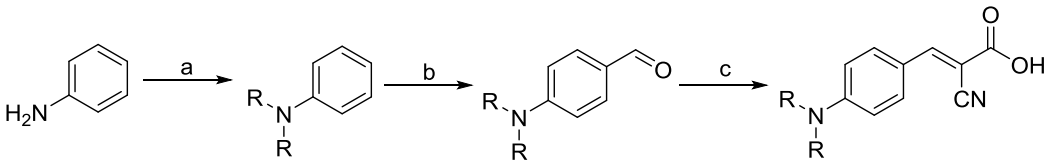
Supporting Information

Materials and Methods

Aniline (Fisher Scientific), *m*-anisidine (Sigma-Aldrich), alkyl bromides (Sigma-Aldrich), phosphorous (V) oxy chloride (Sigma-Aldrich), cyanoacetic acid (Sigma-Aldrich), piperidine (Sigma-Aldrich), tetrabutylammonium bromide (AKSci), potassium carbonate (Fisher-Scientific), L-[^{14}C]-lactic acid sodium salt (Perkin Elmer) were purchased from commercial sources. All other chemicals were of reagent grade quality and purchased from Sigma-Aldrich (St. Louis, MO). The ^{1}H- and ^{13}C-NMR spectra were plotted on a Varian Oxford-500 spectrometer. High-resolution mass spectra (HRMS) were recorded using a Bruker BioTOF II ESI mass spectrometer. Elemental analysis (CHN) results were obtained from Atlantic Microlab services.

Experimental Procedures:

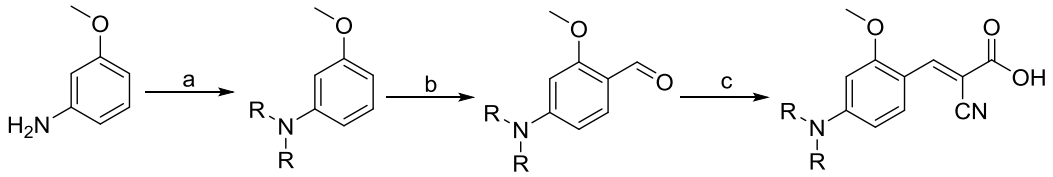
Synthesis of *N, N*-dialkyl cyanocinnamic acids (10-21)



Reagents and conditions: (a) alkylbromide,K_2CO_3, sodium stearate, ethanol, 100^oC, overnight, (b) i) $POCl_3$/DMF 0^oC-80^oC, 2-4h, ii) Na_2CO_3, (c) $CNCH_2COOH$, Piperidine, CH_3CN, 80^oC, 8-20 h

To a solution of aniline (10 mmol) in 20 mL ethanol-water, was added alkyl bromide (40 mmol), potassium carbonate (20 mmol), and sodium stearate (20 mmol) and refluxed overnight at 100 ^oC. Upon the completion of the reaction, the reaction mixture was extracted with ethyl acetate and water. The organic layer was dried with anhydrous Mg_2SO_4 and evaporated to obtain the *N, N*-dialkylated aniline. To a solution of dialkylated aniline (10 mmol) in DMF (60 mmol) was added phosphorous oxychloride drop-wise at 0 ^oC and the reaction mixture was refluxed at 80 ^oC for 2-4 hours. The reaction was quenched in a saturated solution of sodium carbonate and the solid was filtered and washed with hexanes to obtain *N, N*-disubstituted benzaldehydes. To a solution of substituted benzaldehyde (10 mmol) in 20 ml acetonitrile, was added cyanoacetic acid (15 mmol) and piperidine (10 mmol) and refluxed for 3-8 h at 80 ^oC. Upon the completion of the reaction, the above solution was poured into a mixture of 3M HCl (10 mL) in ice. The solution was stirred for 10 to 15 minutes and the solid was filtered using a Buchner funnel. The solid was washed with water and acetonitrile. The pure compound was obtained upon recrystallization in ethyl acetate-methanol mixture.

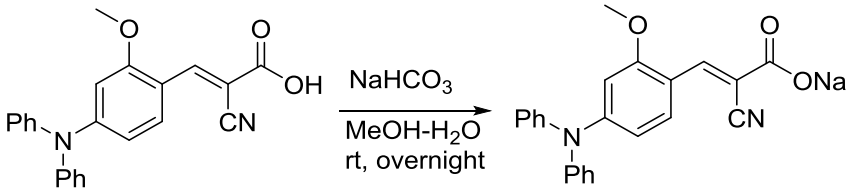
Synthesis of o-methoxy-*N,N*-dialkyl cyanocinnamic acids (22-26, 28-30)



Reagents and conditions: (a) alkylbromide,K_2CO_3, H_2O, tetrabutylammonium bromide, 100^oC, overnight, (b) i) $POCl_3$, DMF 0^oC-80^oC, 2-4h, ii) Na_2CO_3, (c) $CNCH_2COOH$, Piperidine, CH_3CN, 80^oC, 10-20 h

To a solution of *m*-anisidine (10 mmol) in 20 mL water, was added alkyl bromide (40 mmol), potassium carbonate (20 mmol) and tetrabutylammonium bromide (2 mmol) and refluxed overnight at 100 ^oC. Upon the completion of the reaction, the reaction mixture was extracted with ethyl acetate and water. The organic layer was dried with anhydrous Mg_2SO_4 and evaporated to obtain the *N, N*-dialkylated *m*-anisidine. To a solution of dialkylated anisidine (10 mmol) in DMF (60 mmol) was added phosphorous oxychloride dropwise at 0 ^oC and the reaction mixture was refluxed at 80 ^oC for 2-4 hours. In case of *N, N*-diphenyl *o*-methoxy benzaldehyde, the reaction was carried out at room temperature. The reaction was quenched in a saturated solution of sodium carbonate and the solid was filtered and washed with hexanes to obtain *N, N*-disubstituted *o*-methoxy-benzaldehyde. To a solution of the substituted *o*-methoxy benzaldehyde (10 mmol) in 20 ml acetonitrile or ethanol was added cyanoacetic acid (15 mmol) and piperidine (10 mmol) and refluxed for 10-20 h at 80 ^oC. Upon the completion of the reaction, the above solution was poured into a mixture of 3 M HCl (10 mL) in ice. The solution was stirred for 10 to 15 minutes and the solid was filtered using a Buchner funnel. The solid was washed with water and acetonitrile and the pure compound was obtained upon recrystallization in ethyl acetate-methanol mixture.

Synthesis of *o*-methoxy-*N, N*-diphenyl cyanocinnamic acid sodium salt (27)



To a solution of cyanocinnamic acid (10 mmol) in methanol (75 ml) and 1ml of water was added sodium bicarbonate (25 mmol) and stirred at room temperature overnight. The reaction was filtered and methanol was evaporated to obtain sodium salt of cyanocinnamic acid. The product is purified via recrystallization in methanol.

Cells and Culture Conditions

Immortalized rat brain endothelial cells (RBE4, a gift from F. Roux[*], were grown in 1:1 α-MEM and F-10 HAM supplemented with 10% FBS (heat inactivated), 1 ng/ml basic fibroblast growth factor, 0.3 mg/ml geneticin, 1% antibiotic-antimycotic.

[*]Roux, F.; Durieu-Trautmann, O.; Chaverot, N.; Claire, M.; Mailly, P.; Bourre, J. M.; Strosberg, A. D.; Couraud, P. O. *J. Cell Physiol*. **1994**, *159*, 101–113.

MCT1 Inhibition Assay via [^{14}C]-Lactate Uptake in Rat Brain Endothelial Cells (RBE4)

Inhibition of MCT1-mediated lactate transport was carried out using [^{14}C]-lactate and rat brain endothelial cell line RBE4. RBE4 cells were previously shown by PCR to express only MCT1 (data not shown) and this was confirmed by Western Blot. Cells were plated approximately 20-24 hours before each experiment at approximately 10^5 cells per well in 24 well culture dishes. Test compounds were dissolved in DMSO at 1000X concentrations. Test solutions, positive inhibition (α-cyano-hydroxycinnamate, CHC) controls, and vehicle (DMSO) controls were diluted to working concentration in HEPES buffered saline (HBS: 140mM NaCl, 5mM KCl, 2mM $CaCl_2$, 2mM $MgSO_4$, 10mM D-glucose, 10mM HEPES, pH 7.43) containing 3µM [^{14}C]-lactate and 2µM L-lactate. Culture wells were washed twice with 500µL HBS and allowed to equilibrate for 15 minutes at 37^{o}C. The HBS was removed and 250µL test or control solution was added to wells in triplicate. After 15 minutes, media was aspirated from the wells, 500µL ice-cold stop buffer (0.1mM CHC solution in HBS) was added, and the plate placed on ice. A negative uptake control was run at 4^{o}C by treating triplicate wells with DMSO control solution, immediately removing the solution, and adding ice-cold stop buffer. Then the cells were washed twice with ice-cold HBS and solubilized by addition of 250µL of 0.1M NaOH in 5% Triton-X solution with shaking (40 min). A 150µL aliquot was added to 4mL scintillation fluid and radioactivity was determined by scintillation spectrometry. Aliquots from an untreated triplicate set of wells were assayed for total protein per well using the BCA Protein Assay Kit (Pierce Thermoscientific. Rockford,

IL). Inhibition by each test solution was calculated as a percentage of the maximum control uptake. Test compounds were evaluated using 9-12 concentrations ranging over 1000 fold and spanning the $IC_{50.}$

***In Vivo* Studies**

Ethical Considerations

The experimental procedure involving animals that were conducted at the University of Minnesota Duluth (Supporting information: **Figure 1B, 2A and 2B**) was in compliance with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee (IACUC protocol 1307-30773A) at the University of Minnesota. The remaining animal studies were conducted by GenScript Corporation (Piscataway, NJ) according to their approved IACUC protocols IACUC 003.04 (Supporting information: **Figure 1A**), IACUC075.03 (**Figure 1**) and GSIACUC-184115 (**Figure 2**).

Systemic Toxicity Studies

Compound **27** was evaluated for systemic toxicity in healthy CD-1 (ICR) mice weighing ~27g. Compound **27** was dissolved in DMSO, diluted in normal saline and administered by ip injection (6.67 mg/kg, bid and 50 mg/kg, qd) and by oral gavage (50 mg/kg, bid) (N=12). Control animals received 10% DMSO administrations. All treatments were carried out for 21 days (**Figures 1A & 1B**). Body weights were recorded daily. All animals were humanely euthanized. Similarly, salts of compounds **29** and **30** were dissolved in water and administered to mice (N=6) by i.p. injection (70mg/kg b.i.d). Control animals received 10% DMSO. The treatment was continued for 20 days and 14 days for salts of **29** and **30** respectively (**Figures 2A & 2B**).

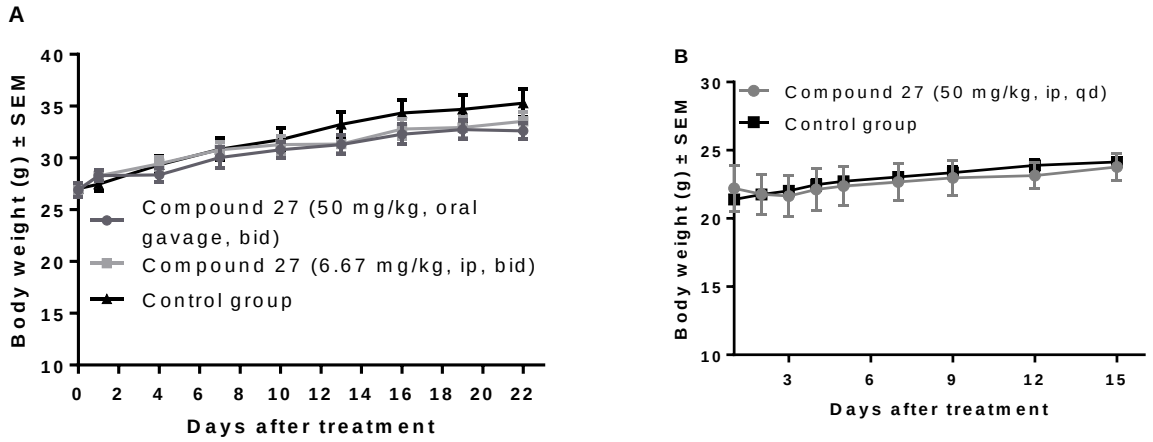


Figure 1: ***In vivo*** **toxicity studies with compound 27 in CD-1 mice (A) Mice received 6.67 mg/kg, ip, bid and 50 mg/kg, oral gavage, bid (N=12 mice per group). Control animals received 10% DMSO in saline. Treatment was carried out for 22 days. (B) Mice were administered with 50 mg/kg, ip, qd (N=6 mice per group). Control mice received 10% DMSO in saline. The study was carried out for 15 days. In both groups, body weight changes were measured every 2-3 days.**

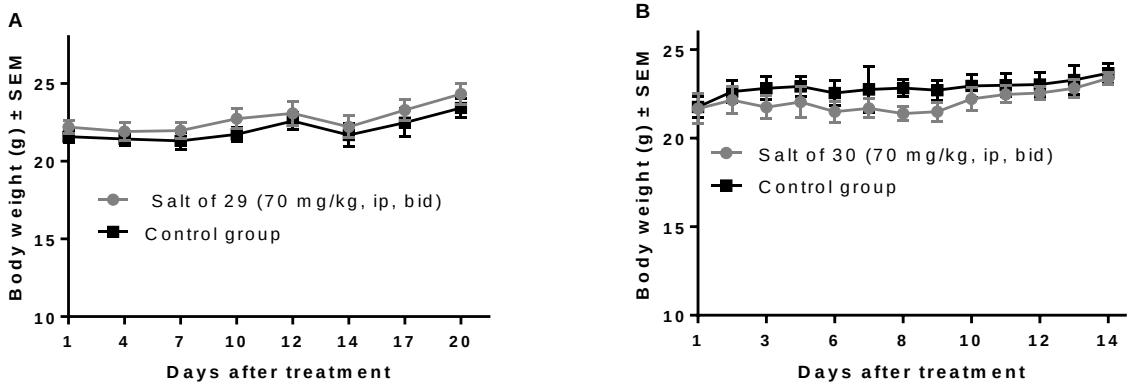


Figure 2: *In vivo* toxicity studies with sodium salts of compounds **29** & **30** in CD-1 mice (**A**) Mice were administered with 70 mg/kg, ip, bid of **29** (N=6 mice per group). The study was carried out for 20 days. (**B**) Mice received 70 mg/kg, ip, bid of **30** (N=6 mice per group). The study was carried out for 14 days. In both studies, body weight changes were measured every 2-3 days.

Pharmacokinetic Study (Figures 3A & 3B)

60 male mice were divided into 2 groups according to different administration routes: p.o group and i.p group. Each group had 30 mice and 3 mice for each time point. The dose of compound **27** was 100 mg/kg. Orbital sinus blood samples were collected at 0, 5, 15, 30 minutes; and at 1, 2, 4, 6, 8, 24 hours. Blood samples were placed into tubes with anticoagulant at room temperature at least 30 minutes prior to centrifugation, then

centrifuged at 10000 rpm for 5 minutes at 4 °C to separate plasma from the blood samples. Following centrifugation, the resulting serum was transferred to clean tubes and stored frozen at -80°C. The plasma samples were analyzed by a validated LC-MS/MS method. The standard non-compartmental model was used to generate the pharmacokinetic parameters, including C_{max}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, CL/F, and Vz/F. The maximum plasma concentration (C_{max}) and the time at which this occurred (T_{max}) were noted directly. The elimination rate constant (k_{el}) was calculated by linear regression of the terminal points of the semi-log plot of plasma concentration against time. Elimination half-life ($t_{1/2}$) was calculated by use of the formula: $t_{1/2}=0.693/k_{el}$. The area under the plasma concentration-time curve to the last measurable plasma concentration ($AUC_{0\text{-}last}$) was calculated by use of the linear trapezoidal rule.

