Supplementary Information for

Reactions of HDDA benzynes with structurally complex, multifunctional natural products

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I. General Experimental Protocols

^{1}H and ^{13}C **NMR spectra** were recorded on AV-500 or HD-500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (δ 0.00 ppm). ^{1}H NMR chemical shifts in C_6D_6 are referenced to CHD_5 (δ 7.16 ppm). Non-first order multiplets in the ^{1}H NMR spectra are designated as "nfom". The following format is used to report the resonances: chemical shift in ppm [multiplicity, coupling constant(s) in Hz, integral, and assignment]. ^{1}H NMR assignments are indicated by the structural environment, e.g., C*Ha*Hb; when two geminal protons are present, the more downfield resonance is, arbitrarily, labeled as H_a. Coupling constant analysis was performed using methods we have reported elsewhere.[1,2] In most cases the ^{13}C NMR chemical shifts were obtained by analysis of the HMBC and phase sensitive HSQC spectra using the maxima determined with the aid of the Mnova software package. Otherwise the carbon spectrum shifts are noted by the inclusion of the descriptor “1-D”. In some instances, particularly so in the case of complex NMR spectra, the chemical shifts of protons were determined from the location of cross peaks in the HSQC spectra. In cases of severely overlapping peaks, the integration of individual peaks are assumed to be the expected value. For example, if three individual CH’s (as evidenced by the HSQC spectrum) are severely overlapped between 1.2 and 1.0 ppm, and the integral value of the range equals 3, it is assumed that each peak corresponds to a single proton.

Infrared spectra were recorded on a Midac Corporation (Prospect 4000) FT-IR spectrometer. The more intense and/or diagnostic peaks are reported; all spectra were collected as thin films on a germanium window using attenuated total reflectance (ATR).

High-resolution **mass spectrometry** (HRMS) measurements were made using electrospray ionization mode (ESI) on a Bruker BioTOF II (ESI-TOF) instrument using poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG) as an added internal standard/calibrant. Samples were introduced as solutions in methanol, doped with either ammonium acetate or sodium formate. HRMS data were collected as ten separate data sets and the average value is reported.

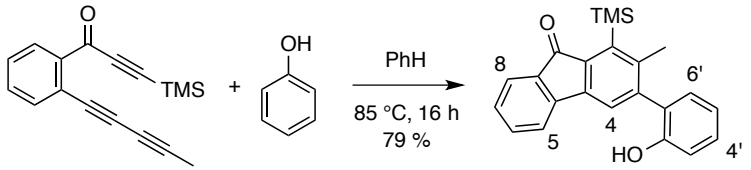
MPLC refers to **medium pressure liquid chromatography** (25-200 psi) that was done on hand-packed columns of silica gel (20-40 μm, 60 Å pore size, Teledyne RediSep Rf Gold® normal-phase silica) using a Waters HPLC pump (M6000), a Waters R401 differential refractive index detector, and a Gilson 112 UV detector. Flash chromatography was performed using E. Merck silica gel (230-400 mesh). Thin layer chromatography was performed on glass-backed plates of silica gel and visualized by UV detection and/or a solution of potassium permanganate or ceric ammonium molybdate (CAM).

Reactions requiring anhydrous conditions were performed in oven-dried glassware under an atmosphere of nitrogen. Anhydrous THF and toluene were taken from a column of activated alumina, immediately prior to use. Reported reaction temperatures refer to the temperature of the external heating or cooling bath unless otherwise noted. HDDA reactions, including those that were carried out at temperatures above the boiling point of the solvent, were typically performed in a screw-capped vial or culture tube fitted with an inert, Teflon®-lined cap. Reactions performed using microwave heating were done using a Biotage Initiator 2.0.

New compounds whose structure numbers do not appear in the main text are assigned here in the Supplementary Information a three-digit number, beginning with **101**.

II. Preparation procedures and characterization data for all new compounds

3-(2-Hydroxyphenyl)-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (5)



1 ***3a*** ***5*** (79%)

Triynone **1** (50 mg, 0.189 mmol) and phenol (**3a**, 27 mg, 0.284 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The residue was purified by MPLC (7:1 Hex:EtOAc) to give **5** (54 mg, 0.149 mmol, 79%) as a yellow oil.

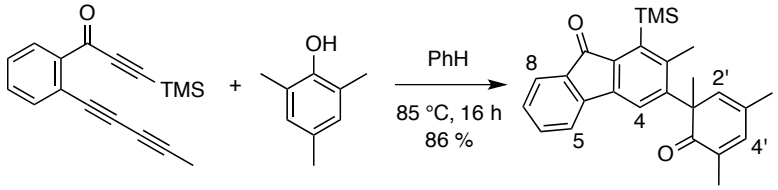
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.61 (ddd, *J* = 7.4, 1.1, 0.8 Hz, 1H, H8), 7.45 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, H6), 7.41 (ddd, *J* = 7.4, 1.1, 0.8 Hz, 1H, H5), 7.40 (q, *J* = 0.5 Hz, 1H, H4), 7.32 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, H4'), 7.27 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, H7), 7.14 (ddd, *J* = 7.5, 1.7, 0.4 Hz, 1H, H6'), 7.03 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, H5'), 7.01 (ddd, *J* = 8.1, 1.1, 0.4 Hz, 1H, H3'), 4.86 (br s, 1H, ArOH), 2.26 (d, *J* = 0.4 Hz, 1H, ArCH_3), and 0.46 (s, 9H, $ArSi(CH_3)_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 1-D): δ 195.3, 152.4, 144.4, 143.8, 143.7, 143.0, 141.7, 140.5, 134.7, 134.0, 130.0, 129.7, 129.0, 128.6, 124.2, 123.4, 121.0, 119.8, 115.8, 22.1, and 2.84.

IR (neat): 3373, 3076, 3047, 2980, 2954, 2896, 1697, 1605, 1593, 1471, 1245, and 847 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{22}NaO_2Si^+$ $[M+Na]^+$ requires 381.1281; found 381.1281.

2-Methyl-3-(1,3,5-trimethyl-6-oxocyclohexa-2,4-dien-1-yl)-1-(trimethylsilyl)-9*H*-fluoren-9-one (4b)



1 ***3b*** ***4b*** (86%)

Triynone **1** (50 mg, 0.189 mmol) and 2,4,6-trimethylphenol (**3b**, 39 mg, 0.284 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The residue was purified by MPLC (7:1 Hex:EtOAc) to give **4b** (65 mg, 0.163 mmol, 86%) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H, H4), 7.56 (ddd, *J* = 7.3, 1.1, 0.9 Hz, H8), 7.49 (ddd, *J* = 7.4, 0.9, 0.9 Hz, 1H, H5), 7.44 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, H6), 7.24 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, H7), 6.83 (dq, *J* = 2.8, 1.4 Hz, 1H, H4'), 5.93 (dqq, *J* = 1.6, 1.6, 0.8 Hz, 1H, H2'), 2.01 (br d, *J* = 1.1 Hz, 3H, 3'-CH_3), 1.97 (dq, *J* = 1.6, 0.3 Hz, 3H, 5'-CH_3), 1.89 (s, 3H, ArCH_3), 1.60 (s, 3H, 1'-CH_3), and 0.38 (s, 9H, Si(CH_3)$_3$). A minor set of resonances were suggestive of the presence of the regioisomer with the attachment at C4 (17.3:1 major:minor) (see copy of ^{1}H NMR spectrum).

^{13}C-NMR (125 MHz, $CDCl_3$,1-D): δ 203.3, 195.5, 147.4, 144.7, 144.3, 143.4, 143.0, 141.6, 140.3, 139.3, 134.5, 134.1, 133.3, 128.6, 128.0, 124.0, 119.5, 119.4, 55.8, 25.7, 21.9, 21.2, 15.9, and 3.0.

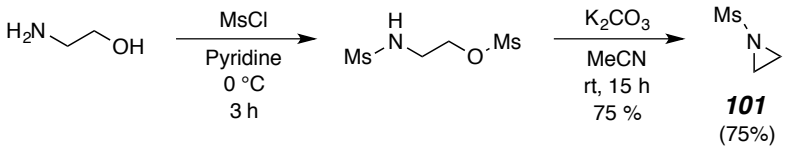
IR (neat): 3059, 2977, 2948, 2919, 2899, 1710, 1662, 1648, 1607, 1469, 1451, 1391, 1297, 1246, 1185, 847 and 766 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{28}NaO_2Si^+$ $[M+Na]^+$ requires 423.1751; found 423.1762.

mp: >230 °C (T_{max} on the mp instrument).

GCMS [EI, *m/z*, (rel int)]: 13.7 min (minor) [400 (8), 385 (100), 369 (15), 355 (17)], 14.1 min (major) [400 (13), 385(100), 369 (10), 355 (16)] (ratio of 2:98 from integrated peak areas of total ion current)

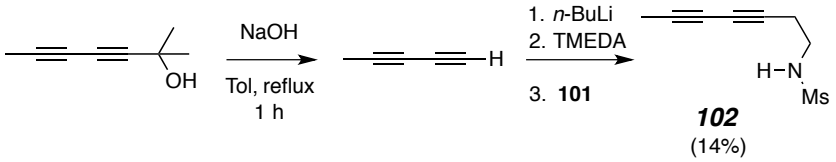
1-(Methylsulfonyl)aziridine (101)



Although this is a known compound[3], past reports of its preparation have involved mesylation of ethylenimine itself, a commodity that is exceedingly difficult to acquire.

Pyridine (20 mL) was added to a 100 mL RBF equipped with a stir bar. This was cooled to 0 °C in an ice bath, and methanesulfonyl chloride (13.3 mL, 172 mmol, 2.09 equiv) was added via syringe over 20 min. Ethanolamine (4.96 mL, 82 mmol, 1 equiv) in pyridine (10 mL) was added dropwise over 10 min and stirred at 0 °C for 3 h. The reaction mixture was transferred to a separatory funnel containing 50 mL of 2:1 (brine:10% citric acid) and the reaction flask was rinsed with an additional 50 mL of 2:1 (brine:10% citric acid). The aqueous layer was extracted with EtOAc (2x50 mL; 4x30 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give crude 2-(methylsulfonamido)ethyl methanesulfonate. This material was dissolved in MeCN (350 mL), and K_2CO_3 (17 g, 123 mmol, 1.5 equiv) was added in one portion. The resulting suspension was stirred at ambient temperature for 15 h, filtered through Celite®, and rinsed with EtOAc. The filtrate was concentrated to ca. 5% of its original volume (concentration, instead, to "dryness" resulted in exothermic decomposition to a dark-colored, intractable mass), and EtOAc (250 mL) was added in one portion, resulting in precipitate formation (most likely, potassium salts). This mixture was washed with brine (2x50 mL), the brine was extracted with additional EtOAc (2x50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a volume of ca. 100 mL. This solution was filtered through silica gel to remove residual water with the aid of some additional EtOAc. A solvent exchange with dry THF was performed by repeatedly concentrating the solution to 5% of its volume followed by the addition of fresh THF (25 mL) (repeated 4 times). The final THF solution was adjusted to a total volume of 50 mL, and the titer of that solution was determined by NMR to be ~1.23 M (50 mL, 1.23 M, 61.6 mmol, 75 % yield), assuming the density of THF (0.89 g•mL^{-1}). A copy of the ^1H NMR spectrum of this solution (in $CDCl_3$) is provided.

N-(Hepta-3,5-diyn-1-yl)methanesulfonamide (102)



***Caution**:* low molecular weight, terminal 1,3-diynes have been reported to detonate[4]; hence we developed the following procedure to avoid handling of neat 1,3-pentadiyne.

2-Methylhepta-3,5-diyn-2-ol (9.76 g, 80 mmol), sodium hydroxide (4.80 g, 120 mmol), and toluene (350 mL, 0.23 M) were placed into a 500 mL round bottom flask equipped with a stir bar and heated to reflux for 1 hour. The solution was cooled, washed with water (100 mL x 2) and brine (100 mL), and dried over $MgSO_4$. This solution was passed through a plug of silica gel (to remove acetone-derived dimers) with additional toluene to give a solution of 1,3-pentadiyne in toluene (~ 500 mL total volume). This was placed into a 1 L three-neck flask equipped with a stir bar and internal thermocouple. The solution was cooled to -70 °C (internal) and *n*-BuLi (30 mL, 2.5 M, 75 mmol) was added over 20 min via syringe, maintaining the temperature at ≤64 °C. This solution was allowed to warm to -20 °C over 2 hours, resulting in a pale yellow suspension. TMEDA (40 mL, 270 mmol) was added via syringe over 10 min resulting in a red homogenous solution. The cooling bath was removed and a solution of aziridine **101** in THF (50 mL, 1.23 M, 61.6 mmol) was added via cannula over 20 min as the temperature slowly rose to 5 °C. The mixture was then stirred at ambient temperature (~20 °C) for an additional 19 h. The mixture was cooled to 10 °C and 1 M HCl (300 mL) was added dropwise over 30 min, maintaining a temperature of ≤17 °C). The mixture was diluted with Et_2O (200 mL) and the organic layer was washed with 1 M HCl (150 mL x 2). The combined aqueous layers were washed with Et_2O (100 mL x 3) and the combined organic layers were washed with $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated to give crude **102**. This residue was purified by flash chromatography (1:1 Hex:EtOAc) to give pure **102** (1.54 g, 8.29 mmol, 14%) as a pale yellow solid. This material has subsequently been prepared in our laboratory by a more efficient route: i) Mitsunobu reaction between hepta-3,5-diyn-1-ol and BocNHMs, followed by ii) Boc removal.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.60 (br t, J = 4.9 Hz, 1H, MsN*H*CH_2CH_2), 3.31 (q, J = 6.4 Hz, 2H, MsNHC*H*$_2CH_2$), 3.01 (s, 3H, C*H*$_3SO_2NHCH_2$), 2.56 (tq, J = 6.3, 1.2 Hz, 2H, $MsNHCH_2CH_2$), and 1.92 (t, J = 1.3 Hz, $CH_2C{\equiv}C\text{-}C{\equiv}CCH_3$).

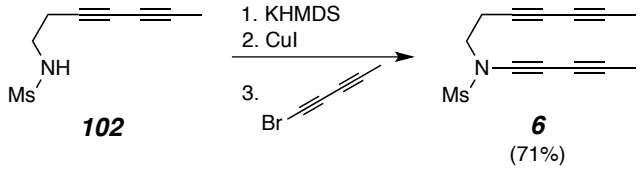
^{13}C-NMR (125 MHz, $CDCl_3$): δ 74.7, 72.1, 67.9, 64.1, 41.7, 41.0, 21.3, and 4.2.

IR (neat): 3237, 3017, 2936, 2913, 2876, 2846, 2206, 2152, 2043, 1446, 1299, 1134, 1071, 980, and 781 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_8H_{11}NNaO_2S^+$ $[M+Na]^+$ requires 208.0403; found 208.0401.

mp: 100-105 °C.

N-(Hepta-3,5-diyn-1-yl)-*N*-(penta-1,3-diyn-1-yl)methanesulfonamide (6)



102 **6** (71%)

1-Bromopenta-1,3-diyne (the procedure for a similar transformation[5] was followed). KOH (14.9 g, 266 mmol, 9.27 equiv based on 2-methylhepta-3,5-diyn-2-ol) was added to a 50 mL RBF equipped with a stir bar. Water (19 mL) was added with cooling in an ice bath. After complete dissolution the solution was cooled to ~0 °C and bromine (2.37 mL, 46.0 mmol, 1.6 equiv based on 2-methylhepta-3,5-diyn-2-ol) was added dropwise via syringe (no needle) over 20 min, resulting in a bright yellow suspension. This mixture was stirred for an additional 30 min at 0 °C. This solution was then added by pipet to a precooled (0 °C) toluene solution of 1,3-pentadiyne [prepared as described above from 2-methylhepta-3,5-diyn-2-ol (3.50 g, 28.7 mmol) and NaOH (1.72 g, 43.0 mmol, 1.5 equiv) to give ~200 mL of 1,3-pentadiyne in toluene] in a 500 mL Erlenmeyer flask equipped with a large stir bar (rod) and wrapped in foil. This two-phase mixture was stirred under a N_2 atmosphere for 3 h at rt. The heterogeneous reaction mixture was then transferred to a separatory funnel with additional toluene (~10 mL) and the aqueous layer was back extracted with toluene (20 mL). The combined organic layers were washed with water (25 mL x 3) and brine (25 mL), and dried over a mixture of $MgSO_4$ and activated 4 Å molecular sieves. This mixture could be stored in a freezer overnight, if necessary. The mixture was filtered through Celite® into a 250 mL additional funnel and that solution was purged with Ar.

Methanesulfonamide **102** (3.54 g, 19.1 mmol) was added to a 500 mL 3-neck RBF equipped with a stir bar, nitrogen inlet, additional funnel, and septum and dissolved in THF (72 mL) and pyridine (39 mL). The solution was cooled to 0 °C and purged with Argon. KHMDS (4.19 g, 21 mmol, 1.1 equiv) in THF (25 mL) was added dropwise over 15 min, the cooling bath was removed, and the mixture was stirred for an additional 15 min. Copper(I) iodide (4.0 g, 21 mmol, 1.1 equiv) was added in one portion by quickly removing and then replacing the septum. The slurry was stirred at ambient temperature under argon for 2.5 h. The 1-bromo-1,3-pentadiyne solution described above was then added dropwise over 2.5 h, and the mixture was stirred at room temp for an additional 20 h. The dark red-brown reaction mixture was transferred to a 1-L separatory funnel with Et_2O (100 mL) and washed with 3:1 NaCl:NH_4OH (100 mL x 4) resulting in a slowly separating emulsion. The combined aq. layers were combined and extracted with Et_2O (100 mL x 2) (centrifugation was necessary to aid in breaking the emulsions). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated (25 °C, 20 torr followed by 25 °C, ~0.2 torr) to give crude **6** as a brown solid. This material was purified by flash column chromatography (30:1 to 3:1 Hex:EtOAc) to give **6** (3.37 g, 13.6 mmol, 71%) as a pale brown oil, which solidified upon storage at -10 °C to give a pale brown solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.65 (t, J = 6.9 Hz, 2H, MsNCH_2CH$_2$), 3.18 (s, 3H, NSO_2CH_3), 2.68 (tq, J = 6.9, 1.1 Hz, 2H, MsNCH$_2$CH_2), 1.98 (s, 3H, NMsC≡C-C≡CCH_3), and 1.91 (t, J = 1.2 Hz, CH$_2$C≡C-C≡CCH_3).

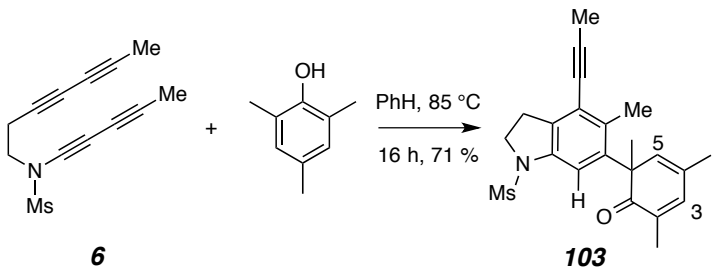
^{13}C-NMR (125 MHz, $CDCl_3$): δ 80.7, 74.7, 71.5 (x2), 67.6, 64.9, 64.0, 60.1, 49.7, 39.6, 19.4, 4.6, and 4.2.

IR (neat): 2932, 2914, 2257, 2167, 1361, 1164, 1093, 953, and 772 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{13}H_{13}NNaO_2S^+$ $[M+Na]^+$ requires 270.0559; found 270.0559.

mp: 91-95 °C (dec).

2,4,6-Trimethyl-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)cyclohexa-2,4-dien-1-one (103)



6 ***103*** (71%)

Tetrayne **6** (50 mg, 0.202 mmol) and 2,4,6-trimethylphenol (55 mg, 0.404 mmol, 2.0 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The resulting residue was purified by MPLC (2:1 Hex:EtOAc) to give **103** (55 mg, 0.143 mmol, 71%).

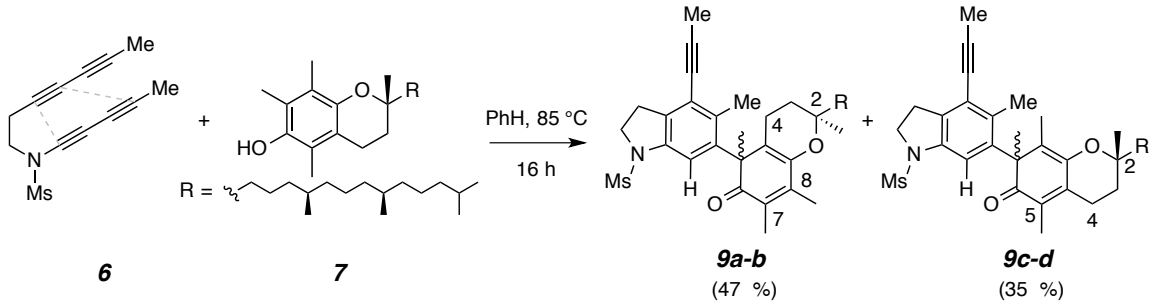
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H, NAr*H*), 6.80 (dq, *J* = 2.4, 1.3 Hz, 1H, *H3*), 5.83 (dqq, *J* = 1.6, 1.6, 0.8 Hz, 1H, *H5*), 4.05 (ddd, *J* = 10.6, 8.9, 7.1 Hz, 1H, $MsNCH_aH_bCH_2$), 3.91 (ddd, *J* = 10.6, 9.5, 8.5 Hz, 1H, $MsNCH_aH_bCH_2$), 3.15 (ddd, *J* = 7, 7, 16.6 Hz, 1H, $MsNCH_2CH_aH_b$), 3.13 (ddd, *J* = 8.5, 8.5, 16.6 Hz, 1H, $MsNCH_2CH_aH_b$), 2.07 (s, 3H, $NArC{\equiv}CCH_3$), 1.97 (br d, *J* = 0.8 Hz, 3H, C2-CH_3), 1.93 (d, *J* = 1.6 Hz, C4-CH_3), 1.87 (s, 3H, $NArCH_3$), and 1.51 (s, 3H, C6-CH_3).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 203.7, 144.7, 141.6, 140.1, 139.7, 134.5, 132.9, 132.8, 127.3, 122.5, 111.6, 94.1, 76.4, 55.3, 50.4, 34.4, 28.2, 25.3, 21.0, 16.9, 15.7, and 4.9.

IR (neat): 3022, 2976, 2919, 2868, 2225 (w), 1662, 1648, 1592, 1452, 1345, 1159, and 969 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{26}NO_3S^+$ $[M+H]^+$ requires 384.1628; found 384.1685.

(2*R*)-2,5,7,8-Tetramethyl-5-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(5*H*)-one (9a-b) and **(2*R*)-2,5,7,8-Tetramethyl-7-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(7*H*)-one (9c-d)**



6 ***7*** ***9a-b*** (47 %) ***9c-d*** (35 %)

Tetrayne **6** (50 mg, 0.202 mmol) and vitamin E (**7**, 183 mg, 0.425 mmol, 2.1 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The resulting residue was purified by MPLC (3:1 Hex:EtOAc) to give, in order of elution, approximately equimolar mixtures of the epimeric pairs **9a/9b** (64 mg, 0.094 mmol, 47%) and **9c/9d** (48 mg, 0.071 mmol, 35%).

Data for 9a-b (faster eluting epimeric pair)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, NAr*H*), 4.071 (ddd, *J* = 10.5, 9.1, 6.7 Hz, 0.5H, $CH_2CH_aCH_bNMs$ in one epimer), 4.070 (ddd, *J* = 10.6, 9.3, 6.8 Hz, 0.5H, $CH_2CH_aCH_bNMs$ in a second epimer), 3.895 (ddd, *J* = 10.9, 9.8, 8.4 Hz, 0.5H, $CH_2CH_aCH_bNMs$ in one epimer), 3.893 (ddd, *J* = 10.5, 9.6, 8.4 Hz, 0.5H, $CH_2CH_aCH_bNMs$ in a second epimer), 3.20–3.09 (m, 2H, CH_2CH_2NMs), 2.8593 (s, 1.5H, NSO_2CH_3 in one epimer), 2.8587 (s, 1.5H, NSO_2CH_3 in a second epimer), 2.082 (s, 1.5H, C8CH_3, in one epimer), 2.080 (s, 1.5H, C8CH_3 in a second epimer), 2.075 (s, 1.5H, NArC≡CCH_3 in one epimer), 2.073 (s, 1.5H, NArC≡CCH_3 in a second epimer), 1.949 (s, 1.5H, C7-CH_3 in one epimer), 1.947 (s, 1.5H, C7-CH_3 in a second epimer), 1.79 (m, 1H, H4a), 1.54 (s, 1.5H, C5-CH_3 in one epimer), 1.53 (s, 1.5H, C5-CH_3 in a second epimer), 1.54-1.38 (m, 7H, includes H4b and H5), 1.45-1.22 (m, 14H), 1.20 (s, 1.5H, C2-CH_3 in one epimer), 1.17-1.01 (m, 7H), 1.12 (s, 1.5H, C2-CH_3 in a second epimer), and 0.88-0.82 (m, 12H, 4 methyl resonances).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 202.7, 146.5, 142.8, 141.8, 141.7, 139.5, 134.1, 132.8, 128.7, 122.4, 113.0, 94.0, 76.5, 75.5, 56.7, 50.4, 40.1, 39.4, 39.2, 37.4, 34.3, 32.7, 31.3, 28.3, 26.9, 24.6, 24.8, 23.3, 22.7, 20.7, 19.8, 19.7, 16.8, 14.3, 11.5, and 4.5.

IR (neat): 2949, 2925, 2867, 2227 (w), 1638, 1584, 1459, 1349, 1160, 1095, and 964 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{42}H_{64}NO_4S^+$ $[M+H]^+$ requires 678.4551; found 678.4572.

Data for 9c-d (slower eluting epimeric pair)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H, NAr*H*), 4.063 (ddd, *J* = 10.6, 8.6, 7.4 Hz, 0.5H, $CH_2CH_aH_bNMs$ in one epimer), 4.062 (ddd, *J* = 10.7, 8.8, 7.8 Hz, 0.5H, $CH_2CH_aH_bNMs$ in a second epimer), 3.90 (ddd, *J* = 10.6, 9.4, 8.6 Hz, 1H, $CH_2CH_aH_bNMs$), 3.19–3.09 (m, 2H, CH_2CH_2NMs), 2.85 (s, 3H, NSO_2CH_3), 2.65 (m, 2H, *H4*), 2.065 (s, 1.5H, NArC≡CCH_3 in one epimer), 2.059 (s, 1.5H, NArC≡CCH_3), 1.91 (s, 3H, 5-CH_3), 1.834 (s, 1.5H, c-NArCH_3), 1.826

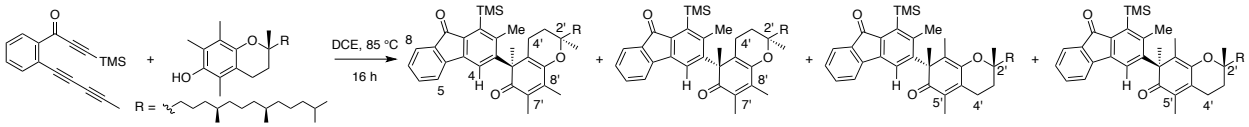
(s, 1.5H, d-NArC*H*$_3$ in a second epimer), 1.830 (m, 2H, *H3*), 1.57-1.46 (m, 3H), 1.51 (s, 3H, 7-C*H*$_3$), 1.45-1.17 (m, 15H), 1.42 (s, 1.5H, C8-C*H*$_3$ in one epimer), 1.41 (s, 1.5H, C8-C*H*$_3$ in a second epimer), 1.30 (s, 1.5H, C2-C*H*$_3$ in one epimer), 1.20 (s, 1.5H, C2-C*H*$_3$ in a second epimer), 1.16-1.10 (m, 3H), 1.10-1.0 (m, 4H), and 0.88-0.82 (m, 12H, four methyl resonances).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 202.5, 143.6, 143.3, 142.0, 139.3, 134.0, 132.6, 128.4, 127.1, 122.5, 113.0, 93.8, 76.5, 76.1, 58.1, 50.5, 41.2, 39.4, 37.4, 34.3, 32.9, 32.1, 28.3, 26.8, 25.4, 24.8, 23.8, 22.9, 22.8, 21.2, 19.8, 16.5, 12.2, 10.7, and 4.6.

IR (neat): 2954, 2925, 2660, 2232 (w), 1633, 1461, 1349, 1160, 1054, and 979 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{42}H_{63}NaNO_4S^+$ $[M+Na]^+$ requires 700.4370; found 700.4375.

(2*R*,5*S*)-2,5,7,8-tetramethyl-5-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(5*H*)-one (10a), (2*R*,5*R*)-2,5,7,8-tetramethyl-5-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(5*H*)-one (10b), (2*R*,7*R*)-2,5,7,8-tetramethyl-7-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(7*H*)-one (10c), and **(2*R*,7*S*)-2,5,7,8-tetramethyl-7-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6(7*H*)-one (10d).**



1 *7* *10a* *10b* *10c* *10d*

Triynone **1** (65 mg, 0.25 mmol) and vitamin E (159 mg, 0.37 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The residue was purified by MPLC (20:1 Hex:EtOAc) to give, in order of elution, (i) **10a** or **10b** contaminated with **7** [repurification of this initial fraction by MPLC (50:1 Hex:EtOAc) gave pure **10a** or **10b,** 34 mg, 0.049 mmol, 20%], (ii) **10a** or **10b** (38 mg, 0.055 mmol, 22%), (iii) **10c** or **10d** (31 mg, 0.045 mmol, 18%), and (iv) **10c** or **10d** (28 mg, 0.040 mmol, 16%) as yellow oils.

Data for 10a or 10b (first eluting fraction)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 1H, Ar*H*4), 7.56 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, Ar*H*8), 7.48 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, Ar*H*5), 7.43 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, Ar*H*6), 7.23 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, Ar*H*7), 2.10 (d, *J* = 1.1 Hz, 3H, C8'CH_3), 1.99 (d, *J* = 1.0 Hz, 3H, C7'CH_3), 1.89 (s, 3H, ArCH_3), 1.83 (ddd, *J* = 16.9, 4.2, 4.2 Hz, C4'Ha), 1.62 (s, 3H, C5'CH_3), 1.60-1.48 (m, 7H, includes C4'Hb), 1.46-1.17 (m, 15H), 1.16-1.02 (m, 7H), 1.14 (s, 3H, C2'CH_3), 0.88-0.84 (m, 12H, 4 methyl resonances), and 0.37 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 202.1, 195.4, 147.2, 143.8, 146.5 (x2), 144.2, 144.1, 143.1, 142.8, 142.4, 139.2, 134.3, 128.4, 123.8, 120.7, 119.2 (x2), 75.7, 57.1, 40.4, 39.4, 37.5, 37.3, 32.8, 31.0, 28.0, 27.0, 24.8, 24.6, 23.4, 22.6, 21.5, 20.8 (x2), 19.9, 19.8, 13.7, 11.6, and 2.9.

IR (neat): 3047, 2949, 2925, 2867, 1712, 1638, 1585, 1463, 1376, 1091, 858, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{46}H_{67}O_3Si^+$ $[M+H]^+$ requires 695.4854; found 695.4844.

Data for 10a or 10b (second eluting fraction)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 1H, Ar*H*4), 7.56 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, Ar*H*8), 7.48 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, Ar*H*5), 7.44 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, Ar*H*6), 7.23 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 1H, Ar*H*7), 2.10 (d, *J* = 1.2 Hz, 3H, C8'CH_3), 1.99 (d, *J* = 1.0 Hz, 3H, C7'CH_3), 1.89 (s, 3H, ArCH_3), 1.83 (ddd, *J* = 17.7, 5.0, 5.0 Hz, C4'Ha), 1.63 (s, 3H, C5'CH_3), 1.66-1.45 (m, 6H, includes C4'Hb), 1.43-1.18 (m, 15H), 1.24 (s, 3H, C2'CH_3), 1.17-1.00 (m, 7H), 0.87-0.83 (m, 12H, 4 methyl resonances), and 0.38 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 202.1, 195.4, 147.3, 146.9, 146.5 (x2), 144.3, 144.2, 143.1, 143.0, 142.5, 139.1, 134.3, 128.5, 123.8, 120.7, 119.2, 119.3, 75.7, 57.1, 39.3, 38.7, 37.4 (x2), 32.7, 31.2, 27.9, 27.0, 25.0, 24.8, 24.7, 24.2, 22.6, 21.4, 20.8 (x2), 19.9, 19.7, 14.2, 11.6, and 2.9.

IR (neat): 3047, 2949, 2926, 2867, 1712, 1638, 1584, 1463, 1376, 1091, 864, and 857 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{46}H_{67}O_3Si^+$ $[M+H]^+$ requires 695.4854; found 695.4853.

Data for 10c or 10d (third eluting fraction) (~10% of a coeluting impurity is observed by ^{1}H NMR analysis; HPLC does not give evidence of a second peak)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H, Ar*H*4), 7.55 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, Ar*H*8), 7.49 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, Ar*H*5), 7.43 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, Ar*H*6), 7.23 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H*7), 2.67 (app t, *J* = 6.8 Hz, 2H, C4'H_2), 1.95 (q, *J* = 0.9 Hz, 3H, C5'CH_3), 1.85 (s, 3H, ArCH_3), 1.86-1.78 (m, 2H, C3'H_2), 1.63-1.48 (m, 6H), 1.61 (s, 3H, C8'CH_3), 1.49 (q, *J* = 0.9 Hz, 3H, C7'CH_3), 1.47-1.16 (m, 17 H), 1.24 (s, 3H, C2CH_3), 1.15-1.03 (m, 7H), 0.868/0.859/0.857/0.847 (d, each *J* = ~6.5 Hz, 3H, 4 CH_3), and 0.37 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 1-D): δ 202.0, 195.5, 147.6, 144.5, 144.2, 143.8, 143.2, 142.6, 142.5, 139.2, 134.4, 134.2, 128.7, 128.5, 127.6, 123.9, 120.8, 119.4, 76.3, 58.7, 41.1, 39.5, 37.7, 37.6, 37.6, 37.4, 32.9 (x2), 32.1, 28.1, 27.1, 25.7, 24.9, 24.6, 24.3, 23.1, 22.9, 22.8, 21.2, 21.1, 19.9, 19.8, 12.4, 10.9, and 3.0.

IR (neat): 3073, 2949, 2926, 2867, 1712, 1632, 1463, 1335, 1246, 856, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{46}H_{67}O_3Si^+$ $[M+H]^+$ requires 695.4854; found 695.4850.

Data for 10c or 10d (fourth eluting fraction)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 1H, Ar*H*4), 7.56 (ddd, *J* = 7.3, 0.9, 0.9 Hz, 1H, Ar*H*8), 7.49 (ddd, *J* = 7.4, 0.9, 0.9 Hz, 1H, Ar*H*5), 7.43 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H*6), 7.23 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H*7), 2.67 (app t, *J* = 7.2 Hz, 2H, C4'H_2), 1.95 (q, *J* = 0.9 Hz, 3H, C5'CH_3), 1.85 (s, 3H, ArCH_3), 1.86-1.81 (m, 2H, C3'H_2), 1.61 (s, 3H, C8'CH_3), 1.54-1.00 (m, ~27H), 1.50 (q, *J* = 0.9 Hz, 3H, C7'CH_3), 1.31 (s, 3H, C2'CH_3), 0.856/0.854/0.825/0.824 (d, each *J* = ~6.6 Hz, 3H, 4 CH_3), and 0.37 (s, 9H, Si(CH_3)$_3$).

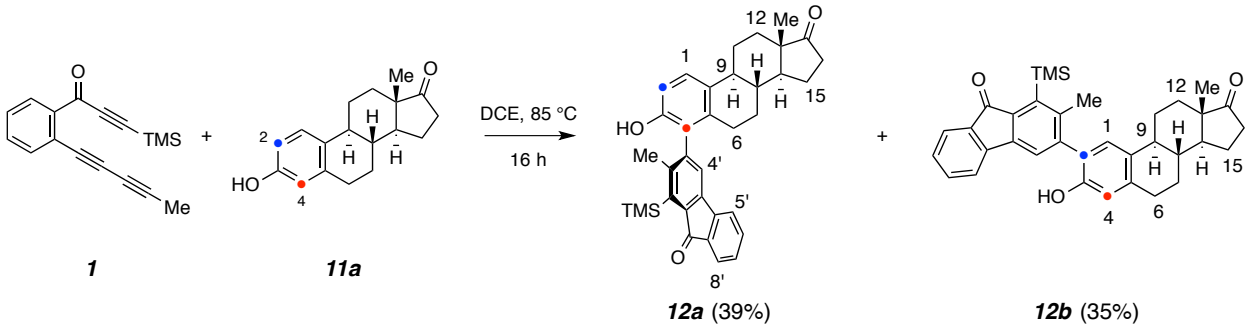
^{13}C-NMR (125 MHz, $CDCl_3$, 1-D): δ 202.0, 195.5, 147.6, 144.5, 144.1, 143.6, 143.1, 142.6, 142.4, 139.2, 134.4, 134.2, 128.6, 128.5, 127.6, 123.9, 120.8, 119.4, 76.3, 58.7, 39.6, 39.5, 37.8, 37.7, 37.6, 37.4, 33.0, 32.9, 32.4, 28.1, 27.0, 25.3, 24.9, 24.6, 23.0, 22.9, 22.8, 21.4, 21.1, 19.9, 19.7, 12.4, 10.8, and 3.1.

IR (neat): 3056, 2950, 2926, 2867, 1712, 1633, 1463, 1378, 1335, 1247, 1087, 858, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{46}H_{67}O_3Si^+$ $[M+H]^+$ requires 695.4854; found 695.4855.

(8*R*,9*S*,13*S*,14*S*)-3-Hydroxy-13-methyl-4-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (12a) and

(8*R*,9*S*,13*S*,14*S*)-3-Hydroxy-13-methyl-2-(2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (12b)



1 ***11a*** ***12a*** (39%) ***12b*** (35%)

Triynone **1** (50 mg, 0.189 mmol) and (77 mg, 0.284 mmol, 1.5 equiv) were combined in a culture tube, dissolved in dichloroethane (7 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1 Hex:EtOAc). The residue was purified by MPLC (5:1 Hex:EtOAc) to give **12a** contaminated with **11a** (77 mg, 50% purity of **12a**; 0.073 mmol, 39%) and **12b**, also contaminated with **11** (45 mg, 80% purity of **12b**; 0.067mmol, 35%). Each fraction was then separately repurified by reverse phase MPLC (C-18, 25-32 μm, 85% MeOH/H_2O) to give the pure samples of **12a** and **12b** that were used for collection of spectral data.

Data for 12a (major isomer)

^{1}H-NMR (500 MHz, $CDCl_3$, an ca. 1.5:1 ratio of major and minor atropisomers): δ 7.61 (d, *J* = 7.30 Hz, 2H, C8'*H*), 7.45 (ddd, *J* = 7.4, 7.4, 1.0 Hz, ~0.4 H, C6'*H* in minor atropisomer), 7.44 (ddd, *J* = 7.4, 7.4, 1.1 Hz, ~0.6 H, C6'*H* in major atropisomer), 7.40 (d, *J* = 7.4 Hz, 1H, ~0.4H, C5'*H* in minor atropisomer), 7.38 (d, *J* = 7.5 Hz, ~0.6 H, C5'*H* in major atropisomer), 7.33 (s, ~0.4H, C4'*H* in minor atropisomer), 7.31 (s, ~0.6H, C4'*H* in major atropisomer), 7.29-7.26 (m, 2H, C7'*H* and C1*H*), 6.87 (d, *J* = 8.5 Hz, ~0.6H, C2*H* in major atropisomer), 6.86 (d, *J* = 8.5 Hz, C2*H* in minor atropisomer), 4.58 (br s, minor, ArO*H*), 4.56 (br s, major, ArO*H*), 2.53 (m, 1H, C6*H*a), 2.49 (m, 1H, C16*H*a), 2.45 (m, 1H, C15*H*a), 2.33 (m, 1H, C9*H*), 2.30 (m, 1H, C6*H*b), 2.18 (s, ~1.8H, ArCH_3 in major atropisomer), 2.17 (s, ~1.2H, ArCH_3 in minor atropisomer), 2.13 (ddd, *J* = 19.6, 9.0, 9.0 Hz, ~0.6H, C16*H*b in major atropisomer), 2.12 (ddd, *J* = 19.0, 8.9, 8.9 Hz, ~0.4H, C16*H*b in minor atropisomer), 2.01 (m, 1H, C11*H*a), 2.00 (m, 1H, C12*H*a), 1.93 (m, 1H, C7*H*a), 1.59 (m, 1H, C15*H*b), 1.58 (m, 1H, C11*H*b), 1.58 (m, 1H, C14*H*), 1.50 (m, 1H, C12*H*b), 1.50 (m, 1H, C8*H*), 1.37 (m, 1H, C7*H*b), 0.94 (s, ~1.2H, C13CH_3 in minor atropisomer), 0.93 (s, ~1.8H, C13CH_3 in major atropisomer), 0.464 (s, ~5.5H, Si(CH_3)$_3$ in major atropisomer), and 0.461 (s, ~3.5H, Si(CH_3)$_3$ in minor atropisomer).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 221.0, 195.1, 150.2, 145.7, 144.6, 144.2, 143.7, 143.6, 140.6, 134.6, 134.3, 133.8, 132.4, 128.9, 127.2, 126.1, 124.0, 123.1, 119.6, 112.8, 50.5, 47.7, 44.4, 37.9, 36.0, 31.5, 28.2, 26.5, 26.1, 21.5, 21.2, 13.9, and 2.8.

IR (neat): 3405 (br), 3056, 2927, 2855, 1731, 1712, 1606, 1590, 1284, 1245, and 845 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{35}H_{37}O_3Si^-$ [M-H$^+$] $^-$ requires 533.2517; found 533.2520.

Data for 12b (minor isomer)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.3 Hz, 1H, C8'*H*), 7.44 (ddd, *J* = 7.3, 7.3, 0.8 Hz, 1H, C6'*H*), 7.39 (m, 1H, C5'*H*), 7.39 (s, ~0.5 H, C4'*H* in one atropisomer), 7.36 (s, ~0.5 H, C4'*H* in the other atropisomer), 7.26 (dd, *J* = 7.3, 7.3 Hz, 1H, C7'*H*), 7.04 (s, 1H, C4*H*), 6.75 (s, ~0.5 H, C1H in one atropisomer), 6.74 (s, ~0.5 H, C1H in the other atropisomer), 4.83-4.76 (m, 1H, ArO*H*), 2.96-2.93 (m, 2H, C6H_2), 2.51 (dd, *J* = 19.2, 9.1 Hz, 1H, C16*H*a), 2.38-2.35 (m, 1H, C15*H*a), 2.30 (m, 1H, C9*H*), 2.29 (s, ~1.5 H, ArCH_3 in one atropisomer), 2.26 (s, ~1.5 H, ArCH_3 in the other atropisomer), 2.15 (ddd, *J* = 17.6, 9.0, 9.0 Hz, 1H, C16*H*b), 2.08 (m, 1H, C11*H*a), 2.05 (m, 1H, C7*H*a), 1.96-1.91 (m, 1H, C12*H*a), 1.65 (m, 1H, C11*H*b), 1.65 (m, 1H, C14*H*), 1.54 (m, 1H, C15*H*b), 1.53 (m, 1H, C8*H*), 1.48 (m, 1H, C7*H*b), 1.47 (m, 1H, C12*H*b), 0.93 (s, 3H, C13CH_3), 0.46 (s, ~4.5 H, Si(CH_3)$_3$ in one atropisomer), and 0.45 (s, ~4.5 H, Si(CH_3)$_3$ in the other atropisomer).

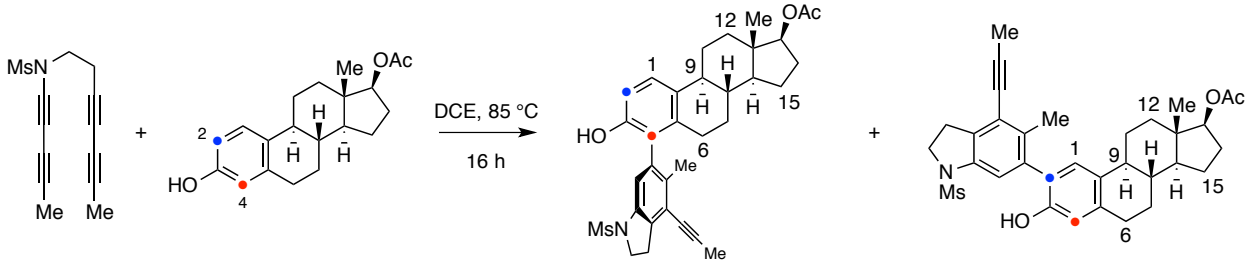
^{13}C-NMR (125 MHz, $CDCl_3$): δ 221.0, 195.2, 150.7, 144.6, 144.4, 143.7, 143.4, 141.7, 140.2, 138.2, 133.7, 134.6, 132.2, 128.8, 126.9, 126.0, 124.0, 123.4, 119.6, 115.5, 50.5, 47.8, 44.0, 38.4, 35.8, 31.6, 29.3, 26.4, 26.0, 22.1, 22.0, 14.0, and 2.8.

IR (neat): 3402 (br), 3053, 2930, 2861, 1710, 1606, 1247, 858, and 847 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{35}H_{37}O_3Si^-$ $[M\text{-}H^+]^-$ requires 533.2517; found 533.2532.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Hydroxy-13-methyl-4-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (13a) and

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Hydroxy-13-methyl-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (13b)



6 ***11b*** ***13a*** ***13b***

Tetrayne **6** (50 mg, 0.202 mmol) and estradiol-17*O*-acetate (95 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in dichloroethane (7 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc). The residue was purified by MPLC (2:1 Hex:EtOAc) to give **13a** and **13b** as a coeluting mixture in a ratio of ~1:1.1 (54 mg, 0.096 mmol, 48%) as a yellow amorphous solid.

^{1}H-NMR data for 13a, extracted from the spectra of the mixture of constitutional isomers, which shows atropisomers in a ratio of ca. 2:1 for some of its protons in close proximity to the biaryl bond.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.23 (dd, J = 8.8, 1.1 Hz, ~0.6H, C1*H* in the major atropisomer), 7.22 (dd, J = 8.6, 0.8 Hz, ~0.4H, C1*H* in the minor atropisomer), 7.12 (s, ~0.3H, NAr*H* in on atropisomer), 7.10 (s, ~0.7H, NAr*H* in other atropisomer), 6.79 (d, J = 8.5 Hz, ~0.6 H, C2*H* in the major atropisomer), 6.78 (d, J = 8.6 Hz, ~0.4H, C2*H* in the minor atropisomer) 4.68 (dd, J = 8.9, 8.0 Hz, 1H, C17*H*), 4.08-3.96 (m, 2H, MsNCH_2CH_2), 3.29-3.18 (m, 2H, MsNCH_2CH_2), 2.44–2.37 (m, 1H, H6a), 2.22 (m, 1H, C9*H*), 2.24-2.16 (m, 2H, C16H_2), 2.15 (m, 1H, H6b), and 2.14 (s, 3H, NArC≡CCH_3), 2.09 (s, 1.9H, NArCH_3 in the major atropisomer), and 2.07 (s, 1.1H, NArCH_3 in the minor atropisomer).

^{1}H-NMR data for 13b, extracted from the spectra of the mixture of constitutional isomers, which shows atropisomers in a ratio of ca. 1:1 for some of its protons in close proximity to the biaryl bond.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.21 (s, ~0.5 H, NAr*H* in the one atropisomer), 7.18 (s, ~0.5 H, NAr*H* in the other atropisomer), 6.95 (s, 1H, C1*H*), 6.67 (br s, 0.5H, C4*H* in one atropisomer), 6.66 (br s, 0.5H, C4*H* in the other atropisomer), 4.68 (dd, J = 8.9, 8.0 Hz, 1H, C17*H*), 4.08-3.96 (m, 2H, MsNCH_2CH_2), 3.29-3.18 (m, 2H, MsNCH_2CH_2), 2.86 (m, 2H, C6H_2), 2.22 (m, 1H, C9*H*), 2.24-2.16 (m, 2H, C16H_2), 2.21 (br s, ~1.8H, NArCH_3 in one atropisomer), 2.19 (br s, ~1.2H, NArCH_3 in the other atropisomer), and 2.14 (s, 3H, NArC≡CCH_3).

Proton resonances that cannot be distinguished with confidence as arising from **13a** vs. **13b**

2.86 and 2.85 (two singlets, NSO_2CH_3), 2.32 (m, 1H), 2.060, 2.058, 2.052, and 2.046 (four s, C17OCOCH_3), 1.92-1.88 (m, 2H), 1.86-1.82 (m, 1H), 1.78-1.65 (m, 3H), 1.61-1.17 (m, ~15H), 0.84, and 0.85 (overlapping singlets, 2H and 4H, C13CH_3).

^{13}C-NMR data for 13a, extracted from the spectra of the mixture of constitutional isomers.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 150.1, 135.4, 132.6, 132.3, 126.1, 122.3, 114.8, 112.4, 28.3, 23.2, and 17.7.

^{13}C-NMR data for 13b, extracted from the spectra of the mixture of constitutional isomers.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 150.0, 137.7, 127.1, 137.4, 132.1, 122.7, 115.2, 114.6, 29.5, 27.2, and 17.1.

Carbon resonances that cannot be distinguished with confidence as arising from **13a** vs. **13b**:

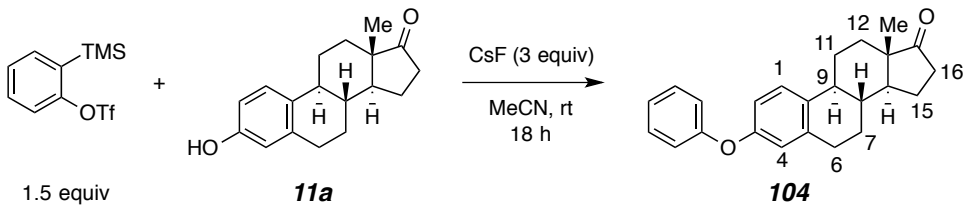
δ 139.9, 134.3,133.8, 122.5, 94.7, 82.8, 75.8, 50.3, 49.8, 43.8, 42.8, 38.1, 36.9, 36.8, 34.4, 28.3, 27.5, 27.3, 27.1, 26.5, 26.4, 21.2, 12.1, and 4.63.

IR and HRMS data from the mixture of 13a and 13b:

IR (neat): 3452, 3020, 2977, 2925, 2873, 2241, 1730, 1347, 1248, and 1159 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{40}NO_5S^+$ $[M+H]^+$ requires 562.2622; found 562.2642.

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-phenoxy-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (104)



CsF (114 mg, 0.75 mmol, 3 equiv) and estrone (68 mg, 0.25 mmol, 1 equiv) were combined in a culture tube and suspended in acetonitrile (4 mL, 0.06 M). 2-(Trimethylsilyl)phenyl trifluoromethane-sulfonate (91 μL, 0.375 mmol, 1.5 equiv) was added and the tube was sealed with a Teflon-lined cap. The solution was stirred overnight (14-16 h) at room temperature, filtered through Celite™, concentrated, and passed through a plug of silica (1:1 Hex:EtOAc). The residue was purified by MPLC (10:1 Hex:EtOAc) to give **104**[6] (80 mg, 0.23 mmol, 92%) as a white amorphous solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.6, 7.4 Hz, 2H, OPhH_m), 7.24 (d, *J* = 8.4 Hz, 1H, C1*H*), 7.08 (tt, *J* = 8.3, 1.0 Hz, 1H, OPhH_p), 7.00 (dd, *J* = 8.8, 1.0 Hz, 2H, OPhH_o), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1H, C2*H*), 6.75 (d, *J* = 2.5 Hz, C3*H*), 2.89-2.86 (m, 2H, C6H_2), 2.50 (dd, *J* = 19.3, 8.9 Hz, 1H, C16*H*a), 2.43-2.38 (m, 1H, C15*H*a), 2.28 (ddd, *J* = 10.9, 10.9, 3.6 Hz, 1H, C9*H*), 2.14 (ddd, *J* = 18.8, 8.9, 8.9 Hz, 1H, C16*H*b), 2.05 (m, 1H, C11*H*a), 2.00 (m, 1H, C7*H*a), 1.96 (m, 1H, C12*H*a), 1.62 (m, 1H, C11*H*b), 1.60 (m, 1H, C8*H*), 1.51 (m, 1H, C14*H*), 1.50 (m, 1H, C15*H*b), 1.49 (m, 1H, C12*H*b), 1.44 (m, 1H, C7*H*b), and 0.92 (s, 3H, CH_3).

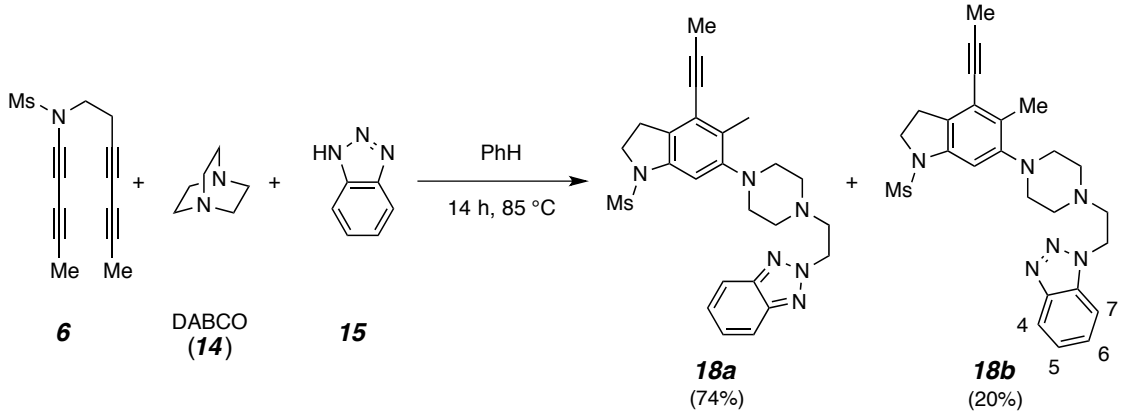
^{13}C-NMR (125 MHz, $CDCl_3$,1-D): δ 220.9, 157.5, 155.1, 138.3, 134.8, 129.7, 126.7, 123.0, 119.1, 118.8, 116.5, 50.5, 48.1, 44.2, 38.3, 36.0, 31.7, 29.6, 26.5, 26.0, 21.7, and 14.0.

IR (neat): 3062, 2929, 2860, 1737, 1590, 1488, 1238, and 1211 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{24}H_{26}NaO_2^+$ $[M+Na]^+$ requires 369.1825; found 369.1827.

2-(2-(4-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)piperazin-1-yl)ethyl)-2*H*-benzo[*d*][1,2,3]triazole (**18a**) and

1-(2-(4-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)piperazin-1-yl)ethyl)-1*H*-benzo[*d*][1,2,3]triazole (**18b**)



Tetrayne **6** (50 mg, 0.202 mmol), DABCO (27 mg, 0.243 mmol, 1.2 equiv), and benzotriazole (27 mg, 0.222 mmol, 1.1 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (1:1 Hex:EtOAc +1% NEt_3) to give, in order of elution, **18a** (72 mg, 0.150 mmol, 74%) and **18b** (19 mg, 0.040 mmol, 20%) both as pale yellow oils

Data for 18a (major isomer)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.87 (nfom, 2H, NNNArH_o), 7.39 (nfom, 2H, NNNArH_m), 7.07 (s, 1H, NAr*H*), 4.89 (t, *J* = 6.9 Hz, 2H, CH_2NNNAr), 3.94 (t, *J* = 8.3 Hz, 2H, MsNCH_2CH$_2$), 3.19 (t, *J* = 7.0 Hz, 2H, (CH$_2$)$_2$NCH_2), 3.11 (t, *J* = 8.5 Hz, 2H, MsNCH$_2$CH_2), 2.85 (t, *J* = 4.6 Hz, 4H, ArN(CH_2CH$_2$)$_2$N), 2.80 (s, 3H, NSO$_2$CH_3), 2.70 (br s, 4H, ArN(CH$_2$CH_2)$_2$N), 2.30 (s, 3H, ArCH_3), and 2.12 (s, 3H, NArC≡CCH_3).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 151.6, 144.4, 139.9, 130.0, 128.4, 126.3, 122.2, 118.0, 105.3, 93.9, 76.3, 57.3, 54.0, 53.4, 51.8, 50.5, 34.2, 28.0, 15.6, and 4.5.

IR (neat): 3062, 2945, 2916, 2820, 2227 (w), 1590, 1465, 1449, 1345, 1158, 969, and 862 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{31}N_6O_2S^+$ [M+H]$^+$ requires 479.2224; found 479.2233.

Data for 18b (minor isomer)

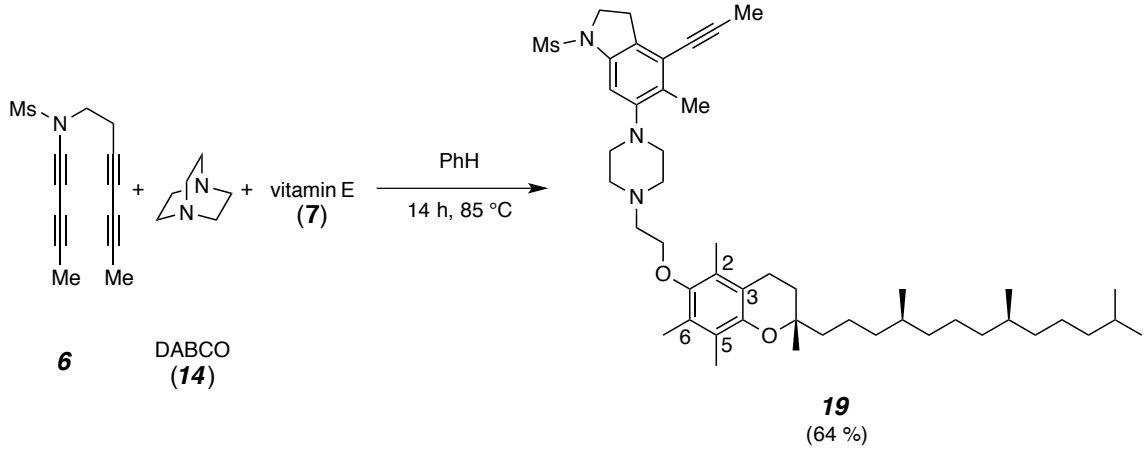
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (ddd, *J* = 8.4, 0.9, 0.9 Hz, 1H, *H7*), 7.61 (ddd, *J* = 8.4, 0.9, 0.9 Hz, 1H, *H4*), 7.52 (ddd, *J* = 8.3, 6.9, 0.9 Hz, 1H, *H6*), 7.38 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1H, *H5*), 7.07 (s, 1H, NAr*H*), 4.80 (t, *J* = 6.8 Hz, 2H, CH_2NNNAr), 3.95 (t, *J* = 8.3 Hz, 2H, CH$_2$CH_2NMs), 3.12 (t, *J* = 8.7 Hz, 2H, CH_2CH$_2$NMs), 3.03 (t, *J* = 7.0 Hz, 2H, CH_2CH$_2$NNNAr), 2.85 (br t, *J* = 4.7 Hz, 4H, ArN(CH_2CH$_2$)$_2$NCH$_2$), 2.81 (s, 3H, NSO$_2$CH_3), 2.69 (br s, 4H, ArN(CH$_2$CH_2)$_2$CH$_2$), 2.30 (s, 3H, NArCH_3), and 2.12 (s, 3H, NArC≡CCH_3).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 151.5, 145.9, 140.0, 133.3, 130.0, 128.6, 127.4, 124.0, 122.3, 120.1, 109.6, 105.3, 93.9, 76.3, 57.4, 53.4, 51.8, 50.5, 46.1, 34.2, 28.0, 15.7, and 4.6.

IR (neat): 3059, 2945, 2917, 2819, 2231 (w), 1590, 1453, 1343, 1158, 969, and 782 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{31}N_6O_2S^+$ [M+H]$^+$ requires 479.2224; found 479.2239.

5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-6-(4-(2-(((*S*)-2,5,7,8-tetramethyl-2-((4*S*,8*S*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)ethyl)piperazin-1-yl)indoline (19)



Tetrayne **6** (50 mg, 0.202 mmol), DABCO (27 mg, 0.243 mmol, 1.2 equiv), and vitamin E (98 mg, 0.222 mmol, 1.1 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (2:1 Hex:EtOAc) to give **19** (103 mg, 0.130 mmol, 64%) as a pale yellow oil

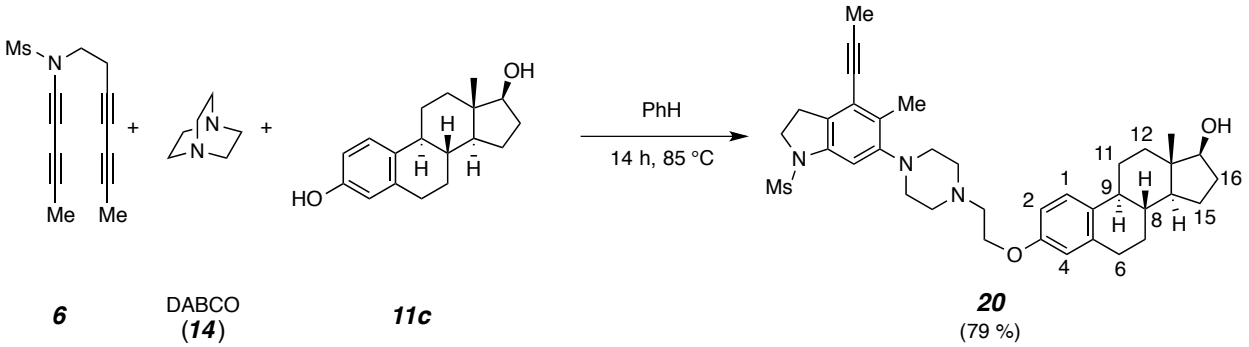
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.13 (s, 1H, NAr*H*), 3.95 (t, *J* = 8.4 Hz, 2H, CH_2CH_2NMs), 3.82 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2OAr), 3.12 (t, *J* = 8.4 Hz, 2H, CH_2CH_2NMs), 2.94 (br t, *J* = 4.6 Hz, 2H, $ArN(CH_2CH_2)_2N$), 2.86 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2OAr), 2.81 (s, 3H, NSO_2CH_3), 2.75 (br s, 4H, $ArN(CH_2CH_2)_2N$), 2.57 (t, *J* = 6.7 Hz, 2H, $ArCH_2CH_2C(CH_3)OCH2$), 2.33 (s, 3H, NArCH3), 2.19 (s, 3H, C6-CH_3), 2.15 (s, 3H, C5-CH_3), 2.12 (s, 3H, NArC≡CCH_3), 2.08 (s, 3H, C2-CH_3), 1.81 (ddd, *J* = 13.8, 7.1, 7.1 Hz, 2H, $ArCH_2CH_aH_bC(CH_3)OCH_2$), 1.75 (ddd, *J* = 13.3, 6.5, 6.5 Hz, 2H, $ArCH_2CH_aH_bC(CH_3)OCH_2$), 1.56-1.49 (m, 3H), 1.47-1.33 (m, 4H), 1.32-1.23 (m, 7H), 1.23 (s, 3H, $ArCH_2CH_2C(CH_3)OCH_2$), 1.23-1.10 (m, 4H), 1.10-1.0 (m, 4H), 0.865 (d, *J* = 6.8 Hz, 3H, $MeCHCH_{3a}$), 0.864 (d, *J* = 6.8 Hz, 3H, $MeCHCH_{3b}$), 0.85 (d, *J* = 6.5 Hz, 3H, Me_a), and 0.84 (d, *J* = 6.6 Hz, 3H, Me_b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 151.8, 148.3, 147.7, 140.0, 130.0, 128.3, 127.8, 125.8, 122.8, 122.2, 117.5, 105.1, 93.8, 76.4, 74.8, 70.4, 58.3, 54.2, 52.0, 50.5, 40.1, 39.4, 37.5, 37.4, 34.1, 32.8, 31.4, 28.0, 27.9, 24.7, 23.9, 22.8, 20.6, 21.2, 19.8, 15.8, 13.0, 12.1, 11.9, and 4.6.

IR (neat): 2957, 2925, 2867, 2811, 2229 (w), 1590, 1463, 1350, 1160, 1091, and 969 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{48}H_{76}N_3O_4S^+$ $[M+H]^+$ requires 790.5551; found 790.5627.

(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-3-(2-(4-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)piperazin-1-yl)ethoxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (20)



6 DABCO (***14***) ***11c*** ***20*** (79 %)

Tetrayne **6** (50 mg, 0.202 mmol), DABCO (27 mg, 0.243 mmol, 1.2 equiv), and 17β-estradiol (61 mg, 0.222 mmol, 1.1 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (1:1 Hex:EtOAc+1% NEt_3) to give **17** (100 mg, 0.159 mmol, 79%) as a white amorphous solid.

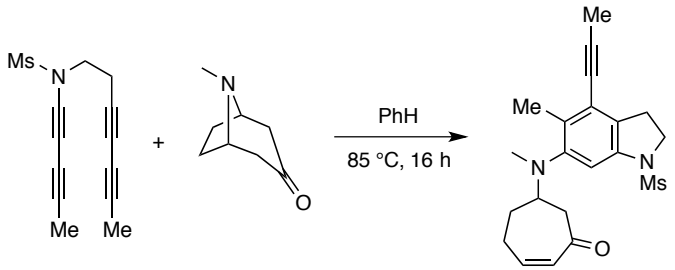
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 1H, H_1), 7.12 (s, 1H, NAr*H*), 6.72 (dd, *J* = 8.6, 2.7 Hz, 1H, *H2*), 6.65 (d, *J* = 2.7 Hz, 1H, *H4*), 4.12 (t, *J* = 6.2 Hz, 2H, CH_2OAr), 3.95 (t, *J* = 8.5 Hz, 2H, CH_2CH_2NMs), 3.73 (dd, *J* = 8.5, 8.5 Hz, 1H, *H17*), 3.12 (t, *J* = 8.3 Hz, 2H, CH_2CH_2NMs), 2.91 (br t, *J* = 4.7 Hz, 4H, ArN(CH_2CH_2)$_2$N), 2.87 (t, *J* = 5.8 Hz, 2H, CH_2CH_2OAr), 2.84 (m, 2H, *H6*), 2.80 (s, 3H, NSO_2CH_3), 2.74 (br s, 4H, ArN(CH_2CH_2)$_2$N), 2.32 (s, 3H, NArCH_3), 2.31 (dddd, *J* = 13.2, 4.0, 4.0, 4.0 Hz, 1H, *H7eq*), 2.19 (ddd, *J* = 11.1, 11.1, 4.3 Hz, 1H, *H9*), 2.12 (s, 3H, NArC≡CCH_3), 2.11 (m, 1H, *H16a*), 1.94 (ddd, *J* = 12.4, 3.3, 3.3 Hz, 1H, *H12eq*), 1.88 (dddd, *J* = 2.5, 2.5, 5.7, 12.3 Hz, 1H, *H11eq*), 1.70 (dddd, *J* = 3.2, 7.2, 10, 12.4 Hz, 1H, *H15a*), 1.53–1.40 (m, 3H), 1.39–1.28 (m, 3H), 1.18 (ddd, *J* = 12.1, 11.0, 7.3 Hz, *H14*), and 0.78 (s, 3H, C13CH_3).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.6, 151.7, 140.0, 138.0, 132.9, 130.0, 128.4, 126.3, 122.9, 114.7, 112.1, 105.3, 93.8, 81.8, 76.3, 65.8, 57.3, 53.9, 51.9, 50.5, 50.1, 44.0, 43.3, 38.8, 36.7, 34.1, 30.6, 29.8, 27.9, 27.2, 26.3, 23.2, 15.7, 11.1, and 4.5.

IR (neat): 3434, 3047, 2923, 2868, 2826, 2235 (w), 1590, 1465, 1449, 1347, 1251, 1158, 1054, and 969 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{37}H_{50}N_3O_4S^+$ $[M+H]^+$ requires 632.3517; found 632.3546.

6-(Methyl(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)amino)cyclohept-2-en-1-one (**23**)



6 tropinone (***21***) ***23*** (75%)

Tetrayne **6** (50 mg, 0.202 mmol) and tropinone (**21**) (45 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc). The resulting residue was purified by MPLC (3:1 +1% Hex:EtOAc + NEt_3) to give, **23** (59 mg, 0.152 mmol, 75%) as a pale yellow oil.

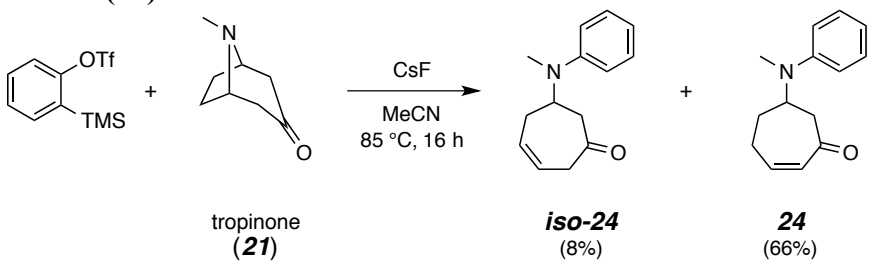
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.13 (s, 1H, Ar*H*), 6.58 (ddd, *J* = 11.6, 5.4, 5.4 Hz, 1H, *H3*), 5.99 (d, *J* = 12.0 Hz, 1H, *H2*), 3.97 (ddd, *J* = 10.6, 8.7, 8.7 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.96 (ddd, *J* = 10.5, 9, 9 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.41 (dddd, *J* = 8.3, 8.3, 4, 4 Hz, 1H, $(CH_2)_2CHN$), 3.13 (t, *J* = 8.5, 2H, $CH_3SO_2NCH_2CH_2$), 2.93 (dd, *J* = 14.8, 8.6 Hz, 1H, $COCH_aH_b$), 2.82 (s, 3H, CH_3SO_2N), 2.74 (dd, *J* = 14.8, 3.9 Hz, 2H, $COCH_aH_b$), 2.59 (s, 3H, NCH_3), 2.51 (m, 1H, $HC{=}CHCH_aH_b$), 2.35 (m, 1H, $HC{=}CHCH_aH_b$), 2.28 (s, 3H, $NArCH_3$), 2.12 (s, 3H, $NArC{\equiv}CCH_3$), and 2.06–1.95 (m, 2H, $HC{=}CHCH_2CH_2$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 201.6, 151.0, 146.6, 139.7, 132.5, 131.7, 129.3, 122.4, 107.9, 94.1, 76.3, 57.2, 50.5, 47.3, 37.1, 34.2, 30.7, 28.0, 27.7, 15.8, and 4.5.

IR (neat): 3022, 2947, 2927, 2801, 2231, 1657, 1589, 1459, 1345, 1158, 1061, and 970 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{26}N_2NaO_3S^+$ $[M+Na]^+$ requires 409.1556; found 409.1560.

6-(Methyl(phenyl)amino)cyclohept-3-en-1-one (iso-24) and **6-(methyl(phenyl)amino)-cyclohept-2-en-1-one (24)**



2-(Trimethylsilyl)phenyl triflate (50 mg, 0.168 mmol) and tropinone (**21**) (28 mg, 0.201 mmol, 1.2 equiv) were combined in a culture tube and dissolved in acetonitrile (6 mL, 0.03 M). CsF (28 mg, 0.185 mmol, 1.1 equiv) was added and the culture tube was sealed with a Teflon-lined cap. The suspension was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, concentrated, and passed through a plug of silica (2:1 Hex:EtOAc). The resulting residue was purified by MPLC (5:1 Hex:EtOAc) to give, in order of elution **iso-24** (3 mg, 0.014 mmol, 8%) and **24** (24 mg, 0.111 mmol, 66%) as a pale yellow oils.

Iso-24 (minor)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 8.6, 7.2 Hz, 2H, NArH_m), 6.82 (dd, *J* = 8.8, 0.8 Hz, 2H, NArH_o), 6.77 (tt, *J* = 7.3, 0.9 Hz, 1H, NArH_p), 5.91 (ddddd, *J* = 11.1, 6.6, 5.1, 1.7, 1.2 Hz, 1H, C4*H*), 5.68 (ddddd, *J* = 11.0, 6.7, 4.8, 1.8, 1.2 Hz, 1H, C3*H*), 4.43 (dddd, *J* = 9.5, 9.5, 4.2, 4.2 Hz, 1H, C6*H*), 3.30 (ddddd, *J* = 16.3, 3.7, 1.9, 1.9, 1.9 Hz, 1H, C2*H*a), 3.13 (dd, *J* = 16.2, 6.9 Hz, C2*H*b), 2.92 (dd, *J* = 13.9, 10.4 Hz, 1H, C7*H*a), 2.79 (s, 3H, NCH_3), 2.77 (ddd, *J* = 13.8, 4.4, 1.3 Hz, 1H, C7*H*b), and 2.60-2.46 (m, 2H, C5H_2).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 207.2, 149.3, 129.6, 129.3, 122.5, 118.0, 114.2, 55.3, 47.3, 43.5, 32.6, and 31.4.

IR (neat): 3059, 3026, 2923, 2854, 2813, 1706, 1598, 1503, and 1266 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{14}H_{17}NNaO^+$ $[M+Na]^+$ requires 238.1202; found 238.1201

24 (major)

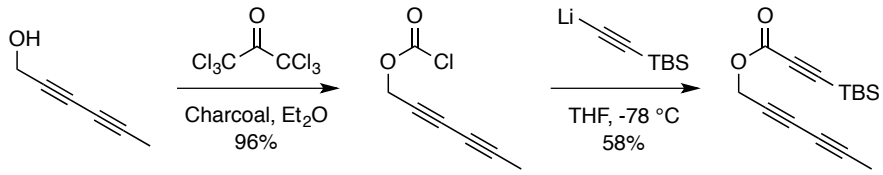
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.6, 7.1 Hz, 2H, NArH_m), 6.80 (dd, *J* = 8.7, 0.8 Hz, 2H, NArH_o), 6.76 (tt, *J* = 7.3, 0.9 Hz, 1H, NArH_p), 6.62 (ddd, *J* = 11.9, 6.4, 4.6 Hz, 1H, C3*H*), 6.05 (dddd, *J* = 12.2, 2.2, 1.1, 1.1 Hz, 1H, C2*H*), 4.23 (dddd, *J* = 9.1, 9.1, 4.6, 4.6 Hz, 1H, C6*H*), 2.91 (dd, *J* = 15.4, 8.9 Hz, 1H, C7*H*a), 2.84 (dddd, *J* = 15.4, 4.8, 0.8, 0.8 Hz, 1H, C7*H*b), 2.77 (s, 3H, NCH_3), 2.65-2.58 (nfom, 1H, C4Ha), 2.53-2.45 (nfom, 1H, C4*H*b), 2.18–2.12 (nfom, 1H, *C5Ha*), and 2.02 (dddd, *J* = 13.2, 9.5, 9.5, 3.7 Hz, 1H, C5*H*b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 201.5, 149.7, 146.1, 132.5, 129.3, 117.8, 114.2, 54.4, 47.7, 31.7, 31.0, and 28.3.

IR (neat): 3094, 3059, 3023, 2815, 1655, 1598, 1503, 1286, and 751 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{14}H_{17}NNaO^+$ $[M+Na]^+$ requires 238.1202; found 238.1193

Hexa-2,4-diyn-1-yl 3-(tert-butyldimethylsilyl)propiolate (25)



25

Triphosgene (742 mg, 2.5 mmol) was added to a 15 mL round bottom flask and dissolved in anhydrous ether (10 mL). Activated charcoal (20 mg) was added and the suspension was stirred for 1 h at room temperature. Hexa-2,4-diyn-1-ol (471 mg, 5 mmol) in ether (3 mL) was added dropwise and the resulting mixture was stirred overnight at room temperature. The slurry was filtered through Celite^{TM} (eluting with additional ether) and concentrated to give crude hexa-2,4-diyn-1-yl carbonochloridate (750 mg, 4.79 mmol). TBS acetylene (771 mg, 5.5 mmol) was added to a 25 mL round bottom flask, placed under nitrogen, dissolved in THF (10 mL), and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 2.16 mL, 5.4 mmol) was added dropwise over 5 min and the solution was stirred at 0 °C for 1 h. The mixture was cooled to -78 °C, and hexa-2,4-diyn-1-yl carbonochloridate (750 mg, 4.79 mmol) in THF (5 mL) was added in one portion. After being stirred at -78 °C for 2 h then -20 °C for 30 min, the reaction was quenched at -20 °C by the addition of acetic acid (1 mL). The mixture was transferred to a separatory funnel with additional ether (50 mL) and washed with $NaHCO_3$ (25 mL x 3) and brine (25 mL). The ether layer was dried ($MgSO_4$), filtered, concentrated, and passed through a plug of silica (10:1 Hex:EtOAc). The resulting residue was purified by MPLC (50:1 Hex:EtOAc) to give **25** (725 mg, 2.78 mmol, 58%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.79 (q, J = 1.1 Hz, 2H, CH_2OCO), 1.94 (t, J = 1.1 Hz, 3H, C≡CCH_3), 0.97 (s, 9H, Si(CCH_3)$_3$), and 0.18 (s, 6H, Si(CH_3)$_2$).

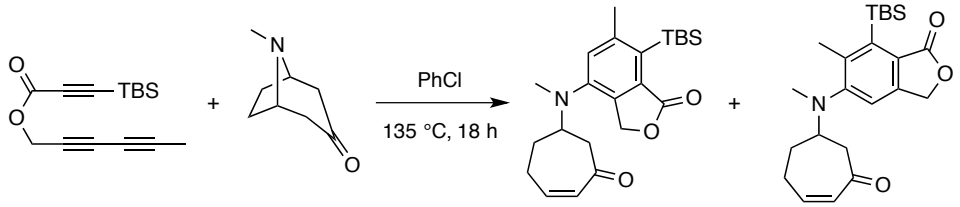
^{13}C-NMR (125 MHz, $CDCl_3$, 1-D): δ 152.1, 94.7, 94.5, 78.3, 72.7, 67.6, 63.6, 53.9, 26.1, 16.7, 4.5, and -5.1.

IR (neat): 2954, 2931, 2859, 2264, 2174, 1719, 1364, and 1203 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{15}H_{20}NaO_2Si^+$ $[M+Na]^+$ requires 283.1125; found 283.1123

mp: 36-38 °C.

7-(*tert*-Butyldimethylsilyl)-6-methyl-4-(methyl(3-oxocyclohept-4-en-1-yl)amino)isobenzofuran-1(3*H*)-one (**27a**) and **7-(*tert*-butyldimethylsilyl)-6-methyl-5-(methyl(3-oxocyclohept-4-en-1-yl)amino)isobenzofuran-1(3*H*)-one** (**27b**)



Triyne **25** (53 mg, 0.202 mmol) and tropinone (**21**) (45 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in chlorobenzene (7.5 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18 h) in an oil bath at 135 °C, cooled, and passed through a plug of silica (10:1 to 1:3 Hex:EtOAc). The resulting residue was purified by MPLC (3:1 Hex:EtOAc) to give, **27a** (39 mg, 0.098 mmol, 49%) and **27b** (32 mg, 0.080 mmol, 40%) each as a pale yellow oil.

27a (major)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 1H, Ar*H*), 6.67 (ddd, *J* = 11.5, 6.3, 5.0 Hz, 1H, C3*H*), 6.05 (dddd, *J* = 12.0, 2.1, 1.2, 1.2 Hz, 1H, C2*H*), 5.15 (s, 2H, CH_2OCO), 3.73 (dddd, *J* = 8.6, 8.6, 5.0, 5.0 Hz, 1H, C6*H*), 2.98 (dd, *J* = 15.0, 8.6 Hz, 1H, C7*H*a), 2.81 (ddd, *J* = 14.9, 0.8, 0.8 Hz, 1H, C7*H*b), 2.76 (s, 3H, NCH_3), 2.63 (ddddd, *J* = 18.5, 6.9, 6.9, 3.6, 1.5 Hz, 1H, C4*H*a), 2.54 (s, 3H, ArCH_3), 2.47 (ddddd, *J* = 18.4, 9.0, 4.7, 4.0, 2.0 Hz, C4*H*b), 2.18–2.13 (m, 1H, C5H_a), 2.09 (dddd, *J* = 14.0, 9.2, 9.2, 3.7 Hz, 1H, C5H_b), 1.02 (s, 9H, SiC(CH_3)$_3$), 0.43 (s, 3H, Si(CH_3)a(CH_3)b), and 0.42 (s, 3H, Si(CH_3)a(CH_3)b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 200.8, 171.2, 148.3, 147.0, 146.4, 136.8, 133.1, 132.7, 130.1, 124.1, 67.6, 56.4, 47.3, 33.2, 31.0, 28.2, 27.6, 25.9, 19.7, and 1.1.

IR (neat): 3027, 2929, 2854, 1766, 1662, 1587, 1471, 1249, 1085, 1029, and 823 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO_3Si^+$ $[M+H]^+$ requires 400.2302; found 400.2302

27b (minor)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.09 (s, 1H, Ar*H*), 6.66 (ddd, *J* = 11.2, 6.1, 5.1 Hz, 1H, C3*H*), 6.04 (br d, *J* = 12 Hz, C2*H*), 5.15 (s, 2H, CH_2OCO), 3.49 (dddd, *J* = 8.7, 8.7, 4.8, 4.8 Hz, 1H, C6H), 2.98 (dd, *J* = 14.7, 8.5 Hz, 1H, C7*H*a), 2.77 (dd, *J* = 15.1, 5.0 Hz, 1H, C7*H*b), 2.72 (s, 3H, NCH_3), 2.62-2.55 (m, 1H, C4*H*a), 2.46 (s, 3H, ArCH_3), 2.47-2.38 (m, 1H, C4Hb), 2.17 (dddd, *J* = 14.1, 8.1, 4.3, 4.3 Hz, 1H, C5H_a), 2.09 (dddd, *J* = 13.9, 8.8, 8.8, 3.5 Hz, 1H, C5H_b) 1.05 (s, 9H, SiC(CH_3)$_3$), 0.47 (s, 3H, Si(CH_3)a(CH_3)b), and 0.45 (s, 3H, Si(CH_3)a(CH_3)b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 201.4, 170.9, 157.2, 156.2, 146.7, 146.4, 142.3, 132.7, 125.6, 114.6, 67.7, 57.3, 46.7, 34.8, 30.7, 28.5, 27.7, 21.5, 19.3, and 1.4.

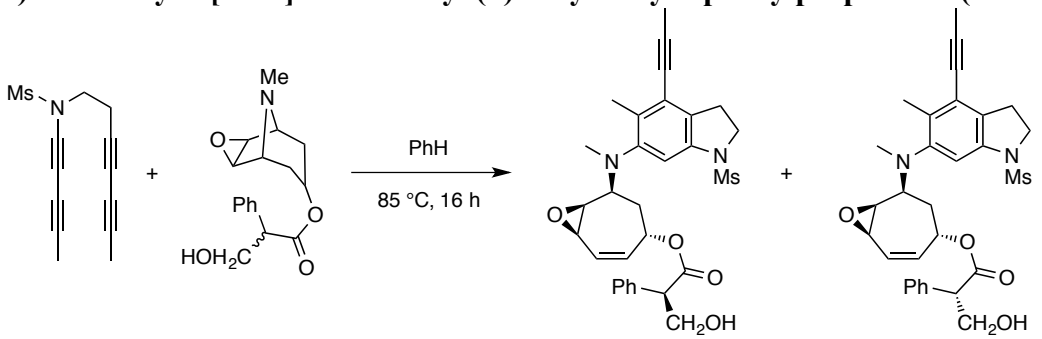
IR (neat): 3021, 2930, 2884, 2855, 2806, 1756, 1655, 1586, 1459, 1261, 1089, 1035, and 823 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO_3Si^+$ $[M+H]^+$ requires 400.2302; found 400.2314

(±)-(1*R*,4*S*,6*S*,7*S*)-6-(Methyl(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)amino)-8-oxabicyclo[5.1.0]oct-2-en-4-yl (*R*)-3-hydroxy-2-phenylpropanoate (30a or 30b)

and

(±)-(1*R*,4*S*,6*S*,7*S*)-6-(Methyl(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)amino)-8-oxabicyclo[5.1.0]oct-2-en-4-yl (*S*)-3-hydroxy-2-phenylpropanoate (30a or **30b)**



6 Scopalamine (***28***) ***30a*** or ***30b*** ***30a*** or ***30b***

Tetrayne **6** (30 mg, 0.122 mmol) and scopolamine (**28**) (74 mg, 0.243 mmol, 1.2 equiv) were combined in a culture tube, dissolved in benzene (4 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (3:2 Hex:EtOAc + 1% NEt_3) to give in order of elution **30a** (16 mg, 0.029 mmol, 24 %) and **30b** (16 mg, 80% purity (from ^{1}H NMR integration) 0.025 mmol, 21 %; contaminated with ca. 20 mol% of the coeluting deacetylated alcohol **105**).

Data for 30a (the faster eluting diastereomer)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 3H, CHArH_mH_p), 7.14 (m, 2H, CHArH_o), 7.14 (s, 1H, NMsAr*H*), 5.81 (ddd, *J* = 12.3, 5.7, 0.8 Hz, 1H, $O_{(oxiranyl)}$C*H*C=CH), 5.66 (dddd, *J* = 12.3, 5.6, 0.8, 0.8 Hz, 1H, $O_{(oxiranyl)}$CHC=C*H*), 5.37 (ddd, *J* = 5.0, 4.2, 2.9 Hz, 1H, HC=CHC*H*O(C=O), 3.99 (ddd, *J* = 10.6, 8.9, 8.1 Hz, 1H, MsNCH_a $H_b$$CH_2$), 3.97 (ddd, *J* = 10.6, 8.6, 8.6 Hz, 1H, MsNCH_a $H_b$$CH_2$) 3.91 (dd, *J* = 11.3, 8.3 Hz, 1H, CHC$H_a$$H_b$OH), 3.65 (dd, *J* = 11.3, 5.5 Hz, 1H, CHC$H_a$$H_b$OH), 3.60 (dd, *J* = 11.1, 1.5 Hz, 1H, C*H*NCH_3Ar), 3.57 (dd, *J* = 4.5, 1.4 Hz, 1H, $O_{(oxiranyl)}$C*H*CHN), 3.53 (dd, *J* = 8.2, 5.4 Hz, 1H, C*H*CH_2OH), 3.16–3.11 (m, 2H, MsNCH_2CH_2), 3.13 (ddd, *J* = 5.6, 4.7, 0.9 Hz, $O_{(oxiranyl)}$C*H*C=), 2.84 (s, 3H, C$H_3$$SO_2$N), 2.77 (s, 3H, NC$H_3$Ar), 2.39 (ddd, *J* = 14.3, 11.1, 3.1 Hz, 1H, ArMeNCHC$H_a$$H_b$), 2.32 (s, 3H, NArC$H_3$), 2.18 (s, 3H, NArC≡CC$H_3$), and 1.82 (ddd, *J* = 14.4, 4.8, 1.7 Hz, ArMeNCHC$H_a$$H_b$)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.0, 150.7, 140.1, 135.5, 132.8, 129.6, 128.7, 128.2 (x2), 127.9, 127.2, 122.4, 106.8, 94.1, 76.5, 69.0, 64.4, 62.5, 56.1, 53.9, 50.6, 48.1, 34.6, 34.3, 28.0, 27.6, 16.7, and 4.6.

IR (neat): 3030, 2954, 2928, 2881, 2858, 2806, 2229, 1719, 1589, 1458, 1345, 1158, 1058, and 971 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{30}H_{35}N_2O_6S^+$ $[M+H]^+$ requires 551.2210; found 551.2232.

Data for 30b (the slower eluting diastereomer)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 3H, CHArH_mH_p), 7.16 (m, 2H, CHArH_o), 7.09 (s, 1H, NMsAr*H*), 5.89 (ddd, *J* = 12.3, 6.3, 0.7 Hz, 1H, *H*C=CHCO(CO)), 5.81 (dddd, *J* = 12.4, 5.4, 1.4, 1.0 Hz, 1H, HC=C*H*CHO(CO)), 5.40 (ddd, *J* = 4.9, 4.1, 3.0 Hz, 1H, HC=CHC*H*O(CO)), 4.01–3.91 (m, 1H, MsNC$H_aH_bCH_2$), 3.93 (dd, *J* = 11.0, 8.5 Hz, 1H, CHCH_aH_bOH), 3.87 (ddd, *J* = 10.5, 8.7, 8.7 Hz, 1H, MsNCH$_a$$H_bCH_2$), 3.72 (dd, *J* = 11.0, 5.6 Hz, 1H, CHCH$_a$$H_b$OH), 3.65 (dd, *J* = 8.4, 5.6 Hz, 1H, C*H*CH$_2$OH), 3.61 (dd, *J* = 11.3, 1.7 Hz, 1H, C*H*NCH$_3$Ar), 3.59 (dd, *J* = 4.6, 1.3 Hz, 1H, O$_{(oxiranyl)}$C*H*CHNCH$_3$Ar), 3.18 (ddd, *J* = 5.6, 4.5, 1.1 Hz, O$_{(oxiranyl)}$C*H*CH=C), 3.11 (br t, *J* = 8.3 Hz, 2H, MsNCH$_2$C*H*$_2$), 2.73 (s, 3H, C*H*$_3$SO$_2$N), 2.72 (s, 3H, NC*H*$_3$Ar), 2.41 (ddd, *J* = 14.6, 11.4, 3.3 Hz, 1H, ArMeNCHCH_aH_b), 2.18 (s, 3H, NArC*H*$_3$), 2.17 (s, 3H, NArC≡CC*H*$_3$), and 1.76 (ddd, *J* = 14.4, 4.5, 1.7 Hz, ArMeNCHCH$_a$$H_b$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.6, 150.7, 139.8, 135.2, 133.1, 130.0, 128.8, 128.3, 128.2, 127.7, 127.0, 122.4, 107.0, 94.0, 76.4, 69.1, 64.6, 62.3, 56.3, 54.3, 50.6, 48.4, 34.4, 34.3, 28.0, 28.2, 16.4 and 4.6.

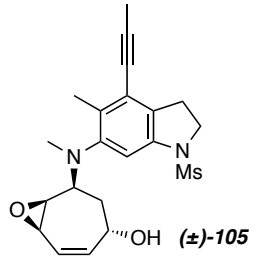
IR (neat): 3500, 3021, 2951, 2881, 2849, 2809, 2223, 1719, 1589, 1459, 1343, 1158, 1058, 970, 930, 860, and 785 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{30}H_{35}N_2O_6S^+$ $[M+H]^+$ requires 551.2210; found 551.2226.

The co-eluting compound in this sample was assigned as the (deacylated) alcohol **105**:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.39 (ddd, *J* = 2.8, 5.0, 5.0 Hz, 0.27H, C*H*OH);

HRMS calcd for $[C_{21}H_{27}N_2O_4S]^+$ $[M+H]^+$ requires 403.1686, found: 403.1701.

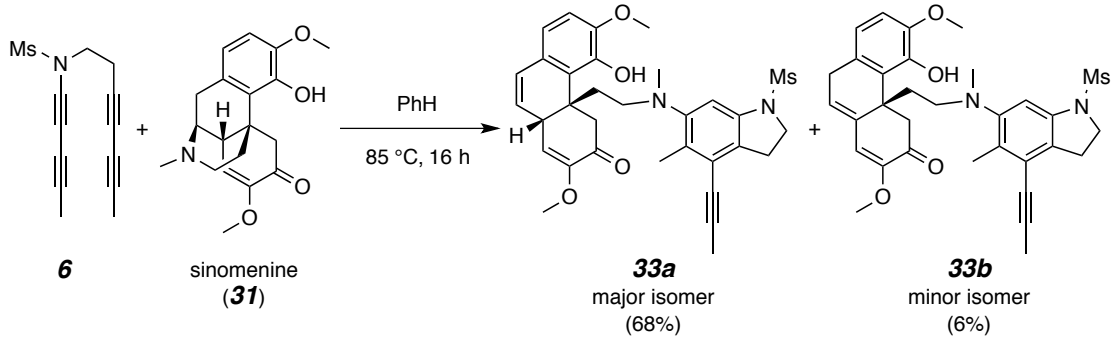


(±)-105

(4a*R*,10a*S*)-5-Hydroxy-2,6-dimethoxy-4a-(2-(methyl(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)amino)ethyl)-4a,10a-dihydrophenanthren-3(4*H*)-one (**33a**)

and

(*R*)-5-Hydroxy-2,6-dimethoxy-4a-(2-(methyl(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)amino)ethyl)-4a,9-dihydrophenanthren-3(4*H*)-one (**33b**)



Tetrayne **6** (50 mg, 0.202 mmol) and sinomenine (**31**) (obtained by free basing the commercial HCl salt through partitioning between DCM and $NaHCO_3$(sat); 129 mg, 0.392 mmol, 1.9 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc). The resulting residue was purified by MPLC (1:1 Hex:EtOAc) to give in order of elution **33b** (7 mg, 0.012 mmol, 6%) and **33a** (79 mg, 0.137 mmol, 68 %). The crude reaction mixture (prior to silica gel plug) contained the same ratio of alkene isomers (**33a** and **33b**) that was obtained following purification by MPLC.

Data for 33a (major isomer)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.79 (s, 1H, MsNAr*H*), 6.65 (d, *J* = 8.2 Hz, 1H, MeOAr*H3*), 6.55 (d, *J* = 8.2 Hz, 1H, MeOAr*H4*), 6.40 (dd, *J* = 9.6, 0.9 Hz, 1H, CH_3OAr*H*C=CH), 6.11 (s, 1H, ArO*H*), 5.85 (dd, *J* = 9.5, 5.8 Hz, 1H, CH_3OArHC=C*H*), 5.35 (d, *J* = 3.2 Hz, 1H, *H*C=COCH_3), 3.98–3.90 (m, 2H, MsNCH_2CH_2), 3.87 (d, *J* = 17.4 Hz, CH_aH_bCO), 3.85 (s, 3H, ArOCH_3), 3.48 (s, 3H, HC=COCH_3), 3.33 (ddd, *J* = 5.7, 3.1, 0.8 Hz, 1H, =CH(C*H*)HC=), 3.14–3.05 (m, 2H, MsNCH_2CH_2), 2.99 (ddd, *J* = 12.9, 10.8, 5.5 Hz, 1H, $CH_2CH_aH_bNCH_3$), 2.80 (s, 3H, CH_3SO_2N), 2.71 (ddd, *J* = 12.8, 10.8, 4.9 Hz, $CH_2CH_aH_bNCH_3$), 2.53 (d, *J* = 17.7 Hz, 1H, CH_aH_bCO), 2.51 (s, 3H, CH_3NAr), 2.22 (s, 3H, NArCH_3), 2.11 (s, 3H, NArC≡CCH_3), 2.04 (ddd, *J* = 13.3, 10.7, 4.9 Hz, 1H, C$H_aH_bCH_2NCH_3$Ar), and 1.96 (ddd, *J* = 13.6, 10.9, 5.3 Hz, 1H, $CH_aH_bCH_2NCH_3$Ar).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 194.0, 152.1, 150.8, 146.8, 145.4, 139.7, 130.7, 128.8, 128.1, 124.6, 122.1, 122.0, 121.7, 119.2, 113.8, 108.5, 106.1, 93.7, 76.4, 56.5, 54.7, 52.3, 50.6, 46.4, 42.4, 43.9, 41.9, 36.1, 34.1, 28.0, 15.9, and 4.5.

IR (neat): 3463, 2998, 2936, 2843, 2241, 1690, 1588, 1478, 1345, 1276, 1157, 1061, 969, and 791 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{37}N_2O_6S^+$ $[M+H]^+$ requires 577.2367; found 577.2361.

Data for 33b (minor isomer)

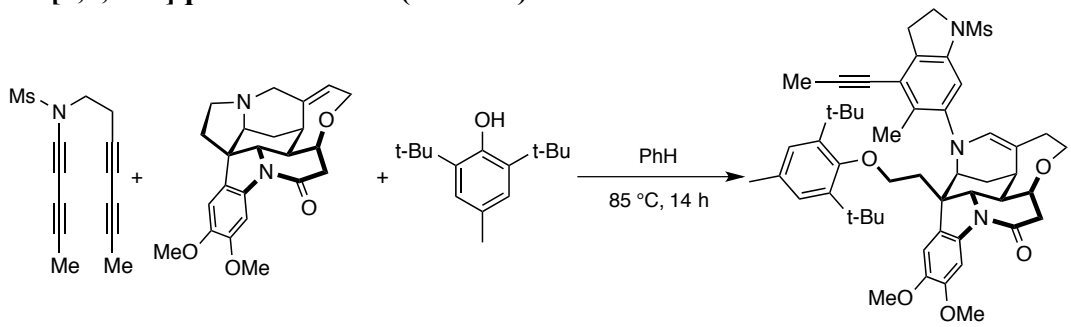
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H, NMsArH), 6.79 (d, *J* = 8.3 Hz, 1H, MeOAr*H3*), 6.63 (ddd, *J* = 8.3, 0.9, 0.9 Hz, 1H, MeOAr*H4*), 6.24 (s, 1H, $CH_3OC{=}CH$), 6.13 (t, *J* = 4.0 Hz, 1H, $CH_2CH{=}C$), 6.10 (s, 1H, ArO*H*), 4.11 (d, *J* = 16.6 Hz, 1H, $COCH_aH_b$), 3.98–3.86 (m, 2H, $MsNCH_2CH_2$), 3.90 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, $CH{=}COCH_3$), 3.52 (br d, *J* = 4 Hz, 2H, $CH_2CH{=}C$), 3.13–3.03 (m, 2H, $MsCH_2CH_2$), 2.76 (s, 3H, CH_3SO_2N), 2.67 (d, *J* = 16.6 Hz, 1H, $COCH_aH_b$), 2.62 (ddd, *J* = 12.0, 12.0, 4.5 Hz, 1H, $CH_2CH_aH_bNCH_3Ar$), 2.50 (ddd, *J* = 12.7, 11.6, 4.6 Hz, 1H, $CH_aH_bCH_2NCH_3Ar$), 2.41 (s, 3H, NCH_3Ar), 2.29 (ddd, *J* = 11.9, 11.9, 4.7 Hz, 1H, $CH_2CH_aH_bNCH_3Ar$), 2.13 (s, 3H, $NArCH_3$), 2.11 (s, 3H, $NArC{\equiv}CCH_3$), and 2.02 (ddd, *J* = 12.9, 11.5, 4.2 Hz, 1H, $CH_aH_bCH_2NCH_3Ar$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 193.8, 152.1, 149.4, 145.1, 144.4, 139.6, 135.1, 130.9, 128.0, 126.9, 126.8, 123.6, 122.0, 118.9, 117.0, 109.6, 106.0, 93.6, 76.4, 56.3, 55.2, 52.9, 52.4, 50.5, 48.4, 42.5, 34.0, 33.7, 31.0, 28.0, 15.7, and 4.6.

IR (neat): 3452, 3020, 2925, 2852, 2235, 1683, 1589, 1459, 1345, 1280, 1235, 1158, 1094, 1048, and 971 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{37}N_2O_6S^+$ $[M+H]^+$ requires 577.2367; found 577.2387.

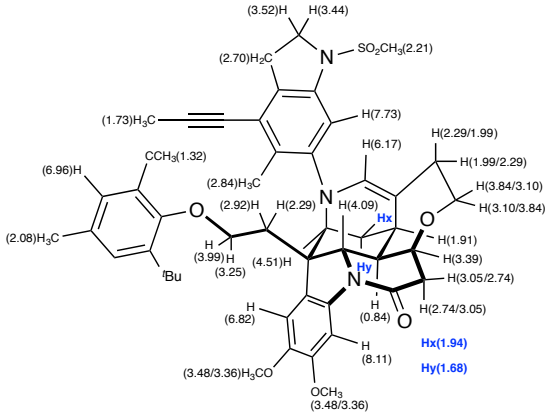
(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-6a-(2-(2,6-di-*tert*-butyl-4-methylphenoxy)ethyl)-8,9-dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2,3,4a,4a^1,5,6,6a,6a^1,13,13a-decahydro-12*H*-6,4-(epiminometheno)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12-one (37a–Δ^{20})



6 Brucine (***34***) BHT ***37a***-Δ^{20} (39%)

Tetrayne **6** (50 mg, 0.202 mmol), brucine (122 mg, 0.303 mmol, 1.5 equiv), and BHT (67 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (3:2 Hex:EtOAc + 1% NEt_3) to give **37a–Δ^{20}** (67 mg, 0.078 mmol, 39%).

Data for (37a–Δ^{20}) The NMR spectral data of a $CDCl_3$ solution of this enamine changed over the time course of extensive NMR studies; this reactivity could be arrested by performing the NMR analyses in benzene-d_6 instead.



^{1}H-NMR (500 MHz, C_6D_6): δ 8.11 (s, 1H), 7.73 (s, 1H), 6.96 (s, 2H), 6.82 (s, 1H), 6.17 (br s, 1H), 4.51 (br dd, *J* = 2.7, 2.7 Hz, 1H), 4.09 (d, *J* = 9.7 Hz, 1H), 3.99 (ddd, *J* = 13.1, 9.2, 4.4 Hz, 1H), 3.84 (dd, *J* = 13.0, 7.2 Hz, 1H), 3.52 (m, 1H), 3.48 (s, 3H), 3.44 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.39 (m, 1H), 3.36 (s, 3H), 3.25 (ddd, *J* = 12.3, 9.0, 4.8 Hz, 1H), 3.10 (dd, *J* = 12.8, 5.3 Hz, 1H), 3.05 (dd, *J* = 15.8, 8.3 Hz, 1H), 2.92 (ddd, *J* = 13.3, 13.3, 4.5 Hz, 1H), 2.84 (s, 3H), 2.74 (dd, *J* = 15.7, 5.2 Hz, 1H), 2.75–2.64 (m, 2H), 2.29 (m, 1H), 2.29 (m, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 1.99 (m, 1H), 1.94 (m, 1H), 1.91 (m, 1H), 1.73 (s, 3H), 1.68 (m, 1H), 1.32 (br s, 18H), and 0.84 (ddd, *J* = 9.8, 3.7, 3.7 Hz, 1H).

^{13}C-NMR (125 MHz, C_6D_6): δ 170.8, 155.6, 151.1, 149.2, 147.5, 143.1, 141.4, 136.6, 130.3, 130.0, 129.2, 127.8, 127.6, 123.7, 123.6, 109.7, 109.3, 107.3, 102.0, 94.7, 77.5, 77.2, 72.6, 67.2, 62.9, 59.1, 56.6, 55.3, 53.6, 52.6, 50.1, 41.9, 41.4, 35.5, 34.5, 33.7, 32.0, 27.9, 28.7, 27.3, 21.1, 17.5, and 3.9.

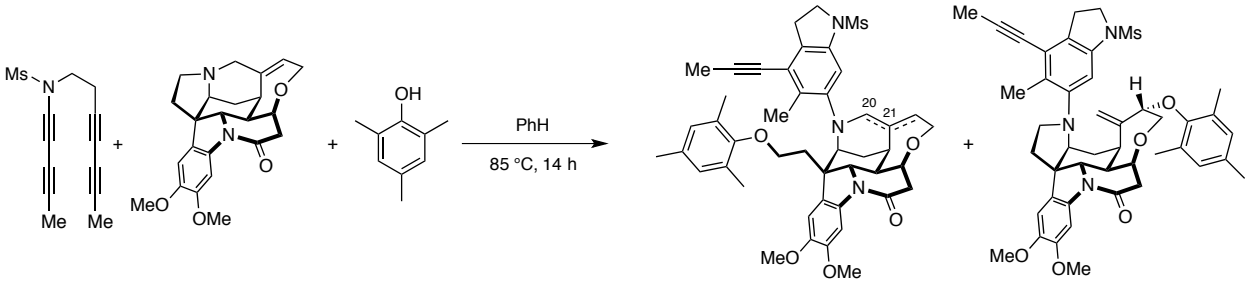
IR (neat): 3001, 2951, 2876, 2826, 2229, 1674, 1592, 1498, 1464, 1386, 1351, 1276, 1214, 1160, 1110, 992, and 857 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{51}H_{64}N_3O_7S^+$ $[M+H]^+$ requires 862.4459; found 862.4496.

(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-6a-(2-(Mesityloxy)ethyl)-8,9-dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-4a,4a^1,5,6,6a,6a^1,13,13a-octahydro-6,4-(epiminomethano)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12(2*H*)-one (37b–Δ^{20})

(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-6a-(2-(Mesityloxy)ethyl)-8,9-dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2,3,4a,4a^1,5,6,6a,6a^1,13,13a-decahydro-12*H*-6,4-(epiminometheno)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12-one (37b–Δ^{21}) and

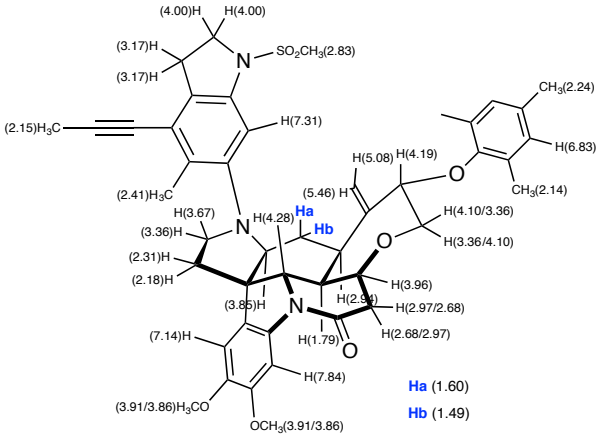
(3S,4aR,4a^{1}R,5aS,8aR,8a1S,15aS)-3-(mesityloxy)-10,11-dimethoxy-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-4-methylene-3,4,4a,4a^1,5,5a,6,7,8,8a1,15,15a-dodecahydro-2H,14H-indolo[3,2,1-ij]oxepino[2,3,4-de]pyrrolo[2,3-h]quinolin-14-one (38b)



6 brucine (***34***) 2,4,6-trimethylphenol (***3b***) ***37b-Δ^{20}*** (10%) ***37b-Δ^{21}*** (57%) ***38b*** (4%)

Tetrayne **6** (50 mg, 0.202 mmol), brucine (122 mg, 0.303 mmol, 1.5 equiv), and 2,4,6-trimethylphenol (34 mg, 0.253 mmol, 1.25 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (3:2 Hex:EtOAc + 1% NEt_3) to give, in order of elution, **38b** (6 mg, 0.008 mmol, 4 %, single component), **37b–Δ^{21}** (90 mg, 0.12 mmol, 57%, single component), and **37b–Δ^{20}** [15 mg, 0.02 mmol, 10 %, mixture of, predominantly, **37b–Δ^{20}** along with **37b–Δ^{21}** (7:3 ratio)].

Data for 38b



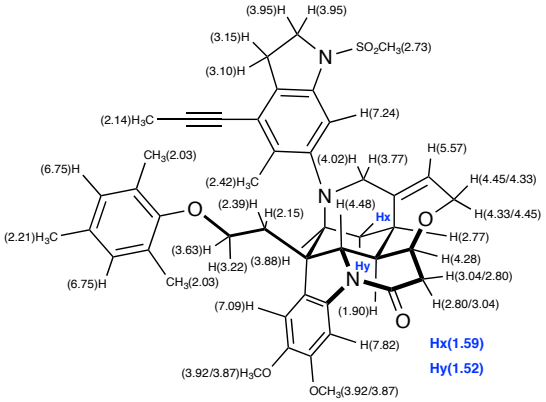
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.31 (s, 1H), 7.14 (s, 1H), 6.83 (s, 2H), 5.46 (dd, *J* = 1.3, 1.3 Hz, 1H), 5.08 (d, *J* = 1.6 Hz, 1H), 4.28 (d, *J* = 10.9 Hz, 1H), 4.19 (br dd, *J* = 9.8, 4.9 Hz, 1H), 4.10 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.00 (m, 2H), 3.96 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.85 (m, 1H), 3.64 (ddd, *J* = 9.0, 9.0, 4.4 Hz, 1H), 3.36 (dd, *J* = 10.7, 10.1 Hz, 1H), 3.27 (ddd, *J* = 9.6, 7.4, 7.4 Hz, 1H), 3.17 (dd, *J* = 8.6, 8.6 Hz, 2H), 2.97 (dd, *J* = 18.1, 7.9 Hz, 1H), 2.94 (m, 1H), 2.83 (s, 3H), 2.68 (dd, *J* = 18.1, 2.5 Hz, 1H), 2.41 (s, 3H), 2.31 (ddd, *J* = 12.9, 8.8, 7.3 Hz, 1H), 2.24 (s, 3H), 2.18 (ddd, *J* = 12.5, 7.7, 4.5 Hz), 2.15 (s, 3H), 2.14 (s, 6H), 1.79 (ddd, *J* = 11.0, 11.0, 2.5 Hz, 1H), 1.60 (ddd, *J* = 12, 12, 12 Hz, 1H), and 1.49 (ddd, *J* = 12.8, 6.0, 3.7 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.7, 153.0, 148.8, 146.3, 146.2, 140.1, 134.3, 133.2, 129.9, 129.8, 129.5, 128.6, 122.5, 114.0, 107.7, 106.7, 100.6, 94.5, 80.4, 76.3, 76.0, 74.3, 64.0, 64.6, 56.4, 56.2, 52.8, 50.6, 47.9, 43.7, 42.2, 42.1, 40.6, 34.2, 31.1, 28.1, 20.6, 17.1, 16.9, and 4.6.

IR (neat): 3001, 2957, 2928, 2864, 2238, 1662, 1590, 1499, 1464, 1349, 1215, 1160, 1122, 1017, 972, and 854 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{45}H_{52}N_3O_7S^+$ $[M+H]^+$ requires 778.3520; found 778.3529.

Data for (37b–Δ^{21})



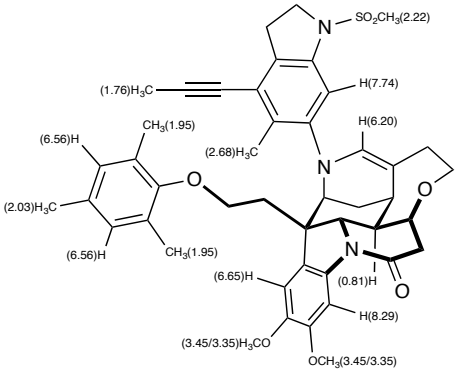
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.24 (s, 1H), 7.09 (s, 1H), 6.75 (s, 2H), 5.57 (dd, *J* = 2.8, 2.8 Hz, 1H), 4.48 (d, *J* = 10.3 Hz, 1H), 4.45 (br d, *J* = 17.2 Hz), 4.33 (br d, *J* = 17.8 Hz, 1H), 4.28 (ddd, *J* = 8.3, 2.8, 2.8 Hz, 1H), 4.02 (br d, *J* = 11.1 Hz, 1H), 3.95 (m, 2H), 3.92 (s, 3H), 3.88 (m, 1H), 3.87 (s, 3H), 3.77 (dd, *J* = 11.1, 0.8 Hz, 1H), 3.63 (ddd, *J* = 9.2, 8.3, 6.4 Hz, 1H), 3.22 (ddd, *J* = 9.5, 7.6, 5.4 Hz, 1H), 3.15 (ddd, *J* = 16.4, 9.5, 7.1 Hz, 1H), 3.10 (ddd, *J* = 16.5, 9.6, 7.8 Hz, 1H), 3.04 (dd, *J* = 17.6, 8.3 Hz, 1H), 2.80 (dd, *J* = 17.6, 2.9 Hz), 2.77 (br ddd, *J* = 11.6, 11.6, 4.6 Hz, 1H), 2.73 (s, 3H), 2.42 (s, 3H), 2.39 (ddd, *J* = 13.3, 8.0, 5.5 Hz, 1H), 2.21 (s, 3H), 2.15 (m, 1H), 2.14 (s, 3H), 2.03 (s, 6H), 1.90 (ddd, *J* = 10.7, 10.7, 3.1 Hz, 1H), 1.59 (ddd, *J* = 13.1, 4.1, 4.1 Hz, 1H), and 1.52 (ddd, *J* = 12.9, 11.4, 11.4 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.5, 153.0, 148.8, 146.5, 146.4, 140.1, 136.6, 134.5, 133.2, 129.6, 129.5, 129.4, 129.3, 128.3, 125.6, 122.8, 106.9, 106.3, 100.4, 94.2, 77.0, 76.4, 73.3, 69.6, 65.4, 65.1, 56.4, 56.2, 53.0, 50.5, 48.5, 46.5, 42.7, 41.8, 35.0, 34.1, 31.1, 28.0, 20.7, 17.2, 16.1, and 4.6.

IR (neat): 3003, 2920, 2861, 2829, 2232, 1667, 1589, 1498, 1464, 1400, 1378, 1214, 1158, 973, and 852 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{45}H_{52}N_3O_7S^+$ $[M+H]^+$ requires 778.3520; found 778.3552.

Data for the minor cycloalkene (37b–Δ^{20}) (only the diagnostic and clearly observable protons and carbons are identified within the spectrum of the 7:3 mixture of **37b–Δ^{20}** and **37b–Δ^{21}**; this interpretation was guided by the NMR data observed for the pure enamine **37a–Δ^{20}**.



^{1}H-NMR (500 MHz, C_6D_6): δ 8.29 (s, 1H), 7.74 (s, 1H), 6.65 (s, 1H), 6.56 (s, 2H), 6.20 (br s, 1H), 3.45 (s, 3H), 3.35 (s, 3H), 2.68 (s, 3H), 2.22 (s, 3H), 2.03 (s, 3H), 1.95 (s, 6H), 1.76 (s, 3H), and 0.81 (ddd, J = 9.7, 3.6, 3.6 Hz, 1H).

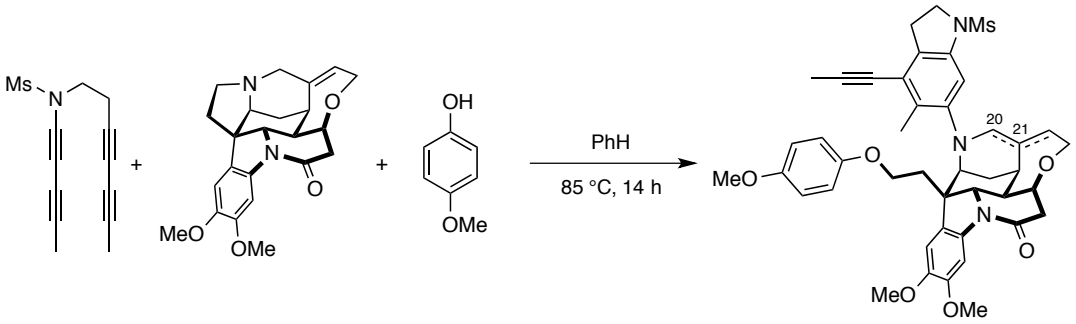
^{13}C-NMR (125 MHz, C_6D_6, only the resonances associated with the diagnostic protons listed above are reported): δ 154.6, 151.0, 149.3, 146.7, 132.7, 130.5, 130.0, 129.5, 129.0, 123.5, 109.4, 108.7, 108.3, 102.1, 94.7, 77.2, 55.4, 56.8, 52.5, 33.5, 20.4, 17.2, 16.0, and 4.6.

IR (neat): 2998, 2927, 2876, 2829, 2224, 1671, 1592, 1497, 1464, 1349, 1159, and 852 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{45}H_{52}N_3O_7S^+$ $[M+H]^+$ requires 778.3520; found 778.3557.

(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-8,9-dimethoxy-6a-(2-(4-methoxyphenoxy)ethyl)-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2,3,4a,4a^1,5,6,6a,6a^1,13,13a-decahydro-12*H*-6,4-(epiminometheno)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12-one (37c–Δ^{20}) and

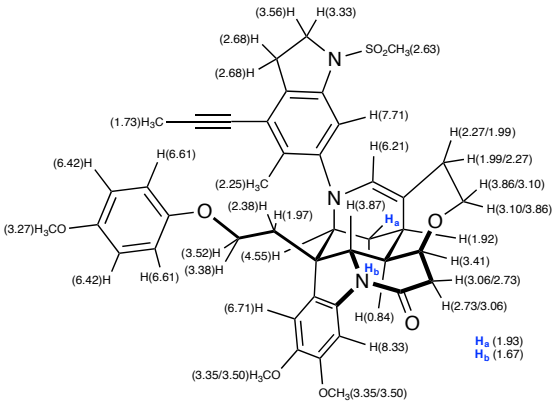
(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-8,9-dimethoxy-6a-(2-(4-methoxyphenoxy)ethyl)-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-4a,4a^1,5,6,6a,6a^1,13,13a-octahydro-6,4-(epiminomethano)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12(2*H*)-one (37c–Δ^{21})



6 brucine (***34***) ***37c*-Δ^{20}** (5%) ***37c*-Δ^{21}** (61%)

Tetrayne **6** (50 mg, 0.202 mmol), brucine (122 mg, 0.303 mmol, 1.5 equiv), and 4-methoxyphenol (32 mg, 0.253 mmol, 1.25 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (3:2 Hex:EtOAc + 1% NEt_3) to give, in order of elution, **37c–Δ^{20}** (8 mg, 0.011 mmol, 5%) and **37c–Δ^{21}** (94 mg, 0.123 mmol, 61 %).

Data for (37c–Δ^{20}) The NMR spectral data of a $CDCl_3$ solution of this enamine changed over the time course of extensive NMR studies; this reactivity could be arrested by performing the NMR analyses in benzene-d_6 instead



^{1}H-NMR (500 MHz, C_6D_6): δ 8.33 (s, 1H), 7.71 (s, 1H), 6.71 (s, 1H), 6.61 (nfod, J_{app} = 9.2 Hz, 2H), 6.42 (nfod, J_{app} = 9.2 Hz, 2H), 6.21 (br s, 1H), 4.55 (br dd, J = 3, 3 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 3.86 (dd, J = 13.0, 7.2 Hz, 1H), 3.56 (m, 1H), 3.52 (m, 1H), 3.50 (s, 3H), 3.41 (ddd, J = 8.5, 5.3, 4.2 Hz, 1H), 3.38 (m, 1H), 3.35 (s, 3H), 3.33 (m, 1H), 3.27 (s, 3H), 3.10 (ddd, J = 12.6,

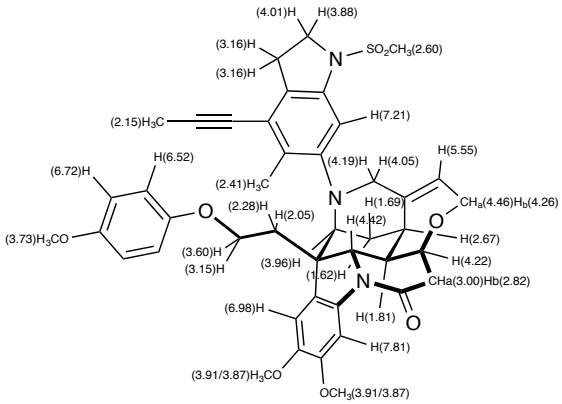
12.6, 5.1 Hz, 1H), 3.06 (dd, *J* = 15.7, 8.2 Hz, 1H), 2.73 (dd, *J* = 15.7, 5.3 Hz, 1H), 2.68 (dd, *J* = 8.0, 8.0 Hz, 2H), 2.63 (s, 3H), 2.38 (ddd, *J* = 13.7, 8.7, 7.3 Hz, 1H), 2.27 (ddd, *J* = 15.0, 12.2, 7.3 Hz, 1H), 2.25 (s, 3H), 1.99 (m, 1H), 1.97 (m, 1H), 1.93 (m, 1H), 1.92 (m, 1H), 1.73 (s, 3H), 1.67 (dd, *J* = 10.7, 2.6 Hz, 1H), and 0.84 (ddd, *J* = 9.9, 3.6, 3.6 Hz, 1H).

^{13}C-NMR (125 MHz, C_6D_6): δ 171.5, 154.4, 152.7, 151.0, 149.2, 146.8, 141.4, 136.3, 130.3, 130.0, 129.7, 123.4, 123.3, 115.4, 114.7, 109.9, 108.2, 108.0, 102.0, 94.5, 77.6, 77.2, 64.9, 67.1, 63.8, 56.2, 56.4, 55.4, 54.8, 52.7, 50.1, 41.4, 38.8, 34.3, 33.5, 28.8, 27.8, 27.4, 17.2, and 3.9.

IR (neat): 3044, 3001, 2933, 2884, 2834, 2229, 1672, 1591, 1506, 1464, 1391, 1348, 1229, 1159, 1111, and 829 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{43}H_{48}N_3O_8S^+$ $[M+H]^+$ requires 766.3157; found 766.3190.

Data for (37c–Δ^{21})



^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.21 (s, 1H), 6.98 (s, 1H), 6.72 (nfod, J_{app} = 9.2 Hz, 2H), 6.52 (nfod, J_{app} = 9.1 Hz, 2H), 5.55 (dd, *J* = 3.1, 3.1 Hz, 1H), 4.46 (ddd, *J* = 17.9, 4.2, 1.4 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 4.26 (ddd, *J* = 17.6, 4.6, 1.5 Hz, 1H), 4.22 (ddd, *J* = 8.0, 3.3, 3.3 Hz, 1H), 4.19 (dd, *J* = 11.4, 1.0 Hz, 1H), 4.05 (dd, *J* = 11.1, 0.7 Hz, 1H), 4.01 (m, 1H), 3.96 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.91 (s, 3H), 3.88 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.60 (ddd, *J* = 9.5, 7.2, 7.2 Hz, 1H), 3.16 (m, 2H), 3.15 (m, 1H), 3.00 (dd, *J* = 17.4, 8.2 Hz, 1H), 2.82 (dd, *J* = 17.3, 3.2 Hz, 1H), 2.67 (ddd, *J* = 10.5, 10.5, 4.1 Hz, 1H), 2.60 (s, 3H), 2.41 (s, 3H), 2.28 (ddd, *J* = 12.8, 7.3, 5.4 Hz, 1H), 2.15 (s, 3H), 2.05 (ddd, *J* = 12.6, 7.2, 7.2 Hz, 1H), 1.81 (ddd, *J* = 10.2, 10.2, 3.5 Hz, 1H), 1.69 (ddd, *J* = 13.8, 10.0, 10.0 Hz, 1H), and 1.62 (ddd, *J* = 13.4, 4.4, 4.4 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.9, 153.9, 152.5, 148.9, 146.4, 147.0, 140.1, 136.3, 134.6, 129.3, 128.7, 128.1, 126.3, 122.8, 115.6, 114.6, 106.1 (x2), 100.7, 94.3, 76.5, 74.6, 73.4, 68.5, 64.6, 63.9, 56.4, 56.3, 55.8, 52.5, 50.6, 49.6, 46.8, 43.1, 41.4, 34.9, 33.8, 30.6, 28.1, 17.3, and 4.6.

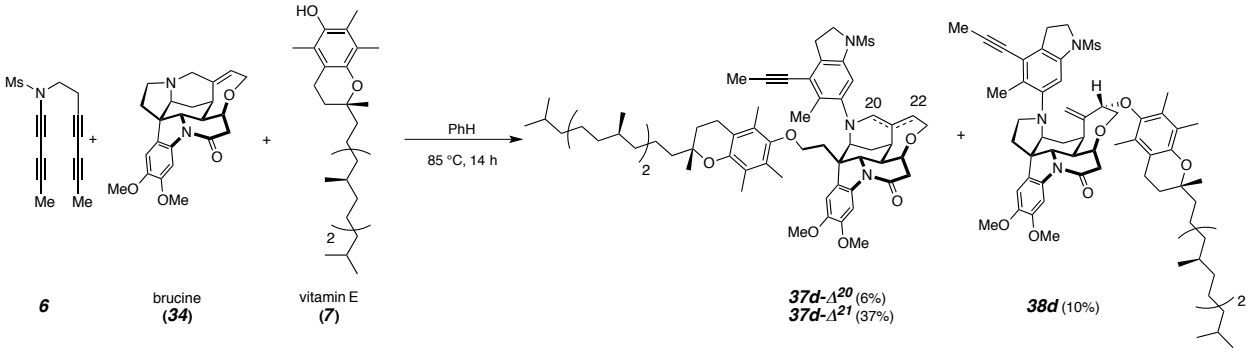
IR (neat): 3056, 3003, 2932, 2873, 2832, 2232, 1667, 1590, 1505, 1464, 1398, 1347, 1218, 1158, 1035, 972 and 827 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{43}H_{48}N_3O_8S^+$ $[M+H]^+$ requires 766.3157; found 766.3198.

(3*S*,4a*R*,4a^1*R*,5a*S*,8a*R*,8a$_1$*S*,15a*S*)-10,11-dimethoxy-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-4-methylene-3-(((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)-3,4,4a,4a^1,5,5a,6,7,8,8a$_1$,15,15a-dodecahydro-2*H*,14*H*-indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinolin-14-one (38d),

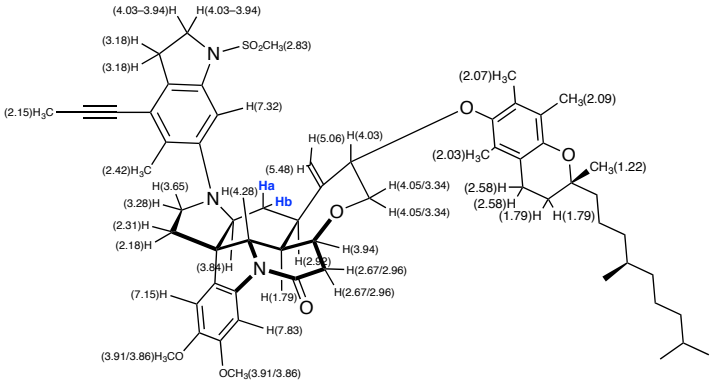
(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-8,9-Dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-6a-(2-(((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)ethyl)-2,3,4a,4a^1,5,6,6a,6a^1,13,13a-decahydro-12*H*-6,4-(epiminometheno)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12-one (37d–Δ^{20}), and

(4a*R*,4a^1*R*,6*S*,6a*R*,6a^1*S*,13a*S*)-8,9-Dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-6a-(2-(((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)ethyl)-4a,4a^1,5,6,6a,6a^1,13,13a-octahydro-6,4-(epiminomethano)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12(2*H*)-one (37d–Δ^{21})



Tetrayne **6** (50 mg, 0.202 mmol), brucine (123 mg, 0.303 mmol, 1.5 equiv), and vitamin E (110 mg, 0.255 mmol, 1.26 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (2:1 Hex:EtOAc + 1% NEt_3) to give, in order of elution, **38d** (22 mg, 0.021 mmol, 10 %) followed by **37d–Δ^{20}** and **37d–Δ^{21}** as a coeluting mixture (93 mg, 0.087 mmol, 43%; 1:5.7 ratio).

