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The Asymmetric Synthesis of 4,4-Disubstituted-2-Imidazolidinones: Potent NK_1 Antagonists

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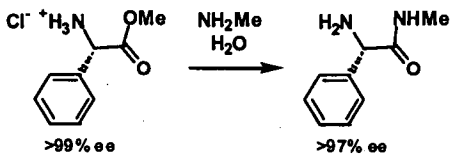
Supporting Information

General Procedures. Melting points were determined on a Mel-Temp apparatus and were uncorrected. Microanalysis and optical rotations were performed by Robertson Microlit Laboratories. ^1H NMR and ^{13}C NMR were recorded at ambient temperature on an Avance-500 (500 MHz) Bruker nuclear magnetic resonance spectrometer at the frequency indicated. Chemical shifts for NMR spectra are reported as δ in units of parts per million (ppm) relative to residual $CHCl_3$ for proton (δ 7.26, singlet) and $CDCl_3$ for carbon (δ 77.0, triplet). The data are reported as follows: chemical shift, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (reported as a *J* value in Hertz (Hz)), integration. The number of protons (n) for a given resonance is indicated by nH. Mass spectral analyses were recorded on JEOL model JMS-HX110A spectrometers and are reported in units of mass to charge (*m/e*). X-Ray data were collected on an Enraf-Nonius CAD-4 diffractometer.

All moisture and / or air sensitive experiments were performed under a positive pressure of nitrogen or argon in flame dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by nitrogen flushed syringe or cannula. Reaction solutions were stirred with Teflon coated magnetic stir bars unless otherwise indicated. Commercial solvents and reagents were used without further purification.

Analytical thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel plates (0.25 mm thickness). Subsequent to elution, ultraviolet illumination at 254 nm, while heating on a hot plate allowed for visualization of UV active material. Staining with a 5% ethanolic solution of phosphomolybdic acid (PMA) or an ethanolic solution of *p*-anisaldehyde (2.5%), sulfuric acid (3.5%) and acetic acid (1%) allowed for further visualization. Flash chromatography was performed using Selecto silica gel 60 (230-400 mesh) or Biotage and HPLC grade solvents. Columns were typically packed as a slurry (for Biotage commercial pre-packed columns were used) and equilibrated with the appropriate solvent prior to use.

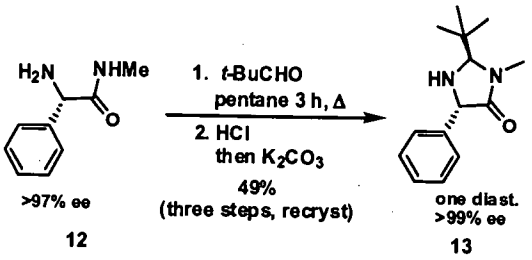
Copies of ^1H and ^{13}C spectra of all relevant compounds are provided.



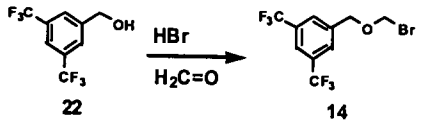
11 12

(*S*)-2-Amino-*N*-methyl-2-phenyl-acetamide (12). (*S*)-Phenylglycine methyl ester hydrochloride **11** (100g, 496 mmol, 1 equiv.) was added to methylamine (160 mL, 40% in H_2O, 4 equiv.) in a cool water bath at 10-16°C over a period of 15 minutes. After complete addition, the solution was warmed to room temperature and stirred for 1 h. The reaction was monitored by TLC in 98:2 EtOAc/MeOH. Upon completion, the reaction

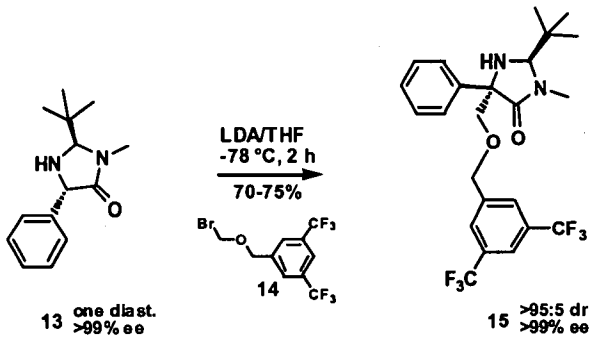
was quenched with brine (25% in H_2O, 500 mL). Extracted the solution with 1:1 THF/EtOAc (4 x 400 mL). Combined organic phases, dried (Na_2SO_4) and concentrated. Dried on high vacuum to give **12** (79.47 g, 98%) as a oil. TLC (EtOAc/MeOH 98:2): $R_f$sm 0.27, $R_f$prod 0.04; stain: pma. $[\alpha]^{25}_D$ = +93.56 (c 0.79, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.83 (d, J = 4.73 Hz, 3H), 4.54 (s, 1H), 7.03 (br s, 1H), 7.27-7.4 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 25.9, 59.6, 126.8, 127.8, 128.6, 141, 173.6. HRMS: calcd. for $C_9H_{13}N_2O$ (M+H) 165.1028; found (M+H) 165.1029. Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 63.63; H, 7.33; N, 16.39.



(*R*)-2-*tert*-Butyl-3-methyl-(*S*)-5-phenyl-imidazolidin-4-one (13). A mixture of **12** (79.44 g, 483.8 mmol, 1 equiv.), pentane (550 mL), and trimethylacetaldehyde (65.7 mL, 604.8 mmol, 1.25 equiv.) was heated to 65°C in a system equipped with a condenser, Dean-Stark trap and nitrogen inlet. The mixture was heated for 3 h and the suspension dissolved. The solution was cooled to room temperature and stirred overnight (16 h). Concentrated the solution and redissolved in MeOH (140-150 mL). Cooled in an ice bath for 30 min and then slowly added saturated HCl-MeOH (300 mL) via a dropping funnel over a 30 min period. The solution was stirred at 0°C and warmed to room temperature under nitrogen overnight. Concentrated on high vac to yield a crude, yellow oil (109.1 g). The oil was redissolved in methylene chloride (800 mL) and washed with 25% K_2CO_3 (w/w, 400 mL). The aqueous portion was washed again with methylene chloride (2 x 400 mL). Combined organics, dried (Na_2SO_4) and concentrated to give a yellow solid (98.7 g). The crude solid was recrystallized out of hot MTBE (300 mL). Cooled to 0°C to give **13** as a white solid (54.88 g, 49%), mp 110.4-111.5 °C. Mother liquor still contained product. This could be isolated by another recrystallization or by chromatography. TLC (CH_2Cl_2/MeOH(NH_3) 98:2): $R_f$sm 0.63, $R_f$prod 0.47; stain: pma. $[\alpha]^{25}_D$ = +60.61 (c 1.05, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 9H), 2.26 (br s, 1H), 3.02 (s, 3H), 4.31 (s, 1H), 4.67 (s, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 25.6, 31.4, 37.7, 62.5, 83.5, 127.2, 127.9, 128.7, 139.8, 174.2. HRMS: calcd. for $C_{14}H_{21}N_2O$ (M+H) 233.1654; found (M+H) 233.1651. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.12; H, 8.75; N, 12.02.

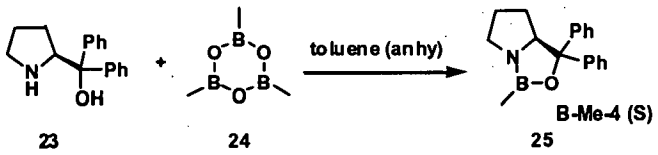


1-Bromomethoxymethyl-3,5-bis-trifluoromethyl-benzene (14). A flame-dried one-neck 200 mL RBF was charged with 3,5-bis(trifluoromethyl)benzyl alcohol **22** (50 g, 204.8 mmol, 1 equiv.) and paraformaldehyde (6.76 g, 225.3 mmol, 1.1eqiv.). The solid mixture was dissolved while under nitrogen with a heat gun until the solution was homo geneous. This process took approximately 20 min using a heat gun. Allowed solution to cool to room temperature. Next HBr gas was bubbled into the solution at a fast rate at ambient temperature. The reaction was continued for 2.5 h. Over this time period the solution changed from clear/white to orange. The layers were separated and the lower aqueous layer was drained. Diluted the upper layer with hexane (150 mL) and again removed any aqueous remnants. Dried light orange hexane layer over $MgSO_4$ overnight, during which time more of the color dissipated. Filtered and concentrated. Short path distillation (high vac, 75°C to give pure **14** (67.86 g, 98%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 2H), 5.76 (s, 2H), 7.81 (s, 2H), 7.85 (s, 1H).



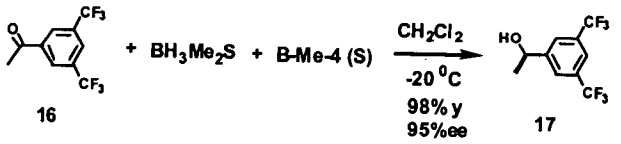
(*S*)-5-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-(*R*)-2-*tert*-butyl-3-methyl-5-phenyl-4-imidazolidin-4-one (15). All reagents were deoxygenated under Ar prior to use. **13** (42.05 g, 181 mmol, 1 equiv.) was dissolved in dry THF from a still (550 mL) while agitating with a mechanical stirrer. The solution was cooled to approximately –78°C in dry ice/acetone and a solution of 1.5 M LDA•THF in cyclohexane (124.3 mL, 186.5 mmol, 1.03 equiv.) was added over a 20 min period. This led to the formation of a dark orange/brown solution. This solution was allowed to stir at –78°C for 30 min. Next, bromide **14** (64.0 g, 190 mmol, 1.05 equiv.) was slowly added via syringe over 20 min. Stirred at –78°C and monitored by TLC in 4:1 Hex/EtOAc. Reaction complete after 2 h. The reaction was quenched with sat. aq. NH_4Cl (300 mL) at –78°C and then warmed to room temperature while stirring vigorously. Separated phases and washed organic with H_2O (2 x 150 mL). Aqueous layer was washed with EtOAc (300 mL). Combined organics, dried (Na_2SO_4) and concentrated to give a crude, light yellow solid (90 g). Recrystallized out of hot pentane to give **15** (33.66 g). The mother liquor was again concentrated to an orange solid and recrystallized out of pentane (150 mL) to give an additional 10.50 g of product (Overall yield = 44.16 g, 50%), mp: 114.8-115.3 °C. The mother liquor (46.7 g, approximately 50% pure by NMR) still contained product which could be isolated. $[\alpha]^{25}_D$ = +14.84 (c 0.96, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (s, 9H), 2.5 (d, J = 6.0 Hz, 1H), 3.0 (s, 3H), 3.6 (d, J = 9.5 Hz, 1H), 4.04 (d, J = 9.5 Hz, 1H), 4.29 (d, J = 6.3 Hz, 1H), 4.61 (d, J = 12.9 Hz, 1H), 4.67 (d, J = 12.9 Hz, 1H), 7.26-7.29 (m, 2H), 7.35 (t, J = 7.25 Hz, 2H), 7.72 (s, 2H), 7.8 (s, 1H), 7.82 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 25.6, 31.2, 36.2, 66.9, 71.6, 77.8, 82.8, 121.4, 122.2, 124.4, 126.3, 126.9, 127.6, 128.2, 1131.6 (q, J = 132.5 Hz), 139.9, 140.8, 174.0. HRMS: calcd. for $C_{24}H_{27}N_2O_2$ (M+H) 489.1977; found (M+H) 489.1983. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 59.01; H, 5.37; N, 5.73. Found: C, 58.92; H, 5.32; N, 5.75.

STEP 1:

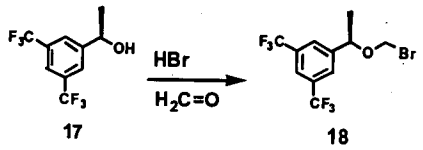


(*R*)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethanol (17). (Step 1): A flame-dried 50mL one-necked flask was charged with S-Prolinol 22 (5.10 g, 20.1 mmol, 1.0 eq) and 56 mL of anhydrous toluene. This cloudy solution was heated up to 140~150 °C. 36 mL of dry toluene was azeotropically distilled through a Dean-Stark trap with an air condenser. Another 36 mL of toluene was added. This azeotropical distillation was repeated three times to ensure 23 was totally dry. After the third azotropical distillation was done, another 36 mL of anhydrous toluene was added. The solution was allowed to cool down to room temperature. Methylboroxin 24 (1.90 mL, 13.5 mmol, 0.67 eq) was syringed in within 5 minutes. White solid was formed at about 6 minutes after completion of the addition. The reaction mixture was stirred at room temperature for 30 minutes. Then 36 mL of toluene was distilled off ("Gel-like" material which came out first could be the excess boroxin 24). Another 36 mL of dry toluene was added and distilled off again. Repeated the distillation one more time, then 20 mL of 1.0 M of CBS catalyst B-Me-4(S) 25 solution in toluene was prepared. The almost colorless solution can be used in CBS reduction directly.
Note: The commercially available CBS was found to give lower %ee.

