

# SUPPORTING INFORMATION

## Identification of new diamine scaffolds with activity against

### *Mycobacterium tuberculosis*

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## **Experimental Section.**

**Materials and Methods.** All reagents and 1,2-dichloroethane (reagent grade) were purchased from Sigma-Aldrich. Dichloromethane and methanol (both of HPLC grade) were purchased from VWR, and used as received. Polymer-bound trimethylammonium cyanoborohydride was purchased from EMD Biosciences, Inc.. Synthesis of the library was performed using equipment and 2-ml capacity Flex Chem 96-well reaction blocks, both by SciGen, and 96-well collection blocks purchased from Matrix Technologies Corporation. Evaporation of the solvents was performed on a SpeedVac AES System (Thermo Savant). All necessary chromatographic purifications were done on CombiFlash<sup>TM</sup> Sg100 system using ReadySep pre-packed silica gel columns. Merck silica gel 60F<sub>254</sub> plates were used for analytical thin-layer chromatography. Mass spectra were obtained by positive ion Electrospray Ionization using Perkin-Elmer/Sciex API-365 operating in Q1 Scan mode (RTI International, Research Triangle Park). NMR data were recorded in CDCl<sub>3</sub> at 400 MHz on Bruker AV-400 at the University of Maryland, College Park.

**Generating the Library/General Synthetic Procedure.** Diamines in each group were combined in quantities of 50 mg each, dissolved in 5 ml of 1,2-dichloroethane (DCE), and stored as stock solutions in sealed vials at a temperature below -4°C. Individual carbonyl compounds were organized on a 96-well master plate as 1.2 M solutions in DCE. Each well of a 96-well reaction plate was charged with 0.3 ml of a 9:1 mixture of DCE:AcOH and 0.3 ml of a proper diamine stock solution (approximately 0.002 mmol of individual diamine compound). After the addition of 0.1 ml of the appropriate carbonyl compound from the master plate (0.12 mmol) and followed by (15 min later) the addition of a polymer-bound sodium cyanoborohydride (0.012 g

of 4.2 mmol/g coverage, 0.05 mmol per well), the reaction blocks were sealed, placed on a shaker, and the reactions were allowed to proceed for 24-36 hours at RT. At the end, the reaction mixtures were filtered into 96-well collection plates, the filtrates were evaporated to dryness under reduced pressure in a SpeedVac, and the residual samples were advanced into screening.

**Resynthesis of Library Hits.** The same protocol was applied to the synthesis of desired hit compounds, and the reactions were carried out in individual vials.

To prepare the hits of homopiperazine series, a 1:4:2 molar ratio of the reagents was used; piperazine compounds were synthesized using a 1:2:2 ratio of the reagents (homopiperazine:carbonyl compound:cyanoborohydride). Crude products were purified on CombiFlash (silica gel, mobile phase: A = DCM, B= DCM/MeOH/NH<sub>4</sub>OH in ratio 600:400:10 respectively, gradually increasing content of B from 0 to 50% within 25 min).

***N,N'*-Bis(2-adamantyl)homopiperazine (SQ775).** 41%. <sup>1</sup>H NMR: δ 2.94 (m, 2H), 2.87 (m, 8H), 2.08-1.98 (m, 8H), 1.87-1.65 (m, 18H), 1.48 (q, *J* = 12 Hz, 20 Hz, 4H). Mass spectrum (ESI) *m/z* (MH)<sup>+</sup> 369.3.

***N,N'*-Bis(cyclooctyl)homopiperazine (SQ777).** 72%. <sup>1</sup>H NMR: δ 3.04 (m, 2H), 2.94 (m, 8H), 2.04 (q, *J* = 12 Hz, 4 Hz, 2H), 1.83 (m, 4H), 1.7 (dd, *J* = 16 Hz, 8 Hz, 4H), 1.57 (m, 4H), 1.52-1.36 (m, 16 H). Mass spectrum (ESI) *m/z* (MH)<sup>+</sup> 321.3.

***N,N'*-Bis(*cis,trans*-2-decahydronaphthyl)homopiperazine (SQ778).** 42%. <sup>1</sup>H NMR: δ 3.13-2.77 (m, 14H), 2.02 (m, 2H), 1.17-1.16 (m, 28H). Mass spectrum (ESI) *m/z* (MH)<sup>+</sup> 373.4.

***N,N'*-Bis(2-myrtanyl)homopiperazine (SQ779).** 54%.  $^1\text{H NMR}$   $\delta$  5.46 (m, 2H), 3.11 (m, 4H), 2.81 (m, 8H), 2.37(m, 2H), 2.24 (m, 2H), 2.07 (m, 2H), 1.92 (m, 2H), 1.31 (m, 2H), 1.25 (m, 6H), 1.08 (m, 2H), 1.06 (m, 2H), 0.86 (m, 6H). Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 369.3.

***N,N'*-Bis(2-ethoxybenzyl)homopiperazine (SQ780).** 61%.  $^1\text{H NMR}$   $\delta$  7.41 (dd,  $J=7.6$  Hz, 1.6 Hz, 2H), 7.2 (td,  $J=6.4$  Hz, 1.6 Hz, 0.8 Hz, 2H), 6.92 (td,  $J=7.2$  Hz, 6.4 Hz, 1.2 Hz, 0.08 Hz, 2H), 6.84 (d,  $J=8.4$  Hz, 2H), 4.02 (q,  $J=13.8$  Hz, 7.2 Hz, 4H), 3.76 (m, 4H), 2.82 (m, 8H), 1.89 (m, 2H), 1.41 (t,  $J=14$  Hz, 7 Hz, 6H). Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 369.3.

***N,N'*-Bis(2-methoxybenzyl)homopiperazine (SQ782).** 61%.  $^1\text{H NMR}$   $\delta$  7.39 (dd,  $J=7.6$  Hz, 1.6 Hz, 2H), 7.21 (td,  $J=8$  Hz, 6.4 Hz, 1.6 Hz, 2H), 6.91 (td,  $J=7.6$  Hz, 6.8 Hz, 0.8 Hz, 2H), 6.84 (d,  $J=8$  Hz, 2H), 3.79 (s, 6H), 3.75 (m, 4H), 2.83 (m, 8H), 1.86 (q,  $J=12$  Hz, 8 Hz, 2H). Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 340.5.

***N*-1-(4-Chlorobenzhydryl)-*N'*-2-methoxybenzylpiperazine (SQ784).** 15%.  $^1\text{H NMR}$ :  $\delta$  7.36-7.17 (group of signals, 11H), 6.91 (td,  $J = 7.2$  Hz, 1 Hz, 1H), 6.86 (d,  $J = 8$  Hz, 1H), 4.20 (s, 1H), 3.81 (s, 3H), 3.60 (br s, 2H), 2.54-2.42 (br m, 8H). Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 407.2, 409.3.

***N*-Benzyl-*N'*-(4-benzyloxybenzyl)piperazine (SQ786).** 76%.  $^1\text{H NMR}$ :  $\delta$  7.44-7.21 (group of signals, 12H), 6.92 (ddd,  $J = 8$  Hz, 2.8 Hz, 2 Hz, 2H), 5.05 (s, 2H), 3.52 (s, 2H), 3.47 (s, 2H), 2.49 (m, 8H). Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 373.2.

***N,N'*-Bis(4-benzyloxybenzyl)homopiperazine (SQ776).** 72%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 493.3.

***N,N'*-Bis(1-perillyl)homopiperazine (SQ781).** 48%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 369.3.

***N*-(2-Fluorophenyl)-*N'*-(2-decahydronaphthyl) piperazine (SQ765).** 49%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 317.3.

***N*-(2-Fluorophenyl)-*N'*-(2-decahydronaphthyl)piperazine (SQ774).** 15%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 317.4.

***N*-(4-Chlorobenzhydryl)-*N'*-(2-decahydronaphthyl)piperazine (SQ783).** 20%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 423.2, 425.4.

***N*-(4-Chlorobenzhydryl)-*N'*-(2-methoxybenzyl)piperazine (SQ784).** 20%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 407.2, 409.3.

***N*-Benzyl-*N'*-(2-murtanyl)piperazine (SQ788).** 20%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 311.4.

***N*-Benzyl-*N'*-(1-perillyl)piperazine (SQ789).** 35%. Mass spectrum (ESI)  $m/z$  (MH)<sup>+</sup> 311.2.

**MIC Determination.** An aliquot of a frozen stock of *M. tuberculosis* H37Rv (ATCC 25618) was thawed and grown in Middlebrook 7H9 (Difco) supplemented with bovine serum albumin (BSA), dextrose, and catalase to an O.D.<sub>600</sub> of 0.2 at 37°C with 5% CO<sub>2</sub>. Experimental (hits) and control (INH, EMB) drug compounds were serially diluted from 50 to 0.39 μM. Each well was inoculated with a 1:100 dilution of the H37Rv culture. MIC<sub>99</sub> for each compound was determined after 10-14 days of incubation at 37°C with 5% CO<sub>2</sub>.

**Cytotoxicity.** Cytotoxicity of the compounds was determined with the HepG2 cell line in the MTS assay. The HepG2 cell line (ATCC HB-8065) was seeded overnight at 5x10<sup>4</sup> cells per well in 96-well plates at 37°C and 5% CO<sub>2</sub> in EMEM with essential amino acids and glutamine (BioFluids) supplemented with 10% heat-inactivated fetal bovine serum (FBS). Cells were

exposed to dilutions of experimental and control drugs in triplicate for 72hr, with each compound at a range of concentrations from 15-200  $\mu$ M. Chlorpromazine (Sigma) was run as a control at the same concentrations. CellTiter 96 AQueous Assay (Promega) was used for determination of HepG2 cell viability. Briefly, a solution of MTS salt (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) and phenazine methosulfate was added to each well and incubated for 2hr at 37°C and 5% CO<sub>2</sub>. Absorbance from each well was read using a BioRad microplate reader at 490nm. Viability of drug-exposed wells was compared to those in drug-free control wells, and a curve relating viability to drug concentration was created.

**LogP Determination.** Octanol/water partition coefficient logP of the diamines was calculated using the online services of Advanced Chemistry Development, Inc. (ACD) (<http://www.acdlabs.com>).

### ***In Vivo* Efficacy Studies.**



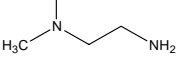
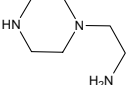
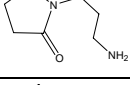
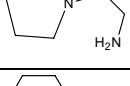
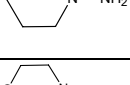
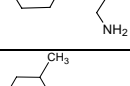
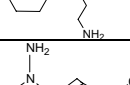
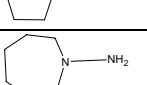
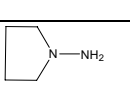
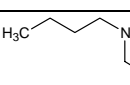
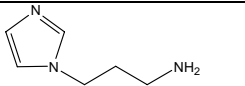
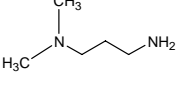
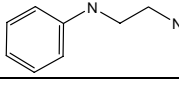

**Mycobacterial inoculum.** An aliquot of a frozen stock of *M.tuberculosis* H37Rv Pasteur was prepared and stored as described.<sup>12</sup>

**Mice.** Female C3H mice (8 weeks old) were purchased from Charles River (Raleigh, NC). Mice were housed in the BSL-2 facility of BIOQUAL, Inc. (Rockville, MD), and were allowed to acclimatize for at least 4 days prior to infection.

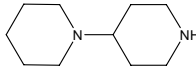
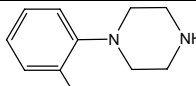
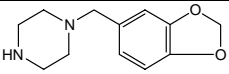
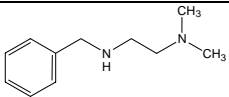
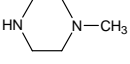
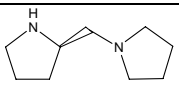
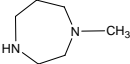
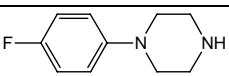
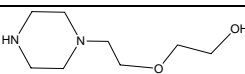

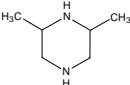
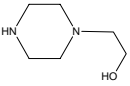
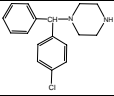
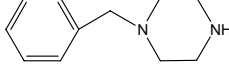
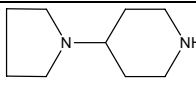
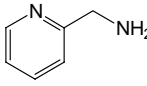
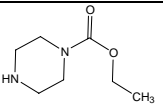
**Infection.** A frozen sample of stock *M. tuberculosis* culture of known viability and CFU count was thawed and diluted to a concentration of approximately 5 x 10<sup>6</sup> CFU/ml. Mice were infected intravenously (iv) through lateral tail vein with 10<sup>6</sup> CFU in 0.2 ml of PBS confirmed by culture count.

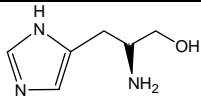
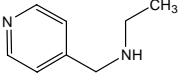
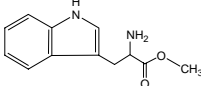
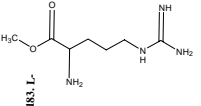
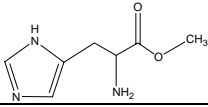
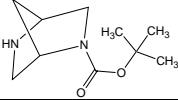
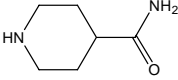
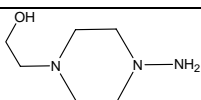
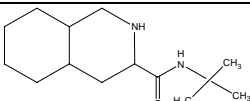
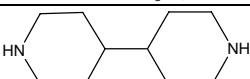
**Drug Treatment.** Chemotherapy was initiated 7 days after inoculation and continued for 10 days. Tested compounds were administrated daily by gavage at a dose of 10mg/kg as 5% solutions in 5:95 mixture of ethanol and water, 200  $\mu$ L per mouse, 5 days/week, using one group of six mice for every compound. Uninfected mice and infected untreated mice were used as controls. Body weights of mice in all groups were monitored starting from day 0 through day 21.

**Table 1.** Diamines used in synthesis

| #     | Group of diamines 1                      | Structure   |
|-------|--|---|
| d-21  | 1-(2-Aminoethyl)piperidine               |    |
| d-23  | 4-(2-Aminoethyl)morpholine               |    |
| d-35  | N,N-Dimethylethylenediamine              |    |
| d-41  | 1-(2-Aminoethyl)piperazine               |    |
| d-48  | 1-(3-Aminopropyl)-2-pyrrolidinone        |    |
| d-50  | 1-(2-Aminoethyl)-pyrrolidine             |    |
| d-56  | 1-Aminopiperidine                        |    |
| d-72  | 4-(3-Aminopropyl)morpholine              |  |
| d-91  | 1-(3-Aminopropyl)pipecoline              |  |
| d-144 | (S)-1-Amino-2-(methoxymethyl)pyrrolidine |  |
| d-149 | 1-Aminohomopiperidine                    |  |
| d-151 | 1-Amonopyrrolidine, HCL                  |  |
| d-156 | 3-(Dibutylamino)propylamine              |  |
| d-161 | 1-(3-Aminopropyl)iminazol                |  |
| d-167 | 3-(Dimethylamino)propylamine             |  |
| d-198 | N-Phenylethyldiamine                     |  |

|                            |   |  |
|----------------------------|---|--|
| d-281                      | 2-(2-Aminoethyl)-1-methylpyrrolidine        |  |
| d-289                      | 4,4'-Methylenebis-(2-Methylcyclohexylamine) |  |
| d-291                      | ®-(+)-3-Aminoquinuclidine, 2HCL             |  |
| d-293                      | 4,4'-Methylenebis(cyclohexylamine)          |  |
| <b>Group of diamines 2</b> |   |  |
| d-84                       | 4-Amino-1-benzylpiperidine                  |  |
| d-170a                     | 2-(4-Aminophenyl)ethylamine                 |  |
| d-201                      | N,N,2,21-Tetramethyl-1,3-propanediamine     |  |
| d-207                      | Ethyl 4-amino-1-piperidinecarboxylate       |  |
| d-215                      | alpha-Methyltryptamine                      |  |
| d-222                      | 4-Amino-2,2,6,6-tetramethylpiperidine       |  |
| d-227                      | 3-Aminopyrrolidine                          |  |
| d-254                      | (S)-(+)-2-(Aminomethyl)pyrrolidine          |  |
| d-264                      | 3-Aminoquinonuclidine                       |  |
| d-275                      | 5-Methoxytryptamine                         |  |
| d-292                      | 1,8-Diamine-p-menthane                      |  |
| d-296                      | 4-(Aminomethyl)-piperidine                  |  |

|       |   |   |
|-------|---|---|
|       | <b>Group of diamines 3</b>                |   |
| d-32  | 4-Piperidinopiperidine                    |    |
| d-96a | 1-(2-Fluorophenyl)piperazine              |    |
| d-114 | 1-Piperonylpiperazine                     |    |
| d-127 | N'-Benzyl-N,N-dimethylethylenediamine     |    |
| d-128 | 1-Methylpiperazine                        |    |
| d-130 | (S)-(+)-(2-Pyrrolidinylmethyl)pyrrolidine |    |
| d-133 | 1-Methylhomopiperazine                    |    |
| d-168 | 1-(4-Fluorophenyl)piperazine              |    |
| d-252 | 1-(2-(2-Hydroxyethoxy)ethyl)piperazine    |   |
| d-270 | Homopiperazine                            |  |
| d-271 | 2,6-Dimethylpiperazine                    |  |
| d-286 | 1-(2-Hydroxyethyl)piperazine              |  |
| d-294 | 1-(4-Chlorobenzhydryl)piperazine          |  |
| d-290 | 1-Benzylpiperazine                        |  |
| d-295 | 4-(1-Pyrrolidinyl)piperidine              |  |
|       | <b>Group of diamines 4</b>                |   |
| d-3   | 2-(Aminomethyl)pyridine                   |  |
| d-40  | Ethyl 1-piperazine carboxylate            |  |

|            |  |   |
|------------|--|---|
| d-107      | Histidinol   |    |
| d-136      | 4-(Ethylaminomethyl)pyridine                                       |    |
| d-173D L   | D,L-Tryptophan methyl ester  |    |
| d-183 L    | L-Arginine methyl ester  |    |
| d-189 L    | L-Histidine methyl ester   |    |
| d-1951S,4S | tret-Butyl(1S,4S)-(-)-2,5-diazobicyclo[2.2.1]heptane-2-carboxylate |    |
| d-202      | Isonipecotamide  |    |
| d-246      | 1-Amino-4-(2-hydroxyethyl)piperazine                               |    |
| d-258      | (3S(3a,4Ab)8Ab)-N-t-butyl-D-eahydro-3-isoquinolinecarboxamide      |  |
| d-280      | 4,4'-Bipiperidine  |  |

**Table 2.** Carbonyl compounds used for preparation of the library.

| <b>Position on Plate</b> | <b>Reagent #</b> | <b><i>Ketones</i></b>                   |
|--------------------------|------------------|---|
| b1                       | c-97             | 3-Acetyl-1-propanol                     |
| b2                       | c-98             | 2-Adamantanone                          |
| b3                       | c-99             | 1-Adamantyl methyl ketone               |
| b4                       | c-100            | Cyclobutanone                           |
| b5                       | c-101            | 1,4-Cyclohexanedione monoethylene ketal |
| b6                       | c-102            | 2-Decalone                              |
| b7                       | c-103            | (4-Fluorophenyl)acetone                 |
| b8                       | c-104            | Geranylacetone                          |
| b9                       | c-105            | 5-Hydroxy-2-adamantanone                |
| b10                      | c-106            | 3-Hydroxy-2-butanone                    |
| b11                      | c-107            | 4-(4-Hydroxyphenyl)-2-butanone          |
| b12                      | c-108            | 4-Methylcyclohexanone                   |

|     |       |                                  |
|-----|-------|----------------------------------|
| c1  | c-25  | 1,4-Benzodioxan-6-carboxaldehyde |
| c2  | c-26  | 4-Benzyloxybenzaldehyde          |
| c3  | c-27  | Benzyloxyacetaldehyde            |
| c4  | c-28  | 2-Chlorobenzaldehyde             |
| c5  | c-29  | 4-Chlorobenzaldehyde             |
| c6  | c-109 | 1-Methyl-4-piperidone            |
| c7  | c-31  | 2-Chloro-4-fluorobenzaldehyde    |
| c8  | c-32  | 3-(4-Chlorophenoxy)-benzaldehyde |
| c9  | c-33  | 5-(4-Chlorophenyl)furfural       |
| c10 | c-34  | trans-Cinnamaldehyde             |
| c11 | c-35  | (S)-(-)-Citronellal              |
| c12 | c-36  | Cyclohexanecarboxaldehyde        |

|     |       |   |
|-----|-------|---|
| d1  | c-37  | Cyclopropanecarboxaldehyde                      |
| d2  | c-38  | 2,4-Dichlorobenzaldehyde                        |
| d3  | c-39  | 2,4-Difluorobenzaldehyde                        |
| d4  | c-40  | 2,5-Difluorobenzaldehyde                        |
| d5  | c-41  | 2,3-Dihydroxybenzaldehyde                       |
| d6  | c-42  | 2,4-Dihydroxybenzaldehyde                       |
| d7  | c-43  | 2,5-Dimethoxy-3-tetrahydrofurancarboxaldehyde   |
| d8  | c-44  | 4-(Dimethylamino)benzaldehyde                   |
| d9  | c-45  | 2,5-Dimethylbenzaldehyde                        |
| d10 | c-110 | Nerylacetone (Geranylacetone ~ 35% Neryacetone) |
| d11 | c-47  | Diphenylacetaldehyde                            |
| d12 | c-48  | 2-Ethoxybenzaldehyde                            |

|    |      |                      |
|----|------|----------------------|
| e1 | c-49 | 4-Ethoxybenzaldehyde |
|----|------|----------------------|

|     |       |                         |
|-----|-------|-------------------------|
| e2  | c-50  | 3-Ethoxysalicylaldehyde |
| e3  | c-111 | (1R)-(+)-Nopinone       |
| e4  | c-52  | 3-Fluoro-p-anisaldehyde |
| e5  | c-53  | 2-Fluorobenzaldehyde    |
| e6  | c-54  | 4-Fluorobenzaldehyde    |
| e7  | c-55  | 3-Fluorosalicylaldehyde |
| e8  | c-56  | 2-Furaldehyde           |
| e9  | c-112 | Norcamphor              |
| e10 | c-113 | 2-Phenylcycloheptanone  |
| e11 | c-59  | Hydrocinnamaldehyde     |
| e12 | c-60  | 3-Hydroxybenzaldehyde   |

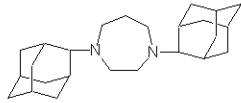
|     |       |                                 |
|-----|-------|---------------------------------|
| f1  | c-61  | 4-Hydroxybenzaldehyde           |
| f2  | c-62  | 2-Hydroxy-4-methoxybenzaldehyde |
| f3  | c-63  | 5-(Hydroxymethyl)furfural       |
| f4  | c-64  | 4-Hydroxy-3-nitrobenzaldehyde   |
| f5  | c-65  | Cyclooctanone                   |
| f6  | c-66  | Indole-3-carboxaldehyde         |
| f7  | c-67  | Isobutyraldehyde                |
| f8  | c-68  | 4-Isopropylbenzaldehyde         |
| f9  | c-69  | Isovaleraldehyde                |
| f10 | c-70  | 2-Methoxycinnamaldehyde         |
| f11 | c-71  | 2-Methoxy-1-naphthaldehyde      |
| f12 | c-114 | 3-Quinuclidinone hydrochloride  |

|     |       |                                    |
|-----|-------|------------------------------------|
| g1  | c-73  | 2,3-(Methylenedioxy)benzaldehyde   |
| g2  | c-74  | 4-Methyl-5-imidazolecarboxaldehyde |
| g3  | c-75  | 1-Methylindole-3-carboxaldehyde    |
| g4  | c-76  | 1-Methyl-2-pyrrolecarboxaldehyde   |
| g5  | c-77  | 4-(Methylthio)benzaldehyde         |
| g6  | c-78  | 3-Methyl-2-thiophenecarboxaldehyde |
| g7  | c-79  | (1R)-(-)-Myrtenal                  |
| g8  | c-115 | Tetrahydro-4H-pyran-4-one          |
| g9  | c-81  | 2-Naphthaldehyde                   |
| g10 | c-82  | 2-Nitrobenzaldehyde                |
| g11 | c-83  | 5-Norbornene-2-carboxaldehyde      |
| g12 | c-84  | (S)-(-)-Perillaldehyde             |

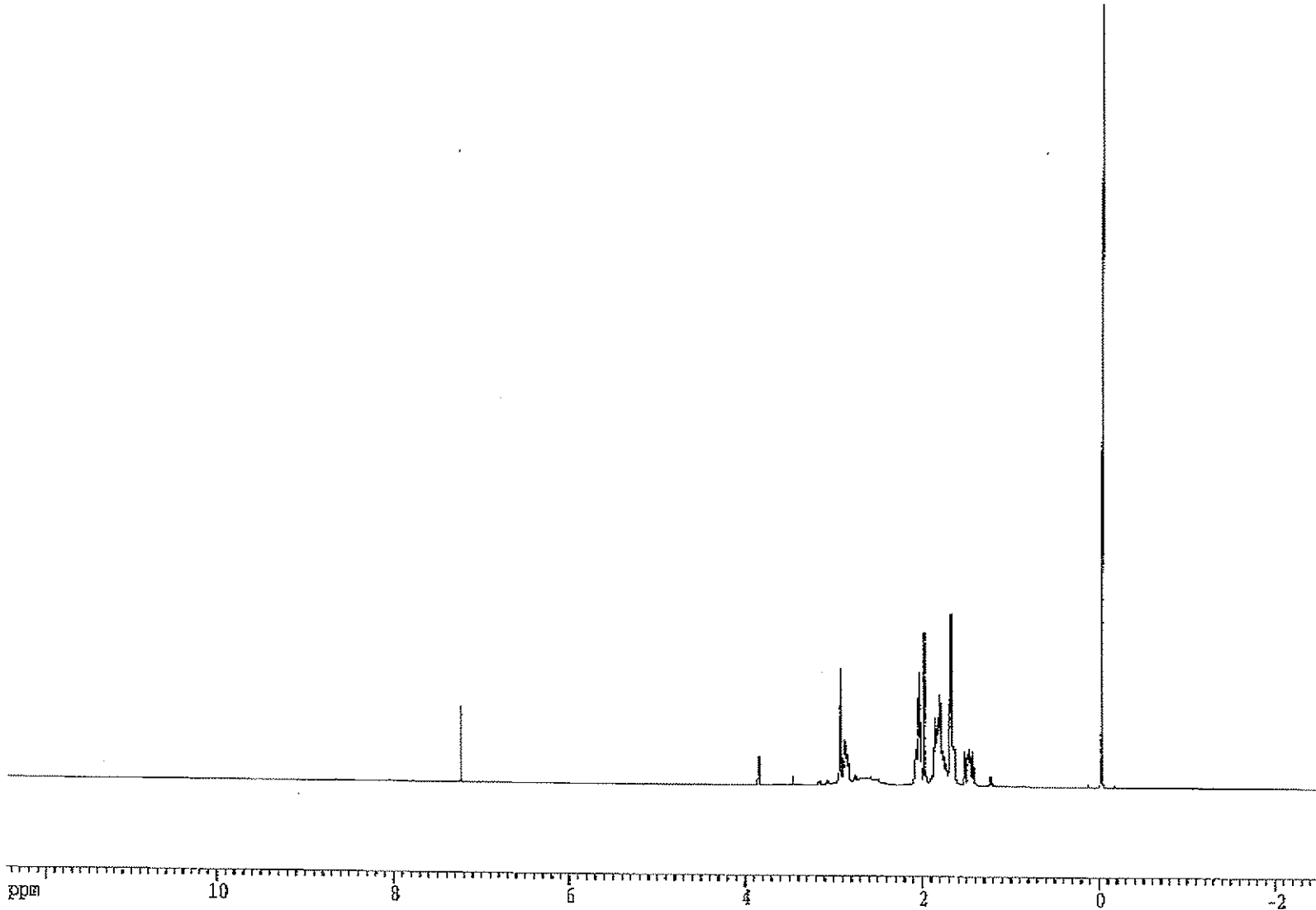
|    |       |                           |
|----|-------|---------------------------|
| h1 | c-116 | $\beta$ -Tetralone        |
| h2 | c-86  | Trimethylacetaldehyde     |
| h3 | c-87  | 2-Pyridinecarboxaldehyde  |
| h4 | c-88  | 3-Pyridinecarboxaldehyde  |
| h5 | c-89  | 4-Pyridinecarboxaldehyde  |
| h6 | c-90  | Pyrrole-2-carboxaldehyde  |
| h7 | c-91  | 4-Quinolinecarboxaldehyde |

|     |       |  |
|-----|-------|--|
| h8  | c-92  | 1,2,3,6-Tetrahydrobenzaldehyde                   |
| h9  | c-93  | 2-Thiophenecarboxaldehyde                        |
| h10 | c-94  | $\alpha,\alpha,\alpha$ -Trifluoro-p-tolualdehyde |
| h11 | c-95  | 2,3,4-Trimethoxybenzaldehyde                     |
| h12 | c-117 | o-Anisaldehyde                                   |

APPENDIX  
NMR Spectra



<sup>1</sup>H NMR for SQ775



Current Data Parameters  
NAME marina\_775  
EXPNO 1  
PROCNO 1

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PULPROG zg  
TD 32768  
SOLVENT CDCl3  
NS 32  
ES 2  
SWH 5995.204 Hz  
FIDRBS 0.182959 Hz  
AQ 2.7329011 sec  
RG 101.6  
DW 83.400 usec  
SE 129.11 usec  
TE 305.0 K  
D1 2.0000000 sec

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P1 8.00 usec  
PL1 0.00 dB  
SFO1 400.1320007 MHz

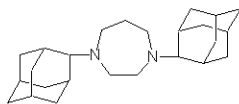
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GB 0  
PC 0.10

1D NMR plot parameters  
CX 22.00 cm  
CY 13.00 cm  
F1P 12.449 ppm  
F1 4981.03 Hz  
F2P -2.535 ppm  
F2 -1014.18 Hz  
P0MCM 0.68105 ppm  
HZCM 272.50925 Hz/1

