

#### Terms & Conditions

Electronic Supporting Information files are available without a subscription to ACS Web Editions. The American Chemical Society holds a copyright ownership interest in any copyrightable Supporting Information. Files available from the ACS website may be downloaded for personal use only. Users are not otherwise permitted to reproduce, republish, redistribute, or sell any Supporting Information from the ACS website, either in whole or in part, in either machine-readable form or any other form without permission from the American Chemical Society. For permission to reproduce, republish and redistribute this material, requesters must process their own requests via the RightsLink permission system. Information about how to use the RightsLink permission system can be found at <http://pubs.acs.org/page/copyright/permissions.html>



ACS Publications

MOST TRUSTED. MOST CITED. MOST READ.

Copyright © 1997 American Chemical Society

**REVISED**

JUL 10 1997

**Synthesis of Benzofuran Derivatives on Solid Support via SmI<sub>2</sub>-Mediated Radical Cyclization**

Xiaohui Du and Robert W. Armstrong\*

*Department of Chemistry and Biochemistry  
University of California  
Los Angeles, California 90095***Supporting Information**

**General Methods.** CH<sub>2</sub>Cl<sub>2</sub>, THF, and methanol were distilled immediately prior to use: THF from sodium/benzophenone ketyl, CH<sub>2</sub>Cl<sub>2</sub> from P<sub>2</sub>O<sub>5</sub> and methanol from magnesium turnings. Acetyl chloride was distilled over PCl<sub>5</sub>. HMPA was distilled over CaH<sub>2</sub> at reduced pressure and stored in 4Å molecular sieves. Anhydrous DMF and N-methylpyrrolidinone, 0.1 M SmI<sub>2</sub> solution in THF, vanillin and all the halides were purchased from Aldrich and used directly. P<sub>1</sub>-t-Bu was purchased from Fluka and used directly. Rink resin was purchased from Advanced ChemTech. The loading level of the polymer was 0.81mmol/g. NMR spectra were obtained with a Bruker ARX-400, or AM-360 spectrometer in CDCl<sub>3</sub> or CDCl<sub>3</sub>/MeOD mixed solvent. Spectra was referenced to residual CHCl<sub>3</sub> at 7.26ppm. Unless otherwise noted spectra were taken in CDCl<sub>3</sub>. Coupling constants are listed in hertz. IR spectra were obtained with a Nicolet 510P FT-IR spectrometer.

**Synthesis of 3-iodo-4-acetoxy-5-methoxybenzoic acid (2).** 4-Hydroxy-3-iodo-5-methoxybenzaldehyde (1g, 3.6mmol) was dissolved in 2ml THF and 25ml of CH<sub>2</sub>Cl<sub>2</sub>. The solution was cooled down to -20°C. To this solution, Et<sub>3</sub>N (1.1ml, 8.0mmol) was added followed by dropwise addition of acetyl chloride (0.28ml, 4.0mmol) under nitrogen. The reaction is complete within half an hour. The solvents were removed in vacuo and the reaction mixture were treated with water, extracted with ether (3 x 20ml). The extract was washed with saturated NH<sub>4</sub>Cl, saturated NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). The solvent was evaporated to give **4-acetoxy-3-iodo-5-**

**methoxybenzaldehyde** (1.14g, 99%) which was carried to the next step without further purification: IR (neat) ( $\text{cm}^{-1}$ ) 3077, 2944, 2851, 1761, 1700, 1588, 1572, 1462, 1415, 1385, 1275, 1040.  $^1\text{H}$  NMR (400 MHz)  $\delta$  9.87 (s, 1H), 7.87 (d, 1H,  $J = 1.7$ ), 7.44 (d, 1H,  $J = 1.6$ ), 3.89 (s, 3H), 2.39 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz)  $\delta$  189.6, 167.2, 152.4, 145.9, 136.0, 133.8, 110.8, 92.1, 56.4, 20.7. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 319.9546, found 319.9547.

$\text{NaClO}_2$  (312mg, 3.5mmol) and  $\text{NaH}_2\text{PO}_4$  (414mg, 3.5mmol) were dissolved in water (4ml). The resulting solution was added dropwise to the mixture of 4-acetoxy-3-iodo-5-methoxybenzaldehyde (220mg, 0.69mmol), *t*-BuOH (no distillation, 12ml), and 2M solution of 2-methyl-2-butene in THF (3.5ml, 7mmol). After reaction was complete (within half an hour), THF and *t*-BuOH were removed. The reaction was diluted with water, extracted with  $\text{CH}_2\text{Cl}_2$  (1 x 5ml). Then a 2N HCl solution was added dropwise to the aqueous mix until pH = 3, which was extracted with  $\text{CH}_2\text{Cl}_2$  three times. The extract was washed with brine, dried with  $\text{MgSO}_4$ . The solvent was removed to give **2** (229mg, 99%) which was used without further purification: IR (neat) ( $\text{cm}^{-1}$ ) 2965, 1765, 1692, 1590, 1572, 1458, 1418, 1292, 1171, 1044.  $^1\text{H}$  NMR (400 MHz)  $\delta$  8.16 (d, 1H,  $J = 1.8$ ), 7.65 (d, 1H,  $J = 1.8$ ), 3.89 (s, 3H), 2.40 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz)  $\delta$  170.1, 167.3, 151.5, 145.2, 132.6, 128.9, 113.7, 91.5, 56.4, 20.8. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 335.9495, found 335.9489.

**5-Carbamido-3-methoxy-1-iodo-2-phenol (3).** Fmoc-protected Rink amine resin (240mg, 0.19mmol) was deprotected with 20% piperidine/DMF for half an hour. The resin was filtered off and washed repeatedly with DMF, methanol,  $\text{CH}_2\text{Cl}_2$ . The resin was transferred to a flask and dried *in vacuo* (2mmHg) at 55°C for 2 hours. Then, **2** (229mg, 0.69mmol), DIC (*N,N'*-diisopropylcarbodiimide) (107ul, 0.69mmol), HOBT (1-hydroxybenzotriazole) (93mg, 0.69mmol) and DMF (6ml) were combined with the resin. The mixture was stirred overnight under nitrogen. The resin was filtered off and washed repeatedly with DMF, methanol and  $\text{CH}_2\text{Cl}_2$ . The resin was dried as before (*in vacuo* at

55°C for 2 hours). 2.5ml anhydrous THF was added to the dried resin followed by a 2M solution of NaOMe made *in situ* (2.5ml, 1.9mmol Na). The mixture was stirred at room temperature for 2 hours, filtered, and washed with methanol, THF and CH<sub>2</sub>Cl<sub>2</sub>. A small portion of the resin was cleaved with 20% trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR of the cleaved product showed the clean deprotection of the acetate and the formation of the polymer-bound phenol **3**: <sup>1</sup>H NMR (360 MHz)  $\delta$  7.56 (d, 1H, *J* = 1.0), 7.13 (d, 1H, *J* = 1.2), 3.62 (s, 3H). HRMS (EI) *m/z* (*M*<sup>+</sup>) calcd 292.9549, found 292.9551.

**Representative Procedure for Coupling of 3 with various organohalides.**

To a suspension of polymer-bound **3** (200mg, 0.16mmol) in N-methylpyrrolidinone (6ml) was added P<sub>1</sub>-t-Bu (206ul, 0.81mmol) and cinnammyl bromide (0.24ml, 0.81mmol). The mixture was stirred under nitrogen at 50°C for 20 hours. The resin was filtered off and washed with methanol, THF and CH<sub>2</sub>Cl<sub>2</sub>.

**TFA cleavage of 4a.** <sup>1</sup>H NMR (360 MHz)  $\delta$  7.69 (s, 1H), 7.31 (s, 1H), 6.63 (br, 2H), 6.15-6.06 (m, 1H), 5.39 (dd, 1H, *J* = 1.3, 17.2), 5.26 (d, 1H, *J* = 10.3), 4.60 (d, 2H, *J* = 5.9), 3.80 (s, 3H). HRMS (EI) *m/z* (*M*<sup>+</sup>) calcd 332.9862, found 332.9863.

**TFA cleavage of 4h.** <sup>1</sup>H NMR (360 MHz)  $\delta$  7.70 (s, 1H), 7.44 (s, 1H), 6.11 (br, 2H), 5.17 (s, 1H), 5.00 (s, 1H), 4.47 (s, 2H), 3.89 (s, 3H), 1.93 (s, 3H). HRMS (EI) *m/z* (*M*<sup>+</sup>) calcd 347.0018, found 347.0023.

