Electronic Supplementary Material (ESI) for Green Chemistry

An efficient and expeditious Fmoc protection of amines and amino acids in aqueous media

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General methods and experimental procedures

All commercial reagents were used as received unless otherwise mentioned. For analytical and preparative thin-layer chromatography, Merck, 0.2 mm and 0.5 mm Kieselgel GF 254 percoated were used, respectively. The spots were visualized using UV light. Infrared spectra were recorded on a Perkin Elmer spectrum 1000. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX400 spectrometer at 400 and 100.62, respectively. ^{1}H shifts are reported relative to internal TMS. Carbonshifts are given relative to the ^{13}C signal of $CDCl_3$ (δ 77.0 ppm), DMSO (δ 39.5 ppm), CD_3CO (δ 29.8 ppm) and CD_3OD (δ 49 ppm). Chemical ionization and high resolution mass spectra were recorded at the Mass Spectrometry Unit at the University of Santiago de Compostela, Spain. The electron impact mass spectra were recorded at the Department of Chemistry, FCT, using a Micromas GCT-TOF. High performance liquid chromatography (HPLC) were conducted on a Schimadzu (Japan) system equipped with an LC-20 AT pump, UV-dectector (SPD-M20A), and a Rheodyne 7125injector. The chiral stationary column used was a Chiralpak-IA (250mm X 4 mm). The mobile phase consisted of 10 % isopropyl alcohol : 90 % hexane containing 0.1 % TFA. The flow rate was set at 1 ml/min and the elution of analytes was monitored at 254 nm. *N*-FMOC α-amino acids were dissolved in isopropanol at a concentration of 0.5mg/ml and injected as a volume of 10µl.[1] Optical rotations were measured at 22 ºC on an AA-1000 polarimeter (0.5 dm cell) at 589 nm. The concentrations (c) are expressed in g/100 mL.

General procedure for the *N*-Fmoc protection of amines: To Fmoc chloride (1.2 mmol) was added the amine (1mmol) and water 1.5 mL and the reaction mixture stirred at 60 ^{o}C. The reaction was monitored by thin layer chromatography using ethyl acetate and hexane as eluent (3:7). After consumption of the amine the reaction product was filtered, washed with water and recrystallized from hot ethanol to afford the pure product.

General procedure for the *N*-Fmoc protection of α-amino acids

To the mixture of the two solids, the amino acid (1 mmol) and Fmoc chloride (1.2 mmol) it was added 1.5 mL of water:ethanol (3:1). The reaction mixture was stirred at 60 ^{o}C for particular time. After completion of reaction monitored by TLC the solution was acidified with HCl (1M)

untill pH 4-5 at O ^{o}C and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated affording the pure *N*-Fmoc α-amino acids. Determination of the enantiomeric purity of *N*-FMOC amino acids was accomplished by HPLC analysis as stated above in general methods and experimental procedures.

***N*-(9-Fluorenylmethoxycarbonyl)aniline (3a)**[2]: solid pale brown, obtained in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, *J*=7.4 Hz), 7.63 (d, 2H, *J*=7.0 Hz), 7.43-7.05 (m, 8H), 6.63(br s, 1H), 4.56 (d, 2H, *J*=6.4 Hz), 4.28 (t, 1H, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 47.1, 66.8, 118.81, 120.0, 123.6, 124.9, 127.1, 127.8, 129.1, 137.7, 141.4,143.8, 153.4. MSEI(+) m/z: 315 $[M]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-4-methylaniline (3b)**: colorless solid obtained in 83 % yield (mp 195-197ºC). IR(KBr) ν_{max}: 3327 (N-H), 1697 (C=O), 1527 (C=C), 1234 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, *J*=7.4 Hz), 7.62 (d, 2H, *J*=6.6 Hz), 7.43-7.31 (m, 6H), 7.11 (d, 2H, *J*=7.7 Hz), 6.59 (br s, 1H), 4.54 (d, 2H, *J*=6.5 Hz), 4.27 (t, 1H, *J*=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.7, 47.2, 66.80, 118.9, 120.0, 125.0, 127.1, 127.8, 129.6, 133.2, 135.1, 141.4, 143.8, 153.5. MSEI(+) m/z: 329 $[M]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$. HRMSEI calcd for $C_{22}H_{20}NO_2$ $[MH]^+$ 330,1494 obtained 330.1494.

***N*-(9-Fluorenylmethoxycarbonyl)-3-hydroxyaniline (3c)**[3]: Colorless solid obtained in 81 % yield. ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2CO$) δ: 7.98 (bs, 1H), 7.80 (s, 1H), 7.48 (d, 2H, *J*=7.1 Hz), 7.36 (d, 2H, *J*=6.9 Hz), 7.26 – 6.78 (m, 6H), 6.69 (s, 1H), 6.26 (d, *J*=6.8 Hz), 4.16 (d, 2H, *J*=6.5 Hz), 3.98 (t, 1H, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$/$(CD_3)_2CO$) δ: 46.5, 65.9, 105.4, 109.6, 119.3, 124.5, 126.5, 127.1, 129.0, 139.3, 140.7, 143.4, 153.0, 157.0. MSEI(+) m/z: 331 $[M]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$.

***N*-(9-Fluorenylmethoxycarbonyl)-3-chloroaniline (3d):** Colorless solid obtained in 87 % yield (mp 163-165ºC). IR(KBr) ν_{max}: 3307 (N-H), 1699 (C=O), 1520 (C=C), 1233 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, *J*=7.3 Hz), 7.61 (d, 2H, *J*=7.1 Hz), 7.49-7.03 (m, 8H), 6.65 (br s, 1H), 4.57 (d, 2H, *J*=6.2 Hz), 4.28 (t, 1H, *J*=6.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 47.0, 67.0, 116.7, 118.8, 120.1, 123.6, 124.9, 127.2, 127.8, 130.0, 134.8, 138.9, 141.4, 143.6, 153.1. MSEI(+) m/z: 349 $[M]^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 152.9 $[C_7H_4ClNO]^+$, 126 $[C_7H_4ClNH]^+$. HRMSCI calcd for $C_{21}H_{16}ClNO_2$ $[M]^+$ 349,0870 obtained 349.0863.

***N*-(9-Fluorenylmethoxycarbonyl)-4-bromoaniline (3e):** Colorless solid obtained in 80 % yield (mp 203-205ºC). IR(KBr) ν_{max}: 3333 (N-H), 1702 (C=O), 1530 (C=C), 1231 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, *J*=7.5 Hz), 7.61 (d, 2H, *J*=7.3 Hz), 7.43-7.38 (m, 6H), 7.33 (t, 2H, *J*=7.4 Hz), 7.26 (m, 2H), 6.62 (br s, 1H), 4.57 (d, 2H, *J*=6.3 Hz), 4.26 (*t*, 1H, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 47.1, 66.9, 116.1, 120.1, 120.3, 124.9, 124.9, 127.1, 127.8, 132.0, 136.7, 141.4, 143.6, 153.2. MSCI(+) m/z: 394 $[MH]^+$, 197 $[C_7H_4BrNO]^+$, 179 [9-methyl-9H-fluorene]$^+$, 165 [9H-fluorene]$^+$. HRMSCI calcd for $C_{21}H_{16}BrNO_2$ $[M]^+$ 393,0364 obtained 393.0355.

***N*-(9-Fluorenylmethoxycarbonyl)-4-fluroaniline (3f):** Colorless solid obtained in 84 % yield (mp 172-174ºC). IR(KBr) ν_{max}: 3338 (N-H), 1699 (C=O), 1528 (C=C), 1220 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, 2 H, *J*=7.6 Hz), 7.61 (d, 2H, *J*=7.1 Hz), 7.43 (d, 1H, *J*=7.4 Hz), 7.41 (d, 1H, *J*=7.5 Hz), 7.33 (t, 4H, *J*=7.3 Hz), 7.00 (d, 1H, *J*=8.4 Hz), 6.98 (d, 1H, *J*=8.5 Hz), 6.62 (br s, 1H), 4.56 (d, 2H, *J*=6.4 Hz), 4.28 (t, 1H, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 47.1, 66.9, 115.6, 115.8, 120.1, 120.6, 124.9, 127.1, 127.8, 128.2, 133.6, 141.4, 143.7, 153.6, 160.3. MSCI(+) m/z: 333 $[M]^+$, 314$[M-F]^+$, 179 [9-methyl-9H-fluoreneH]$^+$, 138 $[C_7H_4FNO]^+$. HRMSCI calcd for $C_{21}H_{16}FNO_2$ $[M]^+$ 333,1165 obtained 313.1154.

***N*-(9-Fluorenylmethoxycarbonyl)benzylamine[4] (3g):** Colorless solid obtained in 88 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, 2H, *J*=6.8 Hz), 7.59 (d, 2H, *J*=6.0 Hz), 7.40-7.28 (m, 9H), 5.06 (br s, 1H), 4.47 (d, 2H, *J*=5.6 Hz), 4.40 (m s, 2H), 4.24 (m s, 2H). ^{13}C NMR ($CDCl_3$) δ: 45.0, 47.3, 66.6, 119.9, 125.0, 127.0, 127.5, 127.6, 128.6, 138.4, 141.3, 143, 156.7.

***N*-(9-Fluorenylmethoxycarbonyl)-4-methylbenzylamine (3h):** Colorless solid obtained in 87 % yield (mp 151-153ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, 2H, *J*=6.8 Hz), 7.61 (d, 2H, *J*=6.2 Hz), 7.41-7.16 (m, 8H), 5.09 (br s, 1H), 4.47 (d, 2H, *J*=6 Hz), 4.35 (d, 2H, *J*=3.9 Hz), 4.24 (d, 2H, *J*=5.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.0, 44.8, 47.3, 66.6, 119.9, 124.9, 126.9, 127.5, 127.6, 129.3, 135.3, 137.1, 141.3, 143.9, 156.3. MSCI(+) m/z: 344 $[MH]^+$, 179 [9-methyl-9H-fluoreneH]$^+$, 105 $[C_8H_9]^+$. HRMSCI calcd for $C_{23}H_{21}NO_2$ $[M]^+$ 344,1651 obtained 344,1641.

***N*-(9-Fluorenylmethoxycarbonyl)-4-methoxybenzylamine (3i)[5]:** Colorless solid obtained in 80 % yield. 1H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, 2H, *J*=7.0 Hz), 7.59 (d, 2H, *J*=5.8 Hz), 7.51-7.19 (m, 6H), 6.87 (d, 2H, *J*=6.9 Hz), 4.45 (d, 2H, *J*=5.5 Hz), 4.45-4.22 (m, 5 H) 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 44.6, 47.3, 55.3, 66.6, 114.1, 120.0, 125.0, 127.0, 127.7, 128.9, 130.5,

141.3, 143.9, 156.3, 159.1. MSEI(+) m/z: 359 $[M]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$.

***N*-(9-Fluorenylmethoxycarbonyl)morpholine (3j):** Colorless solid obtained in 80 % yield (mp 113-115ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, 2H, *J*=7.6 Hz), 7.57 (d, 2H, *J*=7.4 Hz), 7.41 (t, 2H, *J*=7.4 Hz), 7.32 (t, 2H, *J*=7.4 Hz), 4.48 (d, 2H, *J*=6.6 Hz), 4.24 (t, 1H, *J*=6.6 Hz), 3.62 (m, 4H), 3.45 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 44.0, 44.2, 47.4, 66.5, 67.3, 120.0, 124.98, 127.1, 127.7, 141.4, 143.9, 155.2. MSCI(+) m/z: 310 $[MH]^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$. HRMSCI calcd for $C_{19}H_{20}NO_3$ $[M]^+$ 310,1443 obtained 310,1449.

***N*-(9-Fluorenylmethoxycarbonyl)pyrrolidine (3k)[6]:** Pale yellow solid obtained in 82 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78(d, 2H, *J*=7.5 Hz), 7.64 (d, 2H, *J*=7.4 Hz), 7.41 (t, 2H, *J*=7.4 Hz), 7.32 (t, 2H, *J*=7.4 Hz), 4.40 (d, 2H, *J*=7.2 Hz), 4.26 (t, 1H, *J*=7.1 Hz), 3.45 (t, 4 H, *J*=6.7 Hz), 1.93-1.86 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 25.6, 44.8, 47.4, 67.0, 119.9, 125.1, 126.9, 127.6, 141.3, 144.2, 155.2.

***N*-(9-Fluorenylmethoxycarbonyl)piperidine (3l)[7]:** Pale yellow solid obtained in 84 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, 2H, *J*=7.5 Hz), 7.60 (d, 2H, *J*=7.4 Hz), 7.38 (t, 2H, *J*=7.3 Hz), 7.30 (t, 2H, *J*=7.1 Hz), 4.41 (d, 2H, *J*=7.0 Hz), 4.27 (t, 1H, *J*=6.9 Hz), 3.46 (t, 4 H, *J*=5.5 Hz), 1.66-1.54 (m, 6 H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 24.6, 44.8, 47.4, 67.1, 119.9, 125.00, 127.0, 127.6, 141.3, 144.2, 155.2.

***N*-(9-Fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (3m):** Colorless solid obtained in 80 % yield (mp 122-124ºC). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.79 (d, 2H, *J*=7.3 Hz), 7.63 (d, 2H, *J*=7.1 Hz), 7.38 (t, 2H, *J*=7.3 Hz), 7.30 (t, 2H, *J*=7.1 Hz), 4.34 (d, 2H, *J*=6.8 Hz), 4.21 (m, 1H), 3.87 (s, 2H), 2.56 (s, 1H). ^{13}C NMR (CD_3OD) δ: 31.0, 48.0, 68.0, 72.0, 81.2, 120.8, 126.1, 128.1, 128.7, 142.5, 145.2, 158.5. MSEI(+) m/z: 278 $[MH]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$. HRMSCI calcd for $C_{18}H_{16}NO_2$ $[M]^+$ 278,1181 obtained 278,1172.

***N*-(9-Fluorenylmethoxycarbonyl)cyclohexylamine (3n)[7, 8]:** Colorless solid obtained in 80 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, 2H, *J*=7.2 Hz), 7.51 (d, 2H, *J*=7.1 Hz), 7.31 (t, 2H, *J*=7.1 Hz), 7.22 (t, 2H, *J*=7.1 Hz), 5.03 (br s, 1H), 4.29 (d, 2H, *J*=5.2 Hz), 4.13 (m, 1H), 3.91 (d, 1H, *J*=5 Hz), 2.15-2.05 (m, 2H), 1.88 (m, 2H), 1.59-1.51 (m, 4 H), 1,35 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 23.2, 32.7, 47.0, 52.5, 66.0, 119.6, 124.8, 126.7, 127.3, 141.0, 143.8, 155.7.

***N*-(9-Fluorenylmethoxycarbonyl)octylamine (3o):** Pale yellow solid obtained in 82% yield (mp 91-93ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78(d, 2H, *J*=7.2 Hz), 7.61 (d, 2H, *J*=7.5 Hz), 7.42-7.30 (m, 4 H), 4.75 (br s, 1H), 4.41 (d, 2H, *J*=5.0 Hz), 4.26-4.23 (m, 1H), 3.20 (m, 2H), 1.66-1.29 (m, 12H), 0.89 (t, 3H, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.1 14.3, 22.6, 26.7, 29.2, 29.9, 31.8, 41.1, 46.8, 47.3, 66.4, 119.9, 124.9, 127.0, 127.6, 141.3, 144.0, 144.3, 156.4. MSEI(+) m/z: 352 $[MH]^+$, 196 [(9H-fluoren-9-yl)methanol]$^+$, 178 [9-methyl-9H-fluorene-H]$^+$, 165 [9H-fluorene-H]$^+$. HRMSCI calcd for $C_{23}H_{30}NO_2$ $[MH]^+$ 352,2271 obtained 352,2293.

***N*-(9-Fluorenylmethoxycarbonyl)ethanolamine (3p)[9]:** Colorless solid obtained in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, 2H, *J*=7.5 Hz), 7.60 (d, 2H, *J*=7.7 Hz), 7.40 (t, 2H, *J*=7.3 Hz), 7.31 (dt, 2H, *J*=1 and 7.4 Hz), 5.17 (br s, 1H), 4.44 (d, 2H, *J*=6.7 Hz), 4.23 (t, 1H, *J*=6.6 Hz), 3.71 (d, 2H, *J*= 4.4 Hz), 3.71 (d, 2H, *J*= 4.5 Hz), 2.13 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 43.5, 47.2, 62.3, 66.8, 112.0, 125.0, 127.0, 127.7, 141.3, 143.9, 157.1.

***N*-(9-Fluorenylmethoxycarbonyl)ethylamine (3q)[6]:** Colorless solid obtained in 87 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, 2H, *J*=7.5 Hz), 7.60 (d, 2H, *J*=7.4 Hz), 7.40 (t, 2H, *J*=7.4 Hz), 7.31 (t, 2H, *J*=7.4 Hz), 4.73(br s, 1H), 4.41 (d, 2H, *J*=6.3 Hz), 4.22 (t, 1H, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 15.3, 35.9, 47.3, 66.5, 119.9, 125.0, 127.0, 127.6, 141.3, 144.3, 144.0, 156.3.

(R)-*N*-(9-Fluorenylmethoxycarbonyl)-1-phenylethanamine (3r)[10]: Colorless solid obtained in 87 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, 2H, *J*=7.4 Hz), 7.59 (d, 2H, *J*=6.2 Hz), 7.41-7.26 (m, 9H), 5.02 (s, 2H) 4.86 (s, 2H), 4.42 (d, 2H, *J*=6.8 Hz), 4.20 (s, 3H), 1.59-1.49 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 22.4, 47.3, 50.7, 66.5, 119.9, 125.0, 125.9, 127.0, 127.4, 127.6, 128.7, 141.3, 143.42, 144.0, 155.6.

***N*-(9-Fluorenylmethoxycarbonyl)dopamine (3s)[11]:** Pale yellow solid obtained in 75 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77(d, 2H, *J*=7.5 Hz), 7.56 (d, 2H, *J*=7.2 Hz), 7.39 (t, 2H, *J*=7.4 Hz), 7.31 (t, 2H, *J*=7.4 Hz), 6.79 (d, 1H, *J*=7.5 Hz), 6.68 (s, 1H), 6.58 (d, 1H, *J*=7.1 Hz), 5.63 (br s, 2H), 4.79 (br s, 1H), 4.40 (d, 2H, *J*=6.5 Hz), 4.21 (t, 1H, *J*=6.4 Hz), 3.39 (m, 2H), 2.68 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 35.4, 42.3, 47.3, 66.6, 115.5, 115.7, 120.0, 121.1, 125.0, 127.1, 127.7, 131.4, 141.3, 142.0, 143.0, 143.9, 156.5.

***N*-(9-Fluorenylmethoxycarbonyl)glycine (3t)[8, 12]:** Colorless solid obtained in 89 % yield. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 7.88 (d, 2H, *J*=7.4 Hz), 7.70 (d, 2H, *J*=7.3 Hz), 7.61 (1H, t, *J*=5.6

Hz), 7.41 (t, 2H, *J*=7.3 Hz), 7.32 ((t, 2H, *J*=7.2 Hz), 4.29 - 4.21 (m, 3H), 3.65 (d, 2H, *J*=5.6 Hz). ^{13}C NMR $(CD_3)_2SO$) δ: 42.1, 46.6, 66.3, 120.1, 125.2, 127.1 127.6, 140.7, 143.8, 156.5, 171.6.

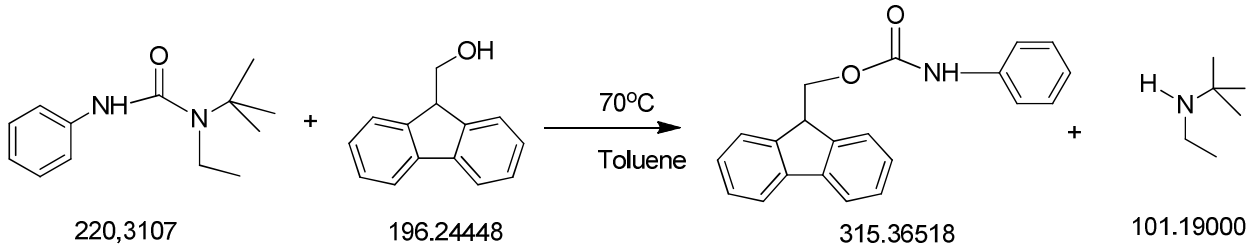
***N*-(9-Fluorenylmethoxycarbonyl)alanine (3u)[13]:** Colorless solid obtained in 86 % yield. $[\alpha]_D^{22}$ = -19º (c 1.5, DMF) (Lit[14] -19º). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 7.87 (d, 2H, *J*=7.5 Hz), 7.72-7.70 (m, 2H), 7.65 (d, 1H, *J*=7.6 Hz), 7.41 (t, 2H, *J*=7.4 Hz), 7.32 (t, 2H, *J*=7.4 Hz), 4.31-4.19 (m, 3H), 4.00 (q, 1H *J*=7.4 Hz), 1.28 (d, 2H, *J*=7.3 Hz). ^{13}C NMR $(CD_3)_2SO$) δ: 17.1, 46.7, 49.3, 65.6, 120.2, 125.3, 127.1, 127.7, 140.8, 143.9, 155.9, 174.5.

***N*-(9-Fluorenylmethoxycarbonyl)proline (3v)[12, 15]:** Colorless solid obtained in 89 % yield. $[\alpha]_D^{22}$ = -30º (c 1.0, DMF) (Lit[14] -32º). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, 2H, *J*=7.5 Hz), 7.70 (d, 2H, *J*=7.4 Hz), 7.59-7.52 (m, 2H), 7.40-7.27 (m, 4H), 5.1 (br, 1H), 4.44-4.09 (m, 4H), 3.57-3.42 (m, 2H), 2.21-1.93 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 23.3, 24.4, 29.1, 31.0, 46.7, 46.9, 47.2, 67.4, 67.9, 120.0, 125.0, 127.1, 127.6, 127.7, 141.3, 143.7, 143.8, 154.5, 156.1, 175.5.

E-Factor and Mass Intensity calculations

Green concept: Comparisons of *N*-(9-fluorenylmethoxycarbonyl)aniline synthesis with reported methods

A) Calculation for the synthesis of *N*-(9-fluorenylmethoxycarbonyl)aniline in toluene.[16]



220,3107 196.24448 315.36518 101.19000

Raw Materials Used		Crude product and Waste	
1-*tert*-butyl-1-ethyl-3-phenylurea	1 g	Crude product	1.125 g
Nucleophile	1.78 g	Organic solvent waste	16.14 g
Toluene	14 mL (16.14 g)	N-ethyl-2-methylpropan-2-amine	0.36 g
Total	18.92 g	Total	17.62

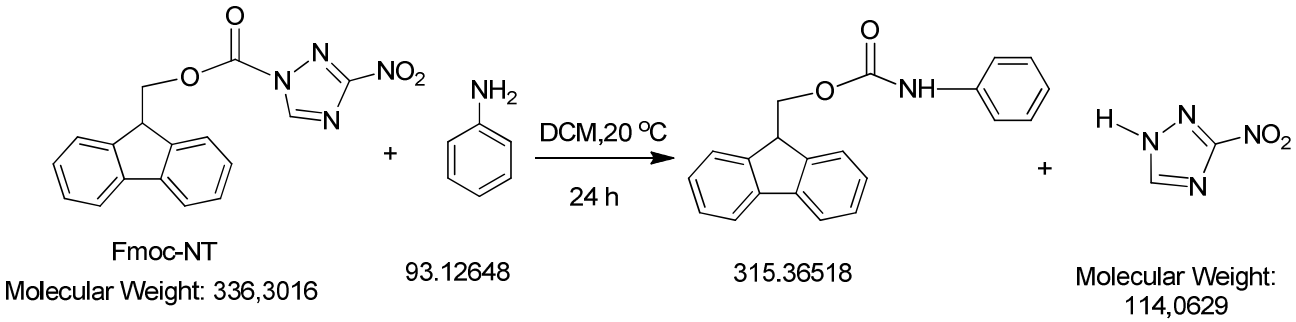
E-Factor (E) = (16.14 g of waste produced / 1.125 g of crude product) = 14.34

Mass Intensity = (18. 92 g of raw material used / 1.125 g of crude product) = 16.81

Considerations:

1. Calculation did not consider for solvent used for column chromatography.
2. Side product excluded from calculations

B) Calculation for the synthesis of *N*-(9-fluorenylmethoxycarbonyl)aniline in dichloromethane.[10]



Fmoc-NT
Molecular Weight: 336,3016

93.12648

315.36518

Molecular Weight: 114,0629

Raw Materials Used		Crude product and Waste	
Aniline	1 g	Crude product	2.14 g
Fmoc-NT	7.72 g	Side product	0.77 g
DCM	45.11 g (60 mL)	Aqueous waste	1097 g
5 % $NaHCO_3$	1097 g	Organic solvent waste	31.95 g
DCM	274.43 g (365 mL)		
Total	1425.26 g	Total	1131.86 g

E-Factor (E) = (1128.95 g of waste produced / 2.14 g of crude product) = 527.54

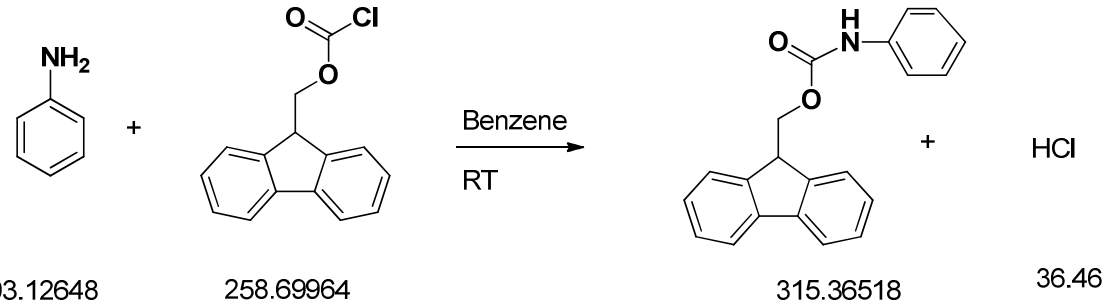
Mass Intensity = (1425.26 g of raw material used / 2.14 g of crude product) = 666.00

Considerations:

1. 90 % organic solvent recovered
2. Calculation did not consider for organic solvents use for column chromatography

   Side product excluded of products' waste

C) Calculation for the synthesis of *N*-(9-fluorenylmethoxycarbonyl)aniline in benzene.[8]



Raw Materials Used		Crude product and Waste	
Aniline	1 g	Crude product	3.18 g
Fmoc chloride	1.96 g	Organic waste	1.11 g
Benzene	10 mL (11.18 g)	Aqueous waste + HCl	0.49 g + 0.36 g
Water	0.49 g (0.49 mL)		
Total	14.63 g	Total	5.14 g

E-Factor (E) = (1.6 g of waste produced / 3.18 g of crude product) = 0.50

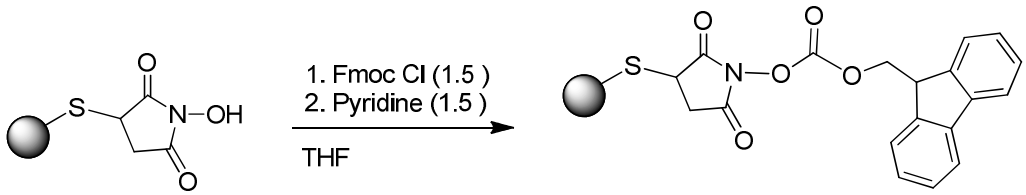
Mass Intensity = (14.63 g of raw material used / 3.18 g of crude product) = 4.60

Consideration:

1. Calculation did not consider solvent for crystallization
2. 90 % solvent recovered

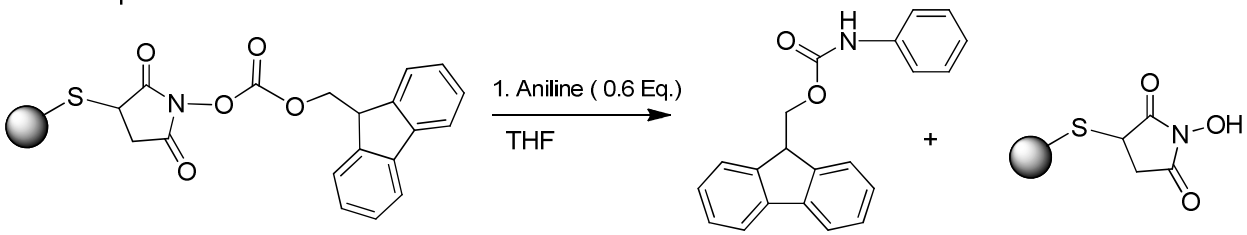
D) Calculation for the synthesis of *N*-(9-fluorenylmethoxycarbonyl)aniline.[2]