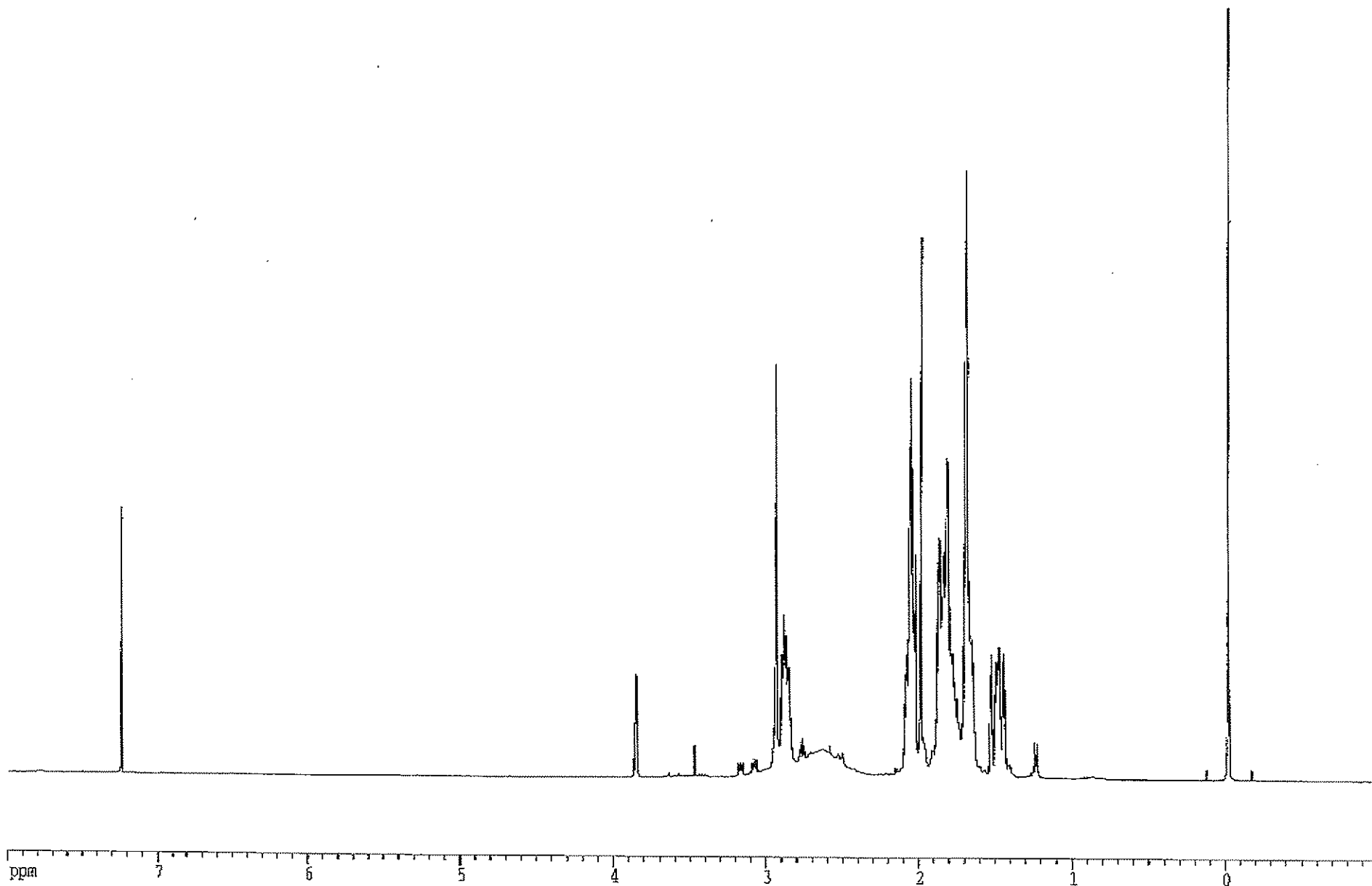
05/20/2004 14:25 301-314-9121

UMCP DEPT BIO CHEMIS

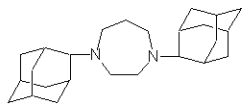
PAGE 02/23



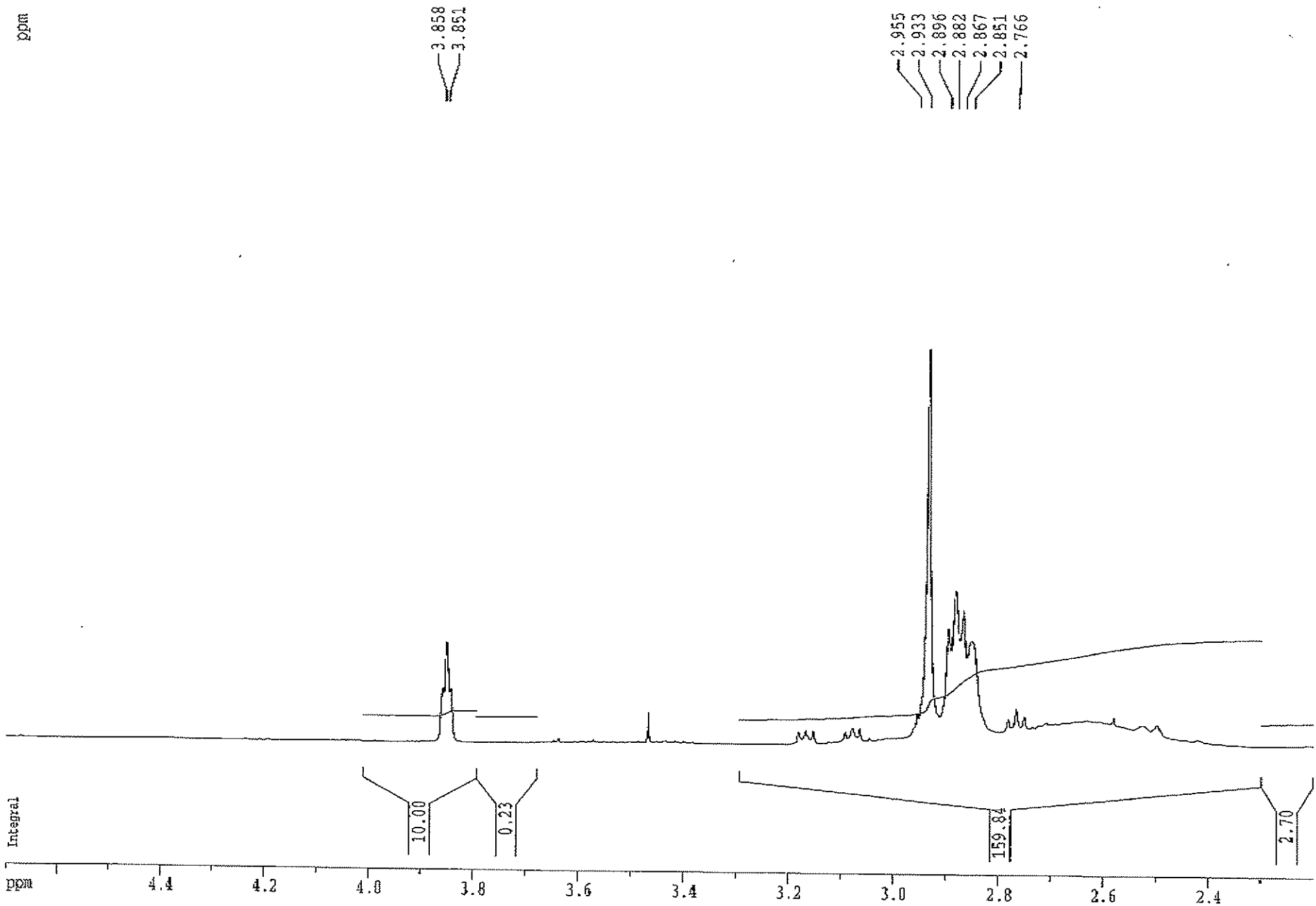
<sup>1</sup>H NMR for SQ775, y scale x 4



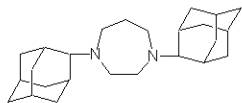
S18



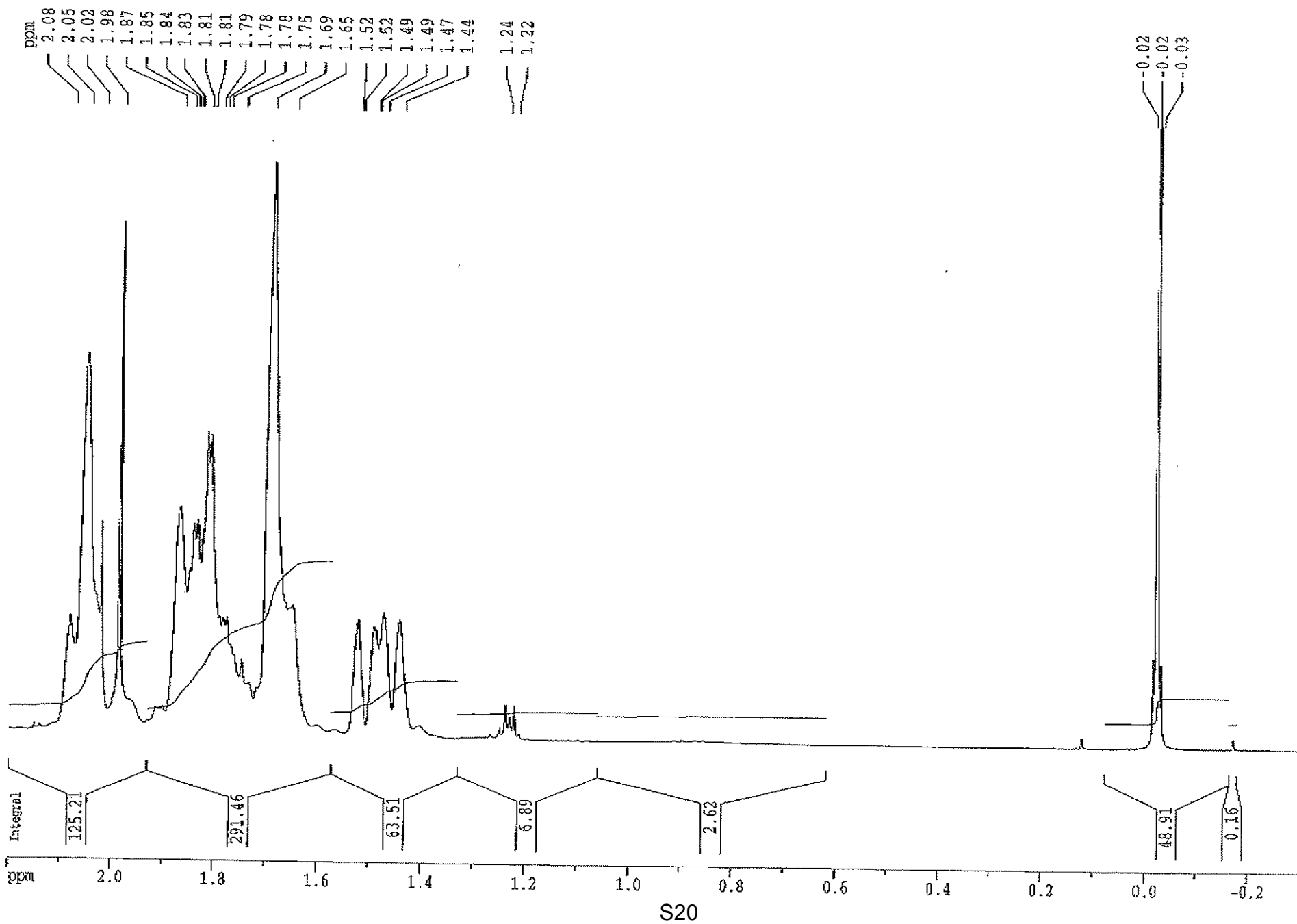
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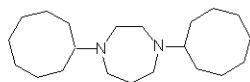


S19

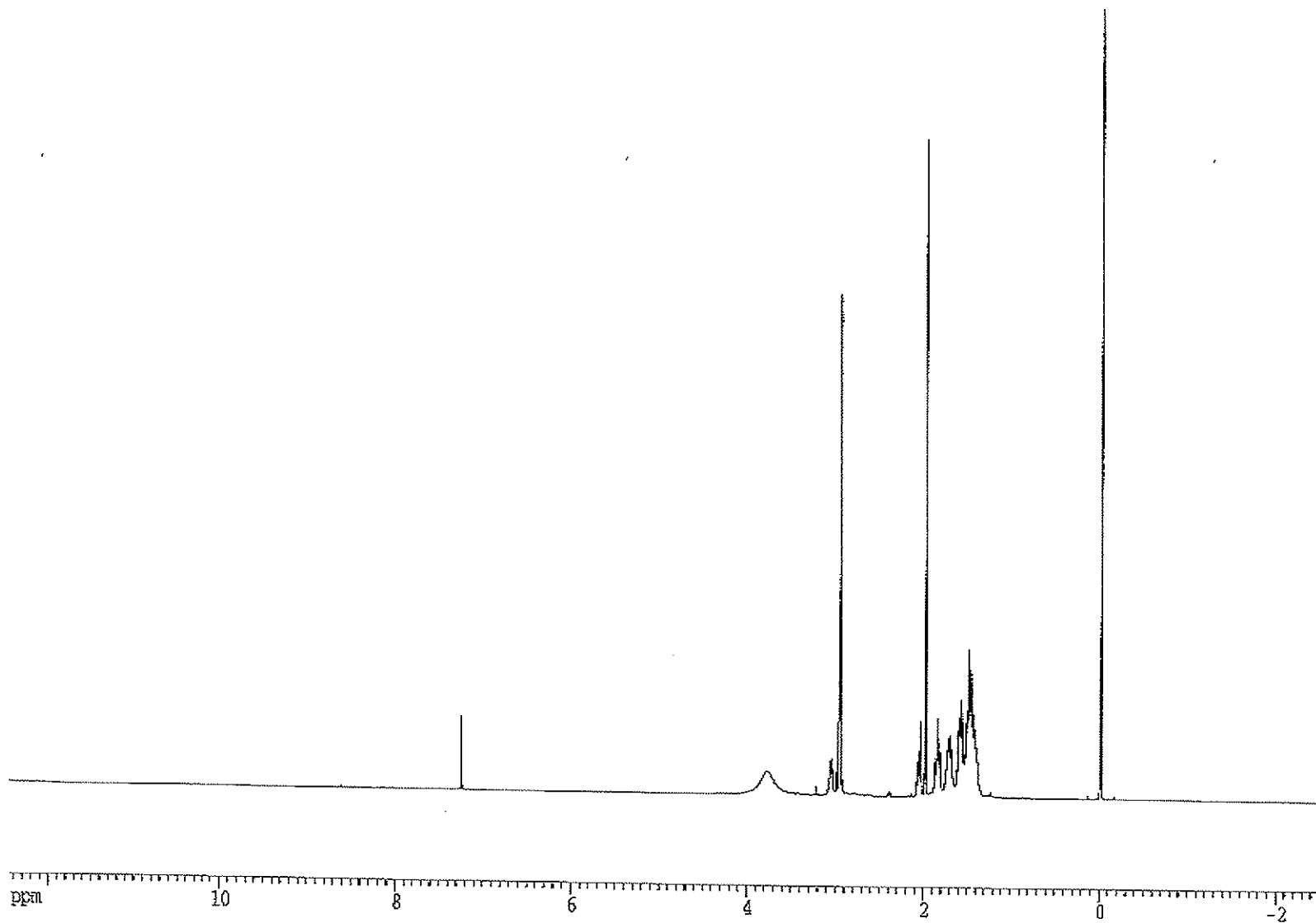


<sup>1</sup>H NMR for SQ775 , y scale x 4





<sup>1</sup>H NMR for SQ777



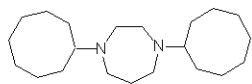
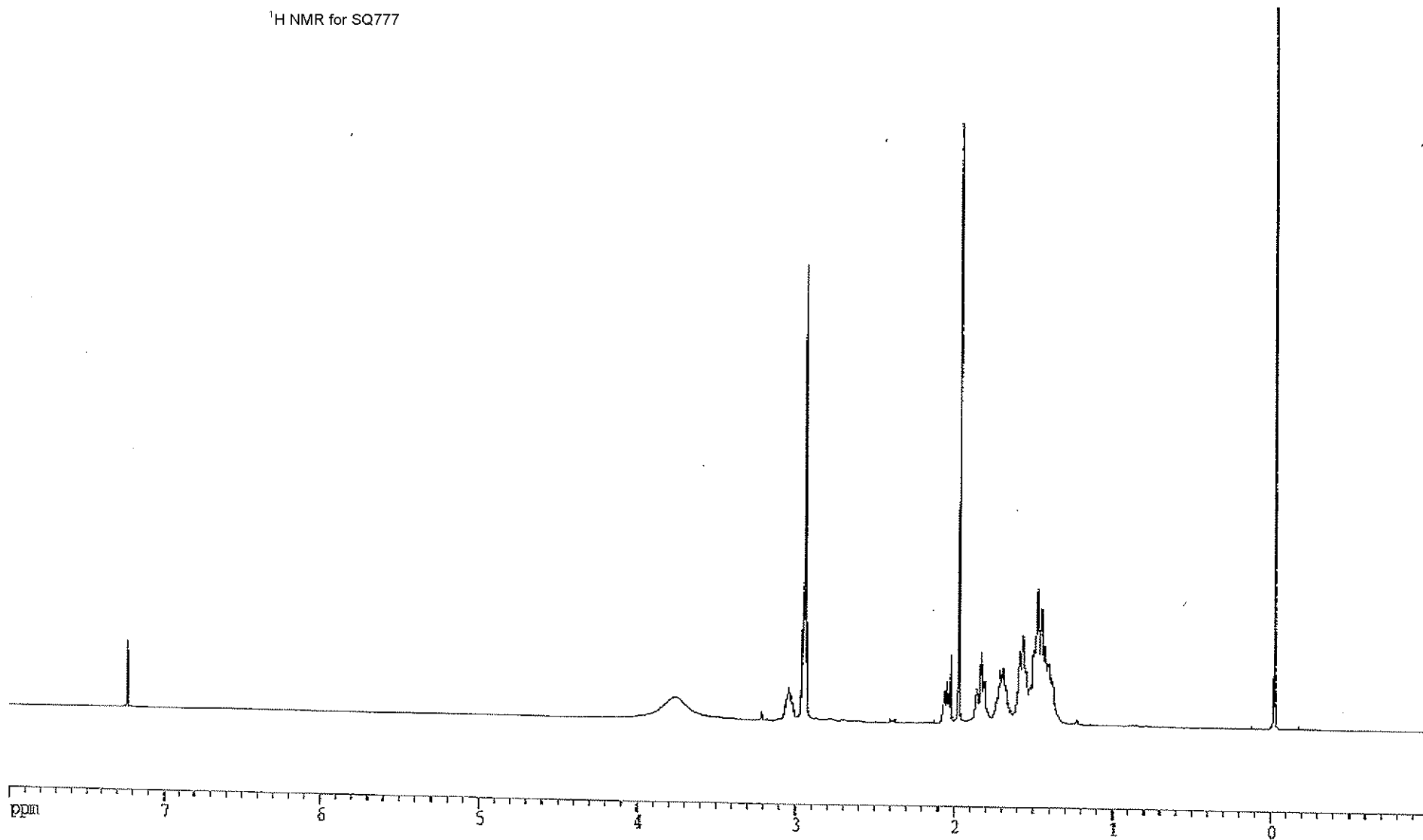
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 PROCNO 1

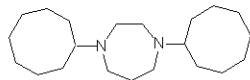
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 NS 33  
 DS 2  
 SWH 5995.204 Hz  
 FIDRES 0.182959 Hz  
 AQ 2.7329011 sec  
 RG 101.6  
 DW 83.400 usec  
 DE 129.11 usec  
 TE 305.0 K  
 D1 2.0000000 sec

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 PL1 0.00 dB  
 SFO1 400.132007 MHz

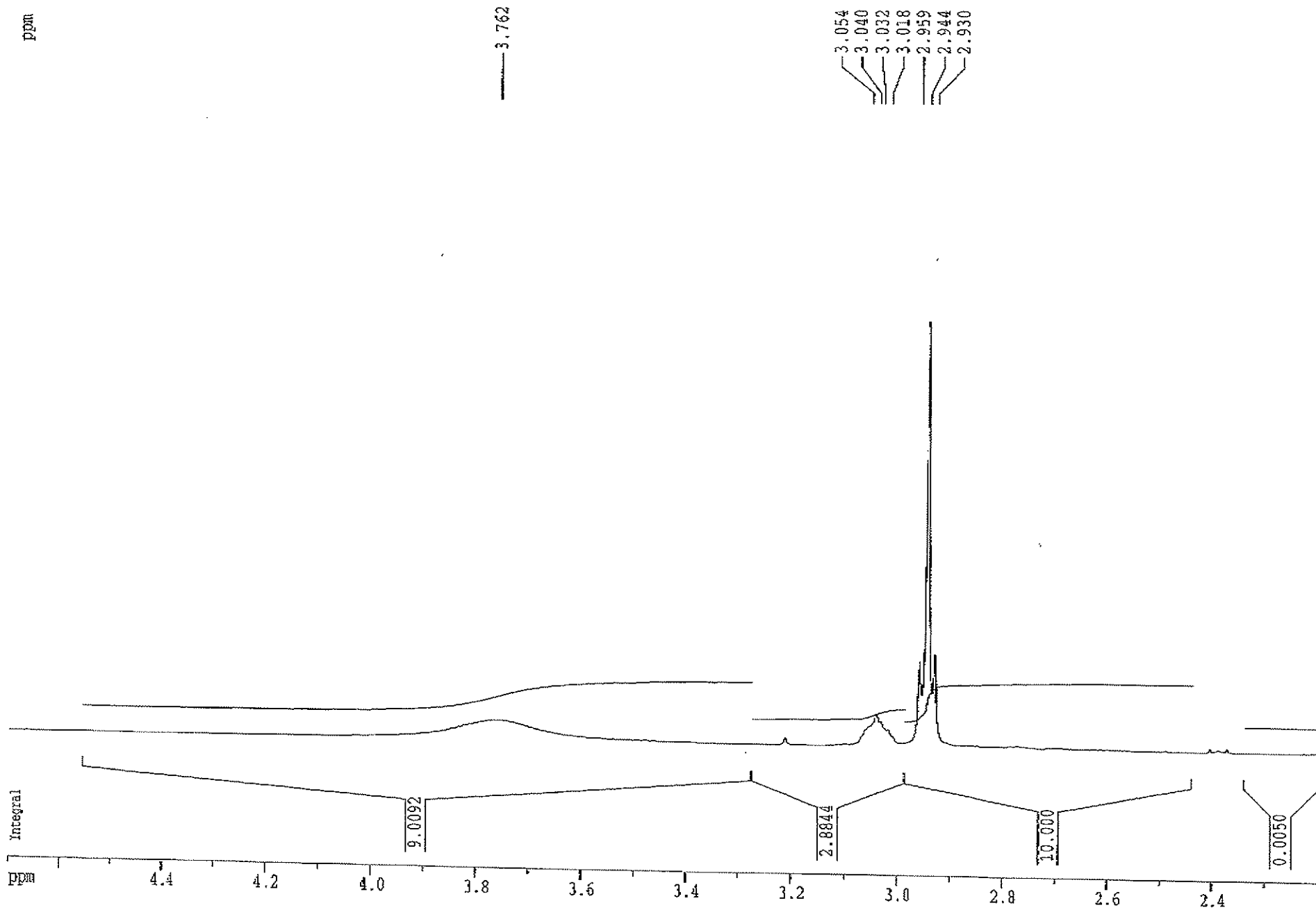
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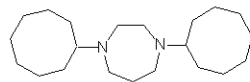
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 CY 13.00 cm  
 FIP 12.449 ppm  
 F1 4981.03 Hz  
 F2P -2.535 ppm  
 F2 -1014.13 Hz  
 ZPCMC 0.68105 ppm  
 HZCM 272.50925 Hz/°

 $^1\text{H}$  NMR for SQ777

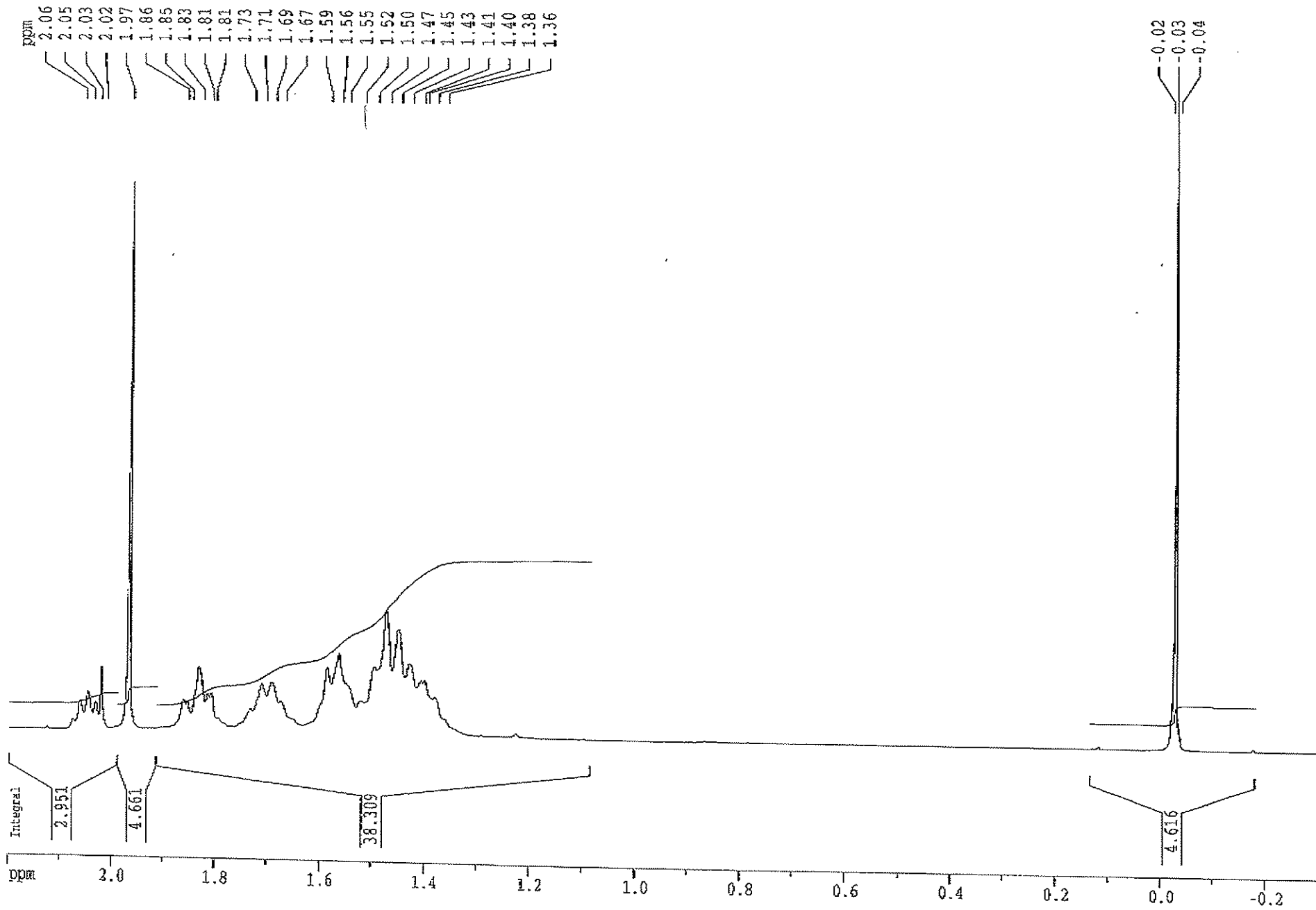


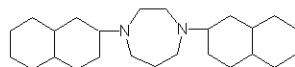
<sup>1</sup>H NMR for SQ777



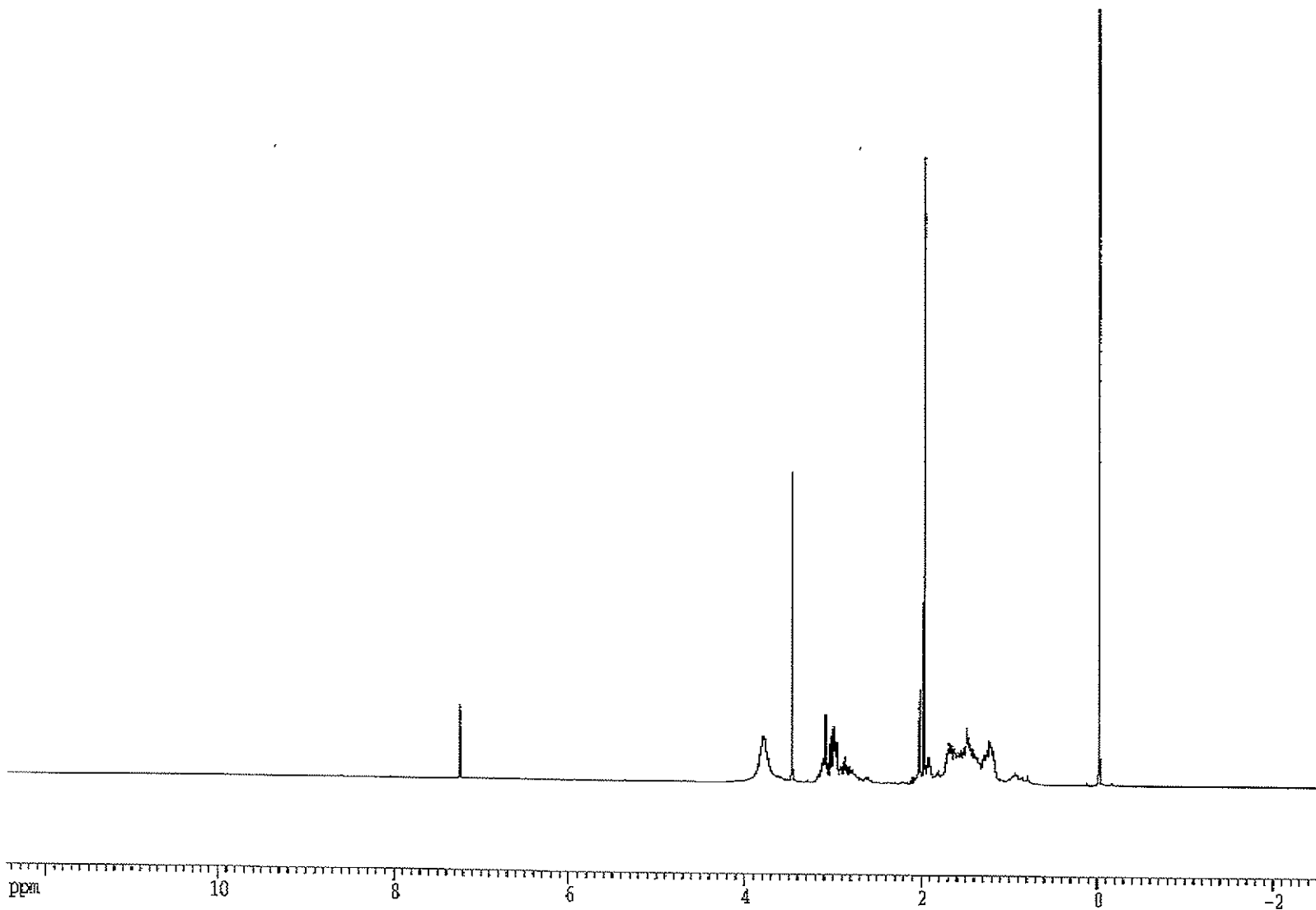


<sup>1</sup>H NMR for SQ777





<sup>1</sup>H NMR for SQ778



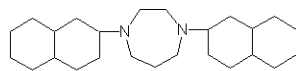
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 DS 2  
 SWH 5995.204 Hz  
 FIDRES 0.182959 Hz  
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 RG 90.5  
 DW 83.400 usec  
 DE 129.11 usec  
 TE 305.0 K  
 D1 2.0000000 sec

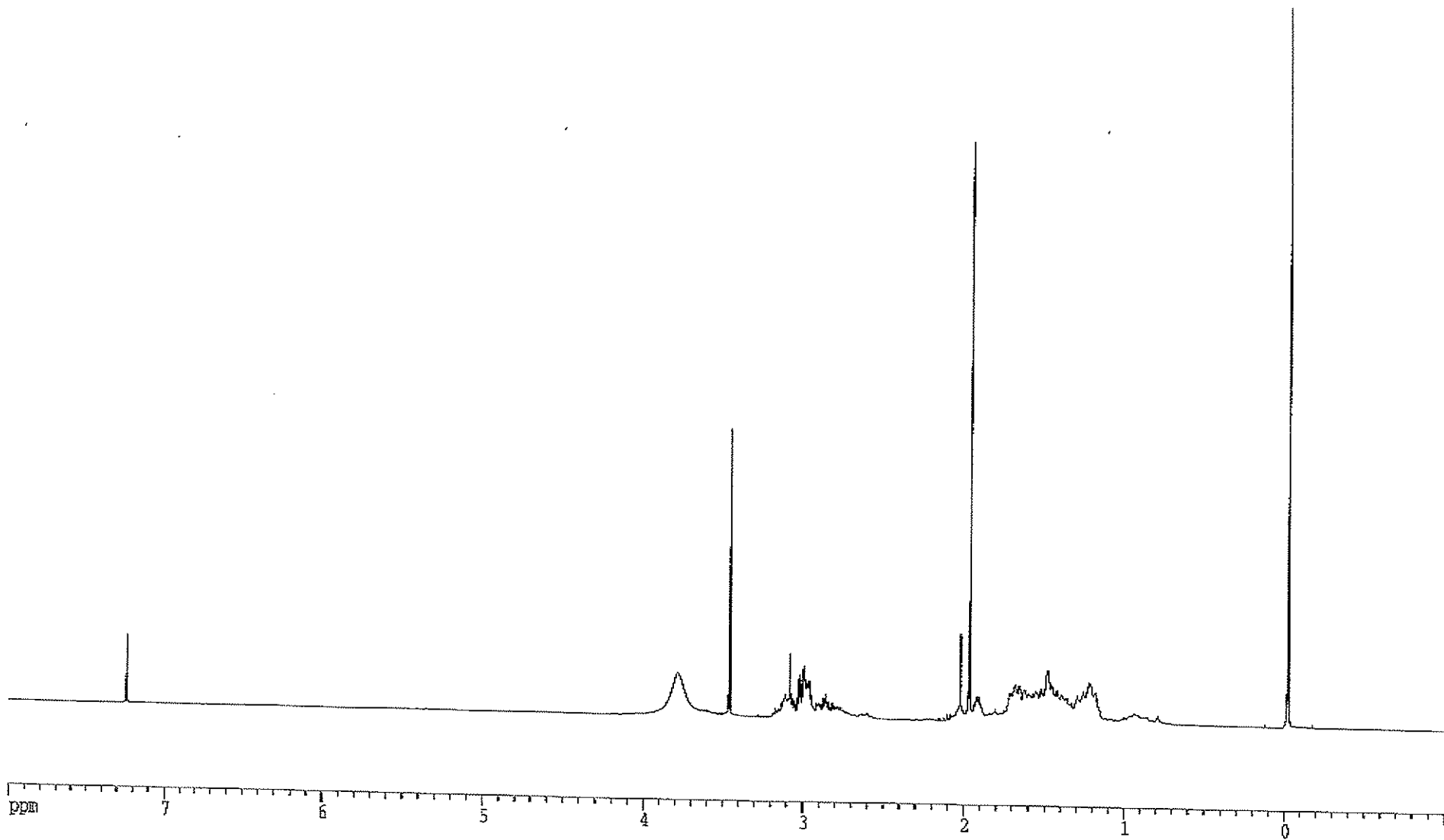
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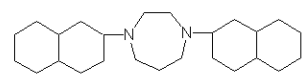
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 LB 0.25 Hz  
 GB 0  
 PC 0.10