Data for (38d)



^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.32 (s, 1H), 7.15 (s, 1H), 5.48 (br dd, *J* = 1, 1 Hz, 1H), 5.06 (d, *J* = 1.6 Hz, 1H), 4.28 (d, *J* = 10.9 Hz, 1H), 4.05 (m, 1H), 4.03 (m, 1H), 4.03-3.94 (m, 2H), 3.94 (ddd, *J* = 7.7, 2.6, 2.6 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.65 (ddd, *J* = 9.4, 9.4,

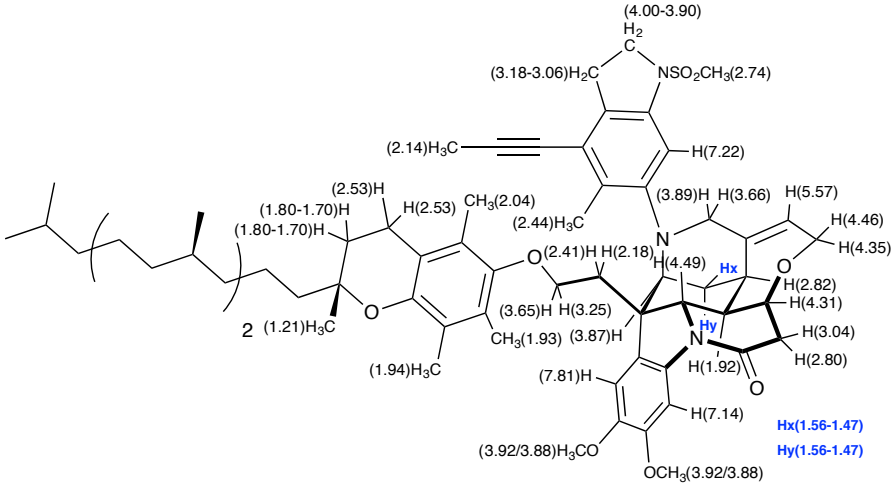
4.7 Hz, 1H), 3.34 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.28 (ddd, *J* = 9.5, 7.6, 7.6 Hz, 1H), 3.18 (br t, *J* = 9 Hz, 2H), 2.96 (dd, *J* = 18.1, 7.8 Hz, 1H), 2.92 (br ddd, *J* = 12, 6 Hz, 1H), 2.83 (s, 3H), 2.67 (dd, *J* = 18.2, 2.2 Hz, 1H), 2.61–2.55 (m, 2H), 2.42 (s, 3H), 2.31 (ddd, *J* = 12.9, 8.9, 6.8 Hz, 1H), 2.18 (ddd, *J* = 12.5, 7.7, 4.6 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.83–1.74 (m, 3H), 1.59 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 1.50-1.47 (m, 1H), 1.6-1.0 (m, est. 25H), 1.22 (s, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), and 0.85 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.7, 149.1, 148.8, 147.9, 147.5, 146.4, 146.3, 140.1, 134.3, 130.1, 129.5, 128.7, 127.2, 123.4, 125.5, 122.4, 117.9, 113.6, 107.7, 106.7, 100.6, 94.4, 80.6, 76.3, 75.9, 74.9, 74.2, 64.7, 64.0, 56.2, 56.3, 52.9, 50.5, 47.8, 43.5, 42.2 (x2), 40.9, 40.3, 39.4, 37.5, 37.4, 34.2, 31.3, 32.8, 30.9, 28.1, 27.9, 24.7, 23.4, 22.7, 21.1, 20.7, 19.8, 17.1, 13.8, 12.9, 11.8, and 4.6.

IR (neat): 2998, 2951, 2926, 2867, 2232, 1664, 1590, 1463, 1351, 1160, and 1087 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{65}H_{90}N_3O_8S^+$ $[M+H]^+$ requires 1072.6443; found 1072.6499.

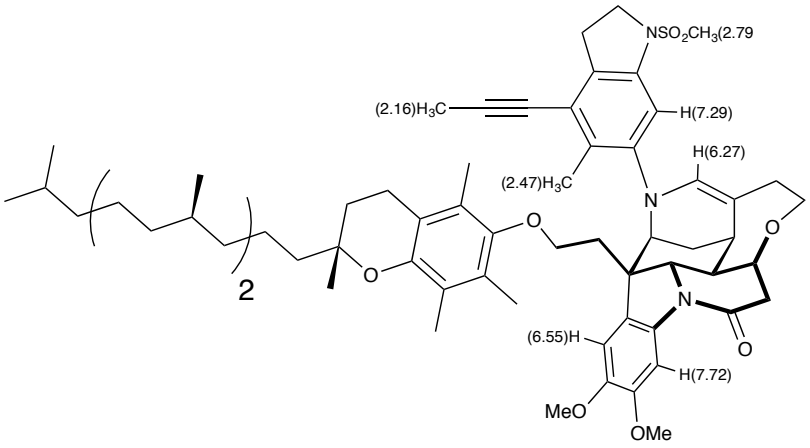
Data for the major cycloalkene (37d–Δ^{21}) (every proton and carbon resonance was identified in the spectra of the 5.7:1 mixture of **37d–Δ^{21}** and **37d–Δ^{20}**)



^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.22 (s, 1H), 7.14 (s, 1H), 5.57 (br dd, *J* = 2.7, 2.7 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.45 (br d, *J* = 17 Hz, 1H), 4.35 (br d, *J* = 17.4 Hz, 1H), 4.31 (ddd, *J* = 8.3, 2.7, 2.7 Hz, 1H), 4.00-3.90 (m, 2H), 3.92 (s, 3H), 3.89 (m, 1H), 3.88 (s, 3H), 3.87 (m, 1H), 3.66 (d, *J* = 10.5 Hz, 1H), 3.65 (m, 1H), 3.25 (ddd, *J* = 9.3, 7.9, 5.2 Hz, 1H), 3.18-3.06 (m, 2H), 3.04 (dd, *J* = 17.8, 8.5 Hz, 1H), 2.82 (m, 1H), 2.80 (dd, *J* = 17.6, 2.6 Hz, 1H), 2.74 (s, 3H), 2.53 (dd, *J* = 6.7, 6.7 Hz, 2H), 2.44 (s, 3H), 2.41 (m, 1H), 2.18 (ddd, *J* = 13.1, 7.3, 7.3 Hz, 1H), 2.14 (s, 3H), 2.04 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.92 (m, 1H), 1.80-1.70 (m, 2H), 1.58-1.46 (m, 3H), 1.46-1.32 (m, 4H), 1.32-1.19 (m, 7H), 1.21 (s, 3H), 1.19-1.00 (m, 8H), and 0.88-0.83 (m, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.3, 148.8, 147.9, 147.4, 146.5, 146.4, 140.0, 136.6, 134.3, 130.0, 129.3, 128.3, 127.7, 125.8, 125.6, 122.9, 122.8, 117.6, 107.0, 106.2, 100.7, 94.1, 77.6, 76.4, 74.9, 73.3, 69.8, 65.6, 65.3, 56.3, 56.2, 53.1, 50.5, 48.2, 46.6, 42.7, 41.7, 40.2, 39.4, 37.5 (x2), 34.8, 34.3, 32.8, 31.2, 30.7, 28.02, 28.01, 24.7, 23.7, 21.1, 19.7, 20.5, 17.3, 12.5, 11.8, 11.7, and 4.6.

Data for the minor cycloalkene (37d–Δ^{20}) (only the diagnostic and clearly observable protons and carbons are identified within the spectra of the 5.7:1 mixture of **37d–Δ^{21}** and **37d–Δ^{20}**; this interpretation was guided by the NMR data observed for pure isomer for the enamine **37a–Δ^{20}**)



^{1}H-NMR (500 MHz, $CDCl_3$): The following resonances indicate the presence of enamine **37–Δ^{20}d**: δ 7.72 (s, 1H), 7.29 (s, 1H), 6.55 (s, 1H), 6.27 (br s, 1H), 2.79 (s, 3H), 2.47 (s, 3H), and 2.16 (s, 3H).

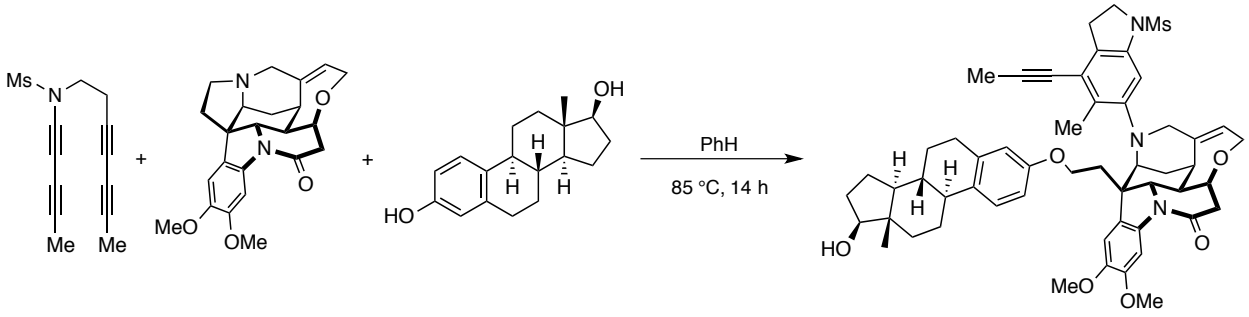
^{13}C-NMR (125 MHz, $CDCl_3$): δ 130.5, 109.8, 106.3, 101.1, 34.4, 17.3, and 4.6.

IR and MS data for the sample of the mixture of 37d–Δ^{20} and 37d–Δ^{21}

IR (neat): 2998, 2951, 2926, 2867, 2282, 1671, 1590, 1498, 1462, 1350, and 1160 cm^{-1}.

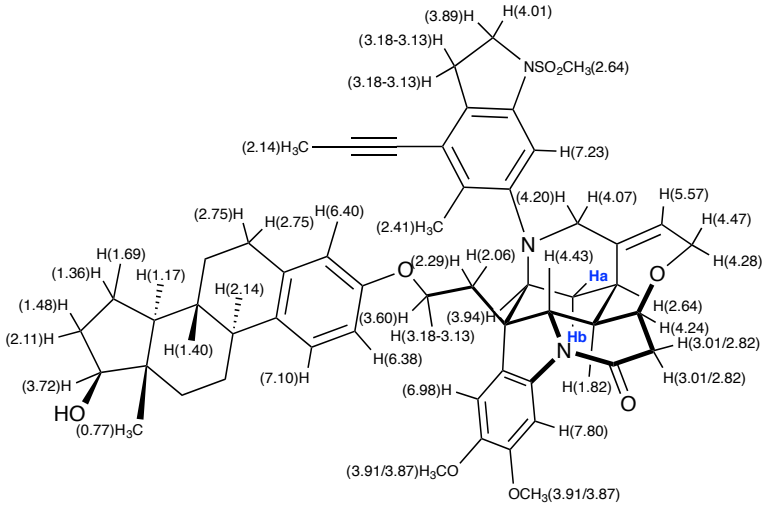
HRMS (ESI-TOF): Calcd for $C_{65}H_{90}N_3O_8S^+$ $[M+H]^+$ requires 1072.6443; found 1072.6457

(4a*R*,4a^{1}*R*,6*S*,6a*R*,6a^{1}*S*,13a*S*)-6a-(2-(((8*R*,9*S*,13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)ethyl)-8,9-dimethoxy-14-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-4a,4a^{1},5,6,6a,6a^{1},13,13a-octahydro-6,4-(epiminomethano)indolo[3,2,1-*ij*]oxepino[2,3,4-*de*]quinolin-12(2*H*)-one (37e–Δ^{21})



6 brucine (***34***) estradiol (***11c***) ***37e***-Δ^{21} (52%)

Tetrayne **6** (50 mg, 0.202 mmol), brucine (120 mg, 0.303 mmol, 1.5 equiv), and 17-β-estradiol (69 mg, 0.253 mmol, 1.25 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica gel (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (1:1 Hex:EtOAc + 1% NEt_3) to give **37e–Δ^{21}** (96 mg, 0.105 mmol, 52%) as a yellow amorphous solid that was contaminated with ~10 % of oxidative dimers of estradiol[7]. Formation of these impurities can be minimized by performing the reaction under an argon atmosphere, which gave rise to a more pure sample of **37e–Δ^{21}** that was used to obtain the characterization data presented below (<5% impurity present).



^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.23 (s, 1H), 7.10 (br d, *J* = 8.3 Hz, 1H), 6.98 (s, 1H), 6.40 (br s, 1H), 6.38 (dd, *J* = 8.3, 2.8 Hz, 1H), 5.57 (br dd, *J* = 2.9, 2.9 Hz, 1H), 4.47 (br d, *J* = 17.4 Hz, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 4.28 (br d, *J* = 17.3 Hz, 1H), 4.24 (ddd, *J* = 8.1, 3.3, 3.3 Hz, 1H), 4.20 (br d, *J* = 11.2 Hz, 1H), 4.07 (br d, *J* = 11.5 Hz, 1H), 4.01 (nfom, 1H), 3.94 (dd, *J* = 9.7, 4.1 Hz), 3.91 (s, 3H), 3.89 (nfom, 1H), 3.87 (s, 3H), 3.72 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.60 (ddd, *J* = 9.6, 7.2, 7.2), 3.18-3.13 (m, 3H), 3.01 (dd, *J* = 17.5, 8.2 Hz, 1H), 2.82 (dd, *J* = 17.4, 3.2 Hz, 1H), 2.75 (m, 2H), 2.64 (s, 3H), 2.64 (m, 1H), 2.41 (s, 3H), 2.29 (m, 1H), 2.28 (m,

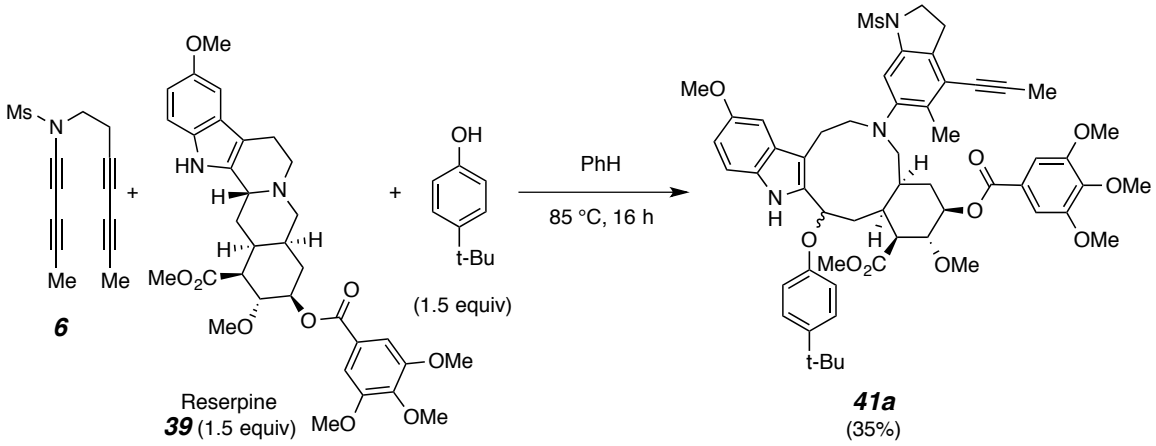
1H), 2.14 (s, 3H), 2.13 (m, 1H), 2.06 (m, 1H), 1.94 (br ddd, *J* = 13, 4, 4 Hz, 1H), 1.89-1.82 (m, 1H), 1.82 (ddd, *J* = 10.1, 10.1, 3.4 Hz, 1H), 1.70 (m, 1H), 1.70-1.63 (m, 2H), 1.49 (m, 1H), 1.46 (m, 1H), 1.40 (m, 1H), 1.36 (m, 1H), 1.30 (m, 1H), 1.28 (m, 1H), 1.18 (ddd, *J* = 12.1, 10.9, 7.3 Hz, 1H), and 0.77 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.0, 156.3, 148.9, 146.9, 146.4, 140.1, 138.0, 136.2, 134.8, 133.0, 129.5, 128.7, 128.0, 126.3, 126.0, 122.8, 114.6, 112.2, 106.3, 106.1, 100.8, 94.2, 81.8, 76.4, 73.6, 73.4, 68.6, 64.6, 64.1, 56.4, 56.2, 52.8, 50.5, 50.0, 49.5, 46.7, 44.0, 43.0, 42.9, 41.4, 38.9, 36.7, 34.0, 33.9, 30.8, 30.6, 29.7, 28.1, 27.2, 26.3, 23.1, 17.2, 11.0, and 4.6.

IR (neat): 3450 (br), 2926, 2867, 2230, 1668, 1590 1497, 1464, 1349, 1158, and 850 cm^{-1}.

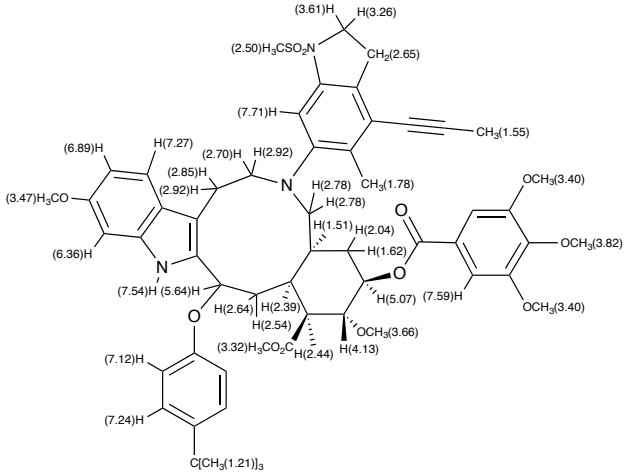
HRMS (ESI-TOF): Calcd for $C_{54}H_{64}N_3O_8S^+$ $[M+H]^+$ requires 914.4409; found 914.4438.

Methyl (1*S*,2*R*,3*R*,4a*S*,14*R*,15a*S*)- and
Methyl (1*S*,2*R*,3*R*,4a*S*,14*S*,15a*S*)-14-(4-(tert-butyl)phenoxy)-2,10-dimethoxy-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-3-((3,4,5-trimethoxybenzoyl)oxy)-2,3,4,4a,5,6,7,8,13,14,15,15a-dodecahydro-1H-benzo[8,9]azecino[5,4-b]indole-1-carboxylate
(**41a-fast and 41a-slow**, although which isomer is which diastereomer remains unassigned)



Tetrayne **6** (50 mg, 0.202 mmol), reserpine (184 mg, 0.303 mmol, 1.5 equiv), and 4-*tert*-butylphenol (46 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (7.5 mL, ~0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc). The resulting residue was purified by MPLC (3:2 Hex:EtOAc) to give, **41a** as a mixture of closely eluting epimers (72 mg, 0.072 mmol, 35%). These were partially fractionated by MPLC to give a sample of each isomer, sufficiently pure of the other for spectral characterization.

Data for 41a-fast (faster eluting isomer)



^{1}H-NMR (500 MHz, C_6D_6): δ 7.71 (br s, 1H), 7.59 (s, 2H), 7.54 (br s, 1H), 7.27 (br d, J = 8.6 Hz, 1H), 7.24 (nfod, J_{app} = 8.8 Hz, 2H), 7.12 (nfod, J_{app} = 8.9 Hz, 2H), 6.89 (dd, J = 8.6, 2.3 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 5.64 (dd, J = 10.9, 6.6 Hz, 1H), 5.07 (ddd, J = 10.9, 9.2, 5.9 Hz, 1H), 4.13 (dd, J = 11.0, 9.1 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 3.61 (nfom, 1H), 3.47 (s, 3H), 3.40 (s, 6H), 3.32 (br s, 3H), 3.26 (nfom, 1H), 2.92 (m, 2H), 2.85 (m, 1H), 2.78 (d, J = 7 Hz, 2H), 2.70 (m, 1H), 2.65 (m, 2H), 2.64 (m, 1H), 2.54 (br d, J = 12 Hz, 1H), 2.50 (br s, 3H), 2.44

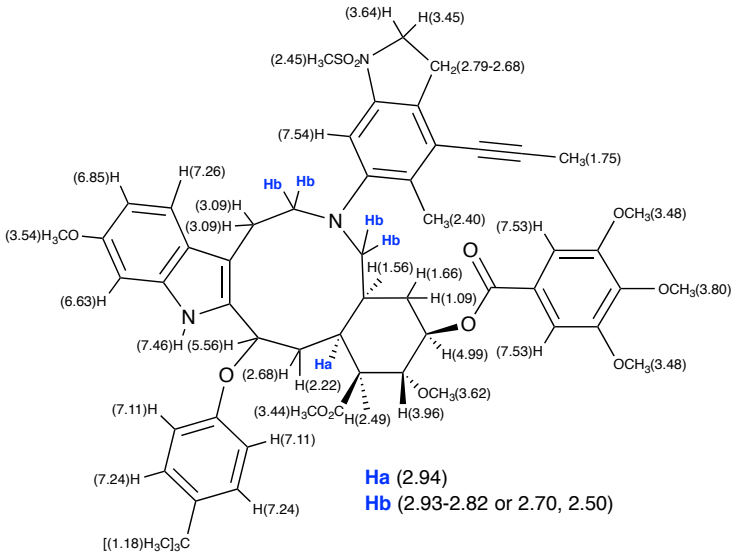
(dd, J = 10.4, 6.6 Hz, 1H), 2.39 (br d, J = 12 Hz, 1H), 2.04 (br ddd, J = 12, 6, 1 Hz, 1H), 1.78 (br s, 3H), 1.62 (br ddd, J = 12, 12, 1 Hz, 1H), 1.55 (s, 3H), 1.51 (m, 1H), and 1.21 (s, 9H).

^{13}C-NMR (125 MHz, C_6D_6): δ 172.5, 165.4, 157.1, 156.4, 153.7, 150.3, 143.5, 140.8, 137.7, 133.7, 131.7, 130.5, 126.5, 125.4, 122.7, 119.8, 115.3, 122.5, 111.8, 109.4, 108.5, 107.5, 94.7, 93.7, 78.7, 78.5, 76.9, 71.8, 60.8, 60.2, 55.5, 54.2, 54.0, 50.9, 50.2, 50.1, 39.0, 34.7, 33.9, 33.1, 32.3, 31.3, 29.5, 27.8, 22.9, 14.4, and 3.7.

IR (neat): 3379 (br), 2998, 2951, 2868, 2835, 2230, 1733, 1714, 1589, 1506, 1461, 1334, 1228, 1159, 1128, and 973 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{56}H_{68}N_3O_{12}S^+$ $[M+H]^+$ requires 1006.4518; found 1006.4569.

Data for 41a-slow (slower eluting isomer)



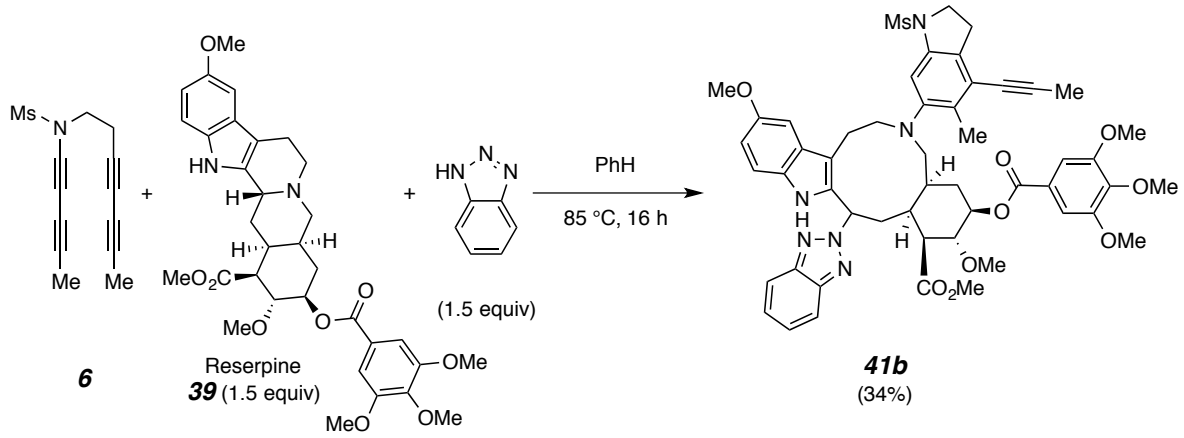
^{1}H-NMR (500 MHz, C_6D_6, 71 °C): δ 7.54 (br s, 1H), 7.53 (s, 2H), 7.46 (br s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.24 (nfod, J_{app} = 8.7 Hz, 2H), 7.11 (nfod, J_{app} = 8.7 Hz, 2H), 6.85 (dd, J = 8.6, 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 5.56 (dd, J = 8.5, 3.0 Hz, 1H), 4.99 (ddd, J = 11.4, 9.2, 5.3 Hz, 1H), 3.96 (dd, J = 11.2, 9.4 Hz, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.62 (s, 3H), 3.54 (s, 3H), 3.48 (s, 6H), 3.44 (br s, 3H), 3.09 (br m, 2H), 2.94 (m, 1H), 2.93-2.82 (m, 2H), 2.79-2.68 (m, 2H), 2.70 (m, 1H), 2.68 (ddd, J = 11.5, 3.4, 3.4 Hz, 1H), 2.50 (m, 1H), 2.49 (m, 1H) [either 2.50 or 2.49 (J = 11.1, 4.2 Hz)], 2.45 (br s, 3H), 2.40 (br s, 3H), 2.22 (m, 1H), 1.75 (br s, 3H), 1.66 (m, 1H), 1.57 (m, 1H), 1.18 (s, 9H), and 1.09 (ddd, J = 12, 12, 12 Hz, 1H).

^{13}C-NMR (125 MHz, C_6D_6, 344 K): δ (C6 of the indoline not identified) 172.7, 164.6, 157.4, 156.7, 153.7, 144.1 (x2), 140.9, 137.4, 133.7, 131.9, 129.9, 126.3, 125.6, 122.7, 122.6, 119.5, 116.2, 112.7, 109.5, 108.5, 108.3, 95.4, 93.5, 79.4, 77.6, 77.4, 77.0, 60.2, 60.0, 57.1, 55.8, 55.0, 52.9, 54.4, 50.9, 50.0, 38.2, 33.8 (x2), 32.7, 31.1, 30.0, 27.8, 25.8, 15.7, and 3.5.

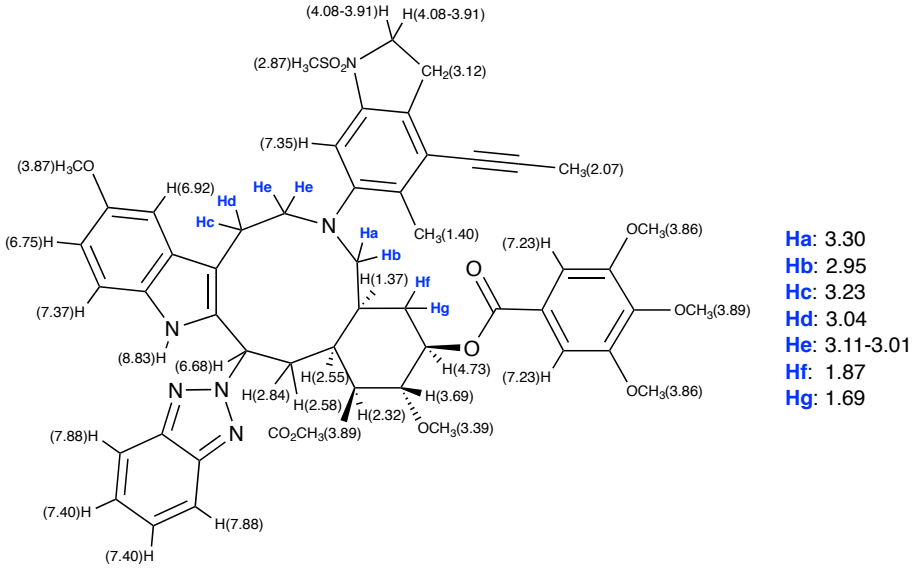
IR (neat): 3387 (br), 3003, 2949, 2875, 2835, 2282, 1731, 1717, 1589, 1505, 1461, 1333, 1224, 1160, 1128, and 976 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{56}H_{68}N_3O_{12}S^+$ $[M+H]^+$ requires 1006.4518; found 1006.4579.

Methyl (1S,2R,3R,4aS,14R,15aS)- or (1S,2R,3R,4aS,14S,15aS)-14-(2H-benzo[d][1,2,3]triazol-2-yl)-2,10-dimethoxy-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-3-((3,4,5-trimethoxybenzoyl)oxy)-2,3,4,4a,5,6,7,8,13,14,15,15a-dodecahydro-1H-benzo[8,9]azecino[5,4-b]indole-1-carboxylate (41b)



Tetrayne **6** (50 mg, 0.202 mmol), reserpine (184 mg, 0.303 mmol, 1.5 equiv), and benzotriazole (36 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (7.5 mL, ~0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc). The resulting residue was purified by MPLC (3:2 Hex:EtOAc) to give, **41** as a co-eluting 24:1 mixture of diastereomers, epimeric at C14 (66 mg, 0.068 mmol, 34%; contaminated with a co-eluting adduct of benzyne **8** and benzotriazole).



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.88 (nfom, 2H), 7.40 (nfom, 2H), 7.37 (m, 1H), 7.35 (s, 1H), 7.23 (s, 2H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.68 (dd, *J* = 12.4, 5.7 Hz, 1H), 4.73 (ddd, *J* = 11.1, 9.1, 5.9 Hz, 1H), 4.08-3.91 (nfom, 2H), 3.887 (s, 3H), 3.886 (s, 3H), 3.87 (s, 3H), 3.86 (s, 6H), 3.69 (dd, *J* = 11.3, 9.1 Hz, 1H), 3.39 (s, 3H), 3.30 (br d, *J* = 12.9 Hz, 1H), 3.23 (m, 1H), 3.12 (m, 2H), 3.04 (m, 1H), 2.95 (br dd, *J* = 13.7, 1.9 Hz, 1H), 2.87 (s, 3H), 2.84 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.58 (ddd, *J* = 12, 12, 6 Hz, 1H), 2.55 (br ddd, *J* =

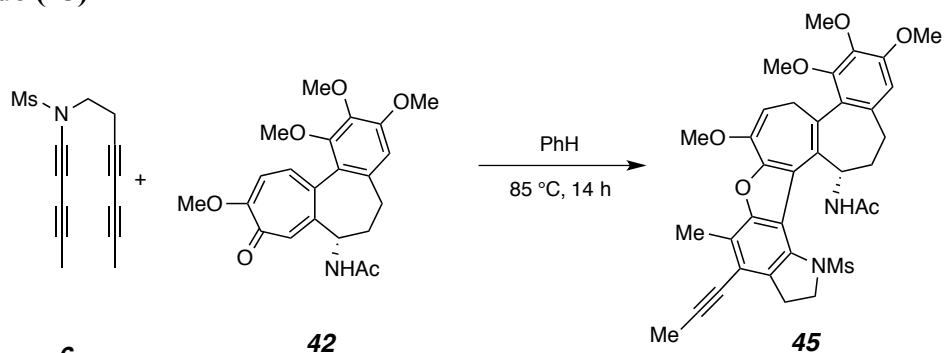
12, 3, 3 Hz, 1H), 2.32 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.07 (s, 3H), 1.87 (br ddd, *J* = 13, 6, 2 Hz, 1H), 1.69 (ddd, *J* = 13.3, 13.3, 11.6 Hz, 1H), 1.40 (s, 3H), and 1.37 (br d, *J* = 13 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.7, 165.1, 157.1, 150.4, 153.0, 144.0, 142.3, 140.5, 137.9, 134.4, 131.0, 128.6, 126.8, 125.1, 122.5, 122.1, 120.0, 118.1, 113.9, 109.5, 109.0, 106.7, 94.8, 94.3, 78.2, 78.0, 76.2, 61.9, 60.9, 60.8, 55.7, 56.1, 54.6, 53.9, 51.8, 51.6, 50.5, 38.8, 34.7, 34.2, 32.7, 29.3, 28.1, 22.8, 13.9, and 4.6.

IR (neat): 3396 (br), 2998, 2940, 2835, 2227, 1731, 1714, 1629, 1589, 1460, 1334, 1223, 1159, and 971 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{52}H_{59}N_6O_{11}S^+$ $[M+H]^+$ requires 975.3957; found 975.4010.

(*S*)-*N*-(2,3,4,7-tetramethoxy-9-methyl-13-(methylsulfonyl)-10-(prop-1-yn-1-yl)-5,12,13,14,15,16-hexahydro-11*H*-benzo[6',7']heptaleno[1',2':4,5]furo[2,3-*g*]indol-14-yl)acetamide (45)



6 ***42*** colchicine (1.5 equiv) ***45*** (59%)

Tetrayne (**6**) (50 mg, 0.202 mmol) and colchicine (121 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in benzene (7.5 mL, ~0.03 M) and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc) and then purified by MPLC (1:3 Hex:EtOAc) to give **45** (77 mg, 0.119 mmol, 59%) as a yellow foam.

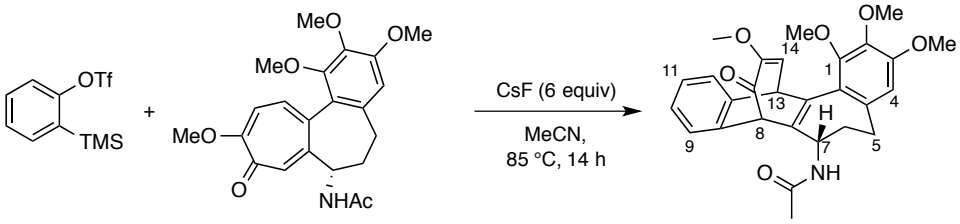
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.53 (s, 1H, Ar*H*), 5.56 (d, *J* = 5.7 Hz, 1H, AcN*H*), 5.14 [dd, *J* = 8.8, 6.5 Hz, 1H, (OMe)C=C*H*], 4.95 (dd, *J* = 5.9, 5.9 Hz, 1H, C*H*NHAc), 4.14 (m, 2H, MsNCH_2CH$_2$), 3.97 (s, 3H, ArOCH_3), 3.92 (s, 3H, ArOCH_3), 3.87 (s, 3H, ArOCH_3), 3.77 (s, 3H, (CH_3O)C=CH), 3.52 [dd, *J* = 13.8, 8.8 Hz, 1H, CH_aH$_b$CH=C(OCH$_3$)], 3.28 (ddd, *J* = 16.6, 11.7, 8.6 Hz, 1H, MsNCH$_2$CH_aH$_b$), 3.03 (ddd, *J* = 16.2, 8.4, 1.5 Hz, 1H, MsNCH$_2$CH$_a$$H_b$), 2.65 (s, 3H, NArC$H_3$), 2.50 (s, 3H, C$H_3SO_2$N), 2.37 [dd, *J* = 6.6, 13.9 Hz, 1H, CH$_a$$H_b$CH=C(OCH$_3$)], 2.37 [m, 1H, ArCH$_2CH_aH_b$CH(NHAc)], 2.37 [m, 1H, ArCH_aH$_b$CH$_2$CH(NHAc)], 2.21 (m, 1H, ArCH$_a$$H_bCH_2$CH(NHAc)), 2.16 (s, 3H, NArC≡CCH_3), 1.96 [m, 1H, ArCH$_2$CH$_a$$H_b$CH(NHAc)], 1.71 (s, 3H, HNCOCH_3)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.7, 152.9, 152.8, 152.1, 150.6, 148.3, 141.0, 137.9, 133.7, 133.2, 131.2, 130.2, 127.9, 125.7, 123.0, 122.2, 117.6, 107.8, 101.1, 94.1, 76.0, 61.2, 61.1, 56.0 (x2), 52.0, 51.9, 40.8, 34.5, 31.8, 30.0, 29.6, 23.5, 13.5, and 4.6.

IR (neat): 3458, 3062, 2995, 2934, 2855, 2235, 1665, 1594, 1490, 1457, 1348, 1249, 1156, 1135, 1095, 1019, and 967 cm^{-1}.

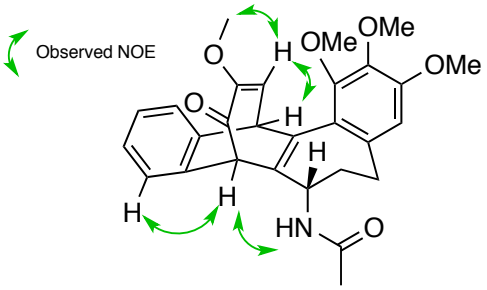
HRMS (ESI-TOF): Calcd for $C_{35}H_{39}N_2O_8S^+$ $[M+H]^+$ requires 647.2422; found 647.2424.

_N_-((7_S_,8_S_,13_R_)-1,2,3,15-tetramethoxy-16-oxo-6,7,8,13-tetrahydro-5_H_-13,8-prop[1]enobenzo[3,4]cyclohepta[1,2-_b_]naphthalen-7-yl)acetamide (46)



(5 equiv) ***42*** colchicine (1.0 equiv) ***46*** (50%)

Colchicine (50 mg, 0.125 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.15 mL, 0.625 mmol, 5 equiv), and CsF (120 mg, 0.79 mmol, 6.3 equiv) were combined in a culture tube, dissolved in acetonitrile (5 mL, ~0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, filtered through Celite, and concentrated. The crude material was passed through a plug of silica (9:1 EtOAc:*i*-PrOH+1% NEt_3), the eluent was removed under reduced pressure and the residue was purified by MPLC (6:1 EtOAc:Hex+1% NEt_3) to give **46** (30 mg, 0.063 mmol, 50%) as a yellow film that solidified upon standing. (If the benzyne precursor is instead used as the limiting reagent (1.5 equiv colchicine, 1.5 equiv CsF) the same procedure gives **46** in a yield of 35%.)



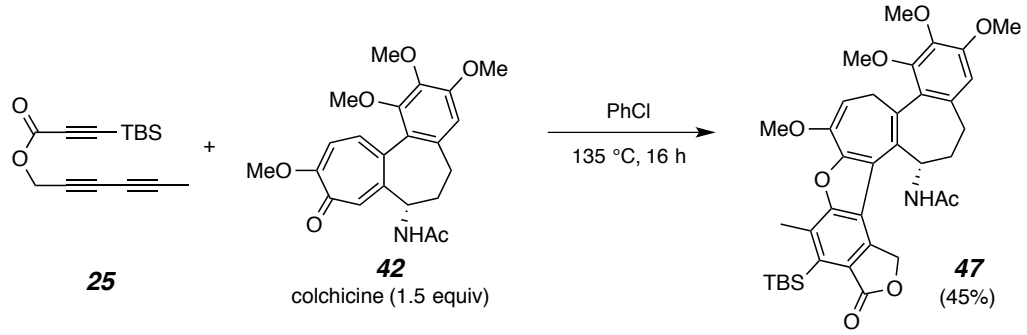
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (nfom, 1H, *H9*), 7.16 (nfom, 1H, *H12*), 7.14–7.10 (m, 2H, *H10-11*), 6.61 (d, *J* = 9.3 Hz, 1H, *H14*), 6.52 (s, 1H, *H1*), 5.84 (br d, *J* = 7.3 Hz, 1H, N*H*Ac), 4.91 (s, 1H, *H8*), 4.53 (d, *J* = 9.3 Hz, 1H, *H13*), 4.52 (ddd, *J* = 12.3, 7.3, 7.3 Hz, 1H, *H7*), 3.95 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, C2-OC*H*$_3$), 3.84 (s, 3H, ArOC*H*$_3$), 3.50 (s, 3H, C15-OC*H*$_3$), 2.32 (dddd, *J* = 11.7, 11.7, 5.8, 5.8 Hz, 1H, H6a), 2.25 (m, 1H, H5a), 1.89 (m, 1H, H5b), and 1.82 (m, 1H, H6b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 186.7, 170.1, 153.1, 152.0, 145.7, 145.0, 142.2, 141.3, 137.1, 135.6, 126.8, 126.7, 125.6, 124.5, 123.9, 122.6, 121.8, 108.5, 61.9, 61.7, 61.3, 56.1, 54.7, 49.0, 48.2, 39.6, 31.5, and 23.2.

IR (neat): 3306 (br), 3065, 2992, 2936, 2853, 2834, 1681, 1542, 1489, 1456, 1322, 1134, and 1095 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{28}H_{30}NO_6^+$ $[M+H]^+$ requires 476.2068; found 476.2078.

(*S*)-*N*-(10-(*tert*-Butyldimethylsilyl)-2,3,4,7-tetramethoxy-9-methyl-11-oxo-5,12,13,14,15,16-hexahydro-11*H*-benzo[6',7']heptaleno[1',2':4,5]furo[3,2-*e*]isofuran-14-yl)acetamide (47)



25 ***42*** colchicine (1.5 equiv) ***47*** (45%)

Triyne **25** (53 mg, 0.202 mmol) and colchicine (121 mg, 0.303 mmol, 1.5 equiv) were combined in a culture tube, dissolved in chlorobenzene (7.5 mL, ~0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 135-140 °C, cooled, and passed through a plug of silica (10:1 Hex:EtOAc to EtOAc). The resulting residue was purified by MPLC (3:2 Hex:EtOAc) to give **47** (60 mg, 0.091 mmol, 45%) as a yellow amorphous foam.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.57 (s, 1H, Ar*H*), 5.58 (d, *J* = 15.7 Hz, C*H*aHbOCO), 5.52 (d, *J* = 8.0 Hz, 1H, AcN*H*), 5.17 (dd, *J* = 8.5, 6.6 Hz, 1H, (MeO)C=C*H*), 5.16 (d, *J* = 15.9 Hz, C*H*aHbOCO), 4.81 (dd, *J* = 7.9, 5.8 Hz, 1H, C*H*NHAc), 4.03 (s, 3H, $ArOCH_3$), 3.92 (s, 3H, $ArOCH_3$), 3.91 (s, 3H, $ArOCH_3$), 3.80 (s, 3H, $(CH_3O)C=CH$), 3.36 [dd, *J* = 14.0, 8.8 Hz, 1H, $CH_aH_bCH=C(OCH_3)$], 2.80 (s, 3H, $ArCH_3$), 2.47 [nfom, 1H, $ArCH_aH_bCH_2CH(NHAc)$], 2.31-2.23 [m, 3H, $CH_aH_bCH=C(OCH_3)$, $ArCH_aH_bCH_2CH(NHAc)$, $ArCH_2CH_aH_bCH(NHAc)$], 2.09 [nfom, 1H, $ArCH_2CH_aH_bCH(NHAc)$], 1.71 (s, 3H, $HNCOCH_3$), 1.08 (s, 9H, $SiC(CH_3)_3$), 0.53 (s, 3H, Si(C*H*$_3$)a(CH$_3$)b), and 0.47 (s, 3H, Si(C*H*$_3$)a(CH$_3$)b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.1, 168.8, 155.5, 153.9, 151.6, 151.1, 148.5, 141.0, 140.1, 137.7, 136.5, 135.8, 131.5, 131.3, 127.2, 126.6, 124.7, 120.9, 107.7, 101.6, 67.2, 61.2, 60.9, 56.2, 56.1, 51.1, 41.7, 31.4, 30.7, 28.4, 23.4, 19.5, 17.6, 1.9, and 0.7.

IR (neat): 3439, 3059, 2934, 2896, 2854, 1763, 1673, 1489, 1459, 1322, 1250, 1089, and 809 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{37}H_{46}NO_8Si^+$ $[M+H]^+$ requires 660.2987; found 660.2996.

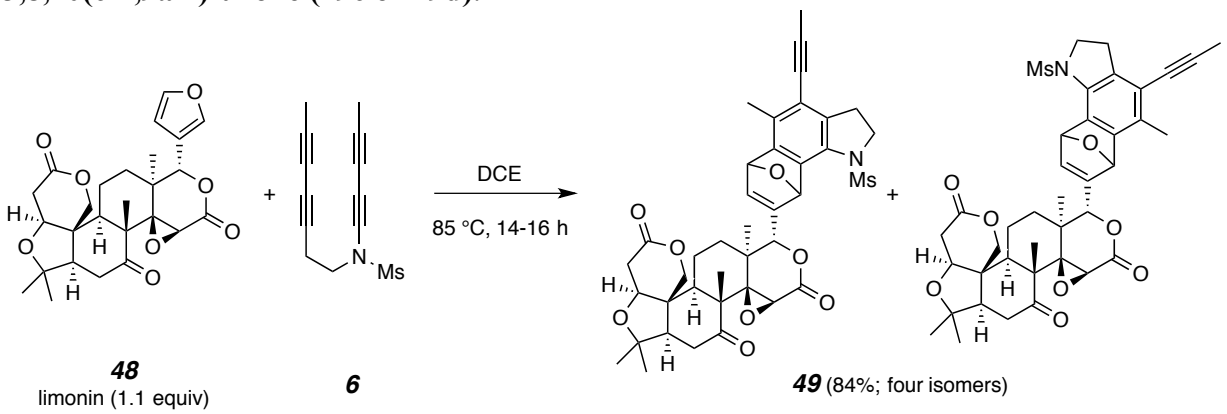
(4aS,6aR,8aR,8bR,9aS,12S,12aS,14aR,14bR)-6,6,8a,12a-Tetramethyl-12-((6*R*,9*R*)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-2,3,6,9-tetrahydro-1H-6,9-epoxybenzo[g]indol-8-yl)decahydro-1H,3H-oxireno[2,3-d]pyrano[4',3':3,3a]isobenzofuro[5,4-f]isochromene-3,8,10(6H,9aH)-trione (**49a** or **49b**),

(4aS,6aR,8aR,8bR,9aS,12S,12aS,14aR,14bR)-6,6,8a,12a-Tetramethyl-12-((6*S*,9*S*)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-2,3,6,9-tetrahydro-1H-6,9-epoxybenzo[g]indol-8-yl)decahydro-1H,3H-oxireno[2,3-d]pyrano[4',3':3,3a]isobenzofuro[5,4-f]isochromene-3,8,10(6H,9aH)-trione (**49a** or **49b**)

and

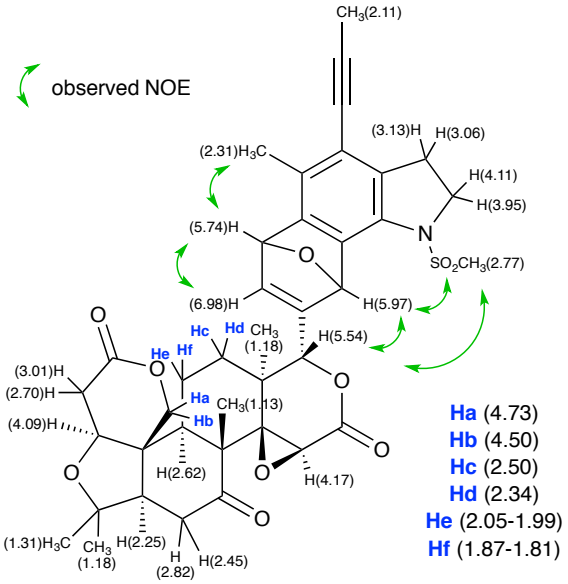
(4aS,6aR,8aR,8bR,9aS,12S,12aS,14aR,14bR)-6,6,8a,12a-Tetramethyl-12-((6*S*,9*S*)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-2,3,6,9-tetrahydro-1H-6,9-epoxybenzo[g]indol-7-yl)decahydro-1H,3H-oxireno[2,3-d]pyrano[4',3':3,3a]isobenzofuro[5,4-f]isochromene-3,8,10(6H,9aH)-trione (49c or 49d),

(4a*S*,6a*R*,8a*R*,8b*R*,9a*S*,12*S*,12a*S*,14a*R*,14b*R*)-6,6,8a,12a-Tetramethyl-12-((6*R*,9*R*)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-2,3,6,9-tetrahydro-1*H*-6,9-epoxybenzo[*g*]indol-7-yl)decahydro-1*H*,3*H*-oxireno[2,3-*d*]pyrano[4',3':3,3a]isobenzofuro[5,4-*f*]isochromene-3,8,10(6*H*,9a*H*)-trione (49c or 49d).



Tetrayne **6** (21 mg, 0.085 mmol) and limonin (44 mg, 0.094 mmol, 1.1 equiv) were combined in a culture tube, dissolved in 1,2-dichloroethane (6 mL, ~0.015 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (3:1 EtOAc:Hex). The eluent was removed under reduced pressure and the residue was purified by MPLC (2:1 EtOAc:Hex) to give, in order of elution, **49a** (8 mg, 0.011mmol, 13%) and a coeluting mixture of **49a-d** (43 mg, 0.060 mmol, 70%) (a:b:c:d = 0.4:1.1:0.8:1.0; from ^{1}H NMR analysis).

Data for 49a



^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.97 (d, *J* = 1.0 Hz, 1H), 5.74 (dd, *J* = 2.0, 1.0 Hz, 1H), 5.54 (d, *J* = 1.6 Hz, 1H), 4.73 (d, *J* = 13.1 Hz, 1H), 4.50 (d, *J* = 13.1 Hz, 1H), 4.17 (s, 1H), 4.11 (nfom, 1H), 4.09 (br d, *J* = 4.2 Hz, 1H), 3.95 (nfom, 1H), 3.13 (m, 1H), 3.06 (m, 1H), 3.01 (dd, *J* = 16.7, 3.9 Hz), 2.82 (dd, *J* = 15, 15 Hz, 1H), 2.77 (s, 3H), 2.70 (dd, *J* = 16.6, 1.5 Hz, 1H), 2.62 (dd, *J* = 12.7, 3.9 Hz, 1H), 2.50 (nfom, 1H), 2.45 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.34 (m, 1H), 2.31 (s, 3H), 2.25 (m, 1H), 2.11 (s, 3H), 2.05-1.99 (m, 1H), 1.87-1.81 (m, 1H), 1.31 (s, 3H), 1.184 (s, 3H), 1.177 (s, 3H), and 1.13 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.2, 169.0, 167.5, 152.5, 148.2, 141.8, 141.6, 135.1, 132.2, 128.6, 119.4, 94.0, 83.9, 81.7, 80.4, 79.1, 78.3, 75.8, 66.9, 65.0, 60.0, 53.7, 51.0, 50.7, 47.6, 47.3, 39.3, 36.3, 35.7, 35.4, 30.3, 28.9, 27.9, 21.1, 20.6, 18.5, 18.4, 16.2, and 4.6.

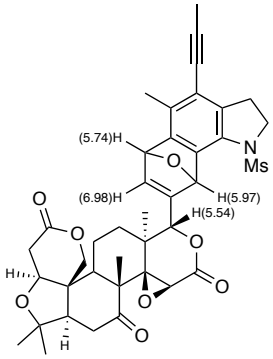
IR (neat): 2960, 2928, 2852, 2224, 1739, 1718, 1344, 1160, 1020, and 836 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{39}H_{47}N_2O_{10}S^+$ $[M+NH_4]^+$ requires 735.2946; found 735.2963.

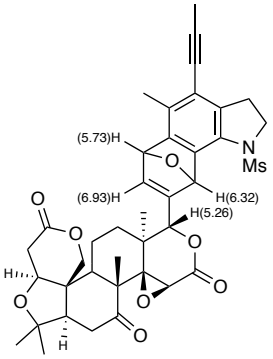
mp: 289-293 °C (decomp).

Data for 49b-d

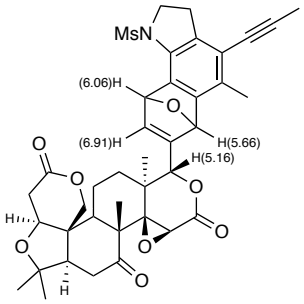
Data for a mixture of cycloadducts **49a-d**. Only the diagnostic and clearly observable protons and carbons are identified from the spectra of the mixture; this interpretation was guided by the NMR data observed for the sample of pure isomer **49a**.



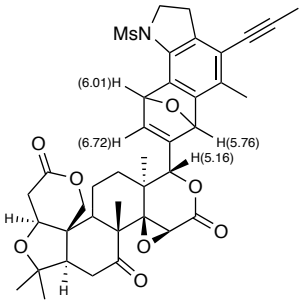
49a



49b



49c



49d

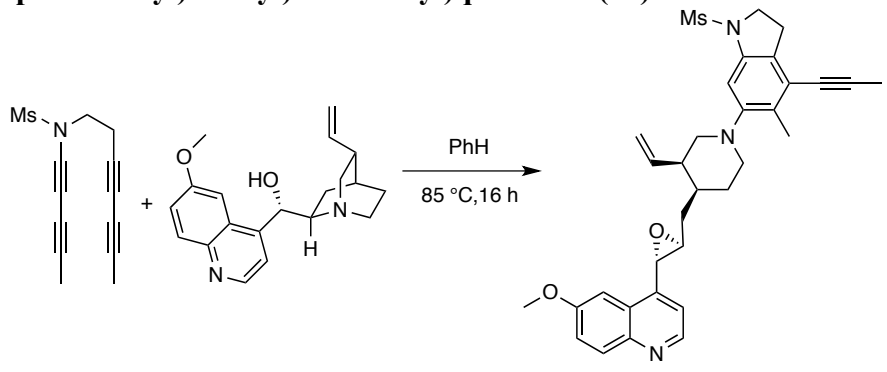
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.93 (br dd, *J* = 1.8 Hz, 1.1 H), 6.91 (dd, *J* = 1.9 Hz, 0.8 H), 6.72 (dd, *J* = 1.6 Hz, 1H), 6.32 (d, *J* = 0.9 Hz, 1.1 H), 6.05 (dd, *J* = 1.9, 0.9 Hz, 0.8 H), 6.01 (br dd, *J* = 1.4, 1.4 Hz, 1H), 5.76 (d, *J* = 0.7 Hz, 1.0 H), 5.73 (br dd, *J* = 0.9, 0.9 Hz, 1.1 H), 5.66 (d, *J* = 0.9 Hz, 0.8 H), 5.26 (d, *J* = 1.1 Hz, 1.1 H), and 5.163 (d, *J* = ca. 1.5, ca. 1H)/5.159 (d, *J* = 1.2 Hz, ca. 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 150.0, 140.5, 139.7, 83.5, 83.4, 83.3, 82.7, 82.6, 81.4, 79.9, and 79.7 (x2).

IR (neat): 2960, 2928, 2873, 2229, 1746, 1716, 1344, 1249, 1158, 1019, and 967 cm^{-1}.

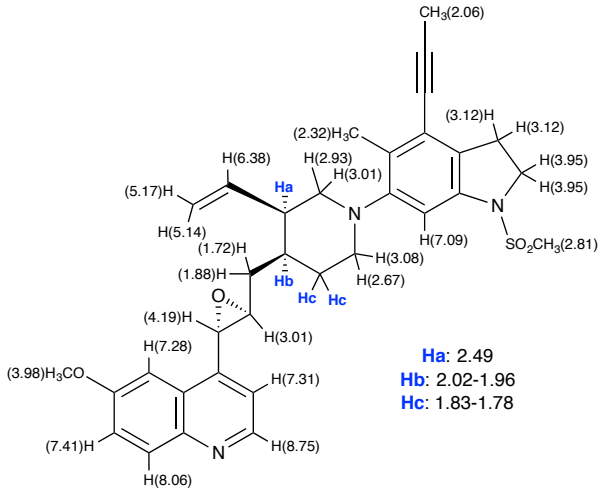
HRMS (ESI-TOF): Calcd for $C_{39}H_{47}N_2O_{10}S^+$ $[M+NH_4]^+$ requires 735.2946; found 735.2975

6-Methoxy-4-((2*S*,3*S*)-3-(((3*R*,4*S*)-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-3-vinylpiperidin-4-yl)methyl)oxiran-2-yl)quinolone (52)



6 ***50*** quinidine (1.5 equiv) ***52*** (49%)

Tetrayne **6** (51 mg, 0.206 mmol) and quinidine (**50**) (166 mg, 0.512 mmol, 2.5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The residue was then purified by MPLC (3:2 Hex:EtOAc +1% NEt_3) to give, **52** (56 mg, 0.098 mmol, 49%) as a pale yellow foam.



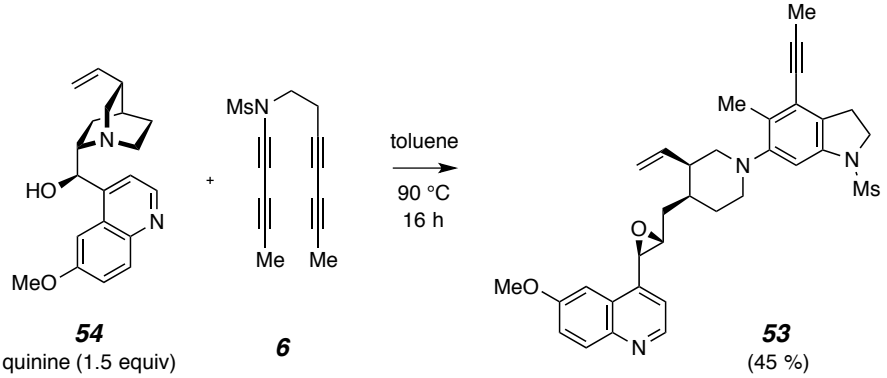
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.28 (d, *J* = 2.7 Hz, 1H), 7.09 (s, 1H), 6.38 (ddd, *J* = 17.2, 9.8, 9.8 Hz, 1H), 5.17 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.14 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.19 (d, *J* = 1.9 Hz, 1H), 3.98 (s, 3H), 3.98–3.93 (nfom, 2H), 3.12 (t, *J* = 8.5 Hz, 2H), 3.08 (ddd, *J* = 11.4, 3.6, 3.6 Hz, 1H), 3.01 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.01 (br ddd, *J* = 5.8, 5.8, 2.1 Hz, 1H), 2.93 (dd, *J* = 11.4, 2.6 Hz, 1H), 2.81 (s, 3H), 2.67 (m, 1H), 2.49 (br dddd, *J* = 9.2, 3.4, 3.4, 3.4 Hz ,1H), 2.32 (s, 3H), 2.06 (s, 3H), 2.02–1.96 (m, 1H), 1.88 (ddd, *J* = 14.1, 5.6, 5.6 Hz, 1H), 1.83–1.78 (m, 2H), and 1.72 (ddd, *J* = 14.3, 8.6, 5.8 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.0, 148.1, 143.9, 142.0, 139.9, 137.2, 131.8, 130.6, 128.7, 128.4, 127.4, 122.2, 121.7, 117.0, 116.7, 105.7, 100.9, 93.8, 76.3, 61.6, 58.0, 55.8, 55.5, 53.2, 50.5, 44.6, 36.6, 36.4, 34.1, 28.6, 28.1, 15.6, and 4.6.

IR (neat): 3066, 2921, 2851, 2798, 2233, 1591, 1468, 1347, 1237, 1159, 969, and 851 cm^{-1}.

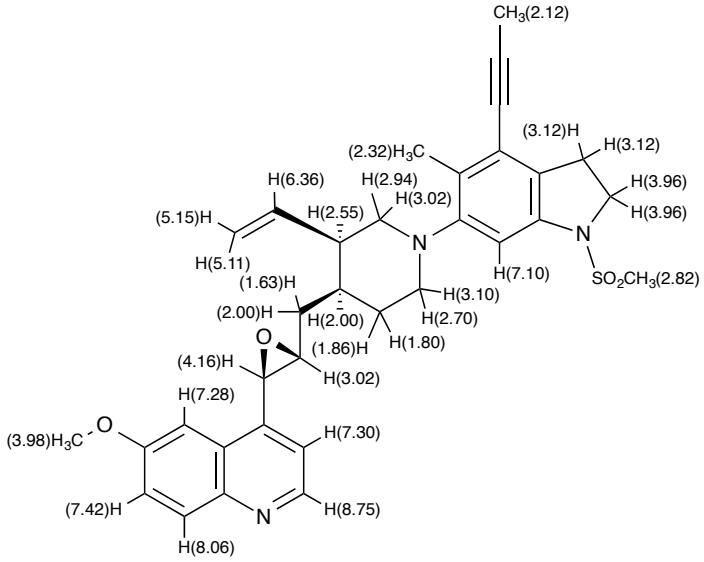
HRMS (ESI-TOF): Calcd for $C_{33}H_{37}N_3NaO_4S^+$ $[M+Na]^+$ requires 594.2397; found 594.2416.

4-((2*R*,3*R*)-3-(((3*R*,4*S*)-3-Ethyl-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-7-yl)piperidin-4-yl)methyl)oxiran-2-yl)-6-methoxyquinoline (53)



Tetrayne **6** (618 mg, 2.5 mmol) and quinine* (**54**, 1.22 g, 3.75 mmol, 1.5 equiv) were combined in a 250 mL round bottom flask equipped with a reflux condenser (no cooling water) and dissolved in toluene (93 mL, 0.03 M). The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, concentrated (25 °C, 0.2 torr), and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The resulting residue was purified by MPLC (3:2 Hex:EtOAc +1% NEt_3) to give, **53** (637 mg, 1.11 mmol, 45%) as a yellow foam.

*The sample of quinine used contained ca. 10% of dihydroquinine (i.e., ethyl in place of vinyl), a common circumstance for samples of natural quinine. The analogous dihydro product **106** (see below) accompanied **53** and evidence of this can be seen in various regions of the ^{1}H NMR spectral data.



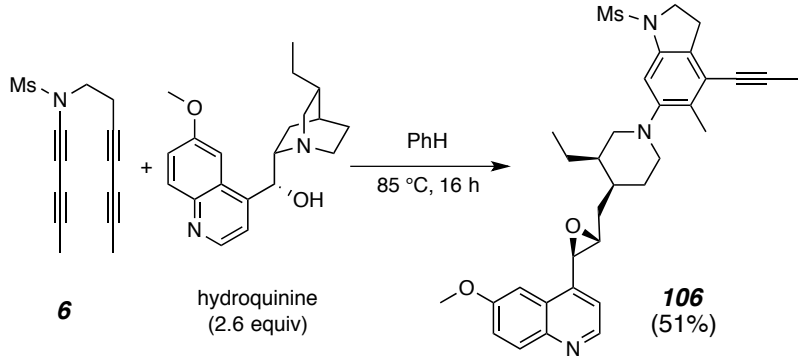
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.4 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.30 (dd, *J* = 4.4, 0.5 Hz, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.10 (s, 1H), 6.36 (ddd, *J* = 17.6, 9.9, 9.9 Hz, 1H), 5.15 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.11 (ddd, *J* = 17.2, 2.0, 0.5 Hz, 1H), 4.16 (d, *J* = 2.1 Hz, 1H), 3.98 (s, 3H), 3.96 (nfom, 2H), 3.12 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.10 (m, 1H), 3.04–3.00 (m, 2H), 2.94 (dd, *J* = 11.4, 2.9 Hz, 1H), 2.82 (s, 3H), 2.70 (ddd, *J* = 11.5, 11.5, 3.1 Hz, 1H), 2.55 (br dddd, *J* = 9, 3, 3, 3 Hz, 1H), 2.32 (s, 3H), 2.12 (s, 3H), 2.00 (m, 2H), 1.86 (dddd, *J* = 13.4, 11.0, 11.0, 3.9 Hz, 1H), 1.80 (dddd, *J* = 13.6, 4, 4, 4 Hz, 1H), and 1.63 (nfom, 1H).

^{13}C-NMR (125 MHz, CDCl3): δ 157.9, 152.4, 147.9, 144.1, 141.4, 139.9, 137.9, 131.7, 130.7, 128.5, 127.5, 122.1, 121.6, 116.9, 116.7, 105.8, 101.1, 93.7, 76.4, 61.2, 58.0, 55.6, 55.2, 53.1, 50.5, 44.2, 36.9, 36.0, 34.1, 29.0, 27.9, 15.8, and 4.5.

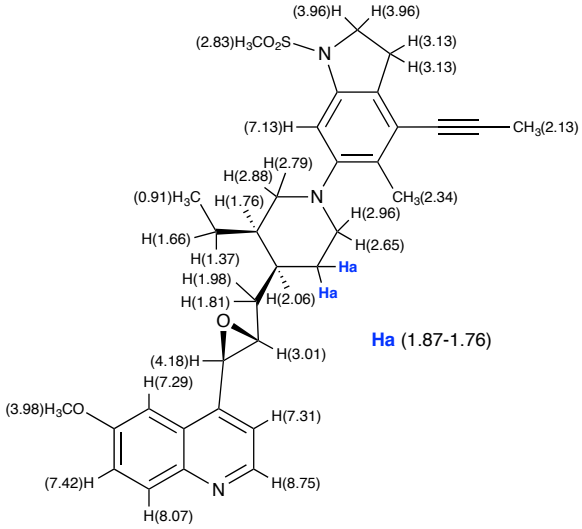
IR (neat): 3072, 3003, 2917, 2853, 2800, 2742, 2225, 1620, 1590, 1467, 1346, 1238, 1159, 910, and 852 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{38}N_3O_4S^+$ $[M+H]^+$ requires 572.2578; found 572.2594.

4-((2*R*,3*R*)-3-(((3*R*,4*S*)-3-Ethyl-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-7-yl)piperidin-4-yl)methyl)oxiran-2-yl)-6-methoxyquinoline (106)



Tetrayne **6** (51 mg, 0.206 mmol) and hydroquinine (168 mg, 0.515 mmol, 2.6 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.03 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The residue was purified by MPLC (3:2 Hex:EtOAc +1% NEt_3) to give **106** (59 mg, 0.103 mmol, 51%) as a pale brown oil.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.29 (d, *J* = 2.7 Hz, 1H), 7.13 (s, 1H), 4.18 (d, *J* = 2.1 Hz, 1H), 3.98 (s, 3H), 3.96 (t, *J* = 8.8 Hz, 2H), 3.13 (t, *J* = 8.2 Hz, 2H), 3.01 (ddd, *J* = 6.8, 4.1, 2.1 Hz, 1H), 2.96 (ddd, *J* = 11.1, 5.7, 3.7 Hz, 1H), 2.88 (m, 1H), 2.83 (s, 3H), 2.79 (dd, *J* = 11.5, 2.6 Hz, 1H), 2.65 (br t, *J* = 8.8 Hz, 1H), 2.34 (s, 3H), 2.13 (s, 3H), 2.06 (m, 1H), 1.98 (ddd, *J* = 14.2, 4.5, 4.5 Hz, 1H), 1.87-1.76 (m, 2H), 1.81 (m, 1H), 1.77 (m, 1H), 1.67 (br m, 1H), 1.37 (ddq, *J* = 15.0, 4.2, 7.4 Hz, 1H), and 0.91 (t, *J* = 7.3 Hz).

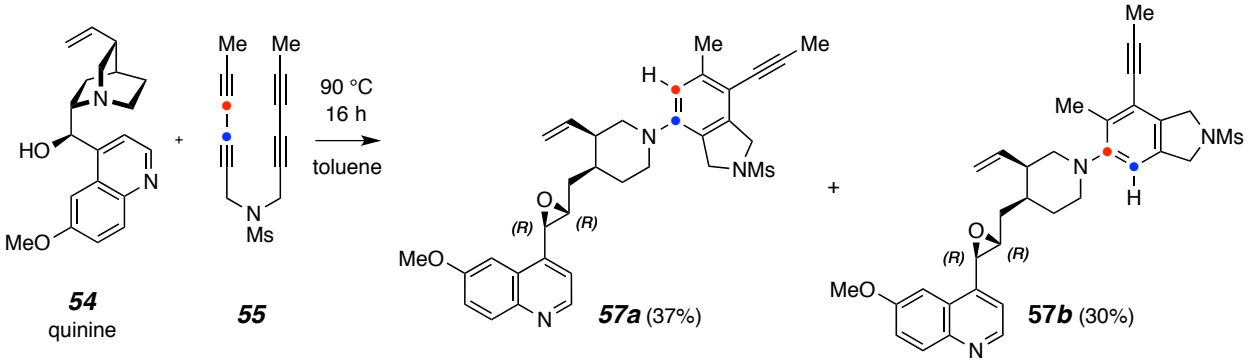
^{13}C-NMR (125 MHz, $CDCl_3$, 1-D): δ 158.2, 152.8, 148.0, 143.9, 142.1, 139.9, 131.8, 130.8, 128.5, 127.6, 122.2, 121.9, 119.9, 106.0, 101.0, 93.9, 76.5, 62.3, 60.5, 55.8, 55.3, 54.3, 50.7, 41.2, 34.3, 29.2, 28.2, 21.2, 15.6, 14.3, 12.5, and 4.7.

IR (neat): 3048, 2956, 2930, 2873, 2802, 2230, 1620, 1590, 1463, 1347, 1237, 1159, 969, and 851 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{40}N_3O_4S^+$ $[M+H]^+$ requires 574.2734; found 574.2746.

6-Methoxy-4-((2*R*,3*R*)-3-(((3*R*,4*S*)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-4-yl)-3-vinylpiperidin-4-yl)methyl)oxiran-2-yl)quinolone (57a) and

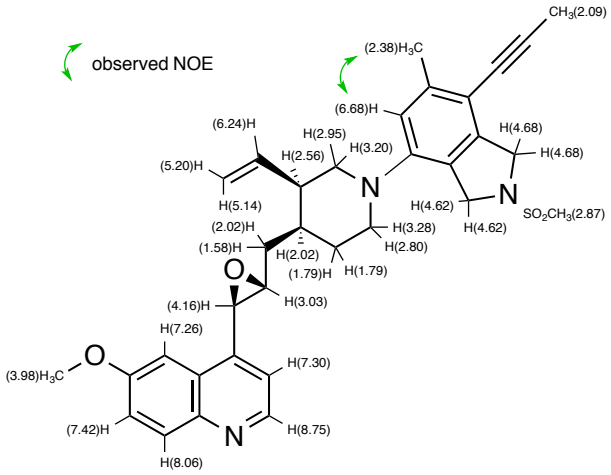
6-Methoxy-4-((2*R*,3*R*)-3-(((3*R*,4*S*)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)-3-vinylpiperidin-4-yl)methyl)oxiran-2-yl)quinolone (57b)



Tetrayne **55** (1.25 g, 5 mmol) and quinine* (2.43 g, 7.5 mmol, 1.5 equiv) were combined in a 500 mL round bottom flask and dissolved in toluene (185 mL, 0.03 M). The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and concentrated (25 °C, 0.2 torr). The crude product was passed through a plug of silica (2:3 Hex:EtOAc +1% NEt_3). The residue was then purified by MPLC (1:1 Hex:EtOAc +1% NEt_3) to give, in order of elution, **57a** (1.06 g, 1.85 mmol, 37 %) and **57b** (0.86 g, 1.50 mmol, 30%), each as a yellow foam.

*The sample of quinine used contained ca. 10% of dihydroquinine (i.e., ethyl in place of vinyl), a common circumstance for samples of natural quinine. Small amounts of the analogous dihydro product accompanied **57a** and evidence of this can be seen in various regions of the NMR spectral data.

Data for 57a



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.4 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.30 (d, *J* = 4.5 Hz, 1H), 7.26 (m), 6.68 (s, 1H), 6.24 (ddd, *J* = 19.8, 9.8, 9.8 Hz, 1H), 5.20 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.14 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.68 (s, 2H), 4.62 (s, 2H), 4.16 (d, *J* = 2.1 Hz, 1H), 3.98 (s, 3H), 3.28 (br d, *J* = 11.6 Hz, 1H), 3.20 (br ddd, *J* = 11.7, 2.7, 2.7 Hz, 1H), 3.03 (ddd, *J* = 8.0, 2.6, 2.6 Hz), 2.95 (dd, *J* = 11.8, 2.8 Hz, 1H), 2.87 (s, 3H),

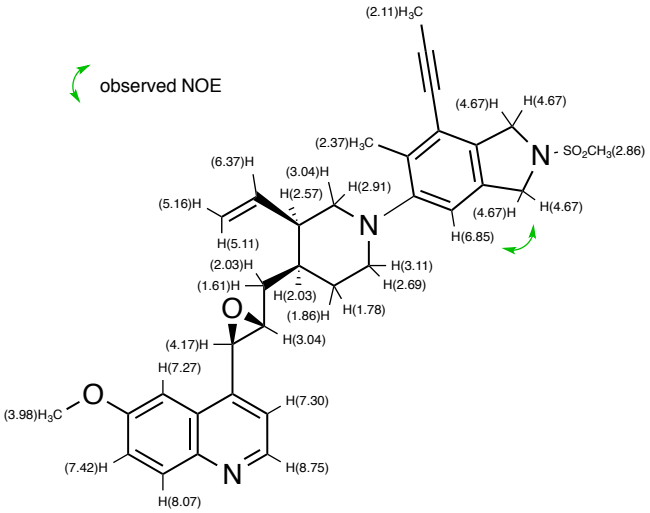
2.80 (ddd, *J* = 11.9, 7.9, 6.6 Hz, 1H), 2.56 (dddd, *J* = 9.2, 3.3, 3.3, 3.3 Hz, 1H), 2.38 (s, 3H), 2.09 (s, 3H), 2.02 (m, 2H), 1.79 (m, 2H), and 1.58 (nfom, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.0, 148.1, 143.9, 141.7, 141.2, 140.2, 137.0, 131.8, 127.4, 126.1, 121.7, 118.5, 118.4, 117.5, 117.0, 112.4, 101.1, 93.0, 75.4, 61.3, 57.2, 55.6, 55.3, 54.4, 53.8, 51.3, 43.5, 37.0, 35.7, 34.7, 28.8, 20.5, and 4.5.

IR (neat): 3040, 2921, 2852, 2799, 1621, 1510, 1339, 1159, 1080, 1031, and 853 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{37}N_3NaO_4S^+$ $[M+Na]^+$ requires 594.2397; found 594.2410.

Data for 57b



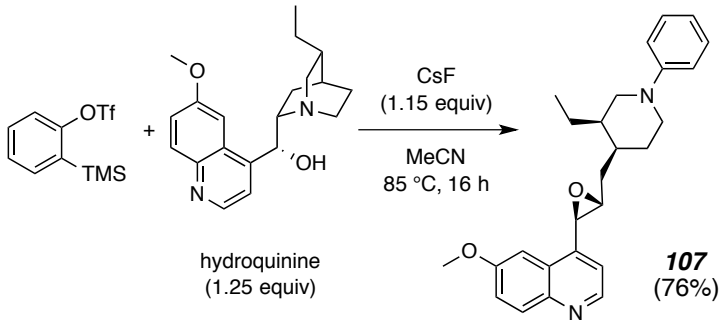
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.30 (d, *J* = 4.5 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 6.85 (s, 1H), 6.37 (ddd, *J* = 17.6, 9.9, 9.9 Hz, 1H), 5.16 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.11 (dd, *J* = 17.3, 2.0 Hz, 1H), 4.67 (br s, 4H), 4.17 (d, *J* = 2.1 Hz, 1H), 3.98 (s, 3H), 3.11 (br d, *J* = 11.6 Hz, 1H), 3.06–3.01 (m, 2H), 2.91 (dd, *J* = 11.4, 2.9 Hz, 1H), 2.86 (s, 3H), 2.69 (ddd, *J* = 11.4, 11.4, 3.0 Hz, 1H), 2.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.37 (s, 3H), 2.11 (s, 3H), 2.06–1.98 (m, 2H), 1.86 (dddd, *J* = 13.6, 10.9, 10.9, 3.9 Hz, 1H), 1.78 (dddd, *J* = 13.5, 3.3, 3.3, 3.3 Hz, 1H), and 1.61 (nfom, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.0, 152.7, 148.1, 144.2, 141.8, 137.8, 135.0, 133.4 (x2), 131.9, 127.5, 121.6, 120.2, 117.0, 116.8, 113.1, 101.1, 94.4, 75.9, 61.0, 58.2, 55.6, 55.3, 54.4 (x2), 53.1, 44.1, 36.1, 36.9, 34.6, 29.0, 16.0, and 4.6.

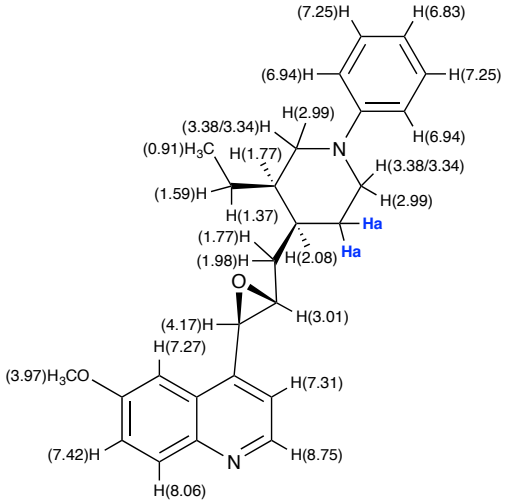
IR (neat): 3070, 2919, 2852, 2800, 2229, 1621, 1508, 1336, 1155, 1079, 913, and 852 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{37}N_3NaO_4S^+$ $[M+Na]^+$ requires 594.2397; found 594.2411.

4-((2*R*,3*R*)-3-(((3*R*,4*S*)-3-Ethyl-1-phenylpiperidin-4-yl)methyl)oxiran-2-yl)-6-methoxyquinoline (107)



2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (50 mg, 0.168 mmol) and hydroquinine (69 mg, 0.210 mmol, 1.25 equiv) were combined in a culture tube and dissolved in acetonitrile (6 mL, 0.03 M). CsF (29 mg, 0.193 mmol, 1.15 equiv) was added and the vial was sealed with a Teflon-lined cap. The suspension was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:3 Hex:EtOAc +1% NEt_3). The residue was purified by MPLC (3:2 Hex:EtOAc +1% NEt_3) to give **107** (51 mg, 0.127 mmol, 76%) as a pale yellow oil.



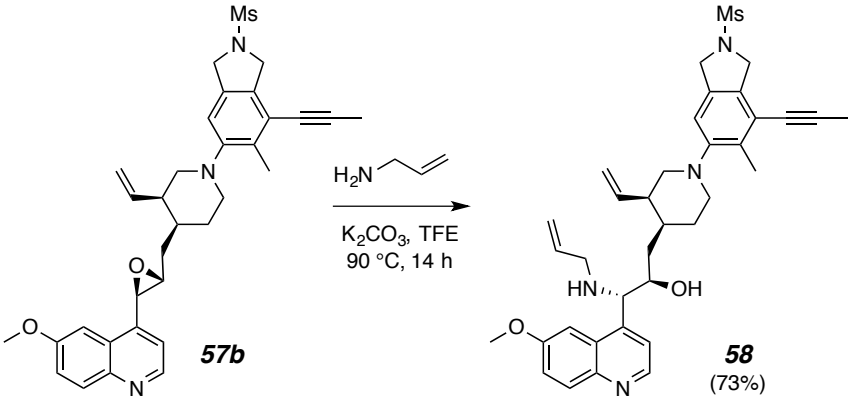
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.31 (d, *J* = 4.5 Hz, 1H), 7.27 (d, *J* = 2.7 Hz, 1H), 7.25 (dd, *J* = 8.8, 7.3 Hz, 2H, NArH_m), 6.94 (dd, *J* = 8.7, 0.7 Hz, 2H, NArH_o), 6.83 (tt, = 7.2, 0.7 Hz, 1H NArH_p), 4.17 (d, *J* = 2.0 Hz, 1H), 3.97 (s, 3H, OCH_3), 3.38 (ddd, *J* = 10.7, 5.2, 5.2 Hz, 1H), 3.34 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.03-2.97 (m, 3H), 2.08 (m, 1H), 1.97 (ddd, *J* = 14.1, 5.4, 4.3 Hz, 1H), 1.85–1.80 (m, 2H), 1.77 (m, 2H), 1.59 (ddq, *J* = 13.6, 9.3, 7.4 Hz, 1H), 1.37 (ddq, Σ*J* = 40.8 Hz including a dq of 4.7, 7.5 Hz, 1H), and 1.01 (dd, *J* = 7.4, 7.4, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.0, 152.3, 148.0, 141.9, 131.8, 129.1, 127.3, 121.6, 119.3, 116.9, 116.8, 116.4, 100.9, 61.7, 55.6, 55.1, 52.3, 47.7, 40.4, 36.3, 33.1, 28.6, 19.7, and 12.3.

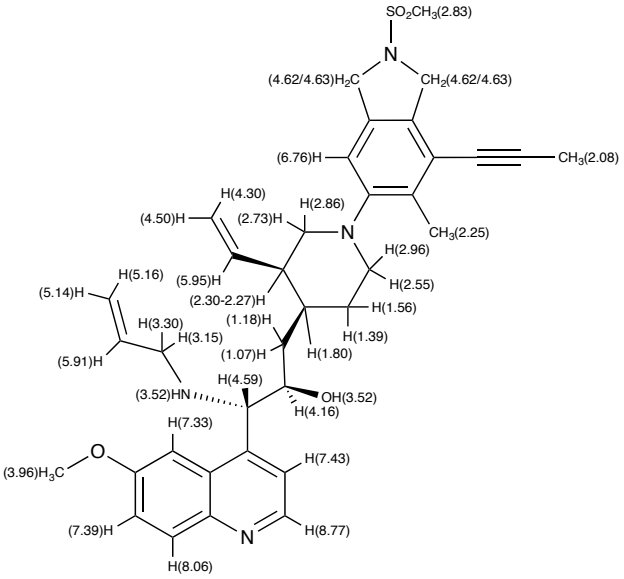
IR (neat): 3057, 3027, 2958, 2932, 2872, 2806, 1620, 1598, 1505, 1474, 1236, and 851 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{31}N_2O_2^+$ $[M+H]^+$ requires 403.2380; found 403.2400.

(1*S*,2*R*)-1-(Allylamino)-1-(6-methoxyquinolin-4-yl)-3-((3*R*,4*S*)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)-3-vinylpiperidin-4-yl)propan-2-ol (58)



Epoxide **57b** (25 mg, 0.044 mmol), allyl amine (0.5 mL), and K_2CO_3 (50 mg) were combined in a culture tube and trifluoroethanol (2.5 mL, 0.02 M) was added. The tube was sealed with a Teflon-lined cap. The suspension, which became homogenous upon warming, was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, concentrated, and passed through a plug of silica (EtOAc +1% NEt_3). The resulting residue was purified by MPLC (1:6 Hex:EtOAc +1% NEt_3) to give **50** (20 mg, 0.032 mmol, 73 %) as a pale yellow solid film



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 4.6 Hz, 1H), 7.40 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.33 (br d, *J* = 2.2 Hz, 1H), 6.76 (s, 1H), 5.95 (ddd, *J* = 17.3, 10.2, 10.2 Hz, 1H), 5.91 (dddd, *J* = 16.2, 10.3, 6.0, 6.0 Hz, 1H), 5.16 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.14 (dddd, *J* = 10.3, 1.6, 1.6, 1.6 Hz, 1H), 4.63 (br s, 2H), 4.62 (br s, 2H), 4.59 (d, *J* = 4.0 Hz, 1H), 4.50 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.30 (dd, *J* = 17.3, 1.7 Hz, 1H), 4.16 (ddd, *J* = 10.7, 4.0, 1.8 Hz, 1H), 3.96 (s, 3H), 3.52 (br s, 2H), 3.30 (dddd, *J* = 14.1, 5.8, 1.4, 1.4 Hz, 1H), 3.15 (dddd, *J* = 14.0, 6.1, 1.3, 1.3 Hz, 1H), 2.96 (br d, *J* = 10.9 Hz, 1H), 2.86 (br ddd, *J* = 11.2, 2.2, 2.2 Hz, 1H), 2.83 (s, 3H), 2.73 (dd, *J* = 11.3, 2.8 Hz, 1H), 2.55 (ddd, *J* = 11.9, 11.9, 2.5 Hz, 1H), 2.30–2.27 (m, 1H), 2.25 (s, 3H), 2.08 (s, 3H), 1.80 (br ddddd, *J* = 12, 11, 4, 4, 4 Hz, 1H),

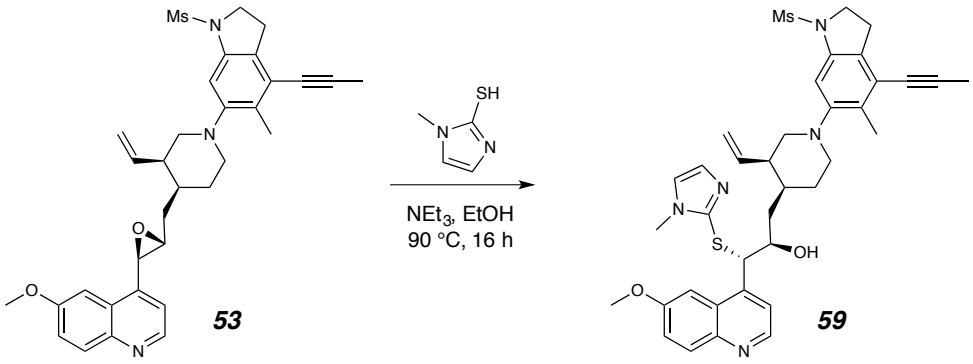
1.56 (dddd, J = 12.7, 12.7, 12.7, 4.0 Hz, 1H), 1.39 (br dddd, J = 13, 4, 4, 4 Hz, 1H), 1.18 (br ddd, J = 14, 11, 1.5 Hz, 1H), and 1.07 (ddd, J = 14.2, 10.7, 3.7 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.9, 152.8, 147.5, 144.9, 143.8, 137.1, 136.1, 134.9, 133.3, 131.8, 128.4, 121.4, 120.0, 119.2, 116.8, 115.9, 113.0, 112.9, 101.3, 94.3, 75.9, 68.9, 61.6, 58.6, 55.6, 54.4, 53.6, 50.1, 42.4, 35.5, 34.5, 34.2, 29.8, 34.5, 15.9, and 4.5.

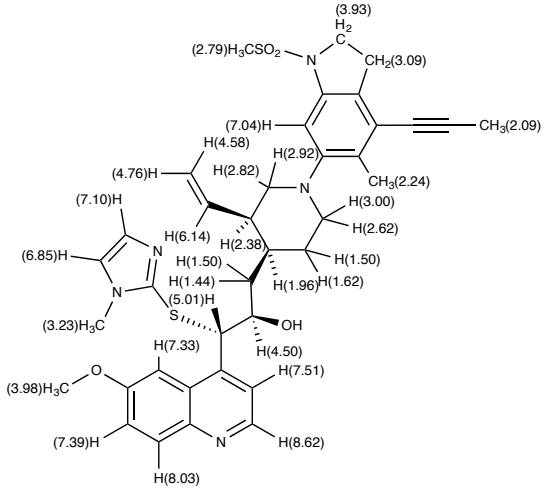
IR (neat): 3070, 2922, 2852, 2228, 1621, 1509, 1463, 1335, 1239, 1154, 1079, 915, and 831 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{36}H_{45}N_4O_4S^+$ $[M+H]^+$ requires 629.3156; found 629.3181.

(1*S*,2*R*)-1-(6-Methoxyquinolin-4-yl)-3-((3*R*,4*S*)-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-3-vinylpiperidin-4-yl)-1-((1-methyl-1*H*-imidazol-2-yl)thio)propan-2-ol (59)



Epoxide **53** (10 mg, 0.018 mmol) and 2-mercapto-1-methylimidazole (10 mg, 0.088 mmol, 5 equiv) and triethylamine (0.025 mL, 0.175 mmol, 10 equiv) were combined in a ½ dram vial, dissolved in EtOH (0.25 mL, 0.07 M), and sealed with a Teflon-lined cap. The solution was heated overnight (14-16 h) in an oil bath at 85 °C, cooled, concentrated under reduced pressure and passed through a plug of silica (EtOAc +1% NEt_3). The resulting residue was purified by MPLC (1:6 Hex:EtOAc +1% NEt_3) to give, **59** (8 mg, 0.012 mmol, 67 %) as a pale yellow, solid film.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.6 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.51 (br d, *J* = 4.7 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.33 (br s, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 7.04 (s, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 6.14 (ddd, *J* = 17.7, 9.9, 9.9 Hz, 1H), 5.01 (d, *J* = 3.0 Hz, 1H), 4.76 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.58 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.50 (ddd, *J* = 10.1, 2.7, 2.7 Hz, 1H), 3.98 (s, 3H), 3.95–3.90 (m, 2H), 3.23 (s, 3H), 3.12–3.07 (m, 2H), 3.00 (br d, *J* = 11.4 Hz, 1H), 2.92 (br ddd, *J* = 11.3, 2.5, 2.5 Hz, 1H), 2.82 (dd, *J* = 11.5, 2.8 Hz, 1H), 2.79 (s, 3H), 2.62 (ddd, *J* = 11.8, 11.8, 2.9 Hz, 1H), 2.40–2.36 (m, 1H), 2.24 (s, 3H), 2.09 (s, 3H), 1.96 (m, Σ*J*s = 34.8 Hz, 1H), 1.62 (dddd, *J* = 12.8, 12.8, 12.8, 4.0 Hz, 1H), 1.54–1.47 (m, 2H), and 1.44 (dd, *J* = 10.0, 2.3 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.1, 152.6, 147.1, 144.1, 142.4, 139.8, 139.6, 137.9, 131.9, 130.6, 129.2, 128.2, 127.3, 122.9, 122.0, 121.5, 120.8, 116.0, 105.6, 101.0, 93.6, 76.2, 71.9, 52.9, 58.4, 55.7, 53.4, 50.5, 42.6, 37.7, 34.3, 34.0, 33.3, 29.5, 27.9, 15.7, and 4.6.

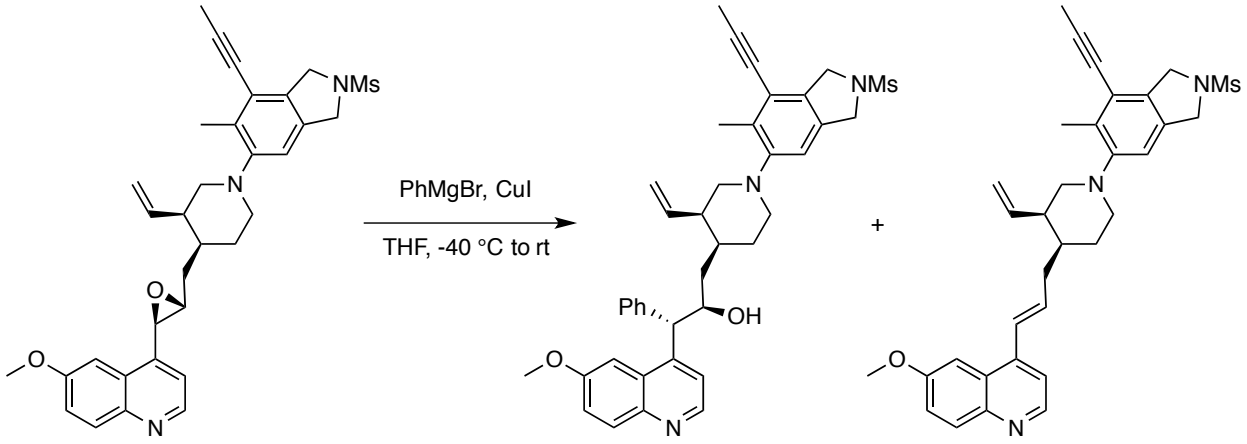
IR (neat): 3244, 3000, 2922, 2855, 2799, 2742, 2233, 1621, 1588, 1509, 1469, 1345, 1231, 1158, and 912 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{37}H_{44}N_5O_4S_2^+$ $[M+H]^+$ requires 686.2829; found 686.2850.

(1S,2R)-1-(6-Methoxyquinolin-4-yl)-3-((3R,4S)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)-3-vinylpiperidin-4-yl)-1-phenylpropan-2-ol (**60**)

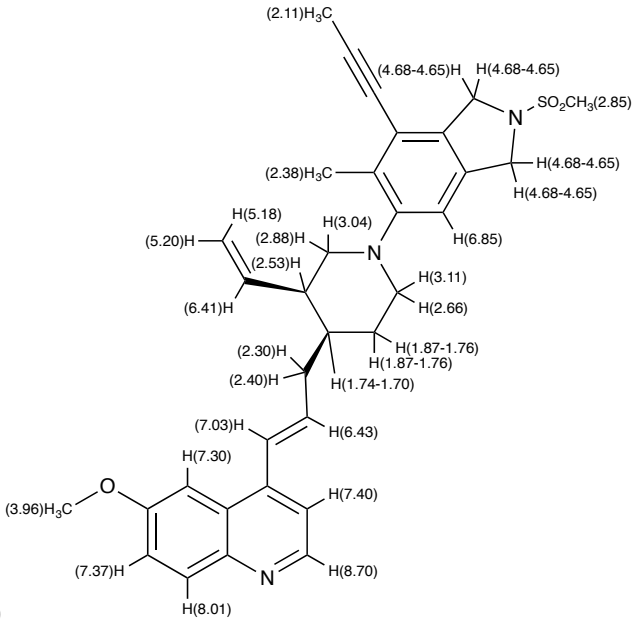
and

6-Methoxy-4-((*E*)-3-((3R,4R)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)-3-vinylpiperidin-4-yl)prop-1-en-1-yl)quinoline (**108**)



57b ***60*** ***108***

Copper iodide (8 mg, 0.04 mmol, 0.5 equiv) was added to a 2-dram vial equipped with a stir bar under a nitrogen atmosphere and suspended in THF (0.5 mL). The suspension was cooled to -40 °C and phenyl bromide (1 mL, 1 mmol, 1 M in THF) was added in one portion and the mixture was stirred at -40 °C for 15 min. This suspension was then transferred by syringe into a 2-dram vial containing **57b** (50 mg, 0.087 mmol) in THF (0.5 mL) at -40 °C. The resulting mixture was then allowed to warm slowly to rt over 30 min and then stirred at room temperature overnight (~13 h). The mixture was quenched by the addition of conc aq NH_3:brine (1:3, 4 mL), and the aqueous layer was extracted with dichloromethane (4x10 mL). The combined organic layer was washed with additional NH_3:brine (1:4, 10 mL), dried ($MgSO_4$), filtered and concentrated. The residue was passed through a plug of SiO_2 (EtOAc+1%NEt3). The resulting residue was purified by MPLC (3:1+1% EtOAc:Hex+NEt_3) to give, in order of elution, **108** (17 mg, 0.031 mmol, 35%) and **60** (22 mg, 0.034 mmol, 39%).



Data for 108 (~90% purity)

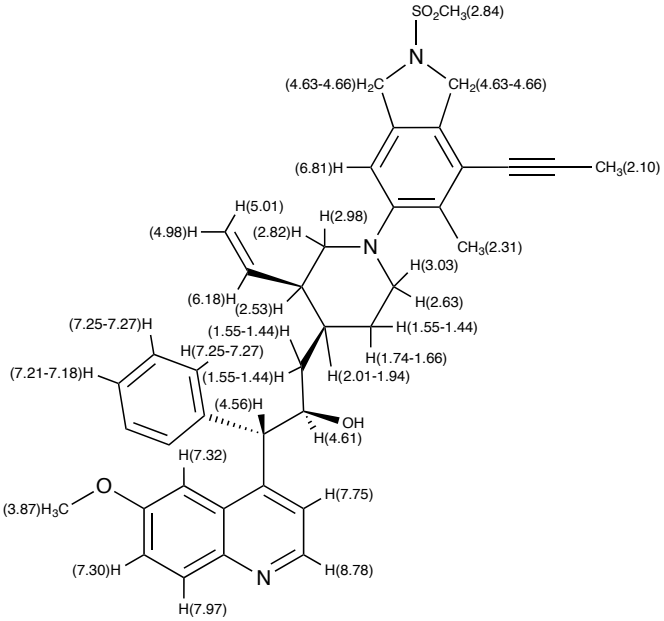
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.6 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 4.6 Hz), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.30 (d, *J* = 2.4 Hz), 7.03 (d, *J* = 15.6 Hz, 1H), 6.85 (s, 1H), 6.43 (ddd, *J* = 15.5, 7.4, 7.4 Hz, 1H), 6.41 (ddd, *J* = 17.2, 9.9, 9.9 Hz, 1H), 5.20 (dd, *J* = 10.4, 2.3 Hz, 1H), 5.18 (ddd, *J* = 17.2, 2.3, 0.7 Hz, 1H), 4.68–4.65 (m, 4H), 3.96 (s, 3H), 3.11 (br d, *J* = 12 Hz, 1H), 3.04 (br ddd, *J* = 11.4, 2.4, 2.4 Hz, 1H), 2.88 (dd, *J* = 11.4, 2.9 Hz, 1H), 2.85 (s, 3H), 2.66 (ddd, *J* = 11.2, 11.2, 2.9 Hz, 1H), 2.53 (dddd, *J* = 9.4, 3.2, 3.2, 3.2 Hz, 1H), 2.40 (dddd, *J* = 14.6, 6.9, 6.9, 1.1 Hz, 1H), 2.38 (s, 3H), 2.30 (dddd, *J* = 14.0, 7.1, 7.1, 1.2 Hz, 1H), 2.11 (s, 3H), 1.87–1.76 (m, 2H), and 1.74-1.70 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.7, 152.8, 147.6, 144.6, 142.1, 137.9, 135.9, 135.0, 133.4 (x2), 131.4, 128.2, 126.5, 121.7, 120.1, 117.6, 116.6, 113.1, 101.6, 94.4, 75.9, 58.5, 55.5, 54.5 (x2), 53.4, 44.1, 38.7, 37.7, 34.6, 28.7, 16.0, and 4.6.

IR (neat): 3073, 2924, 2852, 2797, 2229, 1619, 1467, 1336, and 1155 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{38}N_3O_3S^+$ $[M+H]^+$ requires 556.2628; found 556.2633.

Data for 60



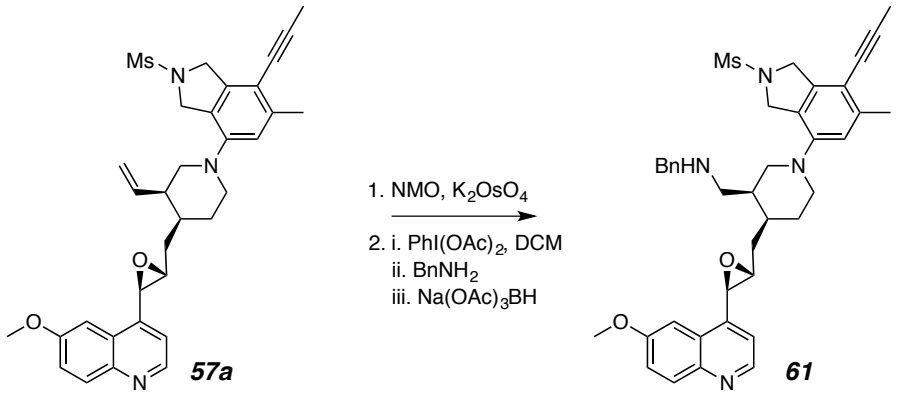
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.78 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.75 (d, *J* = 4.7 Hz, 1H), 7.32 (br d, *J* = 2.6 Hz, 1H), 7.30 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.27–7.25 (m, 4H), 7.21-7.18 (nfom, 1H), 6.81 (s, 1H), 6.18 (ddd, *J* = 17.3, 10.1, 10.1 Hz, 1H), 5.01 (dd, *J* = 17.2, 2.1 Hz, 1H), 4.98 (dd, *J* = 10.2, 2.1 Hz, 1H), 4.66–4.63 (m, 4H), 4.61 (ddd, *J* = 8.2, 8.2, 2.9 Hz, 1H), 4.56 (d, *J* = 7.9 Hz, 1H), 3.87 (s, 3H), 3.03 (br d, *J* = 11 Hz, 1H), 2.98 (ddd, *J* = 11.0, 2.3, 2.3 Hz, 1H), 2.84 (s, 3H), 2.82 (overlapped m containing *J* = 2.7 Hz, 1H), 2.63 (ddd, *J* = 11.7, 11.7, 2.6 Hz, 1H), 2.53 (dddd, *J* = 9.5, 3.4, 3.4, 3.4 Hz, 1H), 2.31 (s, 3H), 2.10 (s, 3H), 2.01–1.94 (m, 1H), 1.74–1.66 (m, 1H), and 1.55–1.44 (m, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.7, 152.9, 147.3, 145.8, 145.4, 144.4, 140.1, 137.9, 135.0, 133.3 (x2), 131.5, 128.8 (x2), 127.1, 121.4, 120.0, 119.6, 116.5, 113.0, 102.1, 94.3, 75.9, 70.7, 58.7, 55.3, 54.2 (x2), 54.0, 53.6, 42.7, 38.7, 34.8, 34.5, 29.7, 16.0, and 4.5.

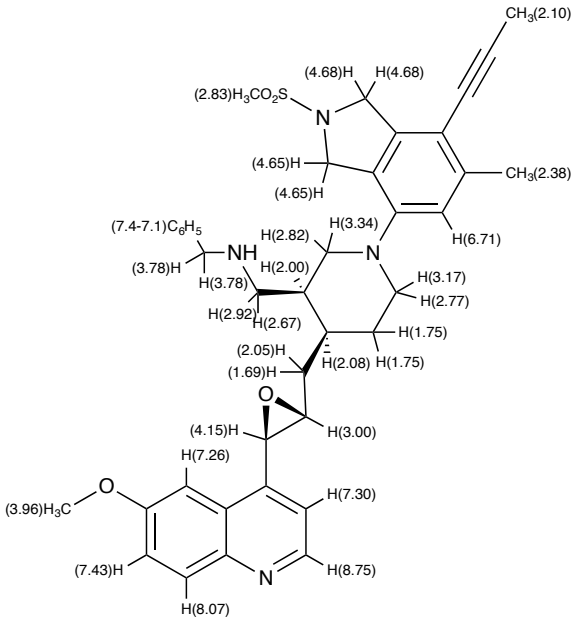
IR (neat): 3362 (br), 3065, 3003, 2919, 2852, 2794, 2227, 1621, 1588, 1465, 1335, 1154, 1077, and 756 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{39}H_{44}N_3O_4S^+$ $[M+H]^+$ requires 650.3047; found 650.3059.

_N_-Benzyl-1-((3_S_,4_S_)-4-(((2_R_,3_R_)-3-(6-methoxyquinolin-4-yl)oxiran-2-yl)methyl)-1-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-4-yl)piperidin-3-yl)methanamine (61)



Alkene **57a** (100 mg, 0.175 mmol) was transferred to a ½ dram vial equipped with a stir bar and dissolved in acetone:water:*tert*-butanol (0.3:0.25:0.5 mL). K_2OsO_4 (pipette tip, ~2-4 mg) and NMO (26 mg, 0.22 mmol, 1.3 equiv) were added and the solution was stirred at ambient temperature for 6 h resulting in a tan suspension. Additional NMO (13 mg, 0.11 mmol, 0.65 equiv) was added and the mixture was stirred overnight (~14 h). The resulting suspension was transferred to a separatory funnel with DCM (~5 mL) and washed with $NaHCO_3$ (5 mL). The aqueous layer was back extracted with additional DCM (3x6 mL), followed by EtOAc (3 x 6 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated to give a sample of crude diol. This material and diacetoxyiodobenzene[8] (62 mg, 0.19 mmol, 1.1 equiv) were combined in a culture tube, dissolved in DCM (4 mL), and sealed with a Teflon-lined cap. After ~2 h complete consumption of diol was evident by TLC. Benzylamine (75 μL, 0.69 mmol, 4 equiv) was added to this solution, and the resulting mixture was stirred for 45 min. Sodium triacetoxyborohydride (112 mg, 0.53 mmol, 3 equiv) was added in one portion and the mixture was stirred for 4 h. Sodium bicarbonate (5 mL) was added in one portion and then transferred to a separatory funnel with DCM (~5 mL). The DCM layer was washed with additional $NaHCO_3$ (5 mL x 2) and the aqueous layers were combined and extracted with DCM (5 mL x2). The organic layers were dried ($MgSO_4$), filtered (Celite®), and concentrated to give crude **61.** This material was passed through a plug of silica (EtOAc +1% NEt_3) and then purified by MPLC (1:6 Hex:EtOAc +1% NEt_3) to give **61** (50 mg, 0.075 mmol, 43 %) as a pale yellow oil. (This material contains a small (5%) amount of **62**, the amount of which grows over time at ambient temperature)



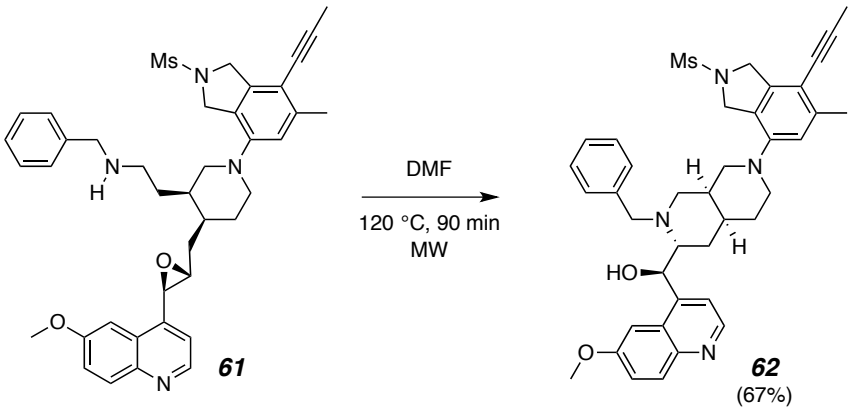
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.4 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.43 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.30 (m, 1H), 7.26 (m, 1H), 7.4-7.1 (m, 5H), 6.71 (s, 1H), 4.68 (br s, 2H), 4.65 (br s, 2H), 4.15 (d, *J* = 2.0 Hz, 1H), 3.96 (s, 3H), 3.78 (s, 2H), 3.34 (br dd, *J* = 11.7, 4.0 Hz, 1H), 3.17 (ddd, *J* = 11.9, 3.2, 3.2 Hz, 1H), 3.00 (ddd, *J* = 8.3, 3.3, 2.7 Hz, 1H), 2.92 (dd, *J* = 11.6, 9.3 Hz, 1H), 2.83 (s, 3H), 2.82 (m, 1H), 2.77 (m, 1H), 2.67 (dd, *J* = 11.6, 4.4 Hz), 2.38 (s, 3H), 2.10 (s, 3H), 2.08 (m, 1H), 2.05 (m, 1H), 2.00 (m, 1H), 1.75 (m, 2H), and 1.69 (ddd, *J* = 14.1, 8.0, 8.0 Hz, 1H).

^{13}C-NMR (125 MHz, CDCl3): δ 158.0, 147.8, 144.3, 141.8, 141.1, 140.1, 138.7, 131.6, 128.7, 128.2, 127.7, 127.5, 126.3, 121.5, 118.6, 118.5, 116.8, 112.4, 101.2, 93.0, 75.4, 61.2, 55.7, 55.0, 54.4, 53.4, 53.5, 53.6, 50.8, 45.8, 38.5, 36.2, 34.7, 34.6, 29.1, 20.5, and 4.6.

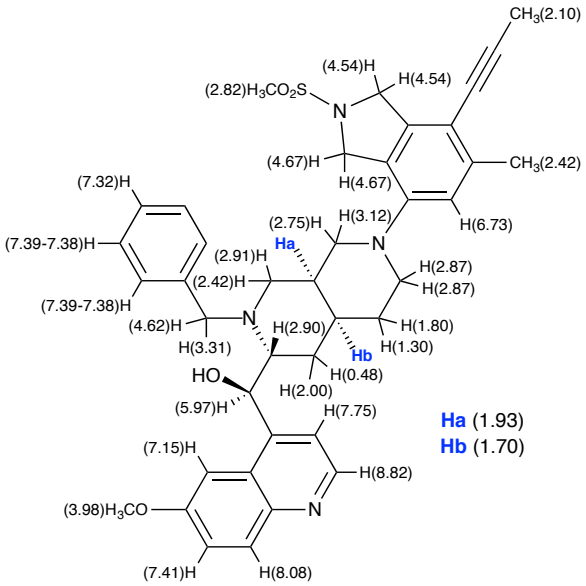
IR (neat): 3269, 3028, 2923, 2852, 2806, 2238, 1681, 1621, 1604, 1335, 1239, 1155, 1078, and 852 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{39}H_{45}N_4O_4S^+$ $[M+H]^+$ requires 665.3156; found 665.3172.

(*R*)-((3*R*,4a*S*,8a*S*)-2-Benzyl-7-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-4-yl)decahydro-2,7-naphthyridin-3-yl)(6-methoxyquinolin-4-yl)methanol (62)



Epoxide **61** (18.2 mg, 0.027 mmol) was dissolved in DMF (5 mL) in a microwave vial. The solution was heated for 1.5 h at 120 °C, cooled, concentrated, and passed through a plug of silica (3:1 EtOAc:Hex +1% NEt_3). The resulting residue was purified by MPLC (1:1 Hex:EtOAc +1% NEt_3) to give **62** (12 mg, 0.018 mmol, 67 %) as a pale yellow oil.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.82 (d, *J* = 4.6 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 4.5 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.39-7.38 (m, 4H), 7.32 (nfom, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 6.73 (s, 1H), 5.97 (d, *J* = 2.8 Hz, 1H), 4.67 (br s, 2H), 4.62 (d, *J* = 13.0 Hz, 1H), 4.54 (br s, 2H), 3.98 (s, 3H), 3.31 (d, *J* = 13.1 Hz, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.91 (m, 1H), 2.90 (m, 1H), 2.87 (m, 2H), 2.82 (s, 3H), 2.75 (dd, *J* = 12.0, 4.3 Hz, 1H), 2.42 (dd, *J* = 12.2, 3.8 Hz, 1H), 2.42 (s, 3H), 2.10 (s, 3H), 2.00 (br dd, *J* = 13.7, 1.8 Hz, 1H), 1.93 (br d, *J* = 11 Hz, 1H), 1.80 (dddd, *J* = 13, 12, 5.5, 5.5 Hz, 1H), 1.70 (dddd, *J* = 13.3, 4.3, 4.3, 4.3 Hz, 1H), 1.30 (br dddd, *J* = 13.5, 2, 2, 2 Hz, 1H), and 0.48 (ddd, *J* = 14.0, 3.8, 3.8 Hz, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.6, 147.9, 147.6, 144.5, 144.2, 144.1, 140.1, 138.1, 132.0, 128.7 (x2), 127.6, 125.8, 120.7, 119.4, 118.3, 118.2, 112.1, 101.6, 92.9, 75.4, 67.6, 63.6, 58.4, 56.7, 55.6, 54.4, 53.6, 50.4, 45.6, 35.1, 34.7, 30.4, 30.3, 23.2, 20.5, and 4.6.

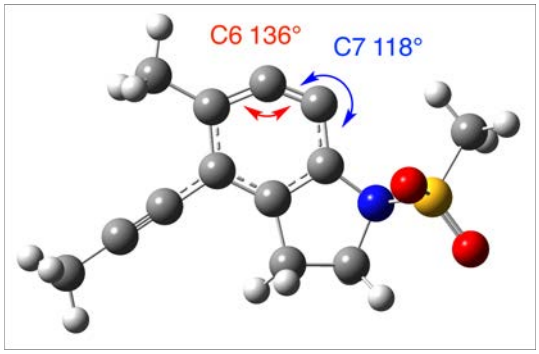
IR (neat): 3405 (br), 3027, 2915, 2851, 2241 (w), 1622, 1604, 1338, 1156, and 1079 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{39}H_{45}N_4O_4S^+$ $[M+H]^+$ requires 665.3156; found 665.3155.

III. Computational methods and results

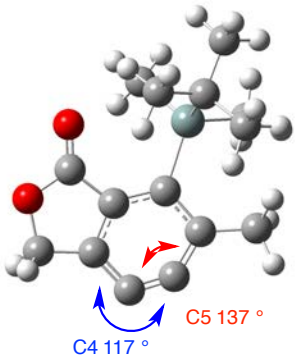
The Gaussian 09 software package was used to perform the density functional theory (DFT) calculations[9]. Geometries were optimized with the M06-2X[10] functional; the 6-31+G(d,p) basis set was used. An SMD continuum solvation model[11] with benzene was used during both geometry optimization and the frequency calculation for each of the benzynes **8**, **26**, and **56**. Harmonic vibrational frequency calculations were carried out at 298 K.

Geometry for benzyne 8 (note the angles at benzyne carbons C6 vs. C7)



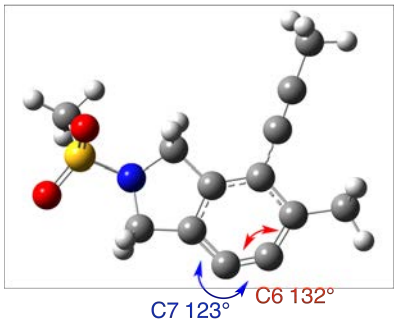
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.532465	0.473676	-0.525758
2	6	0	0.388359	1.851504	-0.481491
3	6	0	-0.758294	2.307129	-0.272600
4	6	0	-2.013689	1.790201	-0.071230
5	6	0	-1.888630	0.362331	-0.121988
6	6	0	-0.646871	-0.263214	-0.338068
7	6	0	-0.313230	-1.733099	-0.362195
8	1	0	-0.335044	-2.139936	0.655750
9	1	0	-1.006100	-2.316029	-0.973744
10	6	0	-3.314138	2.493134	0.168760
11	1	0	-4.041050	2.228617	-0.604994
12	1	0	-3.737784	2.193091	1.131752
13	1	0	-3.173300	3.573929	0.166291
14	6	0	-3.062501	-0.438228	0.069160
15	6	0	-4.057573	-1.109468	0.231894
16	6	0	-5.255511	-1.924524	0.431706
17	1	0	-6.063513	-1.589817	-0.223791
18	1	0	-5.046719	-2.974178	0.211435
19	1	0	-5.601423	-1.853442	1.466161
20	6	0	1.109772	-1.740467	-0.960413
21	1	0	1.776316	-2.482983	-0.523287
22	1	0	1.072814	-1.896715	-2.041337
23	7	0	1.659915	-0.365977	-0.746830
24	16	0	2.916798	-0.228903	0.386613
25	6	0	3.746245	1.232321	-0.191548
26	8	0	3.774132	-1.390230	0.174356
27	8	0	2.394562	0.035505	1.723945
28	1	0	4.098642	1.045238	-1.204799
29	1	0	3.043729	2.065912	-0.156367
30	1	0	4.577288	1.400635	0.495162

Geometry for benzyne 26 (note the angles at benzyne carbons C4 vs. C5)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.896896	0.463305	-0.180678
2	6	0	-2.953822	1.838044	-0.347191
3	6	0	-1.874702	2.460228	-0.266073
4	6	0	-0.545121	2.156876	-0.047898
5	6	0	-0.429968	0.746333	0.175757
6	6	0	-1.609040	-0.039270	0.073767
7	6	0	-3.883725	-0.656809	-0.244157
8	8	0	-3.084944	-1.826615	-0.042007
9	6	0	-1.769643	-1.522589	0.117148
10	8	0	-0.944413	-2.389782	0.235124
11	14	0	1.275816	-0.021795	0.704384
12	6	0	2.326866	1.280200	1.590817
13	6	0	1.054483	-1.364595	2.010666
14	6	0	2.230528	-0.631169	-0.832176
15	6	0	3.592157	-1.159331	-0.351173
16	6	0	1.488546	-1.756211	-1.564975
17	6	0	2.461205	0.525653	-1.814637
18	6	0	0.558014	3.177671	-0.080375
19	1	0	-4.378642	-0.733664	-1.216802
20	1	0	-4.641263	-0.605044	0.543697
21	1	0	2.807047	2.017551	0.944270
22	1	0	1.746636	1.813780	2.352213
23	1	0	3.121900	0.743981	2.121535
24	1	0	1.894536	-1.314794	2.712545
25	1	0	0.135981	-1.215770	2.588760
26	1	0	1.009509	-2.367321	1.583523
27	1	0	4.164246	-1.552640	-1.202995
28	1	0	4.197885	-0.372831	0.114346
29	1	0	3.482111	-1.975248	0.373354
30	1	0	2.080773	-2.080979	-2.432307
31	1	0	1.318055	-2.626723	-0.924967
32	1	0	0.511118	-1.427842	-1.937372
33	1	0	3.021651	0.167305	-2.689464
34	1	0	1.515267	0.942438	-2.182601
35	1	0	3.046311	1.338619	-1.367981
36	1	0	0.843340	3.493300	0.927041
37	1	0	1.445493	2.792346	-0.582824
38	1	0	0.215937	4.060576	-0.623394

Geometry for benzyne 56 (note the angles at benzyne carbons C6 vs. C7)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.122399	-1.774194	-0.056881
2	6	0	1.088921	-2.763041	-0.039294
3	6	0	2.313791	-2.526064	-0.023208
4	6	0	3.017370	-1.337860	-0.008343
5	6	0	2.079503	-0.258624	-0.021927
6	6	0	0.689445	-0.493298	-0.047939
7	6	0	-0.400918	0.541929	-0.040120
8	1	0	-0.466760	1.049234	0.931397
9	1	0	-0.264695	1.296626	-0.822074
10	6	0	-1.376508	-1.721027	-0.049536
11	1	0	-1.780854	-2.039411	0.919134
12	1	0	-1.838008	-2.325054	-0.833410
13	6	0	4.499937	-1.122773	0.017173
14	1	0	4.820921	-0.555518	-0.861897
15	1	0	4.788627	-0.545015	0.900434
16	1	0	5.025388	-2.077592	0.032309
17	6	0	2.565650	1.090490	-0.006067
18	6	0	2.977087	2.229742	0.012433
19	6	0	3.474651	3.604898	0.039301
20	1	0	2.948077	4.220174	-0.694591
21	1	0	3.327558	4.048821	1.027239
22	1	0	4.541946	3.631030	-0.193627
23	7	0	-1.606231	-0.277024	-0.314880
24	16	0	-3.074967	0.346378	0.153164
25	8	0	-4.019363	-0.765600	0.116953
26	8	0	-2.936133	1.134456	1.376653
27	6	0	-3.453974	1.474709	-1.169725
28	1	0	-2.663362	2.223686	-1.228389
29	1	0	-3.532226	0.903364	-2.093523
30	1	0	-4.403668	1.946599	-0.913502

IV. References for Supplementary Information

[1] Hoye, T. R., Hanson, P. R. & Vyvyan, J. R. A practical guide to first-order multiplet analysis in ^{1}H NMR spectroscopy. *J. Org. Chem*. **59**, 4096-4103 (1994).

