Electronic Supplementary Information

Concise Syntheses of N-Aryl-5,6,7-trimethoxyindoles as Antimitoic and Vascular Disrupting Agents: Application of the Copper-mediated Ullmann-type Arylation.

Hsueh-Yun Lee, Jang-Yang Chang, Ling-Yin Chang, Wen-Yang Lai, Mei-Jung Lai, Kuang-Hsing Shih, Ching-Chuan Kuo, Chi-Yen Chang and Jing-Ping Liou

Contents:

General. (A) **Chemistry.** Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with Bruker DRX-500 spectrometer (operating at 500 MHz), with chemical shift in parts per million (ppm, δ) downfield from TMS as an internal standard. High-resolution mass spectra (HRMS) were measured with a JEOL (JMS-700) electron impact (EI) mass spectrometer. Purity of the final compounds were determined using an Agilent 1100 series HPLC system using C-18 column (Agilent ZORBAX Eclipse XDB-C18 5 μm. 4.6 mm × 150 mm) and were found to be ≥ 95%. Flash column chromatography was done using silica gel (Merck Kieselgel 60, No. 9385, 230-400 mesh ASTM). All reactions were carried out under an atmosphere of dry nitrogen.

(B) **Biology. (a) Materials.** Regents for cell culture were obtained from Gibco-BRL Life Technologies (Gaitherburg, MD). Microtubule-associated protein (MAP)-rich tubulin was purchased from Cytoskeleton, Inc. (Denver, CO). [^{3}H]Colchicine (specific activity, 60-87 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, MA).

(b) Cell Growth Inhibitory Assay. Human oral epidermoid carcinoma KB cells, non small cell lung carcinoma H460 cells, colorectal carcinoma HT29 cells, and stomach carcinoma MKN45 cells were maintained in RPMI-1640 medium supplied with 5% fetal bovine serum. KB-VIN10 cells were maintained in growth medium supplemented with 10 nM vincristine, generated from vincristine-driven selection, and displayed overexpression of P-gp170/MDR. Cell in logarithmic phase were cultured at a density of 5000 cells/mL/well in a 24-well plate. KB-VIN10 cells were cultured in drug-free medium for 3 days prior to use. The cells were exposed to various concentrations of the test drugs for 72 h. The methylene blue dye assay was used to evaluate the effect of the test compounds on cell growth as described previously.[1] The IC_{50} value resulting from 50% inhibition of cell growth was calculated graphically as a comparison with the control. Compounds were examined in at least three independent experiments, and the values shown for these compounds are the mean and standard deviation of these data.

(c) Tubulin Polymerization in Vitro Assay.[2,3] Turbidimetric assays of microtubules were performed as described by Bollag et al.[4] In brief, microtubule-associated protein (MAP)-rich tubulin (from bovine brain, Cytoskeleton, Denver, C.O.) had been dissolved in reaction buffer (100 mM PIPES (pH 6.9), 2 mM $MgCl_2$, 1 mM GTP) in

preparing of 4 mg/mL tubulin solution. Tubulin solution (240 μg MAP-rich tubulin per well) was placed in 96-well microtiter plate in the presence of test compounds or 2% (v/v) DMSO as vehicle control. The increase in absorbance was measured at 350 nm in a PowerWave X Microplate Reader (BIO-TEK Instruments, Winooski, VT) at 37 °C and recorded every 30 s for 30 min. The area under the curve (AUC) used to determine the concentration that inhibited tubulin polymerization to 50% (IC_{50}). The AUC of the untreated control and 10μM of colchicine was set to 100% and 0% polymerization, respectively, and the IC_{50} was calculated by nonlinear regression in at least three experiments.

(d) Tubulin Competition-Binding Scintillation Proximity Assay.[5-7] This assay was performed in a 96-well plate. In brief, 0.08 (micro)M of [^{3}H]colchicine was mixed with the test compound and 0.5 (micro)g special long-chain biotin-labeled tubulin (0.5 μg) and then incubated in 100 μl of reaction buffer (80 mM PIPES, pH 6.8, 1 mM EGTA, 10% glycerol, 1 mM $MgCl_2$, and 1 mM GTP) for 2h at 37°C. Then eighty (micro) g of Streptavidin-labeled SPA beads were added to each reaction mixture. Then the radioactive counts were directly measured by a scintillation counter.

(e) Capillary Disruption assays.[8] Capillary disruption assays were carried out in a 96-well plate format using human umbilical vein endothelial cells (HUVECs) plated at 2×10^4 cells per well in 20% FBS M199 medium containing 20 ng/mL VEGF on a Matrigel layer (BD Biosciences). Capillaries were allowed to form over a 4-hour period before the addition of test compound or vehicle control. Images were acquired immediately following compound addition and 4 hours after exposure to test compound. Tube formation was quantified by measuring the network number of capillary structures manually by counting under microscope (original magnification 100X).

HPLC purity determination:

The percentage purity of compounds were determined by an Agilent 1100 series HPLC system using C18 column.

Elution conditions: Mobile phase A-Acetonitrile; Mobile phase B-Water containing 0.1% formic acid + 10 mmol NH_4OAc. The flow-rate was 0.2 ml/min and the injection volume was 5 µl. The system operated at 25 °C. Peaks were detected at 210 nm.

Table 1. Elution condition

Time (min)	Mobile Phase A (ratio)	Mobile Phase B (ratio)
0	10	90
45	90	10
50	10	90
60	10	90

Table 2. Purity of compounds **6-12**

C18 column: Agilent ZORBAX Eclipse XDB-C18 5µm. 4.6 mm × 150 mm column

Compounds	Retention time (min)	% Purity
6	30.63	99.28
7	39.29	99.76
8	39.62	95.12
9	32.64	100.00
10	32.19	99.56
11	42.7	100.00
12	38.67	99.02

HPLC spectrum of compound 6

D-2000: Samples Series: 1243 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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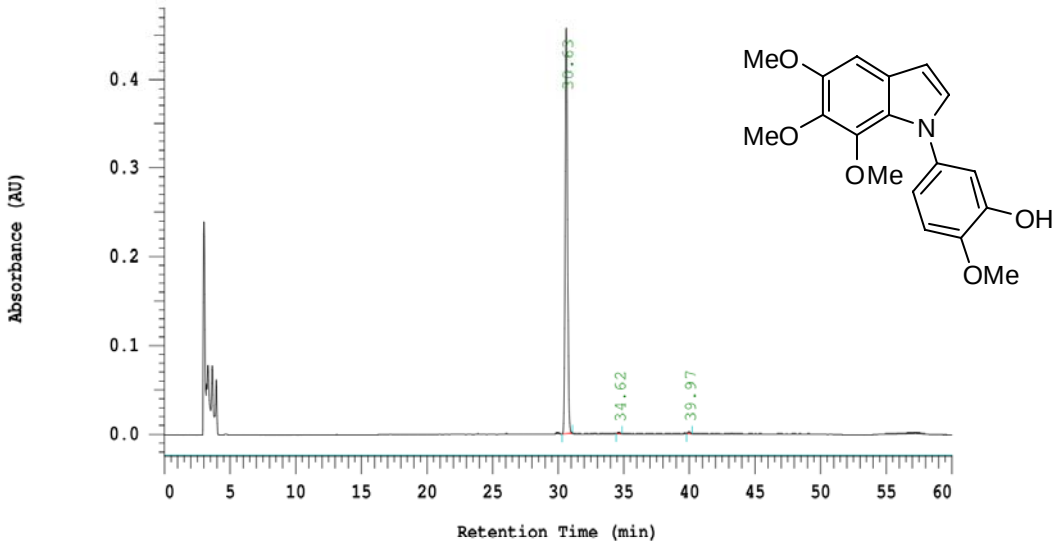
Data Path: C:\Win32app\D2000HSM\samples\DATA\1243\
Processing Method: Purity 2007/12/24
Sample Name: MPTOB330-50 Vial Number: 8
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	30.63	2709622	228648	99.282
2	34.62	8139	796	0.298
3	39.97	11460	1033	0.420
		2729221	230477	100.000

Peak rejection level: 0

HPLC spectrum of compound 7

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Hitachi D-2000 Elite HPLC System Manager Report

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Processing Method: Purity 2007/12/24
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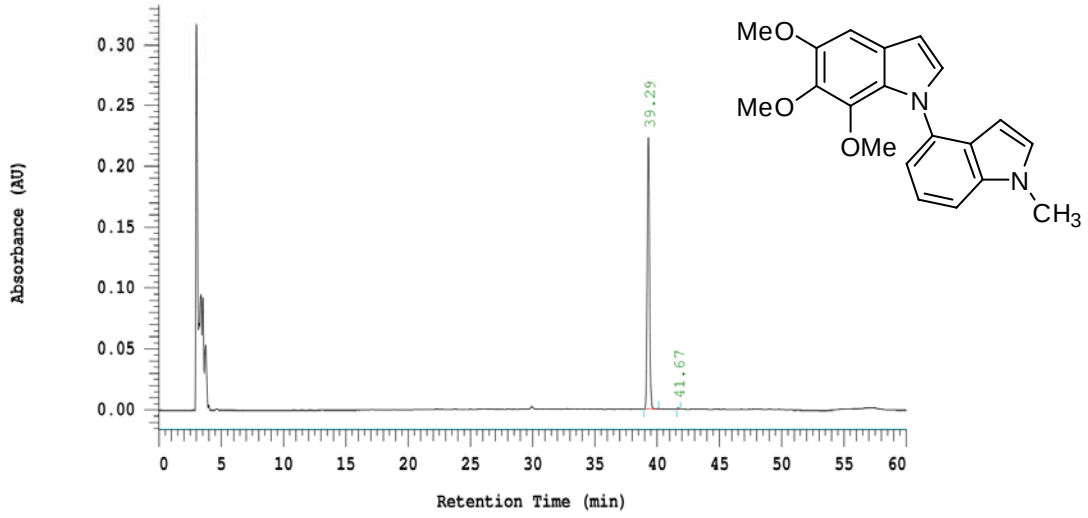
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



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Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	39.29	1370388	111186	99.761
2	41.67	3278	366	0.239
		1373666	111552	100.000

