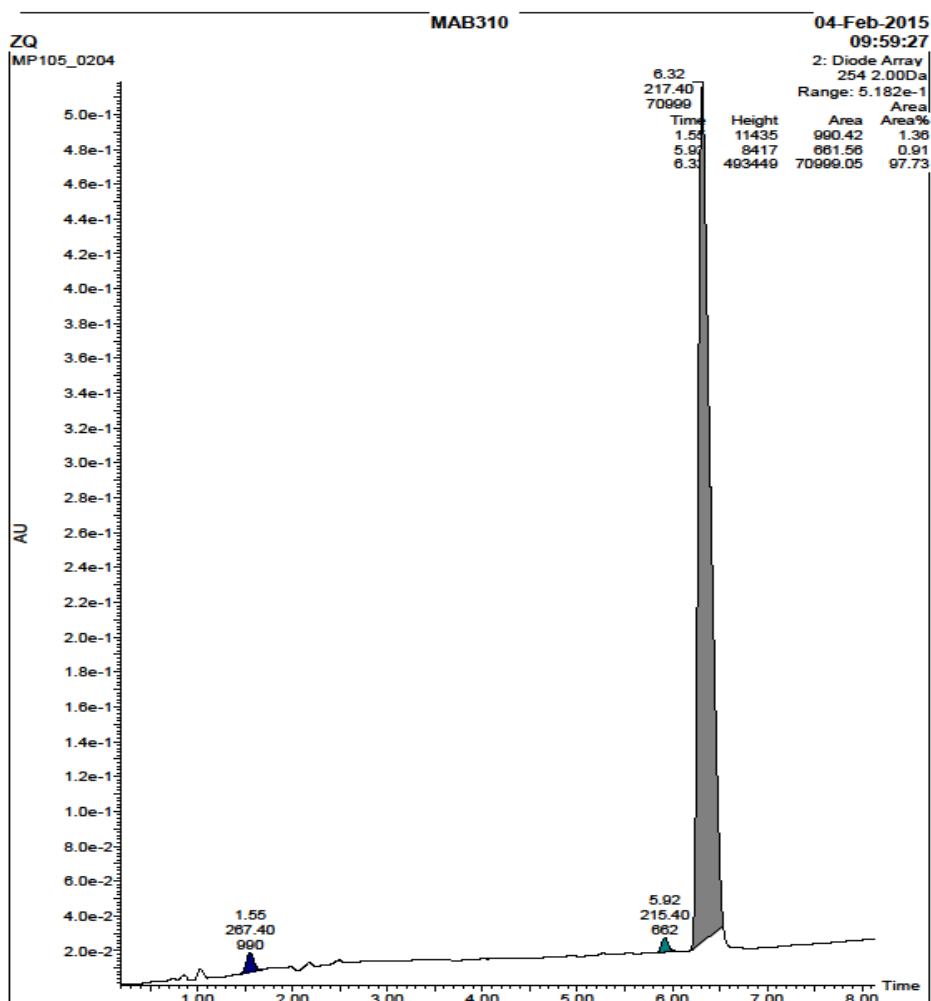
piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 58%. IR (NaCl): 3375, 2934, 1664, 1593, 1528, 1492, 1452, 1373, 1245, 701, 629, 557. ^1H NMR (500 MHz, Chloroform- d) δ 7.36 (d, J = 7.4 Hz, 3H), 7.28 – 7.20 (m, 4H), 7.16 (d, J = 7.1 Hz, 1H), 7.15 – 7.10 (m, 2H), 6.94 (s, 1H), 3.32 (q, J = 6.7 Hz, 2H), 2.71 (dd, J = 10.7, 5.9 Hz, 4H), 2.55 – 2.39 (m, 4H), 2.26 (t, J = 11.5 Hz, 2H), 1.86 (q, J = 7.4 Hz, 2H), 1.79 (t, J = 12.5 Hz, 2H), 1.54 (p, J = 7.4 Hz, 2H), 1.38 (q, J = 7.5 Hz, 2H), 0.98 – 0.85 (m, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 172.6, 140.3, 130.9, 129.3, 128.8, 128.6, 128.6, 126.2, 64.6, 60.5, 50.7, 39.7, 34.4, 33.9, 31.8, 30.4, 20.5, 14.0, 9.5. HRMS calcd for $\text{C}_{27}\text{H}_{38}\text{N}_3\text{O}_2$ (MH^+), 436.2964; found, 436.2955. HPLC 5.94 min; purity: 98.34%.



***N*-(*tert*-butyl)-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (9):**

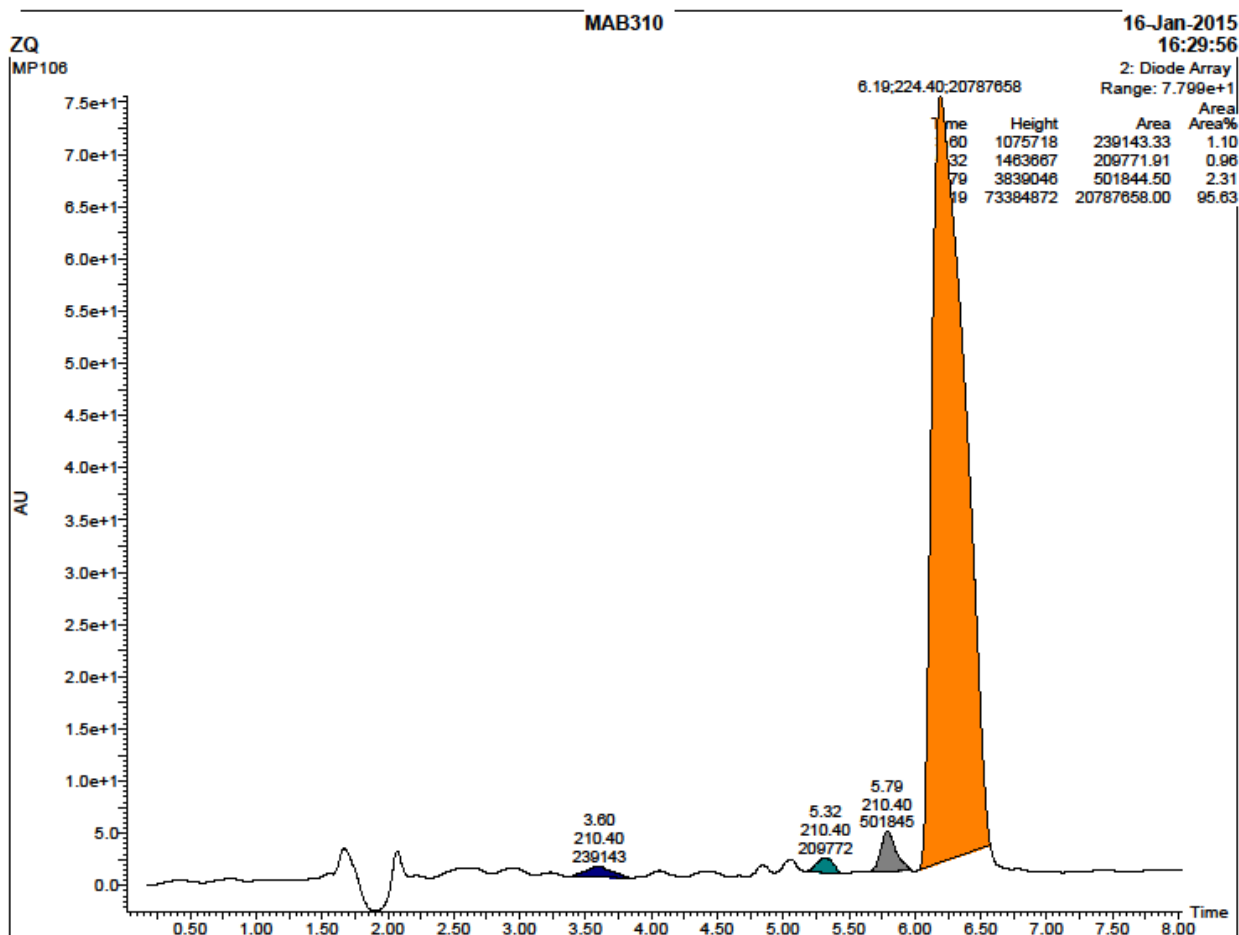


Prepared by the general procedure, using *tert*-butyl isocyanide (49.8 μ l, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 24%. IR (NaCl): 3854, 2936, 2812, 1742, 1671, 1593, 1540, 1492, 1455, 1363, 1295, 1118, 1074, 774, 701. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.36 (m, 3H), 7.25 (q, J = 7.9, 6.9 Hz, 4H), 7.20 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 6.87 (s, 1H), 2.90 (d, J = 12.1 Hz, 2H), 2.84 – 2.76 (m, 2H), 2.68 – 2.58 (m, 2H), 2.46 (d, J = 12.5 Hz, 3H), 2.26 (q, J = 7.6 Hz, 1H), 1.89 (q, J = 7.4 Hz, 3H), 1.40 (s, 9H), 1.12 (t, J = 7.6 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.7, 171.5, 140.0, 130.6, 129.4, 128.8, 128.8, 128.6, 126.4, 64.5, 59.8, 51.3, 50.3, 33.6, 30.3, 28.8, 10.0, 9.7. HRMS calcd for $\text{C}_{27}\text{H}_{38}\text{N}_3\text{O}_2$ (MH^+), 436.2964; found, 436.2977. HPLC 6.32 min; purity: 97.73%.

