

Cycloaddition of Benzo[*d*]thiazoles with Imidazol-4-one Activated Donor-Acceptor Cyclopropanes. Synthesis of Spirocyclic Inhibitors of HIV-1

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General experimentation

All reactions were performed in round-bottom flasks fitted with rubber septa unless otherwise noted. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Air- and moisture-sensitive liquids were transferred by syringe. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (silica gel 60 F₂₅₄, Merck, Germany; Alugram® SIL G UV₂₅₄, Macherey-Nagel; Germany or ПТСХ-АФ-А-УФ, Sorbfil, Russia) TLC plates were visualized by exposure to 254 nm ultraviolet light (UV) or were stained by submersion in acidic ethanolic solution of vanillin followed by brief heating (vanillin). Flash-column chromatography was carried out on silica gel (60 Å, 40–63 µm, VWR). All solvents for chromatography and extractions were “XЧ” grade (>99% purity) and used as received.

All reagents were obtained from commercial suppliers (Acros Organics, Macklin, ACMEC, Lachema, Reanal, DalChem, ChimMed, RusKhim) and were used without further purification. CH₂Cl₂ for reactions was stored over CaH₂ and distilled directly prior use.

Melting points were measured using PHMK 81/3199 melting point apparatus (VEB Wägetechnik Rapido, DDR).

Nuclear magnetic resonance spectra were recorded using Bruker Avance II/Fourier 300 instrument at indicated temperature. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant (*J*) in Hertz, integration. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvents (CHCl₃, δ 7.26 ppm). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvents (CDCl₃, δ 77.16 ppm).

High-resolution mass spectra were recorded on a Bruker micrOTOF-Q II mass spectrometer using electrospray ionization (ESI–TOF).

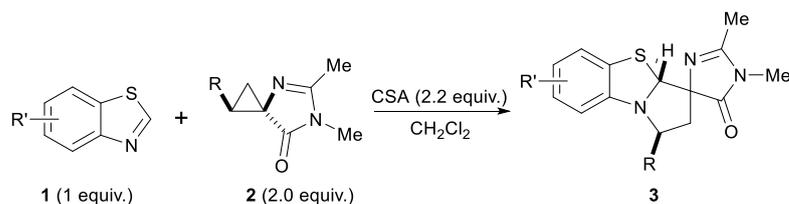
Synthesis of starting materials

Benzo[*d*]thiazole is commercially available. The rest of the benzothiazoles was obtained following the literature method from commercially available anilines or 2-aminobenzo[*d*]thiazoles.^{S1,2}

Donor-acceptor cyclopropanes with imidazole-4-one acceptor group were prepared according to a previously described protocol.^{S3}

Cycloaddition studies

General procedure

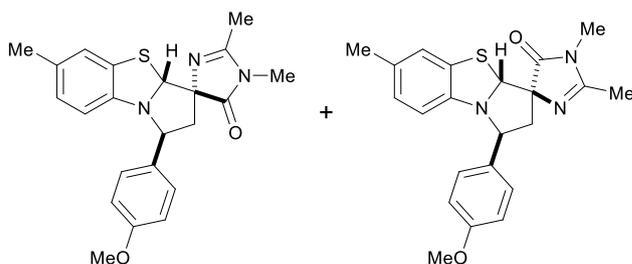


General procedure:

(±)-Camphorsulfonic acid (153 mg, 0.66 mmol, 2.2 equiv.) was added to a stirred solution of a benzothiazole **1** (0.30 mmol, 1 equiv.) and a DAC **2** (0.60 mmol, 2.0 equiv.) in dichloromethane (1.5 mL). The reaction was stirred overnight¹ and then quenched with 1,1,3,3-tetramethylguanidine (0.11 mL, 104 mg, 0.90 mmol, 3.0 equiv.). The resulting mixture was subjected to column chromatography on silica (eluent: hexane/EtOAc, 1/3) to furnish target products **3** (combined yields 29-87%).

¹ *Note:* The completion of the reaction might take 2-5 days for less reactive cyclopropanes **2d-f**. Specific notes are provided for the corresponding examples.

Benzothiazoles scope



1-(4-Methoxyphenyl)-1',2',6-trimethyl-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3aa**

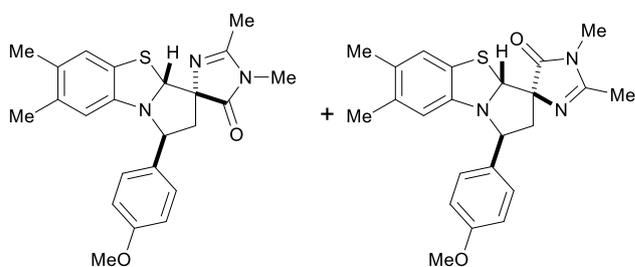
Yield 84 mg (0.21 mmol, 71%). Isolated as a mixture of diastereomers, *dr* = 2.1:1.

Yellowish solid, mp = 161–163 °C. *R_f* = 0.28 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): **trans-3aa**, major diastereomer: δ = 7.41 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.79 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 5.79 (s, 1H), 4.82 (dd, *J* = 10.1, 7.0 Hz, 1H), 3.82 (s, 3H), 3.10 (s, 3H), 2.48–2.29 (m, 2H), 2.24 (s, 3H), 2.18 (s, 3H); **cis-3aa**, minor diastereomer: δ = 7.40 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.75 (s, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.21 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 1H), 5.02 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.82 (s, 3H), 3.03 (s, 3H), 2.48–2.29 (m, 2H), 2.24 (s, 3H), 2.16 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): **trans-3aa**, major diastereomer: δ = 179.8, 161.4, 159.1, 147.8, 135.1, 130.3, 127.6, 127.4 (×2), 125.9, 121.9, 114.3 (×2), 110.3, 80.2, 78.9, 69.2, 55.5, 44.7, 27.0, 20.8, 15.7; **cis-3aa**, minor diastereomer: δ = 181.5, 163.0, 159.1, 147.8, 135.4, 130.2, 127.5 (×2), 127.0, 125.9, 121.7, 114.4 (×2), 109.9, 80.0, 76.5, 68.1, 55.5, 43.1, 26.5, 20.9, 16.0.

HRMS (ESI+) *m/z*: calculated for C₂₂H₂₄N₃O₂S⁺ (M+H⁺) 394.1584, found 394.1588.



1-(4-Methoxyphenyl)-1',2',6,7-tetramethyl-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3ba**

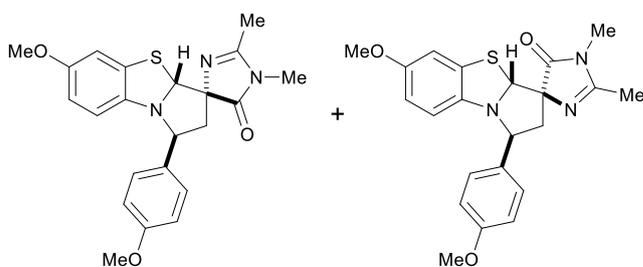
Yield 82 mg (0.20 mmol, 67%). Isolated as a mixture of diastereomers, *dr* = 2.3:1.

Yellowish solid, mp = 97–99 °C. *R_f* = 0.35 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): **trans-3ba**, major diastereomer: δ = 7.42 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.74 (s, 1H), 6.18 (s, 1H), 5.75 (s, 1H), 4.84 (t, *J* = 8.6 Hz, 1H), 3.82 (s, 3H), 3.08 (s, 3H), 2.44–2.33 (m, 2H), 2.23 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H); **cis-3ba**, minor diastereomer: δ = 7.41 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.70 (s, 1H), 6.13 (s, 1H), 5.87 (s, 1H), 5.03 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.44–2.33 (m, 2H), 2.23 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): **trans-3ba**, major diastereomer: δ = 179.6, 161.2, 159.0, 148.2, 135.3, 133.5, 128.6, 127.3 (×2), 123.8, 122.2, 114.3 (×2), 111.9, 80.2, 79.0, 68.9, 55.4, 44.4, 26.9, 19.8, 19.3, 15.6; **cis-3ba**, minor diastereomer: δ = 181.8, 163.0, 159.0, 148.1, 135.6, 133.3, 128.5, 127.3 (×2), 123.3, 122.0, 114.3 (×2), 111.6, 80.0, 76.5, 67.9, 55.4, 43.0, 26.4, 19.8, 19.4, 15.9.

HRMS (ESI+) *m/z*: calculated for C₂₃H₂₆N₃O₂S⁺ (M+H⁺) 408.1740, found 408.1746.



6-Methoxy-1-(4-methoxyphenyl)-1',2'-dimethyl-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one 3ca

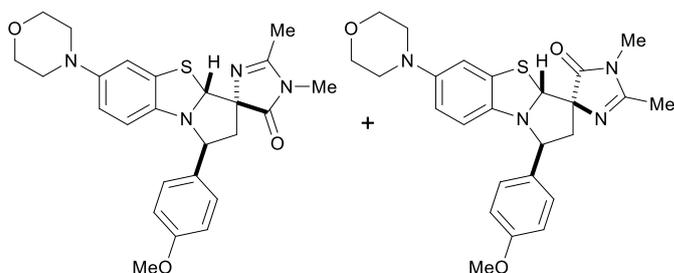
Yield 88 mg (0.22 mmol, 72%). Isolated as a mixture of diastereomers, *dr* = 2.1:1.

Yellowish solid, mp = 114–116 °C. *R_f* = 0.31 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): *trans*-**3ca**, major diastereomer: δ = 7.42 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.38 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.25 (d, *J* = 8.5 Hz, 1H), 5.81 (s, 1H), 4.79 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.10 (s, 3H), 2.48–2.29 (m, 2H), 2.25 (s, 3H); *cis*-**3ca**, minor diastereomer: δ = 7.41 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.35 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.21 (d, *J* = 8.8 Hz, 1H), 5.91 (s, 1H), 4.98 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 3.04 (s, 3H), 2.48–2.29 (m, 2H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): *trans*-**3ca**, major diastereomer: δ = 179.9, 161.4, 159.2, 154.9, 144.3, 134.9, 129.4, 127.6 (×2), 114.3 (×2), 111.1, 110.2, 108.3, 80.9, 78.7, 69.7, 55.9, 55.5, 45.0, 27.0, 15.7; *cis*-**3ca**, minor diastereomer: δ = 181.7, 163.0, 159.2, 154.7, 144.1, 135.3, 128.9, 127.6 (×2), 114.4 (×2), 110.8, 110.0, 108.0, 79.9, 77.3, 68.6, 55.7, 55.5, 43.3, 26.6, 16.0.

HRMS (ESI+) *m/z*: calculated for C₂₂H₂₄N₃O₃S⁺ (M+H⁺) 410.1533; found, 410.1538.



1-(4-Methoxyphenyl)-1',2'-dimethyl-6-morpholino-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3da**

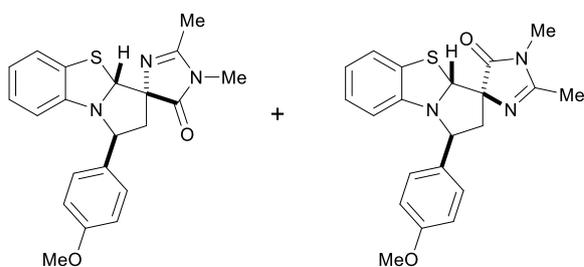
Yield 85 mg (0.18 mmol, 61%). Isolated as a mixture of diastereomers, *dr* = 2.8:1.

Beige solid, mp = 106–108 °C. *R_f* = 0.32 (SiO₂, CH₂Cl₂/MeOH, 20/1).

¹H NMR (300 MHz, CDCl₃, 298K): *trans*-**3da**, major diastereomer: δ = 7.41 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.26 (d, *J* = 8.5 Hz, 1H), 5.81 (s, 1H), 4.79 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.82 (s, 3H), 3.82–3.75 (m, 4H), 3.09 (s, 3H), 3.01–2.91 (m, 4H), 2.49–2.29 (m, 2H), 2.24 (s, 3H); *cis*-**3da**, minor diastereomer: δ = 7.40 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.21 (d, *J* = 8.5 Hz, 1H), 5.91 (s, 1H), 4.79 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.82 (s, 3H), 3.82–3.75 (m, 4H), 3.04 (s, 3H), 3.01–2.91 (m, 4H), 2.49–2.27 (m, 2H), 2.24 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = *trans*-**3da**, major diastereomer: 179.9, 161.3, 159.2, 146.7, 144.4, 134.9, 129.2, 127.6 (×2), 114.3 (×2), 113.9, 111.1¹, 111.0⁹, 80.6, 78.7, 69.4, 67.1 (×2), 55.4, 51.2 (×2), 45.0, 27.0, 15.7; *cis*-**3da**, minor diastereomer: δ = 181.6, 162.9, 158.7, 146.5, 144.1, 135.3, 128.9, 127.6 (×2), 114.3 (×2), 113.6, 111.1, 110.7, 79.8, 76.1, 68.3, 67.1 (×2), 55.4, 50.9 (×2), 45.0, 26.5, 16.0.

HRMS (ESI+) *m/z*: calculated for C₂₅H₂₉N₄O₃S⁺ (M+H⁺) 465.1955; found, 465.1959.



1-(4-Methoxyphenyl)-1',2'-dimethyl-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3ea**

Yield 89 mg (0.23 mmol, 78%). Isolated as a mixture of diastereomers, *dr* = 2.4:1.

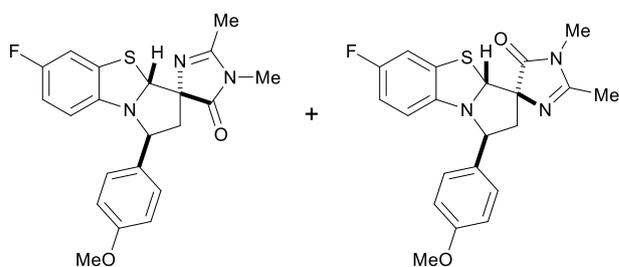
White solid, mp = 179–181 °C. *R_f* = 0.29 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): *trans*-**3ea**, major diastereomer: δ = 7.42 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.89–6.80 (m, 1H), 6.75–6.65 (m, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 4.87 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.82 (s, 3H), 3.10 (s, 3H), 2.55–2.29 (m, 2H), 2.24 (s, 3H); *cis*-**3ea**, minor diastereomer: δ = 7.41 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.89–6.80 (m, 1H), 6.75–6.65 (m, 1H), 6.32 (d, *J* = 7.9 Hz, 1H), 5.91 (s, 1H), 5.06 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.82 (s, 3H), 3.03 (s, 3H), 2.55–2.29 (m, 2H), 2.24 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K):

trans-**3ea**, major diastereomer: δ = 179.6, 161.4, 159.1, 149.9, 135.0, 127.5, 127.3 (×2), 125.5, 121.2, 120.7, 114.4 (×2), 110.3, 79.8, 78.9, 68.9, 55.4, 44.6, 27.0, 15.6; *cis*-**3ea**, minor diastereomer: δ = 181.6, 163.1, 159.1, 149.9, 135.3, 127.4 (×2), 126.9, 125.4, 121.0, 120.7, 114.4 (×2), 109.9, 79.9, 76.2, 67.8, 55.4, 42.9, 26.5, 16.0.

HRMS (ESI+) *m/z*: calculated for C₂₁H₂₂N₃O₂S⁺ (M+H⁺) 380.1427; found, 380.1429.



6-Fluoro-1-(4-methoxyphenyl)-1',2'-dimethyl-1,2-dihydro-3a*H*-spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3fa**

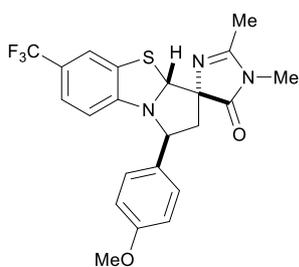
Yield 98 mg (0.25 mmol, 82%). Isolated as a mixture of diastereomers, *dr* = 1.9:1.

White solid, mp = 198–200 °C. *R_f* = 0.32 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃): **trans-3fa**, major diastereomer: δ = 7.40 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.71 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.51 (td, *J* = 8.8, 2.7 Hz, 1H), 6.23 (dd, *J* = 8.6, 4.5 Hz, 1H), 5.83 (s, 1H), 4.81 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.82 (s, 3H), 3.10 (s, 3H), 2.49–2.32 (m, 2H), 2.26 (s, 3H); **cis-3fa**, minor diastereomer: δ = 7.40 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.66 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.53–6.46 (m, 1H), 6.19 (dd, *J* = 8.6, 4.5 Hz, 1H), 5.94 (s, 1H), 4.99 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.82 (s, 3H), 3.04 (s, 3H), 2.49–2.32 (m, 2H), 2.26 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): **trans-3fa**, major diastereomer: δ = 179.5, 161.8, 159.2, 158.0 (d, *J* = 238.2 Hz), 146.5 (d, *J* = 1.4 Hz), 134.6, 129.4 (d, *J* = 9.6 Hz), 127.4 (×2), 114.4 (×2), 111.4 (d, *J* = 23.1 Hz), 110.4 (d, *J* = 8.5 Hz), 108.9 (d, *J* = 27.0 Hz), 80.8, 78.7, 69.5, 55.4, 44.7, 27.0, 15.6; **cis-3fa**, minor diastereomer: δ = 181.5, 163.4, 159.2, 158.0 (d, *J* = 238.2 Hz), 146.5 (d, *J* = 1.4 Hz), 134.9, 129.4 (d, *J* = 9.6 Hz), 127.5 (×2), 114.5 (×2), 111.3 (d, *J* = 22.8 Hz), 110.0 (d, *J* = 8.8 Hz), 108.8 (d, *J* = 27.2 Hz), 79.8, 77.2, 68.4, 55.4, 42.9, 26.5, 15.9.

HRMS (ESI+) *m/z*: calculated for C₂₁H₂₁FN₃O₂S⁺ (M+H⁺) 398.1333; found 398.1336.



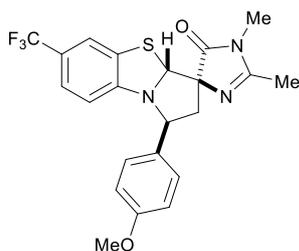
(1*S,3*S**,3*aR**)-1-(4-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *trans*-3ga**

Yield 71 mg (0.16 mmol, 53%). Isolated as a single diastereomer. White solid, mp = 115–117 °C. R_f = 0.28 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃): δ = 7.38 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.10 (dd, J = 8.2, 1.8 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 8.2 Hz, 1H), 5.86 (s, 1H), 4.88 (dd, J = 9.8, 7.4 Hz, 1H), 3.83 (s, 3H), 3.11 (s, 3H), 2.46–2.36 (m, 2H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = 179.2, 162.1, 159.4, 152.6, 134.1, 128.8, 127.2 (×2), 124.4 (J = 248.5 Hz), 123.5 (q, J = 4.0 Hz), 122.7 (q, J = 32.2 Hz), 118.2 (q, J = 3.5 Hz), 114.6 (×2), 109.1, 80.0, 78.7, 68.3, 55.5, 44.4, 27.0, 15.7.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₂S⁺ (M+H⁺) 448.1301; found 448.1303.



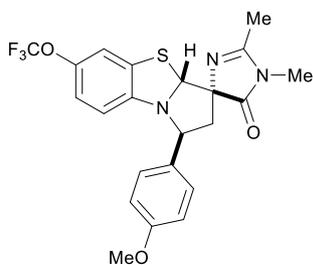
(1*S,3*R**,3*aR**)-1-(4-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *cis*-3ga**

Yield 40 mg (0.09 mmol, 30%). Isolated as a single diastereomer. White solid. R_f = 0.16 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): δ = 7.37 (d, J = 8.7 Hz, 2H), 7.12 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.30 (d, J = 8.3 Hz, 1H), 5.99 (s, 1H), 5.07 (dd, J = 10.3, 7.0 Hz, 1H), 3.83 (s, 3H), 3.04 (s, 3H), 2.47 (dd, J = 13.0, 7.0 Hz, 1H), 2.37 (dd, J = 13.0, 10.3 Hz, 1H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = 181.5, 163.6, 159.4, 152.5, 134.3, 128.3, 127.3 (×2), 123.5 (q, J = 4.1 Hz), 122.9 (q, J = 32.4 Hz), 120.9 (q, J = 258.0 Hz), 117.9 (q, J = 3.9 Hz), 114.6 (×2), 108.6, 79.5, 76.4, 67.2, 55.5, 42.8, 26.5, 16.0.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₂S⁺ (M+H⁺) 448.1301; found 448.1299.



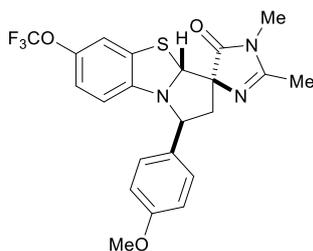
(1*S,3*S**,3*aR**)-1-(4-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethoxy)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *trans*-3ha**

Yield 40 mg (0.09 mmol, 29%). Isolated as a single diastereomer. White solid, mp = 144–146 °C. R_f = 0.38 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): δ = 7.39 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 1.8 Hz, 1H), 6.68 (dd, J = 8.5, 1.8 Hz, 1H), 6.27 (d, J = 8.5 Hz, 1H), 5.86 (s, 1H), 4.84 (dd, J = 10.1, 7.0 Hz, 1H), 3.82 (s, 3H), 3.11 (s, 3H), 2.43 (dd, J = 12.9, 10.1 Hz, 1H), 2.36 (dd, J = 12.9, 7.0 Hz, 1H), 2.26 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = 179.4, 161.9, 159.3, 148.8, 143.1 (q, J = 2.0 Hz), 134.3, 129.4, 127.3 (×2), 120.7 (q, J = 256.1 Hz), 118.5, 114.9, 114.5 (×2), 109.9, 80.6, 78.7, 69.0, 55.5, 44.7, 27.0, 15.7.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₃S⁺ (M+H⁺) 464.1250; found 464.1250.



(1*S,3*R**,3*aR**)-1-(4-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethoxy)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *cis*-3ha**

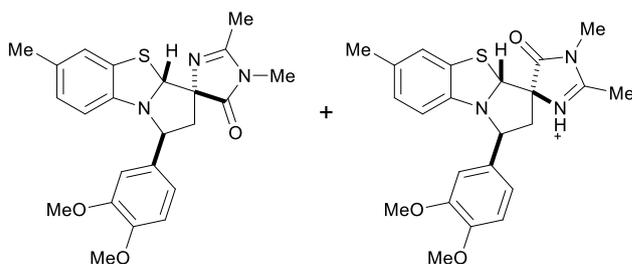
Yield 32 mg (0.07 mmol, 23%). Isolated as a mixture of diastereomers, dr = 1:1.5. White solid, mp = 76–78 °C. R_f = 0.18 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (700 MHz, CDCl₃, 298K): δ = 7.38 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 2.5 Hz, 1H), 6.66 (dd, J = 8.5, 2.5 Hz, 1H), 6.22 (d, J = 8.5 Hz, 1H), 5.97 (s, 1H), 5.03 (dd, J = 10.4, 6.7 Hz, 1H), 3.83 (s, 3H), 3.05 (s, 3H), 2.47–2.29 (m, 2H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 181.6, 163.4, 159.3, 148.7, 142.9 (q, J = 2.0 Hz), 134.6, 129.1, 127.4 (×2), 120.7 (q, J = 256.1 Hz), 118.3, 114.7, 114.6 (×2), 109.5, 79.7, 77.0, 67.9, 55.5, 43.0, 26.6, 16.0.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₃S⁺ (M+H⁺) 464.1250; found 464.1245.

Cyclopropanes scope



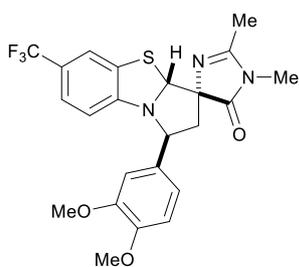
1-(3,4-Dimethoxyphenyl)-1',2',6-trimethyl-1,2-dihydro-3aH-spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,4'-imidazol]-5'(1'H)-one **3ab**

Yield 102 mg (0.24 mmol, 81%). Isolated as a mixture of diastereomers, $dr = 2.1:1$. Yellowish solid, mp = 116–118 °C. $R_f = 0.21$ (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): **trans-3ab**, major diastereomer: $\delta = 7.08$ – 6.95 (m, 2H), 6.83 (d, $J = 8.3$ Hz, 1H), 6.79 (s, 1H), 6.64 (d, $J = 7.9$ Hz, 1H), 6.25 (d, $J = 7.9$ Hz, 1H), 5.80 (s, 1H), 4.81 (dd, $J = 10.3, 6.8$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.09 (s, 3H), 2.48–2.29 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H); **cis-3ab**, minor diastereomer: $\delta = 7.08$ – 6.95 (m, 2H), 6.83 (d, $J = 8.3$ Hz, 1H), 6.74 (s, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 6.22 (d, $J = 7.9$ Hz, 1H), 5.91 (s, 1H), 5.00 (dd, $J = 10.3, 7.0$ Hz, 1H), 3.88 (s, 6H), 3.03 (s, 3H), 2.48–2.29 (m, 2H), 2.24 (s, 3H), 2.15 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): $\delta =$ **trans-3ab**, major diastereomer: $\delta = 179.7, 161.4, 149.5, 148.4, 147.8, 135.5, 130.4, 127.6, 125.9, 121.9, 118.3, 111.4, 110.4, 108.9, 80.1, 78.8, 69.5, 56.0^5, 56.0^4, 44.7, 26.9, 20.8, 15.6$; **cis-3ab**, minor diastereomer: $\delta = 181.7, 163.1, 149.5, 148.4, 147.7, 135.9, 130.2, 127.1, 125.9, 121.6, 118.4, 111.3, 110.1, 109.0, 79.9, 76.5, 68.4, 56.0^1, 56.9^7, 43.0, 26.5, 20.9, 16.0$.

HRMS (ESI+) m/z : calculated for C₂₃H₂₆N₃O₃S (M+H⁺), 424.1689; not found, calculated for C₂₃H₂₆N₃O₄S (M+O+H⁺), 440.1639; found, 440.1641.



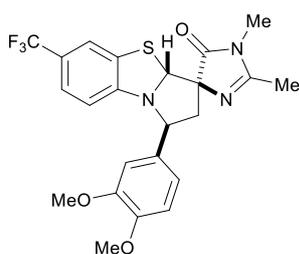
(1*S,3*S**,3*aR**)-1-(3,4-Dimethoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *trans*-3gb**

Yield 59 mg (0.12 mmol, 41%). Isolated as a single diastereomer. Yellowish solid, mp = 157–159 °C. R_f = 0.28 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): δ = 7.18 (s, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.99 (m, 2H), 6.89 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 8.2 Hz, 1H), 5.87 (s, 1H), 4.87 (dd, J = 10.0, 7.1 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.11 (s, 3H), 2.49 – 2.34 (m, 2H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = 179.1, 162.1, 152.6, 149.7, 148.8, 134.5, 128.9, 125.0 (d, J = 245.7 Hz), 123.5 (q, J = 4.3 Hz), 122.8 (q, J = 32.4 Hz), 118.2 (q, J = 3.6 Hz), 118.2, 111.6, 109.3, 108.7, 80.0, 78.6, 68.7, 56.1³, 56.1¹, 44.4, 27.1, 15.7.

HRMS (ESI+) m/z : calculated for C₂₃H₂₃F₃N₃O₃S⁺ (M+H⁺) 478.1407; found 478.1404.