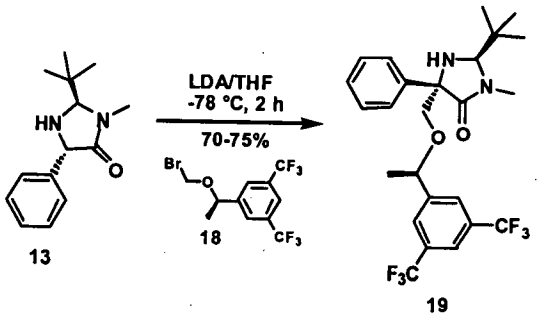
STEP 2:



(Step 2): A 1L oven-dried round-bottomed flask was charged with 3',5'-Bis(trifluoromethyl)acetophenone **16** (102.14 g, 0.4 mol, 1.0 eq) and 780 mL of anhydrous dichloromethane. The resulting colorless solution was transferred into a dry dropping funnel. Another oven-dried 3L round-bottomed flask was cooled to –20°C, and 20 mL of 1.0 M of CBS catalyst (S)B-Me-4 **25** toluene solution was syringed in, followed by 40 mL of 10.0~10.3 M Borane-Methylsulfide complex **26**. Then the 3', 5'-Bis(trifluoromethyl)acetophenone **16** solution was added dropwise through the dropping funnel. (syringe pump is recommended to control the slow addition). The addition was carried out over 2 days. During the addition, the temperature was maintained at –20°C with Cryocool cooling apparatus. Once the addition was finished, the reaction was monitored by TLC in 4:1 Hexane/EtOAc. When **16** was completely consumed, 250 mL of methanol was added slowly. Hydrogen gas was emitted. The reaction solution was then concentrated to give white solid. The solid was dissolved in 500 mL of diethyl ether, then 45 ml of 2.0 M of hydrochloric acid in diethyl ether was added slowly at -20°C. White precipitate was formed. The reaction mixture was warmed up to room temperature and stirred for 30~40 minutes. The mixture was filtered through a funnel, the filtrate was concentrated to give 101.5 g (yield 98.7%) of **17** as a white solid. Chiral HPLC Chiral OD(Chiralcel) column (Hexane/IPA = 98/2) showed 94.6%ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (d, J = 6.6 Hz, 3H), 5.04 (q, J = 6.6 Hz, 1H), 7.78 (s, 1H), 7.84 (s, 2H).

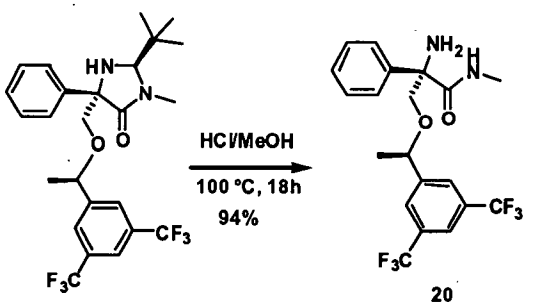


(*R*)-1-(1-Bromomethoxy-ethyl)-3,5-bis-trifluoromethyl-benzene (18). The compound **18** was prepared from **17** in a method analagous to that described for the preparation of **14** from 3,5-bis(trifluoromethyl)benzyl alcohol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.56 (d, J = 6.6 Hz, 3H), 5.02 (q, J = 6.6 Hz, 1H), 5.41 (d, J = 4.4 Hz, 1H), 5.77 (d, J = 4.4 Hz, 1H), 7.8 (s, 2H), 7.85 (s, 1H).



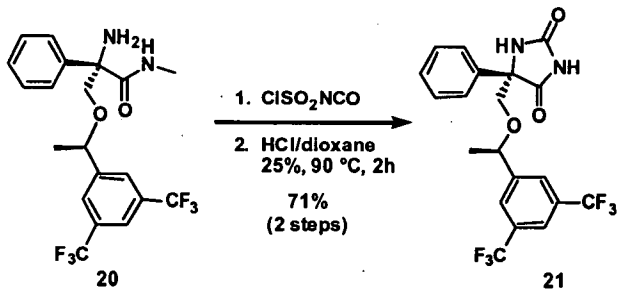
(*S*)-5-[(*R*)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxymethyl]-(*R*)-2-*tert*-butyl-3-methyl-5-phenyl-4-imidazolidin-4-one (19). All reagents were deoxygenated under Ar prior to use. Compound **13** (16.0 g, 63.92 mmol, 1 equiv.) was dissolved in dry THF from a still (200 mL) while agitating with a mechanical stirrer. The solution was cooled to approximately -70°C and a solution of 1M LDA/THF in cyclohexane (44 mL, 65.8 mmol, 1.03 equiv.) was added over a 20 min period. This led to the formation of a dark organe/brown solution. This solution was allowed to stir at -78°C for 30 min. Next, bromide **18** (22.6 g, 67.12 mmol, 1.05 equiv.) was slowly added via syringe over 20 min. The solution became a bit lighter with addition of the **18**. Stirred at -78°C and monitored by TLC in 4:1 Hex/EtOAc. Reaction complete after 2 h. The reaction was

quenched with sat. aq. NH_4Cl (100 mL) and then warmed to room temperature while stirring vigorously. Separated phases and washed organic with H_2O (2 x 50 mL). Dried (Na_2SO_4) and concentrated to give a crude, light yellow solid (32.63 g). Recrystallized out of hot pentane to give **19** (17.65 g, 55%). The mother liquor still contained starting product which could be isolated. mp 107.5-108 °C,TLC (hex/EtOAc 4:1): $R_f$sm 0.13, $R_f$prod 0.5; stain: pma. $[\alpha]^{25}_D$ = +43.16 (c 1.04, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 9H), 1.41 (d, J = 6.3 Hz, 3H), 2.43 (d, J = 7.25 Hz, 1H), 3.04 (s, 3H), 3.36 (d, J = 9.77 Hz, 1H), 3.88 (d, J = 9.77 Hz, 1H), 4.32 (d, J = 7.57 Hz, 1H), 4.6 (q, J = 6.6 Hz, 1H); 7.22-7.26 (m, 2H), 7.31 (t, J = 7.25 Hz, 2H), 7.69 (s, 2H), 7.72 (d, J = 8.5 Hz, 2H) 7.76 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 23.8, 25.6, 31.2, 36.2, 67.0, 76.2, 77.7, 82.9, 121.4, 121.5, 122.2, 124.3, 126.0, 126.3, 127.5, 128.1, 131.8 (q, J = 132.5 Hz), 139.9, 146.5, 174.2. HRMS: calcd. for $C_{25}H_{29}F_6N_2O_2$ (M+H) 503.2133; found (M+H) 503.2126. Anal. Calcd for $C_{25}H_{28}F_6N_2O_2$: C, 59.76; H, 5.62; N, 5.57. Found: C, 59.71; H, 5.60; N, 5.53.



19 20

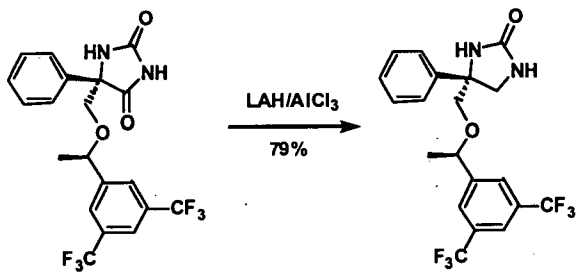
(*S*)-2-Amino-[(*R*)-1-(3,5-bis-trifluoromethyl-phenyl)-ethoxy]-*N*-methyl-2-phenyl-propionamide (20). Compound **19** (18.53 g, 36.87 mmol, 1 equiv.) was dissolved in 160 mL of MeOH. 160 mL concentrated HCl added and the mixture was heated at 87 °C overnight. Cooled to room temperature and concentrated. The resulting residue was taken in 300 mL CH_2Cl_2 and 200 mL saturated aq. K_2CO_3 was added and stirred for 30 minutes (pH of the solution should be higher than 10). Organic layer separated and aqueous layer washed with 2x 200 mL CH_2Cl_2. Combined organic layers were washed with 300 mL of saturated aq. NaCl. Organic layer dried over anhydrous Na_2SO_4, filtered and concentrated to give the product **20** (15 g, 94%) as colorless oil. TLC (hex/EtOAc)1:1): $R_f$sm 0.81, $R_f$prod 0.29; stain: pma. $[\alpha]^{25}_D$ = +48.83 (c 1.03, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (d, J = 6.6 Hz, 3H), 2.02 (br s, 2H), 2.81 (d, J = 5.0, 3H), 3.44 (d, J = 9.1 Hz, 1H), 4.3 (d, J = 9.1 Hz, 1H), 4.7 (q, J = 6.6 Hz, 1H); 7.24-7.3 (m, 1H), 7.31 (t, J = 6.9 Hz, 2H), 7.44 (d, J = 7.25 Hz, 2H), 7.6 (s, 1H), 7.7 (s, 2H), 7.78 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.2, 21.0, 24.0, 26.2, 60.4, 63.6, 75.2, 78.1, 121.5, 122.2, 124.3, 125.1, 126.1, 126.2, 127.8, 128.6, 131.8 (q, J = 132.5 Hz), 140.2, 146.6, 173.7. HRMS: calcd. for $C_{20}H_{21}F_6N_2O_2$ (M+H) 435.1507; found (M+H) 435.1505. Anal. Calcd for $C_{20}H_{20}F_6N_2O_2$: C, 55.30; H, 4.64; N, 6.45. Found: C, 54.95; H, 4.71; N, 6.39.



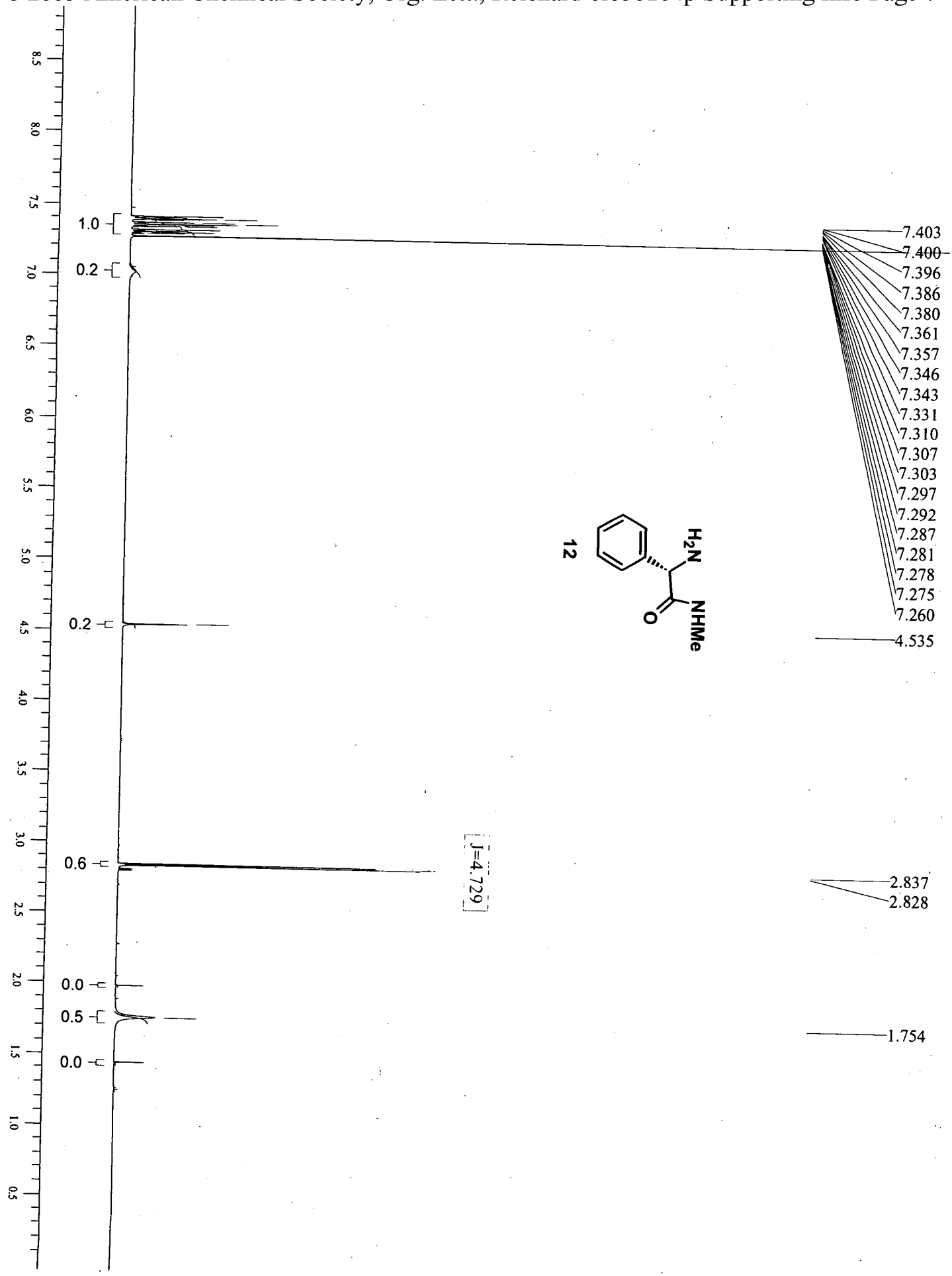
20 21

(*S*)-5-[(*R*)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxymethyl]-5-phenyl-imidazolidine-2,4-dione (21). Amino amide **20** (14.14 g, 32.55 mmol, 1 equiv.) was taken up in dry methylene chloride (120 mL). The solution was cooled to –78°C and chlorosulfonyl isocyanate (2.84 mL, 32.55 mmol, 1 equiv.) was added. The reaction was stirred at 0°C for 3 h and then concentrated to a white solid. The solid was dissolved in 1,4-dioxane (120 mL) and 3 N aqueous HCl (120 mL). Stirred at 90°C for 5 h and stirred at room temperature overnight. Diluted solution with H_2O (250 mL) and extracted with EtOAc (3 x 400 mL). Combined organics,

dried (Na_2SO_4), and concentrated to a crude, white foam (15.80 g). Performed plug chromatography on a 600 mL fritted funnel eluting with 2:1 Hex/EtOAc. Collected and concentrated fractions 2-8 to give pure **21** (10.26 g, 71%). TLC (hex/EtOAc 2:1): R_f sm 0.11, R_f prod 0.29; stain: pma. $[\alpha]^{25}_D$ = -32.82 (c 1.02, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (d, J = 6.6 Hz, 3H), 3.7 (d, J = 9.8 Hz, 1H), 3.93 (d, J = 9.5 Hz, 1H), 4.58 (q, J = 6.6 Hz, 1H); 6.34 (br s, 1H), 7.37-7.39 (m, 3H), 7.47-7.49 (m, 2H), 7.6 (s, 2H), 7.78 (s, 1H), 7.9 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 23.8, 68.9, 72.9, 78.3, 121.8, 122.1, 124.2, 125.3, 126.1, 128.9, 132.0 (q, J = 132 Hz), 134.3, 145.4, 156.8, 173.2. HRMS: calcd. for $C_{20}H_{17}F_6N_2O_3$ (M+H) 447.1143; found (M+H) 447.1146. Anal. Calcd for $C_{20}H_{16}F_6N_2O_3$: C, 53.82; H, 3.61; N, 6.28. Found: C, 53.87; H, 3.54; N, 6.22.