Peak rejection level: 0

HPLC spectrum of compound 8

D-2000: Samples Series: 1244 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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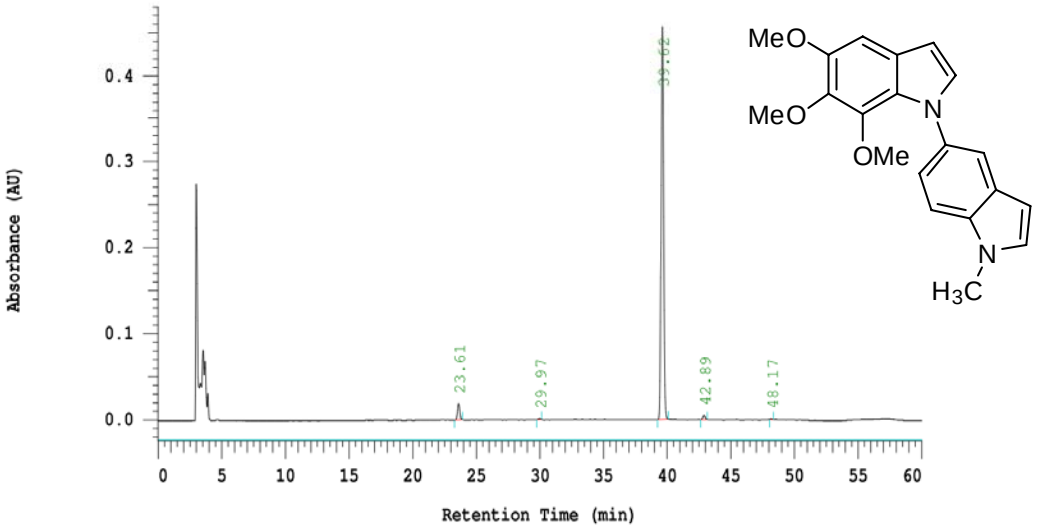
Processing Method: Purity 2007/12/24
Sample Name: MPTOB318-50 Vial Number: 14
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	23.61	110111	9377	3.623
2	29.97	6009	537	0.198
3	39.62	2890839	228179	95.128
4	42.89	28473	2269	0.937
5	48.17	3453	350	0.114
		3038885	240712	100.000

Peak rejection level: 0

HPLC spectrum of compound 9

D-2000: Samples Series: 1244 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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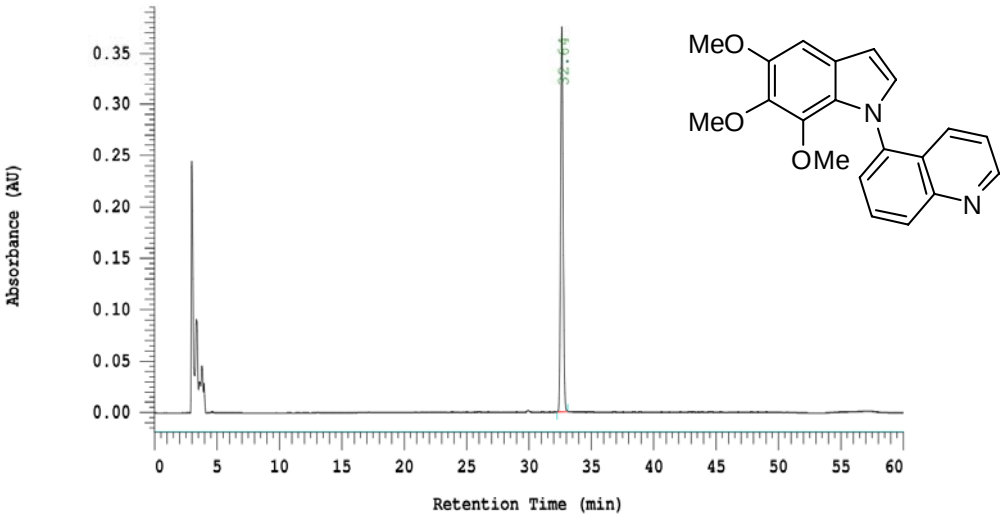
Processing Method: Purity 2007/12/24

Sample Name: MPTOB331-50 Vial Number: 22
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	32.64	2428527	187469	100.000
		2428527	187469	100.000

Peak rejection level: 0

HPLC spectrum of compound 10

D-2000: Samples Series: 1235 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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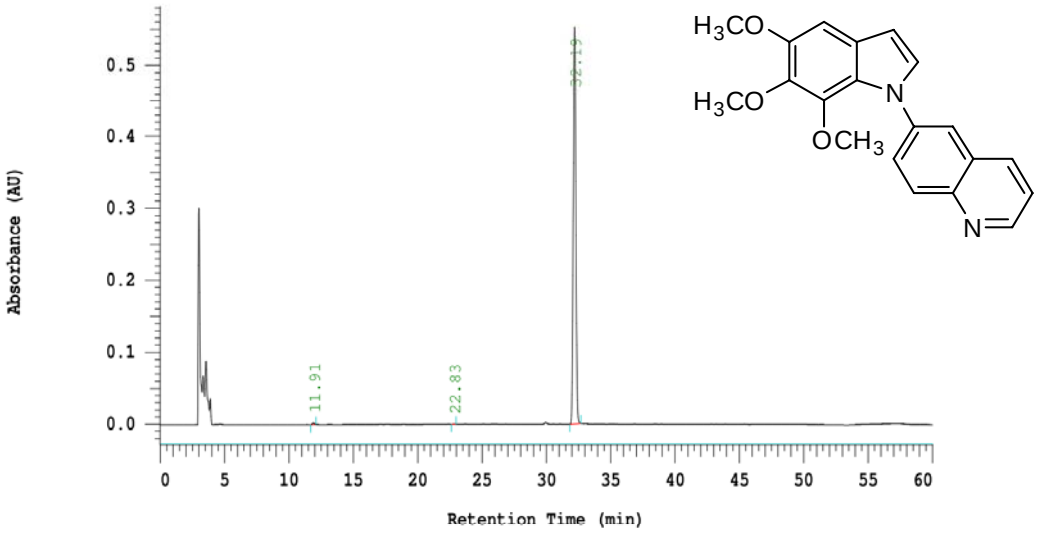
Data Path: C:\Win32app\D2000HSM\samples\DATA\1235\
Processing Method: Purity 2007/12/24
Sample Name: MPTOB301-50 Vial Number: 18
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	11.91	12616	1308	0.355
2	22.83	2944	273	0.083
3	32.19	3536448	276303	99.562
		3552008	277884	100.000

Peak rejection level: 0

HPLC spectrum of compound 11

D-2000: Samples Series: 1235 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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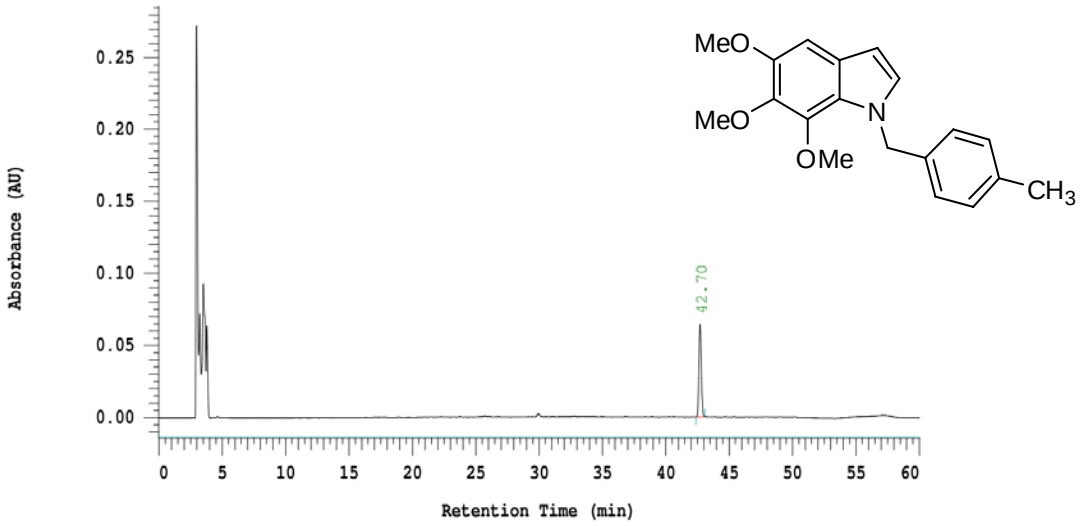
Processing Method: Purity 2007/12/24
Sample Name: MPTOB300-50 Vial Number: 20
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	42.70	408701	32222	100.000
		408701	32222	100.000

Peak rejection level: 0

HPLC spectrum of compound 12

D-2000: Samples Series: 1244 Report Name: modified System: Sys 1

Hitachi D-2000 Elite HPLC System Manager Report

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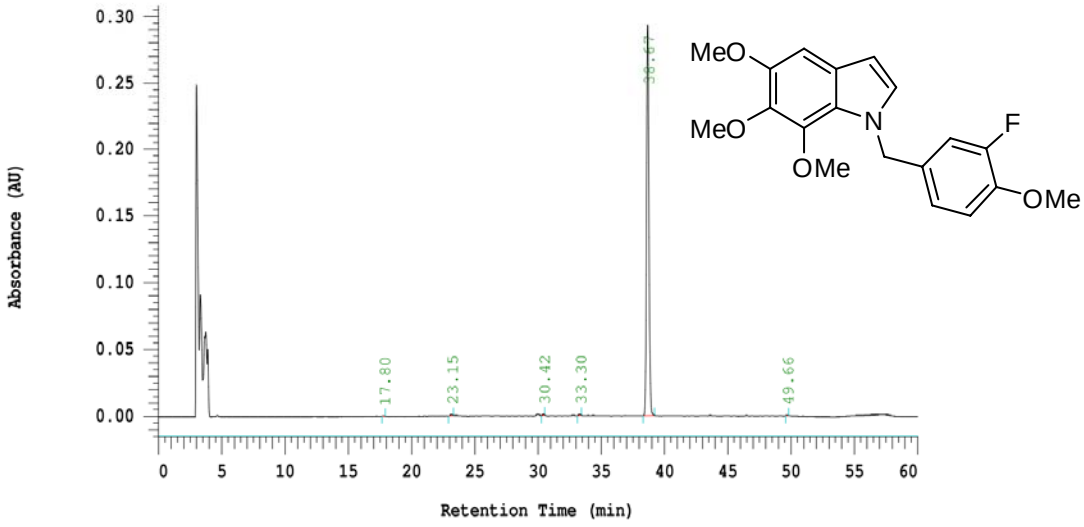
Reported Date and Time: 2010/04/20 04:29 下午
Data Path: C:\Win32app\D2000HSM\samples\DATA\1244\
Processing Method: Purity 2007/12/24
Sample Name: MPTOB299-50 Vial Number: 12
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description:

Chrom Type: Fixed WL Chromatogram, 254 nm



Processing Method: Purity 2007/12/24
Column Type: Column Method Developer: Bob
Method Description:

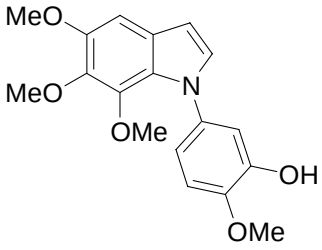
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Height	Conc 1
1	17.80	1829	209	0.099
2	23.15	5869	554	0.317
3	30.42	3663	454	0.198
4	33.30	5096	494	0.275
5	38.67	1835270	146254	99.020
6	49.66	1701	211	0.092
		1853428	148176	100.000

Peak rejection level: 0

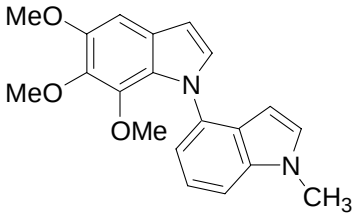
Spectral Data and Procedure of compounds 6-18.