Step I



1 2

Step II



2 90 %

Raw Materials Used		Crude product and Waste	
Aniline	1 g	Crude product	2.83 g
Compound **2**	22.40 g	Organic waste	40.2 g
THF	402.69 g (358 mL)	Resin-NHS recovered	21.75 gm
Total	426.09 g	Total	g

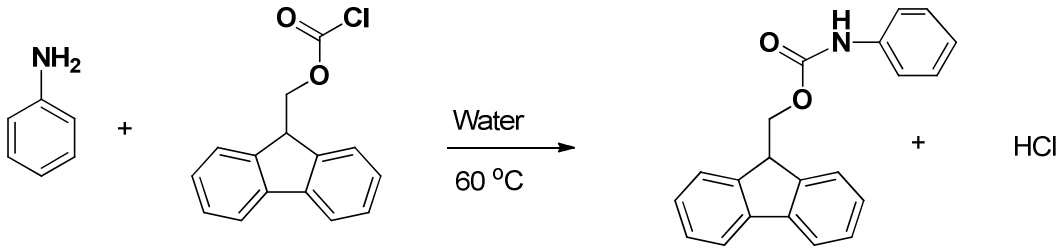
E-Factor (E) = (40.2 g of waste produced / 2.83 g of crude product) = 14.20

Mass Intensity = (426.09 g of raw material used / 2.83 g of crude product) = 150.56

Considerations:

1. 90 % solvent recovered
2. Reagents and solvent used for the preparation of compound 2 did not consider in calculations.
3. THF used for resin washing was not consider in calculations

E) Calculation for the synthesis of *N*-(9-fluorenylmethoxycarbonyl)aniline under catalyst-free conditions in aqueous media (the reported procedure)



90 %

Raw Materials Used		Crude product and Waste	
Aniline	1 g	Crude product	3.04 g
Fmoc chloride	3.33 g	Aqueous waste + HCl	15.36 g
Water	15 mL (15 g)		
Total	19.33 g	Total	18.40 g

E-Factor (E) = (15.36 g of waste produced / 3.04 g of crude product) = 5.05

Mass Intensity = (19.33 g of raw material used / 3.04 g of crude product) = 6.35

Considerations:

1. Calculation did not consider for ethanol used in crystallization

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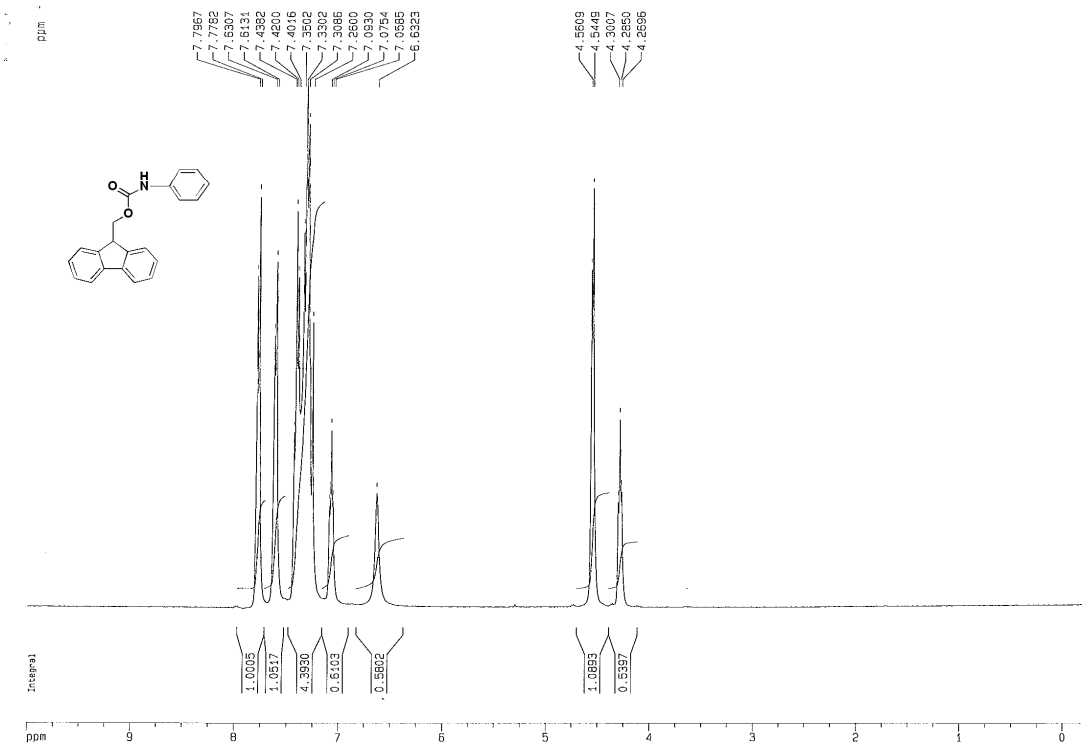
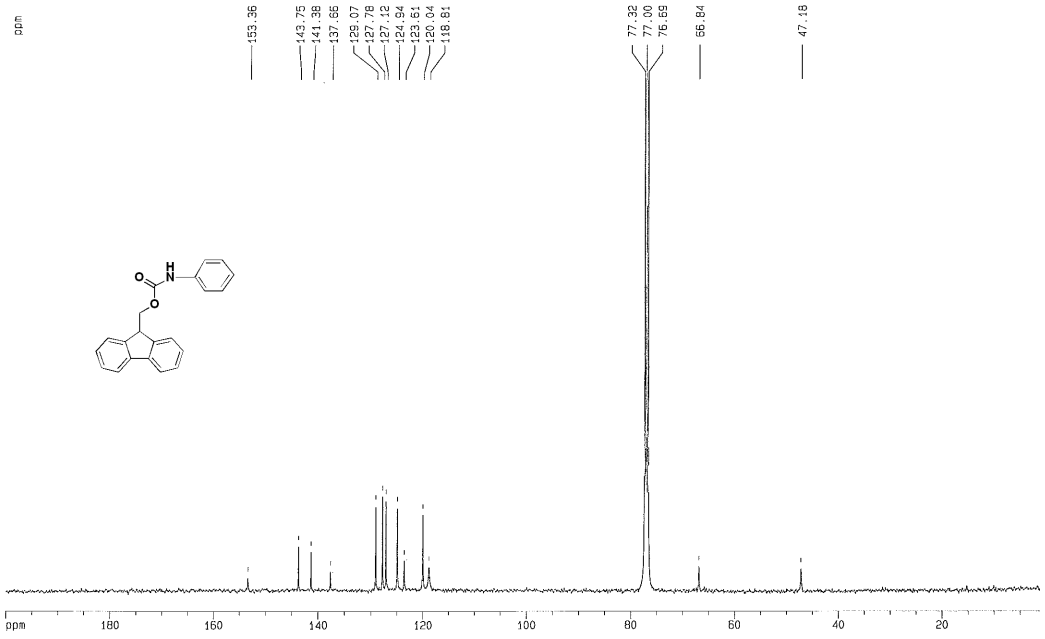
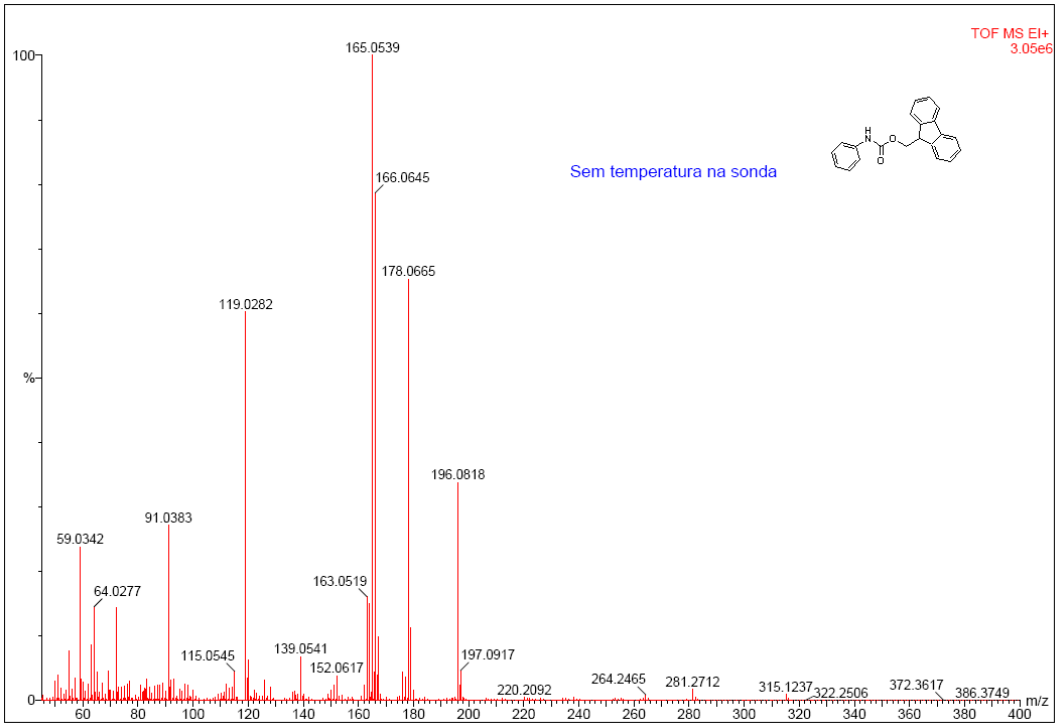
IR, ^{1}H, ^{13}C and MS spectra of compounds



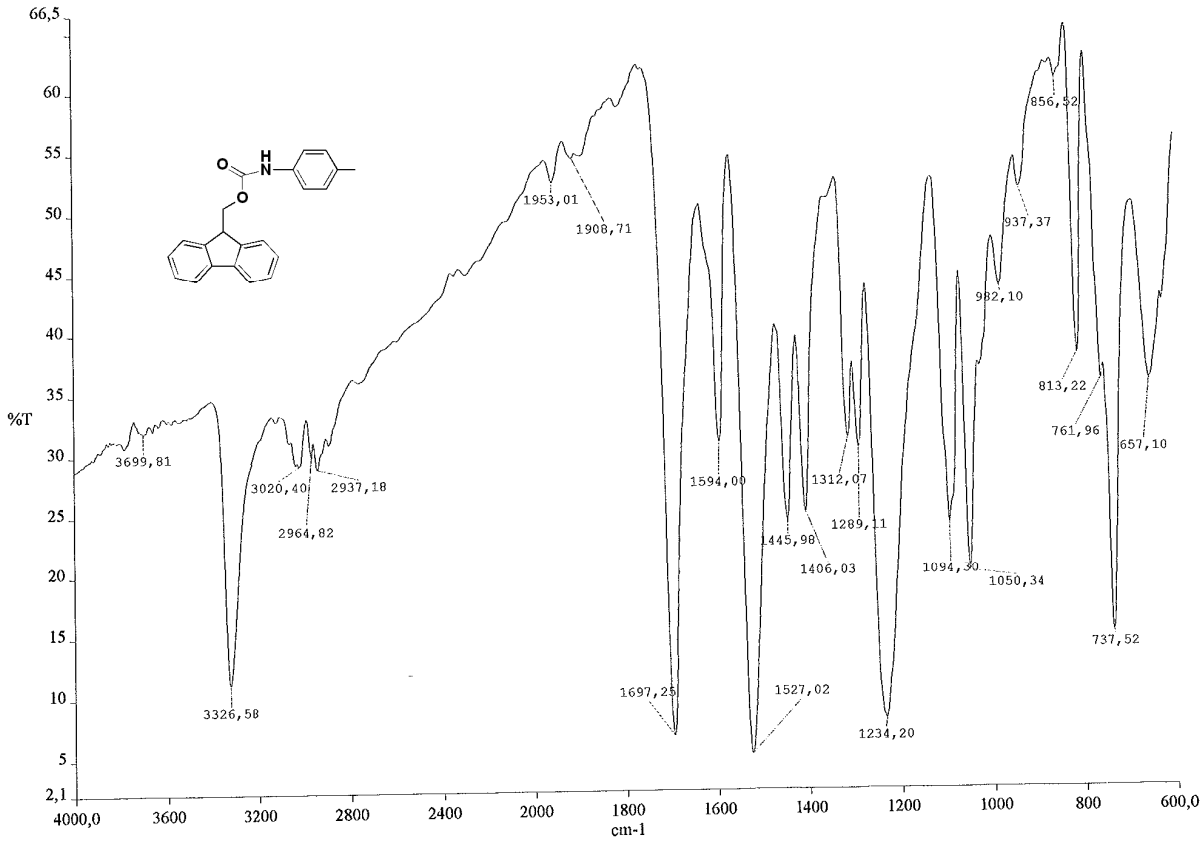
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)aniline (**3a**).



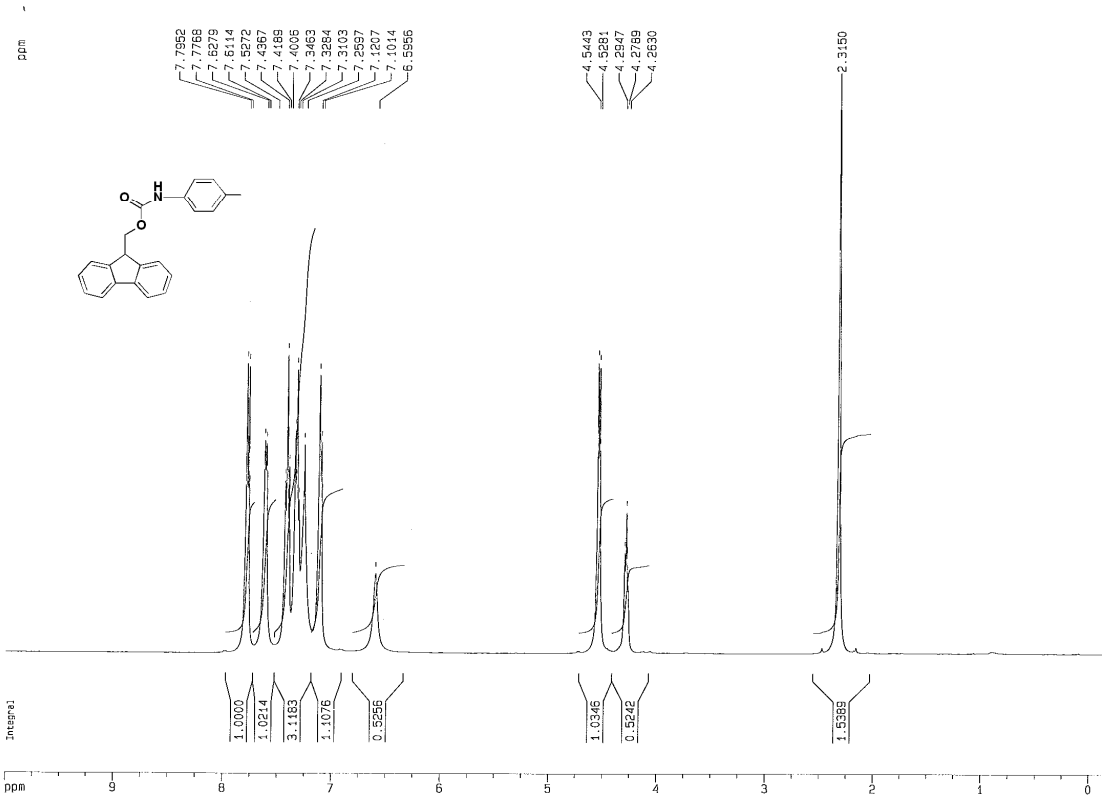
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)aniline (**3a**).



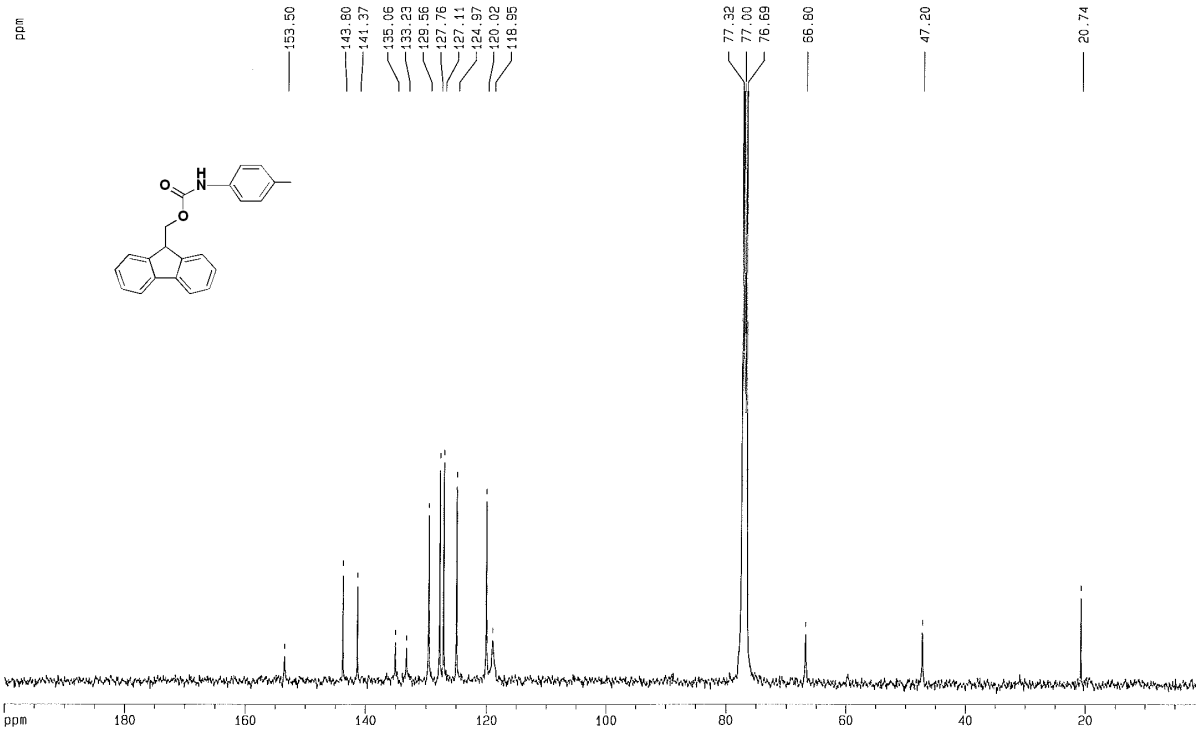
Electron impact mass spectra of *N*-(9-fluorenylmethoxycarbonyl)aniline (**3a**).



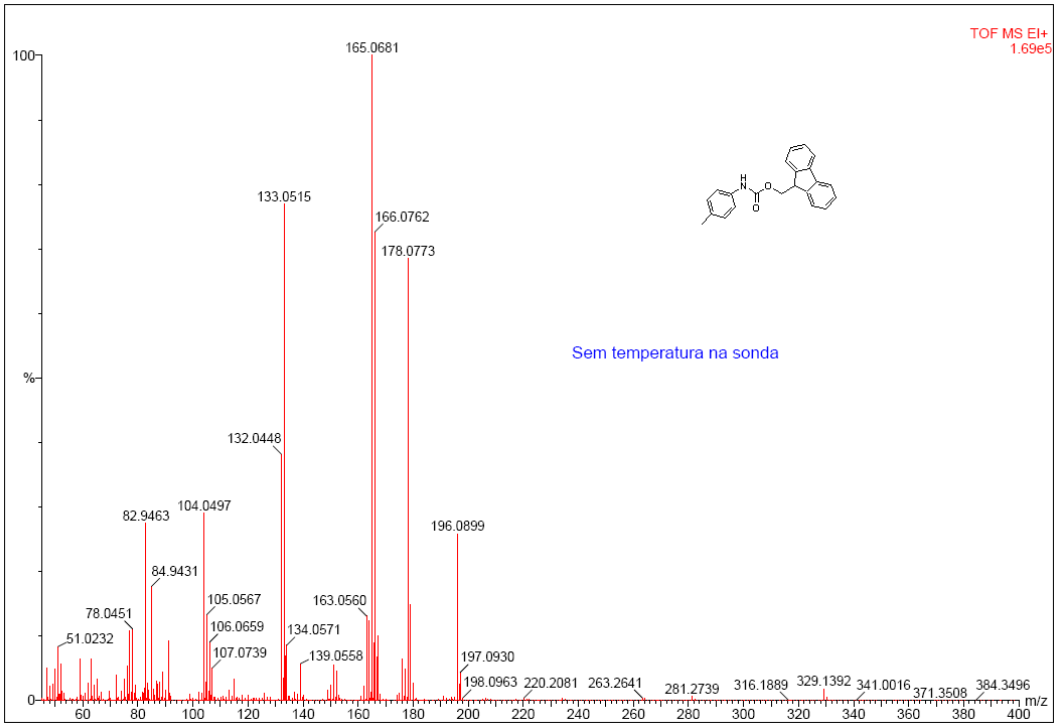
Infrared spectra of of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylaniline (**3b**).



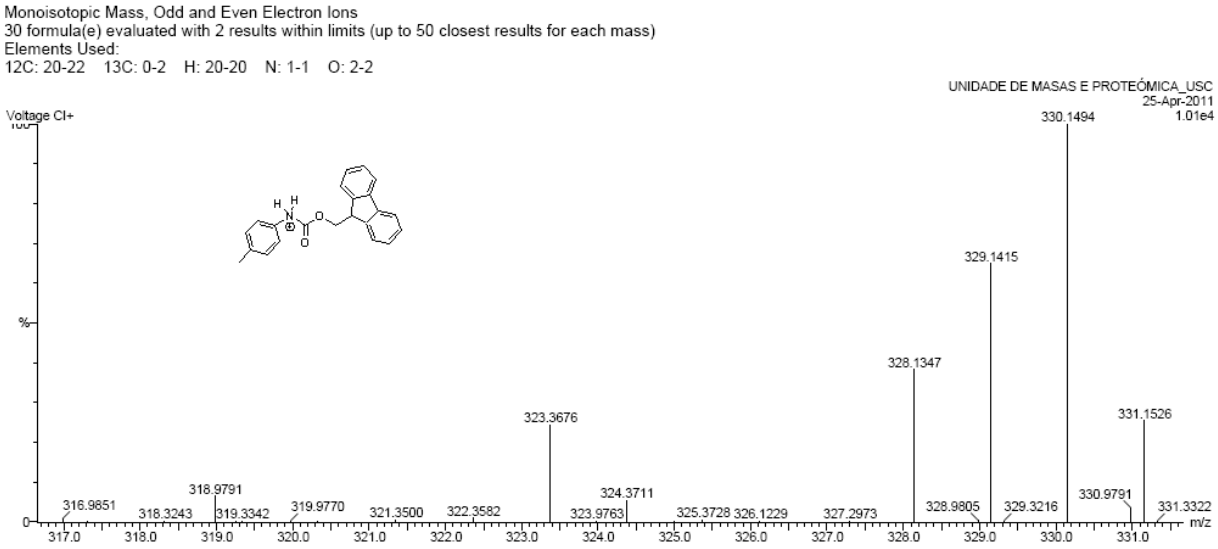
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylaniline (**3b**).



Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylaniline (**3b**).

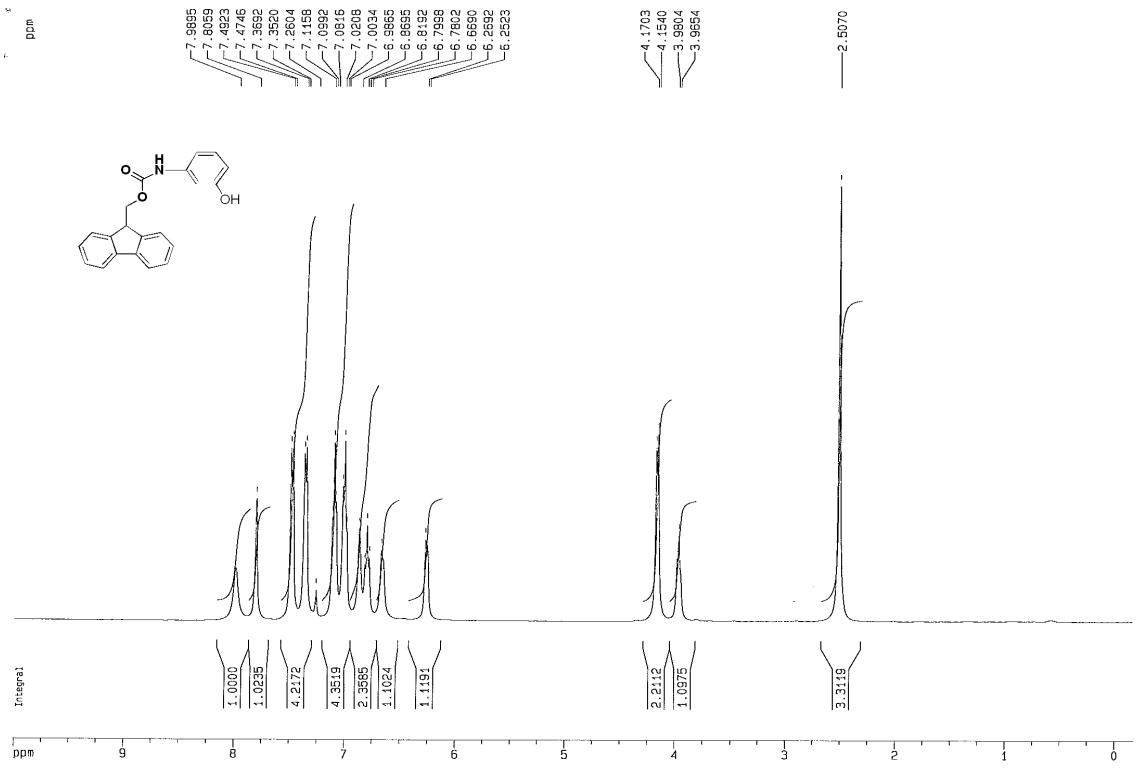


Electron impact mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylaniline (**3b**).

