APPENDIX

ATTEMPTS TOWARDS THE SYNTHESIS OF IBUPROFEN

A . 1 INTRODUCTION

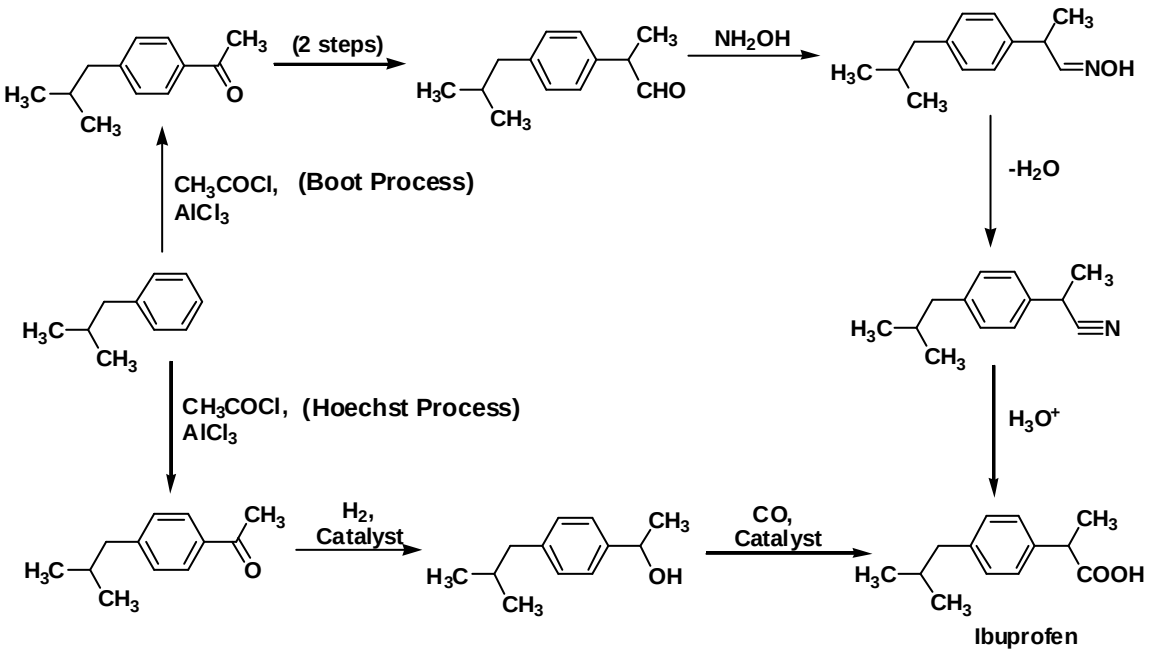
Ibuprofen [(±)-2-(4-isobutylphenyl)] propionic acid, is one of the commonly used anti-inflammatory agents. It is considered to be the prototype for the family of synthetic 2-arylpropionic acids, profens, a sub-class of the non-steroidal anti-inflammatory drugs (NSAIDS). In recent years, the profens have come to dominate this therapeutic class. Ibuprofen, for example, is used to treat arthritis, muscular strain, cephalalgia, and others. The profens have an asymmetric carbon centre attached to a carboxylic acid, a methyl, and an aryl group of varying structure. Some of the available profen drugs are ibuprofen, naproxen, ketoprofen, and flurbiprofen. Ibuprofen is distributed over the counter and naproxen belongs to the top-ten of drugs marketed worldwide in 1989. Ibuprofen is used to relieve the symptoms of a wide range of illnesses such as headaches, backache, period pain, dental pain, neuralgia, rheumatic pain, muscular pain, migraine, cold and flu symptoms and arthritis.

A.1.1 Synthesis of ibuprofen

Two of the most popular ways to obtain ibuprofen are the Boot process and the Hoechst process (Scheme A.1). The Boot process is an older commercial process developed by the Boot Pure Drug Company, and the Hoechst process is a newer process developed by the Hoechst Company. Boot's Company has developed the process for the synthesis of ibuprofen and patented in 1960s *(United States Patent*, 3, 385, 886). This synthesis consists of six steps and resulted in unwanted by-products.

Most of these routes to ibuprofen begin with isobutylbenzene and use Friedel-Crafts acylation. Hoechst process, with the assistance of catalysts, is completed in only three steps. Cheminor Drugs have developed a process for an improved version of production of ibuprofen based on chiral synthesis. This method is significant given that pure (S)-ibuprofen (the active form of ibuprofen) could near halve the regular ibuprofen dosage, besides improving the side-effect profile.