(*R*)-4-[(*R*)-1-(3,5-bistrifluoromethyl-phenyl)-ethoxymethyl]-4-phenyl-imidazolidin-2-one (Sch 425078). $AlCl_3$ (12.2 g, 91.4 mmol, 4 equiv.) was added to a flame-dried 1L 3-neck RBF equipped with stir bar and nitrogen inlet. The flask was cooled to 0°C and slowly added a solution of 1 M LAH in ether (68.6 mL, 68.6 mmol, 3 equiv.). This formed a white slurry which was stirred at 0°C for 15 min. Next, a solution of hydantoin **21** (10.2 g, 22.85 mmol, 1 equiv.) in 150 mL dry THF was added via canula. The solution was warmed to room temp. and stirred for 41 h. The solution was again cooled to 0°C and H_2O (20 mL) was added. Next, added 15% aq. NaOH (w/w, 20 mL) followed by more H_2O (60 mL). The biphasic solution was stirred for 30 min. All emulsion formed was dissolved with 1 N HCl (approximately 300-400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 500 mL). Combined organics, washed with H_2O (200 mL), dried (Na_2SO_4), and concentrated to give the crude (9.86 g). The crude material was initially purified by plug chromatography on a 2L fritted funnel eluting with 1:1 Hex/EtOAc, followed by 98:2 EtOAc to give 8.0 g of material, which still contained 3% of a less polar impurity. The solid was recrystallized from hot MTBE (30 mL) to provide pure Sch 425078 (6.5 g, 79%). TLC (EtOAc/Et_3N 9:1): R_f sm 0.73, R_f prod 0.38; stain: pma. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, J = 6.6 Hz, 3H), 3.46 (d, J = 8.8 Hz, 1H), 3.52 (d, J = 8.8 Hz, 1H), 3.63 (d, J = 8.8 Hz, 1H), 3.74 (d, J = 8.8 Hz, 1H), 4.48 (q, J = 6.3 Hz, 1H); 4.65 (br s, 1H), 5.42 (br s, 1H), 7.24-7.39 (m, 5H), 7.46 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 23.9, 50.7, 63.2, 74.7, 77.9, 121.6, 122.1, 124.2, 124.9, 126.1, 127.7, 128.7, 131.8 (q, J = 132.5 Hz), 142.1, 145.89, 162.7. HRMS: calcd. for $C_{20}H_{19}F_6N_2O_2$ (M+H) 433.1351; found (M+H) 433.1349.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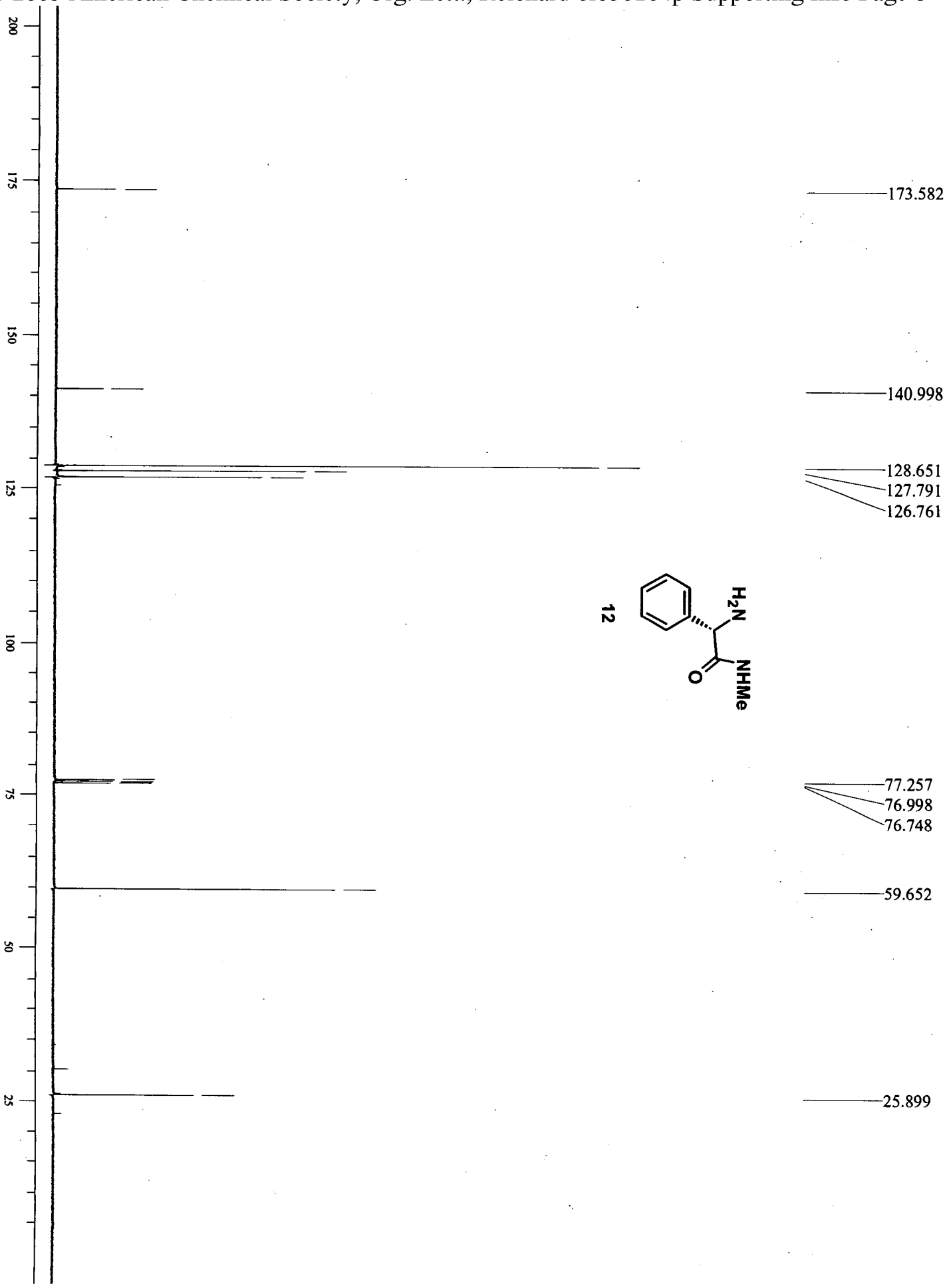

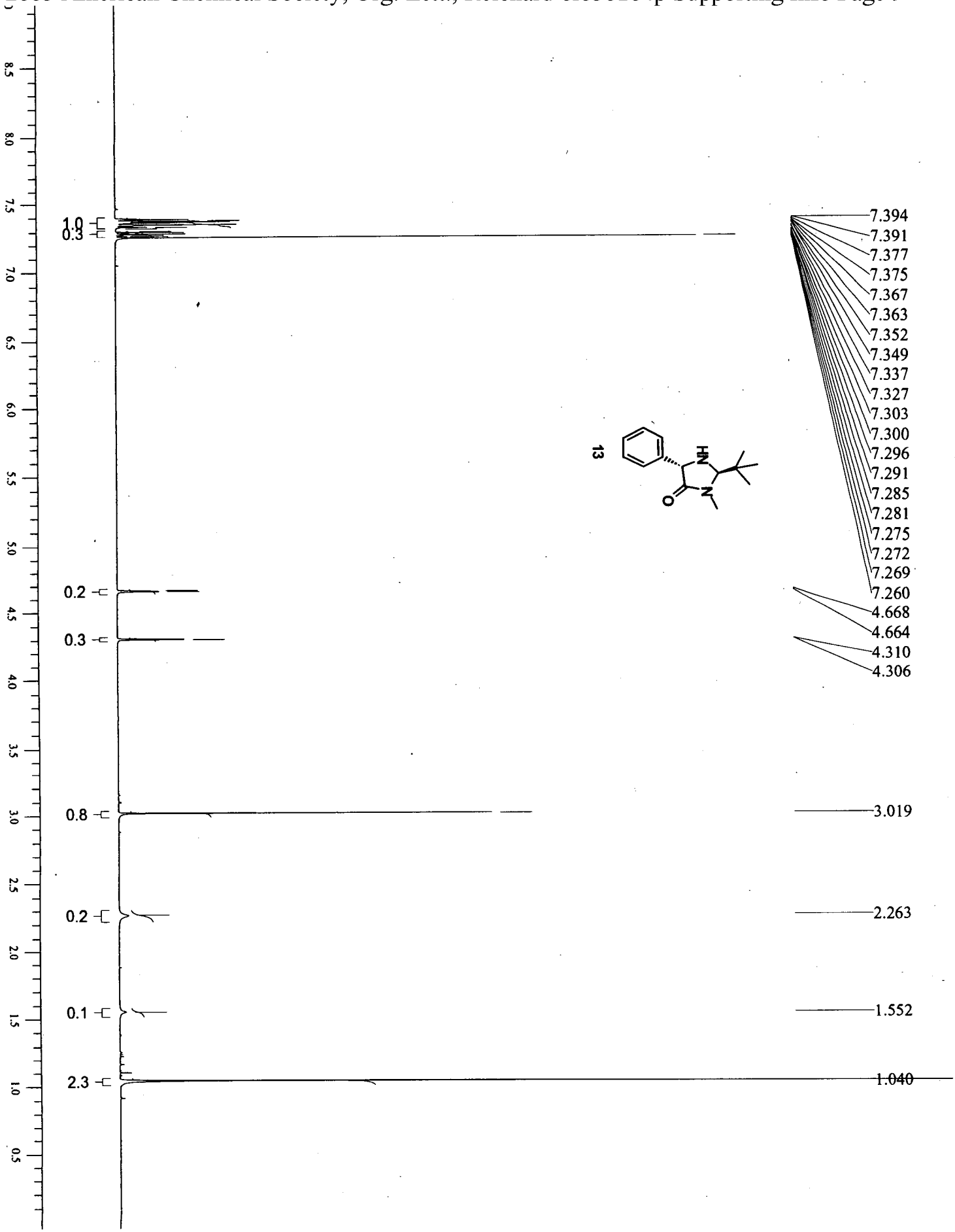
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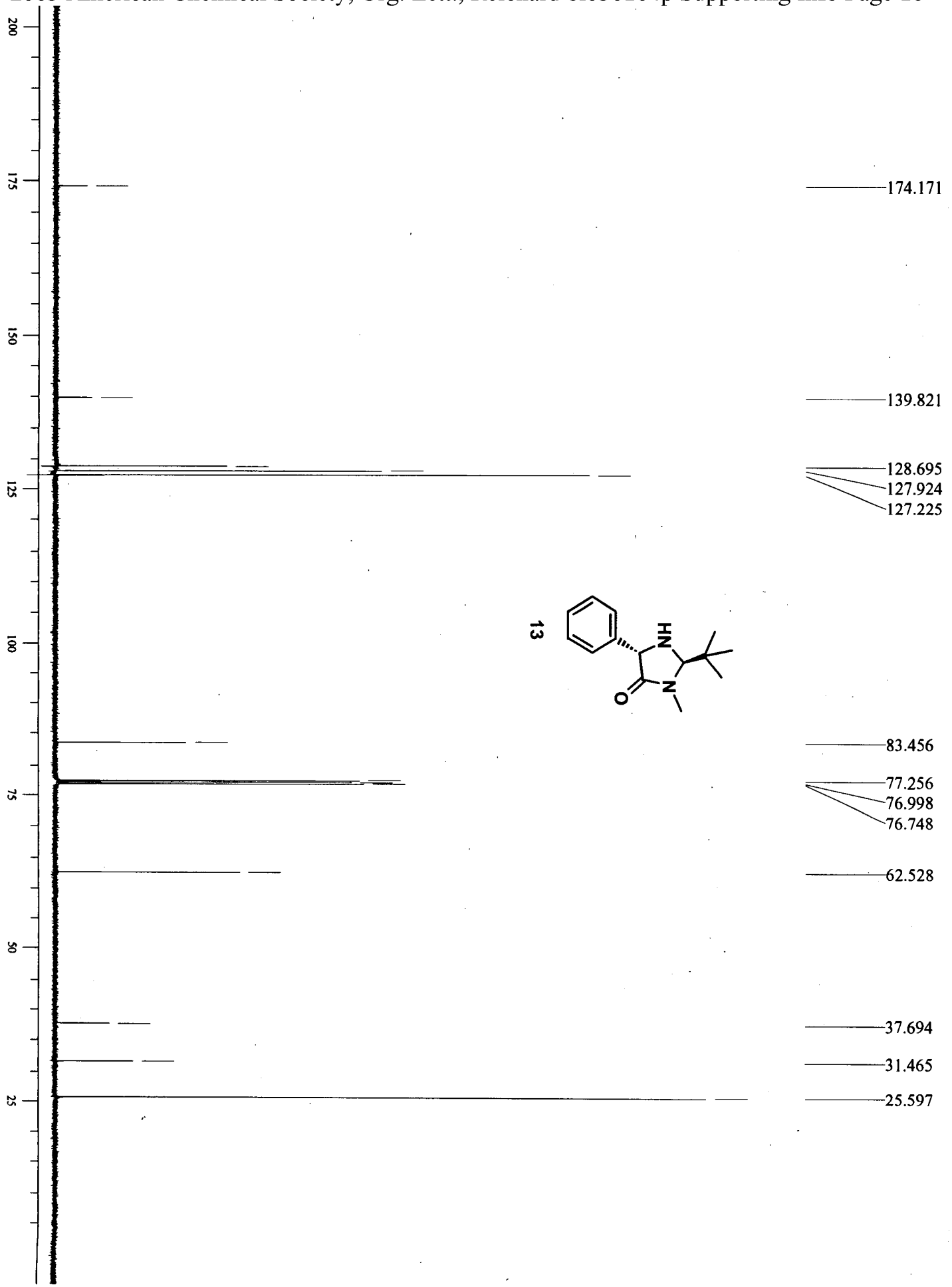