1D NMR plot parameters  
 CX 22.40 cm  
 CY 13.00 cm  
 F1P 12.449 ppm  
 F1 4981.03 Hz  
 F2P -2.535 ppm  
 F2 -1014.18 Hz  
 PPMCM 0.68105 ppm  
 HZCM 272.50925 Hz

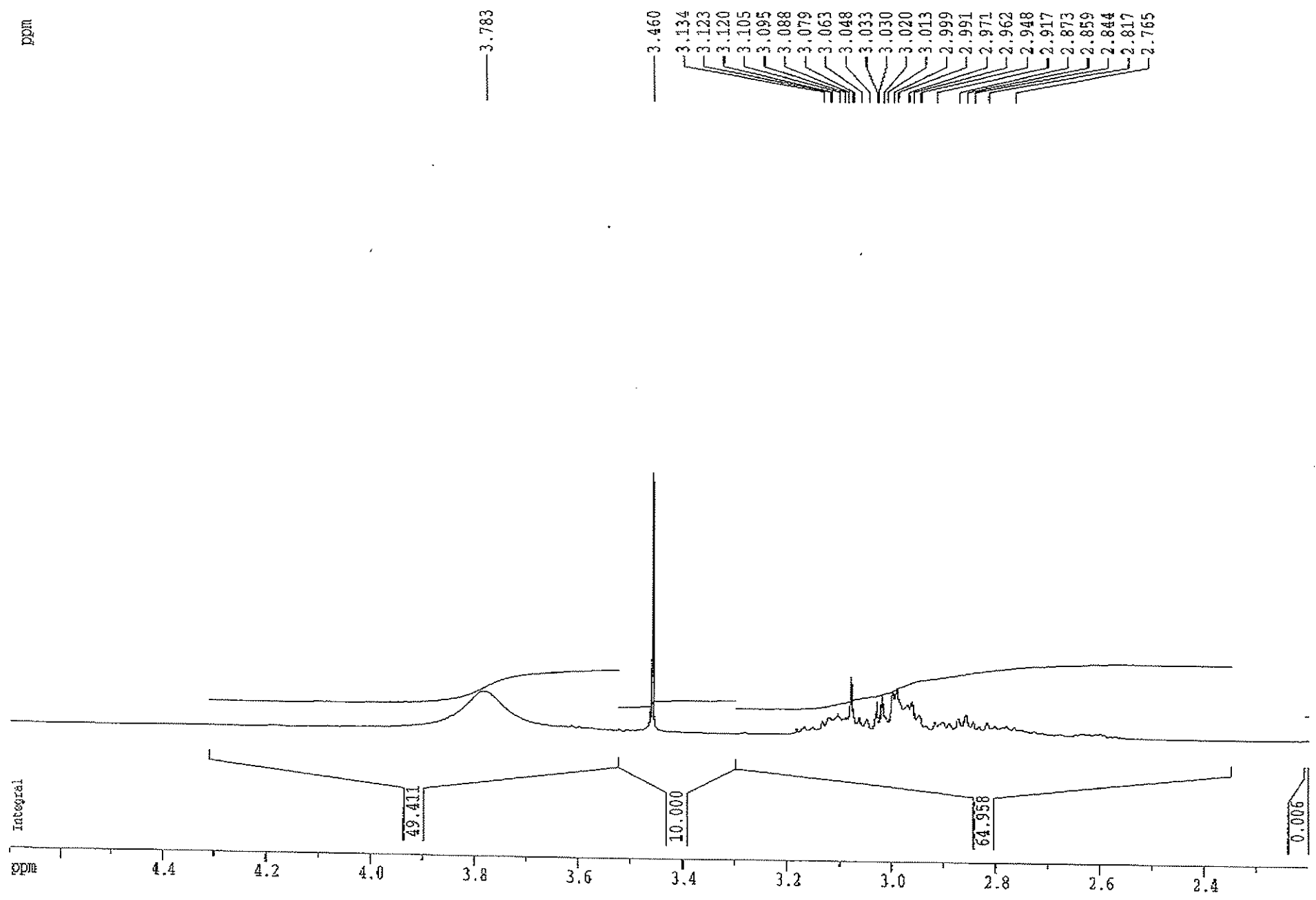


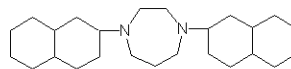
<sup>1</sup>H NMR for SQ778



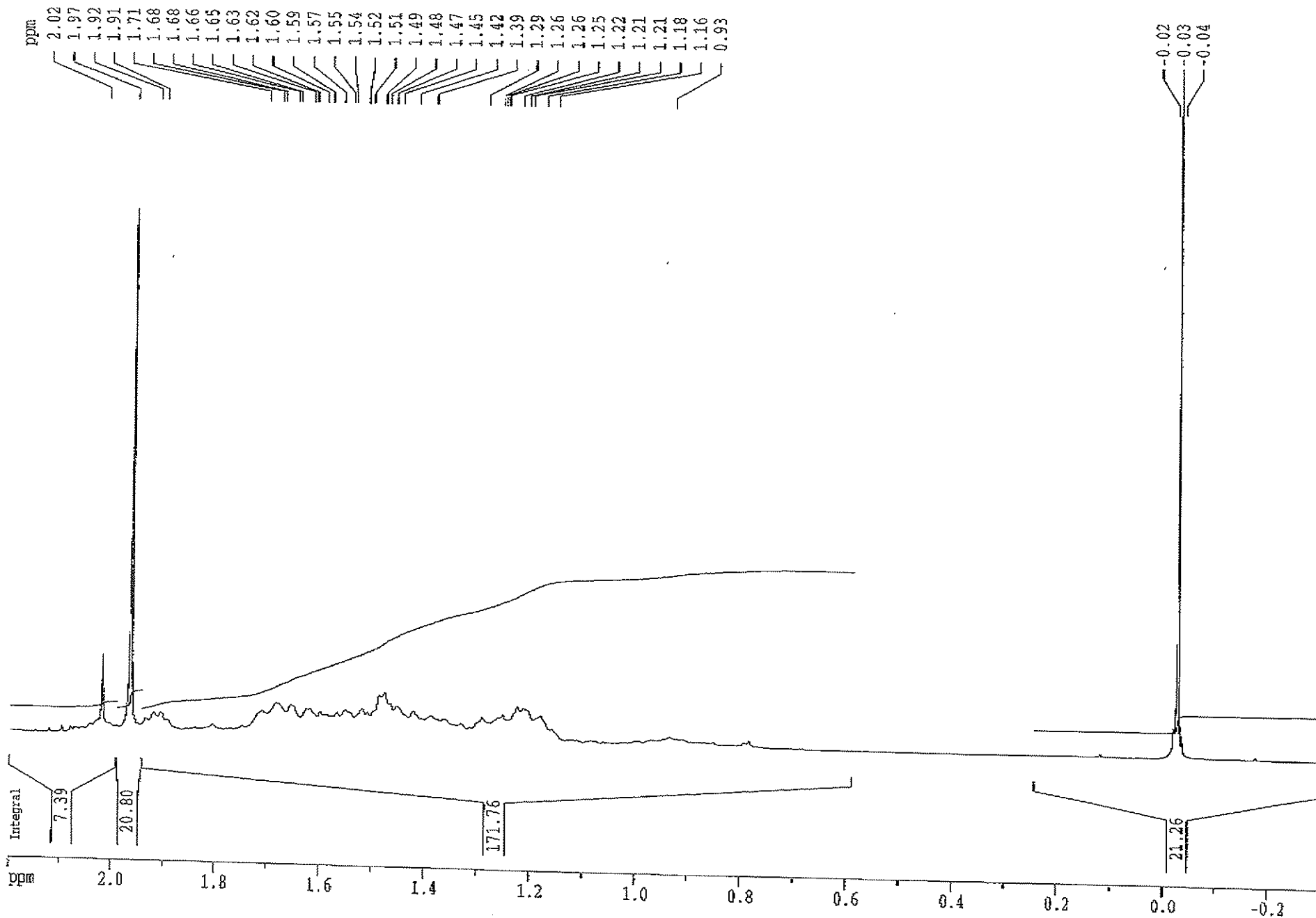


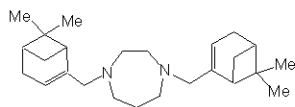
<sup>1</sup>H NMR for SQ778



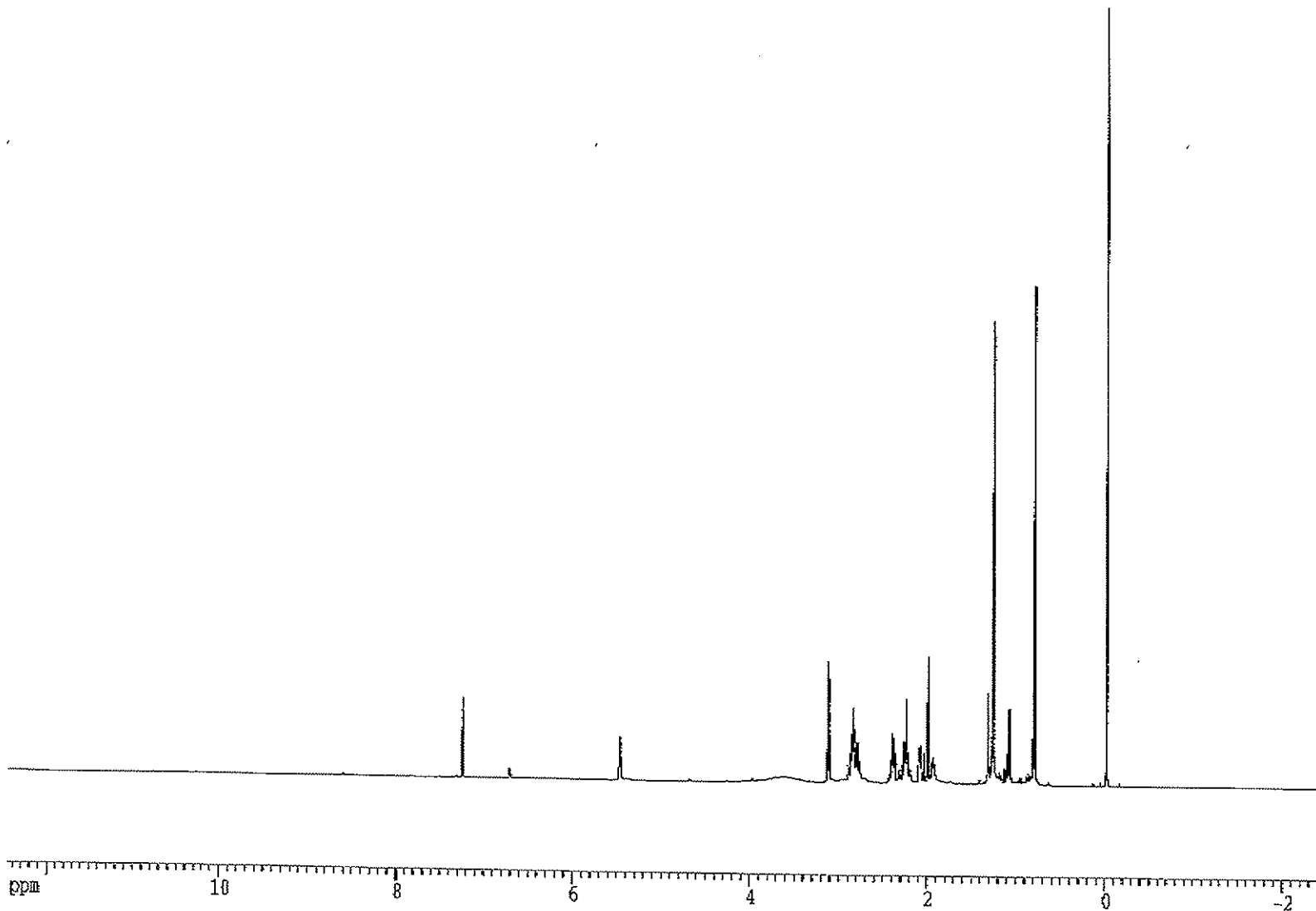


<sup>1</sup>H NMR for SQ778





<sup>1</sup>H NMR for SQ779



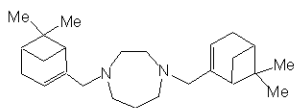
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 DS 2  
 SWH 5995.204 Hz  
 FIDRKS 0.182959 Hz  
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 RG 90.5  
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 DR 129.11 usec  
 TE 305.0 K  
 D1 2.0000000 sec

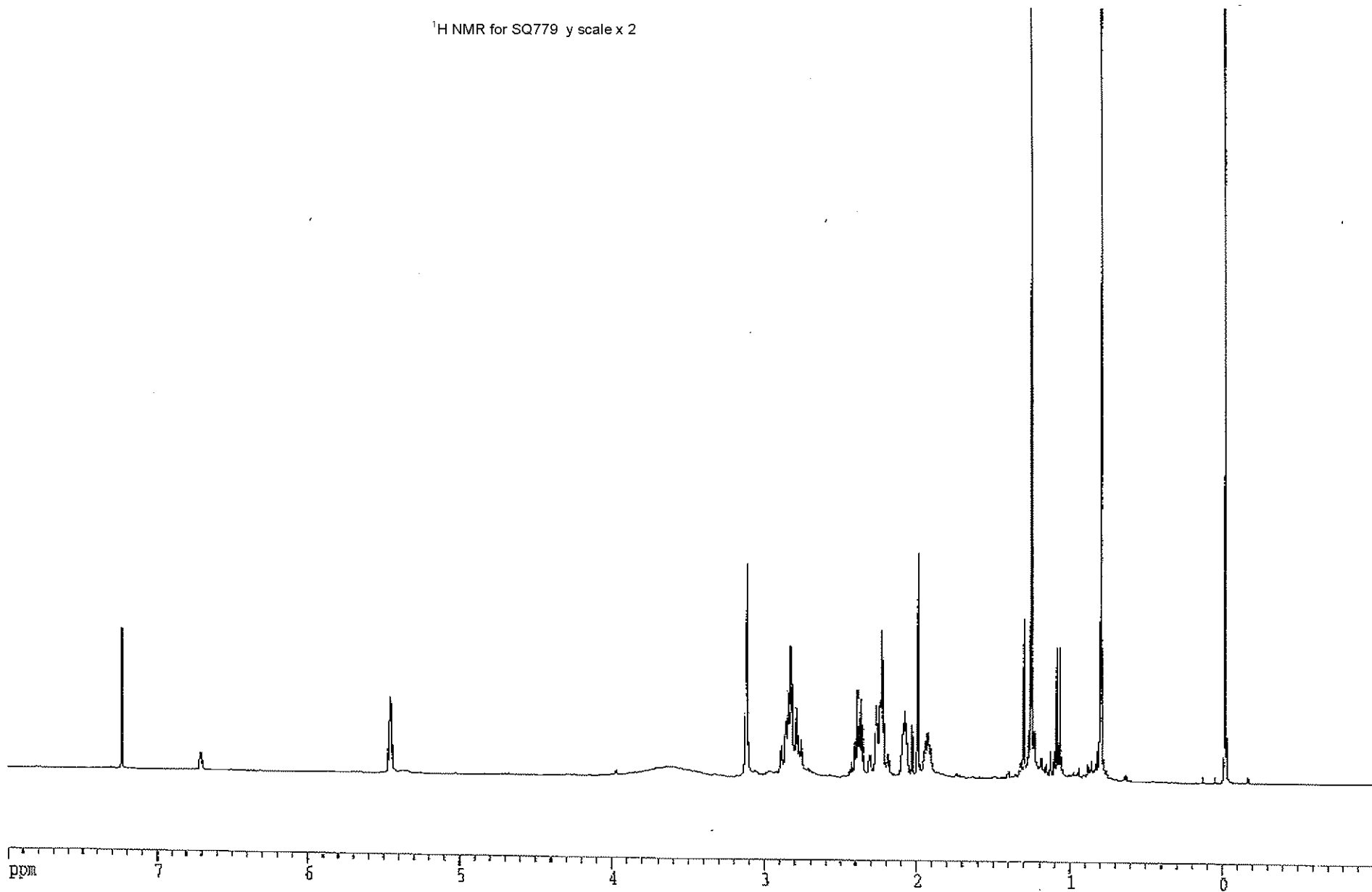
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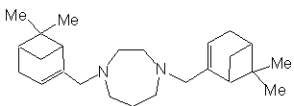
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 PC 0.10

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 CY 13.00 cm  
 F1P 12.449 ppm  
 F1 4981.03 Hz  
 F2P -2.535 ppm  
 F2 -1014.18 Hz  
 PPMCM 0.68105 ppm  
 HZCM 272.50925 Hz/1

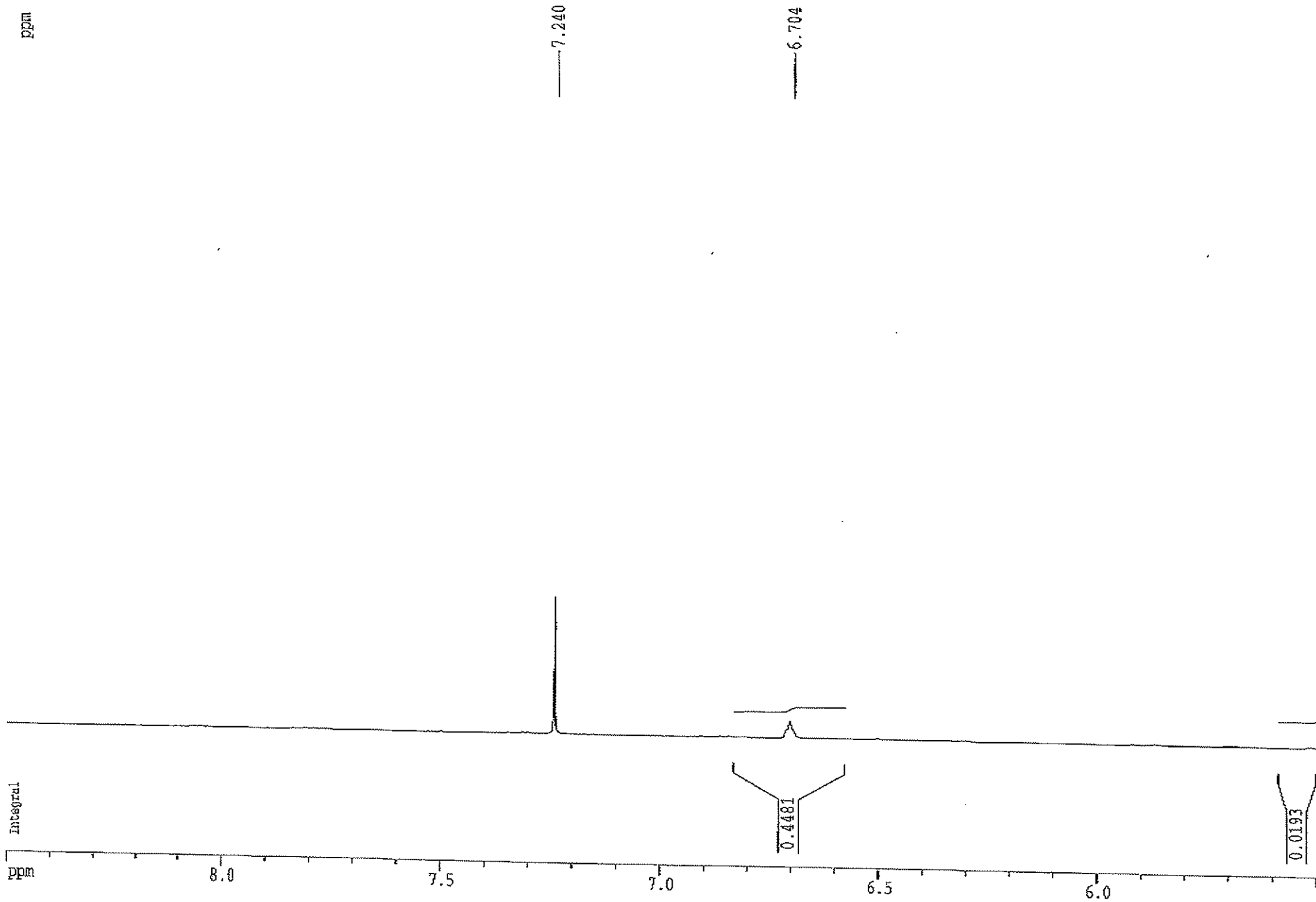


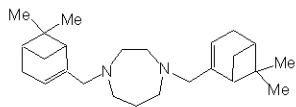
<sup>1</sup>H NMR for SQ779 y scale x 2



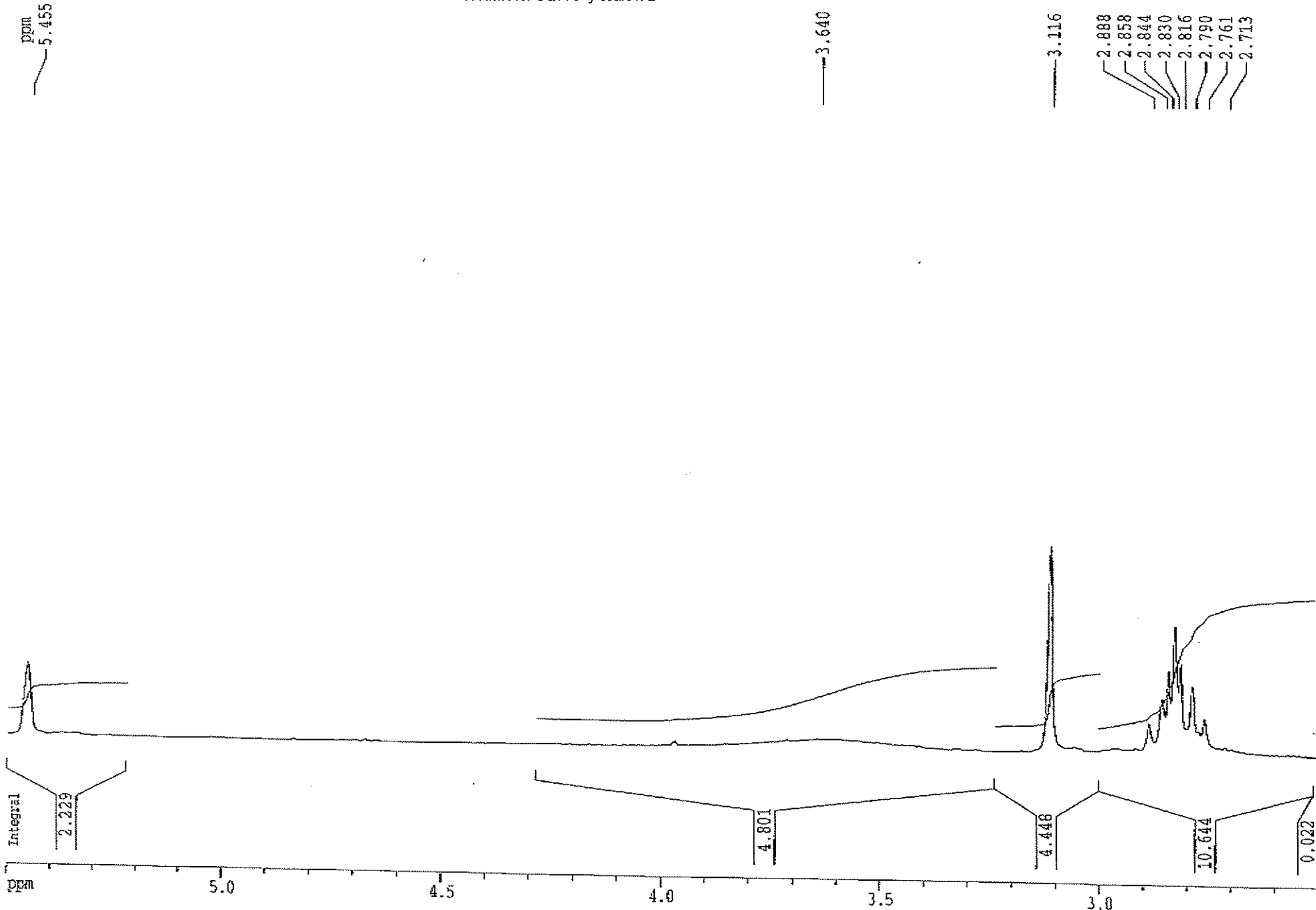


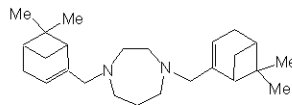
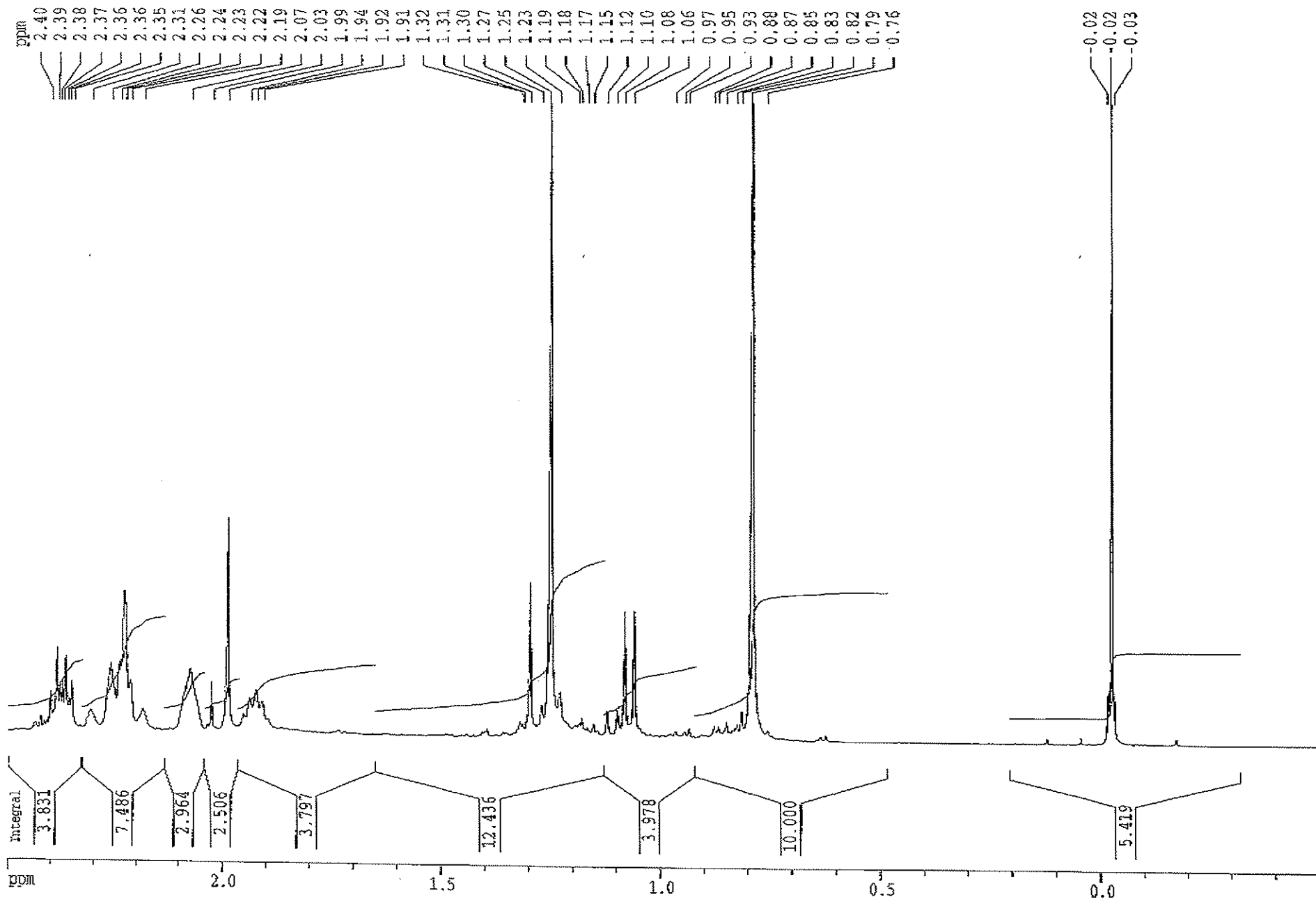
<sup>1</sup>H NMR for SQ779 y scale x 2

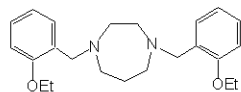




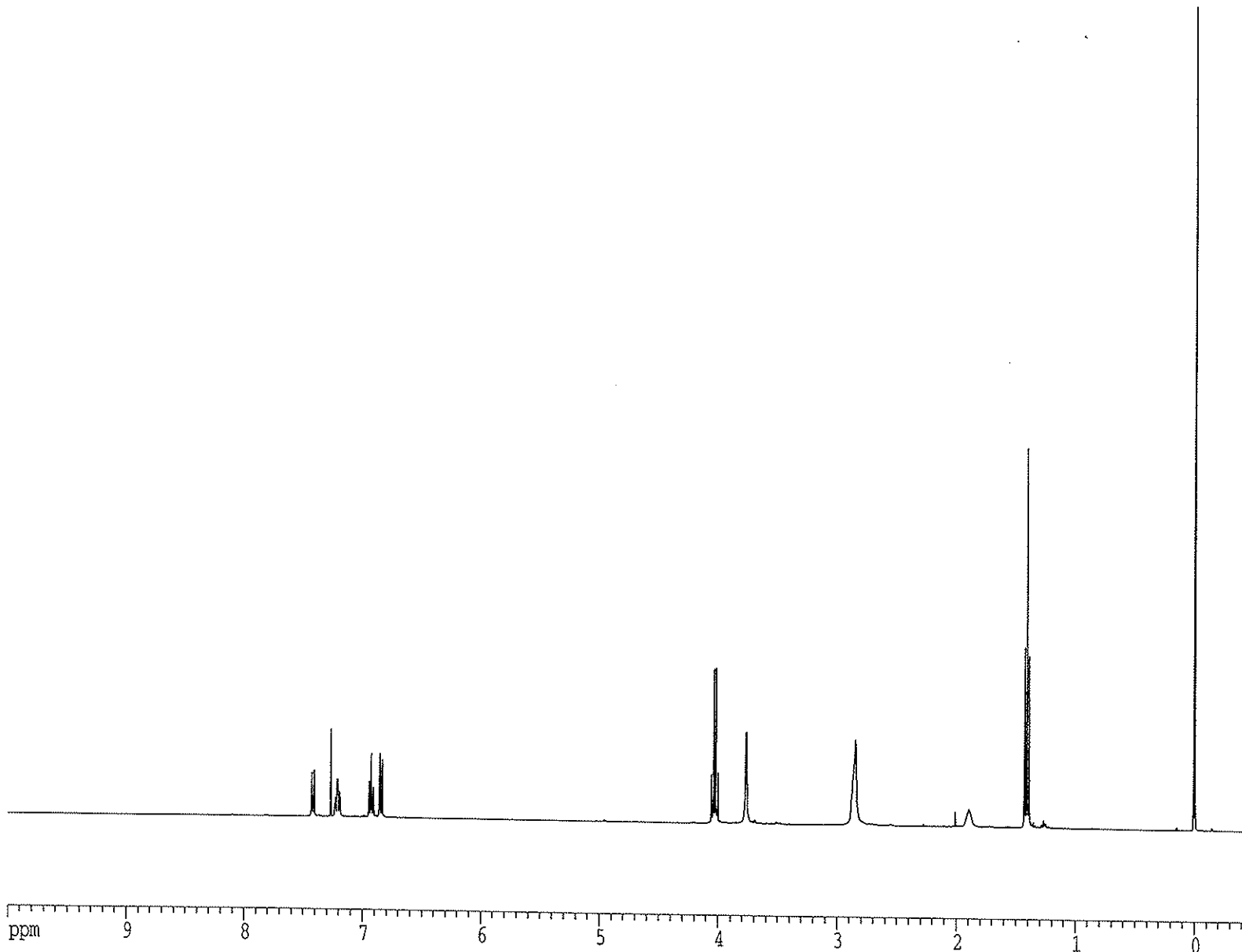
<sup>1</sup>H NMR for SQ779 y scale x 2



<sup>1</sup>H NMR for SQ779 y scale x 2



SQ 780 in CDCl3 , 400MHz, UMCP. yfl.