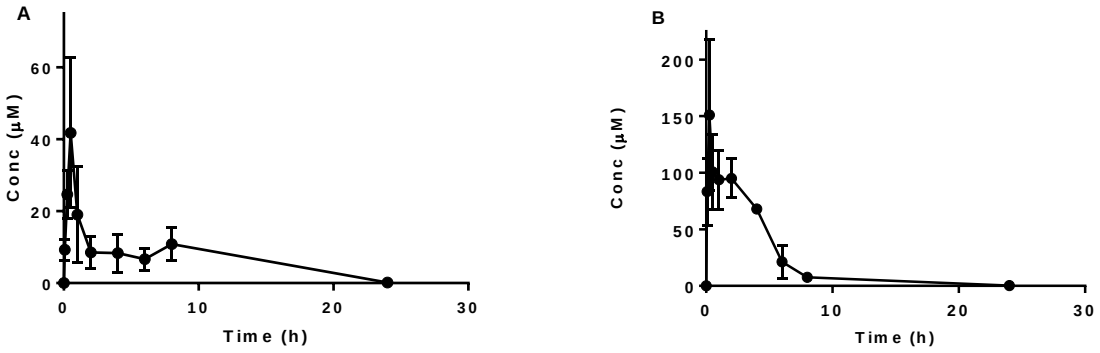


Figure 3: Mean plasma concentration-time profiles of compound **27**: Mice were divided into two groups and 100 mg/kg of compound **27** was administered intragastrically **(A)** and intraperitoneally **(B)** in groups 1 and 2 respectively. Orbital sinus blood samples were collected at 0, 5, 15, 30 minutes; and at 1, 2, 4, 6, 8, 24 hours (N=3 mice per each time interval).

PK parameters (Mean ± SD)								
Dose route		$AUC_{0\text{-}last}$ (µg/L*h)	$AUC_{0\text{-}\infty}$ (µg/L*h)	$t_{1/2Z}$ (h)	T_{max} (h)	Vz/F (L/kg)	CLz/F (L/h/kg)	C_{max} (µg/L)
p.o.	Mean	65740	66011	3.03	0.667	6.55	1.56	17500
	SD	13050	13365	1.26	0.289	1.81	0.322	4233
i.p.	Mean	200796	201474	3.19	0.5	2.35	0.499	61333
	SD	20459	19835	1.16	0.433	1.04	0.0473	16385

Tumor Growth Inhibition Study of Compound 27 in WiDr Tumor Xenograft Model (Figure 1)

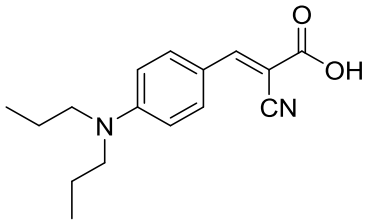
WiDr cancer cells, 7.0×10^6 cells per mouse in 0.1mL of a 1:1 mixture of PBS and matrigel, were implanted subcutaneously in the right flanks of female BALB/c nude mice weighing ~20g. Tumors were allowed to grow to a size of ~100 cubic millimeters before treatments were initiated. Mice were randomly assigned to 3 groups: Group 1 was administered with 50 mg/kg, oral gavage, bid, group 2 was treated with 10 mg/kg, ip, bid and a third group was the control group. Tumors were measured by caliper every two days and tumor volumes calculated using the formula $V = \frac{1}{2} \times a \times b^2$ where 'a' is the long diameter of the tumor and 'b' is the short diameter of the tumor. At the end of the day 22, the mice were euthanized with CO_2 and tumor masses were isolated and weighed. The inhibition amount was determined using the formula $\% \, inhibition = \frac{(C-T)}{C} \times 100$ where C is average tumor weight of the control group and T is the average tumor weight of the test group.

In another study (**Figure 2**), WiDr cancer cells, 5.0×10^6 cells in 0.1ml of a 1:1 mixture of PBS and matrigel, were implanted subcutaneously in the right flank of female BALB/c nude mice weighing ~20g. Treatments were started on day-6 of tumor induction. The mice were randomly assigned to 3 groups (N=8). Group 1 was administered with 100 mg/kg, oral gavage, qid, group 2 was treated with 50 mg/kg, ip, bid and a third group was the control group. Tumor volumes were determined as described above. On day-9, one of the mice in group-2 showed body weight loss of 20% and it was euthanized. Also, on day-15, one more mice from the same group had body weight loss of 19% and was euthanized.

Statistical Analysis

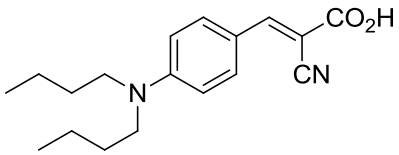
Statistics were computed using GraphPad Prism version 6.0. Mann-Whitney test was used to compare the treated and untreated groups. A *P*-value of ≤ 0.05 was considered significant.

Characterization of Synthesized Compounds



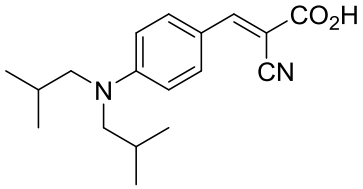
(E)-2-cyano-3-(4-(dipropylamino)phenyl)acrylic acid (12)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.11 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.5 Hz, 2H), 3.38 (t, J = 7.5 Hz, 4H), 1.70 (m, 4H), 1.00 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ190.1, 152.9, 132.4, 129.4, 124.8, 111.9, 111.0, 53.0, 20.6, 11.6 Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.35): C 70.56, H 7.40, N 10.29 Found: C 70.70, H 7.46, N 10.32



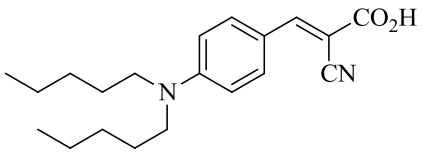
(E)-2-cyano-3-(4-(dibutylamino)phenyl)acrylic acid (13)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.03 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 3.40 (t, J = 7.5 Hz, 4H), 1.54 (m, 4H), 1.34 (m, 4H), 0.93 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.6, 154.3, 152.5, 134.5, 118.7, 118.6, 112.1, 105.0, 50.6, 29.6, 20.2, 14.5. Anal. Calcd for $C_{18}H_{24}N_2O_2$ (300.40): C 71.97, H 8.05, N 9.33. Found: C 71.83, H 8.38, N 9.35



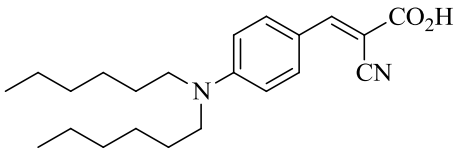
(E)-2-cyano-3-(4-(diisobutylamino)phenyl)acrylic acid (14)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 3.31 (d, J = 7.0 Hz, 4H), 2.17-2.11 (m, 1H), 0.97 (d, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 155.8, 152.9, 134.9, 118.9, 117.5, 112.4, 92.1, 60.3, 27.0, 20.5. Anal. Calcd for $C_{18}H_{24}N_2O_2$ (300.40): C 71.97, H 8.05, N 9.33. Found: C 71.48, H 8.49, N 9.23



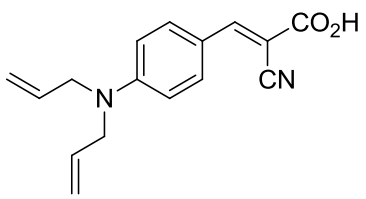
(E)-2-cyano-3-(4-(dipentylamino)phenyl)acrylic acid (15)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 5.0 Hz, 2H), 3.39 (t, J = 8.0 Hz, 4H), 1.68-1.62 (m, 4H), 1.43-1.33 (m, 8H), 0.95 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 155.8, 152.7, 135.1, 118.8, 117.6, 111.6, 91.8, 51.4, 29.4, 27.2, 22.7, 14.2. Anal. Calcd for $C_{20}H_{28}N_2O_2$ (328.46): C 73.14, H 8.59, N 8.53. Found: C 72.61, H 8.37, N 8.16



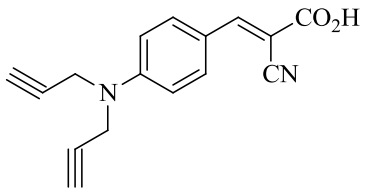
(E)-2-cyano-3-(4-(dihexylamino)phenyl)acrylic acid (16)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 3.39 (t, J = 7.5 Hz, 4H), 1.65 (br m, 4H), 1.36 (br m, 12H), 0.93 (t, J = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 155.8, 152.7, 135.2, 118.8, 117.6, 111.7, 91.8, 51.5, 31.8, 27.4, 26.9, 22.8, 14.2. Anal. Calcd for $C_{22}H_{32}N_2O_2$ (356.51): C 74.12, H 9.05, N 7.86. Found: C 74.18, H 9.99, N 7.74



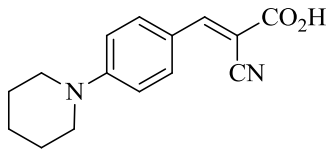
(E)-2-cyano-3-(4-(diallylamino)phenyl)acrylic acid (17)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.90-5.84 (m, 2H), 5.19-5.14 (m, 4H), 4.08 (d, J = 3.0 Hz, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.4, 154.4, 152.9, 134.1, 133.6, 119.5, 118.5, 117.1, 112.7, 94.6, 53.0. Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268.32): C 71.62, H 6.01, N 10.44. Found: C 70.98, H 6.66, N 11.36



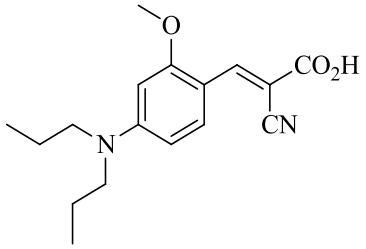
(E)-2-cyano-3-(4-(di(prop-2-yn-1-yl)amino)phenyl)acrylic acid (18)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 4.21 (d, J = 2.0 Hz, 4H), 2.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$: DMSO-D_6(1:1): δ 165.5, 164.9, 151.3, 133.7, 121.9, 117.4, 113.8, 97.0, 78.1, 73.4, 40.2. Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.28): C 72.72, H 4.58, N 12.11. Found: C 70.62, H 4.70, N 10.28



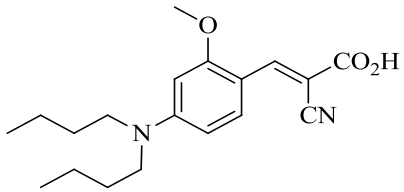
(E)-2-cyano-3-(4-(piperidin-1-yl)phenyl)acrylic acid (22)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.91 (d, J = 9.0 Hz, 2H), 9.02 (d, J = 9.0Hz, 2H), 3.47 (t, J = 5.0 Hz, 4H), 1.62-1.61(m, 2H), 1.57.1.56 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.4, 154.2, 154.2, 134.3, 119.8, 118.4, 113.8, 48.1, 25.6, 24.6.



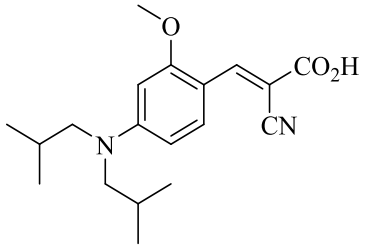
(E)-2-cyano-3-(4-(dipropylamino)-2-methoxyphenyl)acrylic acid (22)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 6.52 (d, J = 9.5 Hz, 1H), 6.19 (s, 1H), 3.90 (s, 3H), 3.41 (t, J = 7.0 Hz, 4H), 1.61 (m, 4H), 0.93 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 162.4, 154.9, 146.9, 130.6, 119.3, 108.3, 106.2, 93.8, 91.3, 56.4, 52.6, 20.9, 11.8. Anal. Calcd for $C_{17}H_{22}N_2O_3$ (302.37): C 67.53, H 7.33, N 9.26. Found: C 67.52, H 7.51, N 9.28; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 325.15 , found 325.15



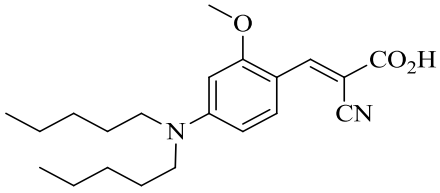
(E)-2-cyano-3-(4-(dibutylamino)-2-methoxyphenyl)acrylic acid (23)

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.0 (br, s, 1H), 8.42 (s, 1H), 8.21 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 9.5 Hz, 1H), 6.17 (s, 1H), 3.89 (s, 3H), 3.44 (t, J = 7.5 Hz, 4H), 1.55 (m, 4H), 1.35 (m, 4H), 0.94 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 162.3, 154.7, 146.8, 130.6, 119.3, 108.2, 106.2, 93.8, 91.3, 56.4, 50.7, 29.8, 20.3, 14.5. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.43): C 69.06, H 7.93, N 8.48. Found: C 68.83, H 7.90, N 8.46; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 353.18 , found 353.18



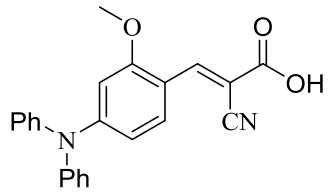
(E)-2-cyano-3-(4-(diisobutylamino)-2-methoxyphenyl)acrylic acid (24)

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.05 (br s, 1H), 8.43 (s, 1H), 8.20 (d, J = 9.5 Hz, 1H), 6.56 (d, J = 9.5 Hz, 1H), 6.23 (s, 1H), 3.89 (s, 3H), 3.35 (d, J = 7.0 Hz, 4H), 2.09-2.03 (m, 2H), 0.91 (d, J = 6.5 Hz, 12H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.1, 162.1, 155.0, 146.9, 130.4, 119.2, 108.3, 106.9, 94.7, 91.6, 59.5, 56.4, 27.2, 20.6. Anal. Calcd for $C_{19}H_{26}N_2O_3$ (330.43): C 69.06, H 7.93, N 8.48. Found: C 68.93, H 7.81, N 8.58; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 353.18 , found 353.18



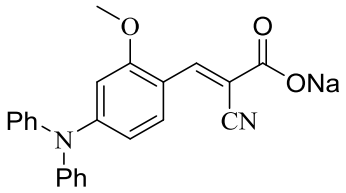
(E)-2-cyano-3-(4-(dipentylamino)-2-methoxyphenyl)acrylic acid (25)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.22 (d, J = 9.5 Hz, 1H), 6.50 (d, J = 9.5 Hz, 1H), 6.17 (s, 1H), 3.90 (s, 3H), 3.43 (t, J = 7.5 Hz, 4H), 1.58 (m, 4H), 1.37-1.30 (m, 8H), 0.91 (t, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 162.4, 154.7, 146.9, 130.6, 119.3, 108.2, 106.2, 93.8, 91.4, 56.4, 50.9, 29.2, 27.3, 22.7, 14.7. Anal. Calcd for $C_{21}H_{30}N_2O_3$ (358.48): C 70.36, H 8.44, N 7.81. Found: C 70.36, H 8.50, N 7.81; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 381.22 , found 381.21