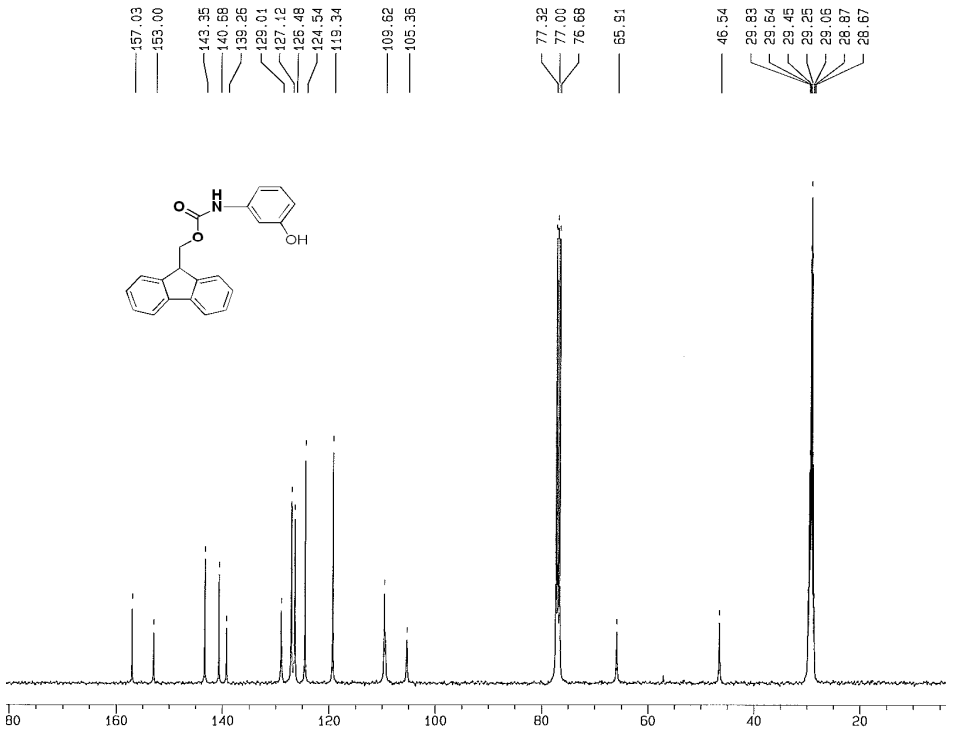


Minimum:	0.20				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
330.1494	100.00	330.1494	0.0	0.0	13.5	2778718.0	12C22 H20 N O2
331.1526	25.37	331.1528	-0.2	-0.6	13.5	5547274.0	12C21 13C H20 N O2

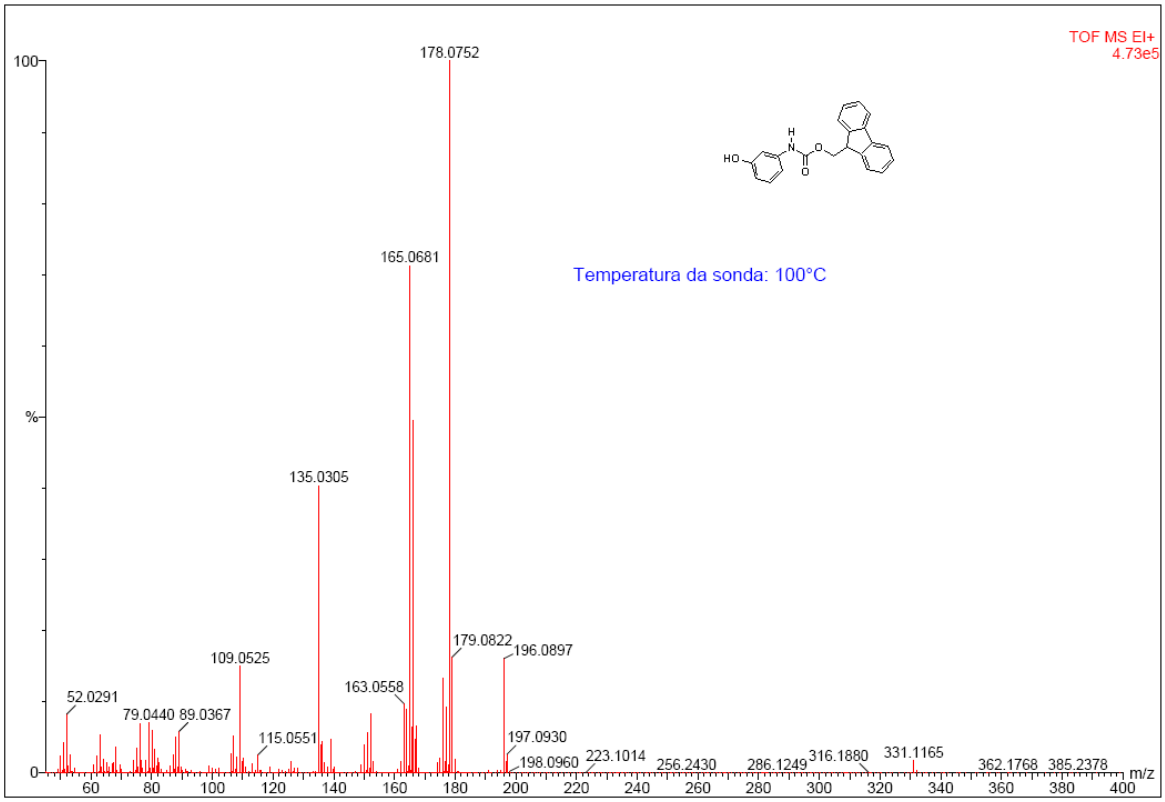
High resolution chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylaniline (**3b**).



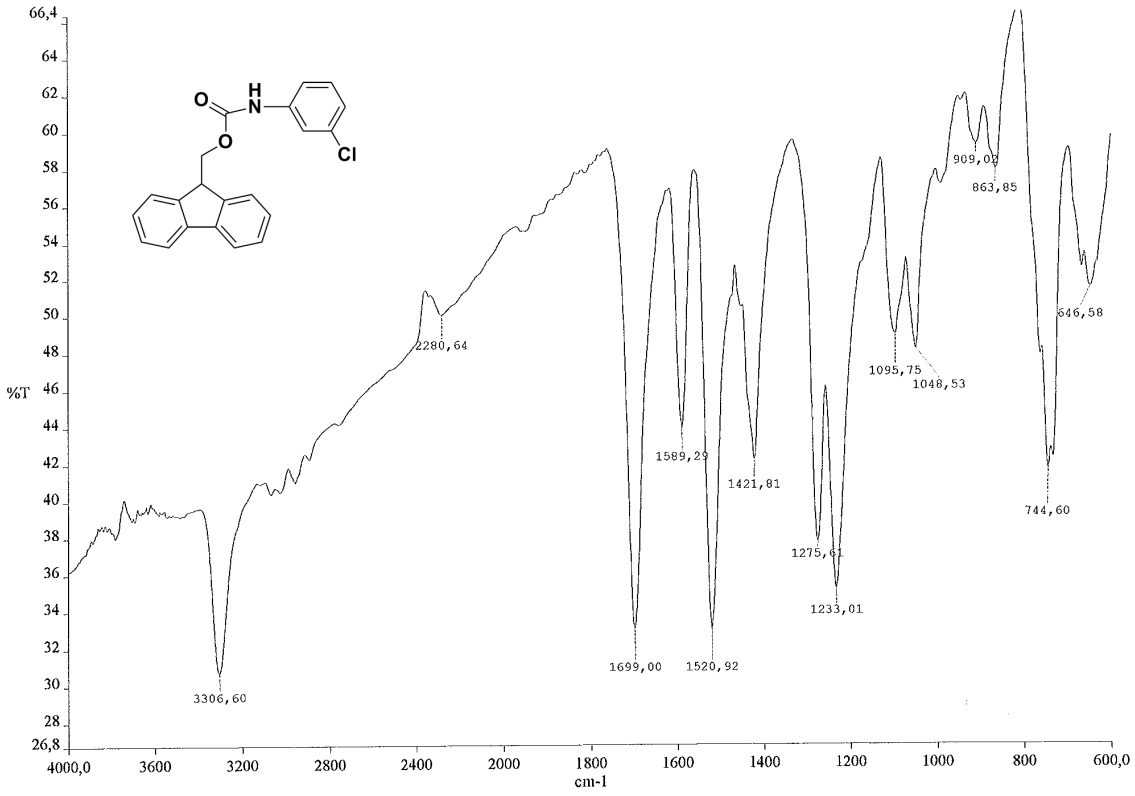
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-hydroxyaniline (**3c**).



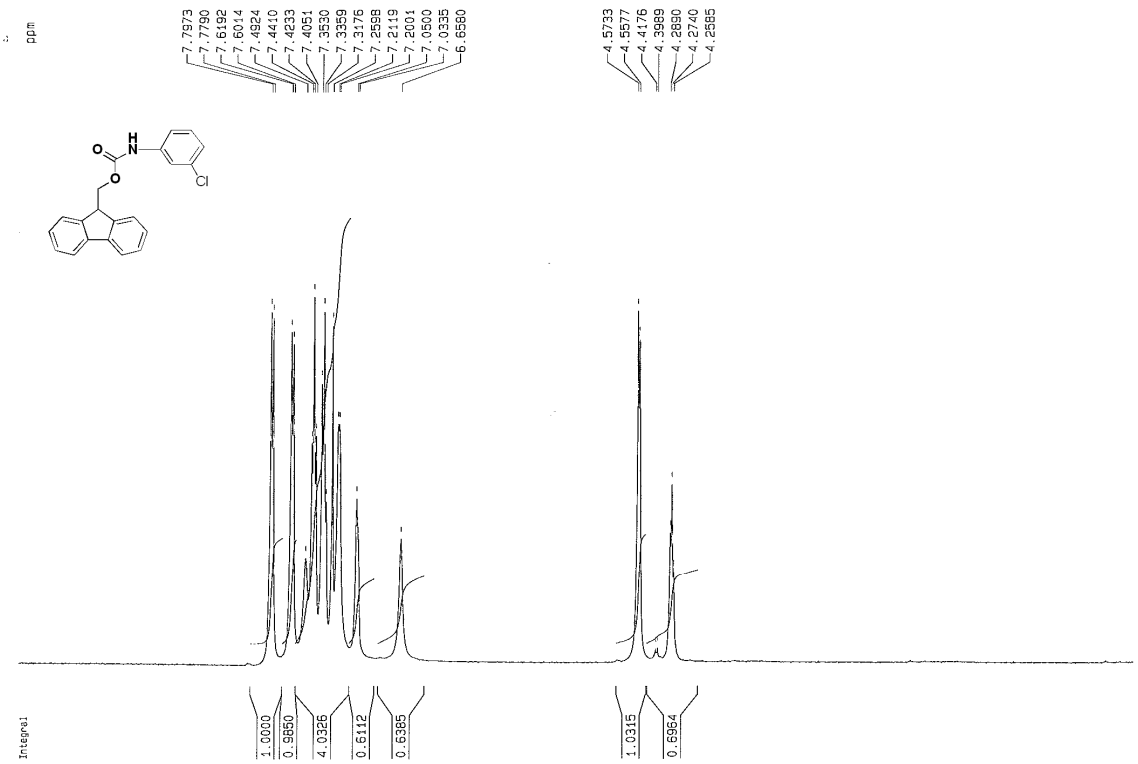
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-hydroxyaniline (**3c**).



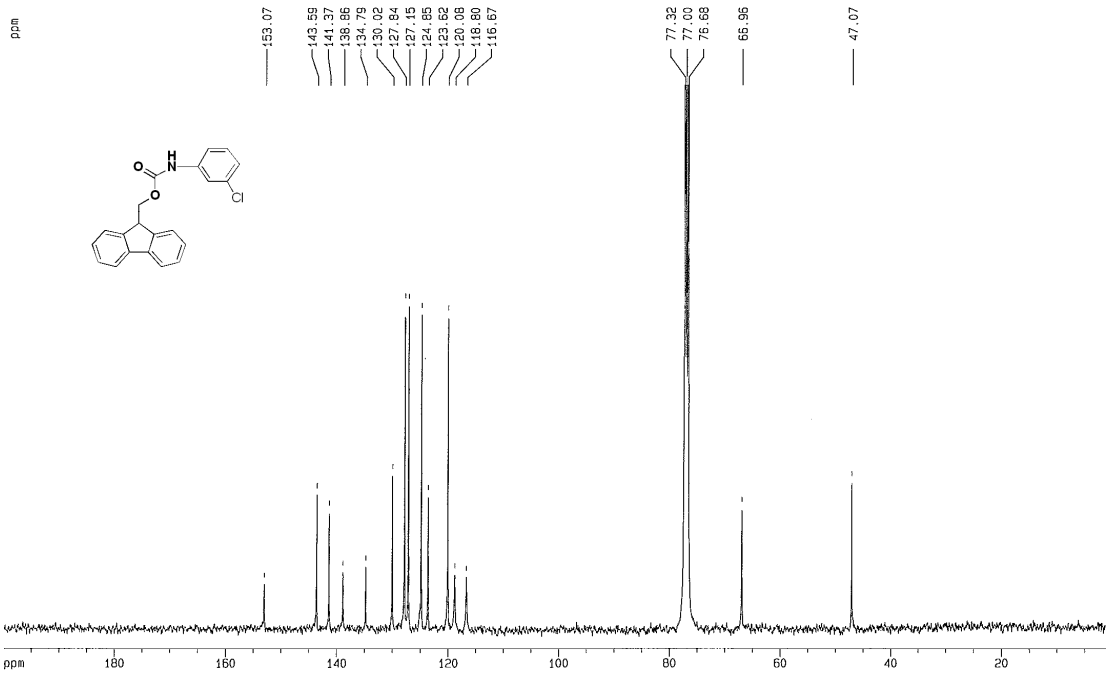
Electron impact mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-hydroxyaniline (**3c**).



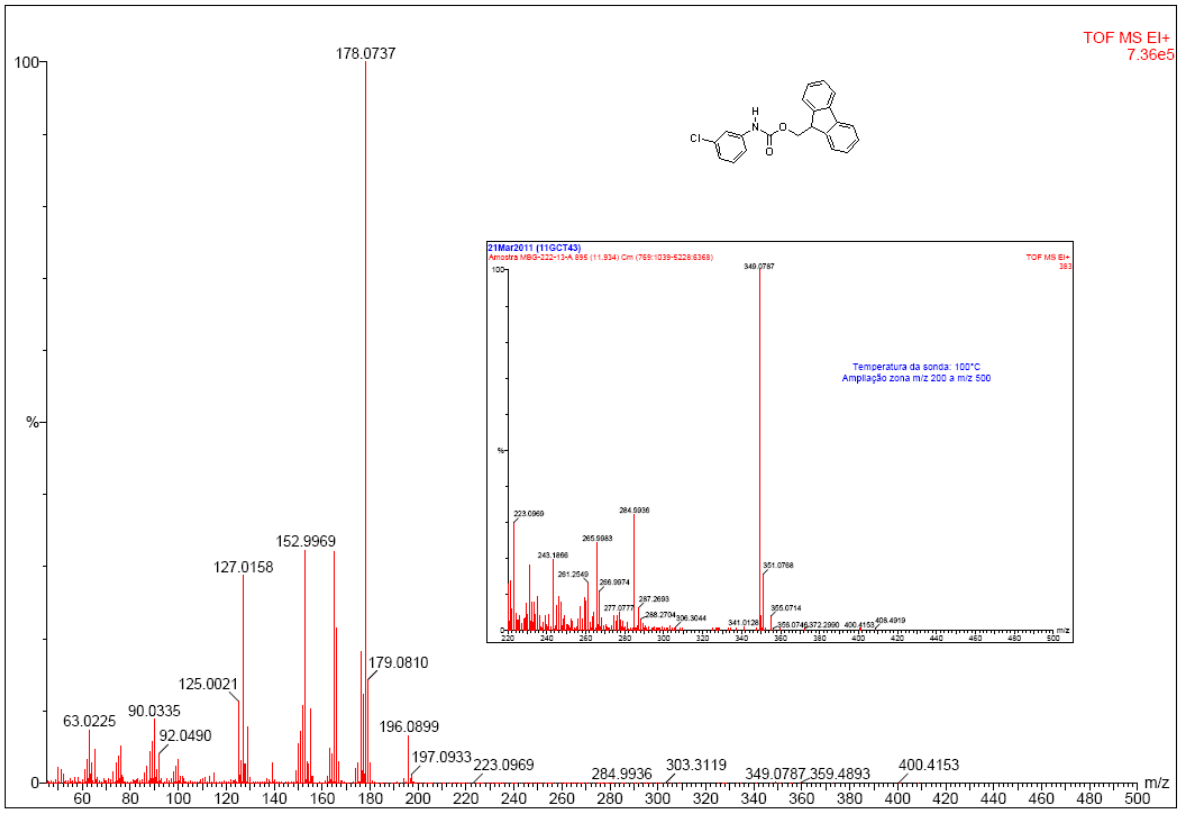
IR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-chloroaniline (**3d**).



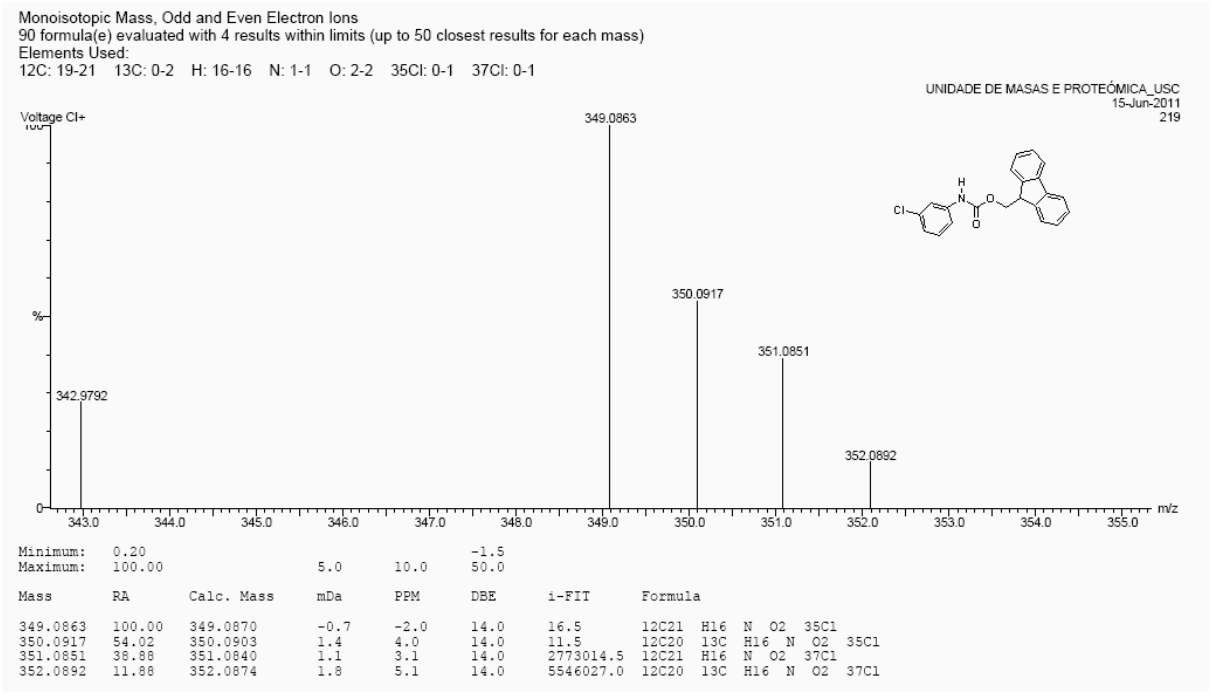
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-chloroaniline (**3d**).



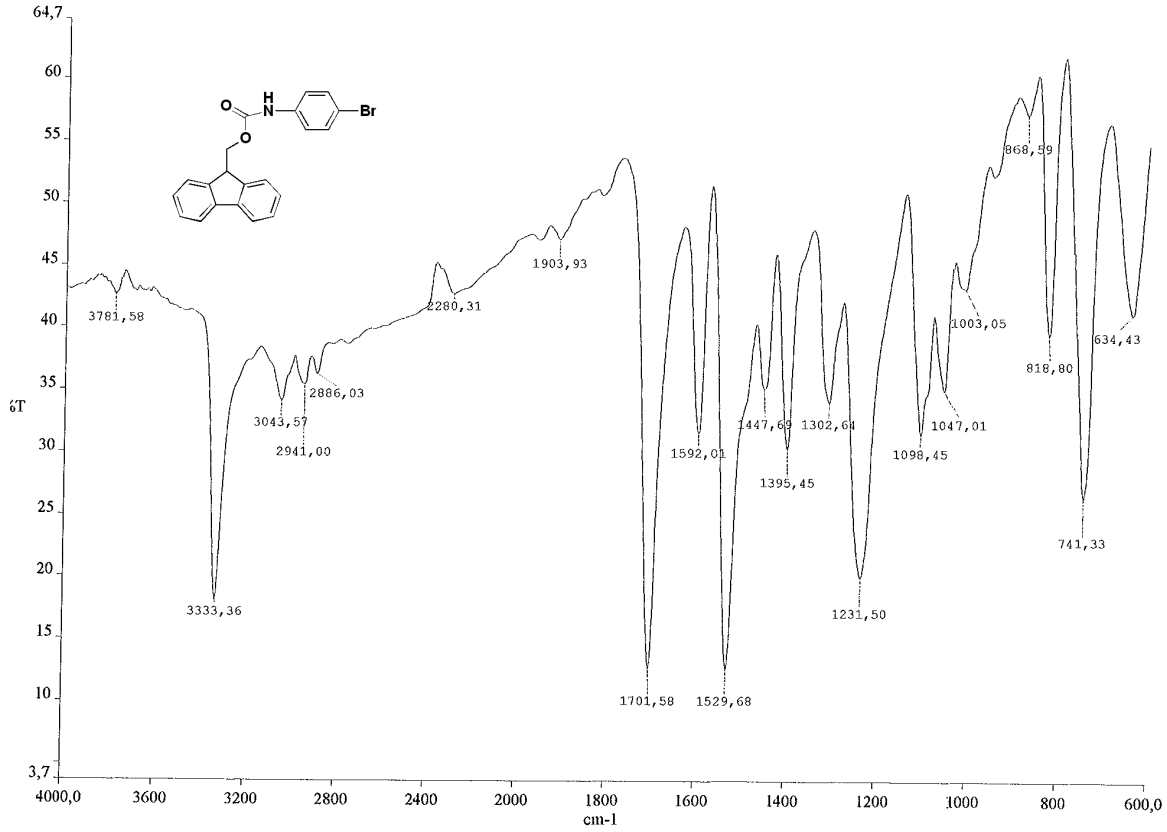
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-chloroaniline (**3d**).



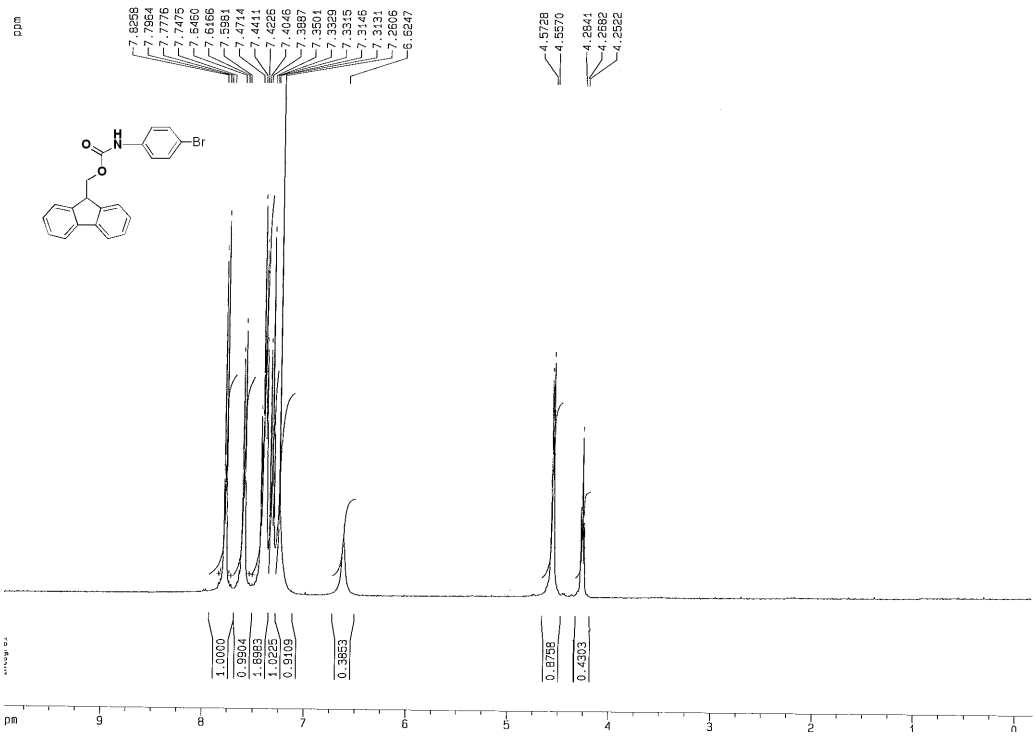
Electron impact mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-chloroaniline (**3d**).



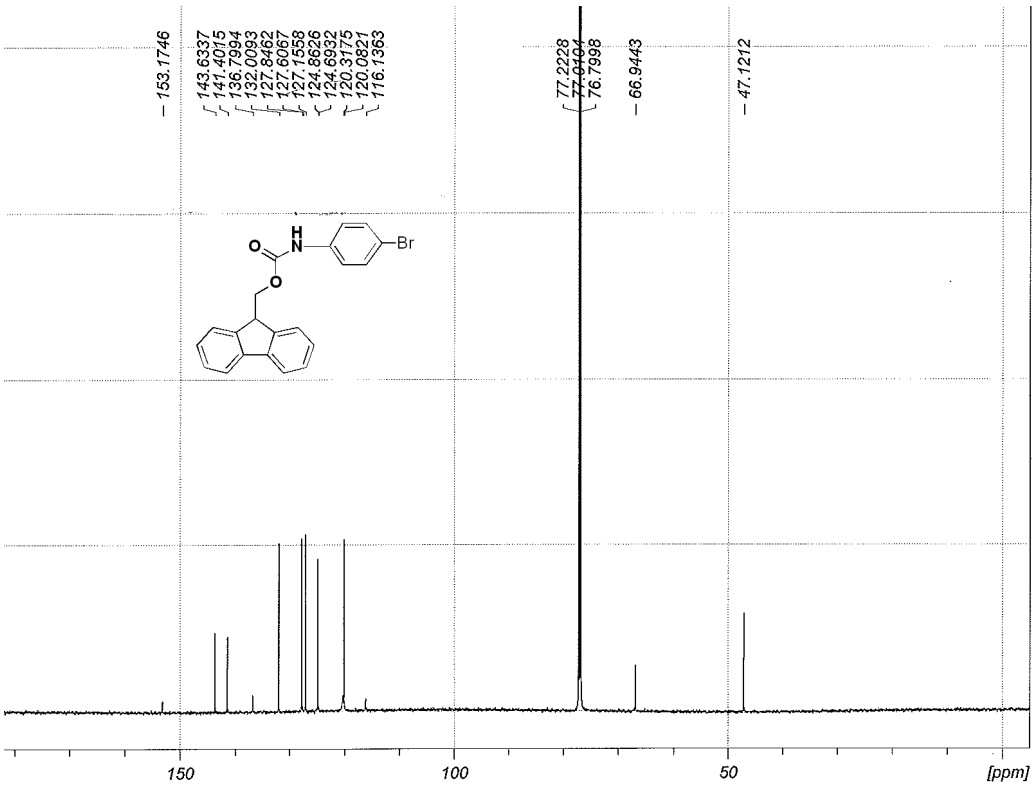
High resolution chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-3-chloroaniline (**3d**).



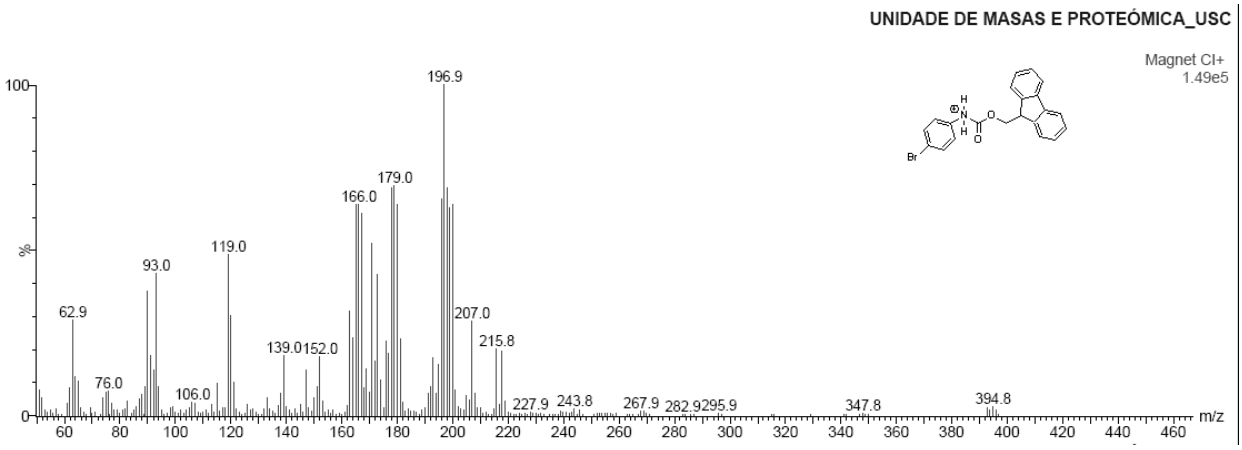
Infrared spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-bromoaniline (**3e**).



Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-bromoaniline (**3e**).

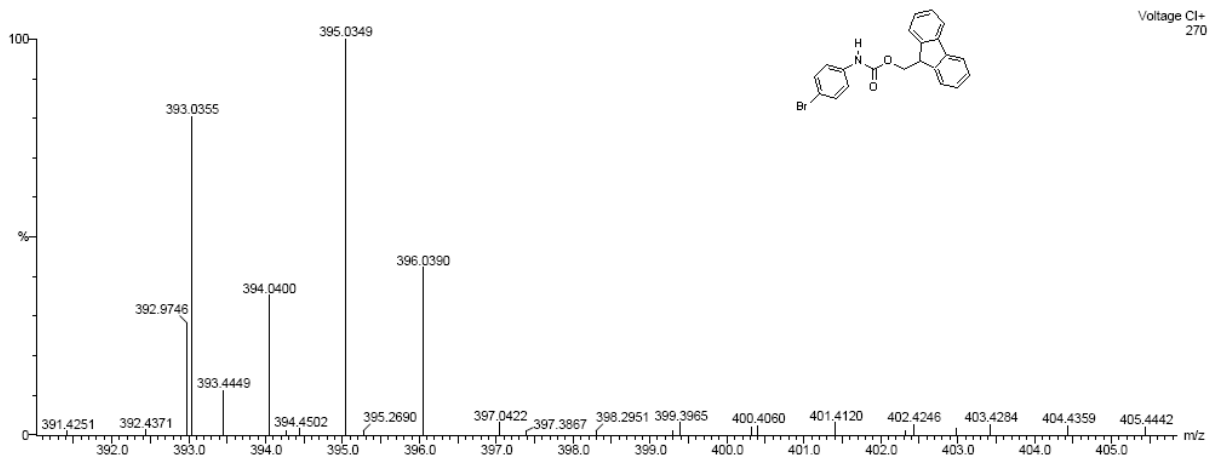


Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-bromoaniline (**3e**).



