Inhibitory effect of cytotoxic nitrogen-containing heterocyclic stilbene analogues on the VEGF protein secretion and the expression of the VEGF, hTERT and c-Myc genes

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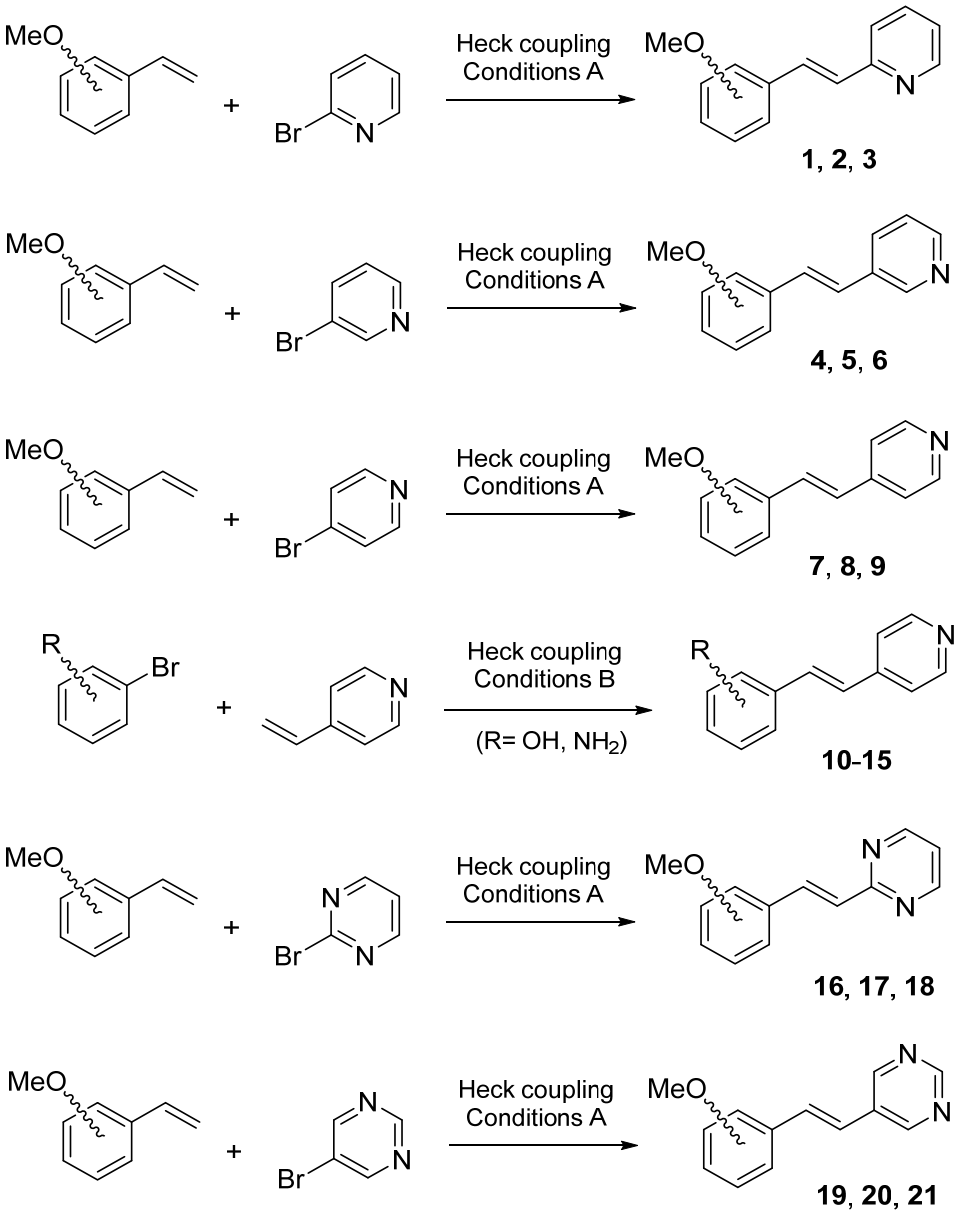
Supporting Information

Contents:

General features. NMR spectra were measured at 25 °C. The signals of the deuterated solvent ($CDCl_3$, CD_3OD or DMSO-d_6) were taken as the reference. Multiplicity assignments of ^{13}C signals were made by means of the DEPT pulse sequence. High resolution mass spectra were run by the electrospray mode (ESMS). IR data were measured with oily films on NaCl plates (oils) or KBr pellets (solids) and are given only for molecules with relevant functional groups (OH, C=O, NH_2). Melting points are not corrected. Experiments which required an inert atmosphere were carried out under dry N_2 in a flame-dried glassware. THF was freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dimethylformamide was freshly distilled from CaH_2. Commercially available reagents were used as received. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. Acronyms used hereafter: DMF = *N,N*-dimethylformamide, TBAB = tetra-*n*-butylammonium bromide.

General reaction conditions of Heck couplings



Heck coupling - Conditions A[1]

The appropriate brominated heterocycle (1 mmol) was placed in a 10-mL glass tube together with the corresponding styrene (1 mmol), tri-*n*-butylamine (0.22 mL, 1.2 mmol), TBAB (0.387 g, 1.2 mmol) and water (3 mL). The mixture was stirred until homogeneity and then treated with $Pd(NH_3)_2Cl_2$ (2 mg, 0.01 mmol). The vessel was sealed with a septum, shaken, and placed into the microwave cavity. Microwave irradiation was initiated with a potency of 70 W, the temperature being then increased from room temperature to 140 ºC. Once this value was reached, the reaction mixture was held at this temperature for 1.5 h. After allowing the mixture to cool down to room temperature, the reaction vessel was opened and the mixture was poured into a separation funnel. Water (10 mL) and EtOAc (10 mL) were added and the organic material was extracted. After further extraction of the aqueous layer with EtOAc, the organic layers were combined and dried over anhydrous Na_2SO_4. The volatiles were removed under reduced pressure to afford an oily residue, which was subjected to column chromatography on silica gel (hexane-EtOAc mixtures) to yield the desired stilbene derivative.

Yields: **1**, 65%; **2**, 67%; **3**, 61%; **4**, 78%; **5**, 79%; **6**, 82%; **7**, 80%; **8**, 79%; **9**, 78%; **16**, 64%; **17**, 60%; **18**, 51%; **19**, 62%; **20**, 59%; **21**, 60%.

Heck coupling - Conditions B[2]

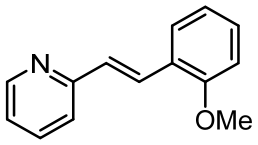
The appropriate bromo aniline or bromo phenol (1 mmol) was placed in a 10-mL glass tube together with 4-vinylpyridine (1 mmol), piperidine (0.15 mL, 1.5 mmol), $Pd(NH_3)_2Cl_2$ (8.4 mg, 0.04 mmol) and DMF (4 mL). The vessel was sealed with a septum, shaken, and placed into the microwave cavity. Microwave irradiation was initiated with a potency of 70 W, the temperature being then increased from room temperature to 140 ºC. Once this value was reached, the reaction mixture was held at this temperature for 1.5 h. After allowing the mixture to cool down to room temperature, the reaction vessel was opened and the reaction mixture was filtered through a Celite pad with EtOAc. The filtrate was poured into a separating funnel, and washed with ammonium chloride (2 x 10 mL) and then with brine (2 x 10 mL). After desiccation of the organic layer over anhydrous Na_2SO_4, the volatiles were removed under reduced pressure. This afforded an oily material which was subjected to column chromatography on silica gel (hexane-EtOAc mixtures) to yield the desired stilbene derivative.

Yields: **10,** 45%; **11**, 47%; **12**, 40%; **13**, 71%; **14**, 72%; **15**, 61%.

[1] N. Sharma, D. Mohanakrishnan, A. Shard, A. Sharma, Saima, A. K. Sinha, D. Sahal, *J. Med. Chem*., 2012, **55**, 297-311.
[2] S.-H. Huang, J.-R. Chen, F.-Y. Tsai, *Molecules*, 2010, **15**, 315-330.

Analytical data of nitrogen-containing stilbene derivatives

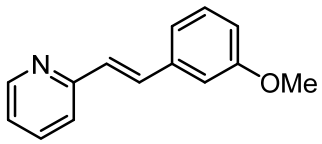
For the biological assays, samples of synthetic resveratrol analogues have been carefully purified by means of preparative HPLC.



1

(*E*)-2-(2-Methoxystyryl)pyridine (1)

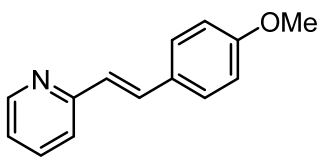
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (1H, br d, J ~ 4.5 Hz), 7.93 (1H, d, J = 16.1 Hz), 7.62 (2H, m), 7.42 (1H, br d, J ~ 7.5 Hz), 7.26 (1H, partially overlapped signal), 7.23 (1H, d, J = 16.1 Hz), 7.10 (1H, dd, J = 8, 4.5 Hz), 6.96 (1H, t, J = 7.3 Hz), 6.90 (1H, d, J = 8.3 Hz), 3.87 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 156.4, 125.6 (C), 149.5, 136.3, 129.3, 128.7, 127.8, 127.3, 121.7, 121.6, 120.7, 110.9 (CH), 55.4 (CH_3); HR ESMS *m/z* 212.1075 $(M+H)^+$. Calcd. for $C_{14}H_{14}NO$, 212.1075.



2

(*E*)-2-(3-Methoxystyryl)pyridine (2)

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, br d, J ~ 4.5 Hz), 7.63 (1H, td, J = 7.8, 2 Hz), 7.60 (1H, td, J = 16.1 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.20-7.10 (4H, br m), 6.86 (1H, dd, J = 8.3, 2.5 Hz), 3.82 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 155.5, 138.1 (C), 149.6, 136.5, 132.6, 129.6, 128.2, 122.0, 121.9, 119.8, 114.2, 112.1 (CH), 55.2 (CH_3); HR ESMS *m/z* 212.1077 $(M+H)^+$. Calcd. for $C_{14}H_{14}NO$, 212.1075.

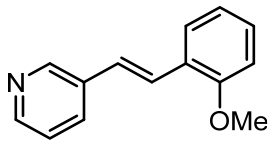


3

(*E*)-2-(4-Methoxystyryl)pyridine (3)

White solid, mp 73-75 ºC, lit.[1] mp 74-76 ºC. Spectral data consistent with those reported.[1]

[1] M. Annapurna, P. V. Reddy, S. P. Singh, M. L. Kantam, Tetrahedron 2013, 69, 10940-10945.

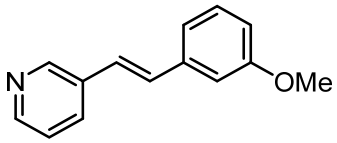


4

(*E*)-3-(2-Methoxystyryl)pyridine (4)

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (1H, br s), 8.46 (1H, dd, *J* = 5, 1.5 Hz), 7.84 (1H, br d, *J* ~ 8.5 Hz), 7.58 (1H, br d, *J* ~ 7.5 Hz), 7.52 (1H, d, *J* = 16.5 Hz), 7.30-7.25 (2H, m), 7.08 (1H, d, *J* = 16.5 Hz), 6.98 (1H, t, *J* = 7.5 Hz), 6.92 (1H, d, *J* = 8.3 Hz), 3.79 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 133.6 (C)*, 148.6, 148.3, 132.6, 129.3, 126.7, 125.8, 125.3, 123.4, 120.8, 111.0 (CH), 55.4 (CH_3); HR ESMS *m/z* 212.1077 $(M+H)^+$. Calcd. for $C_{14}H_{14}NO$, 212.1075.

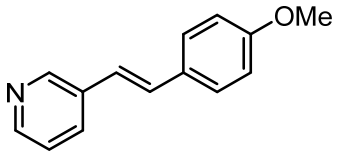
*The missing quaternary signal is overlapped with another signal and has not been allocated.



5

(*E*)-3-(3-Methoxystyryl)pyridine (5)

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (1H, br s), 8.48 (1H, dd, *J* = 5, 1.5 Hz), 7.78 (1H, dt, *J* = 8.3, 1.5 Hz), 7.30-7.25 (2H, m), 7.15-7.00 (4H, br m), 6.84 (1H, dd, *J* = 8, 2.5 Hz), 3.83 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 138.0, 132.8 (C), 148.5, 148.4, 132.5, 130.6, 129.6, 125.1, 123.4, 119.3, 113.8, 111.8 (CH), 55.2 (CH_3); HR ESMS *m/z* 212.1074 $(M+H)^+$. Calcd. for $C_{14}H_{14}NO$, 212.1075.

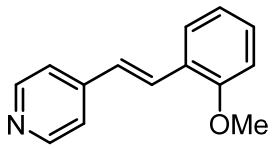


6

(*E*)-3-(4-Methoxystyryl)pyridine (6)

White solid, mp 105-107 ºC, lit.[1] mp 96-98 ºC. Spectral data consistent with those reported.[1]

[1] M. Annapurna, P. V. Reddy, S. P. Singh, M. L. Kantam, Tetrahedron 2013, 69, 10940-10945.

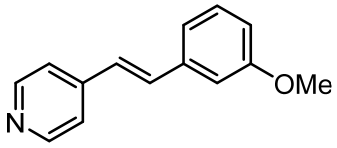


7

(*E*)-4-(2-Methoxystyryl)pyridine (7)

Colorless oil. Spectral data consistent with those reported.[1]

[1] C. Shi, J. Ding, J. Jiang, J. Chen, H. Wu, M. Liu, J. Chem. Res. 2012, 36, 322-325.

