Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Electronic Supplementary Information

Solvent-Free Ruthenium Trichloride-Mediated [2+2+2] Cycloaddition of α,ω-Diynes and Cyanamides: A Convenient Access to 2-Aminopyridines

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Contents

I. General informations

All manipulations were carried out under an argon atmosphere. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV300 or AV400 instruments. All signals are expressed as ppm (δ) and are referenced to the non-deuterated solvent peak $CHCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C) or Methanol-D_4 (3.31 ppm for ^{1}H and 49.00 ppm for ^{13}C). Coupling constants (J) are given in Hz and refer to apparent peak multiplicities. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Melting points were determined with a Kofler Heizbank 7841 apparatus and are uncorrected.

Mass spectrometry analyses (direct introduction by chemical ionization with ammoniac or electrospray) were performed at the Ecole Nationale Supérieure de Chimie de Paris (ENSCP). High resolution mass spectra were performed at the University Pierre and Marie Curie (Paris).

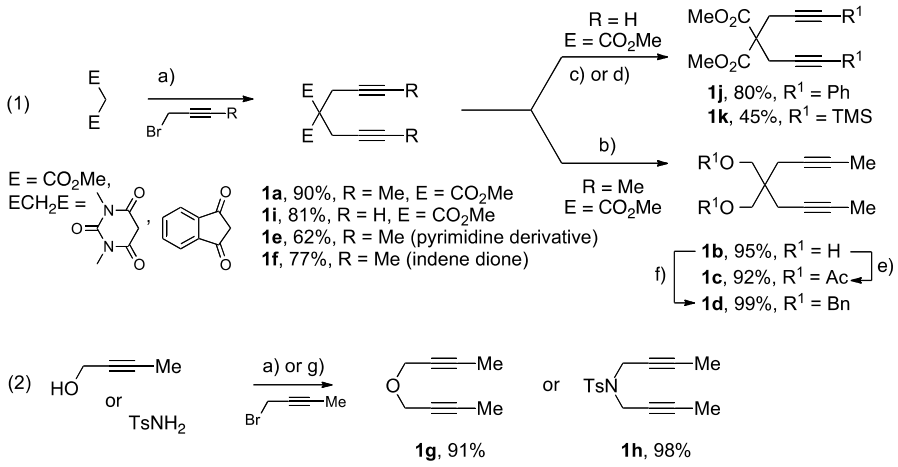
Sigma-Aldrich Silica gel (high-purity grade, pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size) was employed for flash column chromatography. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F254), spots were detected with UV light (254 nm) and revealed with a $KMnO_4$ or *para*-anisaldehyde stain solution.

All reagents were used as received from commercial sources. A freshly opened bottle of ruthenium(III) trichloride hydrate was used for the [2+2+2] cycloadditions.

II. Preparation of diynes and cyanamides

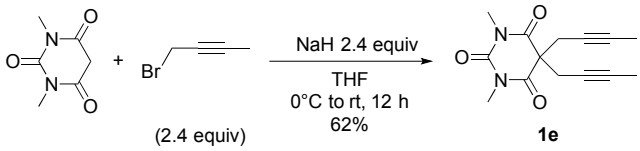
1. Synthesis of diynes **1** and **19**

Diynes **1a-h**[1] and **19**[2] were prepared according to the previously reported literatures.



Preparation of diynes, reaction conditions: a) NaH (2.4 equiv), THF, 0 °C to RT, 12 h; b) LiAlH4 (6 equiv), THF, 0 °C to RT, 1 h; c) PdCl2(PPh3)2 (5 mol %), CuI (2.5 mol %), Iodobenzene (2.5 equiv), Et3N/THF (1:1), 50 °C, 4 h; d) LiHMDS (2.2 equiv), TMSCl (2.5 equiv), THF, -70 °C, 2 h; e) EtN(iPr)2 (4 equiv), Ac2O (4 equiv), DCM, 0 °C to RT, 24 h; f) NaH (2.5 equiv), nBu4I (0.25 equiv), Benzyl bromide (2.5 equiv), THF, 0°C to RT, 12 h; g) K2CO3 (4 equiv), MeCN, reflux, 12 h.

Diyne **1e** was prepared according to the following protocol:



To a suspension of NaH (60% in mineral oil, 2.4 equiv, 14.4 mmol, 0.58 g) in THF (30 mL) at 0 °C was added dropwise a solution of 1,3-dimethylbarbituric acid (1 equiv., 6 mmol, 0.94 g), the reaction mixture was stirred at 0 °C for 1 h, then 1-bromo-2-butyne (2.4 equiv, 14.4 mmol, 1.26 mL) in THF (10 mL) was added to the mixture. Reaction mixture was then allowed to warm up to room temperature

[1] Preparation of diynes, for diyne **1k**, see: (a) M. Ishizaki and O. Hoshino, 2000, **56**, 8813–8819; for diynes **1c** and **1d**, see: (b) C. Liu and R. A. Widenhoefer, *Organometallics*, 2002, **21**, 5666–5673; for diyne **1i**, see: (c) E. Genin, P. Y. Toullec, P. Marie, S. Antoniotti, C. Brancour, J.-P. Genêt and V. Michelet, *Arkivoc*, 2007, 67–78; for diyne **1h**, see: (d) K. T. Sylvester and P. J. Chirik, *J. Am. Chem. Soc.*, 2009, **131**, 8772–8774; for diyne **1f**, see: (e) P. Kumar, K. Zhang and J. Louie, *Angew. Chem. Int. Ed.*, 2012, **51**, 8602–8606; for diyne **1a, 1b** and **1g**, see: (f) M. Amatore, D. Lebœuf, M. Malacria, V. Gandon and C. Aubert, *J. Am. Chem. Soc.*, 2013, **135**, 4576–4579; for diyne **1j**, see: (g) M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc and U. Hennecke, *J. Am. Chem. Soc.*, 2013, **135**, 8133–8136.

[2] For diyne **19**, see: E. Bednářová, E. Colacino, F. Lamaty and M. Kotora, *Adv. Synth. Catal.,* 2016, **358**, 1916-1923.

and stirred for 12 h until completion by TLC. The mixture was finally quenched with saturated ammonium chloride and extracted with Et_2O. The combined organic layers were washed with water and brine. The solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) to afford compound **1e** (0.96 g, 62%) as a white solid. m. p.: 118-120 °C.

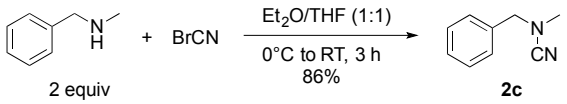
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 – 3.24 (m, 6H), 2.78 – 2.51 (m, 4H), 1.75 – 1.50 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 151.4, 80.0, 72.4, 56.6, 28.8, 28.3, 3.4.

MS (CI, NH_3): m/z = 261 $[M + H]^+$.

2. Synthesis of cyanamides **2**

Cyanamides **2a**-**b** and **2e-f** were purchased from commercial sources. Cyanamides **2d** were prepared according to the reported literature.[3] Cyanamides **2c** was prepared according to the following protocol:



N-Methybenzylamine (1.55 mL, 12.0 mmol, 2 equiv) was added to a solution of cyanogen bromide (0.64 g, 6.0 mmol, 1 equiv) in Et_2O/THF (1:1, 30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Hexane (5 mL) was added, and the mixture was stirred for an additional 10 min. It was then filtered through a pad of Celite, and the filtrate was washed with water (4x25 mL) and brine (2x25 mL). The solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) to afford compound **2c** (0.75 g, 86 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 4.15 (s, 2H), 2.77 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 129.1, 128.8, 128.5, 119.0, 57.3, 37.9.

The ^{1}H NMR data obtained were in agreement with the literature.[4]

[3] For cyanamide **2d**, see: K. Goldberg, D. S. Clarke and J. S. Scott, *Tetrahedron Lett.,* 2014, **55**, 4433-4436.

[4] S. A. Bakunov, A. V. Rukavishnikov and A. V. Tkachev, *Synthesis,* 2000, 1148-1159.

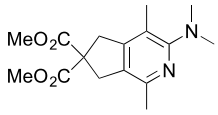
III. Ru-catalyzed [2+2+2] cycloaddition reactions.

General procedure: Ru-catalyzed [2+2+2] cycloaddition of diynes with cyanamides under solvent-free conditions.

A sealed tube was equipped with $RuCl_3 \cdot nH_2O$ (5 mol %) and diyne **1** (1 mmol, 1 equiv), followed by the addition of cyanamide **2** (2.0 mmol, 2.0 equiv) under argon atmosphere. The tube was sealed and the reaction mixture was stirred vigorously at 80 or 110 °C. When the reaction was complete (TLC monitoring), the crude reaction mixture was directly purified by flash chromatography over silica gel to afford cycloadducts. The excess of cyanamide was removed by bulb to bulb distillation.

The $Ru(acac)_3$ catalyst was not efficient for this transformation (80 °C and 110 °C).

Dimethyl 3-(dimethylamino)-1,4-dimethyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3).



Chemical Formula: $C_{16}H_{22}N_2O_4$
Exact Mass: 306.1580

This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), *N*,*N*-dimethylcyanamide **2a** (140 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **3** (225 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 70 °C for 10 minutes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 6H), 3.48 (s, 2H), 3.47 (s, 2H), 2.75 (s, 6H), 2.31 (s, 3H), 2.14 (s, 3H).

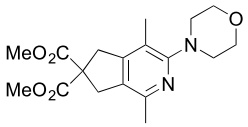
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.6, 150.3, 147.9, 127.2, 117.1, 59.9, 53.2, 42.5, 40.1, 38.7, 21.8, 14.9.

MS (CI, NH_3): m/z = 307 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[5]

Dimethyl 1,4-dimethyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4).

[5] R. M. Stolley, M. T. Maczka and J. Louie, *Eur. J. Org. Chem.*, 2011, 3815–3824.



Chemical Formula: $C_{18}H_{24}N_2O_5$
Exact Mass: 348.1685

This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **4** (330 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

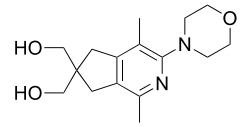
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 – 3.78 (m, 4H), 3.76 (d, J = 4.0 Hz, 6H), 3.50 (s, 2H), 3.48 (s, 2H), 3.12 – 2.99 (m, 4H), 2.33 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 160.2, 150.5, 148.5, 128.3, 117.9, 67.4, 59.9, 53.2, 50.8, 40.0, 38.7, 21.7, 14.4.

MS (CI, NH_3): m/z = 349 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[5]

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-6,6-diyl)dimethanol (5).



Chemical Formula: $C_{16}H_{24}N_2O_3$
Exact Mass: 292.1787

This compound was prepared using diyne **1b** (180 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **3c** (30 mg, 10%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

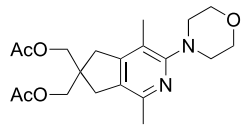
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86– 3.81 (m, 4H), 3.81 – 3.67 (m, 4H), 3.13 – 2.99 (m, 4H), 2.72 – 2.60 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 152.4, 149.1, 130.0, 118.6, 69.5, 67.4, 50.8, 48.7, 37.9, 36.6, 21.7, 14.4.

MS (CI, NH_3): m/z = 293 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[6]

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-6,6-diyl)bis(methylene) diacetate (6).



Chemical Formula: $C_{20}H_{28}N_2O_5$
Exact Mass: 376.1998

This compound was prepared using diyne **1c** (264 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **6** (255 mg, 68%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 102 – 104 °C.

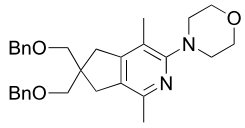
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 4H), 3.89 – 3.73 (m, 4H), 3.16 – 2.92 (m, 4H), 2.78 – 2.70 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H), 2.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 160.1, 151.4, 149.1, 129.2, 118.4, 67.4, 66.9, 50.8, 46.2, 38.1, 36.8, 21.7, 21.0, 14.4.

MS (CI, NH_3): m/z = 377 $[M + H]^+$.

HRMS (ESI^+): calcd. for $C_{20}H_{29}N_2O_5$ $[M+H]^+$: 377.2071, found 377.2072.

4-(6,6-Bis((benzyloxy)methyl)-1,4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)morpholine (7).



Chemical Formula: $C_{30}H_{36}N_2O_3$
Exact Mass: 472.2726

This compound was prepared using diyne **1d** (360 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **7** (390 mg, 83%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 10H), 4.53 (s, 4H), 3.96 – 3.72 (m, 4H), 3.50 (s, 4H), 3.16 – 2.94 (m, 4H), 2.79 – 2.70 (m, 4H), 2.31 (s, 3H), 2.11 (s, 3H).

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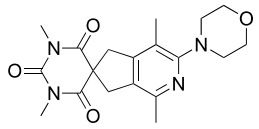
[6] T. Hashimoto, S. Ishii, R. Yano, H. Miura, K. Sakata and R. Takeuchi, *Adv. Synth. Catal.*, 2015, **357**, 3901–3916.

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 152.9, 148.9, 138.8, 130.7, 128.5, 127.6, 118.5, 73.7, 73.4, 67.5, 50.9, 48.1, 38.5, 37.1, 21.7, 14.4.

MS (CI, NH_3): m/z = 473 $[M + H]^+$.

HRMS (ESI^+): calcd. for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2799, found 473.2790.

1,1',3',4-Tetramethyl-3-morpholino-5,7-dihydro-2'*H*-spiro[cyclopenta[*c*]pyridine-6,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (8).



Chemical Formula: $C_{19}H_{24}N_4O_4$
Exact Mass: 372.1798

This compound was prepared using diyne **1e** (260 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded **8** (275 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 175 – 178 °C.

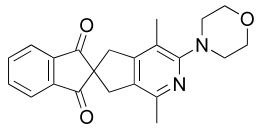
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 – 3.76 (m, 4H), 3.49 (s, 2H), 3.45 (s, 2H), 3.34 (s, 6H), 3.17 – 2.94 (m, 4H), 2.30 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 160.7, 151.4, 150.6, 148.3, 127.3, 117.8, 67.4, 55.8, 50.8, 44.0, 42.6, 29.3, 21.8, 14.5.

MS (CI, NH_3): m/z = 373 $[M + H]^+$.

HRMS (ESI^+): calcd. for $C_{19}H_{25}N_4O_4$ $[M+H]^+$: 373.1870, found 373.1870.

1,4-Dimethyl-3-morpholino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,2'-indene]-1',3'-dione (9).



Chemical Formula: $C_{22}H_{22}N_2O_3$
Exact Mass: 362.1630

This compound was prepared using diyne **1f** (250 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **9** (268 mg, 74%) as a yellow solid. The excess of

cyanamide was removed by bulb to bulb distillation (conditions: $1.0x10^{-3}$ mbar, 90 °C for 10 minutes). m.p. 206 – 209 °C.

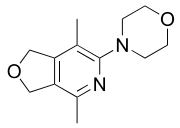
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 2H), 7.93 – 7.85 (m, 2H), 3.89 – 3.73 (m, 4H), 3.23 (s, 2H), 3.22 (s, 2H), 3.14 – 3.01 (m, 4H), 2.31 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 160.6, 151.3, 148.4, 141.7, 136.2, 128.9, 123.9, 118.0, 67.4, 58.5, 50.8, 39.6, 21.8, 14.5.