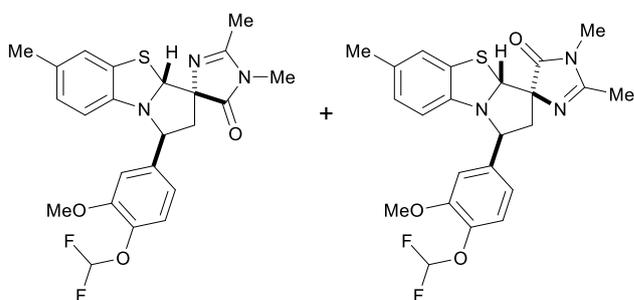
(1*S,3*R**,3*aR**)-1-(3,4-dimethoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *cis*-3gb**

Yield 42 mg (0.09 mmol, 30%). Isolated as a single diastereomer. White solid, mp = 90–92 °C. R_f = 0.11 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): δ = 7.12 (d, J = 1.2 Hz, 1H), 7.09 (dd, J = 8.3, 1.2 Hz, 1H), 6.99 (dd, J = 8.1, 2.1 Hz, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 6.00 (s, 1H), 5.06 (dd, J = 10.2, 7.0 Hz, 1H), 3.89 (s, 3H), 3.04 (s, 3H), 2.46 (dd, J = 13.1, 7.0 Hz, 1H), 2.39 (dd, J = 13.1, 10.2 Hz, 1H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): δ = 181.4, 163.6, 152.5 (q, J = 1.1 Hz), 149.7, 148.7, 134.8, 128.4, 124.4 (q, J = 254.2 Hz), 123.5 (q, J = 3.6 Hz), 122.6 (d, J = 32.5 Hz), 118.2, 117.9 (q, J = 3.4 Hz), 111.5, 108.8, 108.7, 79.4, 76.5, 67.6, 56.0⁵, 56.0³, 42.8, 26.5, 16.0.

HRMS (ESI+) m/z : calculated for C₂₃H₂₃F₃N₃O₃S⁺ (M+H⁺) 478.1407; found 478.1408.



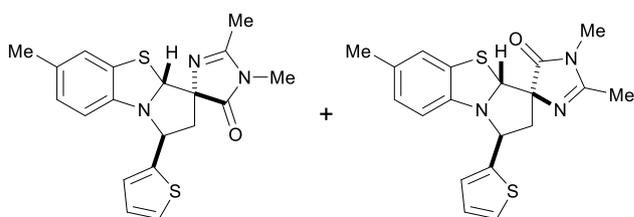
1-(4-(Difluoromethoxy)-3-methoxyphenyl)-1',2',6-trimethyl-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3ac**

Yield 76 mg (0.17 mmol, 55%). Isolated as a mixture of diastereomers, *dr* = 2.1:1. Yellow solid, mp = 82–84 °C. *R_f* = 0.20 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): **trans-3ac**, major diastereomer: δ = 7.20–7.11 (m, 2H), 6.99 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.81 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.56 (t, *J* = 75.5 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.77 (s, 1H), 4.85 (t, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.10 (s, 3H), 2.43–2.33 (m, 2H), 2.25 (s, 3H), 2.19 (s, 3H); **cis-3ac**, minor diastereomer: δ = 7.20–7.14 (m, 2H), 7.01 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.77 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.56 (t, *J* = 75.5 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, 1H), 5.88 (s, 1H), 5.04 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.88 (s, 3H), 3.04 (s, 3H), 2.43–2.33 (m, 2H), 2.25 (s, 3H), 2.17 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): **trans-3ac**, major diastereomer: δ = 179.5, 161.6, 151.7, 147.6, 142.0, 139.2 (t, *J* = 3.0 Hz), 130.7, 127.6, 126.0, 122.7, 122.0, 118.5, 116.3 (t, *J* = 259.1 Hz, 1H), 110.3, 110.0, 80.1, 78.8, 69.3, 56.2, 44.4, 27.0, 20.8, 15.6; **cis-3ac**, minor diastereomer: δ = 181.6, 163.3, 150.9, 147.5, 142.3, 139.2 (d, *J* = 3.0 Hz), 130.6, 127.0, 126.0, 122.7, 121.8, 118.5, 116.3 (t, *J* = 259.1 Hz, 1H), 110.1, 110.0, 79.9, 76.4, 68.3, 56.2, 44.2, 26.5, 20.9, 16.0.

HRMS (ESI+) *m/z*: calcd for C₂₃H₂₄F₂N₃O₃S⁺ (M+H⁺) 460.1501; found 460.1504.



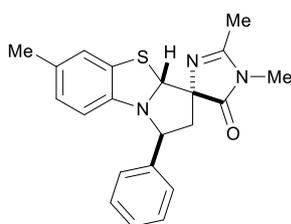
1',2',6-Trimethyl-1-(thiophen-2-yl)-1,2-dihydro-3a*H*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one **3ad**

Yield 43 mg (0.12 mmol, 39% after 3 days). Isolated as a mixture of diastereomers, *dr* = 2.2:1. Beige solid, mp = 156–158°C. *R*_f = 0.28 (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): **trans-3ad**, major diastereomer: δ = 7.27–7.24 (m, 1H), 7.09–7.05 (m, 1H), 7.01 (dd, *J* = 5.1, 1.7 Hz, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 5.75 (s, 1H), 5.11 (dd, *J* = 10.1, 6.6 Hz, 1H), 3.09 (s, 3H), 2.56 (dd, *J* = 12.9, 10.1 Hz, 1H), 2.40 (dd, *J* = 12.9, 6.6 Hz, 1H), 2.23 (s, 3H), 2.19 (s, 3H); **cis-3ad**, minor diastereomer: δ = 7.27–7.24 (m, 1H), 7.09–7.05 (m, 1H), 7.00 (dd, *J* = 5.1, 1.7 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.68 (dd, *J* = 8.1, 7.9 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 1H), 5.32 (t, *J* = 8.5 Hz, 1H), 3.02 (s, 3H), 2.51–2.46 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): **trans-3ad**, major diastereomer: δ = 179.4, 161.6, 147.8, 147.4, 130.8, 127.2, 127.1, 126.0, 124.7, 123.5, 122.0, 110.6, 79.5, 78.9, 65.7, 44.5, 27.0, 20.8, 15.6; **cis-3ad**, minor diastereomer: δ = δ = 181.6, 163.3, 148.4, 147.4, 130.7, 127.5, 127.0, 126.0, 124.8, 123.6, 121.7, 110.4, 80.0, 75.9, 64.7, 43.0, 26.5, 20.9, 16.0.

HRMS (ESI⁺) *m/z*: calcd for C₁₉H₂₀N₃OS₂⁺ (M+H⁺) 370.1042; found 370.1049.



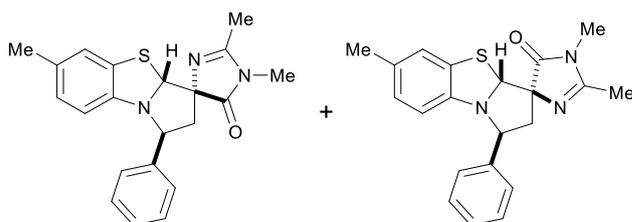
(1*S,3*S**,3*aR**)-1',2',6-Trimethyl-1-phenyl-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *trans*-3ae**

Yield 11 mg (0.03 mmol, 10% after 5 days). Isolated as a single diastereomer. Amorphous yellow solid. $R_f = 0.32$ (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): $\delta = 7.50$ (d, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 1H), 6.80 (d, $J = 1.8$ Hz, 1H), 6.64 (dd, $J = 7.9, 1.8$ Hz, 1H), 6.25 (d, $J = 7.9$ Hz, 1H), 5.79 (s, 1H), 4.88 (dd, $J = 9.6, 7.6$ Hz, 1H), 3.10 (s, 3H), 2.54–2.33 (m, 1H), 2.25 (s, 3H), 2.18 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): $\delta = 179.7, 161.5, 147.8, 143.1, 130.3, 129.0$ ($\times 2$), 127.6, 127.5, 126.3 ($\times 2$), 126.0, 121.9, 110.2, 80.2, 78.9, 69.6, 44.5, 27.0, 20.8, 15.7.

HRMS (ESI+) m/z : calcd for C₂₁H₂₂N₃OS⁺ (M+H⁺) 364.1478; found 364.1482.



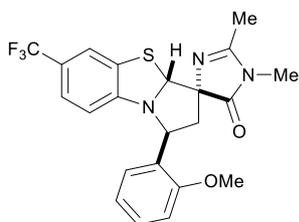
(1*S,3*S**,3*aR**)-1',2',6-Trimethyl-1-phenyl-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *cis*-3ae**

Yield 21 mg (0.06 mmol, 19% after 5 days). Isolated as a mixture of diastereomers, *dr* 1:1.7. White solid, mp = 81–83 °C. $R_f = 0.15$ (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): $\delta = 7.50$ (d, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 1H), 6.76 (d, $J = 1.8$ Hz, 1H), 6.62 (dd, $J = 7.9, 1.8$ Hz, 3H), 6.20 (d, $J = 7.9$ Hz, 1H), 5.90 (s, 1H), 5.07 (dd, $J = 10.3, 7.1$ Hz, 1H), 3.05 (s, 3H), 2.51–2.33 (m, 2H), 2.25 (s, 3H), 2.16 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): $\delta = 181.8, 163.1, 147.7, 143.5, 130.2, 129.1$ ($\times 2$), 127.6, 127.0, 126.3 ($\times 2$), 126.0, 121.7, 109.9, 80.0, 76.6, 68.5, 42.9, 26.6, 21.0, 16.0.

HRMS (ESI+) m/z : calcd for C₂₁H₂₂N₃OS⁺ (M+H⁺) 364.1478; found 364.1482.



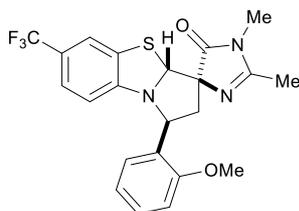
(1*S,3*S**,3*aR**)-1-(2-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *trans*-3gf**

Yield 34 mg (0.08 mmol, 26% after 5 days). Isolated as a single diastereomer. White solid. $R_f = 0.45$ (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): $\delta = 7.58$ (dd, $J = 7.7, 2.1$ Hz, 1H), 7.31 (td, $J = 7.8, 1.7$ Hz, 1H), 7.17 (d, $J = 2.2$ Hz, 1H), 7.11 (dd, $J = 8.3, 2.2$ Hz, 1H), 7.00 (td, $J = 7.5, 1.1$ Hz, 1H), 6.93 (dd, $J = 8.2, 1.1$ Hz, 1H), 6.34 (d, $J = 8.3$ Hz, 1H), 5.82 (s, 1H), 5.20 (dd, $J = 9.9, 7.1$ Hz, 1H), 3.85 (s, 3H), 3.10 (s, 3H), 2.63 (dd, $J = 13.1, 7.1$ Hz, 1H), 2.36 (dd, $J = 13.1, 9.9$ Hz, 1H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): $\delta = 179.5, 161.7, 156.7, 152.5$ (q, $J = 1.3$ Hz), 129.9, 128.9, 128.4, 126.5, 124.6 (d, $J = 261.8$ Hz), 123.6 (q, $J = 4.1$ Hz), 122.3 (q, $J = 32.3$ Hz), 121.2, 118.1 (q, $J = 3.7$ Hz), 110.7, 108.7, 79.7, 78.8, 64.5, 55.4, 42.0, 27.0, 15.7.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₂S⁺ (M+H⁺) 448.1301; found 448.1305.



(1*S,3*R**,3*aR**)-1-(2-Methoxyphenyl)-1',2'-dimethyl-6-(trifluoromethyl)-1,2-dihydro-3*aH*-spiro[benzo[*d*]pyrrolo[2,1-*b*]thiazole-3,4'-imidazol]-5'(1'*H*)-one *cis*-3gf**

Yield 27 mg (0.06 mmol, 21% after 5 days). Isolated as a single diastereomer. Beige solid, mp = 96–98°C. $R_f = 0.19$ (SiO₂, hexane/EtOAc, 1/3).

¹H NMR (300 MHz, CDCl₃, 298K): $\delta = 7.53$ (dd, $J = 7.5, 2.3$ Hz, 1H), 7.31 (td, $J = 7.6, 1.7$ Hz, 1H), 7.13–7.07 (m, 2H), 7.00 (td, $J = 7.5, 1.1$ Hz, 1H), 6.93 (dd, $J = 8.3, 1.1$ Hz, 1H), 6.27 (d, $J = 8.1$ Hz, 1H), 5.95 (s, 1H), 5.34 (dd, $J = 10.0, 7.0$ Hz, 1H), 3.86 (s, 3H), 3.04 (s, 3H), 2.68 (dd, $J = 13.1, 7.0$ Hz, 1H), 2.33 (dd, $J = 13.1, 10.0$ Hz, 1H), 2.25 (s, 3H).

¹³C{¹H} NMR (75 MHz, CDCl₃, 298K): $\delta = 181.6, 163.4, 156.8, 152.4$ (q, $J = 1.2$ Hz), 129.8, 128.9, 128.0, 126.7, 124.7 (q, $J = 271.1$ Hz), 123.6 (q, $J = 4.1$ Hz), 122.0 (d, $J = 32.5$ Hz), 121.1, 117.8 (q, $J = 3.9$ Hz), 110.8, 108.2, 79.5, 76.0, 63.6, 55.4, 40.0, 26.5, 16.0.

HRMS (ESI+) m/z : calculated for C₂₂H₂₁F₃N₃O₂S⁺ (M+H⁺) 448.1301; found 448.1301.

Study of the Epimerization of *trans*-3ga

Compound *trans*-3ga was studied for its configuration stability under varied conditions: 1) in CDCl₃ solution, 2) in in CDCl₃ solution with added AcOH (ca. 15 equiv.), 3) upon heating in CDCl₃ solution at 50 °C, 4) in in CDCl₃ solution with added TFA (ca. 2 equiv.). Under first two conditions we were able to perform direct ¹H NMR monitoring of the isomerization kinetics measuring spectra at indicated times (Figures S1 and S2).

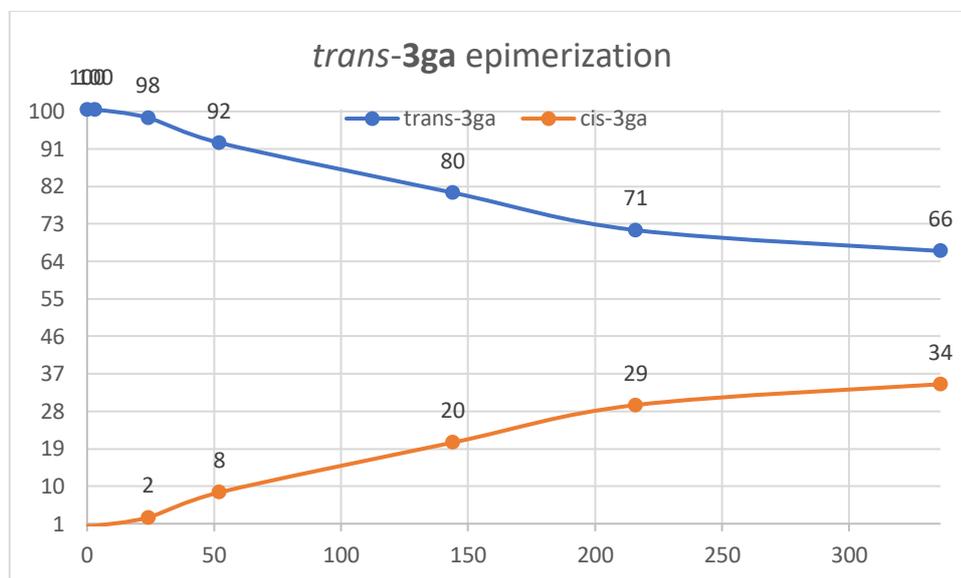


Figure S1. ¹H NMR monitoring of *trans*-3ga isomerization in solution.

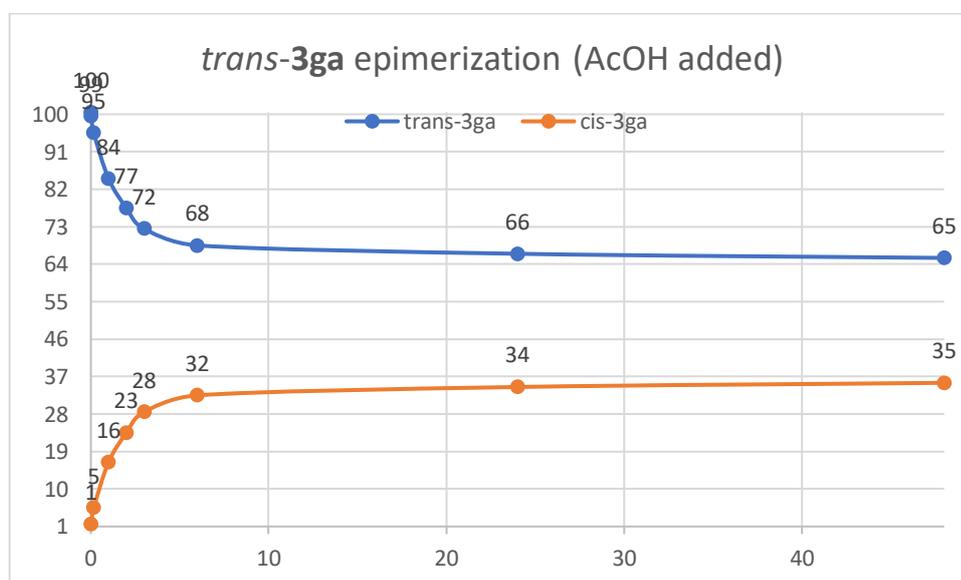


Figure S2. ¹H NMR monitoring of *trans*-3ga isomerization in solution under slightly acidic conditions (AcOH added).

Thermal isomerization was carried out in NMR tube, heated in the oil bath for 50 °C for 2 hours, only control measurement was performed after the indicated time. For the experiment with TFA a kinetics measurement was attempted. However, upon such conditions both isomers coalescent to give broadened spectrum (Figure S3). The broadening disappears, when the acid is neutralized by addition of TMG excess.

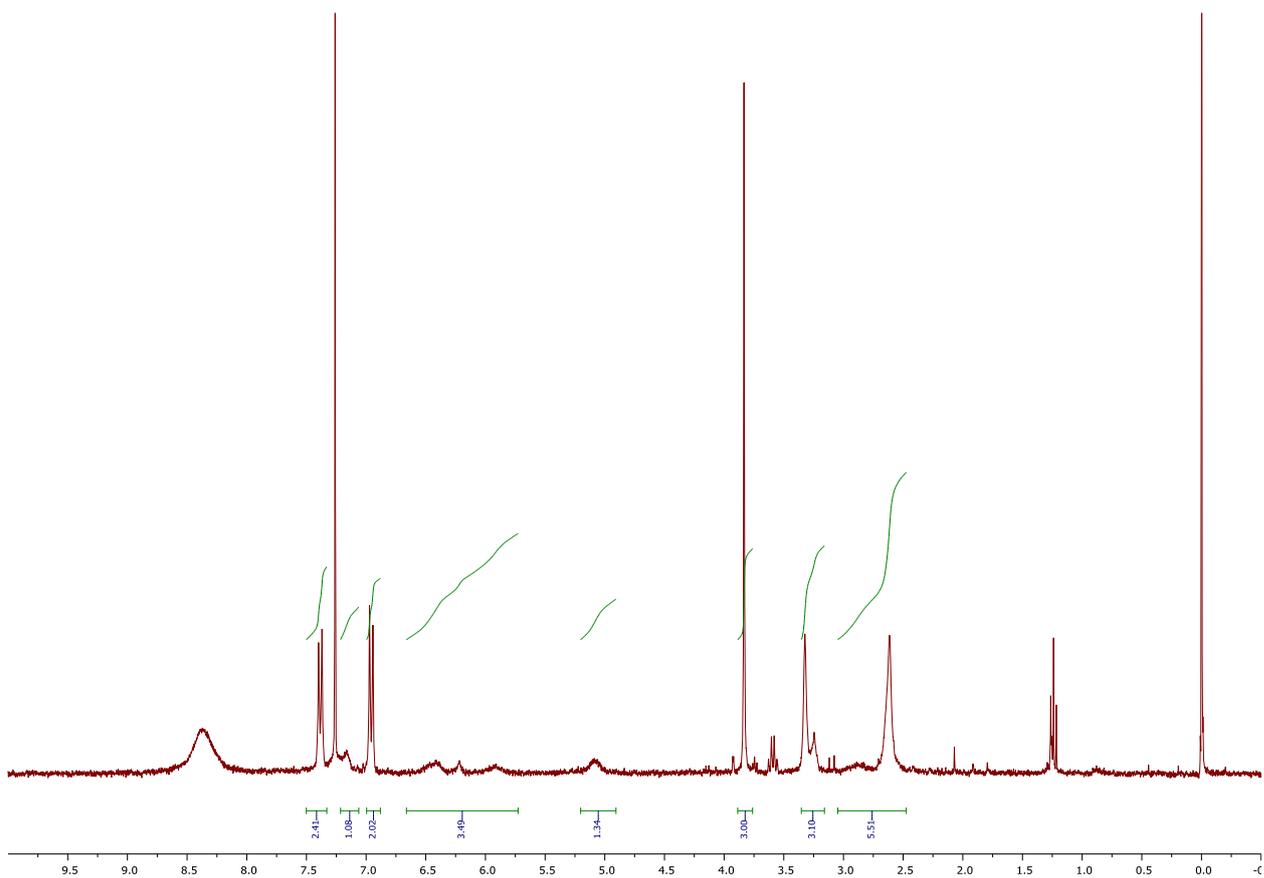


Figure S3. ¹H NMR spectrum for *trans*-3ga with TFA added.

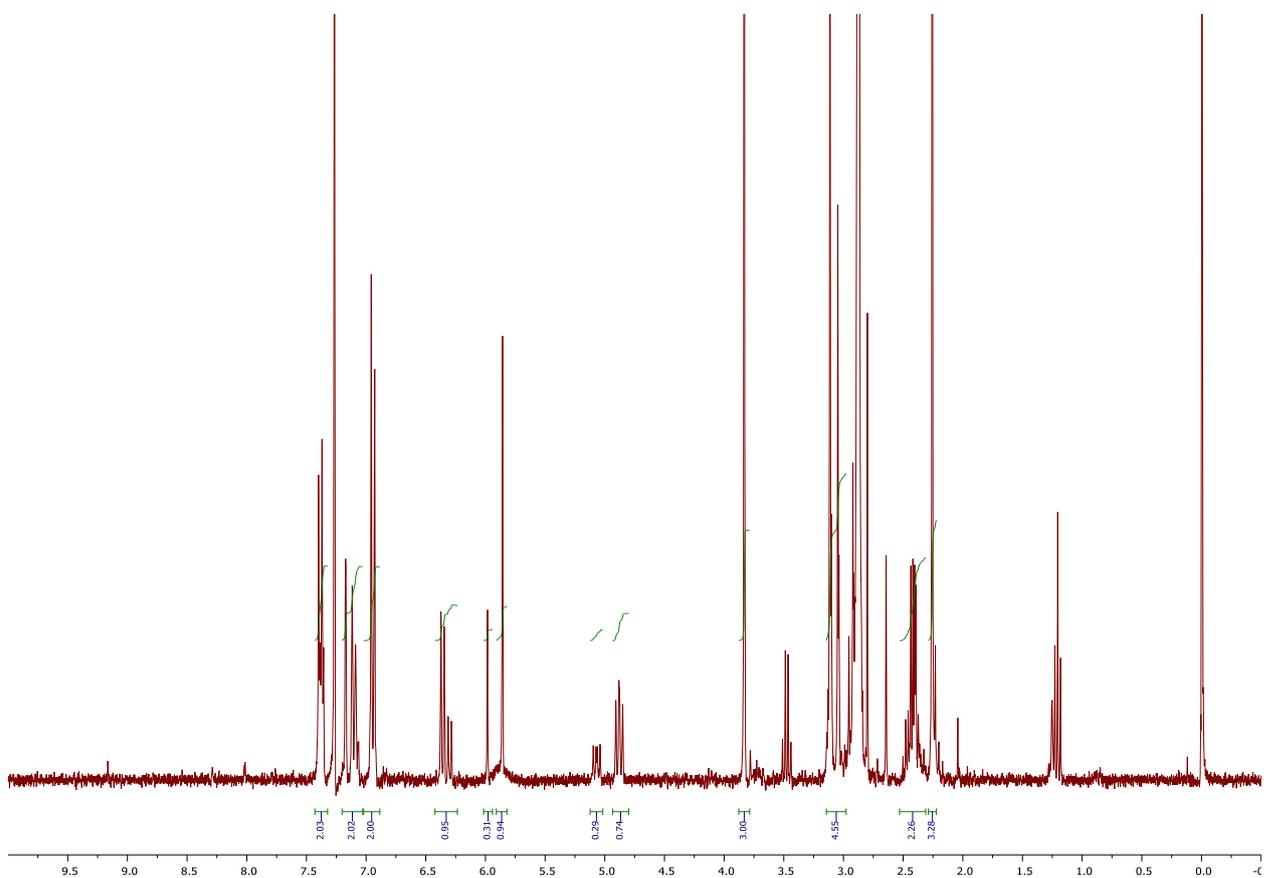


Figure S4. ¹H NMR spectrum for *trans*-3ga with TFA added after TMG quenching.

X-Ray crystallography data

Single crystal X-ray study of *trans*-**3ga** was carried out in Center for molecule composition studies of INEOS RAS with APEX3 software.^{S4} The data were then integrated with SAINT. SADABS was used for scaling, empirical absorption corrections and the generation of data files for structure solution and refinement.

The structures were solved by dual-space algorithm and refined in anisotropic approximation for non-hydrogen atoms against $F^2(hkl)$. Hydrogen atoms of NH, methyl, methylene and aromatic fragments were calculated according to those idealized geometry and refined with constraints applied to C-H and N-H bond lengths and equivalent displacement parameters. All structures were solved with the ShelXT^{S5} program and refined with the ShelXL^{S6} program. Molecular graphics was drawn using OLEX2^{S7} program.

CCDC 2522258 contains the supplementary crystallographic data for *trans*-**3ga**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures>.

Table S11. Crystallographic data for *trans-3ga*

Brutto formula	C ₂₂ H ₂₀ F ₃ N ₃ O ₂ S
Formula weight	447.47
Diffractometer	Bruker SMART APEX II
Scan mode	ω and ϕ scans
Anode [Wavelength, Å]	MoK α [0.71073] ?
Crystal Dimensions, mm	0.02 \times 0.03 \times 0.07
Crystal color	clear light yellow
Crystal system	triclinic
a, Å	7.4518(7)
b, Å	10.5180(10)
c, Å	13.4176(13)
α , °	84.009(3)
β , °	86.084(3)
γ , °	72.303(3)
Volume, Å ³	995.66(17)
Density, gcm ⁻³	1.493
Temperature, K	120
T _{min} /T _{max}	0.6958/0.7461
μ , mm ⁻¹	0.216
Space group	P $\bar{1}$
Z	2
F(000)	464
Reflections collected	14170
Independent reflections	6026
Reflections (I>2 σ (I))	3740
Parameters	306
R _{int}	0.0362
2 θ _{min} - 2 θ _{max} , °	4.080 - 61.130
wR ₂ (all reflections)	0.0964
R ₁ (I> σ (I))	0.0434
GOF	0.934
ρ _{min} / ρ _{max} , eÅ ⁻³	-0.295/0.377
Restraints	28

HIV-1 inhibition studies

Cell Culture and Lentiviral Vector Production

293T cells were cultured in DMEM medium supplemented with 10% FBS and 100 I.U./mL penicillin/100 µg/mL streptomycin solution (all from Gibco, Waltham, MA, USA) in a 37 °C incubator with a humidified atmosphere of 5% CO₂ in air. To generate VSV-G pseudotyped replicative incompetent HIV-based vectors HIV_wt and HIV_mut, 293T cells were co-transfected with HIV-1 packaging vector pCMVΔR8.2 (Addgene plasmid #12263) or pCMVΔR8.2_IN_E212A/L213A, vector for expression of protein G from vesicular stomatitis virus (VSV) pCMV-VSVG (Addgene plasmid #8454), and reporter plasmid pUCHR-inLuc-mR by calcium-phosphate transfection. At 6 h post-transfection, media was replaced. At 48 and 72 h post-transfection, supernatants were harvested, and pseudoviruses were concentrated by centrifugation at 30,000× g for 2 h and resuspended in PBS. The MOI for HIV_wt was determined as amount of integrated DNA per cell.

