An Investigation of Imidazole and Oxazole Syntheses Using Aryl-Substituted TosMIC Reagents

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Supporting Information

1-(tert-Butyl)-4-(4-fluorophenyl)imidazole-5-carbaldehyde (6): A solution of glyoxaldehyde (40% aqueous, 2.4 mL, 20.7 mmol) and *t*-$BuNH_2$ (4.36 mL, 41.5 mmol) in THF (75 mL) was stirred at ambient temperature for 1 h, at which point the isonitrile **2** (3 g, 10.4 mmol) and piperazine (1.12 g, 13.0 mmol) were added. The solution was stirred an additional 18 h before 1N HCl (50 mL) was added and stirred for 2 h at 25 °C. Solid $NaHCO_3$ was added until the pH was neutral, the solution was diluted with TBME and water and the layers were separated. The organic layer was concentrated *in vacuo* to dryness and the product was isolated (1.60 g, 63%) by silica gel chromatography using hexane/EtOAc (3:1). The product cyrstallized on standing: mp = 98-99 °C; IR (neat) 2720, 1700, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (1H, s), 7.89 (1H, s), 7.52 (2H, m), 7.09 (2H, t, J = 8.7 Hz), 1.67 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 163.3 (d, J = 249 Hz), 159.0, 140.3, 131.6 (d, J = 8 Hz), 129.1 (d, J = 3 Hz), 127.2, 115.5 (d, J = 22 Hz), 58.8, 29.5; Anal. Calcd for $C_{14}H_{15}N_2OF$: C, 68.3; H, 6.1; N, 11.4. Found C, 68.3; H, 6.1; N, 11.3.

[4-(4-Fluorophenyl)-1-methylimidazol-5-yl]methan-1-ol (7): A solution of glycolaldehyde dimer (1.0 g, 8.3 mmol) and $MeNH_2$ (40% aqueous, 1.91 mL, 22.2 mmol) in THF (50 mL) was stirred at ambient temperature for 30 min, at which point the isonitrile **2** (3.21 g, 11.1 mmol) and piperazine (1.43 g, 16.6 mmol) were added. The solution was stirred an additional 18 h, diluted with EtOAc and water and the layers were separated. Because a significant amount of material did not dissolve, the solution was filtered and the filter cake was rinsed with EtOAc and set aside (1.4 g). The organic layer and rinse were combined and the aqueous layer was separated. The aqueous layer was extracted again with EtOAc, the organic layers were combined and washed with water. The organic layer was concentrated *in vacuo* to dryness and the residue

was slurried in EtOAc. The crystallized material (0.5 g) and the filter cake from above were both found to be clean product and were combined (1.9 g, 83%) as a white solid: IR (neat) 3516, 1219 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.69 (2H, m), 7.64, (1H, s), 7.22 (2H, t, J = 8.8 Hz), 5.26 (1H, t, J = 5.2 Hz), 4.52 (2H, d, J = 5.2 Hz), 3.67 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.9 (d, J = 243 Hz), 137.8, 137.6, 131.6, 128.4 (d, J = 7.9 Hz), 127.5, 115.0 (d, J = 21.2 Hz), 51.7, 31.1; Anal. Calcd for $C_{11}H_{11}N_2OF$: C, 64.1; H, 5.4; N, 13.6. Found C, 63.7; H, 5.4; N, 13.3.

Ethyl 4-(3,4-dichlorophenyl)-1-(3-pyridylmethyl)imidazole-5-carboxylate (8): A solution of ethyl glyoxylate (50% in toluene, 1.75 mL, 8.82 mmol) and 3-(aminomethyl)pyridine (1.11 g, 10.3 mmol) in THF (50 mL) was stirred at ambient temperature for 5 h, at which point the isonitrile **2b** (2.0 g, 5.88 mmol) and piperazine (0.74 g, 8.8 mmol) were added. The solution was stirred an additional 18 h, diluted with EtOAc and water and the layers were separated. The organic layer was washed with water, concentrated *in vacuo* and subjected to silica gel chromatography with EtOAc to give 1.2 g (54%) of the product as a yellow oil: IR (neat) 1704, 1594, 1209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (2H, m, 7.75 (1H, d, J = 2.0 Hz), 7.69 (1H, s), 7.49 (1H, dd, J = 2.0, 8.4 Hz), 7.44 (1H, m), 7.38 (1H, d, J = 8.4 Hz), 7.23 (1H, m), 5.50 (2H, s), 4.13 (2H, q, J = 7.1 Hz), 1.12 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 149.4, 148.6, 147.1, 141.1, 134.9, 134.1, 132.1, 132.0, 131.6, 129.5, 128.9, 123.7, 118.7, 61.0, 48.5, 13.7; HRMS calc'd for $C_{18}H_{15}N_3O_2Cl_2$ 375.0541, found 375.0540.

2-Methoxy-1-[1-methyl-5-(2-methylpropyl)imidazol-4-yl]benzene (9): A solution of isovaleraldehyde (0.22 mL, 2.09 mmol) and $MeNH_2$ (40% aqueous, 0.21 mL, 2.5 mmol) in DMF (15 mL) was stirred for 1 h before adding TosMIC reagent **2c** (0.5 g, 1.66 mmol) and K_2CO_3 (0.29 g, 2.08 mmol). After 18 h, water and TBME were added and the layers were separated. The organics were washed with water and brine and concentrated *in vacuo*. After silica gel chromatography using EtOAc, the product was isolated (0.25 g, 62%) as an oil which solidified on standing: mp = 53-56 °C; IR (KBr) 2951, 1506, 1238, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, s), 7.31 (1H, dd, J = 1.7, 7.5 Hz), 7.19 (1H, m), 6.89 (1H, m), 6.83 (1H, d, J = 8.1 Hz), 3.70 (3H, s), 3.47 (3H, s), 2.42 (2H, d, J = 7.4 Hz), 1.58 (1H, m), 0.65 (6H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 136.6, 135.7, 131.7, 128.7, 128.3, 125.0, 120.4, 110.9, 55.3, 32.6, 31.7, 28.4, 22.2; HRMS calc'd for $C_{15}H_{20}N_2O$ 244.1576, found 244.1575.

1-Ethyl-4-(4-fluorophenyl)-5-indol-3-ylimidazole (10): To a 100 mL flask was added 50 mL MeOH, indole-3-carboxaldehyde (1.25 g, 8.64 mmol) and $EtNH_2$ (70% aqueous solution, 2.25 mL, 27.6 mmol). After stirring for 48 h at ambient temperature, isonitrile **2** (2.0 g, 6.91 mmol) and piperazine (0.89 g, 10.4 mmol) were added and the solution was stirred an additional 7 h. Water and EtOAc were added and the layers were separated. The organic layer was washed with water and brine and concentrated. After silica gel chromatography using EtOAc:MeOH (19:1), the product was obtained as a white solid (1.03 g, 49%): mp = 185-187 °C; IR (KBr) 3428, 3104, 2975, 1493 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.57 (1H, s), 7.90 (1H, s), 7.56 (1H, d, J = 2.5 Hz), 7.47 (3H, m), 7.12 (2H, m), 6.94 (3H, m), 3.75 (2H, q, J = 7.2 Hz), 1.10 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4 (d, J = 241 Hz), 136.9, 136.7, 136.2, 131.8, 126.9 (d, J = 7.7 Hz), 126.3, 121.6, 121.1, 119.5, 118.5, 114.5 (d, J = 21 Hz), 111.9, 103.3, 39.5, 16.3; Anal. Calcd for $C_{19}H_{16}N_3F$: C, 74.7; H, 5.3; N, 13.8. Found C, 74.6; H, 5.5; N, 13.7.

4-[1-(3-Hydroxypropyl)-4-(4-methoxyphenyl)imidazol-5-yl]phenol (11): A solution of 4-hydroxyphenol (1.0 g, 8.2 mmol) and 3-amino-1-propanol (0.62 g, 8.2 mmol) in MeOH (30 mL) was stirred at ambient temperature for 2.5 h, at which point the isonitrile **2d** (1.64 g, 5.5 mmol) and piperazine (0.7 g, 8.2 mmol) were added. The solution was stirred an additional 18 h, diluted with EtOAc and water and the layers were separated. The organic layer was concentrated *in vacuo* and the residue was dissolved in a minimum amount of EtOAc:MeOH:hexane (2:1:1) and stirred for 30 min. The crystals which had formed were collected by filtration and dried under vacuum to give the product (1.2 g, 67%) as a white solid: mp = 194-195 °C; IR (KBr) 3428, 1519, 1248 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.74 (1H, s), 7.69 (1H, s), 7.30 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.3 Hz), 6.75 (2H, d, J = 8.6 Hz), 4.54 (1H, t, J = 4.8 Hz), 3.80 (2H, t, J = 7.1 Hz), 3.67 (3H, s), 3.28 (2H, q, J = 5.5 Hz), 1.61 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.5, 157.4, 136.5, 136.3, 131.8, 127.8, 127.1, 126.8, 120.9, 115.8, 113.3, 57.4, 54.8, 41.4, 33.1; Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.4; H, 6.2; N, 8.6. Found C, 70.4; H, 6.2; N, 8.6.

4-(4-Fluorophenyl)-5-{3-[4-(4-fluorophenyl)-1-prop-2-enylimidazol-5-yl]propyl}-1-prop-2-enylimidazole (15): A solution of glutaric dialdehyde (50% aqueous, 2.03 mL, 11.2 mmol) and allylamine (1.95 mL, 25.9 mmol) in EtOAc (200 mL) was stirred at 25 °C for 4 h. TosMIC reagent **2** (5.0 g, 17.3 mmol) and piperazine (2.18 g, 25.9 mmol) were added and the solution was stirred for an additional 18 h. Water was added and the layers were separated. The organics were washed with water and brine and concentrated *in vacuo*. After silica gel chromatography using EtOAc, the pure product was obtained (1.92 g,

50%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (4H, m), 7.37 (2H, s), 6.99 (4H, t, J = 8.7 Hz), 5.80 (2H, m), 5.15 (2H, d, J = 10.6 Hz), 4.93 (2H, d, J = 17.1 Hz), 4.30 (4H, d, J = 5.1 Hz), 2.64 (4H, t, J = 7.8 Hz), 1.69 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, J = 244 Hz), 137.54, 136.4, 132.8, 131.3, 128.5 (d, J = 7.9 Hz), 126.5, 118.1, 115.3 (d, J = 21 Hz), 47.2, 29.1, 23.0; HRMS calc'd for $C_{27}H_{26}N_4F_2$ 444.2126, found 444.2128.

Di2-[4-(4-fluorophenyl)-5-(5-methyl(2-furyl))imidazolyl]ethyl disulfide (19): A solution of 5-methylfurfural (1.77 mL, 17.8 mmol), cysteamine di-HCl (2.0 g, 8.9 mmol) and $NaHCO_3$ (1.87 g, 22.2 mmol) in MeOH (30 mL) and water (2 mL) was stirred at ambient temperature for 1 h, at which point the isonitrile **2** (5.14 g, 17.8 mmol) and piperazine (1.91 g, 22.2 mmol) were added. The solution was stirred an additional 18 h, filtered and rinsed with TBME. The product was dried under vacuum to give 4.6 g (86%) of a beige solid: mp = 164-165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (2H, s), 7.49 (4H, m), 7.12 (4H, t, J = 8.9 Hz), 6.58 (2H, d, J = 3.1 Hz), 6.24 (2H, d, J = 3.1 Hz), 4.12 (4H, t, J = 7.0 Hz), 2.86 (4H, t, J = 7.0 Hz), 2.27 (6H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.0 (d, J = 242 Hz), 153.1, 140.4, 139.2, 138.6, 130.6, 127.7 (d, J = 7.8 Hz), 117.9, 114.9 (d, J = 19.1 Hz), 113.7, 107.5, 43.8, 37.2, 13.2; Anal. Calcd for $C_{32}H_{28}N_4S_2O_2F_2$: C, 63.8; H, 4.7; N, 9.3. Found C, 63.6; H, 4.7; N, 9.0.

(2S)-2-[4-(4-Fluorophenyl)-5-(3-thienyl)imidazolyl]-3-hydroxypropanoic acid (33): A solution of 3-thiophenecarboxaldehdye (1.16 g, 10.4 mmol), L-serine (1.09 g, 10.4 mmol) and NaOH (0.42 g, 10.4 mmol) in MeOH (30 mL) and water (3 mL) was stirred at ambient temperature for 5.5 h, at which point the isonitrile **2** (2 g, 6.9 mmol) and piperazine (0.9 g, 10.4 mmol) were added. The solution was stirred an additional 18 h and concentrated under vacuum. The brown syrup was diluted in water, EtOAc and 10% NaOH until the pH was 11. The aqueous layer was collected and acidified to pH 3.5-4.0 with 3N HCl and a white solid precipitated from solution. The product was filtered and rinsed with water and the filter cake was slurried in TBME for 30 min and filtered again. The product was dried under vacuum to give 1.7 g (74%) of a white solid: mp = 206-208 °C; IR (KBr) 3404, 3300-2500, 1620 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (1H, s), 7.73 (1H, dd, J = 2.8, 4.8 Hz), 7.57 (1H, d, J = 2.8 Hz) 7.47 (2H, m), 7.04 (3H, m), 4.37 (1H, dd, J = 4.6, 6.5 Hz), 3.93 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 160.6 (d, J = 243 Hz), 136.9, 135.3, 131.4, 129.8, 129.3, 127.5, (d, J = 7.8 Hz), 127.2, 127.1, 123.2, 114.7 (d, J = 21.3 Hz), 61.9, 60.4; HRMS calc'd for $C_{16}H_{13}N_2O_3FS$ 332.0631, found 332.0631. The enantiomeric excess was determined by

HPLC using a Chiralpak AD column, with EtOH:Hexane:TFA (10:90:0.1) as mobile phase, flow rate of 0.5 mL/min and UV detection at 254 nm. Retention times: S-isomer at 16.9 min, R-isomer at 14.4 min.

(2S)-2-[5-(3-Hydroxy-4-methoxyphenyl)-4-(3-thienyl)imidazolyl]-3-phenylpropanoic acid (34): A solution of L-phenylalanine (0.95 g, 0.58 mmol) and NaOH (0.22 g, 5.4 mmol) in MeOH (20 mL) and water (2 mL) was stirred at ambient temperature for 15 min until a clear solution was obtained. 3-Hydroxy-4-methoxybenzaldehyde (0.82 g, 5.4 mmol) was added and the solution was stirred for 5 h, at which point the isonitrile **2g** (1 g, 3.6 mmol) and piperazine (0.47 g, 5.4 mmol) were added. The solution was stirred an additional 18 h and concentrated under vacuum. The yellow syrup was dissolved in water and EtOAc, brought to pH 10-10.5 with a 10% NaOH solution, transferred to a separatory funnel and the layers were separated. The aqueous layer was acidified with conc. HCl to pH 3.0-3.5. The white solid that precipitated was collected by filtration, rinsed with H_2O and dried in a vacuum oven at 60 °C. The product was obtained as an off-white solid (1.2 g, 79%): IR (KBr) 3600-2350 (broad), 3426, 1725, 1618 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.92 (1H, s), 7.31 (1H, m), 7.21 (3H, m), 7.08 (1H, dd, J = 0.9, 2.8 Hz), 7.01 (1H, d, J = 6.8 Hz), 6.92 (1H, d, J = 8.3 Hz), 6.82 (1H, dd, J = 0.9, 4.9 Hz), 6.39 (1H, s), 6.20 (1H, br s), 4.49 (1H, dd, J = 5.0, 10.6 Hz), 3.80 (3H, s), 3.31 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.2, 148.2, 146.6, 137.1, 136.2, 135.7, 132.1, 128.7, 128.1, 128.0, 126.4, 125.7, 125.2, 121.8, 118.3, 117.9, 112.1, 59.4, 55.4, 37.8; HRMS calc'd for $C_{23}H_{20}N_2O_4S$ 420.1144, found 420.1142. The enantiomeric excess was determined by HPLC using a Chiralpak AD column, with EtOH:Hexane:TFA (20:80:0.1) as mobile phase, flow rate of 1.0 mL/min and UV detection at 254 nm. Retention times: S-isomer at 5.1 min, R-isomer at 9.4 min.

3-[4-(4-Fluorophenyl)-5-(5-methyl(2-furyl))imidazolyl]propanoic acid (35): A solution of 5-methylfurfural (1.43 g, 12.9 mmol), β-alanine (1.16 g, 12.9 mmol) and NaOH (0.52 g, 12.9 mmol) in MeOH (20 mL) and water (2 mL) was stirred at ambient temperature for 1.5 h, at which point the isonitrile **2** (3 g, 10.4 mmol) and piperazine (1.34 g, 15.6 mmol) were added. The solution was stirred an additional 18 h and concentrated under vacuum. The brown syrup was dissolved in water and EtOAc, brought to pH 3.0-3.5 with 3N HCl, transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted a second time with EtOAc and the organic layers were combined and concentrated to 25-30 mL. After standing for 1 h, the product which had crystallized was filtered and rinsed with EtOAc. The product was dried under vacuum to give 2.52 g (76%) of white solid: mp = 195-196 °C; IR (KBr) 3434, 3100-2200 (broad), 1700, 1497 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.84 (1H, s), 7.50 (2H, m), 7.11 (2H, t, J = 8.9

Hz), 6.60 (1H, d, J = 2.9 Hz), 6.26 (1H, d, J = 2.9 Hz), 4.08 (2H, t, J = 7.0 Hz), 2.62 (2H, t, J = 7.0 Hz), 2.30 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 161.0 (d, J = 244 Hz), 153.1, 140.5, 139.0, 138.5, 130.7, 127.7 (d, J = 7.9 Hz), 117.9, 114.9 (d, J = 21.3 Hz), 113.5, 107.5, 40.8, 34.6, 13.2; Anal. Calcd for $C_{17}H_{15}N_2O_3F$: C, 65.0; H, 4.8; N, 8.9. Found C, 65.1; H, 4.8; N, 8.8.

