Supporting information to:

SYNTHESIS OF PYRAZINES ALCALOIDS FROM BOTRYLLUS LEACHI. DIAZINES 43.

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1. General Information

Melting points were determined on a Kofler hot-stage apparatus. The ^{1}H, ^{13}C NMR spectra were recorded on Bruker instruments (AC 200 and Avance 300). Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained from potassium bromide pellets with a Perkin-Elmer FTIR 1650 spectrophotometer.

All reagents were of commercial quality purchased from Aldrich Co. and Acros. Pd-catalyst was prepared according to the literature.

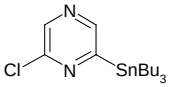
Procedure A for direct lithiation by lithium 2,2,6,6-tetramethylpiperidide. A solution of *n*-butyllithium (1.6M or 2.5M in hexane) was added to cold (-50°C), stirred and anhydrous THF (50 mL) under an atmosphere of dry nitrogen. Then 2,2,6,6-tetramethypiperidine (TMPH) was added. The mixture was warmed to 0°C. After 20 min, the mixture was cooled to the temperature θ_1 and a solution of pyrazine dissolved in 8 mL of THF, added. After a time t_1 at θ_1 , the electrophile was introduced and the stirring was continued for a time t_2 at θ_2. Hydrolysis was then carried out at θ_2 using a solution of ethanol and water (4 : 1). The mixture was evaporated and the residue was extracted with dichloromethane (3x20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

Procedure B for cross-coupling of arylboronic acids with halodiazines under Suzuki conditions.

A mixure of halodiazine, arylboronic acid (*n* equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), aqueous 2M potassium carbonate (1 equiv.) and ethanol (1 mL) in degassed toluene (15 mL) was heated to reflux under nitrogen for a time *t*. The reaction mixture was cooled, diluted with 20 mL of a mixture of water and dichloromethane (1:1) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2. Synthesis of Botryllazine B

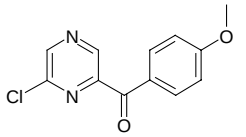
2-chloro-6-tri-*n*-butylstannylpyrazine (4)



A solution of *n*-butyllithium 2.5M (3.15 equiv., 10.83 mL) was added to cold (-50°C), stirred and anhydrous THF (75 mL) under an atmosphere of dry nitrogen. Then 2,2,6,6-tetramethypiperidine (3.15 equiv., 4.69 mL) was added. The mixture was warmed to 0°C. After 20 min, the mixture temperature was carried to -78°C. Chloropyrazine (1 g, 8.73 mmol) was dissolved in 50 mL THF and tri-*n*-butyltin chloride (1 equiv., 2.63 mL) were simultaneously introduced at -100°C into a solution containing the metalating agent (LTMP)

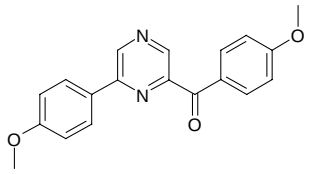
The mixture was then stirred for 2.5 h, during this time, temperature was slowly increased from -100°C at -40°C. Hydrolysis was then carried out at -40°C using a solution of 35% aqueous hydrochloric acid, ethanol and THF (1:4:5). At room temperature, the mixture was made slightly basic with saturated sodium hydrogenocarbonate solution. The mixture was evaporated and the residue was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography and gave after purification by column chromatography (silica gel, eluent: dichloromethane) 3.13 g (89%) of **(4)** as a yellow liquid. ^{1}H NMR ($CDCl_3$) : δ 8.36 (s, 1H, H_5), 8.27 (m, 1H, H_3), 1.53-0.77 (m, 27H, 3Bu); ^{13}C NMR ($CDCl_3$) : δ 170.0 (C_6), 151.2 (C_2), 148.7 (C_5), 142.7 (C_3), 28.9, 27.2, 10.0 (CH_2), 13.5 (CH_3); IR : 2953, 2925, 2871, 2852, 1489, 1463, 1404, 1376, 1169, 1150, 1001, 876 cm^{-1}; IC : 405 (MH^+), 371, 347.

2-chloro-6-(1-oxo-[4-methoxyphenyl]methyl)pyrazine (6)



A solution of 4-methoxybenzoyl chloride (7.7 g, 3 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.) in toluene was heated to 80°C under a nitrogen atmosphere. 2-chloro-6-tri-*n*-butylstannylpyrazine **(4)** (6.1 g, 15.1 mmol) was added and the solution was refluxed for 12 h. After cooling, a mixture of water (30 mL) and dichloromethane (30 mL) was added. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : dichloromethane/cyclohexane (8:2)) and gave 2.63 g (70%) of **(6)** as a yellow solid, mp : 98°C. ^{1}H NMR ($CDCl_3$) : δ 9.08 (s, 1H, H_3), 8.76 (s, 1H, H_5), 8.12 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 6.97 (d, 2H, J=8.7 Hz, $H_{Ph3,5}$), 3.89 (s 3H, OCH_3). ^{13}C ($CDCl_3$) : δ 188.7 (C_7), 164.4 (C_{Ph4}), 149.8 (C_2), 147.6 (C_6), 146.7 (C_3), 143.6 (C_5), 133.7 ($C_{Ph2,6}$), 127.9 (C_{Ph1}), 114.0 ($C_{Ph3,5}$), 55.7 (OCH_3). IR : 3048, 2984, 2939, 2844, 1651, 1594, 1511, 1324, 1268, 1179, 1160, 1021, 961, 841, 774 cm^{-1}. Anal. calcd for $C_{12}H_9ClN_2O_2$ (248.67) : C, 57.96; H, 3.65; N, 11.27. Found: C, 57.90; H, 3.73; N, 10.90.

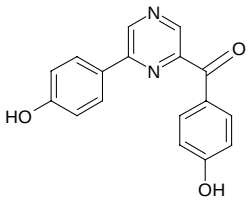
2-(1-oxo-[4-methoxyphenyl]methyl)-6-(4'-methoxyphenyl)pyrazine (8)



Coupling of 4-methoxyphenylboronic acid (470 mg, 2 equiv.) with **(6)** (385 mg, 1.54 mmol) according to the procedure B (*t*=8 h) gave after purification by column chromatography (silica gel, eluent: cyclohexane/ethyl acetate (6:4)) 446 mg (90%) of **(8)** as a yellow solid, mp : 114°C. ^{1}H NMR ($CDCl_3$) : δ 9.14 (s, 1H, H_3), 9.04 (s, 1H, H_5), 8.24 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 8.21 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 7.03 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$), 3,90 (m, 6H, 2xOCH_3). ^{13}C ($CDCl_3$) : δ 190.9 (C_7), 164.1 (C_{Ph4}), 161.6 ($C_{Ph'4}$), 150.3 (C_2), 149.6 (C_6), 143.0 (C_3 and C_5), 133.8 ($C_{Ph2,6}$), 128.8 ($C_{Ph'1}$), 128.6 ($C_{Ph'2,6}$), 128.2 (C_{Ph1}), 114.8 ($C_{Ph'3,5}$), 113.8 ($C_{Ph3,5}$), 55.7 (OCH_3). IR : 3075, 2997, 2938, 2913, 2835, 1649, 1604, 1516, 1342, 1274, 1249, 1164, 1036,

952, 842, 829, 774 cm^{-1}. Anal. calcd for $C_{19}H_{16}N_2O_3$ (320.35) : C, 71.24; H, 5.03; N, 8.74. Found: C, 70.91; H, 5.02; N, 8.72.

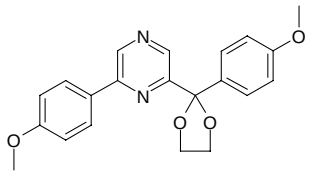
Botryllazine B (1)



Pyridine hydrochloride (10 g) was heated at 220°C for 15 min, and **(8)** (100 mg, 0.31 mmol) was added. The mixture was maintained at this temperature for 1h, then poured on to ice . The solution was extracted with ether (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane/ethyl acetate (5:5)) and gave 83 mg (91%) of **(1)** as a yellow solid, mp >250°C. ^{1}H NMR (CD_3OD) : δ 9.19 (s, 1H, H_5), 8.85 (s, 1H, H_3), 8.07 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 8.00 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 6.92 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$). ^{13}C (CD_3OD) : δ 192.7 (C_7), 165.0 (C_{Ph4}), 161.6 ($C_{Ph'4}$), 152.7 (C_6), 151.8 (C_2), 143.9 (C_5), 143.1 (C_3), 135.3 ($C_{Ph2,6}$), 130.2 ($C_{Ph'2,6}$), 128.9 (C_{Ph1}), 128.4 ($C_{Ph1'}$), 117.4 ($C_{Ph'3,5}$), 116.6 ($C_{Ph3,5}$). IR : 3165, 1644, 1603, 1563, 1515, 1421, 1340, 1275, 1250, 1152, 946, 833, 774 cm^{-1}. Anal. calcd for $C_{17}H_{12}N_2O_3$ (292.30) : C, 69.86; H, 4.14; N, 9.58. Found: C, 69.88; H, 3.89; N, 9.27.

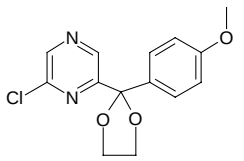
3. Metalation of ketal derivatives

2-(2-(4-methoxyphenyl)-1,3-dioxolan-2-yl)-6-(4'-methoxyphenyl)pyrazine (9)



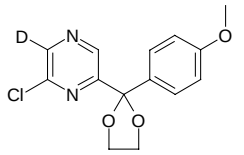
In a flask equipped with a dean stark apparatus, was placed a solution of **(8)** (843 mg, 2.63 mmol), glycol (10 equiv.) and APTS (0.1 equiv.) in toluene and heated under reflux for 12 h. After cooling, a saturated solution of sodium bicarbonate (30 mL) and dichloromethane (30 mL) was added. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : dichloromethane) and gave 939 mg (98%) of **(9)** as a colorless liquid. ^{1}H NMR ($CDCl_3$) : δ 8.87 (s, 1H, H_5), 8.77 (s, 1H, H_3), 7.95 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 7.62 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 6.98 (d, 2H, J=8.7 Hz, $H_{Ph'3,5}$), 6.89 (d, 2H, J=8.7 Hz, $H_{Ph3,5}$), 4.18 (m, 4H, 2xCH_2), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}C ($CDCl_3$) : δ 161.2 ($C_{Ph'4}$), 159.8 (C_{Ph4}), 154.8 (C_2), 151.3 (C_6), 140.4 (C_3), 139.0 (C_5), 132.9 (C_{Ph1}), 128.8 ($C_{Ph'1}$), 128.6 ($C_{Ph'2,6}$), 127.8 ($C_{Ph2,6}$), 114.4 ($C_{Ph'3,5}$), 113.6 ($C_{Ph3,5}$), 108.1 (C_7), 65.5 (CH_2), 55.5 (OCH_3). IR : 2958, 2894, 2836, 1609, 1513, 1422, 1251, 1172, 1032, 834 cm^{-1}. Anal. calcd for $C_{21}H_{20}N_2O_4$, $_{1/2}H_2O$ (364.40+1/2x18.02) : C, 67.55; H, 5.67; N, 7.50. Found: C, 67.65; H,5.84; N, 6.94.

2-chloro-6-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (12)



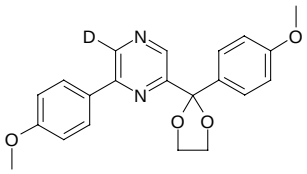
In a flask equipped with a Dean Stark apparatus, was placed a solution of **(6)** (740 mg, 2.98 mmol), glycol (10 equiv.) and APTS (0.1 equiv.) in toluene and heated to reflux for 8 h. After cooling, a solution of saturated of sodium bicarbonate (30 mL) and dichloromethane (30 mL) were added. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : dichloromethane) and gave 854 mg (98%) of **(12)** as a yellow liquid. ^{1}H NMR ($CDCl_3$) : δ 8.79 (s, 1H, H_5), 8.48 (s, 1H, H_3), 7.52 (d, 2H, J=8,7Hz, $H_{Ph2,6}$), 6.87 (d, 2H, J=8.7 Hz, $H_{Ph3,5}$), 4.11 (m, 4H, 2xCH_2), 3.78 (s, 3H, OCH_3). ^{13}C ($CDCl_3$) : δ 159.9 (C_{Ph4}), 155.9 (C_6), 148.8 (C_2), 144.0 (C_3), 139.7 (C_5), 131.9 (C_{Ph1}), 127.6 ($C_{Ph2,6}$), 113.8 ($C_{Ph3,5}$), 107.2 (C_7), 65.6 (CH_2), 55.4 (OCH_3). IR : 2958, 2895, 2837, 1610, 1511, 1390, 1304, 1250, 1175, 1099, 1032, 966, 947, 835 cm^{-1}. Anal. calcd for $C_{14}H_{13}ClN_2O_3$ (292.72) : C, 57.45; H, 4.48; N, 9.57. Found: C, 57.49; H, 4.46; N, 9.68.

3-chloro-2-deutero-5-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (13)



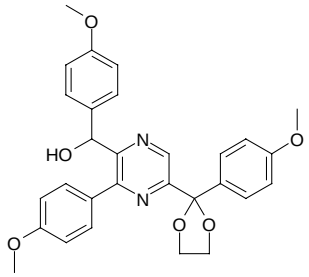
Metalation of **(12)** (710 mg, 2.43 mmol) according to procedure A with *n*-BuLi 1.6M (1.1 equiv., 1.70 mL), TMPH (1.2 equiv., 0.46 mL), t_1=30 min, θ_1=-78°C, followed by addition of ethyl alcohol-d (5 equiv., 0.46 mL) t_2=5 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : dichloromethane) 700 mg (98%) of **(13)** as a yellow liquid. ^{1}H NMR ($CDCl_3$) : δ 8.78 (s, 1H, H_6), 7.54 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 6.88 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 4.11 (m, 4H, 2xCH_2), 3.77 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) : δ 159.9 (C_{Ph4}), 155.9 (C_5), 148.7 (C_3), 143.9 (C_2), 139.6 (C_6), 131.8 (C_{Ph1}), 127.5 ($C_{Ph2,6}$), 113.7 ($C_{Ph3,5}$), 107.2 (C_7), 65.5 (CH_2), 55.3 (OCH_3). IR : 2957, 2895, 2836, 1610, 1511, 1313, 1250, 1172, 1135, 1099, 1033, 1015, 834, 810, 783, 458 cm^{-1}. Anal. calcd for $C_{14}H_{12}ClDN_2O_3$ (293.73) : C, 57.25; H, 4.12; N, 9.54. Found : C, 57.16; H, 4.31; N, 9.56.

2-deutero-3-(4'-methoxyphenyl)-5-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (14)



Coupling of 4-methoxyphenylboronic acid (680 mg, 1.1 equiv.) with **(13)** (1.20 g, 4.08 mmol) according to procedure B (*t*=8 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane) 1.34 g (90%) of **(14)** as a yellow liquid. ^{1}H NMR ($CDCl_3$) : δ 8.79 (s, 1H, H_6), 7.96 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 7.62 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 6.90 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$), 4.10 (m, 4H, 2xCH_2), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) : δ 160.9 ($C_{Ph'4}$), 159.5 (C_{Ph4}), 154.5 (C_5), 150.8 (C_3), 138.8 (C_6), 132.6 (C_2), 128.4 (C_{Ph1} and $C_{Ph1'}$), 128.2 ($C_{Ph2,6}$ and $C_{Ph'2,6}$), 114.1 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 107.8 (C_7), 65.2 (CH_2), 55.1 (OCH_3). IR : 2958, 2895, 2837, 1711, 1608, 1581, 1514, 1373, 1302, 1253, 1174, 1125, 1073, 834, 812 cm^{-1}. Anal. calcd for $C_{21}H_{19}DN_2O_4$ (365.41) : C, 69.03; H, 5.24; N, 7.67. Found: C, 68.98; H, 5.22; N, 7.63.

2-(1-hydroxy-[4''-methoxyphenyl]methyl)-3-(4'-methoxyphenyl)-5-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (10) and 2-(1-hydroxy-[4''-methoxyphenyl]methyl)-3-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)-5-(4'-methoxyphenyl)pyrazine (11)



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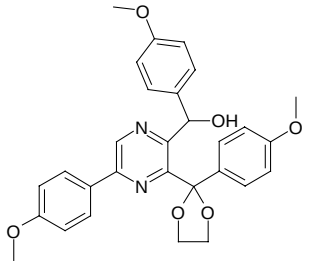

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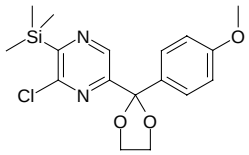
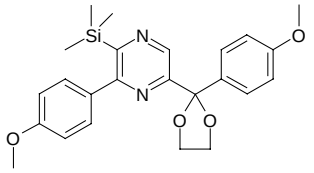
Metalation of **(9)** or **(14)** (200 mg, 0.55 mmol) according to procedure A with *n*-BuLi 1.6M (3.1 equiv., 1.06 mL), TMPH (3.1 equiv., 0.29 mL), t_1=30 min, θ_1=-78°C, followed by addition of *p*-anisaldehyde (3.1 equiv., 0.2 mL) in THF (10 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (6:4)) 192 mg (70%) of **(10)** and **(11)** as yellow liquids. **(10)** ^{1}H NMR ($CDCl_3$) : δ 8.75 (s, 1H, H_6), 7.50 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 7.20 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 6.90 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 6.78 (m, 6H, $H_{Ph3,5,}$ $H_{Ph3,5}$ and $H_{Ph'3,5}$), 5.84 (d, 1H, $J_{CH,OH}$=8.7 Hz, CH), 4.55 (d, 1H, $J_{CH,OH}$=8.7 Hz, OH), 4.10 (m, 4H, 2xCH_2), 3.77 (m, 9H, OCH_3).**(11)** ^{1}H NMR ($CDCl_3$) : δ 8.84 (s, 1H, H_6), 7.90 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 7.33 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 7.05 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 6.92 (m, 6H, $H_{Ph3,5}$ $H_{Ph'3,5}$ and $H_{Ph'3,5}$), 6.25 (d, 1H, $J_{CH,OH}$=8.7 Hz, CH), 4.35 (d, 1H, $J_{CH,OH}$=8.7 Hz, OH), 4.10 (m, 4H, 2xCH_2), 3.77 (m, 9H, OCH_3). **(10 and 11)** ^{13}C NMR ($CDCl_3$) : δ 160.6-159.9 (C_{Ph4}, $C_{Ph'4,}$ $C_{Ph'4}$), 154.3-152.3 (Cpyr), 138.6 ($C_{6(10)}$ and $C_{6(11)}$), 136.2-129.1 ($C_{Ph1,}$ $C_{Ph'1}$ and $C_{Ph''1}$), 129.9-128.1 ($C_{Ph2,6}$,$C_{Ph'2,6}$ and $C_{Ph''2,6}$), 114.1 ($C_{Ph3,5}$, $C_{Ph3,5}$ and $C_{Ph'3,5}$), 108.1 ($C_{7(10)}$ and $C_{7(11)}$), 77.2 (CH), 65.7 (CH_2), 55.7 (OCH_3). IR : 3449, 3002, 2957, 2934, 2897, 2836, 1609, 1512, 1463, 1379, 1308, 1251, 1174, 1096, 1033, 883 ,755 cm^{-1}. HRMS (IC) calculated for $C_{29}H_{29}N_2O_6$: 501.2025. Found : 501.2061.

3-chloro-2-trimethylsilyl-5-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (15)



Metalation of **(12)** (620 mg, 2.12 mmol) according to procedure A with *n*-BuLi 2.5M (1.1 equiv., 0.93 mL), TMPH (1.1 equiv., 0.42 mL), t_1=30 min, θ_1=-78°C, followed by addition of trimethylsilyl chloride (1.1 equiv., 0.30 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : dichloromethane) 603 mg (78%) of **(15)** as colorless liquid. ^{1}H NMR ($CDCl_3$) : δ 8.91 (s, 1H, H_6), 7.55 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 6.88 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 4.11 (m, 4H, 2xCH_2), 3.78 (s, 3H, OCH_3), 0.39 (s, 9H, 3xCH_3). ^{13}C NMR ($CDCl_3$) : δ 161.8 (C_{Ph4}), 159.9 (C_2), 154.5 (C_3 and C_5), 140.0 (C_6), 132.2 (C_{Ph1}), 127.6 ($C_{Ph2,6}$), 113.7 ($C_{Ph3,5}$), 107.2 (C_7), 65.5 (CH_2), 55.3 (OCH_3), -1.6 ($SiMe_3$). IR : 2956, 2898, 1611, 1510, 1250, 1172, 1098, 1053, 1034, 845, 790, 587 cm^{-1} . Anal. calcd for $C_{17}H_{21}ClN_2O_3Si$ (364.91) : C, 55.96; H, 5.80; N, 7.68. Found : C, 56.24; H, 6.12; N, 7.45.

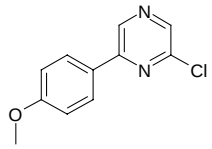
2-trimethylsilyl-3-(4'-methoxyphenyl)-5-(2-[4-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (16)



Coupling of 4-methoxyphenylboronic acid (160 mg, 1.1 equiv.) with **(15)** (360 mg, 0.98 mmol) according to procedure B (*t*=12 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane) 263 mg (61%) of **(16)** as a yellow solid, mp : 116°C. ^{1}H NMR ($CDCl_3$) : δ 8.96 (s, 1H, H_6), 7.60 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 7.40 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 6.94 (d, J=8.7 Hz, 2H, $H_{Ph'3,5}$), 6.88 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 4.13 (m, 4H, 2xCH_2), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 0.10 (s, 9H, 3xCH_3). ^{13}C NMR ($CDCl_3$) : δ 160.3-158.9 ($C_{Ph'4}$, C_{Ph4}, C_2 and C_3), 152.4 (C_5), 139.7 (C_6), 133.2 (C_{Ph1} and $C_{Ph'1}$), 130.8 ($C_{Ph'2,6}$), 127.7 ($C_{Ph2,6}$), 113.5 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 107.9 (C_7), 65.4 (CH_2), 55.4 (OCH_3), -0.2 ($SiMe_3$). IR : 2957, 2884, 2840, 1608, 1507, 1464, 1364, 1300, 1252, 1170, 1077, 1031, 836 cm^{-1}. Anal. calcd for $C_{24}H_{28}N_2O_4Si$ (436.59) : C, 66.03; H, 6.46; N, 6.42. Found: C, 65.83; H, 6.52; N, 6.37.

4. Nucleophilic substitution

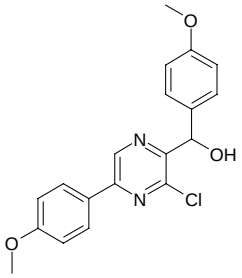
2-chloro-6-(4-methoxyphenyl)pyrazine (18)



Coupling of 4-methoxyphenylboronic acid (917 mg, 0.9 equiv.) with 2,6-dichloropyrazine (1 g, 6.71 mmol) according to procedure B (*t*=8 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/cyclohexane (7:3)) 1.03 g (70%) of **(18)** as a white solid, mp : 86°C. ^{1}H NMR ($CDCl_3$) : δ 8.82 (s,1H, H_5), 8.40 (s, 1H, H_3), 7.94 (d,

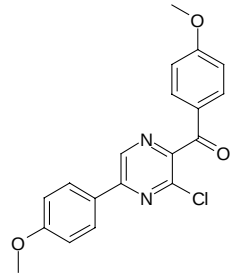
2H, J=8.7 Hz, $H_{Ph2,6}$), 6.97 (d, 2H, J=8.7 Hz, $H_{Ph3,5}$), 3.84 (s, 3H, OCH_3). ^{13}C ($CDCl_3$) : δ 161.7 (C_{Ph4}), 152.3 (C_6), 148.8 (C_2), 141.4 (C_3), 138.7 (C_5), 128.6 ($C_{Ph2,6}$), 127.2 (C_{Ph1}), 114.6 ($C_{Ph3,5}$), 55.5 (OCH_3). IR : 3058, 2971, 2928, 2835, 1605, 1519, 1326, 1260, 1163, 1150, 1027, 929 cm^{-1}. Anal. calcd for $C_{11}H_9ClN_2O$ (220.66) : C, 59.88; H, 4.11; N, 12.70. Found: C, 59.58; H, 4.27; N, 12.64

3-chloro-2-(1-hydroxy-4-methoxyphenylmethyl)-5-(4'-methoxyphenyl)pyrazine (19)



Metalation of **(18)** (530 mg, 2.40 mmol) according to procedure A with *n*-BuLi 2.5M (1.1 equiv., 1.06 mL), TMPH (1.1 equiv., 0.46 mL), t_1=30 min, θ_1=-78°C, followed by addition of *p*-anisaldehyde (1.2 equiv., 0.35 mL) in THF (10 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (7:3)) 728 mg (85%) of **(19)** as a yellow solid, mp : 100°C. ^1H NMR ($CDCl_3$) : δ 8.87 (s, 1H, H_6), 7.98 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 7.29 (d, J=8,7Hz, 2H, $H_{Ph2,6}$), 7.01 (d, J=8.7 Hz, 2H, $H_{Ph'3,5}$), 6.85 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 5.99 (d, $J_{CH,OH}$=7.5 Hz, 1H, CH), 4.60 (d, $J_{CH,OH}$=7.5 Hz, 1H, OH), 3.87 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) : δ 161.8 ($C_{Ph'4}$), 159.6 (C_{Ph4}), 151.7 (C_5), 151.3 (C_2), 146.6 (C_3), 137.3 (C_6), 133.2 (C_{Ph1}), 128.6 ($C_{Ph2,6}$ and $C_{Ph'2,6}$), 127.0 ($C_{Ph1'}$), 114.7 ($C_{Ph'3,5}$), 114.1 ($C_{Ph3,5}$), 71.7 (CH), 55.5 (OCH_3); IR : 3360 , 2932, 2837, 1608, 1579, 1520, 1437, 1418, 1303, 1280, 1256, 1174, 1158, 1042, 1027, 837, 801, 773, 552 cm^{-1} . Anal. calcd for $C_{19}H_{17}ClN_2O_3$ (356.81) : C, 63.96; H, 4.80; N, 7.85. Found : C, 63.82; H, 4.88; N, 7.83.

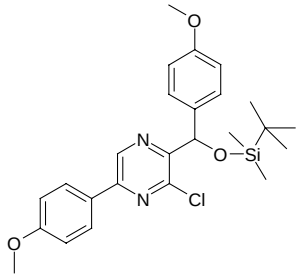
3-chloro-2-(1-oxo-4-methoxyphenylmethyl)-5-(4'-methoxyphenyl)pyrazine (20)



To a solution of **(19)** (450 mg, 1.26 mmol) in 50 mL of THF was added MnO_2 (10 equiv., 1.09 g). The solution was stirred at room temperature for 8 h. The mixture was filtered through celite, and the filtrate was evaporated. After purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (7:3)) 407 mg (91%) of **(20)** was obtained as a white solid, mp : 202°C. ^1H NMR (DMSO) : δ 9.32 (s, 1H, H_6), 8.20 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 7.89 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 7.14 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.10 (d, J=8.7 Hz, 2H, $H_{Ph'3,5}$), 3.87 (s, 6H, 2xOCH_3). ^{13}C NMR (DMSO) : δ 190.1 (C_7), 164.8 (C_{Ph4}), 162.1 ($C_{Ph'4}$), 152.6 (C_5), 147.3 (C_3), 144.5 (C_2), 139.1 (C_6), 133.1 ($C_{Ph2,6}$), 129.4 ($C_{Ph'2,6}$), 127.8 (C_{Ph1}), 126.5 ($C_{Ph'1}$), 115.1 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 56.1 (OCH_3). IR : 3015, 2974, 2935, 2840, 1667,

1605, 1519, 1311, 1299, 1256, 1173, 1164, 1081, 1014, 936, 832, 795 cm^{-1} . Anal. calcd for $C_{19}H_{15}ClN_2O_3$ (354.80) : C, 64.32; H, 4.26; N, 7.90. Found : C, 64.07; H, 4.34; N, 7.80.

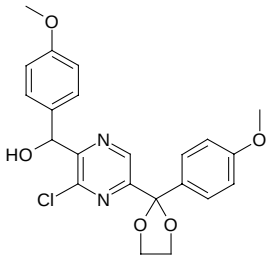
3-chloro-2-(1-hydroxy-*t*-butyldimethylsilyl-4-methoxyphenylmethyl)-5-(4'-methoxyphenylmethyl)pyrazine (21)



Imidazole (1.6 equiv., 280 mg) and *tert*-butyldimethylsilyl chloride (1.2 equiv., 460 mg) were added to a solution of **(19)** (900 mg, 2.52 mmol) in 50 mL of CH_2Cl_2. The solution was stirred at room temperature for 8 h, and then washed with 30mL of water. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : dichloromethane) and gave 880 mg (74%) of **(21)** as a yellow liquid. ^{1}H NMR ($CDCl_3$) : δ 8.88 (s, 1H, H_6), 7.96 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 7.46 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 7.00 (d, J=8.7 Hz, 2H, $H_{Ph'3,5}$), 6.86 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 6.32 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 0.92 (s, 9H, 3xCH_3), 0.08 (s, 3H, CH_3), 0.02 (s, 3H, CH_3). ^{13}C ($CDCl_3$) : δ 161.6 ($C_{Ph'4}$), 159.1 (C_{Ph4}), 152.7 (C_5), 150.8 (C_2), 146.2 (C_3), 138.9 (C_6), 133.9 (C_{Ph1}), 127.6 ($C_{Ph2,6}$ and $C_{Ph'2,6}$), 127.2 ($C_{Ph1'}$), 114.6 ($C_{Ph'3,5}$), 113.8 ($C_{Ph3,5}$), 73.3 (CH), 55.5 (OCH_3), 26.0 (CH_3), 18.5 (C), -4.6 (CH_3). IR : 2955, 2930, 2856, 1608, 1511, 1439, 1374, 1251, 1176, 1158, 864, 836, 778 cm^{-1}. Anal. calcd for $C_{25}H_{31}ClN_2O_3Si$ (471.08) : C, 63.74; H, 6.63; N, 5.95. Found: C, 63.63; H, 6.28; N, 5.84.