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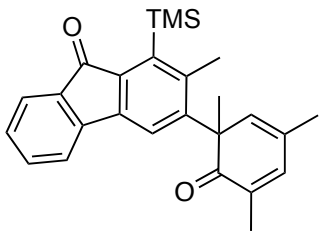
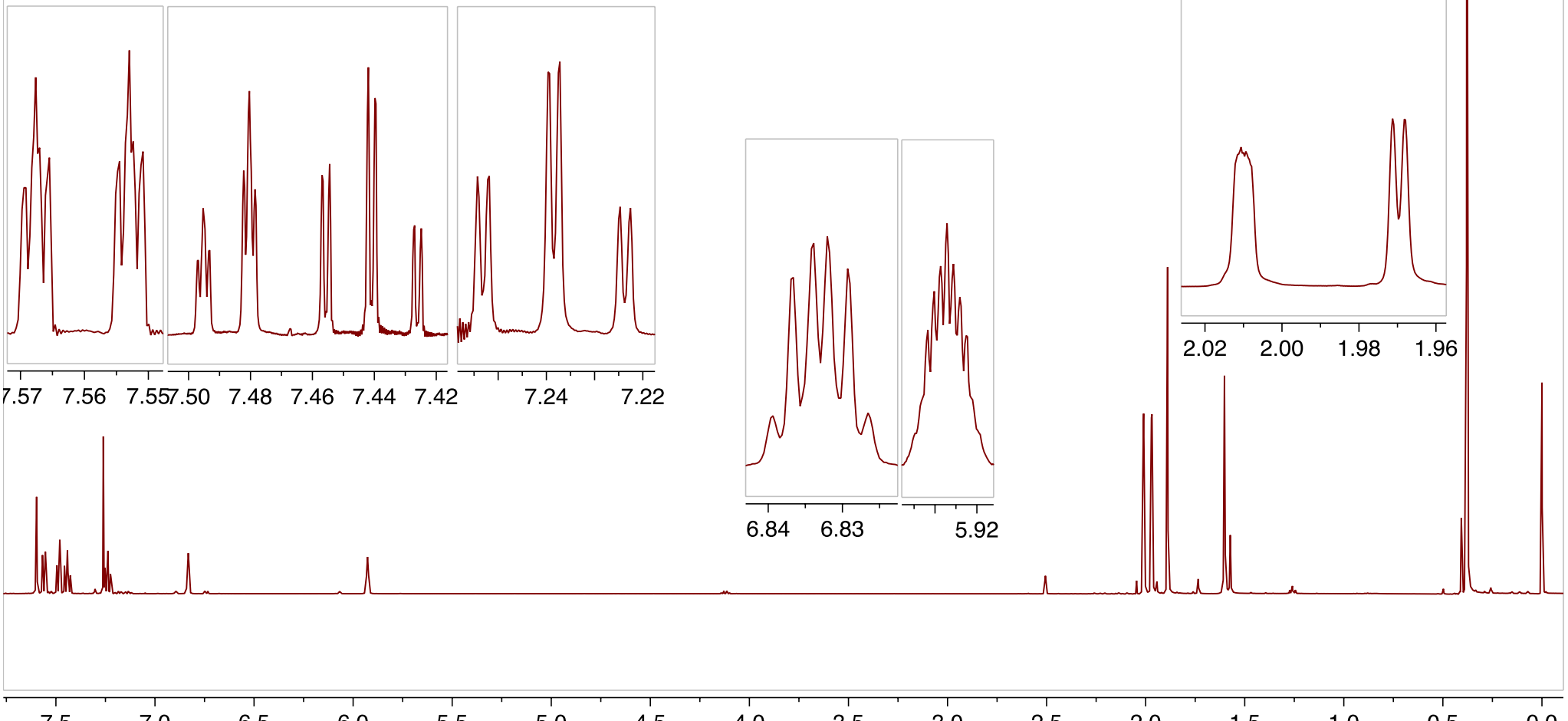
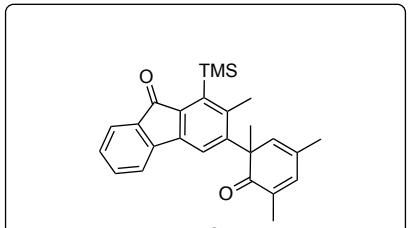
V. **Copies of ^{1}H and ^{13}C NMR spectra** (often ^{1}H, COSY, HSQC, and HMBC)



4b

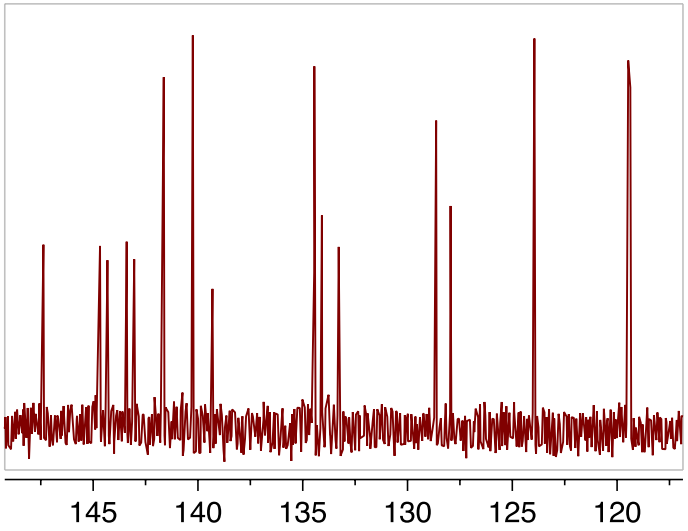
^{1}H NMR (500 MHz) in $CDCl_3$

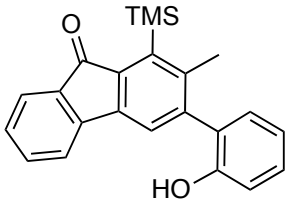




4b

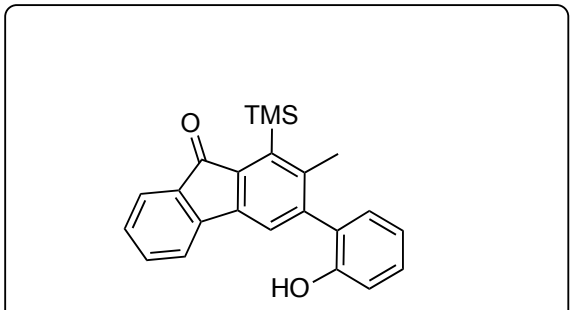
^{13}C NMR (125 MHz) in $CDCl_3$





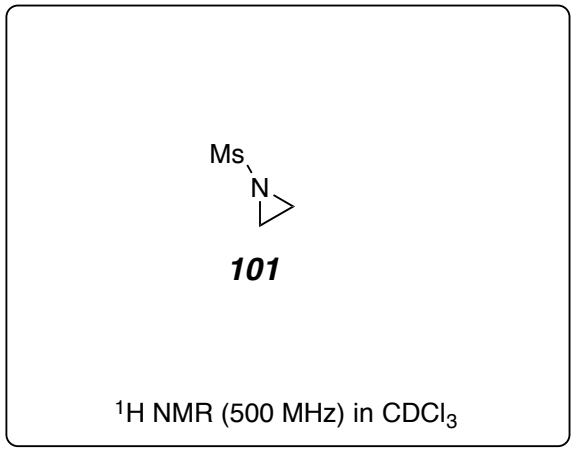
5

^{1}H NMR (500 MHz) in $CDCl_3$



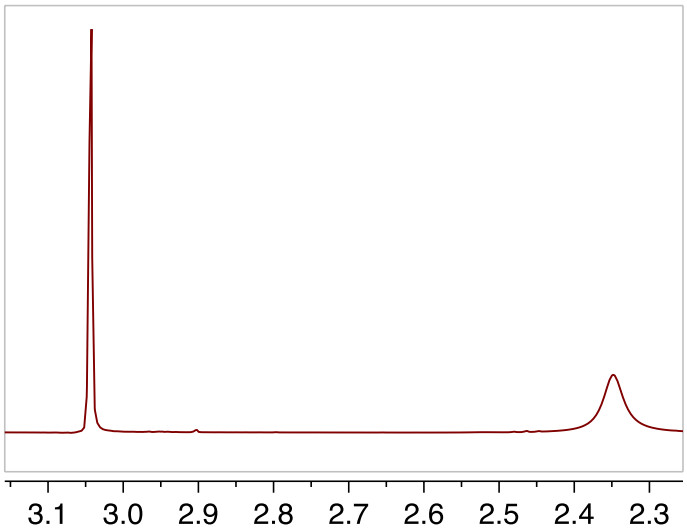
5

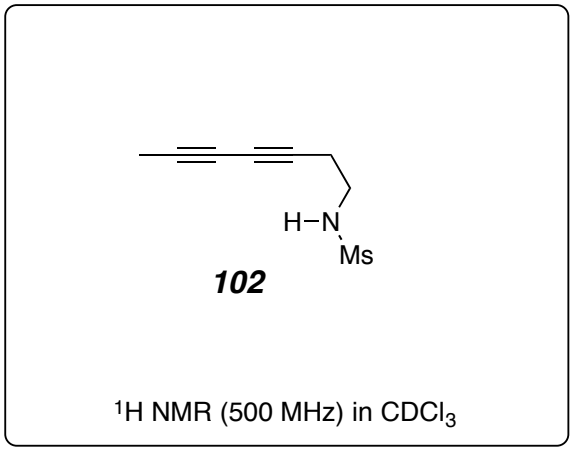
^{13}C NMR (125 MHz) in $CDCl_3$



101

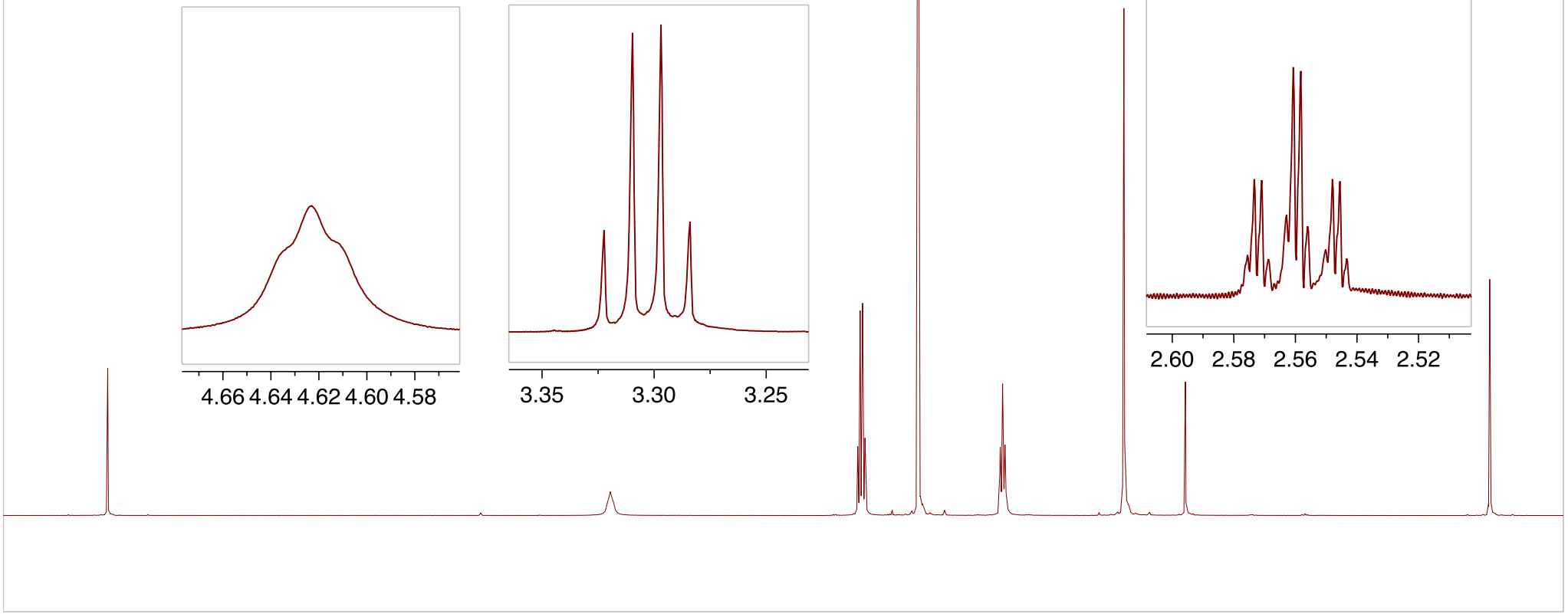
^{1}H NMR (500 MHz) in $CDCl_3$

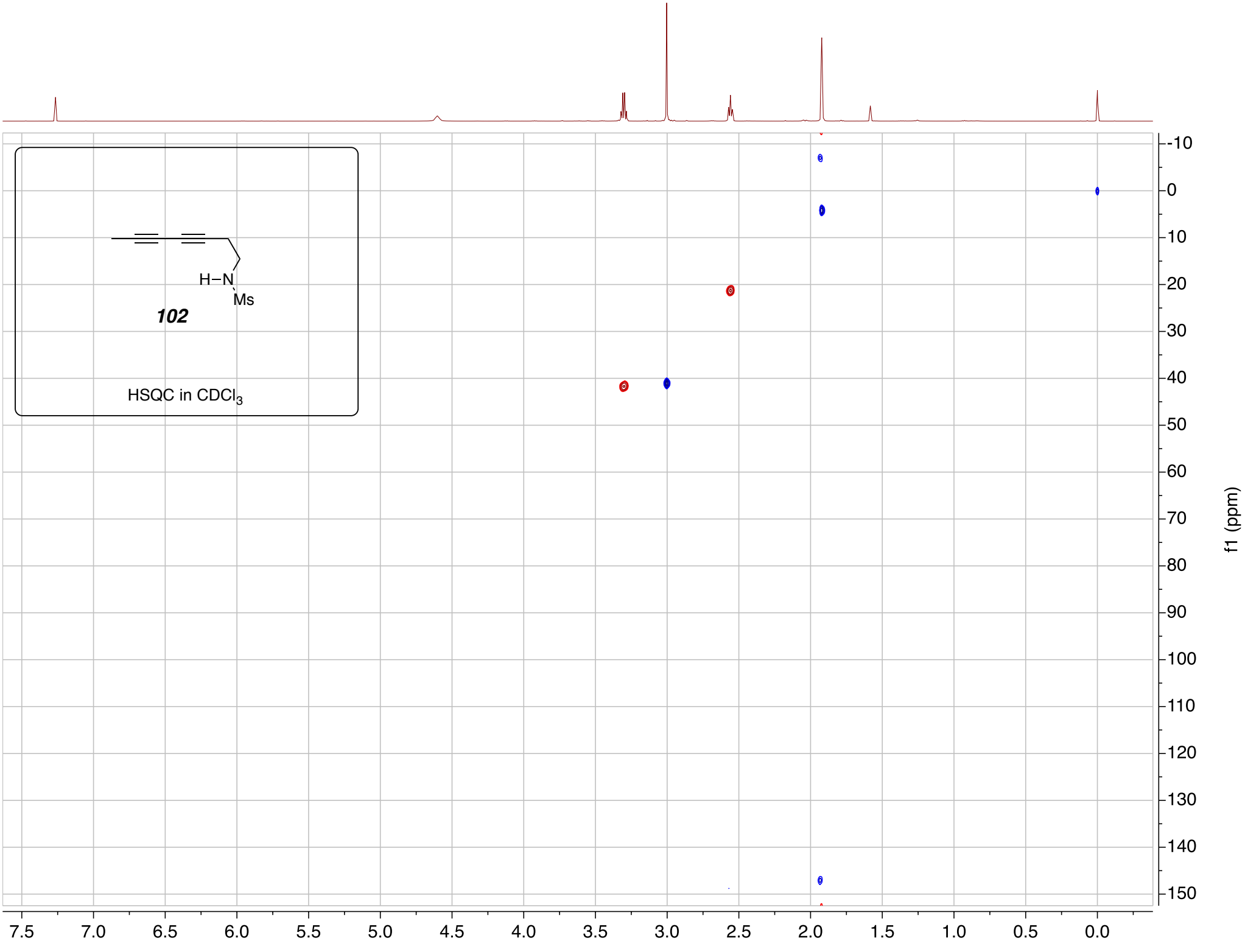


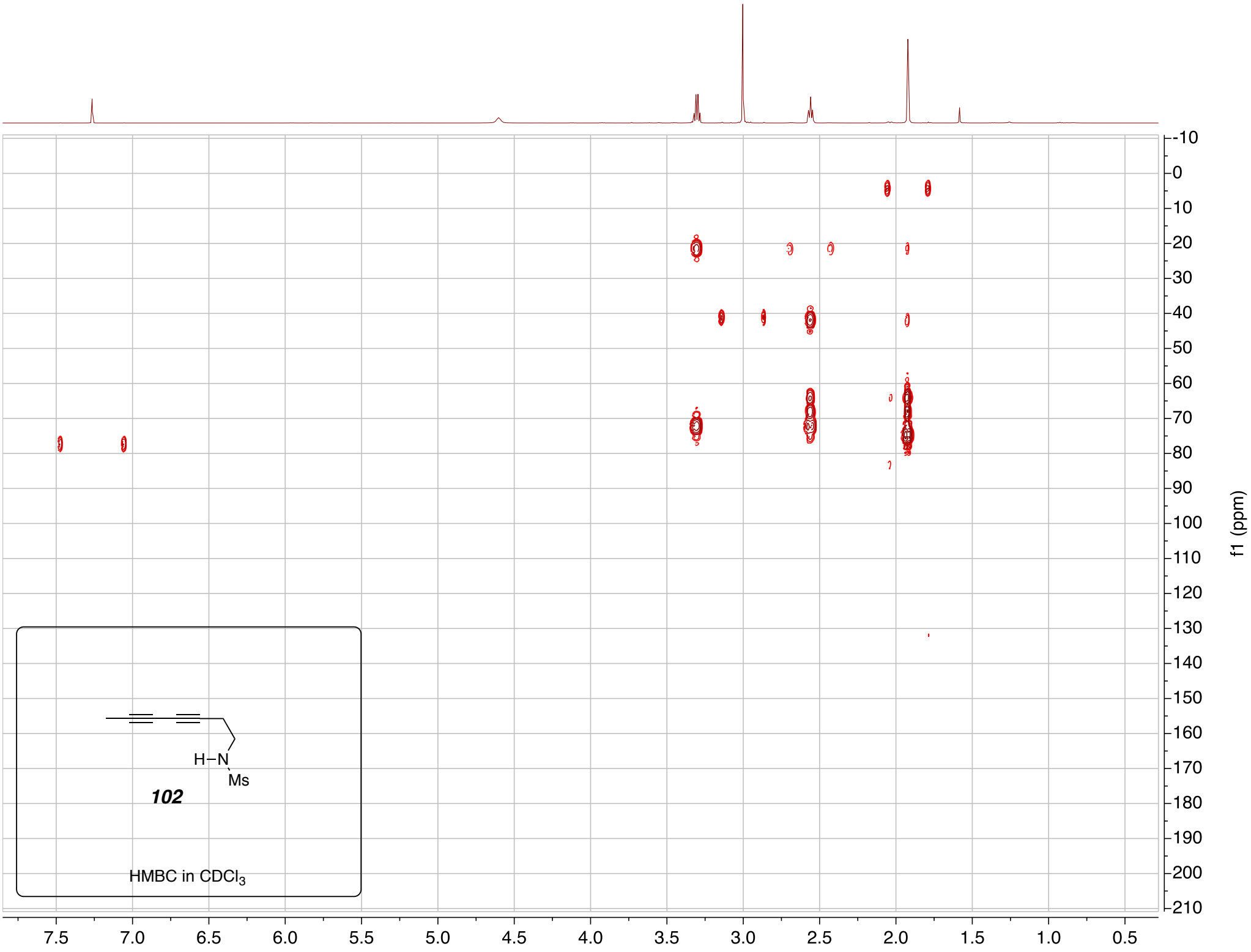


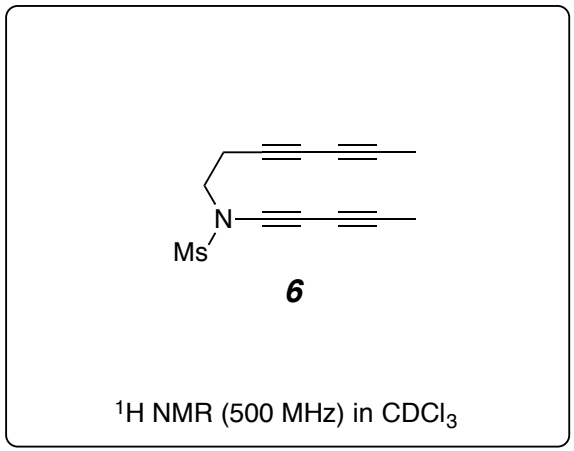
102

^{1}H NMR (500 MHz) in $CDCl_3$



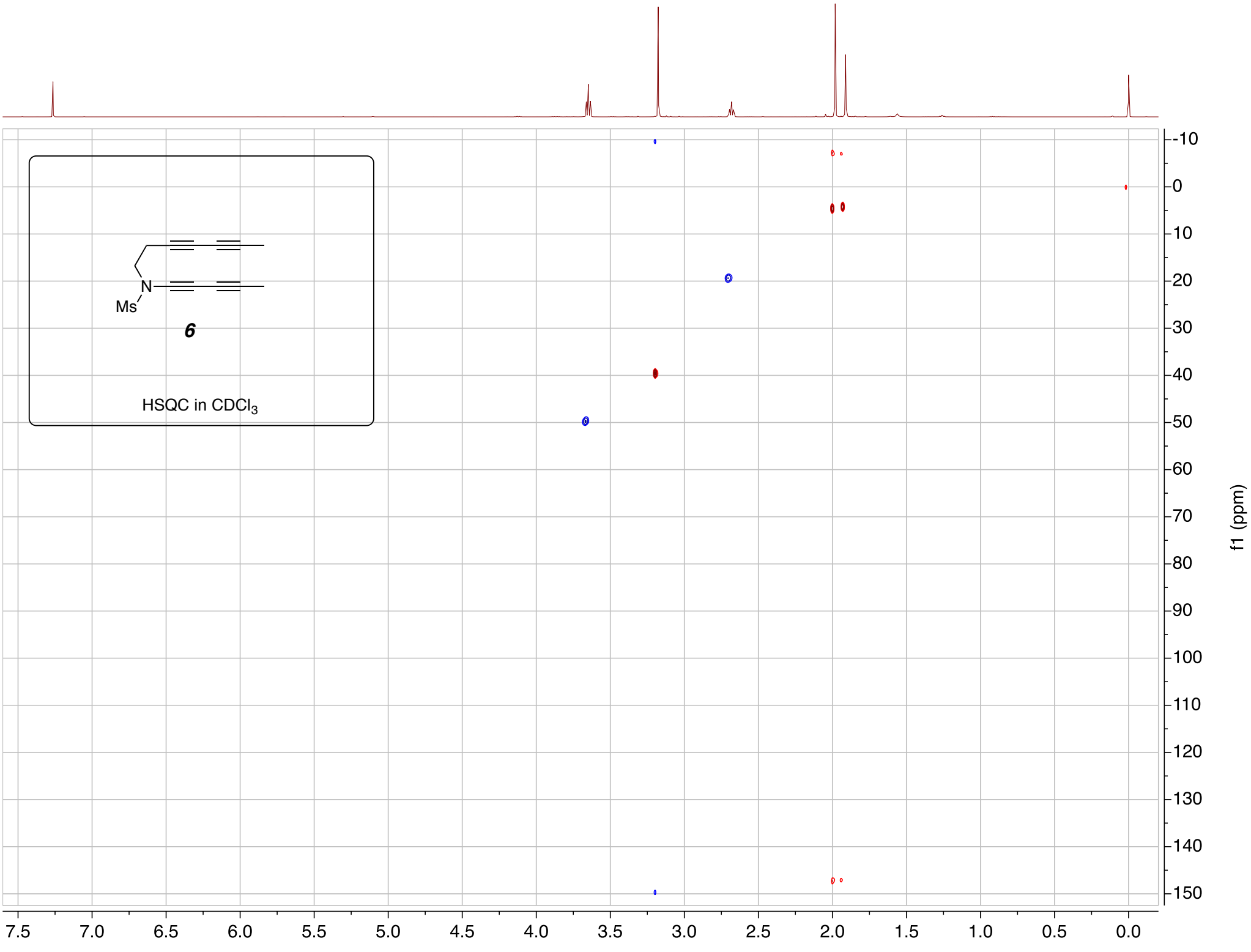

H–N
Ms
102
HSQC in CDCl3
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

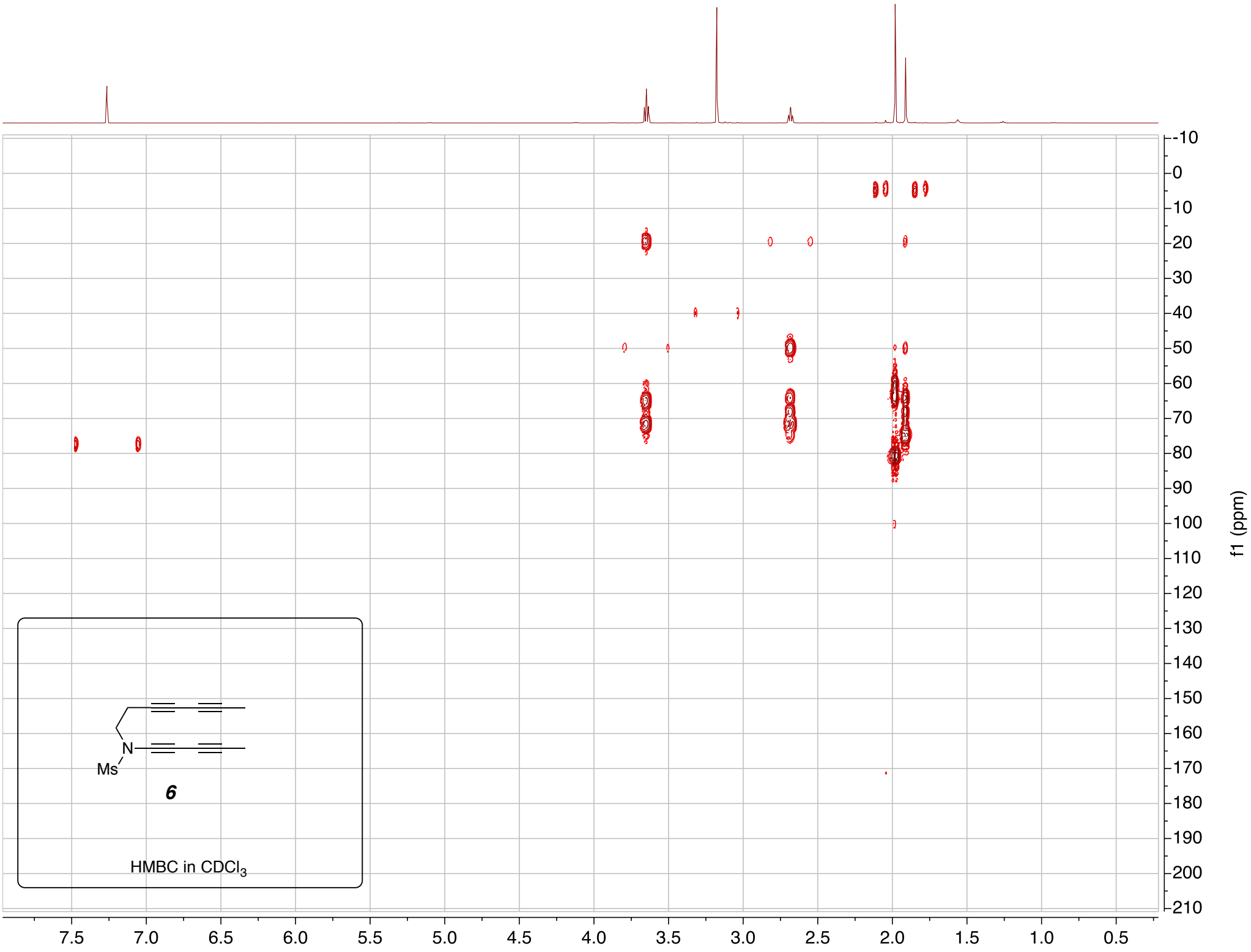

H–N
Ms
102
HMBC in CDCl3
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

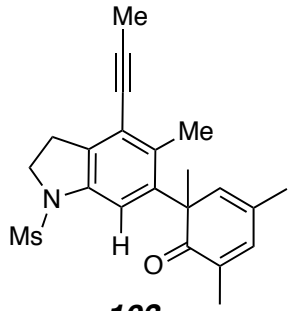


6

^{1}H NMR (500 MHz) in $CDCl_3$

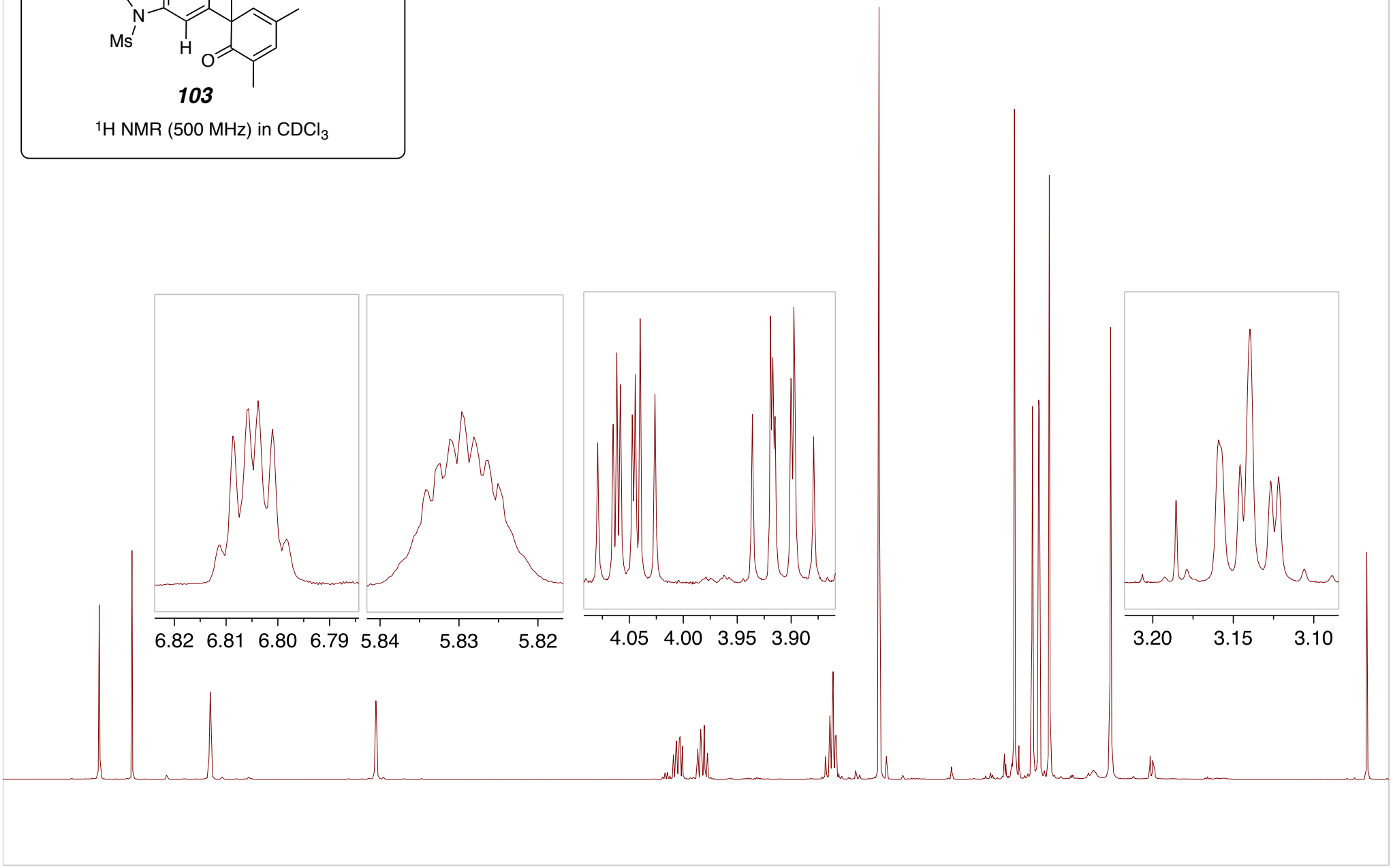

N
Ms
6
HSQC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

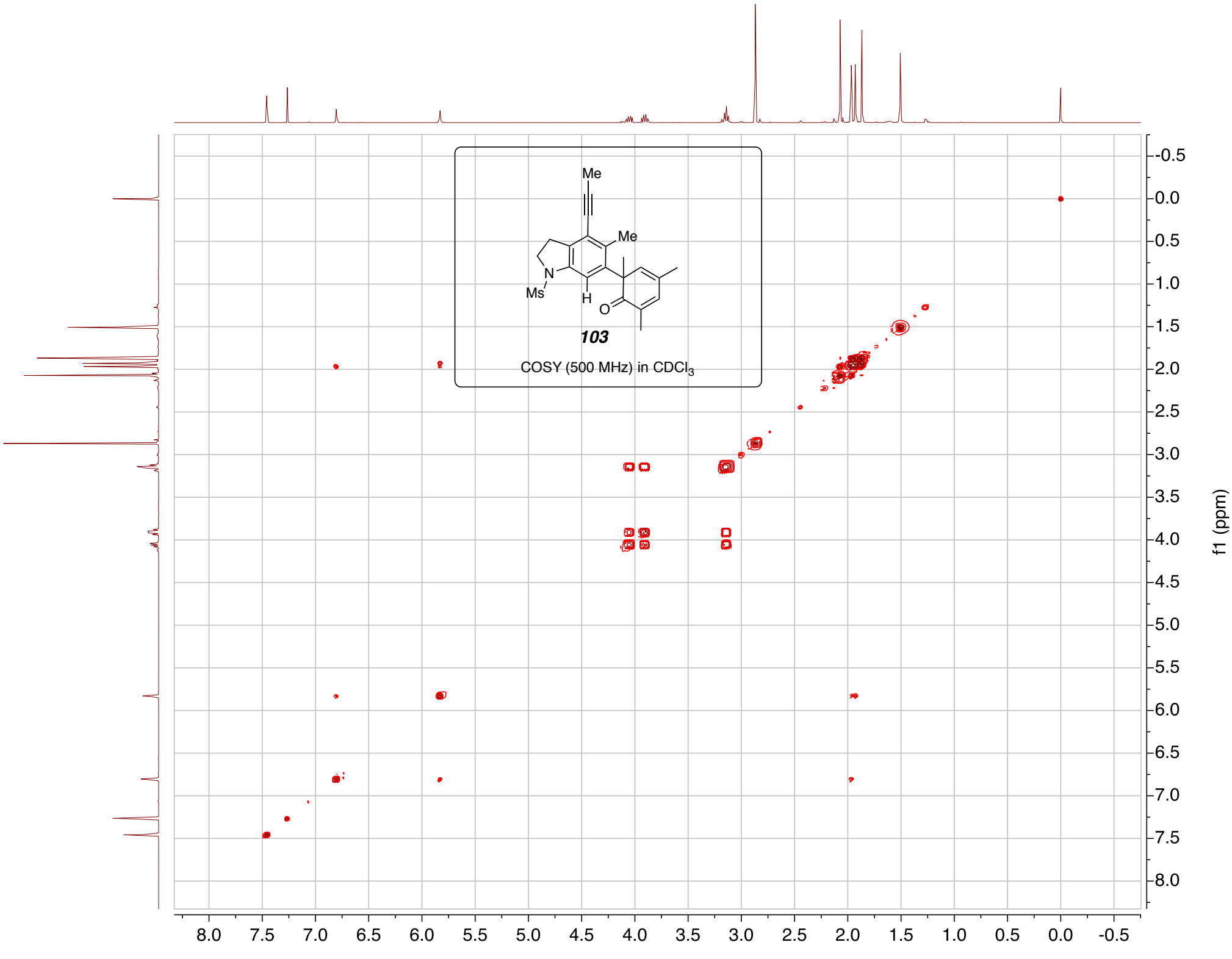

N
Ms
6
HMBC in CDCl3
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

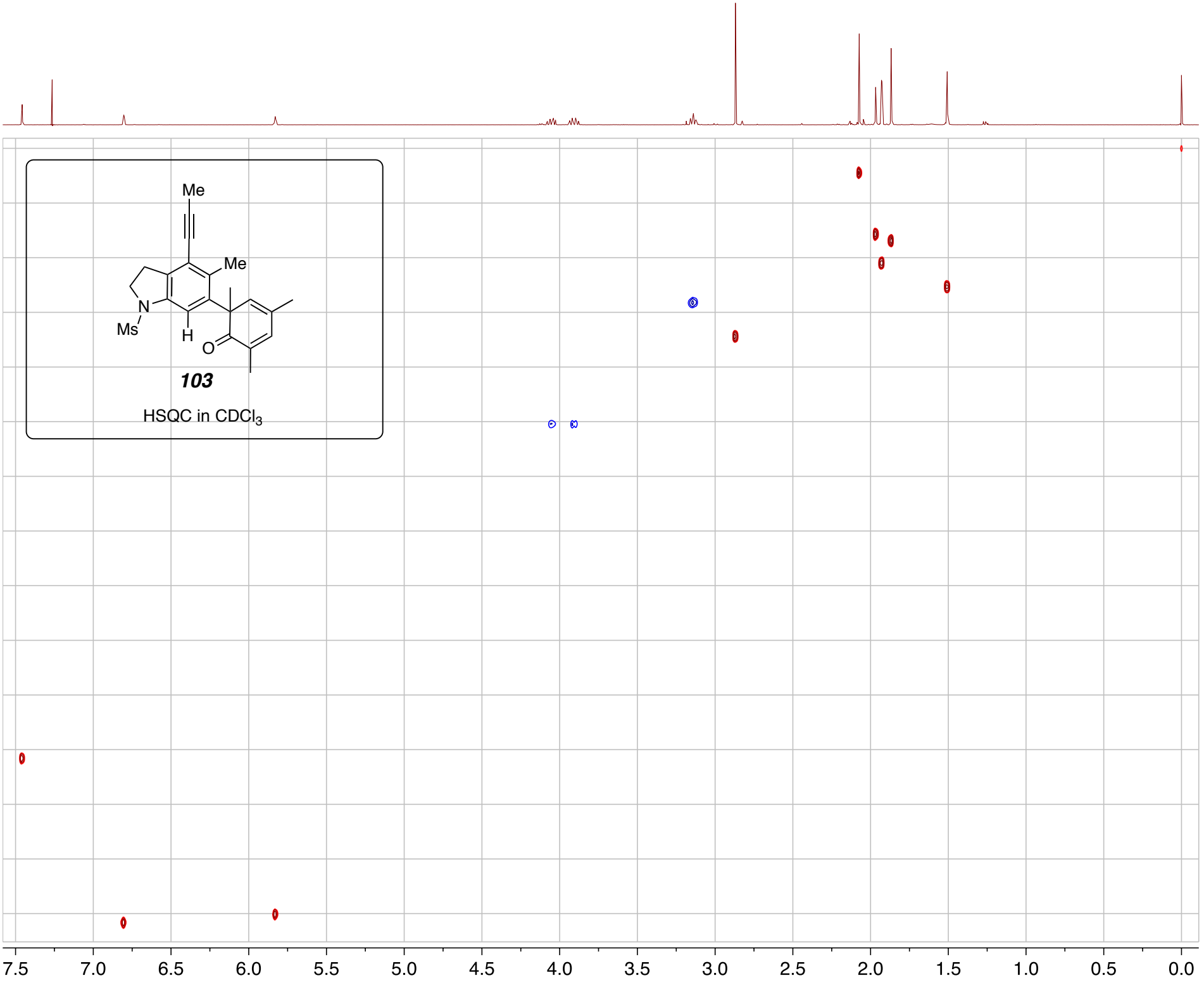


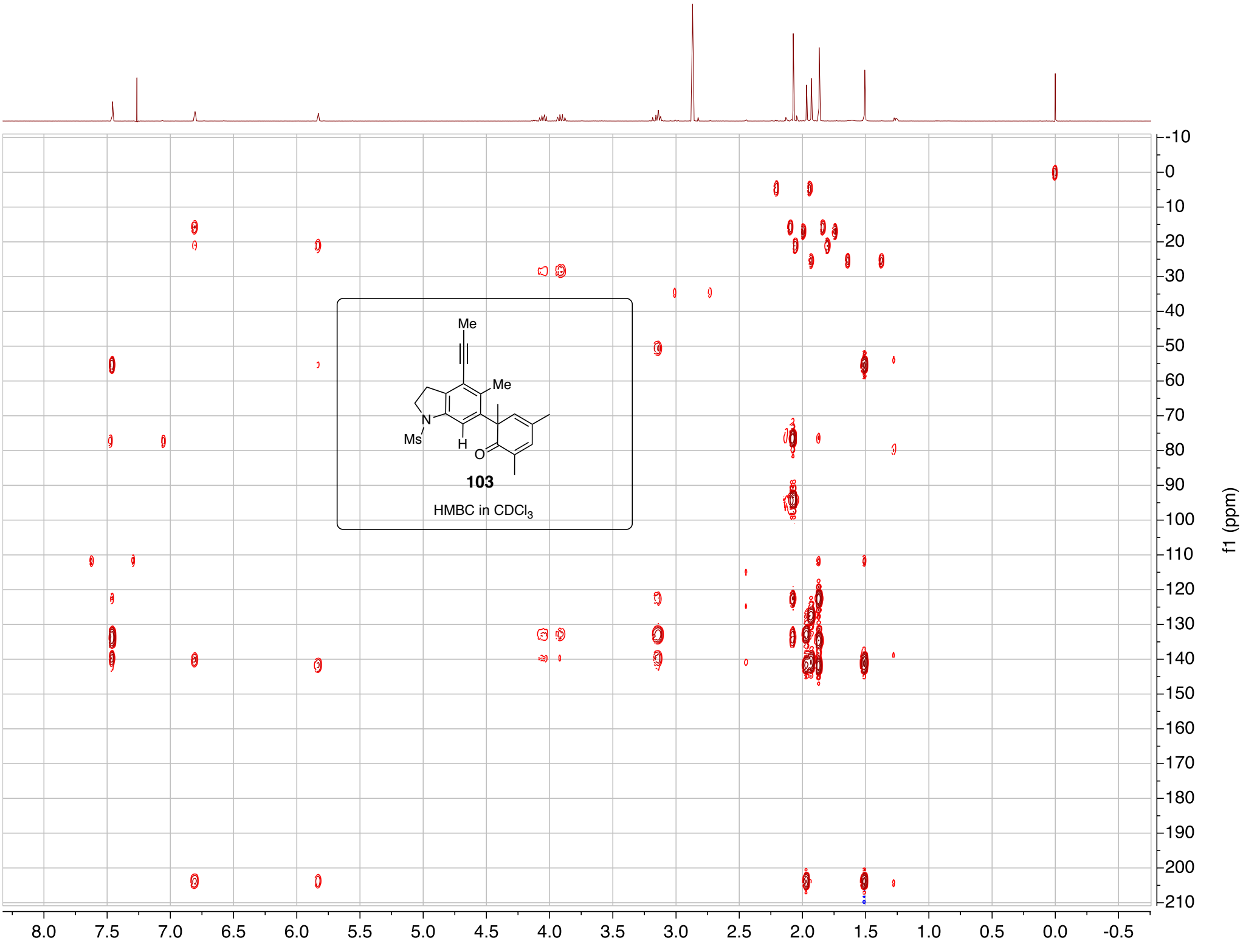
103

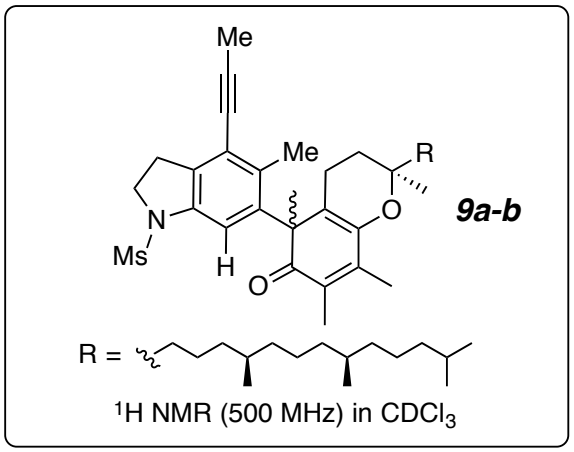
^{1}H NMR (500 MHz) in $CDCl_3$




Me
Me
N
Ms
H
O
103
COSY (500 MHz) in CDCl3
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

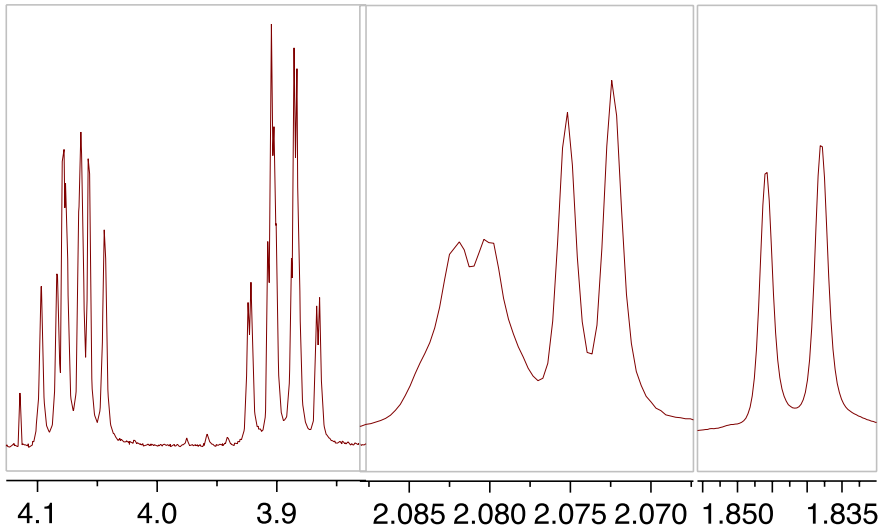

Me
Me
N
Ms
H
O
103
HSQC in CDCl3
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

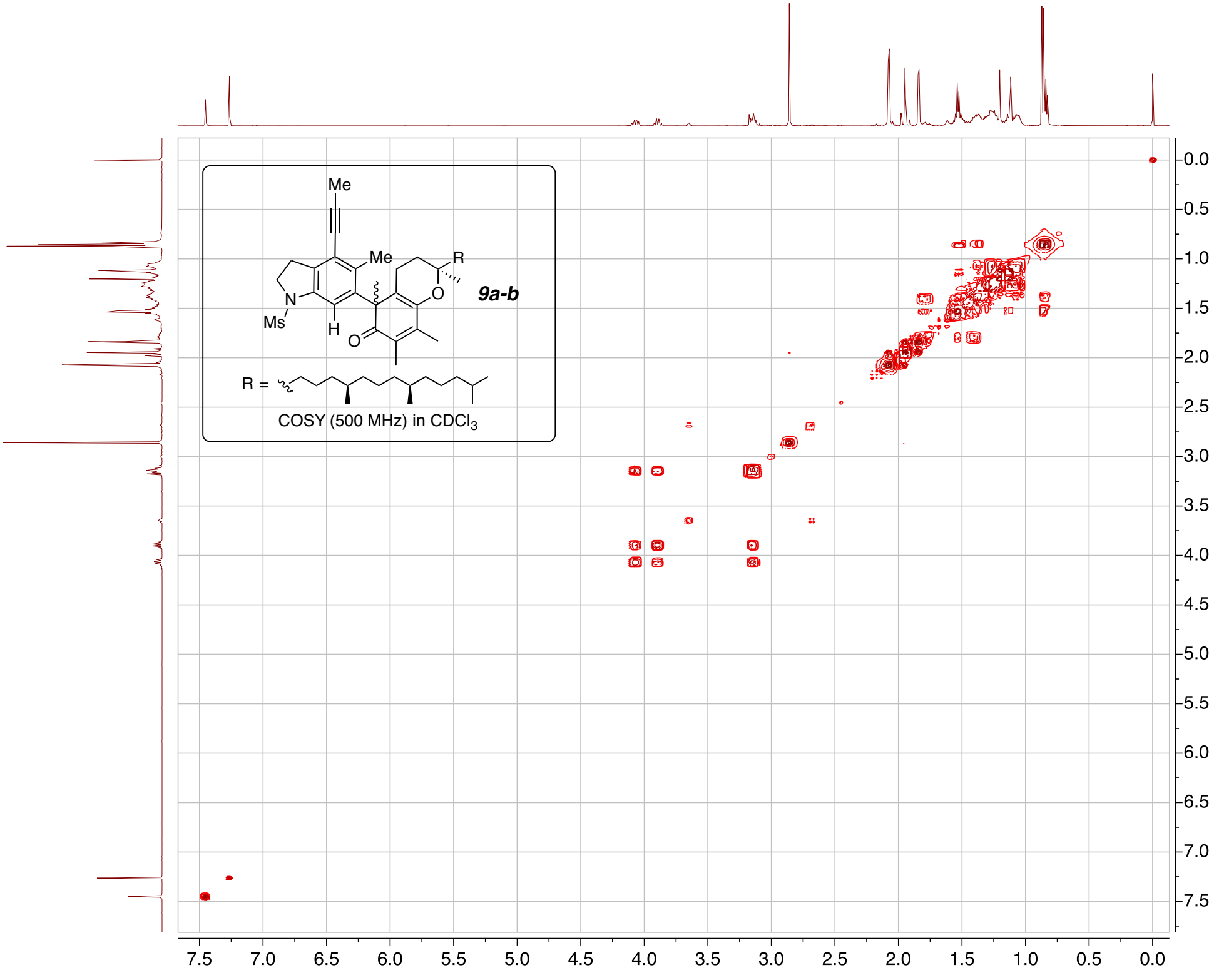

Me
Me
N
Ms
H
O
103
HMBC in CDCl3
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

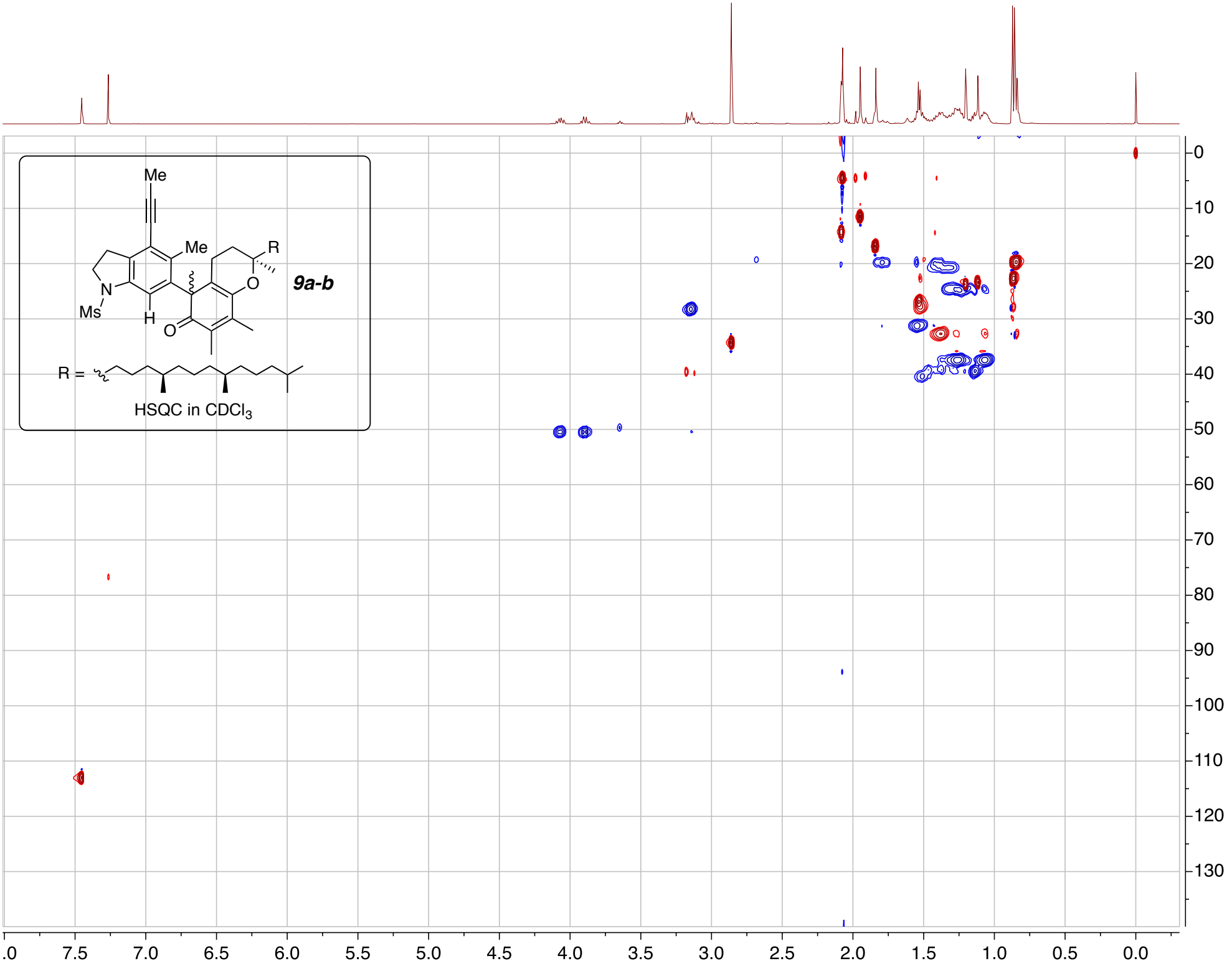


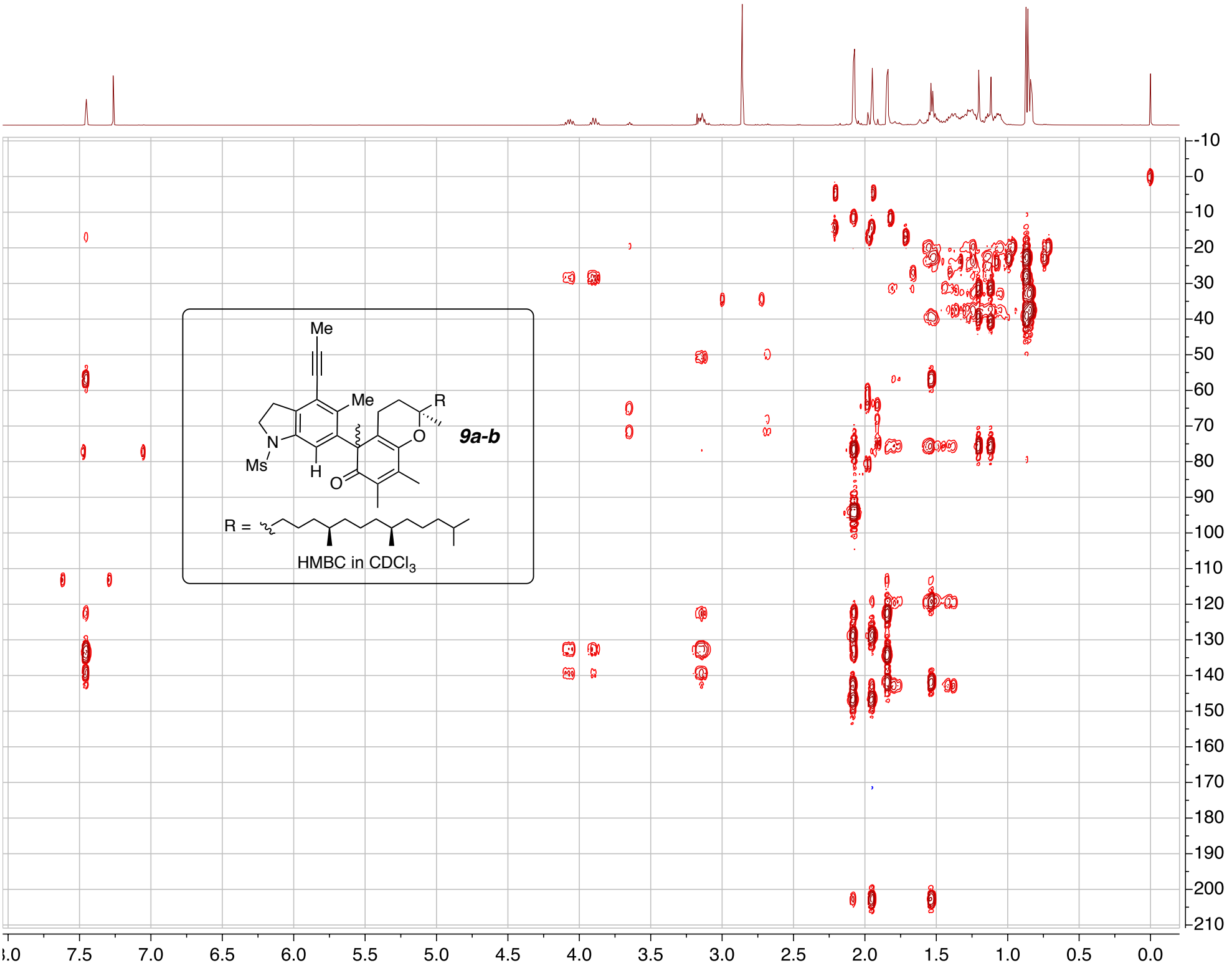
9a-b

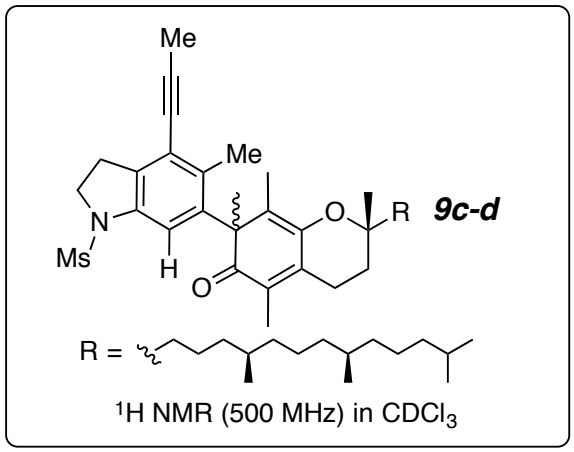
^{1}H NMR (500 MHz) in $CDCl_3$




Me
Me
R
N
Ms
H
O
O
9a-b
R =
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

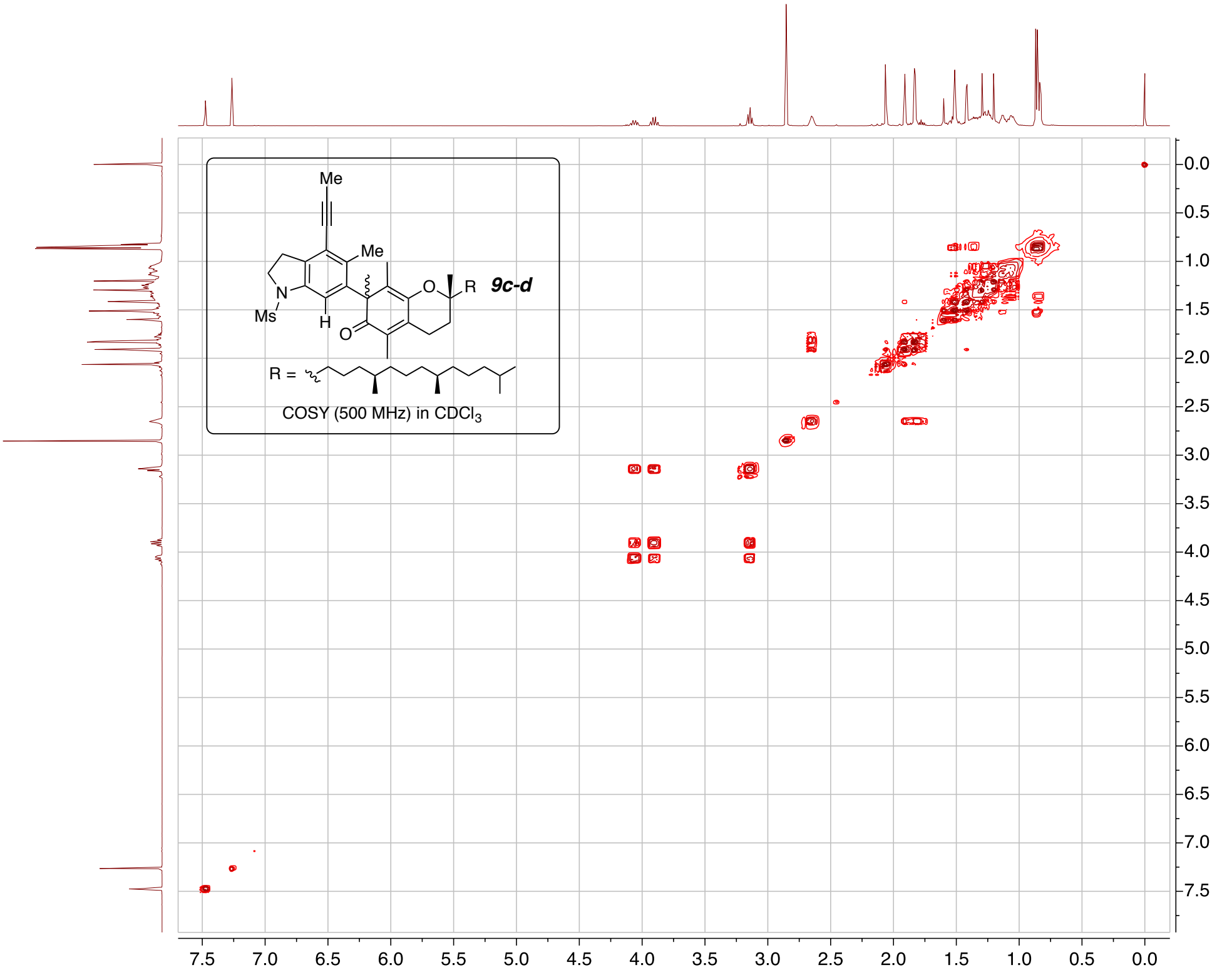

Me
Me
R
N
Ms
H
O
O
9a-b
R =
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

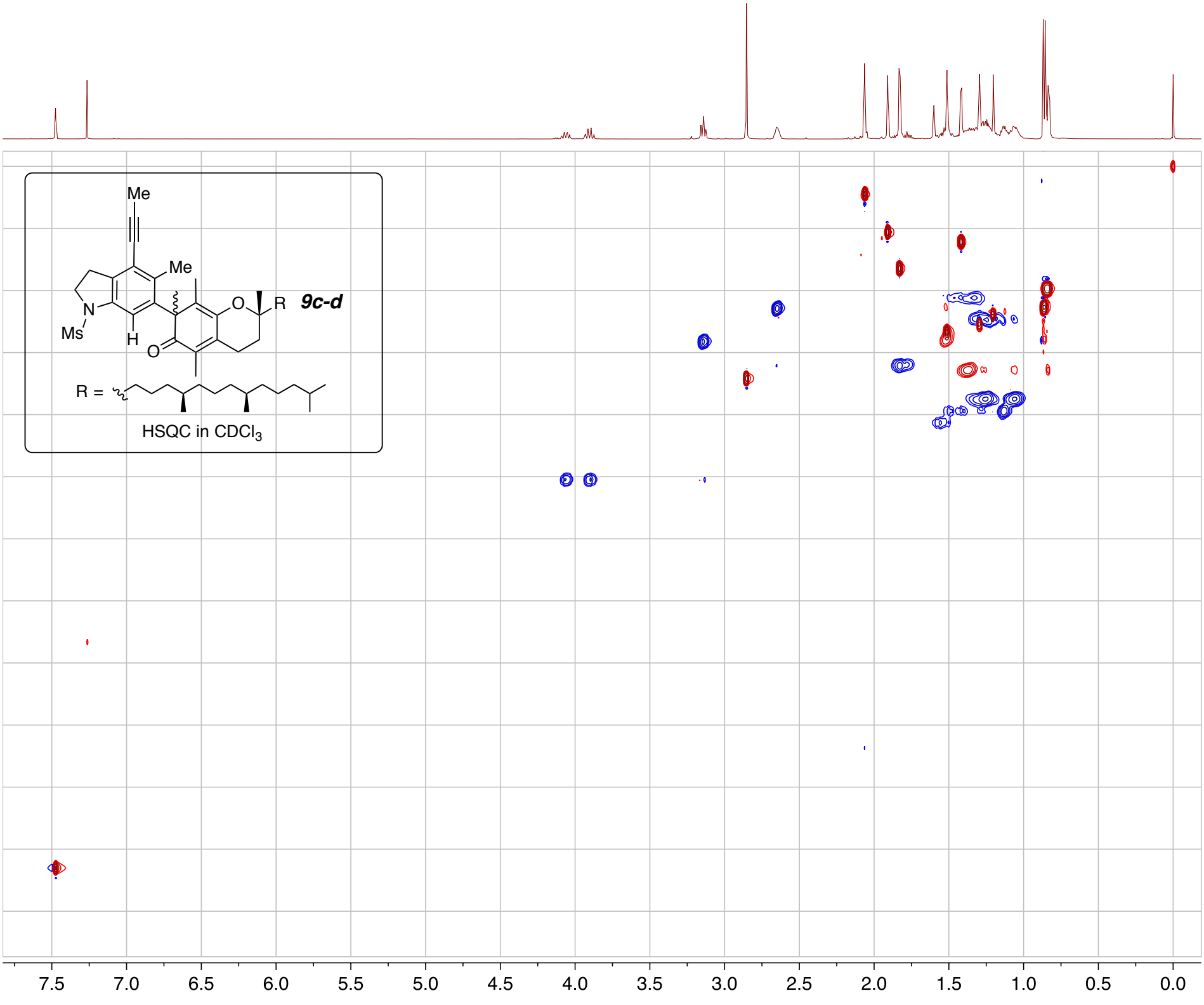

Me
Me
R
N
Ms
H
O
O
9a-b
R =
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

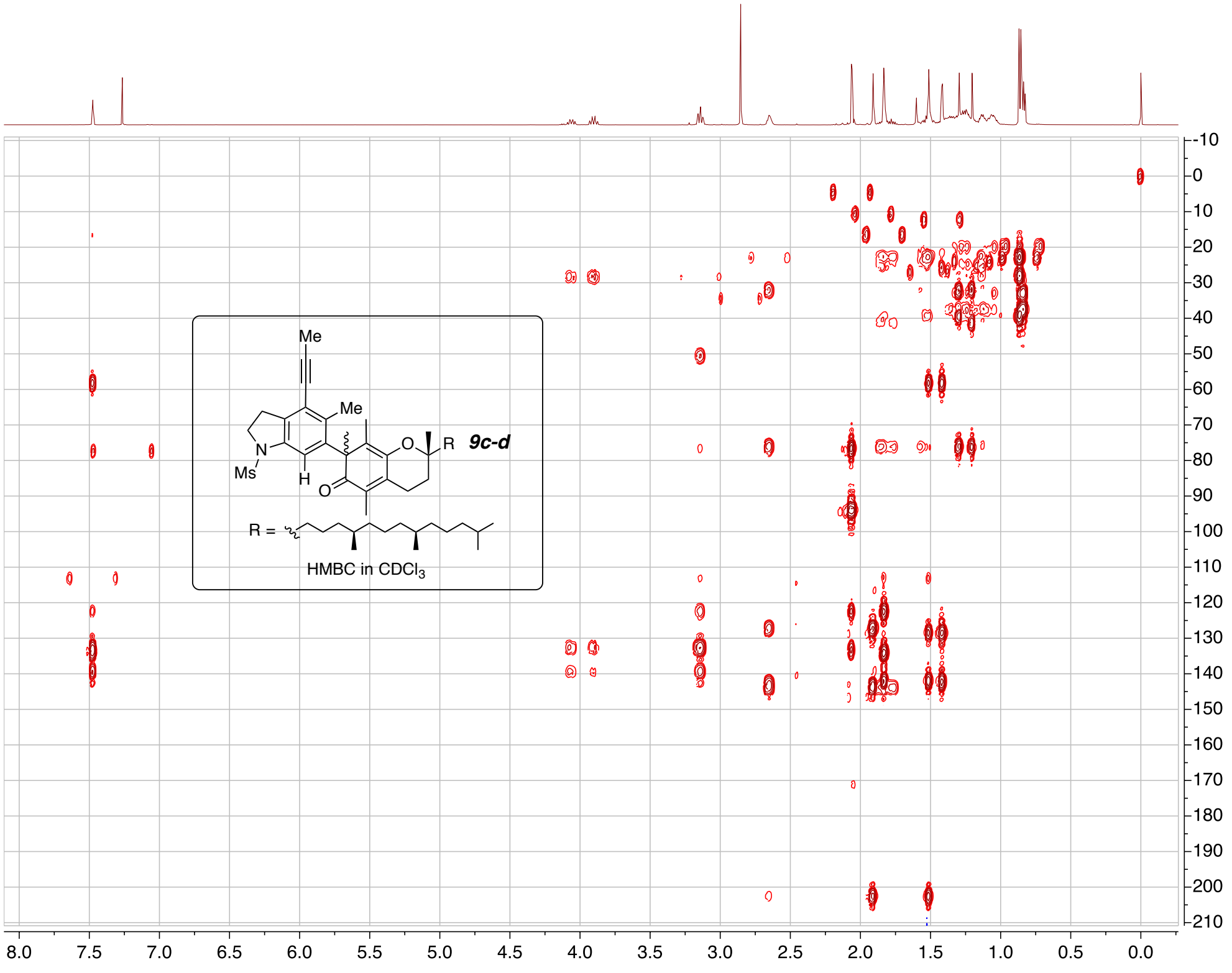


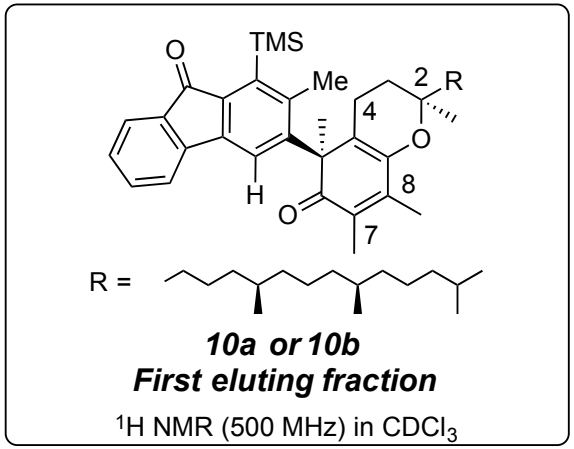
9c-d

^{1}H NMR (500 MHz) in $CDCl_3$

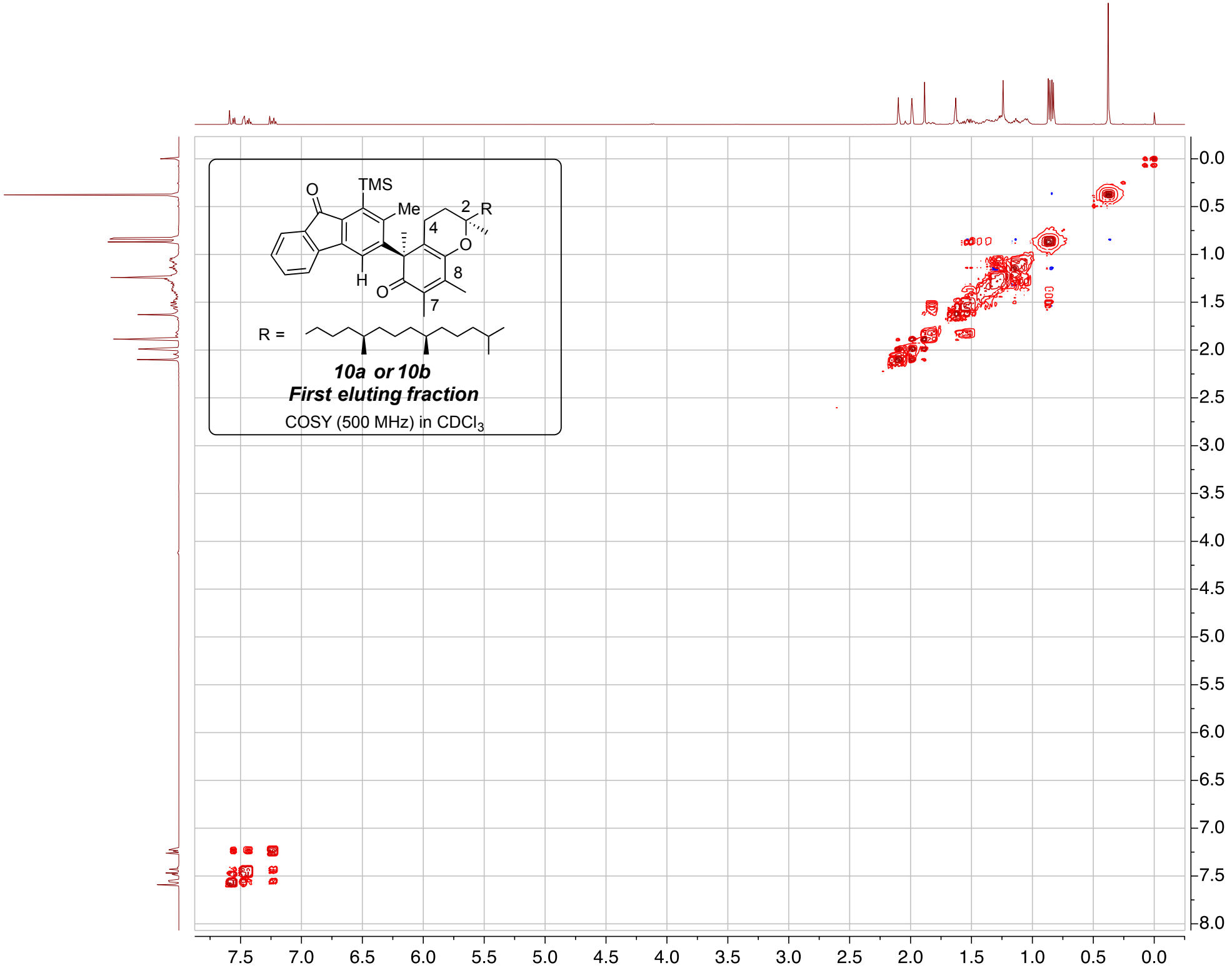

Me
Me
N
Ms
H
O
O
R
9c-d
R =
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

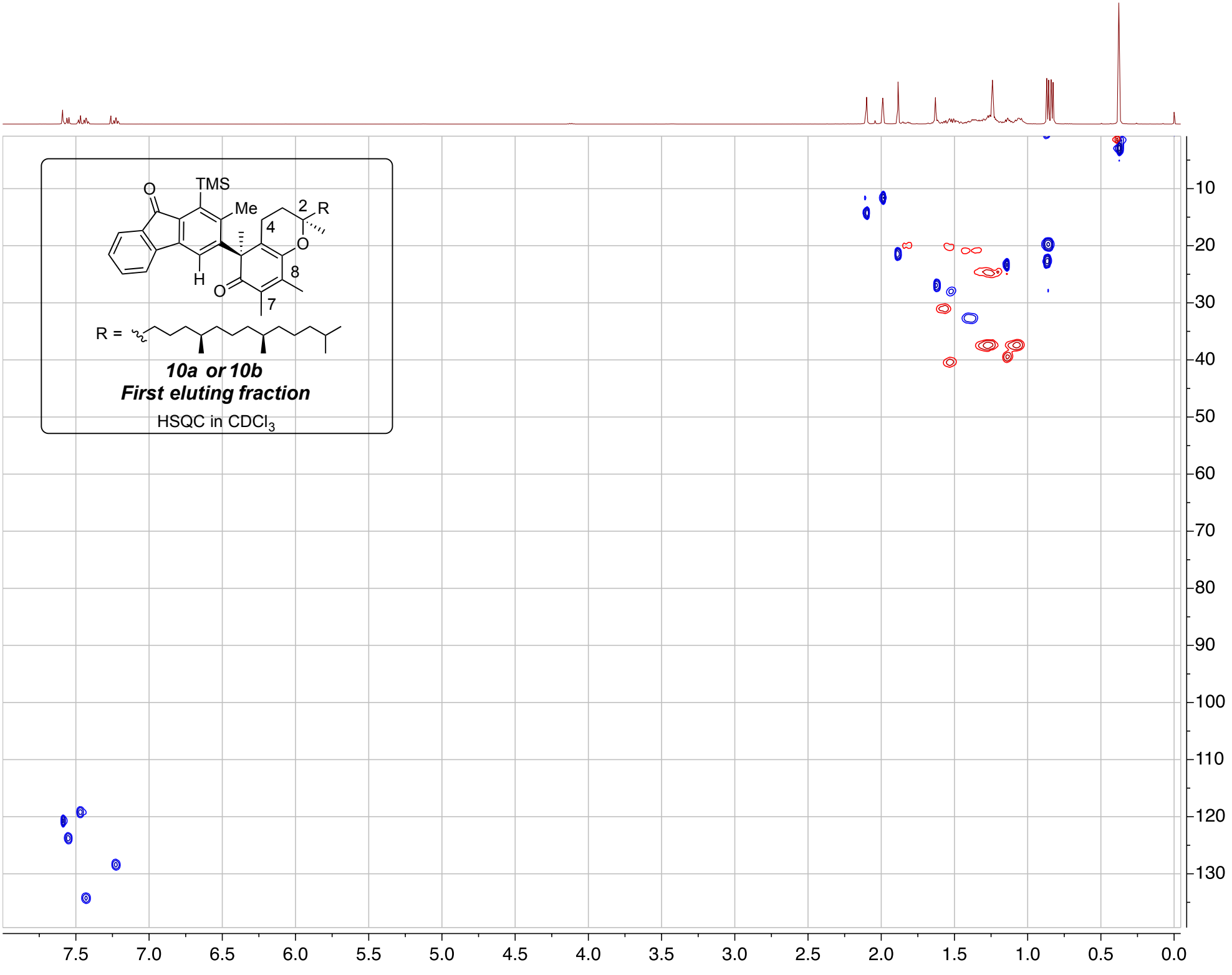

Me
Me
N
Ms
H
O
O
R
9c-d
R =
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

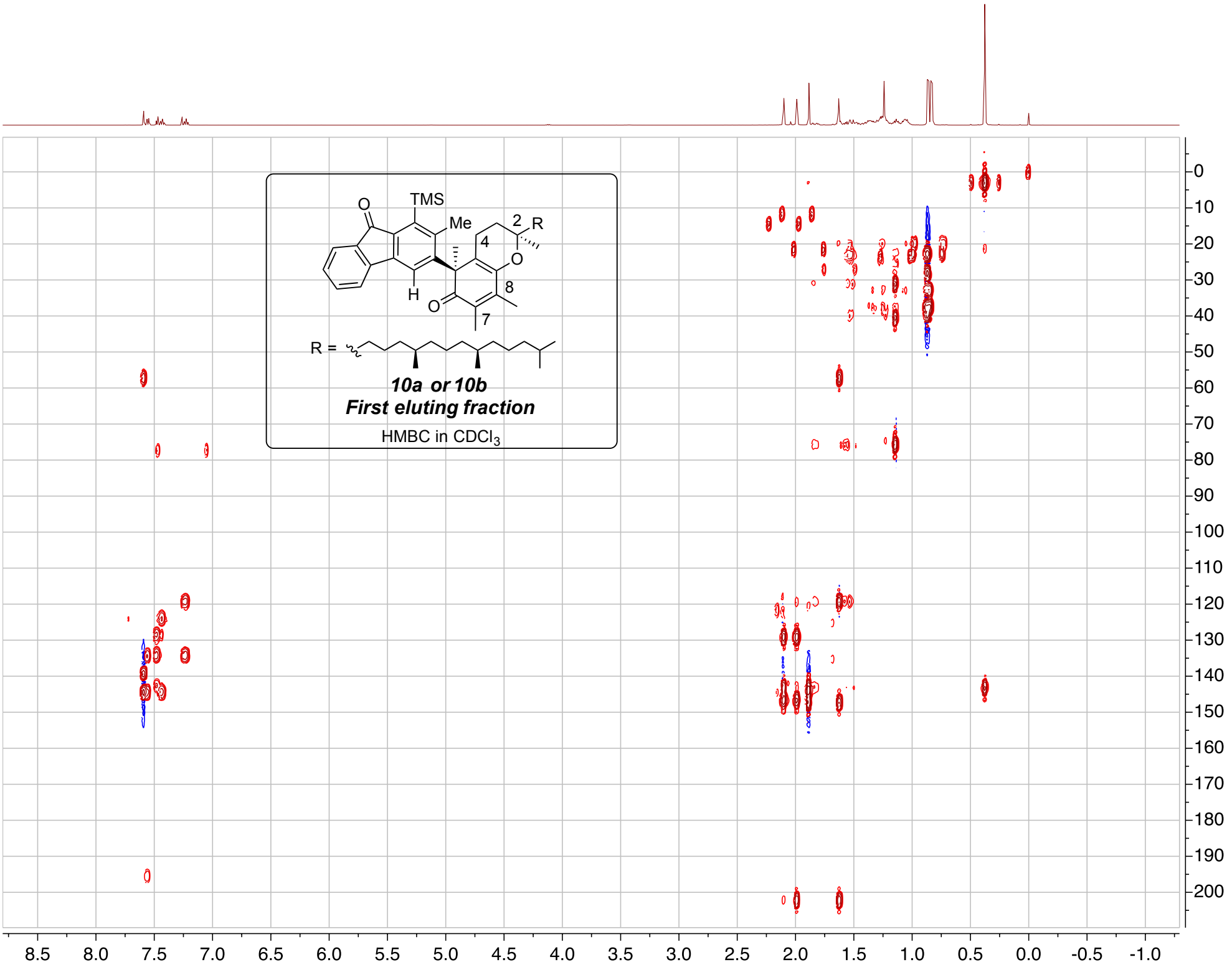

Me
Me
N
Ms
H
O
O
R
9c-d
R =
HMBC in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

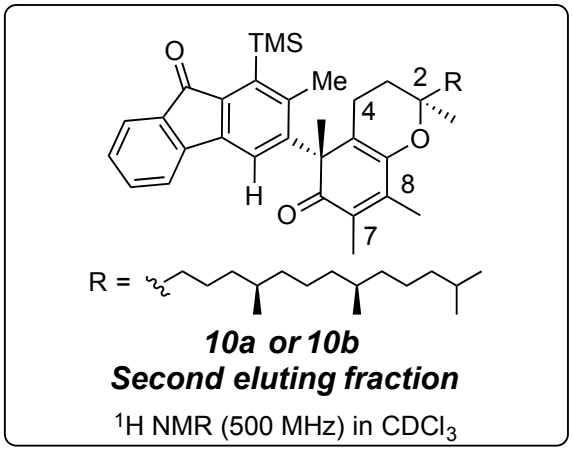


10a or 10b
First eluting fraction
^{1}H NMR (500 MHz) in $CDCl_3$


TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
First eluting fraction
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

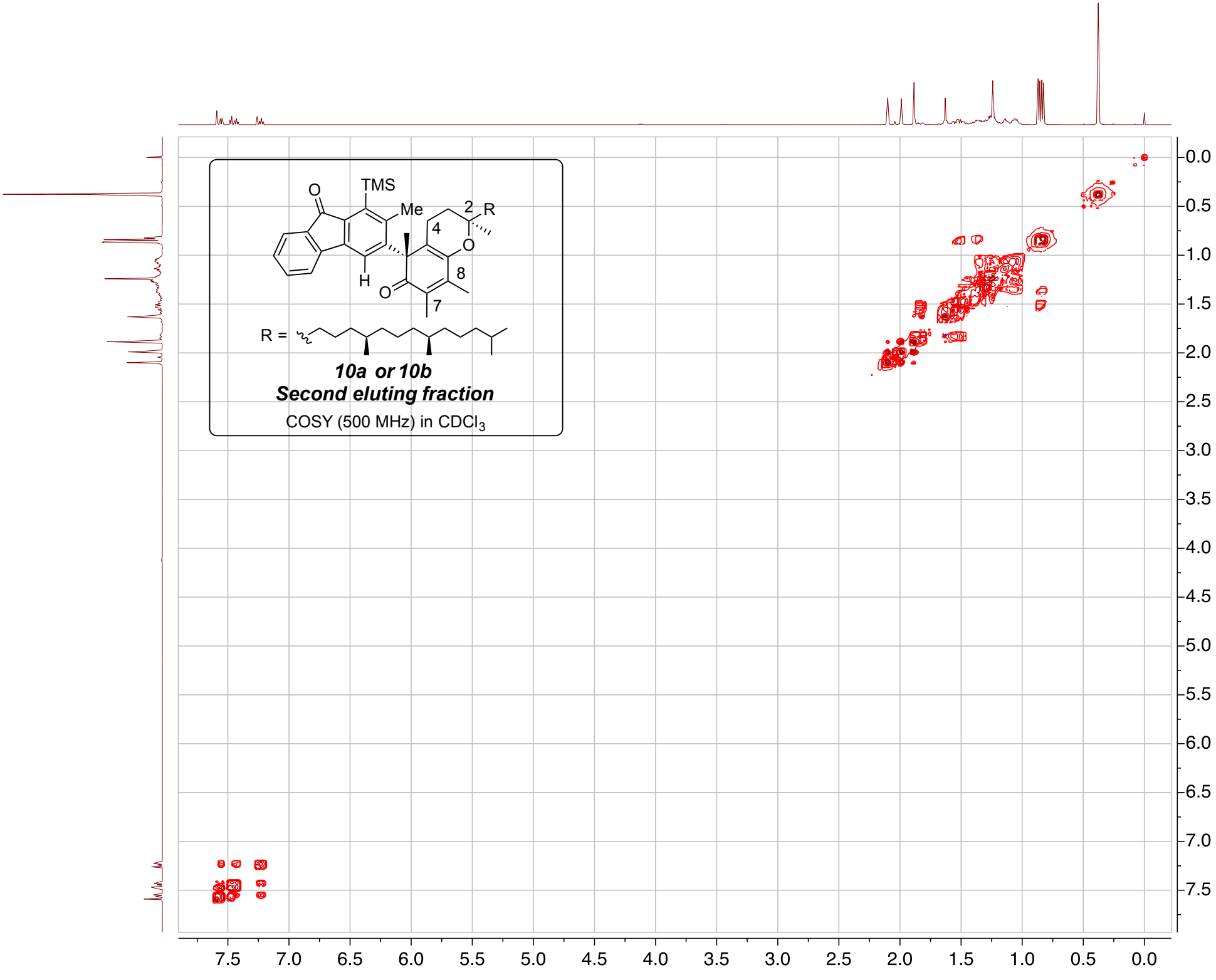

TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
First eluting fraction
HSQC in CDCl3
10
20
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

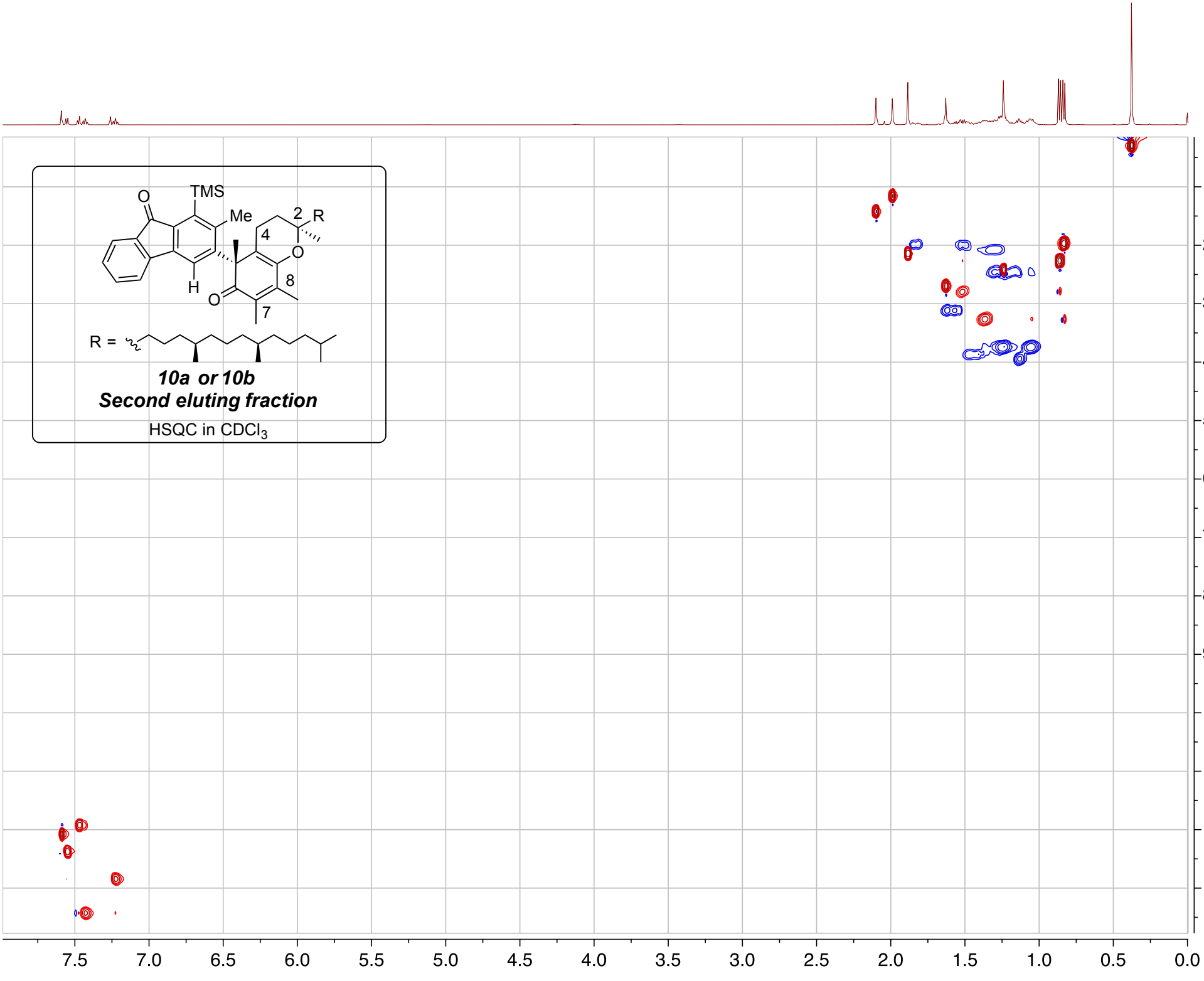

TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
First eluting fraction
HMBC in CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

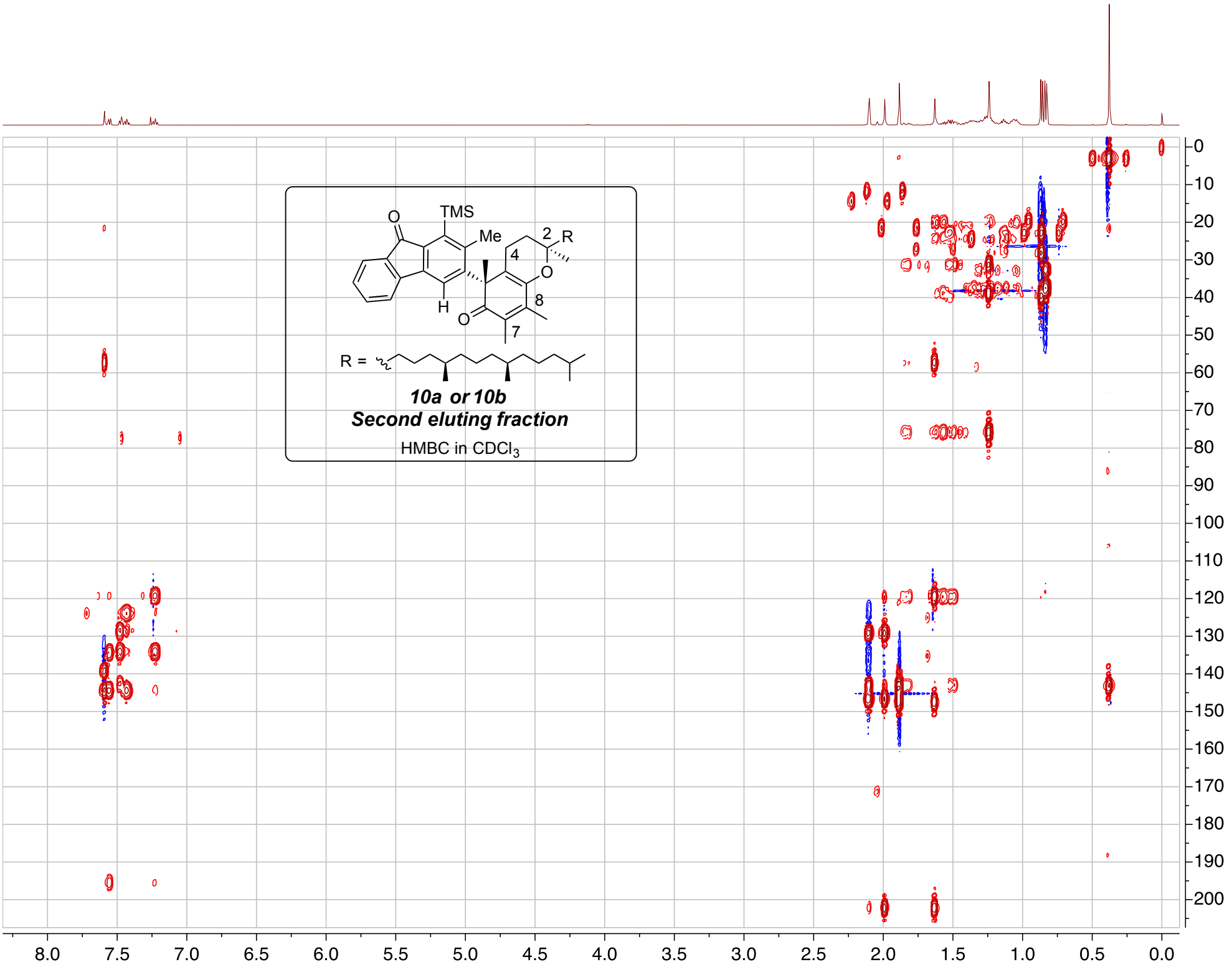


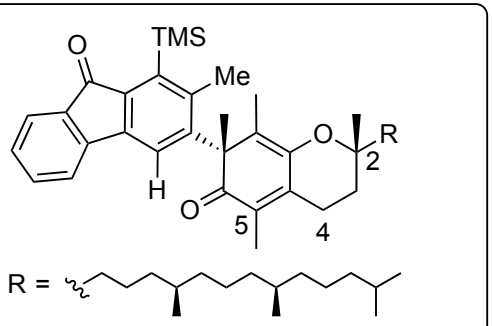
10a or 10b
Second eluting fraction

^{1}H NMR (500 MHz) in $CDCl_3$

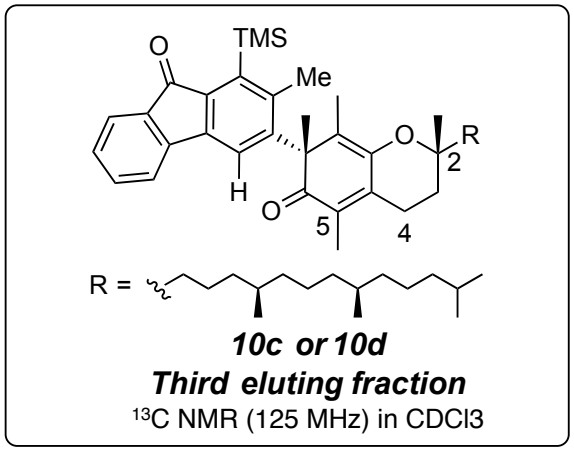

TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
Second eluting fraction
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
Second eluting fraction
HSQC in CDCl3
10
20
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


TMS
Me
2
R
4
O
8
H
O
7
R =
10a or 10b
Second eluting fraction
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



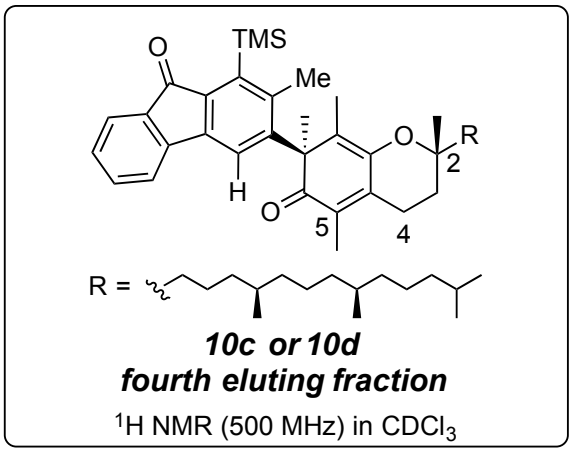
10c or 10d
Third eluting fraction
^{1}H NMR (500 MHz) in $CDCl_3$



10c or 10d

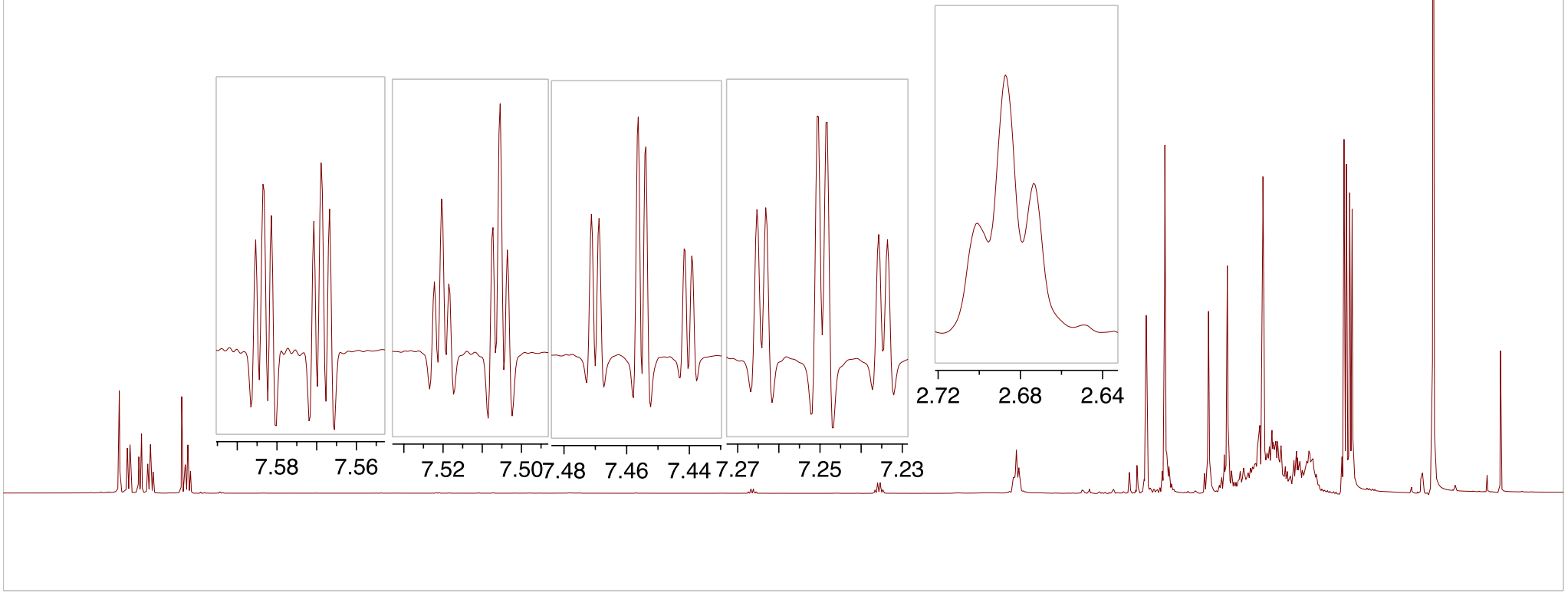
Third eluting fraction

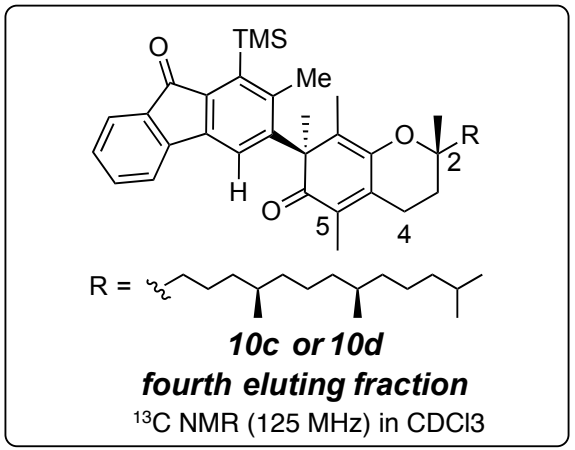
^{13}C NMR (125 MHz) in CDCl3



10c or 10d
fourth eluting fraction

^{1}H NMR (500 MHz) in $CDCl_3$

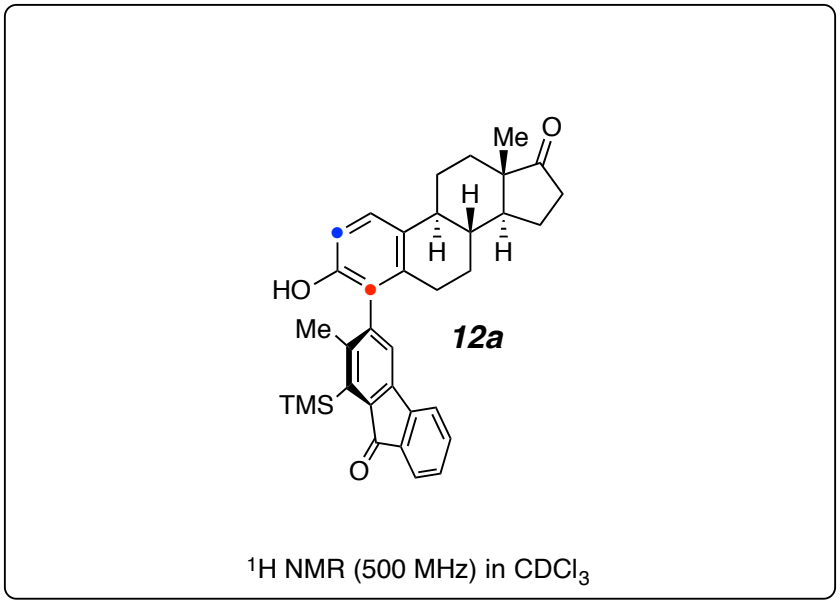


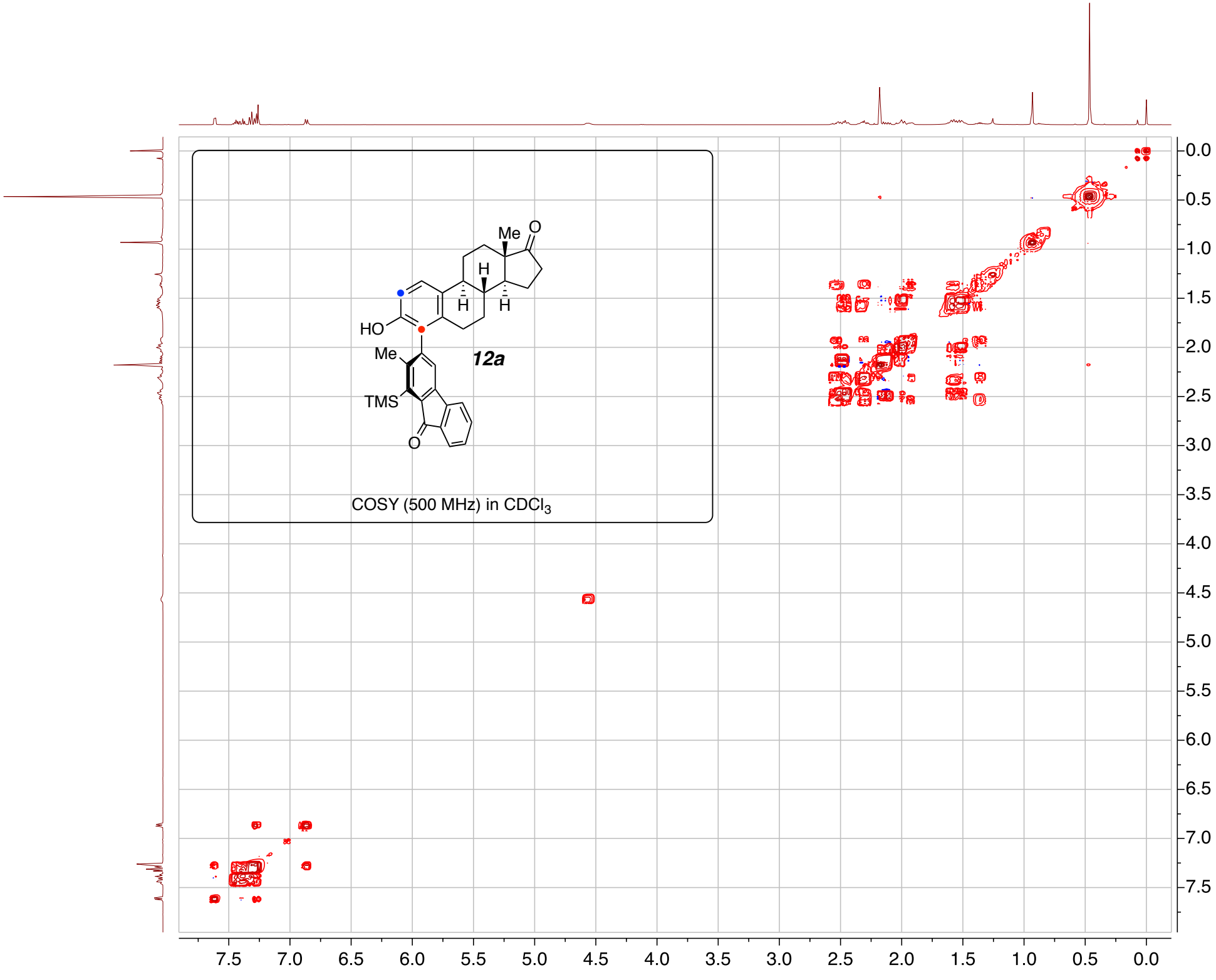


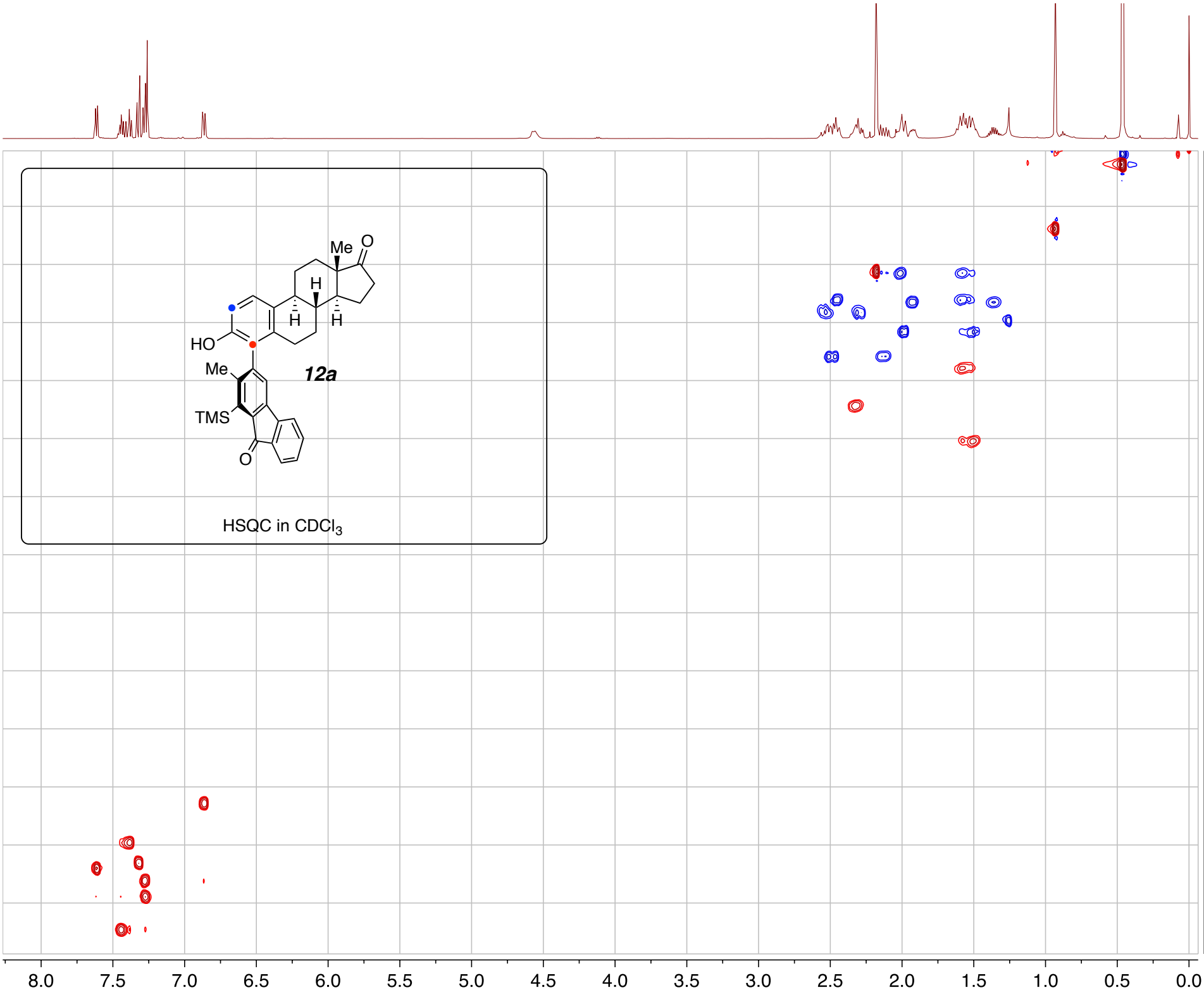
10c or 10d

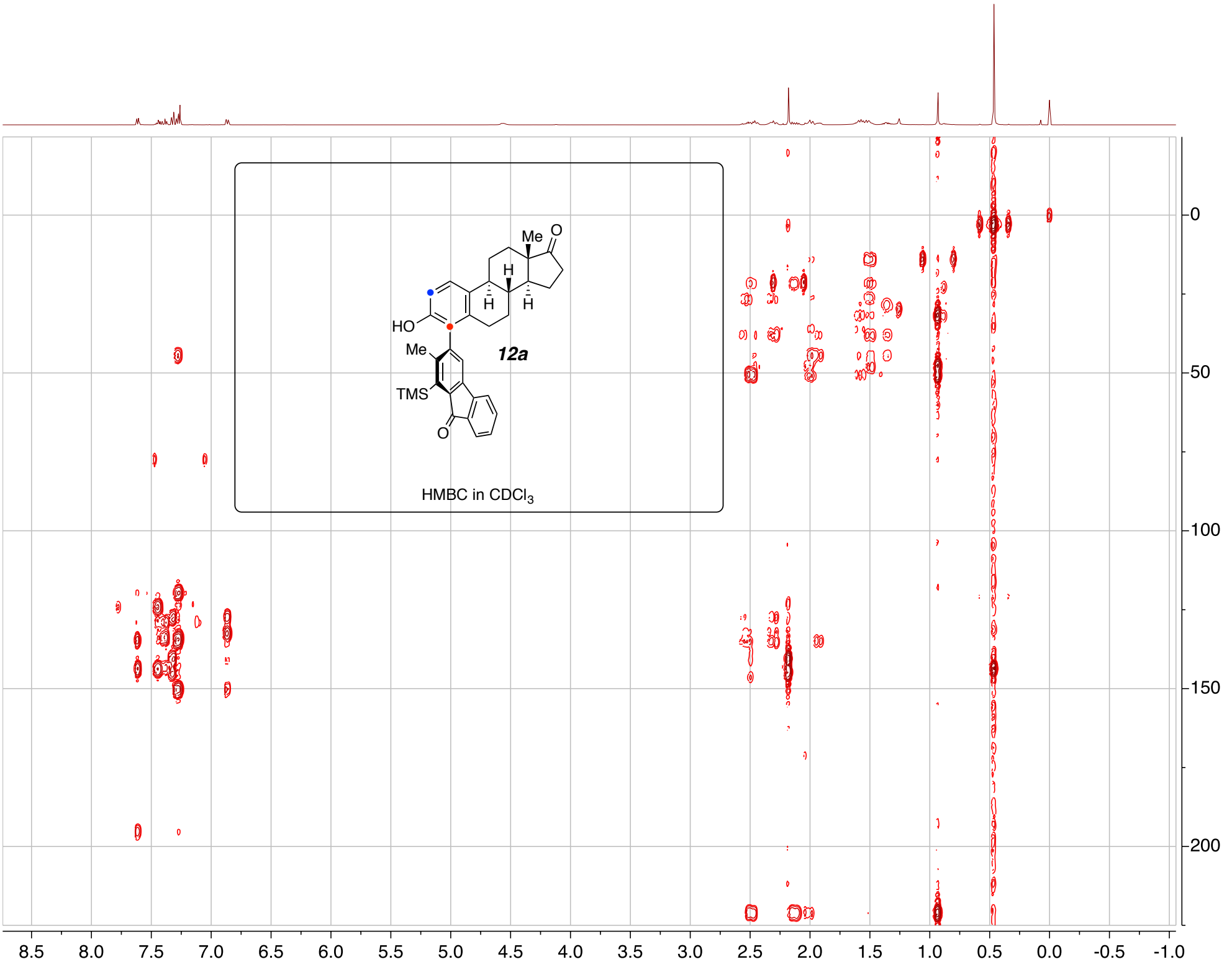
fourth eluting fraction

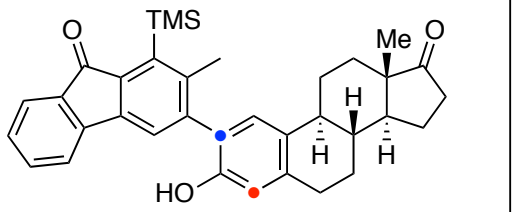
^{13}C NMR (125 MHz) in CDCl3


Me
O
H
H
H
HO
Me
12a
TMS
O
^{1}H NMR (500 MHz) in $CDCl_3$
7.62
7.60
7.45
7.40
7.35
6.88
6.84
2.16
2.12
2.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Me
O
H
H
H
HO
Me
TMS
O
12a
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

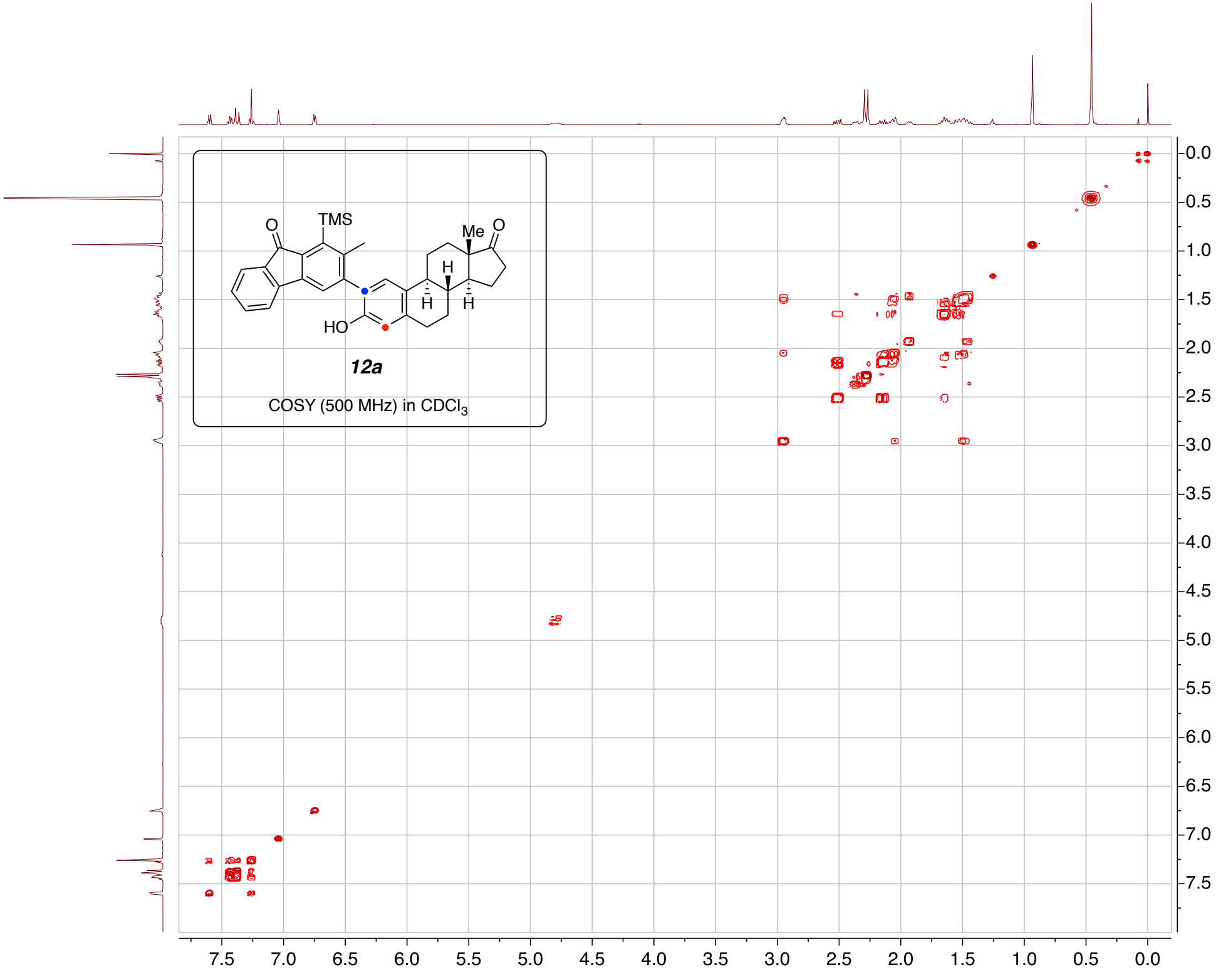

Me
O
H
H
H
HO
Me
TMS
O
12a
HSQC in CDCl3
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

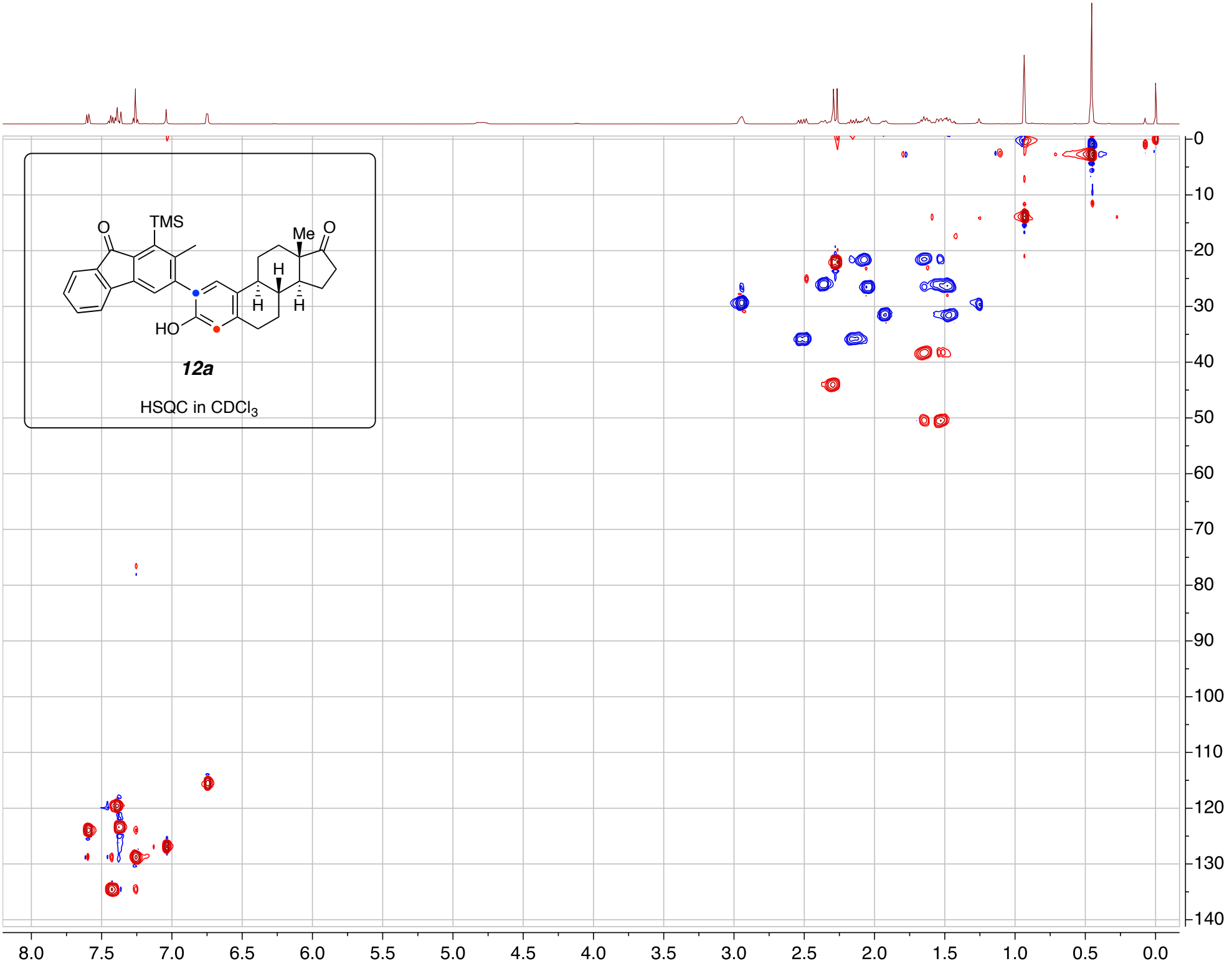

Me
O
H
H
H
HO
Me
TMS
O
12a
HMBC in CDCl3
0
50
100
150
200
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

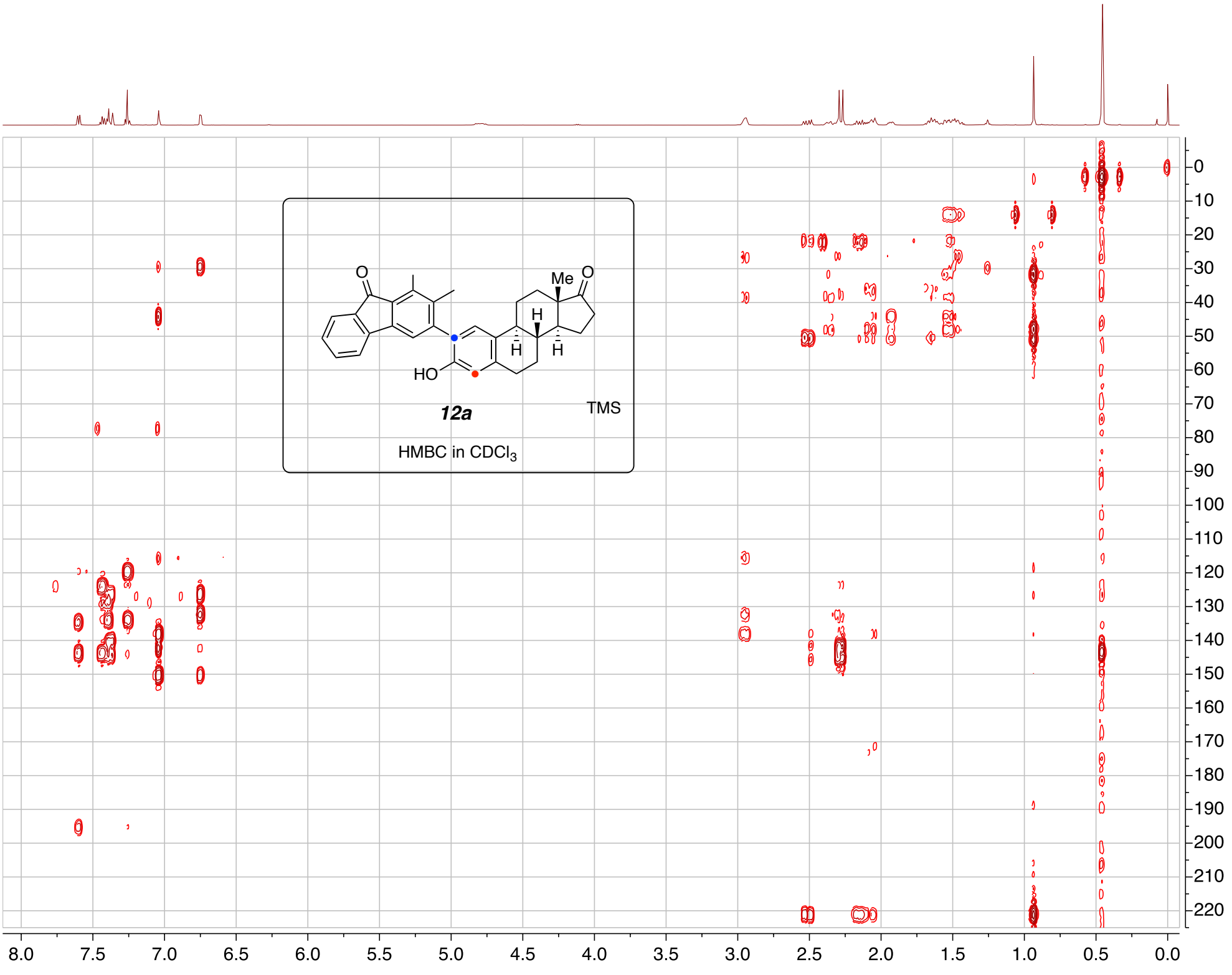


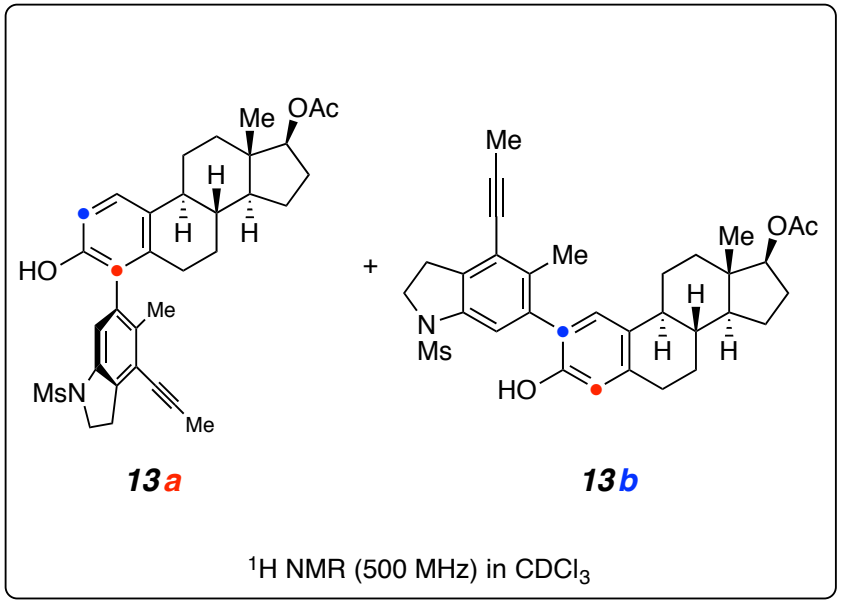
12a

^{1}H NMR (500 MHz) in $CDCl_3$


O
TMS
Me
O
H
H
H
HO
12a
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

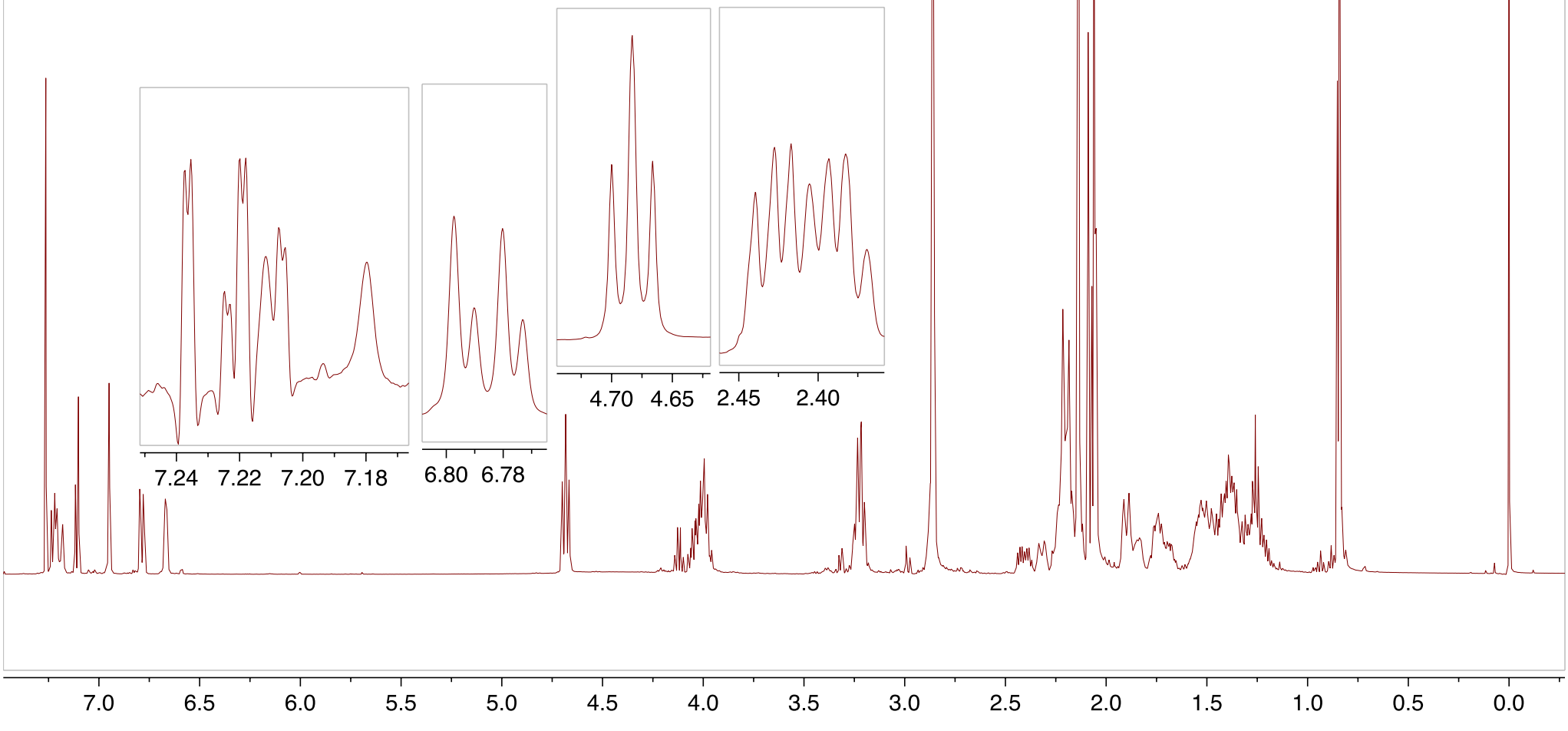

O
TMS
Me
O
H
H
H
HO
12a
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

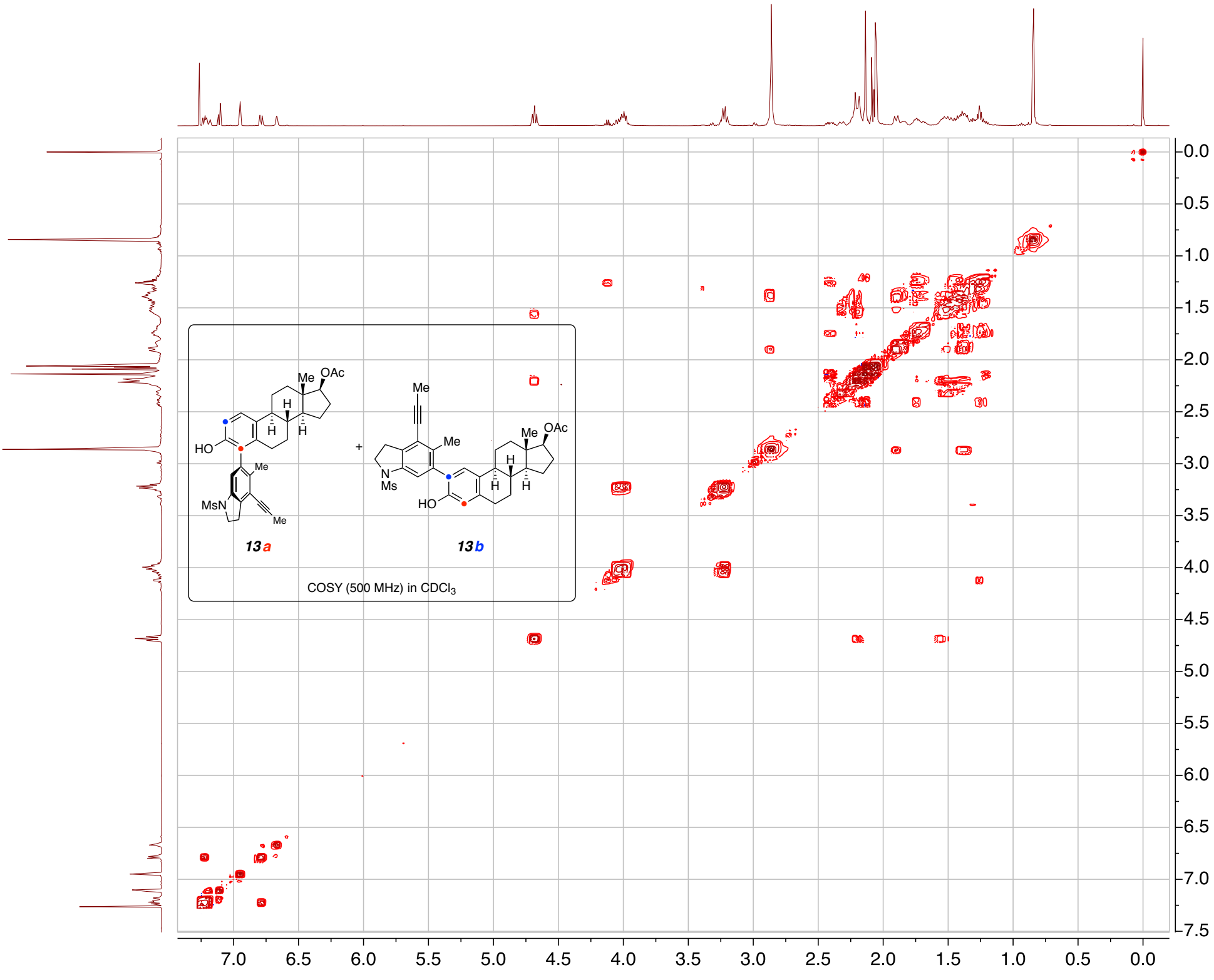

O
Me
O
H
H
H
HO
12a
TMS
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

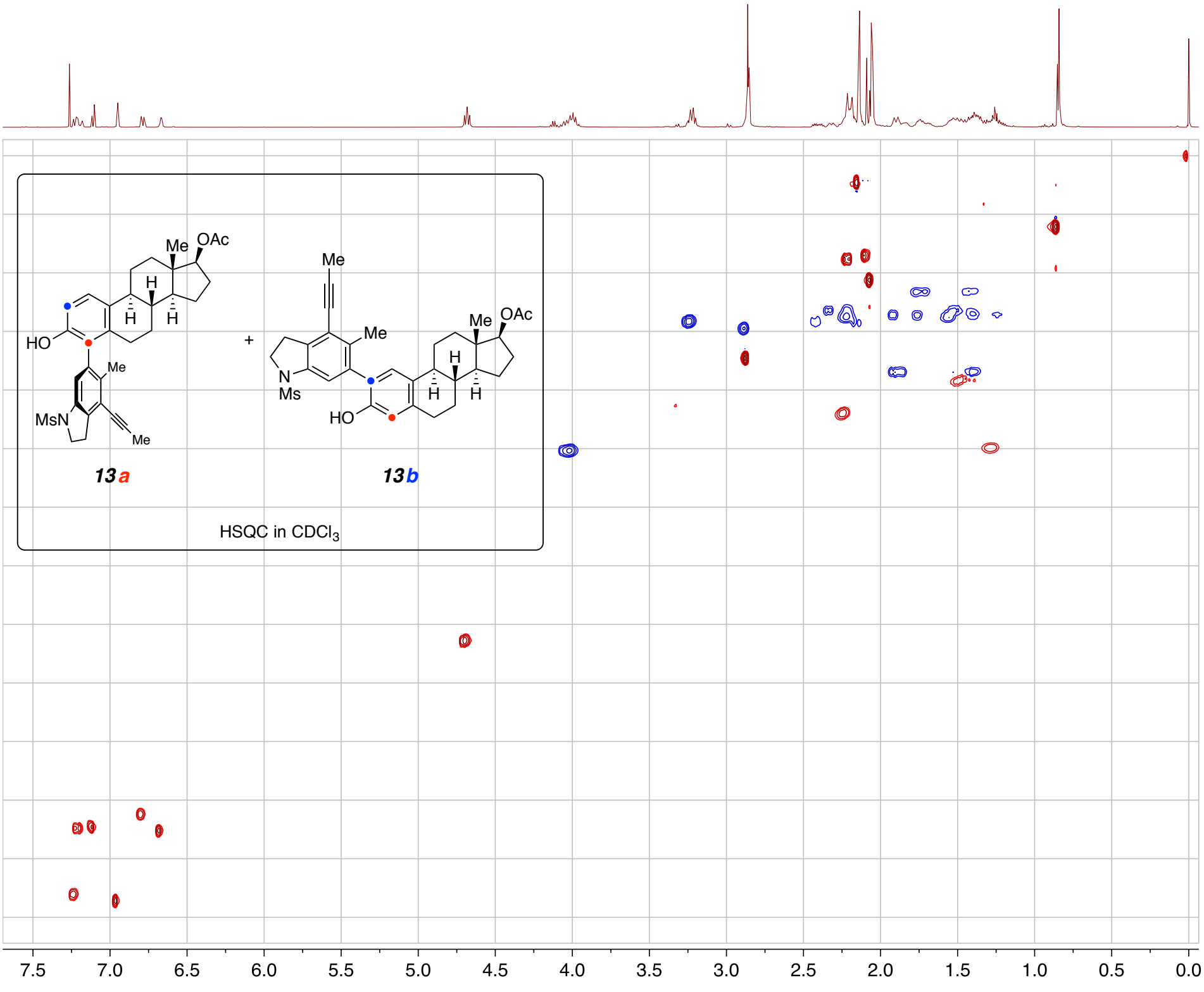


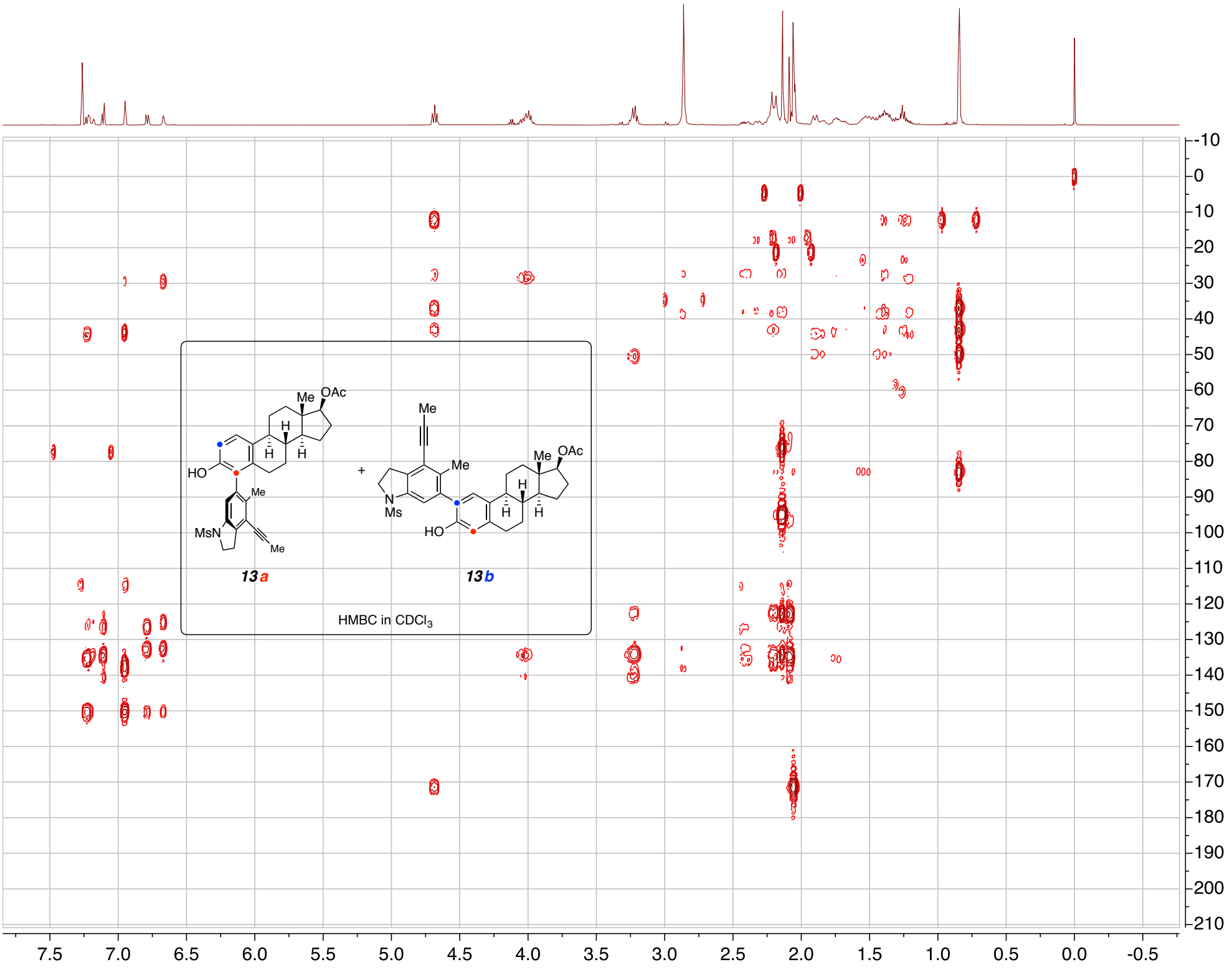
13a ***13b***

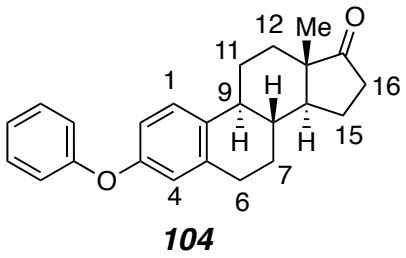
^{1}H NMR (500 MHz) in $CDCl_3$




Me
OAc
H
H
HO
Me
MsN
Me
13a
+
Me
Me
N
Ms
Me
OAc
H
H
HO
13b
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

