Fluorine substituted methoxyphenylalkyl amides as potent melatonin receptor agonists

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Supplementary Information

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Chemistry

Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^{1}H NMR spectra were taken in $CDCl_3$ and recorded on a Bruker DRX 400 (400 MHz) spectrometer, and the chemical shifts are reported in ppm. ^{13}C NMR spectra were taken at 50 MHz on a Bruker AC 200 spectrometer. Tetramethylsilane was used as internal standard. Elemental analyses (C, H, N) were carried out by Service Central de Microanalyse (CNRS), France. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with iodine or phosphomolybdic acid. Flash chromatography was performed using Sorbsil c60-A silica as the stationary phase. Mass spectra were taken on Thermo LTQ™ Orbitrap Velos spectrometer in the Institute of Biology, Medicinal Chemistry & Biotechnology, NHRF, Greece.

N-(2-fluoro-5-methoxybenzyl)acetamide (2a)

2-Fluoro-5-methoxybenzylamine (360 mg, 2.32 mmol) was treated with Et_3N (0.5 mL, 3.70 mmol) and acetic anhydride (0.36 g, 3.48 mmol) in CH_2Cl_2 (10 mL) by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt,

30:70) and trituration with AcOEt, amide **2a** (35%) as an off-white solid, mp 79-80 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 1.97 (s, COCH_3, 3H), 3.73 (s, OCH_3, 3H,), 4.40 (d, J = 5.8 Hz, CH_2NH, 2H), 5.99 (bs, NH, 1H), 6.68-6.76 (m, $H_{arom,}$ 1H), 6.80-6.84 (m, $H_{arom,}$ 1H), 6.92 (t, J = 9.1 Hz, H_3, 1H). ^{13}C NMR δ 23.1 (CH$_3$), 37.7 (CH$_2$NH, J_{F-C} = 3.4 Hz), 55.7 (OCH$_3$), 114.0 (CH, J_{F-C} = 8.0 Hz), 115.0 (CH, J_{F-C} = 4.2 Hz), 115.8 (CH, J_{F-C} = 23.4 Hz), 125.9 (C, J_{F-C} = 16.6 Hz), 155.3 (C, J_{F-C} = 238.2 Hz), 155.7 (C, J_{F-C} = 1.9 Hz), 169.9 (C=O). Found: C, 60.58; H, 6.0. Calc. for $C_{10}H_{12}NO_2F$: C, 60.9; H, 6.1%

***N*-(2-Fluoro-5-methoxyphenylmethyl) propanamide (2b):** 45%, mp 61-62 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.6 Hz, CH$_2$CH_3, 3H), 2.21 (q, J = 7.2 Hz, CH_2CH$_3$, 2H), 3.73 (s, OCH_3, 3H), 4.41 (d, J = 5.9 Hz, CH_2NH, 2H), 5.87 (bs, NH, 1H), 6.68-6.76 (m, H_{arom}, 1H), 6.79-6.84 (m, H_{arom}, 1H), 6.93 (t, 1 J = 9.1 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 9.7 (CH$_3$), 29.6 (CH$_2$CH$_3$), 37.6 (CH$_2$NH, J_{F-C} = 3.4 Hz), 55.7 (OCH$_3$), 114.0 (CH, J_{F-C} = 8.0 Hz), 115.0 (CH, J_{F-C} = 4.2 Hz), 115.8 (CH, J_{F-C} = 23.4 Hz), 126.0 (C, J_{F-C} = 16.6 Hz), 155.3 (C, J_{F-C} = 238.2 Hz), 155.7 (C, J_{F-C} = 1.9 Hz), 173.6 (C=O). Found: C, 62.2; H, 6.3. Calc. for $C_{11}H_{14}NO_2F$: C, 62.5; H, 6.7%.

***N*-(2-Fluoro-5-methoxyphenylmethyl) butanamide (2c):** 43%, mp 54 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, CH$_2$CH$_2$CH_3, 3H), 1.64 (m, CH$_2$CH_2CH$_3$, 2H), 2.15 (t, J = 7.3 Hz, COCH_2, 2H), 3.73 (s, OCH_3, 3H), 4.42 (d, J = 5.9 Hz, CH_2NH, 2H), 5.88 (bs, NH, 1H), 6.67-6.75 (m, H_{arom}, 1H), 6.79-6.84 (m, H_{arom}, 1H), 6.92 (t, J = 9.0 Hz, H_3, 1H). ^{13}C-NMR ($CDCl_3$) δ 13.7 (CH$_3$), 19.1 (CH$_2$CH$_3$), 37.6 (CH$_2$NH, J_{F-C} = 3.4 Hz), 38.6 (COCH$_2$), 55.7 (OCH$_3$), 114.1 (CH, J_{F-C} = 8.0 Hz), 114.9 (CH, J_{F-C} = 4.2 Hz), 115.8 (CH, J_{F-C} = 23.5 Hz), , J_{F-C} = 16.6 Hz), 155.3 (C, J_{F-C} = 238.2 Hz), 155.7 (C, J_{F-C} = 1.9 Hz), 172.8 (C=O). Found: C, 63.75; H, 7.0. Calc. for $C_{12}H_{16}NO_2F$: C, 63.9; H, 7.1%.

***N*-(3-Fluoro-4-methoxyphenylmethyl) acetamide (2d):** 3-Fluoro-4-methoxybenzylamine (360 mg, 2.32 mmol) was treated with Et_3N (0.5 mL, 3.70 mmol) and acetic anhydride (0.36 g, 3.48 mmol) in CH_2Cl_2 (10 mL) by the general procedure to give after purification by flash column chromatography (cyclohexane/AcOEt, 20:80) and trituration with AcOEt, amide **2d** , 48%, as an off-white solid, mp 83-84 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 1.96 (s, COCH_3, 3H), 3.82 (s, OCH_3, 3H), 4.27 (d, J = 5.8 Hz, CH_2NH, 2H), 6.16 (bs, NH, 1H), 6.85 (t, J = 8.3 Hz, H_6, 1H), 6.92-6.97 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 23.2 (CH$_3$), 42.7 (ArCH$_2$, J_{F-C} = 1.1 Hz), 56.3 (OCH$_3$), 113.4 (CH, J_{F-C} = 2.1 Hz), 115.6 (CH, J_{F-C} = 18.5 Hz), 123.5 (CH, J_{F-C} = 3.5 Hz), 131.3 (C, J_{F-C} = 5.9 Hz), 146.9 (C, J_{F-C} = 10.6 Hz), 152.3 (C, J_{F-C} = 246.5 Hz), 169.9 (C=O). Found: C, 60.7; H, 6.1. Calc. for $C_{10}H_{12}NO_2F$: C, 60.9; H, 6.1%

***N*-(3-Fluoro-4-methoxyphenylmethyl) propanamide (2e):** 61%, mp 67-68 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 1.13 (t, J = 7.5 Hz, CH$_2$CH_3, 3H), 2.20 (q, J = 7.5 Hz, 2H, CH_2CH$_3$), 3.83 (s, OCH_3, 3H), 4.30 (d, J = 5.6 Hz, CH_2NH, 2H), 5.96 (bs, NH, 1H), 6.85 (t, J = 8.6 Hz, H_6, 1H), 6.93-6.98 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 9.8 (CH$_3$), 29.6 (CH$_2$CH$_3$), 42.6 (ArCH$_2$), 56.3 (OCH$_3$), 113.4 (CH, J_{F-C} = 2.0 Hz), 115.5 (CH, J_{F-C} = 18.6 Hz), 123.5 (CH, J_{F-C} = 3.5 Hz), 131.5 (C, J_{F-C} = 5.8 Hz), 146.9 (C, J_{F-C} = 10.7 Hz), 152.3 (C, J_{F-C} = 246.2 Hz), 173.6 (C=O). Found: C, 62.3; H, 6.7. Calc. for $C_{11}H_{14}NO_2F$: C, 62.5; H, 6.4%

***N*-(3-Fluoro-4-methoxyphenylmethyl) butanamide (2f):** 60%, mp 82-83 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, CH$_2$CH_3, 3H), 1.60-1.70 (m, CH_2CH$_3$, 2H), 2.16 (t, J = 7.3 Hz, COCH_2, 2H), 3.84 (s, OCH_3, 3H), 4.32 (d, J = 5.8 Hz,

CH_2NH, 2H), 5.84 (bs, N*H*, 1H), 6.87 (t, *J* = 8.3 Hz, H_6, 1H), 6.94-6.99 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 13.7 (*C*H_3), 19.1 (*C*H_2CH$_3$), 38.6 (CO*C*H_2), 42.6 (Ar*C*H_2, J_{F-C} = 1.1 Hz), 56.3 (O*C*H_3), 113.5 (*C*H, J_{F-C} = 2.1 Hz), 115.5 (*C*H, J_{F-C} = 18.6 Hz), 123.5 (*C*H, J_{F-C} = 3.6 Hz), 131.5 (*C*, J_{F-C} = 5.9 Hz), 146.9 (*C*, J_{F-C} = 10.7 Hz), 152.3 (*C*, J_{F-C} = 246.4 Hz), 172.8 (*C*=O). Found: C, 63.8; H, 7.0. Calc. for $C_{12}H_{16}NO_2F$: C, 63.9; H, 7.1%

***N*-(4-Fluoro-3-methoxyphenylmethyl) acetamide (3a):** 4-Fluoro-3-methoxybenzylamine (0.36 g, 2.32 mmol) was treated with Et_3N (0.5 mL, 3.70 mmol) and acetic anhydride (0.36 g, 3.48 mmol) in CH_2Cl_2 (10 mL) by the general procedure to give after 2h of stirring and purification by flash column chromatography (cyclohexane/AcOEt, 30:70) and trituration with AcOEt, amide **3a**, 34%, as a white solid, mp 88-89 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 2.00 (s, CO*C*H_3, 1H), 3.85 (s, O*C*H_3, 3H), 4.35 (d, *J* = 5.8 Hz, CH_2NH, 2H), 5.78 (bs, N*H*, 1H), 6.74-6.78 (m, H_6, 1H), 6.87 (dd, *J* = 1.8 Hz, 8.1 Hz, H_2, 1H), 6.99 (dd, *J* = 8.2 Hz, 11.1 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 23.2 (*C*H_3), 43.2 (*C*H_2NH), 56.2 (O*C*H_3), 113.1 (*C*H, J_{F-C} = 1.9 Hz), 115.9 (*C*H, J_{F-C} = 18.5 Hz), 120.0 (*C*H, J_{F-C} = 6.9 Hz), 134.7 (*C*, J_{F-C} = 3.8 Hz), 147.7 (*C*, J_{F-C} = 10.8 Hz), 151.8 (*C*, J_{F-C} = 245.6 Hz), 169.9 (*C*=O). Found: C, 60.7; H, 5.9. Calc. for $C_{10}H_{12}NO_2F$: C, 60.9; H, 6.1%

N*-(4-Fluoro-3-methoxyphenylmethyl) propanamide (3b):** 37%, mp 77-78 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 1.17 (t, *J* = 7.6 Hz, CH_2CH_3, 3H), 2.23 (q, *J* = 7.6 Hz, CO*C*H_2, 2H), 3.85 (s, O*C*H_3, 3H), 4.37 (d, *J* = 5.8 Hz, CH_2NH 2H), 5.71 (bs, N*H*, 1H), 6.75-6.78 (m, H_6, 1H), 6.87 (dd, *J* = 2.0 Hz, 8.1 Hz, H_2, 1H), 6.99 (q, *J* = 8.3 Hz, 11.2 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8 (C***H_3), 29.7 (***C***H_2CH$_3$), 43.2 (***C***H_2NH), 56.2 (O***C***H_3), 113.1 (*C*H, J_{F-C} = 2.0 Hz), 115.9 (***C***H, J_{F-C} = 18.5 Hz), 119.9 (***C***H, J_{F-C} = 7.0 Hz), 134.8 (***C***, J_{F-C} = 3.8 Hz), 147.7 (***C***, J_{F-C} = 10.8 Hz), 151.8 (***C***, J_{F-C} = 245.5 Hz), 176.6 (***C***=O). Found: C, 62.4; H, 6.6. Calc. for $C_{11}H_{14}NO_2F$: C, 62.5; H, 6.7%

N*-(4-Fluoro-3-methoxyphenylmethyl) butanamide (3c):** 40%, mp 59-60 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 0.94 (t, *J* = 7.3 Hz, $CH_2CH_2CH_3$, 3H), 1.63-1.72 (m, $CH_2CH_2CH_3$, 2H), 2.18 (t, *J* = 7.3 Hz, CO*C*H_2, 2H), 3.85 (s, O*C*H_3, 3H), 4.37 (d, *J* = 5.8 Hz, CH_2NH, 2H), 5.69 (bs, N*H*, 1H), 6.74-6.78 (m, H_6, 1H), 6.88 (dd, *J* = 2.0 Hz, 8.1 Hz, H_2, 1H), 7.00 (dd, *J* = 8.2 Hz, 11.1 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 13.7 (C***H_3), 19.1 (*C*H_2CH$_3$), 38.7 (CO*C*H_2), 43.2 (*C*H_2NH), 56.2 (O*C*H_3), 113.1 (*C*H, J_{F-C} = 1.9 Hz), 116.0 (*C*H, J_{F-C} = 18.5 Hz), 119.9 (*C*H, J_{F-C} = 7.0 Hz), 134.9 (*C*, J_{F-C} = 3.8 Hz), 147.7 (*C*, J_{F-C} = 10.9 Hz), 151.8 (*C*, J_{F-C} = 245.5 Hz), 172.8 (*C*=O). Found: C, 63.8; H, 7.0. Calc. for $C_{12}H_{16}NO_2F$: C, 63.9; H, 7.1%

***N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl] acetamide (4a):** 2-Fluoro-5-methoxyphenylacetonitrile (10.3 mg, 1.03 mmol) and acetic anhydride (10.3 mmol) in anhydrous THF (20 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 9 h by the general procedure to give after purification by flash column chromatography (cyclohexane/AcOEt, 30:70), amide **4a,** 80%, as an off-white solid, mp 53 °C (cyclohexane/AcOEt, 80:20). ^{1}H NMR δ 1.97 (s, CO*C*H_3, 3H), 2.78 (t, *J* = 6.8 Hz, Ar*C*H_2, 2H), 3.46 (q, *J* = 6.8 Hz, CH_2NH, 2H), 3.72 (s, O*C*H_3, 3H), 5.75 (bs, N*H*, 1H), 6.65-6.69 (m, $H_{4,6}$, 2H), 6.90 (t, *J* = 9.4 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 23.2 (*C*H_3), 29.3 (Ar*C*H_2), 39.5 (*C*H_2NH), 55.6 (O*C*H_3), 112.9 (*C*H, J_{F-C} = 8.1 Hz), 115.7 (*C*H, J_{F-C} = 30.1 Hz), 115.8 (*C*H), 126.5 (*C*, J_{F-C} = 18.4 Hz), 155.57 (*C*, J_{F-C} = 236.5 Hz), 155.6 (*C*, J_{F-C} = 1.5 Hz), 170.2 (*C*=O). Found: C, 62.25; H, 6.5. Calc. for $C_{11}H_{14}NO_2F$: C, 62.55; H, 6.7%.

***N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl] propanamide (4b):** 81%, mp 54 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 1.08 (t, J = 7.4 Hz, CH_2CH_3, 3H), 2.13 (q, J = 7.4 Hz, $COCH_2$, 2H), 2.79 (t, J = 7.0 Hz, $ArCH_2$, 2H), 3.46 (q, J = 6.7 Hz, CH_2NH, 2H), 3.72 (s, OCH_3, 3H), 5.70 (bs, NH, 1H), 6.66-6.68 (m, $H_{4,6}$, 2H), 6.90 (t, J = 9.8 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8 (CH_3), 29.4 ($ArCH_2$), 29.6 ($COCH_2$), 39.4 (CH_2NH), 55.6 (OCH_3), 112.9 (CH, J_{F-C} = 8.1 Hz), 115.7 (CH, J_{F-C} = 31.8 Hz), 115.8 (CH, J_{F-C} = 2.9 Hz), 126.5 (C, J_{F-C} = 17.8 Hz), 155.5 (C, J_{F-C} = 236.9 Hz), 155.6 (C, J_{F-C} = 2.1 Hz), 173.8 (C=O). Found: C, 63.7; H, 7.0. Calc. for $C_{12}H_{16}NO_2F$: C, 63.9; H, 7.1%

***N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl] butanamide (4c):** 59%, mp 46-47 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, $CH_2CH_2CH_3$, 3H), 1.50-1.69 (m, CH_2CH_3, 2H), 2.08 (t, J = 7.2 Hz, $COCH_2$, 2H,), 2.79 (t, J = 6.8 Hz, $ArCH_2$, 2H,), 3.47 (q, J = 6.7 Hz, CH_2NH, 2H), 3.73 (s, OCH_3, 3H), 5.60 (bs, NH, 1H), 6.69-6.70 (m, $H_{4,6}$, 2H), 6.91 (t, J = 9.6 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 19.0 (CH_2CH_3), 29.4 ($ArCH_2$), 38.6 ($COCH_2$), 39.4 (CH_2NH), 55.7 (OCH_3), 113.0 (CH, J_{F-C} = 8.1 Hz), 115.6 (CH, J_{F-C} = 18.1 Hz), 115.9 (CH, J_{F-C} = 1.0 Hz), 126.6 (C, J_{F-C} = 17.6 Hz), 155.6 (C, J_{F-C} = 237.0 Hz), 155.7 (C, J_{F-C} = 1.8 Hz), 173.0 (C=O). Found: C, 65.0; H, 7.2. Calc. for $C_{13}H_{18}NO_2F$: C, 65.2; H, 7.6%

***N*-[2-(4-Fluoro-3-methoxyphenyl)ethyl] acetamide (4d):** 4-Fluoro-3-methoxyphenylacetonitrile (10.3 mg, 1.03 mmol) and acetic anhydride (10.3 mmol) in anhydrous THF (20 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 16 h by the general procedure to give after purification by flash column chromatography (cyclohexane/AcOEt, 30:70), amide **4d,** 57%, as an off-white solid, mp 77-78 °C (cyclohexane/AcOEt, 80:20; mp[31] 72-76 °C). ^{1}H NMR δ 1.92 (s, $COCH_3$ 3H), 2.75 (t, J = 7.0 Hz, $ArCH_2$, 2H), 3.46 (q, J = 6.8 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.53 (bs, NH, 1H), 6.65-6.68 (m, H_6, 1H), 6.76 (dd, J = 1.8 Hz, 8.1 Hz, H_2, 1H), 6.97 (dd, J = 8.2 Hz, 11.2 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 23.3 (CH_3), 35.3 (CH_2NH), 40.6 ($ArCH_2$, J_{F-C} = 1.0 Hz), 56.2 (OCH_3), 113.8 (CH, J_{F-C} = 1.8 Hz), 115.9 (CH, J_{F-C} = 18.2 Hz), 120.7 (CH, J_{F-C} = 6.8 Hz), 135.1 (C, J_{F-C} = 3.9 Hz), 147.6 (C, J_{F-C} = 10.8 Hz), 151.2 (C, J_{F-C} = 244.2 Hz), 170.0 (C=O). Found: C, 60.35; H, 6.6. Calc. for $C_{11}H_{14}NO_2F$: C, 62.55; H, 6.7%.

***N*-[2-(4-Fluoro-3-methoxyphenyl)ethyl] propanamide (4e):** 44%, mp 55-56 °C (cyclohexane/AcOEt, 95:5; mp[1] 52-55 °C). ^{1}H NMR δ 1.10 (t, J = 7.5 Hz, CH_2CH_3, 3H), 2.14 (q, J = 7.5 Hz, $COCH_2$, 2H), 2.75 (t, J = 7.0 Hz, $ArCH_2$, 2H), 3.47 (q, J = 6.7 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.48 (bs, NH, 1H), 6.65-6.68 (m, H_6, 1H), 6.75 (dd, J = 1.9 Hz, 8.1 Hz, H_2, 1H), 6.97 (dd, J = 8.2 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8 (CH_3), 29.7 ($COCH_2$), 35.4 (CH_2NH), 40.5 ($ArCH_2$, J_{F-C} = 1.0 Hz), 56.2 (OCH_3), 113.8 (CH, J_{F-C} = 1.8 Hz), 115.9 (CH, J_{F-C} = 18.2 Hz), 120.7 (CH, J_{F-C} = 6.7 Hz), 135.2 (C, J_{F-C} = 3.9 Hz), 147.6 (C, J_{F-C} = 10.7 Hz), 151.2 (C, J_{F-C} = 244.1 Hz), 173.7 (C=O). Found: C, 63.8; H, 7.0. Calc. for $C_{12}H_{16}NO_2F$: C, 63.7; H, 7.1%.

***N*-[2-(4-Fluoro-3-methoxyphenyl)ethyl] butanamide (4f):** 48%, mp 53-54 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 0.90 (t, J = 7.3 Hz, $CH_2CH_2CH_3$, 3H), 1.56-1.66 (m, $CH_2CH_2CH_3$, 2H,), 2.09 (t, J = 7.3 Hz, $COCH_2$, 2H), 2.76 (t, J = 7.0 Hz, $ArCH_2$, 2H,), 3.48 (q, J = 6.8 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.42 (bs, NH, 1H), 6.65-6.69 (m, H_6, 1H), 6.77 (dd, J = 1.9 Hz, 8.1 Hz, H_2, 1H), 6.98 (dd, J = 8.2 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 19.1 (CH_2CH_3), 35.4 (CH_2NH), 38.7 ($COCH_2$), 40.5 ($ArCH_2$), 56.2 (OCH_3), 113.8 (CH, J_{F-C} = 1.8 Hz), 115.9 (CH, J_{F-C} = 18.2 Hz), 120.7 (CH, J_{F-C} = 6.7 Hz),

135.2 (*C*, J_{F-C} = 3.9 Hz), 147.5 (*C*, J_{F-C} = 10.8 Hz), 151.2 (*C*, J_{F-C} = 244.1 Hz), 172.9 (*C*=O). Found: C, 64.95; H, 7.3. Calc. for $C_{13}H_{18}NO_2F$: C, 65.25; H, 7.6%.

***N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl] acetamide (5a):** 3-Fluoro-4-methoxyphenylacetonitrile (10.3 mg, 1.03 mmol) and acetic anhydride (10.3 mmol) in anhydrous THF (20 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 14 h by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt, 30:70), amide **5a,** 59%, as a white solid, mp 77-78 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 1.93 (s, COCH_3, 3H), 2.72 (t, *J* = 6.9 Hz, ArCH_2, 2H), 3.45 (q, *J* = 6.8 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.42 (bs, N*H*, 1H), 6.87-6.91 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 23.1 (*C*H_3), 34.6 (Ar*C*H_2), 40.5 (*C*H_2NH), 56.2 (O*C*H_3), 113.5 (*C*H, J_{F-C} = 2.1 Hz), 116.2 (*C*H, J_{F-C} = 18.0 Hz), 124.2 (*C*H, J_{F-C} = 3.5 Hz), 131.9 (*C*, J_{F-C} = 6.0 Hz), 146.1 (*C*, J_{F-C} = 10.6 Hz), 152.2 (*C*, J_{F-C} = 245.8 Hz), 170.1 (*C*=O). Found: C, 62.35; H, 6.4. Calc. for $C_{11}H_{14}NO_2F$: C, 62.55; H, 6.7%.

***N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl] propanamide (5b):** 67%, mp 102-103 °C (cyclohexane/AcOEt, 90:10; mp[31] 101-104 °C). ^{1}H NMR δ 1.08 (t, *J* = 7.5 Hz, CH_2CH_3, 3H), 2.12 (q, *J* = 7.5 Hz, COCH_2 2H), 2.70 (t, *J* = 6.9 Hz, ArCH_2, 2H), 3.42 (q, *J* = 6.7 Hz, CH_2NH, 2H), 3.83 (s, OCH_3, 3H), 5.61 (bs, N*H*, 1H), 6.84-6.90 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 9.8 (*C*H_3), 29.6 (*C*H_2CH_3), 34.7 (Ar*C*H_2, J_{F-C} = 1.1 Hz), 40.4 (*C*H_2NH), 56.3 (O*C*H_3), 113.6 (*C*H, J_{F-C} = 2.1 Hz), 116.3 (*C*H, J_{F-C} = 17.9 Hz), 124.2 (*C*H, J_{F-C} = 3.5 Hz), 132.0 (*C*, J_{F-C} = 6.0 Hz), 146.1 (*C*, J_{F-C} = 10.6 Hz), 152.3 (*C*, J_{F-C} = 245.8 Hz), 173.7 (*C*=O). Found: C, 63.6; H, 6.9. Calc. for $C_{12}H_{16}NO_2F$: C, 63.7; H, 7.1%.

***N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl] butanamide (5c):** 62%, mp 79-80 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 0.89 (t, *J* = 7.3 Hz, $CH_2CH_2CH_3$, 3H), 1.51-1.69 (m, $CH_2CH_2CH_3$, 2H), 2.08 (t, *J* = 7.1 Hz, COCH_2, 2H), 2.72 (t, *J* = 6.9 Hz, ArCH_2, 2H), 3.45 (q, *J* = 6.9 Hz, CH_2NH, 2H), 3.84 (s, OCH_3, 3H), 5.44 (bs, N*H*, 1H), 6.86-6.92 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 13.7 (*C*H_3), 19.1 (*C*H_2CH_3), 34.8 (Ar*C*H_2, J_{F-C} = 1.1 Hz), 38.7 (CO*C*H_2), 40.4 (*C*H_2NH), 56.3 (O*C*H_3), 113.6 (*C*H, J_{F-C} = 2.2 Hz), 116.4 (*C*H, J_{F-C} = 17.9 Hz), 124.3 (*C*H, J_{F-C} = 3.5 Hz), 132.0 (*C*, J_{F-C} = 6.0 Hz), 146.2 (*C*, J_{F-C} = 10.7 Hz), 152.3 (*C*, J_{F-C} = 245.9 Hz), 172.9 (*C*=O). Found: C, 65.0; H, 7.3. Calc. for $C_{11}H_{14}NO_2F$: C, 65.25; H, 7.6%.

***N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]acetamide (6a):** A mixture of 2-fluoro-5-methoxyphenylacetonitrile (487 mg, 2.95 mmol) and iodomethane (0.5 ml, 1.05 g, 7.38 mmol) in DMF (15 mL) was added dropwise to a stirred slurry of NaH (177 mg, 7.38 mmol) in DMF (6 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was then treated with saturated aqueous NH_4Cl (until pH ~ 6 is attained), extracted with AcOEt and the organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with cyclohexane/AcOEt (98:2) to give *α*,*α*-dimethyl-2-fluoro-5-methoxy-phenylacetonitrile as a yellow oil, 450 mg, 79%. ^{1}H NMR δ 1.76 (s, C(CH_3)$_2$, 6H), 3.77 (s, OCH_3, 3H), 6.76-6.80 (m, H_4, 1H), 6.96-7.01 (m, $H_{3,6}$, 2H). ^{13}C NMR ($CDCl_3$) δ 27.0 (C(*C*H_3)$_2$), 35.2 (*C*(CH$_3$)$_2$, J_{F-C} = 2.1 Hz), 55.7 (O*C*H_3), 113.0 (*C*H, J_{F-C} = 3.7 Hz), 113.7 (*C*H, J_{F-C} = 8.6 Hz), 117.2 (*C*H, J_{F-C} = 24.5 Hz), 123.4 (*C*N), 128.5 (*C*, J_{F-C} = 12.8 Hz), 154.7 (*C*, J_{F-C} = 241.4 Hz), 155.7 (*C*, J_{F-C} = 1.9 Hz).

A solution of *α*,*α*-dimethyl-2-fluoro-5-methoxyphenylacetonitrile (150 mg, 0.78

mmol) and acetic anhydride (12.8 mmol) in anhydrous THF (15 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 12 h by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt, 30:70), amide **6a,** 40%, as an off-yellow solid, mp 54-55 °C (cyclohexane/AcOEt, 80:20). ^{1}H NMR δ 1.32 (s, C(CH_3)$_2$, 6H), 1.86 (s, COCH_3, 3H), 3.56 (d, J = 6.2 Hz, CH_2NH, 2H), 3.75 (s, OCH_3, 3H), 5.20 (bs, NH, 1H), 6.65-6.79 (m, $H_{4,6}$, 2H), 6.93 (m, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 23.4 (*C*H$_3$), 25.8 (C*C*H$_3$), 25.9 (C*C*H$_3$), 38.9 (*C*(CH$_3$)$_2$, $J_{F\text{-}C}$ = 3.7 Hz), 48.4 (*C*H$_2$NH), 55.7 (O*C*H$_3$), 111.8 (*C*H, $J_{F\text{-}C}$ = 8.9 Hz), 114.9 (*C*H, $J_{F\text{-}C}$ = 5.6 Hz), 116.8 (*C*H, $J_{F\text{-}C}$ = 26.5 Hz), 133.8 (*C*, $J_{F\text{-}C}$ = 13.0 Hz), 155.5 (*C*, $J_{F\text{-}C}$ = 1.8 Hz), 156.0 (*C*, $J_{F\text{-}C}$ = 240.2 Hz), 170.0 (*C*=O). Found: C, 65.1; H, 7.5. Calc. for $C_{13}H_{18}NO_2F$: C, 65.3; H, 7.6%.

***N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]propanamide (6b):** 92%, mp 36-37 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 1.04 (t, J = 7.6 Hz, CH$_2$C*H*$_3$, 3H), 1.32 (s, C(C*H*$_3$)$_2$, 6H), 2.07 (q, J = 7.6 Hz, COC*H*$_2$, 2H), 3.56 (d, J = 6.1 Hz, C*H*$_2$NH, 2H), 3.75 (s, OC*H*$_3$, 3H), 5.17 (bs, N*H*, 1H), 6.67-6.71 (m, H$_{arom}$, 1H), 6.75-6.77 (m, H$_{arom}$, 1H), 6.92 (dd, J = 8.8 Hz, 11.9 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 9.9 (*C*H$_3$), 25.9 (C(*C*H$_3$)$_2$), 29.8 (*C*H$_2$CH$_3$), 38.9 (*C*(CH$_3$)$_2$, $J_{F\text{-}C}$ = 3.6 Hz), 48.2 (*C*H$_2$NH), 55.7 (O*C*H$_3$), 111.8 (*C*H, $J_{F\text{-}C}$ = 9.0 Hz), 114.8 (*C*H, $J_{F\text{-}C}$ = 5.6 Hz), 116.8 (*C*H, $J_{F\text{-}C}$ = 26.5 Hz), 133.8 (*C*, $J_{F\text{-}C}$ = 12.9 Hz), 155.5 (*C*), 155.9 (*C*, $J_{F\text{-}C}$ = 240.2 Hz), 173.7 (*C*=O). Found: C, 66.1; H, 7.7. Calc. for $C_{14}H_{20}NO_2F$: C, 66.4; H, 8.0%.

***N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]butanamide (6c):** 95%, mp 51-52 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 0.85 (t, J = 7.3 Hz, CH$_2$C*H*$_3$, 3H), 1.33 (s, C(C*H*$_3$)$_2$, 6H), 1.46-1.64 (m, CH$_2$C*H*$_2$CH$_3$, 2H), 2.03 (t, J = 6.2 Hz, COC*H*$_2$, 2H) 3.57 (d, J = 7.1 Hz, C*H*$_2$NH, 2H), 3.76 (s, OC*H*$_3$, 3H), 5.13 (bs, N*H*, 1H), 6.66-6.79 (m, $H_{4,6}$, 2H), 6.93 (dd, J = 8.8 Hz, 12.0 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 13.6 (*C*H$_3$), 19.1 (*C*H$_2$CH$_3$), 25.9 (C(*C*H$_3$)$_2$), 38.8 (CO*C*H$_2$), 38.9 (*C*(CH$_3$)$_2$, $J_{F\text{-}C}$ = 3.8 Hz), 48.1 (*C*H$_2$NH), 55.7 (O*C*H$_3$), 111.9 (*C*H, $J_{F\text{-}C}$ = 8.9 Hz), 114.8 (*C*H, $J_{F\text{-}C}$ = 5.6 Hz), 116.8 (*C*H, $J_{F\text{-}C}$ = 26.5 Hz), 133.8 (*C*, $J_{F\text{-}C}$ = 12.8 Hz), 155.6 (*C*, $J_{F\text{-}C}$ = 1.6 Hz), 156.0 (*C*, $J_{F\text{-}C}$ = 240.2 Hz), 172.9 (*C*=O). Found: C, 67.1; H, 8.1. Calc. for $C_{15}H_{22}NO_2F$: C, 67.4; H, 8.3%.

***N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]acetamide (6d):** Amide **6d** was prepared as for the isomer **6a**, using *α*,*α*-dimethyl-4-fluoro-3-methoxyphenyl-acetonitrile as starting material. **6d**, 81%, mp 113-114 °C (cyclohexane/AcOEt, 95:5). ^{1}H NMR δ 1.25 (s, C(C*H*$_3$)$_2$, 6H), 1.88 (s, COC*H*$_3$, 3H), 3.43 (d, J = 6.1 Hz, C*H*$_2$NH, 2H), 3.88 (s, OC*H*$_3$, 3H), 5.10 (bs, N*H*, 1H), 6.81-6.85 (m, H_6, 1H), 6.91 (dd, J = 2.2 Hz, 8.2 Hz, H_2, 1H), 7.01 (dd, J = 8.4 Hz, 11.1 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 23.3 (*C*H$_3$), 26.8 ((*C*H$_3$)$_2$), 38.7 (*C*(CH$_3$)$_2$), 50.6 (*C*H$_2$NH), 56.4 (O*C*H$_3$), 111.8 (*C*H, $J_{F\text{-}C}$ = 1.8 Hz), 115.8 (*C*H, $J_{F\text{-}C}$ = 17.9 Hz), 118.3 (*C*H, $J_{F\text{-}C}$ = 6.6 Hz), 142.9 (*C*, $J_{F\text{-}C}$ = 3.7 Hz), 147.4 (*C*, $J_{F\text{-}C}$ = 10.4 Hz), 151.0 (*C*, $J_{F\text{-}C}$ = 244.9 Hz), 170.0 (*C*=O). Found: C, 65.1; H, 7.4. Calc. for $C_{13}H_{18}NO_2F$: C, 65.25; H, 7.6%.

***N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]propanamide (6e):** 57%, yellow oil. ^{1}H NMR δ 1.04 (t, J = 7.7 Hz, CH$_2$C*H*$_3$, 3H), 1.28 (s, C(C*H*$_3$)$_2$, 6H), 2.08 (q, J = 7.6 Hz, C*H*$_2$CH$_3$, 2H), 3.42 (d, J = 6.1 Hz, C*H*$_2$NH, 2H), 3.87 (s, OC*H*$_3$, 3H), 5.10 (bs, N*H*, 1H), 6.81-6.84 (m, H_6, 1H), 6.91 (dd, J = 2.1 Hz, 8.1 Hz, H_2, 1H), 7.00 (dd, J = 8.5 Hz, 11.0 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 9.9 (*C*H$_3$), 26.8 ((*C*H$_3$)$_2$), 29.8 (*C*H$_2$CH$_3$), 38.8 (*C*(CH$_3$)$_2$), 50.3 (*C*H$_2$NH), 56.4 (O*C*H$_3$), 111.7 (*C*H, $J_{F\text{-}C}$ = 1.9 Hz), 115.8 (*C*H, $J_{F\text{-}C}$ = 18.0 Hz), 118.3 (*C*H, $J_{F\text{-}C}$ = 6.6 Hz), 143.0 (*C*, $J_{F\text{-}C}$ = 3.7 Hz), 147.3 (*C*, $J_{F\text{-}C}$ = 10.5 Hz), 151.0 (*C*, $J_{F\text{-}C}$ =

244.9 Hz), 173.7 (*C*=O). ESI-HRMS *m/z* calcd for $C_{14}H_{20}FNO_2$ 254.1478 [M^++1], found 254.1476.

***N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]butanamide (6f):** 51%, yellow oil. ^{1}H NMR δ 0.85 (t, *J* =7.4 Hz, $CH_2CH_2CH_3$, 3H), 1.29 (s, $C(CH_3)_2$, 6H), 1.50-1.59 (m, CH_2CH_3, 2H), 2.03 (t, *J* = 7.3 Hz, $COCH_2$, 2H), 3.43 (d, *J* = 6.1 Hz, CH_2NH, 2H), 3.87 (s, OCH_3, 3H), 5.09 (bs, N*H*, 1H), 6.80-6.84 (m, H_6,1H), 6.91 (dd, *J* = 2.2 Hz, 8.2 Hz, H_2, 1H), 7.00 (q, *J* = 8.5 Hz, 11.0 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 19.2 (CH_2CH_3), 26.8 ($(CH_3)_2$), 38.7 ($C(CH_3)_2$), 38.8 ($COCH_2$), 50.4 (CH_2NH), 56.4 (OCH_3), 111.8 (*C*H, J_{F-C} = 1.7 Hz), 115.8 (*C*H, J_{F-C} = 17.9 Hz), 118.3 (*C*H, J_{F-C} = 6.6 Hz), 143.0 (*C*, J_{F-C} = 3.5 Hz), 147.4 (*C*, J_{F-C} = 10.4 Hz), 151.0 (*C*, J_{F-C} = 244.9 Hz), 172.9 (*C*=O). ESI-HRMS *m/z* calcd for $C_{15}H_{22}FNO_2$ 268.1635 [M^++1], found 268.1639.

***N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]acetamide (7a):** Amide **7a** was prepared as for the isomer **6a**, using *α*,*α*-dimethyl-3-fluoro-4-methoxyphenyl-acetonitrile as starting material. **7a**, 81%, mp 93-94 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 1.26 (s, $C(CH_3)_2$, 6H), 3.63 (d, *J* = 6.1 Hz, CH_2NH, 2H), 3.86 (s, OCH_3, 3H), 5.08 (bs, N*H*, 1H), 6.91 (t, *J* = 8.7 Hz, H_6, 1H), 7.01-7.07 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 23.3 (CH_3), 26.6 ($(CH_3)_2$), 38.2 ($C(CH_3)_2$, J_{F-C} = 1.1 Hz), 50.6 (CH_2NH), 56.3 (OCH_3), 113.4 (*C*H, J_{F-C} = 2.2 Hz), 114.0 (*C*H, J_{F-C} = 18.7 Hz), 121.5 (*C*H, J_{F-C} = 3.4 Hz), 139.8 (*C*, J_{F-C} = 5.2 Hz), 145.8 (*C*, J_{F-C} = 10.9 Hz), 152.2 (*C*, J_{F-C} = 245.3 Hz), 170.0 (*C*=O). Found: C, 65.15; H, 7.4. Calc. for $C_{13}H_{18}NO_2F$: C, 62.25; H, 7.6%.

***N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]propanamide (7b):** 57%, yellow oil. ^{1}H NMR δ 1.05 (t, *J* = 7.6 Hz, CH_2CH_3, 3H), 1.25 (s, $C(CH_3)_2$, 6H), 2.08 (q, *J* =7.6 Hz, CH_2CH_3, 2H), 3.38 (d, *J* = 6.1 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.09 (bs, N*H*, 1H), 6.90 (t, *J* = 8.6 Hz, H_6, 1H), 7.00-7.06 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 19.2 (CH_2CH_3), 26.8 ($(CH_3)_2$), 38.8 ($C(CH_3)_2$, J_{F-C} = 5.0 Hz), 50.3 (CH_2NH), 56.3 (OCH_3), 111.6 (*C*H), 115.7 (*C*H, J_{F-C} = 17.7 Hz), 118.3 (*C*H, J_{F-C} = 6.6 Hz), 142.9 (*C*, J_{F-C} = 3.3 Hz), 147.3 (*C*, J_{F-C} = 10.2 Hz), 150.9 (*C*, J_{F-C} = 244.9 Hz), 172.9 (*C*=O). ESI-HRMS *m/z* calcd for $C_{14}H_{20}FNO_2$ 254.1478 [M^++1], found 254.1473.

