Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Study of Through-Space Substituent-π Interactions Using *N*-Phenylimide Molecular Balances

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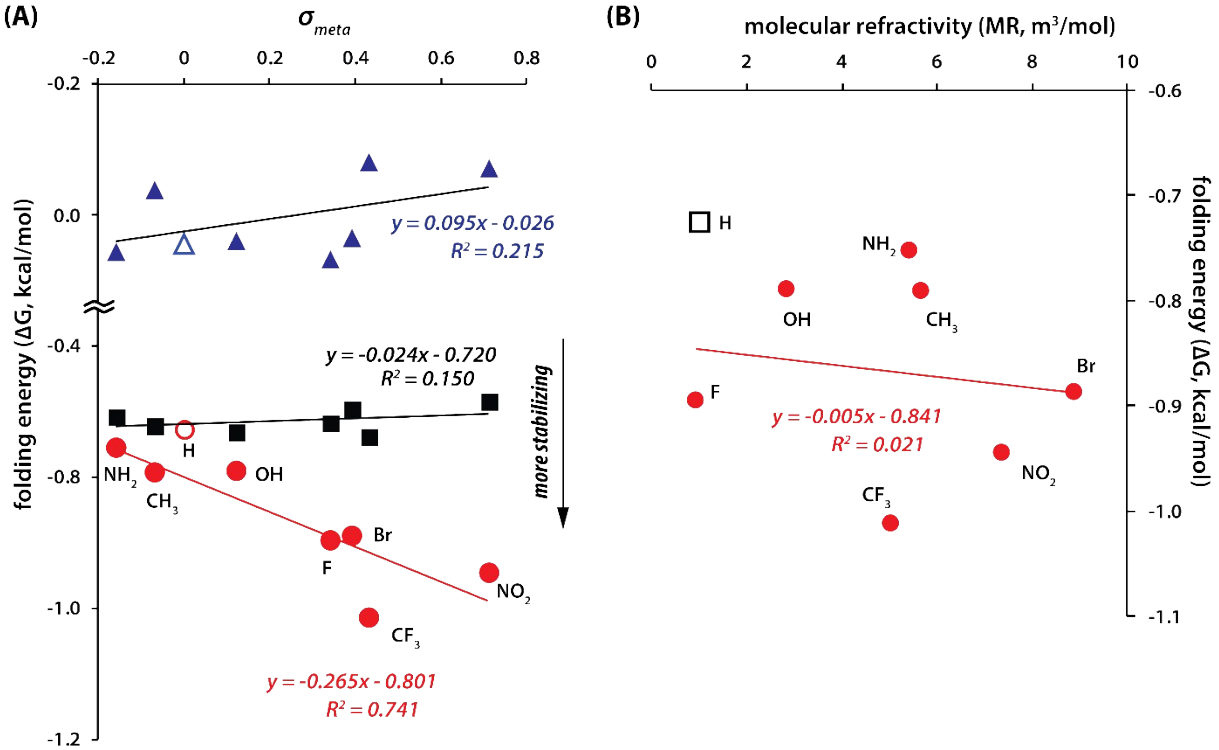


Figure S1. (A) Correlation plots of measured folding energies (ΔG) of substituent-π (**1**) and control balances (**2** and **3**) in C_6D_6 with electrostatic Hammett σ_m parameters: substituted balances **1b-h** (red filled circles), unsubstituted balance **1/2a** (red open circle), substituted **2b-h** (black filled squares), substituted **3b-h** (blue solid triangles), unsubstituted **3a** (blue open triangle). The uns

ubstituted balances **1/2a**, and **3a** were excluded from the linear regression.. **(B)** Correlation of measured folding energies (ΔG) of substituent-π balances (**1**) in C_6D_6 with the dispersion/polarizability molecular refractivity (MR) parameters.

Table S1. ^{1}H NMR measured folding energies for the substituent-π balances **1** (ΔG_1, kcal/mol) and control balances **2** (ΔG_2, kcal/mol) and **3** (ΔG_3, kcal/mol) at 25 °C in C_6D_6. Error for measured folding energies was within ±0.02 kcal/mol.

	Substituent (X)	ΔG_1	ΔG_2	ΔG_3
(a)	H	-0.73	-0.73	-0.05
(b)	NH_2	-0.75	-0.71	-0.06
(c)	CH_3	-0.79	-0.72	0.04
(d)	OH	-0.79	-0.73	-0.04
(e)	F	-0.90	-0.72	-0.07
(f)	Br	-0.89	-0.70	-0.04
(g)	CF_3	-1.01	-0.74	0.08
(h)	NO_2	-0.94	-0.68	0.07

General Experimental

All chemicals were purchased from commercial suppliers and used as received. Flash chromatography was performed using silica gel from Sorbent Technologies (60 Å, 200-400 mesh). NMR spectra were recorded on Bruker Avance III 400 MHz spectrometer. Chemical shifts are reported in ppm (δ) referenced to TMS. HRMS was recorded with a magnetic sector spectrometer using EI sources and the Q-TOF 1 spectrometer using ESI sources.

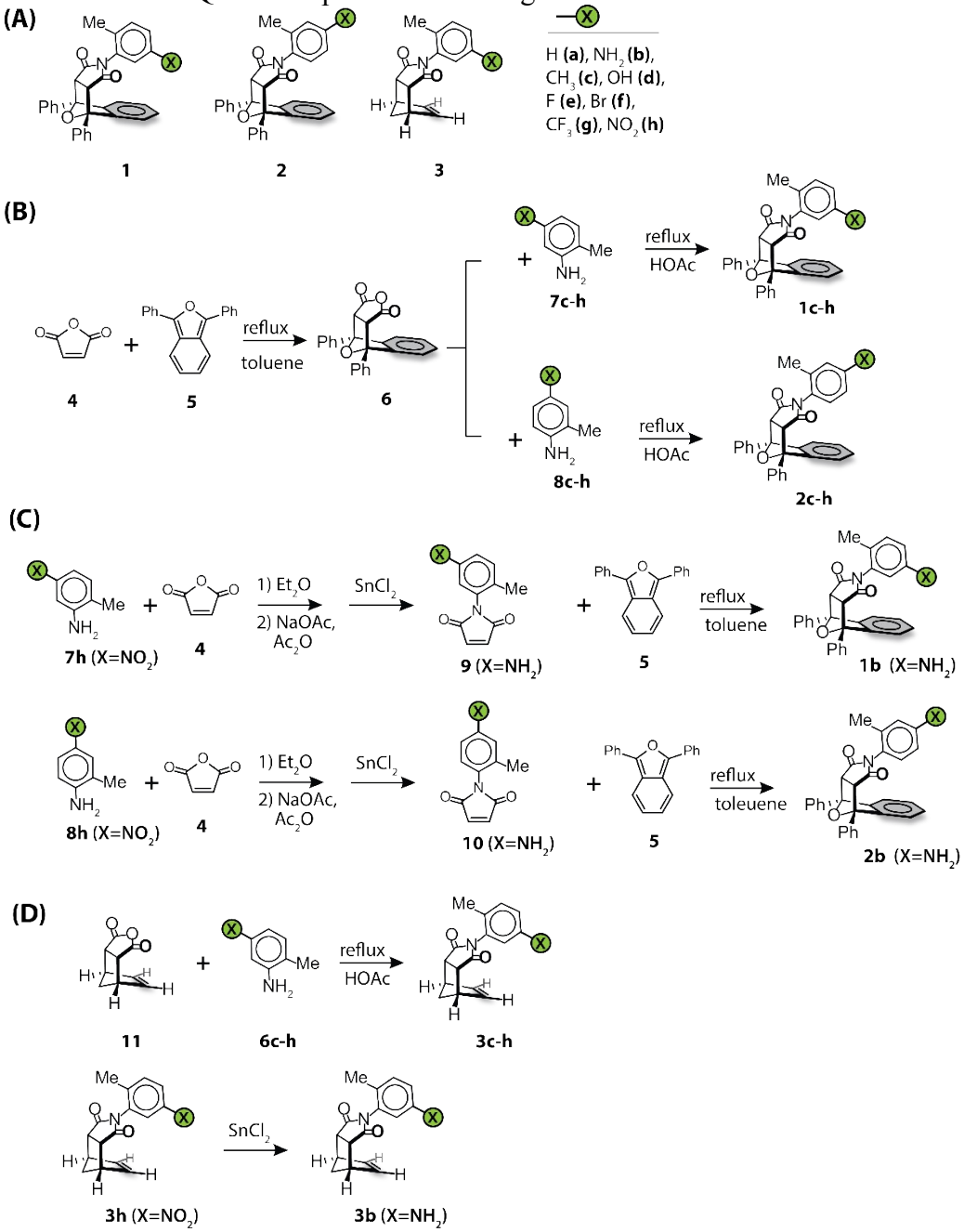
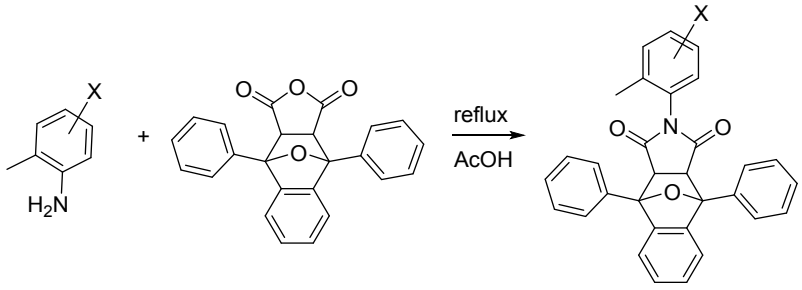


Figure S2. (A) Chart of structures of substituent-π (**1**) and control (**2** and **3**) balances. **(B-D)** The synthetic routes for preparing these molecular balances.

Balances **1a**, **1c-h**, and **2c-h** were prepared following the previously reported procedures[1-2] (Figure S2B) from commercially available maleic anhydride (**4**), 1,3-diphenylisobenzofurane (**5**), and corresponding *o*-toluidine derivatives **7/8c-h**. Balances **1b** and **2b** were prepared in a slightly modified procedure (Figure S2C) via amino maleimide derivatives (**9** and **10**). Balances **3a** and **3c-h** were prepared following the reported procedure (Figure S2D) from *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**10**) and corresponding *o*-toluidine derivatives (**7c-h**), and balance **3b** was prepared via reduction of **3h** using $SnCl_2$. Balances **1**, **1c**, **1e**, **1g**, **2f**, **3a** and bicyclic anhydride **5** have been reported in our previous studies,[2-3] and their synthesis and characterization are not detailed here. All other balances are newly reported compounds and fully characterized.



7/8c-h **6** **1/2c-h**

General synthetic procedure for preparing balances 1/2c-h via the thermal condensation between *o*-toluidine derivatives 7/8c-h and bicyclic anhydride 6 (Figure S2B).

Bicyclic anhydride **6** and *o*-toluidine derivative **7/8c-d** were heated at reflux in glacial acetic acid for 24 h. The solvent was removed under reduced pressure, and then the reaction mixture was dissolved in EtOAc (~50 mL). The organic solution was washed with saturated $NaHCO_3$ aq. (3 x 50 mL). The solvent in the isolated organic layer was removed under vacuum. The crude product was then purified by flash column chromatography (EtOAc: Hex = 1:3 to 1:6) or washed with MeOH.

2-(2,4-Dimethylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2c**)**.** *o*-Toluidine **8c** (80 μL, 0.65 mmol) and anhydride **6** (0.20 g, 0.54 mmol) were used following the general procedure above. The product **2c** was obtained as an off-white solid (0.15 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.04 (m, 4H), 7.56-7.50 (m, 4H), 7.49-7.44 (m, 2H), 7.32-7.28 (m, major 2H), 7.21-7.18 (m, minor 2H), 7.11-6.98 (m, 3H), 6.91 (s, minor 1H), 6.84-6.80 (m, 1H), 5.42 (d, J = 8.0 Hz, major 1H), 4.31 (s, minor 2H), 4.28 (s, major 2H), 2.27 (s, minor 3H), 2.26 (s, major 3H), 2.05 (s, major 3H), 1.06 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.1, 144.8, 144.2, 139.4, 136.6, 136.4, 135.1, 131.5, 131.4, 128.6, 128.5, 128.2, 128.1, 127.6, 127.5, 127.3, 127.1, 126.9, 121.1, 120.9, 90.5, 90.1, 54.5, 54.5, 21.0, 17.5, 16.8. HRMS (EI) Calcd for $C_{32}H_{25}NO_3$: 471.1834; found: 471.1834.

2-(5-Hydroxy-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**1d**). *o*-Toluidine **7d** (0.33 g, 0.27 mmol) and anhydride **6** (0.10 g, 0.27 mmol) were reacted following the abovementioned procedure. The product **1d** was obtained as an off-white solid (0.90 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.05 (m, 4H), 7.58-7.54 (m, 4H), 7.51-7.46 (m, 2H), 7.38-7.34 (m, major 2H), 7.23-7.20 (m, minor 2H), 7.15-7.05 (m, 3H), 6.97 (d, J = 8.4 Hz, minor 1H), 6.75-6.68 (m, 1H), 6.45 (d, J = 2.4 Hz, minor 1H), 5.04 (d, J = 2.4 Hz, major 1H), 4.74 (br, minor 1H), 4.52 (br, major 1H), 4.35 (s, minor 2H), 4.32 (s, major 2H), 2.02 (s, major 3H), 1.01 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 153.8, 144.8, 144.3, 139.7, 136.3, 131.5, 130.9, 128.7, 128.6, 128.2, 127.6, 127.1, 121.2, 121.0, 117.3, 116.8, 114.8, 114.3, 111.5, 90.5, 90.2, 54.6, 16.8, 16.0. HRMS (EI) Calcd for $C_{31}H_{23}NO_4$: 473.1627; found: 473.1626.

2-(4-Hydroxy-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2d**). *o*-Toluidine **8d** (0.33 g, 0.27 mmol) and anhydride **6** (0.10 g, 0.27 mmol) were reacted following the abovementioned procedure. The product **2d** was obtained as an off-white solid (0.060 g, 43%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.07-8.02 (m, 4H), 7.56-7.50 (m, 4H), 7.49-7.44 (m, 2H), 7.33-7.29 (m, major 2H), 7.21-7.18 (m, minor 2H), 7.10-7.03 (m, 2H), 6.68 (d, J = 8.4 Hz, minor 1H), 6.43-6.40 (m, 1H), 6.31 (d, J = 2.4 Hz, minor 1H), 6.24 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, major 1H), 5.72 (br, major 1H), 5.70 (br, minor 1H), 5.25 (d, J = 8.4 Hz, major 1H), 4.32 (s, minor 2H), 4.29 (s, major 2H), 1.95 (s, major 3H), 0.93 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.9, 156.5, 144.9, 144.3, 136.8, 136.2, 128.8, 128.6, 128.3, 128.2, 127.1, 127.1, 122.3, 121.0, 117.4, 113.7, 90.6, 90.2, 54.4, 17.6. HRMS (EI) Calcd for $C_{31}H_{23}NO_4$: 473.1627; found: 473.1629.

2-(4-Fluoro-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2e**). *o*-Toluidine **8e** (33 μL, 0.30 mmol) and anhydride **6** (0.10 g, 0.27 mmol) were reacted following the abovementioned procedure. The product **2e** was obtained as an off-white solid (0.085 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.03 (m, 4H), 7.56-7.51 (m, 4H), 7.50-7.46 (m, 2H), 7.34-7.29 (m, major 2H), 7.22-7.18 (m, minor 2H), 7.12-7.04 (m, 2H), 6.95-6.87 (m, 1H), 6.81 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, minor 1H), 6.74-6.69 (m, major 1H), 5.48 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, major 1H), 4.32 (s, minor 2H), 4.30 (s, major 2H), 2.08 (s, major 3H), 1.07 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 173.0, 163.9, 161.4, 144.8, 144.2, 138.2, 138.2, 136.4, 136.2, 129.0, 129.0, 128.7, 128.7, 128.6, 128.3, 128.2, 127.1, 127.0, 126.2, 121.1, 121.0, 117.6, 117.3, 113.7, 113.5, 90.5, 90.1, 54.5, 54.5, 17.8, 17.0. HRMS (EI) Calcd for $C_{31}H_{22}FNO_3$: 475.1584; found: 475.1583.

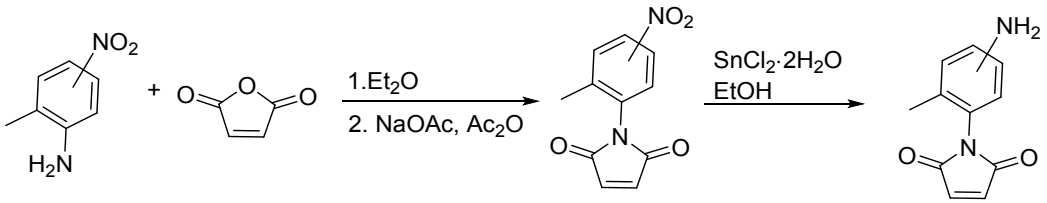
2-(5-Bromo-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**1f**). *o*-Toluidine **7f** (0.10 g, 0.54 mmol) and anhydride **6** (0.20 g, 0.54 mmol) were reacted following the abovementioned procedure. An off-white solid was obtained as product **1f** (0.23 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.02 (m, 4H), 7.57-7.52 (m, 4H), 7.50-7.46 (m, 2H), 7.39-7.30 (m, 3H), 7.21-7.18 (m, minor 2H), 7.15-7.04 (m, 3H), 6.97 (d, J = 8.4 Hz, minor 1H), 5.58 (d, J = 2.0 Hz, major 1H), 4.31 (s, minor 2H), 4.29 (s, major 2H), 2.05 (s, major 3H), 1.04 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.6, 144.8, 144.2, 136.4, 136.1, 134.8, 132.4, 132.1, 131.9, 131.5, 130.8, 130.4, 128.7, 128.7, 128.6, 128.4, 128.3, 127.0, 127.0, 121.1, 121.1, 119.1, 119.0, 90.6, 90.2, 54.6, 54.5, 17.2, 16.6. HRMS (EI) Calcd for $C_{31}H_{22}BrNO_3$: 535.0783; found: 535.0787.

2-(2-Methyl-4-(trifluoromethyl)phenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2g**)**.** *o*-Toluidine **8g** (0.11 g, 0.65 mmol) and anhydride **6** (0.20 g, 0.54 mmol) were reacted following the abovementioned procedure. An off-white solid was obtained as product **2g** (0.21 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.03 (m, 4H), 7.57-7.53 (m, 4H), 7.50-7.46 (m, 3H), 7.39-7.29 (m, 3H), 7.24-7.20 (m, minor 2H), 7.13-7.06 (m, 2H), 5.66 (d, J = 8.2 Hz, major 1H), 4.34 (s, minor 2H), 4.33 (s, major 2H), 2.17 (s, major 3H), 1.17 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 172.8, 172.6, 144.8, 144.2, 137.1, 136.8, 136.3, 136.0, 133.5, 131.6, 131.3, 128.7, 128.7, 128.6, 128.3, 128.2, 128.0, 127.7, 127.7, 127.0, 127.0, 124.8, 123.6, 123.6, 121.1, 121.0, 90.5, 90.2, 54.6, 20.6, 17.7, 17.1. HRMS (EI) Calcd for $C_{32}H_{22}F_3NO_3$: 525.1552; found: 525.1548.

2-(2-Methyl-5-nitrophenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**1h**)**.** *o*-Toluidine **7h** (0.086 g, 0.54 mmol) and anhydride **6** (0.20 g, 0.54 mmol) were reacted following the abovementioned procedure. An off-white solid was obtained as product **1h** (0.21 g, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.00 (m, 5H), 7.91 (d, J = 2.2 Hz, minor 1H), 7.57-7.52 (m, 4H), 7.51-7.43 (m, 4H), 7.38 (d, J = 8.4 Hz, major 1H), 7.23-7.20 (m, minor 2H), 7.14-7.11 (m, major 2H), 7.08-7.05 (m, minor 2H), 6.35 (d, J = 2.2 Hz, major 1H), 4.39 (s, minor 2H), 4.35 (s, major 2H), 2.20 (s, major 3H), 1.20 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 146.5, 144.0, 143.9, 136.0, 131.5, 131.3, 128.9, 128.7, 128.6, 128.4, 127.1, 127.0, 124.2, 123.5, 121.3, 121.1, 90.8, 54.8, 54.7, 18.1. HRMS (EI) Calcd for $C_{31}H_{22}N_2O_5$: 502.1529; found: 502.1539.

2-(2-Methyl-4-nitrophenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2h**)**.** *o*-Toluidine **8h** (0.045 g, 0.30 mmol) and anhydride **6** (0.10 g, 0.27 mmol) were reacted

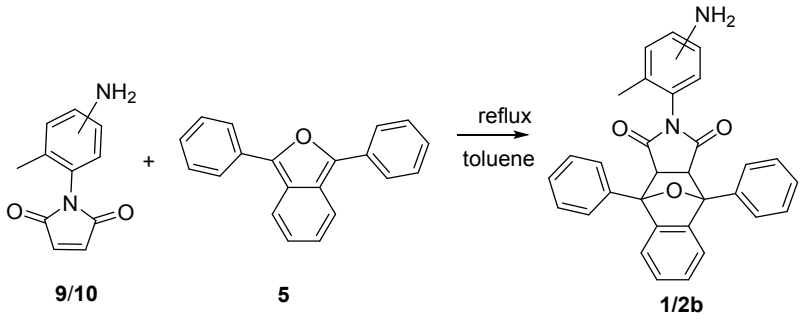
following the abovementioned procedure. A yellow solid was obtained as product **2h** (0.10 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 2.4 Hz, major 1H), 8.07-7.99 (m, 4H), 7.88 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, major 1H), 7.72-7.69 (m, minor 1H), 7.63-7.62 (m, minor 1H), 7.57-7.52 (m, 4H), 7.50-7.46 (m, 2H), 7.40-7.32 (m, 2H), 7.24-7.22 (m, minor 2H), 7.16 (d, J = 8.8 Hz, minor 1H), 7.13-7.06 (m, 2H), 5.69 (d, J = 8.8 Hz, major 1H), 4.38 (s, minor 2H), 4.36 (s, major 2H), 2.21 (s, major 3H), 1.21 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.2, 148.0, 144.8, 144.2, 138.0, 136.2, 135.9, 129.8, 128.8, 128.8, 128.7, 128.4, 128.3, 127.0, 127.0, 125.7, 121.7, 121.2, 121.1, 90.6, 90.3, 54.7, 18.0, 17.3. HRMS (EI) Calcd for $C_{31}H_{22}N_2O_5$: 502.1529; found: 502.1528.



General synthetic procedure for preparing *N*-(nitrophenyl)maleimides 9/10 (Figure S2C).
o-Toluidine **7/8h** and maleic anhydride were stirred in diethyl ether (80 mL) at rt overnight. After the solvent was removed, the remaining solid was added into Ac_2O (20 mL) containing NaOAc (~1.5 g). This mixture was heated at 100 ˚C for 2h. In the reaction mixture, 100 mL water was added and stirred. The precipitate was filtered and used for the next step reduction without further purification. Next, the nitro N-tolylmaleimide was stirred overnight at rt in 5 mL EtOH with $SnCl_2{\cdot}2H_2O$. The reaction mixture was then diluted with $NaHCO_3$ aq (40 mL) and extracted using EtOAc (40 mL). The obtained organic solution was washed again using $NaHCO_3$ aq (40 mL) and the solvent was removed under reduced pressure. The obtained product was used for the next Diels-Alder reaction without further purification.

1-(5-Amino-2-methylphenyl)-1H-pyrrole-2,5-dione (**9**) *o*-Toluidine **7h** (3.0 g, 20 mmol) and maleic anhydride (0.98 g, 10 mmol) were reacted following the abovementioned procedure. The corresponding nitro maleimide intermediate was obtained as an off-white solid (1.8 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 6.93 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 146.6, 144.6, 134.6, 131.8, 130.9, 124.3, 124.0, 18.4. Calcd for $C_{11}H_8N_2O_4$: 232.0484; found: 232.0479. This nitro maleimide intermediate (0.20 g, 0.86 mmol) and $SnCl_2{\cdot}2H_2O$ (2 g, 8.9 mmol) were reacted following the abovementioned procedure. The product **9** was obtained as a yellow solid (0.12 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.2 Hz, 1H), 6.84 (s, 2H), 6.68 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 3.42 (br, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.1, 134.3, 131.7, 130.3, 125.8, 116.6, 115.1, 16.8. HRMS (EI) Calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found: 202.0750.