Transduced cells in presence of tested compounds in 1% DMSO were harvested at 24 h post-transduction, cell number was counted and luciferase activity in cell lysates was measured using BioTek Synergy H1 reader (BioTek Instruments Inc., USA) and luciferase assay system kit (Promega, Madison, WI, USA). Data were corrected on cell amount and normalized to 1% DMSO-treated samples.

Cytotoxicity studies

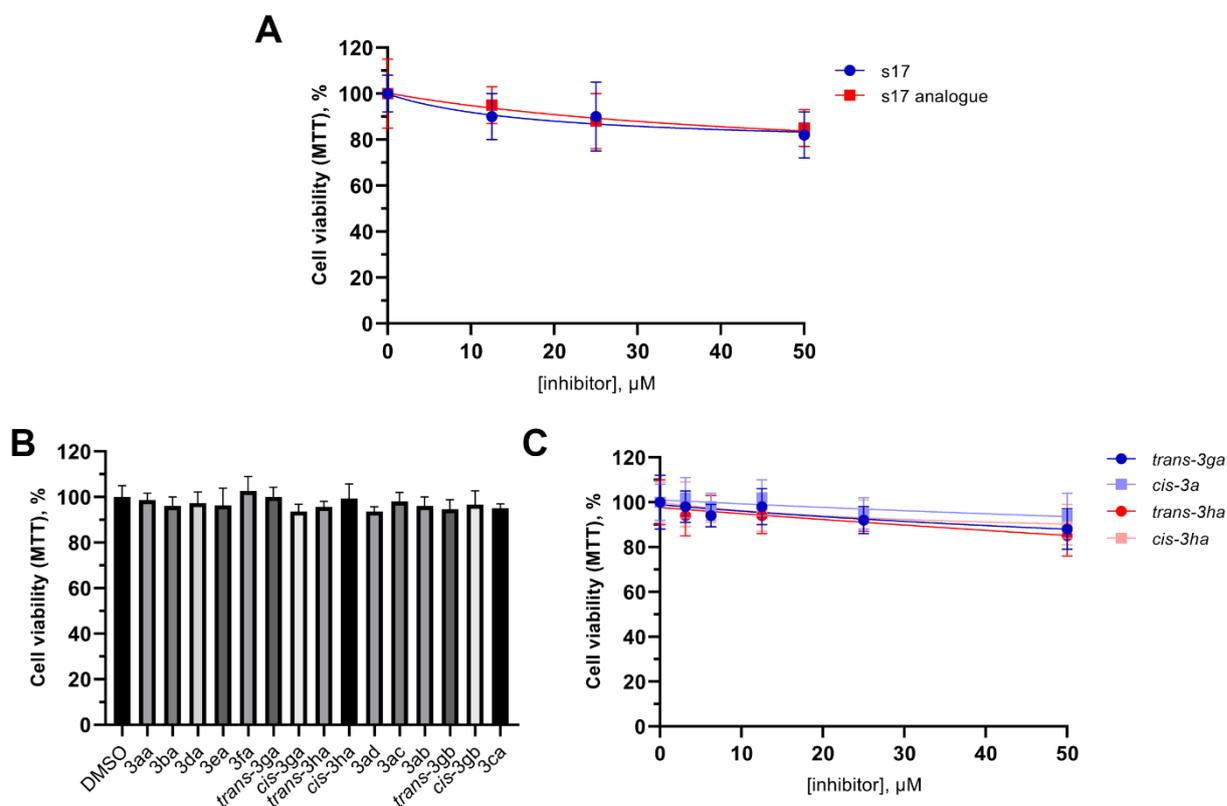
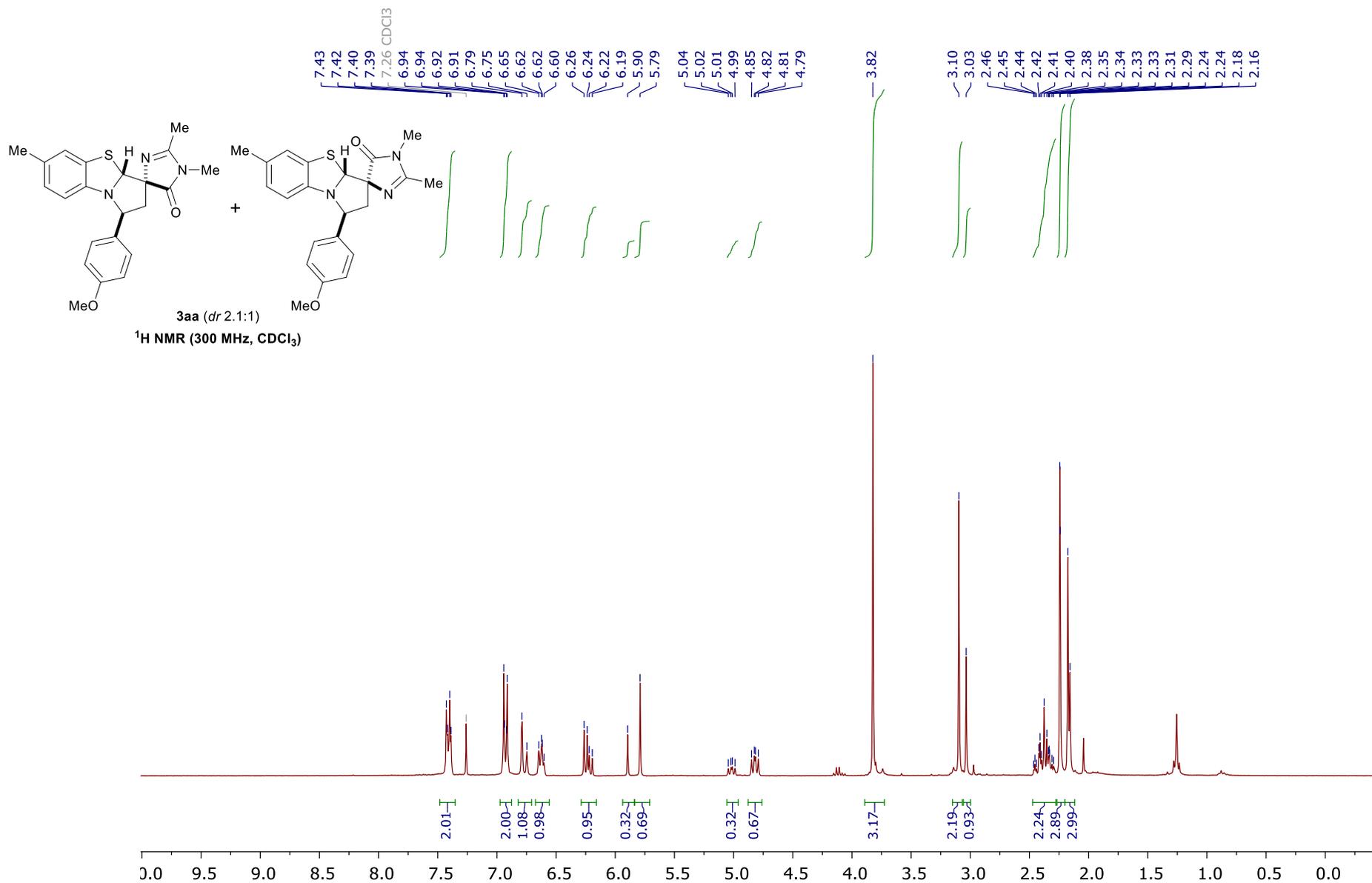


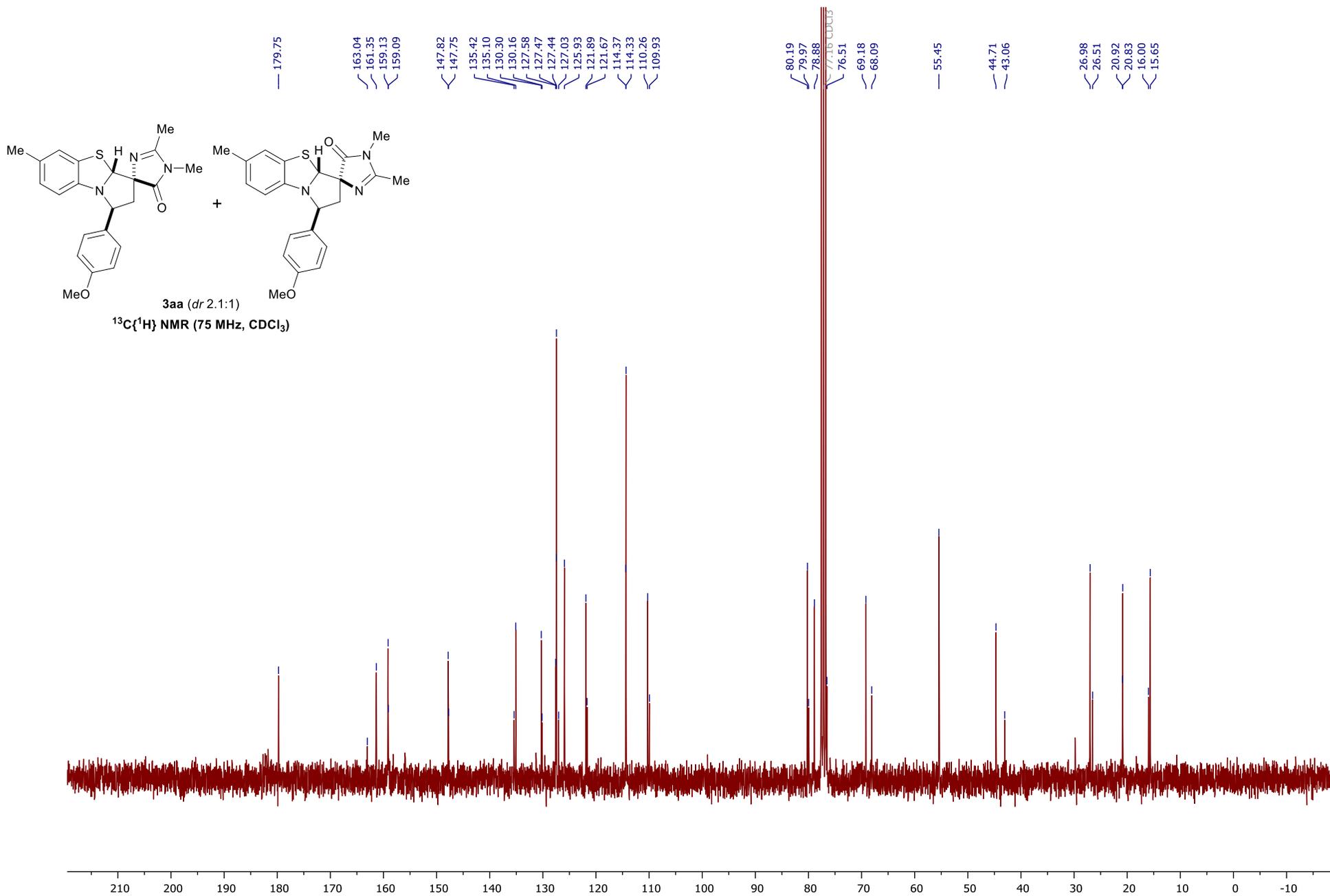
Figure S5. Effect of benzothiazole derivatives of s17 on cell viability measured by MTT assay. **A** – both s17 and s17 analogue did not affect viability of 293T cells. **B** – The effect of 12 µM s17 analogue on cell viability, **C**– The effect of *trans*- and *cis*-3ga, and *trans*- and *cis*-3ha on 293T cells viability. Mean values ± SD (n = 3) are shown.

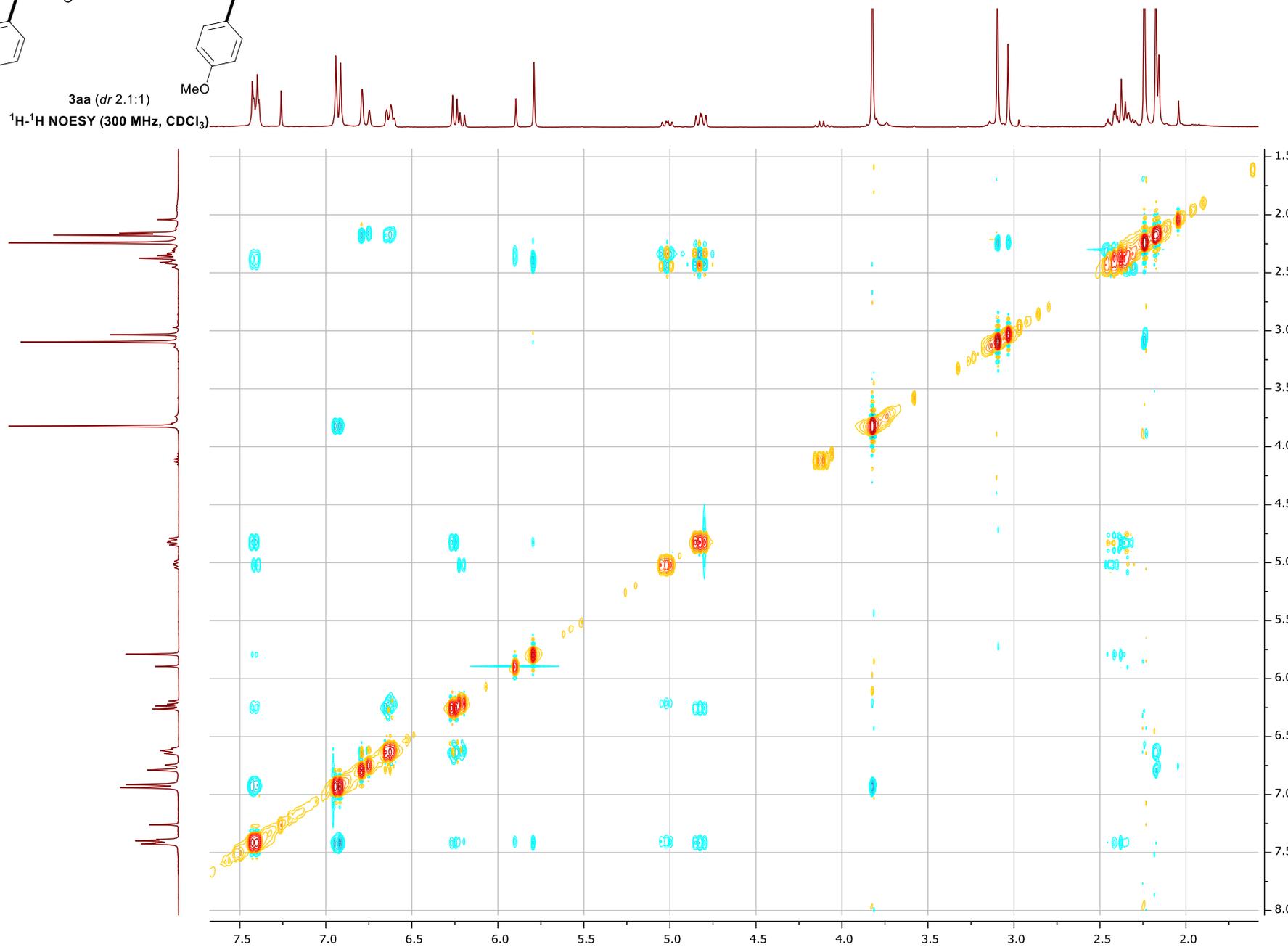
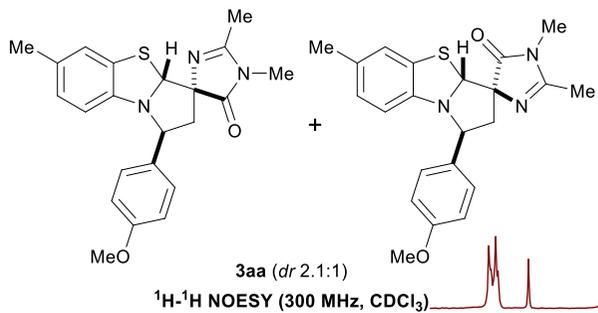
References

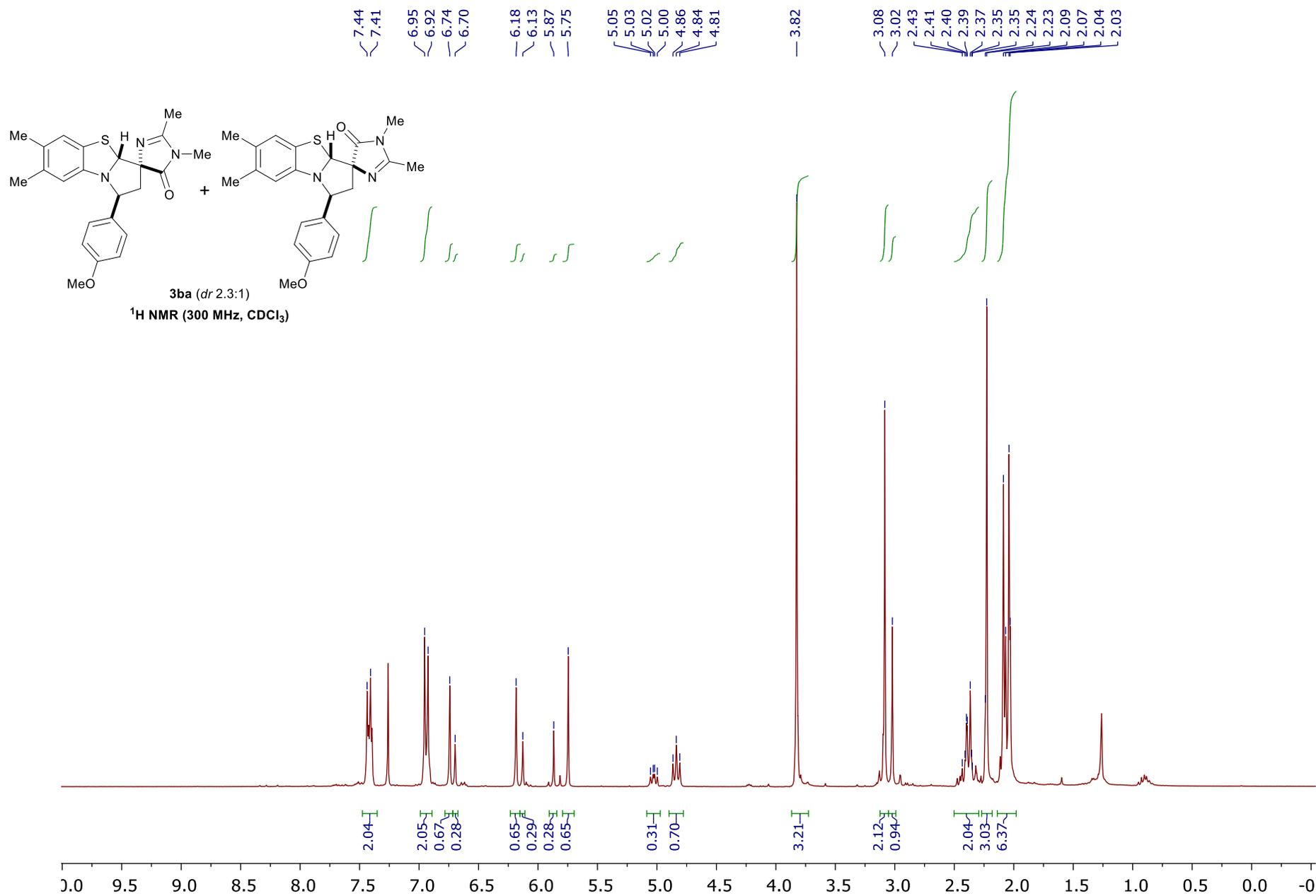
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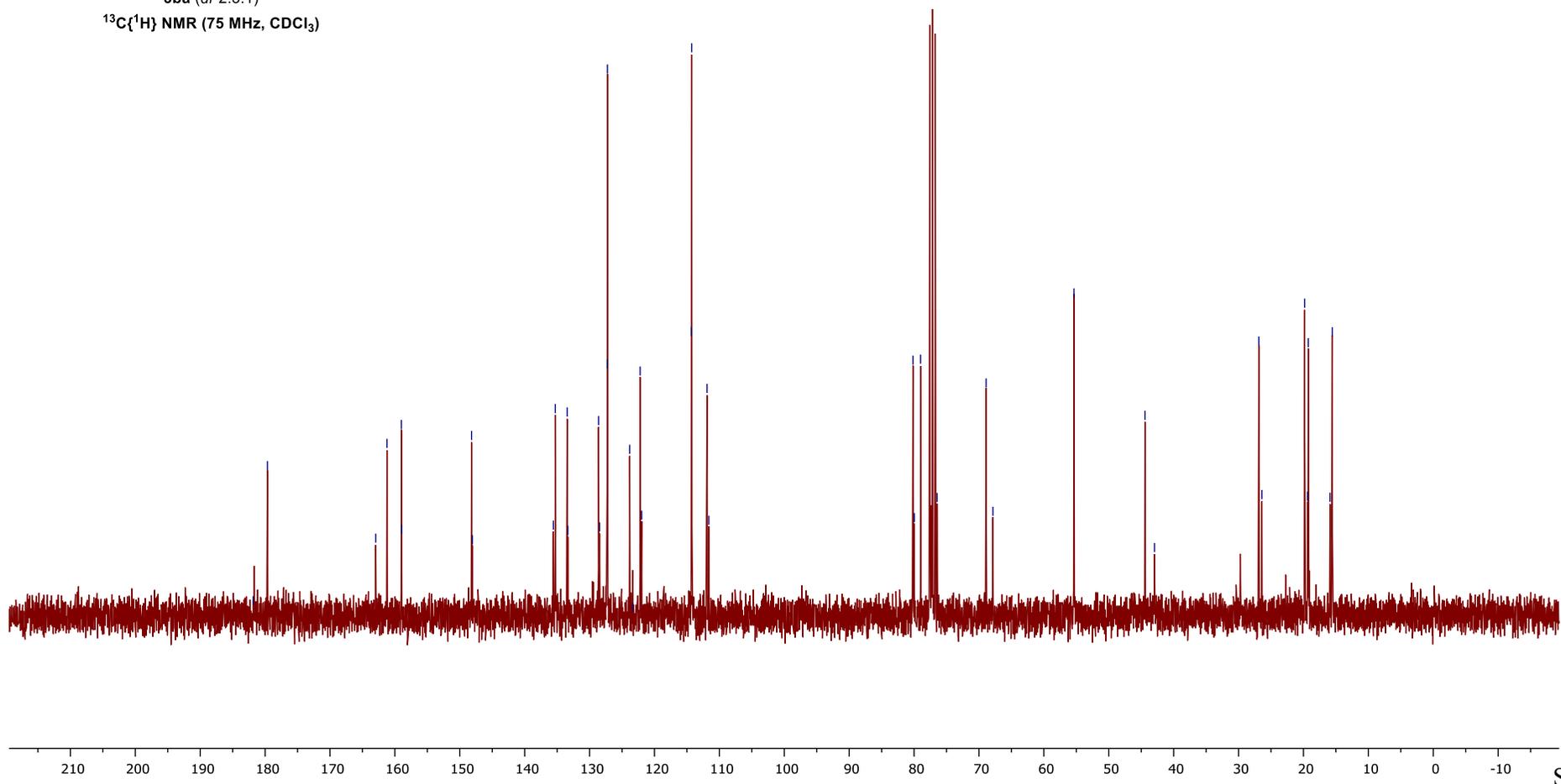
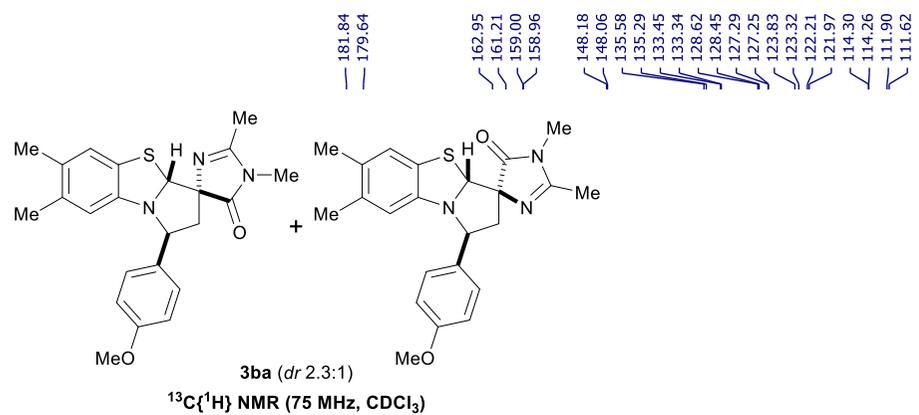
Copies of NMR spectra