MS (CI, NH_3): m/z = 363 $[M + H]^+$.

HRMS (ESI^+): calcd. for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703, found 363.1704.

4,7-Dimethyl-6-morpholino-1,3-dihydrofuro[3,4-*c*]pyridine (10).



Chemical Formula: $C_{13}H_{18}N_2O_2$
Exact Mass: 234.1368

This compound was prepared using diyne **1g** (122 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **10** (150 mg, 64%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: $1.0x10^{-3}$ mbar, 90 °C for 10 minutes).

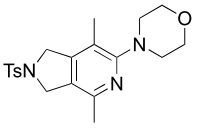
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 2H), 5.00 (s, 2H), 3.86 – 3.81 (m, 4H), 3.12 – 3.07 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 150.1, 146.2, 127.6, 115.1, 73.2, 72.7, 67.3, 50.7, 21.9, 14.6.

MS (CI, NH_3): m/z = 235 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[6]

4-(4,7-Dimethyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)morpholine (11).



Chemical Formula: $C_{20}H_{25}N_3O_3S$
Exact Mass: 387.1617

This compound was prepared using diyne **1h** (275 mg, 1.0 mmol), 4-cyanomorpholine **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl

acetate gradient from 90/10 to 80/20) afforded **11** (280 mg, 72%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: $1.0x10^{-3}$ mbar, 90 °C for 10 minutes).

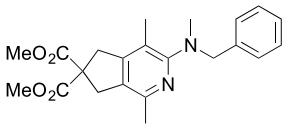
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.52 – 4.40 (m , 4H), 3.85 – 3.75 (m, 4H), 3.10 – 3.00 (m, 4H), 2.41 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 147.7, 146.8, 144.0, 134.1, 130.1, 127.8, 124.8, 116.4, 67.3, 53.5, 52.6, 50.69, 21.7, 14.5.

MS (CI, NH_3): m/z = 388 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[6]

Dimethyl 3-(benzyl(methyl)amino)-1,4-dimethyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (15).



Chemical Formula: $C_{22}H_{26}N_2O_4$
Exact Mass: 382.1893

This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), *N*-benzyl-*N*-methylcyanamide **2c** (292 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) afforded **15** (306 mg, 81%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 120 °C for 10 minutes).

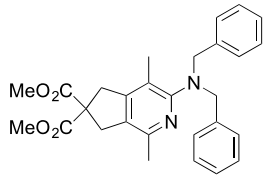
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.28 – 7.16 (m, 1H), 4.26 (s, 2H), 3.77 (s, 6H), 3.55 – 3.45 (m, 4H), 2.67 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.4, 150.4, 148.1, 140.0, 128.4, 128.2, 127.7, 126.8, 117.8, 59.9, 58.4, 53.2, 40.1, 39.8, 38.8, 21.7, 14.8.

MS (CI, NH_3): m/z = 383 $[M + H]^+$.

HRMS (ESI^+): calcd. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965, found 383.1963.

Dimethyl 3-(dibenzylamino)-1,4-dimethyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (16).



Chemical Formula: $C_{28}H_{30}N_2O_4$
Exact Mass: 458.2206

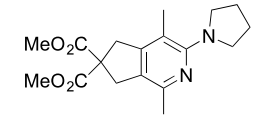
This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), dibenzylcyanamide **2d** (444 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **16** (344 mg, 75%) as a sticky yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10^{-3} mbar, 180 °C for 20 minutes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 10H), 4.25 (s, 4H), 3.76 (s, 6H), 3.49 (s, 4H), 2.29 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 159.9, 150.4, 148.2, 139.9, 128.6, 128.3, 128.2, 126.7, 118.9, 59.7, 55.4, 53.2, 40.1, 38.8, 21.6, 14.5.

MS (CI, NH_3): m/z = 459 $[M + H]^+$.

Dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (17).



Chemical Formula: $C_{18}H_{24}N_2O_4$
Exact Mass: 332.1736

This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), pyrrolidine-1-carbonitrile **2e** (192 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 90/10) afforded **17** (285 mg, 86%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10^{-3} mbar, 80 °C for 10 minutes).

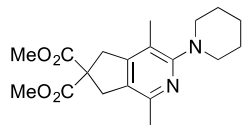
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H), 3.44 (m, 8H), 2.29 (s, 3H), 2.15 (s, 3H), 1.87 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.9, 150.3, 147.4, 124.6, 113.5, 60.0, 53.1, 50.3, 40.1, 38.6, 25.6, 21.7, 15.8.

MS (CI, NH_3): m/z = 333 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[5]

Dimethyl 1,4-dimethyl-3-(piperidin-1-yl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (18).



Chemical Formula: $C_{19}H_{26}N_2O_4$
Exact Mass: 346.1893

This compound was prepared using diyne **1a** (236 mg, 1.0 mmol), piperidine-1-carbonitrile **2f** (220 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **18** (251 mg, 73%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10^{-3} mbar, 80 °C for 10 minutes).

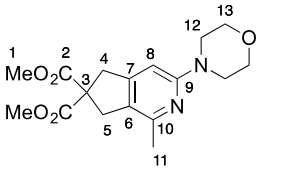
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H), 3.49 (s, 2H), 3.47 (s, 2H), 3.06 – 2.91 (m, 4H), 2.32 (s, 3H), 2.13 (s, 3H), 1.73 – 1.61 (m, 4H), 1.61 – 1.50 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.7, 150.1, 148.1, 127.5, 118.1, 59.8, 53.2, 51.6, 40.01, 38.7, 26.5, 24.8, 21.7, 14.4.

MS (CI, NH_3): m/z = 347 $[M + H]^+$.

The NMR data obtained were in agreement with the literature.[6]

Dimethyl 1-methyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (20)



Chemical Formula: $C_{17}H_{22}N_2O_5$
Exact Mass: 334.1529
20

This compound was prepared using diyne **19** (222 mg, 1.0 mmol), piperidine-1-carbonitrile **2b** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **20** (71 mg, 43%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10^{-3} mbar, 90 °C for 10 minutes). m.p. 110 – 112°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H, H_8), 3.83 – 3.78 (m, 4H, H_{13}), 3.75 (s, 6H, H_1), 3.49 (s, 2H, H_4), 3.47 – 3.41 (m, 6H, $H_{5,12}$), 2.32 (s, 3H, H_{11})

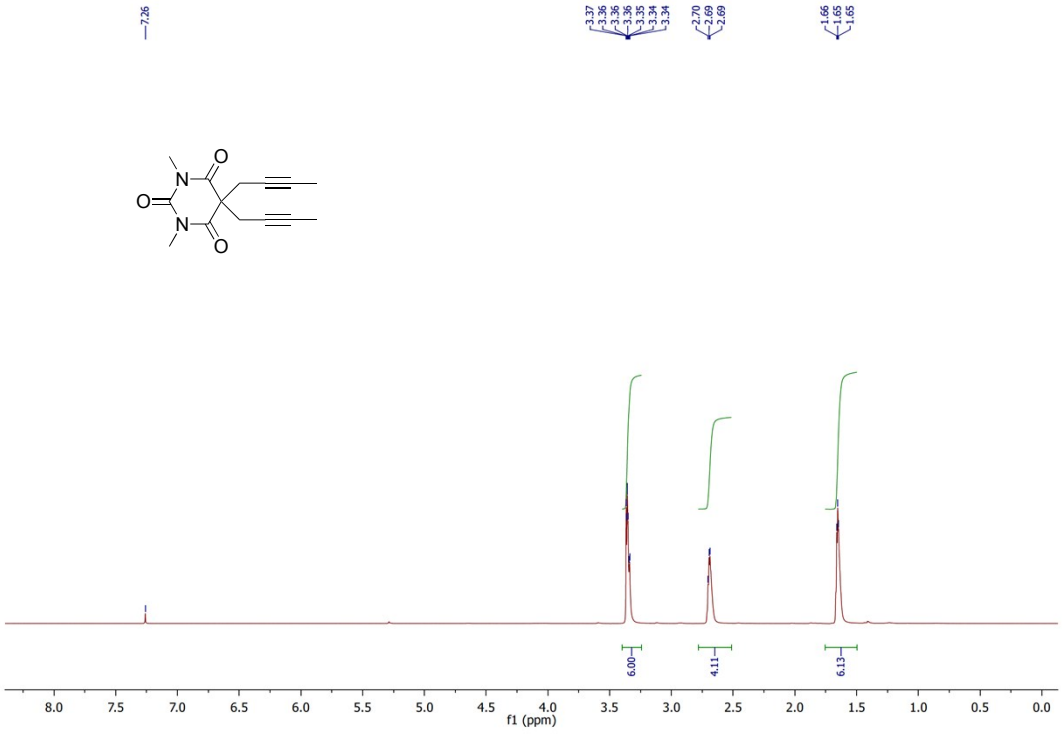
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_2), 159.3 (C_7), 151.7 (C_9), 151.5 (C_{10}), 124.3 (C_6), 100.1 (C_8), 67.0 (C_{13}), 60.0 (C_3), 53.2 (C_1), 46.4 (C_{12}), 40.8 (C_4), 38.0 (C_5), 22.2 (C_{11}).

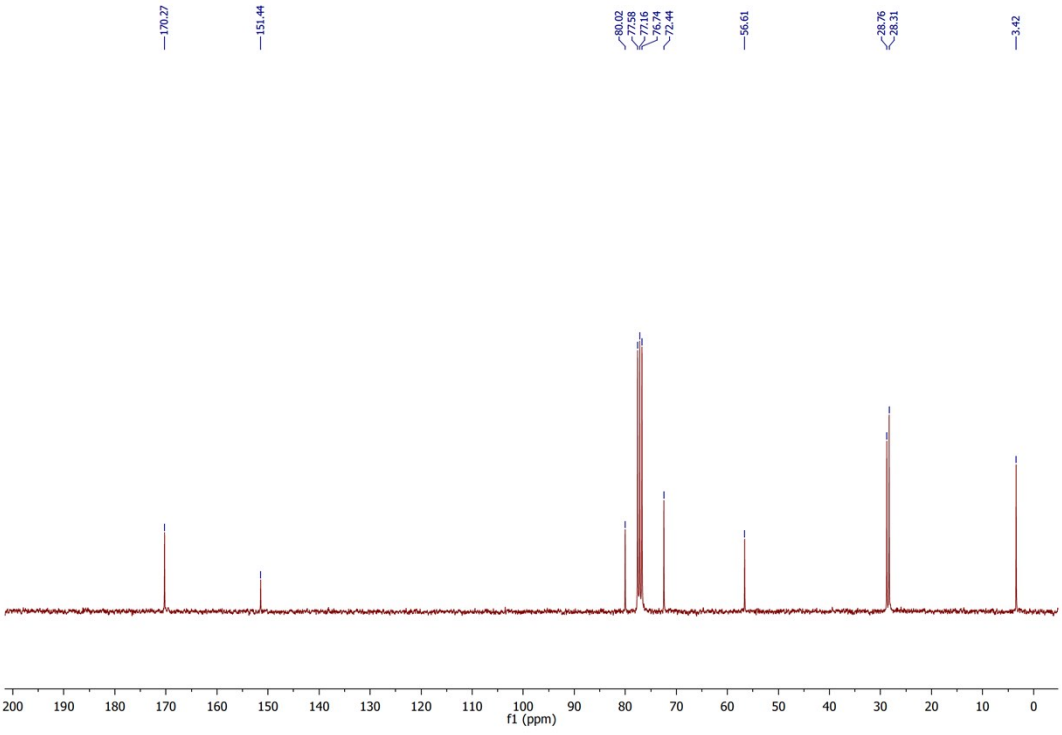
NOESY (400 MHz, $CDCl_3$) H_8 (6.33 ppm) correlates to H_{12} (3.47 – 3.41 ppm), H_5 (3.47 – 3.41 ppm) correlates to H_{11} (2.32 ppm).

HRMS (ESI^+): calcd. for $C_{17}H_{23}N_2O_5$ $[M+H]^+$: 335.1601, found 335.1603.