5. Synthesis of an analogue of Botryllazine A

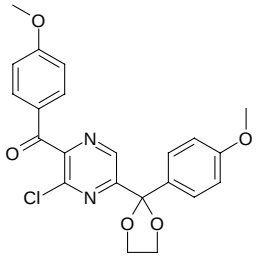
3-chloro-2-(1-hydroxy-4-methoxyphenylmethyl)-5-(2-[4'-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (24)



Metalation of **(12)** (820 mg, 2.80 mmol) according to procedure A with *n*-BuLi 1.6M (1.1 equiv., 1.95 mL), TMPH (1.1equiv., 0.54 mL), t_1=30 min, θ_1=-78°C, followed by addition of *p*-anisaldehyde (1.1 equiv., 0.39 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (5:5)) 985 mg (82%) of **(24)** as yellow solid, mp : 106°C. ^{1}H NMR ($CDCl_3$) : δ 8.72 (s, 1H, H_6), 7.46 (d, J=8.7 Hz, 2H,

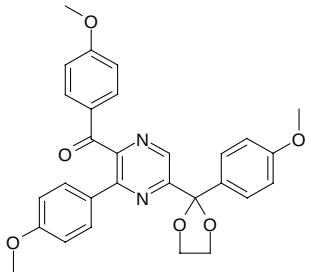
$H_{Ph'2,6}$), 7.17 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 6.77 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$), 5.87 (d, $J_{CH,OH}$=7.5 Hz , 1H, CH), 4.47 (d, $J_{CH,OH}$=7.5 Hz, 1H, OH), 4.04 (m, 4H, CH_2), 3.70 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) : δ 160.3 ($C_{Ph'4}$), 159.9 (C_{Ph4}), 155.3 (C_5), 154.1 (C_2), 146.9 (C_3), 138.6 (C_6), 132.9 (C_{Ph1}), 132.2 ($C_{Ph'1}$), 129.2 ($C_{Ph2,6}$), 127.9 ($C_{Ph'2,6}$), 114.2 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 107.5 (C_7), 72.0 (CH), 65.9 (CH_2), 55.6 (OCH_3); IR : 3994, 2995, 2933, 2896, 2835, 1611, 1510, 1250, 1154, 1092, 1031, 995, 826, 593 cm^{-1} . Anal. calcd for $C_{22}H_{21}ClN_2O_5$ (428.88) : C, 61.61; H, 4.94; N, 6.53. Found : C, 61.55; H, 4.95; N, 6.46.

3-chloro-2-(1-oxo-4-methoxyphenylmethyl)-5-(2-[4'-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (25)



To a solution of **(24)** (1.50 g, 3.50 mmol) in 50 mL of THF was added MnO_2 (10 equiv., 3.00 g). The solution was stirred at room temperature for 8 h. The mixture was filtered through celite, and the filtrate was evaporated. The crude product gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (5:5)) 1.36 g (91%) of **(25)** as a yellow solid, mp : 124°C. ^1H NMR ($CDCl_3$) : δ 8.86 (s, 1H, H_6), 7.78 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 7.58 (d, J=8.7 Hz, 2H, $H_{Ph'2,6}$), 6.94 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$), 4.17 (m, 4H, CH_2), 3.87 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) : δ 189.8 (C_7), 164.8 (C_{Ph4}), 160.1 ($C_{Ph'4}$), 156.6 (C_5), 150.3 (C_2), 145.7 (C_3), 138.6 (C_6), 132.9 ($C_{Ph2,6}$), 131.7 (C_{Ph1}), 127.8 ($C_{Ph'1}$), 127.6 ($C_{Ph'2,6}$), 114.0 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 107.3 (C_8), 65.7 (CH_2), 55.6 (OCH_3). IR : 3003, 2963, 2936, 2838, 1666, 1575, 1320, 1256, 1177, 1103, 999, 937, 916, 832, 642, 549 cm^{-1} . Anal. calcd for $C_{22}H_{19}ClN_2O_5$ (426.86) : C, 61.90; H, 4.49; N, 6.56. Found : C, 61.68; H, 4.57; N, 6.46.

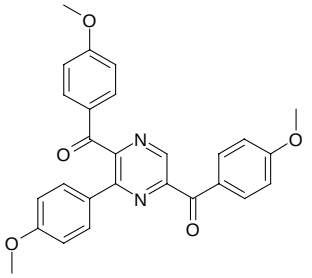
2-(1-oxo-4-methoxyphenylmethyl)-3-(4'-methoxyphenyl)-5-(2-[4''-methoxyphenyl]-1,3-dioxolan-2-yl)pyrazine (26)



Coupling of 4-methoxyphenylboronic acid (930 mg, 2 equiv.) with **(25)** (1.30 g, 3.04 mmol) according to procedure B (*t*=8 h) gave after purification by column chromatography (silica gel, eluent: cyclohexane/ethyl acetate (7:3)) 1.32 g (87%) of **(26)** as a white solid, mp : 68°C. ^1H NMR ($CDCl_3$) : δ 8.83 (s, 1H, H_6), 7.83 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 7.64 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 7.54 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 6.83 (m, 4H, $H_{Ph3,5}$ and $H_{Ph''3,5}$), 6.81 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 4.21 (m, 4H, CH_2), 3.90-3.70 (m, 9H, OCH_3). ^{13}C ($CDCl_3$) : δ 193.2 (C_7), 164.3

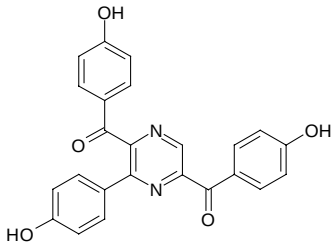
(C_{Ph4}), 160.9 ($C_{Ph'4}$), 159.9 ($C_{Ph''4}$), 155.3 (C_5), 151.5 (C_3), 149.5 (C_2), 137.5 (C_6), 132.9 ($C_{Ph2,6}$), 132.5 (C_{Ph1}), 130.8 ($C_{Ph'2,6}$), 129.0 ($C_{Ph'1}$ and $C_{Ph''1}$), 127.8 ($C_{Ph''2,6}$), 114.1 ($C_{Ph3,5}$, $C_{Ph'3,5}$ and $C_{Ph''3,5}$), 107.9 (C_8), 65.6 (CH_2), 55.5 (OCH_3). IR : 2958, 2985, 2838, 1664, 1598, 1510, 1376, 1306, 1256, 1175, 1150, 1094, 1029, 929, 839 cm^{-1}. Anal. calcd for $C_{29}H_{26}N_2O_6$ (498.54) : C, 69.87; H, 5.26; N, 5.62. Found: C, 69.85; H, 5.22; N, 5.61.

2,5-di-(1-oxo-4-methoxyphenylmethyl)-3-(4'-methoxyphenyl)pyrazine (27)



A solution of hydrochloric acid 6N (6 equiv., 2.8 mL) was added to a solution of **(26)** (1.30 g, 2.61 mmol) in 50 mL of methanol. The solution was stirred at reflux for 2 h. After cooling, a mixture of a saturated sodium hydrogenocarbonate solution (30 mL) and dichloromethane (30 mL) was added. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (6:4)) 1.04 g (88%) of **(27)** as a white solid, mp : 162°C. ^{1}H NMR ($CDCl_3$) : δ 9.09 (s, 1H, H_6), 8.24 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 7.90 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 7.64 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 6.97 (m, 6H, $H_{Ph3,5,}$ $H_{Ph3,5}$ and $H_{Ph''3,5}$), 3.92-3.79 (m, 9H, OCH_3). ^{13}C ($CDCl_3$) : δ 192.8 (C_7), 190.3 (C_8), 164.6 (C_{Ph4} and $C_{Ph''4}$), 161.3 ($C_{Ph'4}$), 151.8 (C_5), 150.6 (C_3), 149.8 (C_2), 141.4 (C_6), 133.8 ($C_{Ph2,6}$ and $C_{Ph''2,6}$), 130.8 ($C_{Ph'2,6}$), 128.5 (C_{Ph1}, $C_{Ph'1}$and $C_{Ph''1}$), 114.3 ($C_{Ph3,5}$, $C_{Ph'3,5}$ and$C_{Ph''3,5}$), 55.7 (OCH_3). IR : 2961, 2933, 2837, 1661, 1598, 1510, 1373, 1333, 1310, 1253, 1208, 1173, 1151, 1029, 921, 837, 760 cm^{-1} . Anal. calcd for $C_{27}H_{22}N_2O_5$ (454.49) : C, 71.36; H, 4.88; N, 6.16. Found : C, 71.11; H, 4.89; N, 6.14.

Analogue of Botryllazine A : 2,5-di-(1-oxo-4-hydroxyphenylmethyl)-3-(4'-methoxyphenyl)pyrazine (28)

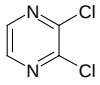


Pyridine hydrochloride (10 g) was heated to 220°C for 15 min, **(27)** (200 mg, 0.44 mmol) was added, and the mixture was kept at this temperature for 1 h then poured into ice. The solution was extracted with ether (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent: ether) and gave 163 mg (90%)of **(28)** as a yellow solid, mp : 200°C. ^{1}H NMR (CD_3OD) : δ 8.96 (s, 1H, H_6), 8.12 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 7.75 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 7.52 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 6.86 (m, 6H, $H_{Ph3,5,}$ $H_{Ph3,5}$ and $H_{Ph'3,5}$). ^{13}C (CD_3OD) : δ 194.5 (C_7), 191.7 (C_8), 165.1 (C_{Ph4} and $C_{Ph4''}$), 160.7 ($C_{Ph'4}$), 152.8 (C_3), 151.8 (C_2 and C_5), 141.9 (C_6), 134.5 ($C_{Ph2,6}$ and $C_{Ph''2,6}$), 131.8 ($C_{Ph'2,6}$), 128.4 ($C_{Ph1,}$ $C_{Ph'1}$ and

$C_{Ph''1}$), 116.5 ($C_{Ph3,5}$, $C_{Ph''3,5}$ and $C_{Ph'3,5}$). IR : 3392, 2812, 2703, 1662, 1647, 1582, 1513, 1375, 1251, 1209, 1157, 971, 845 cm^{-1}. Anal. calcd for $C_{24}H_{16}N_2O_5$ (412.41) : C, 69.90; H, 3.91; N, 6.79. Found: C, 69.98; H, 3.83; N, 6.73.

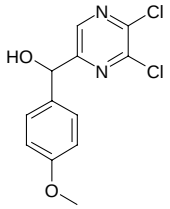
6. Synthesis of Botryllazine A

2,3-Dichloropyrazine (29)



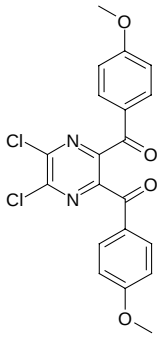
Metalation of chloropyrazine (1 g, 8.73 mmol) according to procedure A with *n*-BuLi 2.5M (1.1 equiv., 3.84 mL), TMPH (1.2 equiv., 1.65 mL), t_1=30 min, θ_1=-78°C, followed by reaction with hexachloroethane (1.2 equiv., 2.8 g) in THF (10 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : dichloromethane) 1.17 g (90%) of **(29)** as a colorless liquid. ^{1}H NMR ($CDCl_3$) : δ 8.28 (s, 2H, H_5 and H_6); ^{13}C NMR ($CDCl_3$) : δ 147.9 (C_{Cl}); 141.8 (CH); IR : 1359, 1194, 1153, 1051, 865, 801, 485 cm^{-1} . Anal. calcd for $C_4H_2Cl_2N_2$ (148.98) : C, 32.25; H, 1.35; N, 18.80. Found : C, 32.26; H, 1.32; N, 18.84.

2,3-Dichloro-5-(1-hydroxy-4-methoxyphenylmethyl)pyrazine (30)



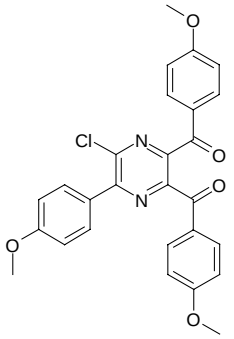
Metalation of **(29)** (1 g, 6.71 mmol) according to procedure A with *n*-BuLi 2.5M (1.2 equiv., 5.03 mL), TMPH (1.2 equiv., 1.38 mL), t_1=30 min, θ_1=-78°C, followed by addition of *p*-anisaldehyde (1.2 equiv., 1 mL) t_2=60 min, θ_2=-78°C gave after purification by column chromatography (silica gel, eluent : cyclohexane/ethyl acetate (7:3)) 1.55 g (81%) of **(30)** as a white solid, mp : 118°C. ^{1}H NMR ($CDCl_3$) : δ 8.26 (s, 1H, H_6), 7.18 (d, J=8.7Hz, 2H, $H_{Ph2,6}$), 6.78 (d, J=8.7Hz, 2H, $H_{Ph3,5}$), 5.70 (d, $J_{CH,OH}$=3.4 Hz, 1H, CH), 3.70 (s, 3H, OCH_3), 3.59 (d, $J_{CH,OH}$=3.4 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 159.8 (C_{Ph4}), 156.1 (C_5), 146.3 (C_2 and C_3), 139.7 (C_6), 133.0 (C_{Ph1}), 128.2 ($C_{Ph2,6}$), 114.4 ($C_{Ph3,5}$), 73.7 (CH), 55.4 (OCH_3); IR : 3309, 2968, 2879, 1609, 1511, 1461, 1388, 1155, 1025, 849, 786, 546 cm^{-1} . Anal. calcd for $C_{12}H_{10}Cl_2N_2O_2$ (285.13) : C, 50.55; H, 3.54; N, 9.82. Found : C, 50.52; H, 3.62; N, 9.79.

2,3-Dichloro-5,6-di-(1-oxo-4-methoxyphenylmethyl)pyrazine (32)



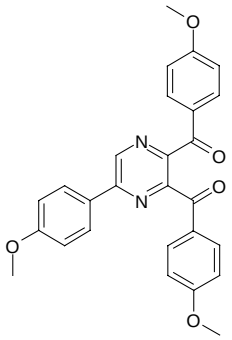
Metalation of **(30)** (1.7 g, 5.96 mmol) according to procedure A with *n*-BuLi 1.6M (4.1 equiv., 15.30 mL), TMPH (4.1 equiv., 4.20 mL), t_1=30 min, θ_1=-78°C, followed by addition of *p*-anisaldehyde (1.2 equiv., 1 mL) t_2=60 min, θ_2=-78°C. the crude product was treated with a solution of saturated sodium hydrogenosulfite. The mixture was filtrated and the precipitate was washed with ether. The aqueous layer was extracted with ether (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product and 2 g of manganese oxide were added to 50 mL of THF. The solution was stirred at room temperature for 12 h. The mixture was filtered through celite and the filtrate was then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : cyclohexane /ethyl acetate (7:3)) and gave 1.76 g (71%) of **(32)** as a yellow solid, mp : 174°C. ^{1}H NMR ($CDCl_3$) : δ 7.96 (d, J=8.7Hz, 4H, 2x$H_{Ph2,6}$), 6.97 (d, J=8.7Hz, 4H, 2x$H_{Ph3,5}$), 3.87 (s, 6H, 2xOCH_3). ^{13}C ($CDCl_3$) : δ 188.3 (C_7), 164.7 (C_{Ph4}), 150.5 (C_5), 146.4 (C_2), 133.2 ($C_{Ph2,6}$), 127.7 (C_{Ph1}), 117.4 ($C_{Ph3,5}$), 55.7 (OCH_3). IR : 2985, 2941, 2841, 1656, 1592, 1508, 1315, 1253, 1174, 1129, 1024, 991, 937, 845, 811, 791, 769, 616, 552 cm^{-1}. Anal. calcd for $C_{20}H_{14}Cl_2N_2O_4$ (417.25) : C, 57.57; H, 3.38; N, 6.71. Found: C, 57.93; H, 3.48; N, 6.67.

2-chloro-3-(4''-methoxyphenyl)-5,6-di-(1-oxo-4-methoxyphenylmethyl)pyrazine (33)



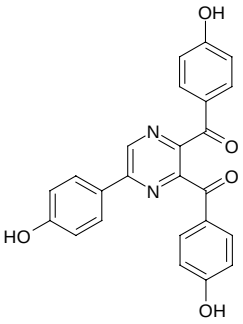
Coupling of 4-methoxyphenylboronic acid (430 mg, 0.9 equiv.) with **(32)** (1.30 g, 3.11 mmol) according to procedure B (*t*=8 h) gave after purification by column chromatography (silica gel, eluent: cyclohexane/ethyl acetate (7:3)) 1.07 g (70%) of **(33)** as a yellow solid, mp : 176°C. ^{1}H NMR ($CDCl_3$) : δ 8.21 (m, 6H, 3x$H_{Ph2,6}$), 7.14 (m, 6H, 3x$H_{Ph3,5}$), 4.05 (m, 9H, 3xOCH_3). ^{13}C ($CDCl_3$) : δ 190.1 (C_7 and C_8), 164.4 (C_{Ph4} and $C_{Ph'4}$), 161.6 ($C_{Ph''4}$), 151.3 (C_5 and C_6), 149.0 (C_3), 144.8 (C_2), 133.4 ($C_{Ph2,6}$ and $C_{Ph'2,6}$), 131.8 ($C_{Ph''2,6}$), 128.2 (C_{Ph1} and $C_{Ph'1}$), 127.3 ($C_{Ph''1}$), 114.0 ($C_{Ph3,5}$, $C_{Ph'3,5}$ and $C_{Ph''3,5}$), 55.7 (OCH_3). IR : 3010, 2937, 2839, 1667, 1650, 1509, 1308, 1294, 1255, 1160, 1025, 975, 848, 828, 617 cm^{-1}. Anal. calcd for $C_{27}H_{21}ClN_2O_5$ (488.93) : C, 66.33; H, 4.33; N, 5.73. Found: C, 66.57; H, 4.29; N, 5.65.

2,3-di-(1-oxo-4-methoxyphenylmethyl)-5-(4''-methoxyphenyl)pyrazine (34)



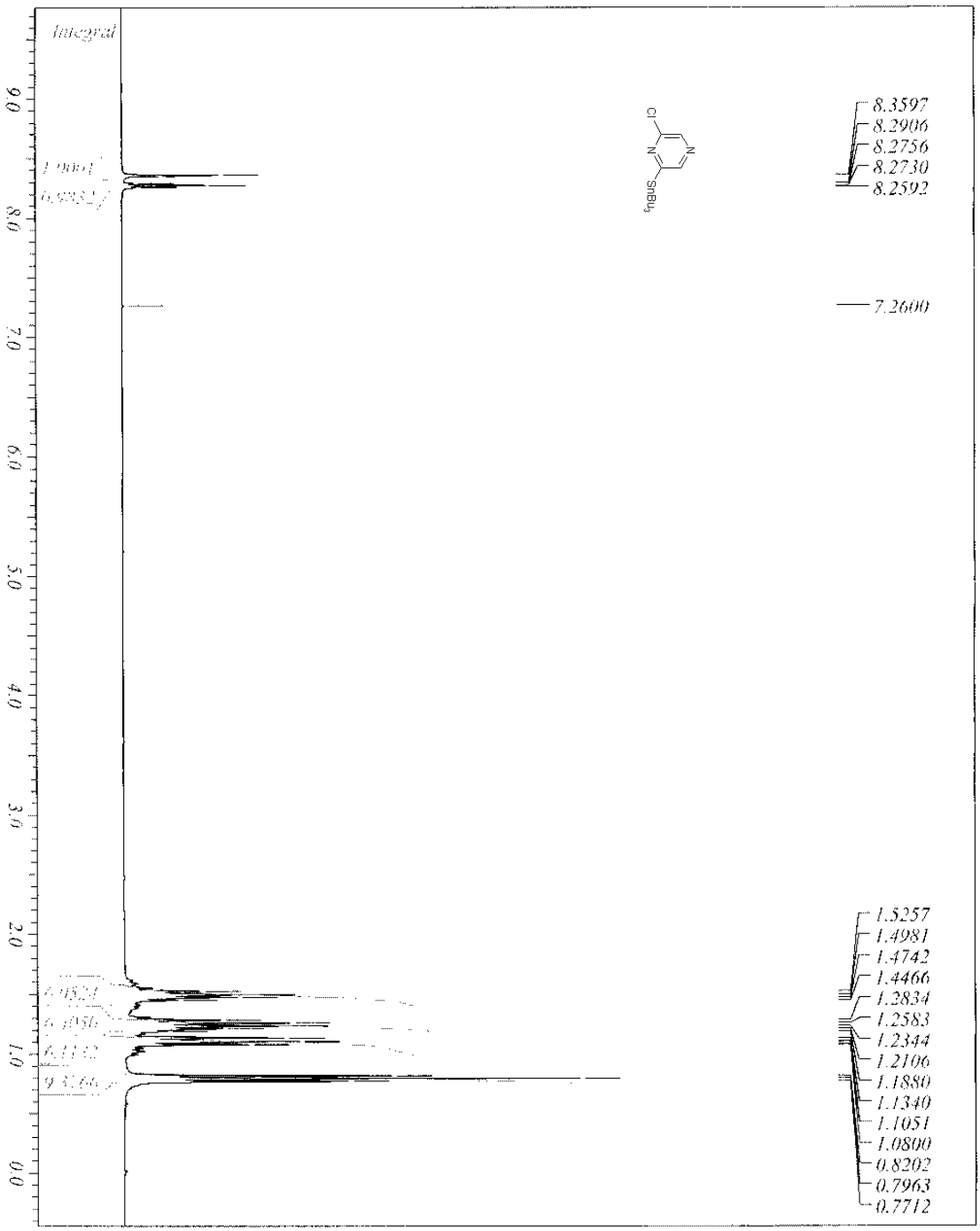
In a flask, was placed a solution of **(33)** (700 mg, 1.43 mmol), triethylamine (10 equiv, 2 mL), formic acid (5 equiv, 0.28 mL) and Pd/C (10%) (0.1 equiv) in acetone and heated at reflux for 3 h. After cooling, a saturated sodium hydrogenocarbonate solution (30 mL) and dichloromethane (30 mL) were added. The aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent : dichloromethane) and gave 488 mg (75%) of **(34)** as a yellow solid, mp : 85°C. ^{1}H NMR ($CDCl_3$) : δ 9.09 (s, 1H, H_6), 8.04 (m, 6H, $H_{Ph2,6}$, $H_{Ph'2,6}$ and $H_{Ph''2,6}$), 7.01 (m, 6H, $H_{Ph3,5}$, $H_{Ph'3,5}$ and $H_{Ph'3,5}$), 3.88 (s, 9H, 3xOCH_3). ^{13}C ($CDCl_3$) : δ 191.3-190.9 (C_7 and C_8), 164.2 (C_{Ph4} and $C_{Ph'4}$), 162.1 ($C_{Ph4''}$), 153.3 (C_5), 150.9 (C_3), 149.3 (C_2), 139.1 (C_6), 133.2 ($C_{Ph2,6}$ and $C_{Ph'2,6}$), 129.1 ($C_{Ph''2,6}$), 128.6 (C_{Ph1} and $C_{Ph'1}$), 127.5 ($C_{Ph1''}$), 114.8 ($C_{Ph''3,5}$), 113.9 ($C_{Ph3,5}$ and $C_{Ph'3,5}$), 55.7 (OCH_3). IR : 2934, 2838, 1654, 1598, 1510, 1307, 1256, 1172, 1119, 1026, 958, 932, 841 cm^{-1}. Anal. calcd for $C_{27}H_{22}N_2O_5$ (454.49) : C, 71.36; H, 4.88; N, 6.16. Found: C, 71.14; H, 4.98; N, 6.11.

Botryllazine A (2)



Pyridine hydrochloride (10 g) was heated to 220°C for 15 min, **(34)** (200 mg, 0.44 mmol) was added, and the mixture was kept at this temperature for 1h and then poured on to ice . The solution was extracted with ether (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent: ether) and gave 163 mg (90%) of **(2)** as a yellow solid, mp : 144°C. ^{1}H NMR (CD_3OD) : δ 9.20 (s, 1H, H_6), 8.07 (d, 2H, J=8.7 Hz, $H_{Ph''2,6}$), 7.87 (d, 2H, J=8.7 Hz, $H_{Ph'2,6}$), 7.85 (d, 2H, J=8.7 Hz, $H_{Ph2,6}$), 6.94 (d, 2H, J=8.7 Hz, $H_{Ph''3,5}$), 6.85 (m, 4H, $H_{Ph3,5}$ and $H_{Ph'3,5}$). ^{13}C (CD_3OD) : δ 193.2 (C_7), 192.7 (C_8), 164.5 (C_{Ph4}), 164.3 ($C_{Ph'4}$), 161.7 ($C_{Ph''4}$), 153.7 (C_3), 152.8 (C_5), 149.7 (C_2), 140.5 (C_6), 134.5 ($C_{Ph'2,6}$), 134.4 ($C_{Ph2,6}$), 130.2 ($C_{Ph''2,6}$), 128.6 ($C_{Ph'1}$), 128.5 (C_{Ph1}), 127.4 ($C_{Ph''1}$), 117.1 ($C_{Ph''3,5}$), 116.2 ($C_{Ph3,5}$ and $C_{Ph'3,5}$). IR : 3274, 2926, 1648, 1590, 1259, 1165, 959, 846 cm^{-1}. Anal. calcd for $C_{24}H_{16}N_2O_5$ (412.41) : C, 69.90; H, 3.91; N, 6.79. Found: C, 69.84; H, 4.08; N, 6.71.