Electron impact mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-bromoaniline (**3e**).

Monoisotopic Mass, Odd and Even Electron Ions
442 formula(e) evaluated with 5 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
12C: 19-21 13C: 0-2 H: 16-16 N: 1-1 O: 2-2 79Br: 0-1 81Br: 0-1



Minimum:	0.30				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
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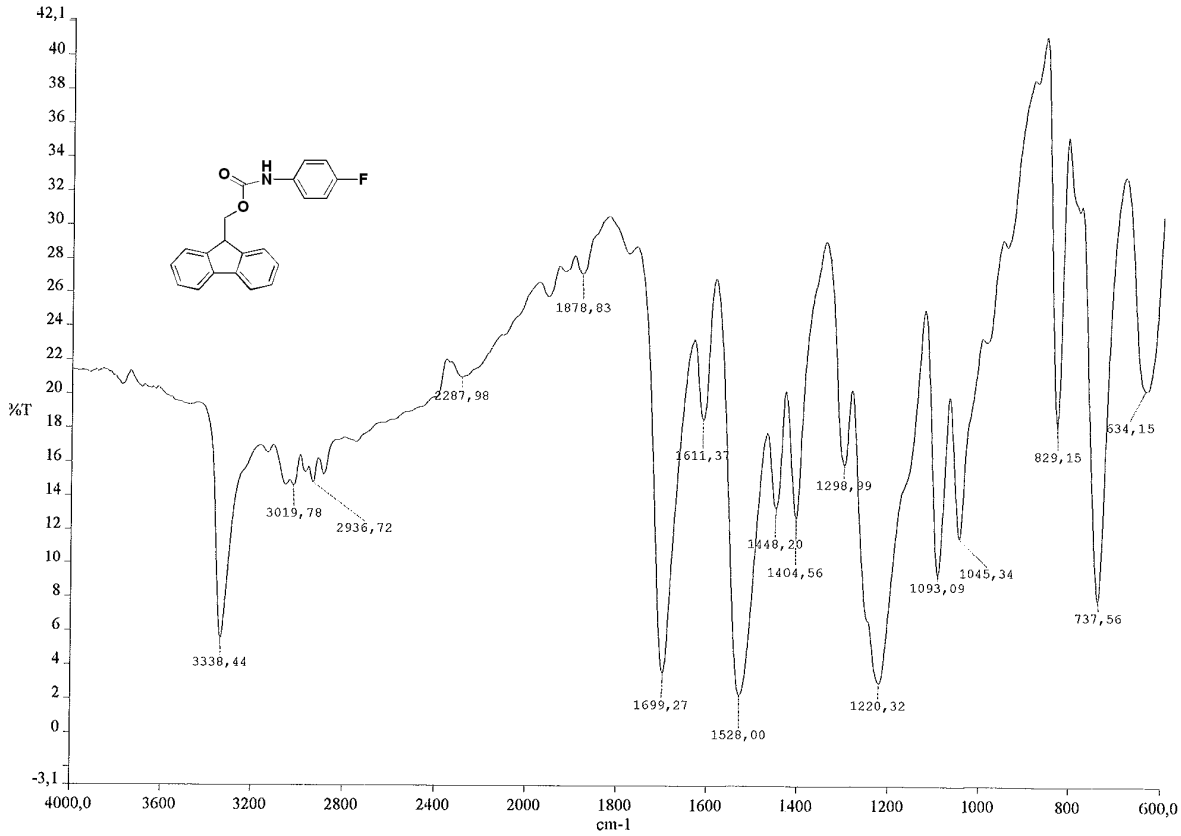
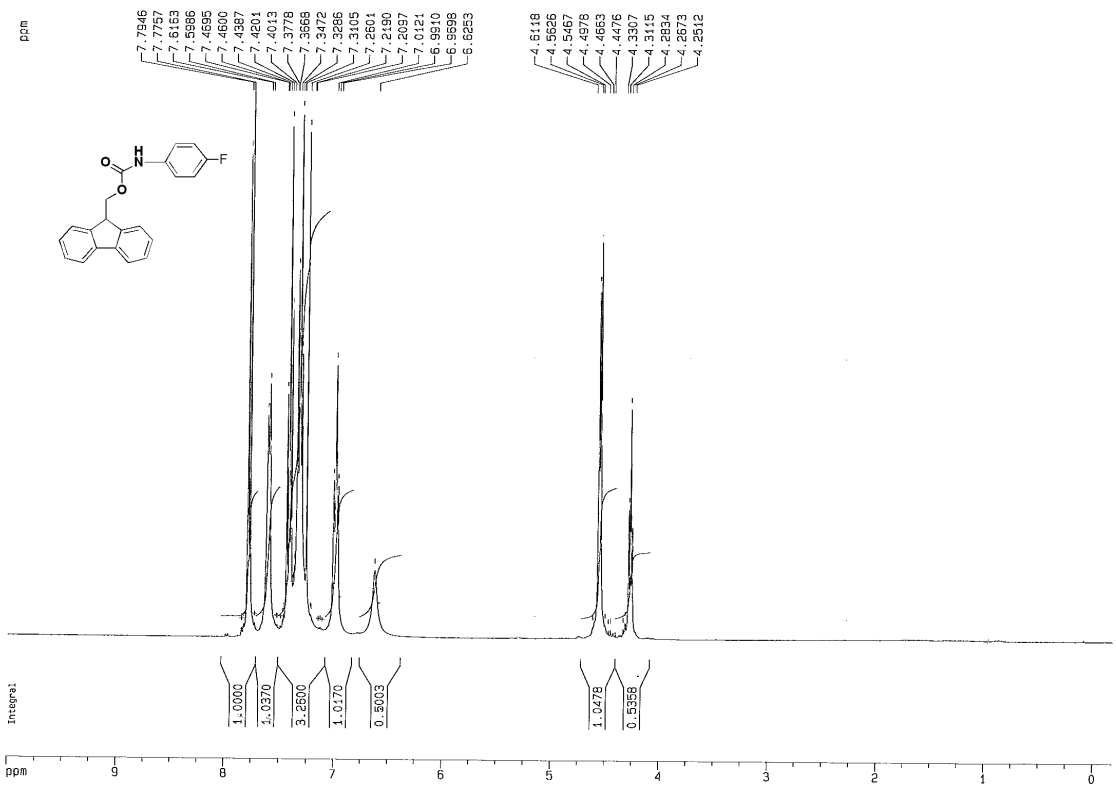
394.0400	35.19	394.0398	0.2	0.5	14.0	12.6	12C20 13C H16 N O2 79Br
395.0349	100.00	395.0344	0.5	1.3	14.0	9.9	12C21 H16 N O2 81Br
396.0390	42.22	396.0377	1.3	3.2	14.0	2773015.0	12C20 13C H16 N O2 81Br

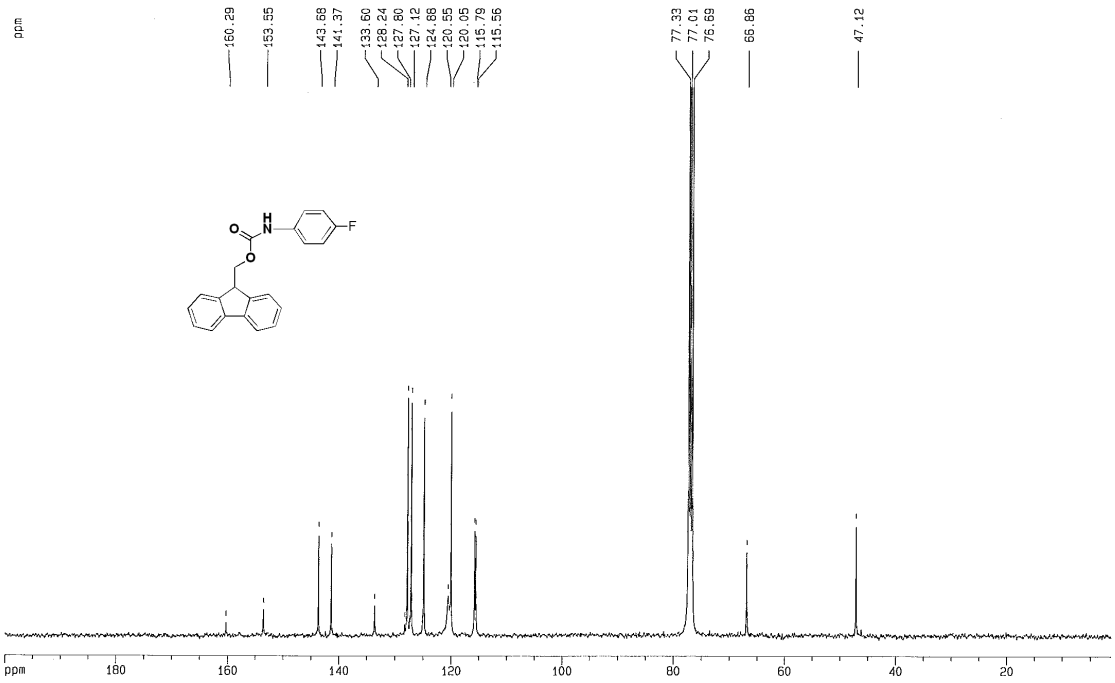
High resolution chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-bromoaniline (**3e**).



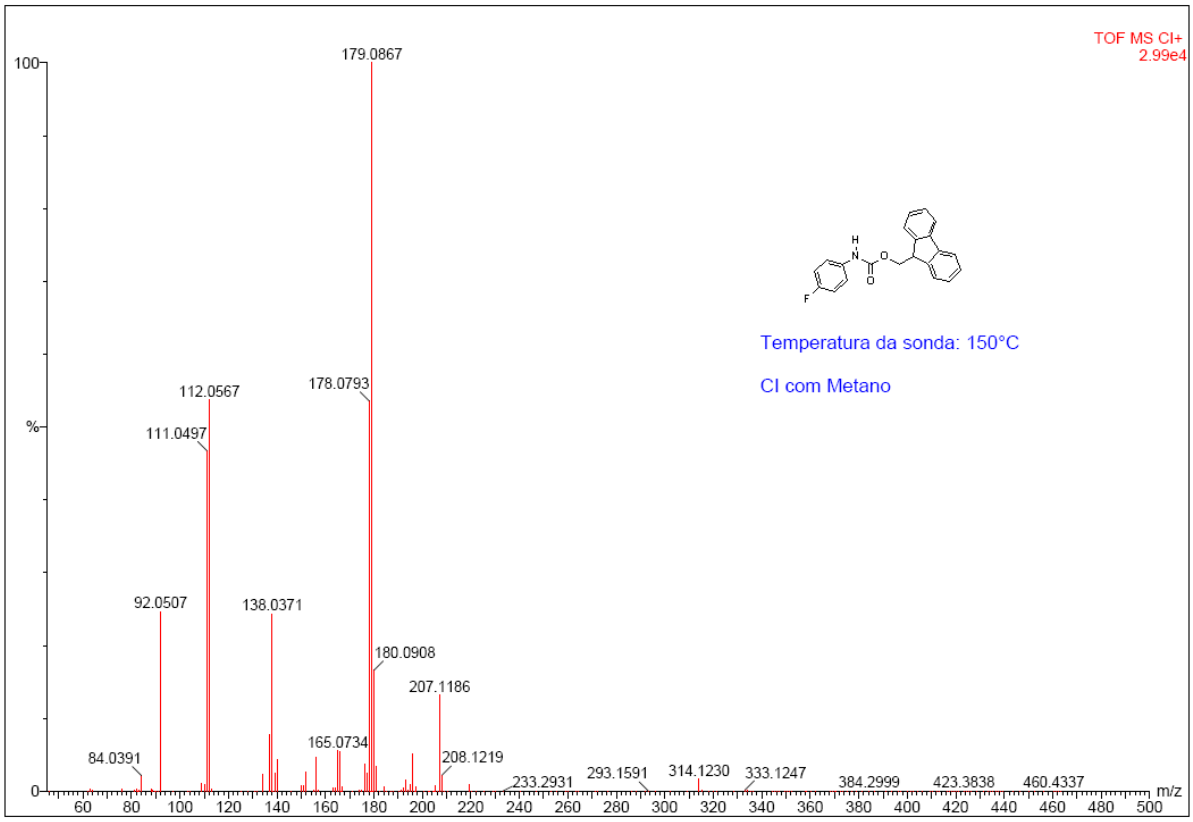
Infrared spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-fluoraniline (**3f**).



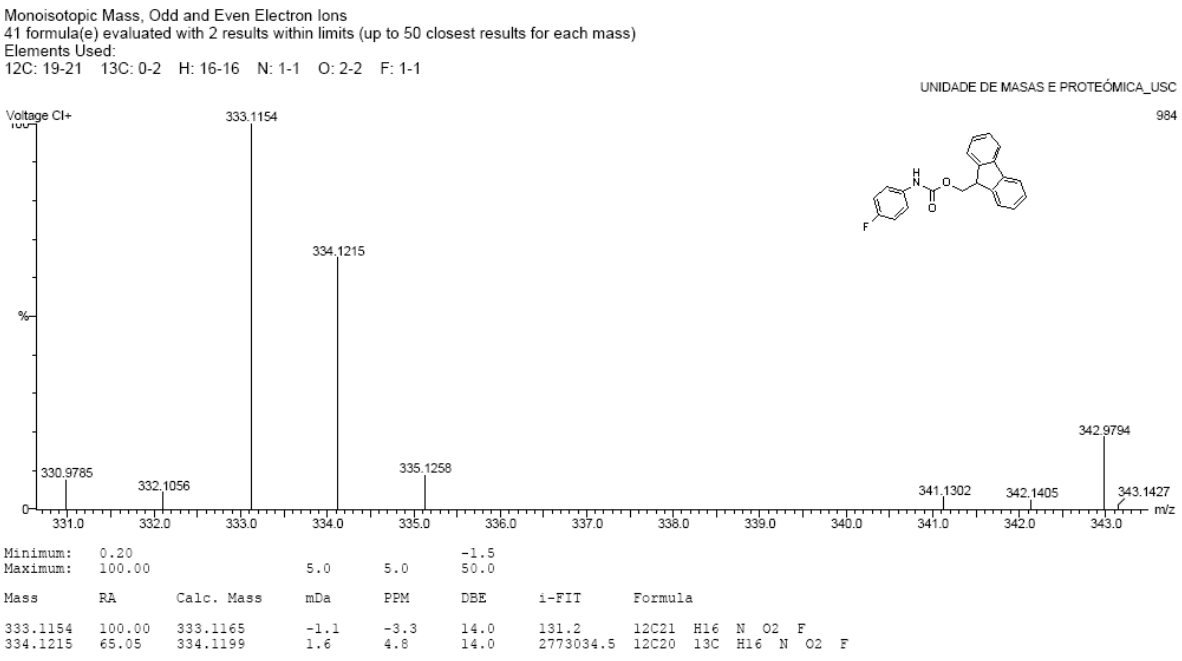
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-fluoraniline (**3f**).



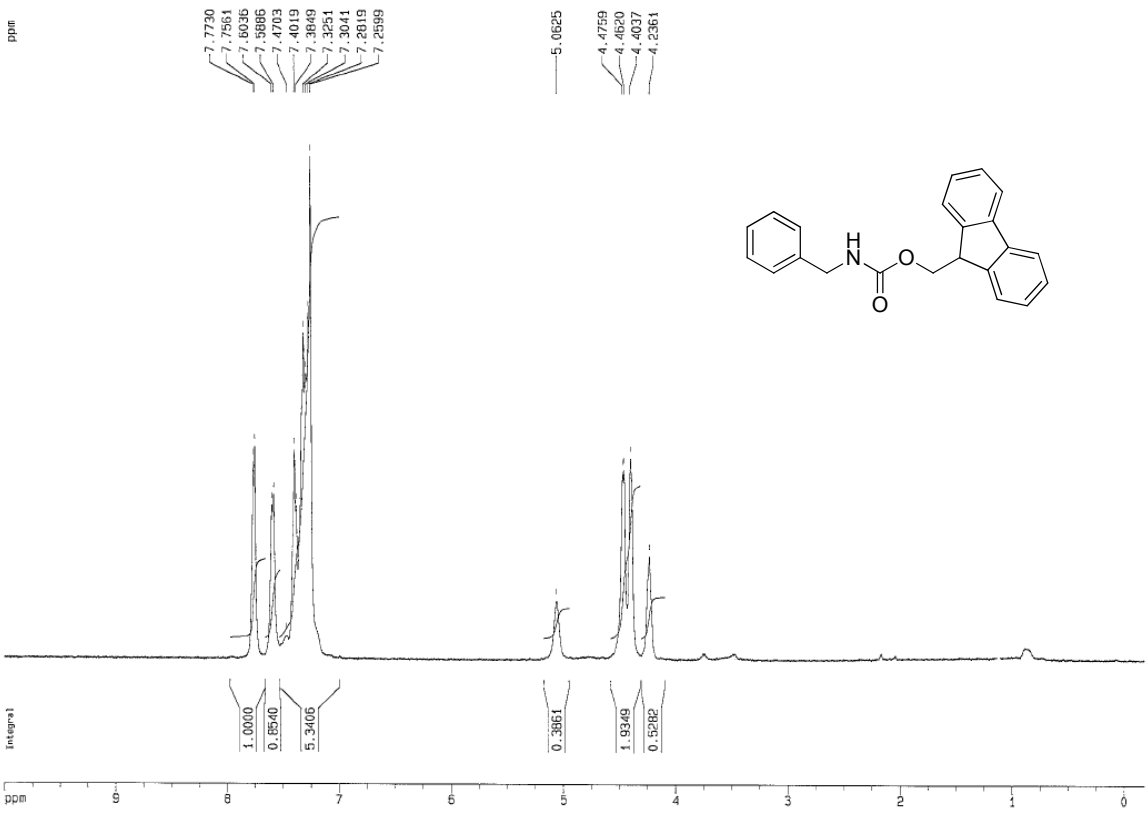
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-fluoraniline (**3f**).



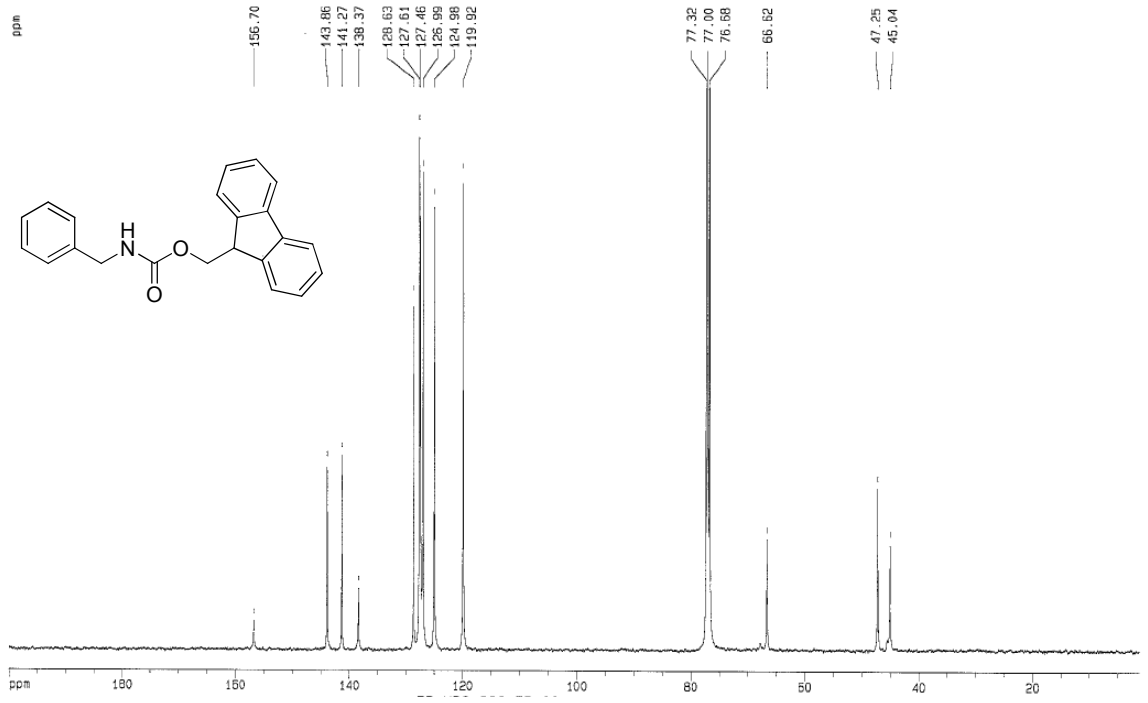
Chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-fluoraniline (**3f**).



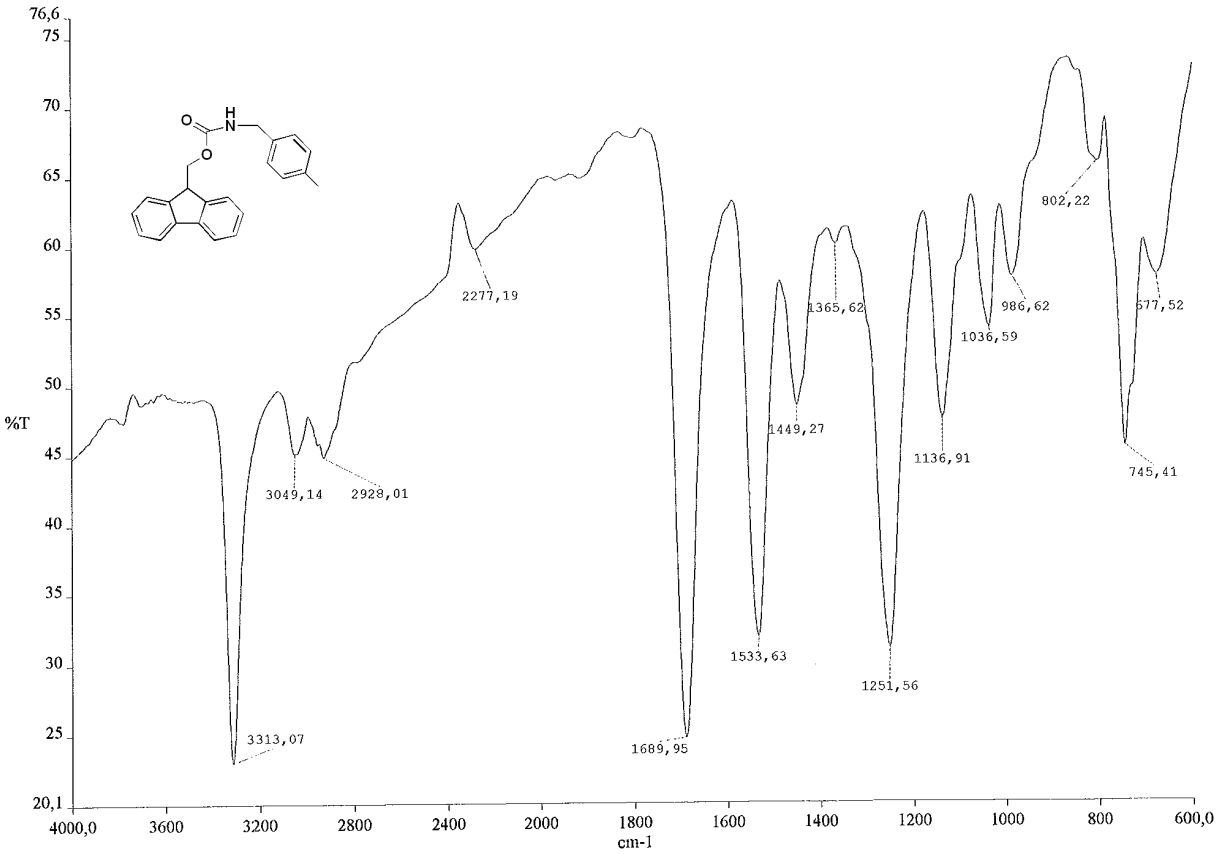
High resolution chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)- 4-fluoraniline (**3f**).



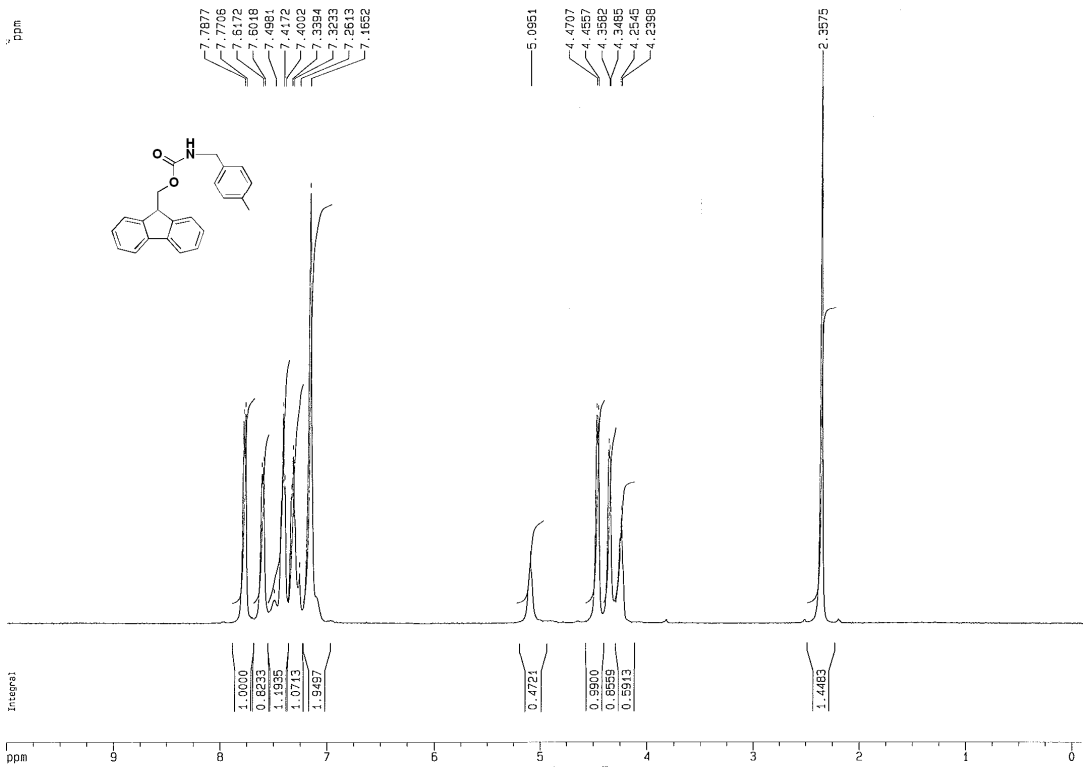
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)benzylamine (**3g**).