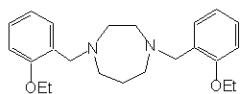
Current Data Parameters  
 NAME 6-contract-0709  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20030709  
 Time 21.27  
 INSTRUM spect  
 PROBHD 5 mm QNP 1H/1  
 PULPROG zg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 64  
 DS 0  
 SWH 8223.685 Hz  
 FIDRES 0.125483 Hz  
 AQ 3.9846387 sec  
 RG 256  
 DW 60.800 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.0000000 sec

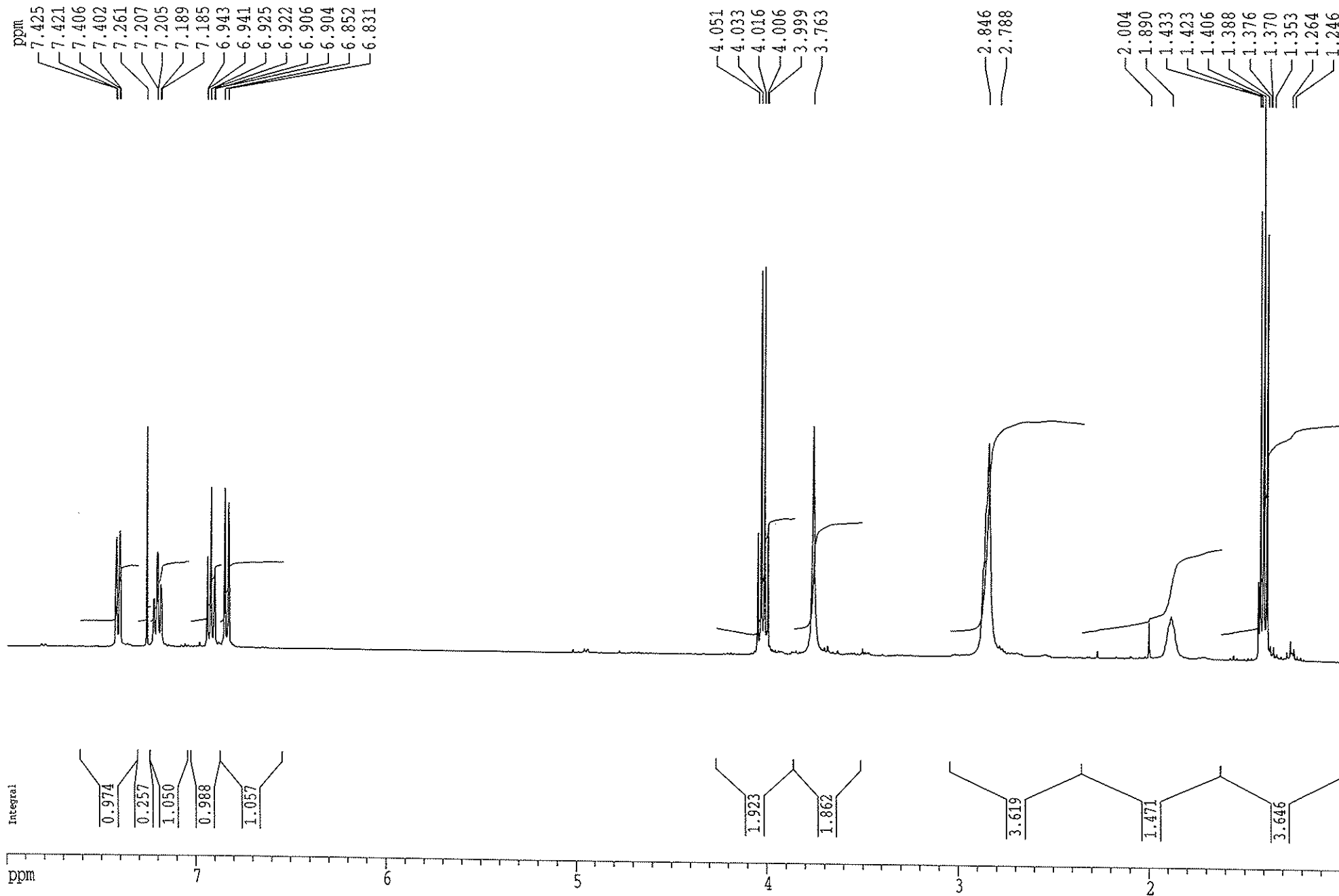
===== CHANNEL f1 =====  
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 P1 9.00 usec  
 PL1 -4.00 dB  
 SFO1 399.7324685 MHz

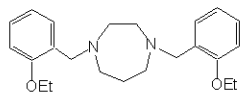
F2 - Processing parameters  
 SI 32768  
 SF 399.7300115 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 2.00

1D NMR plot parameters  
 CX 21.00 cm  
 CY 14.00 cm  
 F1P 10.000 ppm  
 F1 3997.30 Hz  
 F2P -0.500 ppm  
 F2 -199.87 Hz  
 PPMCM 0.50000 ppm/cm  
 HZCM 199.86501 Hz/cm

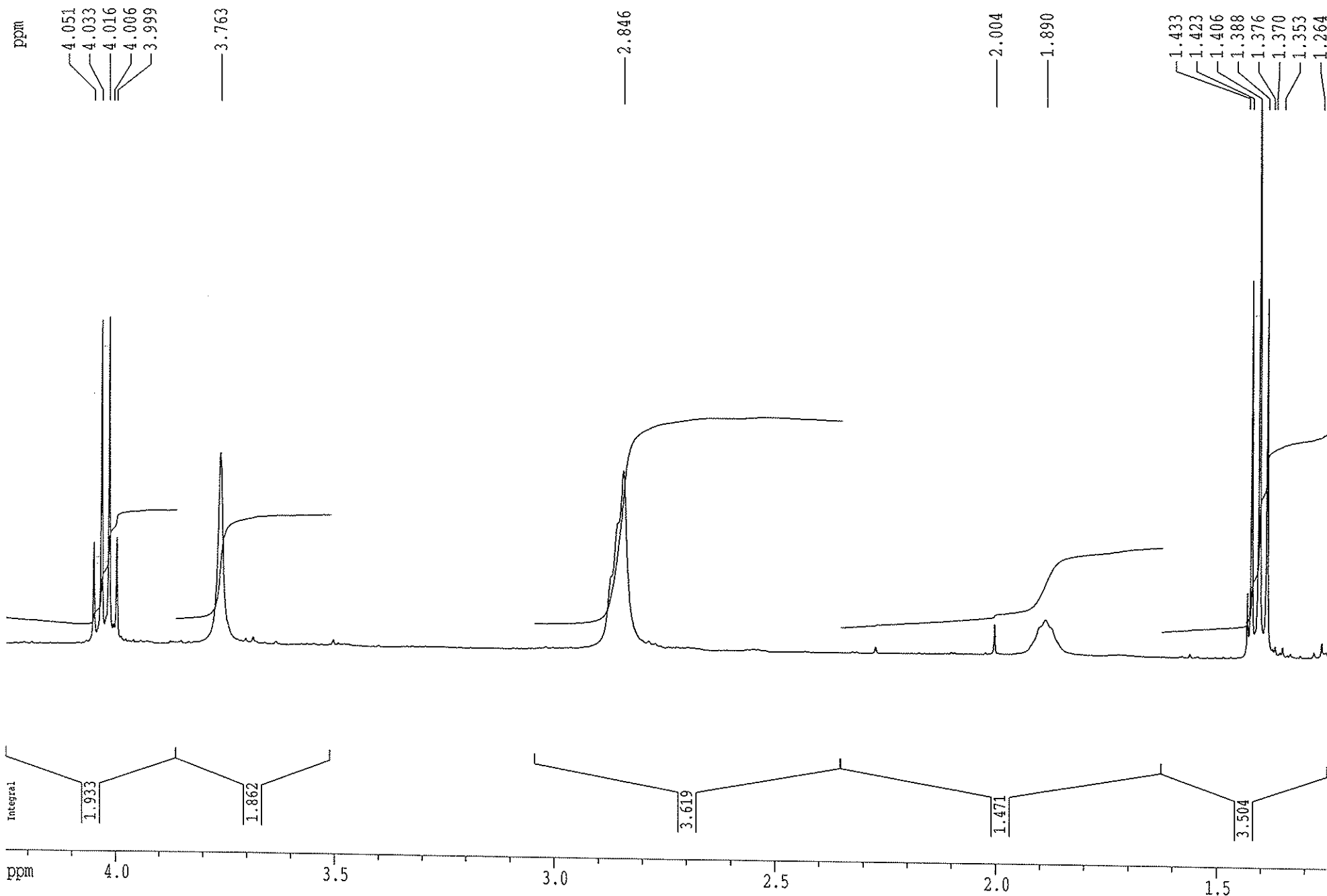


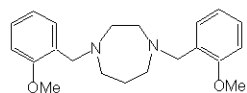
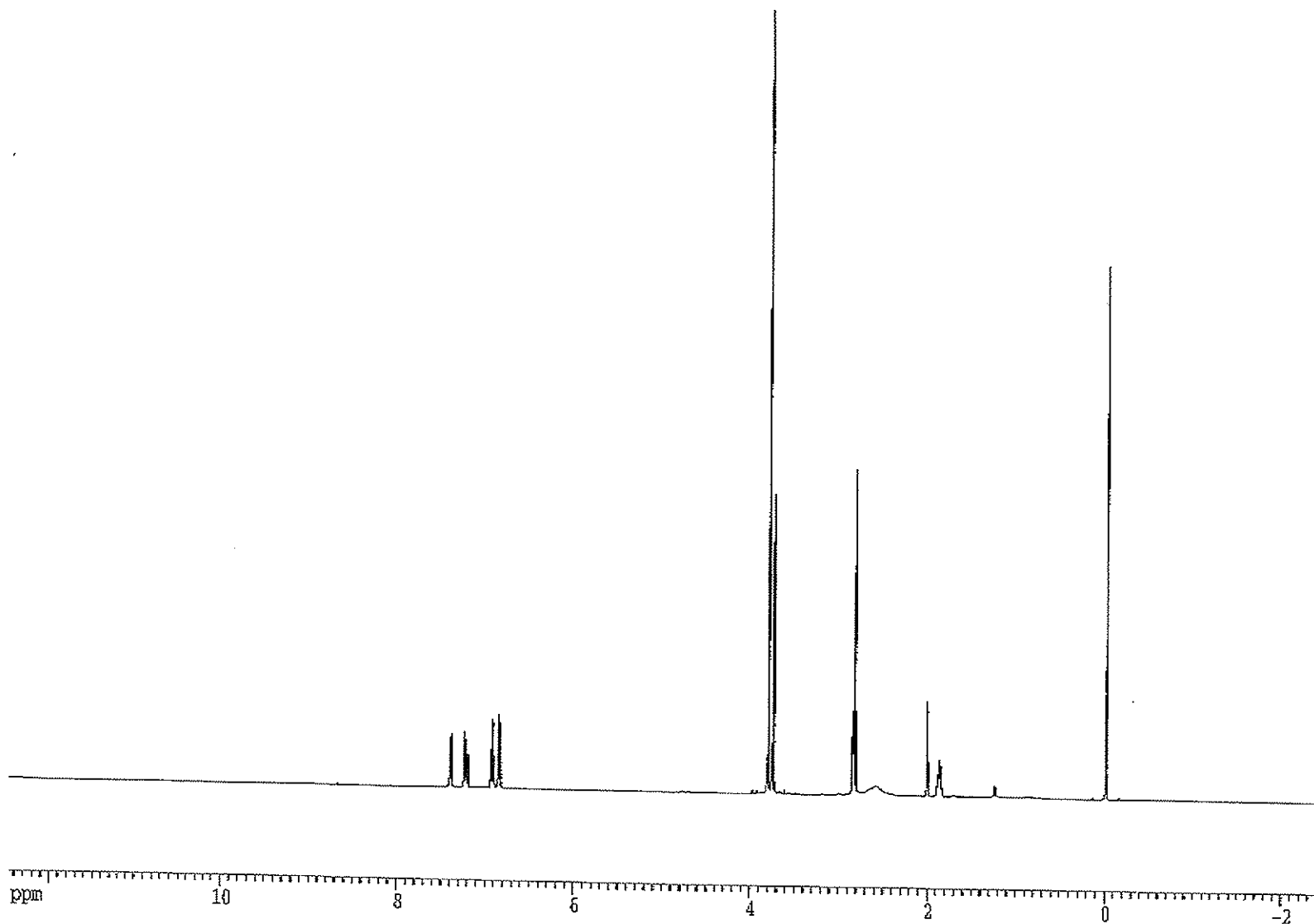
SQ 780 in CDCl3 , 400MHz, UMCP. yf1.





SQ 780 in CDCl<sub>3</sub> , 400MHz, UMCP. yfl.



<sup>1</sup>H NMR for SQ782

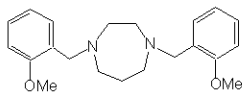
Current Data Parameters  
 NAME marina\_782  
 EXPRO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20040520  
 Time 10.16  
 INSTRUM spect  
 PROBHD 5 mm Multinuc1  
 PULPROG zg  
 TD 32768  
 SOLVENT CDCl3  
 NS 32  
 DS 2  
 SWH 5995.204 Hz  
 FIDRES 0.182959 Hz  
 AQ 2.7329011 sec  
 RG 181  
 DW 83.400 usec  
 DE 129.11 usec  
 TE 305.0 K  
 D1 2.0000000 sec

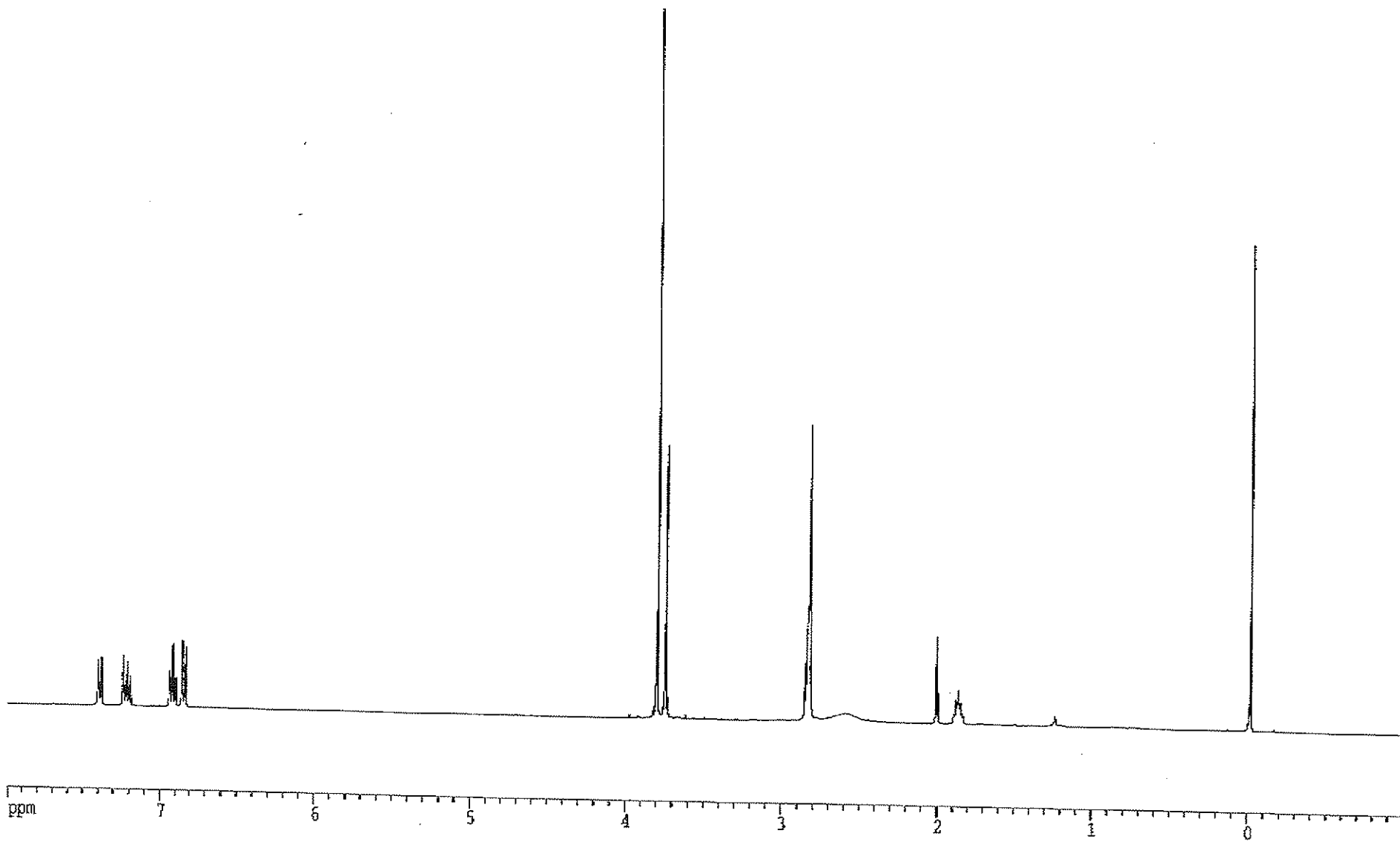
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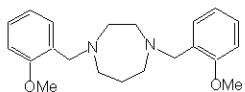
F2 - Processing parameters  
 SI 32768  
 SF 400.1300172 MHz  
 WDW EM  
 SSB 0  
 LB 0.25 Hz  
 GB 0  
 PC 0.10

1D NMR plot parameters  
 CX 22.00 cm  
 CY 13.00 cm  
 FLP 12.449 ppm  
 F1 4981.03 Hz  
 F2P -2.535 ppm  
 F2 -1014.18 Hz  
 PPMCH 0.68105 ppm  
 HZCX 272.50925 Hz/1



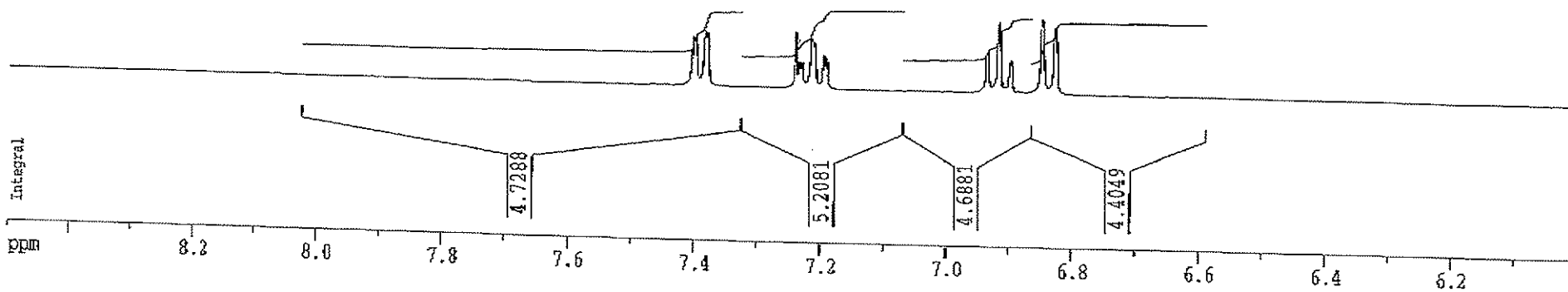
<sup>1</sup>H NMR for SQ782



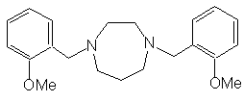


<sup>1</sup>H NMR for SQ782

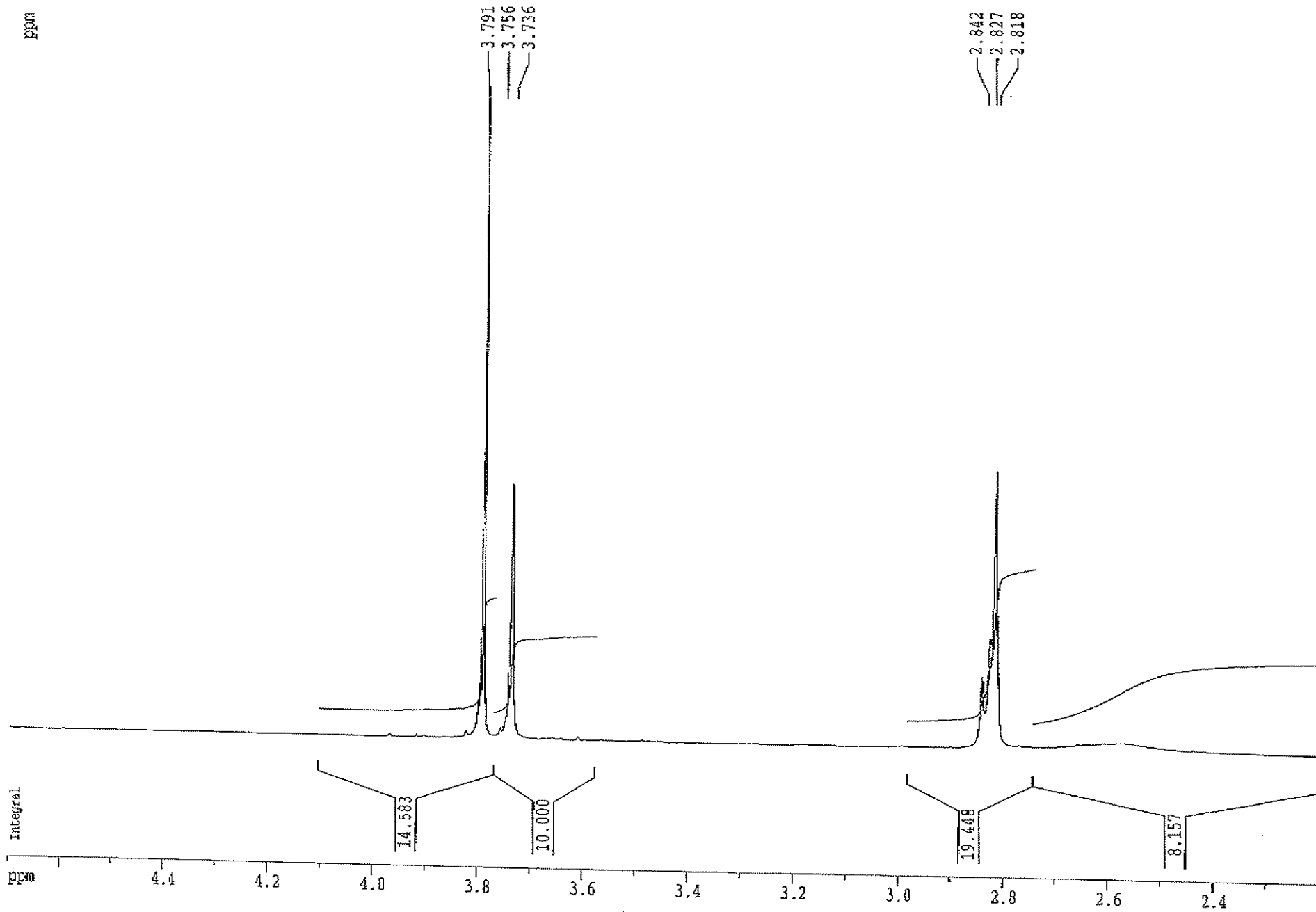
7.403  
7.399  
7.384  
7.380  
7.241  
7.235  
7.231  
7.215  
7.212  
7.196  
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6.916  
6.899  
6.899  
6.889  
6.889

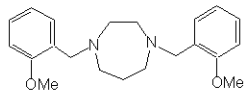


ppm

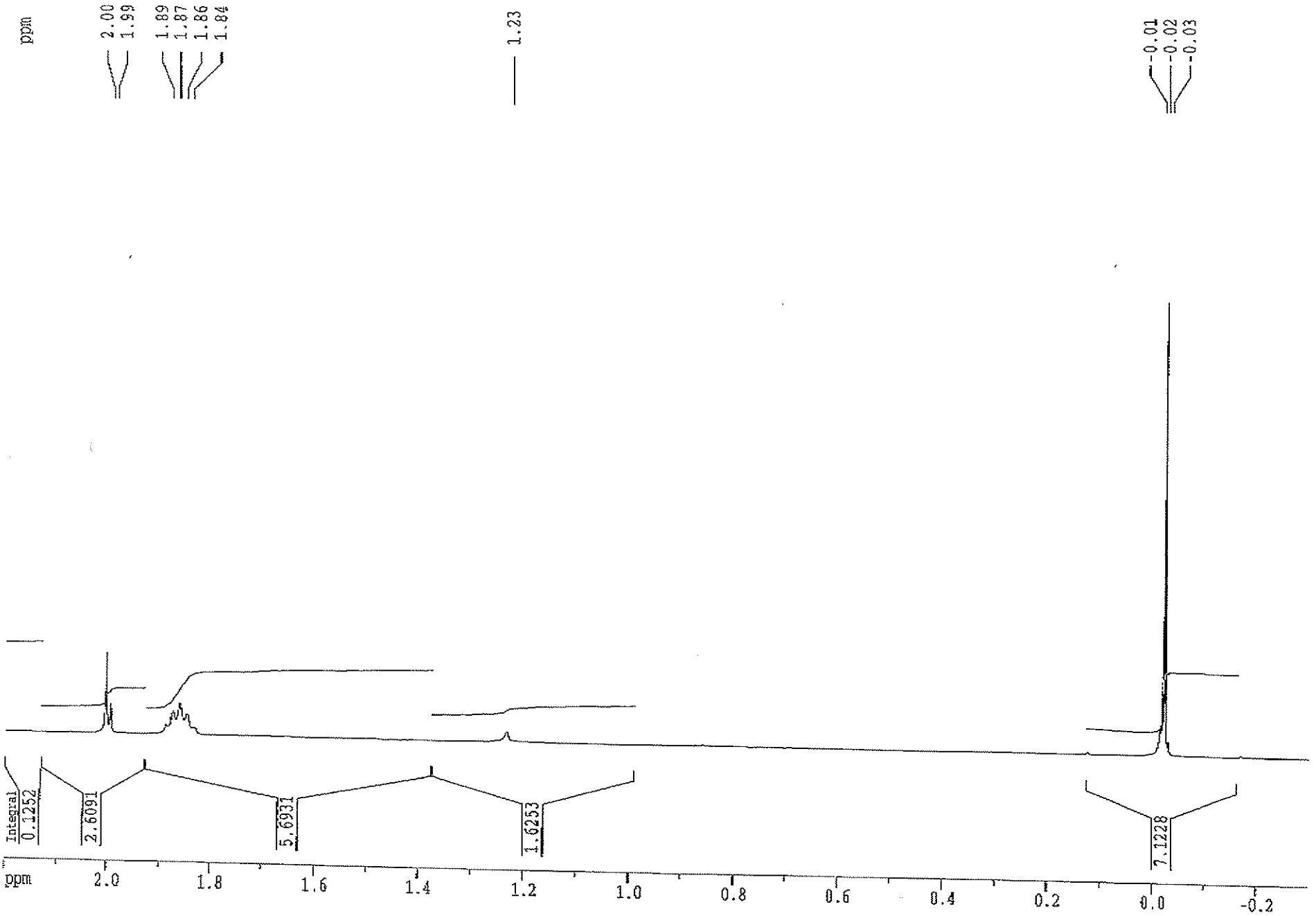


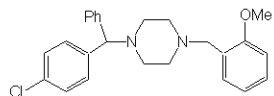
<sup>1</sup>H NMR for SQ782





<sup>1</sup>H NMR for SQ782





<sup>1</sup>H NMR for SQ784

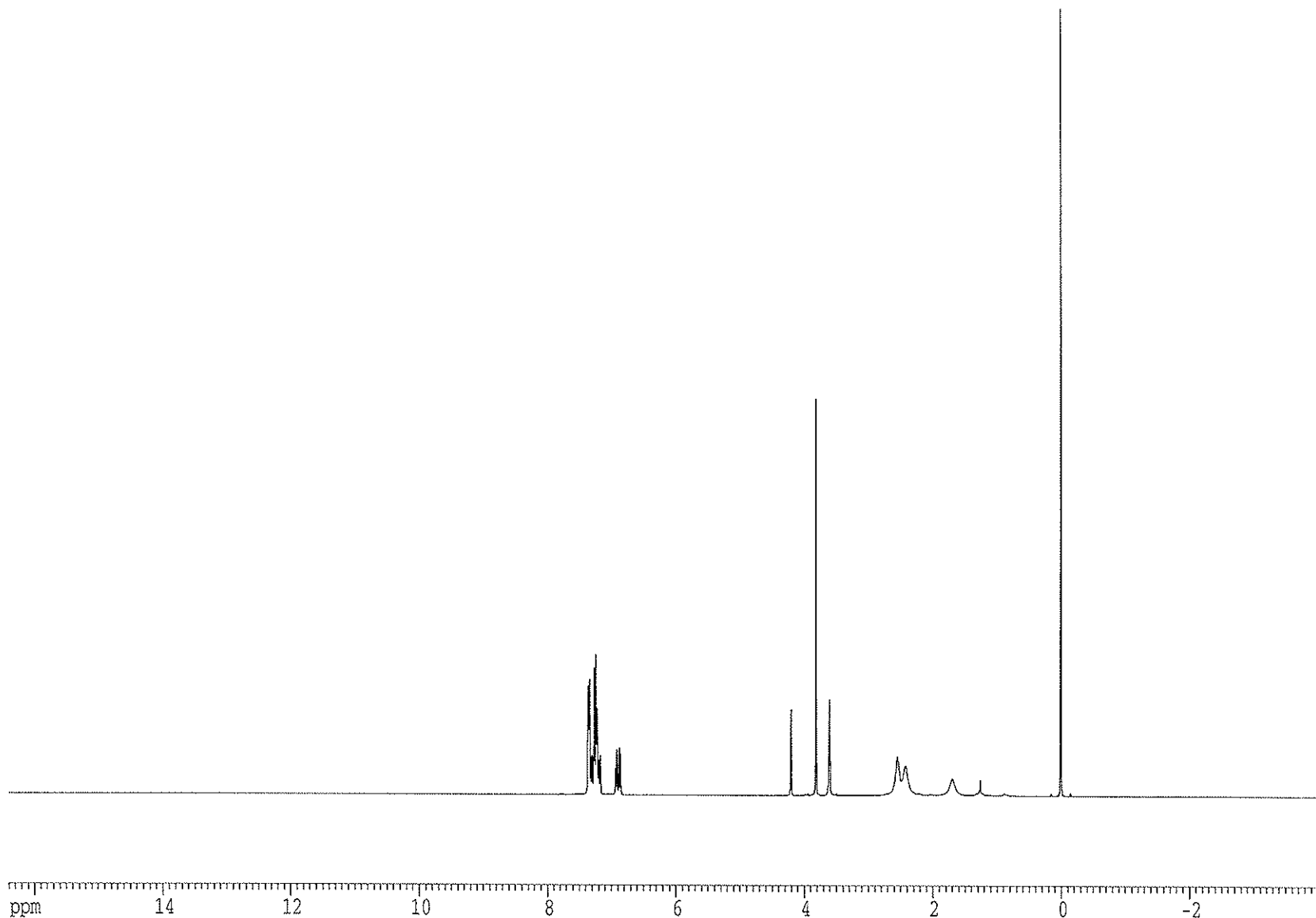
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 NAME 24-marina-1210  
 EXPNO 1  
 PROCNO 1

