BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Supporting Information

for

Vinylogous functionalization of 4-alkylidene-5-aminopyrazoles with methyl trifluoropyruvates

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Detailed experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra

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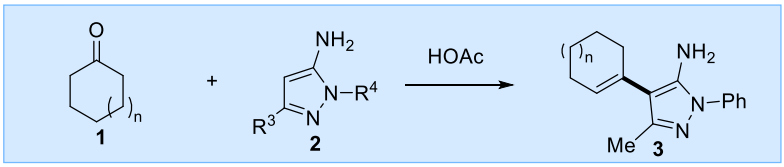
1. General experimental methods

Unless otherwise noticed, commercial reagents were used without any extra purification. Reactions were followed by thin layer chromatography (TLC) using Merck Silica Gel 60 F-254 thin layer plates. For product purification, flash column chromatography using Merck silica gel 60, 0.040–0.063 mm was used. The diastereomeric ratio (dr) was determined via ^{1}H-NMR analysis. NMR spectra were carried out in a Bruker Avance III HD spectrometer at 300 MHz for ^{1}H and at 75 MHz for ^{13}C, in a Bruker AV400 spectrometer at 400 MHz for ^{1}H and at 100 MHz for ^{13}C or in a Bruker Neo500 spectrometer at 500 MHz for ^{1}H and at 126 MHz for ^{13}C using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 for ^{1}H and 77.0 ppm for ^{13}C). Chemical shifts are given in ppm. The carbon type was determined by Distortionless Enhancement by Polarization Transfer (DEPT) experiments. High resolution mass spectra (ESI) were recorded on a TRIPLETOFT5600 spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV. Cyclic ketones **1**, 5-aminopyrazoles **2** and alkyl trifluoropyruvates **4** are commercial reactants and were used without subsequent purification. These reactions have been acquired from the following commercial cases: Aldrich, TCI, BLD and Fluorochem.

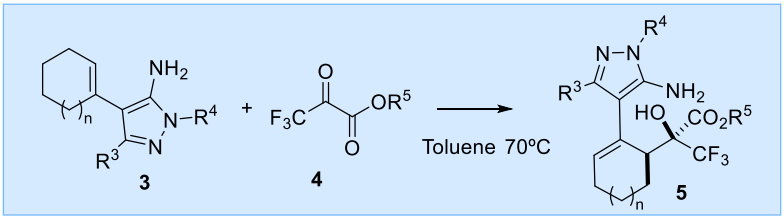
2. Experimental procedures

i. Synthesis of 4-alkenyl-5-aminopyrazoles 3



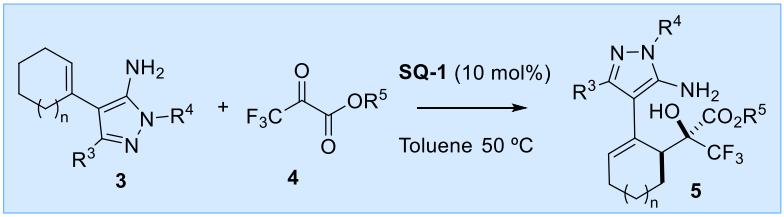
In a 25 mL round-bottomed flask, the 5-aminopyrazole (1 equiv) was dissolved in the cyclic ketone (1.5 equiv) and 0.5 mL glacial acetic acid (if the cyclic ketone was solid 2 mL of CH_2Cl_2 were used as solvent). Next, the reaction mixture was left, with stirring, at room temperature for a period of 3–5 days following the reaction using thin layer chromatography (TLC). The reaction mixture was evaporated under reduced pressure and the crude was purified via column chromatography with hexane:EtOAc mixtures as eluent to afford the corresponding products **3**.

ii. Procedure A for the vinylogous addition of 4-alkenyl-5-aminopyrazoles 3 to alkyl trifluoropyruvates 4.



In a 10 mL round-bottomed flask, the corresponding 4-alkenyl-5-aminopyrazole (**3**, 0.2 mmol, 1 equiv) and the alkyl trifluoropyruvate (**4**, 0.6 mmol, 3 equiv) were dissolved in 2 mL toluene. The reaction mixture was heated at 70 °C with a condenser for 1 day. After this time, the solvent was evaporated under reduced pressure and the diastereoisomeric ratio was evaluated using ^{1}H NMR of the crude reaction mixture. Subsequently, the crude was purified via column chromatography with hexane:EtOAc mixtures or hexane:DCM mixtures as eluent to afford the corresponding alcohols **5**.

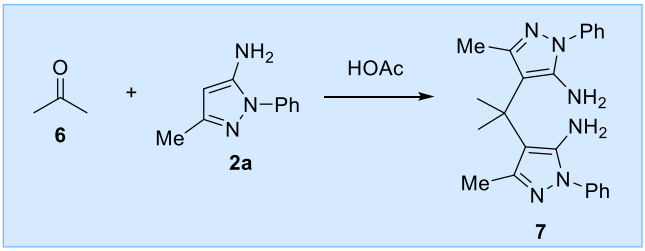
iii. Procedure B for the vinylogous addition of 4-alkenyl-5-aminopyrazoles 3 to alkyl trifluoropyruvates 4.



In a 10 mL round-bottomed flask, the corresponding 4-alkenyl-5-aminopyrazole (**3**, 0.2 mmol, 1 equiv), **SQ-1** (0.02 mmol, 10 mol %) and the alkyl trifluoropyruvate (**4**,

0.6 mmol, 3 equiv) were dissolved in 2 mL toluene. The reaction mixture was heated at 50 °C with a condenser for 1 day. After this time, the solvent was evaporated under reduced pressure and the diastereoisomeric ratio was evaluated using ^{1}H NMR of the crude reaction mixture. Subsequently, the crude was purified via column chromatography with hexane:EtOAc mixtures or hexane:DCM mixtures as eluent to afford the corresponding alcohols **5**.

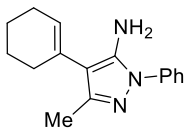
iv. Reaction of acetone with 5-aminopyrazole 2a.



In a 25 mL round-bottomed flask, the 5-aminopyrazole **2a** (0.87 g, 5 mmol) was dissolved in acetone (0.73 mL, 10 mmol) and 0.5 mL glacial acetic acid. Next, the reaction mixture is left, with stirring, at room temperature for a period of 3–5 days following the reaction using thin layer chromatography (TLC). The reaction mixture was evaporated under reduced pressure and the crude was purified via column chromatography with hexane:EtOAc mixtures as eluent to afford the corresponding products **7**.

3. Chacterization of 4-alkenyl-5-aminopyrazoles 3

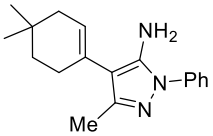
Compound **3aa**[1]:



Following general procedure i), product **3aa** was synthetized using 1.2 mL (12 mmol) of cyclohexanone (**1a**) with 1.39 g (8 mmol) 5-aminopyrazole (**2a**) obtaining 0.98 g (63% yield) of the product **3aa** as a yellow solid (m.p. = 86-90 °C).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.49-7.41 (m, 2H), 7.34-7.27 (m, 1H), 5.67 (tt, *J* = 3.6, 1.7 Hz, 1H), 3.77 (s, 2H), 2.30-2.13 (m, 7H), 1.82-1.60 (m, 4H). **^{13}C RMN (75 MHz, $CDCl_3$)** δ 147.2 (C), 141.6 (C), 138.9 (C), 130.5 (C), 129.4 (CH), 126.8 (CH), 126.2 (CH), 123.5 (CH), 107.1 (C), 29.2 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 13.6 (CH_3).

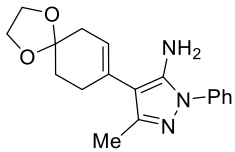
· Compound **3ba**:



Following general procedure i), product **3ba** was synthetized using 1.51 g (12 mmol) of 4,4-dimethylcyclohexan-1-one (**1b**) with 1.39 g (8 mmol) 5-aminopyrazole (**2a**) obtaining 1.06 g (47% yield) of the product **3ba** as a yellow solid (m.p. = 123-126 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.53-7.40 (m, 2H), 7.35-7.27 (m, 1H), 5.59 (tt, *J* = 3.8, 1.8 Hz, 1H), 3.75 (s, 2H), 2.27 (ddt, *J* = 6.5, 4.3, 2.1 Hz, 2H), 2.23 (s, 3H), 1.98 (dd, *J* = 4.1, 2.3 Hz, 2H), 1.50 (t, *J* = 6.4 Hz, 2H), 0.99 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 147.2 (C), 141.6 (C), 138.9 (C), 129.4 (CH), 129.2 (C), 126.8 (CH), 125.2 (CH), 123.5 (CH), 106.8 (C), 39.6 (CH_2), 35.8 (CH_2), 28.3 (CH_3), 28.2 (C), 27.0 (CH_2), 13.6 (CH_3)

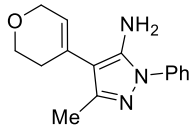
· Compound **3ca**:



Following general procedure i), product **3ca** was synthetized using 0.94 g (6 mmol) of 1,4-dioxaspiro[4.5]decan-8-one (**1c**) with 0.69 g (4 mmol) 5-aminopyrazole (**2a**) obtaining 0.86 g (69% yield) of the product **3ca** as a yellow solid (m.p. = 102-105 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.51-7.39 (m, 1H), 7.34-7.27 (m, 1H), 5.56 (tt, *J* = 3.6, 1.5 Hz, 1H), 4.02 (s, 3H), 3.80 (s, 1H), 2.50 (tt, *J* = 6.0, 1.7 Hz, 1H), 2.47-2.43 (m, 1H), 2.24 (s, 2H), 1.89 (t, *J* = 6.4 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.1 (C), 141.7 (C), 138.8 (C), 130.2 (C), 129.4 (CH), 126.9 (CH), 123.6 (CH), 122.8 (CH), 107.6 (C), 105.9 (C), 64.4 (CH_2), 36.1 (CH_2), 31.4 (CH_2), 28.4 (CH_2), 13.7 (CH_3).

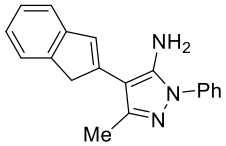
· Compound **3da**:



Following general procedure i), product **3da** was synthetized using 0.56 mL (6 mmol) of tetrahydro-4*H*-pyran-4-one (**1d**) with 0.69 g (4 mmol) 5-aminopyrazole (**2a**) obtaining 0.12 g (11% yield) of the product **3da** as a yellow solid (m.p. = 98-102 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.48 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.33-7.25 (m, 1H), 5.65 (tt, *J* = 2.9, 1.6 Hz, 1H), 4.27 (q, *J* = 2.7 Hz, 2H), 3.88 (t, *J* = 5.4 Hz, 2H), 3.84 (s, 2H), 2.38 (ttd, *J* = 5.4, 2.6, 1.7 Hz, 2H), 2.22 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.8 (C),141.8(C), 138.5 (C), 129.3 (CH), 128.4 (C), 126.9 (CH), 123.5 (CH), 123.5 (CH), 104.8(C), 65.5 (CH_2), 64.3 (CH_2), 29.0 (CH_2), 13.6 (CH_3).

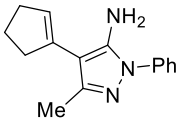
· Compound **3ec**:



Following general procedure i), product **3da** was synthetized using 0.79 g (6 mmol) of 1,3-dihydro-2*H*-inden-2-one (**1e**) with 0.69 g (4 mmol) 5-aminopyrazole (**2a**) obtaining 0.54 g (47% yield) of the product **3da** as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.54-7.46 (m, 2H), 7.47 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.41-7.34 (m, 2H), 7.28 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.15 (td, *J* = 7.3, 1.1 Hz, 1H), 6.79-6.77 (m, 1H), 4.12 (s, 2H), 3.79 (s, 2H), 2.45 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 147.5 (C), 145.5 (C), 142.8 (C), 141.9 (C), 139.9 (C), 138.2 (C), 129.6 (CH), 127.5 (CH), 126.6 (CH), 124.0 (CH), 123.8 (CH), 123.7 (CH), 123.3 (CH), 120.0 (CH), 101.2 (C), 41.1 (CH_2), 14.9 (CH_3)

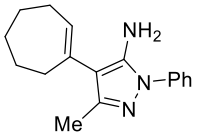
· Compound **3fa**:



Following general procedure i), product **3da** was synthetized using 1.1 mL (12 mmol) of cyclopentanone (**1f**) with 1.39 g (8 mmol) 5-aminopyrazole (**2a**) obtaining 0.10 g (5% yield) of the product **3fa** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.4, 1.2 Hz, 2H), 7.32 – 7.20 (m, 2H), 7.18 – 7.06 (m, 1H), 5.45 (p, *J* = 2.3 Hz, 1H), 3.75 (s, 2H), 2.58 – 2.45 (m, 2H), 2.38 – 2.24 (m, 2H), 2.11 (s, 3H), 1.86 – 1.70 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.4 (C), 142.3(C), 138.5 (C), 135.6 (C), 129.4 (CH), 127.0 (CH), 123.7(CH), 123.7(CH), 101.4(C), 35.3(CH_2), 32.6(CH_2), 23.4(CH_2), 14.4 (CH_3).

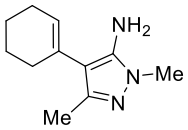
· Compound **3ga**:



Following general procedure i), product **3ga** was synthetized using 1.4 mL (12 mmol) of cycloheptanone (**1g**) with 1.39 g (8 mmol) 5-aminopyrazole (**2a**) obtaining 0.12 g (6% yield) of the product **3ga** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.31 (dd, *J* = 7.4, 1.1 Hz, 1H), 5.84 (t, *J* = 6.6 Hz, 1H), 3.79 (s, 2H), 2.61 – 2.37 (m, 2H), 2.32 – 2.25 (m, 2H), 2.23 (d, *J* = 1.0 Hz, 3H), 1.84 (dtd, *J* = 11.8, 5.6, 3.2 Hz, 2H), 1.73 – 1.50 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.9 (C), 141.3 (C), 138.7 (C), 137.2 (C), 131.5 (CH), 129.4 (CH), 126.9 (CH), 123.5 (CH), 108.9 (C), 33.9 (CH_2), 32.8 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 13.3 (CH_3).

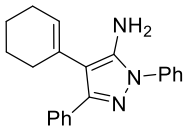
· Compound **3ab**[2]:



Following general procedure i), product **3aa** was synthetized using 0.6 mL (6 mmol) of cyclohexanone (**1a**) with 0.44 g (8 mmol) 5-aminopyrazole (**2b**) obtaining 0.41 g (54% yield) of the product **3ab** as a white solid (m.p. = 178-180 °C).

^{1}H NMR (400 MHz, $CDCl_3$) 5.54 (tt, *J* = 3.5, 1.6 Hz, 1H), 3.60 (s, 3H), 3.45 (s, 1H), 2.22 – 2.15 (m, 4H), 2.14 (s, 3H), 1.75-1.61 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 144.7 (C), 141.5 (C), 130.9 (C), 125.5 (CH), 107.4 (C), 34.1 (CH_3), 29.3 (CH_2), 25.5 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 13.5 (CH_3).

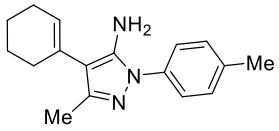
· Compound **3ac**[2]:



Following general procedure i), product **3ac** was synthetized using 0.3 mL (3 mmol) of cyclohexanone (**1a**) with 0.47 g (2 mmol) 5-aminopyrazole (**2c**) obtaining 0.10 g (16% yield) of the product **3ac** as an orange solid (m.p. = 96-106 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H), 7.69 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.41 – 7.34 (m, 2H), 7.34 – 7.27 (m, 2H), 5.84 (tt, *J* = 3.7, 1.7 Hz, 1H), 3.84 (s, 2H), 2.25 (d, *J* = 2.3 Hz, 2H), 2.03 (d, *J* = 1.9 Hz, 2H), 1.68 (t, *J* = 3.2 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 149.0 (C), 142.3 (C), 134.0 (C), 134.3 (C), 131.4 (C), 129.4 (CH), 128.1 (CH), 127.49 (CH), 127.46 (CH), 127.2 (CH), 127.0 (CH), 123.6 (CH), 106.4 (C), 29.4 (CH_2), 25.8 (CH_2), 23.1 (CH_2), 22.2 (CH_2).

· Compound **3ad**:

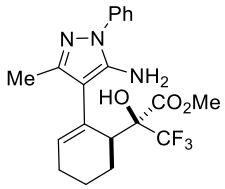


Following general procedure i), product **3ac** was synthetized using 0.3 mL (3 mmol) of cyclohexanone (**1a**) with 0.37 g (2 mmol) 5-aminopyrazole (**2d**) obtaining 0.25 g (46% yield) of the product **3ac** as a yellow solid (m.p. = 91-92 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.11 (m, 2H), 5.66 (tt, *J* = 3.6, 1.7 Hz, 1H), 3.73 (s, 2H), 2.38 (s, 3H), 2.29 – 2.11 (m, 7H), 1.88 – 1.59 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.8 (C), 141.6 (C), 136.7 (C), 136.4 (C), 130.6 (C), 129.9 (CH), 126.0 (CH), 123.6 (CH), 106.9 (C), 29.3 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 22.3 (CH_2), 21.1 (CH_3), 13.6 (CH_3).