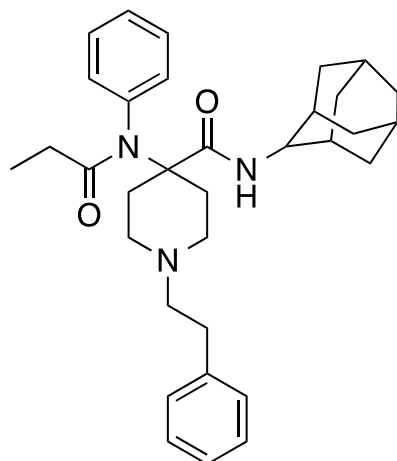


***N*-isopentyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (10):**

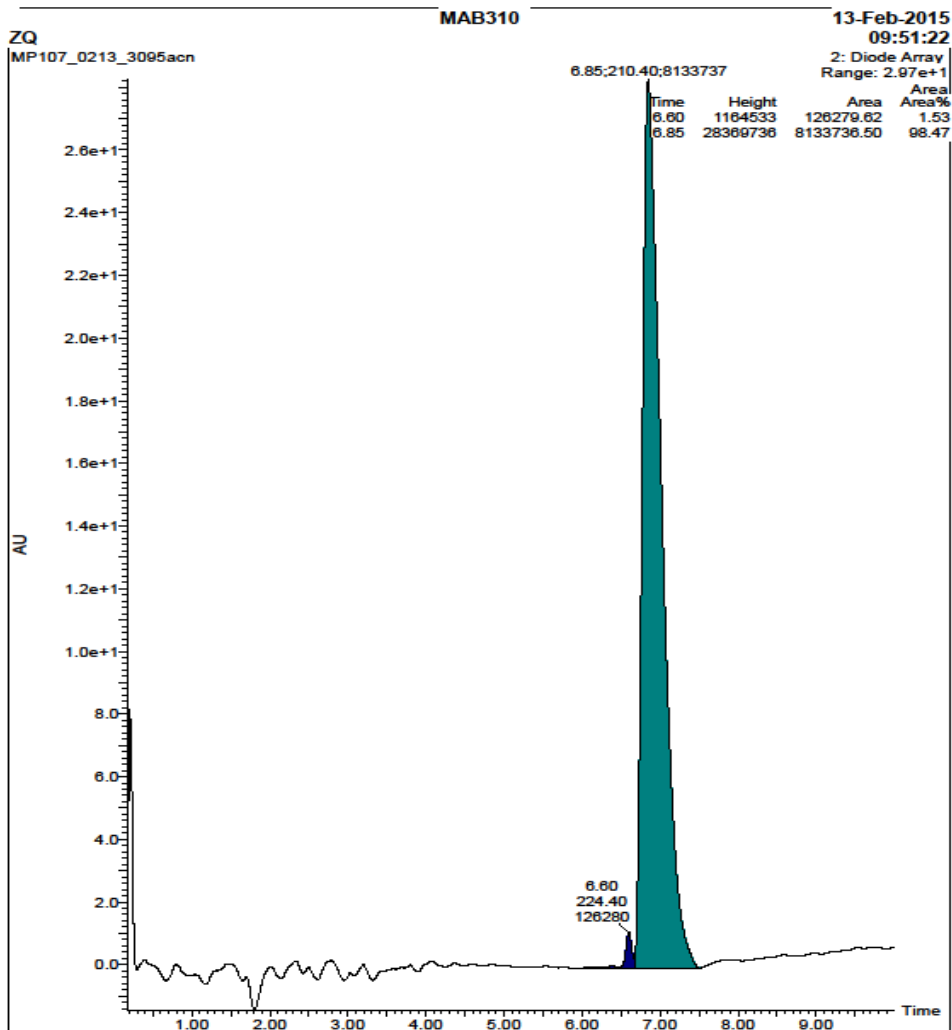
Prepared by the general procedure, using isoamyl isocyanide (42.8 mg, 0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 48% IR (NaCl): 3377, 2952, 1664, 1594, 1525, 1492, 1453, 1373, 1247, 1122, 1086, 748, 701. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 7.4 Hz, 3H), 7.24 (s, 4H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 3.34 (q, *J* = 6.9 Hz, 2H), 2.76 – 2.66 (m, 4H), 2.48 (dd, *J* = 22.7, 12.0 Hz, 3H), 2.26 (t, *J* = 11.4 Hz, 2H), 1.86 (q, *J* = 7.4 Hz, 2H), 1.79 (s, 1H), 1.65 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.54 (s, 2H), 1.45 (q, *J* = 7.1 Hz, 2H), 0.92 (t, *J* = 6.5 Hz, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 175.8, 130.9, 129.4, 128.8, 128.7, 128.6, 126.2, 60.6, 50.7, 38.6, 38.3, 34.5, 34.0, 30.4, 26.2, 22.7. HRMS calcd for C₂₈H₄₀N₃O₂ (MH⁺), 450.3121; found, 450.3117. HPLC 6.19 min; purity: 95.63%.



***N*-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (11):** Prepared by the general procedure, using adamantyl isocyanide (70.9 mg,

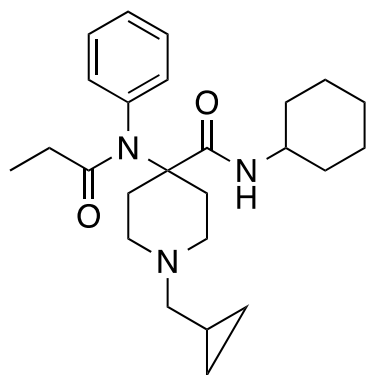


0.44 mmol, 1 eq.) and *N*-phenethyl-4-piperidone (89.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 34%. IR (NaCl): 2906, 2849, 1669, 1594, 1492, 1453, 1359, 1296, 1248, 747, 701. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 7.4 Hz, 3H), 7.24 (s, 4H), 7.15 (t, *J* = 6.3 Hz, 3H), 6.64 (s, 1H), 2.76 – 2.66 (m, 4H), 2.51 (dd, *J* = 10.4, 6.1 Hz, 2H), 2.41 (d, *J* = 13.5 Hz, 2H), 2.29 (t, *J* = 11.4 Hz, 2H), 2.06 (s, 8H), 1.86 (q, *J* = 7.4 Hz, 2H), 1.69 (d, *J* = 7.9 Hz, 6H), 1.52 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 175.6, 171.4, 140.5, 140.4, 130.9, 129.3, 128.8, 128.6, 126.2, 65.1, 60.6, 52.1, 50.8, 41.8, 36.7, 34.6, 34.0, 30.4, 29.7, 9.8. HRMS calcd for C₃₃H₄₄N₃O₂ (MH⁺), 514.3434; found, 514.3421. HPLC 6.85 min; purity: 98.47%.

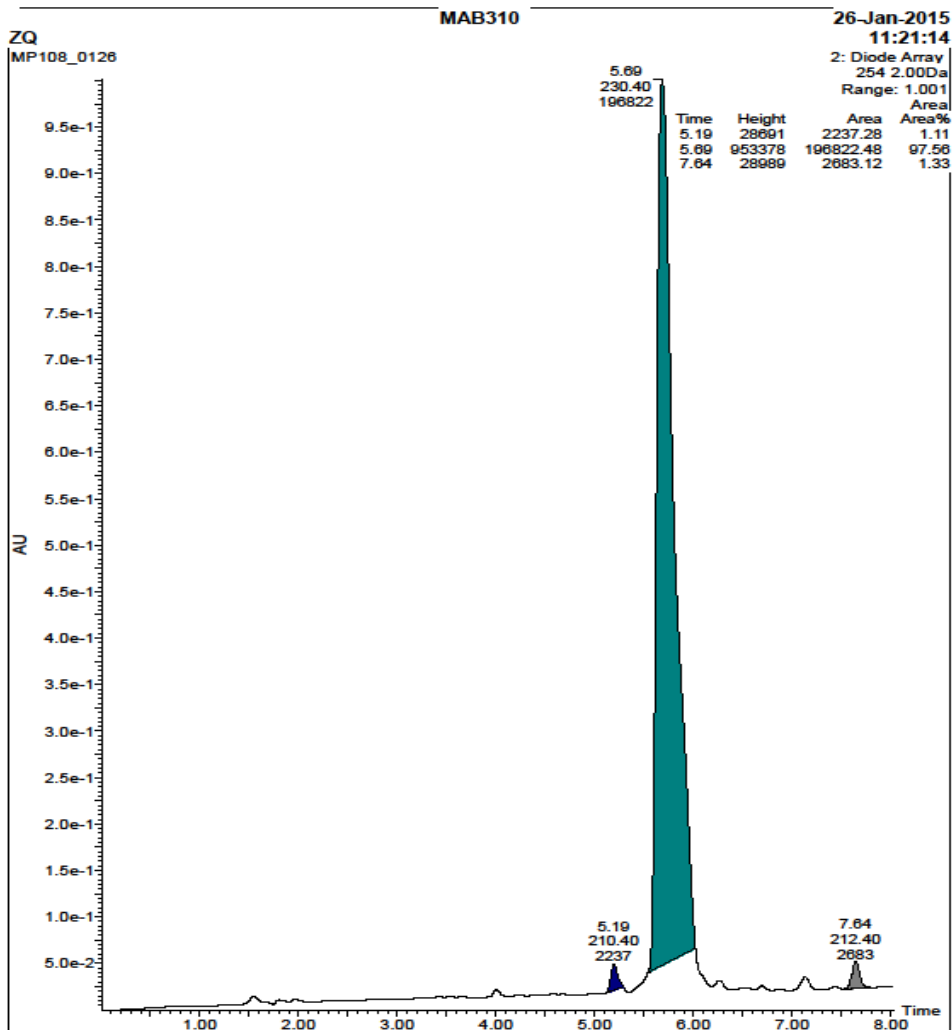


***N*-cyclohexyl-1-(cyclopropylmethyl)-4-(*N*-phenylpropionamido)piperidine-4-carboxamide**

(12): Prepared by the general procedure, using cyclohexyl isocyanide (54.7 μ l, 0.44 mmol, 1 eq.) and *N*-cyclopropylmethyl-4-piperidone (67.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 51%. IR (NaCl): 3361, 2932, 2853, 1666, 1593, 1530, 1491, 1451, 1375, 1249, 1089, 1020, 773, 733, 705.