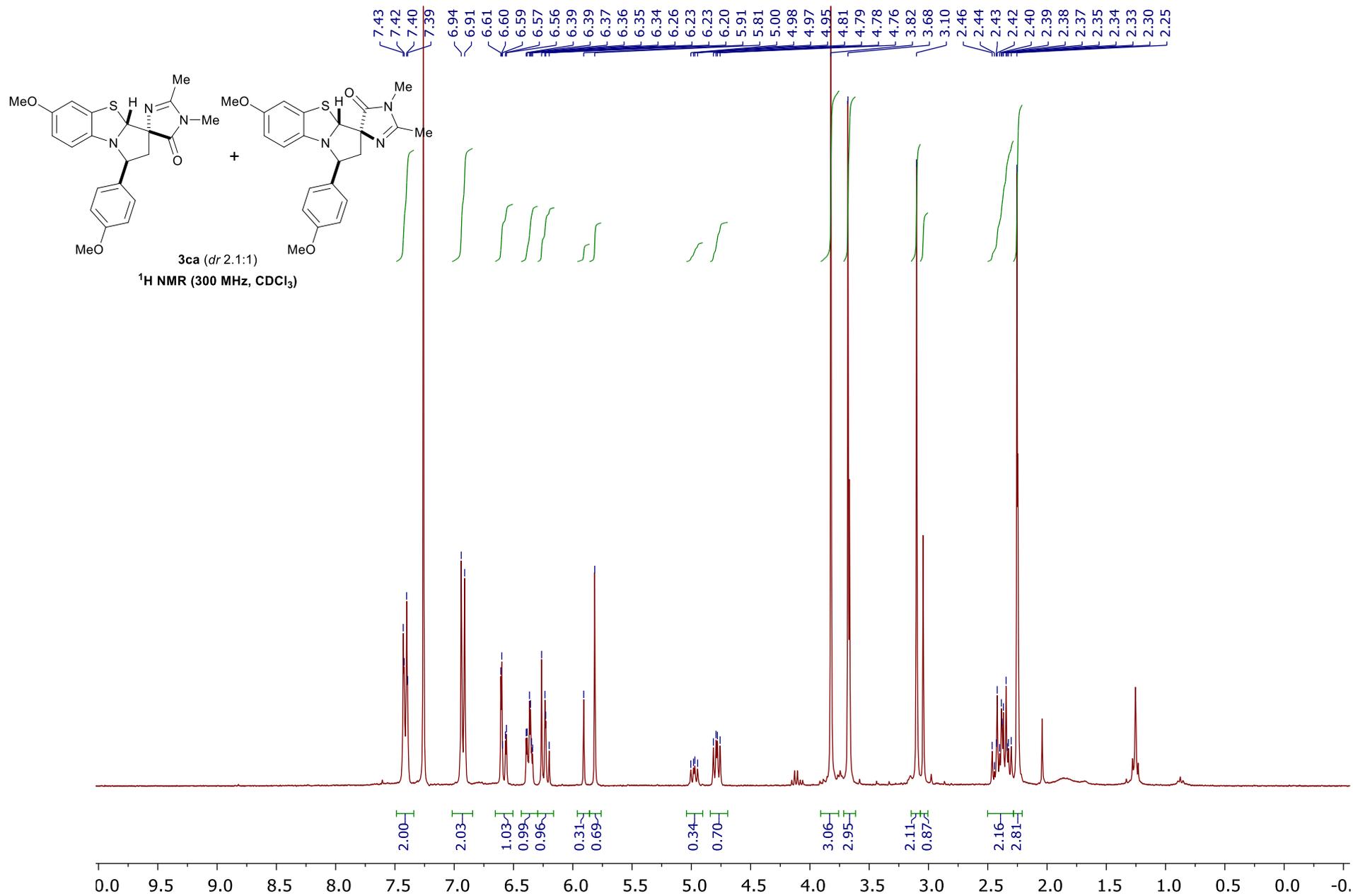


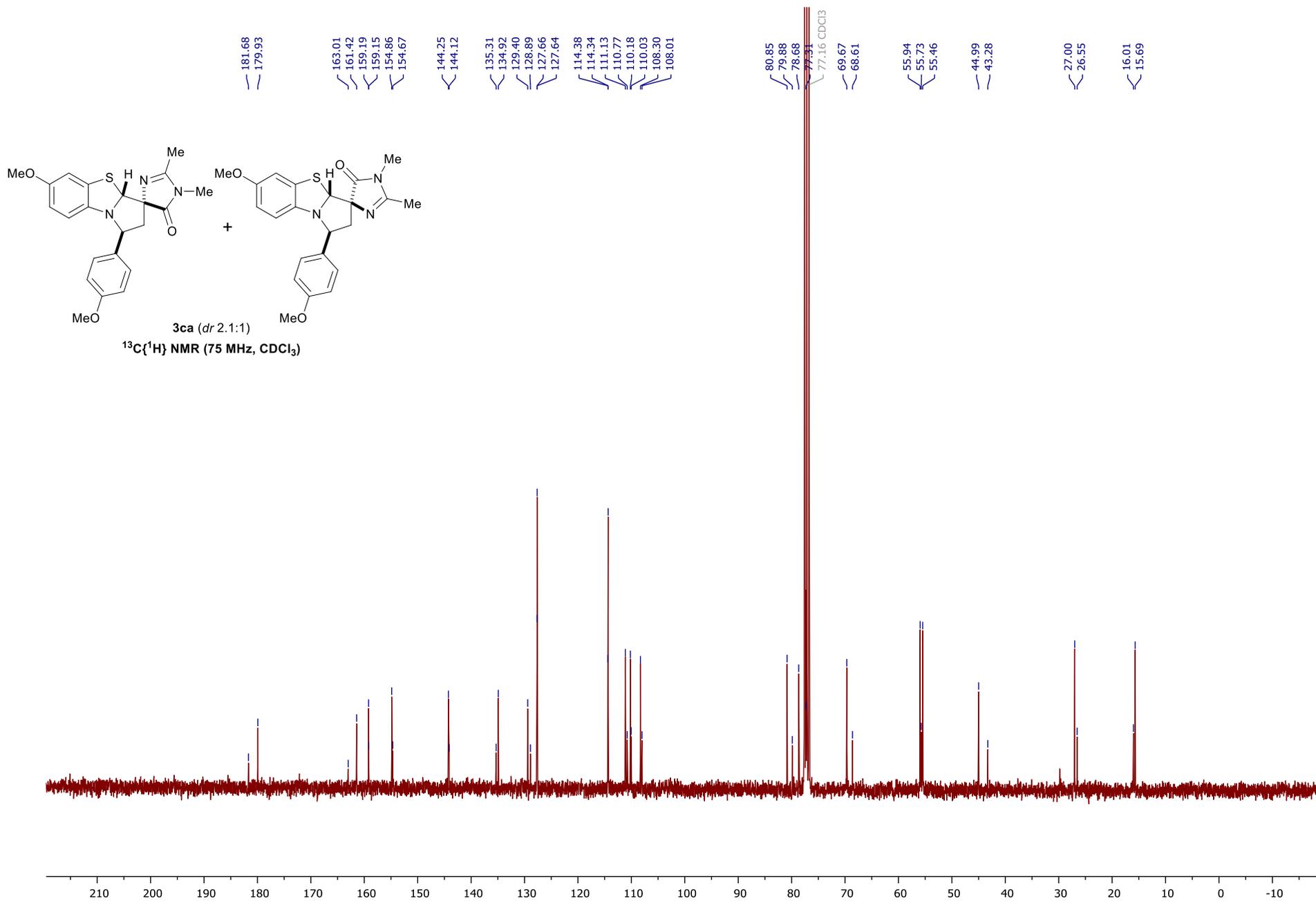


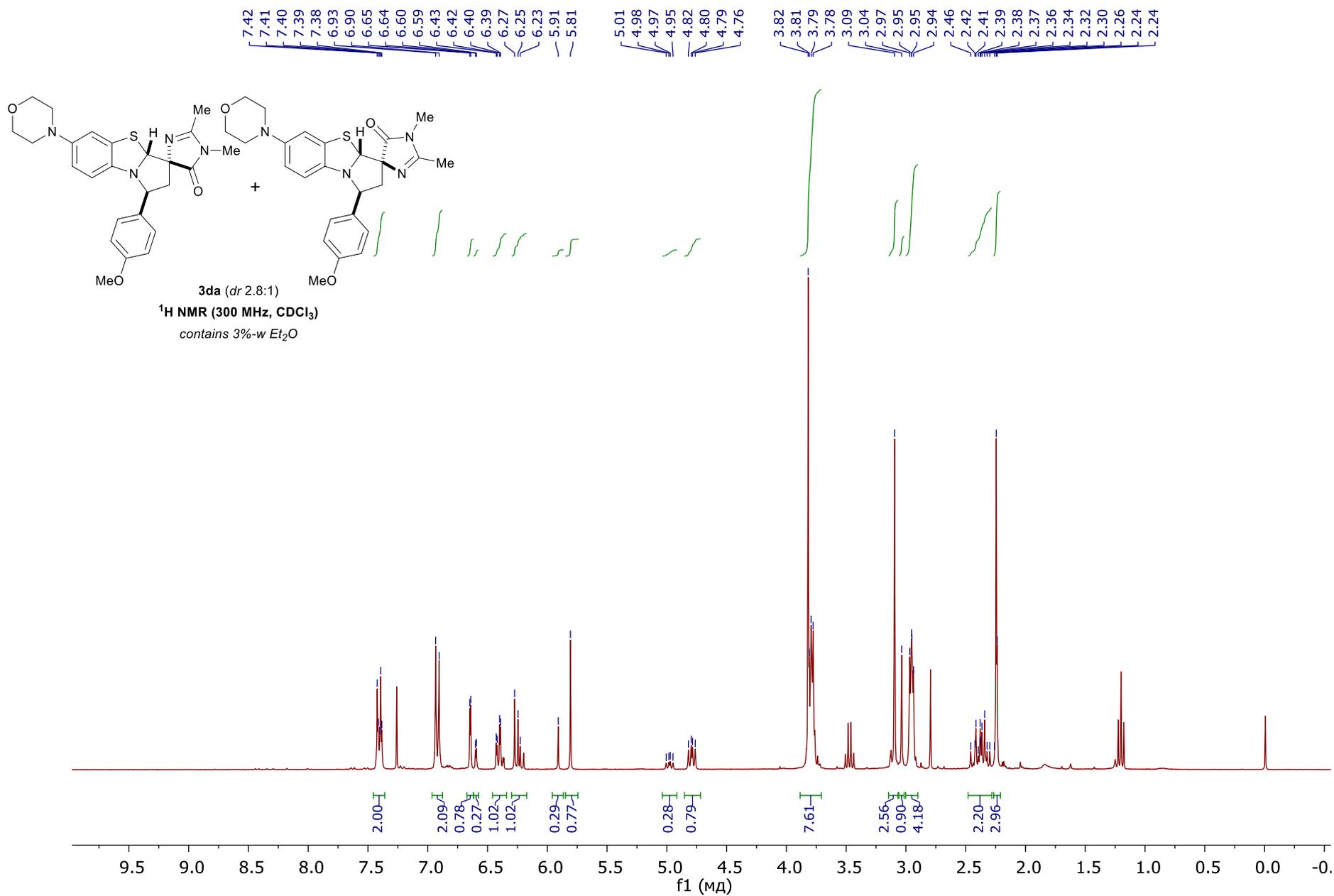


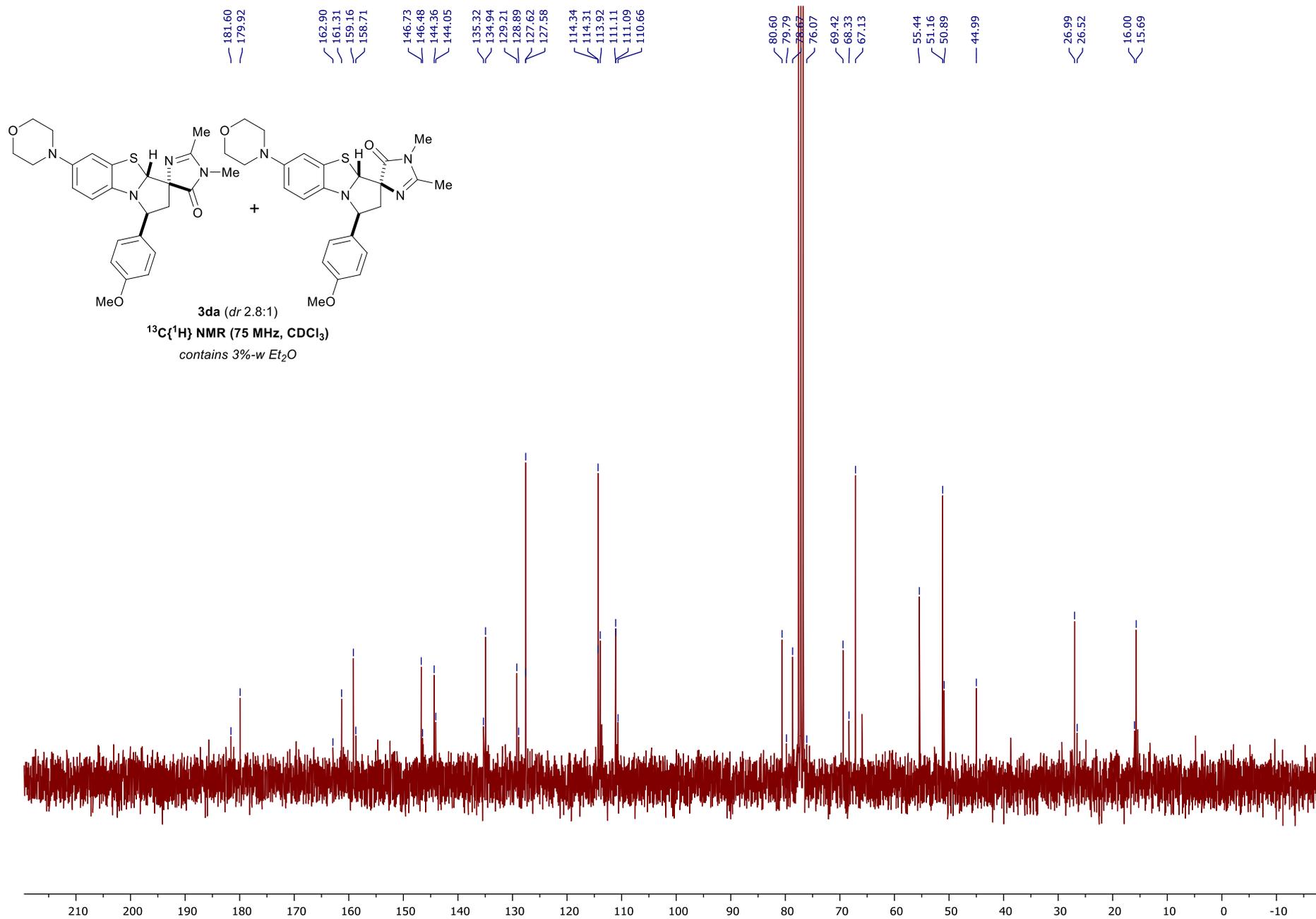


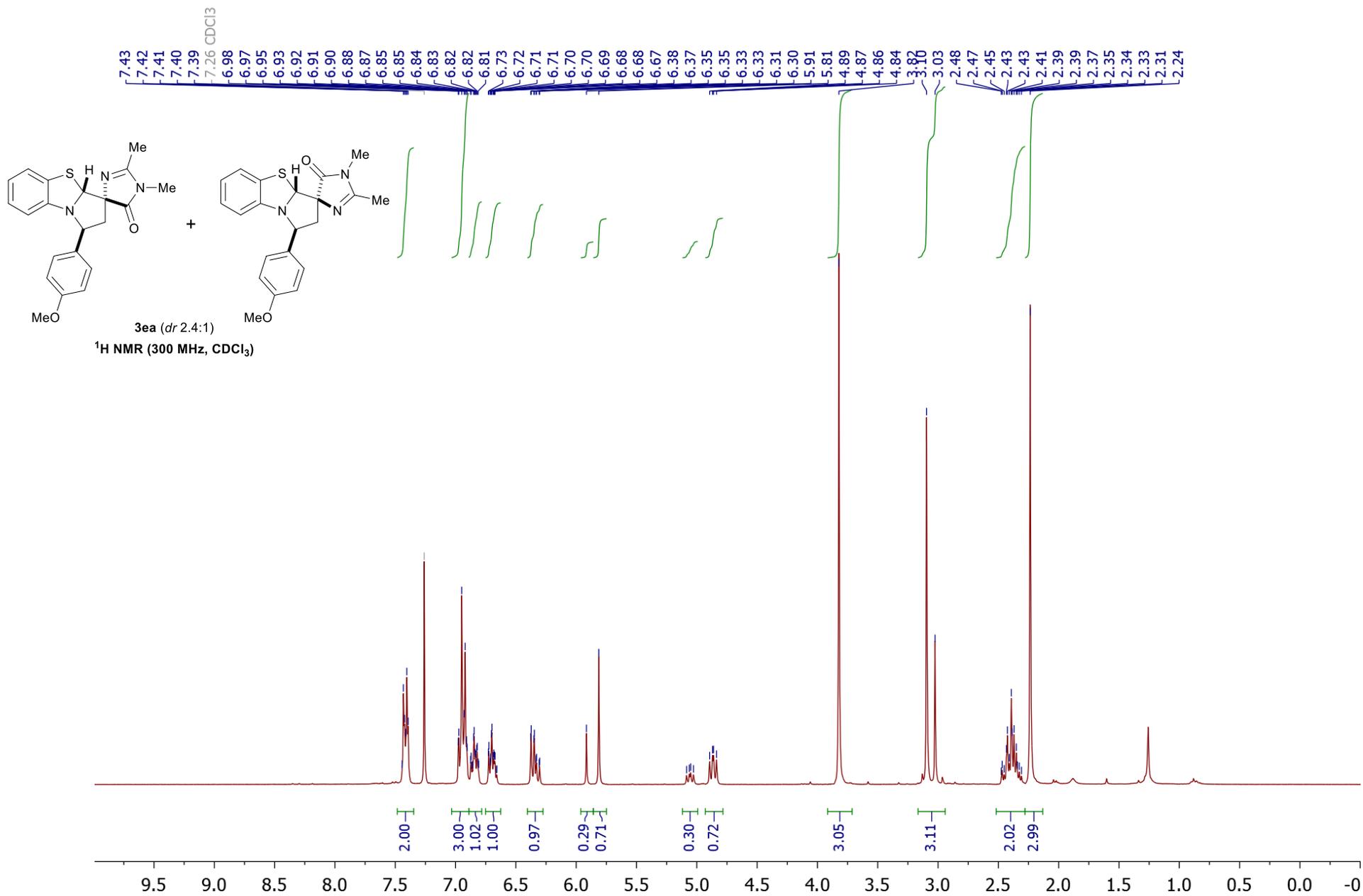


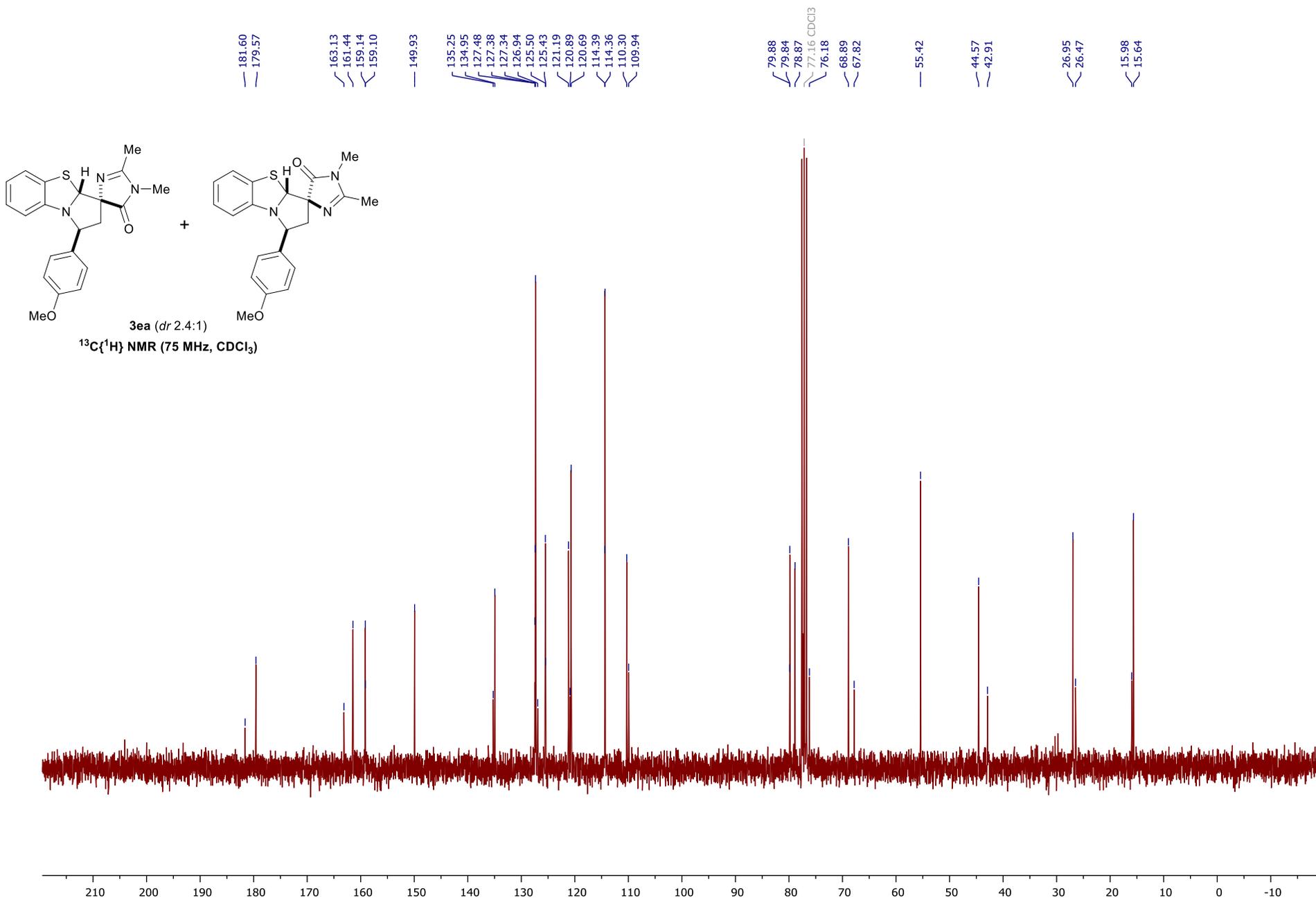


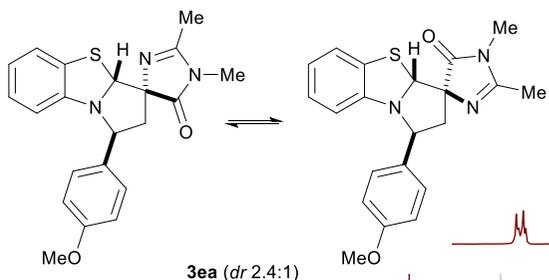




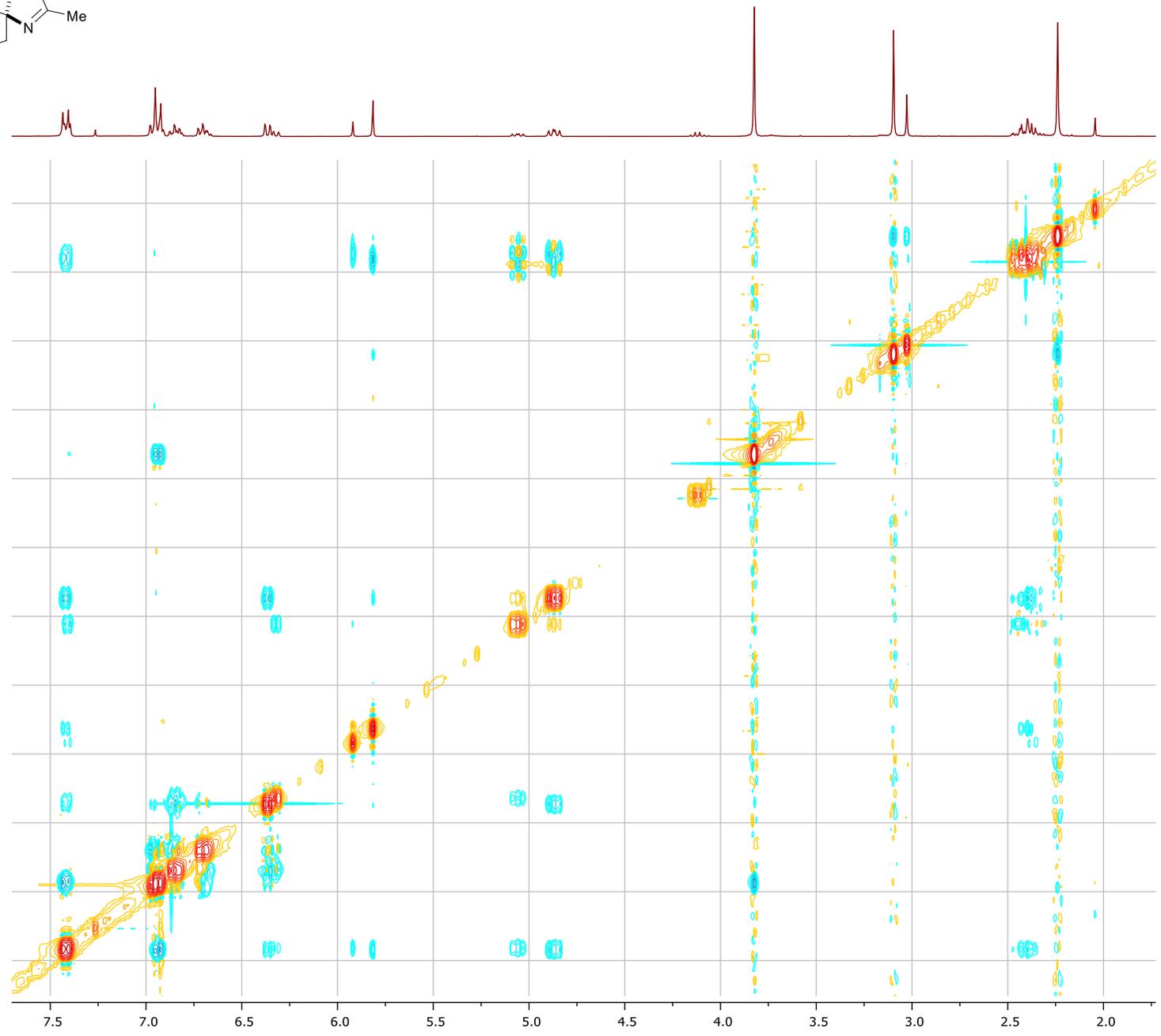


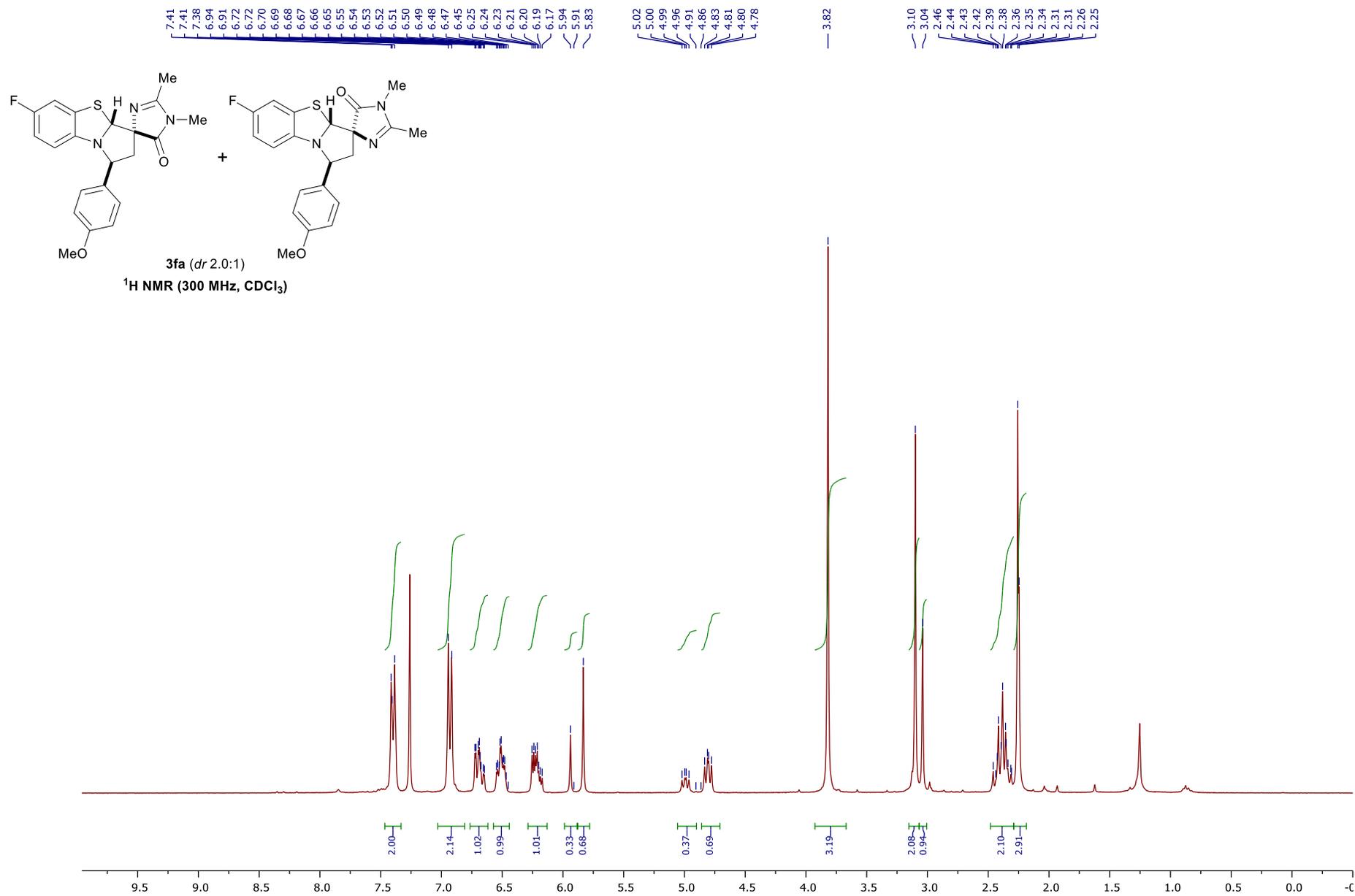


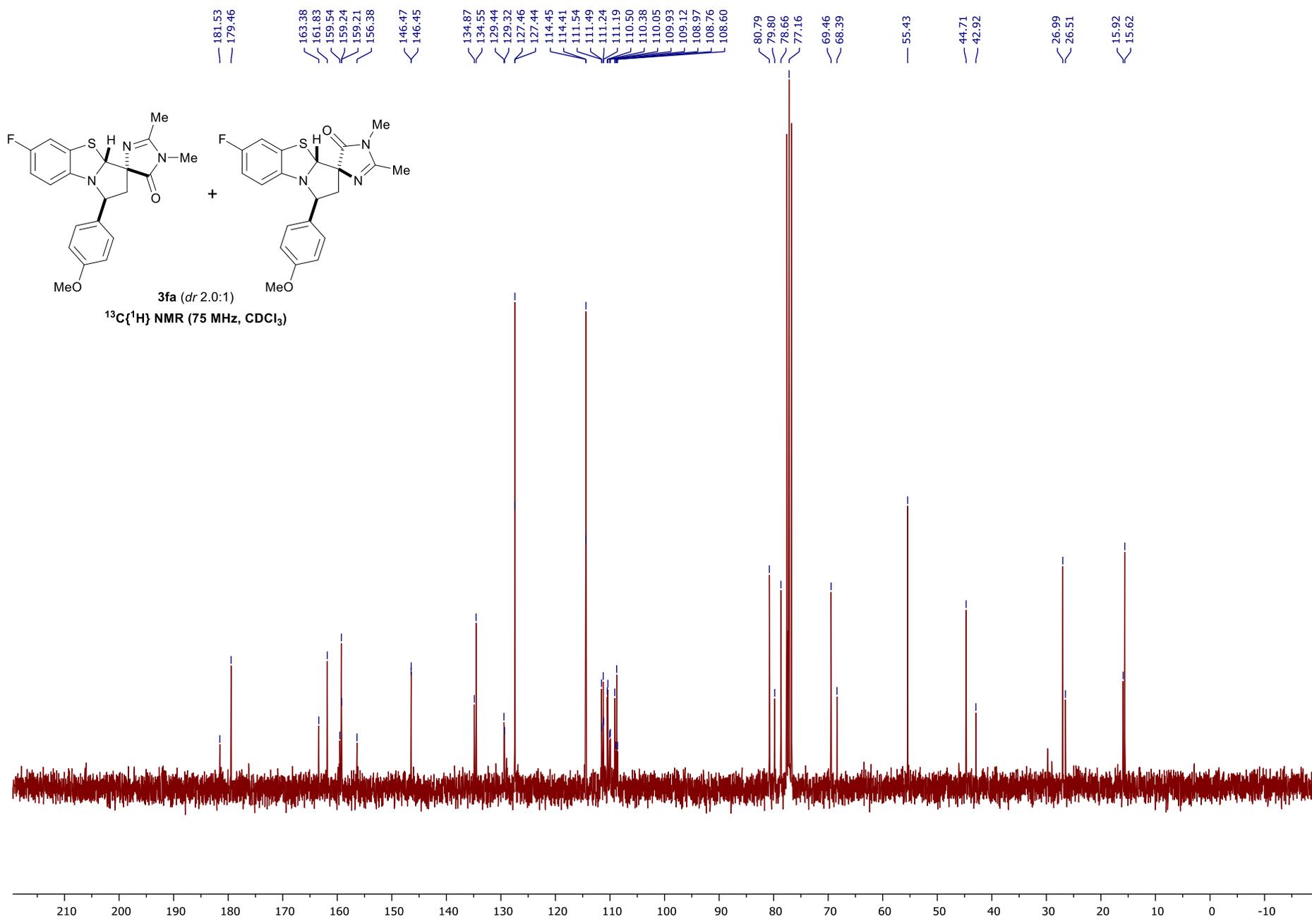


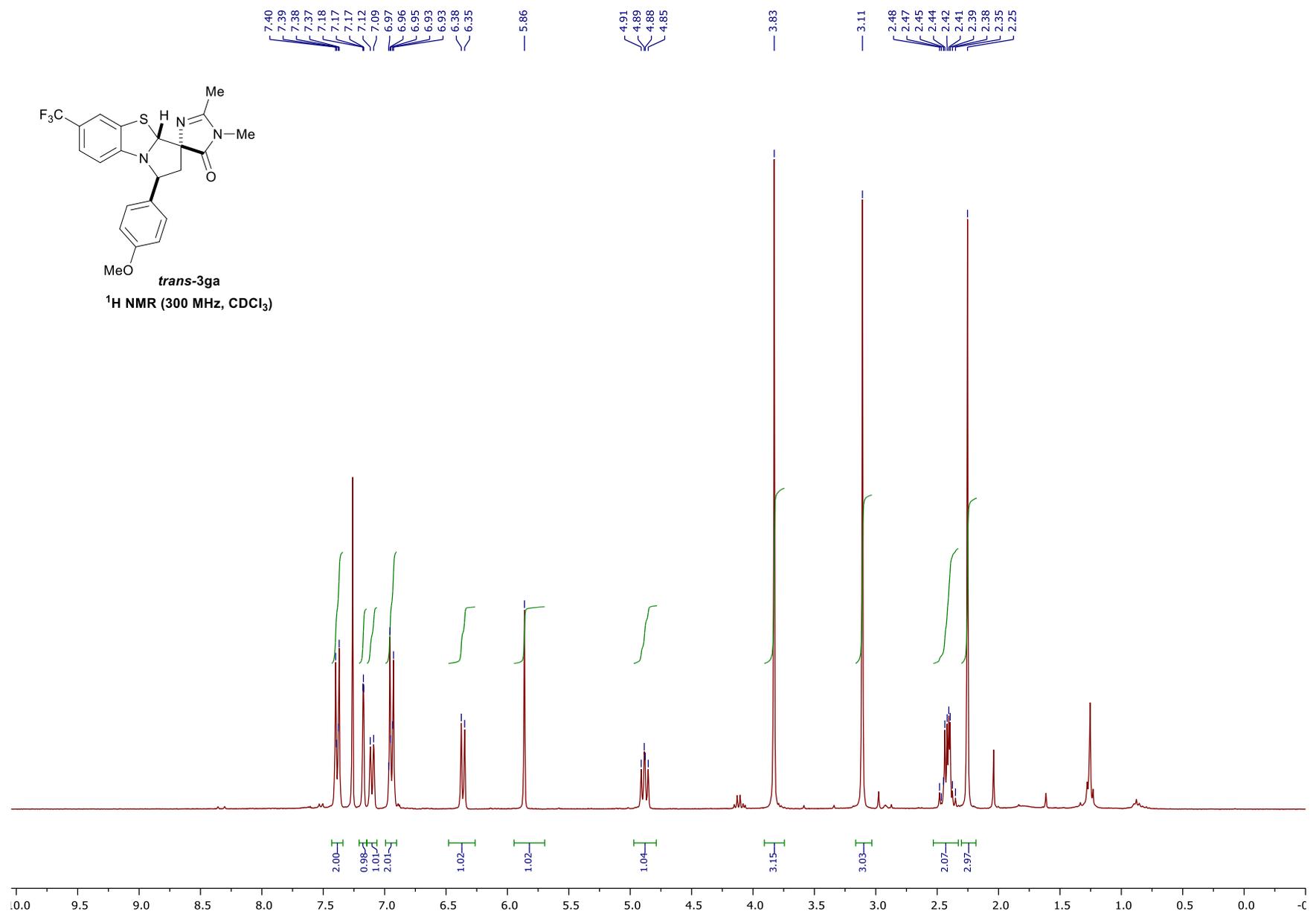