N-{(1R)-1-[1-(2,2-Dimethoxyethyl)-4-(4-fluorophenyl)imidazol-5-yl]-2-phenylethyl}(tert-butoxy)carboxamide (37): A solution of N-*t*-BOC-D-phenylaninal (**36**) (0.25 g, 1.0 mmol) and aminoacetaldehyde dimethyl acetal (0.12 mL, 1.15 mmol) in DMF (5 mL) was stirred at ambient temperature for 2.5 h, at which point the isonitrile **2** (0.28 g, 0.96 mmol) and K_2CO_3 (0.17 g, 1.25 mmol) were added. The solution was stirred an additional 18 h, diluted with TBME and water and the layers were separated. The organic layer was washed with water and concentrated. The product was isolated after chromatography on silica gel eluting with hexane/EtOAc (1:1) to yield a colorless oil (0.39 g, 87%): IR (neat) 3331, 1701, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, s), 7.31 (2H, m), 7.09 (3H, m), 6.98 (2H, t, J = 8.7 Hz), 6.85 (2H, m), 5.62 (1H, d, J = 6.9 Hz), 4.99 (1H, m), 4.17 (1H, t, J = 4.9 Hz), 4.02 (1H, dd, J = 4.9, 14.7 Hz), 3.85 (1H, dd, J = 4.9, 14.7), 3.30 (3H, s), 3.25 (3H, s), 2.99 (1H, dd, J = 6.1, 13.2), 2.88 (1H, dd, J = 9.2, 13.2 Hz), 1.35 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, J = 247 Hz), 154.9, 138.8, 137.8, 137.2, 131.2, 130.6 (d, J = 7.8 Hz), 129.0, 128.4, 126.8, 126.7, 115.0 (d, J = 21.0 Hz), 103.5, 79.7, 55.4, 55.2, 48.2, 47.8, 40.9, 28.3; HRMS calc'd for $C_{26}H_{32}N_3O_4F$ 469.2377, found 469.2375. The enantiomeric excess was determined by HPLC using a Chiralpak AD column, with IPA:Hexane (10:90) as mobile phase, flow rate of 2.0 mL/min and UV detection at 254 nm. Retention times: R-isomer at 9.1 min, S-isomer at 6.3 min.

Ethyl 4-[5-acetyl-4-(4-fluorophenyl)imidazolyl]piperidinecarboxylate (40): To a solution of pyruvaldehyde (40% aqeuous solution, 3.97 mL, 25.94 mmol) in 34 mL of DMF was added ethyl 4-amino-piperidinecarboxylate (4.45 mL, 25.94 mmol). After 10 min, isonitrile **2** (5.0 g, 17.3 mmol) and K_2CO_3 (2.39 g, 17.3 mmol) were added. After 15 h, the solution was diluted with EtOAc and washed with 3 N HCl. The aqueous layers were combined and made basic with excess solid K_2CO_3. The aqueous layer was extracted with EtOAc. The combined organics were washed with water and concentrated *in vacuo*. The product was crystallized from $CHCl_3$/hexane to yield the imidazole product (4.65 g, 75%) as an off-white solid: mp = 118-19 °C; IR (KBr) 1691, 1681, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, s), 7.44 (2H, m), 7.14 (2H, t, J = 8.6 Hz), 5.00 (1H, tt, J = 3.7, 12.1 Hz), 4.35 (2H, m), 4.17 (2H, q, J = 7.1 Hz),

2.93 (2H, m), 2.18 (2H, br d, J = 12.9 Hz), 2.12 (3H, s), 1.80 (2H, dq, J = 4.2, 12.4 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 163.1 (d, J = 246.8 Hz), 155.3, 149.8, 137.4, 131.4 (d, J = 8.2 Hz), 127.0, 115.5 (d, J = 21.5 Hz), 61.6, 54.9, 43.3, 33.4, 30.5, 14.6; Anal. Calcd for $C_{19}H_{22}N_3O_3F$: C, 63.5; H, 6.2; N, 11.7. Found C, 63.1; H, 6.1; N, 11.5.

4-(4-Fluorophenyl)-4-[(4-methylphenyl)sulfonyl]-1,3-oxazoline (43): A solution of the aqueous formaldehyde (37%, 1.56 mL, 20.8 mmol), K_2CO_3 (1.92 g, 13.8 mmol) and isonitrile **2** (4 g, 13.8 mmol) in DMF (20 mL) was stirred at ambient temperature for 3-6 h. The solution was diluted with TBME and water and the layers were separated. The aqueous layer was extracted again with TBME, the organic layers were combined and washed with water. The organic layer was concentrated *in vacuo* and the crystallized from ether/hexane as a white crystalline product (73%): mp 85-86 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (1H, s), 7.34 (4H, s), 7.29 (2H, m), 7.15 (2H, t, J = 8.8 Hz), 5.29 (1H, d, J = 11.1 Hz), 4.62 (1H, d, J = 11.1 Hz), 2.37 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4 (d, J = 245 Hz), 160.1, 145.0, 131.3, 130.6, 130.3 (d, J = 8.6 Hz), 130.0, 129.0, 114.8 (d, J = 21.7 Hz), 95.8, 71.9, 21.0; Anal. Calcd for $C_{16}H_{14}NO_3SF$: C, 60.2; H, 4.4; N, 4.4; S, 10.0. Found C, 59.8; H, 4.3; N, 4.3; S, 9.9.

Ethyl 4-{[4-(4-fluorophenyl)-1,3-oxazolin-2-yl]amino}piperidinecarboxylate (44): To a solution of formaldehyde (37% aqeuous solution, 0.44 mL, 5.8 mmol) in 8 mL of DMF at 0 °C was added ethyl 4-amino-piperidinecarboxylate (1.0 mL, 5.8 mmol). After 10 min, isonitrile **2** (1.12 g, 3.9 mmol) and K_2CO_3 (0.53 g, 3.9 mmol) were added. The solution was allowed to slowly warm to room temperature over 2 h and after 15 h at room temperature, was diluted with TBME and water. The aqueous layer was extracted again with TBME and the combined organics were washed with water and concentrated *in vacuo*. The residue was dissolved in EtOAc and diluted with hexane. After 30 min, the product was collected by filtration and rinsed with hexane (0.91 g, 70%) as an off-white solid: mp = 101-102 °C; IR (KBr) 3313, 1697, 1678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, m), 7.05 (2H, t, J = 8.6 Hz), 6.43 (1H, d, J = 3.0, 4.8 Hz), 4.98 (1H, dd, J = 4.8, 14.0 Hz), 4.76 (1H, dd, J = 3.0, 14.0 Hz), 4.03 (2H, q, J = 7.1 Hz), 3.98 (2H, m), 2.95 (1H, m), 2.82 (2H, m), 1.86 (2H, m), 1.31 (2H, m), 1.16 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCL_3$) δ 168.9, 164.8 (d, J = 210 Hz), 155.4, 130.0 (d, J = 6.8 Hz), 126.8, 115.9 (d, J = 18.0 Hz), 112.9, 72.1, 61.1, 50.8, 42.4, 33.7, 32.8, 14.6; Anal. Calcd for $C_{17}H_{22}N_3O_3F$: C, 60.9; H, 6.5; N, 12.4. Found C, 61.0; H, 6.6; N, 12.4.

General Procedure for the Preparation of 1,4-Disubstituted Imidazoles: A solution of gyoxylic acid (monohydrate or 50% aqueous solution, 21.6 mmol), K_2CO_3 (43.2 mmol) and amine (25.9 mmol) in DMF (50 mL) was stirred at ambient temperature for 3 h, at which point the isonitrile (17.3 mmol) was added. The solution was stirred an additional 18 h, diluted with TBME and water and the layers were separated. The aqueous layer was extracted again with TBME, the organic layers were combined and washed with water. The organic layer was concentrated *in vacuo* to dryness and the residue was either recrystallized or purified by flash chromatography.

Ethyl 4-[4-(4-fluorophenyl)imidazolyl]piperidinecarboxylate (41): The product was crystallized from ether (91%): mp 108-109 °C; IR (KBr) 3125, 2857, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, m), 7.54 (1H, d, J = 1.3 Hz), 7.16 (1H, d, J = 1.3 Hz), 7.03 (2H, t, J = 8.8 Hz), 4.33 (2H, m), 4.15 (2H, q, J = 7.1 Hz), 4.08 (1H, tt, J = 4.0, 11.8 Hz), 2.88 (2H, t, J = 12.4 Hz), 2.10 (2H, dd, J = 1.7, 12.4 Hz), 1.86 (2H, dq, J = 4.4, 12.4 Hz), 1.27 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, J = 245 Hz), 155.3, 141.5, 135.5, 130.4, 126.3 (d, J = 8.5 Hz), 115.3 (d, J = 21.1 Hz), 112.2, 61.6, 55.1, 42.9, 33.2, 14.6; Anal. Calcd for $C_{17}H_{20}N_3O_2F$: C, 64.3; H, 6.4; N, 13.3. Found C, 64.7; H, 6.2; N, 13.3.

2-[4-(4-Fluorophenyl)imidazolyl]-1,1-dimethoxyethane (49): The product was obtained as a yellow oil after chromatography with EtOAc (81%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, m), 7.47 (1H, d, J = 0.9 Hz), 7.15 (1H, d, J = 0.9 Hz), 7.01 (2H, t, J = 8.8 Hz), 4.46 (1H, t, J = 5.1 Hz), 3.98 (2H, d, J = 5.1 Hz), 3.36 (6H, s) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, J = 245 Hz), 141.4, 137.9, 130.5, 126.3 (d, J = 7.8 Hz), 115.3 (d, J = 21.8 Hz), 103.4, 54.9, 49.3; Anal. Calcd for $C_{13}H_{15}N_2O_2F$: C, 62.4; H, 6.0; N, 11.2. Found C, 62.2; H, 5.9; N, 11.1.

1-(tert-Butyl)-4-(4-fluorophenyl)imidazole (50): The neat product crystallized on standing (86%): mp 94-95 °C; IR (KBr) 3131, 2978, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, m), 7.62 (1H, d, J = 0.9 Hz), 7.26 (1H, d, J = 0.9 Hz), 7.03 (2H, t, J = 8.8 Hz), 1.59 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J = 244 Hz), 141.0, 134.5, 130.8, 126.2 (d, J = 8.6 Hz), 115.3 (d, J = 21.1 Hz), 111.9, 55.0, 30.5; Anal. Calcd for $C_{13}H_{15}N_2F$: C, 71.5; H, 6.9; N, 12.8. Found C, 71.2; H, 6.9; N, 12.6.

4-(4-Fluorophenyl)-1-methylimidazole (51): The product was crystallized from TBME (53%): mp 124-125 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, m), 7.43 (1H, d, J = 1.0 Hz), 7.09 (1H, d, J = 1.0

Hz), 7.03 (2H, t, J = 8.8 Hz), 3.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, J = 244 Hz), 141.6, 138.0, 130.5, 126.3 (d, J = 7.9 Hz), 115.5, 115.3 (d, J = 21.5 Hz), 33.4; Anal. Calcd for $C_{10}H_9N_2F$: C, 68.2; H, 5.2; N, 15.9. Found C, 68.5; H, 5.2; N, 15.8.

3-[1-((1R)-1-Phenylethyl)imidazol-4-yl]thiophene (52): The product was obtained as a yellow oil after chromatography with EtOAc (87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, J = 1.2 Hz), 7.53 (1H, dd, J = 1.4, 2.9 Hz), 7.33 (5H, m), 7.17 (2H, m), 5.33 (1H, q, J = 7.0 Hz), 1.88 (3H, d, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 138.7, 136.1, 136.0, 128.9, 128.1, 126.0, 125.7, 125.5, 118.7, 113.7, 56.7, 21.9; Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.8; H, 5.6; N, 11.0; S, 12.6. Found C, 70.6; H, 5.6; N, 10.6, S, 12.2. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column, with IPA:Hexane (10:90) as mobile phase, flow rate of 1.0 mL/min and UV detection at 254 nm. Retention times: R-isomer at 13.8 min, S-isomer at 12.2 min.

2-(4-Phenylimidazolyl)ethan-1-ol (53): The product was crystallized from TBME (79%): mp = 116-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, m), 7.43 (1H, d, J = 1.1 Hz), 7.33 (2H, m), 7.24 (1H, m), 6.97 (1H, d, J = 1.1 Hz), 4.10 (1H, br s), 3.97 (2H, t, J = 4.7 Hz), 3.84 (2H, t, J = 4.7 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 137.5, 133.7, 128.5, 126.8, 124.7, 115.2, 61.2, 50.2; Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found C, 70.0; H, 6.3; N, 14.7.

Methyl (2S)-2-[4-(3,4-dichlorophenyl)imidazolyl]-3-methylbutanoate (54): Glyoxylic acid (50% aqueous solution, 0.23 mL, 2.1 mmol), valine methyl ester hydrochloride (0.37 g, 2.2 mmol) and $NaHCO_3$ (0.41 g, 4.9 mmol) were combined in 4 mL of DMF for 2 h, at which point isonitrile **2b** (0.5 g, 1.47 mmol) and K_2CO_3 (0.22 g, 1.62 mmol) were added. After 18 h, the reaction was diluted with H_2O and TBME. The organic layer was concentrated and the product was chromatographed on silica gel using 2:1 hexane:EtOAc (83%): IR (neat) 2968, 2876, 1747, 1466 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.82 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 1.2 Hz), 7.53 (1H, dd, J = 2.0, 8.4 Hz), 7.37 (1H, d, J = 1.2 Hz), 7.35 (1H, d, J = 8.4 Hz), 4.28 (1H, d, J = 9.5 Hz), 3.72 (3H, s), 2.38 (1H, m), 0.96 (3H, d, J = 6.7 Hz), 0.78 (3H, d, J = 6.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.5, 139.8, 137.6, 134.0, 132.4, 130.3, 130.1, 126.4, 123.9, 114.9, 66.5, 52.5, 32.0, 19.0, 18.4; Anal. Calcd for $C_{15}H_{16}N_2O_2Cl_2$: C, 55.0; H, 4.9; N, 8.6. Found C, 55.3; H, 4.9; N, 8.3. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column, with IPA:Hexane (10:90) as

mobile phase, flow rate of 1.0 mL/min and UV detection at 254 nm. Retention times: S-isomer at 6.5 min, R-isomer at 5.2 min.

4-(4-Fluorophenyl)-1-(2-indol-3-ylethyl)imidazole (55): To a 50 mL flask was added glyoxylic acid (50% aqueous, 0.77 g, 5.19 mmol), tryptamine (0.83 g, 5.19 mmol) and NaOH (50% aqueous, 0.42 g, 5.19 mmol). After 2 h at ambient temperature, isonitrile **2** (1.0 g, 3.46 mmol) and piperazine (0.45 g, 5.19 mmol) were added and stirred for 18 h. The reaction was diluted with EtOAc and H_2O and the layers were separated. The aqueous phase was extracted again with EtOAc and the organics were combined and concentrated. The product was purified by column chromatography on silica gel using EtOAc and subsequently crystallized from 2-PrOH/H_2O to give a white solid (0.66 g, 62%): mp = 173-174 °C; IR (KBr) 3165, 1559, 1492 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 10.82 (1H, s), 7.75 (2H, m), 7.68 (1H, d, J = 1.0 Hz), 7.58 (2H, m), 7.33 (1H, d, J = 8.1 Hz), 7.20 (2H, m), 7.06 (2H, m), 6.98 (1H, m), 4.25 (2H, t, J = 7.3 Hz), 3.19 (2H, t, J = 7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.7 (d, J = 242 Hz), 139.5, 137.7, 136.1, 131.3, 126.9, 125.8 (d, J = 8 Hz), 123.0, 121.0, 118.3, 118.2, 115.4, 115.1 (d, J = 21 Hz), 111.3, 110.4, 46.8, 26.7; Anal. Calcd for $C_{19}H_{16}N_3F$: C, 74.7; H, 5.3; N, 13.8. Found C, 74.6; H, 5.2; N, 13.6.