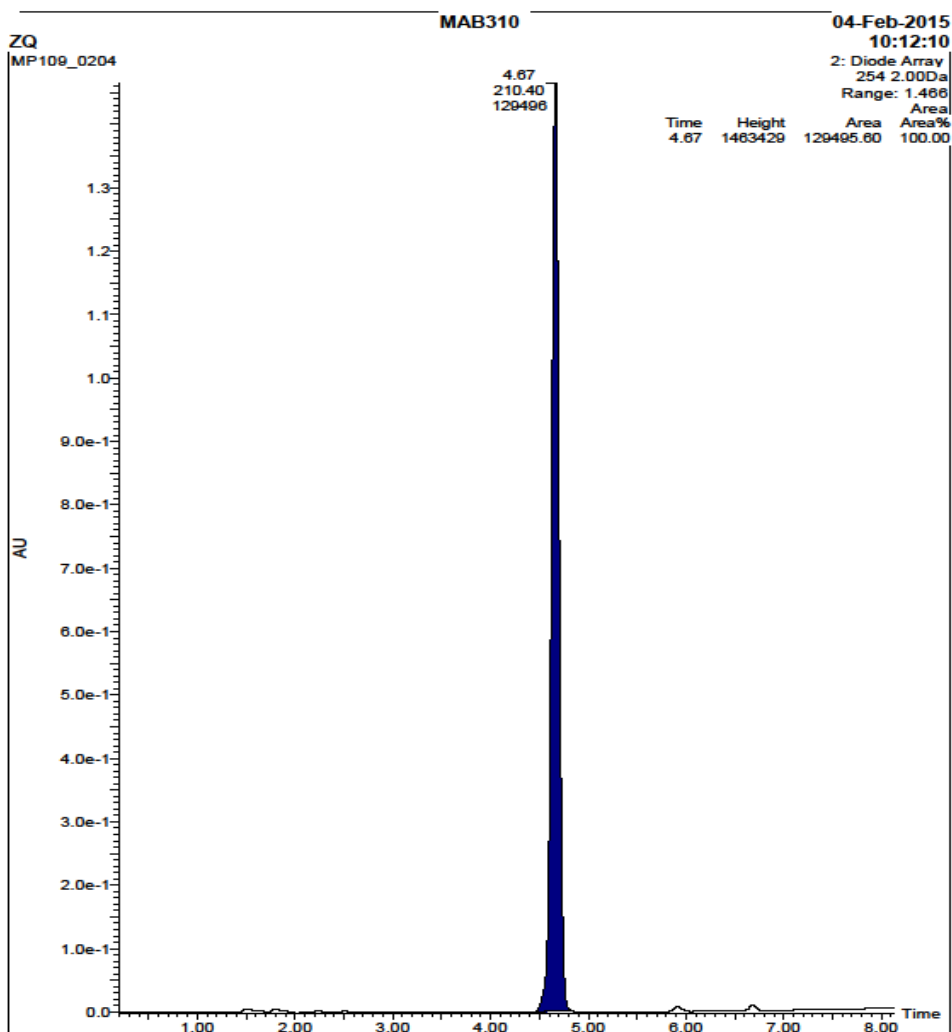
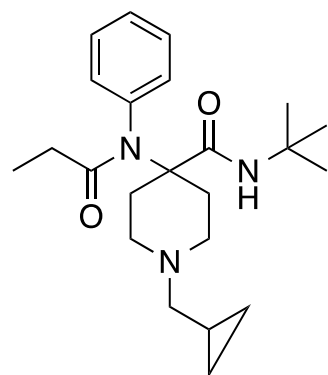


^1H NMR (500 MHz, Chloroform-*d*) δ 7.35 (d, J = 7.4 Hz, 3H), 7.24 (s, 2H), 6.82 (s, 1H), 3.89 – 3.75 (m, 1H), 2.74 (s, 2H), 2.43 (d, J = 13.9 Hz, 2H), 2.20 (d, J = 11.7 Hz, 2H), 2.15 (d, J = 6.6 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.85 (q, J = 7.4 Hz, 2H), 1.78 (s, 2H), 1.71 (dt, J = 13.5, 4.0 Hz, 2H), 1.59 (d, J = 13.7 Hz, 2H), 1.44 – 1.30 (m, 2H), 1.23 (q, J = 12.3, 11.0 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H), 0.76 (s, 1H), 0.44 (d, J = 7.8 Hz, 2H), 0.06 – -0.02 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.7, 171.7, 140.4, 130.9, 129.2, 128.6, 64.6, 63.7, 50.7, 48.5, 34.3, 33.1, 30.3, 25.8, 25.0, 9.6, 8.5, 4.1. HRMS calcd for $\text{C}_{25}\text{H}_{38}\text{N}_3\text{O}_2$ (MH^+), 412.2964; found, 412.2967. HPLC: 5.69 min: purity: 97.56%.



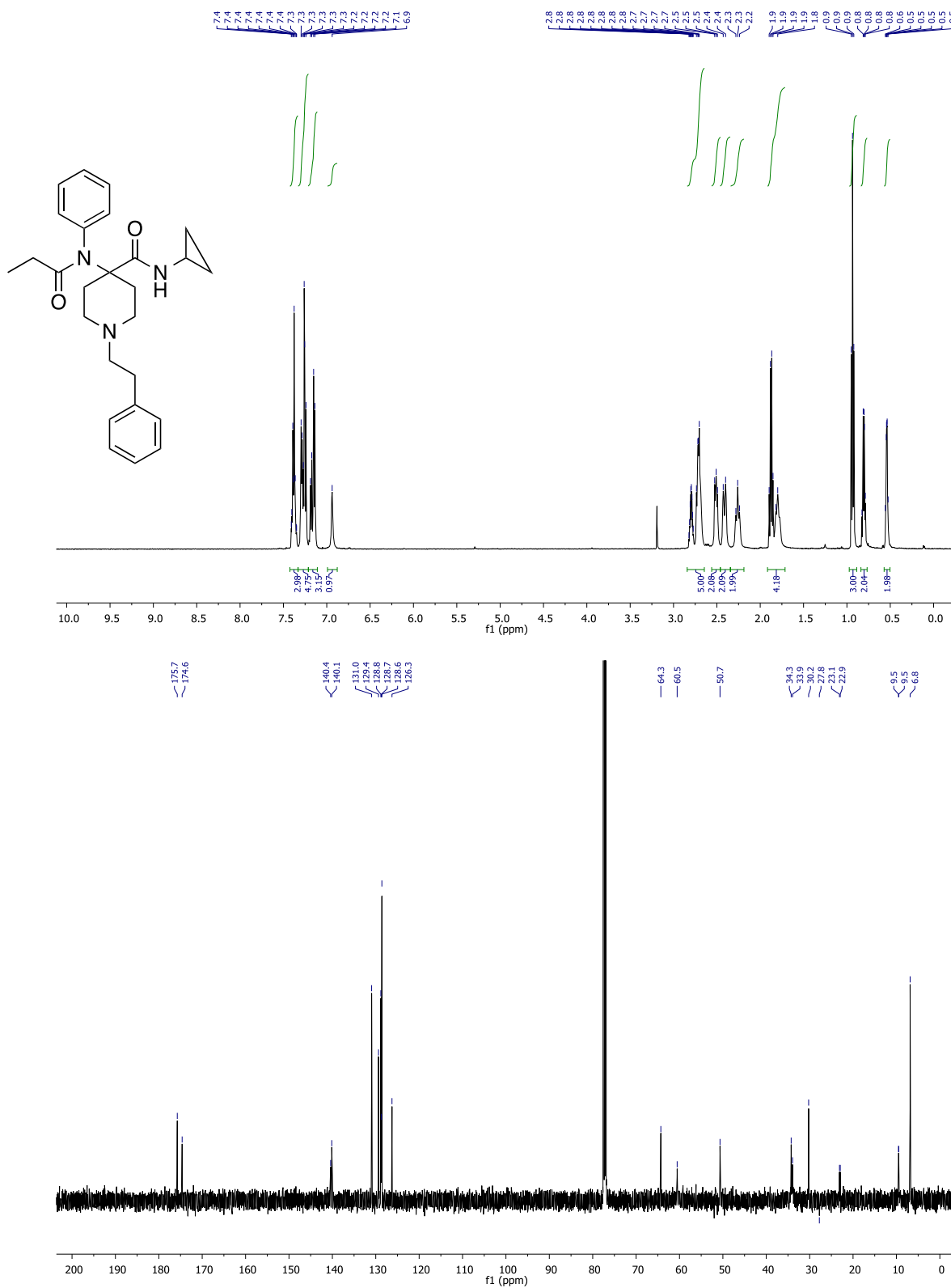
***N*-(*tert*-butyl)-1-(cyclopropylmethyl)-4-(*N*-phenylpropionamido)piperidine-4-carboxamide**

(13): Prepared by the general procedure, using *tert*-butyl isocyanide (49.8 μ l, 0.44 mmol, 1 eq.) and *N*-cyclopropylmethyl-4-piperidone (67.4 mg, 0.44 mmol, 1 eq.) in methanol. Yield: 41%. IR (NaCl): 2969, 2779, 1671, 1593, 1540, 1491, 1451, 1363, 1243, 1021, 770, 704. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.34 (t, J = 5.1 Hz, 3H), 7.24 (s, 2H), 6.80 (s, 1H), 2.75 (s, 2H), 2.41 (d, J = 13.4 Hz, 2H), 2.18 (dd, J = 29.4, 9.1 Hz, 4H), 1.85 (q, J = 7.4 Hz, 2H), 1.75 (s, 2H), 1.38 (s, 9H), 1.30 (s, 1H), 0.92 (t, J = 7.4 Hz, 3H), 0.76 (s, 1H), 0.48 – 0.37 (m, 2H), 0.03 (d, J = 5.1 Hz, 2H). HRMS calcd for $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_2$ (MH^+), 386.2808; found, 386.2820. HPLC: 4.67 min; purity: 100%.