7. Spectra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1.2344
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N
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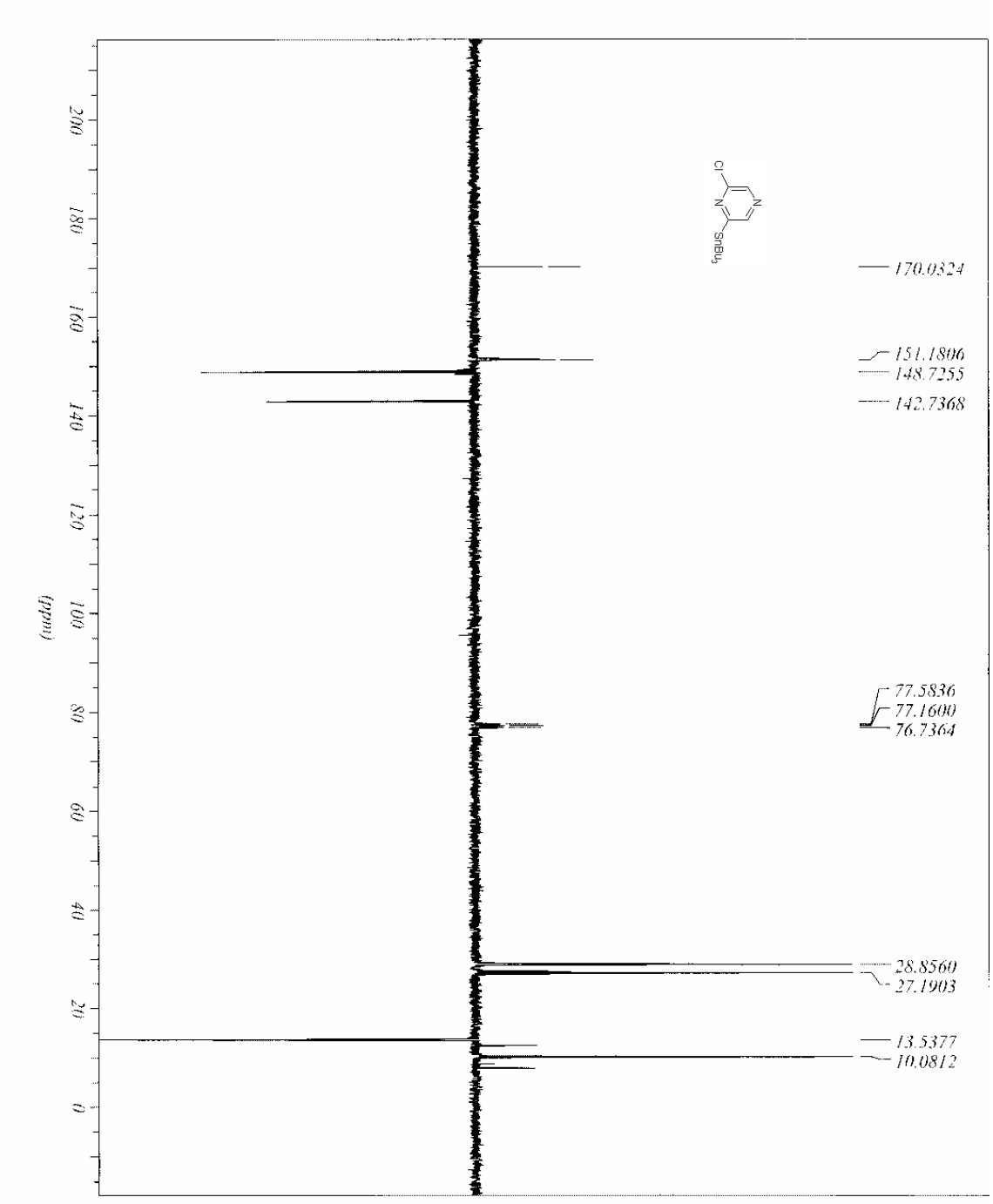
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Cl
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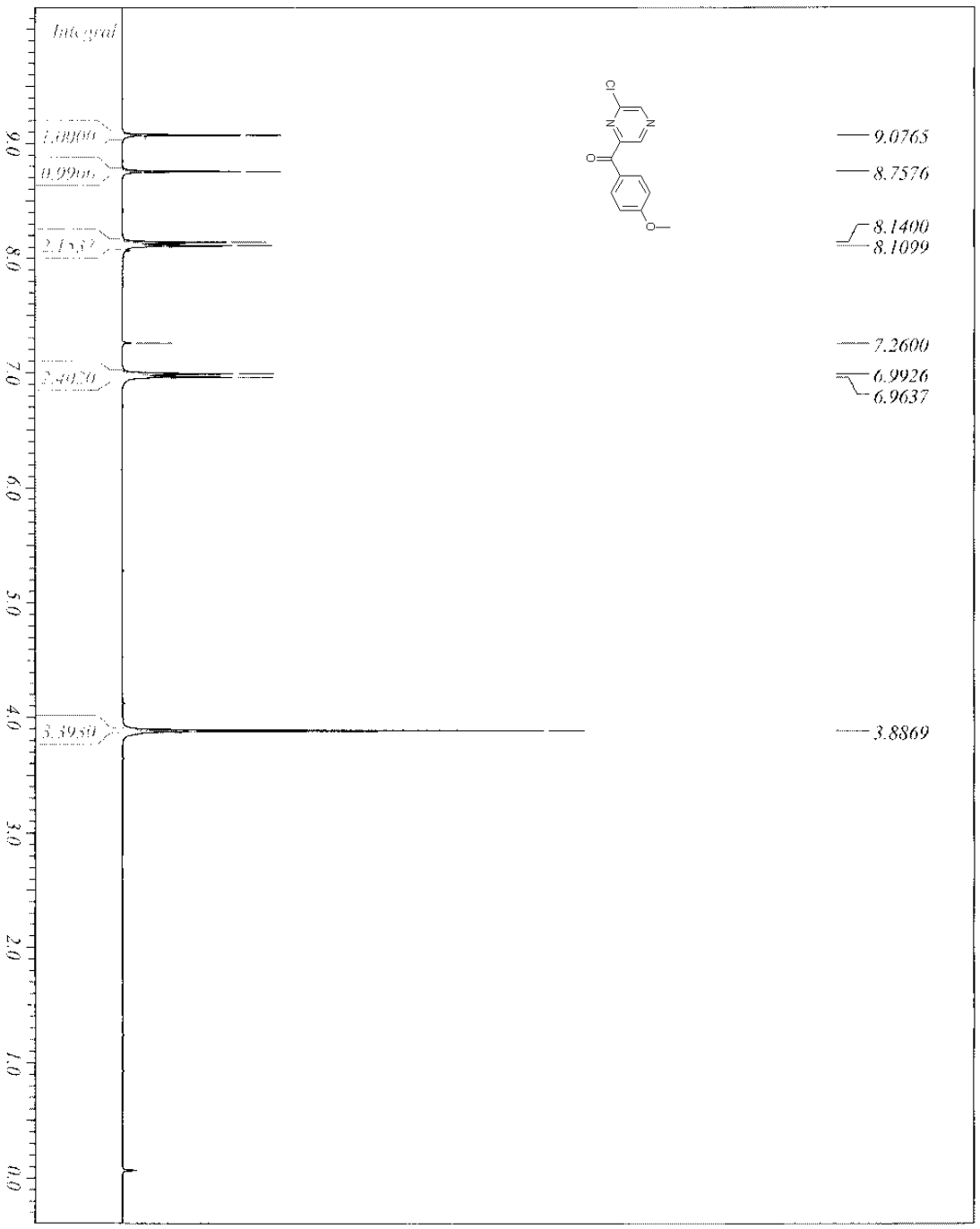
N
SnBu3
(ppm)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8.0
7.0
6.0
5.0
4.0
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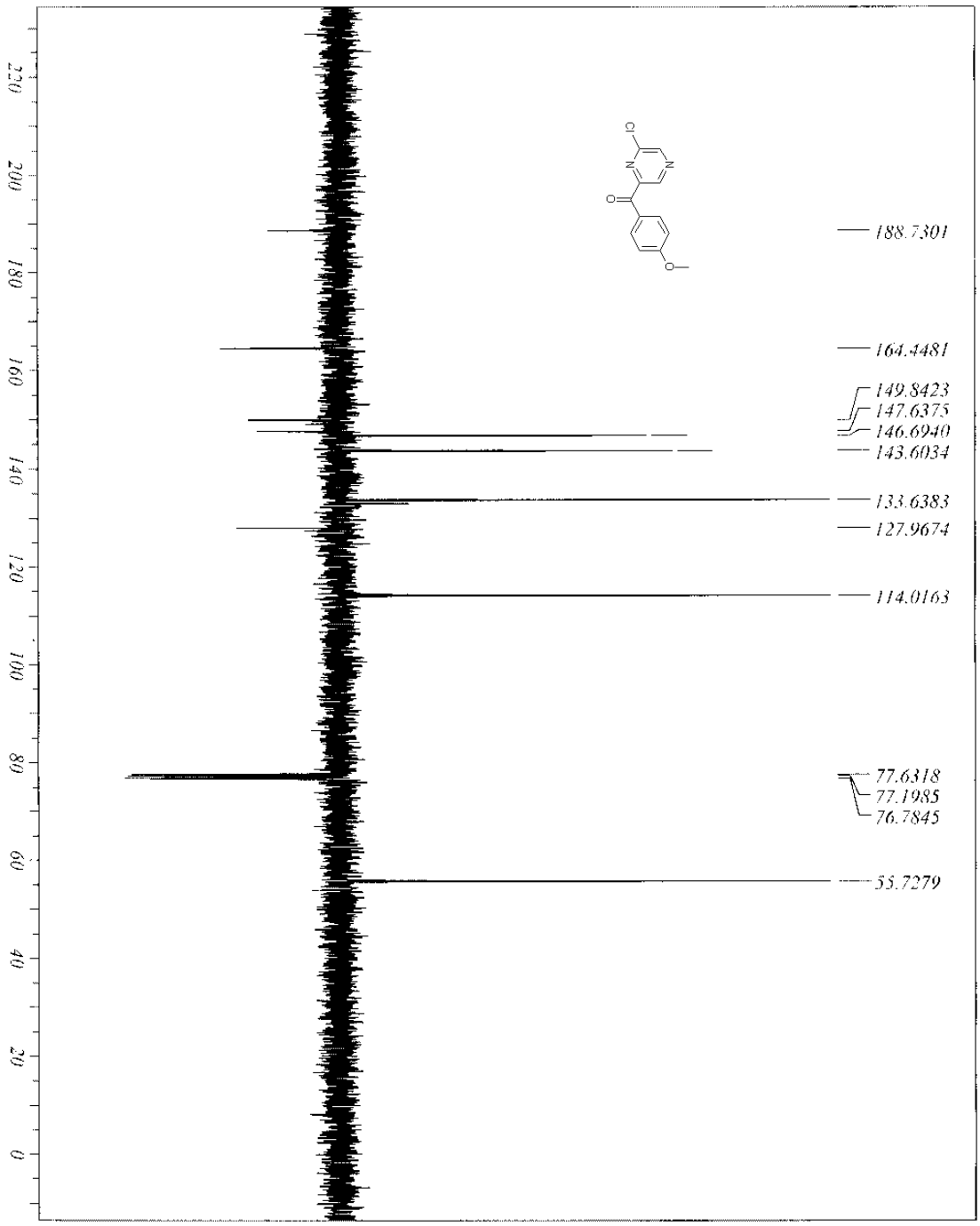
2.0
1.0
0.0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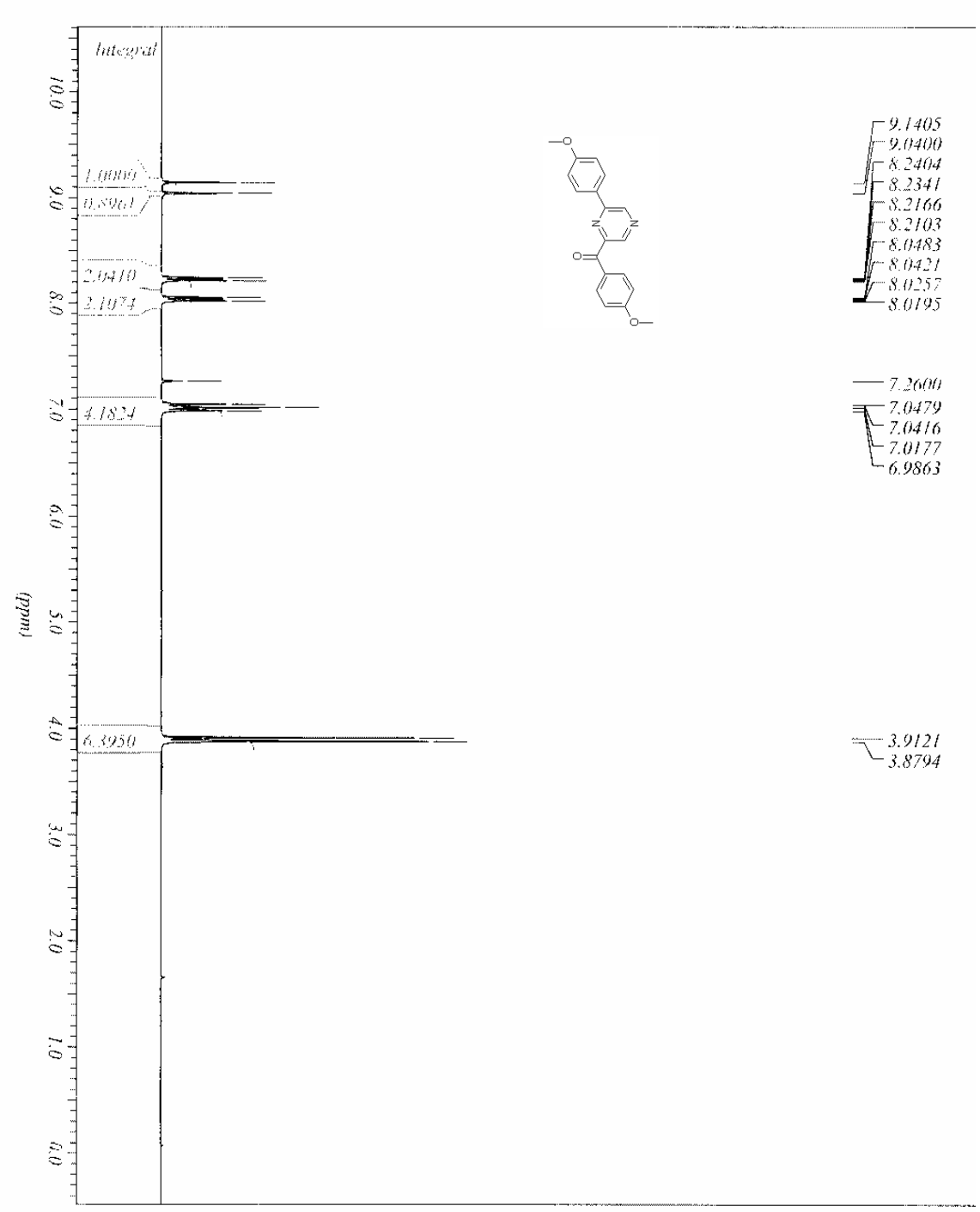
80
60
40
20
0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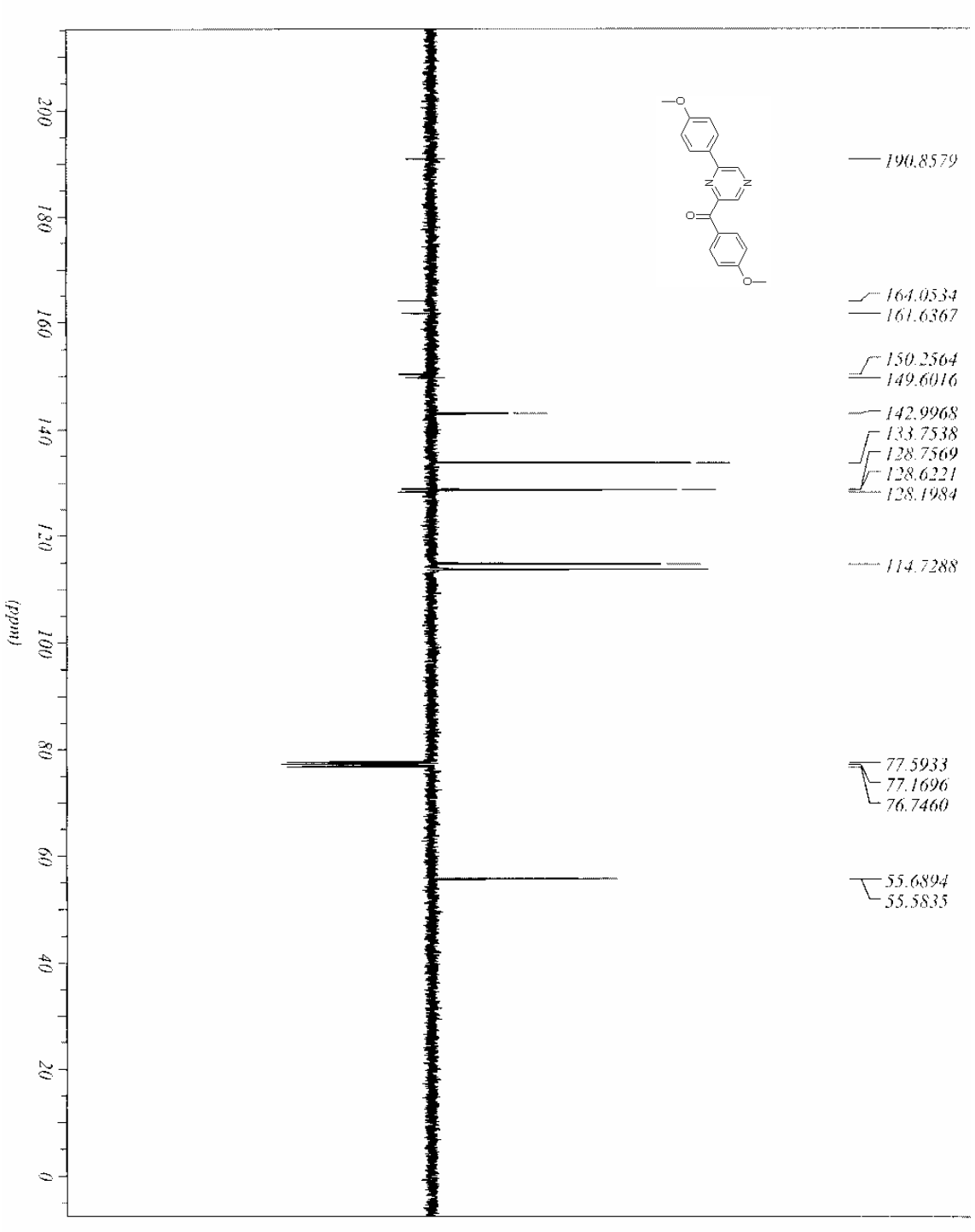
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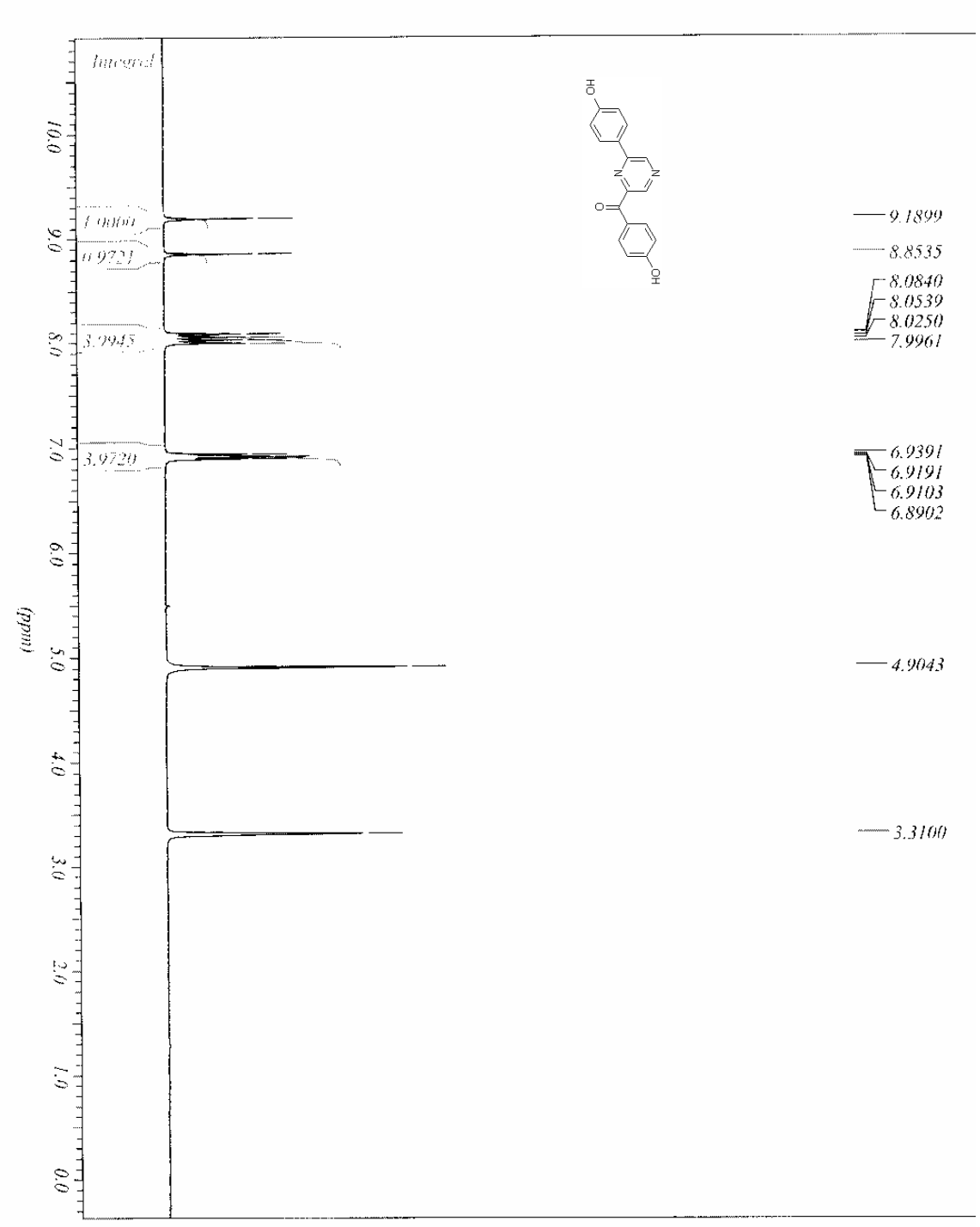
(ppm)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6.9103
6.8902
4.9043
3.3100
HO
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N
O
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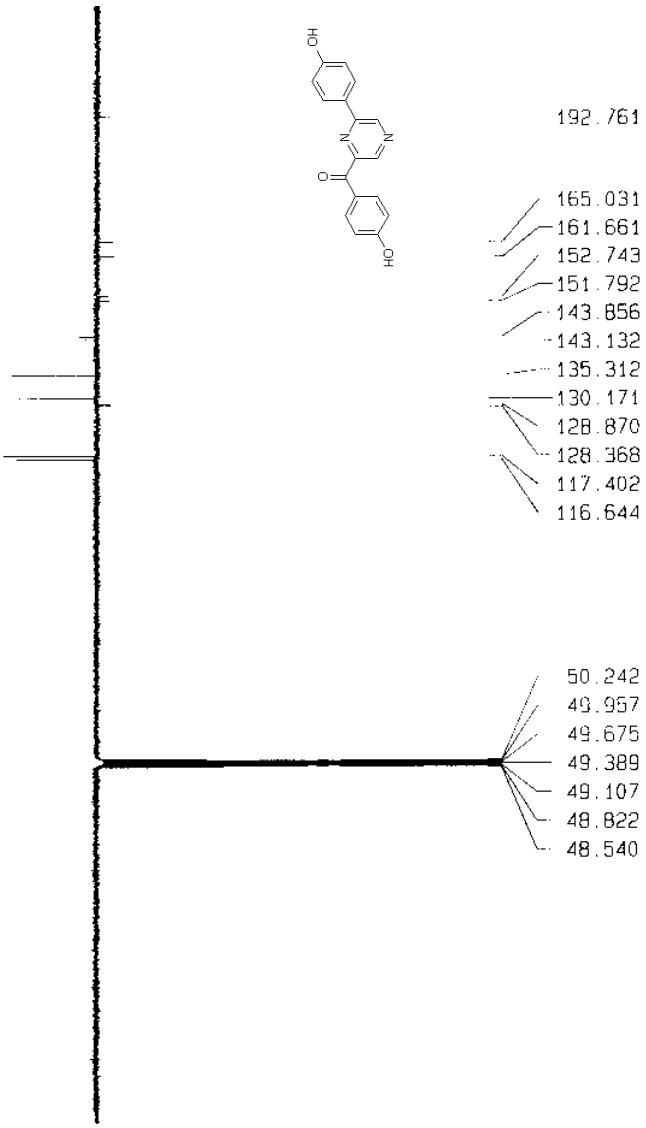
(ppm)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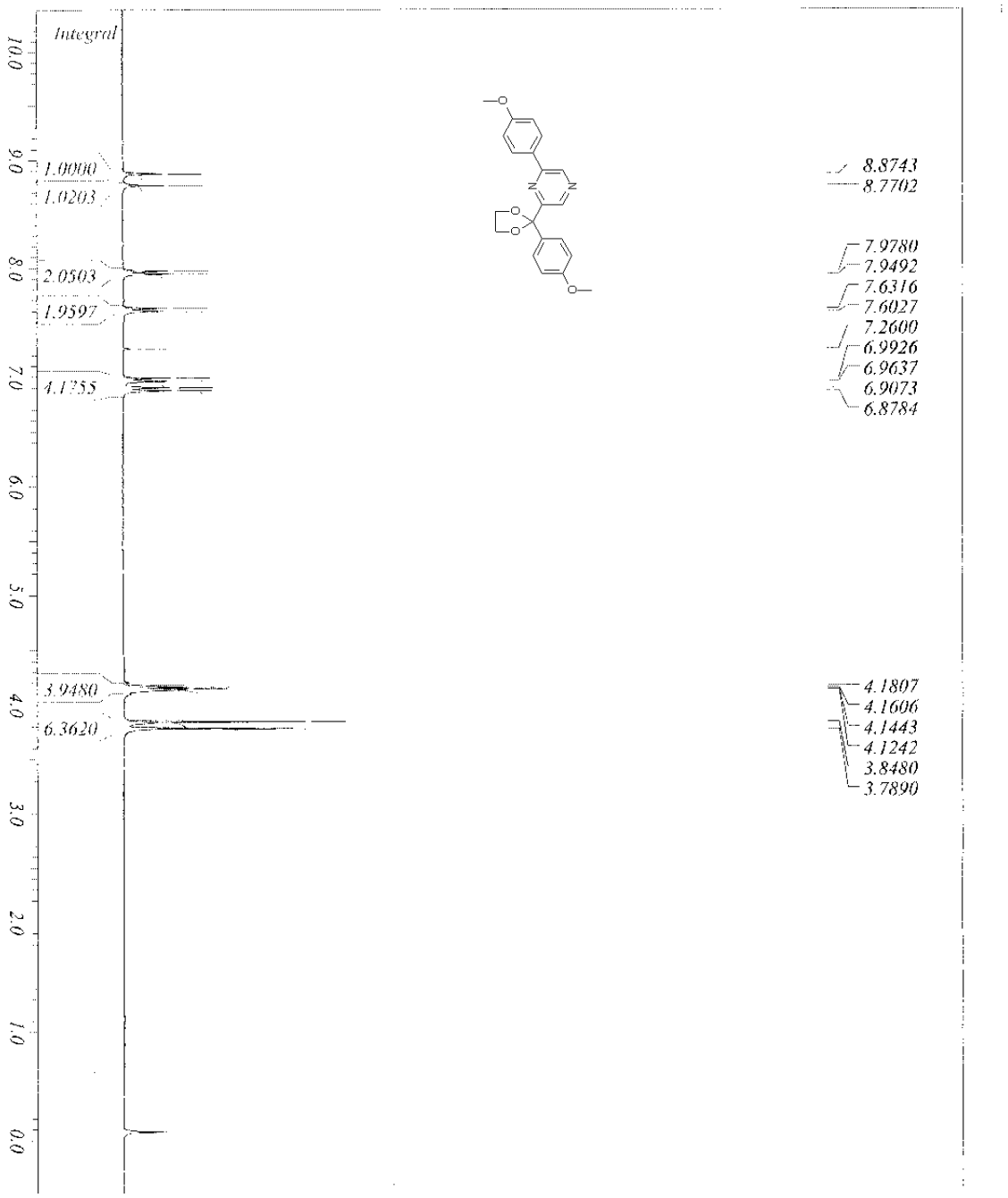
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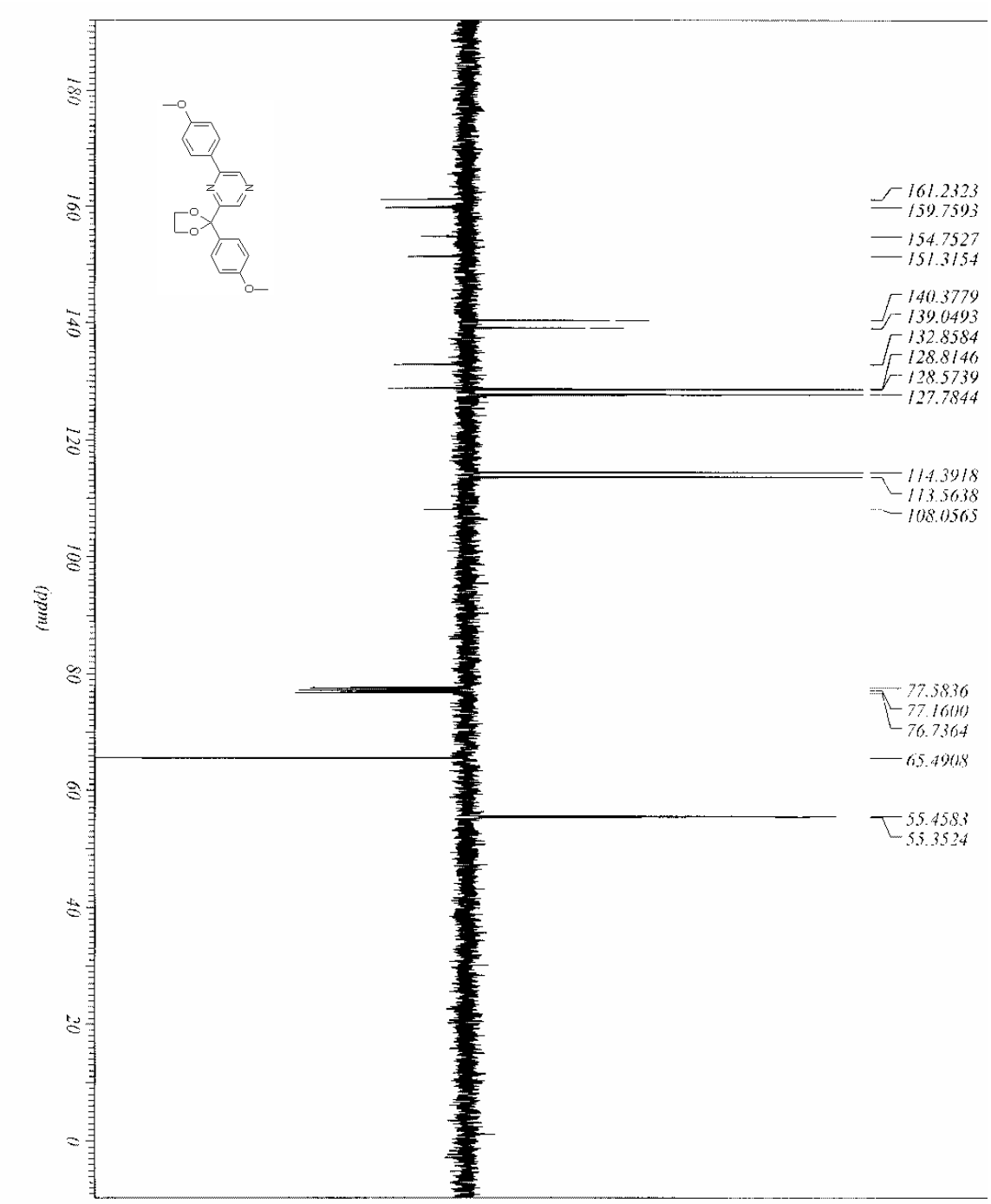