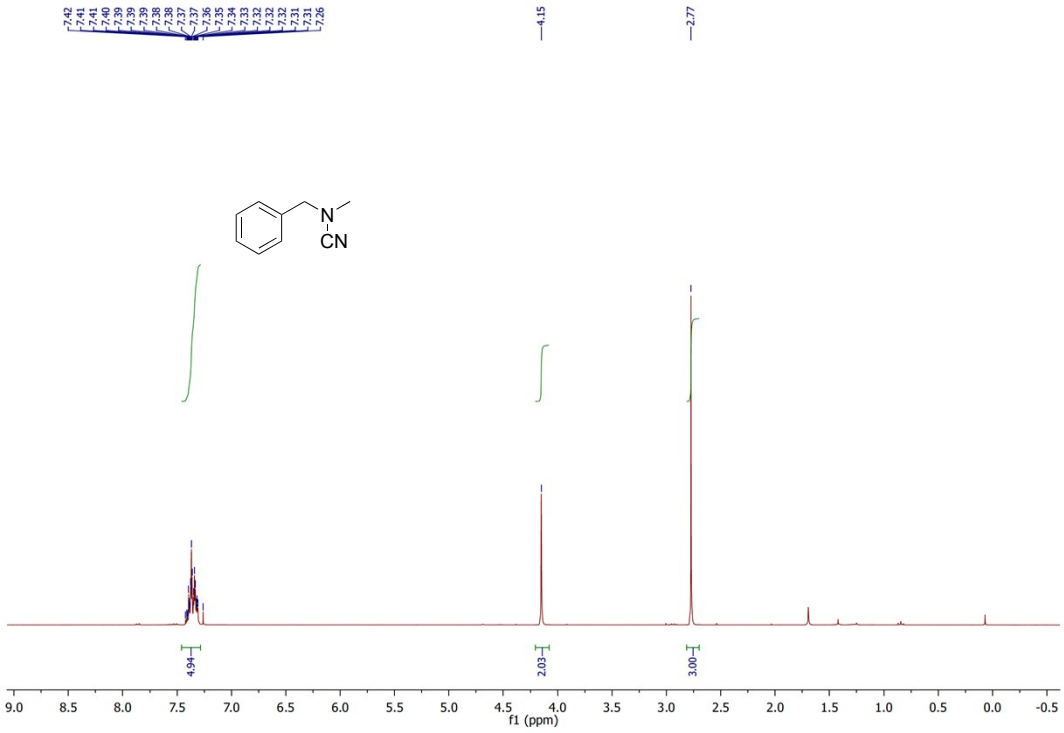
IV. NMR spectra

1e





2c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7.41
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7.39
7.39
7.38
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7.37
7.36
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7.34
7.33
7.32
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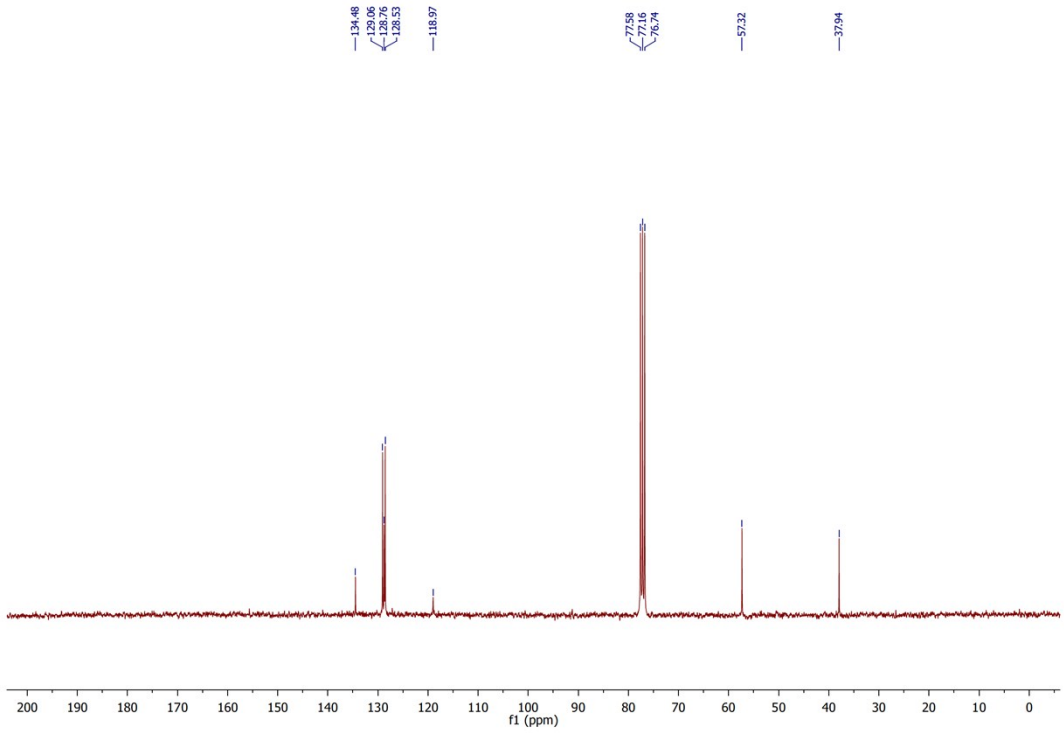
CN
4.94
2.03
3.00
f1 (ppm)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129.06
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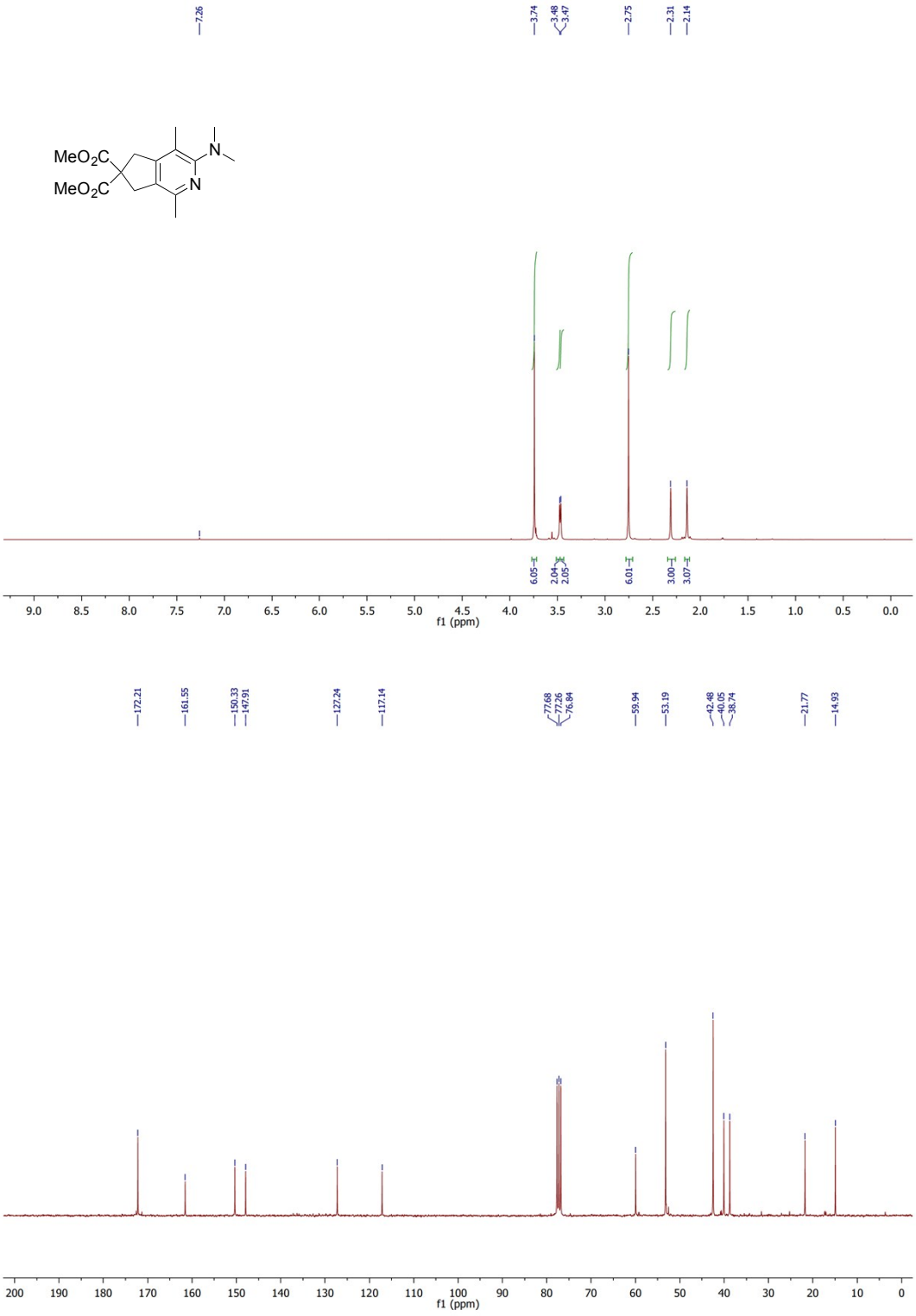
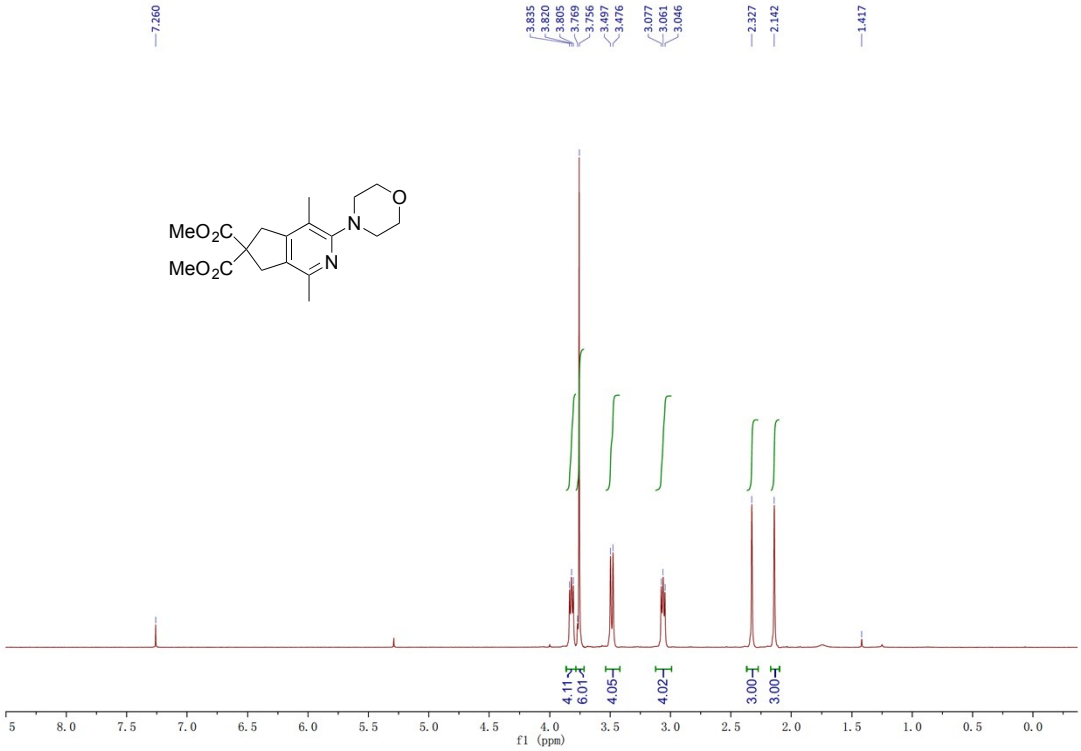
128.53
118.97
77.58
77.16
76.74
57.32
37.94
f1 (ppm)

3


7.26
3.74
3.48
3.47
2.75
2.31
2.14
MeO2C
MeO2C
N
N
6.05
2.04
2.05
6.01
3.00
3.07
f1 (ppm)
172.21
161.55
150.33
147.91
127.24
117.14
77.68
77.26
76.84
59.94
53.19
42.48
40.05
38.74
21.77
14.93
f1 (ppm)

4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2.142
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MeO2C
MeO2C
N
O
N
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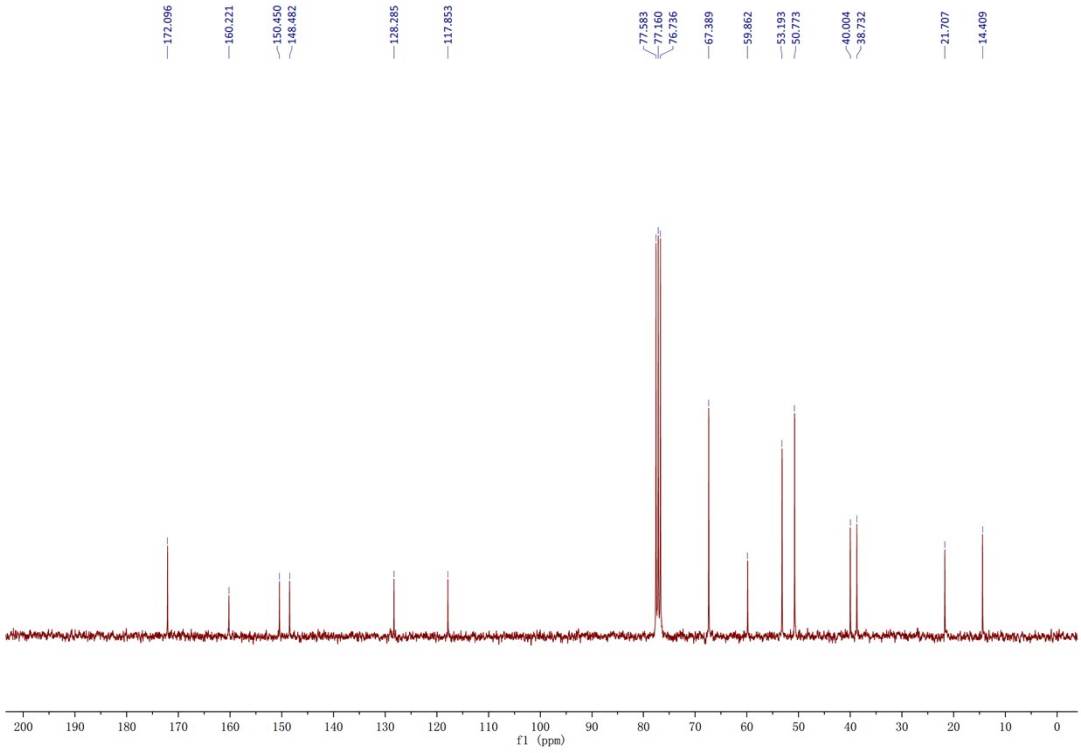
4.05
4.02
3.00
3.00
f1 (ppm)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128.285
117.853
77.583
77.160
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67.389
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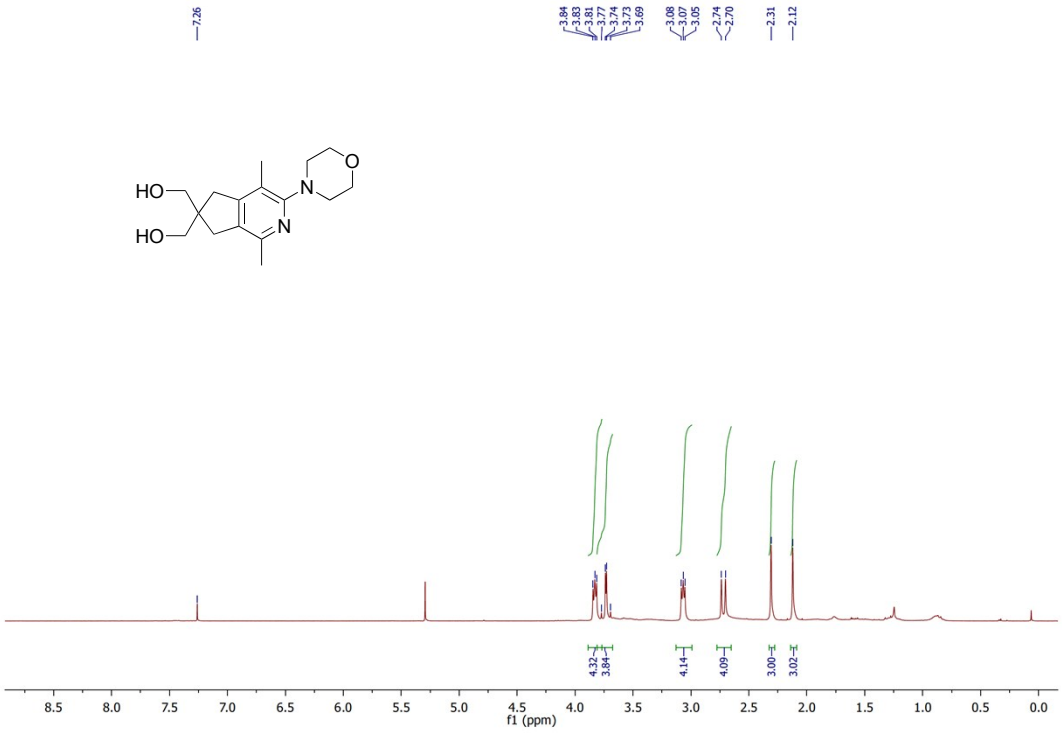
40.004
38.732
21.707
14.409
f1 (ppm)