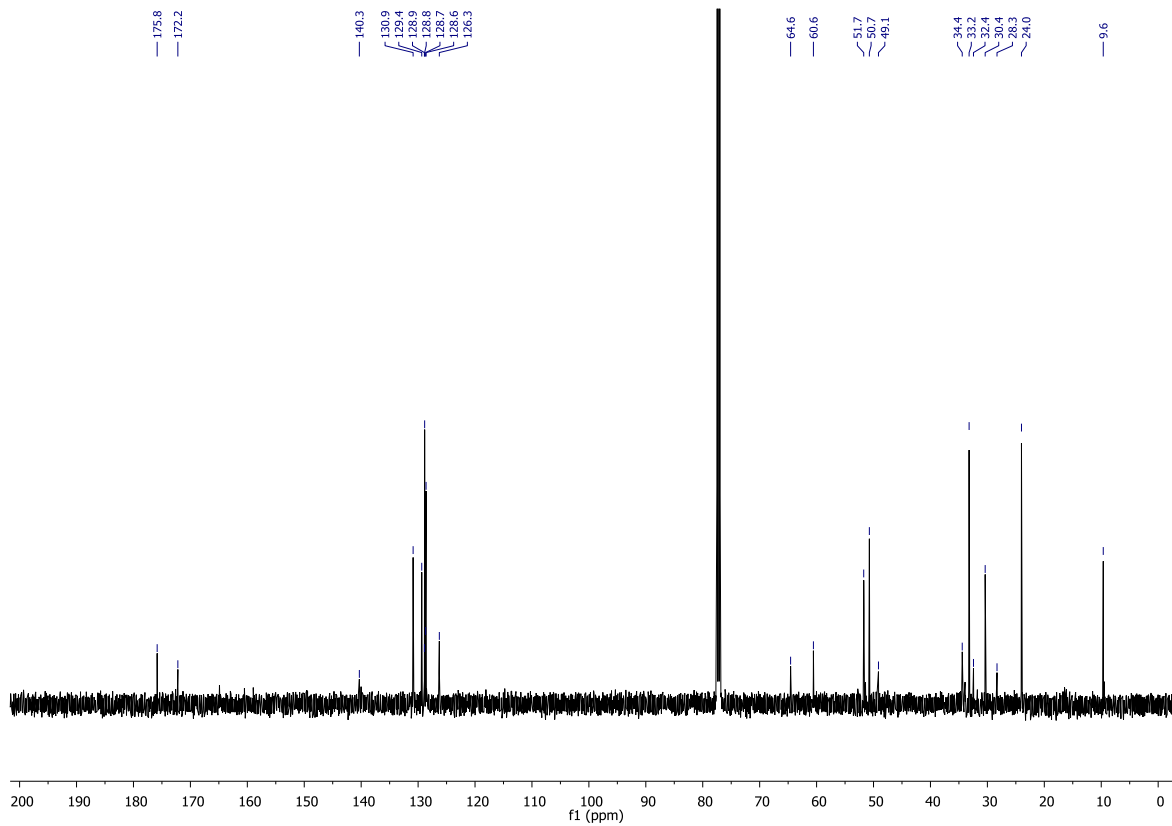
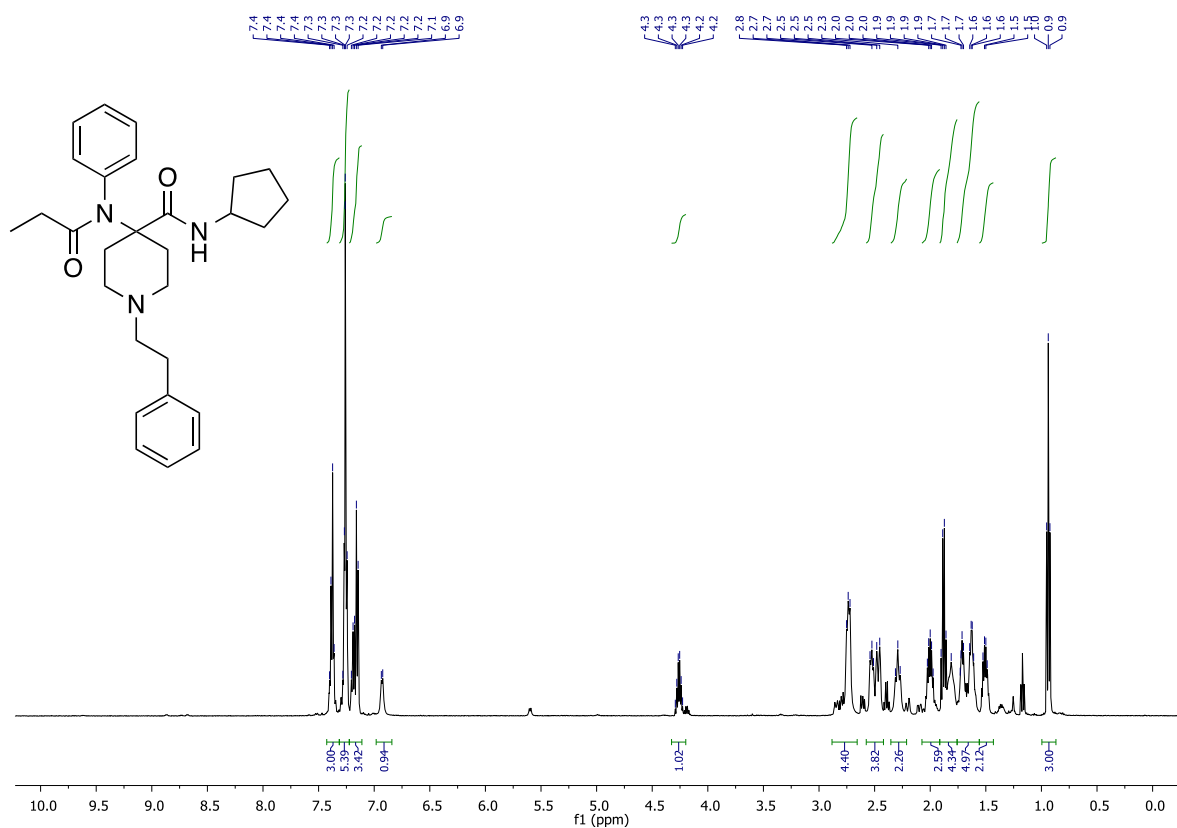