1-(4-Amino-2-methylphenyl)-1H-pyrrole-2,5-dione (**10**). *o*-Toluidine **8h** (1.5 g, 10 mmol) and maleic anhydride (0.98 g, 10 mmol) were reacted following the abovementioned procedure. The corresponding nitro maleimide intermediate was obtained as an off-white solid (1.2 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 2.2 Hz, 1H), 8.14 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 6.93 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 147.8, 138.5, 135.8, 134.7, 129.7, 126.1, 121.9, 18.4. HRMS (EI) Calcd for $C_{11}H_8N_2O_4$: 232.0484; found: 232.0487. This intermediate (0.20 g, 0.86 mmol) and $SnCl_2{\cdot}2H_2O$ (2 g, 8.9 mmol) were reacted following the abovementioned procedure. The product **10** was obtained as a yellow liquid (0.11 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J = 8.4 Hz, 1H), 6.80 (s, 2H), 6.56 (d, J = 2.2 Hz, 1H), 6.52 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 3.72 (br, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 147.4, 137.2, 134.1, 129.4, 119.9, 116.8, 113.1, 17.7. HRMS (EI) Calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found: 202.0744.

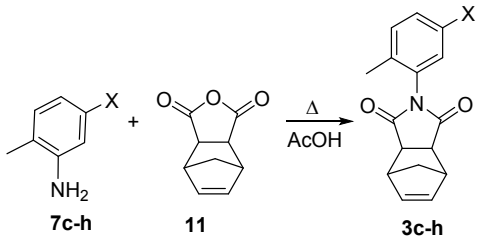


General synthetic procedure for preparing balances 1/2b via the Diels-Alder reaction of maleimide 9/10 and 1,3-diphenylisobenzofuran 5.

N-(aminophenyl)maleimide **9/10** and 1,3-diphenylisobenzofuran **5** were heated at reflux in toluene overnight. The organic solvent was removed under vacuum. The solid crude residue was washed with MeOH to provide the product.

2-(5-Amino-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**1b**). *N*-(aminophenyl)maleimide **9** (0.10 g, 0.49 mmol) and 1,3-diphenylisobenzofuran **5** (0.10 g, 0.37 mmol) were reacted following the abovementioned procedure. The product **1b** was obtained as a yellow solid (0.16 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.02 (m, 4H), 7.56-7.50 (m, 4H), 7.49-7.43 (m, 2H), 7.33-7.29 (m, major 2H), 7.19-7.15 (m, minor 2H), 7.12-7.08 (m, major 2H), 7.05-7.01 (m, minor 2H), 6.97 (d, J = 8.0 Hz, major 1H), 6.86 (d, J = 8.0 Hz, minor 1H), 6.60 (d, J = 8.0 Hz, minor 1H), 6.55 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, major 1H), 6.33 (s, minor 1H), 4.83 (d, J = 2.4 Hz, major 1H), 4.29 (s, minor 2H), 4.28 (s, major 2H), 3.10 (br, 2H), 1.95 (s, major 3H), 0.95 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 144.4, 136.3, 131.3, 130.8, 128.6, 128.6, 128.0, 127.1, 121.1, 116.8, 113.9, 90.5, 54.6, 16.6. HRMS (EI) Calcd for $C_{31}H_{24}N_2O_3$: 472.1787; found: 472.1786.

2-(4-Amino-2-methylphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1H-4,9-epoxybenzo[f]isoindole-1,3(2H)-dione (**2b**). *N*-(aminophenyl)maleimide **10** (0.040 g, 0.20 mmol) and 1,3-diphenylisobenzofuran **5** (0.040 g, 0.15 mmol) were reacted following the abovementioned procedure. The product **2b** was obtained as a yellow solid (0.65 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.04 (m, 4H), 7.56-7.50 (m, 4H), 7.49-7.43 (m, 2H), 7.30-7.26 (m, major 2H), 7.19-7.15 (m, minor 2H), 7.09-7.05 (m, major 2H), 7.05-7.01 (m, minor 2H), 6.69 (d, J = 8.4 Hz, minor 1H), 6.48-6.44 (m, 1H), 6.35 (d, J = 2.4 Hz, minor 1H), 6.27 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, major 1H), 5.29 (d, J = 8.4 Hz, major 1H), 4.27 (s, minor 2H), 4.25 (s, major 2H), 3.40 (br, 2H), 1.97 (s, major 3H), 0.97 (s, minor 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 173.7, 147.2, 144.3, 136.5, 136.4, 128.6, 128.6, 128.2, 128.1, 128.1, 127.1, 121.1, 121.0, 116.6, 113.0, 90.5, 90.1, 54.4, 17.7, 17.0. HRMS (EI) Calcd for $C_{31}H_{24}N_2O_3$: 472.1787; found: 472.1780.



General synthetic procedure for preparing balances 3c-h via the thermal condensation between *o*-toluidine derivatives 7c-h and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (11) (Figure S2D).

Anhydride **11** and *o*-toluidine derivative **7c-d** were heated at reflux in glacial acetic acid for 24 h. The solvent was removed under reduced pressure, and then the reaction mixture was dissolved in EtOAc (~50 mL). The organic solution was washed with saturated $NaHCO_3$ aq. (3 x 50 mL). The solvent in the isolated

organic layer was removed under vacuum. The crude product was then purified by flash column chromatography (EtOAc: Hex = 1:3 to 1:6) or washed with MeOH.

2-(2,5-Dimethylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3c**). *o*-Toluidine **7c** (114 µL, 0.91 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3c** was obtained as an off-white solid (0.20 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.14 (m, 1H), 7.11-7.08 (m, 1H), 6.81 (s, minor 1H), 6.67 (s, major 1H), 6.32-6.28 (m, 2H), 3.52-3.44 (m, 4H), 2.32 (s, 3H), 2.09 (s, major 3H), 2.06 (s, minor 3H), 1.83-1.79 (m, 1H), 1.64-1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 176.5, 136.6, 136.5, 135.2, 134.6, 132.5, 132.3, 130.9, 130.8, 130.2, 130.2, 128.6, 128.1, 52.6, 52.3, 46.7, 45.7, 45.4, 45.1, 20.7, 20.7, 18.4, 17.1. HRMS (EI) Calcd for $C_{17}H_{17}NO_2$: 267.1259; found: 267.1260.

2-(5-Hydroxy-2-methylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3d**). *o*-Toluidine **7d** (0.12 g, 1.01 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3d** was obtained as a light brown solid (0.21 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.4 Hz, major 1H), 7.08 (d, J = 8.4 Hz, major 1H), 6.71 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, minor 1H), 6.32 (d, J = 2.4 Hz, major 1H), 6.30-6.26 (m, 2H), 5.57 (br, minor 1H), 5.44 (br, major 1H), 3.53-3.42 (m, 4H), 2.02 (s, major 3H), 1.99 (s, minor 3H), 1.84-1.76 (m, 1H), 1.66-1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 154.4, 135.2, 134.6, 131.9, 131.7, 127.3, 116.8, 115.1, 114.8, 52.7, 52.3, 46.7, 45.8, 45.4, 45.1, 18.0, 16.7. HRMS (EI) Calcd for $C_{16}H_{15}NO_3$: 269.1052; found: 269.1053.

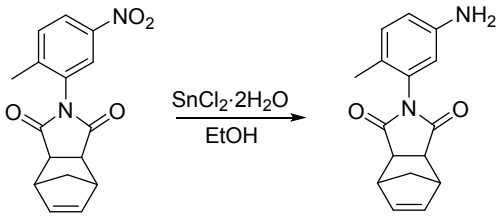
2-(5-Fluoro-2-methylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3e**). *o*-Toluidine **7e** (0.11 g, 0.91 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3e** was obtained as a white solid (0.22 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 1H), 7.03-6.97 (m, 1H), 6.75 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz minor 1H), 6.59 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz major 1H), 6.30-6.26 (m, 2H), 3.51-3.42 (m, 4H), 2.07 (s, major 3H), 2.04 (s, minor 3H), 1.81-1.76 (m, 1H), 1.62-1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.0, 162.0, 161.9, 159.5, 159.4, 135.2, 134.5, 132.0, 132.0, 131.9, 131.8, 131.6, 131.5, 131.5, 131.5, 116.4, 116.3, 116.2, 116.1, 115.5, 115.3, 115.1, 114.9, 52.7, 52.3, 46.7, 45.7, 45.4, 45.1, 18.2, 17.0. HRMS (EI) Calcd for $C_{16}H_{14}FNO_2$: 271.1009; found: 271.1010.

2-(5-Bromo-2-methylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3f**). *o*-Toluidine **7f** (0.18 g, 0.91 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3f** was obtained as a white solid (0.29 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 1H), 7.17-7.13 (m, 1H and minor 1H), 6.98 (d, J = 2.0 Hz, major 1H), 6.33-6.28 (m, 2H), 3.52-3.45 (m, 4H), 2.06 (s, major 3H), 2.03 (s, minor 3H), 1.84-1.79 (m, 1H), 1.65-1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.0, 135.2, 135.0, 134.9, 134.6, 132.4, 132.3, 132.2, 131.1, 130.6, 119.2, 119.2, 52.7, 52.3, 46.7, 45.8, 45.4, 45.1, 18.4, 17.3. HRMS (EI) Calcd for $C_{16}H_{14}BrNO_2$: 331.0208; Found: 331.0202.

2-(2-Methyl-5-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3g**). *o*-Toluidine **7g** (0.16 g, 0.91 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3g** was obtained as an off-white solid (0.28 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.42-7.38 (m, 1H), 7.28 (s, major 1H), 7.08 (s, minor 1H), 6.34-6.29 (m, 2H), 3.54-3.46 (m, 4H), 2.17 (s, minor 3H), 2.14 (s, major 3H), 1.84-1.79 (m, 1H), 1.65-1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.1, 140.3, 140.2, 135.3, 134.7, 131.7, 131.6, 129.5, 129.2, 126.1, 126.1, 125.6, 125.0, 125.0, 52.8, 52.4, 46.8, 45.9, 45.5, 45.2, 19.0, 17.8. HRMS (EI) Calcd for $C_{17}H_{14}F_3NO_2$: 321.0977; found: 321.0975.

2-(2-Methyl-5-Nitrophenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3h**). *o*-Toluidine **7h** (0.15 g, 0.91 mmol) and anhydride **11** (0.15 g, 0.91 mmol) were reacted following the abovementioned procedure. The product **3h** was obtained as a yellow solid (0.24 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.16 (m, 1H), 7.94 (d, J = 2.0 Hz, minor 1H), 7.75 (d, J = 2.0 Hz, major 1H), 7.49-7.45 (m, 1H), 6.40-6.33 (m, 2H), 3.57-3.52 (m, 4H), 2.25 (s, major 3H), 2.22 (s, minor 3H), 1.89-1.84 (m, 1H), 1.69-1.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 175.8, 146.6, 144.1, 135.3, 134.7, 131.8,

131.7, 124.1, 124.1, 124.0, 123.6, 52.8, 52.4, 46.9, 46.0, 45.5, 45.2, 19.2, 18.2. HRMS (EI) Calcd for $C_{16}H_{14}N_2O_4$: 298.0954; Found: 298.0952.



3h **3b**

2-(5-Amino-2-methylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3b**)**.** Balance **3h** (1.2 g, 4.0 mmol) and $SnCl_2 \cdot 2H_2O$ (1.6 g, 7.1 mmol) in 5 mL EtOH were stirred overnight at rt. The reaction mixture was then diluted with $NaHCO_3$ aq. (40 mL) and extracted using EtOAc (40 mL). The organic solution was further washed with $NaHCO_3$ aq. and water (50 mL x 3), and the organic solvent was removed under reduced pressure. The product **3b** was obtained as an off-white solid (0.030 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.04 (m, 1H), 6.67-6.62 (m, 1H), 6.33-6.29 (m, 2H and 1H major), 6.20 (d, J = 2.4 Hz, minor 1H), 3.54-3.45 (m, 2H), 3.18 (br, 2H), 2.00 (s, major 3H), 1.98 (s, minor 3H), 1.82-1.76 (m, 1H), 1.63-1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 176.5, 145.1, 145.1, 135.2, 134.5, 131.7, 131.5, 125.1, 125.0, 116.6, 116.5, 114.6, 114.2, 52.6, 52.2, 46.7, 45.7, 45.4, 45.1, 17.9, 16.6. HRMS (EI) Calcd for $C_{16}H_{16}N_2O_2$: 268.1212; found: 268.1215.

Error analysis for folding ratios and folding energies in solution

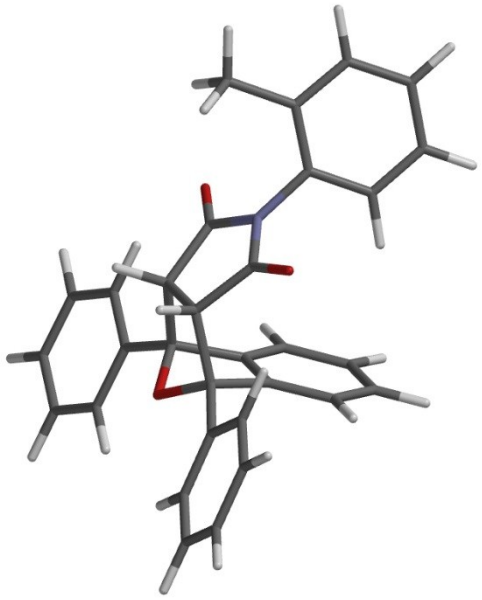
The NMR samples were prepared by dissolving ~10 mg of the purified molecular balances in ~0.6 mL of deuterated solvents of choice, giving a total concentration of ~36 mM (assuming a molecular weight of ~460 and complete dissolution). All ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer. The following parameters were used for ^{1}H NMR recording: 10 ppm spectral width, 64k point counts, acquisition time 4 s, 128 scans with an inter-cycle relaxation delay of 5 s. Measured *folded*/*unfolded* ratios were between 1.0 and 5.5, which means the minor conformer concentration was above 5 mM. At the extreme ratios (~5.5), the minor conformer concentration can be confidently quantified with a precision of 5 %.[4] NMR peak area measurements were carried out using the MestReNova line-fitting function with a zero filing to 256k point counts to reduce error in analysis. Peak area analysis was *exclusively* carried on comparing the integration of the distinctly separated singlets of the reporter *ortho*-methyl groups to suppress the uncertainty due to short relaxation time (less than $5T_1$).[5-8] The signal-to-noise (S/N) ratios for the minor conformer singlet (of methyl group) range are above 150 when the minor concentration is above 2 mM.[9] Therefore, error in line-fitting peak area analysis was safely estimated to be less than 2 %.[5] The uncertainty in *folded*/*unfolded* ratios was estimated to be less than 3 % (Equation S1). The uncertainty in the calculated folding energies (ΔG) thus was estimated to be ± 0.02 kcal/mol (Equation S2), and the uncertainty in the quantified substituent-π energies (ΔΔG) was estimated to be ± 0.03 kcal/mol (Equation S3)

$$\delta_{[folded/unfolded]} = \sqrt{\delta^{2}_{[folded]} + \delta^{2}_{[unfolded]}} \qquad \text{(Equation S1)}$$

$$\delta_{[\Delta G]} = R \times T \times \delta_{[folded/unfolded]} \qquad \text{(Equation S2)}$$

$$\delta_{(\Delta Ga - \Delta Gb)} = \sqrt{\delta^{2}_{(\Delta Ga)} + \delta^{2}_{(\Delta Gb)}} \qquad \text{(Equation S3)}$$

XYZ coordinates for the optimized structures of balances1a-h



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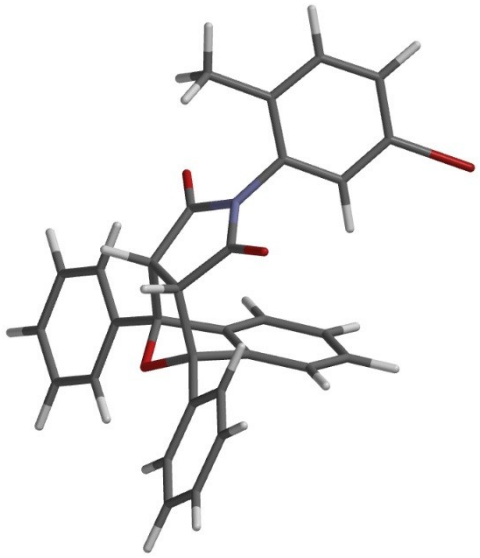

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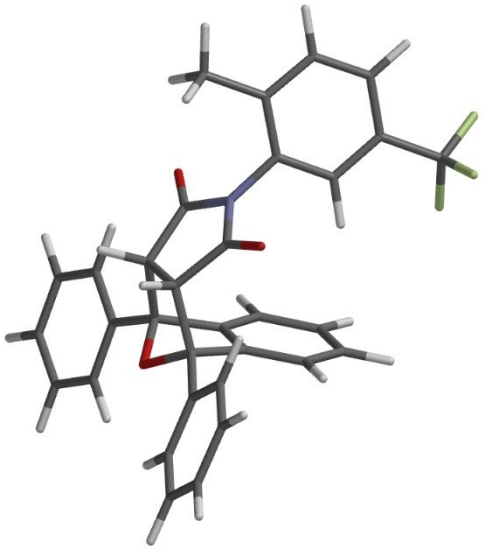

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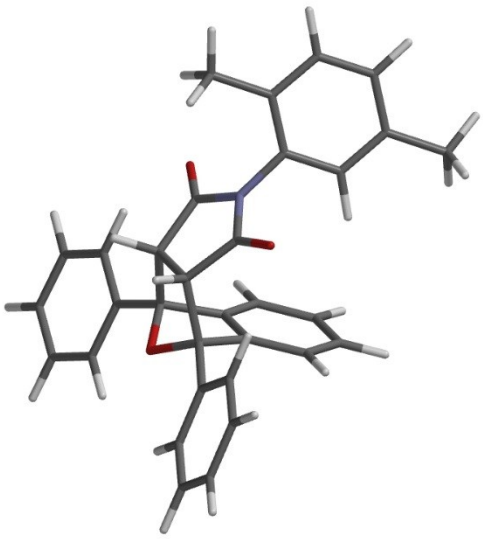

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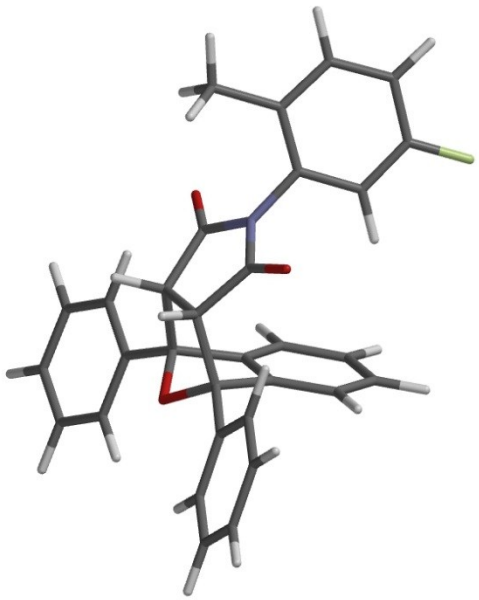

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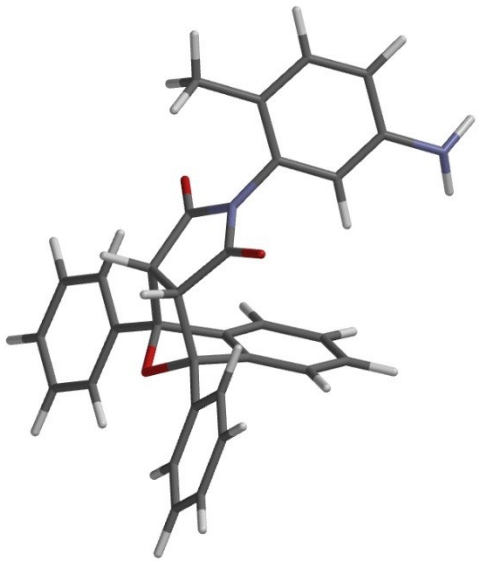

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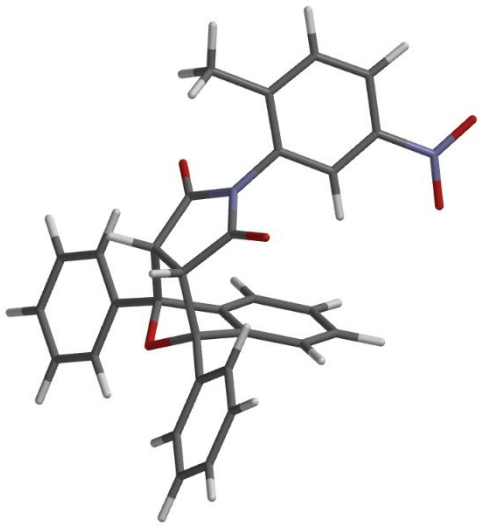

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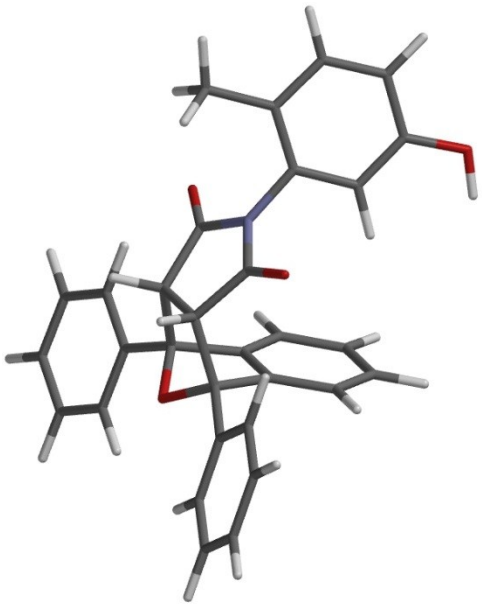

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[1]H NMR and [13]C NMR Spectra

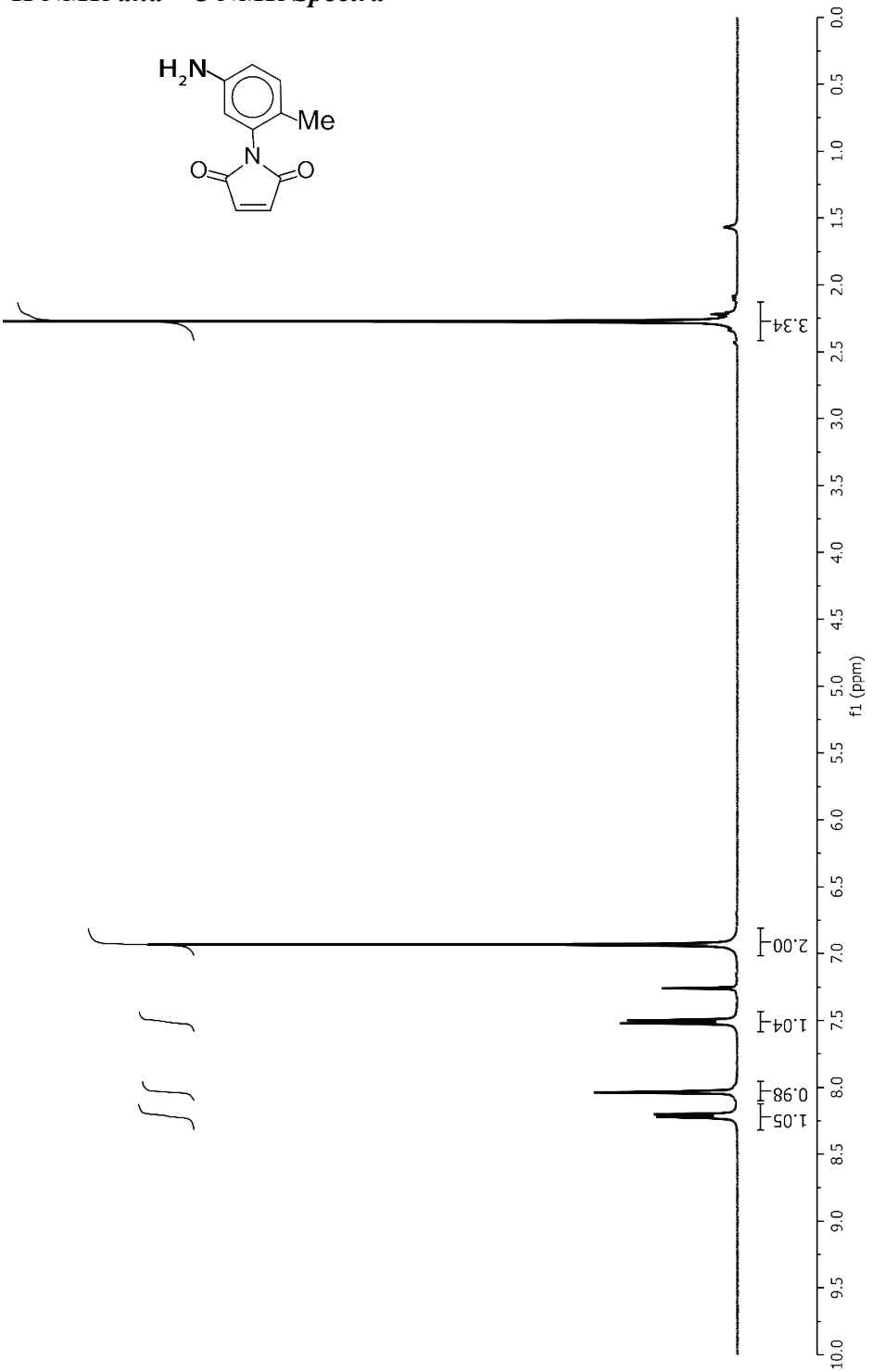

Figure S3 ^{1}H NMR spectrum of maleimide **9** ($CDCl_3$, 400 MHz)