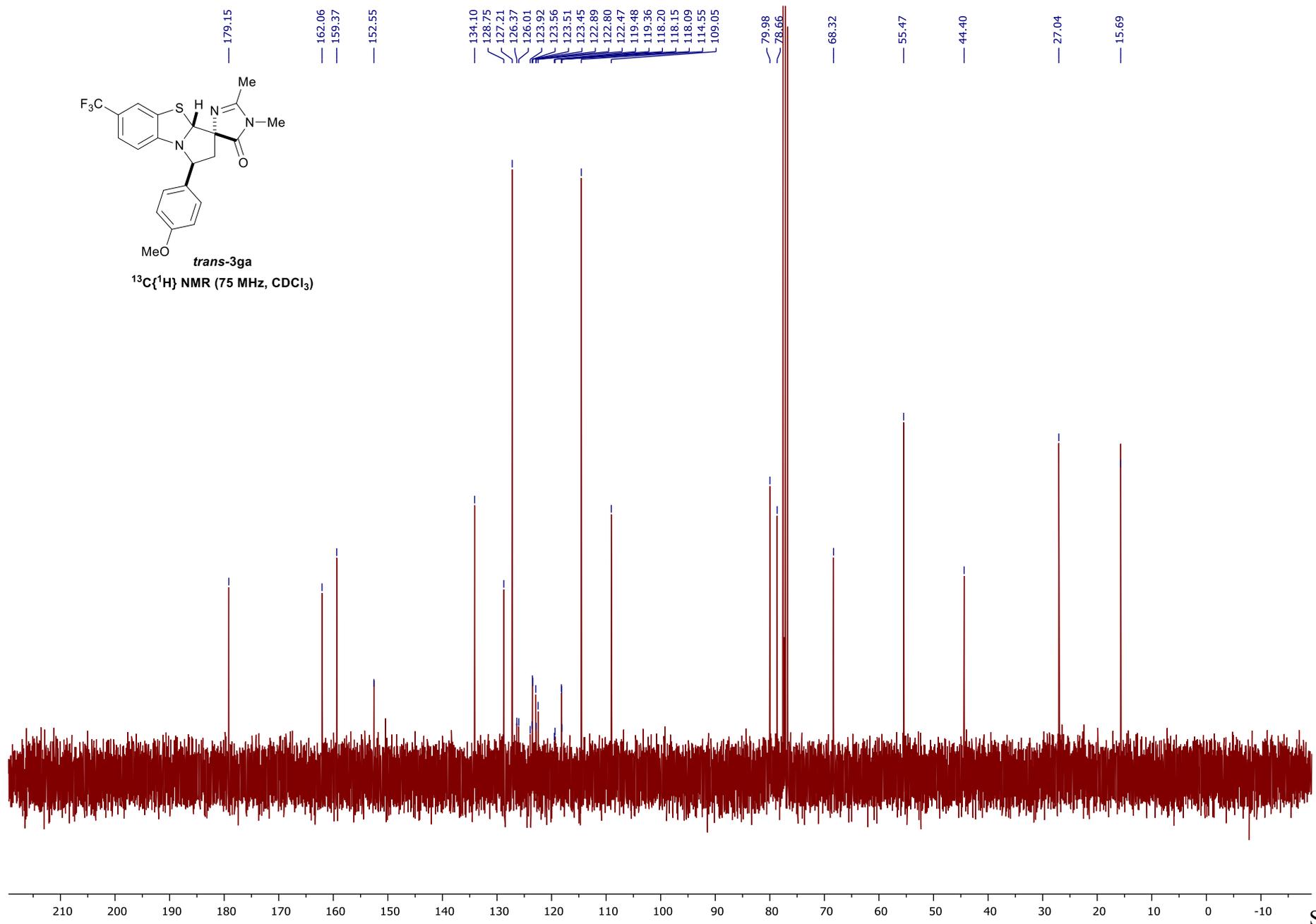
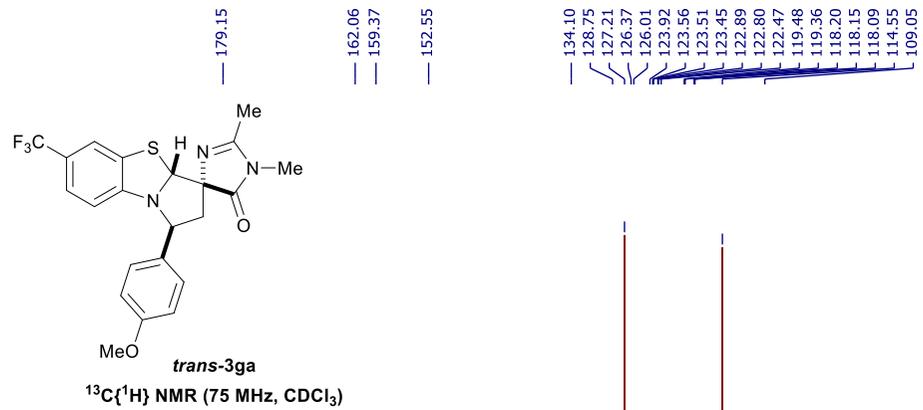
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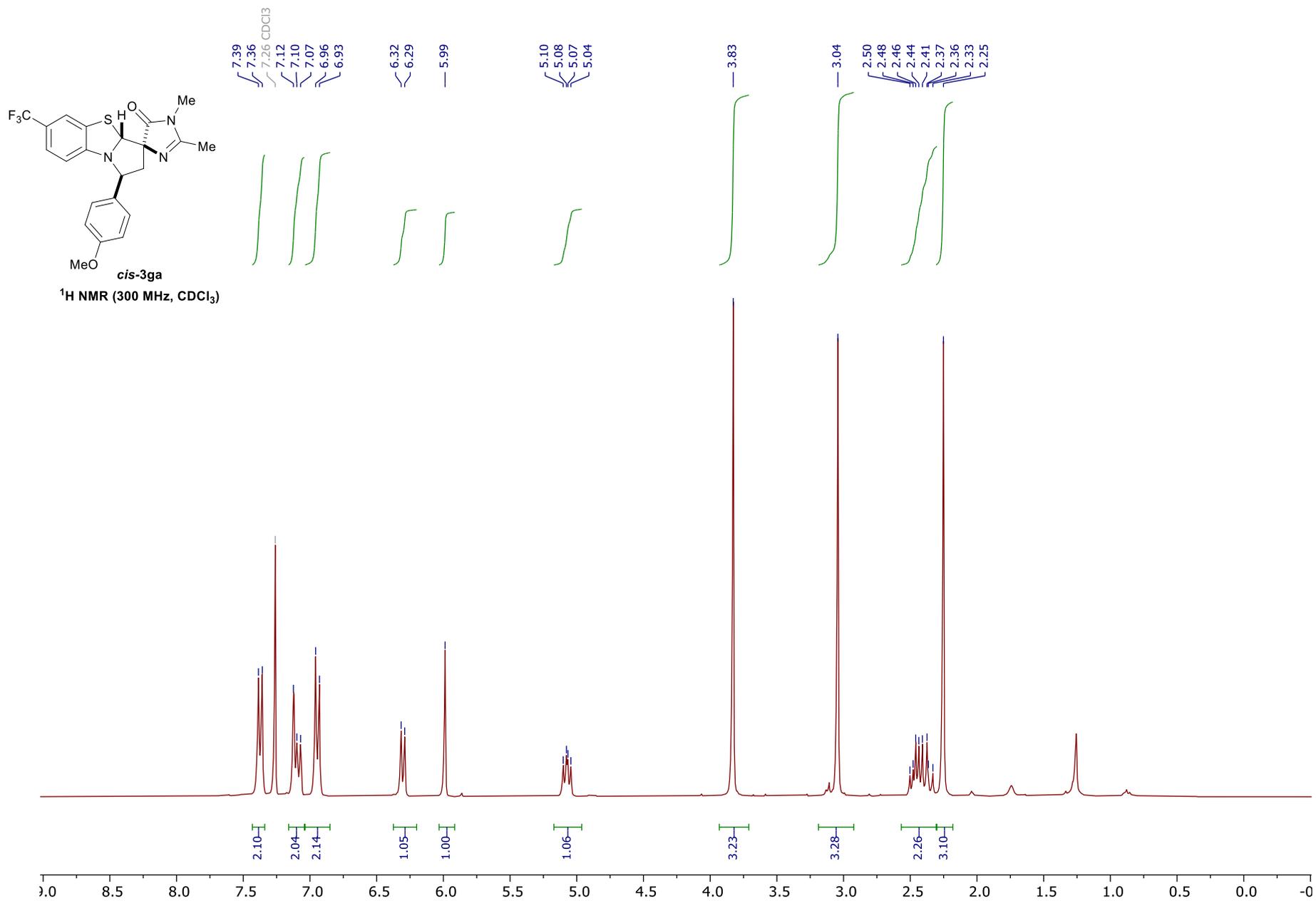


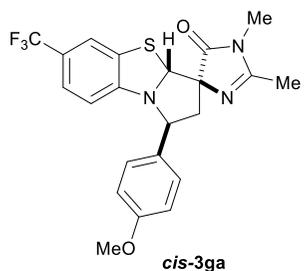




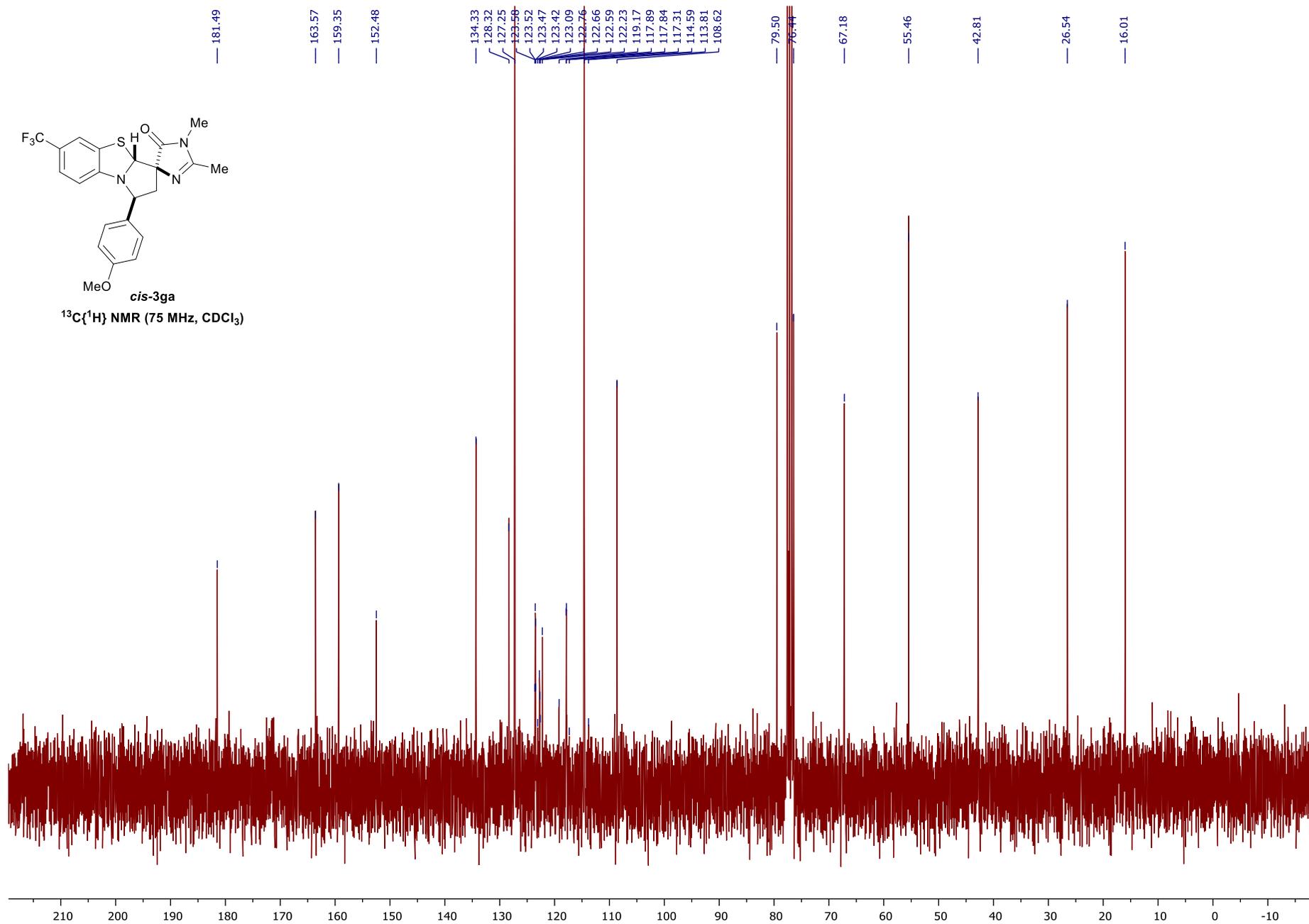


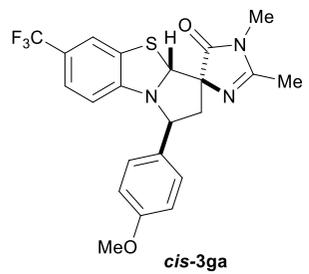




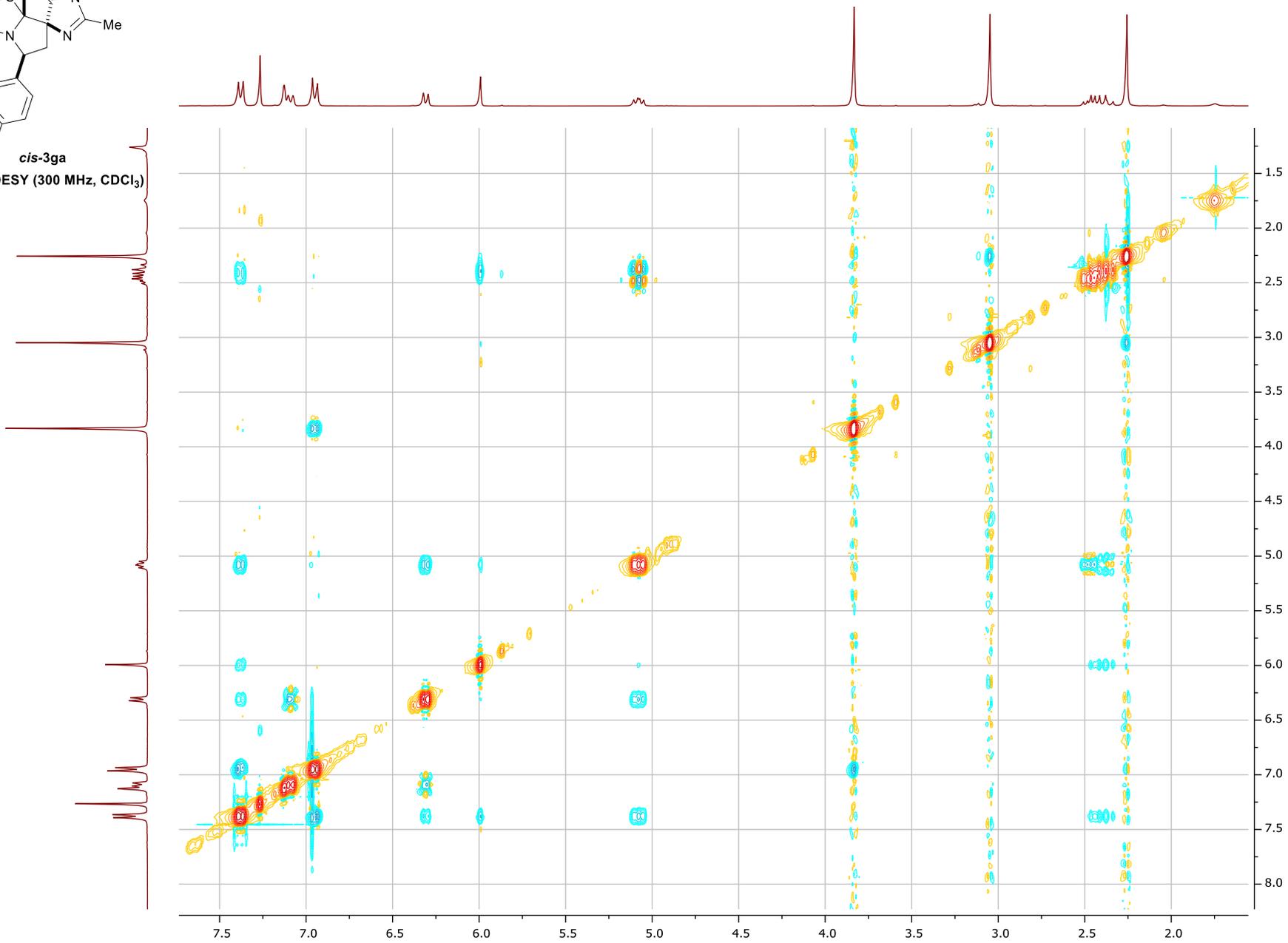


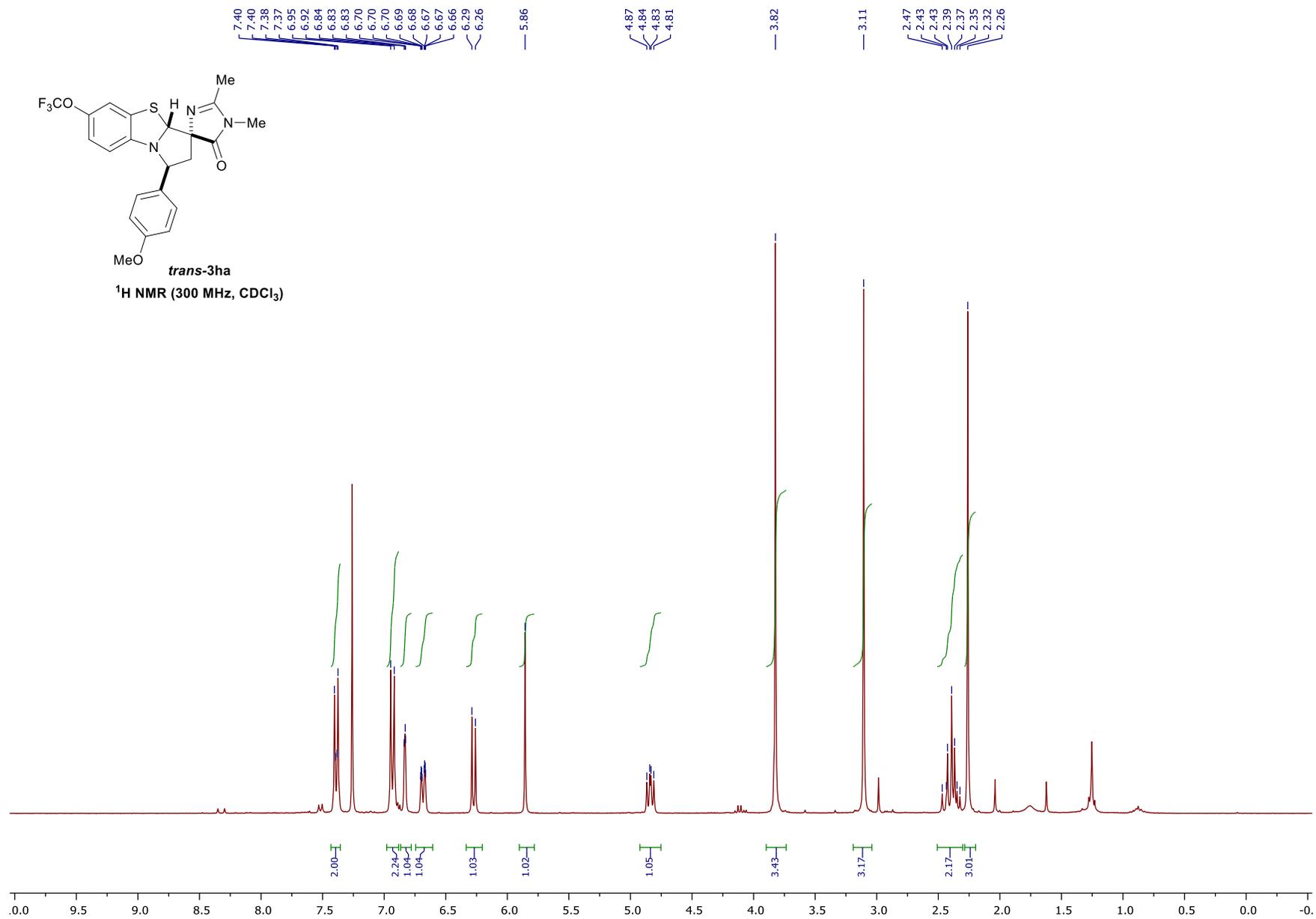
$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)