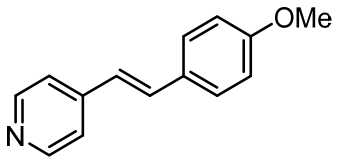


8

(*E*)-4-(3-Methoxystyryl)pyridine (8)

Colorless oil, lit.[1] mp 56-57 ºC. Spectral data consistent with those reported.[1]

[1] C. Shi, J. Ding, J. Jiang, J. Chen, H. Wu, M. Liu, J. Chem. Res. 2012, 36, 322-325.

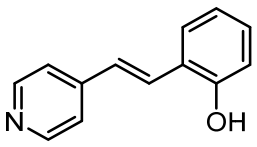


9

(*E*)-4-(4-Methoxystyryl)pyridine (9)

Yellowish solid, mp 138-140 ºC, lit.[1] mp 122-125 ºC. Spectral data consistent with those reported.[1]

[1] C. Shi, J. Ding, J. Jiang, J. Chen, H. Wu, M. Liu, J. Chem. Res. 2012, 36, 322-325.

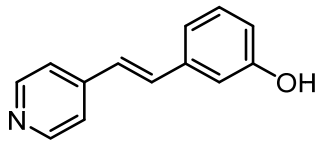


10

(*E*)-2-[2-(Pyridin-4-yl)vinyl]phenol (10)

Yellow solid, mp 173-175 ºC, lit.[1] mp 192-194 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (2H, d, *J* = 5 Hz), 7.66 (1H, d, *J* = 16.5 Hz), 7.60 (1H, d, *J* = 7.8 Hz), 7.50 (2H, d, *J* = 5 Hz), 7.21 (1H, d, *J* = 16.5 Hz), 7.16 (1H, t, *J* = 7.8 Hz), 6.90 (1H, d, *J* = 7.8 Hz), 6.85 (1H, t, *J* = 7.8 Hz) (a distinct OH signal not detected, perhaps merged with the solvent signal); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.6, 144.9, 122.8 (C), 150.0 (x 2), 129.7, 128.4, 127.3, 125.4, 120.6 (x 2), 119.3, 116.0 (CH); IR ν_{max} (cm^{-1}) 3500-3200 (br, OH); HR ESMS *m/z* 198.0919 $(M+H)^+$. Calcd. for $C_{13}H_{12}NO$, 198.0915.

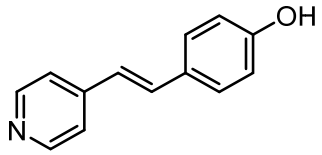
[1] D. Papa, E. Schwenk, E. Klingsberg, J. Am. Chem. Soc. 1951, 73, 253-255.



11

(*E*)-3-[2-(Pyridin-4-yl)vinyl]phenol (11)

White solid, mp 210-212 ºC; ^{1}H NMR (500 MHz, CD_3OD) δ 8.46 (2H, d, *J* = 5.8 Hz), 7.55 (2H, d, *J* = 5.8 Hz), 7.40 (1H, d, *J* = 16.1 Hz), 7.20 (1H, t, *J* = 7.8 Hz), 7.10-7.05 (2H, m), 7.04 (1H, br s), 6.77 (1H, dd, *J* = 7.8, 2.5 Hz) (a distinct OH signal not detected, perhaps merged with the solvent signal); ^{13}C NMR (125 MHz, CD_3OD) δ 159.0, 147.6, 139.0 (C), 150.4 (x 2), 135.5, 130.8, 126.4, 122.5 (x 2), 120.0, 117.1, 114.6 (CH); IR ν_{max} (cm^{-1}) 3500-3200 (br, OH); HR ESMS *m/z* 198.0919 $(M+H)^+$. Calcd. for $C_{13}H_{12}NO$, 198.0919.

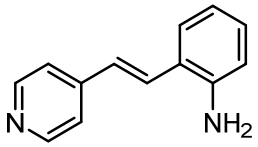


12

(*E*)-4-[2-(Pyridin-4-yl)vinyl]phenol (12)

Yellow solid, mp 265-268 ºC, lit.[1] mp 280-282 ºC. Spectral data consistent with those reported.[2]

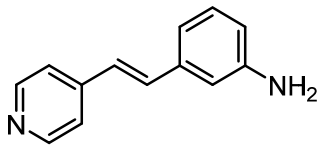
[1] D. Papa, E. Schwenk, E. Klingsberg, J. Am. Chem. Soc. 1951, 73, 253-255.
[2] C. Koopmans, H. Ritter, J. Am. Chem. Soc. 2007, 129, 3502-3503.



13

(*E*)-2-(2-(Pyridin-4-yl)vinyl)aniline (13)

Yellowish solid, mp 180-182 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (2H, br d, *J* ~ 5.8 Hz), 7.70 (1H, d, *J* = 16.2 Hz), 7.58 (2H, br d, *J* ~ 5.8 Hz), 7.48 (1H, d, *J* = 7.6 Hz), 7.01 (1H, t, *J* = 7.6 Hz), 6.97 (1H, d, *J* = 16.2 Hz), 6.67 (1H, d, *J* = 7.6 Hz), 6.57 (1H, t, *J* = 7.6 Hz), 5.50 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.1, 145.3, 119.9 (C), 149.9 (x 2), 129.7, 129.2, 126.1, 124.1, 121.0 (x 2), 116.6, 116.1 (CH); IR ν_{max} (cm^{-1}) 3420, 3320, 3200 (br, NH_2); HR ESMS *m/z* 197.1076 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2$, 197.1079.

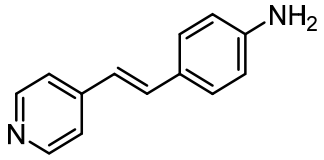


14

(*E*)-3-(2-(Pyridin-4-yl)vinyl)aniline (14)

Yellowish solid, mp 174-176 ºC, lit.[1] mp 191-192 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (2H, br d, *J* ~ 5.8 Hz), 7.52 (2H, br d, *J* ~ 5.8 Hz), 7.37 (1H, d, *J* = 16.2 Hz), 7.05-7.00 (2H, m), 6.85-6.80 (2H, m), 6.57 (1H, br d, *J* ~ 8 Hz), 5.10 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.0, 144.5, 136.7 (C), 150.0 (x 2), 134.1, 129.4, 125.0, 120.9 (x 2), 115.3, 114.8, 112.3 (CH); IR ν_{max} (cm^{-1}) 3400-3200 (br, NH_2); HR ESMS *m/z* 197.1079 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2$, 197.1079.

[1] B. R. Baker, R. E. Gibson, J. Med. Chem. 1971, 14, 315-322.



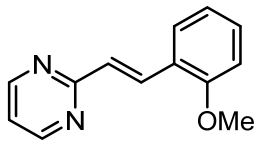
15

(*E*)-4-(2-(Pyridin-4-yl)vinyl)aniline (15)

Yellow solid, mp 270-272 ºC, lit.[1] mp 279-281 ºC (dec.), lit.[2] mp 270-274 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (2H, br d, *J* ~ 5.8 Hz), 7.43 (2H, br d, *J* ~ 5.8 Hz), 7.35-7.30 (3H, m), 6.86 (1H, d, *J* = 16.2 Hz), 6.58 (2H, br d, *J* ~ 8.3 Hz), 5.50 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.2, 123.6 (C),* 149.8 (x 2), 133.7, 128.4 (x 2), 120.2 (x 2), 119.8, 113.8 (x 2) (CH); IR ν_{max} (cm^{-1}) 3400-3200 (br, NH_2); HR ESMS *m/z* 197.1076 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2$, 197.1079.

*The missing quaternary signal is overlapped with another signal and has not been allocated.

[1] B. R. Baker, R. E. Gibson, J. Med. Chem. 1971, 14, 315-322.
[2] S. J. Lord, H. D. Lee, R Samuel, R Weber, N. Liu, N. R. Conley, M. A. Thompson, R. J. Twieg, W. E. Moerner, J. Phys. Chem. B 2010, 114, 14157-14167.

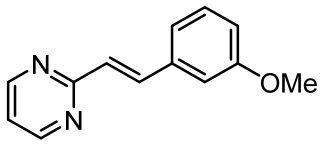


16

(*E*)-2-(2-Methoxystyryl)pyrimidine (16)

Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (2H, d, *J* = 5 Hz), 8.32 (1H, d, *J* = 16.5 Hz), 7.66 (1H, dd, *J* = 7.8, 1.5 Hz), 7.35-7.30 (2H, m), 7.08 (1H, t, *J* = 5 Hz), 7.00 (1H, t, *J* = 7.6 Hz), 6.94 (1H, d, *J* = 8.3 Hz), 3.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 158.0, 125.0 (C),

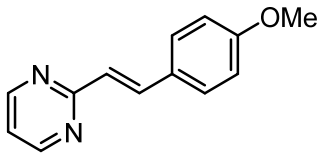
157.0 (x 2), 133.5, 130.2, 128.2, 128.0, 120.7, 118.3, 111.1 (CH), 55.5 (CH_3); HR ESMS *m/z* 213.1025 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.



17

(*E*)-2-(3-Methoxystyryl)pyrimidine (17)

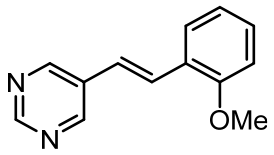
Yellowish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (2H, d, J = 5 Hz), 7.96 (1H, d, J = 16 Hz), 7.31 (1H, t, J = 8 Hz), 7.30-7.20 (2H, m), 7.16 (1H, br s), 7.10 (1H, t, J = 5 Hz), 6.90 (1H, dd, J = 8, 2 Hz), 3.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.9, 137.3 (C), 157.0 (x 2), 138.1, 129.7, 127.6, 120.4, 118.5, 115.2, 112.4 (CH), 55.2 (CH_3); HR ESMS *m/z* 213.1024 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.



18

(*E*)-2-(4-Methoxystyryl)pyrimidine (18)

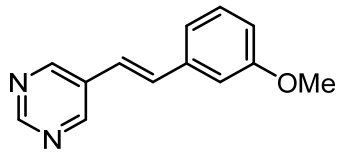
Off-white solid, mp 103-105 ºC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (2H, d, J = 5 Hz), 7.96 (1H, d, J = 16 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.12 (1H, d, J = 16 Hz), 7.05 (1H, t, J = 5 Hz), 6.92 (2H, d, J = 8.3 Hz), 3.82 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 160.5, 128.7 (C), 157.0 (x 2), 137.7, 129.1 (x 2), 125.2, 118.1, 114.2 (x 2) (CH), 55.3 (CH_3); HR ESMS *m/z* 213.1030 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.



19

(*E*)-5-(2-Methoxystyryl)pyrimidine (19)

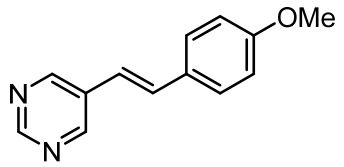
Yellowish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (1H, s), 8.86 (2H, s), 7.59 (1H, d, J = 16.5 Hz), 7.57 (1H, dd, J = 8, 1 Hz), 7.31 (1H, td, J = 7.8, 1.5 Hz), 7.05-6.95 (2H, m), 6.94 (1H, d, J = 7.8 Hz), 3.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 131.6, 125.1 (C), 156.9, 154.2 (x 2), 129.9, 128.0, 127.0, 121.5, 120.8, 111.1 (CH), 55.5 (CH_3); HR ESMS *m/z* 213.1027 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.



20

(*E*)-5-(3-Methoxystyryl)pyrimidine (20)

Yellowish solid, mp 75-77 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (1H, s), 8.82 (2H, s), 7.30 (1H, t, *J* = 8 Hz), 7.16 (1H, d, *J* = 16.5 Hz), 7.10 (1H, d, *J* = 8 Hz), 7.05 (1H, t, *J* = 1.5 Hz), 6.94 (1H, d, *J* = 16.5 Hz), 6.88 (1H, dd, *J* = 8, 1.5 Hz), 3.82 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 137.2, 130.7 (C), 157.0, 154.1 (x 2), 132.5, 129.7, 121.2, 119.3, 114.2, 112.0 (CH), 55.1 (CH_3); HR ESMS *m/z* 213.1032 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.

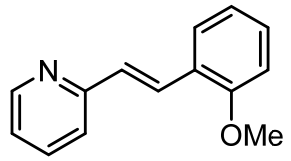


21

(*E*)-5-(4-Methoxystyryl)pyrimidine (21)

Yellowish solid, mp 96-98 ºC. ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (1H, s), 8.91 (2H, s), 7.54 (2H, d, *J* = 8.5 Hz), 7.36 (1H, d, *J* = 16.5 Hz), 6.98 (1H, d, *J* = 16.5 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 3.81 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 161.8, 133.7, 130.4 (C), 156.9, 155.2 (x 2), 134.2, 129.5 (x 2), 119.4, 115.3 (x 2) (CH), 55.8 (CH_3); HR ESMS *m/z* 213.1023 $(M+H)^+$. Calcd. for $C_{13}H_{13}N_2O$, 213.1028.