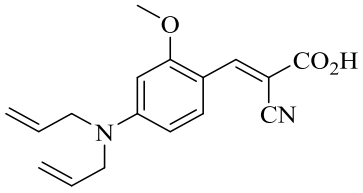
(E)-2-cyano-3-(4-(diphenylamino)-2-methoxyphenyl)acrylic acid (26)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.43 (m, 5H), 7.25 (m, 5H), 6.43 (d, J = 9.5 Hz, 1H), 6.41 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.2, 161.2, 154.6, 147.1, 145.7, 130.7, 130.3, 127.4, 126.6, 118.1, 112.6, 111.7, 100.9, 97.1, 56.3. Anal. Calcd for $C_{23}H_{18}N_2O_3$ (370.41): C 67.97, H 5.46, N 6.89 Found: C 66.0, H 5.39, N 6.28; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 393.12 , found 393.12



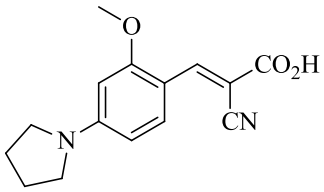
sodium (E)-2-cyano-3-(4-(diphenylamino)-2-methoxyphenyl)acrylate (27)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.95 (d, J = 14.0 Hz, 1H), 7.36 (m, 4H), 7.14 (m, 6H), 6.45 (m, 2H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 159.5, 151.8, 146.7, 141.8, 130.5, 129.4, 126.3, 125.4, 120.8, 115.6, 113.2, 110.4, 103.6, 56.1. Anal. Calcd for $C_{23}H_{17}N_2NaO_3$ (392.39): C 64.48, H 4.94, N 6.54 Found: C 64.08, H 5.06, N 6.46; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 415.10, found 415.10



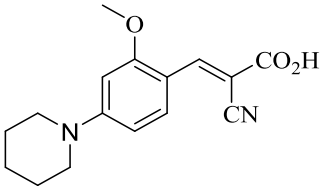
(E)-2-cyano-3-(4-(diallylamino)-2-methoxyphenyl)acrylic acid (28)

^{1}H NMR (500 MHz, CD_3OD): δ 8.59 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 6.44 (d, J = 9.5 Hz, 1H), 6.25 (s, 1H), 5.96-5.89 (m, 2H), 5.25-5.19 (m, 4H), 4.11-4.10 (m, 4H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 166.5, 162.3, 155.4, 147.9, 132.8, 130.4, 118.2, 115.9, 109.4, 105.6, 93.9, 55.0, 52.9. Anal. Calcd for $C_{17}H_{18}N_2O_3$ (298.34): C 68.44, H 6.08, N 9.39. Found: C 68.14, H 6.16, N 9.30



(E)-2-cyano-3-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)acrylic acid (29)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 6.35 (d, J = 7.5 Hz, 1H), 6.09 (s, 1H), 3.90 (s, 3H), 3.41 (m, 4H), 1.99 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 162.2, 153.8, 147.1, 130.4, 119.4, 108.4, 106.6, 94.2, 90.8, 56.4, 48.3, 25.5. Anal. Calcd for $C_{15}H_{16}N_2O_3$ (272.30): C 66.16, H 5.92, N 10.29. Found: C 65.21, H 5.95, N 9.92; HRMS (ESI) m/z: calc'd for $C_{17}H_{22}N_2O_3$ $[M+Na]^+$: 295.11, found 295.10



(E)-2-cyano-3-(2-methoxy-4-(piperidin-1-yl)phenyl)acrylic acid (30)

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.40 (s, 1H), 8.17 (d, *J* = 9 Hz, 1H), 6.68 (d, *J* = 9.5 Hz, 1H), 6.43 (s, 1H), 3.87 (s, 3H), 3.50 (m, 4H), 1.60 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.7, 162.2, 156.2, 146.7, 130.3, 118.8, 109.0, 107.2, 95.5, 56.4, 48.1, 25.6, 24.4 Anal. Calcd for $C_{16}H_{18}N_2O_3$ (286.33): C 67.12, H 6.34, N 9.78 Found: C 66.43, H 6.22, N 9.80

NMR Spectra

10
9
8
7
6
5
4
3
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3.91
5.89

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CN
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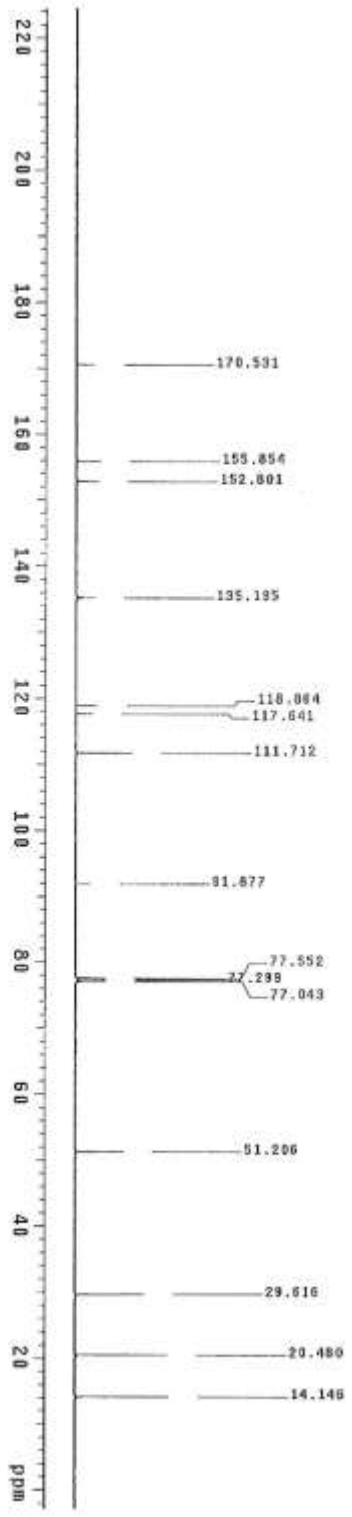
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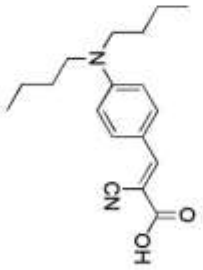
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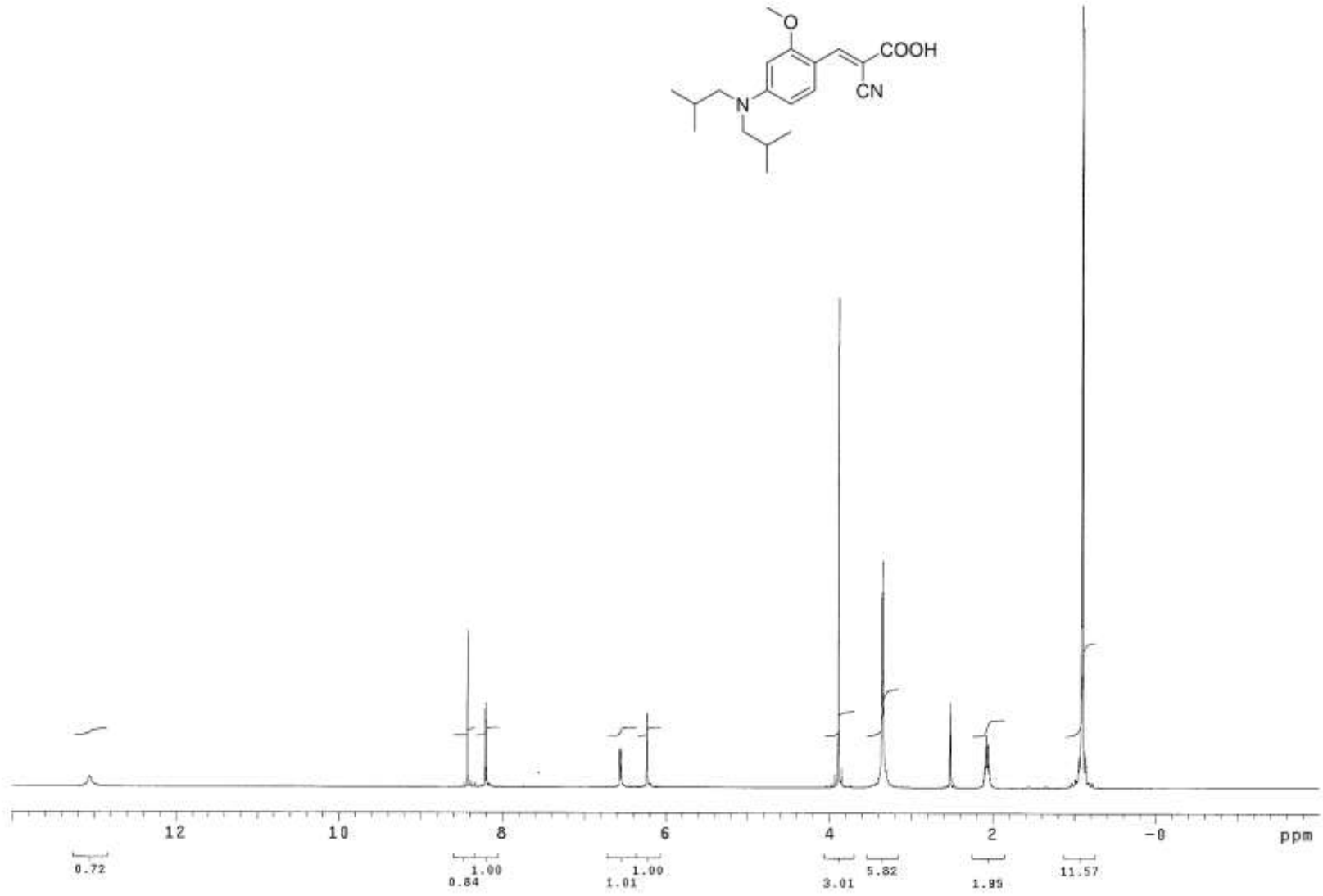
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CN
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2
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1.00
1.01
3.01
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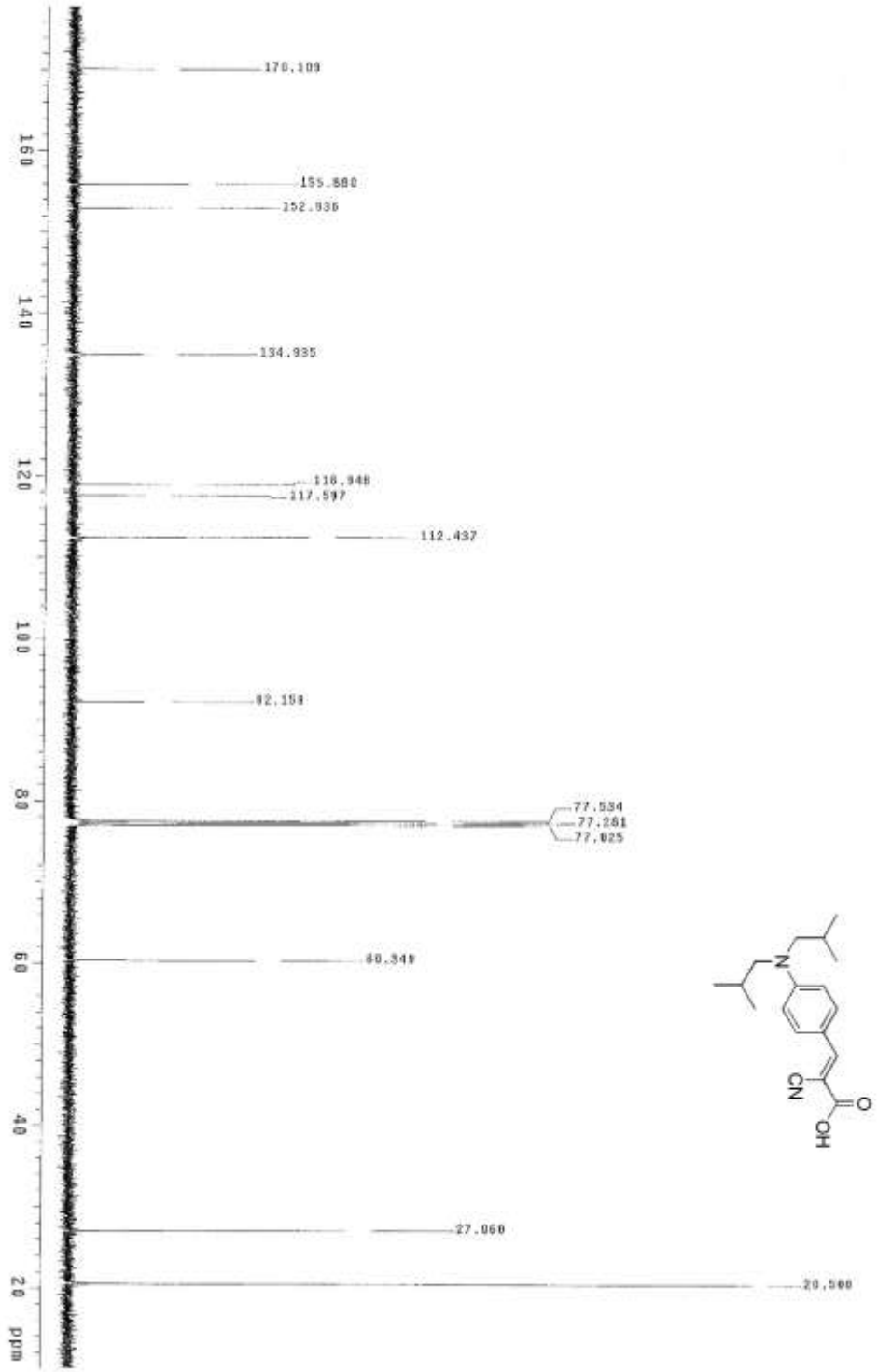
11.57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20.500
160
140
120
100
80
60
40
20
ppm
N
CN
O
OH