2. NMR Spectra of compounds

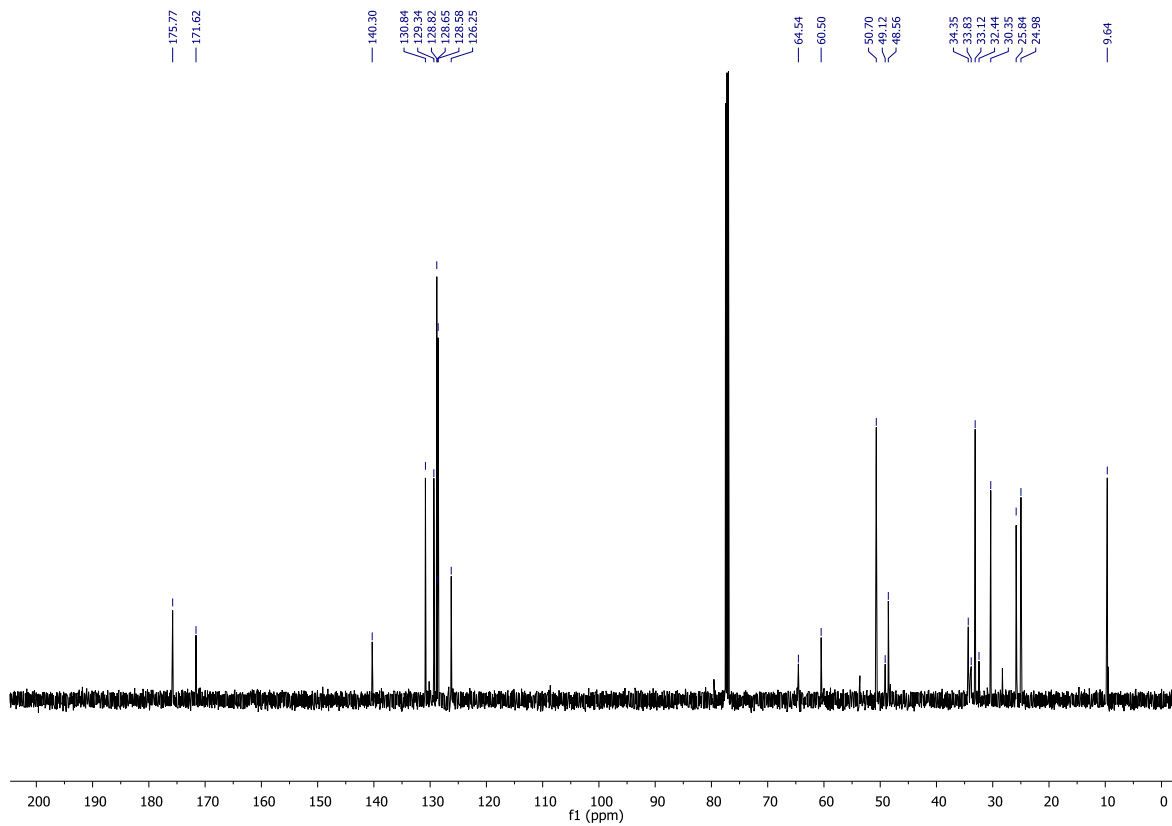
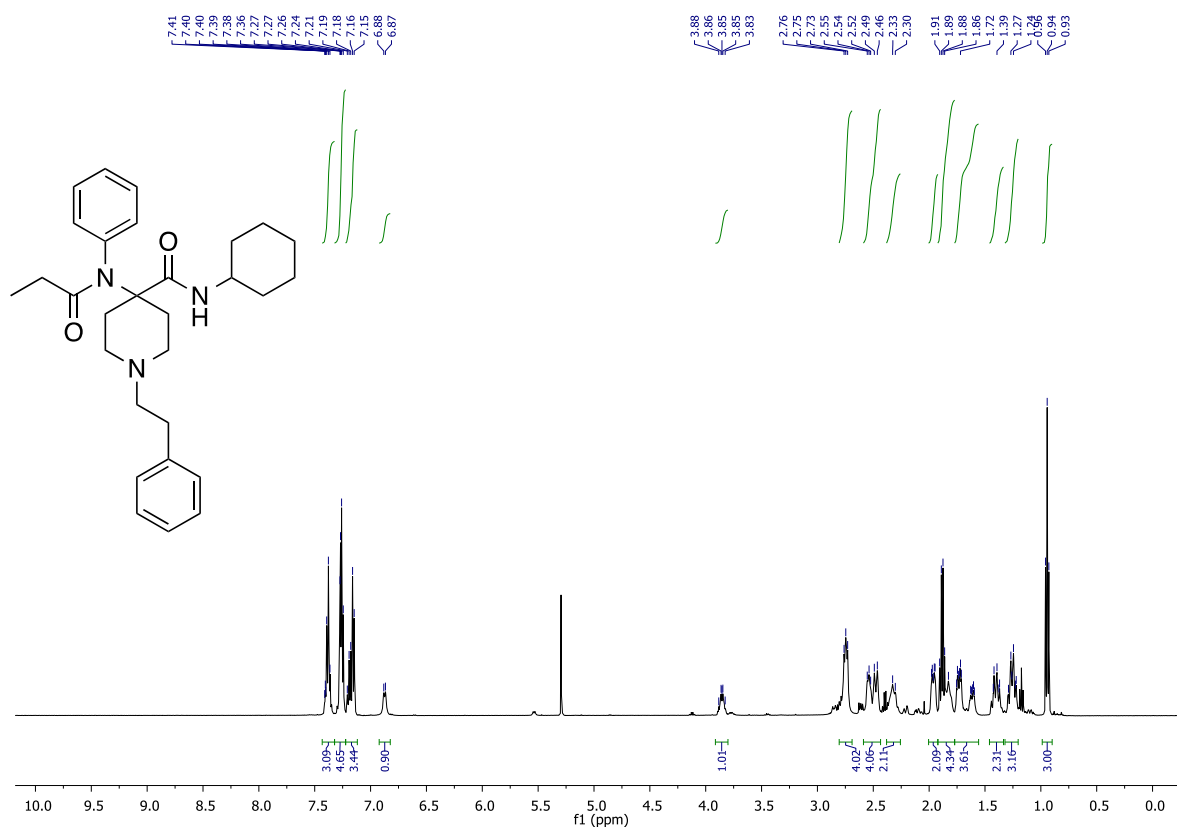
N-cyclopropyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (4)



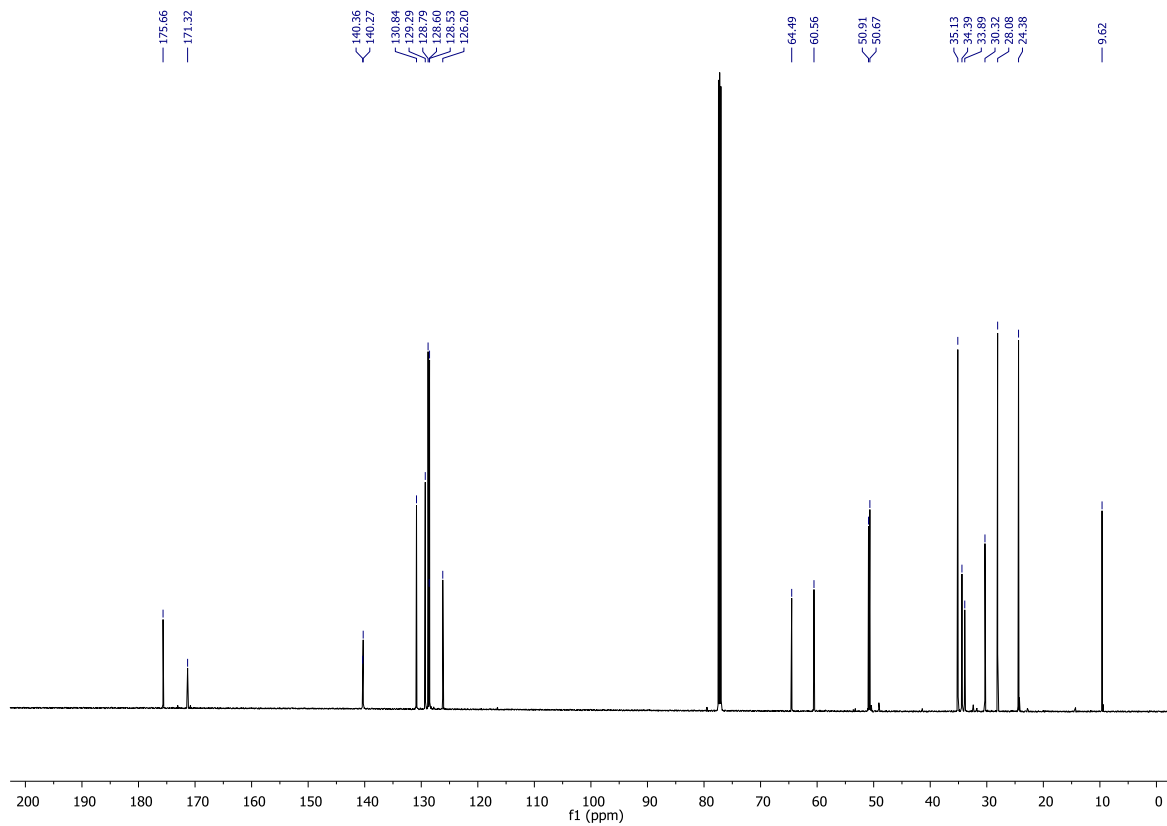
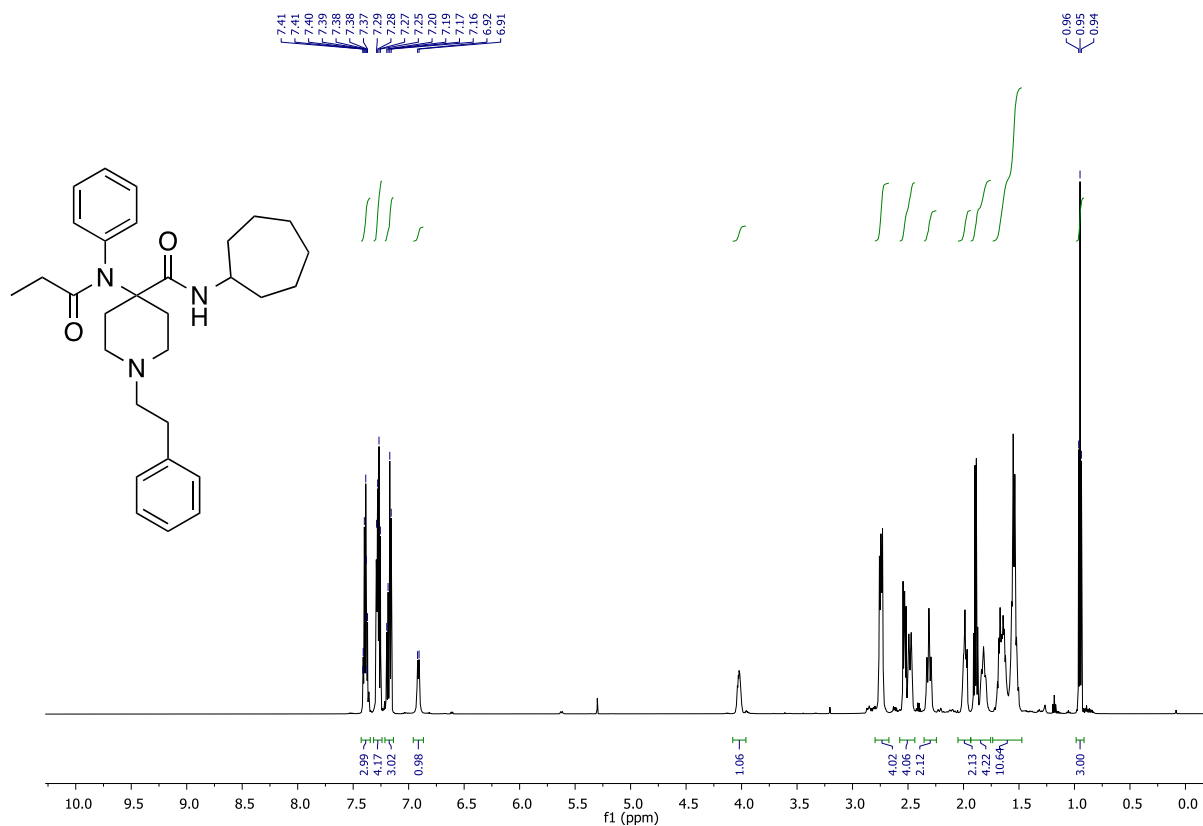
***N*-cyclopentyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (5)**