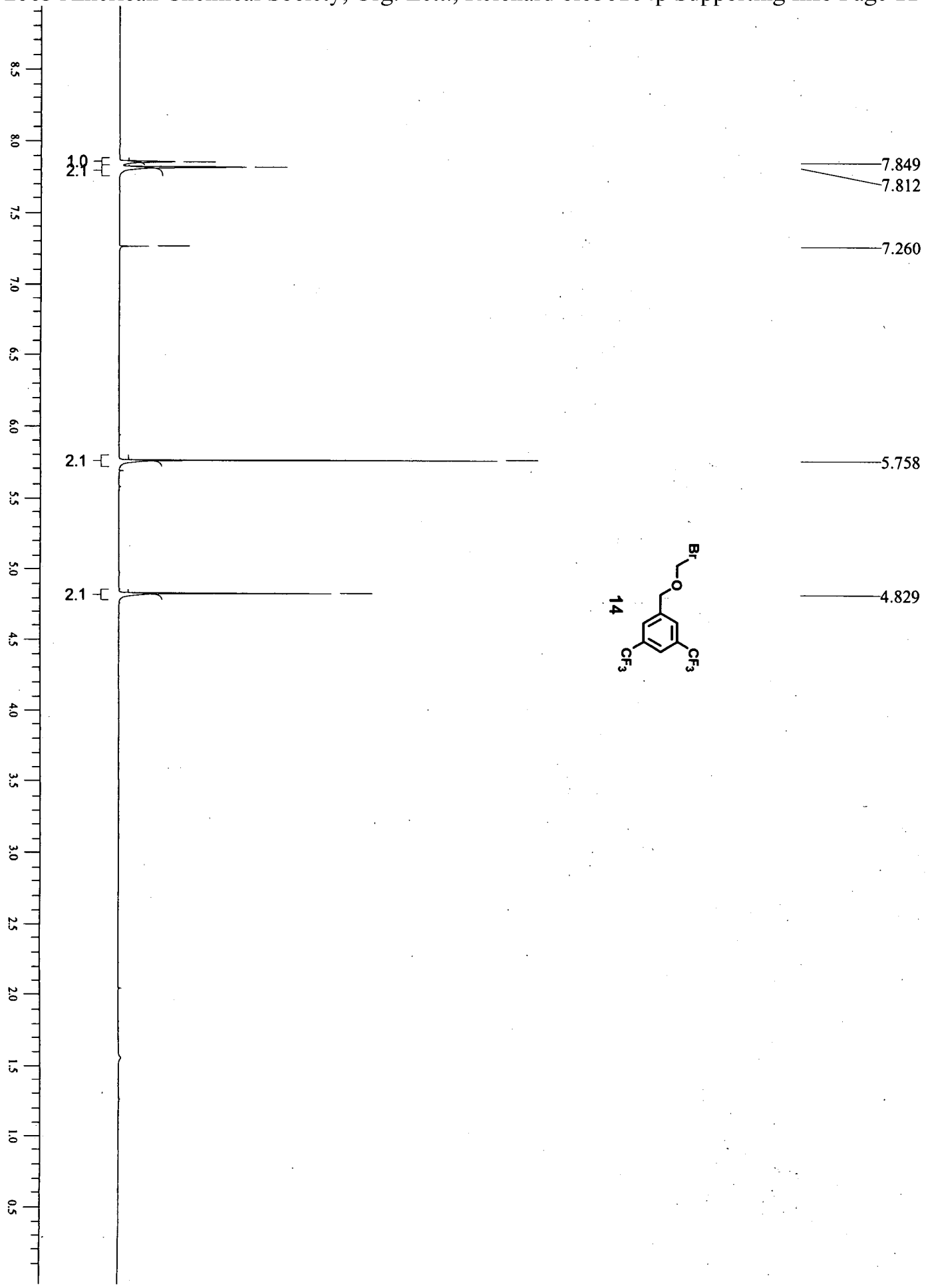
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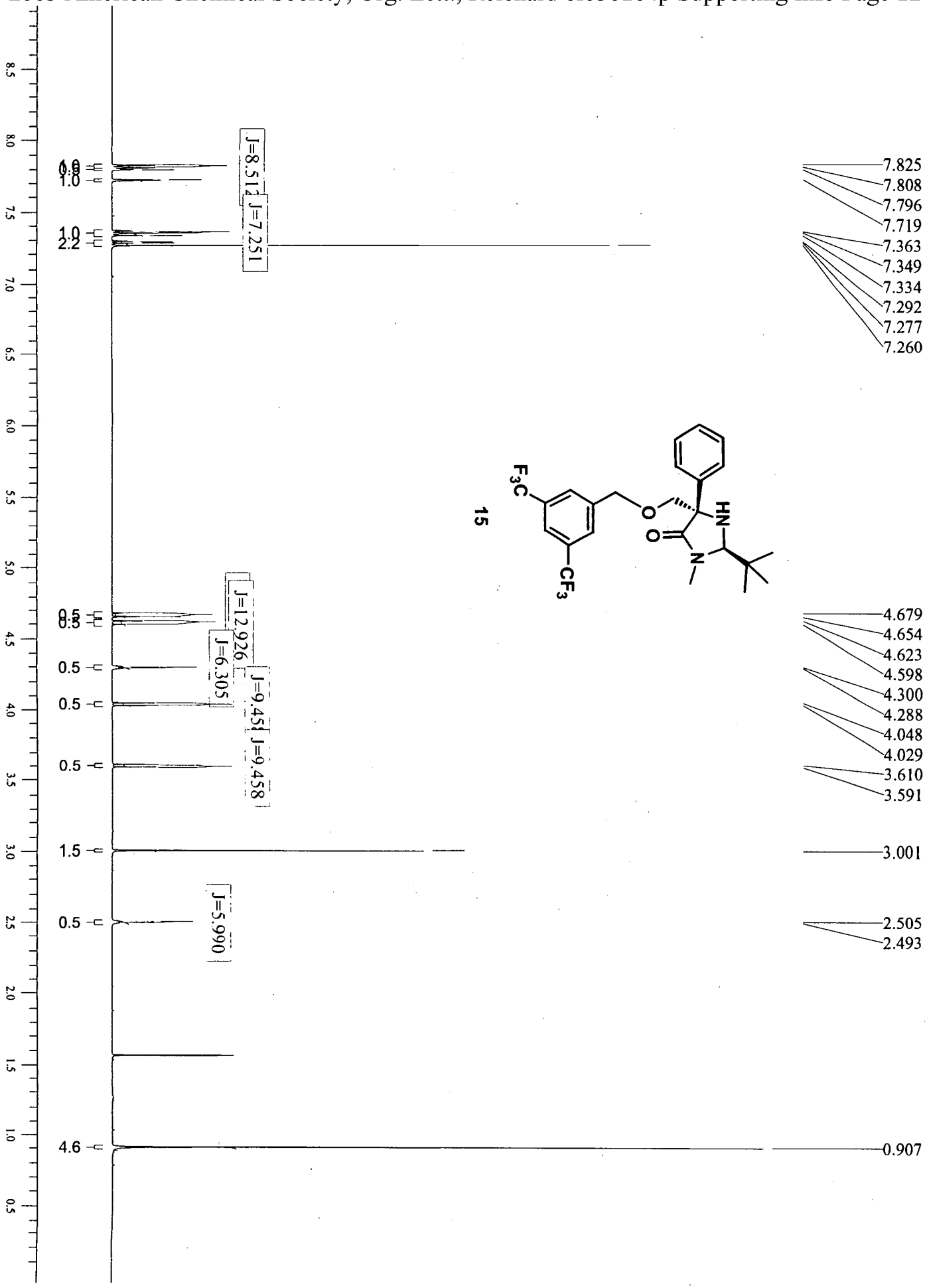
CF3
14



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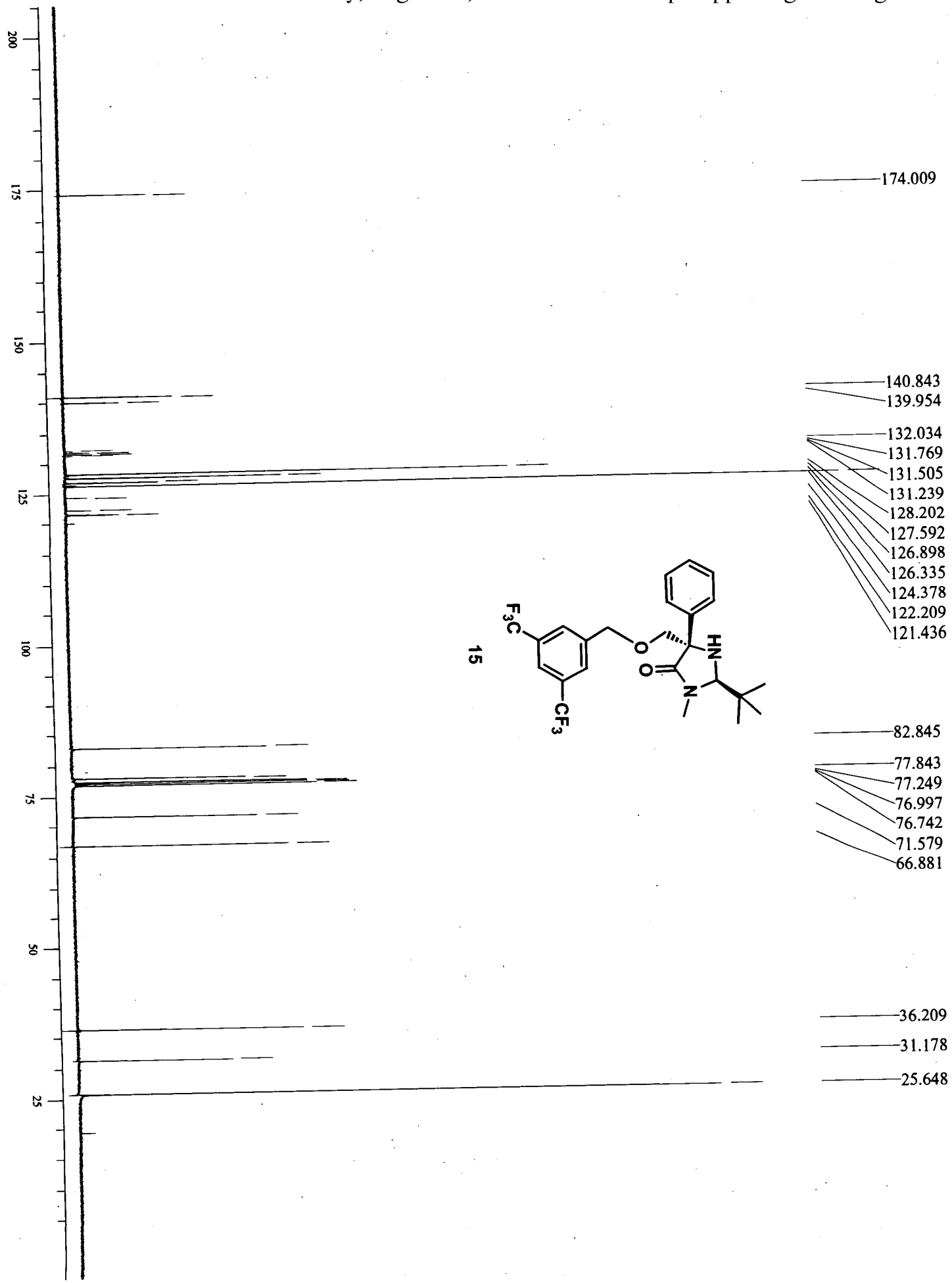