***N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]butanamide (7c):** 77%, yellow oil. ^{1}H NMR δ 0.85 (t, *J* = 7.3 Hz, CH_2CH_3, 3H), 1.25 (s, $C(CH_3)_2$, 6H), 1.50-1.59 (m, *J* =7.3 Hz, CH_2CH_3, 2H), 2.02 (t, *J* =7.3 Hz, 2H, CH_2CH_2), 3.39 (d, *J* = 6.1 Hz, CH_2NH, 2H), 3.85 (s, OCH_3, 3H), 5.10 (bs, N*H*, 1H), 6.90 (t, *J* = 8.6 Hz, H_6, 1H), 7.00-7.06 (m, $H_{2,5}$, 2H). ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 19.1 (CH_2CH_3), 26.6 ($(CH_3)_2$), 38.3 ($C(CH_3)_2$, J_{F-C} = 1.1 Hz), 50.3 (CH_2NH), 56.3 (OCH_3), 113.4 (*C*H, J_{F-C} = 2.2 Hz), 114.0 (*C*H, J_{F-C} = 18.7 Hz), 121.5 (*C*H, J_{F-C} = 3.4 Hz), 139.8 (*C*, J_{F-C} = 5.1 Hz), 145.8 (*C*, J_{F-C} = 10.9 Hz), 152.2 (*C*, J_{F-C} = 245.3 Hz), 172.9 (*C*=O). ESI-HRMS *m/z* calcd for $C_{15}H_{22}FNO_2$ 268.1635 [M^++1], found 268.1630.

***N*-[3-(2-Fluoro-5-methoxyphenyl)propyl] acetamide (8a):** A solution of 3-(2-fluoro-5-methoxyphenylacrylonitrile (180 mg, 1.02 mmol) and acetic anhydride (16.9 mmol) in anhydrous THF (18 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 14 h by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt, 25:75), amide **8a,** 70%, as an off-yellow solid, mp 34-35 °C (cyclohexane/AcOEt, 80:20). ^{1}H NMR δ 1.70-1.84 (m, CH_2CH_2NH, 2H), 1.92 (s, $COCH_3$, 3H), 2.59 (t, *J* = 7.3 Hz, $ArCH_2$, 2H), 3.22 (q, *J* = 6.8 Hz, CH_2NH, 2H), 3.72 (s, OCH_3, 3H), 5.81 (bs, N*H*, 1H), 6.59-

6.67 (m, $H_{4,6}$, 2H), 6.88 (t, J = 8.5 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 23.2 ($CO\mathit{C}H_3$), 26.5 (Ar$\mathit{C}H_2$, $J_{F\text{-}C}$ = 1.4 Hz), 29.8 (Ar$CH_2\mathit{C}H_2$), 38.9 ($\mathit{C}H_2NH$), 55.6 ($O\mathit{C}H_3$), 112.2 (CH, $J_{F\text{-}C}$ = 8.1 Hz), 115.5 (CH, $J_{F\text{-}C}$ = 24.3 Hz), 115.6 (CH, $J_{F\text{-}C}$ = 4.8 Hz), 128.9 (C, $J_{F\text{-}C}$ = 17.8 Hz), 155.4 (C, $J_{F\text{-}C}$ = 236.4 Hz), 155.6 (C, $J_{F\text{-}C}$ = 4.8 Hz), 170.1 (C=O). Found: C, 63.7; H, 7.2 Calc. for $C_{12}H_{16}NO_2F$: C, 64.0; H, 7.2%.

***N*-[3-(2-Fluoro-5-methoxyphenyl)propyl] propanamide (8b):** 81%, mp 38-39 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 1.11 (t, J = 7.5 Hz, $CH_2C\mathit{H}_3$, 3H), 1.71-1.85 (m, Ar$CH_2C\mathit{H}_2$, 2H), 2.15 (q, J = 7.5 Hz, $C\mathit{H}_2CH_3$, 2H), 2.60 (t, J = 7.4 Hz, Ar$C\mathit{H}_2$, 2H), 3.24 (q, J = 6.6 Hz, $C\mathit{H}_2$NH, 2H), 3.73 (s, $OC\mathit{H}_3$, 3H), 5.62 (bs, NH, 1H), 6.61-6.67 (m, $H_{4,6}$, 2H), 6.89 (t, J = 8.5 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8 ($\mathit{C}H_3$), 26.5 (Ar$\mathit{C}H_2$, $J_{F\text{-}C}$ = 1.7 Hz0, 29.7 9Ar$CH_2\mathit{C}H_2$), 29.9 ($\mathit{C}H_2CH_3$), 38.8 ($\mathit{C}H_2$NH), 55.6 ($O\mathit{C}H_3$), 112.3 (CH, $J_{F\text{-}C}$ = 8.1 Hz), 115.5 (CH, $J_{F\text{-}C}$ = 24.3 Hz), 115.6 (CH, $J_{F\text{-}C}$ = 4.9 Hz), 128.9 (C, $J_{F\text{-}C}$ = 17.8 Hz), 155.5 (C, $J_{F\text{-}C}$ = 236.6 Hz), 155.6 (C, $J_{F\text{-}C}$ = 1.9 Hz), 173.7 (C=O). Found: C, 65.0; H, 7.3. Calc. for $C_{13}H_{18}NO_2F$: C, 65.25; H, 7.6%.

***N*-[3-(2-Fluoro-5-methoxyphenyl)propyl] butanamide (8c):** 73%, mp 42-43 °C (cyclohexane/AcOEt, 90:10). ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, $CH_2CH_2C\mathit{H}_3$, 3H), 1.57-1.66 (m, $CH_2C\mathit{H}_2CH_3$, 2H), 1.75-1.82 (m, Ar$CH_2C\mathit{H}_2$, 2H), 2.10 (t, J = 7.3 Hz, $CO\mathit{C}H_2$, 2H), 2.60 (t, J = 7.4 Hz, 2H, Ar$C\mathit{H}_2$), 3.25 (q, J = 6.8 Hz, $C\mathit{H}_2$NH, 2H), 3.73 (s, $OC\mathit{H}_3$, 3H), 5.60 (bs, NH, 1H), 6.62-6.68 (m, $H_{4,6}$, 2H), 6.89 (t, J = 8.9 Hz, H_3, 1H). ^{13}C NMR ($CDCl_3$) δ 13.7 ($\mathit{C}H_3$), 19.1 ($\mathit{C}H_2CH_3$), 26.6 (Ar$\mathit{C}H_2$, $J_{F\text{-}C}$ = 2.0 Hz), 29.9 (Ar$CH_2\mathit{C}H_2$), 38.7 ($CO\mathit{C}H_2$), 38.8 ($\mathit{C}H_2$NH), 55.6 ($O\mathit{C}H_3$), 112.3 (CH, $J_{F\text{-}C}$ = 8.0 Hz), 115.5 (CH, $J_{F\text{-}C}$ = 24.4 Hz), 115.6 (CH, $J_{F\text{-}C}$ = 4.9 Hz), 128.9 (C, $J_{F\text{-}C}$ = 17.7 Hz), 155.5 (C, $J_{F\text{-}C}$ = 236.6 Hz), 155.6 (C, $J_{F\text{-}C}$ = 2.0 Hz), 172.9 (C=O). Found: C, 66.1; H, 7.7. Calc. for $C_{14}H_{20}NO_2F$: C, 66.4; H, 8.0%.

***N*-[3-(4-Fluoro-3-methoxyphenyl)propyl] acetamide (8d):** 3-(4-Fluoro-3-methoxyphenylacrylonitrile (180 mg, 1.02 mmol) and acetic anhydride (16.9 mmol) in anhydrous THF (18 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 14 h by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt, 20:80), amide **8d,** 66%, as a buff oil. ^{1}H NMR δ 1.74-1.82 (m, Ar$CH_2C\mathit{H}_2$, 2H), 1.93 (s, $CO\mathit{C}H_3$, 3H), 2.57 (t, J = 7.4 Hz, Ar$C\mathit{H}_2$, 2H), 3.24 (q, J = 7.0 Hz, $C\mathit{H}_2$NH, 2H), 3.84 (s, $OC\mathit{H}_3$, 3H), 5.62 (bs, NH, 1H), 6.63-6.66 (m, H_6, 1H), 6.75 (dd, J = 1.8 Hz, 8.2 Hz, H_2, 1H), 6.93 (dd, J = 8.3 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 23.2 ($\mathit{C}H_3$), 31.3 (Ar$CH_2\mathit{C}H_2$), 32.8 (Ar$\mathit{C}H_2$), 39.1 ($\mathit{C}H_2$NH), 56.2 ($O\mathit{C}H_3$), 113.5 (CH, $J_{F\text{-}C}$ = 1.7 Hz), 115.7 (CH, $J_{F\text{-}C}$ = 18.1 Hz), 120.3 (CH, $J_{F\text{-}C}$ = 6.6 Hz), 137.7 (C, $J_{F\text{-}C}$ = 3.9 Hz), 147.3 (C, $J_{F\text{-}C}$ = 10.8 Hz), 150.9 (C, $J_{F\text{-}C}$ = 243.3 Hz), 170.1 (C=O). ESI-HRMS *m/z* calcd for $C_{12}H_{16}FNO_2$ 226.1165 [M^++1], found 226.1169.

***N*-[3-(4-Fluoro-3-methoxyphenyl)propyl] propanamide (8e):** 77%, yellow oil. ^{1}H NMR δ 1.10 (t, J = 7.6 Hz, $CH_2C\mathit{H}_3$, 3H), 1.73-1.81 (m, 2 Ar$CH_2C\mathit{H}_2$, H), 2.14 (q, J = 7.6 Hz, $CO\mathit{C}H_2$, 2H), 2.56 (t, J = 7.5 Hz, Ar$C\mathit{H}_2$, 2H), 3.24 (q, J = 7.1 Hz, $C\mathit{H}_2$NH, 2H), 3.83 (s, $OC\mathit{H}_3$, 3H), 5.65 (bs, NH, 1H), 6.62-6.66 (m, H_6, 1H), 6.74 (dd, J = 1.9 Hz, 8.2 Hz, H_2, 1H), 6.92 (dd, J = 8.3 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8 ($\mathit{C}H_3$), 29.7 ($CO\mathit{C}H_2$), 31.3 (Ar$CH_2\mathit{C}H_2$), 32.9 (Ar$\mathit{C}H_2$), 39.0 ($\mathit{C}H_2$NH), 56.2 ($O\mathit{C}H_3$), 113.5 (CH, $J_{F\text{-}C}$ = 1.8 Hz), 115.7 (CH, $J_{F\text{-}C}$ = 18.1 Hz), 120.3 (CH, $J_{F\text{-}C}$ = 6.7 Hz), 137.7 (C, $J_{F\text{-}C}$ = 3.8 Hz), 147.3 (C, $J_{F\text{-}C}$ = 10.8 Hz), 150.9 (C, $J_{F\text{-}C}$ = 243.2 Hz), 173.7 (C=O). ESI-HRMS *m/z* calcd for $C_{14}H_{20}FNO_2$ 254.1478 [M^++1], found 254.1479.

***N*-[3-(4-Fluoro-3-methoxyphenyl)propyl] butanamide (8f):** 66%, yellow oil. ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, $CH_2C\mathit{H}_3$, 3H), 1.55-1.65 (m, $C\mathit{H}_2CH_3$, 2H), 1.73-1.80 (m, Ar$CH_2C\mathit{H}_2$,

2H), 2.09 (t, *J* = 7.3 Hz, COCH_2, 2H), 2.55 (t, *J* = 7.5 Hz, 2H, ArCH_2), 3.23 (q, *J* = 6.8 Hz, CH_2NH, 2H), 3.82 (s, OCH_3, 3H), 5.72 (bs, N*H*, 1H), 6.62-6.65 (m, H_6, 1H), 6.73 (dd, *J* = 1.7 Hz, 8.2 Hz, H_2, 1H), 6.91 (dd, *J* = 8.3 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 13.6 (*C*H_3), 19.1 (*C*H_2CH_3), 31.3 (ArCH$_2$*C*H_2), 32.9 (Ar*C*H_2), 38.6 (COCH_2), 38.9 (*C*H_2NH), 56.1 (OCH_3), 113.5 (*C*H, $J_{F\text{-}C}$ = 1.8 Hz), 115.6 (*C*H, $J_{F\text{-}C}$ = 18.1 Hz), 120.2 (*C*H, $J_{F\text{-}C}$ = 6.6 Hz), 137.7 (*C*, $J_{F\text{-}C}$ = 3.8 Hz), 147.3 (*C*, $J_{F\text{-}C}$ = 10.8 Hz), 150.8 (*C*, $J_{F\text{-}C}$ = 243.2 Hz), 173.0 (*C*=O). ESI-HRMS *m/z* calcd for $C_{14}H_{20}FNO_2$ 254.1478 [M^++1], found 254.1477.

***N*-[3-(3-Fluoro-4-methoxyphenyl)propyl] acetamide (9a):** 3-(3-Fluoro-4-methoxy phenylacrylonitrile (180 mg, 1.02 mmol) and acetic anhydride (16.9 mmol) in anhydrous THF (18 mL) was hydrogenated in the presence of Raney-Ni at 50 °C for 14 h by the general procedure to give, after purification by flash column chromatography (cyclohexane/AcOEt, 85:15), amide **9a**, 92%, as an off-yellow solid, mp 49–50 °C. ^{1}H NMR δ 1.68-1.82 (m, ArCH$_2$CH_2, 2H), 1.92 (s, COCH_3, 3H), 2.54 (t, *J* = *7*.3 Hz, ArCH_2, 2H), 3.22 (q, *J* = 6.9 Hz, CH_2NH, 2H), 3.82 (s, OCH_3, 3H), 5.71 (bs, N*H*, 1H), 6.83-6.89 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 23.2 (*C*H_3), 31.0 (ArCH$_2$*C*H_2), 32.2 (Ar*C*H_2, $J_{F\text{-}C}$ = 1.2 Hz), 39.0 (*C*H_2NH), 56.3 (OCH_3), 113.4 (*C*H, $J_{F\text{-}C}$ = 2.2 Hz), 115.8 (*C*H, $J_{F\text{-}C}$ = 17.9 Hz), 123.8 (*C*H, $J_{F\text{-}C}$ = 3.5 Hz), 134.5 (*C*, $J_{F\text{-}C}$ = 6.0 Hz), 145.7 (*C*, $J_{F\text{-}C}$ = 10.6 Hz), 152.2 (*C*, $J_{F\text{-}C}$ = 245.4 Hz), 170.1 (*C*=O). Found: C, 63.7; H, 7.2. Calc. for $C_{12}H_{16}NO_2F$: C, 64.0; H, 7.2%.

***N*-[3-(3-Fluoro-4-methoxyphenyl) propyl]propanamide (9b):** 76%, mp 51-52 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 1.08 (t, *J* = 7.4 Hz, CH$_2$CH_3, 3H), 1.66-1.81 (m, ArCH$_2$CH_2, 2H), 2.13 (q, *J* = 7.5 Hz, CH_2CH$_3$, 2H), 2.52 (t, *J* = 7.3 Hz, ArCH_2, 2H), 3.21 (q, 2H, *J* = 6.7 Hz, CH_2NH), 3.80 (s, OCH_3, 3H), 5.78 (bs, N*H*, 1H), 6.81-6.87 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 9.8 (*C*H_3), 29.6 (COCH_2), 31.1 (ArCH$_2$*C*H_2), 32.2 (Ar*C*H_2, $J_{F\text{-}C}$ = 0.9 Hz), 38.9 (*C*H_2NH), 56.2 (OCH_3), 113.4 (*C*H, $J_{F\text{-}C}$ = 2.1 Hz), 115.8 (*C*H, $J_{F\text{-}C}$ = 17.9 Hz), 123.7 (*C*H, $J_{F\text{-}C}$ = 3.5 Hz), 134.5 (*C*, $J_{F\text{-}C}$ = 6.0 Hz), 145.6 (*C*, $J_{F\text{-}C}$ = 10.8 Hz), 152.2 (*C*, $J_{F\text{-}C}$ = 245.2 Hz), 173.8 (*C*=O). Found: C, 65.1; H, 7.4. Calc. for $C_{13}H_{18}NO_2F$: C, 65.3; H, 7.6%.

***N*-[3-(3-Fluoro-4-methoxyphenyl)propyl] butanamide (9c):** 70%, mp 52-53 °C (cyclohexane/AcOEt, 85:15). ^{1}H NMR δ 0.9 (t, *J* = 7.3 Hz, CH$_2$CH_3, 3H), 1.52-1.68 (m, CH_2CH$_3$, 2H), 1.70-1.83 (m, ArCH$_2$CH_2, 2H), 2.09 (t, *J* = 7.2 Hz, COCH_2, 2H), 2.54 (t, *J* = 7.3 Hz, ArCH_2, 2H), 3.23 (q, *J* = 6.9 Hz, CH_2NH, 2H), 3.82 (s, OCH_3, 3H), 5.56 (bs, N*H*, 1H), 6.82-6.89 (m, H_{arom}, 3H). ^{13}C NMR ($CDCl_3$) δ 13.7 (*C*H_3), 19.1 (*C*H_2CH_3), 31.2 (ArCH$_2$*C*H_2), 32.2 (Ar*C*H_2, $J_{F\text{-}C}$ = 1.2 Hz), 38.7 (COCH_2), 38.9 (*C*H_2NH), 56.3 (OCH_3), 113.5 (*C*H, $J_{F\text{-}C}$ = 2.1 Hz), 115.9 (*C*H, $J_{F\text{-}C}$ = 17.8 Hz), 123.8 (*C*H, $J_{F\text{-}C}$ = 3.5 Hz), 134.5 (*C*, $J_{F\text{-}C}$ = 6.1 Hz), 145.7 (*C*, $J_{F\text{-}C}$ = 10.7 Hz), 152.3 (*C*, $J_{F\text{-}C}$ = 245.5 Hz), 172.9 (*C*=O). Found: C, 66.1; H, 8.0. Calc. for $C_{14}H_{20}NO_2F$: C, 66.4; H, 8.0%.

***N*-[1-(4-Fluoro-3-methoxyphenyl)propan-2-yl]butanamide (10):** A solution of 4-fluoro-3-methoxybenzaldehyde (0.63 g, 4.10 mmol) in nitroethane (1.20 ml, 16.8 mmol) was treated with ammonium acetate (0.87 g, 11.3 mmol) and acetic acid (13 mL). The resulting mixture was refluxed for 3 h and then the solvent was removed under reduced pressure to give a residue, which was dissolved in dichloromethane (10 mL). Water (3 mL) was then added and the aqueous layer was washed with dichloromethane (2 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave *E*-1-fluoro-2-methoxy-4-(2-nitro

propen-1-yl) benzene as an orange crystalline solid: 0.35 g (1.64 mmol, 40%), mp 89-90 °C; ^{1}H NMR δ 2.43 (s, CH_3, 2H), 3.90 (s, OCH_3, 3H), 6.96-7.01 (m, H$_{arom}$, 2H), 7.09-7.19 (m, H$_{arom}$, 1H), 8.01 (s, ArCH=C, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H$_3$), 56.3 (O*C*H$_3$), 115.1 (*C*H, J_{F-C} = 2.6 Hz), 116.6 (*C*H, J_{F-C} = 19.0 Hz), 122.9 (*C*H, J_{F-C} = 7.2 Hz), 128.9 (*C*, J_{F-C} = 4.1 Hz), 132.7 (Ar*C*H=C), 147.6 (*C*NO$_2$), 147.9 (*C*, J_{F-C} = 11.0 Hz), 153.2 (*C*, J_{F-C} = 252.3 Hz).

A solution of *E*-1-fluoro-2-methoxy-4-(2-nitropropen-1-yl)benzene (0.35 g, 1.64 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (0.59 g, 15.5 mmol) in THF (40 mL). After completion of addition, the mixture was refluxed for 2 h and then allowed to reach ambient temperature. After cooling to 0 °C, water (20 mL) was added. The mixture was filtered, and the filtrate was taken up in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL) and brine (25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give crude *α*-methyl-*β*-(4-fluoro-3-methoxyphenyl)ethanamine, which was used in the next step without further purification.

Triethylamine (0.30 mL) and butyric anhydride (2.3 mL, 1.4 mmol) were added to a cooled solution (0 °C) of *α*-methyl-*β*-(4-fluoro-3-methoxyphenyl)ethanamine (0.30 g, 1.64 mmol) in dichloromethane (4 mL). The ice bath was removed and the solution stirred for 30 min. The solvent was evaporated *in vacuo*, and the residue was taken up in ethyl acetate (50 mL) and washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil, which was chromatographed (flash column, cyclohexane/ethyl acetate, 50:50) to give the desired amide **10** as a white powder: 70%, mp 82-83 °C (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR δ 0.87 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.08 (d, *J* = 6.6 Hz, 3H, CH_3), 1.54-1.63 (m, CH_2CH$_3$, 2H), 2.07 (t, *J* = 7.4 Hz, COCH_2, 2H), 2.60 (dd, *J*= 7.4 Hz, 13.6 Hz, ArCH, 1H), 2.78 (dd, *J*= 5.9 Hz, 13.6 Hz, ArCH, 1H), 3.84 (s, OCH_3, 3H), 4.16-4.26 (m, CHNH, 1H), 5.32 (bs, NH, 1H), 6.63-6.66 (m, H_6, 1H), 6.76 (dd, *J* = 1.5 Hz, 8.1 Hz, H_2, 1H), 6.94 (dd, *J* = 8.2 Hz, 11.3 Hz, H_5, 1H). ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_2CH_3), 19.1 (CH_2CH_3), 20.0 (CH_3), 38.8 ($COCH_2$), 42.2 (*C*HNH), 45.9 (Ar*C*H$_2$, *J* = 1.0 Hz), 56.2 (O*C*H$_3$), 114.3 (CH, J_{F-C} = 1.8 Hz), 115.6 (*C*H, J_{F-C} = 18.2 Hz), 121.5 (*C*H, J_{F-C} = 6.7 Hz), 134.4 (*C*, J_{F-C} = 3.9 Hz), 147.4 (*C*, J_{F-C} = 10.7 Hz), 151.2 (*C*, J_{F-C} = 244.1 Hz), 172.2 (*C*=O). Found: C, 66.1; H, 8.0. Calc. for $C_{14}H_{20}NO_2F$: C, 66.4; H, 8.0%.

Biology

Measurement of pigment aggregation[2]

Flat-bottomed 96-well cell culture plates containing approximately 6-8 x 10^3 melanophores / well were used for pigment aggregation experiments. One hour prior to all concentration-response experiments, growth medium in each well was aspirated and replaced with 0.7 x L-15 medium (containing 1 mg · mL^{-1} bovine albumin). In 0.7 x L-15 medium pigment remained fully dispersed throughout the cells. The change in distribution of pigment granules within melanophores was quantitated using a Bio-Tek microtiter plate reader (model EL3115, Anachem, Luton, UK) by measuring the change in absorbance (630 nm), before and after drug treatment. The fractional change in absorbance, 1- (A_f/A_i) where A_i is the initial absorbance before drug treatment and A_f is the final absorbance, was calculated. All drugs were freshly prepared from 10^{-2} M stock solutions in methanol or DMSO kept at -20 ^{o}C. The maximal concentration of

solvent was 1 % v/v which did not cause pigment redistribution in melanophores (data not shown). Antagonists were incubated with cells for 60 min before the addition of melatonin. Antagonist potency (pk_B) was estimated by constructing dose-response curves of melatonin in the absence and presence of a single concentration of antagonist (10^{-5} M). Estimated pk_B values were calculated from the equation log (concentration ratio – 1) – log [antagonist].

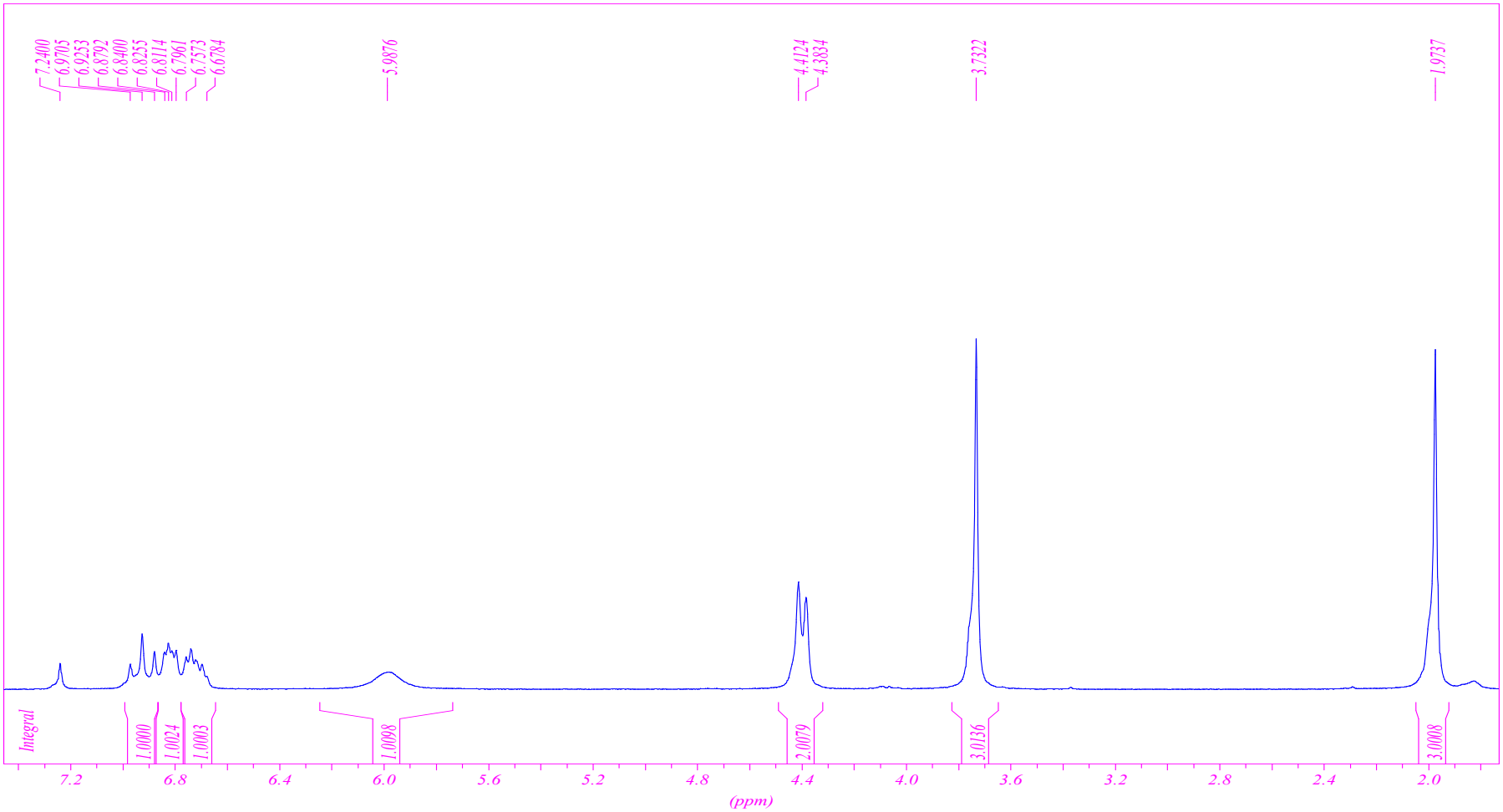
Reference

1 F. Claudi, M. Cardellini, G. M. Cingolani, A., Piergentili, G. Peruzzi and W. Balduini, *J.Med.Chem*. 1990, **33**, 2408.

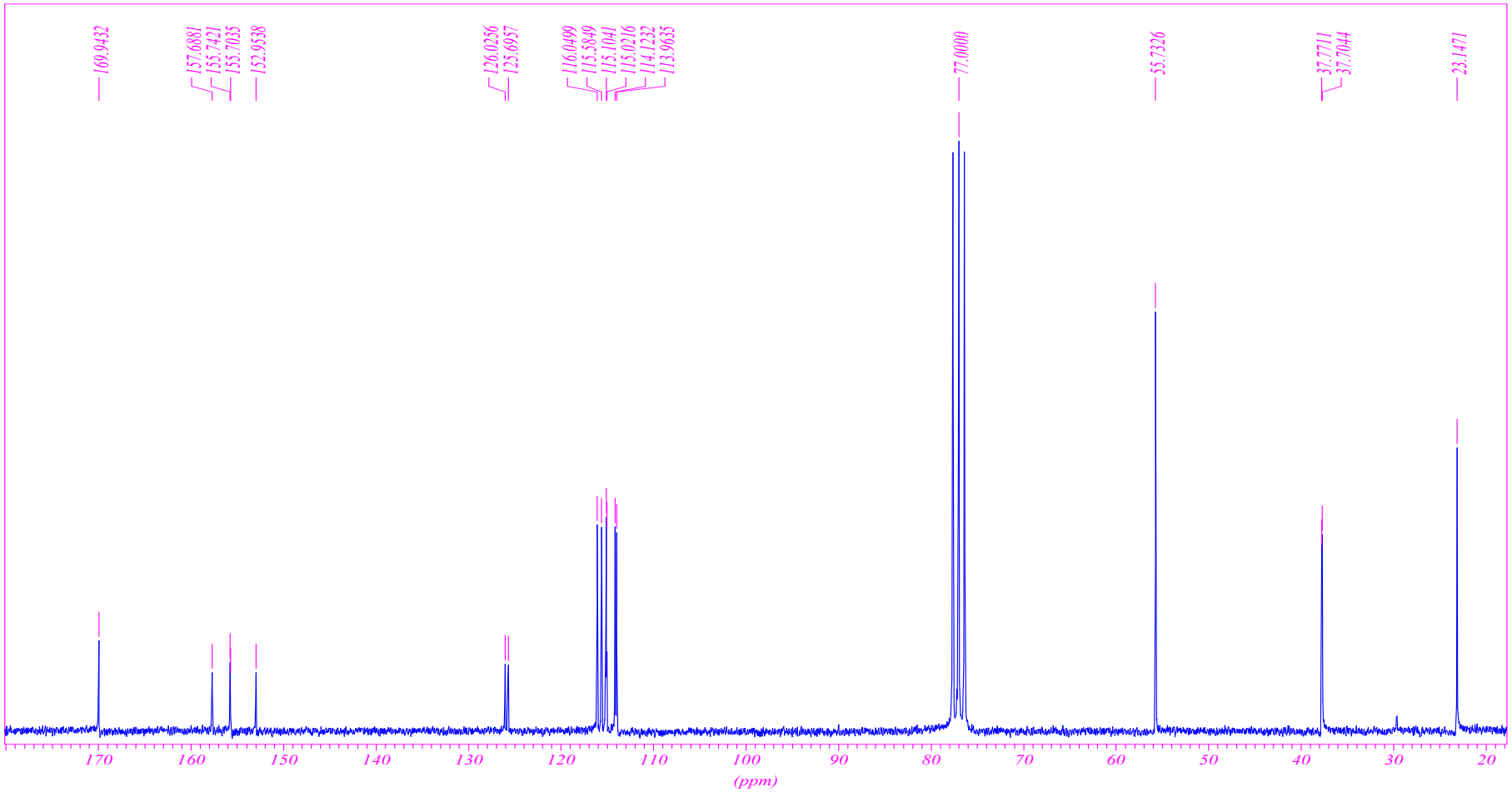
2 D. Sugden, L.K. Yeh and M.T. Teh, *Reprod. Nutr. Dev.* 1999, **39,** 335.

Spectra

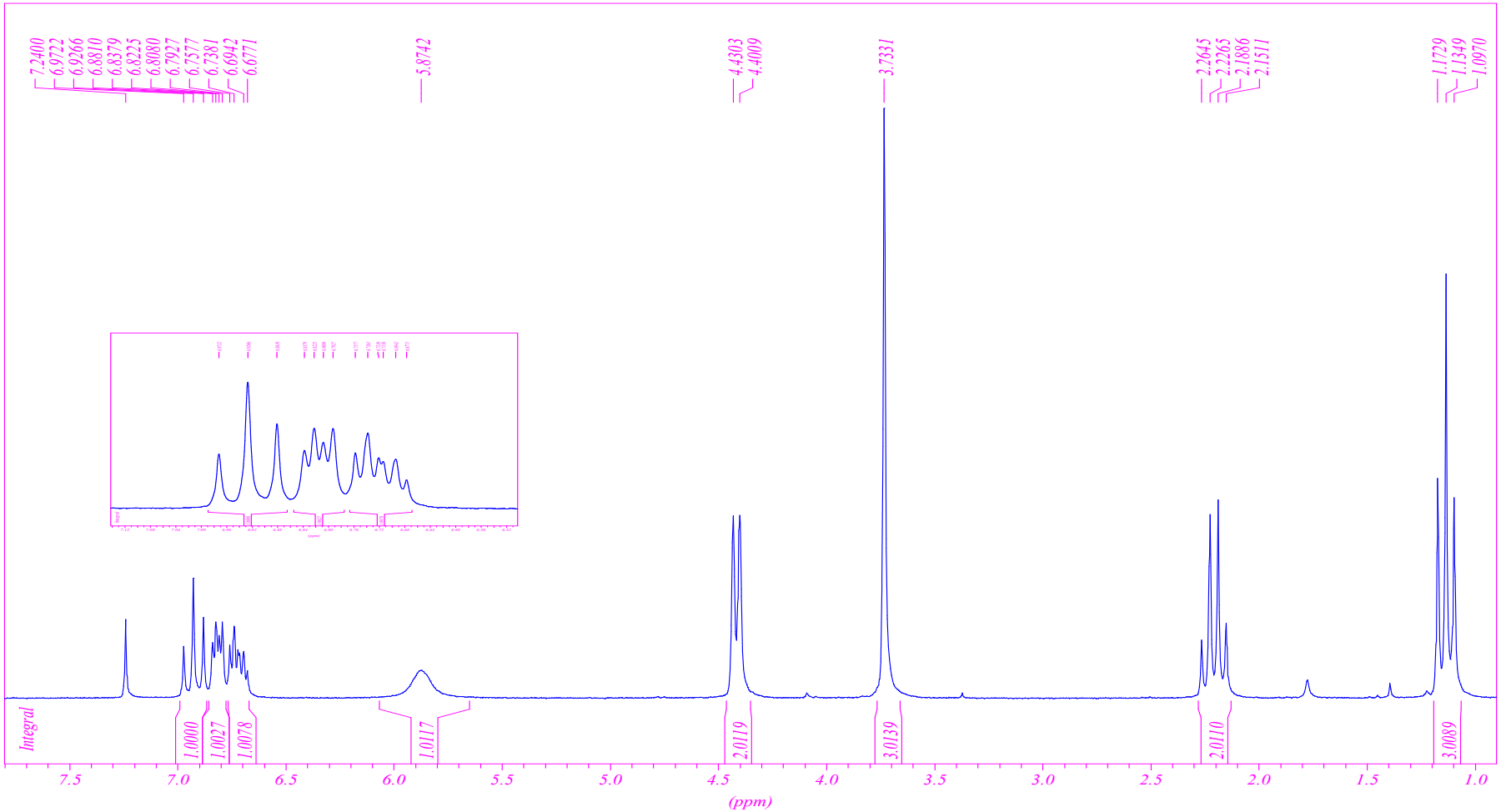
1. **^{1}HNMR($CDCl_3$) of *N*-(2-fluoro-5-ethoxybenzyl)acetamide (2a)**



2. **^{13}C NMR ($CDCl_3$) of *N*-(2-fluoro-5-methoxybenzyl)acetamide (2a)**



3. **^{1}H NMR ($CDCl_3$) of *N*-(2-Fluoro-5-methoxyphenylmethyl)propanamide (2b)**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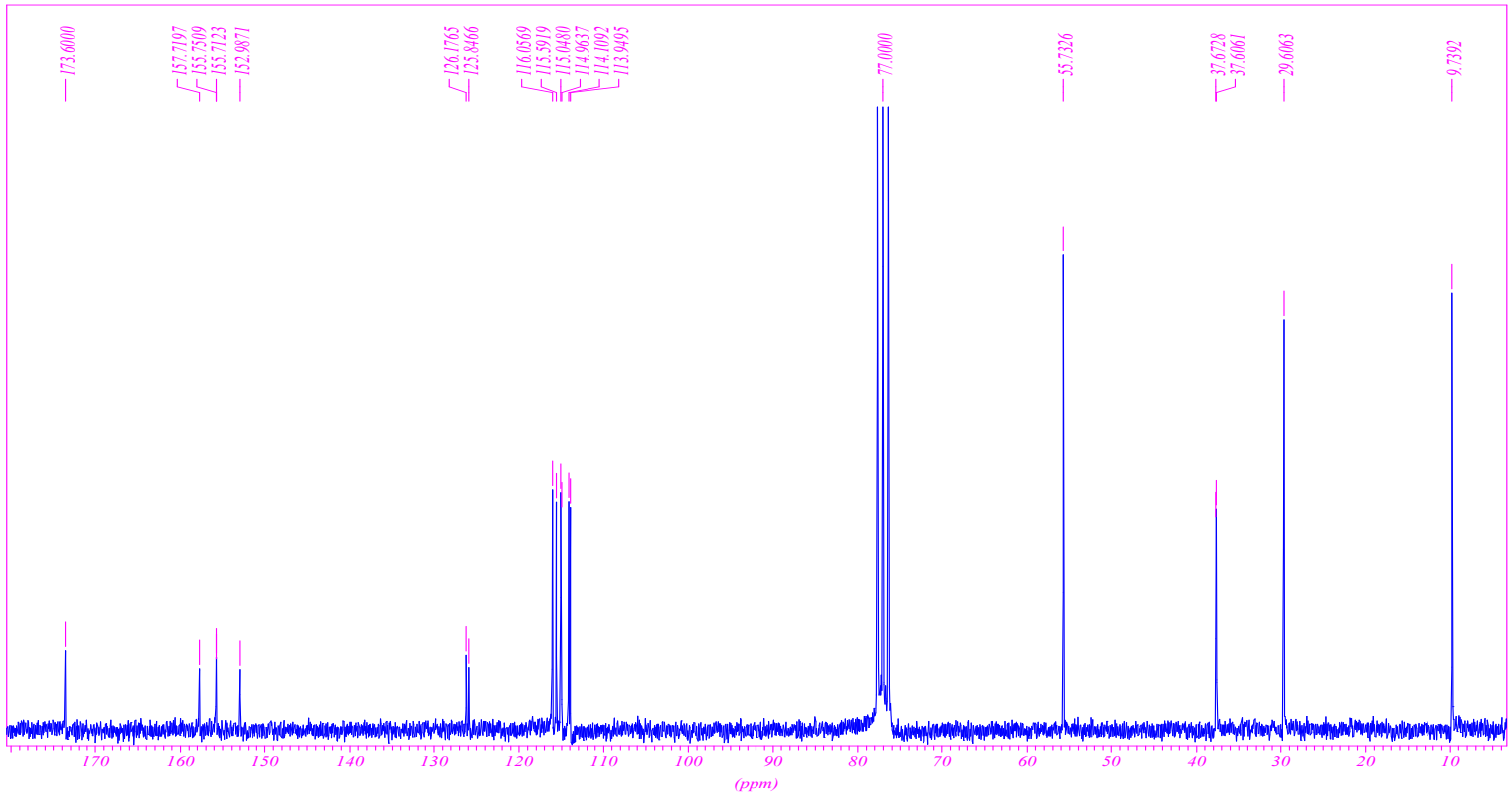
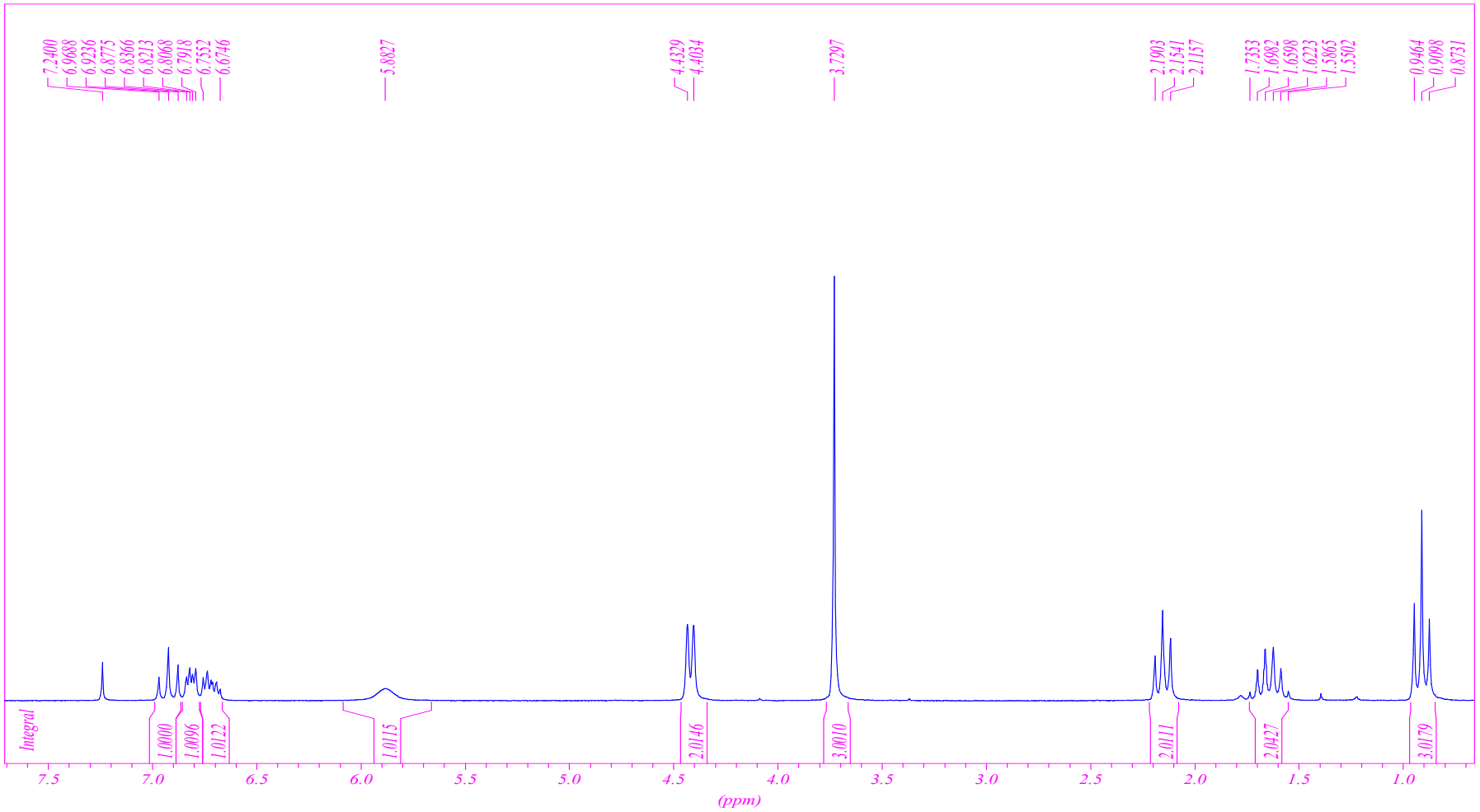
6.6771
5.8742
4.4303
4.4009
3.7331
2.2645
2.2265
2.1886
2.1511
1.1729
1.1349
1.0970
Integral
1.0000
1.0027
1.0078
1.0117
2.0119
3.0139
2.0110
3.0089
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