However, the human body can convert the inactive (R) form into the (S) form, so eventually 100 % of the ibuprofen taken becomes active. The process discovered by Cheminor is therefore unlikely to have commercial significance. It has three major types of effect which are all linked to its primary action, the inhibition of an enzyme known as arachidonate cyclooxygenase or COX of which there are two types COX-1 and COX-2.



Scheme A.1 Boot's and Hoechst synthesis of ibuprofen

In this appendix, synthesis of ibuprofen by Friedel-Crafts alkylation of isobutylbenzene with lactic acid and its derivatives was attempted using various acid catalysts like Zn-zeolite-Y, $AlCl_3$, $AlCl_3$/MCM-41 and $AlCl_3/SiO_2$.

A .2 RESULTS AND DISCUSSION

A.2.1 Catalytic activity of Na-zeolite-Y, H-zeolite-Y, H-zeolite-b and MCM-41

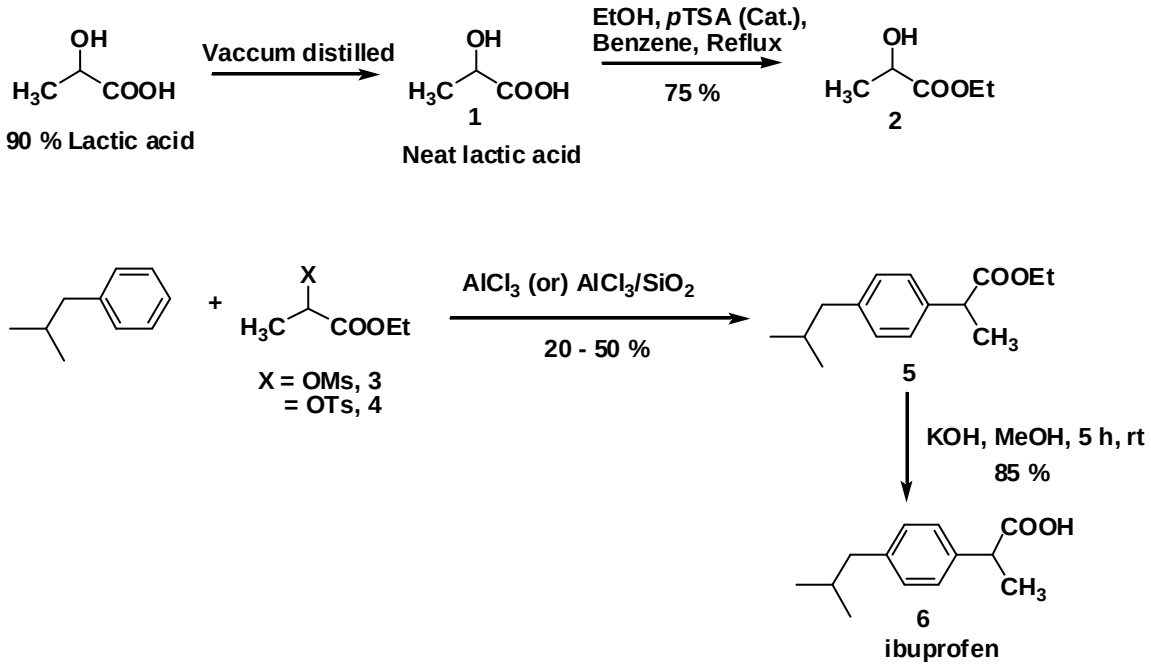
Solid acids like Na-zeolite-Y, H-zeolite-Y, H-zeolite-β and MCM-41 were employed as catalysts for the reaction of isobutylbenzene and lactic acid. The reaction was carried out either neat or in the presence of solvents. Analysis of the reaction products by FTIR and mass spectrometry indicated the polymerization of lactic acid under the reaction conditions. In order to suppress the polymerization of lactic acid, catalyst loading, reaction temperature (298 K - 373 K) and isobutylbenzene to lactic acid ratio (1:1-10:1) were varied. The results of these parameter variations indicted that though the polymerization was suppressed considerably there was no product formation observed by this method.