**TFA cleavage of 4i.** <sup>1</sup>H NMR (360 MHz) (CDCl<sub>3</sub>-CD<sub>3</sub>OD)  $\delta$  7.75 (s, 1H), 7.42 (s, 1H), 5.81 (s, 1H), 5.63 (s, 1H), 4.54 (s, 2H), 3.94 (m, 4H), 3.84 (m, 4H). HRMS (FAB) *m/z* (*M*+H) calcd 433.0624, found 433.0626.

**Representative Procedure for SmI<sub>2</sub>-mediated Cyclization of 4.** To the flask with dried polymer-bound **4b** (180mg, 0.146mmol) under argon, was added HMPA (1.01ml, 5.84mmol). Then 0.1M solution of SmI<sub>2</sub> in THF (15ml, 1.46mmol) was added into the flask. The resulting deep-purple mixture was stirred for one hour, filtered and washed with methanol, THF, and CH<sub>2</sub>Cl<sub>2</sub>. After cleavage of the resin with 20% trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> with slow filtration, the residue was concentrated *in vacuo*.

The crude reaction mix was chromatographed in CH<sub>2</sub>Cl<sub>2</sub> with an increasing gradient of methanol. The cyclized product **5-carbamido-7-methoxy-3-phenylmethyl-2,3-dihydrobenzofuran (5b)** (26mg) was obtained in 63% combined yield based on the initial Rink resin **1** loading of 0.81mmol/g: IR (neat) (cm<sup>-1</sup>) 3355, 3195, 2938, 1655, 1595, 1497, 1455, 1389, 1208, 1115. <sup>1</sup>H NMR (360 MHz)  $\delta$  7.37 (s, 1H), 7.34-7.14 (m, 5H), 6.84 (s, 1H), 5.92 (br, 2H), 4.68 (t, 1H,  $J$  = 9.0), 4.46 (dd, 1H,  $J$  = 5.7, 9.1), 3.91 (s, 3H), 3.81-3.73 (m, 1H), 3.01 (dd, 1H,  $J$  = 6.9, 13.7), 2.89 (dd, 1H,  $J$  = 8.7, 13.7). <sup>13</sup>C NMR (101 MHz)  $\delta$  151.8, 144.5, 138.6, 131.3, 129.1, 128.6, 126.7, 116.2, 111.7, 77.9, 56.1, 43.6, 40.9. HRMS (EI)  $m/z$  (M<sup>+</sup>) calcd 283.1208, found 283.1211.

**5-Carbamido-7-methoxy-3-methyl-2,3-dihydrobenzofuran (5a).** Started from 200mg resin, got 19mg product after chromatograph (57%). IR (neat) (cm<sup>-1</sup>) 3359, 3195, 2961, 1655, 1595, 1503, 1464, 1402, 1119. <sup>1</sup>H NMR (360 MHz)  $\delta$  7.32 (d, 1H,  $J$  = 1.0), 7.23 (s, 1H), 6.07 (br, 2H), 4.81 (t, 1H,  $J$  = 9.0), 4.21 (dd, 1H,  $J$  = 7.5, 8.7), 3.61-3.55 (m, 1H), 3.90 (s, 3H), 1.33 (d, 3H,  $J$  = 6.9). <sup>13</sup>C NMR (91 MHz)  $\delta$  169.4, 151.5, 144.3, 133.5, 126.6, 115.7, 111.4, 79.9, 56.1, 36.7, 19.3. HRMS (EI)  $m/z$  (M<sup>+</sup>) calcd 207.0895, found 207.0893.

**5-Carbamido-7-methoxy-3-(2-methoxy)phenylmethyl-2,3-dihydrobenzofuran (5c).** 152mg resin, 22mg product (58%). IR (neat) (cm<sup>-1</sup>) 3355, 3196, 3004, 2940, 1655, 1597, 1495, 1464, 1387, 1244, 1115. <sup>1</sup>H NMR (360 MHz)  $\delta$  7.36 (d, 1H,  $J$  = 1.5), 7.27-7.23 (m, 1H), 7.01 (dd, 1H,  $J$  = 1.1, 7.3), 6.90-6.85 (m, 3H), 5.97 (br, 2H), 4.64 (t, 1H,  $J$  = 9.0), 4.46 (dd, 1H,  $J$  = 5.6, 9.1), 3.90 (s, 3H), 3.86-3.80 (m, 1H), 3.82 (s, 3H), 2.99 (dd, 1H,  $J$  = 6.7, 13.3), 2.87 (dd, 1H,  $J$  = 8.6, 13.3). <sup>13</sup>C NMR (101 MHz)  $\delta$  169.4, 157.6, 151.8, 144.4, 131.9, 131.0, 128.0, 127.1, 126.0, 120.2, 116.4, 111.5, 110.3, 78.2, 56.0, 55.2, 41.7, 36.1. HRMS (EI)  $m/z$  (M<sup>+</sup>) calcd 313.1314, found 313.1318.

**5-Carbamido-3-ethyl-7-methoxy-2,3-dihydrobenzofuran (5d).** 195mg resin, 22mg product as an inseparable mixture of **5d** and the radical disproportionation

product in 9:1 ratio (61%). IR (neat) ( $\text{cm}^{-1}$ ) 3372, 3200, 2963, 1653, 1593, 1482, 1399, 1211, 1117.  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.33 (d, 1H,  $J = 1.4$ ), 7.24 (d, 1H,  $J = 0.8$ ), 6.01 (br, 2H), 4.76 (t, 1H,  $J = 9.1$ ), 4.37 (dd, 1H,  $J = 6.4, 9.0$ ), 3.90 (s, 3H), 3.48-3.41 (m, 1H), 1.84-1.75 (m, 1H), 1.65-1.57 (m, 1H), 0.96 (t, 3H,  $J = 7.5$ ).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  169.4, 151.8, 144.3, 132.1, 126.3, 116.1, 111.4, 78.0, 56.1, 43.4, 27.4, 11.1. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 221.1052, found 221.1050.

**5-Carbamido-7-methoxy-3-(2-propyl)-2,3-dihydrobenzofuran (5e).**

68mg resin, 7.7mg products as an inseparable mixture of **5e** and the radical disproportion product (60%). Both compound can be readily assigned from the NMR spectra. IR (neat) ( $\text{cm}^{-1}$ ) 3378, 3198, 2961, 1653, 1593, 1503, 1399, 1304, 1117. **5e**:  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.33 (d, 1H,  $J = 1.4$ ), 7.25 (s, 1H), 4.64 (t, 1H,  $J = 9.3$ ), 4.52 (m, 1H), 3.90 (s, 3H), 3.44-3.38 (m, 1H), 2.04-1.96 (m, 1H), 0.94 (d, 3H,  $J = 6.8$ ), 0.85 (d, 3H,  $J = 6.8$ ).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  169.4, 152.2, 144.3, 130.7, 126.1, 116.8, 111.4, 75.2, 56.0, 48.2, 31.5, 19.8, 18.0. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 235.1208, found 235.1208.

**5-Carbamido-7-methoxy-3-(1-methyl)vinyl-2,3-dihydrobenzofuran (radical disproportionation product):**  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.37 (d, 1H,  $J = 1.5$ ), 7.14 (s, 1H), 6.05 (br, 2H), 4.90 (s, 1H), 4.87 (t, 1H,  $J = 1.5$ ), 4.78 (t, 1H,  $J = 9.5$ ), 4.48 (m, 1H), 4.21 (dd, 1H,  $J = 6.8, 9.8$ ), 3.91 (s, 3H), 1.63 (s, 3H).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  169.2, 152.1, 144.5, 143.7, 130.0, 126.6, 116.4, 113.6, 111.7, 76.6, 56.1, 50.4, 18.6. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 233.1052, found 233.1053.