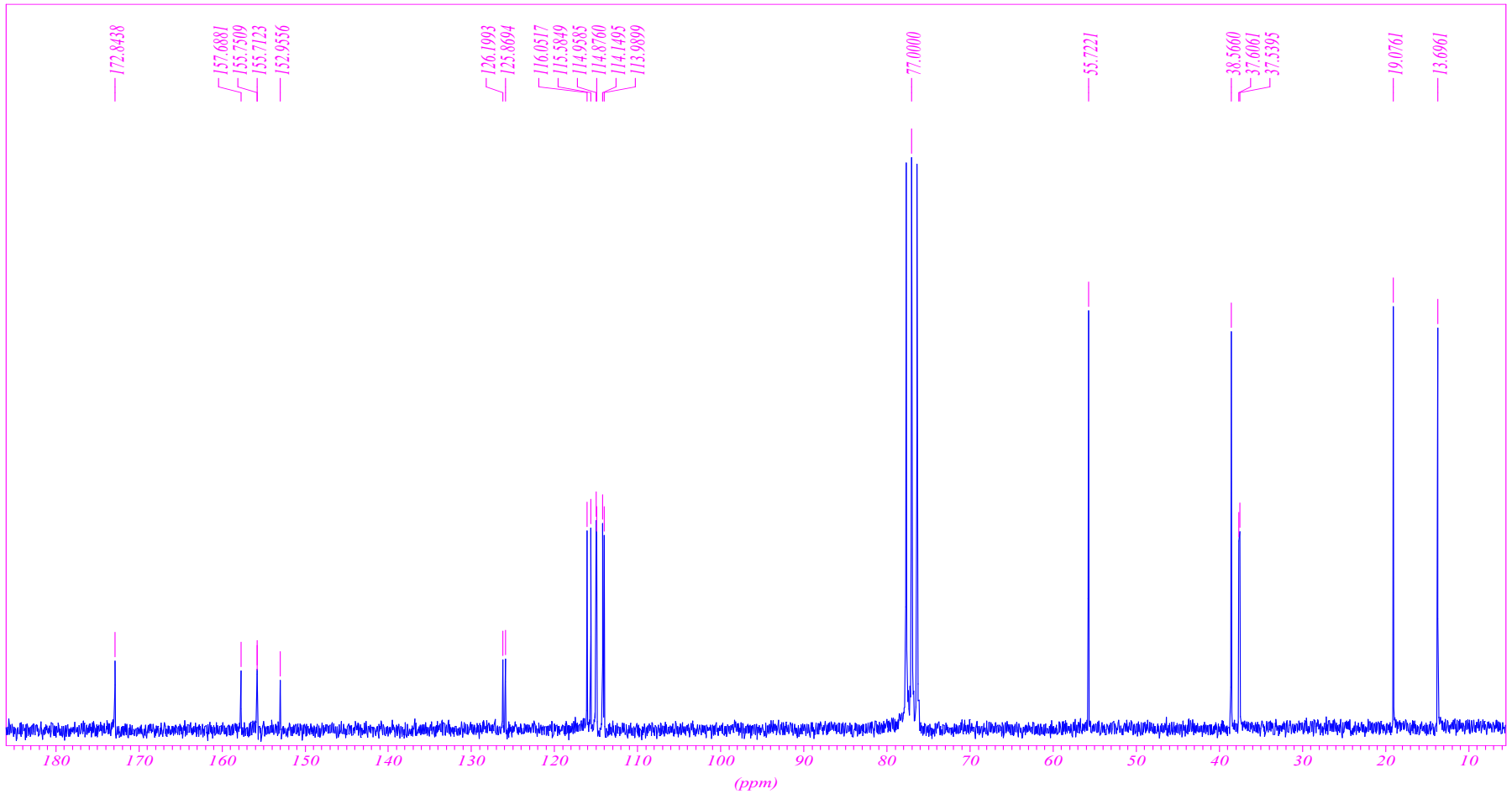
4. **^{13}C NMR ($CDCl_3$) of *N*-(2-Fluoro-5-methoxyphenylmethyl)propanamide (2b)**



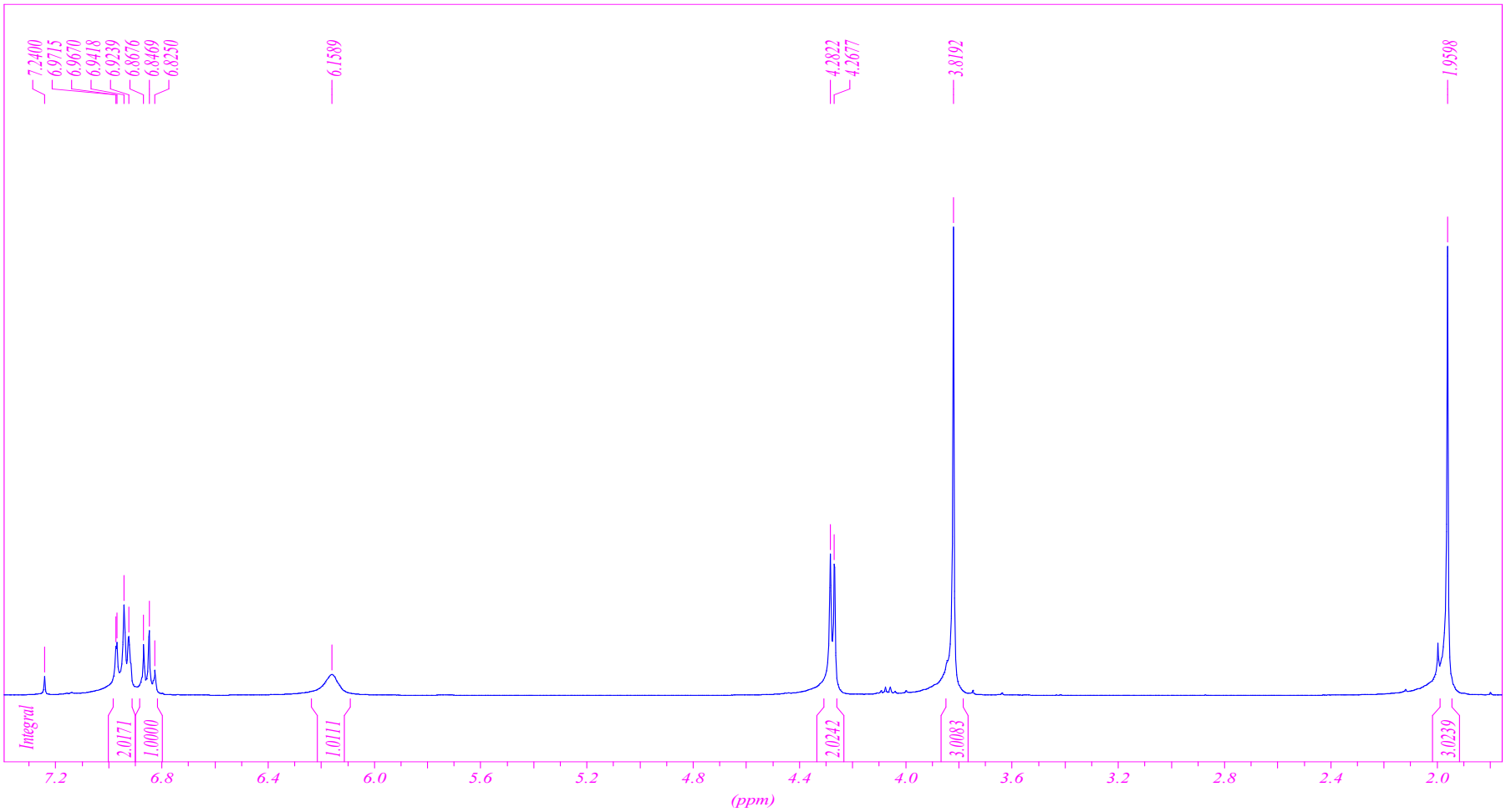
5. **^{1}H NMR ($CDCl_3$) of *N*-(2-Fluoro-5-methoxyphenylmethyl)butanamide (2c)**



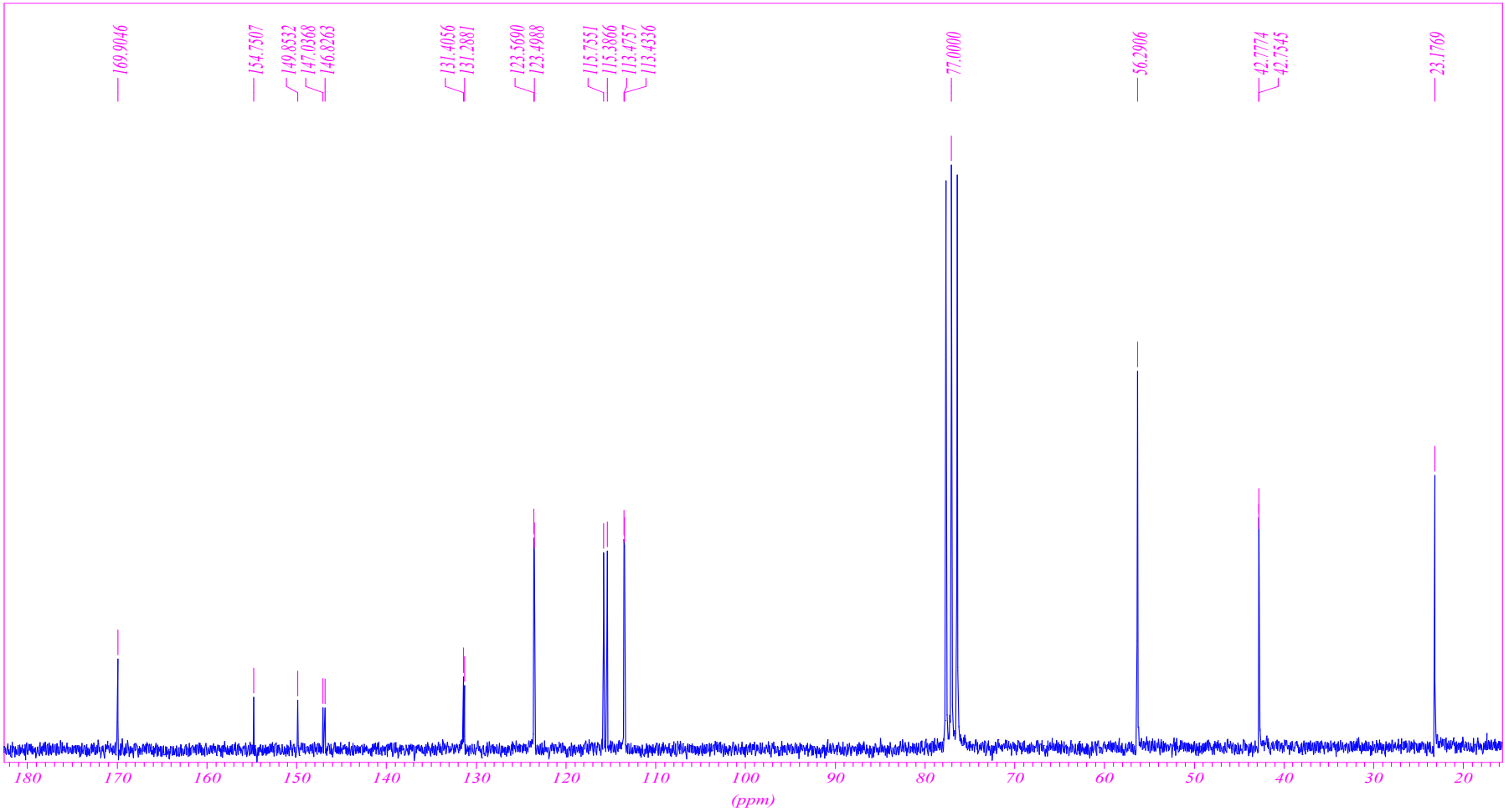
6. **^{13}C NMR($CDCl_3$) of *N*-(2-Fluoro-5-methoxyphenylmethyl)butanamide (2c)**



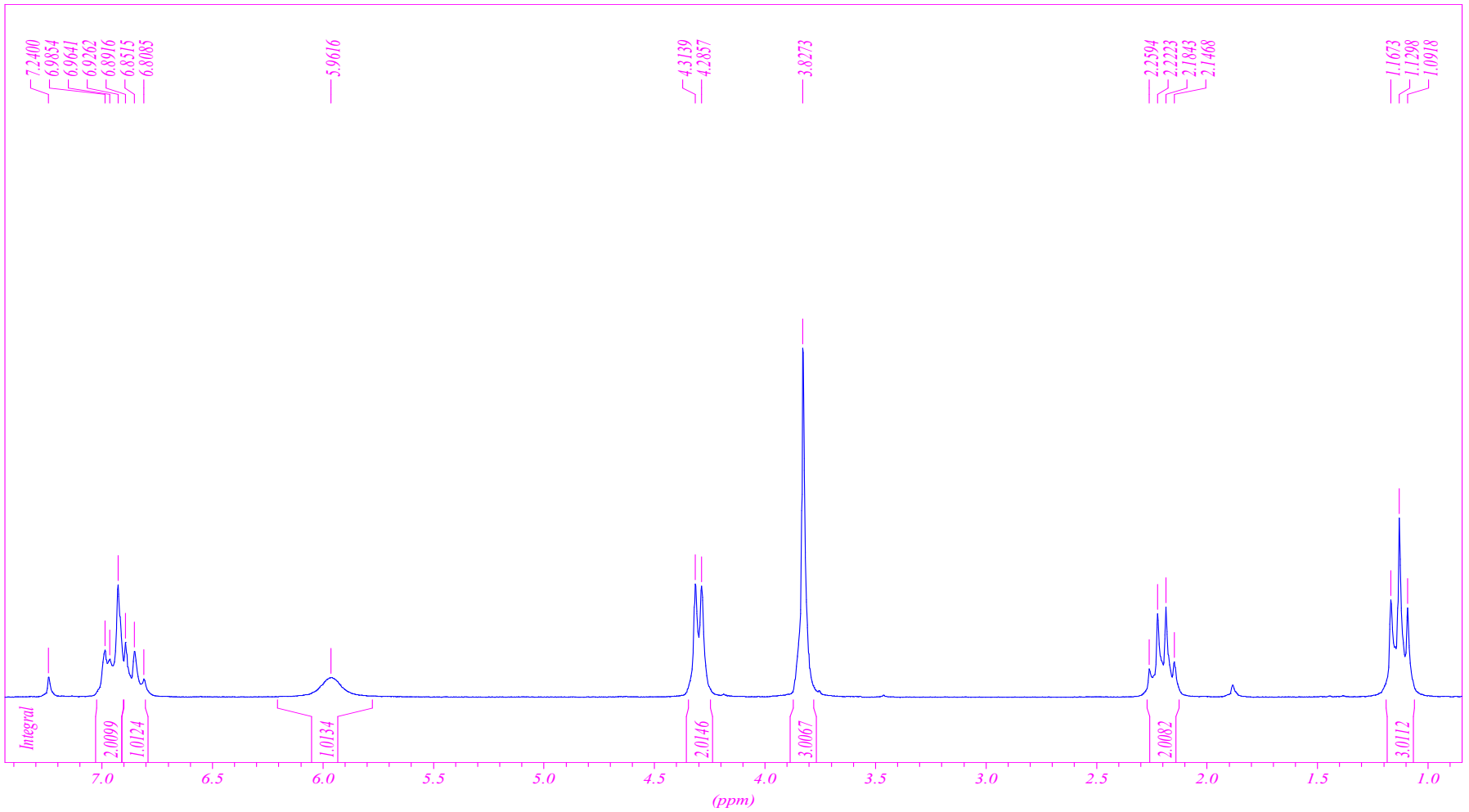
7. **^{1}H NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)acetamide (2d)**



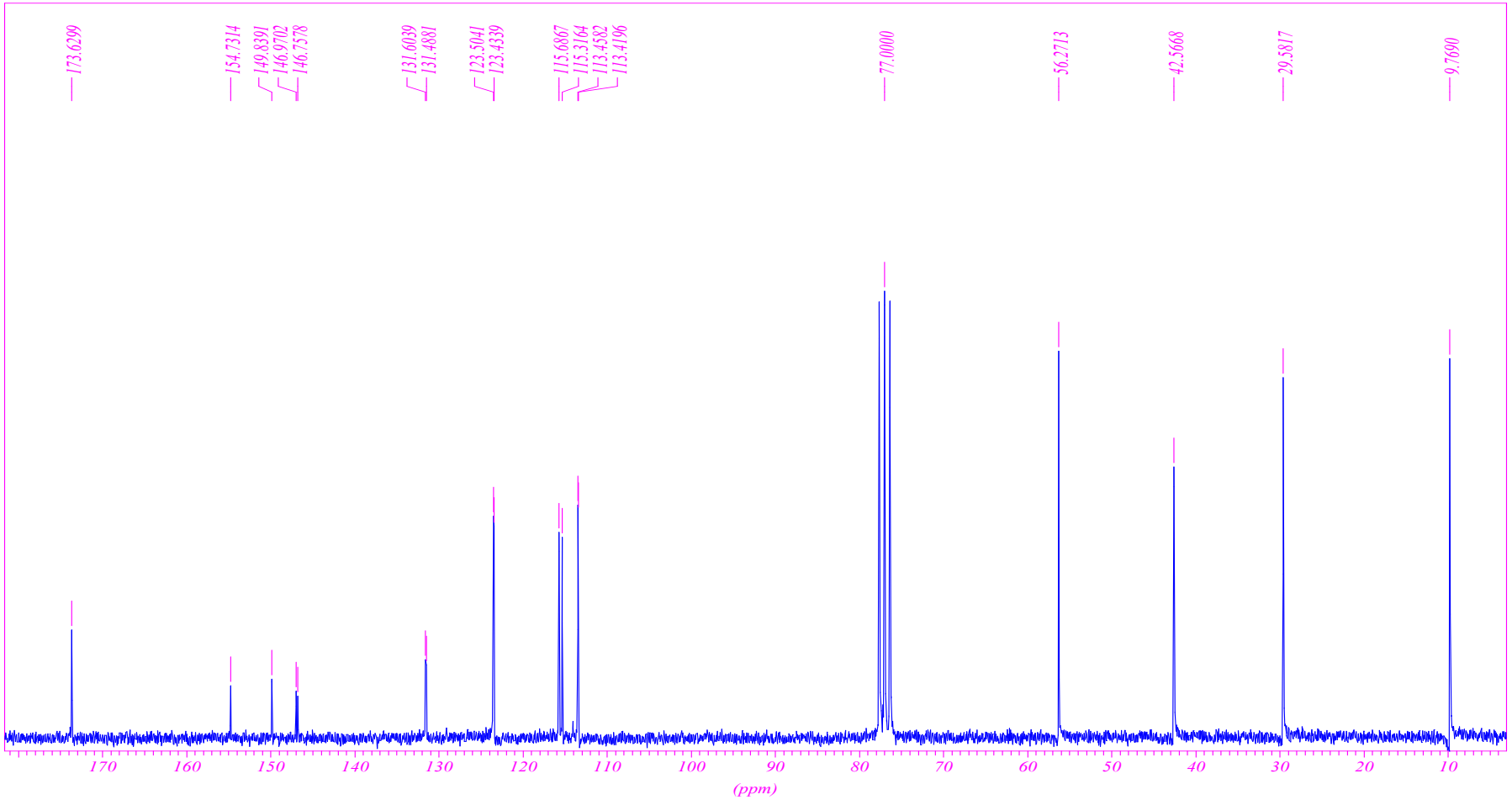
8. **^{13}C NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)acetamide (2d)**



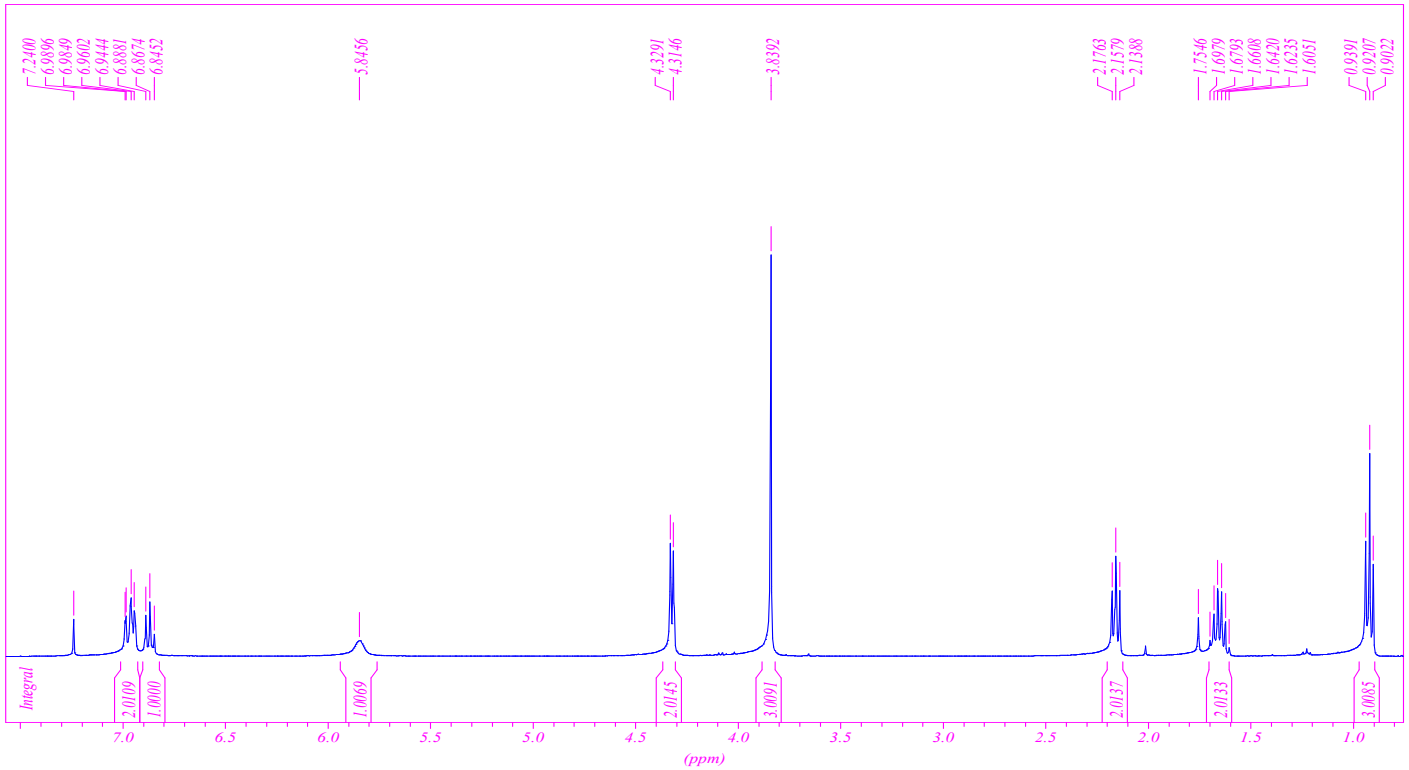
9. **^{1}H NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)propanamide (2e)**


7.2400
6.9854
6.9641
6.9262
6.8916
6.8515
6.8085
5.9616
4.3139
4.2857
3.8273
2.2594
2.2223
2.1643
2.1468
1.1673
1.1298
1.0918
Integral
2.0099
1.0124
1.0134
2.0146
3.0067
2.0082
3.0112
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

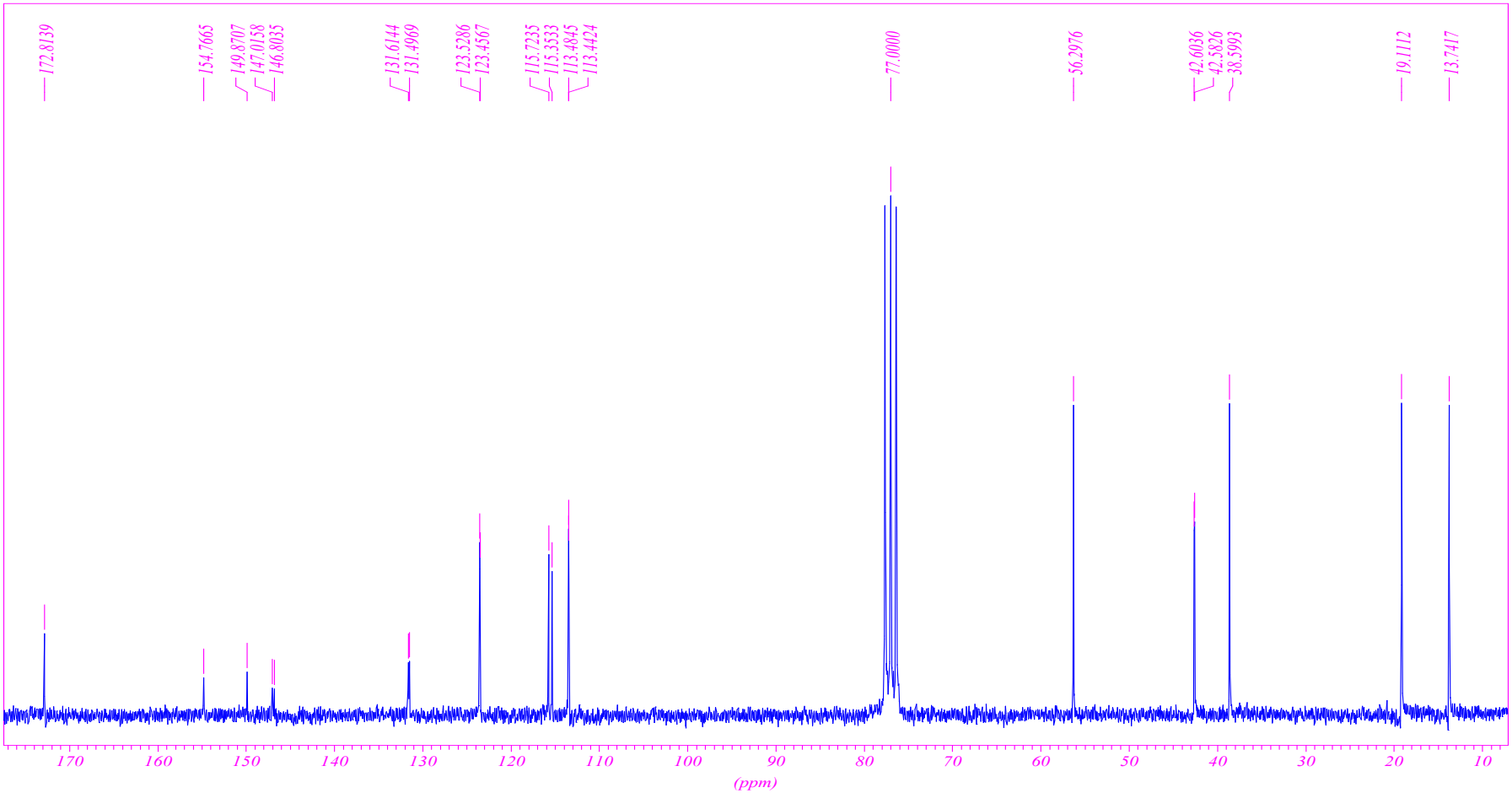
10. **^{13}C NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)propanamide (2e)**



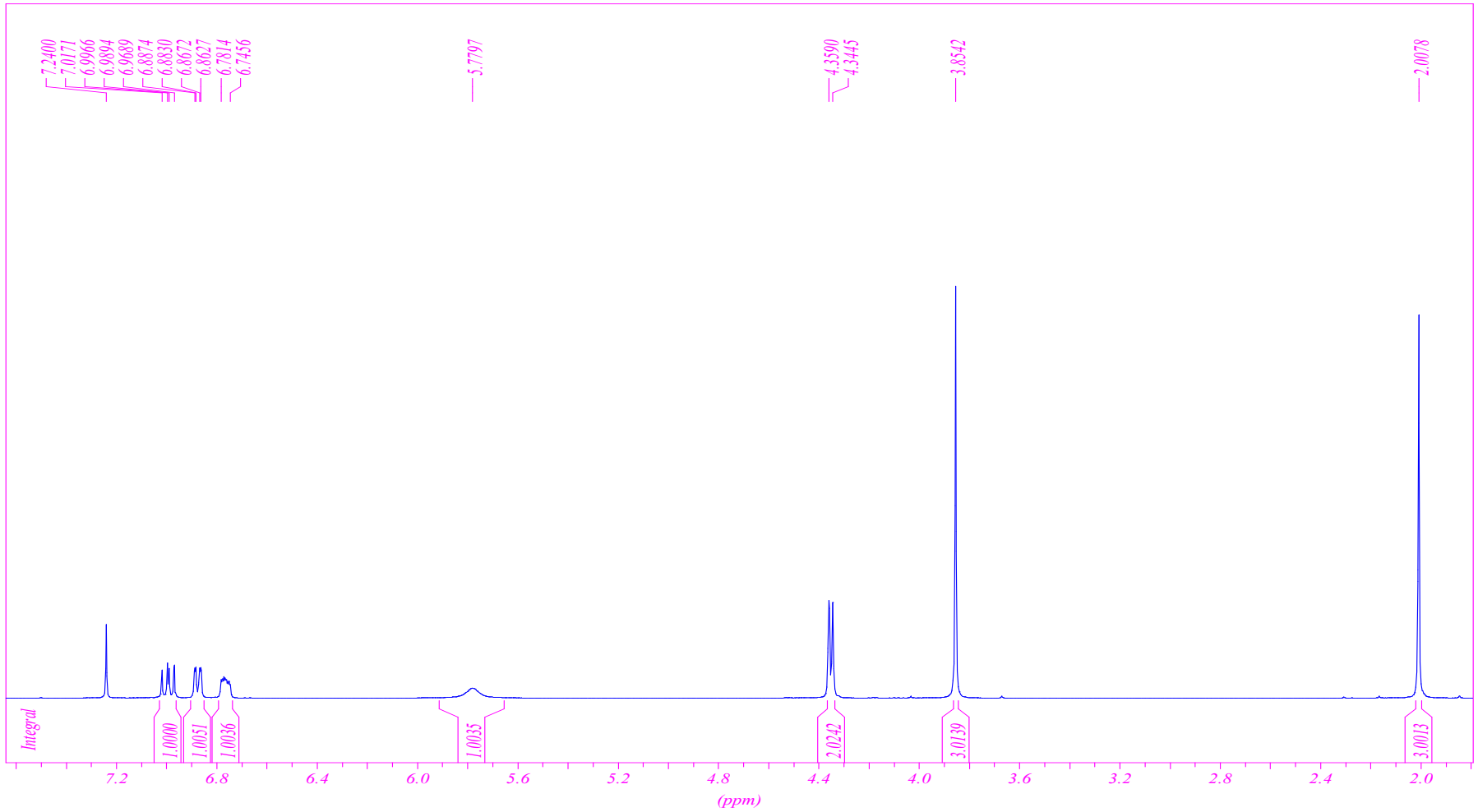
11. **^{1}H NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)butanamide (2f)**



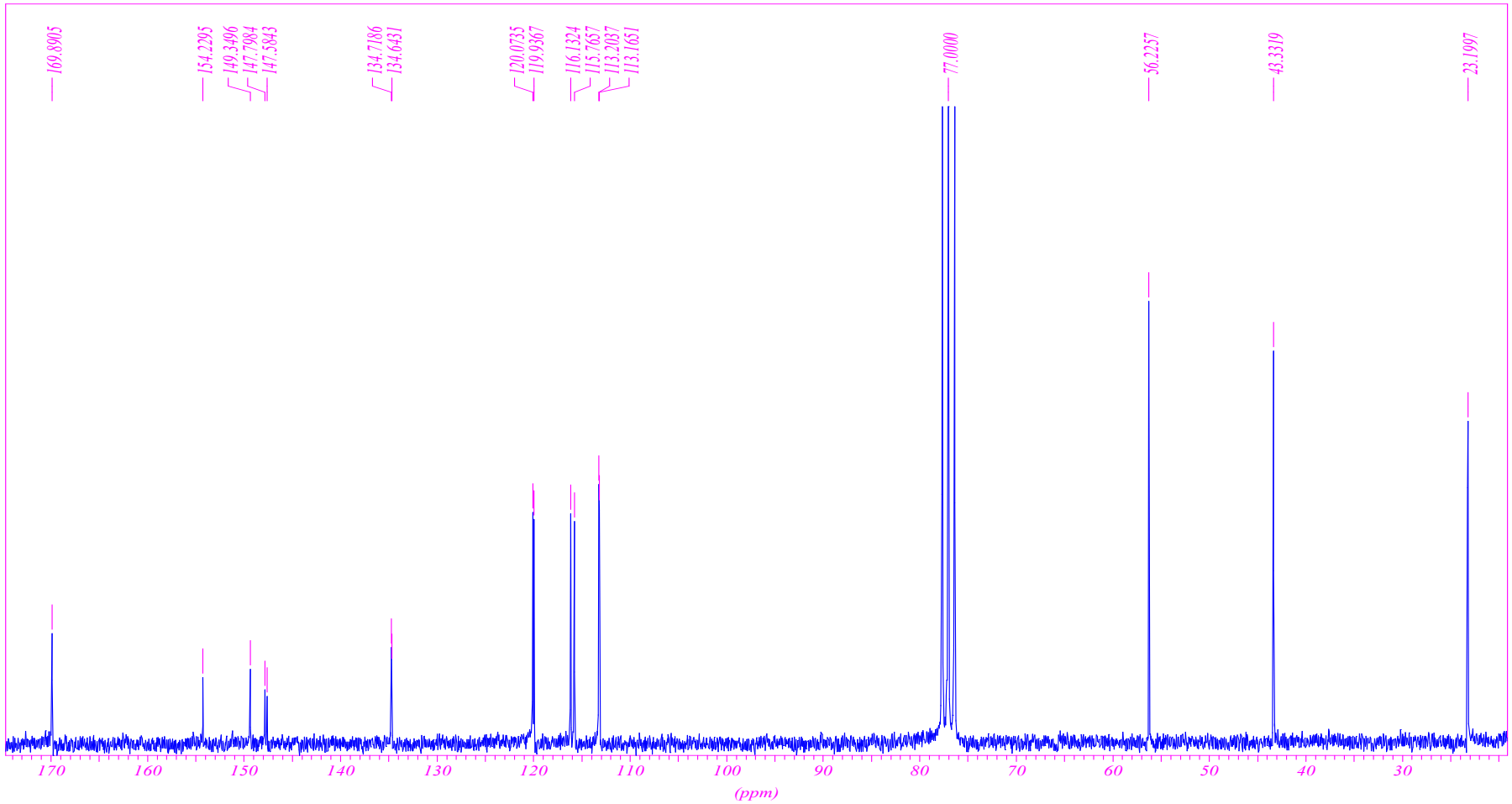
12. **^{13}C NMR ($CDCl_3$) of *N*-(3-Fluoro-4-methoxyphenylmethyl)butanamide (2f)**



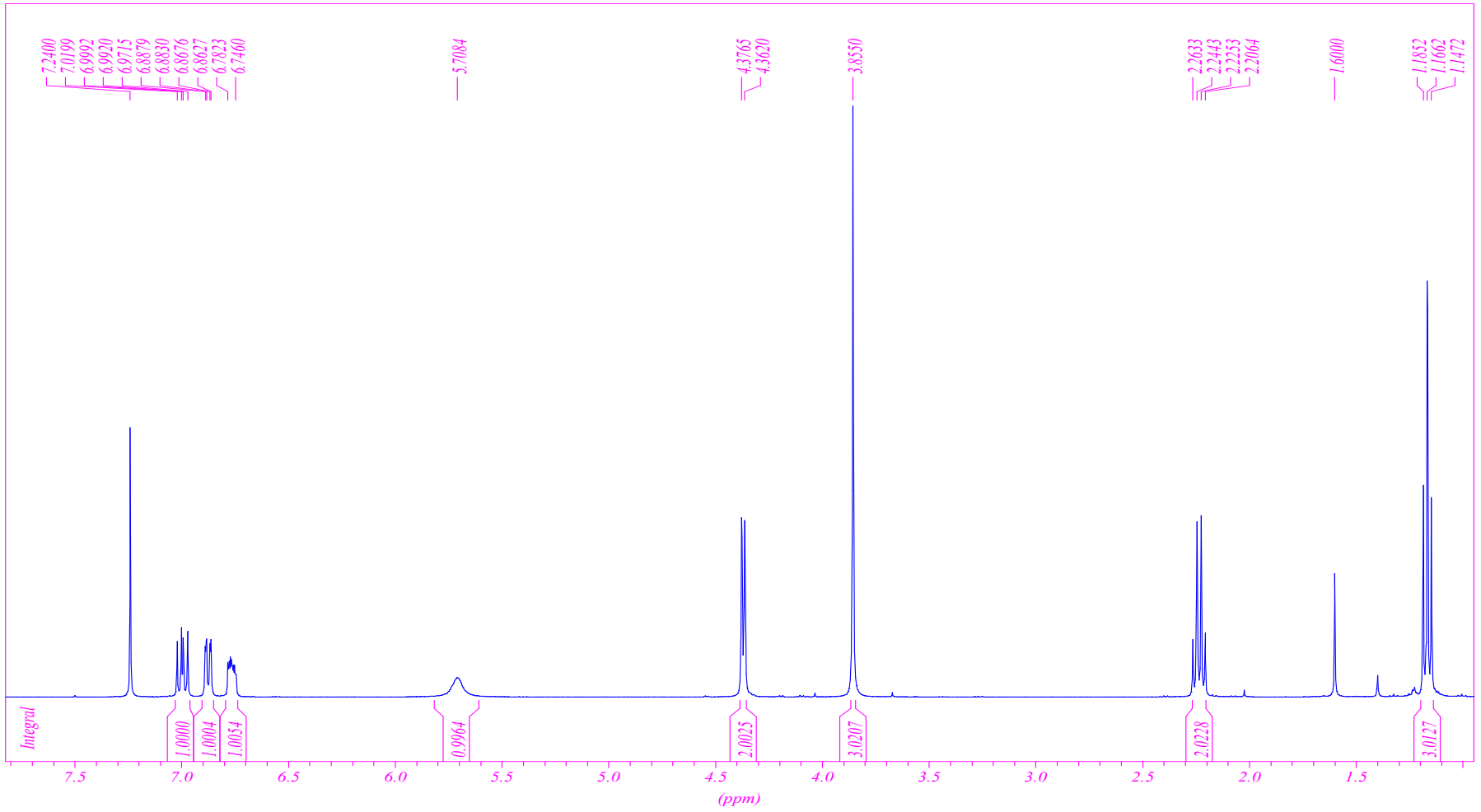
13. **^{1}H NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)acetamide (3a)**