3.7890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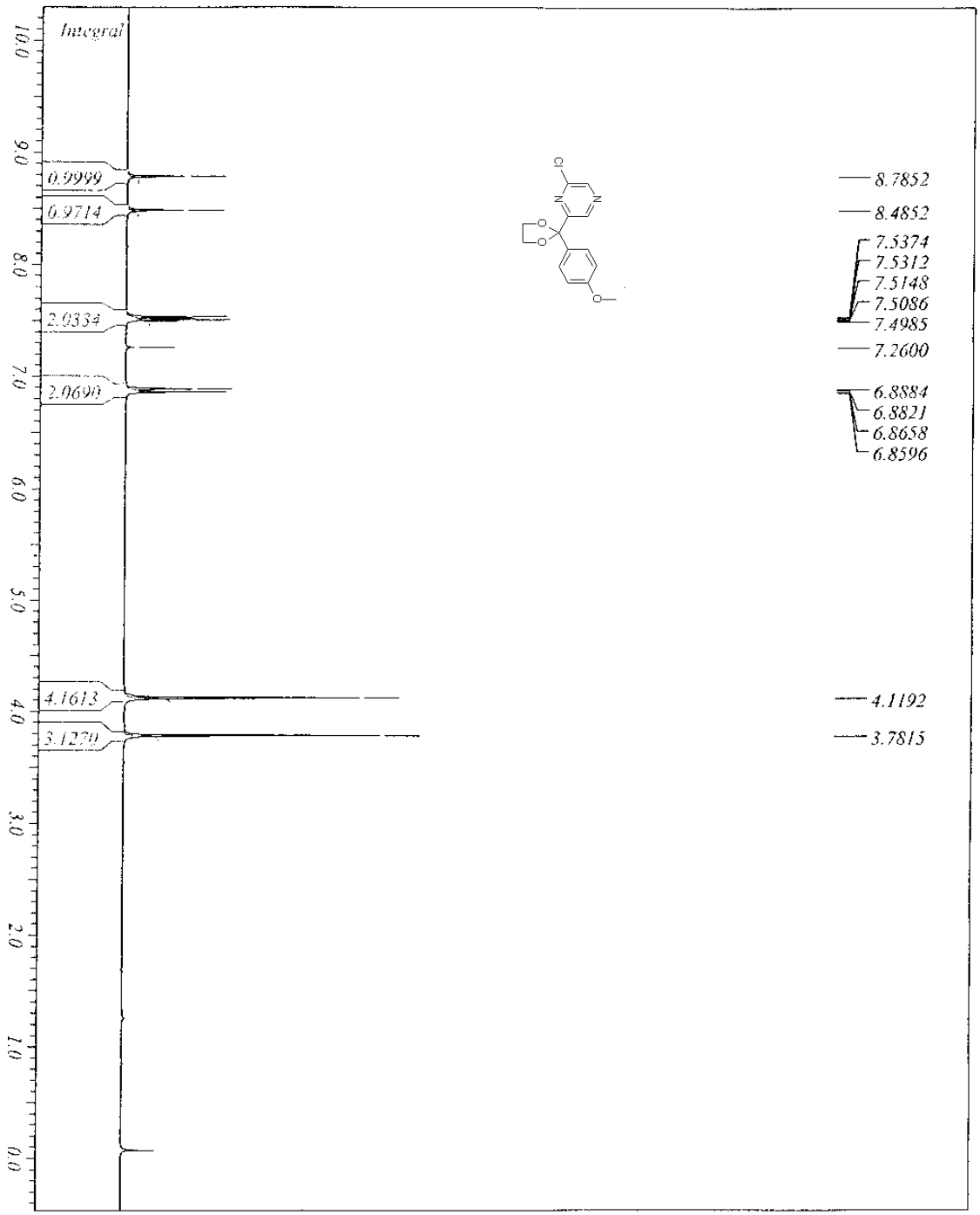
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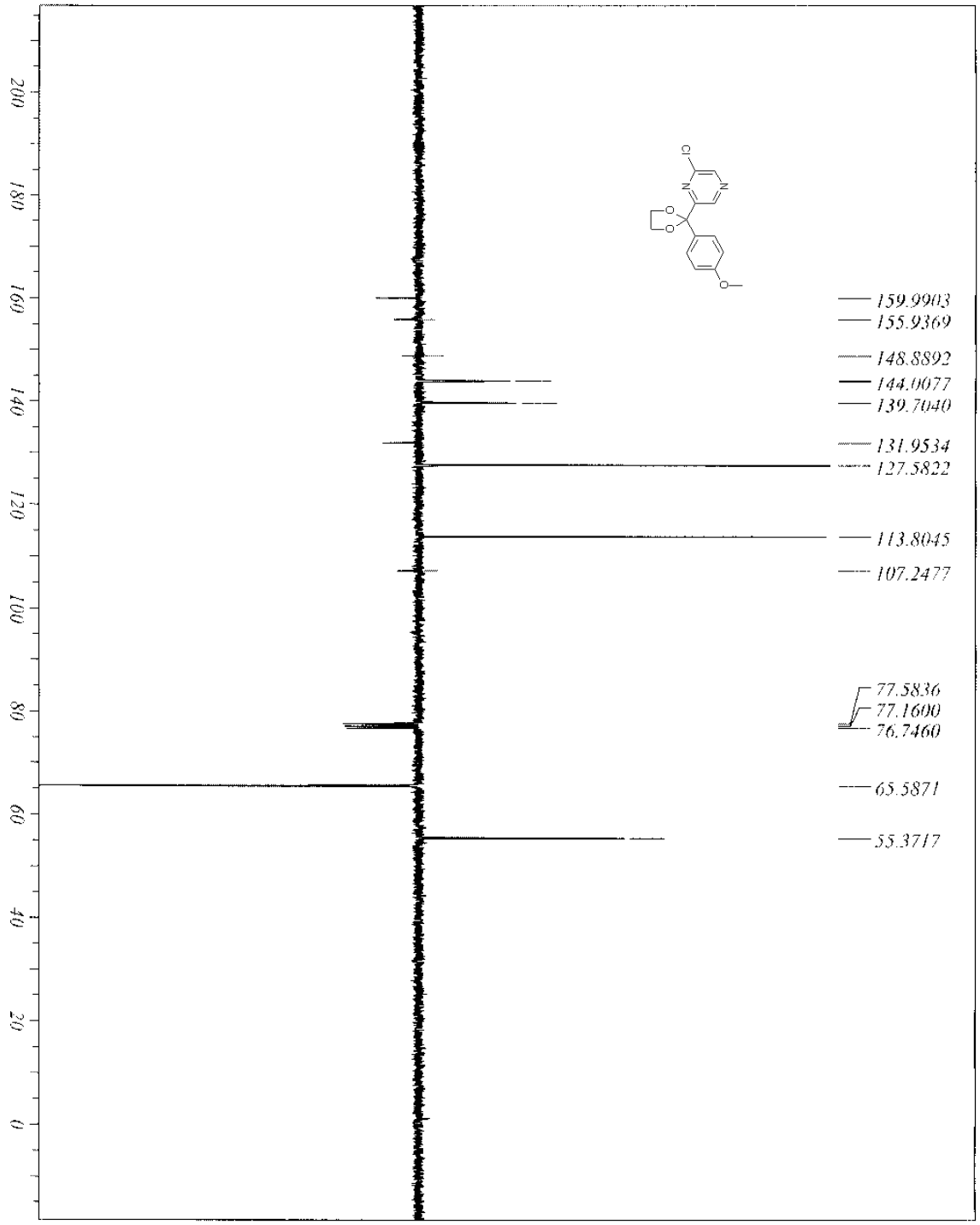
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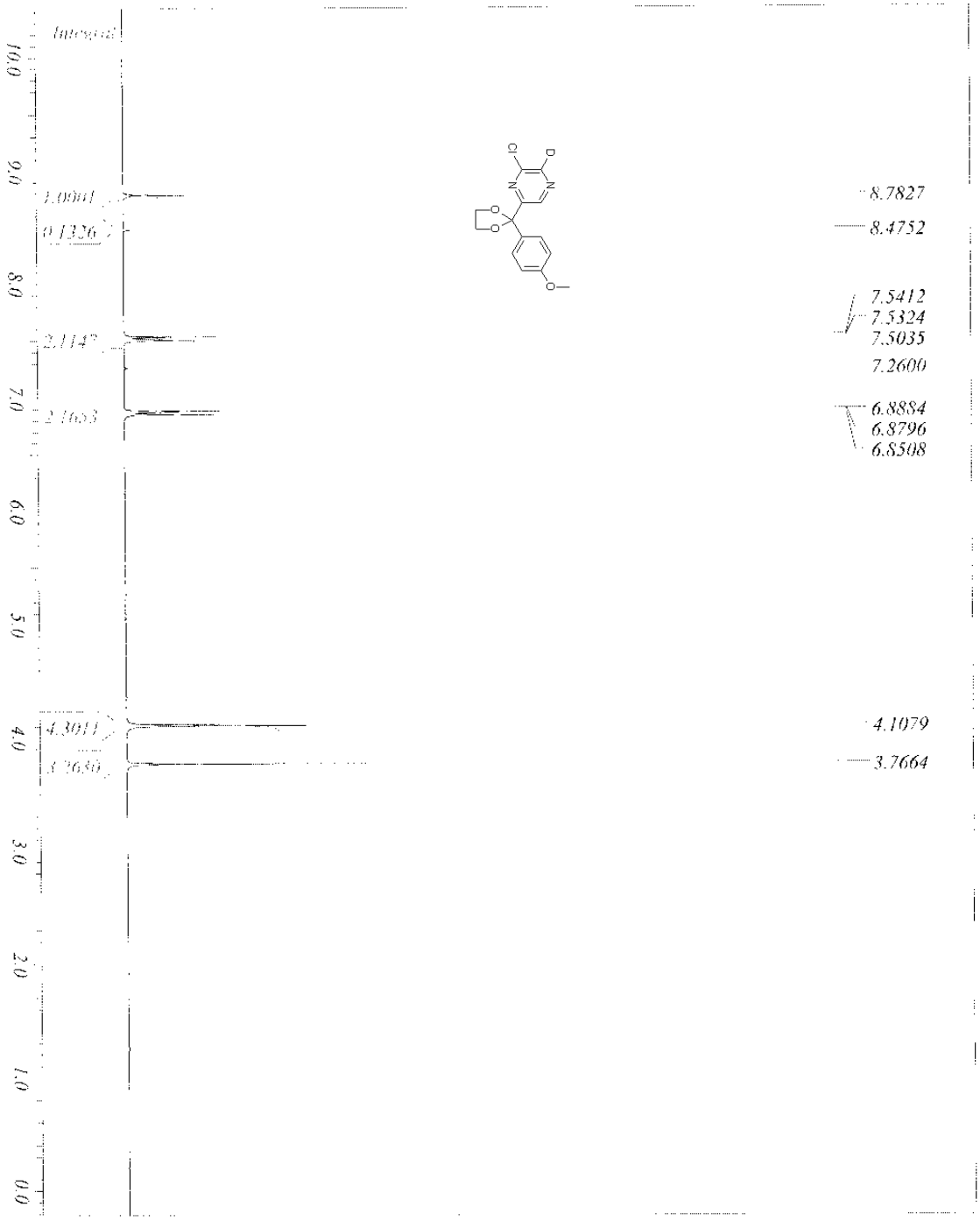
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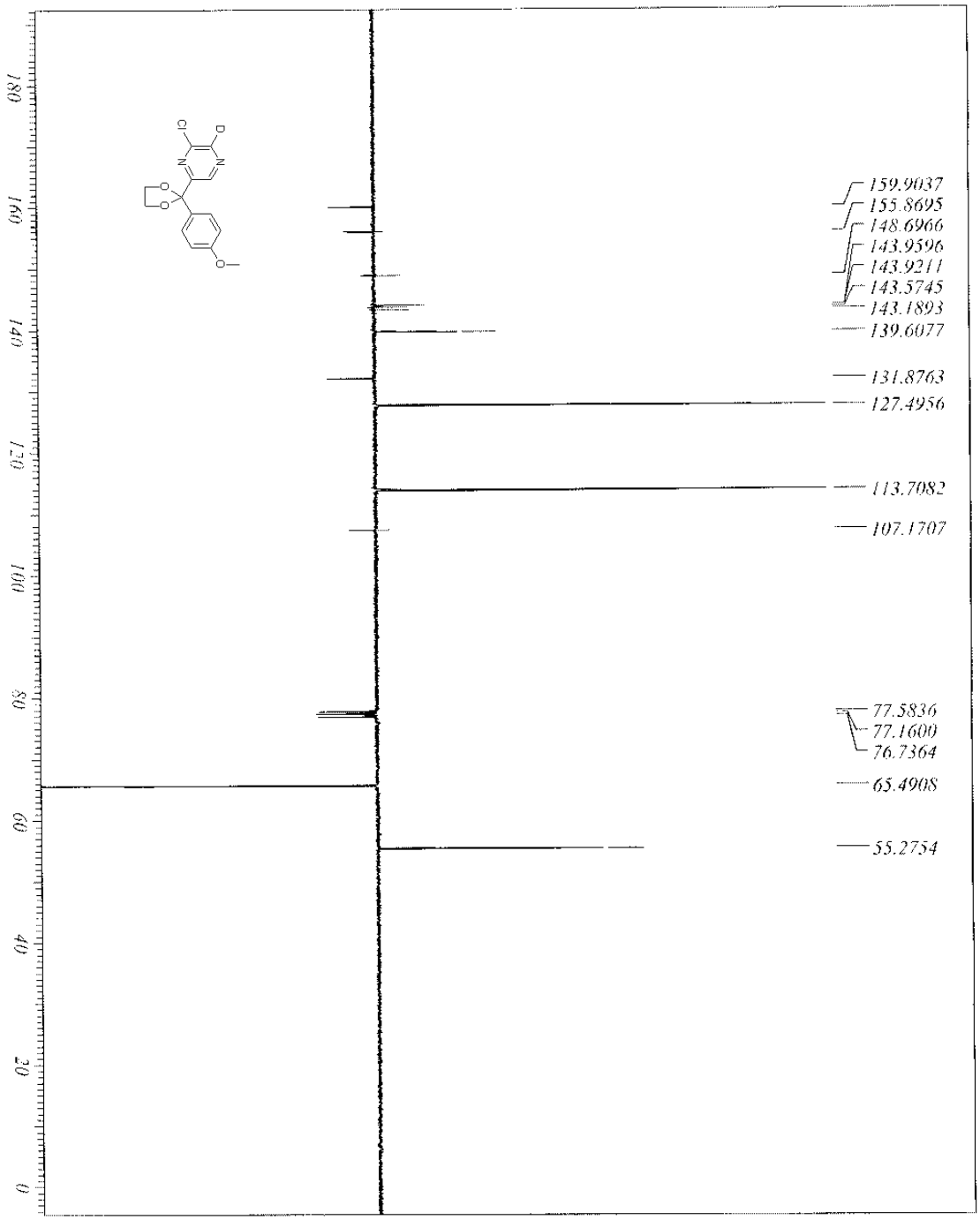
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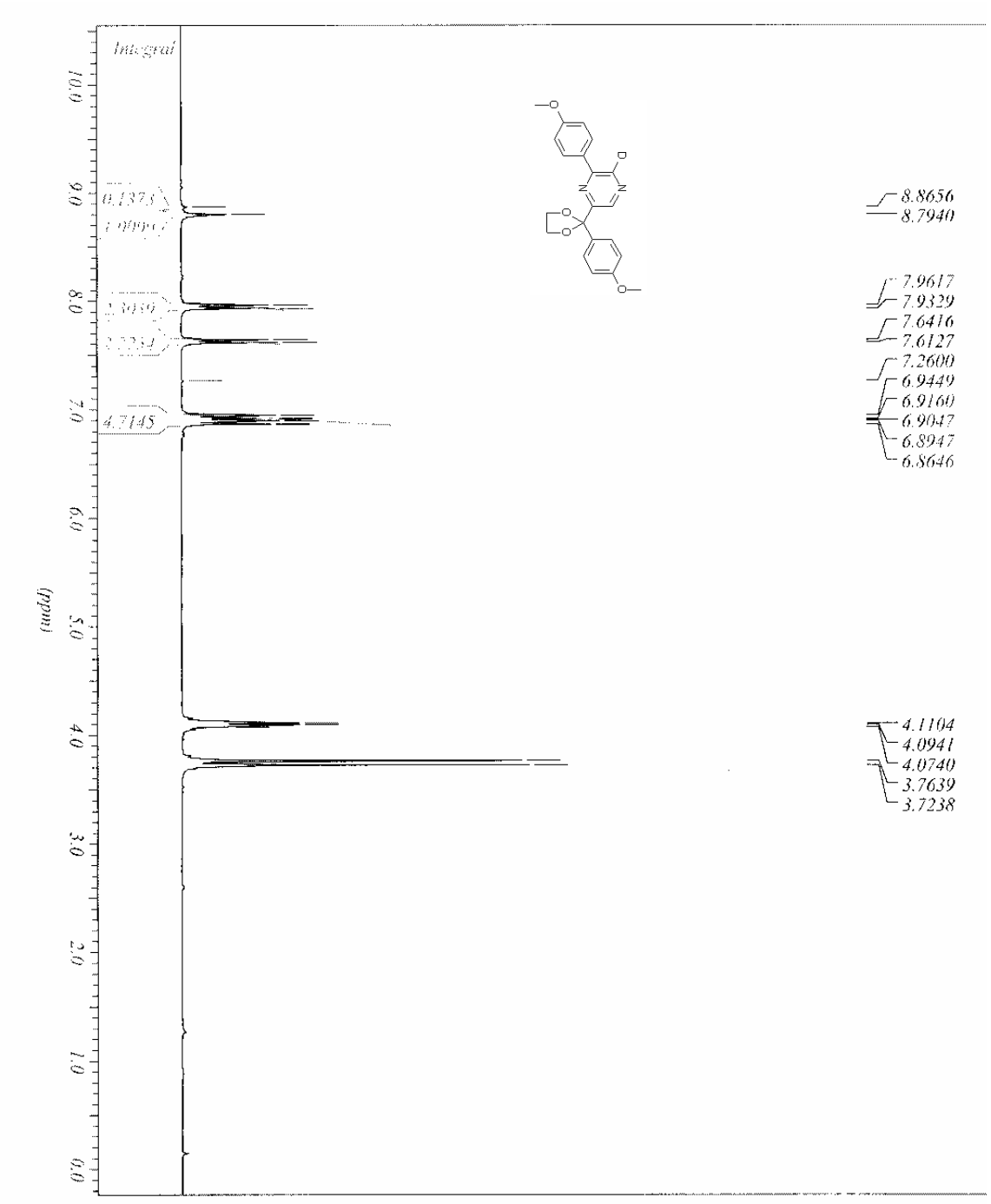
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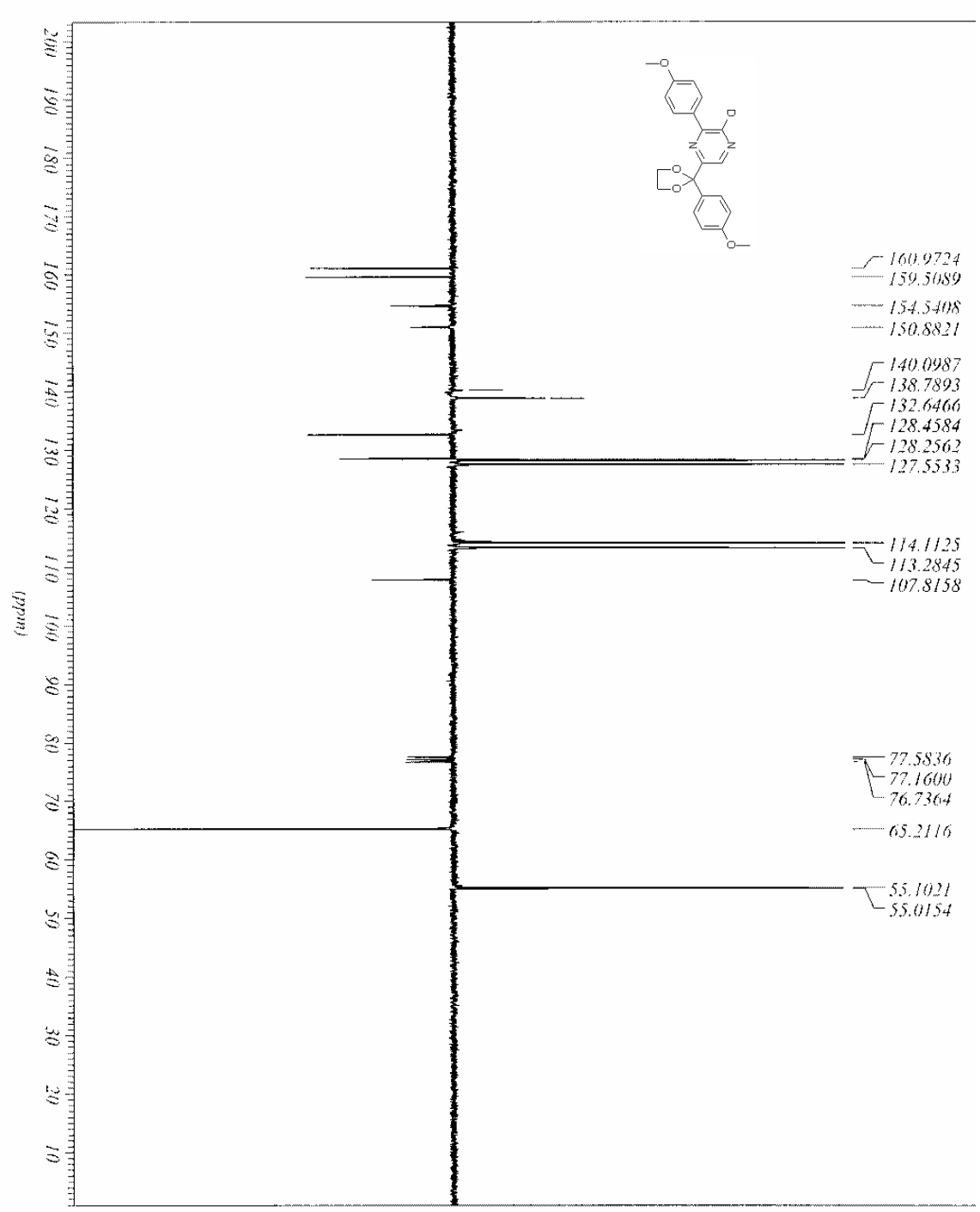
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107.8158
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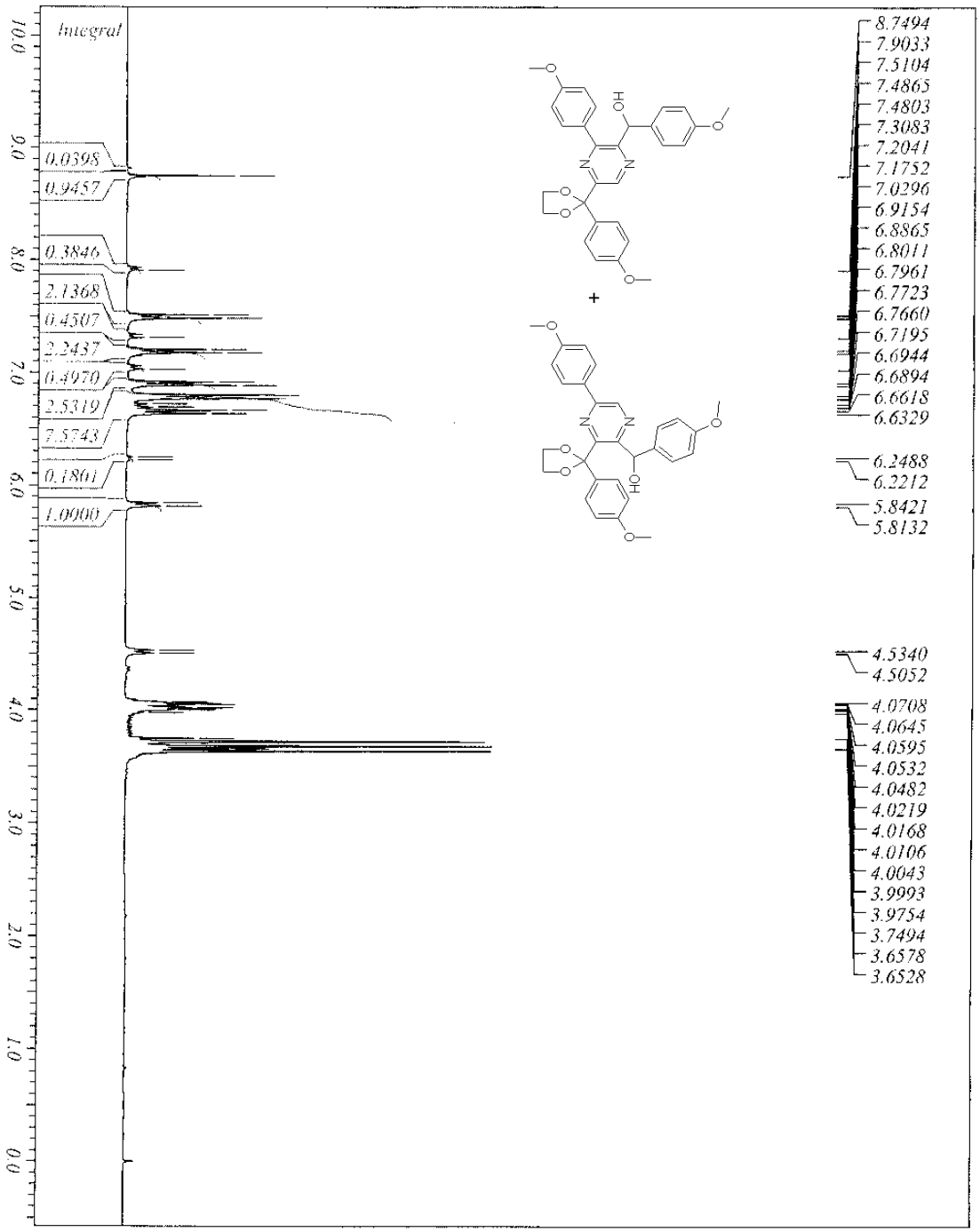
77.1600
76.7364
65.2116
55.1021
55.0154
(ppm)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0.0398
0.9457
0.3846
2.1368
0.4507
2.2437
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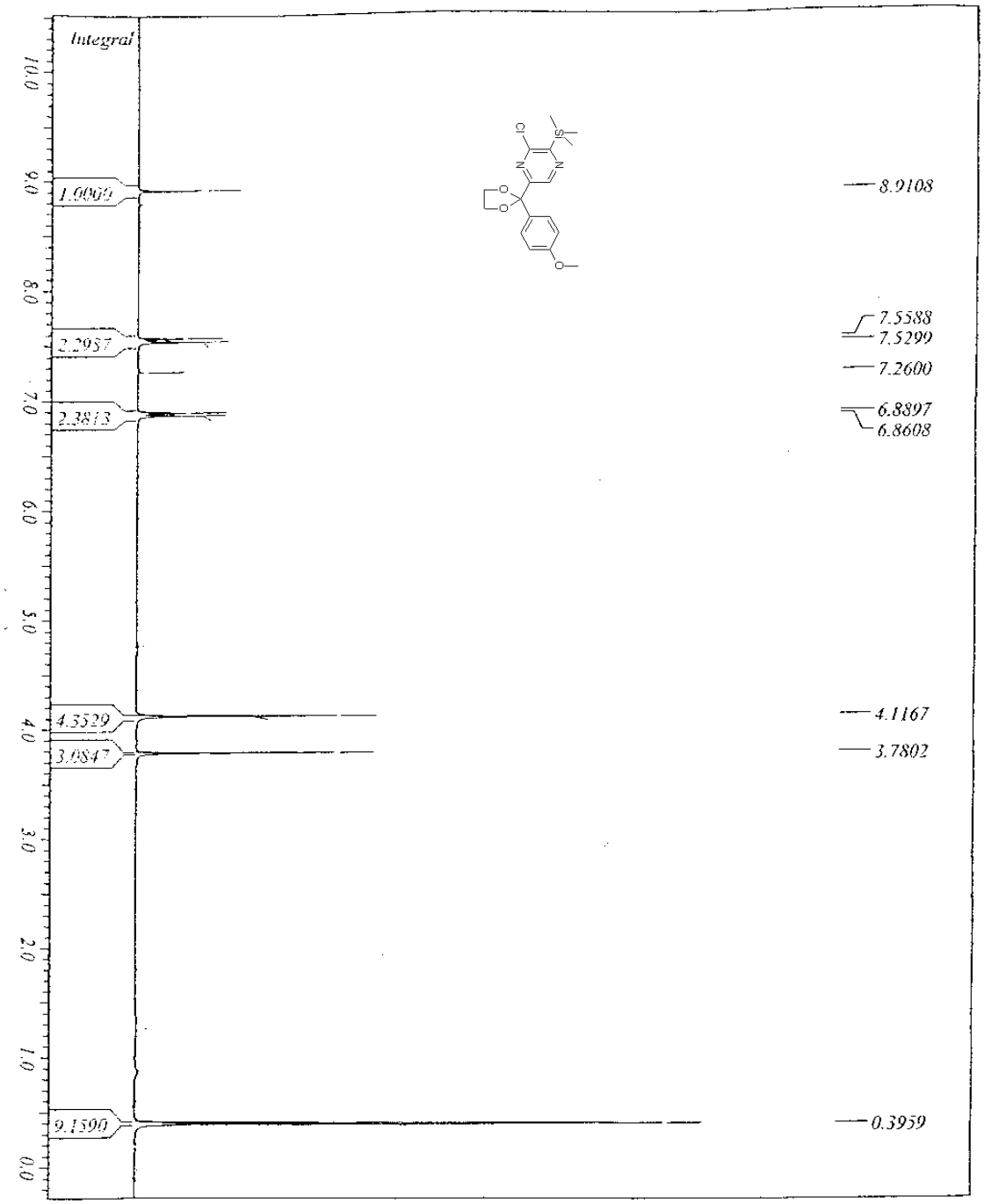
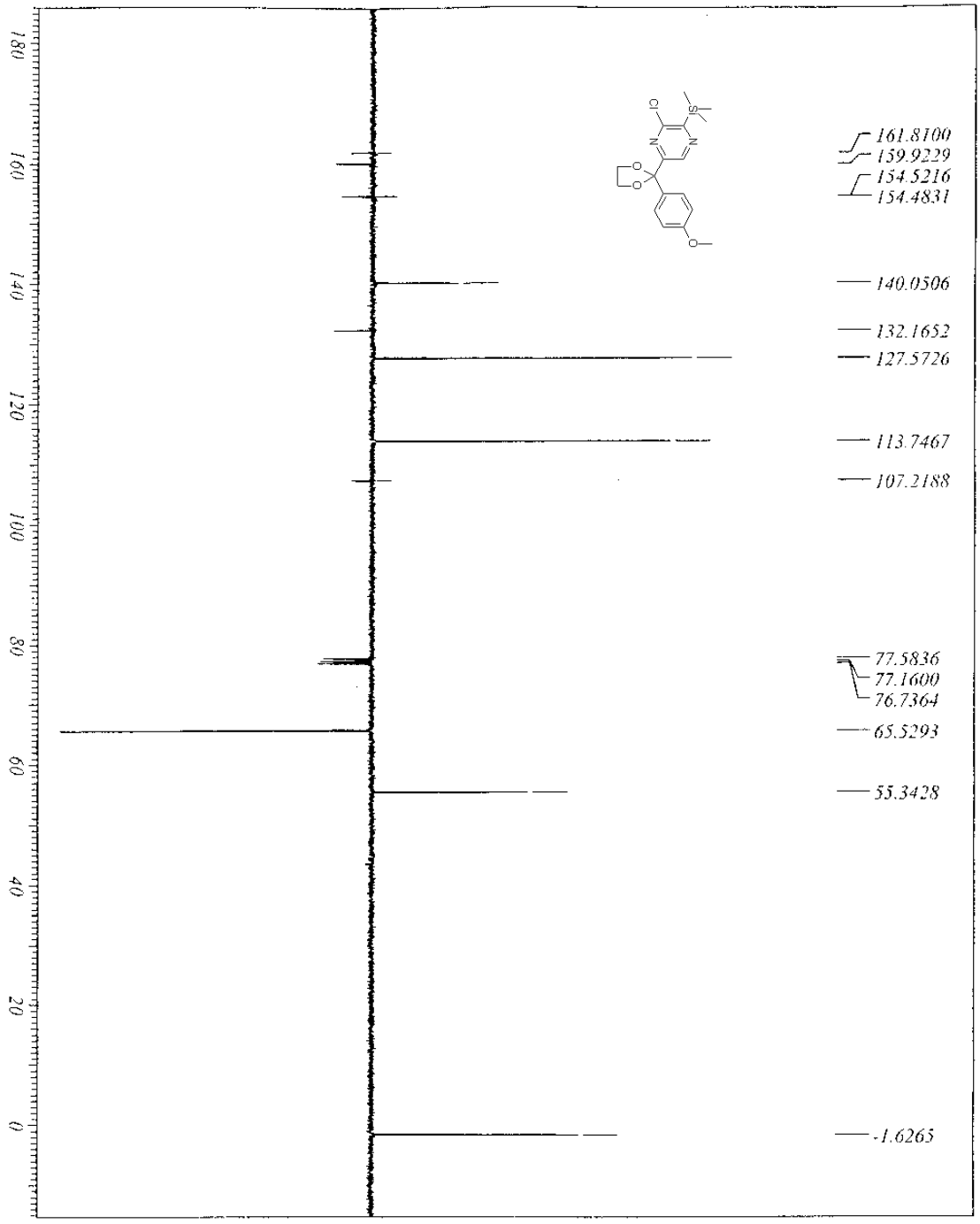
2.5319
7.5743
0.1801
1.0000
8.7494
7.9033
7.5104
7.4865
7.4803
7.3083
7.2041
7.1752
7.0296
6.9154
6.8865
6.8011
6.7961
6.7723
6.7660
6.7195
6.6944
6.6894
6.6618
6.6329
6.2488
6.2212
5.8421
5.8132
4.5340
4.5052
4.0708
4.0645
4.0595
4.0532
4.0482
4.0219
4.0168
4.0106
4.0043
3.9993
3.9754
3.7494
3.6578
3.6528