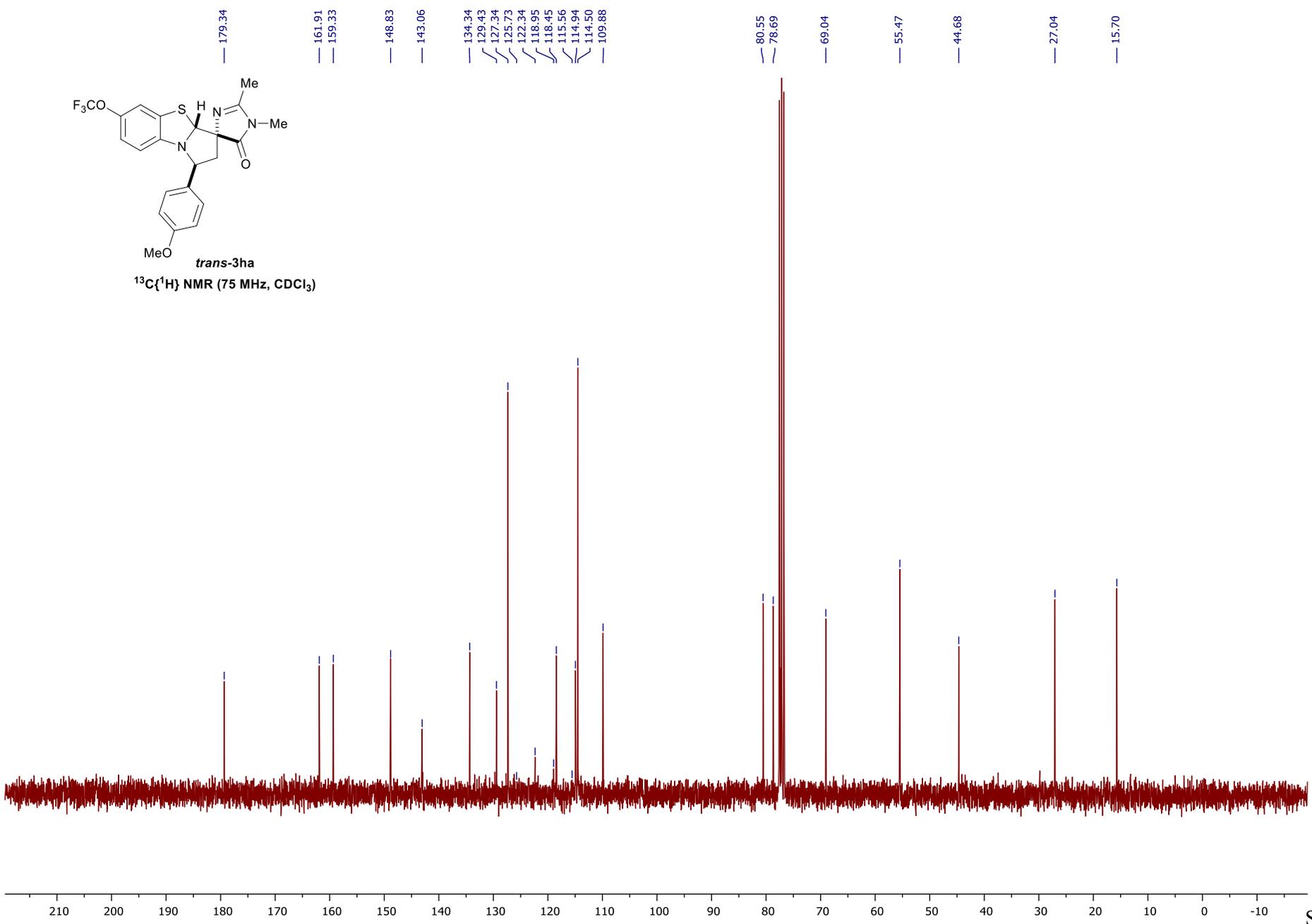
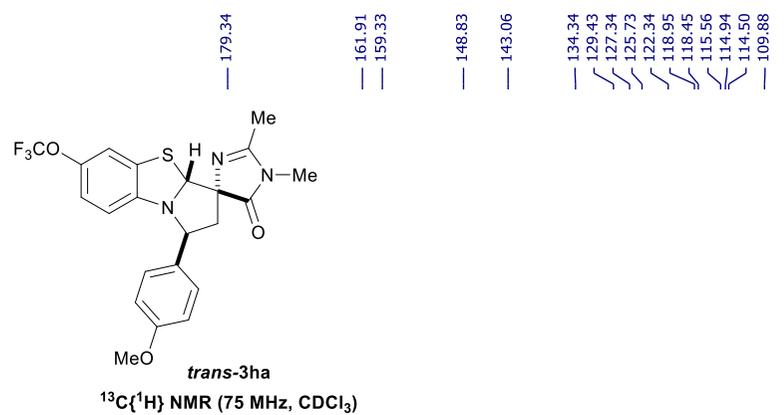


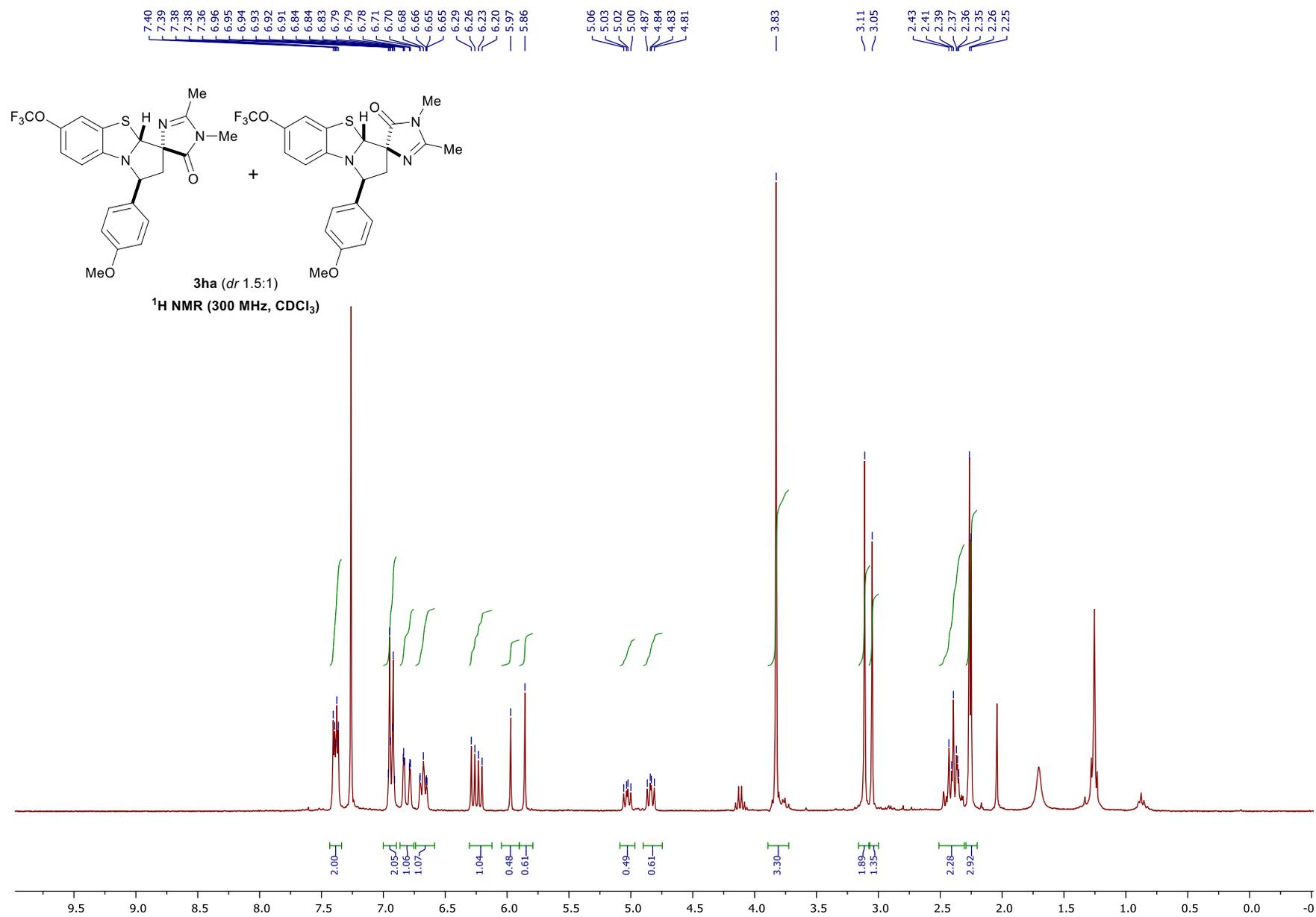


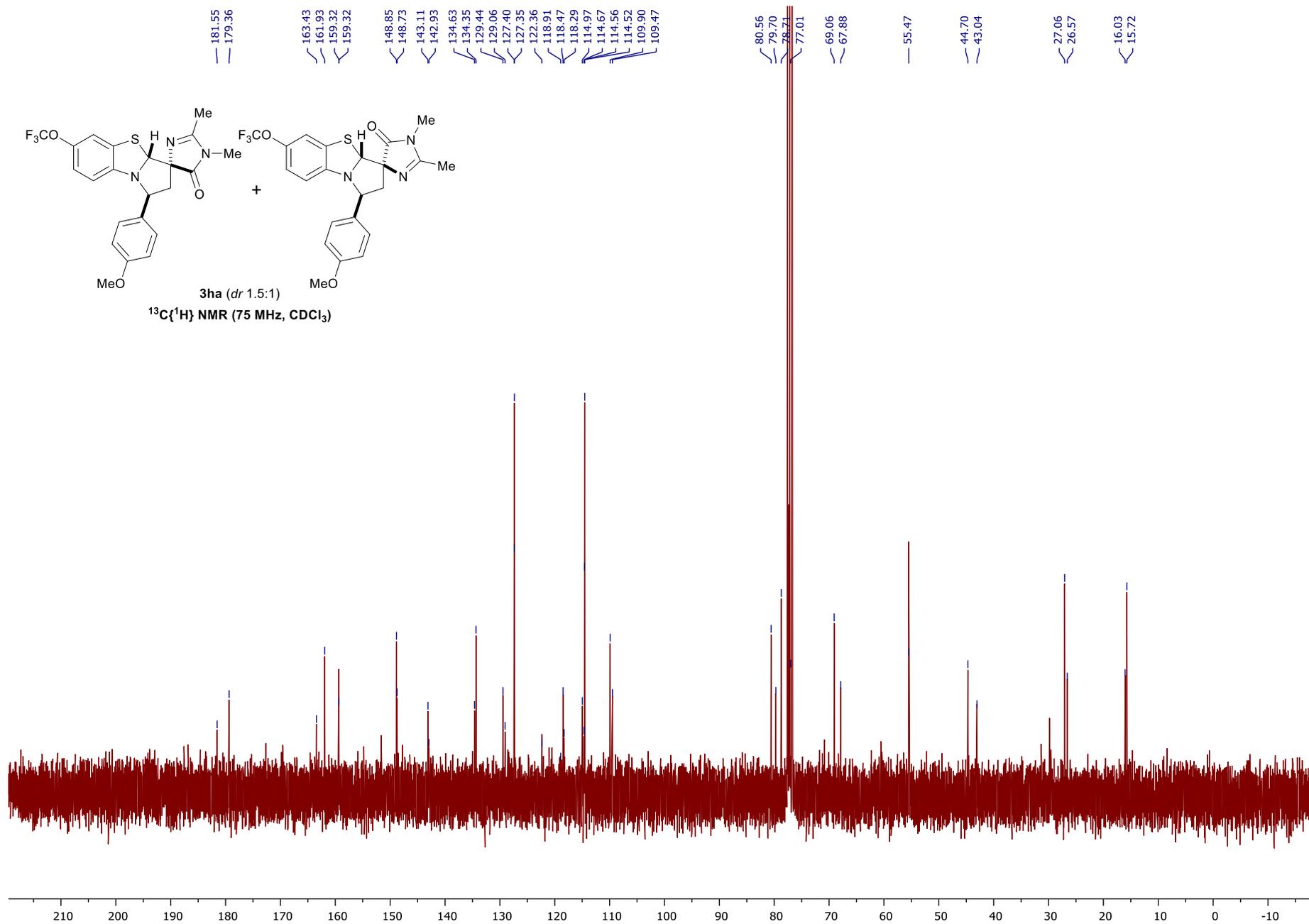
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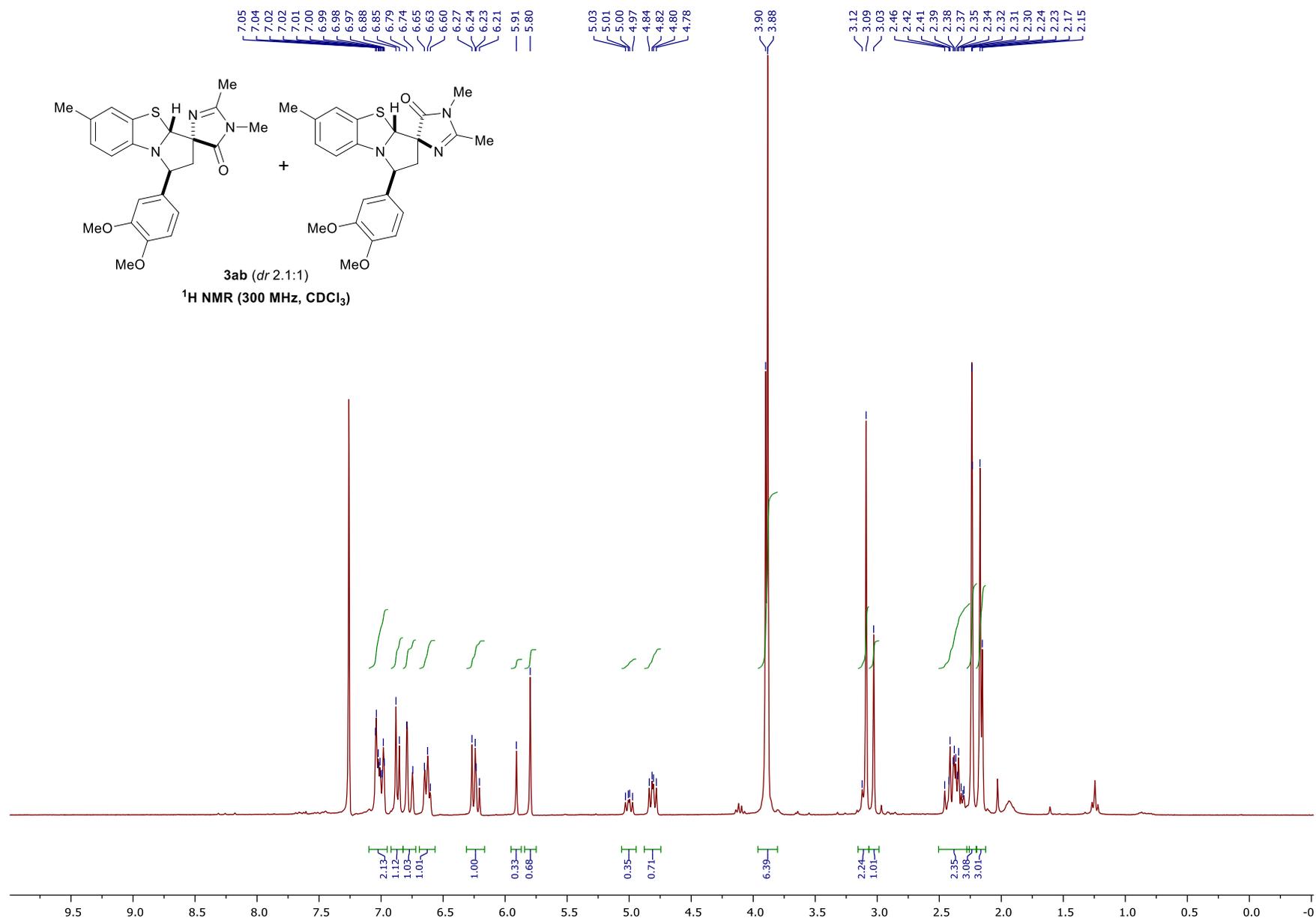


