

Efficient Enantioselective Synthesis of 3-Aminochroman Derivatives Through Ruthenium-SYNPHOS Catalyzed Asymmetric Hydrogenation

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General information.

All reactions were run under an atmosphere of argon. Reaction vessels were flame-dried under vacuum and cooled under a stream of argon. Dichloromethane, methanol, ethanol, isopropanol and toluene were distilled on calcium hydride. Tetrahydrofuran, dioxane and ethyl acetate were distilled on sodium/benzophenone. These solvents were degassed prior to use.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded using a Bruker AVANCE 300 (300 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) relative to the singlet at 7.26 ppm for deuteriochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, quint, quintuplet, m, multiplet, br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Bruker AVANCE 300 (75 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.16 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. High resolution mass spectra were performed by the "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)". Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F 254), spots were detected with UV light and revealed with KMnO_4 solutions. Enantiomeric excesses were determined either by chiral supercritical fluid chromatography (SFC) on a BERGER instrument, or by HPLC analyses with Waters 600 system. Those analyses were performed using stationary phase column: Chiralpak AD-H, AS-H or OD-H. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium lamp).

Typical preparation of $[\text{Ru}(\text{diphosphine})]\text{Br}_2$

A dry 10 mL Schlenk tube was equipped with a magnetic stirrer bar, a stopper and connected to a supply of vacuum/argon. The flask was charged with $[\text{Ru}(\text{cycloocta-1.5-diene})(2\text{-methylallyl})_2]$ (0.01mmol) and of chiral diphosphine (0.011 mmol), then evacuated and filled with argon. Degassed anhydrous acetone (1 mL) was introduced via syringe under a stream of argon. Methanolic HBr (2.2 equiv) was added dropwise to the solution. The mixture was degassed with 3 vacuum/argon cycles and stirred for 30 min at r.t. under a stream of argon. The orange precipitate was concentrated under vacuum. The crude orange-brown solid was used as catalyst in the hydrogenation reaction without further purification.

Typical preparation of [Ru(H)(diphosphine)(COT)]⁺BF₄⁻

A dry 10 mL Schlenk tube was equipped with a magnetic stirrer bar, a stopper and connected to a supply of vacuum/argon. The flask was charged with [Ru(cycloocta-1.5-diene)(2-methylallyl)₂] (0.01 mmol) and of chiral diphosphine (0.011 mmol), then evacuated and filled with argon. Degassed anhydrous CH₂Cl₂ (1 mL) was introduced via syringe under a stream of argon. The mixture was degassed with 3 vacuum/argon cycles. A solution of HBF₄ Me₂O in CH₂Cl₂ (2 equiv) was added dropwise to the solution at 0°C. The mixture was stirred for 30 min at r.t. under a stream of argon. The orange precipitate was concentrated under vacuum. The crude orange-brown solid was used as catalyst in the hydrogenation reaction without further purification.

Typical preparation of [RuCl(diphosphine)₂(μ-Cl)₃][NH₂Me₂]

[RuCl₂(*p*-cymene)]₂ (12.8 mmol), diphosphine (25.6 mmol) and dimethylamine hydrochloride (19.2 mmol) were charged in a 500 mL reactor equipped with a condenser. The system was connected to a supply of vacuum/argon. Degassed anhydrous toluene (250 mL) was added and the mixture was degassed by 3 vacuum/argon cycles at r.t.. The mixture was refluxed for 7h and then cooled to r.t.. The red-orange suspension was homogenized by adding degassed CH₂Cl₂ (200 mL). The dark orange solution was filtered to eliminate excess dimethylamine hydrochloride crystals. CH₂Cl₂ was distilled off and orange solids were collected by filtration of the toluene solution. The solids were dried under reduced pressure at 45°C for 18h to give an orange-red powder.

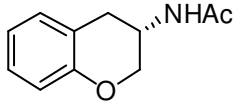
Typical preparation of [RuCl(diphosphine)(*p*-cymene)]⁺Cl⁻

[RuCl₂(*p*-cymene)]₂ (0.2 mmol), diphosphine (0.4 mmol) were placed in a 50 mL Schlenk tube equipped with a magnetic stirrer bar and a condenser. The system was connected to a supply of vacuum/argon. The mixture was degassed by 3 vacuum/argon cycles at r.t. degassed EtOH (15 mL) and anhydrous CH₂Cl₂ (6 mL) were added to the mixture. The orange mixture was refluxed (50°C) for 1.5h and then cooled to r.t.. The deep orange solution was filtered through a short pad of Celite under argon, eluting with degassed EtOH (5 mL) and anhydrous CH₂Cl₂ (5 mL). The solvents were evaporated under vacuum to give an orange solid.

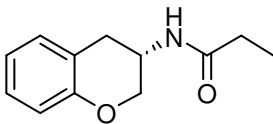
General procedure for Ru-(*S*)-Synphos catalyzed asymmetric hydrogenation of trisubstituted enamide derived from 3-chromanones :

In a round-bottomed tube were placed under an argon atmosphere the enamide (1mmol, 1 equiv) and the chiral preformed or *in situ* generated catalyst (0.01mmol, 1mol% of Ru). The mixture was degassed by three vacuum/argon cycles before adding 3mL of desired solvent. The resulting mixture was placed under the desired hydrogen pressure and temperature for 20h. After removal of the solvent, the conversion was determined by ¹H NMR analysis of the crude mixture. Subsequently, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 7:3). The enantiomeric excesses were determined by HPLC or SFC analysis.

(*S*)-*N*-(chroman-3-yl)acetamide-2a

 Yield = 96%, ee = 84%. HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, λ = 215 nm, *t*_R [(*S*)-enantiomer] = 12.27 min (majo.), *t*_R [(*R*)-enantiomer] = 23.50 min (mino.). ¹H NMR (CDCl₃, 300MHz) : δ 7.14 (t, *J* = 8.1Hz, 1H), 7.05 (d, *J* = 7.5Hz, 1H), 6.91 (td, *J* = 7.5Hz, *J* = 1.2Hz, 1H), 6.85 (dd, *J* = 8.1Hz, *J* = 1.5Hz, 1H), 5.88 (s large, 1H), 4.45-4.53 (m, 1H), 4.17 (ddd, *J* = 10.8Hz, *J* = 3.3Hz, *J* = 2.1Hz, 1H), 4.09 (dd, *J* = 11.1Hz, *J* = 1.8Hz, 1H), 3.13 (dd, *J* = 16.8Hz, *J* = 5.1Hz, 1H), 2.75 (dt, *J* = 16.8Hz, *J* = 2.4Hz, 1H), 1.96 (s, 3H). ¹³C NMR (CDCl₃, 75MHz) : δ 169.9, 153.8, 130.5, 127.8, 121.3, 119.3, 116.8, 68.1, 42.3, 30.7, 23.2. HRMS (ESI)¹ *m/z* calculated for C₁₁H₁₃NO₂ : 191.0646, found 191.0916. [α]_D²⁴ = +22.16 (c = 1; CHCl₃).

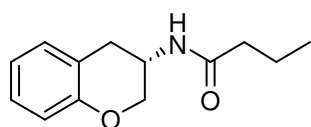
(*S*)-*N*-(chroman-3-yl)propionamide-2b

 Yield% = 93%, ee = 80%. SFC : Chiralcel AD-H, scCO₂/MeOH 90/10, flow 4 mL/min, P = 150 bar, λ = 215 nm) *t*₁ [(*R*)-enantiomer] = 2.90 min (mino), *t*₂ [(*S*)-enantiomer] = 3.24 min (majo). ¹H NMR (CDCl₃, 300MHz) : δ 7.13 (t, *J* = 7.5Hz, 1H), 7.05 (d, *J* = 7.2Hz, 1H), 6.90 (td, *J* = 7.5Hz, *J* = 1.2Hz, 1H), 6.85 (d, *J* = 8.1Hz, 1H), 5.84 (d large, *J* = 5.6Hz, 1H), 4.46-4.53 (m, 1H), 4.15 (ddd, *J* = 11.1Hz, *J* = 3.6Hz, *J* = 2.1Hz, 1H), 4.09 (dd, *J* = 11.1Hz, *J* = 1.8Hz, 1H), 3.12 (dd, *J*

¹ Renaud, J. L.; Dupau, P.; Hay, A. E.; Guingouain, M.; Dixneuf, P. H.; Bruneau, C. *Adv. Synth. Catal.* **2003**, 345, 230

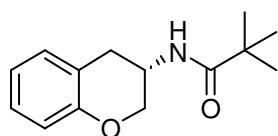
= 16.8Hz, $J = 5.1\text{Hz}$, 1H), 2.74 (d, $J = 16.8\text{Hz}$, 1H), 2.16 (q, $J = 7.5\text{Hz}$, 2H), 1.12 (t, $J = 7.5\text{Hz}$, 3H). ^{13}C NMR (75MHz, CDCl_3) : δ 173.5, 153.8, 130.5, 127.7, 121.2, 119.3, 116.8, 68.1, 42.0, 30.7, 29.6, 9.6. HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{NNa}$: 228.1000, found 228.0995. $[\alpha]_{\text{D}}^{24} = -17.15$ ($c = 1$; CHCl_3).

(S)-N-(chroman-3-yl)butyramide-2c



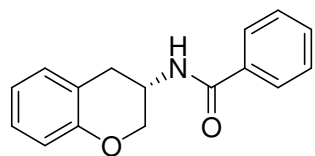
Yield% = 92%, ee = 77%. SFC : Chiralcel AS-H, $\text{scCO}_2/\text{MeOH}$ 90/10, flow 4 mL/min, P = 150 bar, $\lambda = 215$ nm) t_1 [(R)-enantiomer] = 2.92 min (mino), t_2 [(S)-enantiomer] = 3.67 min (majo). ^1H NMR (CDCl_3 , 300MHz) : δ 7.14 (t, $J = 7.2\text{Hz}$, 1H), 7.05 (d, $J = 7.2\text{Hz}$, 1H), 6.90 (td, $J = 7.5\text{Hz}$, $J = 1.2\text{Hz}$, 1H), 6.85 (d, $J = 8.4\text{Hz}$, 1H), 5.80 (d large, $J = 3.9\text{Hz}$, 1H), 4.47-4.54 (m, 1H), 4.16 (ddd, $J = 11.1\text{Hz}$, $J = 3.6\text{Hz}$, $J = 2.4\text{Hz}$, 1H), 4.08 (dd, $J = 11.1\text{Hz}$, $J = 1.8\text{Hz}$, 1H), 3.12 (dd, $J = 16.8\text{Hz}$, $J = 5.4\text{Hz}$, 1H), 2.74 (d, $J = 16.8\text{Hz}$, 1H), 2.12 (t, $J = 7.2\text{Hz}$, 2H), 1.63 (h, $J = 7.5\text{Hz}$, 2H), 0.90 (t, $J = 7.5\text{Hz}$, 3H). ^{13}C NMR (75MHz, CDCl_3) : δ 172.7, 153.8, 130.5, 127.7, 121.2, 119.3, 116.8, 68.2, 42.0, 38.6, 30.7, 19.0, 13.6. HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{NNa}$: 242.1157, found 242.1151. $[\alpha]_{\text{D}}^{24} = -14.61$ ($c = 1$; CHCl_3).

(S)-N-(chroman-3-yl)pivalamide-2d



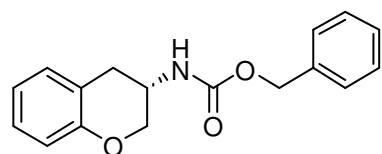
Yield% = 88%, ee = 80%. SFC : Chiralcel AD-H, $\text{scCO}_2/\text{MeOH}$ 95/5, flow 4 mL/min, P = 150 bar, $\lambda = 215$ nm) t_1 [(R)-enantiomer] = 4.11 min (mino), t_2 [(S)-enantiomer] = 8.83 min (majo). ^1H NMR (CDCl_3 , 300MHz) : δ 7.13 (dd, $J = 7.2\text{Hz}$, $J = 0.6\text{Hz}$, 1H), 7.05 (d, $J = 7.2\text{Hz}$, 1H), 6.91 (dd, $J = 7.5\text{Hz}$, $J = 1.2\text{Hz}$, 1H), 6.86 (d, $J = 8.4\text{Hz}$, 1H), 5.93 (d large, $J = 5.4\text{Hz}$, 1H), 4.43-4.50 (m, 1H), 4.12 (dd, $J = 3.6\text{Hz}$, $J = 1.8\text{Hz}$, 2H), 3.12 (dd, $J = 16.8\text{Hz}$, $J = 5.4\text{Hz}$, 1H), 2.73 (ddd, $J = 16.8\text{Hz}$, $J = 3.0\text{Hz}$, $J = 1.2\text{Hz}$, 1H), 1.14 (s, 9H). ^{13}C NMR (75MHz, CDCl_3) : δ 178.3, 153.8, 130.4, 127.7, 121.2, 119.4, 116.8, 68.2, 42.1, 38.7, 41.7, 27.5. HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{NNa}$: 256.1313, found 256.1308. $[\alpha]_{\text{D}}^{24} = -6.60$ ($c = 1$; CHCl_3).

(S)-N-Chroman-3-yl-benzamide-2e



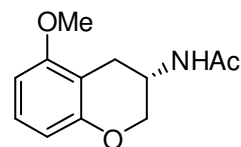
Yield% = 91%, ee = 76%. SFC : Chiralcel AS-H, scCO₂/MeOH 90/10, flow 3 mL/min, P = 150 bar, λ = 215 nm) t_1 [(R)-enantiomer] = 8.75 min (mino), t_2 [(S)-enantiomer] = 10.07 min (majo). ¹H NMR (CDCl₃, 300MHz) : δ 7.71 (d, J = 7.2Hz, 2H), 7.37-7.51 (m, 3H), 7.15 (t, J = 7.5Hz, 1H), 7.08 (d, J = 7.5Hz, 1H), 6.93 (dd, J = 8.7Hz, J = 0.9Hz, 1H), 6.88 (d, J = 7.2Hz, 1H), 6.46 (d large, J = 7.5Hz, 1H), 4.67-4.75 (m, 1H), 4.30 (ddd, J = 6.0Hz, J = 3.9Hz, J = 2.4Hz, 1H), 4.20 (dd, J = 10.8Hz, J = 1.5Hz, 1H), 3.23 (dd, J = 16.8Hz, J = 5.1Hz, 1H), 2.91 (d, J = 16.8Hz, 1H). ¹³C NMR (75MHz, CDCl₃) : δ 167.3, 153.9, 134.2, 131.6, 130.6, 128.5, 127.8, 126.9, 121.4, 119.3, 116.9, 68.2, 42.8, 30.8. $[\alpha]_D^{24}$ = -36.34 (c = 1; CHCl₃).

(S)-benzyl chroman-3-ylcarbamate-2f



Yield% = 60%, ee = 40%. SFC : Chiralcel AS-H, scCO₂/MeOH 90/10, flow 2 mL/min, P = 150 bar, λ = 215 nm) t_1 [(R)-enantiomer] = 9.00 min (mino), t_2 [(S)-enantiomer] = 9.54 min (majo). ¹H NMR (CDCl₃, 300MHz) : δ 7.34-7.39 (m, 5H), 7.12 (t, J = 7.8Hz, 1H), 7.04 (d, J = 7.2Hz, 1H), 6.89 (td, J = 7.5Hz, J = 1.2Hz, 1H), 6.83 (d, J = 8.1Hz, 1H), 6.34 (d large, J = 1.5Hz, 1H), 5.09 (s, 2H), 4.24-4.27 (m, 1H), 4.10-4.14 (m, 2H), 3.13 (dd, J = 16.8Hz, J = 4.5Hz, 1H), 2.77(d, J = 16.8Hz, 1H). ¹³C NMR (75MHz, CDCl₃) : δ 155.7, 153.8, 136.2, 130.4, 128.5, 128.2, 127.8, 121.2, 119.1, 116.8, 68.2, 68.0, 66.9, 43.9, 31.0. $[\alpha]_D^{24}$ = -15.87 (c = 1; CHCl₃).