5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3.81
3.77
3.74
3.73
3.69
3.08
3.07
3.05
2.74
2.70
2.31
2.12
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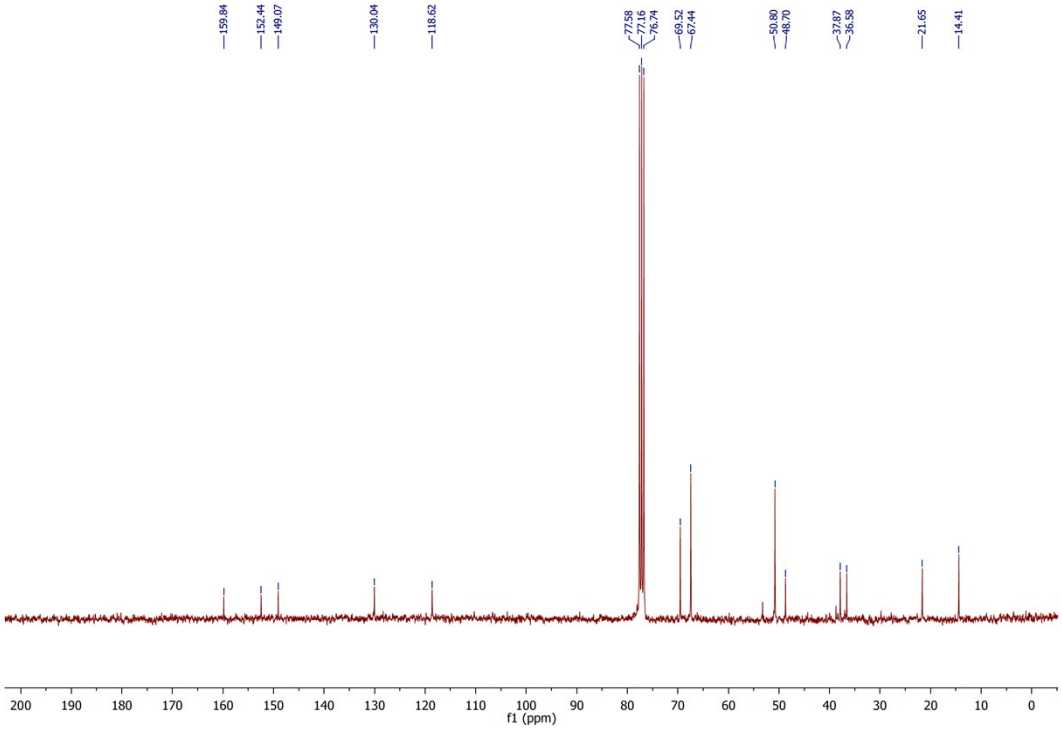
HO
N
O
N
4.32
3.84
4.14
4.09
3.00
3.02
f1 (ppm)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149.07
130.04
118.62
77.58
77.16
76.74
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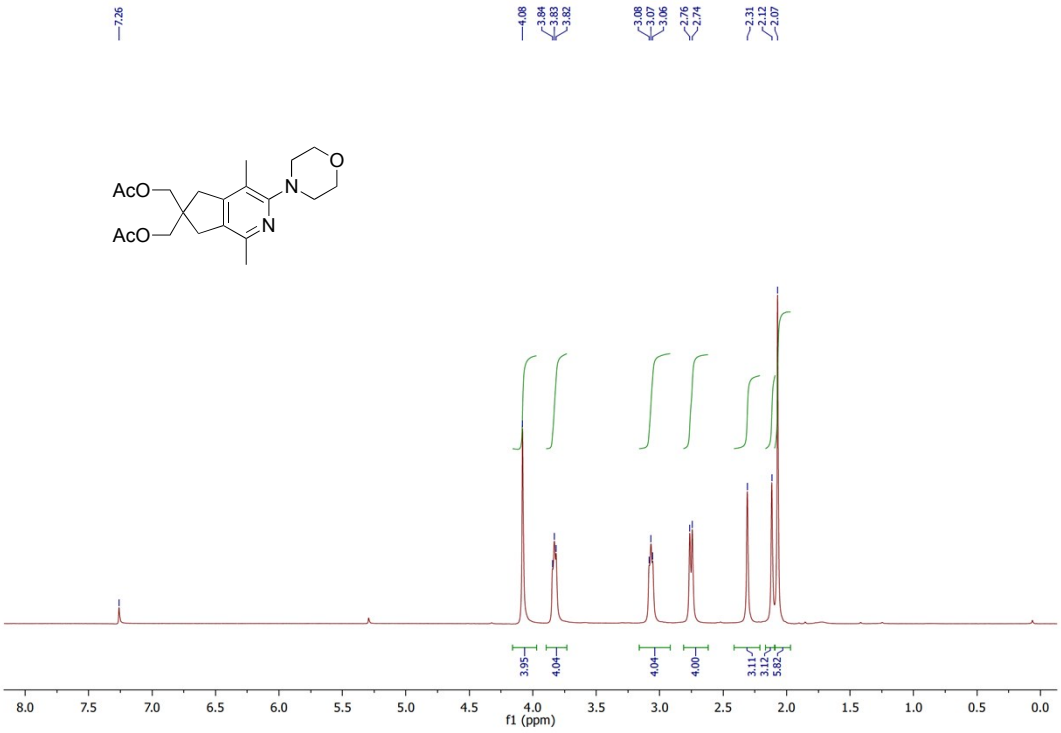
48.70
37.87
36.58
21.65
14.41
f1 (ppm)

6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4.08
3.84
3.83
3.82
3.08
3.07
3.06
2.76
2.74
2.31
2.12
2.07
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AcO
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O
N
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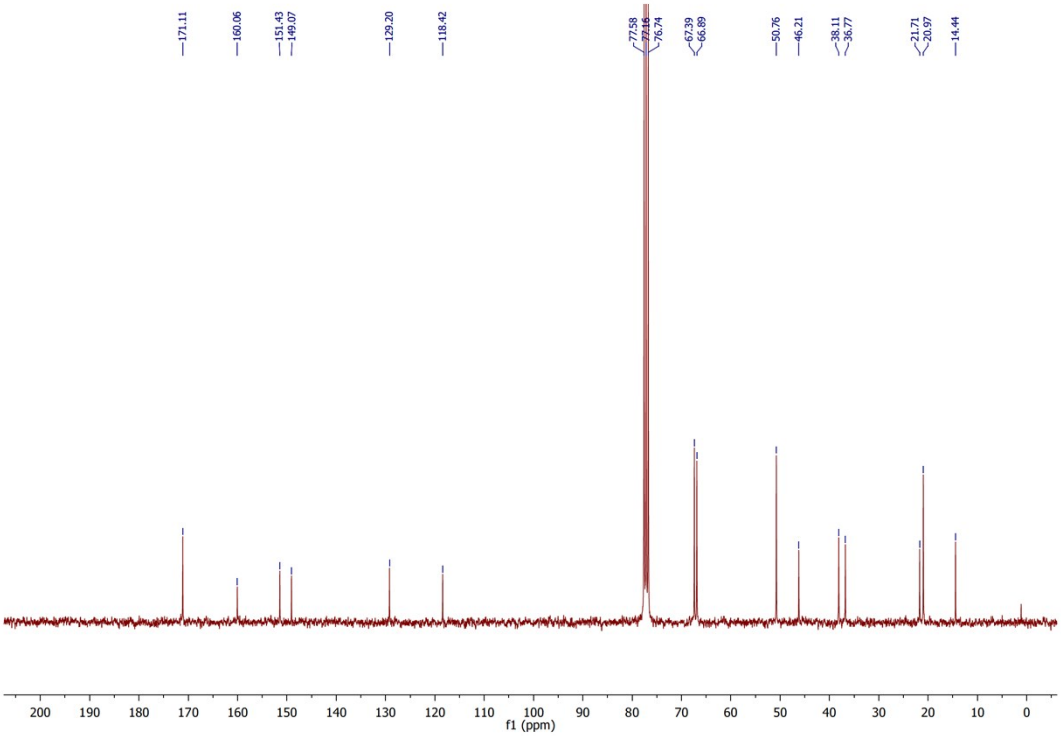
3.12
5.82
f1 (ppm)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77.16
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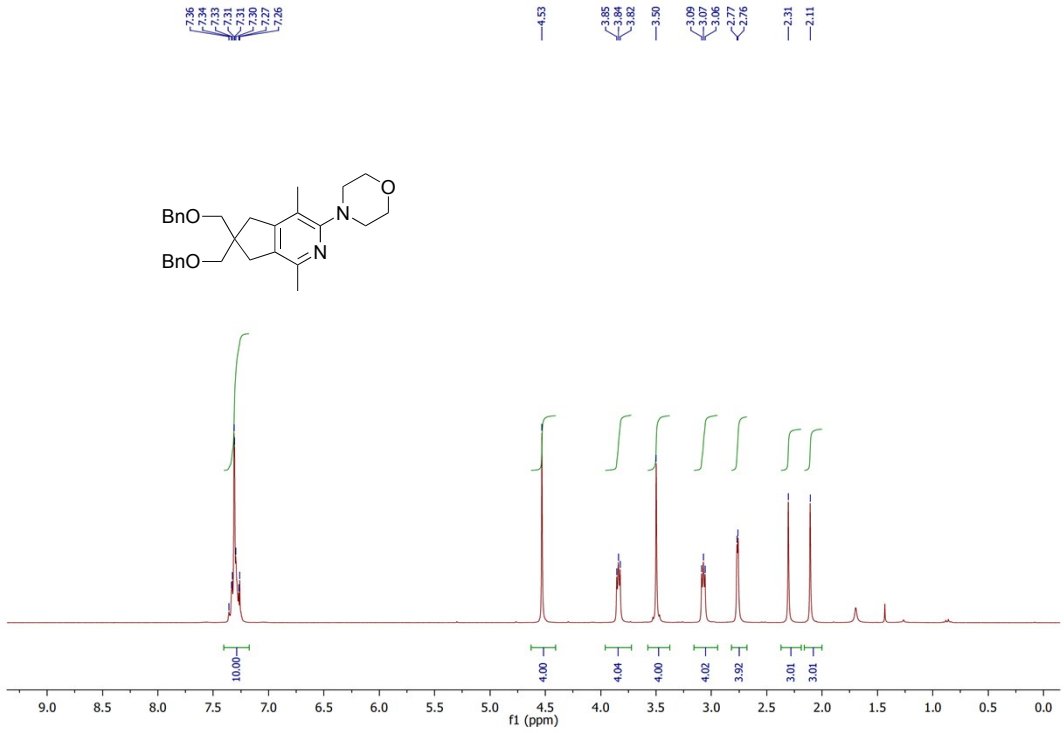
36.77
21.71
20.97
14.44
f1 (ppm)

7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7.31
7.30
7.27
7.26
4.53
3.85
3.84
3.82
3.50
3.09
3.07
3.06
2.77
2.76
2.31
2.11
BnO
BnO
O
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N
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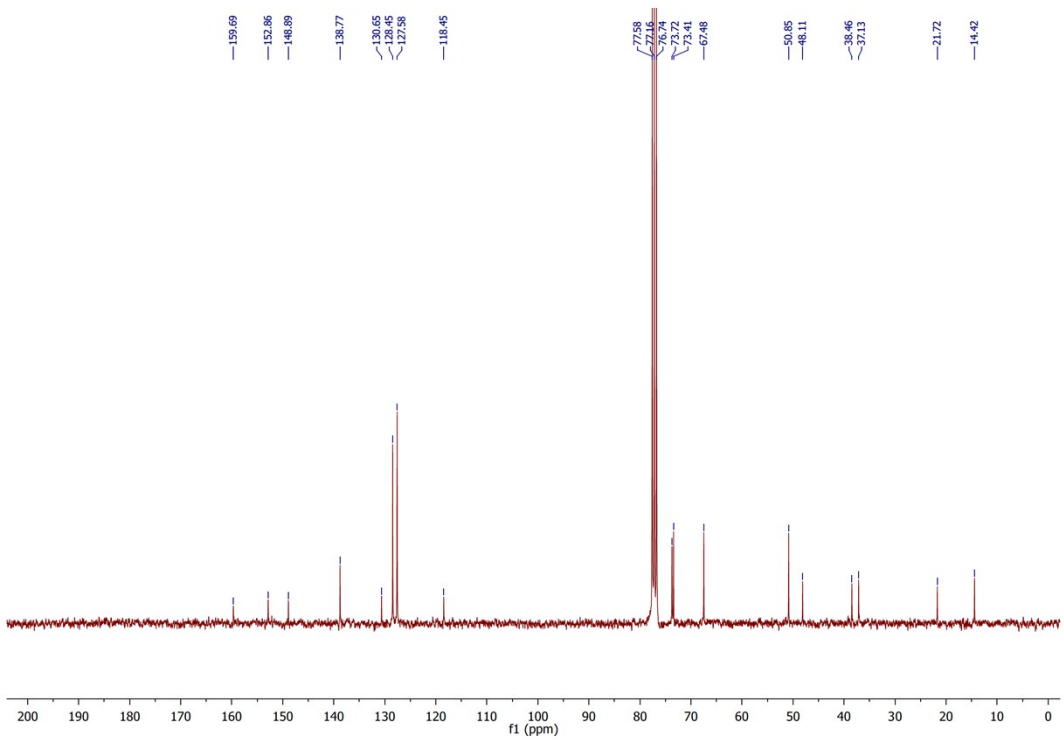
4.00
4.02
3.92
3.01
3.01
f1 (ppm)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118.45
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77.16
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38.46
37.13
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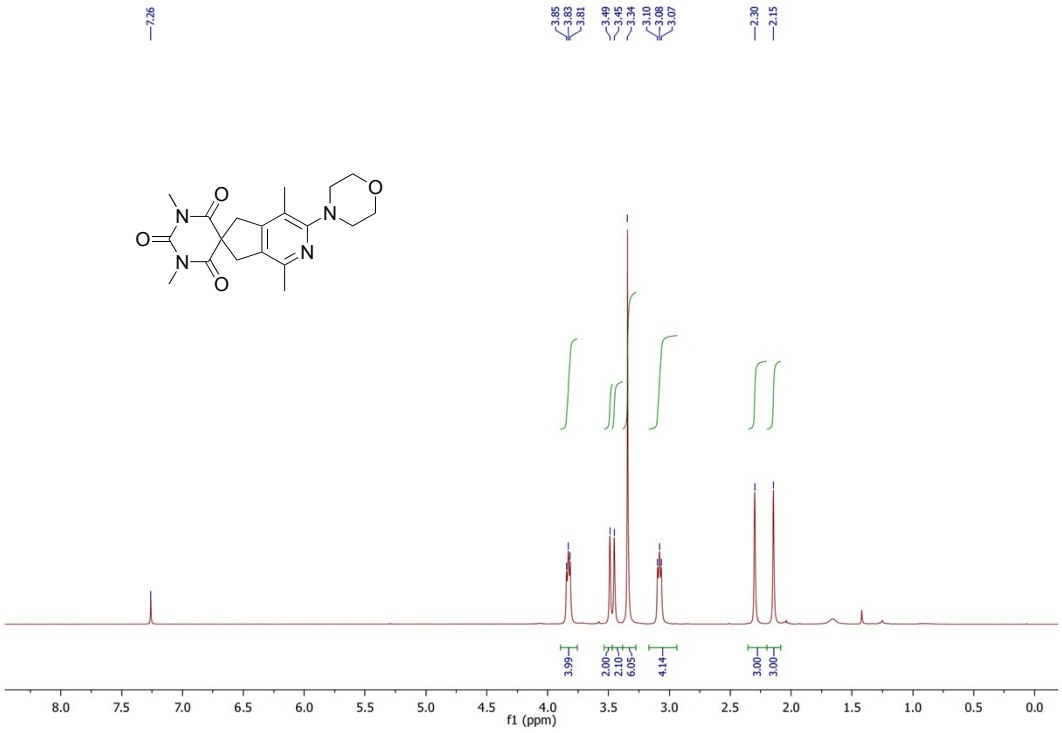
14.42
f1 (ppm)