A.2.2 Catalytic activity of Zn-zeolite -Y

The Lewis acid character of the zeolite was enhanced by employing Zn-zeolite-Y as catalyst for the reaction of isobutylbenzene and lactic acid. The reaction was carried out either neat or in the presence of solvents at different temperatures (318 K-373 K). All the experimental variations employed for the reaction did not yield ibuprofen. ^{1}H- and ^{13}C-NMR of the product formed using Zn-zeolite-Y catalyst under different reaction conditions indicated the formylation of side chain of isobutylbenzene. However, the structure of the product formed was not completely characterized.

A.2.3 Catalytic activity of $AlCl_3$, $AlCl_3$/MCM-41 and $AlCl_3/SiO_2$

Friedel-Crafts type alkylation of isobutylbenzene with various lactic acid derivatives were explored for the synthesis of ibuprofen instead of reaction with lactic acid itself. The supported (MCM-41 and SiO_2) and unsupported $AlCl_3$ were employed as catalysts for Friedel-Crafts alkylation. Mesylate and tosylate of ethyl lactate were the lactic acid derivatives used for the reaction. The scheme for the synthesis of ibuprofen employing lactic acid derivatives is shown below



Scheme A.2 Synthesis of ibuprofen over $AlCl_3$ and $AlCl_3/SiO_2$.

90 % lactic acid was dehydrated by vaccum distillation and immediately heated with ethanol in presence of catalytic amount of *p*TSA with azeotropic removal of water to afford ethyl lactate (2) in 75 % yield. Mesylation and tosylation of ethyl lactate in presence of triethylamine or pyridine at 273 K afforded the corresponding ethyl-2-(methylsulphonyloxy) propanoate (3) and ethyl-2-(tosyloxy) propanoate (4). Friedel-Crafts alkylation of mesylate or tosylate with isobutylbenzene for single step synthesis of ethyl-2-(4-isobutylphenyl) propanoate was carried out by heating with $AlCl_3$ under

neat reaction conditions. Ethyl-2-(4-isobutylphenyl) propanoate (5) formed in 50 % yield was hydrolysed with KOH in methanol to afford the racemic ibuprofen (6) in 85 % yield. The reaction was extended with $AlCl_3$ supported on MCM-41. The supported catalyst was found to be ineffective for the Friedel-Crafts alkylation of mesylates and tosylates with isobutylbenzene. The ineffectiveness of $AlCl_3$/MCM-41 could be possibly due to poor anchoring of $AlCl_3$ on MCM-41 surface. However, $AlCl_3/SiO_2$ was found to be active for the Friedel-Crafts reaction (20 %). The work up for the procedure for the supported catalyst involves simple filtration compared to acid work up employed for unsupported $AlCl_3$.

A.3.3 EXPERIMENTAL SECTION

A.3.3.1 Preparation of ethyl-2-(methylsulphonyloxy) propanoate (3)

To a solution of ethyl lactate (1 g, 8.47 mmol) and triethylamine (1.77 ml, 12.71 mmol) in 15 ml of dry DCM was added portionwise MsCl (723 µl, 9.32 mmol) at 0 °C. The resultant mixture was stirred at 273 K for an hour and then at room temperature for 2 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography over silica gel (100 – 200 mesh) afforded pure ethyl-2-(methylsulphonyloxy) propanoate **3** (1.25 g, 75 %). **Physical data for 3: ^{1}H NMR [400 MHz, $CDCl_3$]** δ 5.15 (q, *J* = 7 Hz, 1H), 4.33 (q, *J* = 7.5 Hz, 2H), 3.15 (s, 3H), 1.62 (d, *J* = 7 Hz, 3H), 1.35 (t, *J* = 7.5 Hz, 3H).

A.3.3.2 Preparation of ethyl-2-(tosyloxy) propanoate (4)

To a solution of ethyl lactate (1 g, 8.47 mmol) in 5 ml of dry pyridine was added portionwise TsCl (1.77 g, 9.32 mmol) at 273 K. The resultant mixture was stirred at 273 K for an hour and then at room temperature for 2 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography over silica gel (100 – 200 mesh) afforded pure ethyl-2-(tosyloxy) propanoate **4** (1.05 g, 45 %). **Physical data for 4: ^{1}H NMR [400 MHz, $CDCl_3$]** δ 7.78 (d, 2H), 7.30 (d, 2H), 4.10 (q, 2H), 2.46 (s, 3H), 1.50 (d, 3H), 1.21 (t, 3H).