General Procedure for the Preparation of 4,5-Disubstituted Imidazoles: A solution of the aldehyde (25.9 mmol) and NH_4OH (30% aqueous, 69.2 mmol) in THF (75 mL) was stirred at ambient temperature for 3-8 h, at which point the TosMIC reagent (17.3 mmol) and piperazine (25.9 mmol) were added. The solution was stirred an additional 18 h, diluted with EtOAc and water and the layers were separated. The organic layer was washed with water, saturated $NaHCO_3$ solution and concentrated *in vacuo* to dryness. The products were isolated by crystallization or chromatography. The ^{13}C spectra of the 4,5-disubstituted imidazoles in Table 4 were collected at 25 °C. Due to annular tautomerism, the width of some signals in the ^{13}C spectrum (10-20 Hz) under these conditions makes them undetectable and accounts for less than the expected number of resonances for these compounds.[1]

1-[4-(4-Fluorophenyl)imidazol-5-yl]-4-methoxybenzene (58): The product was crystallized from toluene (65%) as a white solid: IR (KBr) 3432, 1522 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.73 (1H, s), 7.47 (2H, m), 7.35 (2H, d, J = 8.5 Hz), 7.14 (2H, t, J = 8.8 Hz(, 6.93 (2H, d, J = 8.5 Hz), 3.75 (3H, s) ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.9 (d, J = 241 Hz), 158.4, 135.0, 128.8, 115.0 (d, J = 21), 113.9, 55.0; Anal. Calcd for $C_{16}H_{13}N_2OF$: C, 71.6; H, 4.9; N, 10.4. Found C, 71.2; H, 4.9; N, 10.3.

4-(4-Fluorophenyl)-5-(2-methylpropyl)imidazole (59): The product was crystallized from TBME (66%) as a white solid: IR (KBr) 3516, 1219 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (1H, br s), 7.60 (2H, m), 7.56, (1H, s), 7.18 (2H, t, J = 8.9 Hz), 2.59 (2H, d, J = 7.3 Hz), 1.91 (1H, m), 0.84 (6H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4 (d, J = 240 Hz), 134.6, 133.7, 132.4, 127.8, 125.6, 114.8 (d, J = 21.1 Hz), 33.8, 28.2, 22.1; Anal. Calcd for $C_{13}H_{15}N_2F$: C, 71.5; H, 6.9; N, 12.8. Found C, 63.7; H, 5.4; N, 13.3.

4-(4-Fluorophenyl)imidazol-5-yl]methan-1-ol (60): The product was crystallized from EtOAc (23%) as a white solid: mp = 184-185 °C; IR (KBr) 3400, 1243 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.49 (1H, br s), 7.72 (2H, m), 7.61 (1H, s), 7.22 (2H, t, J = 8.7 Hz), 5.30 (1H, br s), 4.53 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.7 (d, J = 243 Hz), 134.2, 128.1 (d, J = 8 Hz), 115.0 (d, J = 21), 54.2; Anal. Calcd for $C_{10}H_9N_2OF$: C, 62.5; H, 4.7; N, 14.6. Found C, 62.1; H, 4.7; N, 14.3.

4-(4-Fluorophenyl)-5-(4-pyridyl)imidazole (61):[2] The product was crystallized from acetone/hexane (2:1) as a beige solid (60%): mp = 249 °C; IR (KBr) 3450, 1606 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.48 (1H, br s), 8.45 (2H, d, J = 6.0 Hz), 7.87 (1H, s), 7.49 (2H, m), 7.40 (2H, d, J = 6.0 Hz), 7.27 (2H, t, J = 8.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.7 (d, J = 245 Hz), 149.6, 140.9, 136.4, 131.1, 130.3 (d, J = 8 Hz), 128.4, 120.7, 115.6 (d, J = 22 Hz); Anal. Calcd for $C_{14}H_{10}N_3F$: C, 70.3; H, 4.2; N, 17.6. Found C, 70.2; H, 4.5; N, 17.3.

4-[4-(4-Fluorophenyl)imidazol-5-yl]phenol (62): The product was crystallized from toluene/EtOAc as a beige solid (72%): mp = 175-176 °C; IR (KBr) 3419, 3221, 1520, 1271 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.65 (1H, br s), 7.71 (1H, s), 7.48 (2H, m), 7.23 (2H, d, J = 8.6 Hz), 7.12 (2H, t, J = 8.9 Hz), 6.77 (2H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.8 (d, J = 243 Hz), 156.7, 134.8, 130.7, 129.0, 128.7 (d, J = 8 Hz), 123.1, 115.3, 114.9 (d, J = 21.7 Hz); HRMS calc'd for $C_{15}H_{11}N_2OF$ 254.0855, found 254.0859.

5-Cyclohex-3-enyl-4-phenylimidazole (63): The product was crystallized from EtOAc/TBME (1:1) as a white solid (81%): mp = 208-209 °C; IR (KBr) 3434, 1647, 1586 cm^{-1}; ^1H NMR (100 °C, 400 MHz, DMSO-d_6) δ 11.62 (1H, br s), 7.52 (2H, d, J = 7.7 Hz), 7.51 (1H, s), 7.37 (2H, m), 7.22 (1H, m), 5.72 (2H,

m), 3.12 (1H, m), 2.34 (1H, m), 2.15 (3H, m), 1.85 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.8, 134.1, 128.2, 127.0, 126.6, 126.5, 125.9, 31.4, 31.3, 28.8, 25.3; Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.3; H, 7.2; N, 12.5. Found C, 80.1; H, 7.2; N, 12.2.

3-(5-Ethylimidazol-4-yl)thiophene (64): The product was crystallized from TBME (78%) as a white solid: mp = 126-127 °C; IR (KBr) 3450, 1595 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.50 (1H, br s), 7.55 (1H, dd, J = 2.9, 4.9 Hz), 7.52 (1H, s), 7.43 (1H, d, J = 2.9 Hz), 7.37 (1H, d, J = 4.9 Hz), 2.73 (2H, q, J = 7.5 Hz), 1.18 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 133.4, 126.4, 125.7, 118.2, 18.9, 13.8; Anal. Calcd for $C_9H_{10}N_2S$: C, 60.6; H, 5.7; N, 15.7. Found C, 60.4; H, 5.7; N, 15.3.

5-((1E)-2-Phenylvinyl)-4-[3-(trifluoromethyl)phenyl]imidazole (65): The product was chromatographed on silica gel using EtOAc to give the product (41%) as a tan solid: mp = 66-70 °C; IR (KBr) 3410, 3100, 1616, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.77 (1H, d, J = 7.3 Hz), 7.67 (1H, s), 7.52 (2H, m), 7.35-7.02 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 136.0, 135.0, 133.9, 131.1, 129.6, 129.5, 129.2, 128.7, 127.8, 126.3, 124.7, 124.6, 124.0, 115.9; HRMS calc'd for $C_{18}H_{13}N_2F_3$ 314.1031, found 314.1028.

4,5-bis(4-Fluorophenyl)imidazole (66): The product was crystallized from EtOAc/toluene (54%) as a white powder: mp = 240 °C; IR (KBr) 3434, 1523, 1509 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.51 (1H, br s), 7.77, (1H, s), 7.45 (4H, m), 7.18 (4H, t, J = 8.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.1 (d, J = 244 Hz), 135.4, 129.6, 129.3 (d, J = 8 Hz), 115.3 (d, J = 22 Hz); Anal. Calcd for $C_{15}H_{10}N_2F_2$: C, 70.3; H, 3.9; N, 10.9. Found C, 70.5; H, 4.2; N, 10.9.

3-(1,3-Oxazol-4-yl)thiophene (68): Glyoxylic acid monohydrate (0.25 g, 2.7 mmol), isonitrile **2g** (0.6 g, 2.16 mmol) and K_2CO_3 (0.75 g, 5.4 mmol) were combined in 10 mL of DMF. After 18 h, the solution was diluted with water and extracted with TBME. The combined organic layers were washed with water and concentrated *in vacuo*. The product was isolated by chromatography with hexane:EtOAc (2:1) as yellow oil (0.26 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, s), 7.79 (1H, s), 7.62 (1H, dd, J = 1.3, 2.8 Hz), 7.31 (2H,m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 136.6, 133.3, 132.1, 126.5, 125.3, 121.6.

1-({[4-(4-Fluorophenyl)(1,3-oxazol-5-yl)]methyl}sulfonyl)-4-methylbenzene (69): A solution of chloroacetaldehyde (50% aqueous, 3.29 mL, 25.9 mmol), K_2CO_3 (2.99 g, 21.6 mmol) and isonitrile **2** (5 g, 17.3 mmol) in DMF (35 mL) was stirred at ambient temperature for 15 h, warmed for 3 h at 95°C and cooled again to room temperature. The solution was diluted with TBME and water and the layers were separated. The aqueous layer was extracted again with TBME, the organic layers were combined and washed with water. The organic layer was concentrated *in vacuo* to a volume of ~25 mL and the product crystallized on standing as a white solid (3.6 g, 63%): mp 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.61 (2H, d, J = 8.2 Hz), 7.51 (2H, m), 7.24 (2H, d, J = 8.2 Hz), 7.03 (2H, t, J = 8.8 Hz), 4.58 (2H, s), 2.40 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (d, J = 247 Hz), 151.2, 145.5, 139.6, 135.4, 135.1, 129.9, 128.9 (d, J = 8.3 Hz), 128.3, 126.3, 115.6 (d, J = 21.6 Hz), 53.9, 21.5; Anal. Calcd for $C_{17}H_{14}NO_3SF$: C, 61.6; H, 4.3; N,4.2; S, 9.7. Found C, 62.0; H, 4.3; N, 4.1; S, 9.9.

Ethyl 4-(2-naphthyl)-1,3-oxazole-5-carboxylate (70): Ethyl glyoxylate (50% in toluene, 1.16 mL, 5.8 mmol), isonitrile **2f** (1.5 g, 4.7 mmol) and piperazine (0.61 g, 7.05 mmol) were combined in 25 mL of THF and stirred for 18 h. The reaction was diluted with EtOAc and water and the layers were separated. After concentrating the solution, the residue was purified by silica gel chromatography using hexane:EtOAc (1:1) and the product was crystallized from TBME/hexane as beige solid (0.99g, 80%): mp 74-75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.74 (1H, s), 8.60 (1H, s), 8.10 (1H, dd, J = 1.2, 8.7 Hz), 7.96 (3H, m), 7.56 (2H, m), 4.33 (2H, q, J = 7.2 Hz), 1.27 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.7, 153.6, 144.6, 136.2, 133.1, 132.2, 128.8, 128.3, 127.4, 127.3, 127.1, 127.0, 126.4, 126.0, 61.2, 13.8; Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N,5.2. Found C, 71.6; H, 5.0; N, 5.2.

4-[4-(4-Fluorophenyl)(1,3-oxazol-5-yl)]-2-propylthiopyrimidine (72): Bisulfite adduct **71** (12.7 g, 44.4 mmol), isonitrile **2** (7.7 g, 26.6 mmol), K_2CO_3 (7.4 g, 53.0 mmol) and piperazine (5.7 g, 66.6 mmol) were combined in 100 mL of EtOAc and stirred for 18 h. The reaction was diluted with EtOAc, water and 10% NaOH and the layers were separated. After concentrating the solution, the residue was purified by silica gel chromatography using hexane:EtOAc (3:1) and the product was crystallized from EtOAc/hexane as an off-white solid (5.2 g, 62%): mp 68-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (1H, d, J = 5.2 Hz), 8.00 (1H, s), 7.94 (2H, m), 7.22 (1H, d, J = 5.2 Hz), 7.10 (2H, t, J = 8.8 Hz), 2.91 (2H, t, J = 7.3 Hz), 1.57 (2H, m), 0.88 (3H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 163.2 (d, J = 249 Hz), 157.8, 154.6,

151.0, 142.7, 140.8, 131.5 (d, J = 8 Hz), 127.3, 115.1 (d, J = 22 Hz), 111.9, 32.6, 22.2, 13.3; Anal. Calcd for $C_{16}H_{14}N_3OSF$: C, 60.9; H, 4.5; N,13.3. Found C, 60.9; H, 4.5; N, 13.3.

Tosylisonitriles **2b-2i** were prepared by the literature method.[3] Isonitrile **2h** is a known compound.[3,4]

(3,4-Dichlorophenyl)[(4-methylphenyl)sulfonyl]methanisocyanide (2b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 8.3 Hz), 7.47 (1H, d, J = 8.3 Hz), 7.37 (3H, m), 7.20 (1H, dd, J = 2.1, 8.3 Hz), 5.55 (1H, s), 2.47 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 147.1, 135.5, 133.3, 130.8, 130.5, 130.3, 130.0, 129.9, 127.6, 126.8, 75.2, 21.8; IR (KBr) 2135 cm^{-1}.

(2-Methoxyphenyl)[(4-methylphenyl)sulfonyl]methanisocyanide (2c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 8.1 Hz), 7.40 (1H, m), 7.35 (1H, m), 7.30 (2H, d, J = 8.1 Hz), 6.98 (1H, t, J = 7.5 Hz), 6.83 (1H, d, J = 8.3 Hz), 6.24 (1H, s), 3.69 (3H, s), 2.43 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 157.1, 146.2, 132.2, 131.5, 130.4, 1296, 128.9, 121.0, 116.0, 111.1, 70.0, 55.8, 21.7; IR (KBr) 2135 cm^{-1}.

(4-Methoxyphenyl)[(4-methylphenyl)sulfonyl]methanisocyanide (2d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (2H, d, J = 8.2 Hz), 7.31 (2H, d, J = 8.2 Hz), 7.23 (2H, d, J = 8.8 Hz), 6.87 (2H, d, J = 8.8 Hz), 5.55 (1H, s), 3.80 (3H, s), 2.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 161.5, 146.4, 130.5, 130.1, 129.9, 129.7, 118.4, 114.2, 76.2, 55.4, 21.7; IR (KBr) 2135 cm^{-1}.

[(4-Methylphenyl)sulfonyl]naphthylmethanisocyanide (2e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, d, J = 8.4 Hz), 7.92 (2H, m), 7.65 (2H, d, J = 8.3 Hz), 7.57 (2H, m), 7.44 (2H, m), 7.31 (2H, d, J = 8.3 Hz), 6.51 (1H, s), 2.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 146.6, 133.6, 131.6, 130.9, 130.6, 130.4, 129.8, 129.0, 127.7, 127.4, 126.4, 124.8, 123.1, 122.6, 73.1, 21.7; IR (KBr) 2135 cm^{-1}.

[(4-Methylphenyl)sulfonyl]-2-naphthylmethanisocyanide (2f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (3H, m), 7.79 (1H, d, J = 1.4 Hz), 7.61 (2H, d, J = 8.2 Hz), 7.54 (2H, m), 7.40 (1H, dd, J = 1.8, 8.5 Hz), 7.28 (2H, d, J = 8.2 Hz), 5.77 (1H, s), 2.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 146.6, 134.0, 132.6, 130.6, 130.3, 129.8, 128.9, 128.7, 128.4, 127.8, 127.7, 127.0, 124.6, 124.0, 76.8, 21.7; IR (KBr) 2135 cm^{-1}.

[(4-Methylphenyl)sulfonyl]-3-thienylmethanisocyanide (2g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, J = 8.4 Hz), 7.33 (4H, m), 7.10 (1H, dd, J = 1.5, 4.9 Hz), 5.71 (1H, s), 2.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 146.6, 130.4, 130.0, 129.8, 127.5, 127.2, 127.1, 126.8, 72.7, 21.8; IR (KBr) 2135 cm^{-1}.

[(4-Methylphenyl)sulfonyl][3-(trifluoromethyl)phenyl]methanisocyanide (2i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 7.4 Hz), 7.57 (4H, m), 7.43 (1H, s), 7.33 (2H, d, J = 8.1 Hz), 5.67 (1H, s), 2.46 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 147.2, 131.9, 131.5, 131.1, 130.4, 129.9, 129.8, 129.4, 128.1, 127.4, 125.2, 125.1, 121.6, 75.8, 21.6; IR (KBr) 2135 cm^{-1}.