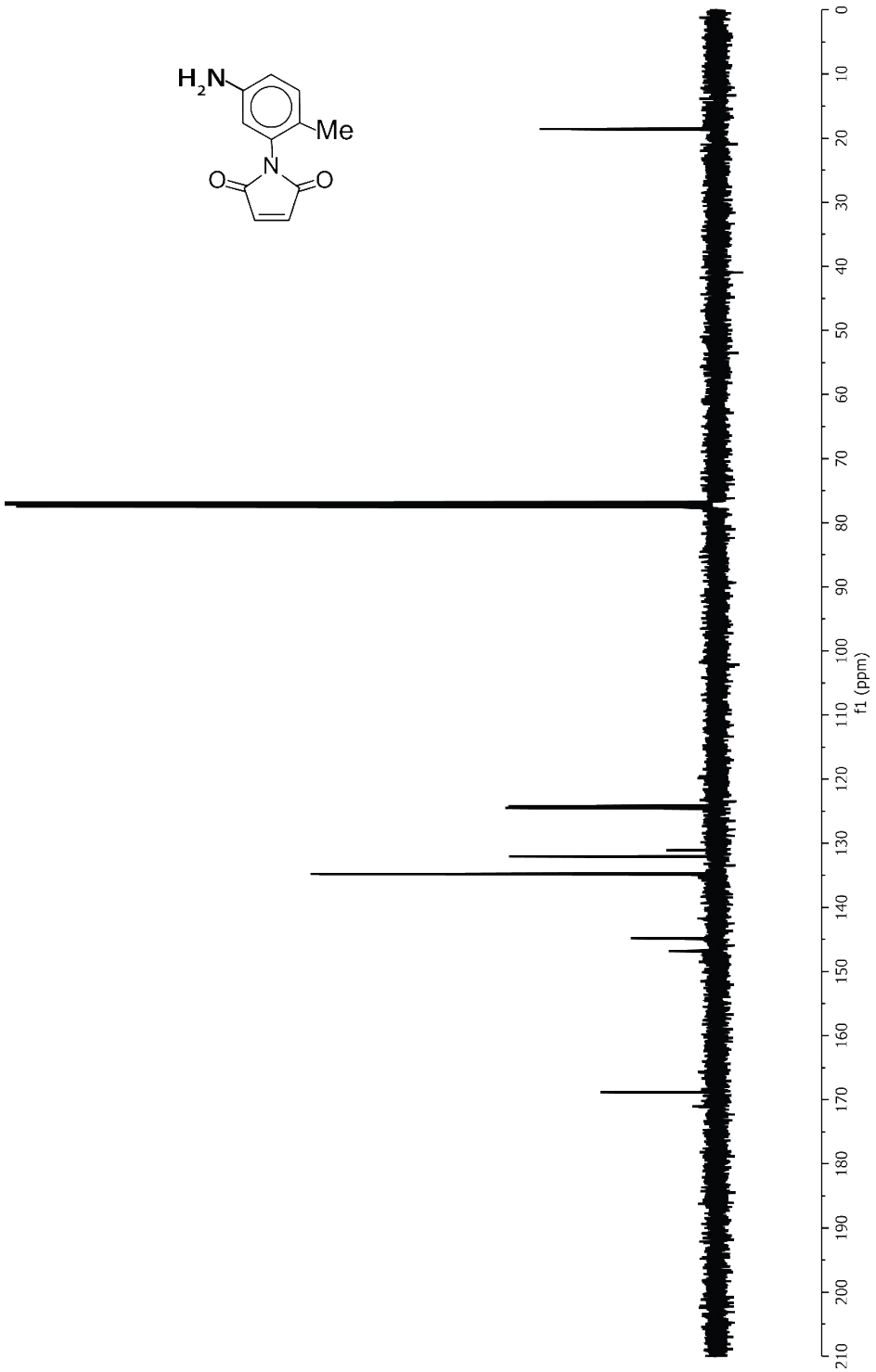

Figure S4. ^{13}C NMR spectrum of maleimide **9** ($CDCl_3$, 100 MHz)

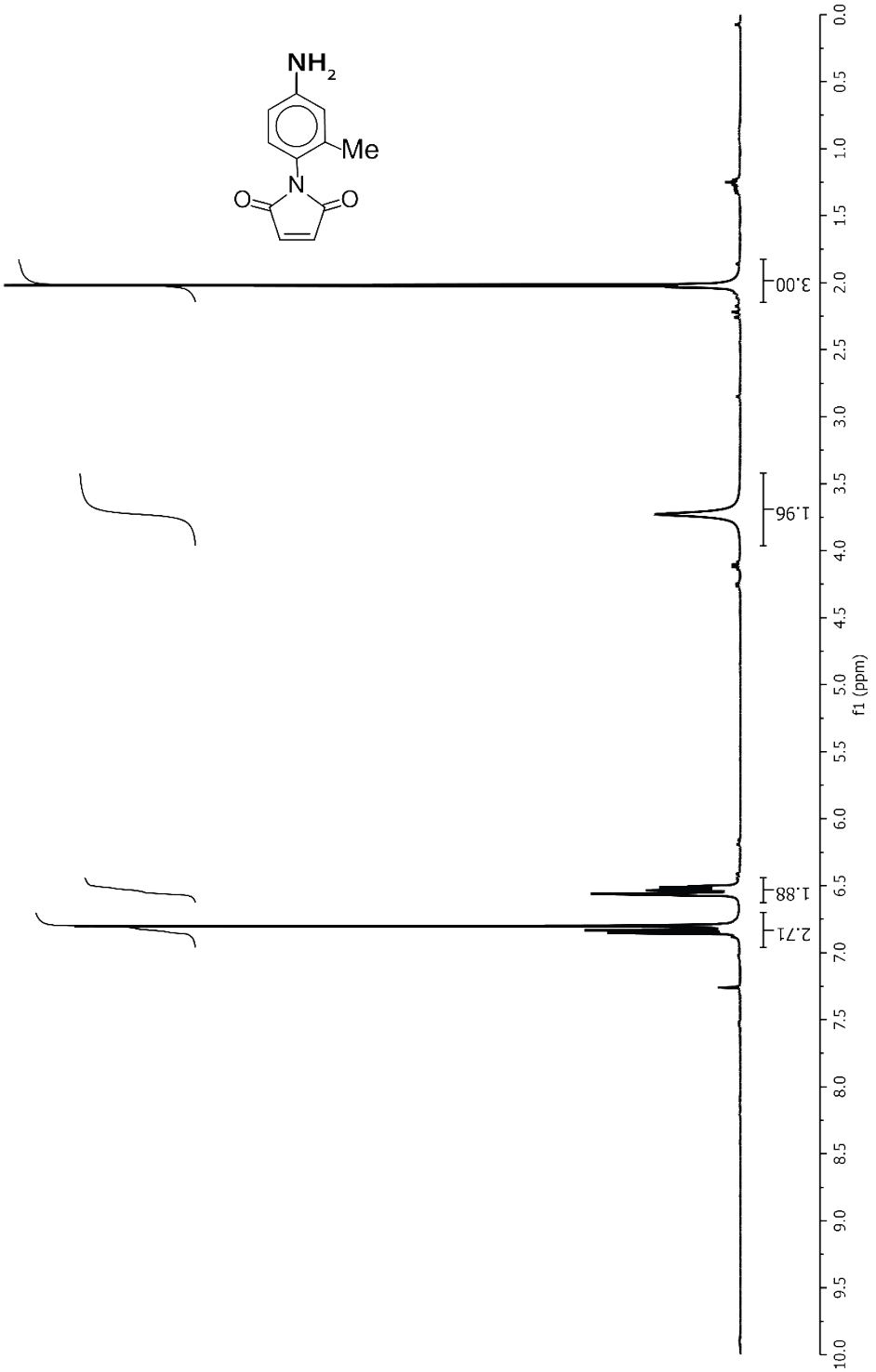

Figure S 5 ^{1}H NMR spectrum of maleimide **10** ($CDCl_3$, 400 MHz)

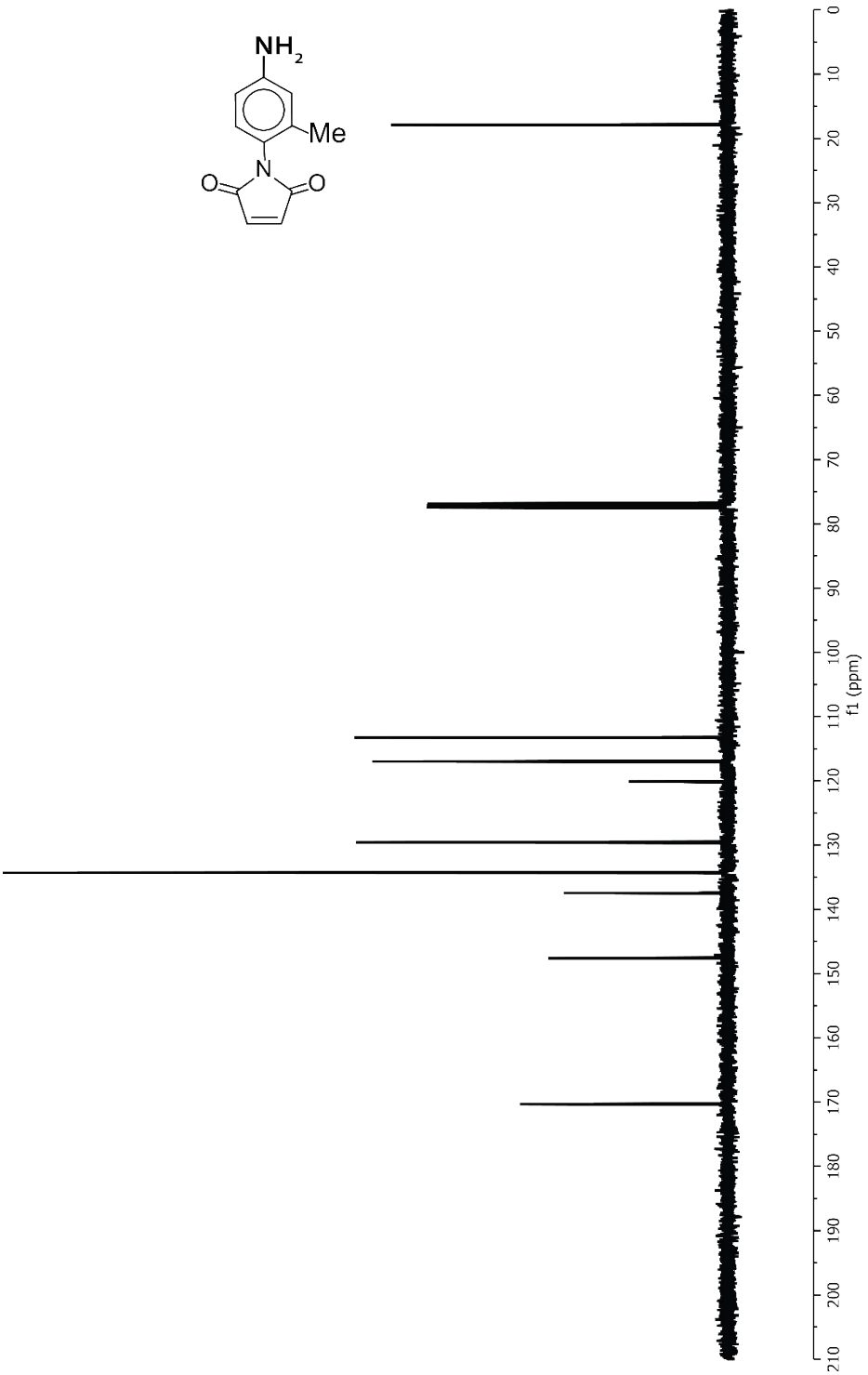

Figure S6. ^{13}C NMR spectrum of maleimide **10** ($CDCl_3$, 100 MHz)

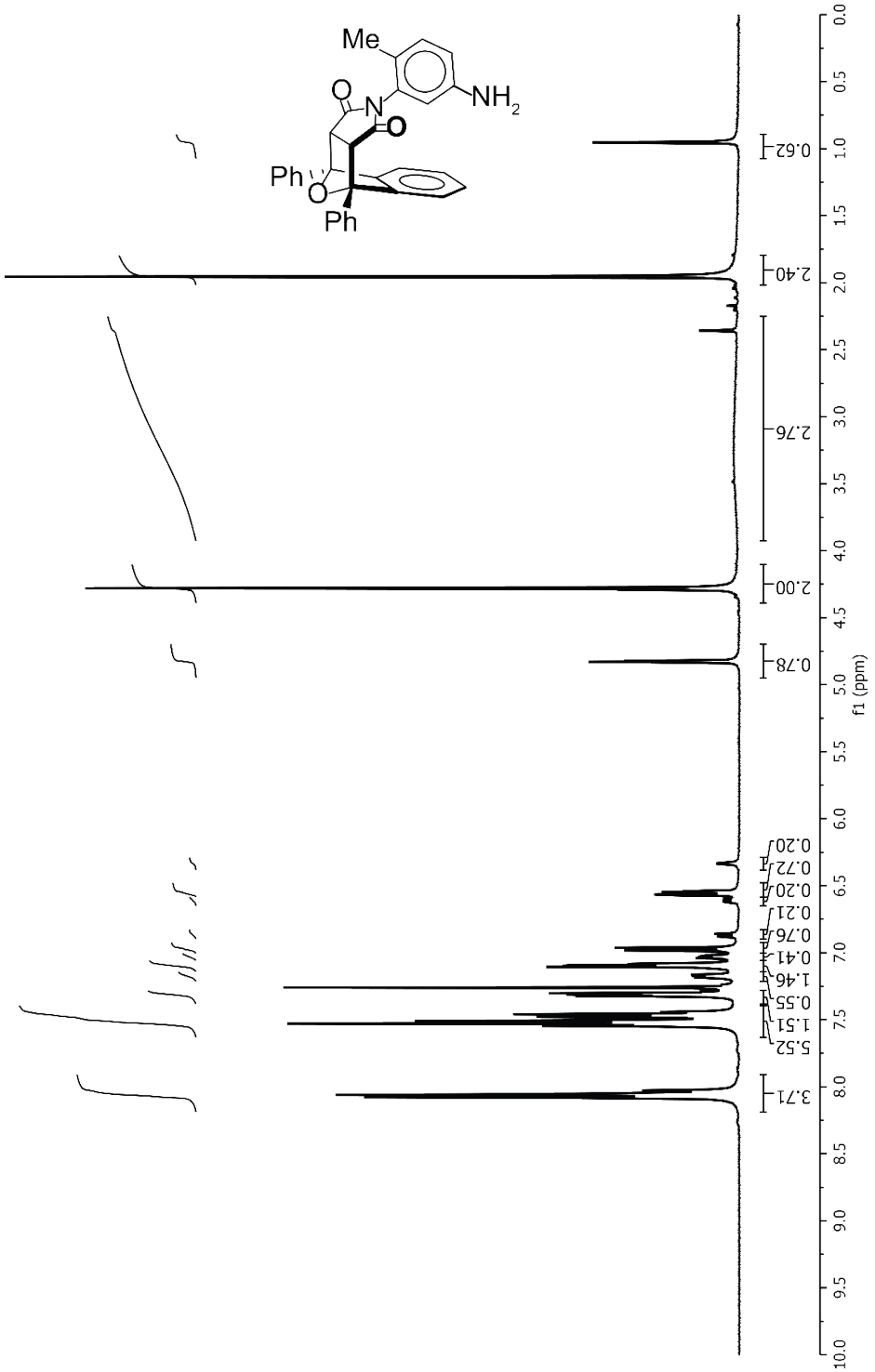

Figure S 7. ^{1}H NMR spectrum of balance **1b** ($CDCl_3$, 400 MHz)

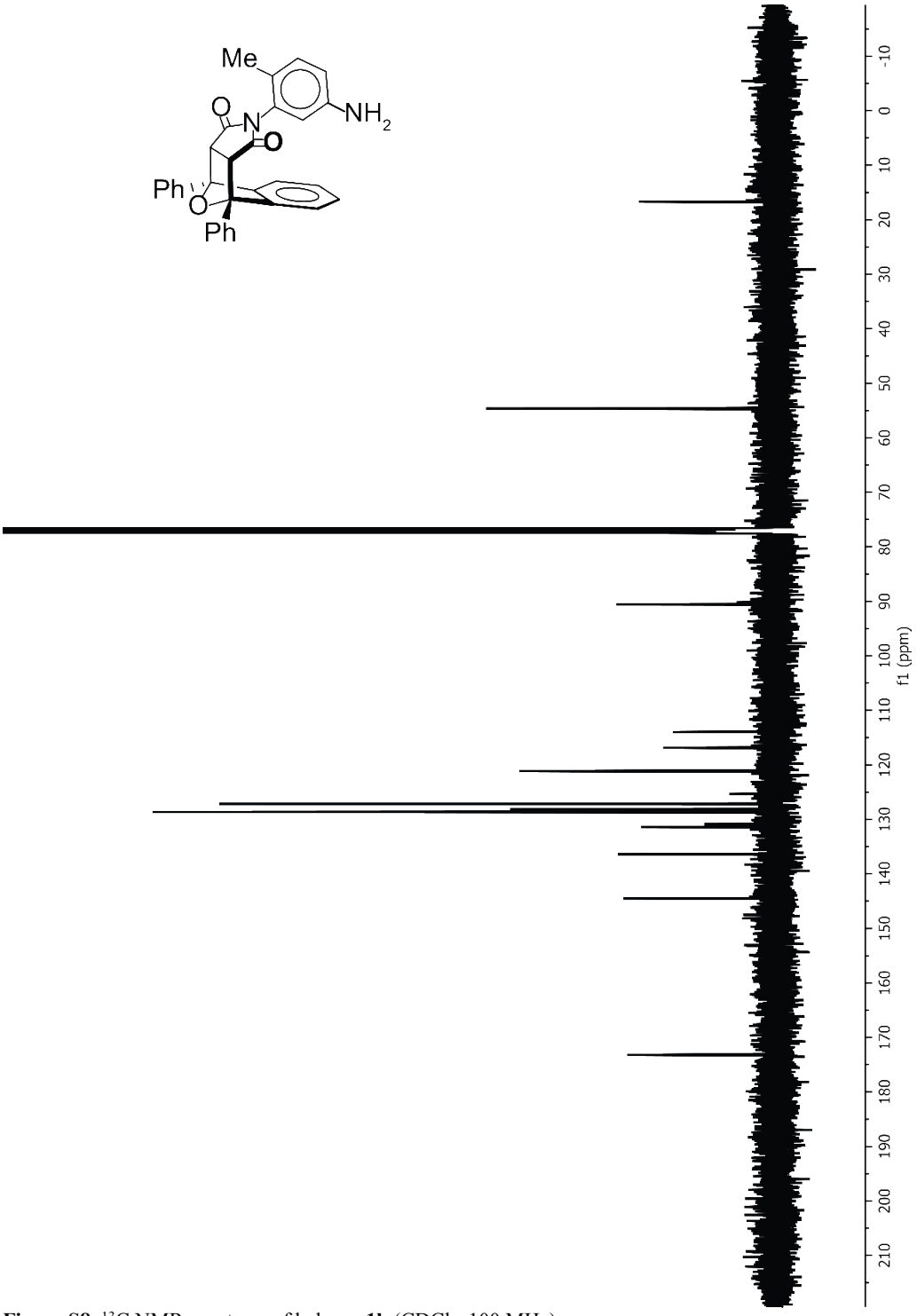

Figure S8. ^{13}C NMR spectrum of balance **1b** ($CDCl_3$, 100 MHz)

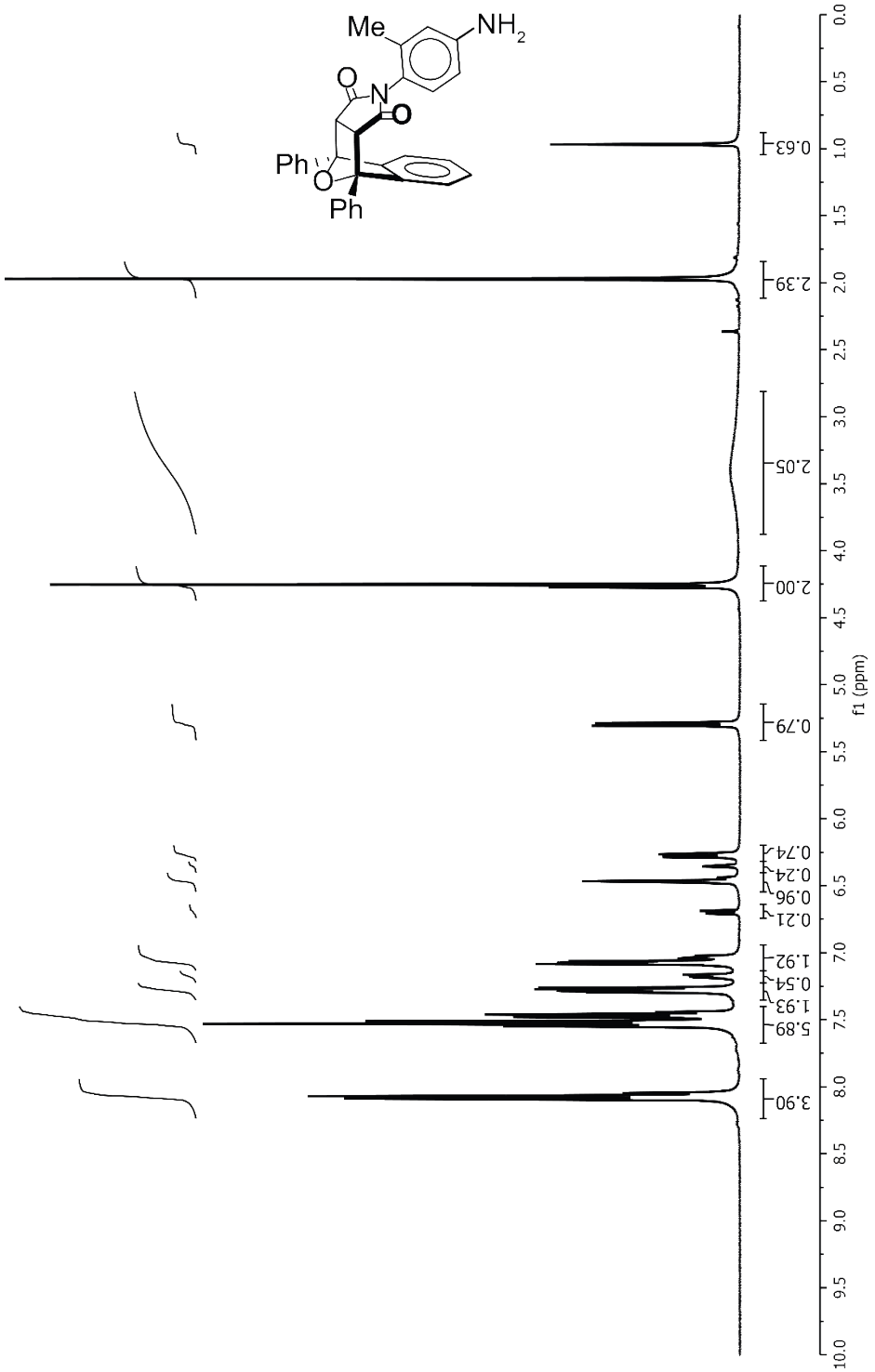

Figure S9. ^{1}H NMR spectrum of balance **2b** ($CDCl_3$, 400 MHz)