1.02
2.00
2.03
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8.29
5.17
8
7
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3
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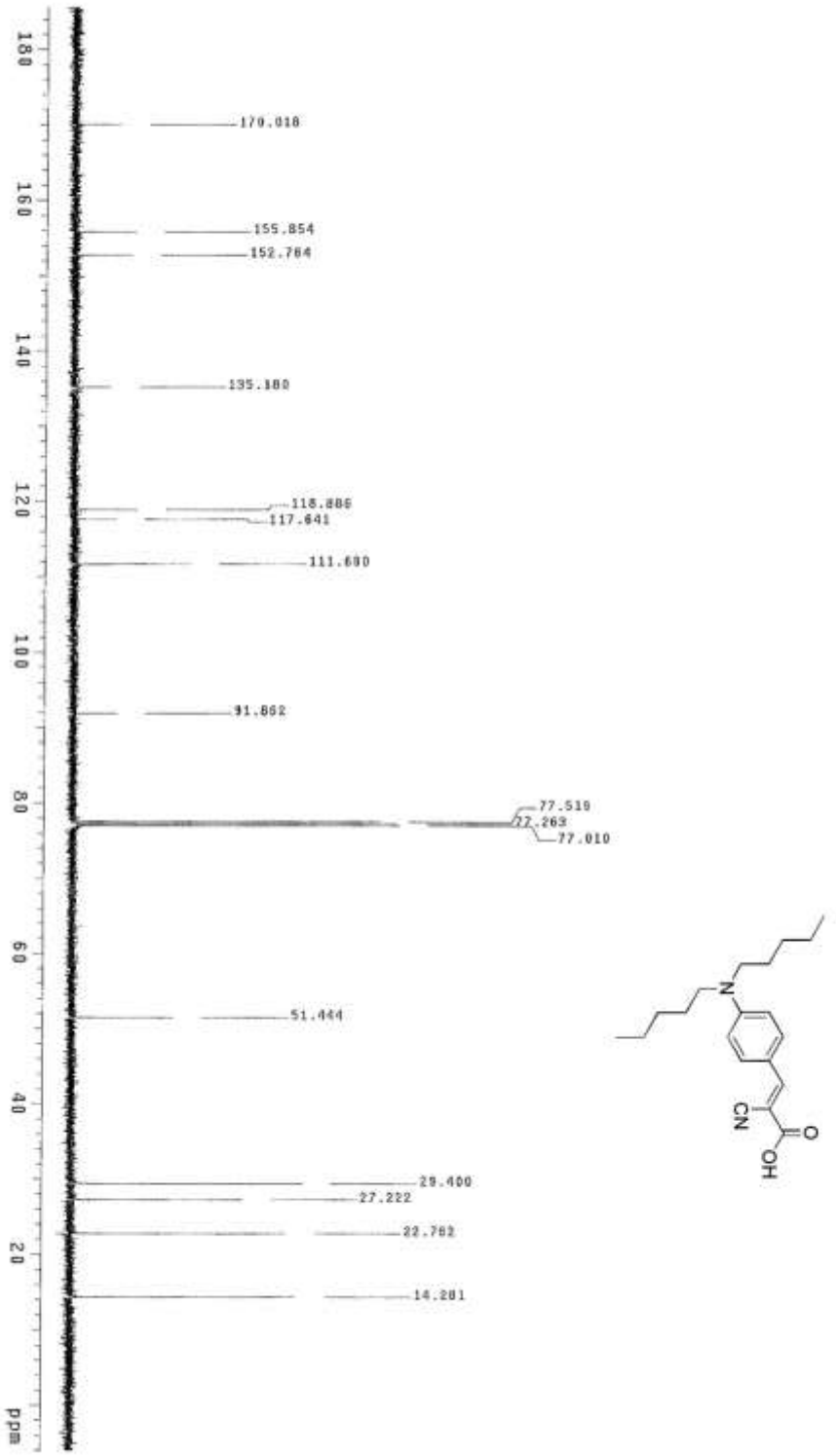
CN
O
OH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20
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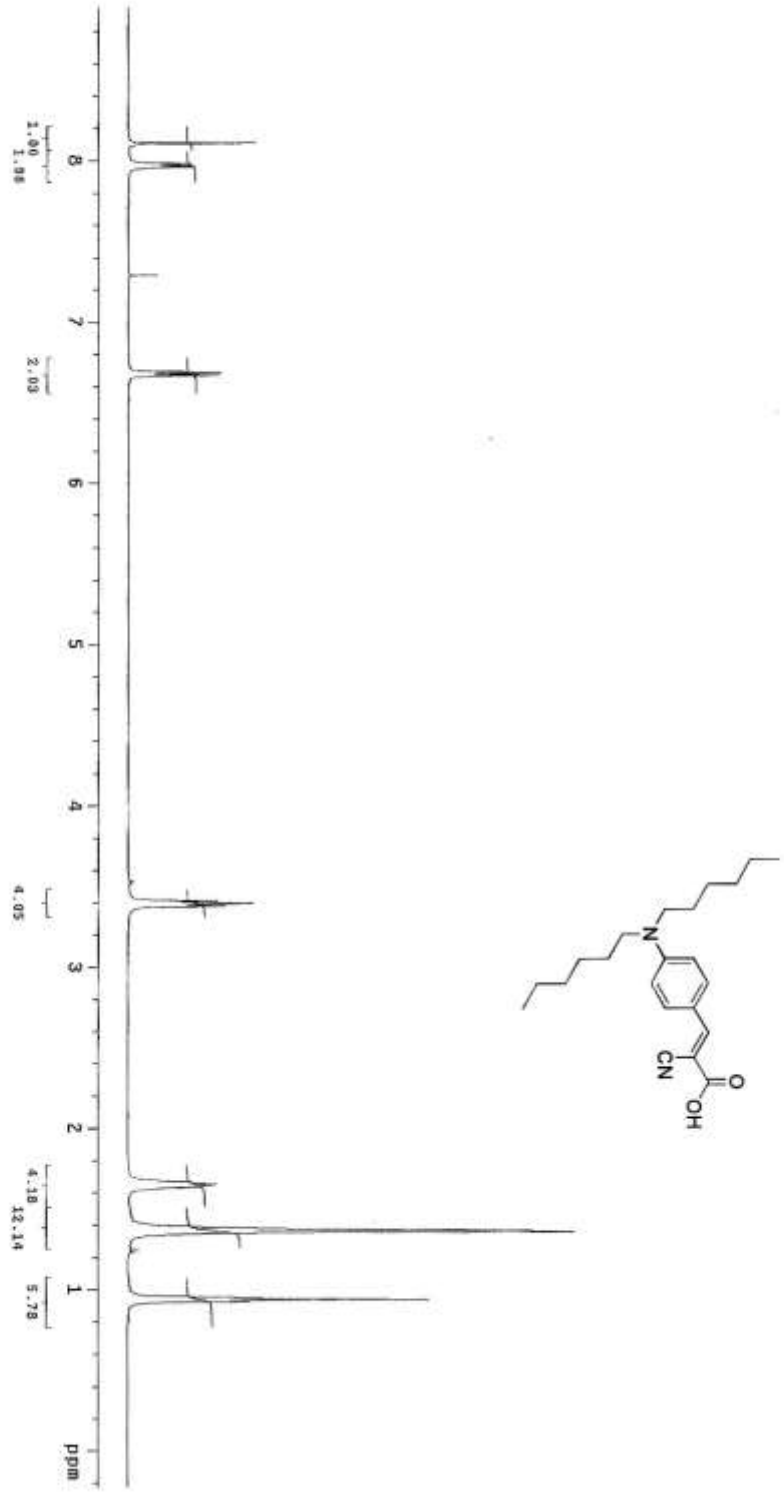
O
OH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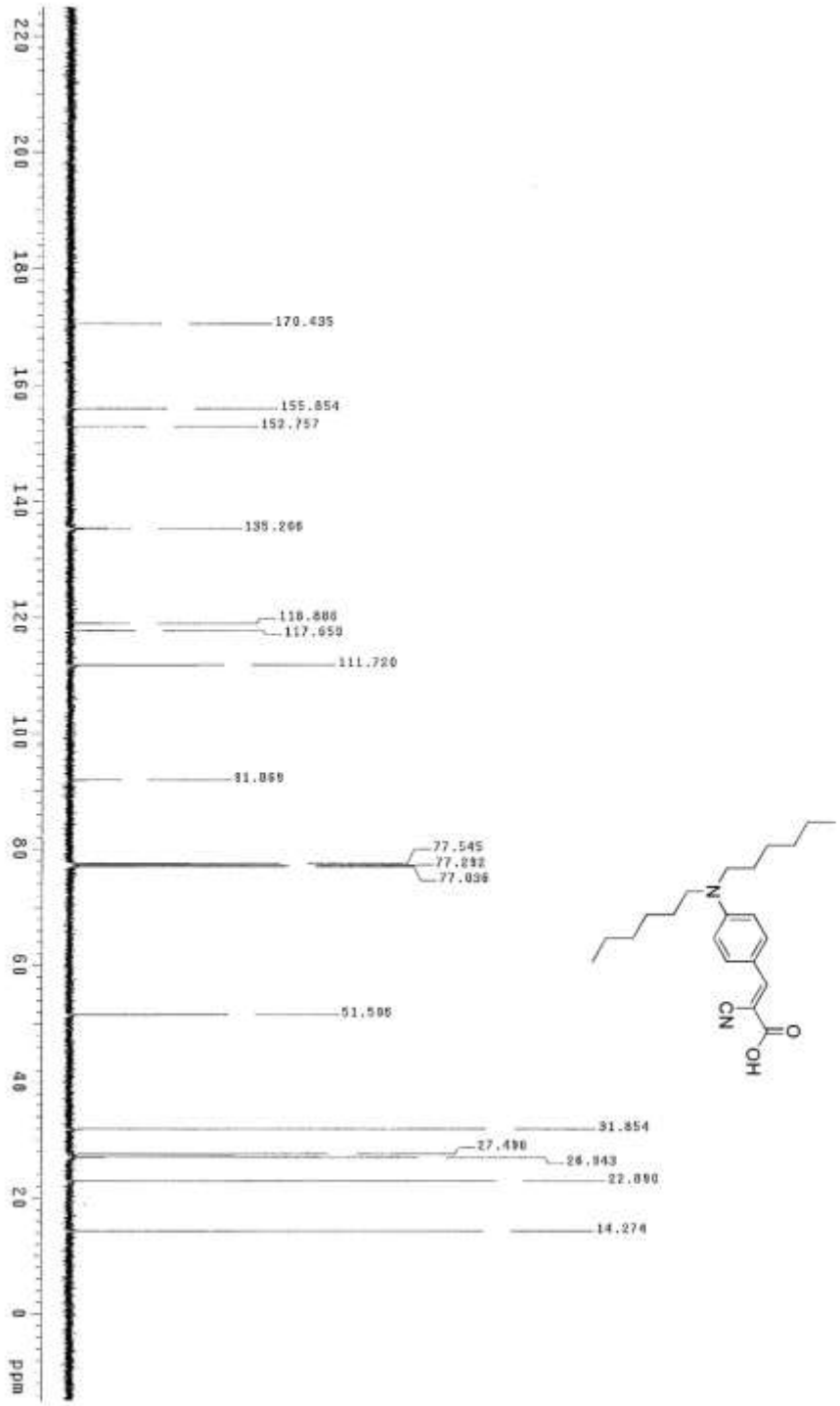
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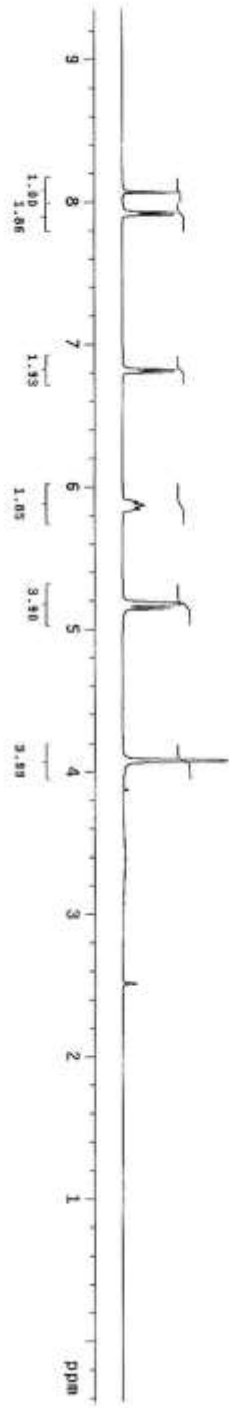
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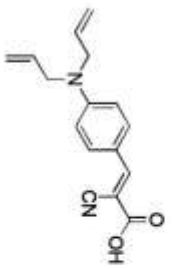
N
CN
O
OH

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140
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80
60
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0
ppm