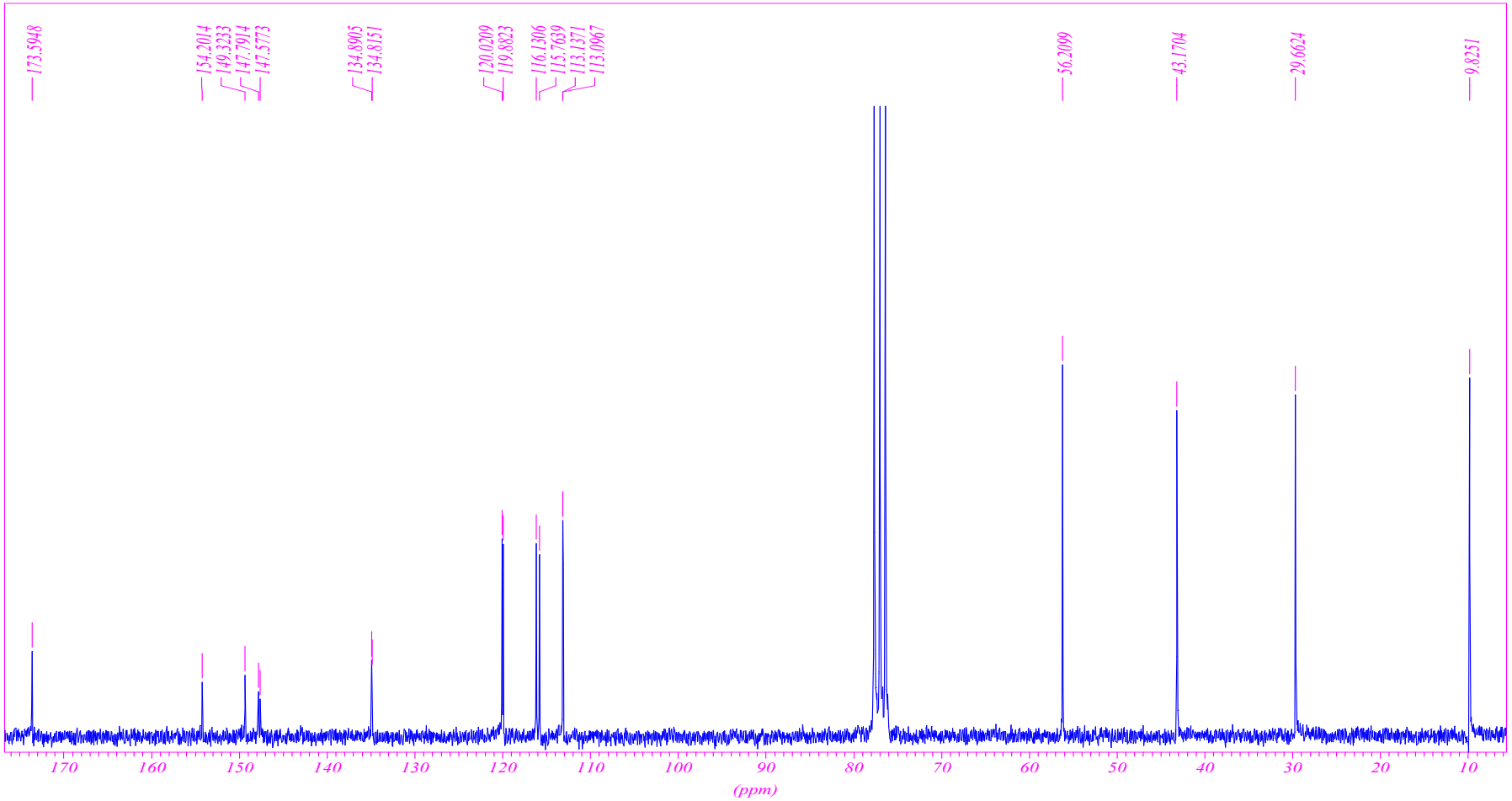
14. **^{13}C NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)acetamide (3a)**



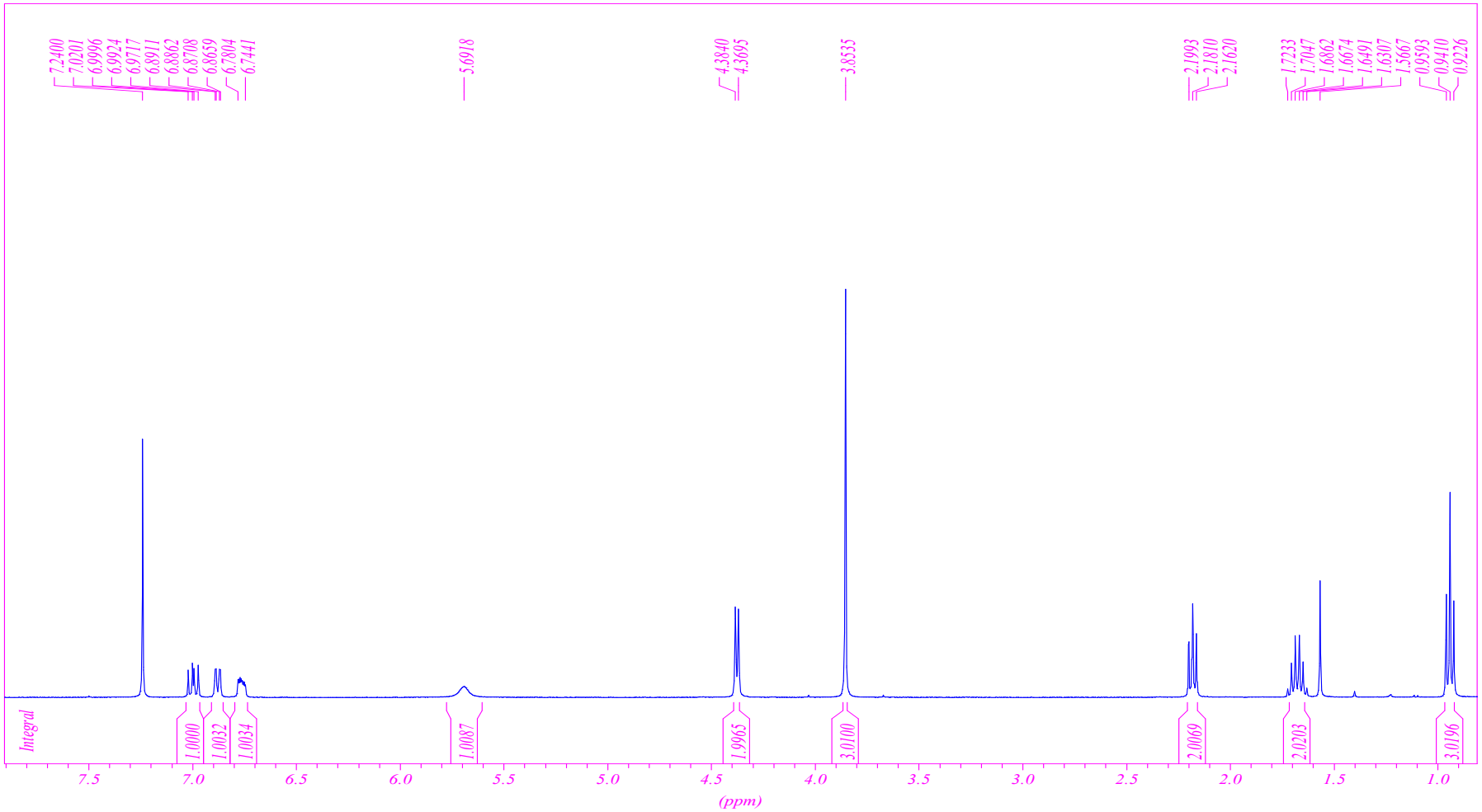
15. **^{1}H NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)propanamide (3b)**



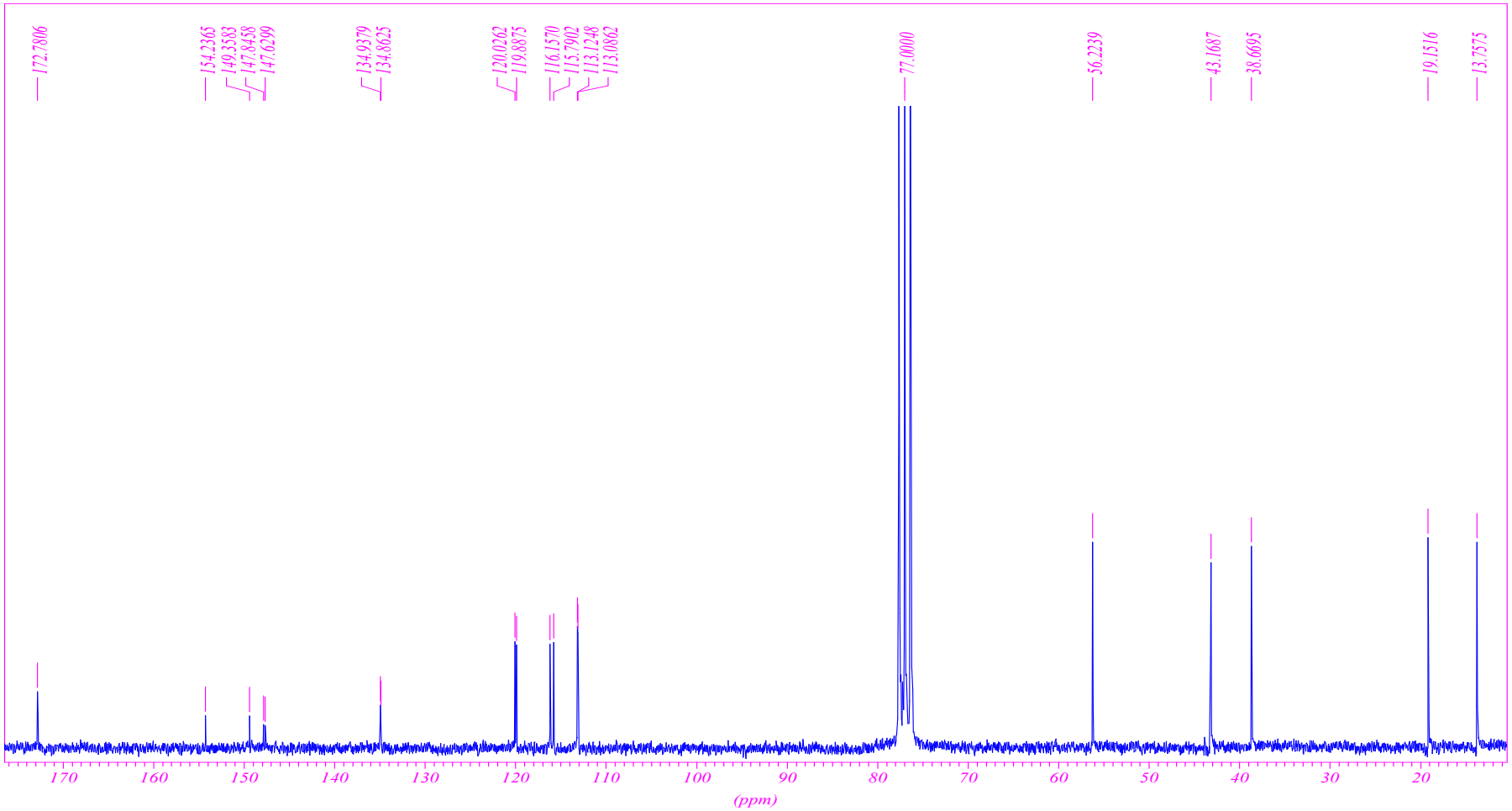
16. **^{13}C NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)propanamide (3b)**



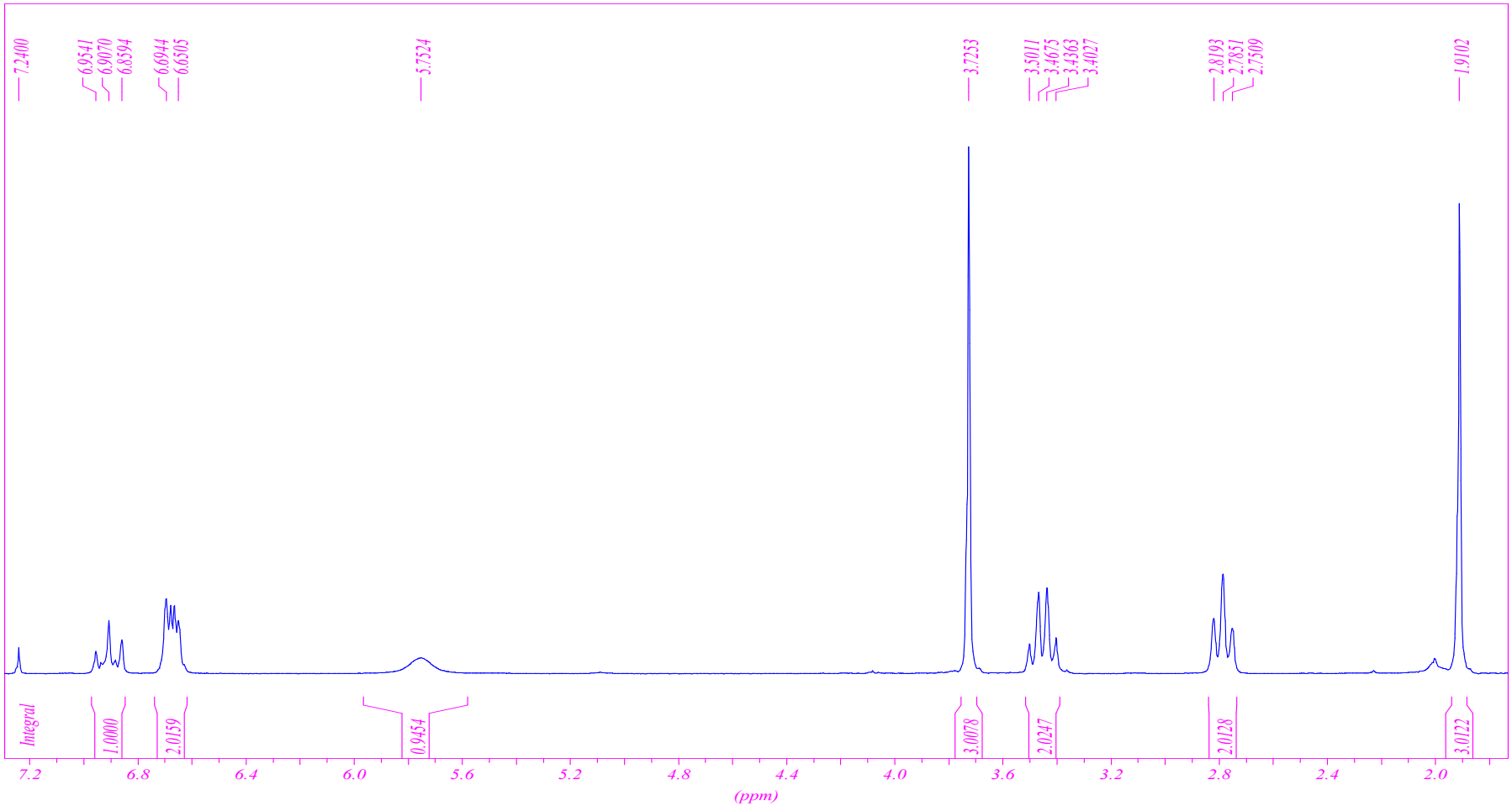
17. **^{1}H NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)butanamide (3c)**



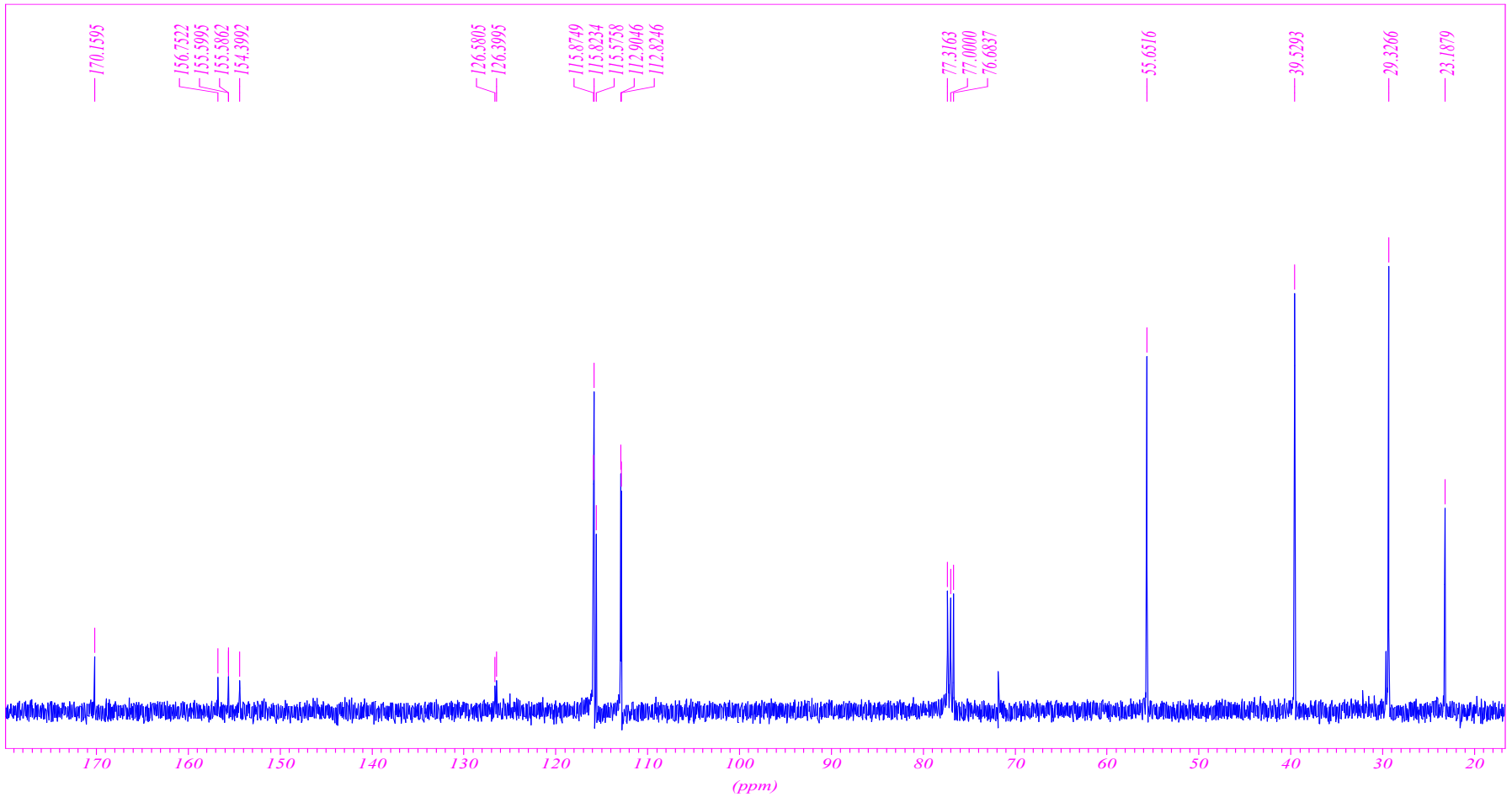
18. **^{13}C NMR ($CDCl_3$) of *N*-(4-Fluoro-3-methoxyphenylmethyl)butanamide (3c)**



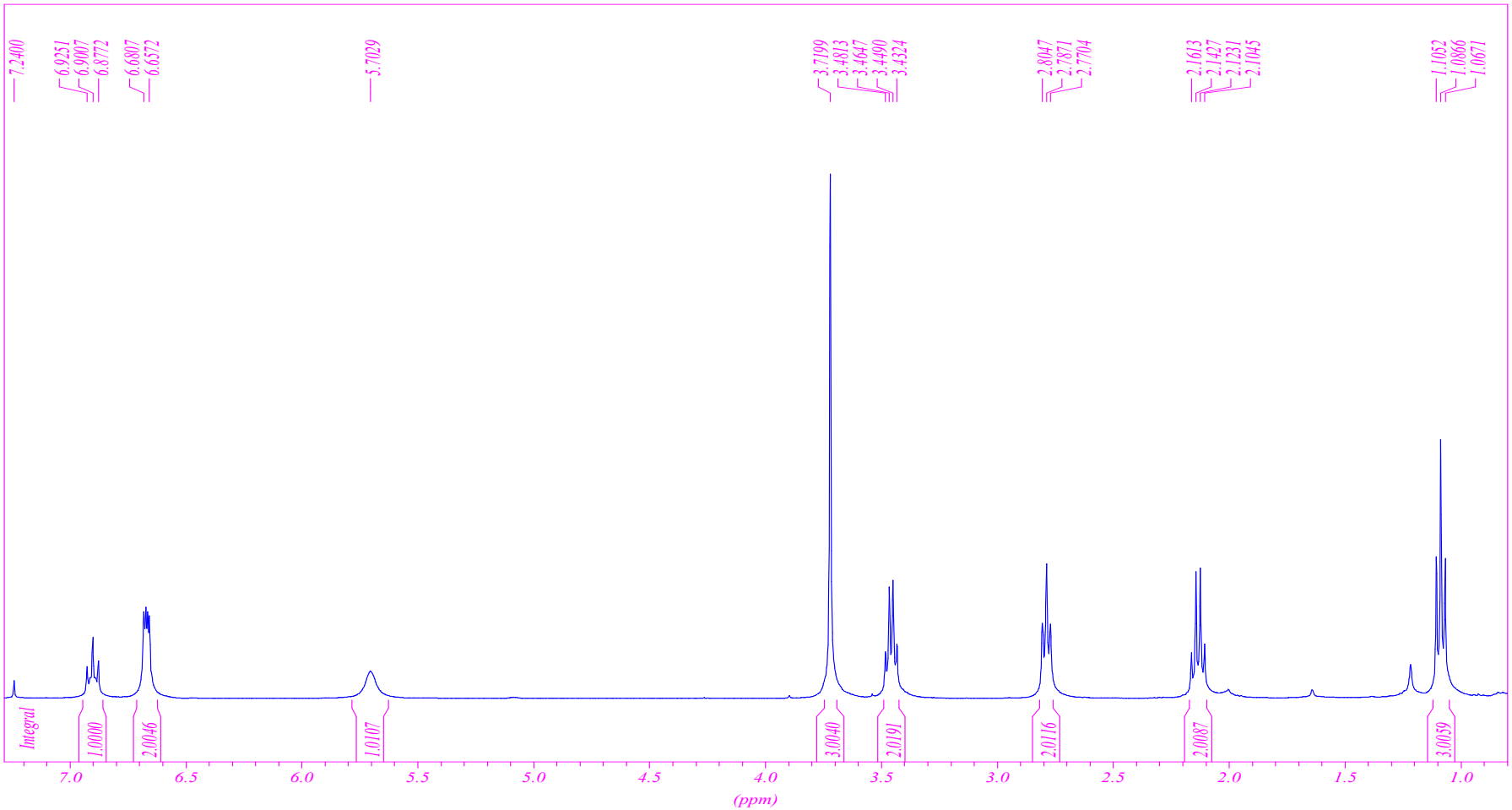
19. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]acetamide (4a)**



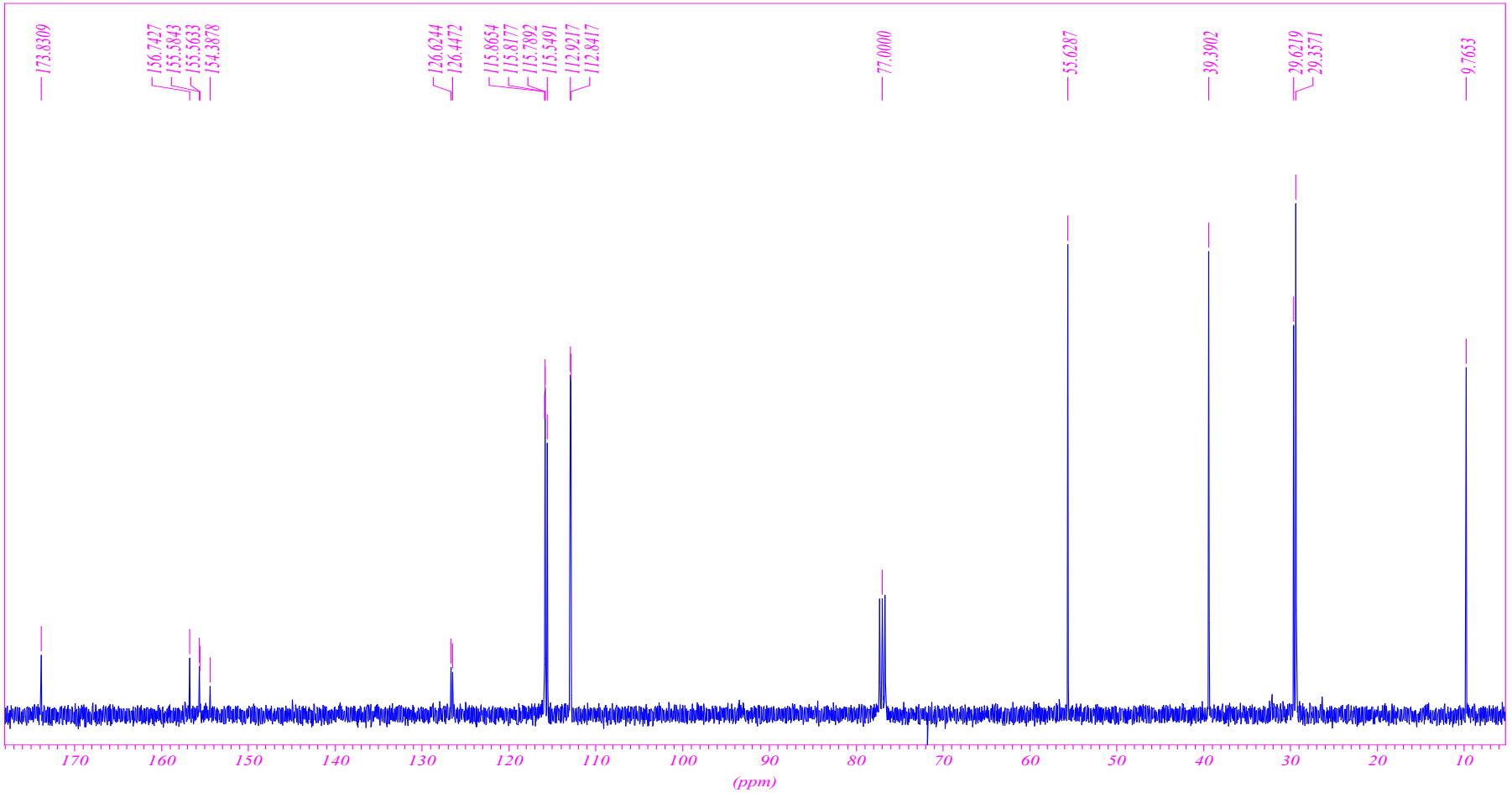
20. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]acetamide (4a)**



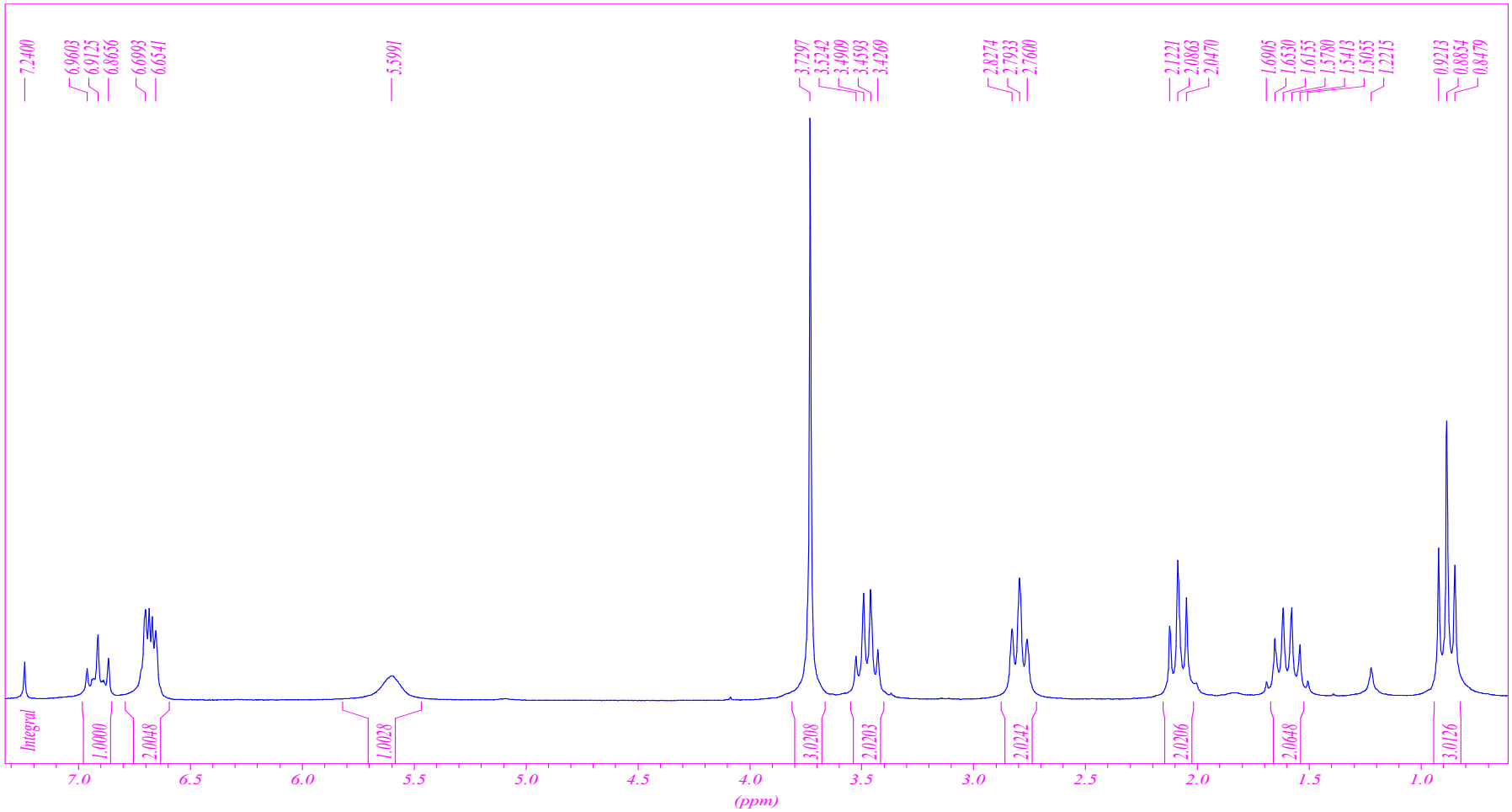
21. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]propanamide (4b)**



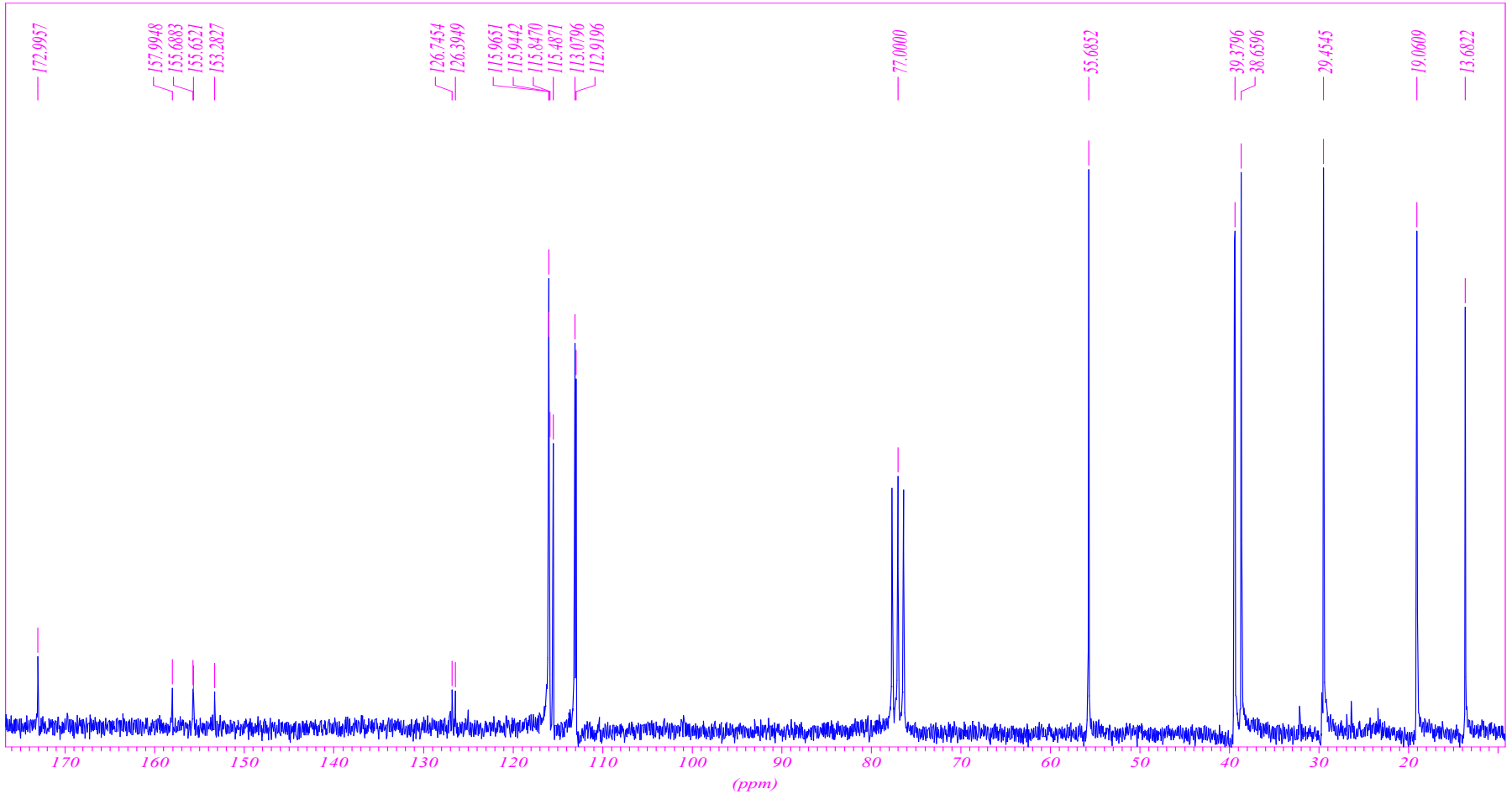
22. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]propanamide (4b)**



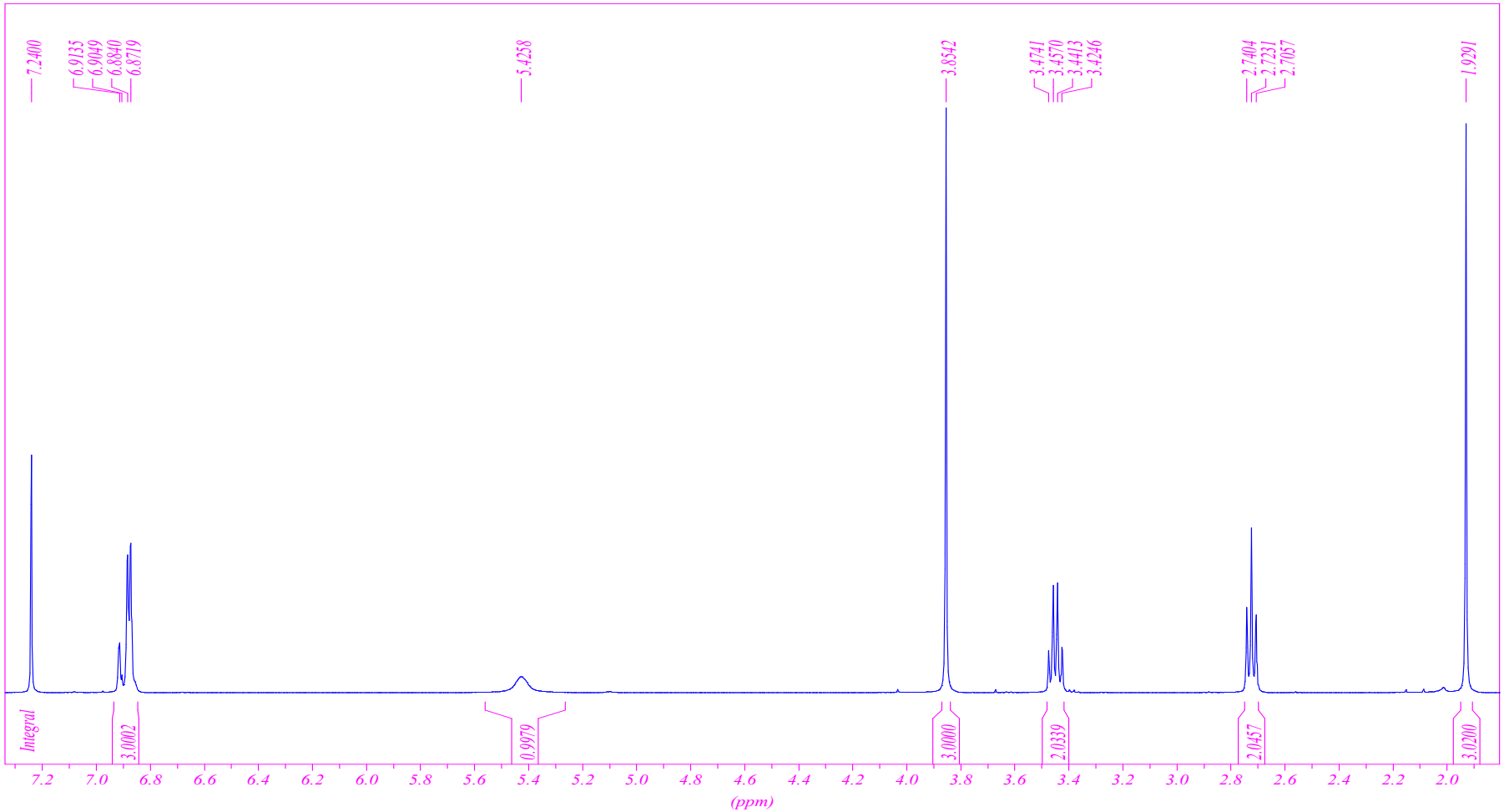
23. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]butanamide (4c)**