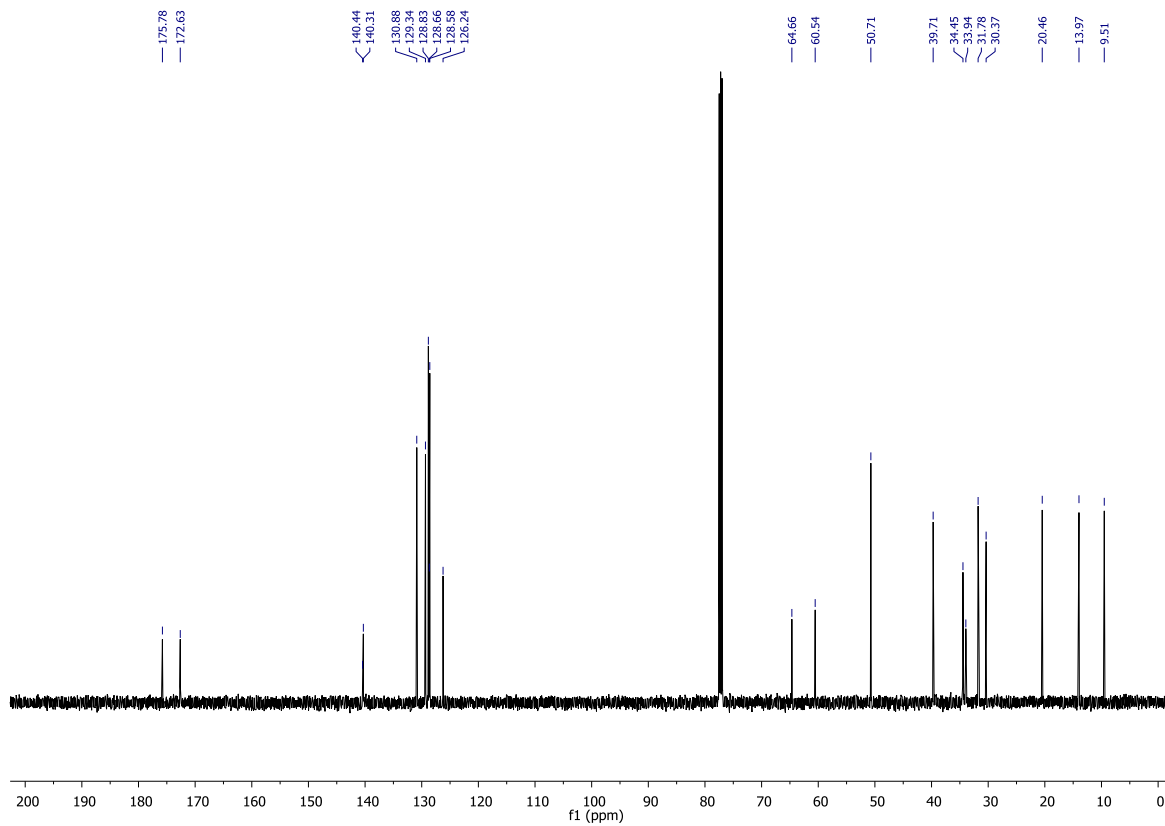
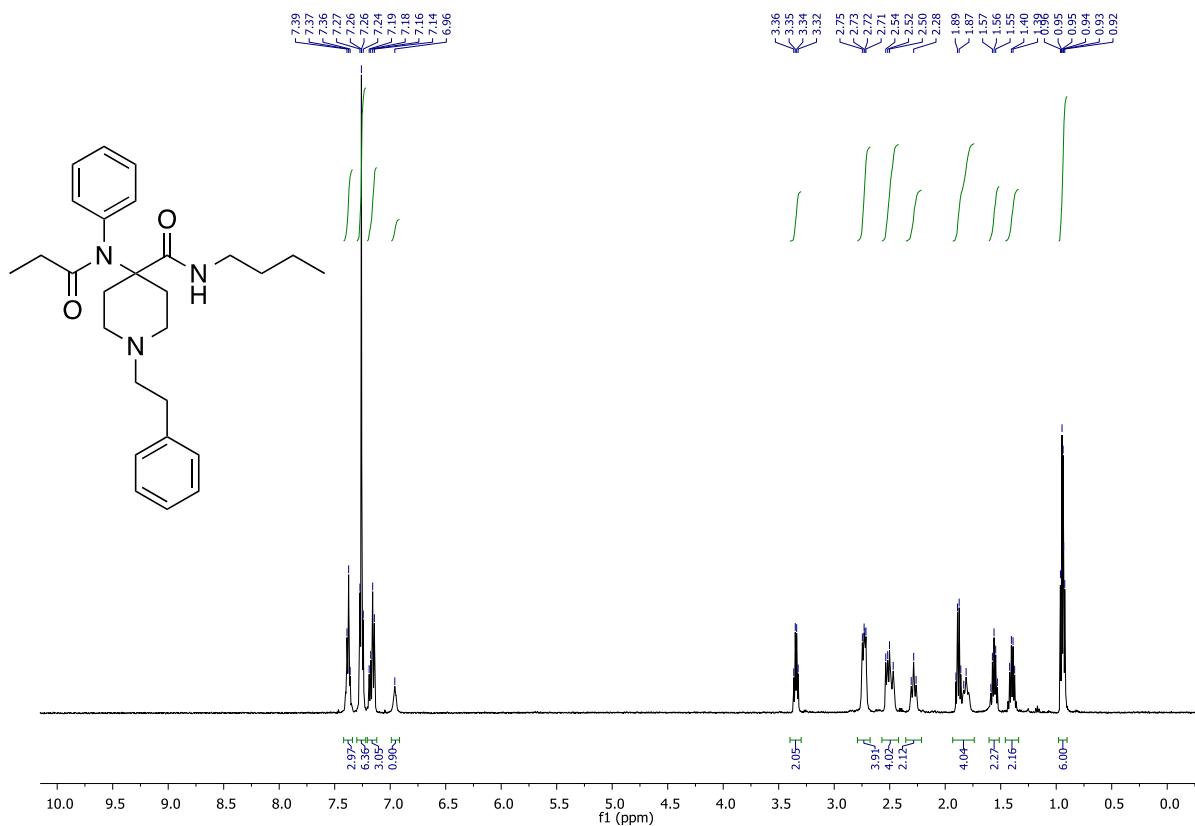
***N*-cyclohexyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (6)**



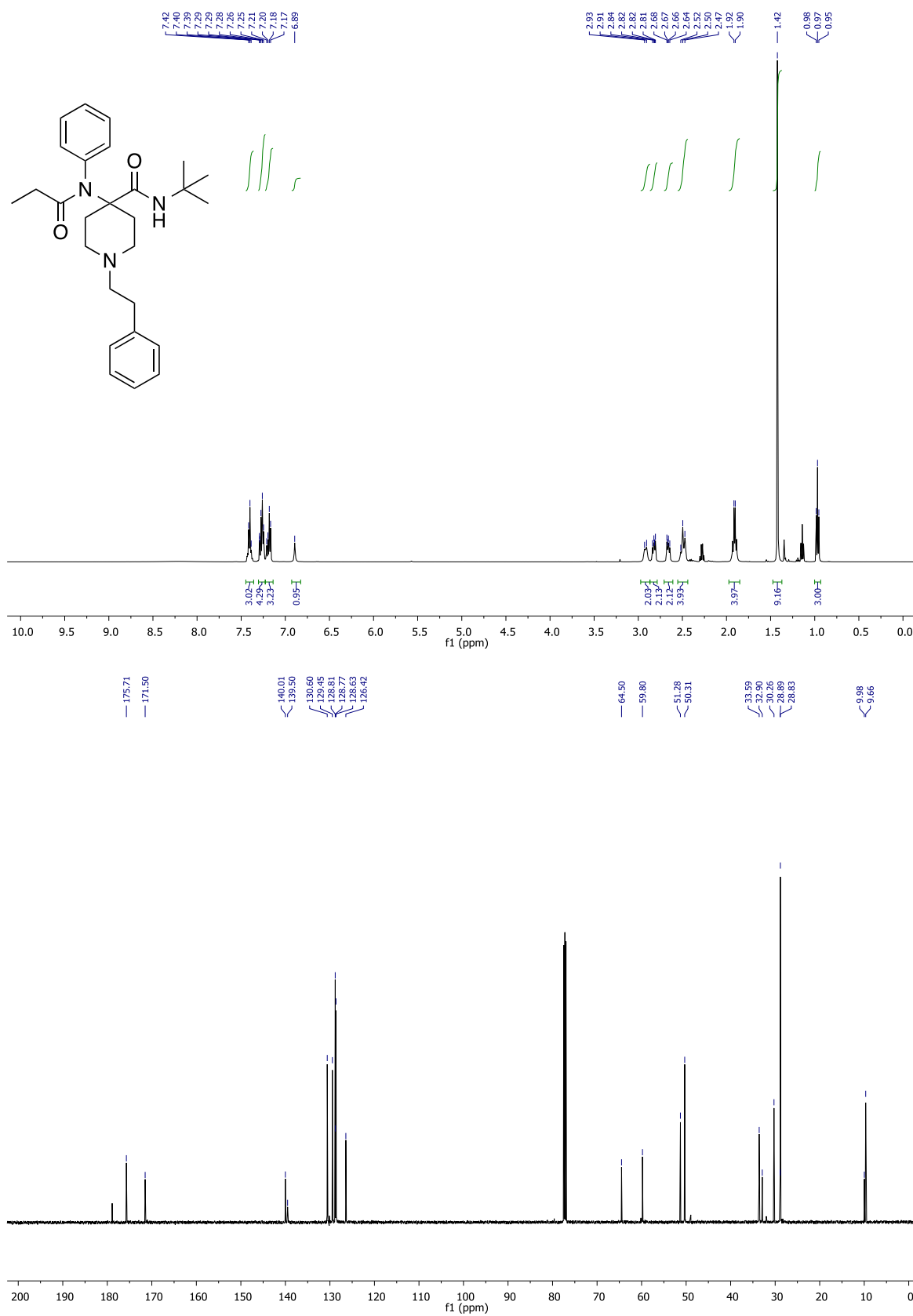
***N*-cycloheptyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (7)**