N
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O
OH

9
8
7
6
5
4
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1.95
1.95

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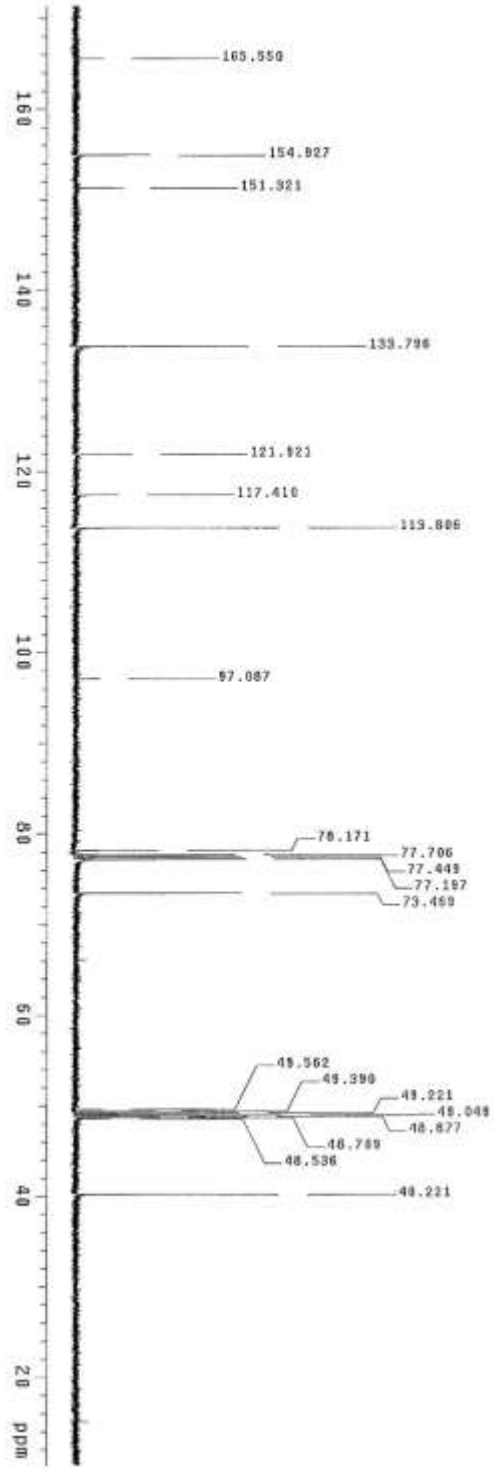
O
OH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49.562
49.390
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48.877
48.789
48.536
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140
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60
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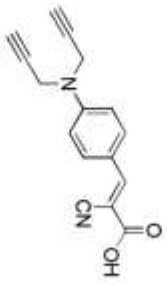
20
ppm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CN
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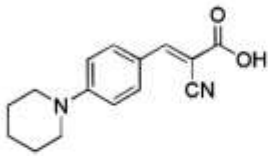
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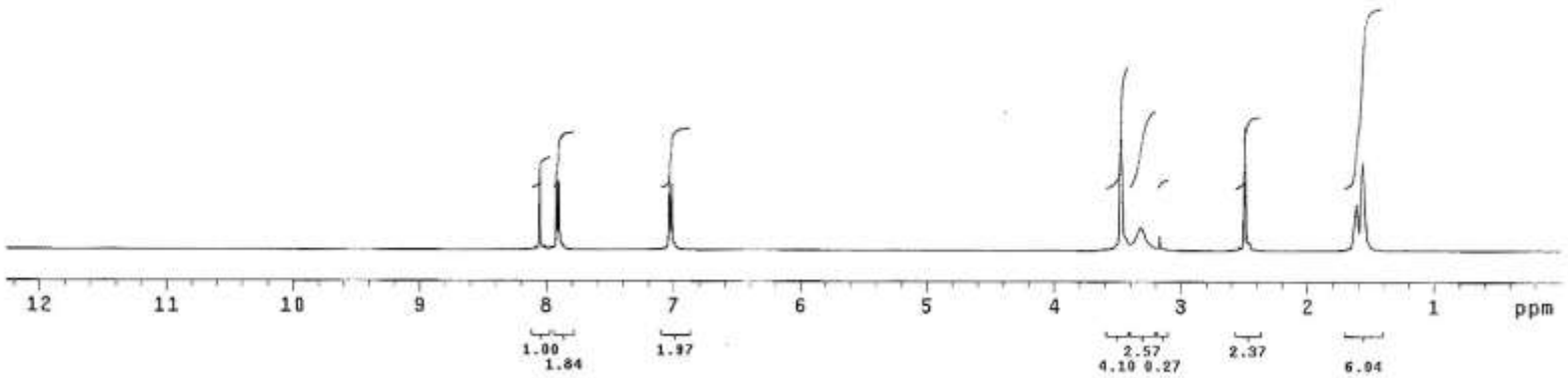
OH
CN
N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8
7
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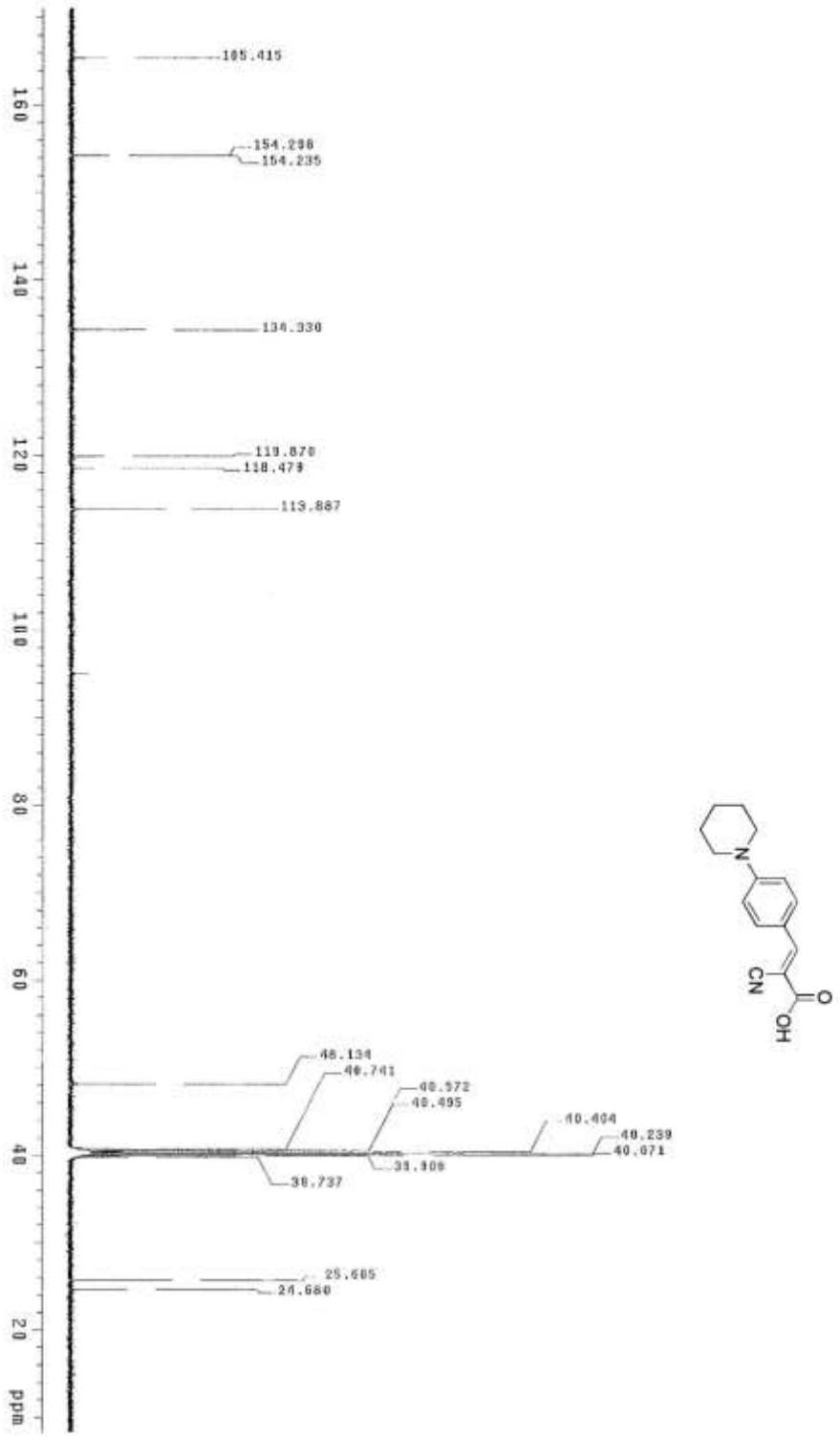
6.04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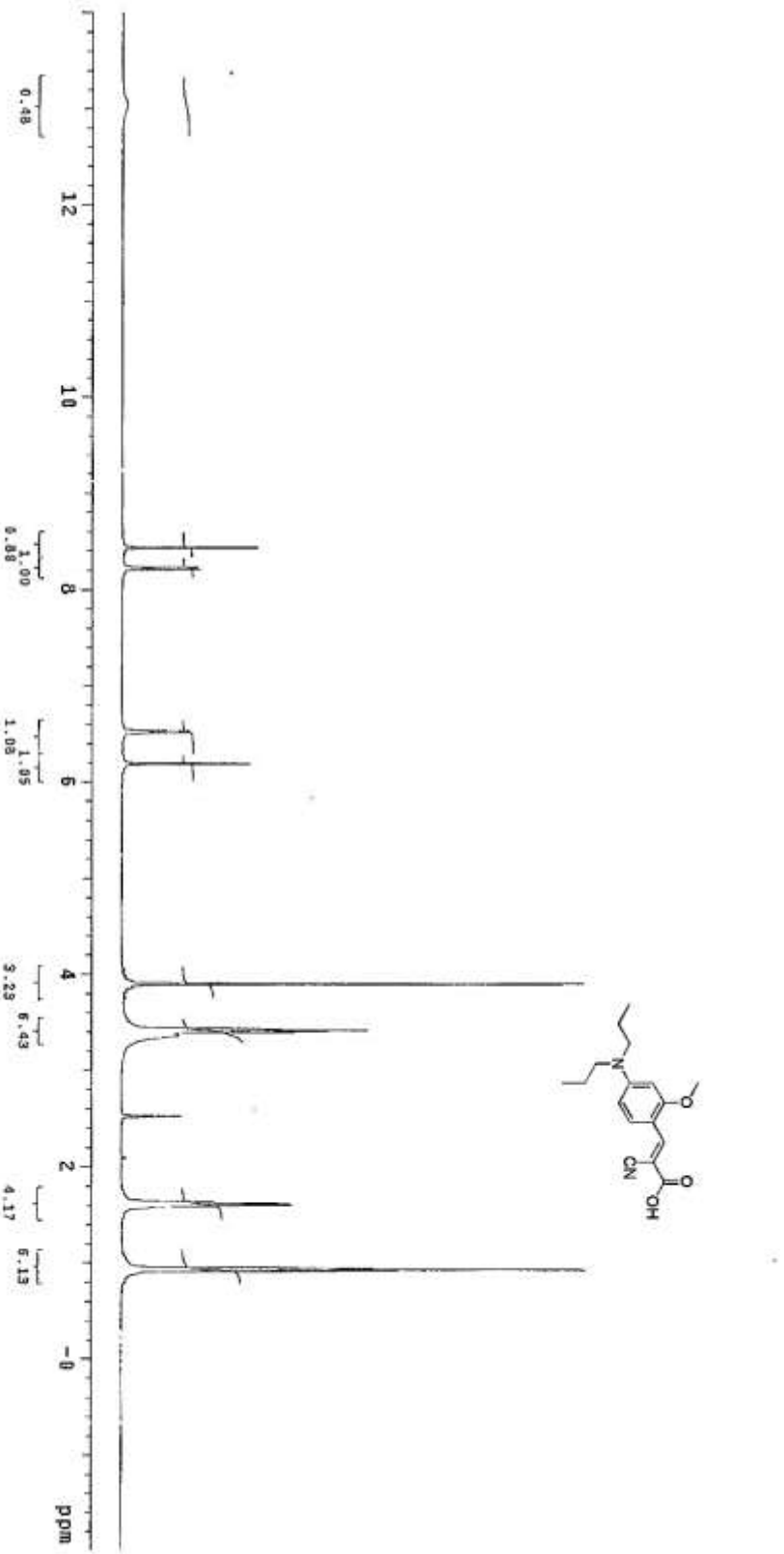
O
OH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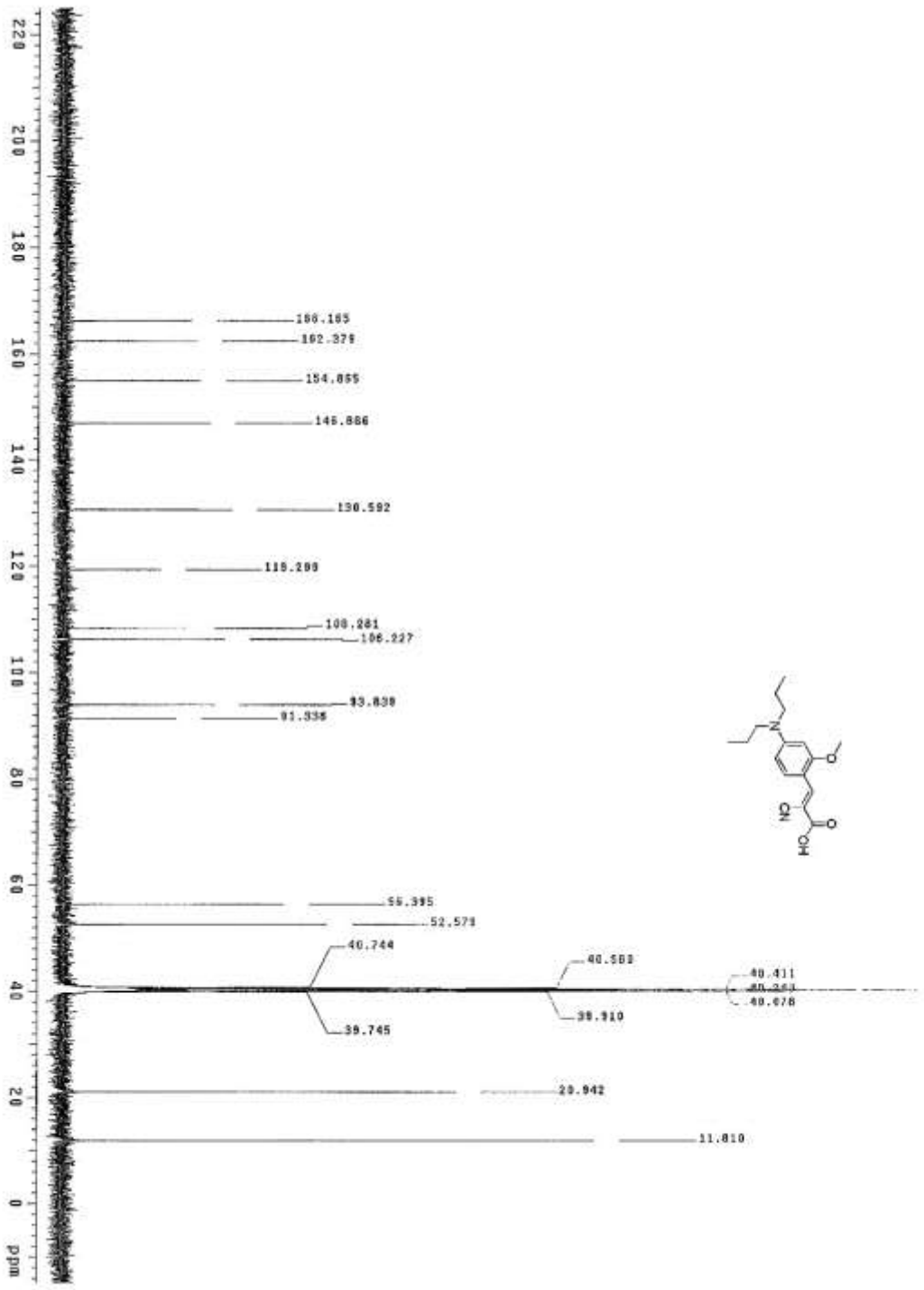
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40.411
40.678
39.910
39.745
29.942
11.810
N
O
OH
O

13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
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6.99
6.91