A.3.3.3 Preparation of ethyl-2-(4-isobutylphenyl) propanoate (5)

$AlCl_3$ (1.5 g, 10.20 mmol) or $AlCl_3$/MCM-41 (500 mg) was added to isobutylbenzene (2.73 g, 20.41 mmol) at 273 K. Ethyl-2-(methylsulphonyloxy) propanoate was added to the cold solution portionwise and the mixture was warmed to room temperature. It was then heated to 353 K for 8 h and then cooled to room temperature. The reaction mixture was quenched with dil. HCl at 273 K and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. Purification of the crude compound by column chromatography over silica gel using hexane as an eluent yielded the pure product **5.** (2.38 g, 50 %). **Physical data for 5: ^{1}H NMR [400 MHz, $CDCl_3$]** δ 7.12-7.63 (m, 4H), 4.23 (m, 2H), 3.66 (m, 1H), 2.64 (d, *J* = 8 Hz, 2H), 2.41 (m, 1H), 1.54 (m, 3H), 1.13 (m, 3H), 0.91 (m, 6H).

A.3.3.4 Preparation of ibuprofen (6)

To a solution of ethyl-2-(4-isobutylphenyl) propanoate (1 g, 4.27 mmol) in 6 ml of MeOH was added a solution of KOH (479 mg, 8.55 mmol) in 5 ml of water. The resultant solution was stirred at room temperature for 4 h. Methanol was removed under reduced pressure and the resulting solution was extracted with EtOAc and the organic mixture was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound **6** (750 mg, 85 %). **Physical data for 6: ^{1}H NMR [400 MHz, $CDCl_3$]** δ 7.15 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 3.64 (q, *J* = 7.2 Hz, 1H), 2.37 (d, *J* = 7.1 Hz, 2H), 1.75 (m, 1H), 1.43 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 6H).