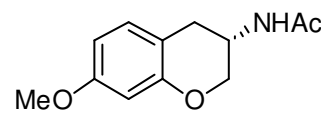
(S)-N-(5-methoxychromen-3-yl)acetamide-2g



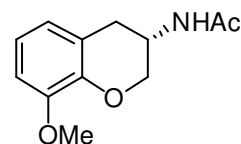
Yield% = 85%. ee = 34%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, λ = 215 nm, t_R [(S)-enantiomer] = 13.44 min (majo.), t_R [(R)-enantiomer] = 29.38 min (mino.). ¹H NMR (CDCl₃, 300MHz) : δ 7.09 (t, J = 8.4Hz, 1H), 6.48 (dd, J = 14.4Hz, J = 8.1Hz, 2H), 5.90 (s large, 1H), 4.45-4.51 (m, 1H), 4.12 (ddd, J = 10.8Hz, J = 3.6Hz, J = 2.1Hz, 1H), 4.02 (dd, J = 10.8Hz, J = 1.8Hz, 1H), 3.79 (s, 3H), 2.86 (dd, J = 17.7Hz, J = 5.7Hz, 1H), 2.72 (dt, J = 17.7Hz, J = 2.4Hz, 1H), 1.95 (s, 3H). ¹³C NMR (CDCl₃, 75MHz) : δ 169.8, 158.5, 154.6,

127.4, 109.4, 108.5, 102.5, 67.7, 55.4, 41.7, 25.6, 23.4. HRMS (ESI) m/z calculated for $C_{12}H_{15}O_3NNa$: 244.0950, found 244.0944. $[\alpha]_D^{24} = +12.80$ (c = 1; $CHCl_3$).

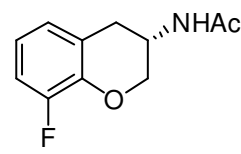
(S)-N-(7-methoxychromen-3-yl)acetamide-2h

 Yield% = 89%. ee = 74%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_R [(S)-enantiomer] = 20.10 min (majo.), t_R [(R)-enantiomer] = 27.81 min (mino.). 1H NMR ($CDCl_3$, 300MHz) : δ 6.94 (d, $J = 5.4$ Hz, 1H), 6.50 (dd, $J = 5.4$ Hz, $J = 2.4$ Hz, 1H), 6.40 (d, $J = 2.7$ Hz, 1H), 5.86 (s large, 1H), 4.42-4.50 (m, 1H), 4.15 (ddd, $J = 10.8$ Hz, $J = 3.6$ Hz, $J = 2.4$ Hz, 1H), 4.06 (dd, $J = 10.8$ Hz, $J = 1.8$ Hz, 1H), 3.76 (s, 3H), 3.04 (dd, $J = 16.5$ Hz, $J = 5.1$ Hz, 1H), 2.67 (dt, $J = 16.5$ Hz, $J = 2.4$ Hz, 1H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) : δ 169.8, 159.4, 154.6, 131.0, 111.1, 108.3, 101.7, 68.2, 55.4, 42.3, 30.1, 23.5. HRMS (ESI) m/z calculated for $C_{12}H_{15}O_3NNa$: 244.0950, found 244.0944. $[\alpha]_D^{24} = +24.51$ (c = 1; $CHCl_3$).

(S)-N-(8-methoxychromen-3-yl)acetamide-2i

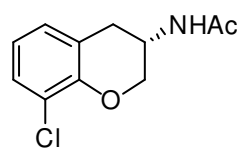
 Yield% = 93%. ee = 91%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_R [(S)-enantiomer] = 16.22 min (majo.), t_R [(R)-enantiomer] = 23.95 min (mino.). 1H NMR ($CDCl_3$, 300MHz) : δ 6.87 (t, $J = 8.1$ Hz, 1H), 6.76 (d, $J = 7.2$ Hz, 1H), 6.67 (d, $J = 7.8$ Hz, 1H), 5.96 (s large, 1H), 4.47-4.54 (m, 1H), 4.32 (dt, $J = 11.1$ Hz, $J = 2.7$ Hz, 1H), 4.12 (dd, $J = 11.1$ Hz, $J = 1.5$ Hz, 1H), 3.88 (s, 3H), 3.12 (dd, $J = 16.8$ Hz, $J = 5.4$ Hz, 1H), 2.77 (dt, $J = 16.8$ Hz, $J = 2.4$ Hz, 1H), 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) : δ 169.8, 148.2, 143.1, 122.1, 120.9, 120.1, 109.3, 68.5, 55.7, 42.0, 30.4, 23.3. HRMS (ESI) m/z calculated for $C_{12}H_{15}O_3NNa$: 244.0950, found 244.0944. $[\alpha]_D^{24} = +13.33$ (c = 1; $CHCl_3$).

(S)-N-(8-fluorochromen-3-yl)acetamide-2j

 Yield% = 97%. ee = 92%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_R [(S)-enantiomer] = 16.34 min (mino.), t_R [(R)-enantiomer] = 17.32 min (majo.). 1H NMR ($CDCl_3$, 300MHz) : δ 6.90-6.97 (m, 1H), 6.81-6.86 (m, 2H), 5.95 (s large, 1H), 4.47-4.54 (m,

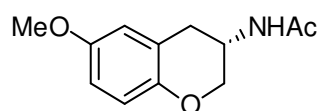
1H), 4.27 (ddd, $J = 11.1\text{Hz}$, $J = 3.6\text{Hz}$, $J = 2.1\text{Hz}$, 1H), 4.09-4.15 (m, 1H), 3.11 (dd, $J = 16.8\text{Hz}$, $J = 5.4\text{Hz}$, 1H), 2.80 (dt, $J = 17.1\text{Hz}$, $J = 3.0\text{Hz}$, 1H), 1.96 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz) : δ 169.9, 151.3, 142.0, 125.3, 121.9, 120.7, 114.2, 68.4, 41.9, 30.3, 23.3. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{NFNa}$: 232.0750, found 232.0744. $[\alpha]_{\text{D}}^{24} = +10.69$ (c = 1; CHCl_3).

(S)-N-(8-chlorochroman-3-yl)acetamide-2k



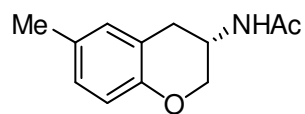
Yield% = 92%. ee = 93%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_{R} [(*S*)-enantiomer] = 17.96 min (majo.), t_{R} [(*R*)-enantiomer] = 29.05 min (mino.). ^1H NMR (CDCl_3 , 300MHz) : δ 7.23 (dt, $J = 7.8\text{Hz}$, $J = 0.9\text{Hz}$, 1H), 6.97 (dd, $J = 6.9\text{Hz}$, $J = 0.9\text{Hz}$, 1H), 6.85 (t, $J = 7.8\text{Hz}$, 1H), 5.83 (s large, 1H), 4.49-4.55 (m, 1H), 4.33 (ddd, $J = 11.4\text{Hz}$, $J = 3.6\text{Hz}$, $J = 2.4\text{Hz}$, 1H), 4.17 (dd, $J = 11.1\text{Hz}$, $J = 1.8\text{Hz}$, 1H), 3.13 (dd, $J = 17.1\text{Hz}$, $J = 5.1\text{Hz}$, 1H), 2.82 (dt, $J = 17.1\text{Hz}$, $J = 2.4\text{Hz}$, 1H), 1.97 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz) : δ 169.9, 149.5, 128.9, 128.6, 121.7, 121.4, 121.1, 68.9, 42.0, 30.7, 23.3. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{NFNa}$: 248.0454, found 248.0449. $[\alpha]_{\text{D}}^{24} = -8.40$ (c = 1; CHCl_3).

(S)-N-(6-methoxychroman-3-yl)acetamide-2l



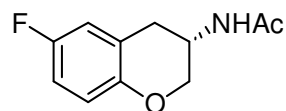
Yield% = 94%. ee = 91%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_{R} [(*S*)-enantiomer] = 15.71 min (majo.), t_{R} [(*R*)-enantiomer] = 37.58 min (mino.). ^1H NMR (CDCl_3 , 300MHz) : δ 6.78 (d, $J = 9.0\text{Hz}$, 1H), 6.70 (dd, $J = 9.0\text{Hz}$, $J = 2.7\text{Hz}$, 1H), 6.57 (d, $J = 2.7\text{Hz}$, 1H), 5.94 (s large, 1H), 4.43-4.48 (m, 1H), 4.12 (ddd, $J = 10.8\text{Hz}$, $J = 3.3\text{Hz}$, $J = 2.1\text{Hz}$, 1H), 4.03 (dd, $J = 10.8\text{Hz}$, $J = 1.5\text{Hz}$, 1H), 3.74 (s, 3H), 3.10 (dd, $J = 16.8\text{Hz}$, $J = 5.1\text{Hz}$, 1H), 2.73 (d, $J = 16.8\text{Hz}$, 1H), 1.96 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz) : δ 169.8, 154.0, 147.7, 119.9, 117.5, 114.6, 113.9, 68.1, 55.7, 42.3, 31.0, 23.4. HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{NNa}$: 244.0950, found 244.0944. $[\alpha]_{\text{D}}^{24} = +16.24$ (c = 1; CHCl_3).

(S)-N-(6-methylchroman-3-yl)acetamide-2m



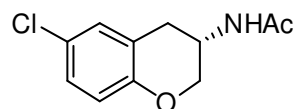
Yield% = 97%. ee = 91%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, λ = 215 nm, t_R [(*S*)-enantiomer] = 11.33 min (majo.), t_R [(*R*)-enantiomer] = 23.51 min (mino.). ^1H NMR (CDCl_3 , 300MHz) : δ 6.94 (dd, J = 8.1Hz, J = 1.8Hz, 1H), 6.85 (s, 1H), 6.75 (d, J = 8.4Hz, 1H), 5.95 (s large, 1H), 4.42-4.49 (m, 1H), 4.14 (ddd, J = 10.8Hz, J = 3.3Hz, J = 2.1Hz, 1H), 4.05 (dd, J = 10.8Hz, J = 1.8Hz, 1H), 3.08 (dd, J = 16.8Hz, J = 5.4Hz, 1H), 2.71 (dt, J = 16.8Hz, J = 2.4Hz, 1H), 2.26 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz) : δ 169.9, 151.6, 130.7, 130.6, 128.4, 119.0, 116.6, 68.1, 42.6, 30.7, 23.4, 20.5. HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{NNa}$: 228.1001, found 228.0995. $[\alpha]_D^{24}$ = +25.15 (c = 1; CHCl_3).

(S)-N-(6-fluorochroman-3-yl)acetamide-2n



Yield% = 95%. ee = 94%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, λ = 215 nm, t_R [(*S*)-enantiomer] = 12.27 min (majo.), t_R [(*R*)-enantiomer] = 23.50 min (mino.). ^1H NMR (CDCl_3 , 300MHz) : δ 6.73-6.87 (m, 3H), 5.88 (s large, 1H), 4.42-4.50 (m, 1H), 4.14 (ddd, J = 11.1Hz, J = 3.6Hz, J = 2.4Hz, 1H), 4.05 (dd, J = 11.1Hz, J = 1.8Hz, 1H), 3.11 (dd, J = 17.1Hz, J = 5.4Hz, 1H), 2.75 (d, J = 17.1Hz, 1H), 1.96 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz,) : δ 169.9, 157.2, 149.7, 120.6, 117.8, 116.2, 114.6, 68.1, 41.9, 30.8, 23.3. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{NFNa}$: 232.0750, found 232.0744. $[\alpha]_D^{24}$ = +5.60 (c = 1; CHCl_3).

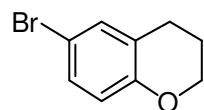
(S)-N-(6-chlorochroman-3-yl)acetamide-2o



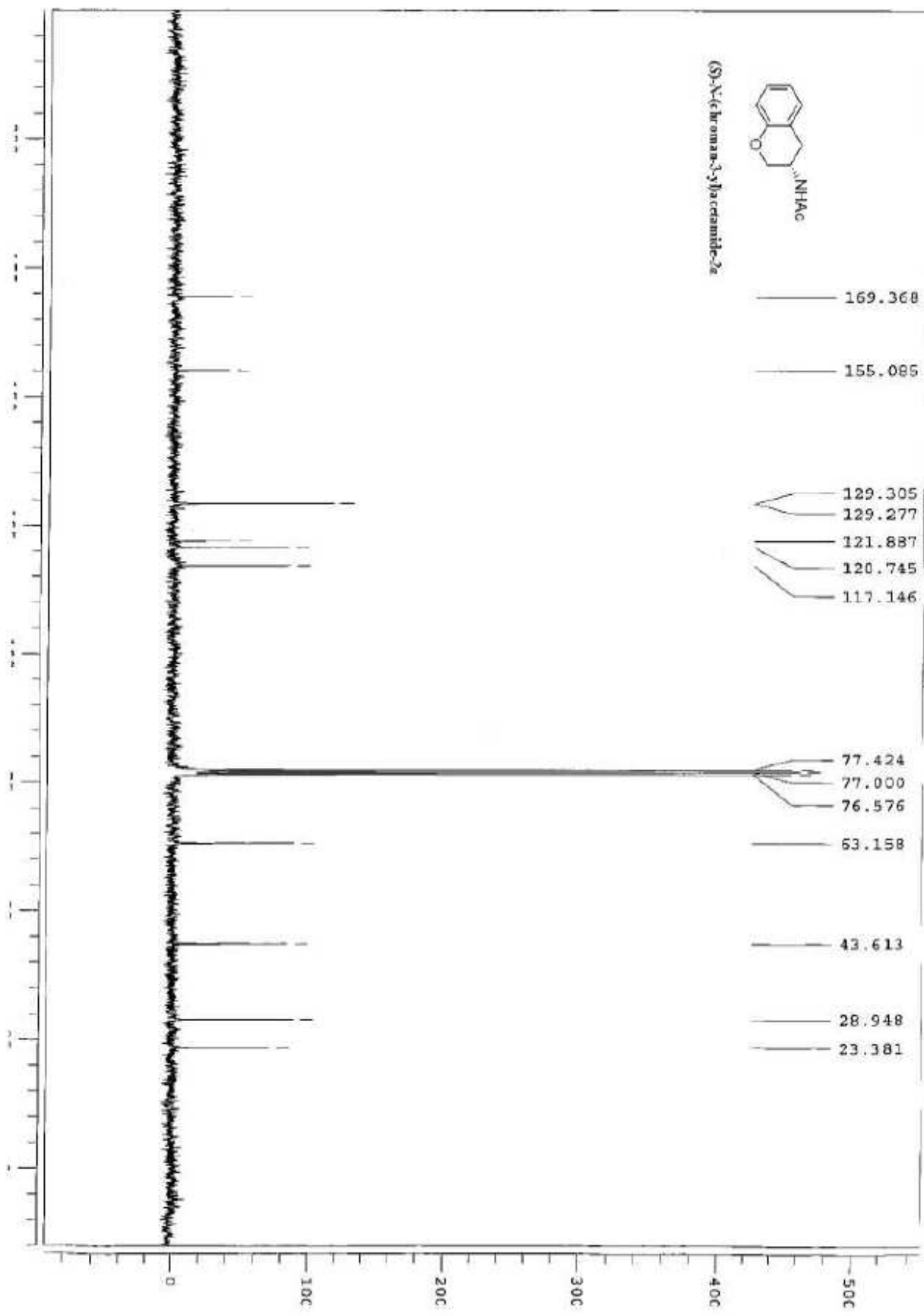
Yield% = 93%. ee = 95%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, λ = 215 nm, t_R [(*S*)-enantiomer] = 13.42 min (majo.), t_R [(*R*)-enantiomer] = 38.96 min (mino.). ^1H NMR (CDCl_3 , 300MHz) : δ 7.09 (dd, J = 8.7Hz, J = 2.5Hz, 1H), 7.03 (d, J = 2.5Hz, 1H), 6.79 (d, J = 8.7Hz, 1H), 5.78 (s large, 1H), 4.45-4.50 (m, 1H), 4.17 (ddd, J = 11.1Hz, J = 3.5Hz, J = 2.3Hz, 1H), 4.07 (dd, J = 11.1Hz, J = 1.9Hz, 1H), 3.08 (dd, J = 16.8Hz, J = 5.2Hz, 1H), 2.73 (td, J = 17.0Hz, J = 2.5Hz, 1H), 1.97 (s, 3H). ^{13}C NMR (CDCl_3 , 75MHz) : δ 169.9, 152.4, 130.0,