2-Methoxy-5-(5,6,7-trimethoxy-indol-1-yl)-phenol (6)



To a solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), potassium carbonate (92 mg, 0.67 mmol) and copper (II) oxide (3.81 mg, 0.048 mmol) in DMF (3 mL), 5-iodo-2-methoxyphenol (288 mg, 1.15 mmol) was added and heated by microwave at 160 ^{o}C for 10 minutes. The reaction was quenched with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to afford **6** as a yellow solid (14 mg, 9%; n-hexane/ethyl acetate = 3:1). mp 124.9- 126.5 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (s, 3H), 3.88 (s, 3H) 3.91 (s, 3H), 3.95 (s, 3H), 5.69 (s, 1H), 6.49 (d, *J* = 3.0 Hz, 1H), 6.87-6.95 (m, 3H), 7.03-7.07 (m, 2H). MS (EI) m/z 329 (M^+, 32%), 61 (100%). HRMS (EI) calcd for $C_{18}H_{19}NO_5$ (M^+), 329.1263; found, 329.1263.

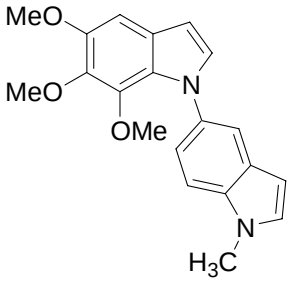
5,6,7-Trimethoxy-1'-methyl-1'H-[1,4']biindolyl (7)



To a solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), cesium carbonate (314 mg, 0.96 mmol) and copper (II) oxide (3.81 mg, 0.048 mmol) in DMF (3 mL), 4-bromo-N-methylindole (201 mg, 0.96 mmol) was added and heated to reflux for 48 hours. The reaction was quenched with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to afford **7** as a white solid (8 mg, 4.9%; n-hexane/ethyl acetate = 2:1). mp 119.4-121.9 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 6.26 (d, *J* = 3.1 Hz,

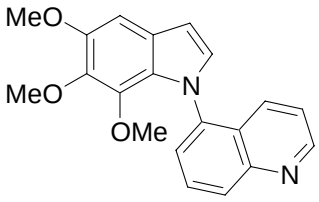
1H), 6.57 (d, *J* = 3.0 Hz, 1H), 6.94 (s, 1H), 7.03 (d, *J* = 3.1 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.26-7.31 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H). MS (EI) m/z 336 (M^+, 100%). HRMS (EI) calcd for $C_{20}H_{20}N_2O_3$ (M^+), 336.1474; found, 336.1475.

5,6,7-Trimethoxy-1'-methyl-1'H-[1,5']biindolyl (8)



To a solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), cesium carbonate (314 mg, 0.96 mmol) and copper (II) oxide (3.81 mg, 0.048 mmol) in DMF (3 mL), 5-bromo-N-methylindole (201 mg, 0.96 mmol) was added and heated to reflux for 48 hours. The reaction was quenched with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to afford **8** as a white solid (12 mg, 7%; n-hexane/ethyl acetate = 3:1). mp 112.7-115.4 ^oC. ^1H NMR (500 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 6.51 (s, 1H), 6.52 (s, 1H), 6.91 (s, 1H), 7.13 (d, *J* = 2.9 Hz, 1H), 7.14 (d, *J* = 2.8 Hz, 1H), 7.29~7.36 (m, 2H), 7.66 (s, 1H). MS (EI) m/z 207 (100%), 336 (M^+, 27%). HRMS (EI) calcd for $C_{20}H_{18}O_3N_2$ (M^+), 336.1474; found, 336.1476.

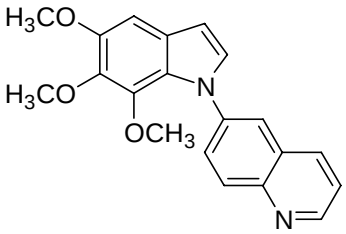
5-(5,6,7-Trimethoxy-indol-1-yl)-quinoline (9)



To a mixture of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), cesium carbonate (314 mg, 0.96 mmol) and copper (II) oxide (3.81 mg, 0.048 mmol) in DMF (3 mL), 5-iodo-2-methoxyphenol (288 mg, 1.15 mmol) was added and heated by microwave at 160 ^oC for 10 minutes. The reaction was quenched with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to

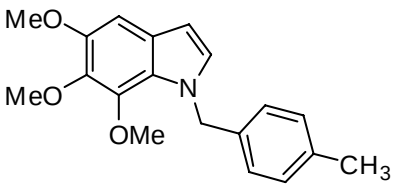
afford **9** as a yellow solid (14 mg, 9%; n-hexane/ethyl acetate = 3:1). mp 135.9-137.4 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13 (s, 3H), 3.80 (s, 3H), 3.94 (s, 3H), 6.64 (d, *J* = 3.07 Hz, 1H), 6.95 (s, 1H), 7.13 (d, *J* = 3.0 Hz, 1H), 7.40 (dd, *J* = 4.3, 8.3 Hz, 1H), 7.67 (d, *J* = 7.21 Hz, 1H), 7.81-7.87 (m, 2H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.95 (d, *J* = 3.2 Hz, 1H). MS (EI) m/z 334 (M^+,100%), 319 (82%). HRMS (EI) calcd for $C_{20}H_{18}N_2O_3$ (M^+), 334.1317; found, 334.1315.

1-Quinolyl-5,6,7-trimethoxyindole (10)



To a solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmole), cesium carbonate (314 mg, 0.96 mmole) and copper (II) oxide (3.81 mg, 0.048 mmole) in DMF (3mL), 6-bromoquinoline (199 mg, 0.96 mmole) was added and refluxed for 2 days. The reaction was quenched with water and extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column over silica gel to afford **10** (12 mg, 7%; n-hexane/ethyl acetate = 2:1) as a white solid; mp 123.3-125.4 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 6.61 (d, *J* = 3.0 Hz, 1H), 6.93 (s, 1H), 7.22 (d, *J* = 3.0 Hz, 1H), 7.46 (dd, *J* = 4.2, 8.2 Hz, 1H), 7.84-7.87 (m, 2H), 8.16-8.22 (m, 2H), 8.95 (dd, *J* = 1.5, 4.1 Hz, 1H). MS (EI) m/z 334 (M^+, 100%). HRMS (EI) calcd for $C_{20}H_{18}O_3N_2$ (M^+), 334.1317; found, 334.1317.

1-(4'-Methylbenzyl)-5,6,7-trimethoxyindole (11)

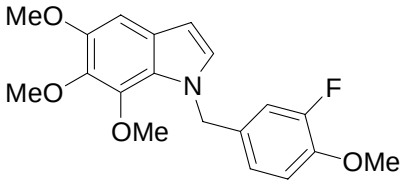


5,6,7-trimethoxy-1-(4-methylbenzyl)-1*H*-indole

A solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), KOH (40 mg, 0.72 mmol) and KI (79 mg, 0.48 mmol) in DMF (2 mL) was stirred at room temperature for 30 minutes. To the solution, 4-methylbenzyl bromide (222 mg, 1.2 mmol) was added and

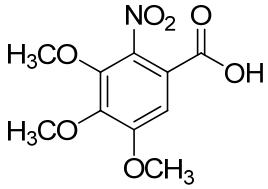
stirred for 1.5 hours. The reaction was quenched with water and extracted by ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to afford **11** as a yellow liquid (59 mg, 40%; n-hexane/ethyl acetate = 6:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.71 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.50 (s, 2H), 6.39 (d, *J* = 2.9 Hz, 1H), 6.83 (s, 1H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 3.0, 1H), 7.08 (d, J = 7.86 Hz, 2H). MS (EI) m/z 311 (M^+, 23%), 105 (100%). HRMS (EI) calcd for $C_{19}H_{21}O_3N$ (M^+), 311.1521; found, 311.1521.

1-(3'-Fluoro-4'-methoxybenzyl)-5,6,7-trimethoxy-1H-indole (12)



A solution of 5,6,7-trimethoxyindole (100 mg, 0.48 mmol), KOH (40 mg, 0.72 mmol) and KI (79 mg, 0.48 mmol) in DMF (2 mL) was stirred at room temperature for 30 minutes. To the solution, 3-fluoro-4-methoxybenzyl chloride (167 mg, 0.96 mmol) was added at 0 ^{o}C and stirred for 1.5 hours. The reaction was quenched with water and extracted by ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to afford **12** as an oil (51 mg, 34%; n-hexane/ethyl acetate = 6:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.44 (s, 2H), 6.40 (d, *J* = 2.8, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.80-6.88 (m, 3H), 6.95 (d, *J* = 2.9 Hz, 1H). MS (EI) m/z 345 (M^+, 25%), 139 (100%). HRMS (EI) calcd for $C_{19}H_{20}O_4NF$ (M^+), 345.1376; found, 345.1375.

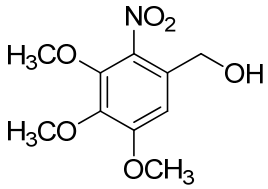
3,4,5-Trimethoxy-2-nitrobenzoic acid (14)



To a stirred solution of methyl 3,4,5-trimethoxy-2-nitrobenzoate (2 g, 7.37 mmole) in methanol, potassium hydroxide (0.83g, 14.47mmole) was added and heated to reflux for 1hour. The solution was evaporated and the residue was quenched with 3N HCl

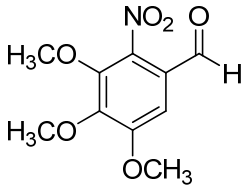
(20 mL) followed by extraction with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to afford **14** as a white solid (1.8 g, 95%; n-hexane/ethyl acetate = 1:1). mp 166.5-168.5 ^oC. ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 6H), 3.99 (s, 3H), 7.35 (s, 1H).

3,4,5-Trimethoxy-2-nitrobenzylalcohol (15)



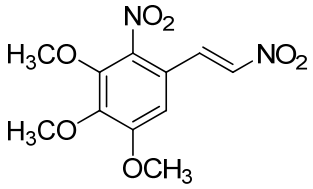
To a solution of compound **14** (1.89 g, 7.37 mmole) in THF, 1M borane-THF (14 mL) was added and refluxed overnight. The solvent was evaporated and the residue was quenched with water followed by extraction with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified with column chromatography to offer **15** as a pale yellow solid (1.432 g, 80%; n-hexane/ethyl acetate = 1:1). mp 71.8-73.6 ^oC. ^1H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 3H), 3.99 (s, 3H), 4.62 (s, 2H), 6.83 (s, 1H).