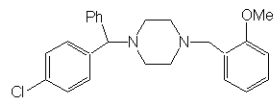
F2 - Acquisition Parameters  
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 Time 1.04  
 INSTRUM spect  
 PROBHD 5 mm QNP 1H/1  
 PULPROG zg30  
 TD 65536  
 SOLVENT CDC13  
 NS 128  
 DS 0  
 SWH 8223.685 Hz  
 FIDRES 0.125483 Hz  
 AQ 3.9846387 sec  
 RG 287.4  
 DW 60.800 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.0000000 sec

===== CHANNEL f1 =====  
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 P1 9.50 usec  
 PL1 -4.00 dB  
 SFO1 399.7324685 MHz

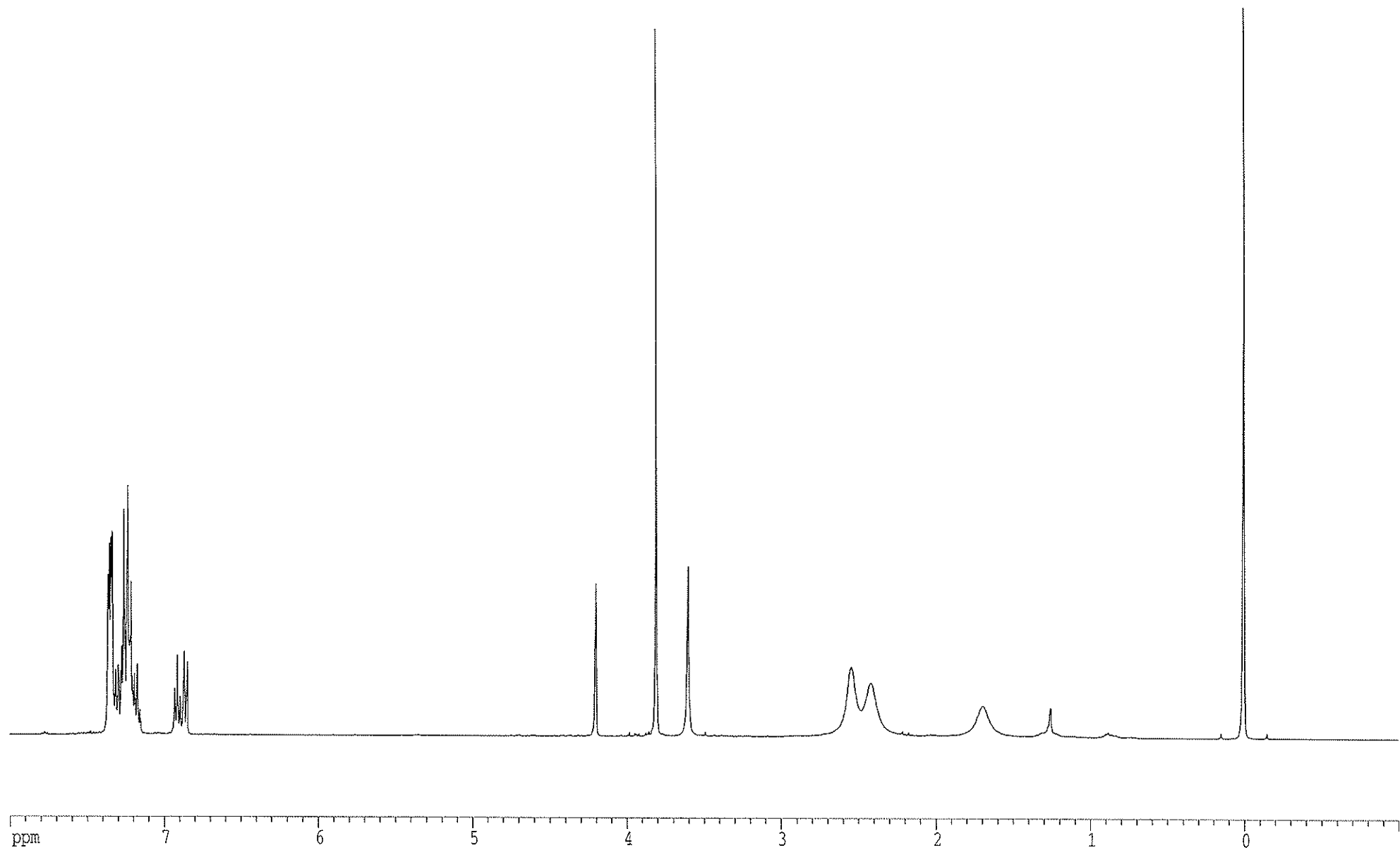
F2 - Processing parameters  
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 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 2.00

1D NMR plot parameters  
 CX 22.00 cm  
 CY 13.00 cm  
 F1P 16.412 ppm  
 F1 6560.42 Hz  
 F2P -4.161 ppm  
 F2 -1663.27 Hz  
 PPMCM 0.93514 ppm  
 HZCM 373.80380 Hz/4

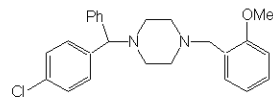




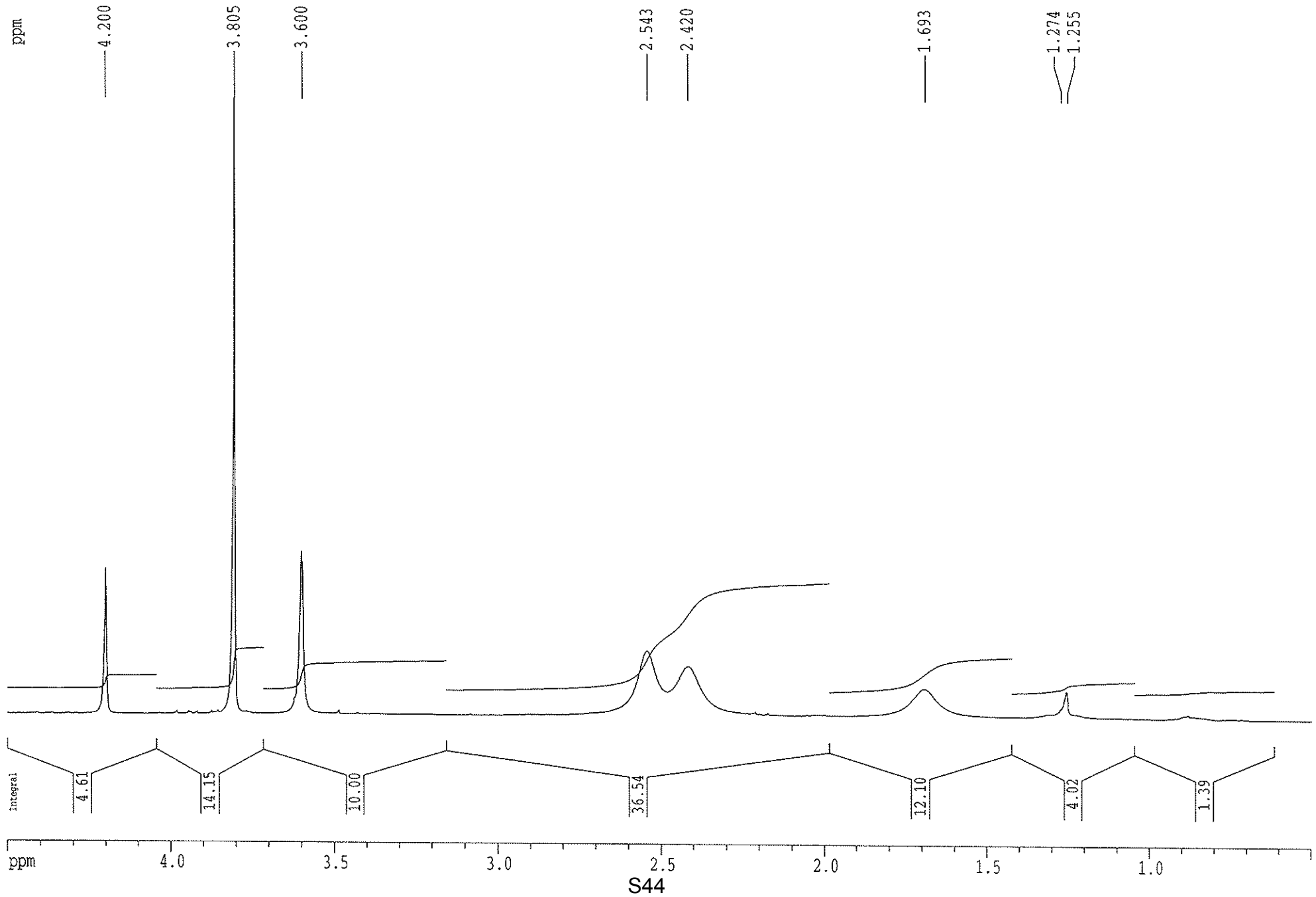
<sup>1</sup>H NMR for SQ784 y scale x 2

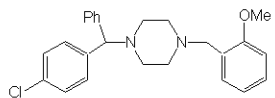


S43

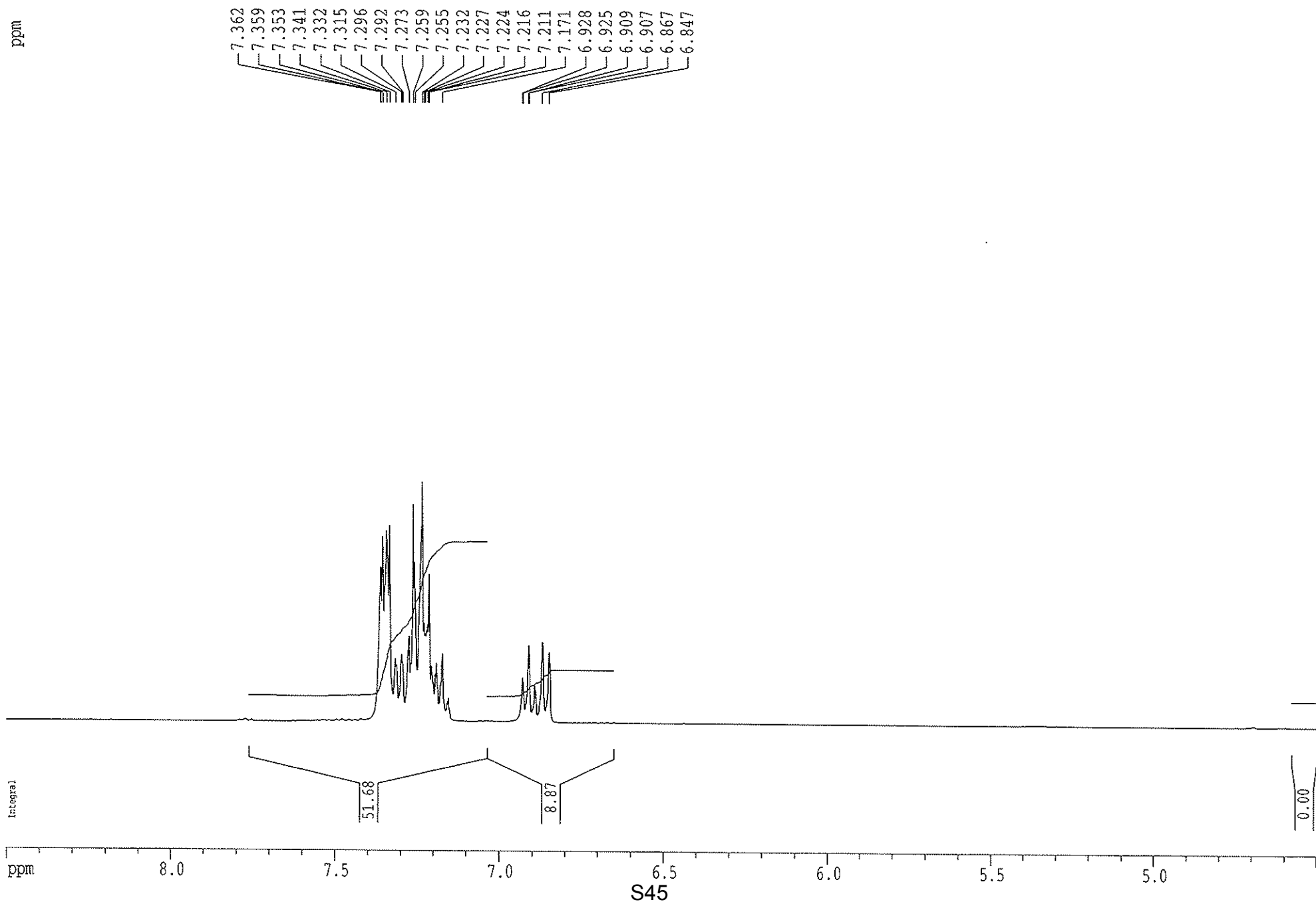


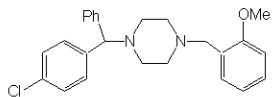
<sup>1</sup>H NMR for SQ784 y scale x 2



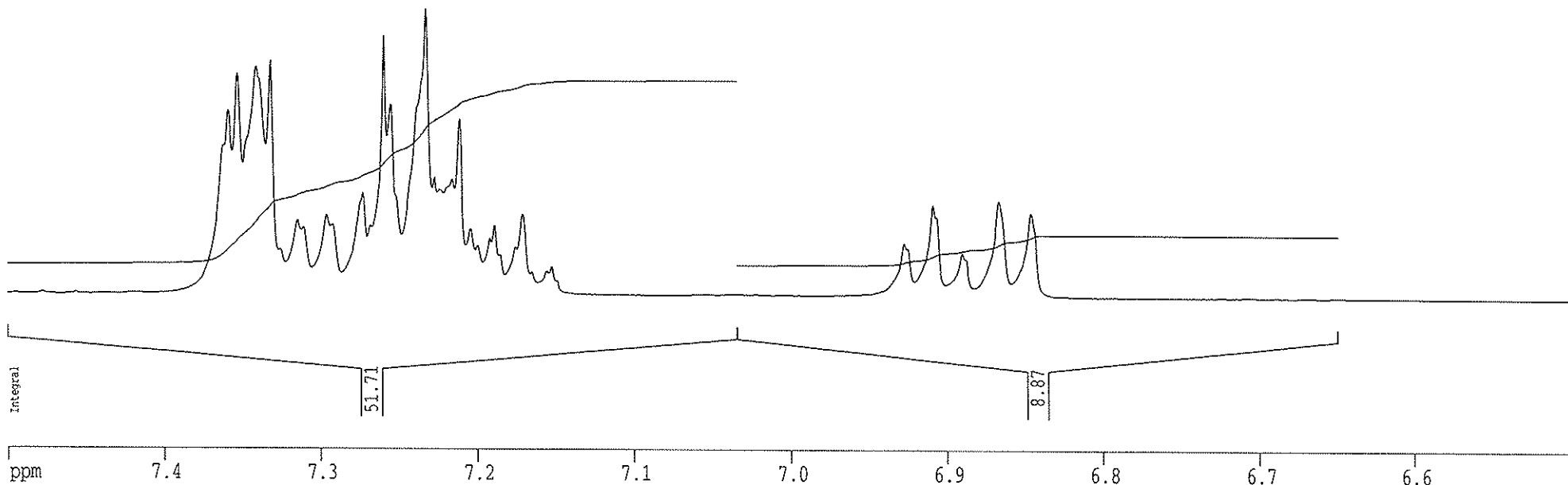
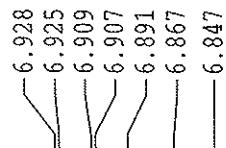
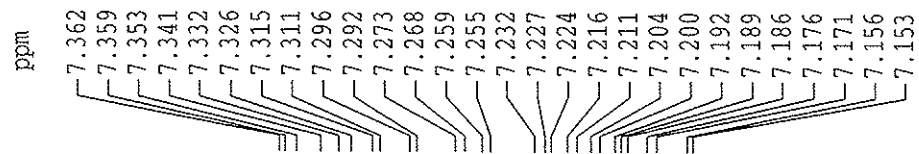


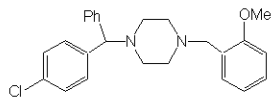
<sup>1</sup>H NMR for SQ784 y scale x 2



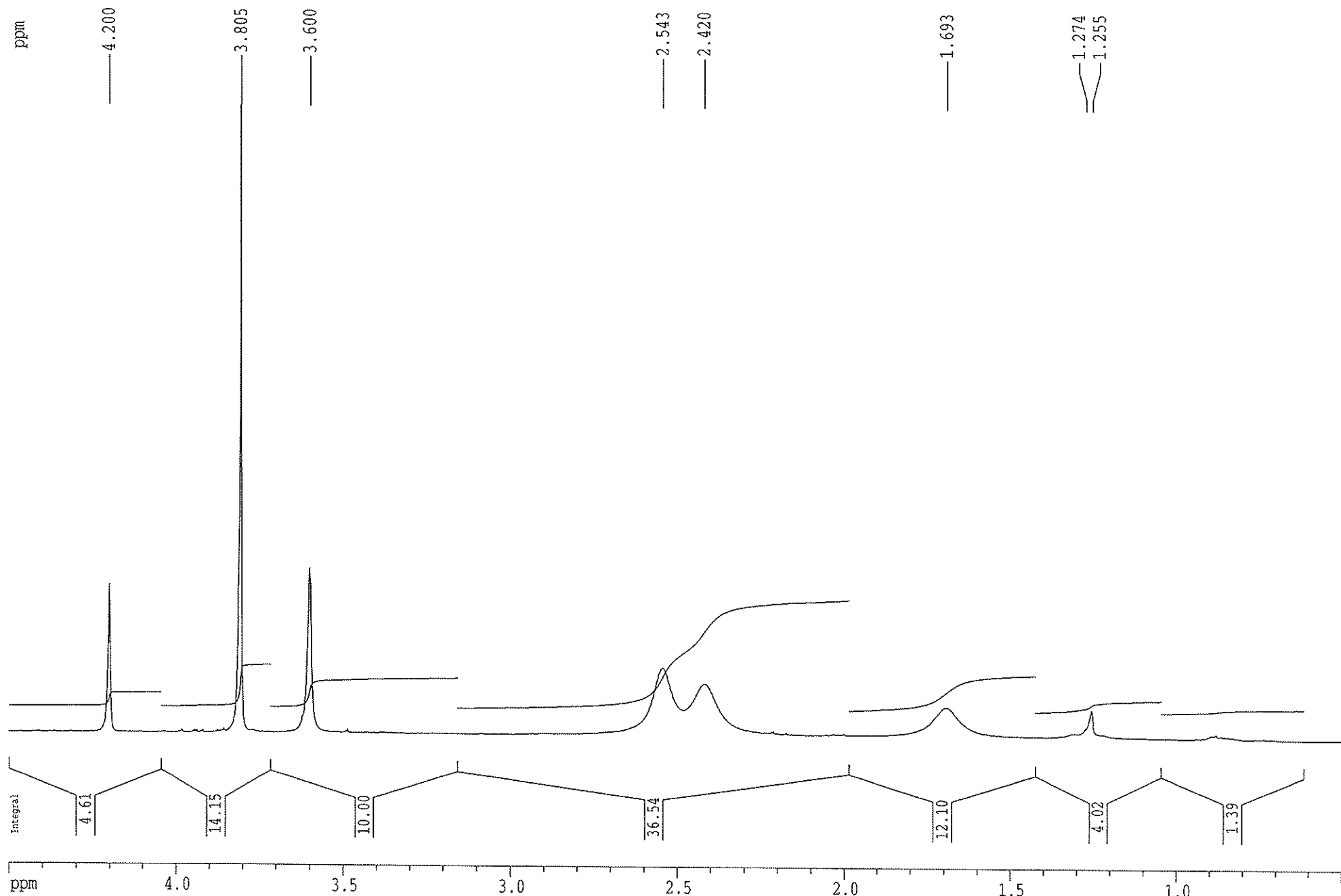


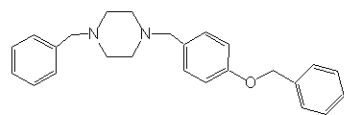
<sup>1</sup>H NMR for SQ784 y scale x 2



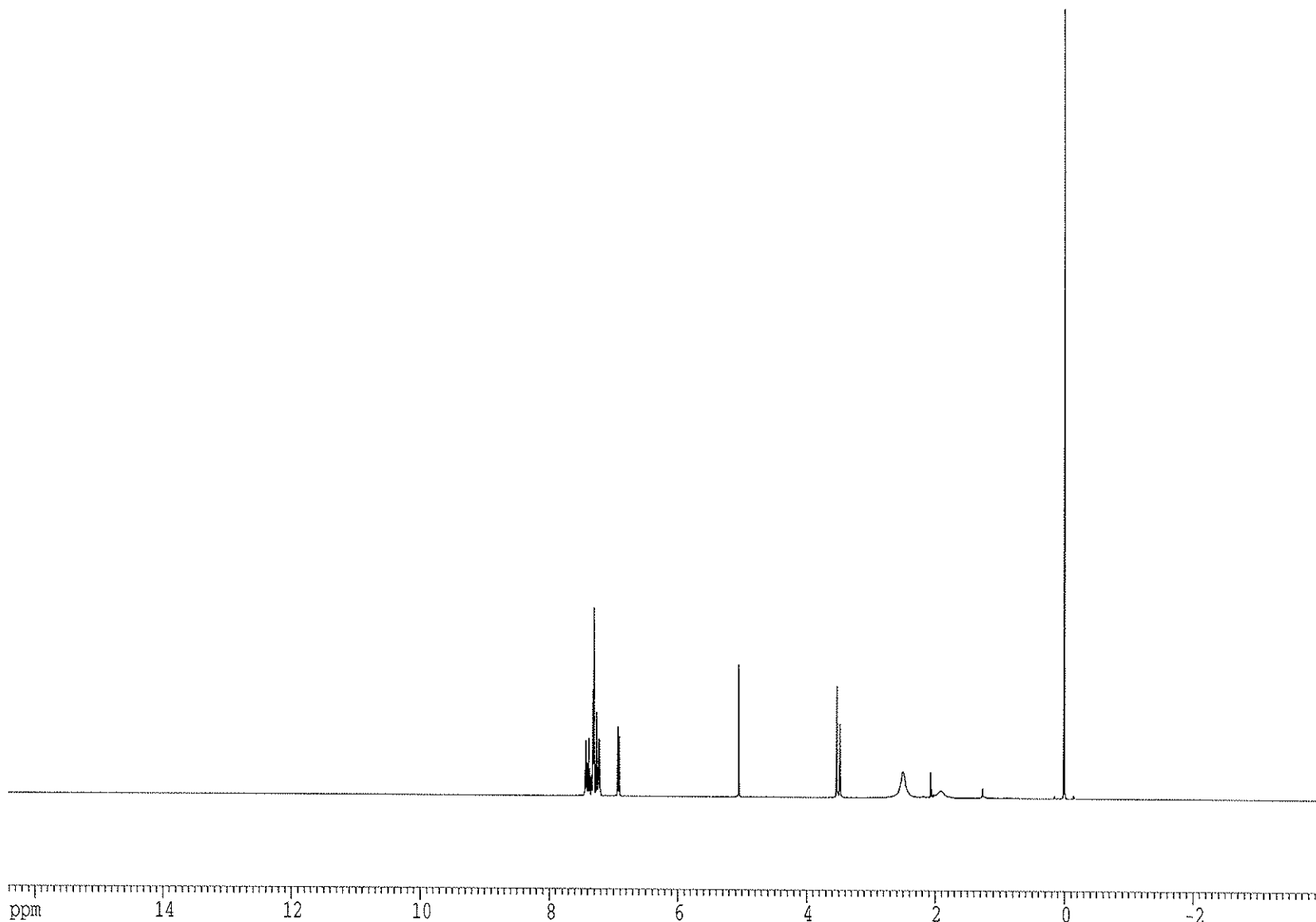


<sup>1</sup>H NMR for SQ784 y scale x 2





<sup>1</sup>H NMR for SQ786



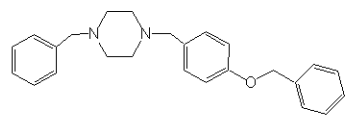
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 EXPNO 1  
 PROCNO 1

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 PULPROG zg30  
 TD 65536  
 SOLVENT CDC13  
 NS 128  
 DS 0  
 SWH 8223.685 Hz  
 FIDRES 0.125483 Hz  
 AQ 3.9846387 sec  
 RG 322.5  
 DW 60.800 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.0000000 sec

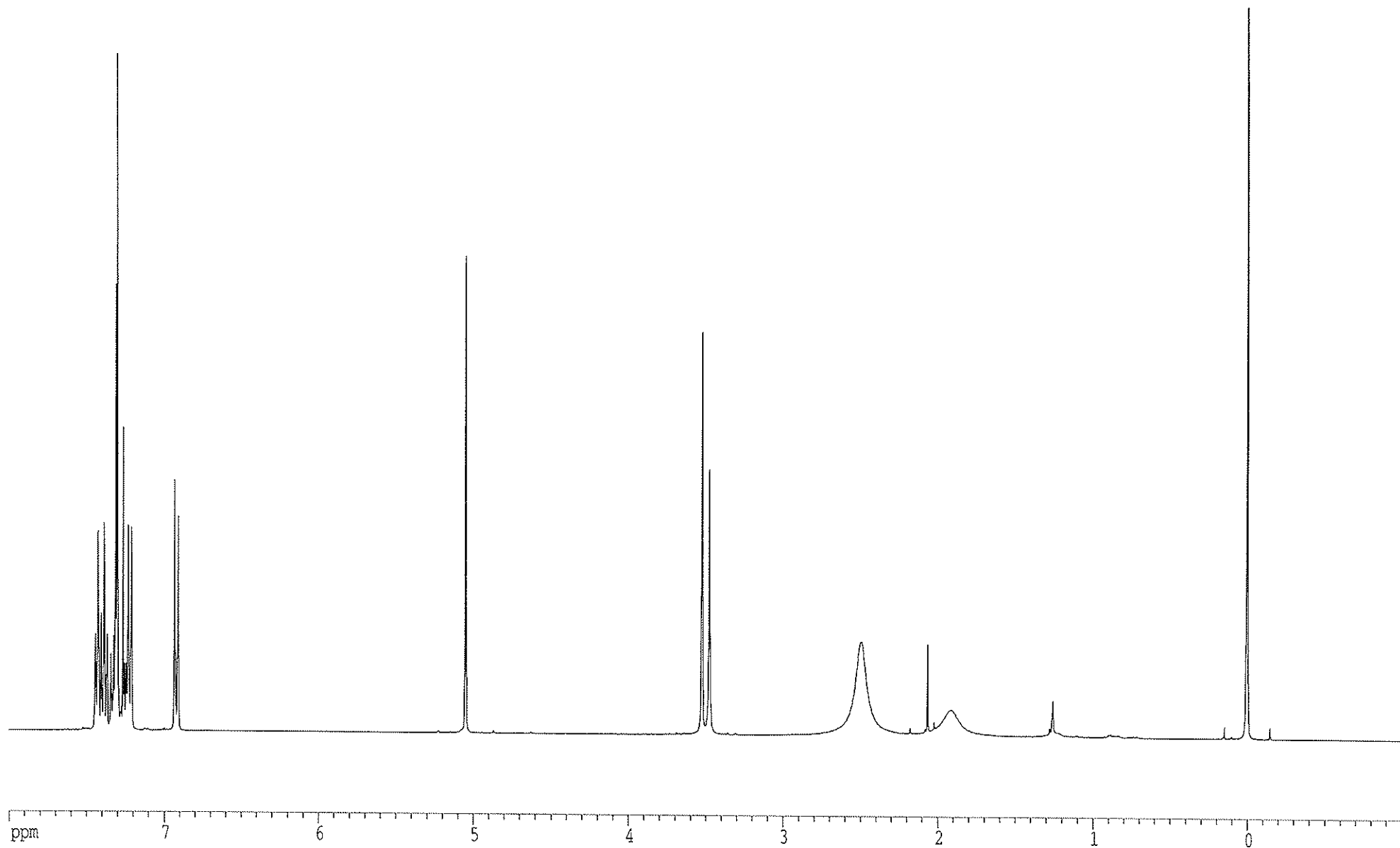
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 P1 9.50 usec  
 PL1 -4.00 dB  
 SFO1 399.7324685 MHz

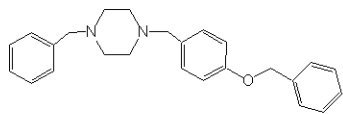
F2 - Processing parameters  
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 SF 399.7300120 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 2.00

1D NMR plot parameters  
 CX 22.00 cm  
 CY 13.00 cm  
 F1P 16.412 ppm  
 F1 6560.42 Hz  
 F2P -4.161 ppm  
 F2 -1663.27 Hz  
 PPMCM 0.93514 ppm  
 HZCM 373.80380 Hz/1