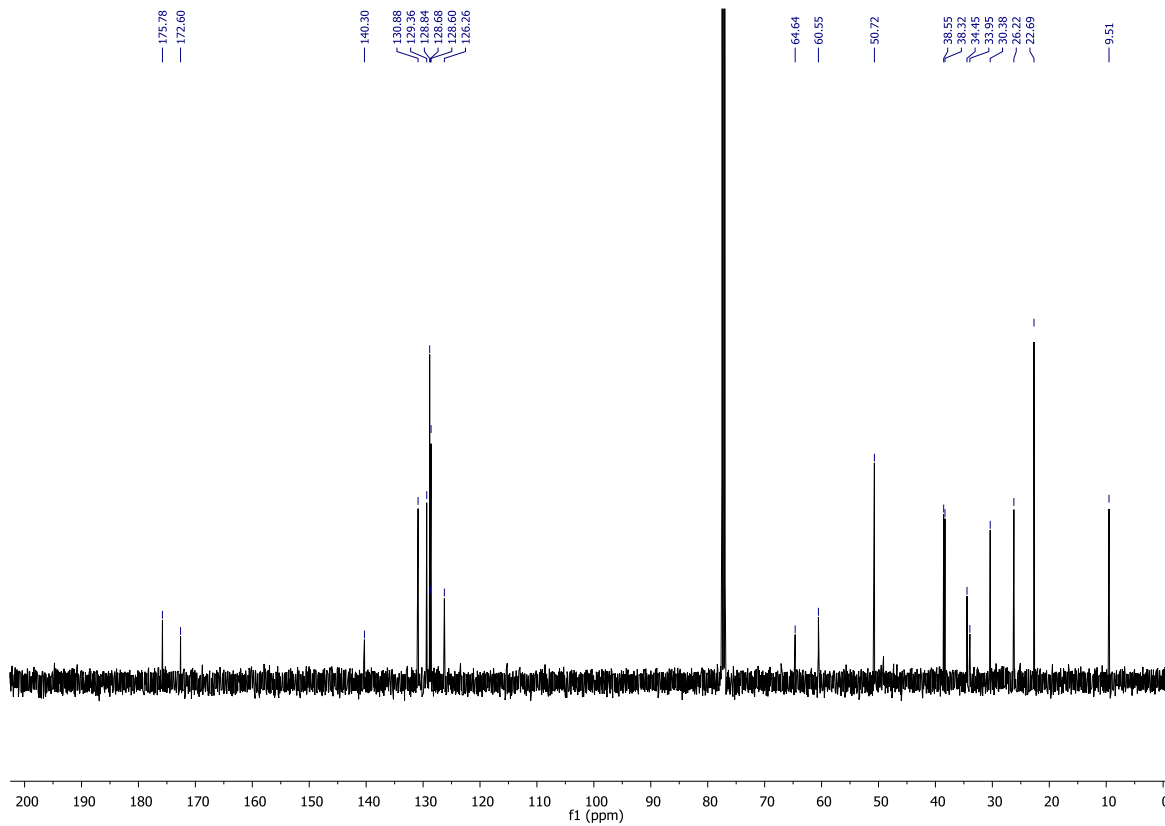
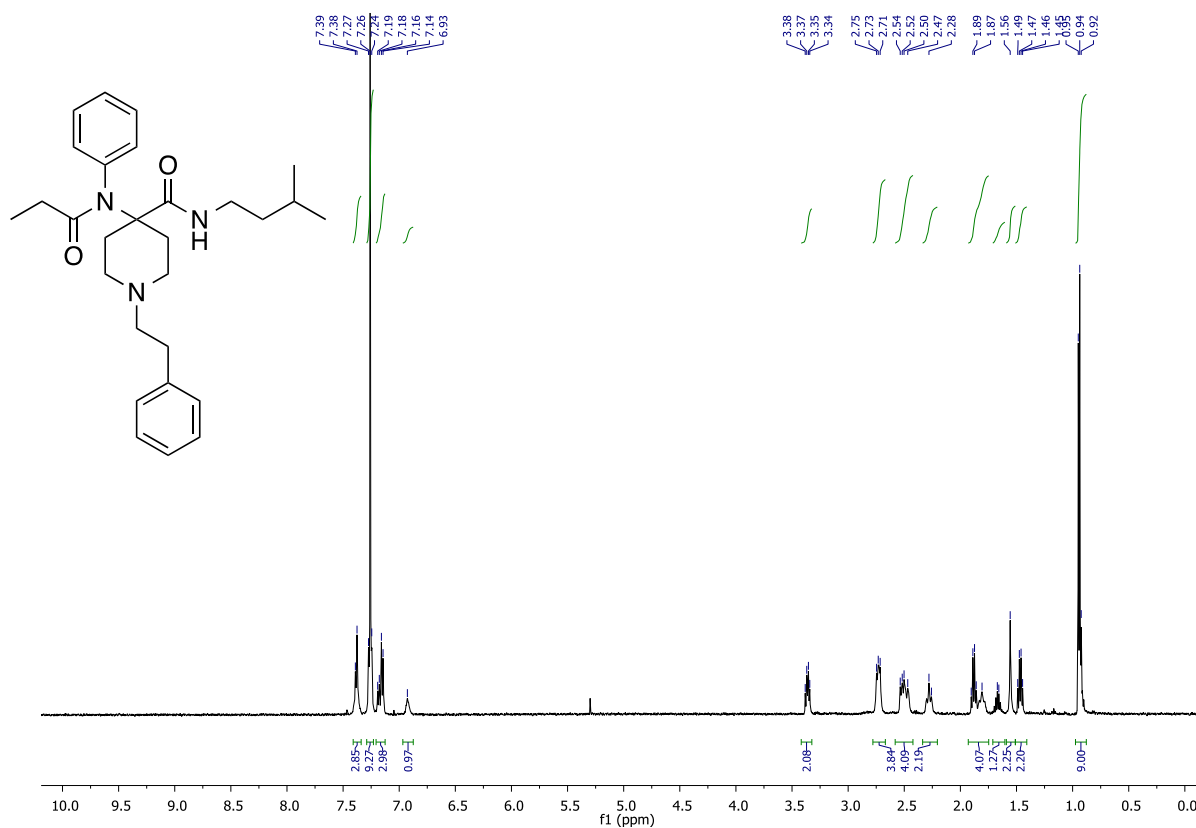
***N*-butyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (8)**