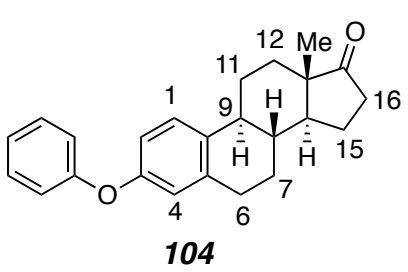

Me
OAc
H
H
H
HO
Me
MsN
Me
+
Me
Me
N
Ms
Me
OAc
H
H
H
HO
13a
13b
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Me
OAc
H
H
H
HO
Me
MsN
Me
13a
+
Me
Me
N
Ms
Me
OAc
H
H
H
HO
13b
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5



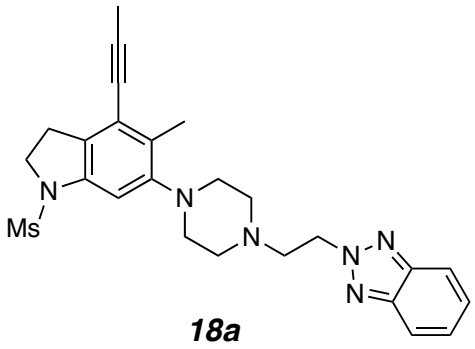
104

^{1}H NMR (500 MHz) in $CDCl_3$



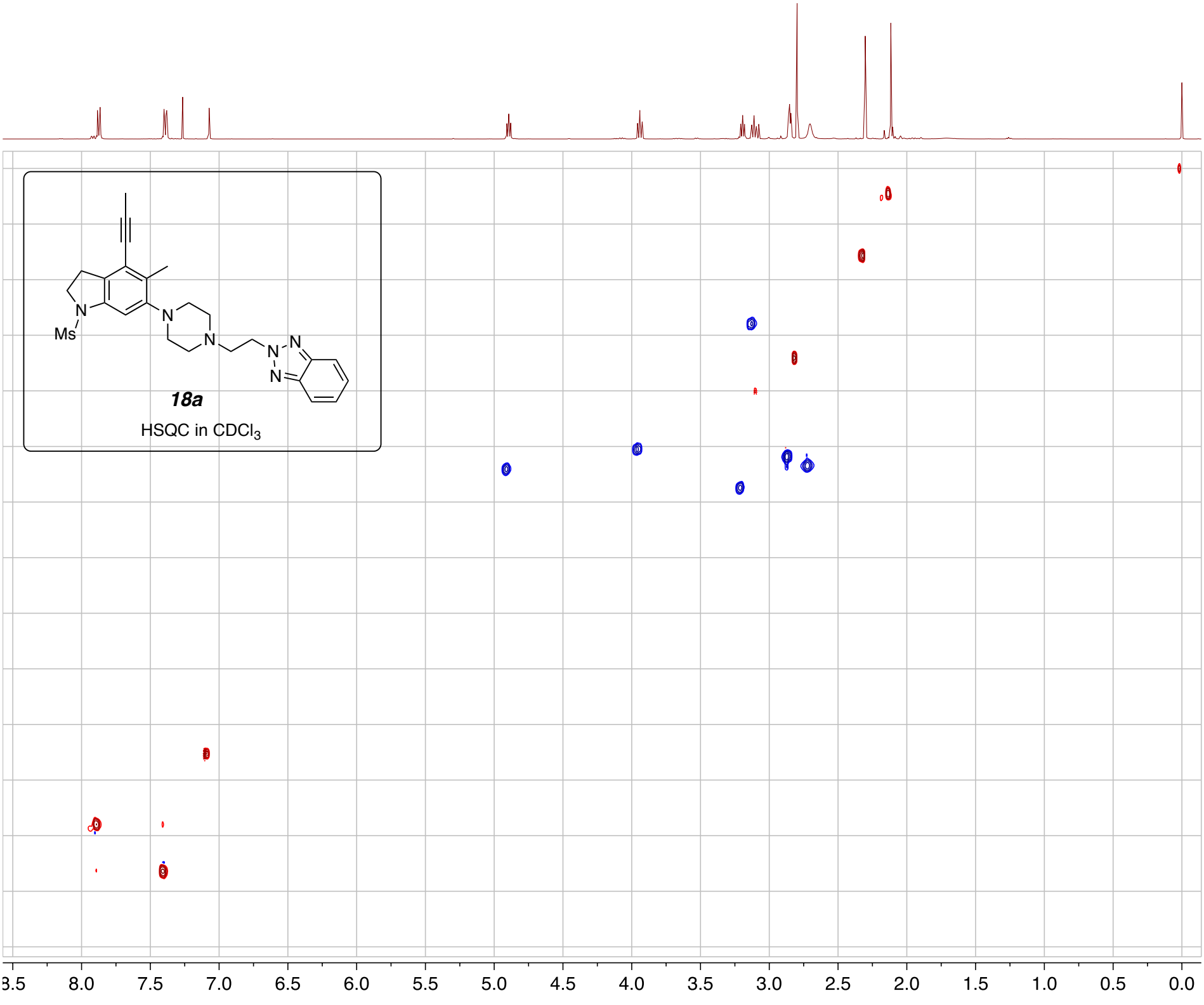
104

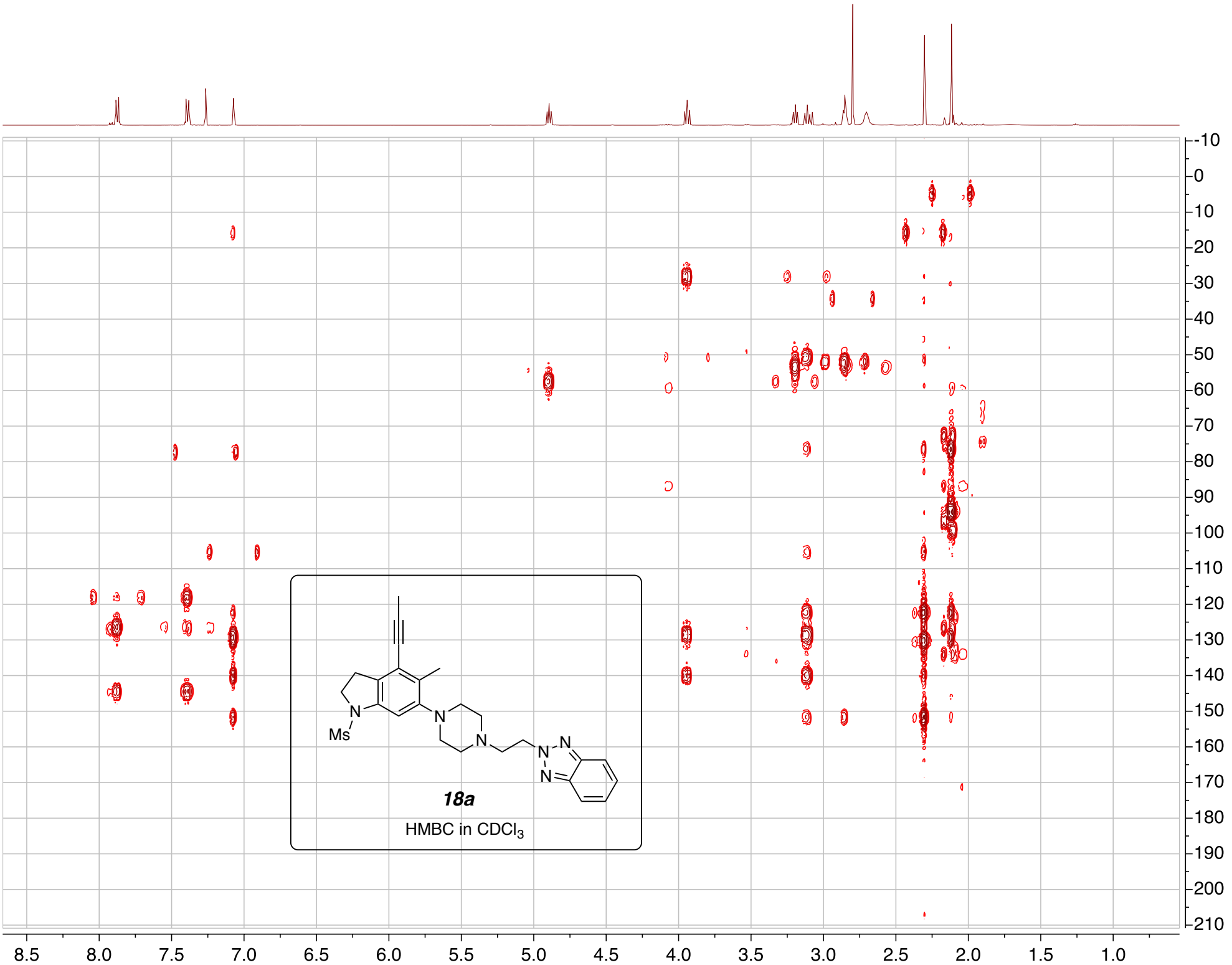
^{13}C NMR (125 MHz) in $CDCl_3$

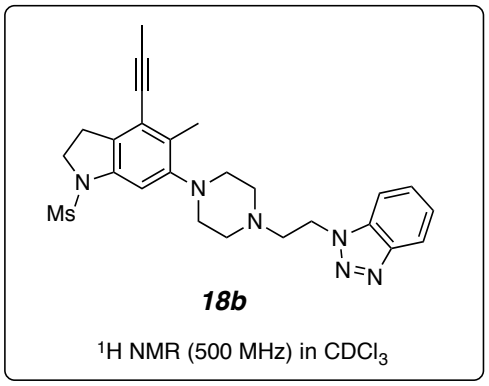


18a

^{1}H NMR (500 MHz) in $CDCl_3$

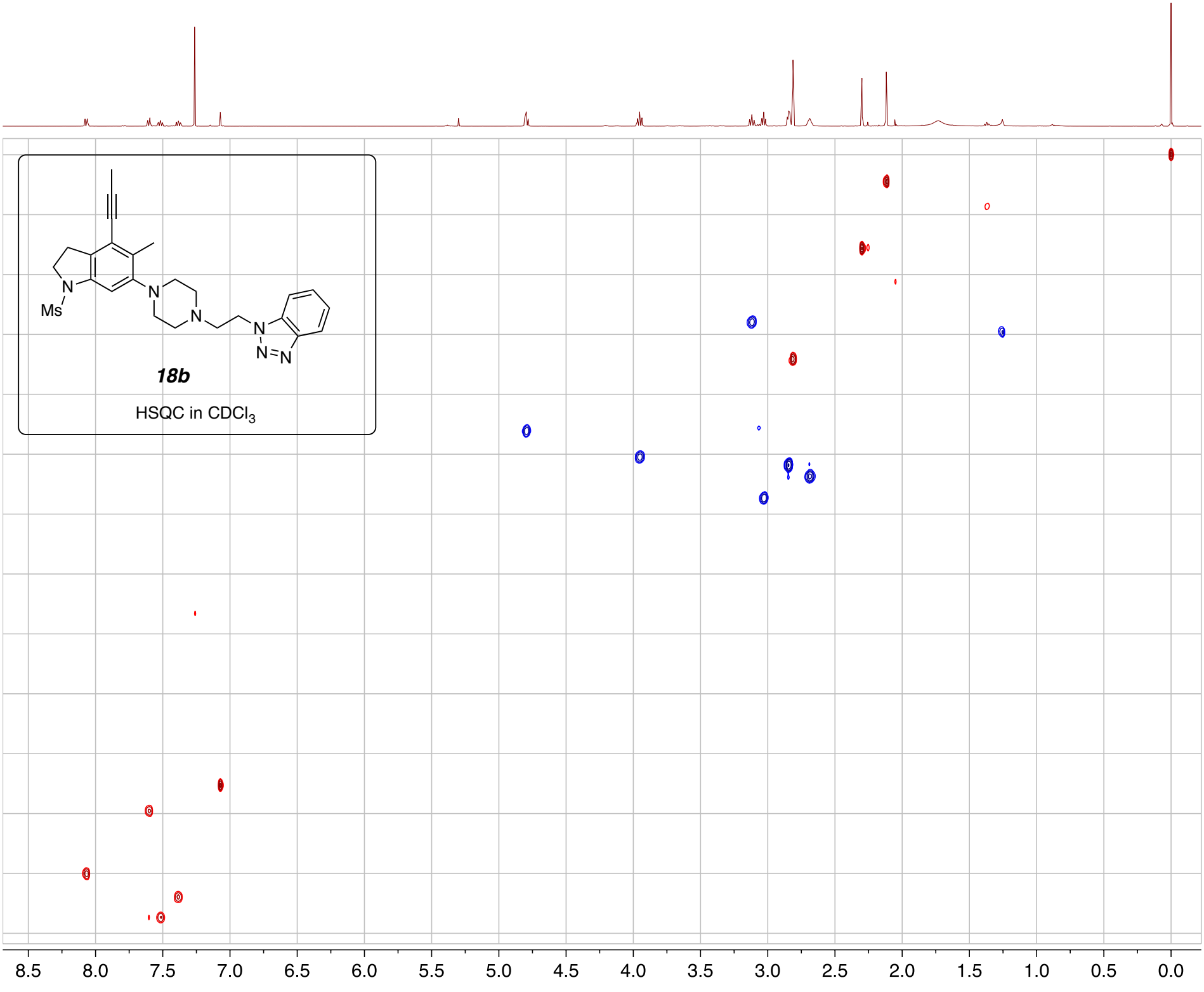

Ms
N
N
N
N
N
N
18a
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

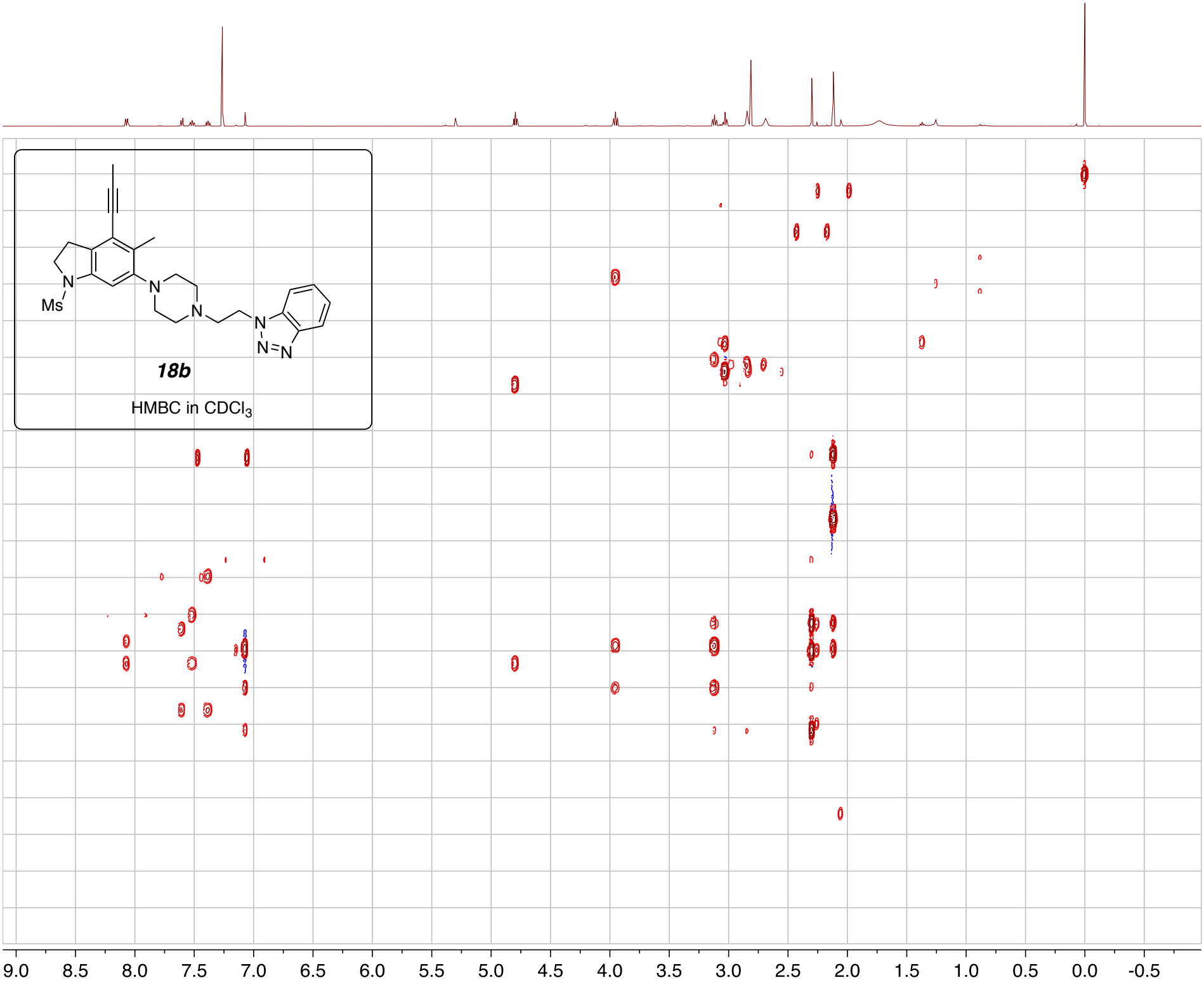

Ms
N
N
N
N
N
N
18a
HMBC in CDCl3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

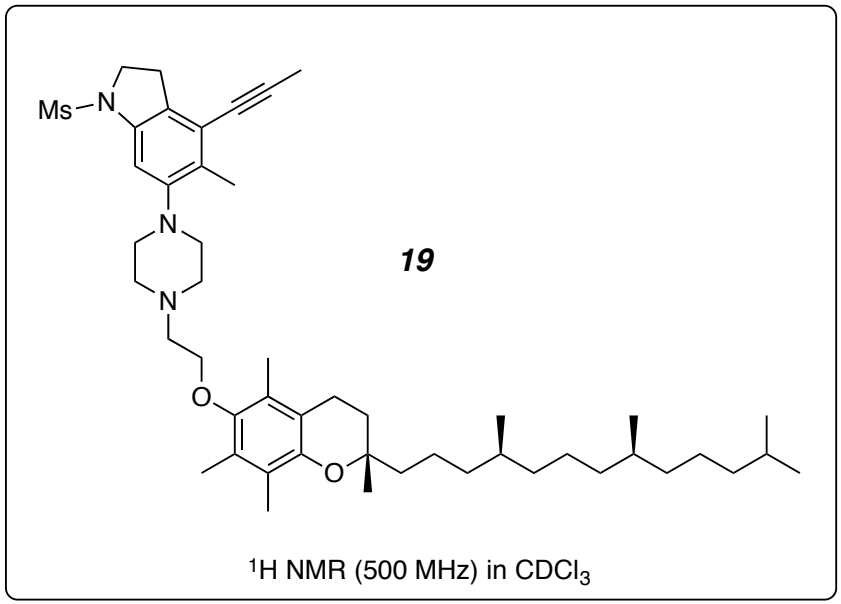


18b

^{1}H NMR (500 MHz) in $CDCl_3$

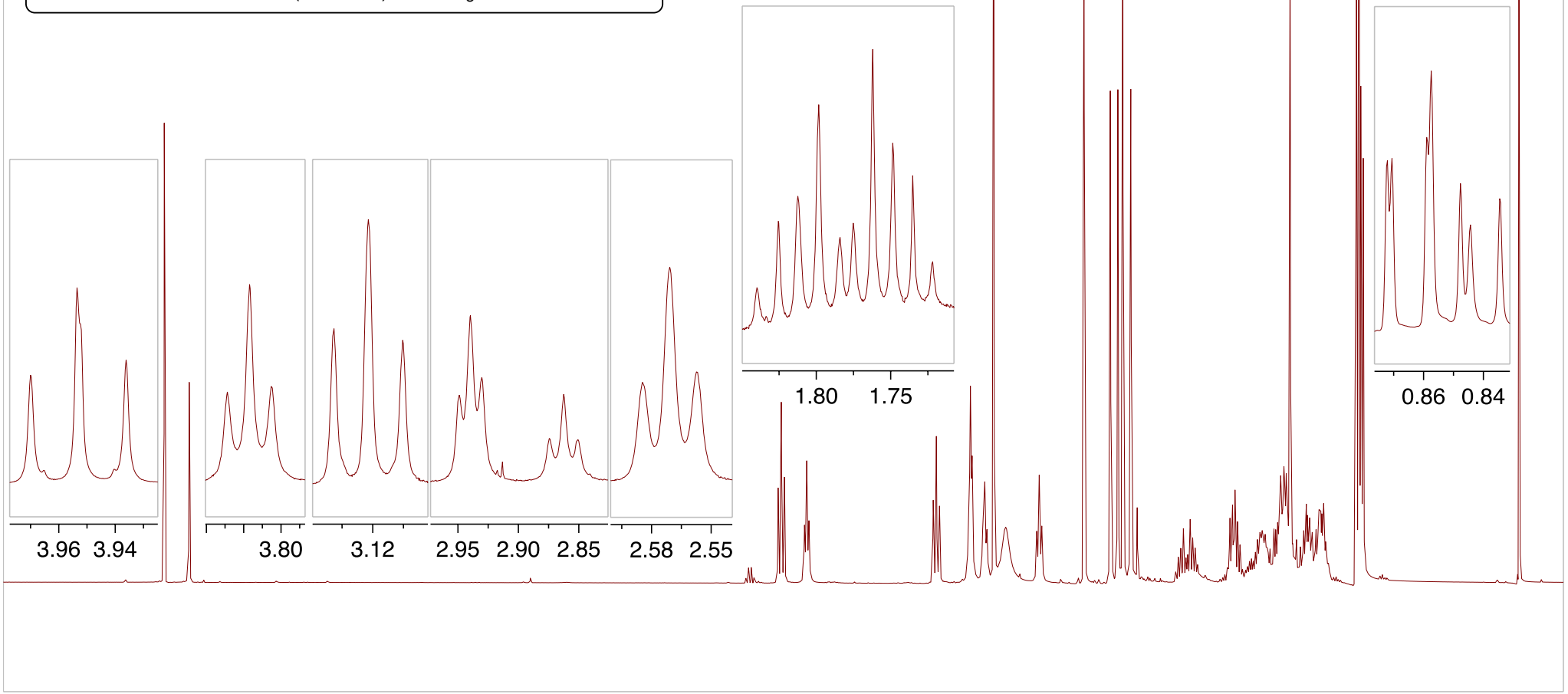

Ms
N
N
N
N
N
N
18b
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

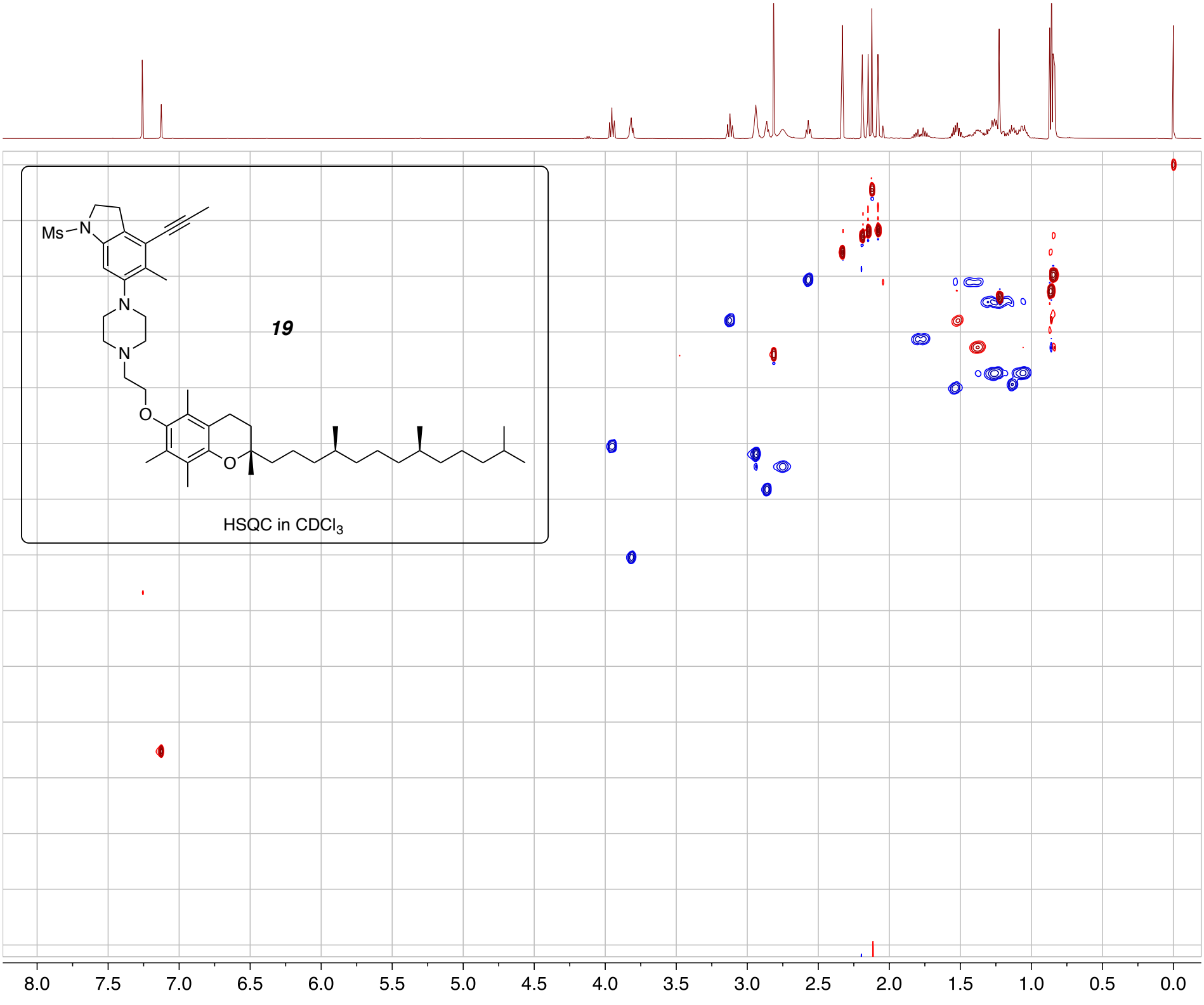

Ms
18b
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

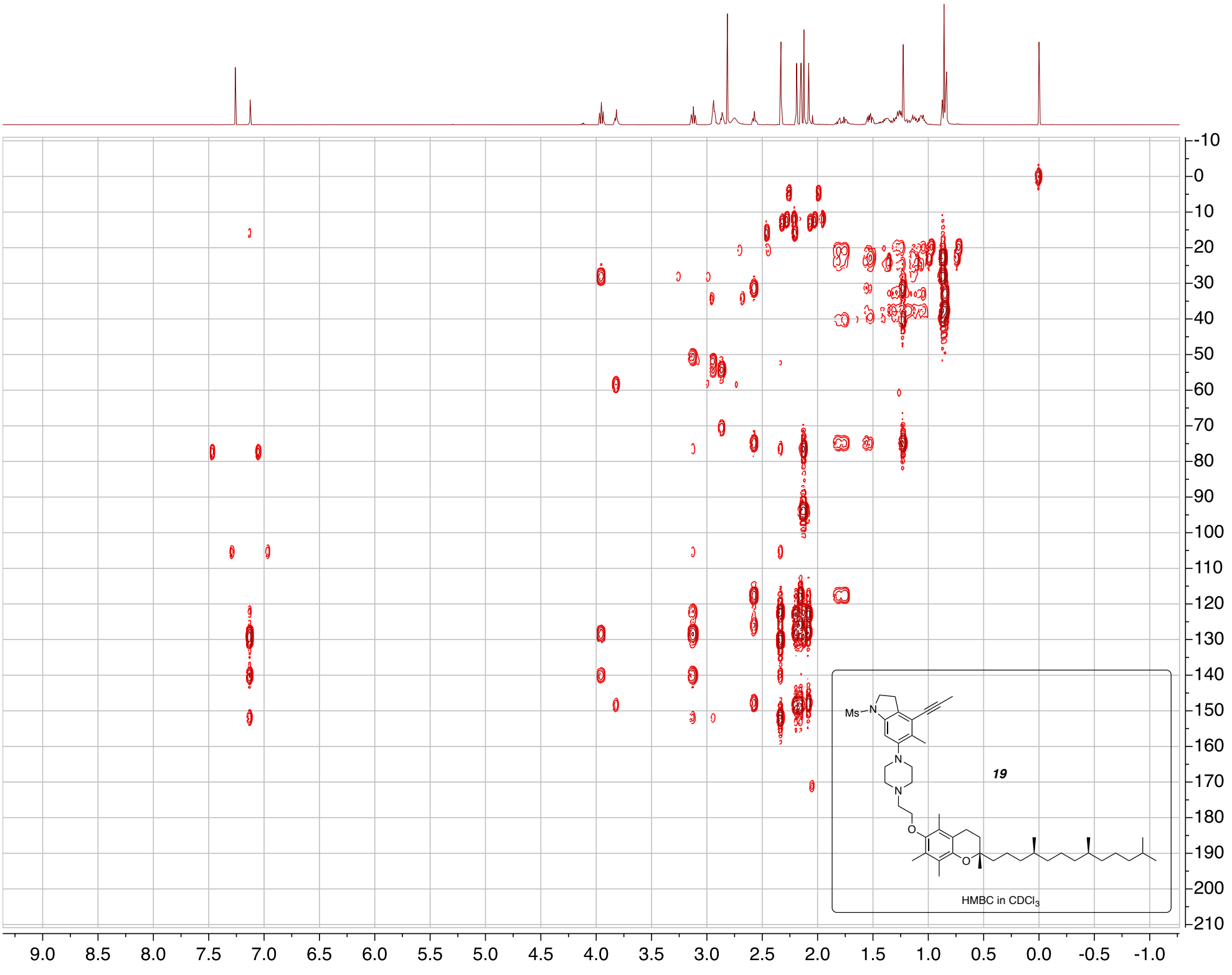


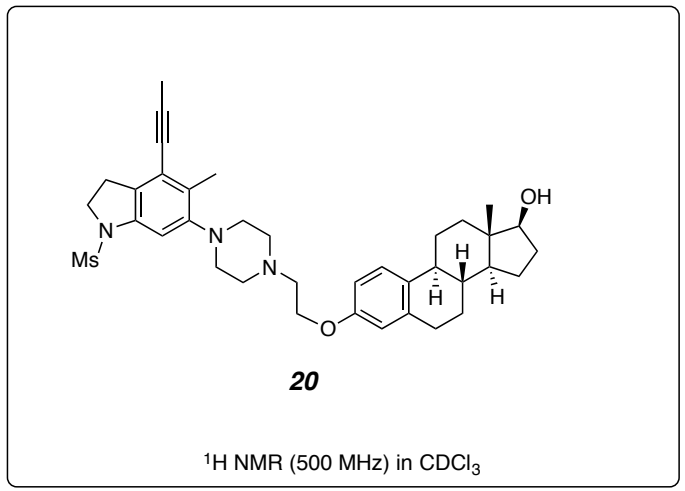
19

^{1}H NMR (500 MHz) in $CDCl_3$



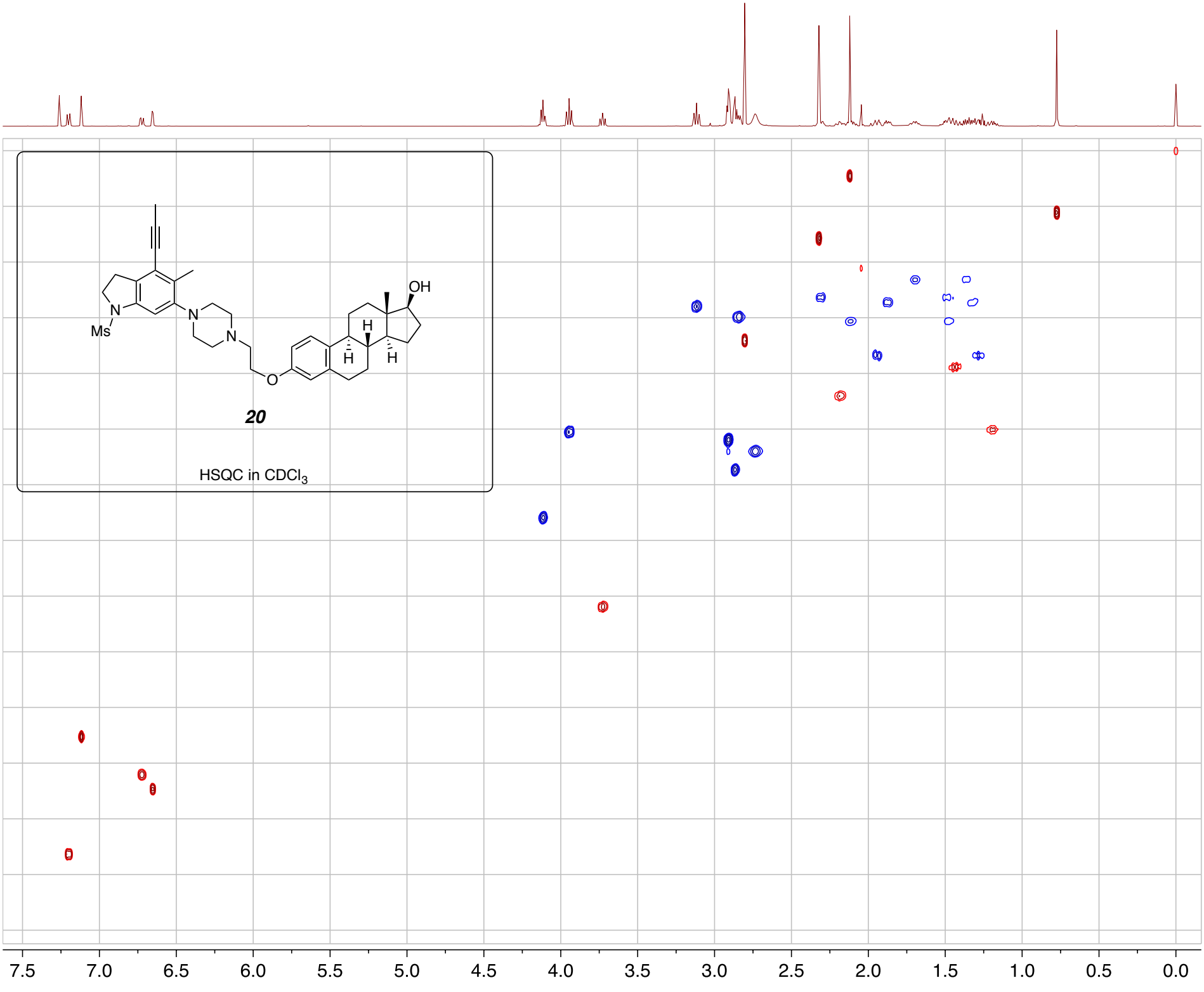

Ms
N
N
N
O
O
19
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

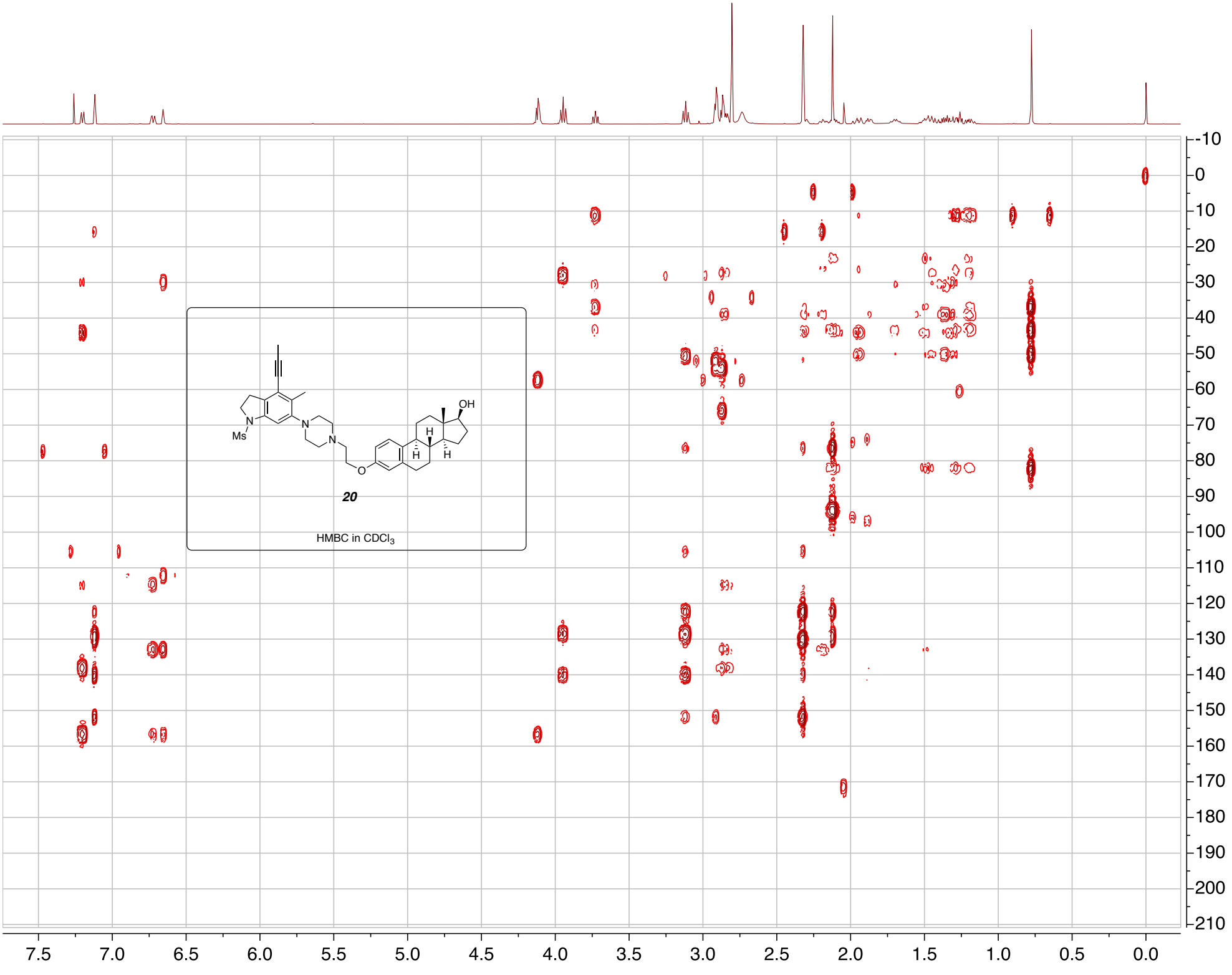

Ms
N
N
N
O
O
19
HMBC in CDCl3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
-10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

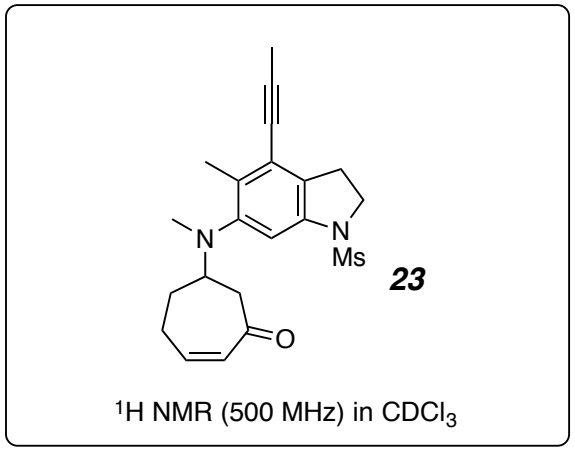


20

^{1}H NMR (500 MHz) in $CDCl_3$

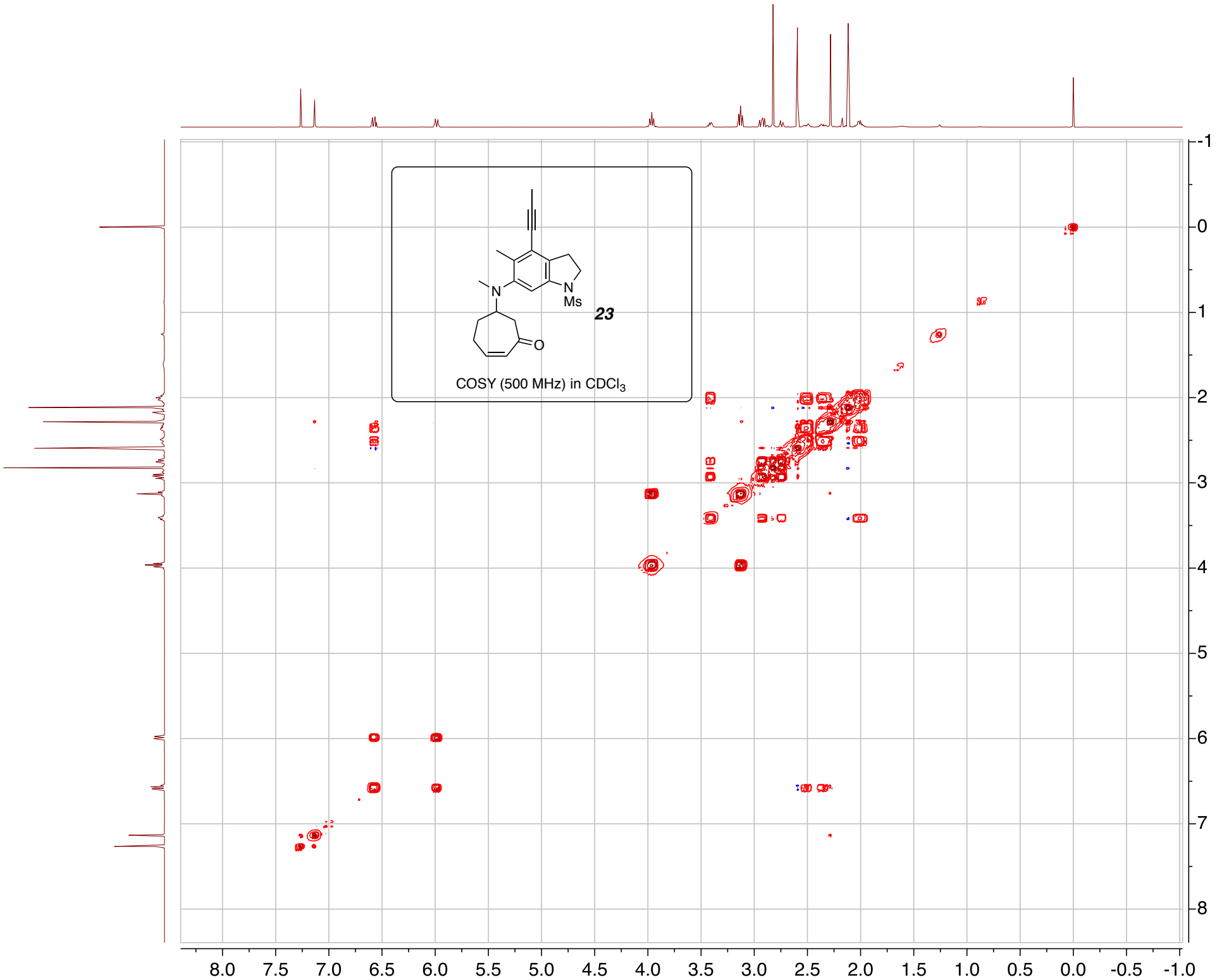

OH
N
N
N
Ms
H
H
H
O
20
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

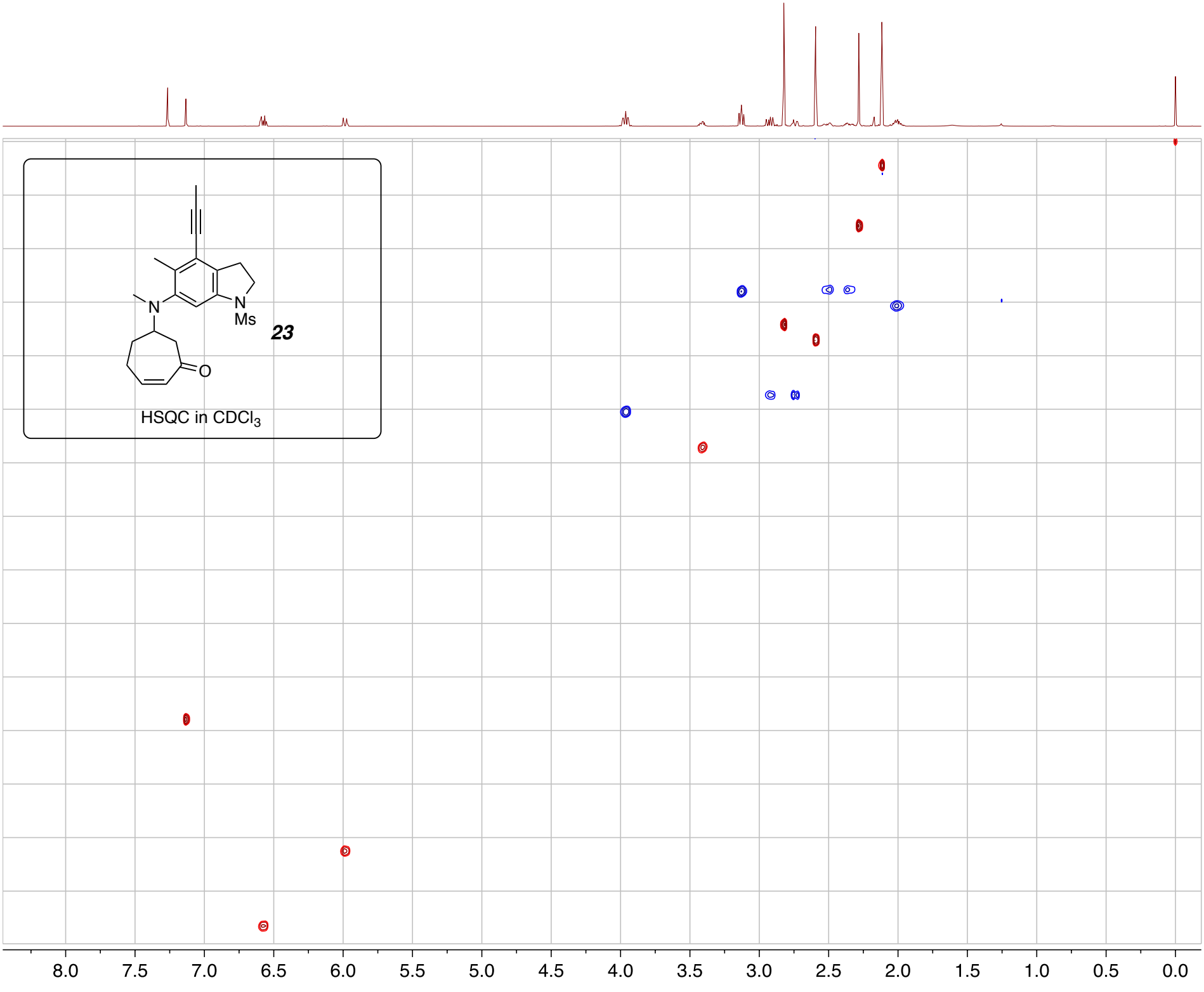

OH
N
Ms
N
N
O
H
H
H
20
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

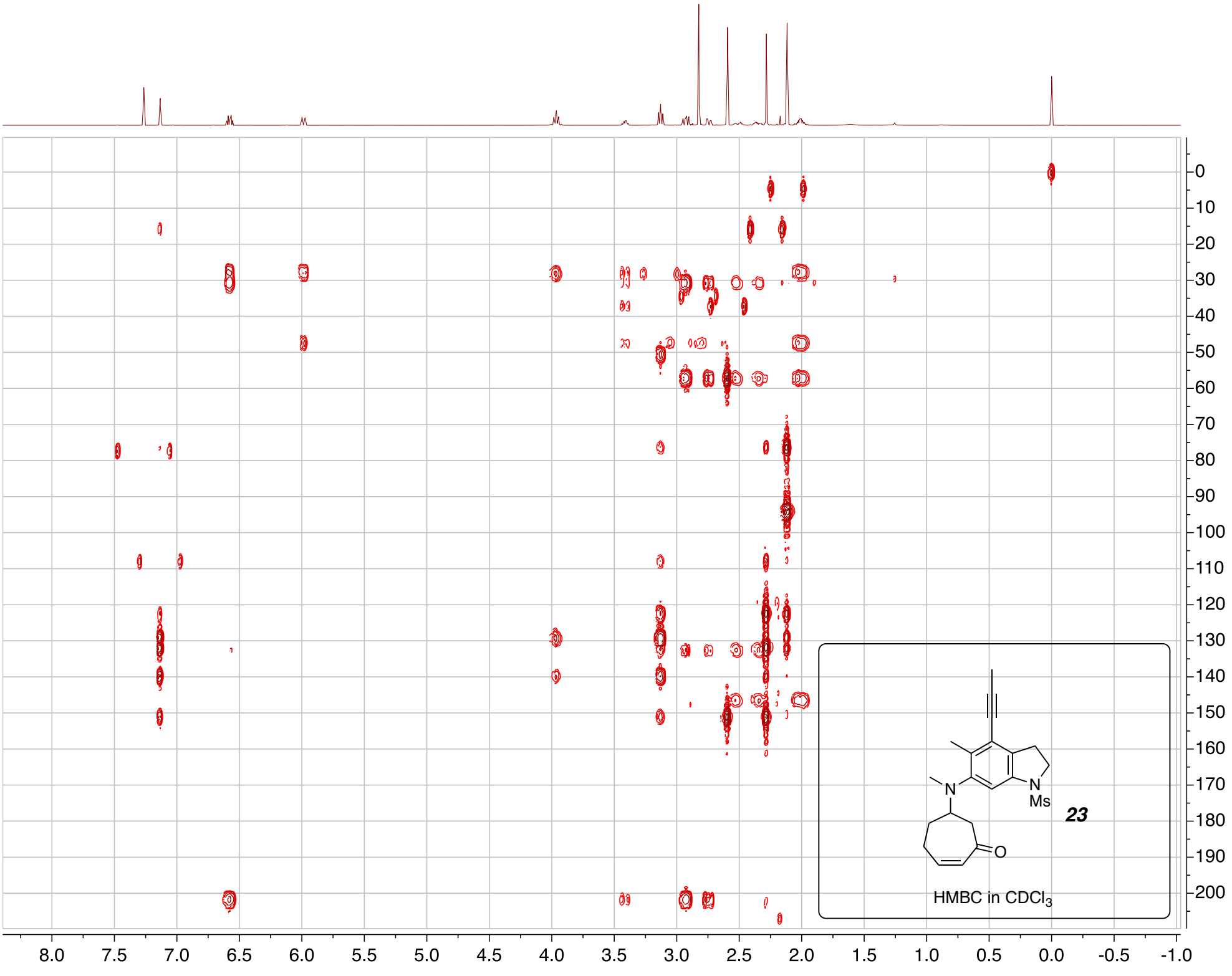


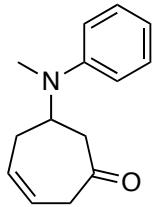
23

^{1}H NMR (500 MHz) in $CDCl_3$


N
N
Ms
O
23
COSY (500 MHz) in CDCl3
-1
0
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

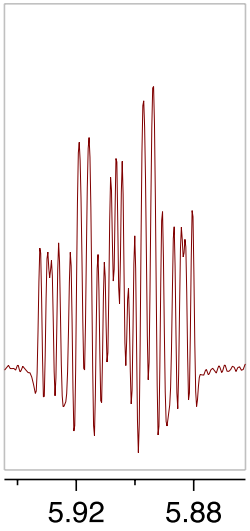

N
N
Ms
O
23
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

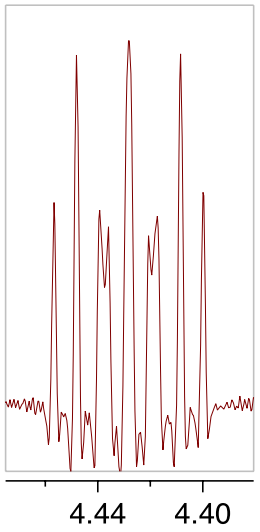

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
N
N
Ms
O
23
HMBC in CDCl3

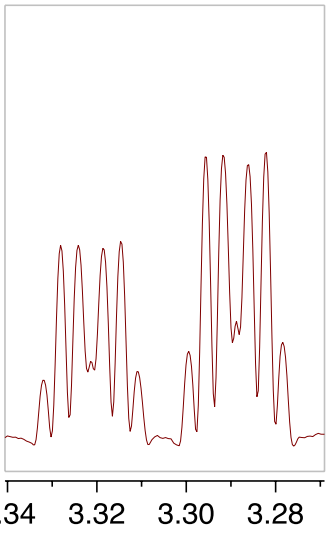


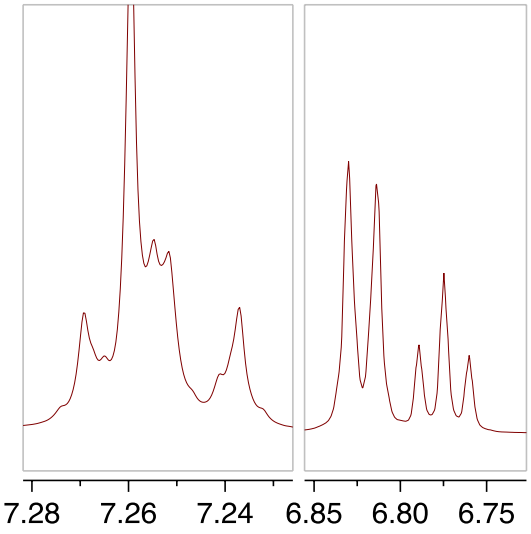
iso-24

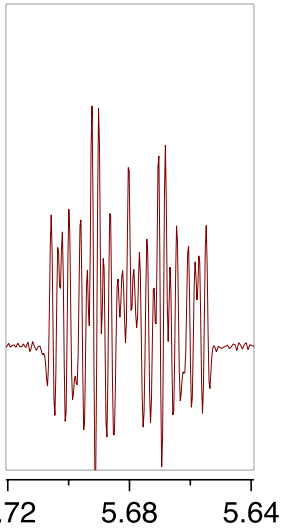
^{1}H NMR (500 MHz) in $CDCl_3$

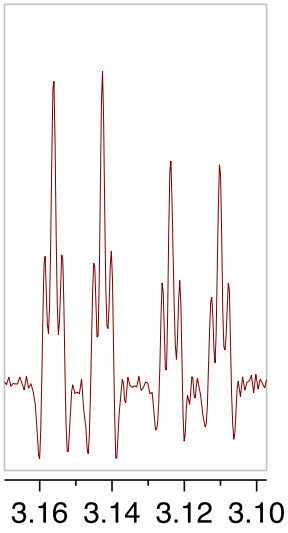


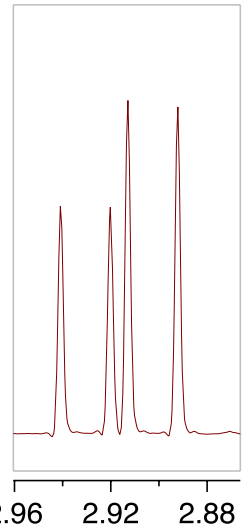


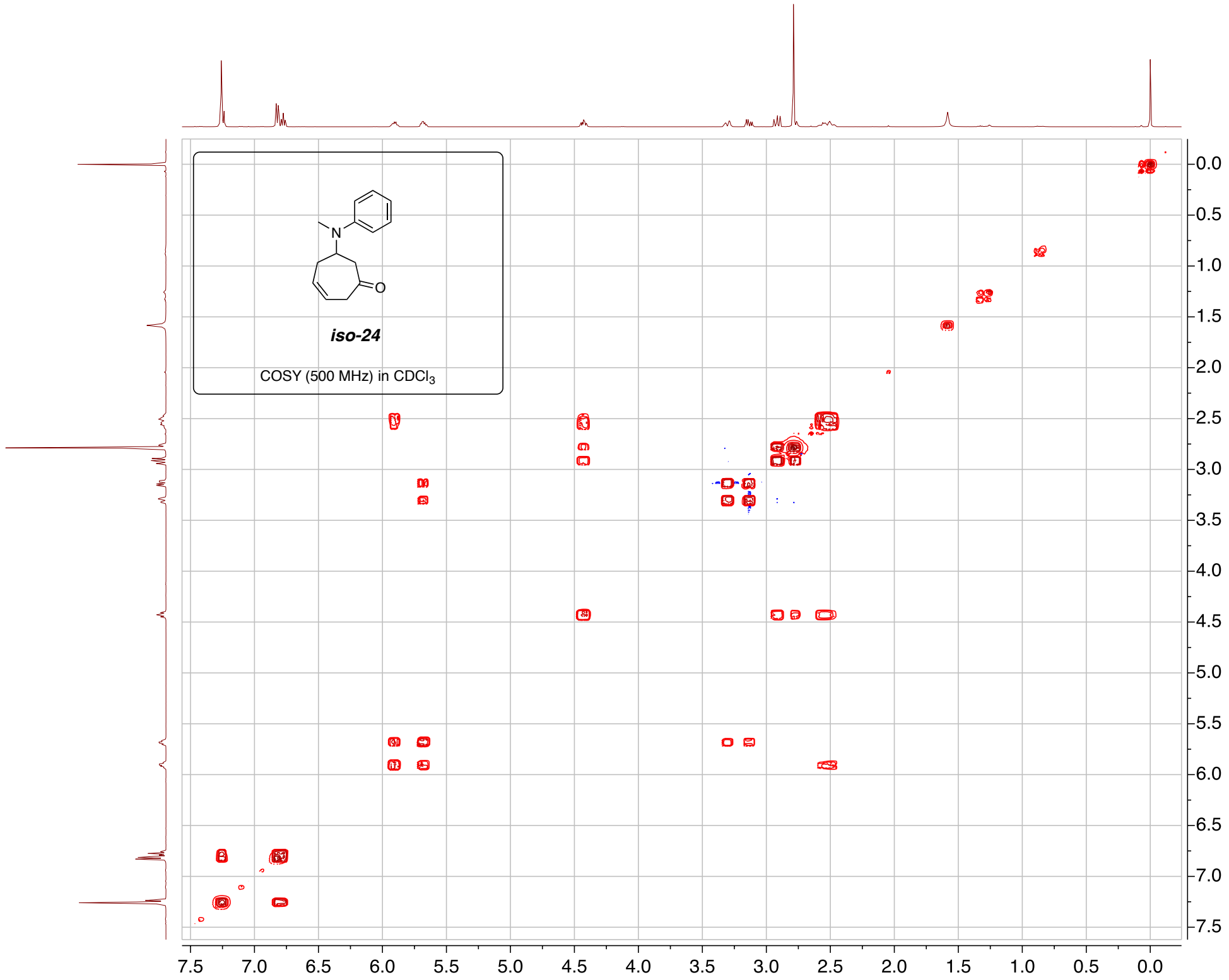


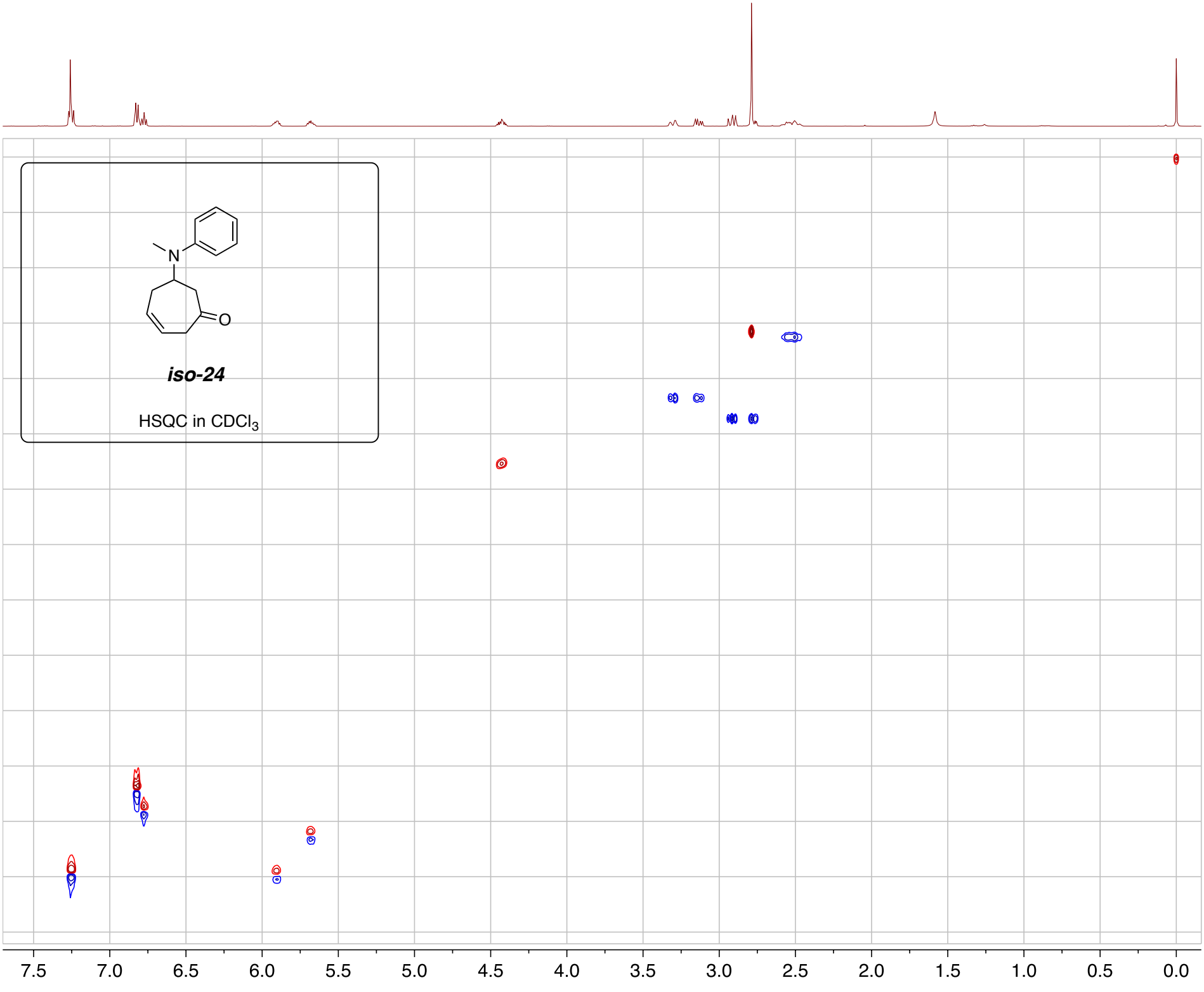


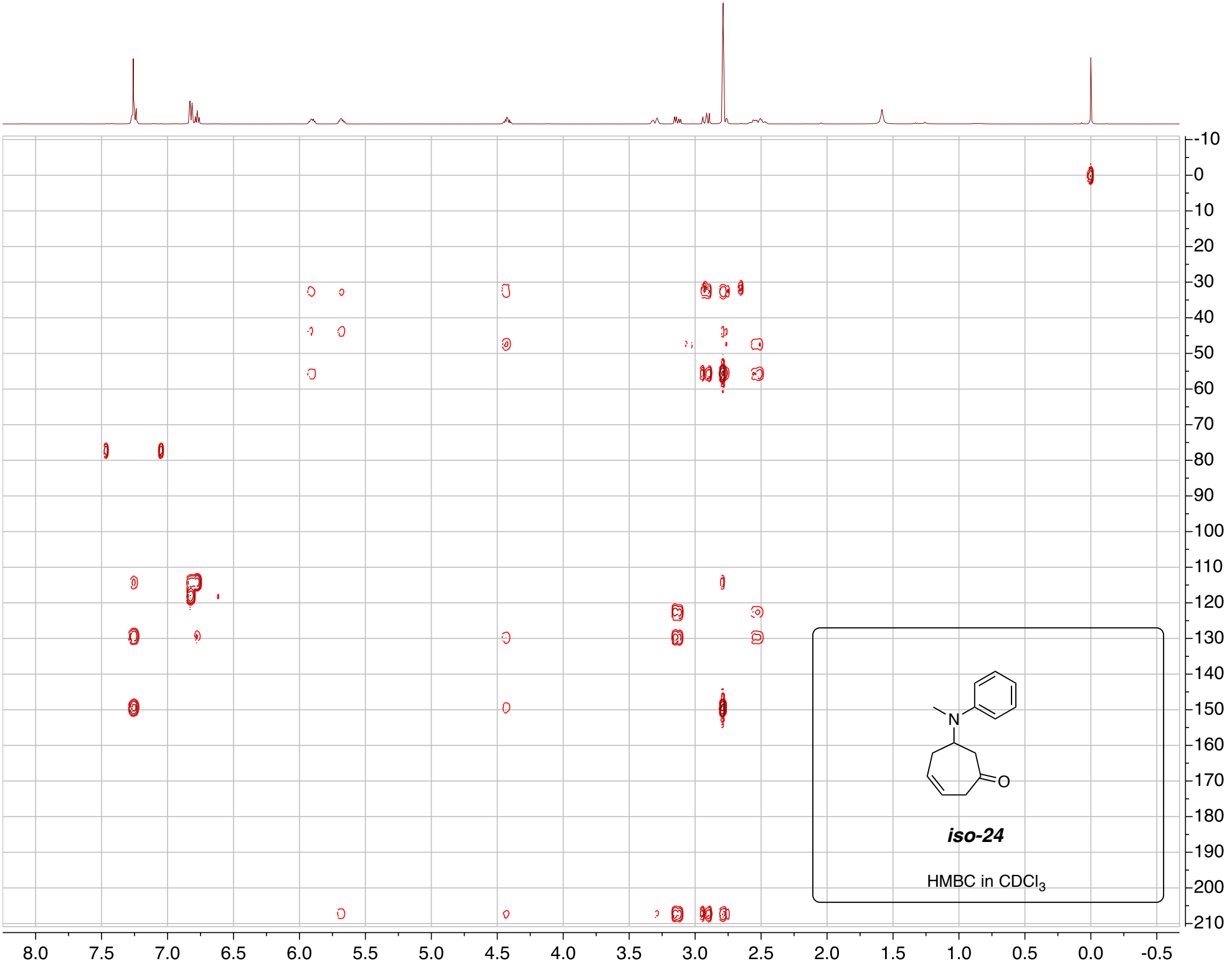


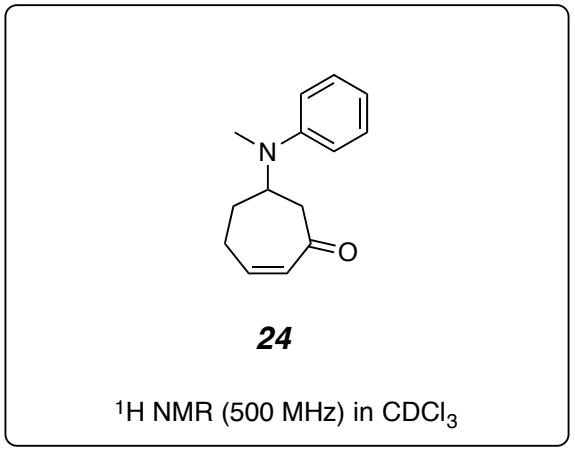





N
O
iso-24
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

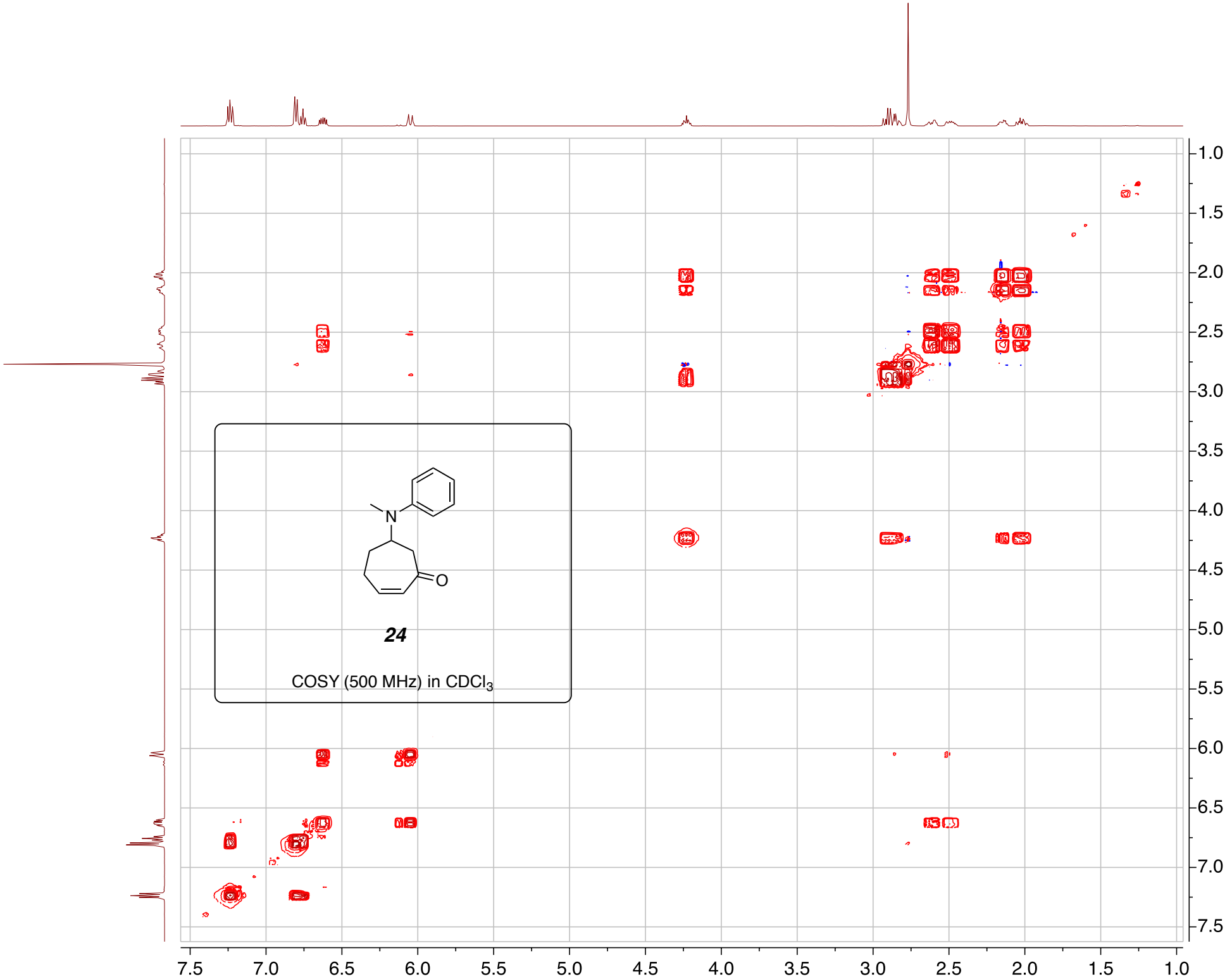

N
O
iso-24
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

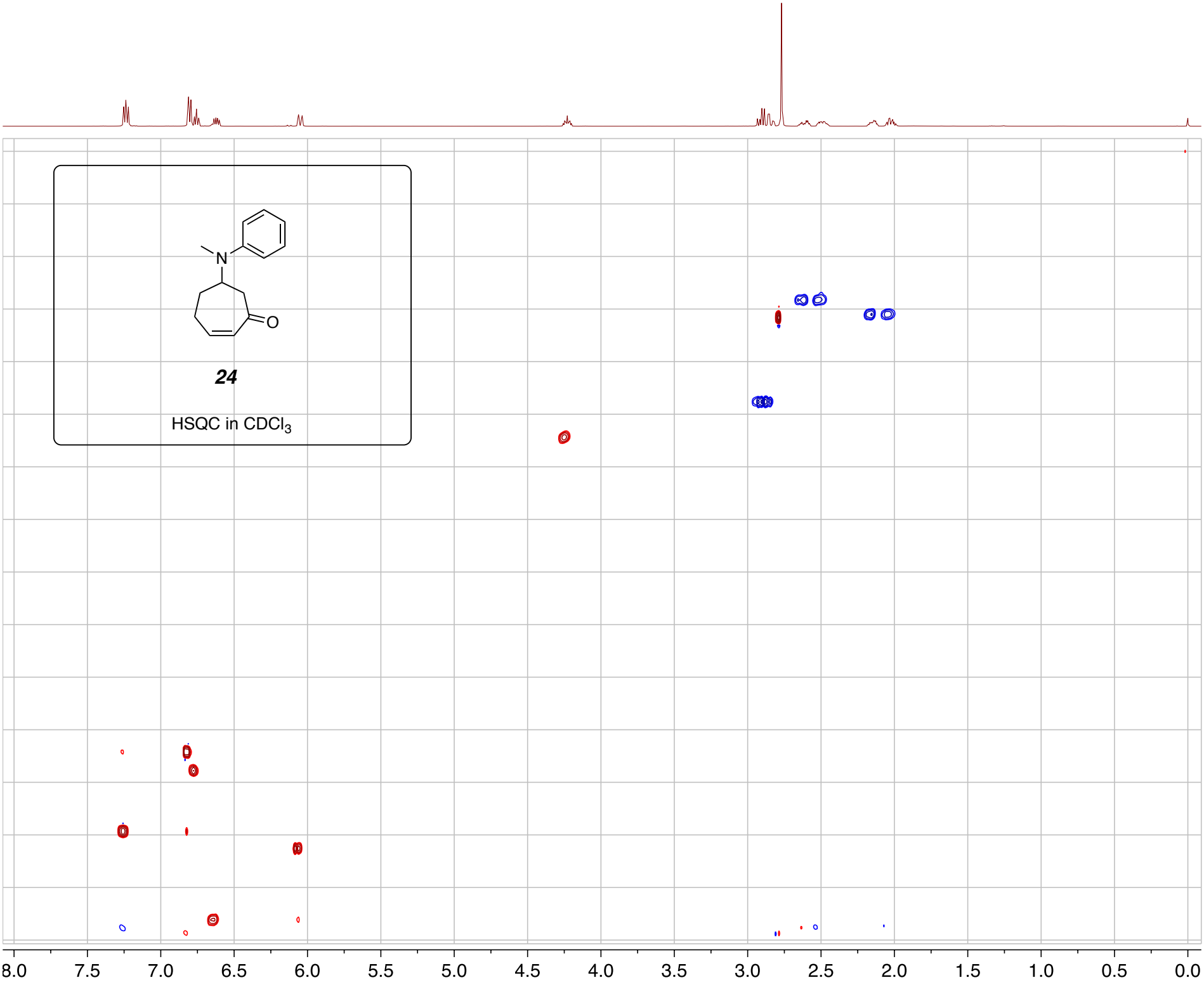

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
N
O
iso-24
HMBC in CDCl3

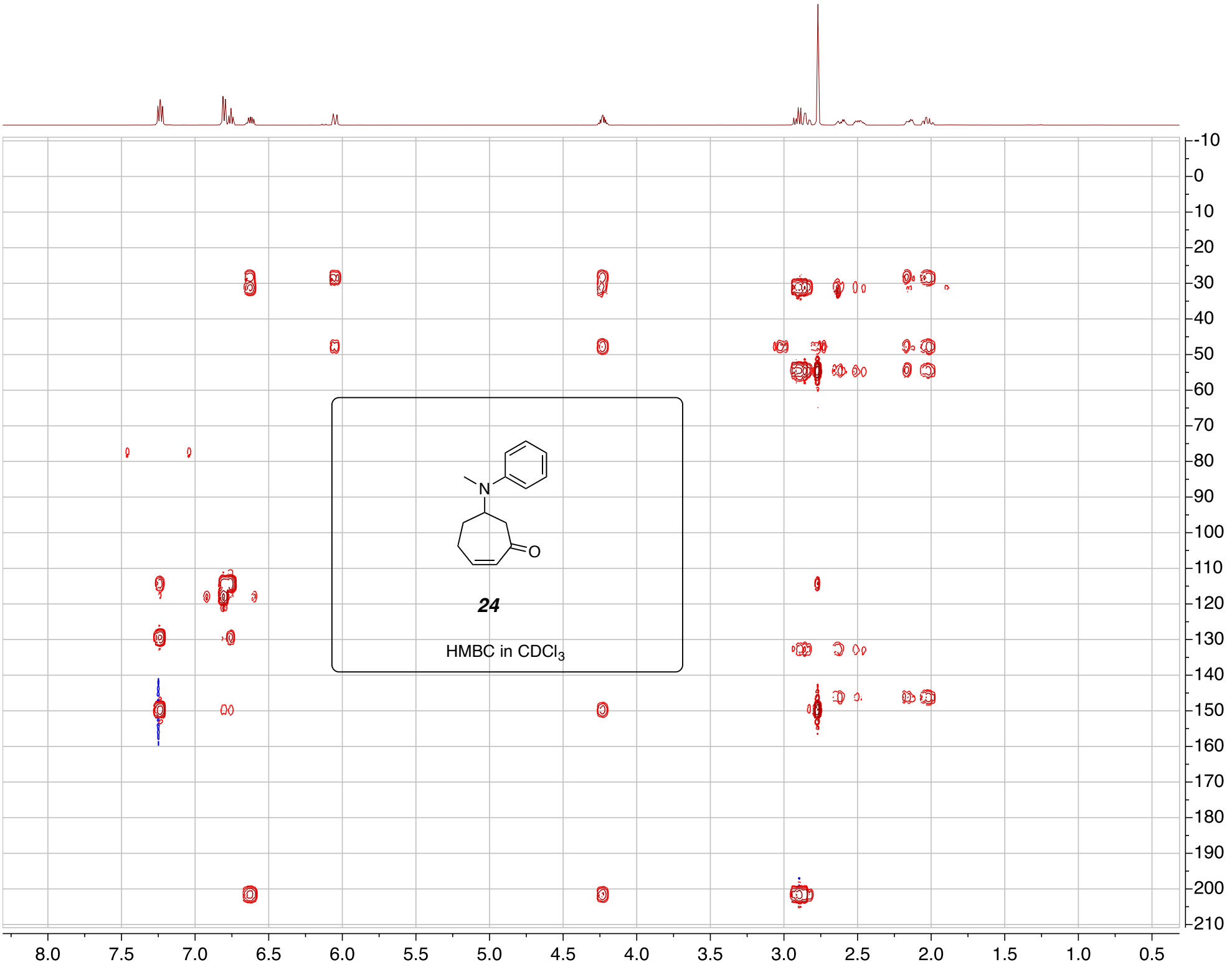


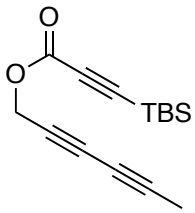
24

^{1}H NMR (500 MHz) in $CDCl_3$


N
O
24
COSY (500 MHz) in CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

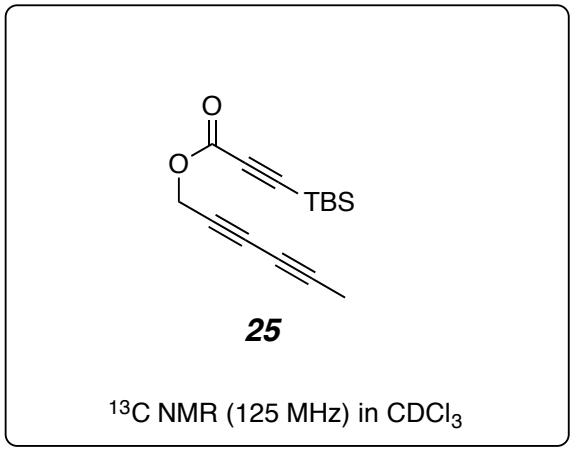

N
O
24
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


N
O
24
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5



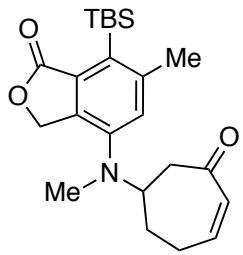
25

^{1}H NMR (500 MHz) in $CDCl_3$



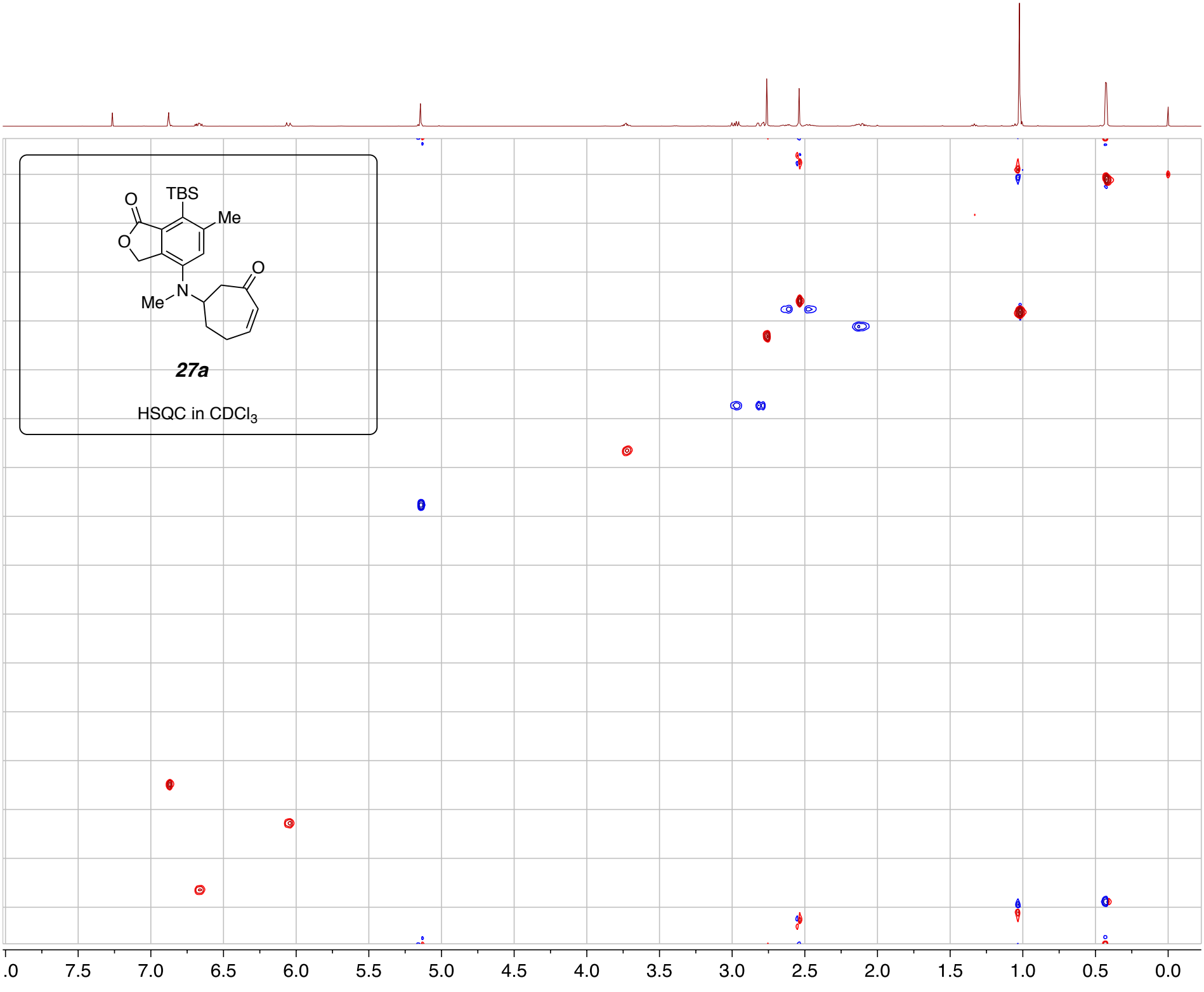
25

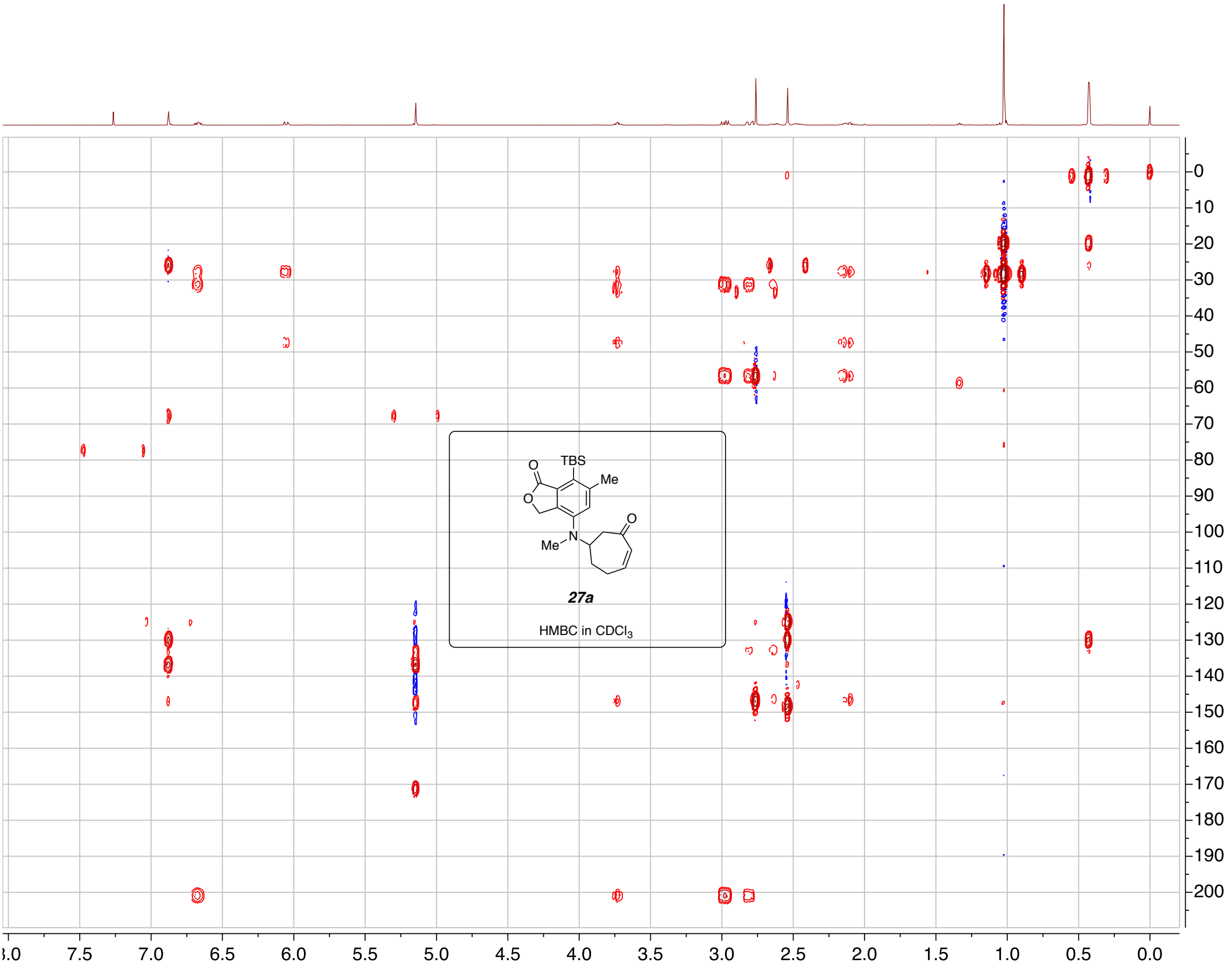
^{13}C NMR (125 MHz) in $CDCl_3$

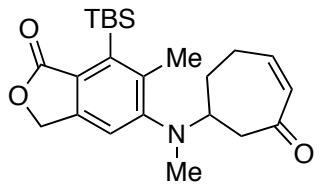


27a

^{1}H NMR (500 MHz) in $CDCl_3$

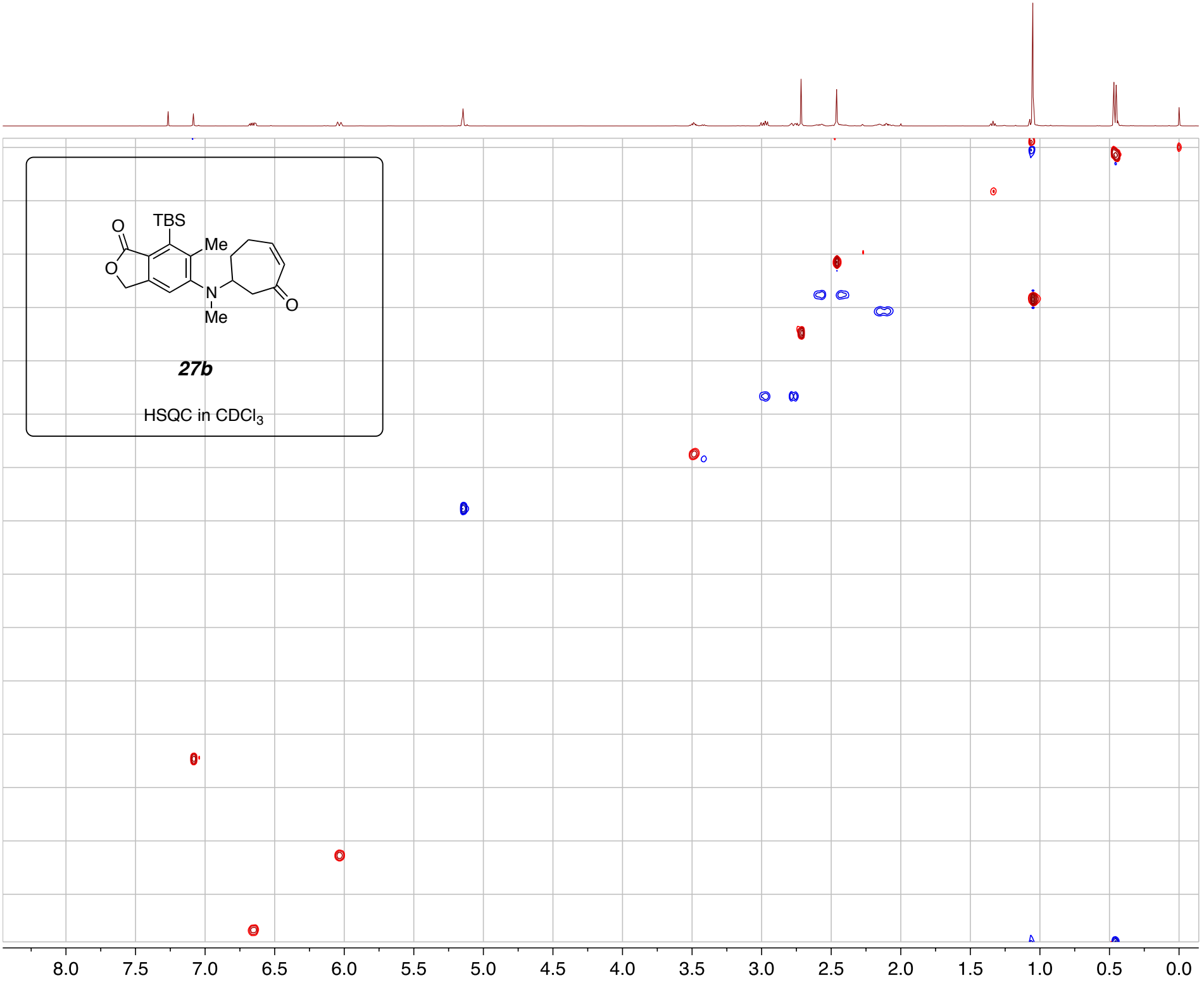

TBS
Me
O
O
O
N
Me
27a
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

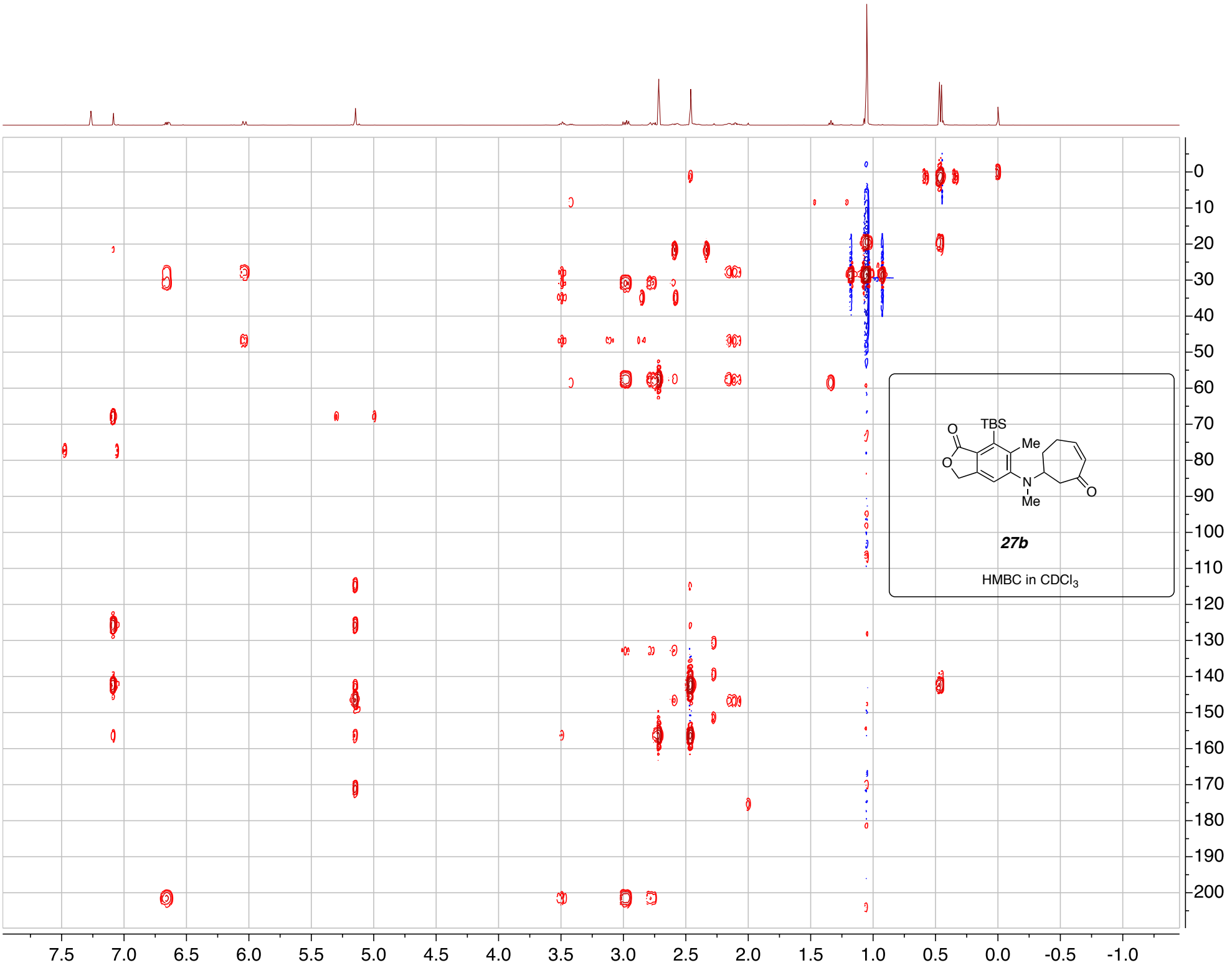

TBS
Me
O
O
O
N
Me
27a
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

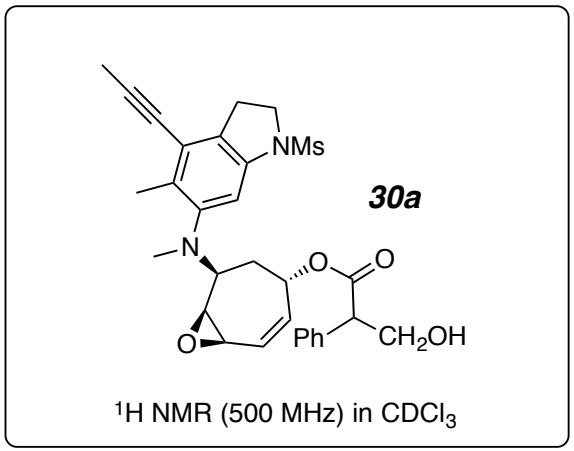


27b

^{1}H NMR (500 MHz) in $CDCl_3$

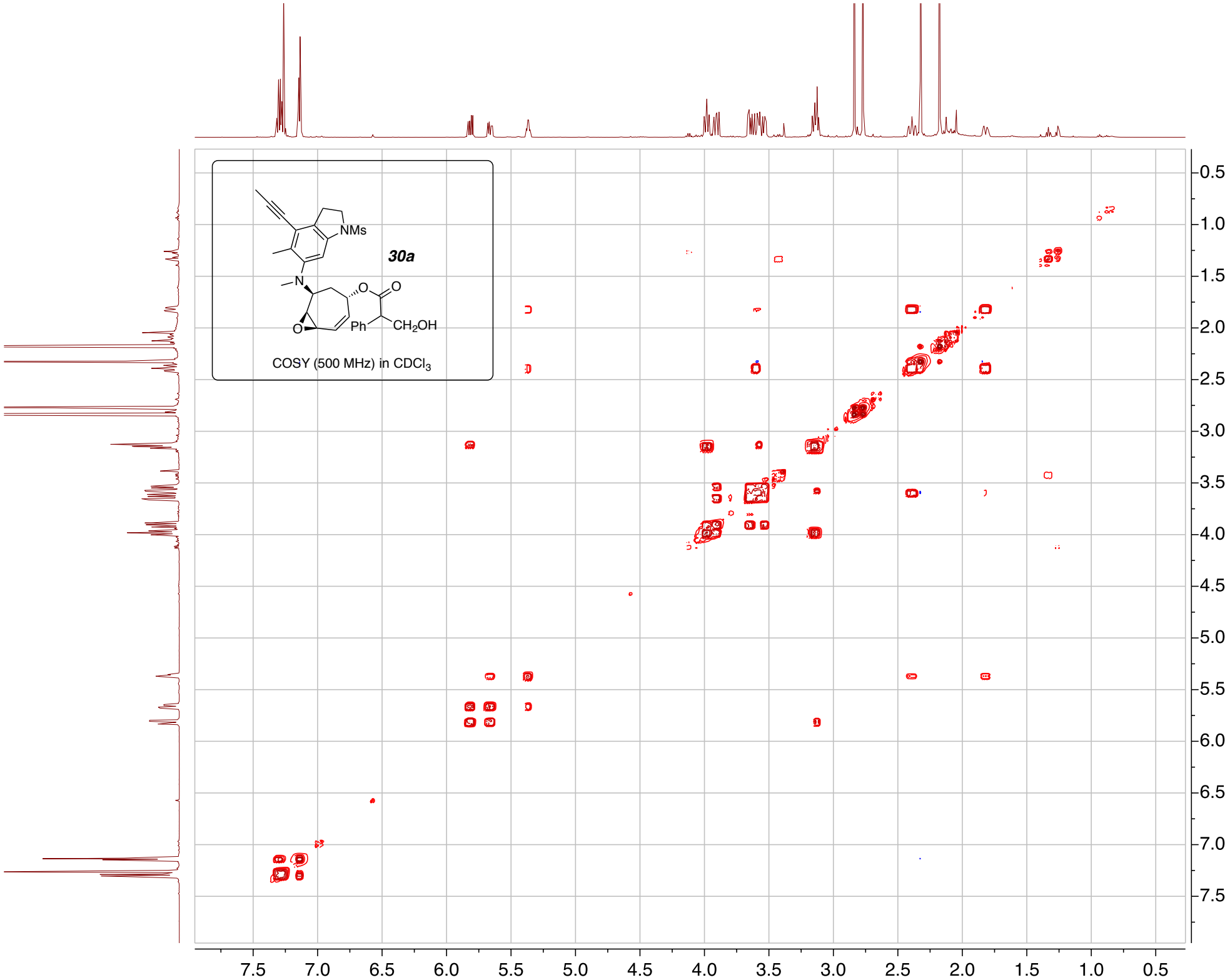

TBS
O
O
Me
N
Me
O
27b
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

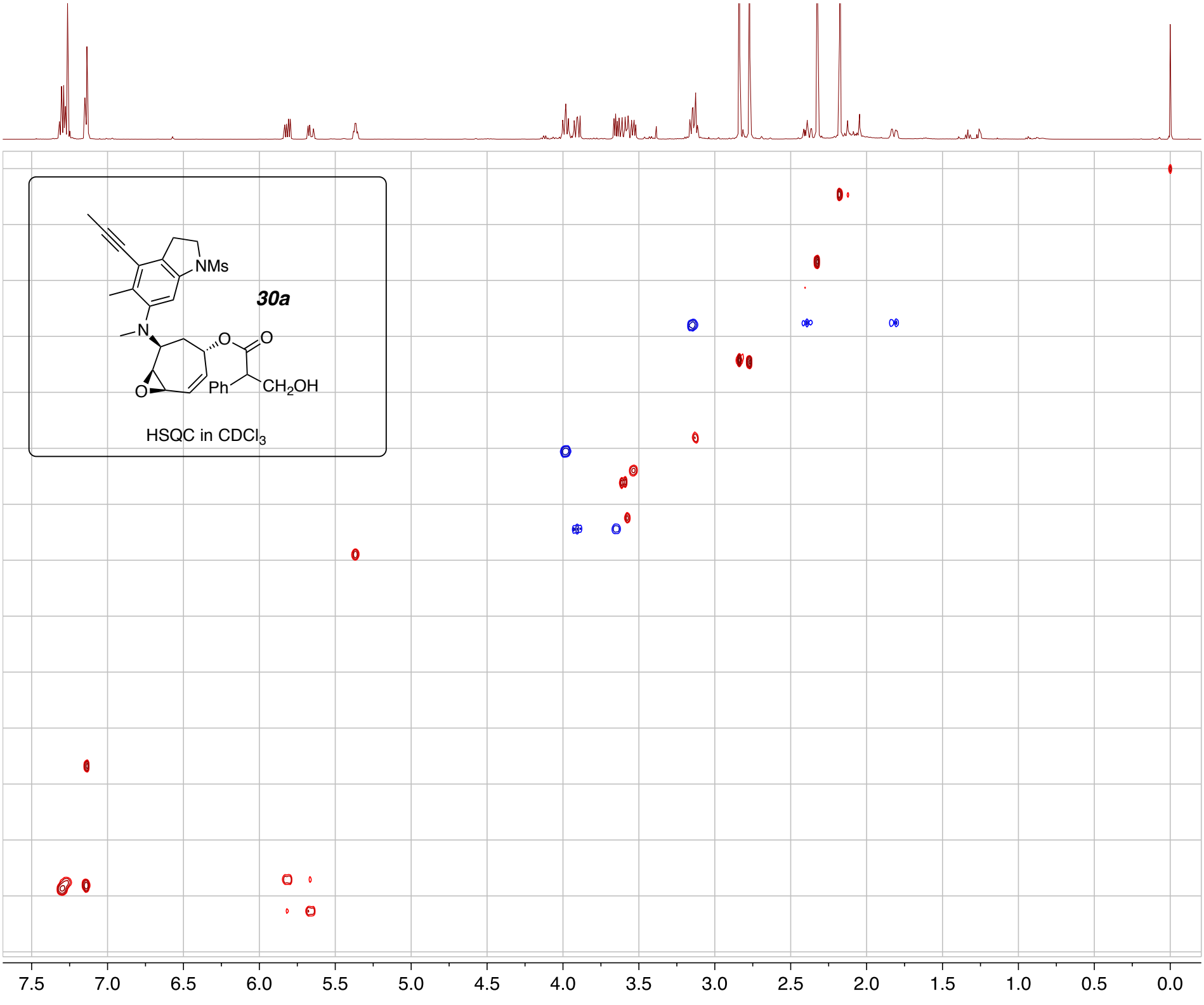

TBS
Me
N
Me
O
O
O
27b
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

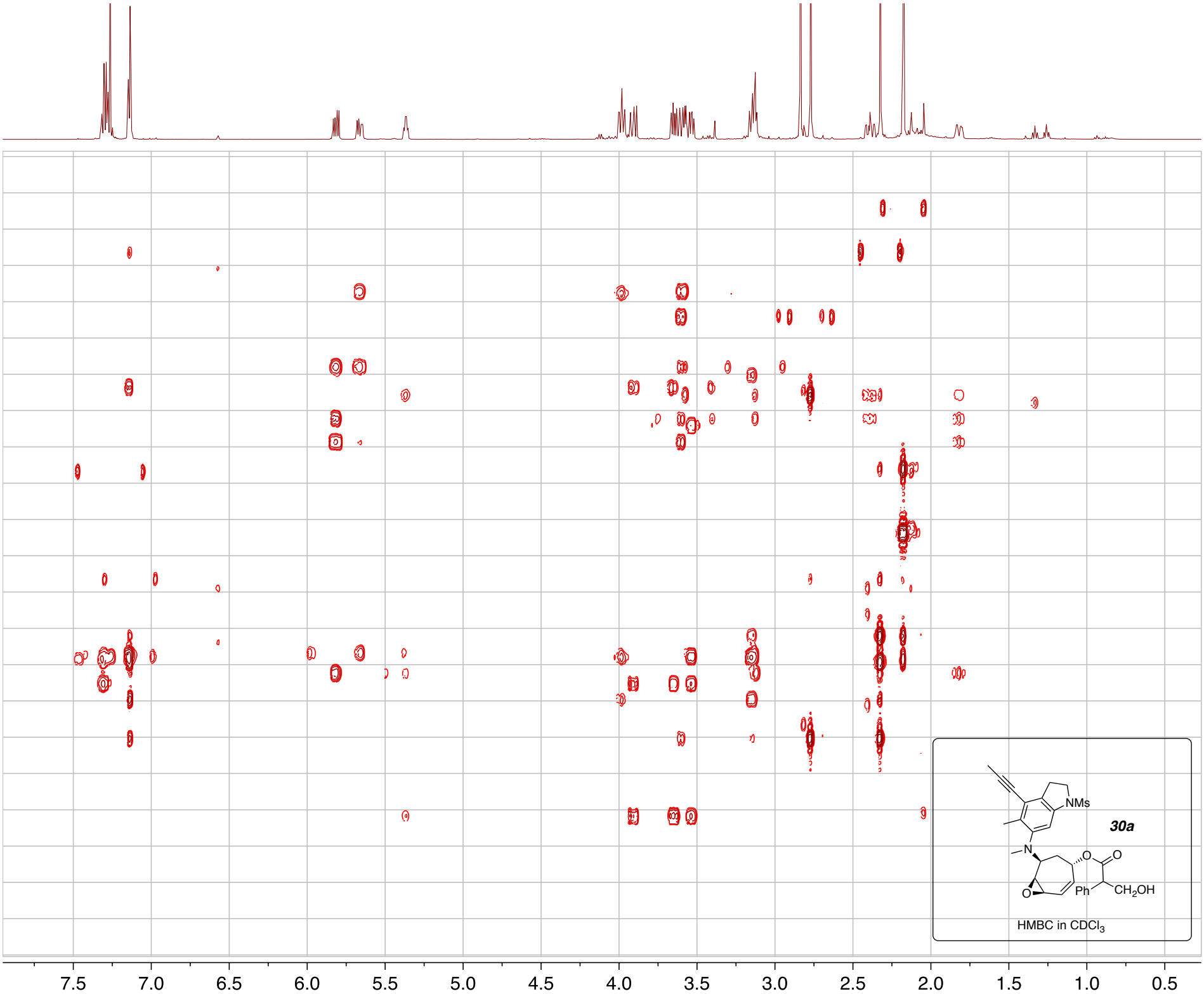


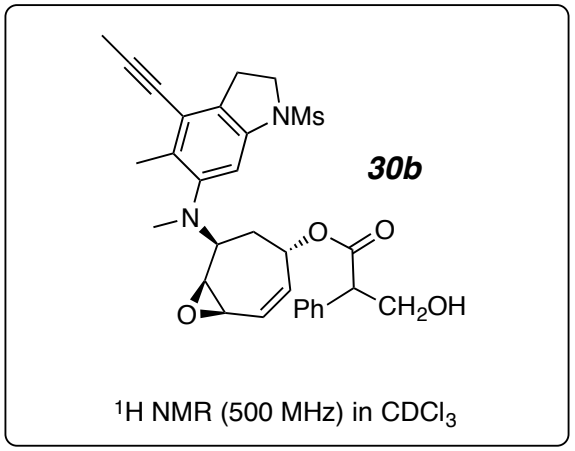
30a

^{1}H NMR (500 MHz) in $CDCl_3$

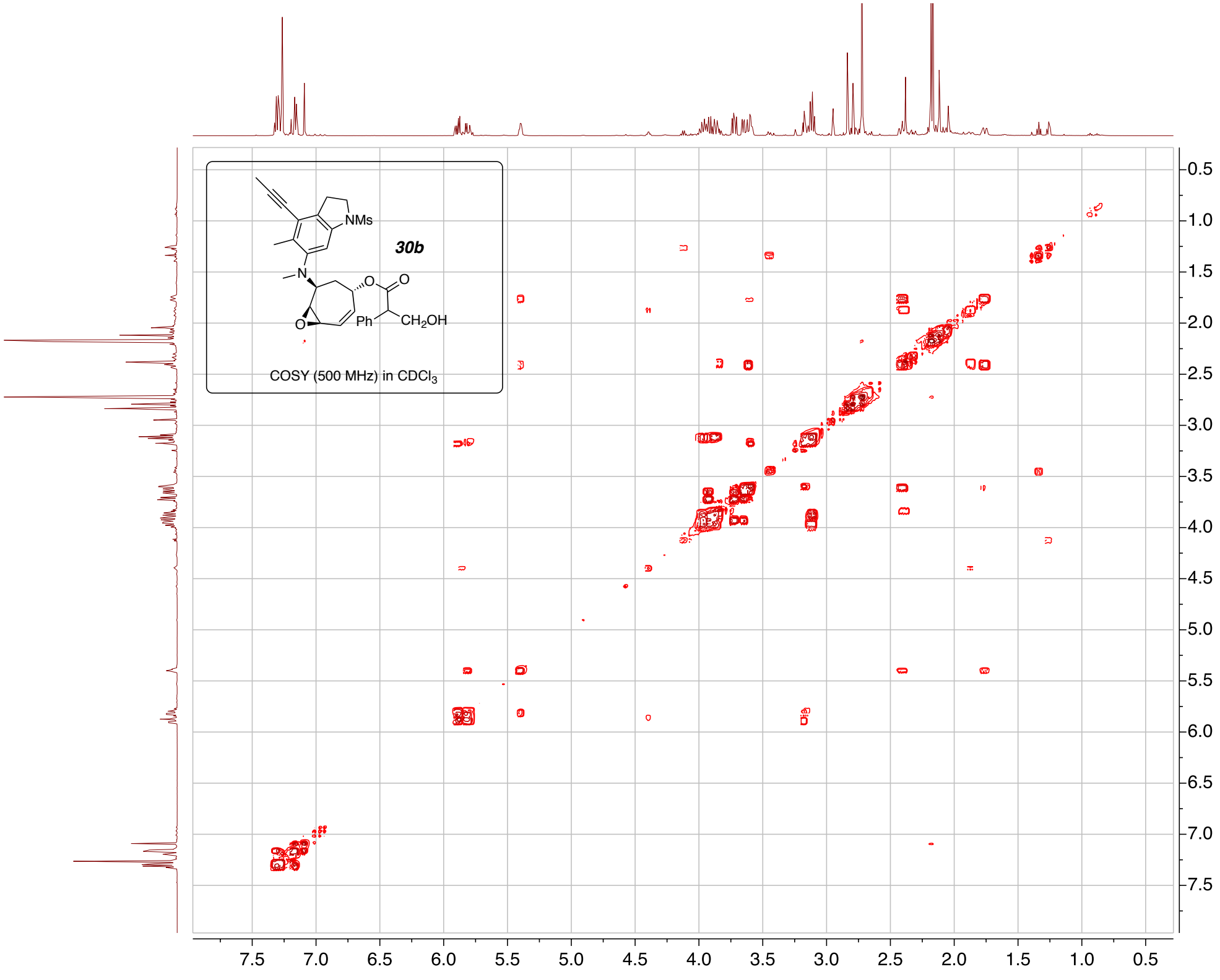

NMs
30a
N
O
O
O
Ph
CH2OH
COSY (500 MHz) in CDCl3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

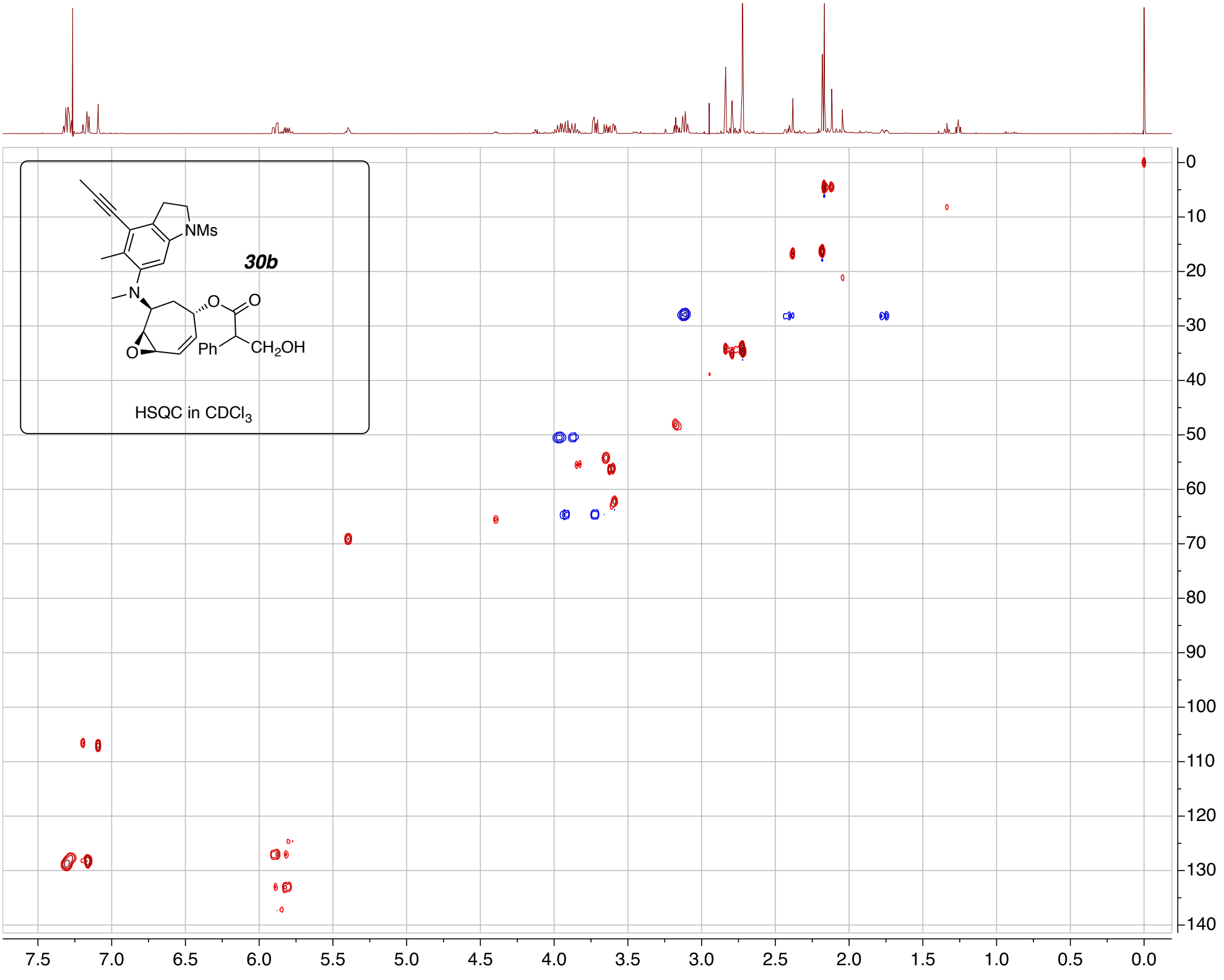

NMs
30a
N
O
O
O
Ph
CH2OH
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

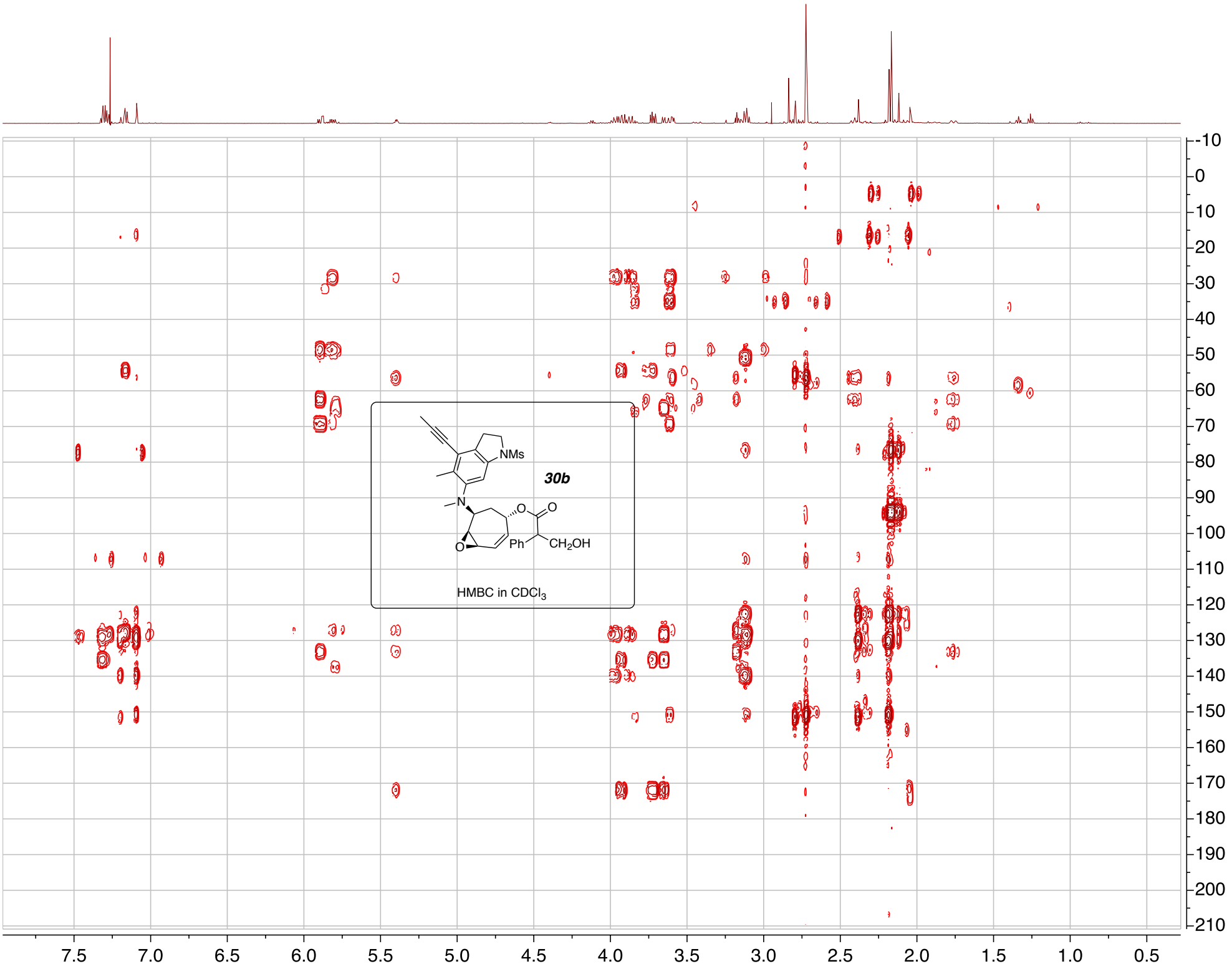

NMs
30a
Ph
CH2OH
HMBC in CDCl3

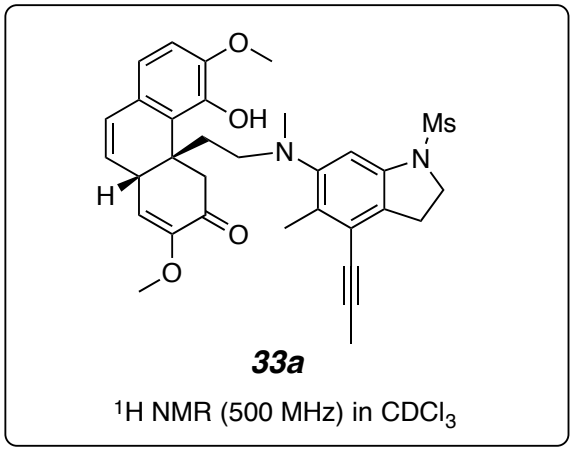

NMs
30b
N
O
O
O
Ph
CH2OH
1H NMR (500 MHz) in CDCl3

3.64 3.60
3.18 3.16
5.88 5.81
5.40
4.00 3.95 3.90 3.85
3.72 3.69
4.42 4.40 4.38
2.43 2.40
1.78 1.76 1.74
.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


NMs
30b
N
O
O
O
Ph
CH2OH
COSY (500 MHz) in CDCl3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