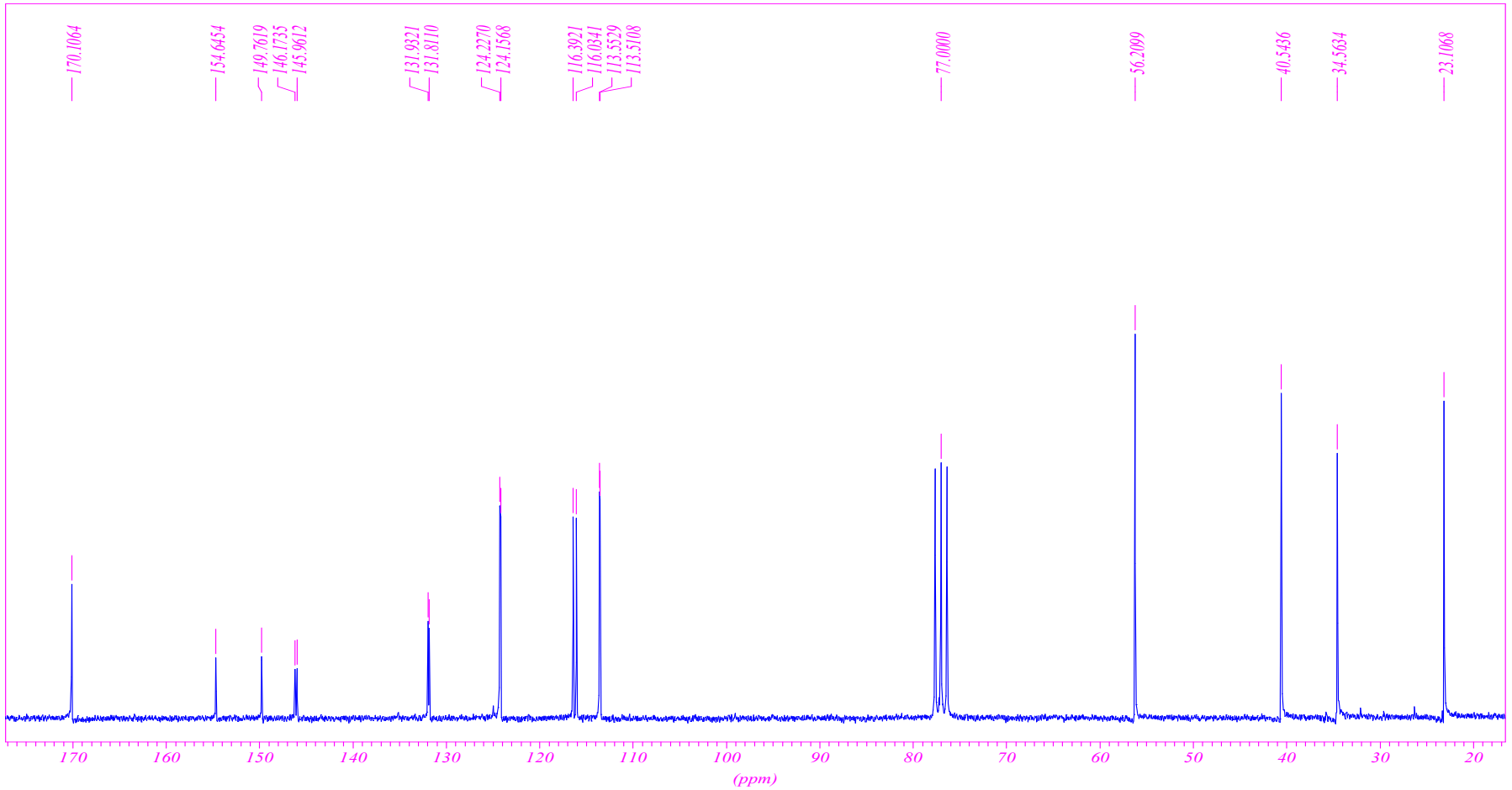
24. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)ethyl]butanamide (4c)**



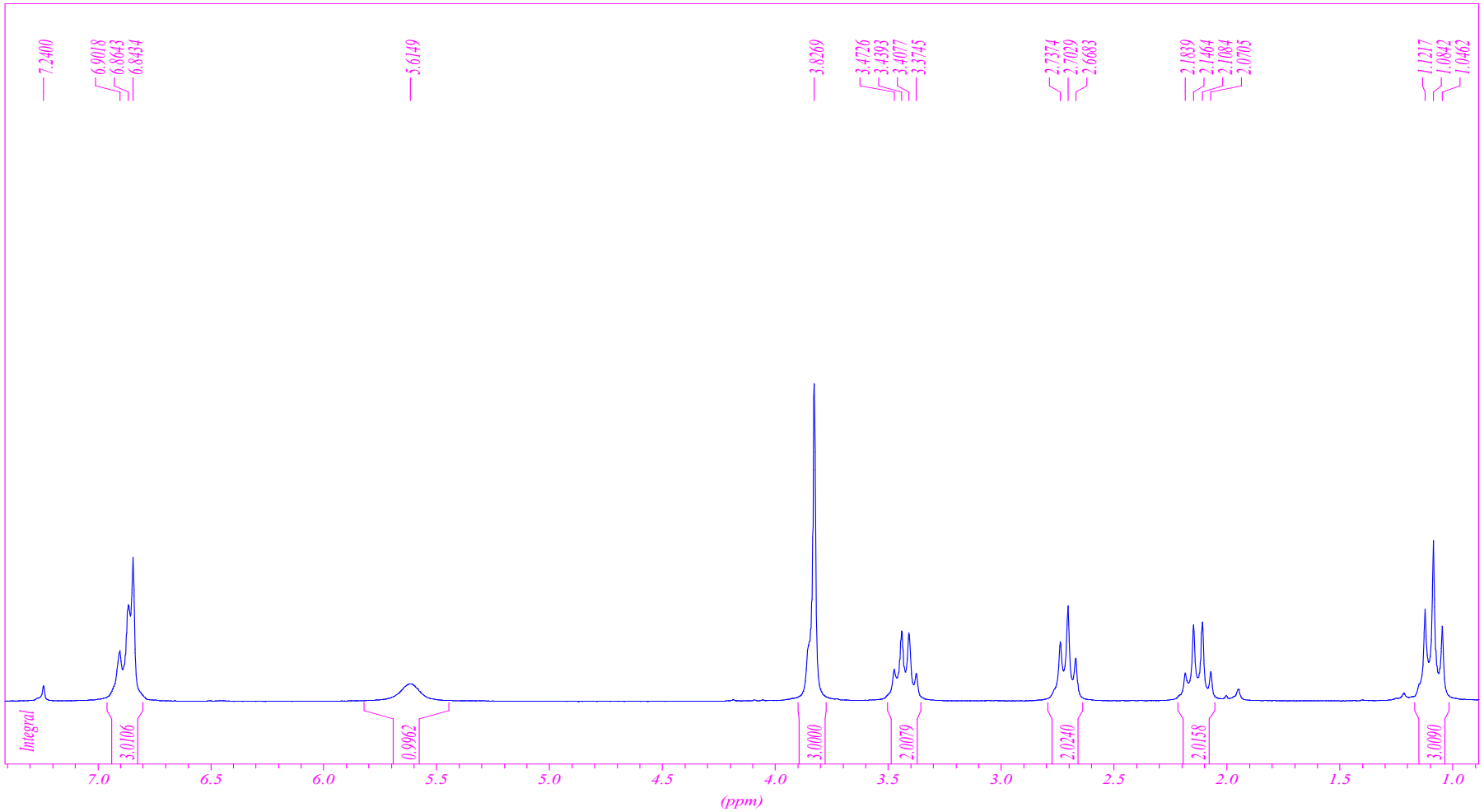
25. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]acetamide (5a)**



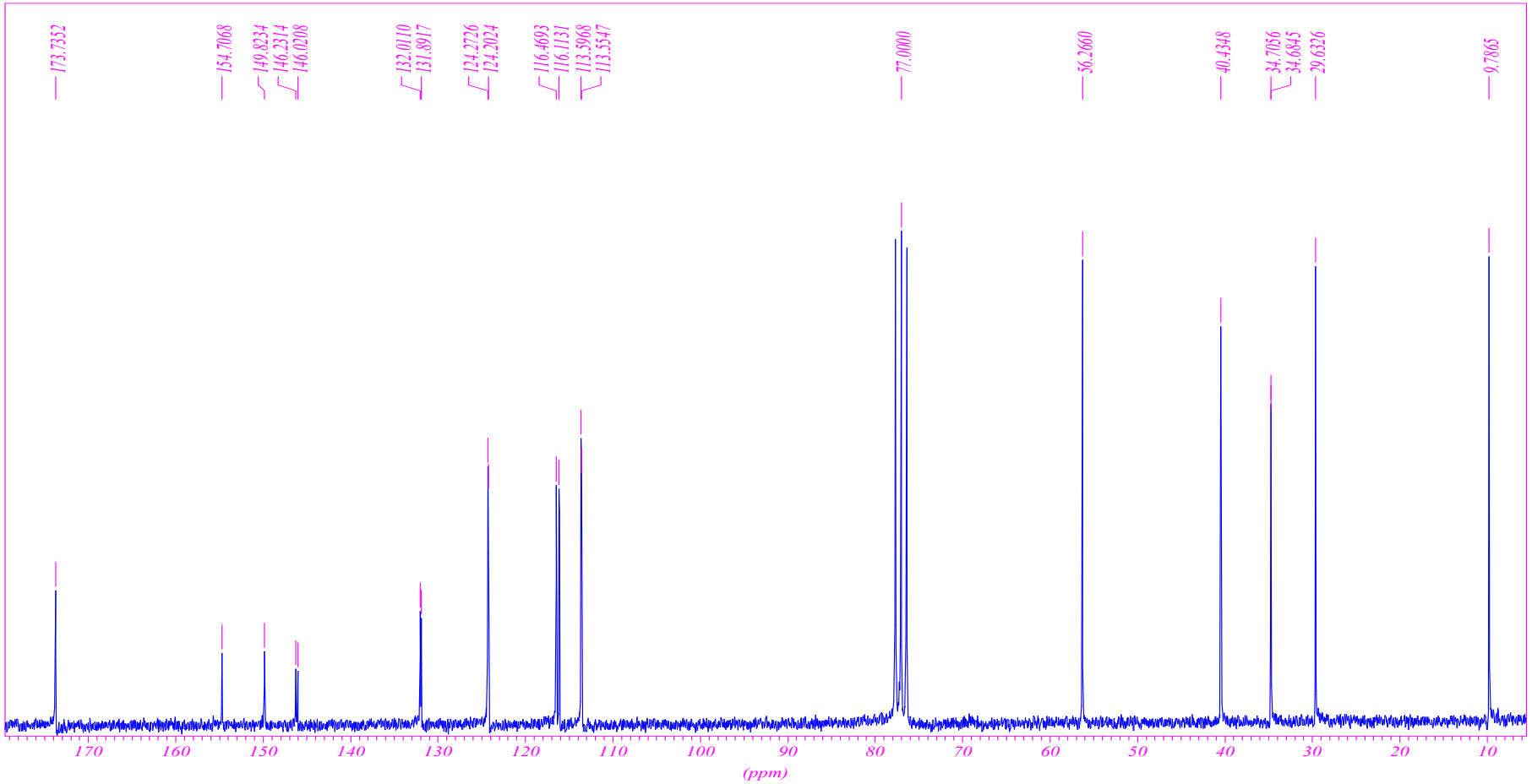
26. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]acetamide (5a)**



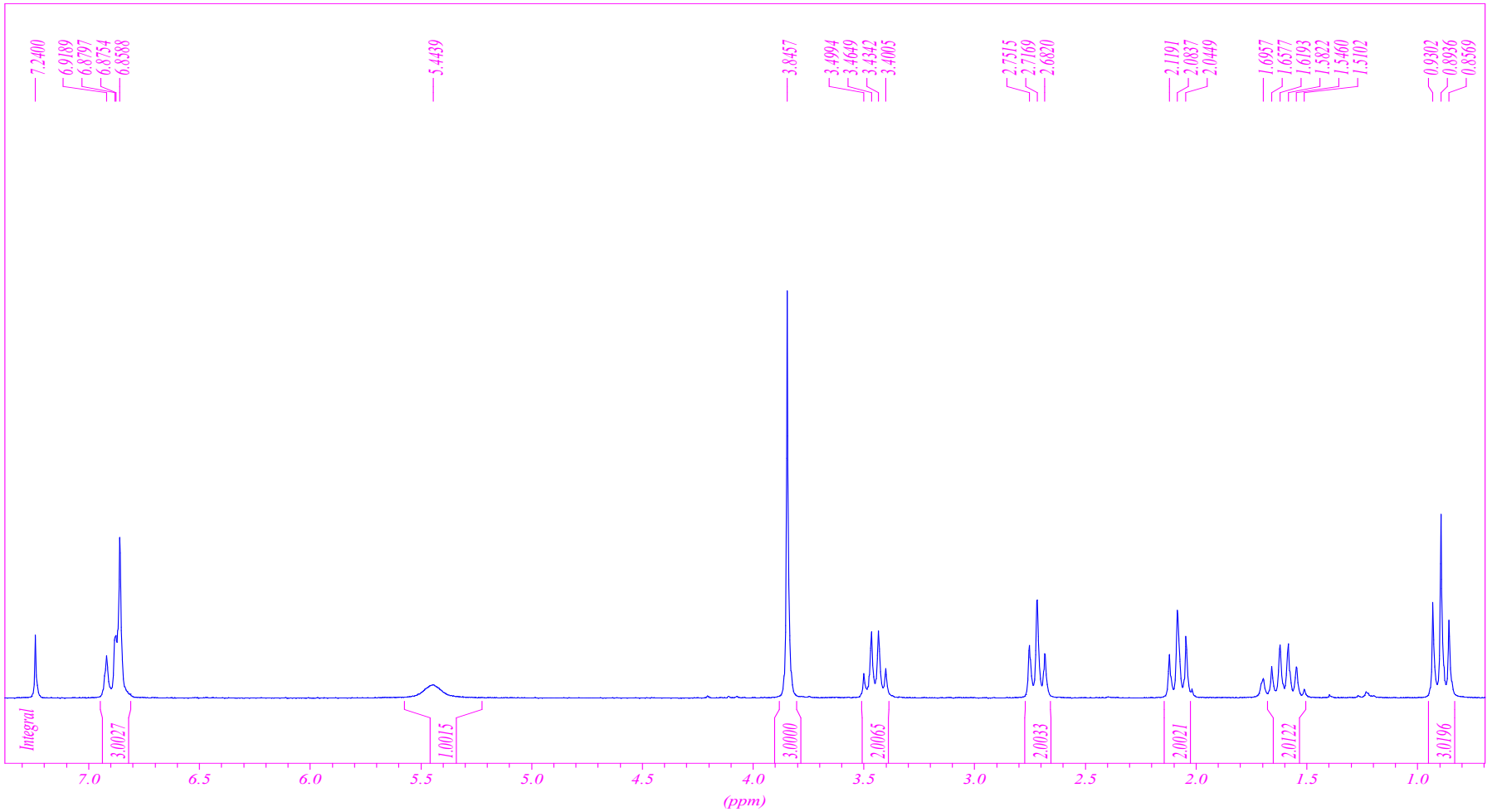
27. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]propanamide (5b)**



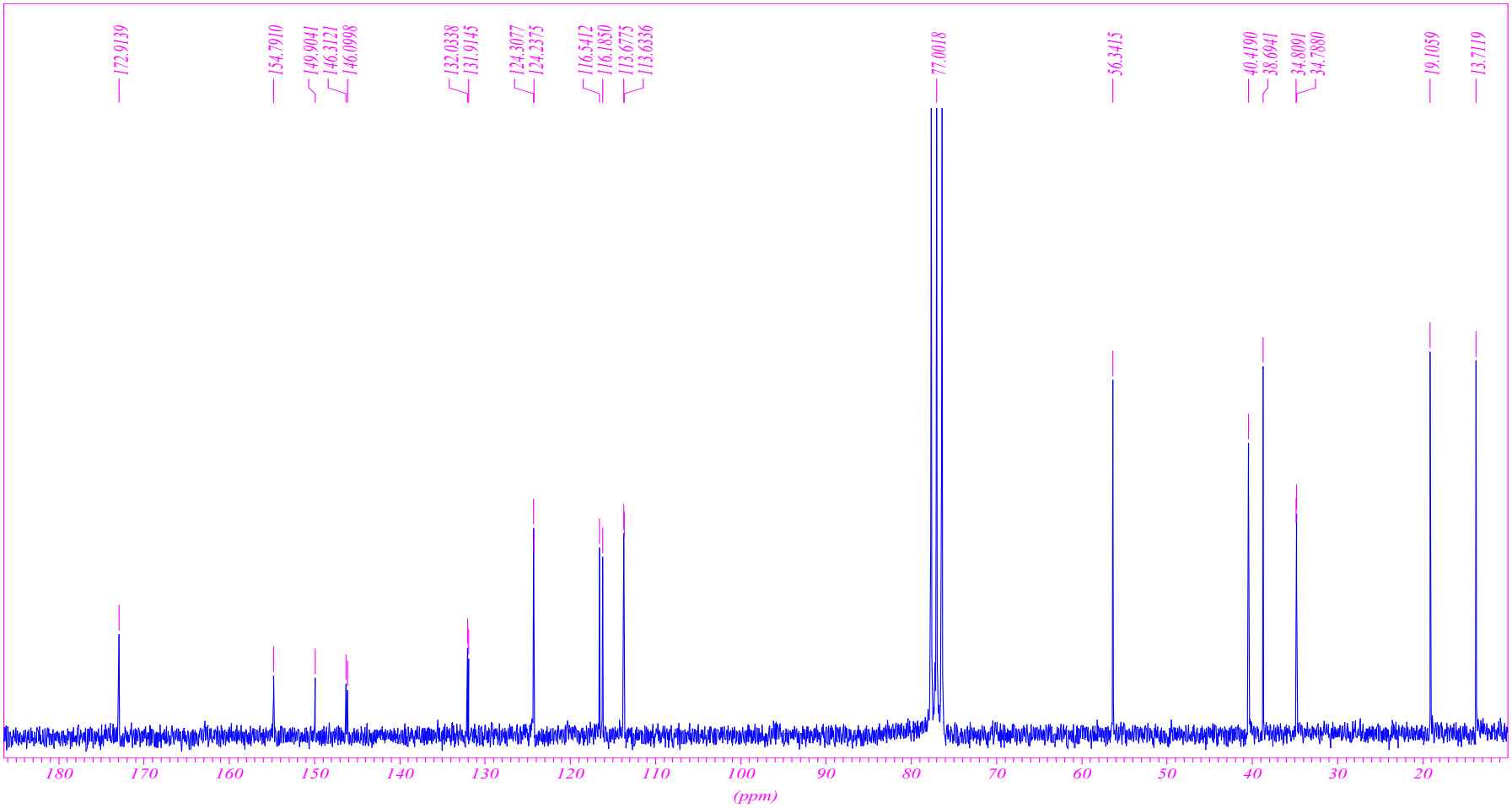
28. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]propanamide (5b)**



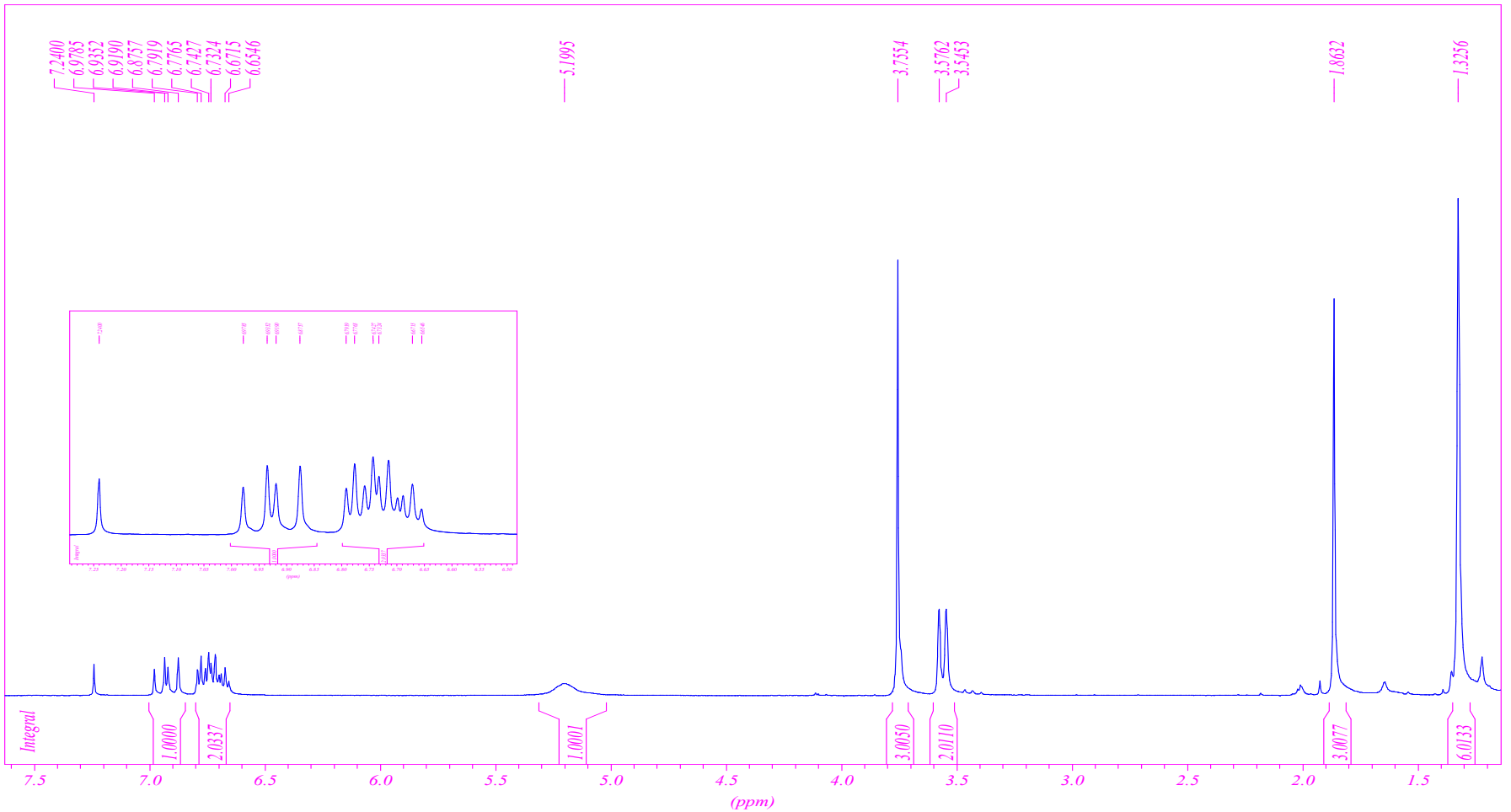
29. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]butanamide (5c)**



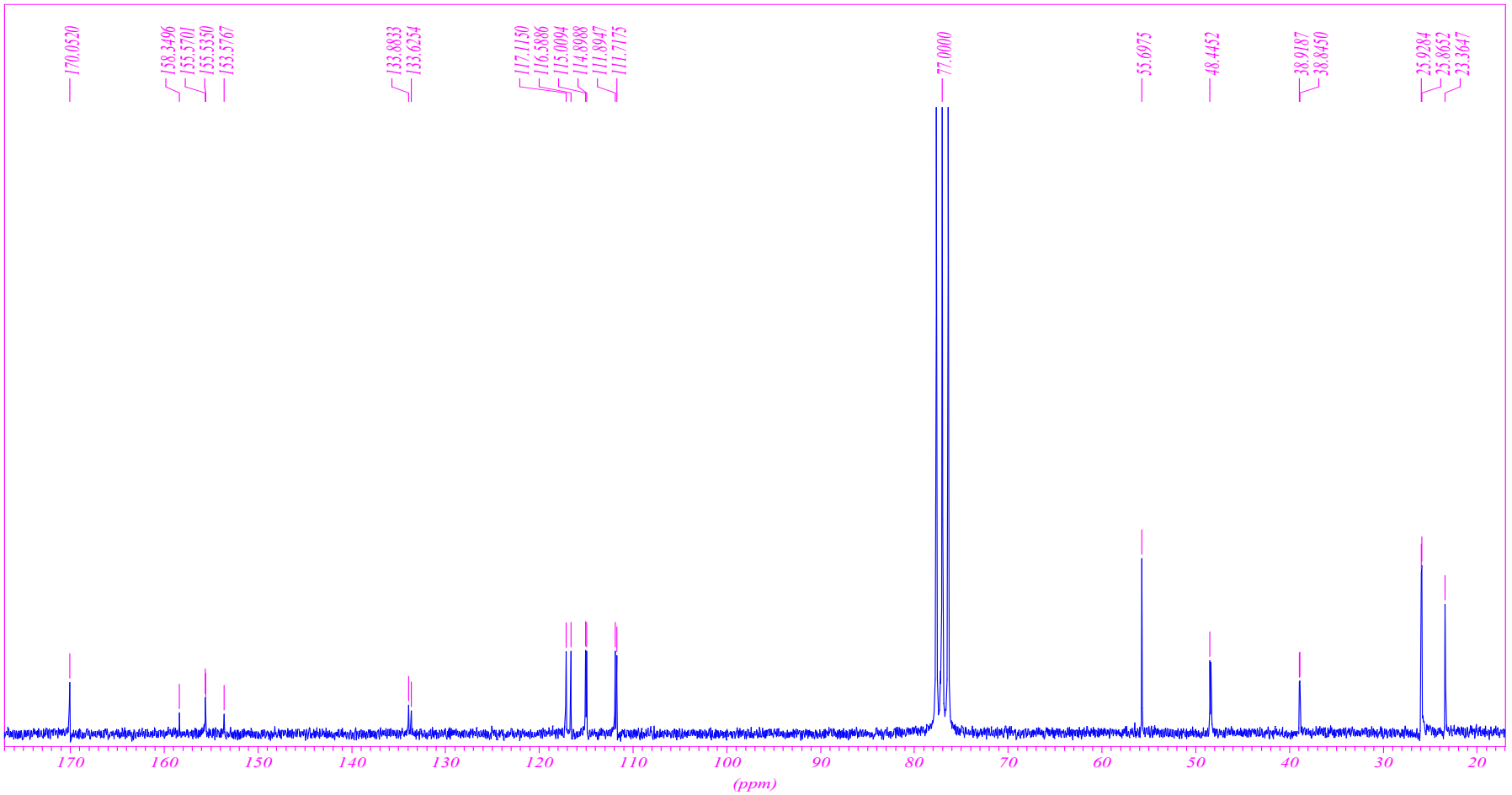
30. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)ethyl]butanamide (5c)**



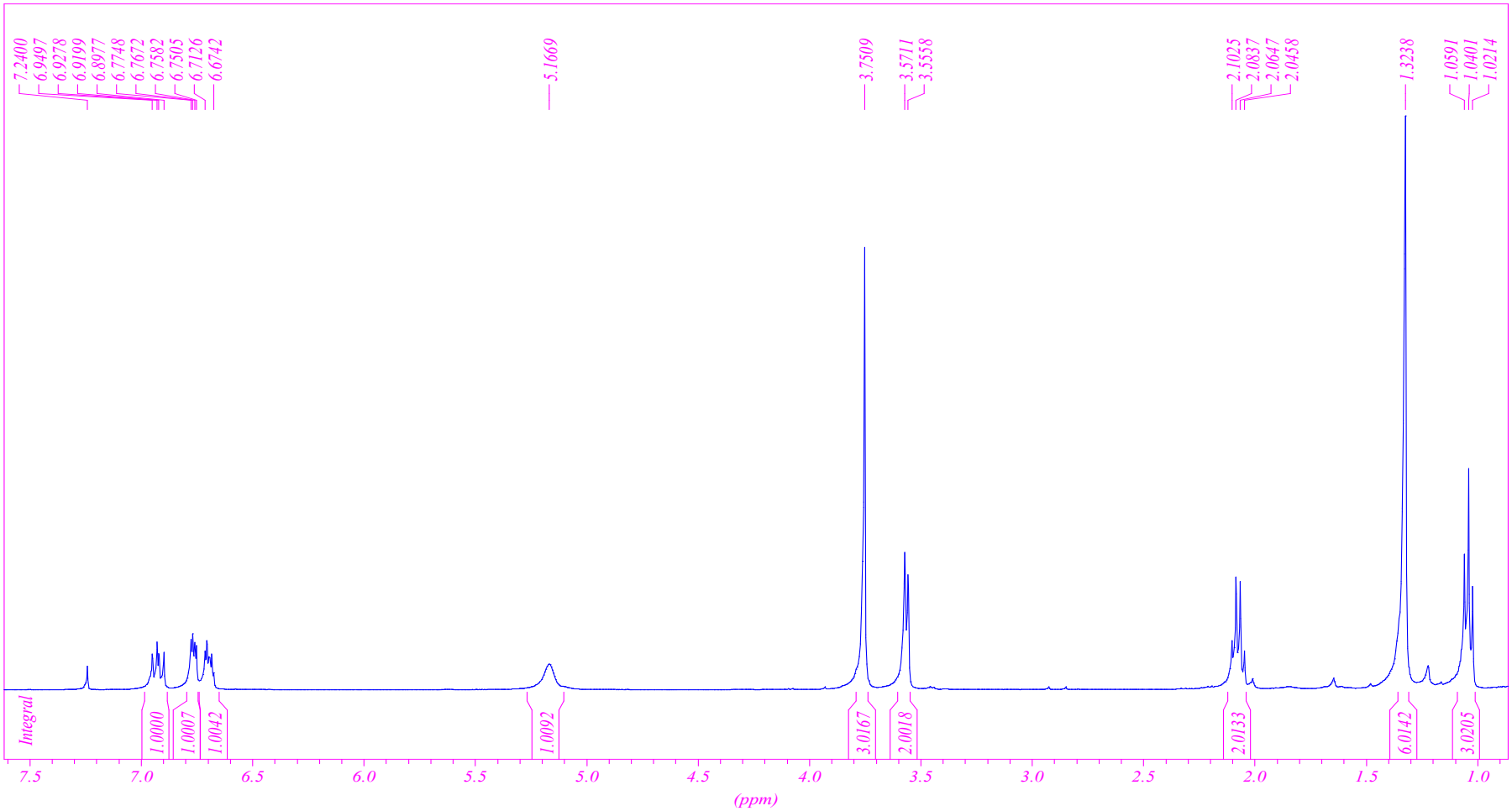
31. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]acetamide (6a)**


7.2400
6.9785
6.9352
6.9190
6.8757
6.7919
6.7765
6.7427
6.7324
6.6715
6.6546
5.1995
3.7554
3.5762
3.5453
1.8632
1.3256
Integral
1.0000
2.0337
1.0001
3.0050
2.0110
3.0077
6.0133
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

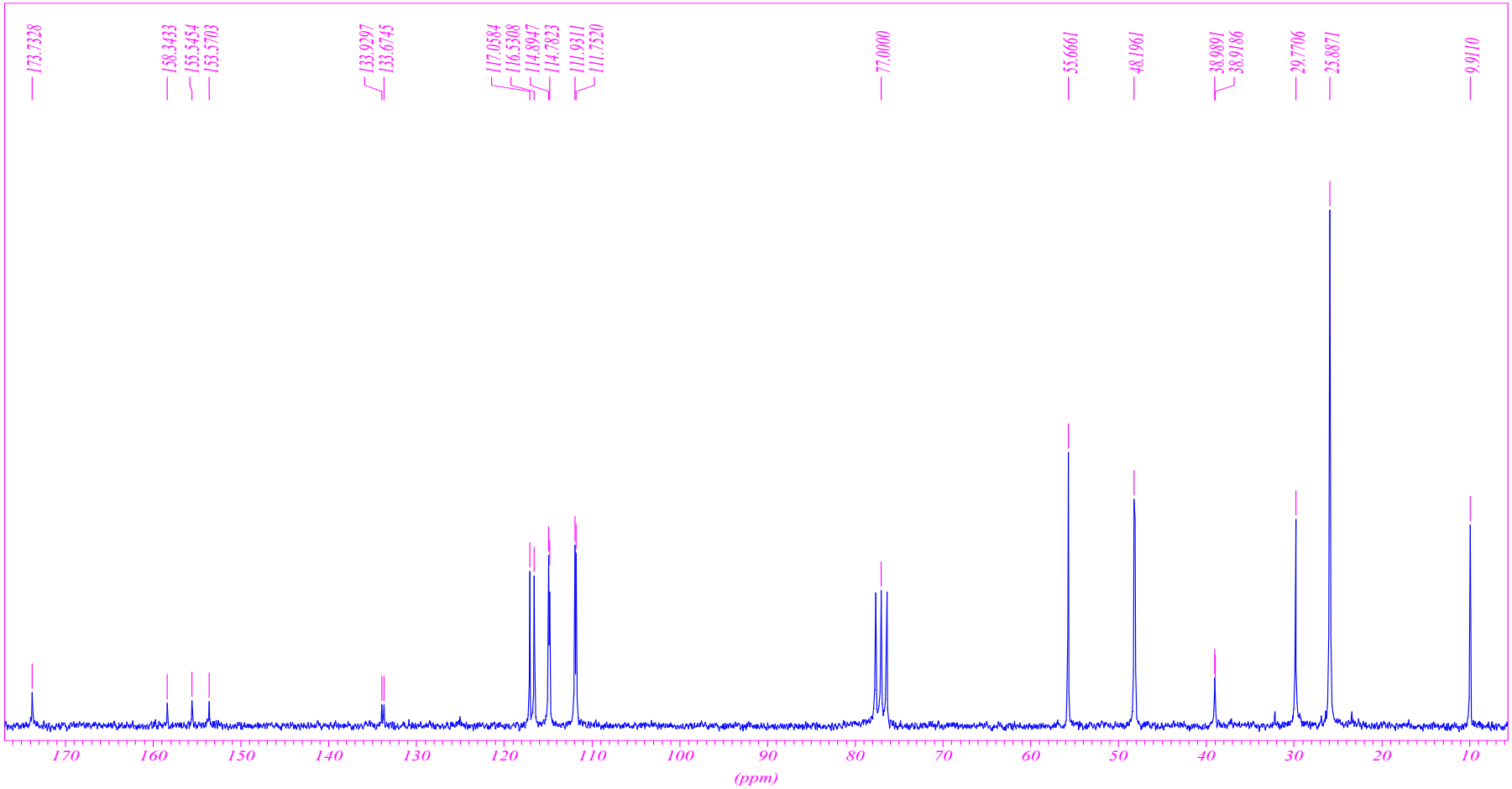
32. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]acetamide (6a)**



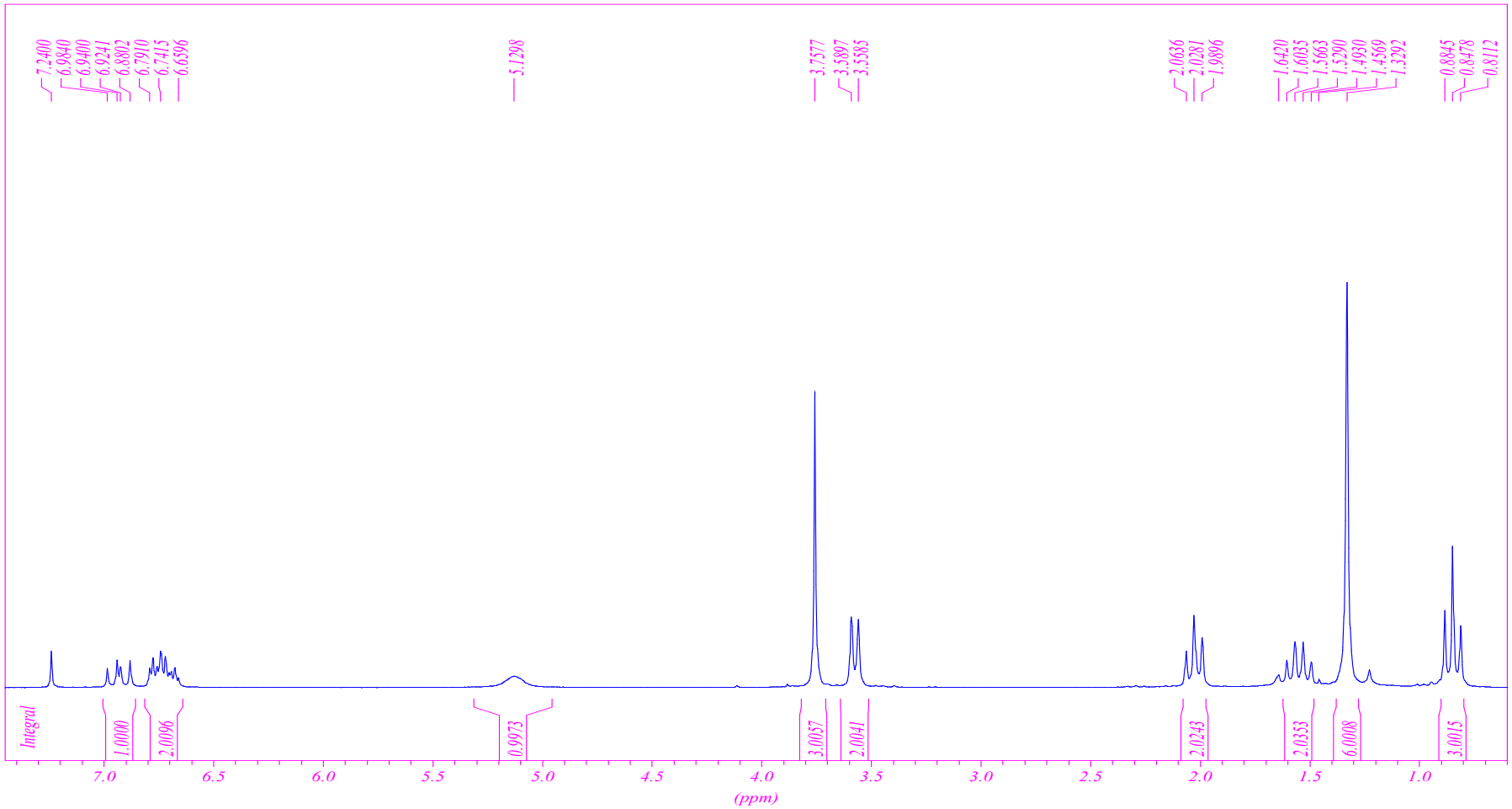
33. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]propanamide (6b)**



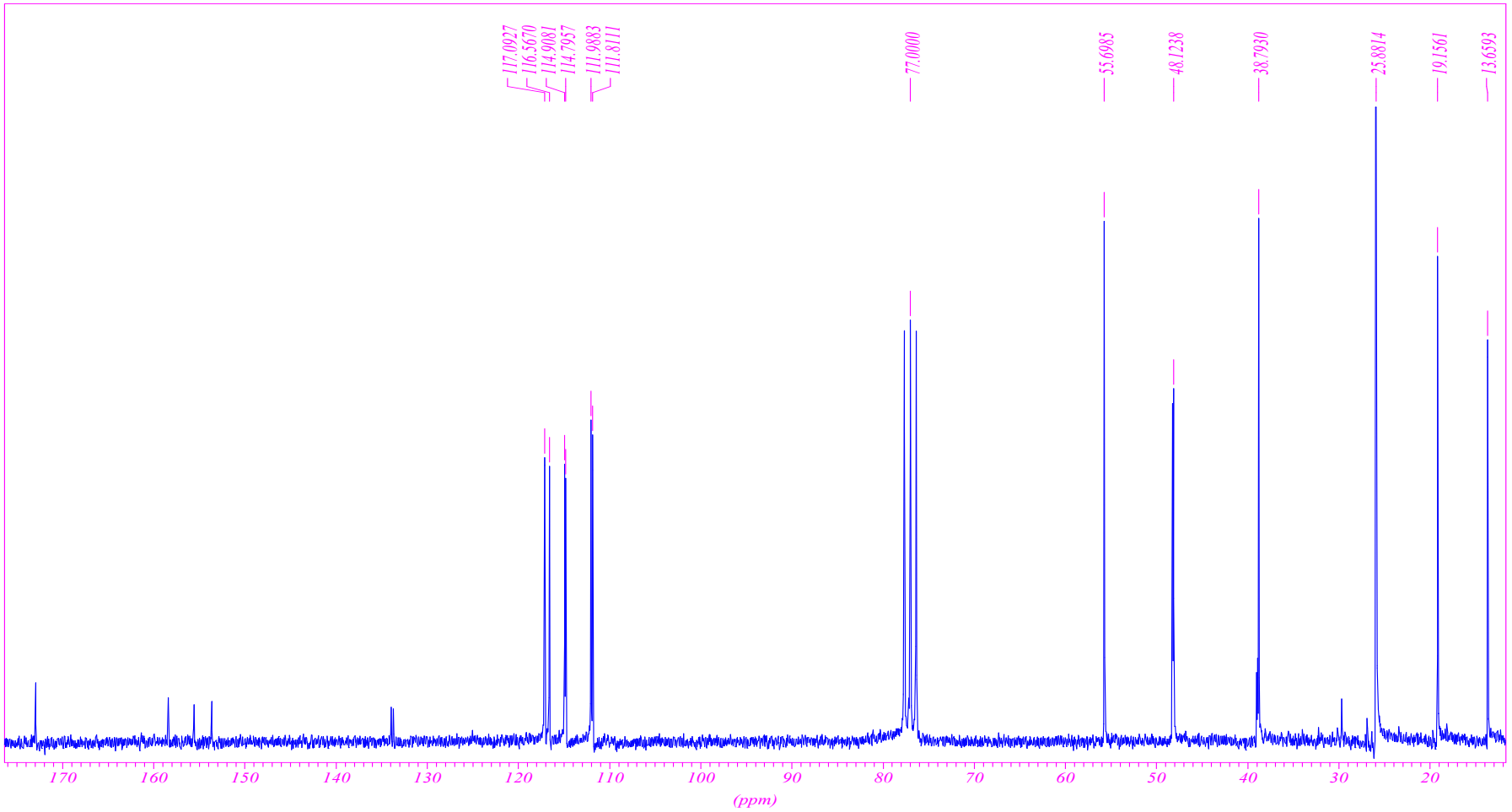
34. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]propanamide (6b)**