NMR spectra of nitrogen-containing stilbene derivatives



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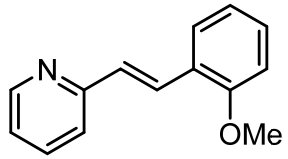

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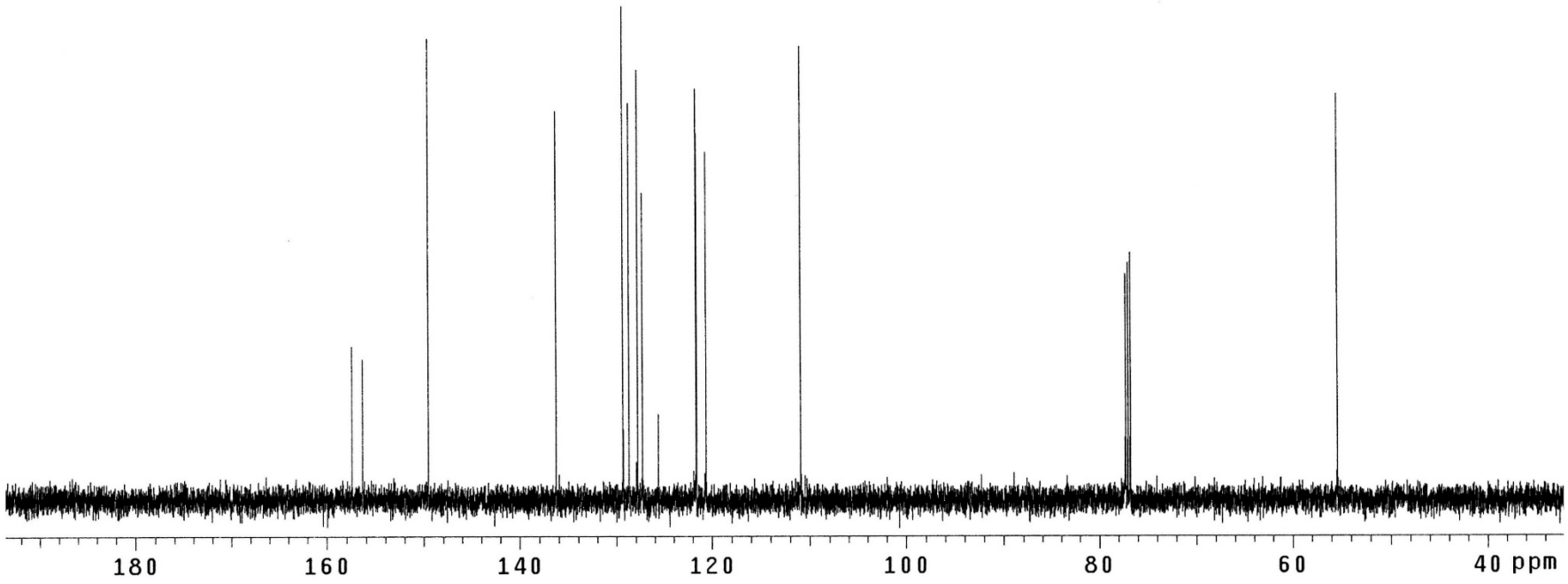

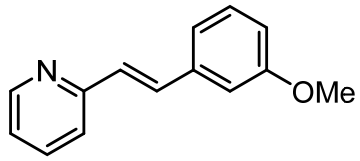

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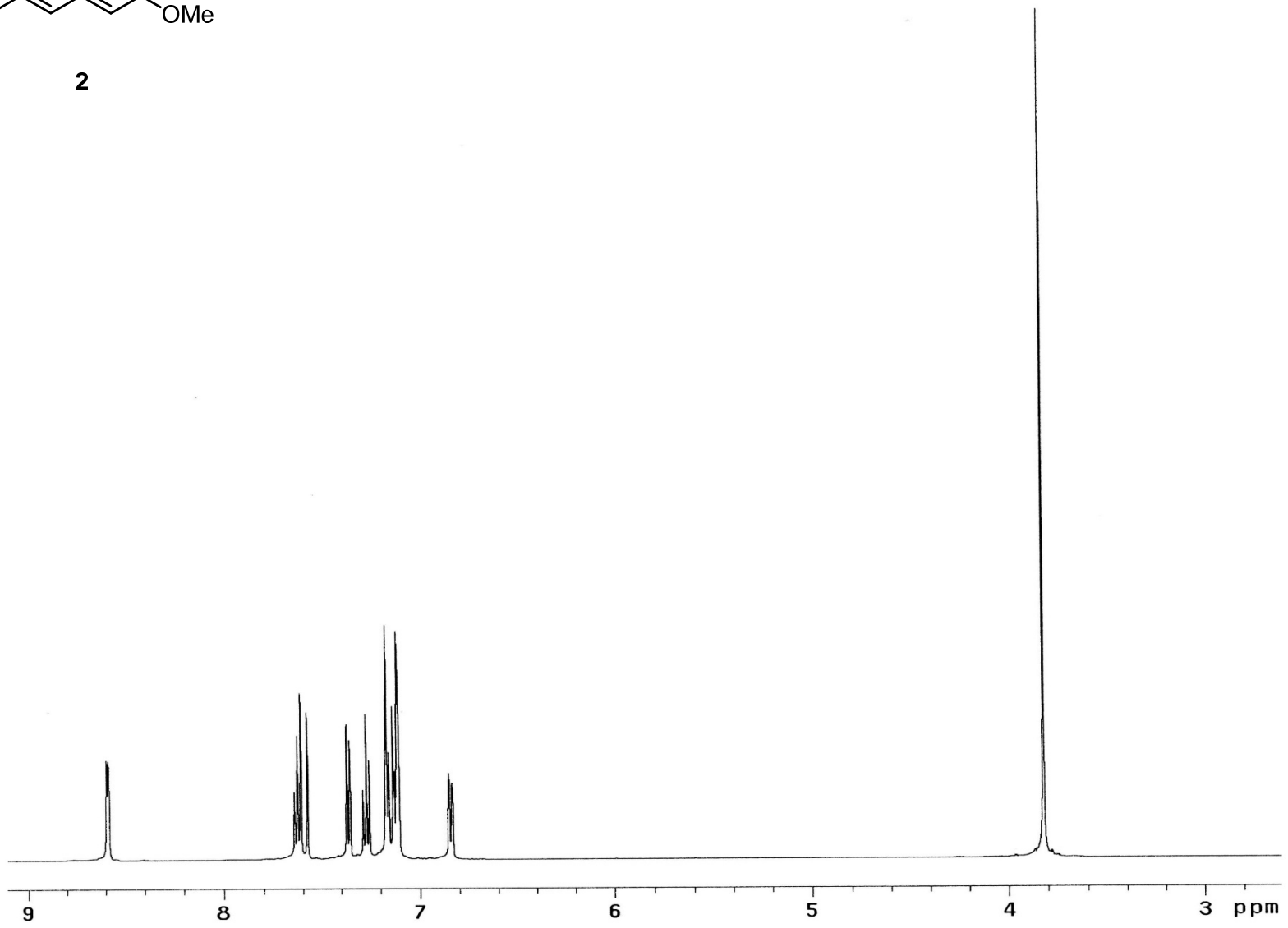

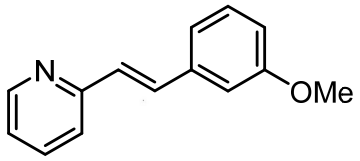

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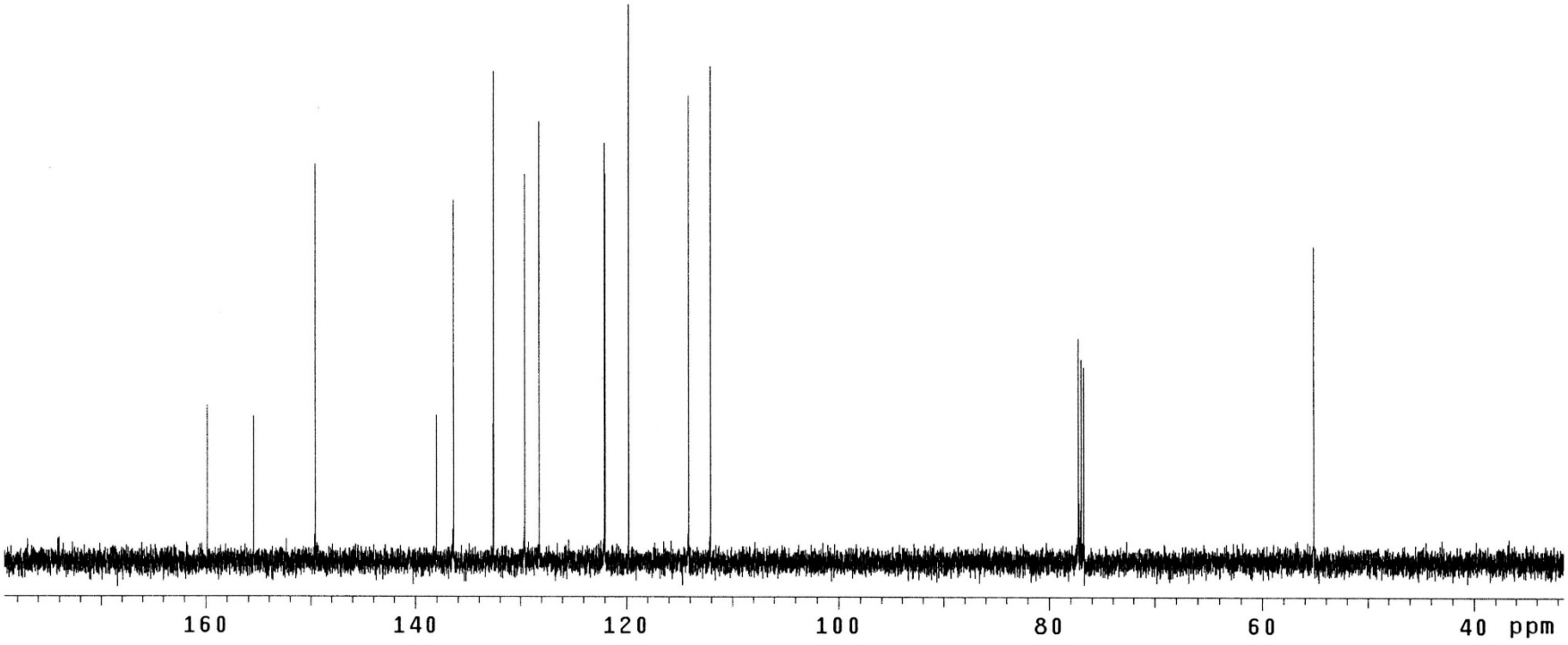

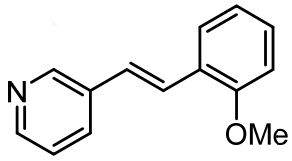

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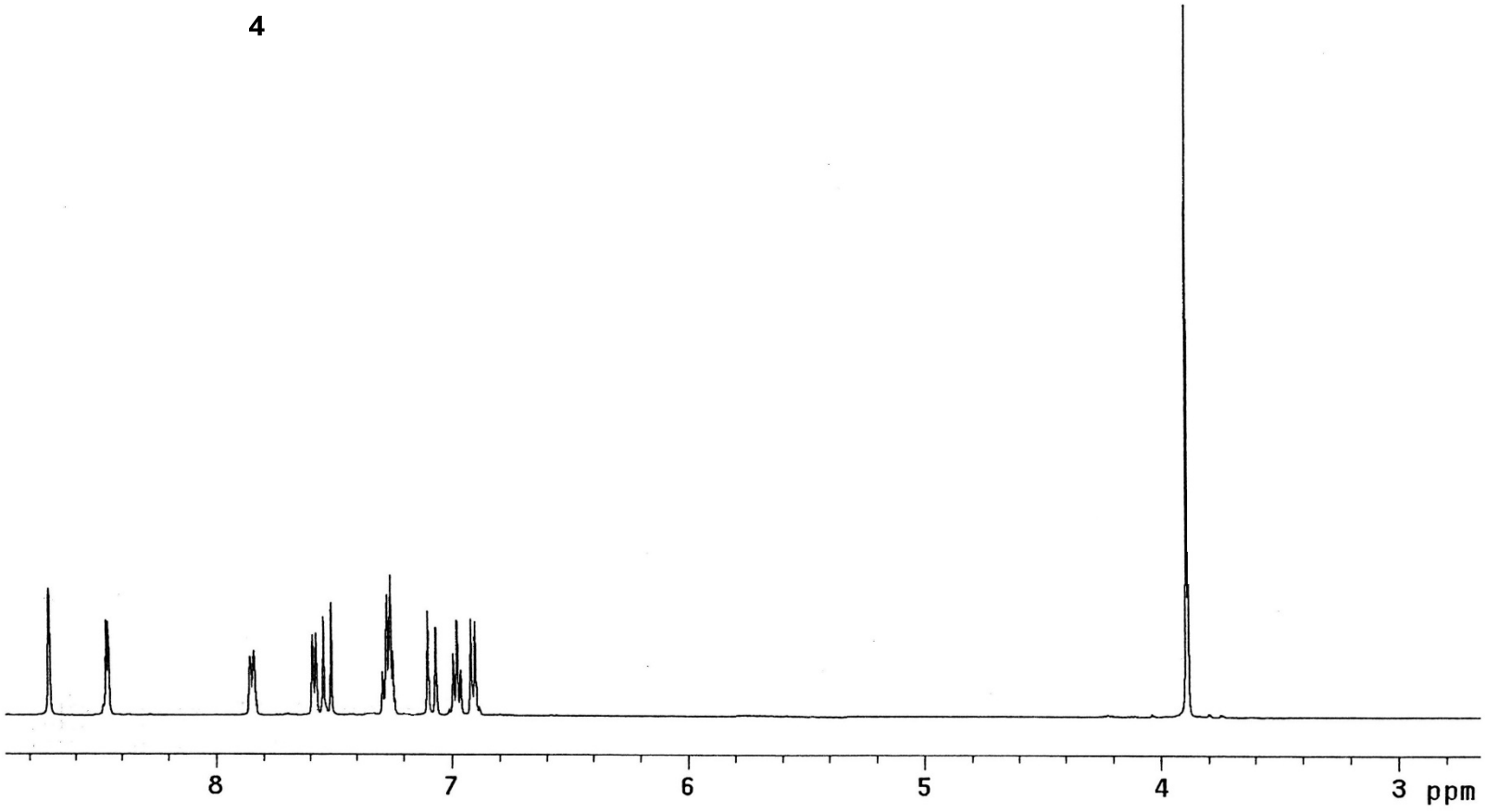