8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3.81
3.49
3.45
3.34
3.10
3.08
3.07
2.30
2.15
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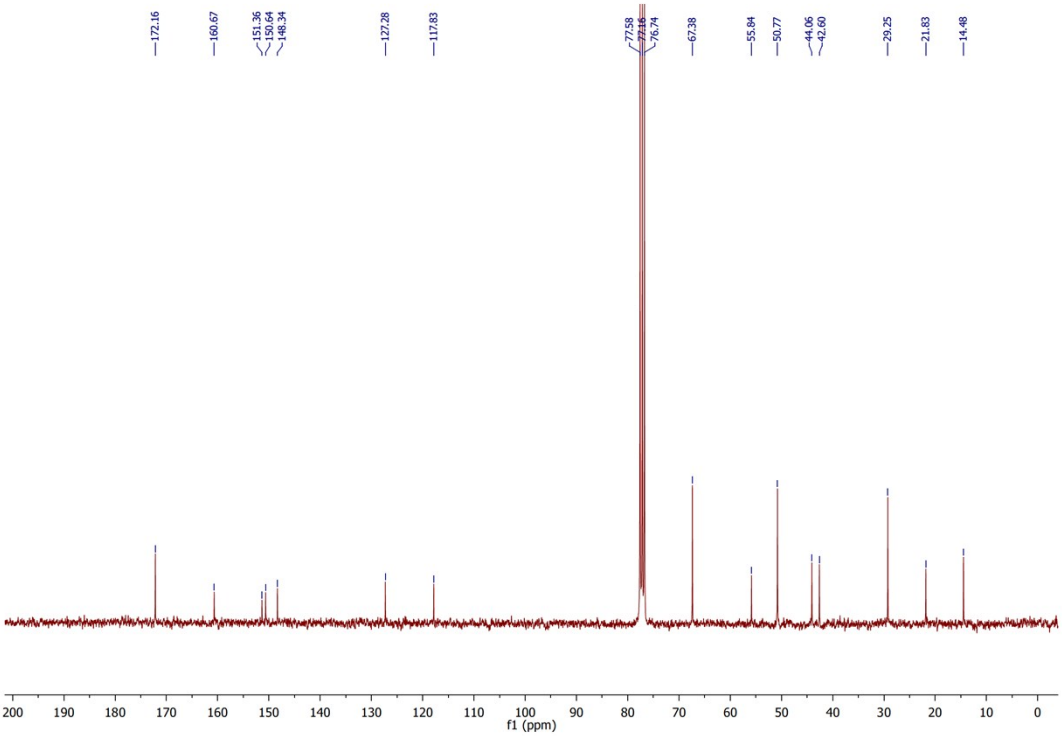
6.05
4.14
3.00
3.00
f1 (ppm)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148.34
127.28
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77.58
77.16
76.74
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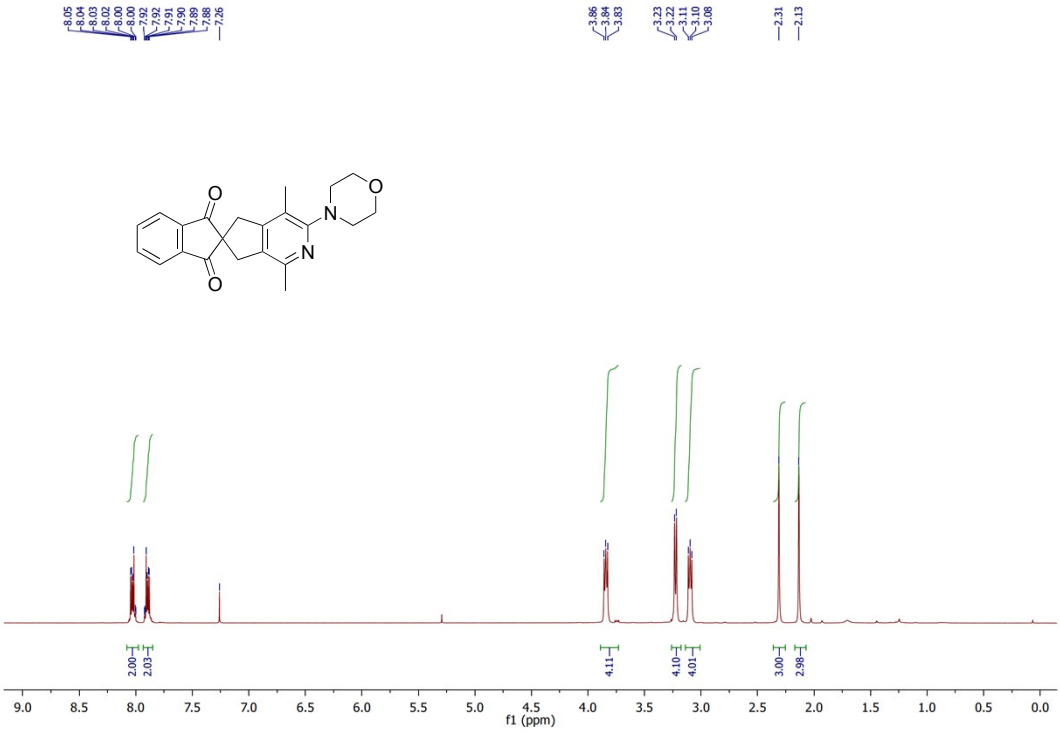
42.60
29.25
21.83
14.48
f1 (ppm)

9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8.02
8.00
8.00
7.92
7.92
7.91
7.90
7.89
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4.01
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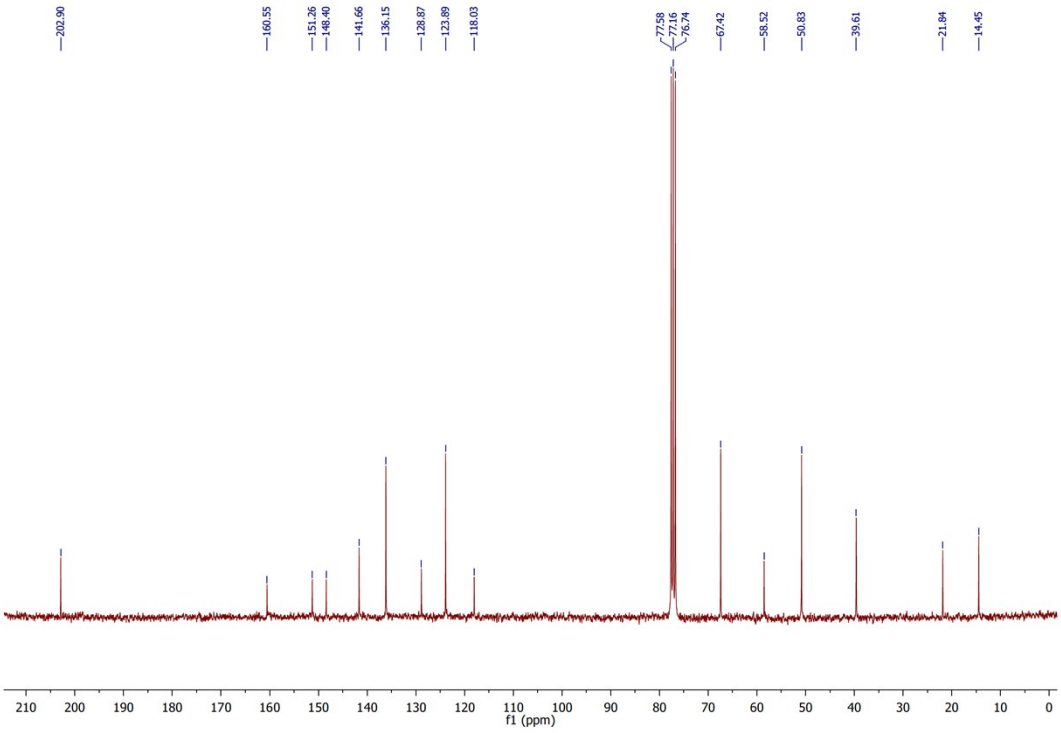
2.98
f1 (ppm)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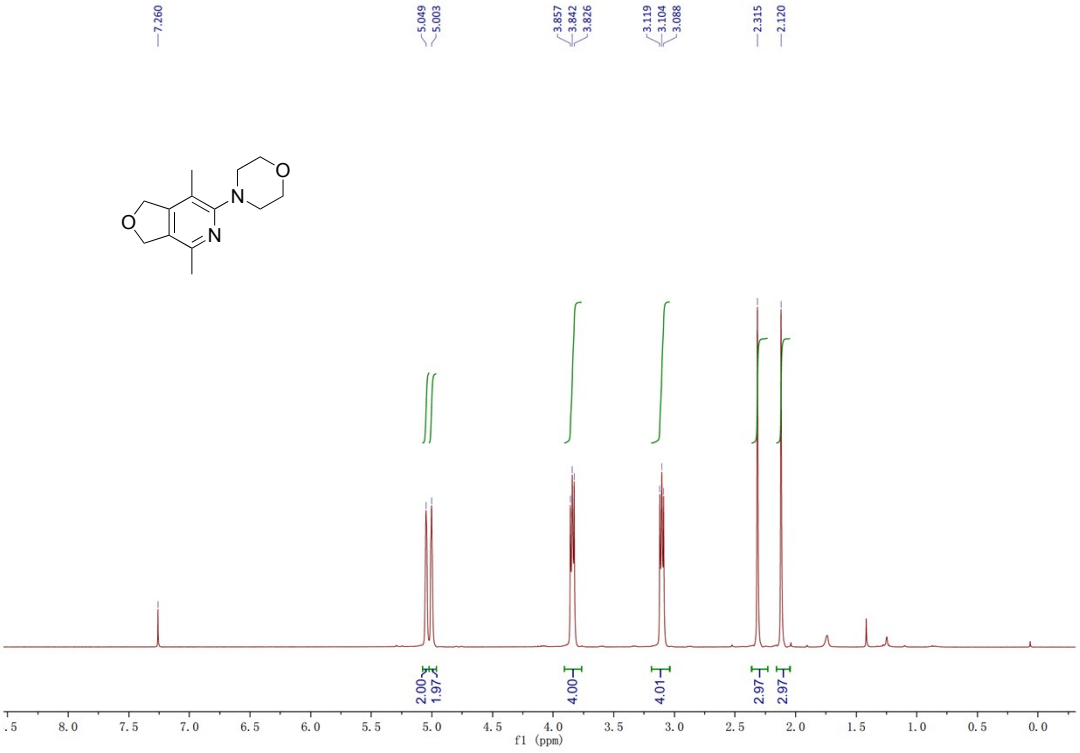
39.61
21.84
14.45
f1 (ppm)

10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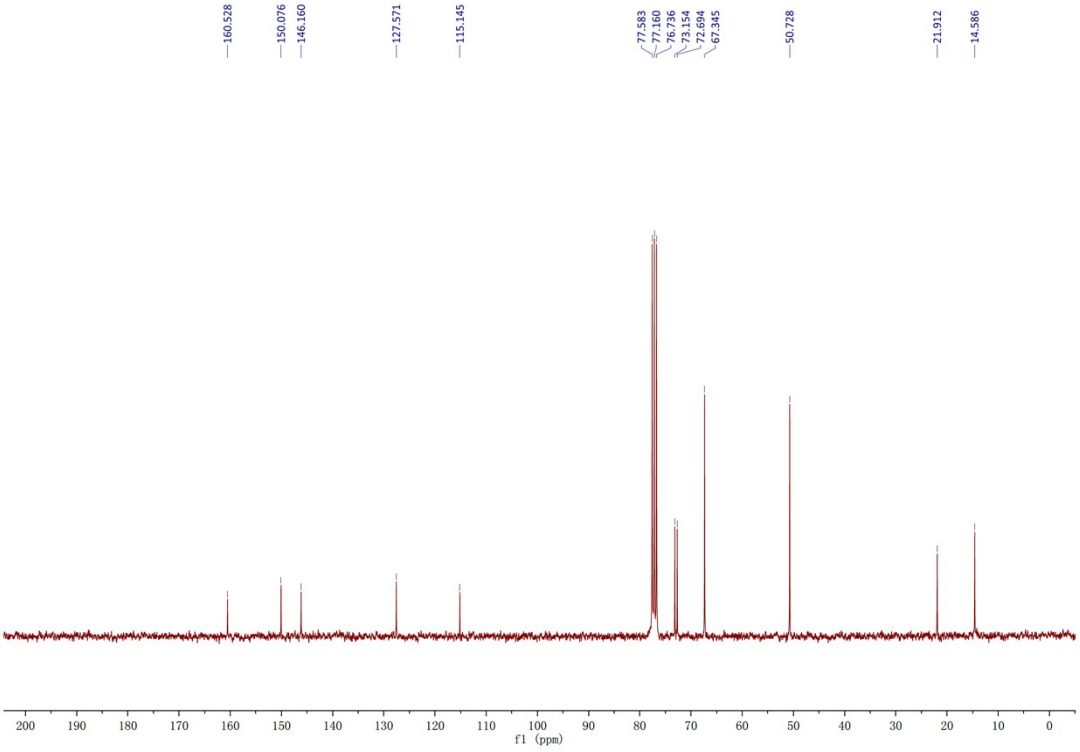
1.97
4.00
4.01
2.97
2.97
f1 (ppm)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77.160
76.736
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50.728
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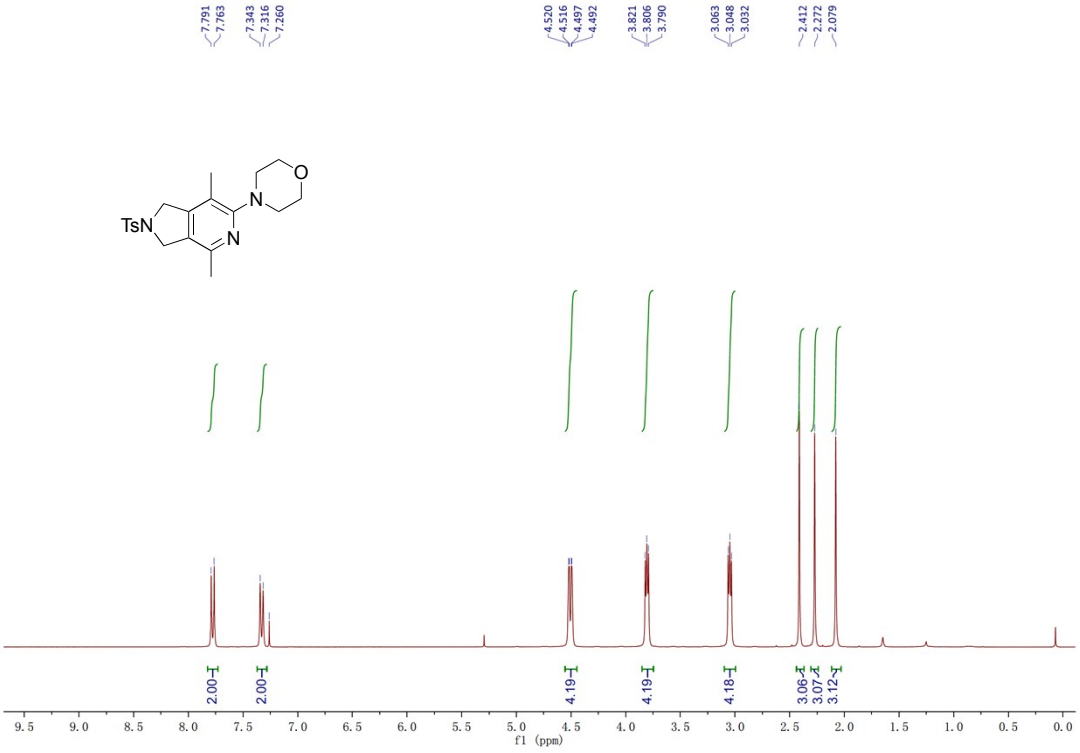
14.586
f1 (ppm)