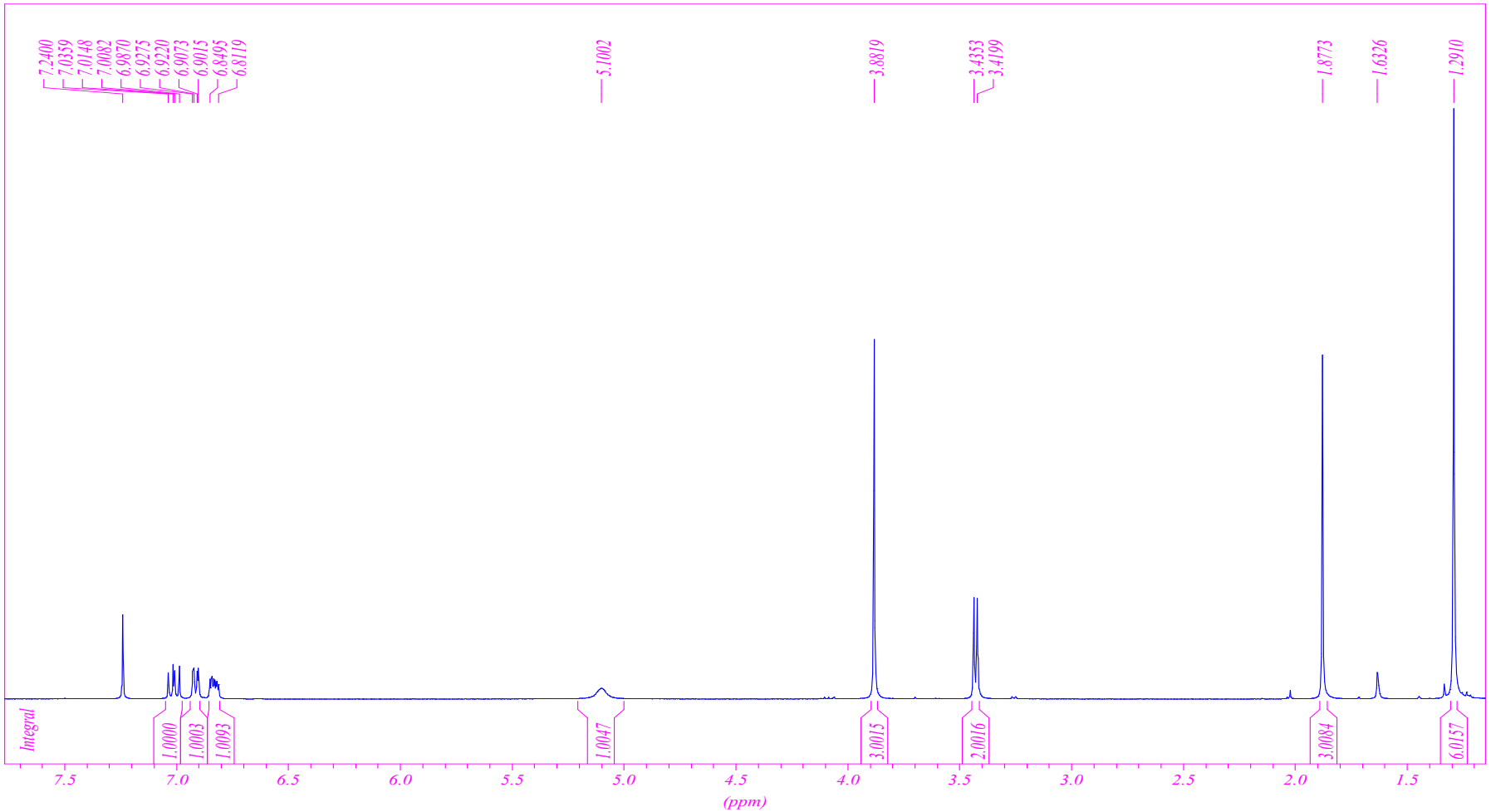
35. **^{1}H NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]butanamide (6c)**



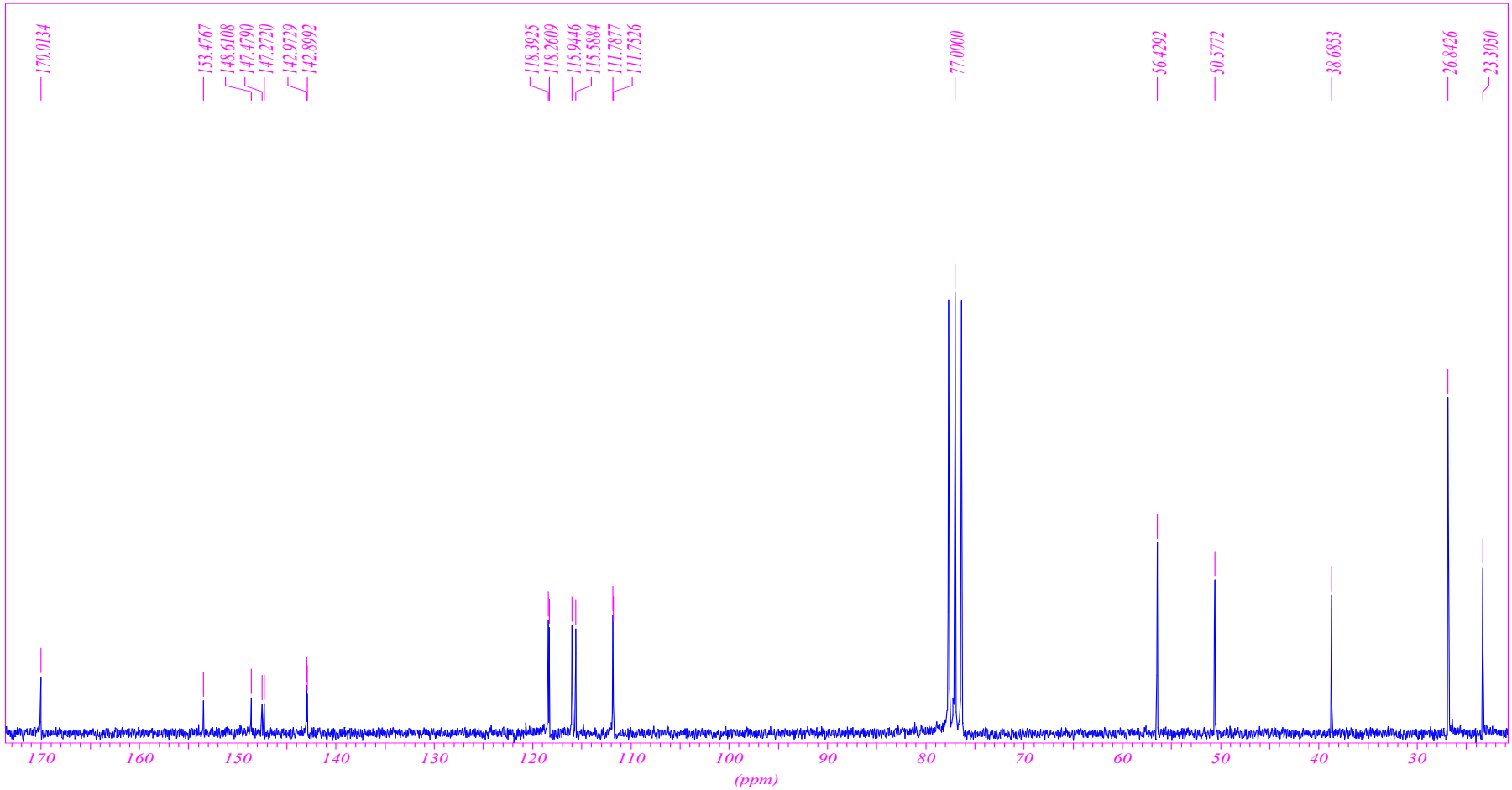
36. **^{13}C NMR ($CDCl_3$) of *N*-[2-(2-Fluoro-5-methoxyphenyl)-2-methylpropyl]butanamide (6c)**



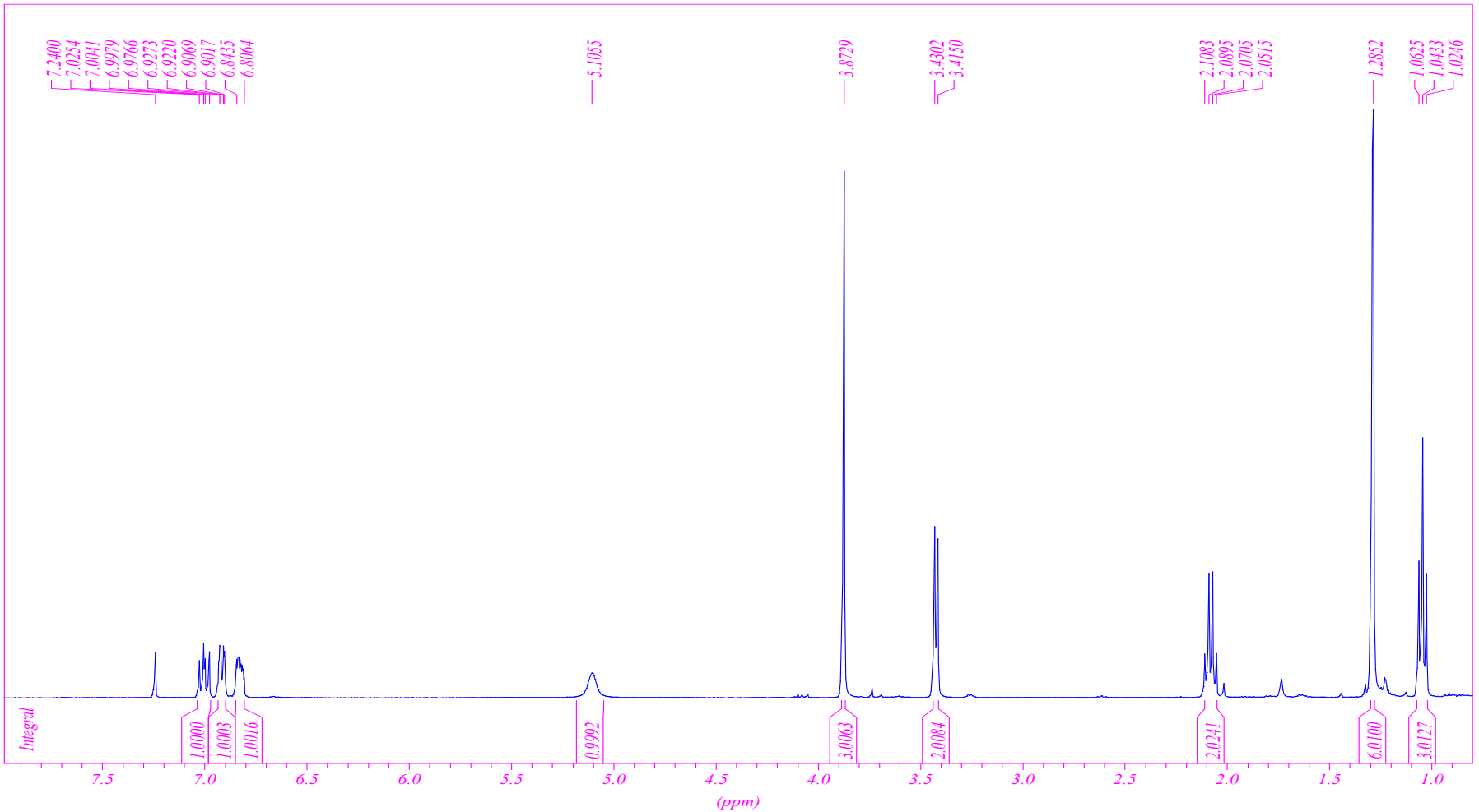
37. **^{1}H NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]acetamide (6d)**



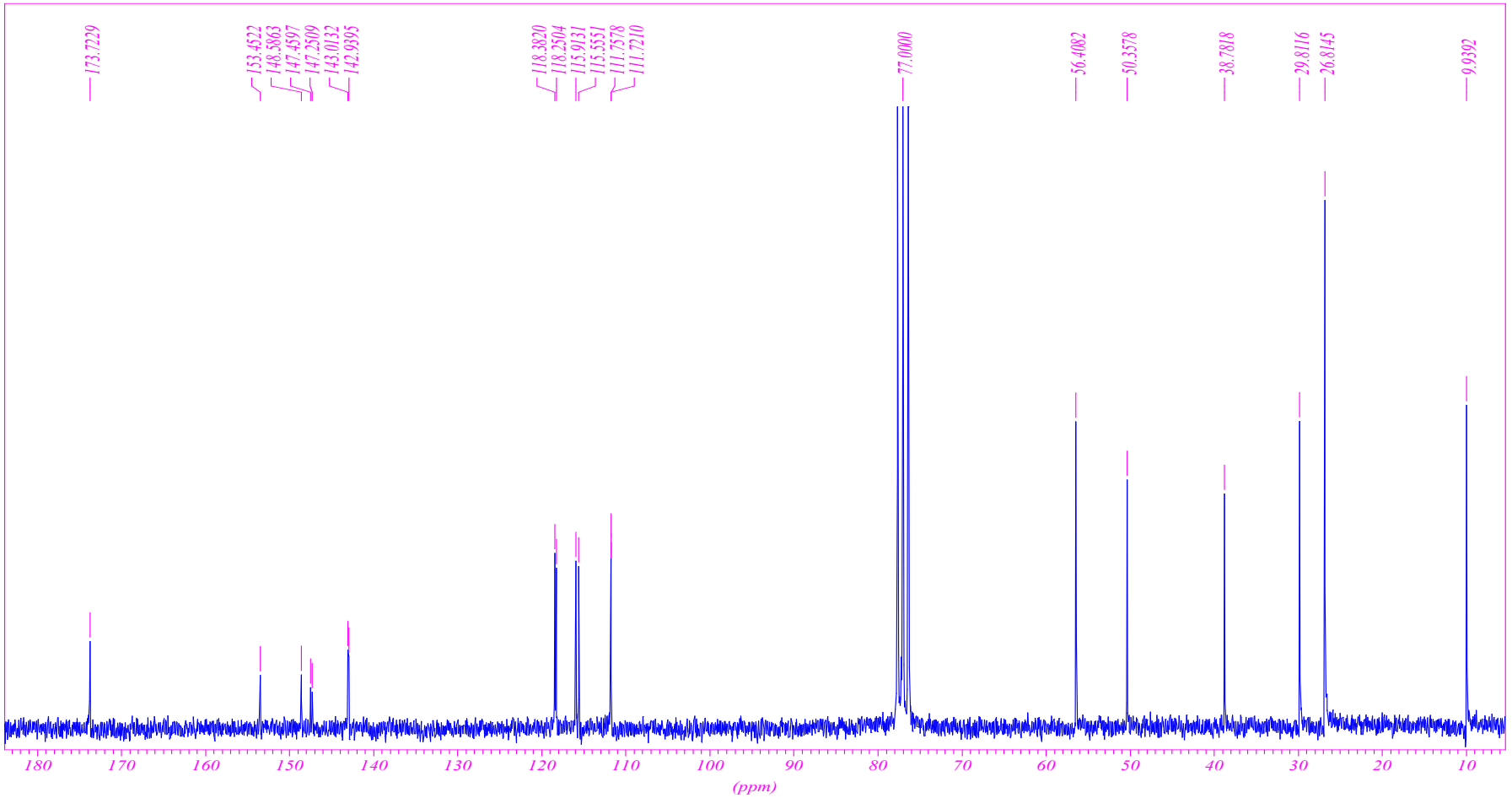
38. **^{13}C NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]acetamide (6d)**



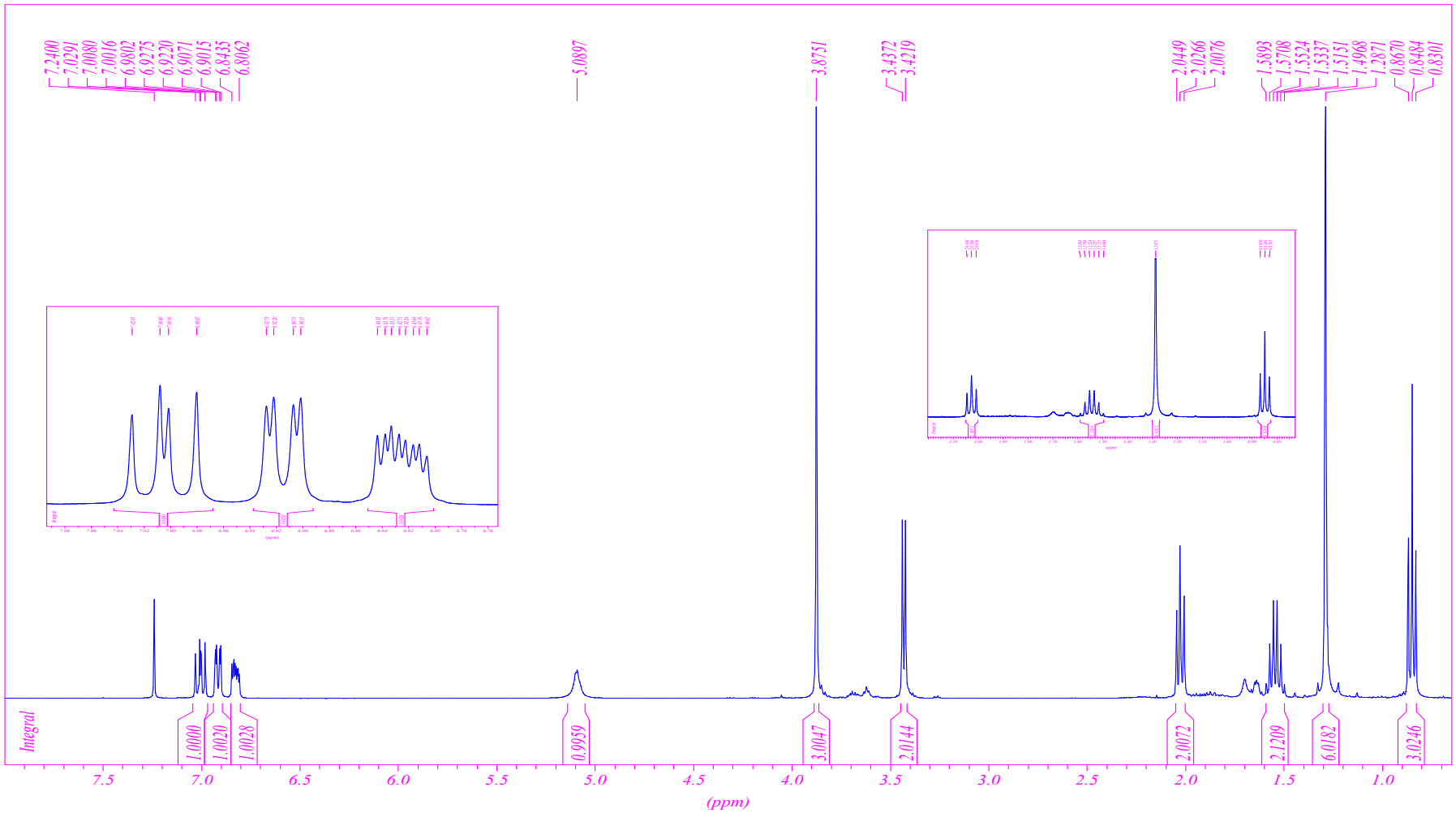
39. **^{1}H NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]propanamide (6e)**



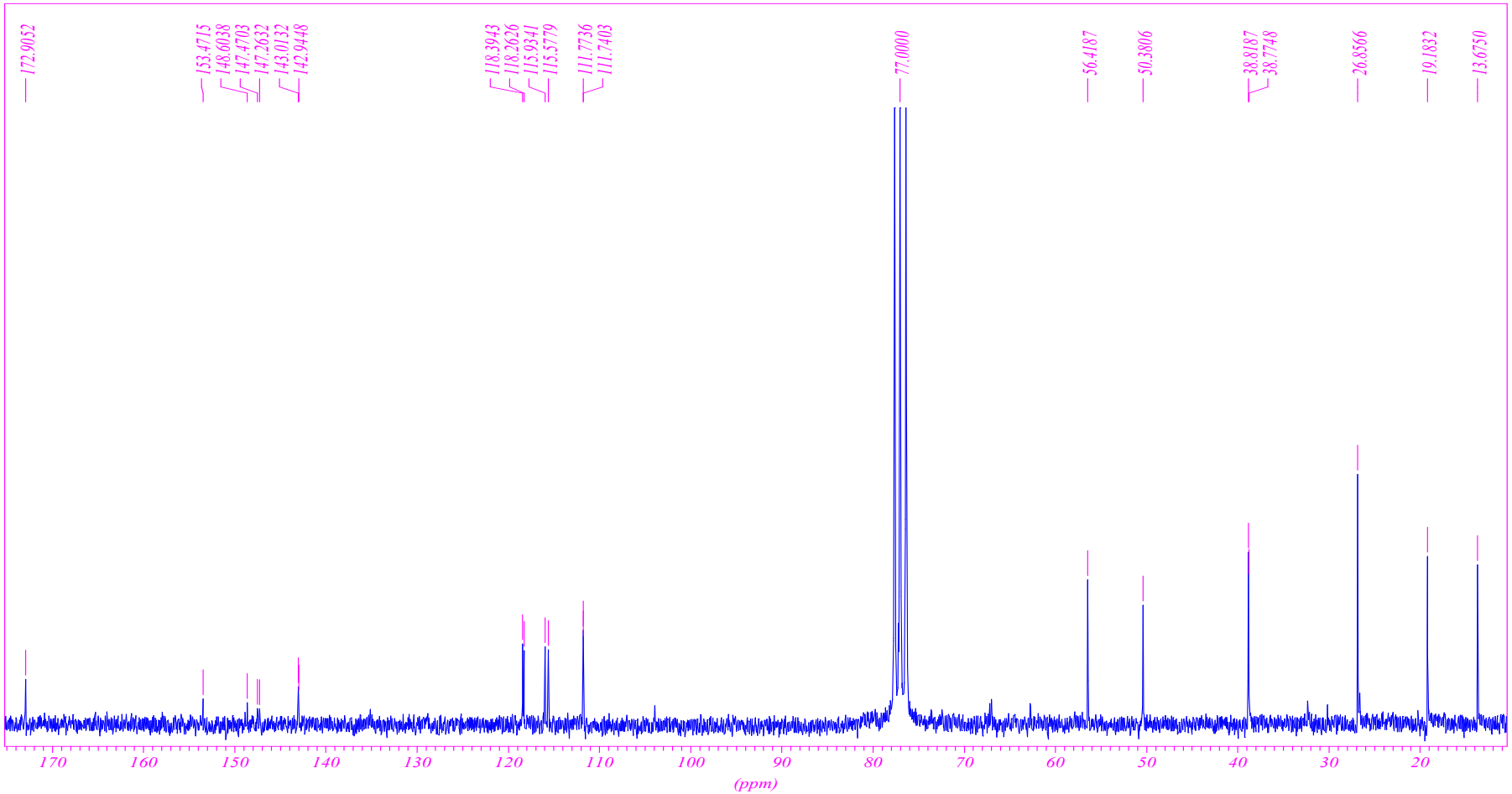
40. **^{13}C NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]propanamide (6e)**



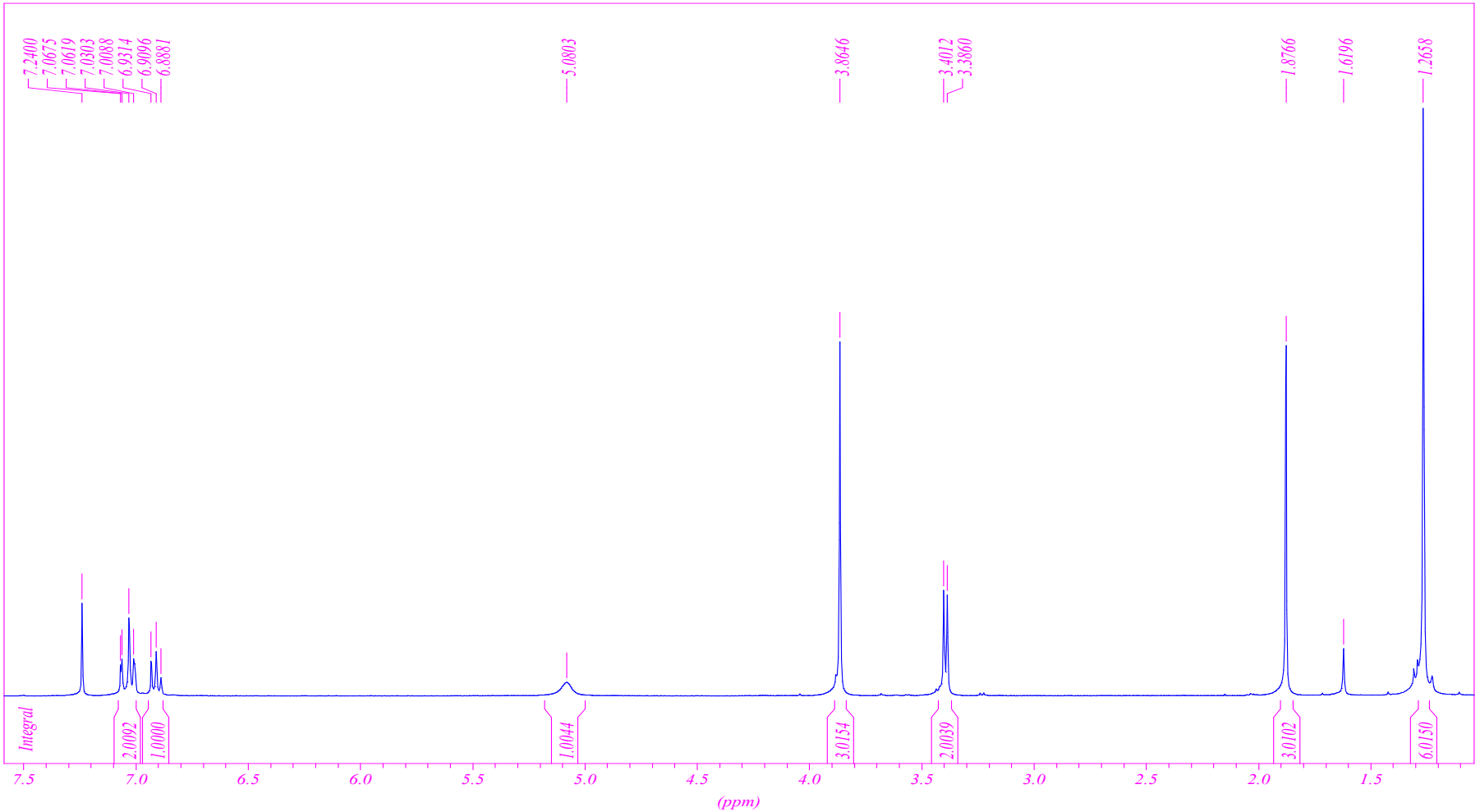
41. **^{1}H NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]butanamide (6f)**



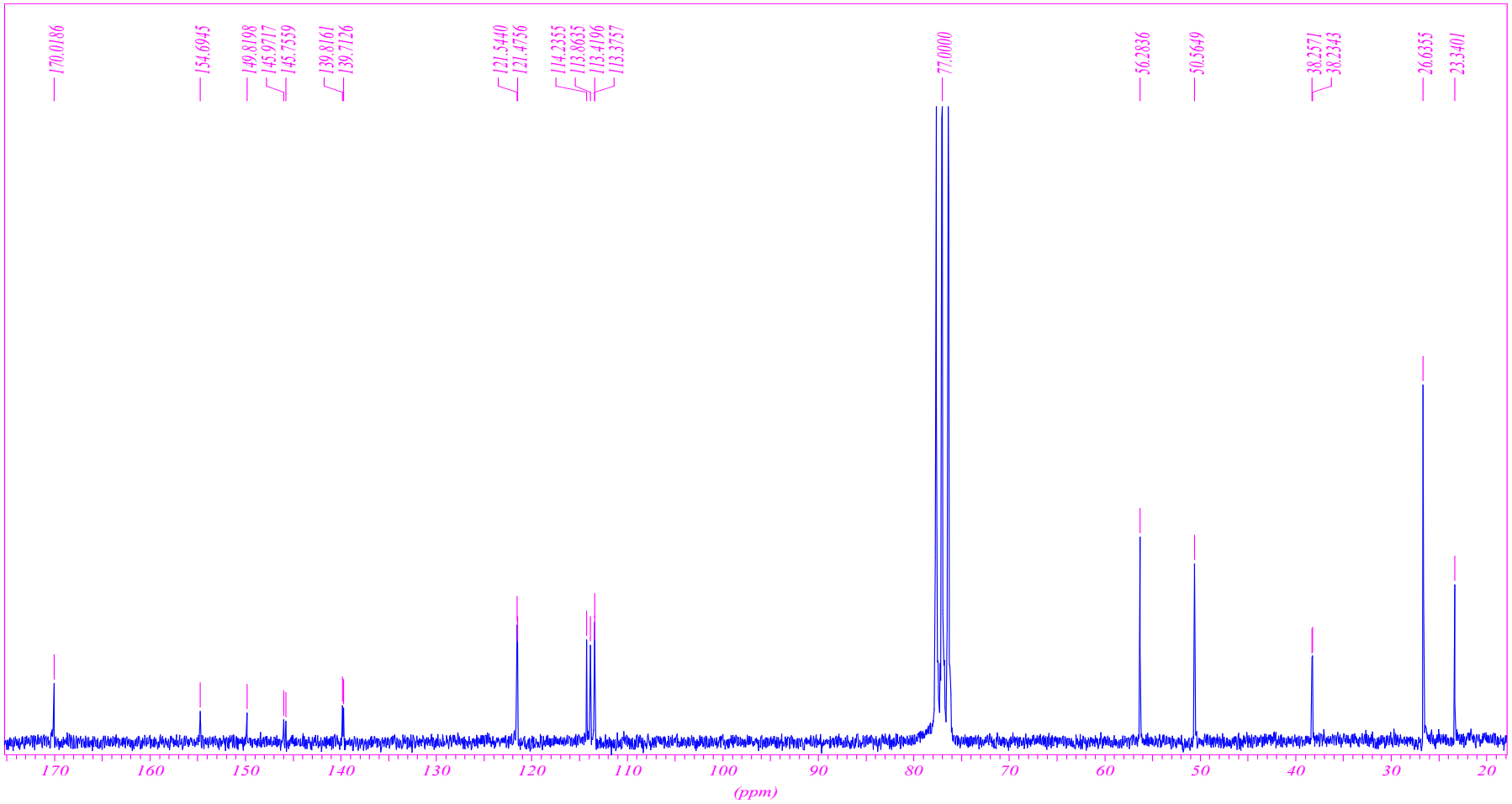
42. **^{13}C NMR ($CDCl_3$) of *N*-[2-[4-Fluoro-3-methoxyphenyl)-2-methylpropyl]butanamide (6f)**



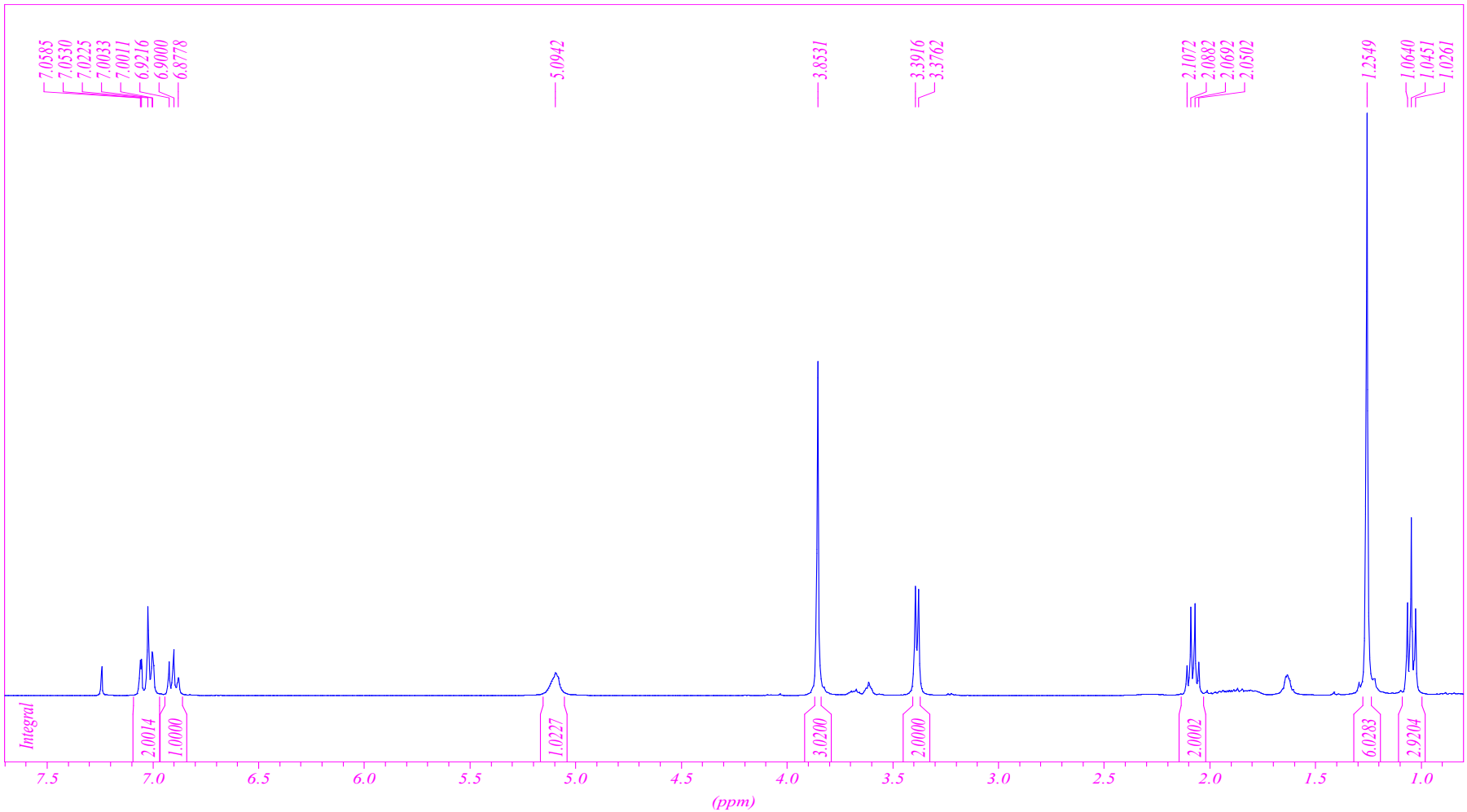
43. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]acetamide (7a)**



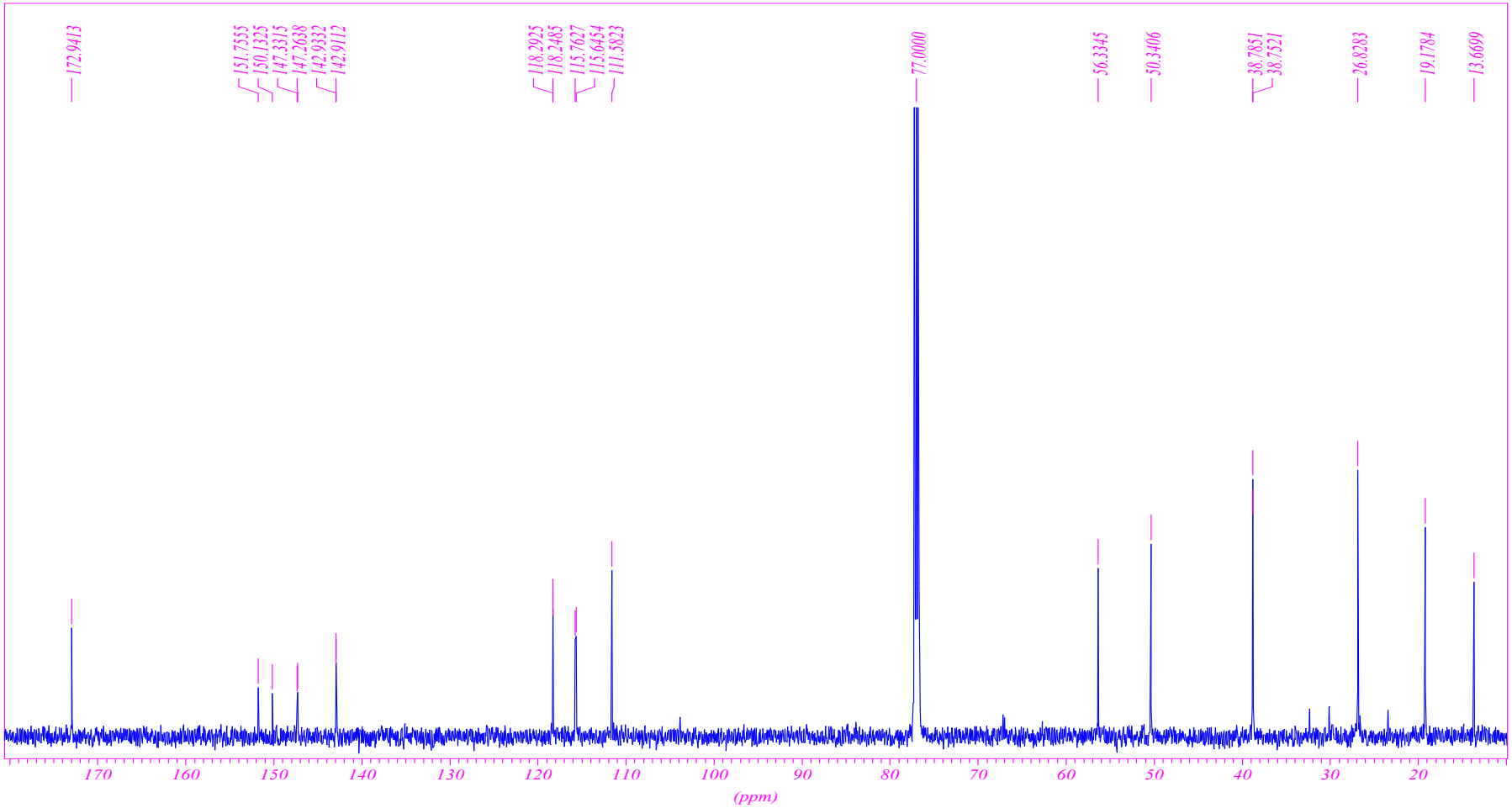
44. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]acetamide (7a)**