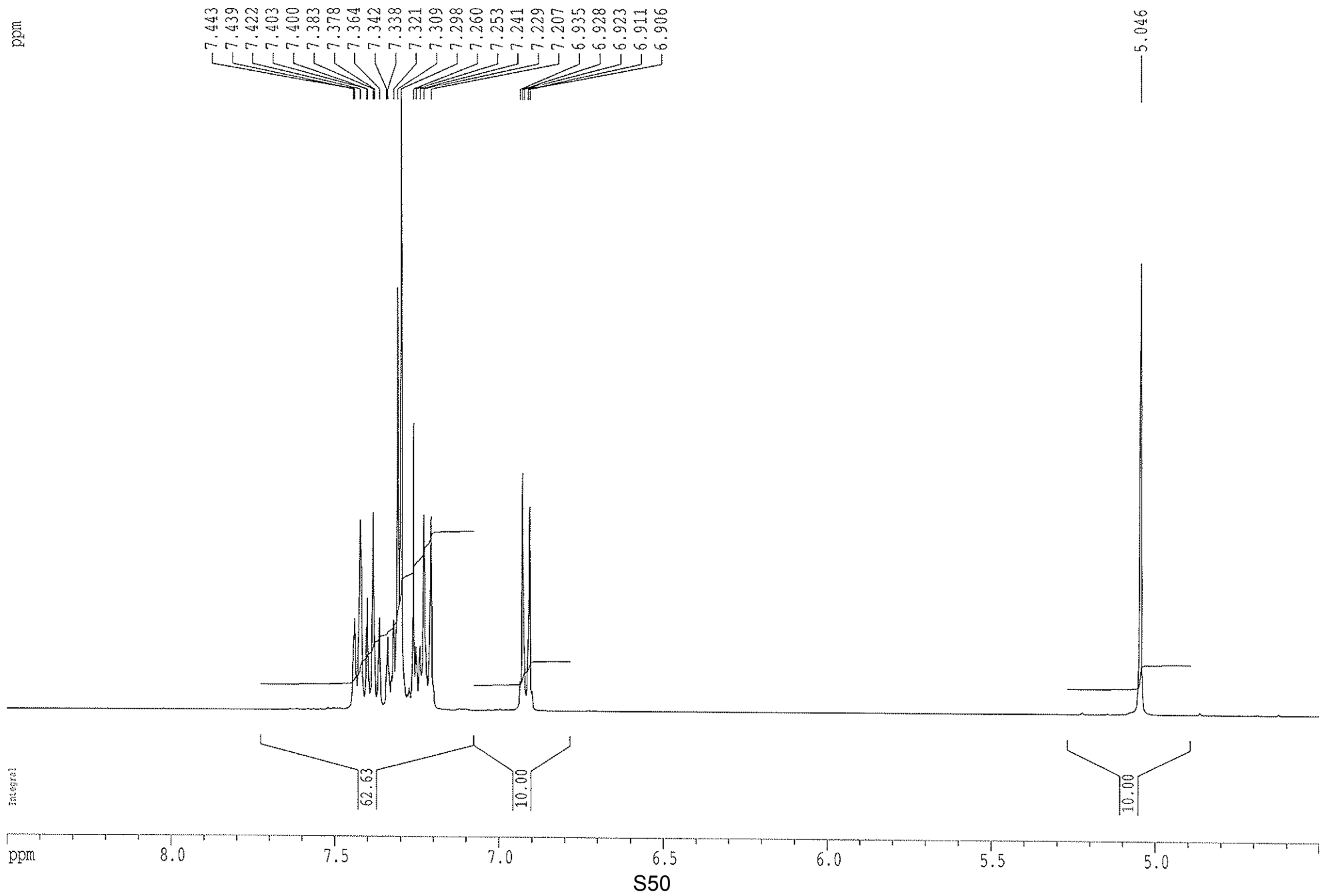


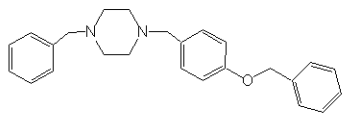
<sup>1</sup>H NMR for SQ786 y scale x 4



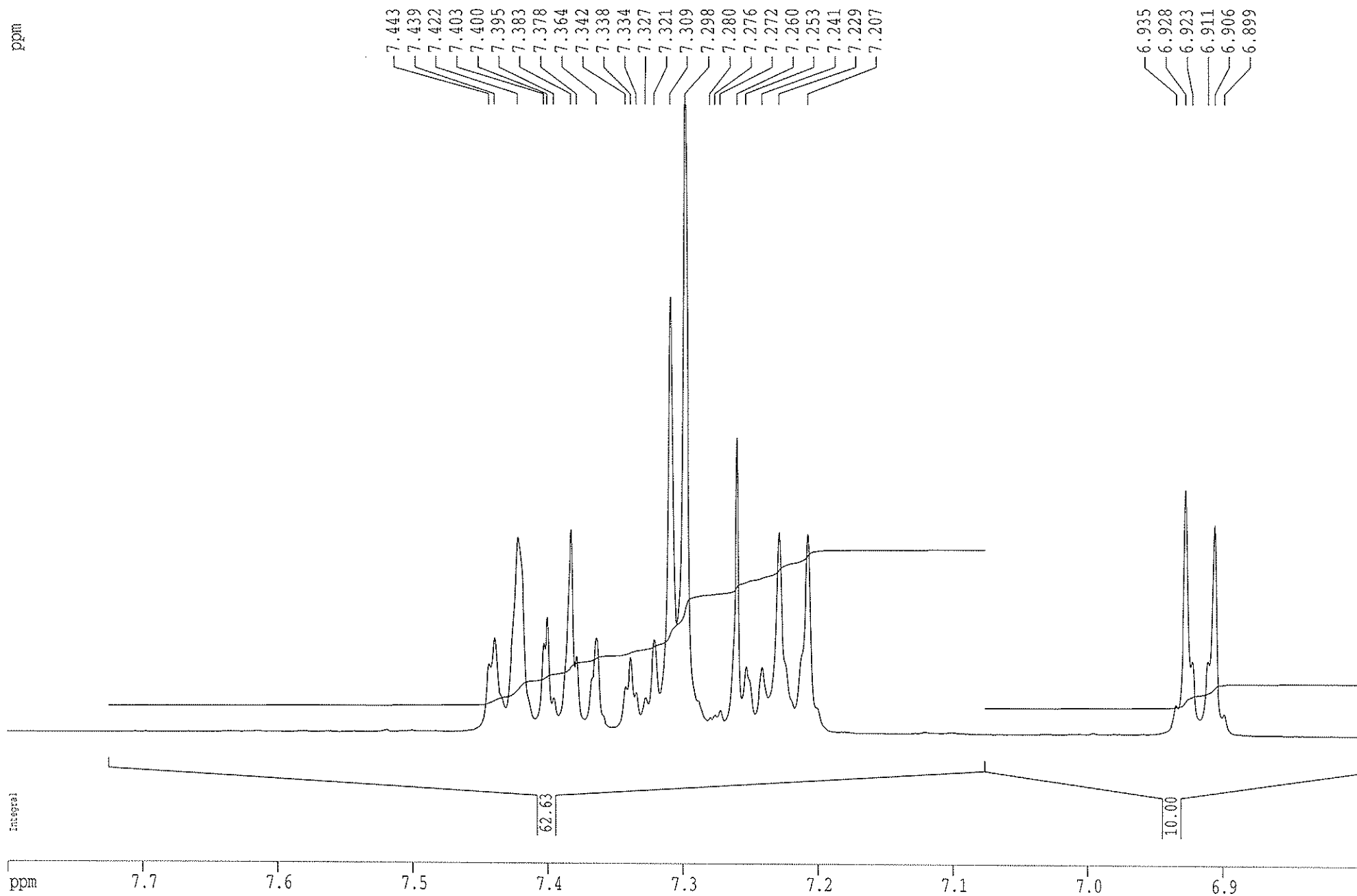


<sup>1</sup>H NMR for SQ786 y scale x 4

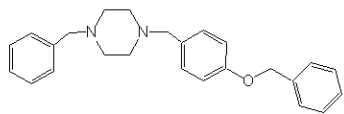




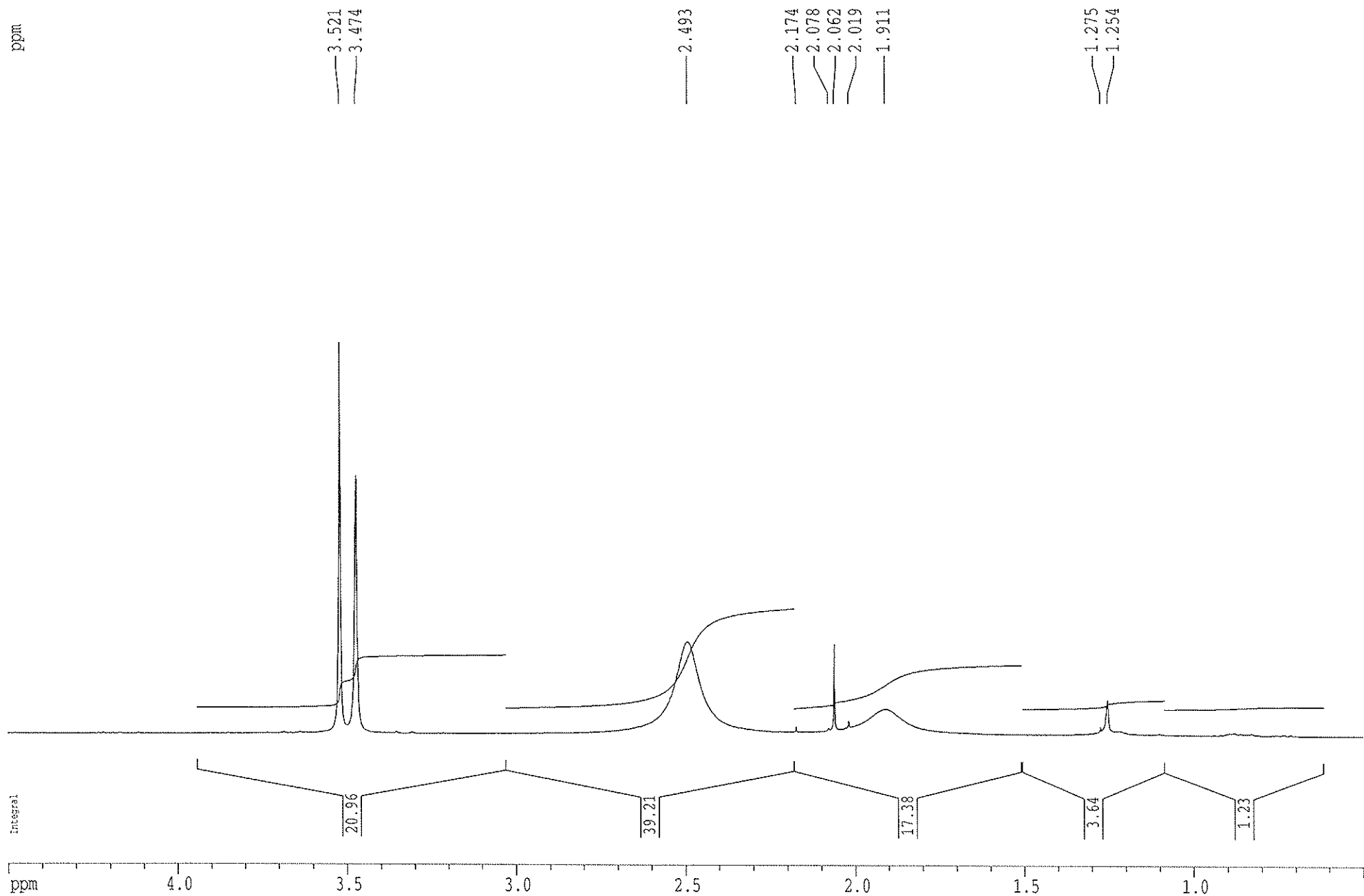
<sup>1</sup>H NMR for SQ786 y scale x 4



S51



<sup>1</sup>H NMR for SQ786 y scale x 4



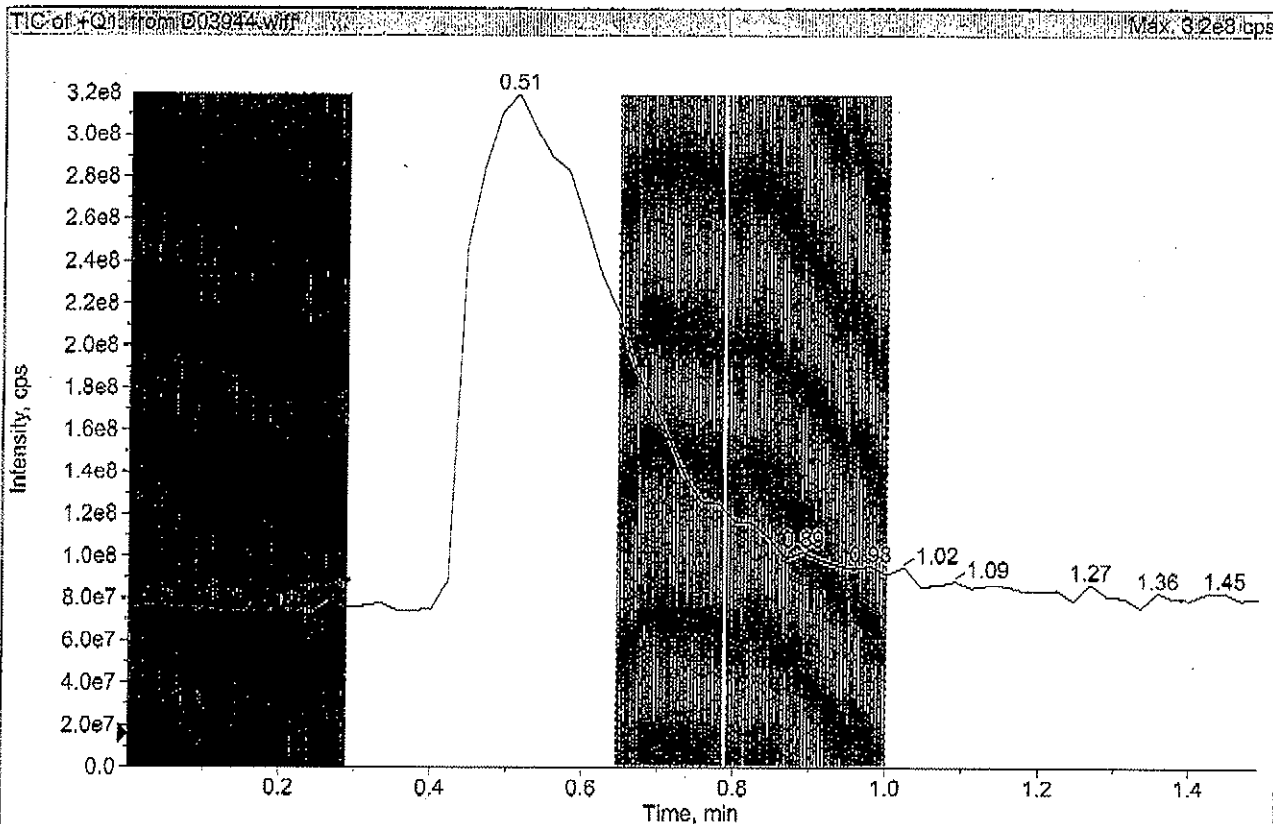
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 05:45:32 PM  
Printing Date: Mon, Aug 30, 2004

Acq. Date: Monday, August 30, 2004  
Acq. Time: 17:21  
Sample Name: 24-030-6  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

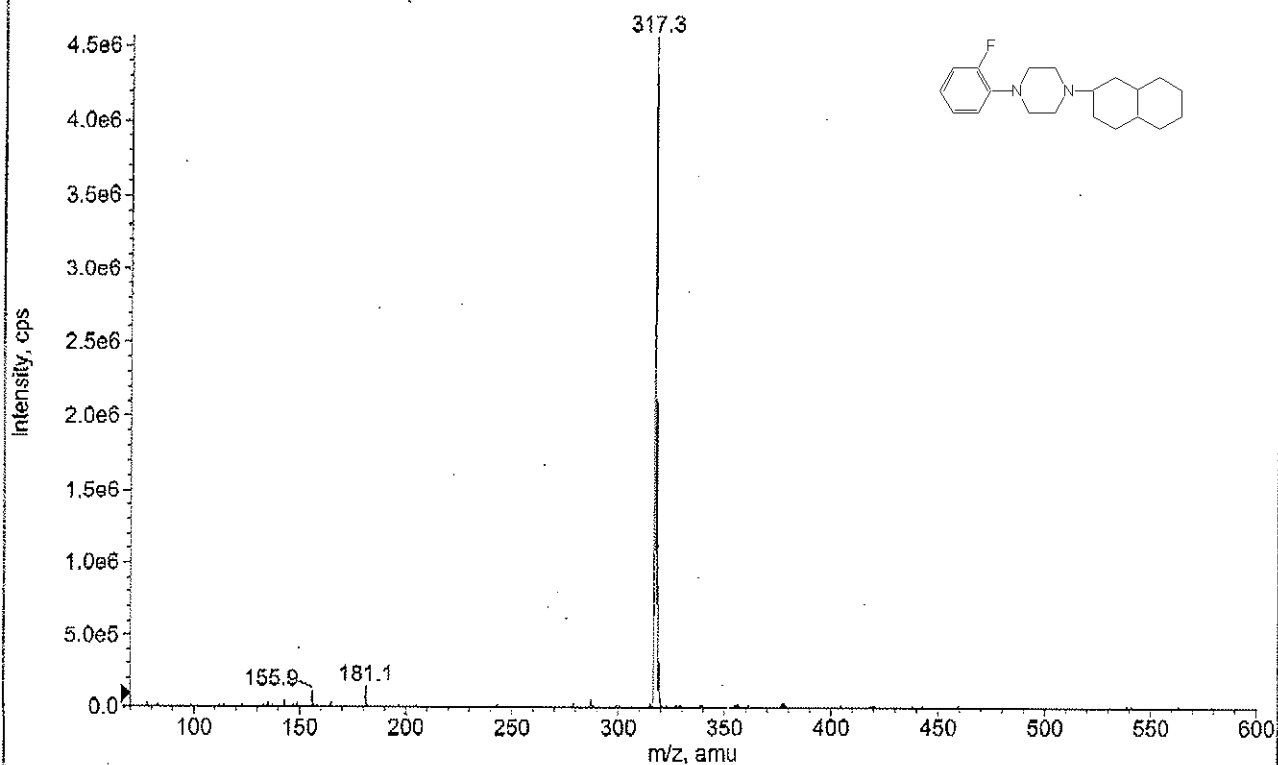
RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03944.wiff

PE Sciex API 365



Q1: 0.645 to 1.002 min from D03944.wiff, subtracted (0.000 to 0.289 min) Max: 4.0e6 cps



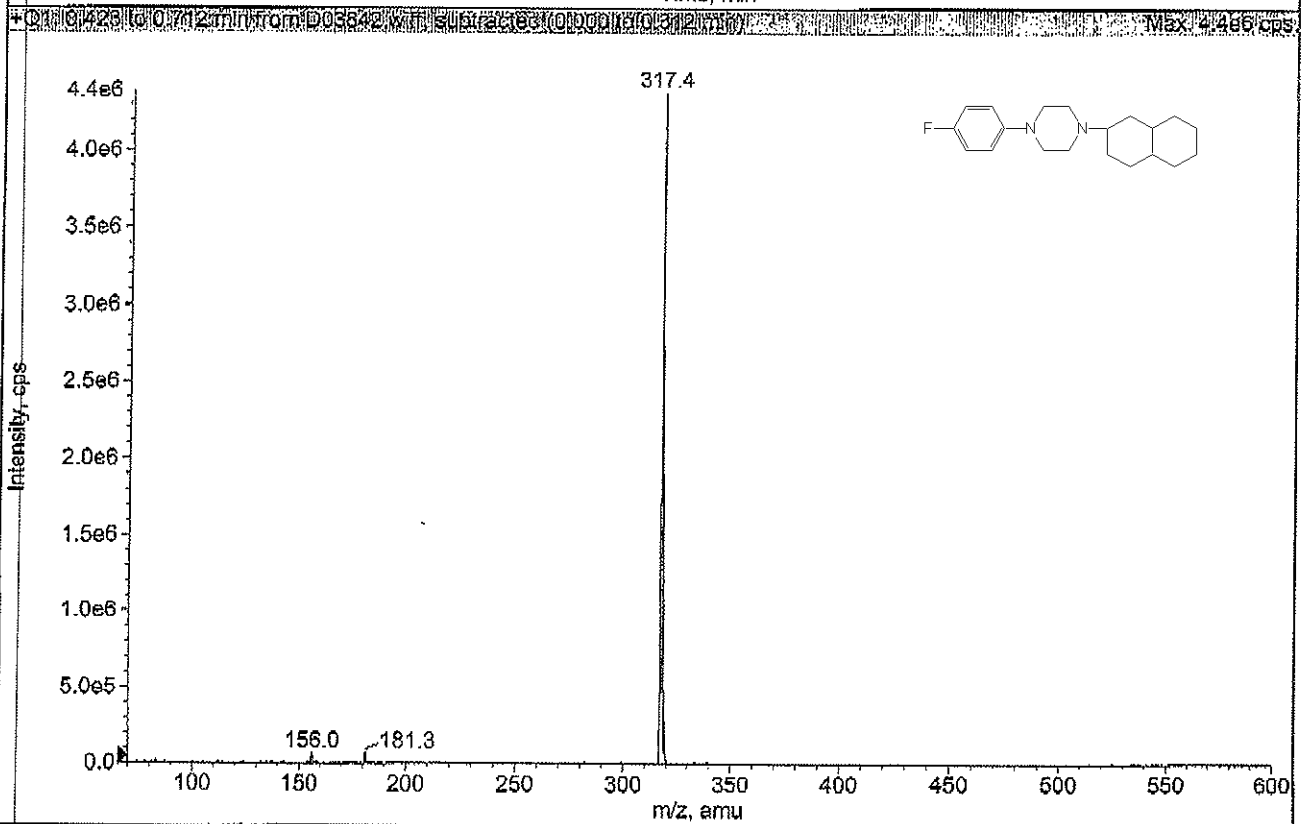
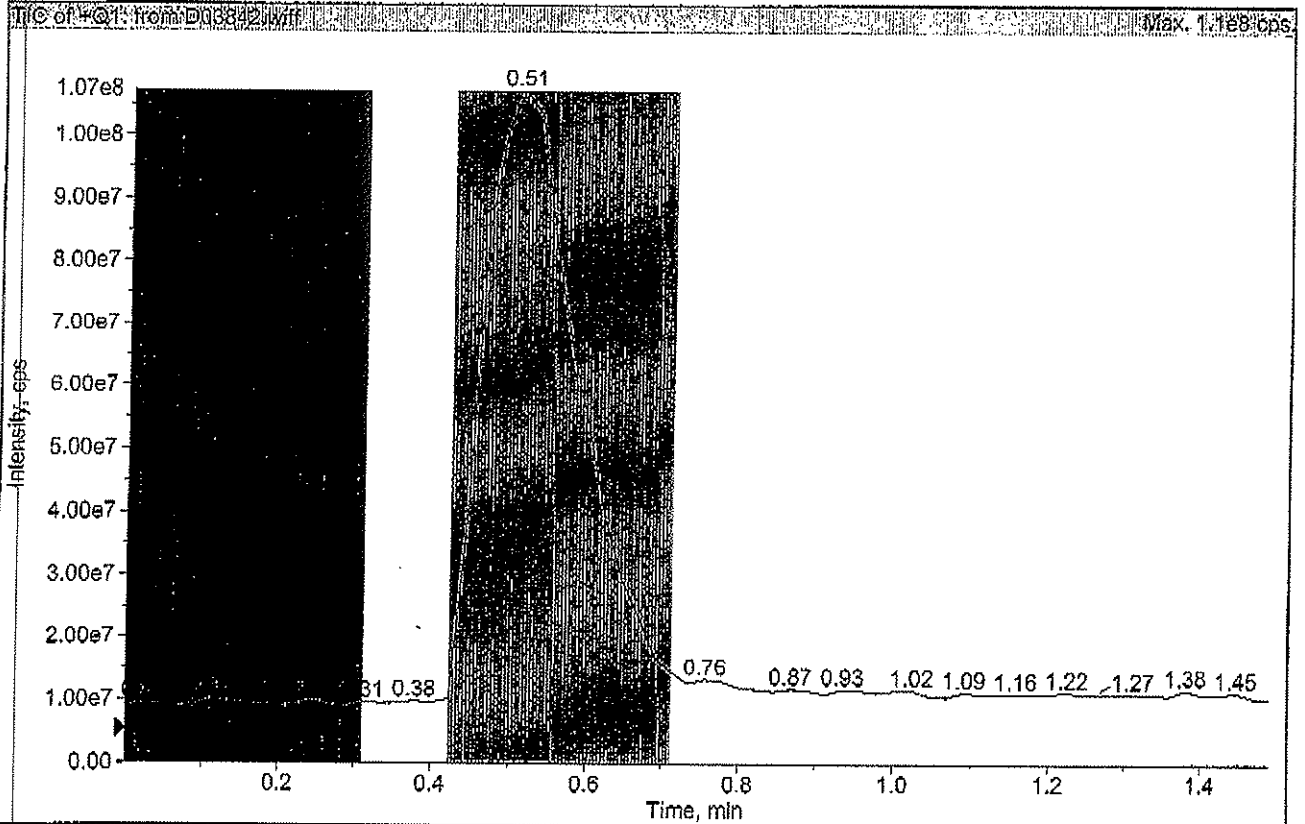
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 10:20:07 AM  
Printing Date: Tue, Jul 27, 2004

Acq. Date: Monday, July 26, 2004  
Acq. Time: 15:32  
Sample Name: 24-026-7  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03842.wiff

PE Sciex API 365



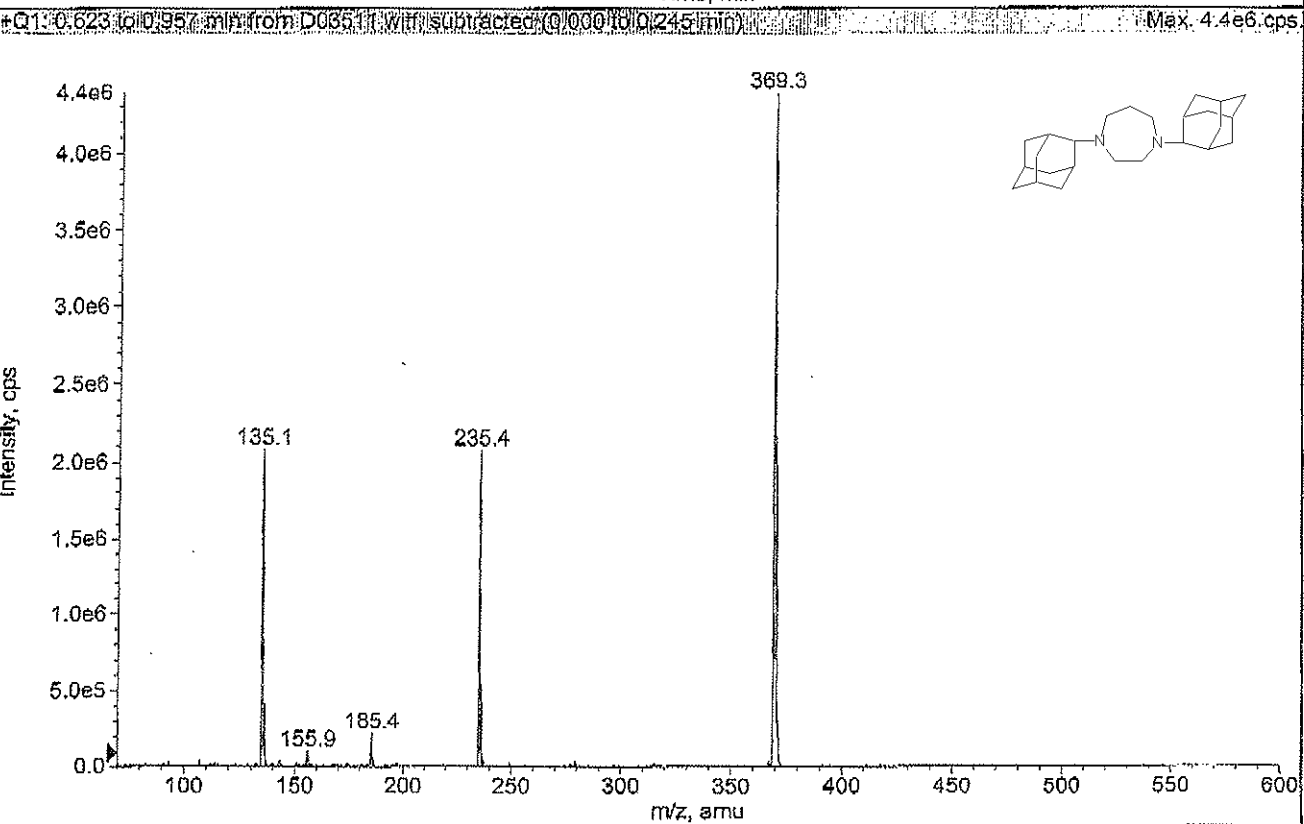
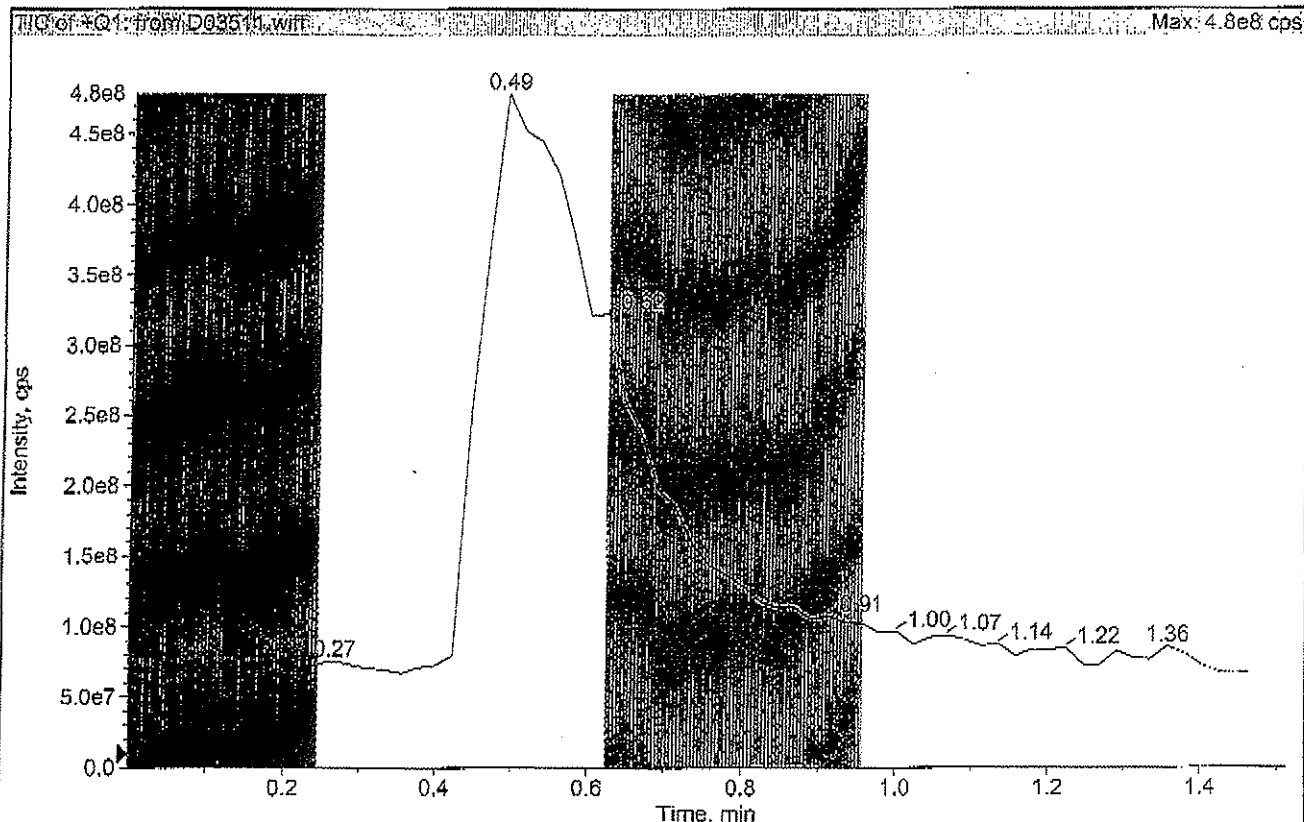
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 06:56:11 PM  
Printing Date: Tue, Jun 1, 2004

Acq. Date: Tuesday, June 01, 2004  
Acq. Time: 18:54  
Sample Name: 24-016-48  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03511.wiff

FE Sciex API 365



## Display Report

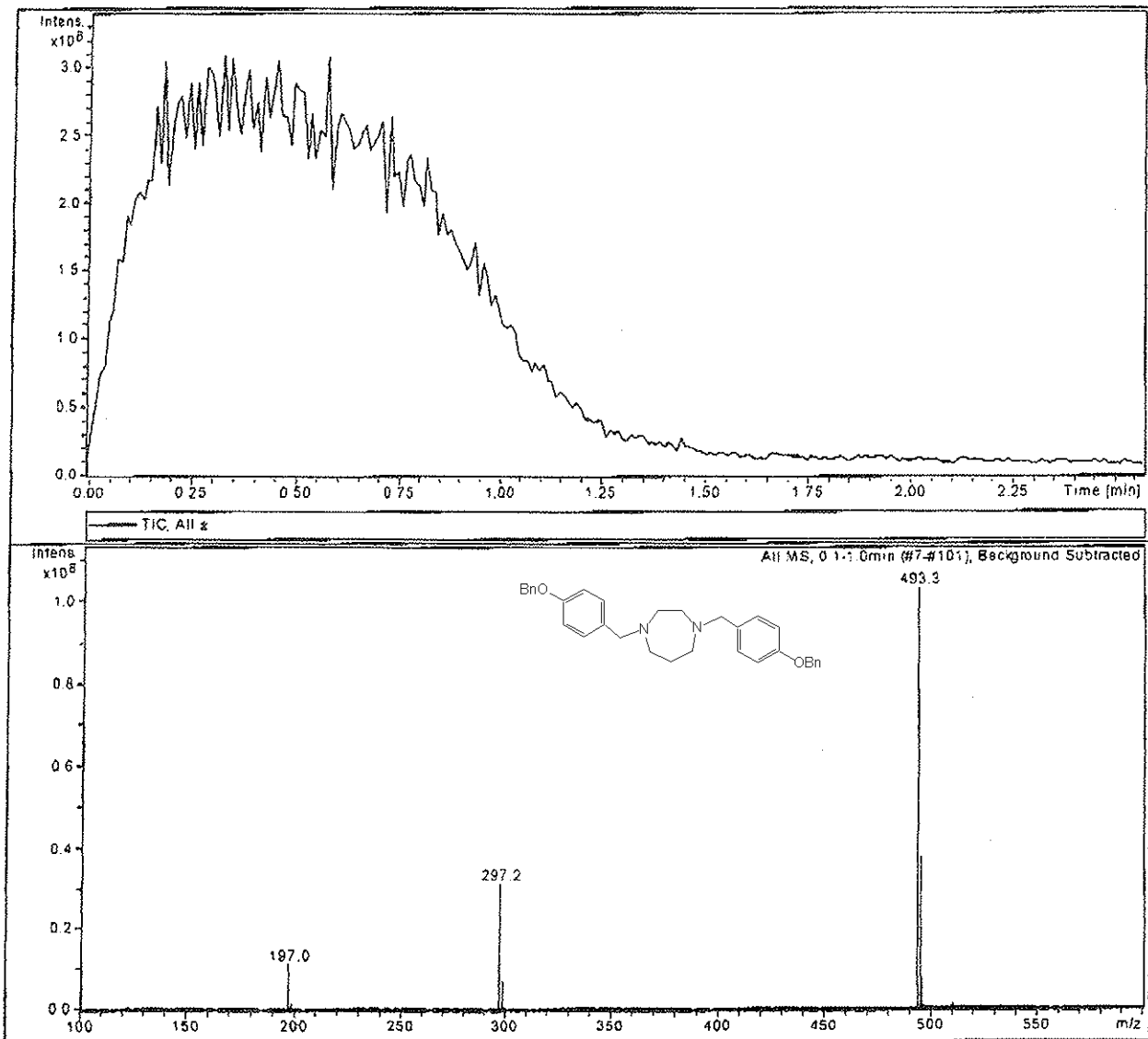
Page 1 of 1

Analysis Info

|                  |                                 |            |                                  |
|------------------|---------------------------------|------------|----------------------------------|
| FileName         | D:\Data\20020559.d\Analysis.yep | Print Date | Thursday, 10 October 2002, 11:44 |
| Acquisition Date | Wednesday, 10/09/02, 19:13:24   | Operator   | Administrator                    |
| Method           | Copy of 102401A.M               | Instrument | Esquire-LC 00033                 |
| Comment          | 8738-118U   21<br>♀             |            |                                  |