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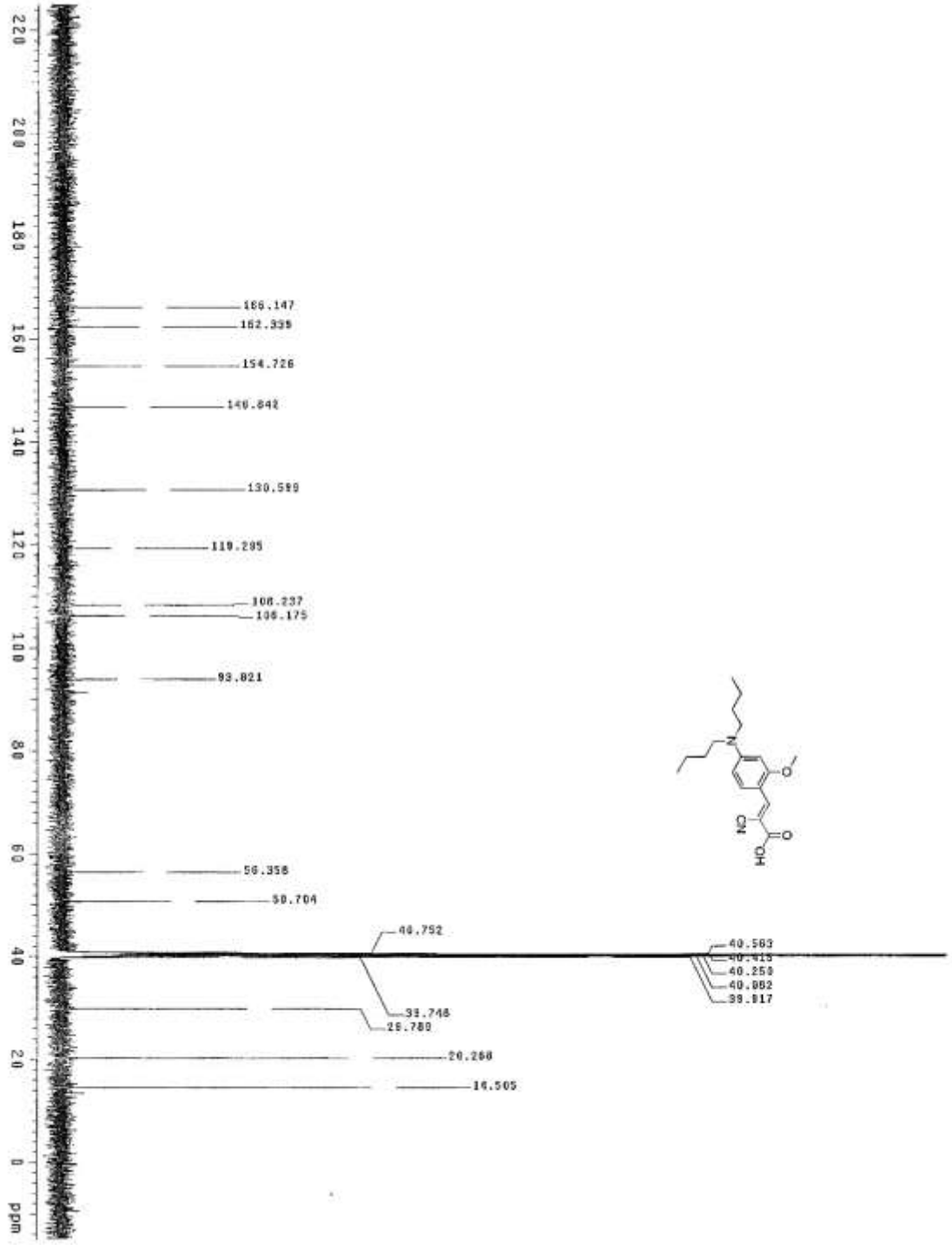
CN
O
OH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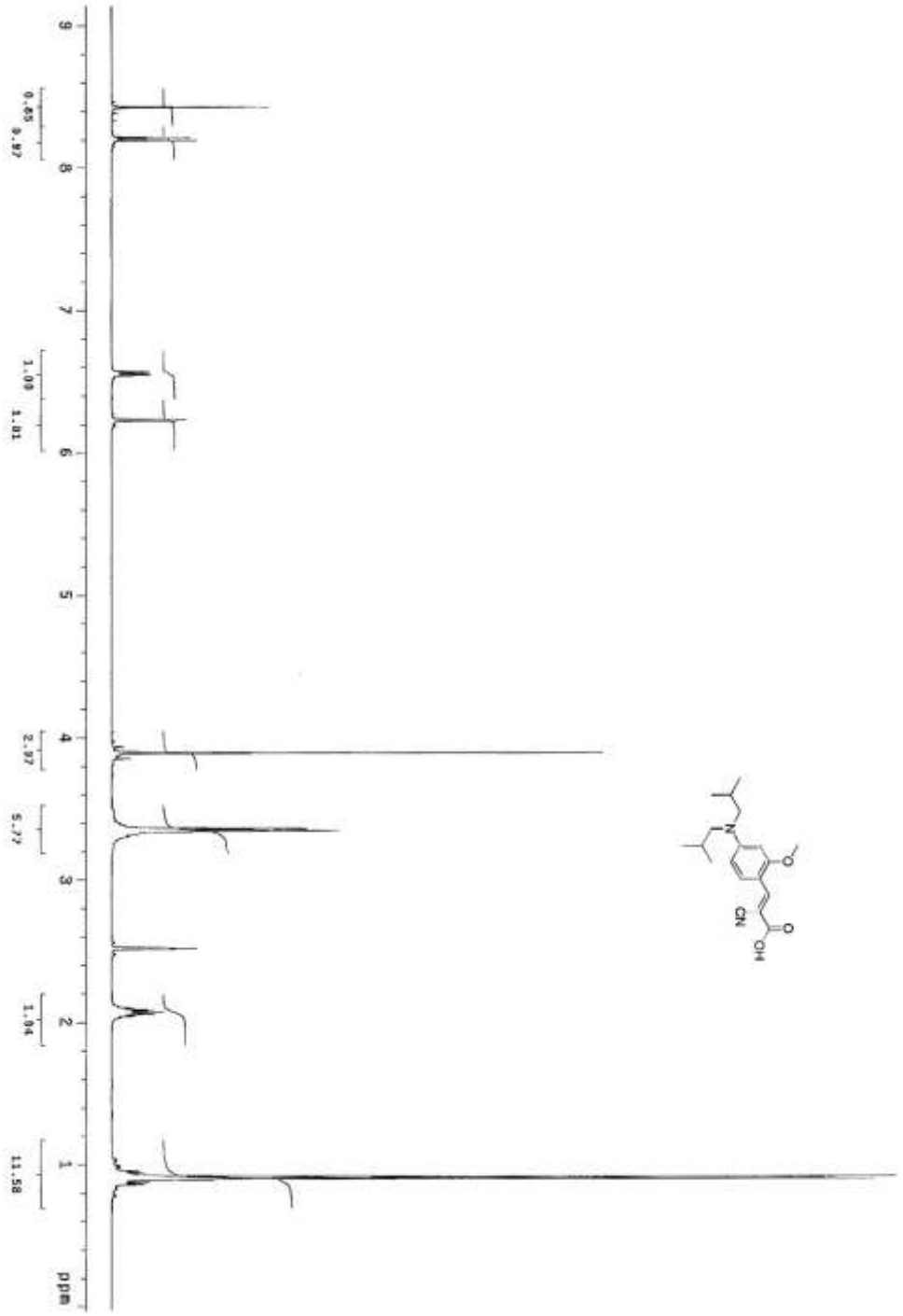
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7
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4
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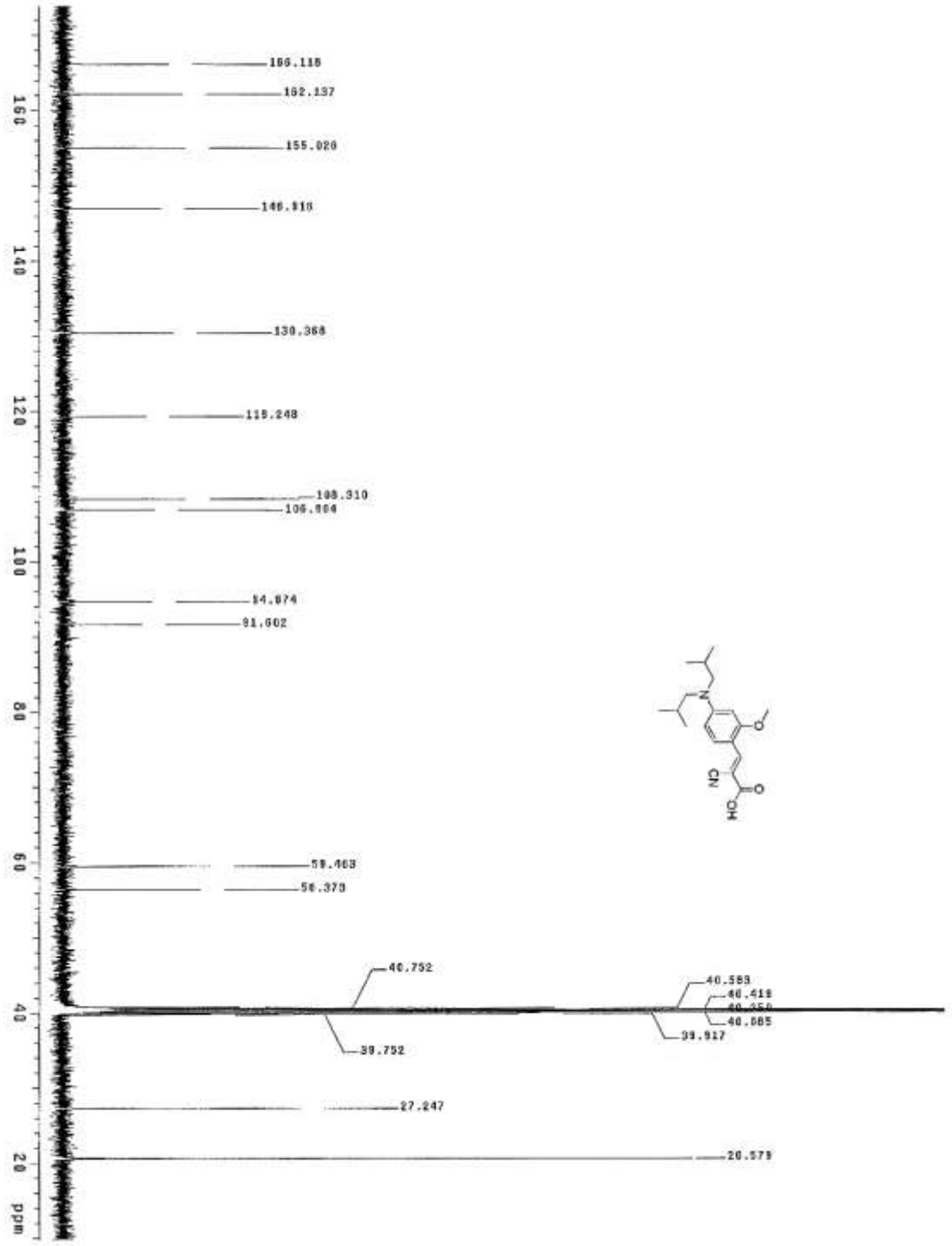
N
O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120
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80
60
40
20
ppm
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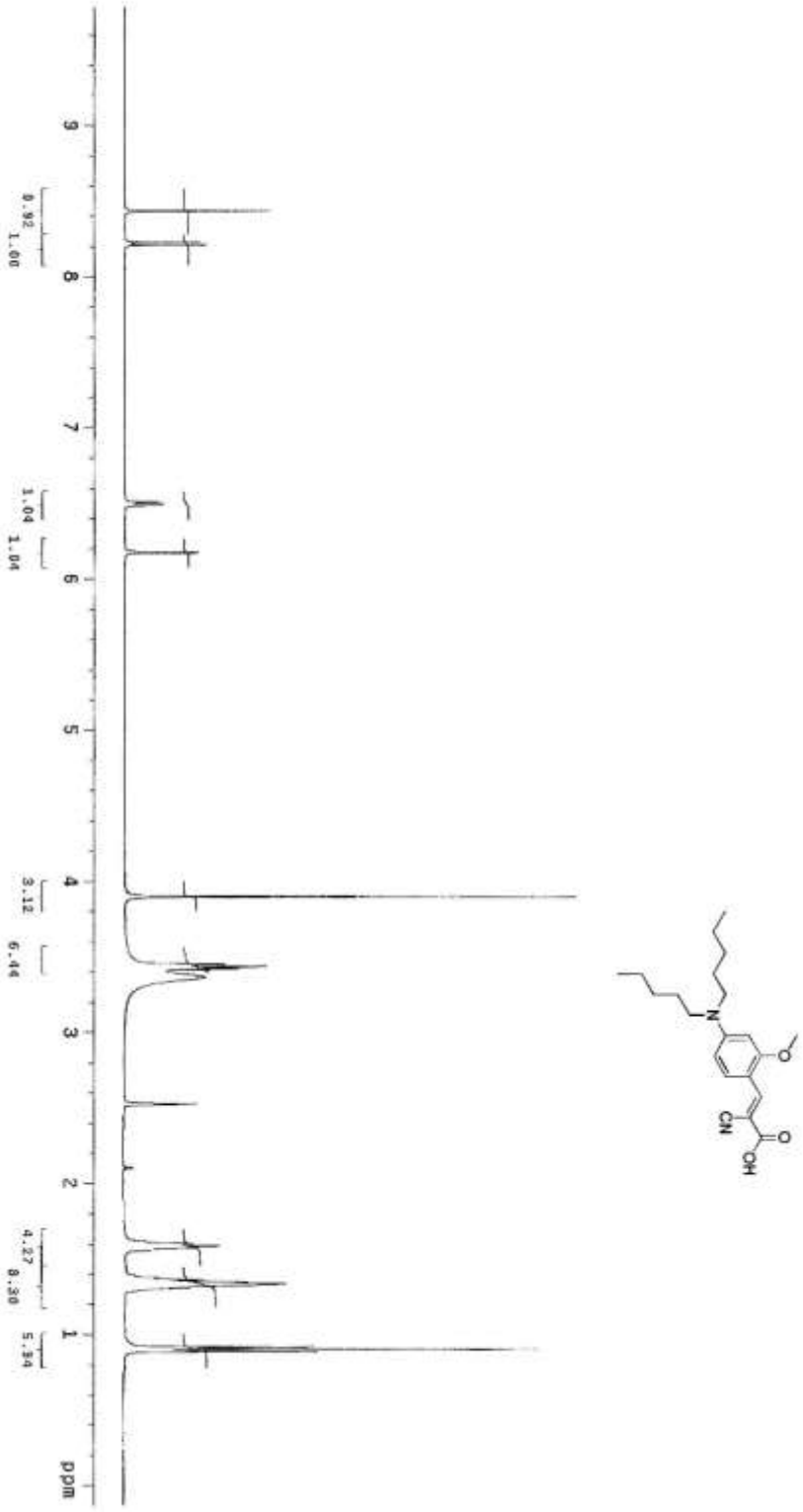
O
CN
OH


9
8
7
6
5
4
3
2
1
ppm
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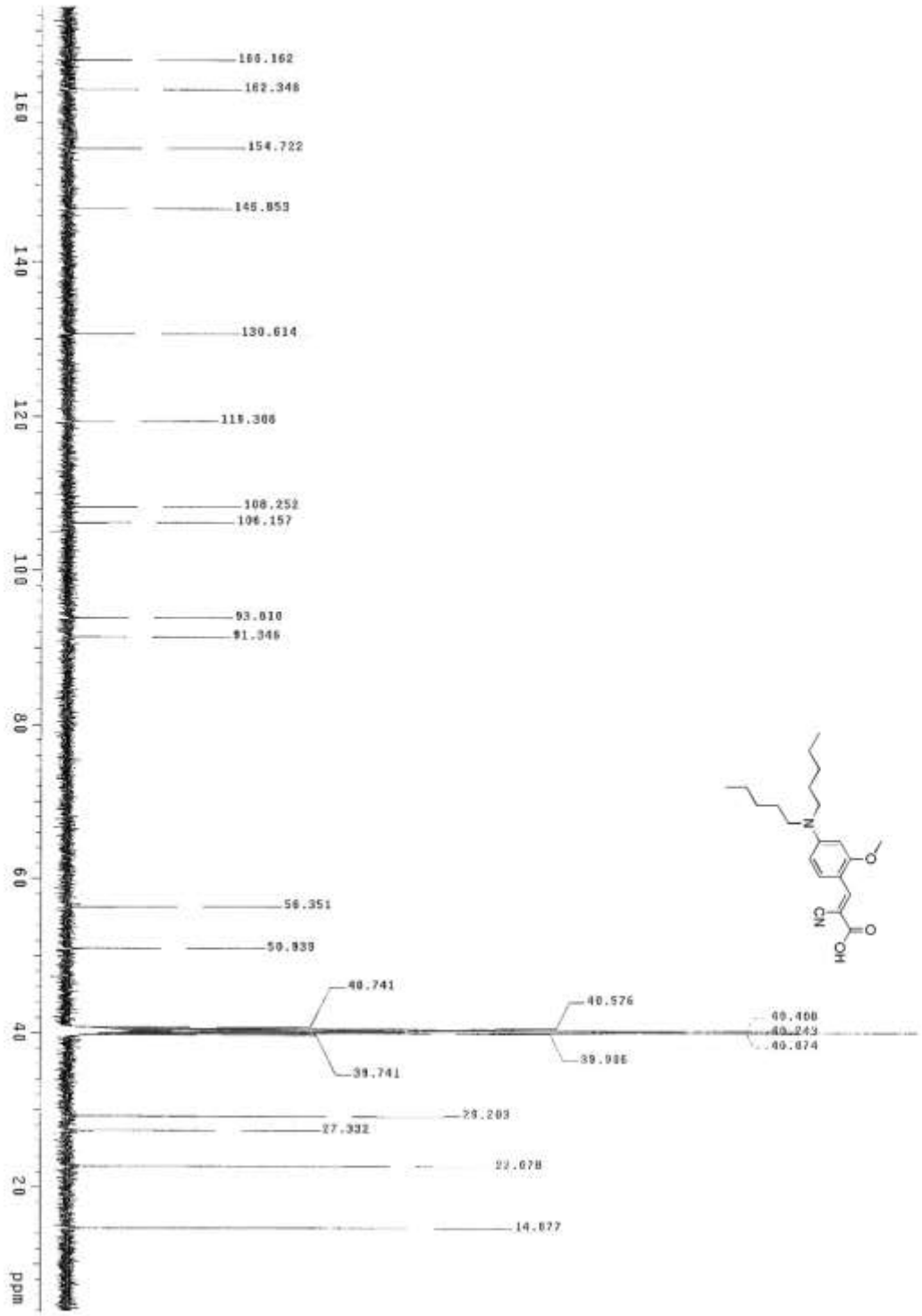
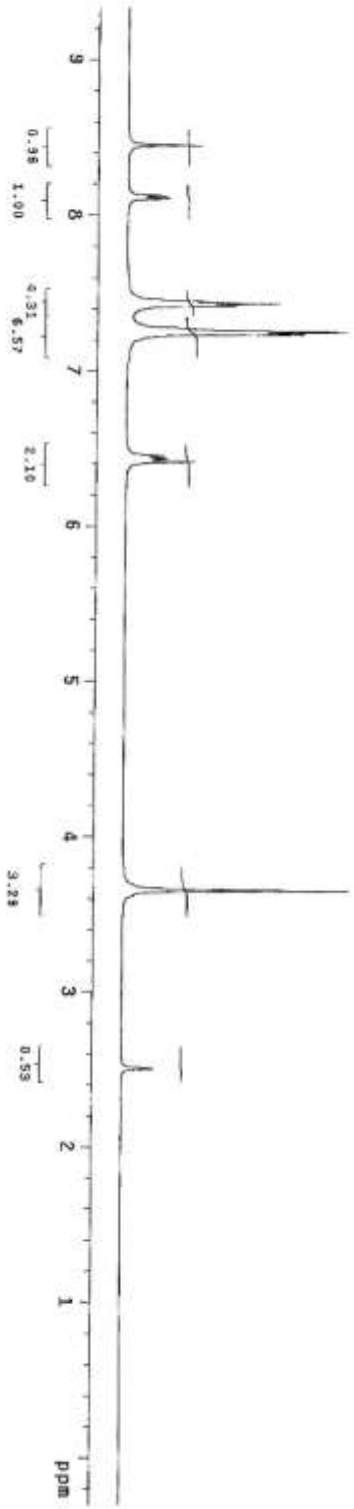
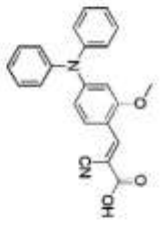
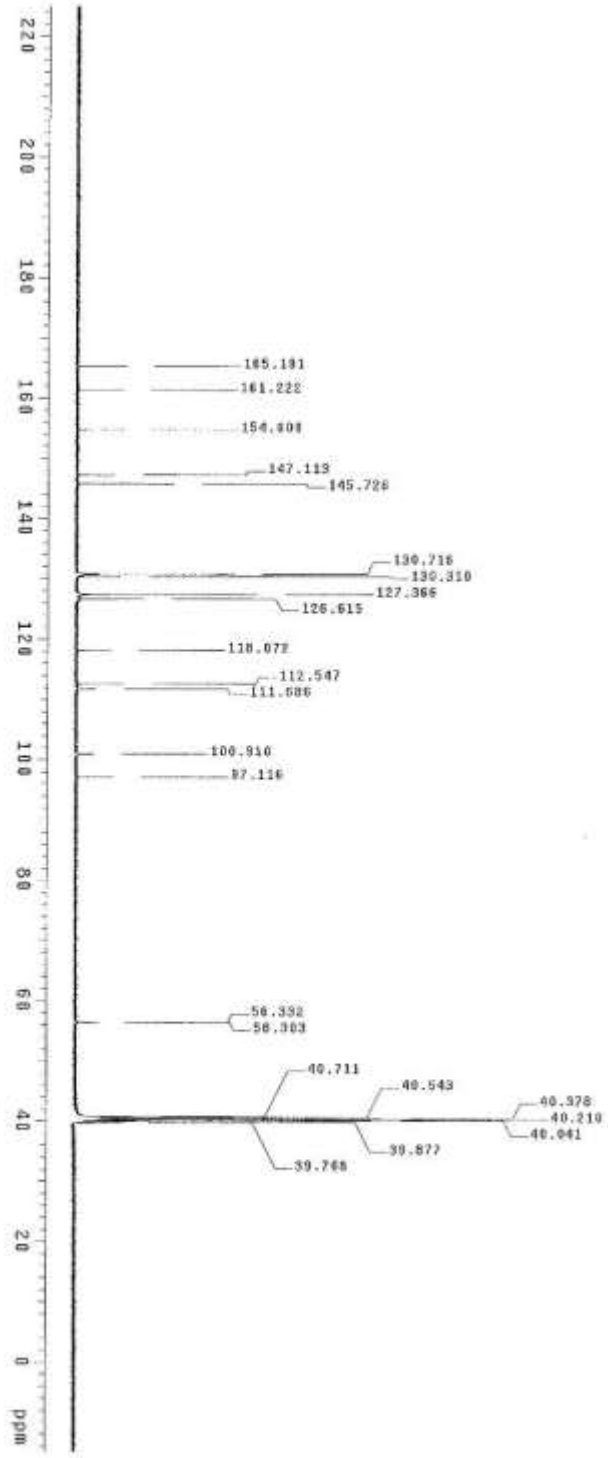
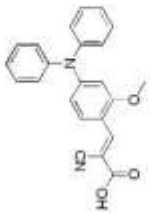
1.00
1.04
1.04
3.12
6.44
4.27
8.30
5.34
N
O
CN
O
OH