3,4,5-Trimethoxy-2-nitrobenzaldehyde (16)



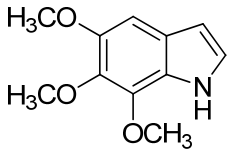
To a solution of compound **15** (1.79 g, 7.37 mmole) in dry dichloromethane, pyridinium dichromate (5.54 g, 14.74 mmole) and molecular sieve (5.54 g) were added and stirred at room temperature overnight. The mixture was filtered and the filtrate was collected and concentrated *in vacuo*. The residue was purified with column chromatography to afford **16** as a pale green solid (1.15 g, 65%; n-hexane/ethyl acetate = 1:1). mp 75.6-77.8 ^oC. ^1H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.00 (s, 6H), 7.22 (s, 1H), 9.88 (s, 1H).

1,2,3-Trimethoxy-4-nitro-5-(2-nitrovinyl)benzene (17)



To a solution of ammonium acetate (1.59 g, 20.74 mmole) and compound **16** (1 g, 4.15 mmole) in acetic acid (7 mL), nitromethane (1.12 mL, 20.74 mmole) was added and heated at 100 ^{o}C for 1.5 hours. After cooling, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was evaporated *in vacuo* and the residue was purified with column chromatography to afford **17** as a yellow solid (1 g, 85%; n-hexane/ethyl acetate = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H), 3.96 (S, 3H), 4.00 (s, 3H), 6.77 (s, 1H), 7.45 (d, *J* =13.4 Hz, 1H), 7.89 (d, *J* =13.4 Hz, 1H).

5,6,7-Trimethoxyindole (18)



To a reaction mixture of Fe power, EtOH (12 mL) and acetic acid(9 mL), a mixture of compound **17** (300 mg, 1.05 mmole) and acetic acid (12 ml) was added dropwise and heated at 100 ^{o}C for 2 hours. After cooling, the reaction was filtrated and the filtrate was collected and concentrated *in vacuo*. The residue was quenched with water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over Mg_2SO_4 and concentrated *in vacuo*. The residue was purified o with column chromatography to afford **18** as a black brown solid (65 mg, 30%; n-hexane/ethyl acetate = 2:1); mp 82.0-84.3 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.89 (s, 3H), 4.07 (s, 3H), 6.44 (dd, *J* =2.60, 2.51 Hz, 1H), 6.85 (s, 1H), 7.13 (dd, *J* = 2.70, 2.64 Hz, 1H).

References of Supplementary Information

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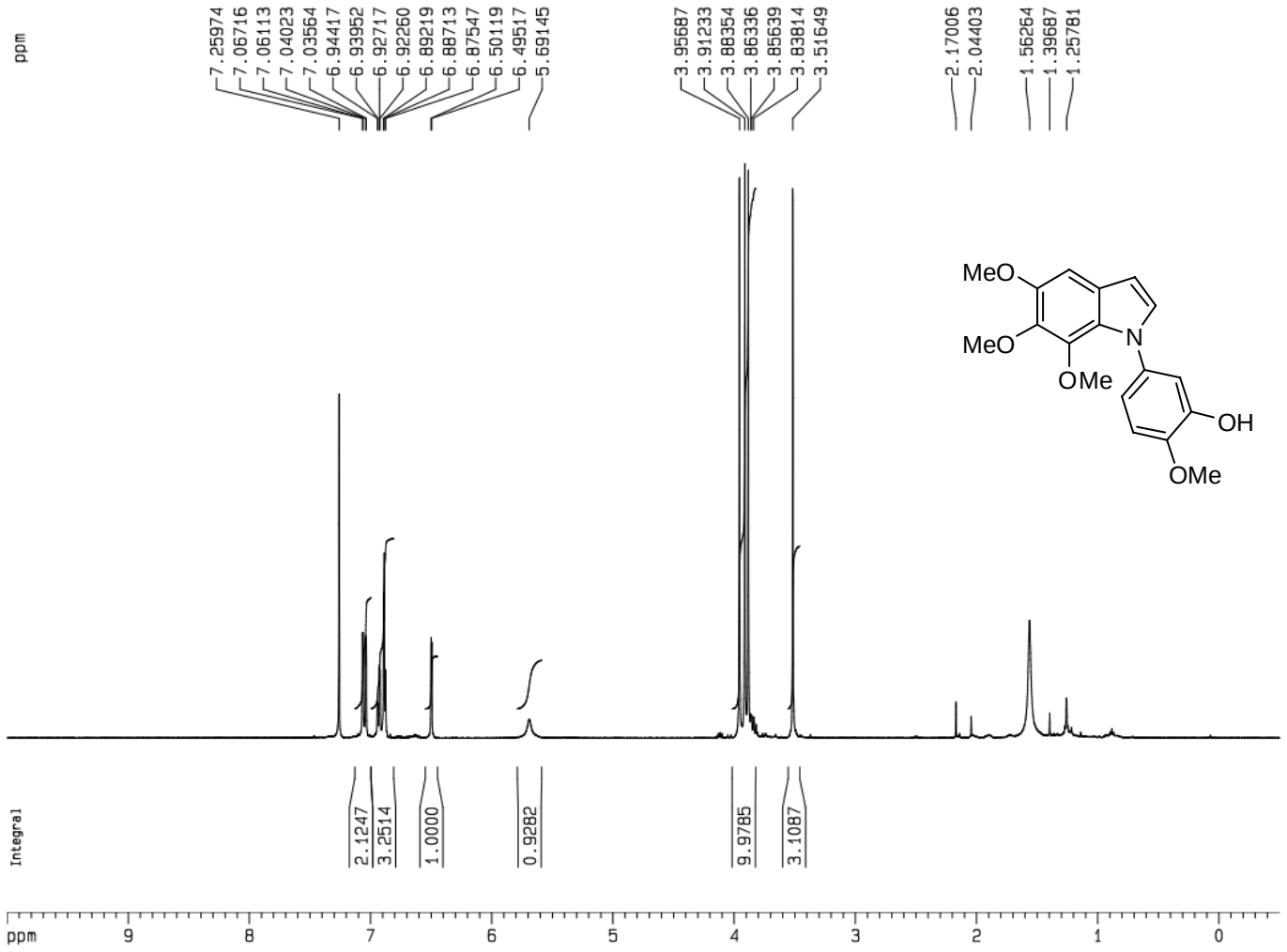
^{1}H Spectra for compound 6

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PROCNO                  1

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TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
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FIDRES        0.305176 Hz
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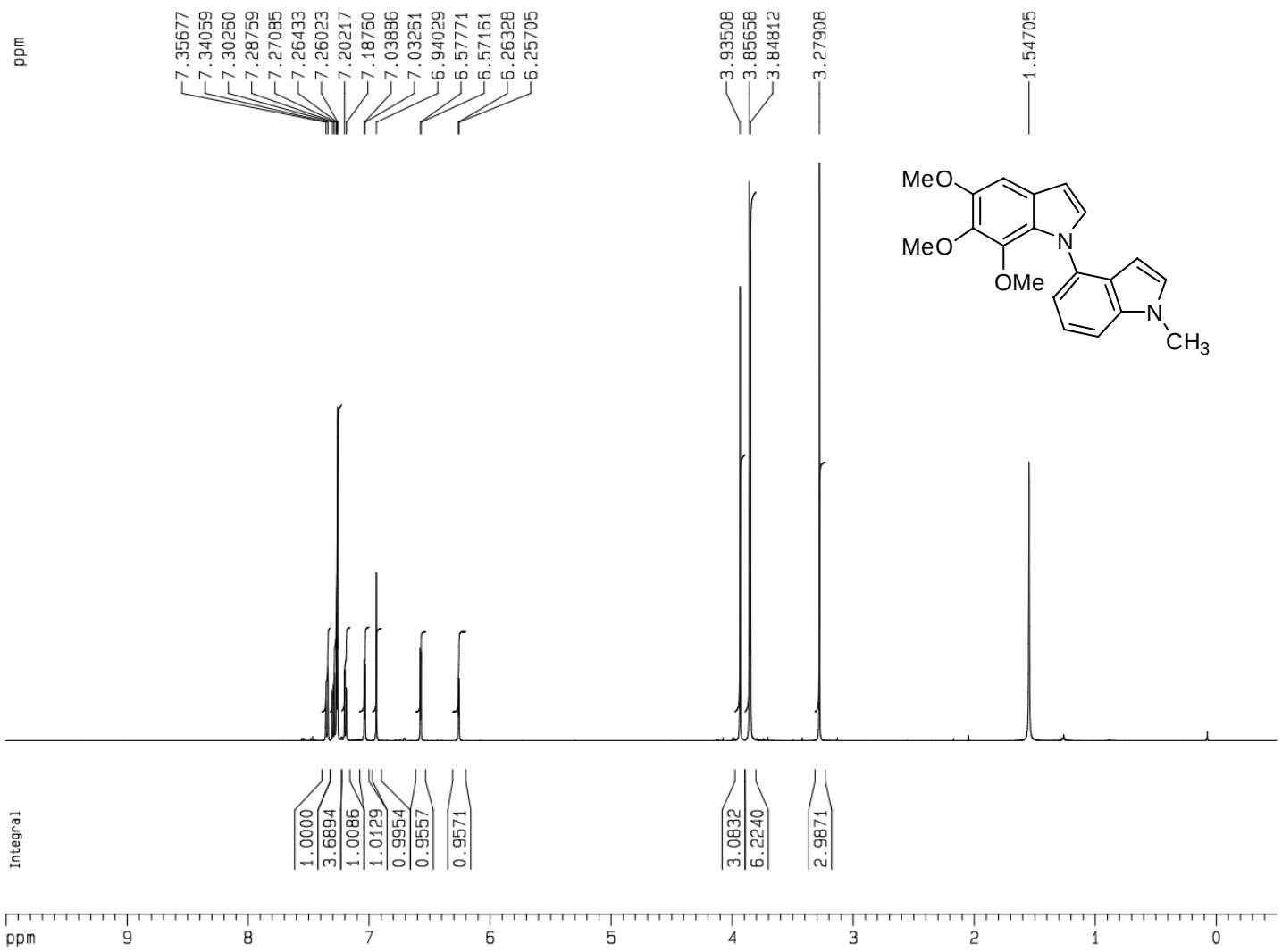
RG                  1024
DW                50.000 usec
DE                 6.50 usec
TE                299.9 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 13.50 usec
PL1                -5.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                  16384
SF          500.1300136 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                 1.40

1D NMR plot parameters
CX                 22.00 cm
CY                 10.00 cm
F1P               10.000 ppm
F1                5001.30 Hz
F2P               -0.500 ppm
F2               -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```

^{1}H Spectra for compound 7

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EXPNO                  1
PROCNO                 1