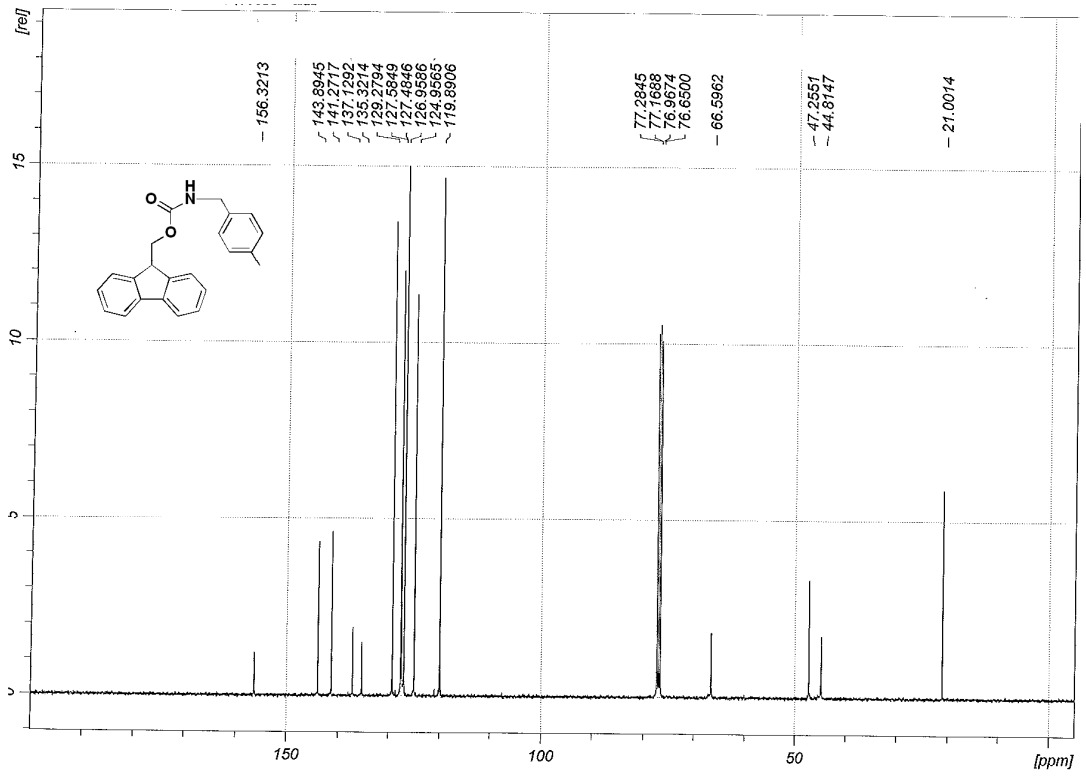
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)benzylamine (**3g**).



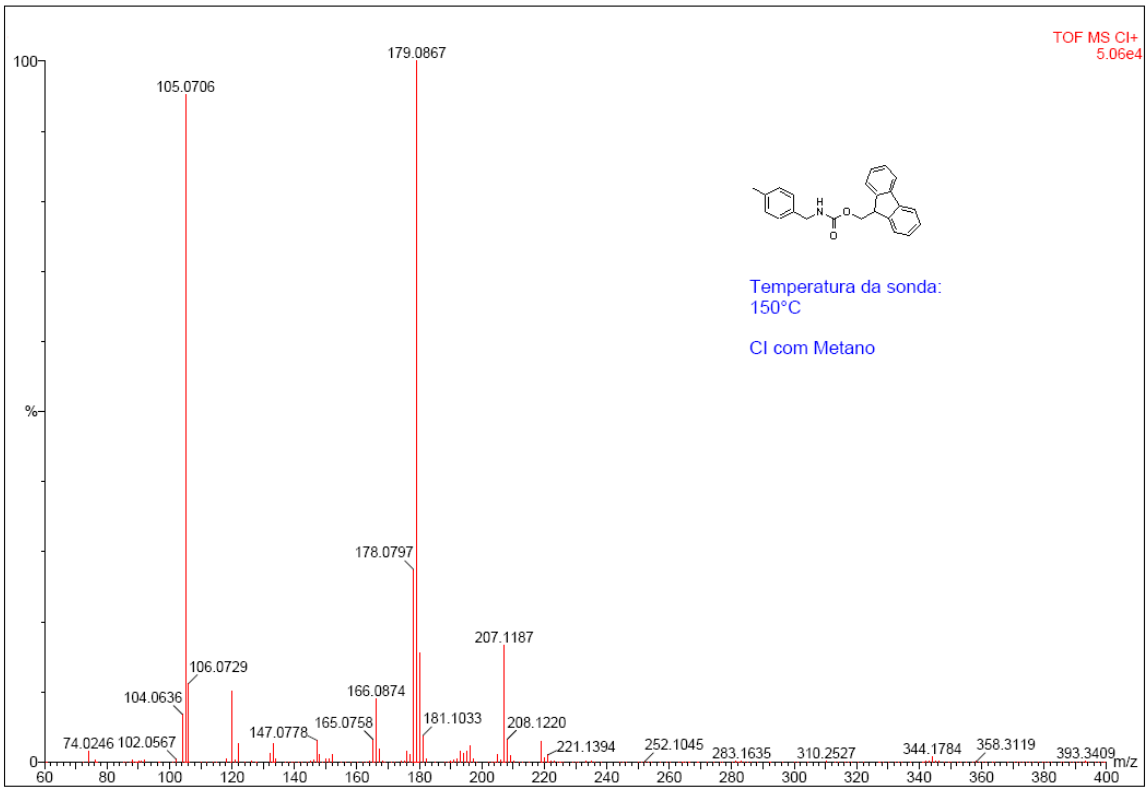
Infrared spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylbenzylamine (**3h**).



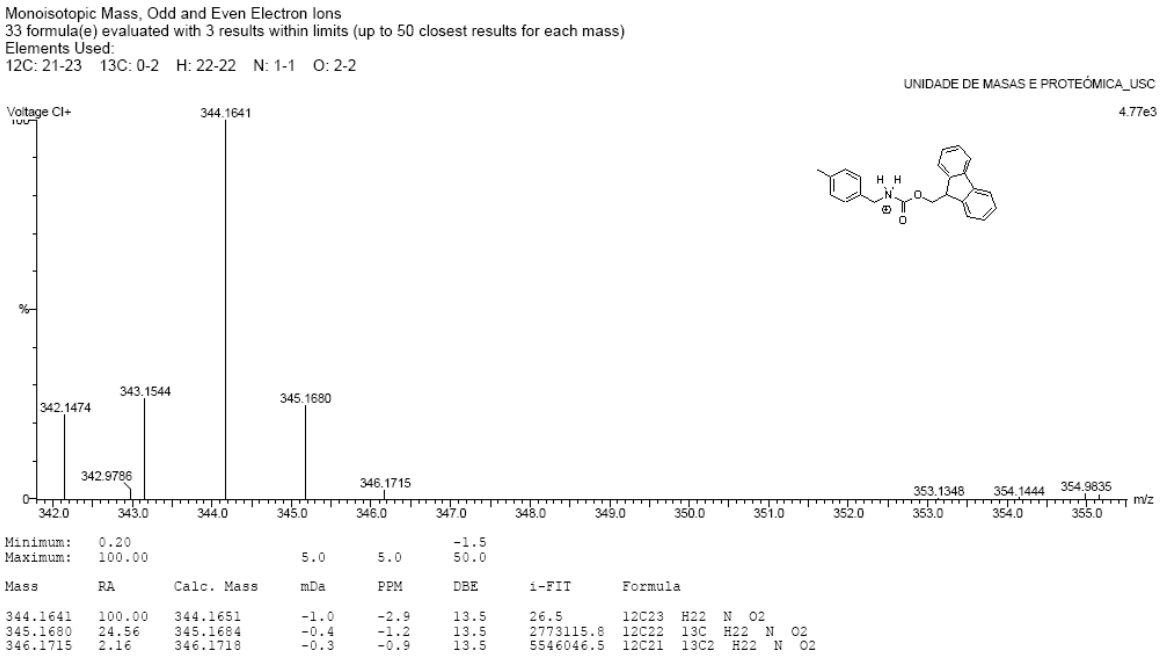
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylbenzylamine (**3h**).



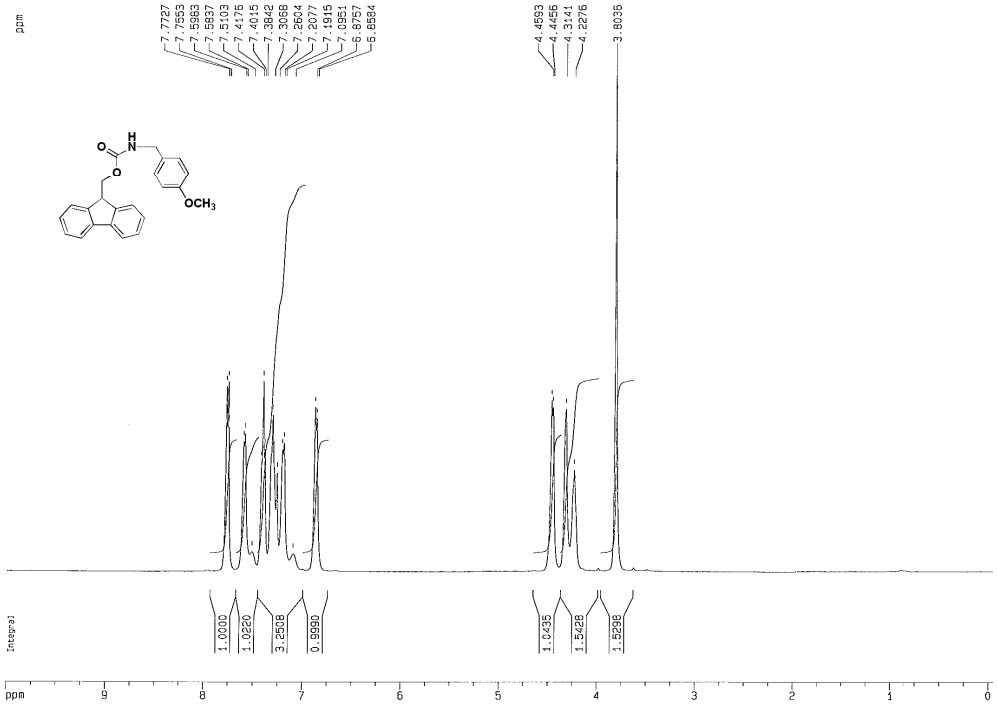
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylbenzylamine (**3h**).



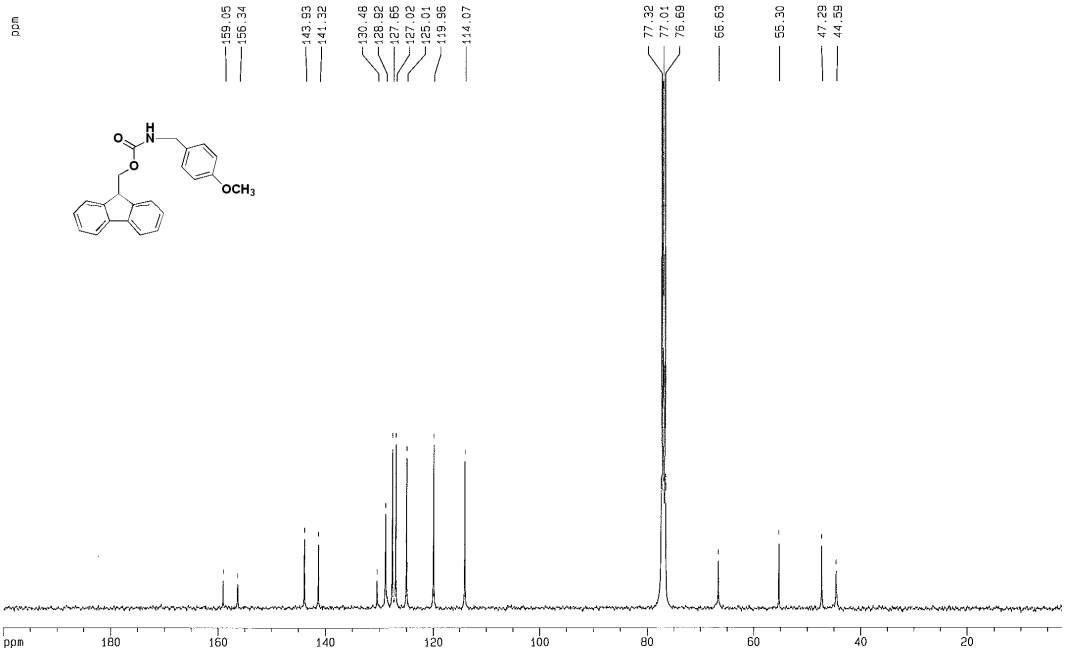
Chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylbenzylamine (**3h**).



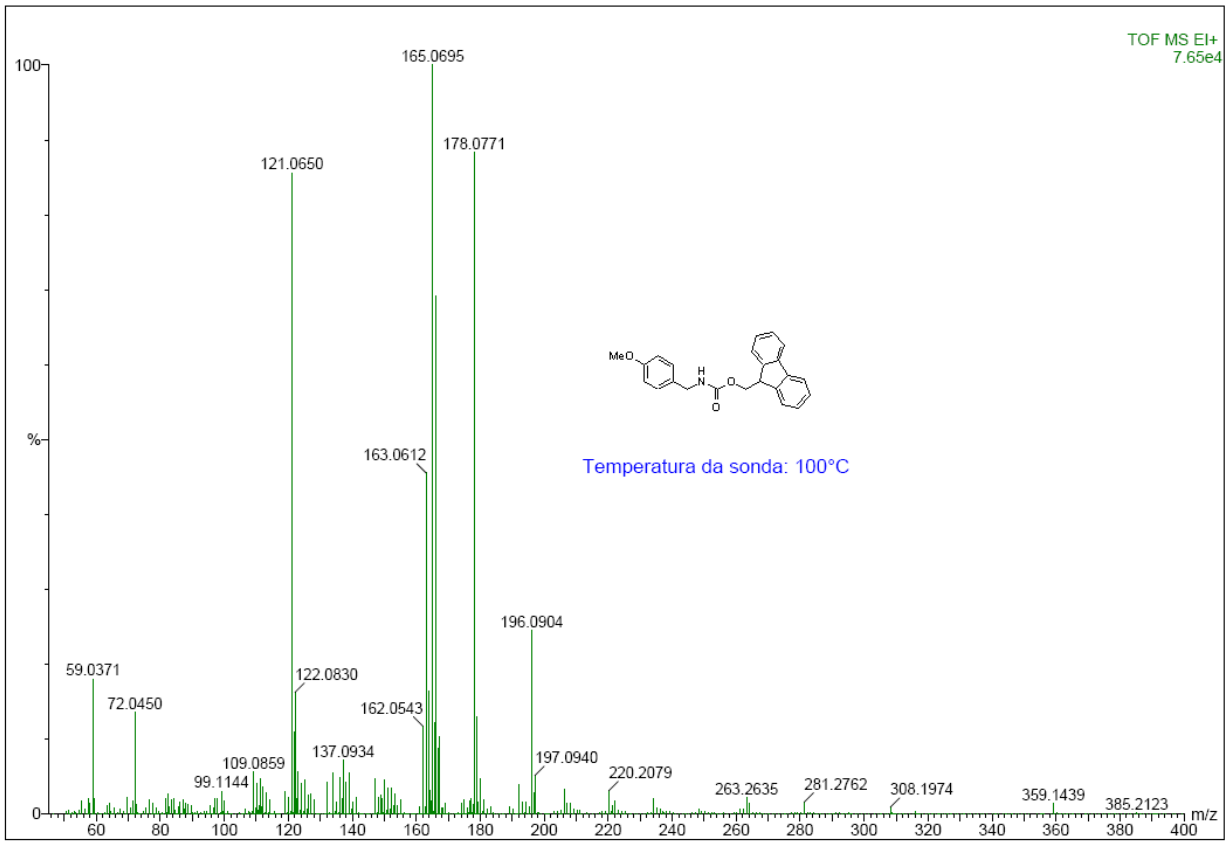
High resolution chemical ionization mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methylbenzylamine (**3h**).



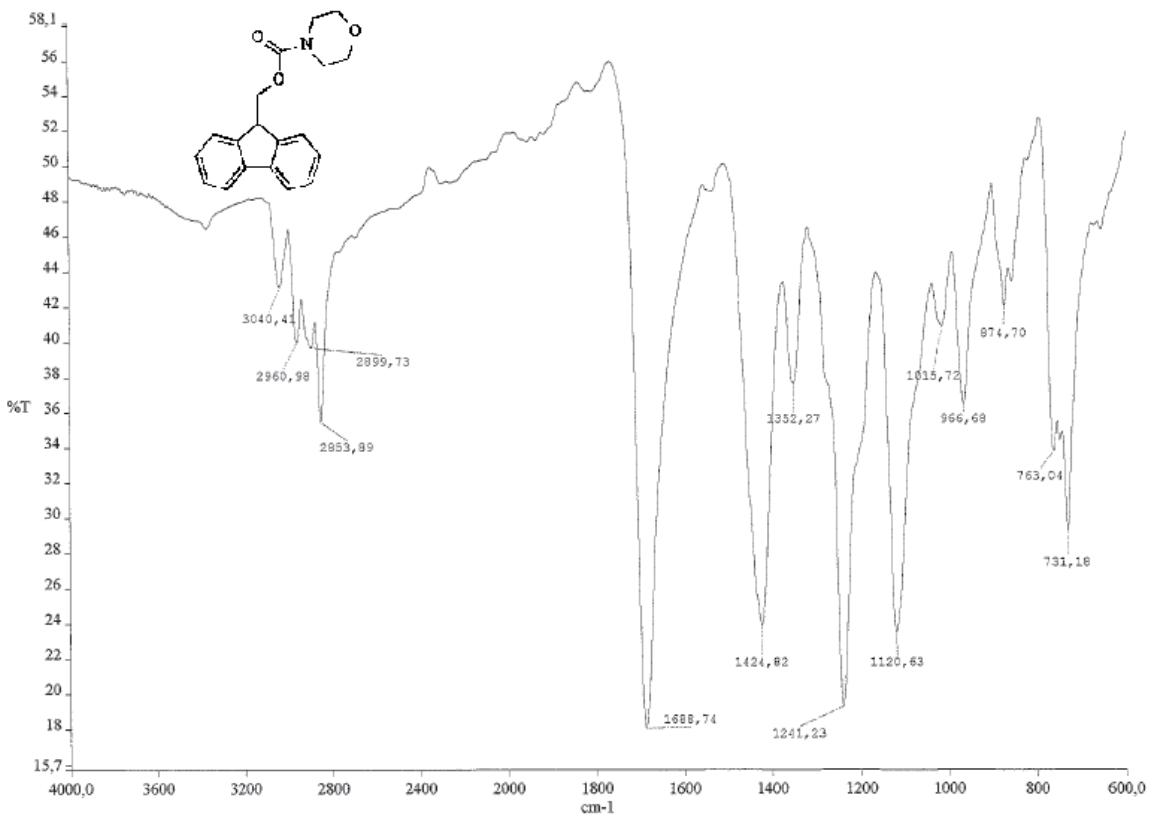
Proton NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methoxylbenzylamine (**3i**).



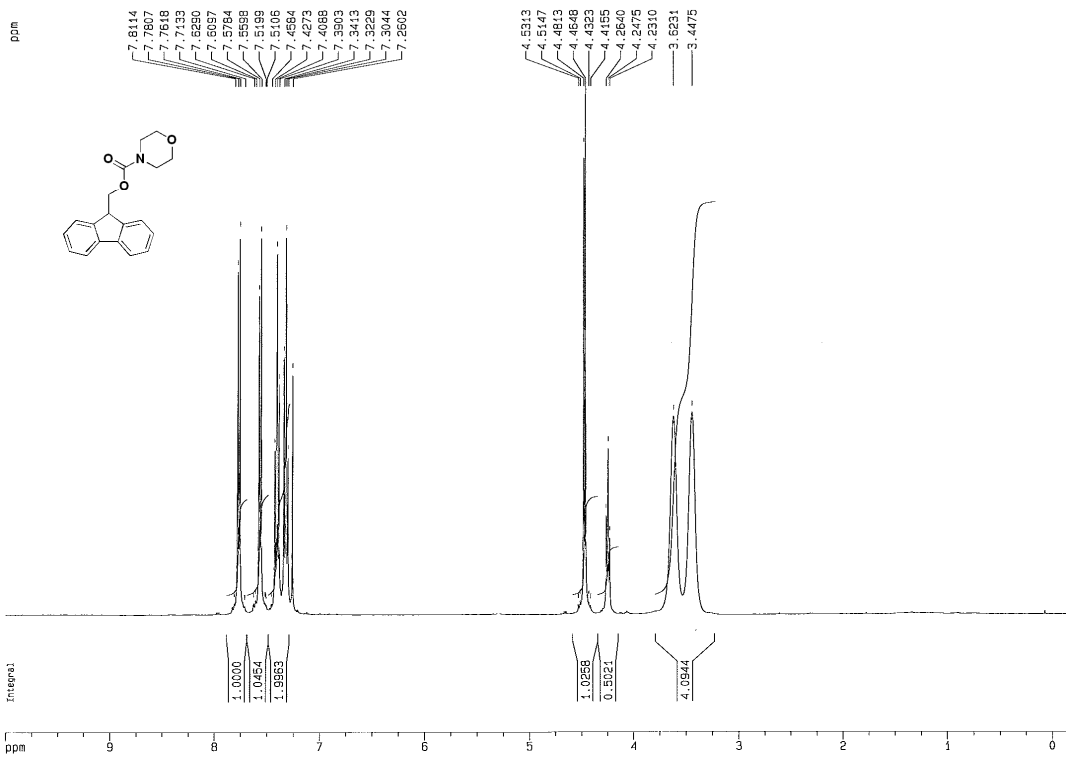
Carbon NMR spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methoxylbenzylamine (**3i**).



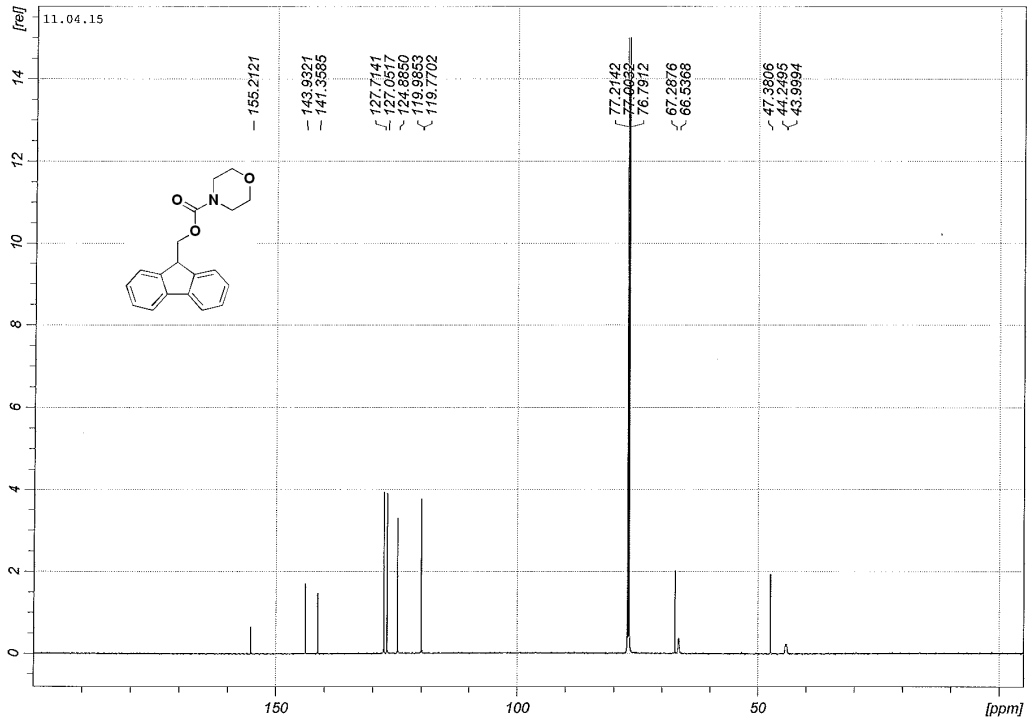
Electron impact mass spectra of ***N***-(9-fluorenylmethoxycarbonyl)-4-methoxylbenzylamine (**3i**).



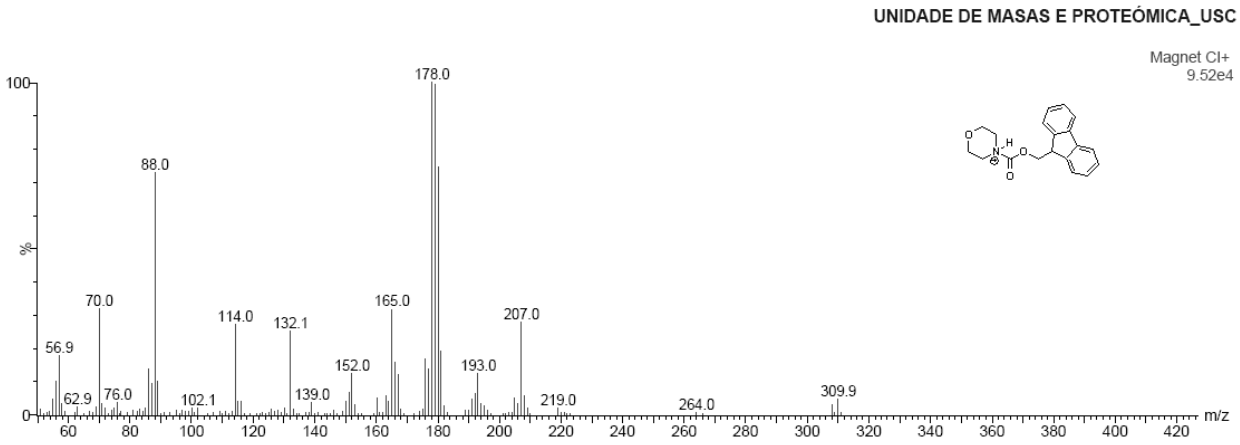
Infrared spectra of *N*-(9-Fluorenylmethoxycarbonyl)morpholine (**3j**).



Proton NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)morpholine (**3j**).

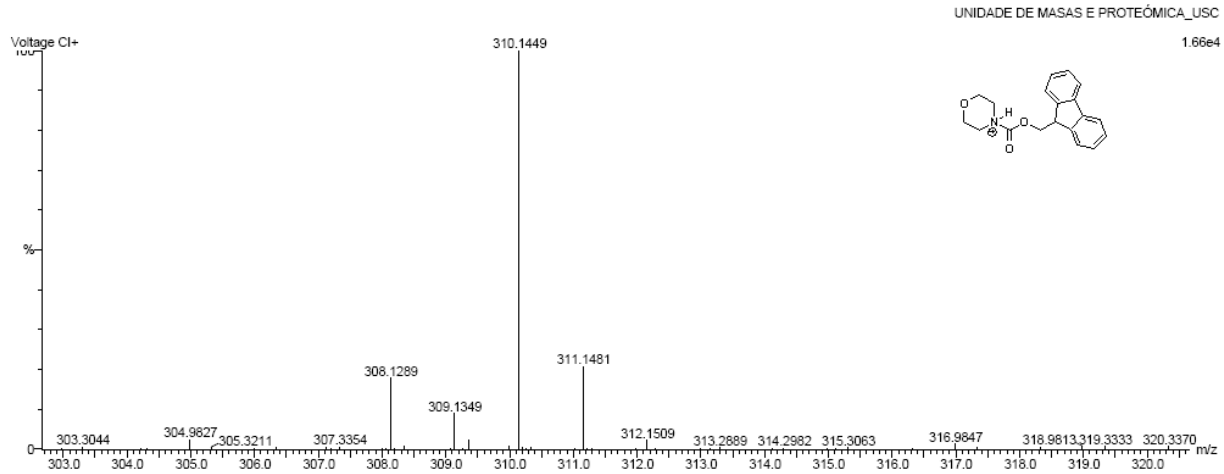


Carbon NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)morpholine (**3j**).