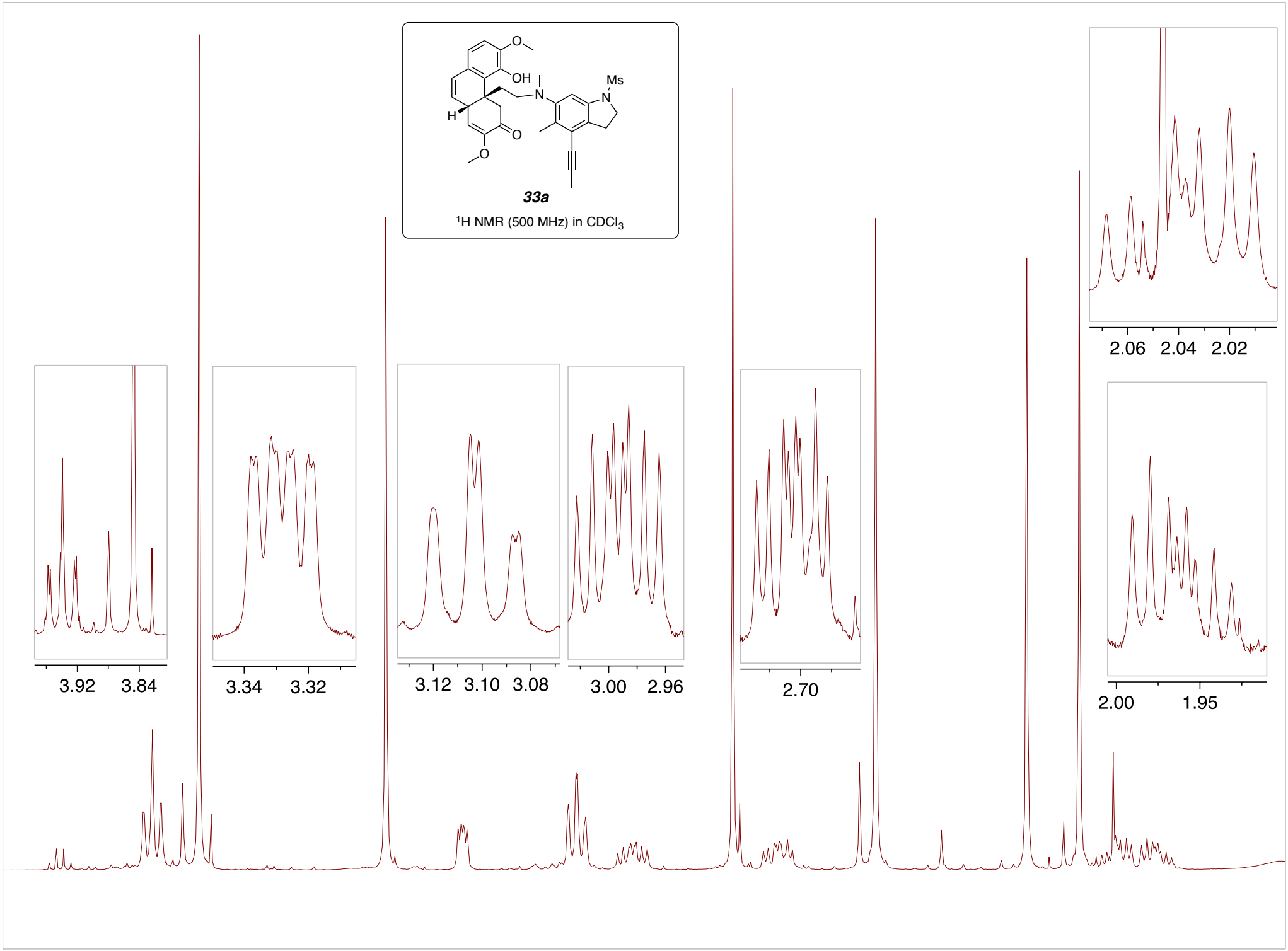

NMs
30b
N
O
O
O
Ph
CH2OH
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

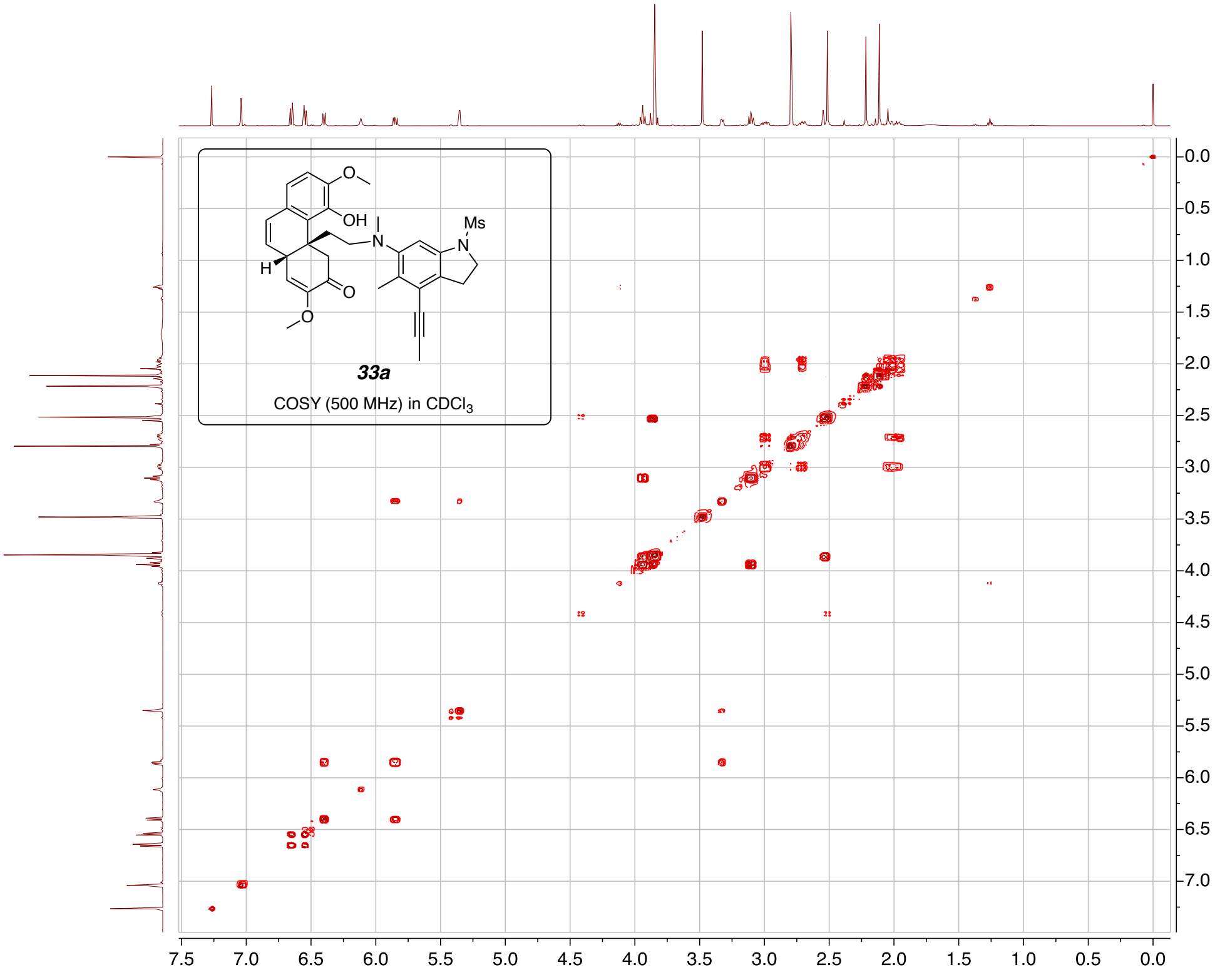

NMs
30b
N
O
O
O
Ph
CH2OH
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

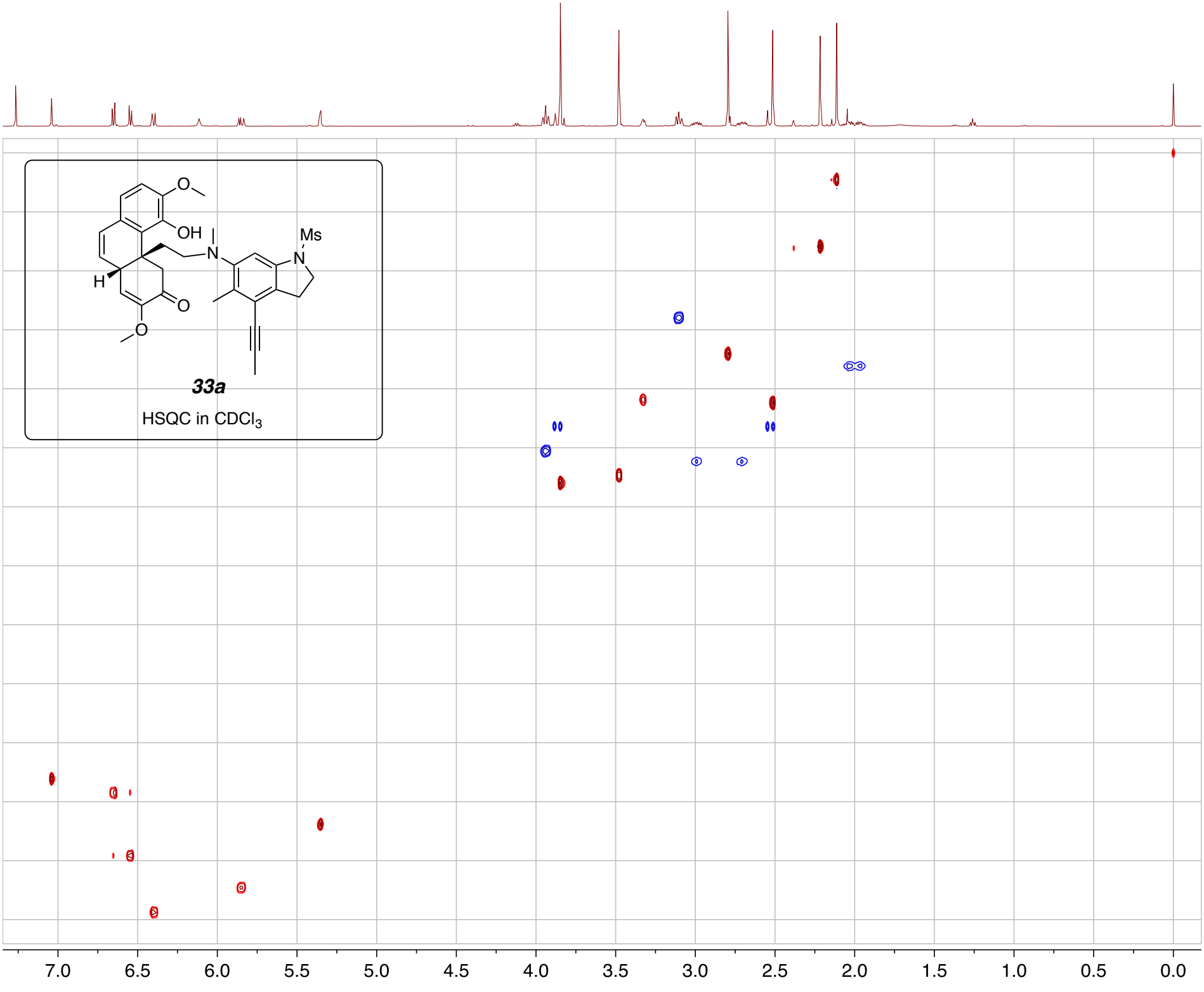


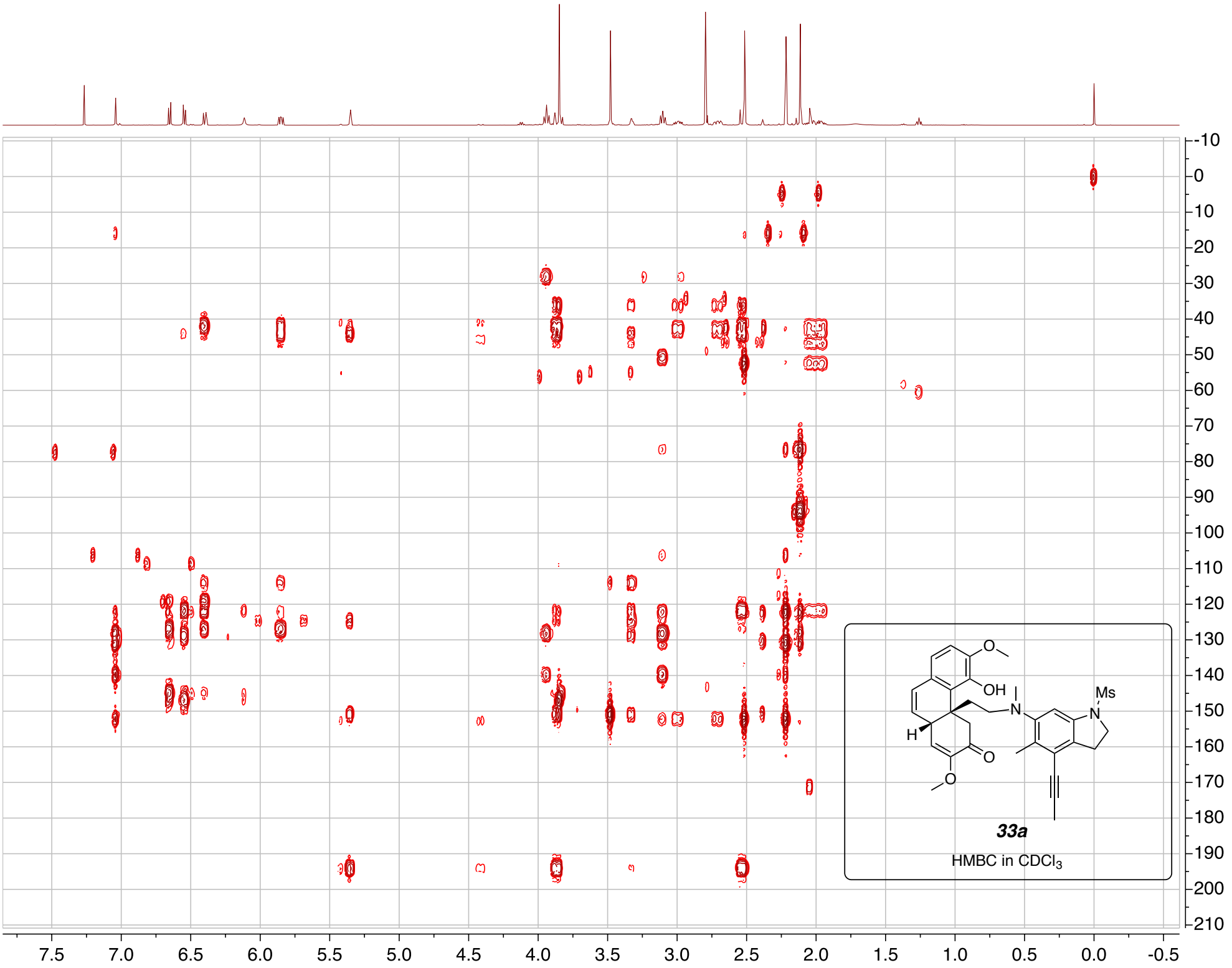
33a

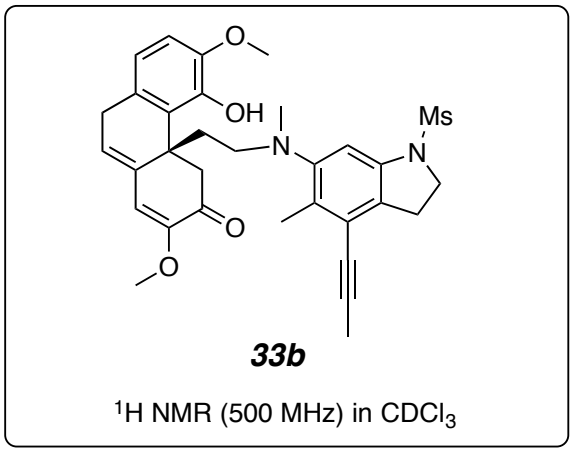
^{1}H NMR (500 MHz) in $CDCl_3$


O
OH
N
Ms
N
H
O
O
33a
1H NMR (500 MHz) in CDCl3
3.92
3.84
3.34
3.32
3.12
3.10
3.08
3.00
2.96
2.70
2.06
2.04
2.02
2.00
1.95
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8


O
OH
N
Ms
N
H
O
O
33a
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

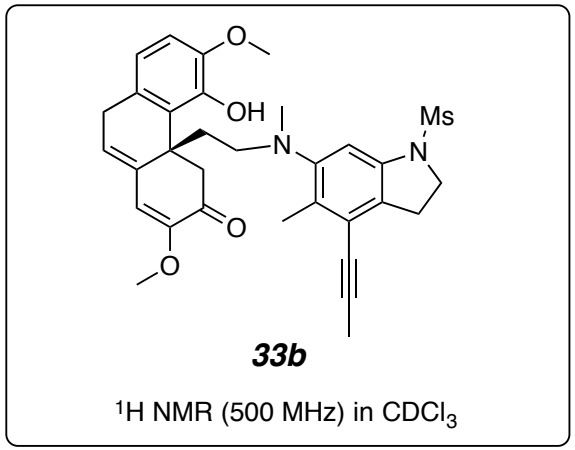

O
OH
N
Ms
N
H
O
O
33a
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
OH
N
Ms
N
H
O
O
33a
HMBC in CDCl3



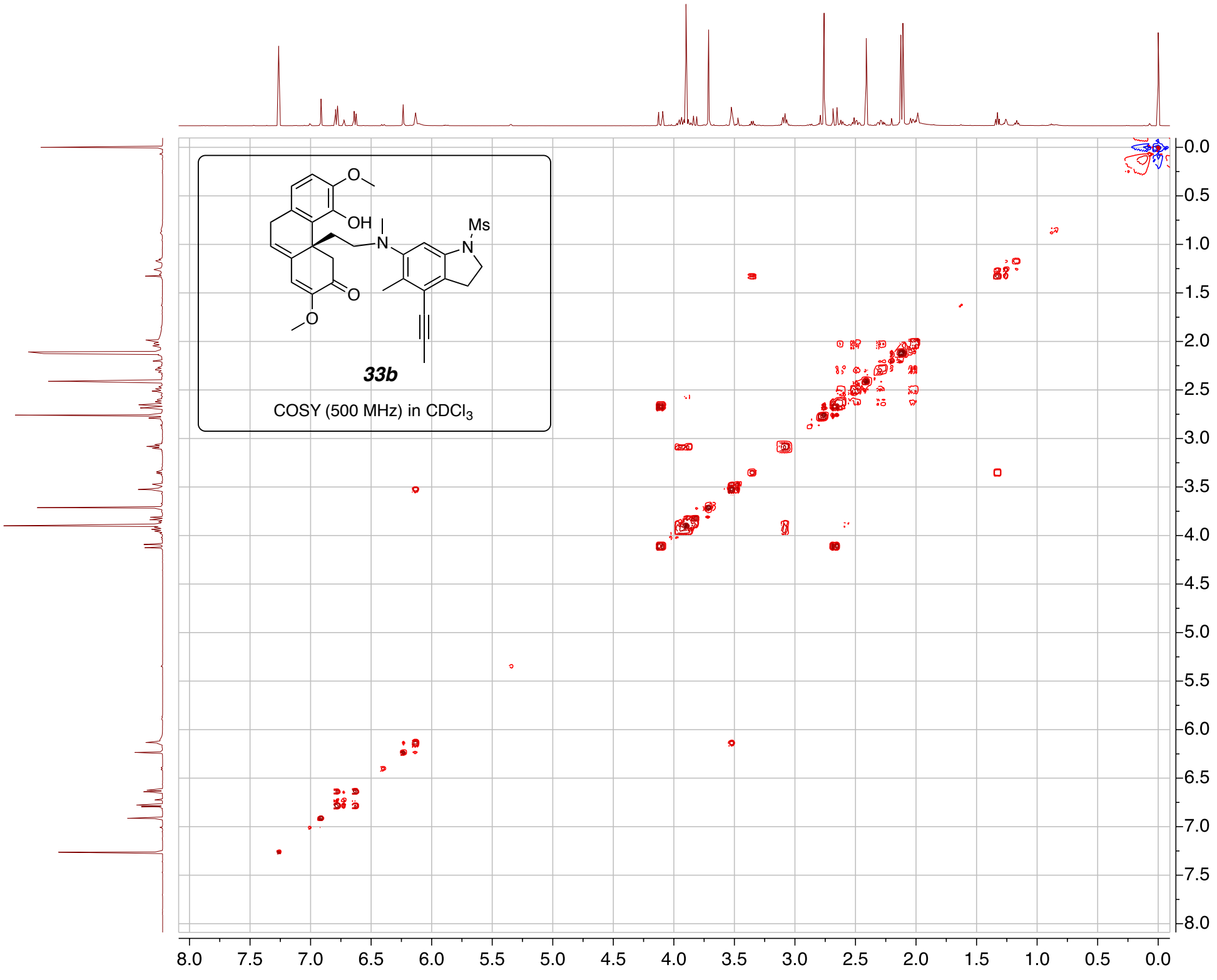
33b

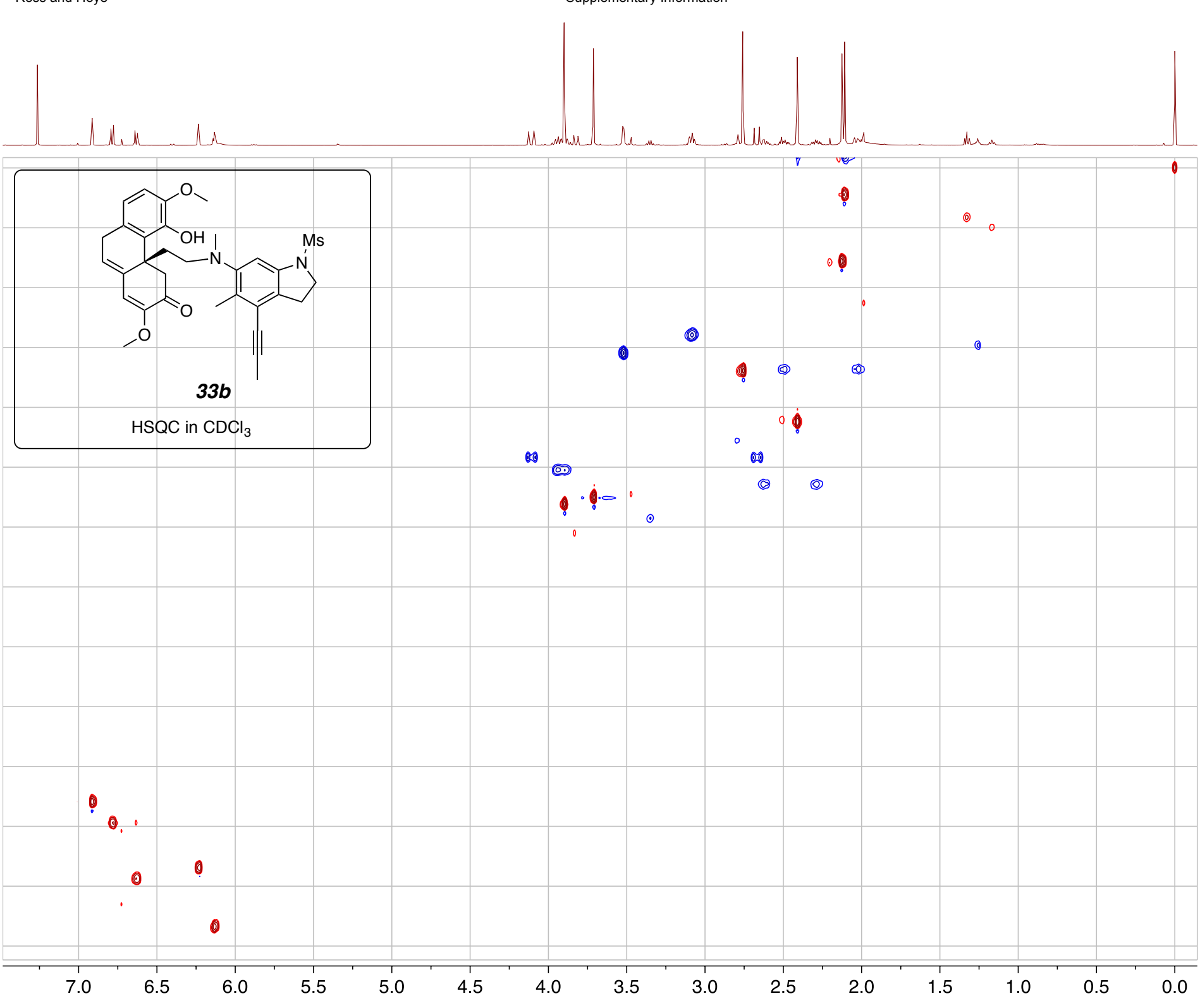
^{1}H NMR (500 MHz) in $CDCl_3$

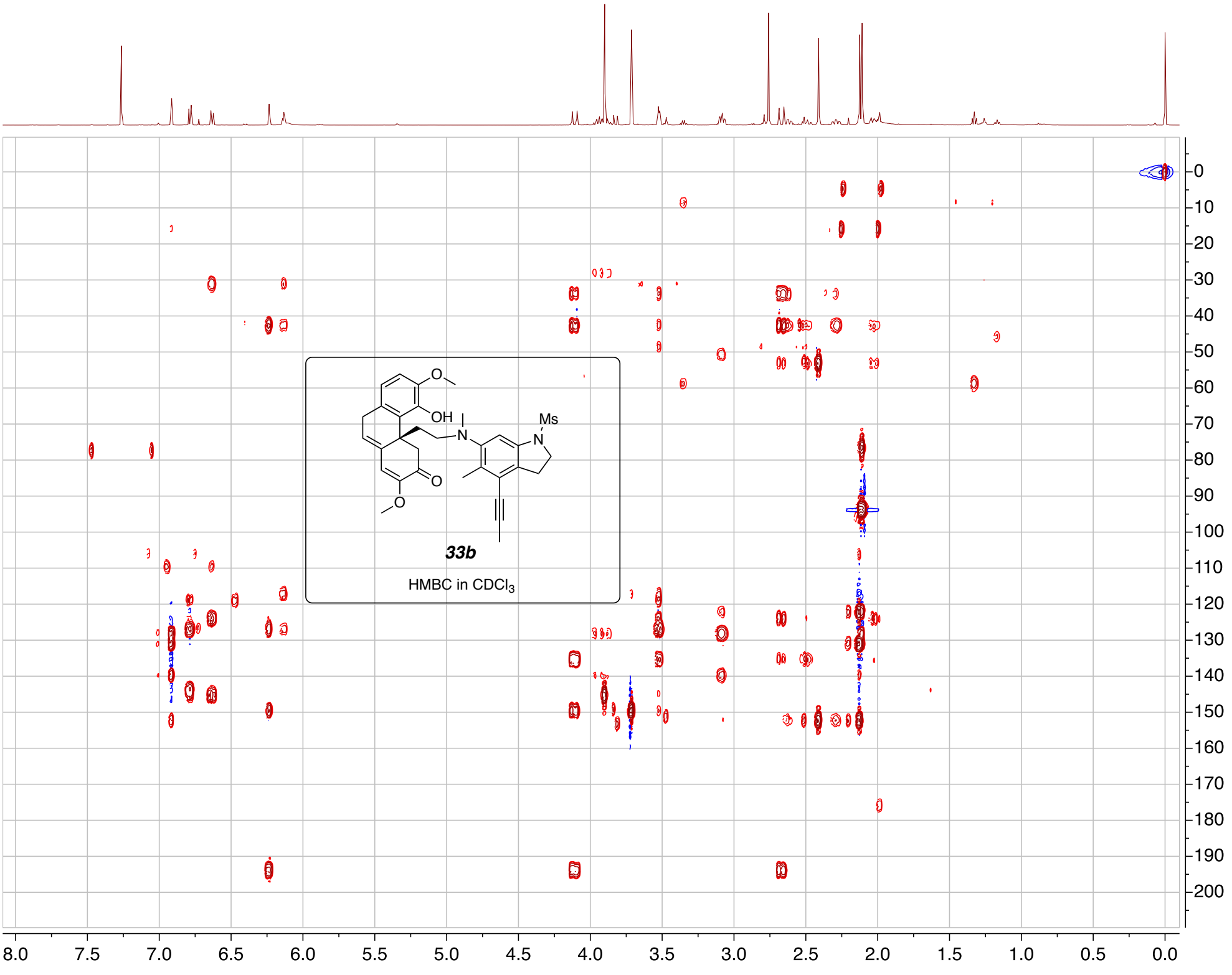


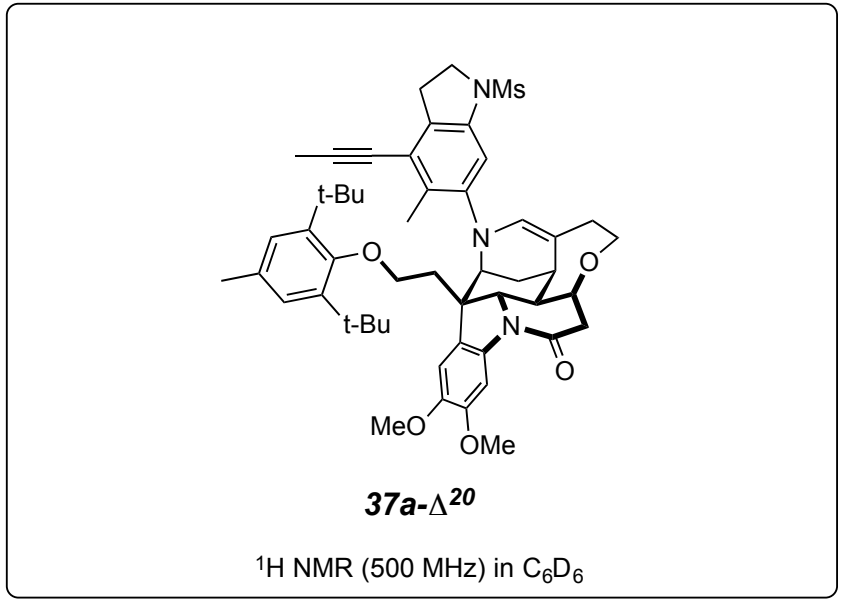
33b

^{1}H NMR (500 MHz) in $CDCl_3$


O
OH
N
Ms
N
O
O
33b
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

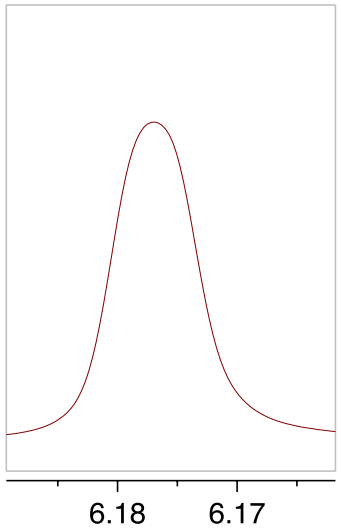

OH
N
Ms
N
O
O
O
33b
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


OH
N
Ms
N
O
O
O
33b
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



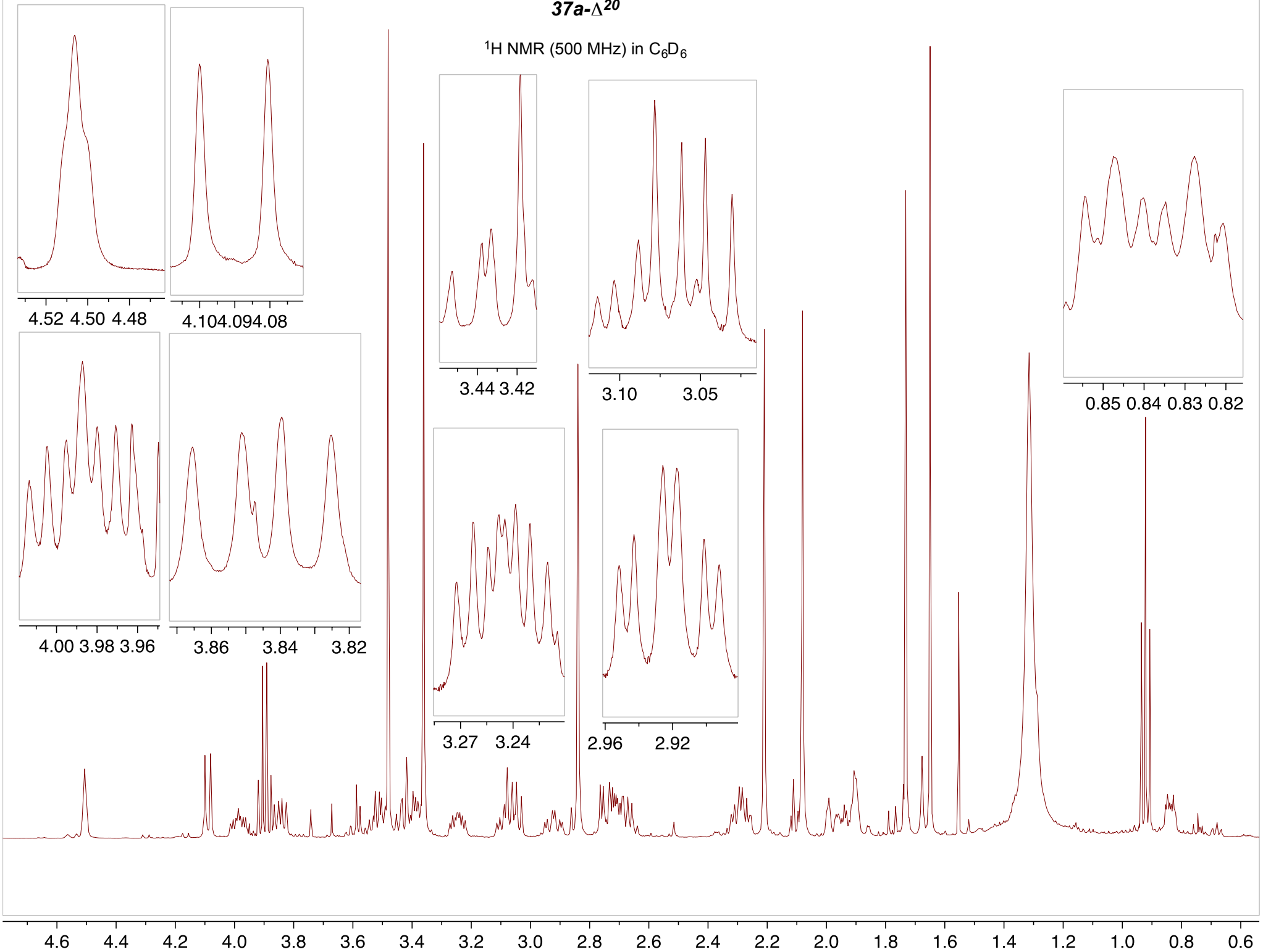
***37a*-Δ^{20}**

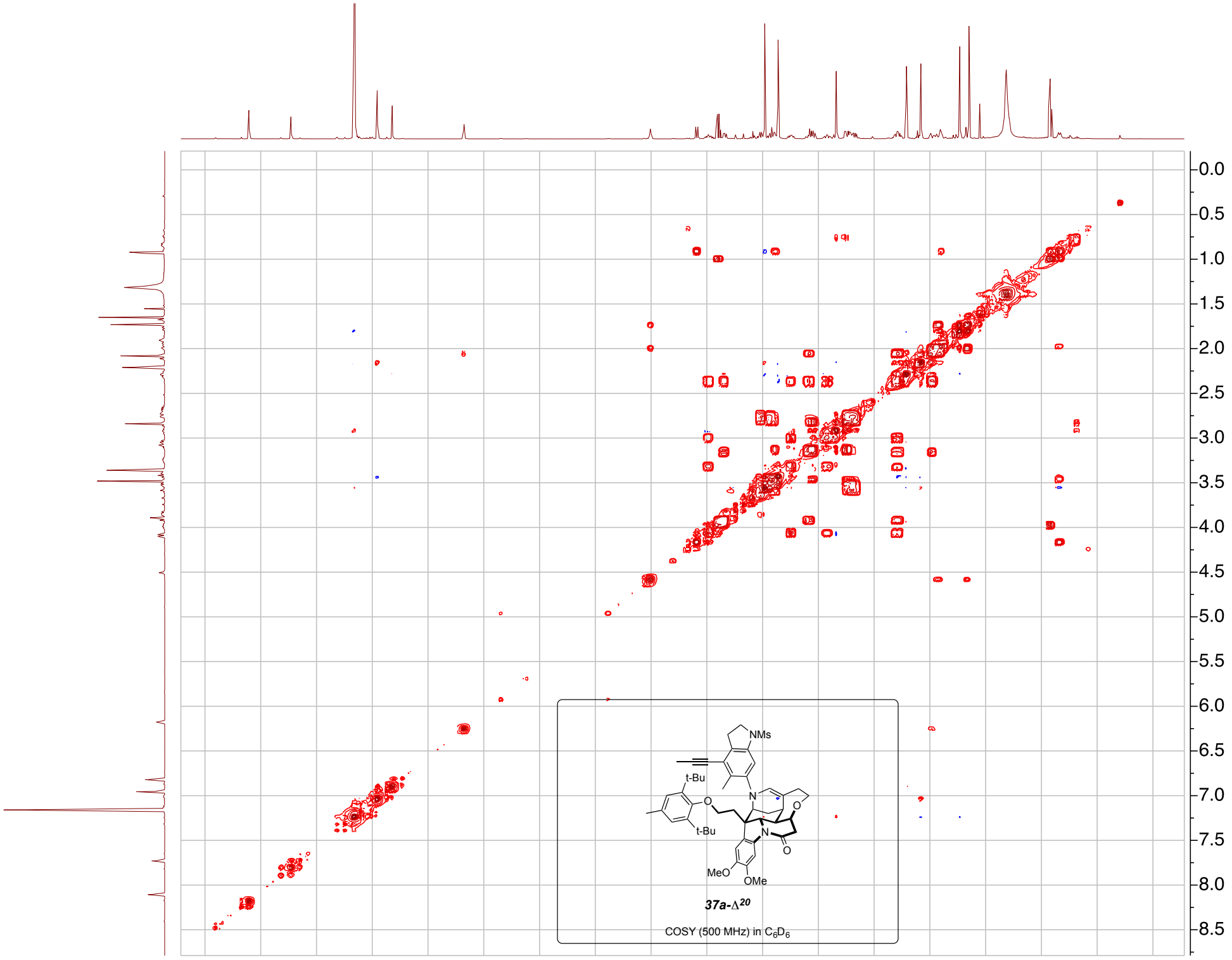
^{1}H NMR (500 MHz) in C_6D_6

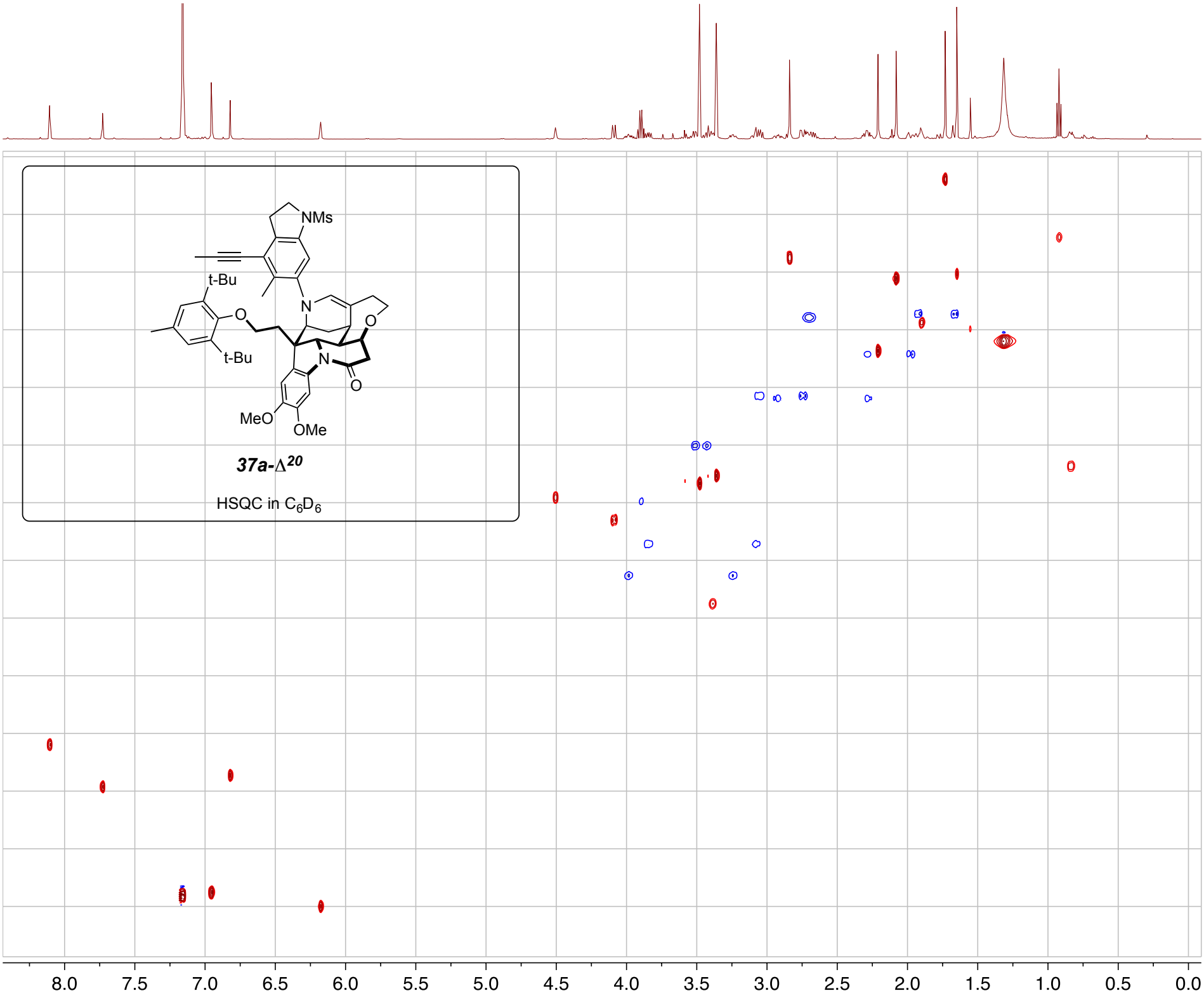


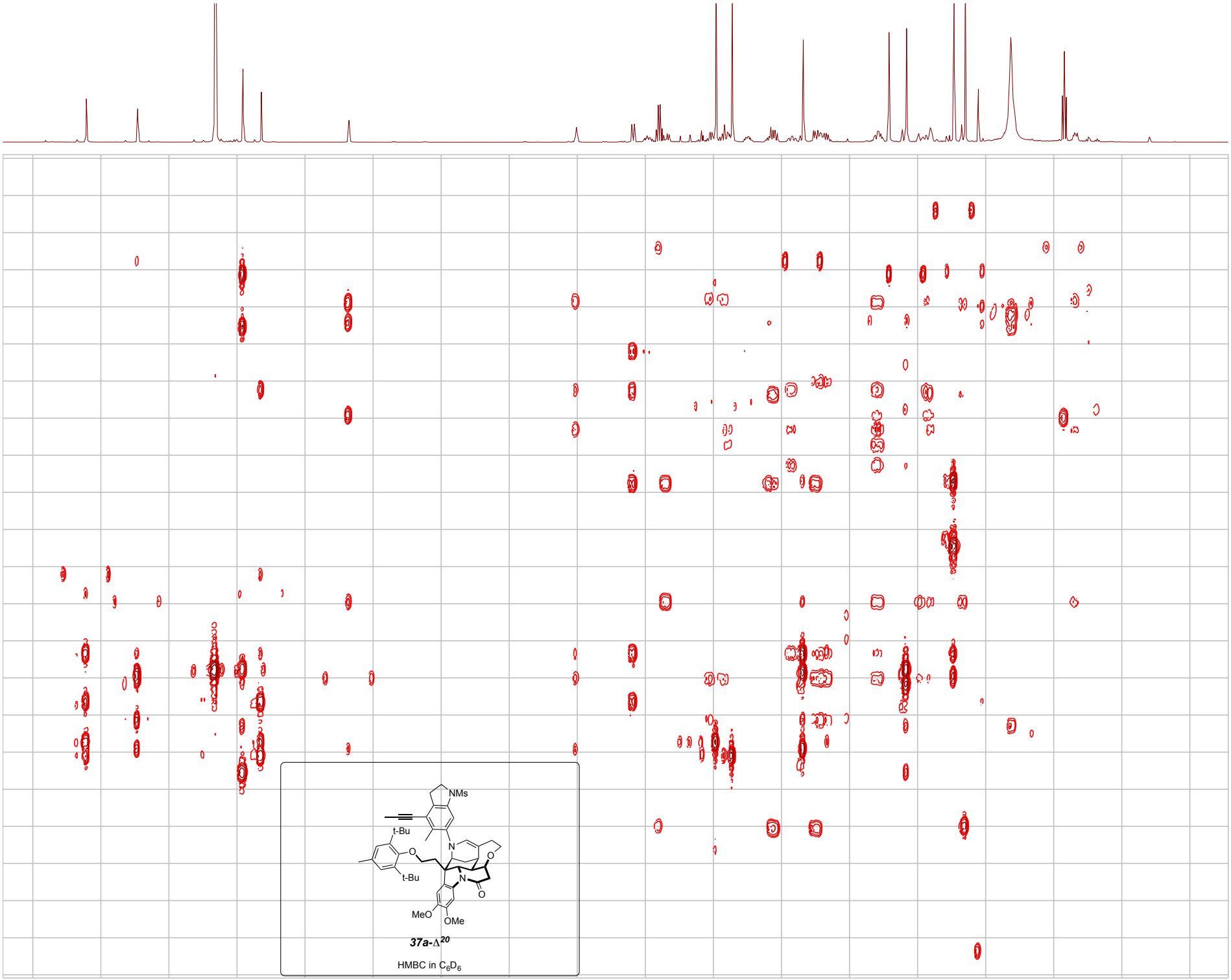
***37a*-Δ^{20}**

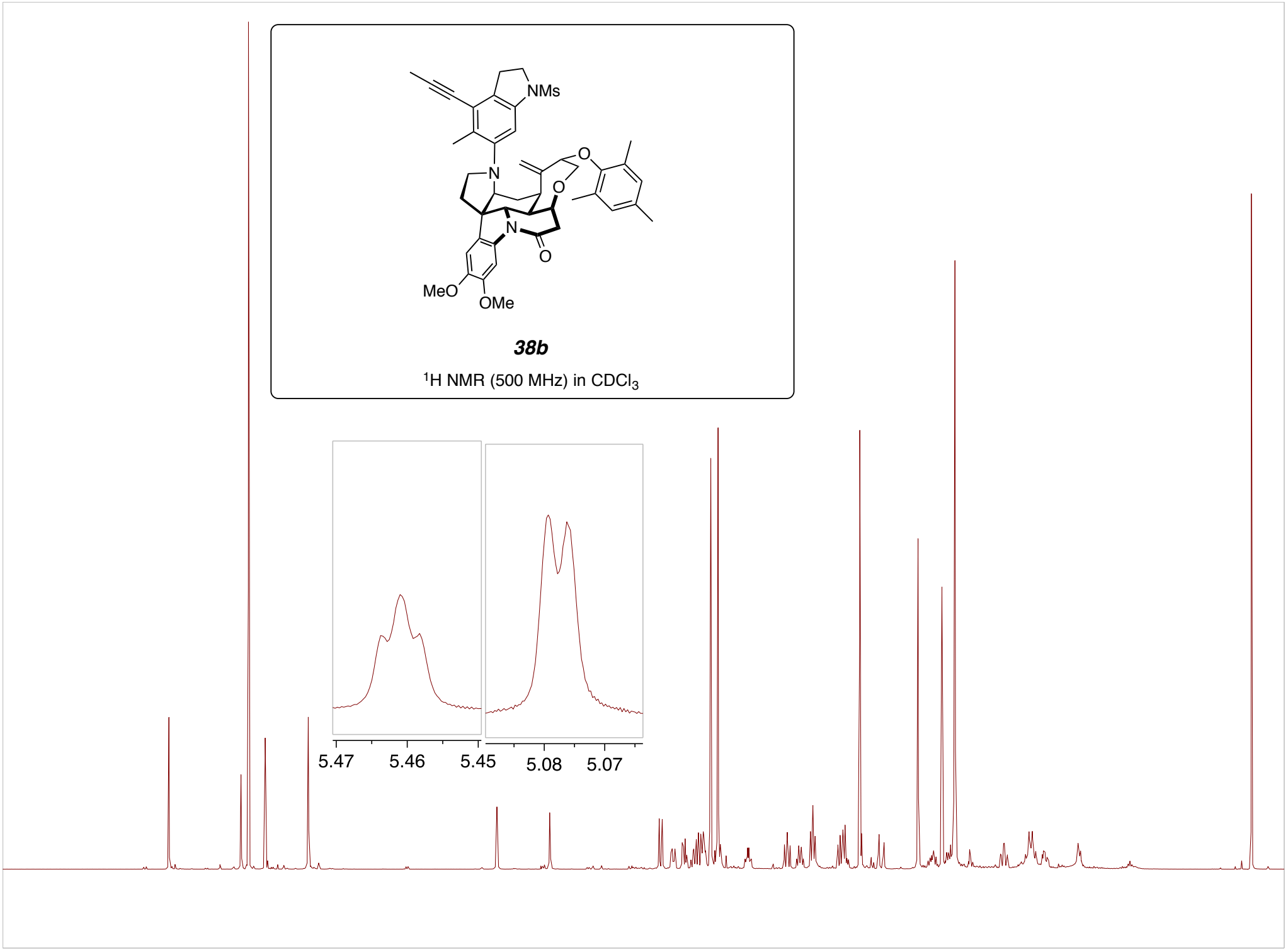
^{1}H NMR (500 MHz) in C_6D_6

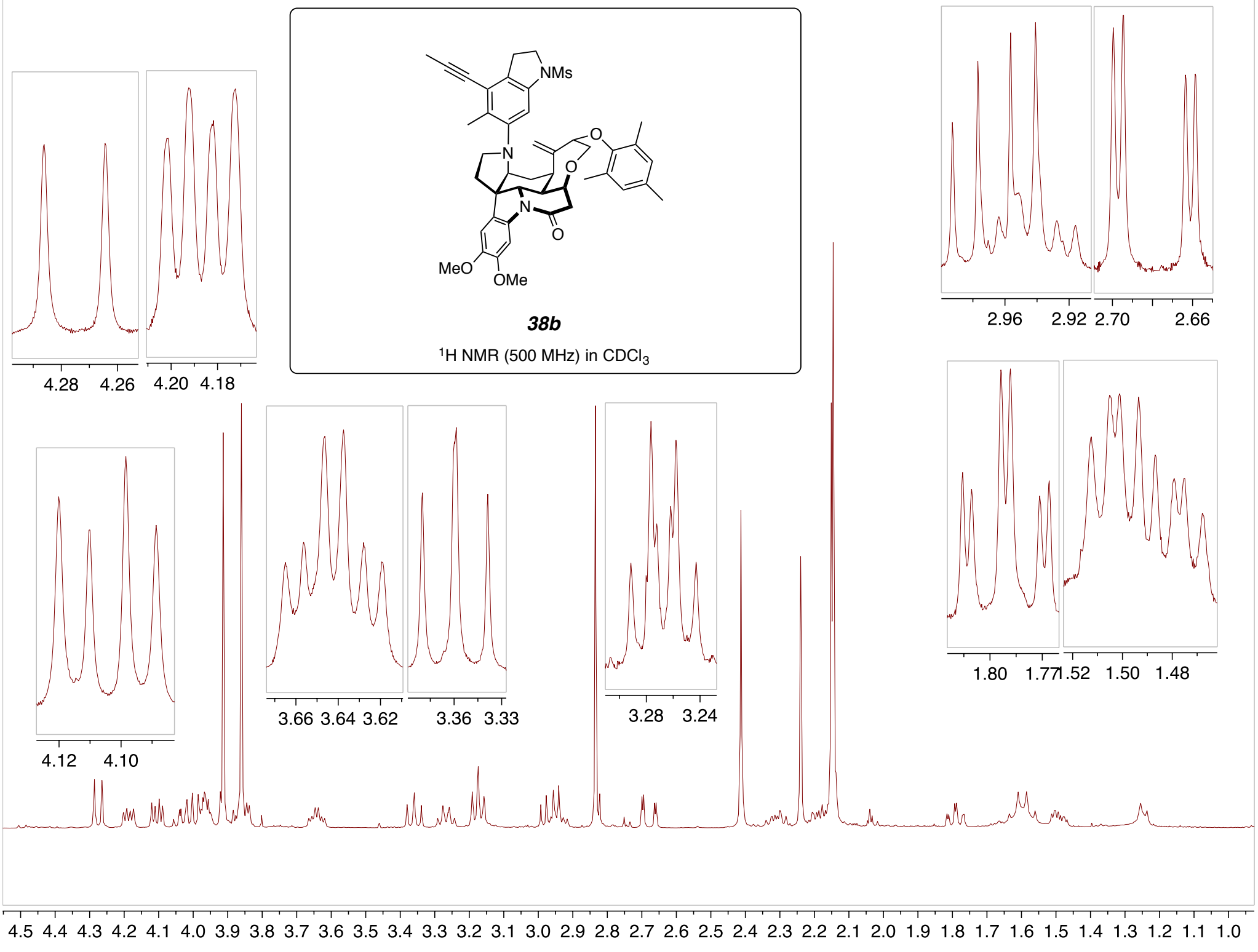


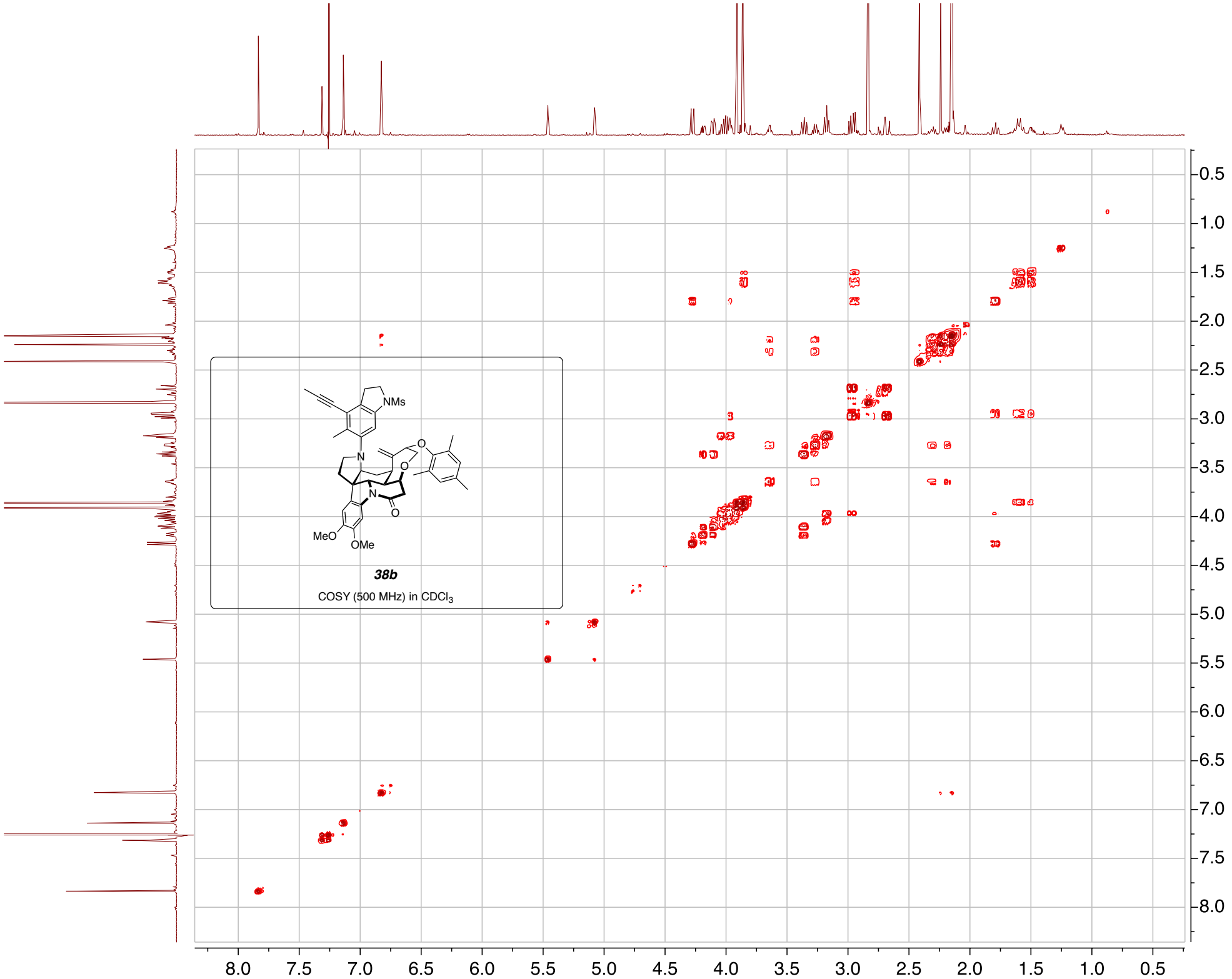

NMs
t-Bu
t-Bu
O
N
O
N
O
MeO
OMe
37a-Δ20
COSY (500 MHz) in C6D6
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5

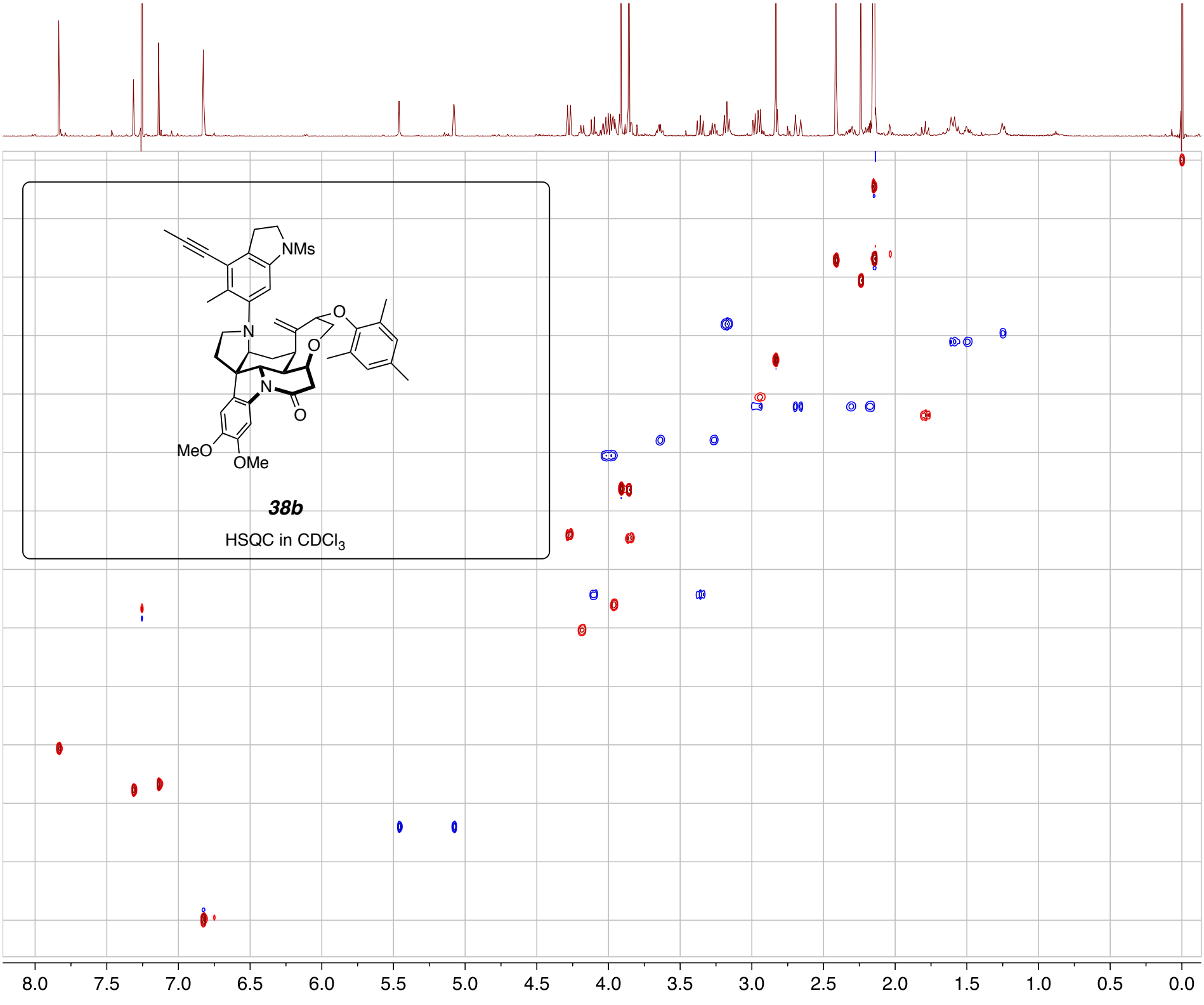

NMs
t-Bu
t-Bu
O
N
O
N
O
MeO
OMe
37a-Δ20
HSQC in C6D6
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

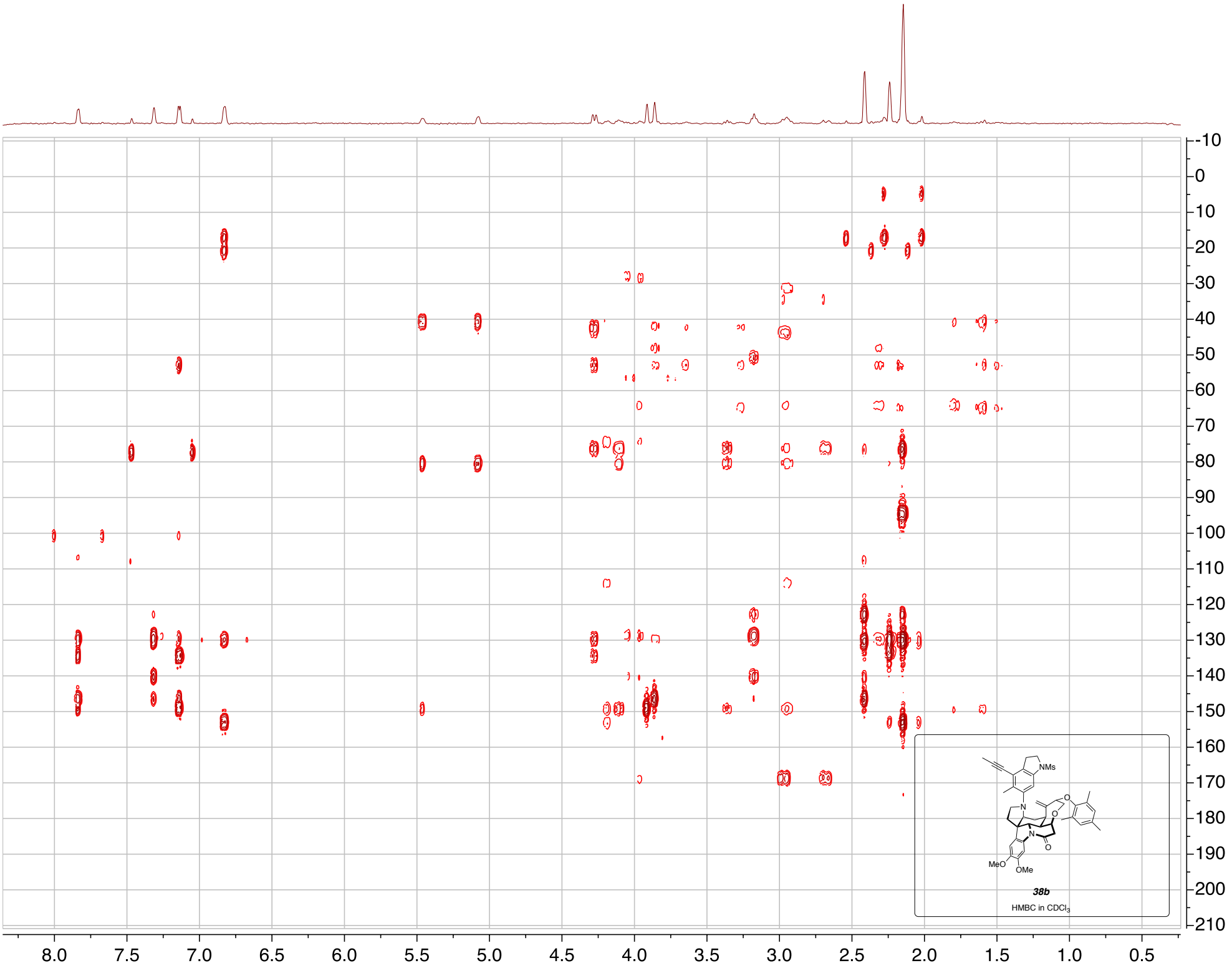

NMs
t-Bu
t-Bu
N
O
O
N
O
MeO
OMe
37a-Δ20
HMBC in C6D6
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

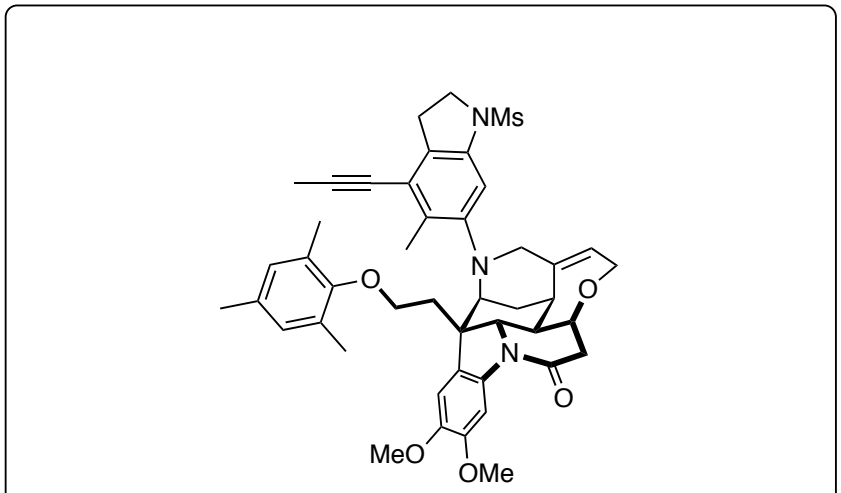

NMs
N
O
O
N
O
MeO
OMe
38b
1H NMR (500 MHz) in CDCl3
5.47
5.46
5.45
5.08
5.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NMs
N
O
O
N
O
MeO
OMe
38b
^{1}H NMR (500 MHz) in $CDCl_3$
4.28 4.26 4.20 4.18
2.96 2.92 2.70 2.66
4.12 4.10
3.66 3.64 3.62 3.36 3.33
3.28 3.24
1.80 1.77 1.52 1.50 1.48
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0


NMs
N
O
O
N
O
MeO
OMe
38b
COSY (500 MHz) in CDCl3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

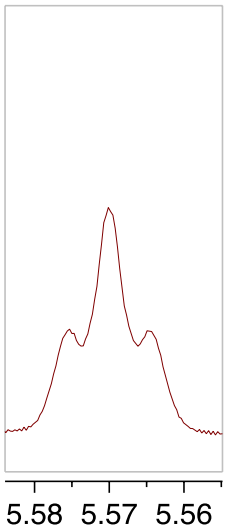

NMs
N
O
O
N
O
MeO
OMe
38b
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NMs
N
O
O
N
O
MeO
OMe
38b
HMBC in CDCl3



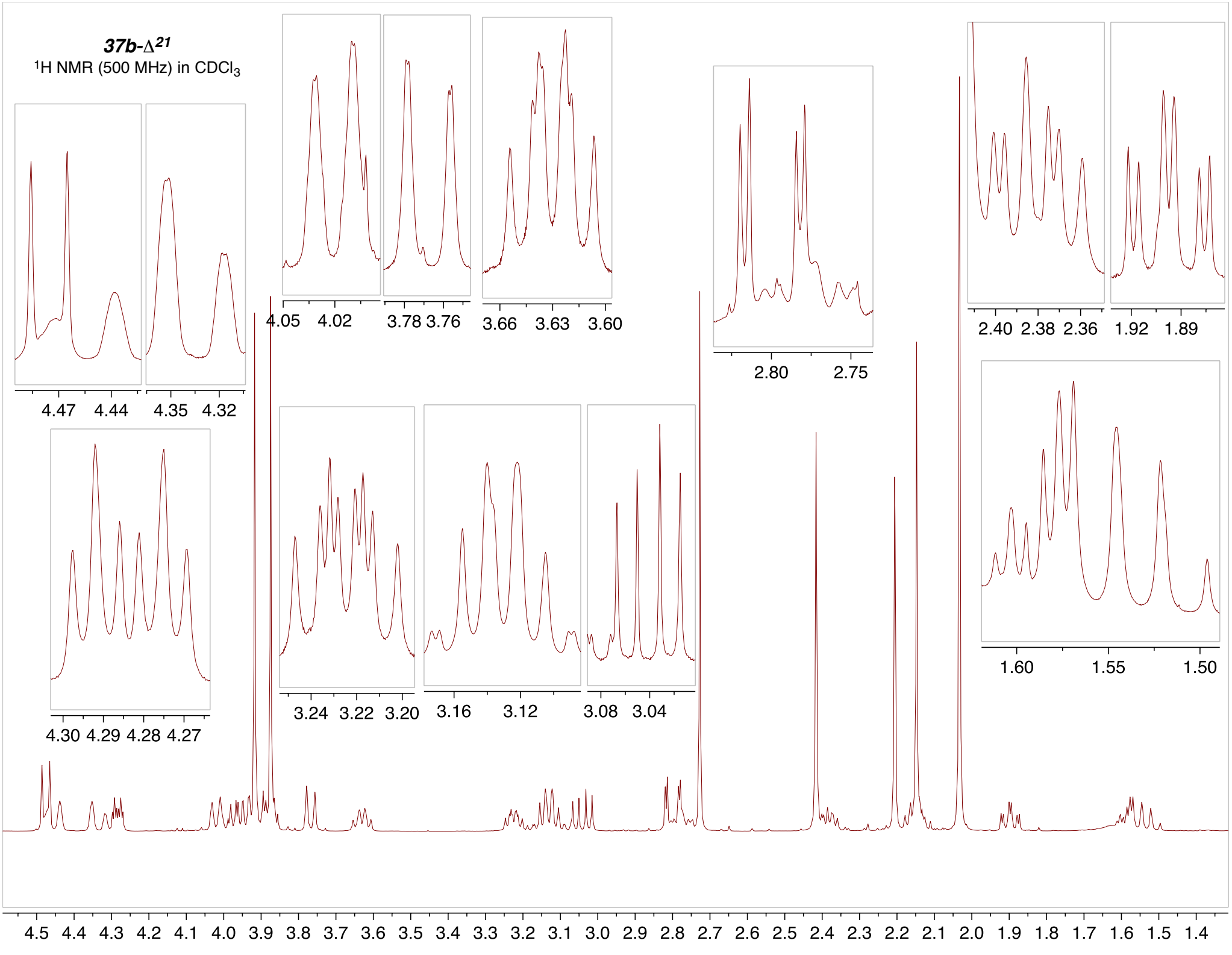
***37b*-Δ^{21}**

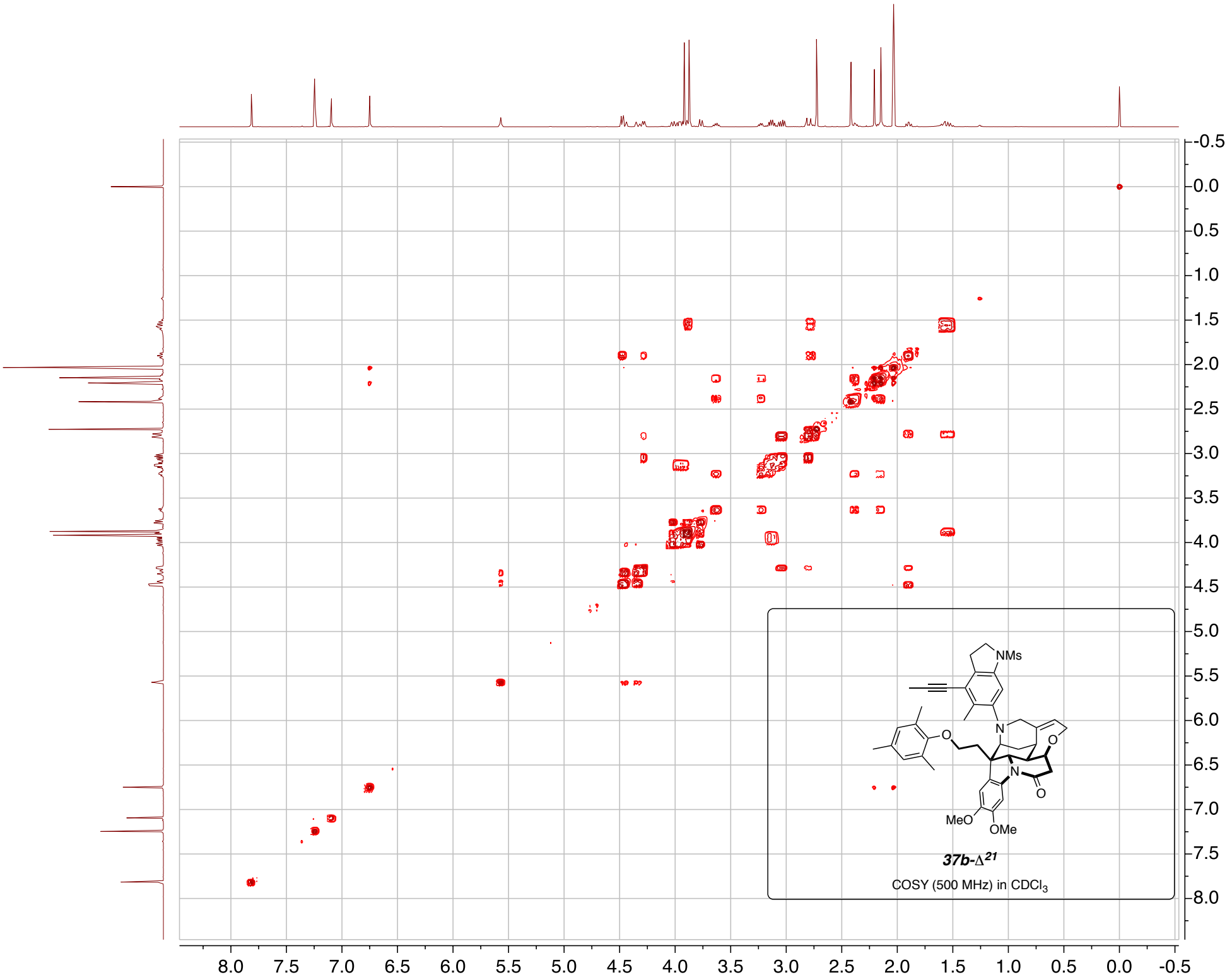
^{1}H NMR (500 MHz) in $CDCl_3$

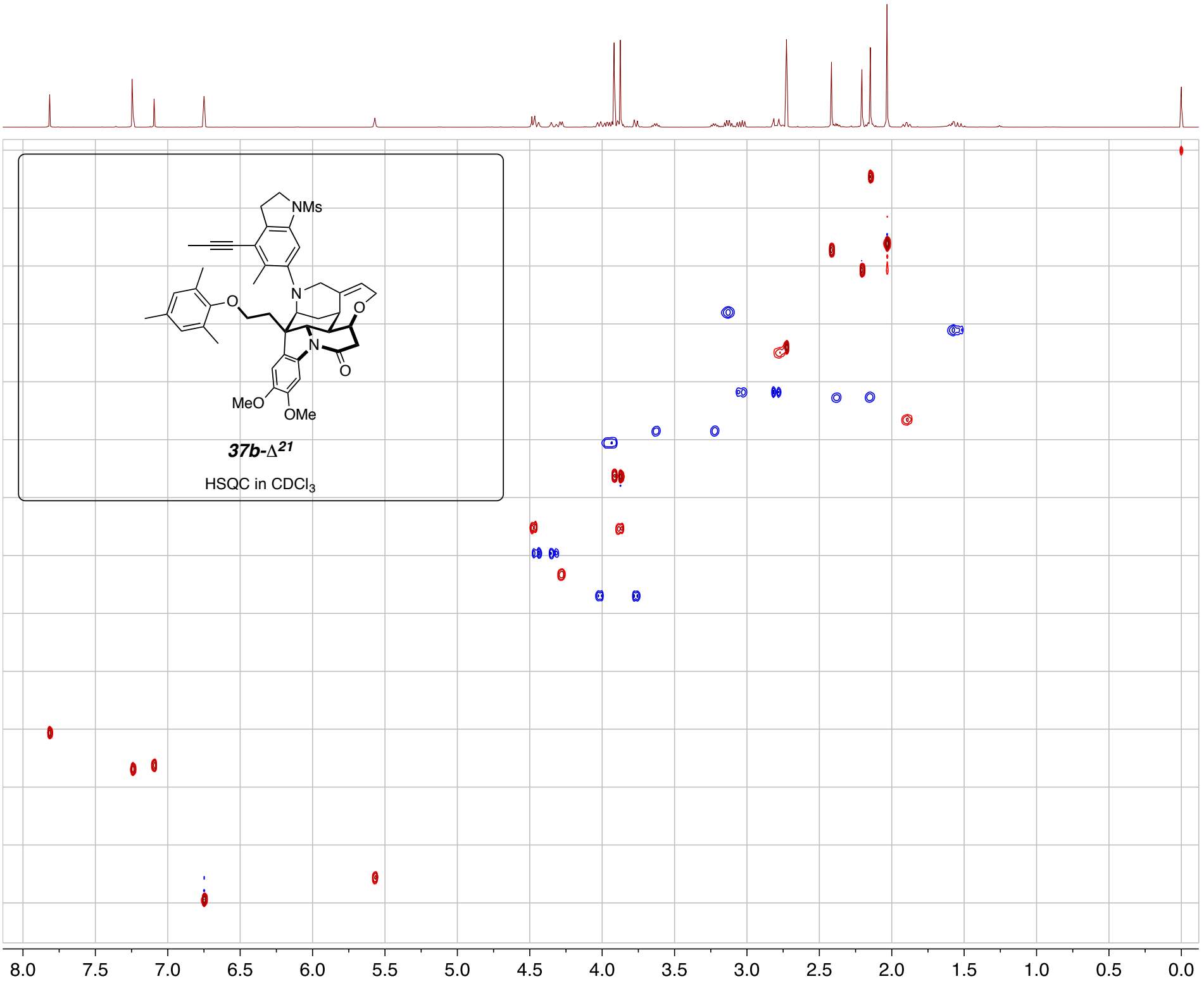


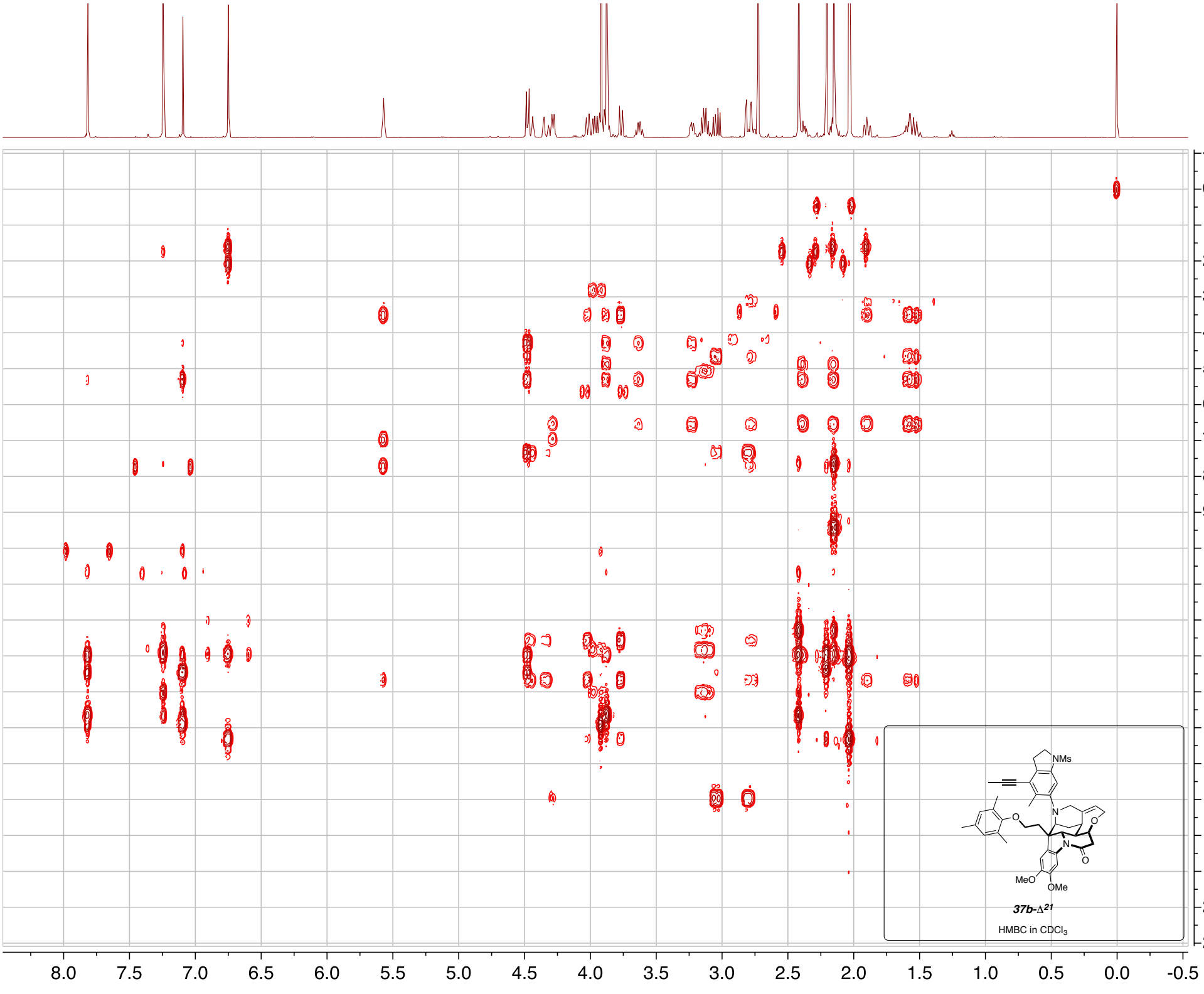
***37b*-Δ^{21}**

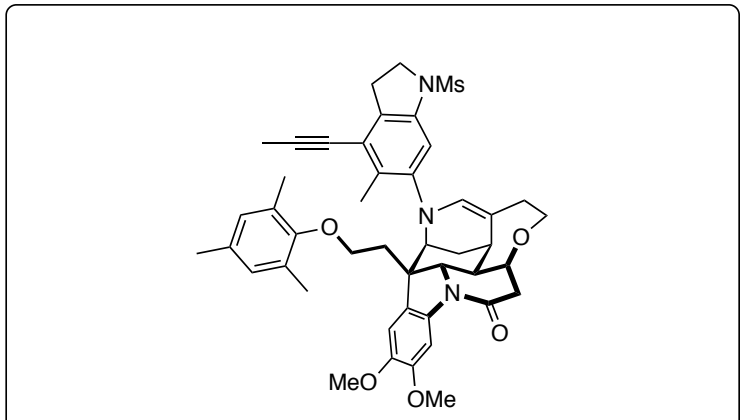
^{1}H NMR (500 MHz) in $CDCl_3$




NMs
N
O
O
N
O
MeO
OMe
37b-Δ21
COSY (500 MHz) in CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0

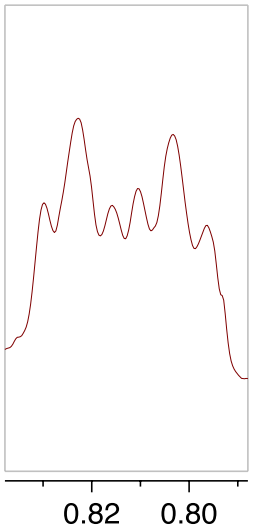

NMs
N
O
O
N
O
MeO
OMe
37b-Δ21
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

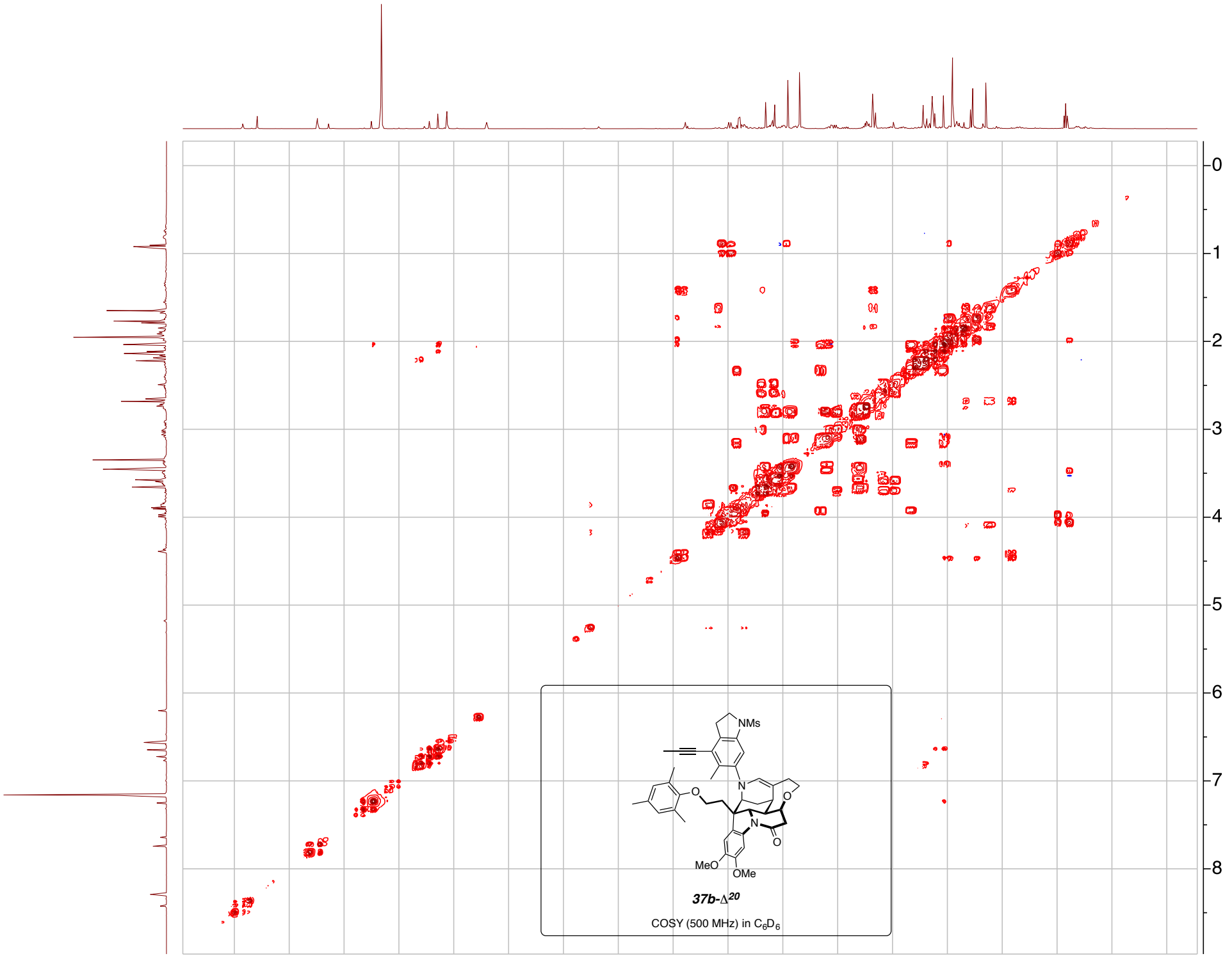

NMs
N
O
N
O
O
MeO
OMe
37b-Δ21
HMBC in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

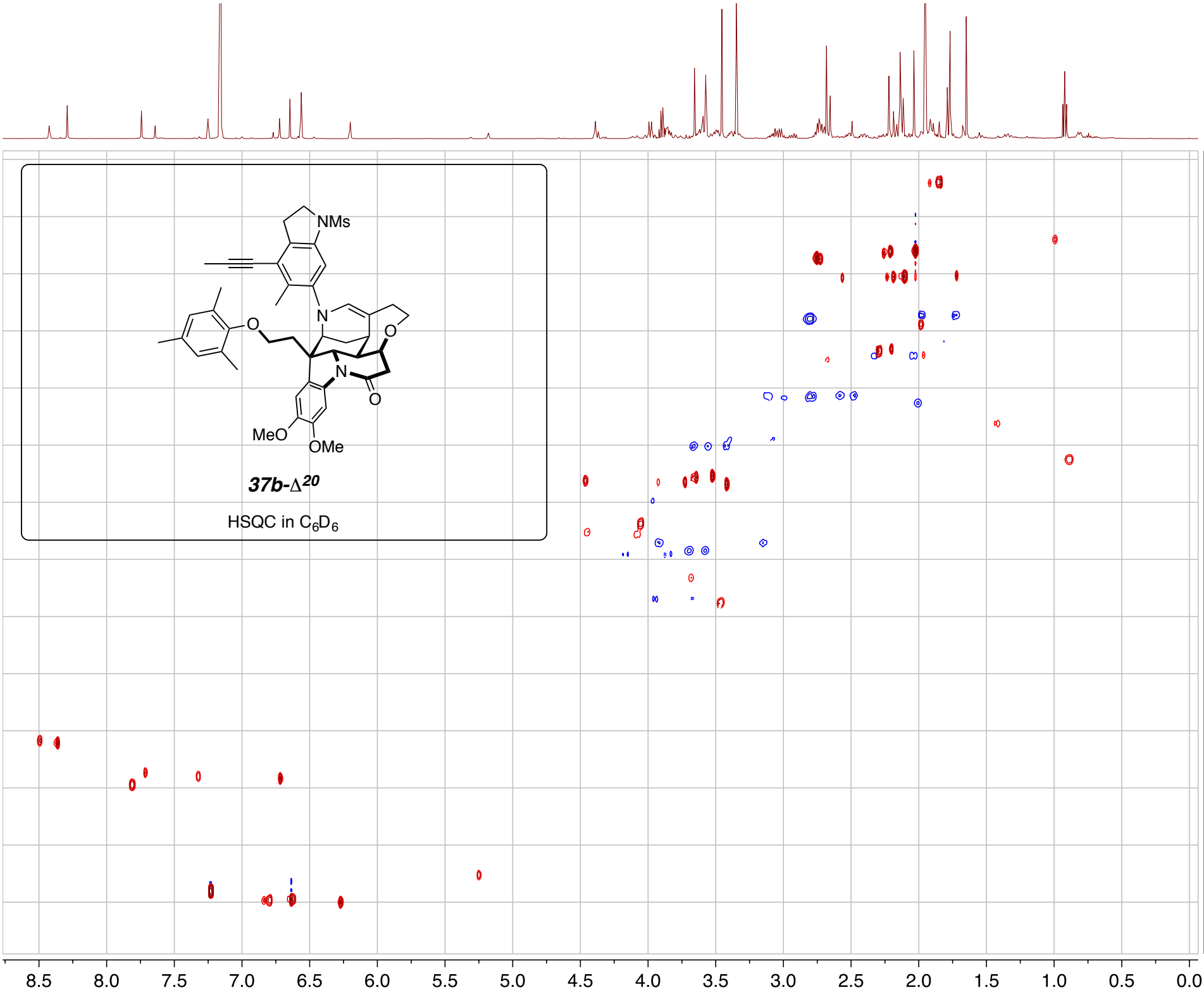


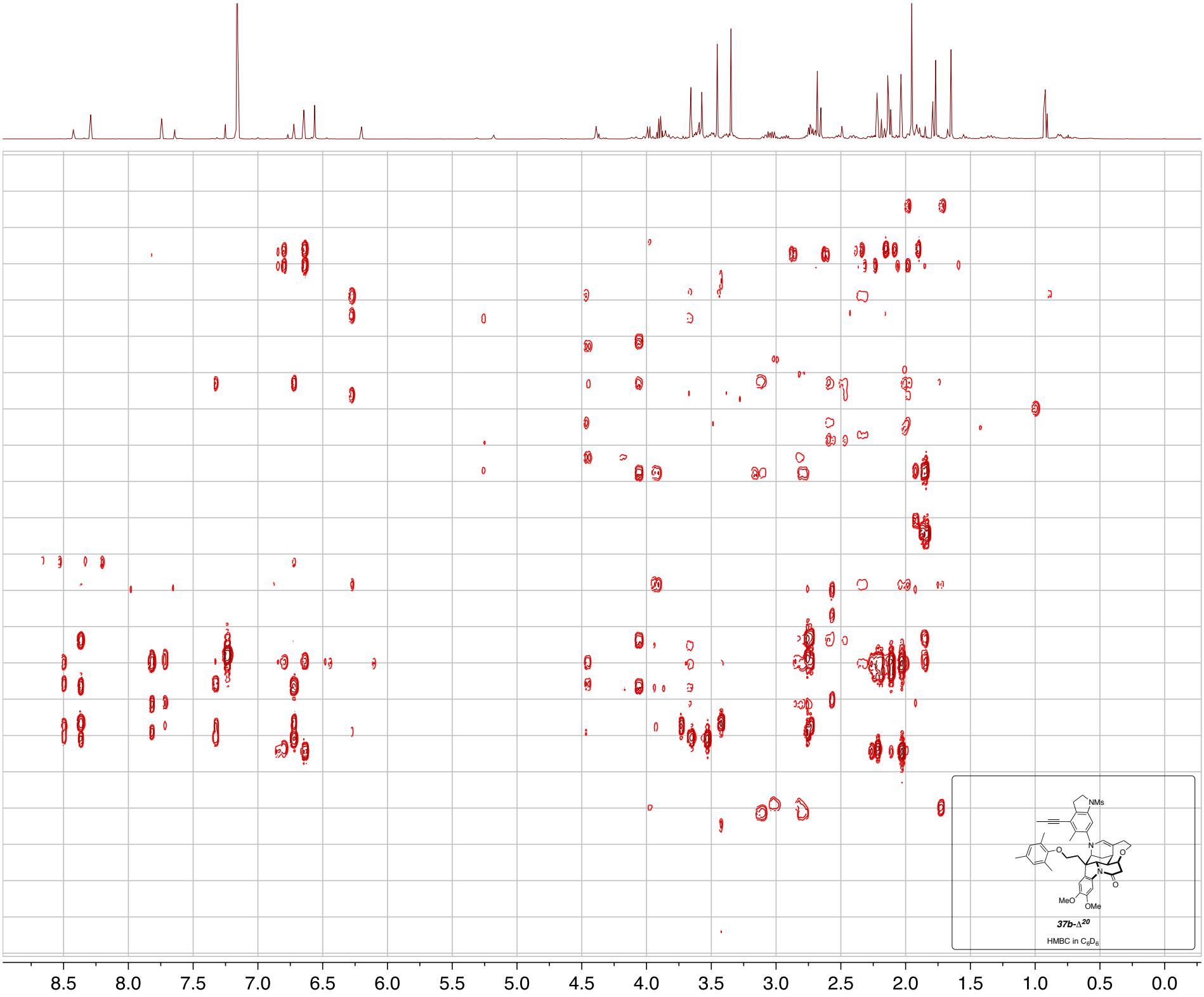
***37b*-Δ^{20}**

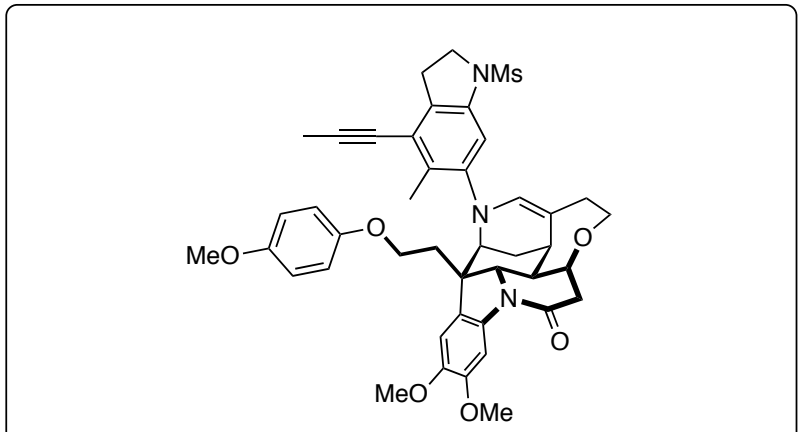
^{1}H NMR (500 MHz) in C_6D_6




NMs
N
O
O
N
O
MeO
OMe
37b-Δ20
COSY (500 MHz) in C6D6
0
1
2
3
4
5
6
7
8
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

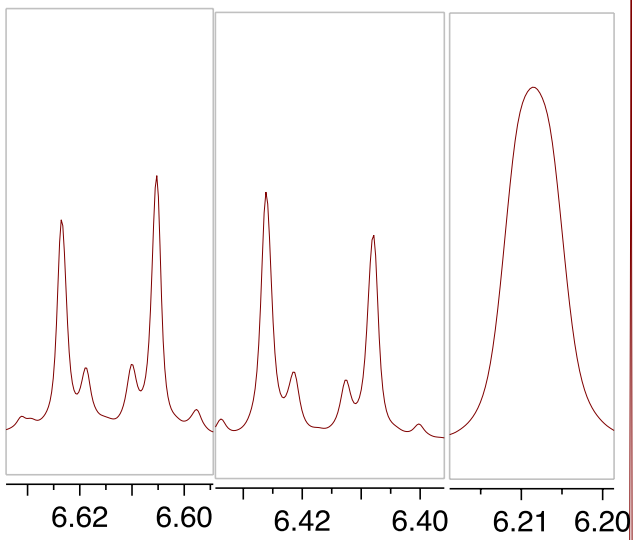

NMs
N
O
O
N
O
MeO
OMe
37b-Δ20
HSQC in C6D6
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NMs
N
O
N
O
MeO
OMe
37b-Δ20
HMBC in C6D6



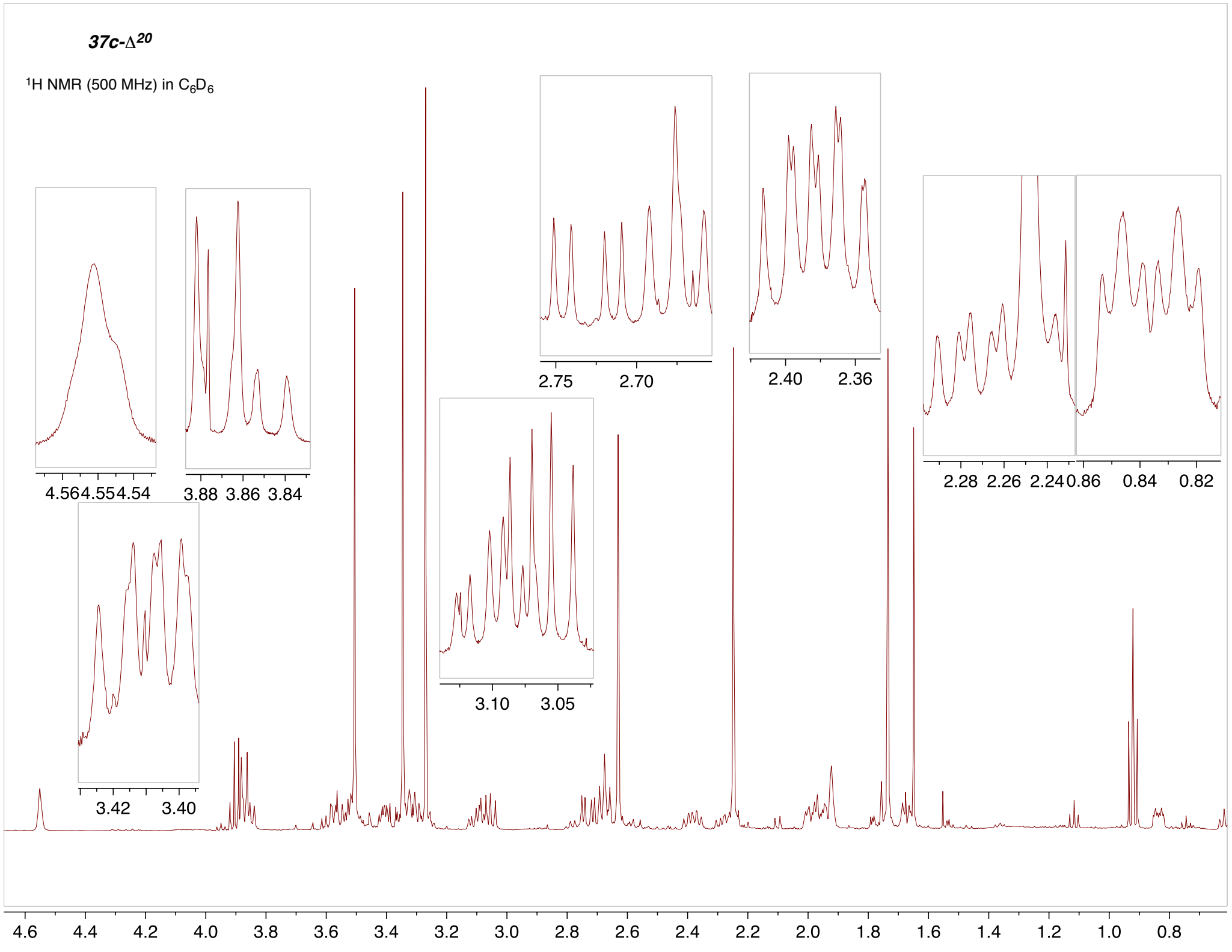
***37c*-Δ^{20}**

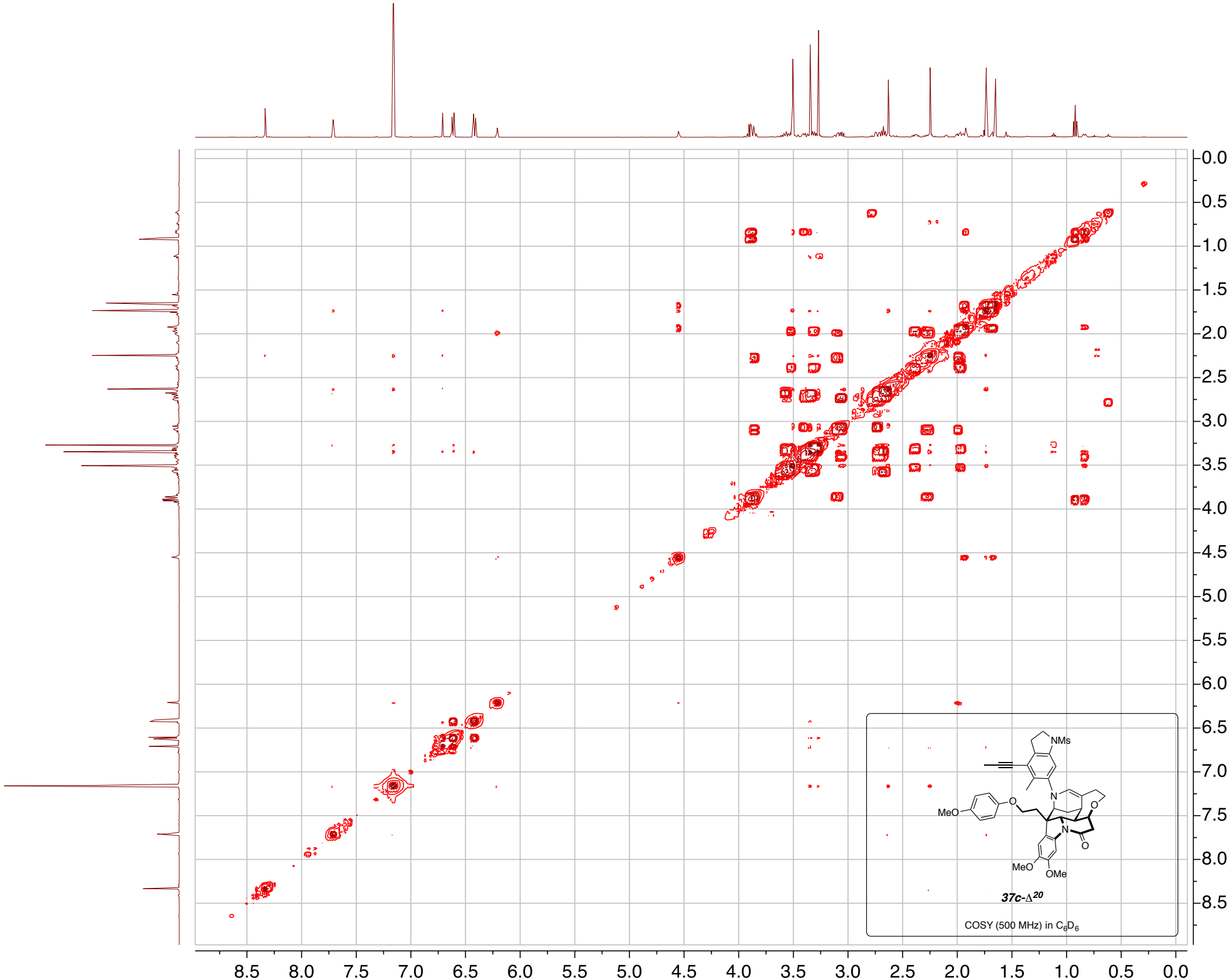
^{1}H NMR (500 MHz) in C_6D_6

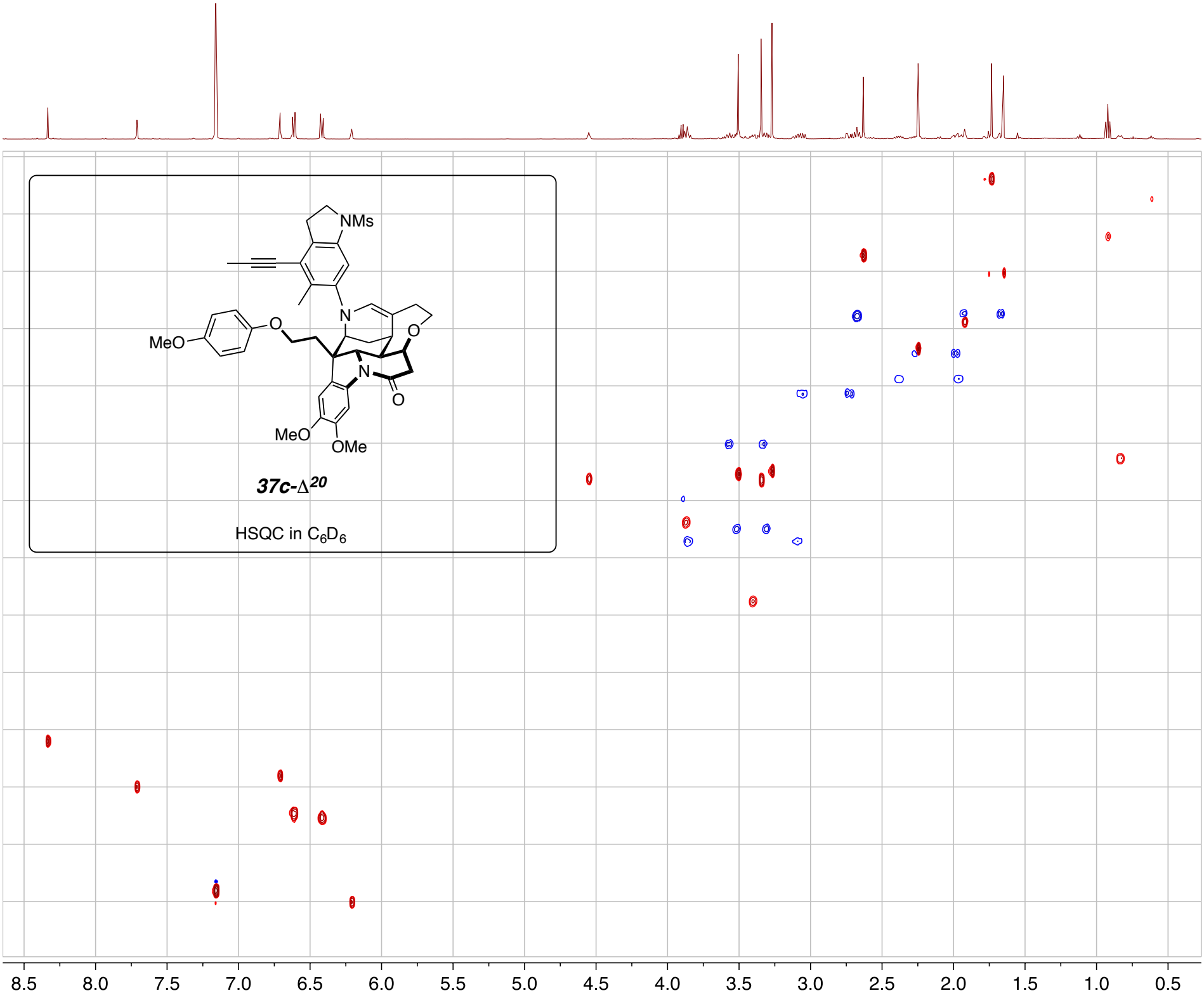


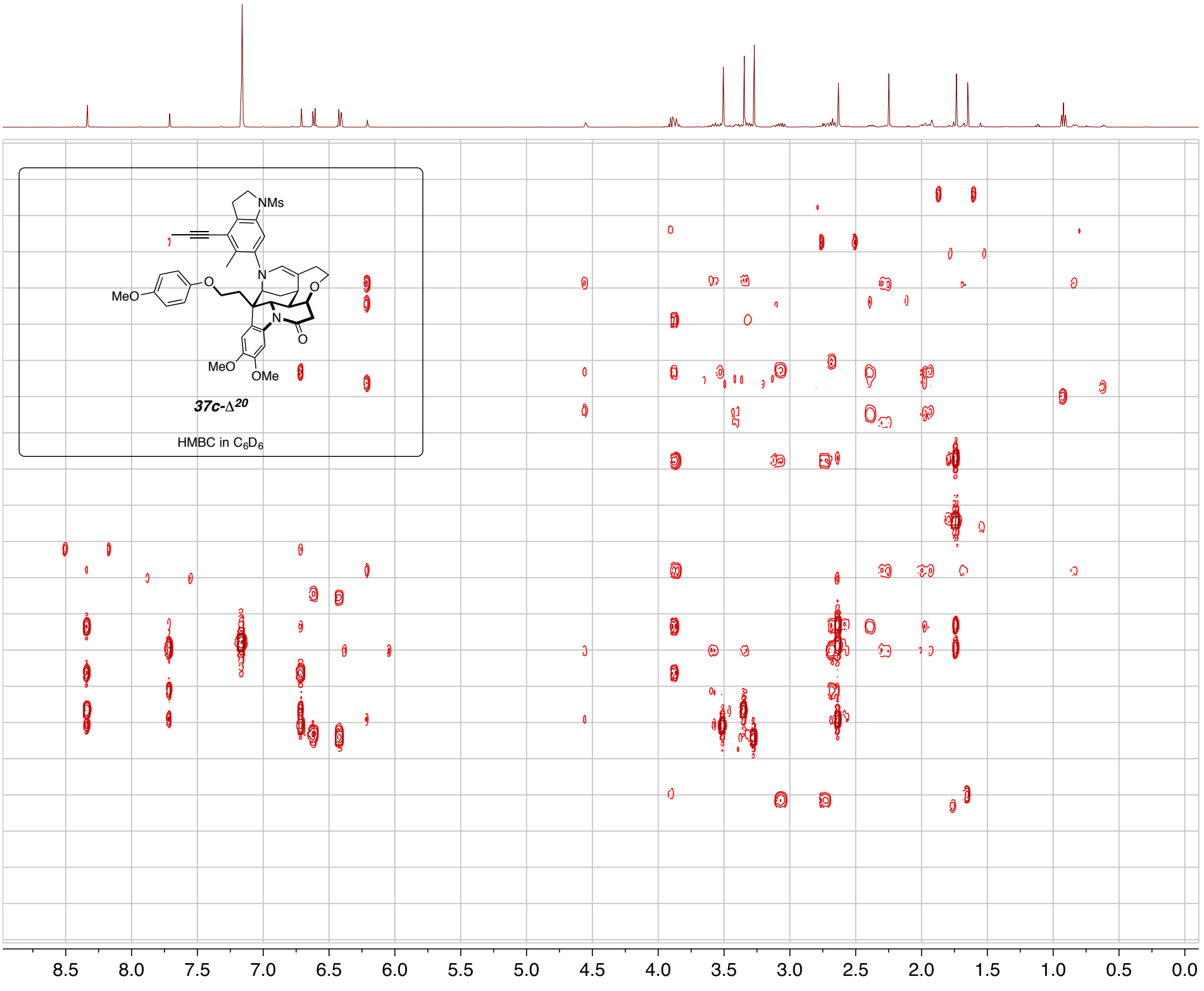
***37c*-Δ^{20}**

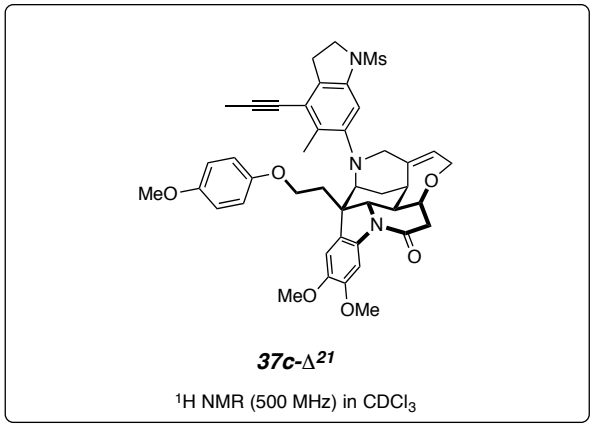
^{1}H NMR (500 MHz) in C_6D_6




NMs
MeO
MeO
OMe
37c-Δ20
COSY (500 MHz) in C6D6

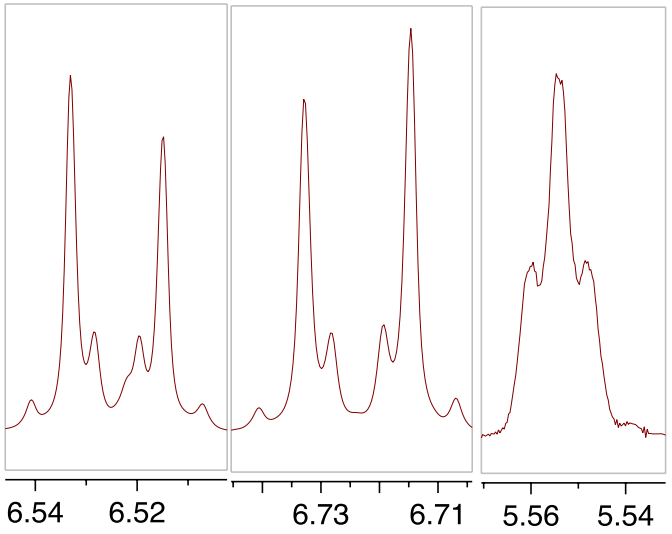

NMs
N
O
MeO
O
N
O
MeO
OMe
37c-Δ20
HSQC in C6D6
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

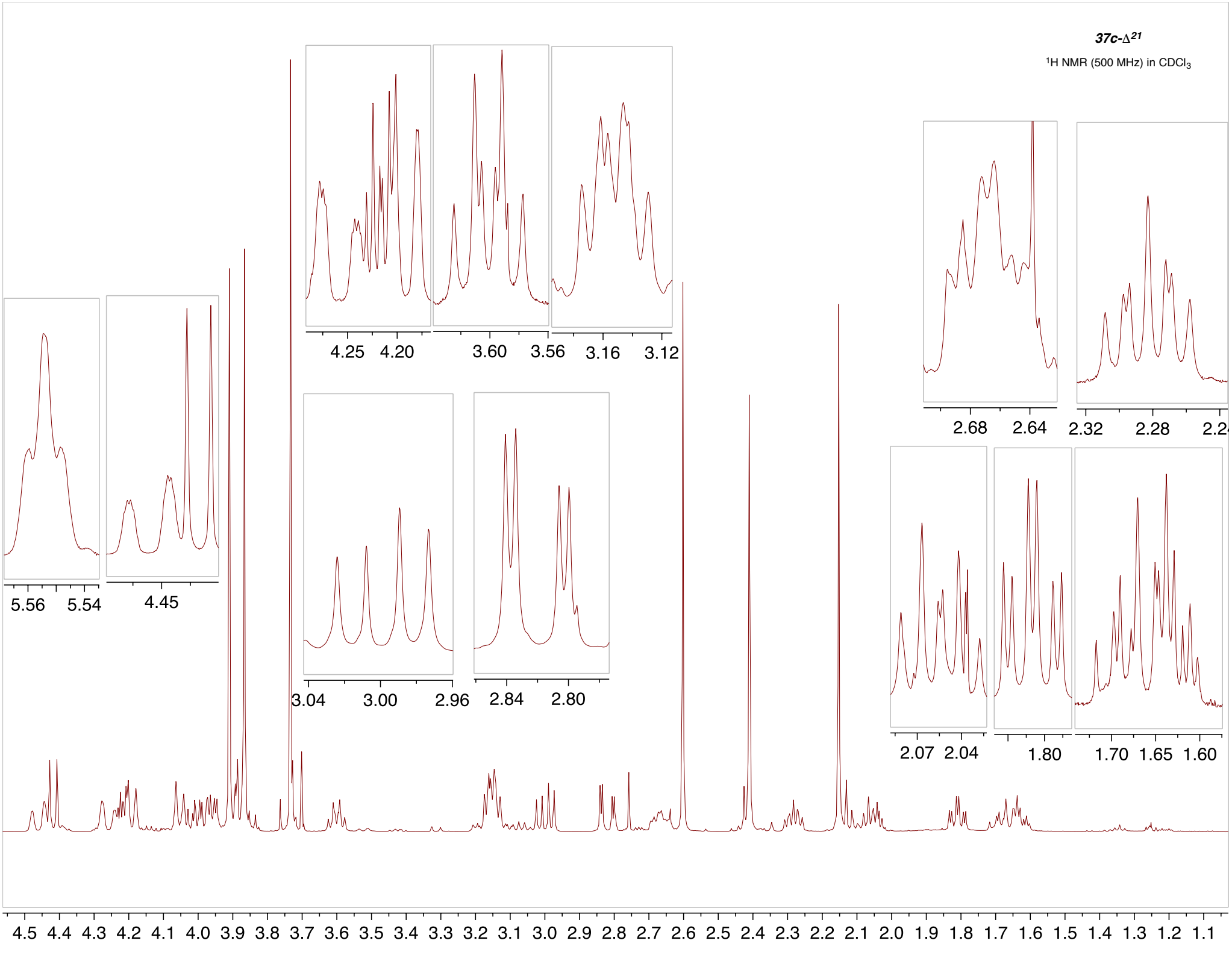

NMs
N
O
MeO
O
N
O
MeO
OMe
37c-Δ20
HMBC in C6D6
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

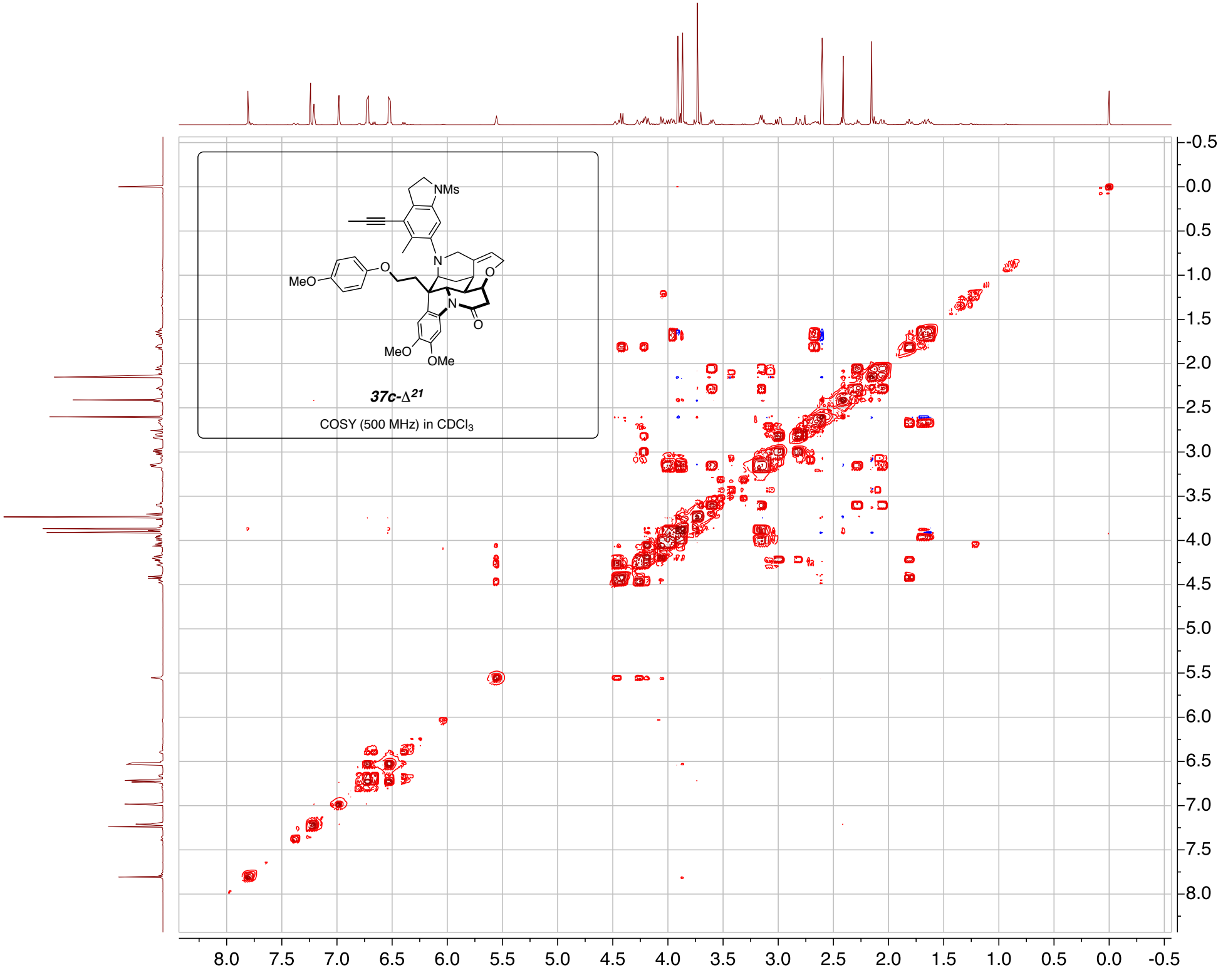


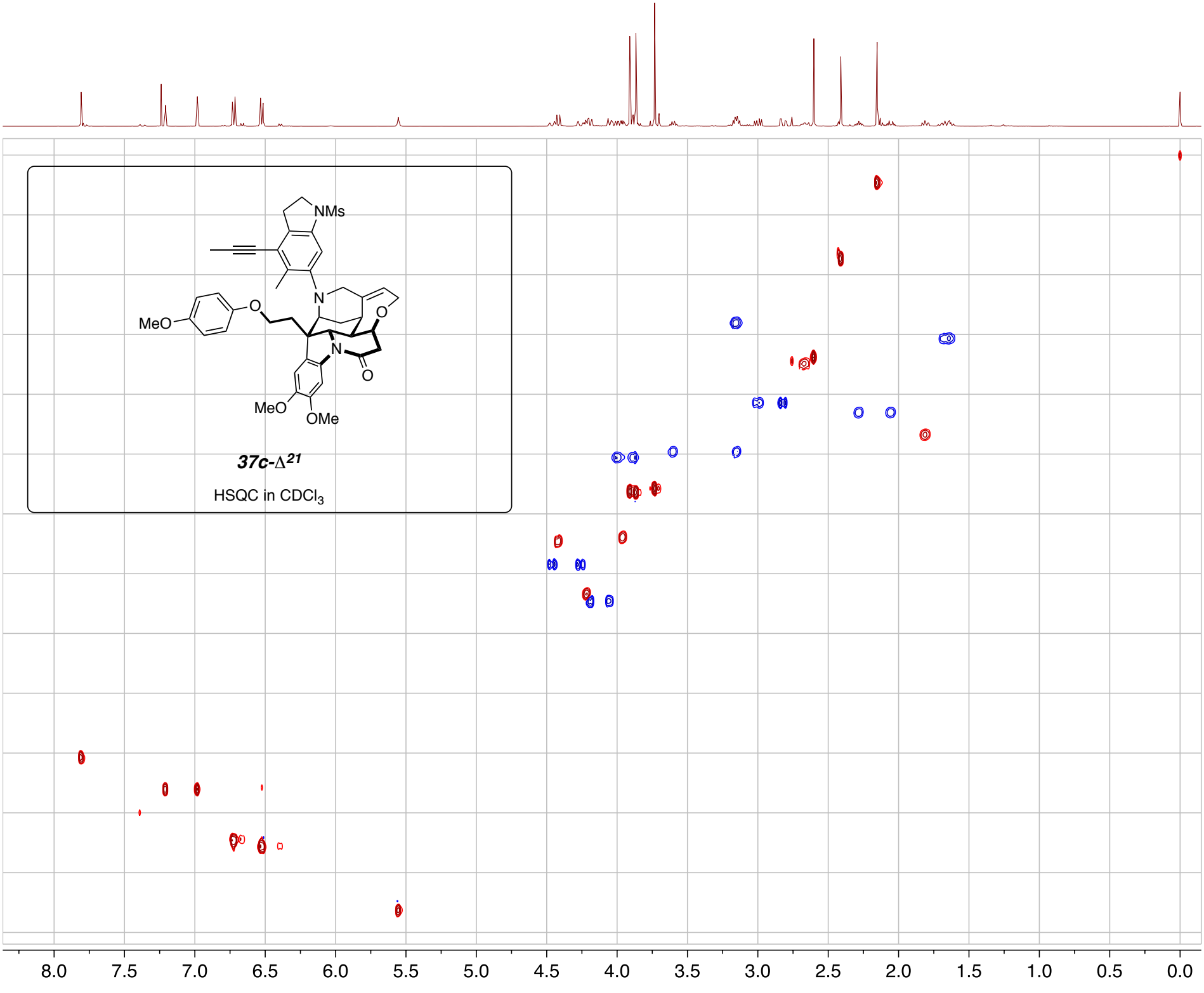
***37c*-Δ^{21}**

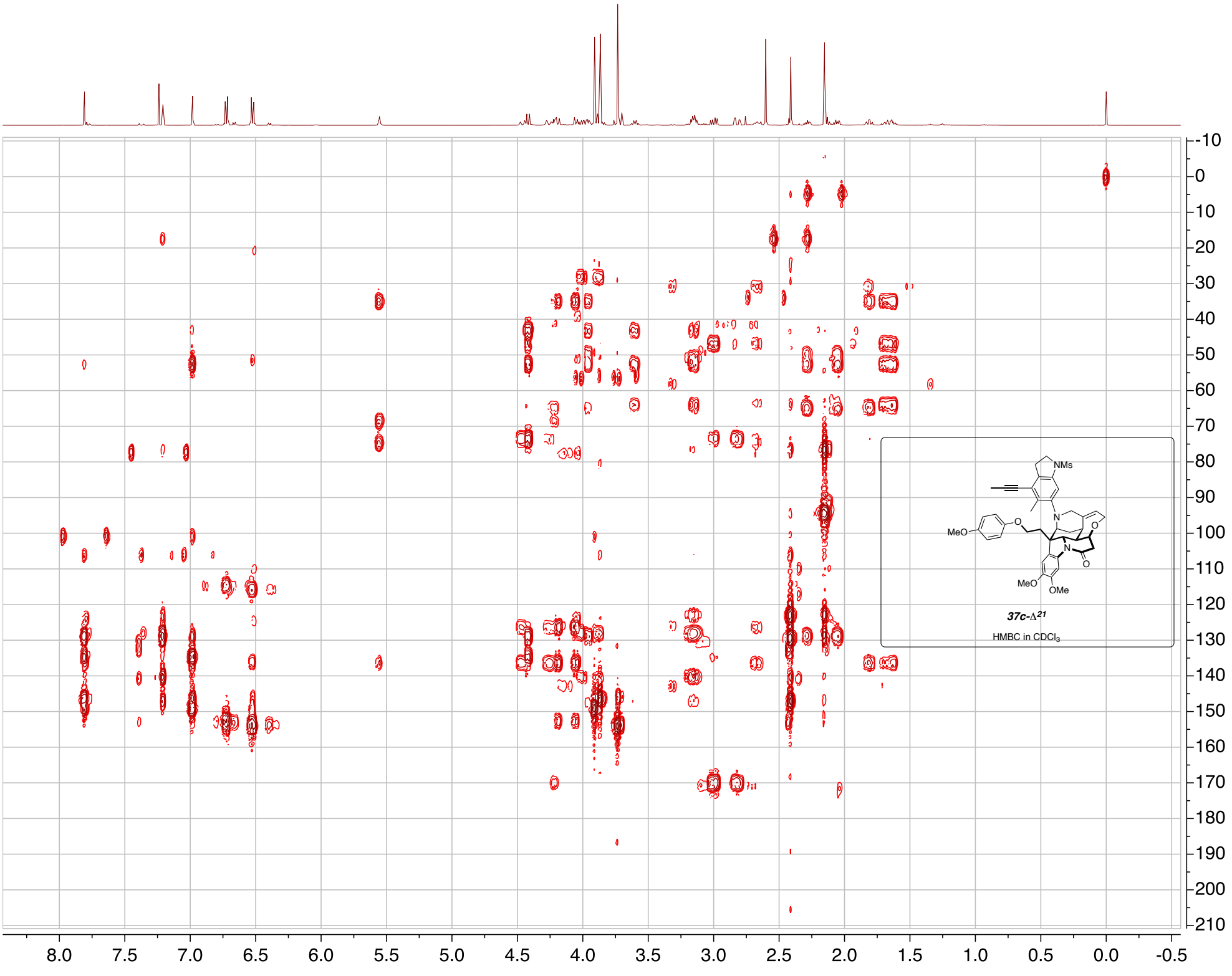
^{1}H NMR (500 MHz) in $CDCl_3$

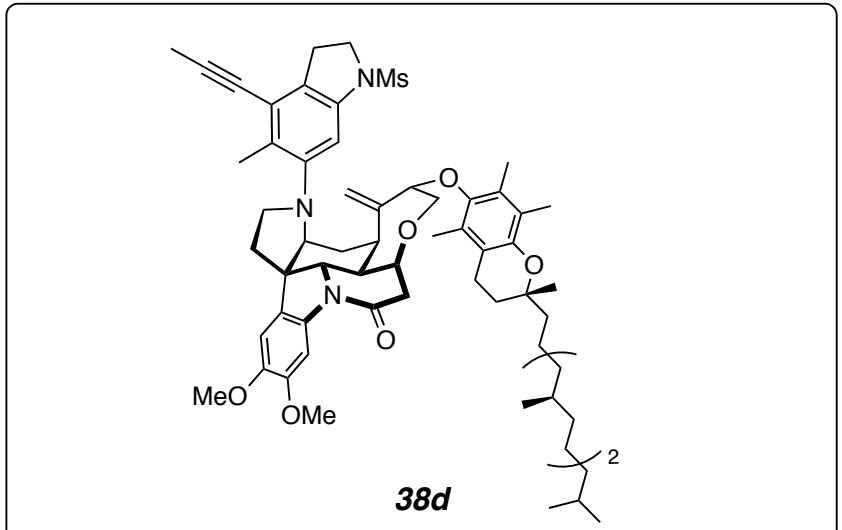



37c-Δ21
1H NMR (500 MHz) in CDCl3
5.56 5.54
4.45
4.25 4.20
3.60 3.56 3.16 3.12
3.04 3.00 2.96
2.84 2.80
2.68 2.64
2.32 2.28
2.07 2.04
1.80
1.70 1.65 1.60
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1


NMs
N
O
MeO
O
N
O
MeO
OMe
37c-Δ21
COSY (500 MHz) in CDCl3
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


NMs
N
O
MeO
O
N
O
MeO
OMe
37c-Δ21
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NMs
MeO
MeO
OMe
37c-Δ21
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