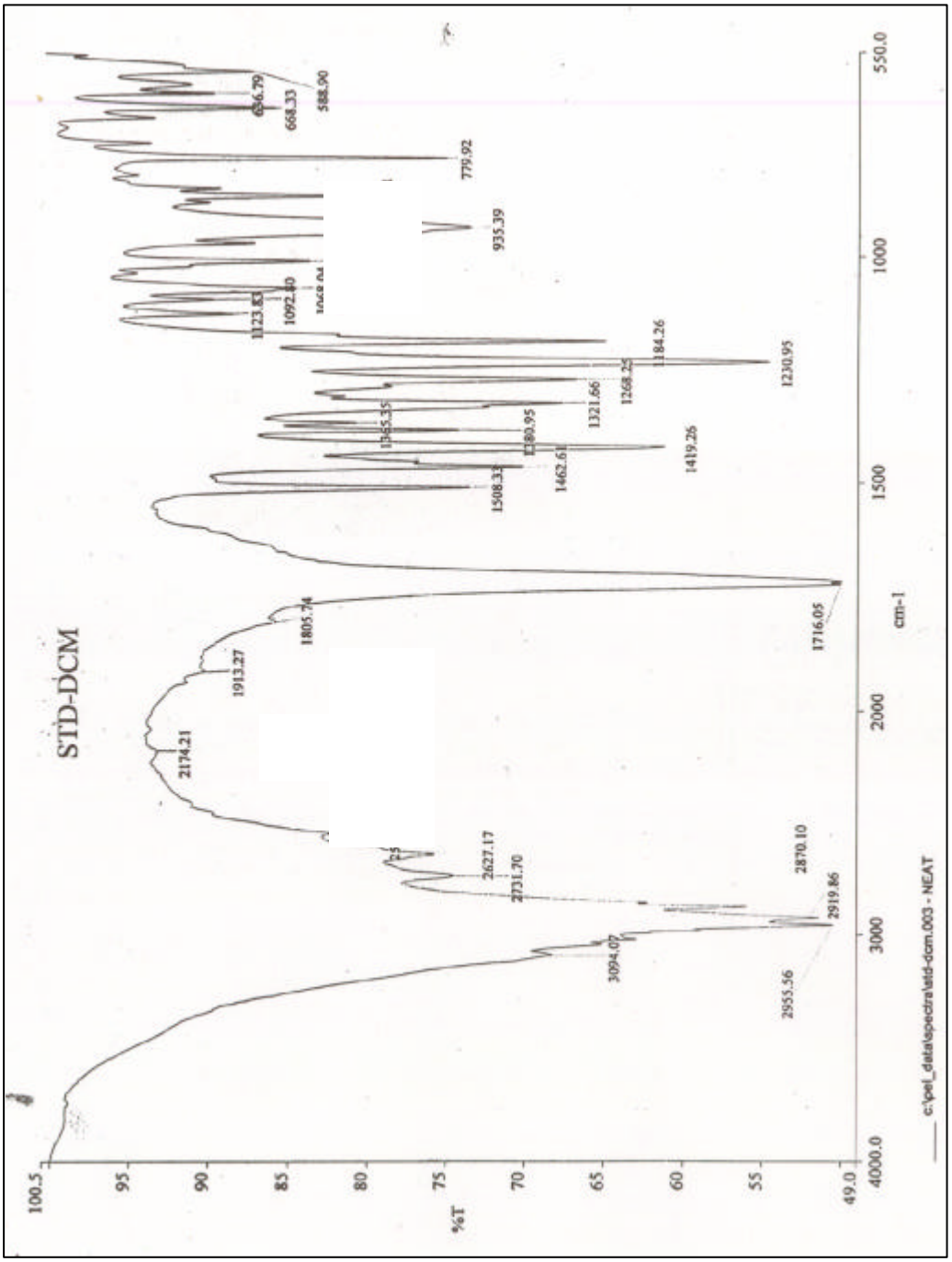


Fig. A.1 IR Spectrum of ibuprofen **6**

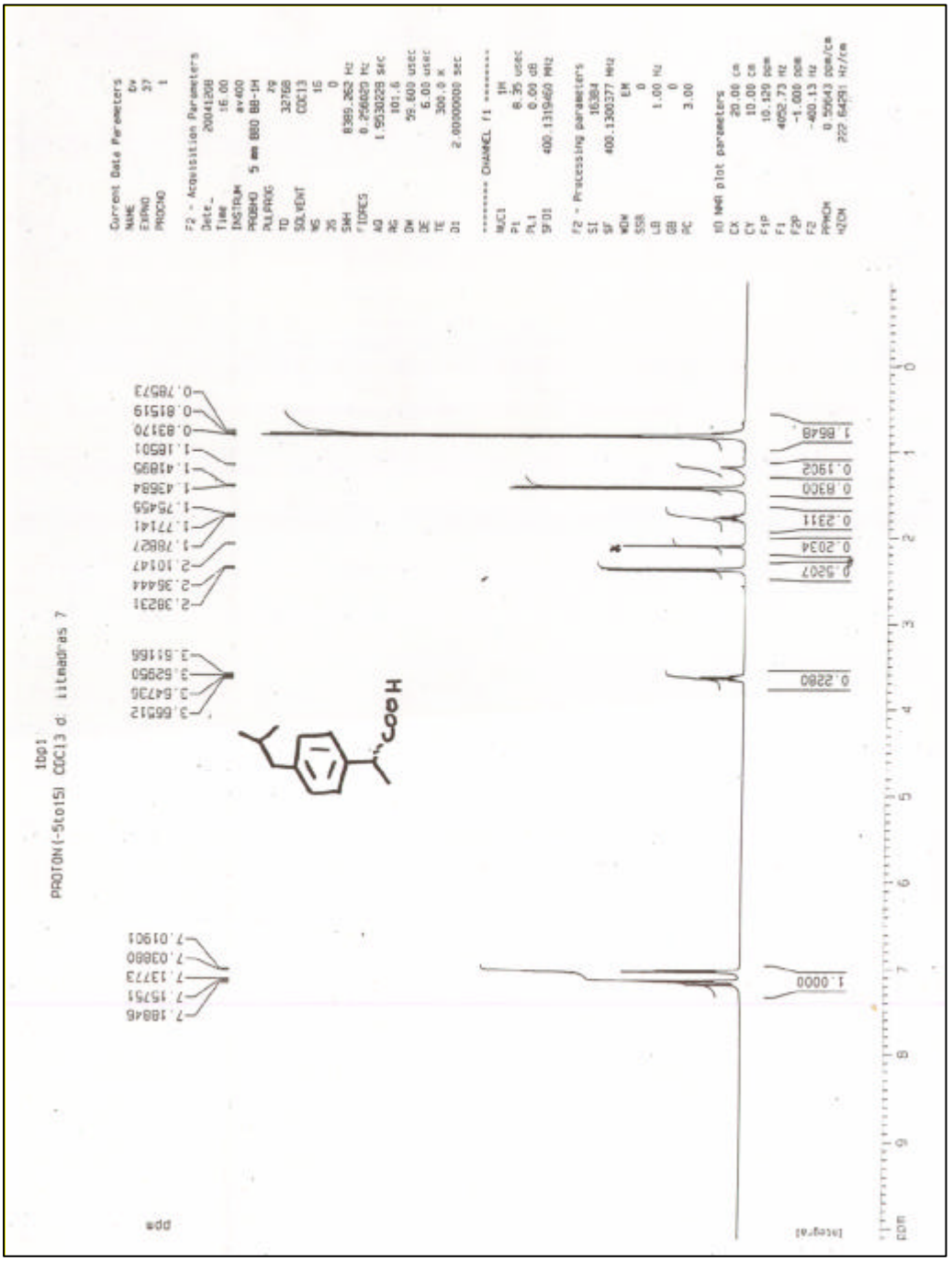