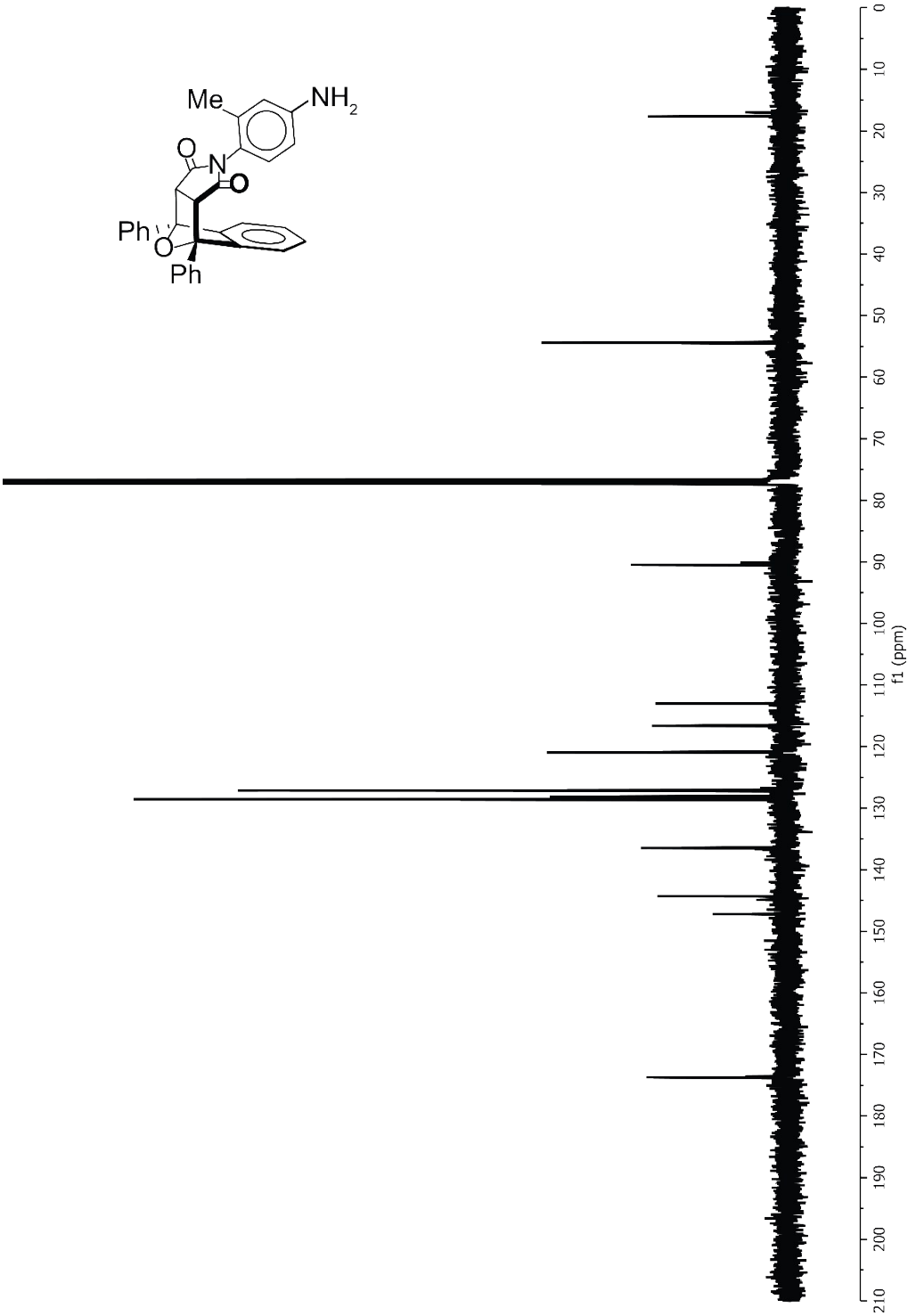

Figure S10. ^{13}C NMR spectrum of balance **2b** ($CDCl_3$, 100 MHz)

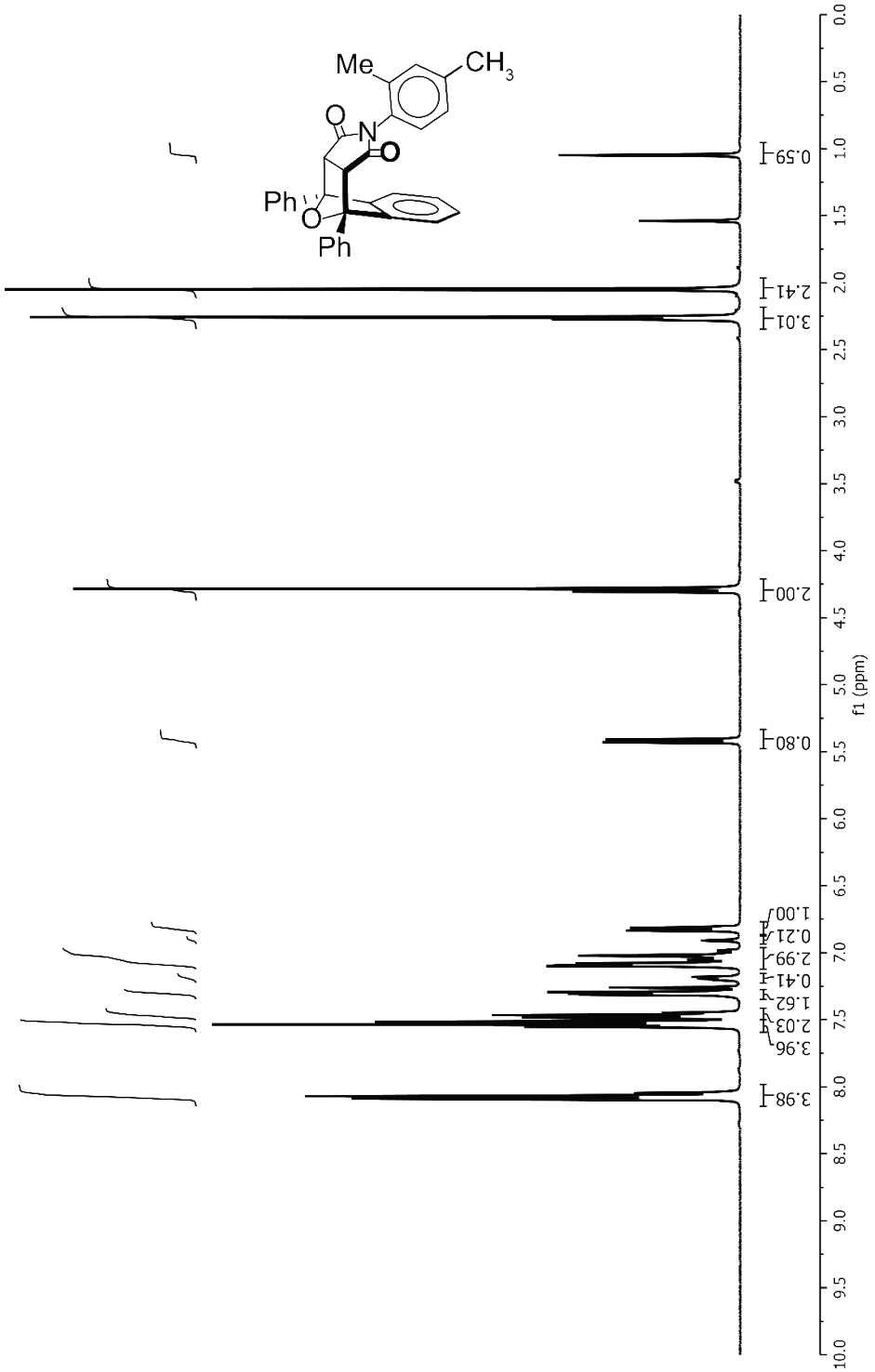

Figure S11. ^{1}H NMR spectrum of balance **2c** ($CDCl_3$, 400 MHz)

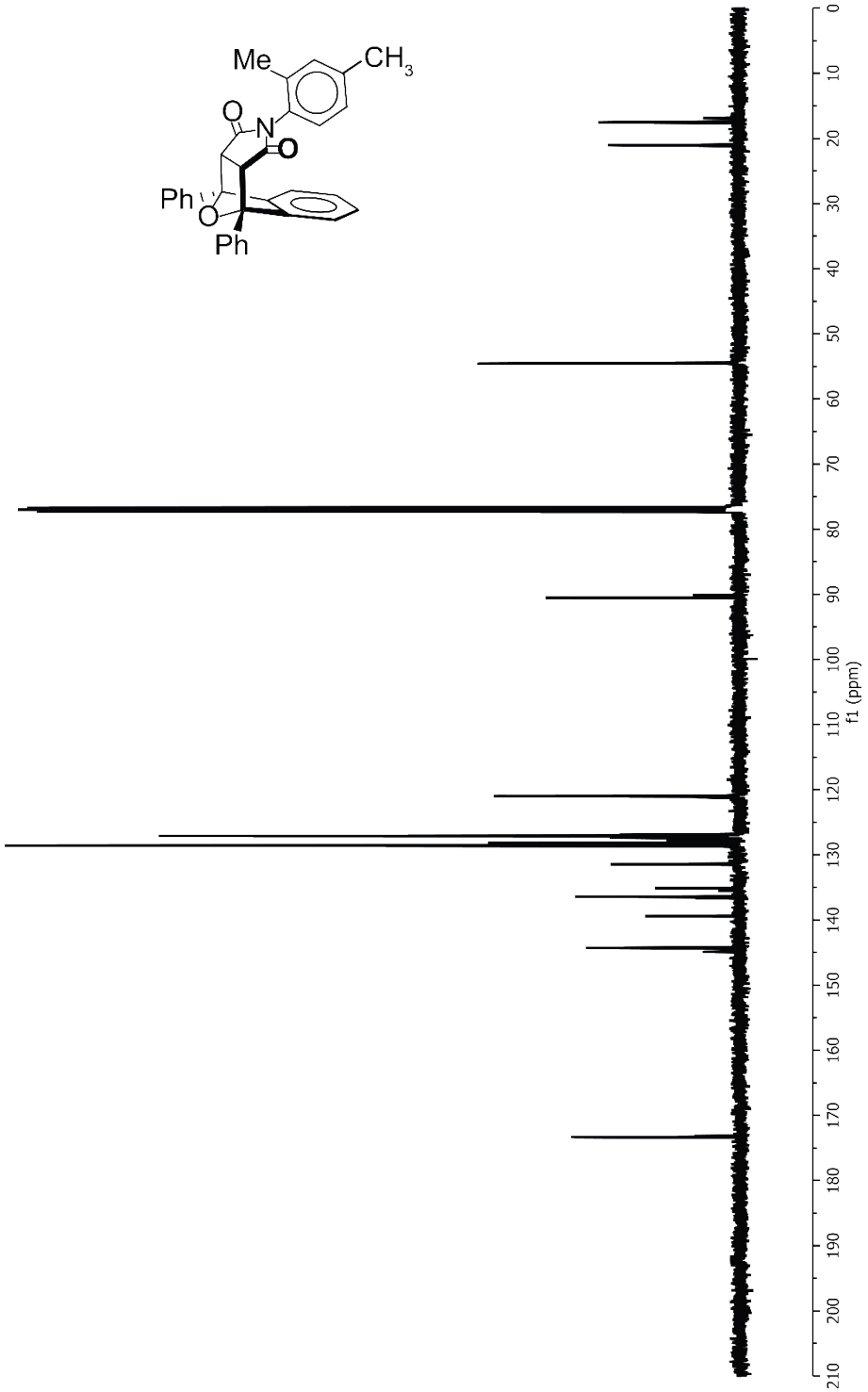

Figure S12. ^{13}C NMR spectrum of balance **2c** ($CDCl_3$, 100 MHz)

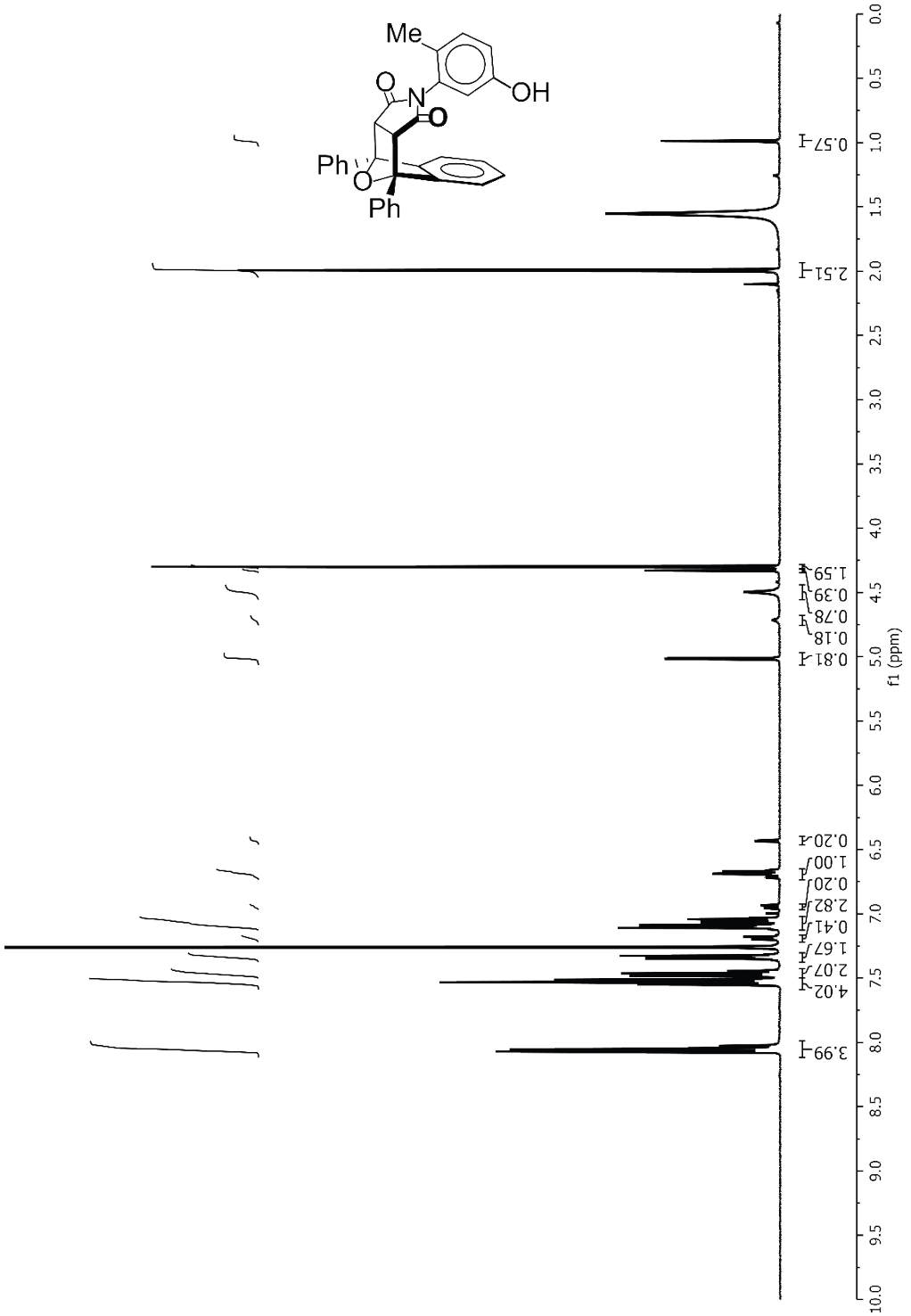

Figure S13. ^{1}H NMR spectrum of balance **1d** ($CDCl_3$, 400 MHz)

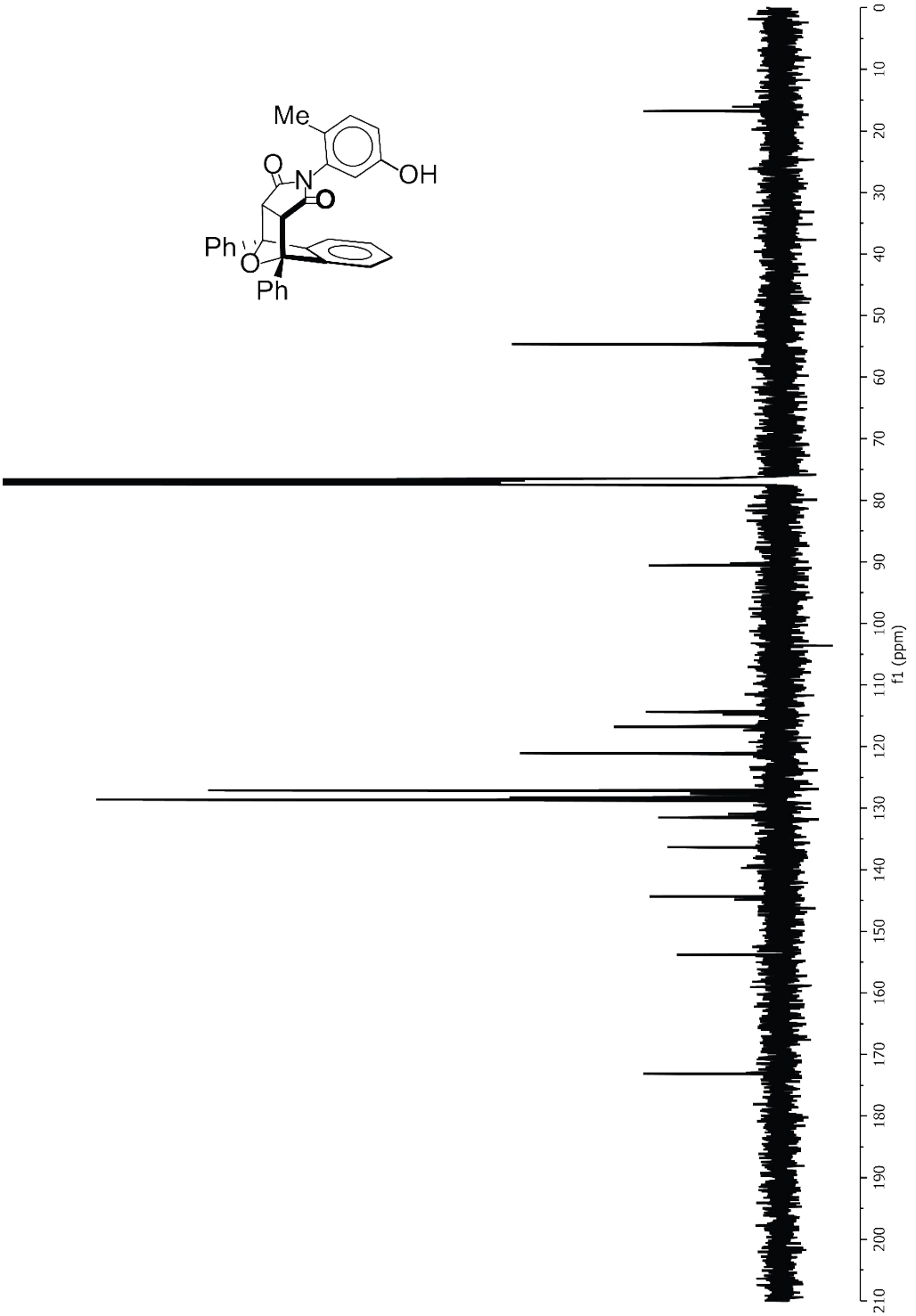

Figure S14. ^{13}C NMR spectrum of balance **1d** ($CDCl_3$, 100 MHz)

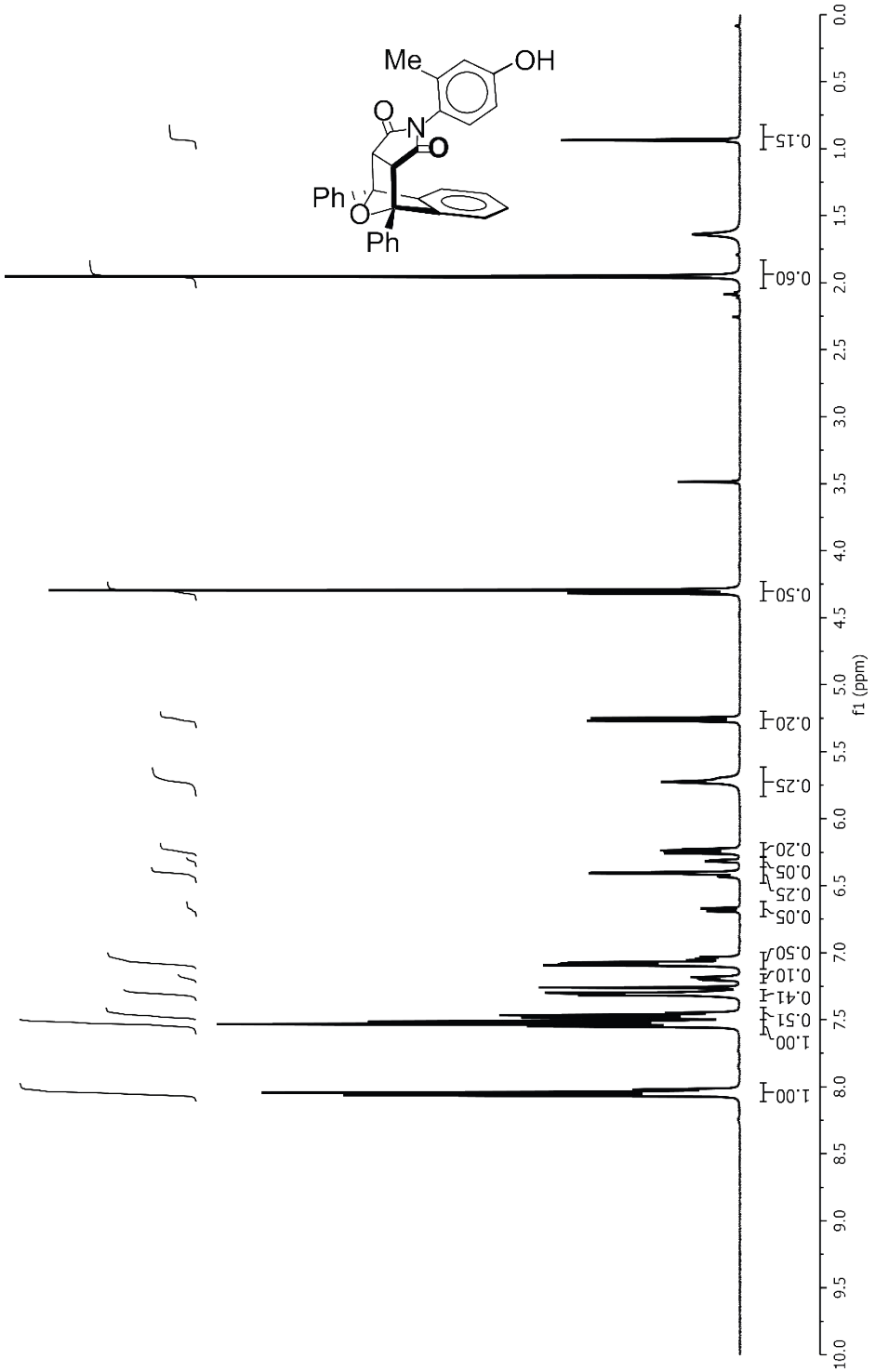

Figure S15. ^{1}H NMR spectrum of balance **2d** ($CDCl_3$, 400 MHz)