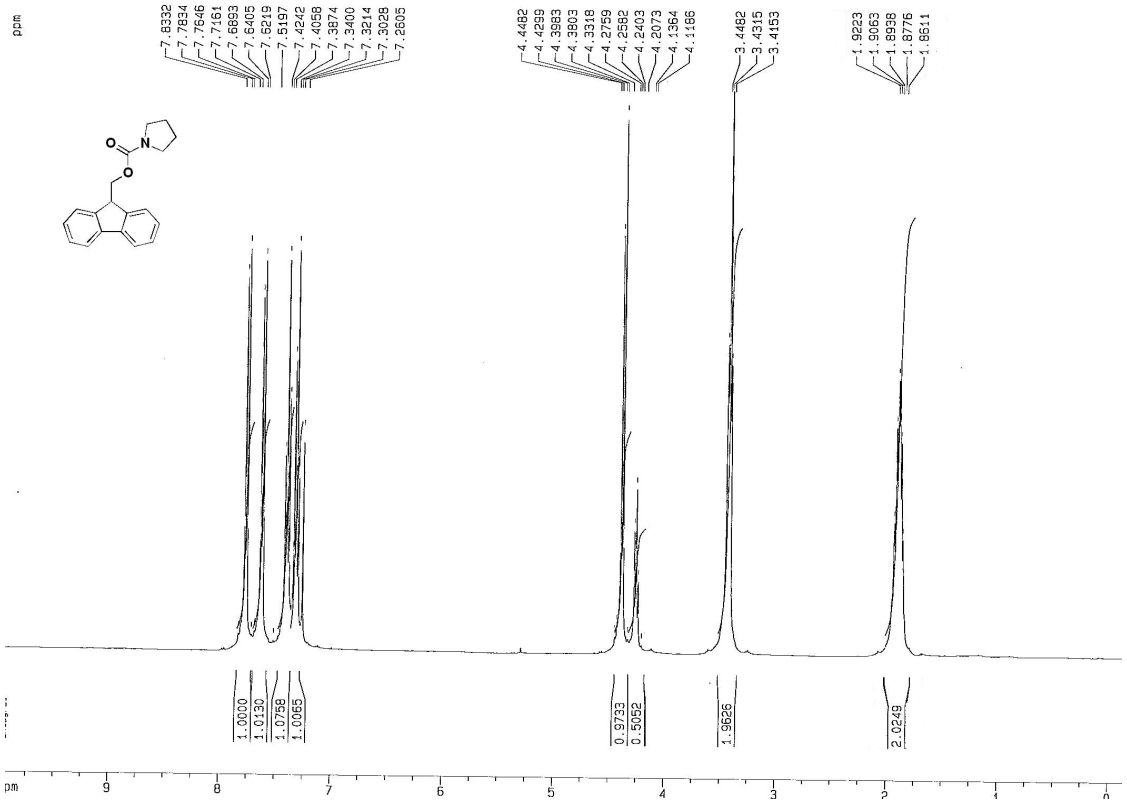
Chemical ionization mass spectra of *N*-(9-Fluorenylmethoxycarbonyl)morpholine (**3j**).

Monoisotopic Mass, Odd and Even Electron Ions
73 formula(e) evaluated with 3 results within limits (up to 50 closest results for each mass)
Elements Used:
12C: 17-19 13C: 0-2 H: 20-20 N: 1-1 O: 3-3

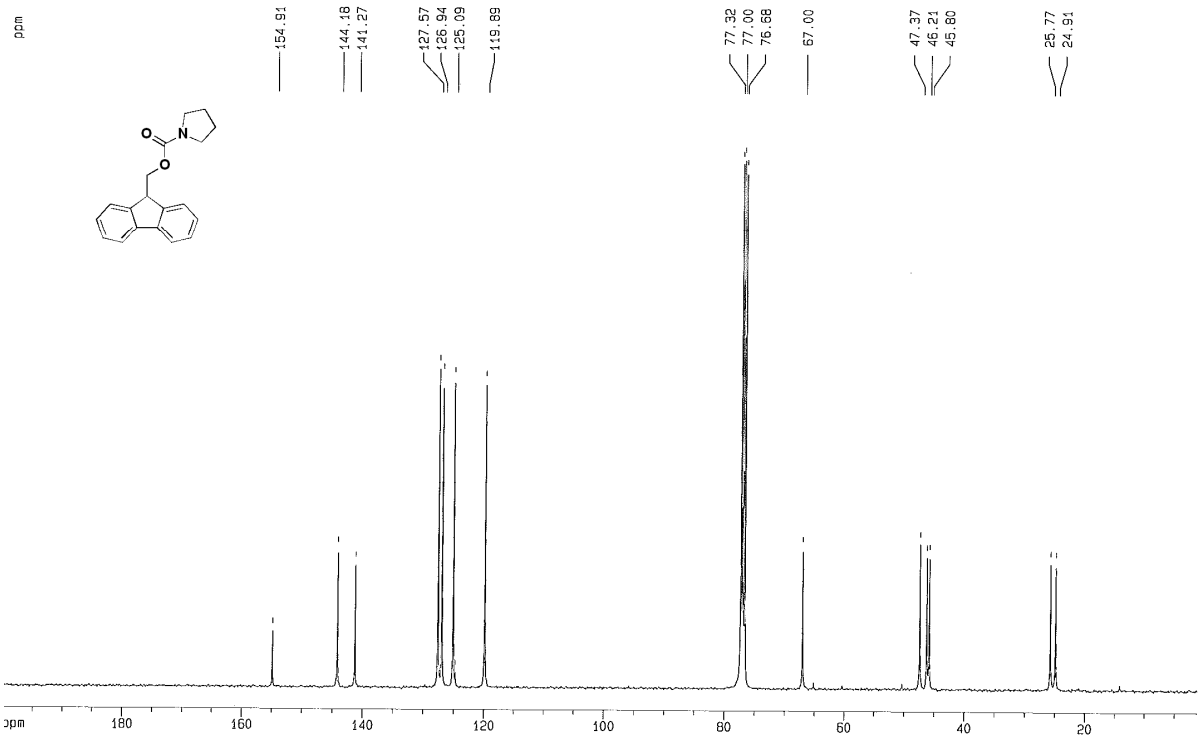


Minimum:	0.20				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
310.1449	100.00	310.1443	0.6	1.9	10.5	31.4	12C19 H20 N O3
311.1481	20.60	311.1477	0.4	1.3	10.5	74.1	12C18 13C H20 N O3
312.1509	2.05	312.1510	-0.1	-0.3	10.5	2773037.0	12C17 13C2 H20 N O3

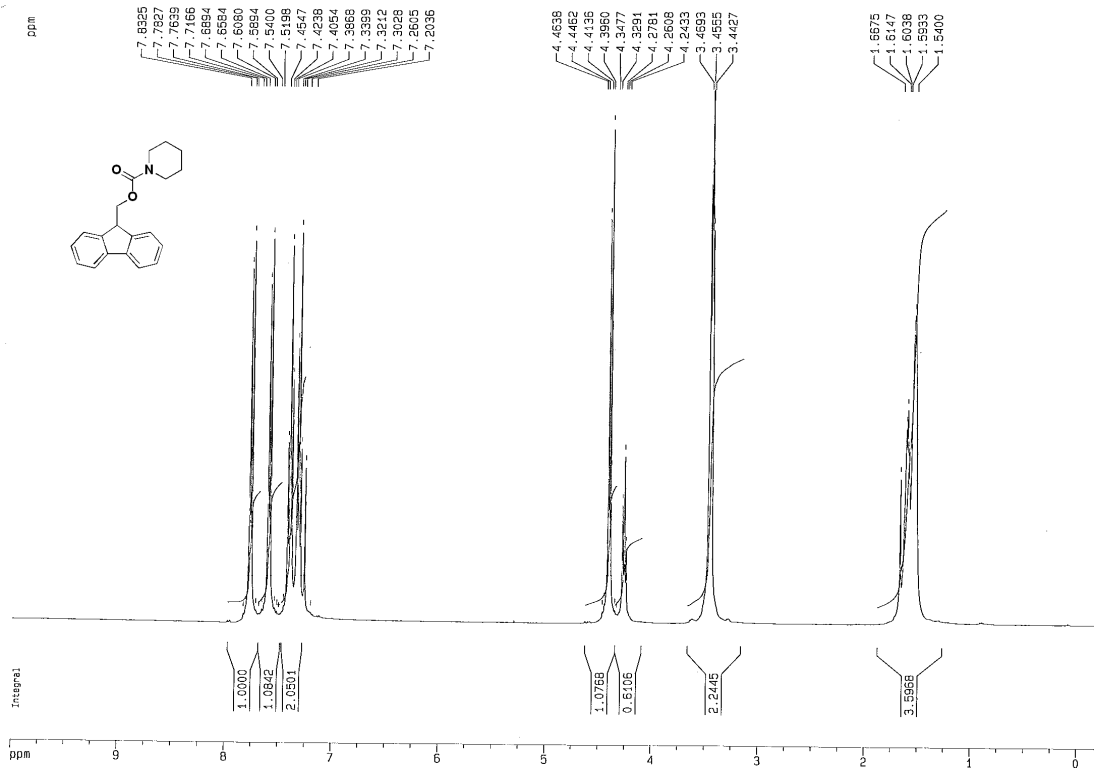
High resolution chemical ionization mass spectra of *N*-(9-Fluorenylmethoxycarbonyl)morpholine (**3j**).



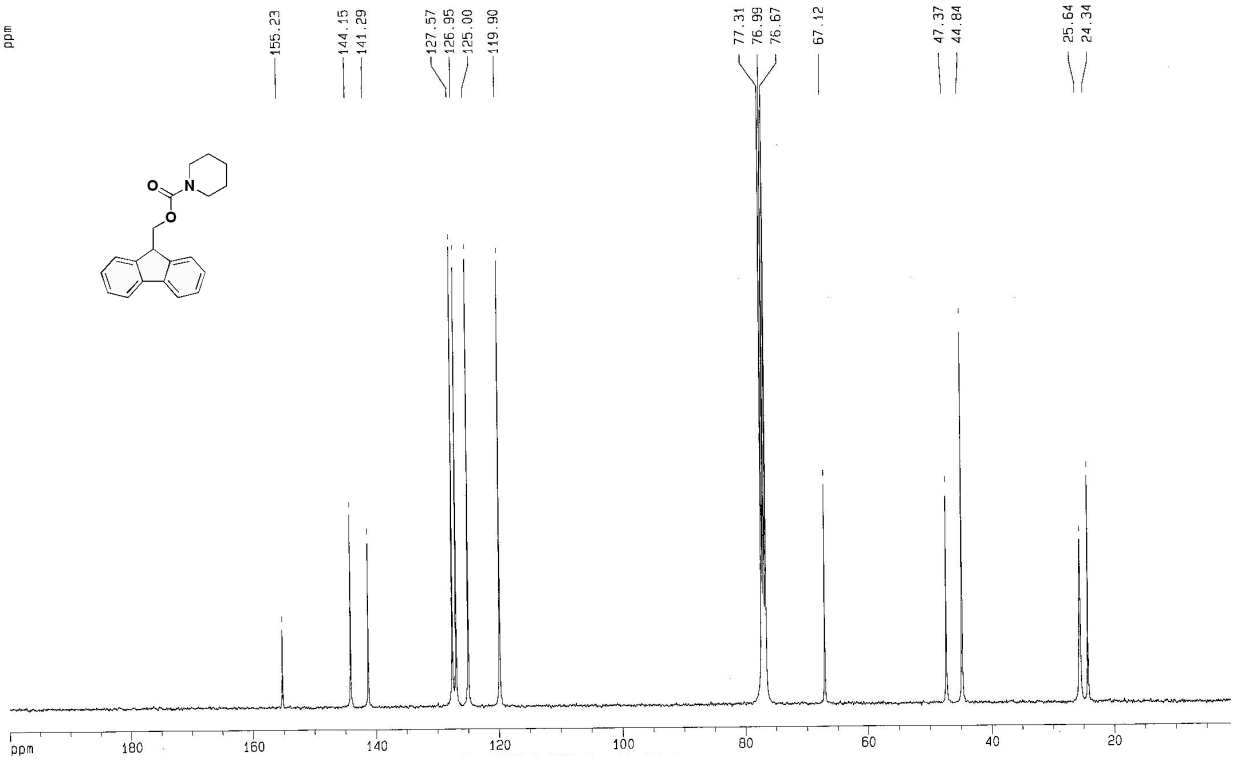
Proton NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)pyrrolidine (**3k**).



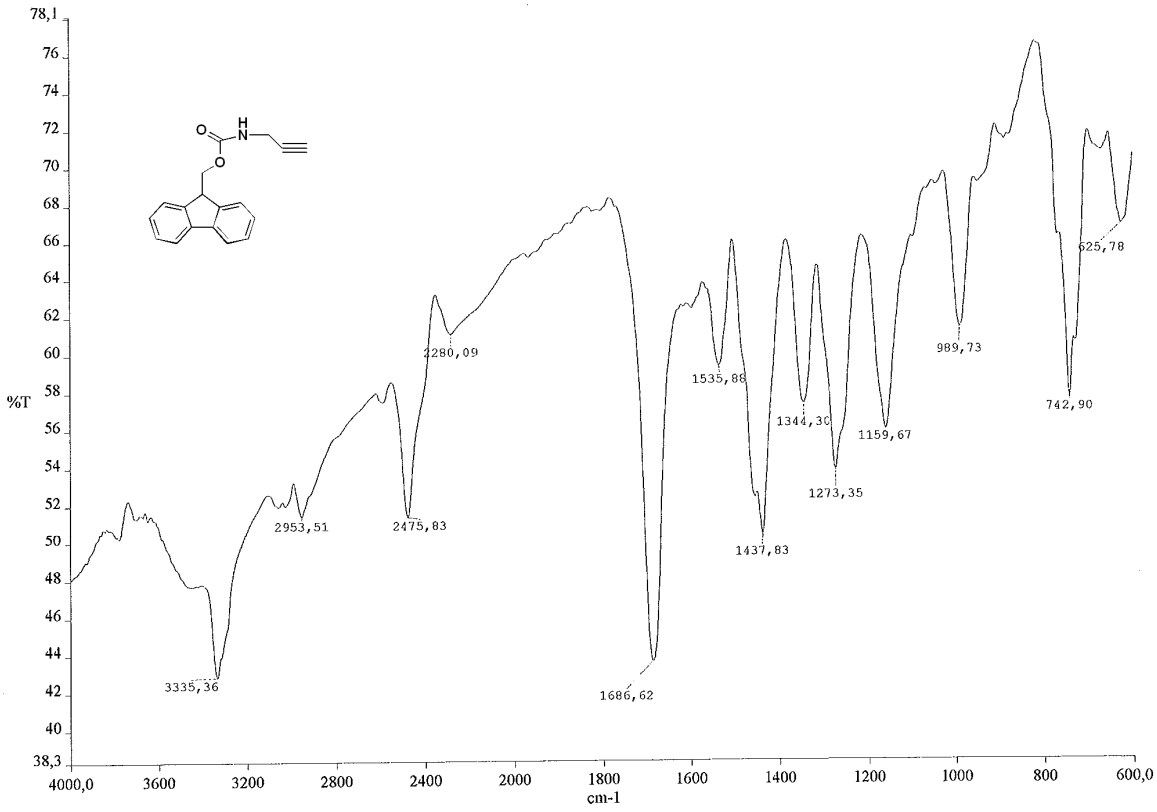
Carbon NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)pyrrolidine (**3k**).



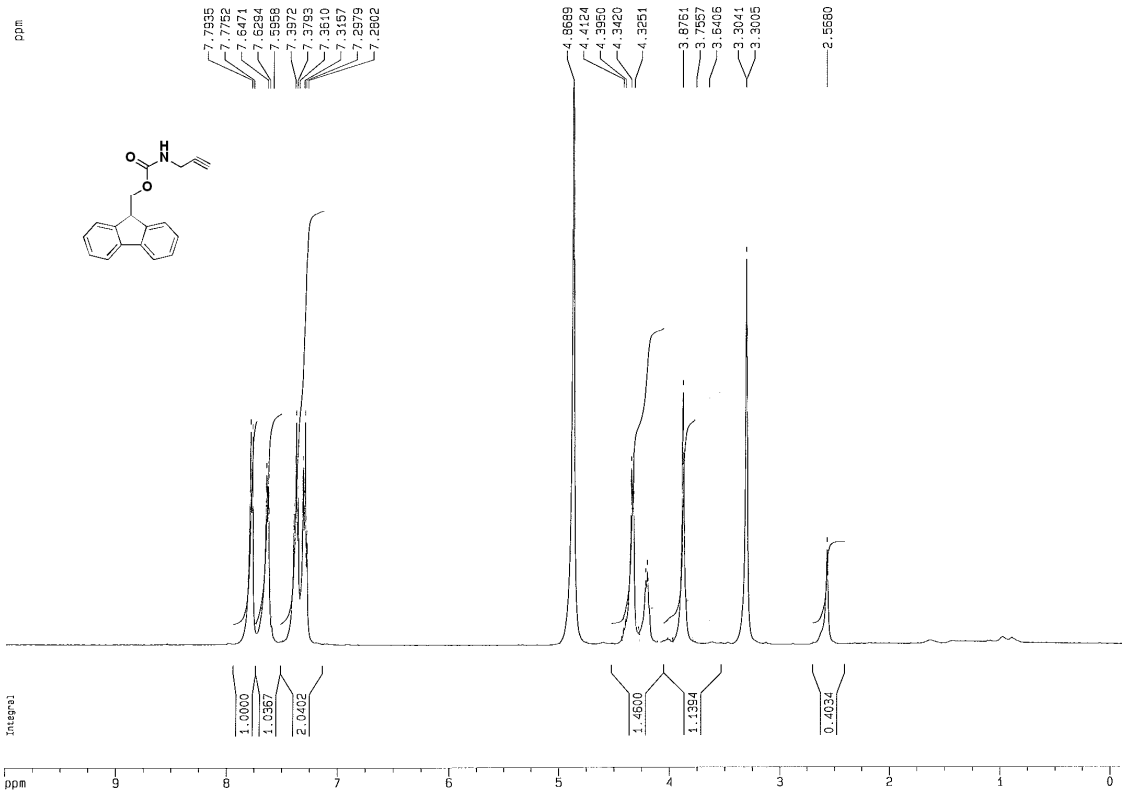
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)piperidine (**3l**).



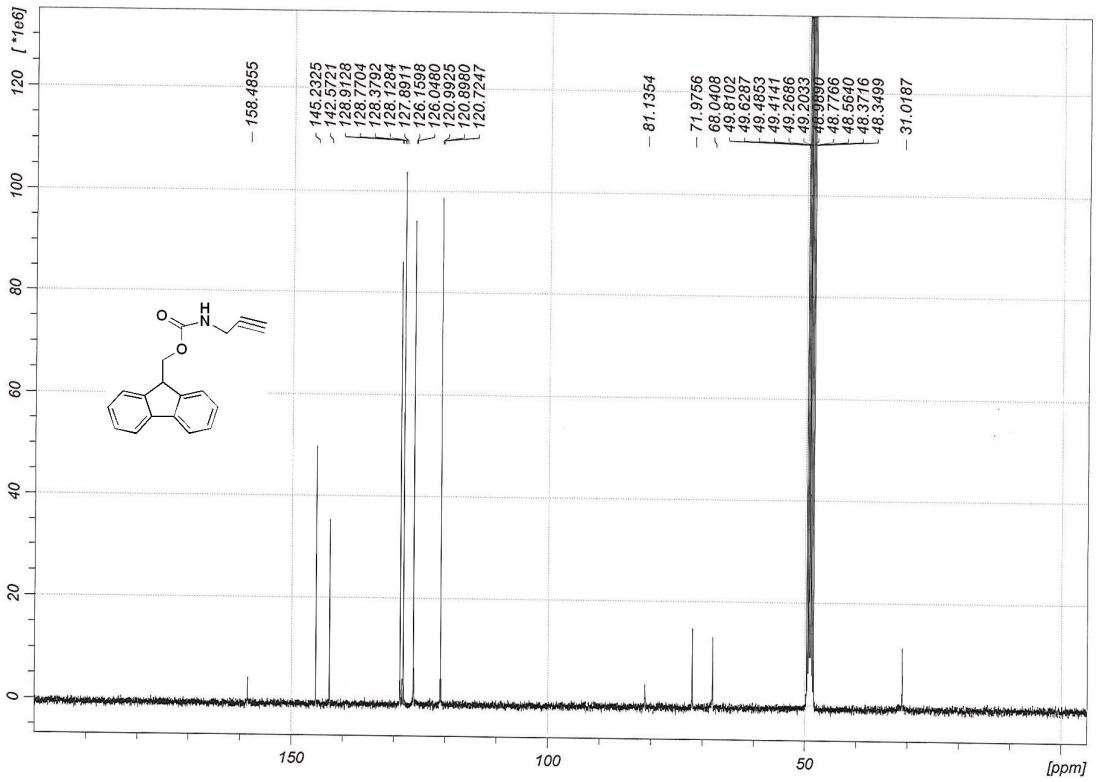
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)piperidine (**3l**).



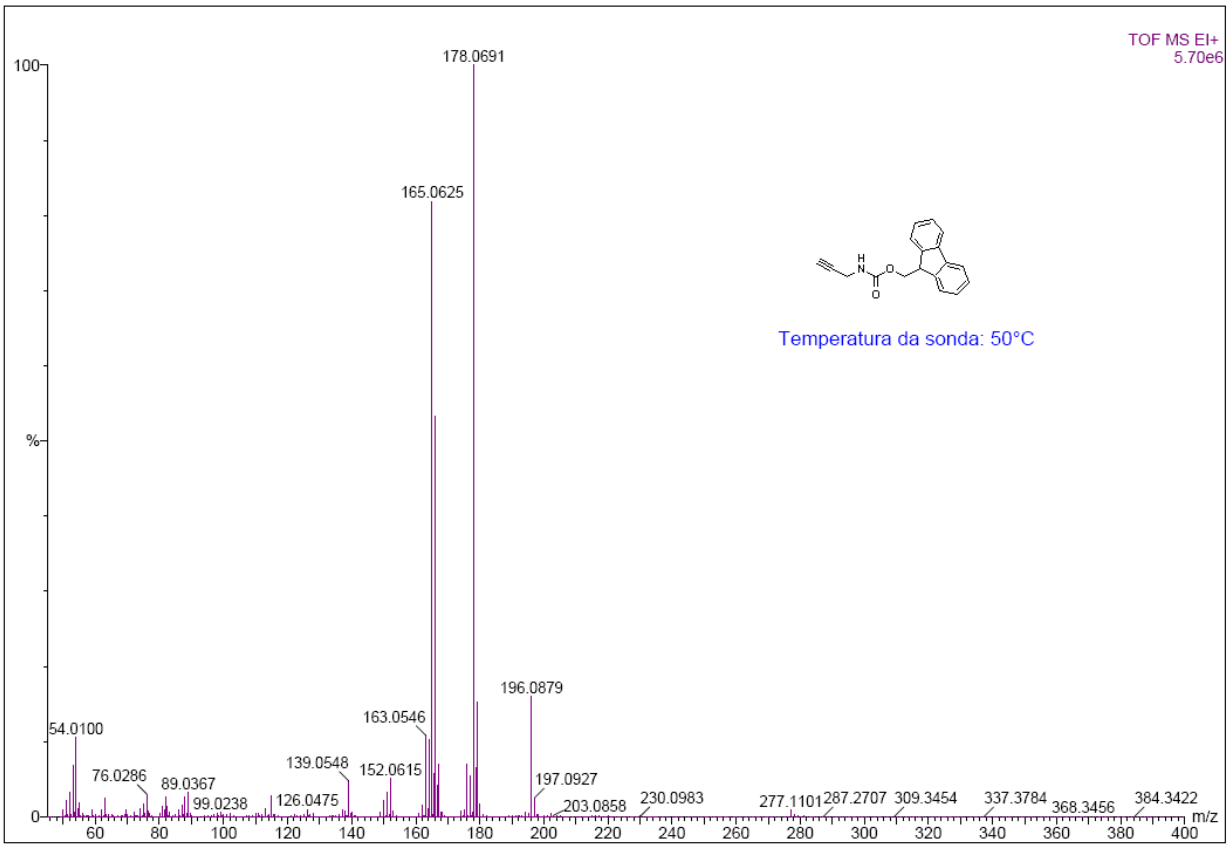
Infrared spectra of *N*-(9-Fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (**3m**).



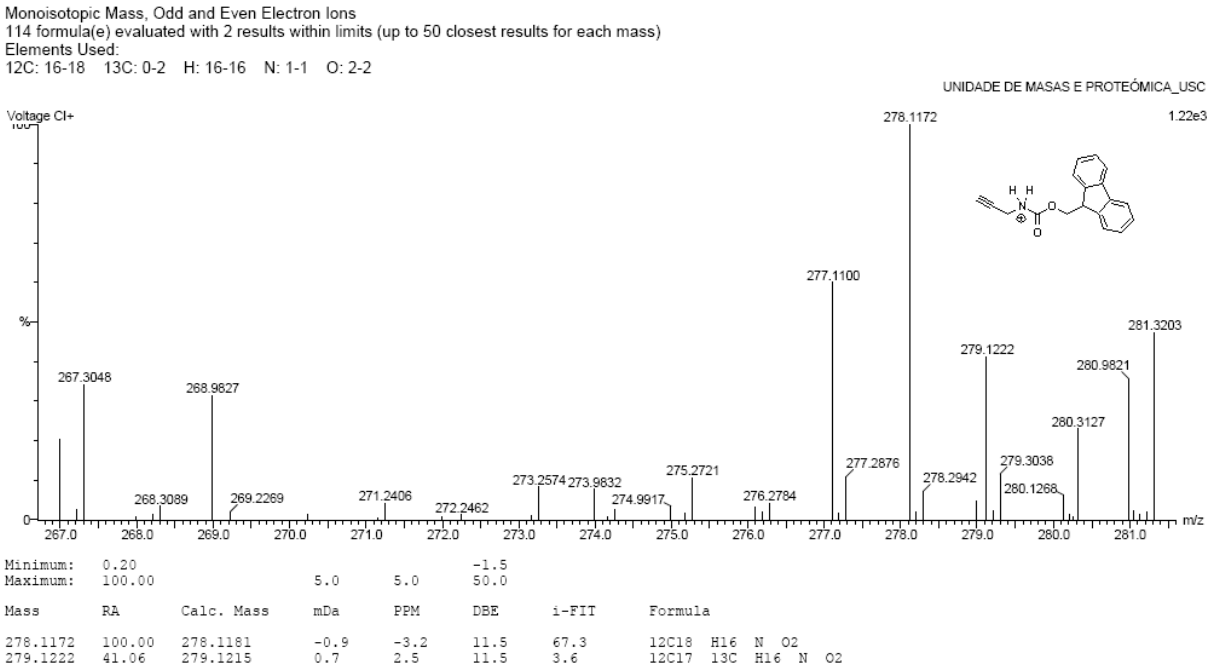
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (**3m**).



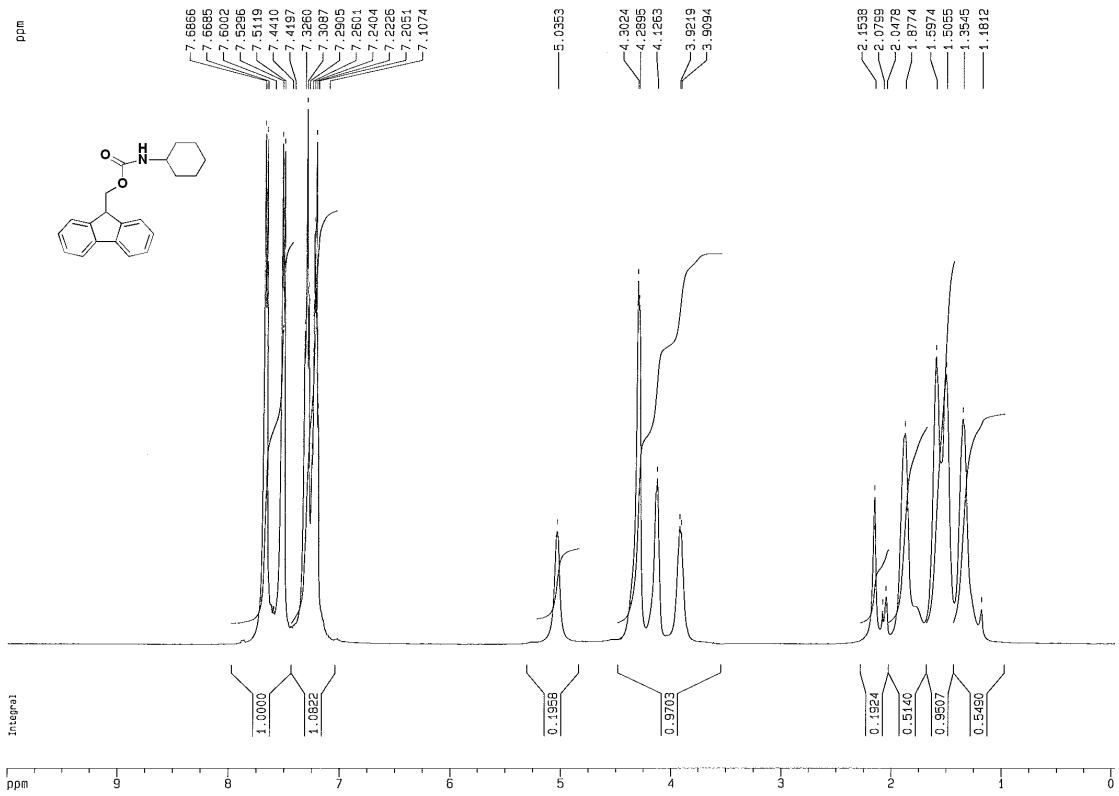
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (**3m**).