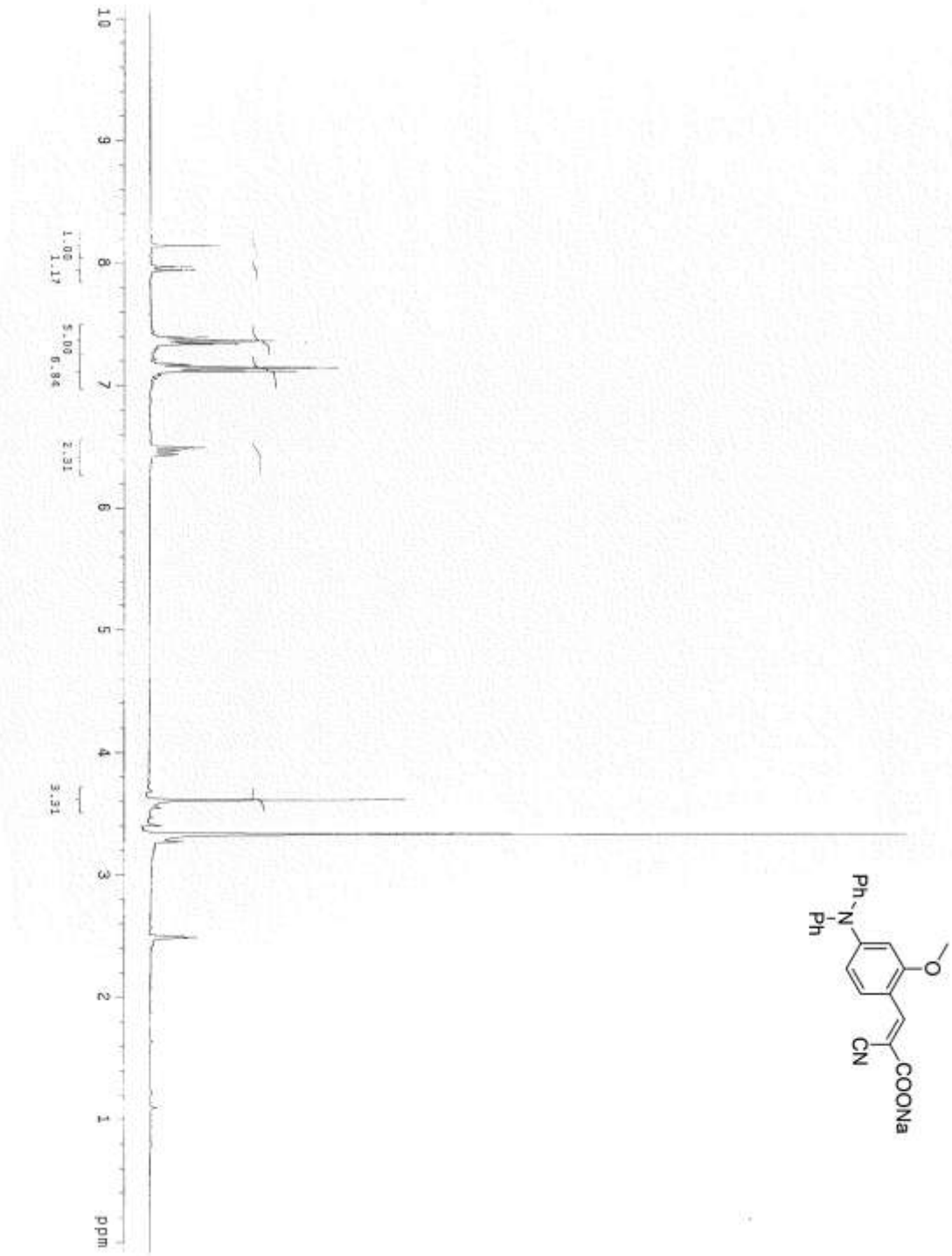

160.162
152.348
154.722
146.859
130.614
118.308
108.252
106.157
93.810
91.346
56.351
50.939
40.741
40.576
40.408
40.243
40.074
39.741
39.906
29.203
27.332
22.078
14.077
ppm
160
140
120
100
80
60
40
20
N
O
CN
O
OH

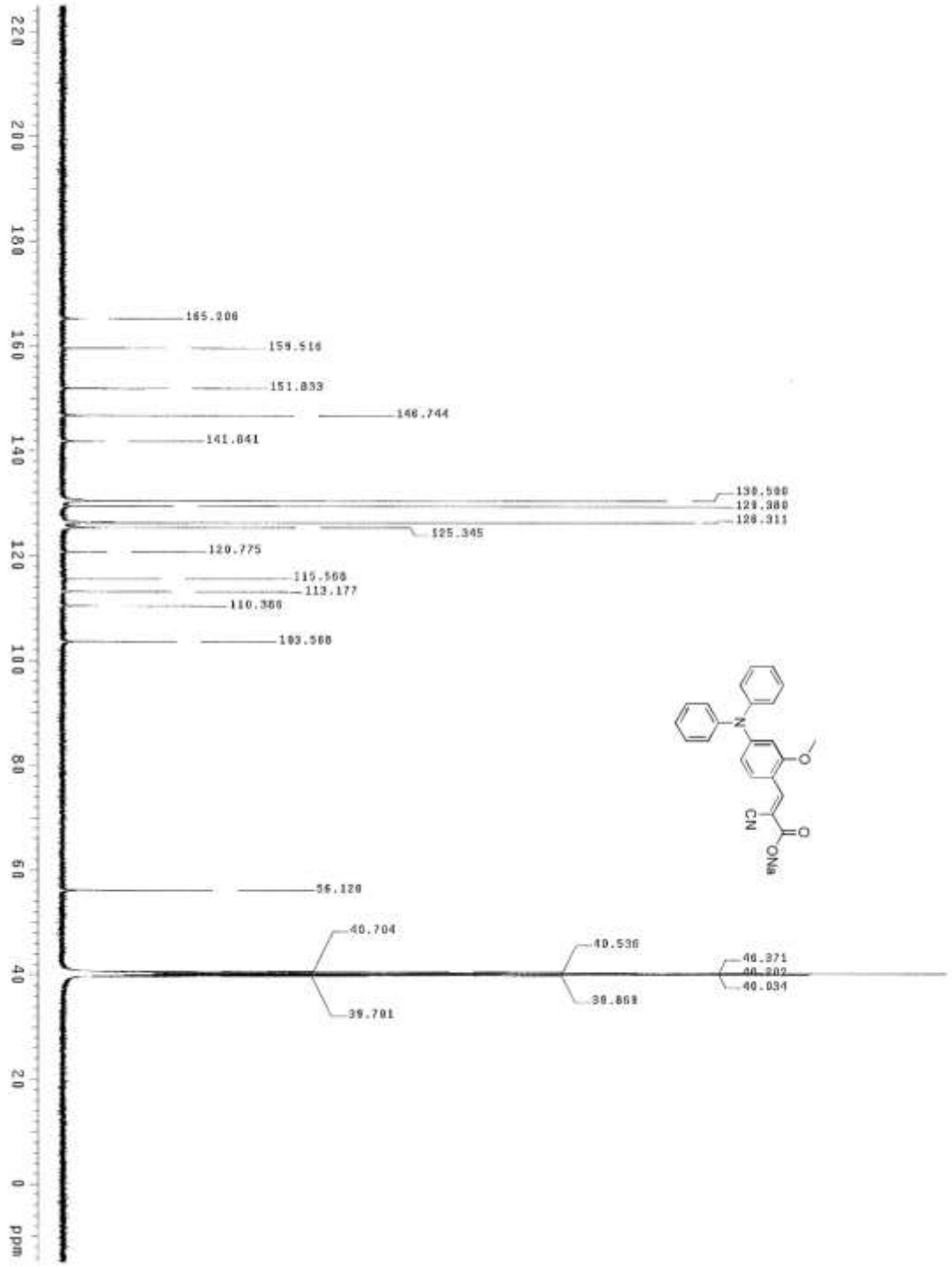

9
8
7
6
5
4
3
2
1
ppm
0.36
1.00
0.31
6.57
2.10
3.29
0.53


N
O
CN
O
OH


220
200
180
160
140
120
100
80
60
40
20
0
ppm
165.191
161.222
154.808
147.113
145.728
130.716
130.310
127.366
126.615
118.078
112.547
111.686
100.910
97.116
58.332
58.303
40.711
40.543
40.378
40.210
40.041
39.877
39.765