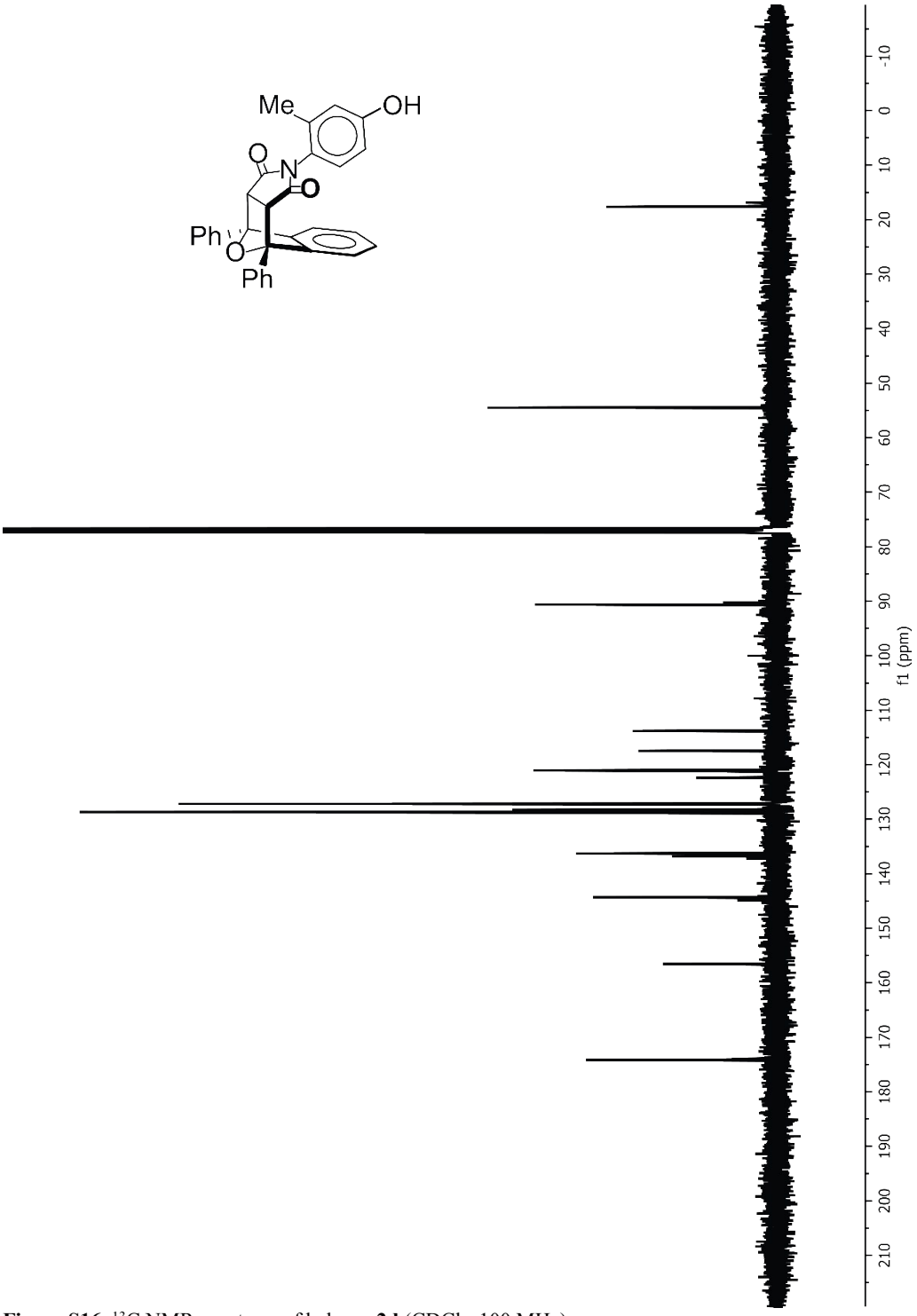

Figure S16. ^{13}C NMR spectrum of balance **2d** ($CDCl_3$, 100 MHz)

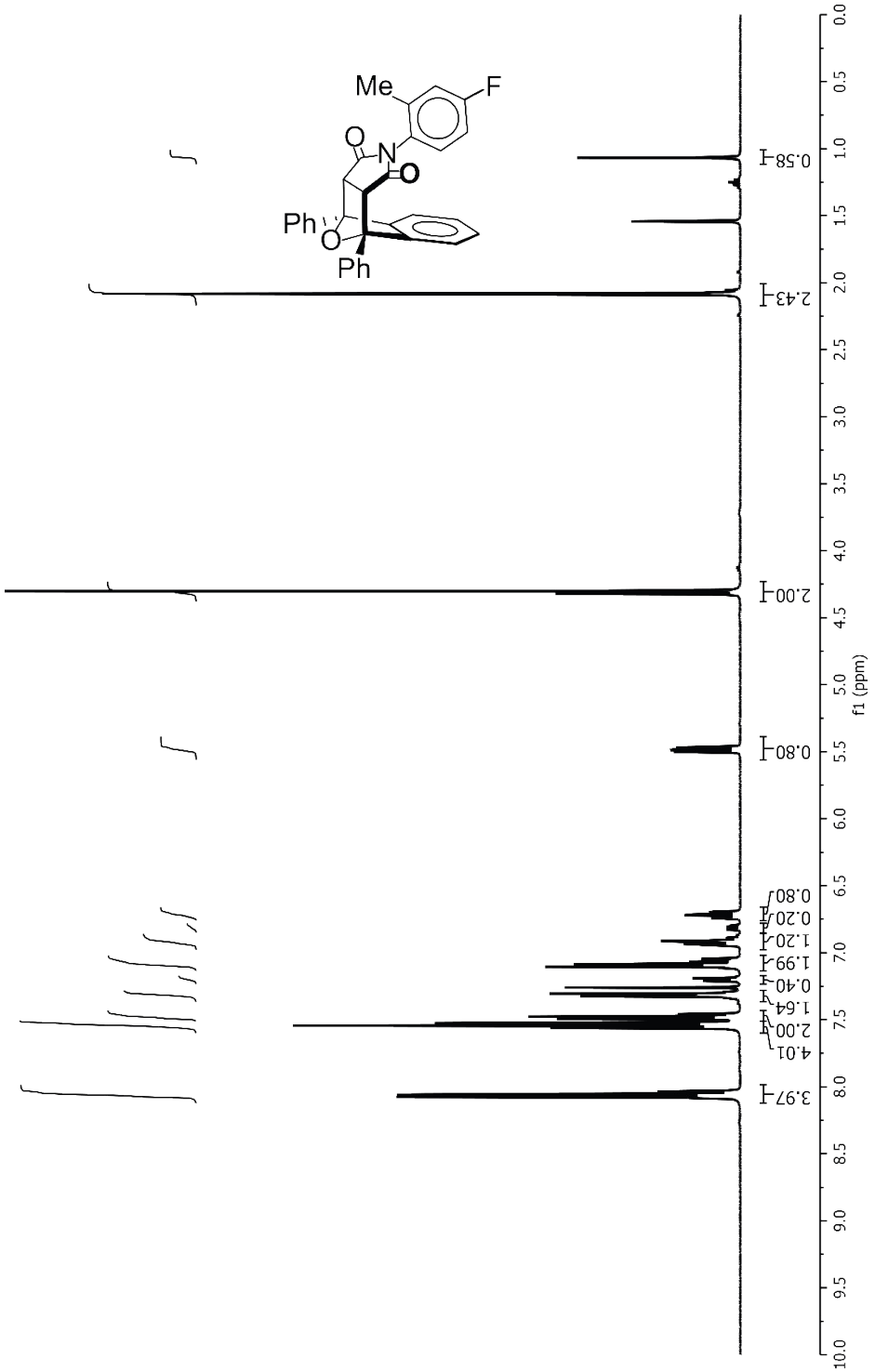

Figure S17. ^{1}H NMR spectrum of balance **2e** ($CDCl_3$, 400 MHz)

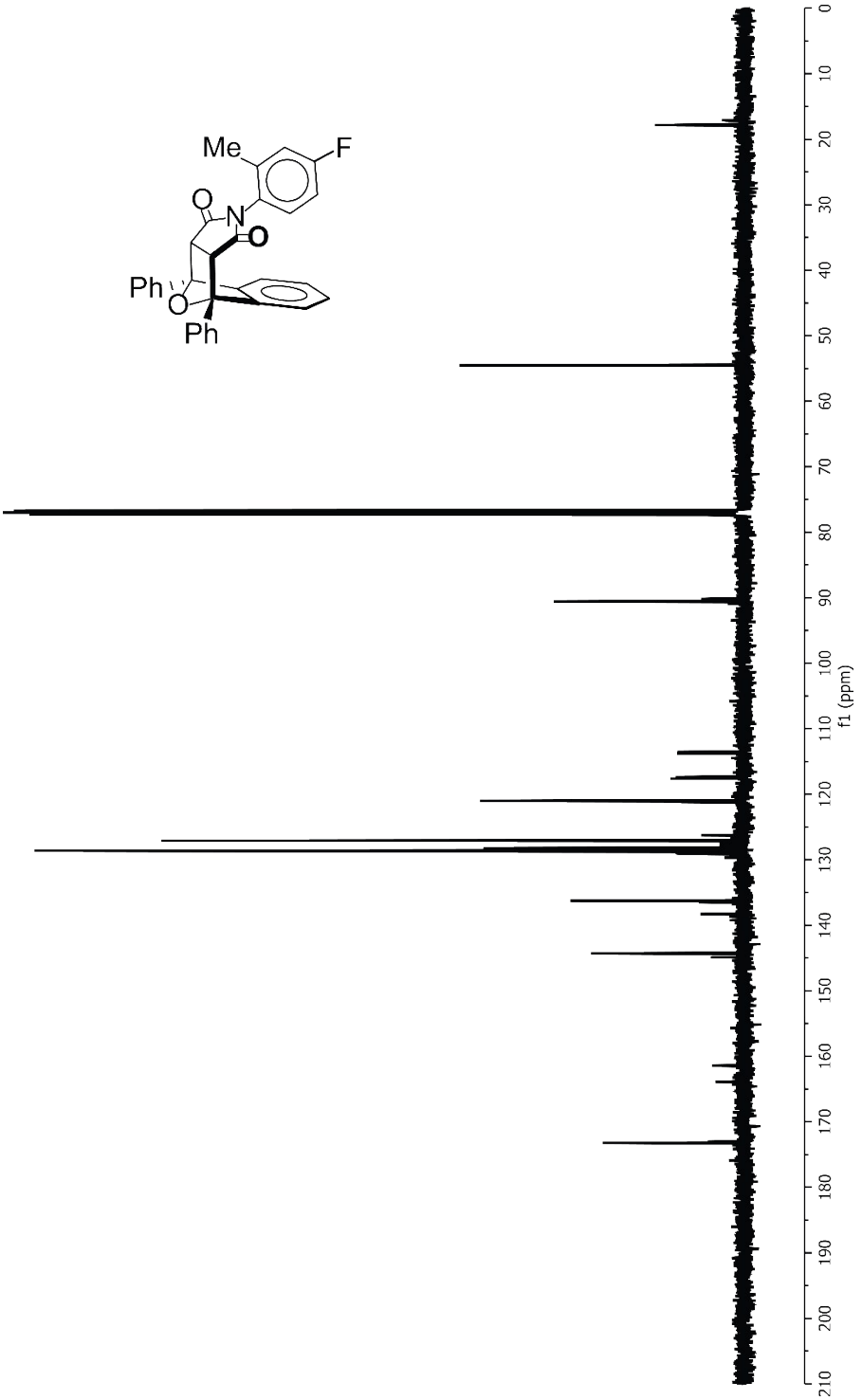

Figure S18. ^{13}C NMR spectrum of balance **2e** ($CDCl_3$, 100 MHz)

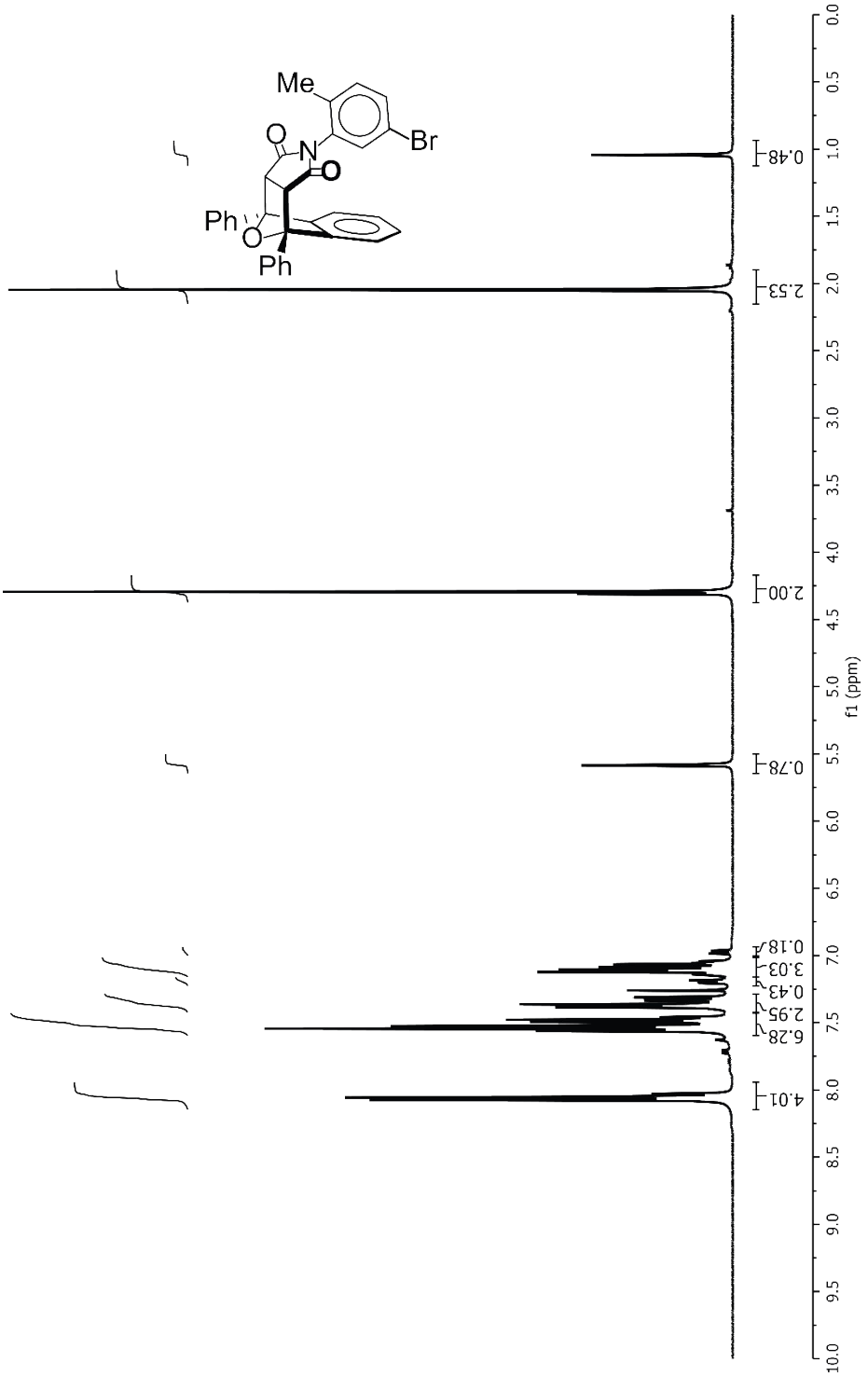

Figure S19. ^{1}H NMR spectrum of balance **1f** ($CDCl_3$, 400 MHz)

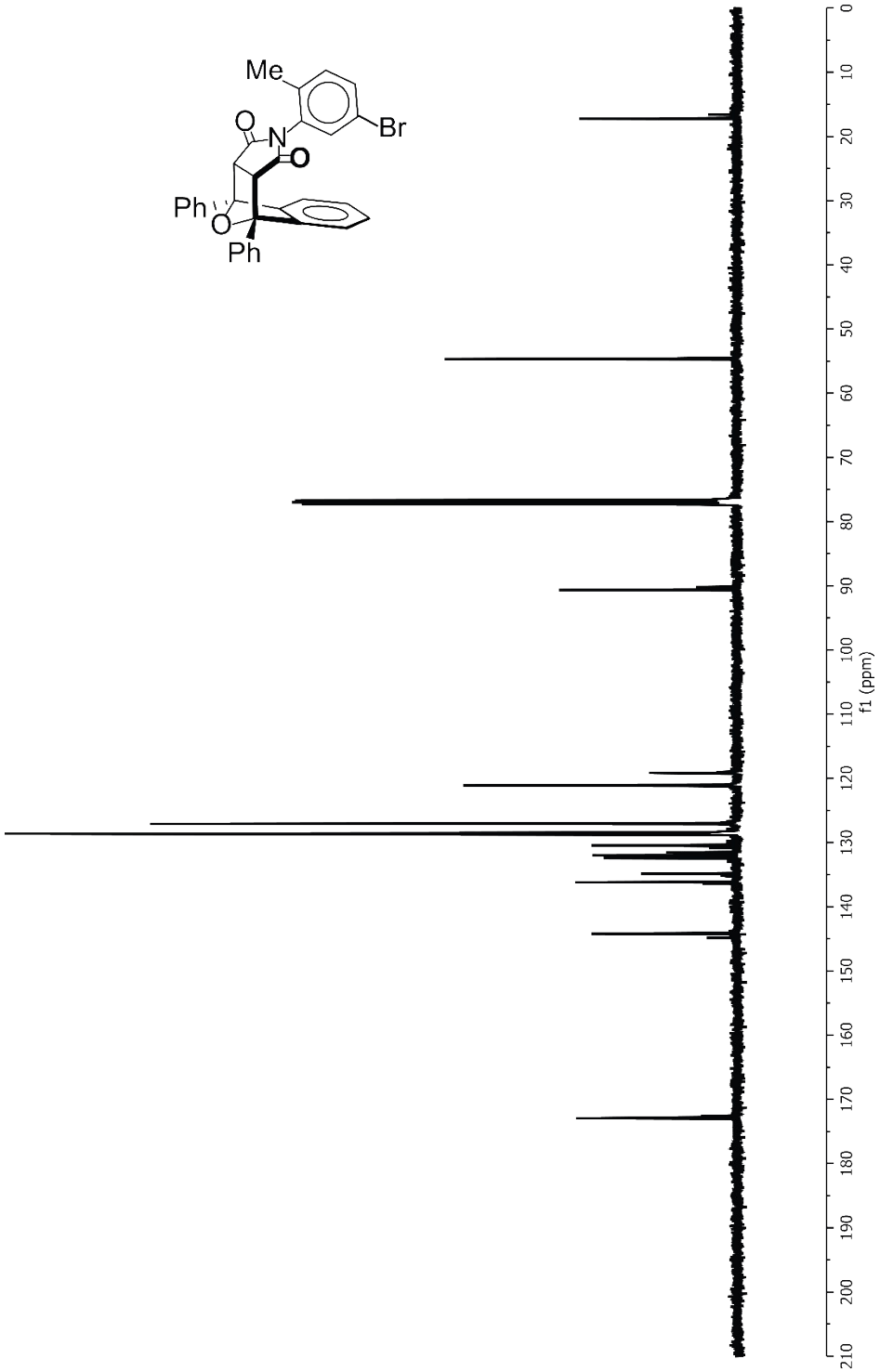

Figure S20. ^{13}C NMR spectrum of balance **1f** ($CDCl_3$, 100 MHz)

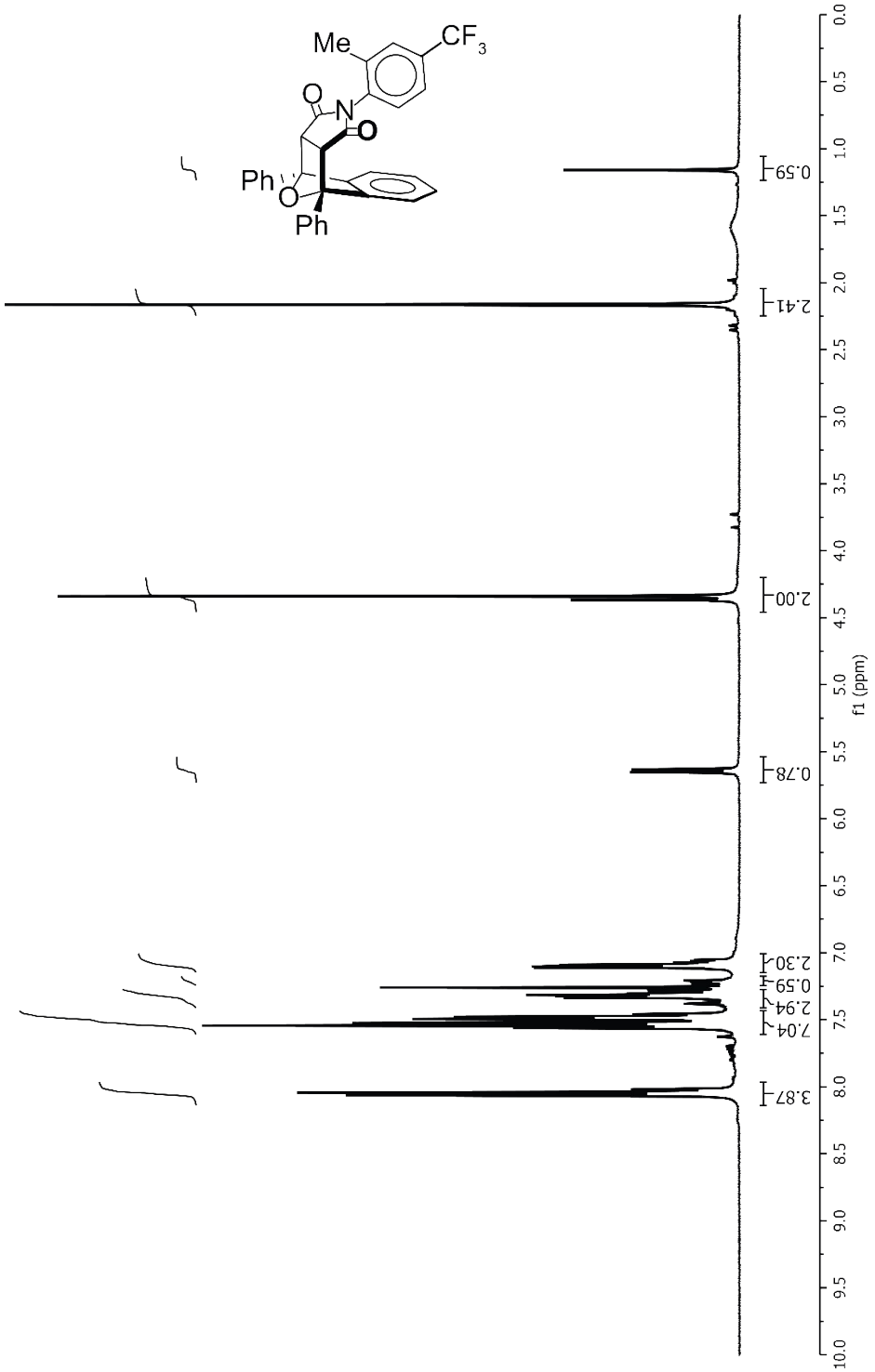

Figure S21. ^{1}H NMR spectrum of balance **2g** ($CDCl_3$, 400 MHz)