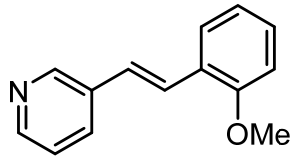

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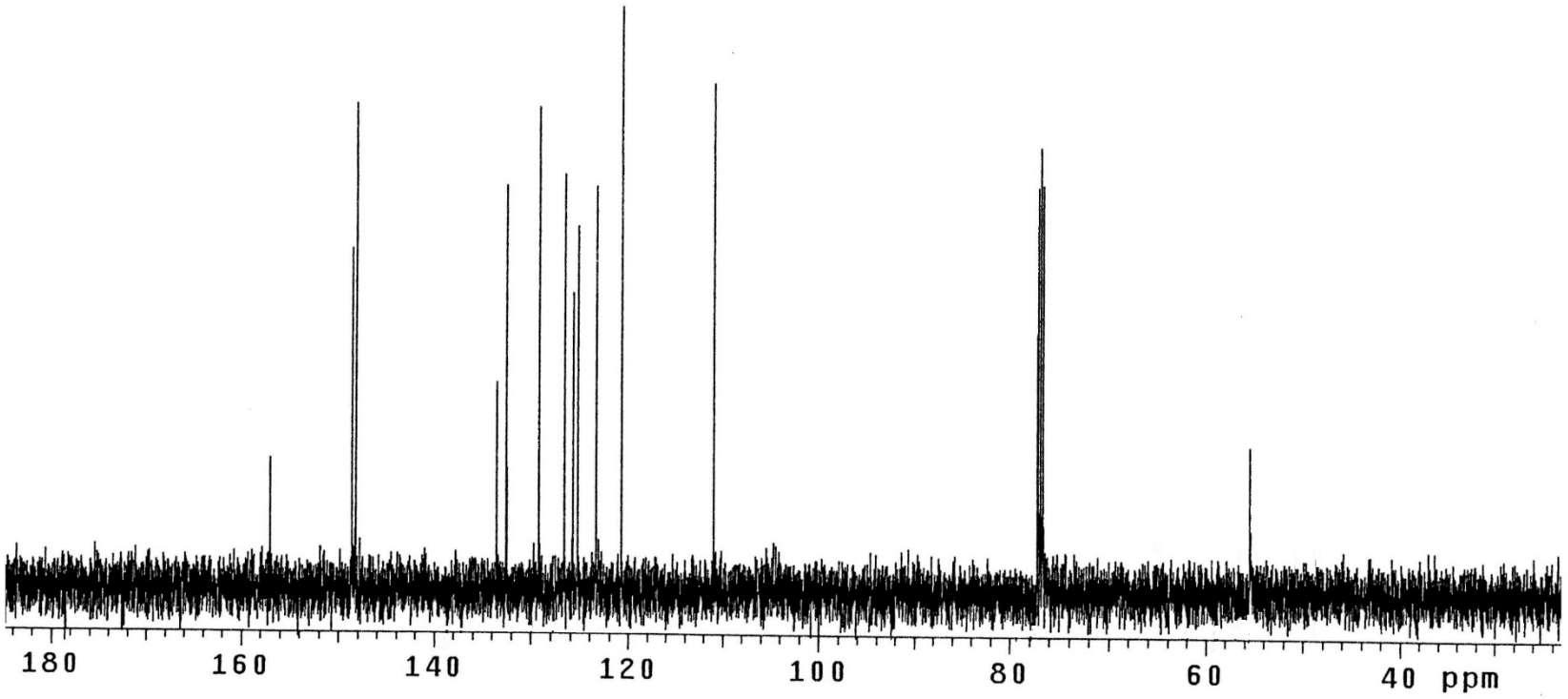

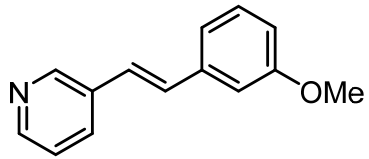

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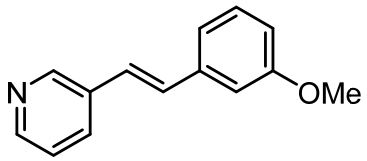

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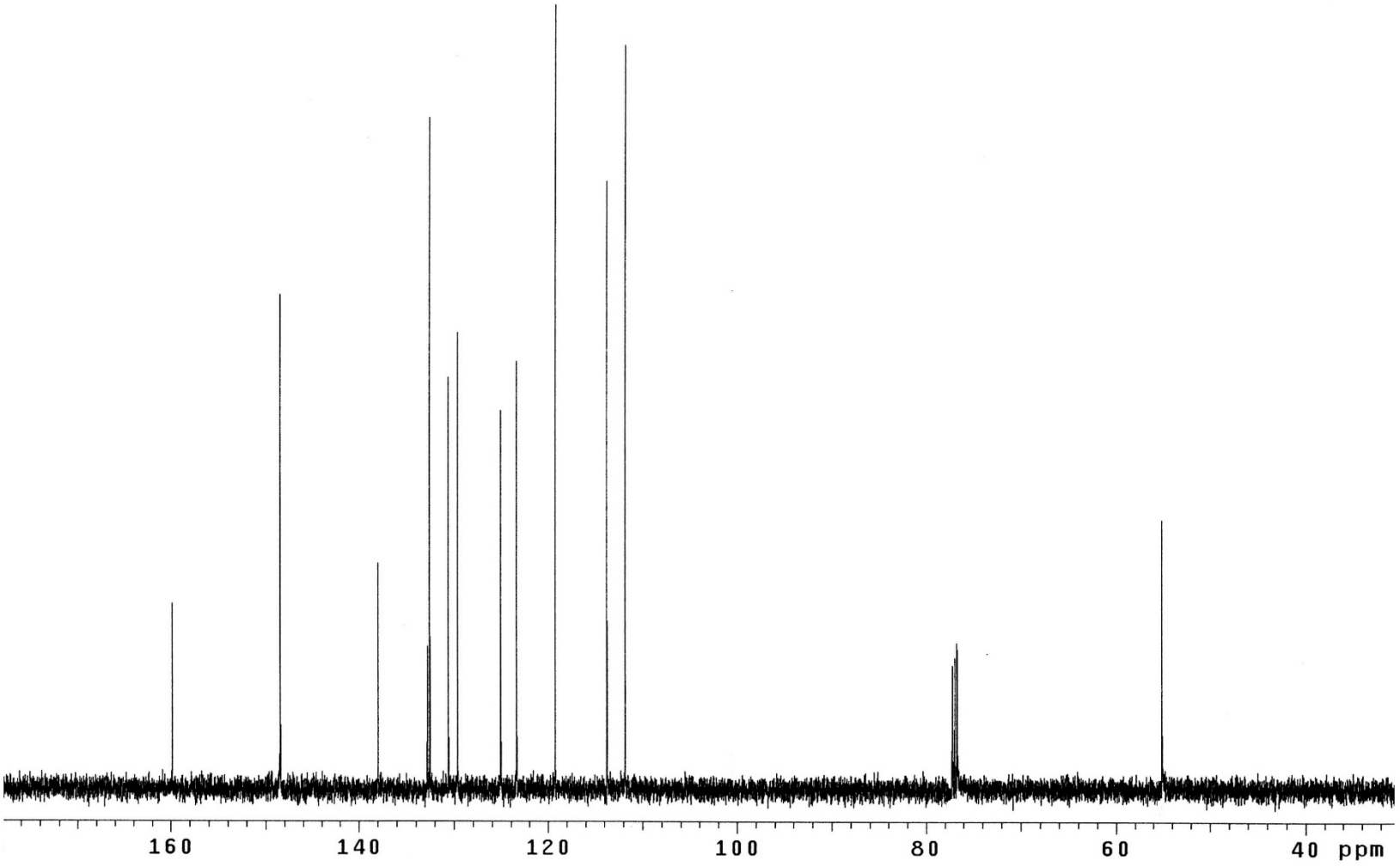

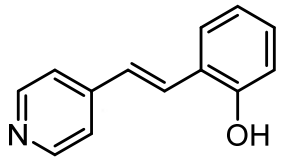

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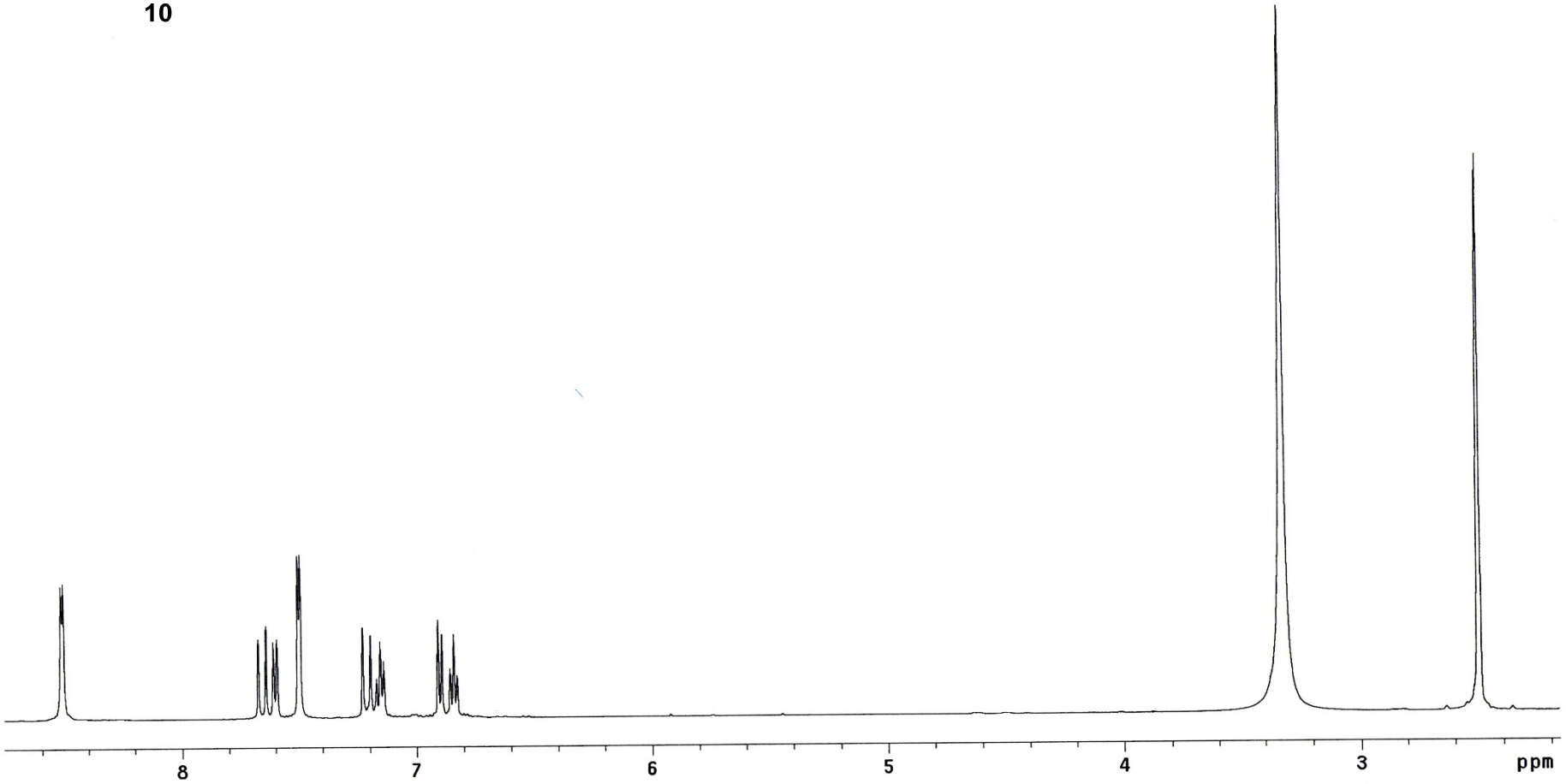

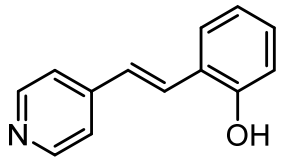

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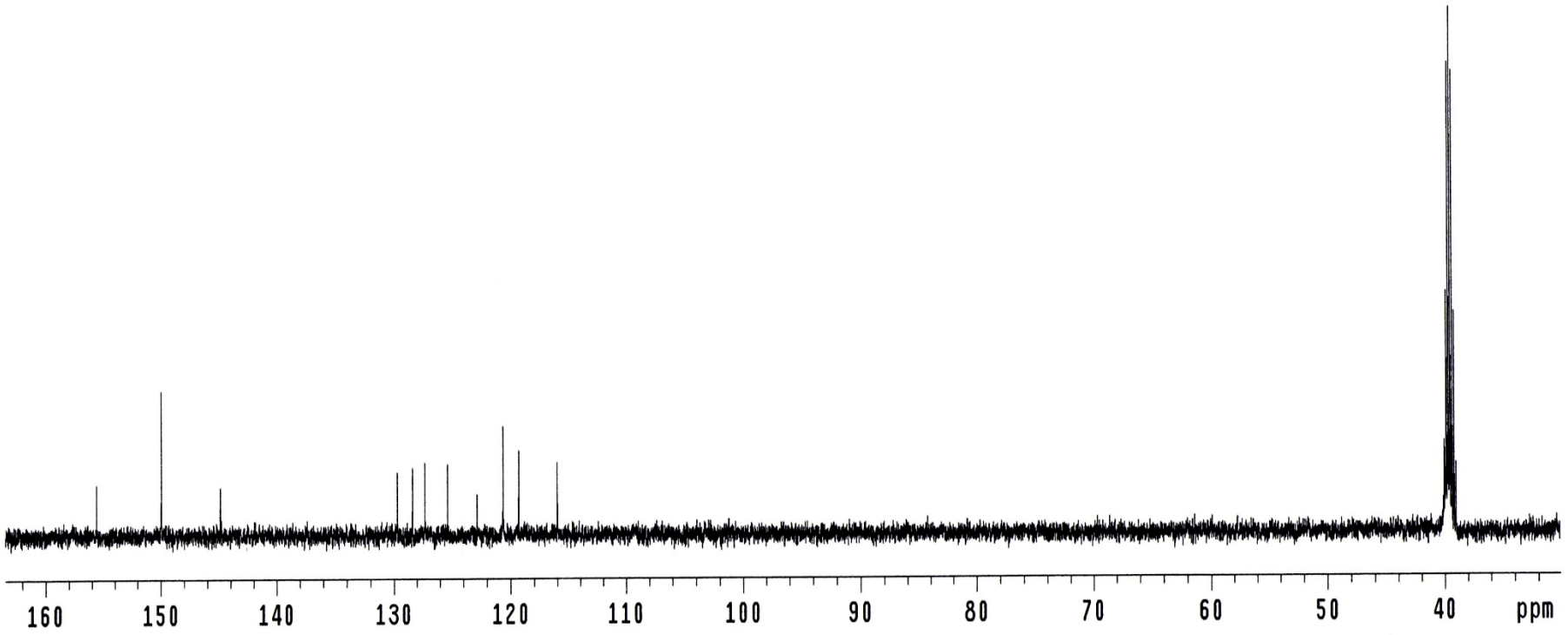