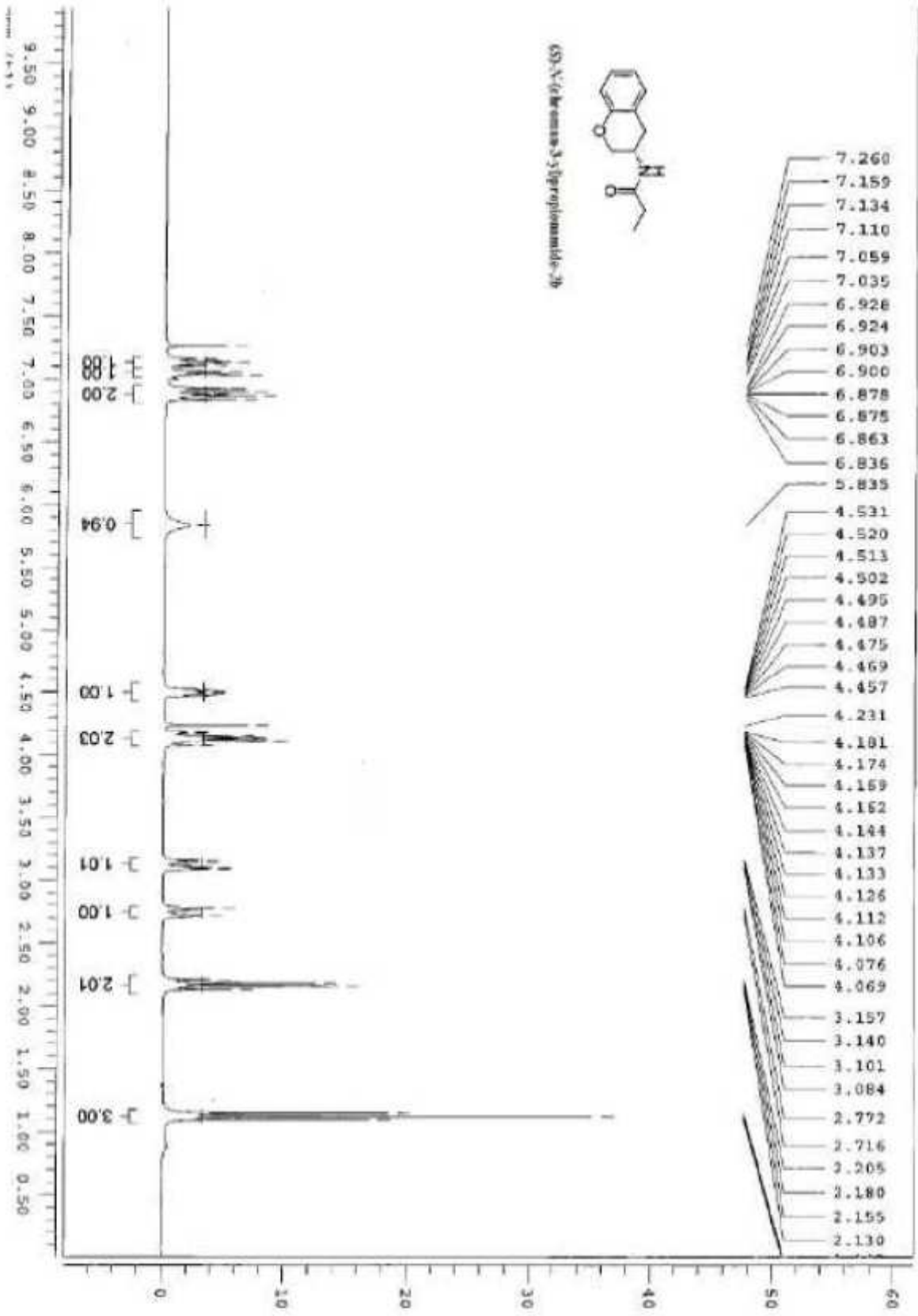
127.8, 125.6, 120.9, 118.2, 68.2, 41.9, 30.6, 23.3. HRMS (ESI) m/z calculated for $C_{11}H_{12}O_2NClNa$: 248.0454, found 248.0449. $[\alpha]_D^{24} = +54.20$ (c = 1; $CHCl_3$).

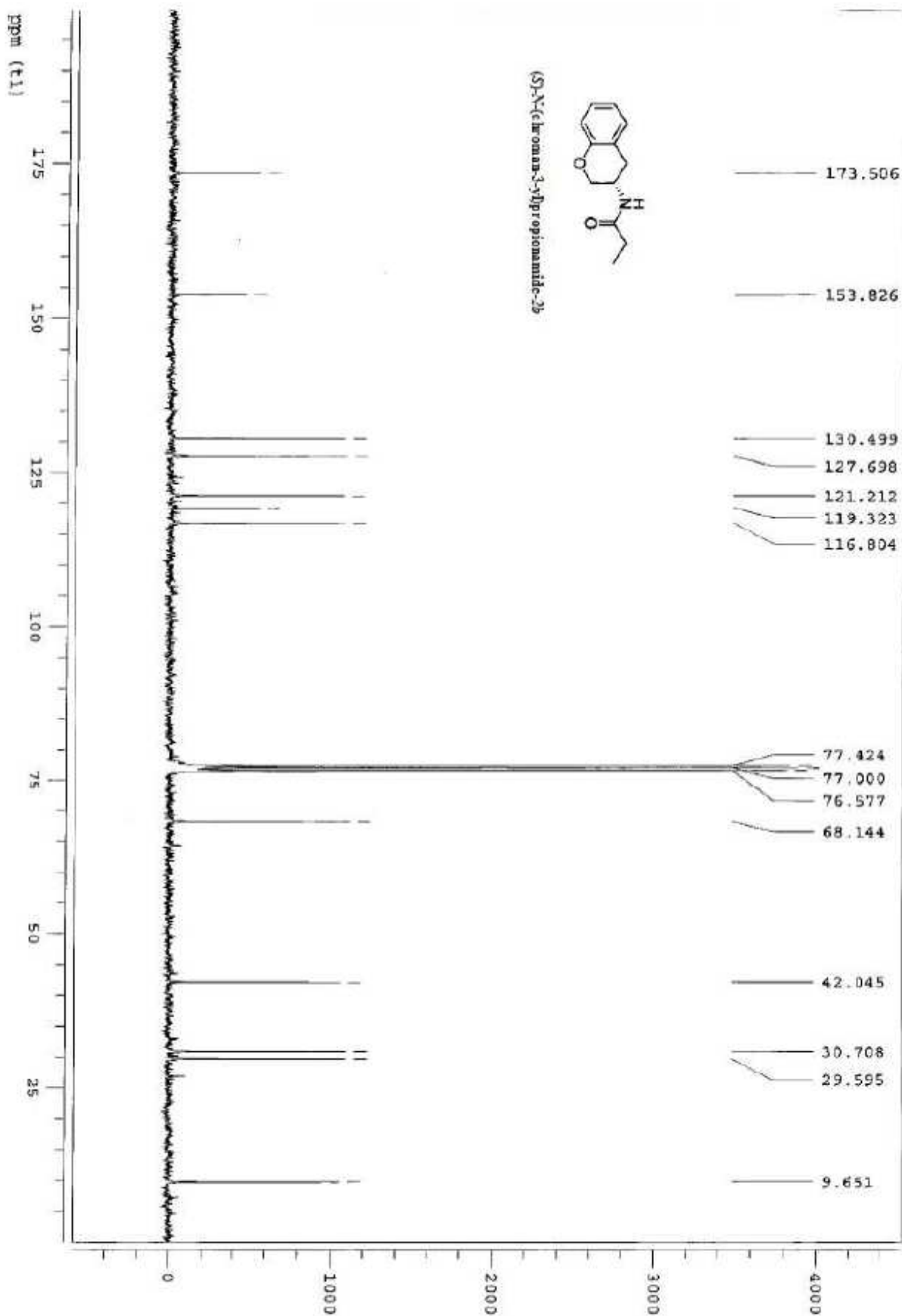
(S)-N-(6-bromochroman-3-yl)acetamide-2p

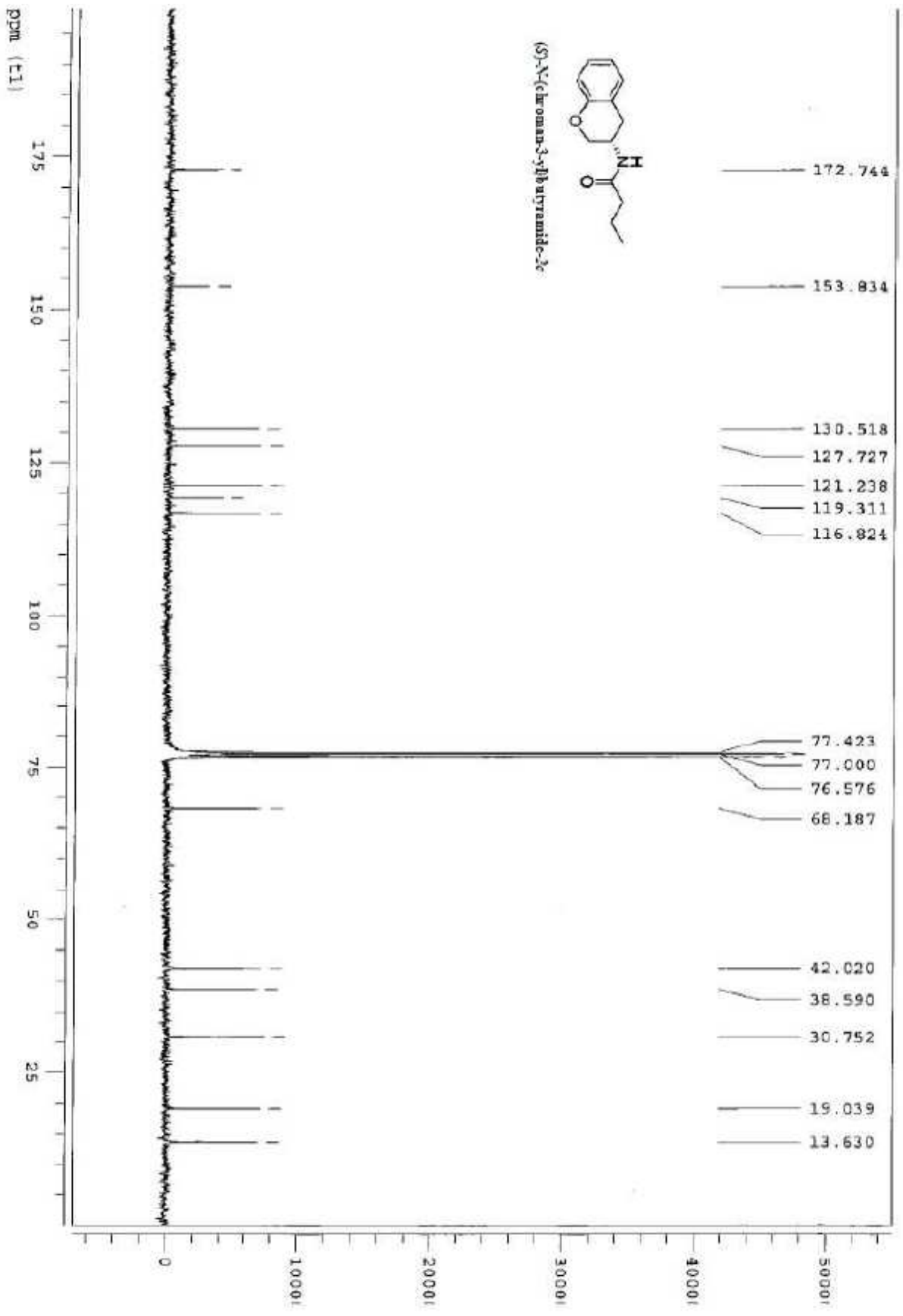


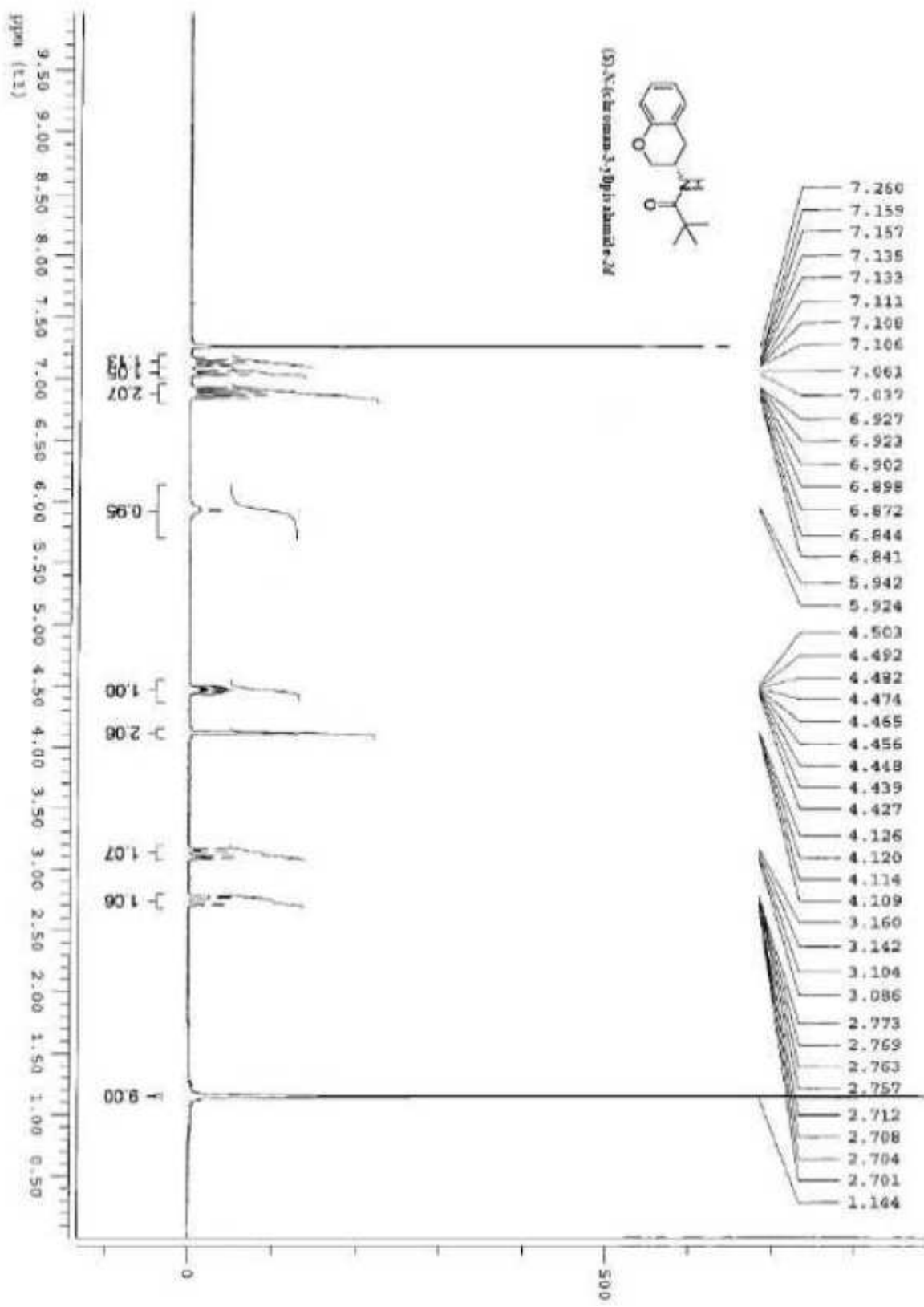
Yield% = 92%. ee = 96%, HPLC: Chiralcel AS-H column, *n*-Hexane/*i*PrOH 70/30, flow 1 mL/min, $\lambda = 215$ nm, t_R [(*S*)-enantiomer] = 13.20 min (majo.), t_R [(*R*)-enantiomer] = 42.61 min (mino.). 1H NMR ($CDCl_3$, 300MHz) : δ 7.15 (dd, $J = 8.6Hz$, $J = 2.4Hz$, 1H), 7.10 (d, $J = 2.3Hz$, 1H), 6.66 (d, $J = 8.5Hz$, 1H), 5.87 (d large, $J = 5.6Hz$, 1H), 4.35-4.40 (m, 1H), 4.08 (ddd, $J = 11.1Hz$, $J = 3.6Hz$, $J = 2.2Hz$, 1H), 4.00 (dd, $J = 11.1Hz$, $J = 1.9Hz$, 1H), 3.01 (dd, $J = 16.8Hz$, $J = 5.1Hz$, 1H), 2.66 (d, $J = 16.8Hz$, 1H), 1.89 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) : δ 169.9, 153.0, 132.9, 130.7, 121.5, 118.6, 113.2, 68.2, 41.9, 30.5, 23.3. HRMS (ESI) m/z calculated for $C_{11}H_{12}O_2NBrNa$: 291.9949, found 241.9944. $[\alpha]_D^{24} = +27.72$ (c = 1; $CHCl_3$).