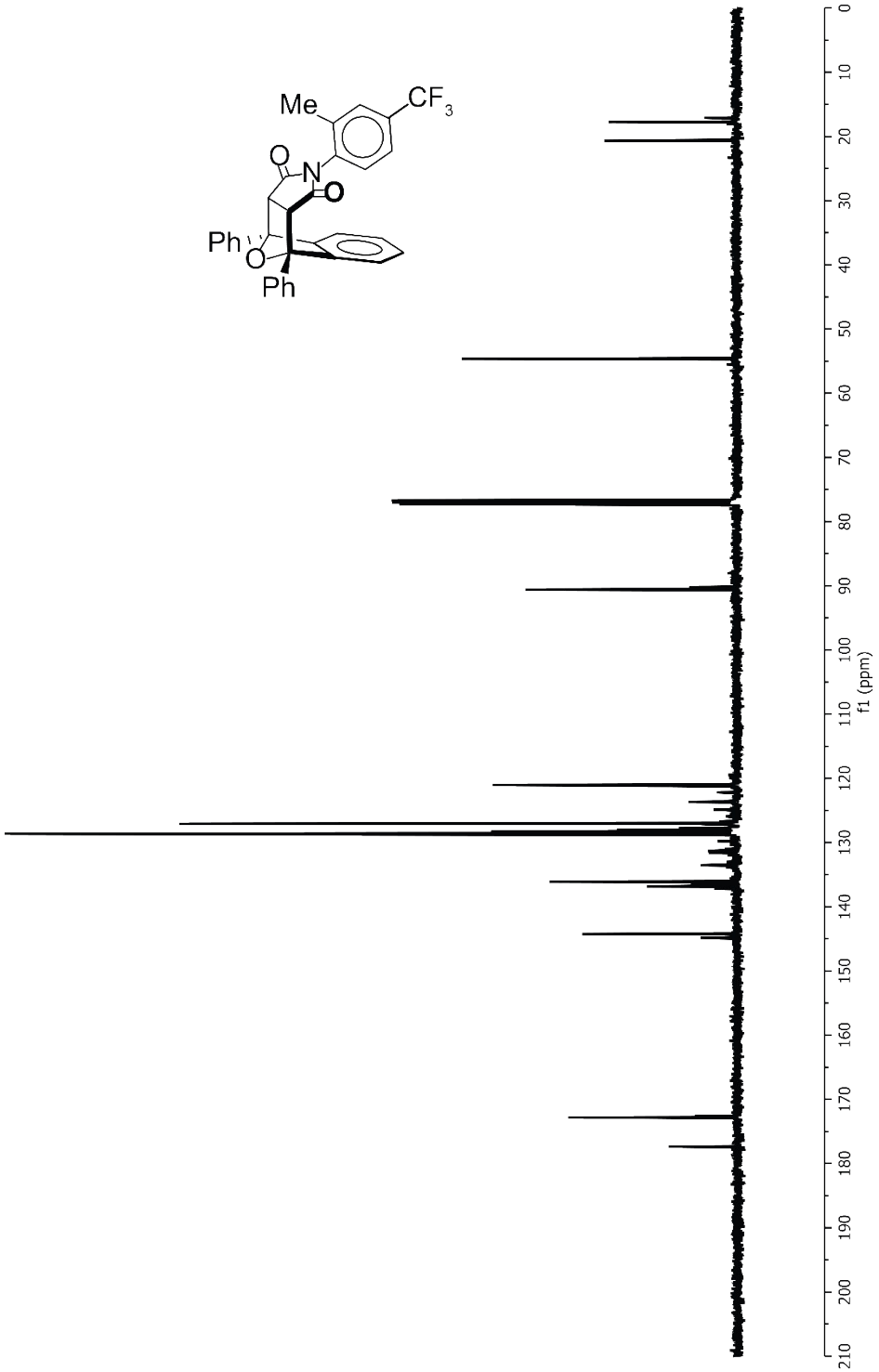

Figure S22. ^{13}C NMR spectrum of balance **2g** ($CDCl_3$, 100 MHz)

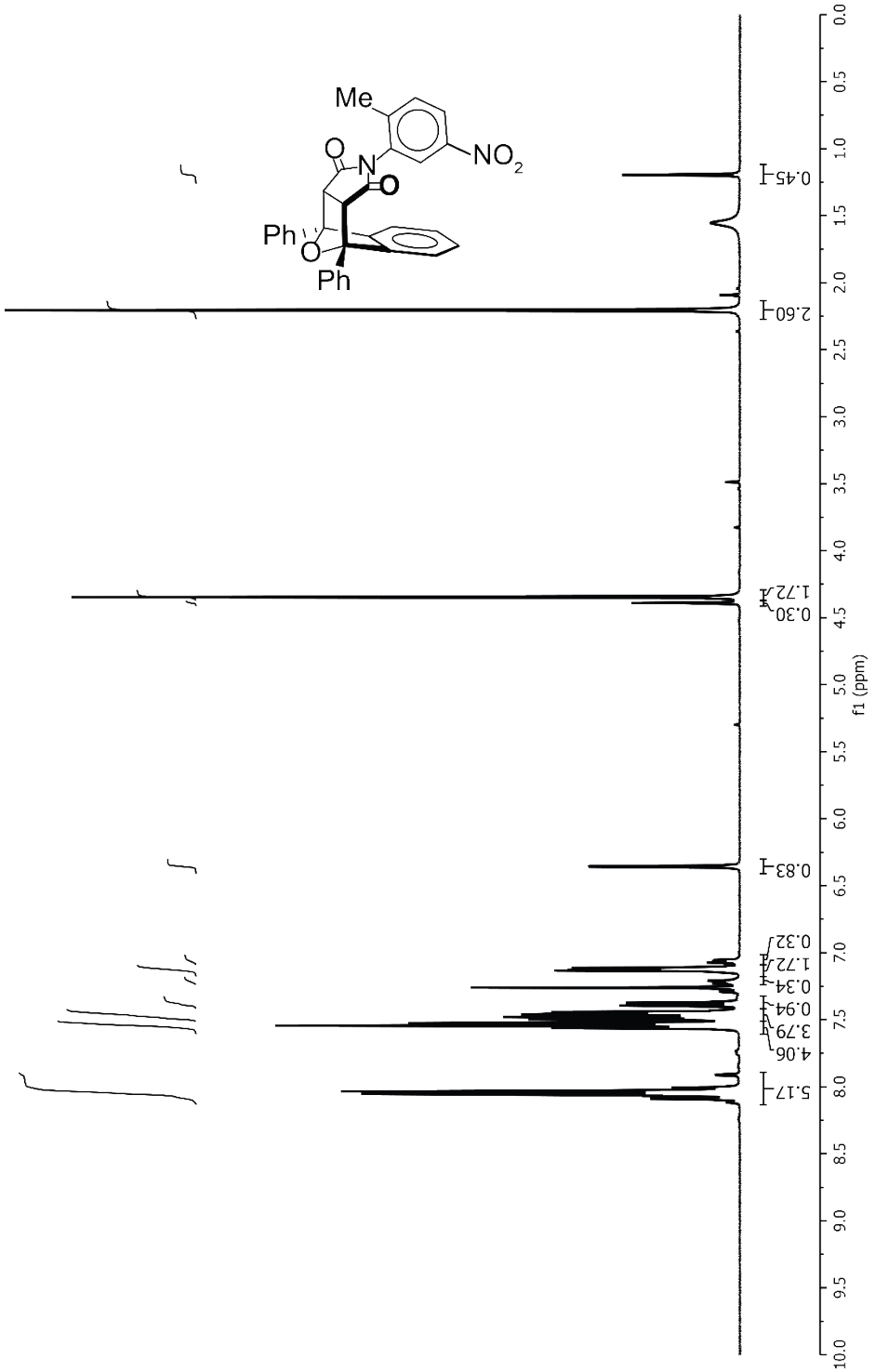

Figure S23. ^{1}H NMR spectrum of balance **1h** ($CDCl_3$, 400 MHz)

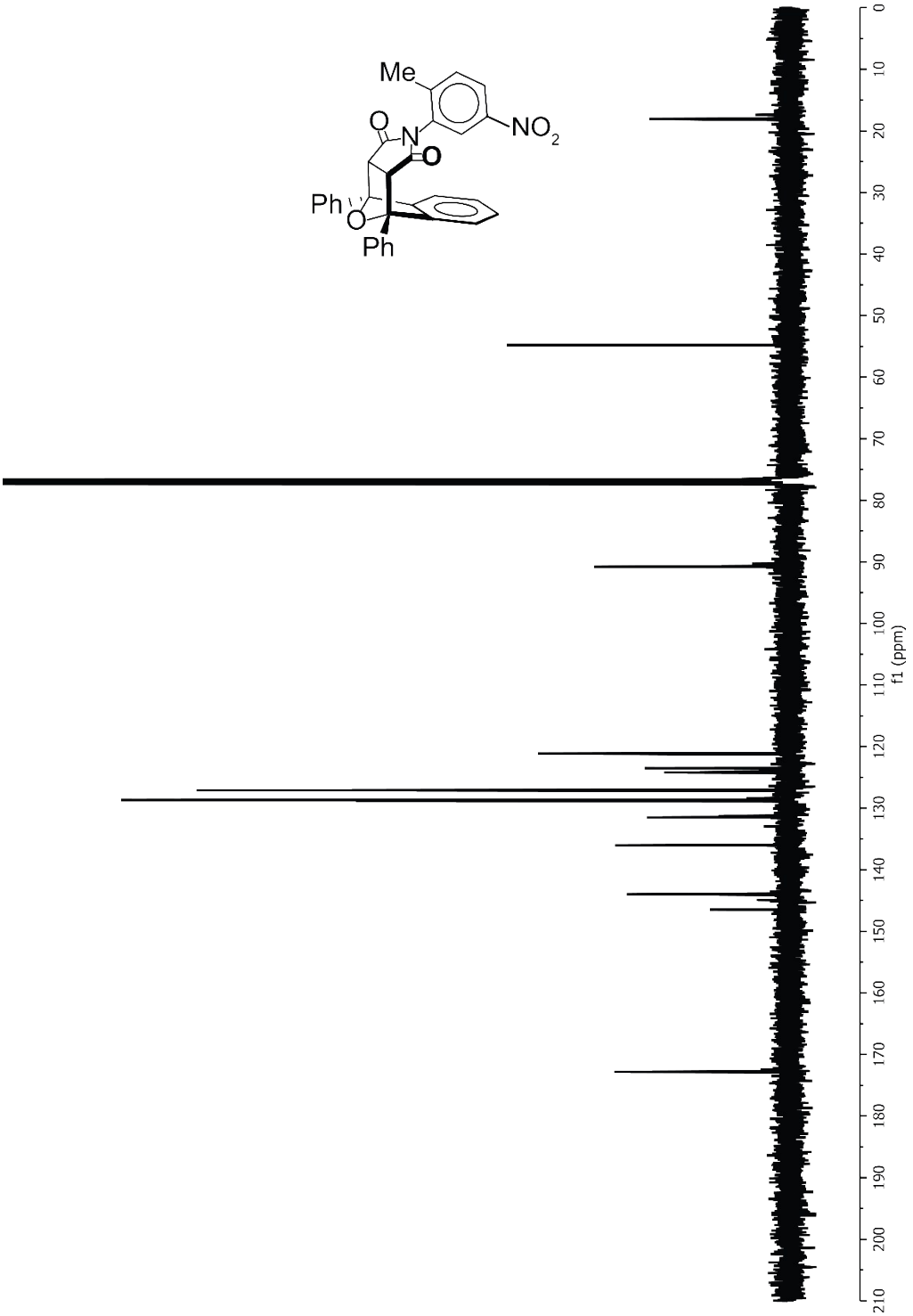

Figure S24. ^{13}C NMR spectrum of balance **1h** ($CDCl_3$, 100 MHz)

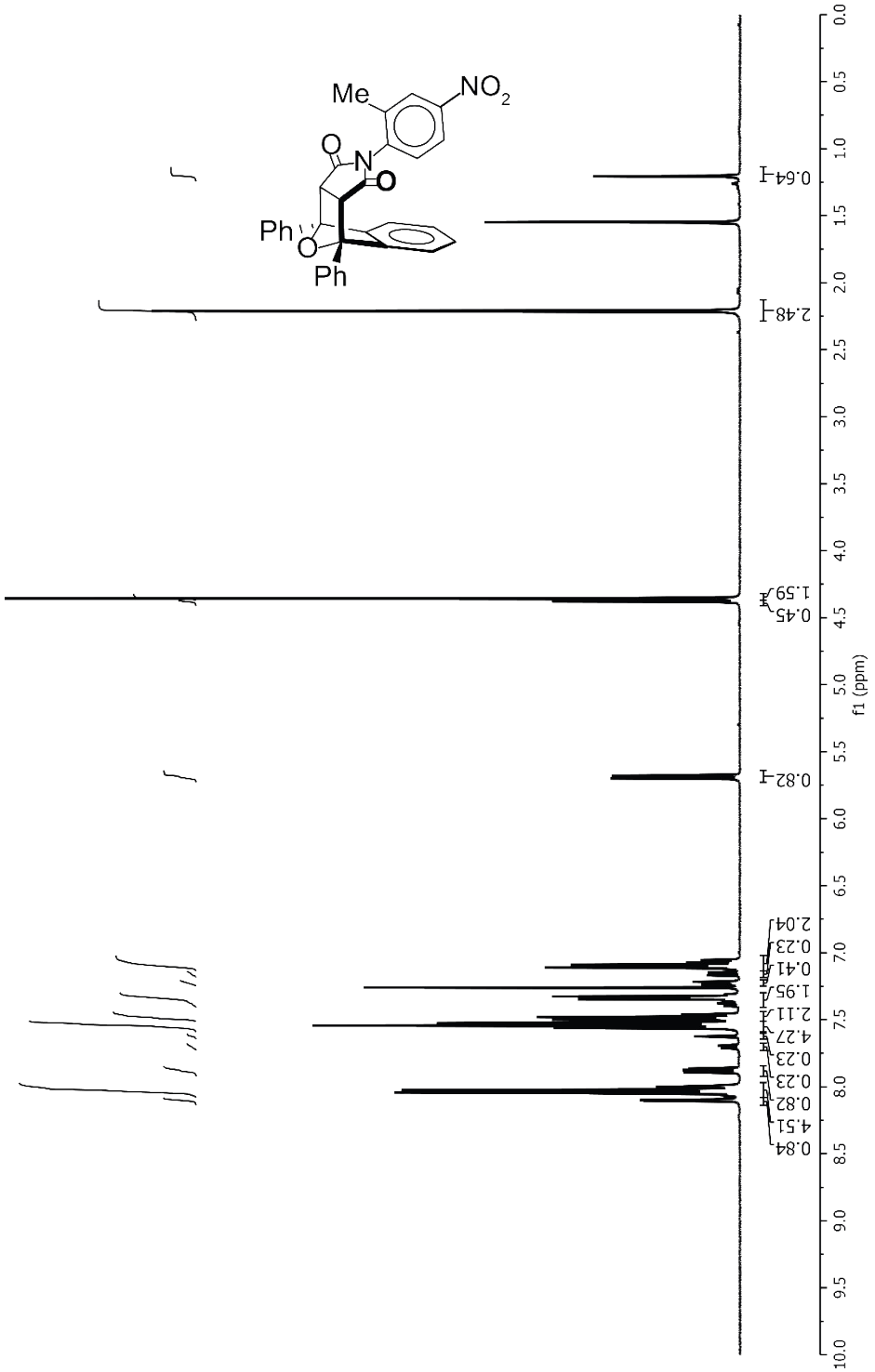

Figure S25. ^{1}H NMR spectrum of balance **2h** ($CDCl_3$, 400 MHz)

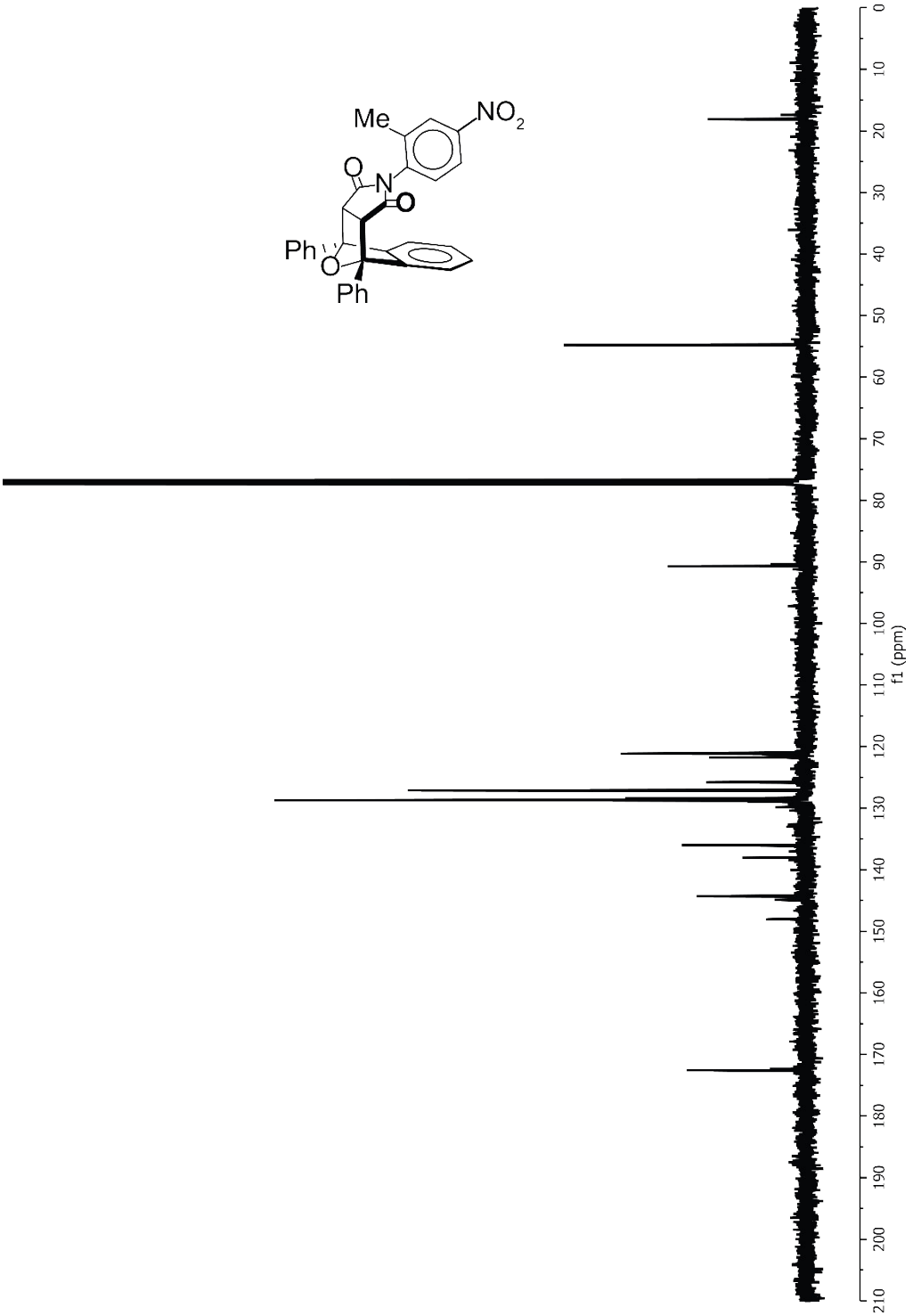

Figure S26. ^{13}C NMR spectrum of balance **2h** ($CDCl_3$, 100 MHz)

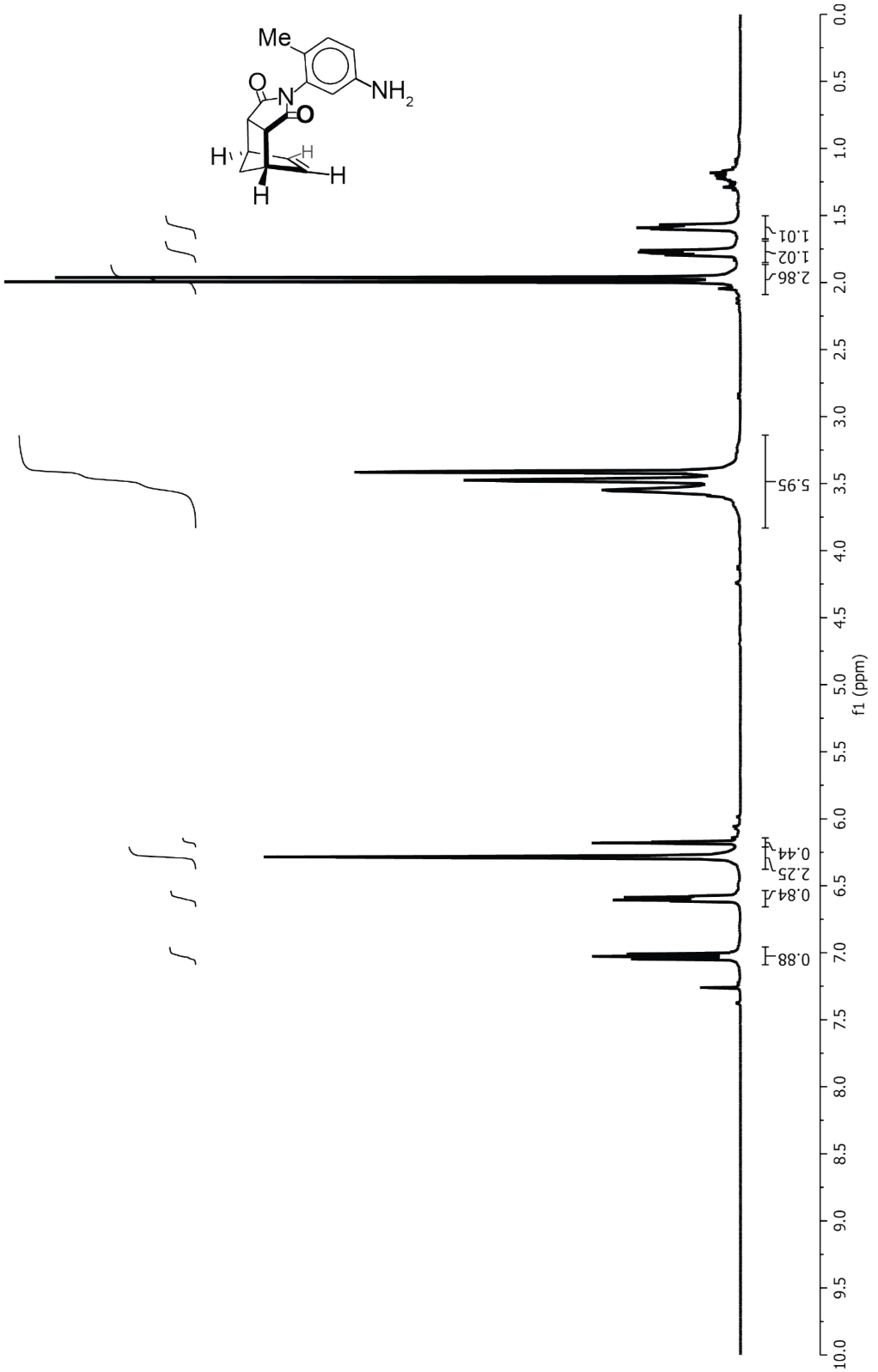

Figure S27. ^{1}H NMR spectrum of balance **3b** ($CDCl_3$, 400 MHz)

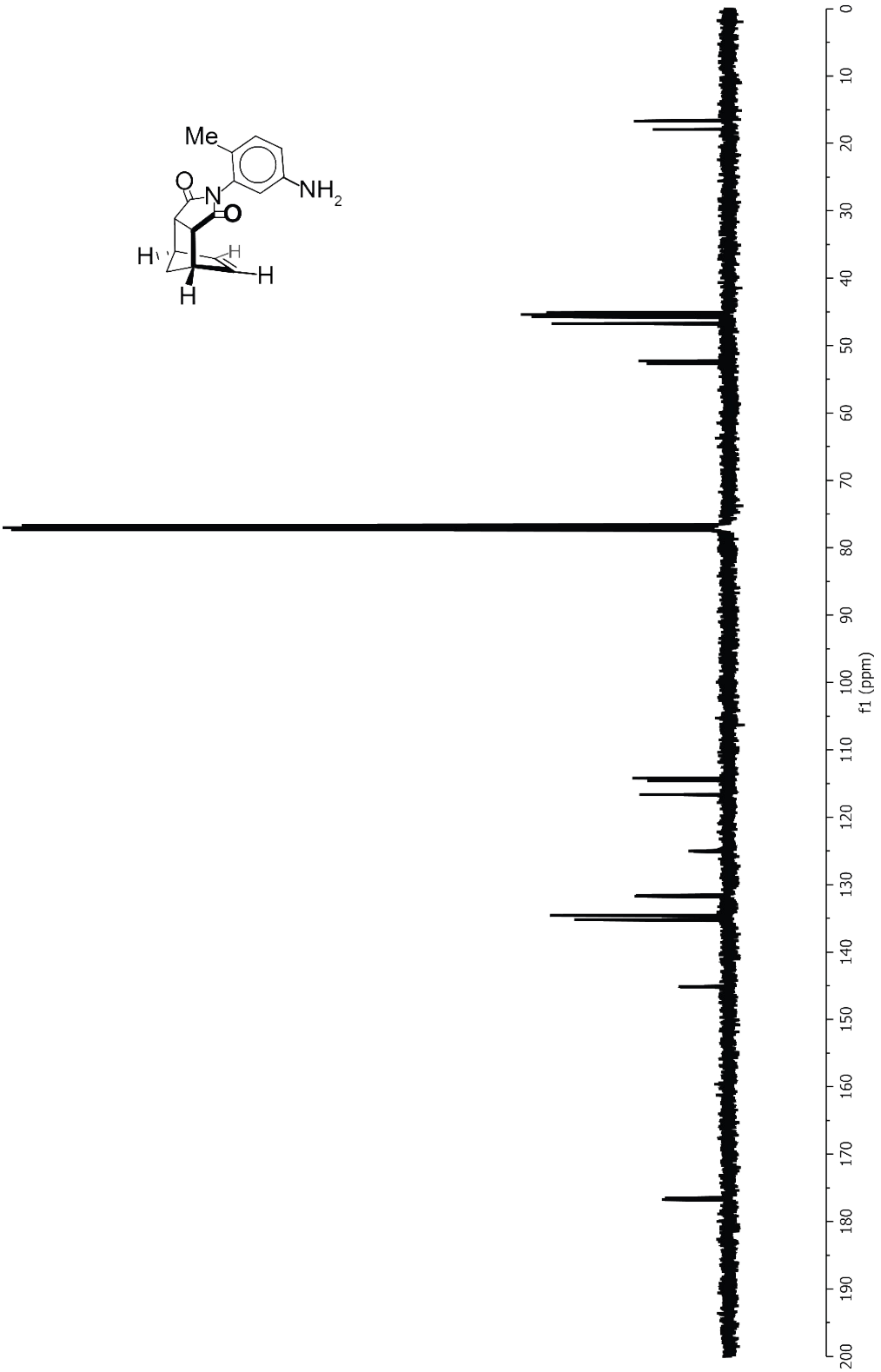

Figure S28. ^{13}C NMR spectrum of balance **3b** ($CDCl_3$, 100 MHz)