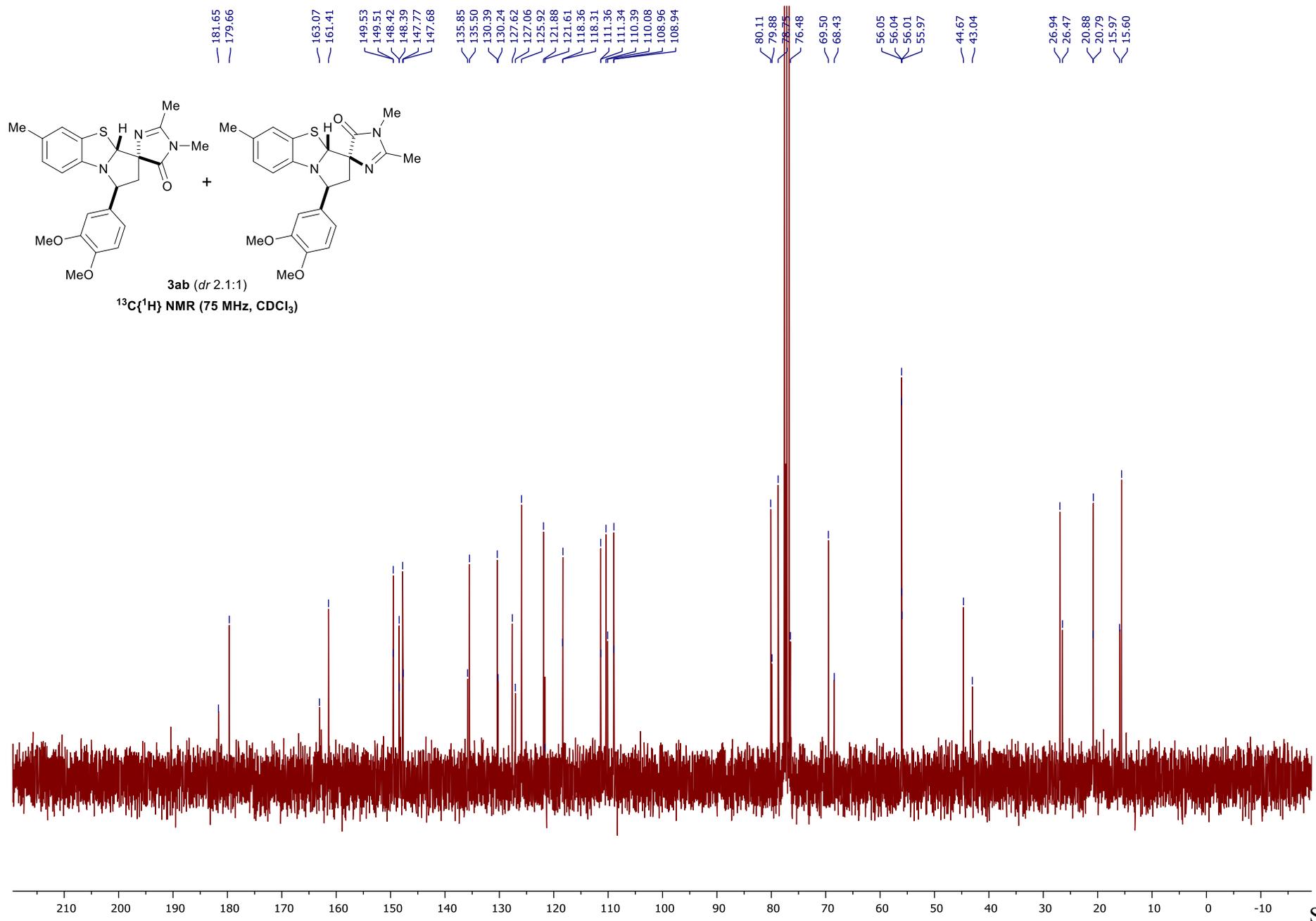


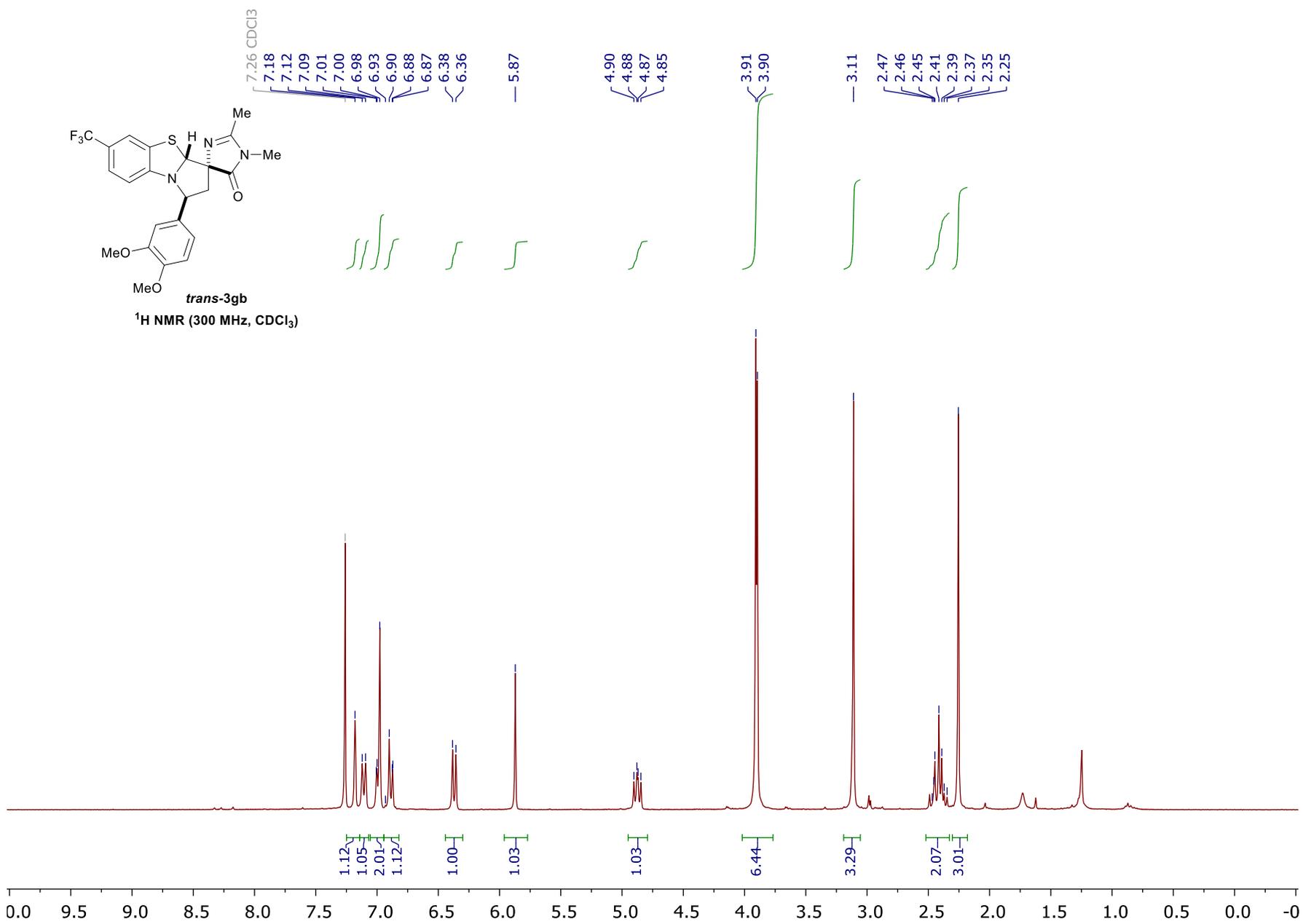


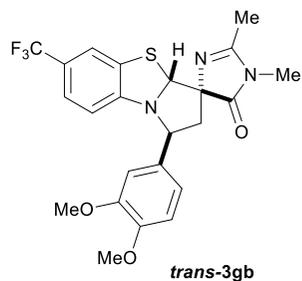




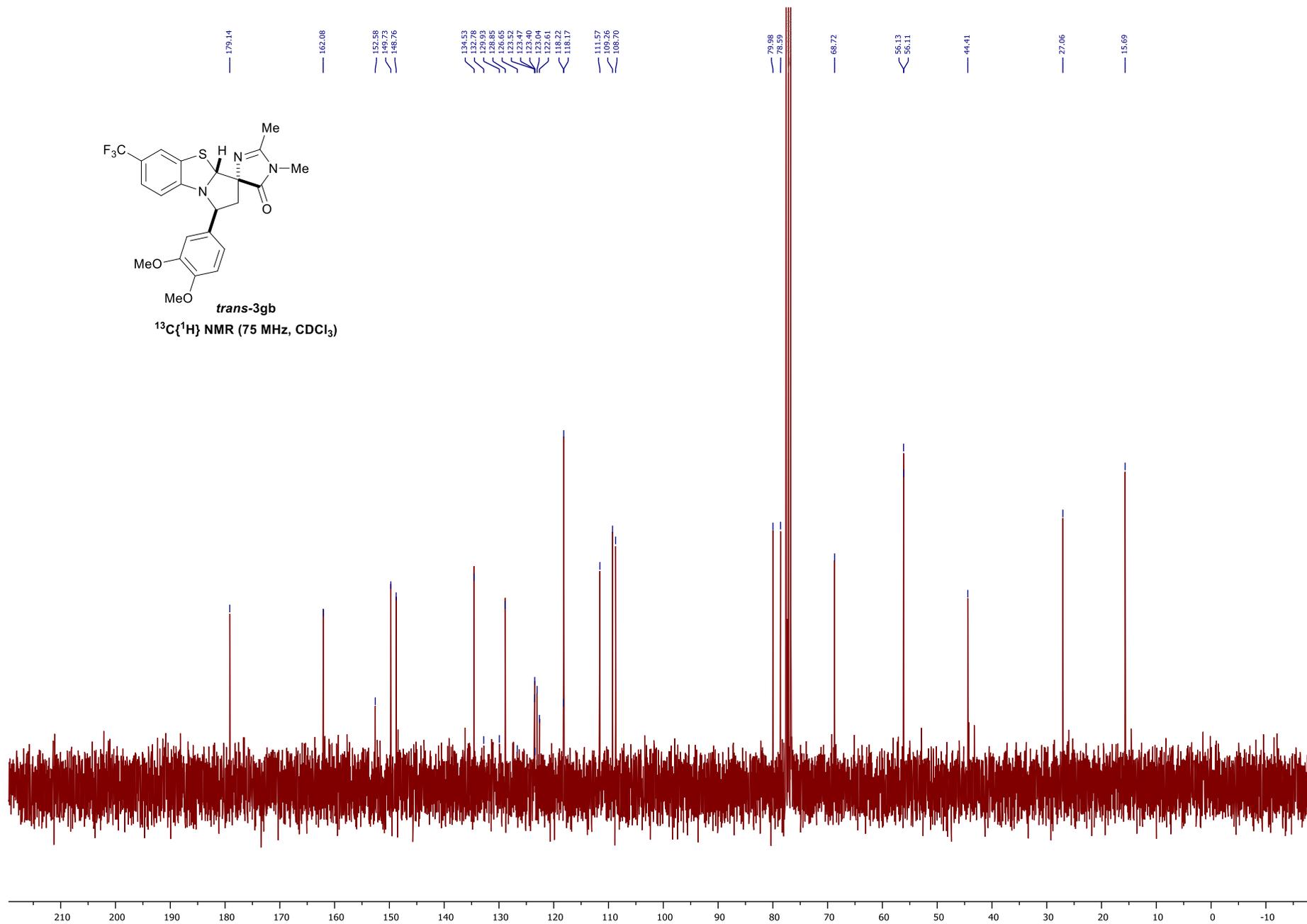


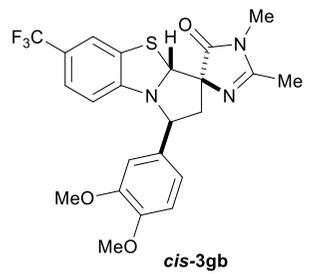




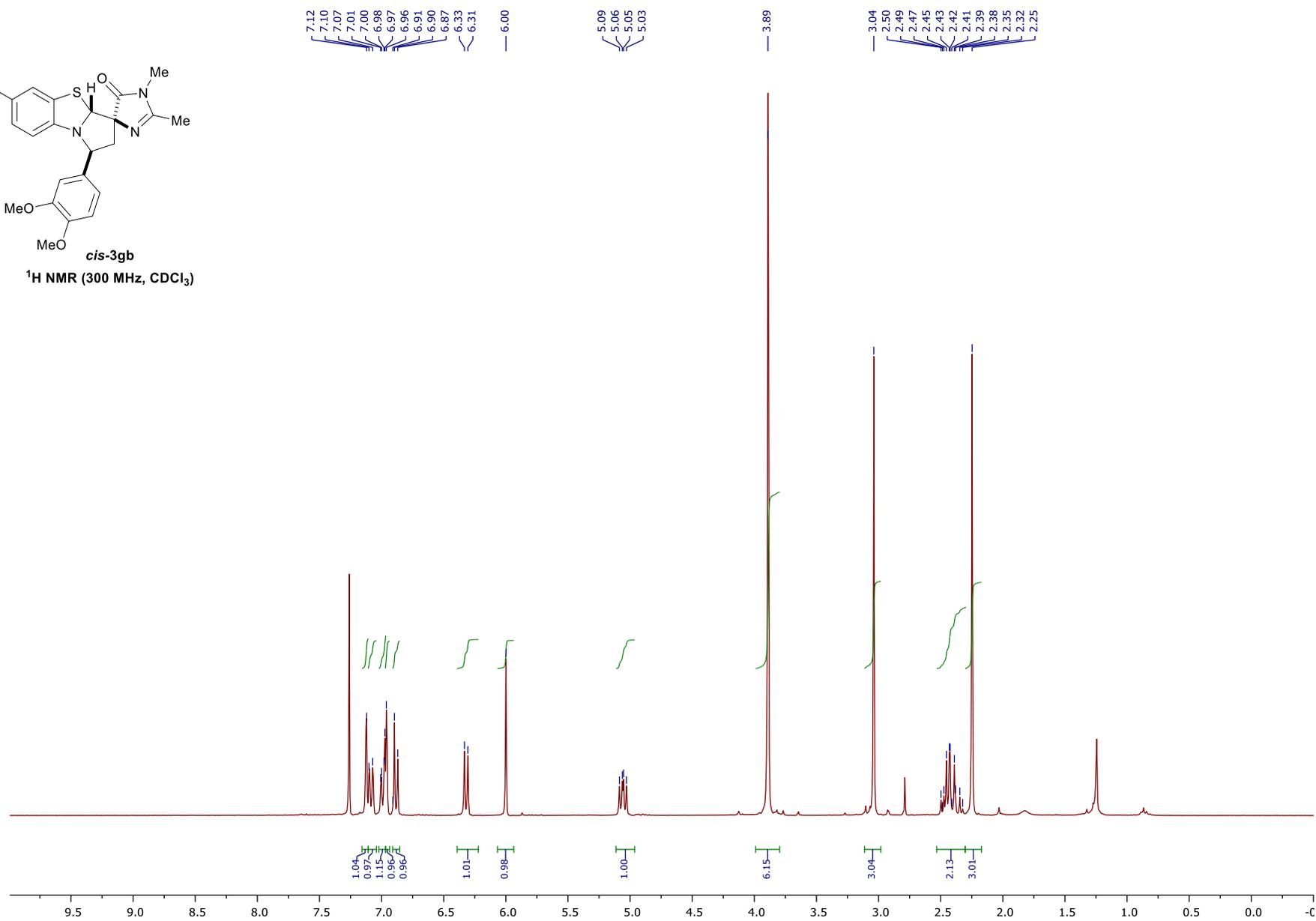


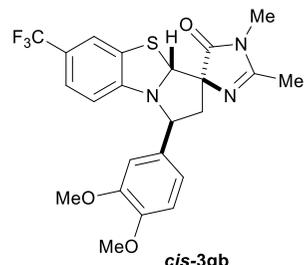
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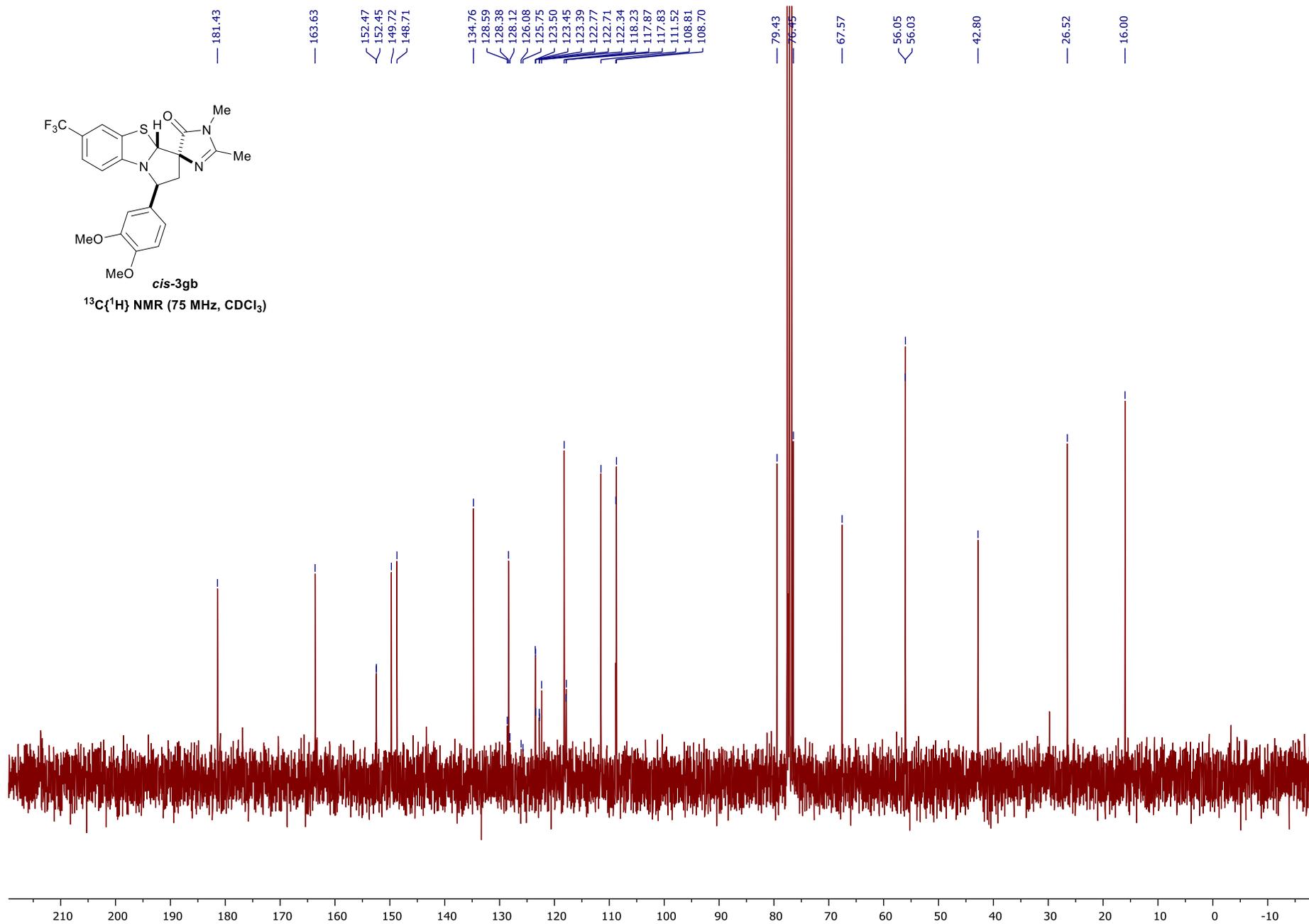


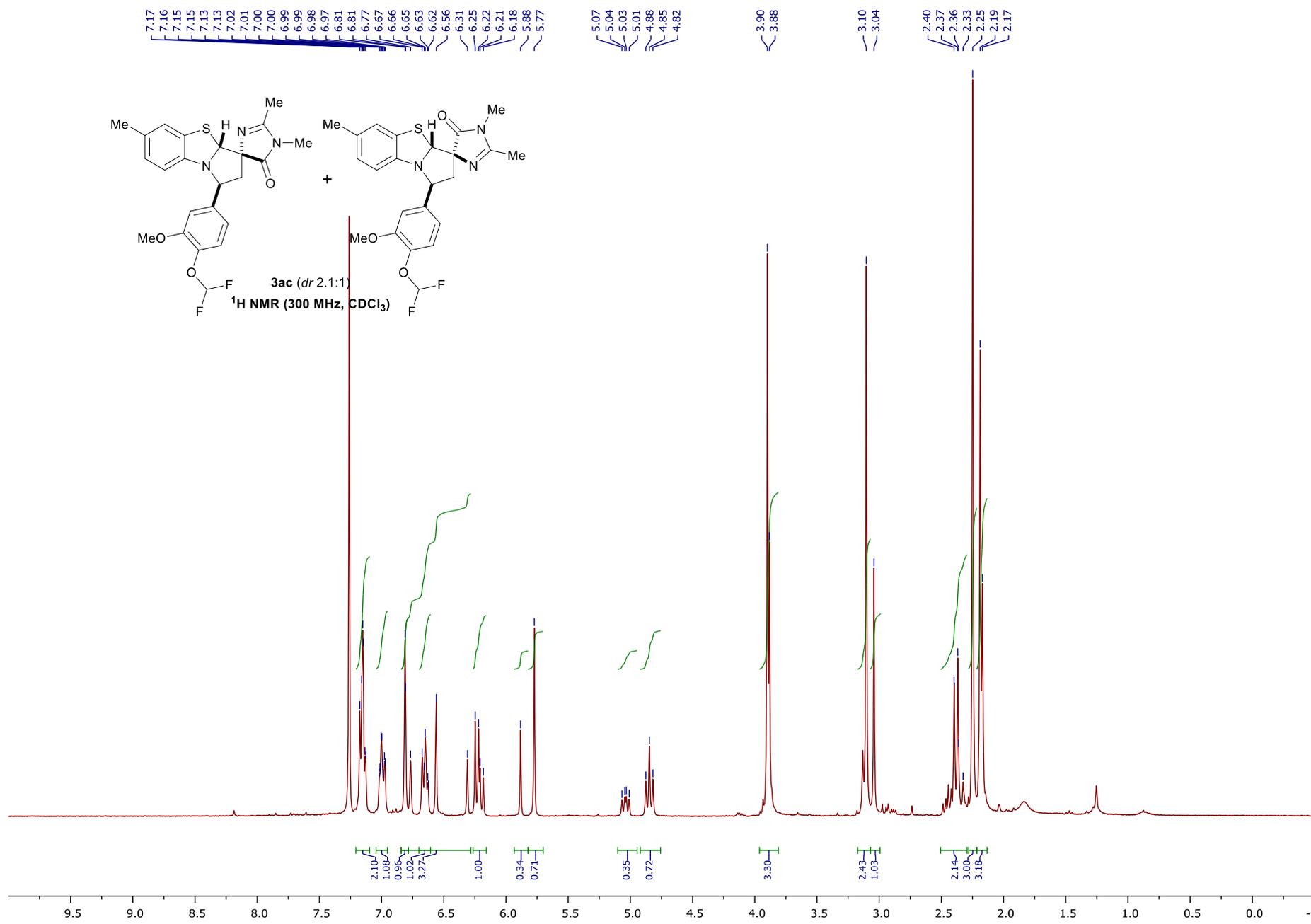
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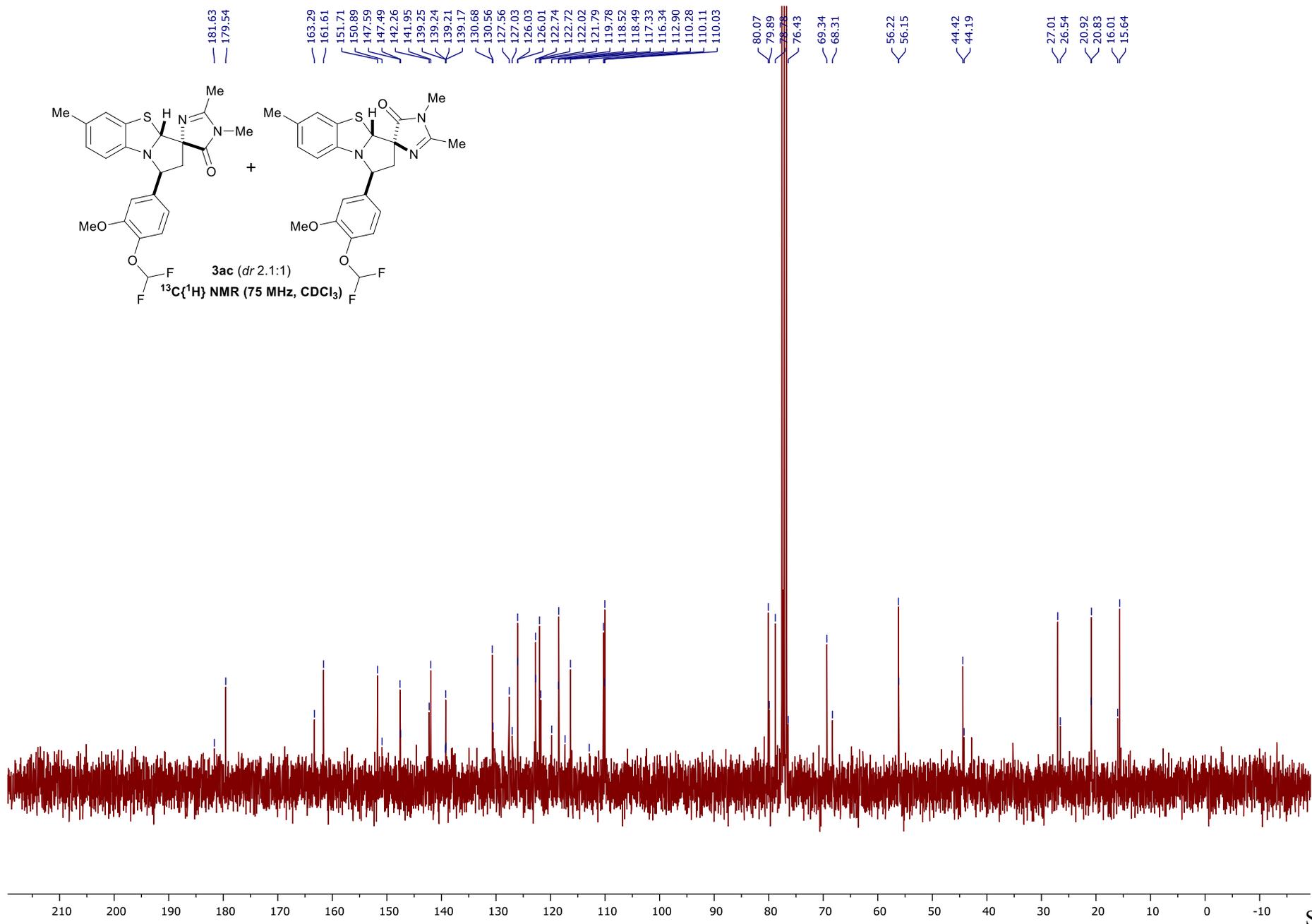


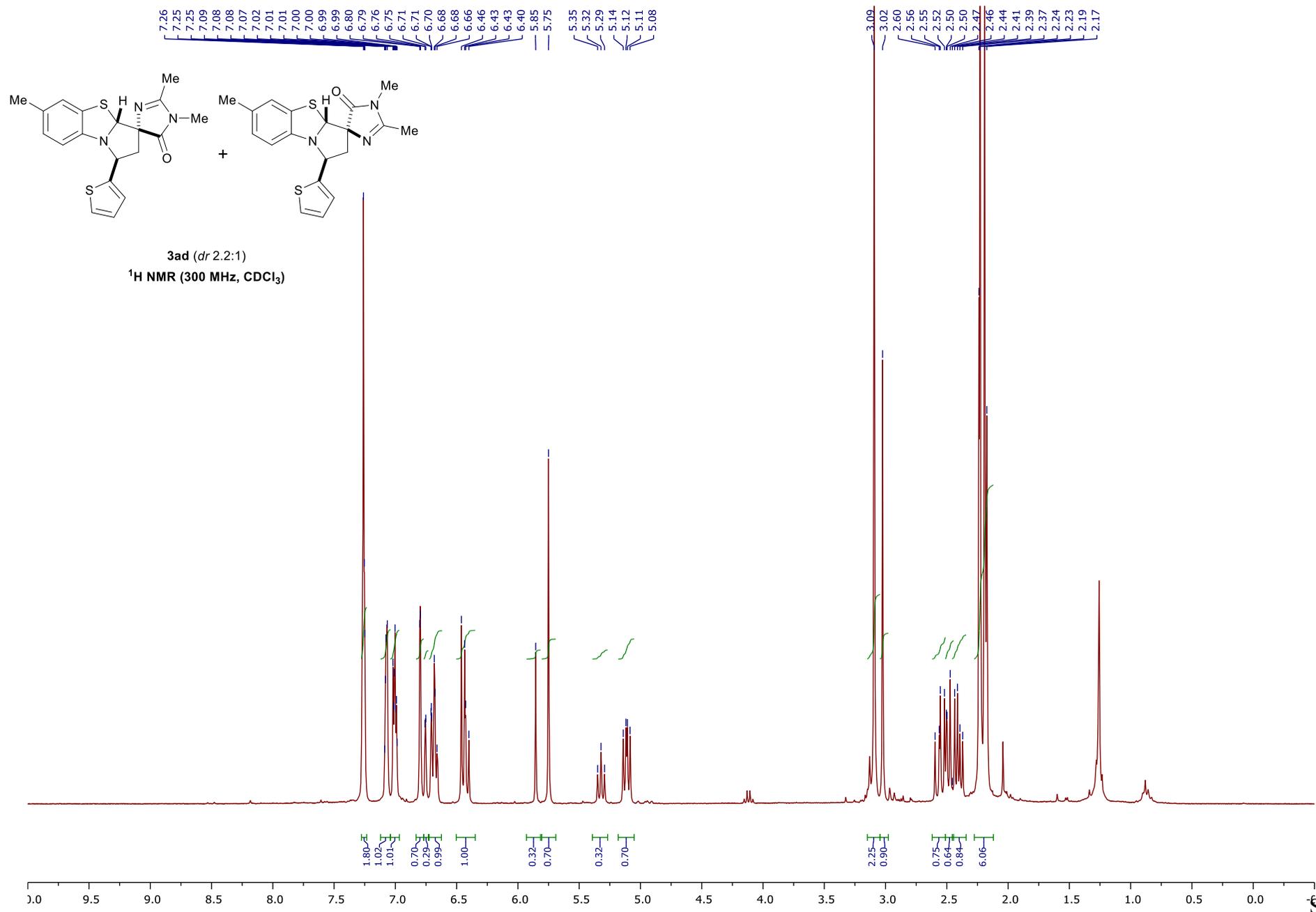


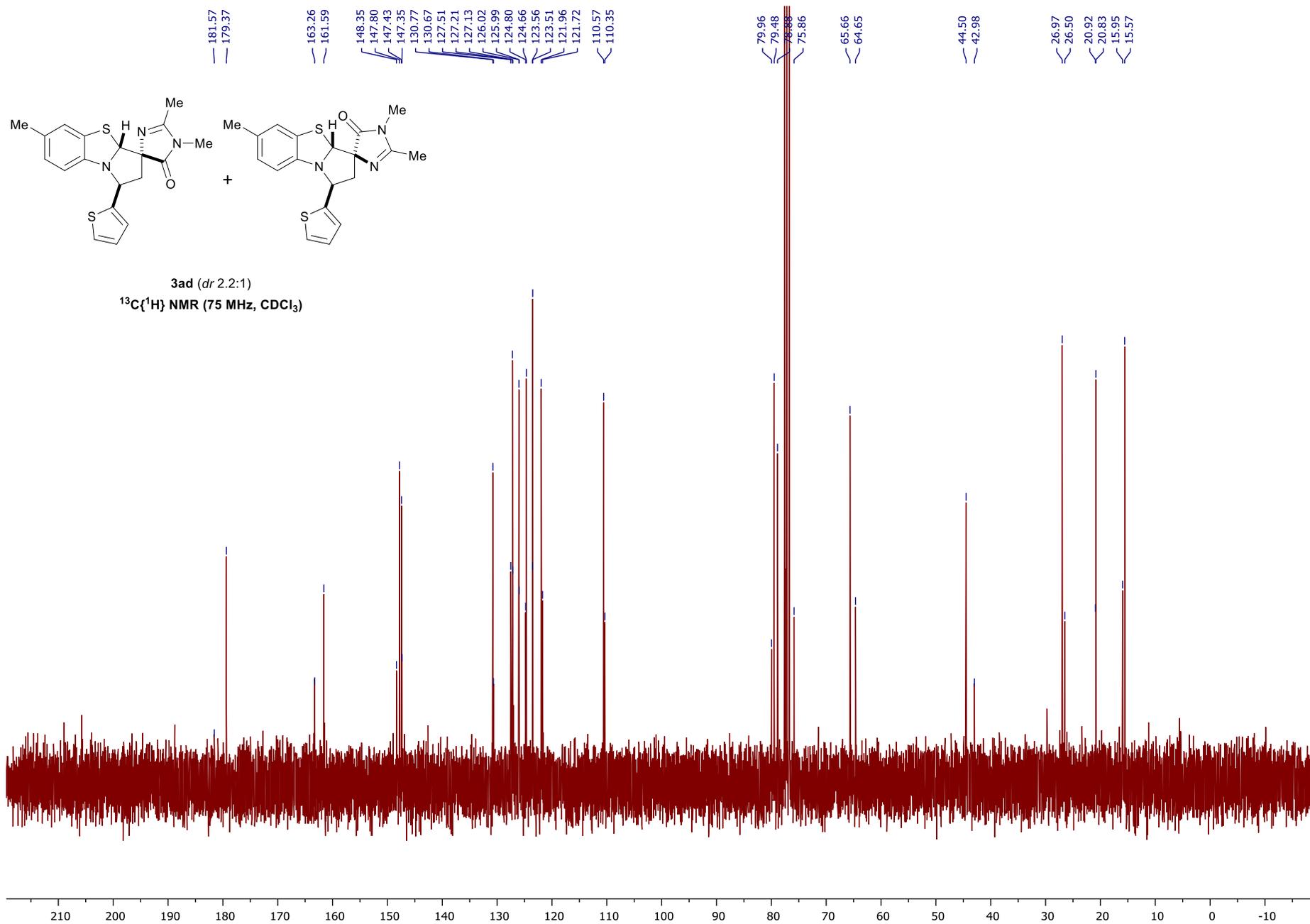
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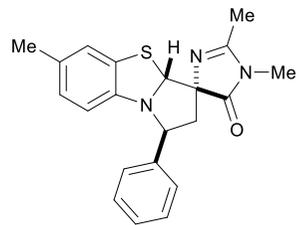