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Time              11.54
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PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.305176 Hz
AQ             1.6384500 sec
RG                456.1
DW                50.000 usec
DE                 6.50 usec
TE                300.1 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                10.20 usec
PL1               -2.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                16384
SF          500.1300136 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1              5001.30 Hz
F2P              -0.500 ppm
F2             -250.06 Hz
PPMCM           0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```
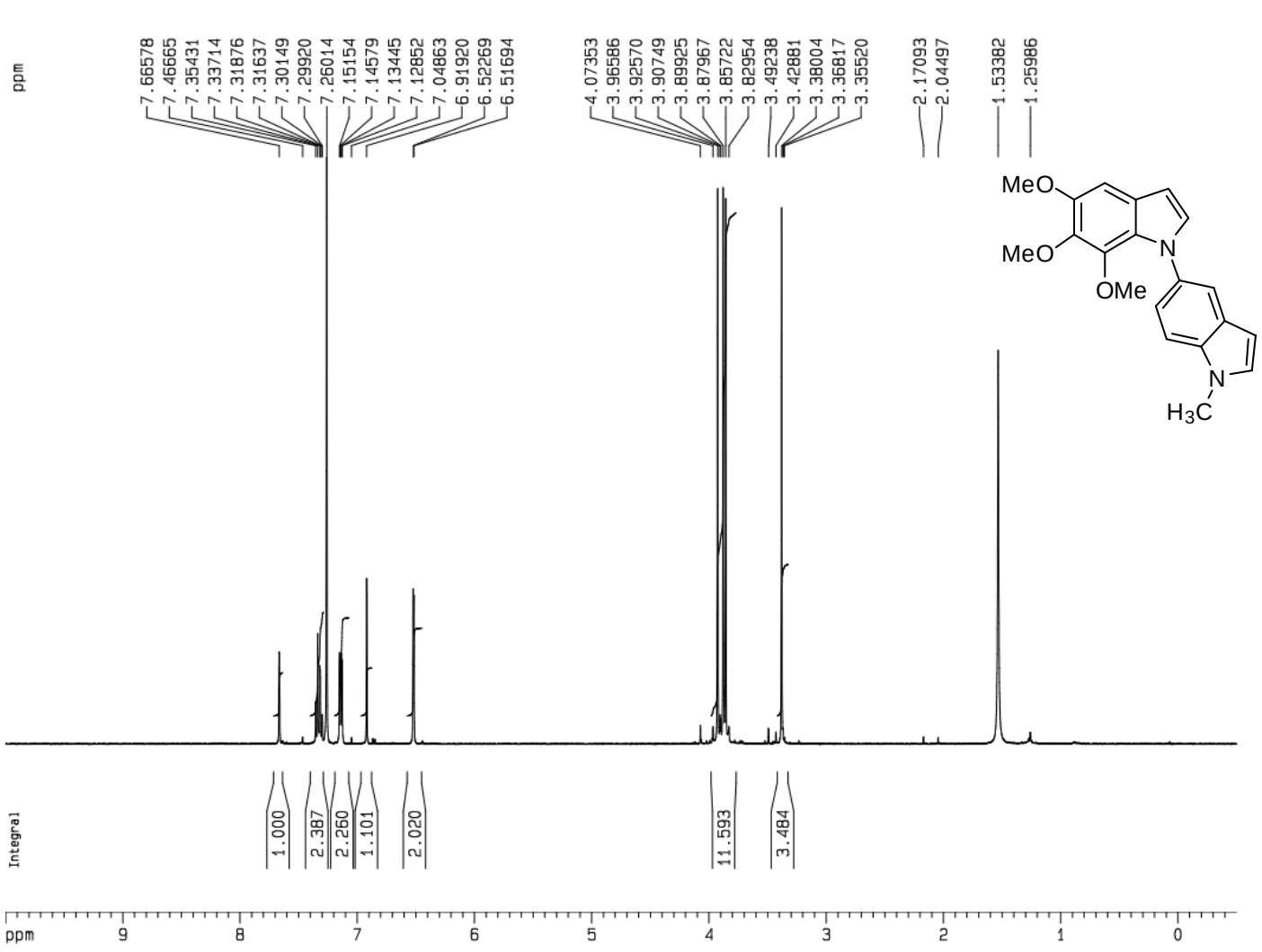

^{1}H Spectra for compound 8

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NAME          0303-12178
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
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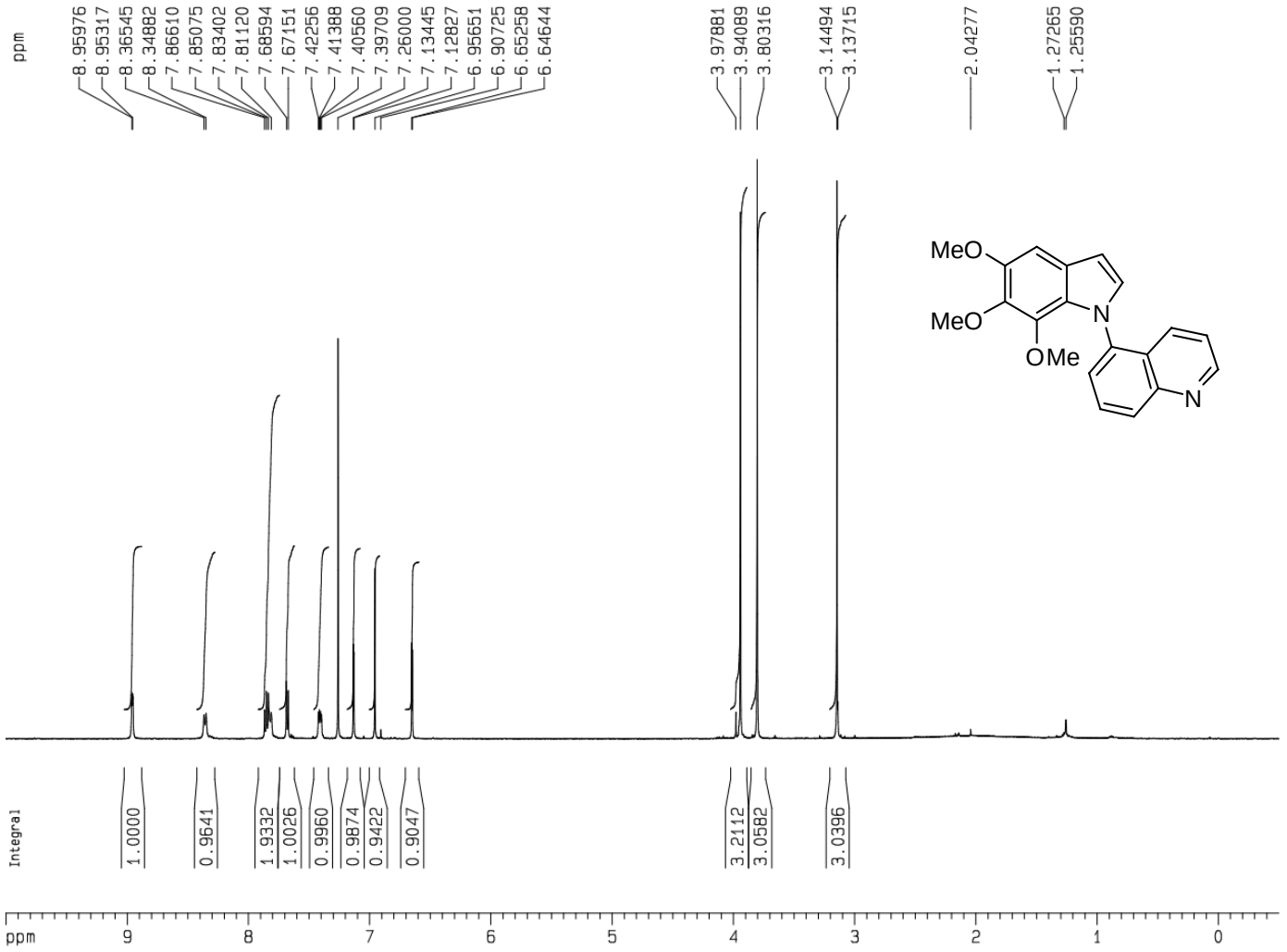
Time               15.24
INSTRUM            spect
PROBHD   5 mm TXI 13C Z
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES        0.305176 Hz
AQ            1.6384500 sec
RG                645.1
DW               50.000 usec
DE                6.50 usec
TE                300.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

-------- CHANNEL f1 --------
NUC1                   1H
P1                 13.50 usec
PL1                -5.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 16384
SF          500.1300136 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1               5001.30 Hz
F2P              -0.500 ppm
F2               -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```

^{1}H Spectra for compound 9

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Current Data Parameters
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EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
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Time               11.29
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ             1.5860212 sec
RG                1625.5
DW                48.400 usec
DE                 6.50 usec
TE                300.0 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 12.90 usec
PL1                -5.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 16384
SF          500.1300136 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 22.00 cm
CY                 10.00 cm
F1P               10.000 ppm
F1              5001.30 Hz
F2P               -0.500 ppm
F2              -250.06 Hz
PPMCM           0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```
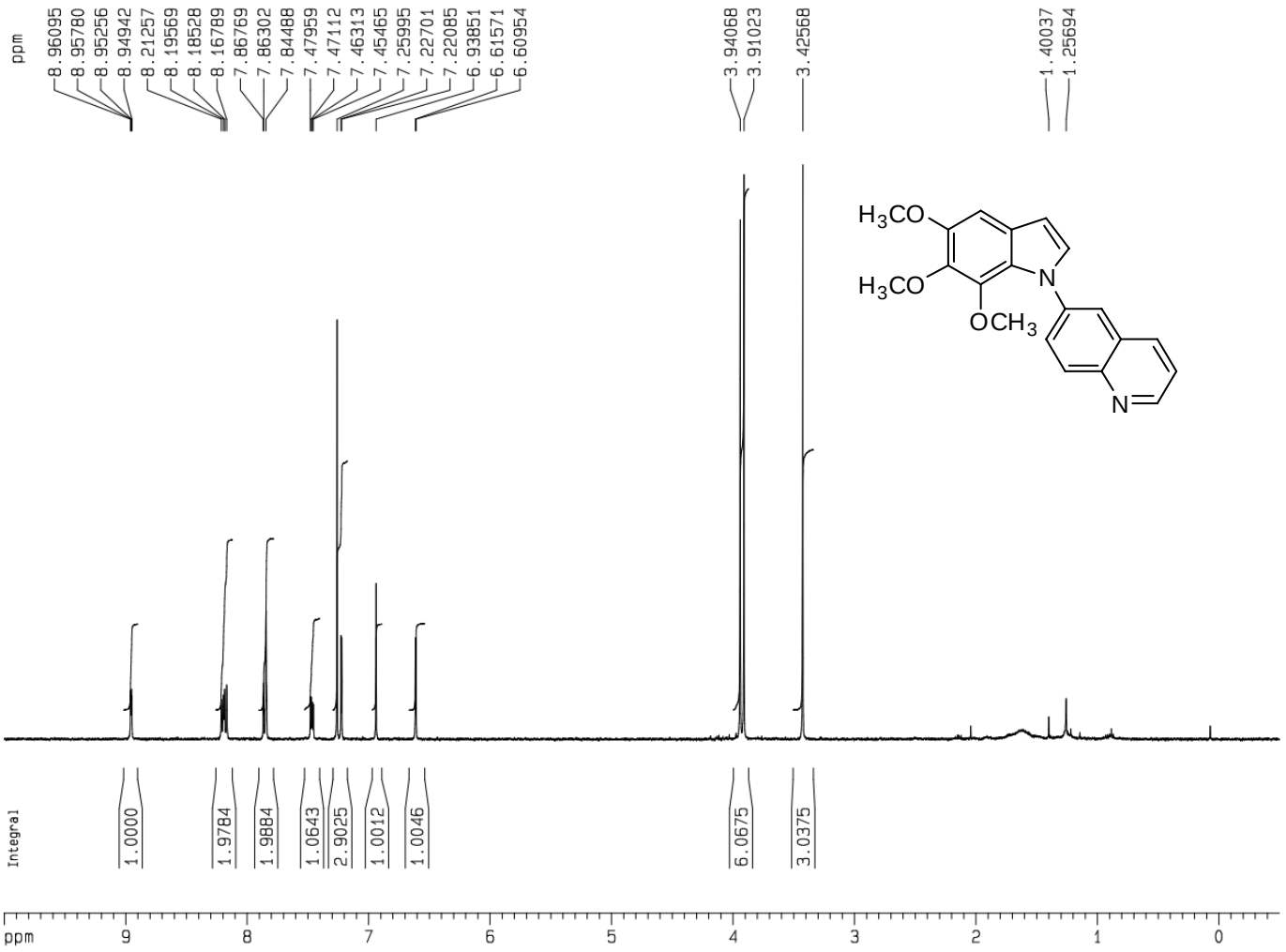