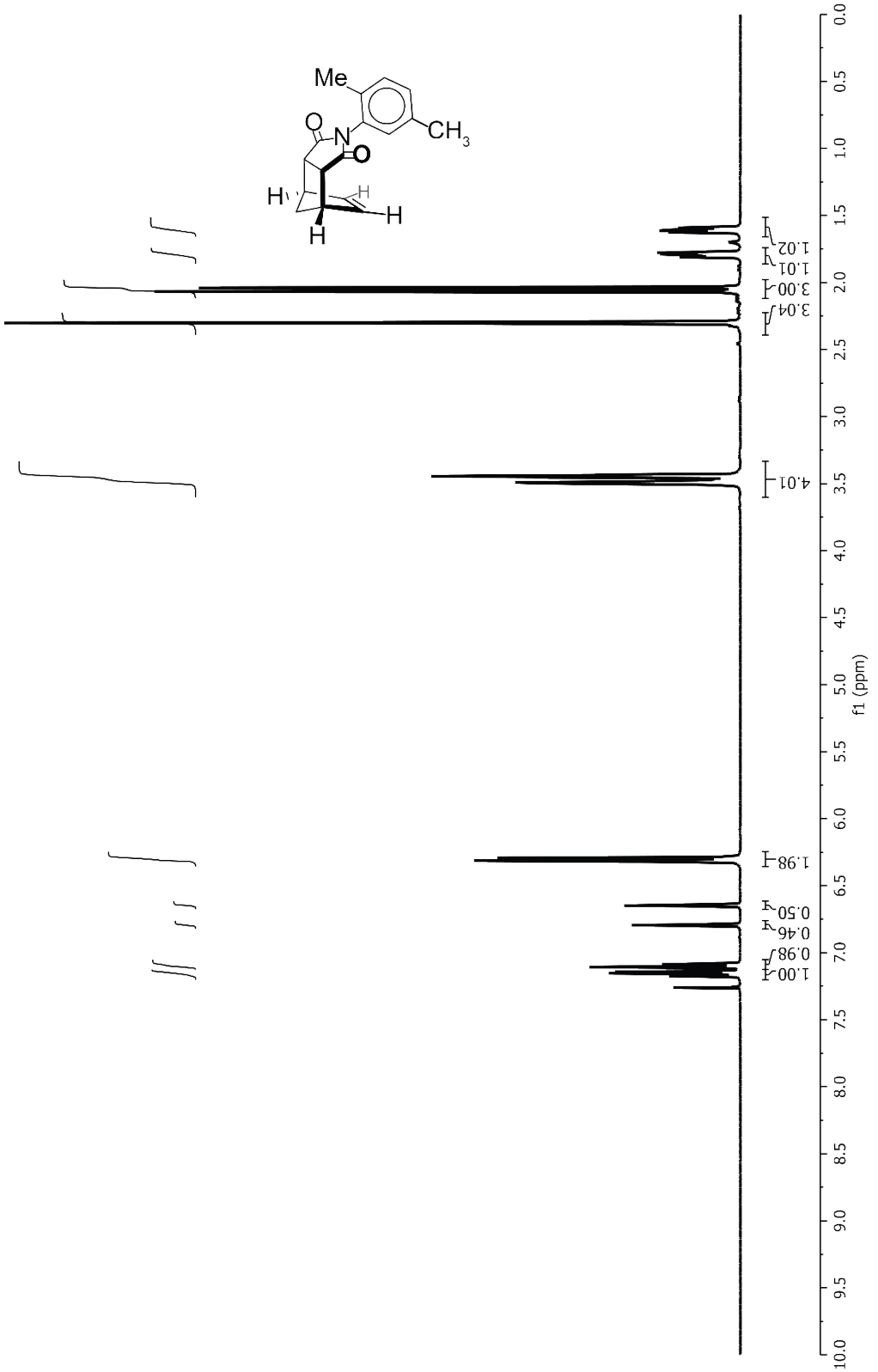

Figure S29. ^{1}H NMR spectrum of balance **3c** ($CDCl_3$, 400 MHz)

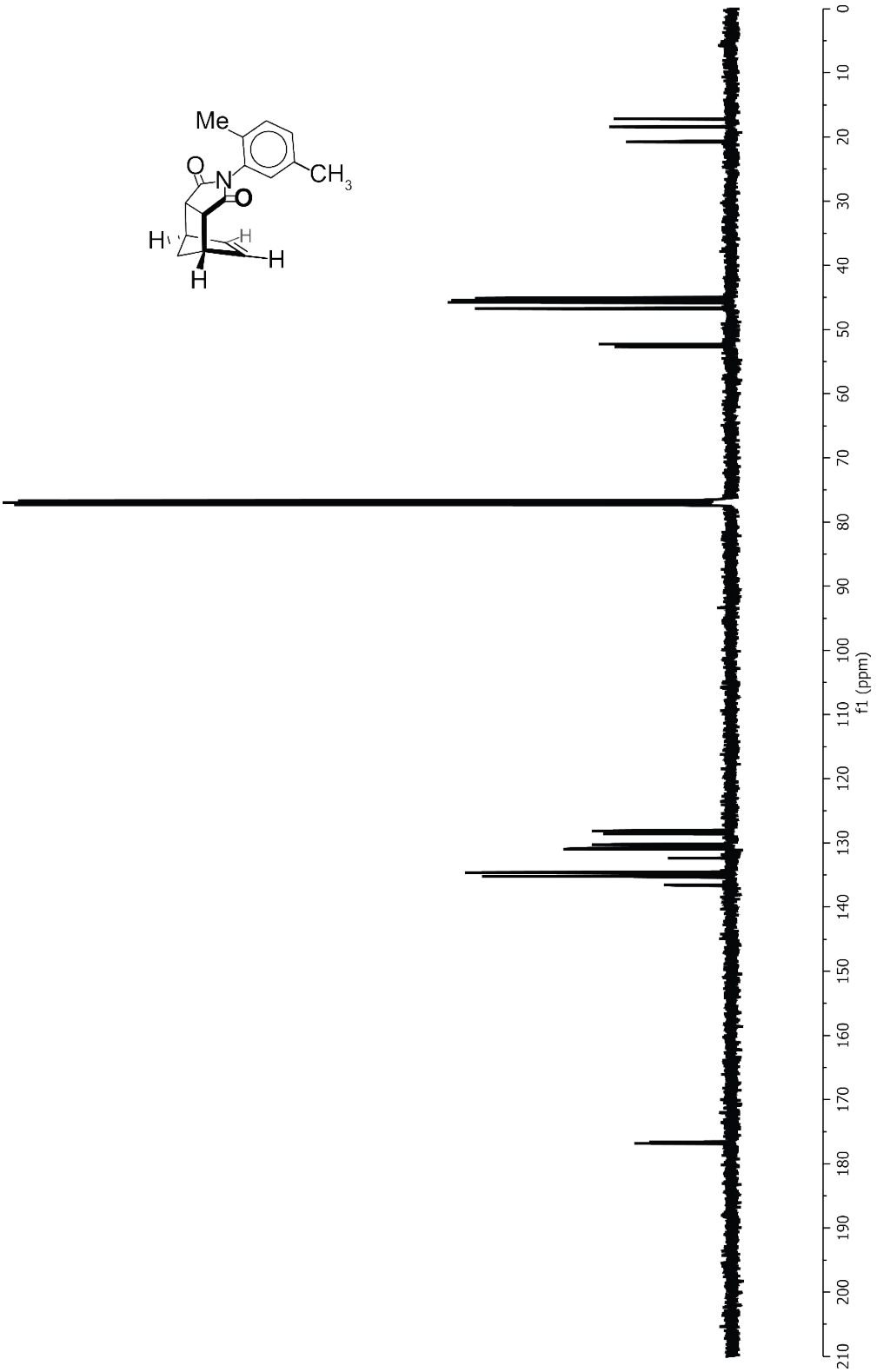

Figure S30. ^{13}C NMR spectrum of balance **3c** ($CDCl_3$, 100 MHz)

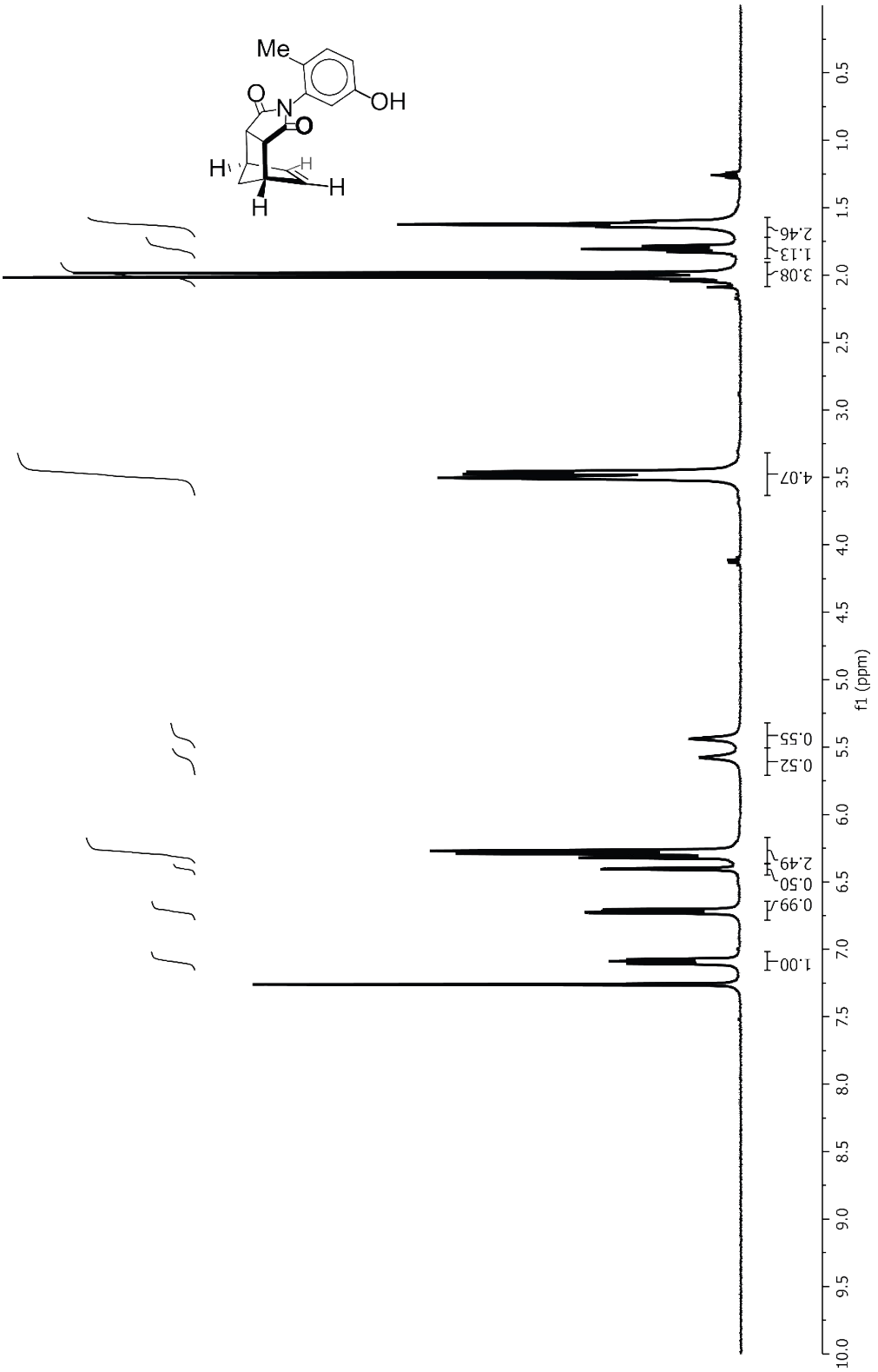

Figure S31. ^{1}H NMR spectrum of balance **3d** ($CDCl_3$, 400 MHz)

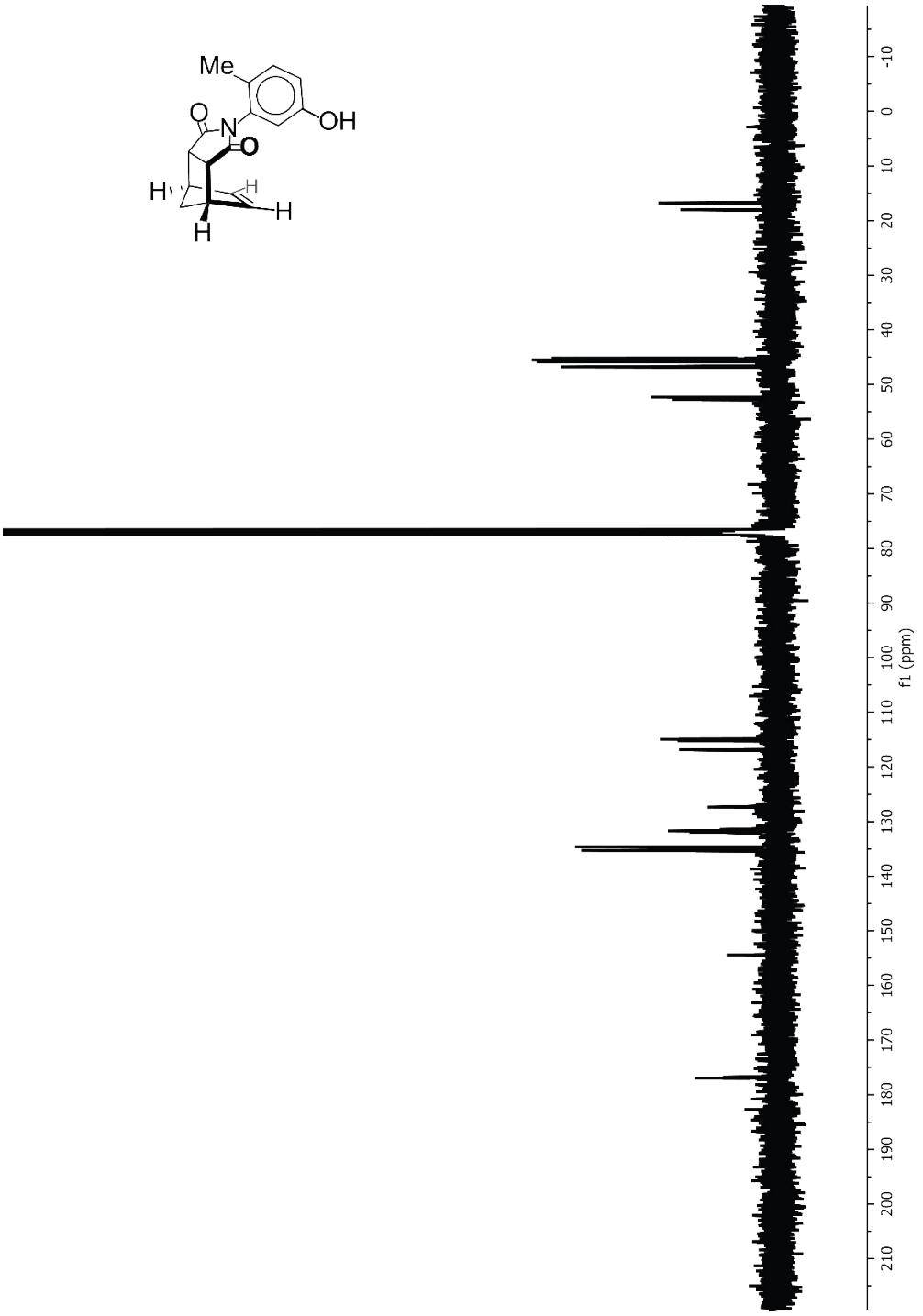

Figure S32. ^{13}C NMR spectrum of balance **3d** ($CDCl_3$, 100 MHz)

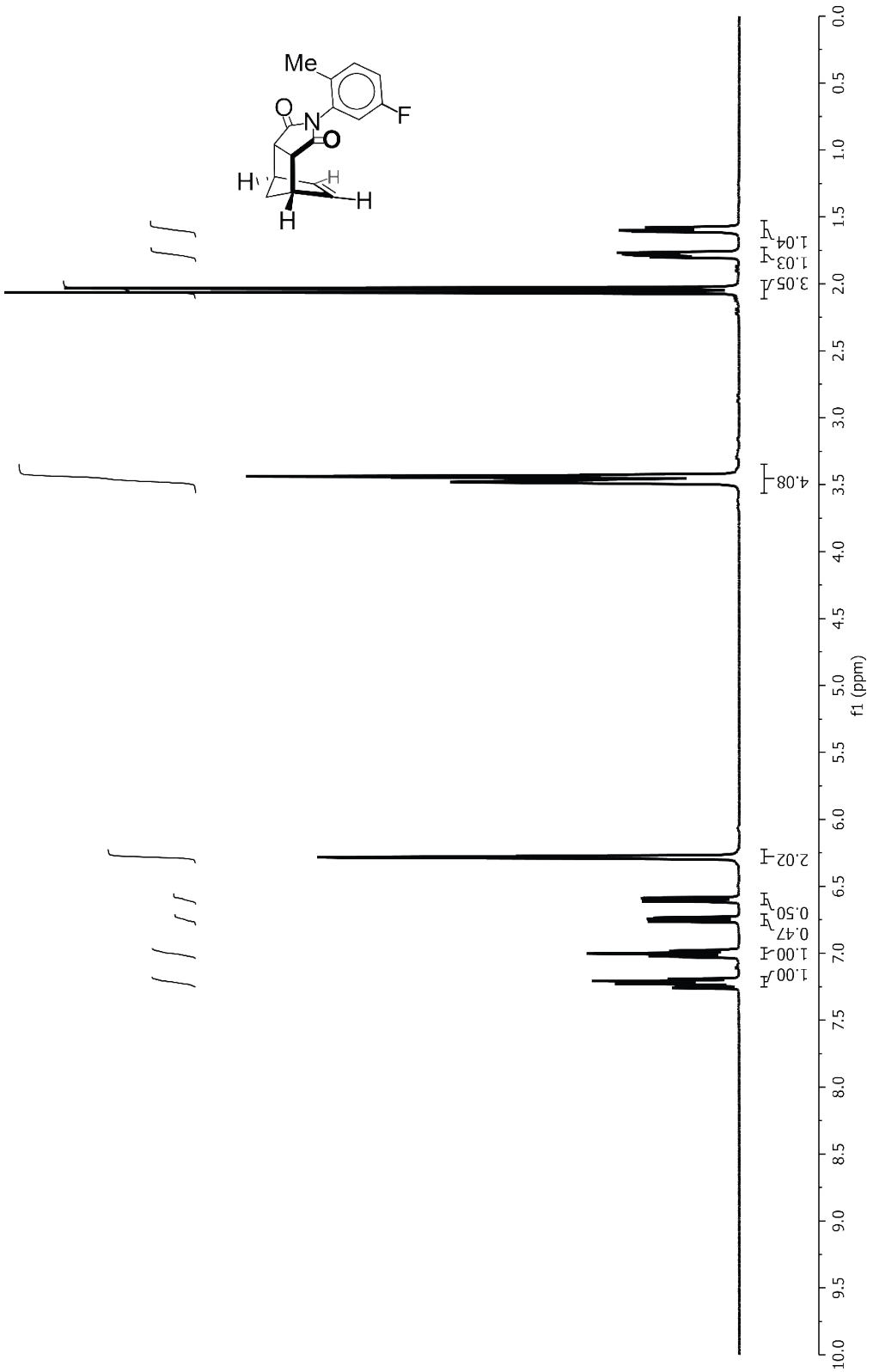

Figure S33. ^{1}H NMR spectrum of balance **3e** ($CDCl_3$, 400 MHz)

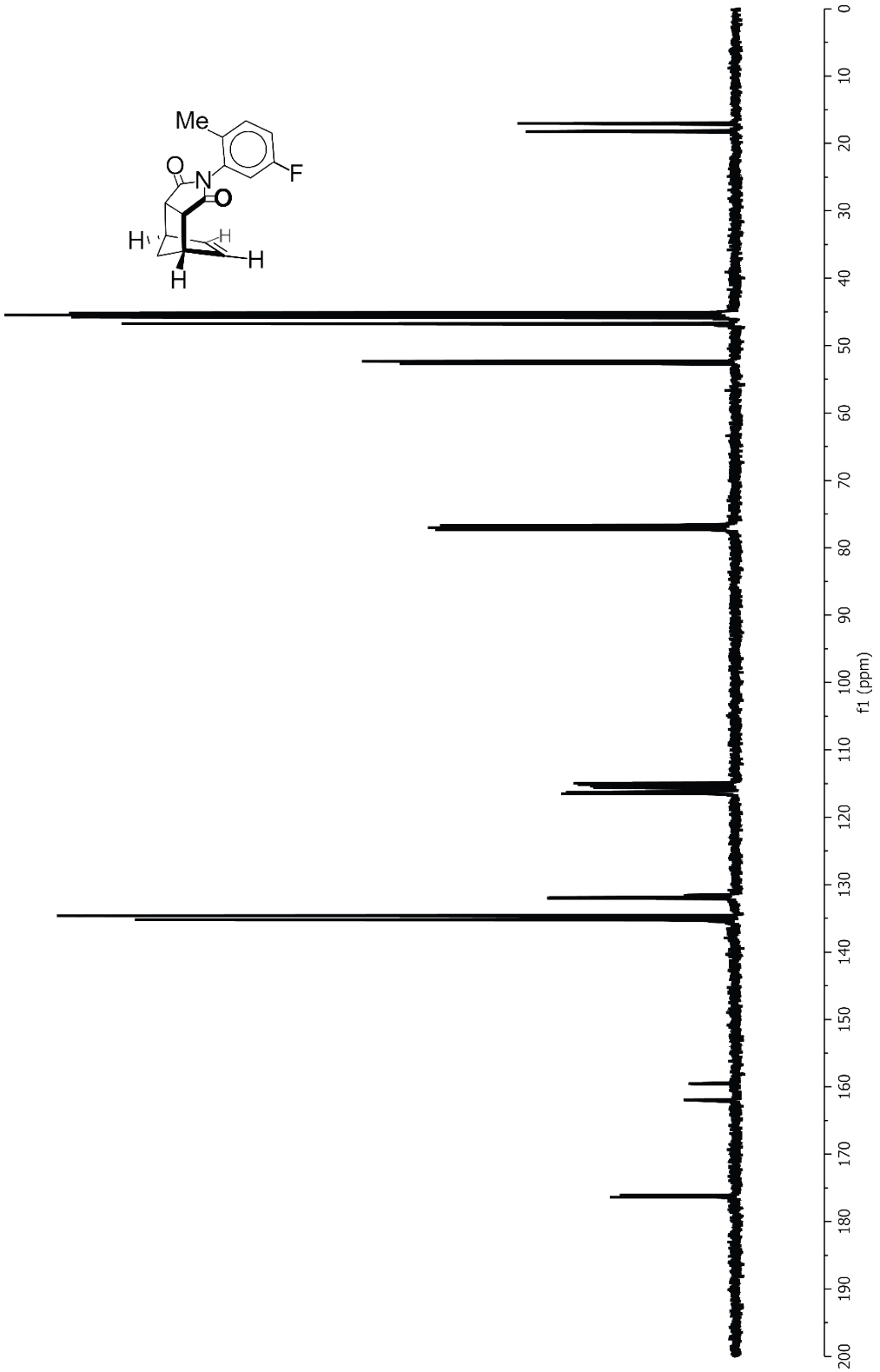

Figure S34. ^{13}C NMR spectrum of balance **3e** ($CDCl_3$, 100 MHz)