160.117
159.464
154.251
153.260
152.305
138.593
136.180
133.040
131.225
129.960
129.060
128.763
128.231
128.055
114.818
114.213
114.149
113.940
113.881
108.206
95.733
78.013
77.585
77.152
71.955
71.733
65.386
65.270
55.729
55.643
55.586
30.122


Integral
1.0000
2.2957
2.3813
4.3529
3.0847
9.1590
8.9108
7.5588
7.5299
7.2600
6.8897
6.8608
4.1167
3.7802
0.3959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154.5216
154.4831
140.0506
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107.2188
77.5836
77.1600
76.7364
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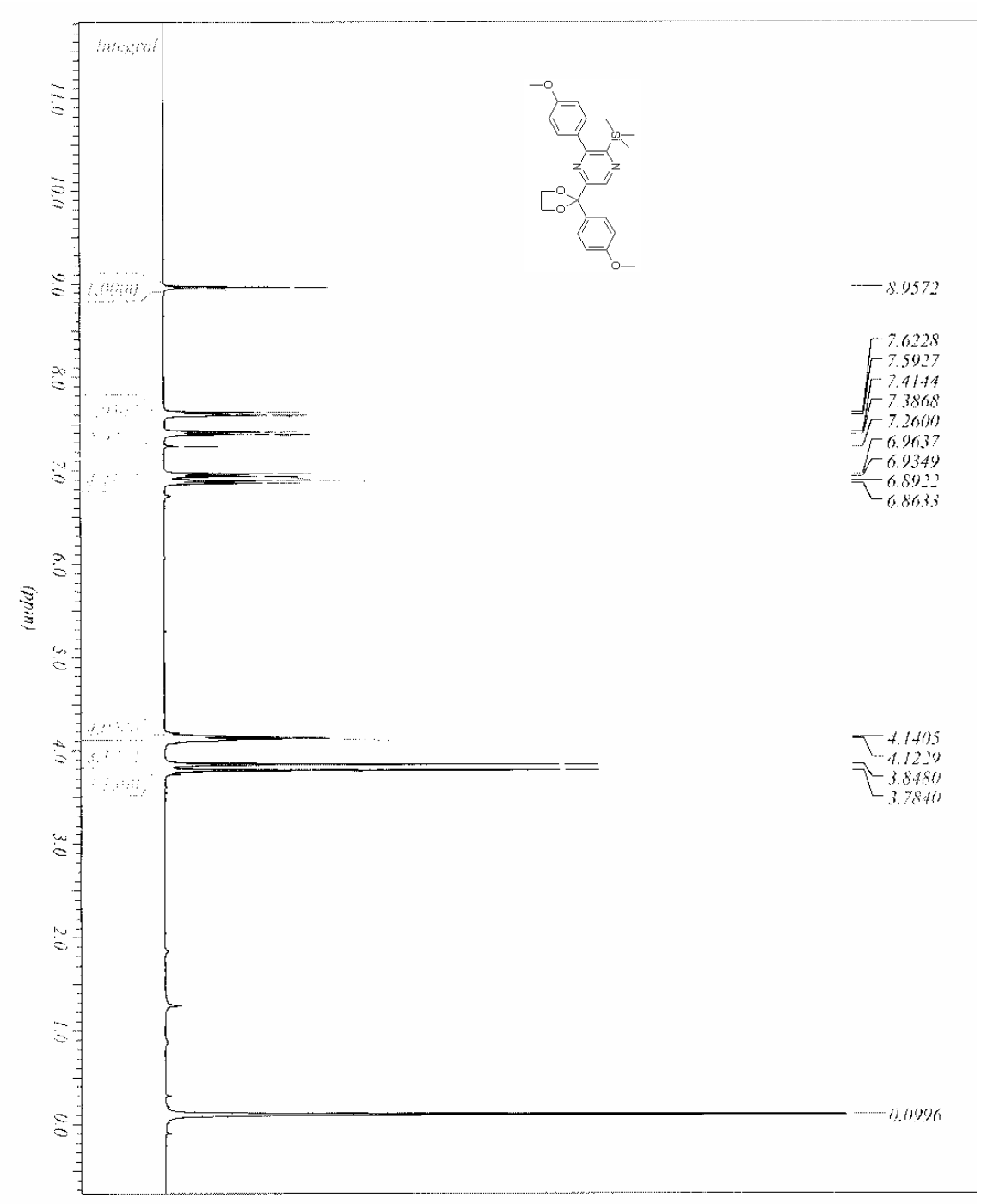
55.3428
-1.6265


integral
8.9572
7.6228
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7.4144
7.3868
7.2600
6.9637
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6.8933
6.8633
4.1405
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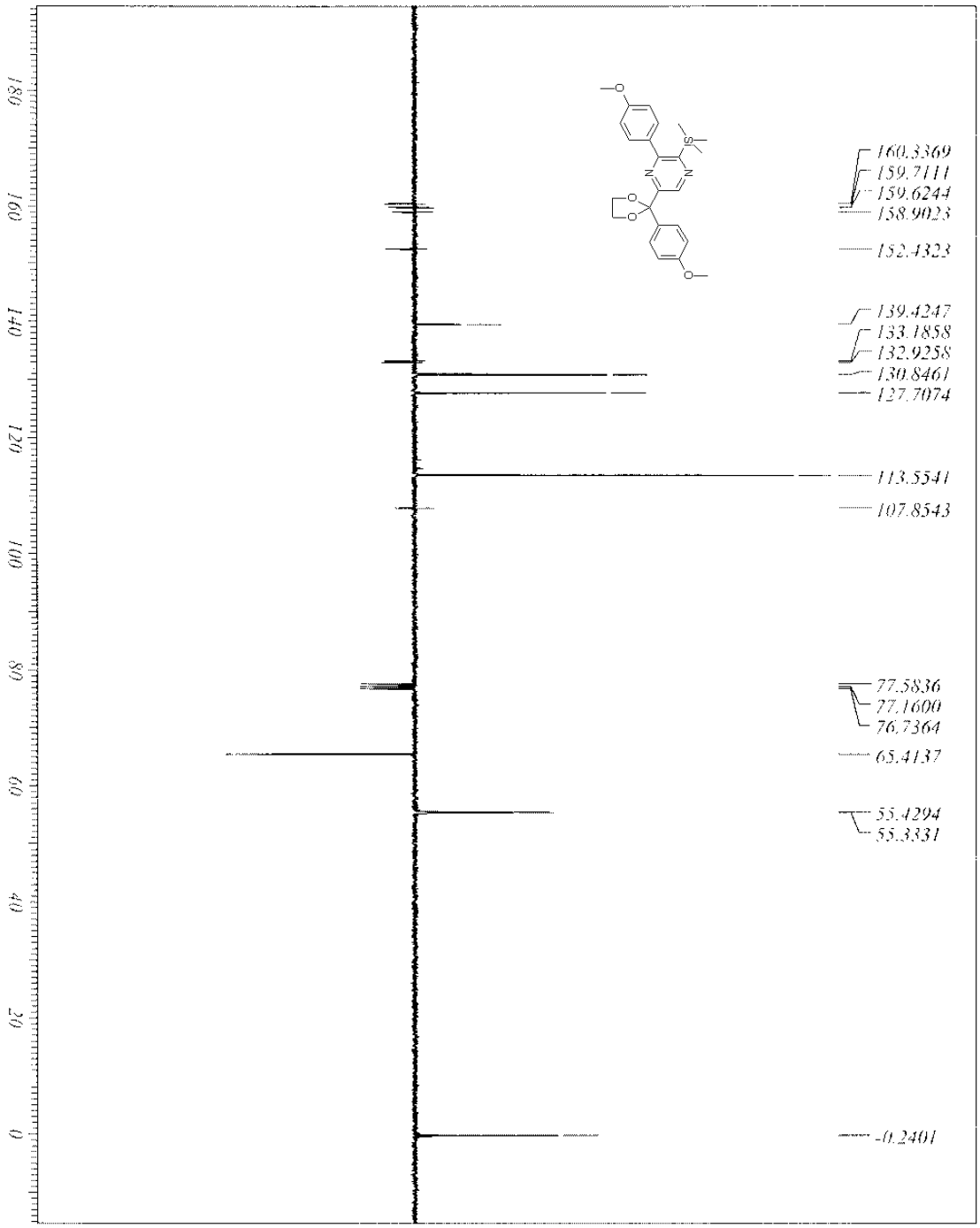
3.8480
3.7840
0.0996
(ppm)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159.6244
158.9023
152.4323
139.4247
133.1858
132.9258
130.8461
127.7074
113.5541
107.8543
77.5836
77.1600
76.7364
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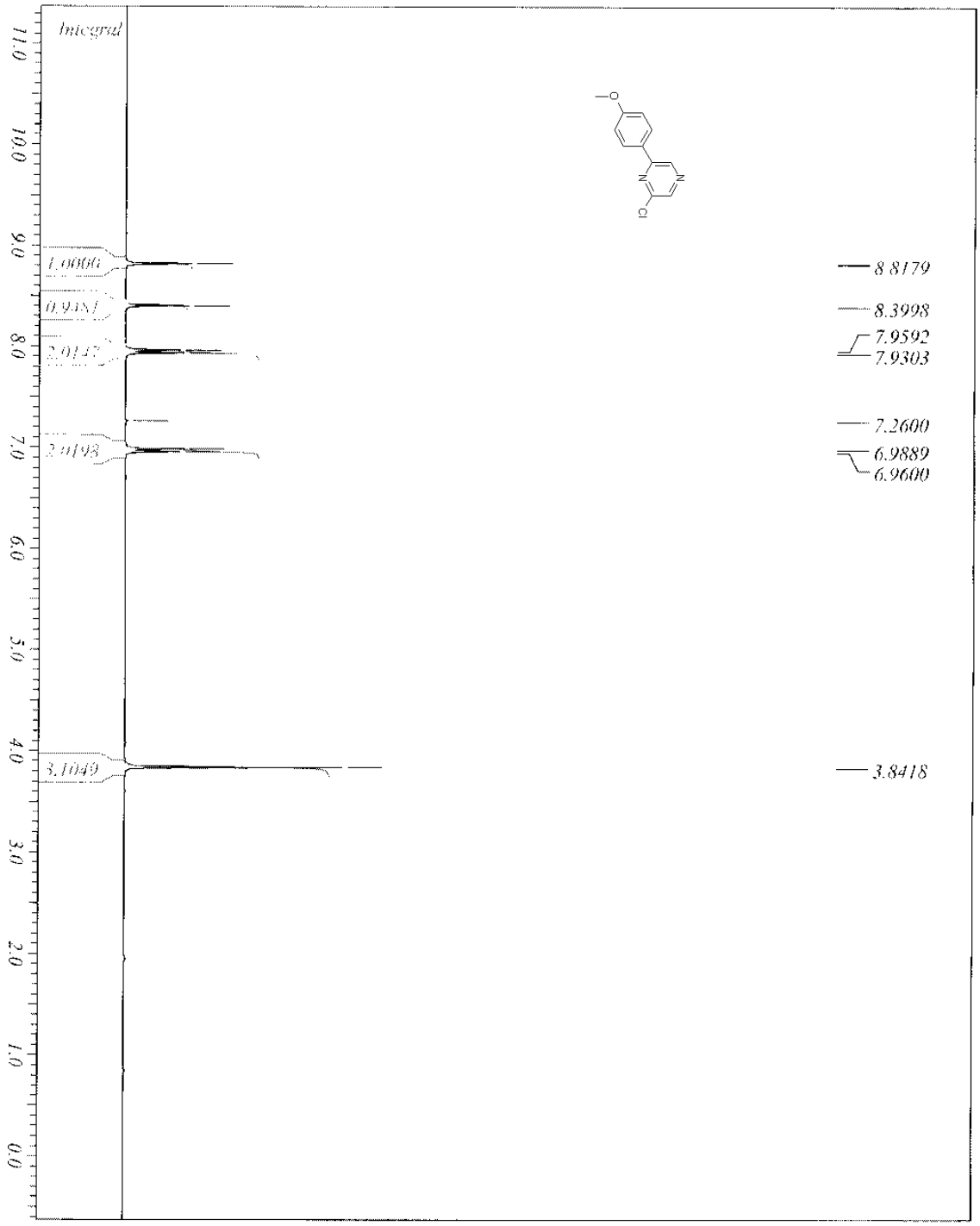
55.4294
55.3331
-0.2401
180
160
140
120
100
80
60
40
20
0


Integral
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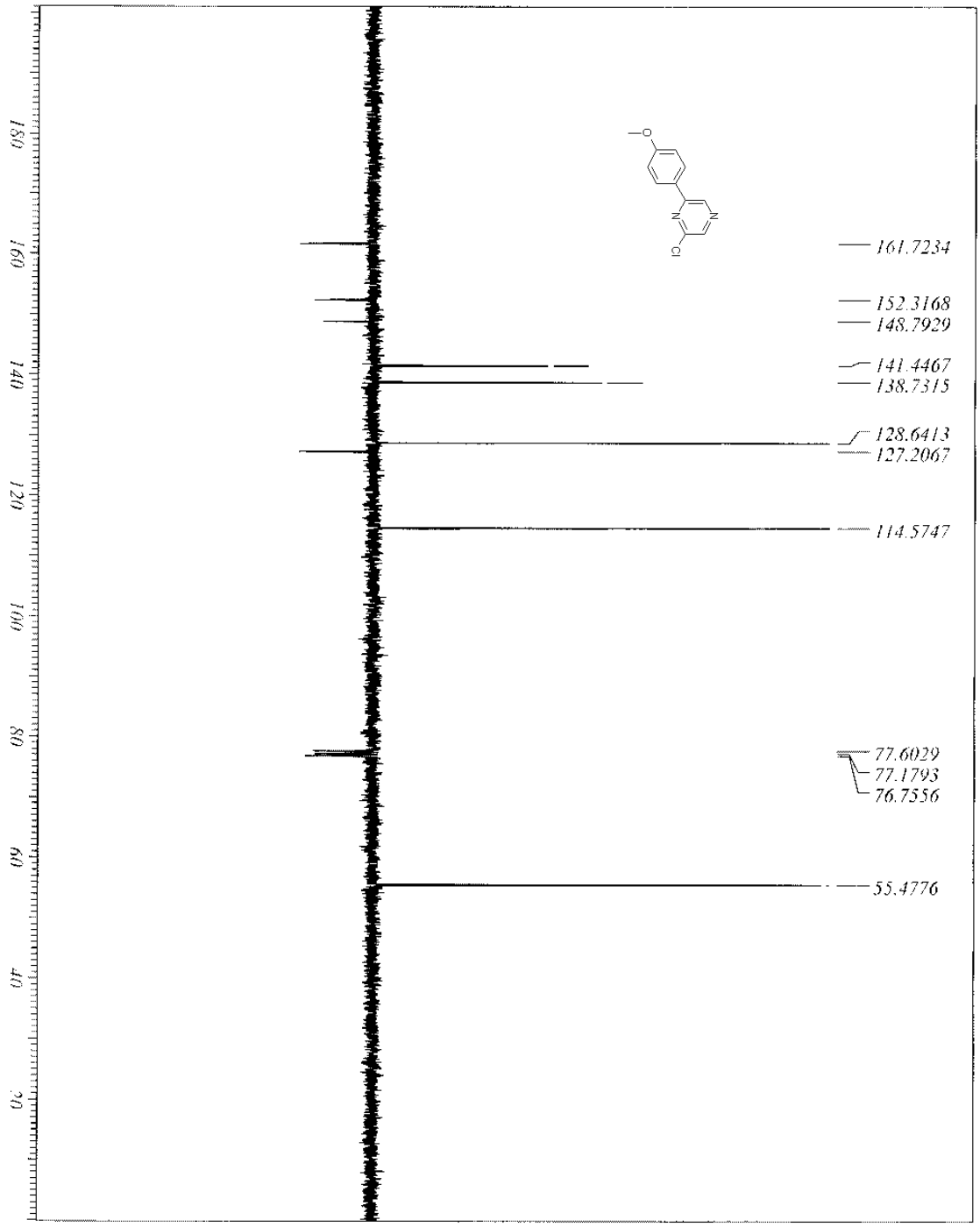
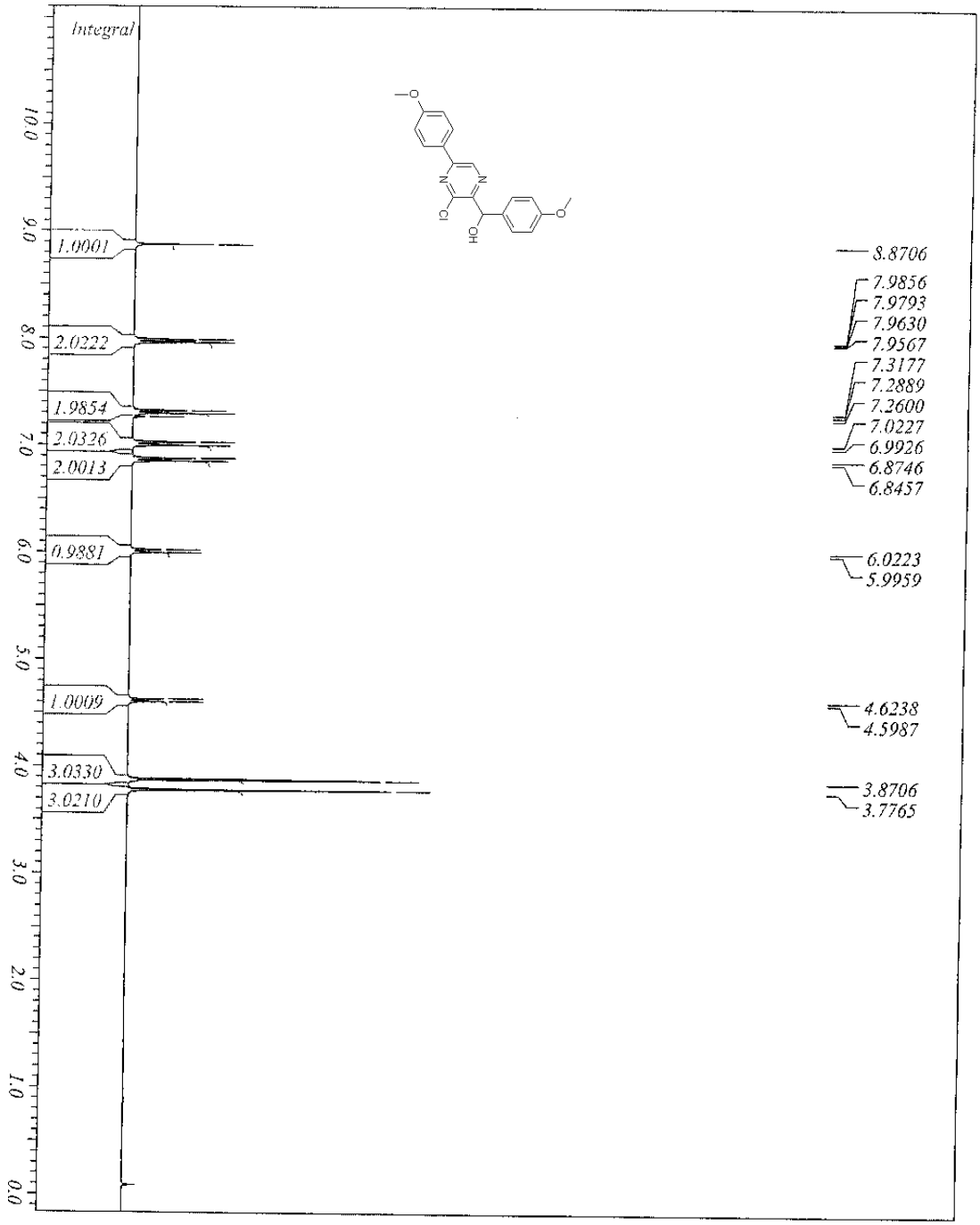
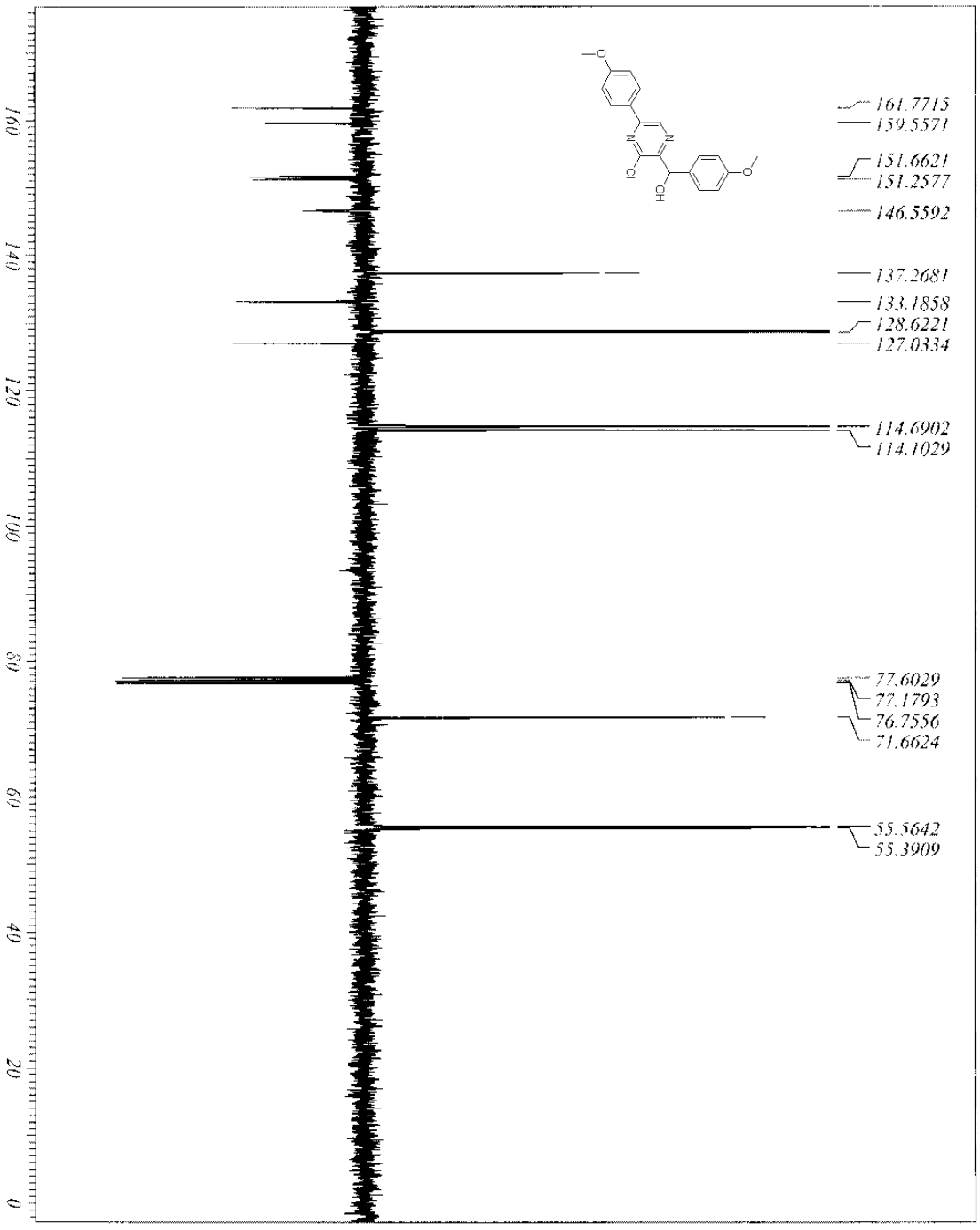
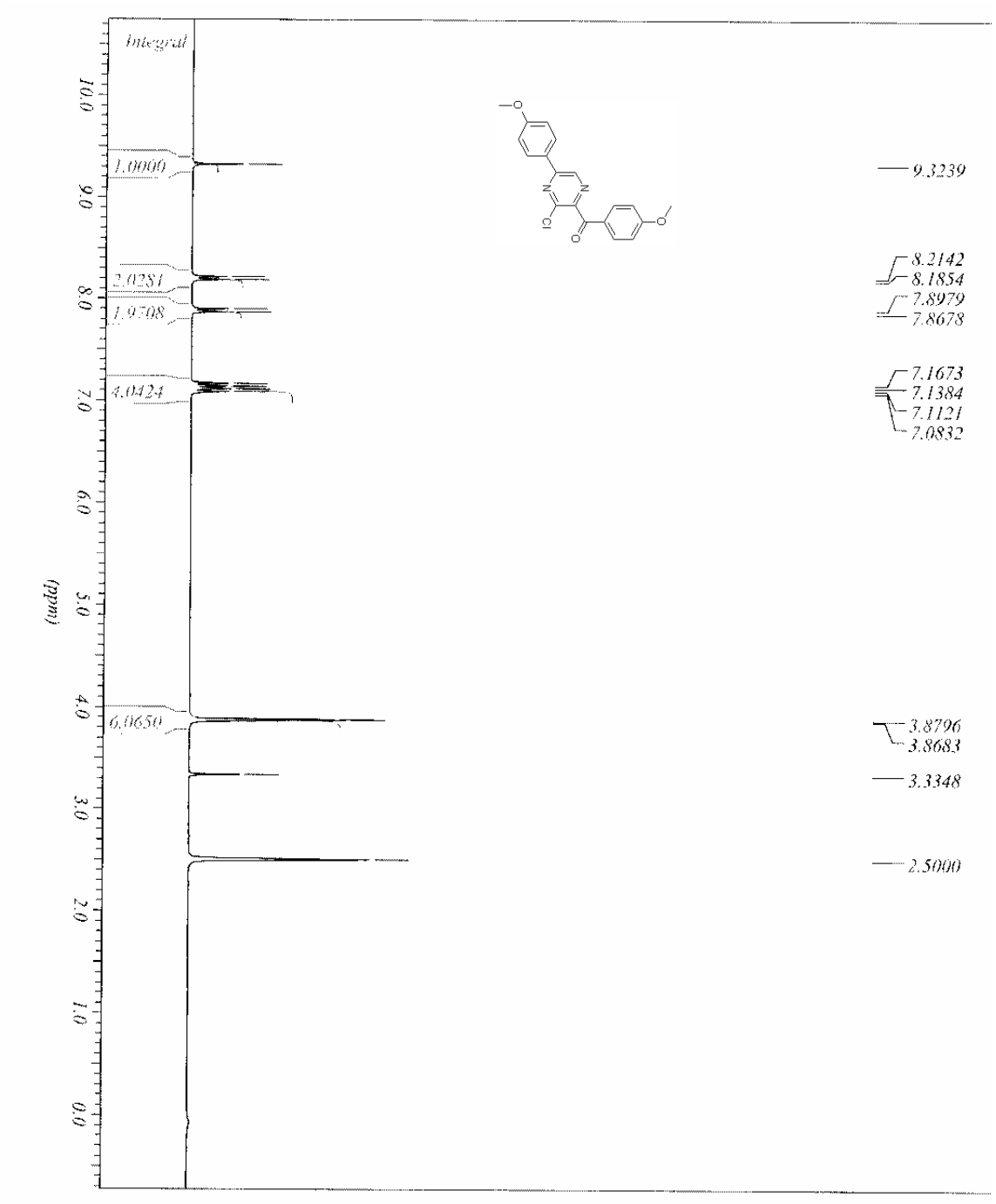
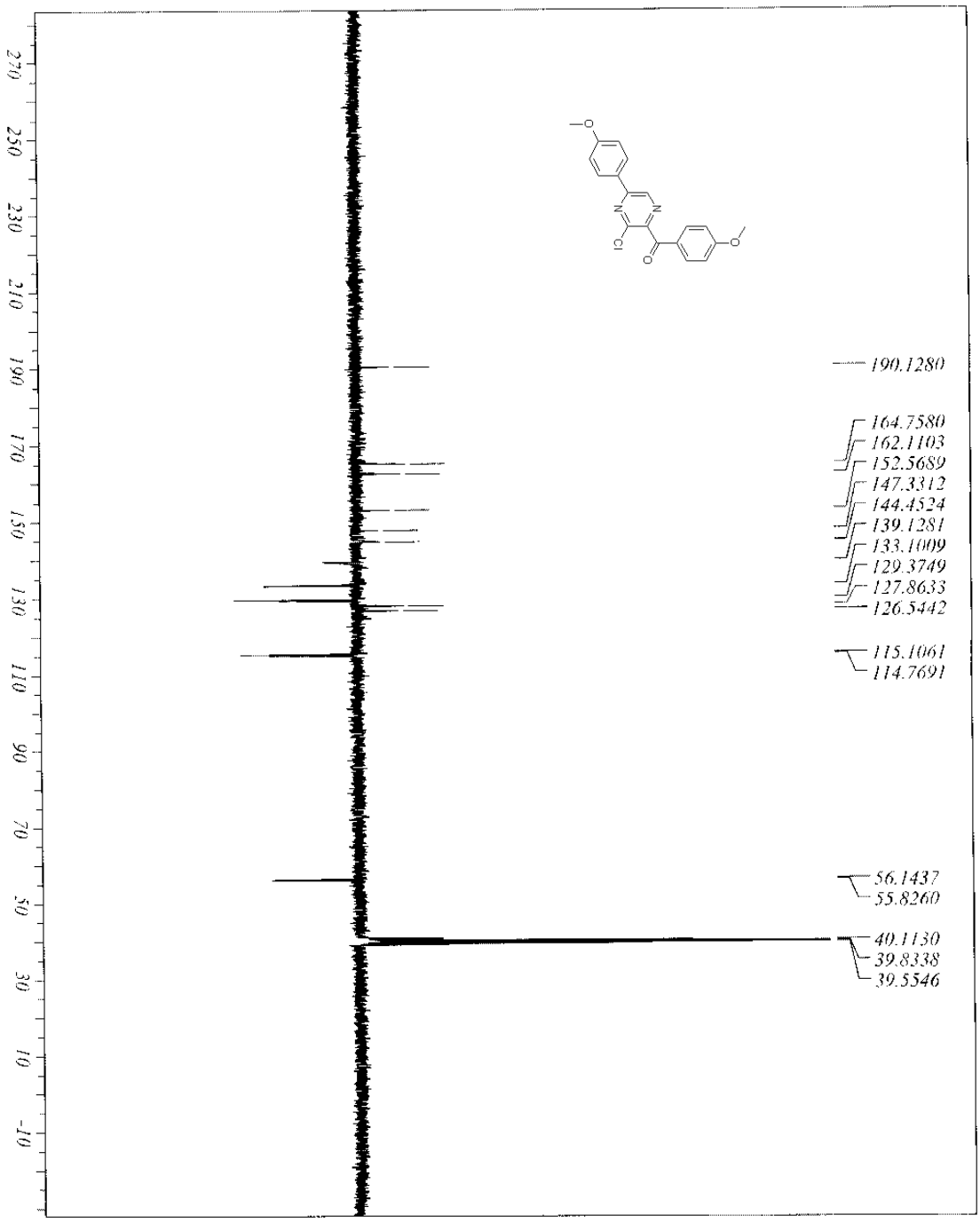
2.0198
3.1049
8.8179
8.3998
7.9592
7.9303
7.2600
6.9889
6.9600
3.8418
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


161.7234
152.3168
148.7929
141.4467
138.7315
128.6413
127.2067
114.5747
77.6029
77.1793
76.7556
55.4776


Integral
1.0001
2.0222
1.9854
2.0326
2.0013
0.9881
1.0009
3.0330
3.0210
8.8706
7.9856
7.9793
7.9630
7.9567
7.3177
7.2889
7.2600
7.0227
6.9926
6.8746
6.8457
6.0223
5.9959
4.6238
4.5987
3.8706
3.7765


161.7715
159.5571
151.6621
151.2577
146.5592
137.2681
133.1858
128.6221
127.0334
114.6902
114.1029
77.6029
77.1793
76.7556
71.6624
55.5642
55.3909
160
140
120
100
80
60
40
20
0