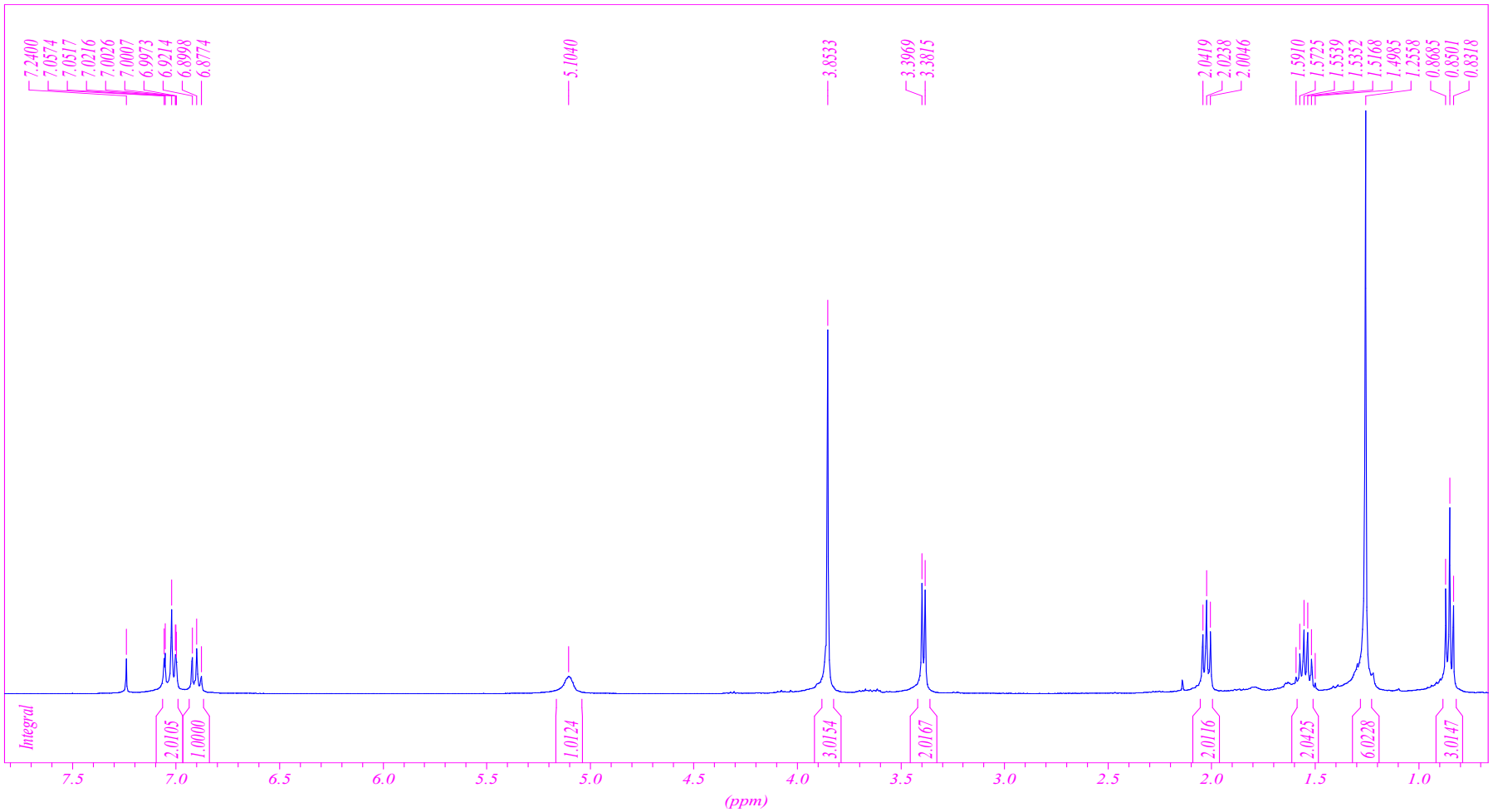
45. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]propanamide (7b)**


7.0585
7.0530
7.0225
7.0033
7.0011
6.9216
6.9000
6.8778
5.0942
3.8531
3.3916
3.3762
2.1072
2.0882
2.0692
2.0502
1.2549
1.0640
1.0451
1.0261
Integral
2.0014
1.0000
1.0227
3.0200
2.0000
2.0002
6.0283
2.9204
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

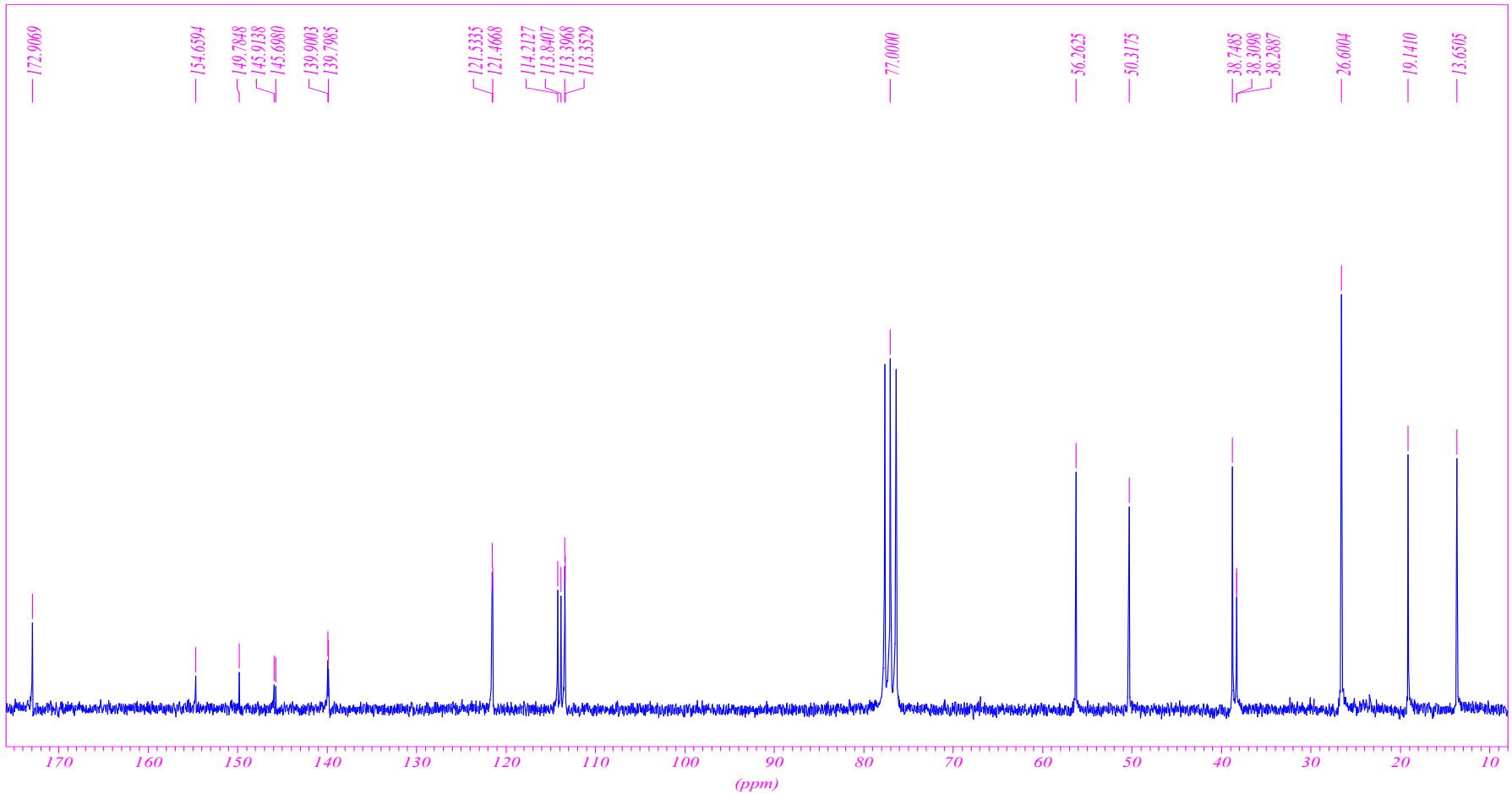
46. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]propanamide (7b)**



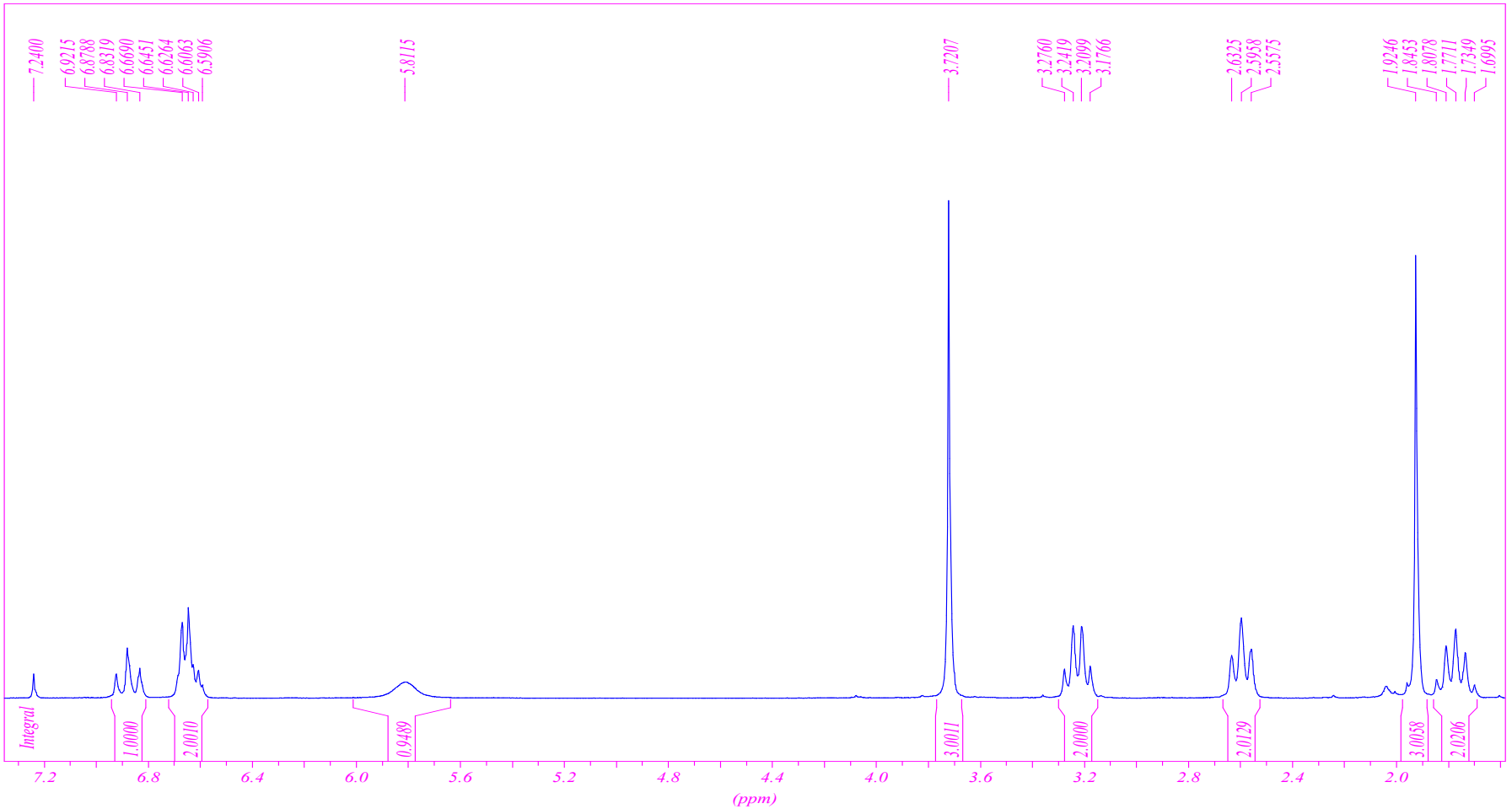
47. **^{1}H NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]butanamide (7c)**



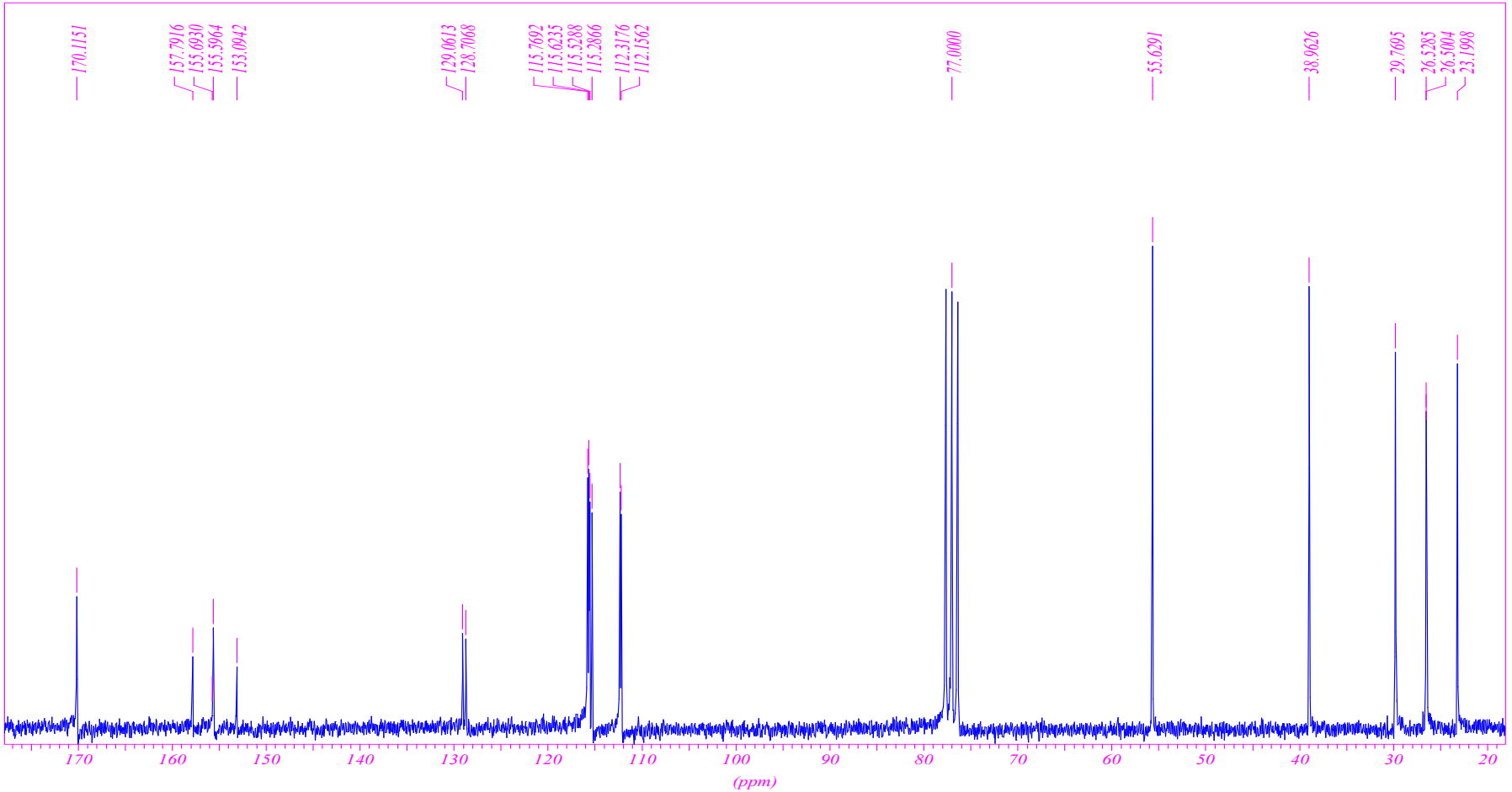
48. **^{13}C NMR ($CDCl_3$) of *N*-[2-(3-Fluoro-4-methoxyphenyl)-2-methylpropyl]butanamide (7c)**



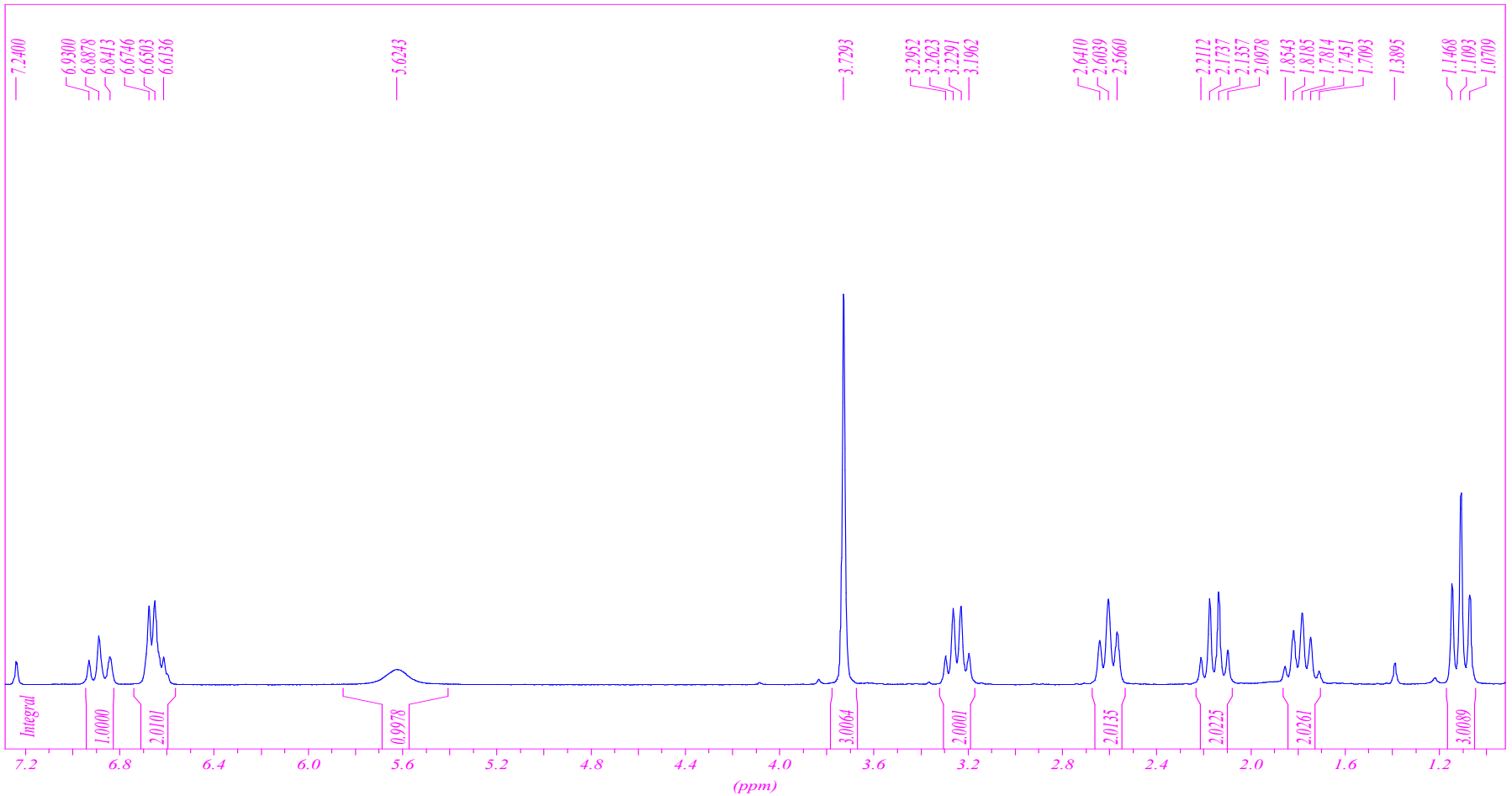
49. **^{1}H NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]acetamide (8a)**



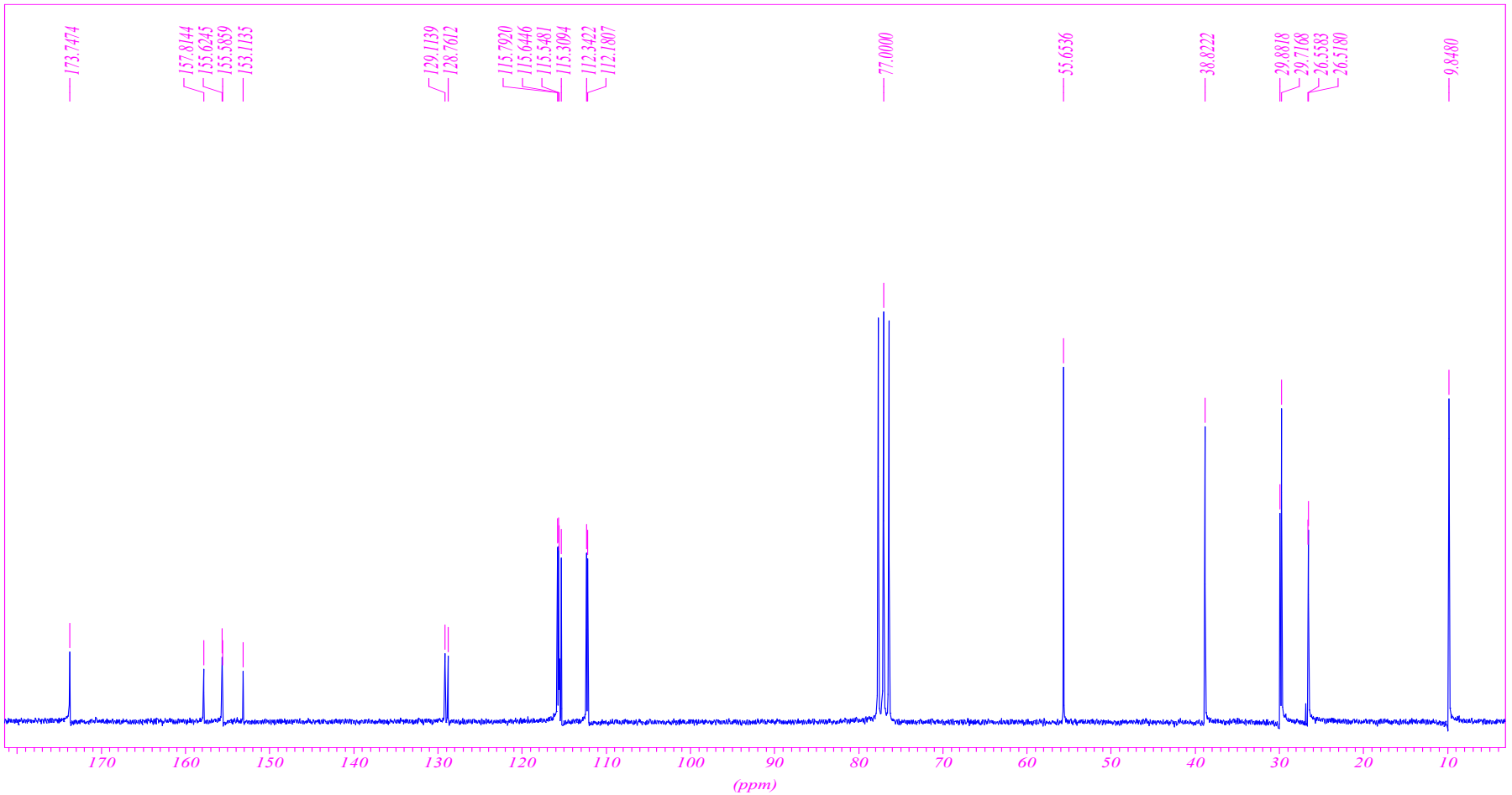
50. **^{13}C NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]acetamide (8a)**



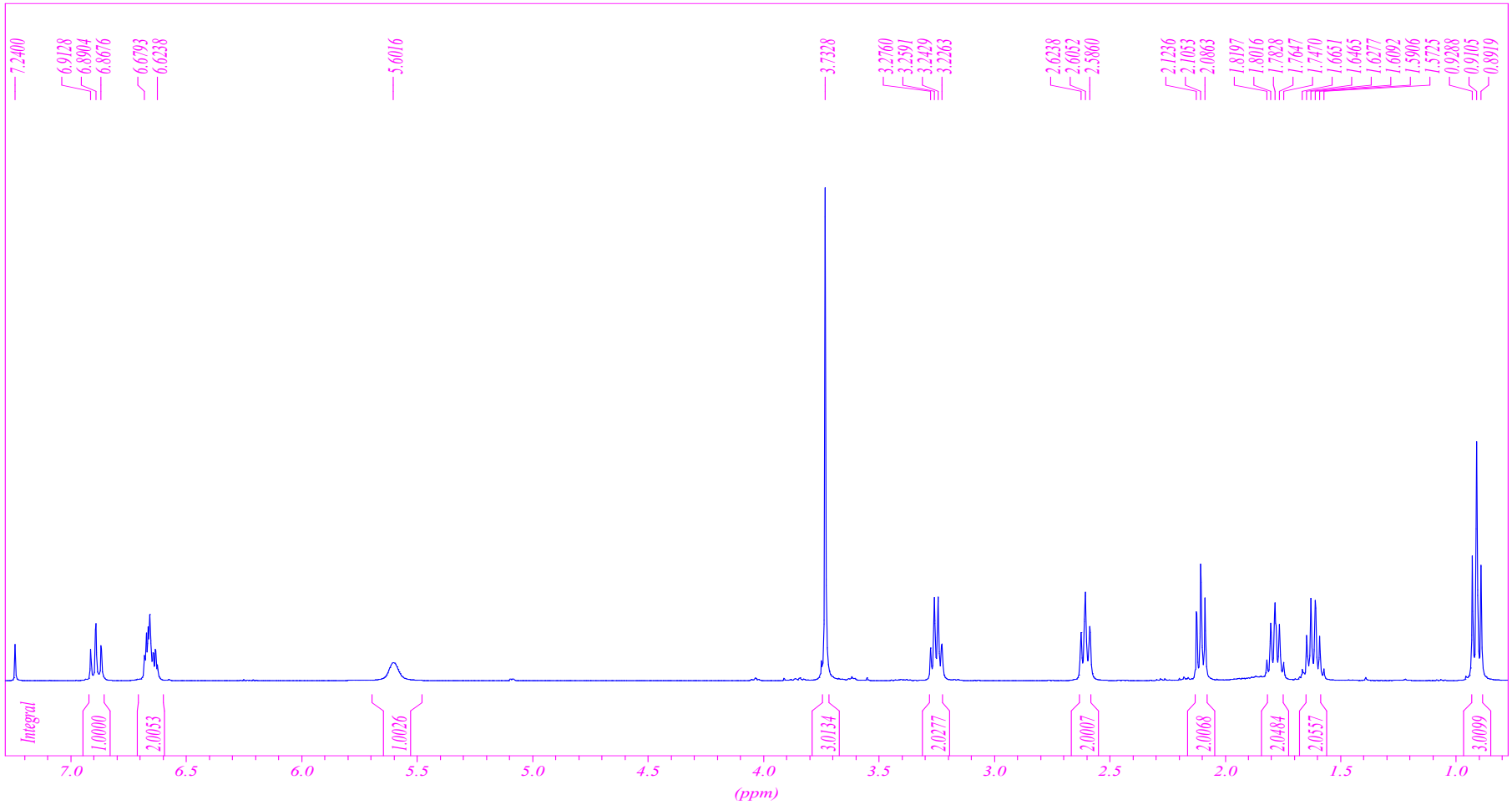
51. **^{1}H NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]propanamide (8b)**



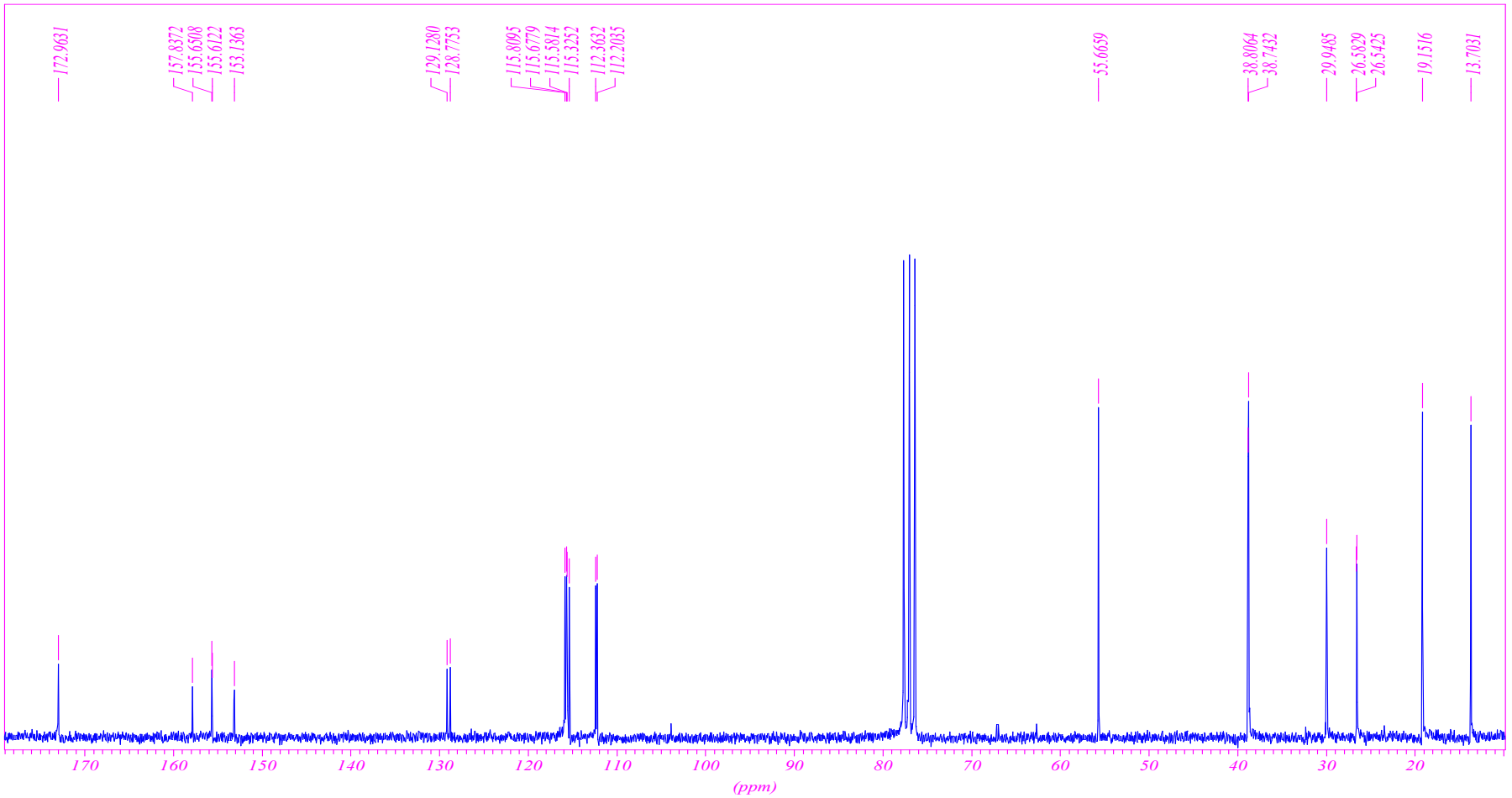
52. **^{13}C NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]propanamide (8b)**



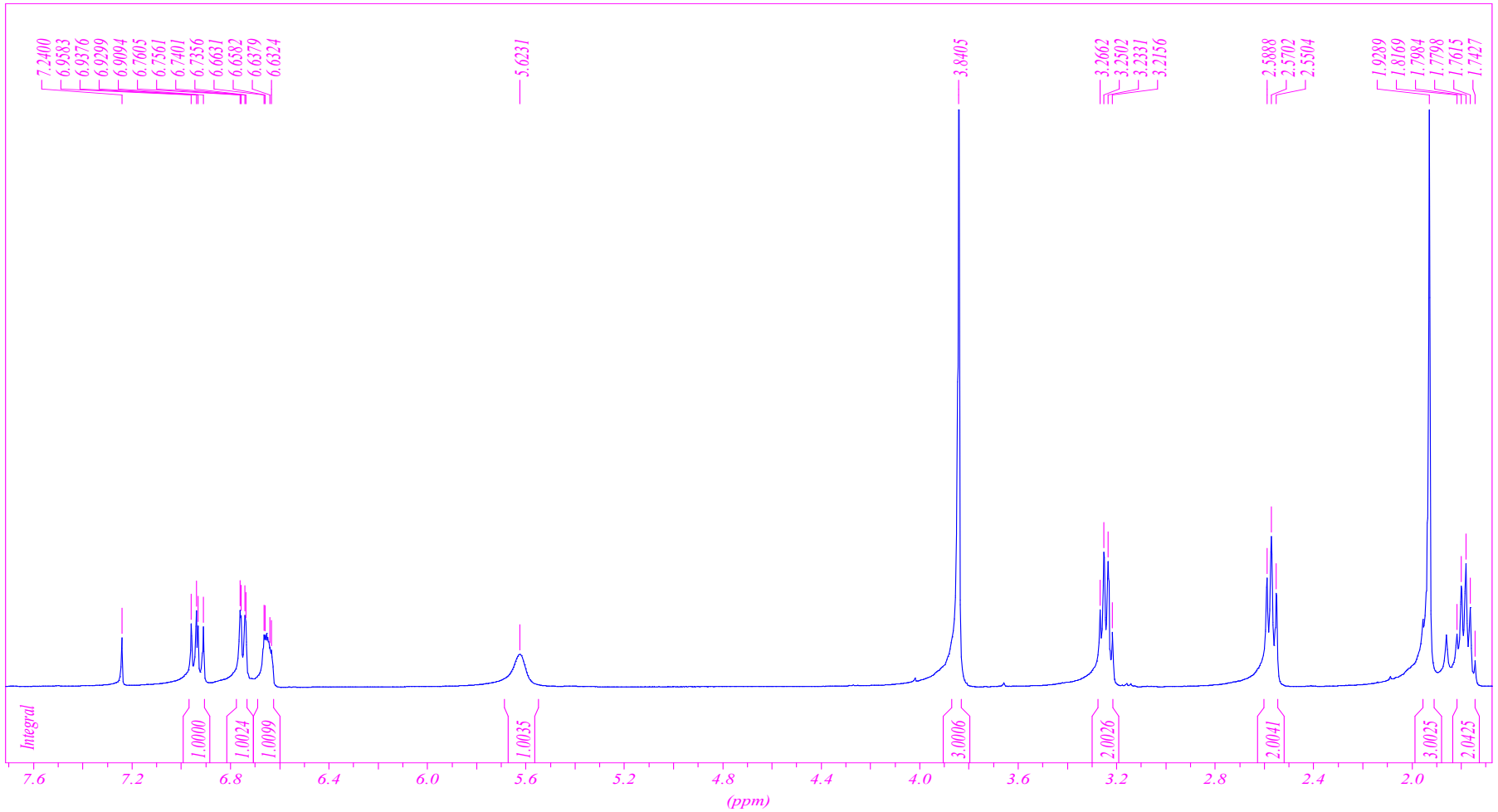
53. **^{1}H NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]butanamide (8c)**



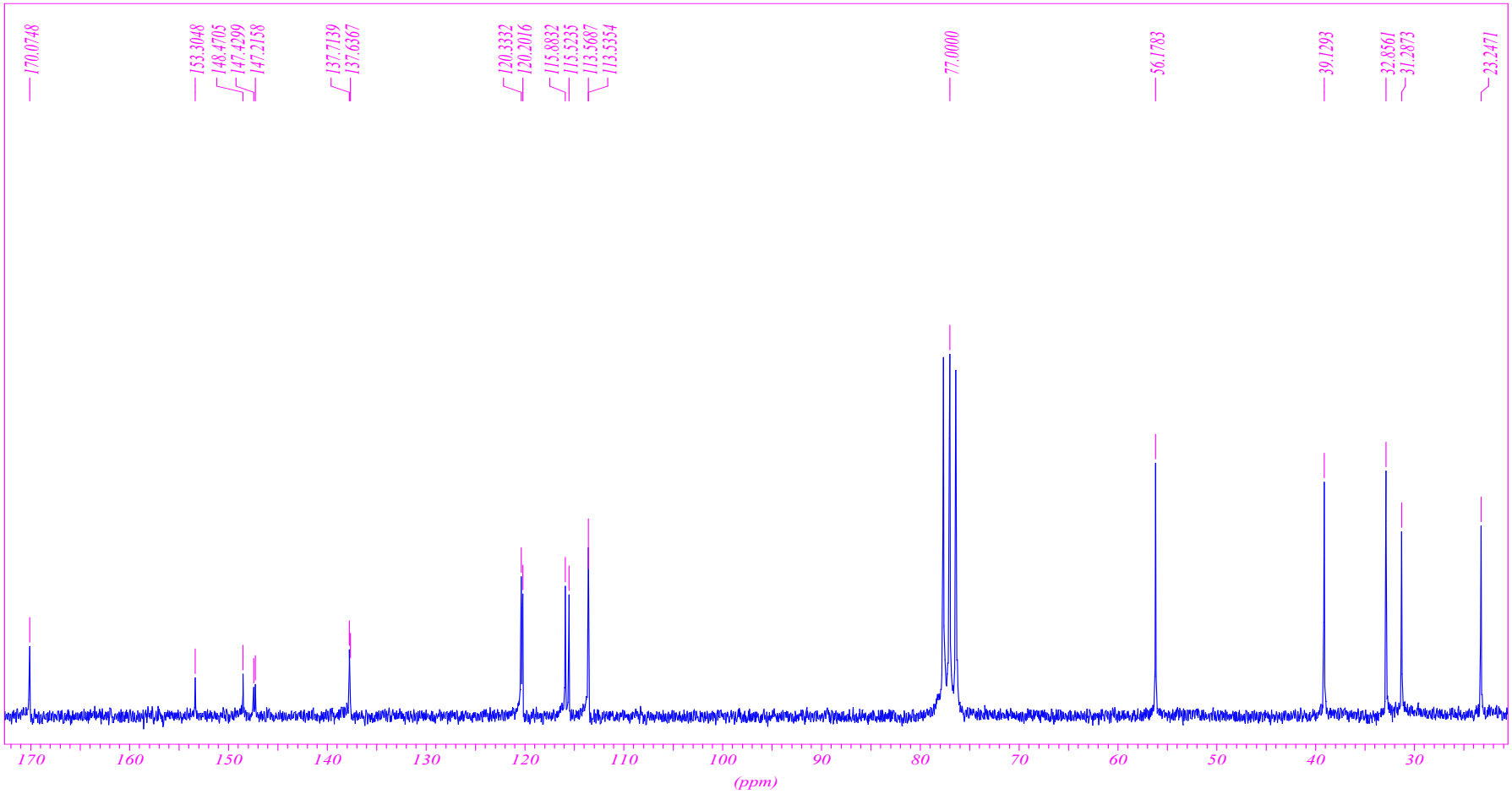
54. **^{13}C NMR ($CDCl_3$) of *N*-[3-(2-Fluoro-5-methoxyphenyl)propyl]butanamide (8c)**



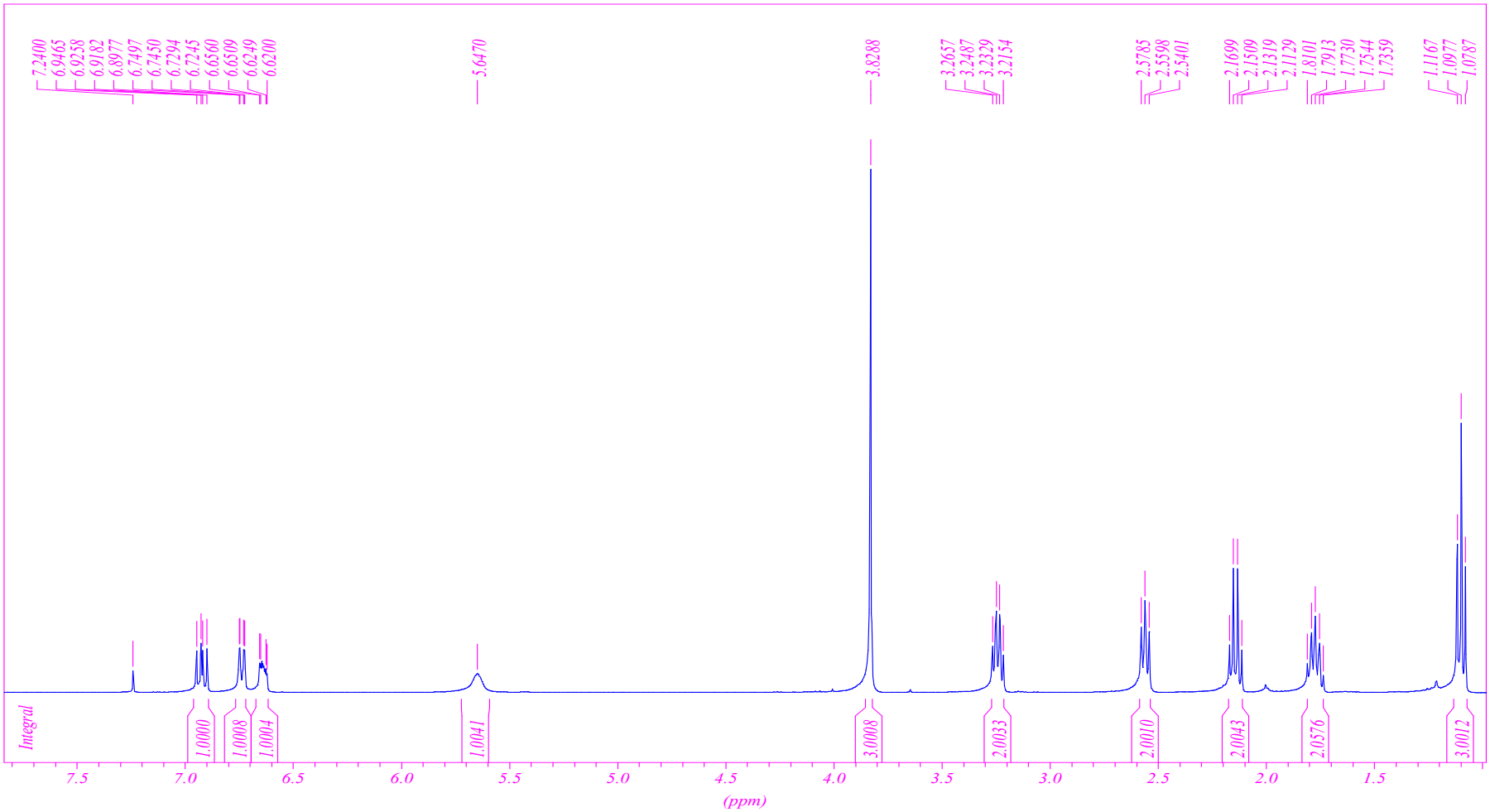
55. **^{1}H NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]acetamide (8d)**