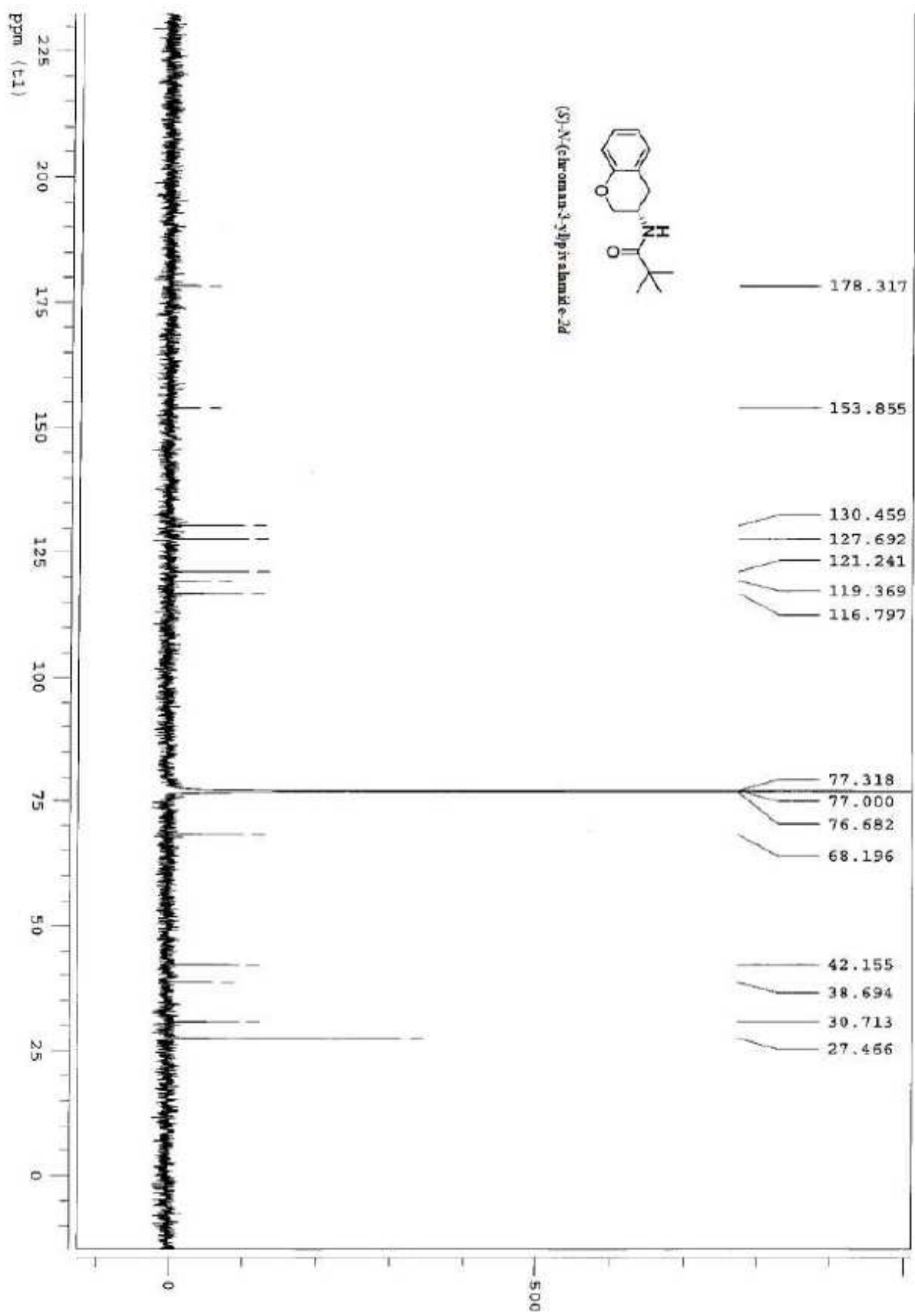


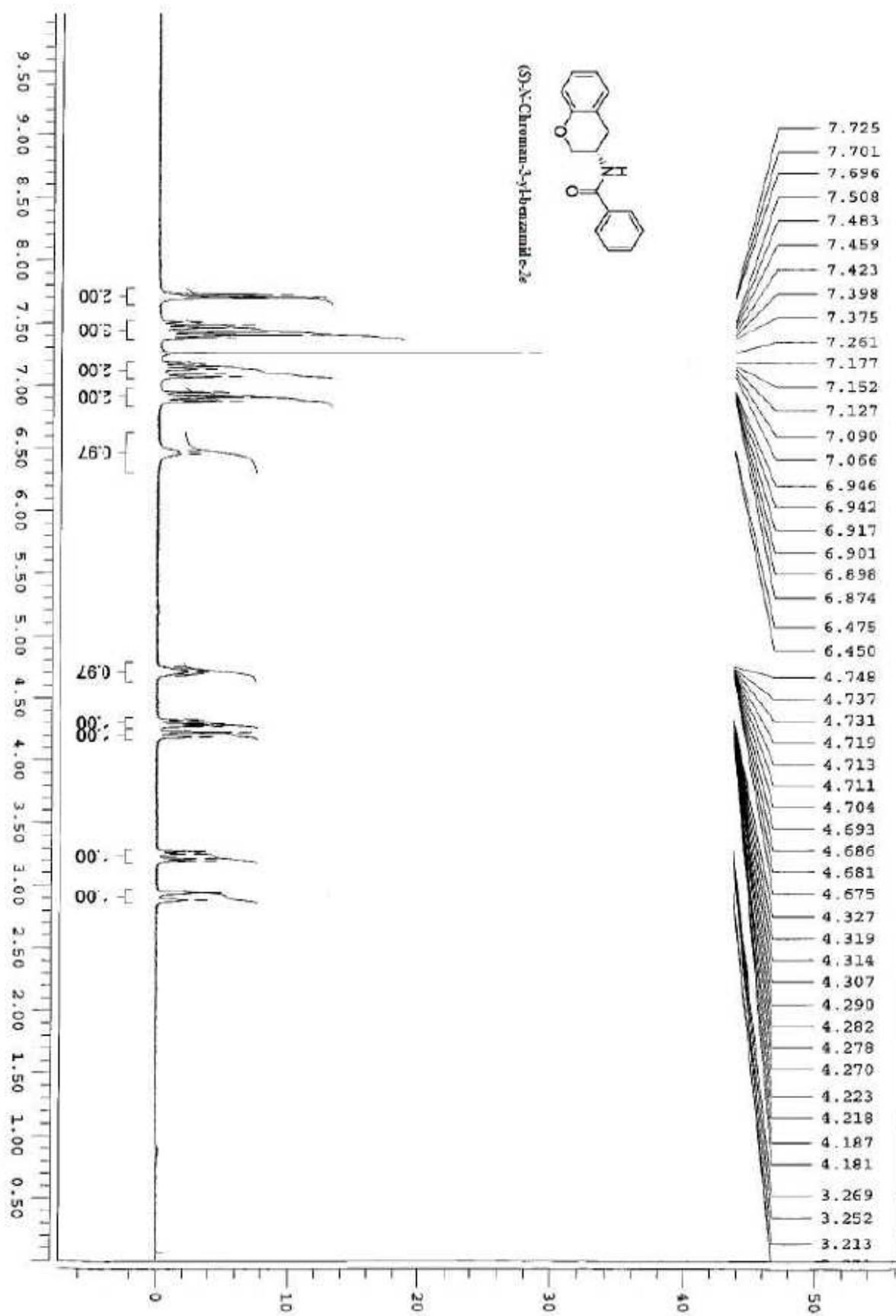


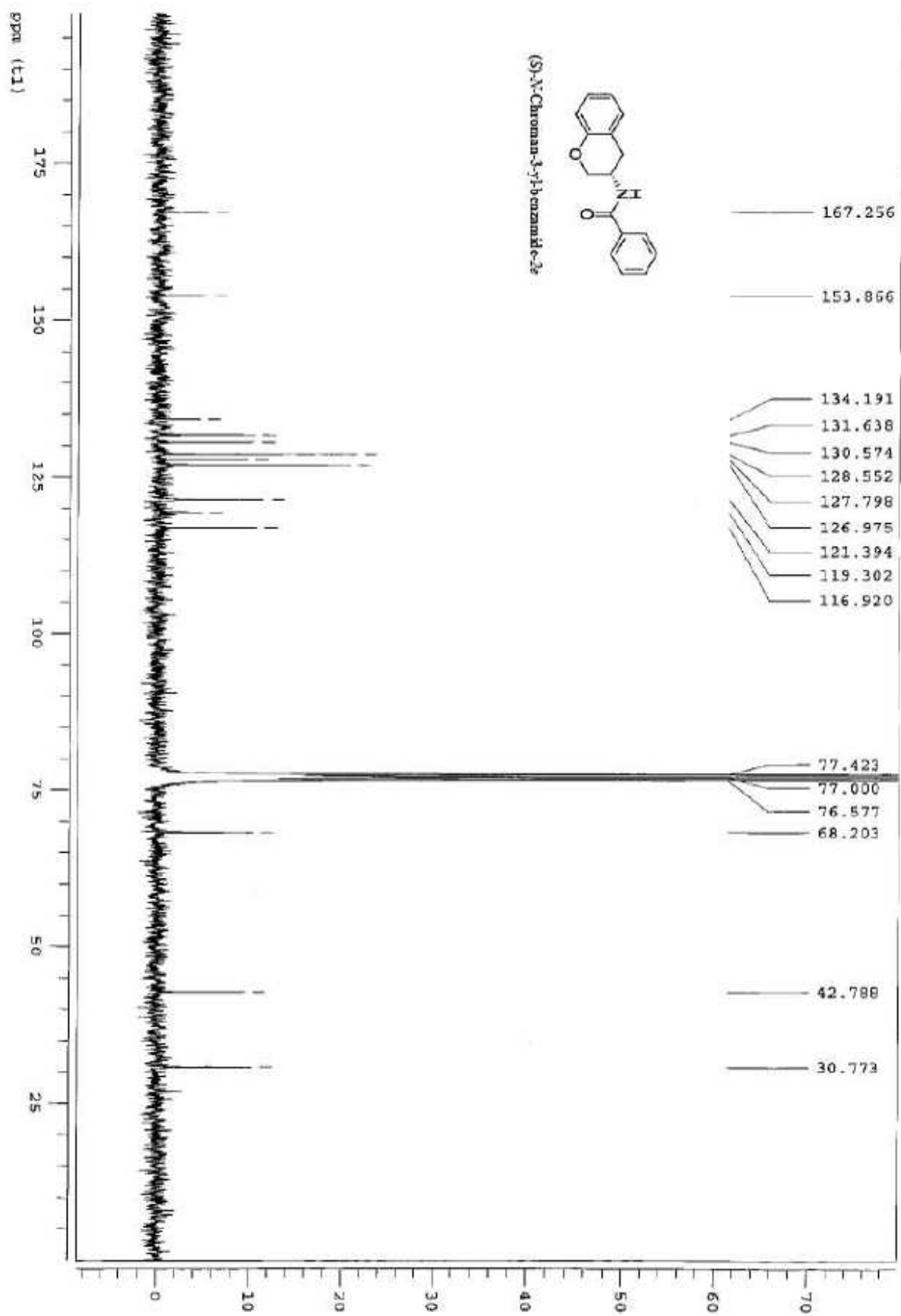


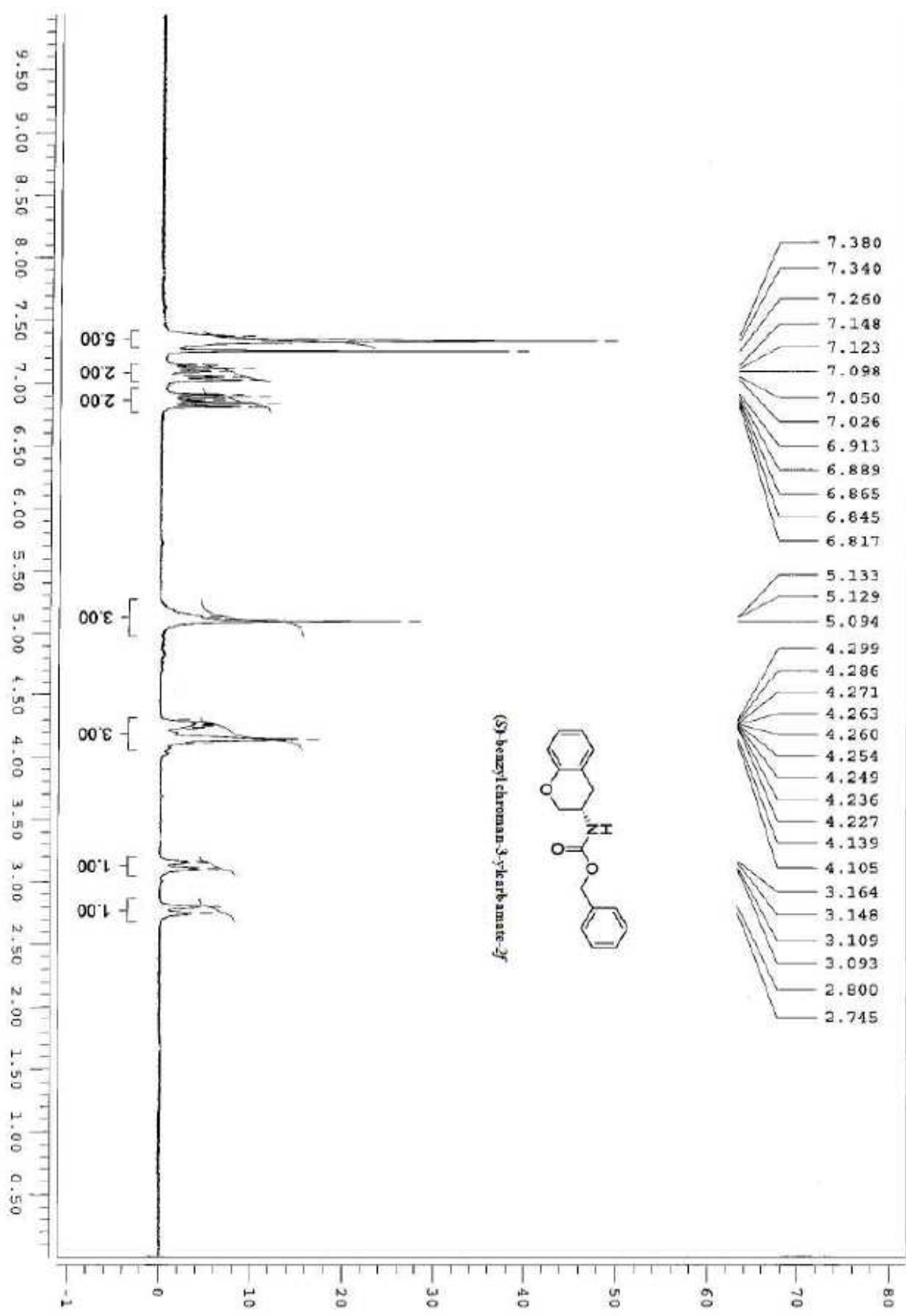


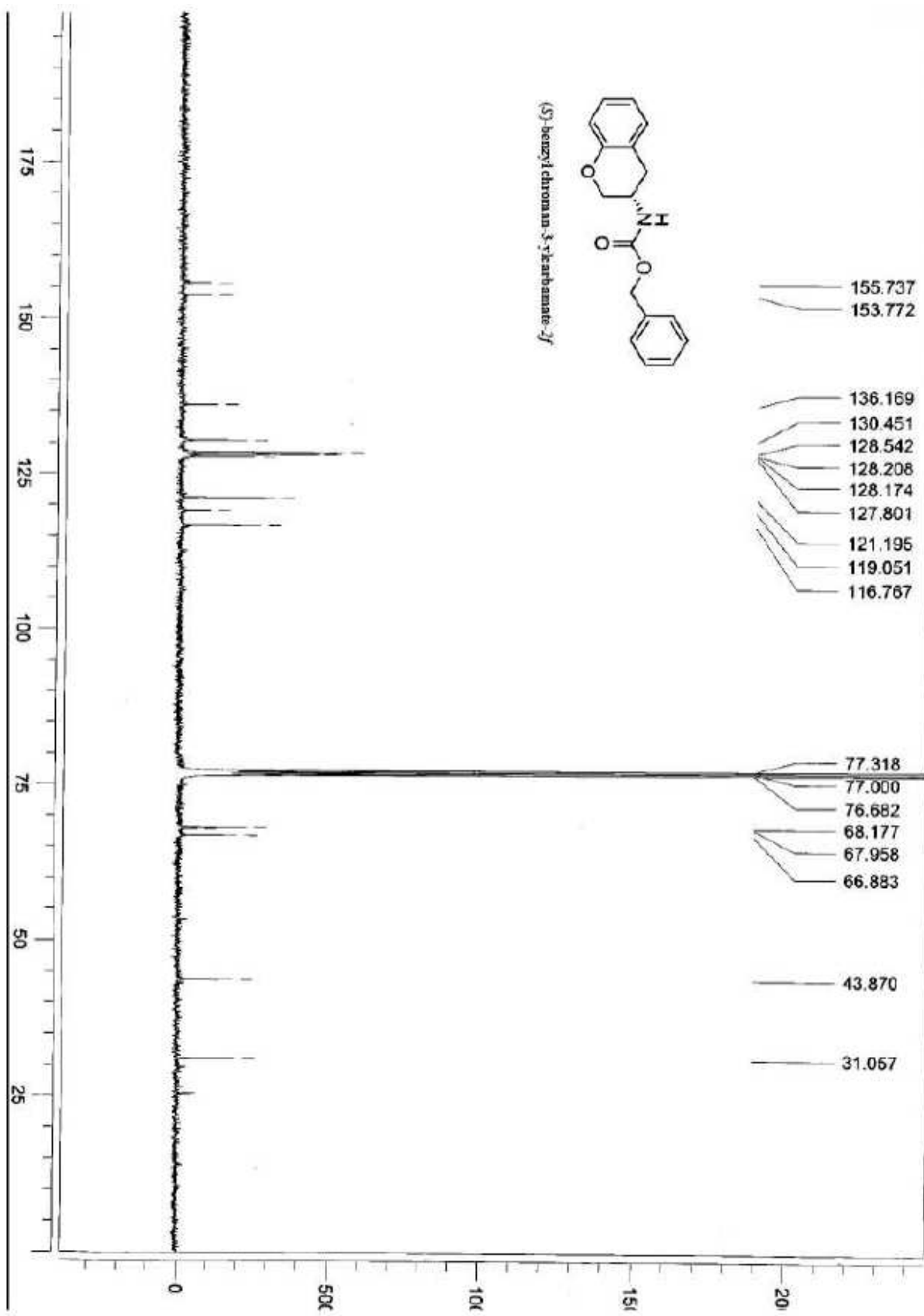


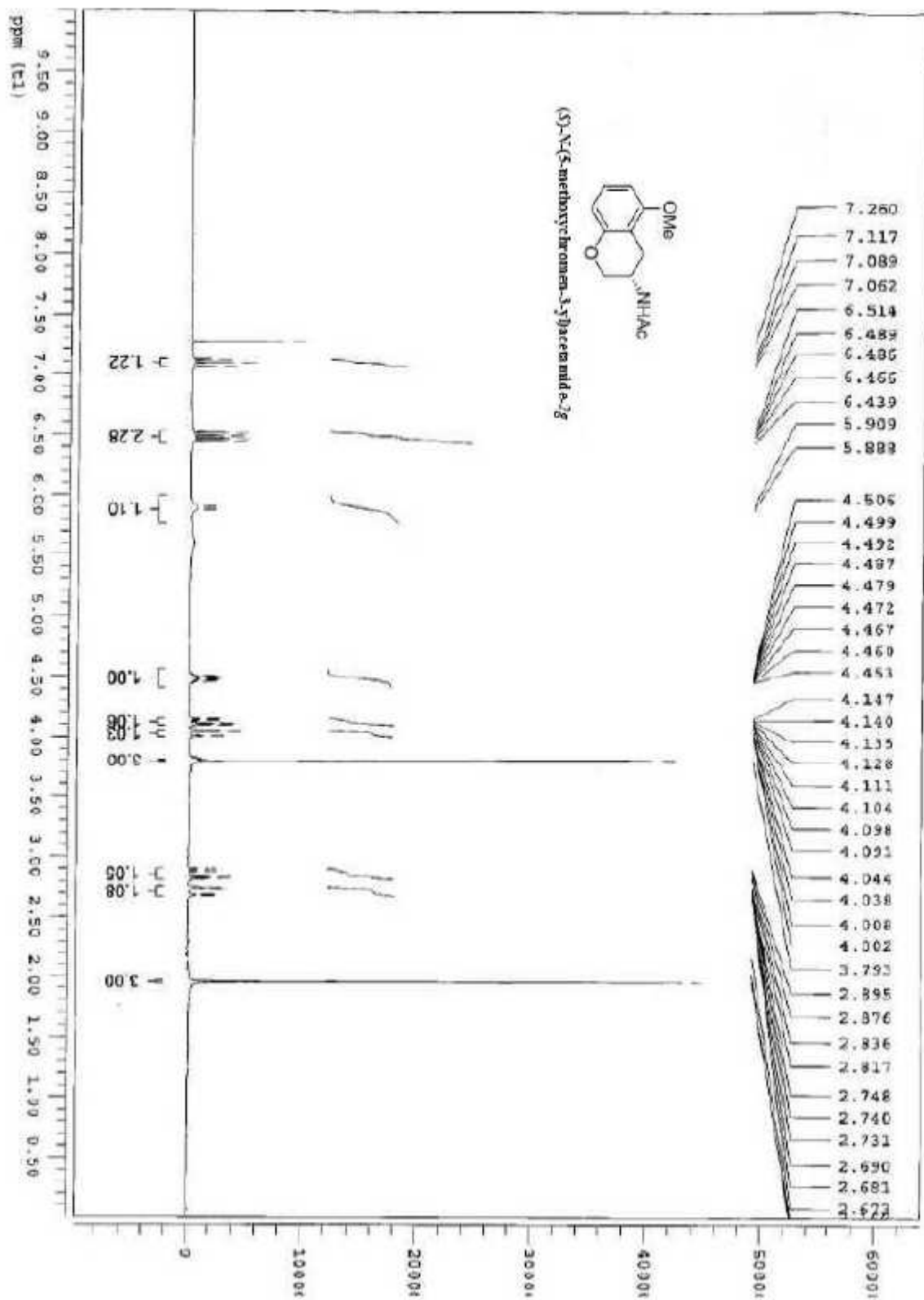


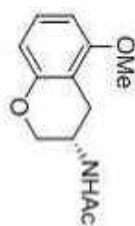