**1-[3-(5-Carbamido-7-methoxy-2H,3H-benzofurfuryl)]ethanol (5f).** *t*-BuOH (12 equiv.) was added at the same time as HMPA. 200mg resin, 16mg cyclized product and 2mg radical disproportionation product (might be from elimination) (48%). IR (neat) ( $\text{cm}^{-1}$ ) 3351, 2942, 1659, 1591, 1404, 1304, 1206, 1119.  $^1\text{H}$  NMR (360 MHz) ( $\text{CDCl}_3\text{-CD}_3\text{OD}$ )  $\delta$  7.29 (s, 2H), 4.72 (t, 1H,  $J = 9.0$ ), 4.32 (dd, 1H,  $J = 6.4, 9.0$ ), 3.83 (s, 3H), 3.63 (t, 2H,  $J = 6.3$ ), 3.59-3.55 (m, 1H), 1.94-1.86 (m, 1H), 1.81-1.73 (m,

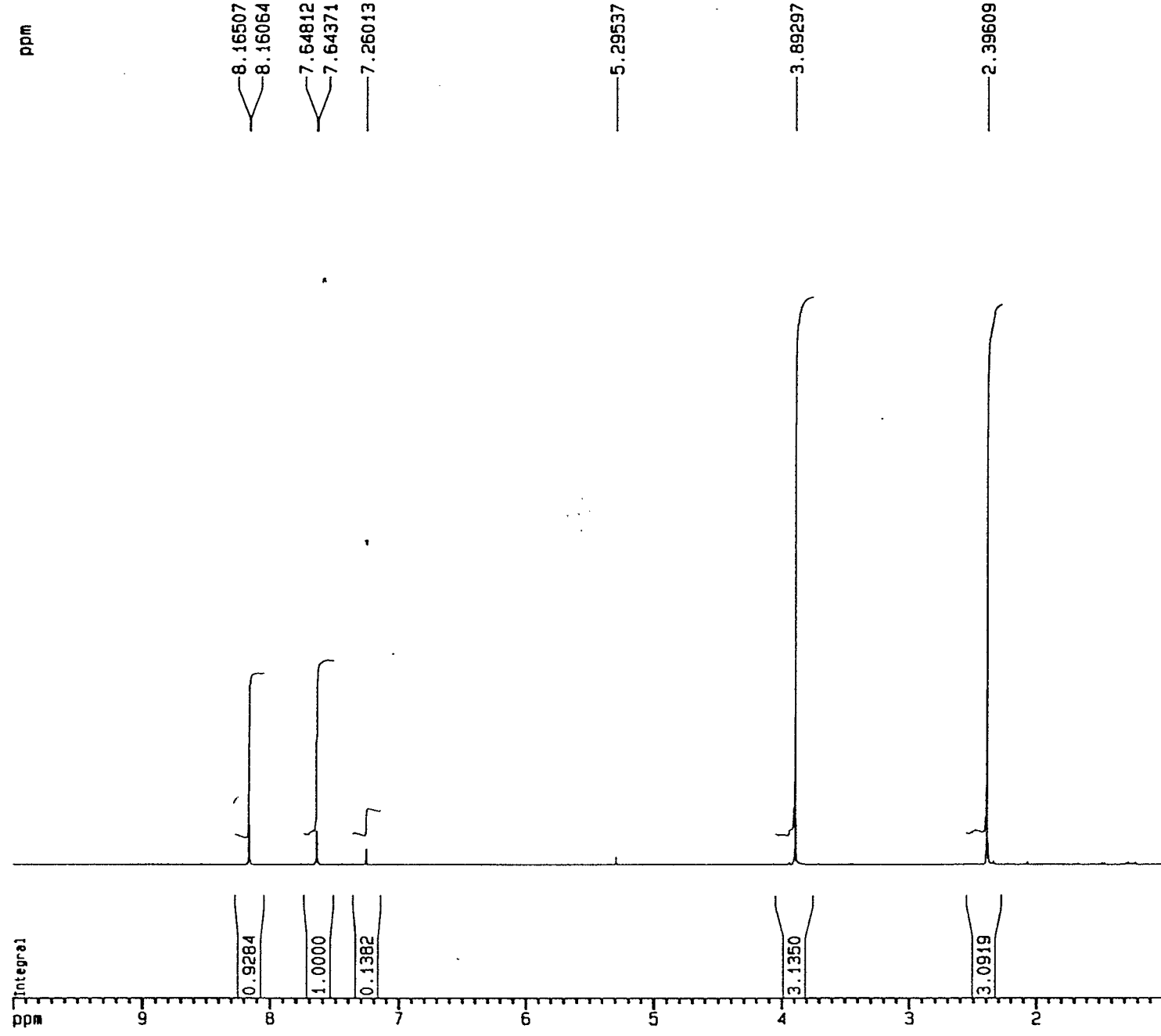
1H).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  170.2, 151.5, 144.1, 131.8, 131.0, 126.0, 116.6, 111.5, 78.5, 59.5, 55.9, 38.8, 37.1. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 237.1001, found 237.1000.

**Compound (5g).** 230mg resin, 24mg product (51%). IR (neat) ( $\text{cm}^{-1}$ ) 3370, 3198, 2936, 2859, 1653, 1593, 1401, 1302, 1117.  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.34 (d, 1H,  $J = 1.5$ ), 7.22 (d, 1H,  $J = 0.8$ ), 6.16 (br, 2H), 4.81-4.76 (m, 1H), 3.90 (s, 3H), 3.19 (dd, 1H,  $J = 7.0, 14.6$ ), 2.10-2.05 (m, 1H), 1.89-1.41 (m, 6H), 1.36-1.30 (m, 1H).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  169.6, 151.2, 144.6, 134.8, 126.3, 115.5, 111.3, 84.5, 56.0, 40.6, 28.3, 27.2, 21.8, 20.2. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 247.1208, found 247.1203.

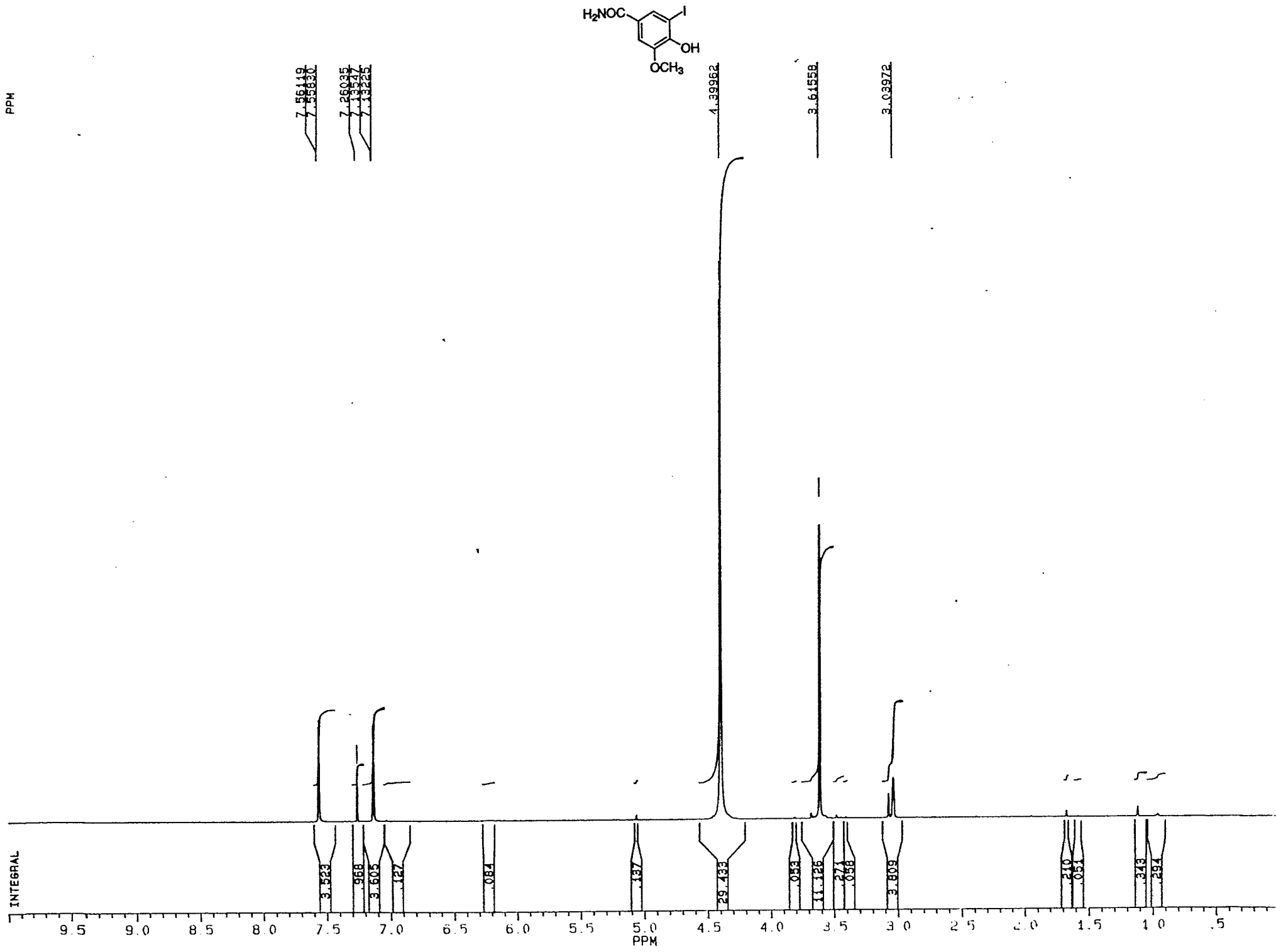
**5-Carbamido-7-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran (5h).** 200mg resin, 16mg product (43%). IR (neat) ( $\text{cm}^{-1}$ ) 3360, 3193, 2959, 1655, 1597, 1401, 1308, 1113, 1061.  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.31 (d, 1H,  $J = 1.5$ ), 7.18 (d, 1H,  $J = 1.4$ ), 4.37 (s, 2H), 3.92 (s, 3H), 1.36 (s, 6H).  $^{13}\text{C}$  NMR (101 MHz)  $\delta$  169.3, 151.0, 144.4, 137.9, 126.7, 114.4, 111.3, 85.9, 56.2, 42.4, 27.5. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 221.1052, found 221.1047.