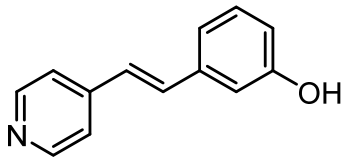

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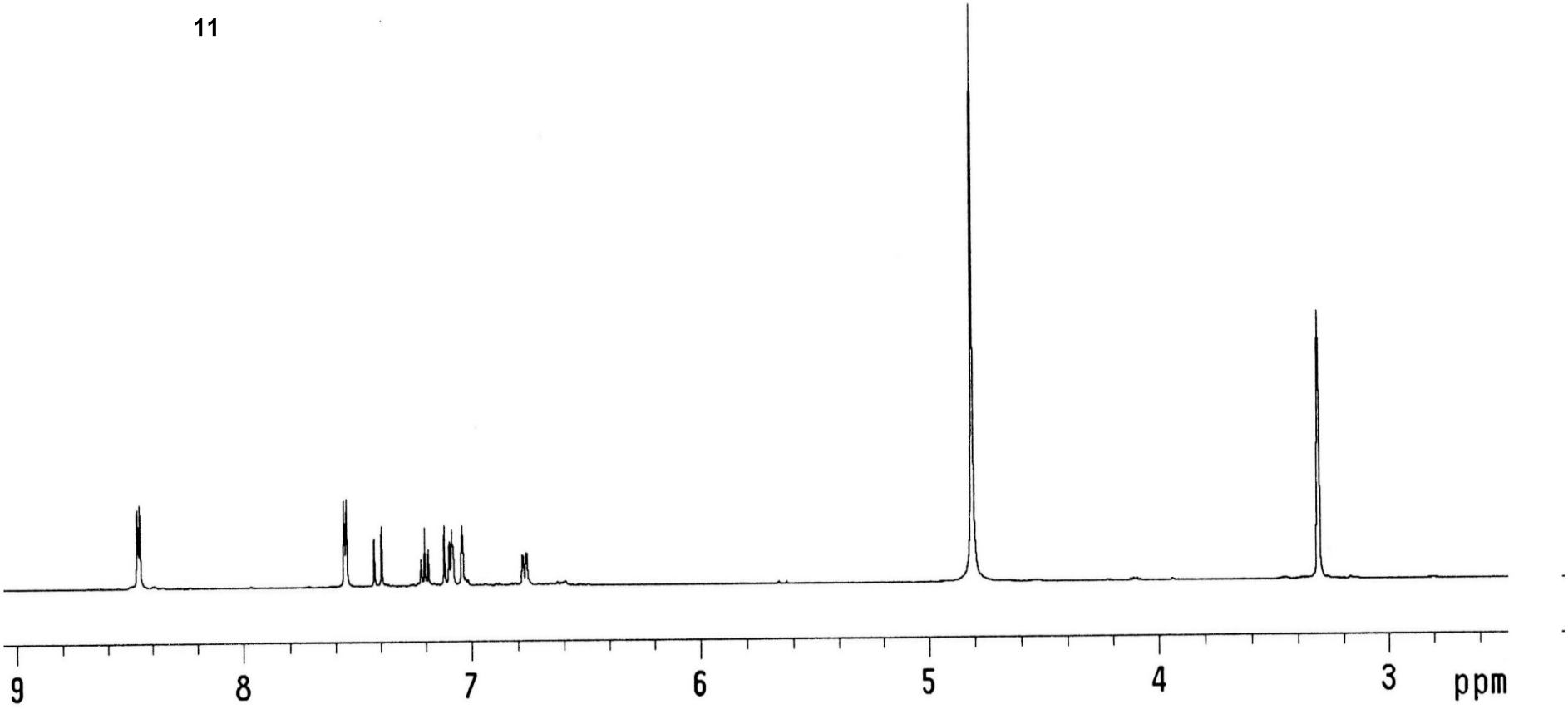

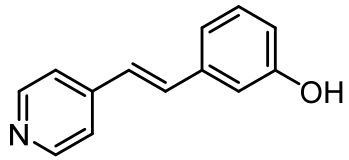

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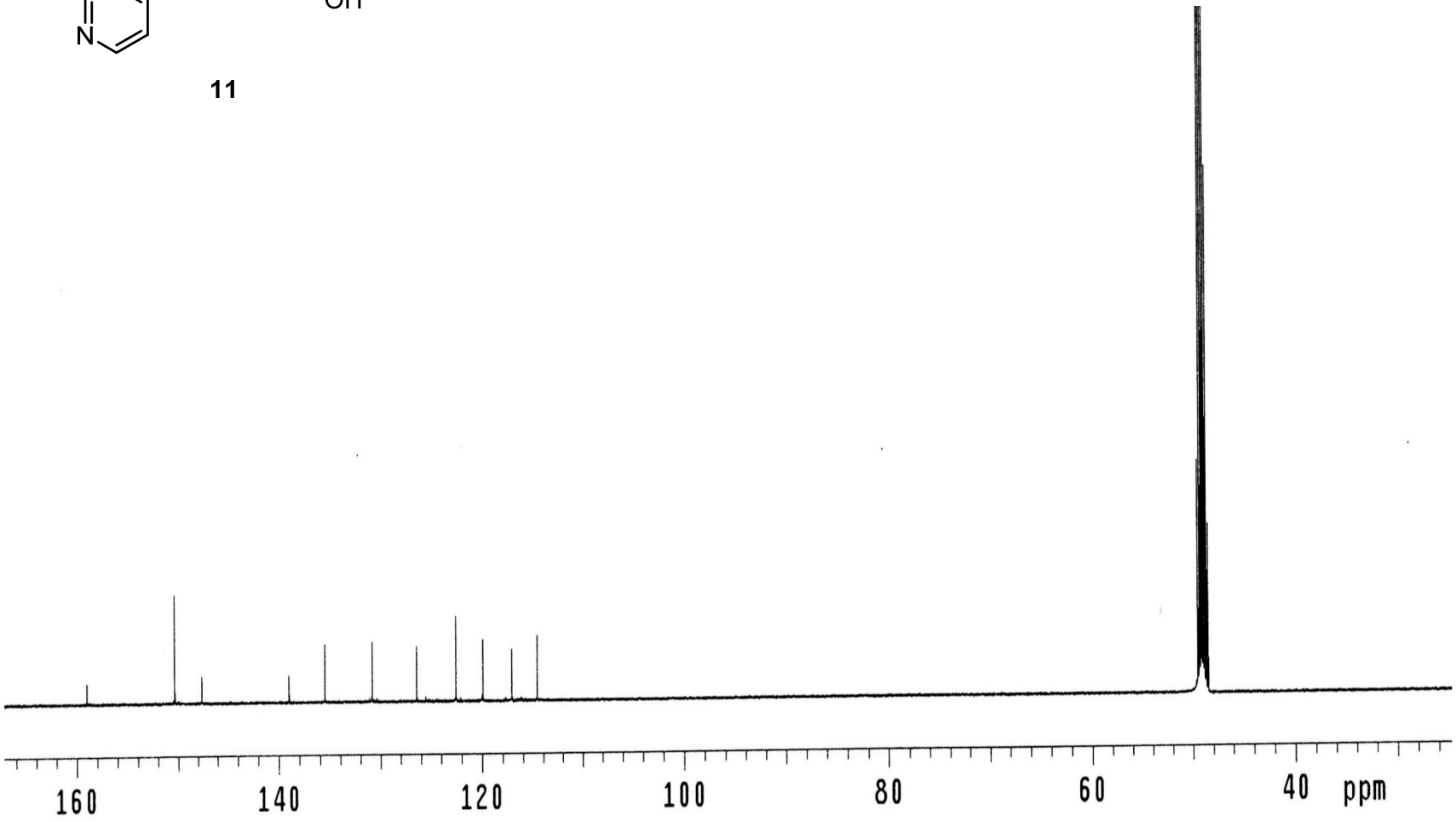

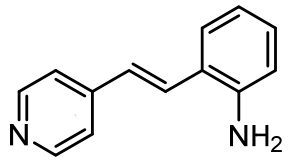

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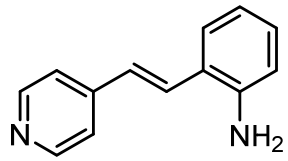

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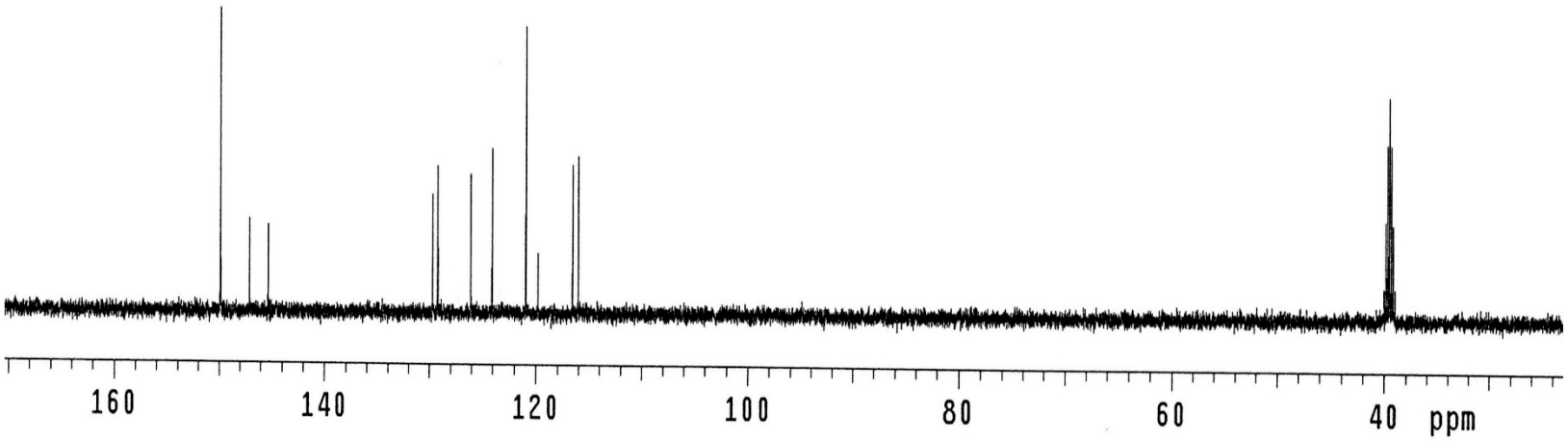

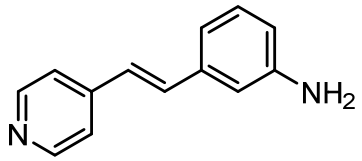

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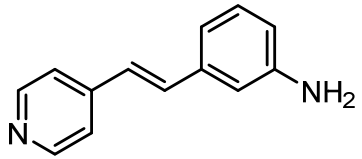

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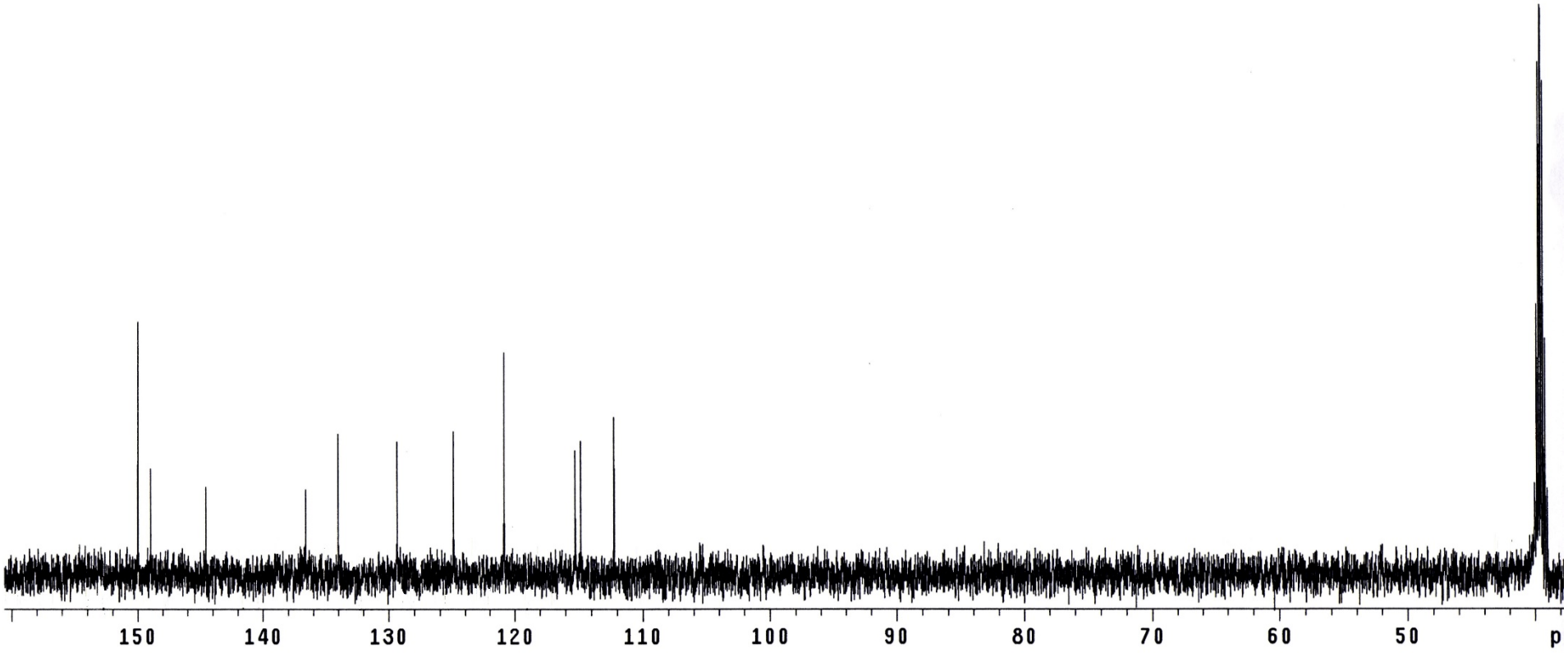