Fig. A.2 ^{1}H NMR Spectrum of ibuprofen **6**

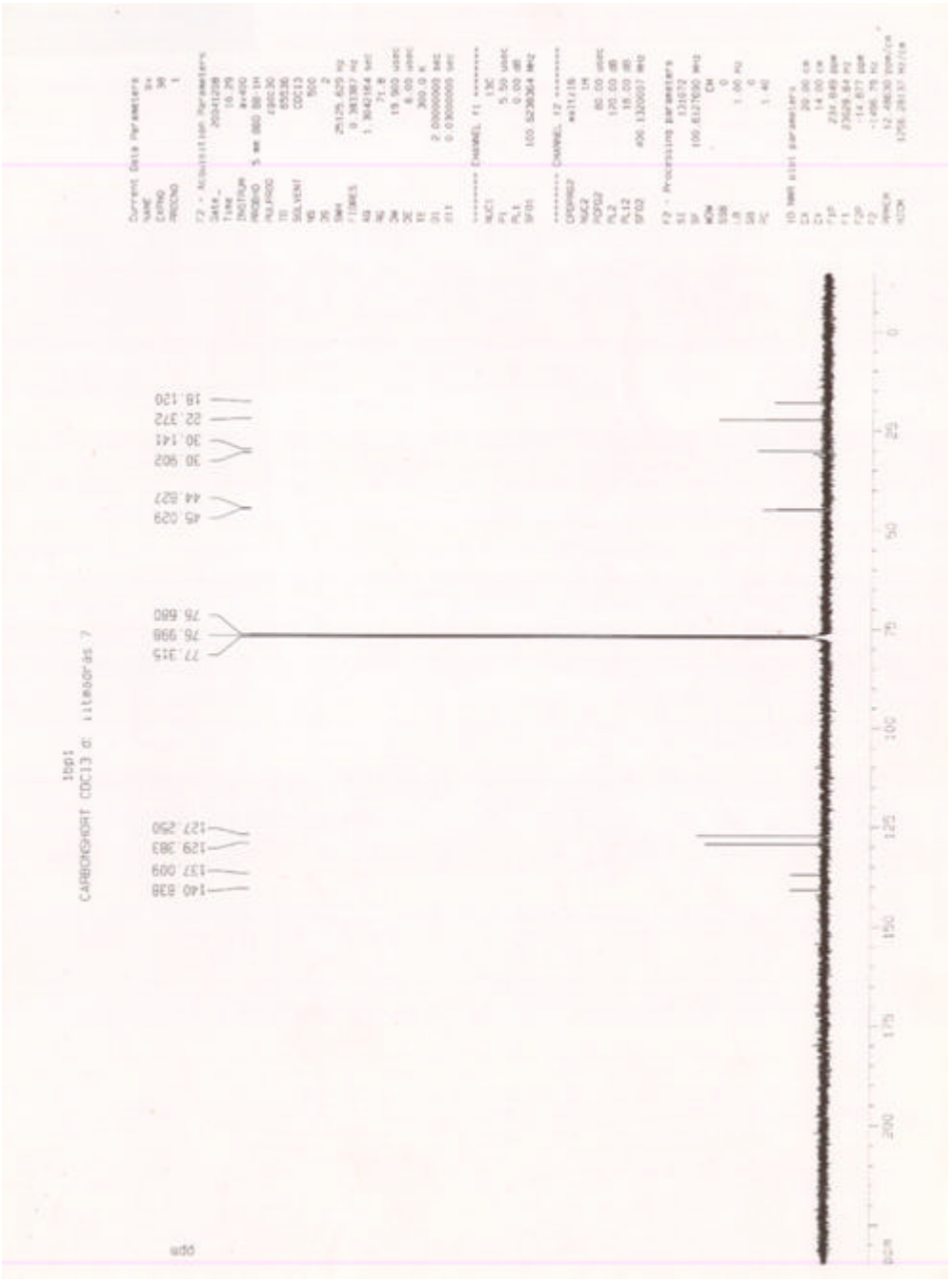