Acquisition Parameter

|                   |             |                 |            |                          |            |
|-------------------|-------------|-----------------|------------|--------------------------|------------|
| Ion Source Type   | ESI         | Ion Polarity    | Positive   | Alternating Ion Polarity |            |
| Mass Range Mode   | Std/Normal  | Scan Begin      | 100.00 m/z | Scan End                 | 600.00 m/z |
| Skim 1            | 11.0 Volt   | Cap Exit Offset | 29.0 Volt  | Trap Drive               | 55.0       |
| Accumulation Time | 832 $\mu$ s | Averages        | 8 Spectra  | Auto MS/MS               | Off        |



Bruker Daltonics DataAnalysis 2.0

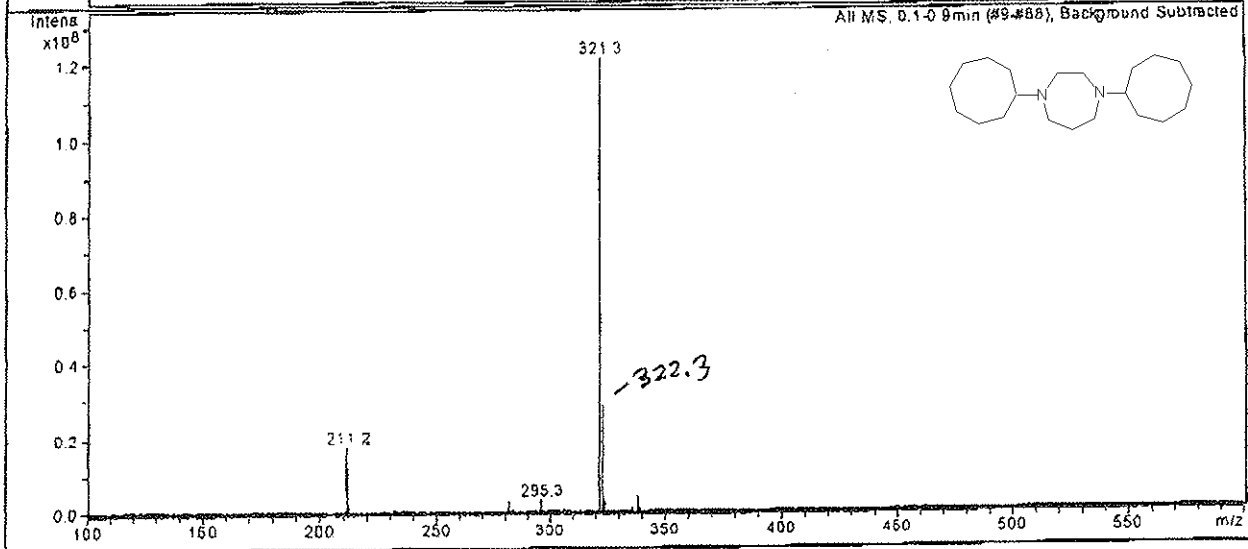
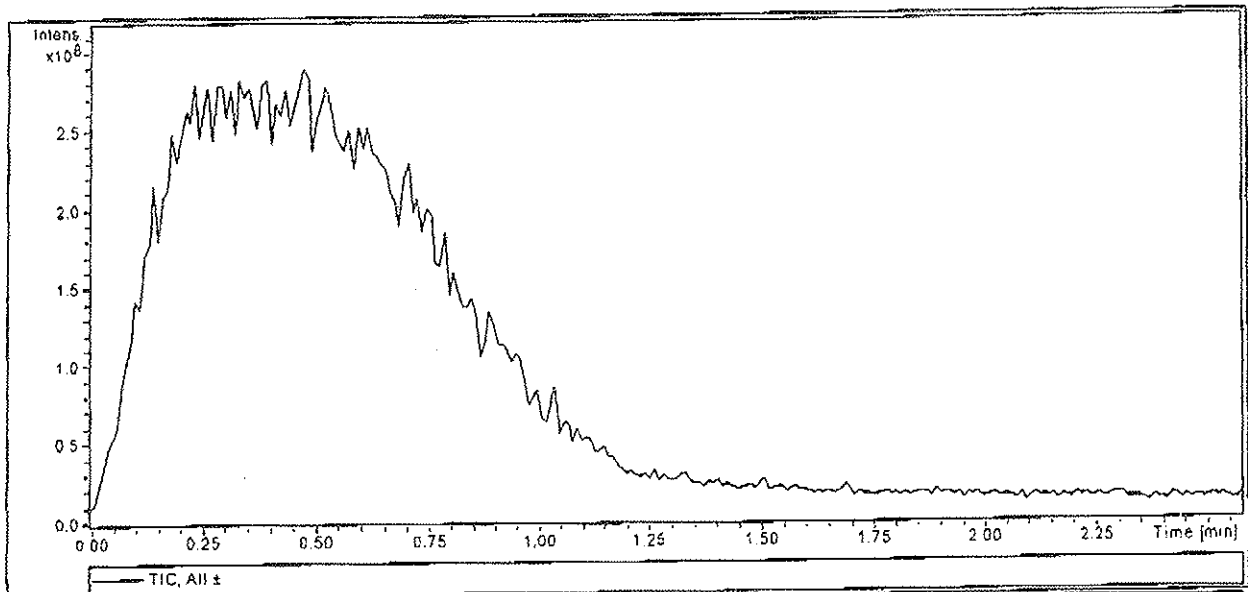
# Display Report

## Analysis Info

|                  |                                 |            |                                  |
|------------------|---------------------------------|------------|----------------------------------|
| FileName         | D:\Data\20020560.d\Analysis.yep |            |                                  |
| Acquisition Date | Wednesday, 10/09/02, 19:18:19   | Print Date | Thursday, 10.October.2002, 11:45 |
| Method           | Copy of 102401A.M               | Operator   | Administrator                    |
| Comment          | 8738-118V   22<br>♀             | Instrument | Esquire-LC 00033                 |

## Acquisition Parameter

|                   |            |                 |            |                          |            |
|-------------------|------------|-----------------|------------|--------------------------|------------|
| Ion Source Type   | ESI        | Ion Polarity    | Positive   | Alternating Ion Polarity |            |
| Mass Range Mode   | Std/Normal | Scan Begin      | 100.00 m/z | Scan End                 | 600.00 m/z |
| Skim 1            | 11.0 Volt  | Cap Exit Offset | 29.0 Volt  | Trap Drive               | 55.0       |
| Accumulation Time | 1026 µs    | Averages        | 8 Spectra  | Auto MS/MS               | Off        |

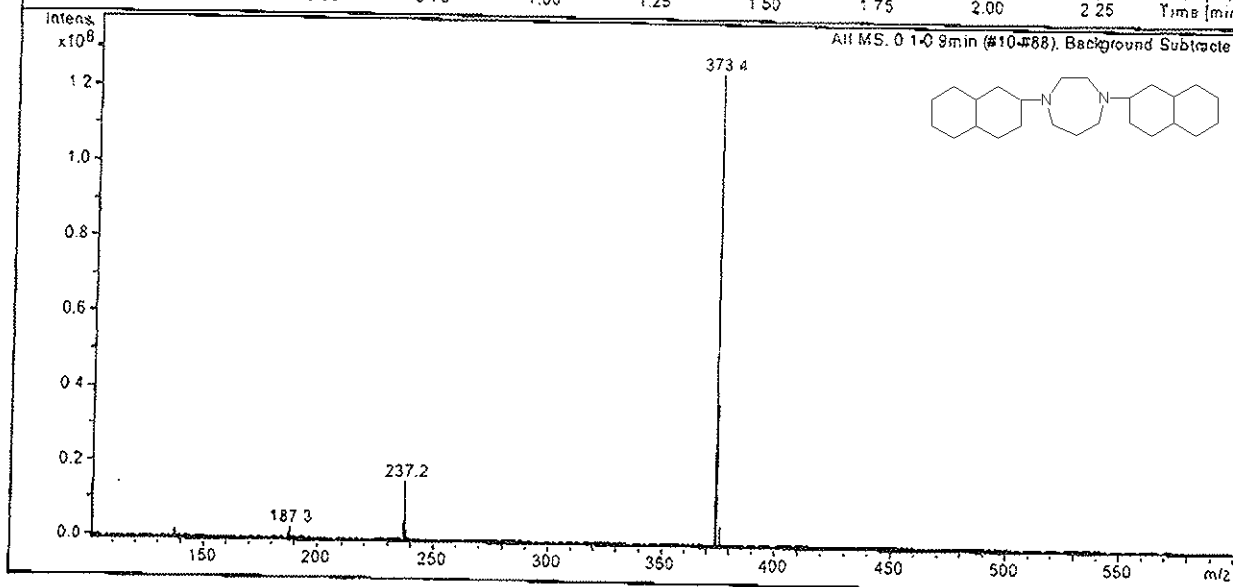
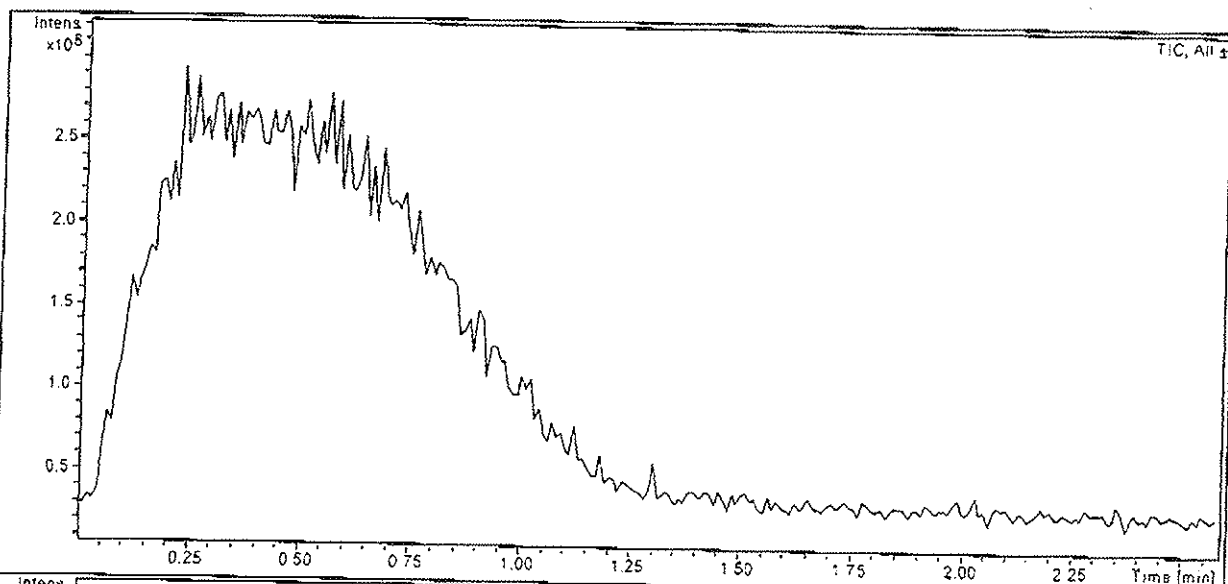


**Analysis Info**

|                  |                                 |            |                                    |
|------------------|---------------------------------|------------|------------------------------------|
| FileName         | D:\Data\20020465.d\Analysis.yep |            |                                    |
| Acquisition Date | Wednesday, 09/11/02, 10:33:33   | Print Date | Thursday, 12 September 2002, 09:36 |
| Method           | Copy of 102401A.M               | Operator   | Administrator                      |
| Comment          | 8738-115H   8<br>♀              | Instrument | Esquire-LC 00033                   |

**Acquisition Parameter**

|                   |            |                 |            |                          |            |
|-------------------|------------|-----------------|------------|--------------------------|------------|
| Ion Source Type   | ESI        | Ion Polarity    | Positive   | Alternating Ion Polarity |            |
| Mass Range Mode   | Std/Normal | Scan Begin      | 100.00 m/z | Scan End                 | 600.00 m/z |
| Skim 1            | 11.0 Volt  | Cap Exit Offset | 29.0 Volt  | Trap Drive               | 55.0       |
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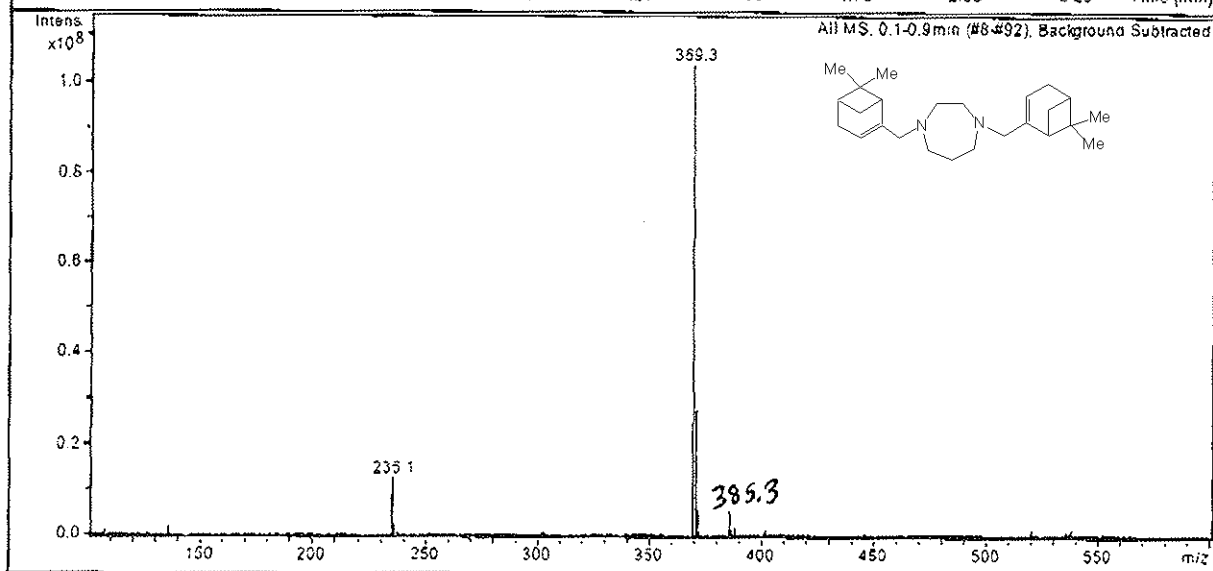
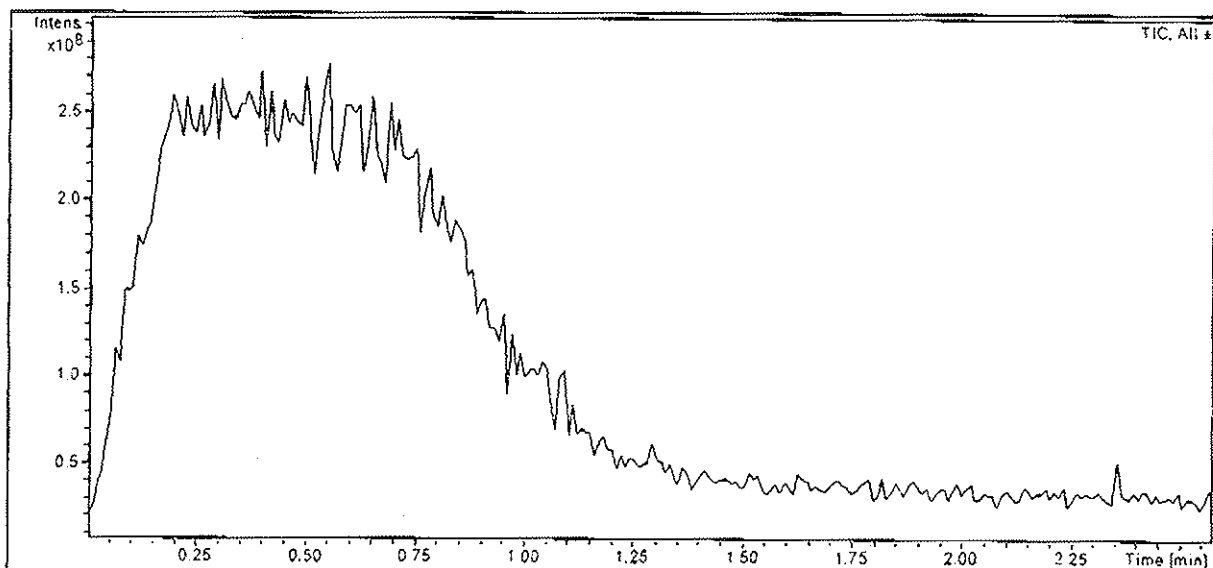


**Analysis Info**

|                  |                                 |            |                                     |
|------------------|---------------------------------|------------|-------------------------------------|
| FileName         | D:\Data\20020466.d\Analysis.yep |            |                                     |
| Acquisition Date | Wednesday, 09/11/02, 10:38:18   | Print Date | Thursday, 12 September, 2002, 09:38 |
| Method           | Copy of 102401A.M               | Operator   | Administrator                       |
| Comment          | 8738-1151   9<br>C              | Instrument | Esquire-LC 00033                    |

**Acquisition Parameter**

|                   |             |                 |            |                          |            |
|-------------------|-------------|-----------------|------------|--------------------------|------------|
| Ion Source Type   | ESI         | Ion Polarity    | Positive   | Alternating Ion Polarity |            |
| Mass Range Mode   | Std/Normal  | Scan Begin      | 100.00 m/z | Scan End                 | 600.00 m/z |
| Skim 1            | 11.0 Volt   | Cap Exit Offset | 29.0 Volt  | Trap Drive               | 55.0       |
| Accumulation Time | 441 $\mu$ s | Averages        | 8 Spectra  | Auto MS/MS               | Off        |



Bruker Daltonics DataAnalysis 2.0

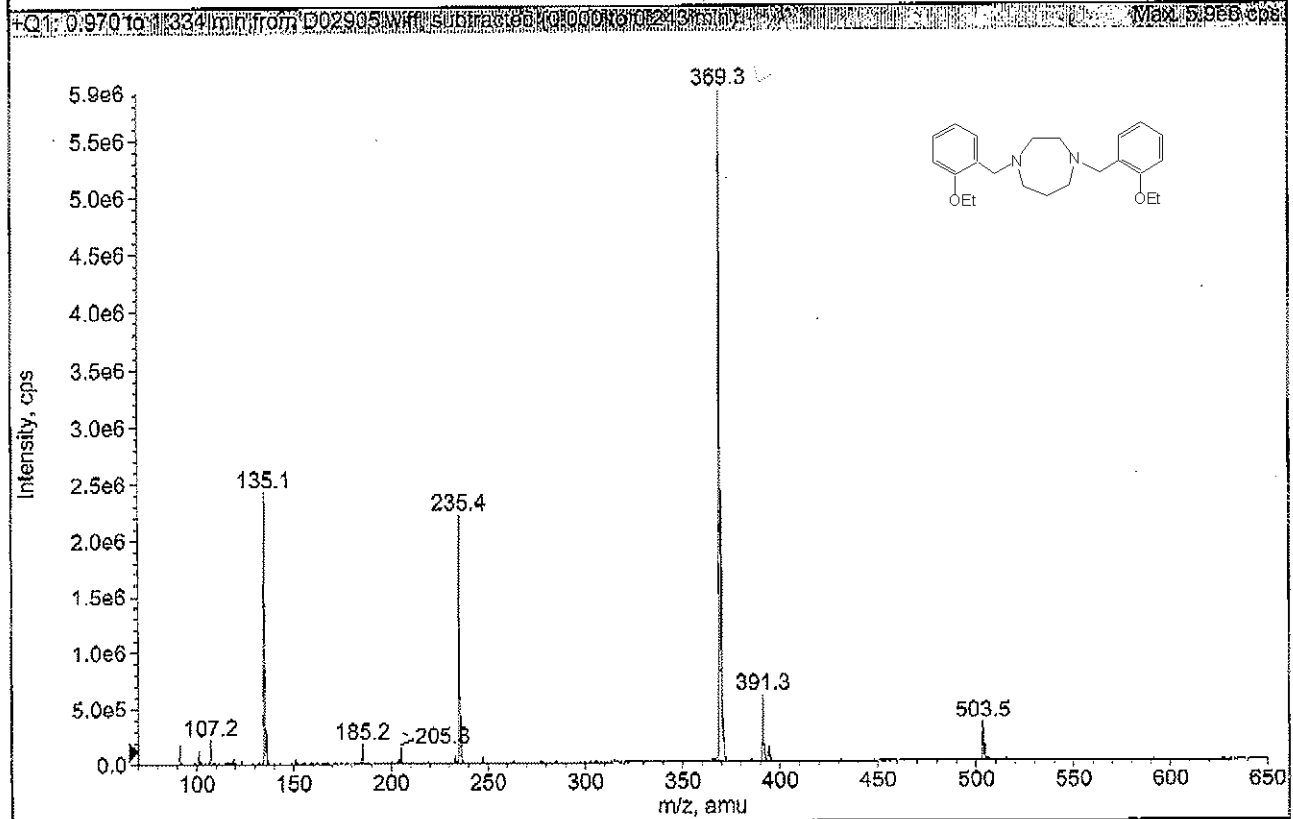
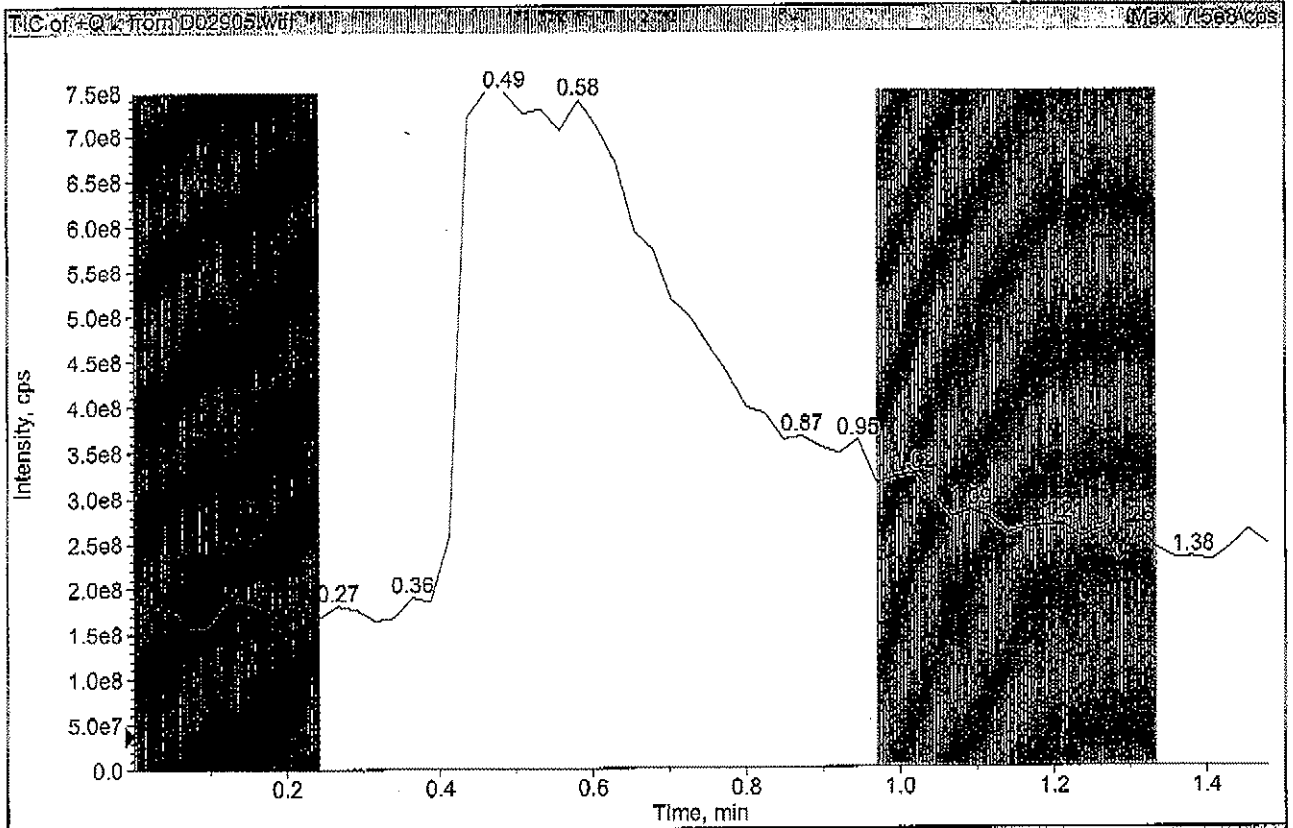
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 03:29:54 PM  
Printing Date: Fri, Oct 10, 2003

Acq. Date: Friday, October 10, 2003  
Acq. Time: 15:09  
Sample Name: 19-165-6  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D02908.wiff

PE Sciex API 365

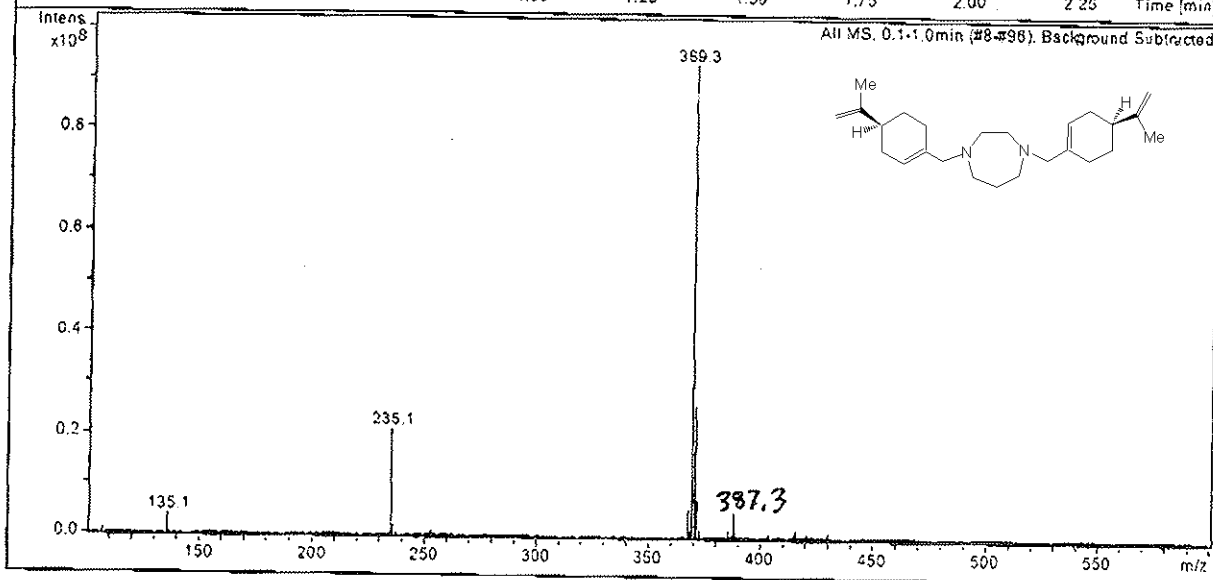
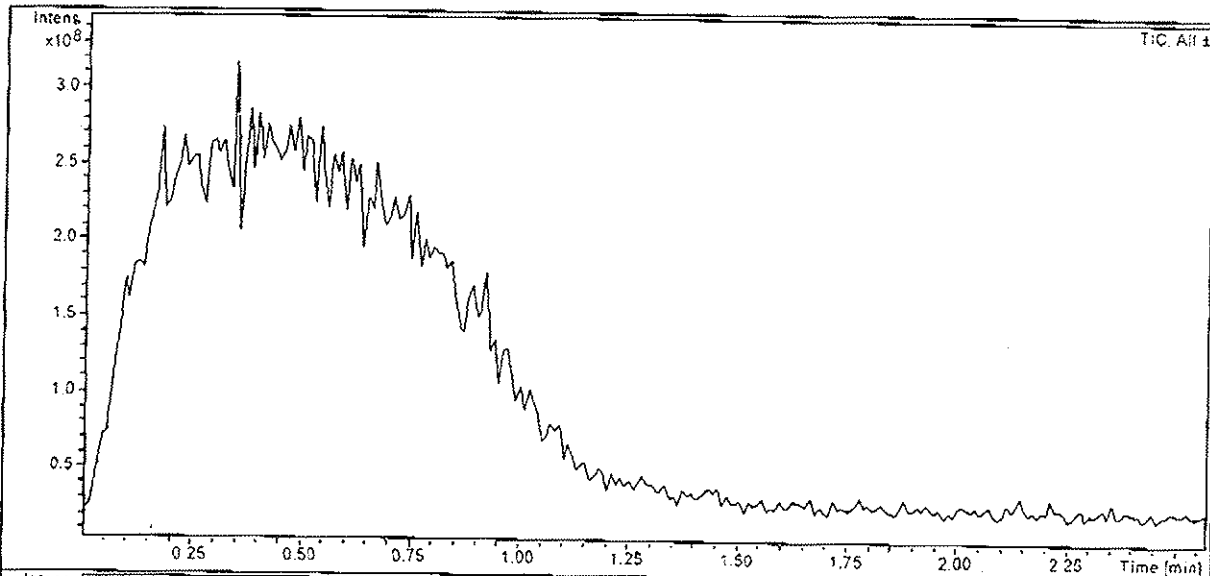


**Analysis Info**

|                  |                                 |            |                              |
|------------------|---------------------------------|------------|------------------------------|
| FileName         | D:\Data\20020468.d\Analysis.yep | Print Date | Thursday, 12 September 2002, |
| Acquisition Date | Wednesday, 09/11/02, 10:47:56   | Operator   | Administrator                |
| Method           | Copy of 102401A.M               | Instrument | Esquire-LC 00033             |
| Comment          | 8738-115K   11<br>♀             |            |                              |