**N-[3-(5-Carbamido-7-methoxy-2H,3H-benzofurfuryl)]morpholine (5i).** 220mg resin, 6mg product (11%). IR (neat) ( $\text{cm}^{-1}$ ) 3353, 3202, 2961, 1655, 1597, 1497, 1387, 1115, 1053.  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.32 (d, 1H,  $J = 1.2$ ), 7.23 (s, 1H), 5.80 (br,  $\text{NH}_2$ ), 4.68 (d, 1H,  $J = 8.8$ ), 4.30 (d, 1H,  $J = 8.8$ ), 3.92 (s, 3H), 3.62 (m, 4H), 2.52 (s, 2H), 2.39 (m, 4H), 1.37 (s, 3H).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  168.9, 151.4, 144.4, 135.5, 126.5, 115.1, 111.5, 82.8, 67.1, 66.7, 56.1, 55.6, 47.2, 24.4. HRMS (EI)  $m/z$  ( $\text{M}+\text{H}$ ) calcd 307.1658, found 307.1653.

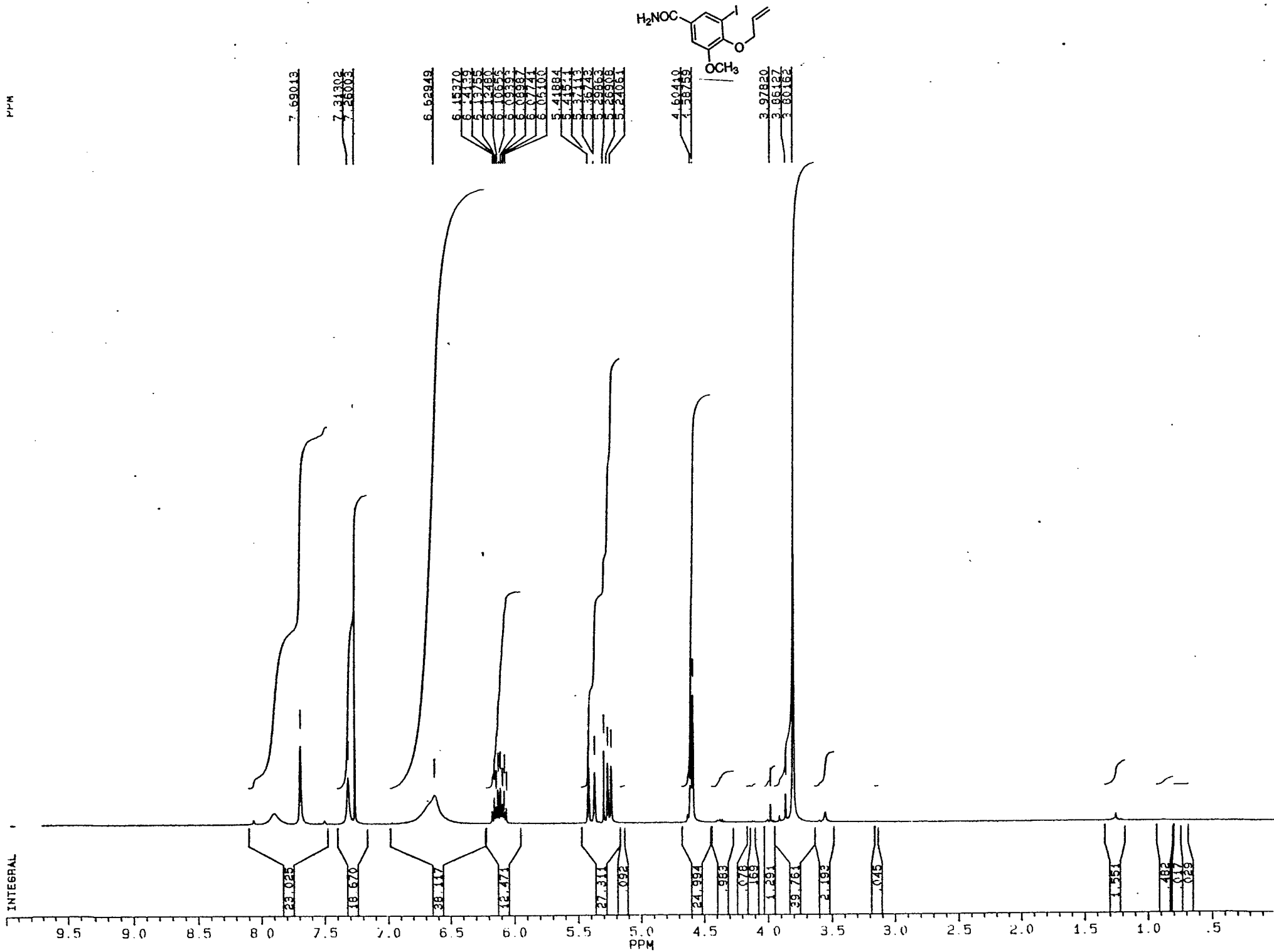
**5-Carbamido-7-methoxy-3-methylbenzofuran (5j).** 194mg resin, 12mg product (37%). IR (neat) ( $\text{cm}^{-1}$ ) 3378, 3191, 1657, 1595, 1402, 1256, 1209, 1115, 1055.  $^1\text{H}$  NMR (360 MHz)  $\delta$  7.55 (d, 1H,  $J = 1.1$ ), 7.47 (d, 1H,  $J = 1.1$ ), 7.36 (s, 1H), 4.05 (s, 3H), 2.25 (d, 1H,  $J = 1.2$ ).  $^{13}\text{C}$  NMR (91 MHz)  $\delta$  169.9, 146.6, 145.4, 130.5, 128.7, 116.5, 111.5, 106.1, 56.3, 7.9. HRMS (EI)  $m/z$  ( $\text{M}^+$ ) calcd 205.0739, found 205.0743.