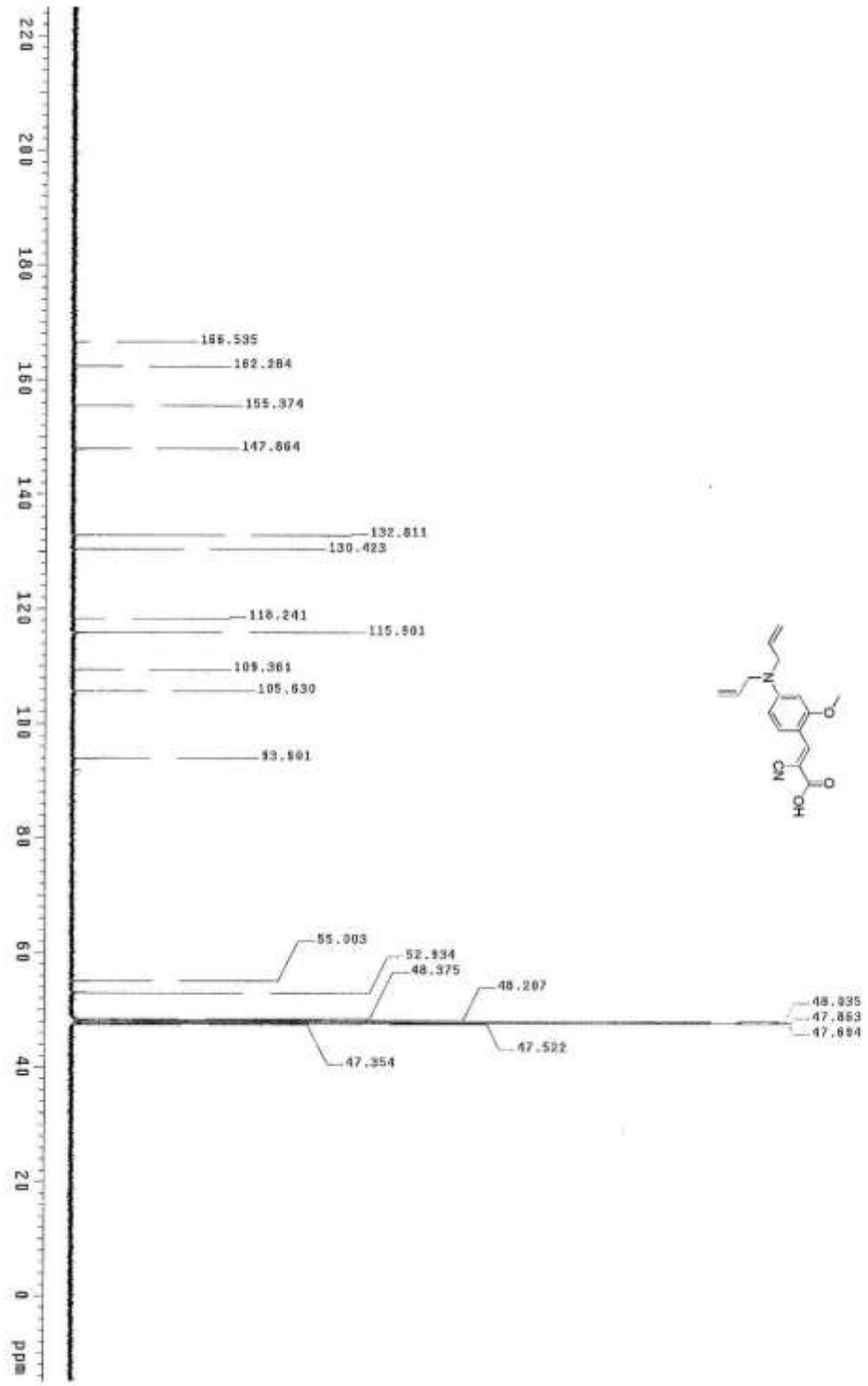


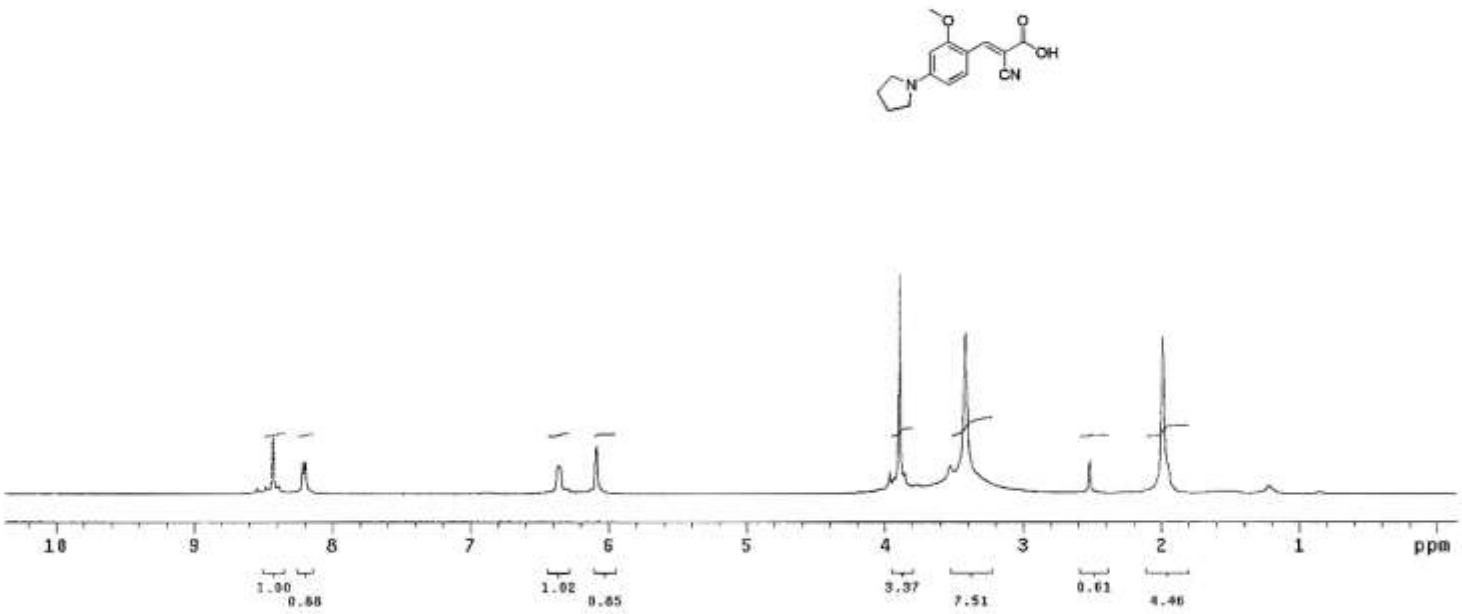

10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.17
5.00
6.84
2.31
3.31
Ph
N
Ph
O
CN
COONa

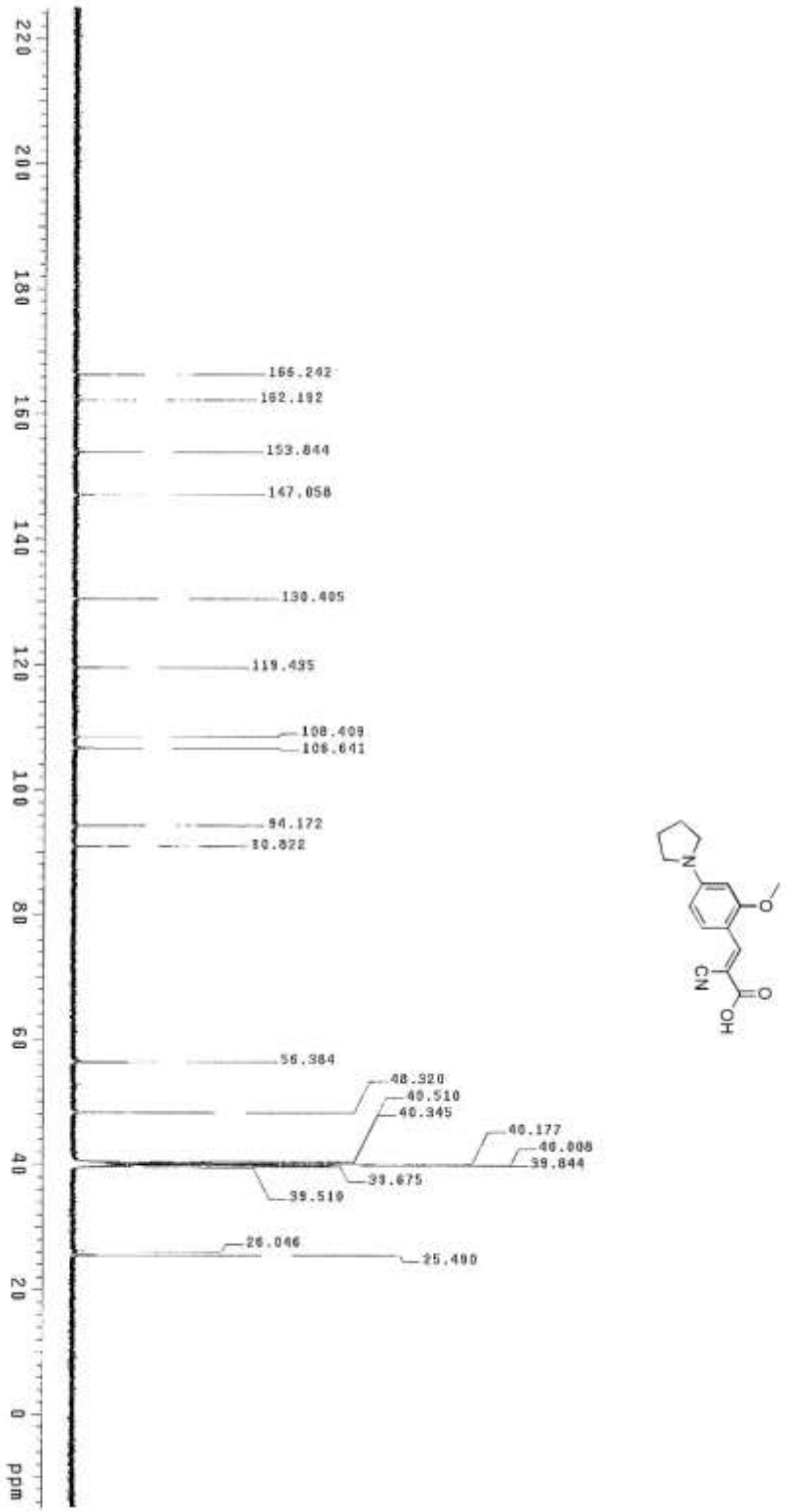

165.206
159.516
151.833
148.744
141.841
130.500
129.380
128.311
125.345
120.775
115.568
113.177
110.366
103.568
56.120
40.704
40.536
40.371
40.202
40.034
39.868
39.701
ppm
CN
O
ONa

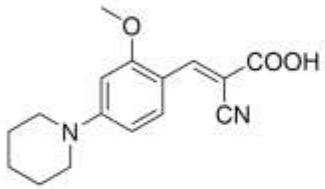
9
8
7
6
5
4
3
2
1
ppm
1.91
1.90
1.07
1.07
1.93
4.46
11.53
0.49
3.35
1.95

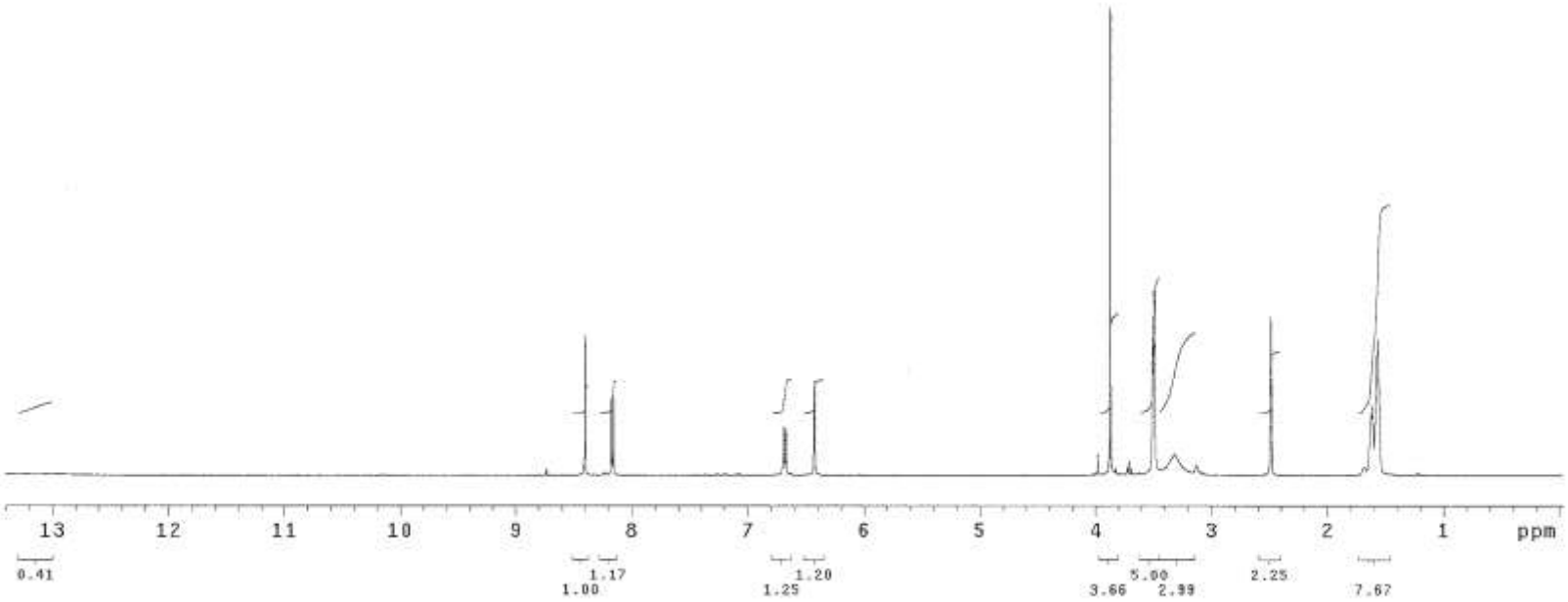
N
O
CN
O
OH

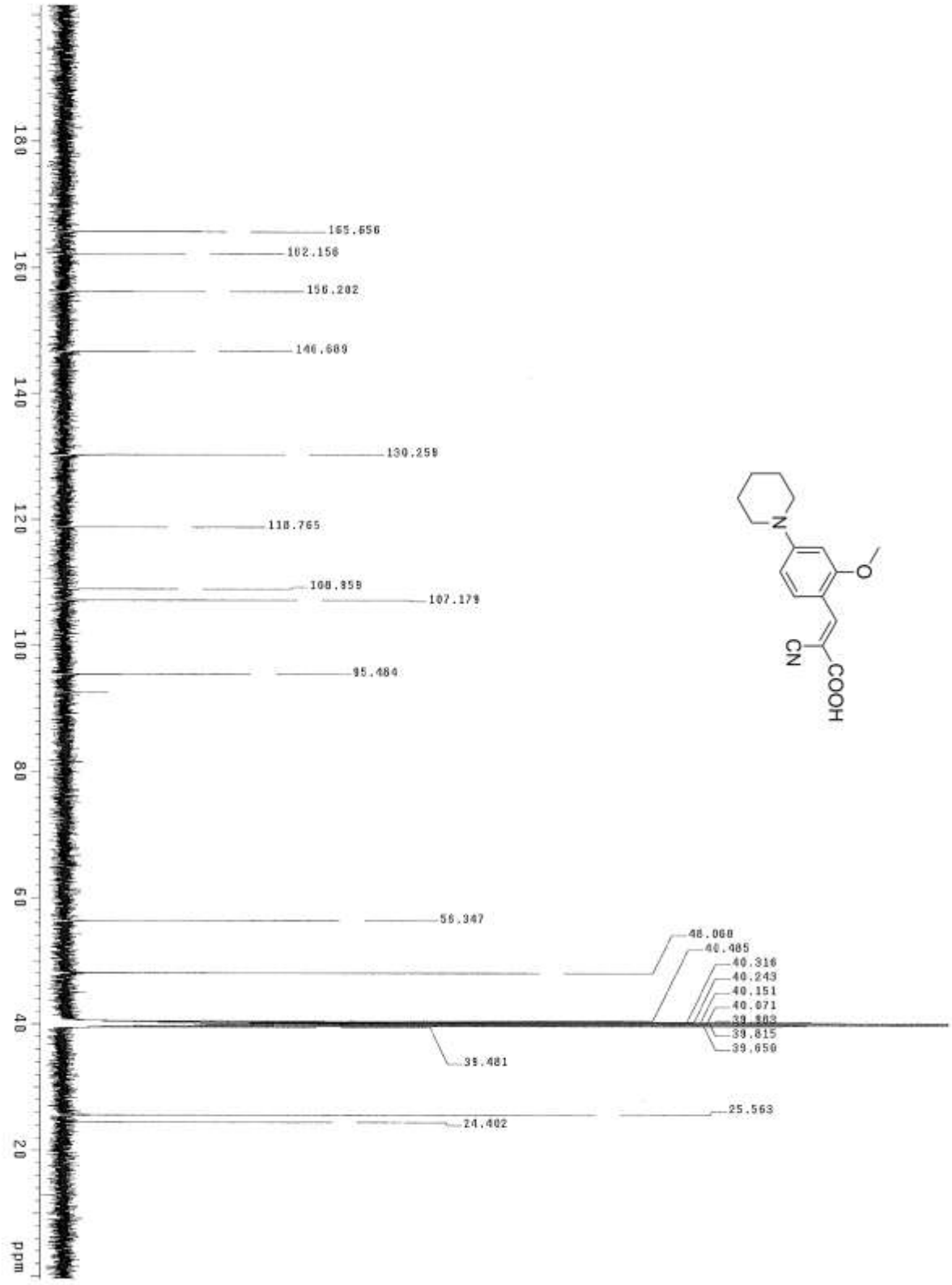

220
200
180
160
140
120
100
80
60
40
20
0
ppm
166.535
162.384
155.374
147.864
132.811
130.423
118.241
115.801
109.361
105.630
93.501
55.003
52.934
48.375
48.207
48.035
47.863
47.694
47.522
47.354
N
O
CN
HO


O
O
OH
CN
N
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.68
1.02
0.65
3.37
7.51
0.61
4.46


166.242
162.182
153.844
147.058
130.405
119.495
108.409
108.641
94.172
90.822
56.384
48.320
48.510
48.345
48.177
48.008
39.844
39.675
39.510
26.046
25.490
ppm


O
COOH
CN
N


13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.41
1.00
1.17
1.25
1.20
3.66
5.00
2.99
2.25
7.67


165.656
162.156
156.282
146.689
130.259
118.765
108.959
107.179
95.484
55.347
48.060
40.485
40.316
40.243
40.151
40.071
39.903
39.815
39.650
39.481
25.563
24.402
N
O
CN
COOH
180
160
140
120
100
80
60
40
20
ppm