Integral
1.0000
2.0251
1.9708
4.0424
6.0650
9.3239
8.2142
8.1854
7.8979
7.8678
7.1673
7.1384
7.1121
7.0832
3.8796
3.8683
3.3348
2.5000
(ppm)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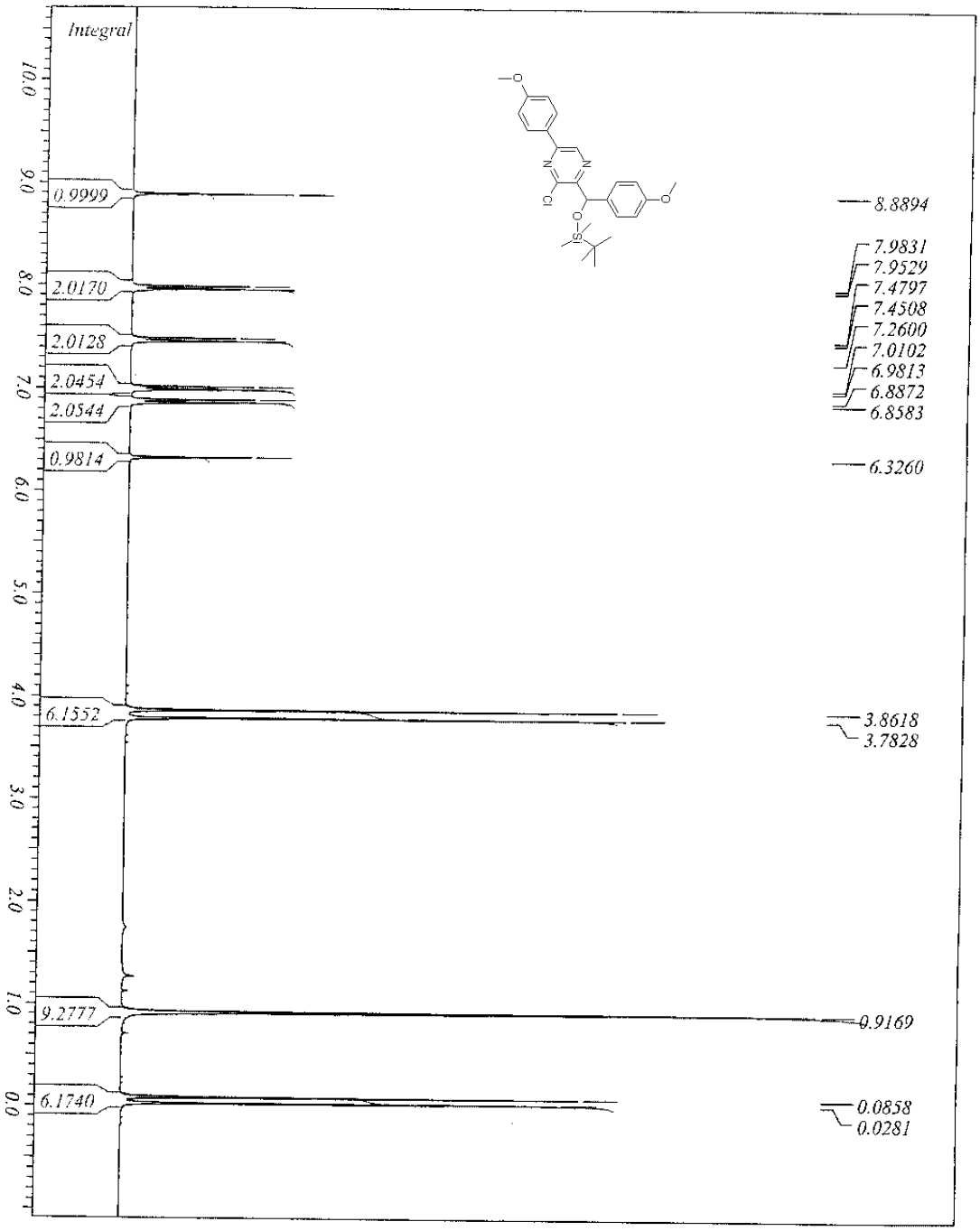
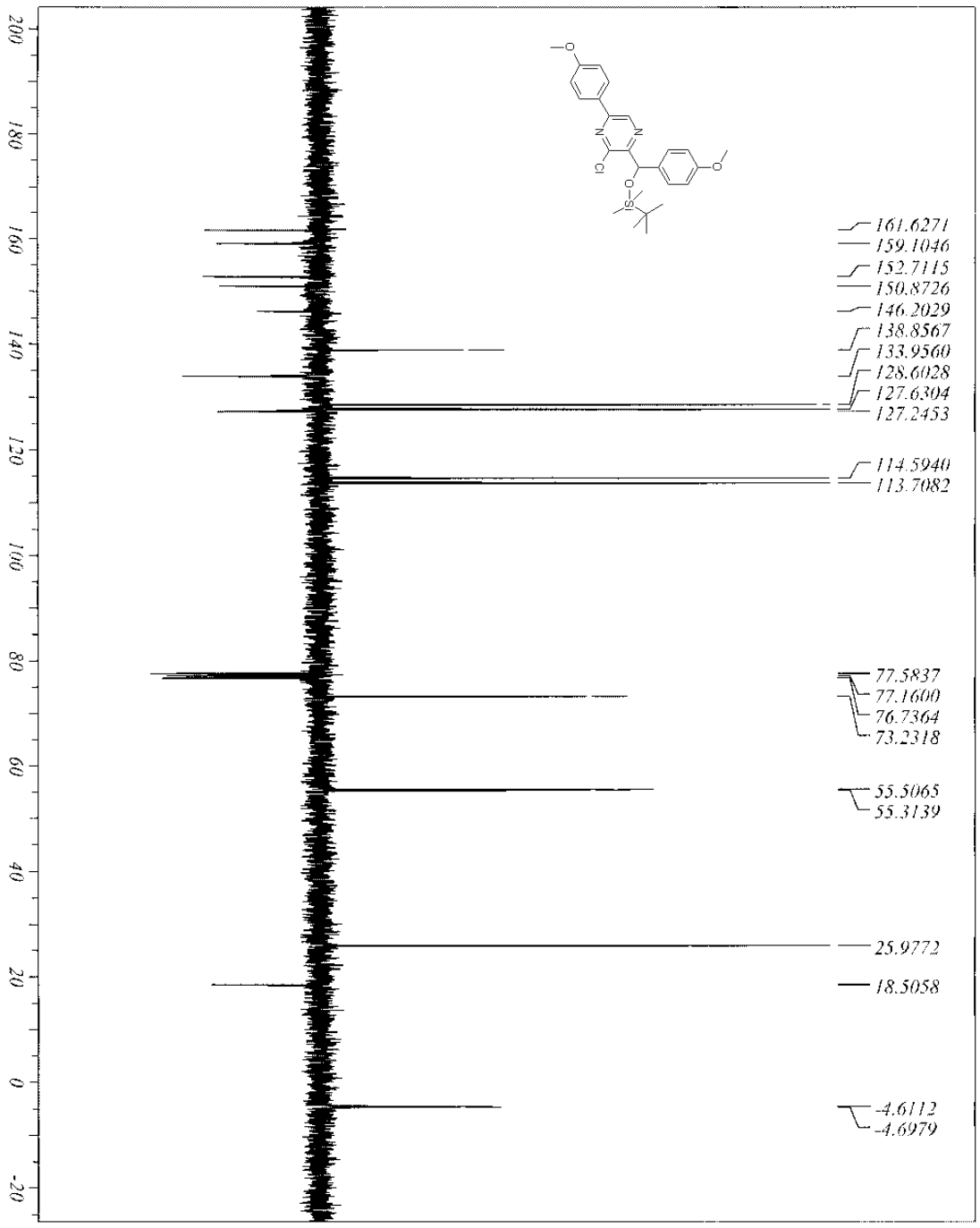
164.7580
162.1103
152.5689
147.3312
144.4524
139.1281
133.1009
129.3749
127.8633
126.5442
115.1061
114.7691
56.1437
55.8260
40.1130
39.8338
39.5546


Integral
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.9999
2.0170
2.0128
2.0454
2.0544
0.9814
6.1552
9.2777
6.1740
8.8894
7.9831
7.9529
7.4797
7.4508
7.2600
7.0102
6.9813
6.8872
6.8583
6.3260
3.8618
3.7828
0.9169
0.0858
0.0281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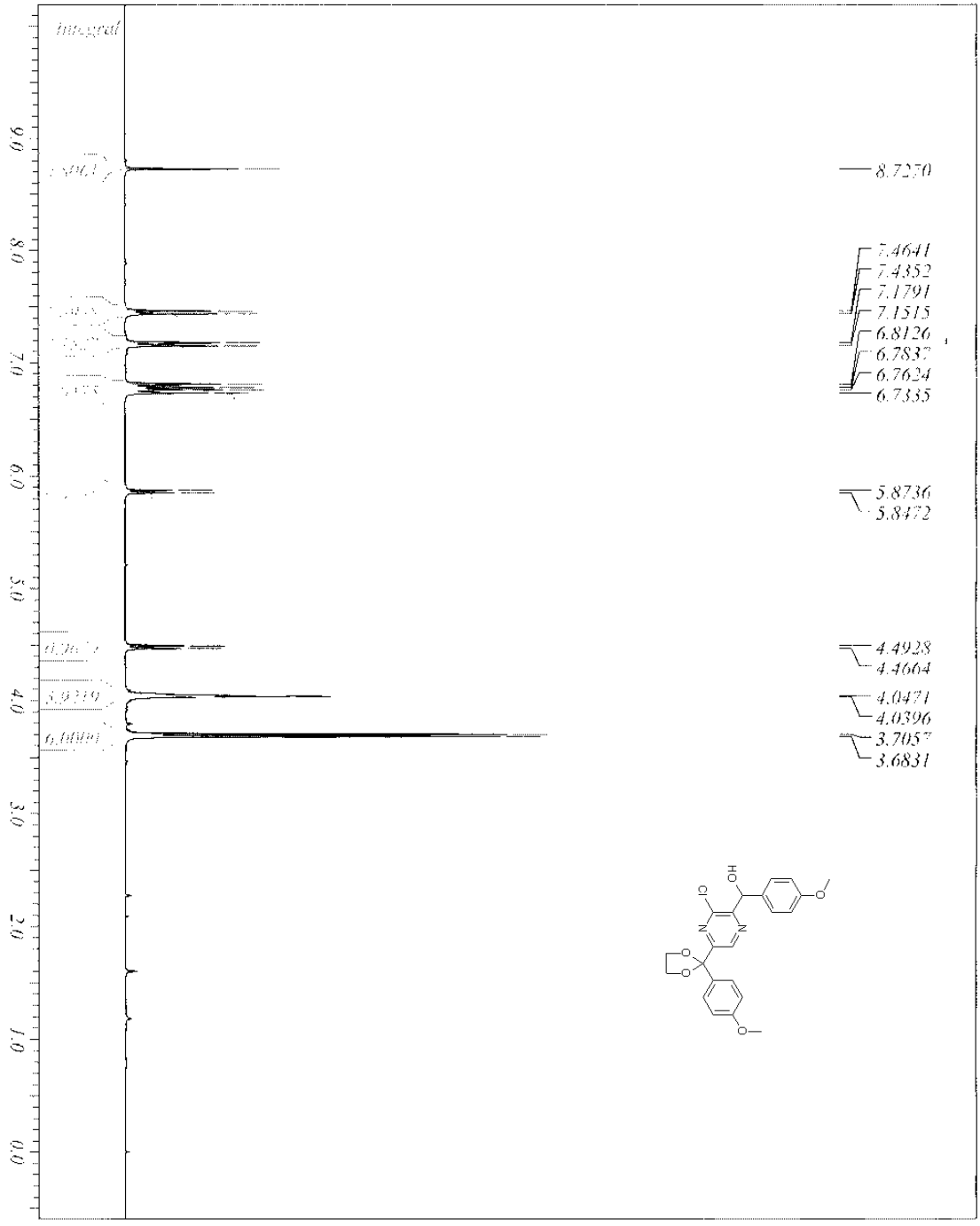
159.1046
152.7115
150.8726
146.2029
138.8567
133.9560
128.6028
127.6304
127.2453
114.5940
113.7082
77.5837
77.1600
76.7364
73.2318
55.5065
55.3139
25.9772
18.5058
-4.6112
-4.6979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7.4352
7.1791
7.1515
6.8126
6.7837
6.7624
6.7335
5.8736
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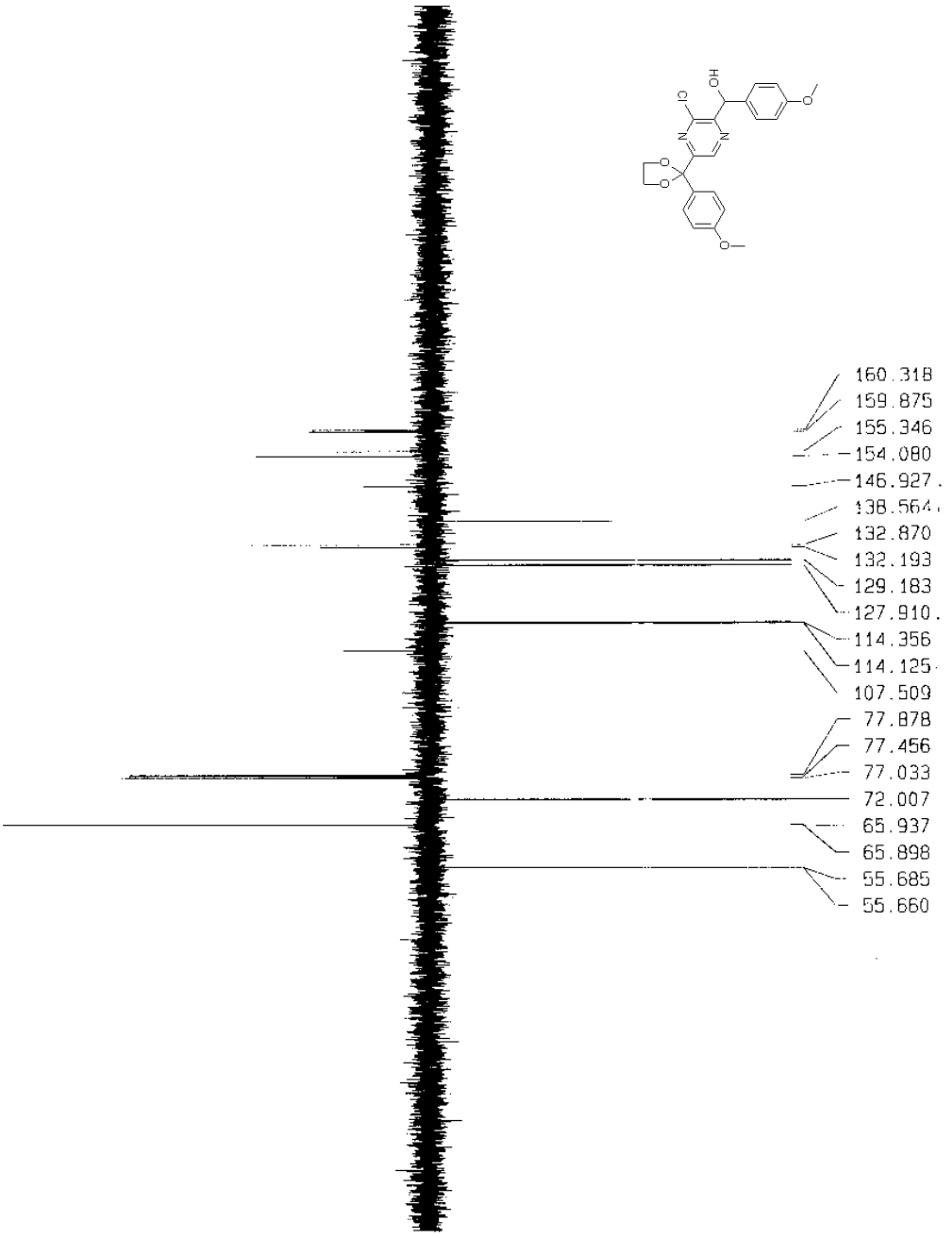
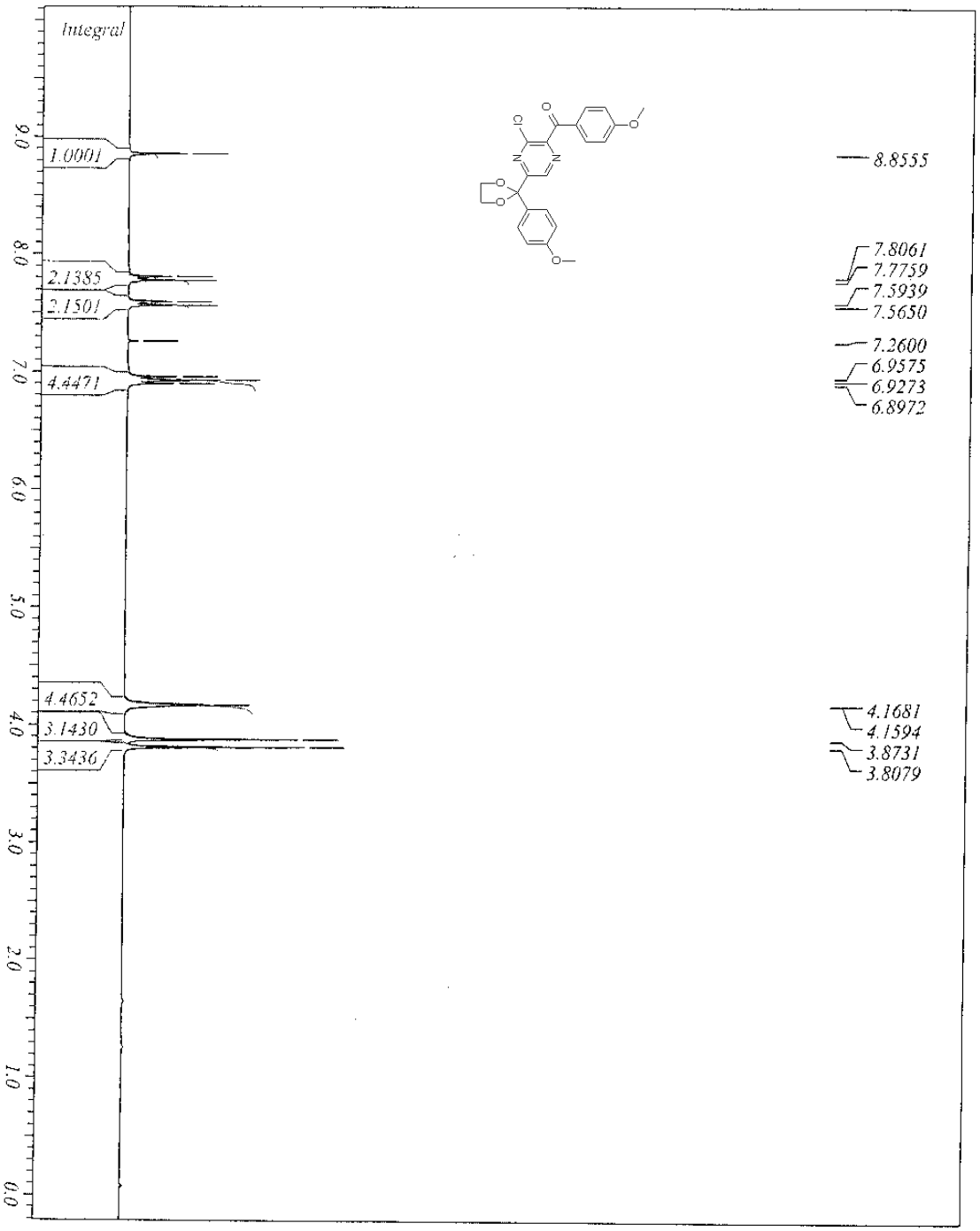
4.4664
4.0471
4.0396
3.7057
3.6831


160.318
159.875
155.346
154.080
146.927
138.564
132.870
132.193
129.183
127.910
114.356
114.125
107.509
77.878
77.456
77.033
72.007
65.937
65.898
55.685
55.660


Integral
1.0001
2.1385
2.1501
4.4471
4.4652
3.1430
3.3436
8.8555
7.8061
7.7759
7.5939
7.5650
7.2600
6.9575
6.9273
6.8972
4.1681
4.1594
3.8731
3.8079
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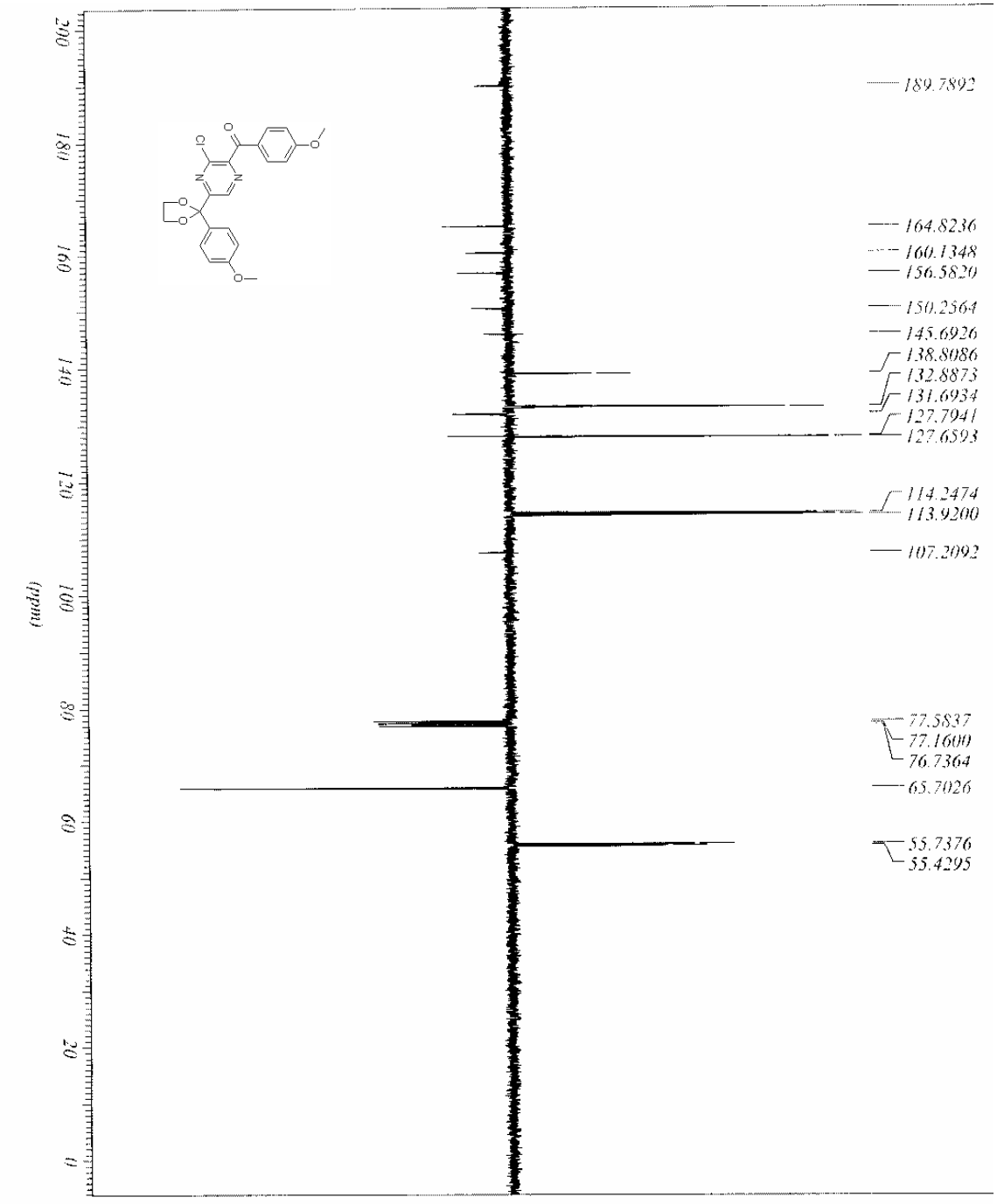
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


189.7892
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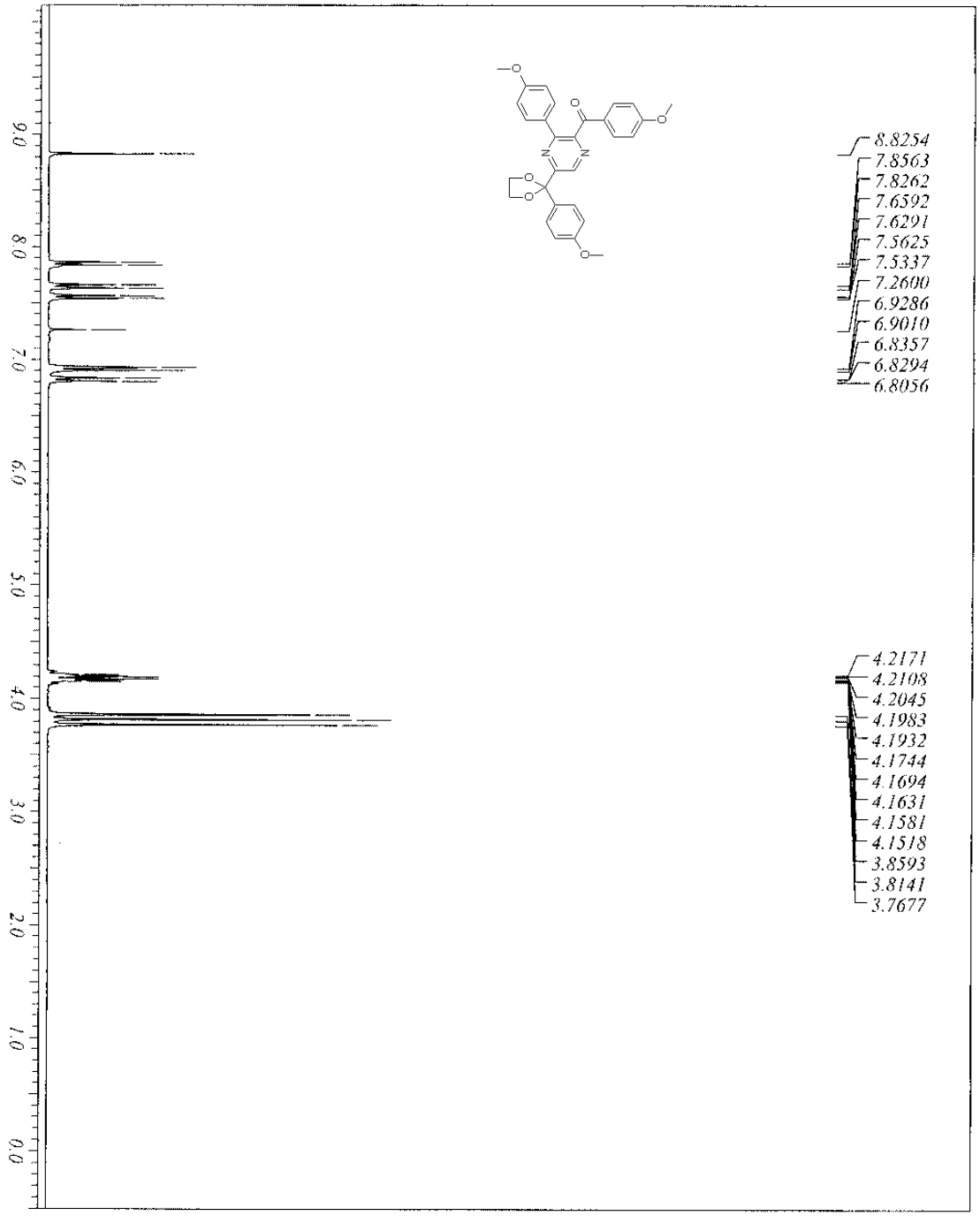
160.1348
156.5820
150.2564
145.6926
138.8086
132.8873
131.6934
127.7941
127.6593
114.2474
113.9200
107.2092
77.5837
77.1600
76.7364
65.7026
55.7376
55.4295
(ppm)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7.8262
7.6592
7.6291
7.5625
7.5337
7.2600
6.9286
6.9010
6.8357
6.8294
6.8056
4.2171
4.2108
4.2045
4.1983
4.1932
4.1744
4.1694
4.1631
4.1581
4.1518
3.8593
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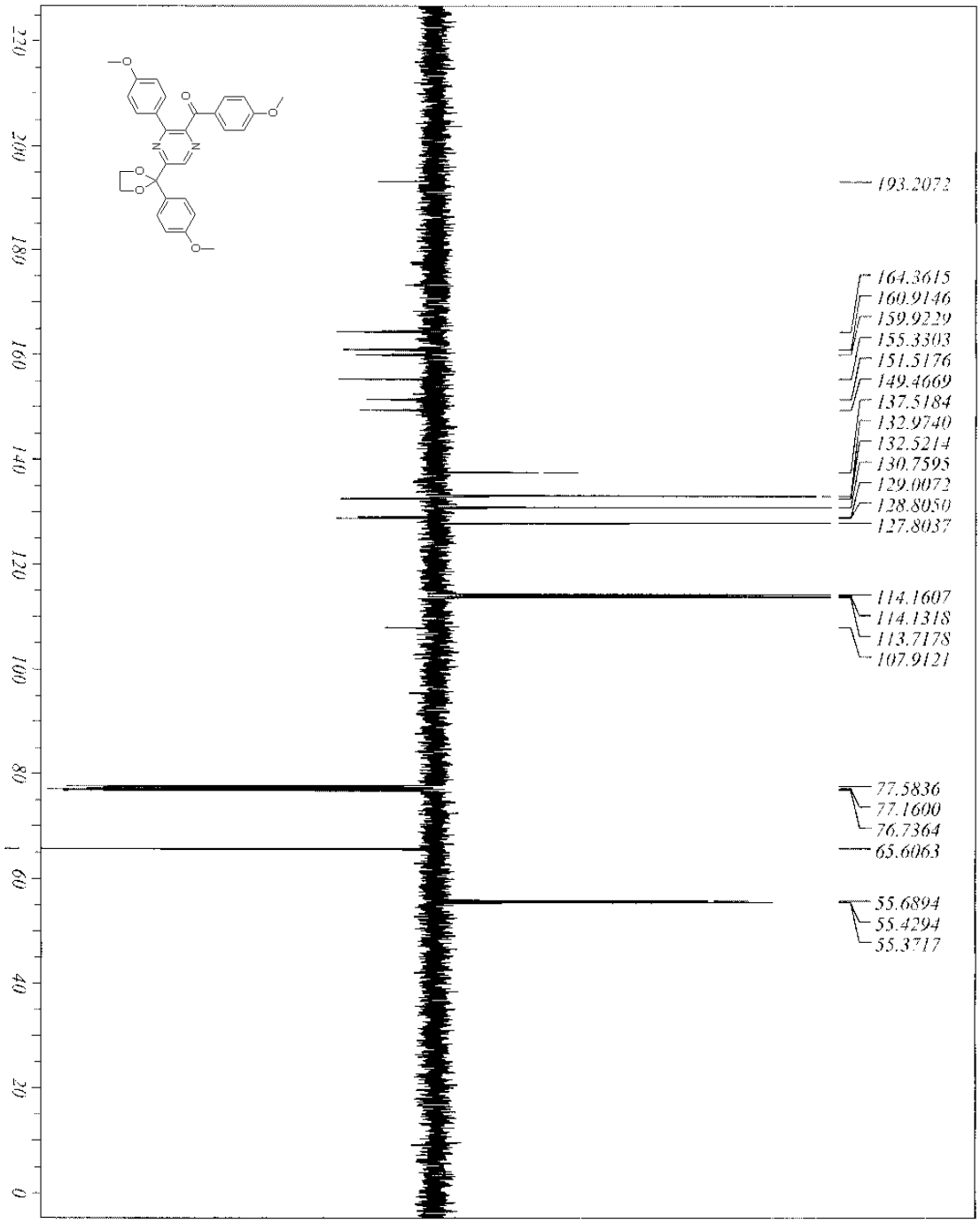
3.7677
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