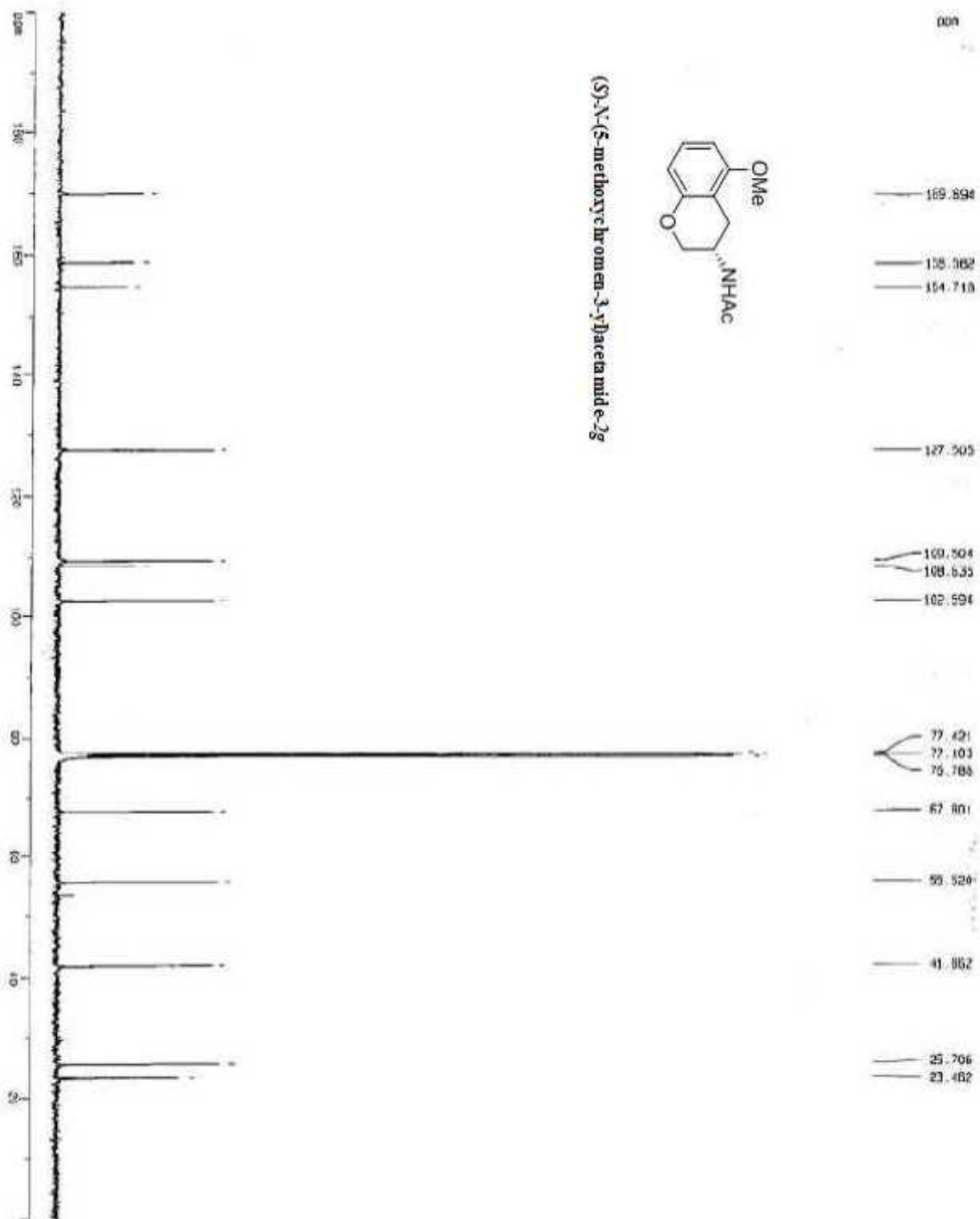


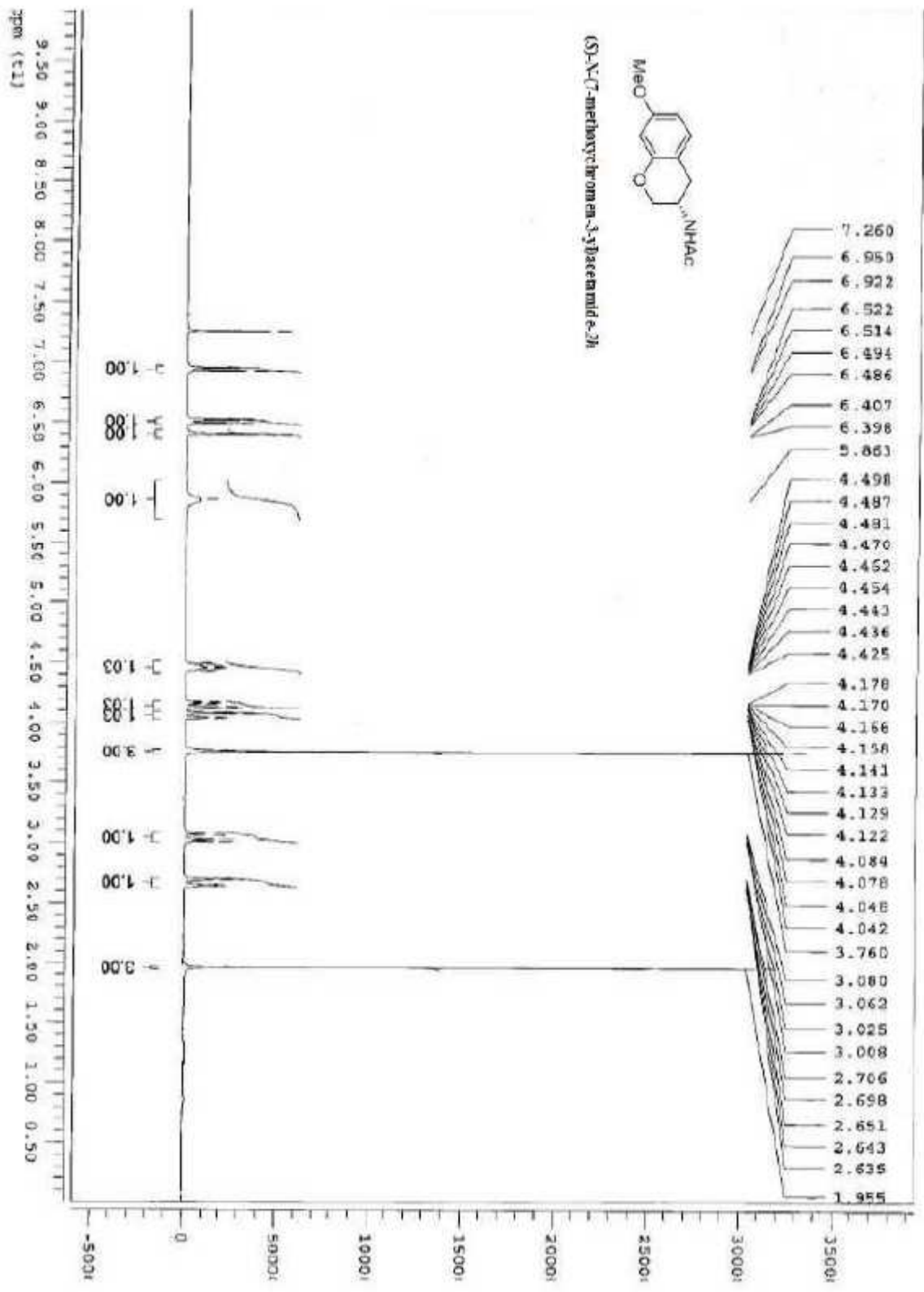






(S)-N-(5-methoxyphenyl)ornen-3-ylacetamide-2g





ppm

169.906

159.467

154.615

131.091

111.106

100.315

101.751

77.411

77.008

76.701

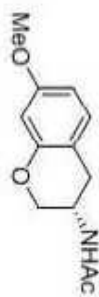
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35.427