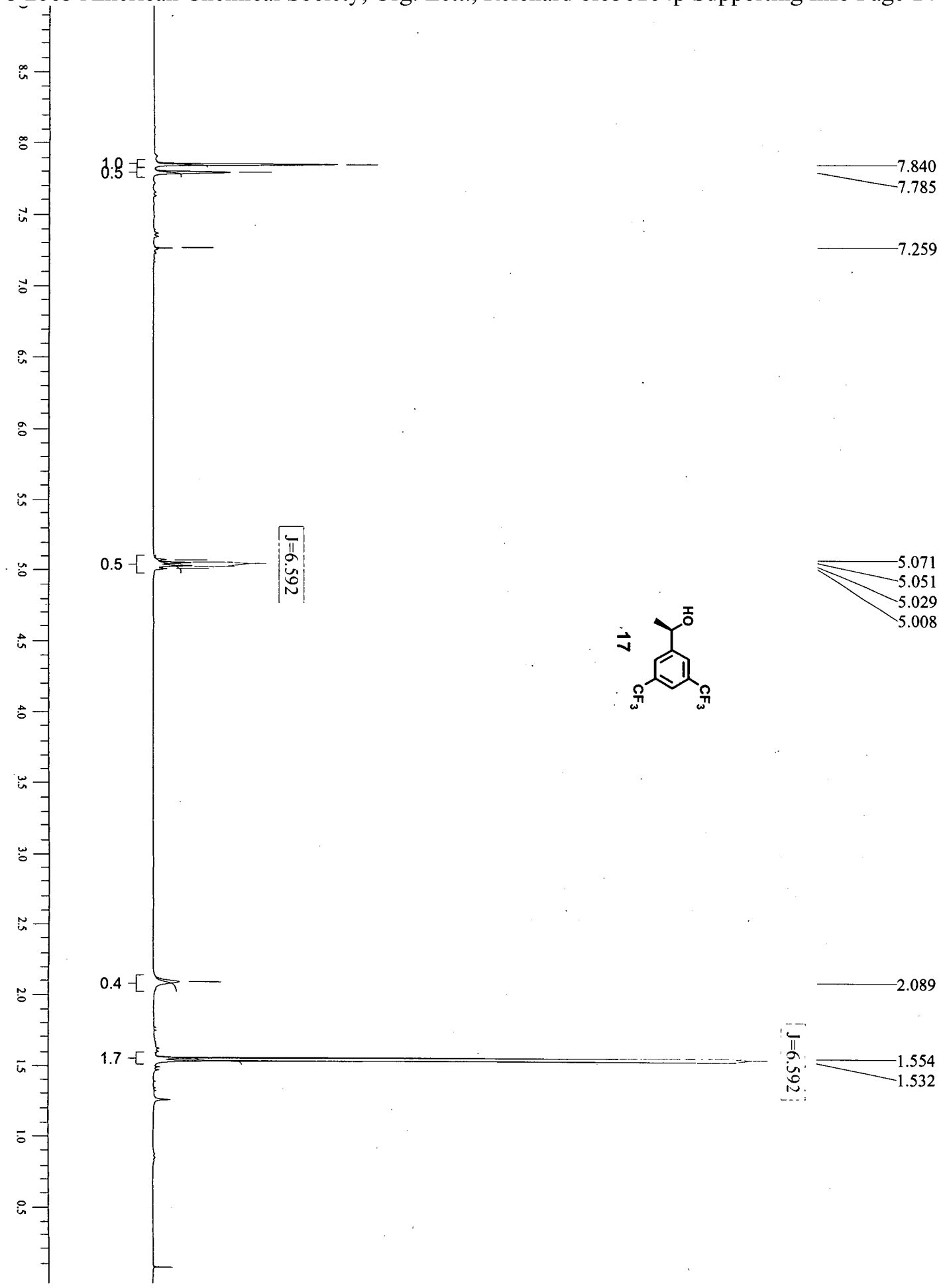
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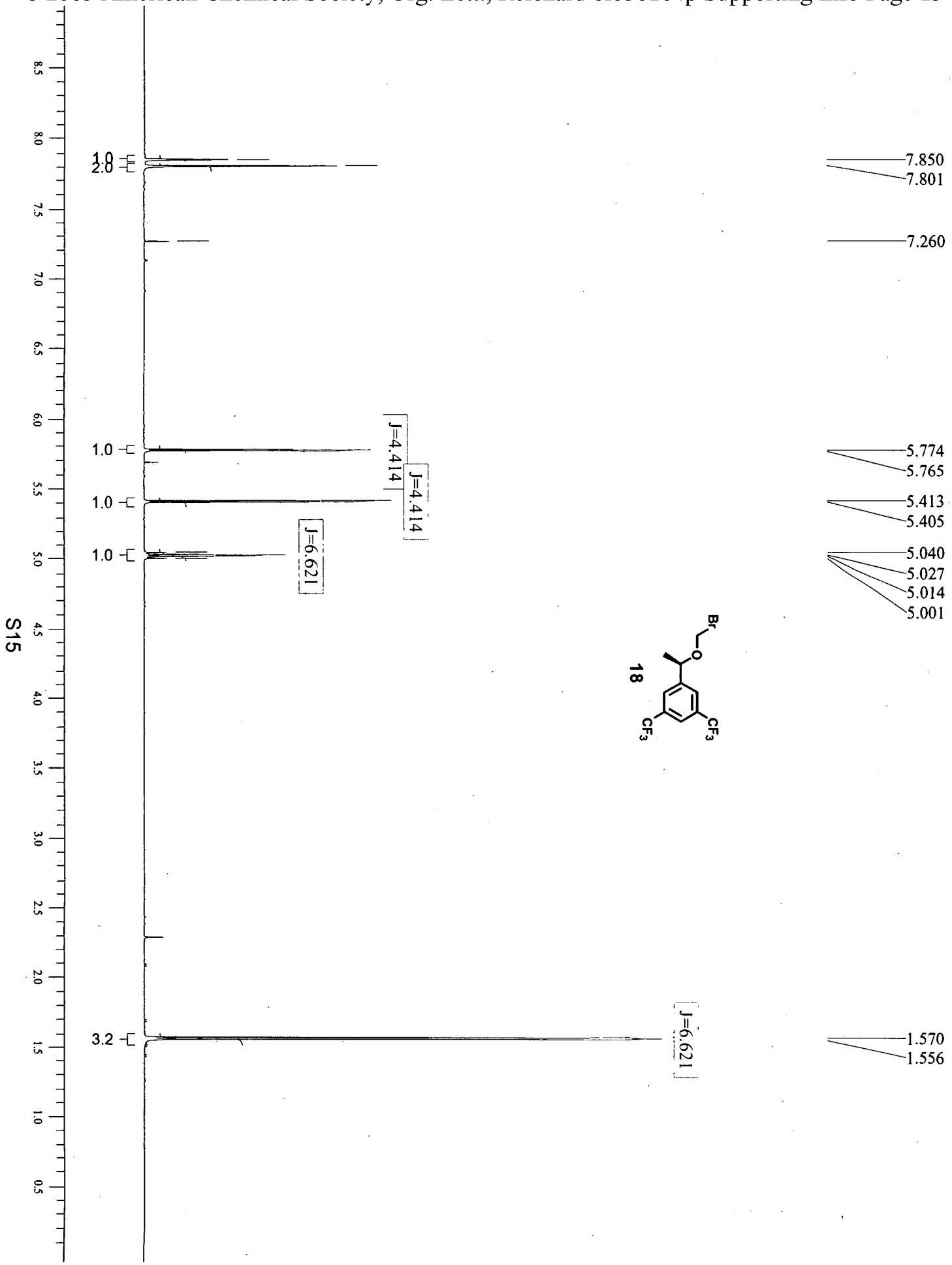
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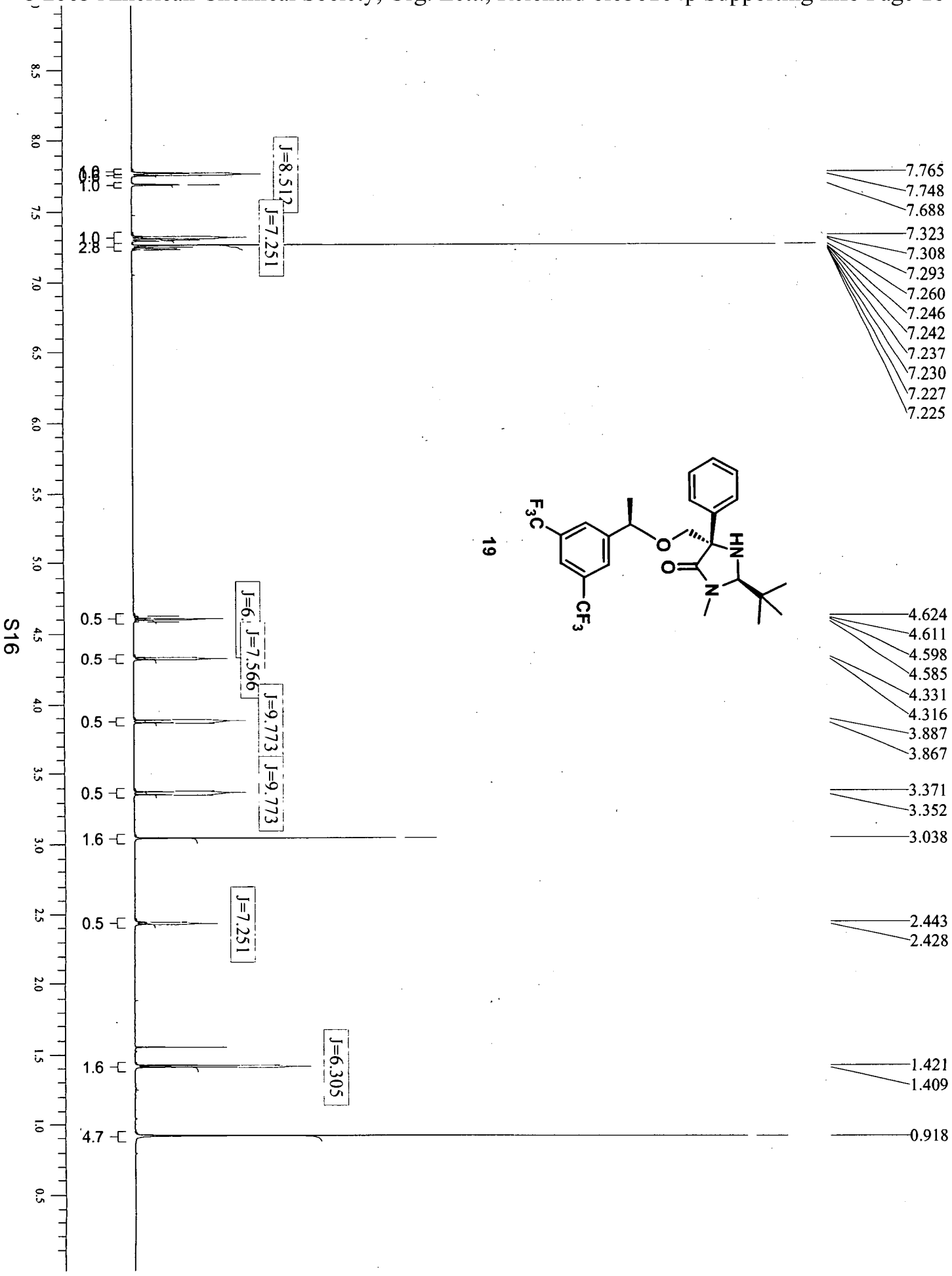
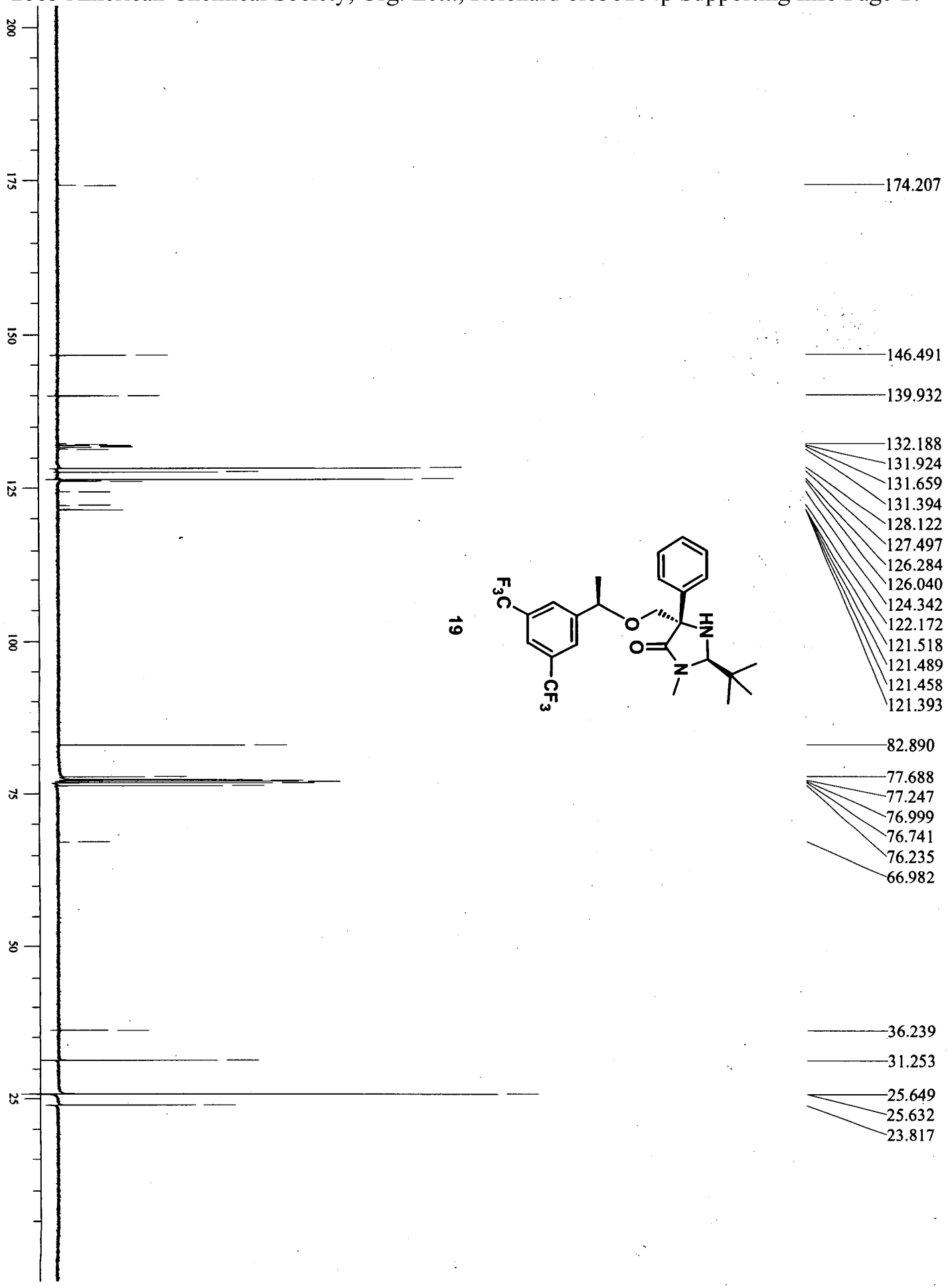
18