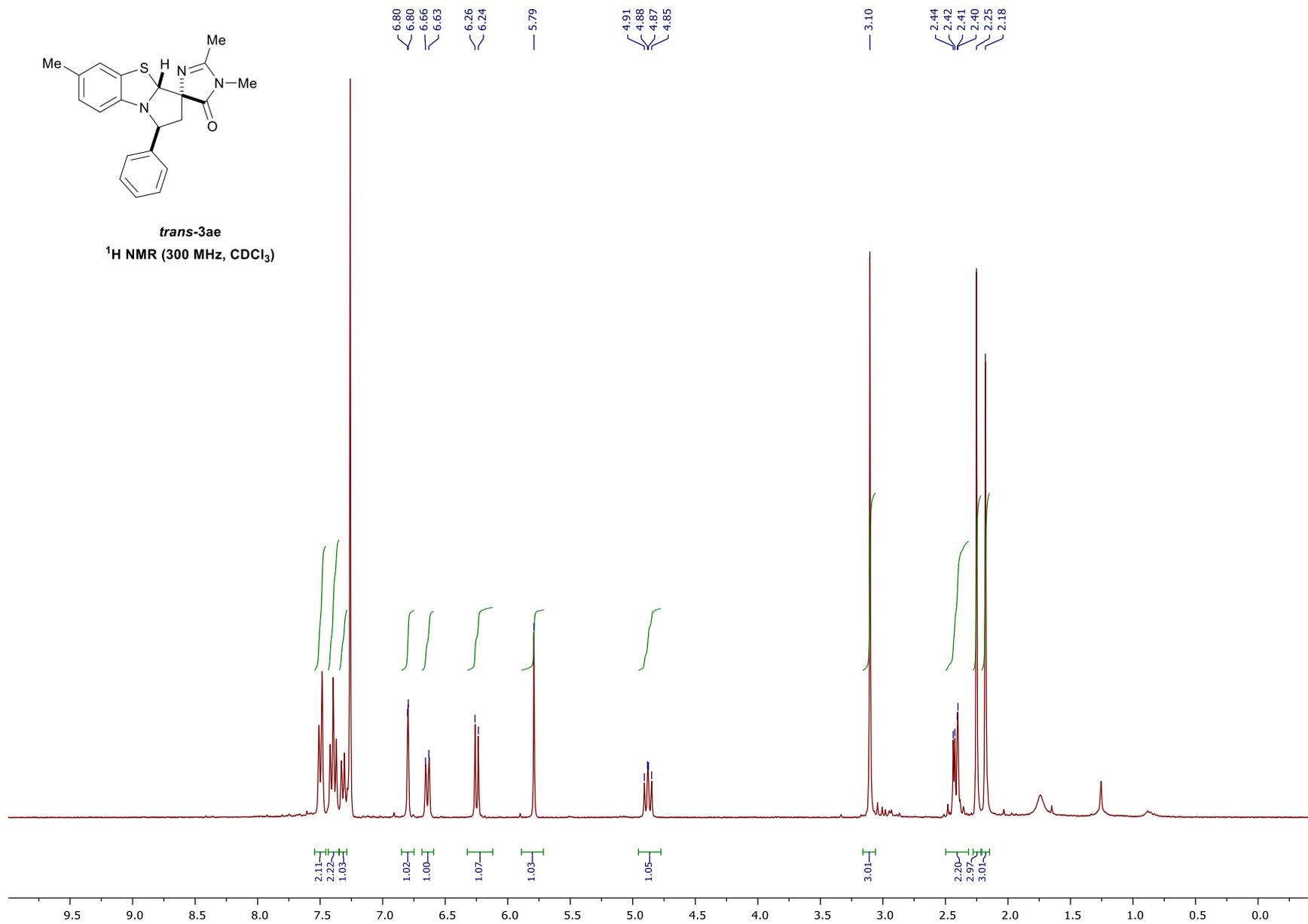


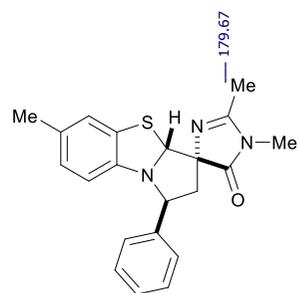






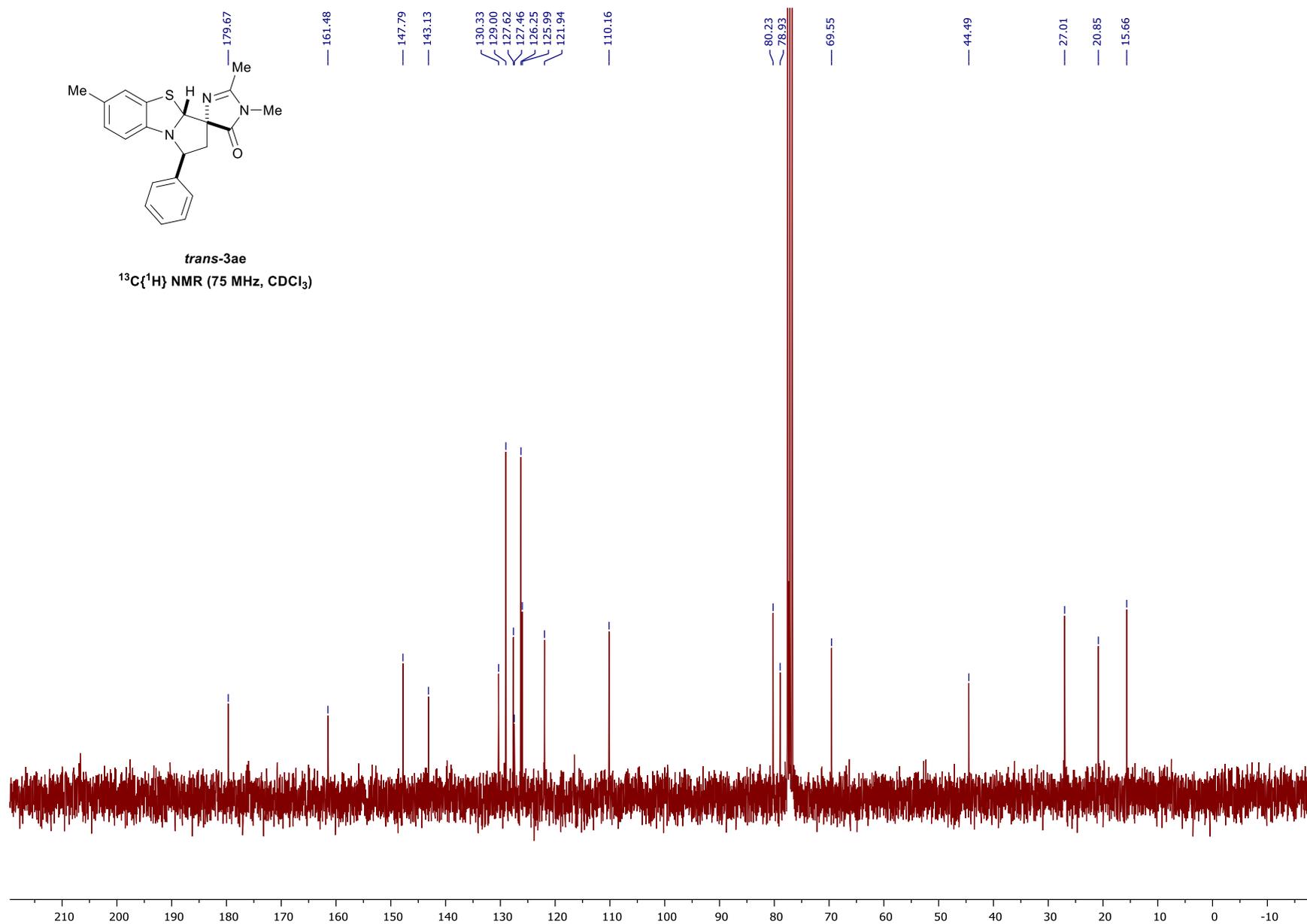
trans-3ae
¹H NMR (300 MHz, CDCl₃)

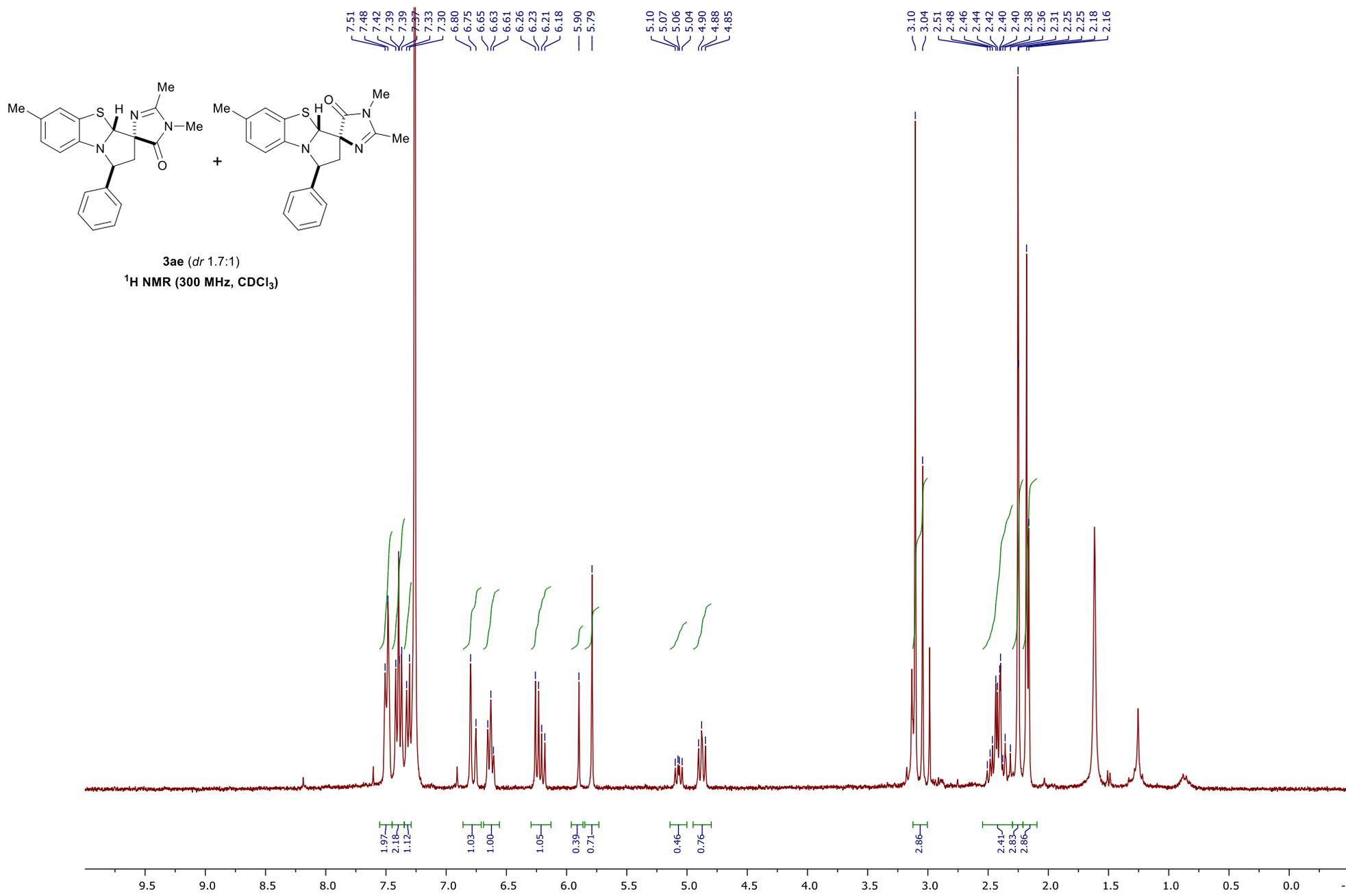


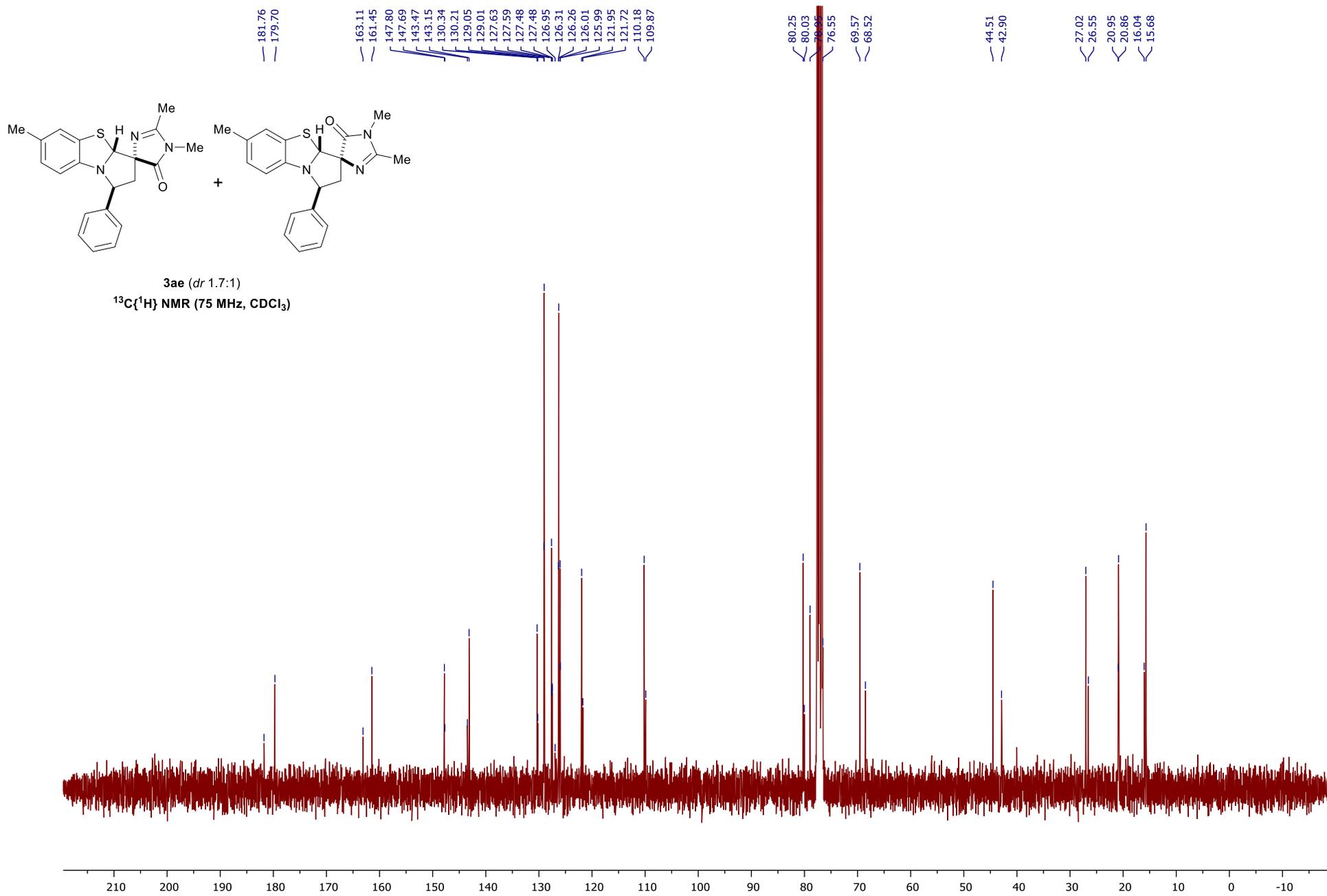


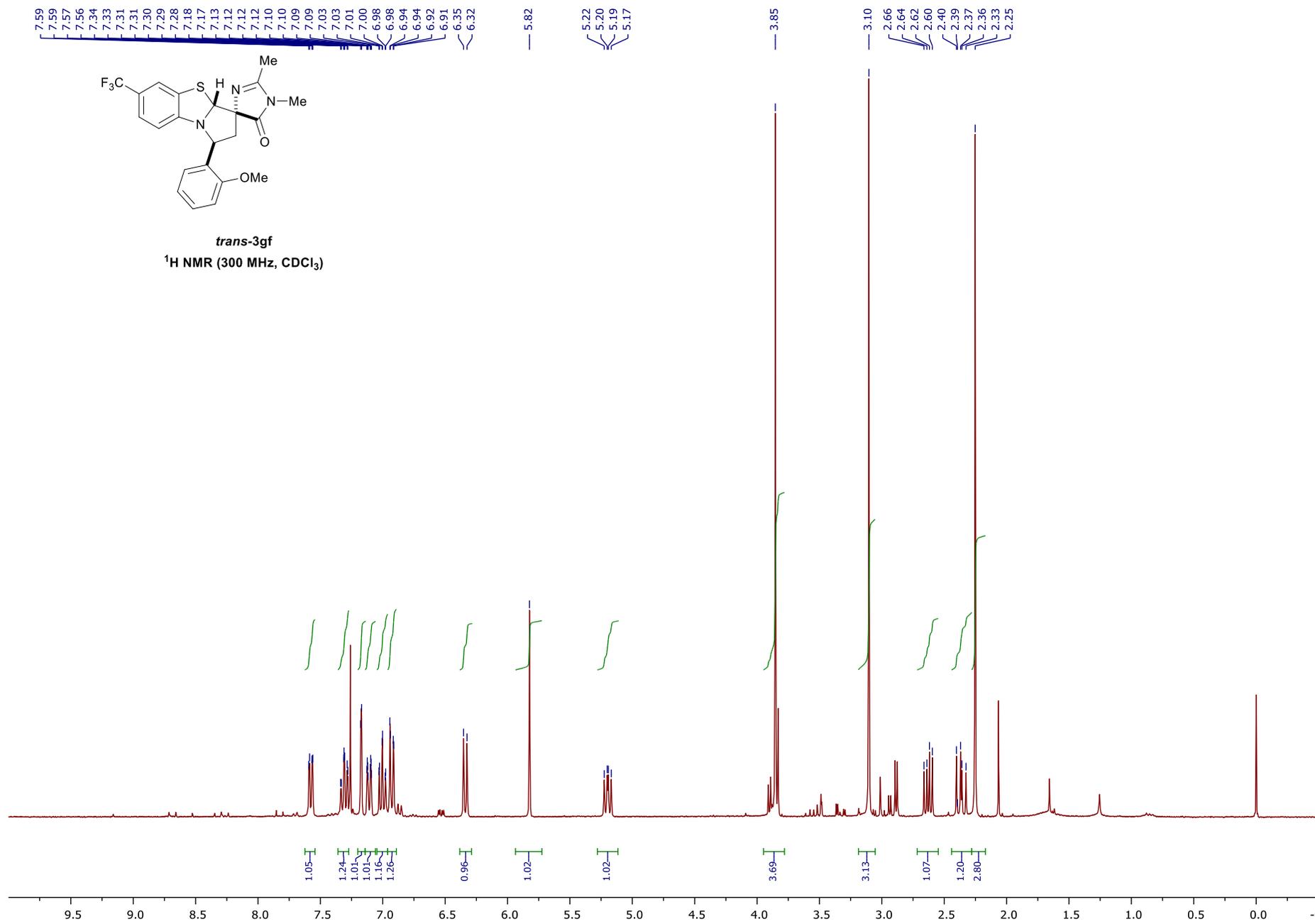
trans-3ae

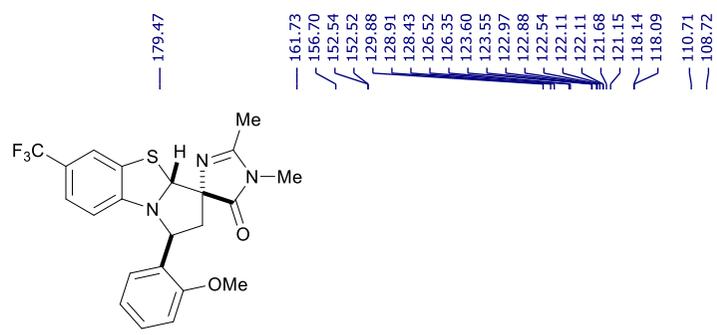
$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)





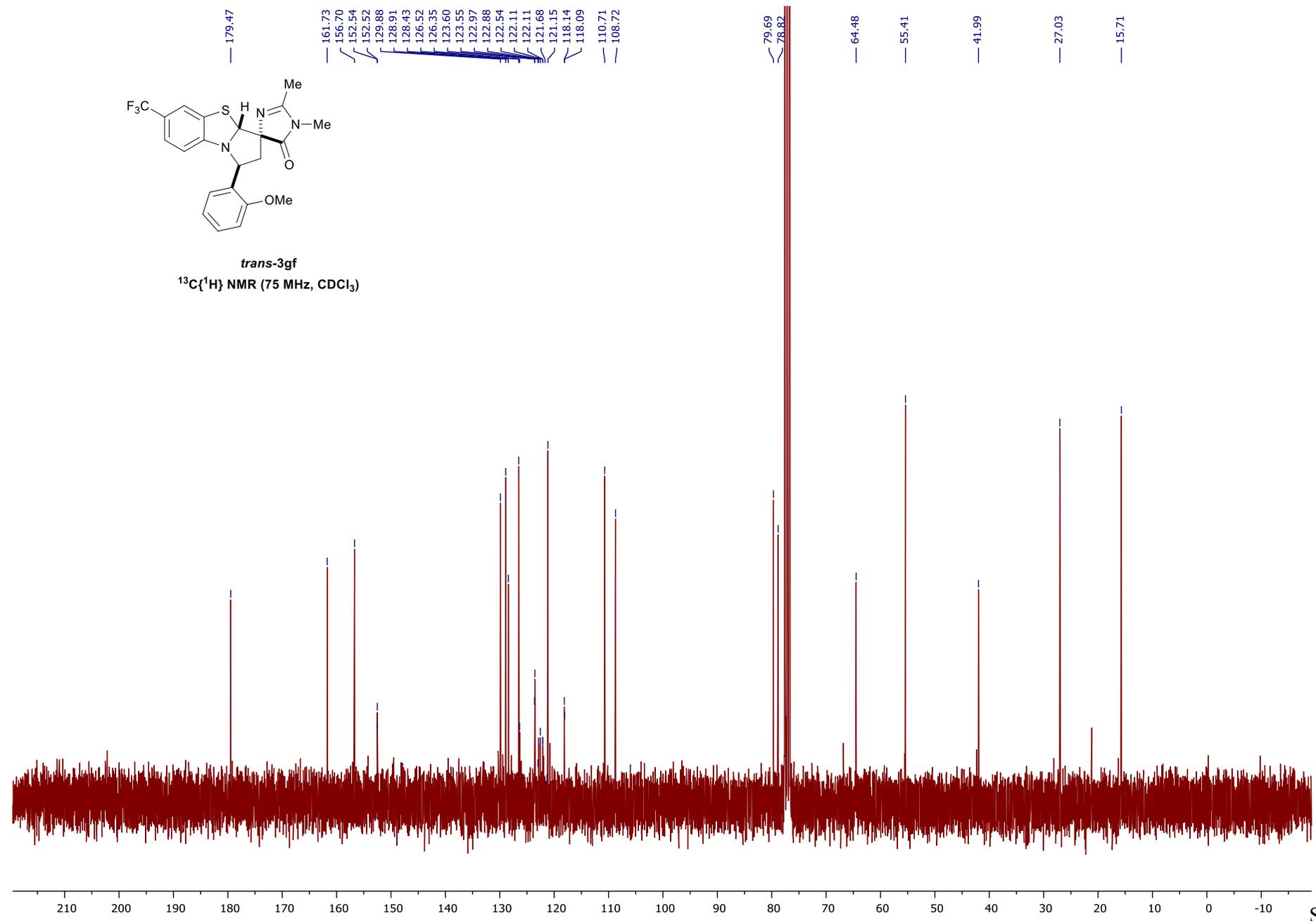


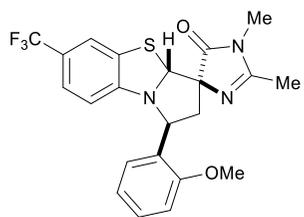




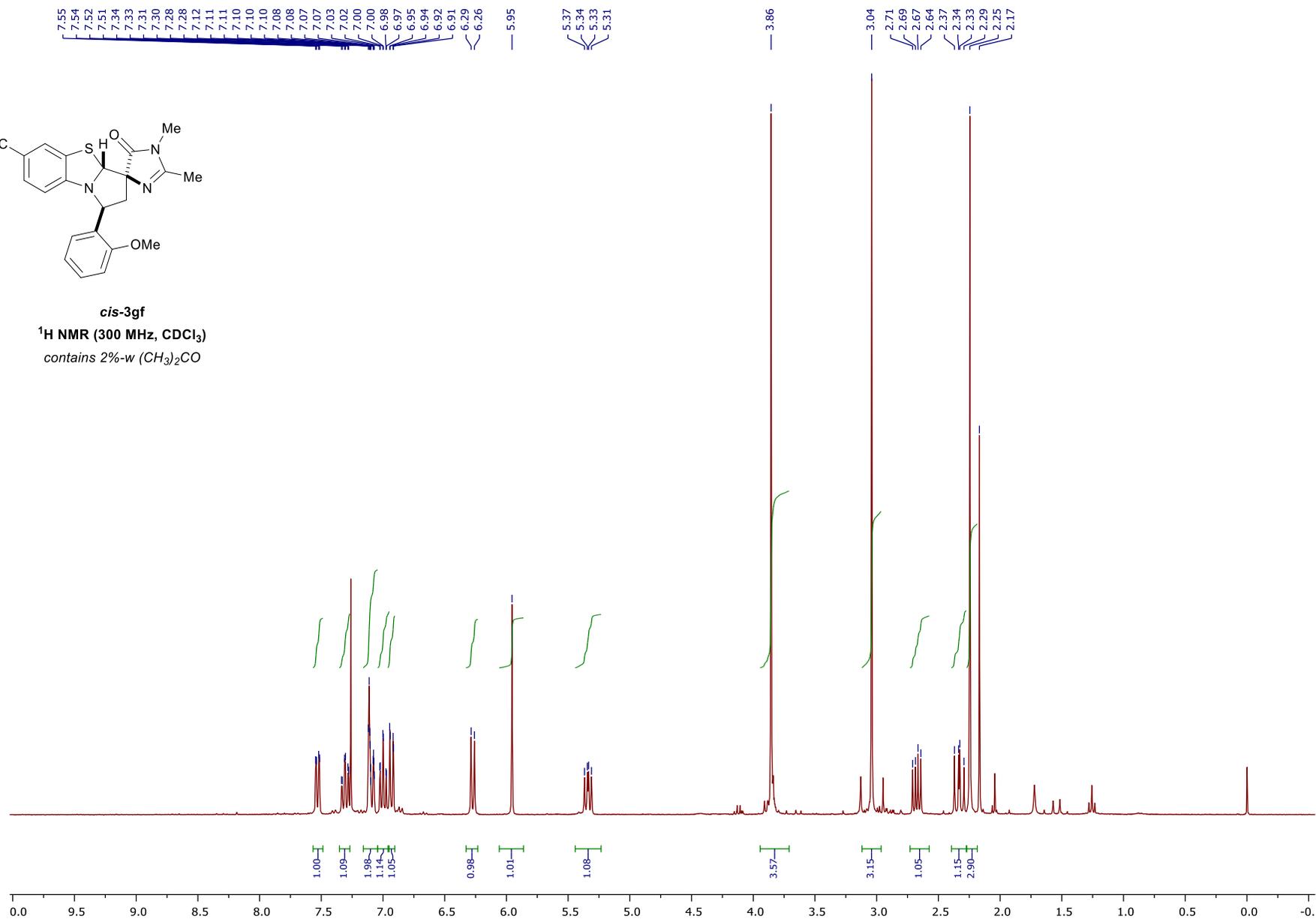
trans-3gf

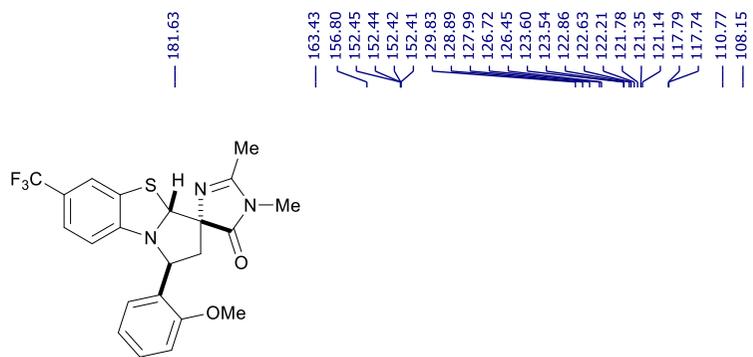
$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)





cis-3gf
¹H NMR (300 MHz, CDCl₃)
 contains 2%-w (CH₃)₂CO





cis-3gf

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)

contains 2%-w (CH_3) $_2CO$