42.375

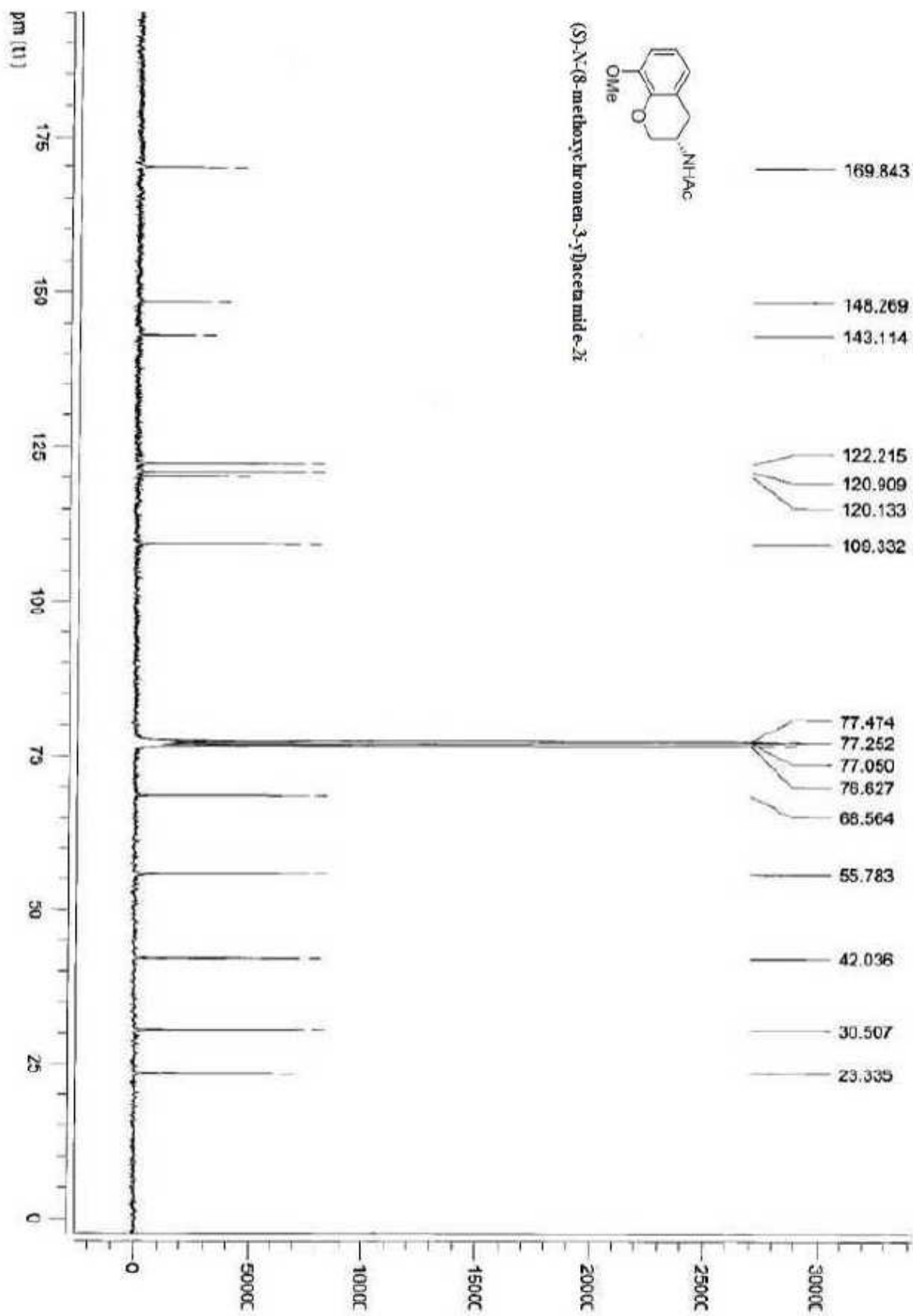
30.123

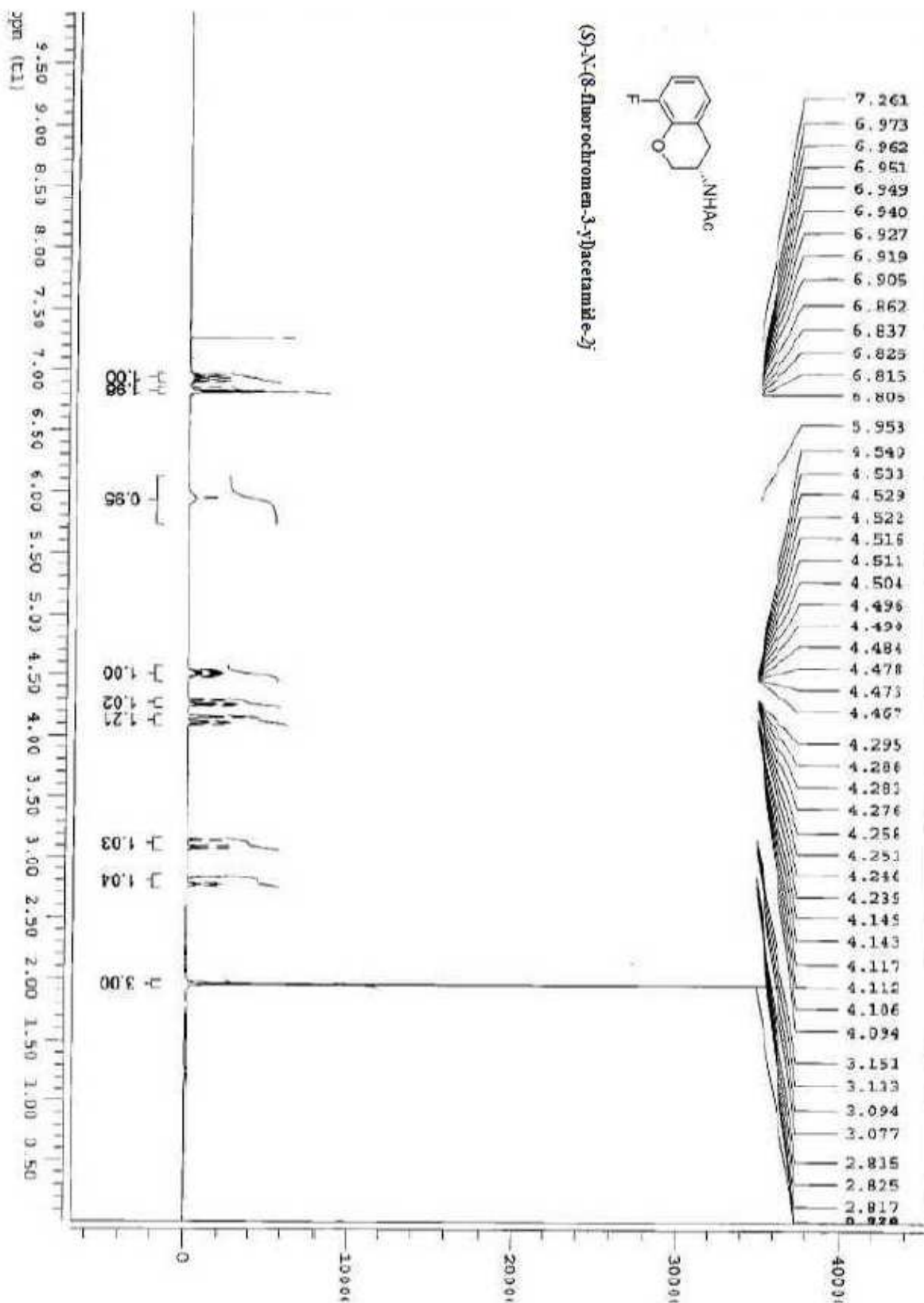
23.512

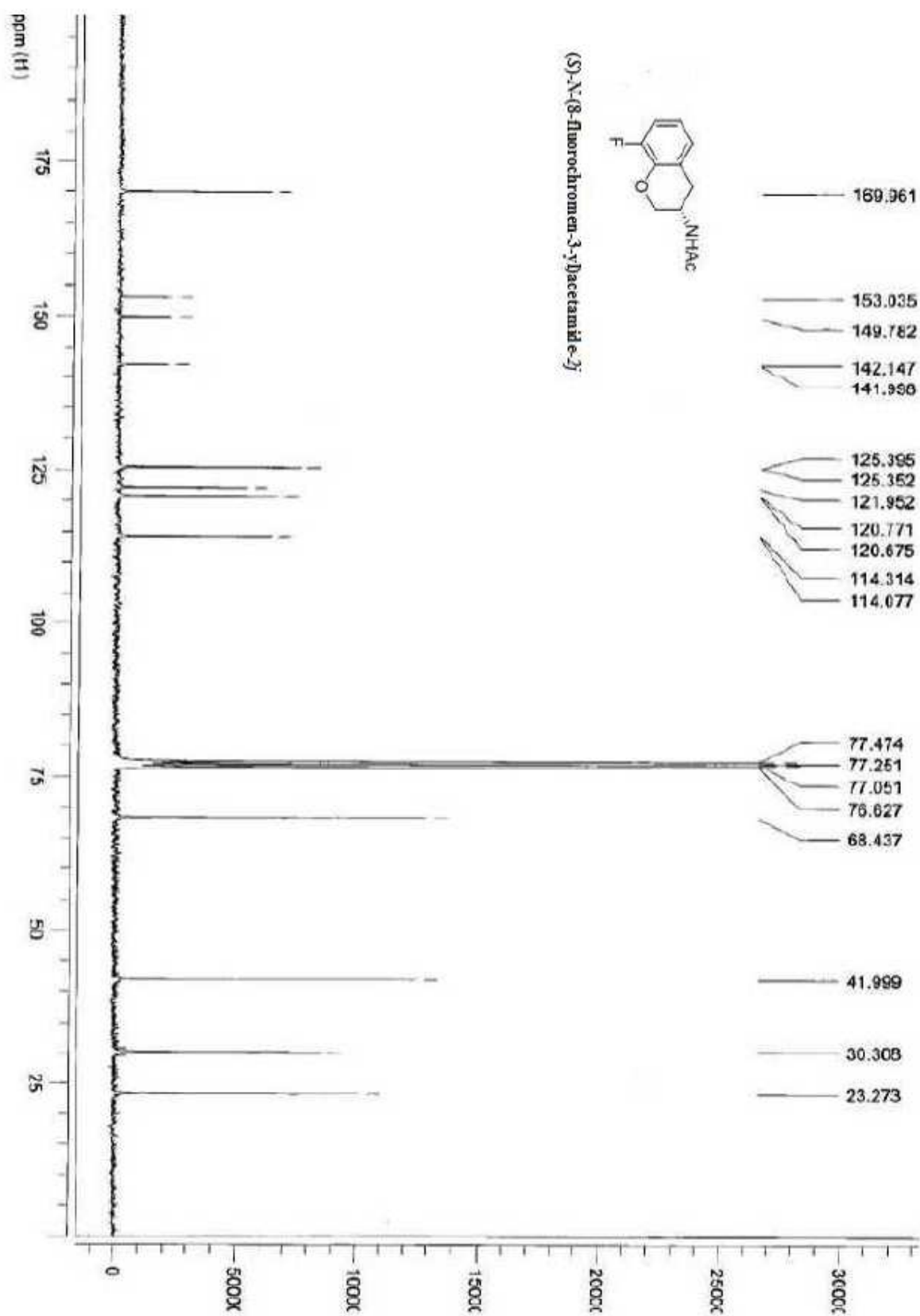


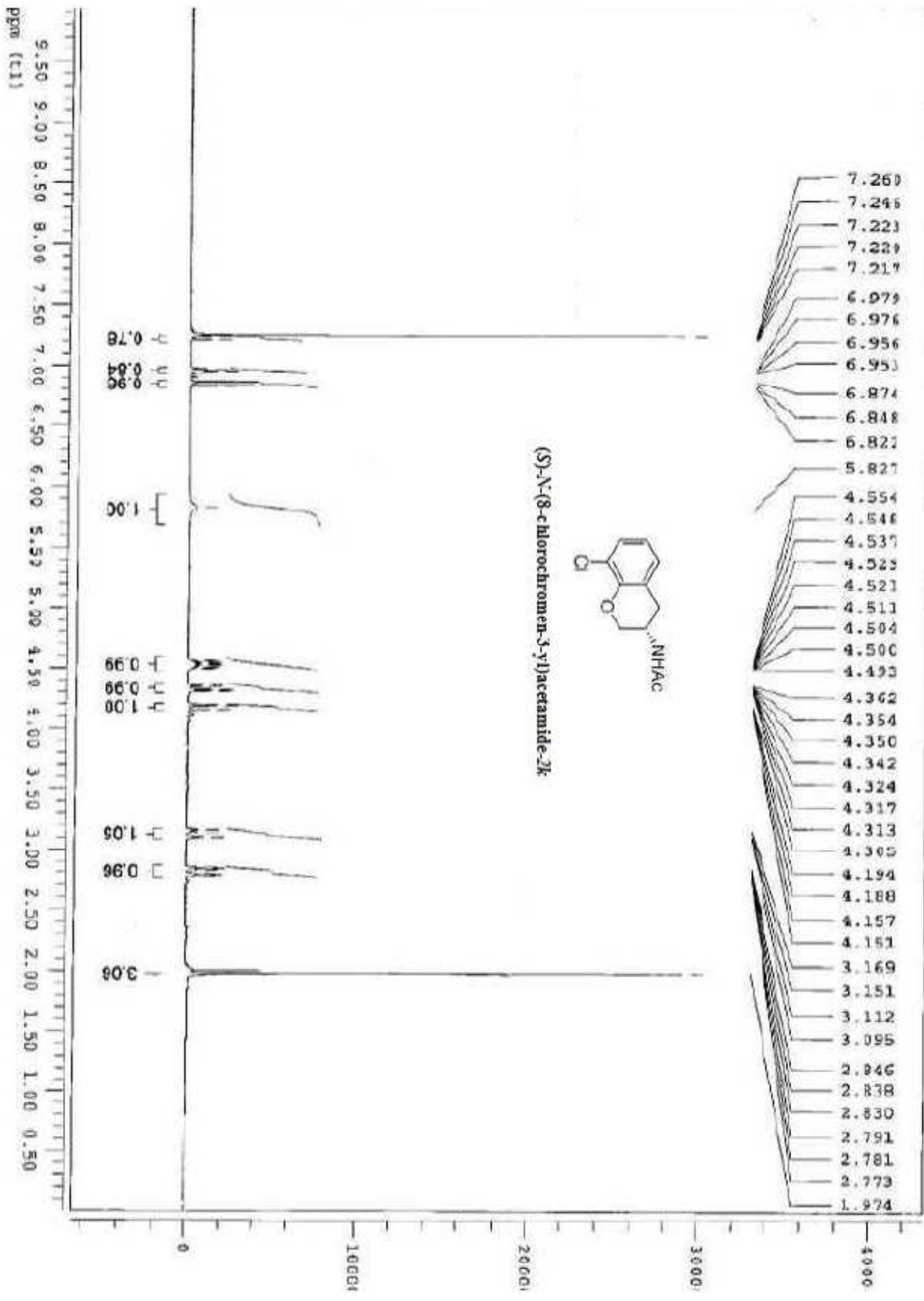
(S)-N-(7-methoxychromen-3-yl)acetamide (2h)