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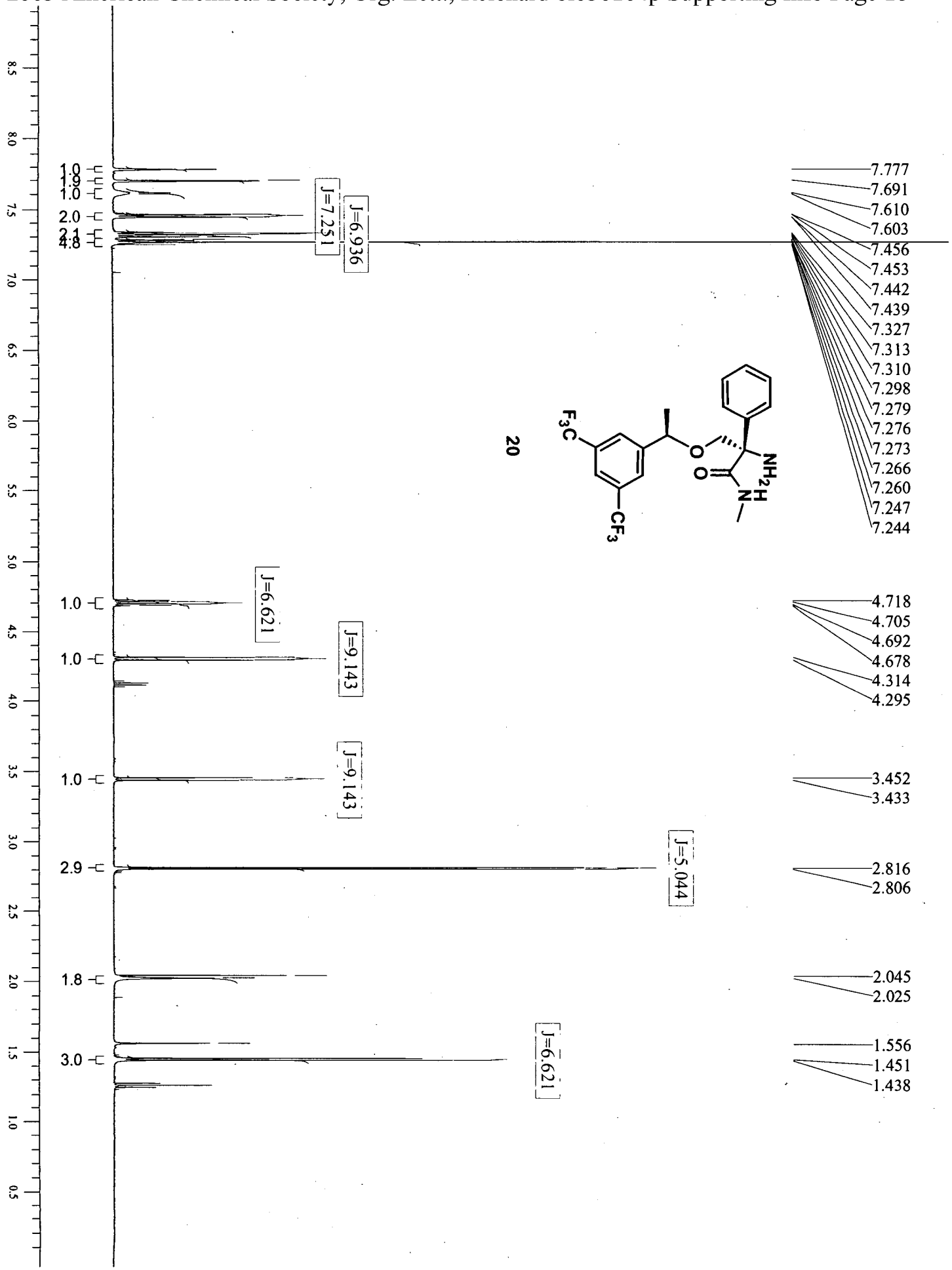