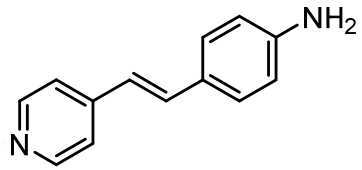

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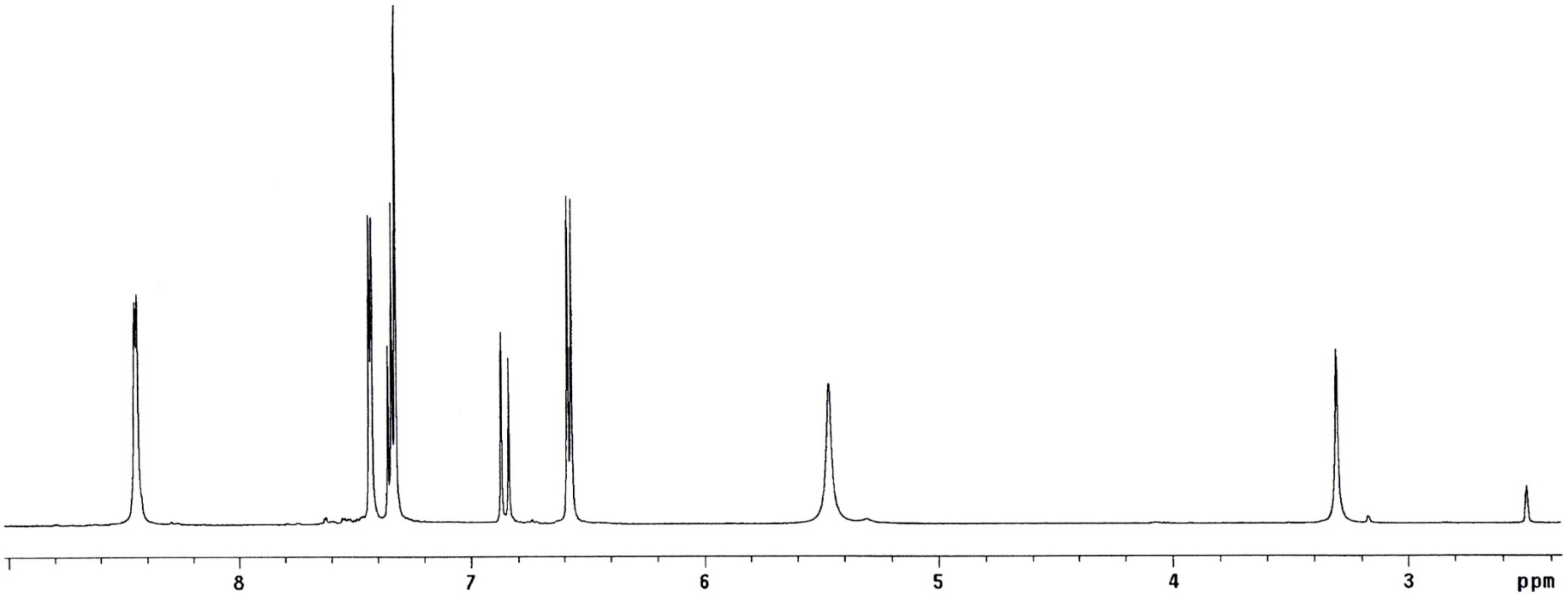

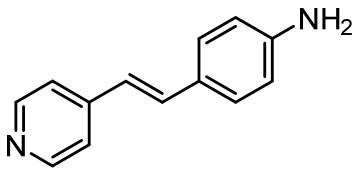

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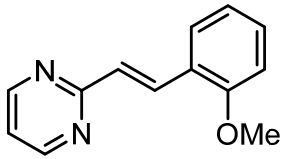

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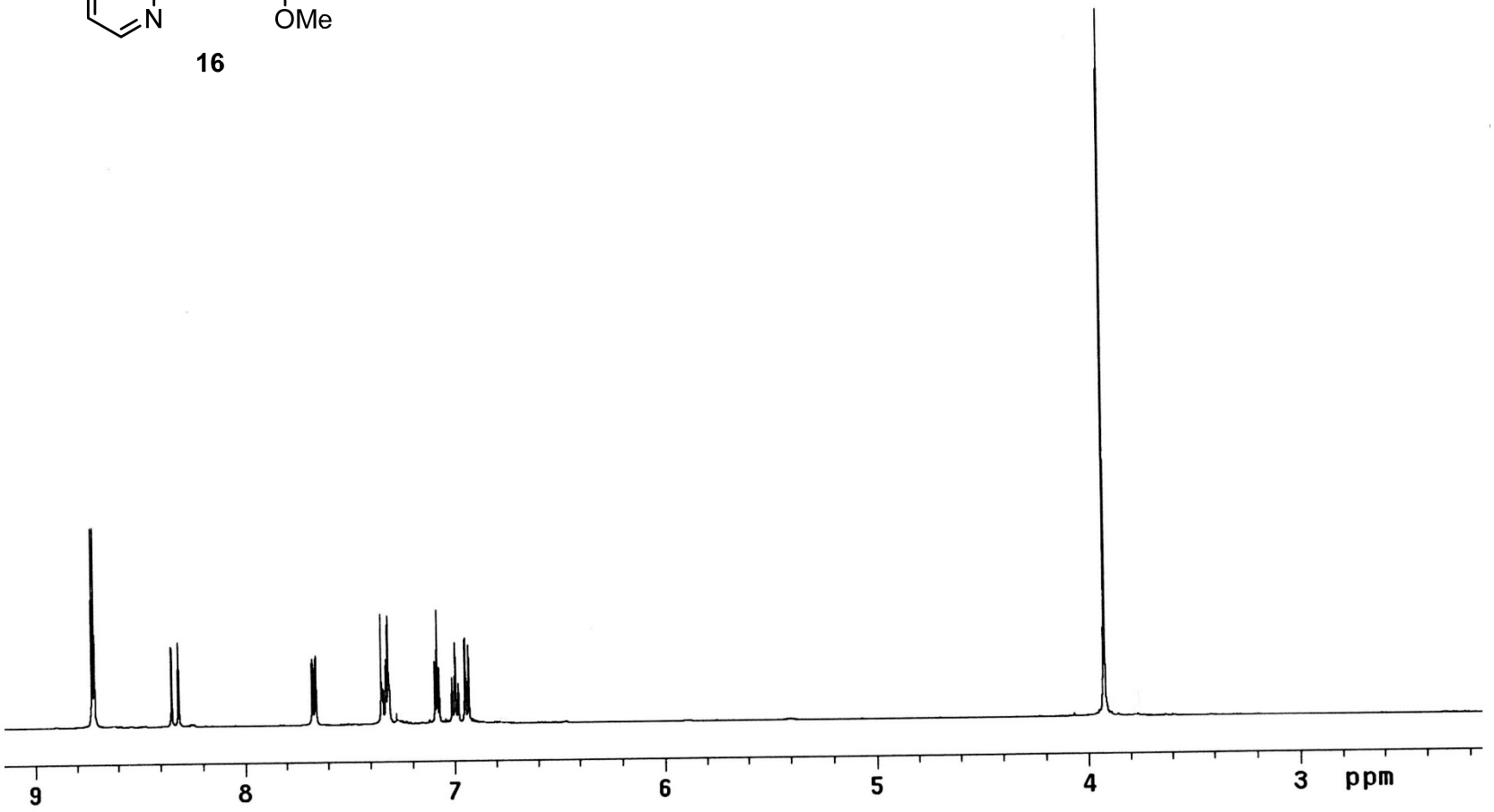

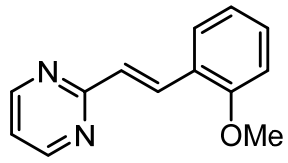

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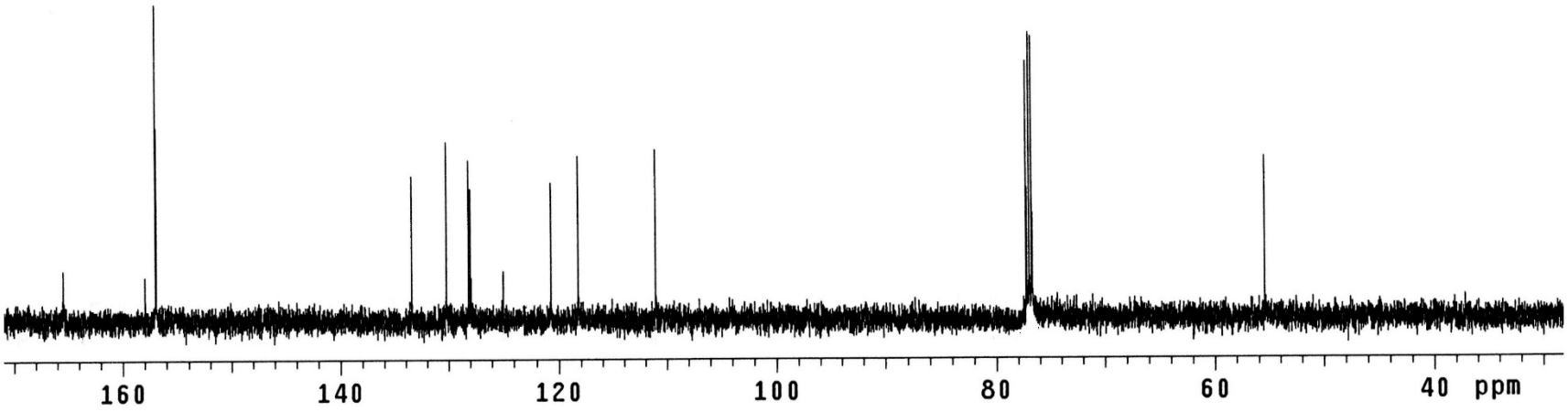

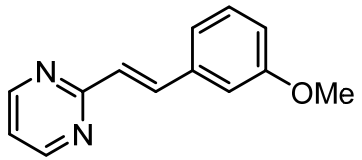

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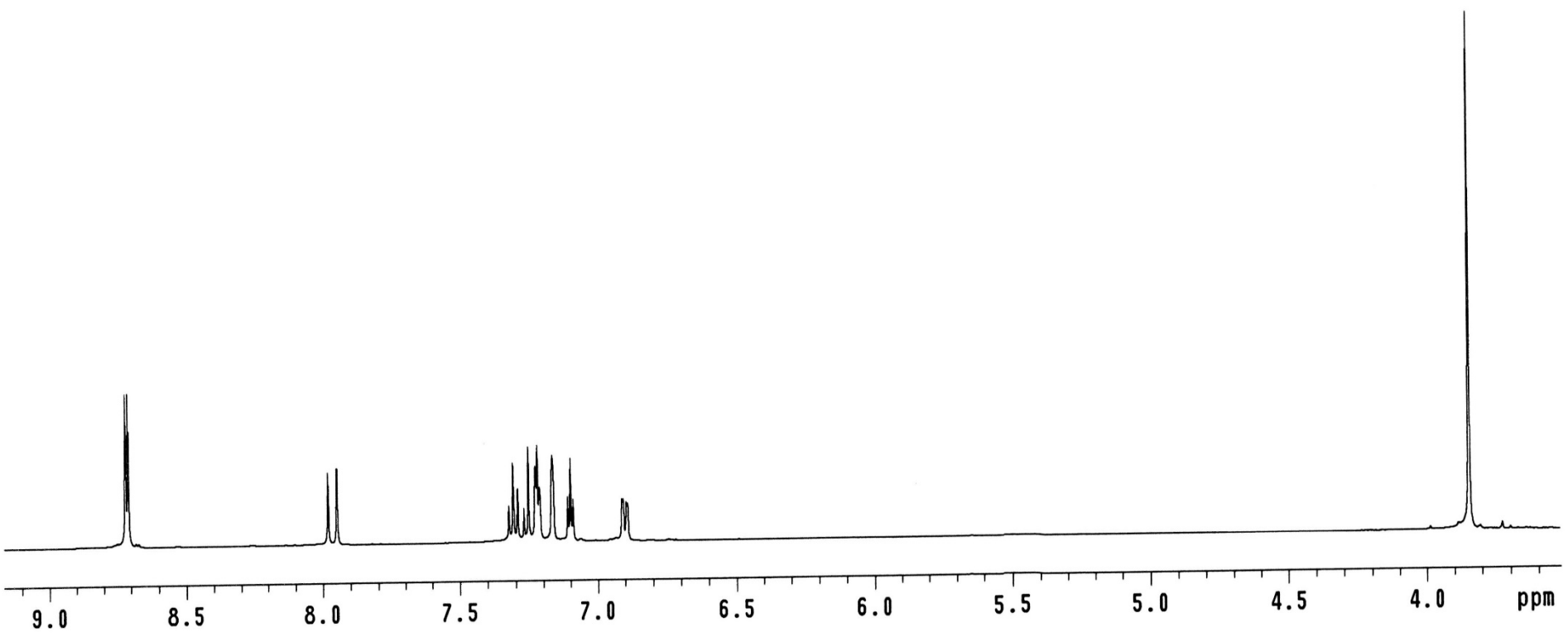