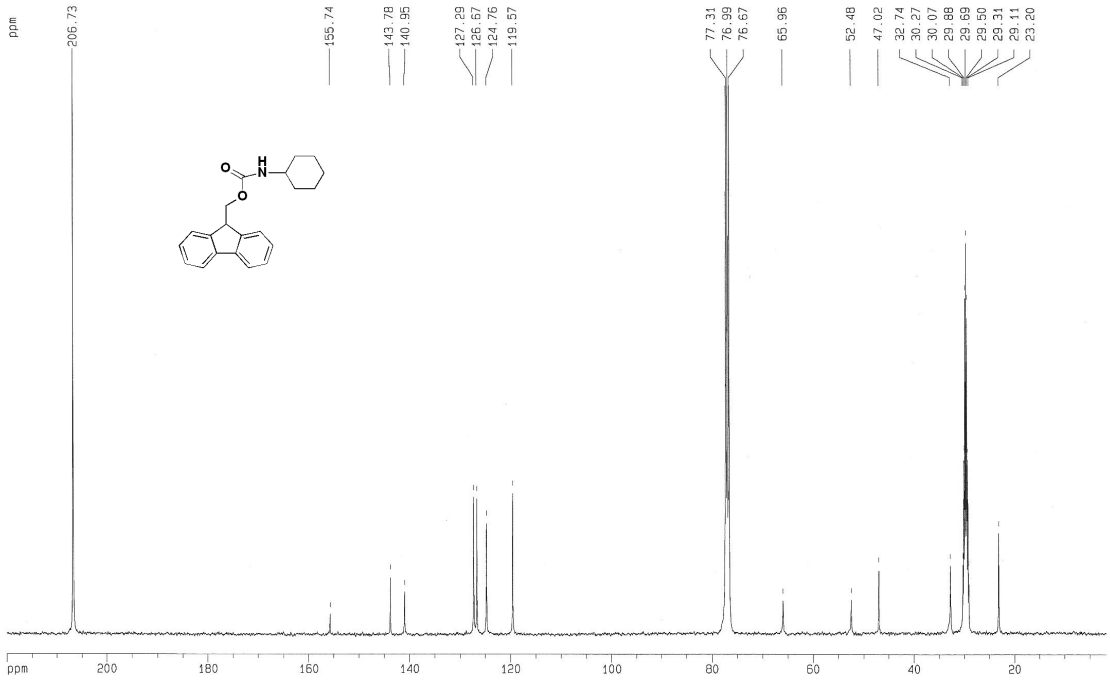
Electron impact mass spectra of *N*-(9-fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (**3m**).



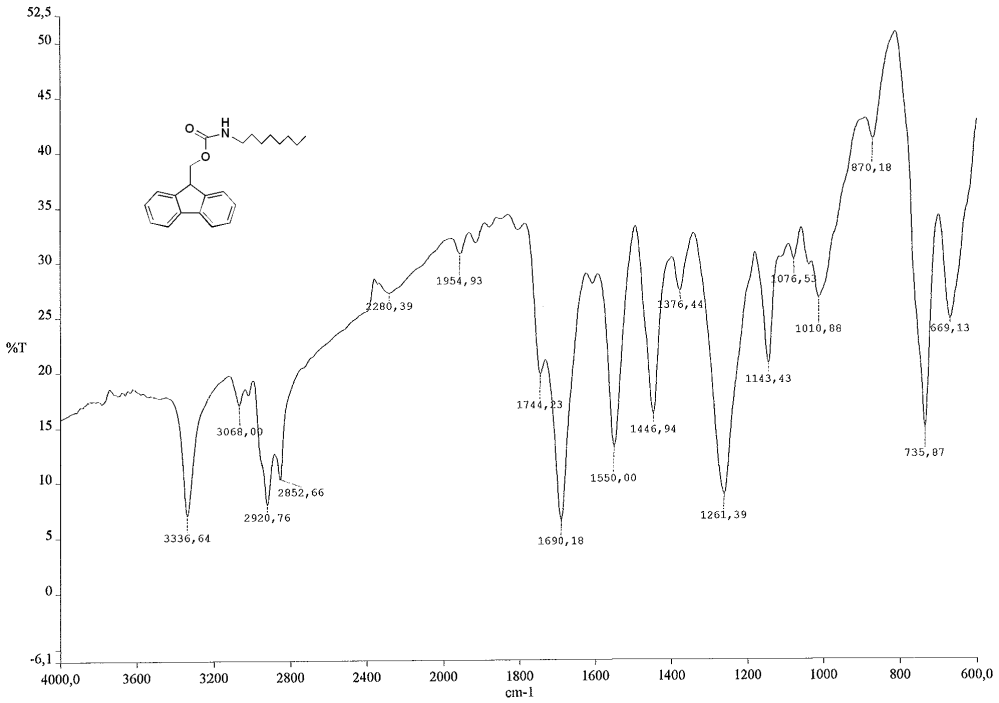
High resolution chemical ionization spectra of *N*-(9-fluorenylmethoxycarbonyl)-prop-2-yn-1-amine (**3m**).



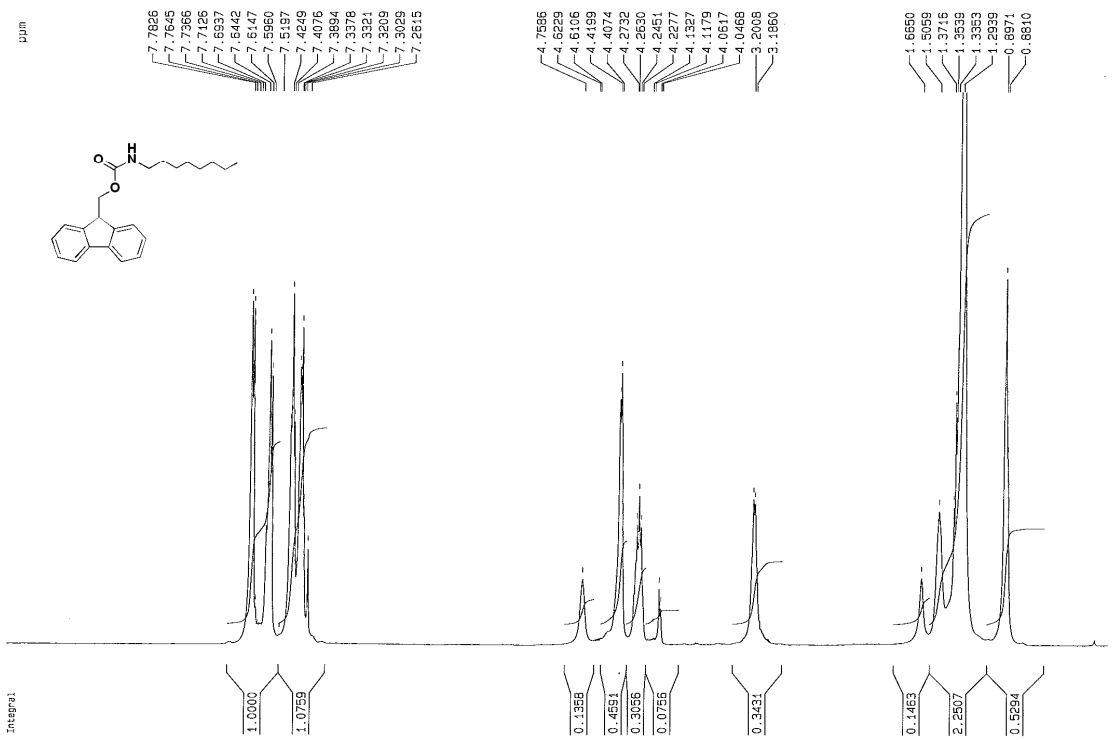
Proton NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)cyclohexylamine (**3n**).



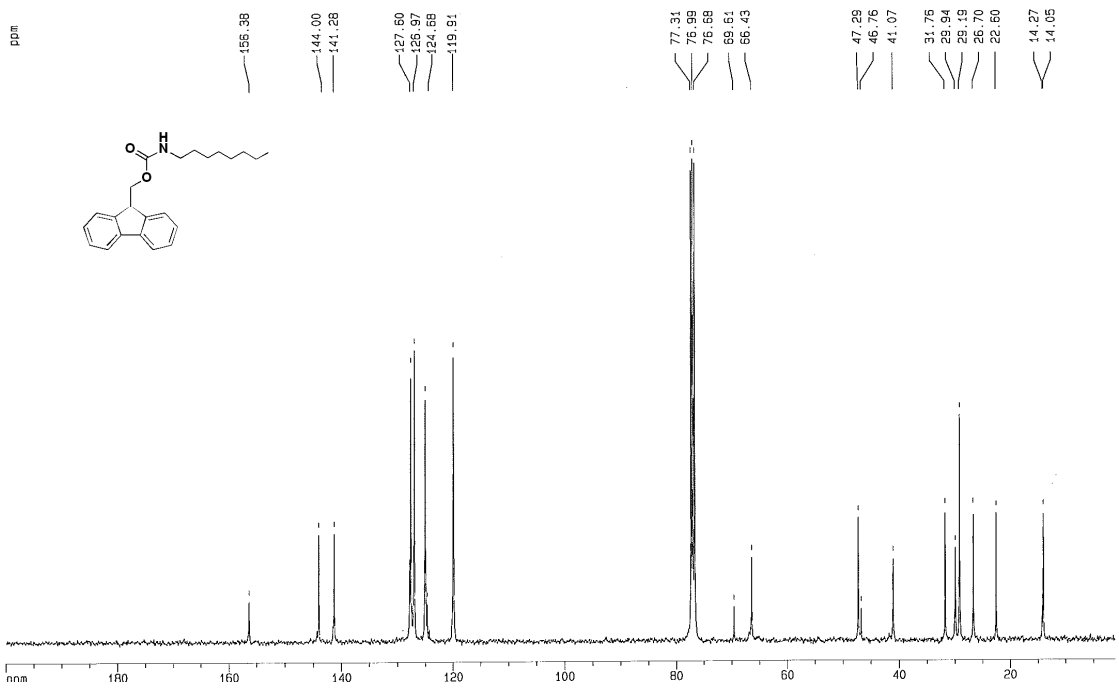
Carbon NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)cyclohexylamine (**3n**).



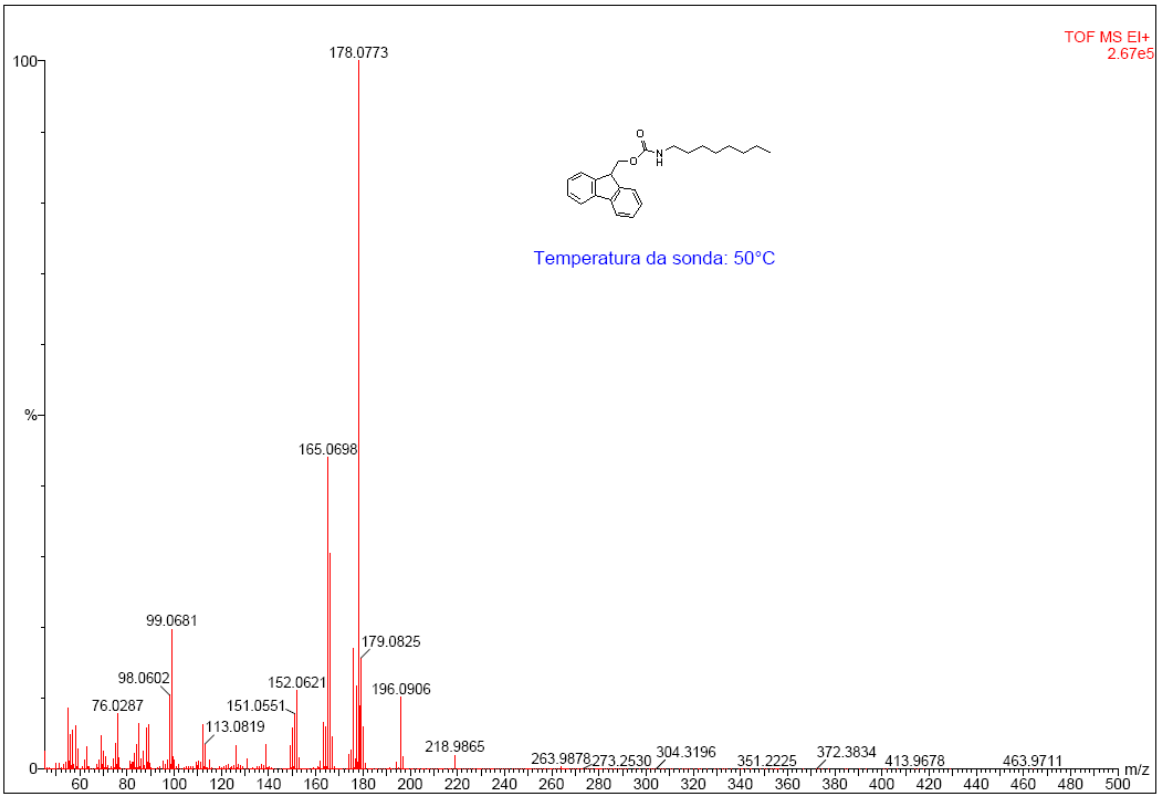
Infrared spectra of spectra of *N*-(9-fluorenylmethoxycarbonyl)octylamine (**3o**).



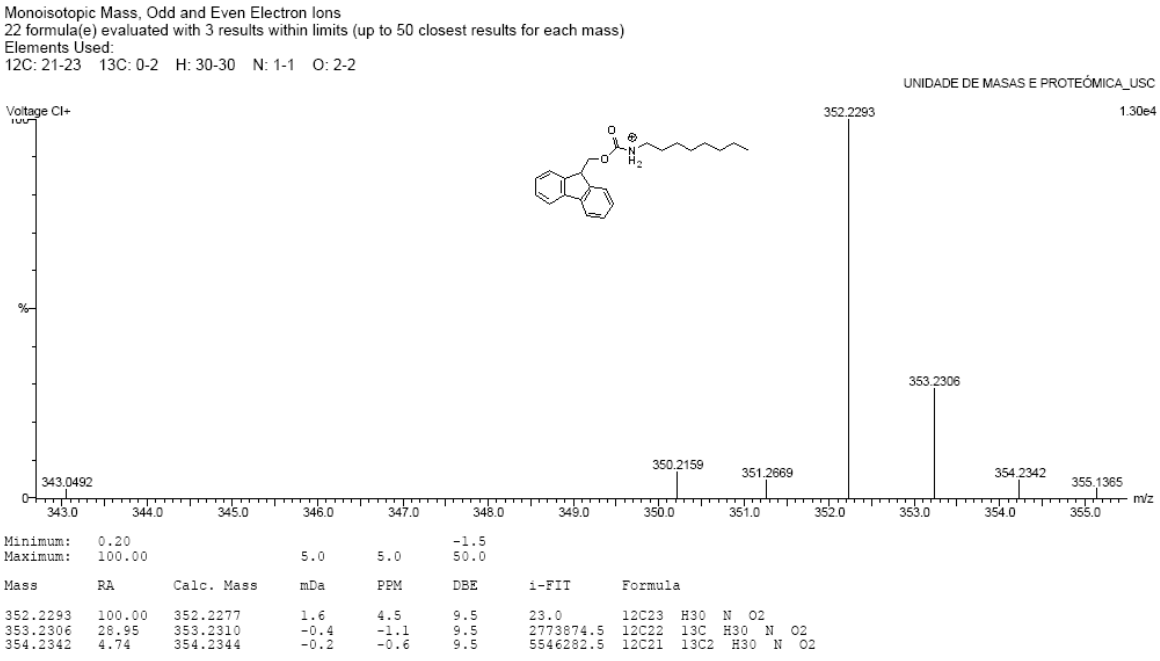
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)octylamine (**3o**).



Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)octylamine (**3o**).

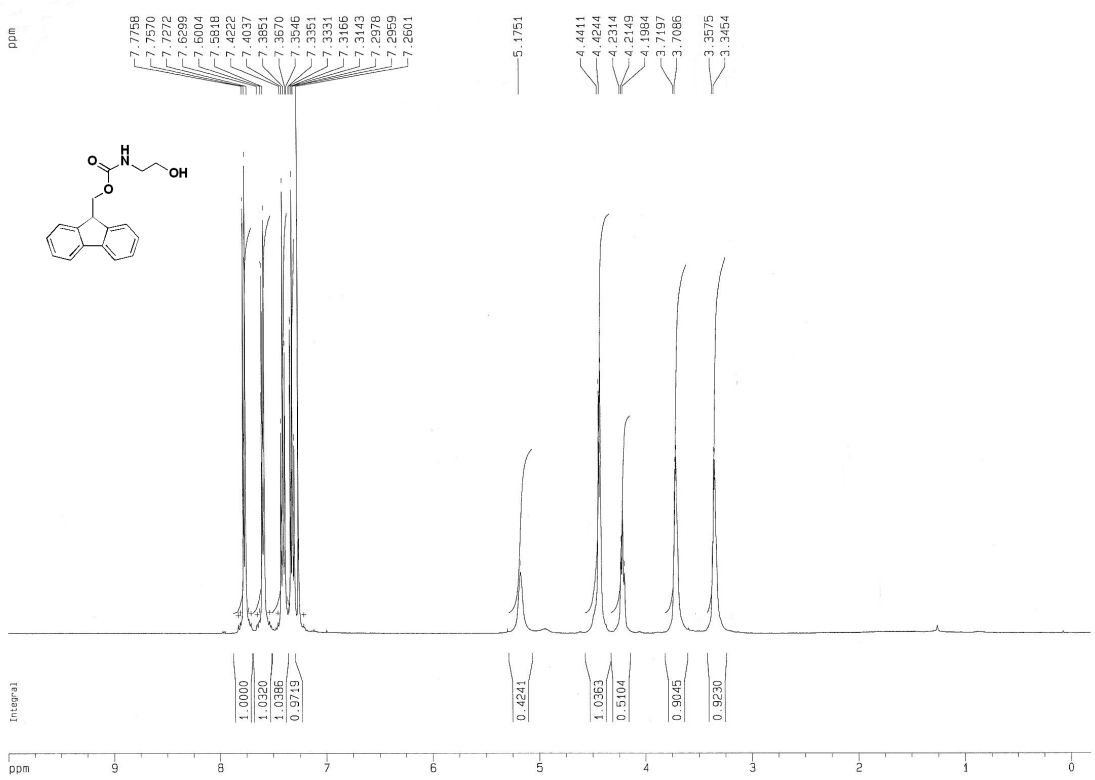


Electron impact mass spectra of *N*-(9-fluorenylmethoxycarbonyl)octylamine (**3o**).

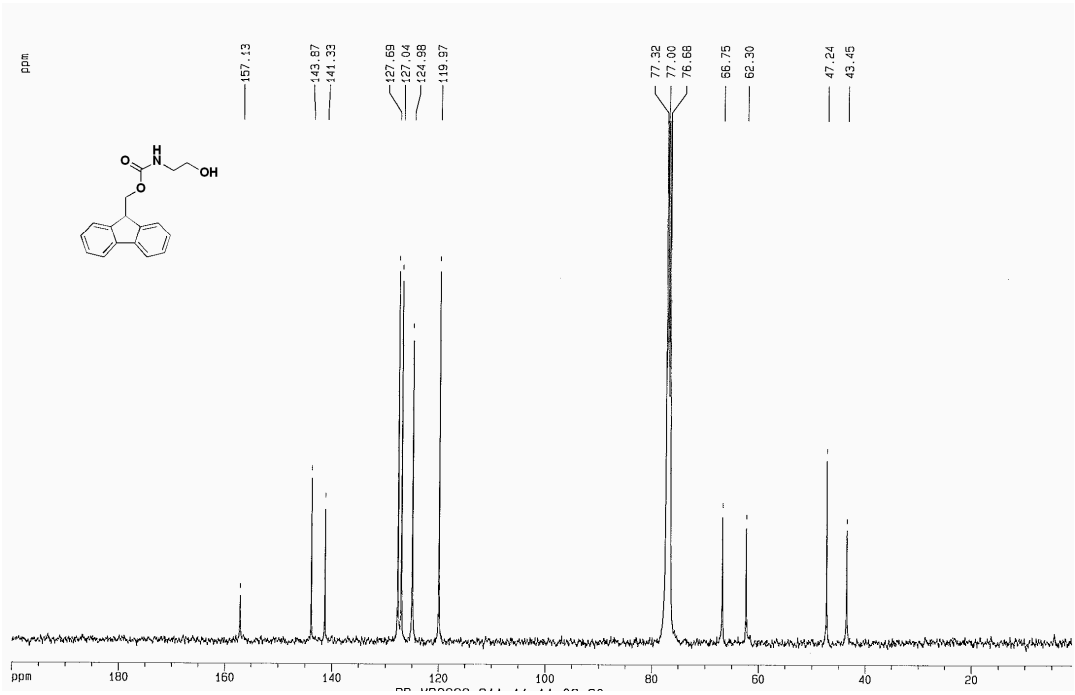


Minimum:	0.20				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
352.2293	100.00	352.2277	1.6	4.5	9.5	23.0	12C23 H30 N O2
353.2306	28.95	353.2310	-0.4	-1.1	9.5	2773874.5	12C22 13C H30 N O2
354.2342	4.74	354.2344	-0.2	-0.6	9.5	5546282.5	12C21 13C2 H30 N O2

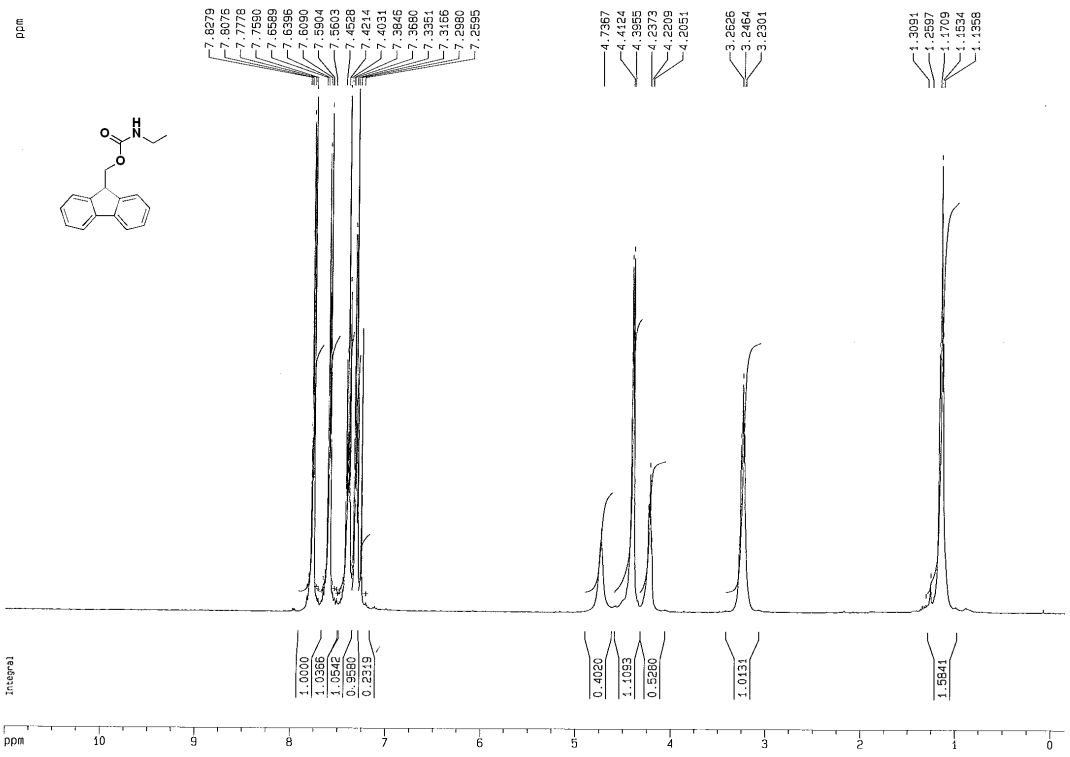
High resolution chemical ionization mass spectra of *N*-(9-fluorenylmethoxycarbonyl)octylamine (**3o**).



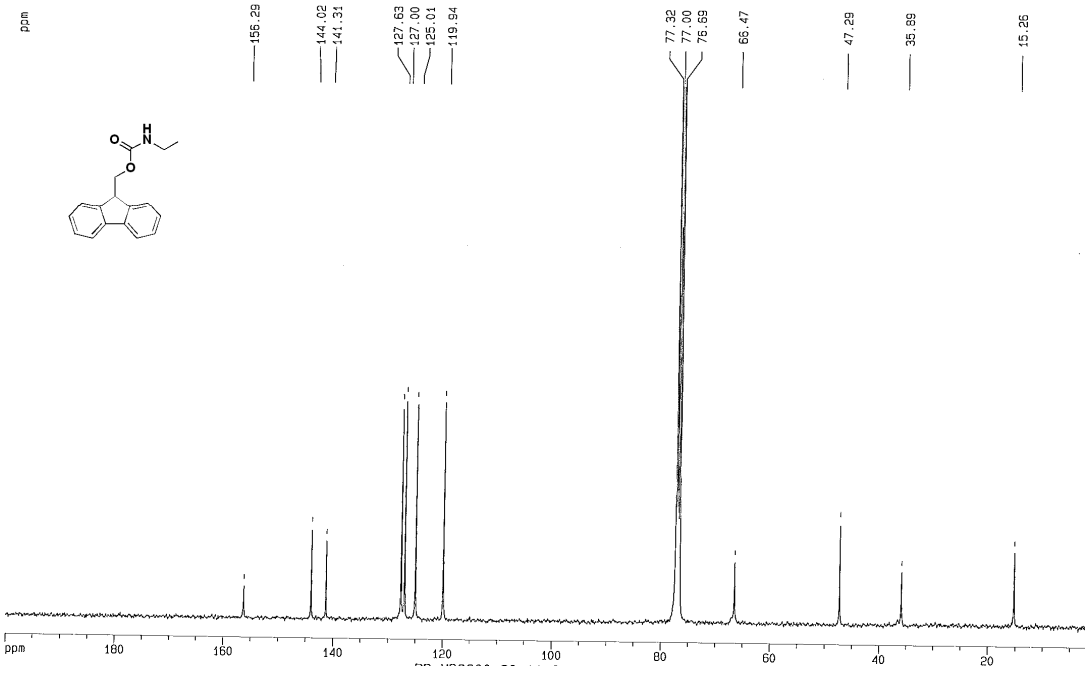
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)ethanolamine **(3p).**



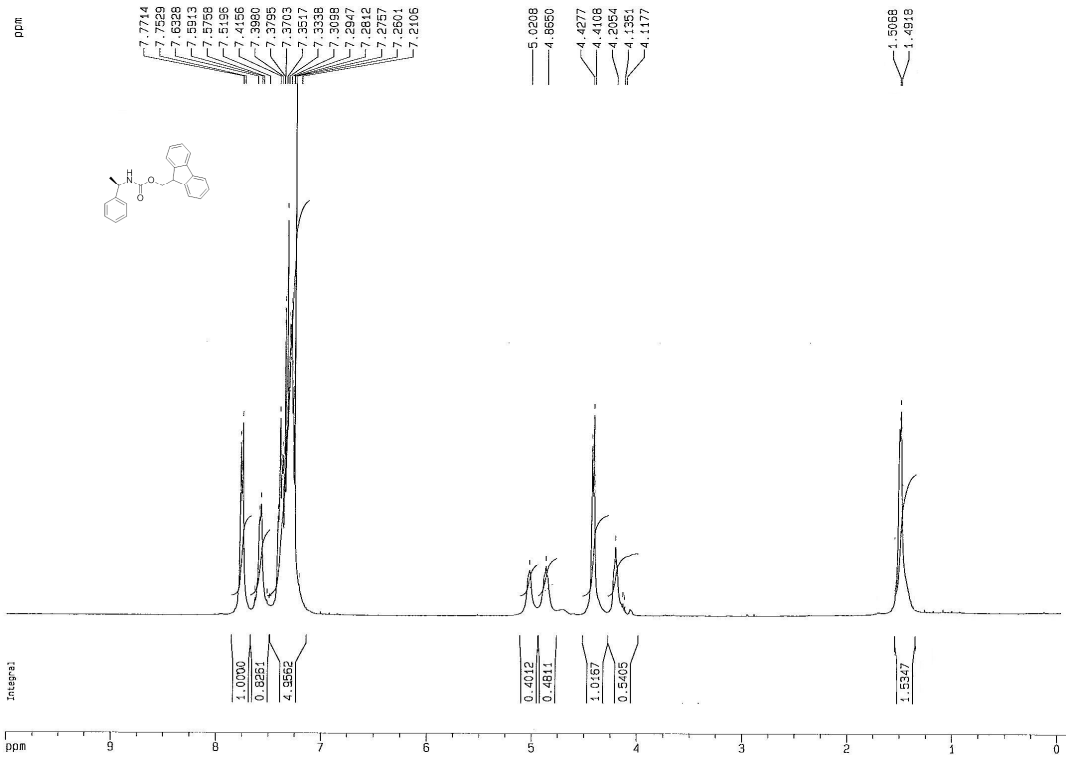
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)ethanolamine **(3p).**