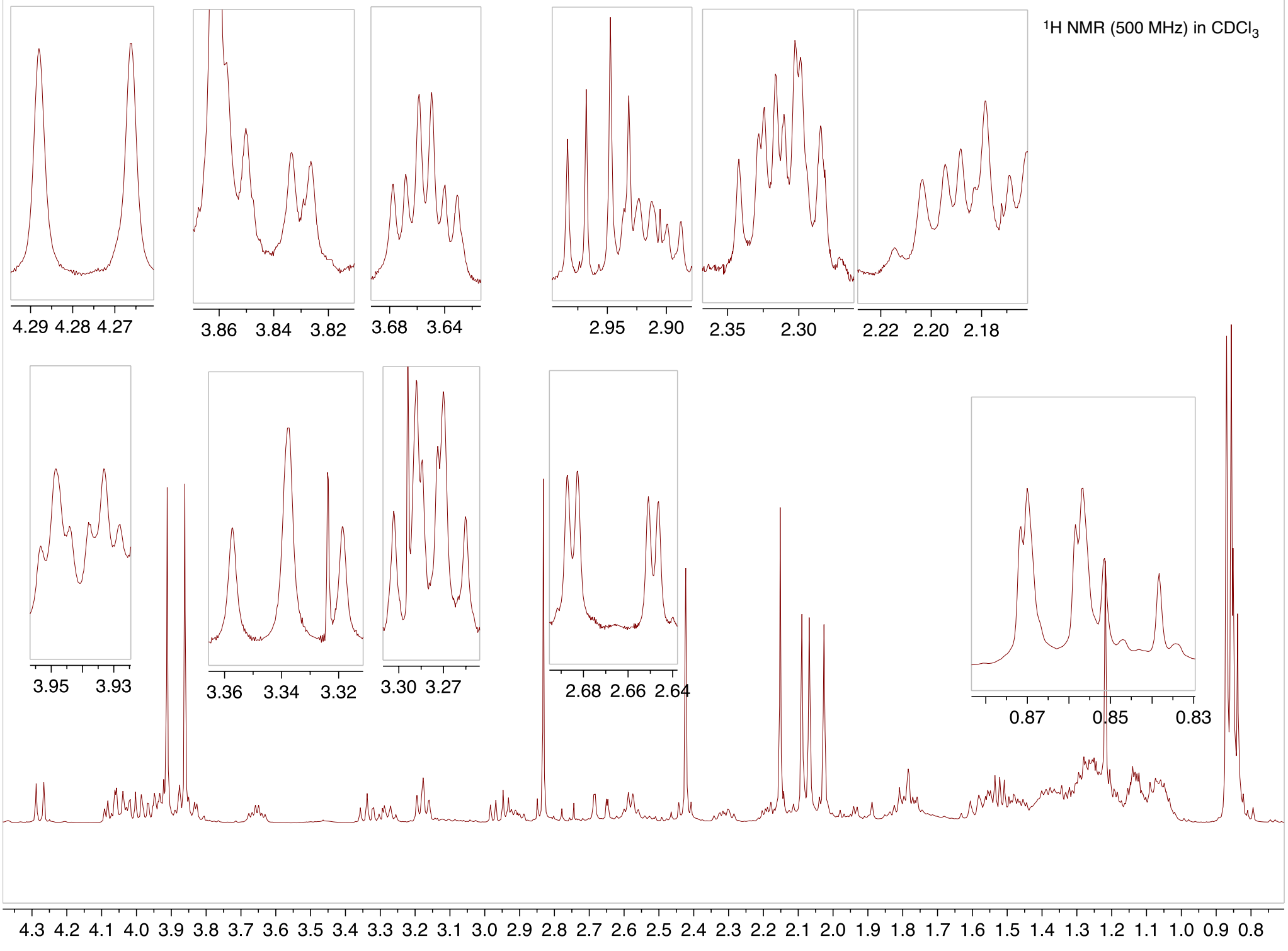


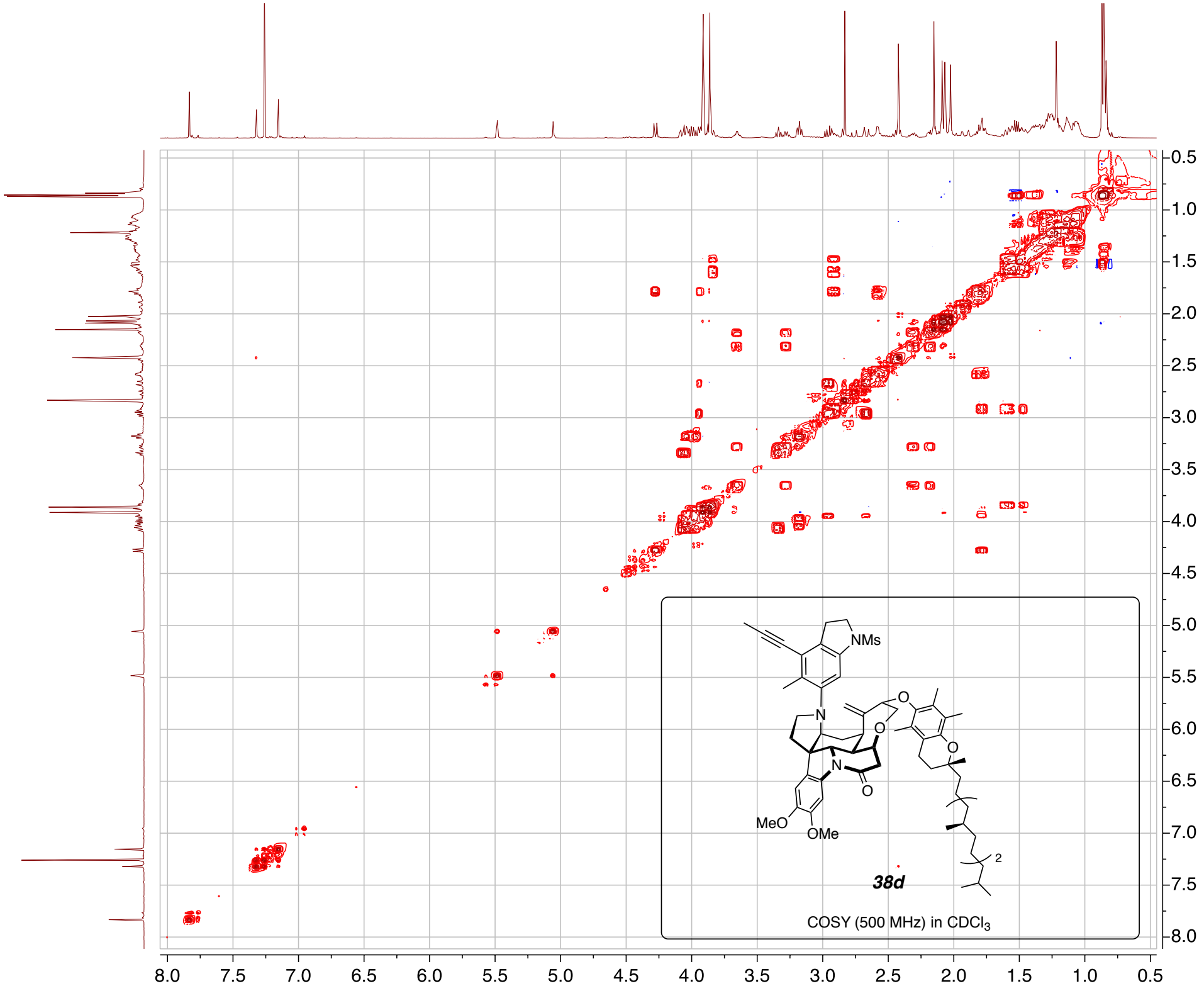
38d

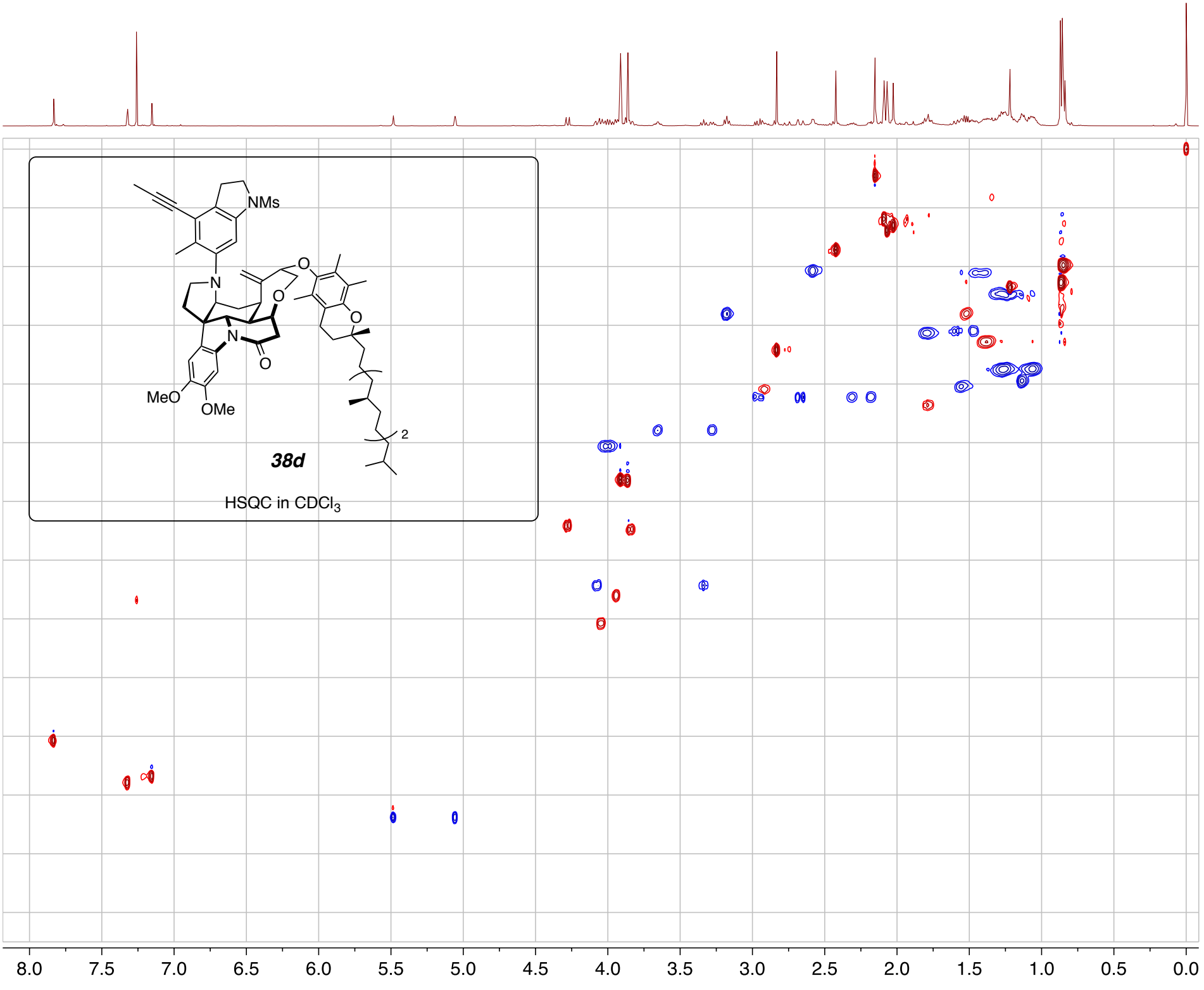
^{1}H NMR (500 MHz) in $CDCl_3$

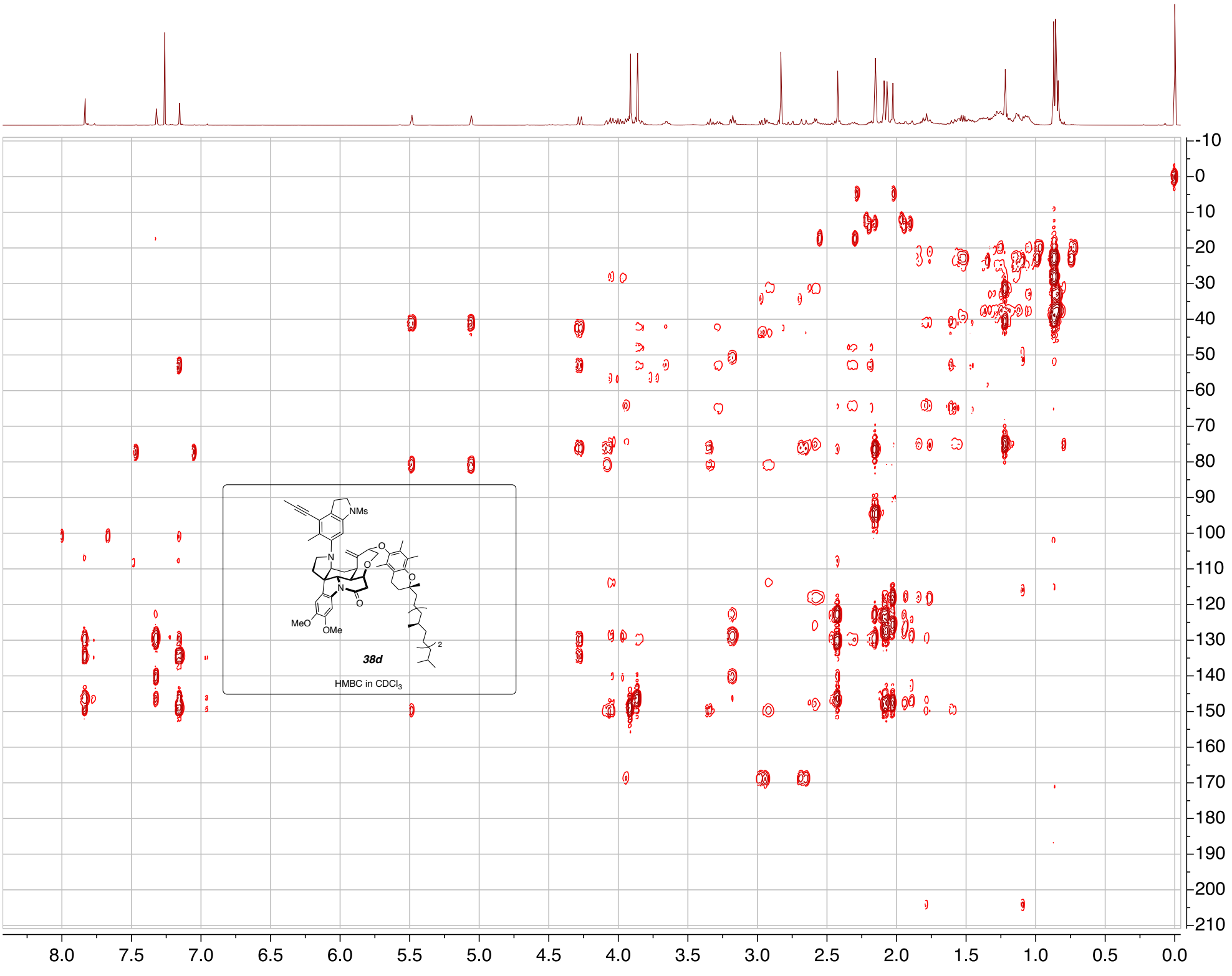
38d

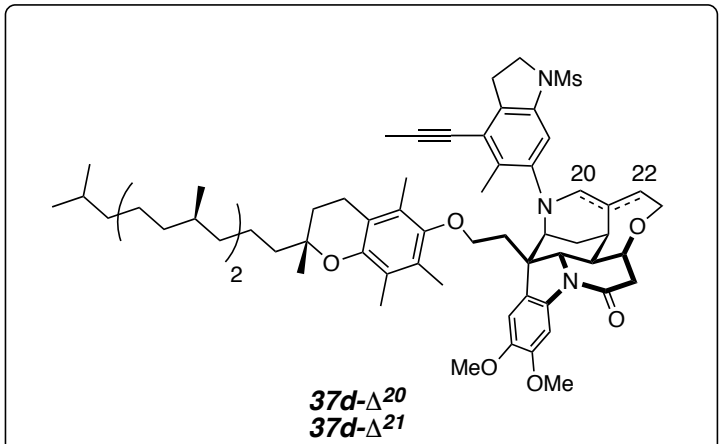
^{1}H NMR (500 MHz) in $CDCl_3$




NMs
N
O
O
O
N
O
MeO
OMe
2
38d
COSY (500 MHz) in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

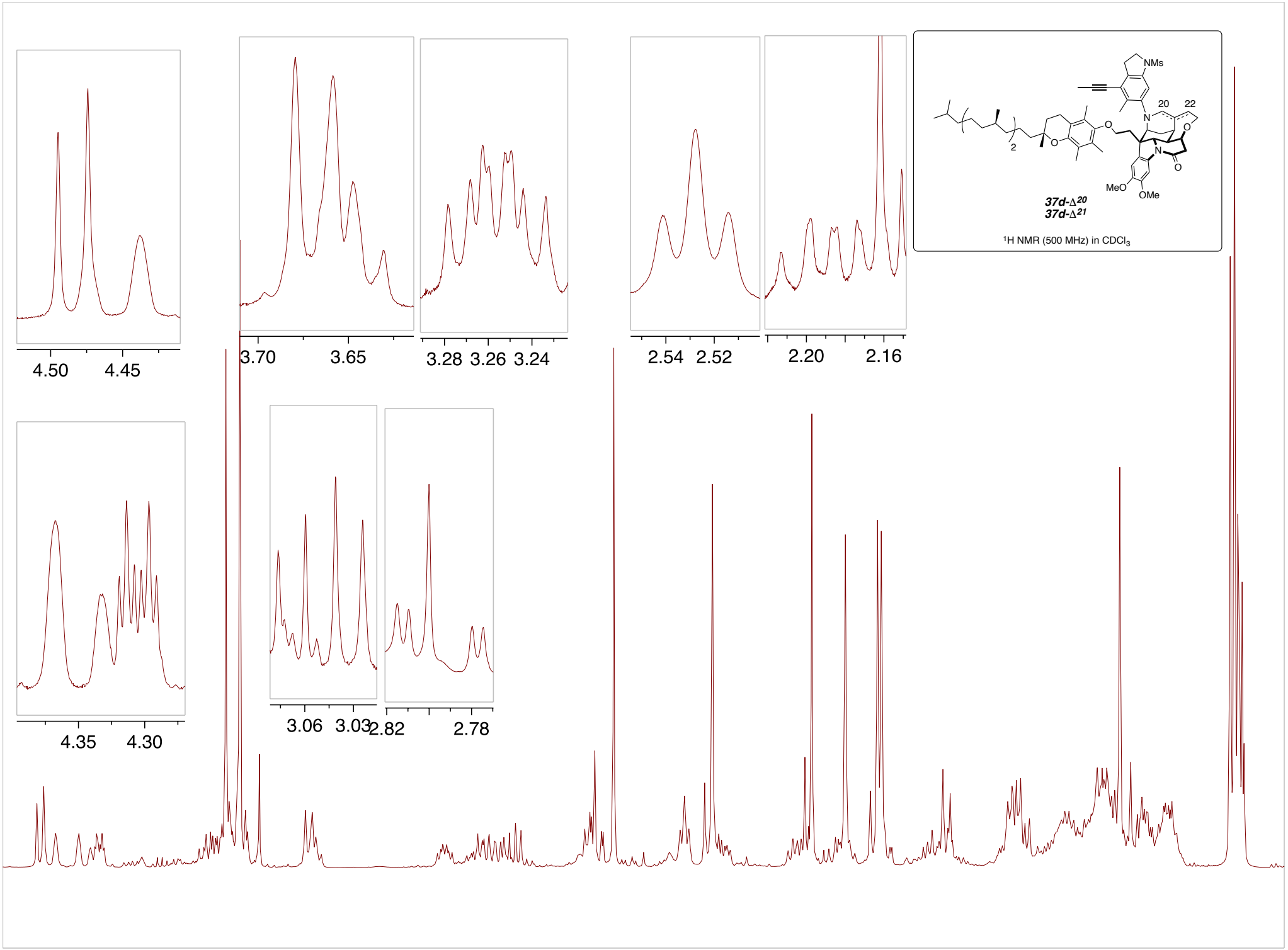

NMs
N
O
O
O
N
O
MeO
OMe
2
38d
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

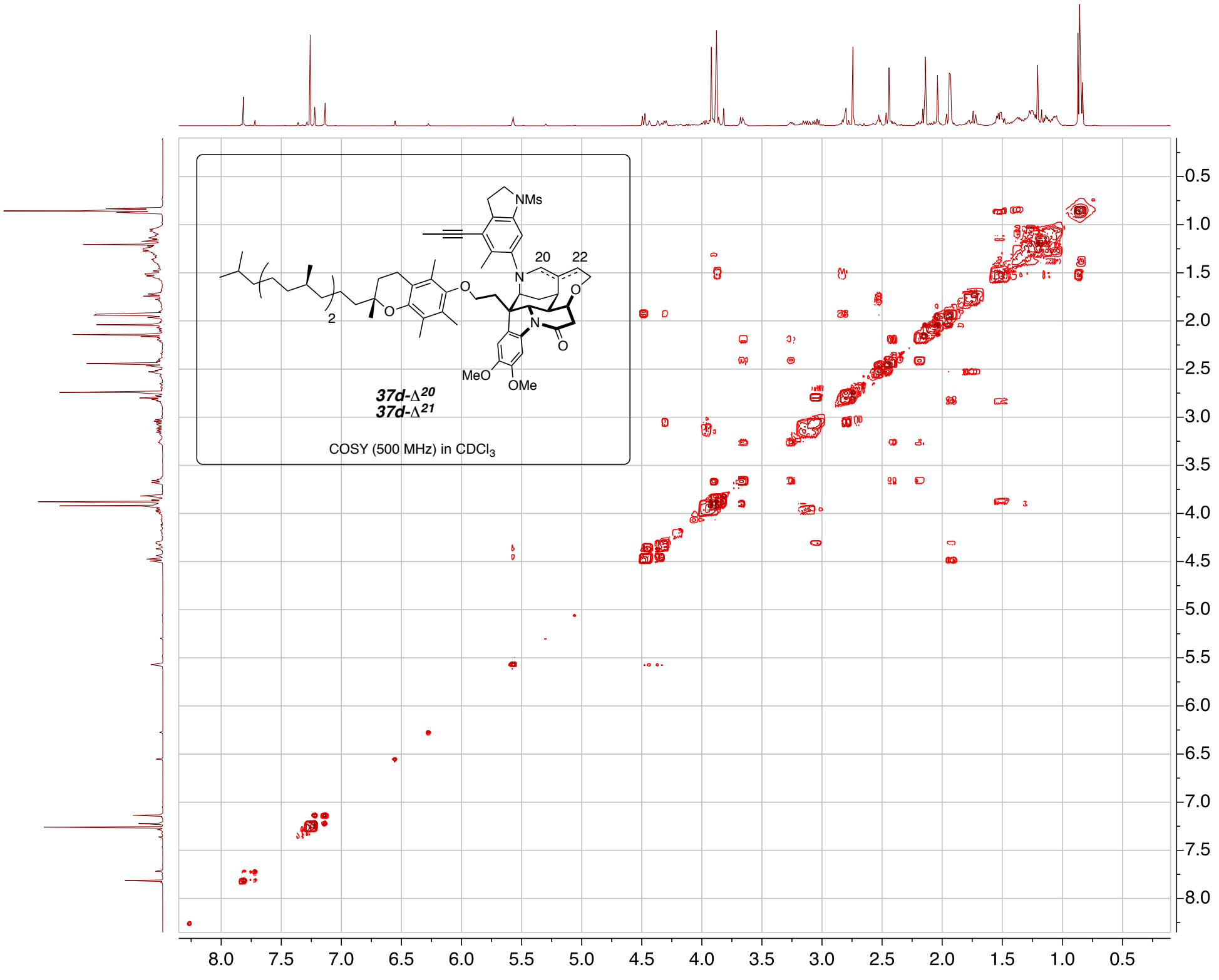

NMs
N
O
O
O
N
O
MeO
OMe
38d
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

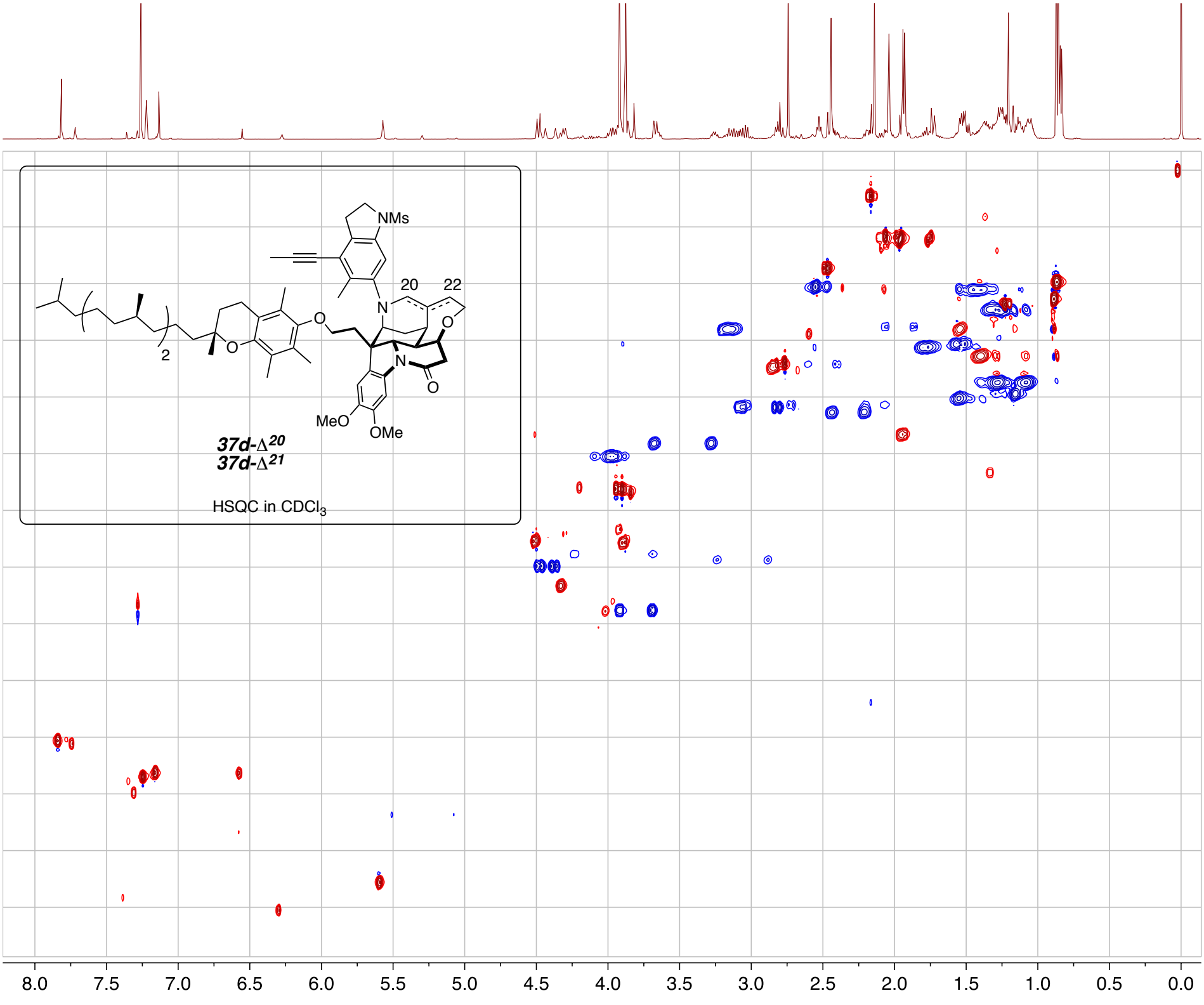


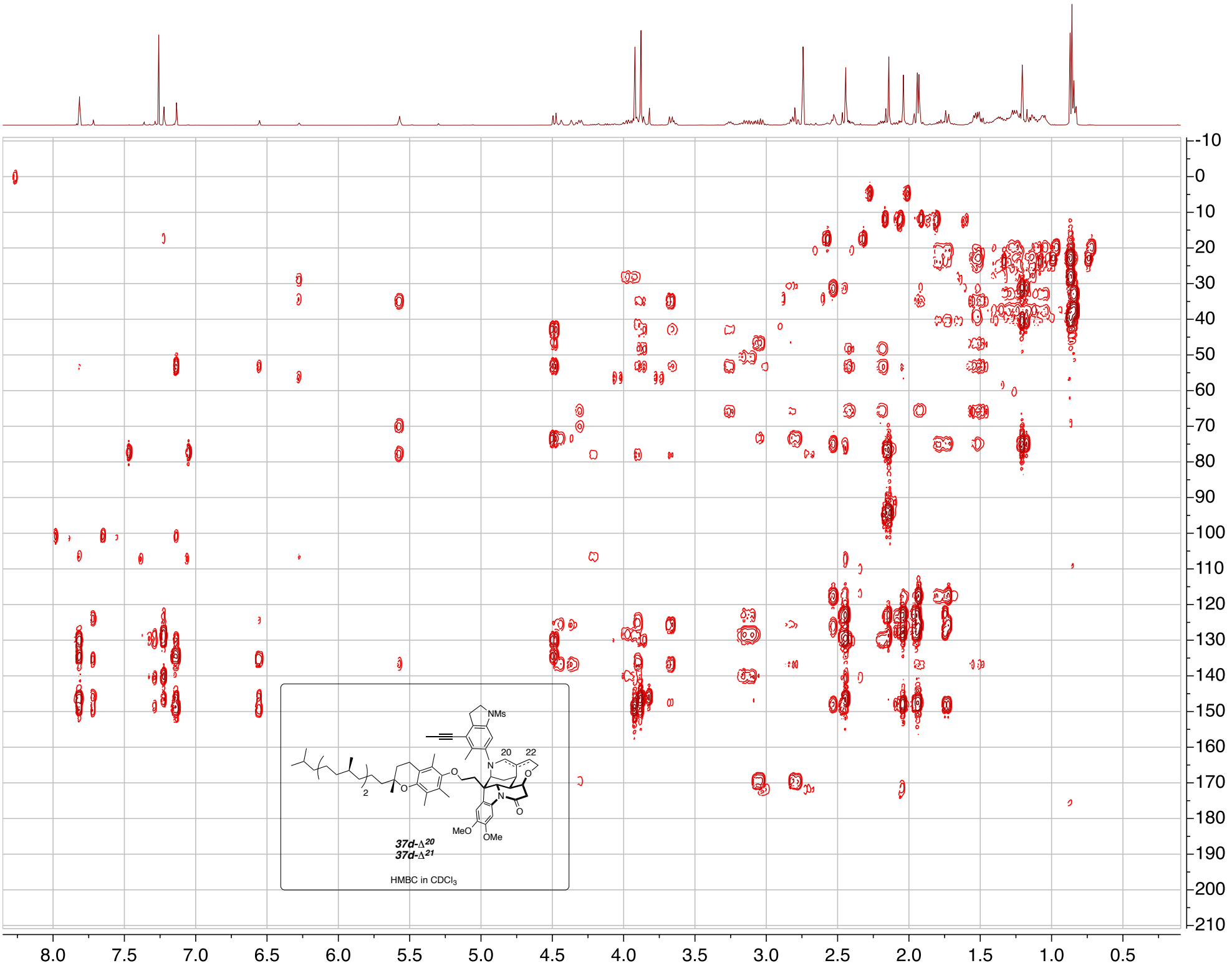
***37d*-Δ^{20}**
***37d*-Δ^{21}**

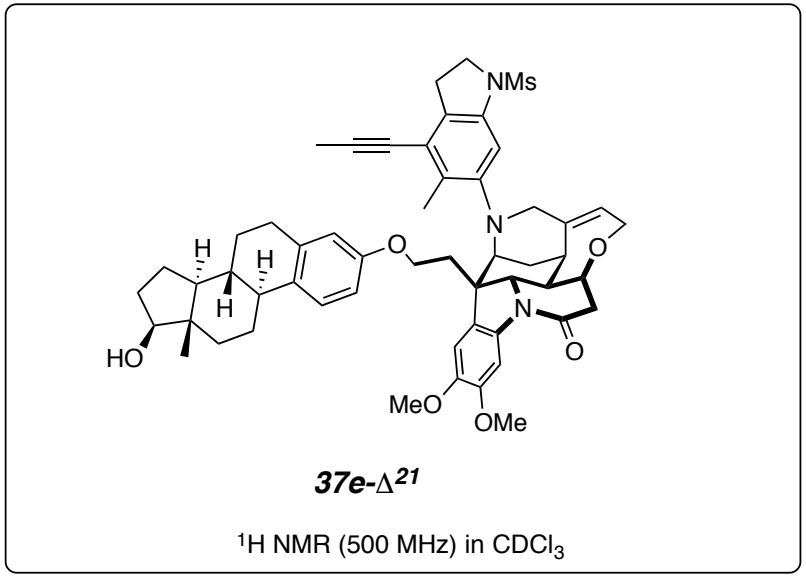
^{1}H NMR (500 MHz) in $CDCl_3$


NMs
20
22
N
O
O
N
O
2
MeO
OMe
37d-Δ20
37d-Δ21
1H NMR (500 MHz) in CDCl3
4.50 4.45
3.70 3.65
3.28 3.26 3.24
2.54 2.52
2.20 2.16
4.35 4.30
3.06 3.03
2.82 2.78
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8


NMs
20
22
N
O
O
N
O
2
O
MeO
OMe
37d-Δ20
37d-Δ21
COSY (500 MHz) in CDCl3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

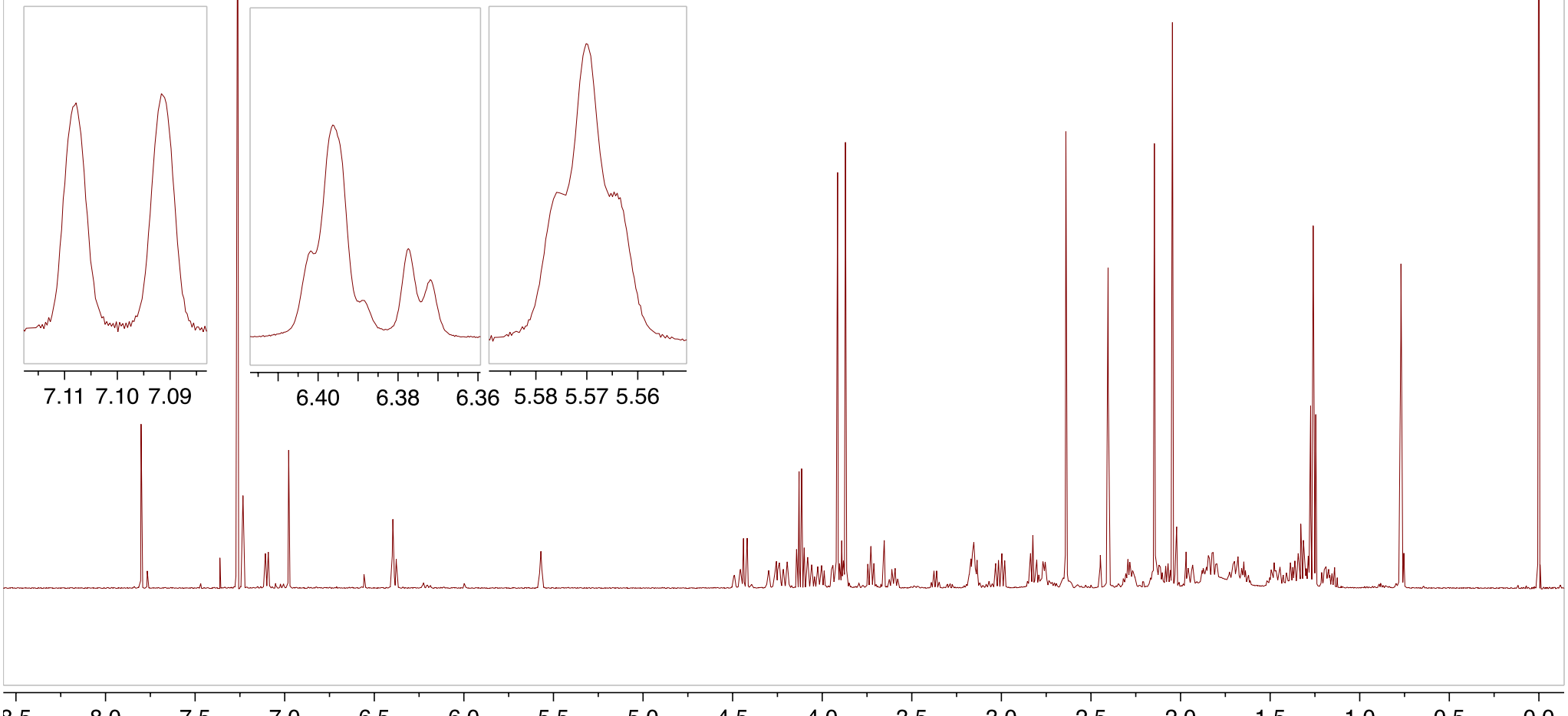

NMs
20
22
N
O
O
N
O
2
O
MeO
OMe
37d-Δ20
37d-Δ21
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

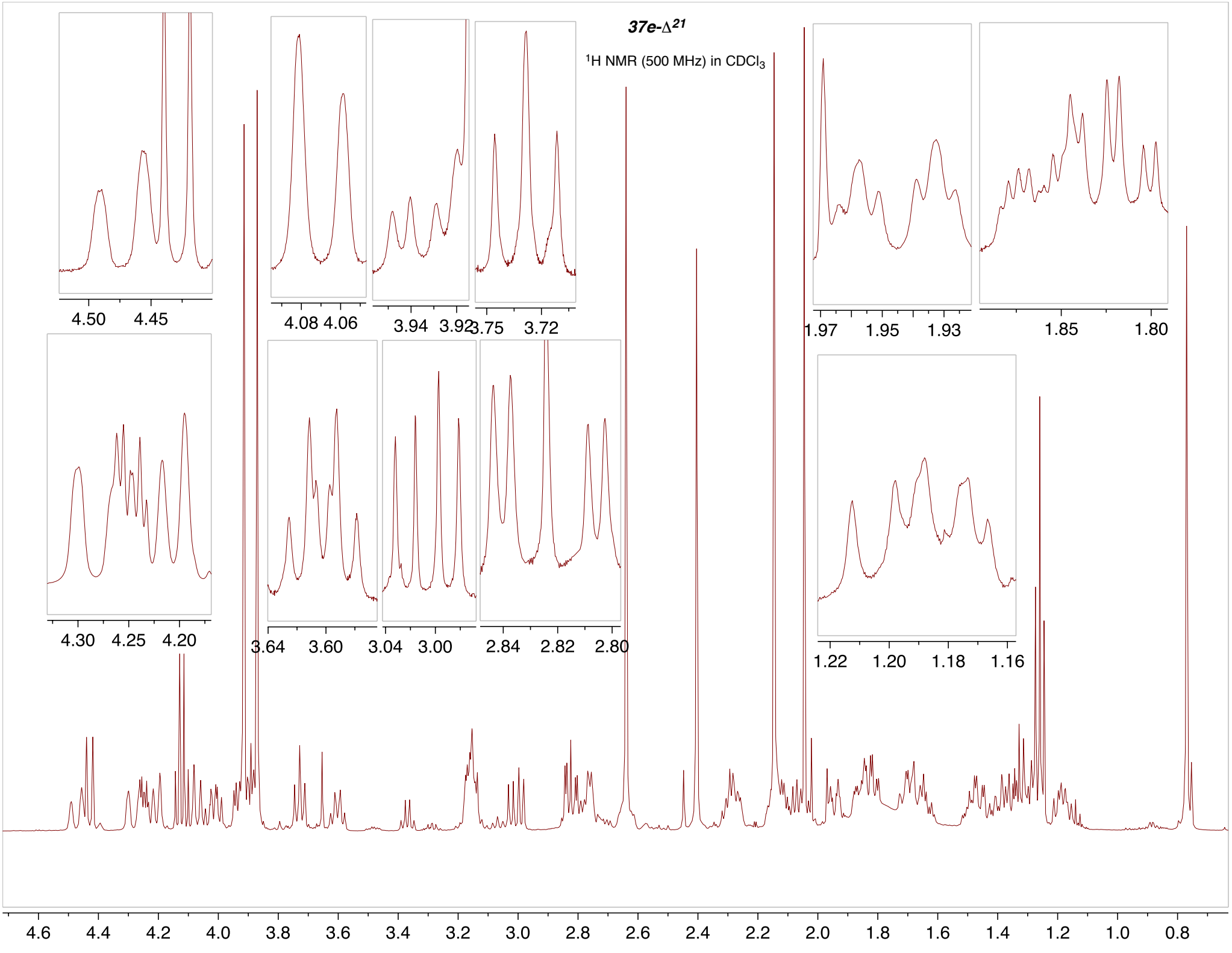

NMs
20
22
N
O
O
N
O
2
O
MeO
OMe
37d-Δ20
37d-Δ21
HMBC in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

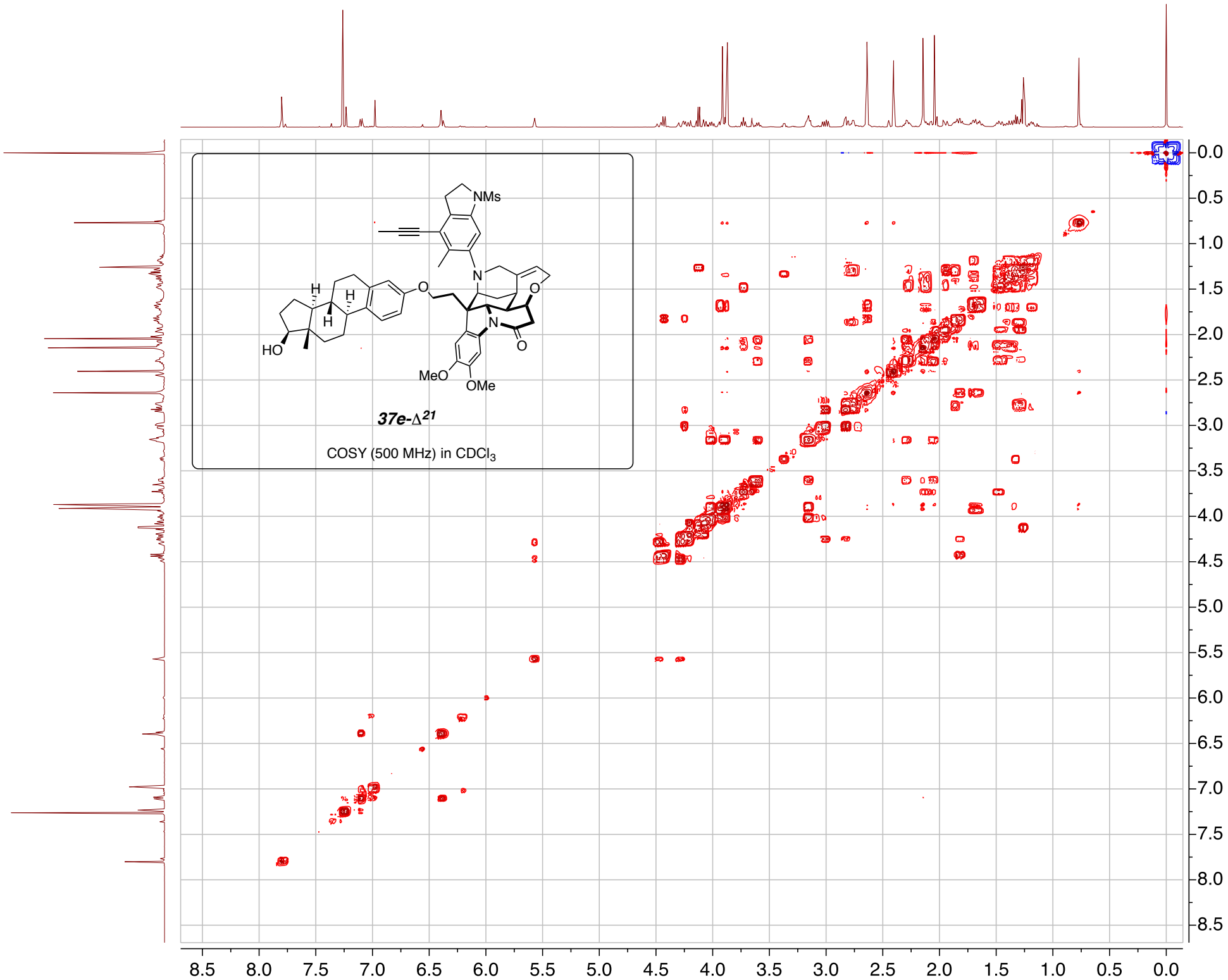


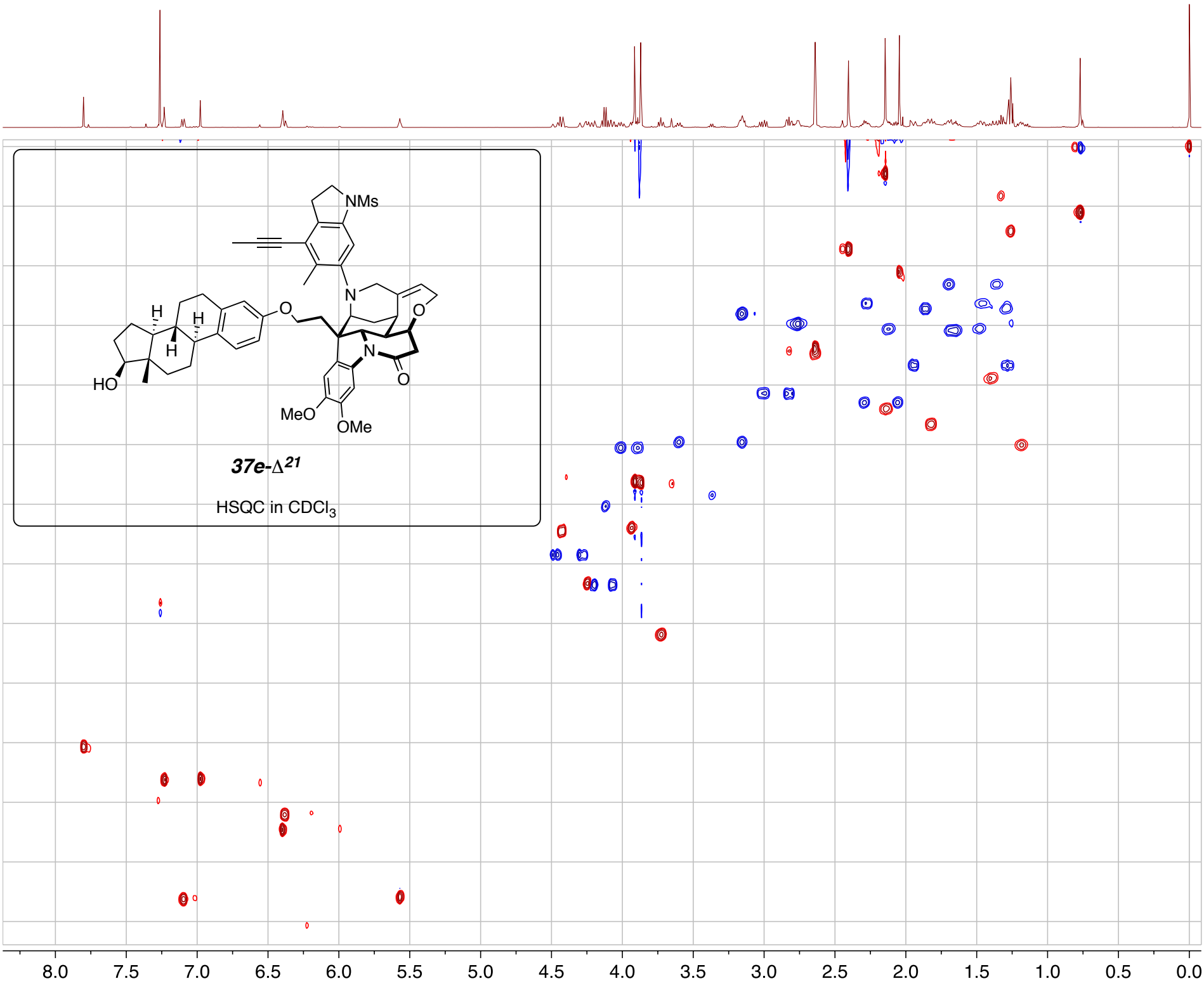
***37e*-Δ^{21}**

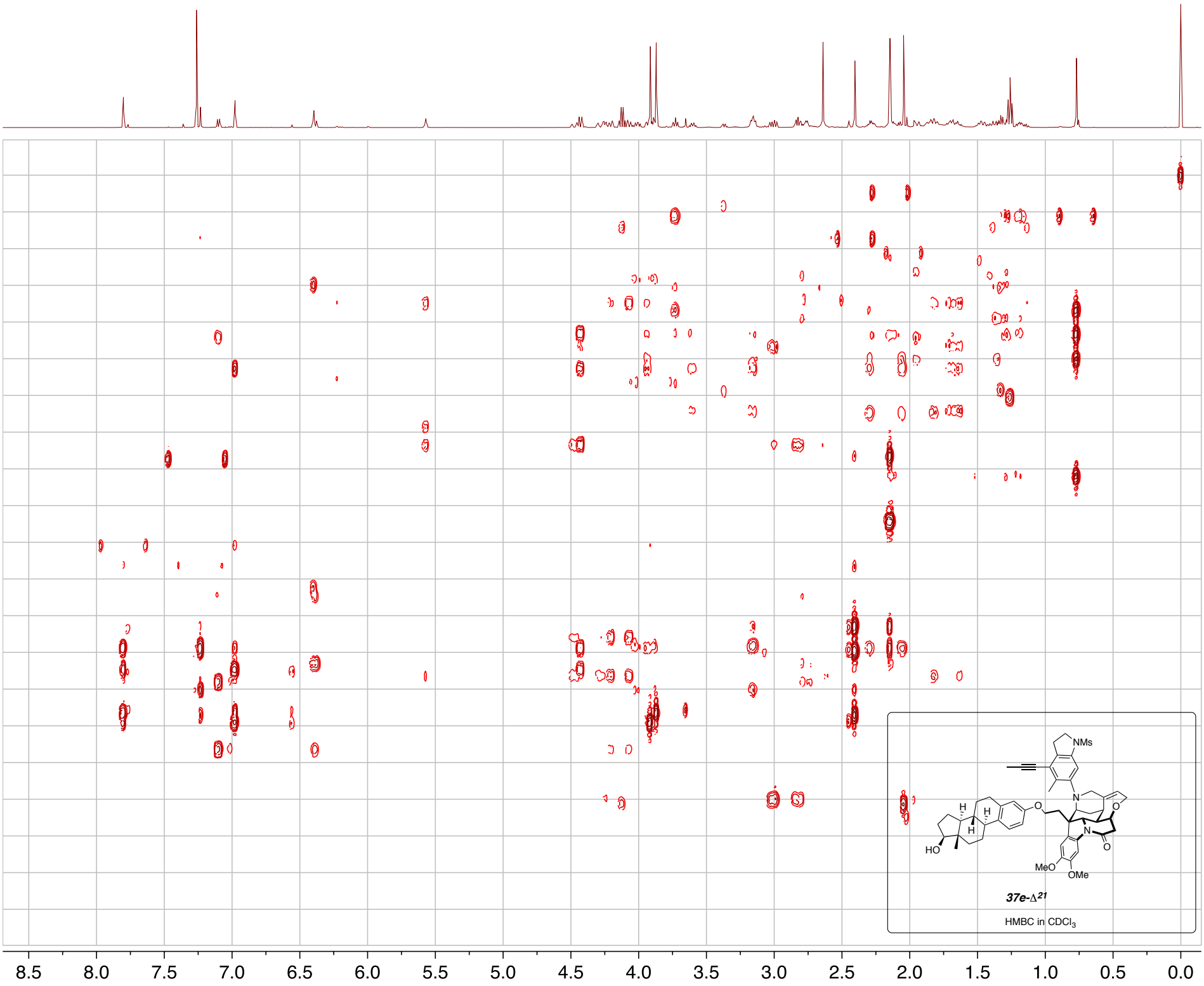
^{1}H NMR (500 MHz) in $CDCl_3$

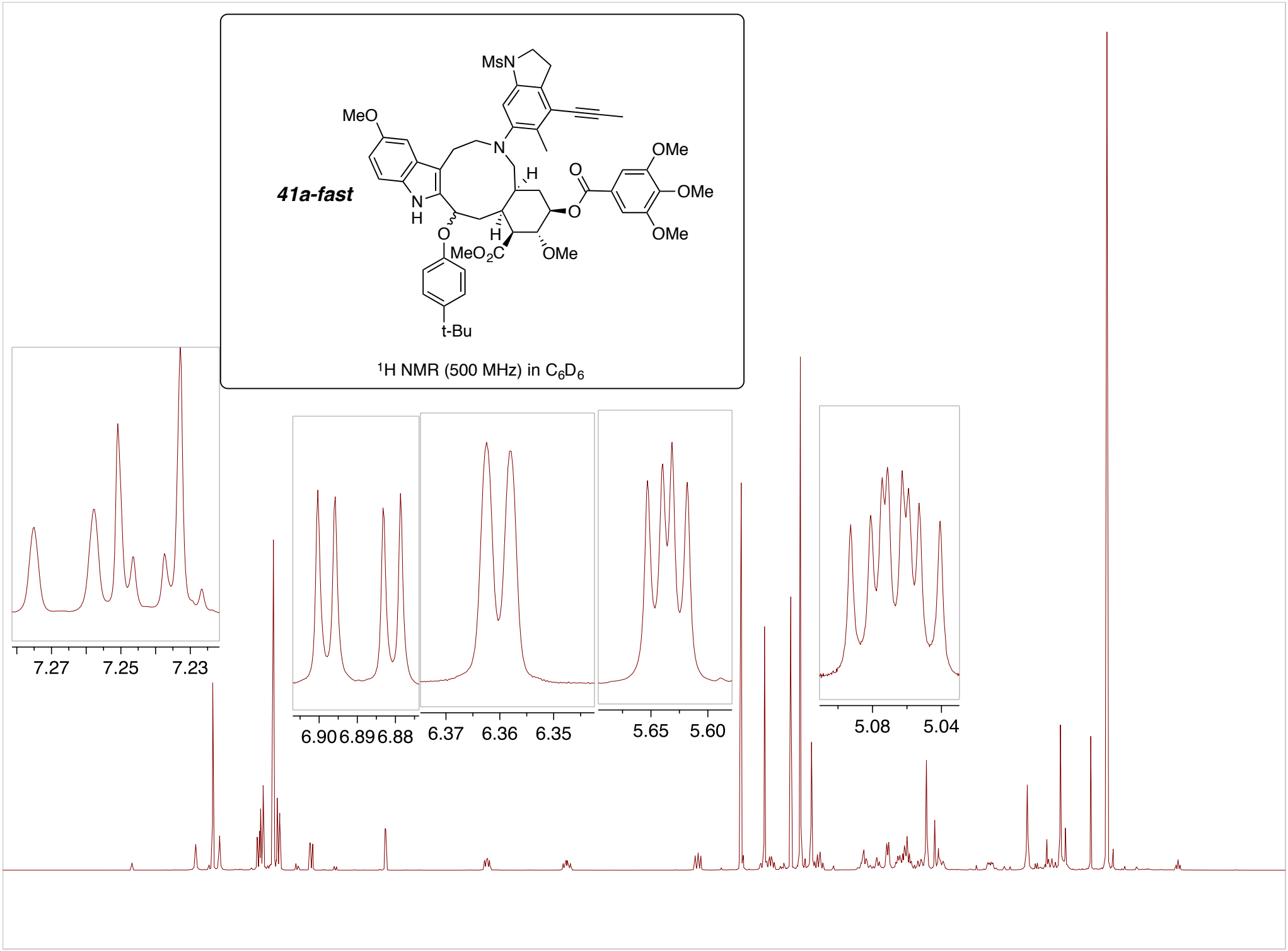


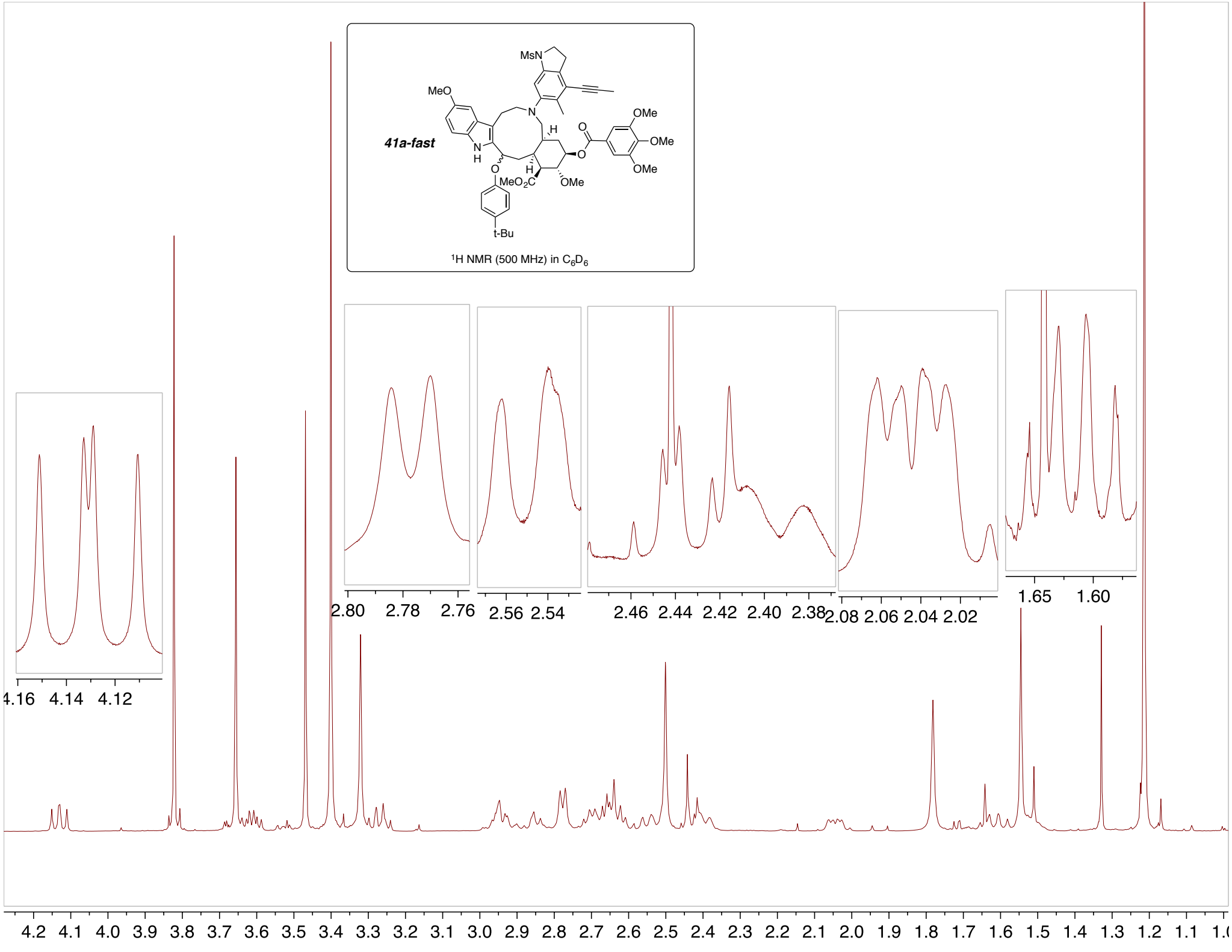

37e-Δ21
1H NMR (500 MHz) in CDCl3
4.50 4.45
4.08 4.06
3.94 3.92
3.75 3.72
1.97 1.95 1.93
1.85 1.80
4.30 4.25 4.20
3.64 3.60
3.04 3.00
2.84 2.82 2.80
1.22 1.20 1.18 1.16
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8

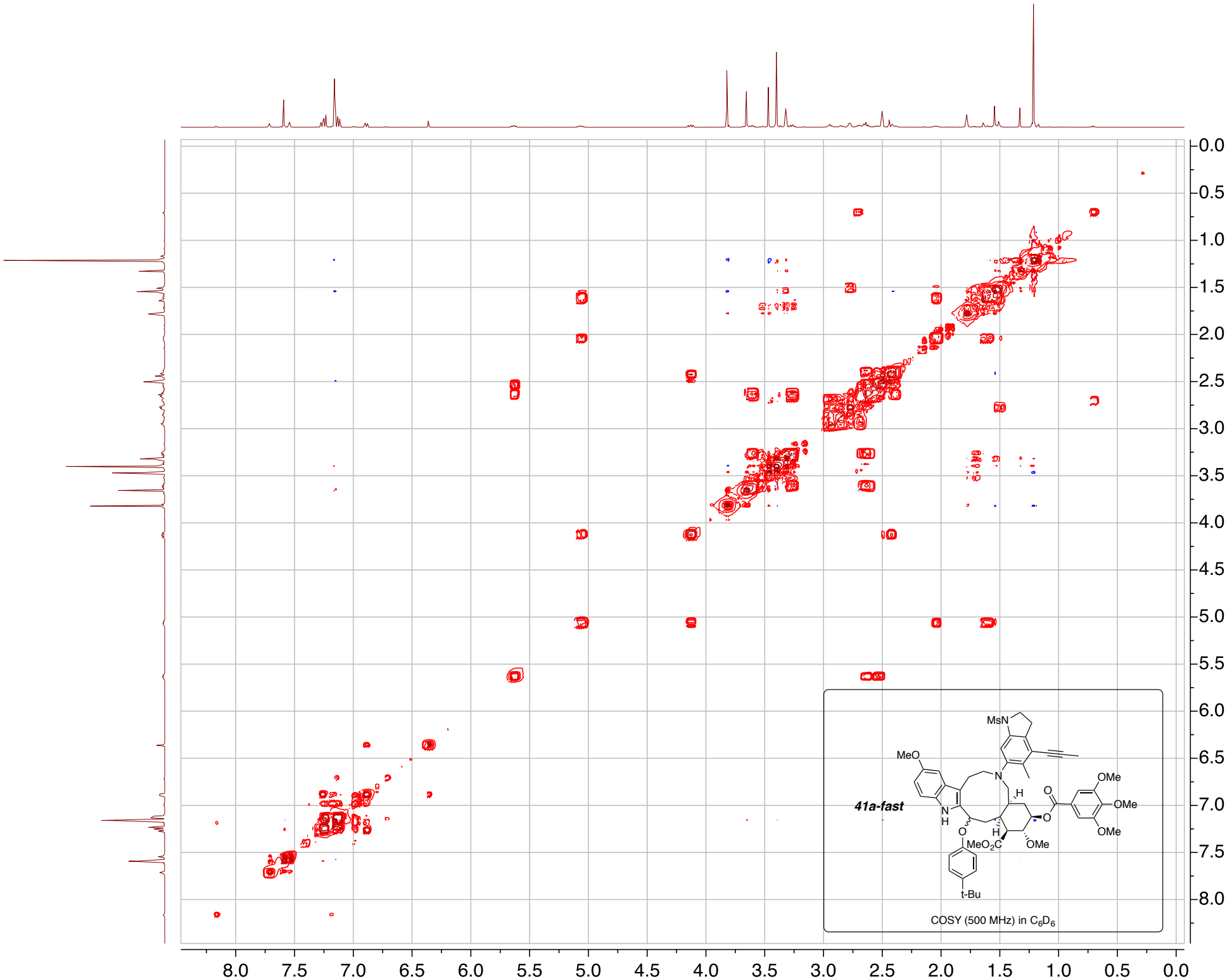

NMs
N
O
O
H
H
H
HO
N
O
MeO
OMe
37e-Δ21
COSY (500 MHz) in CDCl3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

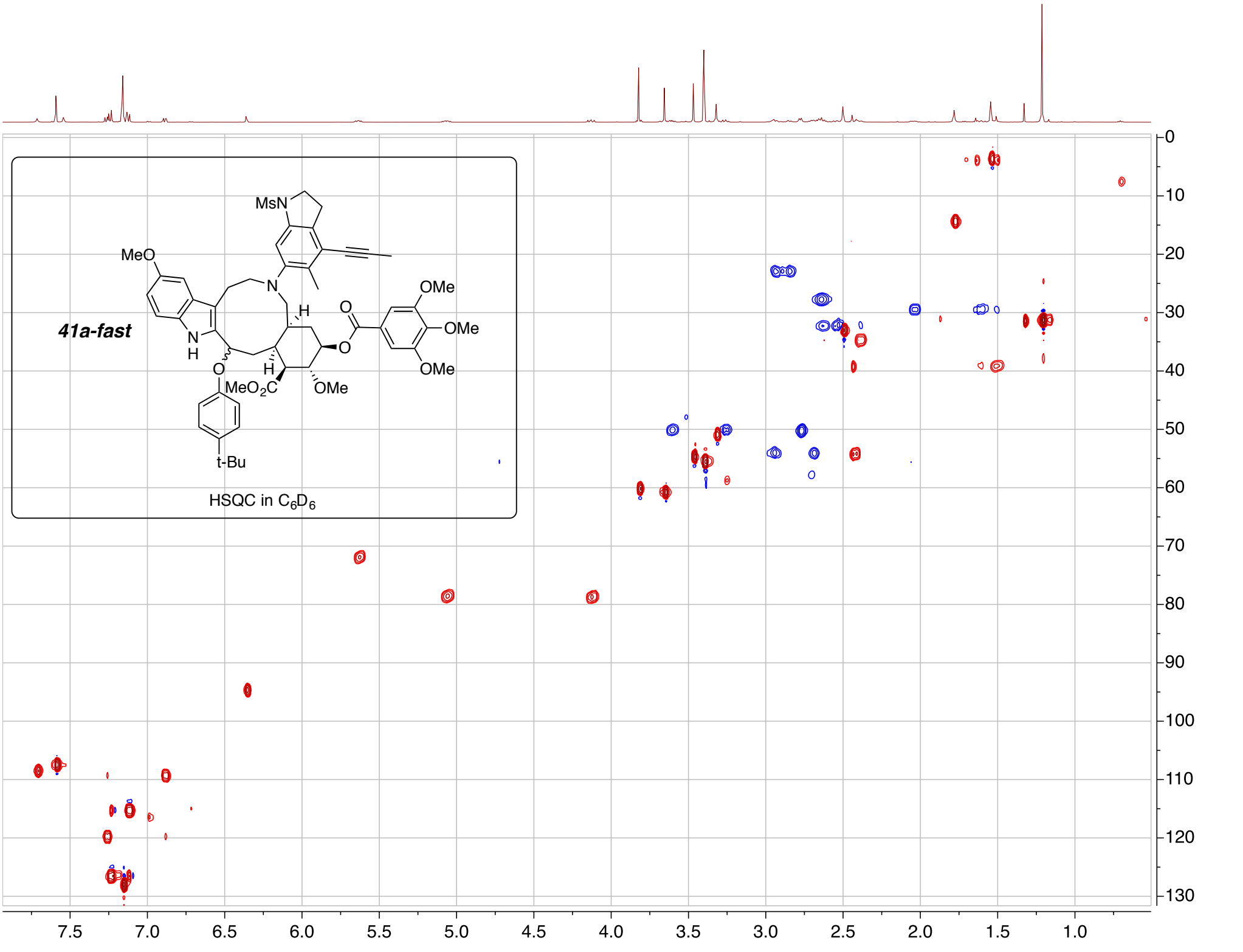

NMs
N
O
O
H
H
H
HO
N
O
MeO
OMe
37e-Δ21
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

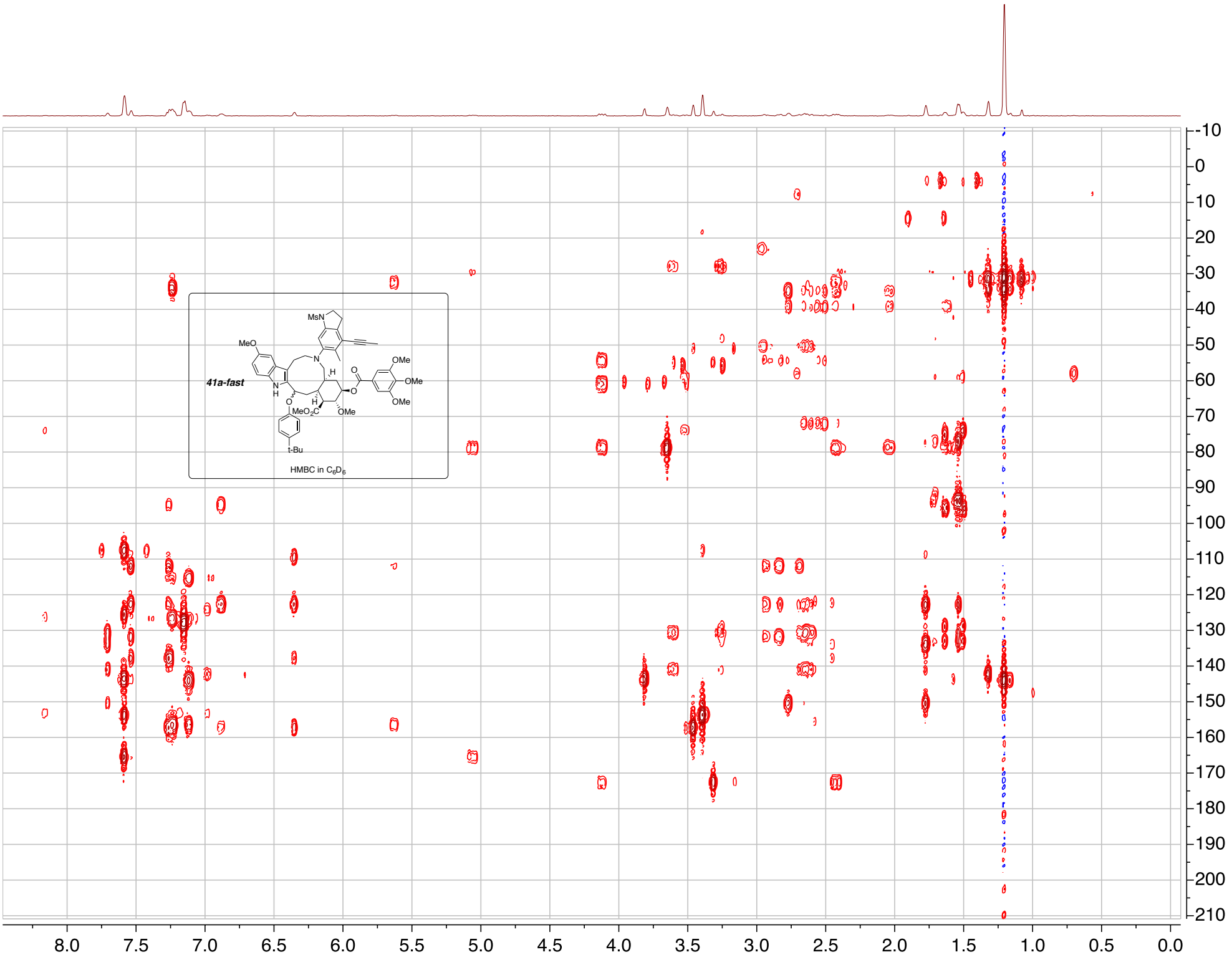

NMs
N
O
H
H
H
HO
O
N
O
MeO
OMe
37e-Δ21
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

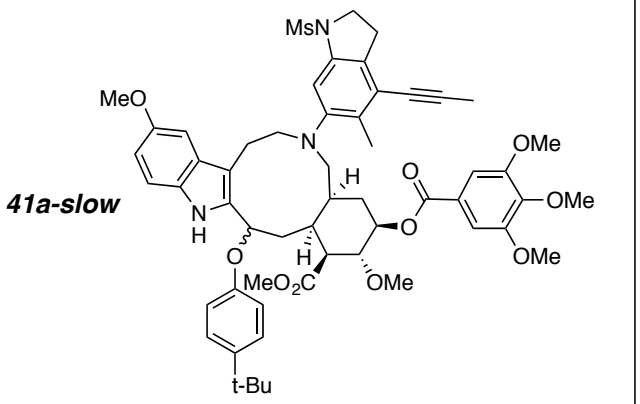

MsN
MeO
N
H
OMe
OMe
OMe
O
O
O
H
H
N
O
MeO2C
OMe
t-Bu
41a-fast
1H NMR (500 MHz) in C6D6
7.27
7.25
7.23
6.90
6.89
6.88
6.37
6.36
6.35
5.65
5.60
5.08
5.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


41a-fast
MsN
MeO
N
H
O
OMe
OMe
OMe
MeO2C
OMe
t-Bu
1H NMR (500 MHz) in C6D6
4.16 4.14 4.12
2.80 2.78 2.76
2.56 2.54
2.46 2.44 2.42 2.40 2.38
2.08 2.06 2.04 2.02
1.65 1.60
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1


41a-fast
MsN
MeO
N
H
O
OMe
OMe
OMe
MeO2C
t-Bu
COSY (500 MHz) in C6D6
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

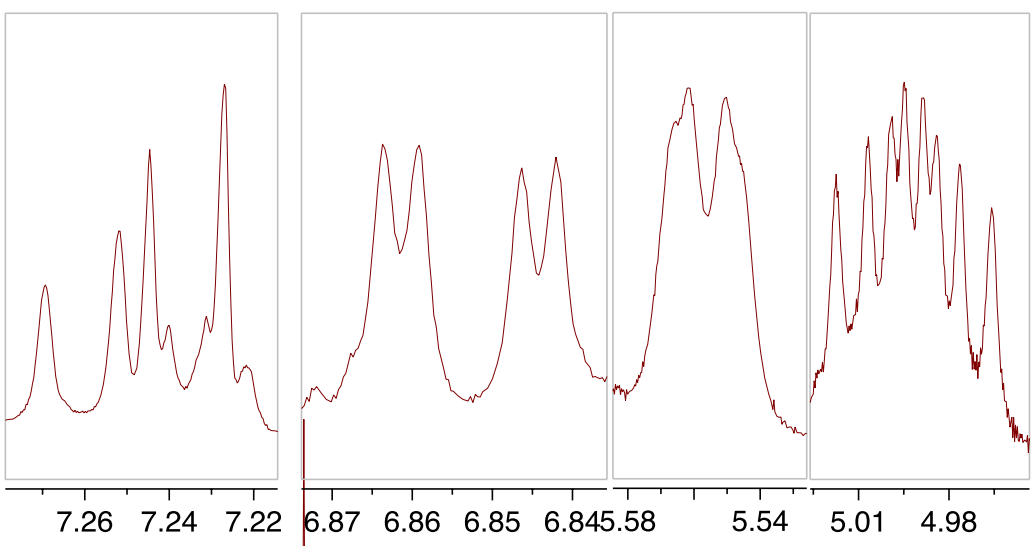

41a-fast
MsN
MeO
N
H
O
H
O
O
OMe
OMe
OMe
MeO2C
OMe
t-Bu
HSQC in C6D6
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

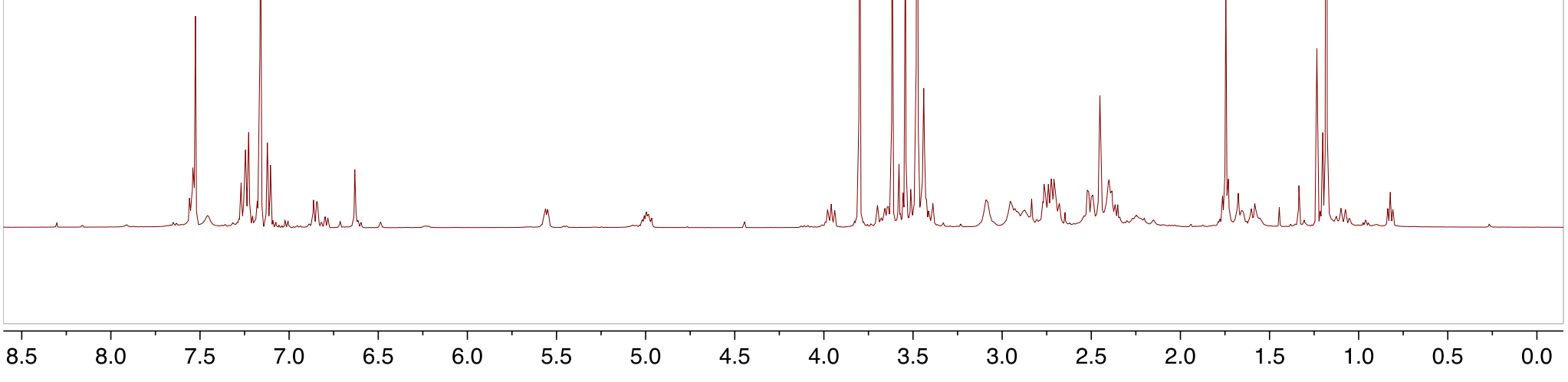

41a-fast
HMBC in C_6D_6
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

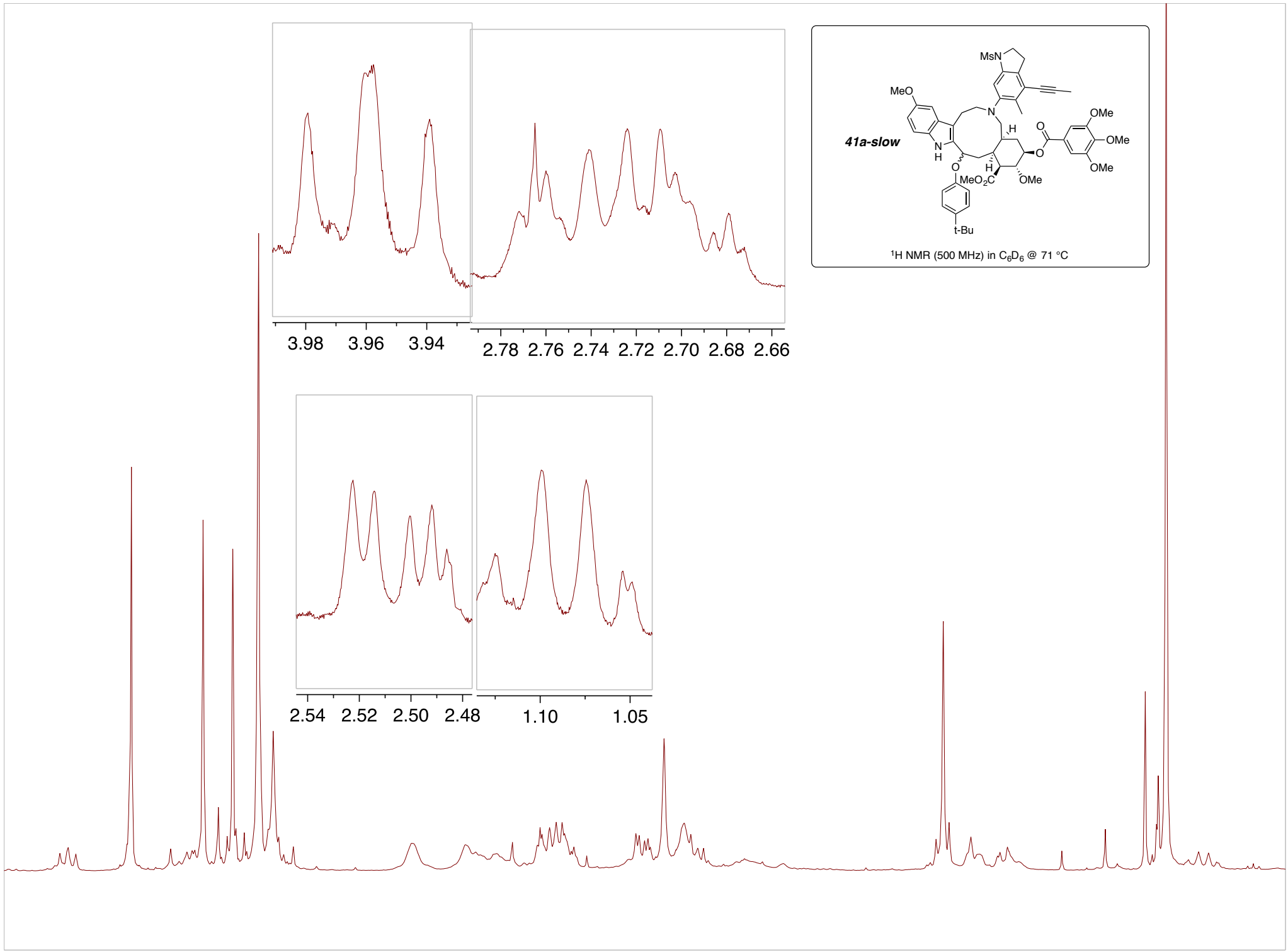


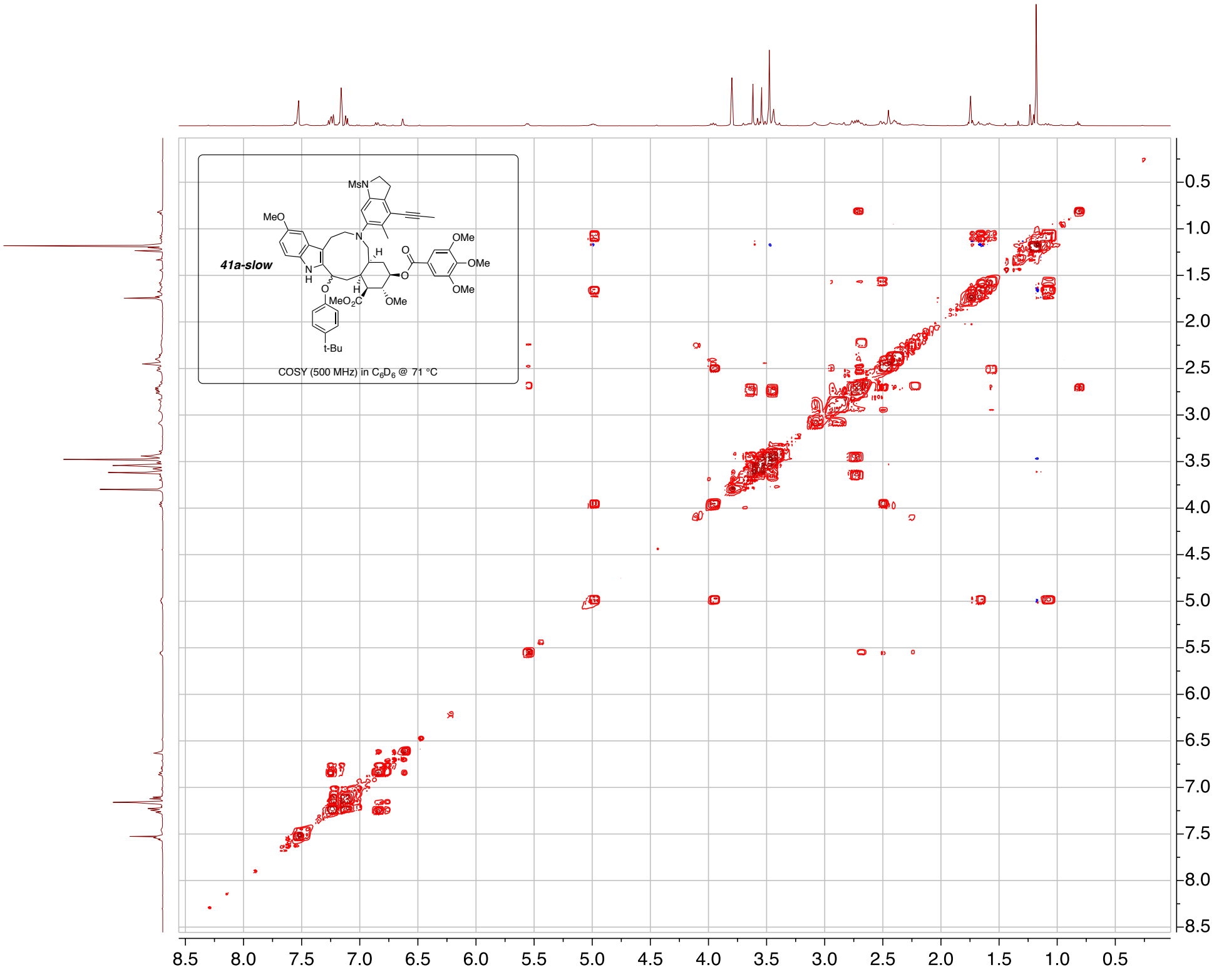
41a-slow

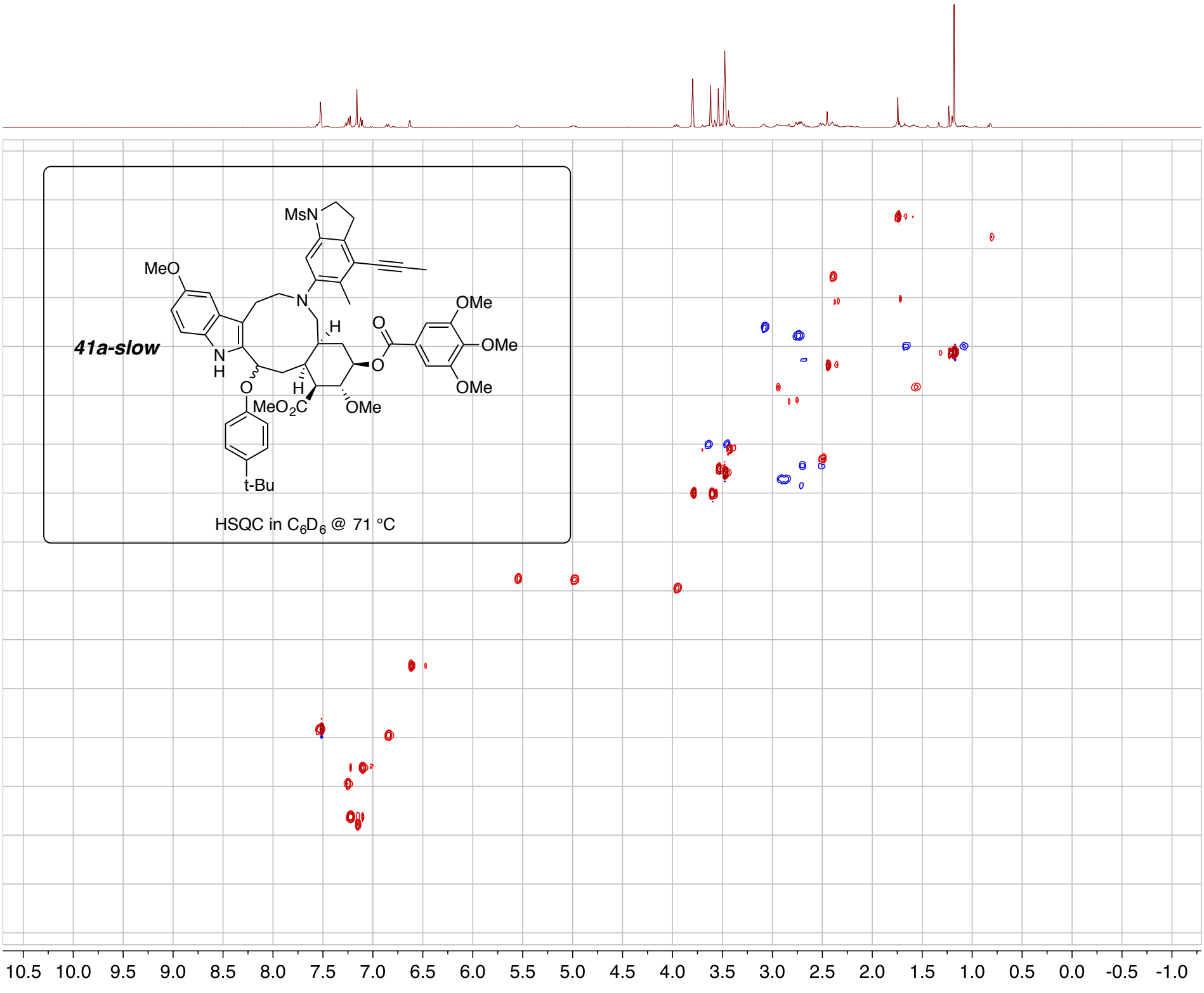
^{1}H NMR (500 MHz) in C_6D_6 @ 71 °C

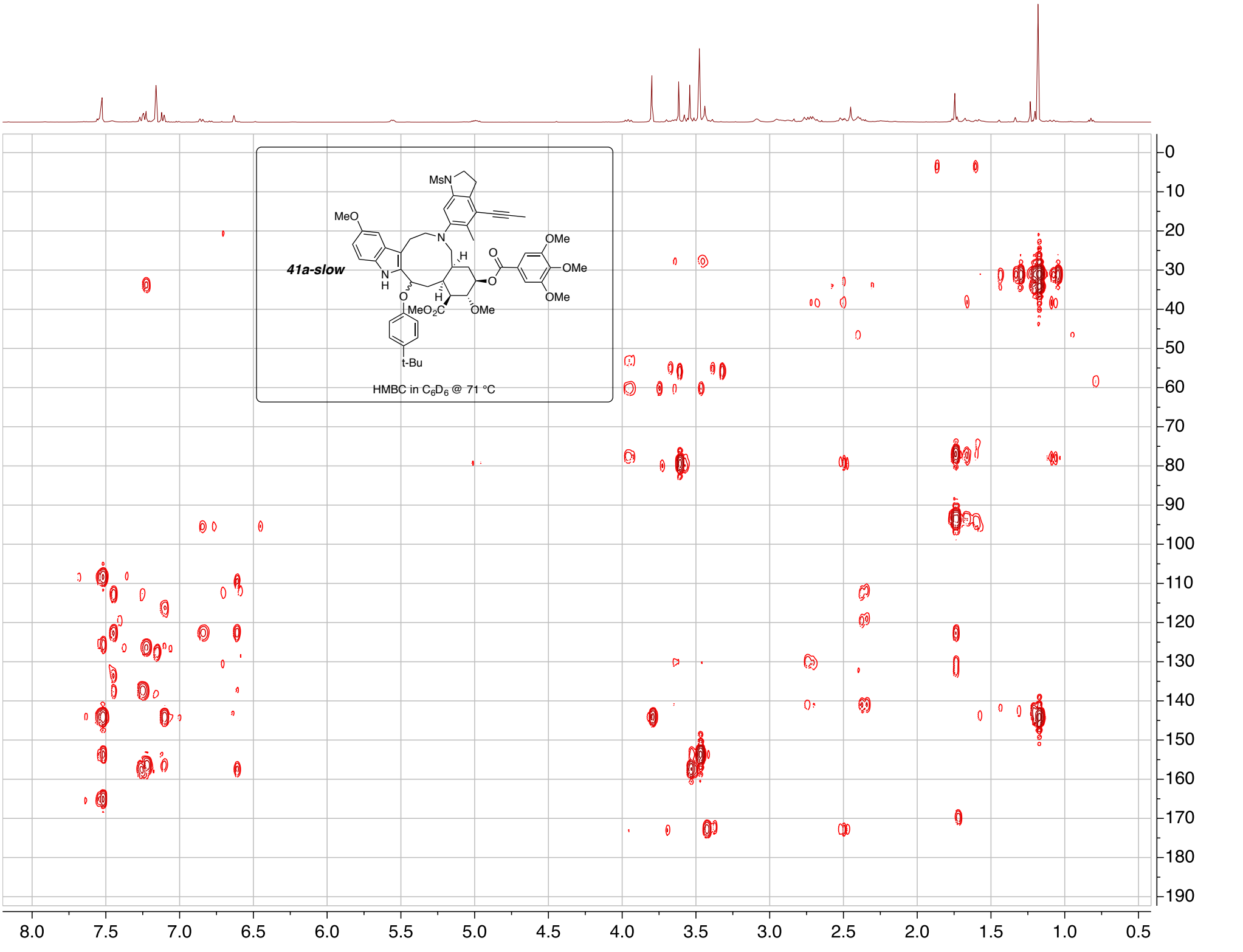


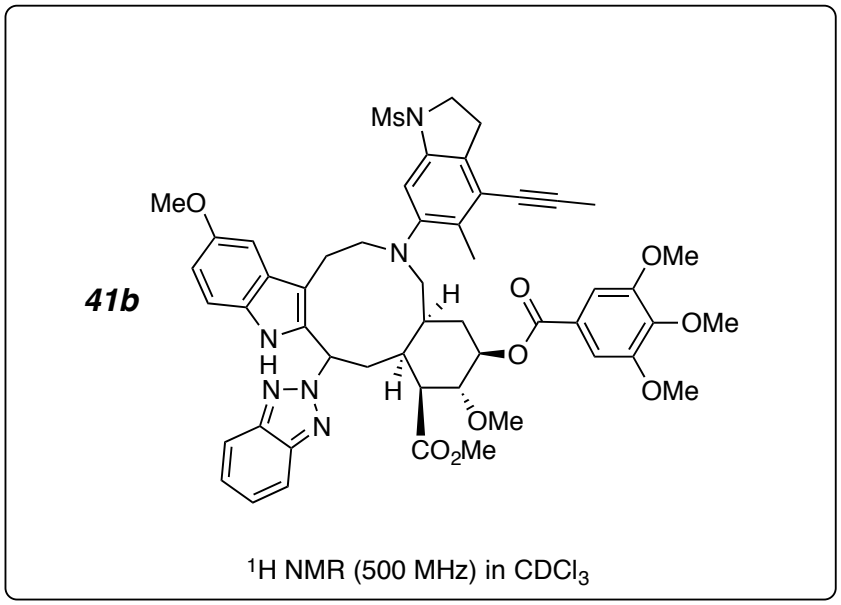


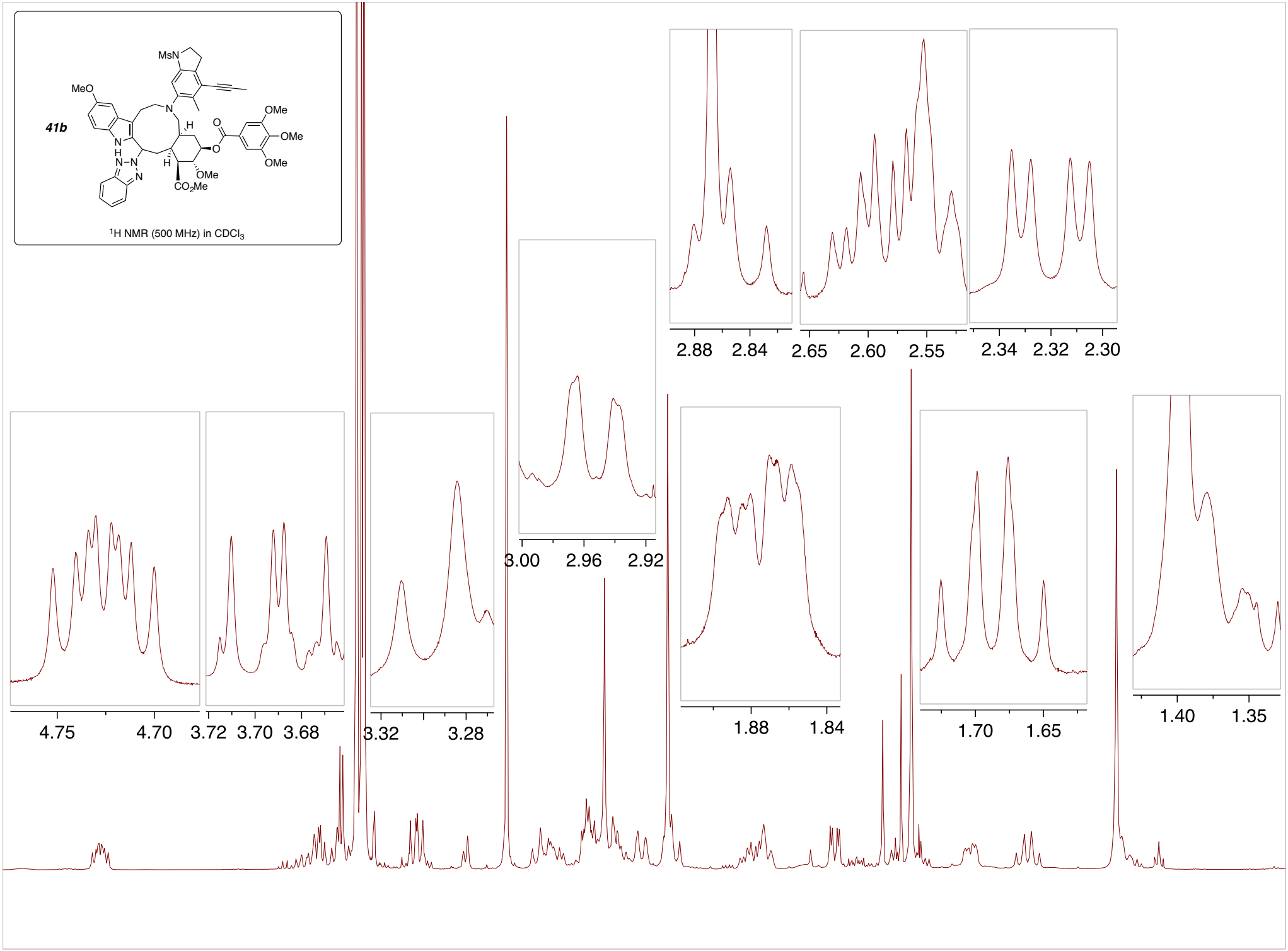

MsN
MeO
N
H
OMe
OMe
OMe
O
O
O
H
H
MeO2C
OMe
t-Bu
41a-slow
1H NMR (500 MHz) in C6D6 @ 71 °C
3.98 3.96 3.94
2.78 2.76 2.74 2.72 2.70 2.68 2.66
2.54 2.52 2.50 2.48
1.10 1.05
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9

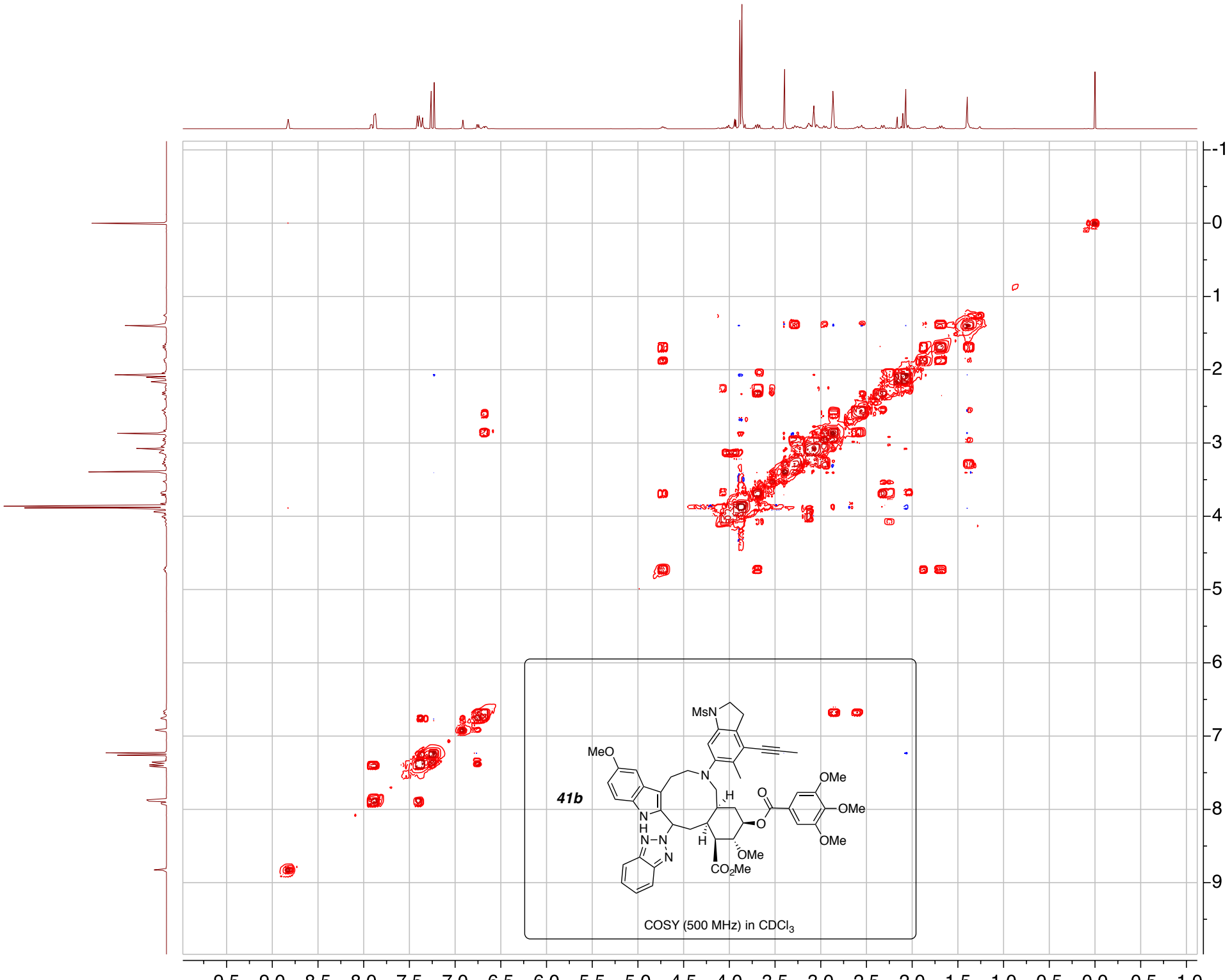

41a-slow
COSY (500 MHz) in C_6D_6 @ 71 °C
MsN
MeO
OMe
OMe
OMe
OMe
MeO_2C
t-Bu
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

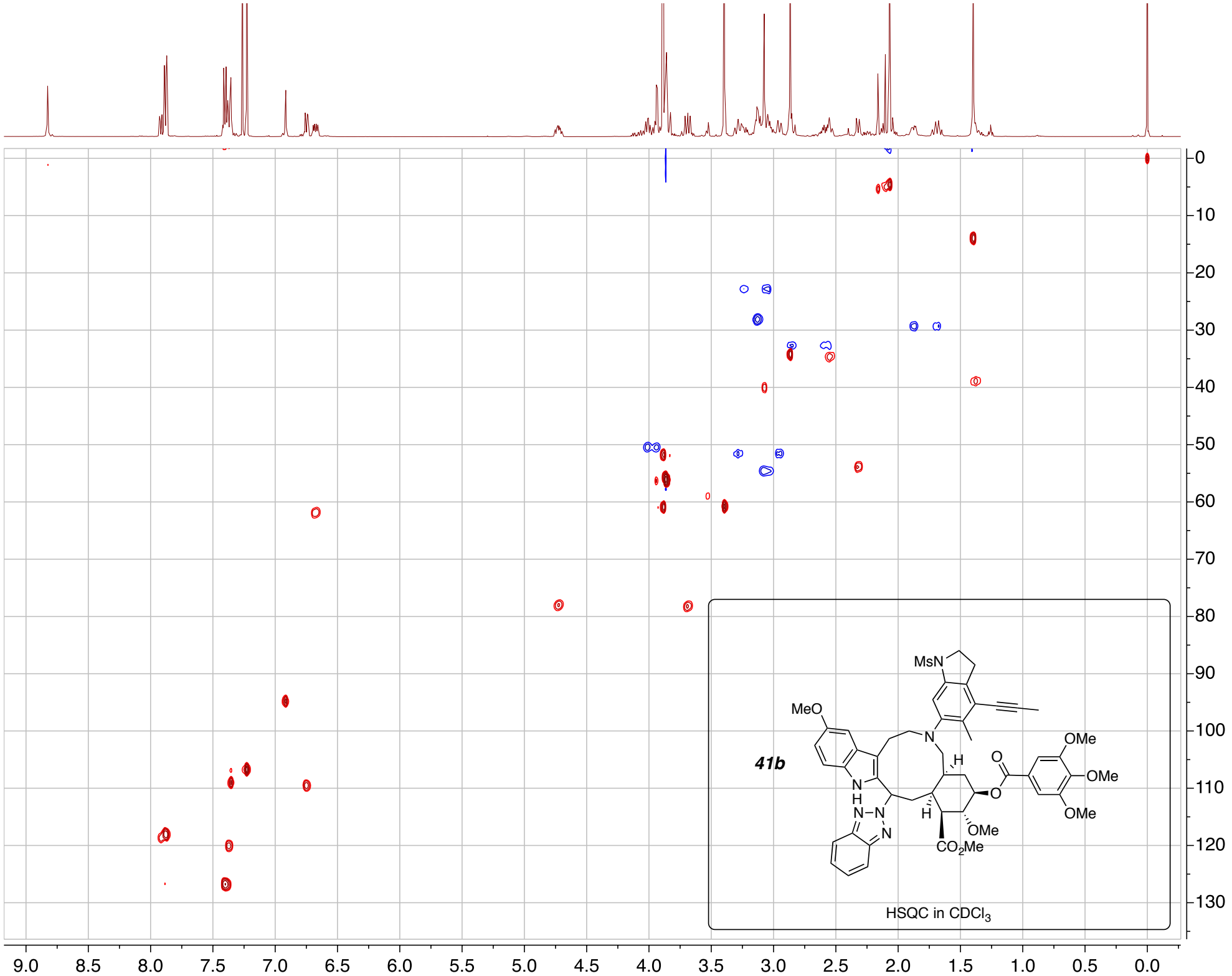

41a-slow
MsN
MeO
N
H
O
OMe
OMe
OMe
MeO2C
OMe
t-Bu
HSQC in C6D6 @ 71 °C
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

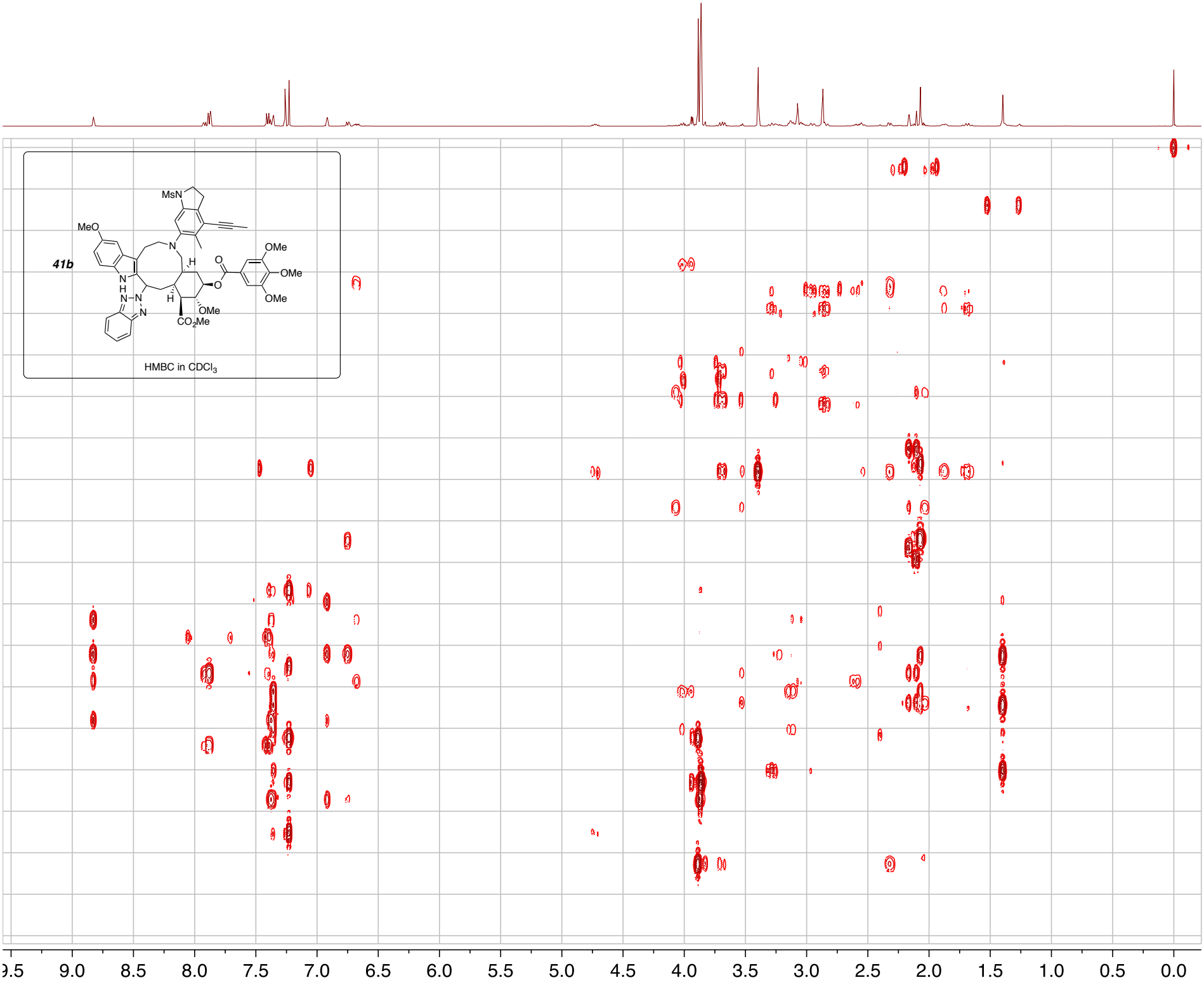

41a-slow
MsN
MeO
N
H
O
OMe
OMe
OMe
MeO2C
OMe
t-Bu
HMBC in C6D6 @ 71 °C
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

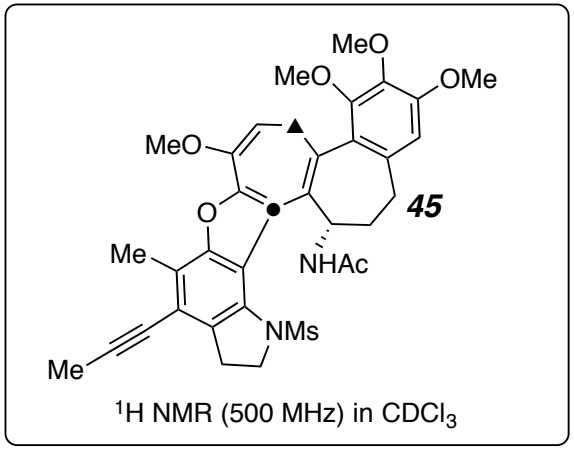

41b
MsN
MeO
N
H
OMe
O
OMe
O
N
H
N–N
N
H
OMe
CO2Me
OMe
1H NMR (500 MHz) in CDCl3
7.88
7.86
6.70
6.68
6.66
6.76
6.75
6.74
6.73
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


41b
MsN
MeO
OMe
OMe
OMe
OMe
CO2Me
1H NMR (500 MHz) in CDCl3
4.75
4.70
3.72
3.70
3.68
3.32
3.28
3.00
2.96
2.92
2.88
2.84
2.65
2.60
2.55
2.34
2.32
2.30
1.88
1.84
1.70
1.65
1.40
1.35
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0

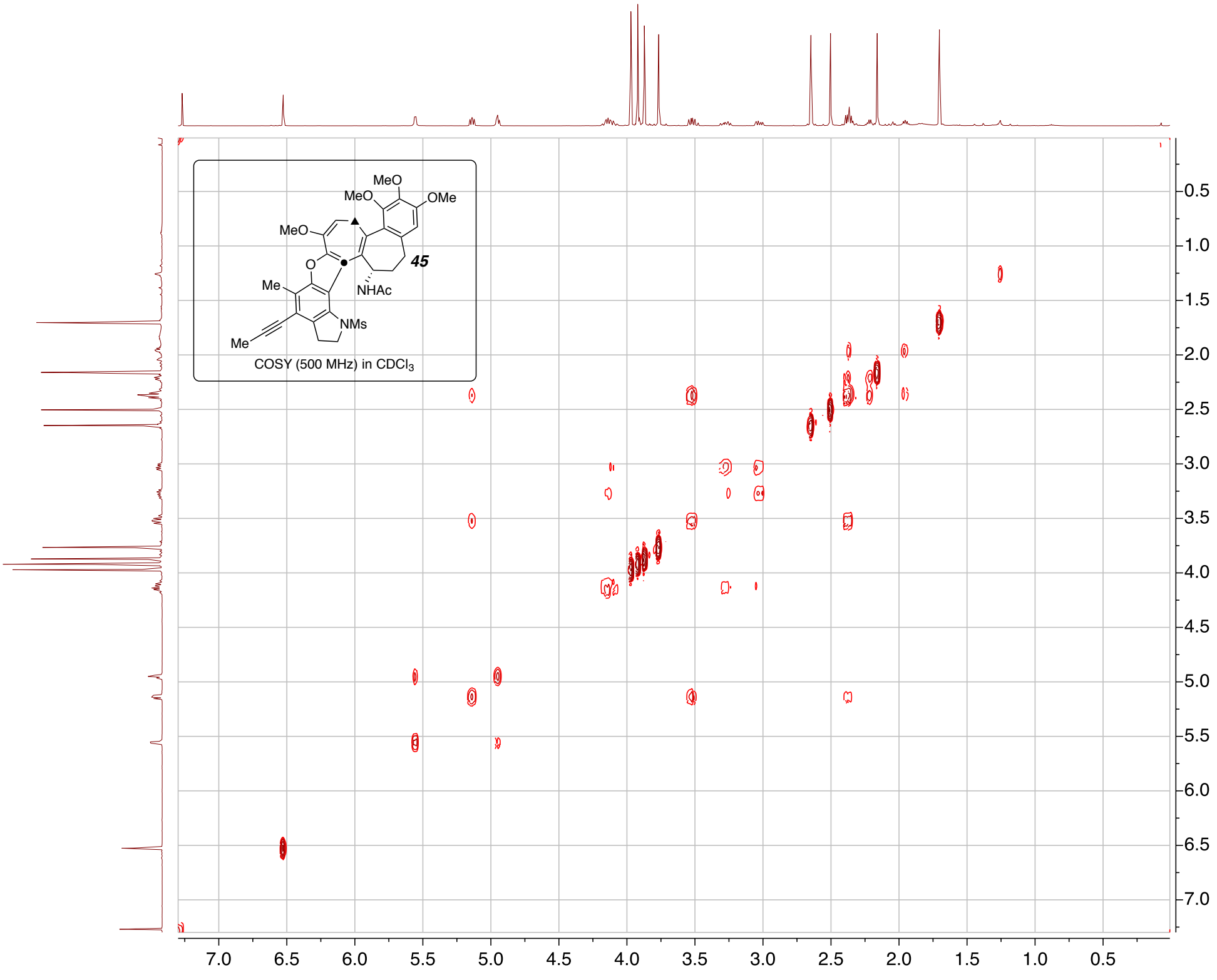

41b
MsN
MeO
N
H
O
OMe
OMe
OMe
N
H
N–N
N
H
O
OMe
CO2Me
COSY (500 MHz) in CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
-1 0 1 2 3 4 5 6 7 8 9

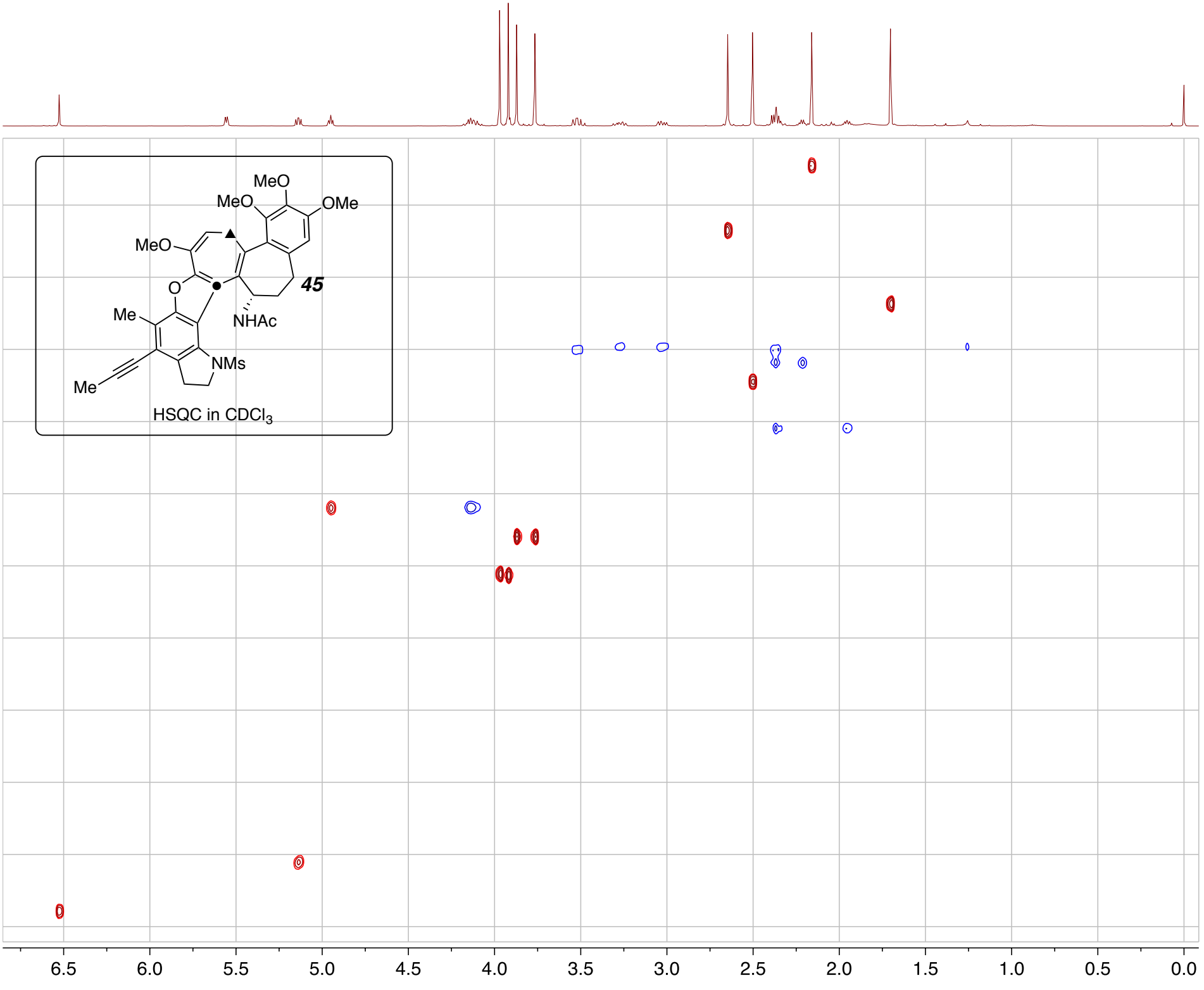

41b
MsN
MeO
N
H
O
OMe
OMe
OMe
N
H
N–N
N
H
OMe
CO2Me
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

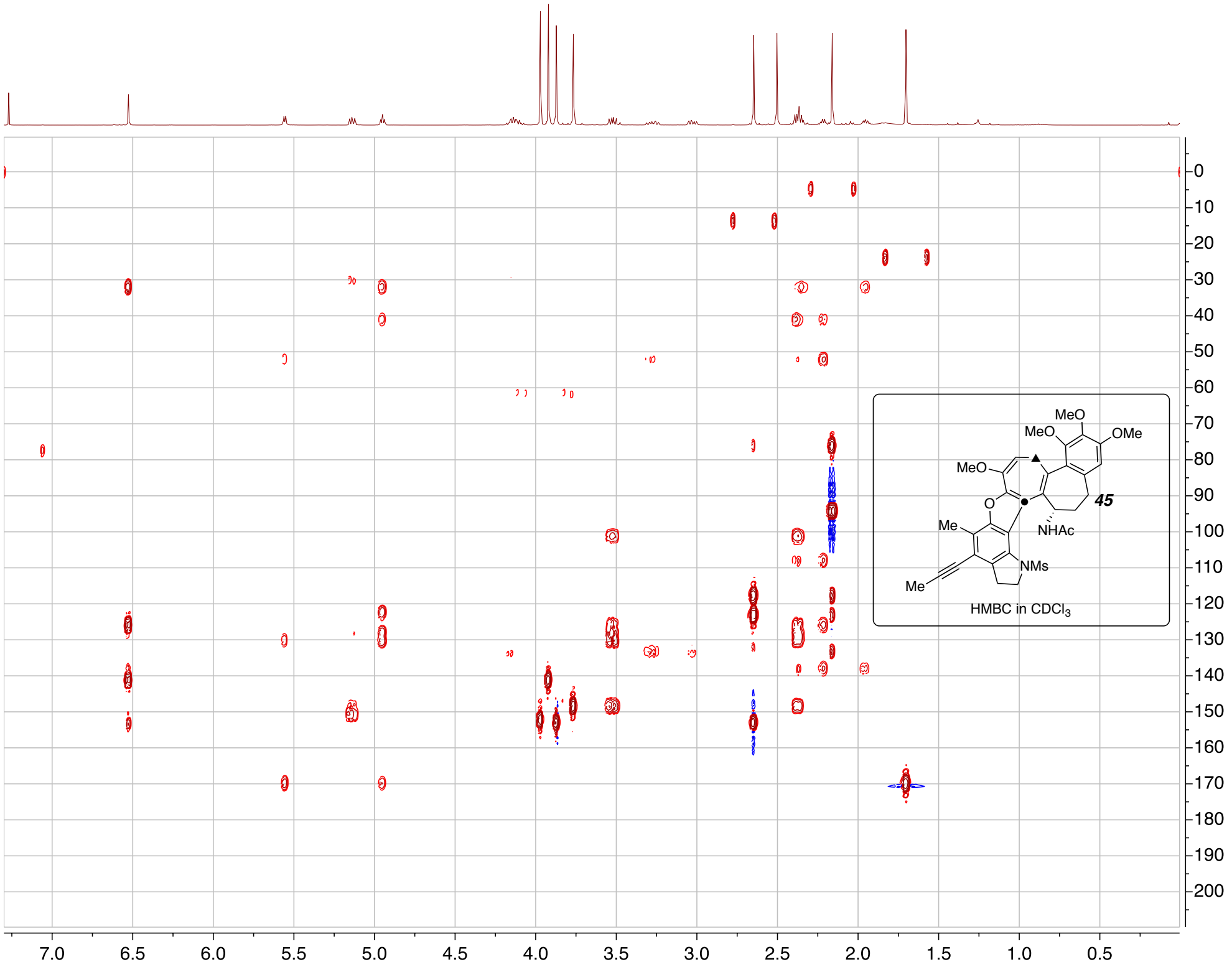

41b
HMBC in CDCl3

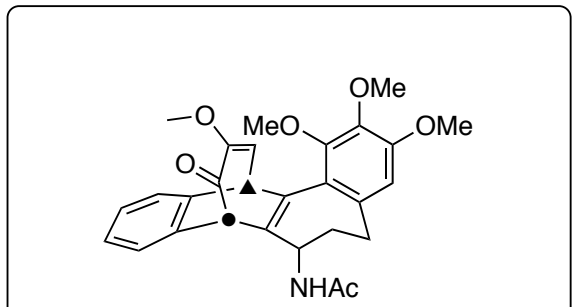


^{1}H NMR (500 MHz) in $CDCl_3$


MeO
MeO
OMe
MeO
O
45
Me
NHAc
NMs
Me
COSY (500 MHz) in CDCl3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

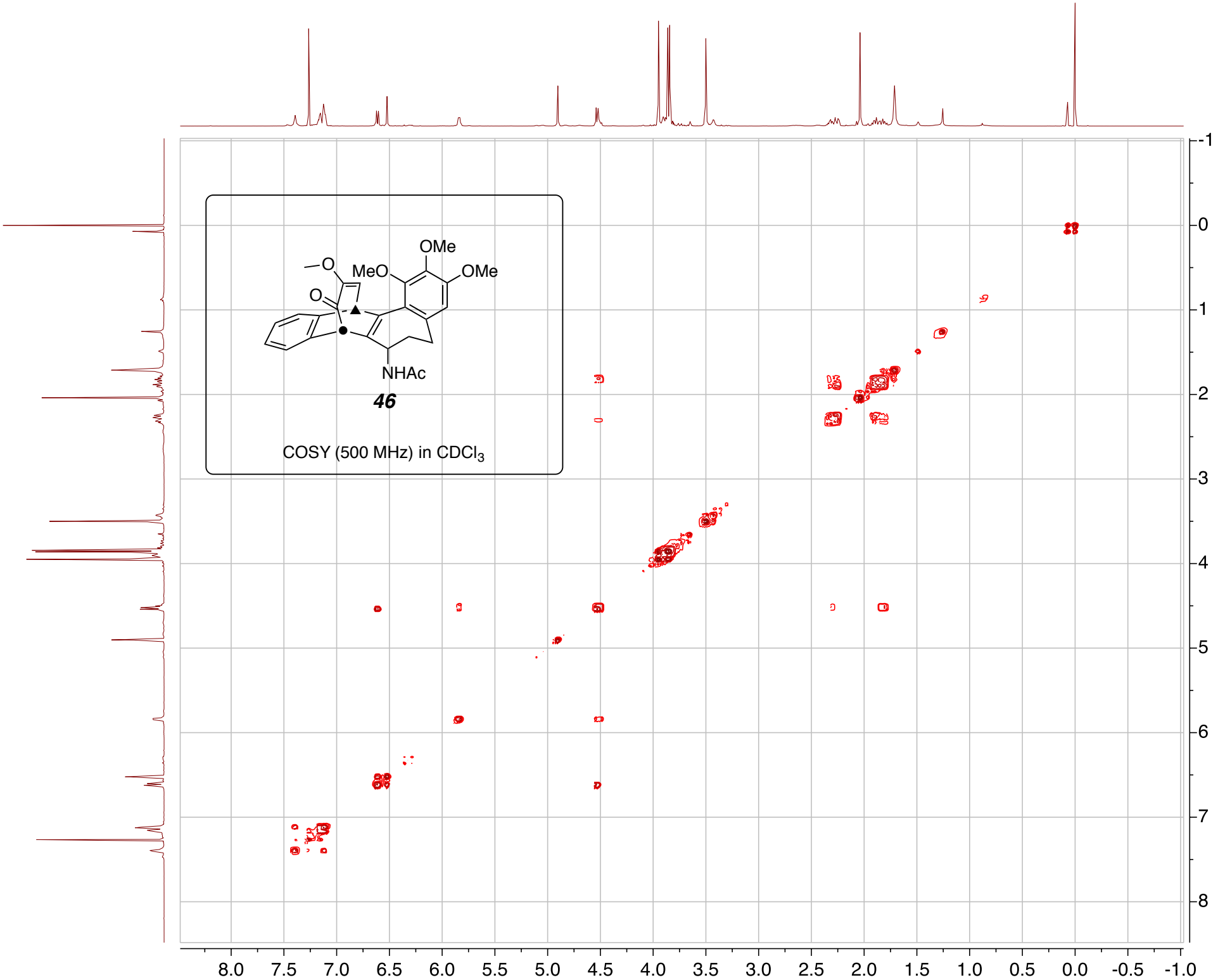

MeO
MeO
OMe
MeO
O
45
Me
NHAc
NMs
Me
HSQC in CDCl3
10
20
30
40
50
60
70
80
90
100
110
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

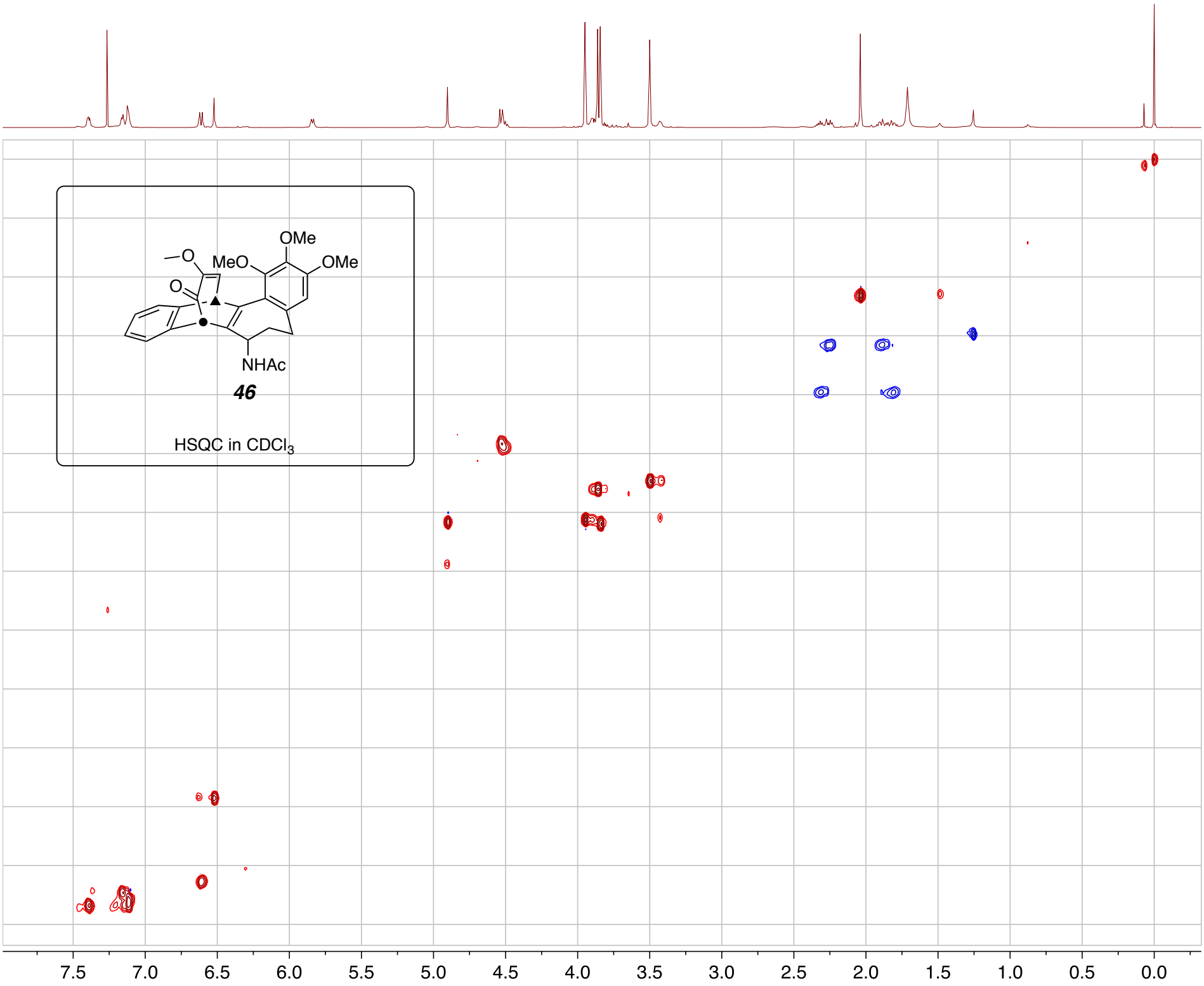

MeO
MeO
OMe
MeO
O
45
Me
NHAc
NMs
Me
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