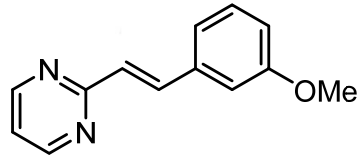

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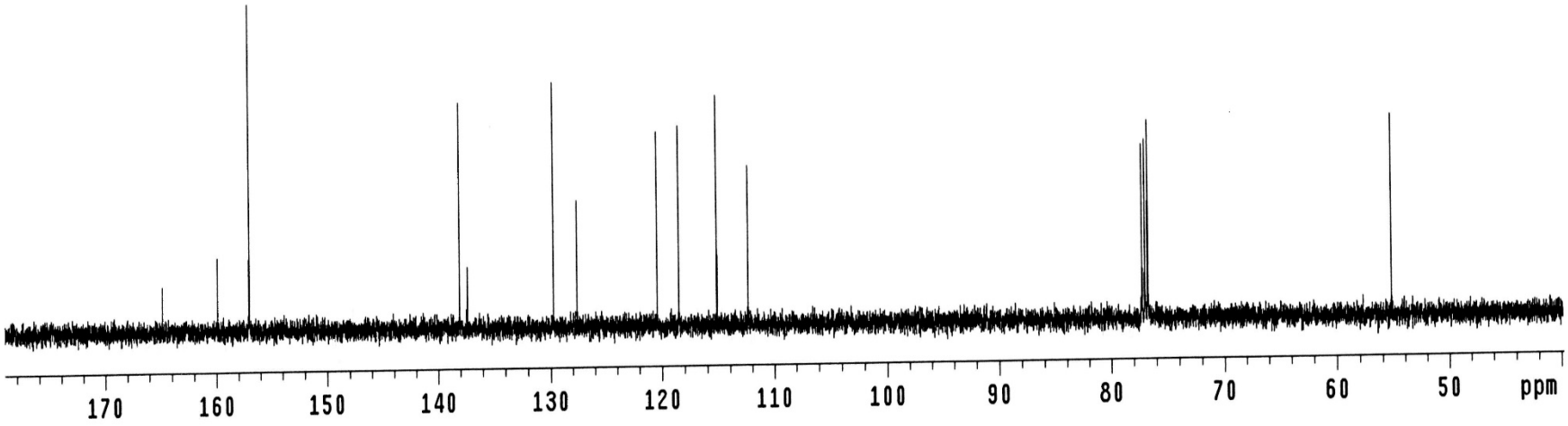

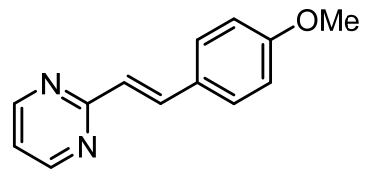

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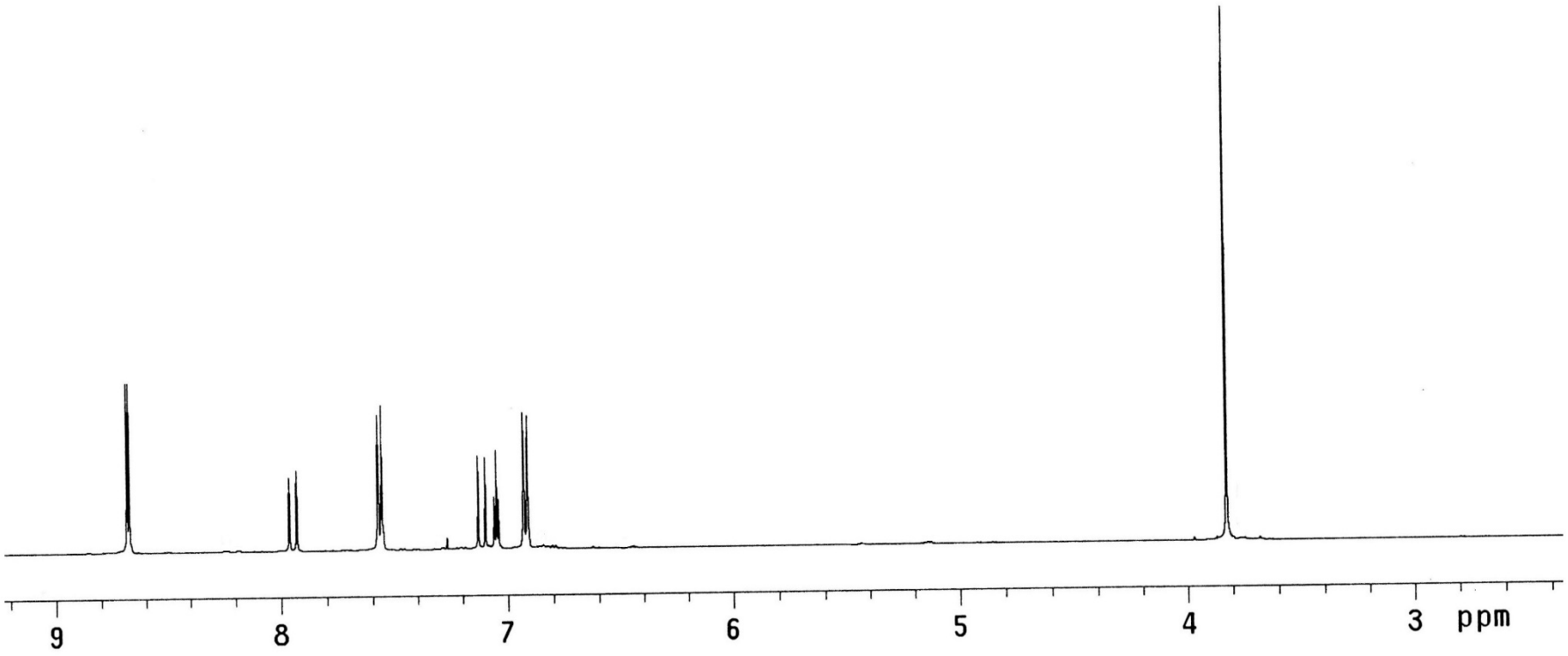

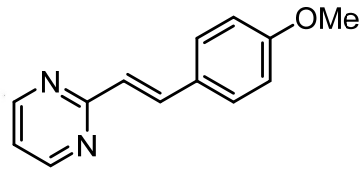

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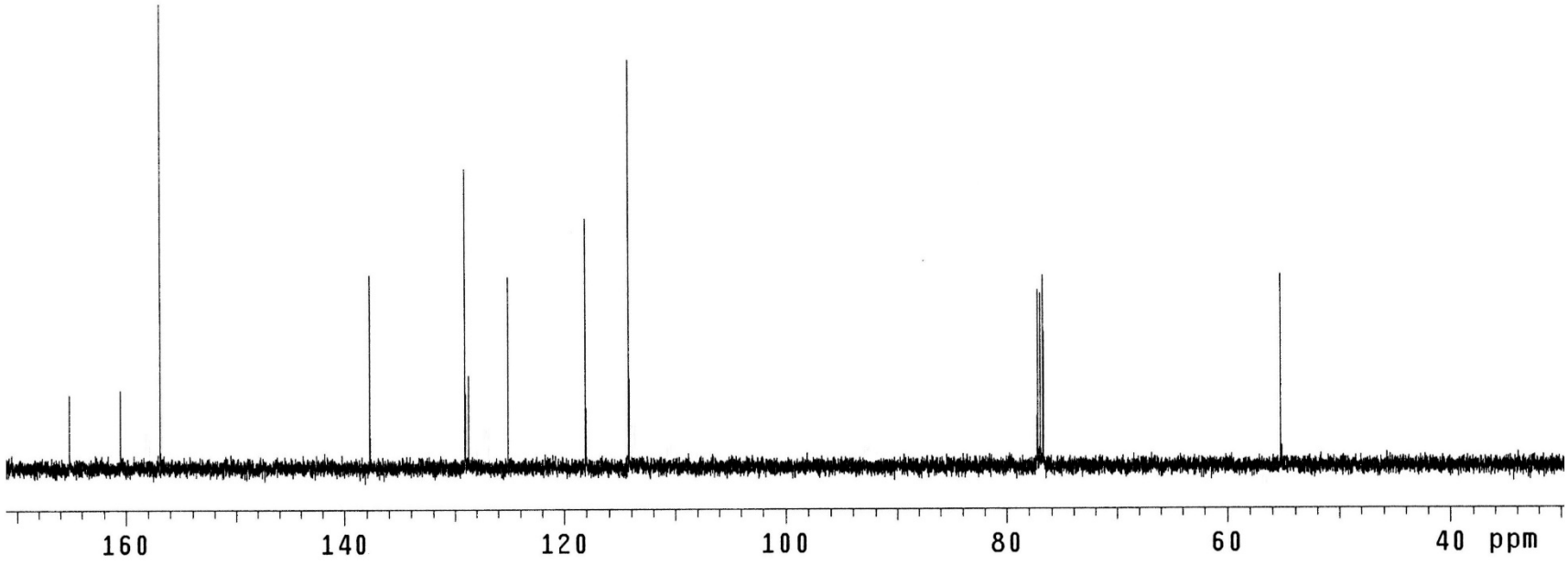

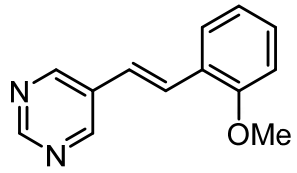

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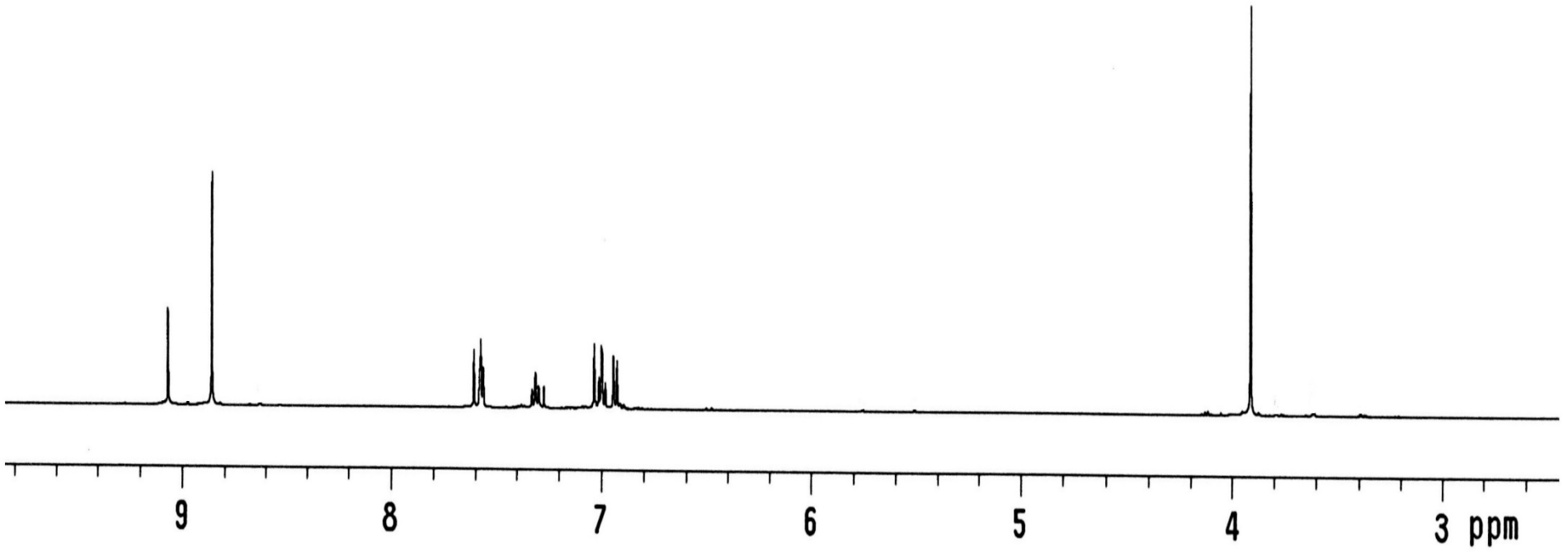