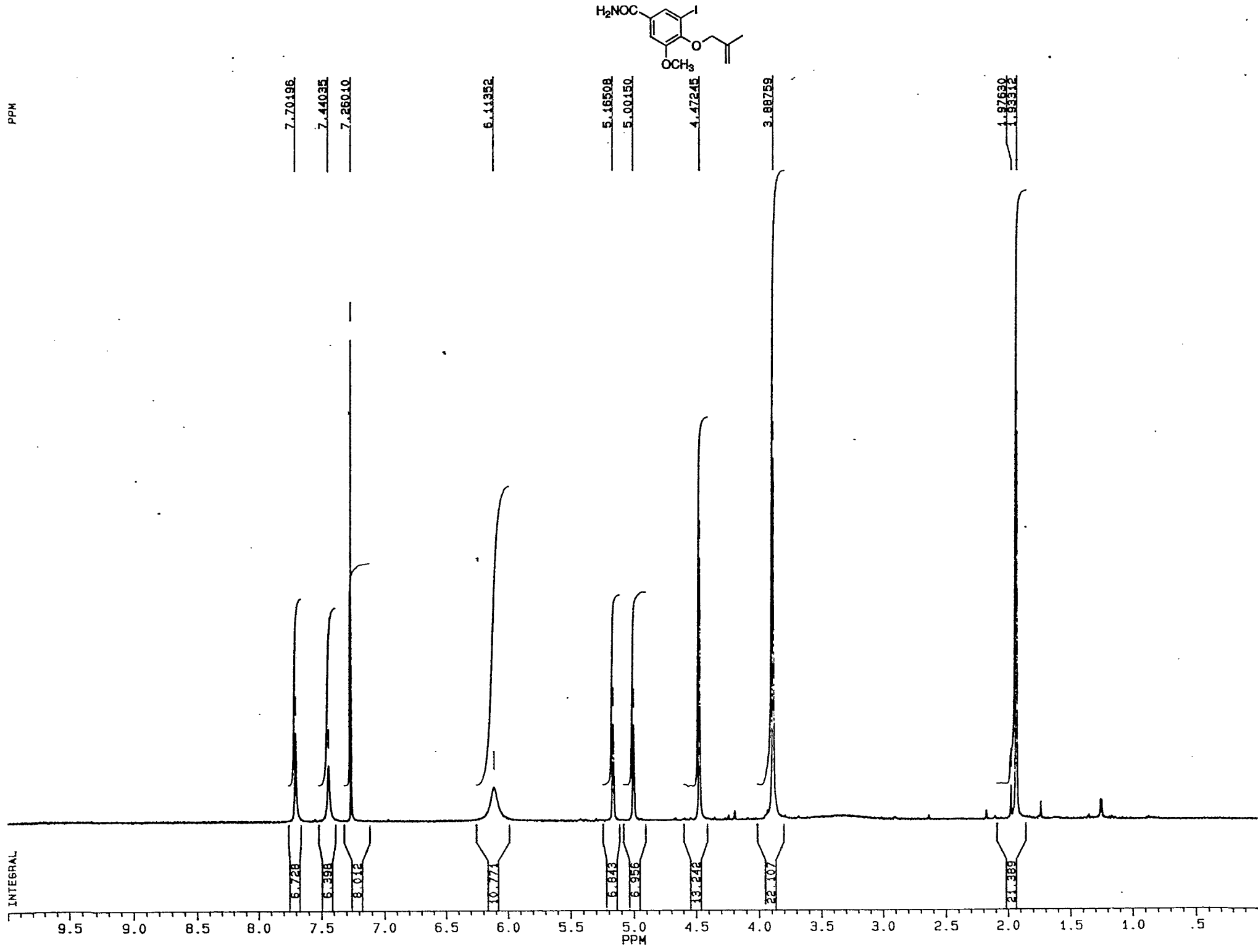


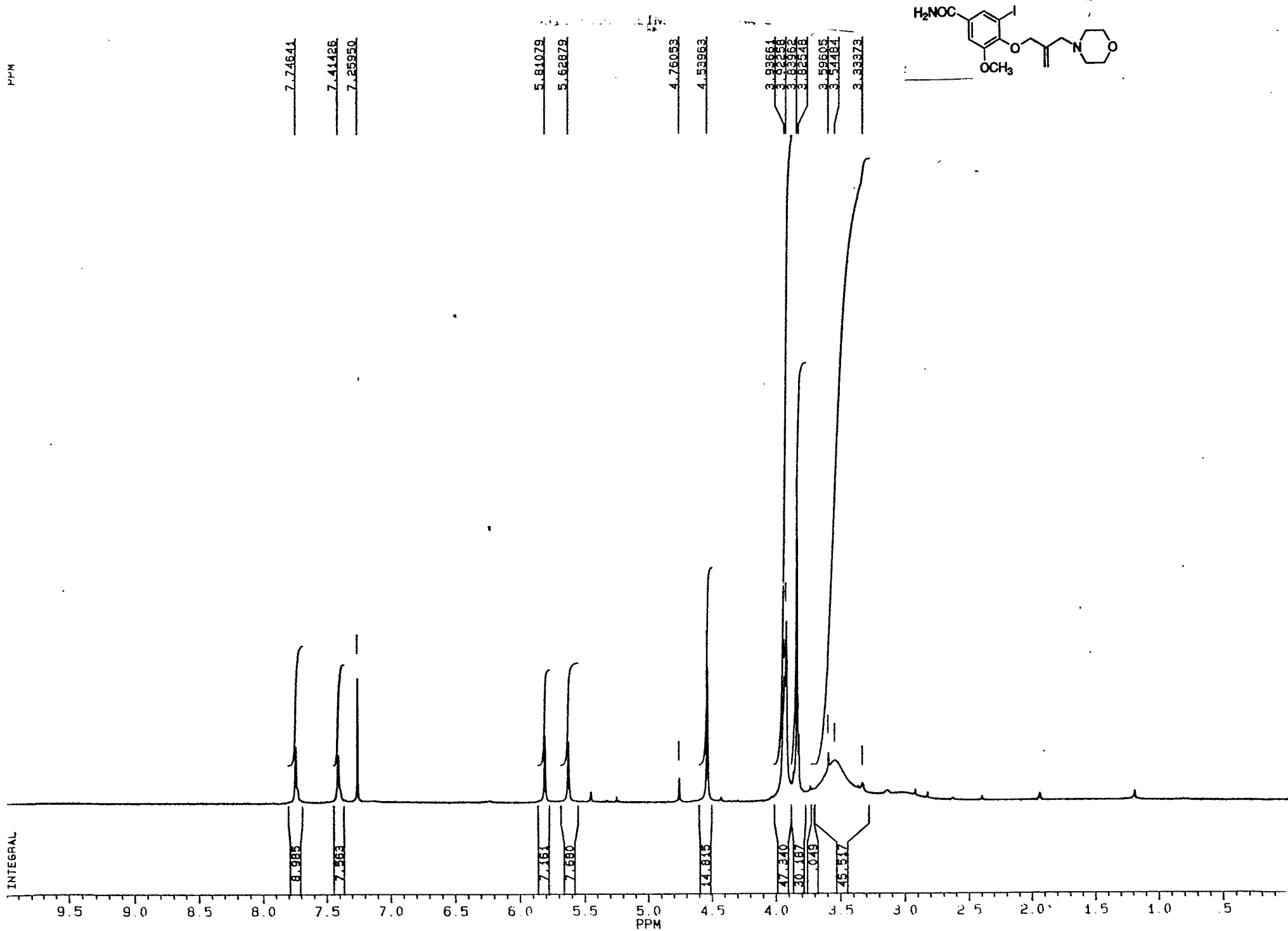


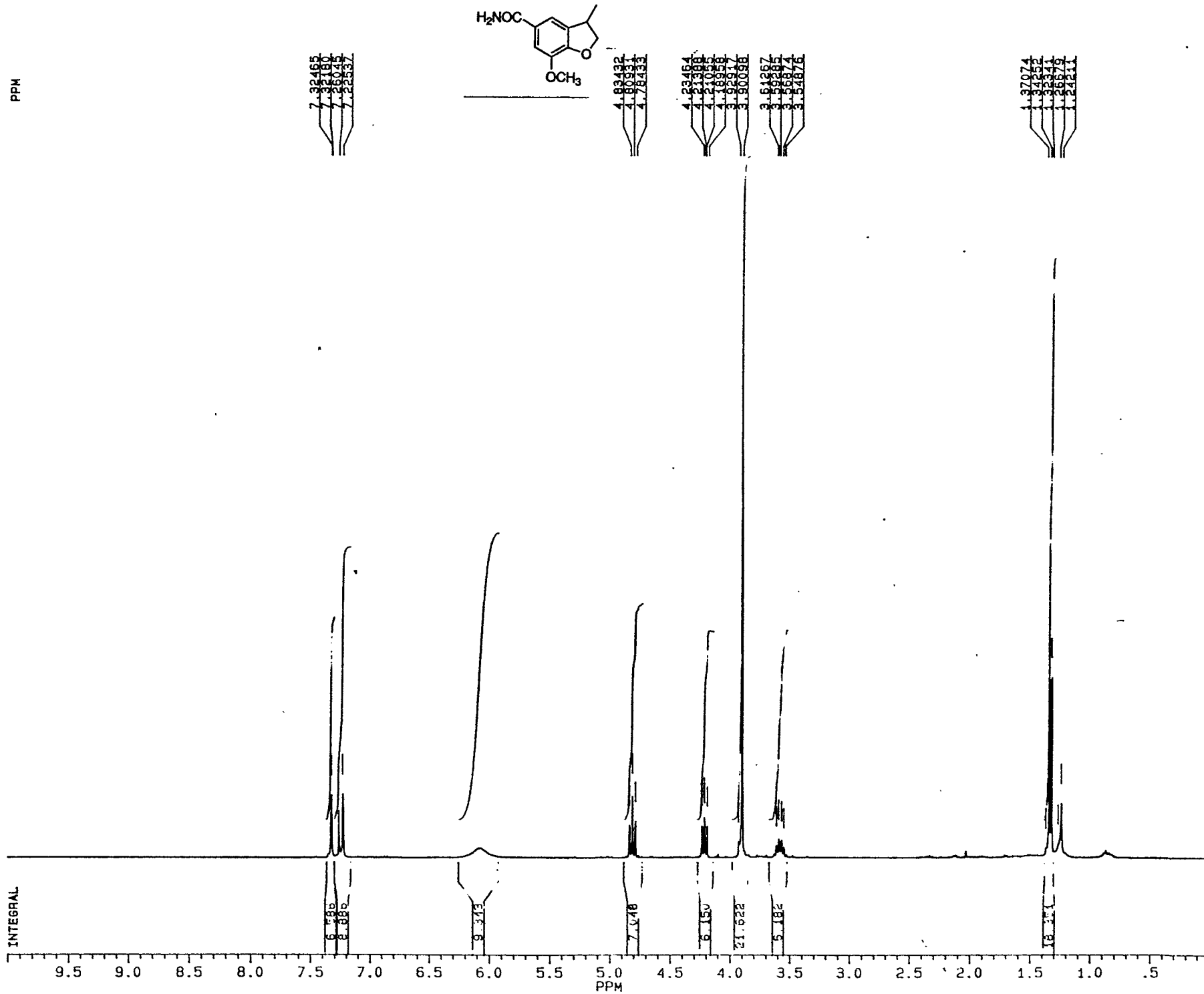