**Acquisition Parameter**

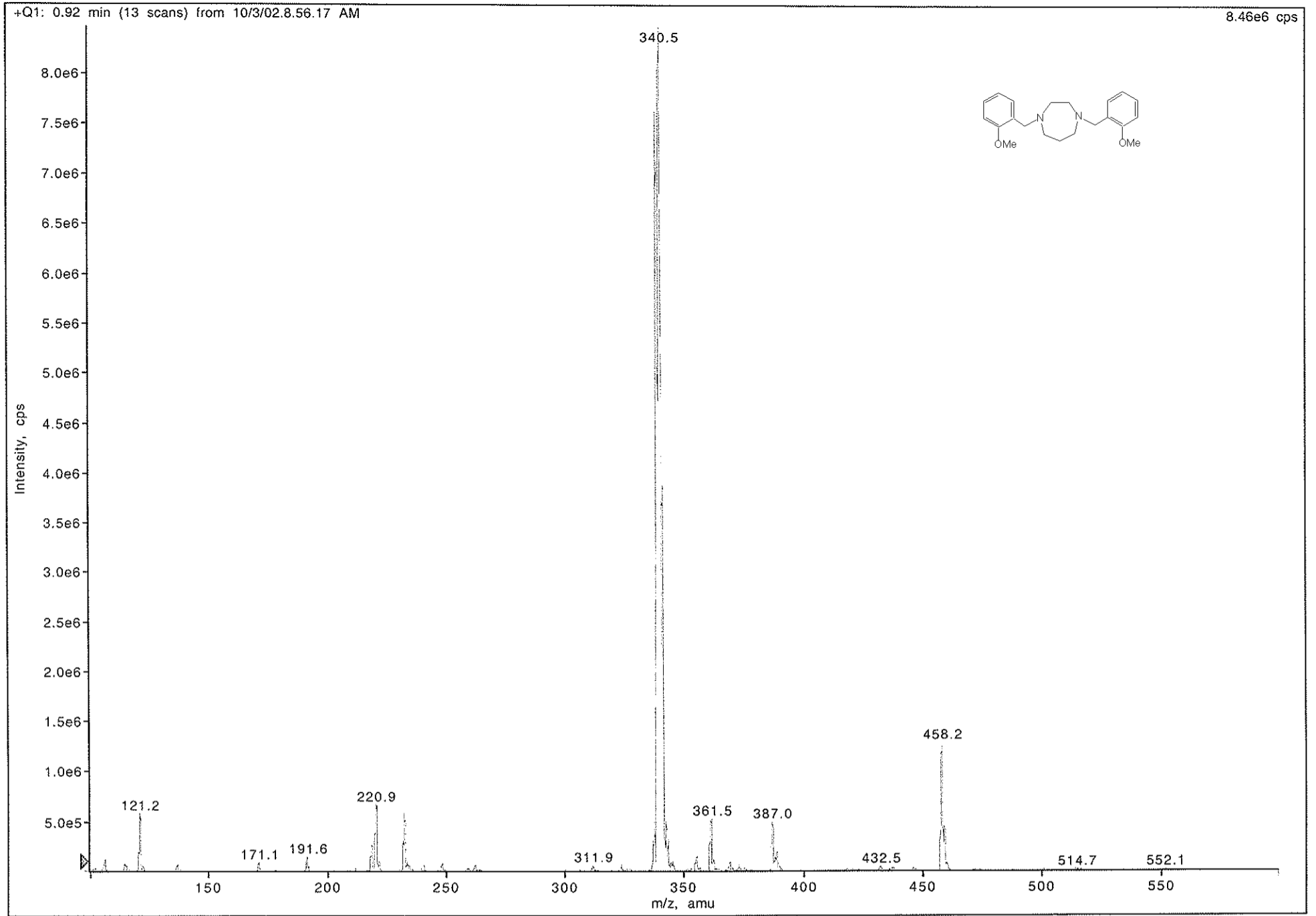
|                   |            |                 |            |                          |            |
|-------------------|------------|-----------------|------------|--------------------------|------------|
| Ion Source Type   | ESI        | Ion Polarity    | Positive   | Alternating Ion Polarity |            |
| Mass Range Mode   | Std/Normal | Scan Begin      | 100.00 m/z | Scan End                 | 600.00 m/z |
| Skim 1            | 11.0 Volt  | Cap Exit Offset | 29.0 Volt  | Trap Drive               | 55.0       |
| Accumulation Time | 420 µs     | Averages        | 8 Spectra  | Auto MS/MS               | Off        |



10/3/02.8.56.17 AM (19-067 #13)

Period 1, Expt. 1; Mass range: 100.0 to 600.0 by 0.1 amu; Dwell: 1.0 ms; Pause: 5.0 ms

Acq. Time: Thu, Oct 3, 2002 at 8:56:18 AM



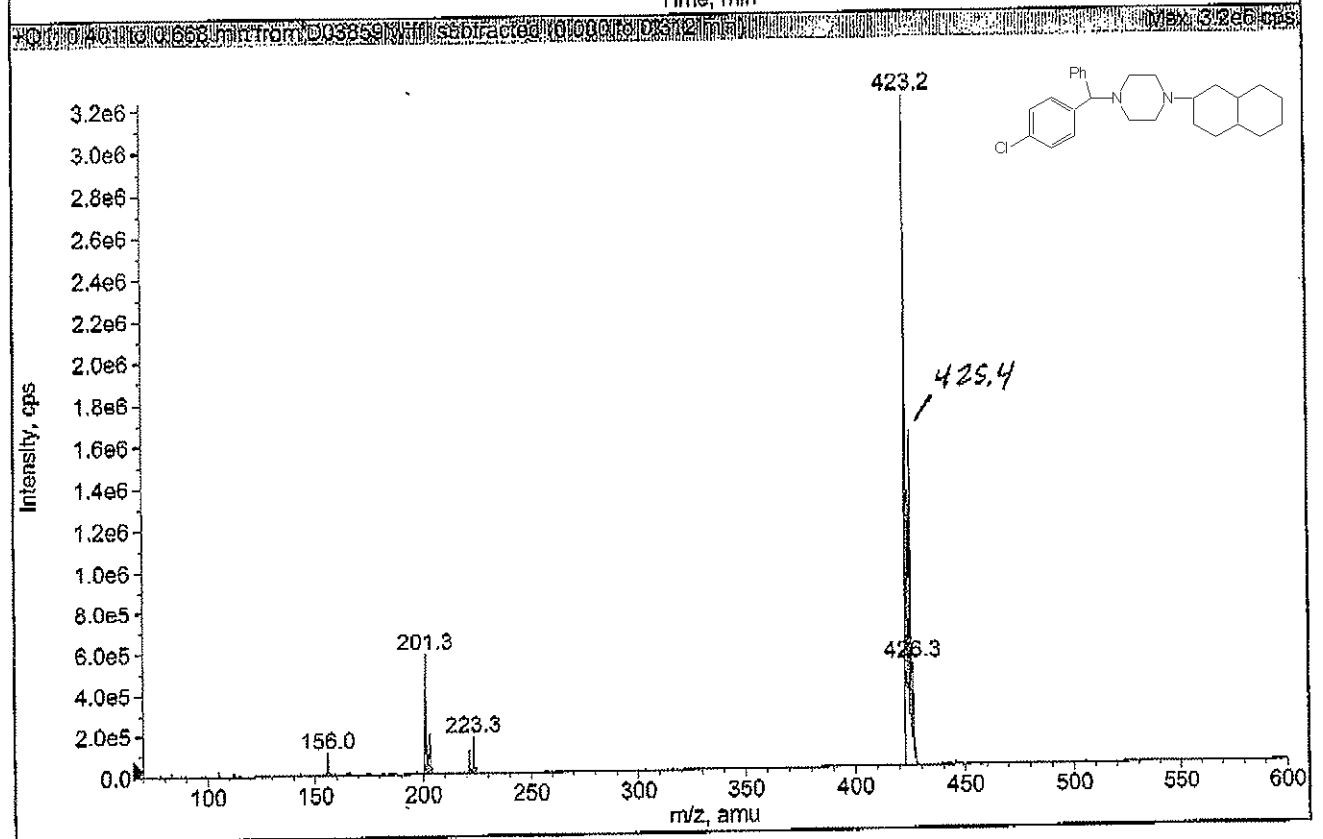
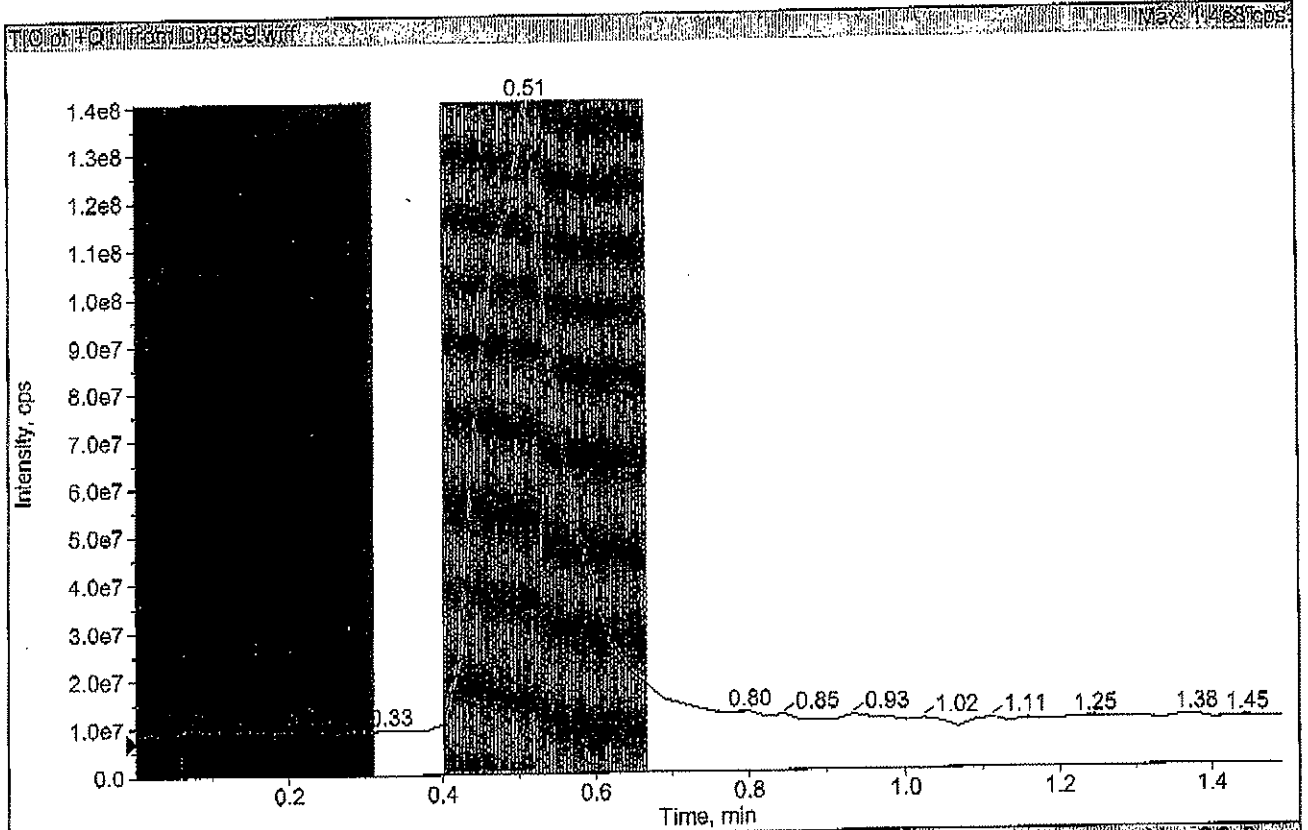
Analyt Version: 1.1  
Operator: gardner  
Printing Time: 10:29:39 AM  
Printing Date: Tue, Jul 27, 2004

Acq. Date: Monday, July 26, 2004  
Acq. Time: 20:02  
Sample Name: 24-026-24  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

PE Sciex API 365

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03859.wiff



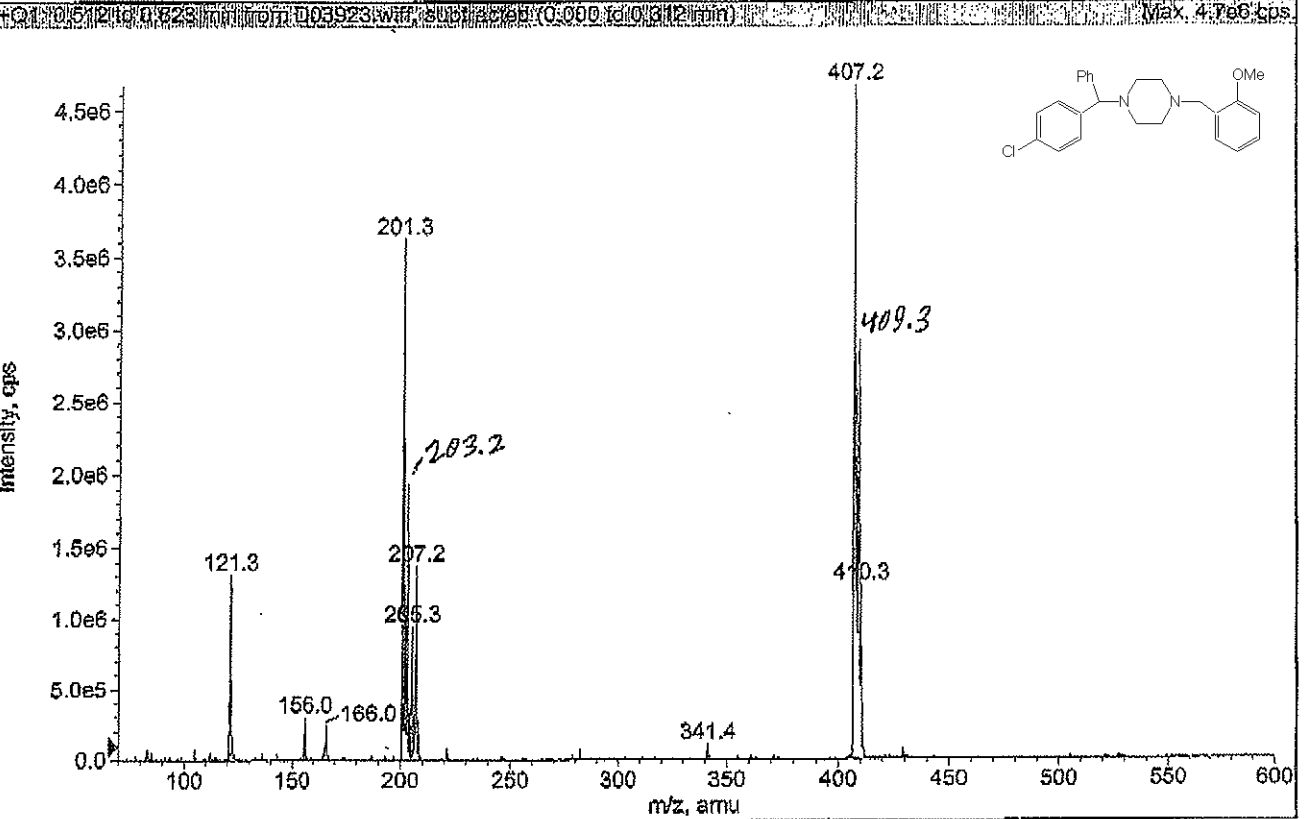
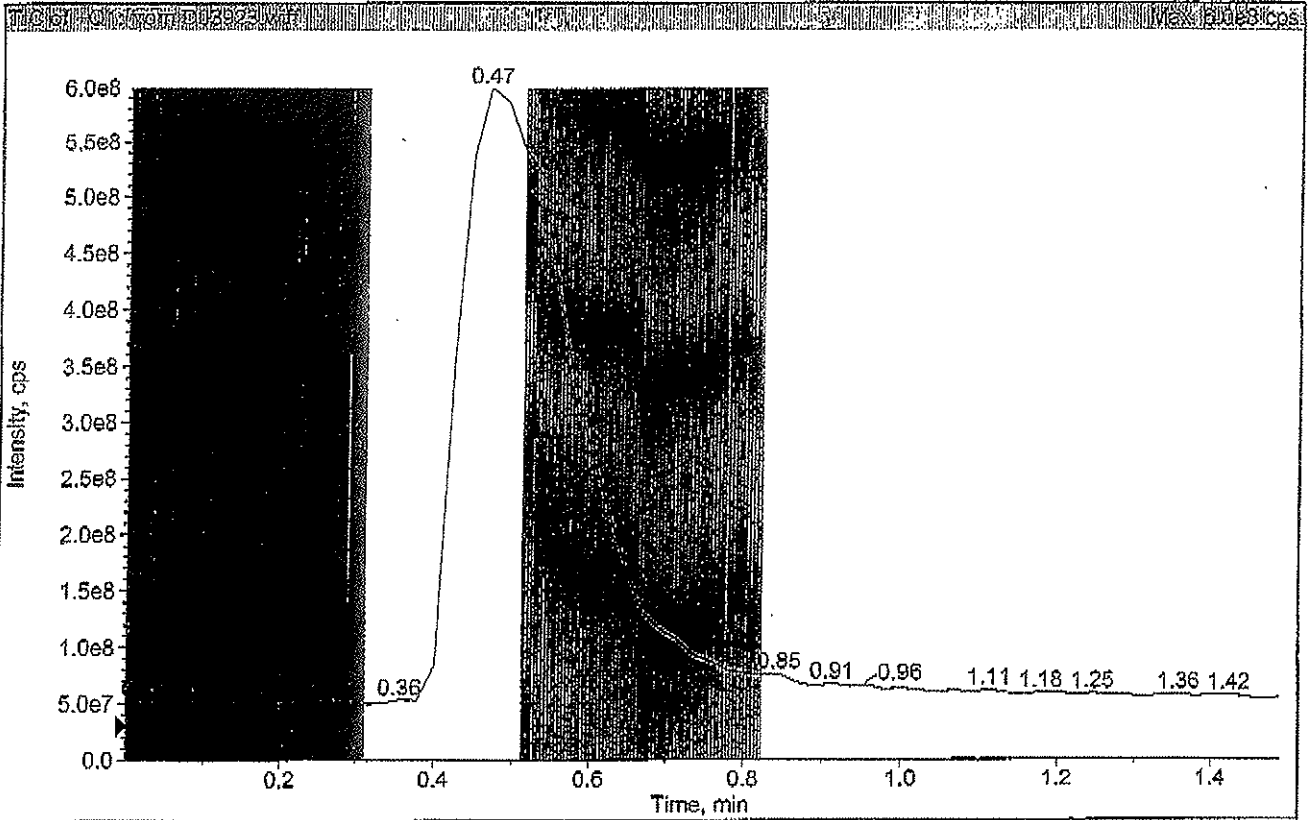
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 03:57:32 PM  
Printing Date: Tue, Aug 3, 2004

Acq. Date: Tuesday, August 03, 2004  
Acq. Time: 15:34  
Sample Name: 24-029-59  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03923.wiff

PE Sciex API 365



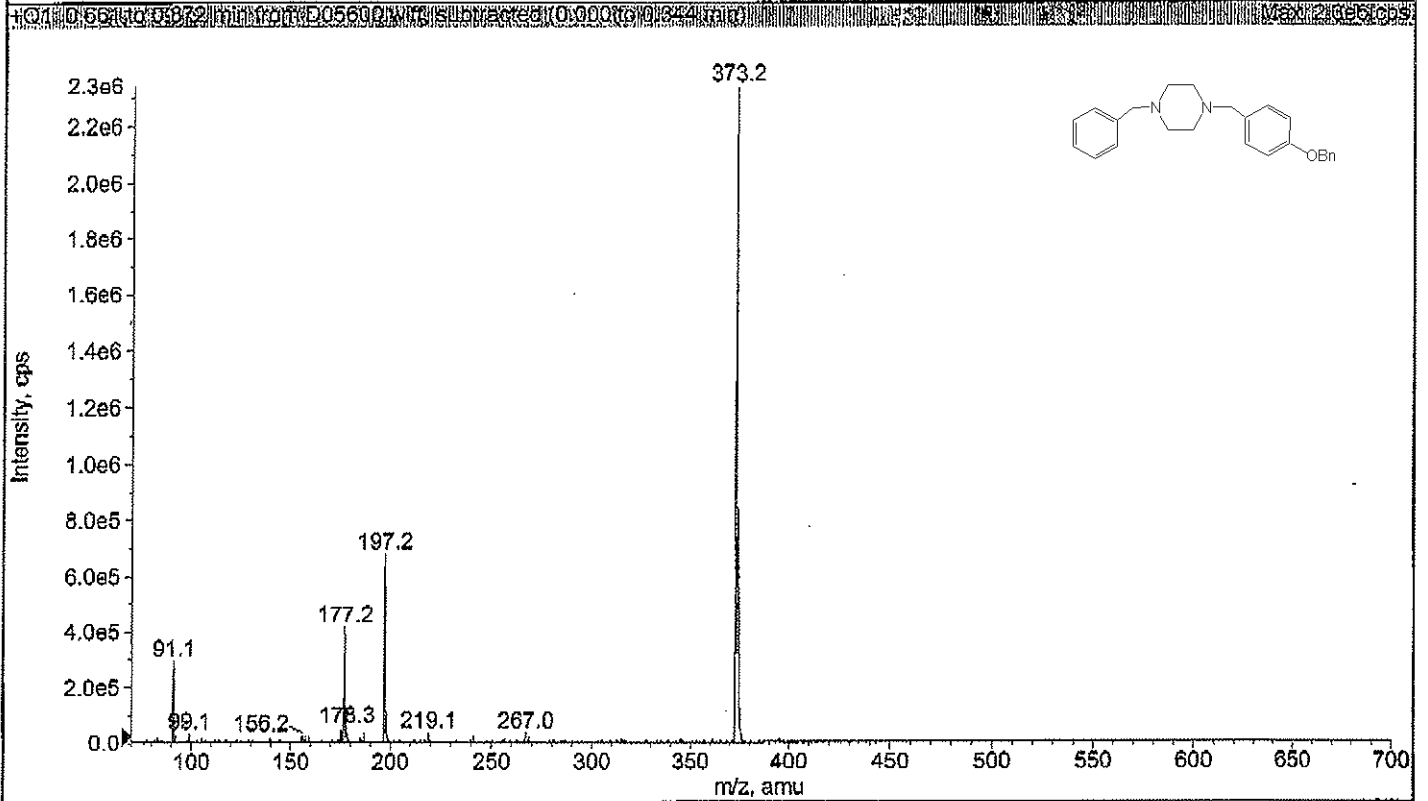
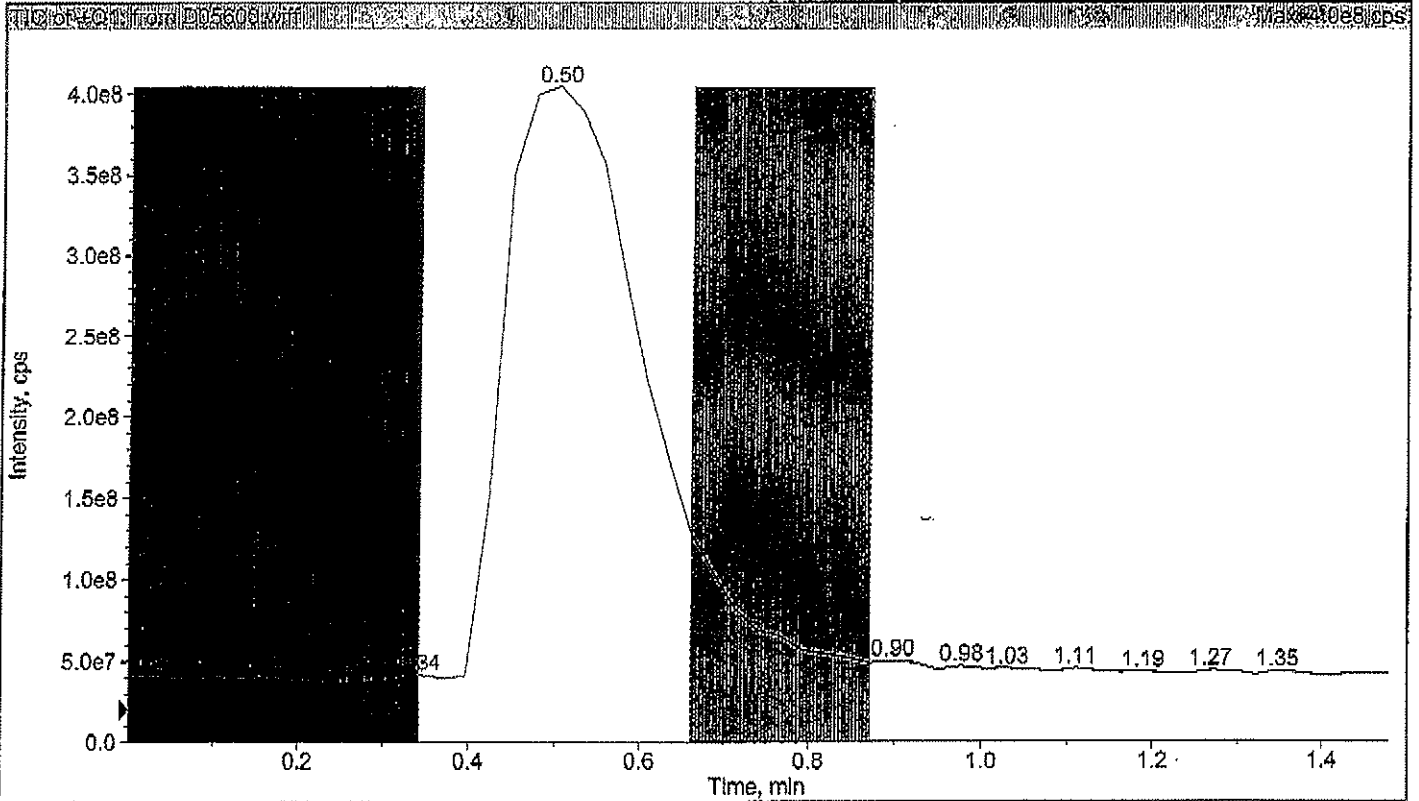
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 12:36:01 PM  
Printing Date: Thu, Aug 25, 2005

Acq. Date: Thursday, August 25, 2005  
Acq. Time: 12:31  
Sample Name: 24-113-34  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D05600.wiff

PE Sciex API 365



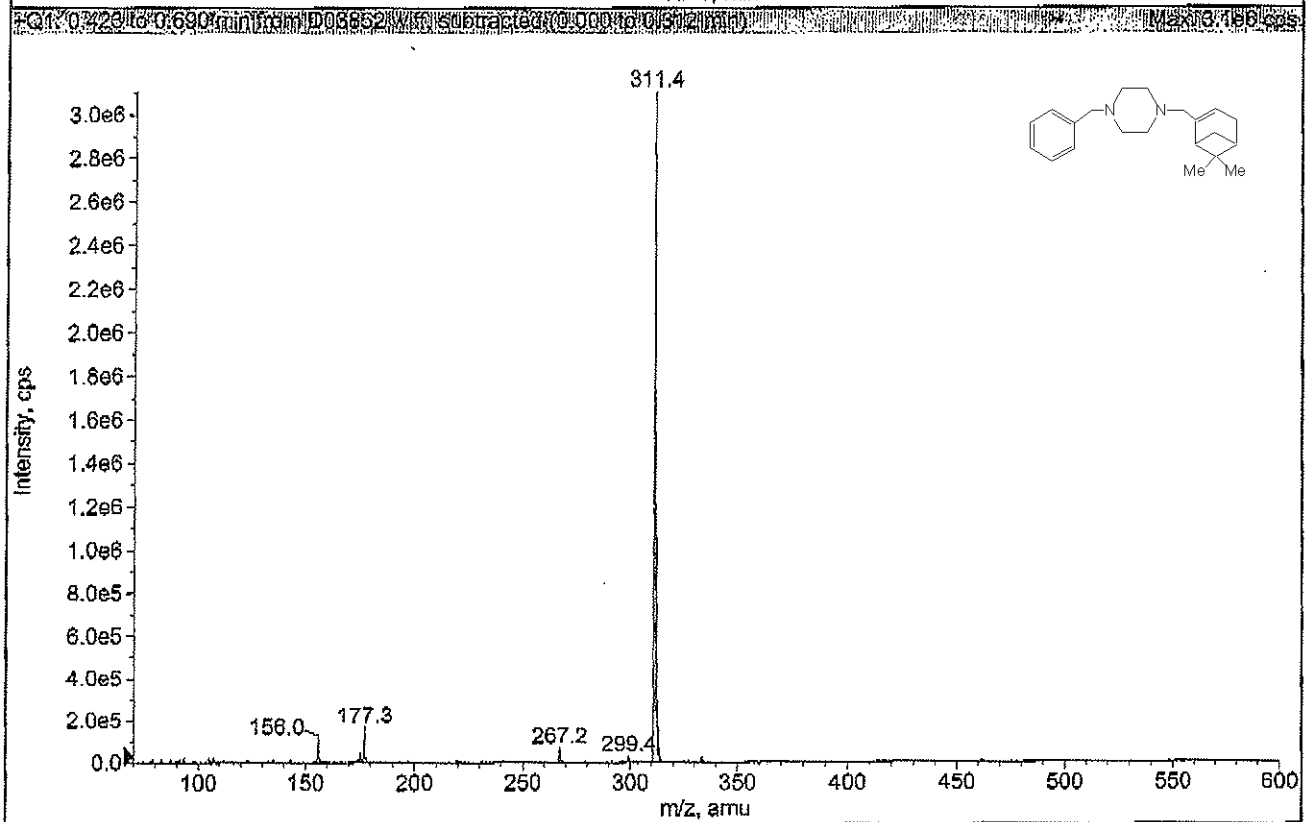
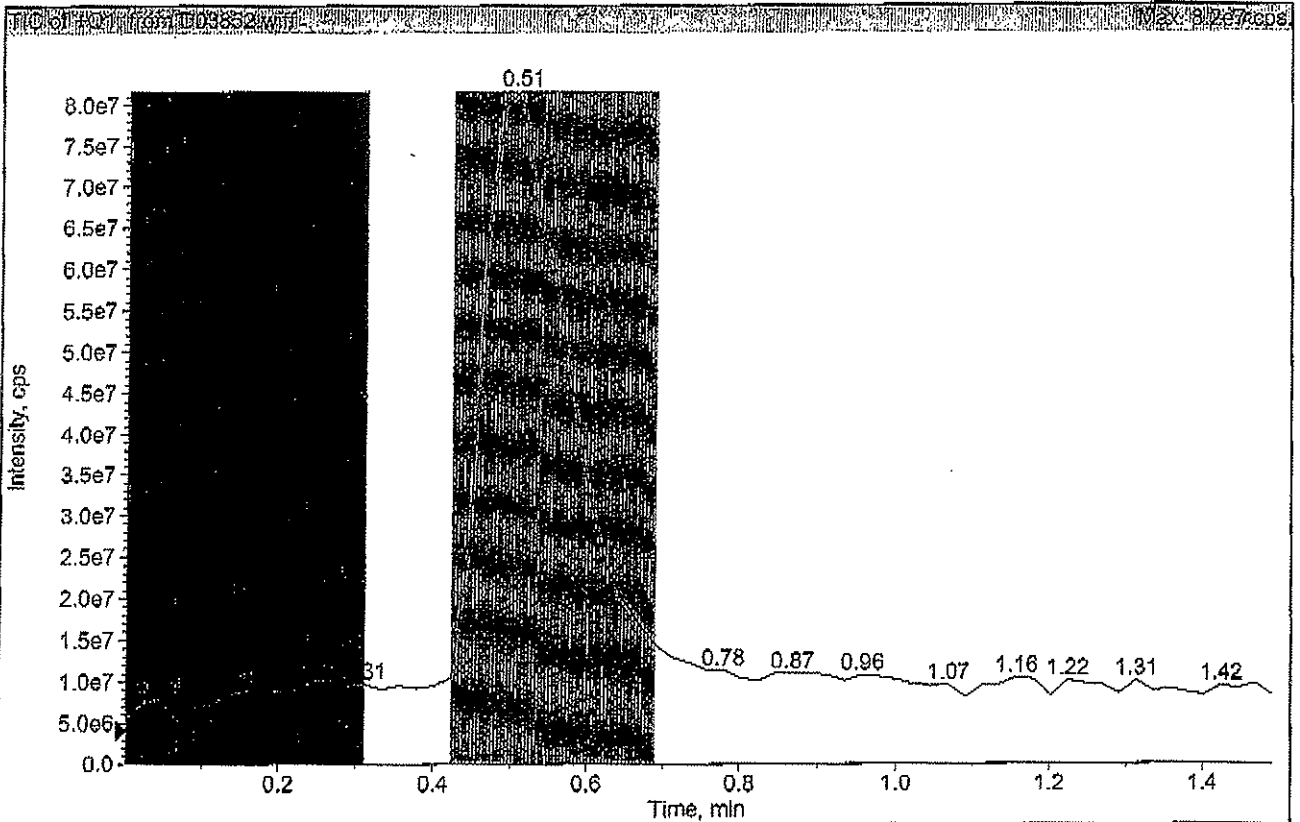
Analyst Version: 1.1  
Operator: gardner  
Printing Time: 10:28:05 AM  
Printing Date: Tue, Jul 27, 2004

Acq. Date: Monday, July 26, 2004  
Acq. Time: 19:50  
Sample Name: 24-026-17  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03852.wiff

PE Sciex API 365



Analyst Version: 1.1  
Operator: gardncx  
Printing Time: 10:38:03 AM  
Printing Date: Tue, Jul 27, 2004

Acq. Date: Monday, July 26, 2004  
Acq. Time: 20:21  
Sample Name: 24-026-35  
Sample ID:  
Polarity/Scan Type: Positive Q1 Scan

RTI International

Results Name: N/A  
Method Name: N/A  
Project: N/A  
Acq. File: D03870.wiff

PE Sciex API 365