193.2072
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160.9146
159.9229
155.3303
151.5176
149.4669
137.5184
132.9740
132.5214
130.7595
129.0072
128.8050
127.8037
114.1607
114.1318
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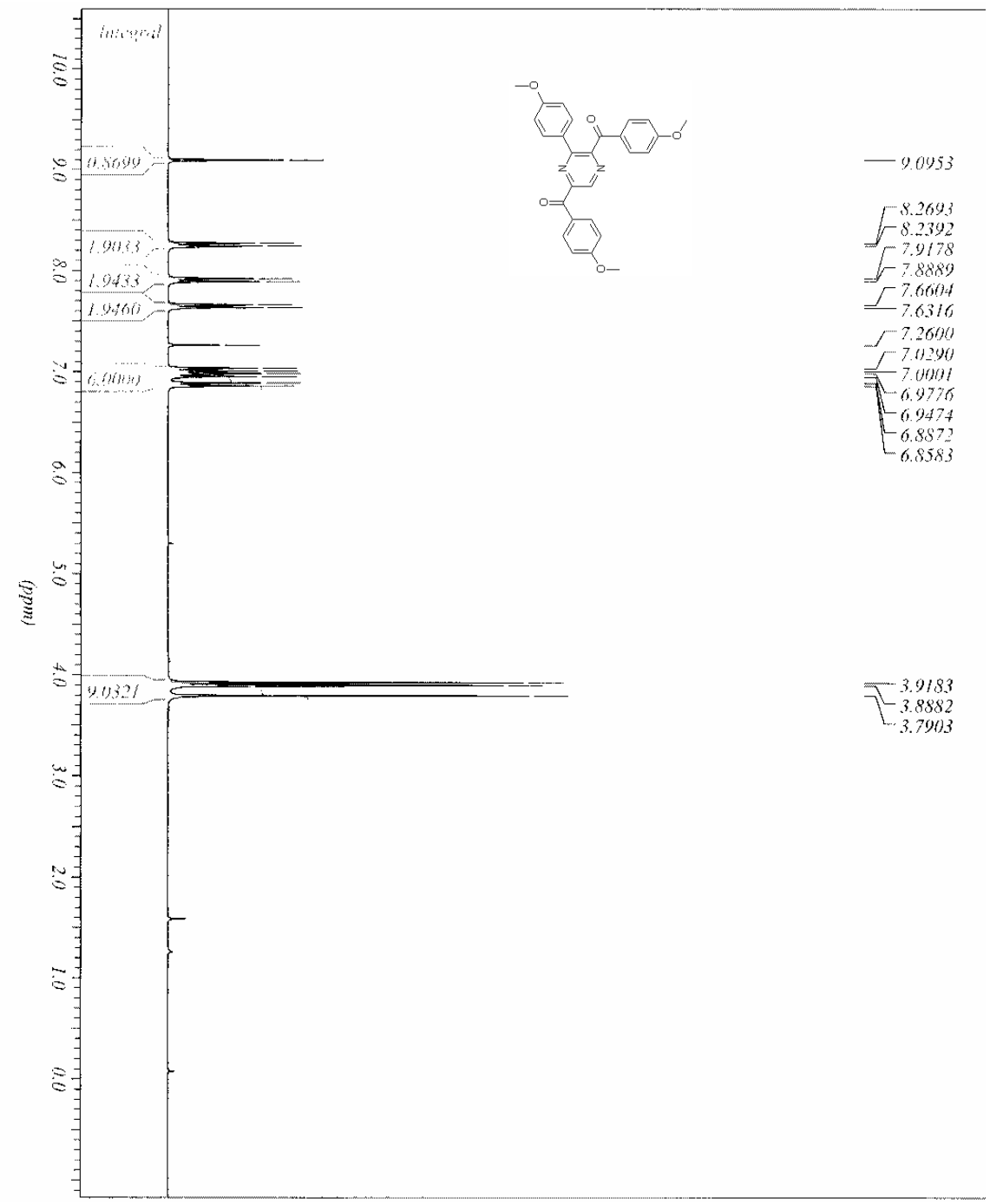
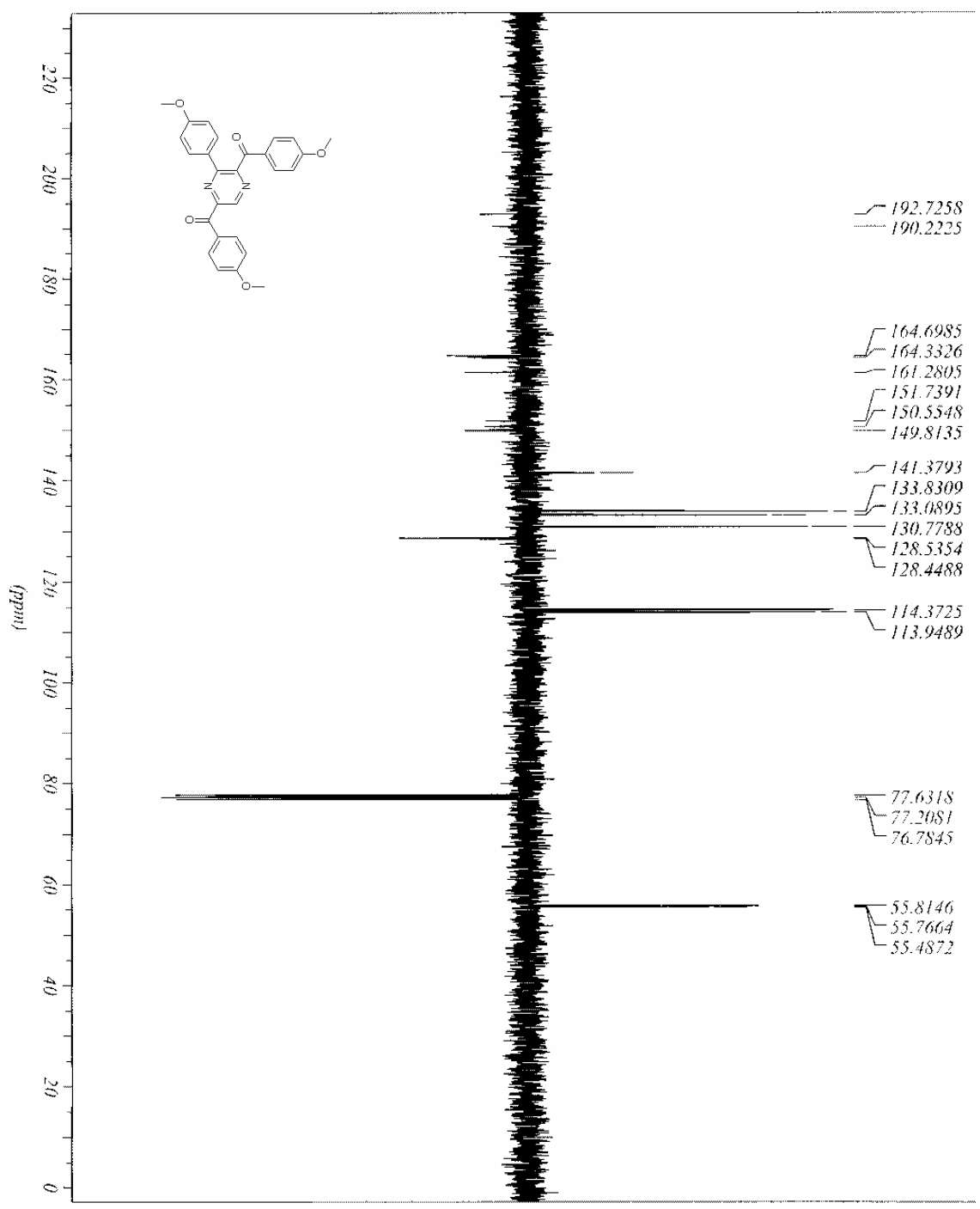
107.9121
77.5836
77.1600
76.7364
65.6063
55.6894
55.4294
55.3717


Integral
0.8699
1.9033
1.9433
1.9460
6.0000
9.0321
9.0953
8.2693
8.2392
7.9178
7.8889
7.6604
7.6316
7.2600
7.0290
7.0001
6.9776
6.9474
6.8872
6.8583
3.9183
3.8882
3.7903
(ppm)


192.7258
190.2225
164.6985
164.3326
161.2805
151.7391
150.5548
149.8135
141.3793
133.8309
133.0895
130.7788
128.5354
128.4488
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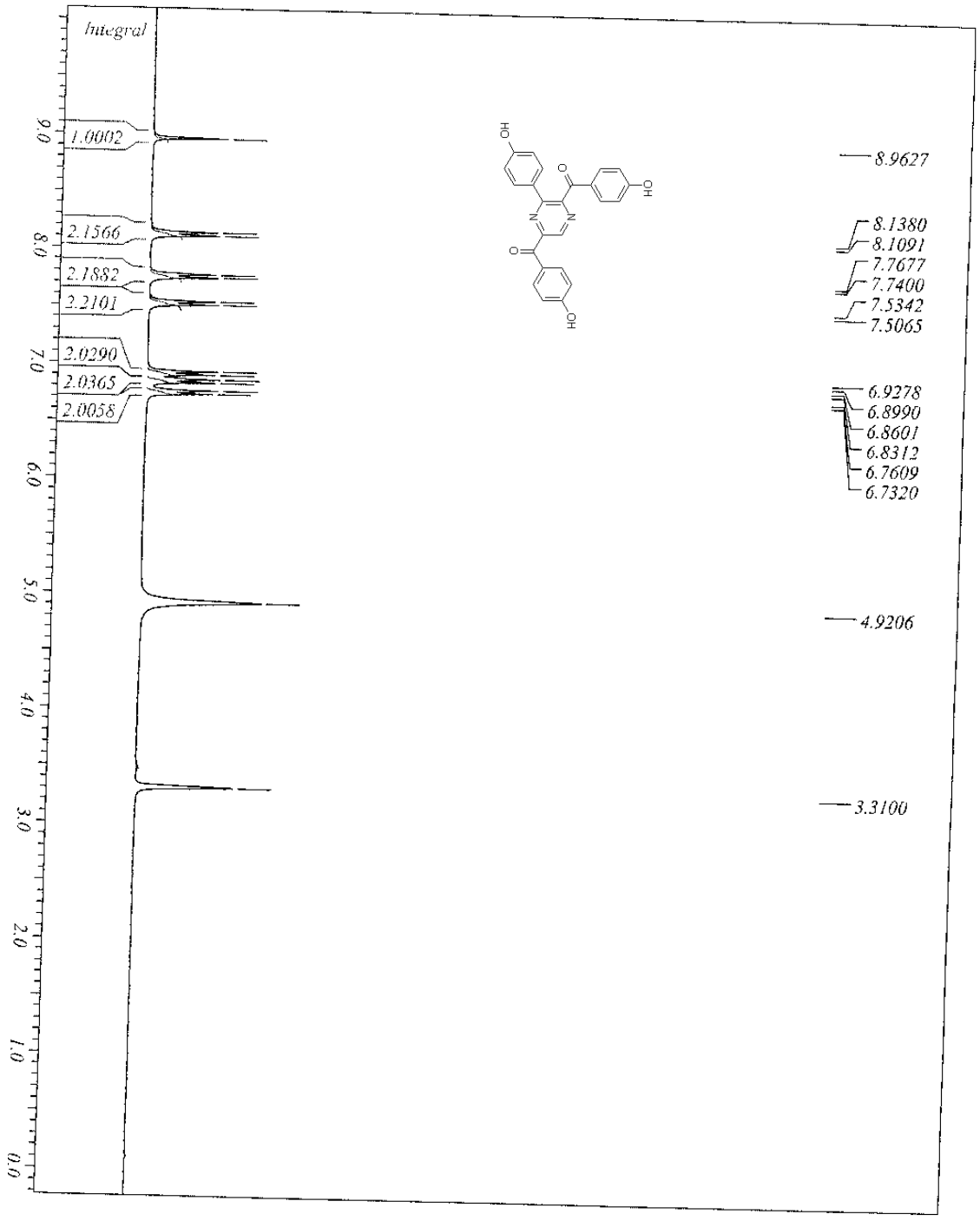
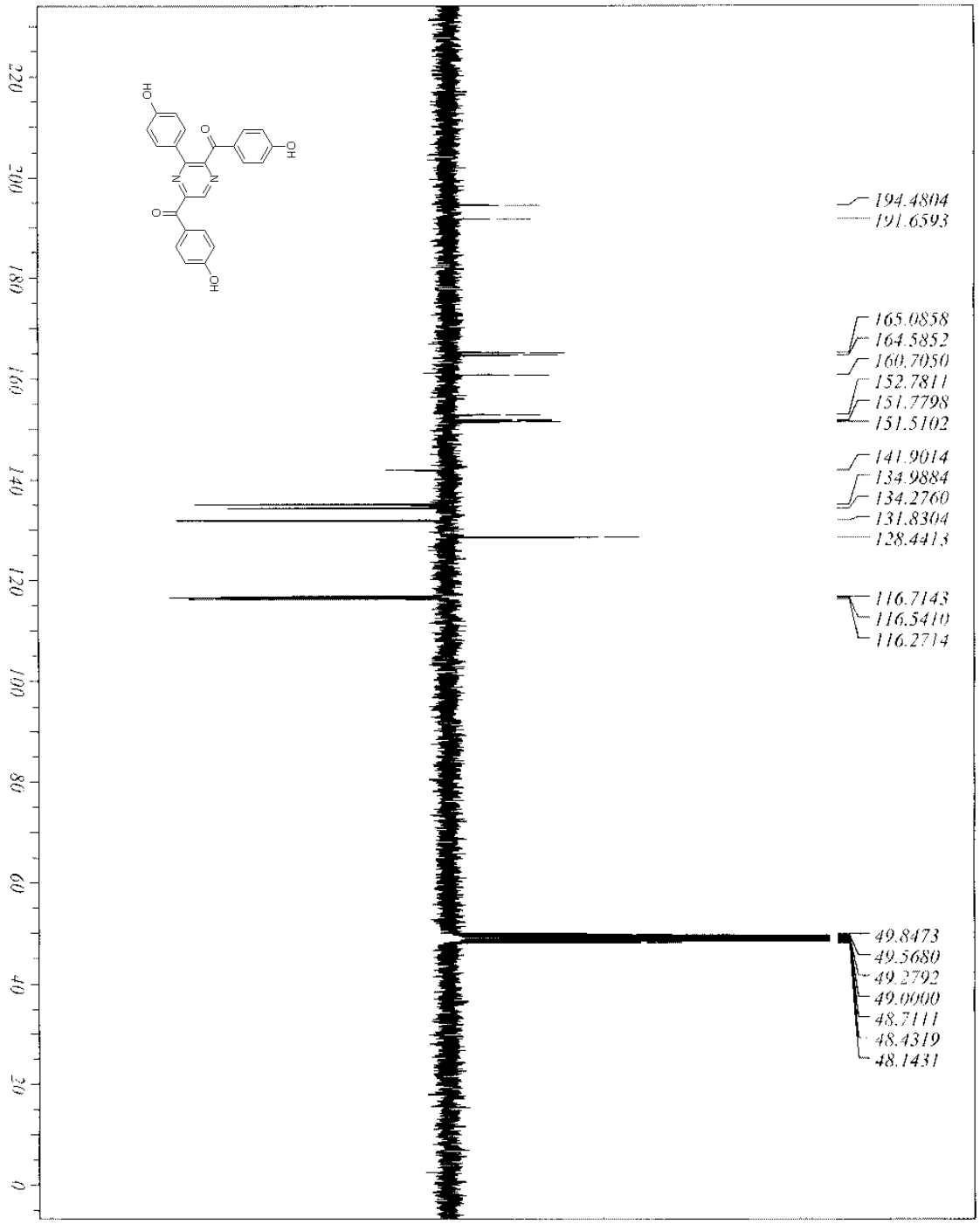
113.9489
77.6318
77.2081
76.7845
55.8146
55.7664
55.4872
(ppm)


Integral
1.0002
2.1566
2.1882
2.2101
2.0290
2.0365
2.0058
8.9627
8.1380
8.1091
7.7677
7.7400
7.5342
7.5065
6.9278
6.8990
6.8601
6.8312
6.7609
6.7320
4.9206
3.3100
OH
O
N
OH
O
N
OH


194.4804
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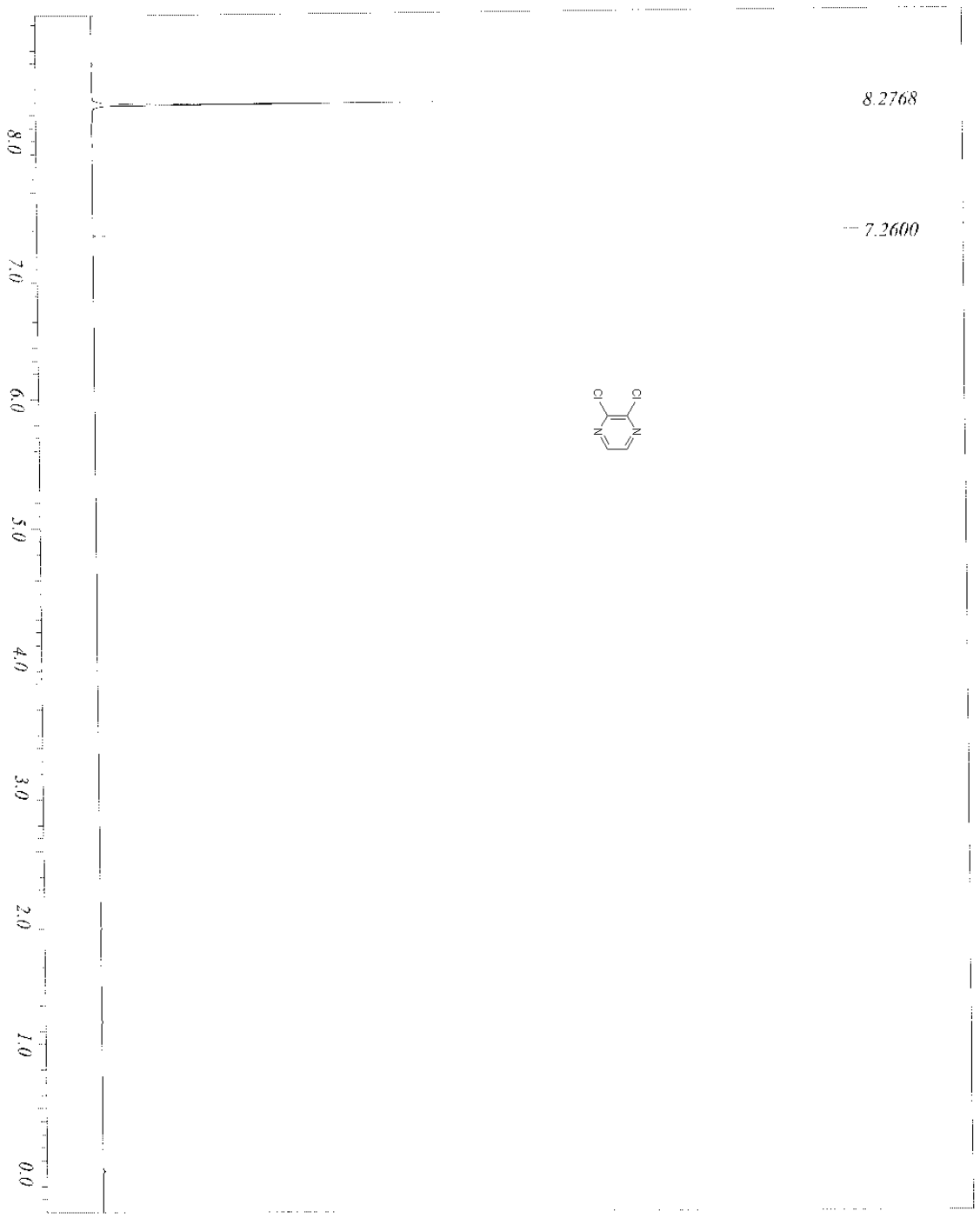
165.0858
164.5852
160.7050
152.7811
151.7798
151.5102
141.9014
134.9884
134.2760
131.8304
128.4413
116.7143
116.5410
116.2714
49.8473
49.5680
49.2792
49.0000
48.7111
48.4319
48.1431
220
200
180
160
140
120
100
80
60
40
20
0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7.2600
Cl
Cl
N
N
8.0
7.0
6.0
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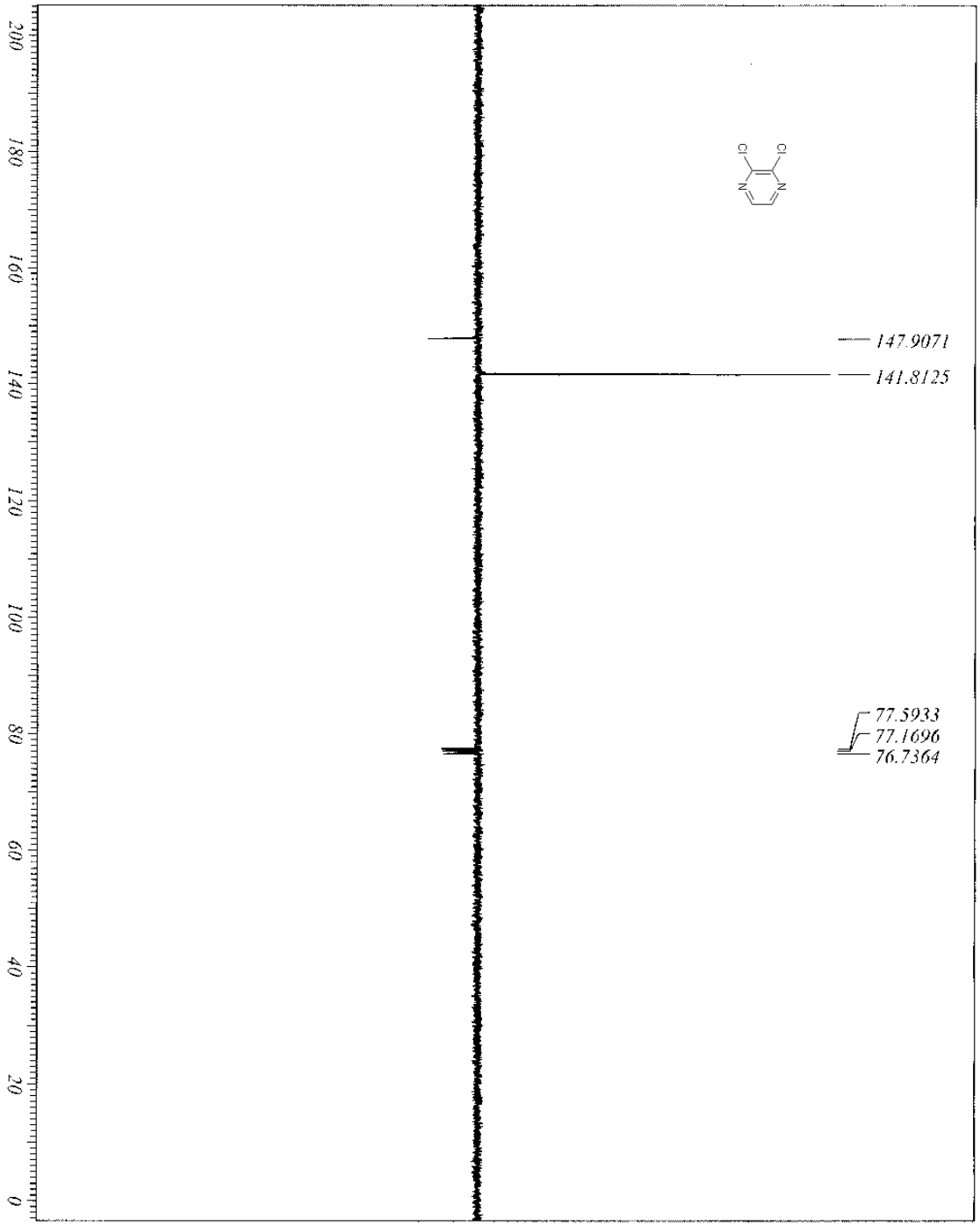
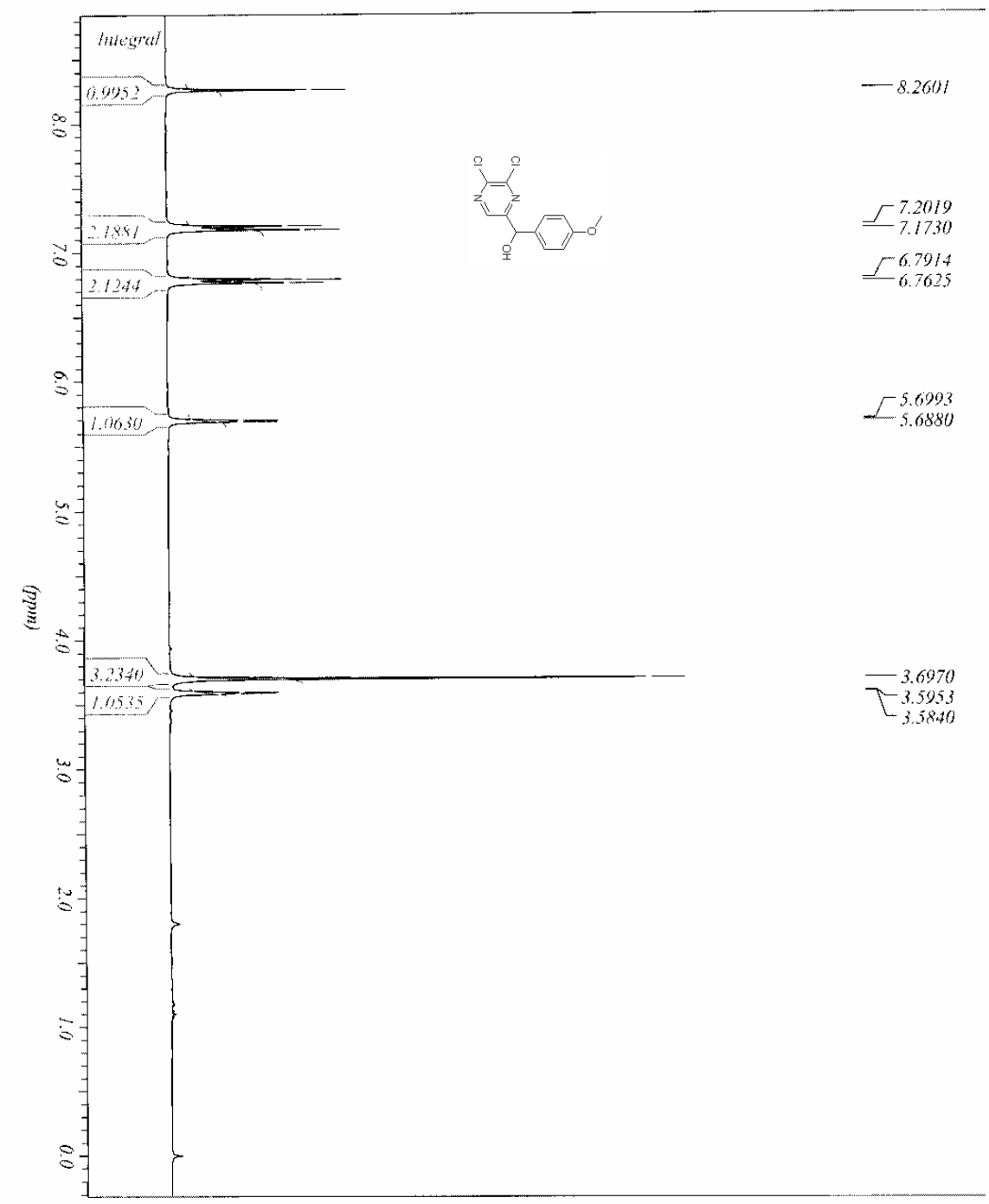
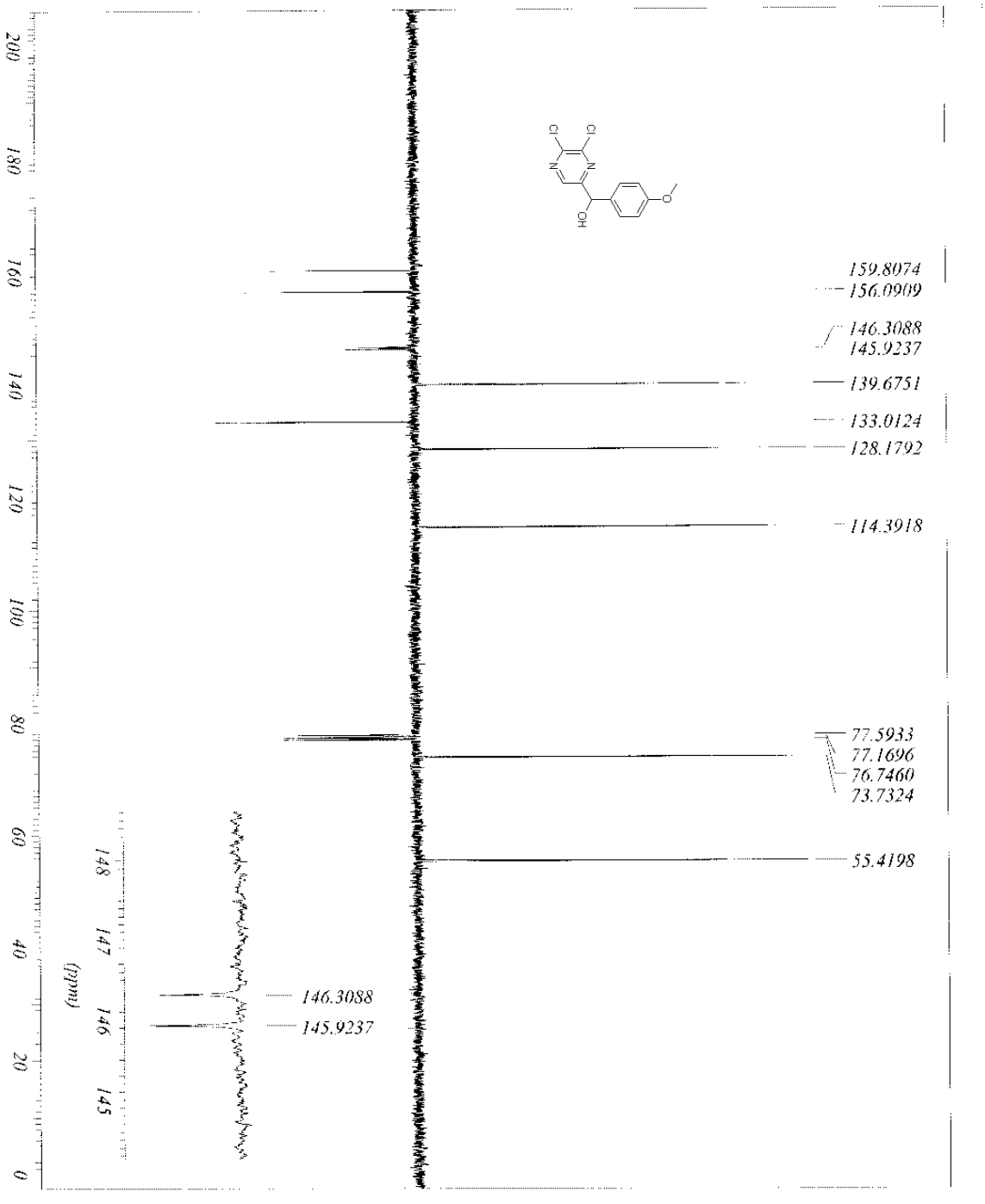
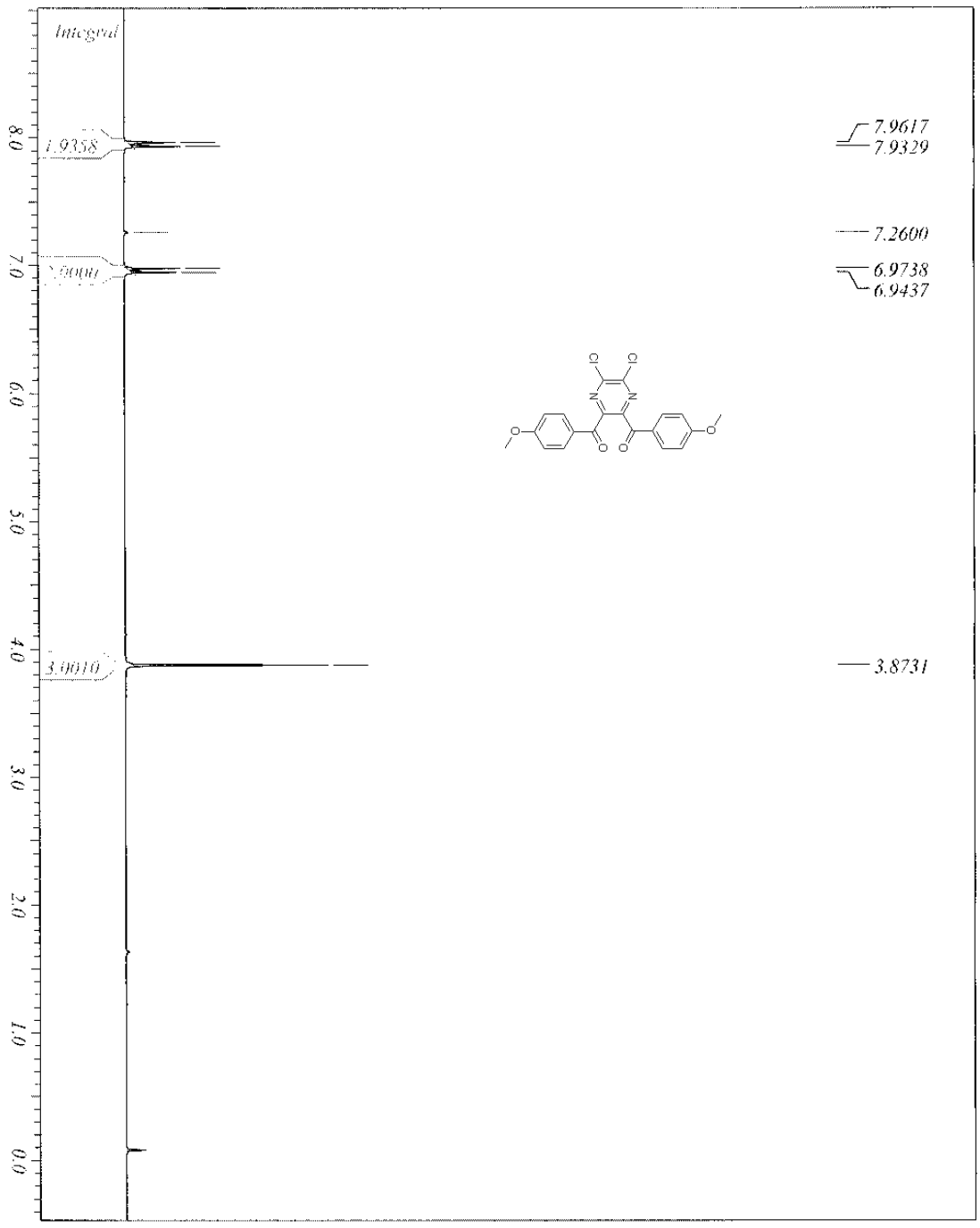
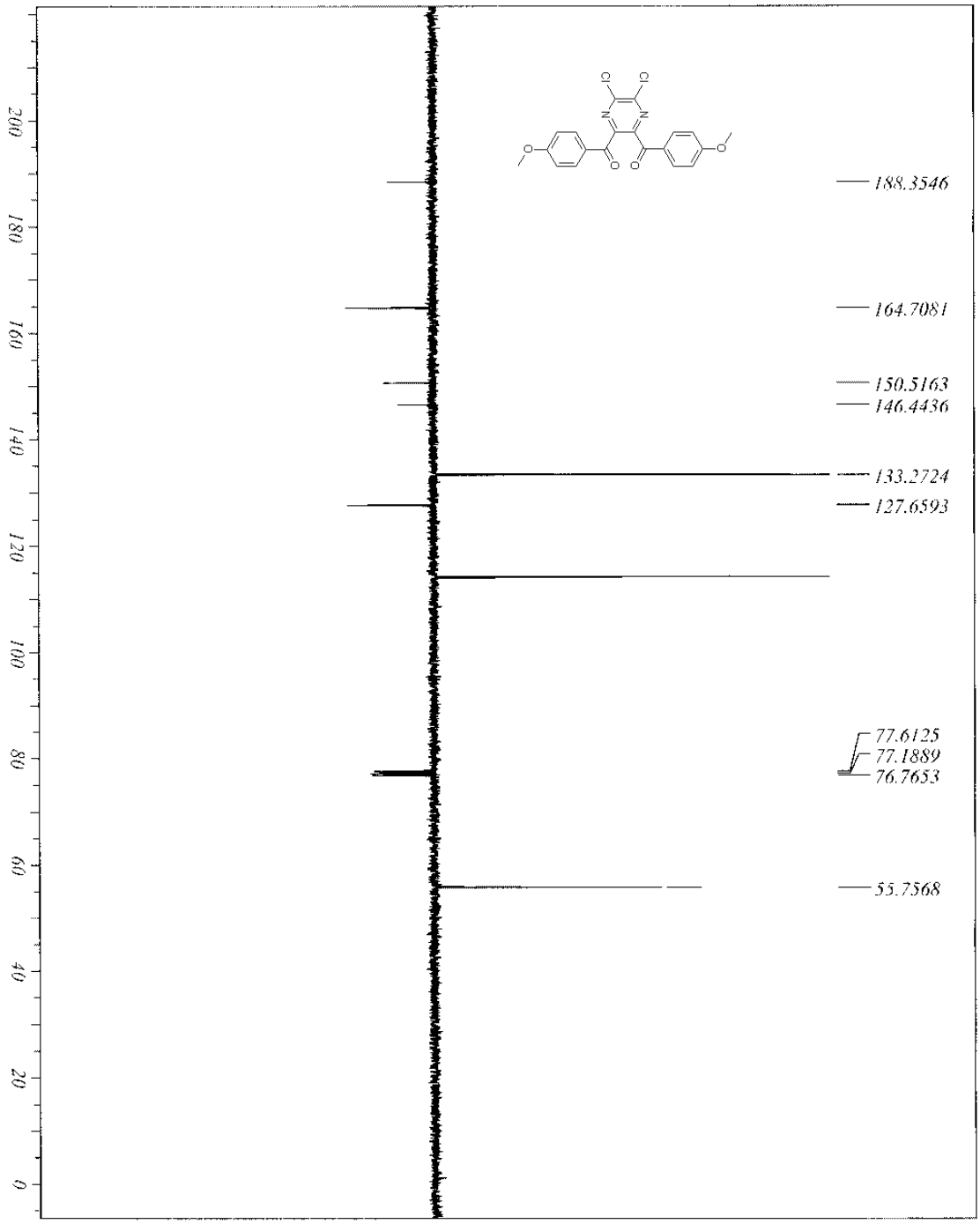
4.0
3.0
2.0
1.0
0.0