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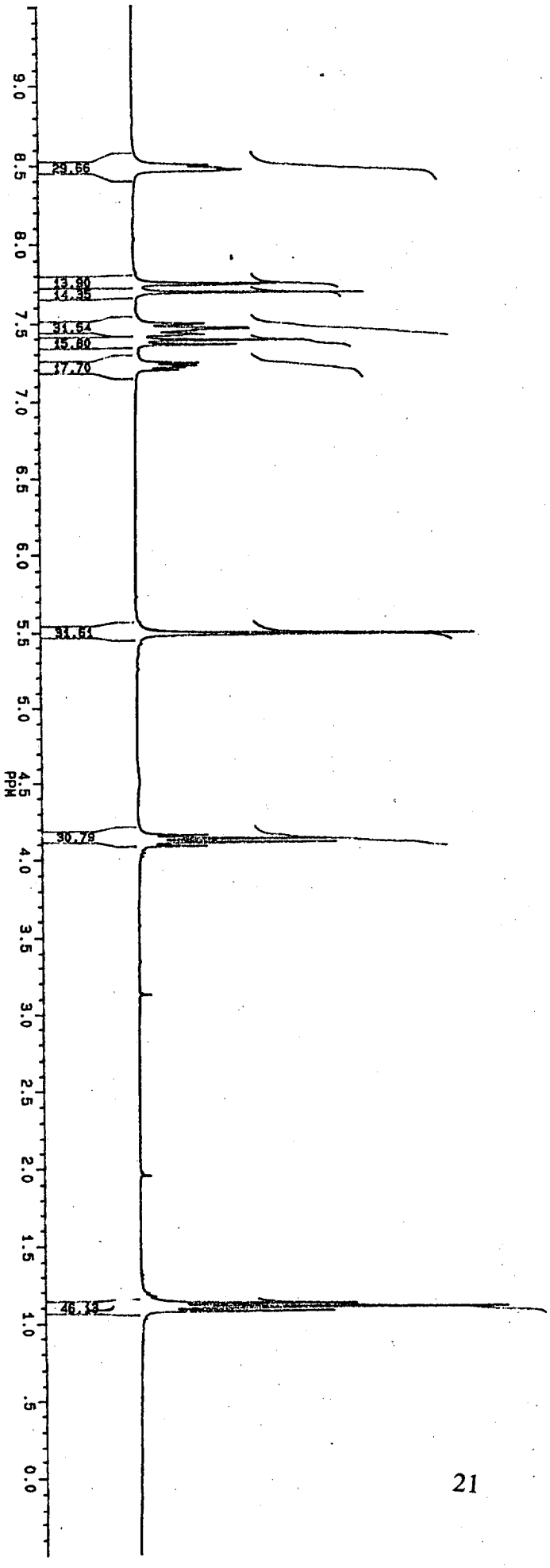
3. Sisko, J.; Mellinger, M. , Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett.* **1996**, *37*, 8113. Sisko, J.; Mellinger, M. , Sheldrake, P. W.; Baine, N. H. *Org. Synth.*, accepted for publication.
4. van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.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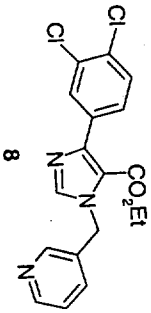
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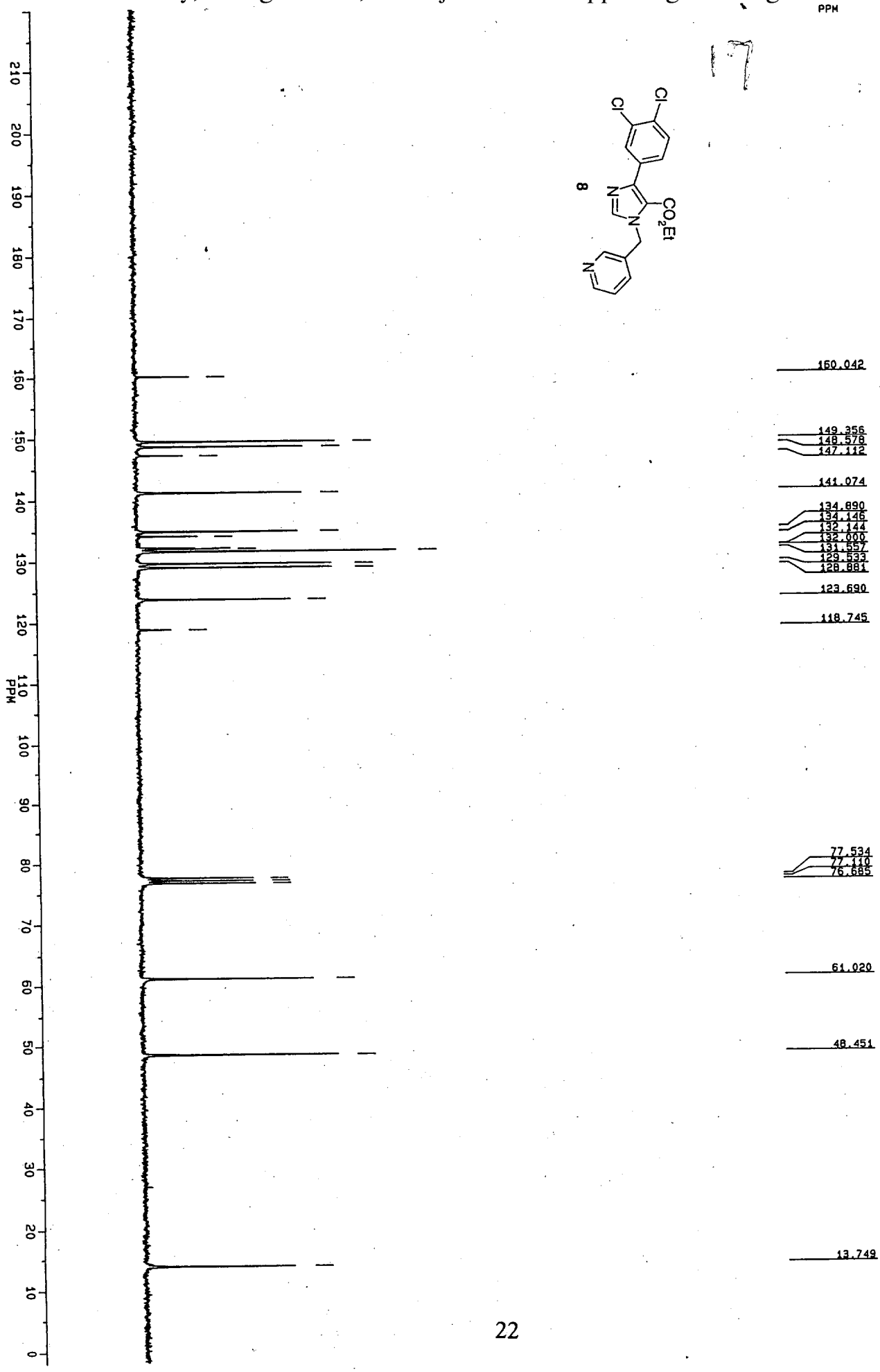

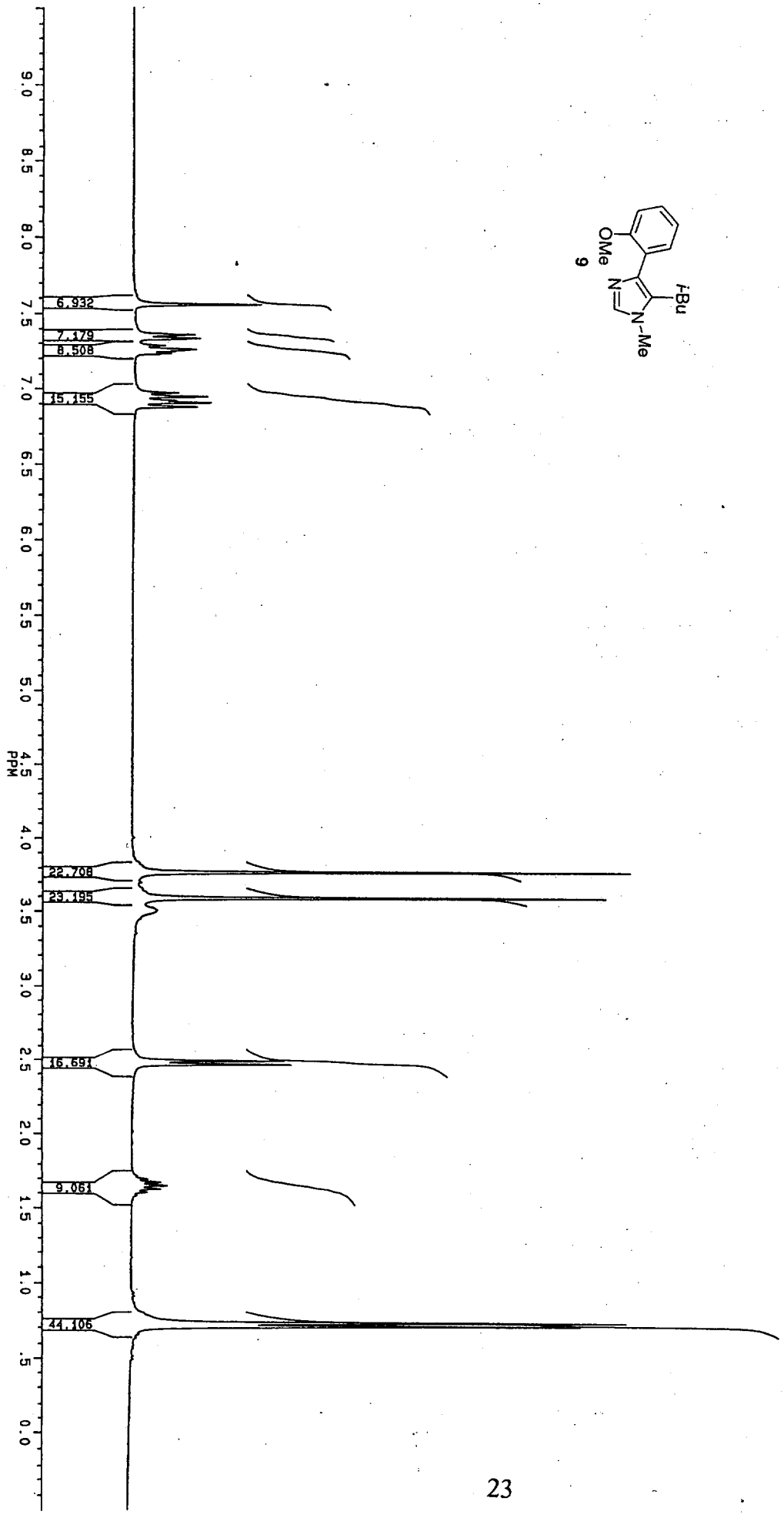
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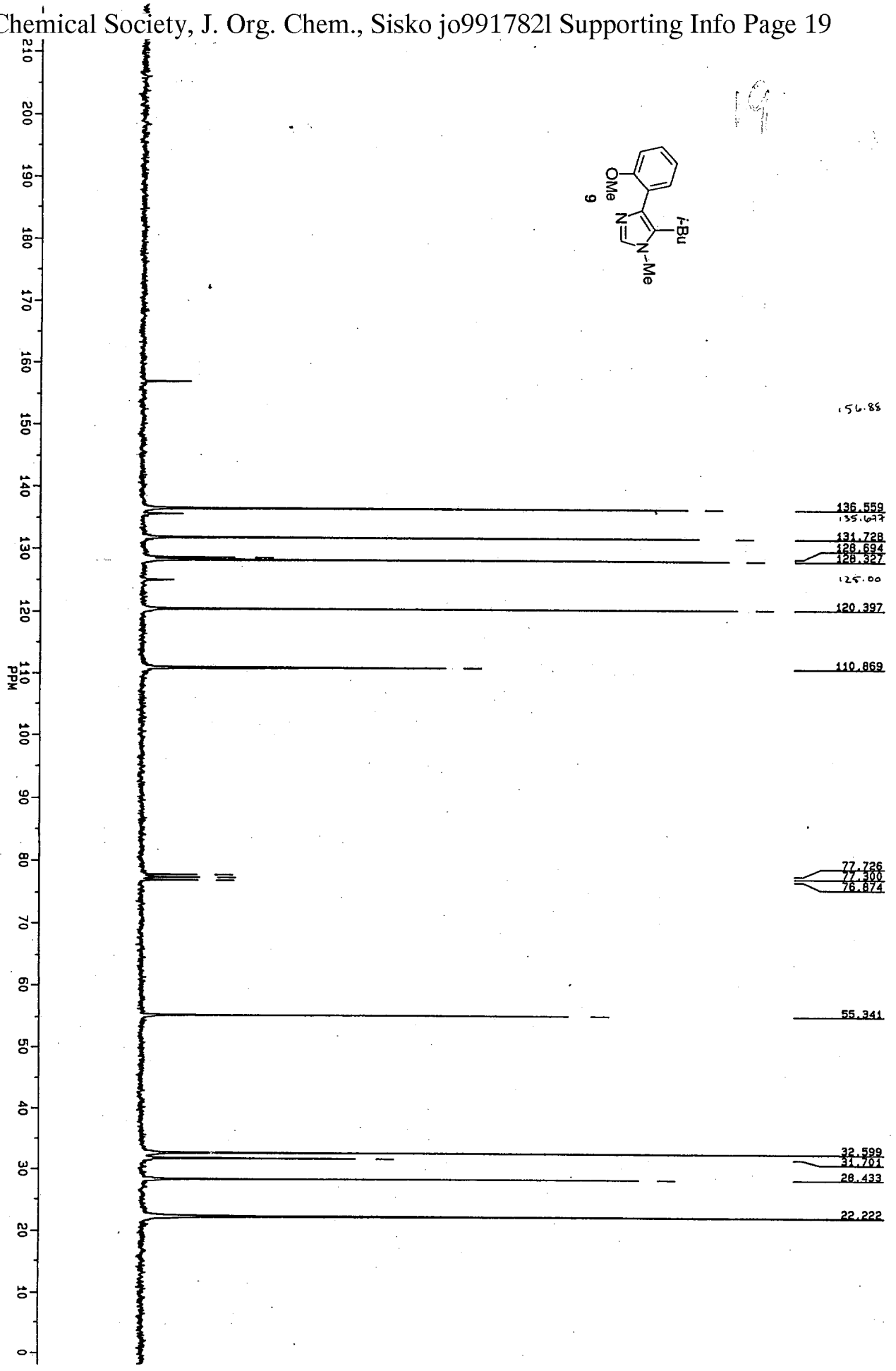