^{1}H Spectra for compound 10




```
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NAME          1210-12169
EXPNO                  1
PROCNO                 1

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Time               14.34
INSTRUM            spect
PROBHD   5 mm TXI 13C Z
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES         0.305176 Hz
AQ             1.6384500 sec
RG                7298.2
DW                50.000 usec
DE                 6.50 usec
TE                300.0 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                10.20 usec
PL1               -2.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 16384
SF           500.1300136 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1              5001.30 Hz
F2P              -0.500 ppm
F2              -250.06 Hz
PPMCM           0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```
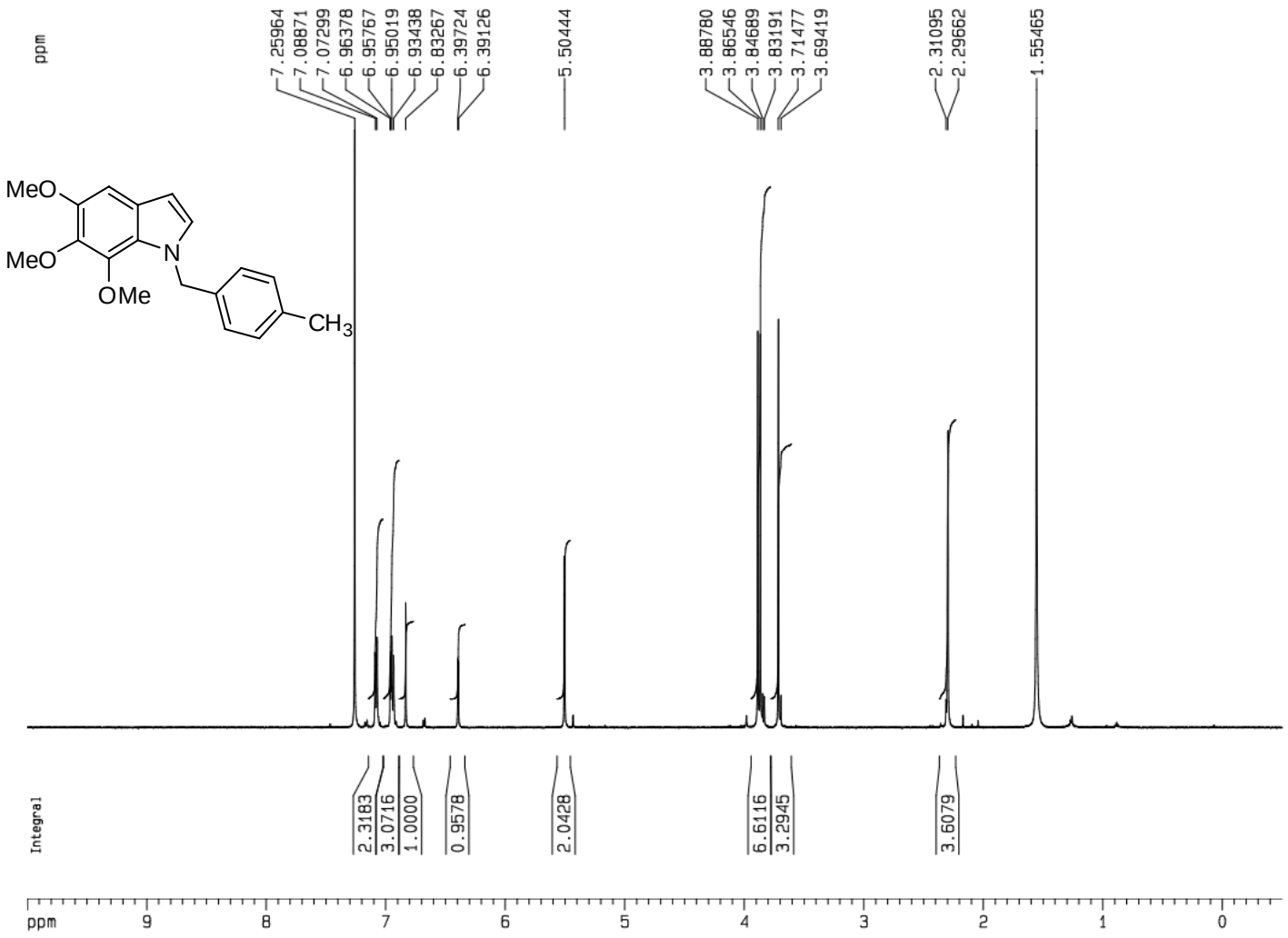

^{1}H Spectra for compound 11




```
Current Data Parameters
NAME          1030-12149
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081030
Time               10.44
INSTRUM            spect
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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH          10000.000 Hz
FIDRES           0.305176 Hz
AQ            1.6384500 sec
RG                1625.5
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DE                 6.50 usec
TE                300.0 K
D1           1.00000000 sec
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MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 12.70 usec
PL1                -5.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 16384
SF          500.1300136 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.40

1D NMR plot parameters
CX                22.00 cm
CY                20.00 cm
F1P               10.000 ppm
F1              5001.30 Hz
F2P               -0.500 ppm
F2              -250.06 Hz
PPMCM           0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```
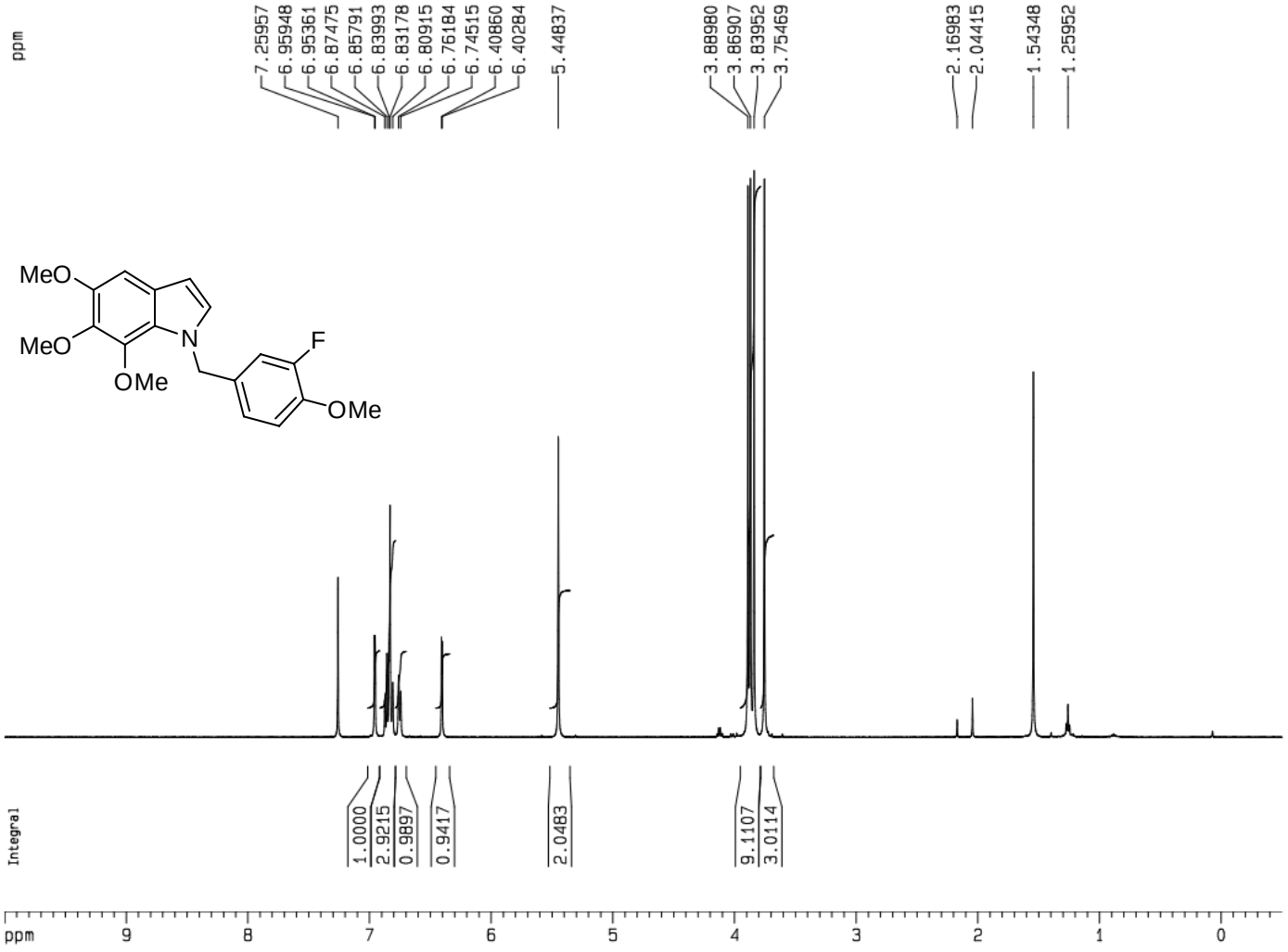