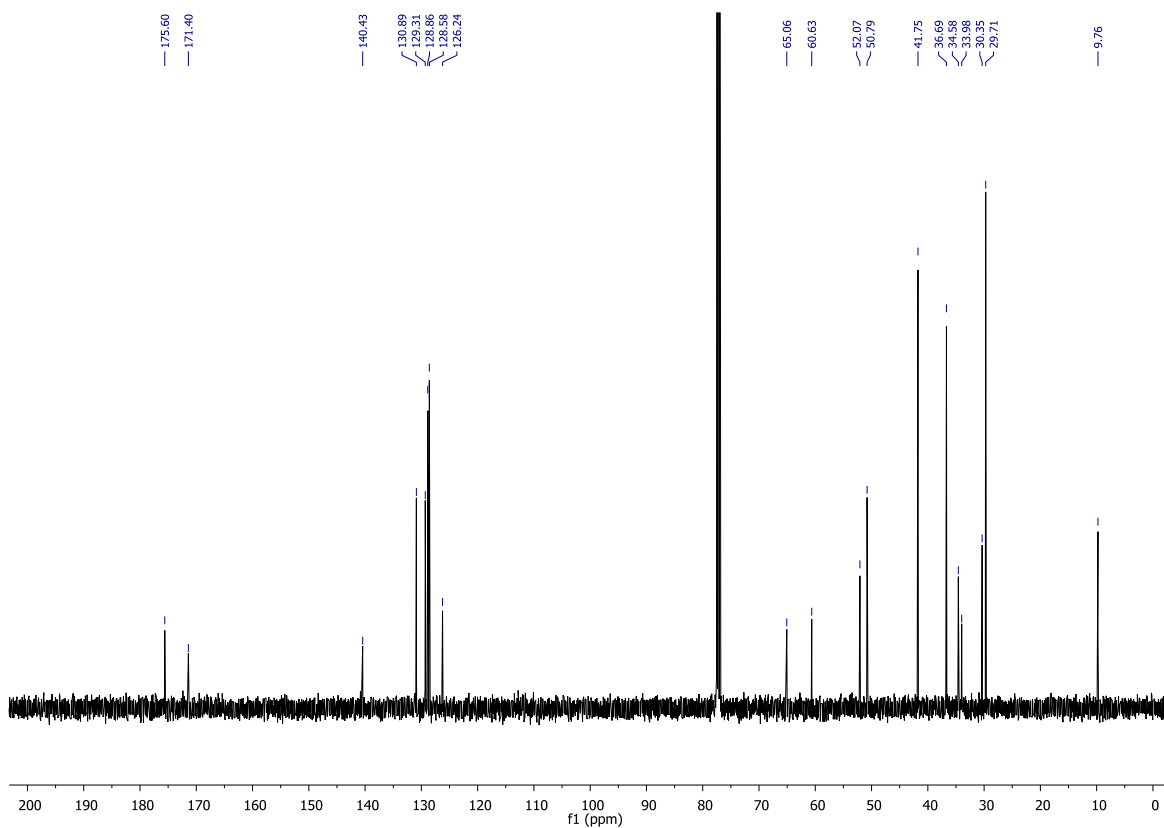
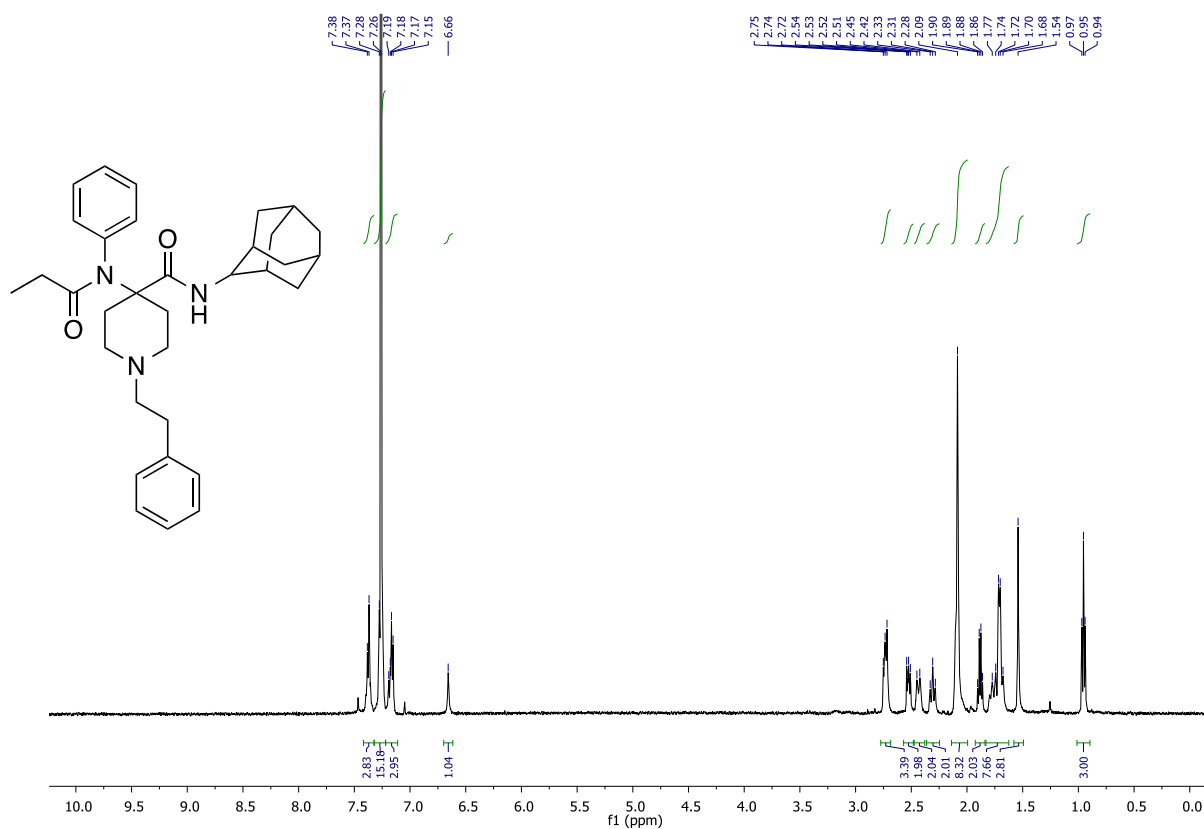
***N*-(*tert*-butyl)-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (9)**



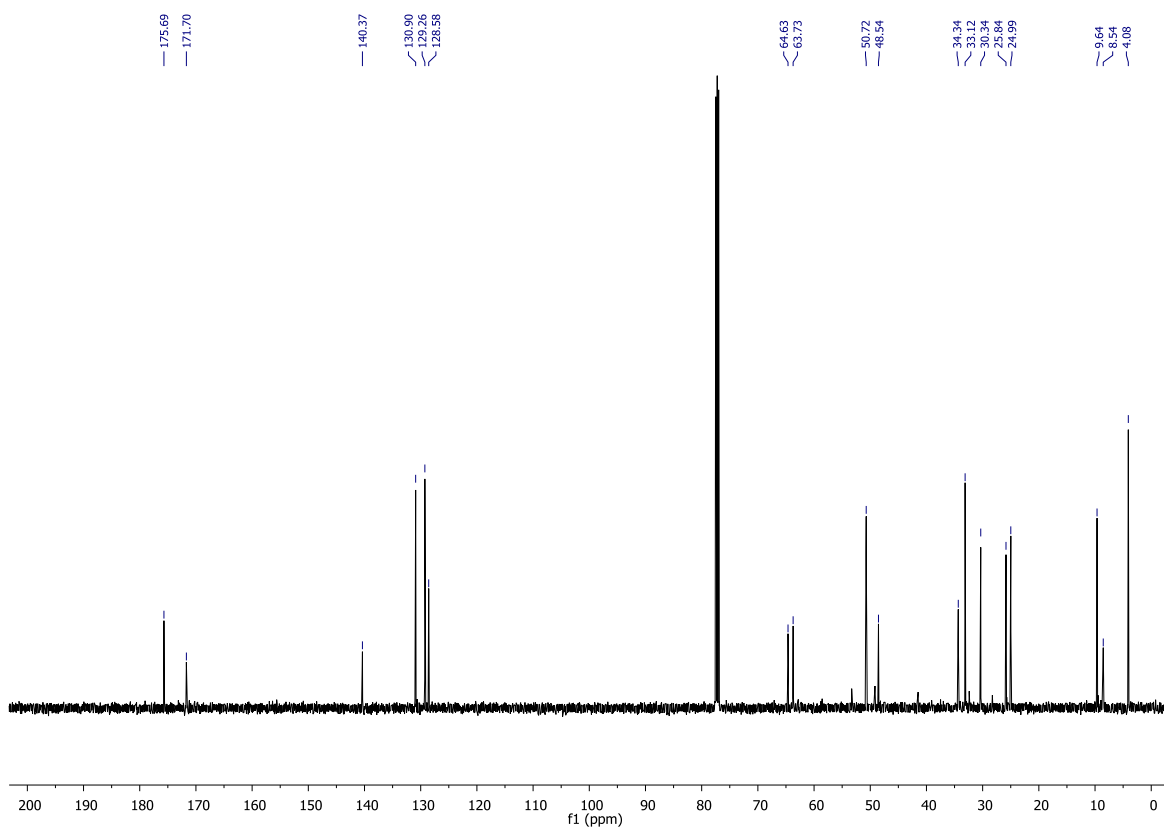
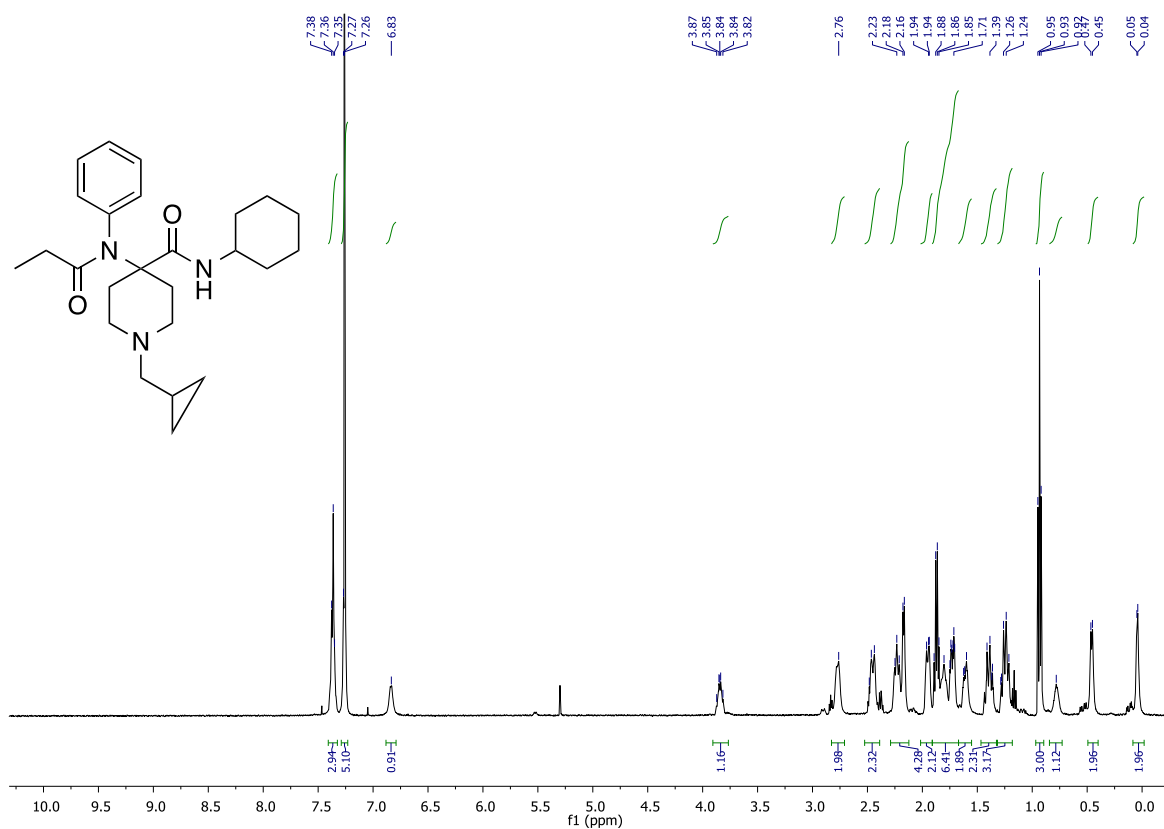
***N*-isopentyl-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (10)**



***N*-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (11)**



***N*-cyclohexyl-1-(cyclopropylmethyl)-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (12)**



***N*-(*tert*-butyl)-1-(cyclopropylmethyl)-4-(*N*-phenylpropionamido)piperidine-4-carboxamide (13)**