11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7.260
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4.516
4.497
4.492
3.821
3.806
3.790
3.063
3.048
3.032
2.412
2.272
2.079
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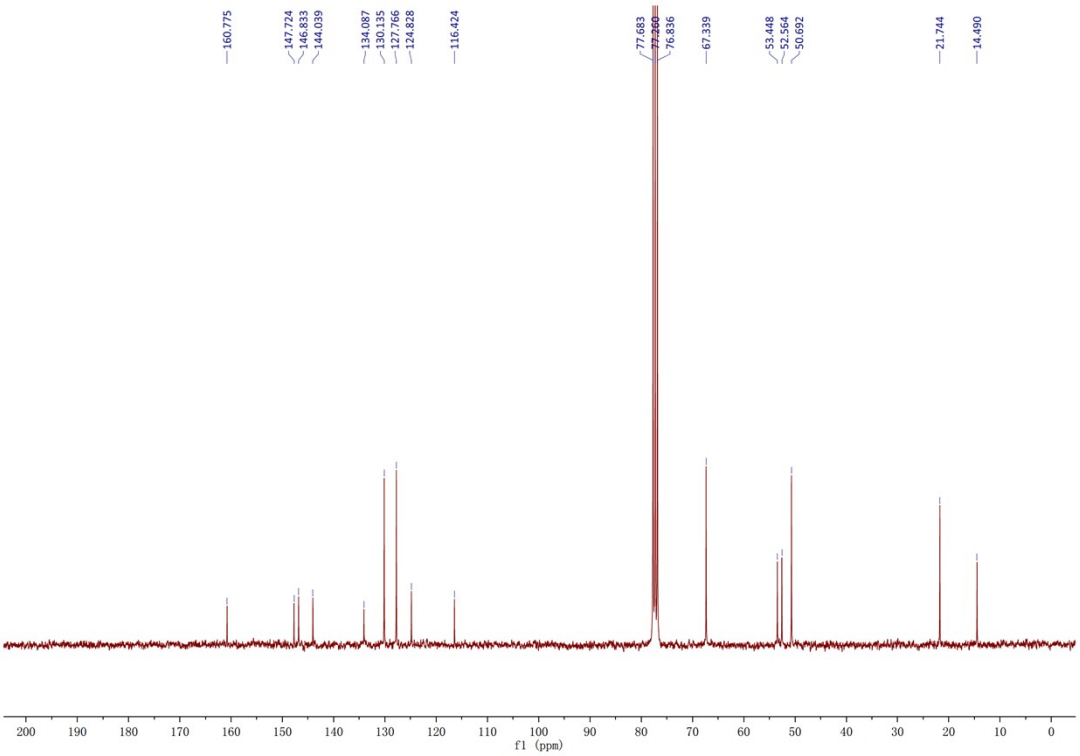
2.00
4.19
4.19
4.18
3.06
3.07
3.12
f1 (ppm)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144.039
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130.135
127.766
124.828
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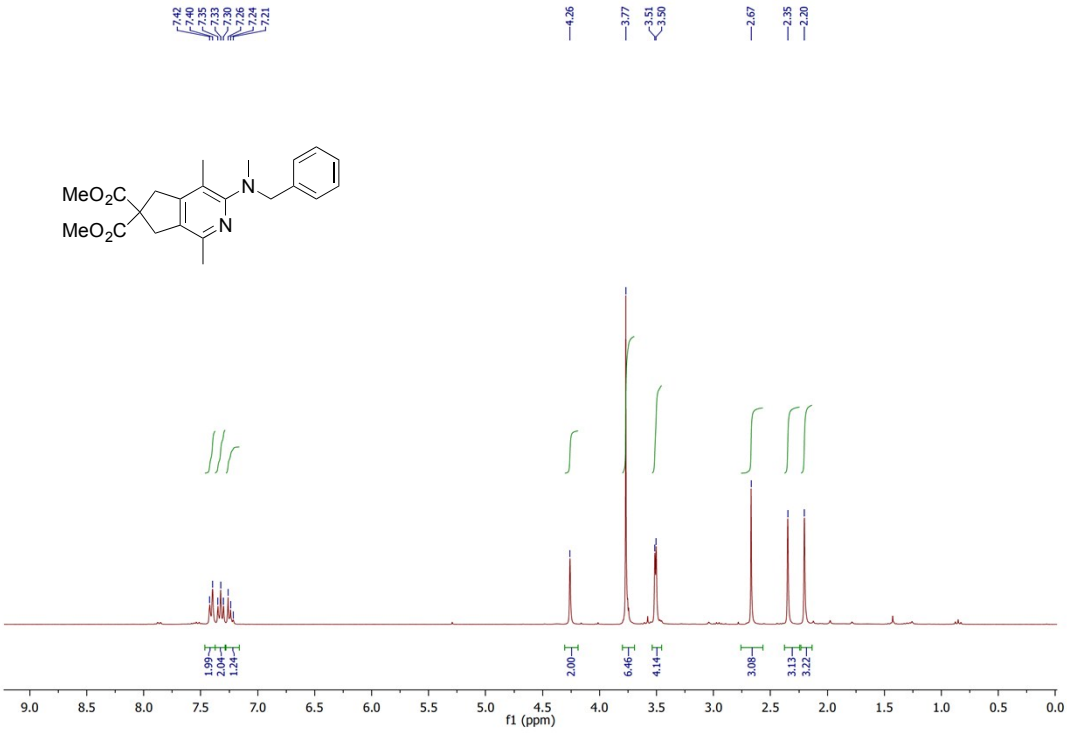
f1 (ppm)

15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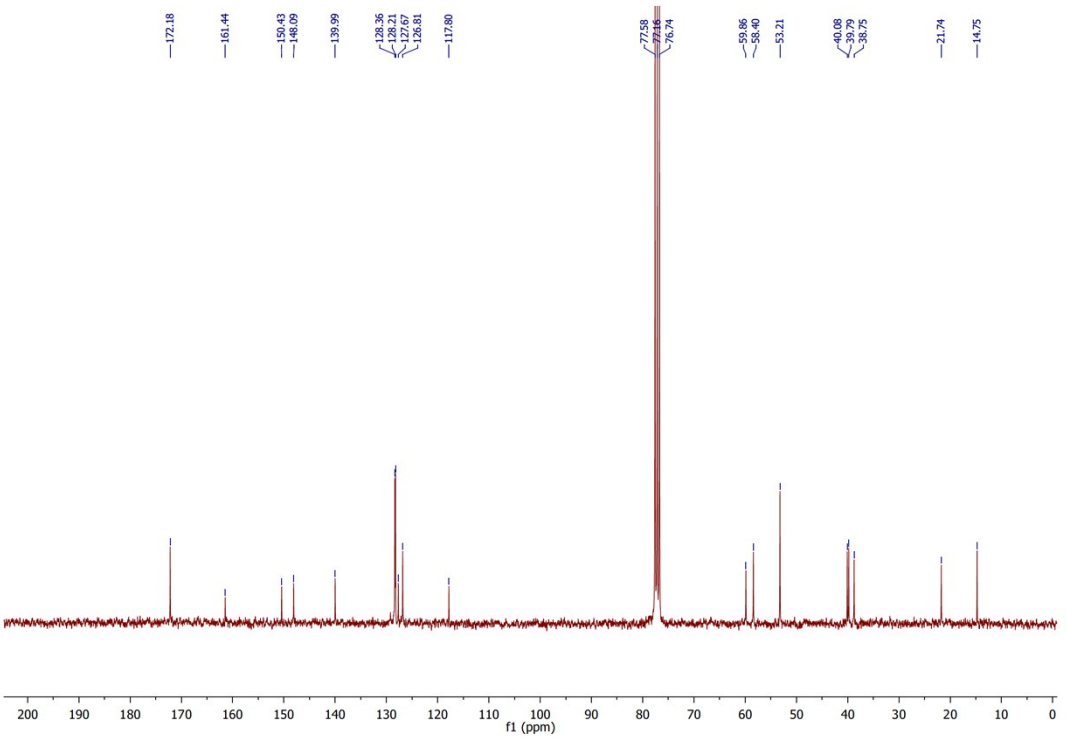
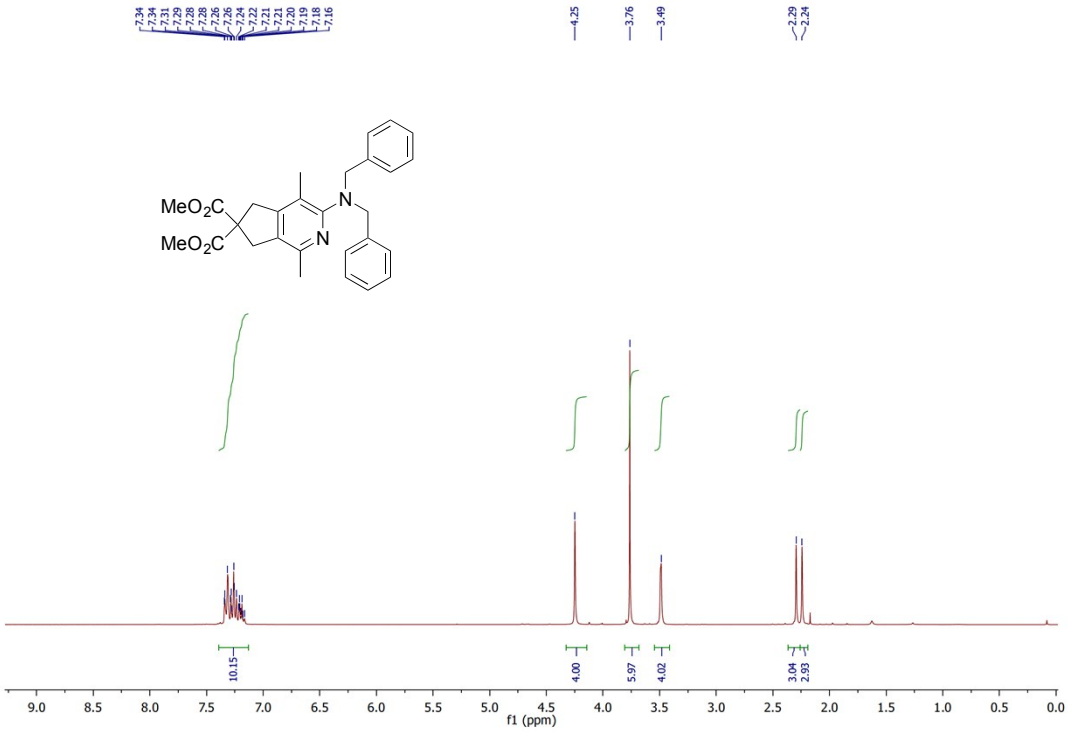
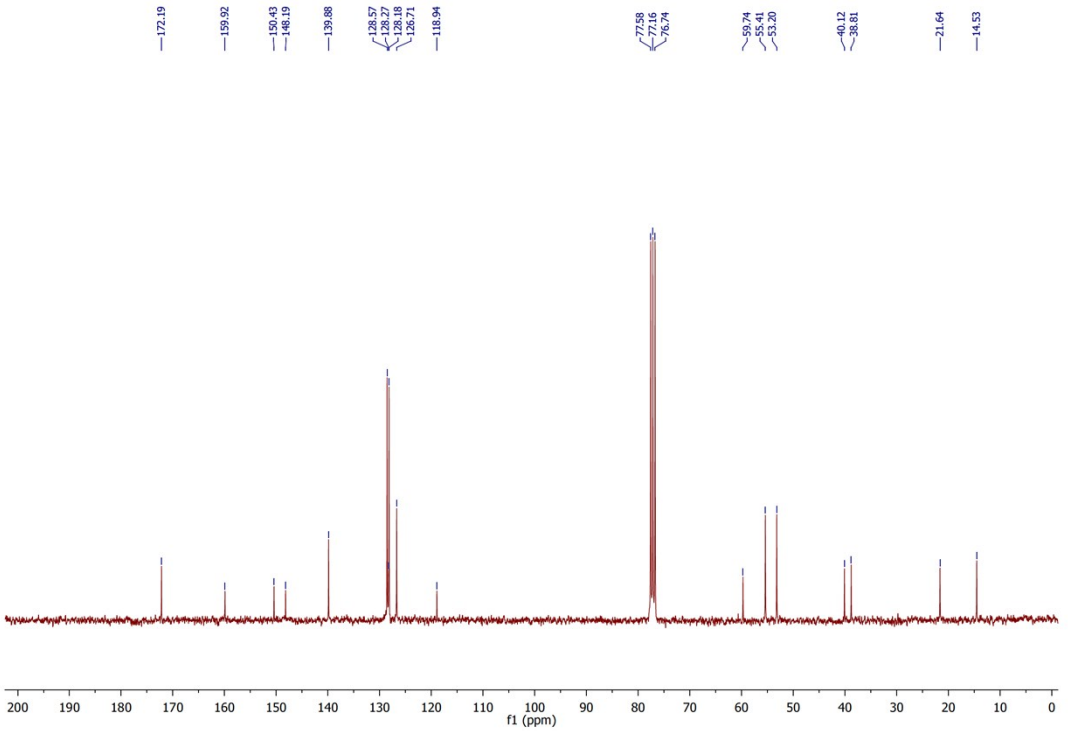
7.40
7.35
7.33
7.30
7.26
7.24
7.21
4.26
3.77
3.51
3.50
2.67
2.35
2.20
MeO2C
MeO2C
N
N
1.99
2.04
1.24
2.00
6.46
4.14
3.08
3.13
3.22
f1 (ppm)