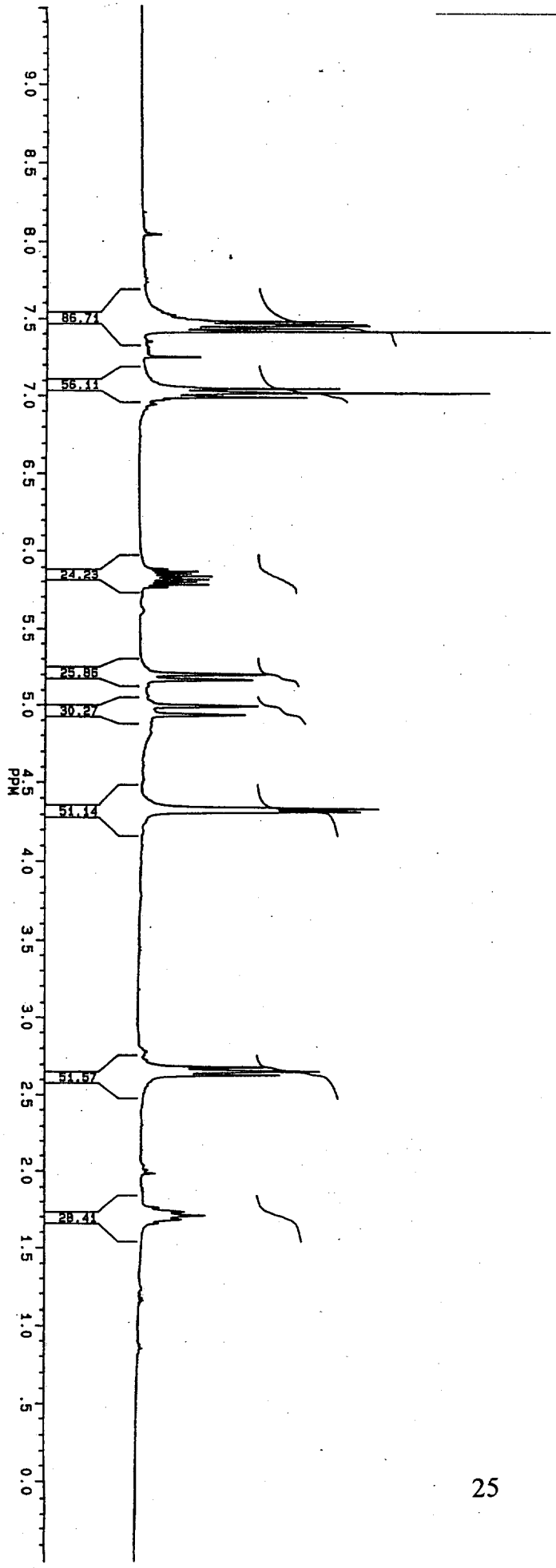

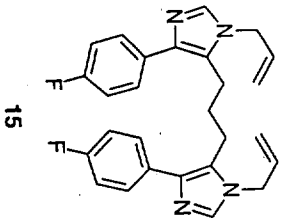

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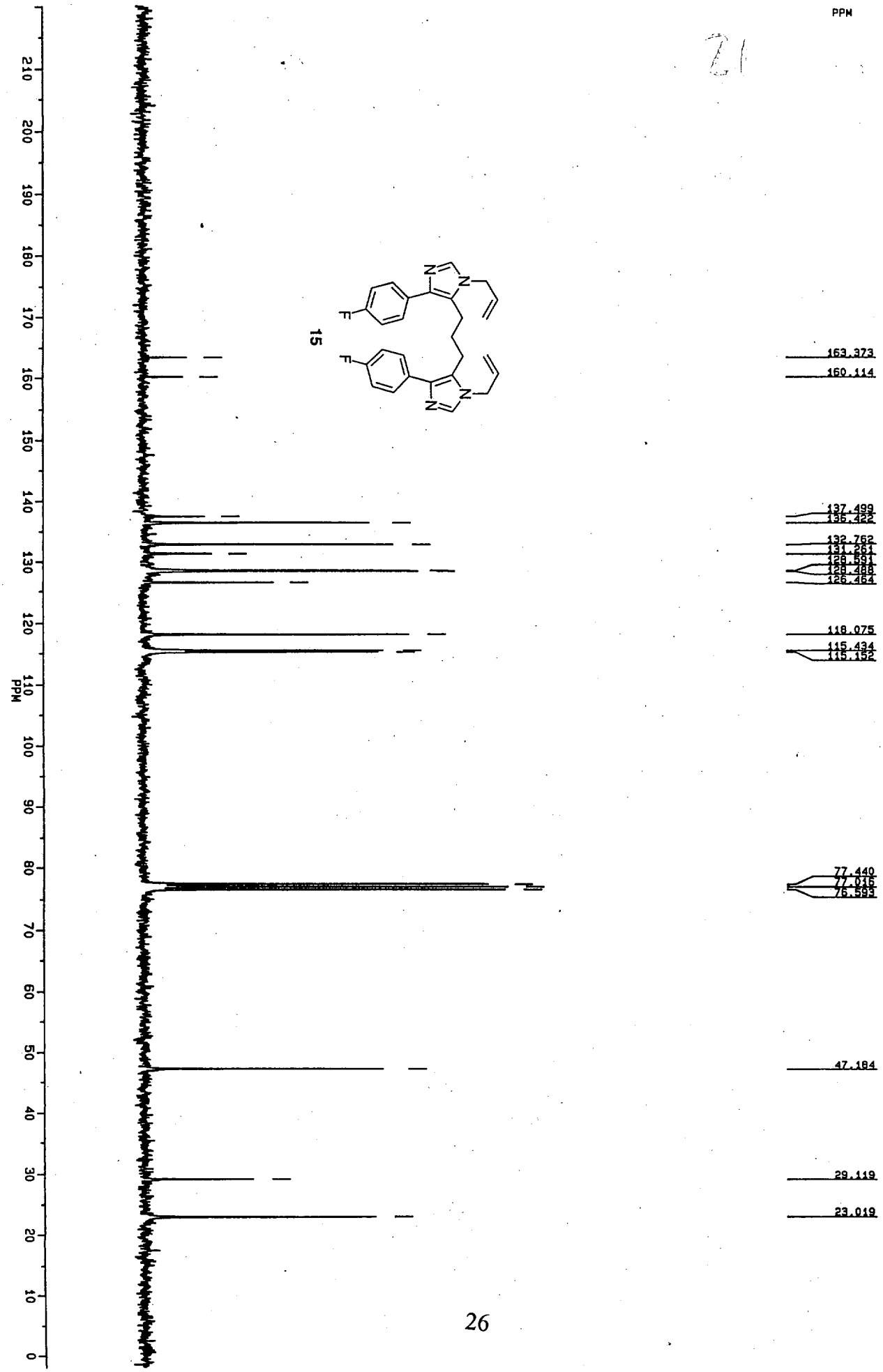