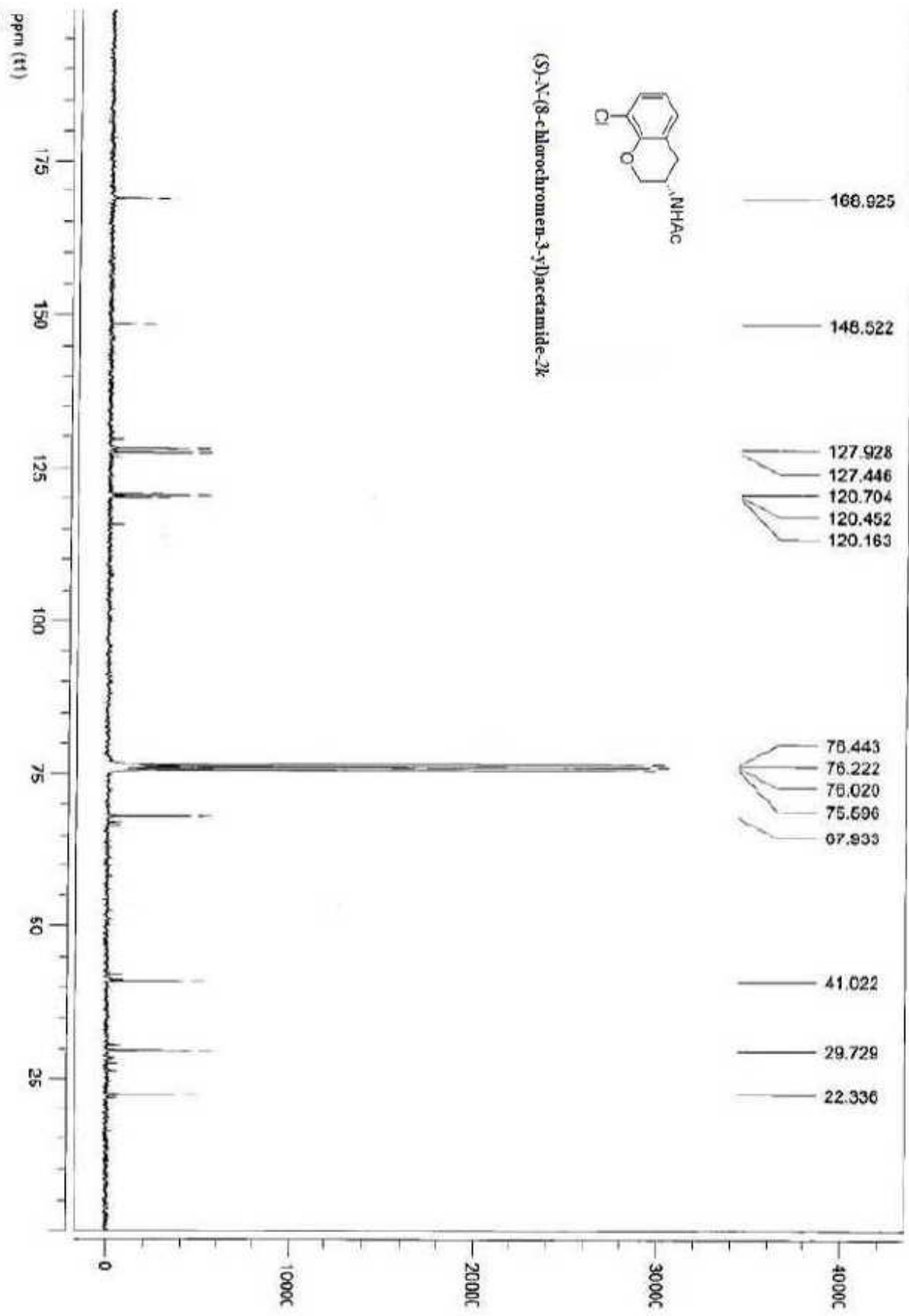


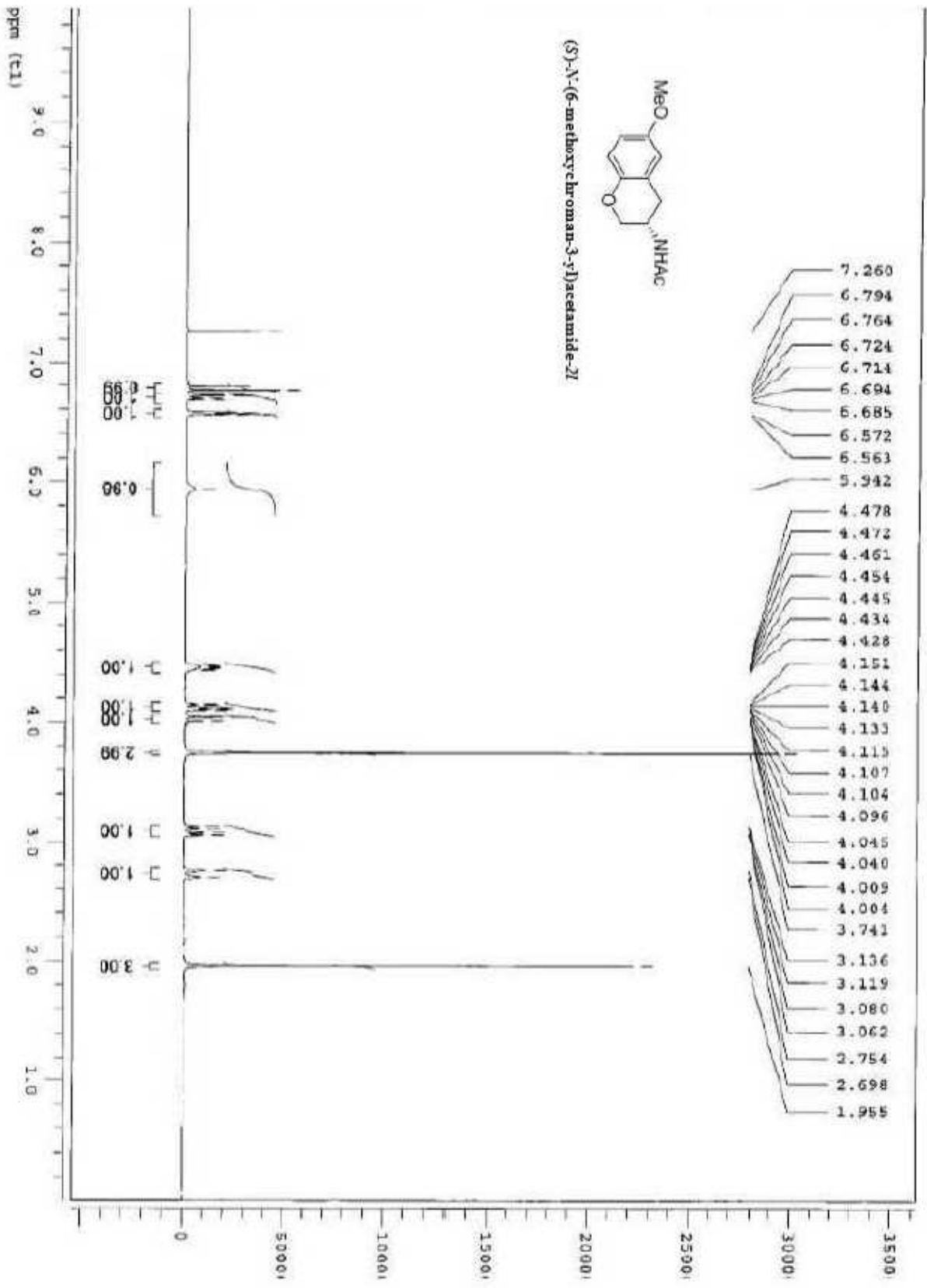


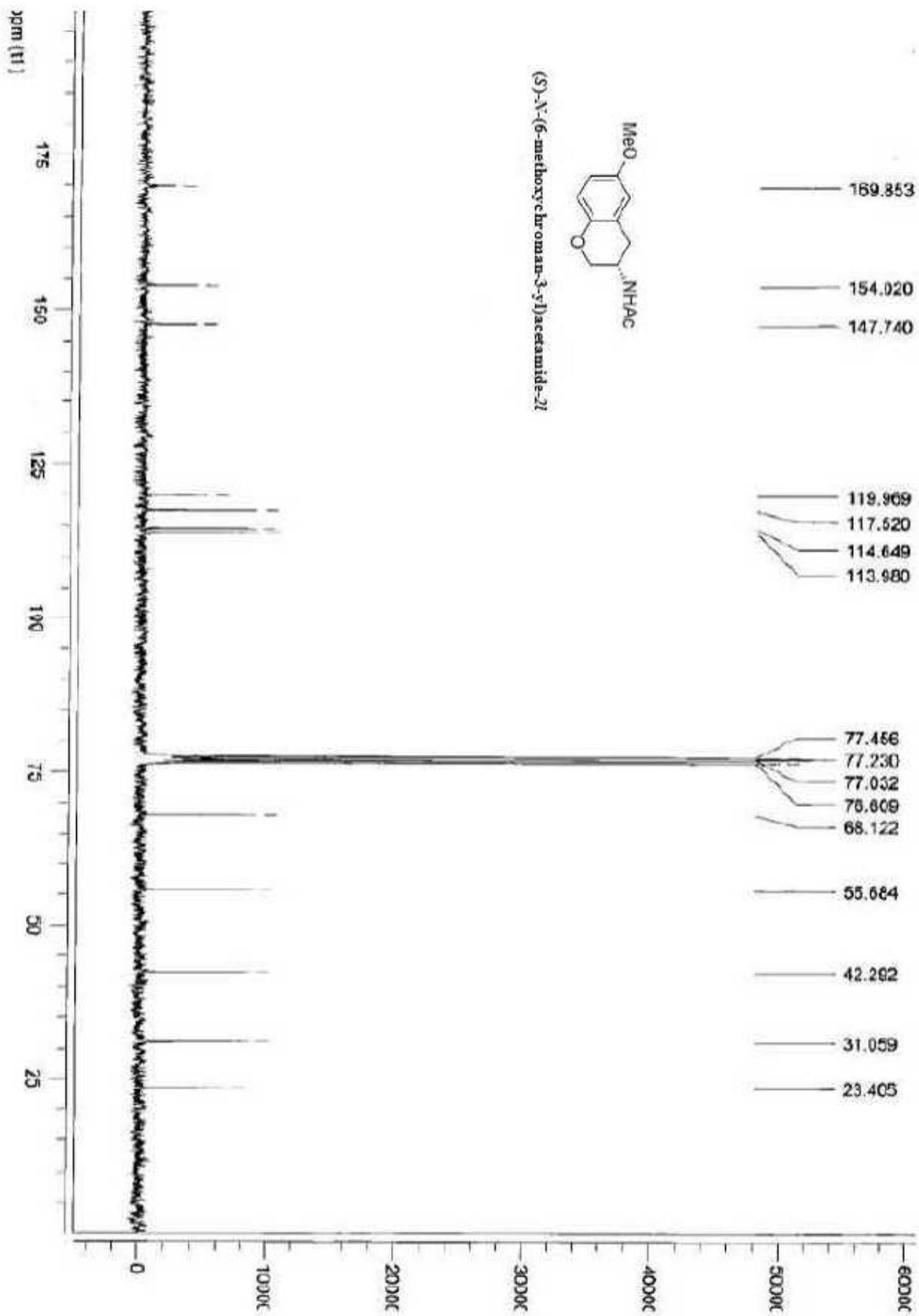


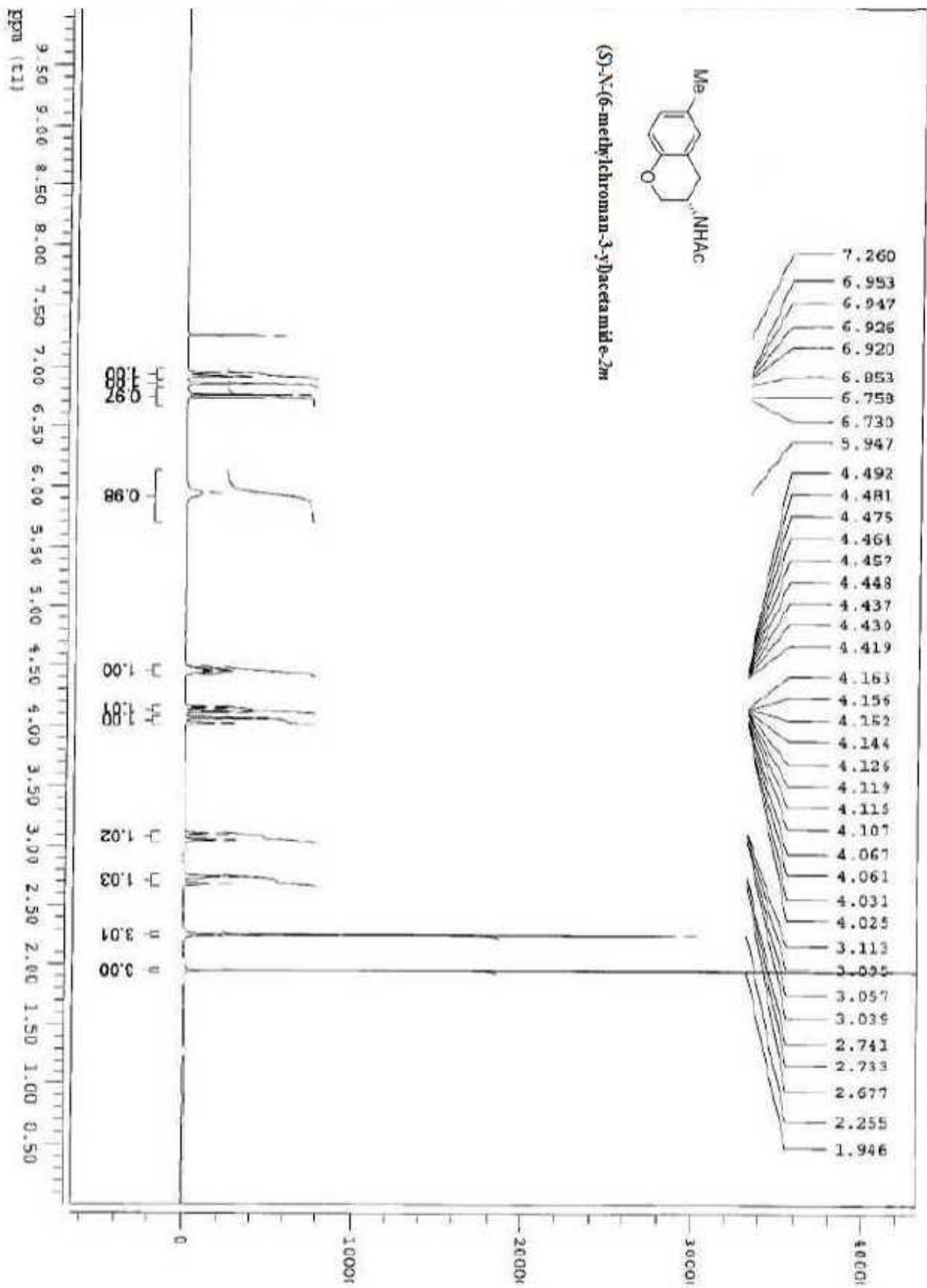


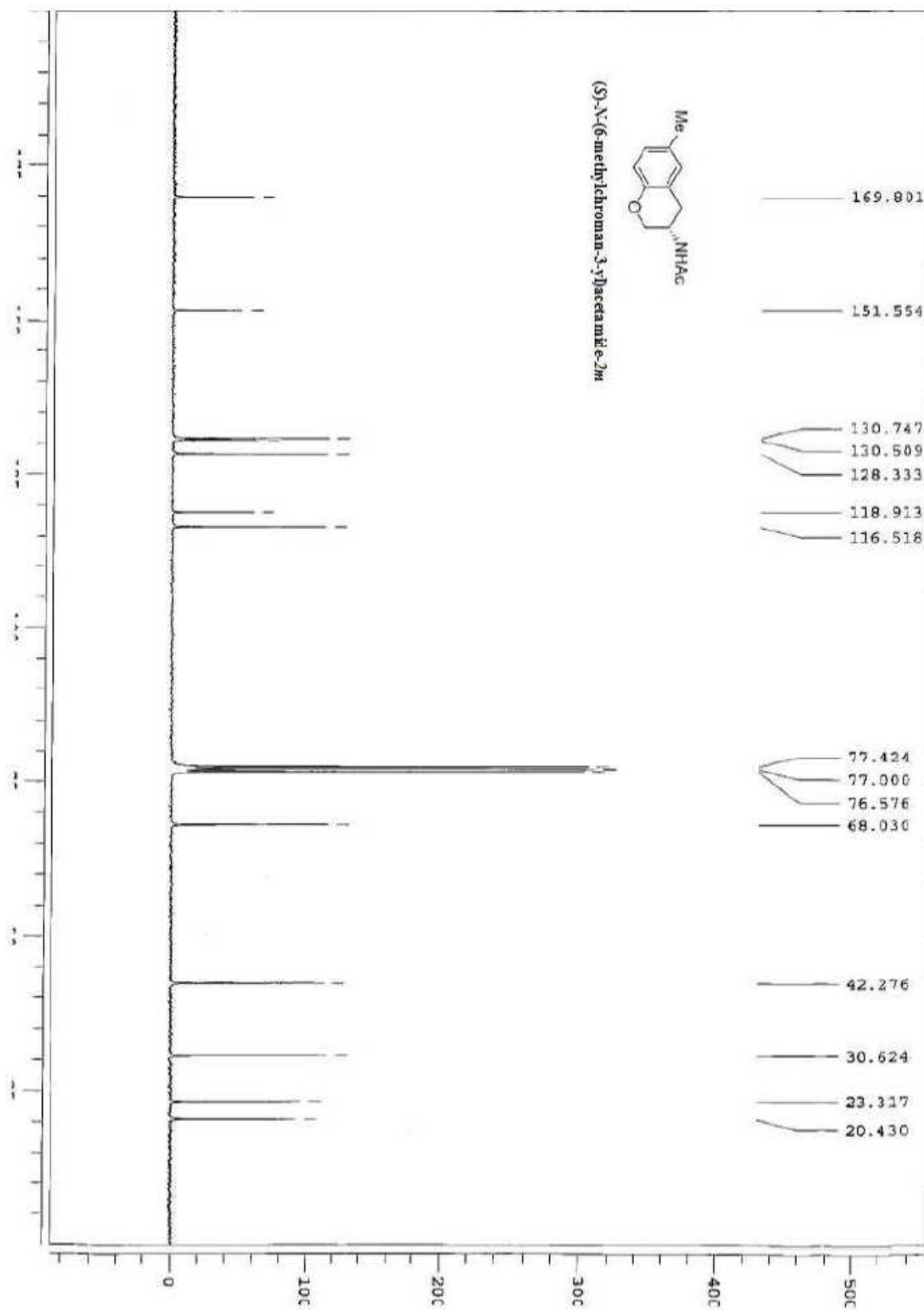


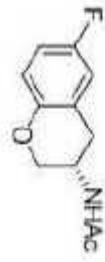




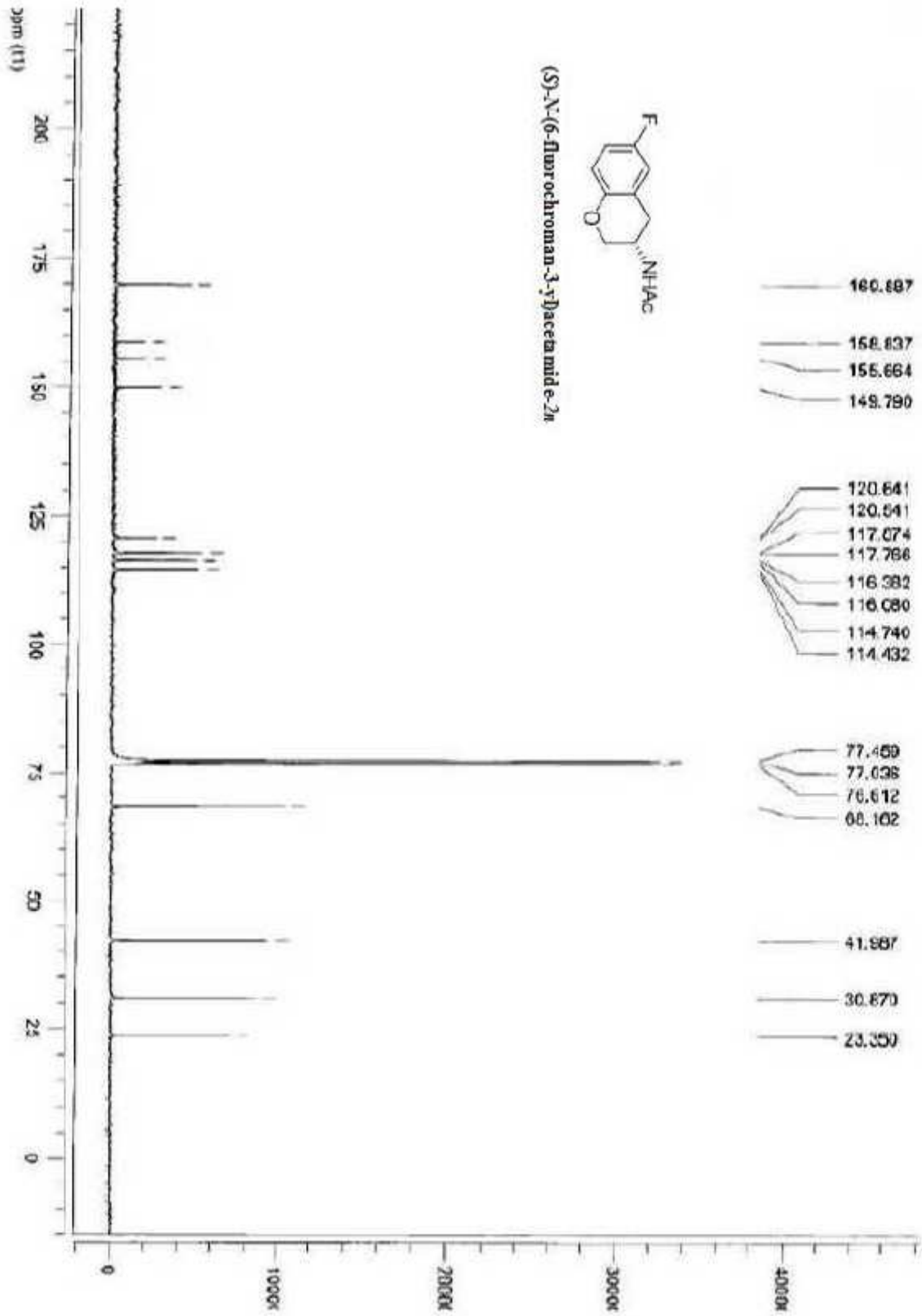


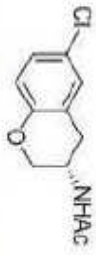




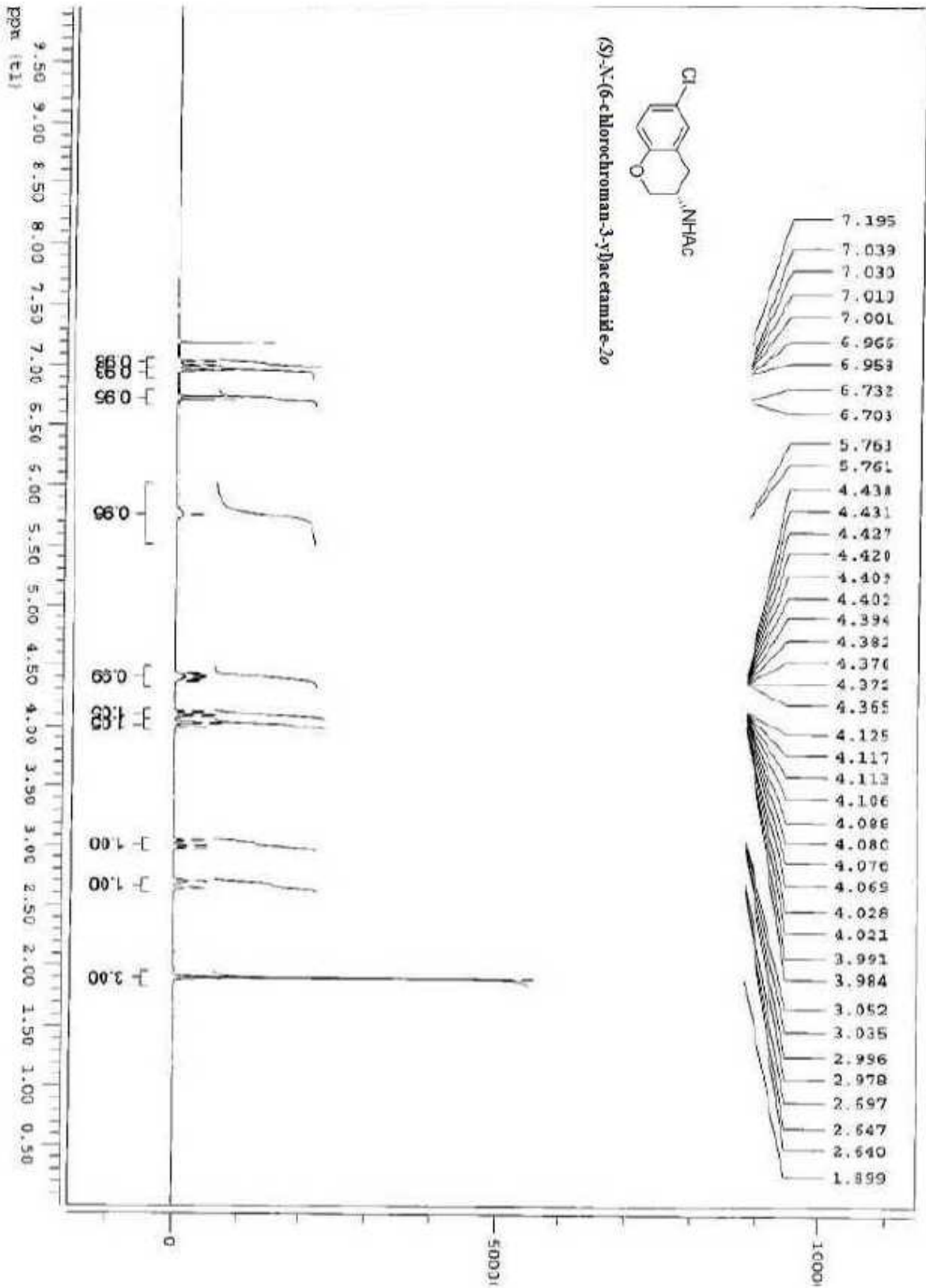