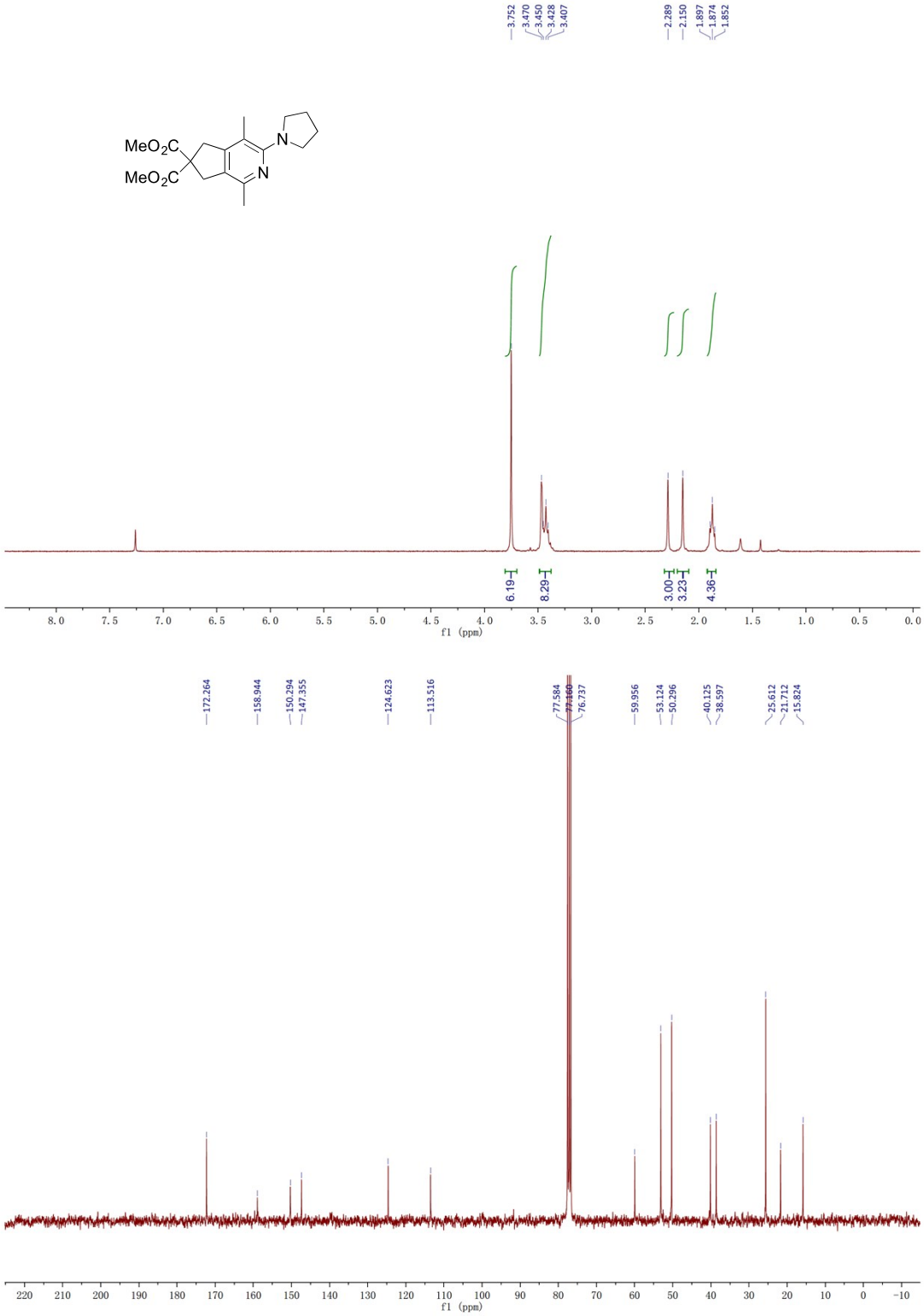

172.18
161.44
150.43
148.09
139.99
128.36
128.21
127.67
126.81
117.80
77.58
77.16
76.74
59.86
58.40
53.21
40.08
39.79
38.75
21.74
14.75
f1 (ppm)

16

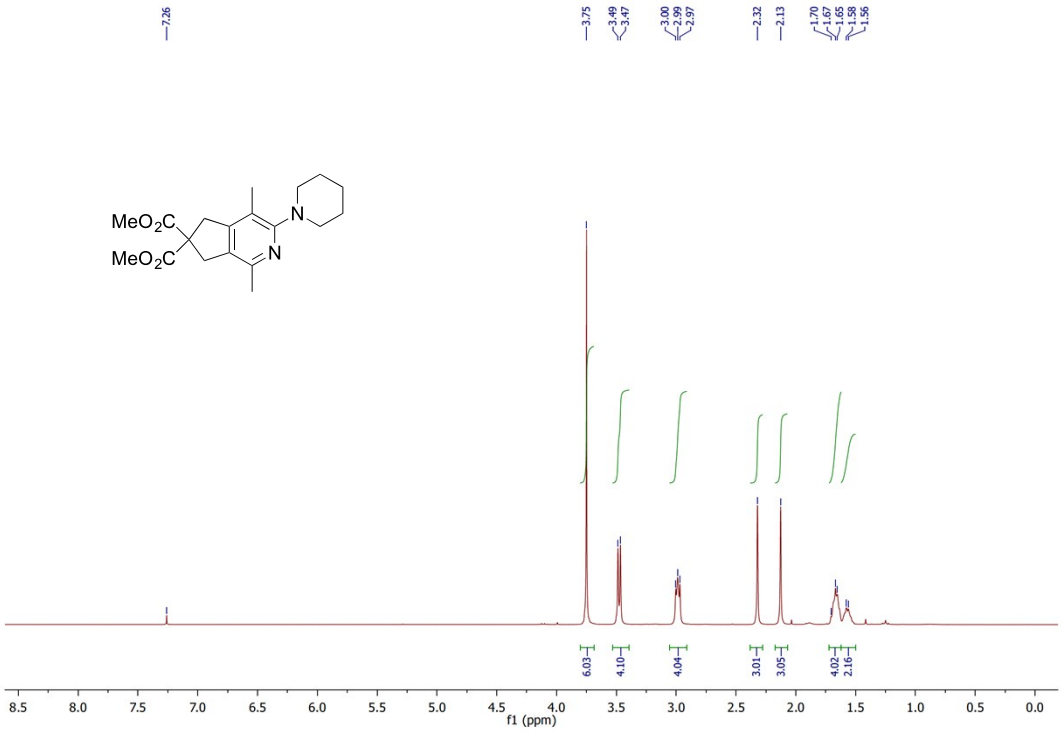

7.34
7.34
7.31
7.29
7.28
7.28
7.26
7.24
7.22
7.21
7.21
7.20
7.19
7.18
7.16
4.25
3.76
3.49
2.29
2.24
MeO2C
MeO2C
N
N
10.15
4.00
5.97
4.02
3.04
2.93
f1 (ppm)

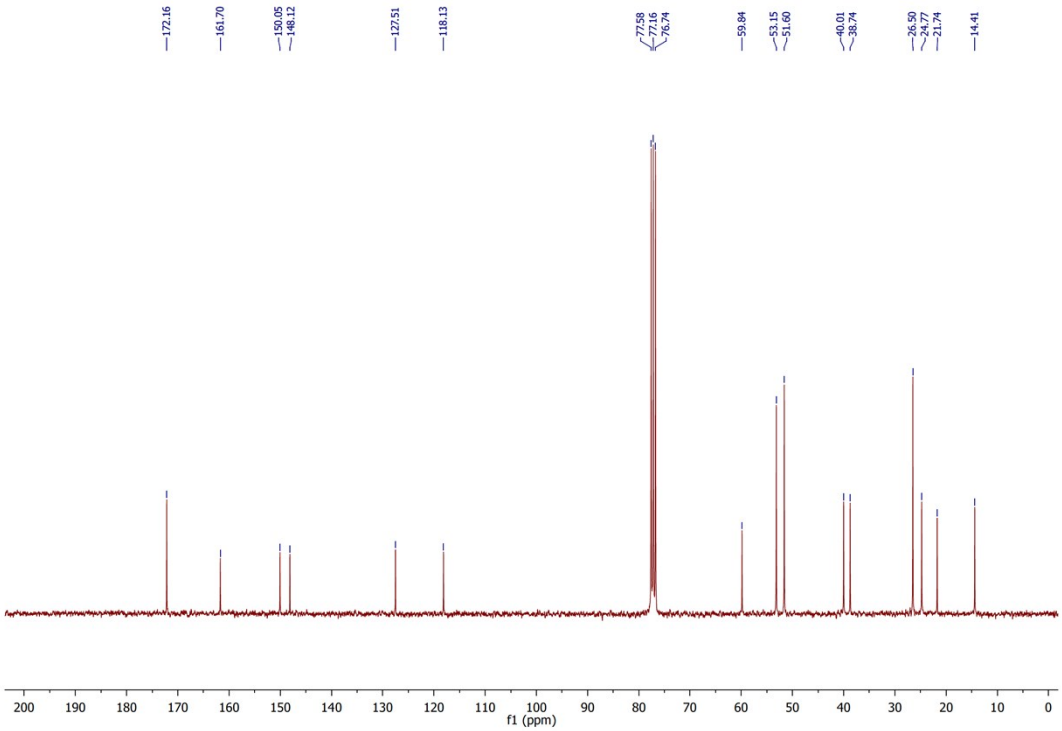

172.19
159.92
150.43
148.19
139.88
128.57
128.27
128.18
126.71
118.94
77.58
77.16
76.74
59.74
55.41
53.20
40.12
38.81
21.64
14.53
f1 (ppm)

17

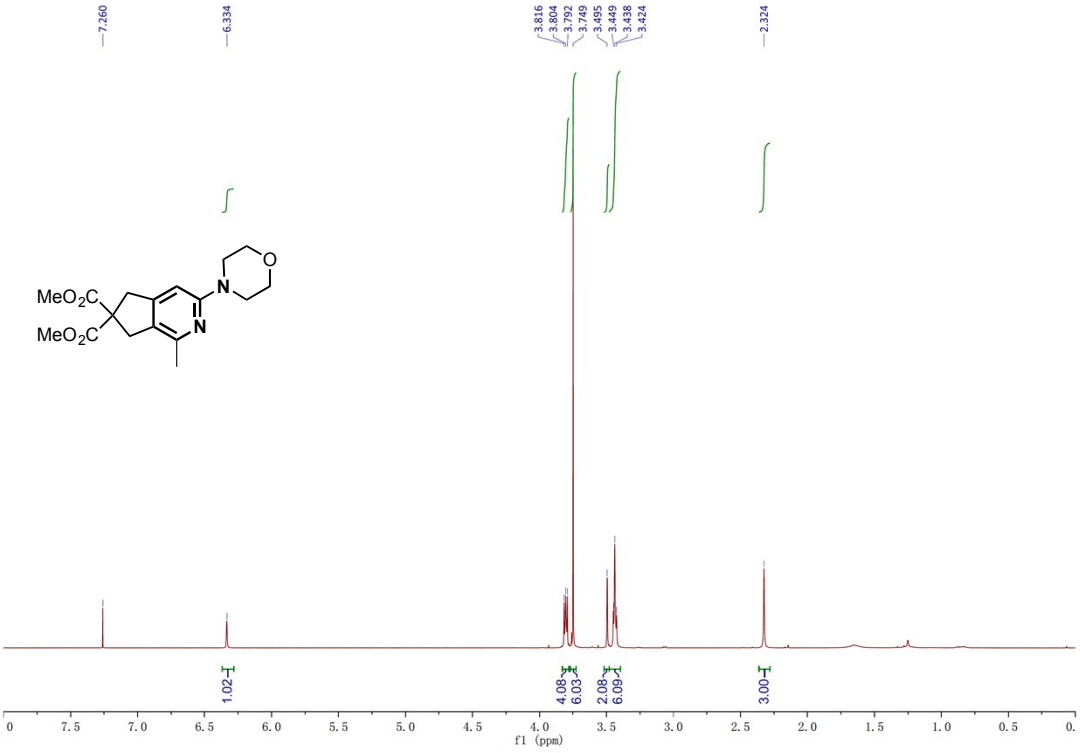

3.752
3.470
3.450
3.428
3.407
2.289
2.150
1.897
1.874
1.852
MeO2C
MeO2C
N
N
6.19
8.29
3.00
3.23
4.36
f1 (ppm)
172.264
158.944
150.294
147.355
124.623
113.516
77.584
77.160
76.737
59.956
53.124
50.296
40.125
38.597
25.612
21.712
15.824
f1 (ppm)

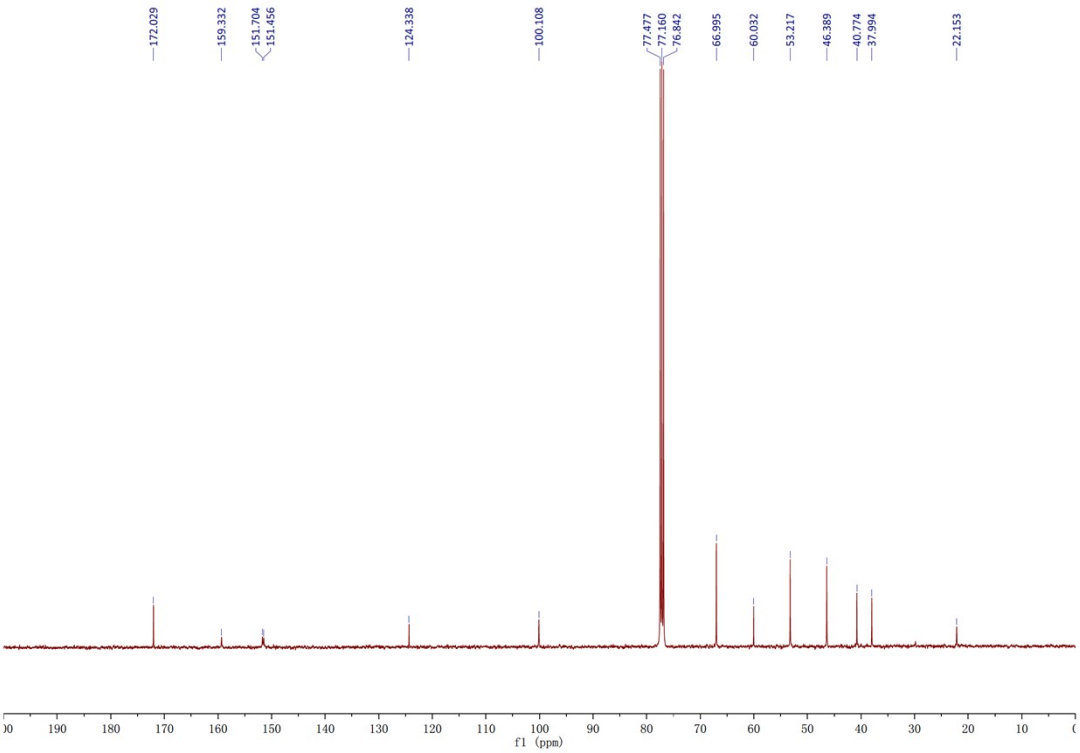
18


7.26
3.75
3.49
3.47
3.00
2.99
2.97
2.32
2.13
1.70
1.67
1.65
1.58
1.56
MeO2C
MeO2C
N
N
6.03
4.10
4.04
3.01
3.05
4.02
2.16
f1 (ppm)