4. Characterization of products 5

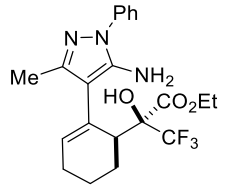
· Compound **5aaa**:



Following general procedure A, product **5aaa** was synthetized as colorless oil in 64% yield (0.128 mmol, 52.4 mg). Diastereoisomeric ratio (7:1) was determined via ^{1}H NMR analysis. The enantiomeric excess was determined by HPLC using a chiral stationary phase (Chiralpak® AYH), using hexane:iPrOH 80:20, 1.0mL/min, first enantiomer t_R = 4.77 min, second enantiomer t_R = 6.17 min.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.51 (m, 2H), 7.46 (t, *J*= 7.7 Hz, 2H), 7.37-7.29 (m, 1H), 5.89 (td, *J* = 3.9, 1.4 Hz, H), 4.06 (s, 1H), 3.74 (s, 2H), 3.54 (s, 3H), 3.38-3.30 (m, 1H), 2.19 (ddd, *J* = 7.7, 3.7, 1.9 Hz, 2H), 2.13 (s, 3H), 2.10-1.88 (m, 3H), 1.74-1.52 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.6 (C), 147.5 (C), 143.1 (C), 138.7 (C), 135.5 (CH), 129.5 (CH), 127.2 (CH), 126.4 (C), 123.8 (CH), 123.72 (q, *J* = 288.8 Hz, CF_3), 104.5 (C), 79.5 (q, *J* = 27.4 Hz, C), 53.8 (CH_3), 40.7 (CH), 25.5 (CH_2), 24.7 (q, *J* = 2.5 Hz, CH_2), 19.31 (CH_2), 12.64 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.51. **HRMS (ESI)** m/z 410.1689 $[M+H]^+$ $C_{20}H_{23}F_3N_3O_3^+$ requires 410.1686.

· Compound **5aab**:

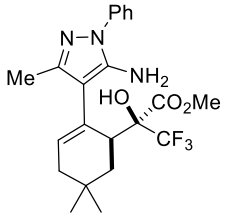


Following general procedure A, product **5aab** was synthetized as colorless oil in 56% yield (0.112 mmol, 50.9 mg). Diastereoisomeric ratio (6:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.49-7.41 (m, 2H), 7.32 (tt, *J* = 7.0, 1.3 Hz, 1H), 5.88 (td, *J* = 3.9, 1.3 Hz, 1H), 4.10-4.01 (m, 2H), 3.76-3.63 (m, 3H), 3.33 (s, 1H), 2.27-2.16 (m, 2H), 2.13 (s, 3H), 2.12-2.06 (m, 1H), 2.03-1.96 (m, 1H), 1.95-1.82 (m, 1H), 1.63 (dtd, *J* = 13.0, 6.8, 2.8 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.1 (C), 147.5 (C), 143.2 (C), 138.6 (C), 135.4 (CH), 129.5 (CH), 127.2 (CH), 126.4 (C), 123.77 (CH), 123.77 (q, *J* = 288.9 Hz, CF_3), 104.6 (C), 79.6 (q, *J* = 27.4 Hz), 63.6 (CH2), 40.5 (CH), 25.5 (CH_2), 24.7 (q, *J* = 2.4 Hz, CH_2), 19.1 (CH_2), 13.5 (CH_3), 12.7 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.04. **HRMS (ESI)** m/z 424.1847 $[M+H]^+$ $C_{21}H_{25}F_3N_3O_3^+$ requires 424,1843.

.

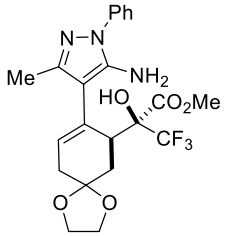
Compound **5baa**:



Following general procedure A, product **5baa** was synthetized as colorless oil in 54% yield (0.108 mmol, 47.5 mg). Diastereoisomeric ratio (6:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.49-7.42 (m, 2H), 7.38-7.29 (m, 1H), 5.78 (dt, *J* = 6.1, 2.1 Hz, 1H), 4.31 (s, 1H), 3.75 (s, 2H), 3.60 (s, 3H), 3.34 (dtt, *J* = 9.7, 3.8, 2.0 Hz, 1H), 2.08 (s, 3H), 2.03 (dd, *J* = 4.1, 2.1 Hz, 1H), 1.91-1.58 (m, 3H), 1.06 (s, 3H), 1.05 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.1 (C), 147.9 (C), 143.1 (C), 138.5 (C), 135.2 (CH), 129.5 (CH), 127.6 (q, *J* = 273.5 Hz, CF_3), 127.4 (CH), 124.1 (CH), 104.0 (C), 79.8 (q, *J* = 26.9 Hz, C), 53.8 (CH_3), 40.8 (CH), 39.0 (CH_2), 36.7 (CH_2), 31.8 (CH_3), 29.2 (C), 24.3 (CH_3), 12.3 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -72.76. **HRMS (ESI)** m/z 438.2005 $[M+H]^+$ $C_{22}H_{27}F_3N_3O_3^+$ requires 438.1999.

· Compound **5caa**:

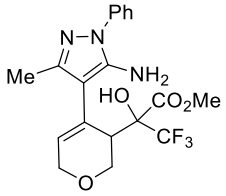


Following general procedure A, product **5caa** was synthetized as colorless oil in 29% yield (0.058 mmol, 27.2 mg). Diastereoisomeric ratio (7:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.48-7.42 (m, 1H), 7.35-7.29 (m, 1H), 5.81 (td, *J* = 3.9, 1.6 Hz, 1H), 5.77 (s, 1H), 4.1-3.96 (m, 4H), 3.83 (s, 2H), 3.77-3.70 (m, 1H), 3.48 (s, 3H), 2.52-2.48 (m, 1H), 2.31-2.25 (m, 1H), 2.19-2.14 (m, 1H), 2.13 (s, 2H) . **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.1 (C), 147.8 (C), 144.0 (C), 138.6 (C), 135.8 (C), 131.8 (CH), 129.5 (CH), 127.2 (CH), 126.6 (C), 123.8 (CH), 106.7 (C), 79.8 (q, *J* = 27.0 Hz, C), 64.9 (CH_2), 64.7 (CH_2), 53.1 (CH_3), 36.5 (CH_2), 32.7 (CH_2), 30.3 (CH), 12.5 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -72.77. **HRMS (ESI)** m/z 468.1738 $[M+H]^+$ $C_{22}H_{25}F_3N_3O_5^+$ requires 468.1741.

.

Compound **5daa**:

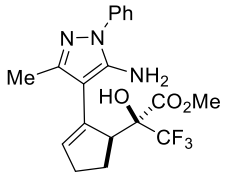


Following general procedure A, product **5daa** was synthetized as yellow oil in 66% yield (0.132 mmol, 54.2 mg). Diastereoisomeric ratio (1.13:1) was determined via ^{1}H NMR analysis.

Diastereoisomer 1: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.50-7.43 (m, 2H), 7.37-7.30 (m, 1H), 5.96 (dt, *J* = 2.9, 1.5 Hz, 1H), 4.70 (s, 1H), 4.45 (d, *J* = 12.5 Hz, 1H), 4.42-4.30 (m, 2H), 3.94-3.88 (m, 1H), 3.83 (d, *J* = 2.5 Hz, 2H), 3.43 (s, 3H), 3.28 (s, 1H), 2.18 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.8 (C), 147.2 (C), 143.7 (C), 138.4 (C), 130.9 (CH), 129.60 (CH), 127.3 (CH), 125.7 (C), 123.8 (q, *J* = 284.8 Hz, CF_3), 123.6 (CH), 102.4 (C), 79.80 (q, *J* = 28.0 Hz, C), 66.6 (CH_2), 66.0 (CH_2), 53.0 (CH_3), 39.5 (CH), 13.0 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.62. **HRMS (ESI)** m/z 412.1482 $[M+H]^+$ $C_{19}H_{21}F_3N_3O_4^+$ requires 412.1479.

Diastereoisomer 2: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 5.92 (t, *J* = 2.3 Hz, 1H), 4.34 (d, *J* = 2.9 Hz, 1H), 4.32 (t, *J* = 2.3 Hz, 1H), 4.29-4.24 (m, 1H), 4.17 (d, *J* = 12.2 Hz, 1H), 3.92 (s, 2H), 3.85 (d, *J* = 1.1 Hz, 3H), 3.79 (dd, *J* = 12.2, 2.7 Hz, 1H), 3.16 (s, 1H), 2.21 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.8 (C), 146.6 (C), 142.6 (C), 138.5 (C), 129.9 (CH), 129.5 (CH), 127.2 (CH), 125.8 (C), 123.7 (CH), 104.4 (C), 80.2 (q, *J* = 28.8 Hz, C), 66.3 (CH_2), 65.8 (CH_2), 53.8 (CH_3), 40.2 (CH), 13.3 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -74.68. **HRMS (ESI)** m/z 412.1485 $[M+H]^+$ $C_{19}H_{21}F_3N_3O_4^+$ requires 412.1479.

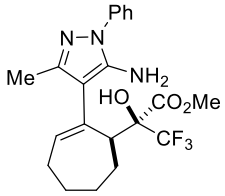
· Compound **5faa**:



Following general procedure A, product **5faa** was synthetized as orange oil in 27% yield (0.054 mmol, 21.3 mg). Diastereoisomeric ratio (6:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.6, 1.4 Hz, 2H),7.47 (t, *J* = 7.6 Hz, 2H), 7.37-7.29 (m, 1H), 5.91 (q, *J* = 2.2 Hz, 1H), 3.93 (s, 1H), 3.78-3.69 (m, 2H), 3.50 (s, 3H), 2.57 (dddd, *J* = 17.5, 6.4, 5.1, 2.5Hz, 1H), 2.49-2.35 (m, 2H), 2.23-2.15 (m, 1H), 2.13 (s, 3H), 2.04-1.87 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.2 (C), 147.8 (C), 143.4 (C), 138.5 (C), 136.7 (CH), 131.5 (C), 129.5 (CH), 127.3 (CH), 123.8 (CH), 99.5 (C), 78.8 (q, *J* = 27.6 Hz, C), 53.7 (CH_3), 49.5 (CH), 31.9 (CH_2), 25.0 (q, *J* = 2.5 Hz, CH_2), 12.7 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -74.65. **HRMS (ESI)** m/z 447,1526 $[M+H]^+$ $C_{19}H_{21}F_3N_3O_3^+$ requires 396.1530.

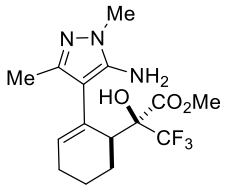
· Compound **5gaa**:



Following general procedure A, product **5gaa** was synthetized as orange oil in 80% yield (0.160 mmol, 68.0 mg). Diastereoisomeric ratio (6:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.48- 7.40 (m, 2H), 7.34-7.28 (m, 1H), 5.94 (dd, *J* = 8.9, 5.2 Hz, 1H), 4.02 (s, 1H), 3.71 (s, 2H), 3.46 (t, *J* = 6.3 Hz, 1H), 3.34 (s, 3H), 2.85- 2.66 (m, 1H), 2.21 (s, 3H), 2.18-1.96 (m, 3H), 1.92-1.69 (m, 3H), 1.51-1.36 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.1 (C), 147.2 (C), 142.4 (C), 138.6 (C), 136.5 (CH), 130.0 (C), 129.5 (CH), 127.0 (CH), 123.6 (q, *J* = 288.0 Hz, CF_3), 123.3 (CH), 107.3 (C), 80.7 (q, *J* = 28.2 Hz, C), 53.5 (CH_3), 47.0 (CH), 26.7 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 24.6 (CH_2), 13.4 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.52. **HRMS (ESI)** m/z 424.1849 $[M+H]^+$ $C_{21}H_{25}F_3N_3O_3^+$ requires 424.1843.

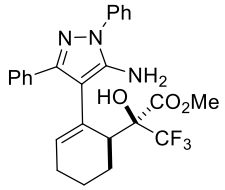
· Compound **5aba**:



Following general procedure A, product **5aba** was synthetized as yellow solid in 46% yield (0.092 mmol, 32.2 mg) (m. p.= 99-107 °C). Diastereoisomeric ratio (4:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (td, *J* = 3.9, 1.3 Hz, 1H), 3.98 (s, 1H), 3.56 (s, 3H), 3.48-3.36 (m, 5H), 3.27 (tq, *J* = 5.3, 1.8 Hz, 1H), 2.21-2.12(m, 2H), 2.04 (s, 3H), 2.02-1.93 (m, 2H), 1.91-1.80 (m, 1H), 1.59 (tdq, *J* = 9.0, 5.9, 2.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.7 (C), 145.3 (C), 143.1 (C), 134.9(CH),126.7 (C), 123.75 (q, *J* = 289.1 Hz, CF_3), 105.1 (C), 79.6 (q, *J* = 27.4 Hz, C), 53.7 (CH_3), 40.6 (CH), 34.1 (CH_3), 25.5 (CH_2), 24.7 (q, *J* = 2.3 Hz, CH_2), 19.1 (CH_2), 12.6 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.55. **HRMS (ESI)** m/z 348.1531 $[M+H]^+$ $C_{15}H_{20}F_3N_3O_3^+$ requires 348.1530.

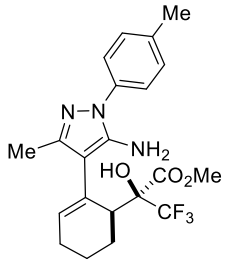
· Compound **5aca**:



Following general procedure A, product **5aca** was synthetized as yellow solid in 41% yield (0.082 mmol, 39.3 mg) (mp 186–200 °C). Diastereoisomeric ratio (6:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.77 (m, 2H), 7.64 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.50 (t, *J* =7.7 Hz, 2H), 7.43-7.28 (m, 4H), 6.13 (td, *J* = 3.8, 1.1 Hz, 1H), 4.05 (s, 1H), 3.83 (s, 2H), 3.48 (s, 3H), 3.11 (s, 1H), 2.36-2.28 (m, 2H), 2.17-1.94 (m, 2H), 1.88-1.60 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.9 (C), 148.5 (C), 144.1 (C), 138.7 (C), 135.5 (CH), 133.8 (C), 129.6 (CH), 128.4 (CH), 127.8(CH), 127.6 (CH), 127.4 (C), 126.3 (CH), 124.1 (CH), 123.6 (q, *J* = 288.9 Hz, CF_3), 103.3 (C), 79.6 (q, *J* = 27.7 Hz, C), 53.9 (CH_3), 40.2 (CH), 25.8 (CH_2), 24.9 (q, *J* = 1.8 Hz, CH_2), 18.4 (CH_2). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.71. **HRMS (ESI)** m/z 348.1531 $[M+H]^+$ $C_{15}H_{20}F_3N_3O_3^+$ requires 348.1530.

· Compound **5ada**:

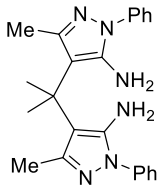


Following general procedure A, product **5ada** was synthetized as yellow solid in 45% yield (0.09 mmol, 38.2 mg) (mp 163–167 °C). Diastereoisomeric ratio (7:1) was determined via ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.88 (td, *J* = 3.9, 1.4 Hz, 1H), 4.07 (s, 1H), 3.70 (s, 2H), 3.53 (s, 3H), 3.37-3.30 (m, 1H), 2.39 (s, 3H), 2.19 (dd, *J* = 6.2, 3.6 Hz, 2H), 2.12 (s, 3H), 2.07-1.84 (m, 3H), 1.73-1.55 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.6 (C), 147.3 (C), 143.1 (C), 137.3 (C), 136.0 (C), 135.5 (CH), 130.1 (CH), 126.4 (C), 123.9 (CH), 123.8 (q, *J* = 288.8 Hz, CF_3), 104.3 (C), 79.7 (q, *J* = 27.3 Hz, C), 53.8 (CH_3), 40.8 (CH), 25.6 (CH_2), 24.7 (q, *J* = 2.4 Hz, CH_2), 21.1 (CH_3), 19.4 (CH_2), 12.6 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -73.51. **HRMS (ESI)** m/z 424.1839 $[M+H]^+$ $C_{21}H_{25}F_3N_3O_3^+$ requires 424.1843.

5. Characterization of product 7

· Compound **7**:

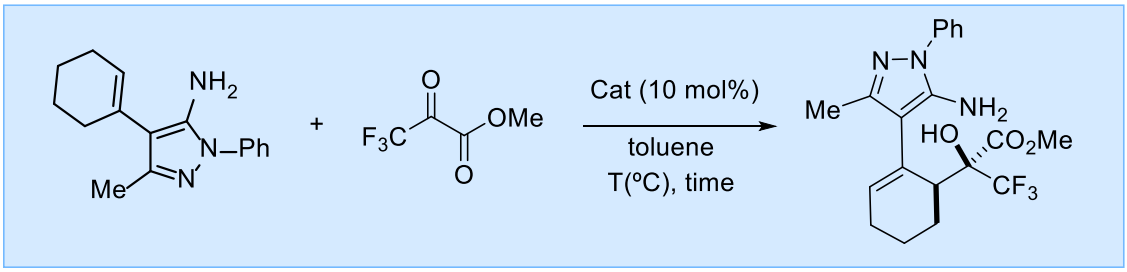


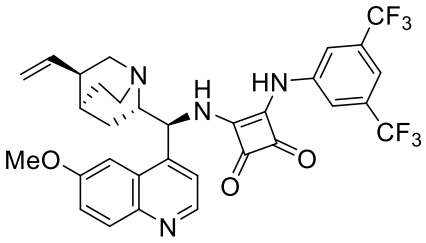
Following procedure iv, product **7** was synthetized as a colorless oil in 37% yield (0.93 mmol, 360 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.38 (m, 8H), 7.35-7.25 (m, 2H), 3.61 (s, 4H), 2.34 (s, 6H), 1.72 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 146.4 (C), 142.4 (C), 138.4 (C), 129.4 (CH), 127.2 (CH), 124.0 (CH), 106.9 (C), 33.7 (C), 29.4 (CH_3), 16.1 (CH_3). **HRMS (ESI)** m/z 387.2300 $[M+H]^+$ $C_{23}H_{27}N_6^+$ requires 387.2292.