^{1}H Spectra for compound 12

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Current Data Parameters
NAME          1127-12163
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20081127
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PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.305176 Hz
AQ             1.6384500 sec
RG                912.3
DW                50.000 usec
DE                 6.50 usec
TE                300.0 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                13.00 usec
PL1               -5.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                16384
SF           500.1300136 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P               10.000 ppm
F1              5001.30 Hz
F2P               -0.500 ppm
F2              -250.06 Hz
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HZCM            238.69839 Hz/cm
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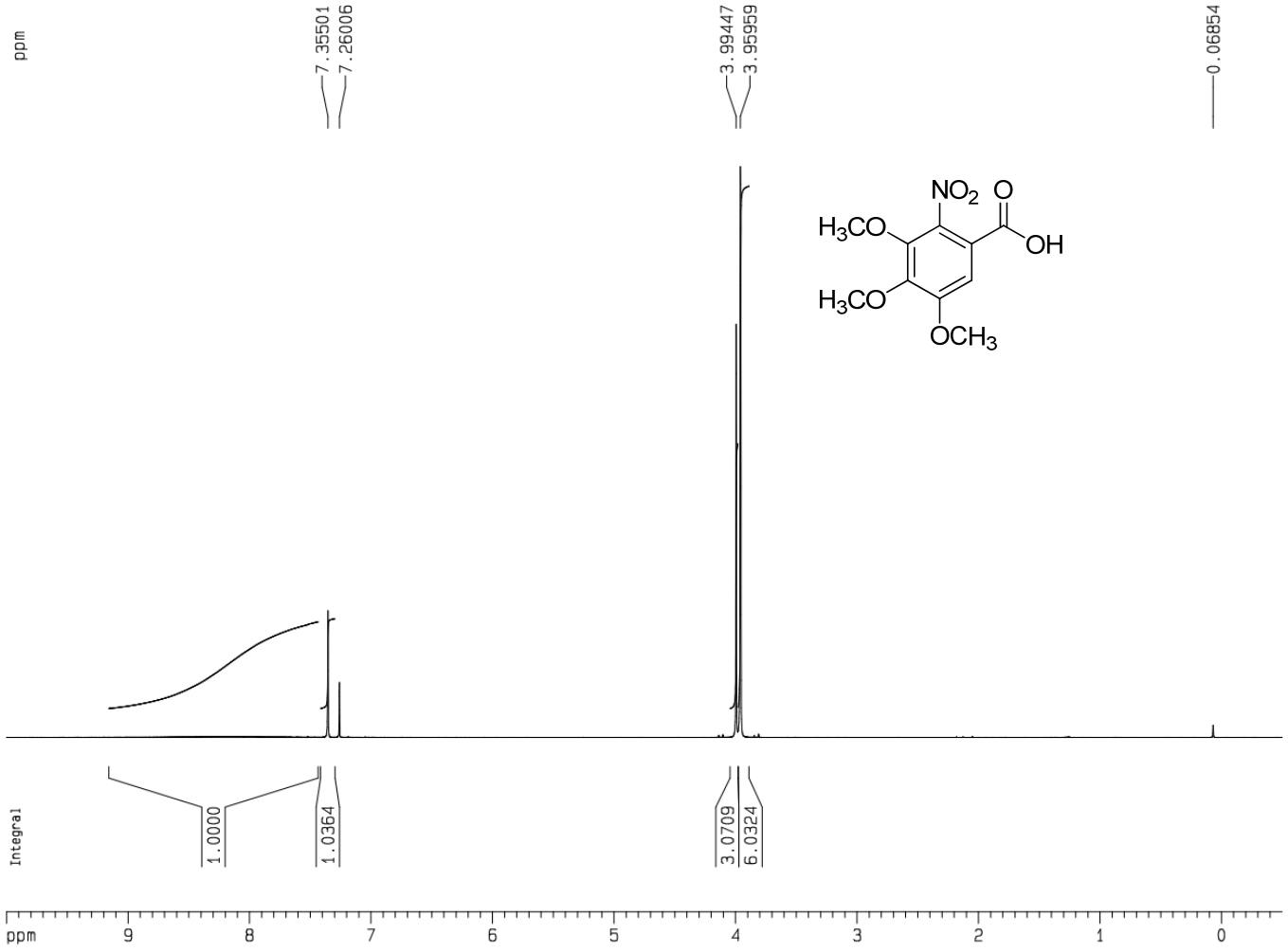
^{1}H Spectra for compound 14




```
Current Data Parameters
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EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
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Time              15.51
INSTRUM           spect
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PULPROG             zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES         0.305176 Hz
AQ            1.6384500 sec
RG               2896.3
DW               50.000 usec
DE                6.50 usec
TE               300.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

-------- CHANNEL f1 --------
NUC1                  1H
P1                13.50 usec
PL1               -5.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                16384
SF          500.1300136 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1              5001.30 Hz
F2P              -0.500 ppm
F2              -250.06 Hz
PPMCM           0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```
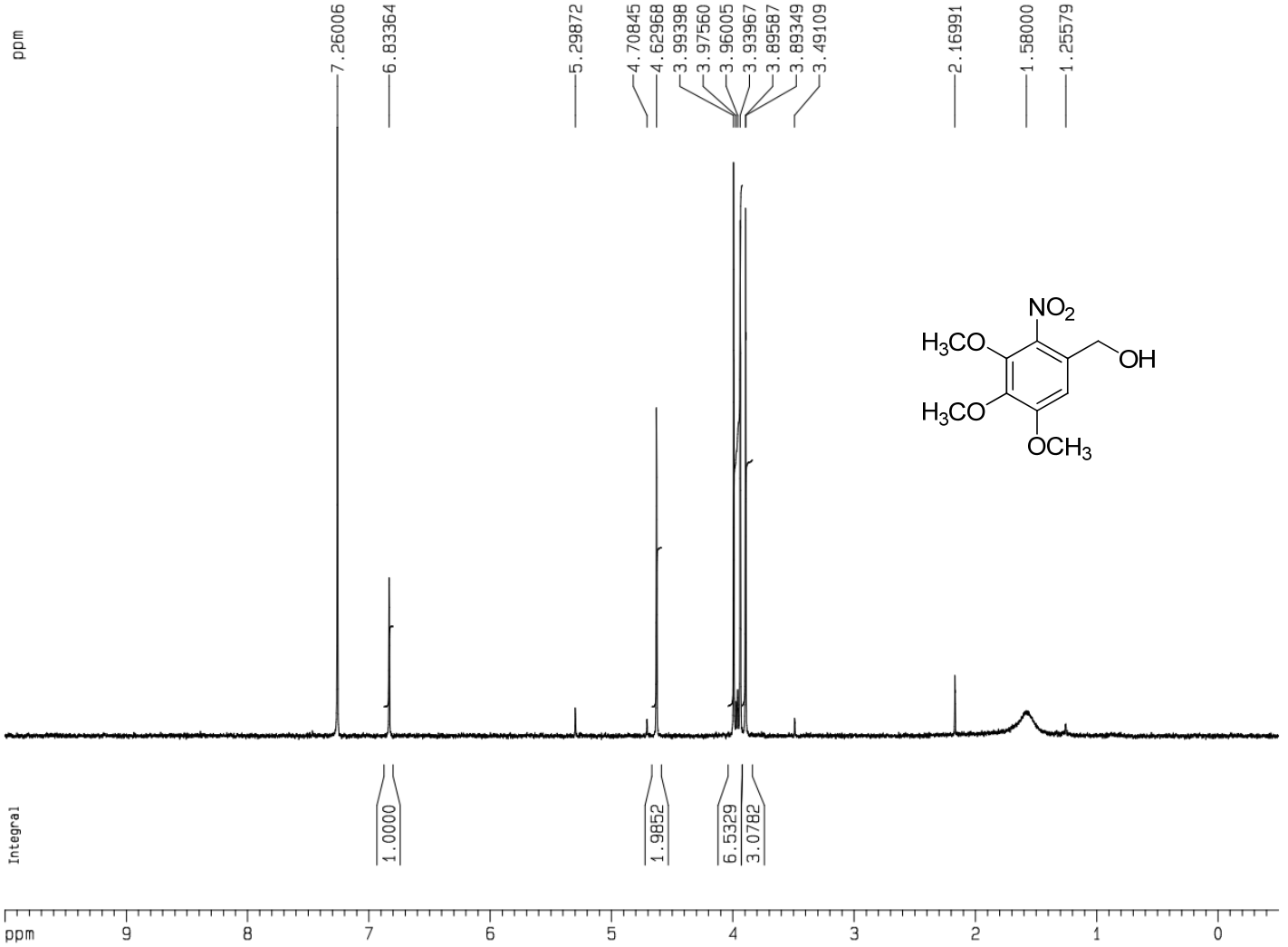

^{1}H Spectra for compound 15

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EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
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Time              15.18
INSTRUM           spect
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PULPROG             zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES         0.305176 Hz
AQ            1.6384500 sec
RG                13004
DW               50.000 usec
DE                6.50 usec
TE                299.8 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
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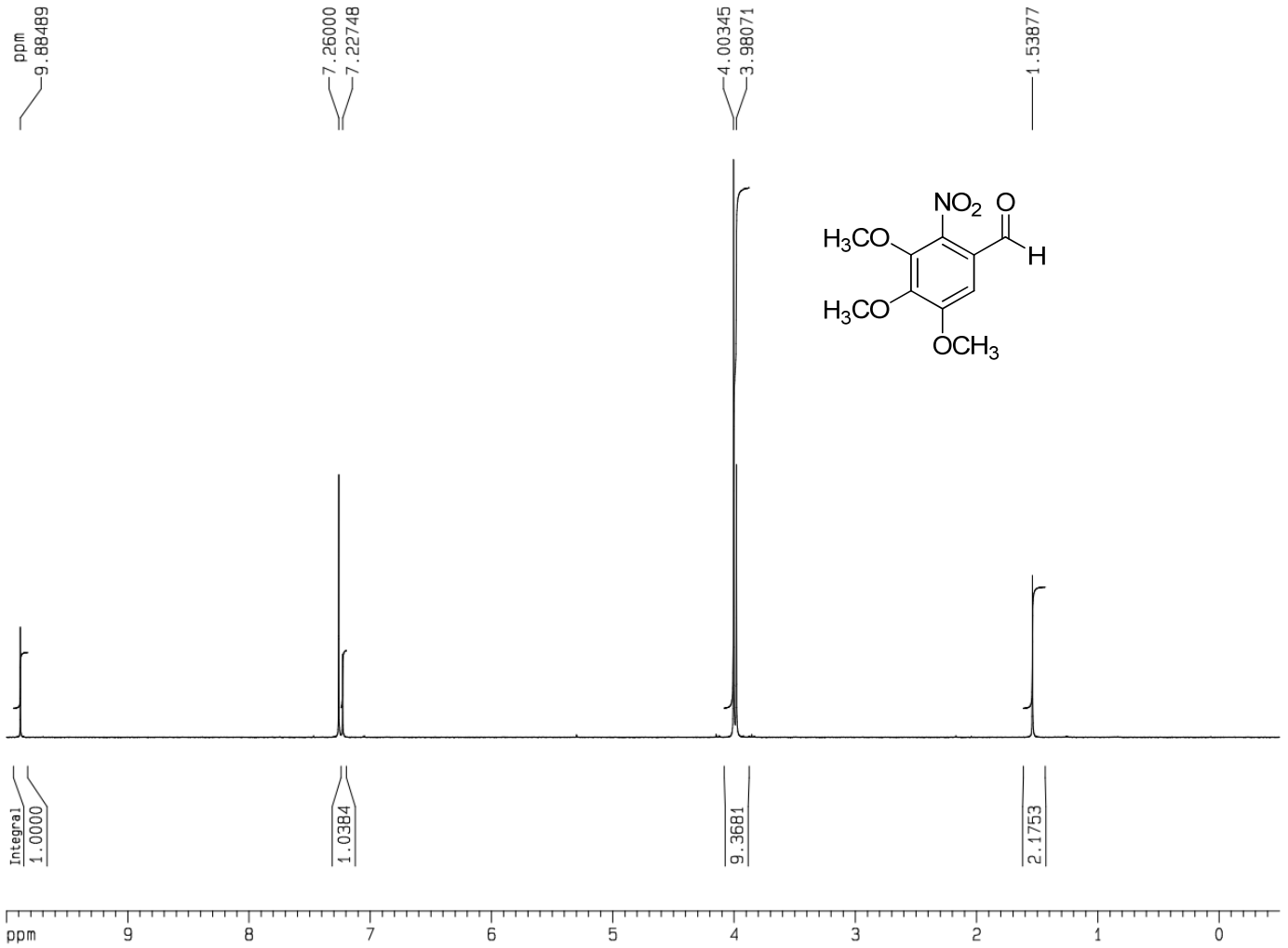
P1                10.70 usec
PL1               -2.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                16384
SF          500.1300136 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.40

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1               5001.30 Hz
F2P               -0.500 ppm
F2              -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM          238.69839 Hz/cm
```