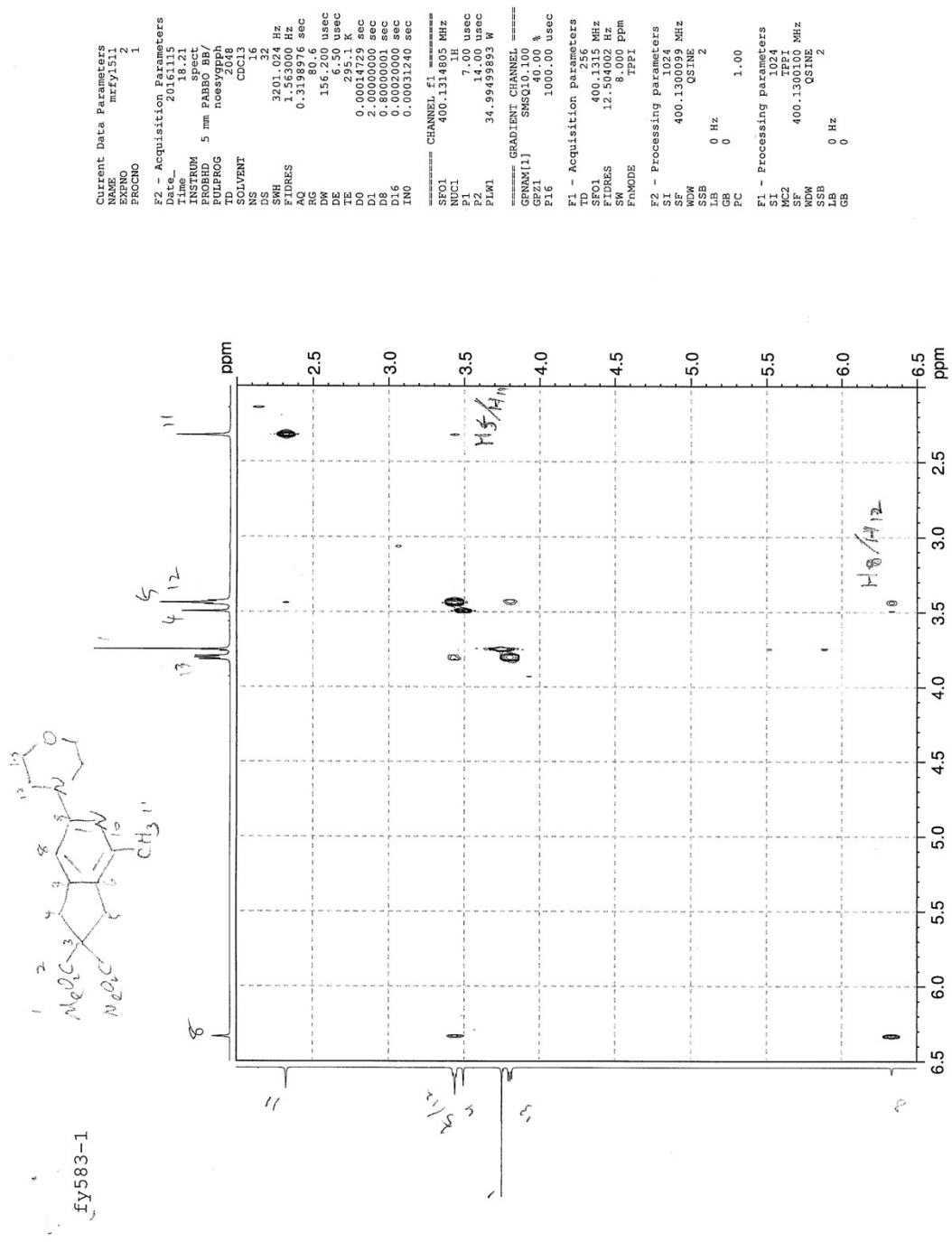

172.16
161.70
150.05
148.12
127.51
118.13
77.58
77.16
76.74
59.84
53.15
51.60
40.01
38.74
26.50
24.77
21.74
14.41
f1 (ppm)

20

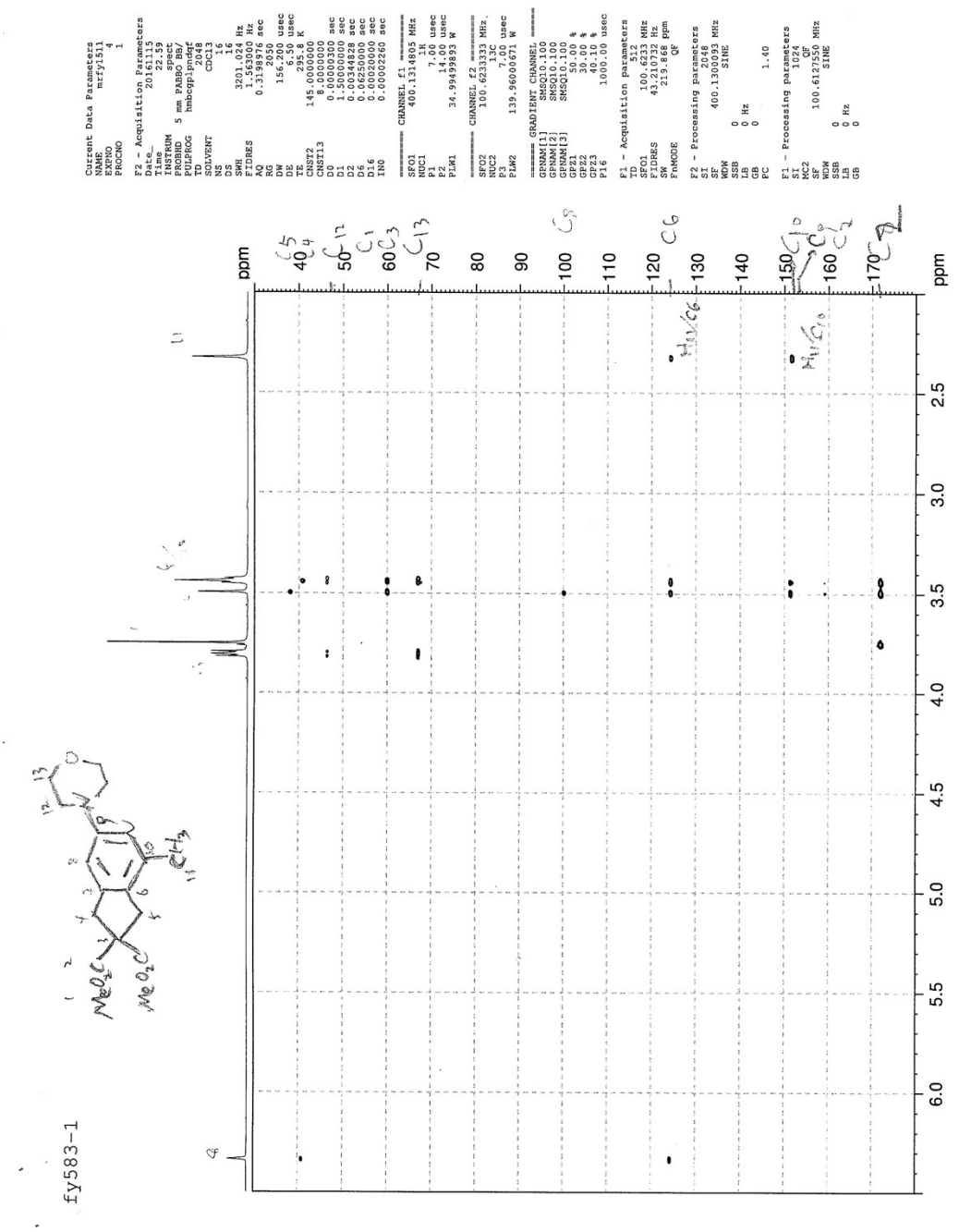

7.260
6.334
3.816
3.804
3.792
3.749
3.495
3.449
3.438
3.424
2.324
MeO2C
MeO2C
N
O
N
1.02
4.08
6.03
2.08
6.09
3.00
f1 (ppm)


172.029
159.332
151.704
151.456
124.338
100.108
77.477
77.160
76.842
66.995
60.032
53.217
46.389
40.774
37.994
22.153
f1 (ppm)

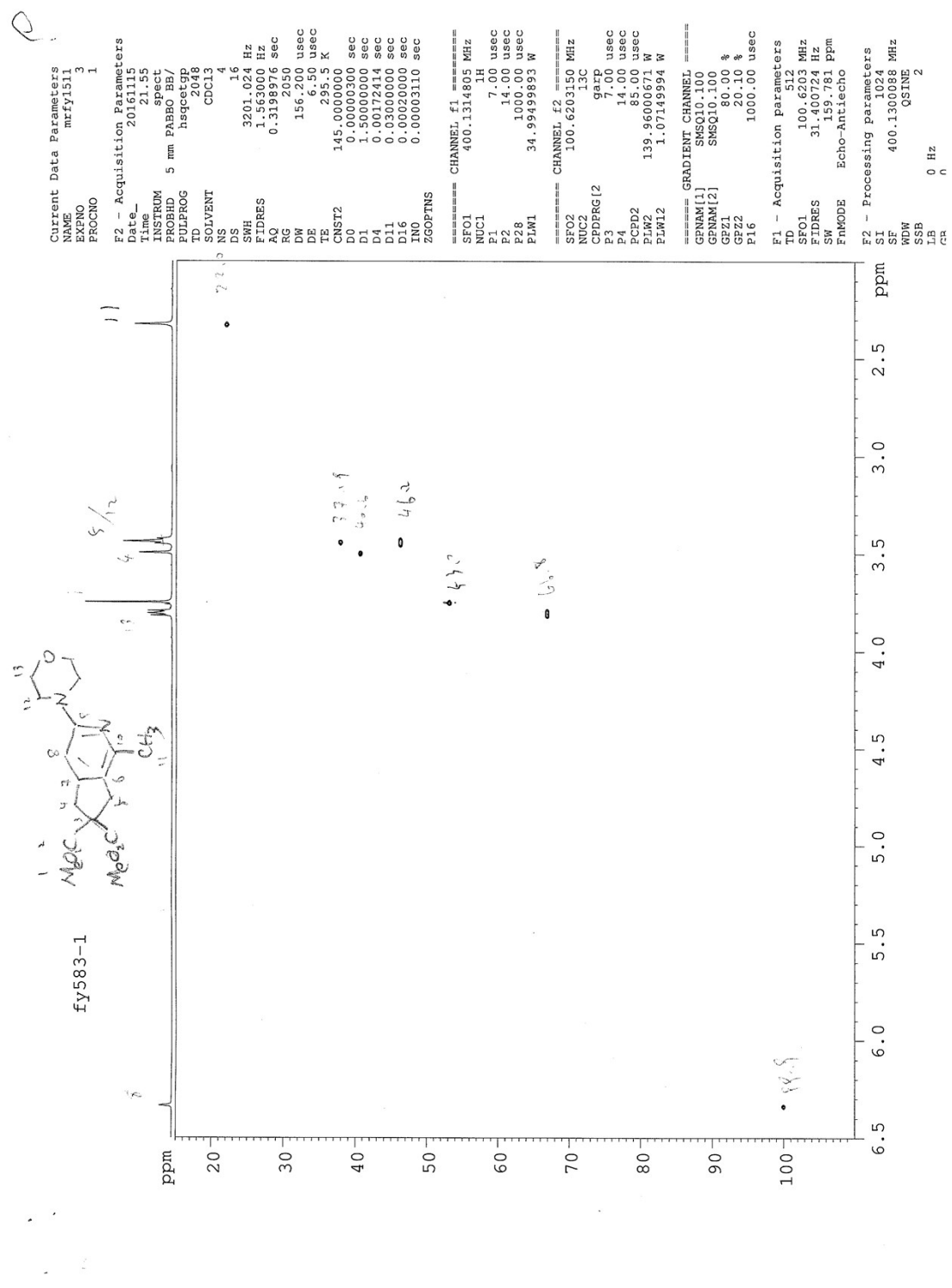
NOESY


Current Data Parameters
NAME mrfy1521
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161115
Time 18.21
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 16
DS 16
SWH 3201.024 Hz
FIDRES 1.563000 Hz
AQ 0.3198976 sec
RG 80.6
DW 156.200 usec
DE 6.50 usec
TE 295.1 K
D0 0.00014729 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
IN0 0.00031240 sec
======== CHANNEL f1 ========
SFO1 400.1314805 MHz
NUC1 1H
P1 7.00 usec
P2 14.00 usec
PLW1 34.99499893 W
======== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 400.1315 MHz
FIDRES 12.504002 Hz
SW 8.000 ppm
FnMODE TPPI
F2 - Processing parameters
SI 1024
SF 400.1300099 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 400.1300100 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
ppm
fy583-1

HMBC


fy583-1
Current Data Parameters
NAME mrfy1511
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161115
Time 22.59
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG hmbcgplpndqf
TD 2048
SOLVENT CDCl3
NS 16
DS 16
SWH 3201.024 Hz
FIDRES 1.563000 Hz
AQ 0.319836 sec
RG 2050
DW 156.200 usec
DE 6.50 usec
TE 295.8 K
CNST2 145.0000000
CNST13 8.0000000
D0 0.000003000 sec
D1 1.50000000 sec
D2 0.00345828 sec
D5 0.00250000 sec
D16 0.00020000 sec
IN0 0.00002260 sec
CHANNEL f1
SFO1 400.1314805 MHz
NUC1 1H
P1 7.00 usec
P2 14.00 usec
PLW1 34.99499893 W
CHANNEL f2
SFO2 100.6233333 MHz
NUC2 13C
P3 7.00 usec
PLW2 139.96000671 W
GRADIENT CHANNEL
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPZ1 50.00 %
GPZ2 80.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 100.6233 MHz
FIDRES 43.210732 Hz
SW 219.868 ppm
FnMODE QF
F2 - Processing parameters
SI 2048
SF 400.1300093 MHz
WDW SINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 QF
SF 100.6127550 MHz
WDW SINE
SSB 0
LB 0 Hz
GB 0
ppm
MeO2C
MeO2C
Et-I3
C5
C4
C12
C1
C3
C13
C8
C6
C10
C9
C2
C7
H1/C6
H11/C10
ppm

HSQC


Current Data Parameters
NAME mrfy1511
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161115
Time 21.55
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG hsqcetgp
TD 2048
SOLVENT CDCl3
NS 4
DS 16
SWH 3201.024 Hz
FIDRES 1.563000 Hz
AQ 0.3198976 sec
RG 2050
DW 156.200 usec
DE 6.50 usec
TE 295.5 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
IN0 0.00003110 sec
ZGOPTNS
CHANNEL f1
SFO1 400.1314805 MHz
NUC1 1H
P1 7.00 usec
P2 14.00 usec
P28 1000.00 usec
PLW1 34.99499893 W
CHANNEL f2
SFO2 100.6203150 MHz
NUC2 13C
CPDPRG[2 garp
P3 7.00 usec
P4 14.00 usec
PCPD2 85.00 usec
PLW2 139.96000671 W
PLW12 1.07149994 W
GRADIENT CHANNEL
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 100.6203 MHz
FIDRES 31.400724 Hz
SW 159.781 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 1024
SF 400.1300988 MHz
WDW QSINE
SSB 2
LB 0 Hz
fy583-1
ppm