200
180
160
140
120
100
80
60
40
20
0
147.9071
141.8125
77.5933
77.1696
76.7364


Integral
0.9952
2.1881
2.1244
1.0630
3.2340
1.0535
8.2601
7.2019
7.1730
6.7914
6.7625
5.6993
5.6880
3.6970
3.5953
3.5840
(ppm)


159.8074
156.0909
146.3088
145.9237
139.6751
133.0124
128.1792
114.3918
77.5933
77.1696
76.7460
73.7324
55.4198
146.3088
145.9237
(ppm)


Integral
1.9358
2.0000
3.0010
7.9617
7.9329
7.2600
6.9738
6.9437
3.8731
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


188.3546
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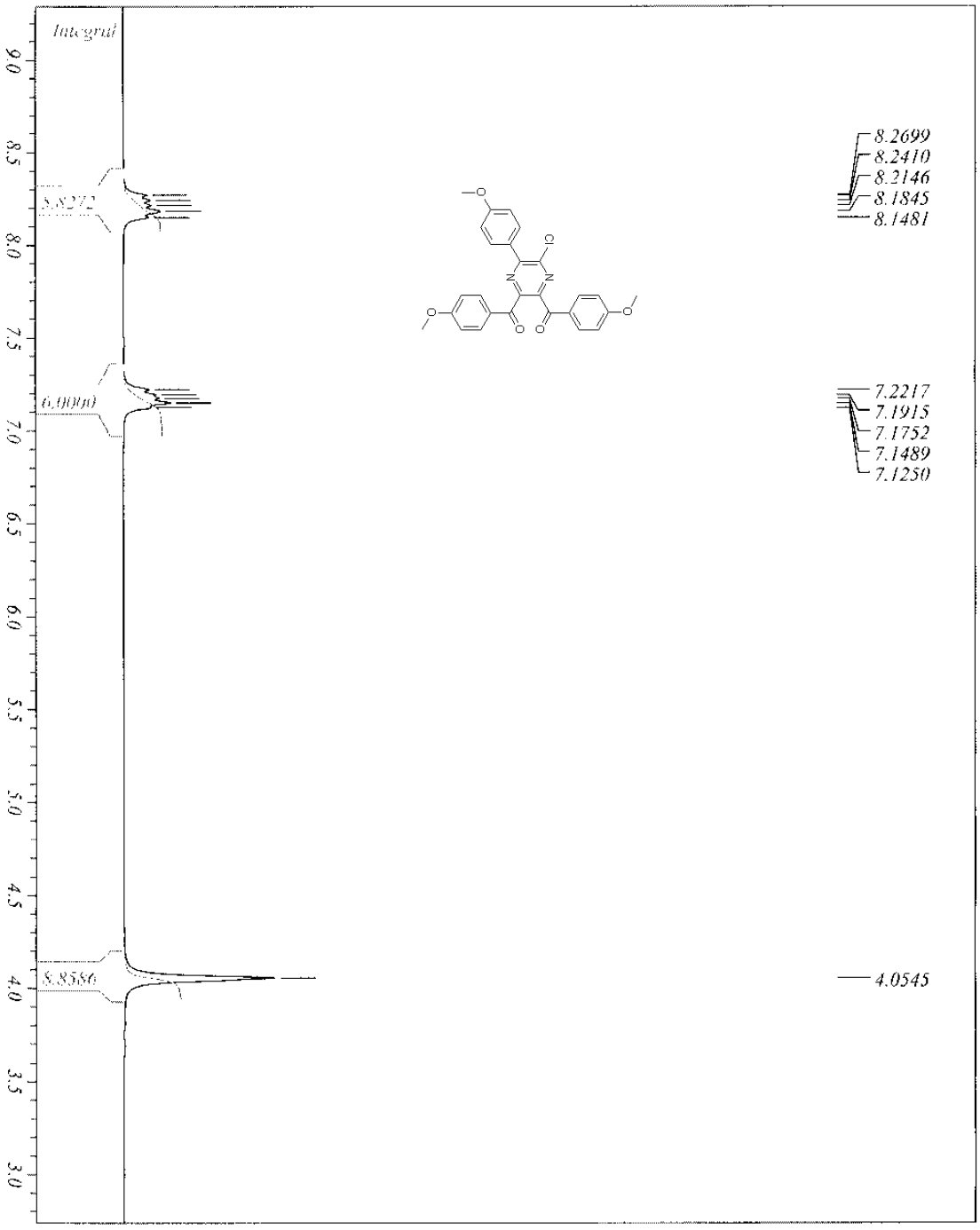
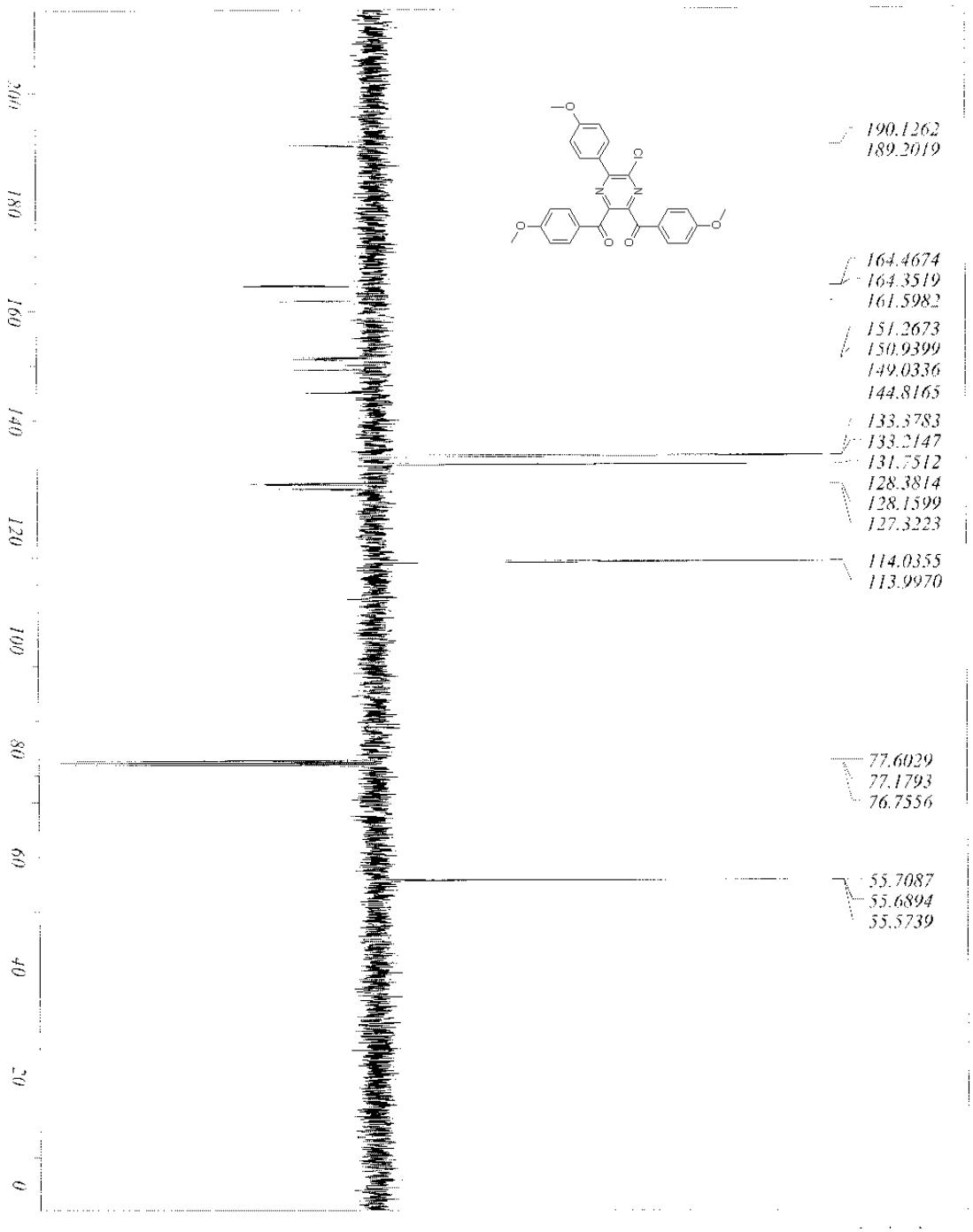
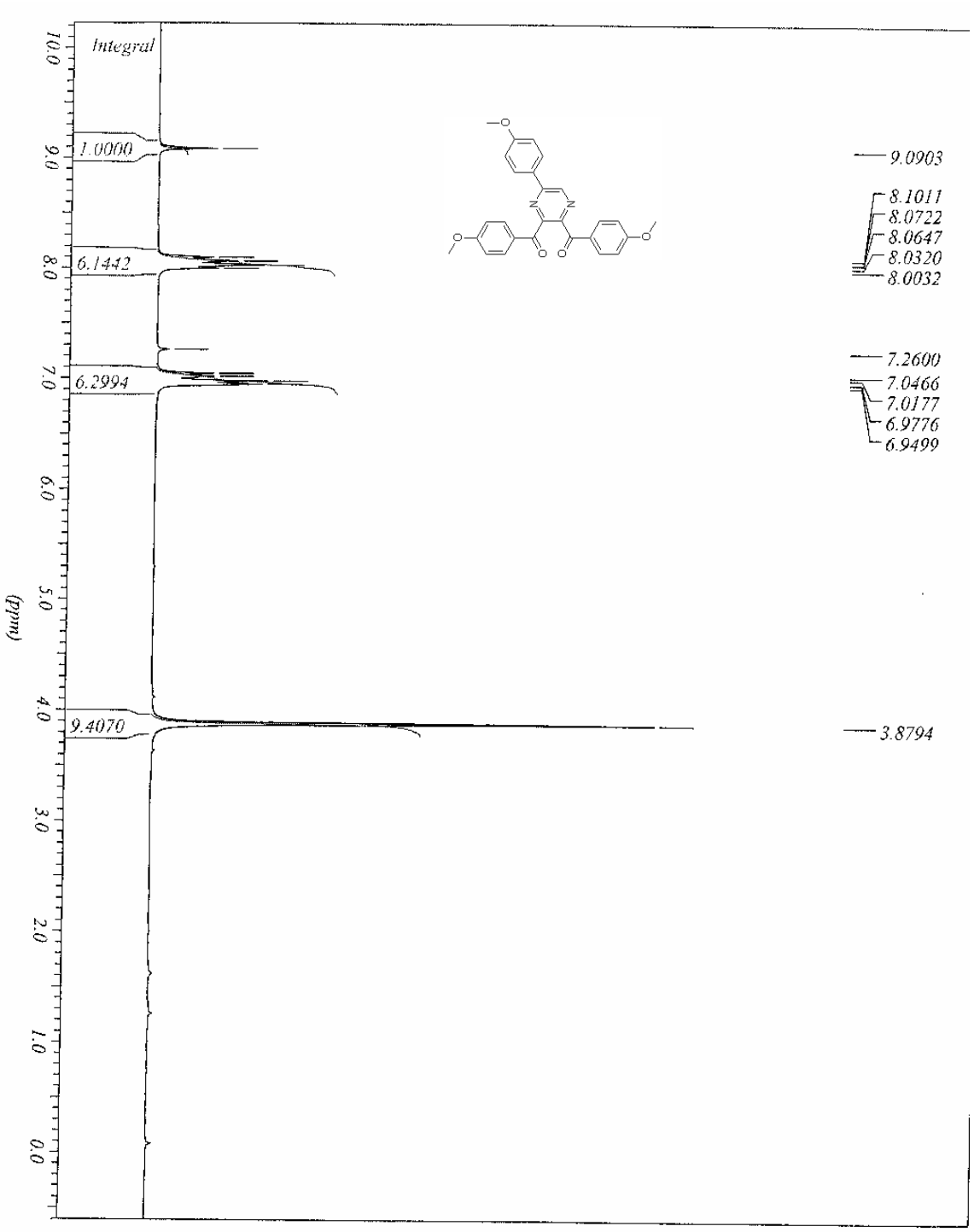
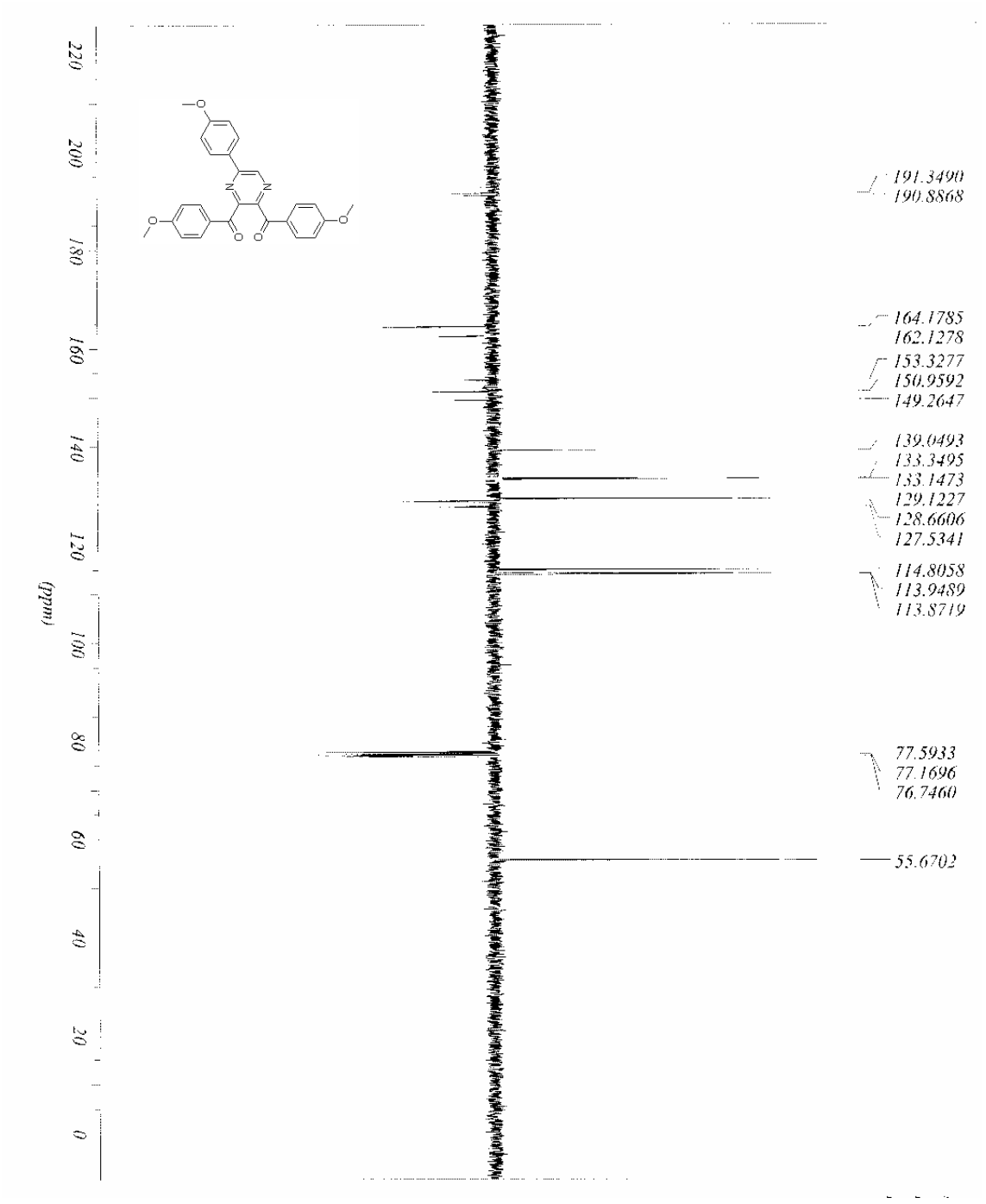
150.5163
146.4436
133.2724
127.6593
77.6125
77.1889
76.7653
55.7568


Integral
8.8272
6.0000
8.8586
8.2699
8.2410
8.2146
8.1845
8.1481
7.2217
7.1915
7.1752
7.1489
7.1250
4.0545
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


190.1262
189.2019
164.4674
164.3519
161.5982
151.2673
150.9399
149.0336
144.8165
133.3783
133.2147
131.7512
128.3814
128.1599
127.3223
114.0355
113.9970
77.6029
77.1793
76.7556
55.7087
55.6894
55.5739
200
180
160
140
120
100
80
60
40
20
0


Integral
1.0000
6.1442
6.2994
9.4070
9.0903
8.1011
8.0722
8.0647
8.0320
8.0032
7.2600
7.0466
7.0177
6.9776
6.9499
3.8794
(ppm)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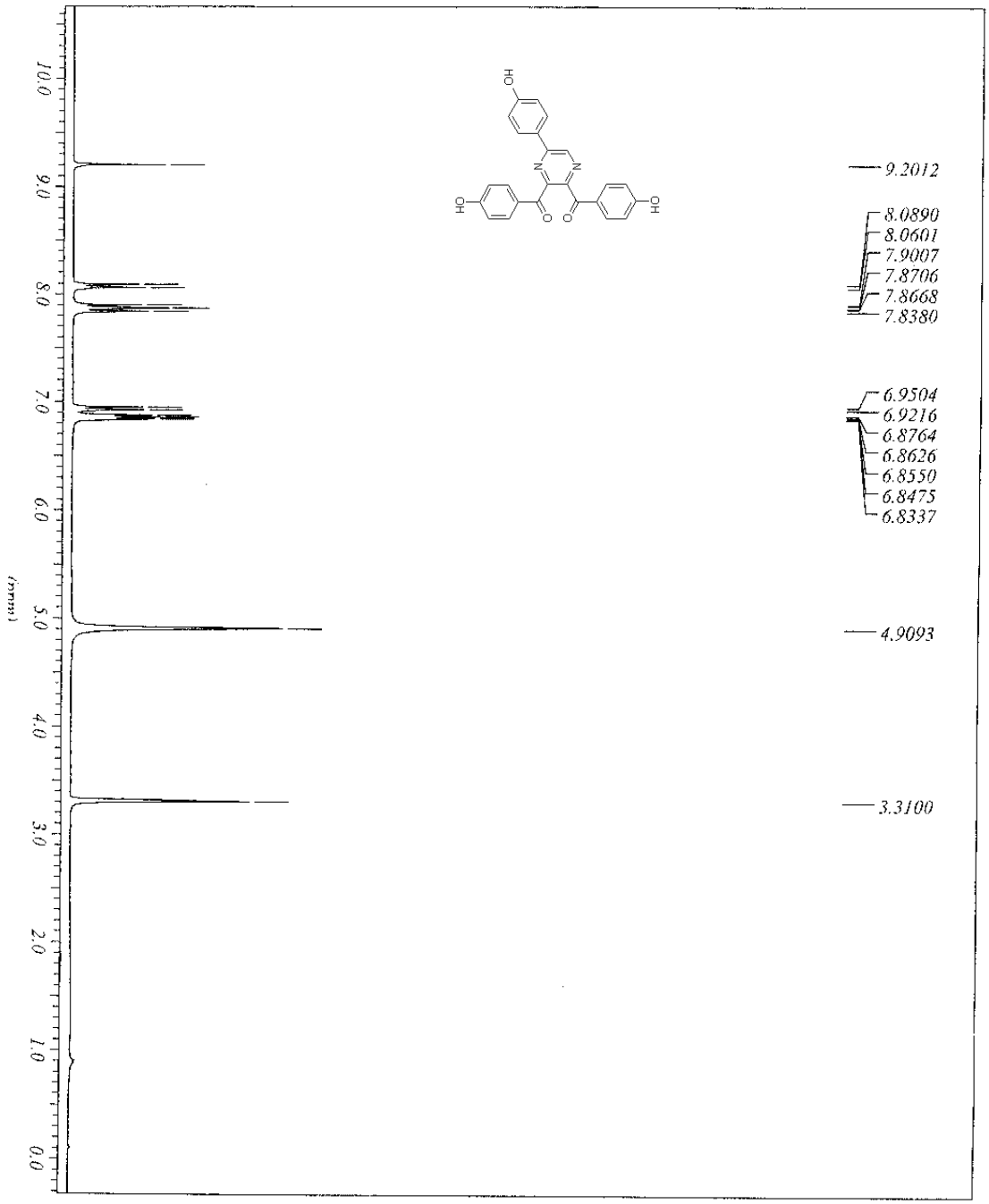
190.8868
164.1785
162.1278
153.3277
150.9592
149.2647
139.0493
133.3495
133.1473
129.1227
128.6606
127.5341
114.8058
113.9489
113.8719
77.5933
77.1696
76.7460
55.6702
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)


9.2012
8.0890
8.0601
7.9007
7.8706
7.8668
7.8380
6.9504
6.9216
6.8764
6.8626
6.8550
6.8475
6.8337
4.9093
3.3100
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9.0
8.0
7.0
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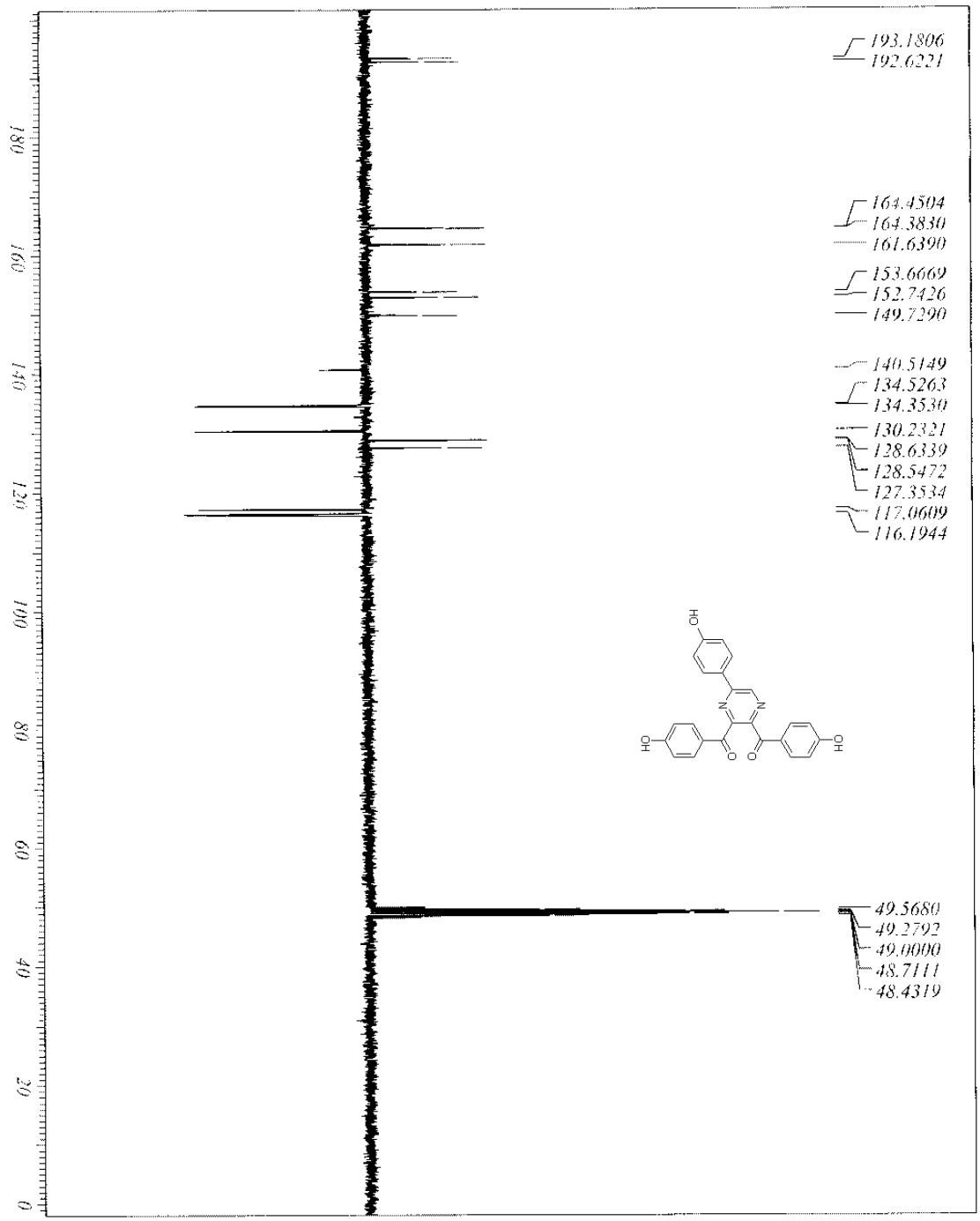
4.0
3.0
2.0
1.0
0.0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192.6221
164.4504
164.3830
161.6390
153.6669
152.7426
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140.5149
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134.3530
130.2321
128.6339
128.5472
127.3534
117.0609
116.1944
49.5680
49.2792
49.0000
48.7111
48.4319
0
20
40
60
80
100
120
140
160
180
OH
N
N
O
O
HO
HO

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