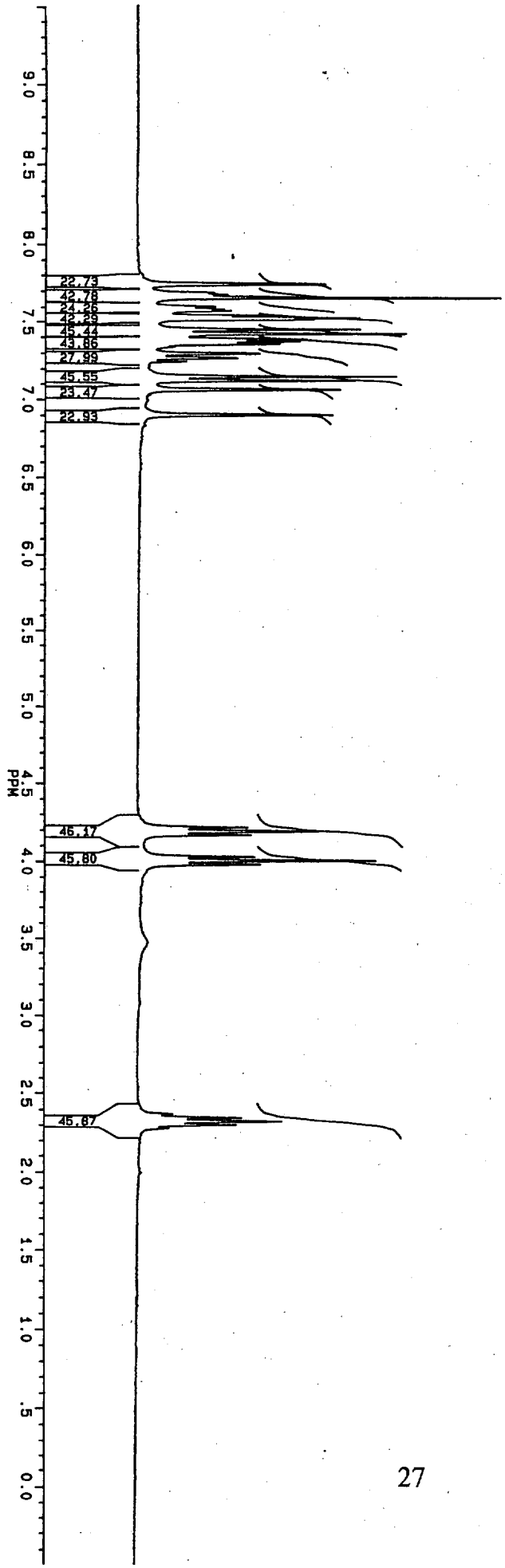

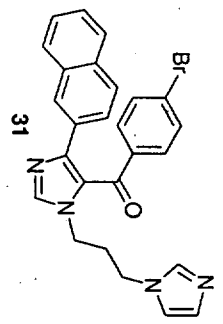

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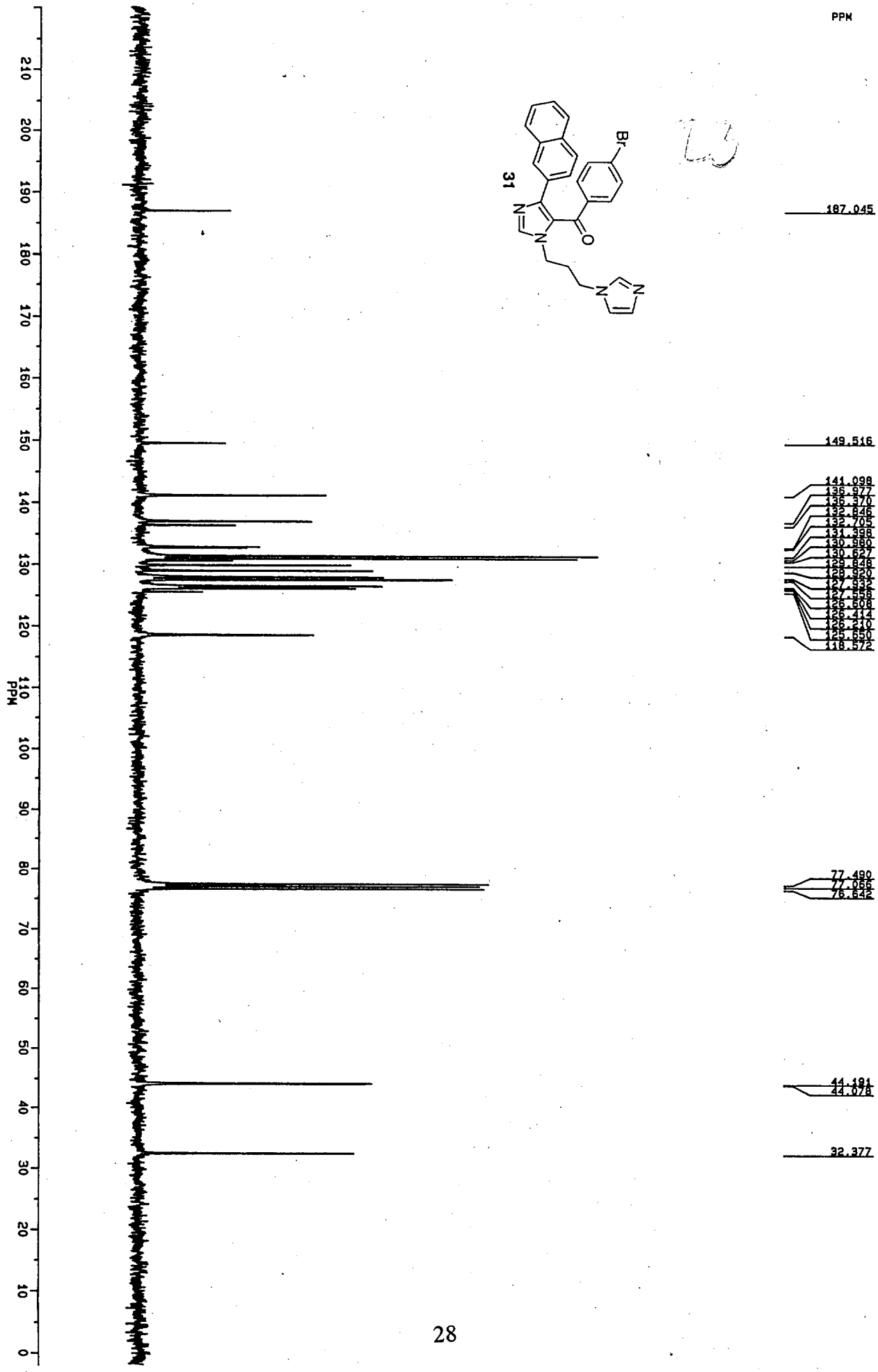
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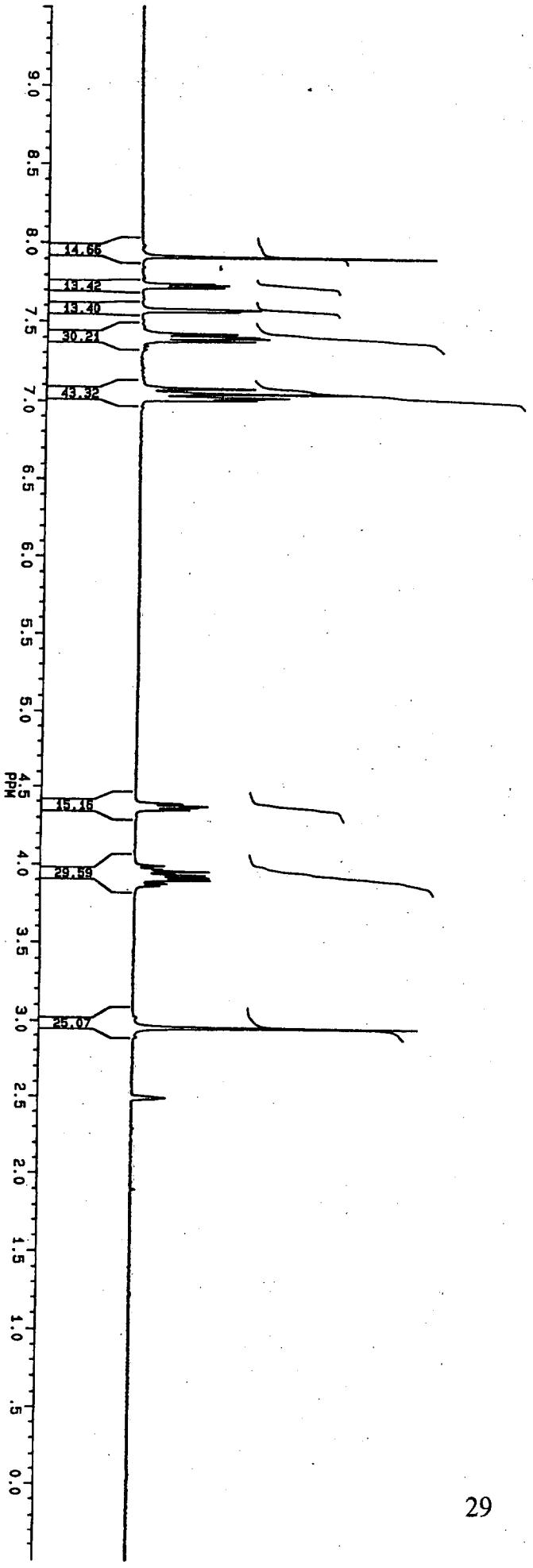
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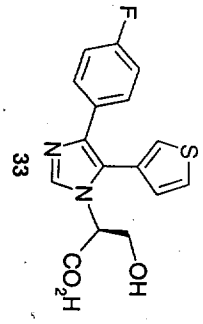
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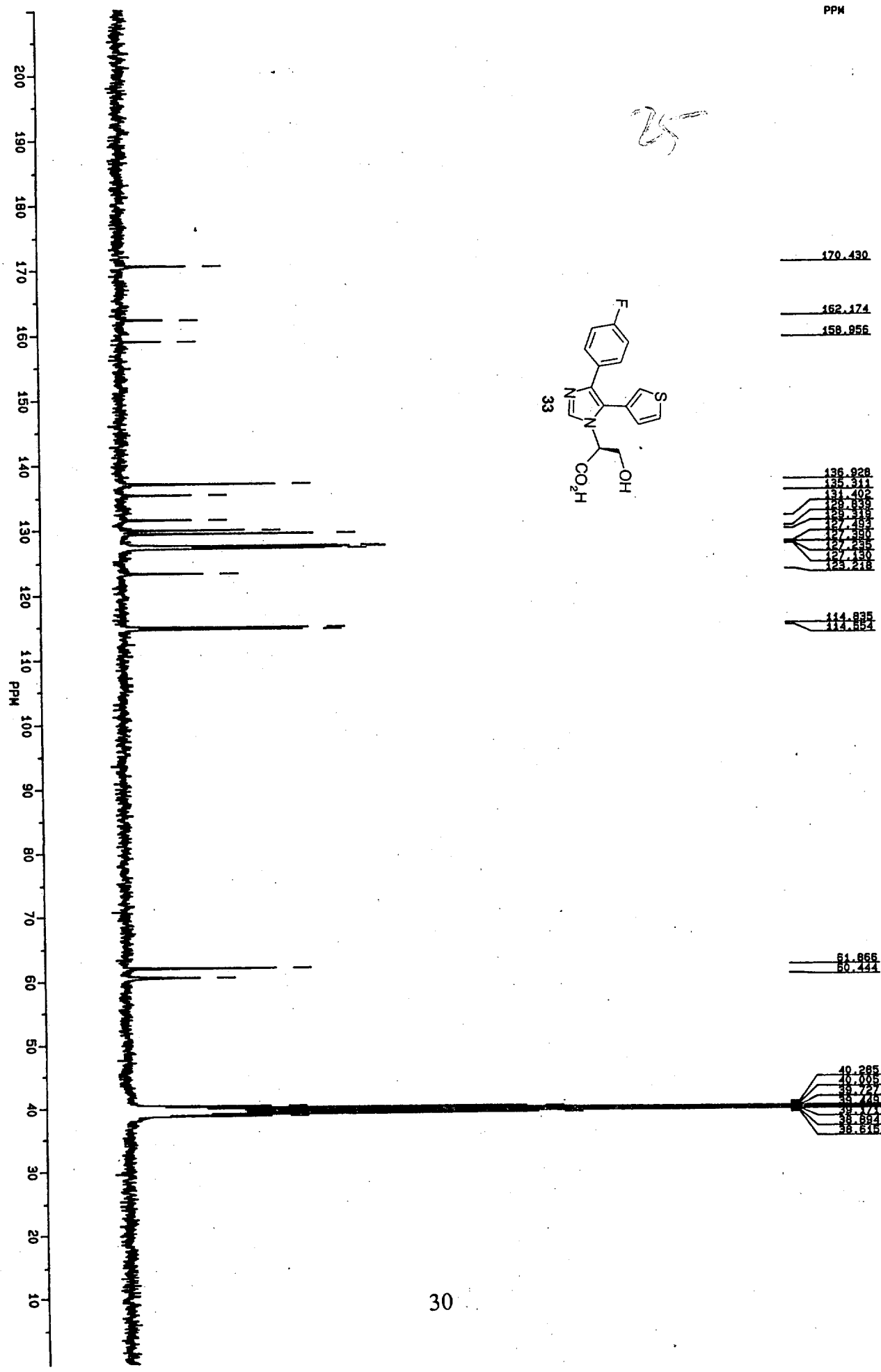
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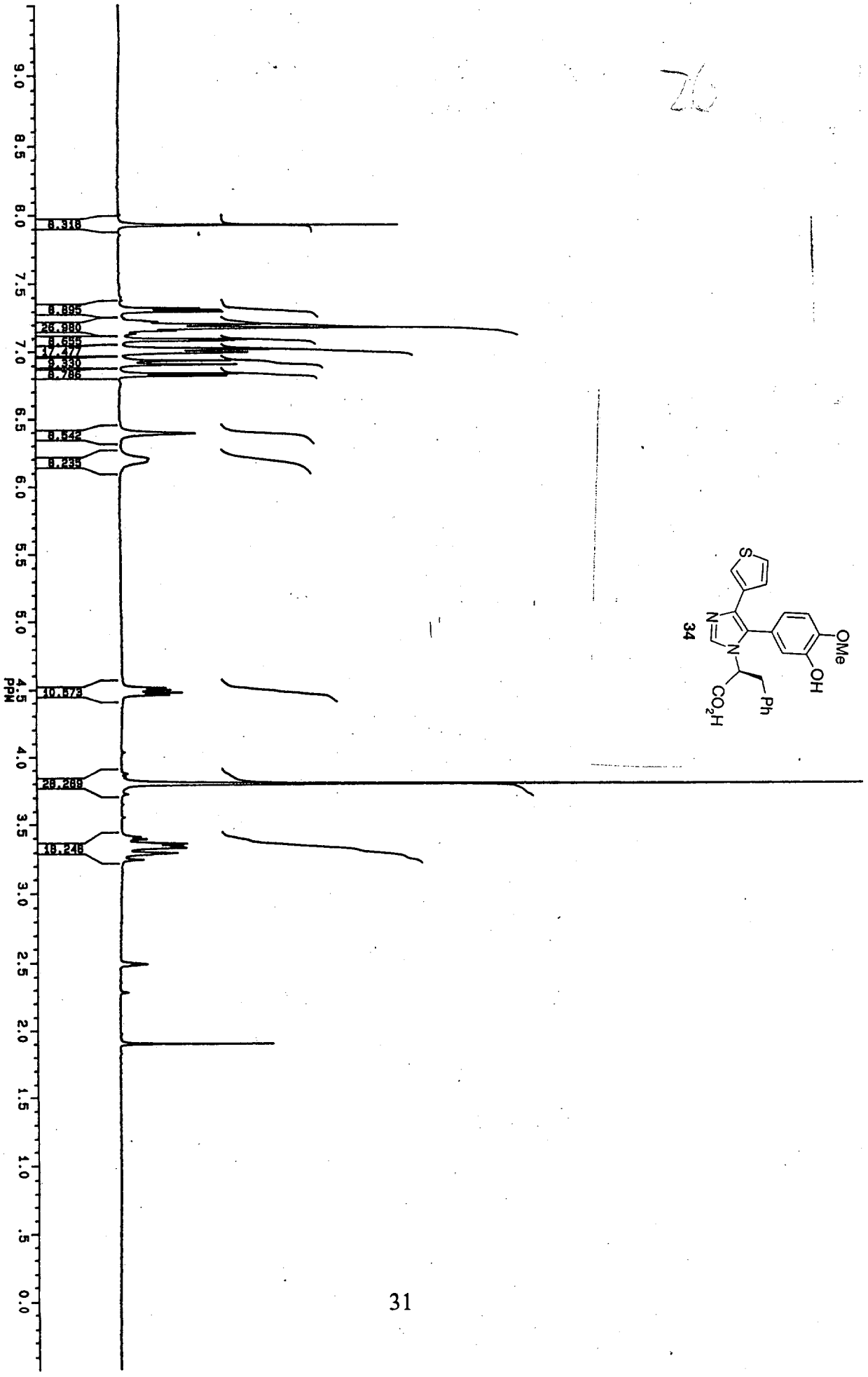
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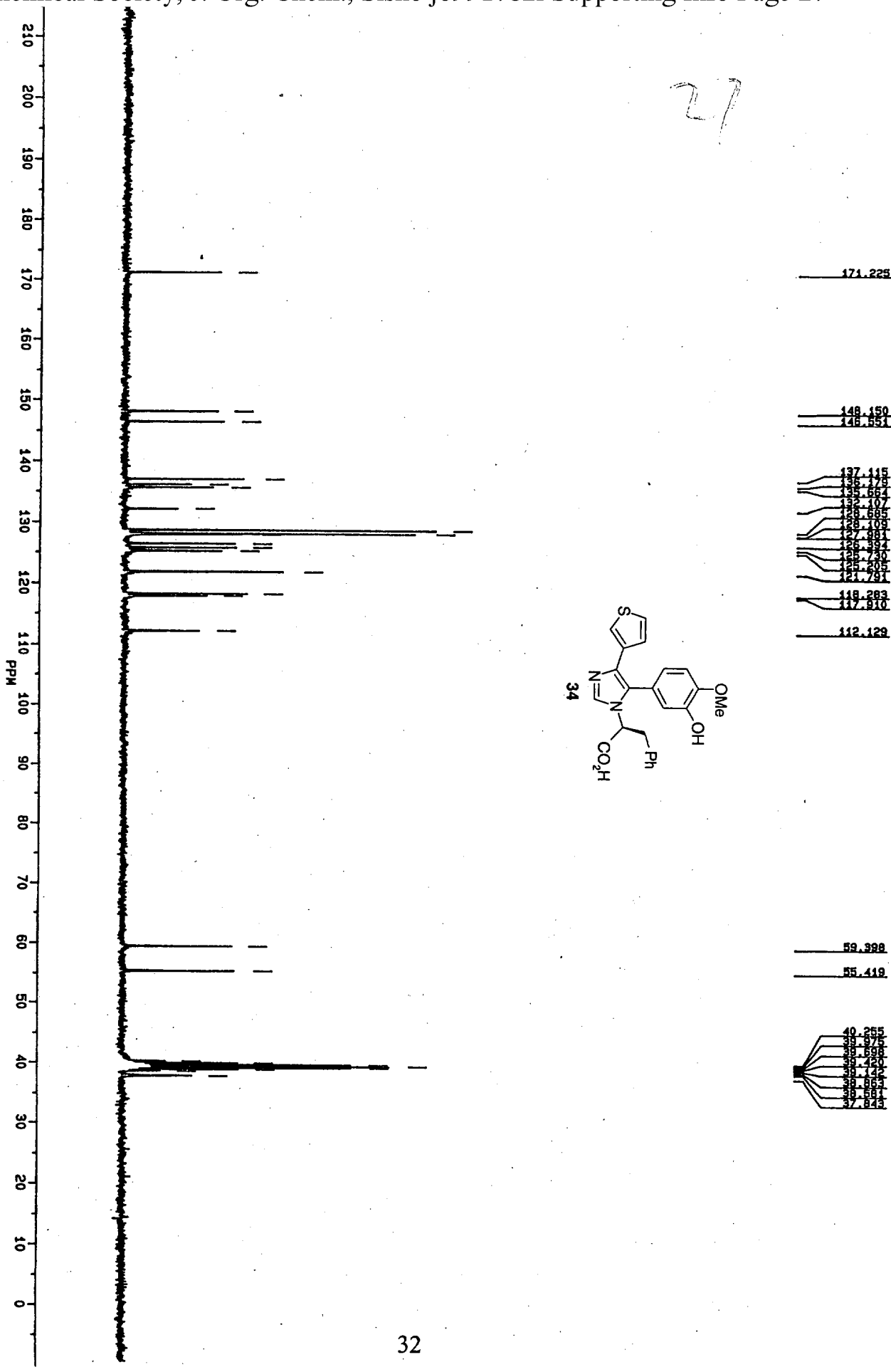
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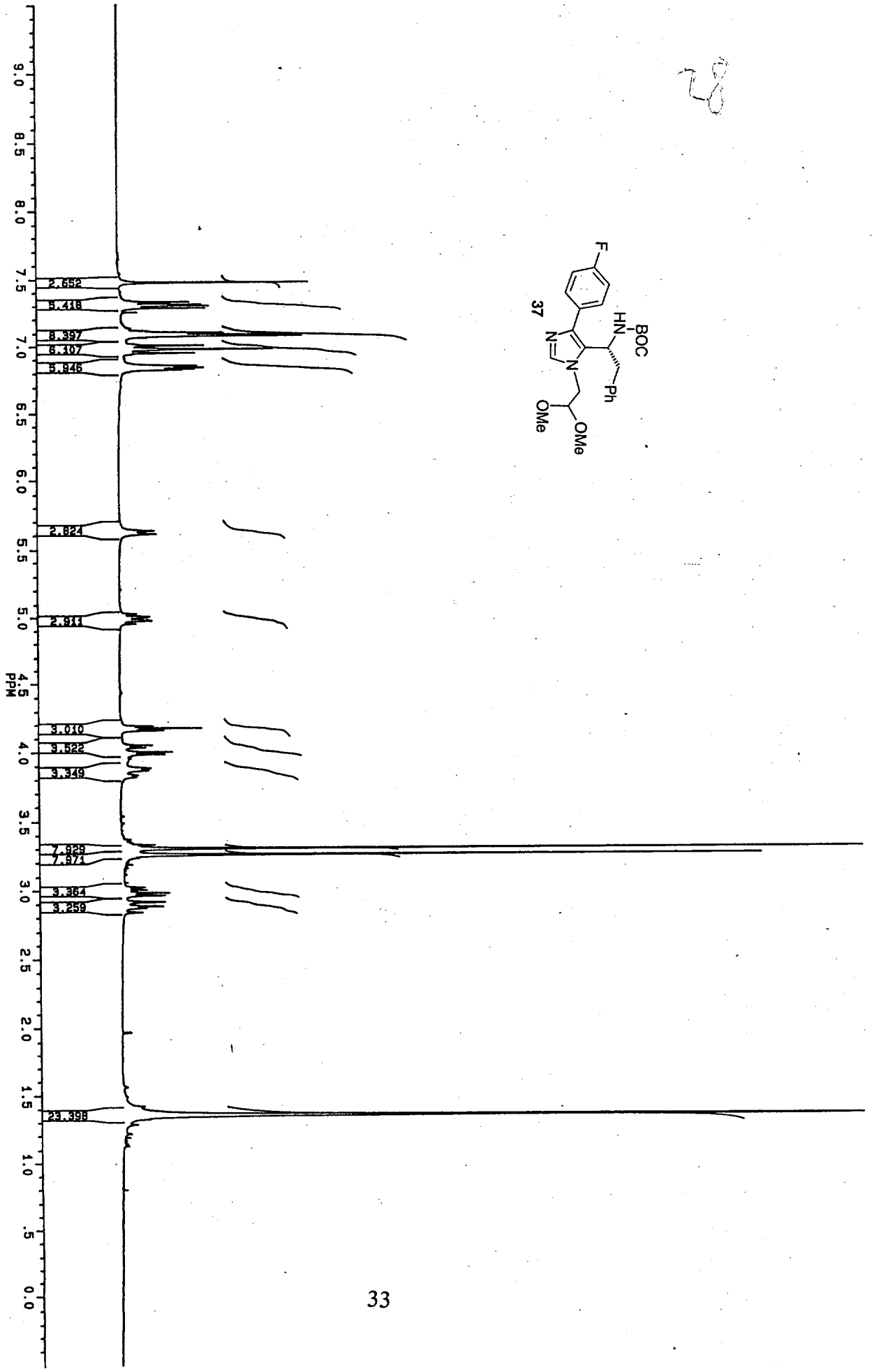
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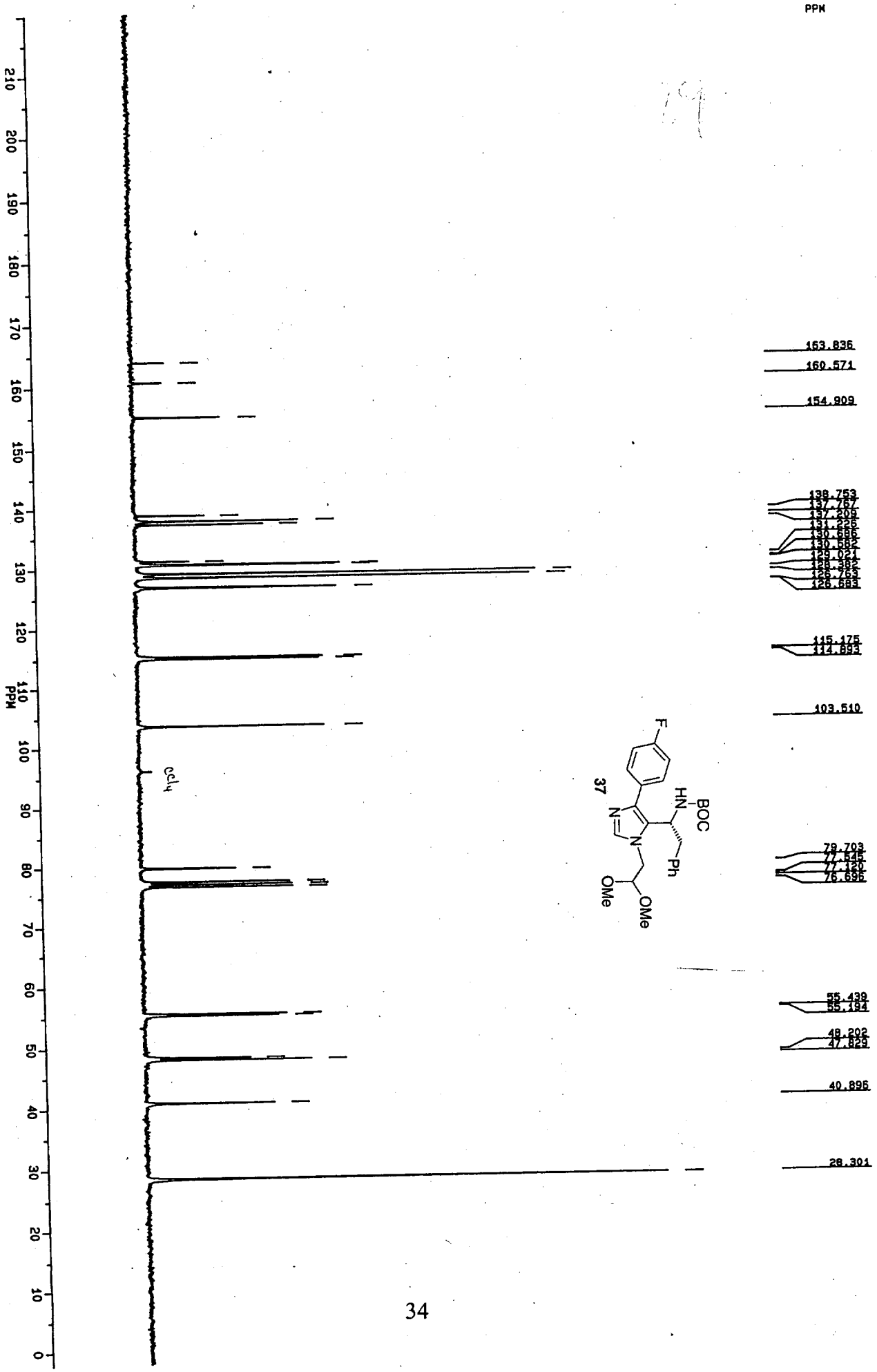
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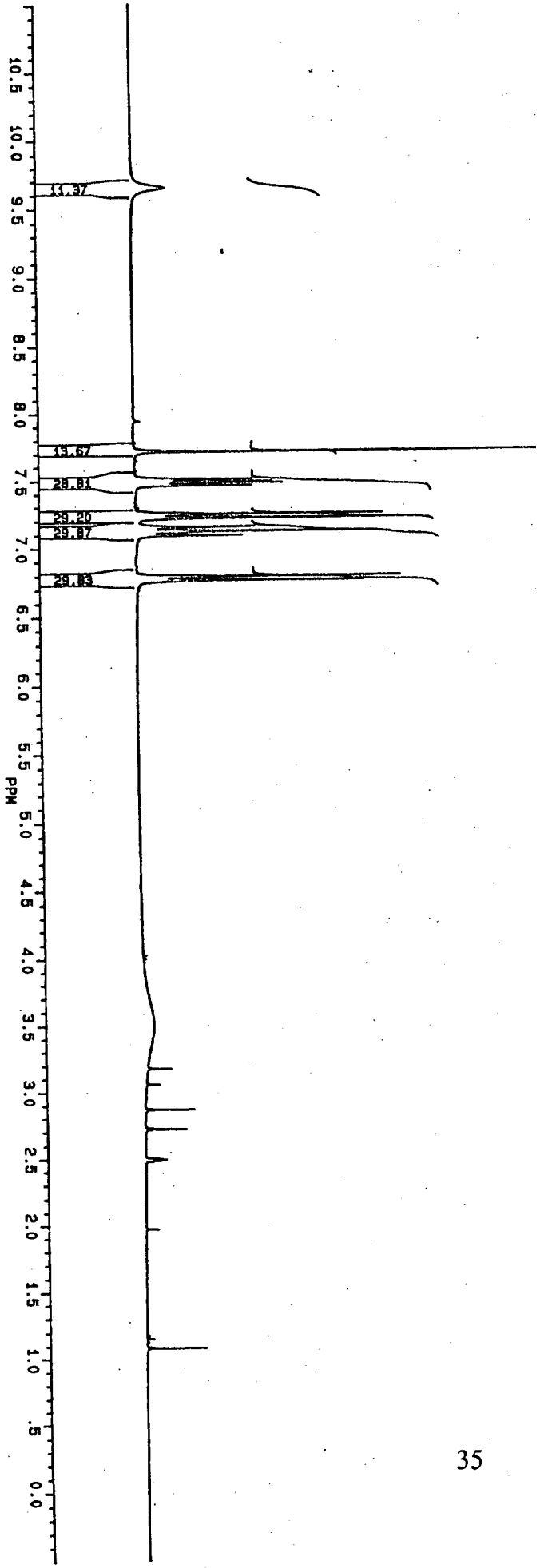