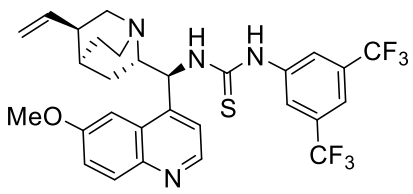
6. Asymmetric reactions

Scheme S.1 - Optimization of the organocatalyst.

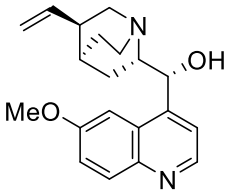




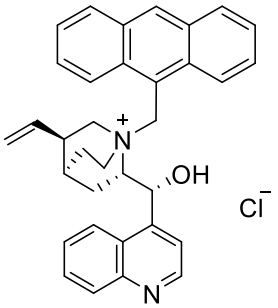
rt, 5 dies, 30% yield, 6:1 dr, 0% ee
50ºC, 1 day, 52% yield, 7:1 dr, 0% ee



50ºC, 3 days, 58% yield, 7:1 dr, 0% ee



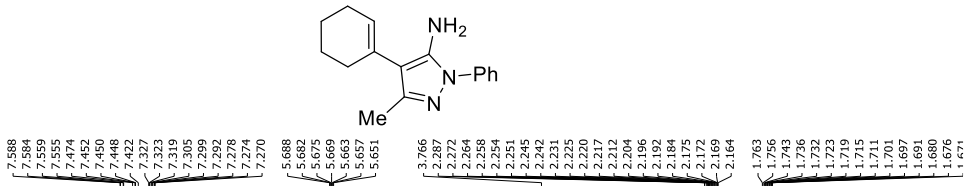
50ºC, 3 days, 51% yield,6:1 dr, 0% ee

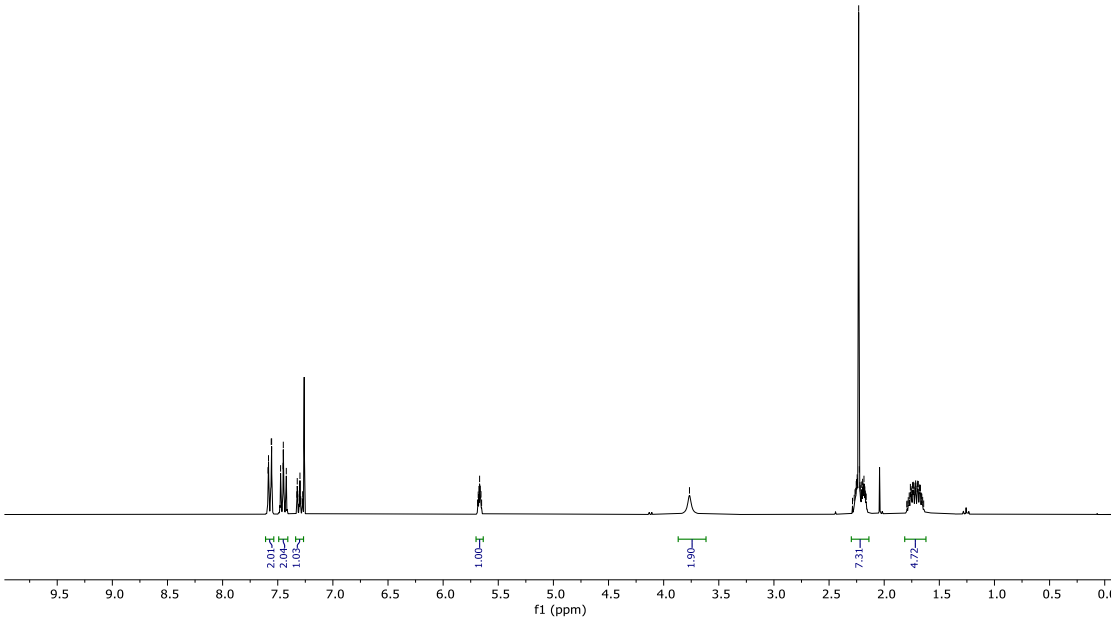


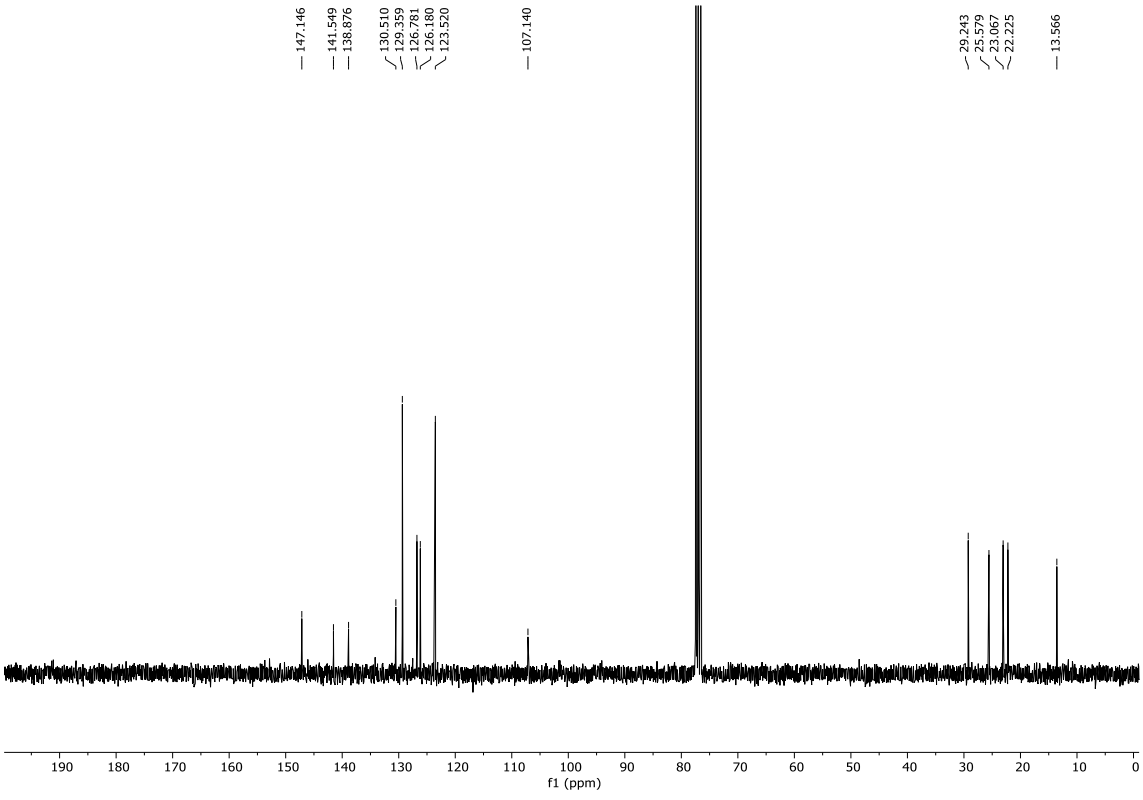
50ºC, 3 days, 55%, 7:1 dr, 0% ee

7. NMR data

· Compound **3aa**:

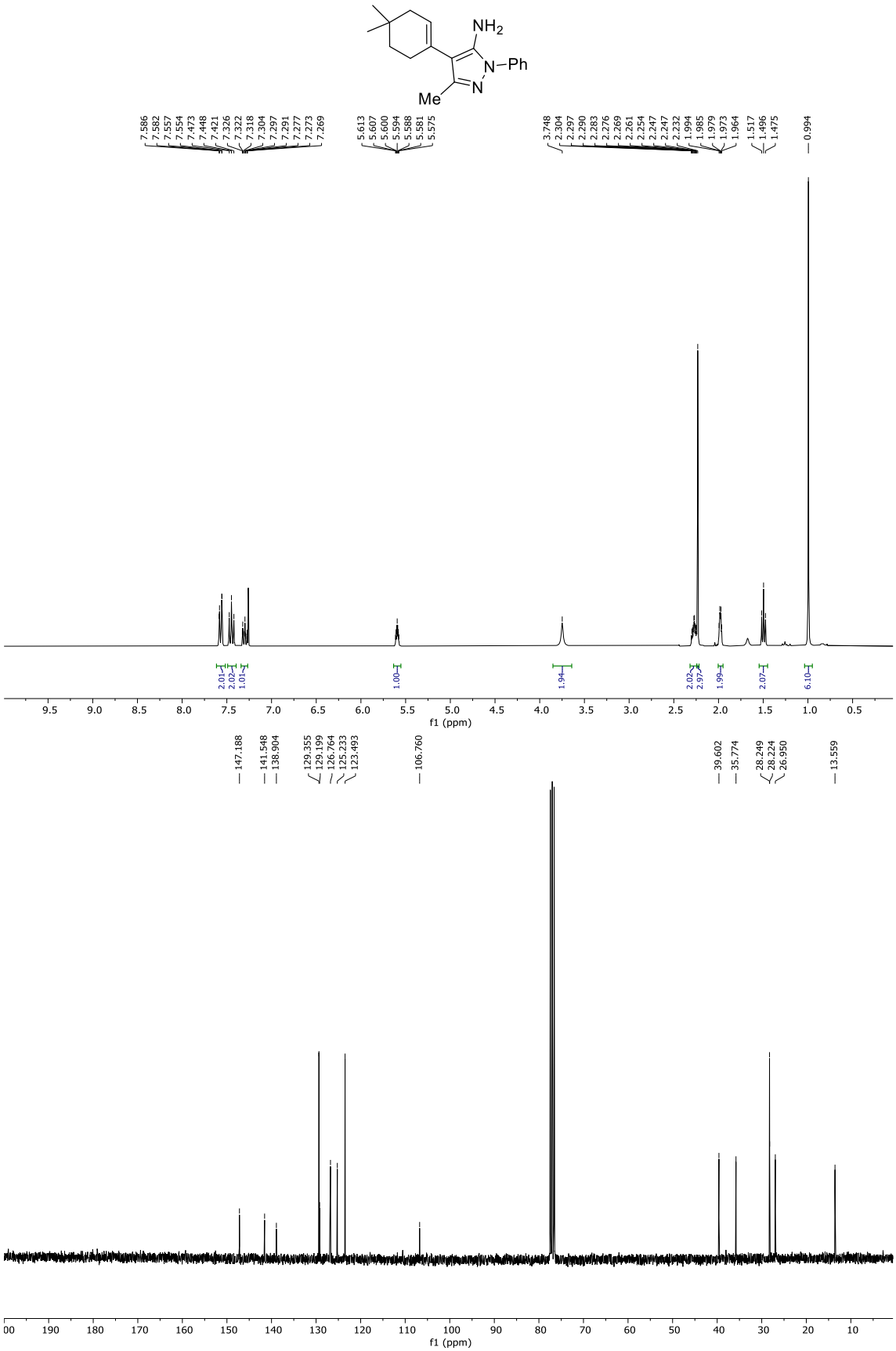






·

Compound **3ba**:



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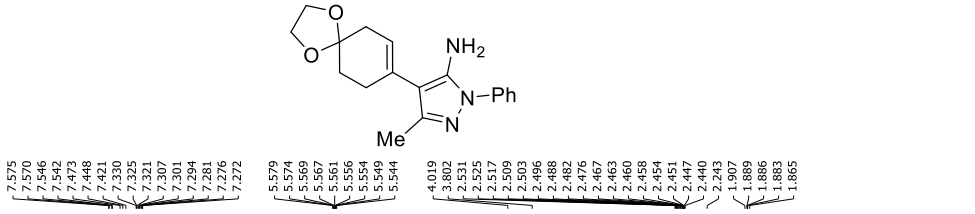
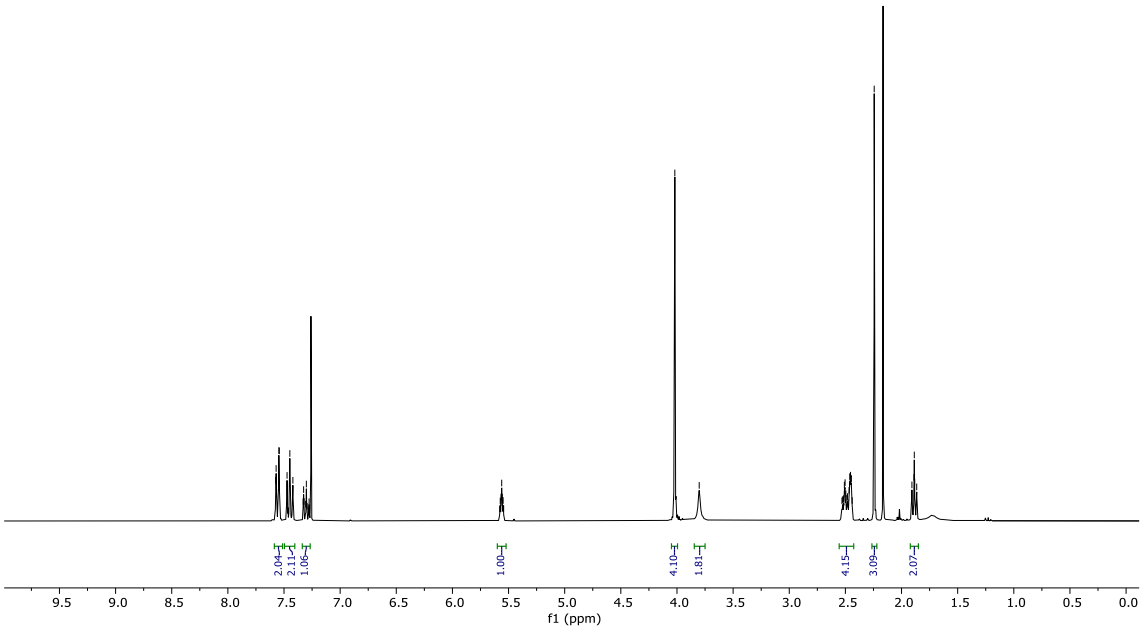
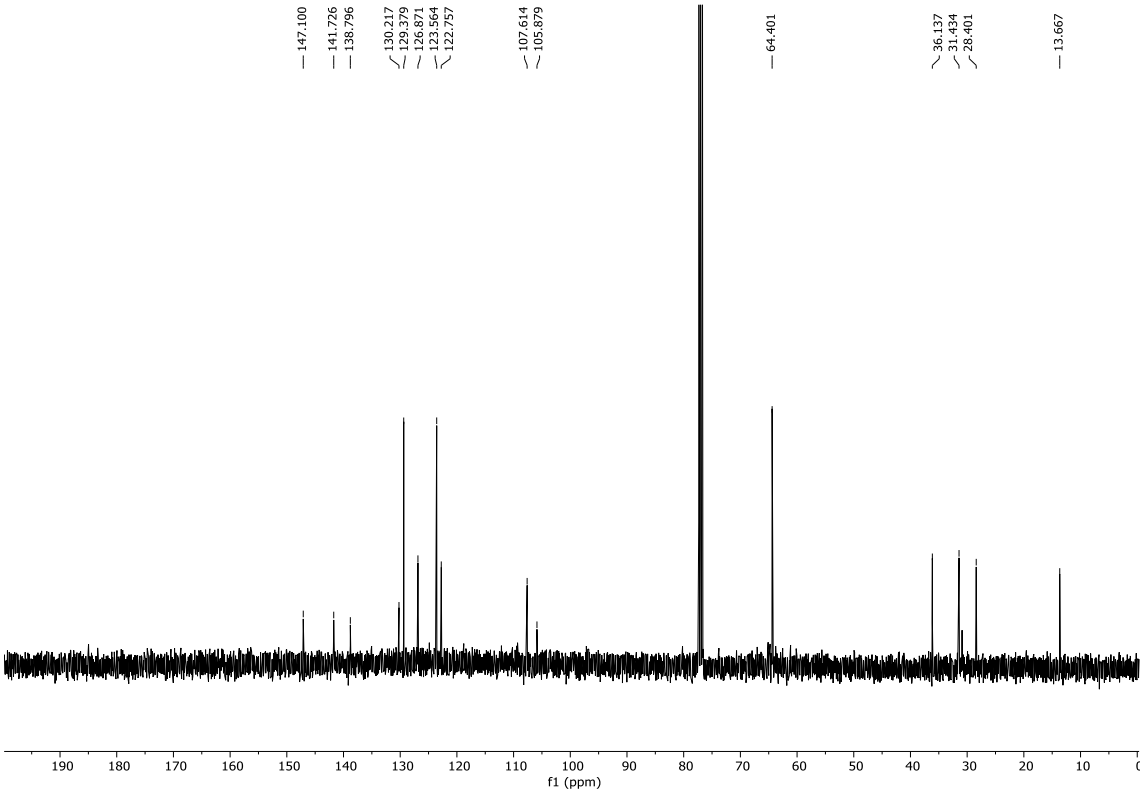
Compound **3ca**:

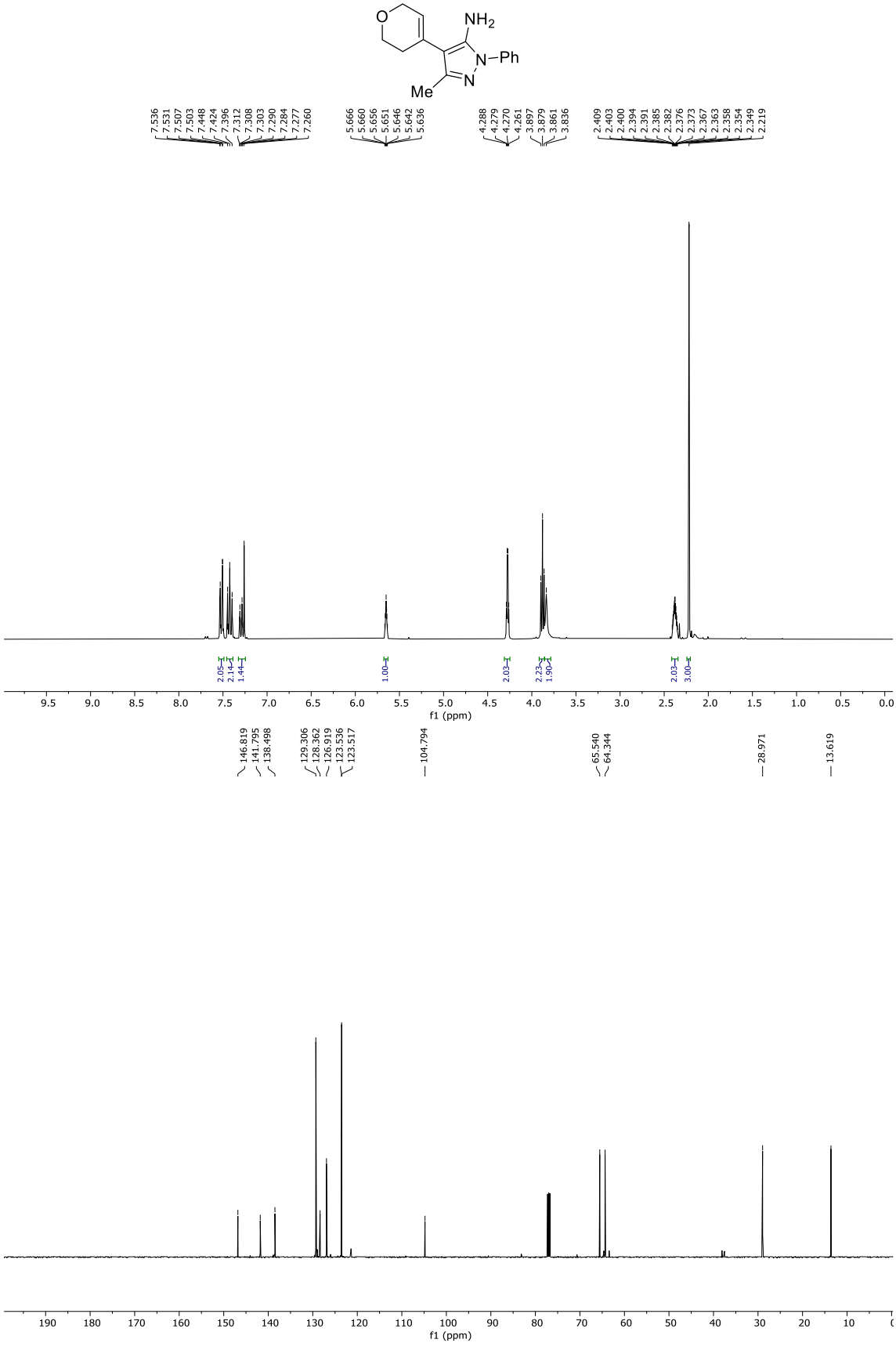






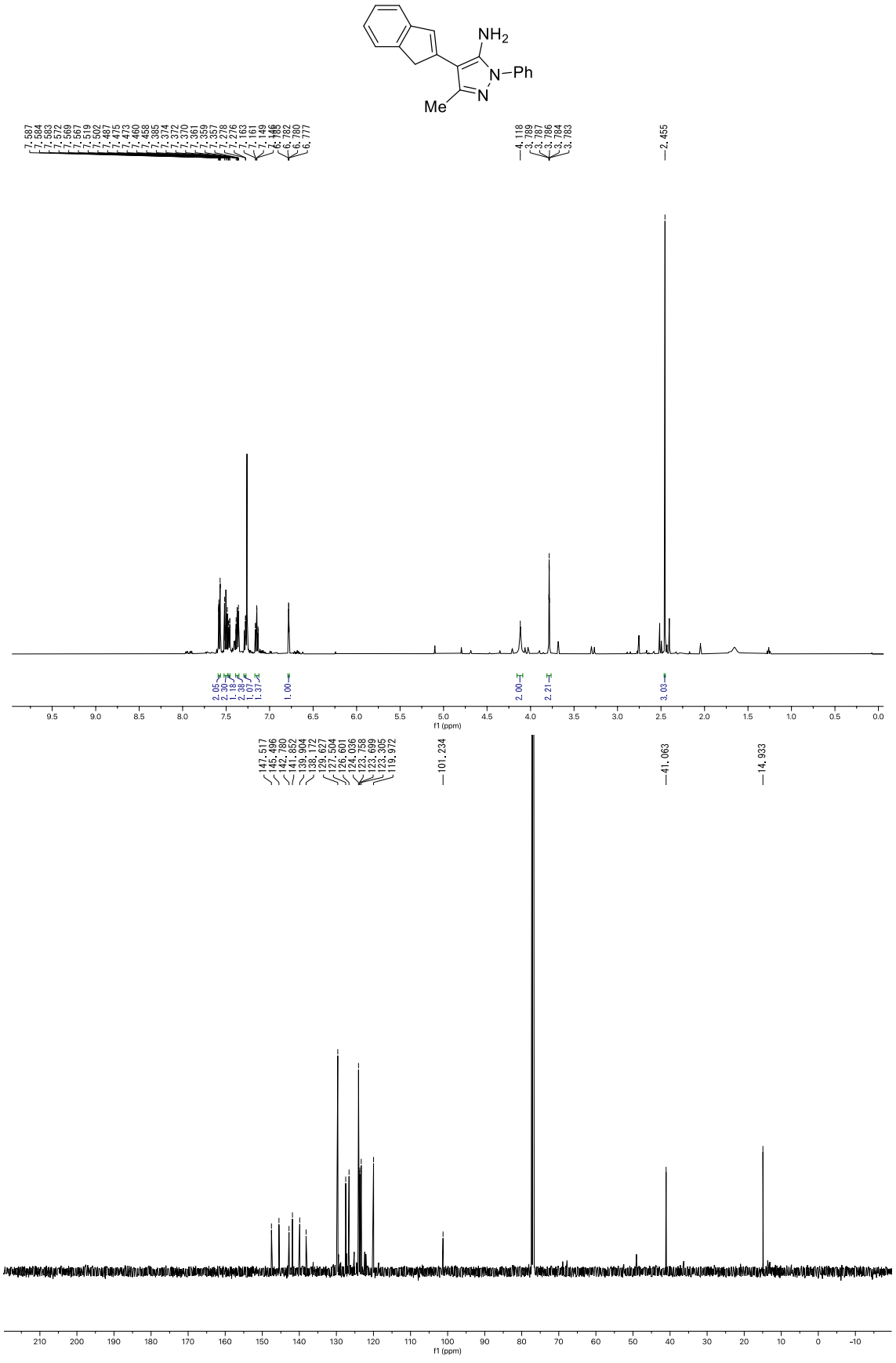
.

Compound **3da**:



.

Compound **3ea**:



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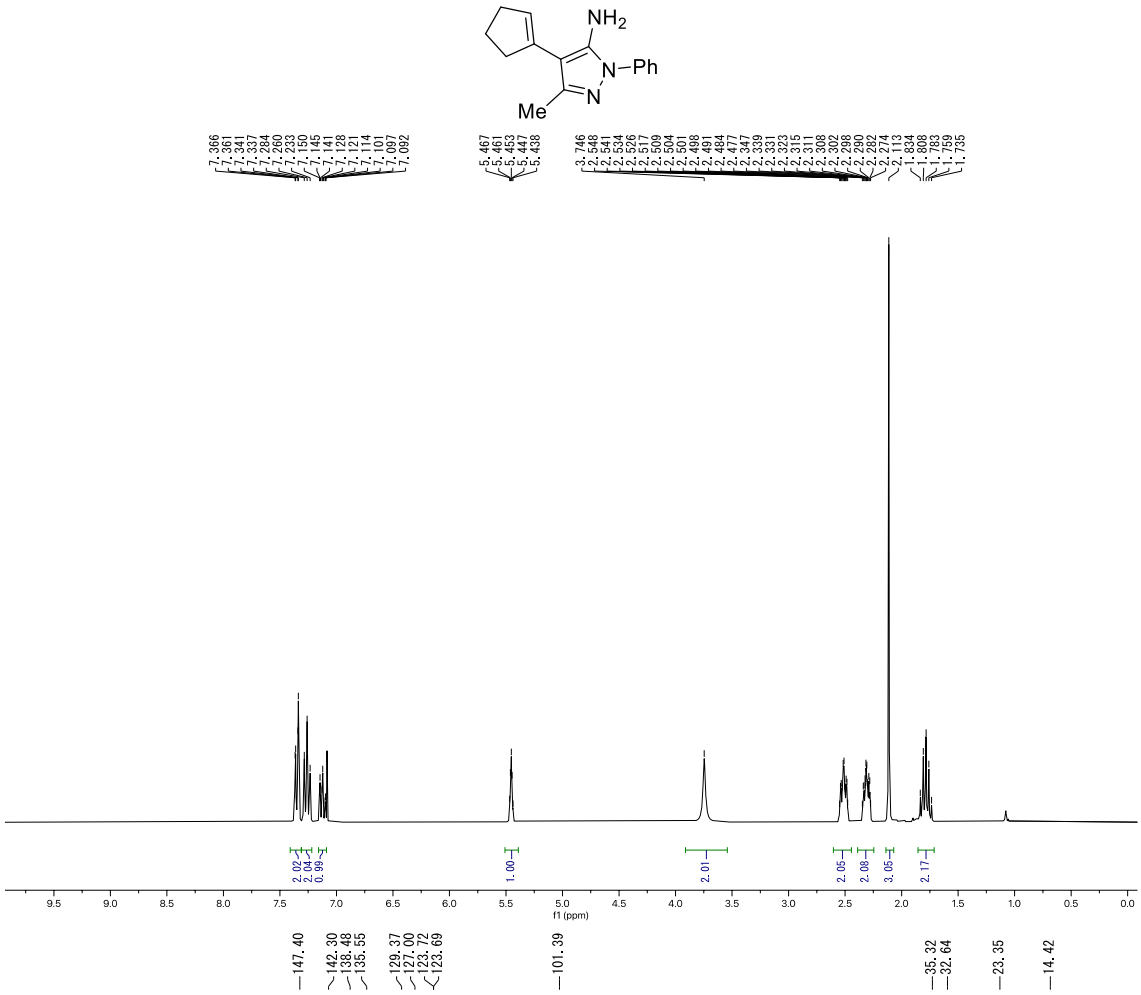
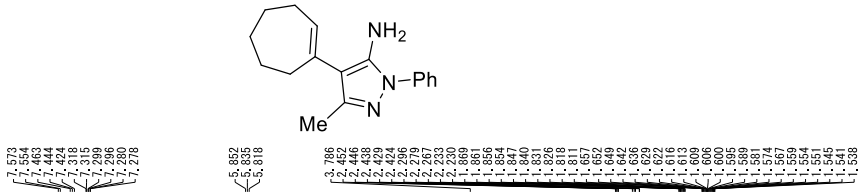
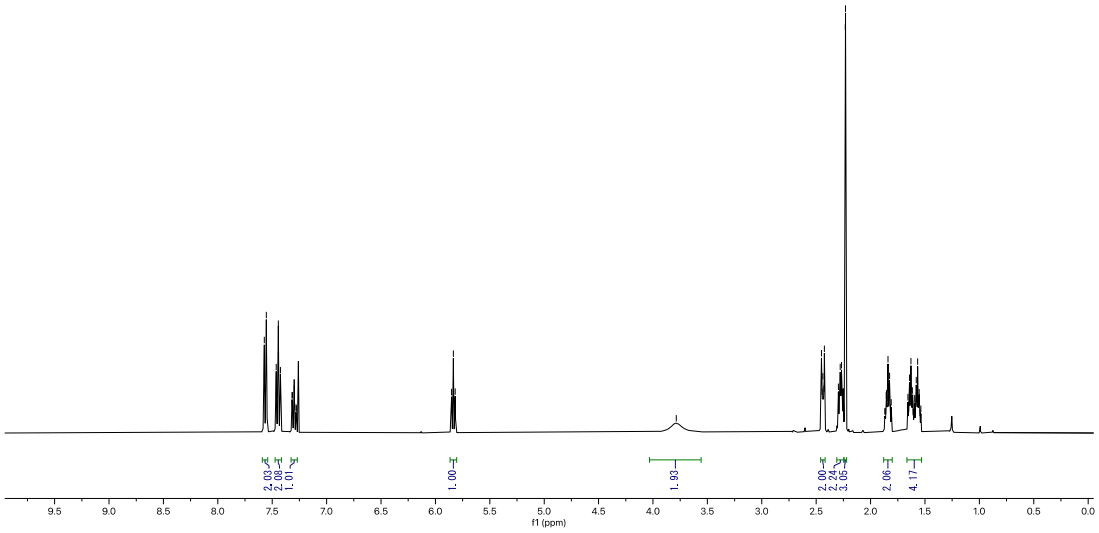
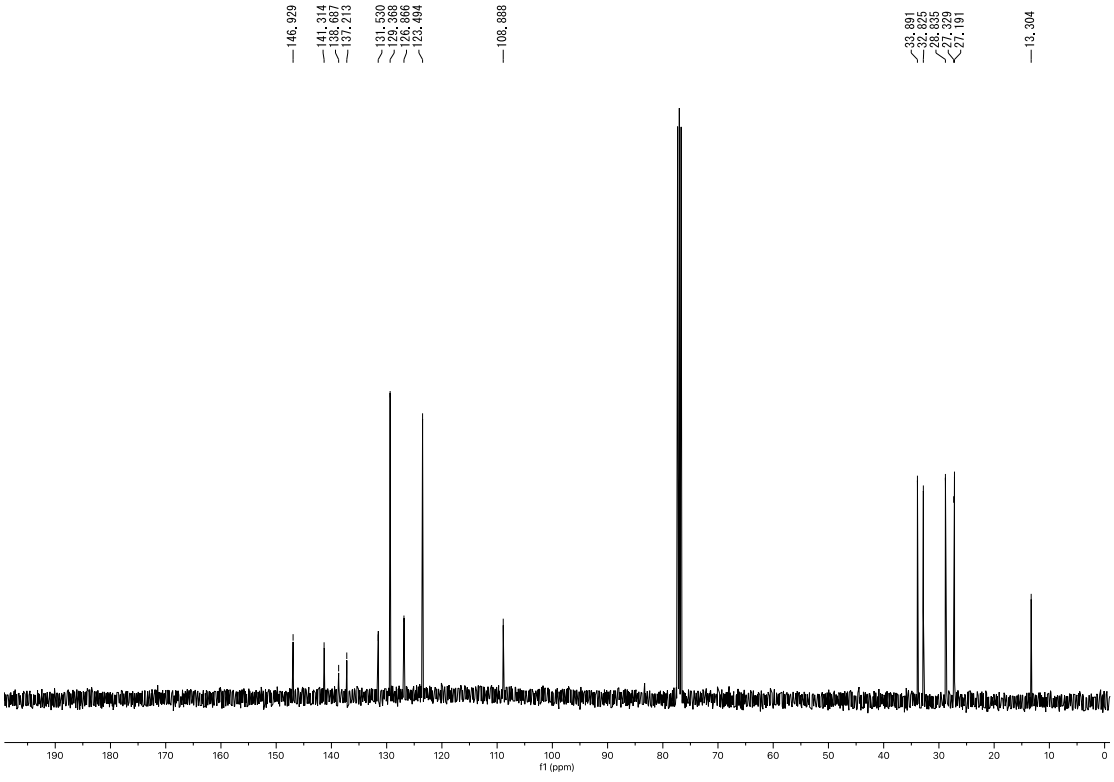
Compound **3fa**:



· Compound **3ga**:

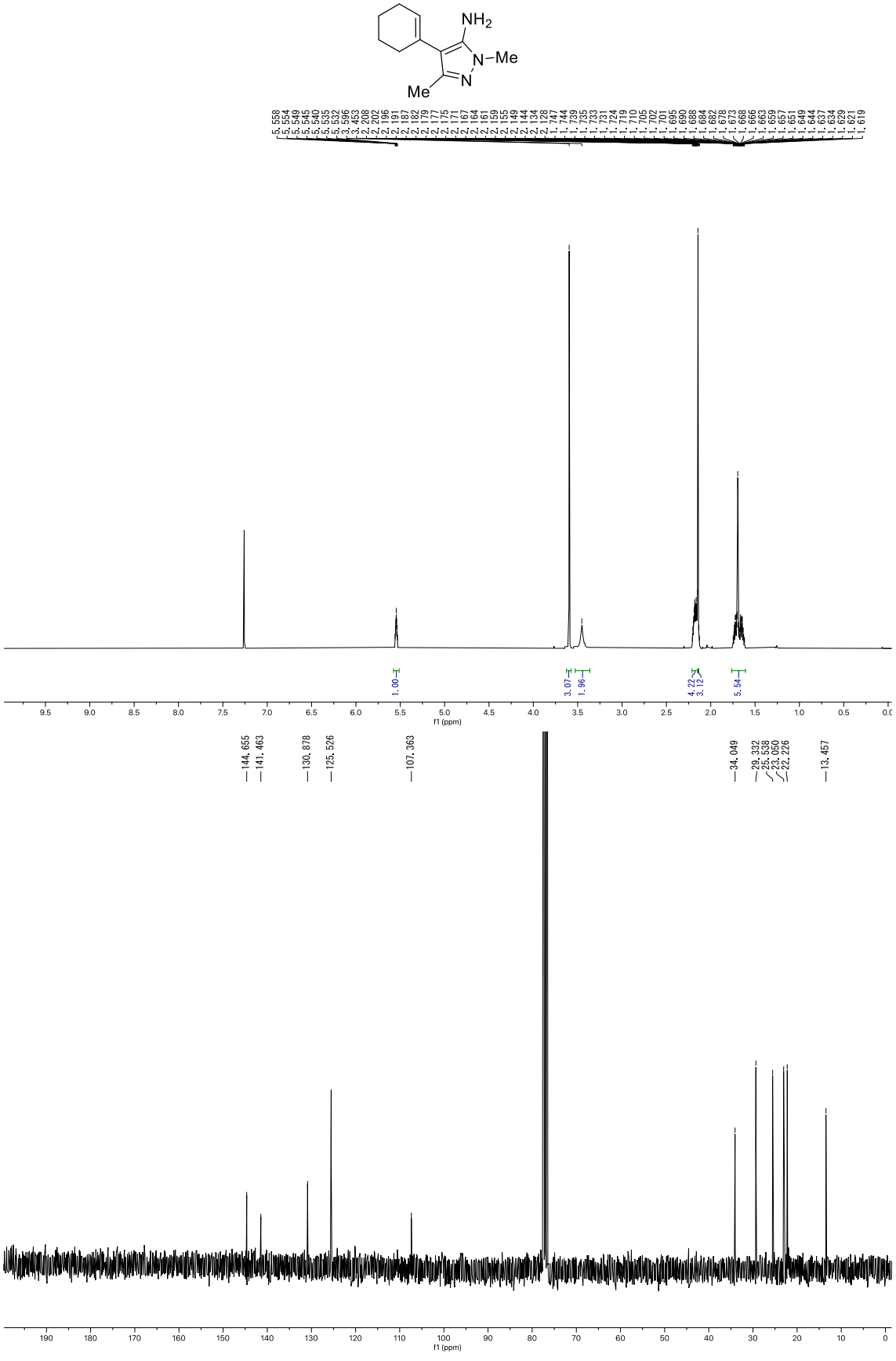






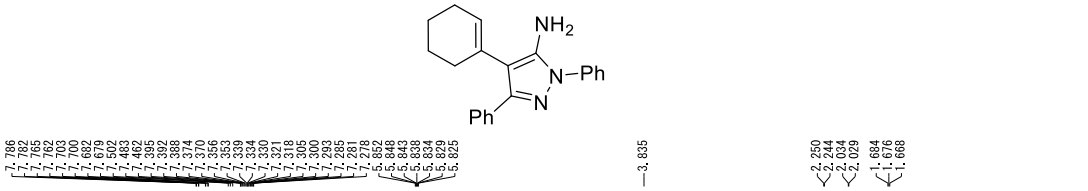
·

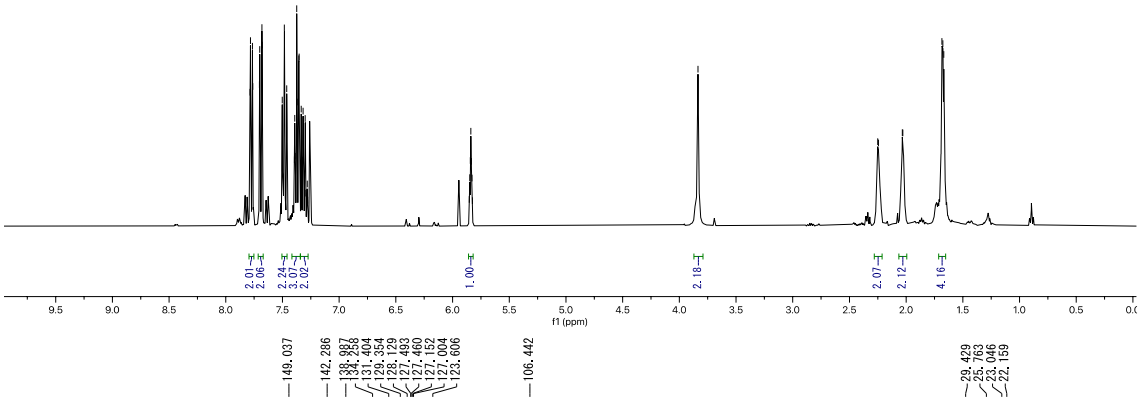
Compound **3ab**:

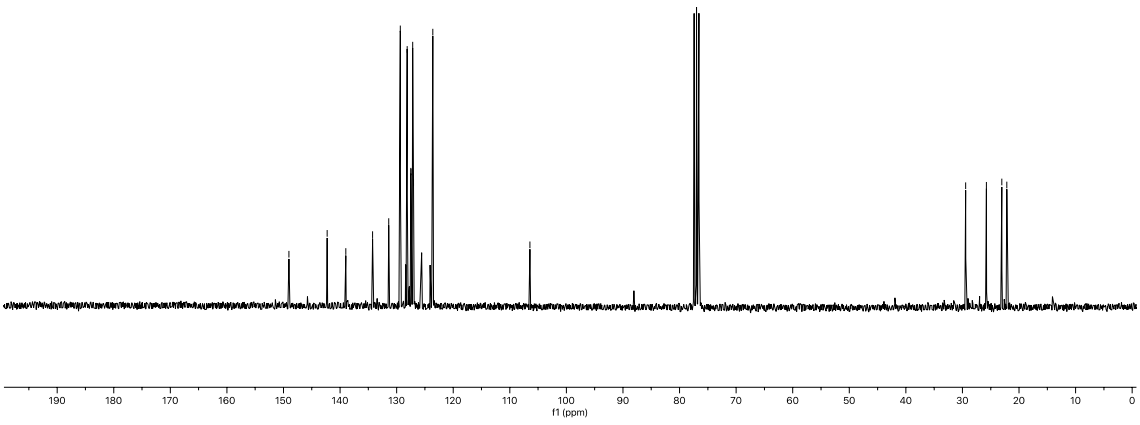


.

Compound **3ac**:

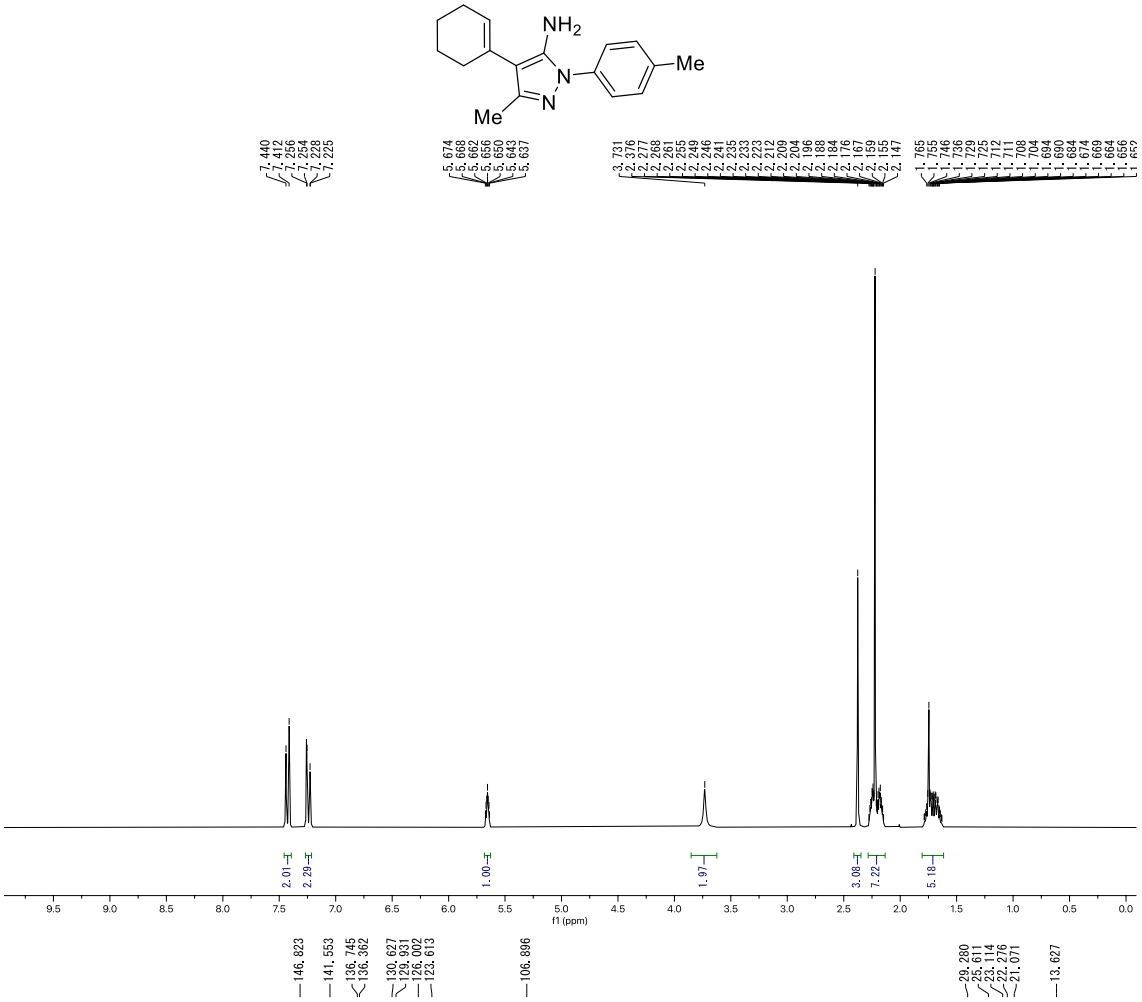






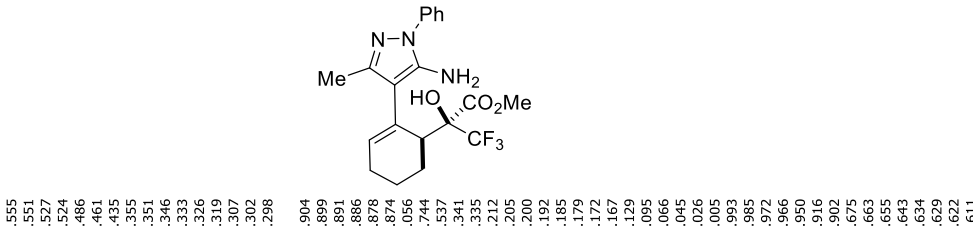
.

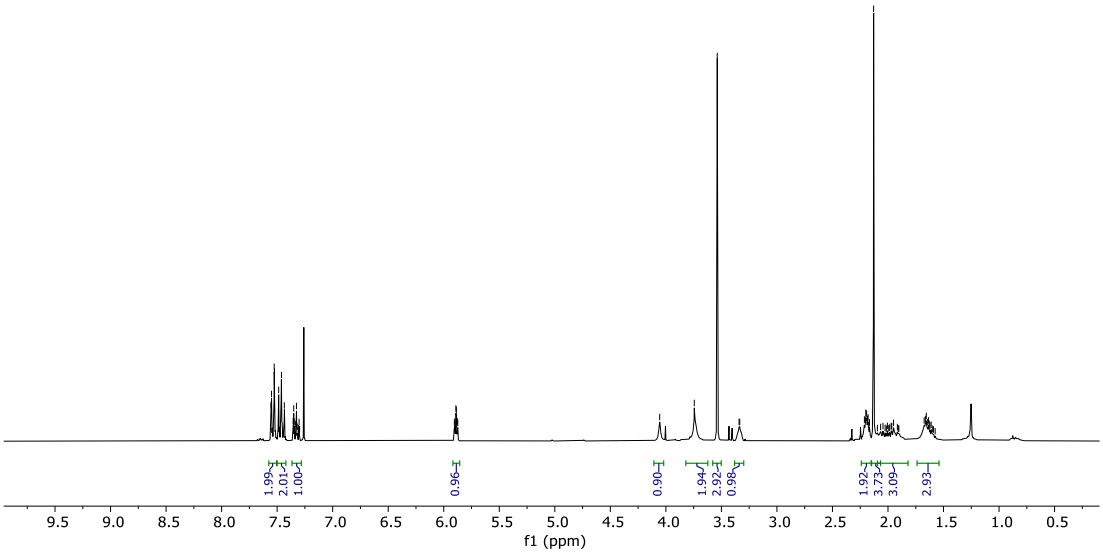
Compound **3ad**:

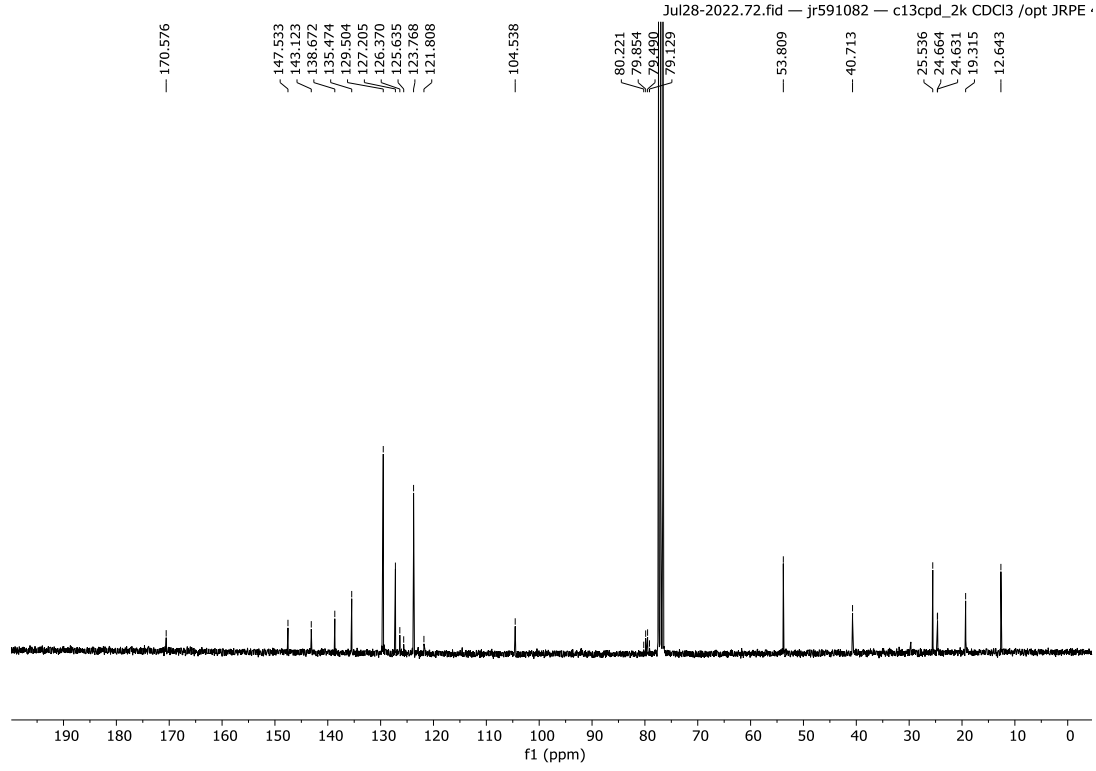


.