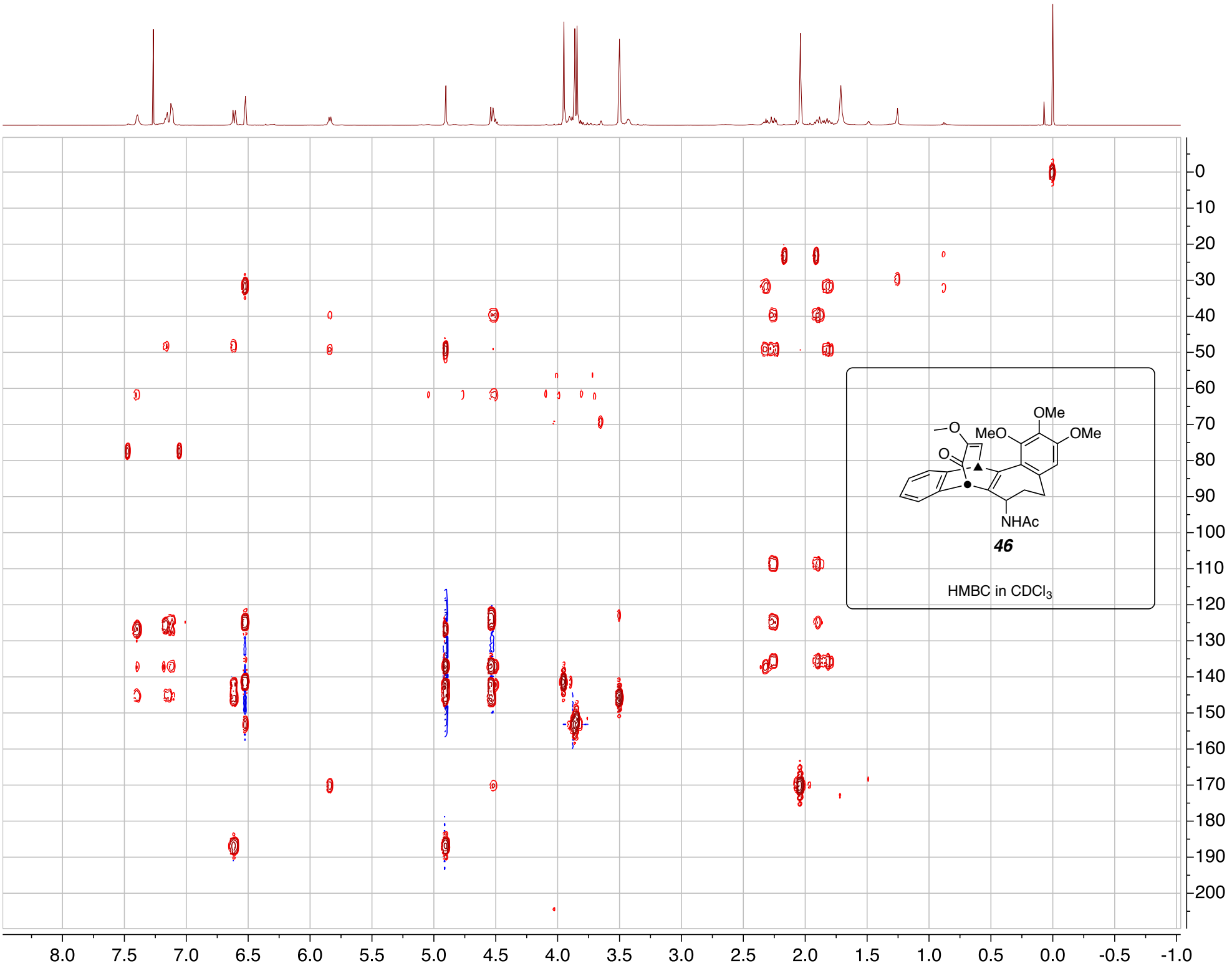


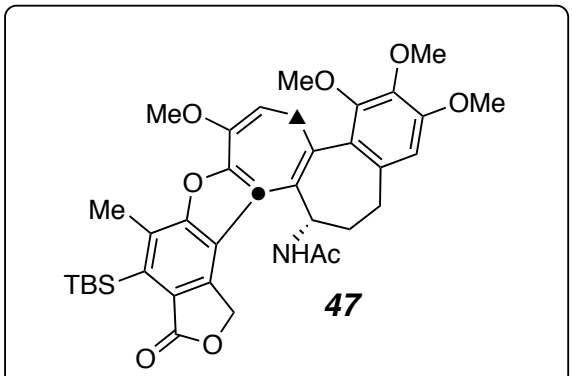
46

^{1}H NMR (500 MHz) in $CDCl_3$

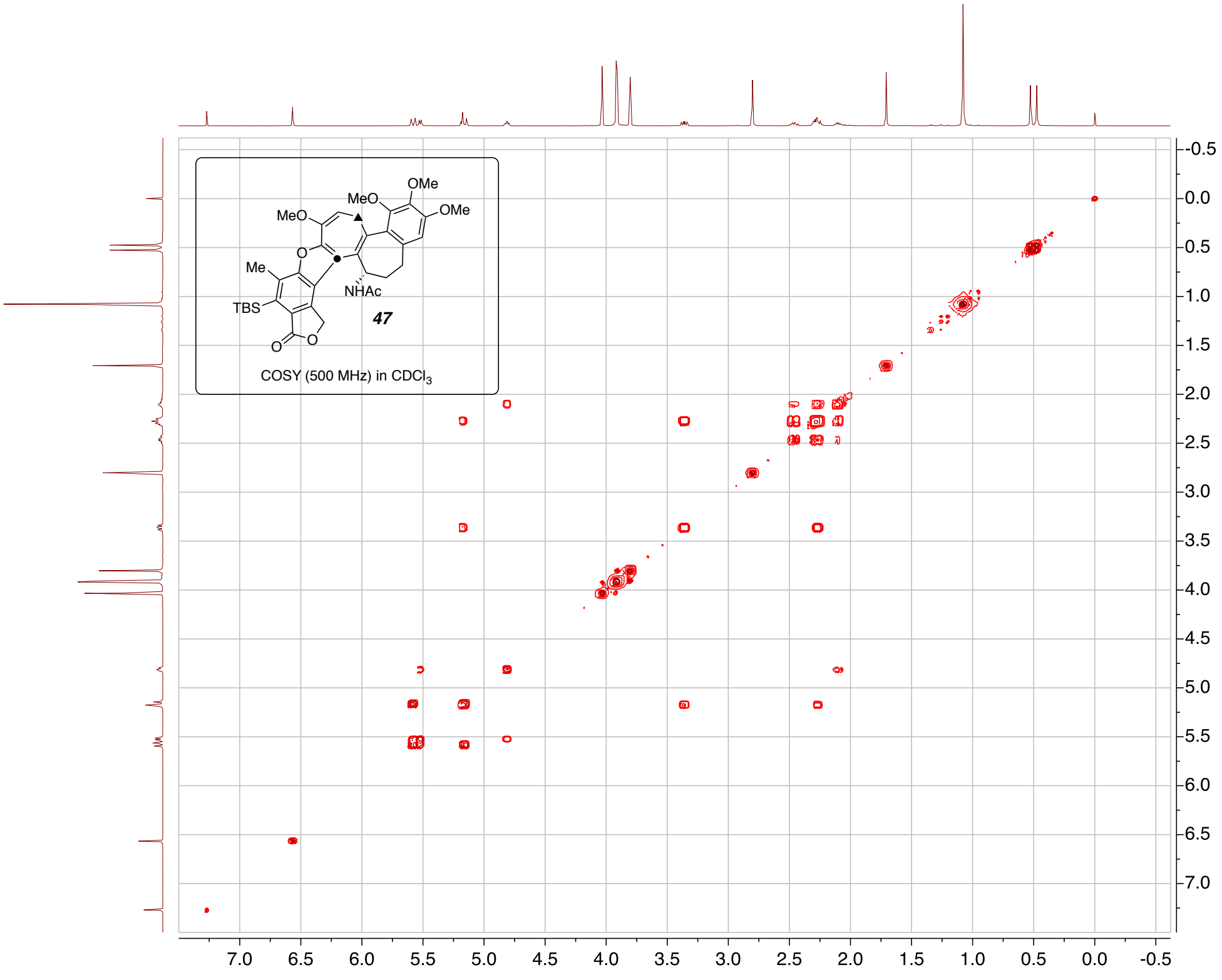

OMe
MeO
OMe
O
O
NHAc
46
COSY (500 MHz) in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1
0
1
2
3
4
5
6
7
8

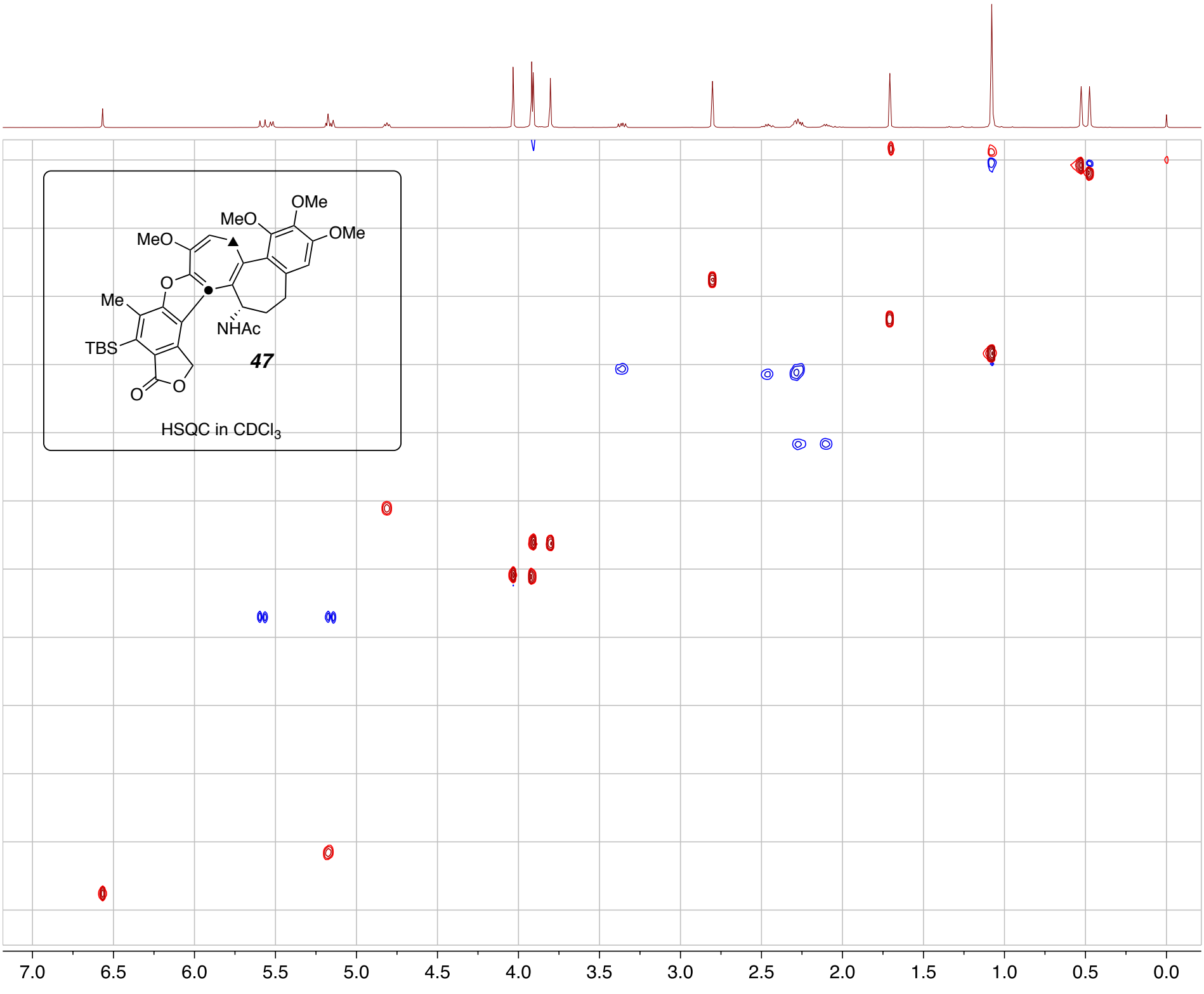

OMe
MeO
OMe
O
O
NHAc
46
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

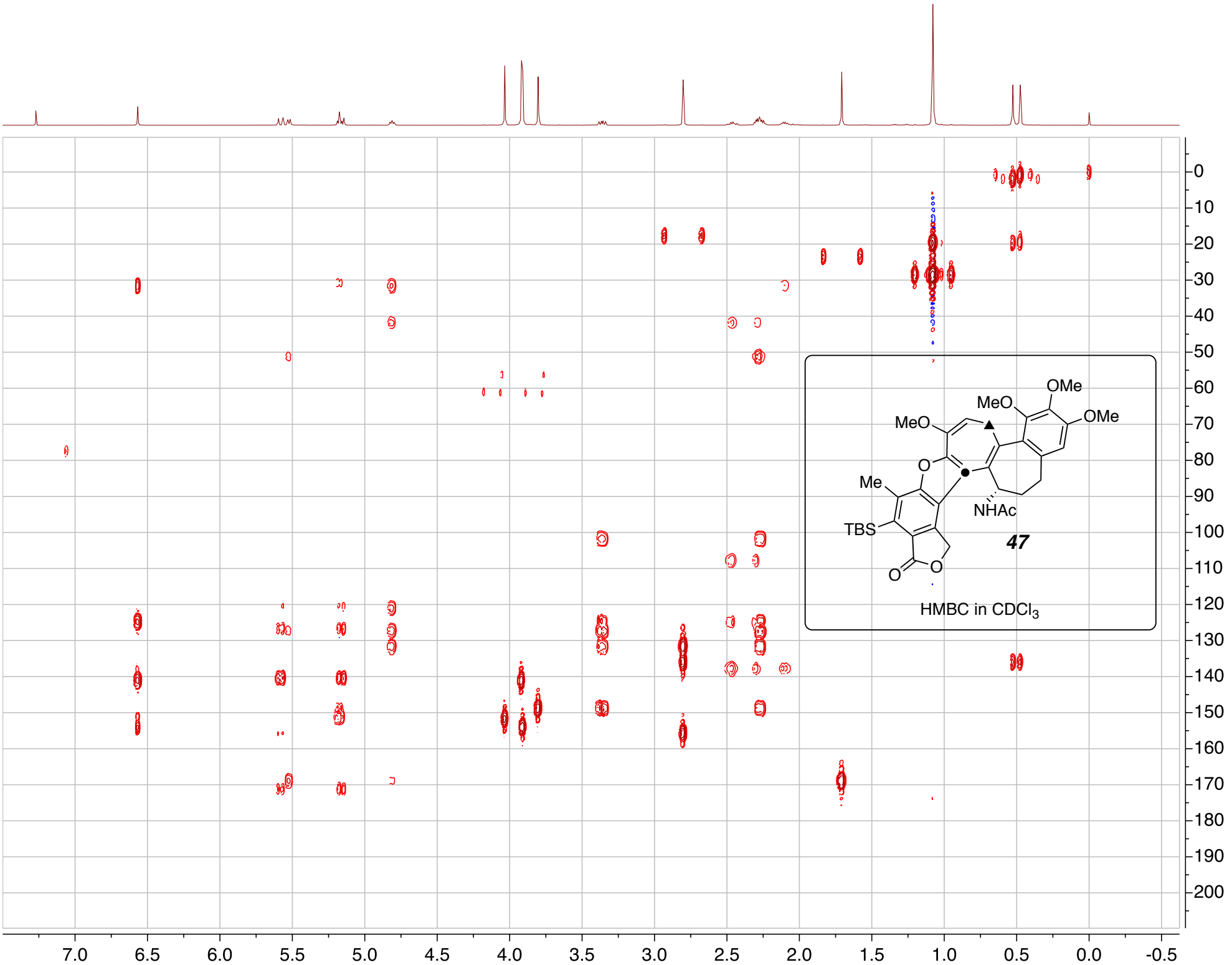

OMe
MeO
OMe
O
O
NHAc
46
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

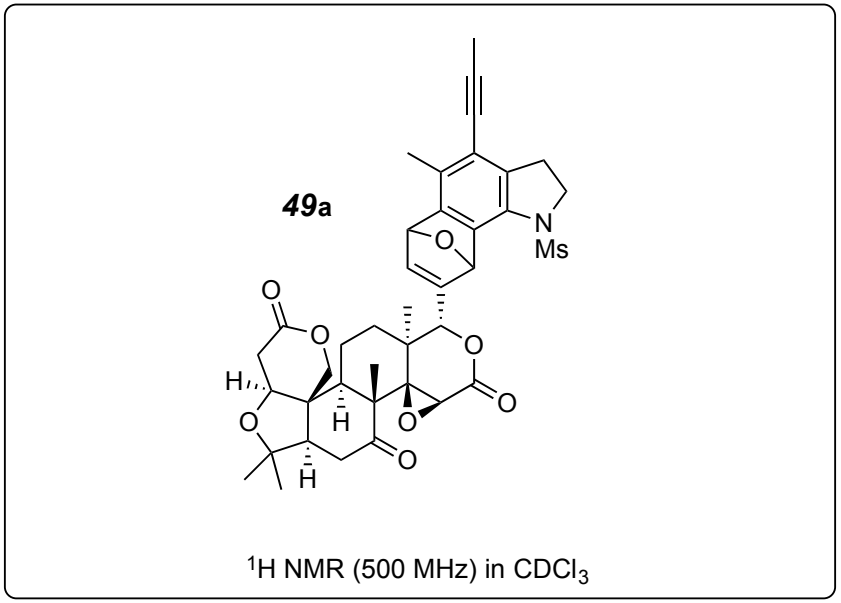


^{1}H NMR (500 MHz) in $CDCl_3$

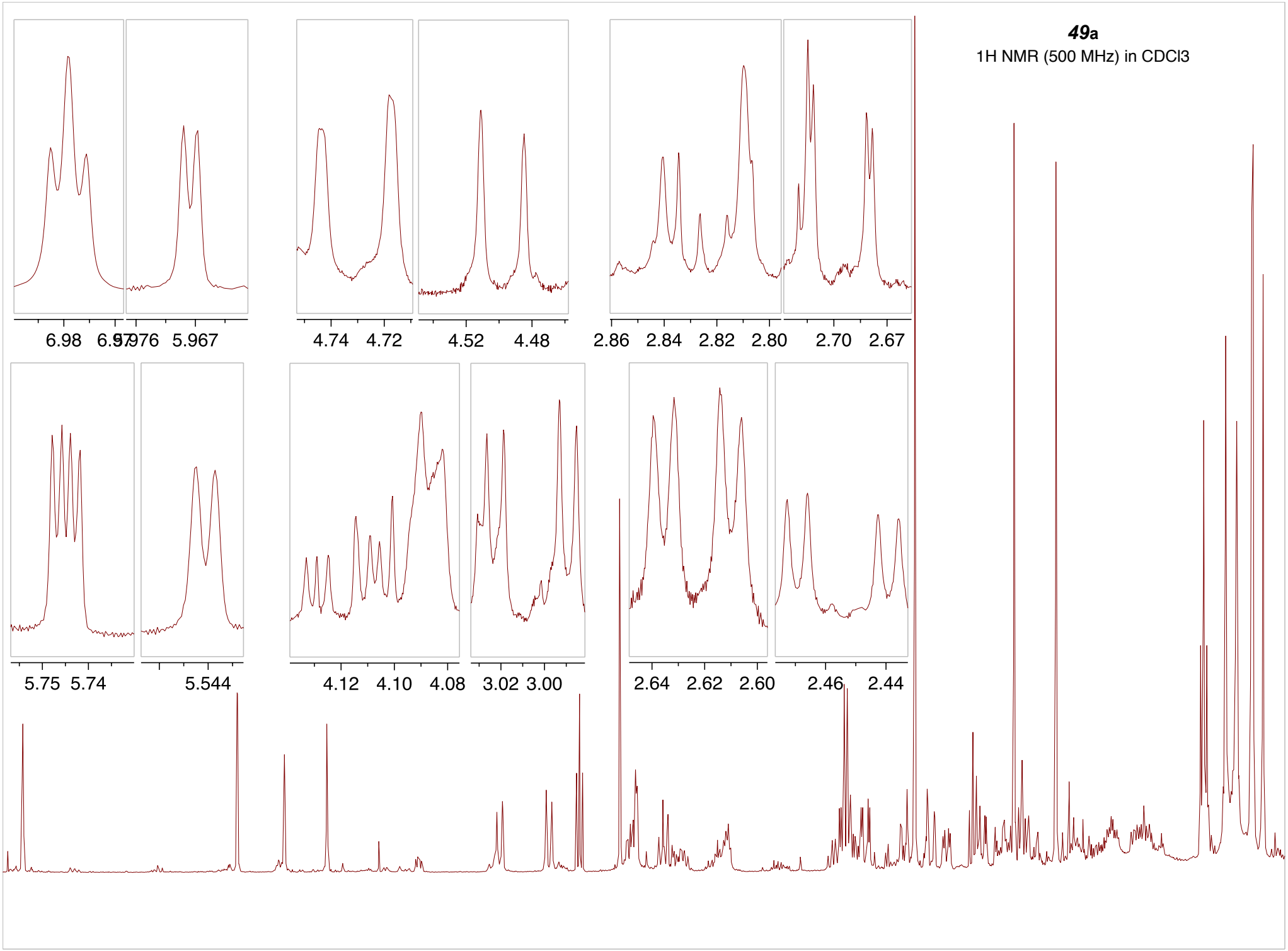

OMe
MeO
MeO
OMe
O
Me
NHAc
TBS
O
O
47
COSY (500 MHz) in CDCl3
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

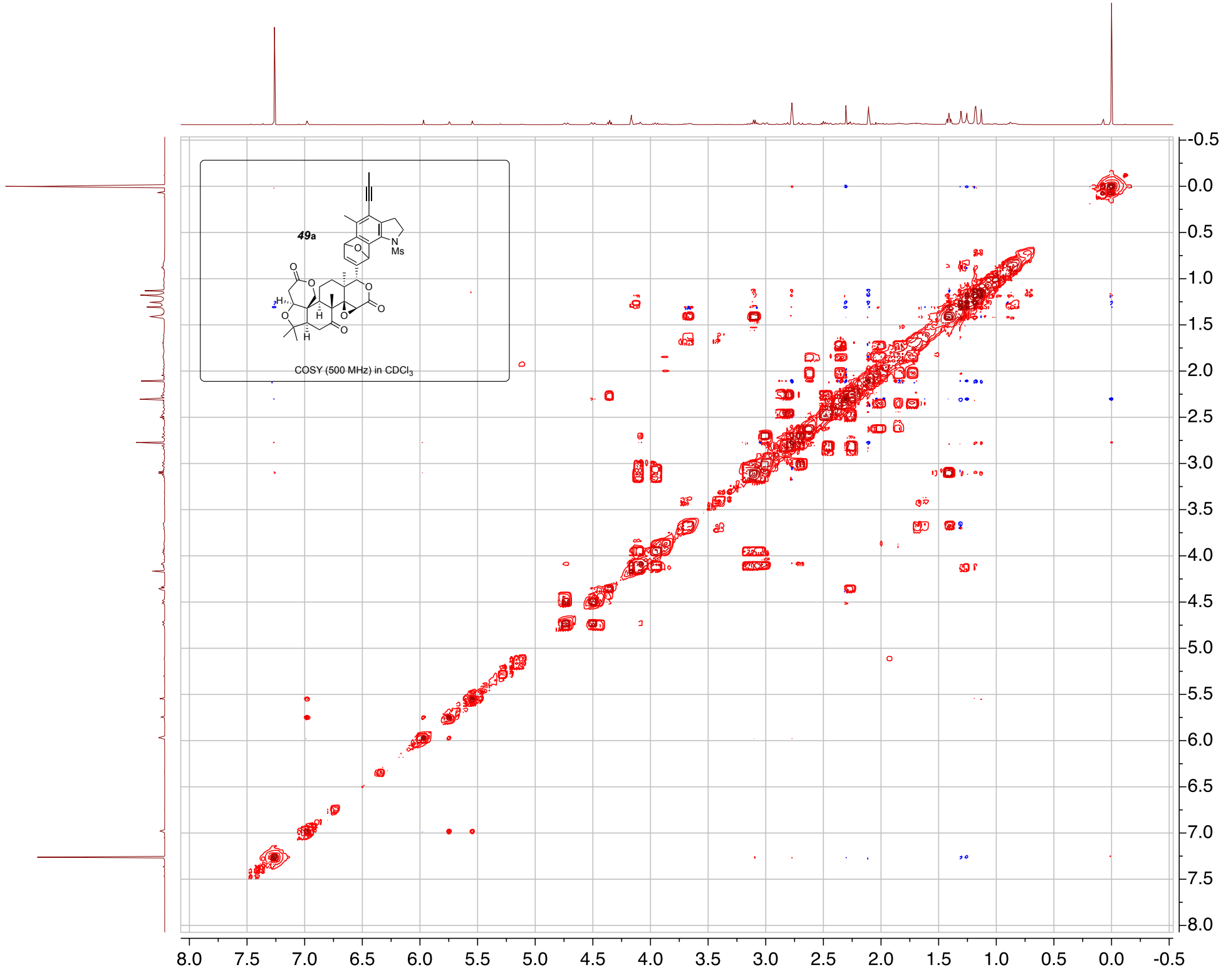

MeO
OMe
MeO
OMe
O
Me
NHAc
TBS
O
O
47
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

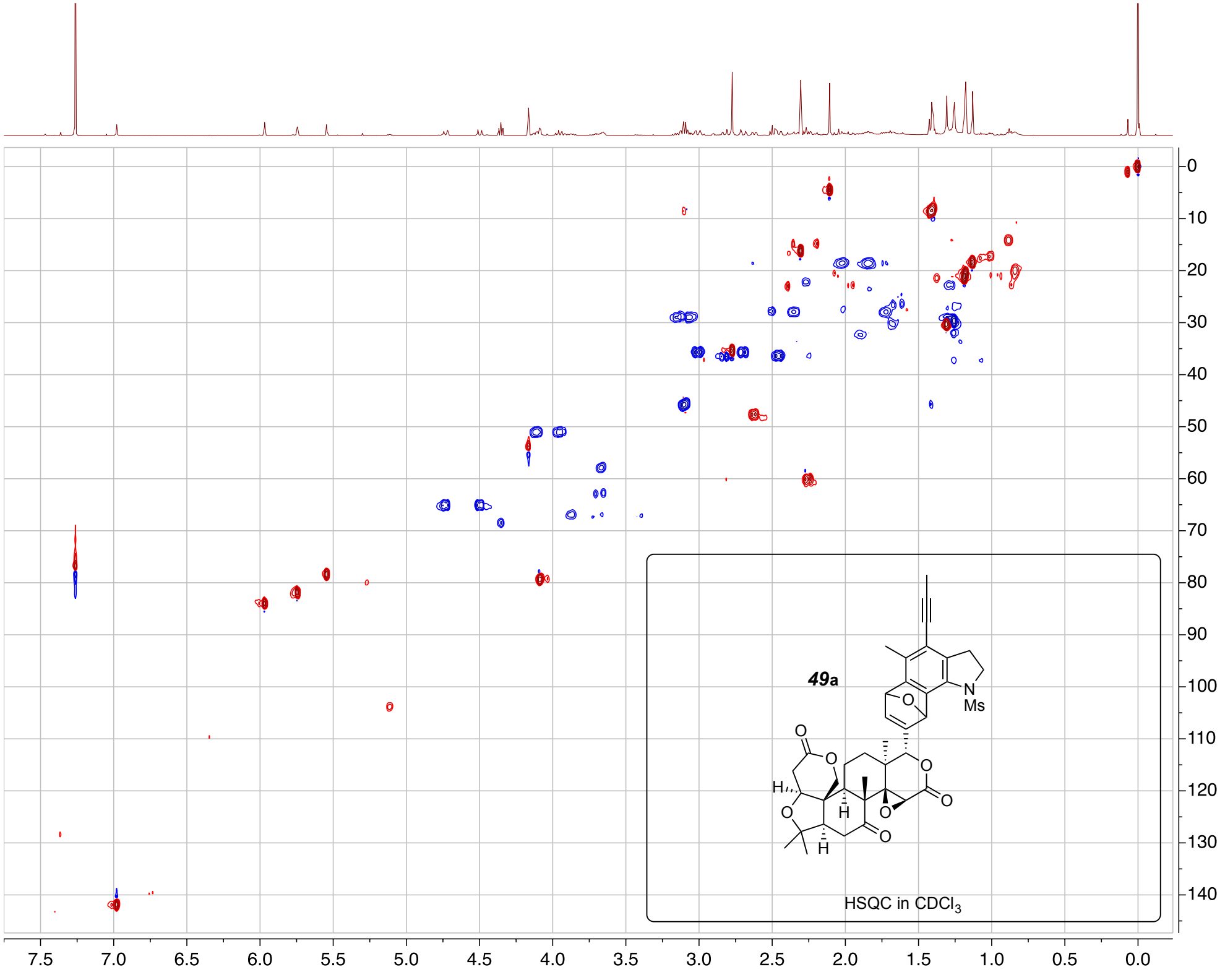

MeO
OMe
MeO
OMe
O
Me
NHAc
TBS
O
O
47
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

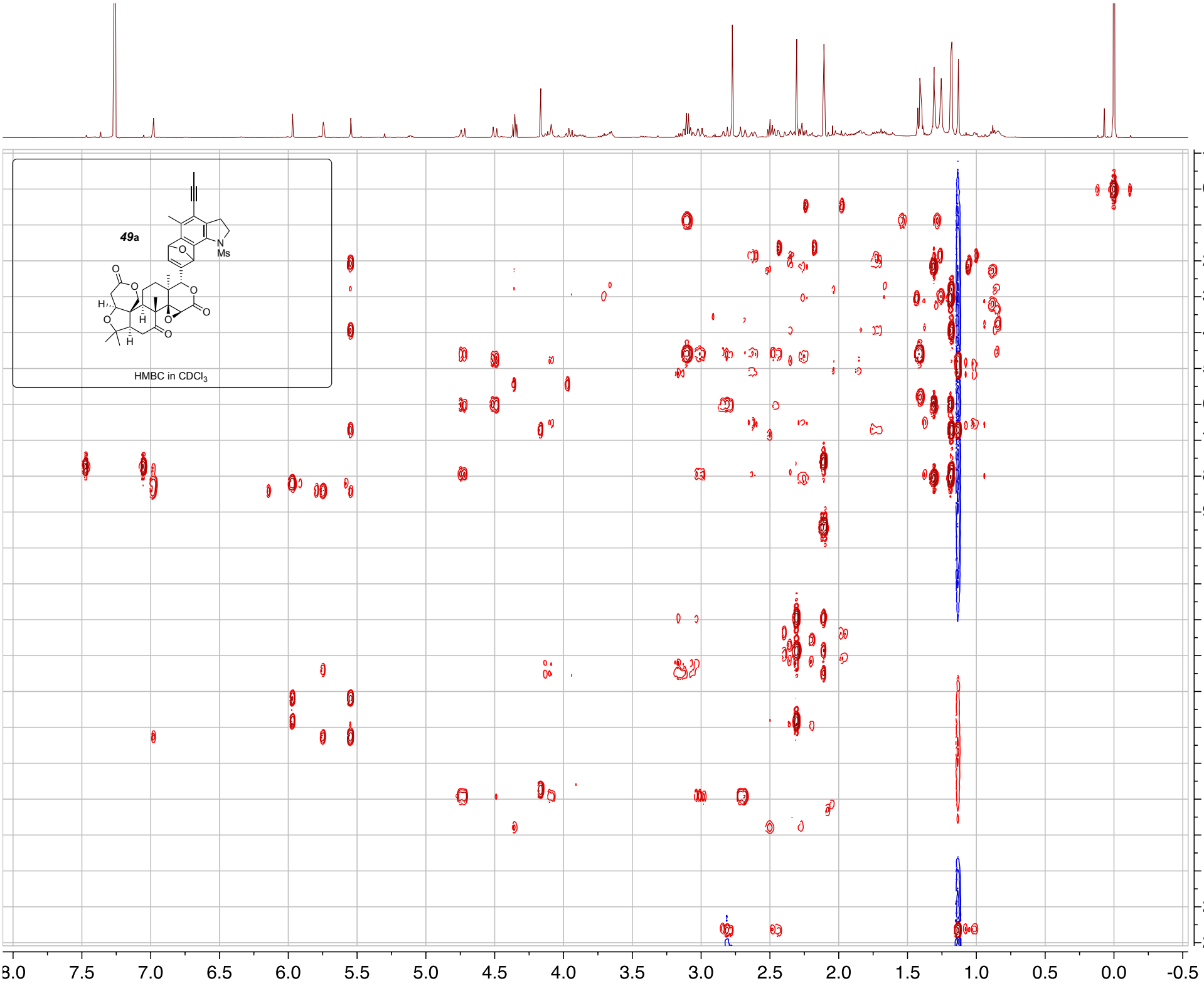


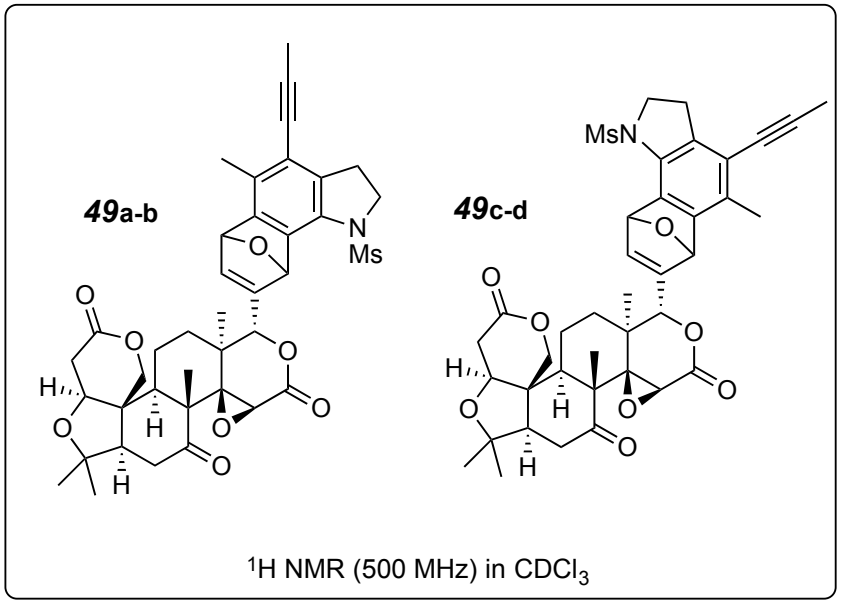
^{1}H NMR (500 MHz) in $CDCl_3$


49a
1H NMR (500 MHz) in CDCl3
6.98
6.97
5.976
5.967
4.74
4.72
4.52
4.48
2.86
2.84
2.82
2.80
2.70
2.67
5.75
5.74
5.544
4.12
4.10
4.08
3.02
3.00
2.64
2.62
2.60
2.46
2.44
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

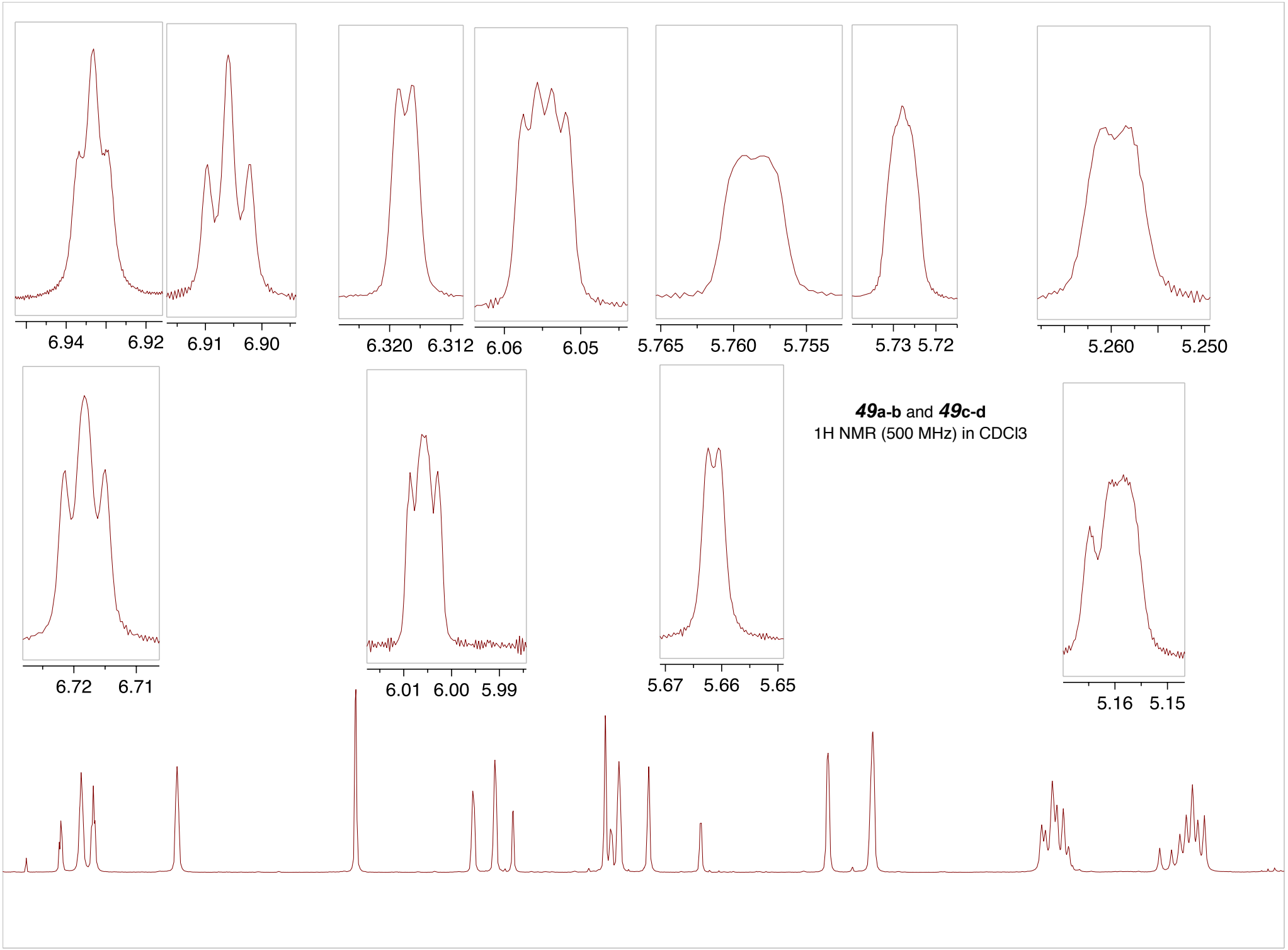

49a
N
Ms
O
H
COSY (500 MHz) in CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0

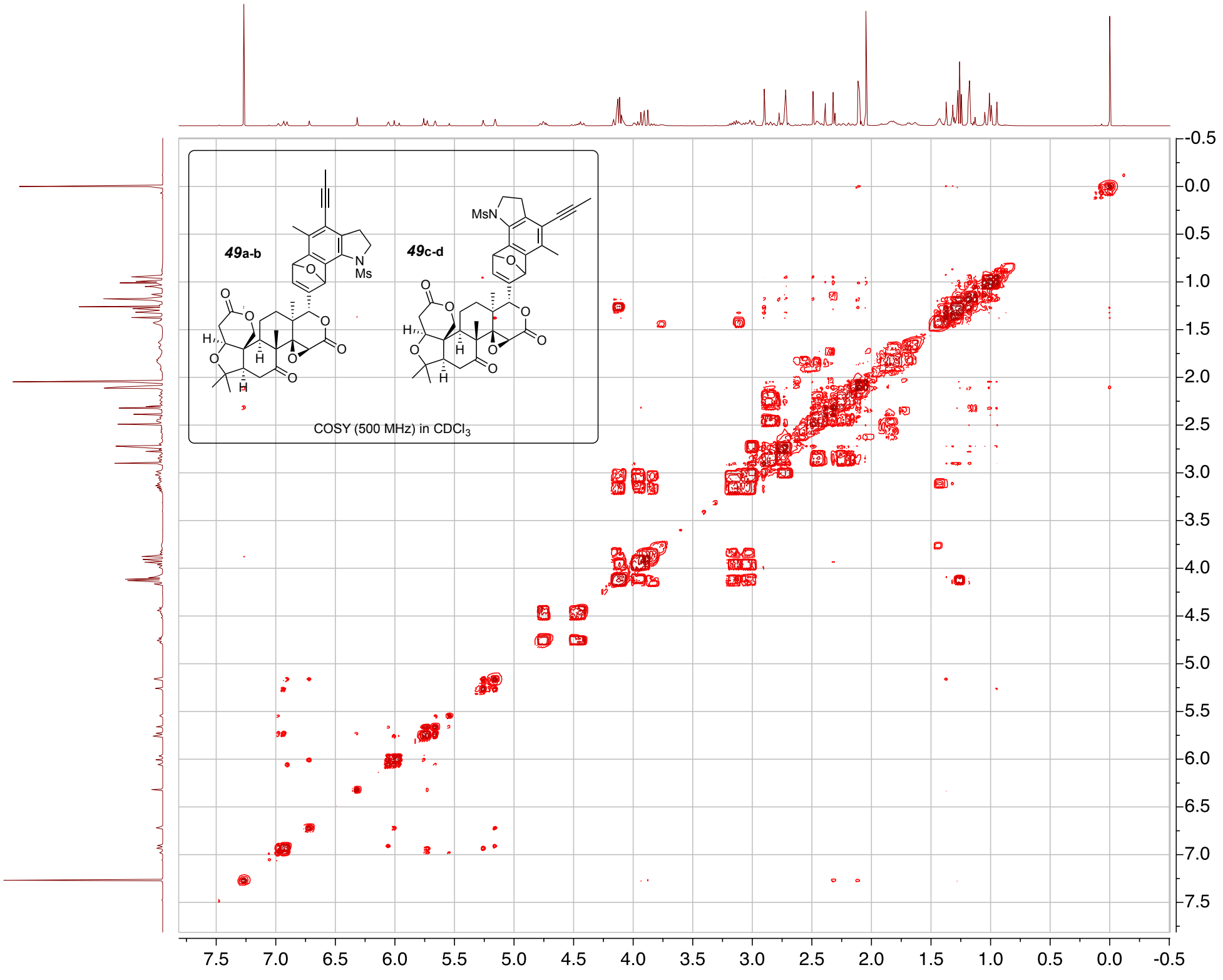

49a
N
Ms
O
O
O
O
O
O
O
O
H
H
H
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

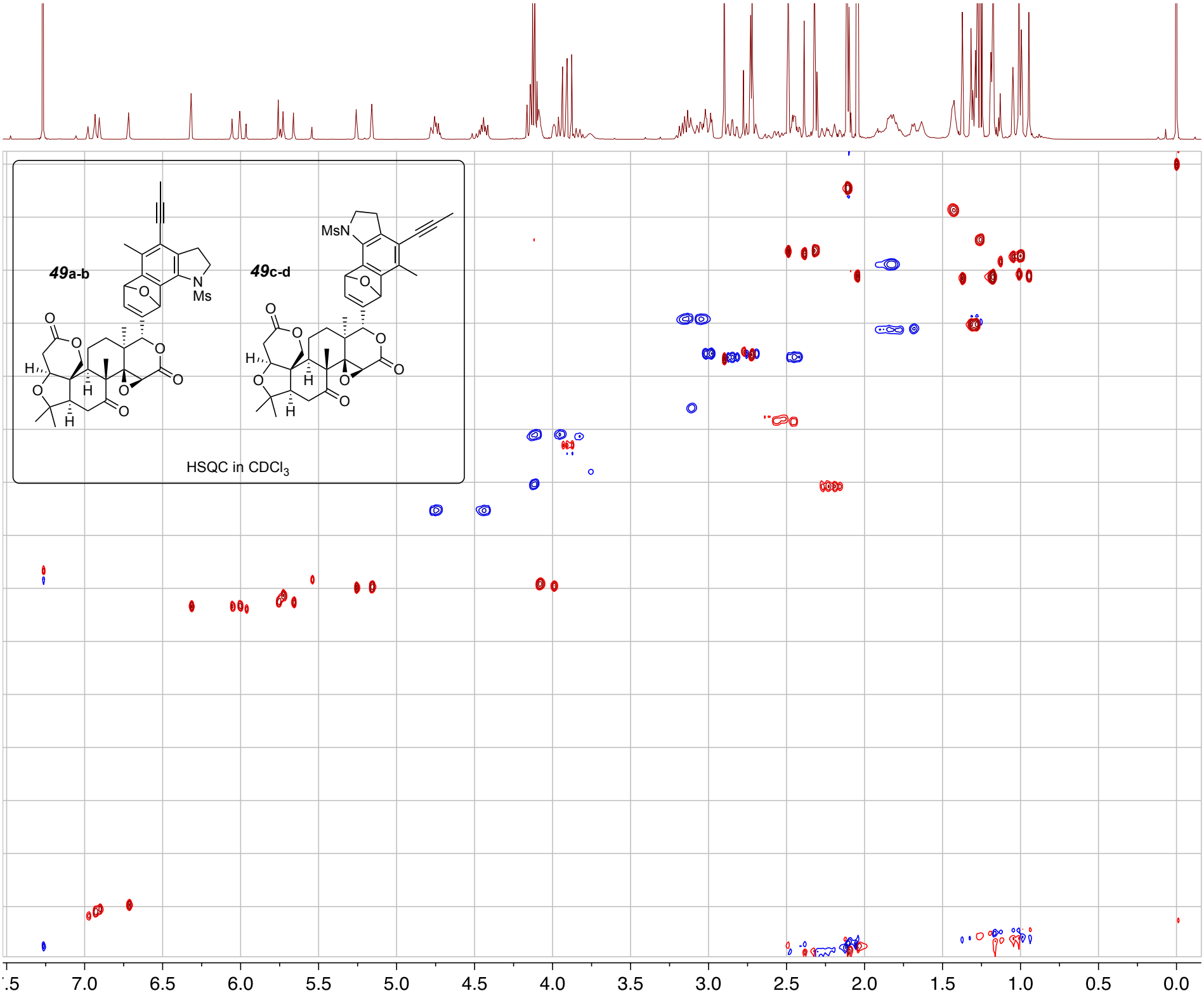

49a
N
Ms
O
H
H
H
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

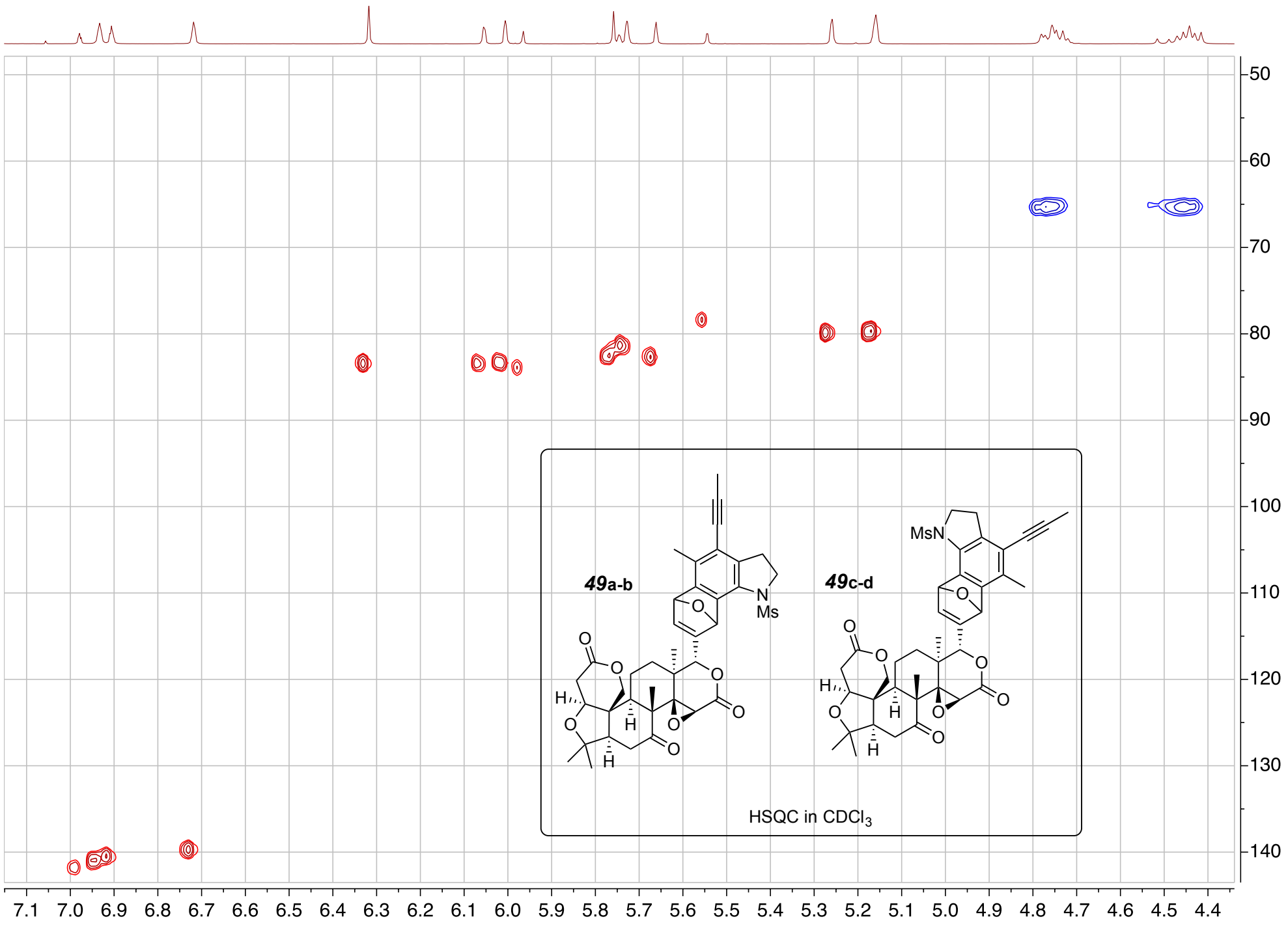

49a-b
49c-d
N
Ms
MsN
O
H
^{1}H NMR (500 MHz) in $CDCl_3$

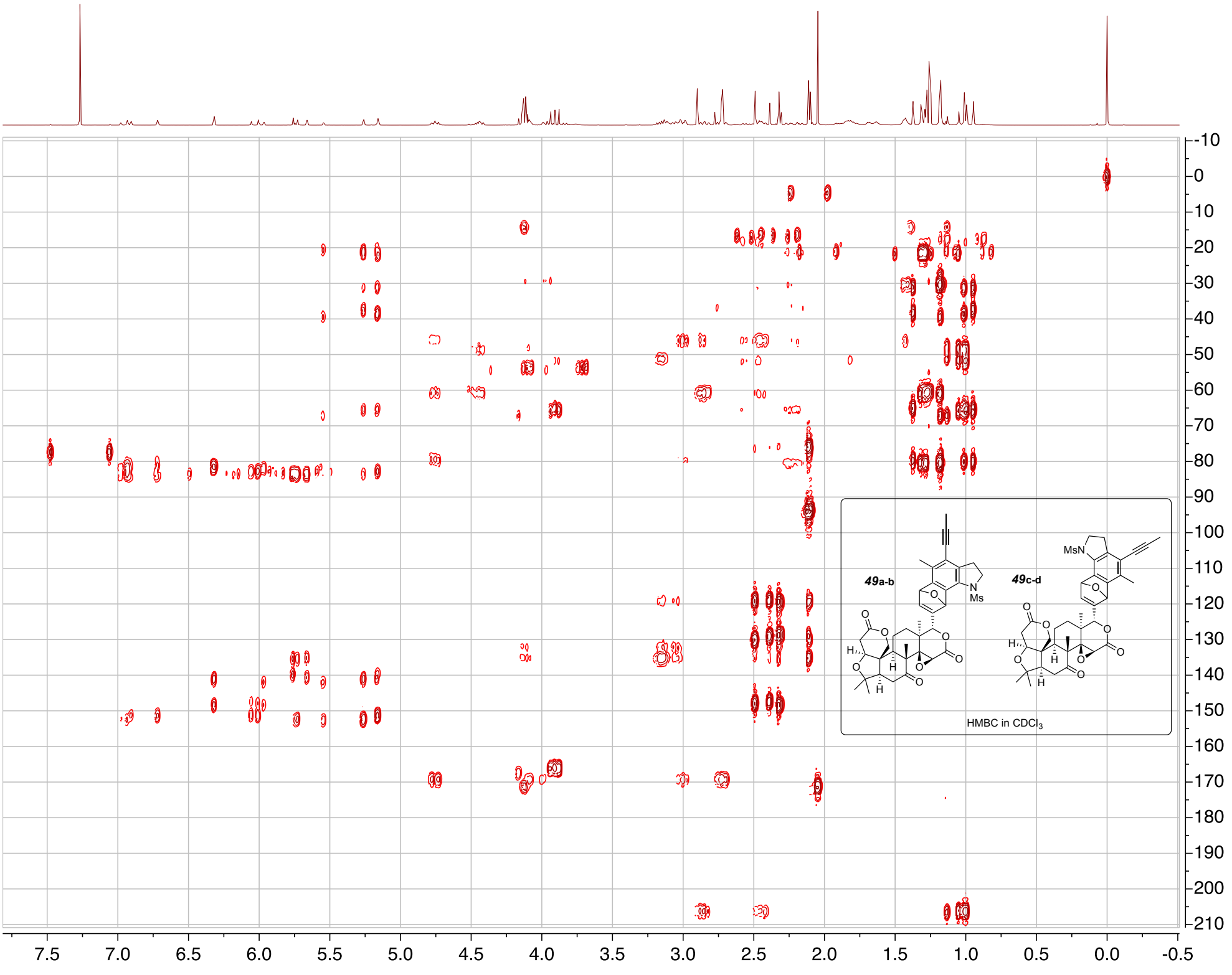
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

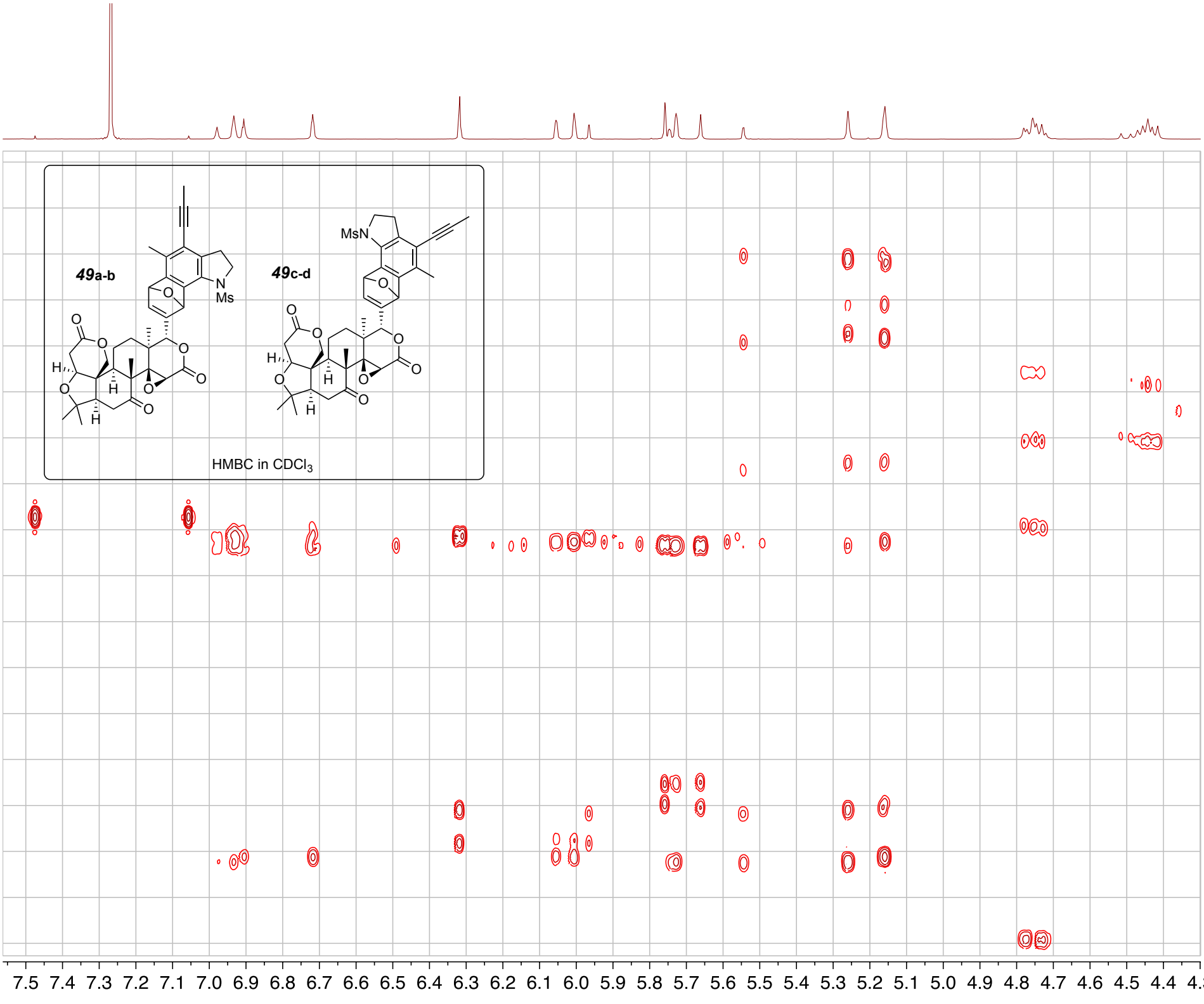

6.94
6.92
6.91
6.90
6.320
6.312
6.06
6.05
5.765
5.760
5.755
5.73
5.72
5.260
5.250
6.72
6.71
6.01
6.00
5.99
5.67
5.66
5.65
5.16
5.15
49a-b and 49c-d
1H NMR (500 MHz) in CDCl3
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3

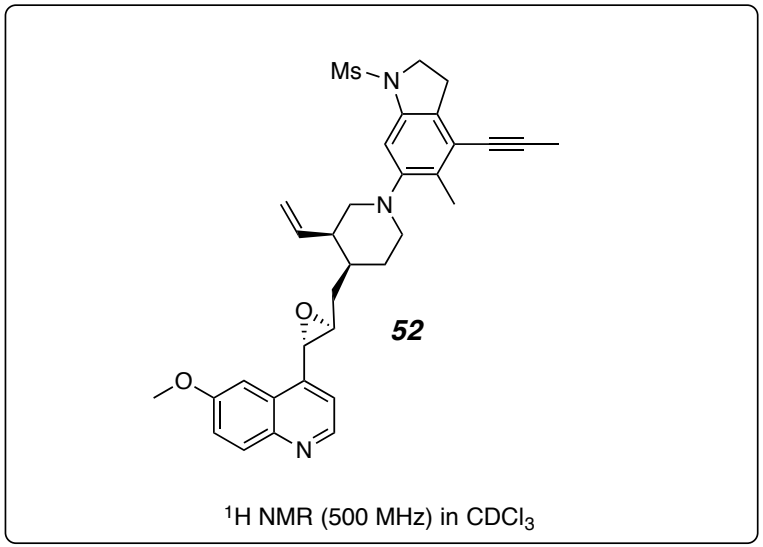

49a-b
49c-d
MsN
N
Ms
COSY (500 MHz) in CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5


49a-b
N
Ms
49c-d
MsN
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

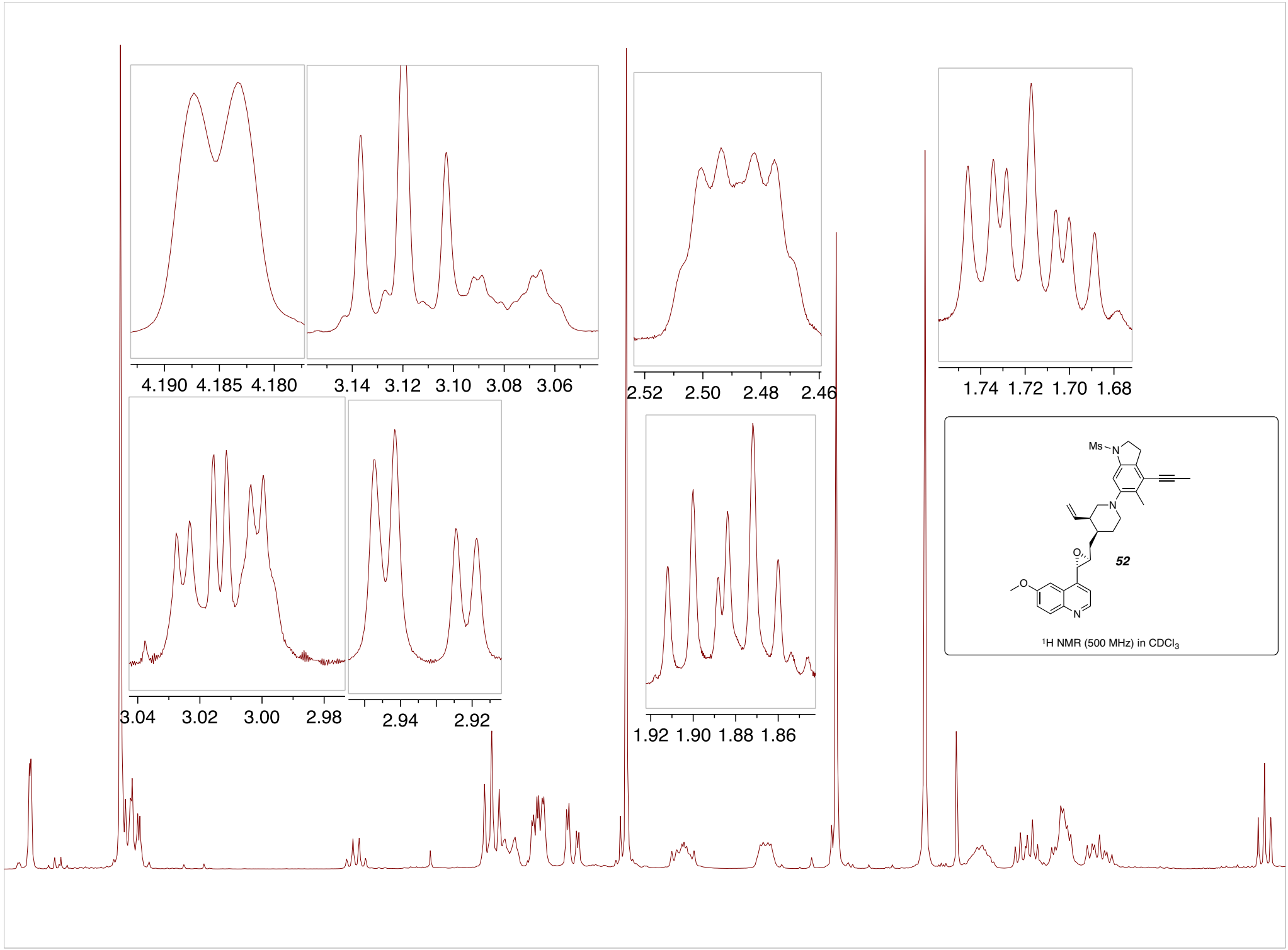

50
60
70
80
90
100
110
120
130
140
7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4
49a-b
49c-d
MsN
N
Ms
O
H
HSQC in CDCl3

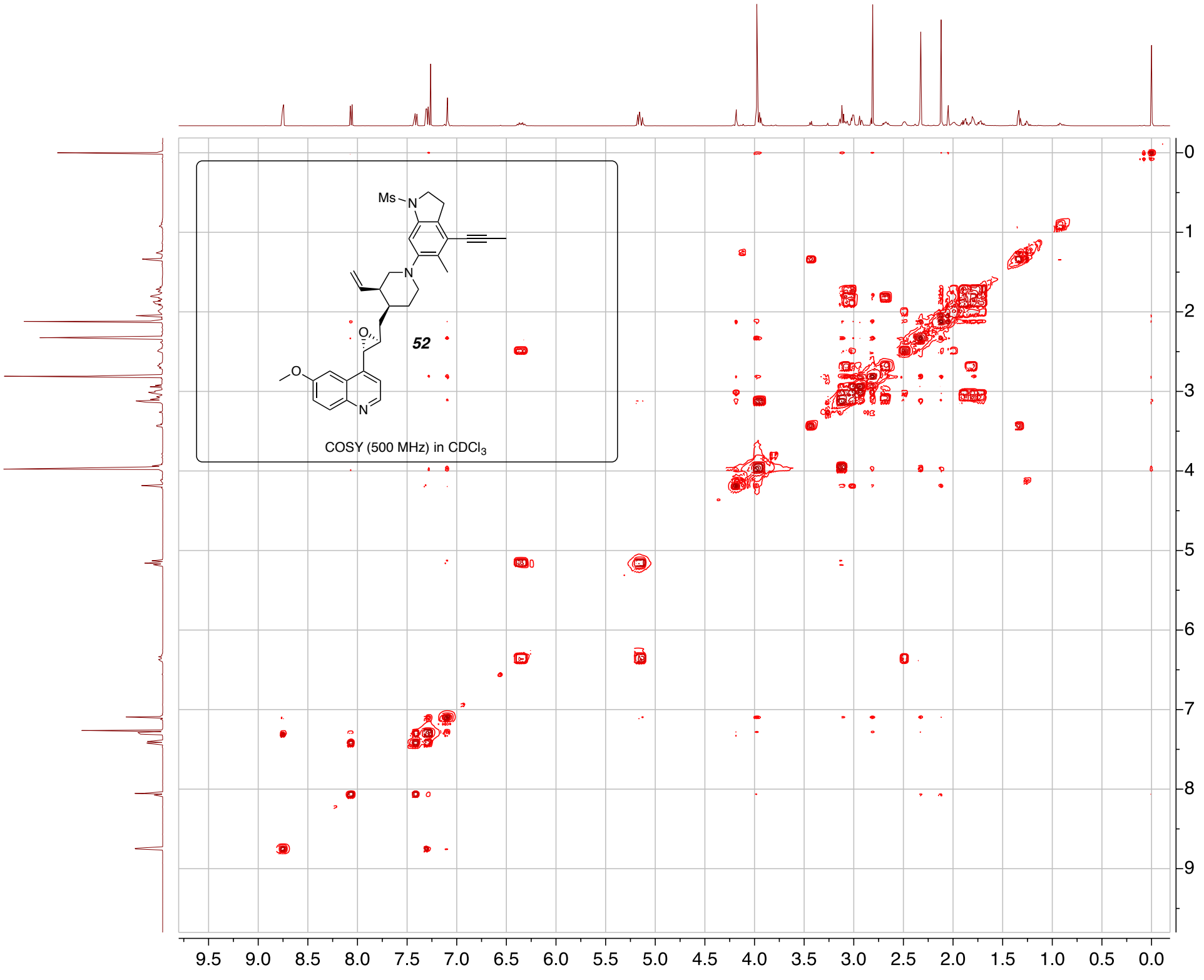

49a-b
N
Ms
49c-d
MsN
HMBC in CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

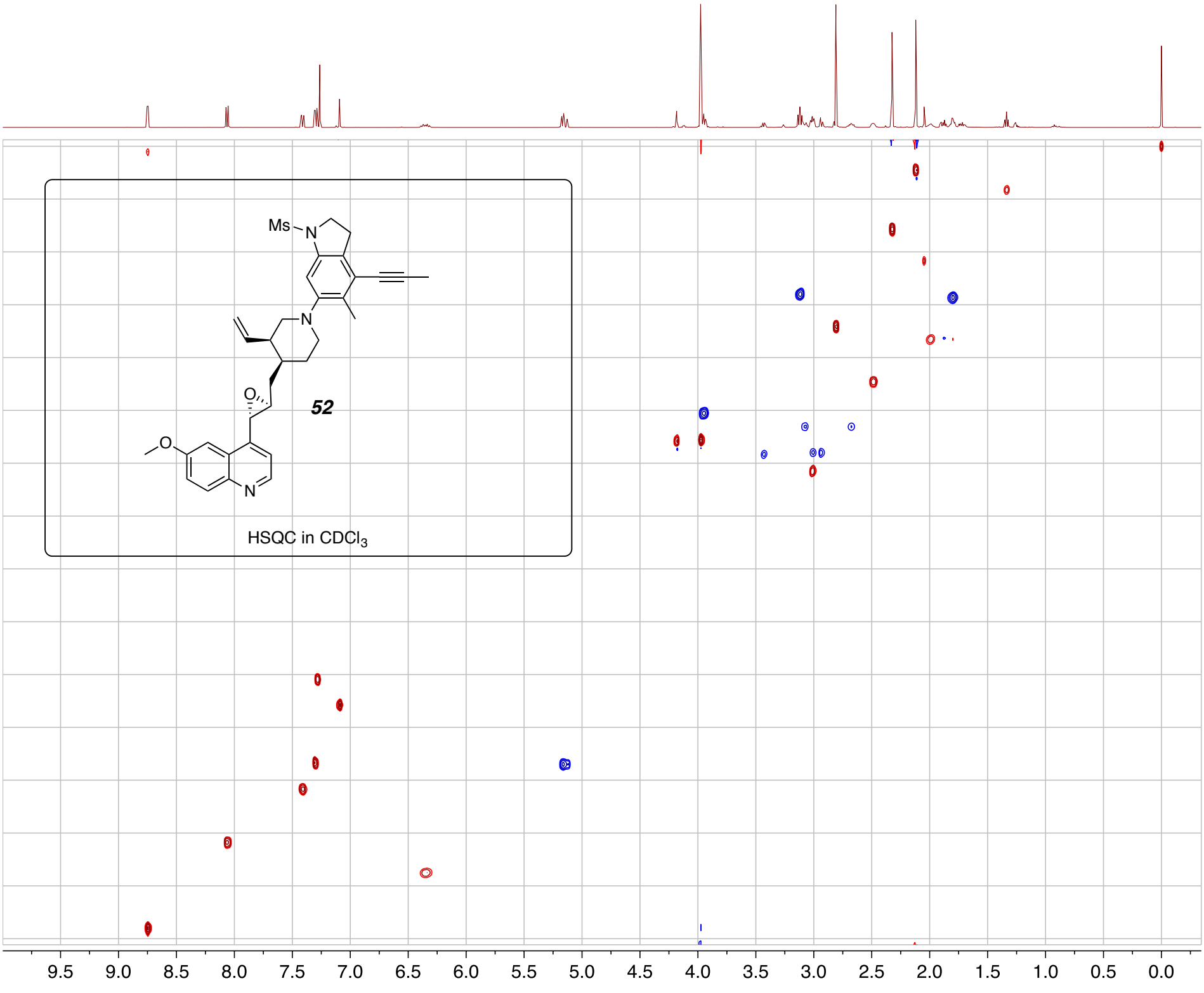

49a-b
N
Ms
49c-d
MsN
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3

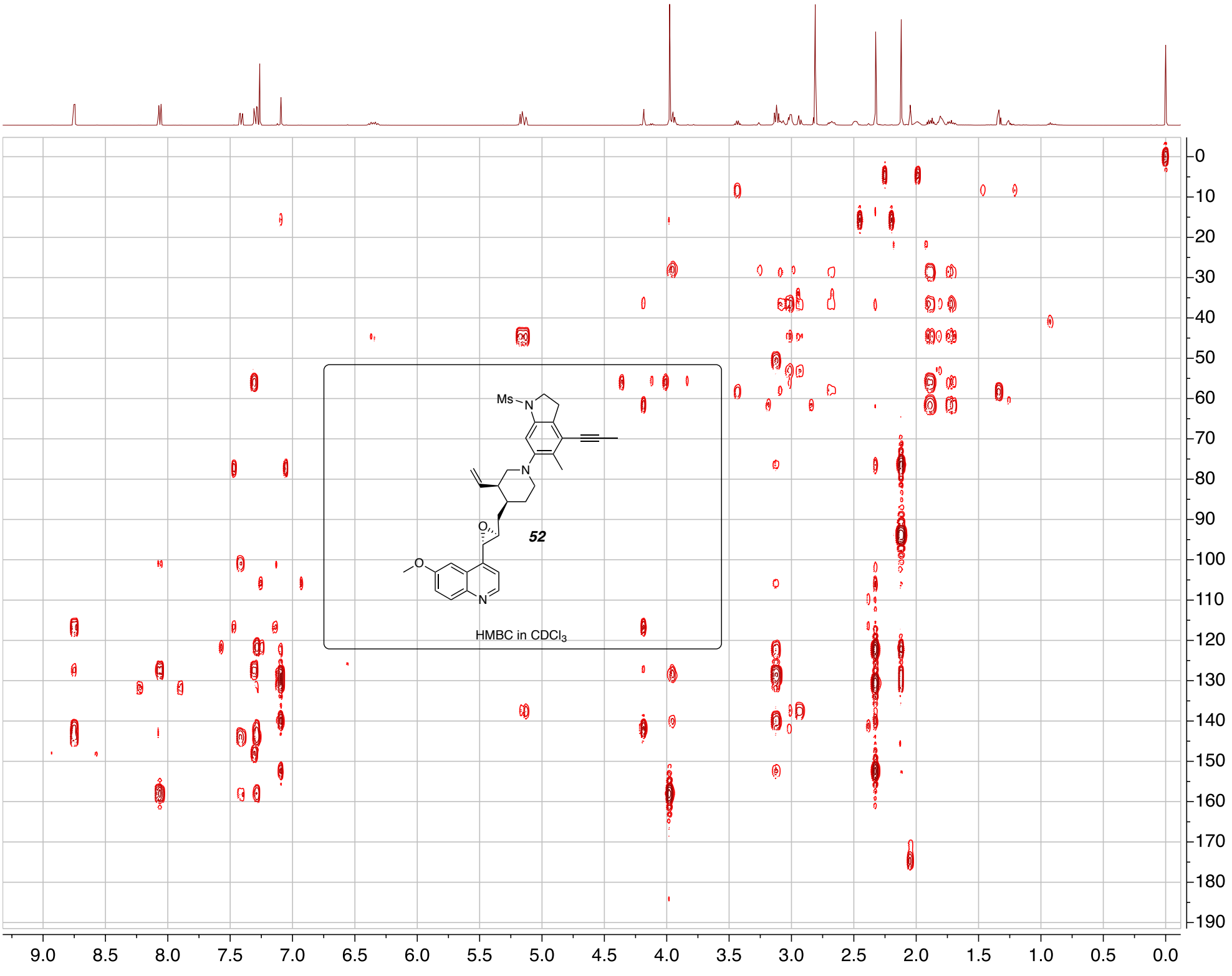


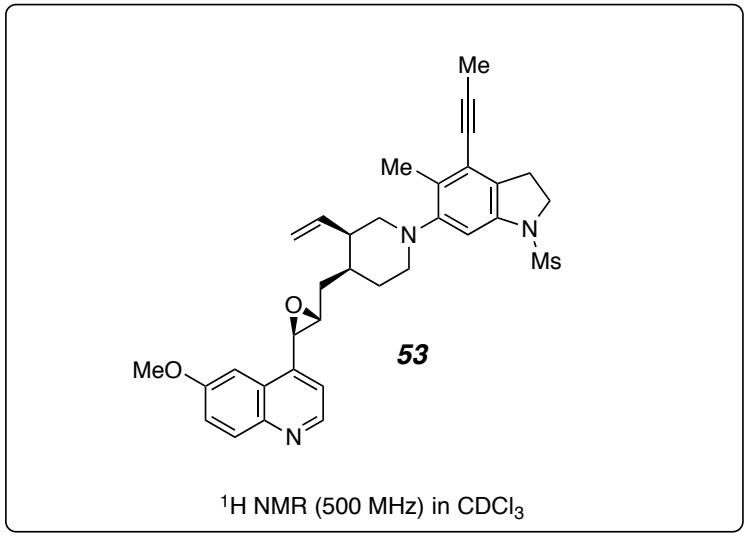
^{1}H NMR (500 MHz) in $CDCl_3$


4.190 4.185 4.180
3.14 3.12 3.10 3.08 3.06
2.52 2.50 2.48 2.46
1.74 1.72 1.70 1.68
3.04 3.02 3.00 2.98
2.94 2.92
1.92 1.90 1.88 1.86
Ms
N
N
O
O
N
52
^{1}H NMR (500 MHz) in $CDCl_3$
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4

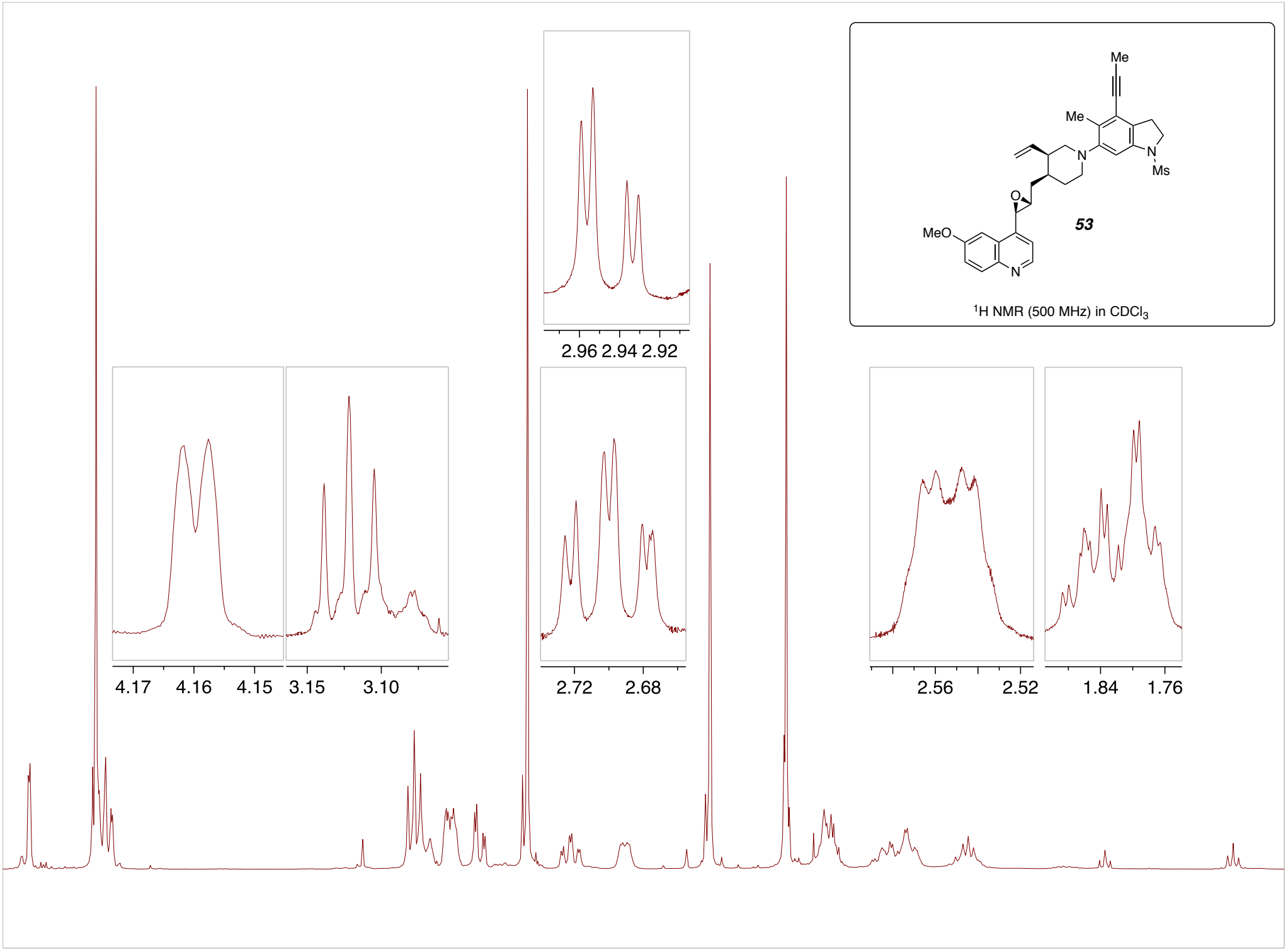

Ms
N
N
O
O
N
52
COSY (500 MHz) in CDCl3
0
1
2
3
4
5
6
7
8
9
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

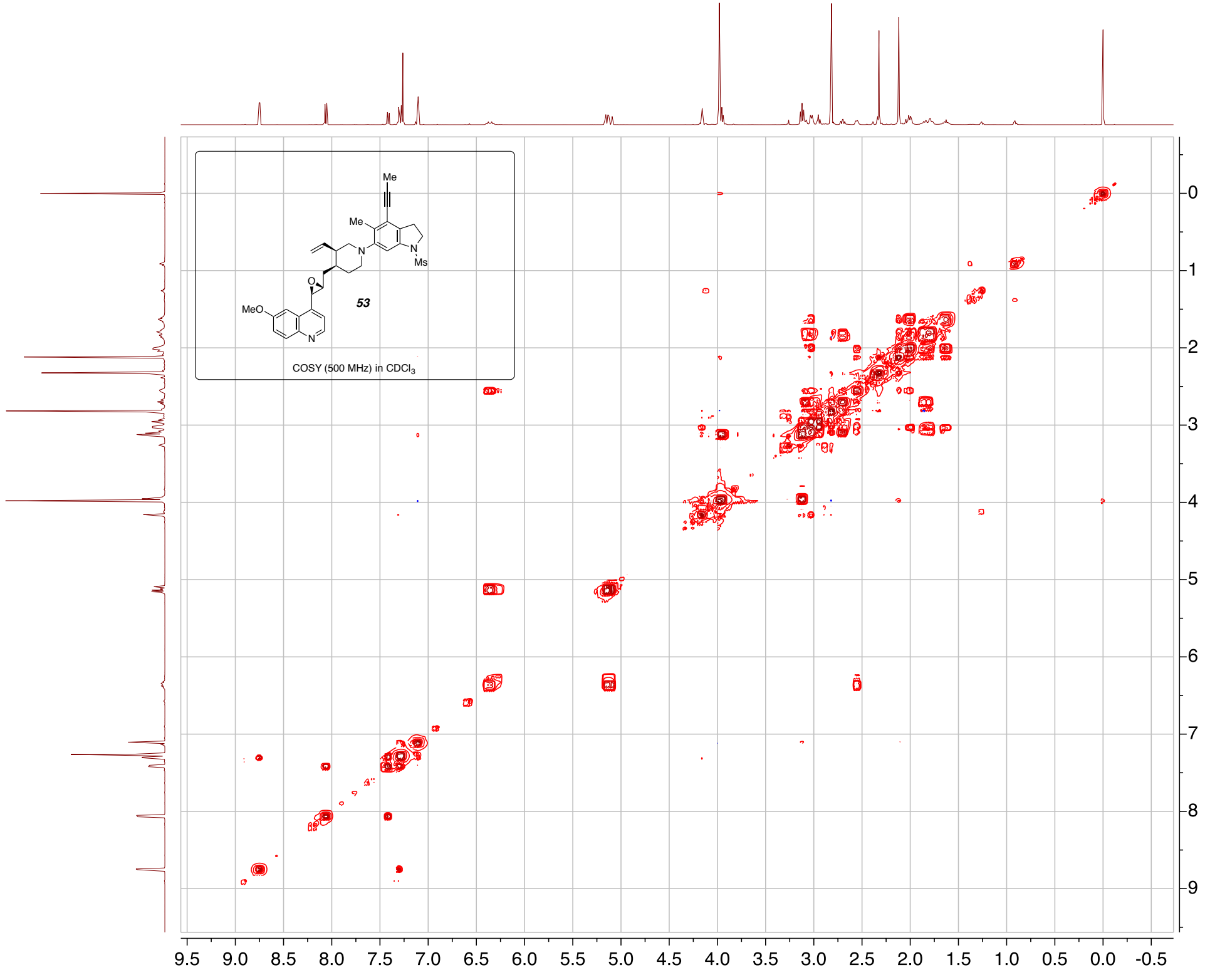

Ms
N
N
O
O
N
52
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

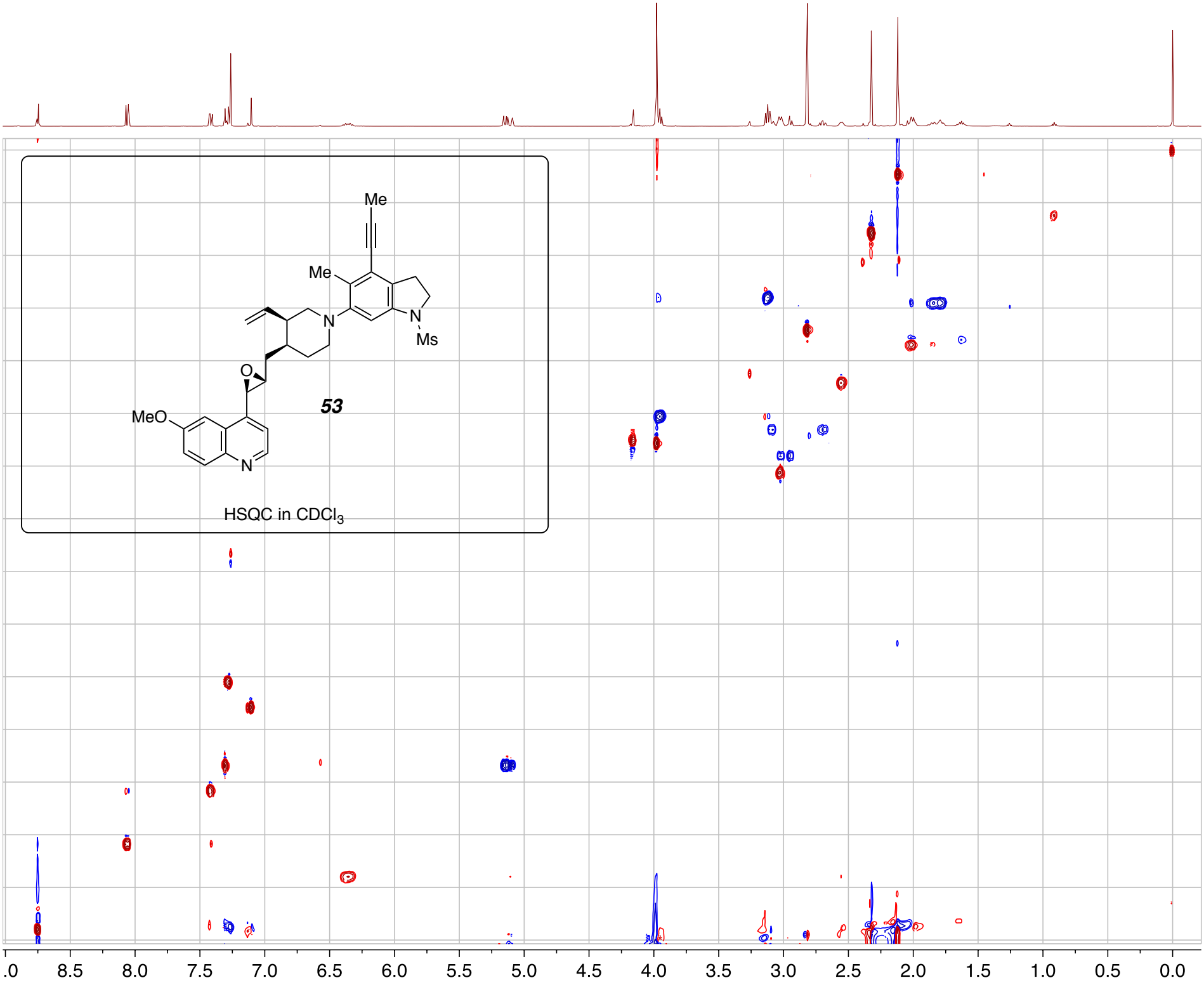

Ms
N
N
O
O
N
52
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

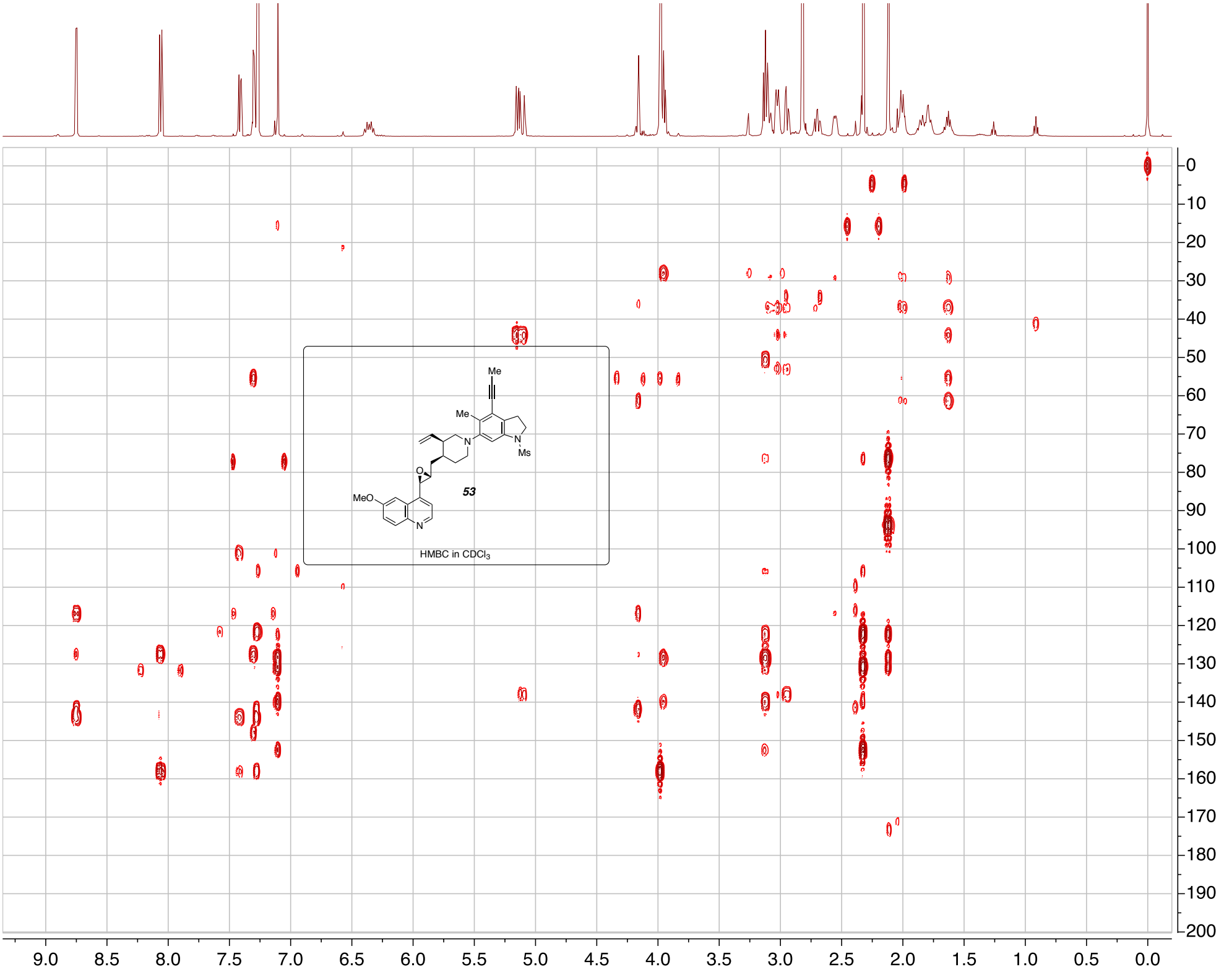


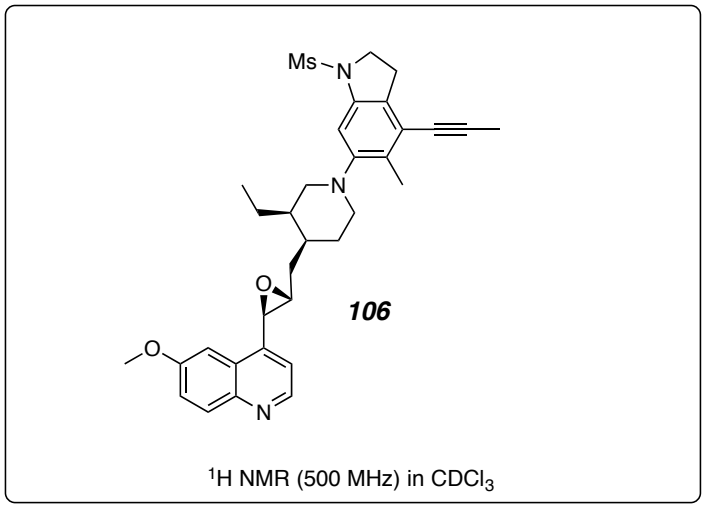
^{1}H NMR (500 MHz) in $CDCl_3$


Me
Me
N
N
Ms
O
MeO
N
53
^{1}H NMR (500 MHz) in $CDCl_3$
2.96 2.94 2.92
4.17 4.16 4.15 3.15 3.10
2.72 2.68
2.56 2.52 1.84 1.76
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8


Me
Me
N
N
Ms
O
MeO
N
53
COSY (500 MHz) in CDCl3
0
1
2
3
4
5
6
7
8
9
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

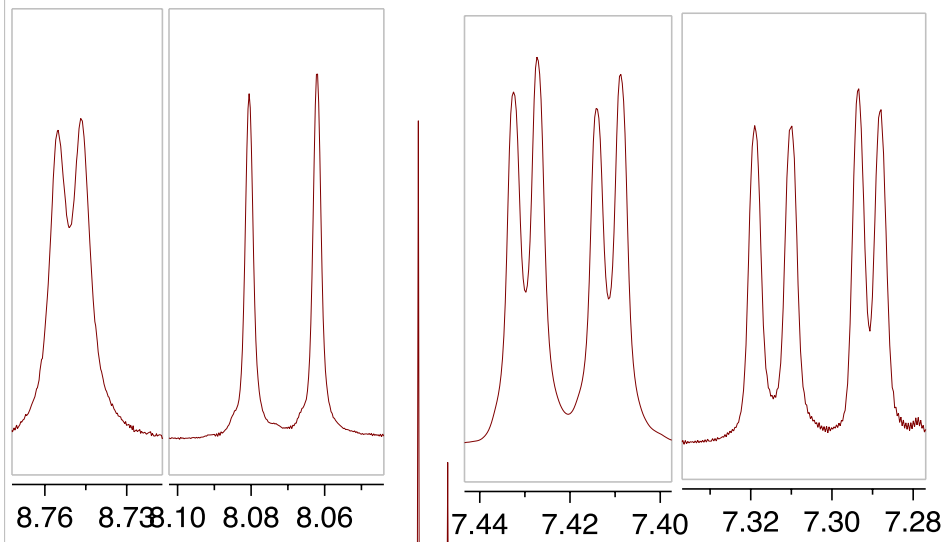

Me
Me
N
N
Ms
O
MeO
N
53
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

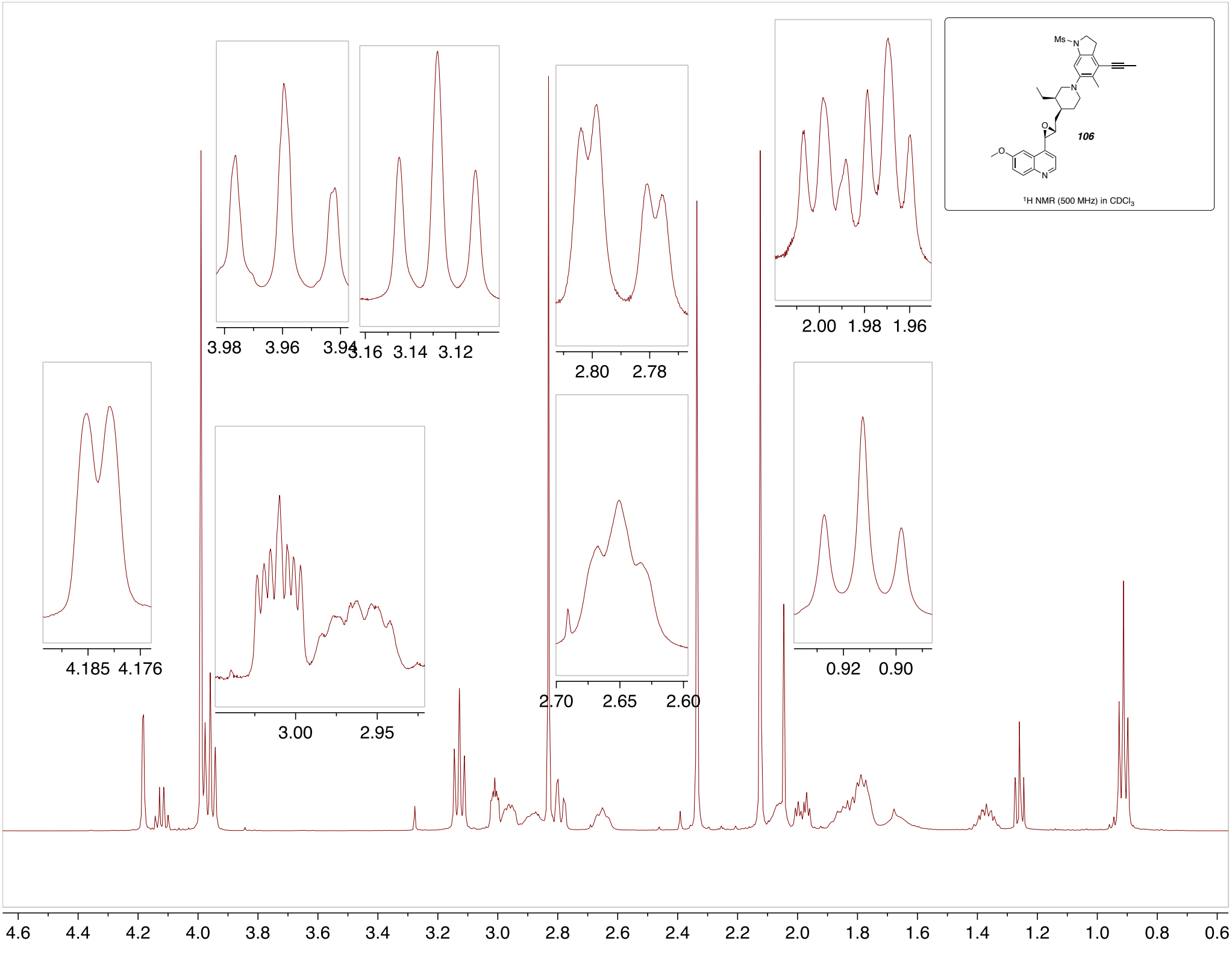

Me
Me
N
N
Ms
O
MeO
N
53
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

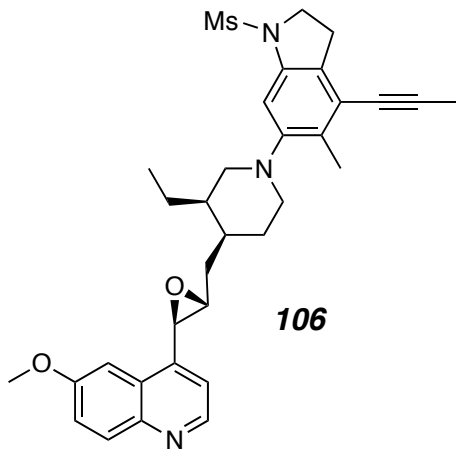


106

^{1}H NMR (500 MHz) in $CDCl_3$

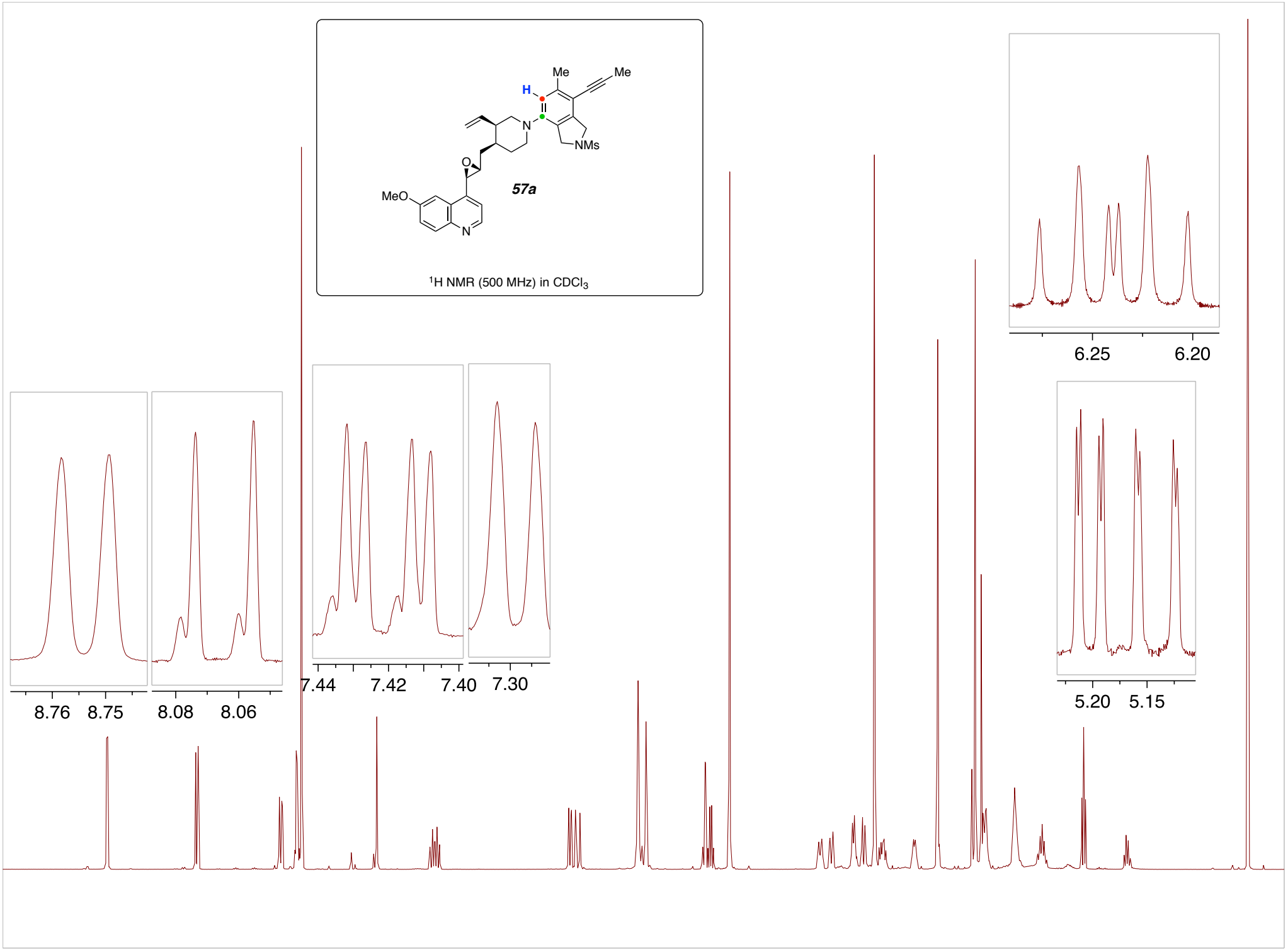


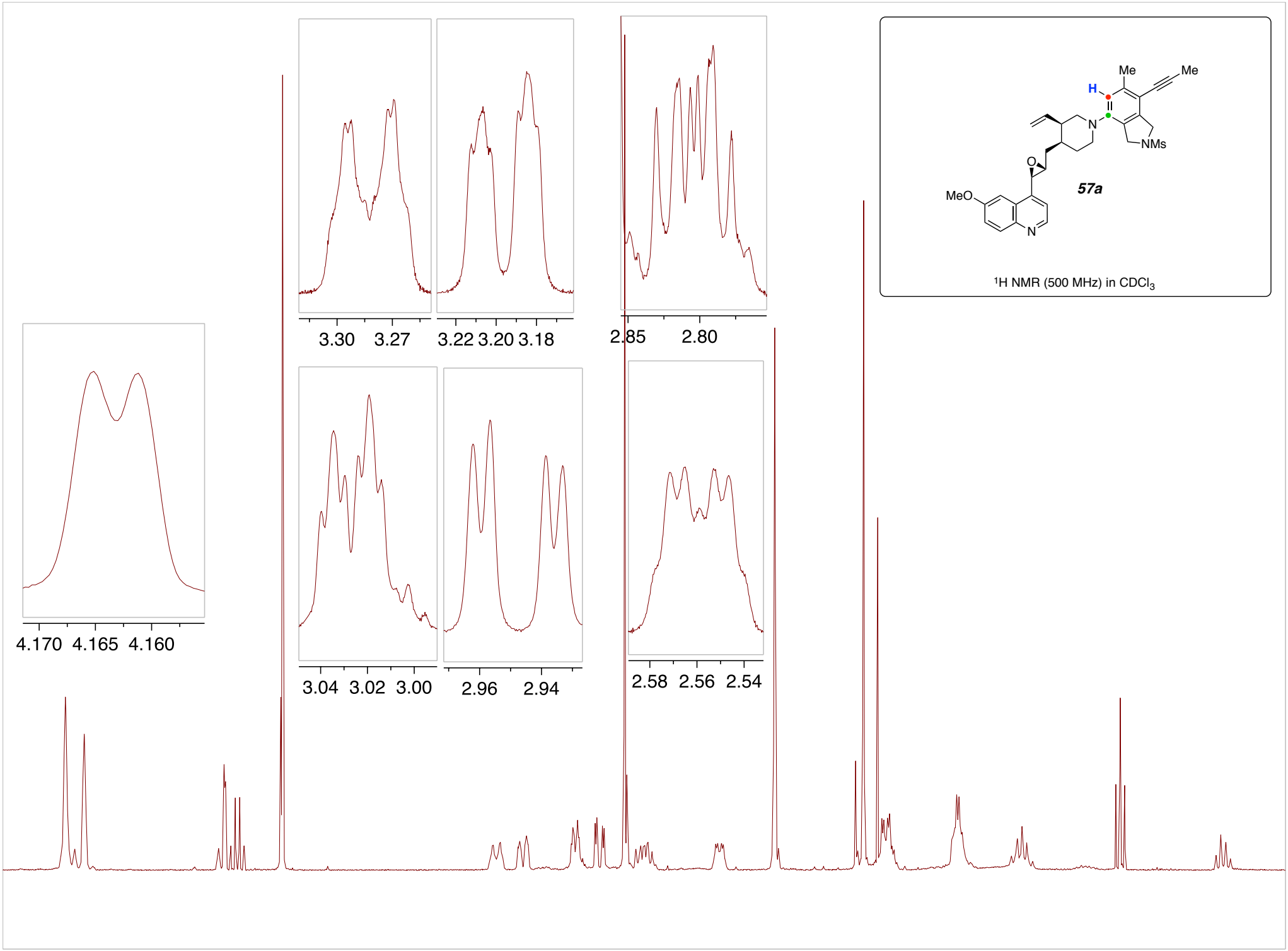

Ms
N
N
O
O
N
106
1H NMR (500 MHz) in CDCl3
3.98 3.96 3.94
3.16 3.14 3.12
2.80 2.78
2.00 1.98 1.96
4.185 4.176
3.00 2.95
2.70 2.65 2.60
0.92 0.90
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6

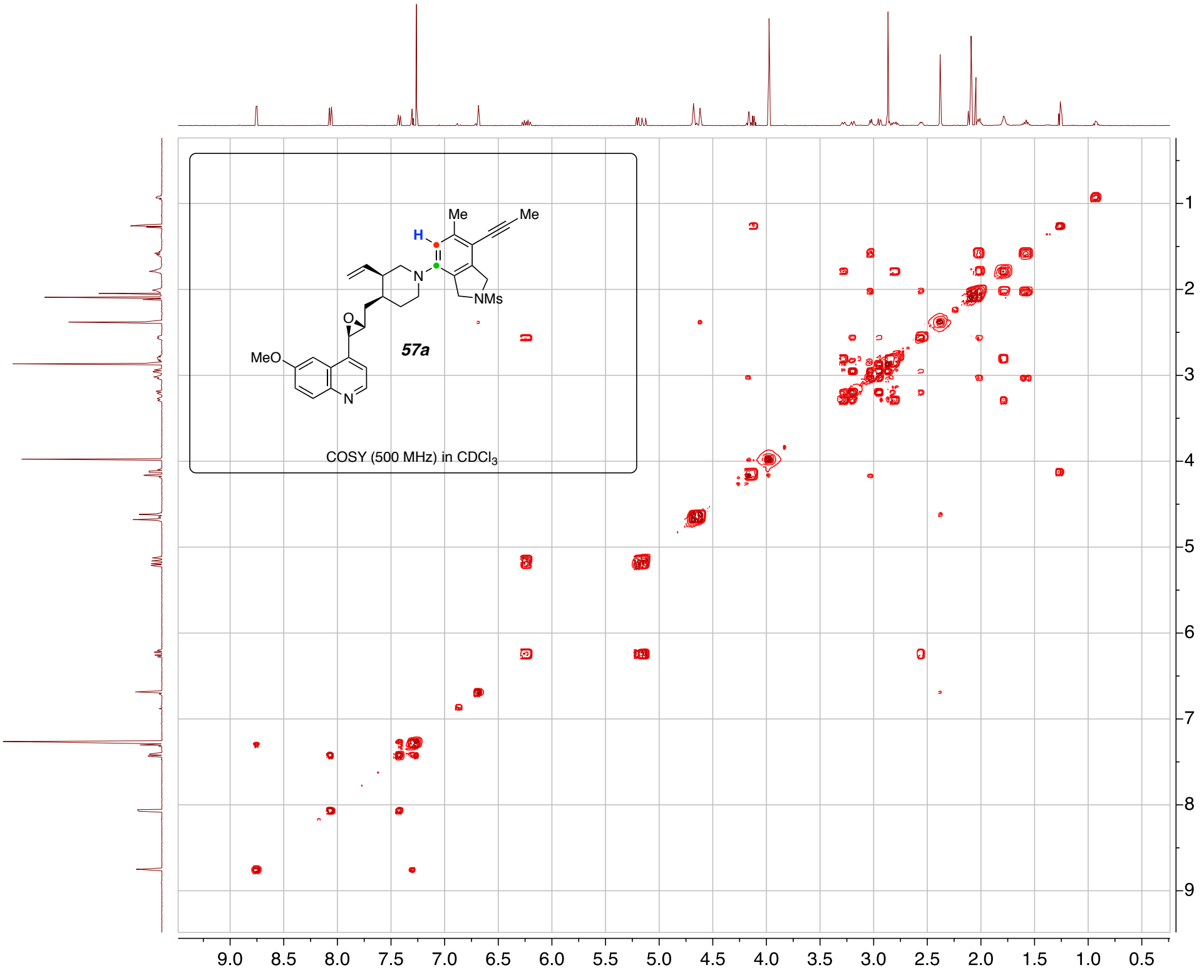


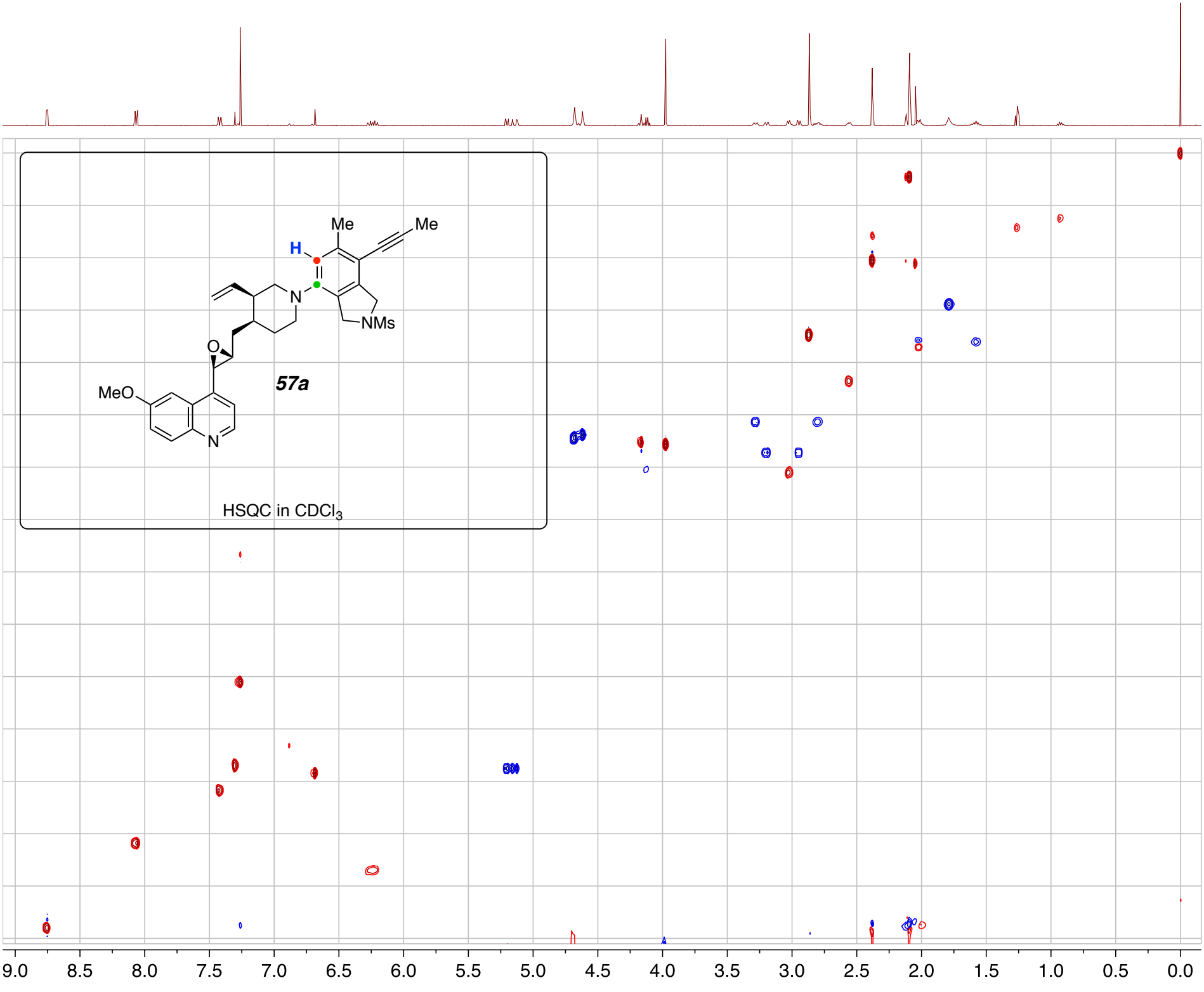
106

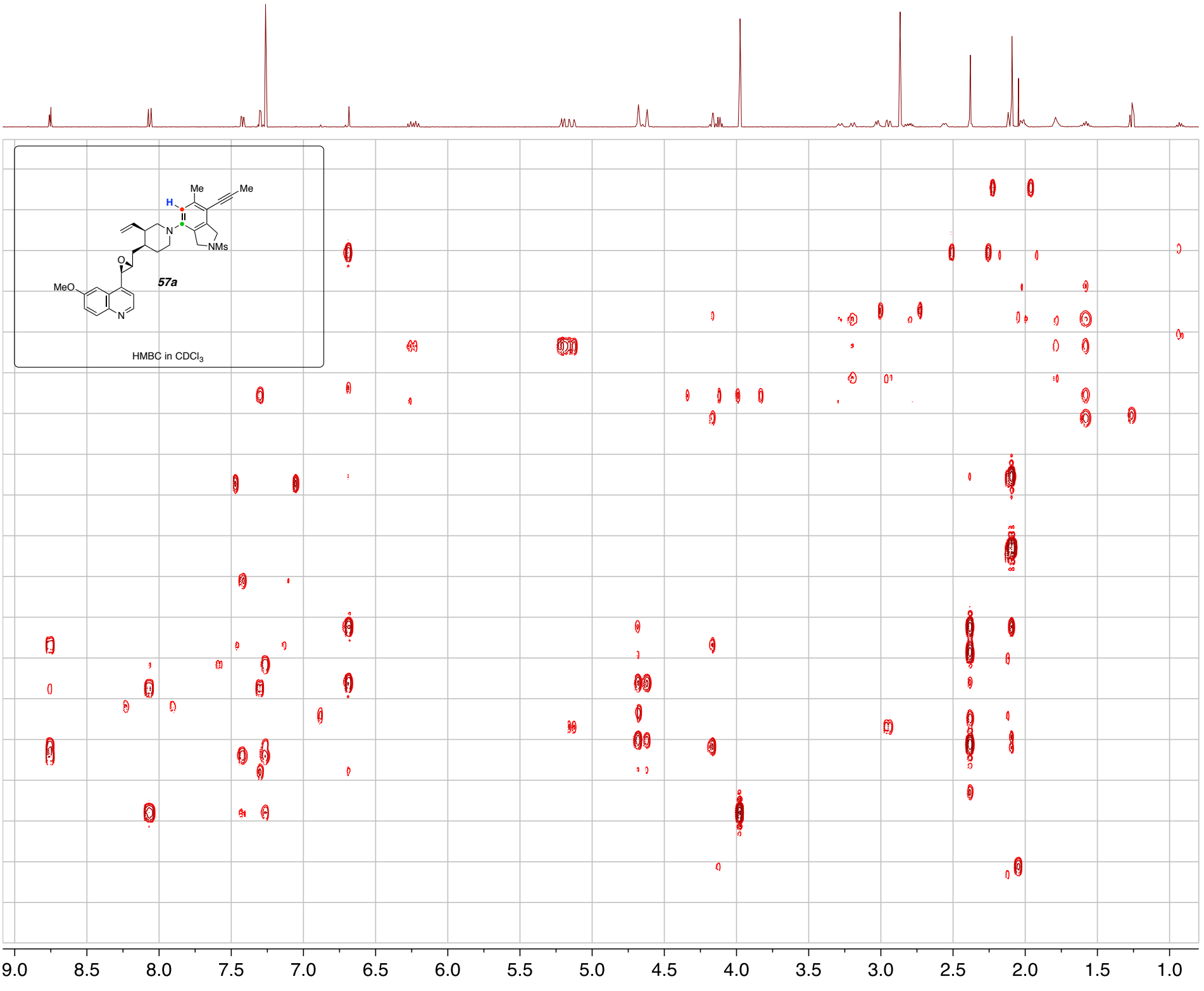
^{13}C NMR (125 MHz) in $CDCl_3$

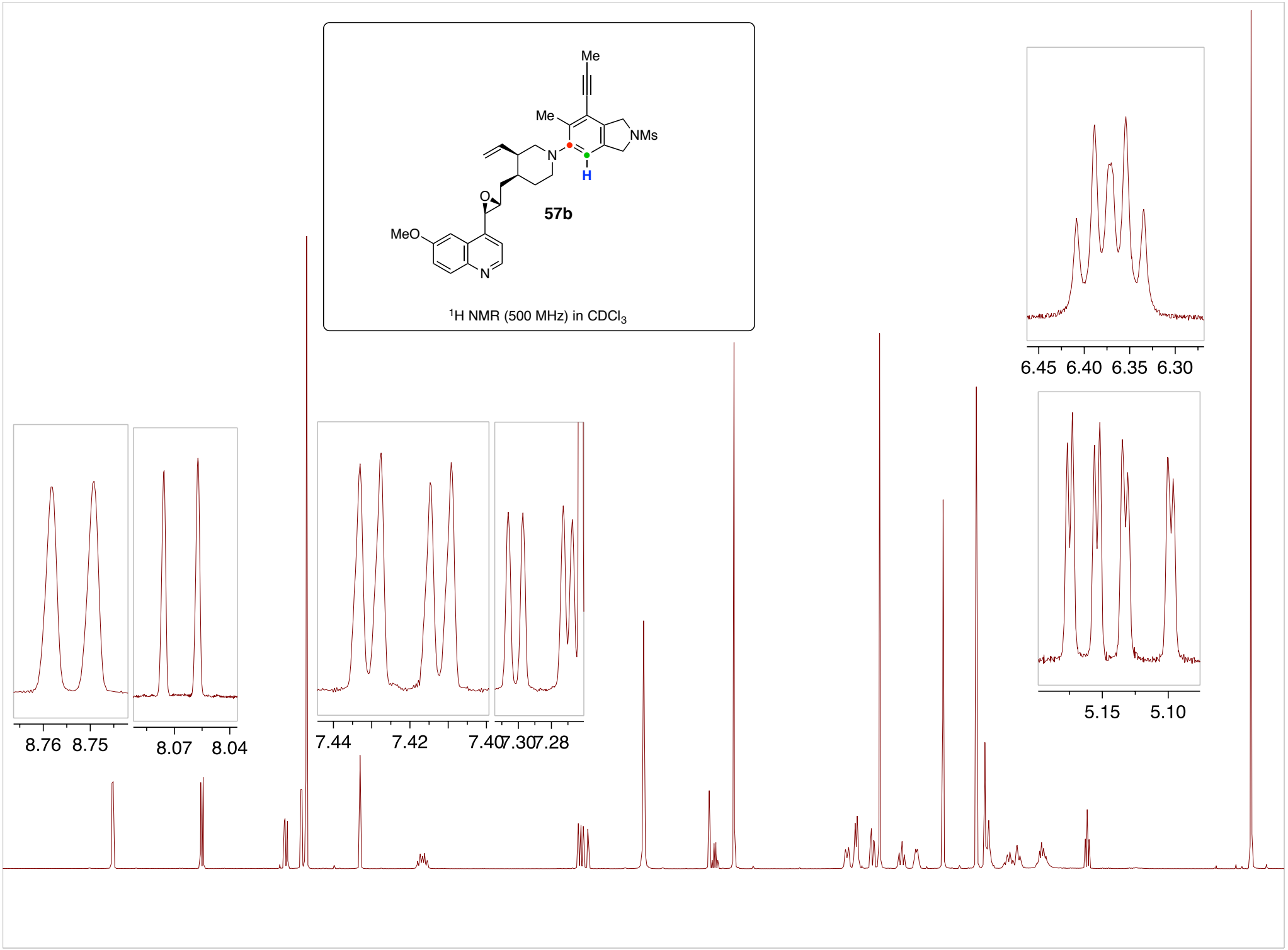

Me
Me
H
N
NMs
O
MeO
N
57a
^{1}H NMR (500 MHz) in $CDCl_3$
8.76 8.75
8.08 8.06
7.44 7.42 7.40 7.30
6.25 6.20
5.20 5.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

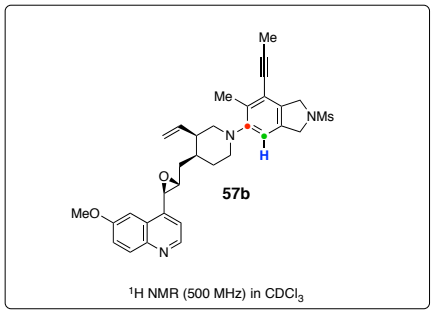

Me
Me
H
N
NMs
O
MeO
N
57a
^{1}H NMR (500 MHz) in $CDCl_3$
4.170 4.165 4.160
3.30 3.27
3.22 3.20 3.18
2.85 2.80
3.04 3.02 3.00
2.96 2.94
2.58 2.56 2.54
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8


Me
Me
H
N
NMs
O
MeO
N
57a
COSY (500 MHz) in CDCl3
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