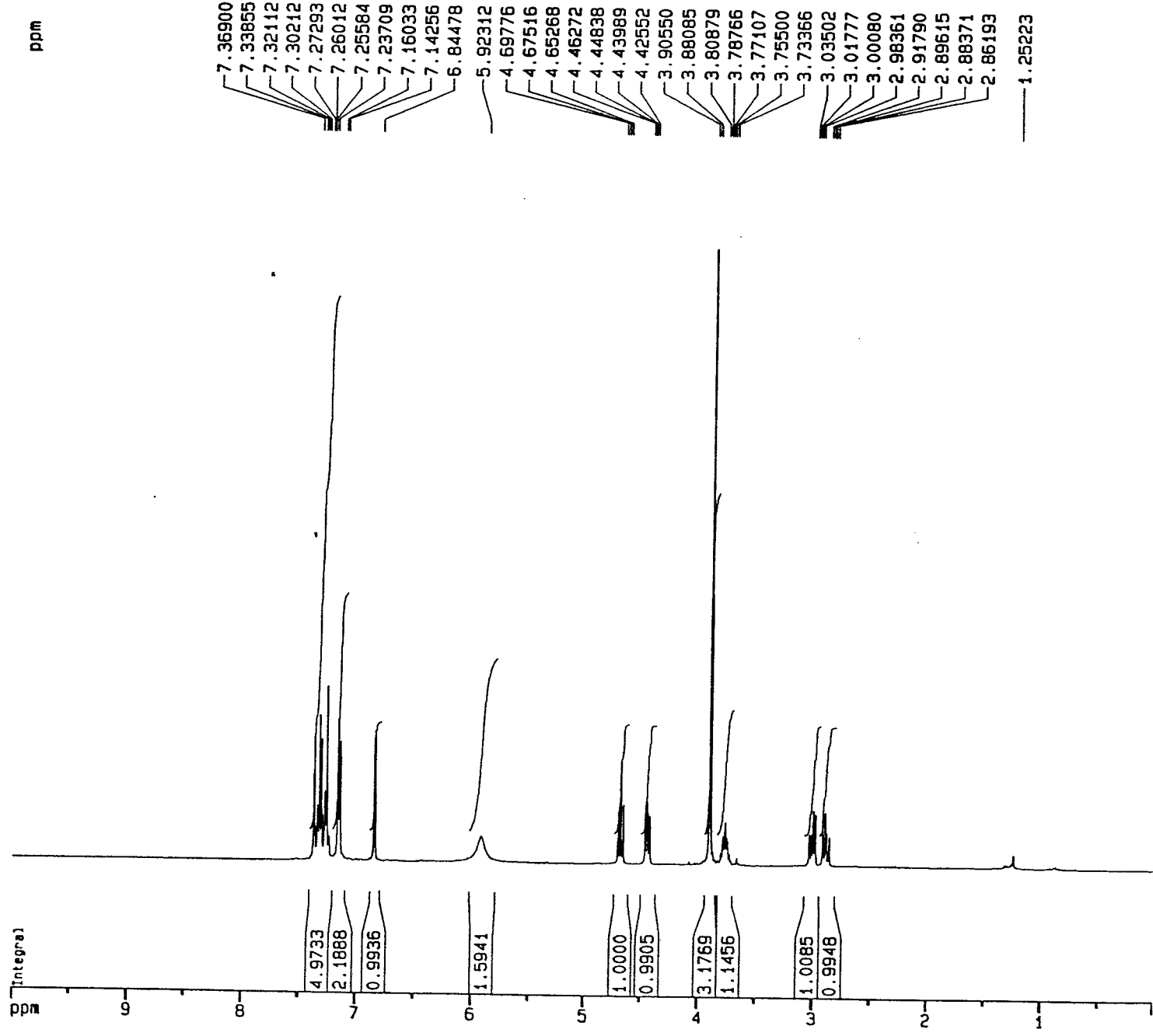
PPM

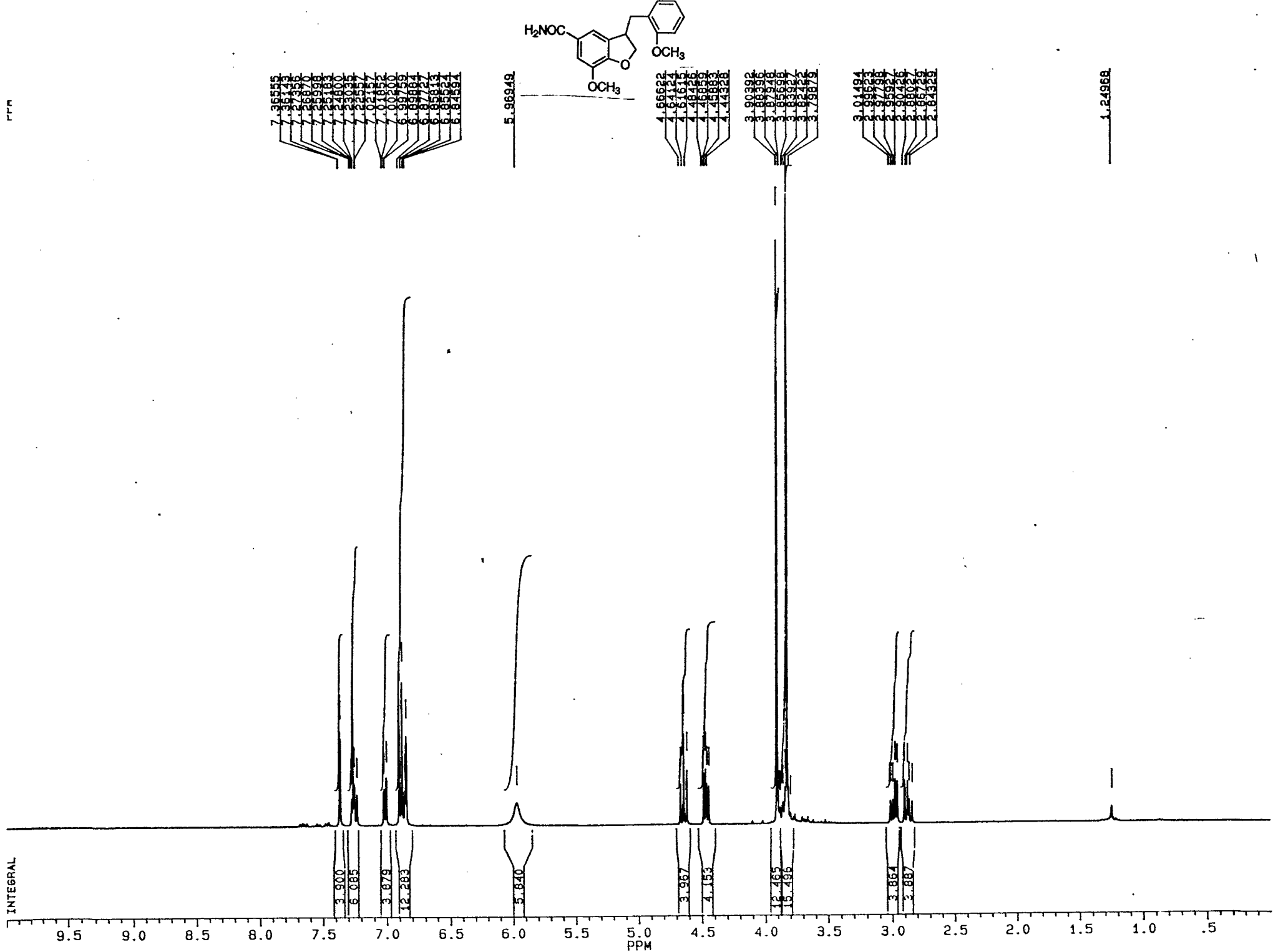