Fig. A.3 ^{13}C- Spectrum of ibuprofen **6**

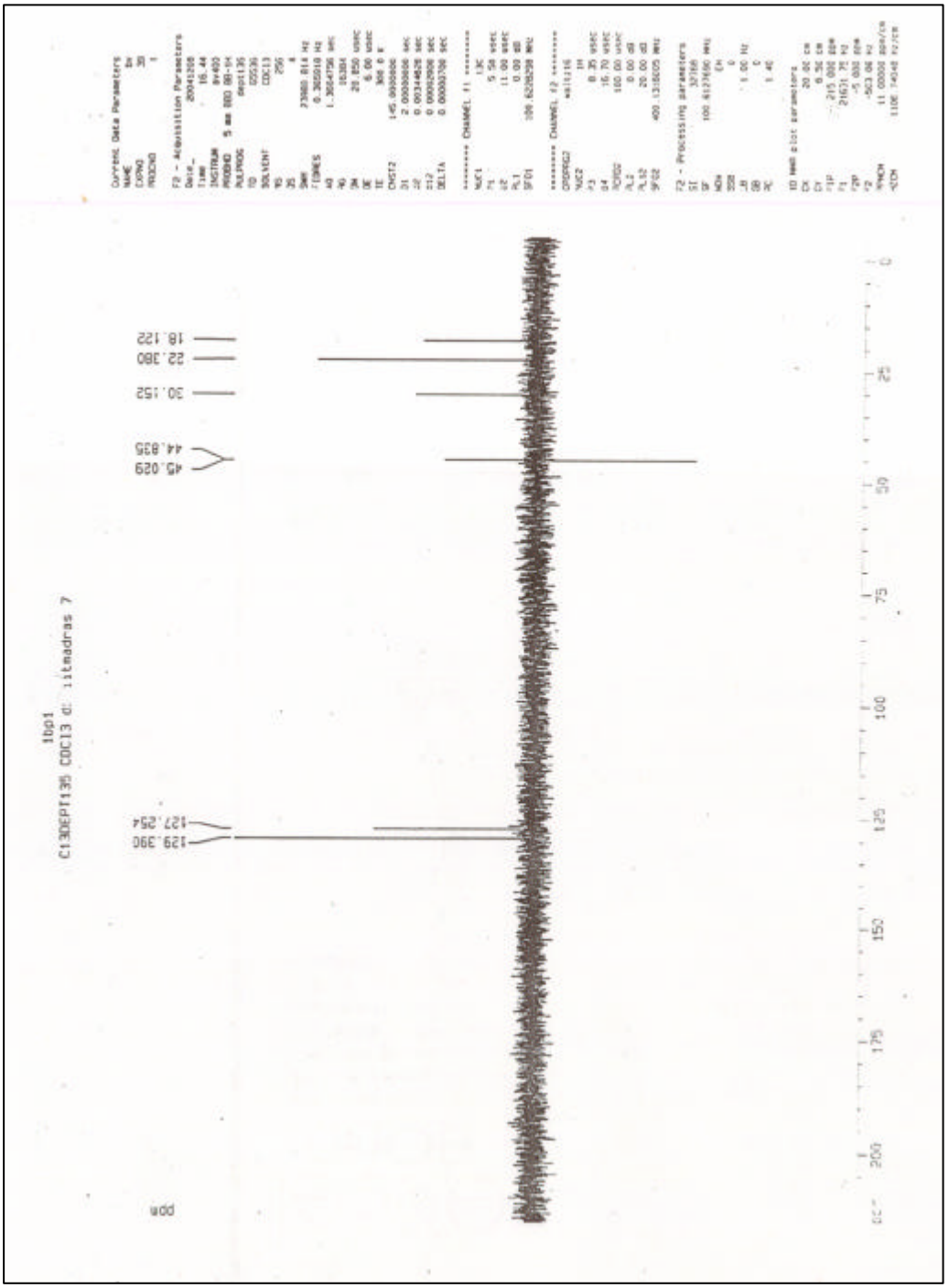


Fig. A.4 ^{13}C-DEPT Spectrum