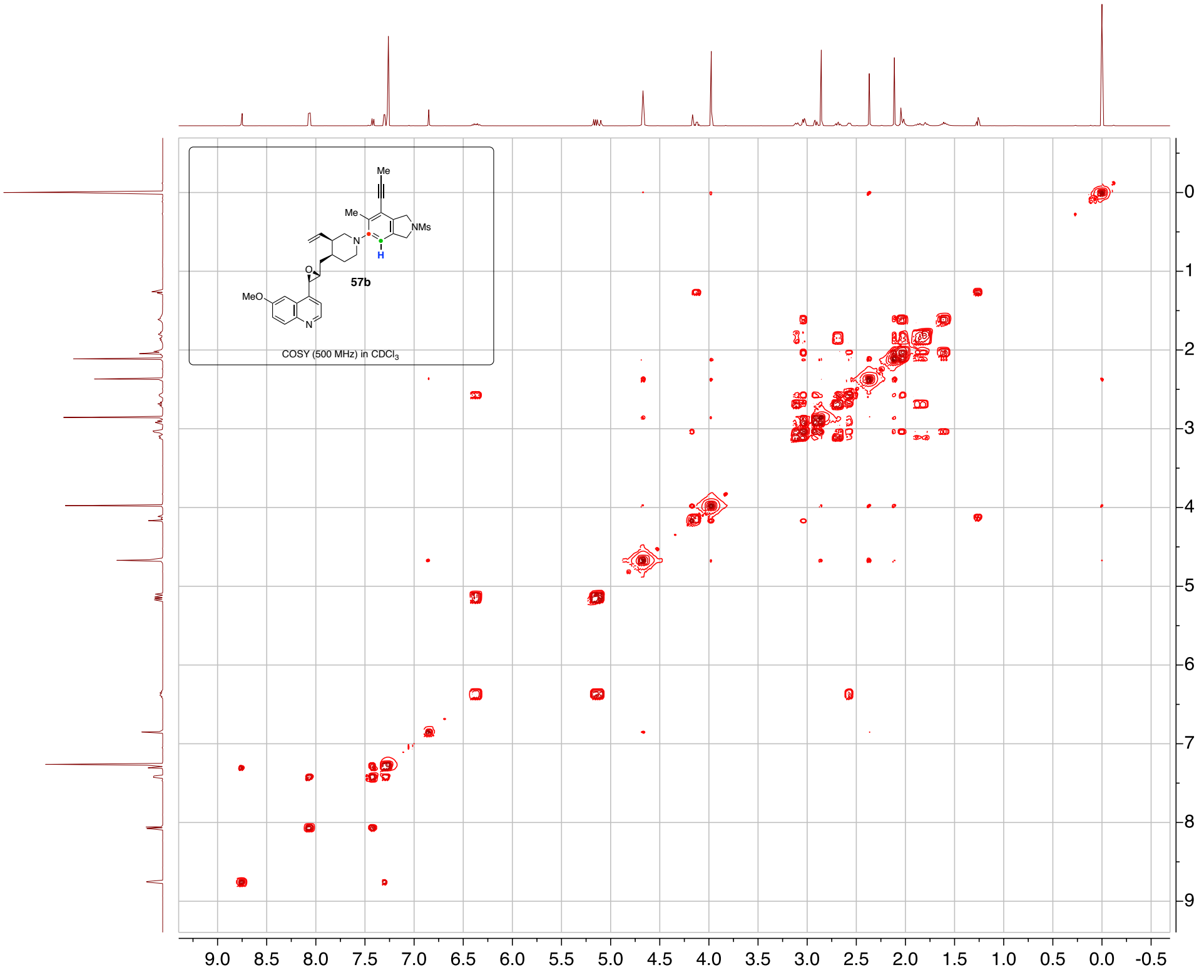

Me
Me
H
N
NMs
O
MeO
N
57a
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

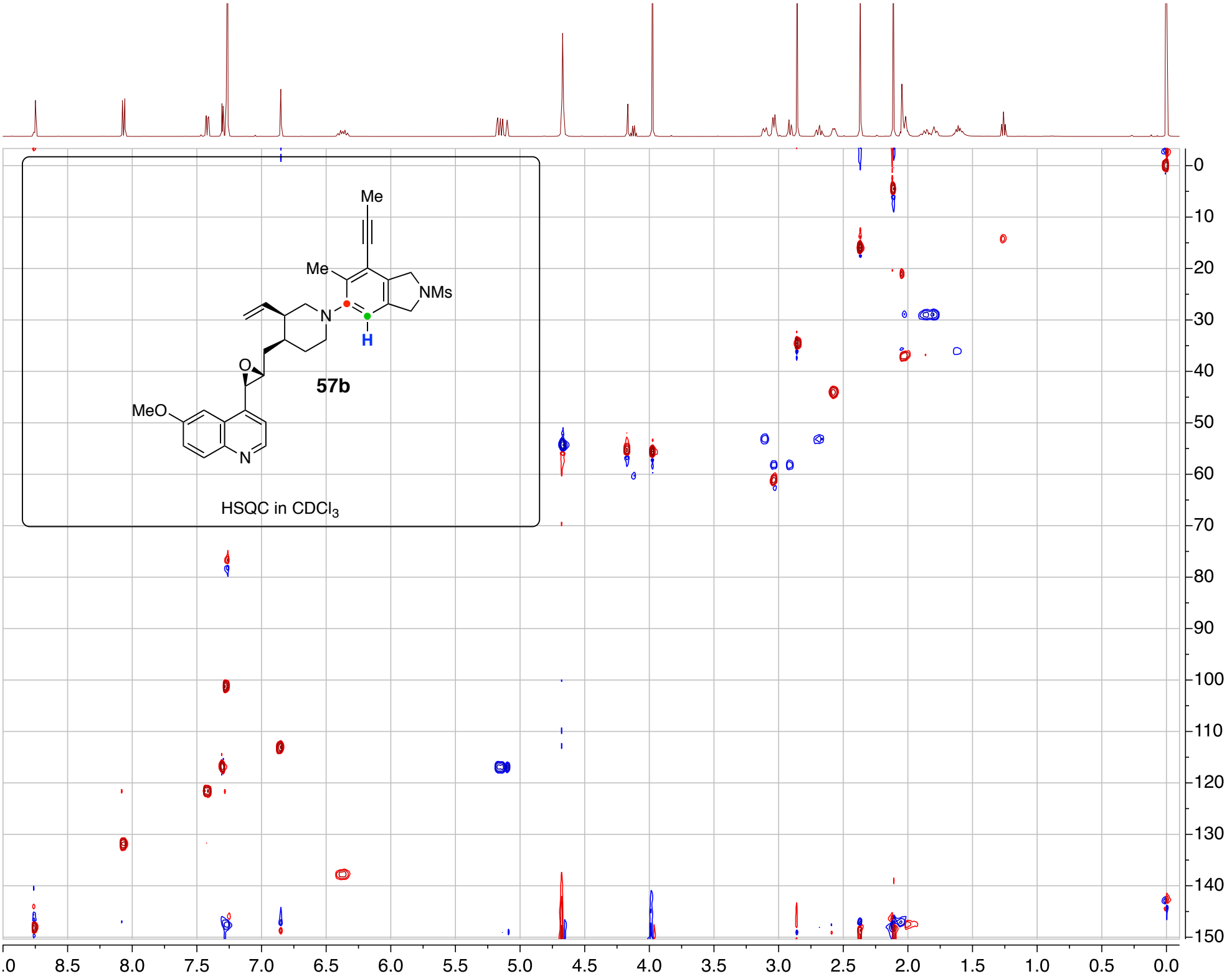

Me
Me
H
N
NMs
O
MeO
N
57a
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

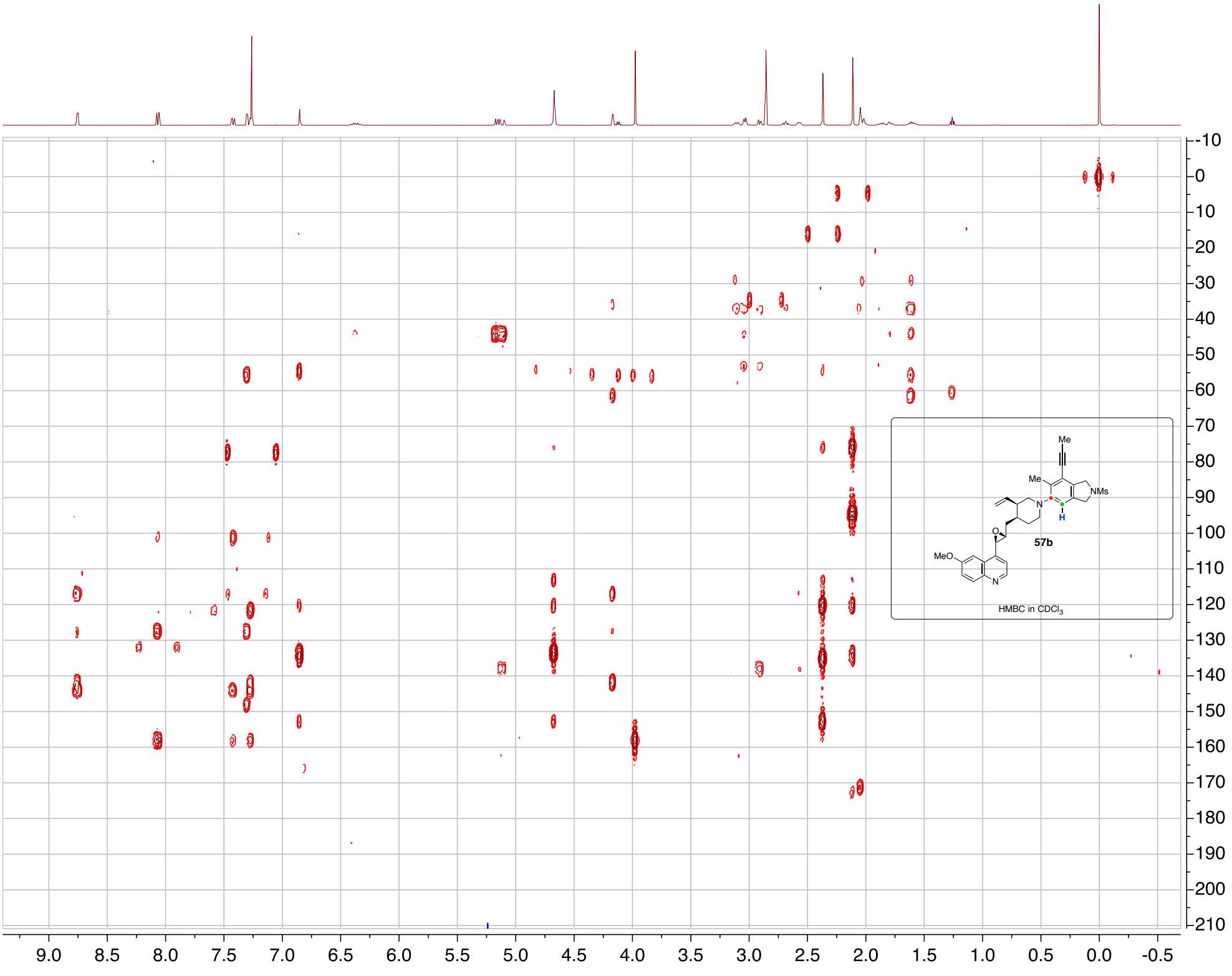

Me
Me
NMs
N
H
O
MeO
N
57b
^{1}H NMR (500 MHz) in $CDCl_3$
8.76 8.75
8.07 8.04
7.44 7.42 7.40 7.30 7.28
6.45 6.40 6.35 6.30
5.15 5.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

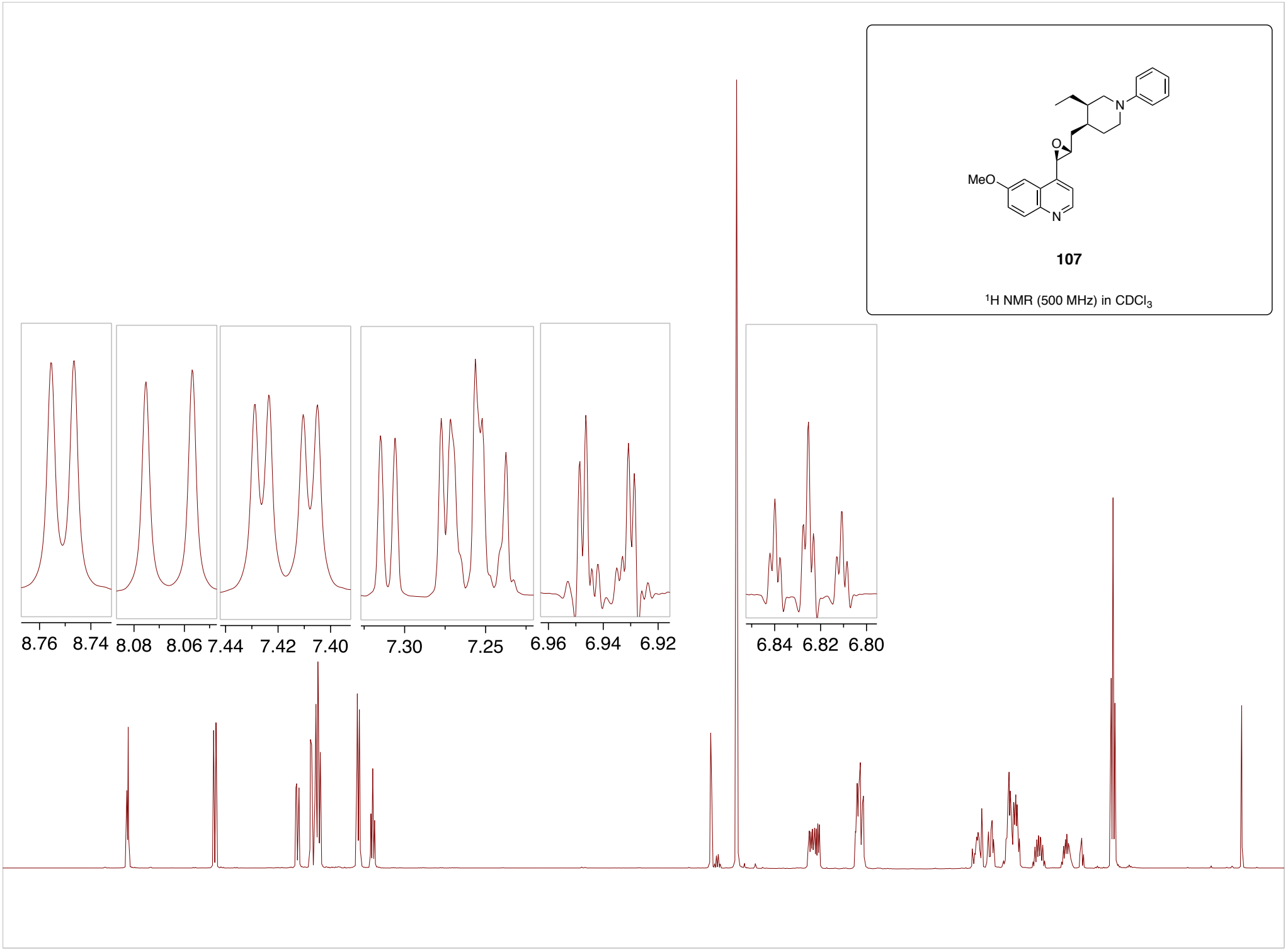


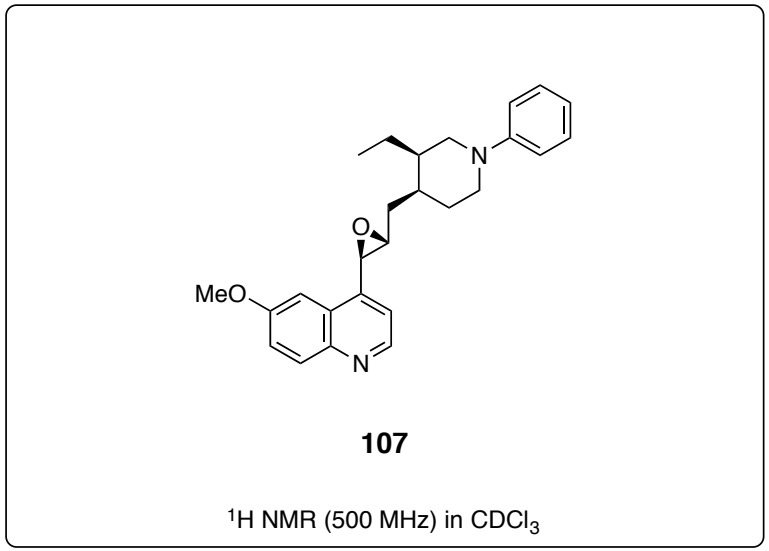
^{1}H NMR (500 MHz) in $CDCl_3$


Me
Me
NMs
N
H
O
MeO
N
57b
COSY (500 MHz) in CDCl3
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Me
Me
NMs
N
H
O
57b
MeO
N
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

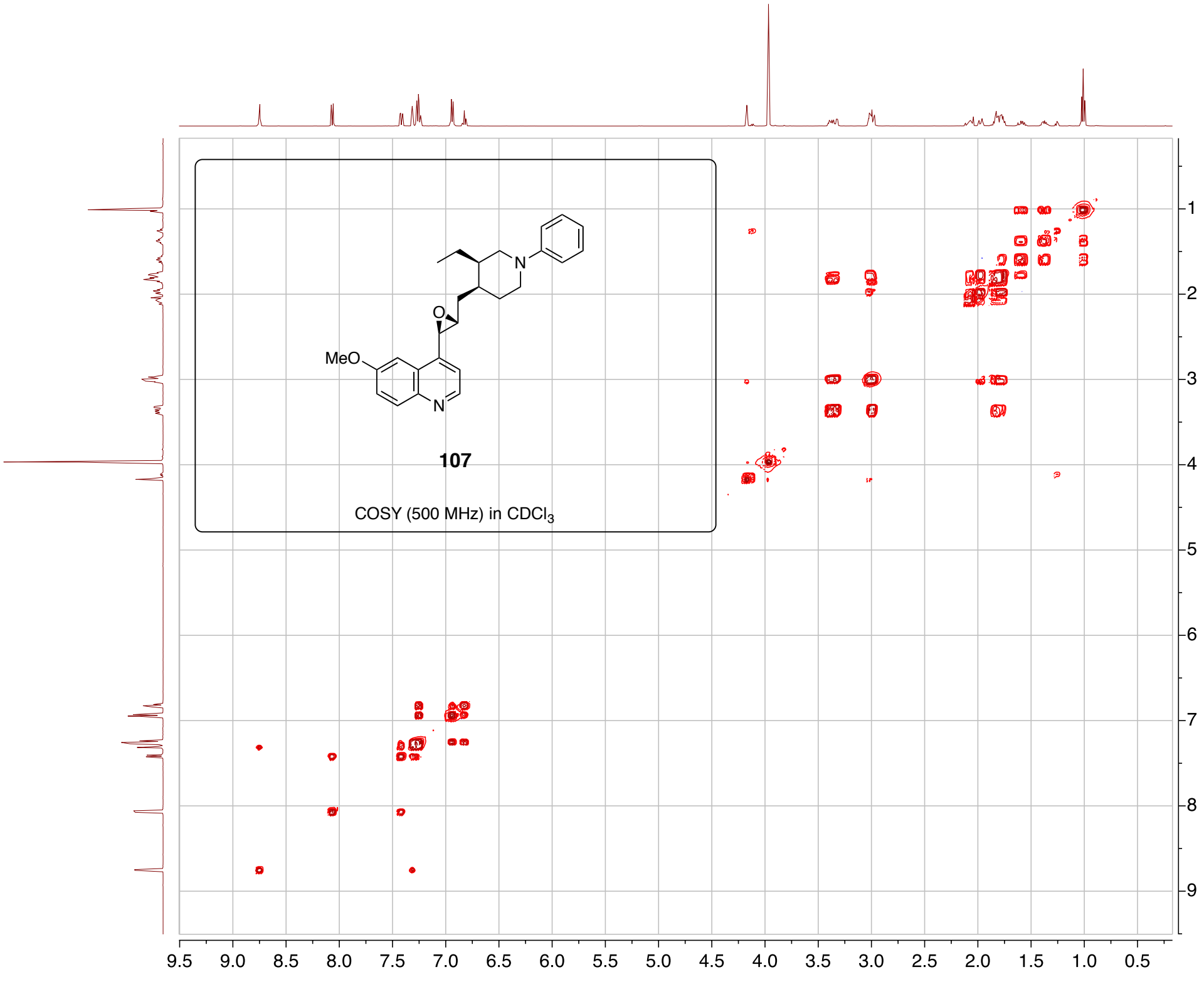

Me
Me
NMs
N
H
O
57b
MeO
N
HMBC in CDCl3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

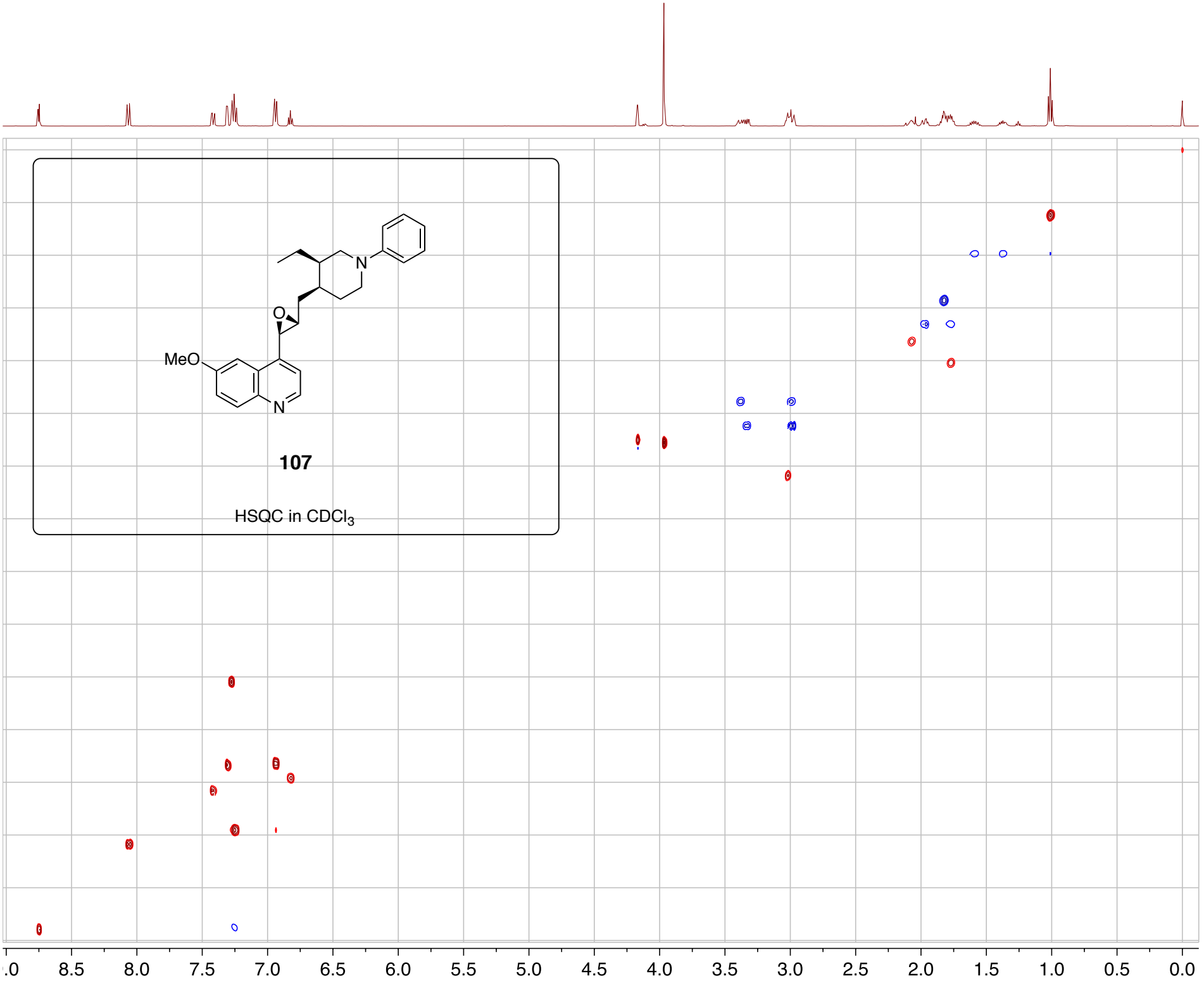

MeO
N
O
N
107
^{1}H NMR (500 MHz) in $CDCl_3$
8.76 8.74 8.08 8.06 7.44 7.42 7.40 7.30 7.25 6.96 6.94 6.92 6.84 6.82 6.80
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

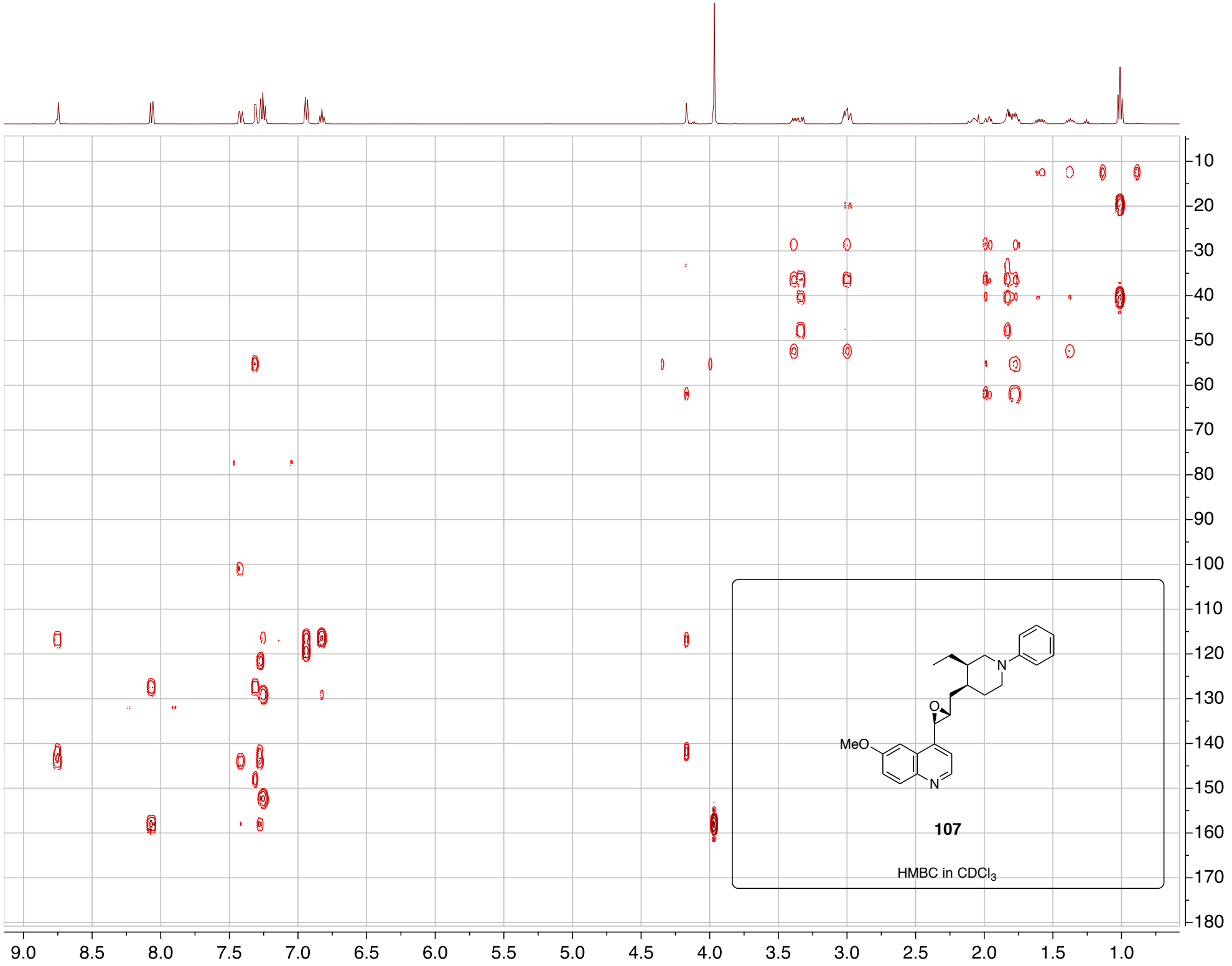


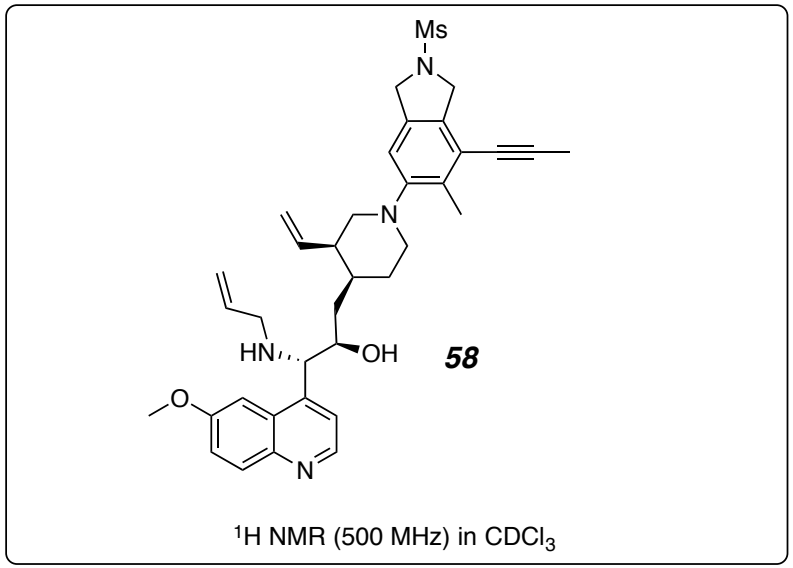
107

^{1}H NMR (500 MHz) in $CDCl_3$

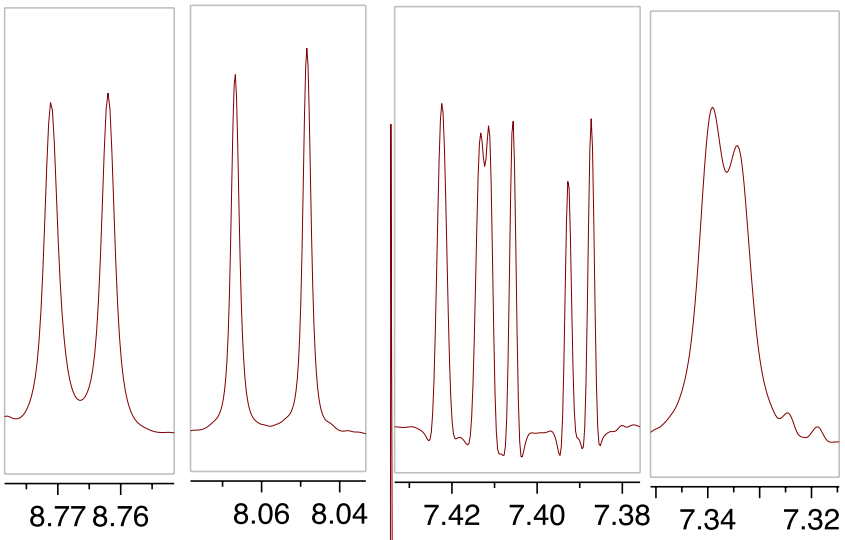

MeO
N
O
N
107
COSY (500 MHz) in CDCl3
1
2
3
4
5
6
7
8
9
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

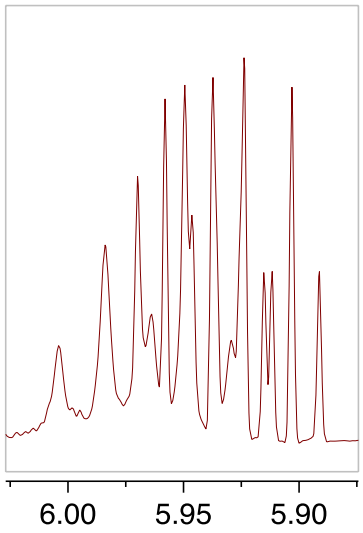

MeO
O
N
N
107
HSQC in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

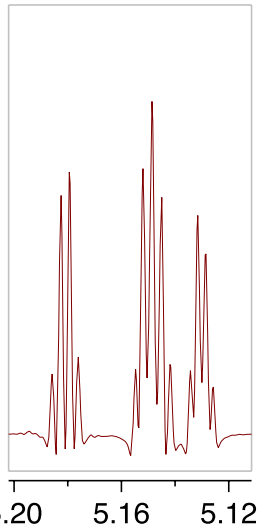

MeO
N
O
N
107
HMBC in CDCl3



^{1}H NMR (500 MHz) in $CDCl_3$

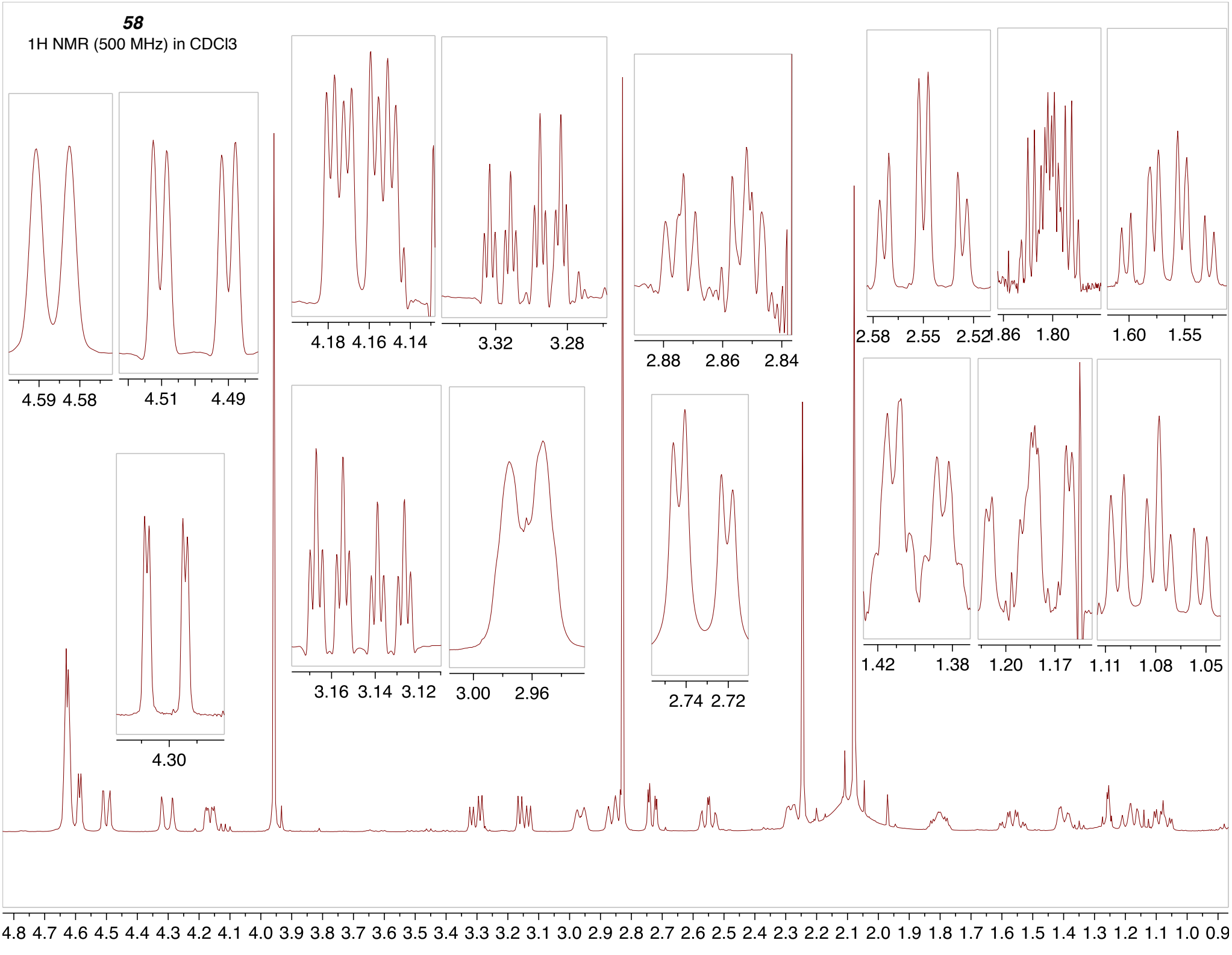


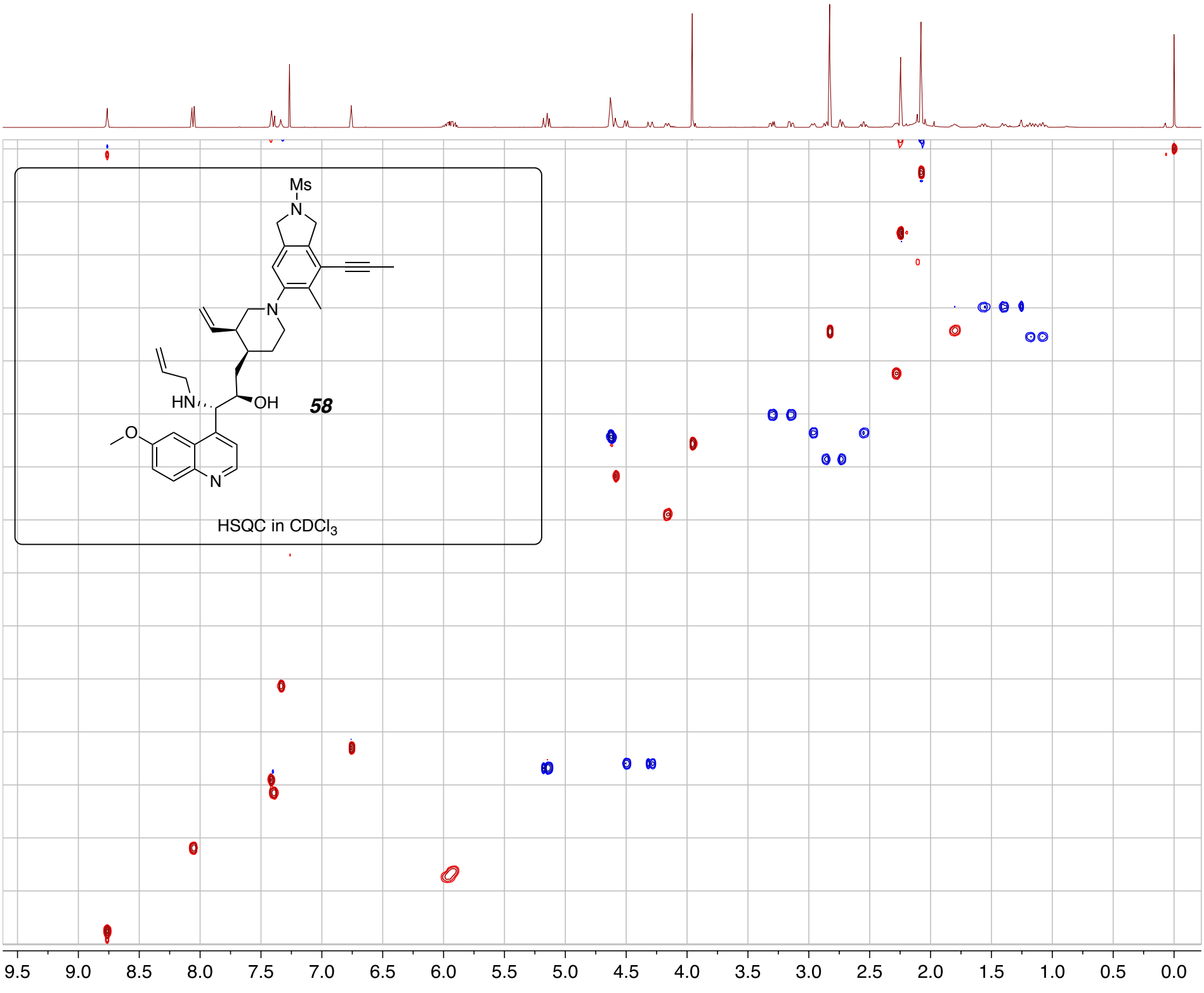


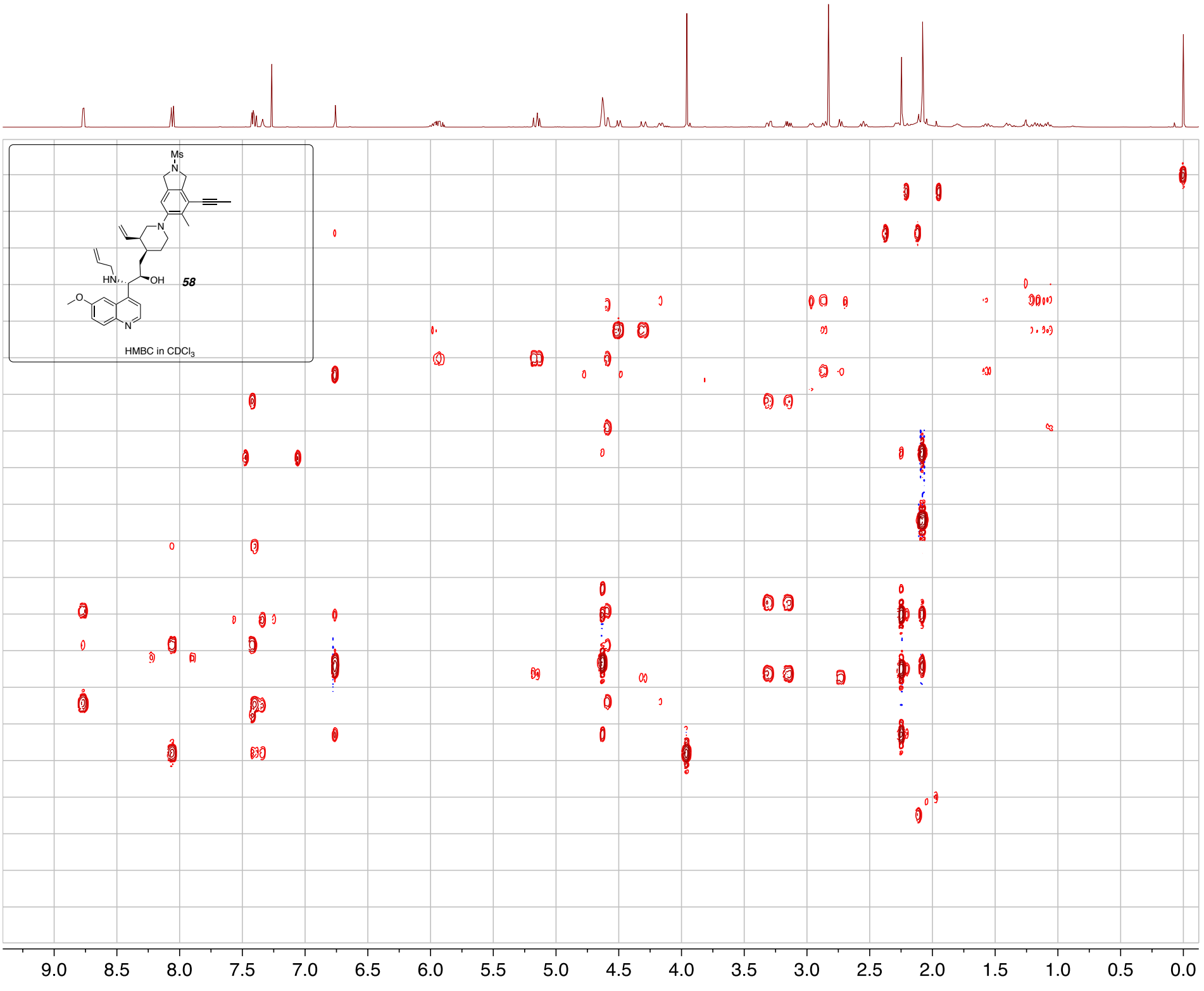


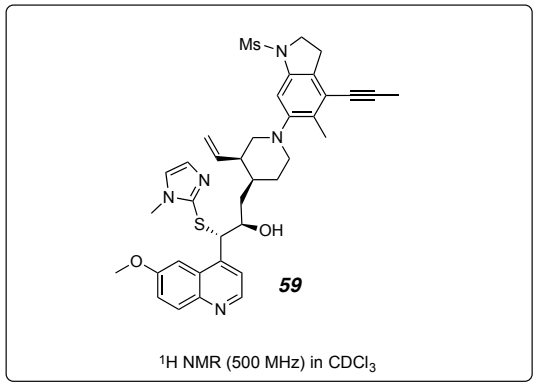
58

1H NMR (500 MHz) in CDCl3



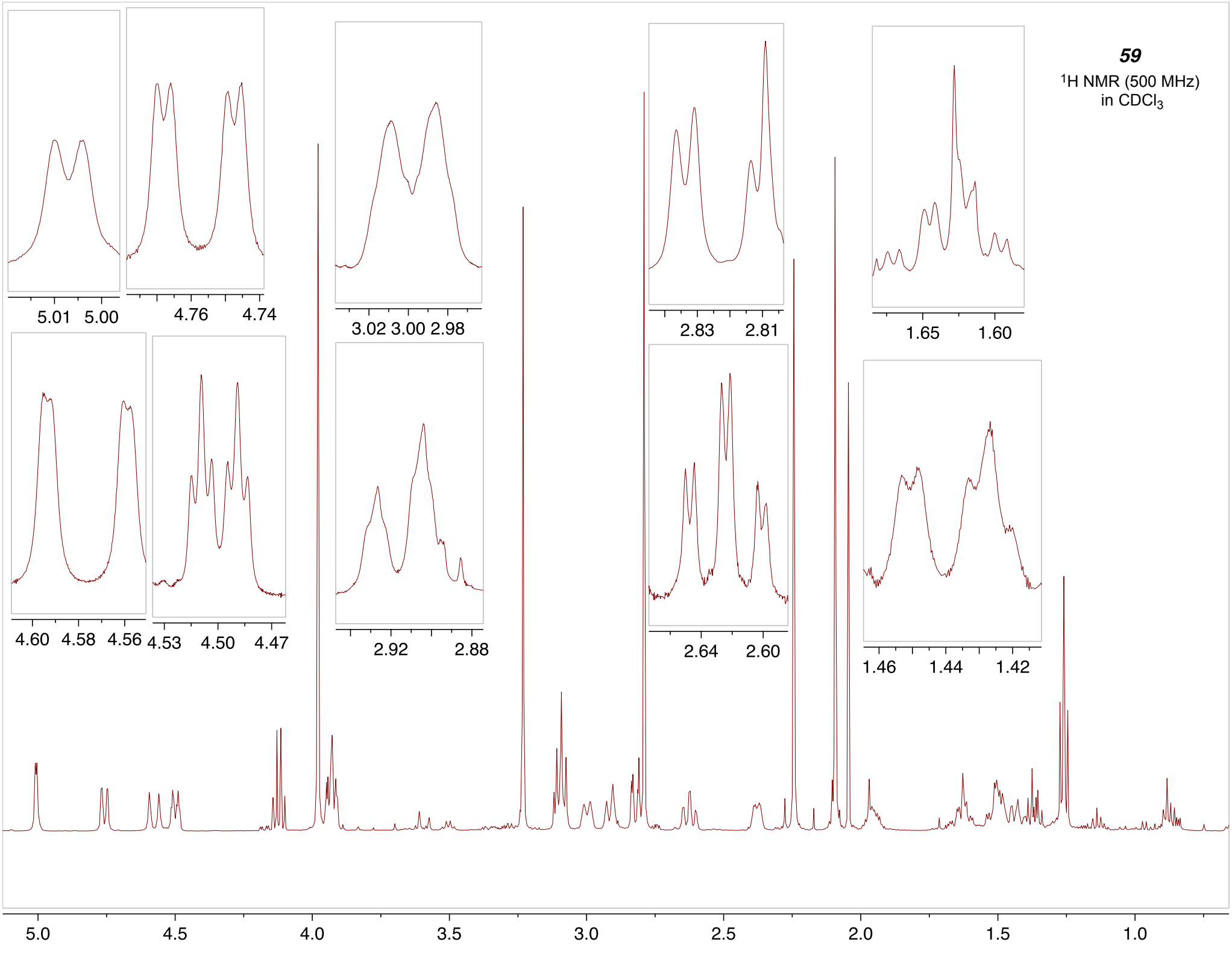

Ms
N
N
HN
OH
O
N
58
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

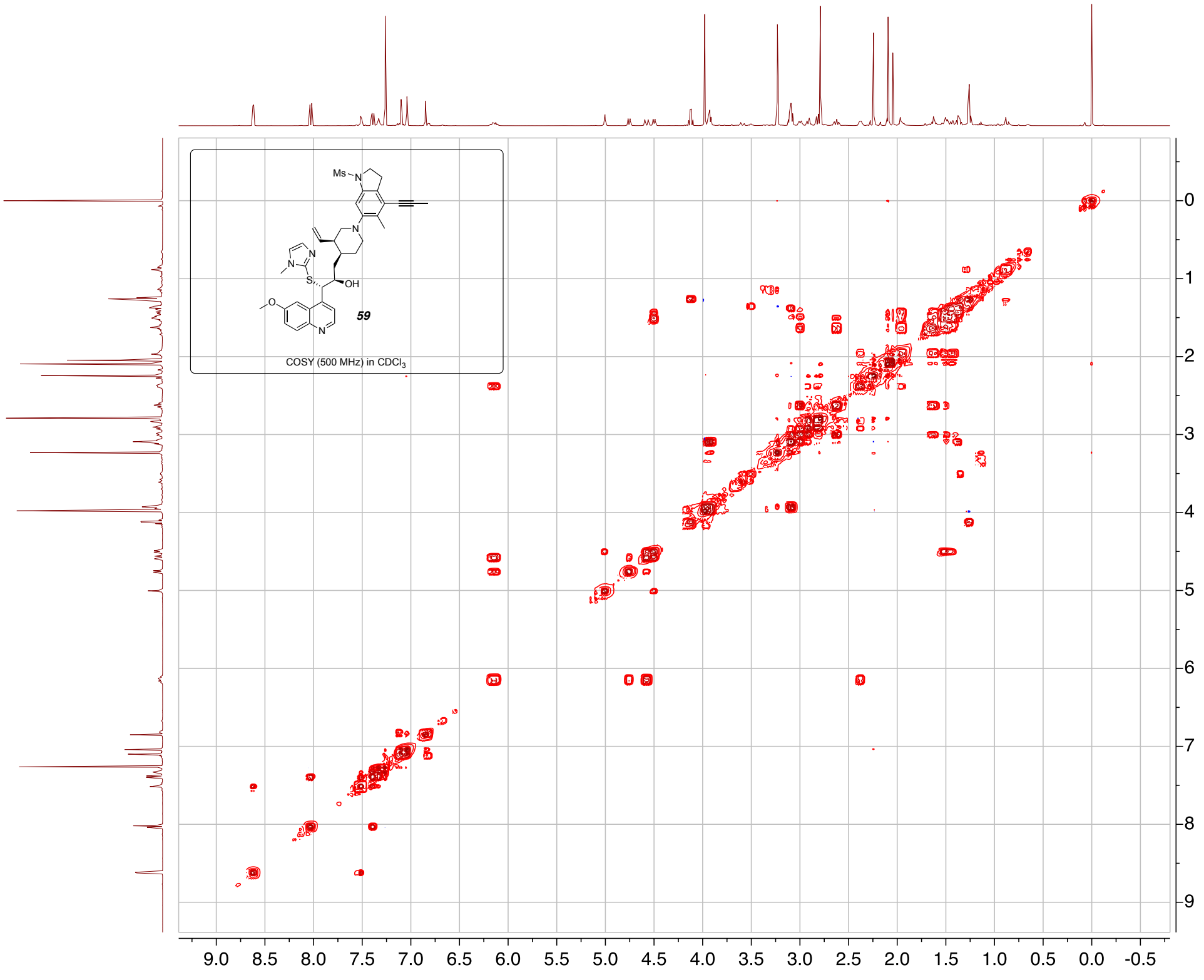

Ms
N
N
HN
OH
58
O
N
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

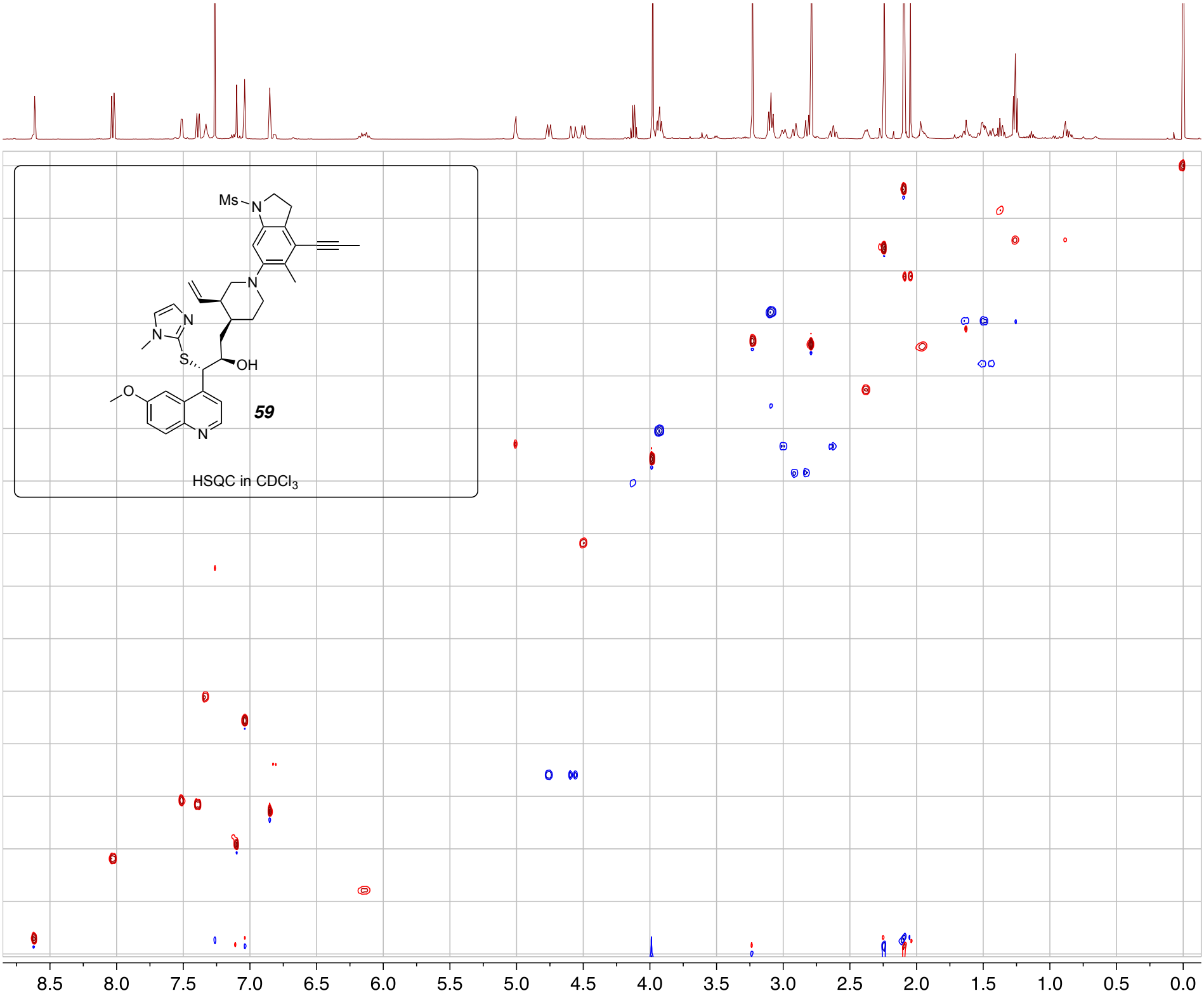


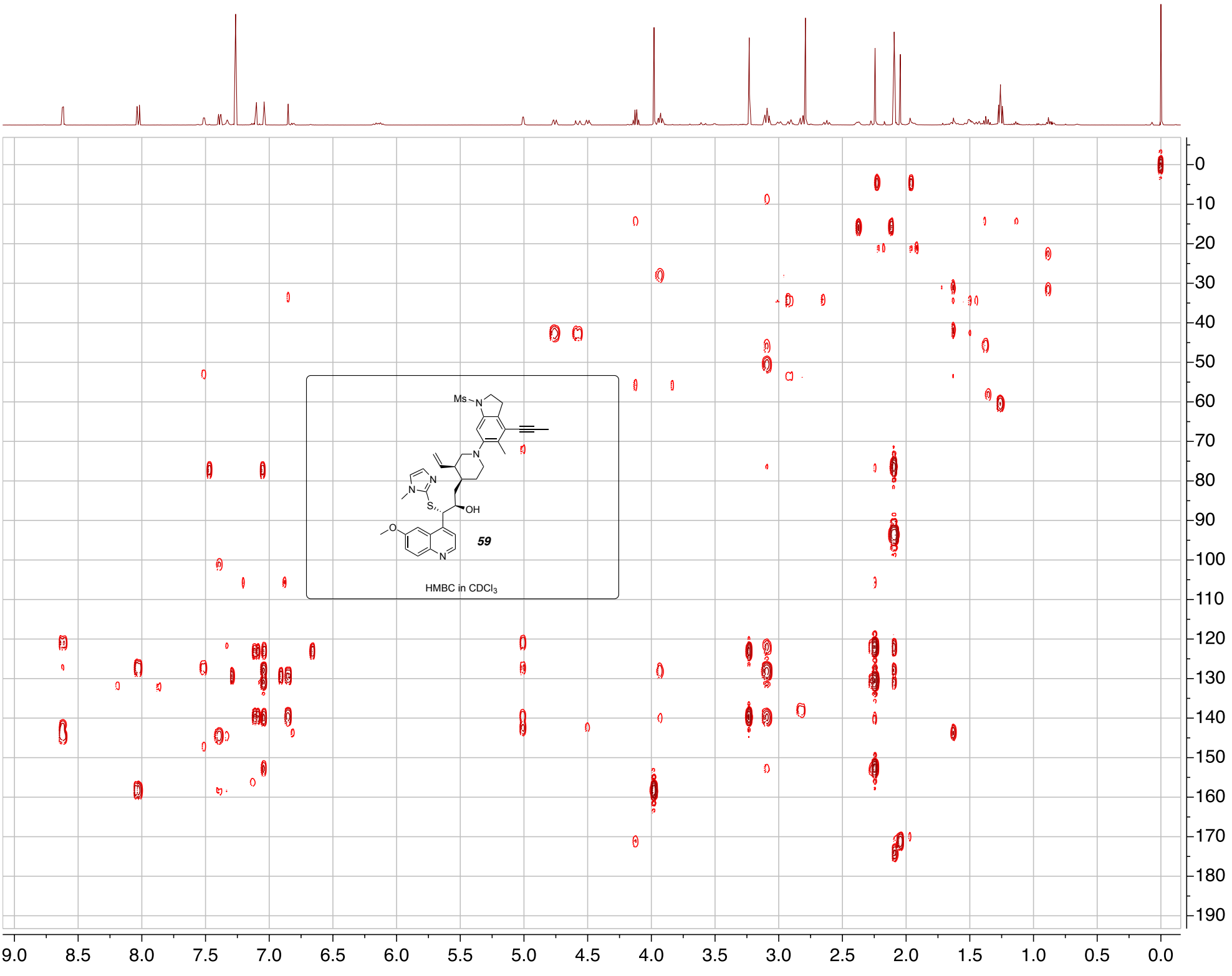
59

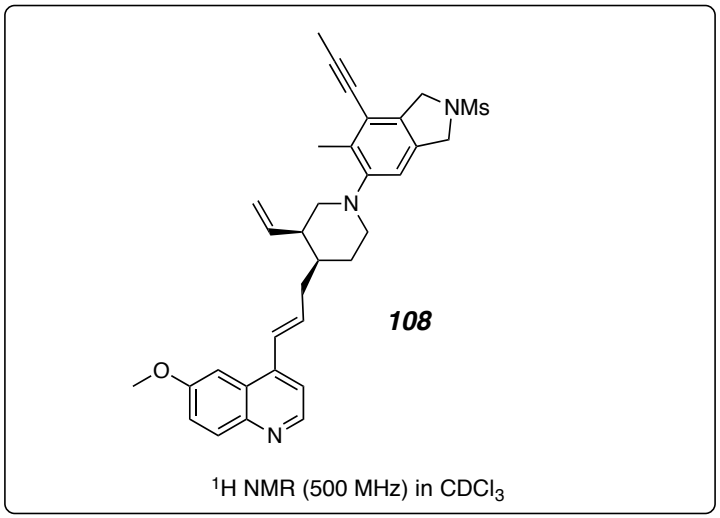
^{1}H NMR (500 MHz) in $CDCl_3$


59
^{1}H NMR (500 MHz)
in $CDCl_3$
5.01 5.00
4.76 4.74
3.02 3.00 2.98
2.83 2.81
1.65 1.60
4.60 4.58 4.56
4.53 4.50 4.47
2.92 2.88
2.64 2.60
1.46 1.44 1.42
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0


Ms
N
N
N
S
OH
O
N
59
COSY (500 MHz) in CDCl3
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

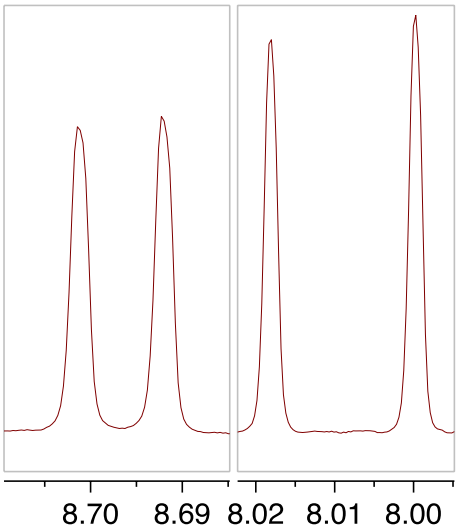

Ms
N
N
N
N
S
OH
O
N
59
HSQC in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

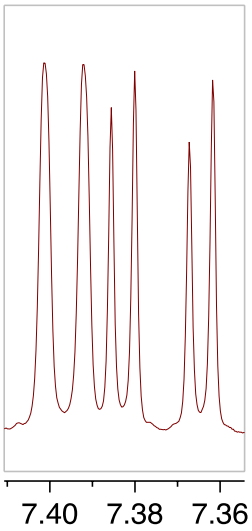

Ms
N
N
N
N
S
OH
O
59
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

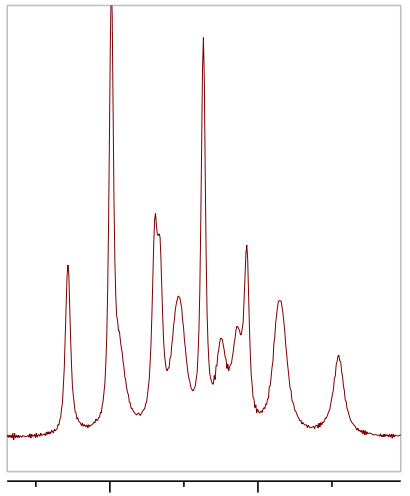


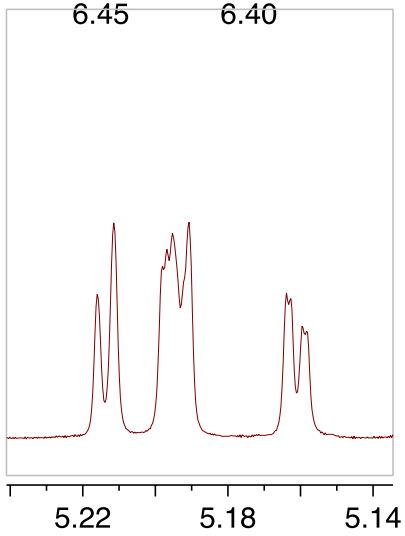
108

^{1}H NMR (500 MHz) in $CDCl_3$



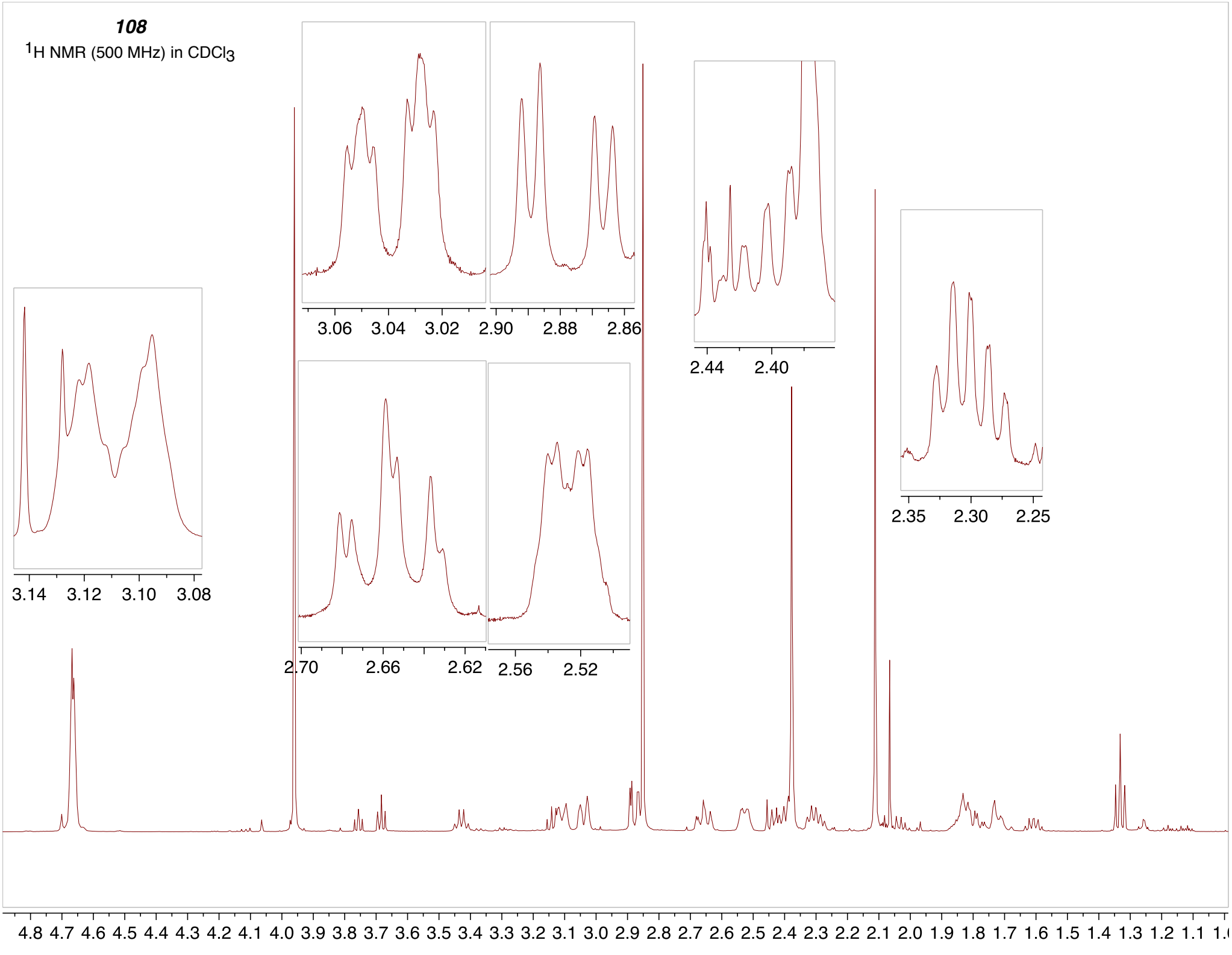


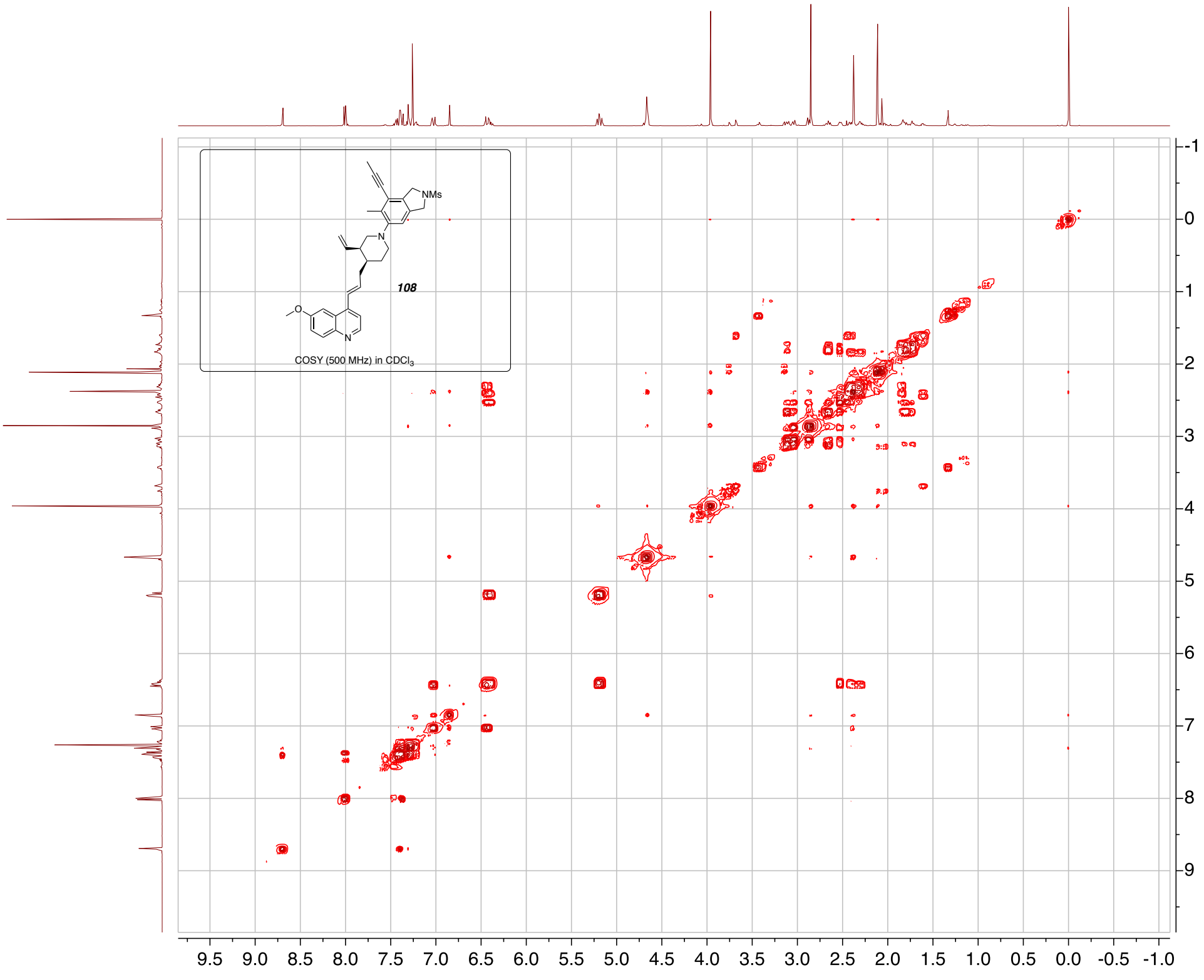


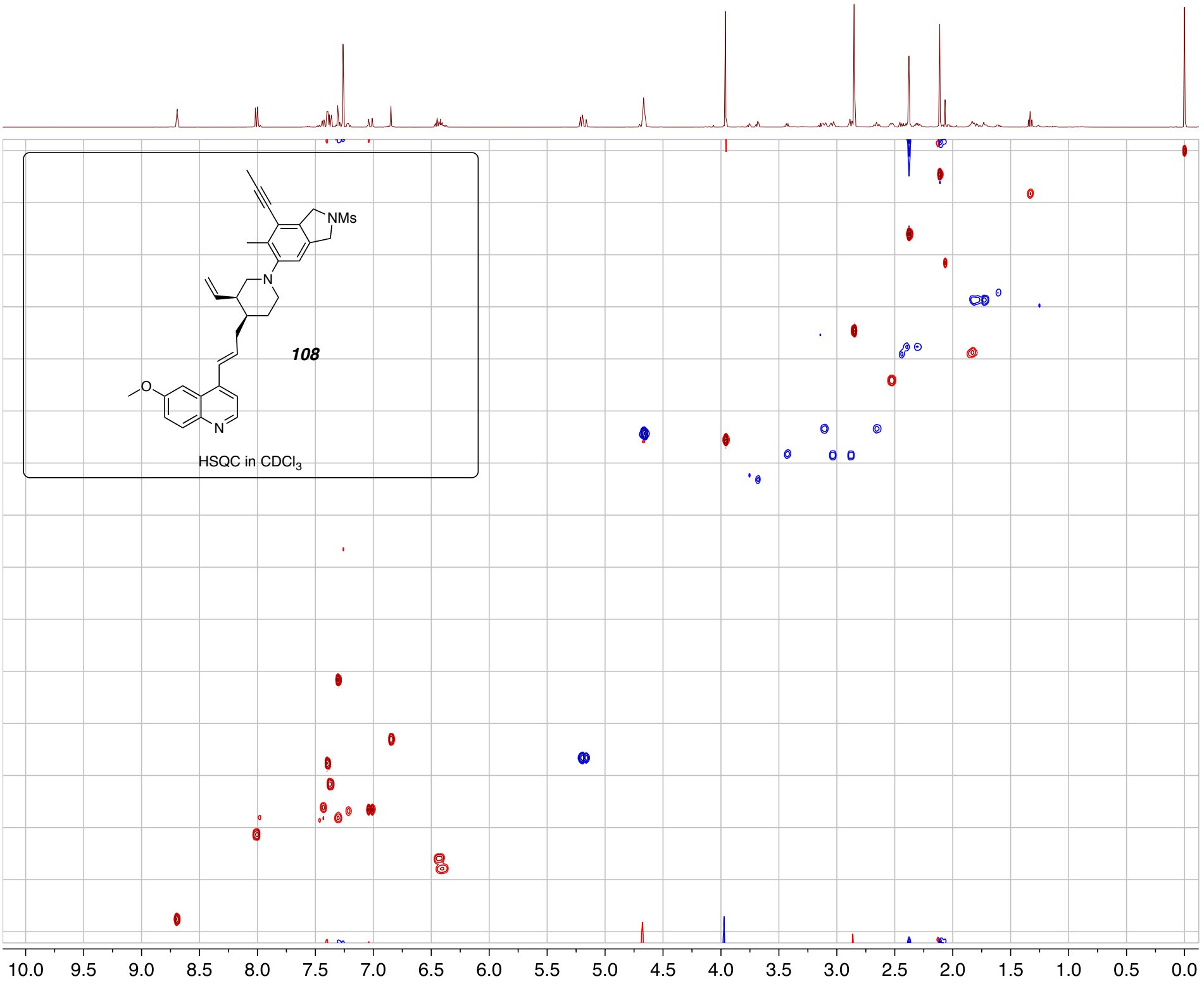


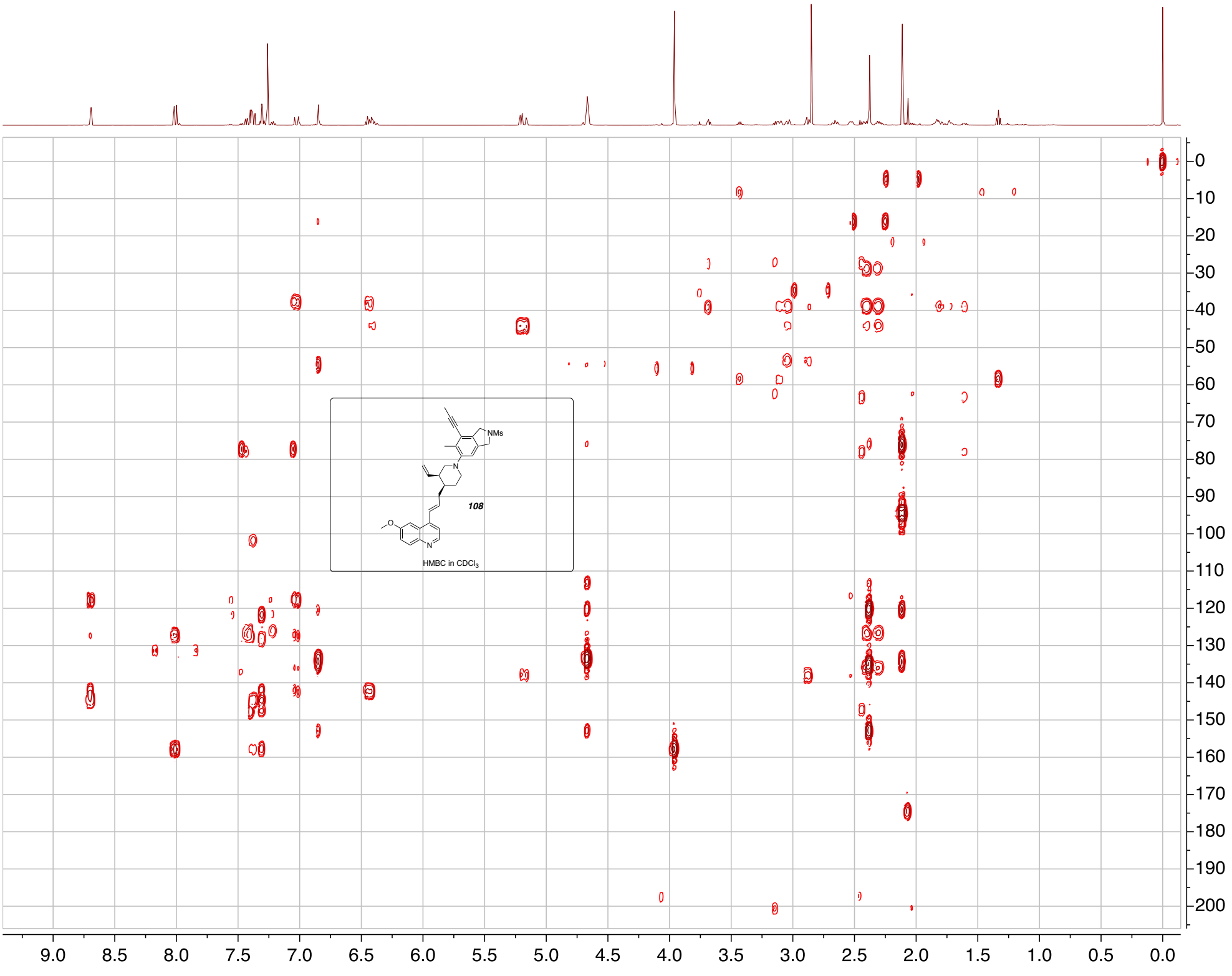
108

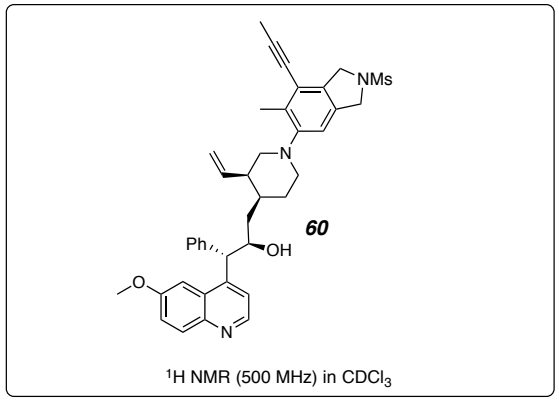
^{1}H NMR (500 MHz) in $CDCl_3$



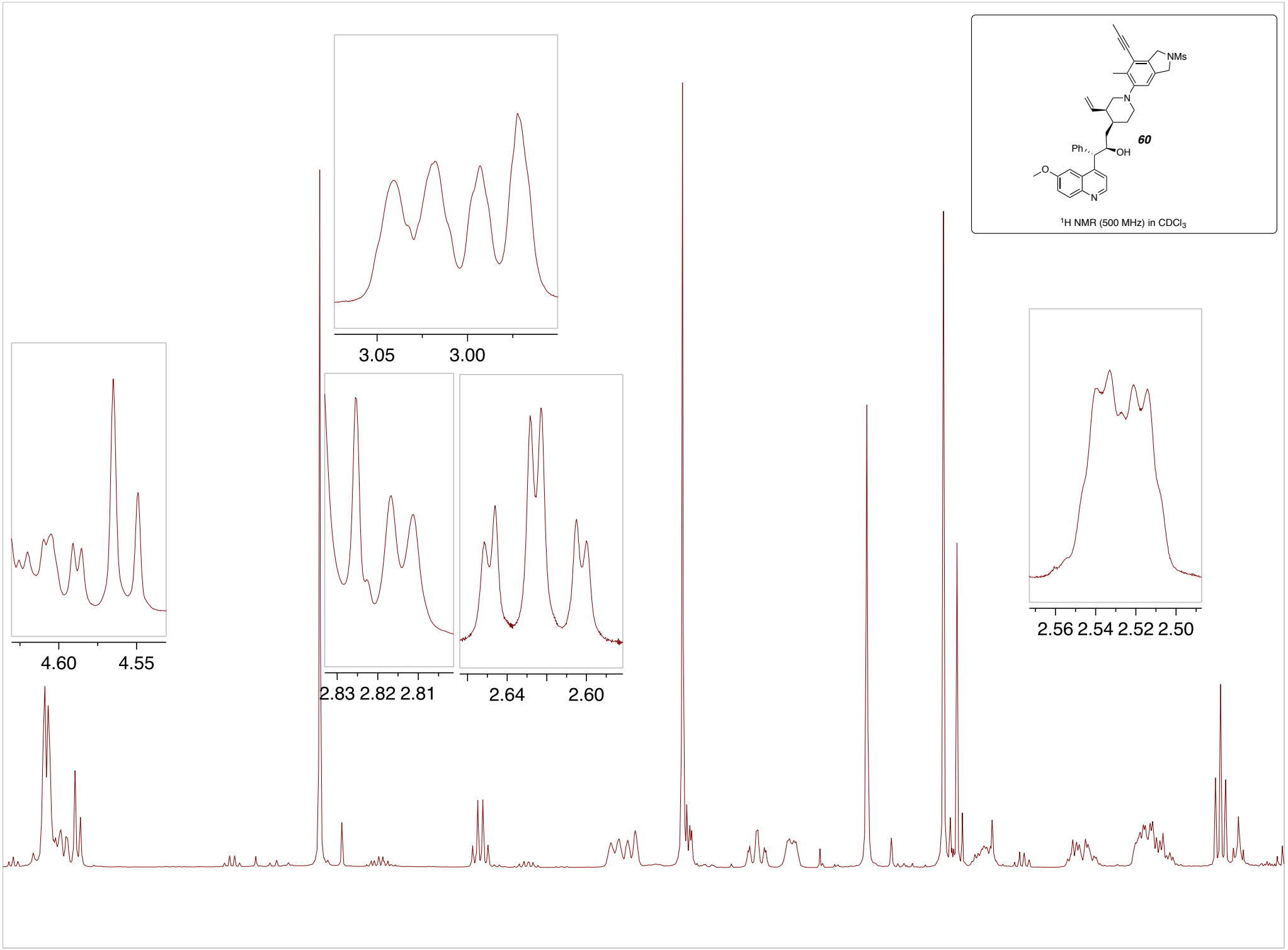

NMs
N
O
N
108
COSY (500 MHz) in CDCl3
-1
0
1
2
3
4
5
6
7
8
9
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

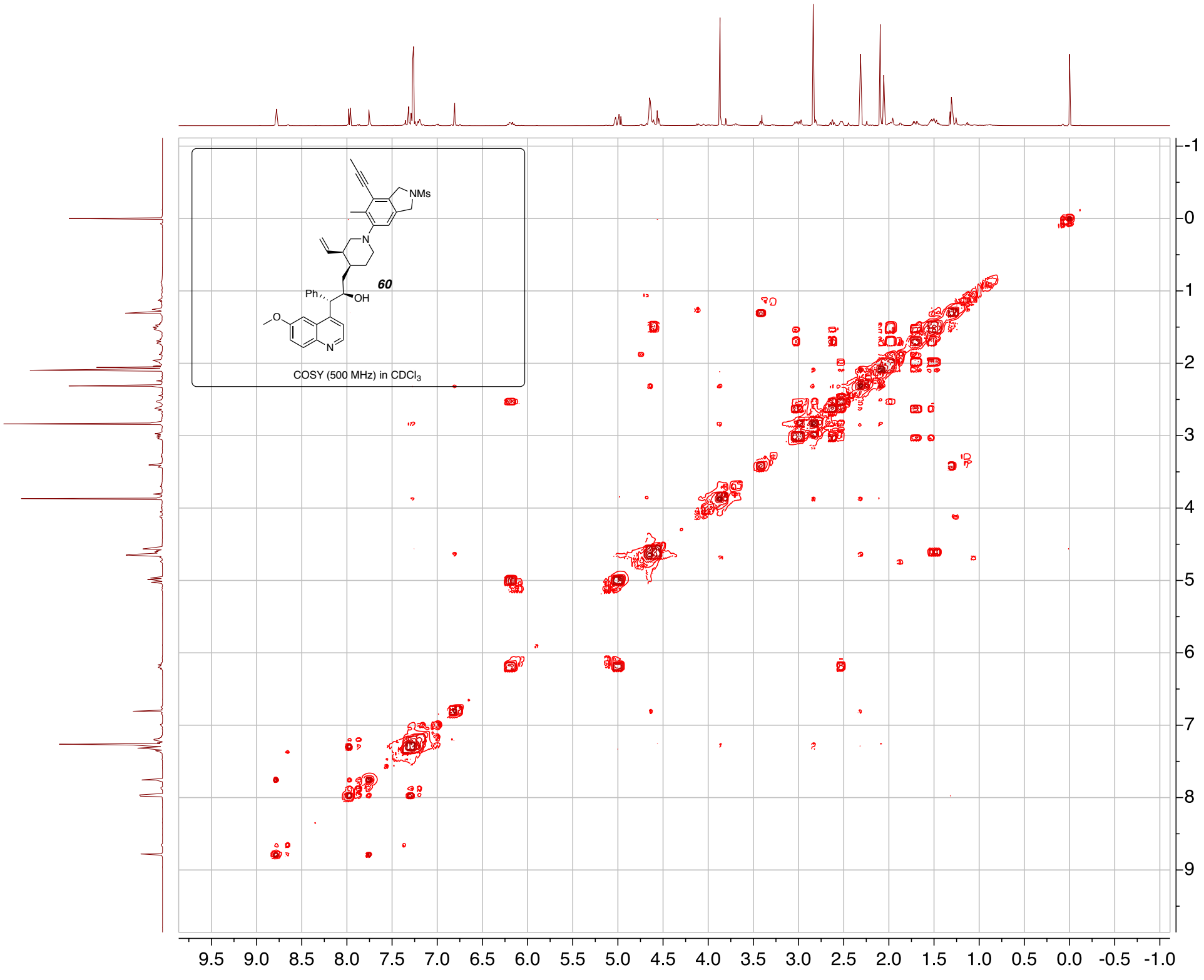

NMs
N
O
N
108
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

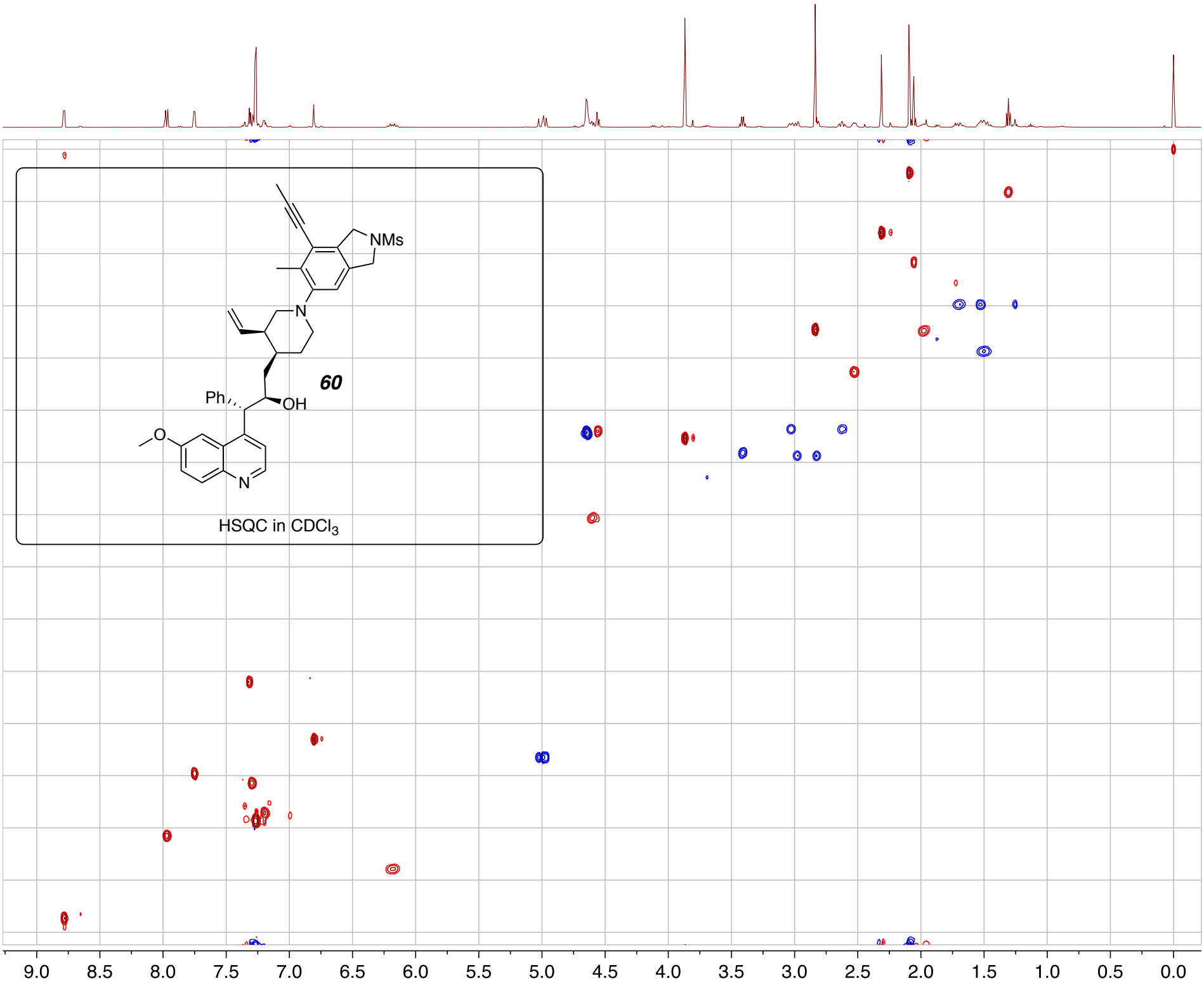

NMs
N
108
O
N
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

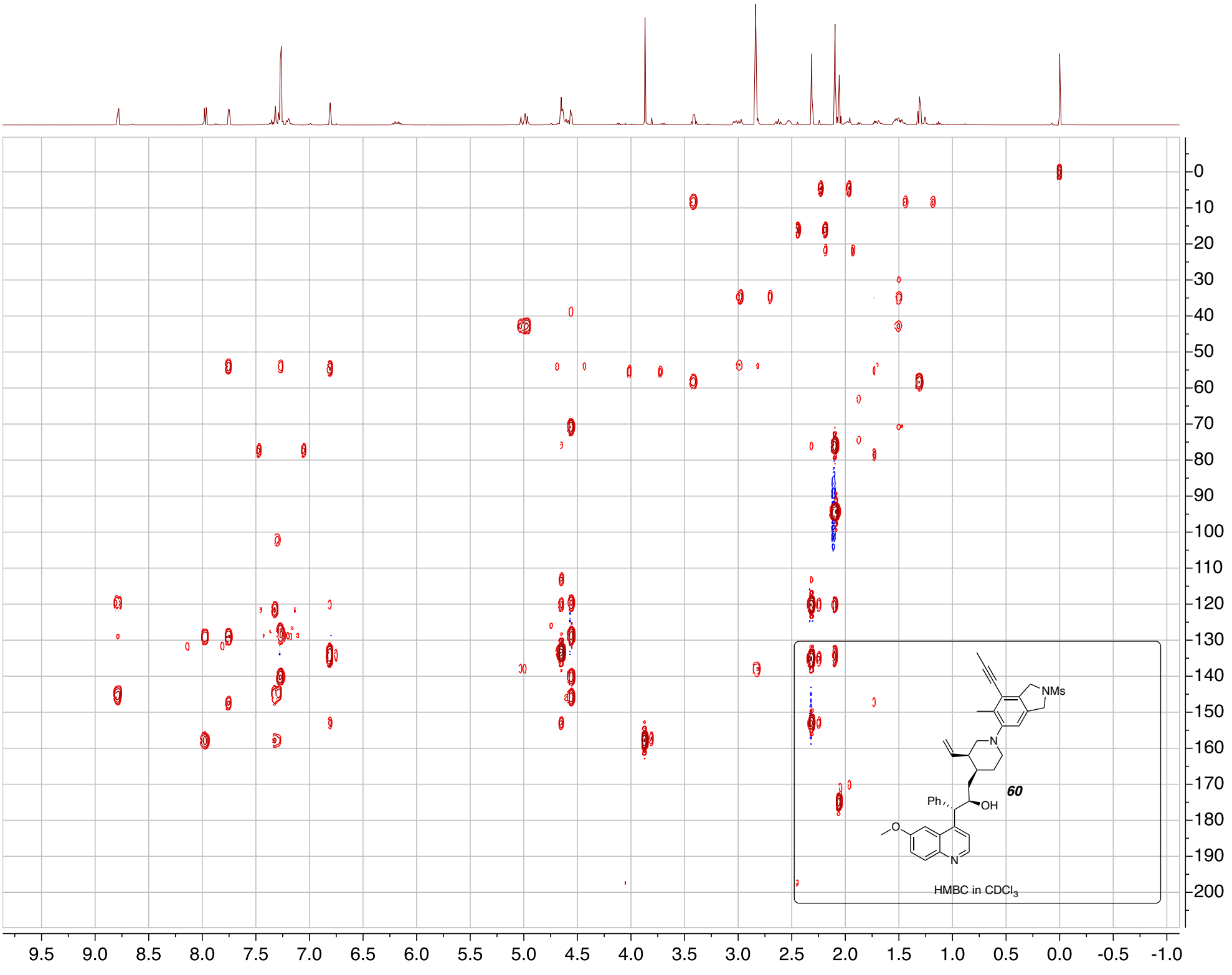


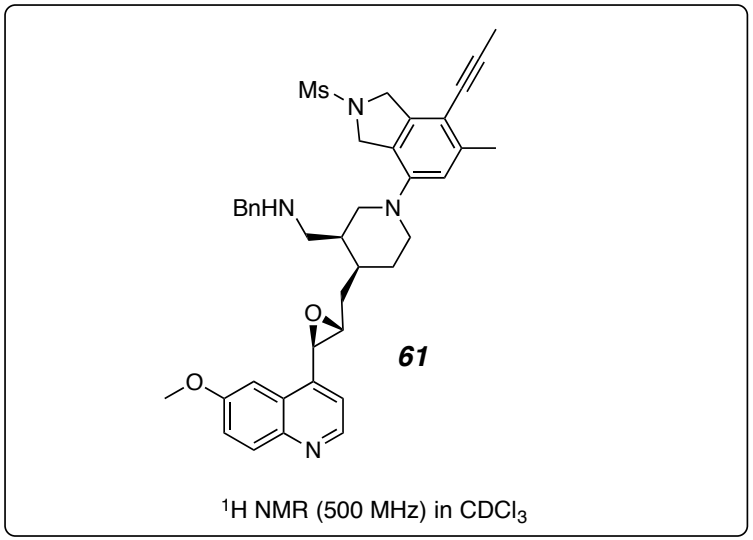
^{1}H NMR (500 MHz) in $CDCl_3$


NMs
N
60
Ph
OH
O
N
^{1}H NMR (500 MHz) in $CDCl_3$
3.05
3.00
4.60
4.55
2.83 2.82 2.81
2.64
2.60
2.56 2.54 2.52 2.50
4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2


NMs
N
60
Ph
OH
O
N
COSY (500 MHz) in CDCl3
-1
0
1
2
3
4
5
6
7
8
9
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

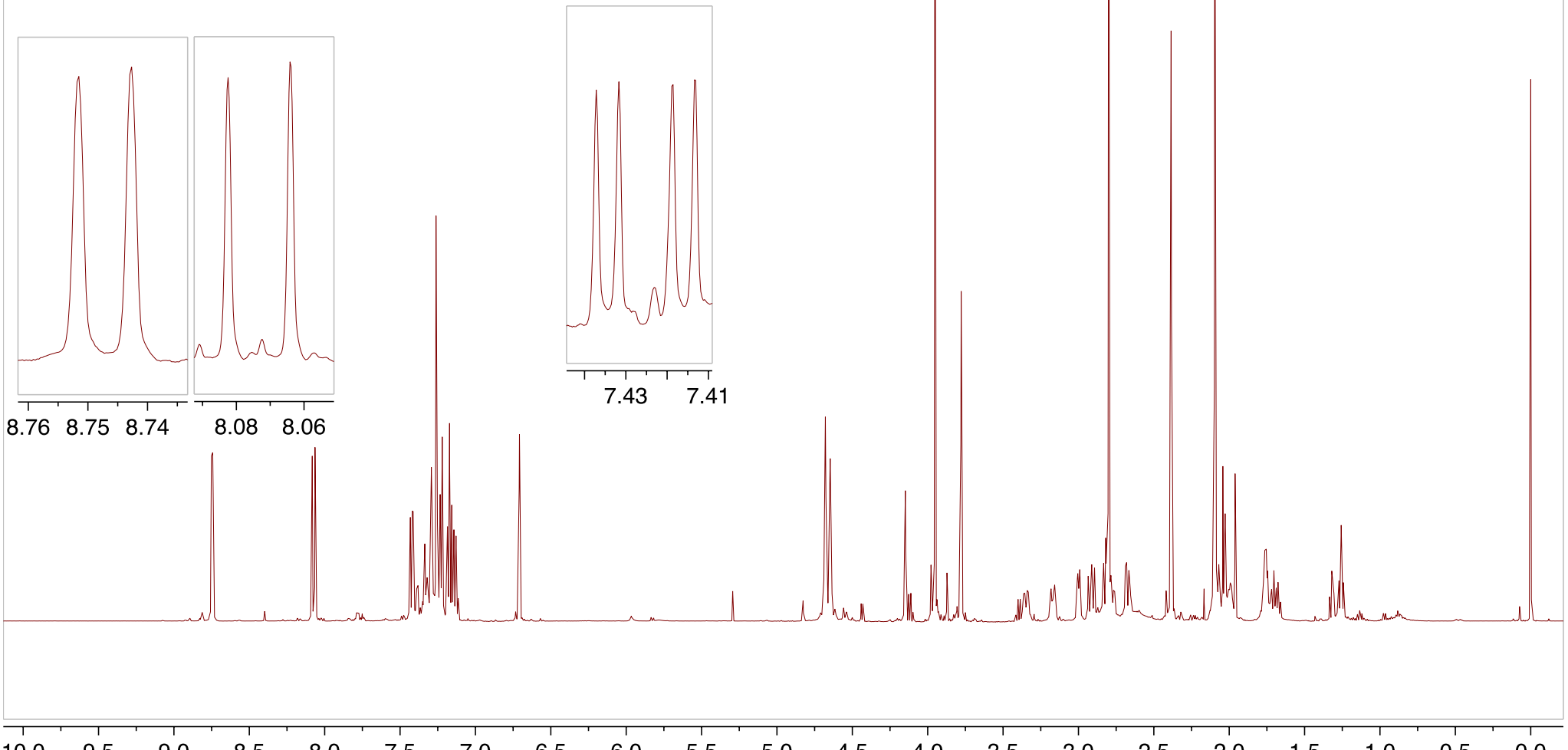

NMs
N
60
Ph
OH
O
N
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

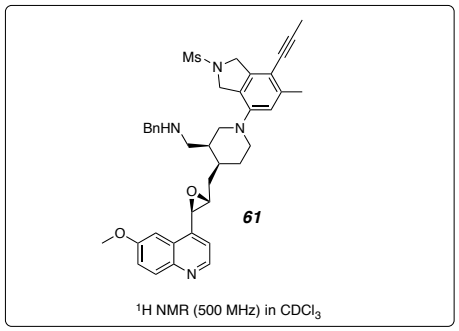

NMs
N
60
Ph
OH
O
N
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

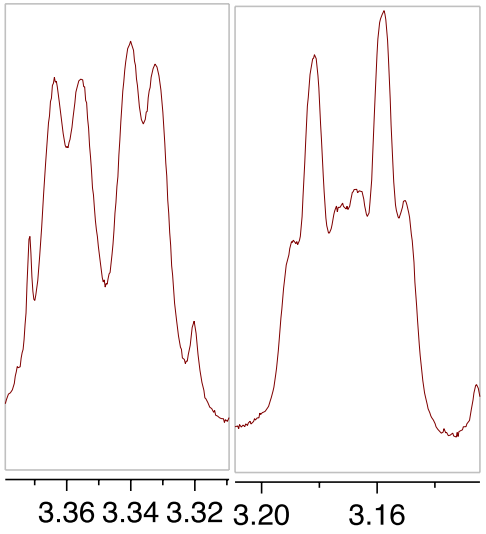


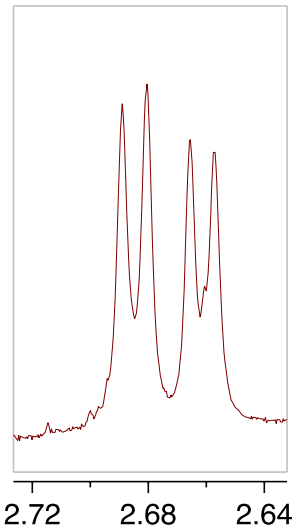
61

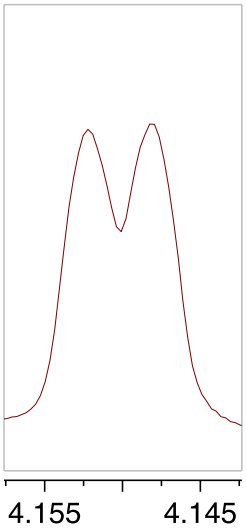
^{1}H NMR (500 MHz) in $CDCl_3$

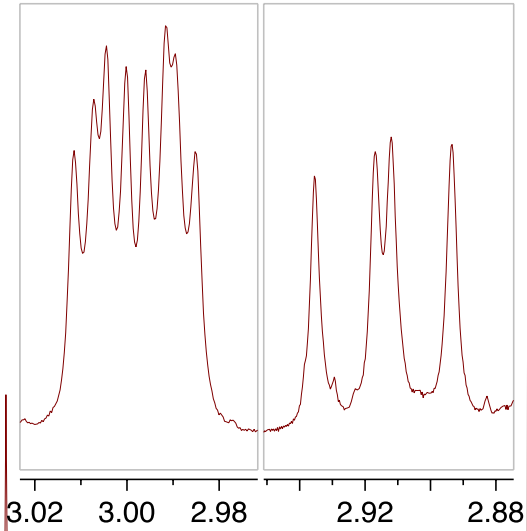


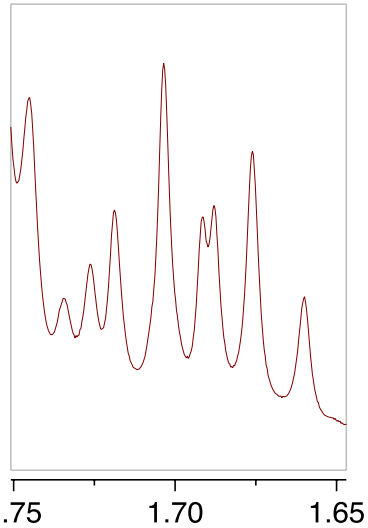

Ms
N
BnHN
N
O
O
N
61
^{1}H NMR (500 MHz) in $CDCl_3$

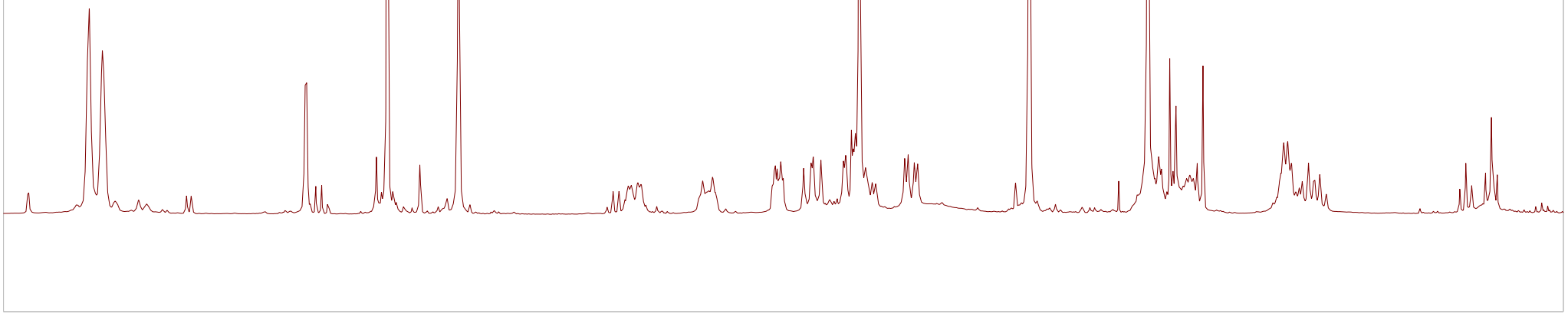

3.36 3.34 3.32 3.20 3.16

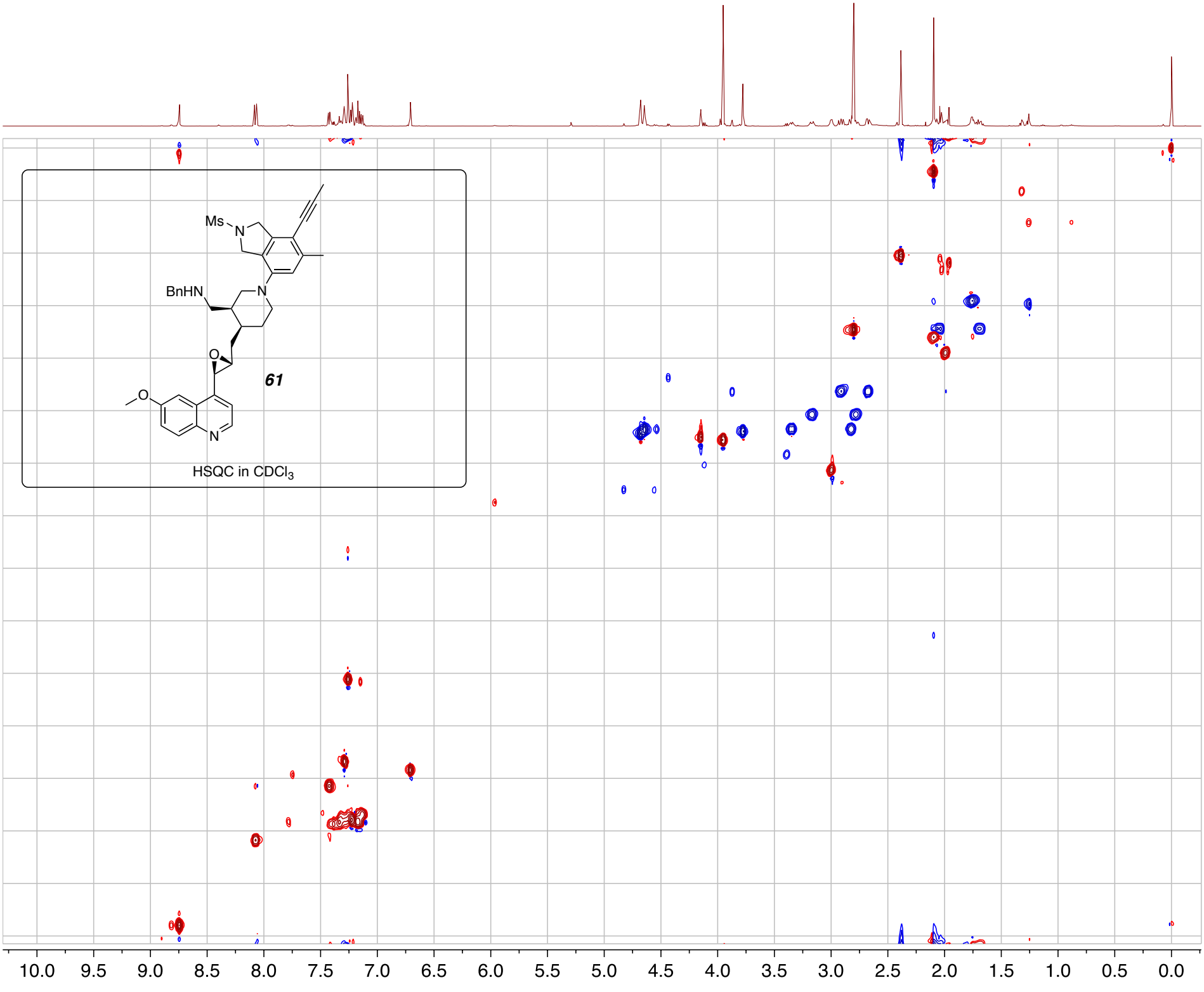

2.72 2.68 2.64


4.155 4.145


3.02 3.00 2.98 2.92 2.88


1.75 1.70 1.65


4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2


Ms
N
BnHN
N
O
O
N
61
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
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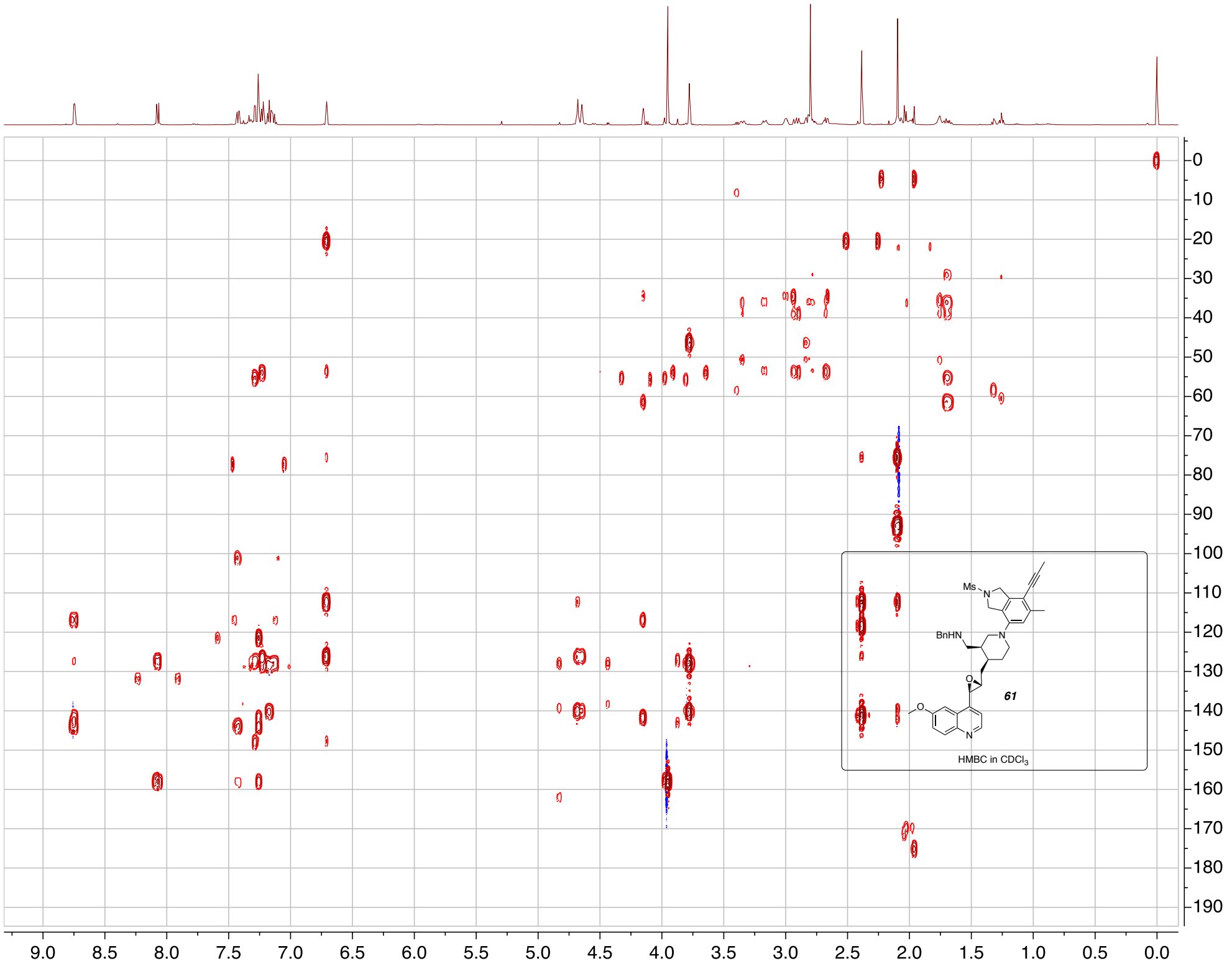
2.0
1.5
1.0
0.5
0.0


Ms
N
BnHN
N
O
61
O
N
HMBC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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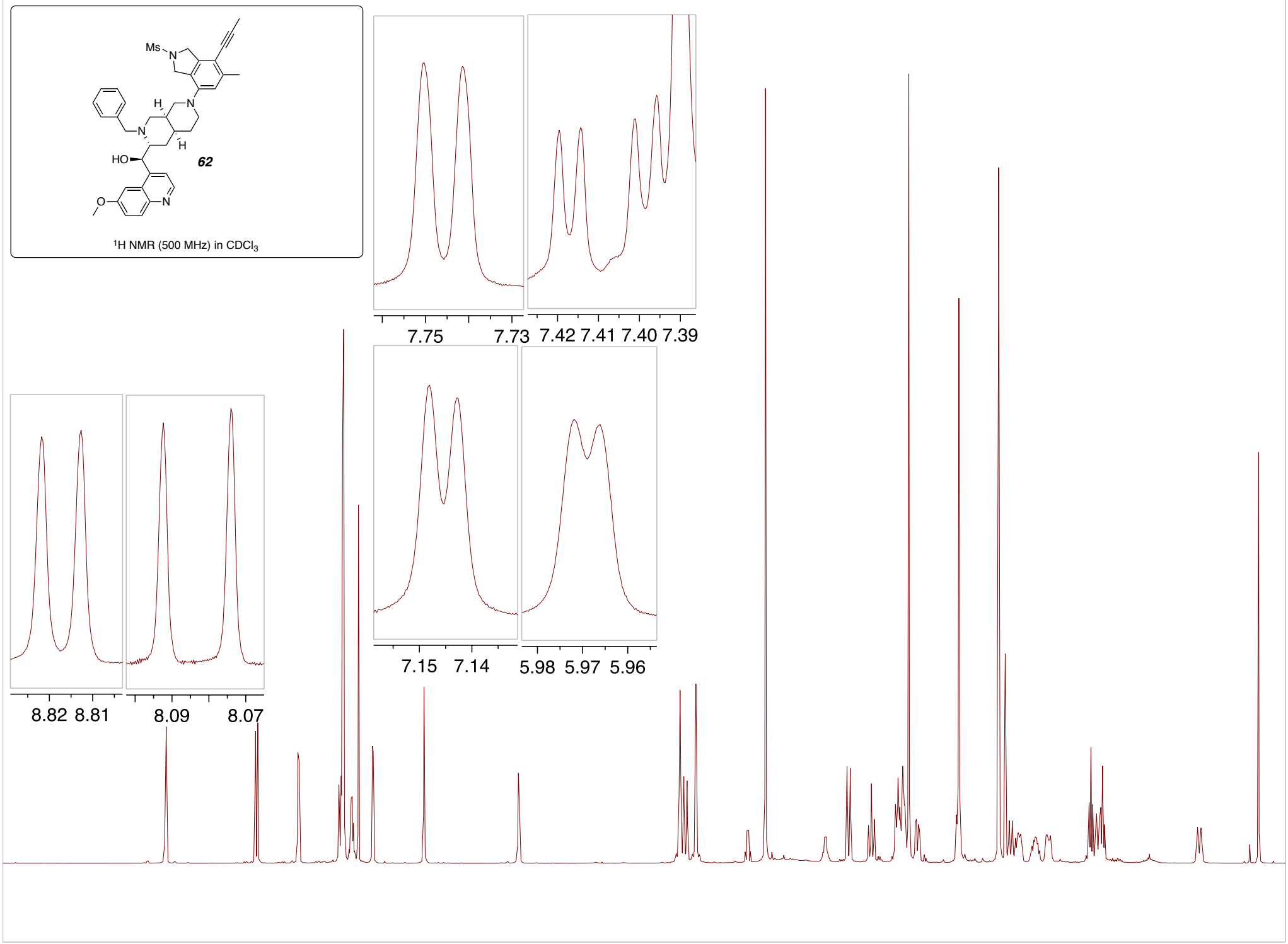
0.5
0.0


Ms
N
H
N
N
H
HO
62
O
N
^{1}H NMR (500 MHz) in $CDCl_3$
7.75
7.73
7.42
7.41
7.40
7.39
8.82
8.81
8.09
8.07
7.15
7.14
5.98
5.97
5.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.0
1.5
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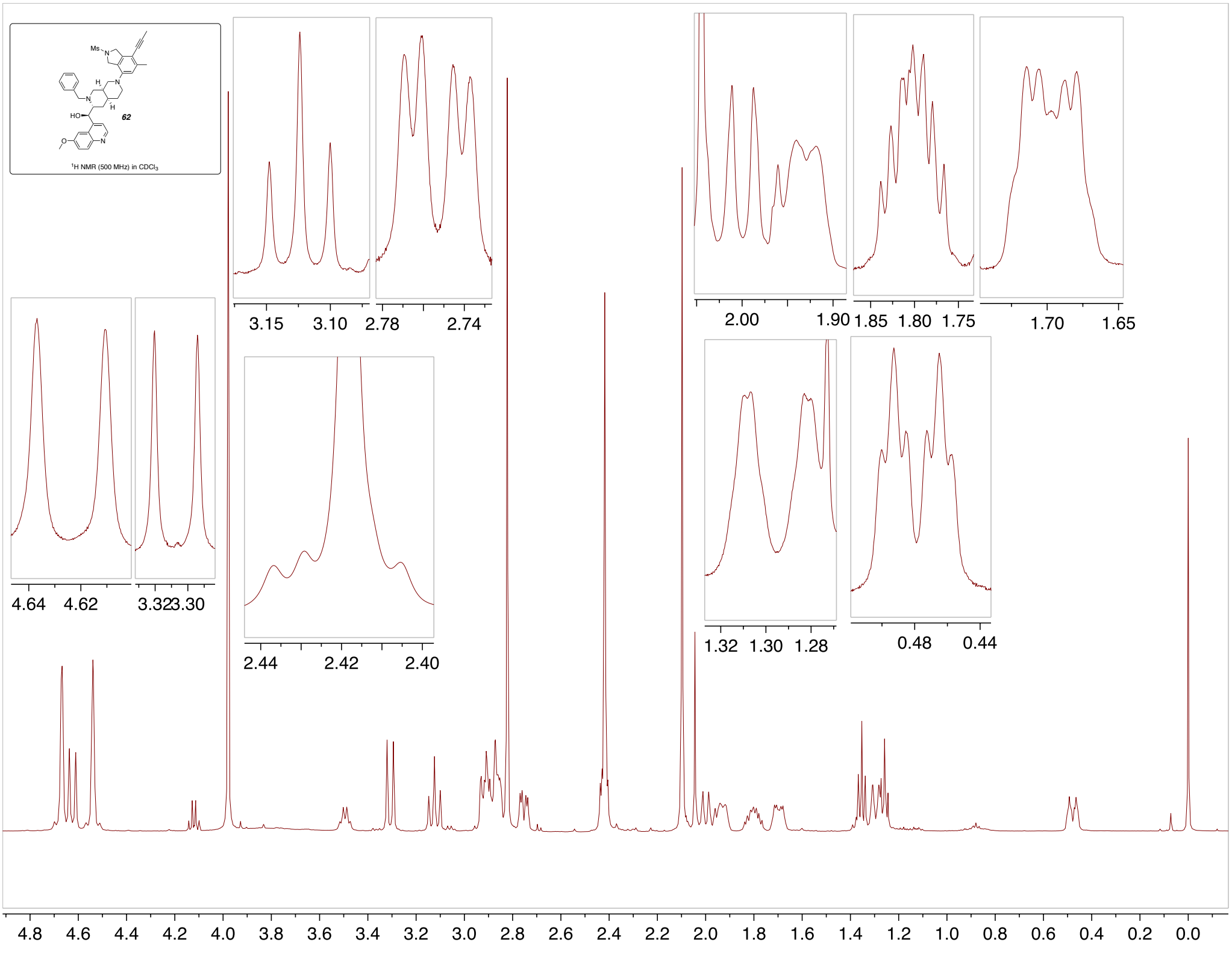
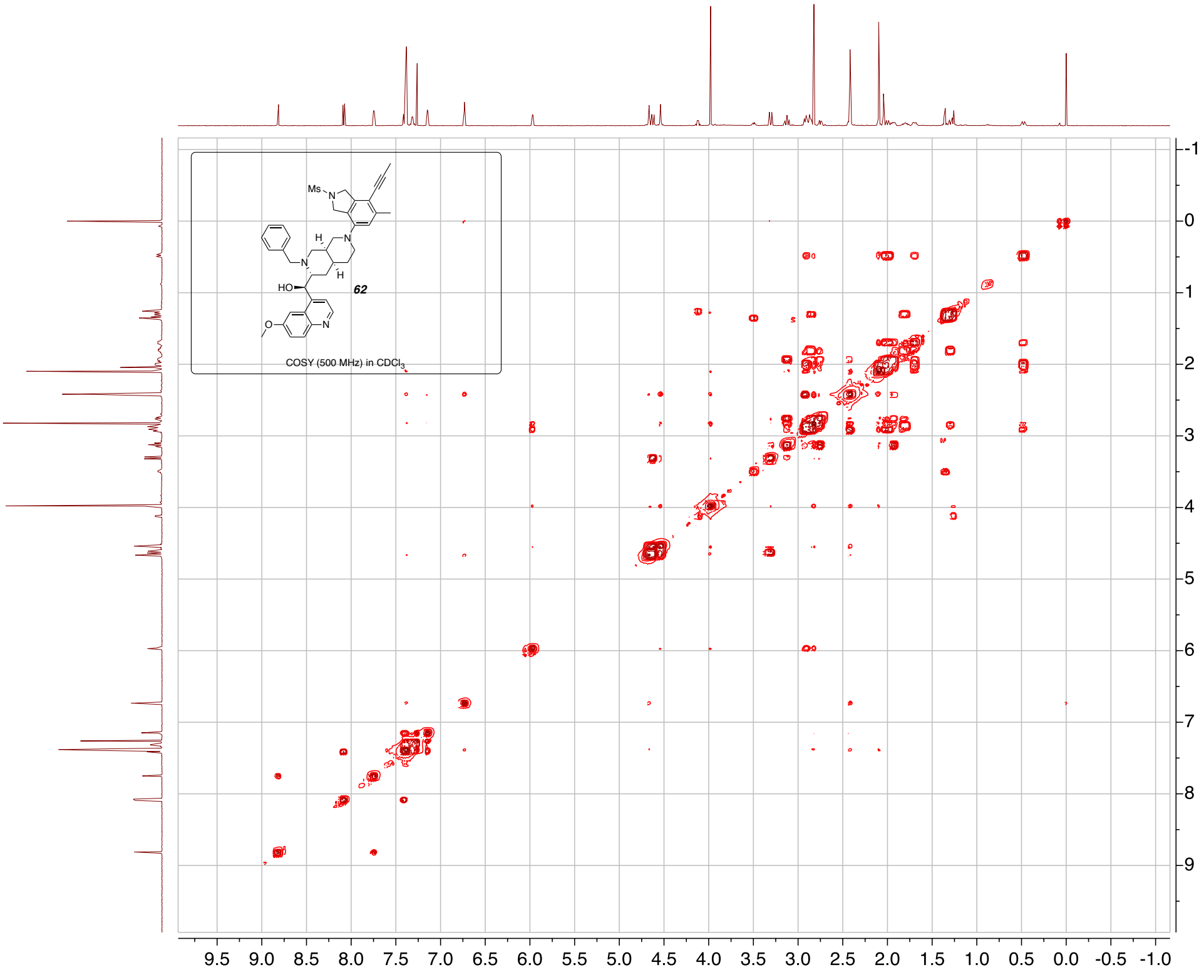
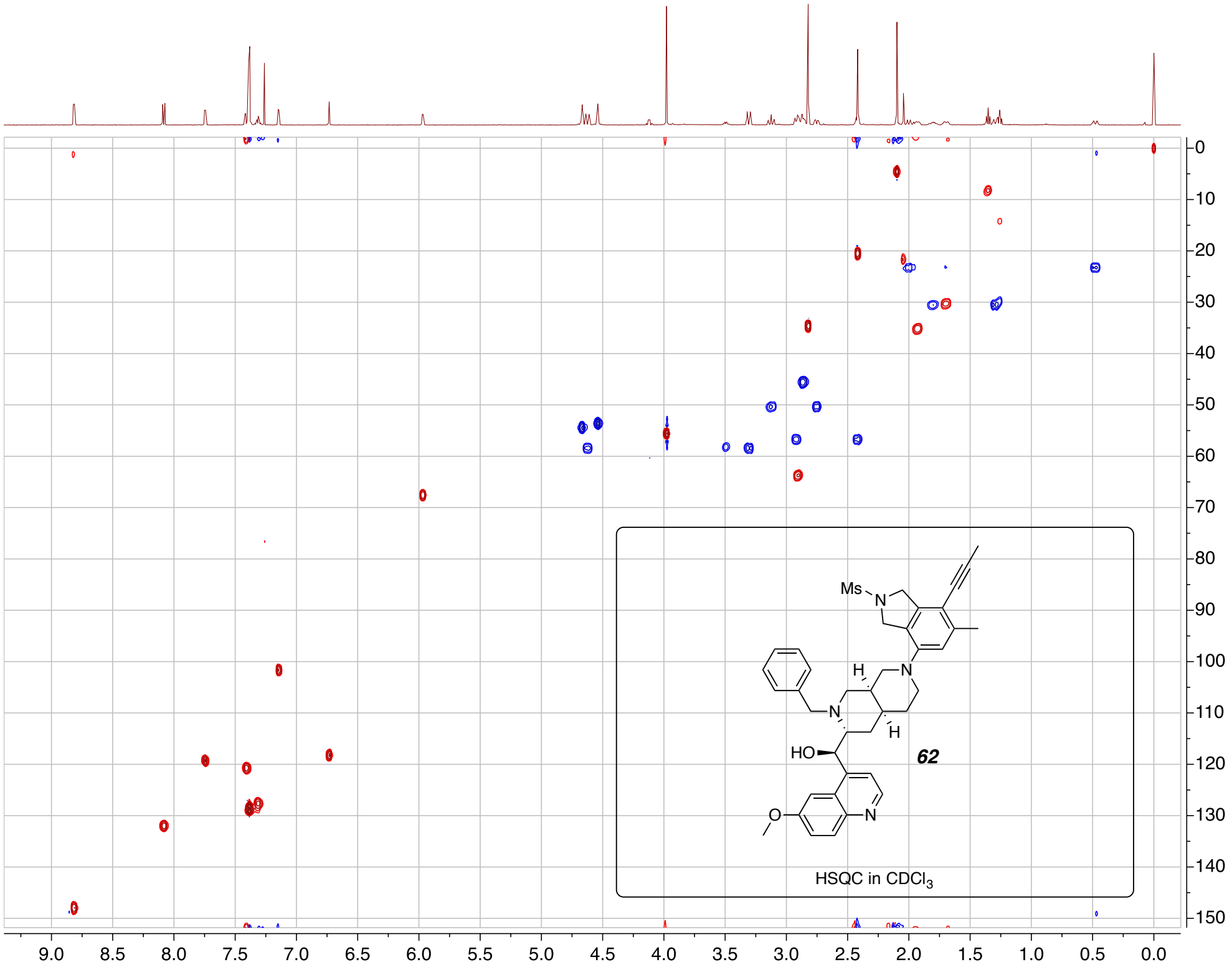
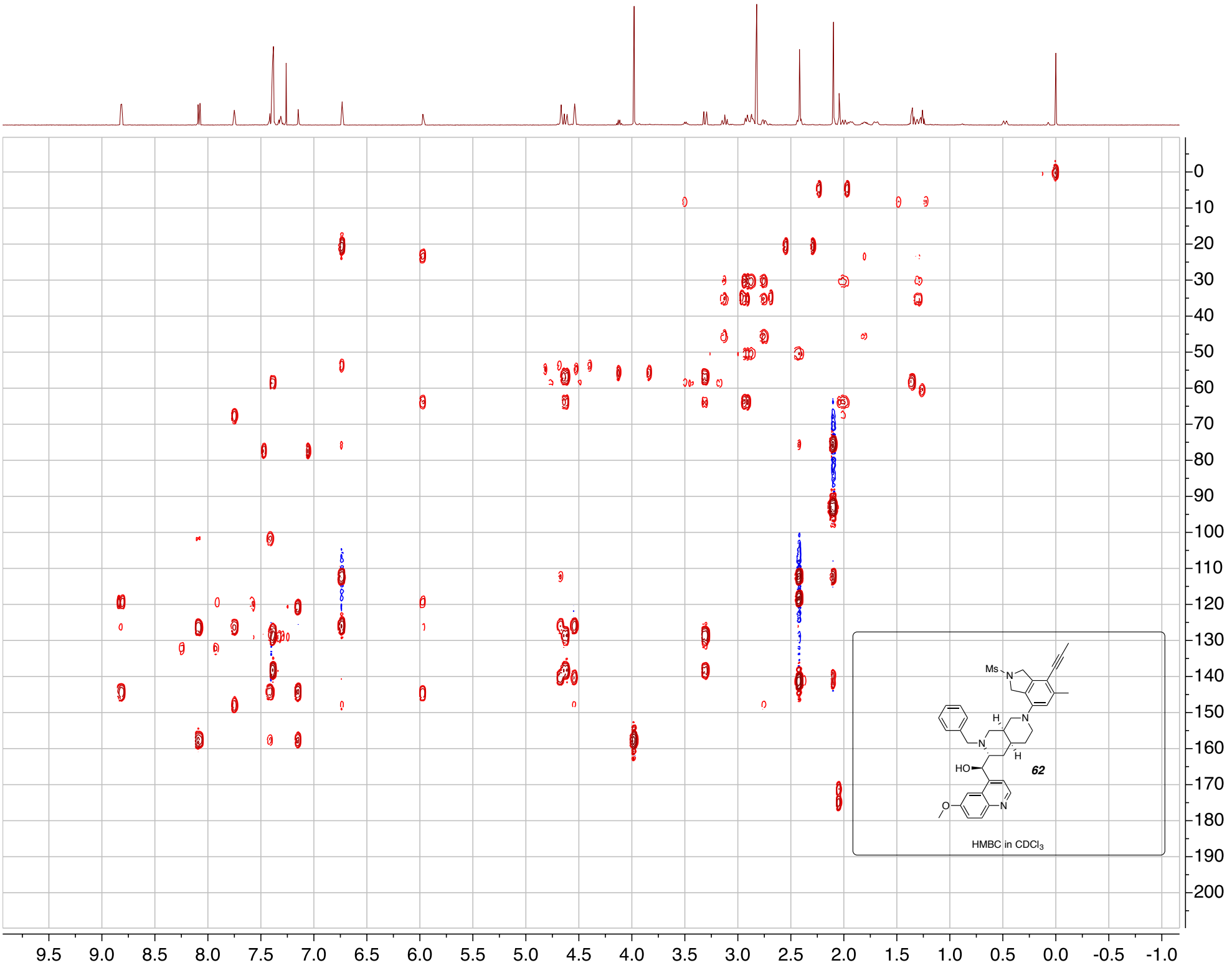
0.0


Ms
N
H
N
N
H
HO
62
O
N
^{1}H NMR (500 MHz) in $CDCl_3$
3.15
3.10
2.78
2.74
2.00
1.90
1.85
1.80
1.75
1.70
1.65
4.64
4.62
3.32
3.30
2.44
2.42
2.40
1.32
1.30
1.28
0.48
0.44
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0


Ms
N
H
N
N
H
HO
62
O
N
COSY (500 MHz) in CDCl3
-1
0
1
2
3
4
5
6
7
8
9
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


Ms
N
H
N
N
H
HO
62
O
N
HSQC in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
Ms
N
H
N
N
H
HO
62
O
N
HMBC in CDCl3