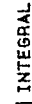




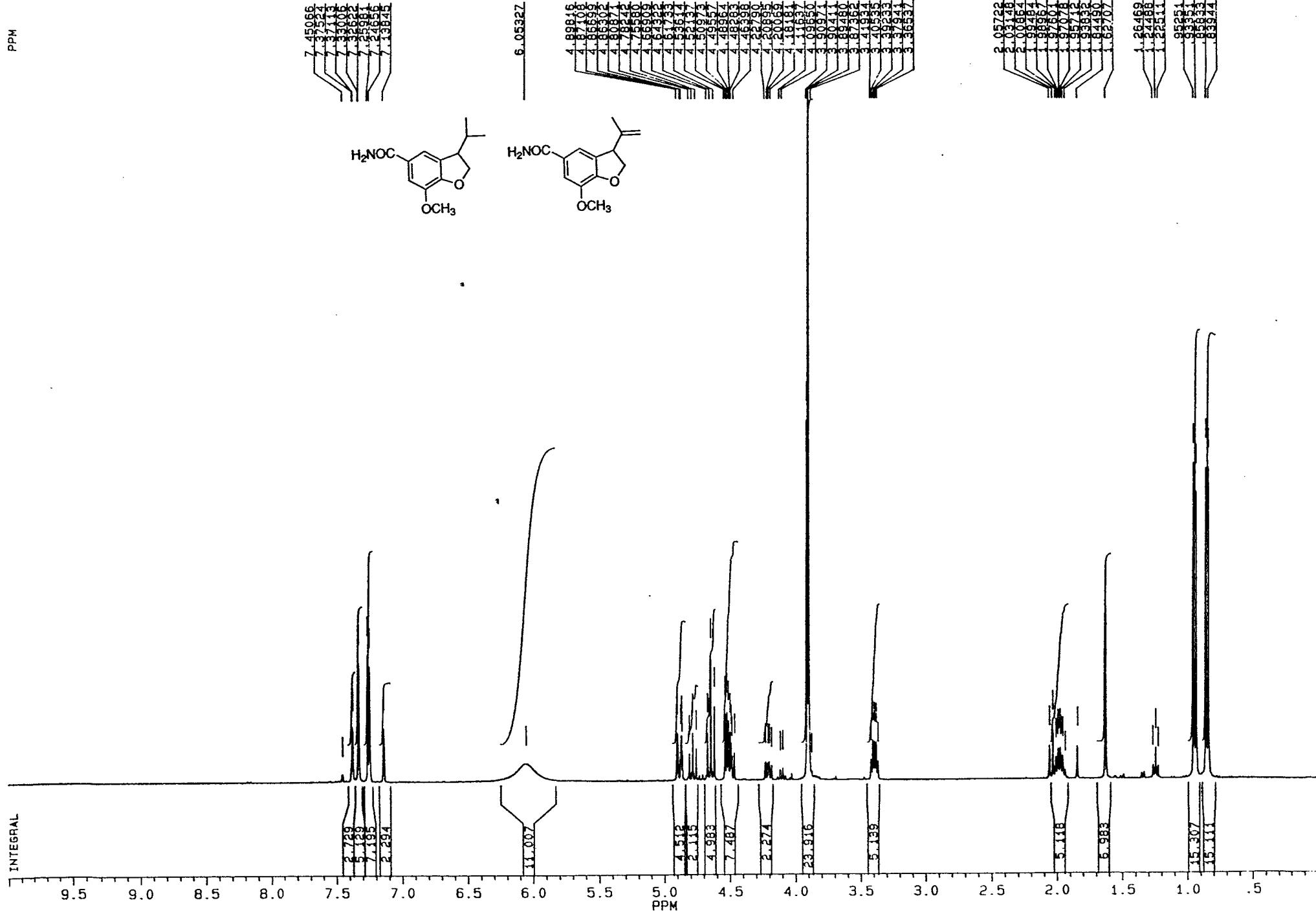


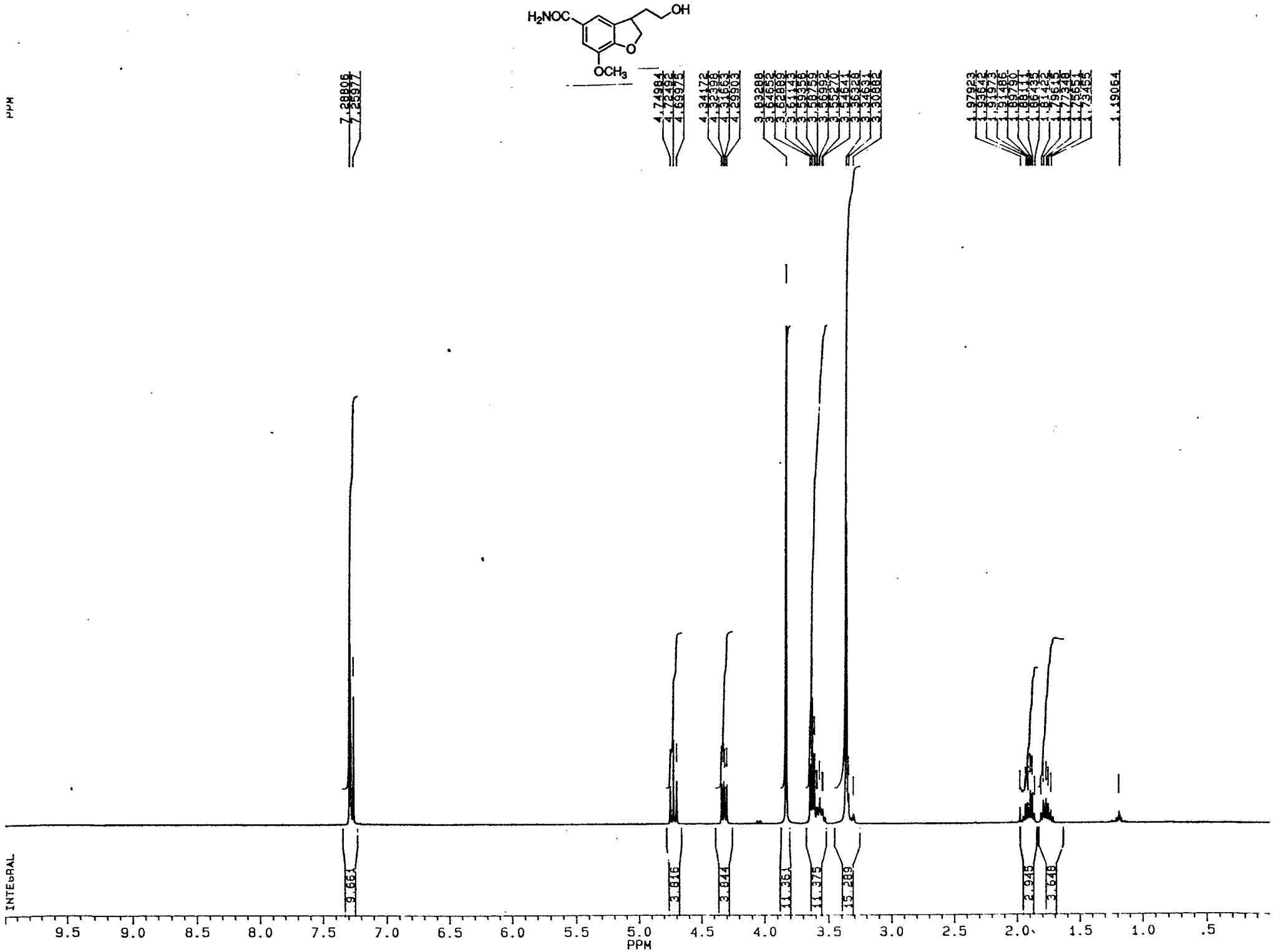