of ibuprofen **6**

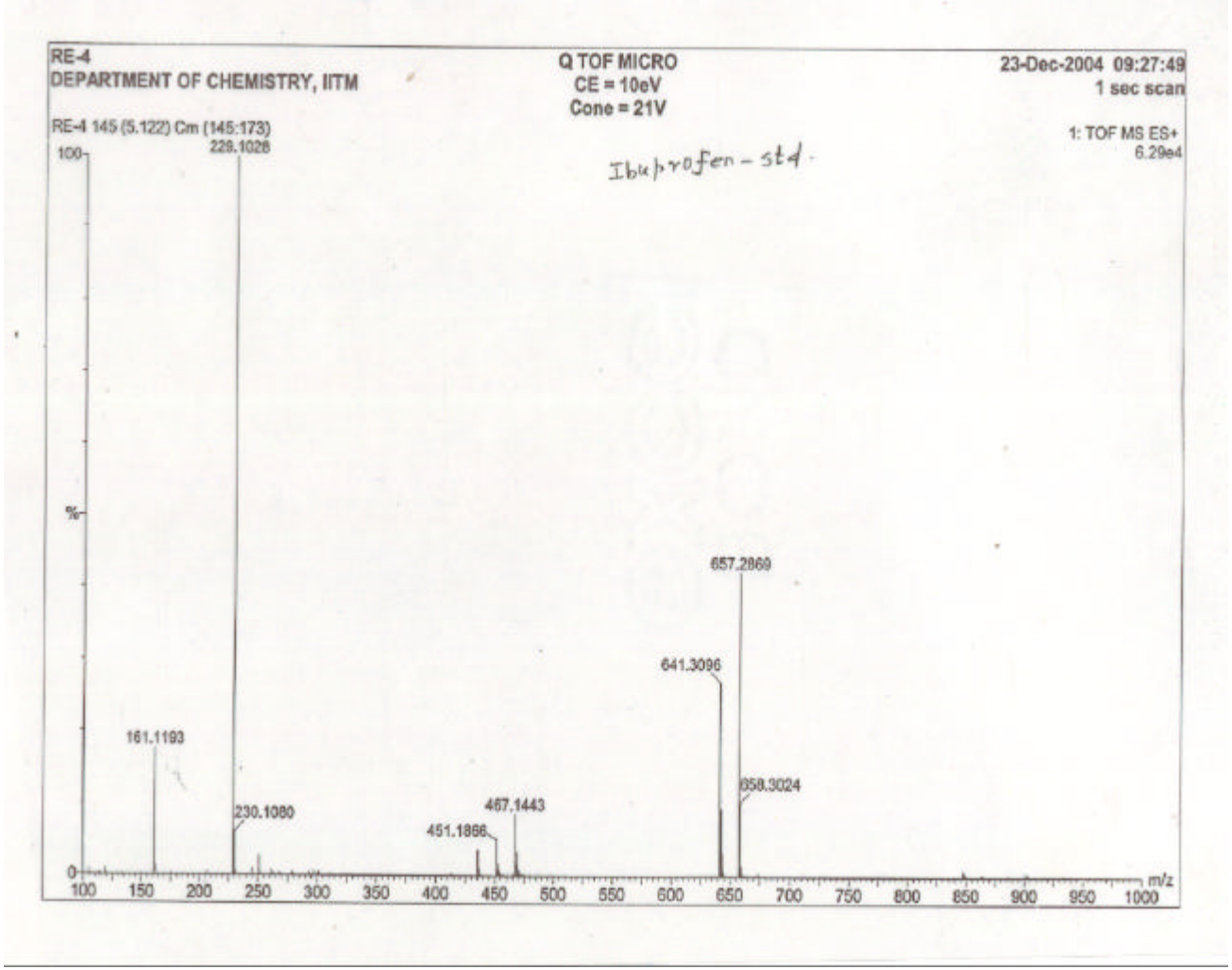


Fig. A.5 ESI(MS) Spectrum of ibuprofen **6**