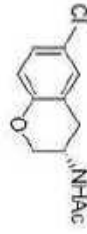
(S)-N-(6-Fluorochroman-3-yl)acetamid mid e-2H



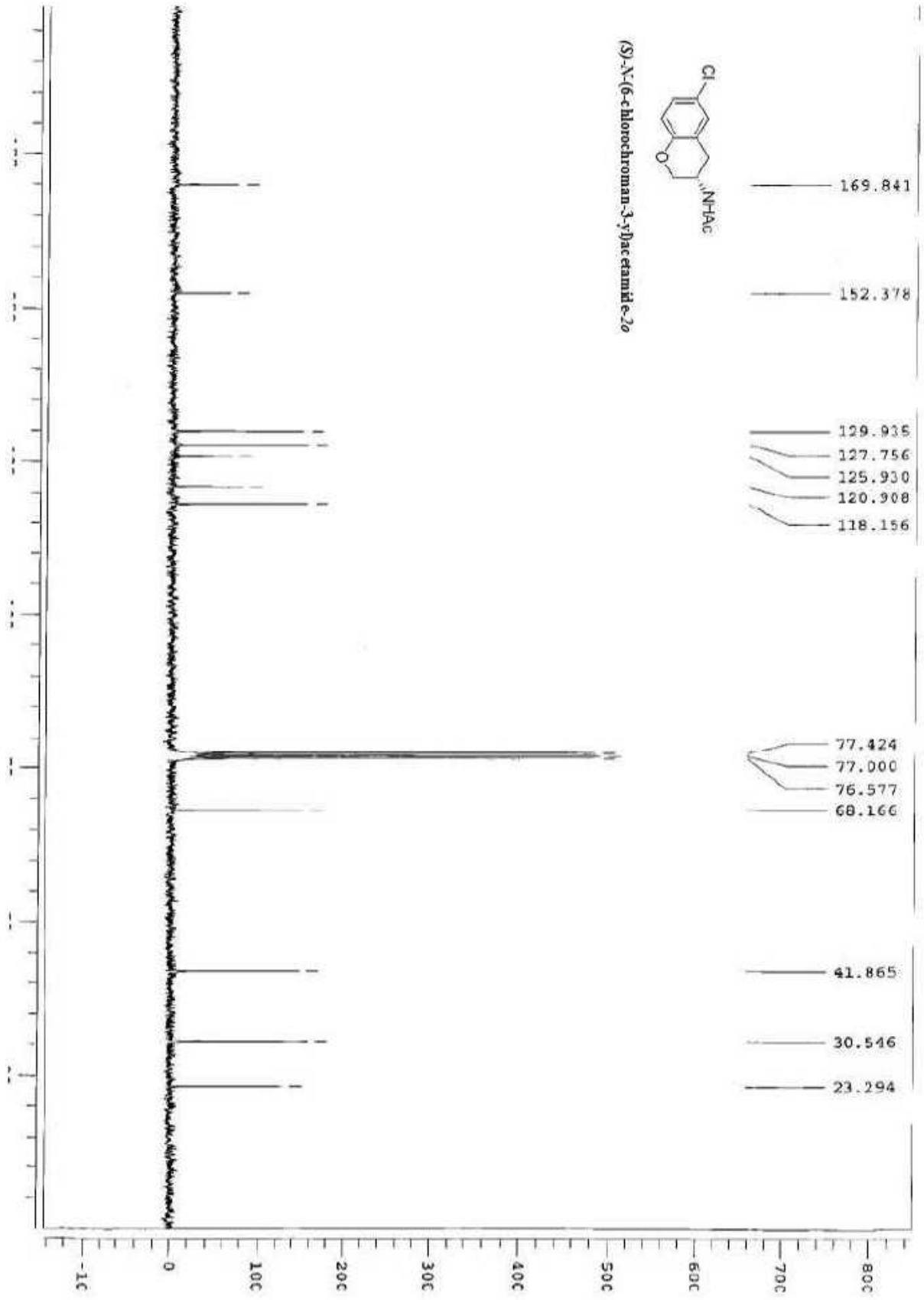


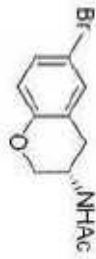
(S)-N-(6-chlorochroman-3-yl)acetamide-2o



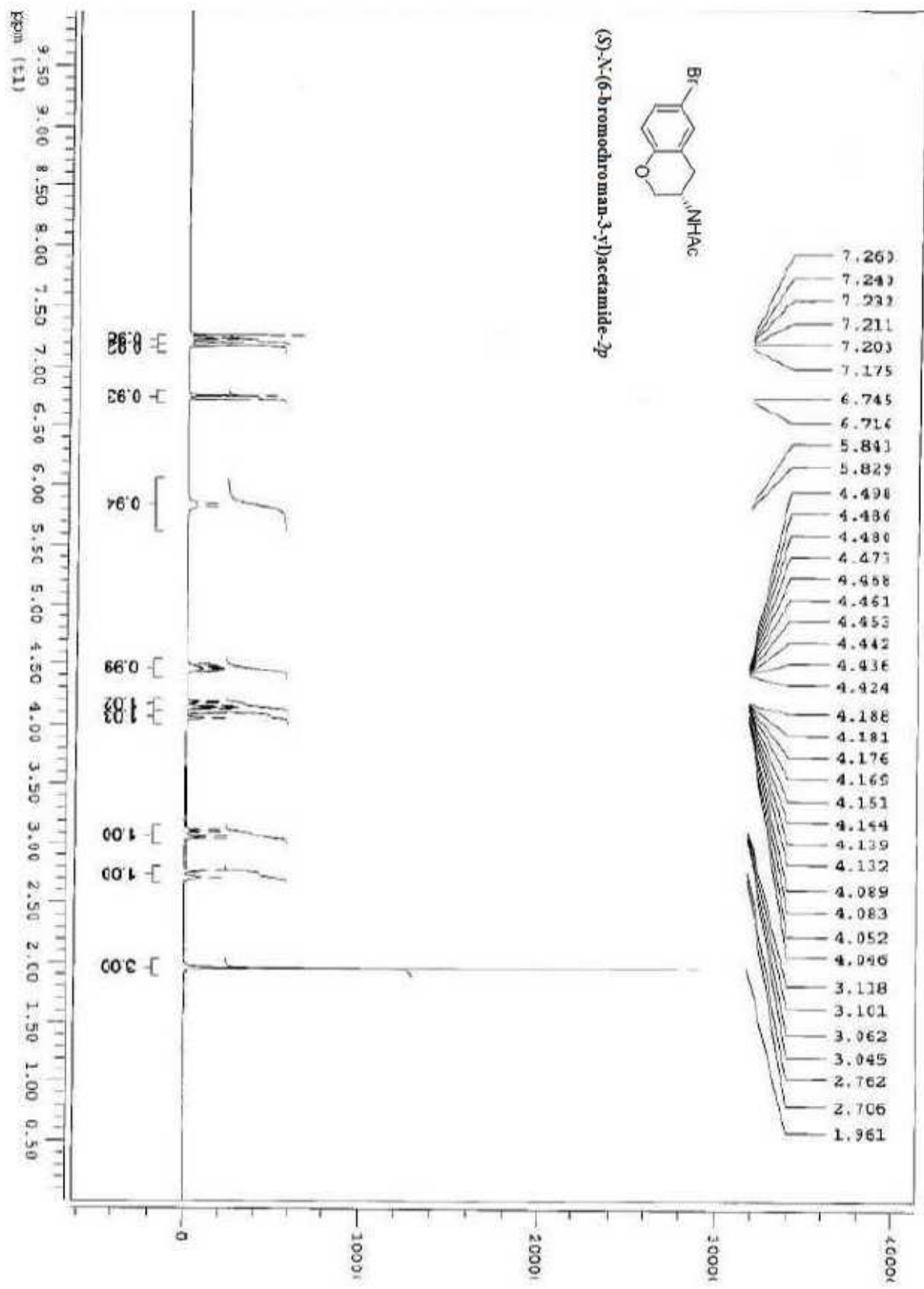


(S)-N-(6-chlorochroman-3-yl)acetamide-2o





(S)-N-(6-bromochroman-3-yl)acetamide-2p



(S)-N-(6-bromochroman-3-yl)acetamide-2p