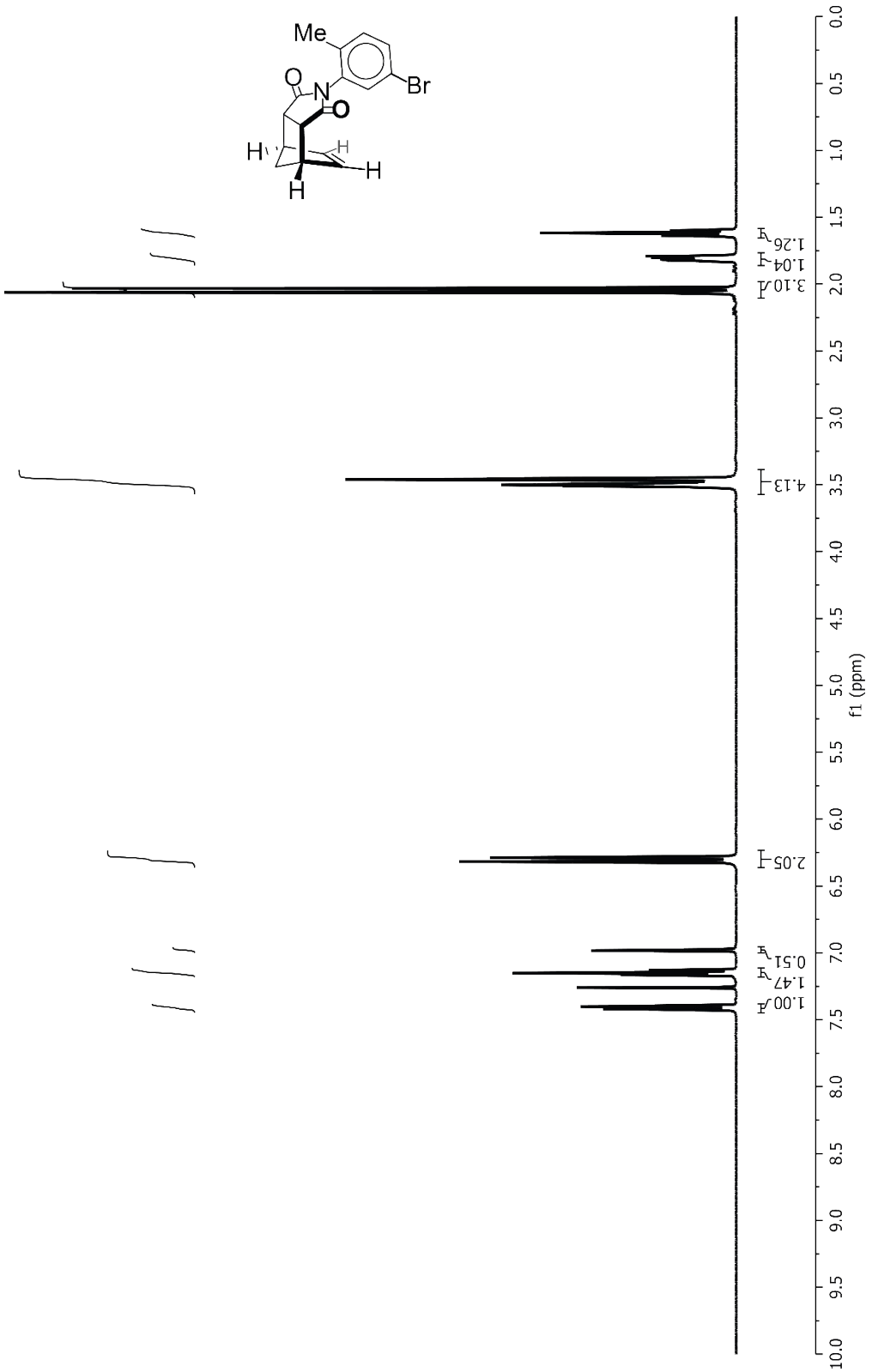

Figure S35. ^{1}H NMR spectrum of balance **3f** ($CDCl_3$, 400 MHz)

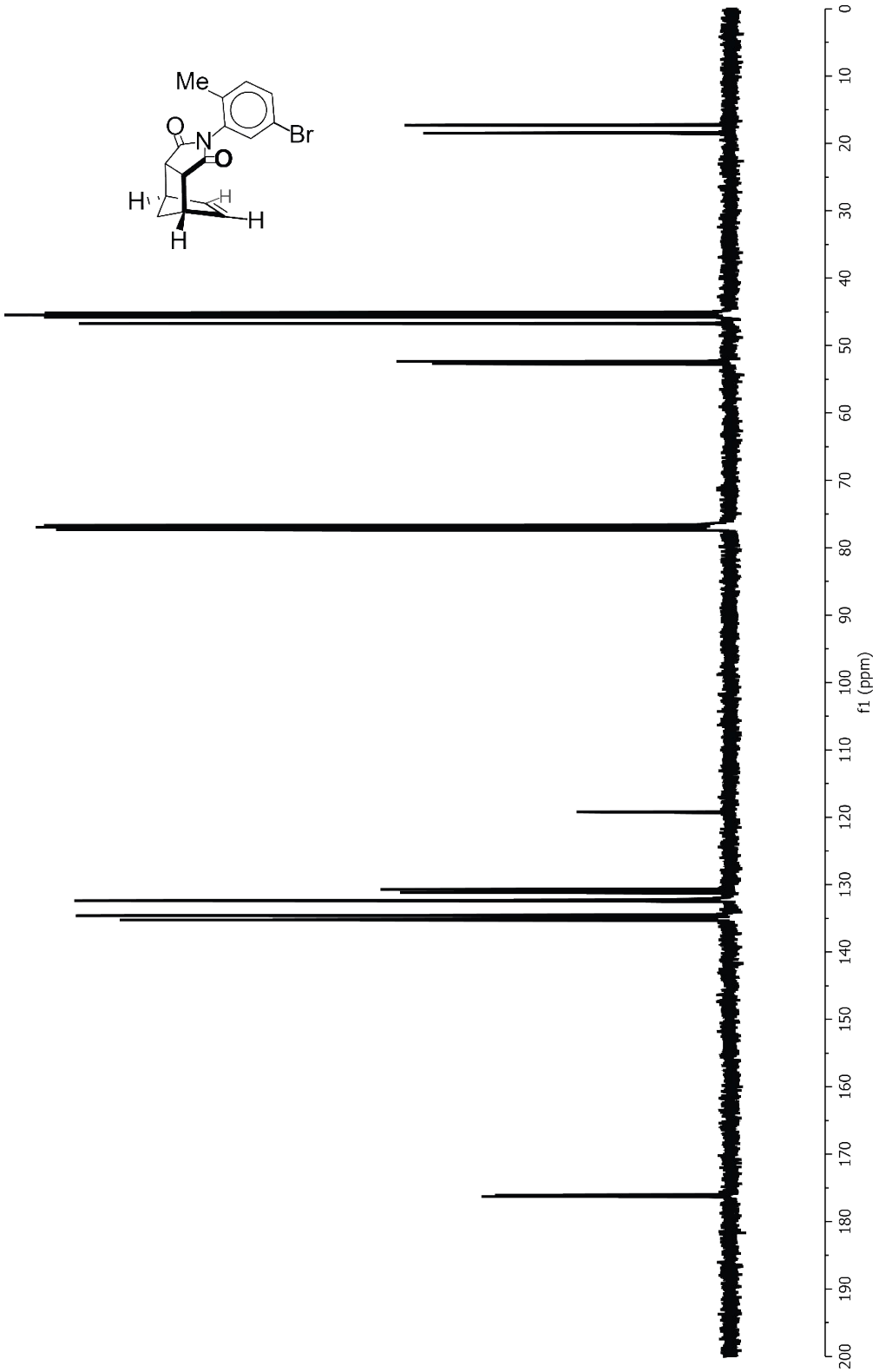

Figure S36. ^{13}C NMR spectrum of balance **3f** ($CDCl_3$, 100 MHz)

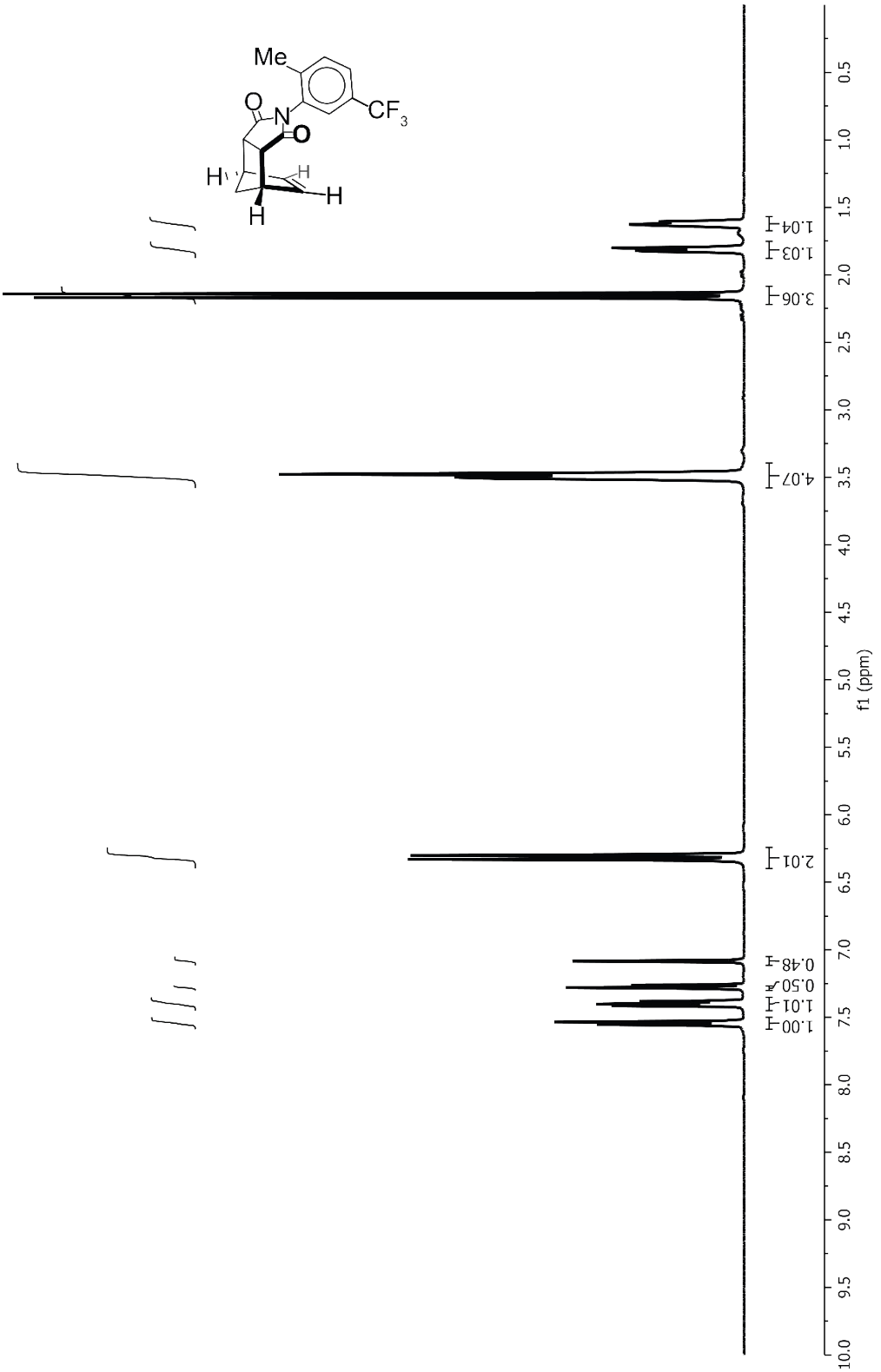

Figure S37. ^{1}H NMR spectrum of balance **3g** ($CDCl_3$, 400 MHz)

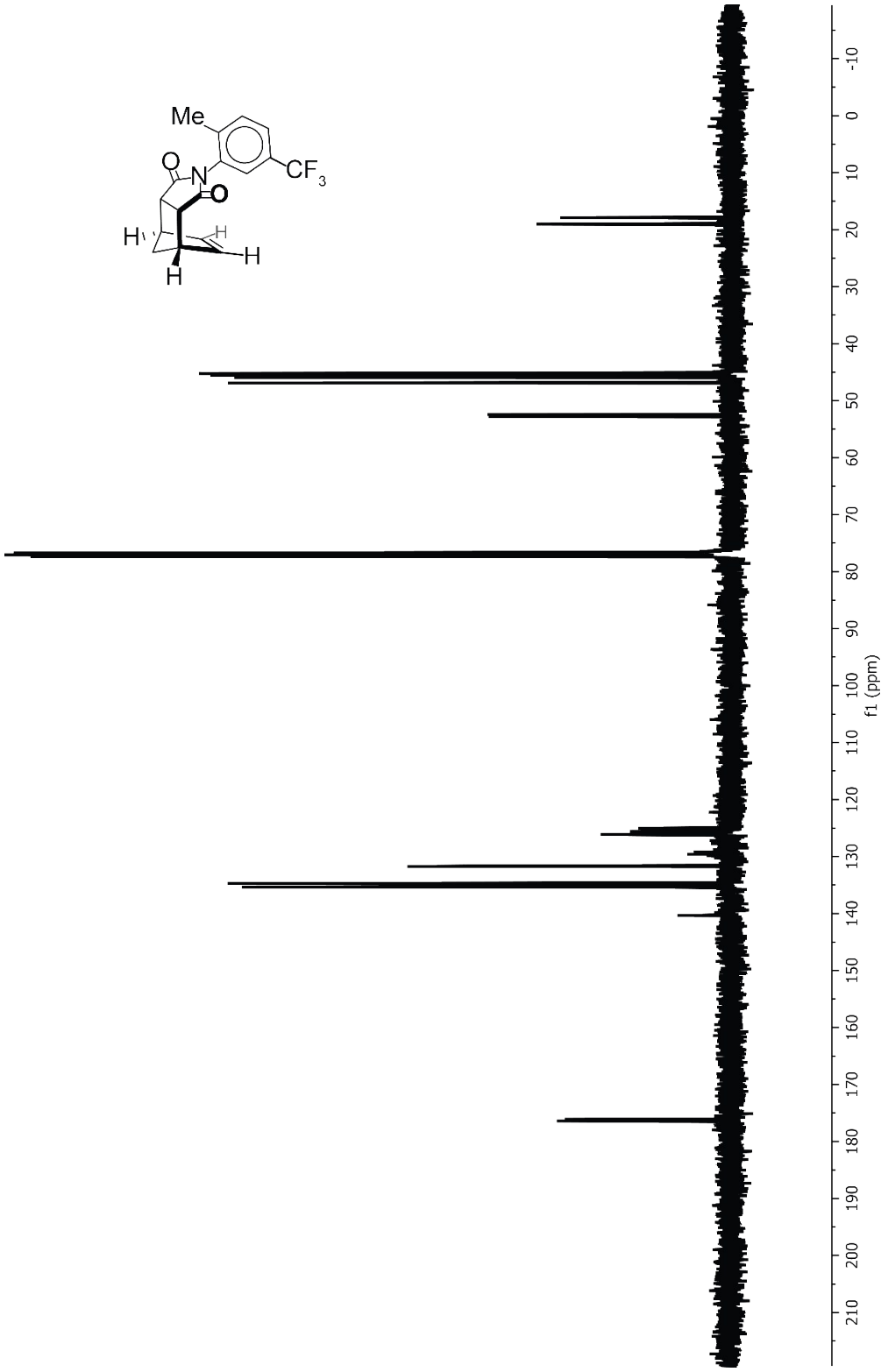

Figure S38. ^{13}C NMR spectrum of balance **3g** ($CDCl_3$, 100 MHz)

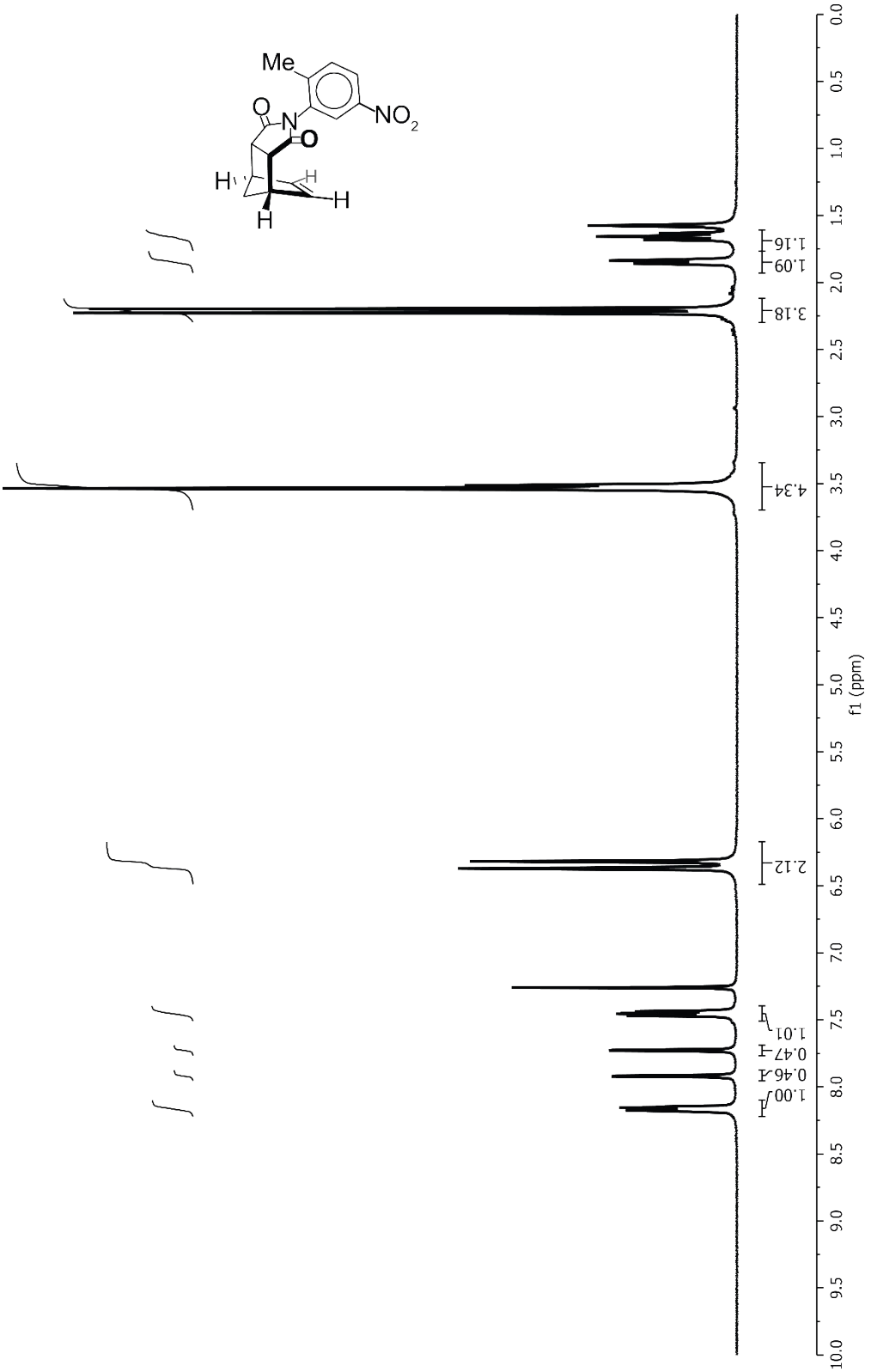

Figure S39. ^{1}H NMR spectrum of balance **3h** ($CDCl_3$, 400 MHz)

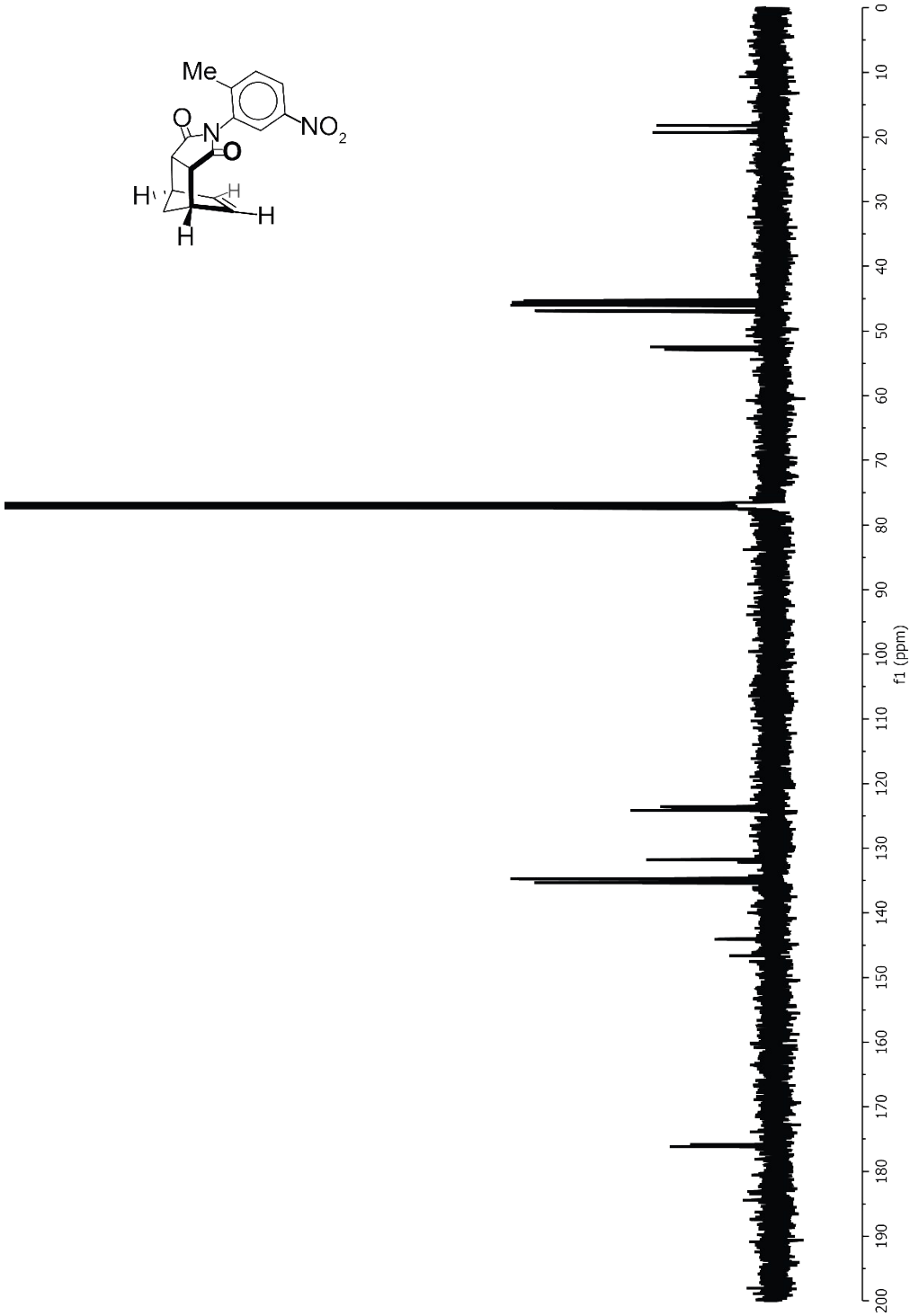

Figure S40. ^{13}C NMR spectrum of balance **3h** ($CDCl_3$, 100 MHz)

References

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