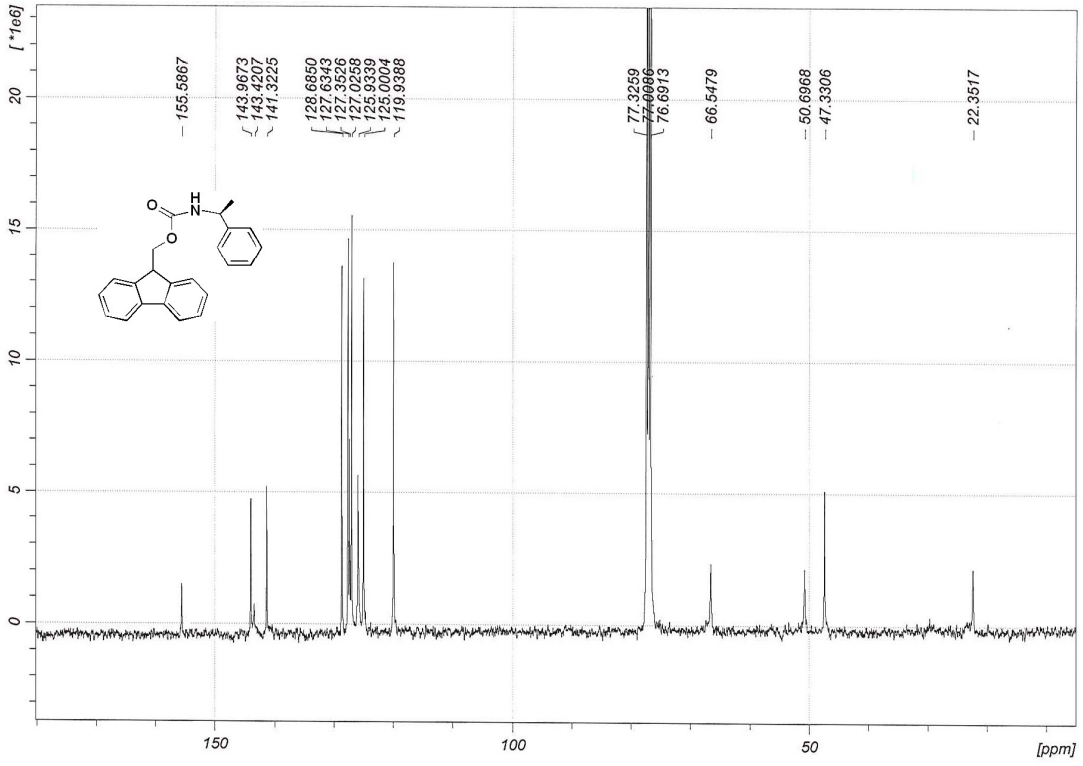
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)ethylamine **(3q).**



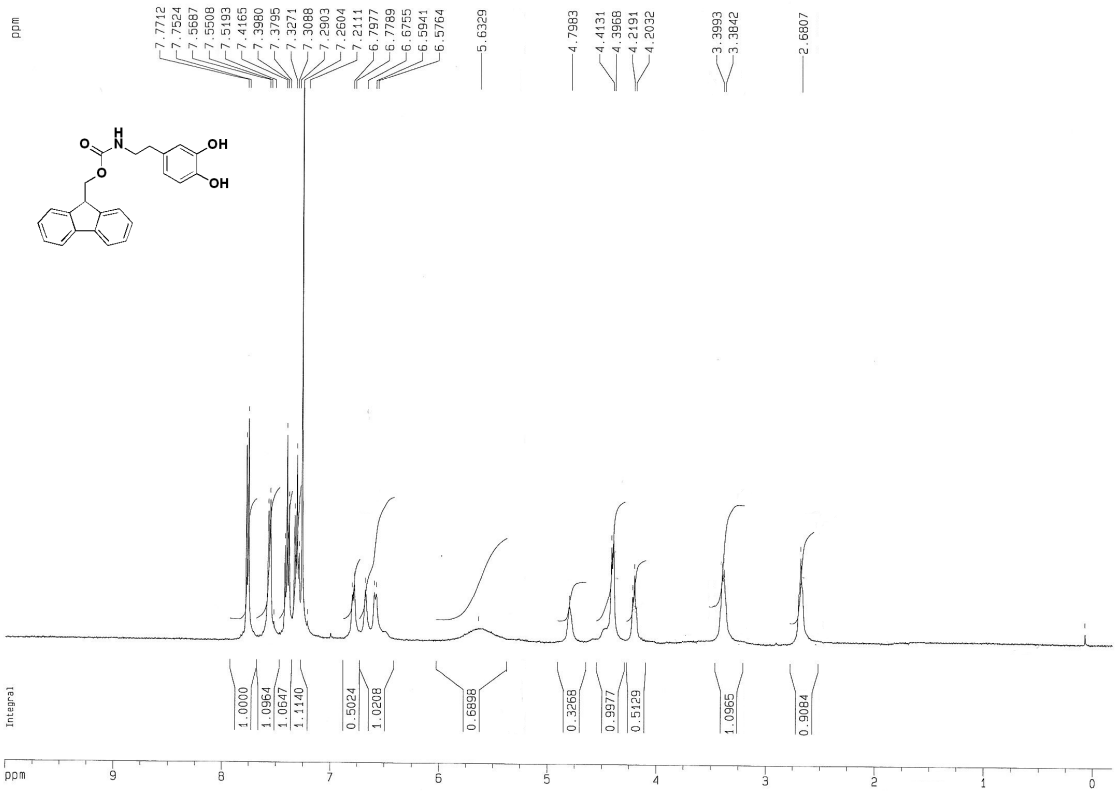
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)ethylamine **(3q).**



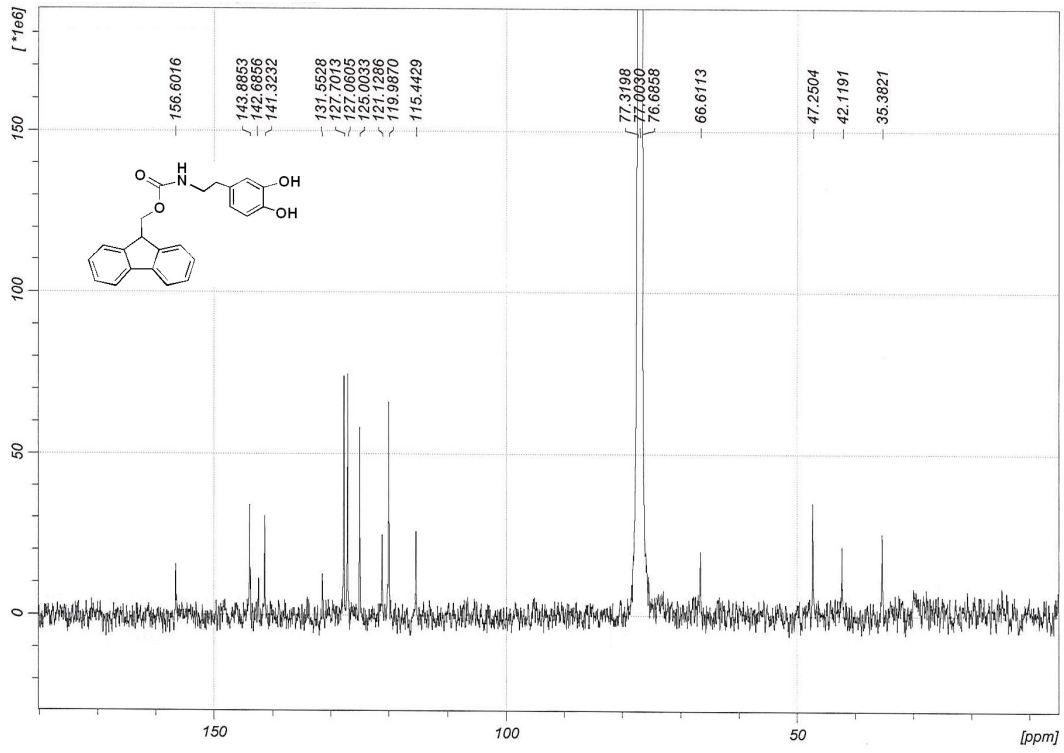
Proton NMR spectra of (R)-*N*-(9-fluorenylmethoxycarbonyl)-1-phenylethanamine **(3r).**



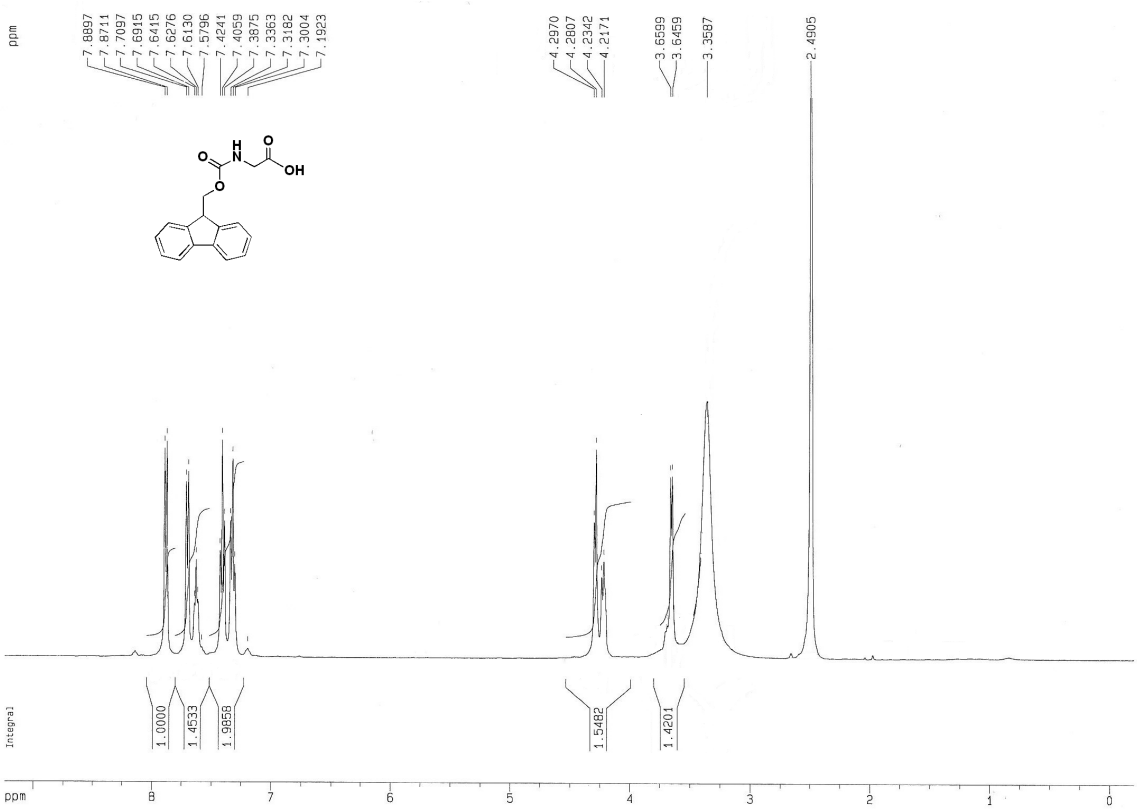
Carbon NMR spectra of (R)-*N*-(9-fluorenylmethoxycarbonyl)-1-phenylethanamine **(3r).**



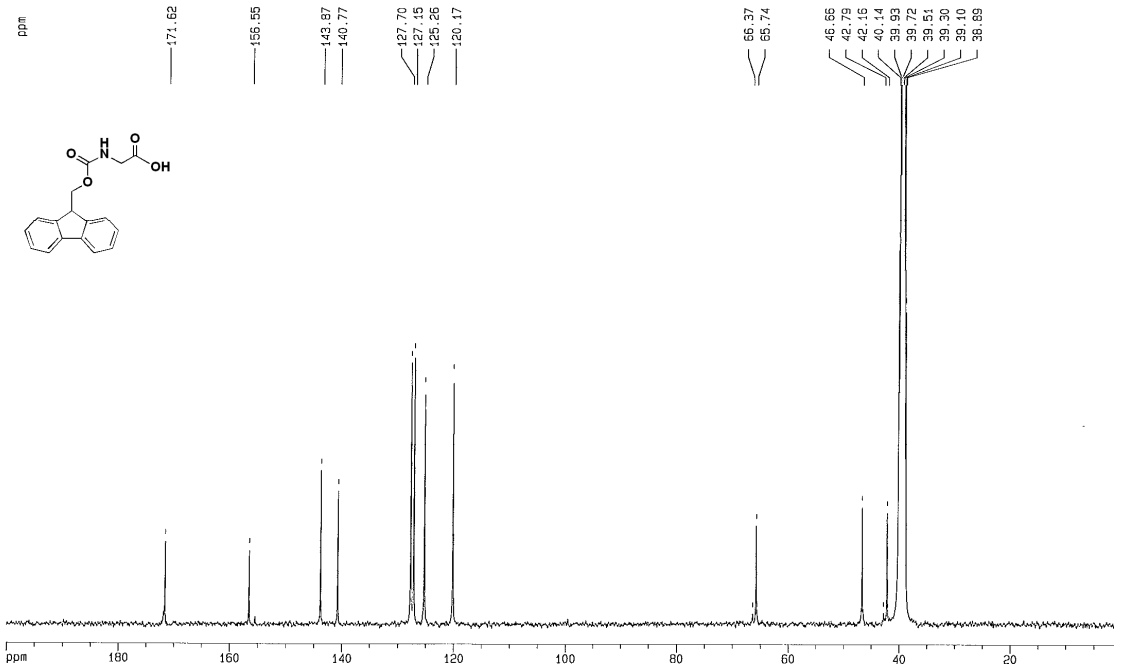
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)dopamine (**3s**).



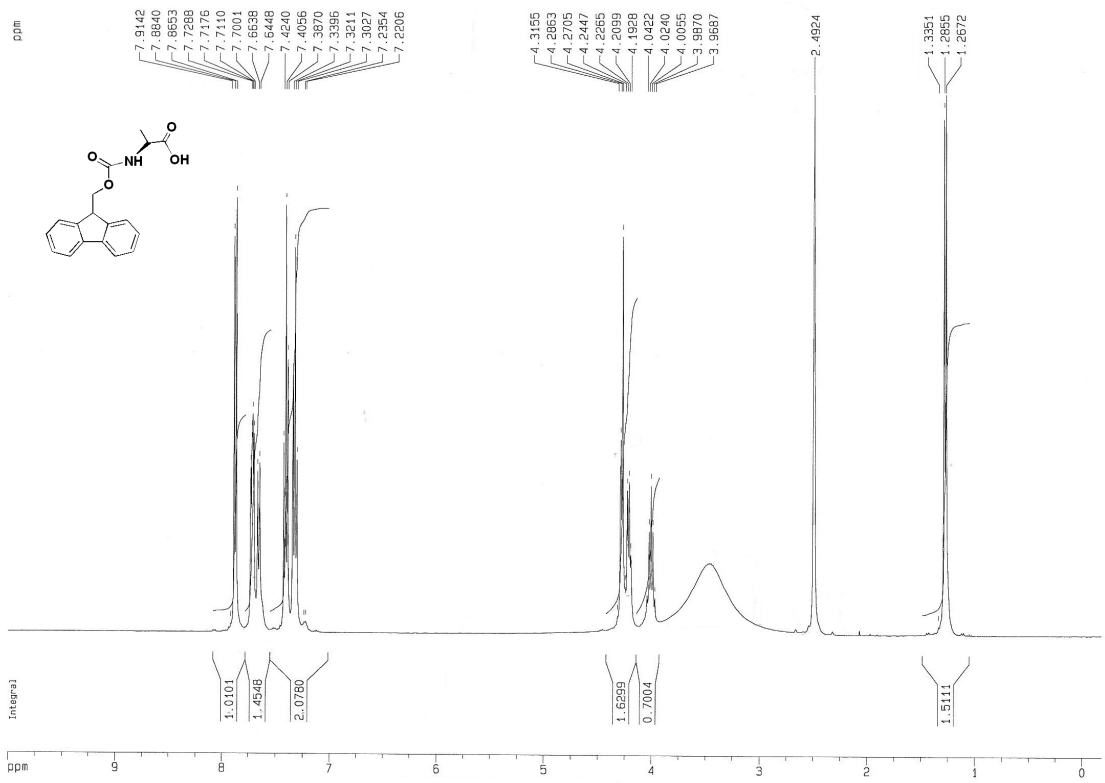
Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)dopamine (**3s**).



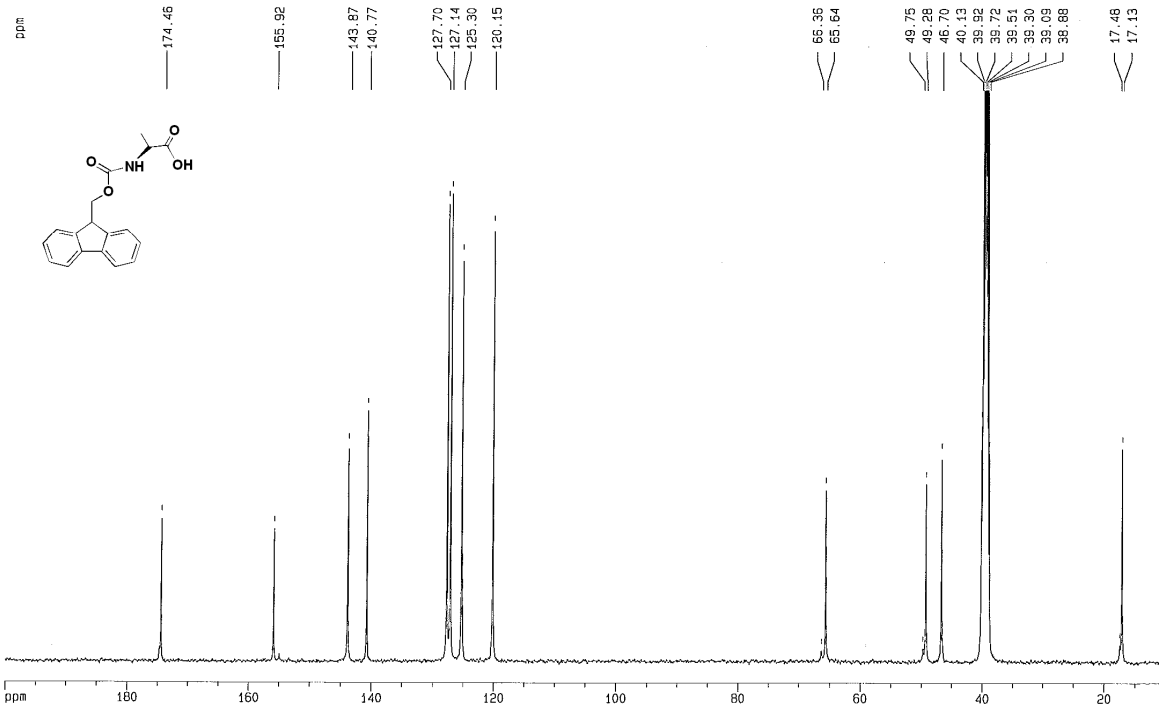
Proton NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)glycine (**3t**).



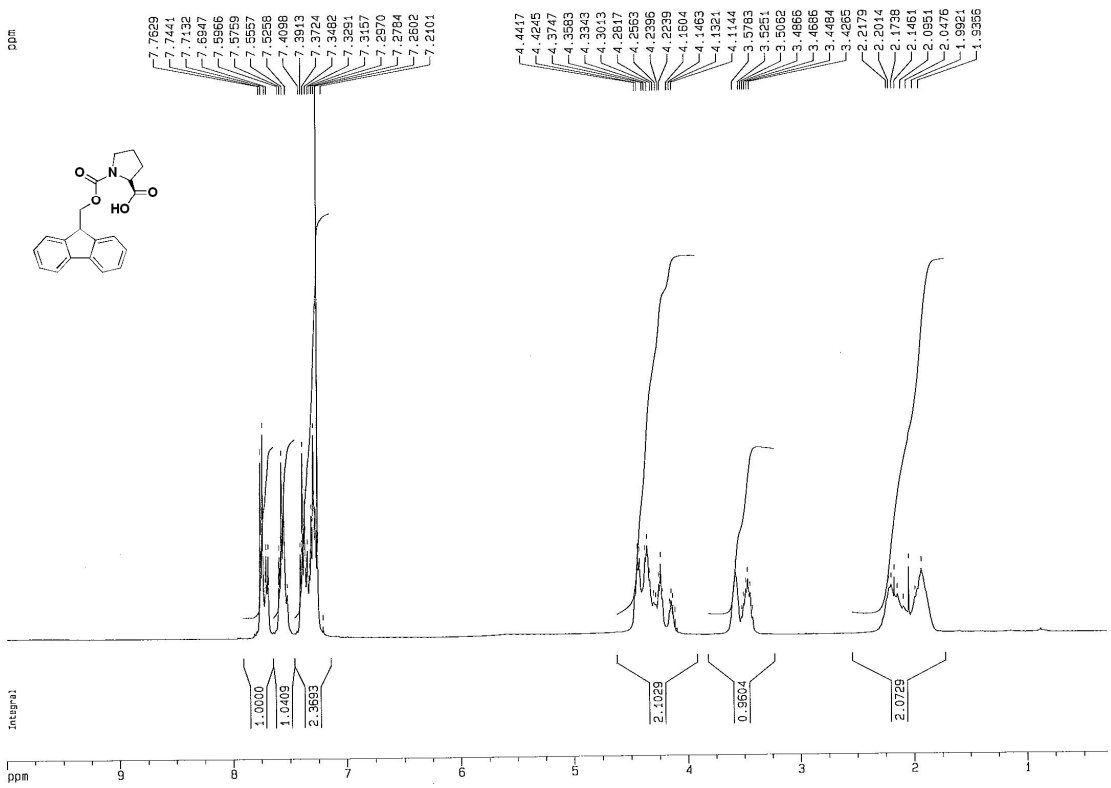
Carbon NMR spectra of *N*-(9-Fluorenylmethoxycarbonyl)glycine (**3t**).



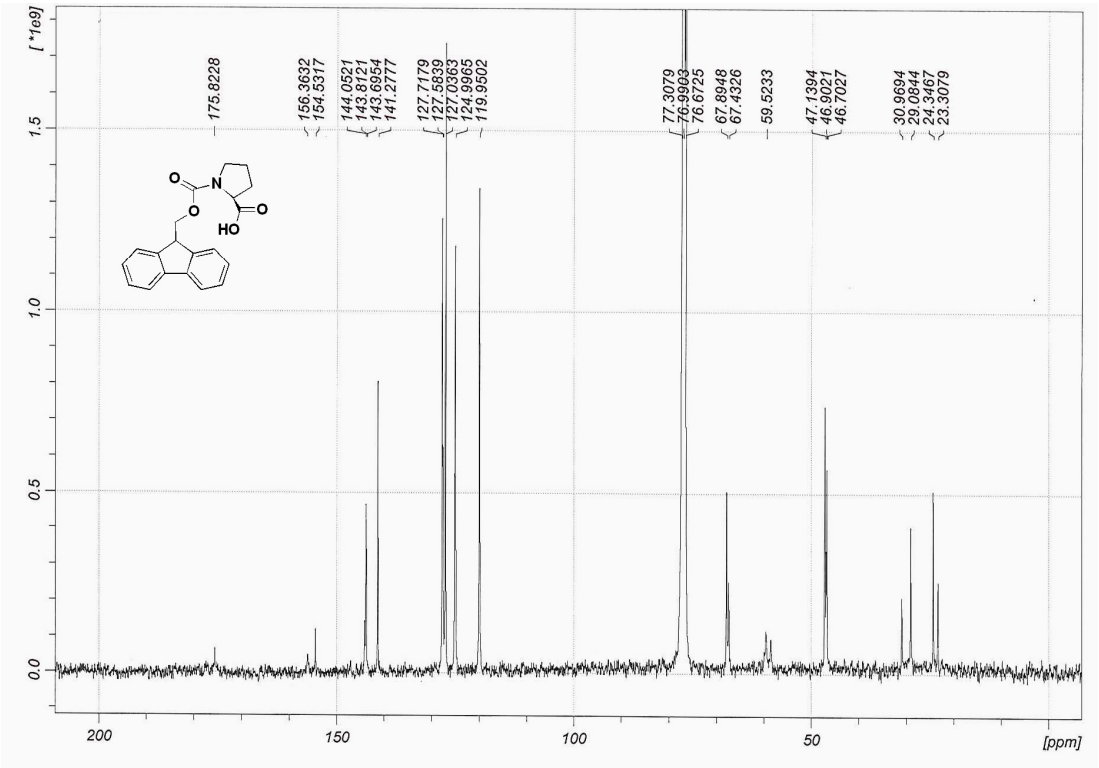
Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)alanine (**3u**).



Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)alanine (**3u**).



Proton NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)proline (**3v**).



Carbon NMR spectra of *N*-(9-fluorenylmethoxycarbonyl)proline (**3v**).

HPLC analysis of *N*-Fmoc α-amino acids

The HPLC - SHIMADZU(Japan), LC-20 AT pump.

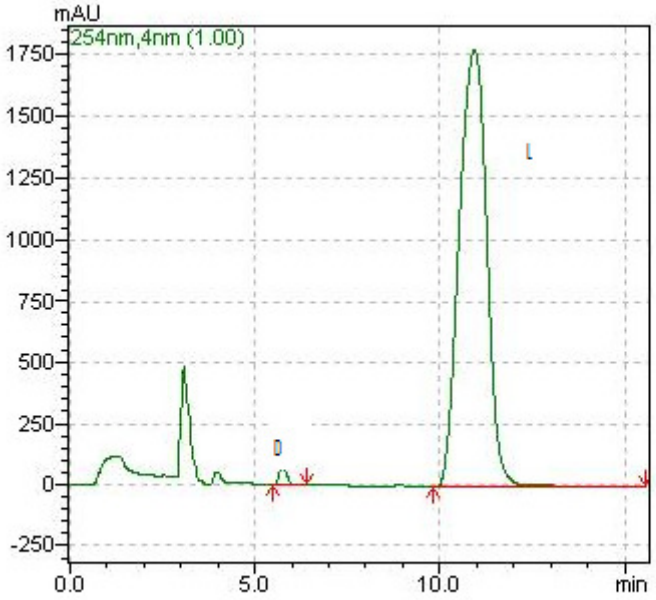
UV-dectector (SPD-M20A).

Chiralpak-IA (250mm X 4 mm).

Mobile phase consisted of 10 % Isopropyl alcohol : 90 % hexane containing 0.1 % TFA, flow rate 1 mL/ min.

Chromatograms for determination of the enantiomeric purity of

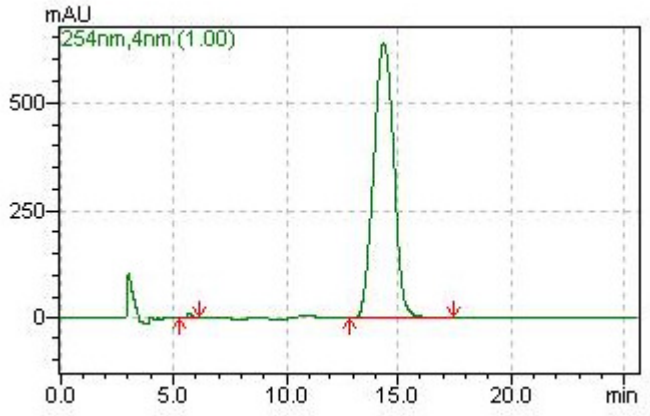
***N*-(9-Fluorenylmethoxycarbonyl)alanine (3u)**



No.	RT	Area	% Ratio	D or L
1	5.7	1065762	1.01 = 1	D
2	10.9	93498980	98.87 = 99	L

Chromatograms for determination of the enantiomeric purity of

N-(9-Fluorenylmethoxycarbonyl)proline (3v)



No.	RT	Area	% Ratio	D or L
1	5.9	195628	0.5	D
2	14.3	39836285	99.5	L