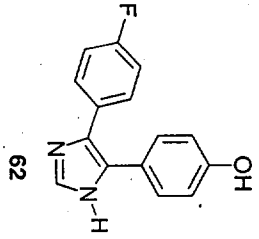

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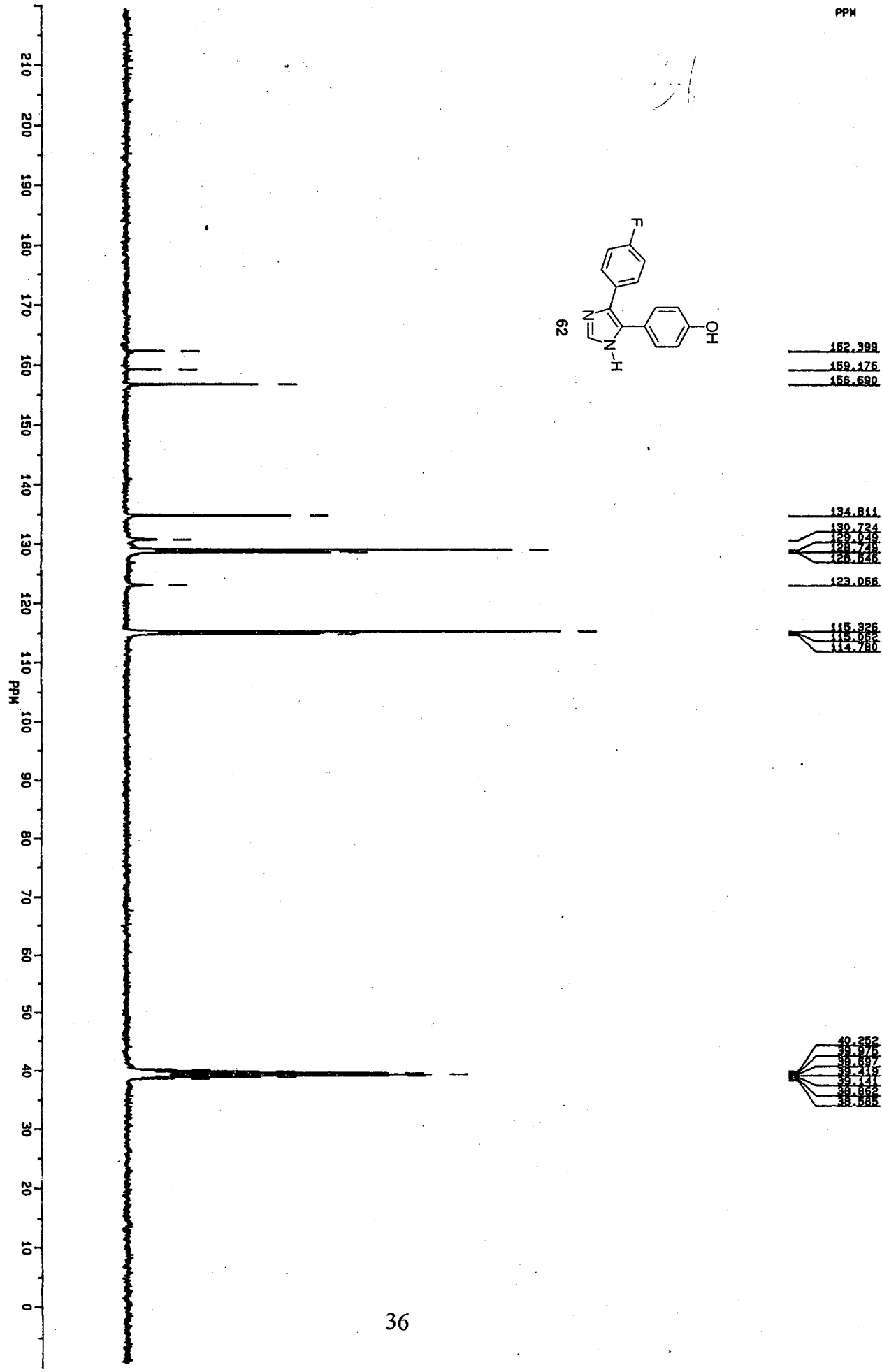

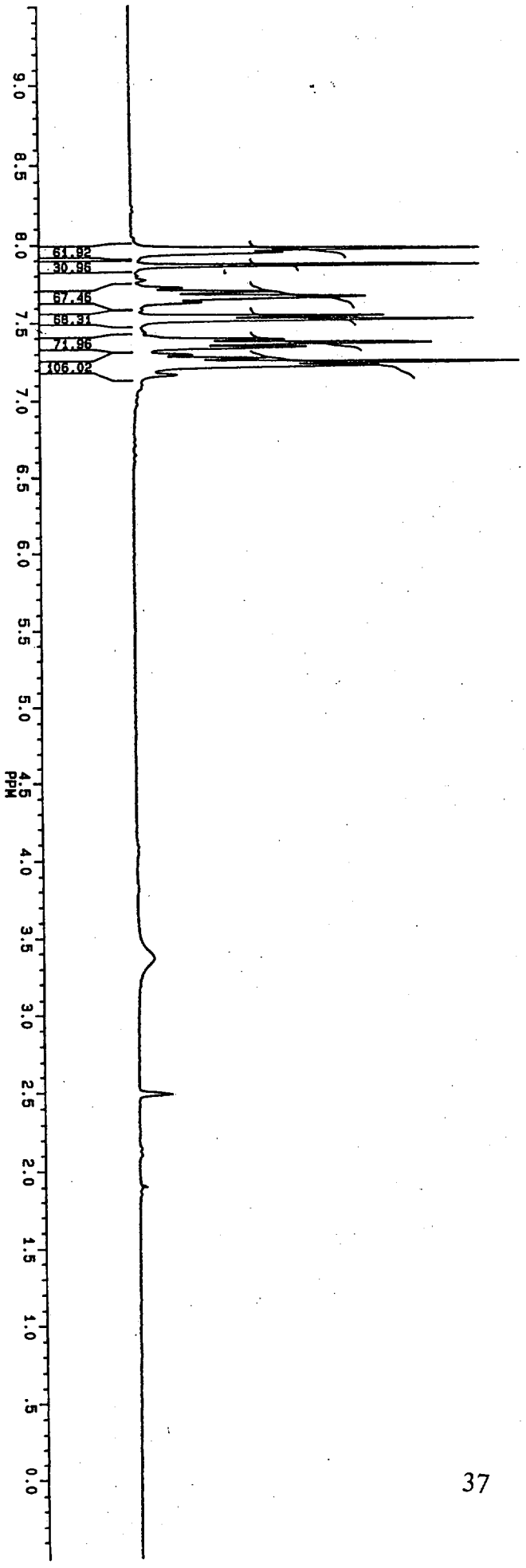

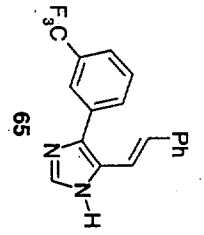

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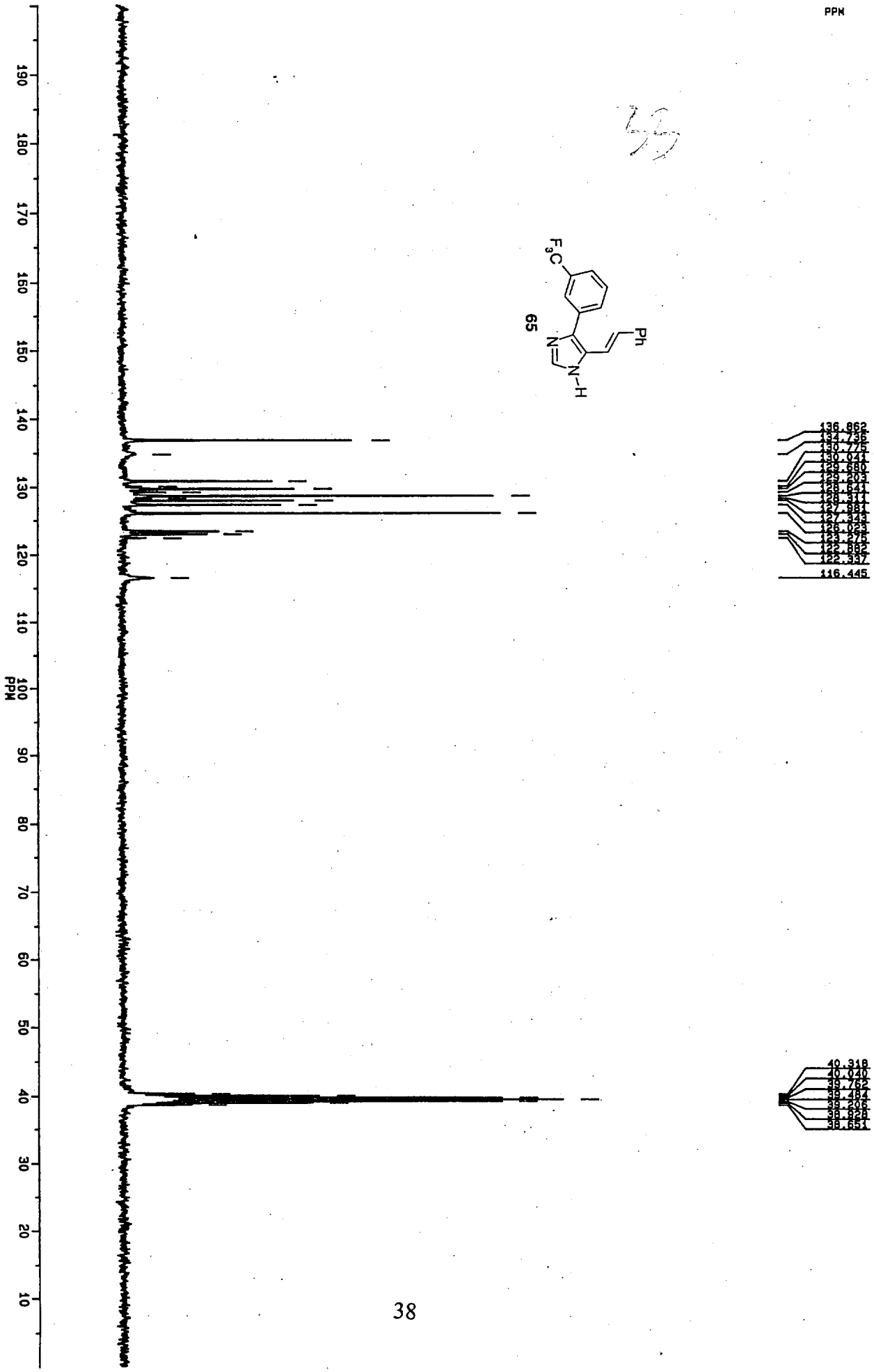
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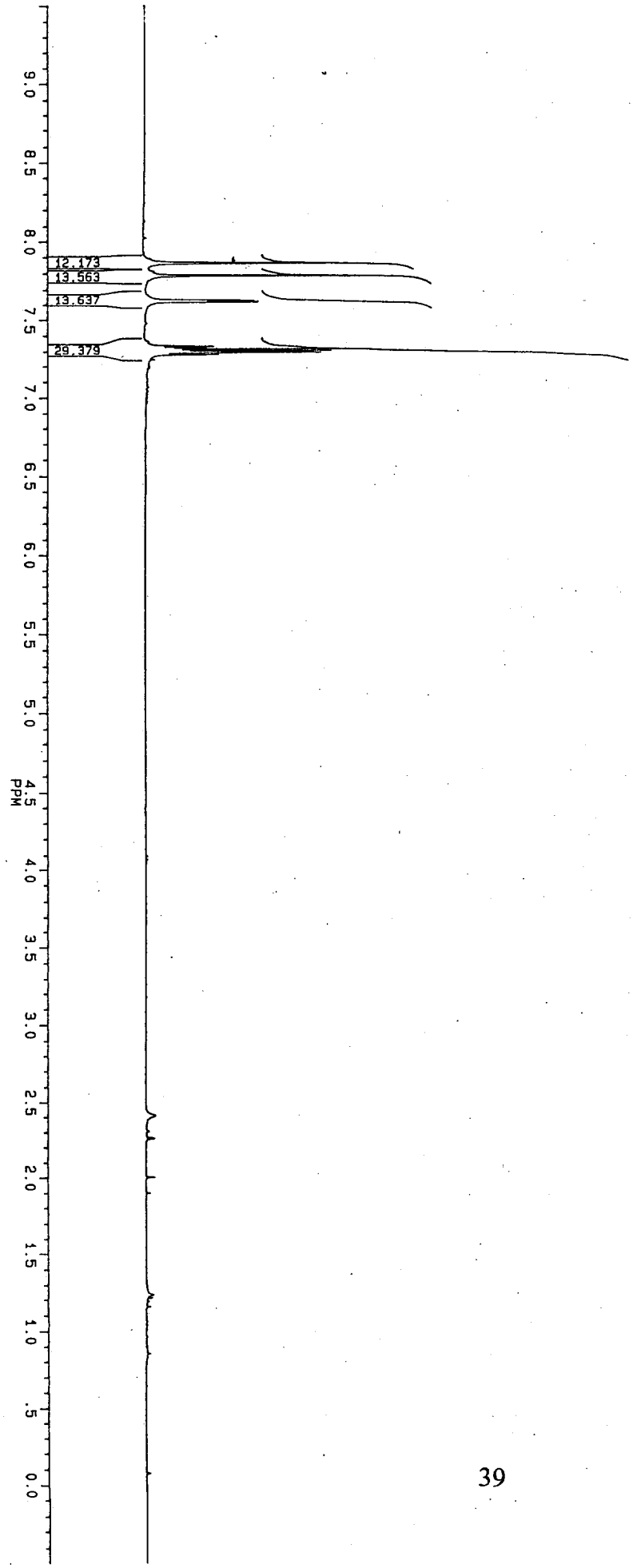
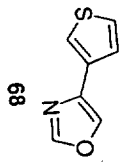
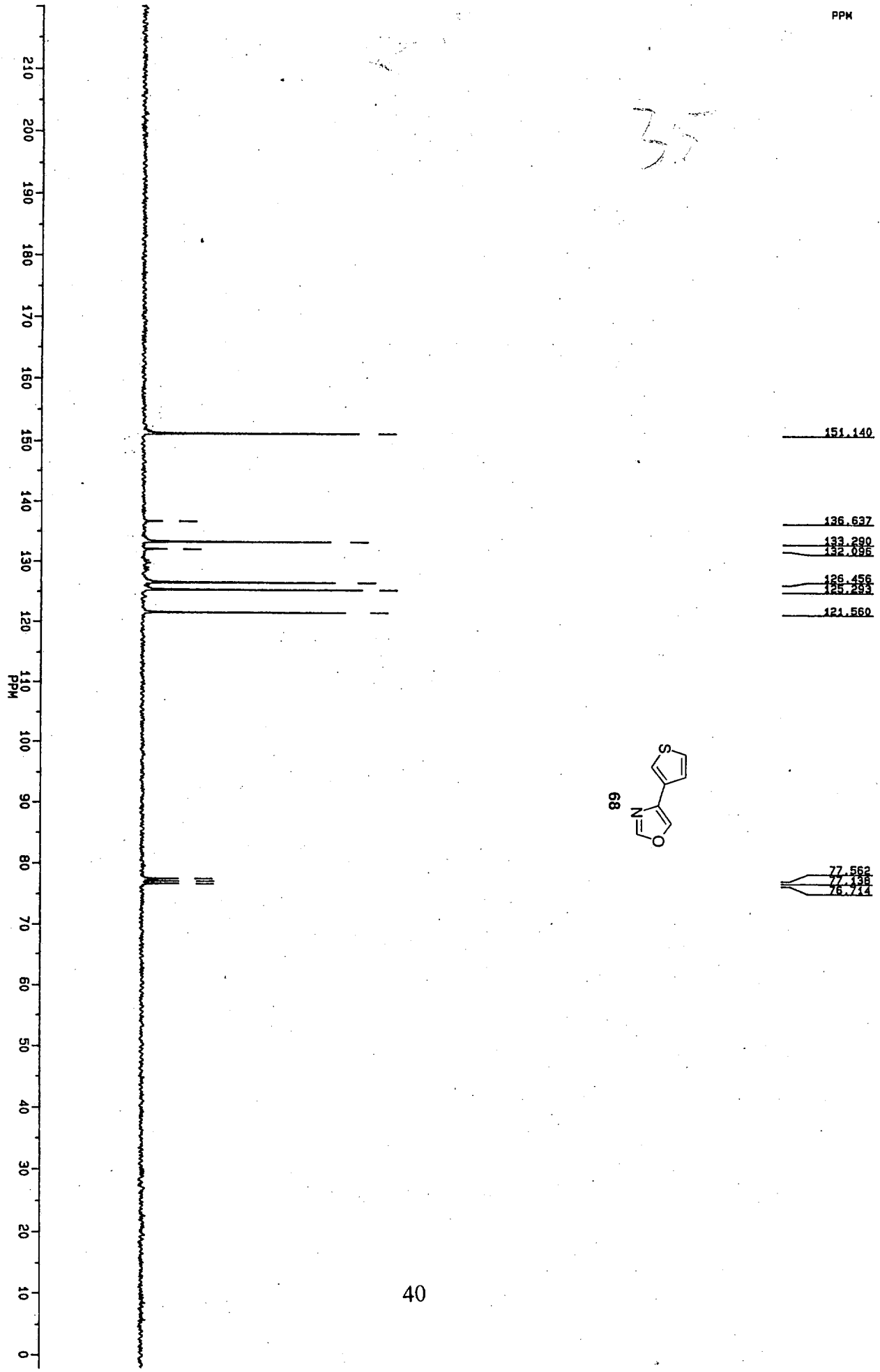
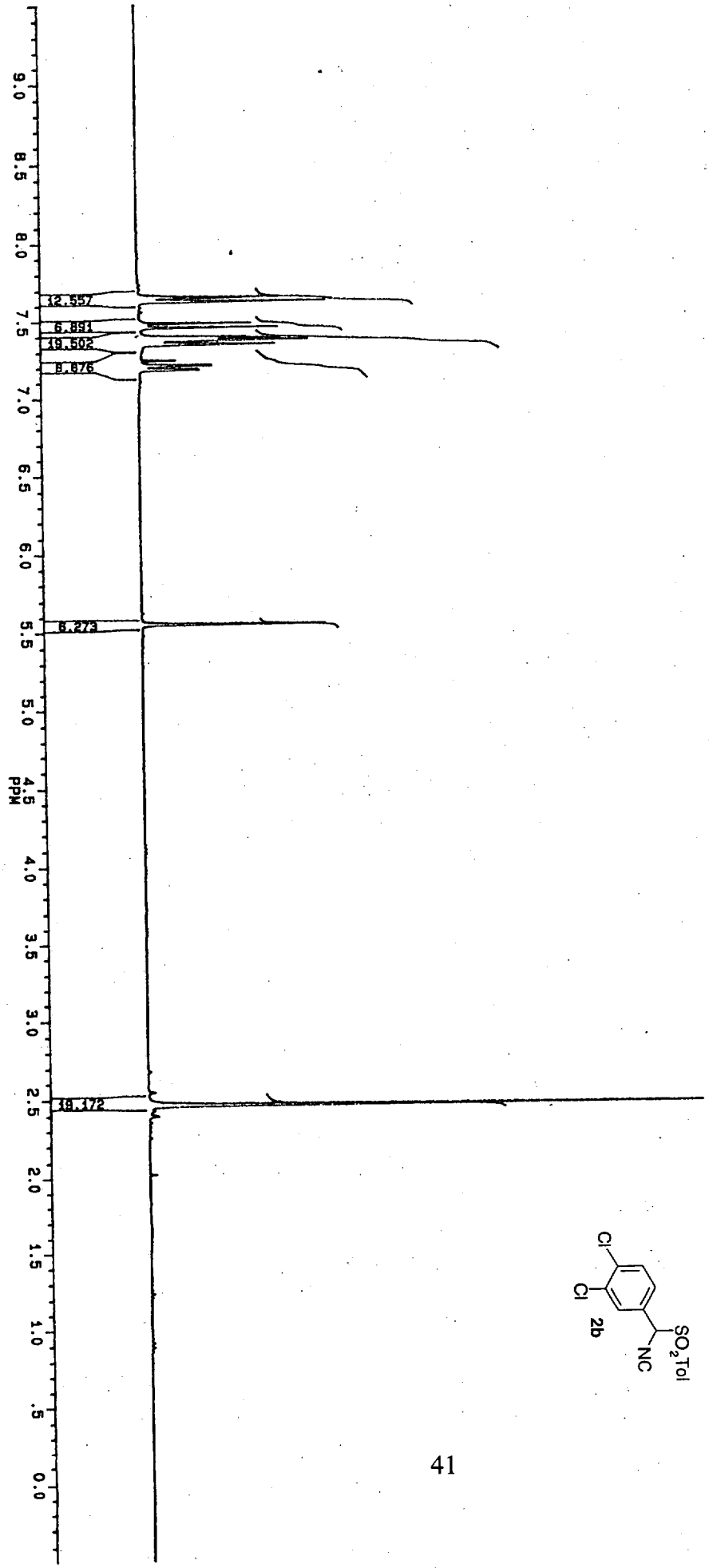
PPM