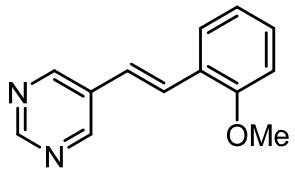

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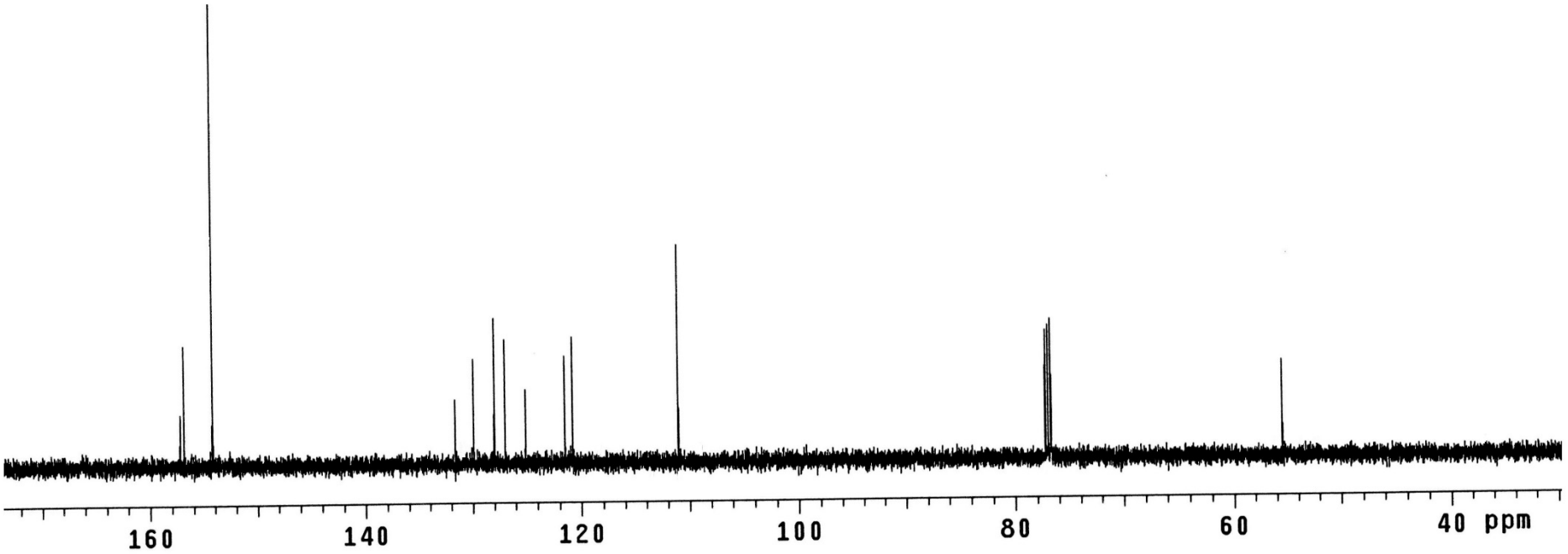

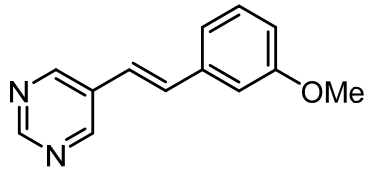

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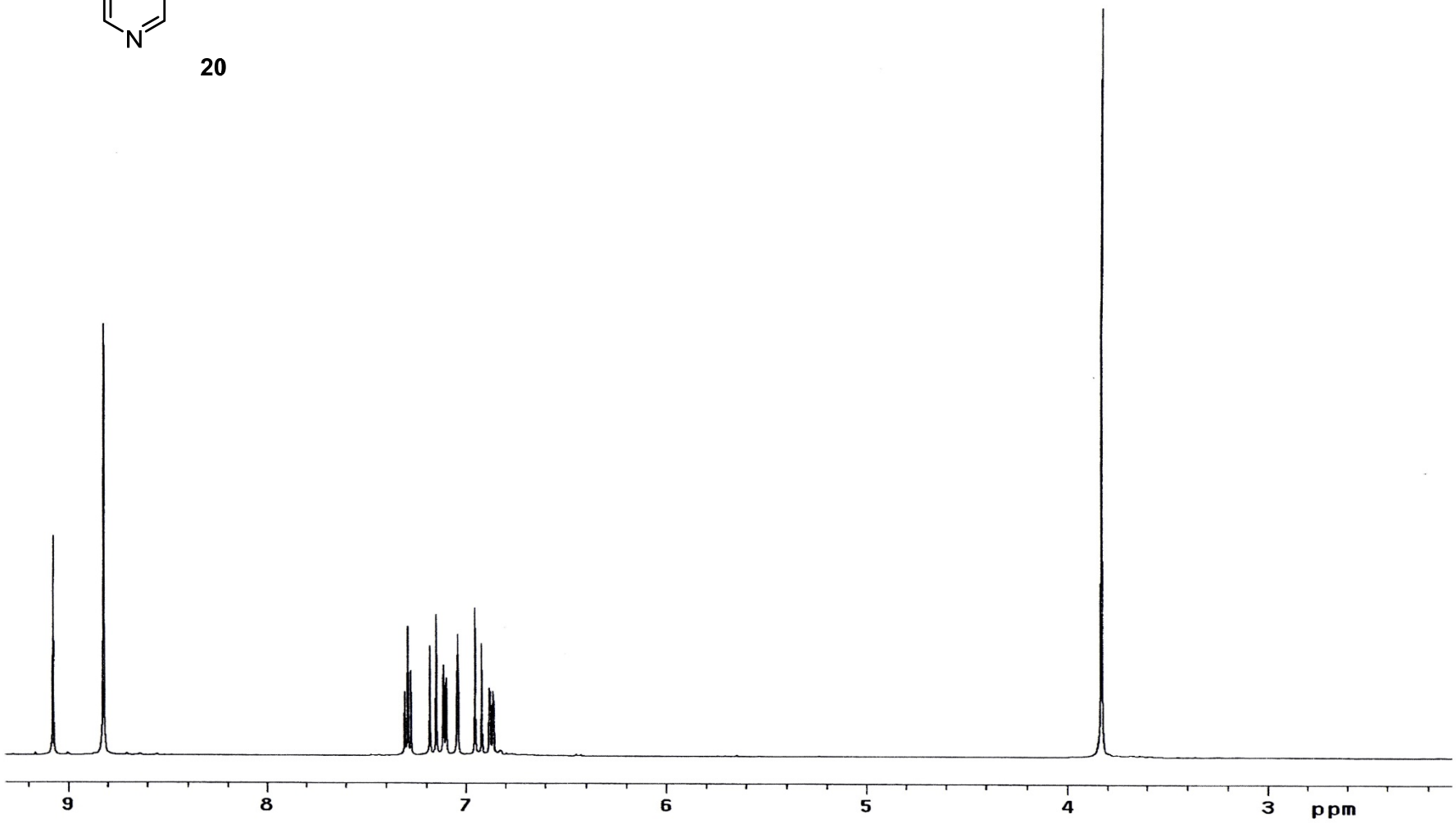

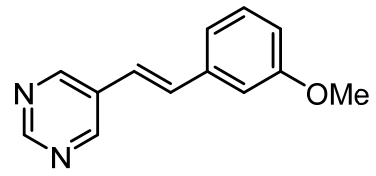

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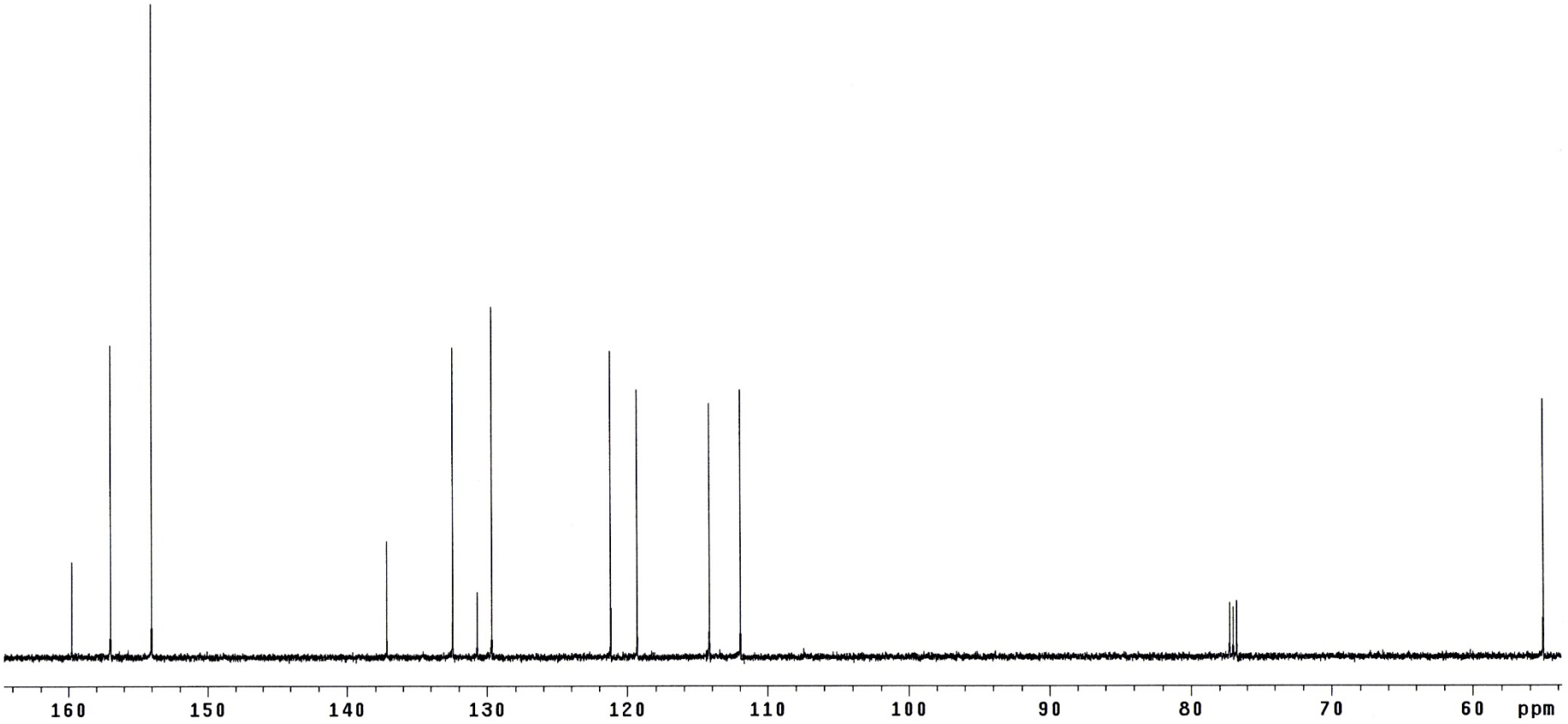

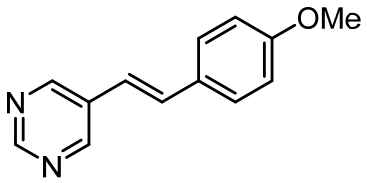

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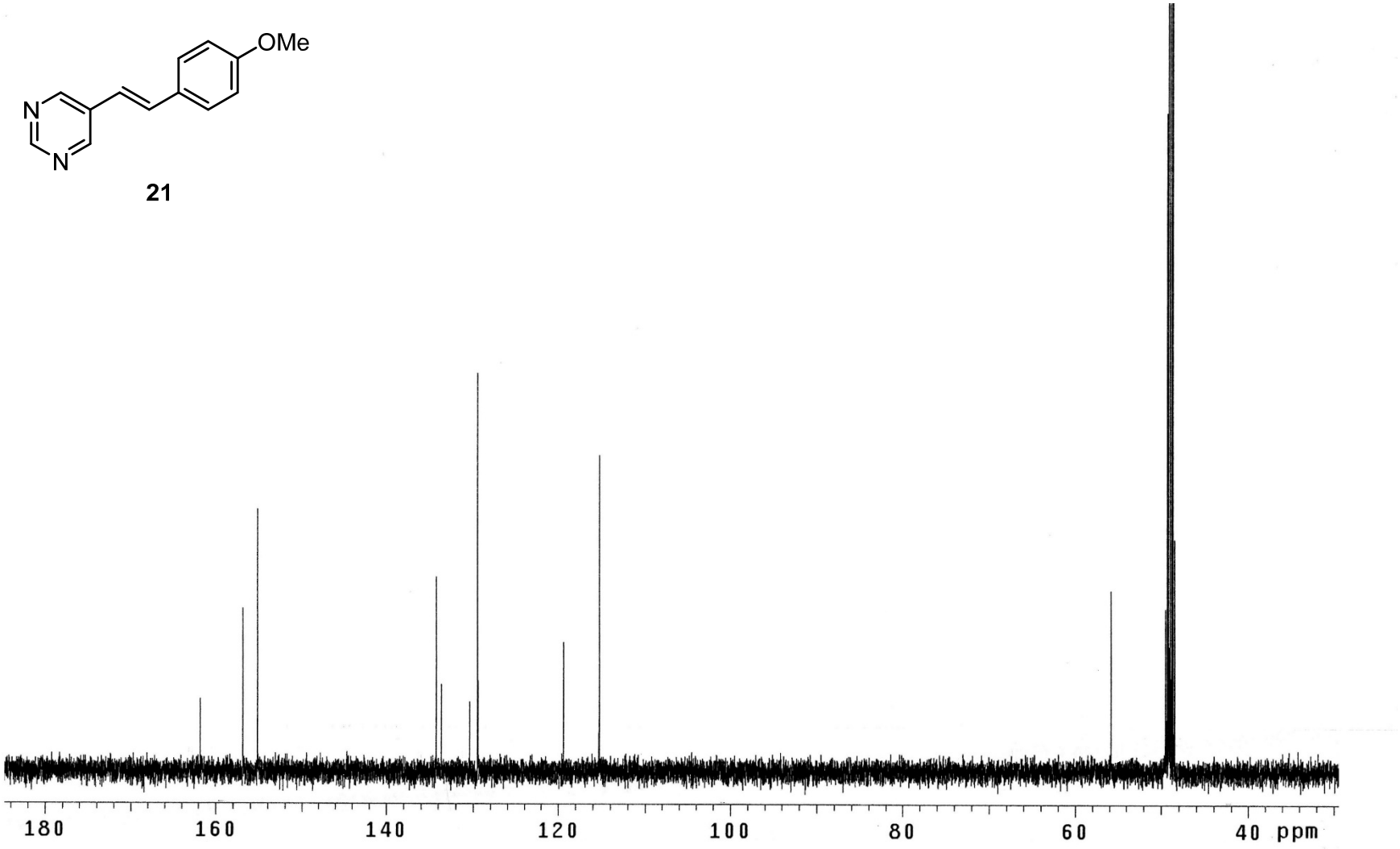
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