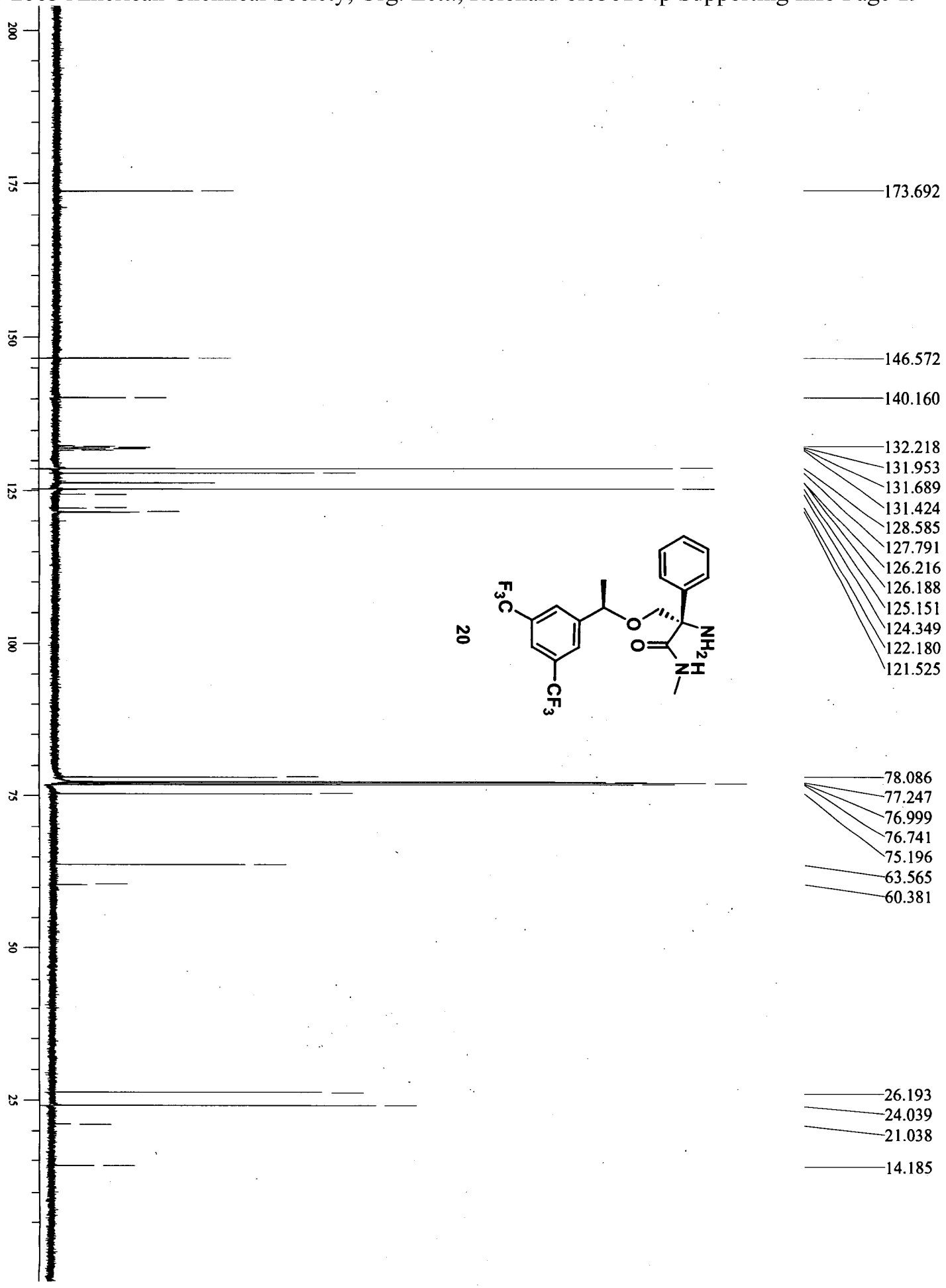

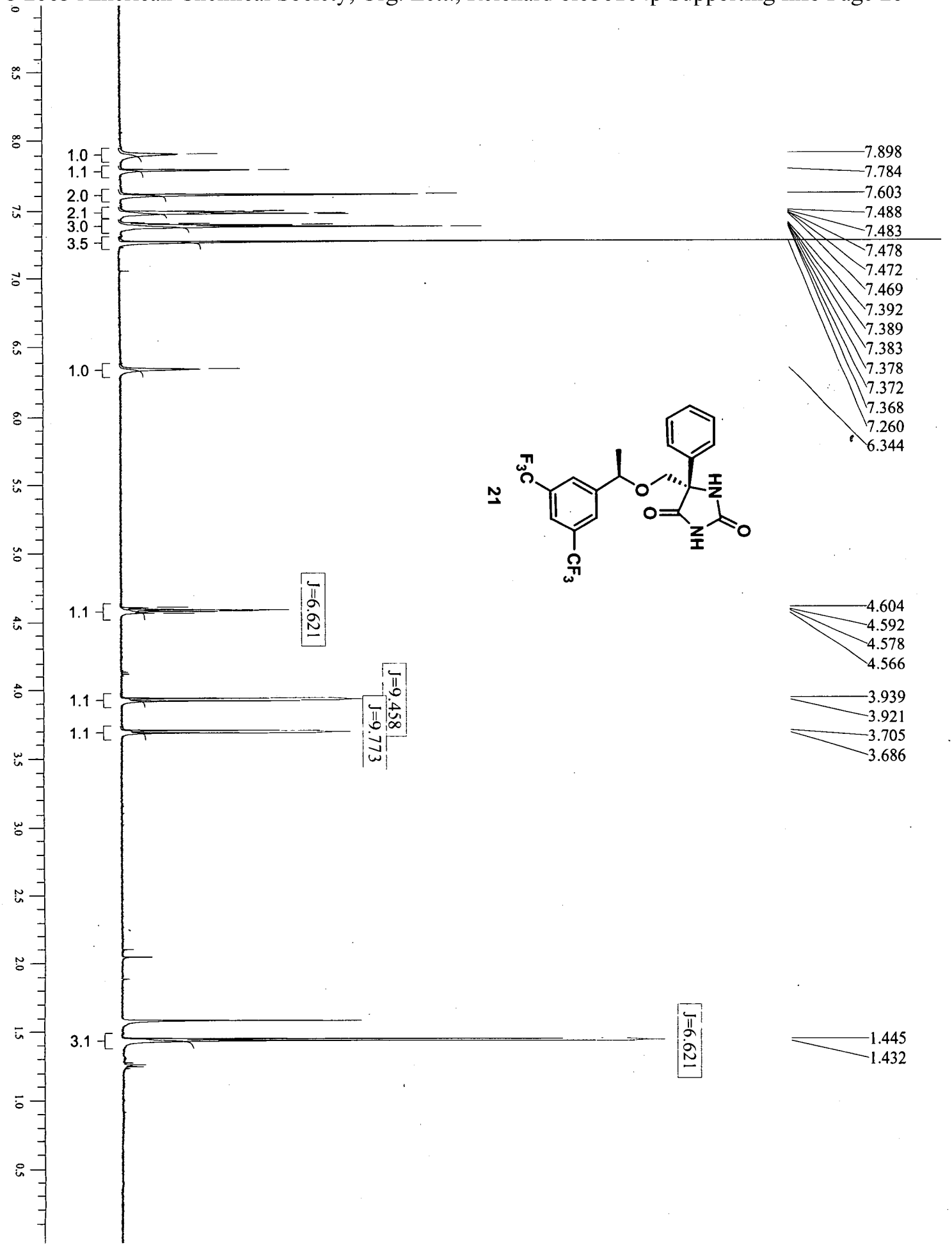
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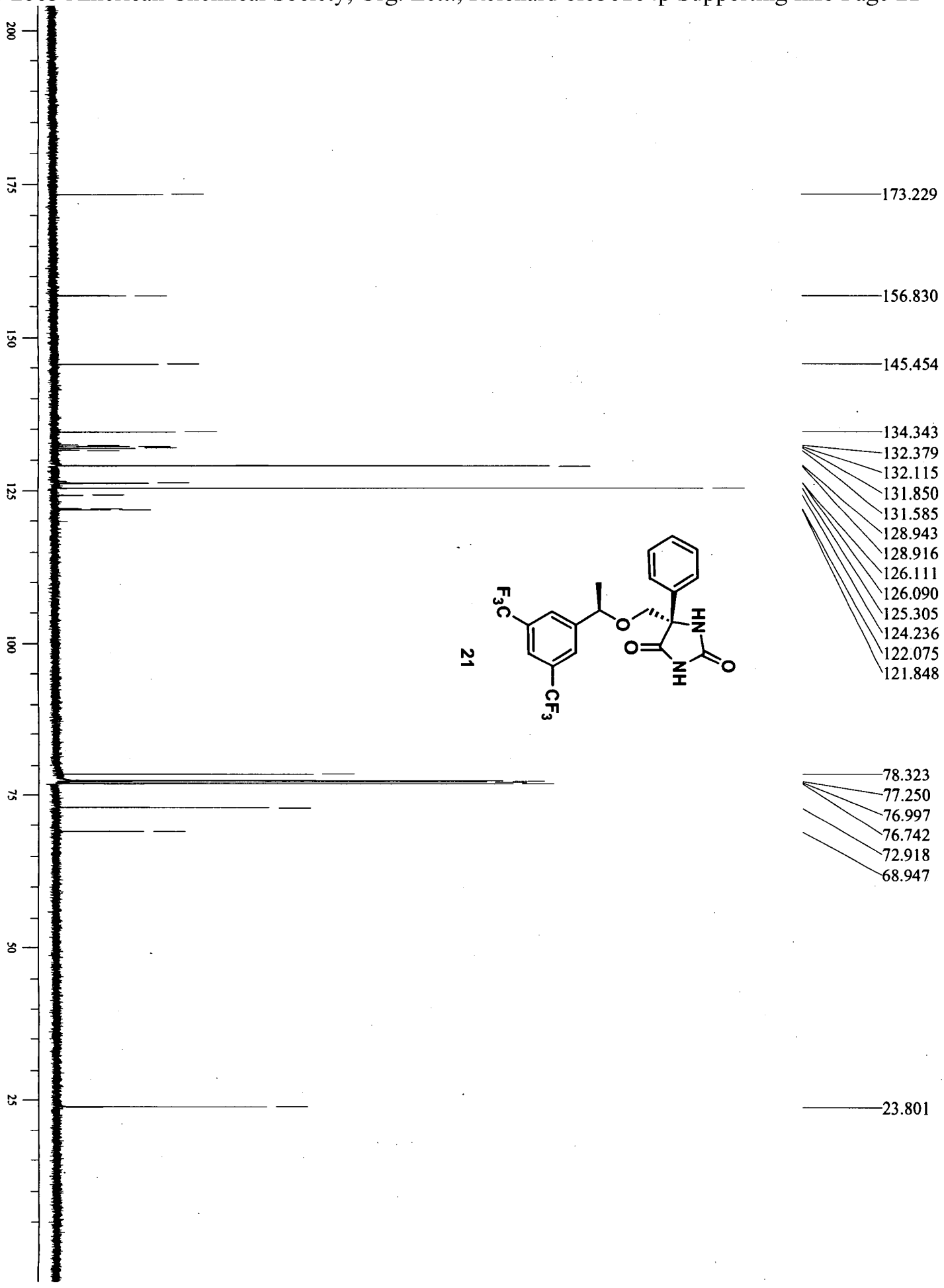
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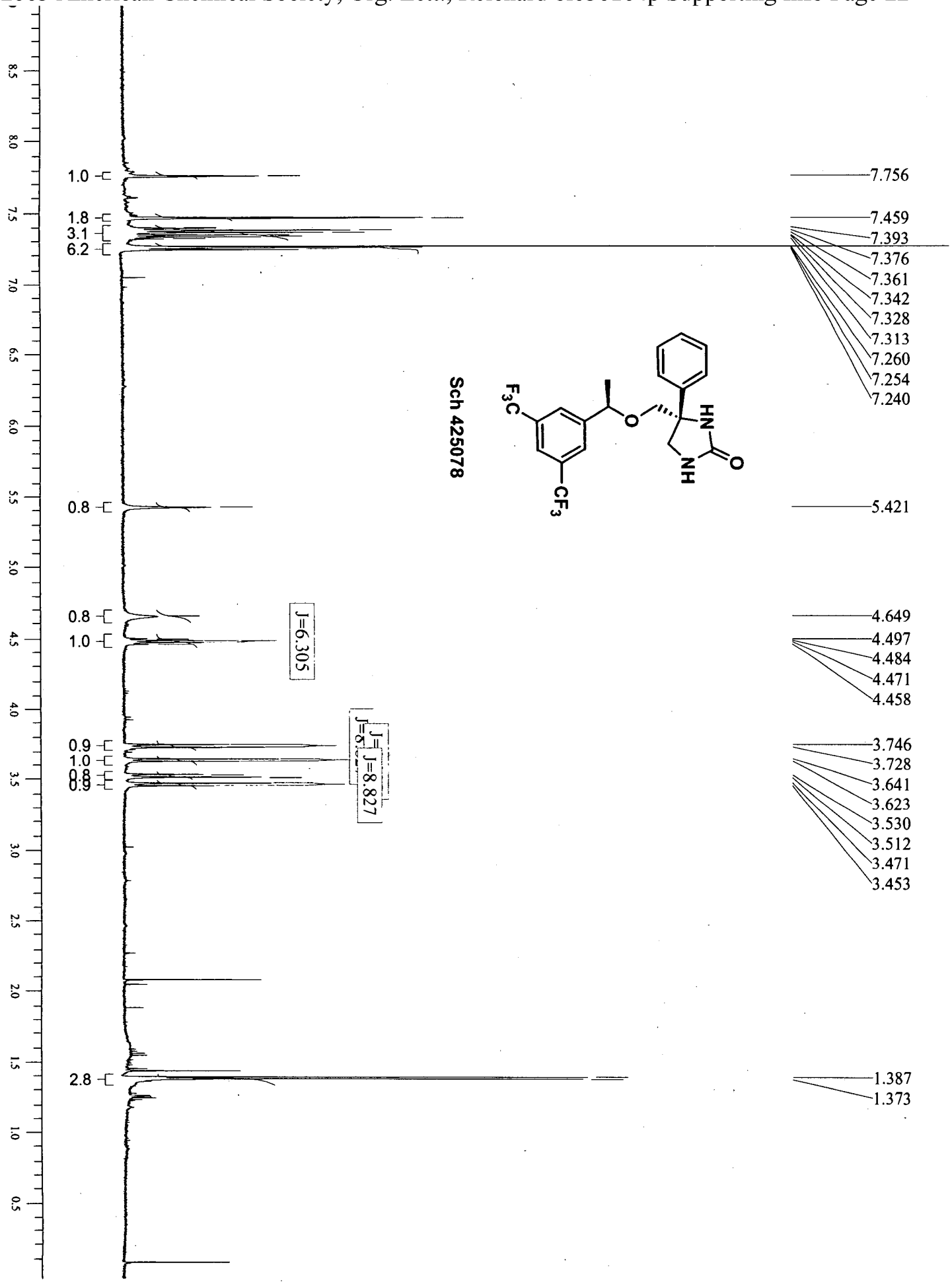

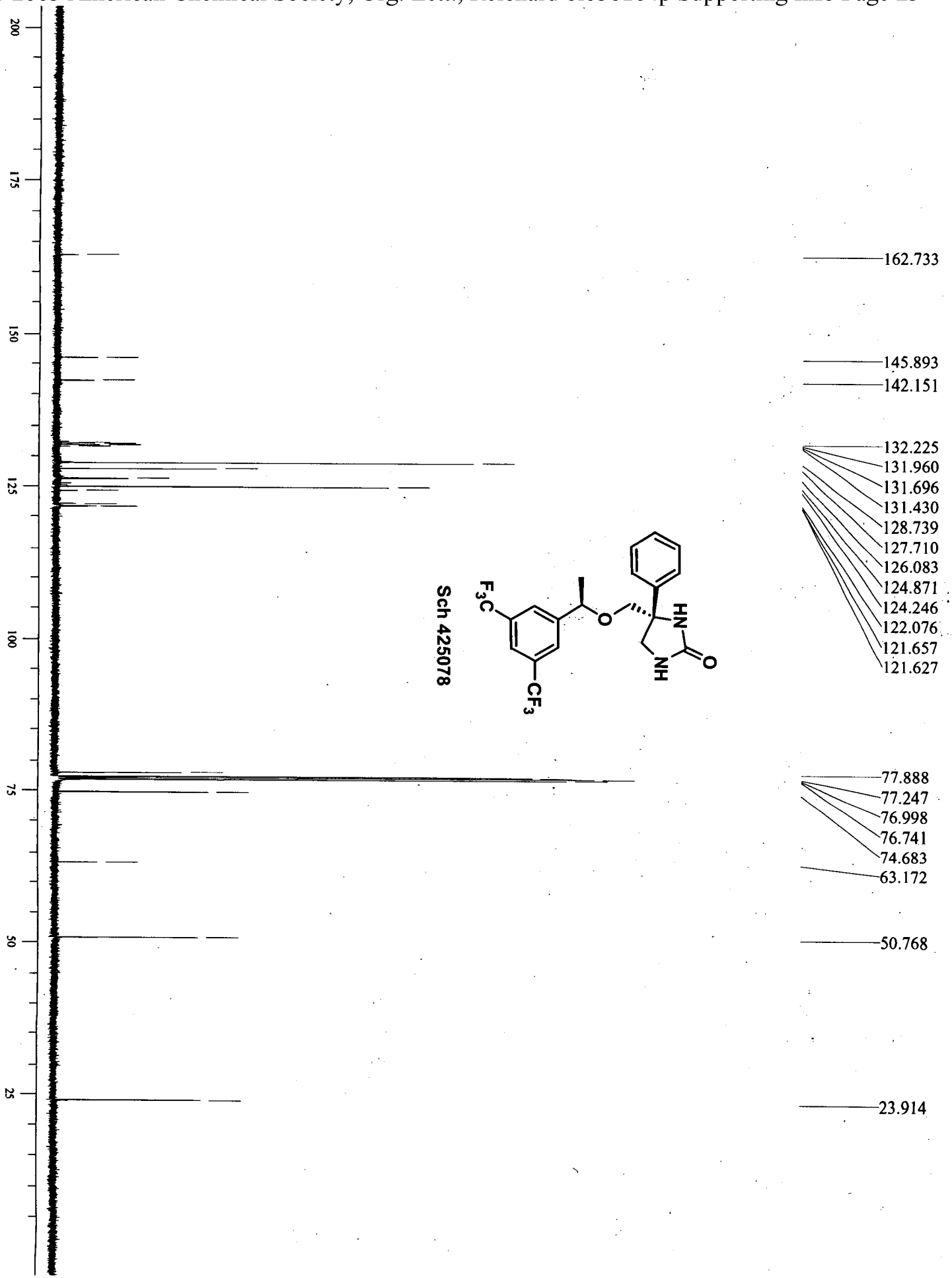

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H9C 0.2236 0.4337 -0.5536 0.0686 1.0
H10A 0.1342 0.4510 -0.0119 0.0655 1.0
H10B 0.1491 0.3823 0.0725 0.0655 1.0
H10C 0.2246 0.4280 0.0467 0.0655 1.0
H11A 0.0673 0.4165 -0.3477 0.0733 1.0
H11B 0.1096 0.3661 -0.5109 0.0733 1.0
H11C 0.0800 0.3486 -0.2508 0.0733 1.0
H13 0.4004 0.4411 -0.0619 0.0599 1.0
H14 0.4866 0.5177 -0.1070 0.0711 1.0
H15 0.5569 0.5280 -0.4364 0.0771 1.0
H16 0.5419 0.4602 -0.7211 0.0950 1.0
H17 0.4583 0.3809 -0.6764 0.0826 1.0
H18A 0.4500 0.3162 -0.0878 0.0485 1.0
H18B 0.4678 0.2956 -0.3533 0.0485 1.0
H20 0.4380 0.2332 0.0732 0.0479 1.0
H21A 0.4926 0.1480 -0.0637 0.0745 1.0
H21B 0.4465 0.1571 -0.3096 0.0745 1.0
H21C 0.5150 0.2046 -0.2291 0.0745 1.0
H23 0.2631 0.2149 -0.1804 0.0524 1.0
H25 0.1781 0.0904 0.2341 0.0647 1.0
H27 0.4075 0.1312 0.2478 0.0605 1.0
 #======================================
loop_
     _atom_site_aniso_label
     _atom_site_aniso_U_11
     _atom_site_aniso_U_22
     _atom_site_aniso_U_33
     _atom_site_aniso_U_12
     _atom_site_aniso_U_13
     _atom_site_aniso_U_23
C1 0.053(1) 0.055(1) 0.036(1) 0.002(1) 0.002(1) -0.004(1)
N2 0.045(1) 0.062(1) 0.038(1) 0.000(1) -0.001(1) -0.008(1)
C3 0.038(1) 0.054(1) 0.033(1) -0.001(1) 0.001(1) -0.002(1)
N4 0.036(1) 0.061(1) 0.033(1) 0.002(1) 0.001(1) -0.005(1)
C5 0.041(1) 0.052(1) 0.035(1) 0.001(1) 0.005(1) -0.002(1)
O6 0.071(1) 0.078(1) 0.040(1) 0.002(1) 0.013(1) -0.013(1)
C7 0.067(2) 0.072(2) 0.057(2) -0.006(2) -0.019(2) -0.014(2)
C8 0.042(1) 0.056(1) 0.044(1) 0.008(1) -0.002(1) 0.001(1)
C9 0.073(2) 0.063(2) 0.070(2) 0.009(2) -0.004(2) 0.016(2)
C10 0.063(2) 0.080(2) 0.054(2) 0.020(2) 0.009(2) -0.009(2)
C11 0.044(1) 0.095(2) 0.081(3) 0.008(2) -0.011(2) 0.001(2)
C12 0.046(1) 0.055(1) 0.045(2) 0.005(1) 0.001(1) -0.001(1)
C13 0.050(1) 0.069(2) 0.061(2) -0.005(1) 0.003(2) -0.015(2)
C14 0.069(2) 0.067(2) 0.078(2) -0.008(2) -0.003(2) -0.017(2)
C15 0.070(2) 0.060(2) 0.101(3) -0.012(2) 0.007(2) 0.002(2)
C16 0.108(3) 0.094(2) 0.084(3) -0.044(2) 0.039(2) -0.008(2)
C17 0.108(2) 0.074(2) 0.065(2) -0.034(2) 0.037(2) -0.015(2)
C18 0.035(1) 0.053(1) 0.057(2) -0.003(1) 0.003(1) 0.003(1)
O19 0.038(1) 0.054(1) 0.063(1) -0.004(1) -0.007(1) 0.008(1)
C20 0.036(1) 0.053(1) 0.055(2) 0.003(1) -0.004(1) 0.002(1)
C21 0.051(2) 0.070(2) 0.102(3) 0.012(2) 0.022(2) -0.001(2)
C22 0.042(1) 0.044(1) 0.052(2) 0.006(1) 0.000(1) -0.004(1)
C23 0.041(1) 0.050(1) 0.066(2) 0.002(1) 0.000(2) -0.002(2)
C24 0.042(1) 0.053(1) 0.081(2) -0.003(1) 0.007(2) -0.002(2)
C25 0.064(2) 0.054(2) 0.076(2) -0.006(1) 0.015(2) -0.002(2)
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C26 0.072(2) 0.050(1) 0.060(2) 0.003(1) 0.007(2) 0.002(2)
C27 0.057(2) 0.054(1) 0.055(2) 0.005(1) -0.002(2) 0.001(2)
C28 0.046(2) 0.079(2) 0.131(4) -0.009(2) 0.001(2) 0.017(3)
F29 0.053(1) 0.130(2) 0.163(3) -0.033(1) -0.001(2) 0.022(2)
F30 0.068(1) 0.273(4) 0.130(2) -0.022(2) -0.034(2) 0.055(3)
F31 0.064(1) 0.104(2) 0.338(6) 0.023(1) -0.043(3) -0.012(3)
C32 0.110(3) 0.067(2) 0.068(2) 0.001(2) 0.009(3) 0.008(2)
F33 0.139(4) 0.178(3) 0.181(4) -0.038(3) 0.008(4) 0.113(3)
F34 0.195(3) 0.104(2) 0.124(3) 0.085(2) 0.052(3) 0.045(2)
F35 0.304(7) 0.083(2) 0.067(2) -0.013(4) -0.059(3) 0.007(2)
F33' 0.159(8) 0.153(7) 0.163(8) -0.026(7) -0.063(7) 0.092(5)
F34' 0.366(15) 0.043(3) 0.087(6) -0.051(5) -0.034(9) -0.001(4)
F35' 0.234(11) 0.154(8) 0.064(5) -0.016(9) 0.045(7) -0.001(6)
 #=============================================================
#Molecular geometry