Compound **5aaa**:







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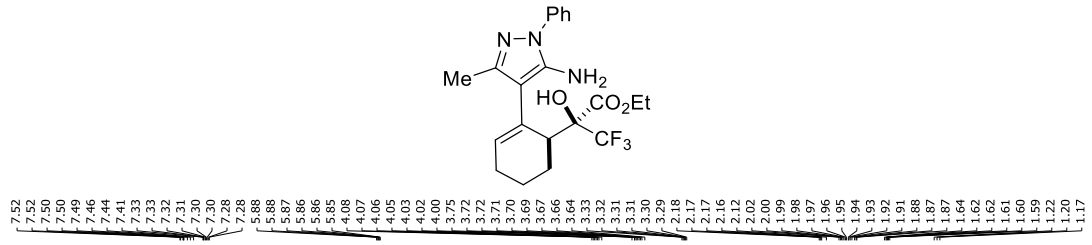
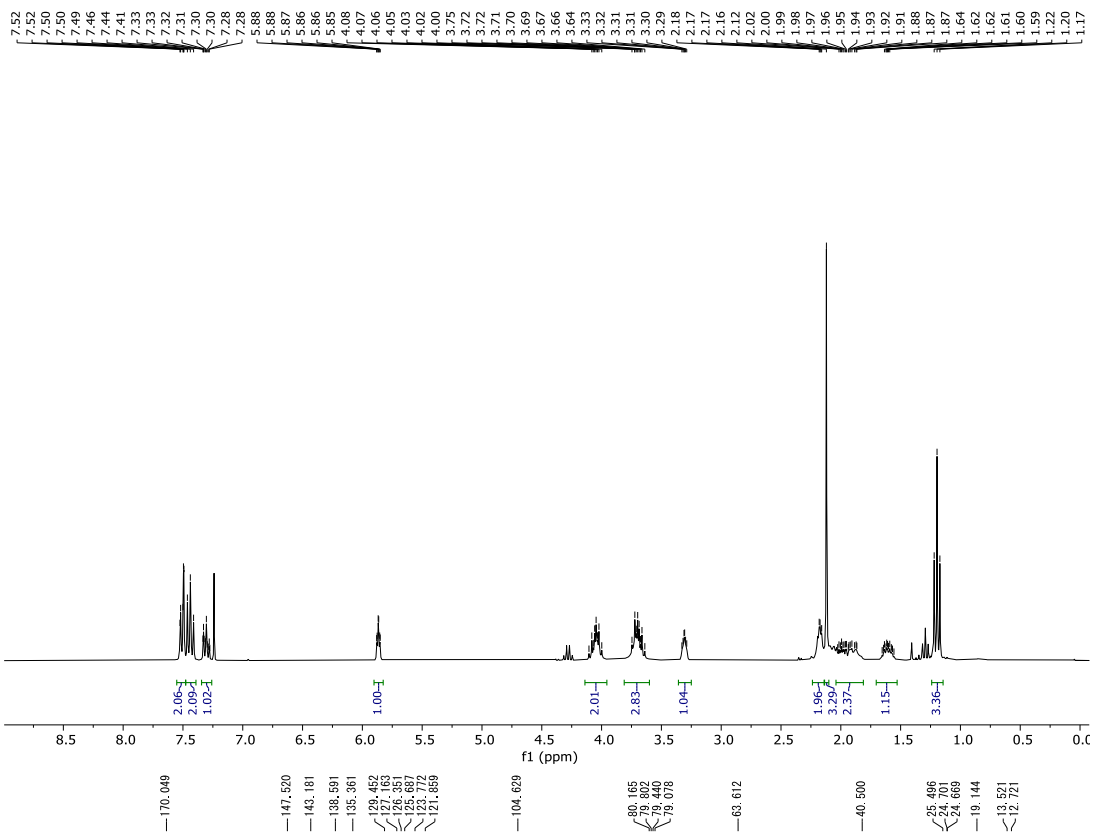
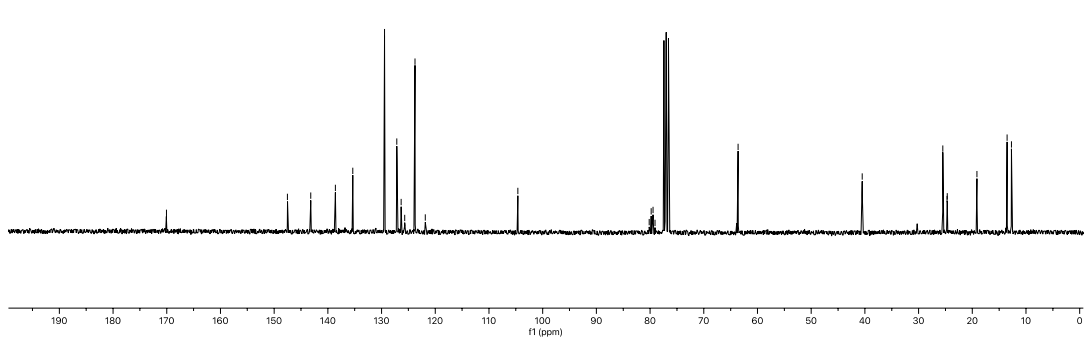
Compound **5aab**:

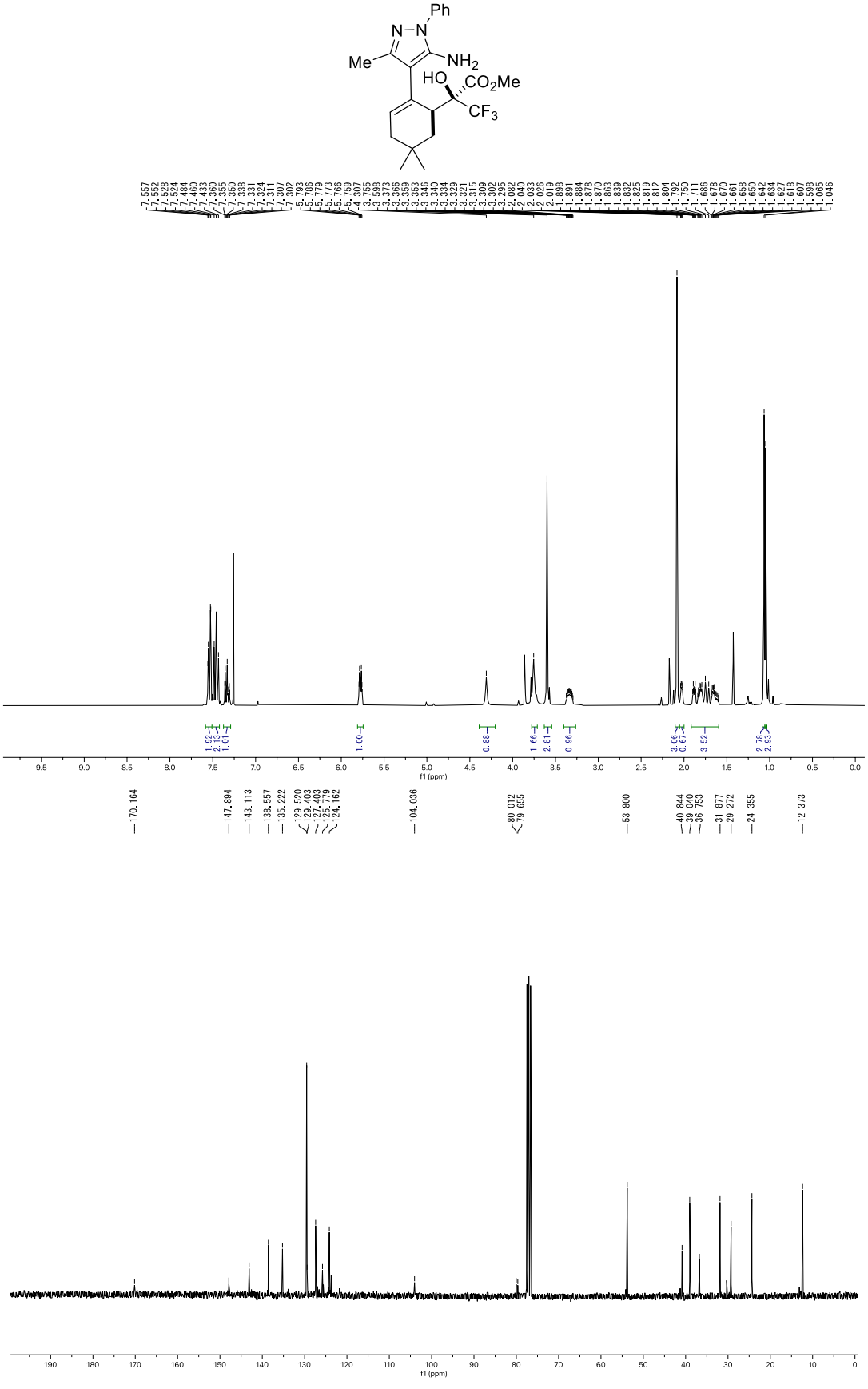




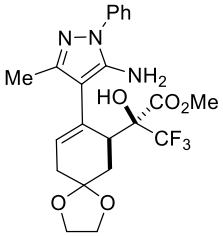


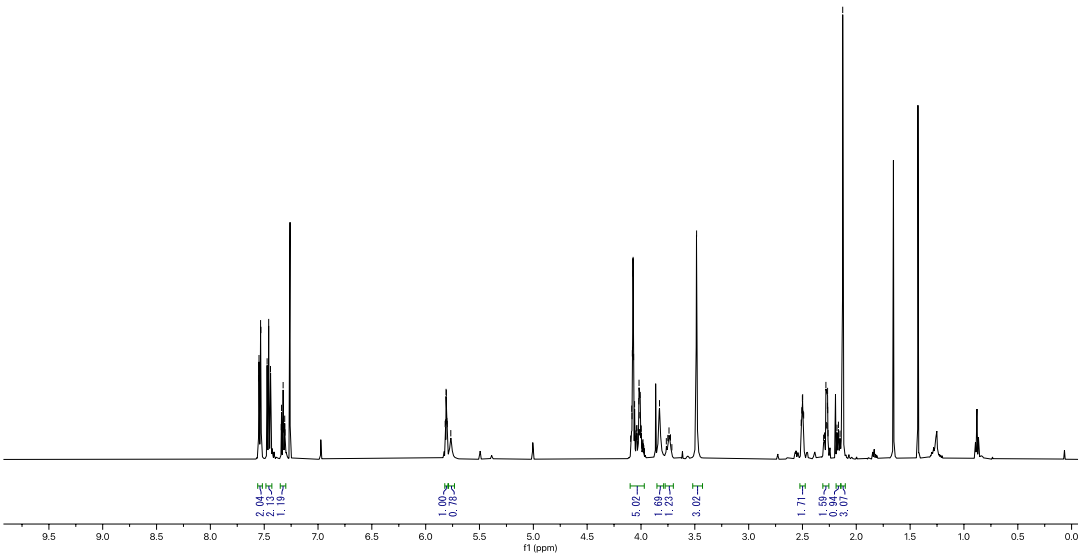
.

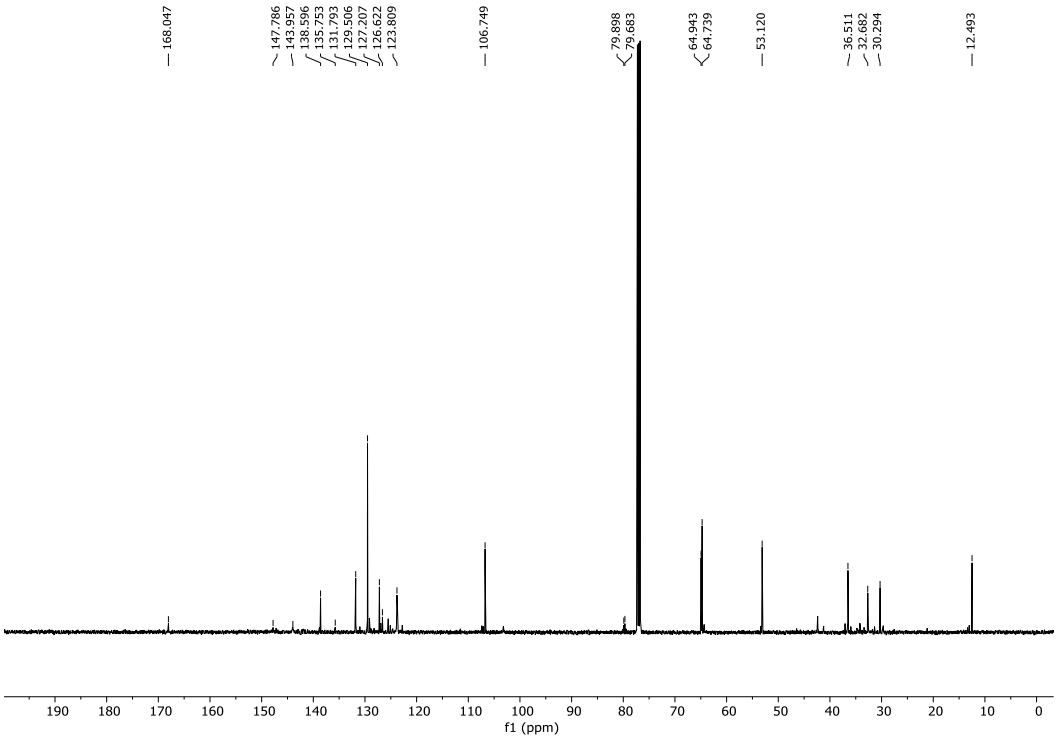
Compound **5baa**:



· Compound **5caa**:

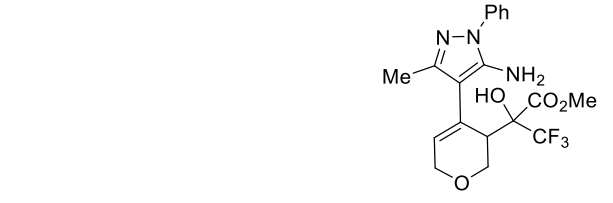


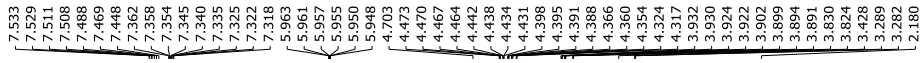


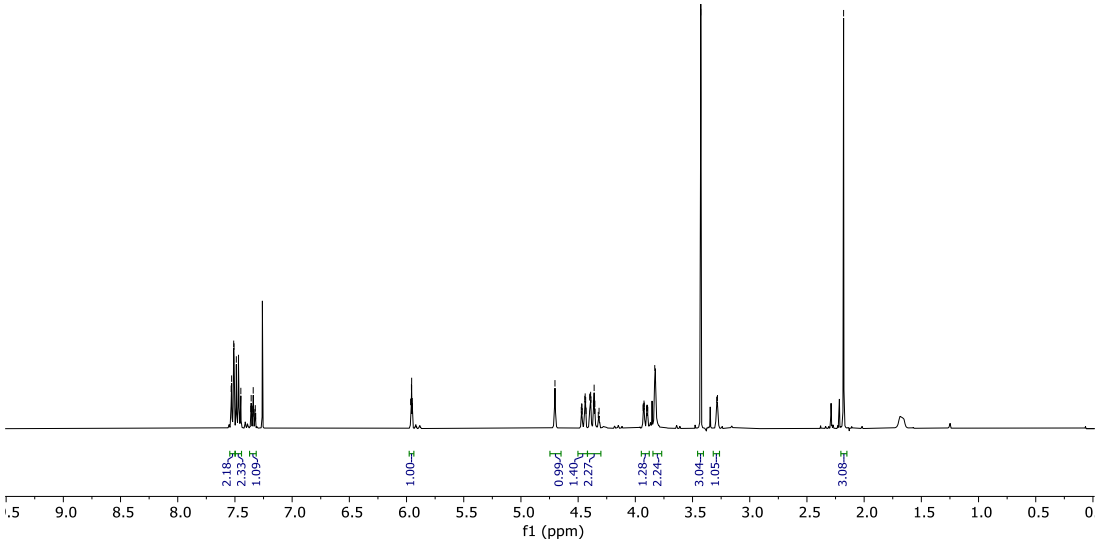


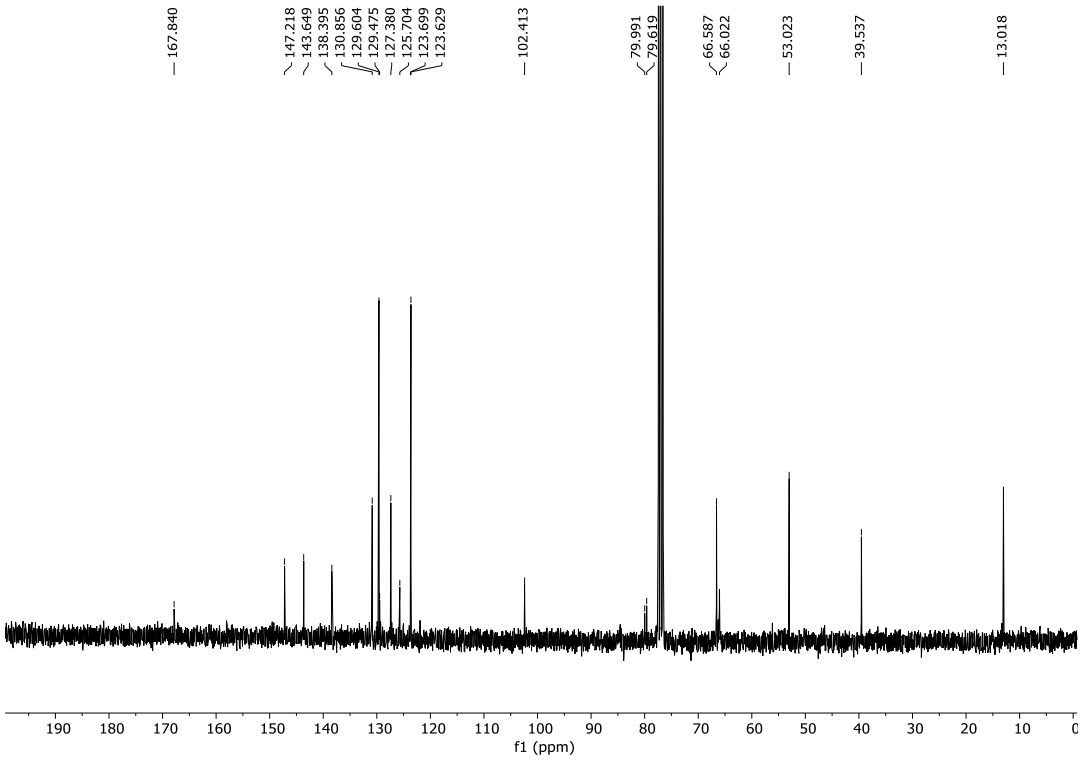
·

Compound **5daa-diastereoisomer 1**:









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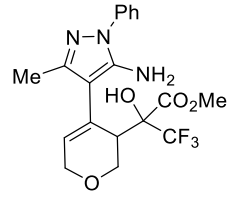
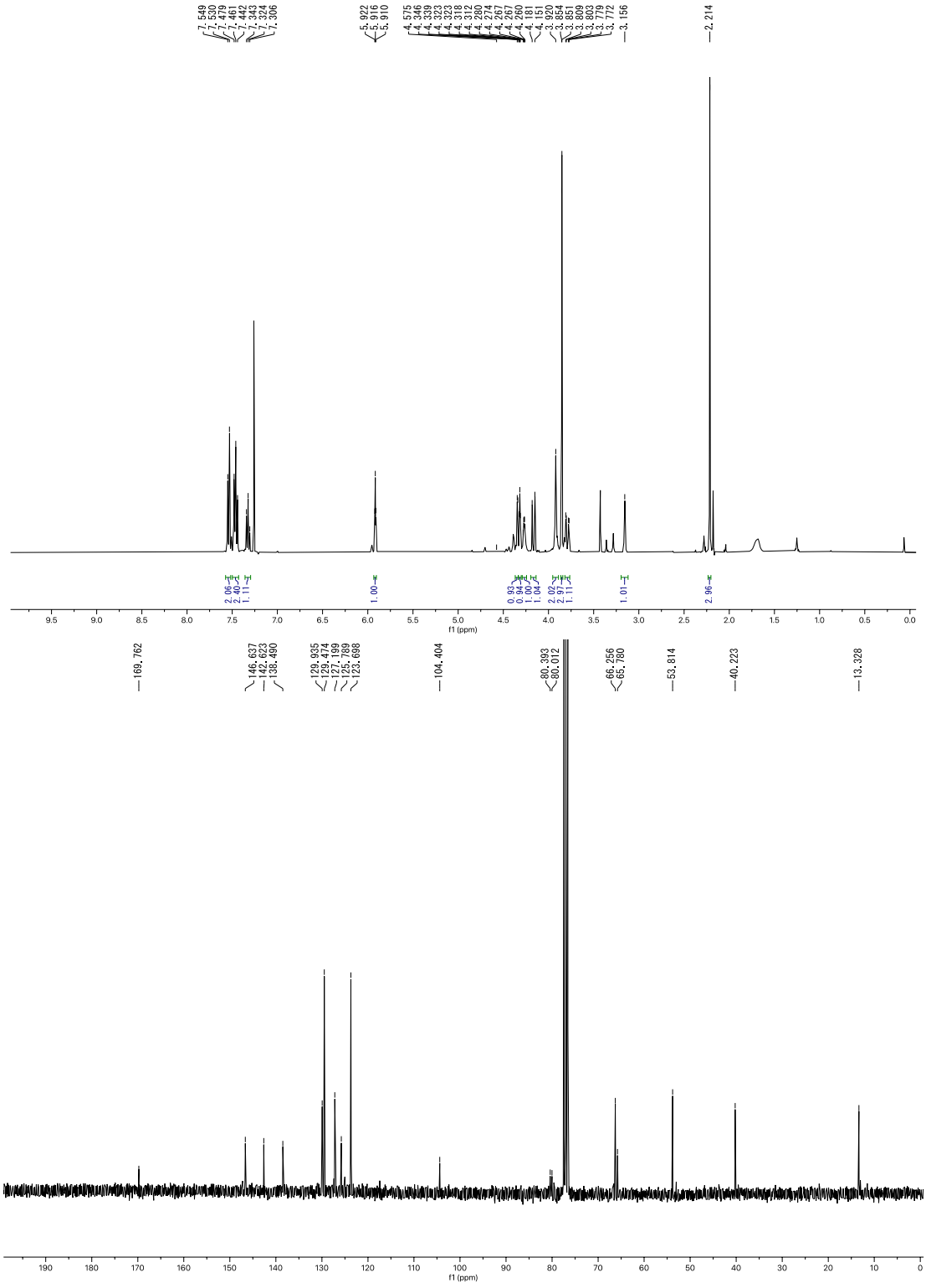
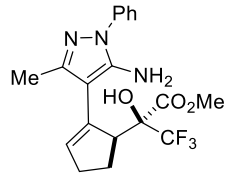
Compound **5daa-diastereoisomer 2**:

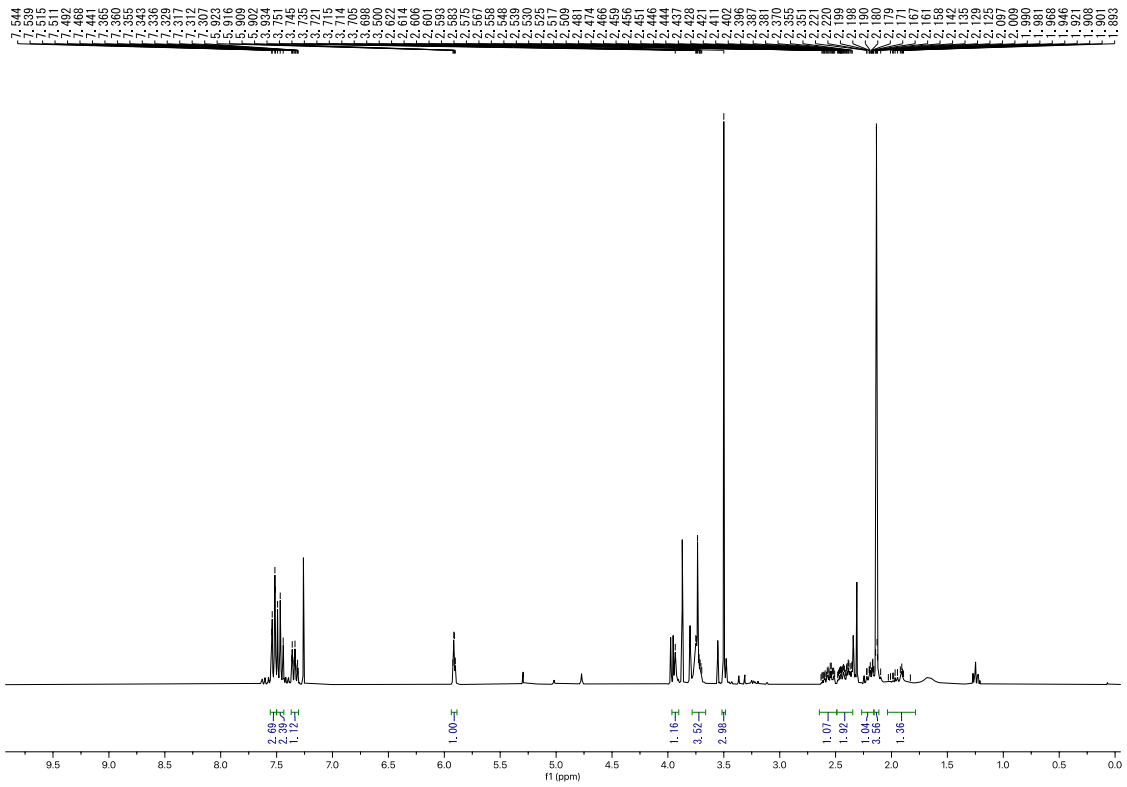


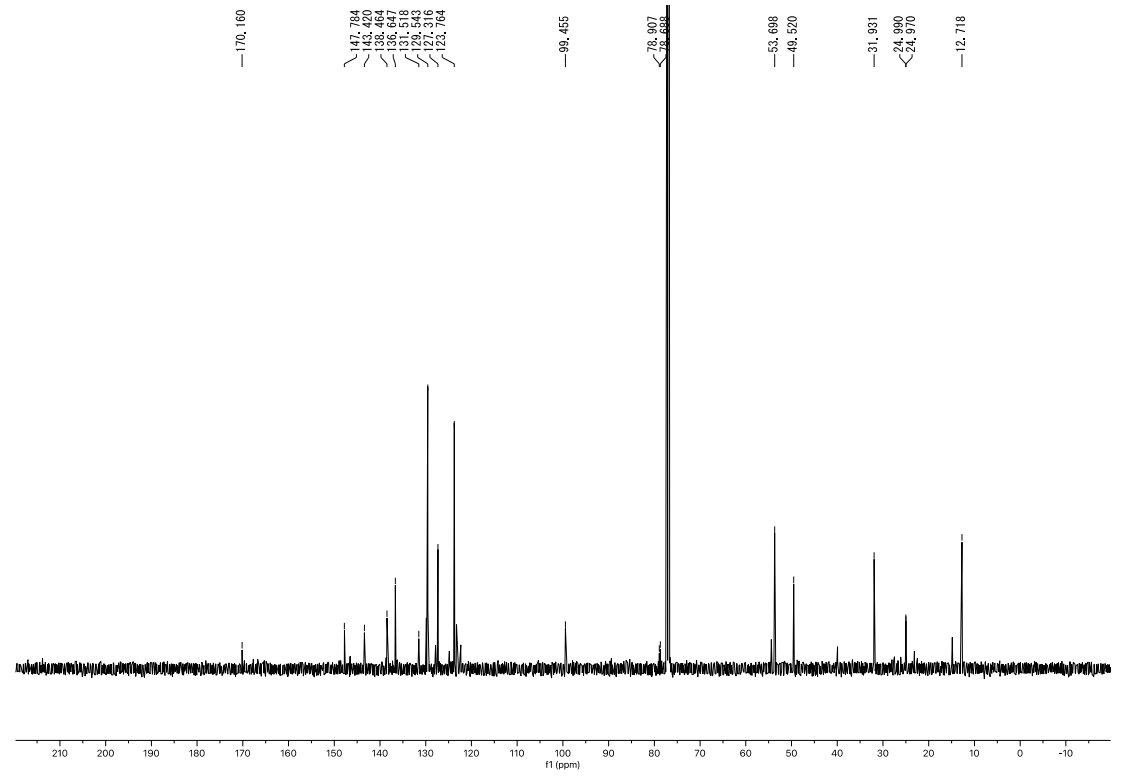


.

Compound **5faa**:







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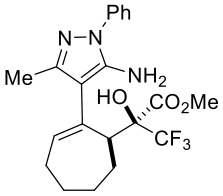
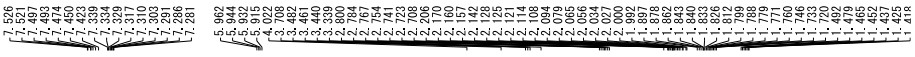
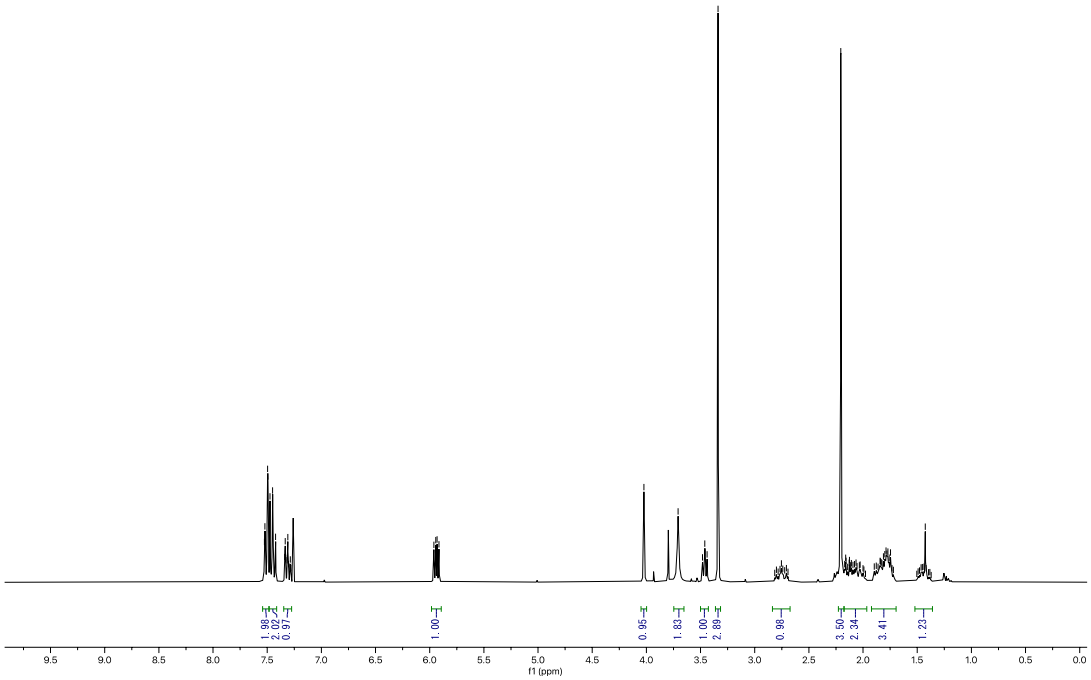
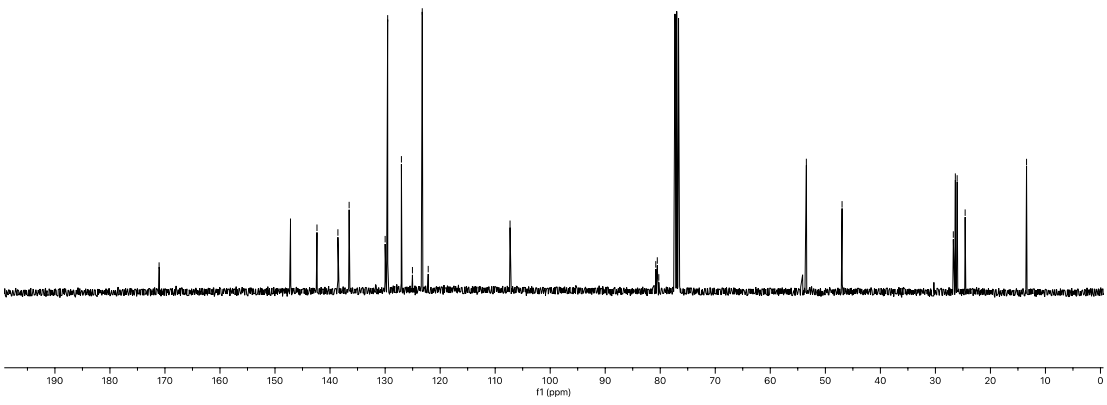
Compound **5gaa**:









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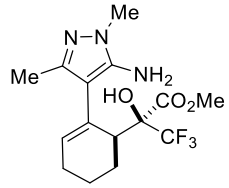
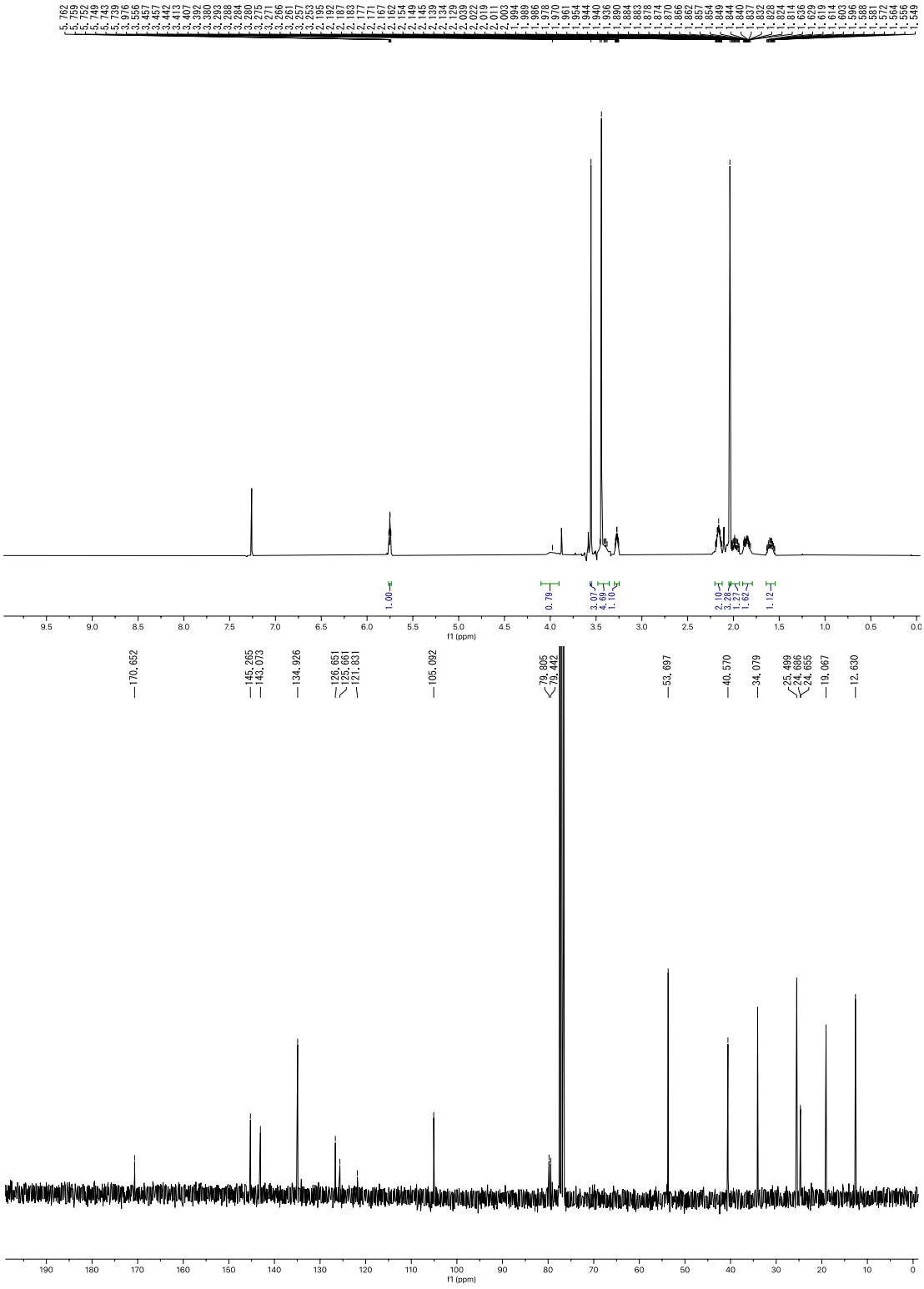
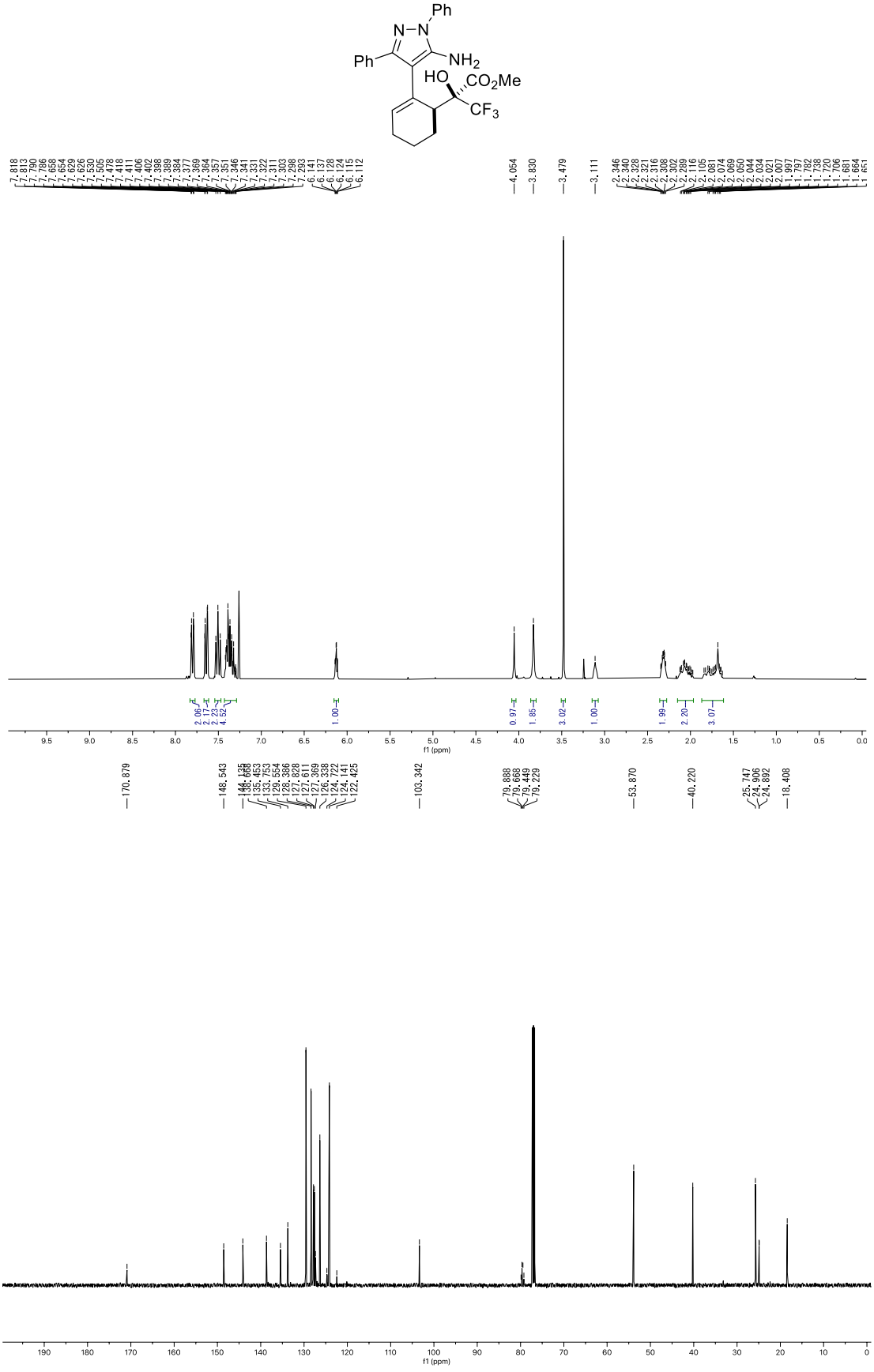
Compound **5aba**:

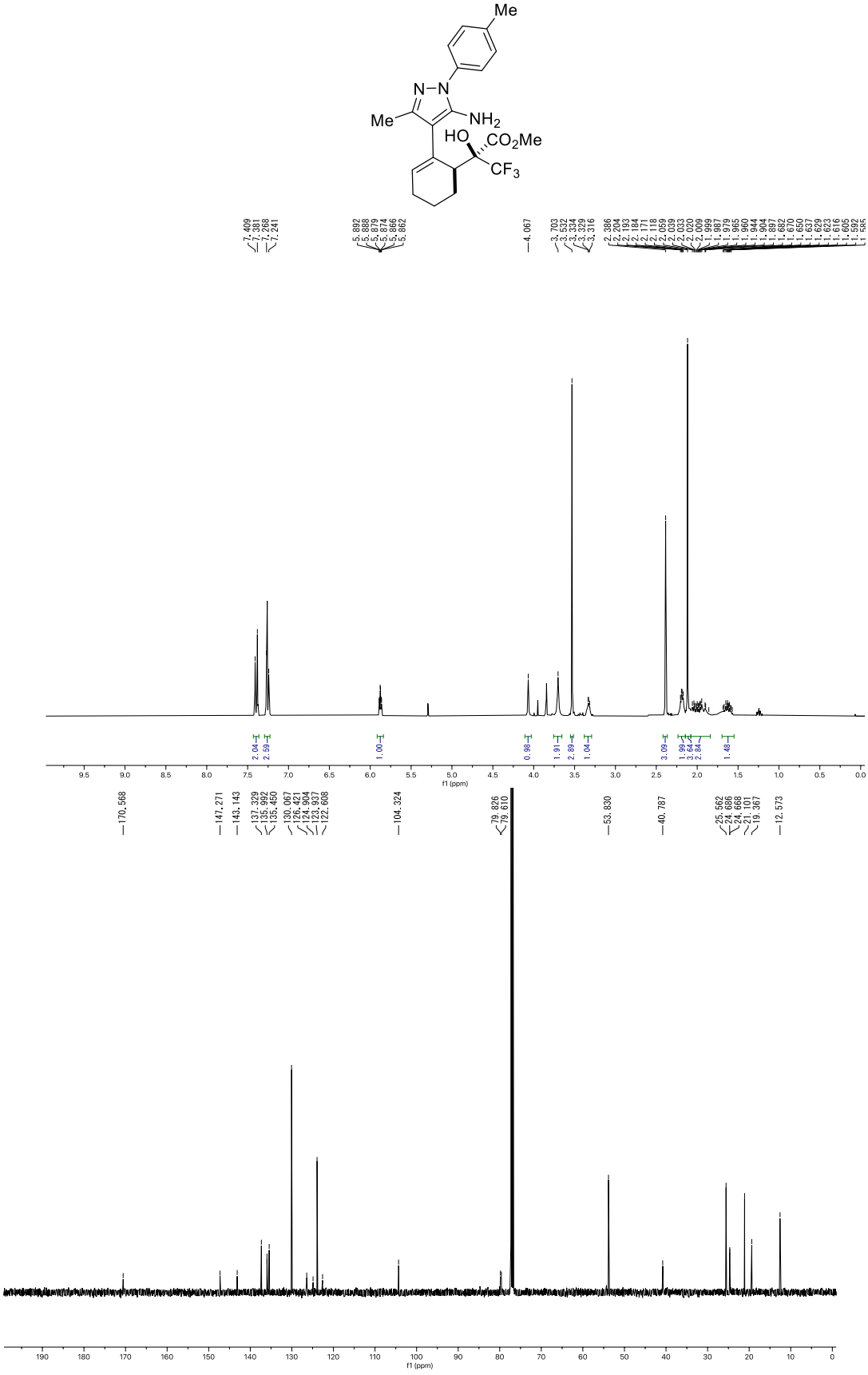




Compound **5aca**:

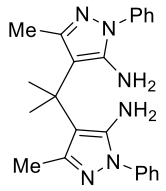


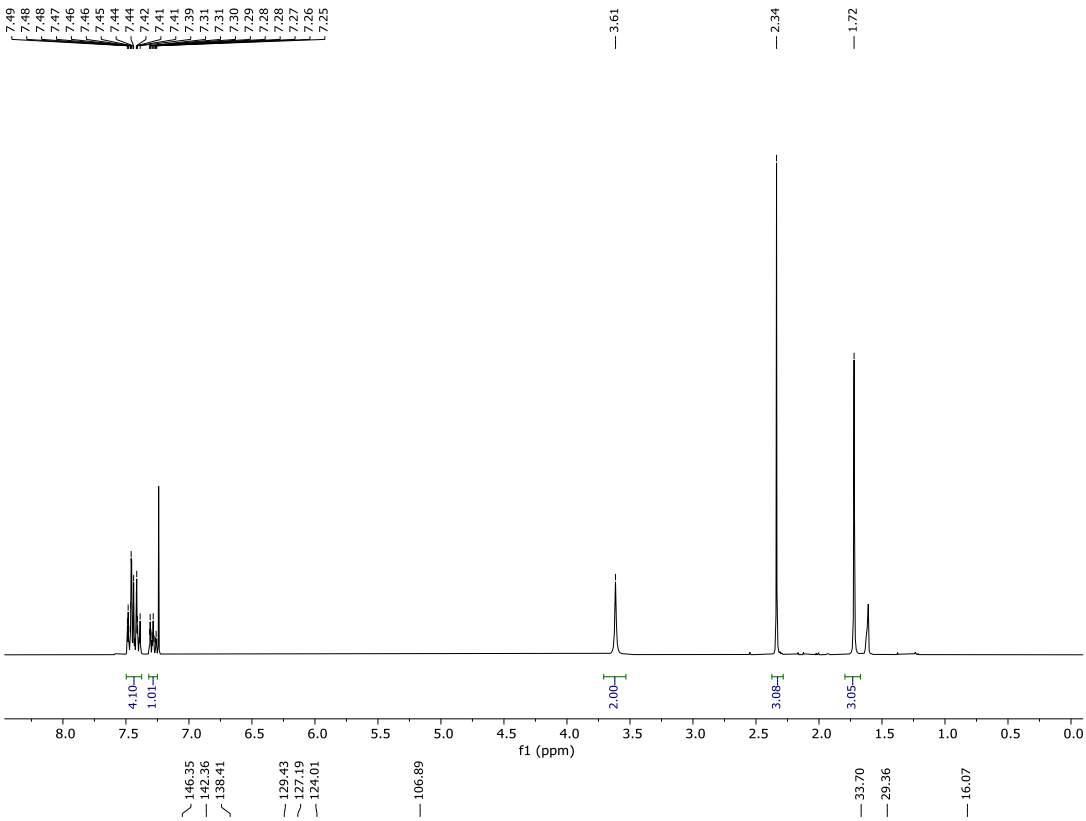
Compound **5ada**:

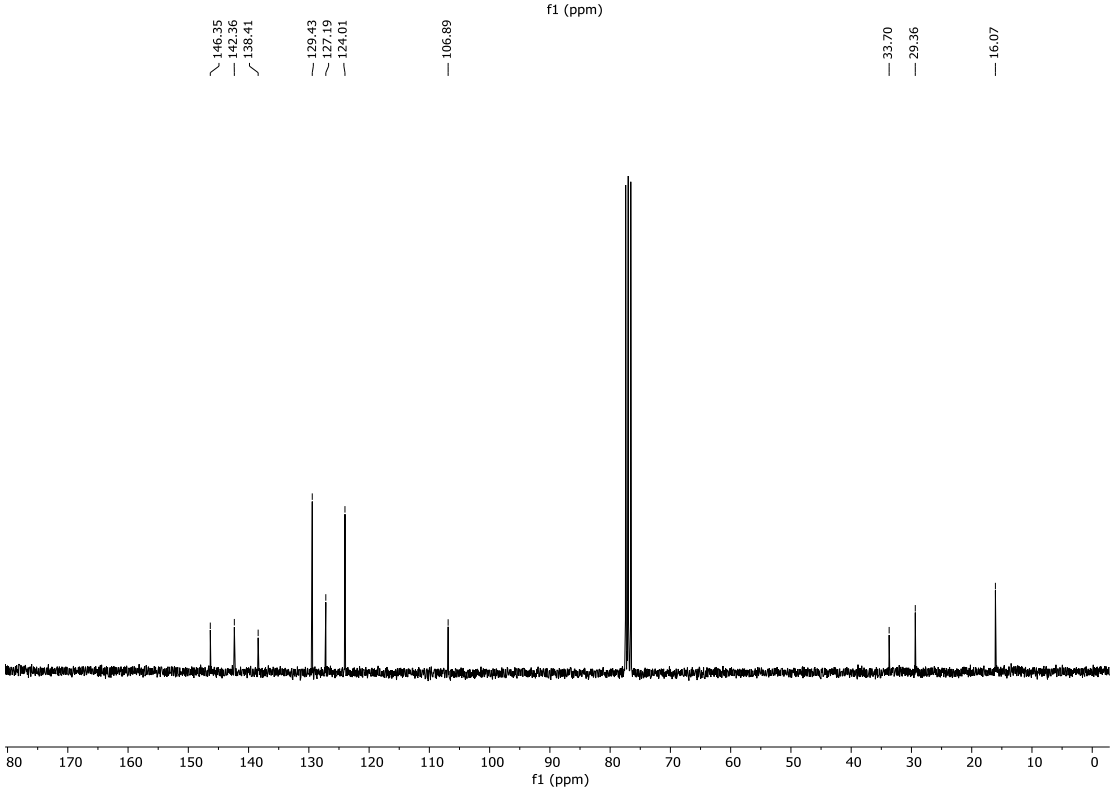


.

Compound **7**:

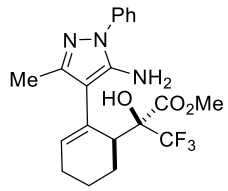

Me
N
N
Ph
NH2
NH2
Me
N
N
Ph


7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.42
7.41
7.41
7.39
7.31
7.31
7.30
7.29
7.28
7.28
7.27
7.26
7.25
3.61
2.34
1.72
4.10
1.01
2.00
3.08
3.05
f1 (ppm)


146.35
142.36
138.41
129.43
127.19
124.01
106.89
33.70
29.36
16.07
f1 (ppm)

7. HPLC DATA

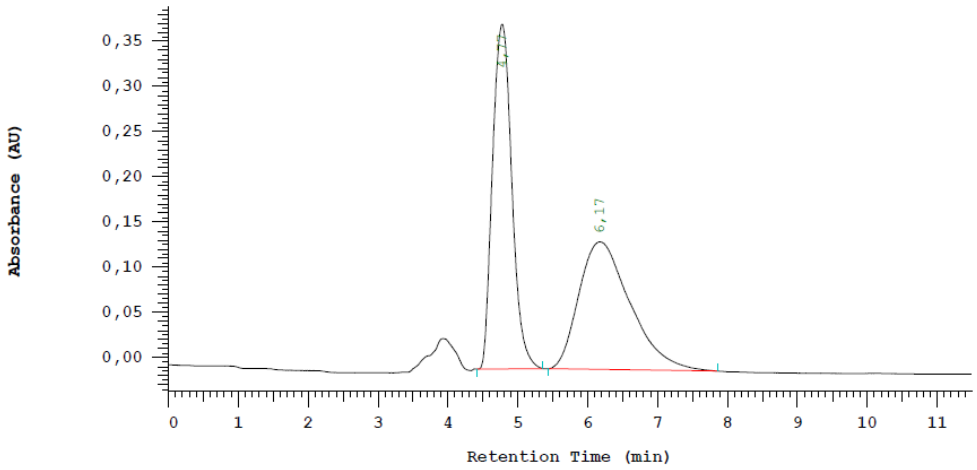
· Compound **5aaa**:



Data Path: C:\WIN32APP\HSM\CARLOS\DATA\LC-1032 AYH 8020 1mL\
Processing Method: Carlos-2

Application: Carlos
Sample Name: LC-1032 AYH 8020 1mL

Series:LC-1032 AYH 8020 1mL
Vial Number: 1



No.	RT	Area	Area %	Name
1	4,77	3655370	50,375	
2	6,17	3600990	49,625	
		7256360	100,000	

8. References

1. Li, C.; Zhang, F.; Shen, Z. *Tetrahedron*, **2020**, *76*, 131727.
2. Winters, G.; Sala, A.; De Paoli, A.; Conti, M. *Synthesis* **1984**, 1050-1052.