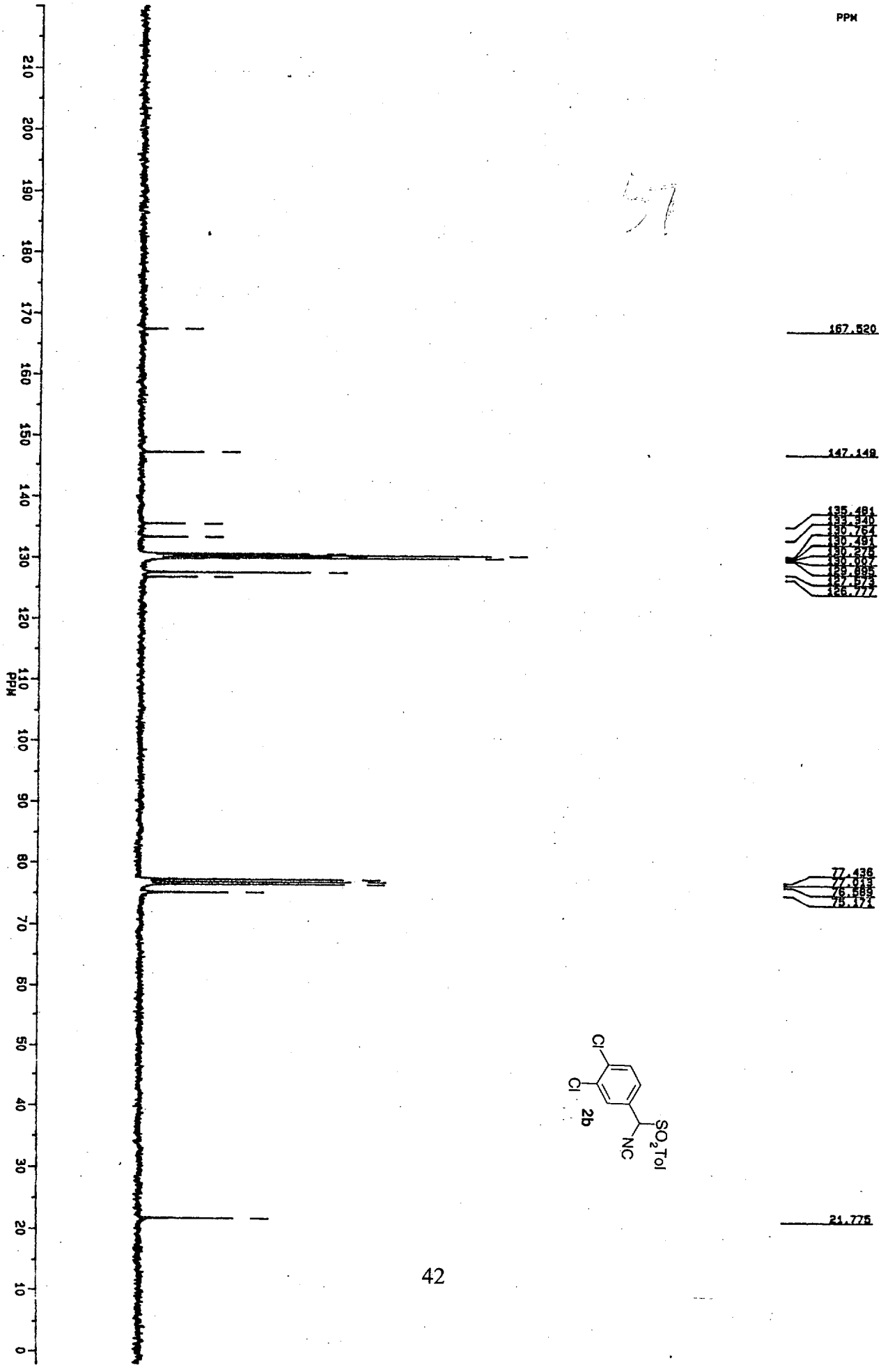


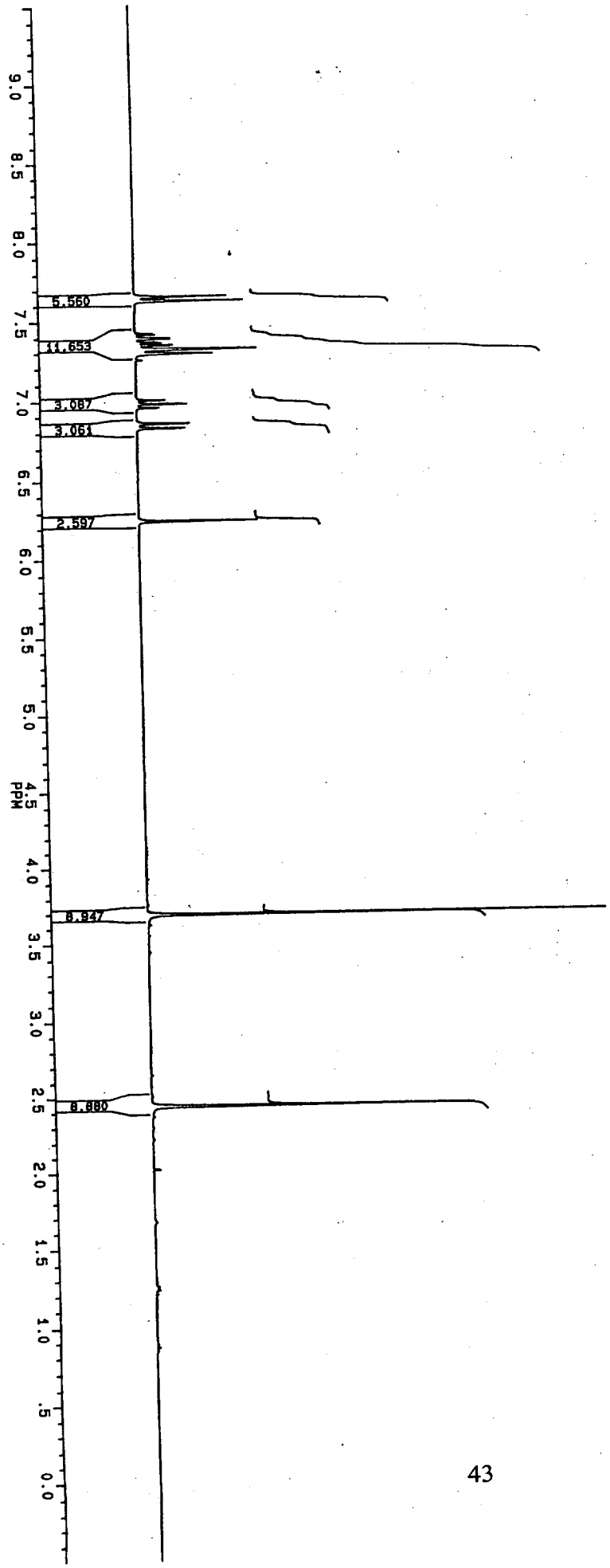
68



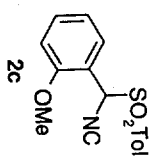

12.557
6.891
10.502
8.676
8.273
18.472
PPM
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Cl
Cl
2b
NC
SO2Tol

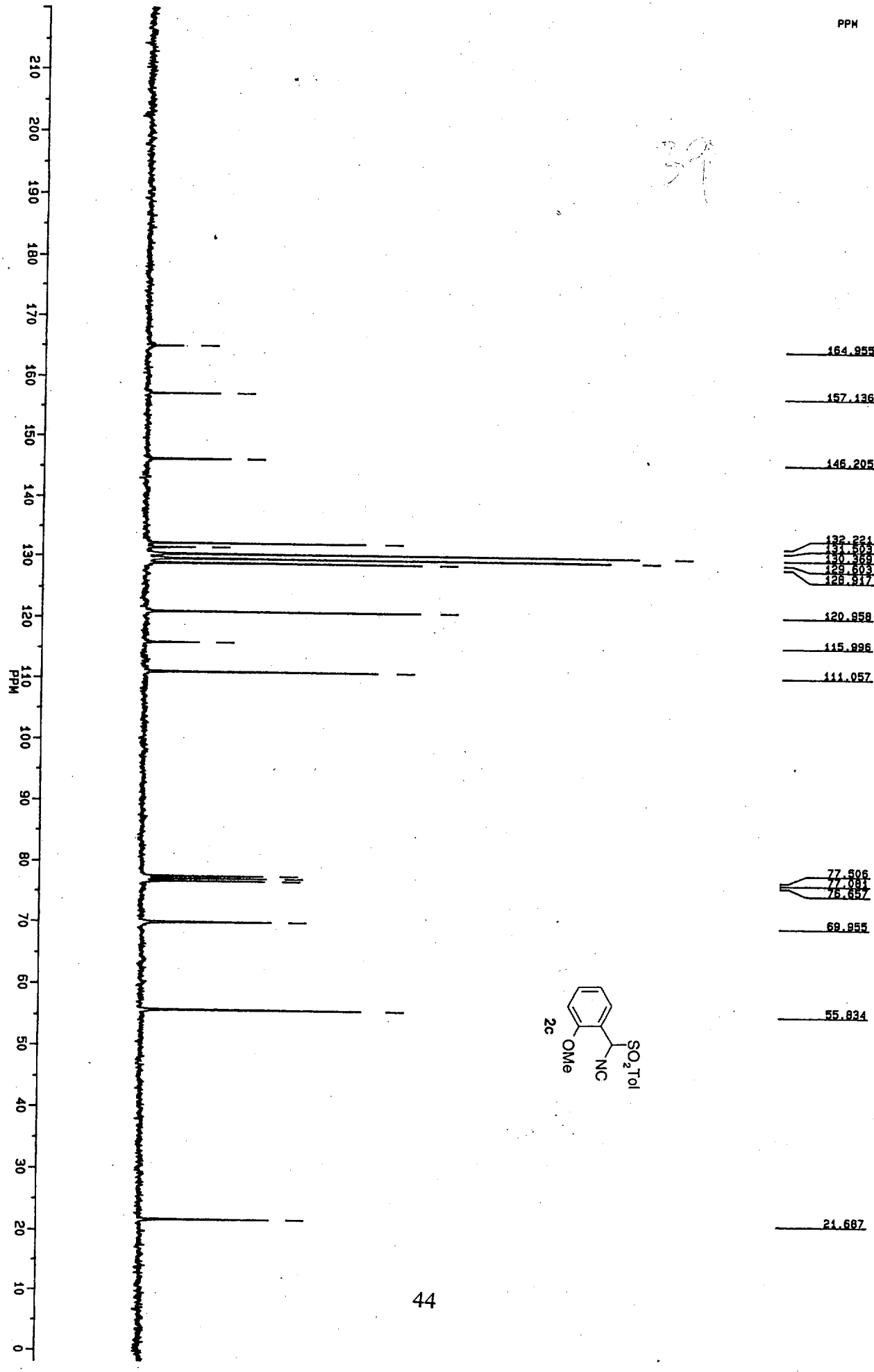


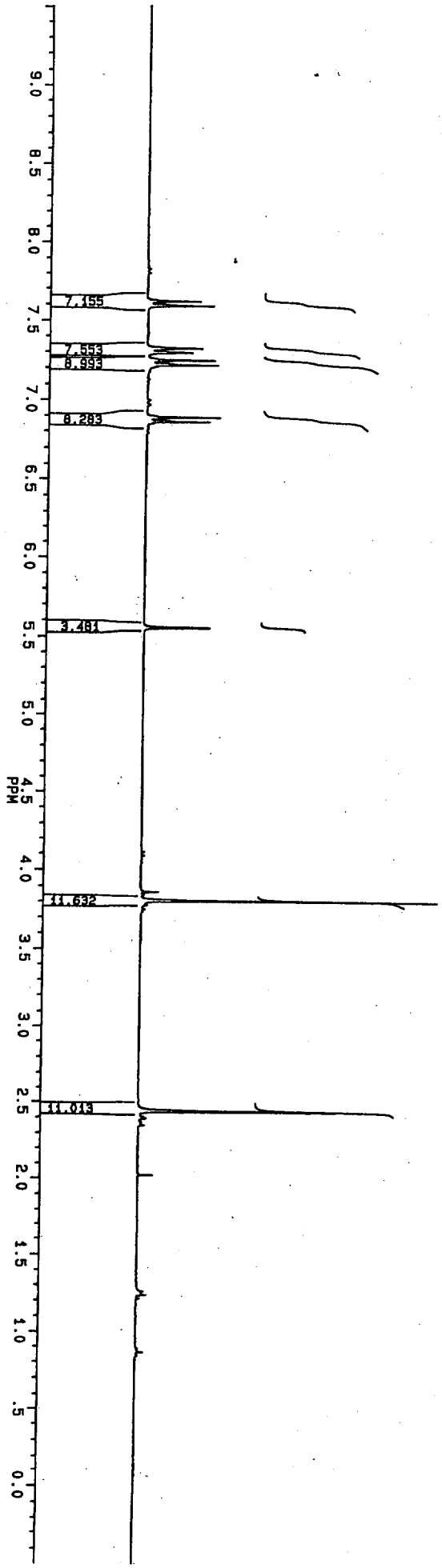


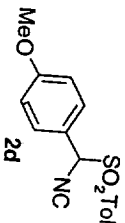
38



2c




7.455
7.553
8.993
8.283
3.481
11.632
11.013
PPM


MeO
SO2Tol
NC
2d