^{1}H Spectra for compound 16

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EXPNO                 1
PROCNO                1

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PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH          10330.578 Hz
FIDRES        0.315264 Hz
AQ           1.5860212 sec
RG              2896.3
DW               48.400 usec
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TE               300.0 K
D1          1.00000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.10 usec
PL1               -2.00 dB
SFO1        500.1330008 MHz

F2 - Processing parameters
SI                16384
SF          500.1300136 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1              5001.30 Hz
F2P              -0.500 ppm
F2             -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM         238.69839 Hz/cm
```
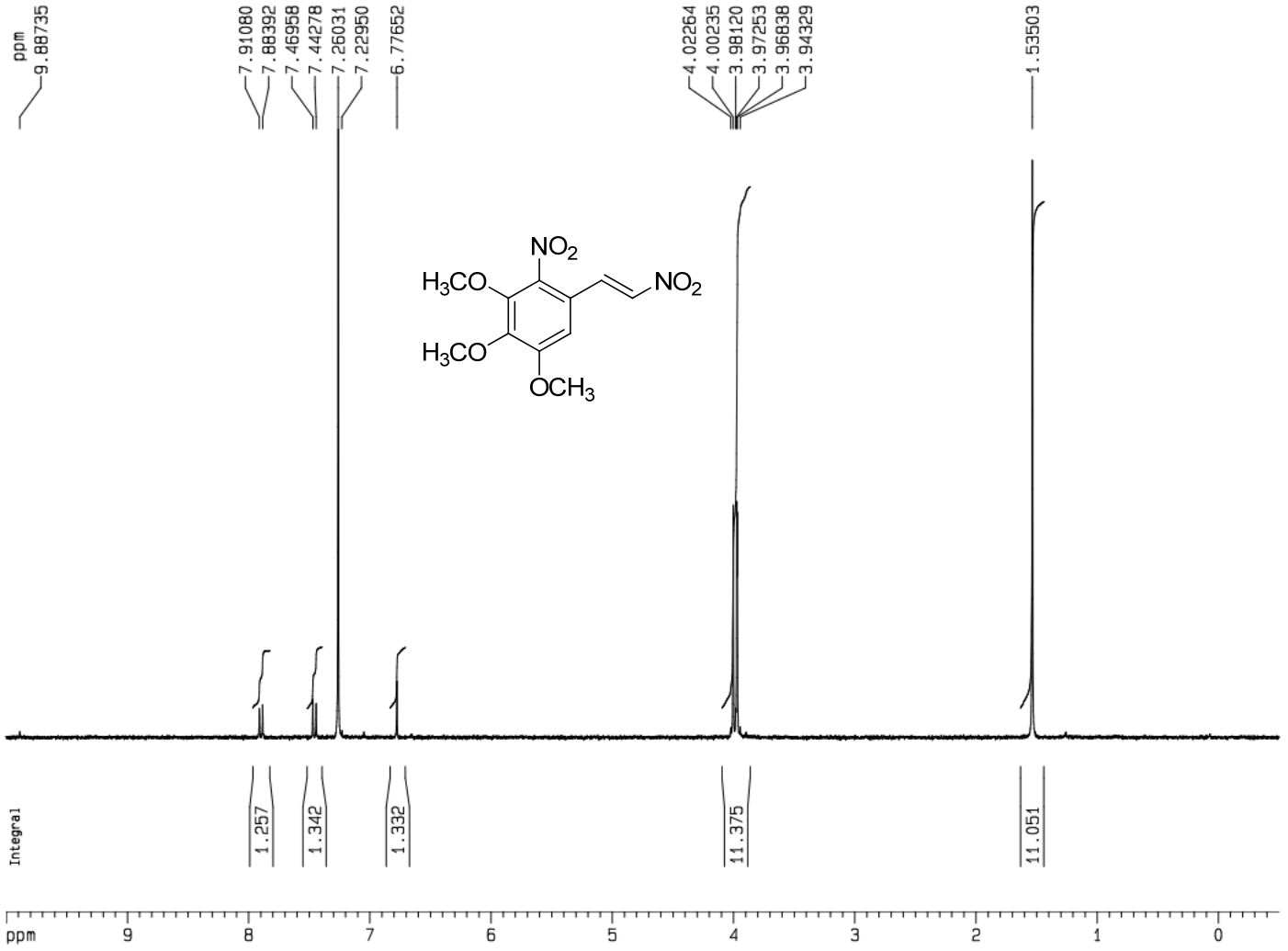
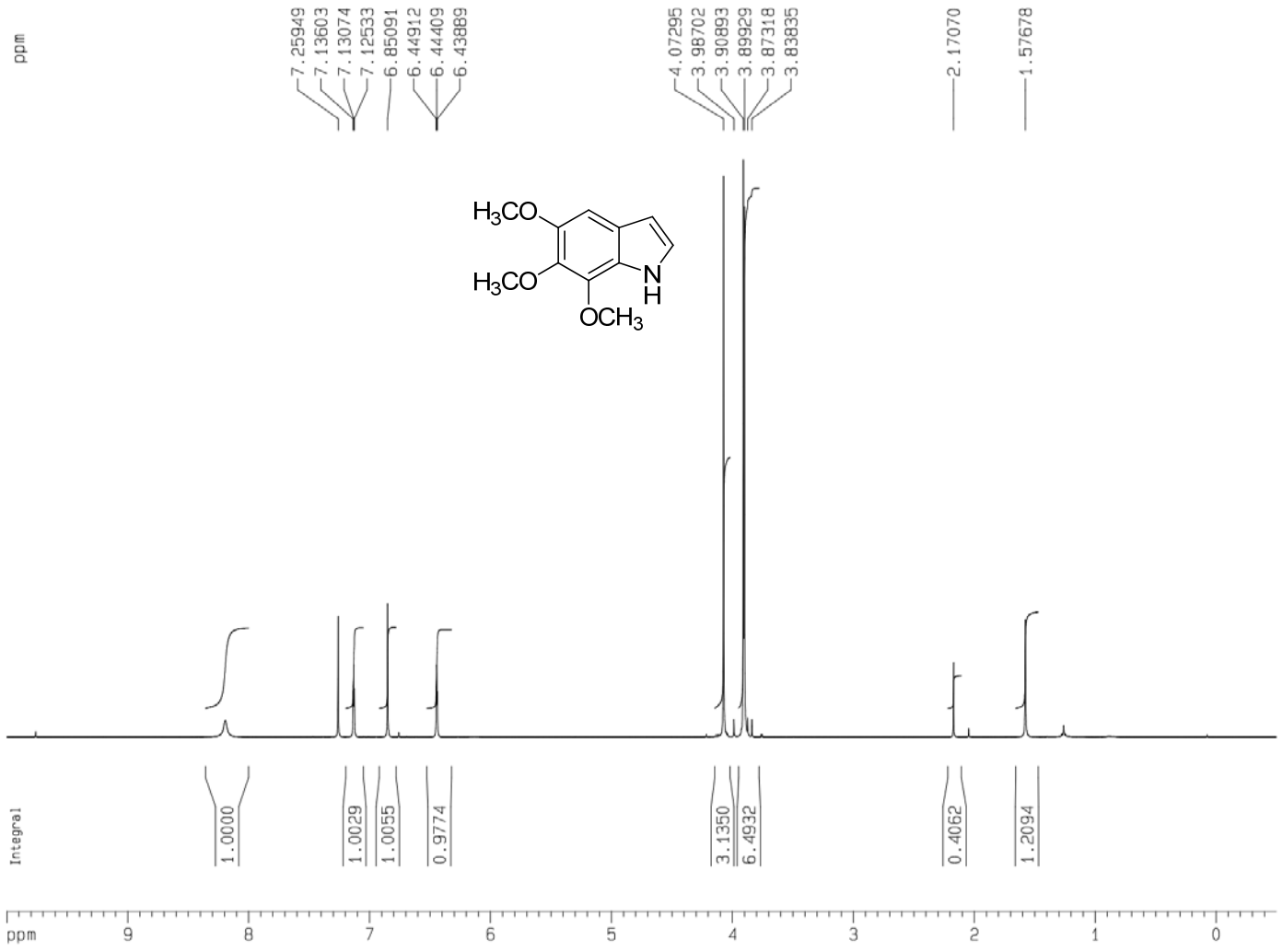

^{1}H Spectra for compound 17




```
Current Data Parameters
NAME          1213-1232a
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20071214
Time              11.29
INSTRUM           spect
PROBHD   5 mm TXI 13C Z
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                     4
DS                     2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ             1.5860212 sec
RG                7298.2
DW                48.400 usec
DE                 6.50 usec
TE                300.0 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                10.80 usec
PL1               -2.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                 16384
SF          500.1300136 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.00

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1             5001.30 Hz
F2P              -0.500 ppm
F2             -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM         238.69839 Hz/cm
```

^{1}H Spectra for compound 18




```
Current Data Parameters
NAME          0103-1236
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20080103
Time              10.57
INSTRUM           spect
PROBHD   5 mm Dual 13C/
PULPROG            zg30
TD                32768
SOLVENT            DMSO
NS                   16
DS                    2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ            1.5860212 sec
RG                645.1
DW               48.400 usec
DE                6.50 usec
TE               300.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                12.60 usec
PL1               -5.00 dB
SFO1        500.1330008 MHz

F2 - Processing parameters
SI                16384
SF          500.1300136 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P               10.000 ppm
F1              5001.30 Hz
F2P               -0.500 ppm
F2              -250.06 Hz
PPMCM          0.47727 ppm/cm
HZCM         238.69839 Hz/cm
```