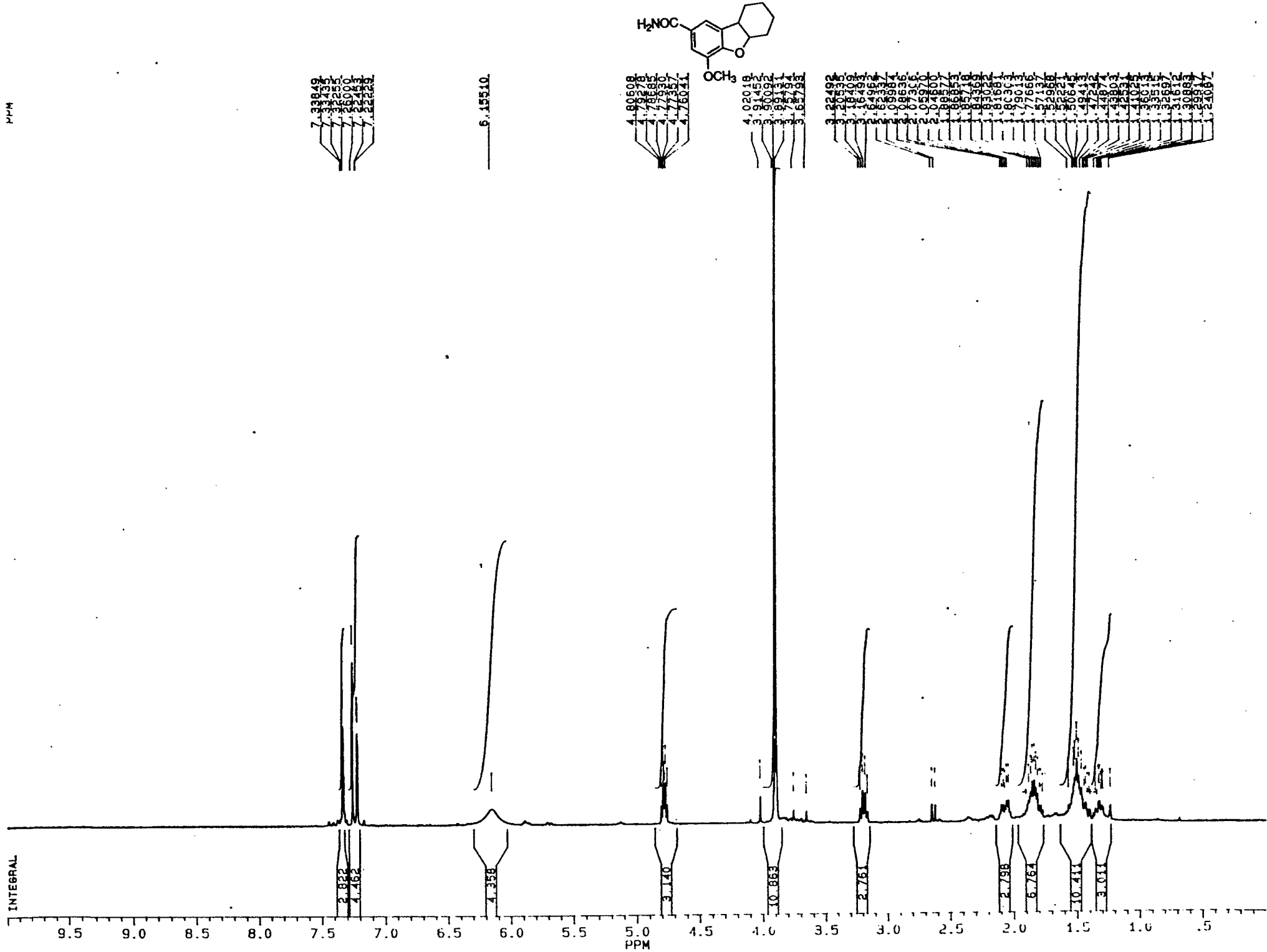


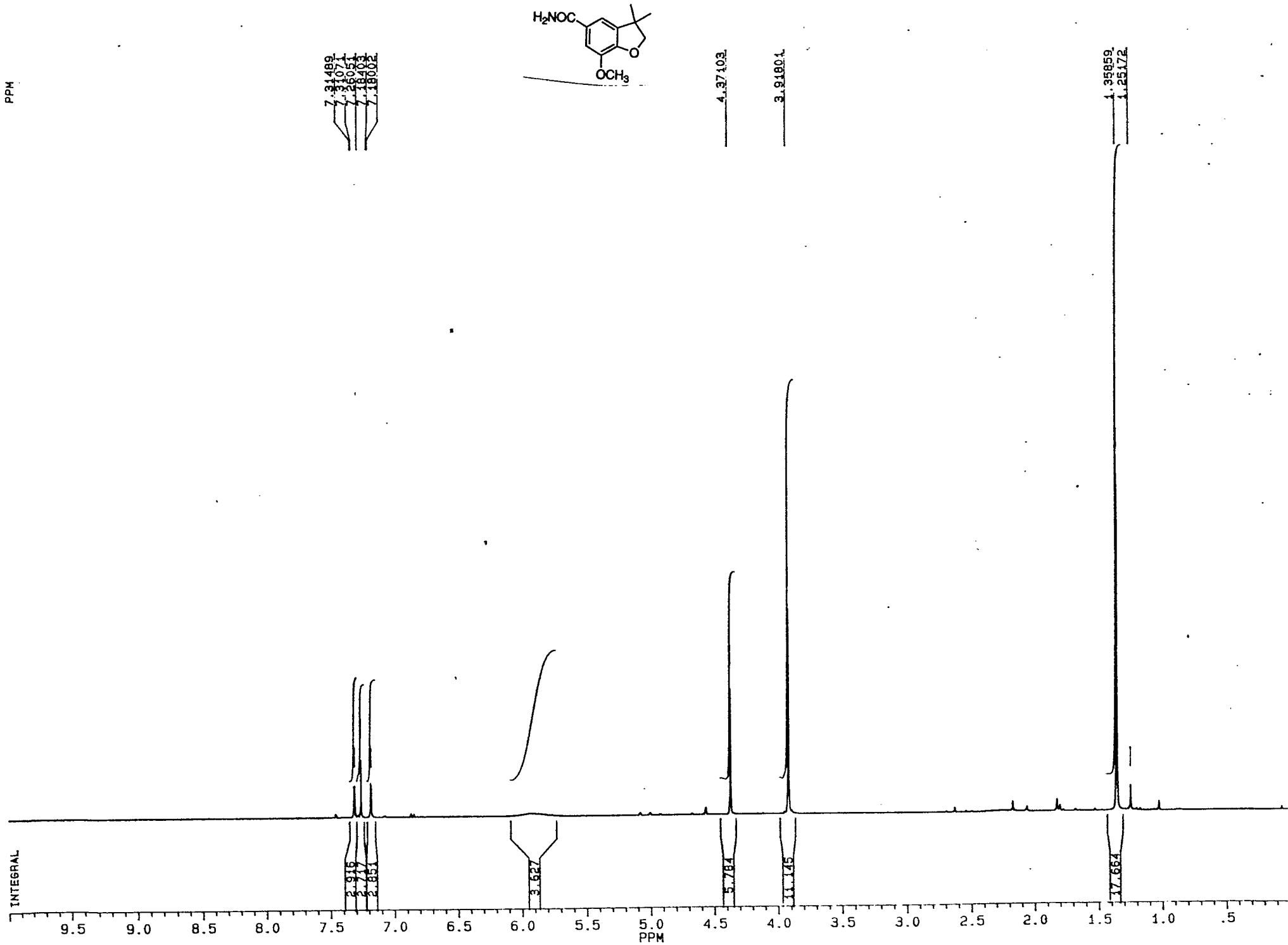












PPM

INTEGRAL