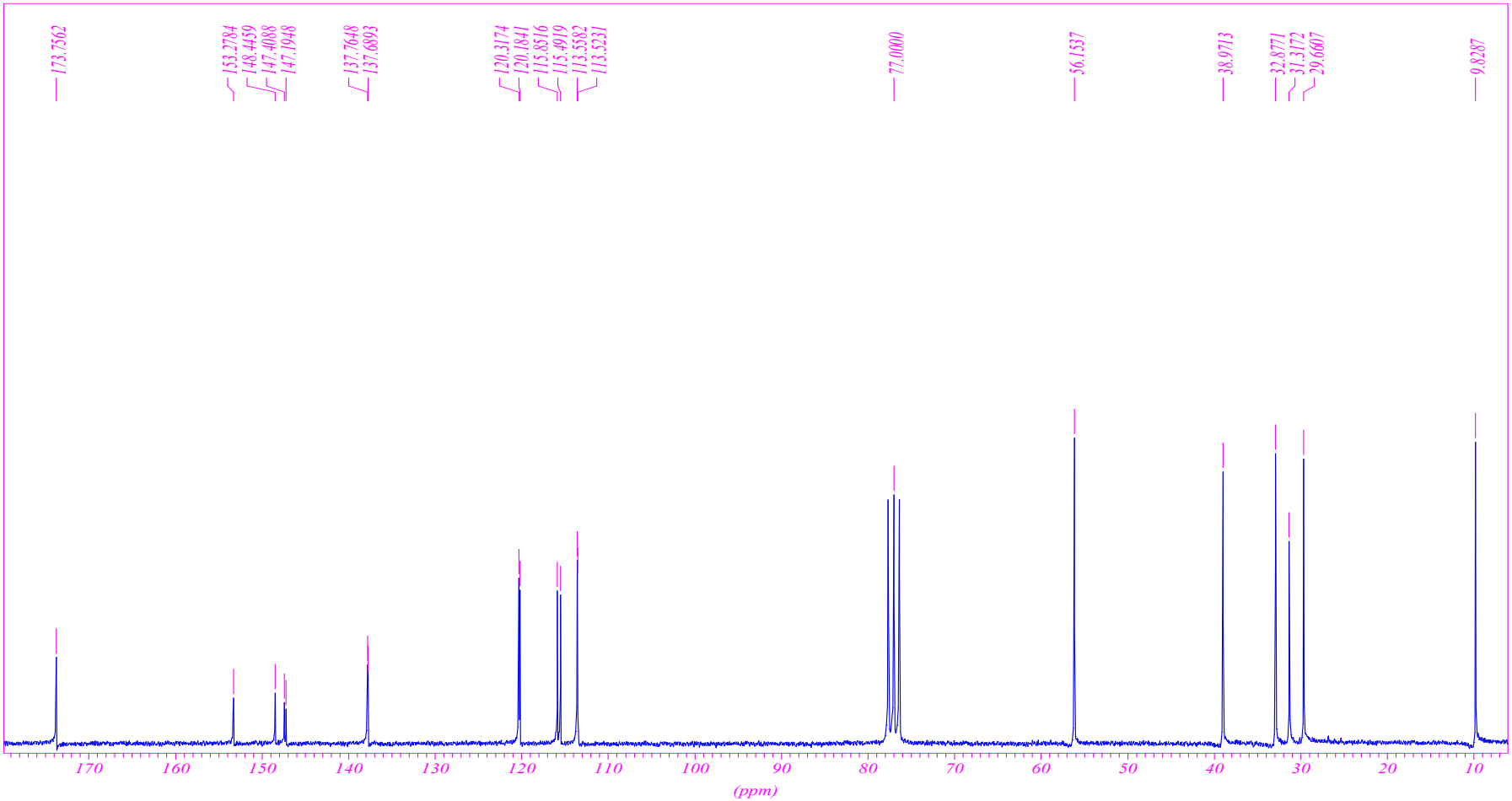
56. **^{13}C NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]acetamide (8d)**



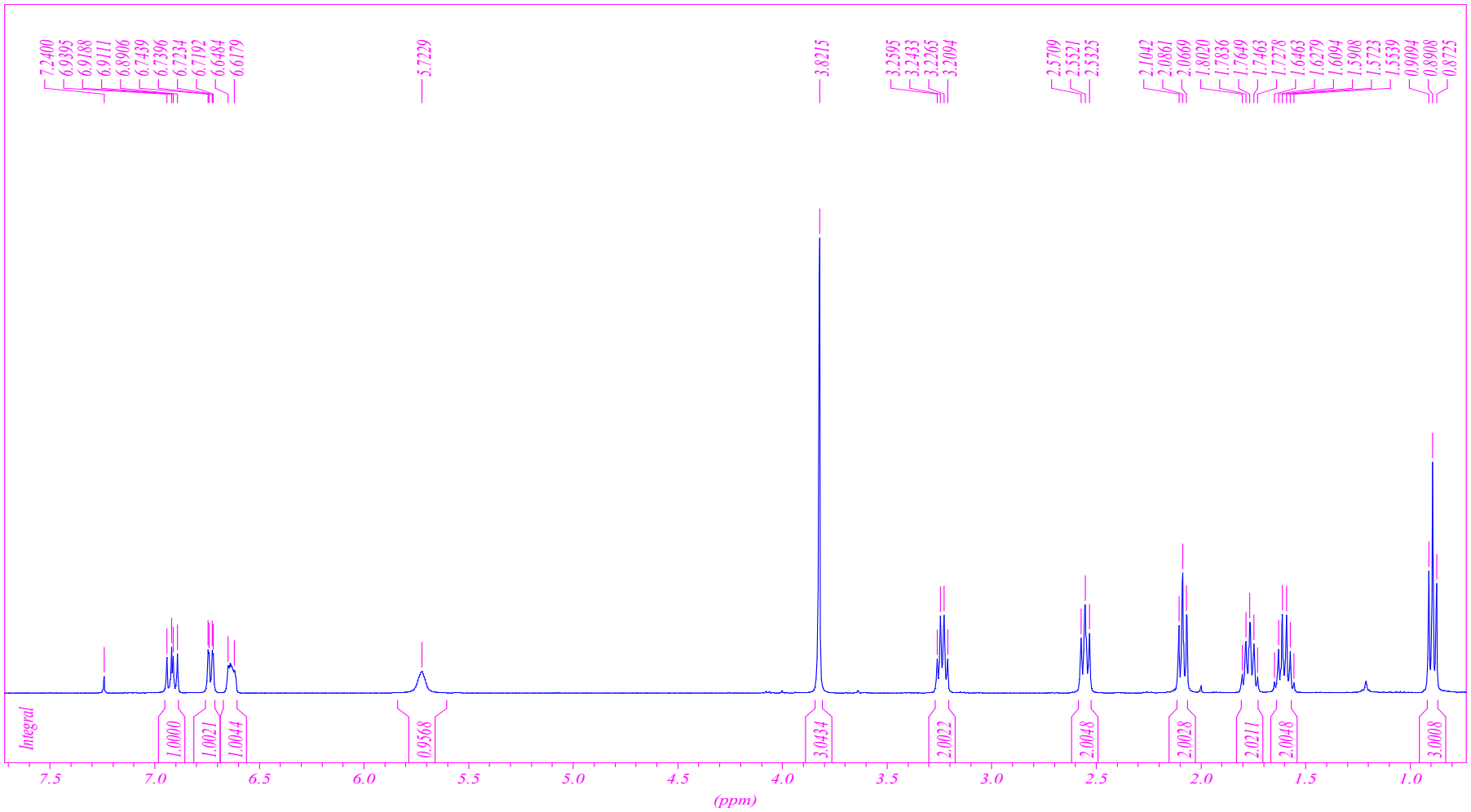
57. **^{1}H NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]propanamide (8e)**



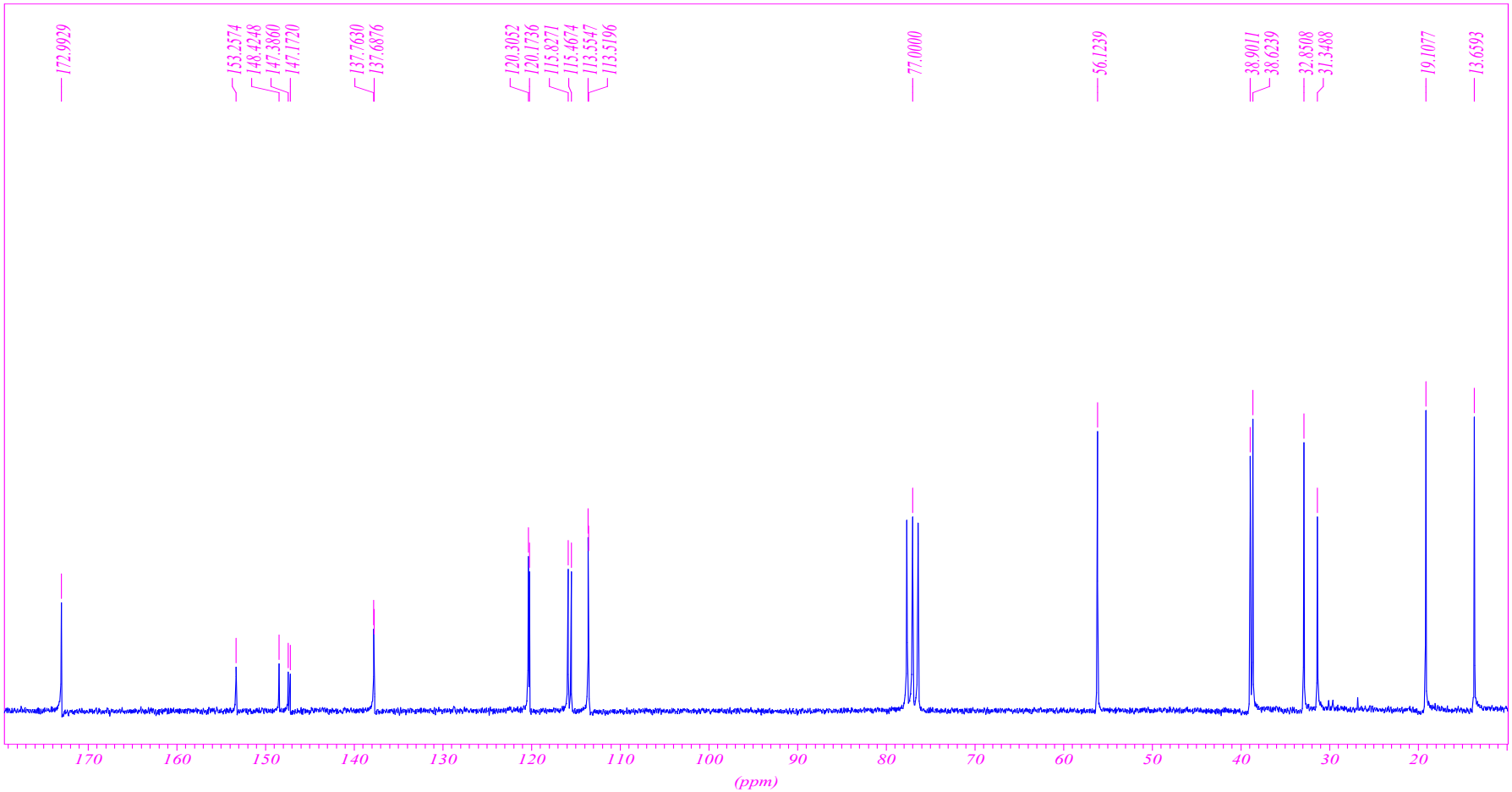
58. **^{13}C NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]propanamide (8e)**



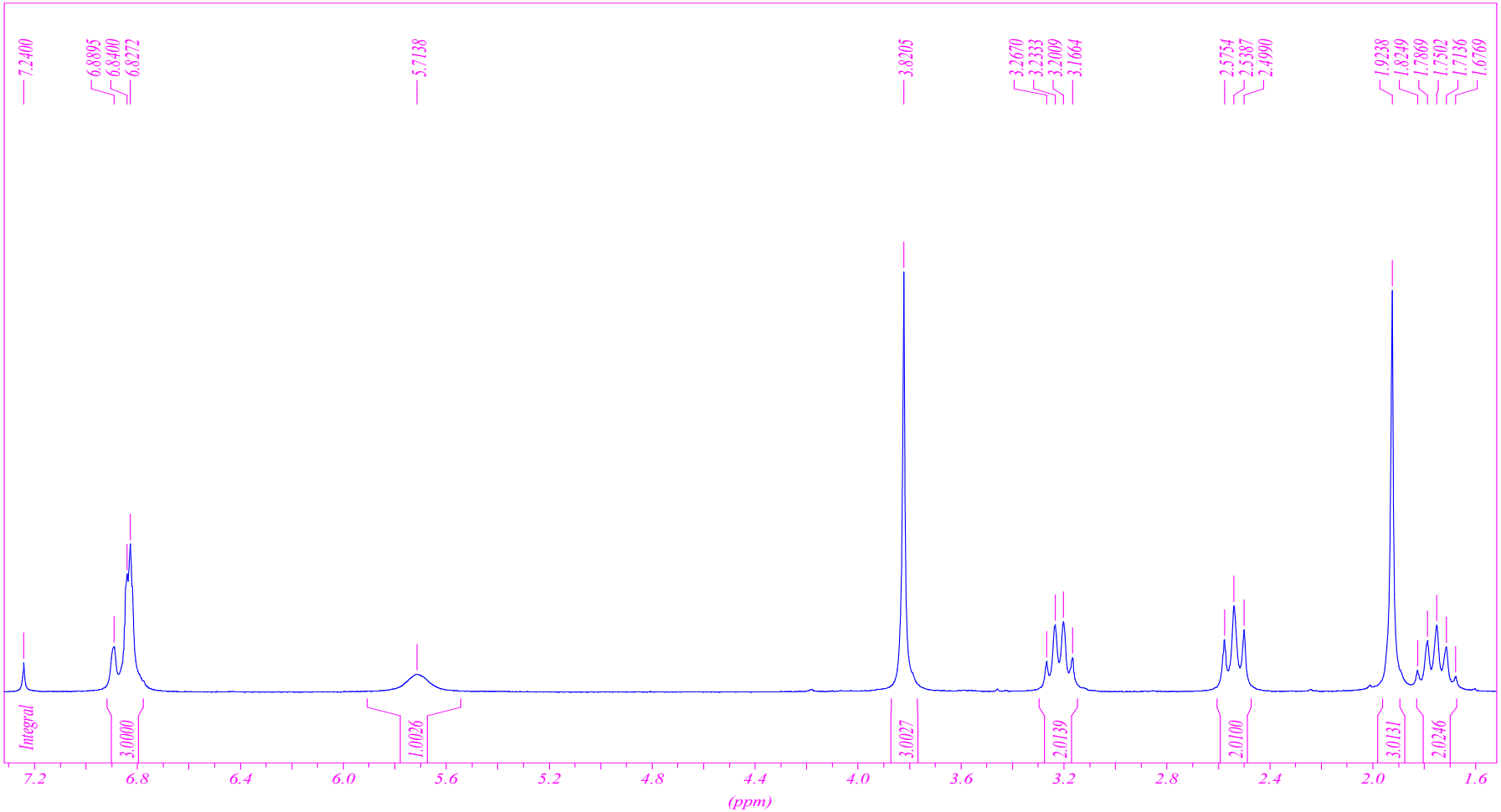
59. **^{1}H NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]butanamide (8f)**



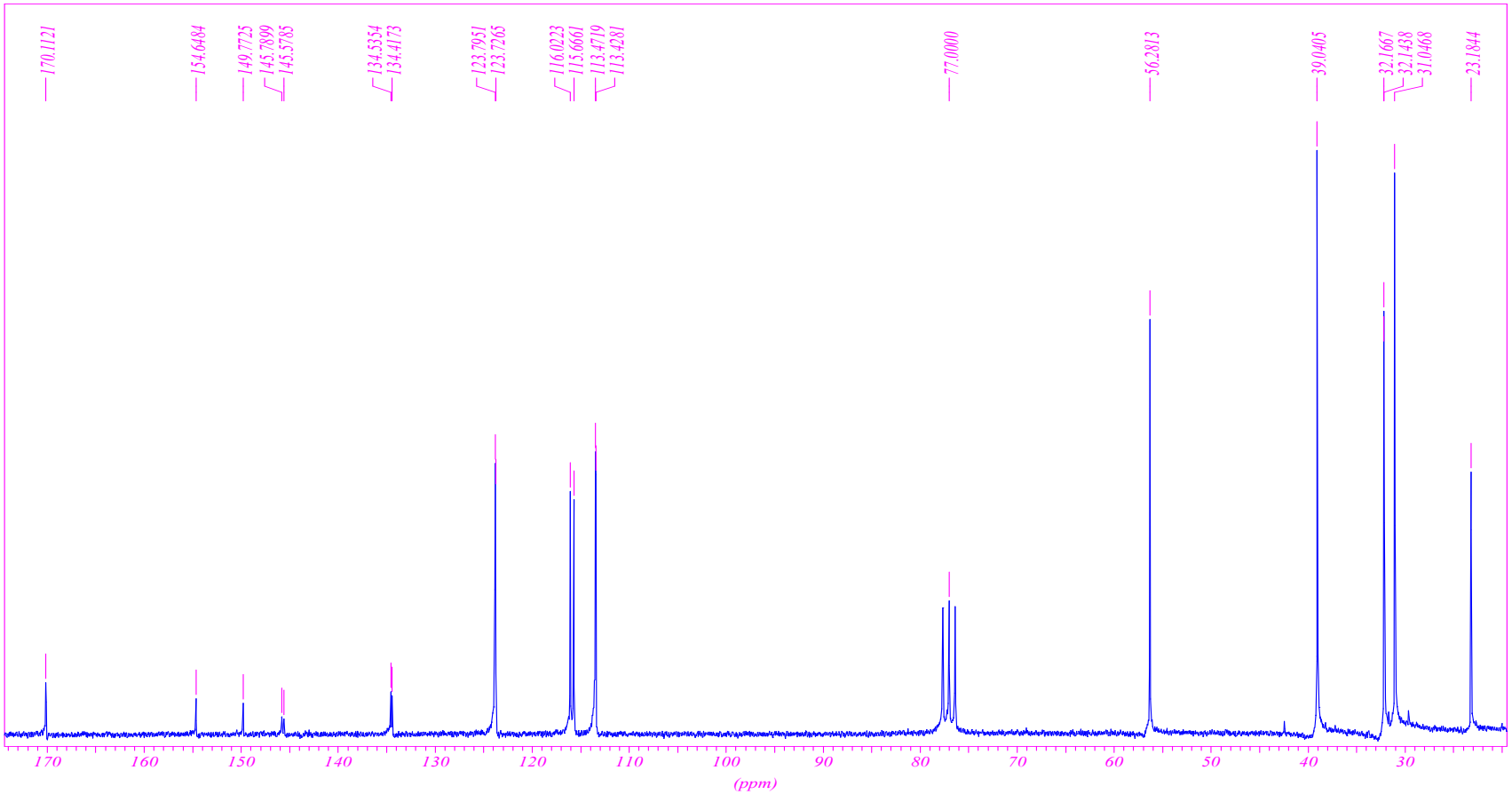
60. **^{13}C NMR ($CDCl_3$) of *N*-[3-(4-Fluoro-3-methoxyphenyl)propyl]butanamide (8f)**


172.9929
153.2574
148.4248
147.3860
147.1720
137.7630
137.6876
120.3052
120.1736
115.8271
115.4674
113.5547
113.5196
77.0000
56.1239
38.9011
38.6239
32.6508
31.3488
19.1077
13.6593
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

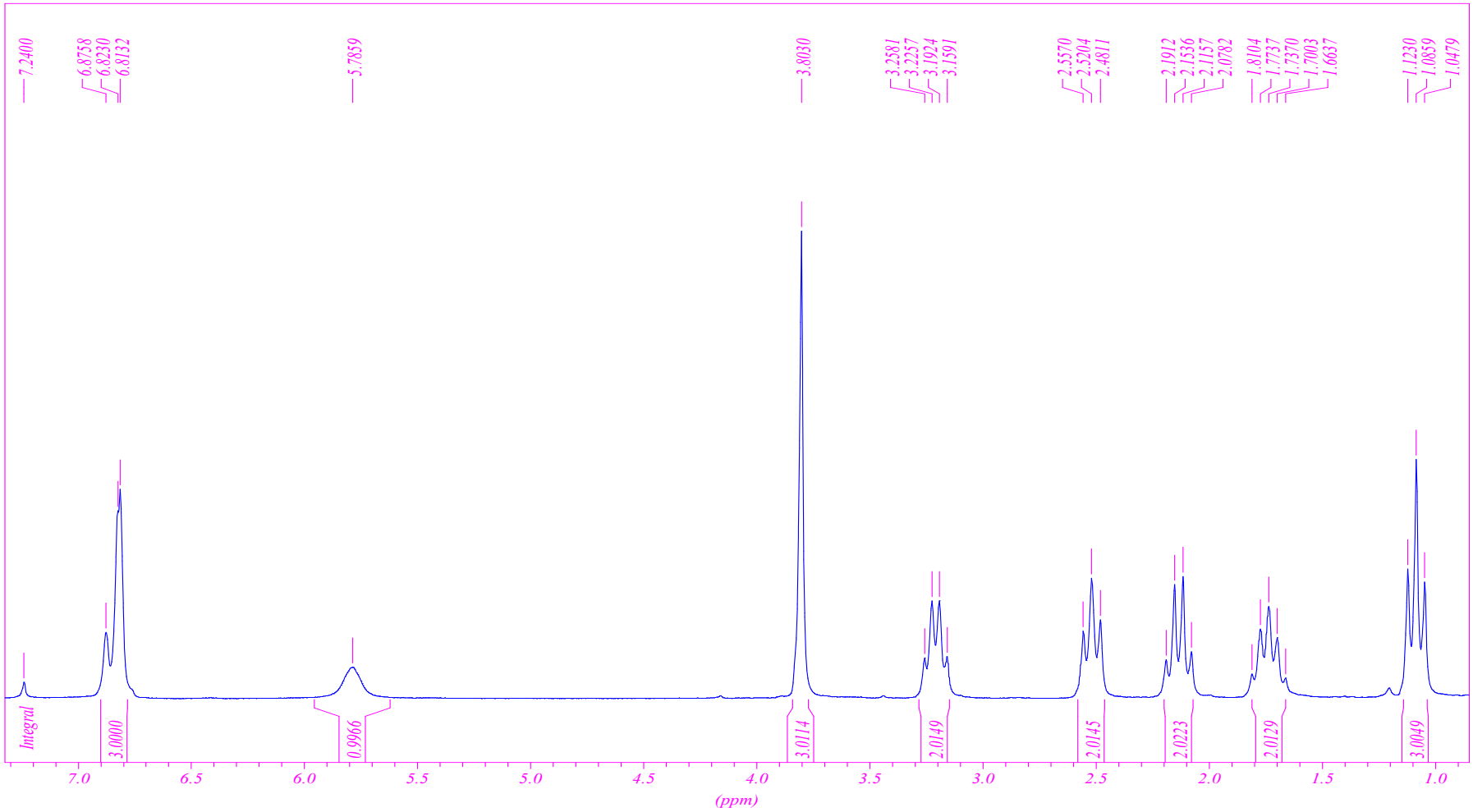
61. **^{1}H NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]acetamide (9a)**



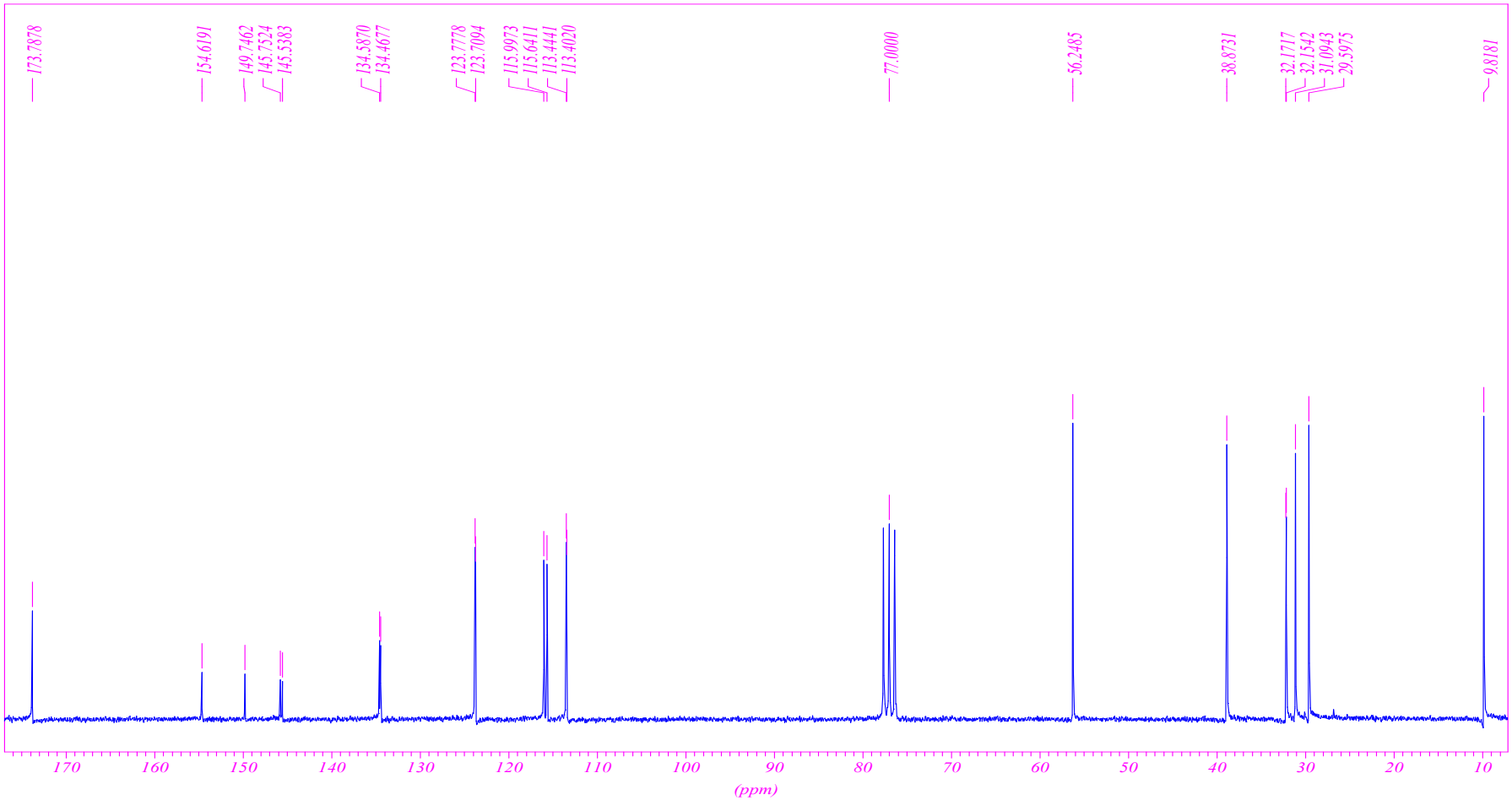
62. **^{13}C NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]acetamide (9a)**



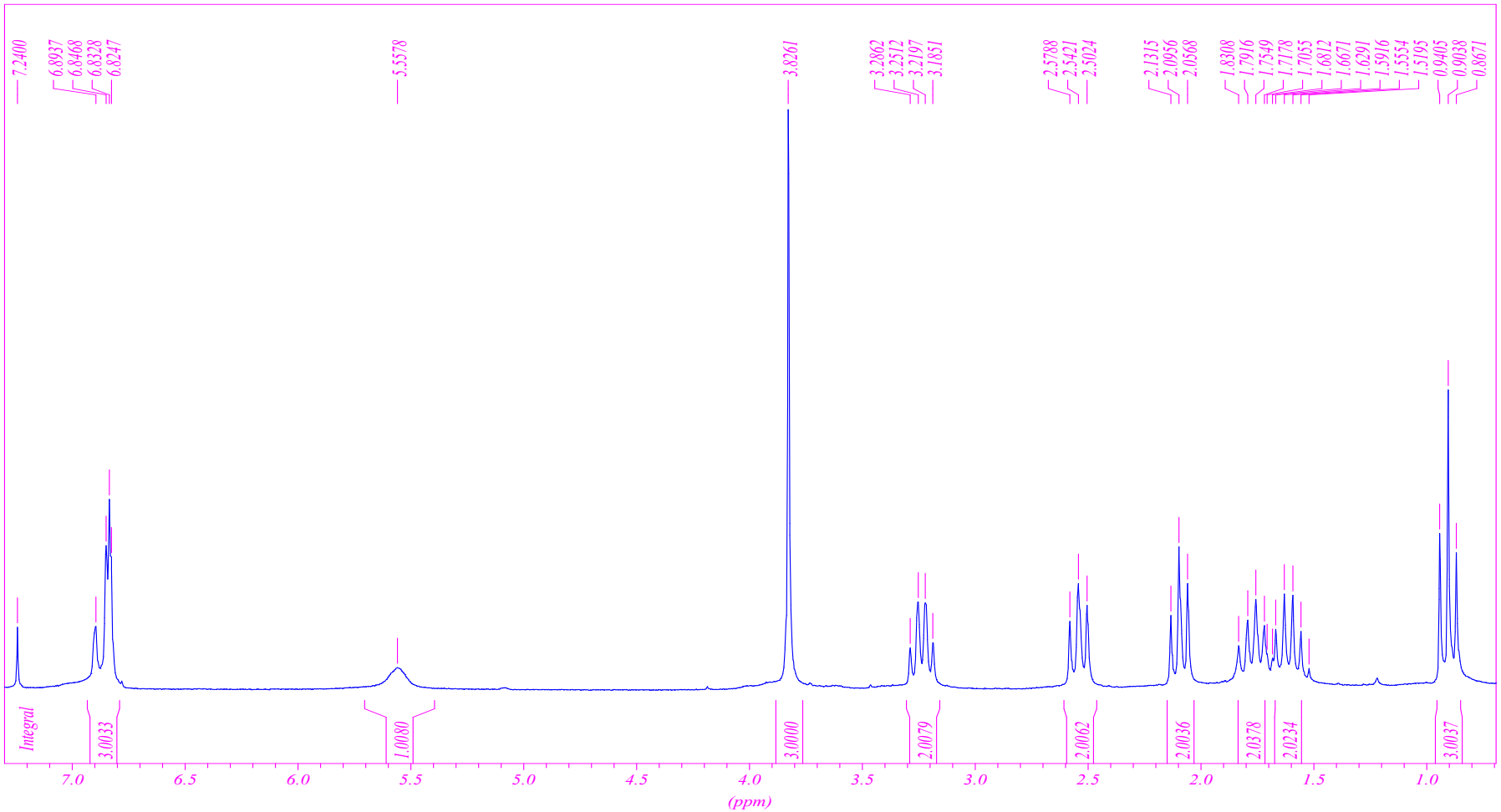
63. **^{1}H NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]propanamide (9b)**



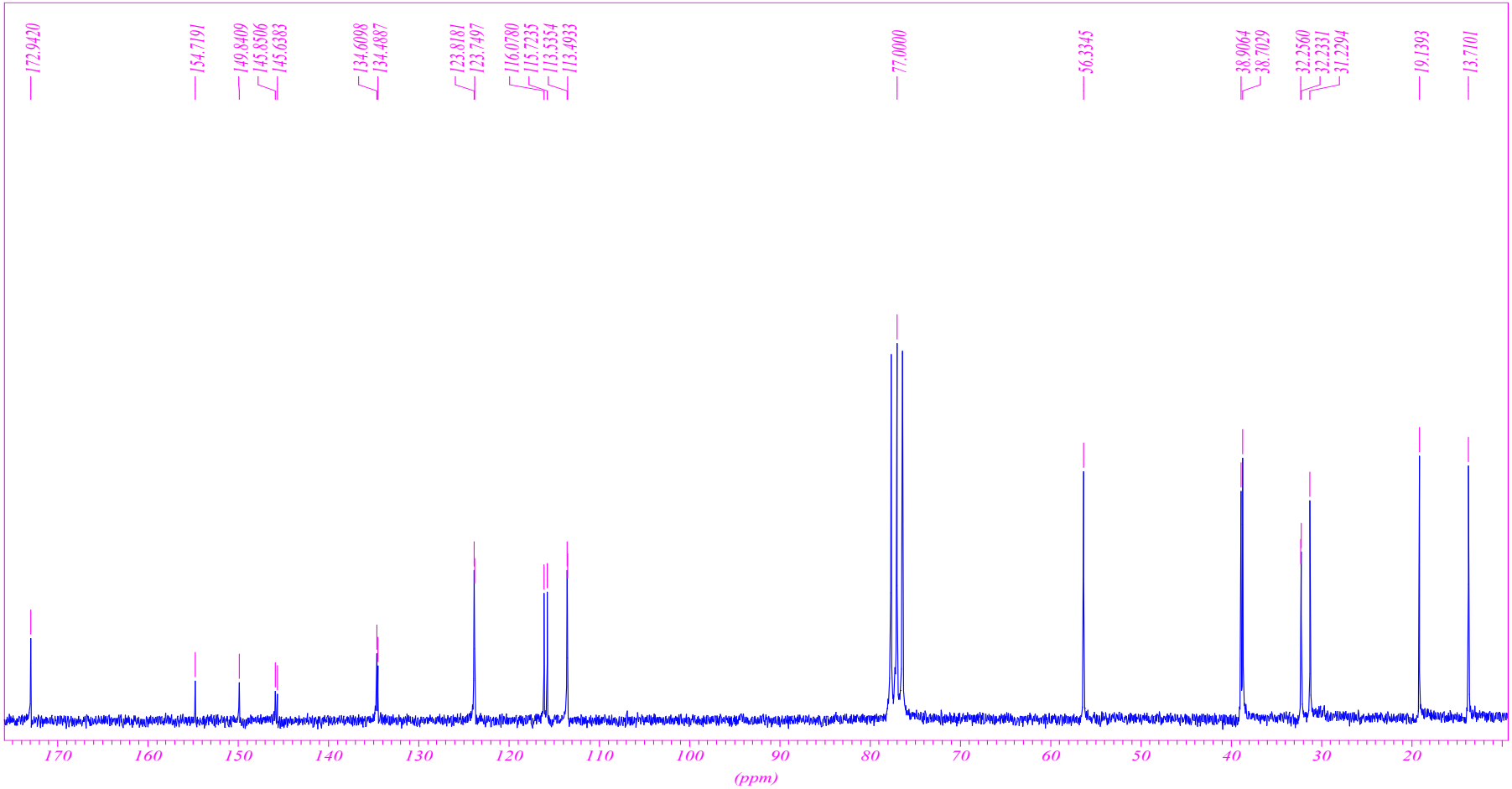
64. **^{13}C NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]propanamide (9b)**



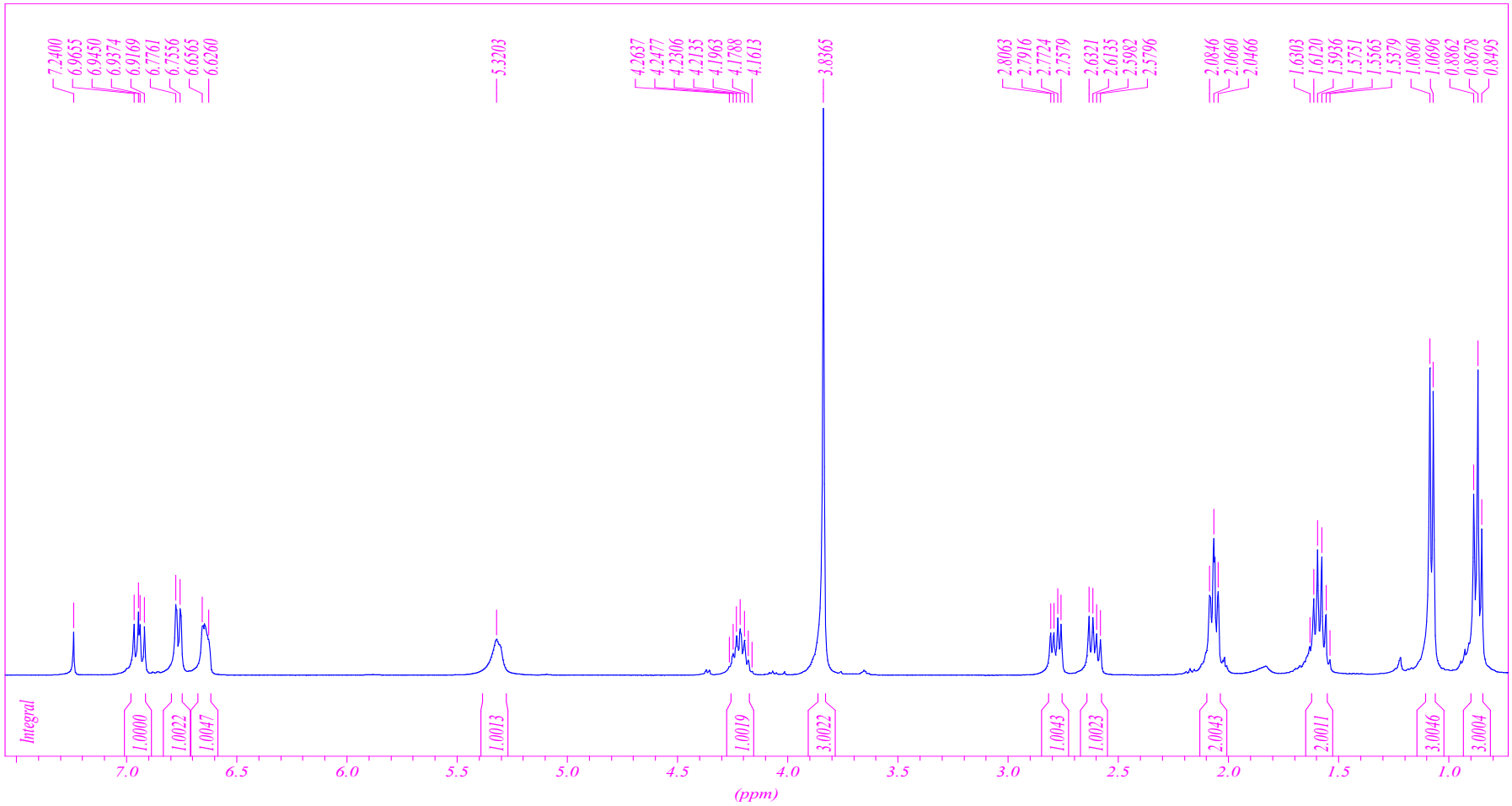
65. **^{1}H NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]butanamide (9c)**



66. **^{13}C NMR ($CDCl_3$) of *N*-[3-(3-Fluoro-4-methoxyphenyl)propyl]butanamide (9c)**



67. **^{1}H NMR ($CDCl_3$) of *N*-[1-(4-Fluoro-3-methoxyphenyl)propan-2-yl]butanamide (10)**



68. **^{13}C NMR ($CDCl_3$) of *N*-[1-(4-Fluoro-3-methoxyphenyl)propan-2-yl]butanamide (10)**