loop_
      _geom_bond_atom_site_label_1
      _geom_bond_atom_site_label_2
      _geom_bond_distance

C1-N2 1.345(4)
C1-C5 1.532(4)
C1-O6 1.226(4)
N2-C3 1.460(4)
N2-C7 1.444(5)
C3-N4 1.464(4)
C3-C8 1.553(4)
N4-C5 1.464(4)
C5-C12 1.520(4)
C5-C18 1.535(4)
C8-C9 1.523(5)
C8-C10 1.526(5)
C8-C11 1.535(5)
C12-C13 1.386(4)
C12-C17 1.387(6)
C13-C14 1.381(5)
C14-C15 1.366(7)
C15-C16 1.368(7)
C16-C17 1.396(7)
C18-O19 1.414(4)
O19-C20 1.413(4)
C20-C21 1.518(5)
C21-C22 1.520(5)
C22-C23 1.386(5)
C22-C27 1.389(4)
C23-C24 1.396(5)
C24-C25 1.368(5)
C24-C28 1.511(5)
C25-C26 1.398(5)
C26-C27 1.378(5)
C26-C32 1.491(6)
C28-F29 1.302(5)
C28-F30 1.322(7)
C28-F31 1.291(5)
C32-F33 1.371(7)
C32-F34 1.277(7)
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C32-F35 1.272(7)
C32-F33' 1.407(12)
C32-F34' 1.140(9)
C32-F35' 1.281(12)
C3-H3 1.05
N4-H4 0.98
C7-H7A 1.05
C7-H7B 1.05
C7-H7C 1.05
C9-H9A 1.05
C9-H9B 1.05
C9-H9C 1.05
C10-H10A 1.05
C10-H10B 1.05
C10-H10C 1.05
C11-H11A 1.05
C11-H11B 1.05
C11-H11C 1.05
C13-H13 1.00
C14-H14 1.00
C15-H15 1.00
C16-H16 1.00
C17-H17 1.00
C18-H18A 1.05
C18-H18B 1.05
C20-H20 1.05
C21-H21A 1.05
C21-H21B 1.05
C21-H21C 1.05
C23-H23 1.00
C25-H25 1.00
C27-H27 1.00


loop_
     _geom_angle_atom_site_label_1
     _geom_angle_atom_site_label_2
     _geom_angle_atom_site_label_3
     _geom_angle

N2-C1-C5 108.1(3)
N2-C1-O6 125.4(3)
C5-C1-O6 126.4(3)
C1-N2-C3 113.6(2)
C1-N2-C7 119.8(3)
C3-N2-C7 124.7(2)
N2-C3-N4 103.8(2)
N2-C3-C8 114.4(2)
N4-C3-C8 111.1(2)
C3-N4-C5 110.7(2)
C1-C5-N4 103.7(3)
C1-C5-C12 115.5(2)
C1-C5-C18 107.1(2)
N4-C5-C12 112.6(2)
N4-C5-C18 110.6(2)
C12-C5-C18 107.2(3)
C3-C8-C9 110.8(3)
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C3-C8-C10 106.8(3)
C3-C8-C11 111.4(3)
C9-C8-C10 109.6(3)
C9-C8-C11 109.9(3)
C10-C8-C11 108.2(3)
C5-C12-C13 120.0(3)
C5-C12-C17 121.6(3)
C13-C12-C17 118.2(3)
C12-C13-C14 120.9(4)
C13-C14-C15 120.8(4)
C14-C15-C16 119.1(4)
C15-C16-C17 121.0(5)
C12-C17-C16 119.9(4)
C5-C18-O19 107.8(3)
C18-O19-C20 115.5(2)
O19-C20-C21 110.8(3)
O19-C20-C22 107.2(3)
C21-C20-C22 112.3(2)
C20-C22-C23 120.0(3)
C20-C22-C27 120.7(3)
C23-C22-C27 119.2(3)
C22-C23-C24 119.4(3)
C23-C24-C25 121.7(3)
C23-C24-C28 117.3(3)
C25-C24-C28 121.0(3)
C24-C25-C26 118.4(3)
C25-C26-C27 120.6(3)
C25-C26-C32 119.7(3)
C27-C26-C32 119.6(3)
C22-C27-C26 120.6(3)
C24-C28-F29 113.5(4)
C24-C28-F30 112.1(4)
C24-C28-F31 112.3(4)
F29-C28-F30 105.7(4)
F29-C28-F31 108.6(3)
F30-C28-F31 104.1(5)
C26-C32-F33 111.5(4)
C26-C32-F34 112.9(4)
C26-C32-F35 113.2(4)
C26-C32-F33' 111.5(6)
C26-C32-F34' 118.7(6)
C26-C32-F35' 111.8(6)
F33-C32-F34 102.2(4)
F33-C32-F35 104.5(5)
F34-C32-F35 111.7(5)
F33'-C32-F34' 105.6(9)
F33'-C32-F35' 104.4(8)
F34'-C32-F35' 103.7(9)
N2-C3-H3 110.7
N4-C3-H3 113.9
C8-C3-H3 103.3
C3-N4-H4 109.2
C5-N4-H4 109.2
N2-C7-H7A 109.5
N2-C7-H7B 109.2
N2-C7-H7C 109.5
H7A-C7-H7B 109.5
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H7A-C7-H7C 109.5
H7B-C7-H7C 109.5
C8-C9-H9A 109.5
C8-C9-H9B 109.5
C8-C9-H9C 109.5
H9A-C9-H9B 109.5
H9A-C9-H9C 109.5
H9B-C9-H9C 109.5
C8-C10-H10A 109.5
C8-C10-H10B 109.5
C8-C10-H10C 109.5
H10A-C10-H10B 109.5
H10A-C10-H10C 109.5
H10B-C10-H10C 109.5
C8-C11-H11A 109.5
C8-C11-H11B 109.5
C8-C11-C11C 109.5
H11A-C11-H11B 109.5
H11A-C11-H11C 109.5
H11B-C11-H11C 109.5
C12-C13-H13 119.5
C14-C13-H13 119.5
C13-C14-H14 119.6
C15-C14-H14 119.6
C14-C15-H15 120.4
C16-C15-H15 120.4
C15-C16-H16 119.5
C17-C16-H16 119.5
C12-C17-H17 120.1
C16-C17-H17 120.1
C5-C18-H18A 109.9
C5-C18-H18B 109.9
O19-C18-H18A 109.9
O19-C18-H18B 109.9
H18A-C18-H18B 109.5
O19-C20-H20 111.1
C21-C20-H20 105.9
C22-C20-H20 109.6
C20-C21-H21A 109.5
C20-C21-H21B 109.5
C20-C21-H21C 109.5
H21A-C21-H21B 109.5
H21A-C21-H21C 109.5
H21B-C21-H21C 109.5
C22-C23-H23 120.3
C24-C23-H23 120.3
C24-C25-H25 120.8
C26-C25-H25 120.8
C22-C27-H27 119.7
C26-C27-H27 119.7

loop_
     _geom_torsion_atom_site_label_1
     _geom_torsion_atom_site_label_2
     _geom_torsion_atom_site_label_3
     _geom_torsion_atom_site_label_4
     _geom_torsion
```

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C5-C1-N2-C3 3.4(3)
C5-C1-N2-C7 -161.8(3)
O6-C1-N2-C3 179.9(2)
O6-C1-N2-C7 14.7(4)
N2-C1-C5-N4 -2.7(3)
N2-C1-C5-C12 -126.5(3)
N2-C1-C5-C18 114.3(3)
O6-C1-C5-N4 -179.1(3)
O6-C1-C5-C12 57.1(4)
O6-C1-C5-C18 -62.1(4)
C1-N2-C3-N4 -2.7(3)
C1-N2-C3-C8 118.6(3)
C7-N2-C3-N4 161.7(3)
C7-N2-C3-C8 -77.0(4)
N2-C3-N4-C5 0.7(3)
C8-C3-N4-C5 -122.7(3)
N2-C3-C8-C9 -58.5(4)
N2-C3-C8-C10 -177.8(3)
N2-C3-C8-C11 64.3(4)
N4-C3-C8-C9 58.6(3)
N4-C3-C8-C10 -60.6(3)
N4-C3-C8-C11 -178.6(3)
C3-N4-C5-C1 1.2(3)
C3-N4-C5-C12 126.7(3)
C3-N4-C5-C18 -113.4(3)
C1-C5-C12-C13 147.0(3)
C1-C5-C12-C17 -37.0(5)
N4-C5-C12-C13 28.2(4)
N4-C5-C12-C17 -155.9(3)
C18-C5-C12-C13 -93.7(4)
C18-C5-C12-C17 82.2(4)
C1-C5-C18-O19 -53.5(3)
N4-C5-C18-O19 58.9(3)
C12-C5-C18-O19 -178.0(3)
C5-C12-C13-C14 174.6(3)
C17-C12-C13-C14 -1.5(5)
C5-C12-C17-C16 -175.5(4)
C13-C12-C17-C16 0.5(6)
C12-C13-C14-C15 1.5(6)
C13-C14-C15-C16 -0.3(7)
C14-C15-C16-C17 -0.7(7)
C15-C16-C17-C12 0.6(7)
C5-C18-O19-C20 -158.8(3)
C18-O19-C20-C21 -79.4(3)
C18-O19-C20-C22 157.7(3)
O19-C20-C22-C23 5.6(4)
O19-C20-C22-C27 -173.7(3)
C21-C20-C22-C23 -116.3(4)
C21-C20-C22-C27 64.4(4)
C20-C22-C23-C24 -178.9(3)
C27-C22-C23-C24 0.4(5)
C20-C22-C27-C26 179.2(3)
C23-C22-C27-C26 -0.1(5)
C22-C23-C24-C25 -0.4(5)
C22-C23-C24-C28 177.9(4)
C23-C24-C25-C26 0.1(5)
C28-C24-C25-C26 -178.1(4)
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C23-C24-C28-F29 172.6(4)
C23-C24-C28-F30 52.9(5)
C23-C24-C28-F31 -63.9(6)
C25-C24-C28-F29 -9.2(6)
C25-C24-C28-F30 -128.8(4)
C25-C24-C28-F31 114.4(5)
C24-C25-C26-C27 0.2(5)
C24-C25-C26-C32 -179.5(4)
C25-C26-C27-C22 -0.2(5)
C32-C26-C27-C22 179.4(3)
C25-C26-C32-F33 2.5(6)
C25-C26-C32-F34 117.0(5)
C25-C26-C32-F35 -114.9(5)
C25-C26-C32-F33' -177.2(6)
C25-C26-C32-F34' 59.7(10)
C25-C26-C32-F35' -60.8(8)
C27-C26-C32-F33 -177.1(4)
C27-C26-C32-F34 -62.7(6)
C27-C26-C32-F35 65.5(6)
C27-C26-C32-F33' 3.2(7)
C27-C26-C32-F34' -119.9(9)
C27-C26-C32-F35' 119.6(7)

#=============================================================================
Hydrogen_bonded_distance_(Donor_Acceptor) 'N4...O6 (at x, y, 1 + z)  3.200(3)'

 #===END
```